Studies on The Synthesis of New Classes of Crown Ether-Type/Polyether Macrocycles and Optically Active Aza-Oxo-Thia Polyether Macrocycles

A thesis submitted for the partial fulfilment of the degree of Doctor of Philosophy

By

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March 2017

DEDICATED to

MY BELOVED PARENTS

BROTHER

Sumit

BUA FUFA JI

SISTER

Seema

Declaration

*I hereby declare that the matter embodied in this thesis entitled "*Studies on The Synthesis of New Classes of Crown Ether-Type/Polyether Macrocycles and Optically Active Aza-Oxo-Thia Polyether Macrocycles*" is the result of investigations carried out by me under the supervision of* ***Dr. S. Arulananda Babu*** *at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, SAS Nagar Mohali, India. This work has not been submitted in part or full for the award of any degree, a diploma or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate it clearly with due acknowledgements. In keeping with the general practice in reporting scientific observations, acknowledgements has been made whenever the work was described based on the findings of other investigators. Any omission that might have occurred due to oversight or error in judgment is regretted. A complete bibliography of the books and journals referred to is given at the end of the thesis.*

Naveen

Date:

Place:

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. S. Arulananda Babu
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Date:

Place:

Acknowledgments.

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List of publications from thesis work.

1) **Naveen;** Parella, R.; Babu, S. A. *Tetrahedron Lett.* **2013**, *54*, 2255.

Title: *RCM strategy-based entry into new crown ether/polyether macrocyclic systems derived from hydroxy benzaldehydes.*

2) **Naveen**; Babu, S. A.; Kaur, G.; Aslam, N. A.; Karanam, M. *RSC Advances* **2014**, *4*, 18904.
Title: *Glaser-Eglinton-Hay sp-sp coupling and macrocyclization: construction of a new class of polyether macrocycles having a 1,3-diyne unit.*

3) **Naveen**; Aslam, N. A.; Babu, S. A.; Singh, D. K.; Rana, A. *Synlett* **2014**, *25*, 2201.
Title: *Magnetically separable nano Fe_3O_4 catalyzed direct azidation of allylic and benzylic alcohols followed by copper-catalyzed click reaction.*

4) **Naveen**; Babu, S. A.; Aslam, N. A.; Sandhu, A.; Singh, D. K.; Rana, A. *Tetrahedron* **2015**, *71*, 7026.
Title: *Direct azidation of allylic/benzylic alcohols and ethers followed by the click reaction: one-pot Synthesis of 1,2,3-triazoles and 1,2,3-triazole moiety embedded macrocycles.*

5) **Naveen**; Babu, S. A. *Tetrahedron* **2015**, *71*, 7758.
Title: *Ring-closing metathesis reaction-based synthesis of new classes of polyether macrocyclic systems.*.

6) **Naveen**; Babu, S. A. *Tetrahedron Lett.* **2016**, *57*, 5690.
Title: *An efficient entry into new classes of optically active aza-oxo polyether macrocycles via the ring closing metathesis-based macrocyclization*.

7) **Naveen**; Babu, S. A. *Tetrahedron Lett*. **2016**, 57, 5801.
Title: *EDC/DMAP-Mediated direct condensation of dicarboxylic acids and diols: A concise synthesis of extra large polyether macrocyclic lactones and their X-ray structures.*

8) **Naveen**; Rajkumar, V.; Babu, S. A.; Gopalakrishnan, B. *J. Org. Chem.* **2016**, *81*, 12197.
Title: *Pd(II)-Catalyzed, substrate design-facilitated chemoselective acetoxylation over cyclization of remote ε-C(sp^2)-H bonds in heteroaryl-aryl-based biaryl systems.*

9) **Naveen**; Babu, S. A. *Synlett* **2017**, *28*, 253.
Title: *Exploitation of intramolecular Glaser-Eglinton-Hay macrocyclization for the synthesis of new classes of optically active aza/oxo/thia polyether macrocycles from amino alcohol building blocks*

10) **Naveen**; Babu, S. A. manuscript to be submitted.
Title: *The Pd(II)-Catalyzed bidentate directing group-enabled chemo- and regioselective remote ε-C-H and ortho acetoxylation of 3-phenylpropan-1-amine systems.*

11) **Naveen**; Babu, S. A. manuscript to be submitted.
Title: *EDC/DMAP-Mediated direct synthesis of extra large polyether macrocyclic lactones and their X-ray structures study.*

List of publications as a co-author.

12) Parella, R.; **Naveen**; Babu, S. A. *Catal. Comm*. **2012**, *29*, 118.
Title: Magnetic nano Fe_3O_4 and $CuFe_2O_4$ as heterogeneous catalysts: A green method for the stereo- and regioselective reactions of epoxides with indoles/pyrroles.

13) Parella, R.; **Naveen**; Kumar, A.; Babu, S. A. *Tetrahedron Lett*. **2013**, *54*, 1738.
Title: *Catalytic Friedel-Crafts acylation: magnetic nanopowder $CuFe_2O_4$ as an efficient and magnetically separable catalyst.*

14) Rajkumar, V.; **Naveen**; Babu, S. A. *ChemistrySelect* **2016**, *6*, 1207.
Title: Pd(II)-Promoted directing group-enabled regioselective C-H arylations of the C-3 position of 2- or 3-(aminoalkyl)-thiophene and furfurylamine derivatives.

Patents applicationfiled from thesis work.

1) Inventors**:** Babu, S. A. and **Naveen.** Indian Patent Application No. 3532/DEL/2012.
Title: *Preparation of new crown ether/polyether macrocyclic systems.*

2) Inventors**:** Babu, S. A. and **Naveen.** Indian Patent Application No. 2152/DEL/2013.
Title: *Novel class of crown ether/polyether macrocyclic compound and the process of preparation there of.*

Conferences/Symposia.

1) Participated in the *7th Junior National Organic Symposium (J-NOST)* held Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (14-17 December, 2011).

2) Oral presentation entitled "Synthesis of new crown ether/polyether macrocyclic systems using RCM and Glaser-Eglinton-Hay routes" **Naveen**, R. Parella and S. A. Babu at the *9th Junior National Organic Symposium (J-NOST)* held at the Indian Institute of Science Education and Research (IISER) Bhopal, India (4 to 6 December 2013).

3) Oral presentation entitled "Synthesis of new Classes of enantiopure crown/polyether macrocycles using enantiopure amino alcohols and α-methyl benzyl amines as chiral building blocks" **Naveen** and S. A. Babu at the *3rd National Conference on Chirality (NCC)* held at the Department of Chemistry, Faculty of Science, M. S. University of Baroda, Vadodara, India (18-19 December 2015). (IInd Best oral presentation award).

4) Poster presentation entitled "Palladium-catalyzed regioselective remote oxidative acetoxylation of arylalkylamines derivatives at ε positions using bidentate auxiliary" **Naveen**, V. Rajkumar at the *18th CRSI National Symposium in Chemistry* held at the Panjab University Chandigarh, India (5-7 February, 2016).

Preamble

Charles Pedersen, Donald Cram and Jean-Marie Lehn were awarded the Nobel Prize in chemistry for their pioneering work on crown ethers/polyether macrocycles and cryptands (nitrogen derivatives of crown ethers). Since the serendipitous discovery of crown ethers by Charles J. Pedersen, numerous macrocyclic polyethers/crown ethers (oxo crowns), aza and thia crown ethers, combination of oxo-aza-thia crown ethers have been synthesized and their properties have been studied by Pederson and numerous research groups. In the research area pertaining to the supramolecular chemistry, crown ethers/polyether macrocycles and cryptands occupy a major place. Alongside their well-established ability to encapsulate metal cations to form inclusion complexes, crown ether/polyether macrocycles have found a wide-range of uses in chemical- and biological sciences and chemical industries.

Given the importance of crown ethers/polyether macrocycles and cryptands in various research fields of biology, chemistry and material science has inspired the synthesis of numerous examples of derivatized versions of archetypal (classical) crown ether systems (e.g., 18-crown-6 and dibenzo 18-crown-6 system). This thesis work aims to contribute to the library of derivatized versions of archetypal (classical) crown ether systems, by synthesizing new classes of polyether macrocycles (crown ethers), oxo/thia polyether macrocycles, optically active aza/oxo/thia polyether macrocycles and periphery modified polyether macrocycles using ring closing metathesis, Glaser-Eglinton-Hay coupling and EDC-DMAP coupling reactions. Additionally, a part of this thesis work reports the synthesis of phenolic compounds *via* the Pd(II)-catalyzed C-H actoxylation and 1,2,3-triazoles from the reaction of allylic/benzylic alcohols/ethers with $TMSN_3$ catalyzed by nano Fe_3O_4 and $Cu(OTf)_2$.

Accordingly, this thesis entitled *"**Studies on The Synthesis of New Classes of*** **Crown Ether-Type/Polyether Macrocycles** ***and Optically Active Aza-Oxo-Thia Polyether Macrocycles**"* consists of the following **five chapters** along with objectives of the thesis. Individual chapters contain the sub-sections, such as, introduction, results and discussion, conclusions, experimental section and references. The first four chapters deals on the synthesis of new classes of crown ether-type/polyether macrocycles and optically active aza-oxo-thia polyether macrocycles by exploiting the ring closing metathesis, Glaser-Eglinton-Hay coupling and EDC-DMAP coupling strategies. The fifth chapter reports some miscellaneous works including the synthesis of phenolic compounds *via* the Pd(II)-catalyzed C-H actoxylation and

1,2,3-triazoles from the reaction of allylic/benzylic alcohols/ethers with $TMSN_3$ catalyzed by nano Fe_3O_4 and $Cu(OTf)_2$.

Chapter 1: *Ring-closing metathesis reaction-based synthesis of new classes of polyether macrocyclic systems derived from 2-hydroxy benzaldehydes.*

Chapter 2: *Glaser-Eglinton-Hay sp-sp coupling and macrocyclization: construction of new classes of polyether macrocycles having a 1,3-diyne or triazole unit and thia-polyether macrocycles.*

Chapter 3: *Exploitation of Glaser-Eglinton-Hay and ring closing metathesis-based strategies for the synthesis of new classes of optically active aza-oxo-thia polyether macrocycles from chiral amino alcohol and α-methylbenzylamine building blocks.*

The Chapter 3 is subdivided into Chapter 3a and Chapter 3b.

Chapter 3a: *Exploitation of Glaser-Eglinton-Hay coupling strategy for the synthesis of new classes of optically active aza-oxo-thia polyether macrocycles from chiral amino alcohol building blocks.*

Chapter 3b: *Exploitation of ring closing metathesis-based strategy for the synthesis of new classes of optically active aza-oxo polyether macrocycles from chiral amino alcohol and α-methylbenzylamine building blocks.*

Chapter 4: *EDC/DMAP-Mediated direct condensation of dicarboxylic acids and diols: A concise synthesis of extra-large polyether macrocyclic lactones and their X-ray structures.*

Chapter 5: *Miscellaneous Works*.

The Chapter 5 is subdivided into Chapter 5a and Chapter 5b.

Chapter 5a: *Pd(II)-Catalyzed, substrate design-facilitated chemo- and regioselective acetoxylation over cyclization of remote ε-C(sp^2)-H bonds in heteroaryl-aryl-based biaryl and 3-phenylpropan-1-amine systems.*

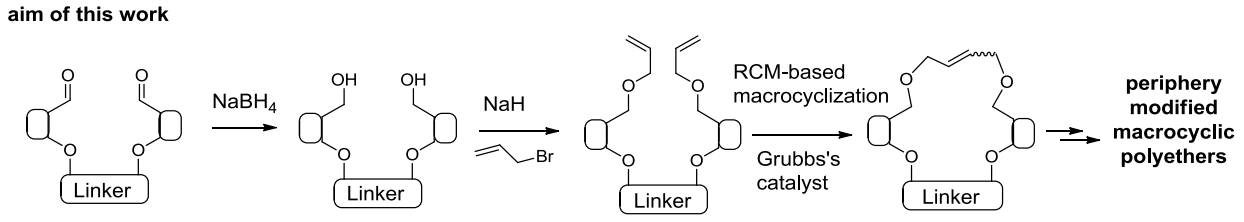
Chapter 5b: *Direct azidation of allylic/benzylic alcohols and ethers followed by the click reaction: one-pot synthesis of 1,2,3-triazoles.*

Objectives

The research work carried out is mainly focused on the synthesis of new classes of macrocyclic polyethers *via* the ring closing metathesis /Glaser-Eglinton-Hay coupling /EDC-DMAP coupling reactions. The objectives of this thesis work are outlined below.

Objective 1 (Chapter 1):

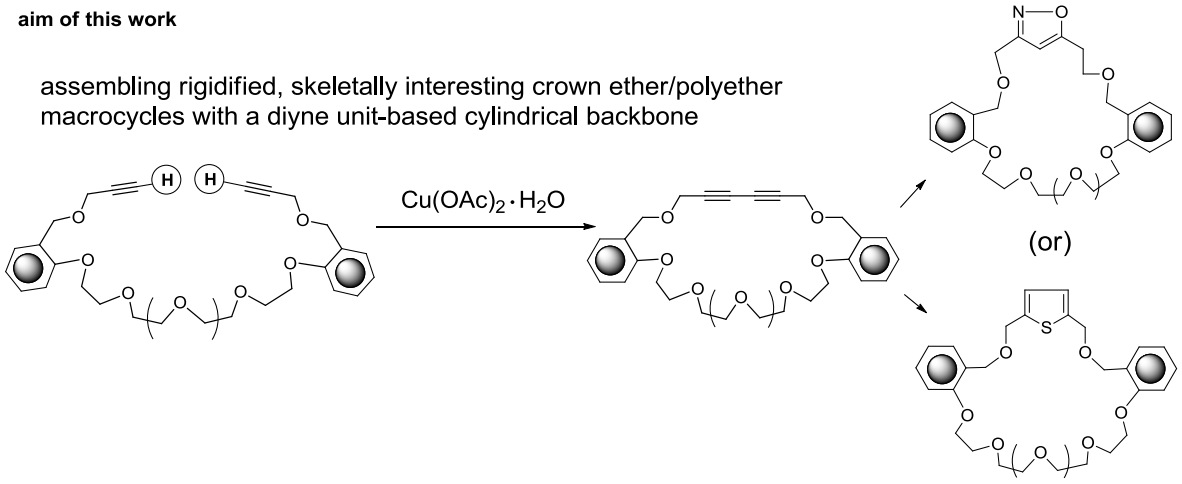
Ring closing metathesis reaction is one of the cornerstone tools for the construction of carbon-carbon double bonds and cyclic olefins. Notably, numerous natural products and a variety of five-, six- and seven- membered synthetic building blocks and several medium- or large-sized macrocycles as well as a variety of mechanically interlocked macrocyclic compounds (e.g., catenanes and rotaxanes, etc) have been synthesized *via* the ring closing metathesis reaction. Taking an impetus from the papers dealing on the celebrated ring closing metathesis reactions, a part of this thesis envisages to report the investigations on the synthesis of new classes crown ether/polyether macrocyclic molecules starting from simple starting materials, such as, 2-hydroxy benzaldehydes. Accordingly, it was envisaged to contribute to the library of crown ether/polyether macrocyclic molecules by synthesizing a wide range of new crown ether-type polyether, aza-polyether, bis aza-polyether macrocycles and dilactone moiety embedded polyether macrocycles (macrolides). It was also envisaged to perform the post-ring closure modifications after the ring-closure reaction and it was planned to carry out the installation of different functional groups and functional group modification on the periphery of the polyether/crown ether macrocycles obtained in the RCM reactions.



Objective 2 (Chapter 2):

The Glaser-Eglinton-Hay-type strategy was largely used for the synthesis of 1,3-diyne unit-based rigidified shape persistent macrocyclic systems. Given the importance derivatized

versions of archetypal (classical) crown ether systems in various areas of biology, chemistry and material sciences, it is believed that the incorporation of a 1,3-diyne unit as a part of crown ether/polyether macrocycles could provide directionally precise rigidity to polyether macrocycles and perhaps, new insights on their supramolecular chemistry. A survey of literature revealed that the synthesis of crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone has not been explored well. Taking an impetus from the papers dealing on the celebrated Glaser-Eglinton-Hay coupling reactions, a part of this thesis envisages to report the investigations on the synthesis of new classes of 18-40 membered crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone via the Glaser-Eglinton-Hay macrocylization. Further it was envisaged to report (i) the synthesis of periphery modified polyether macrocycles installed with thiophene and isoxazole functionalities from crown ether-type macrocycles having a 1,3-diyne unit, which can be assembled via the Glaser-Eglinton-Hay macrocylization, and (ii) the synthesis of bis-1,2,3-trazoles appended polyether macrocycles having a 1,3-diyne unit using Glaser-Eglinton-Hay macrocylization strategy.



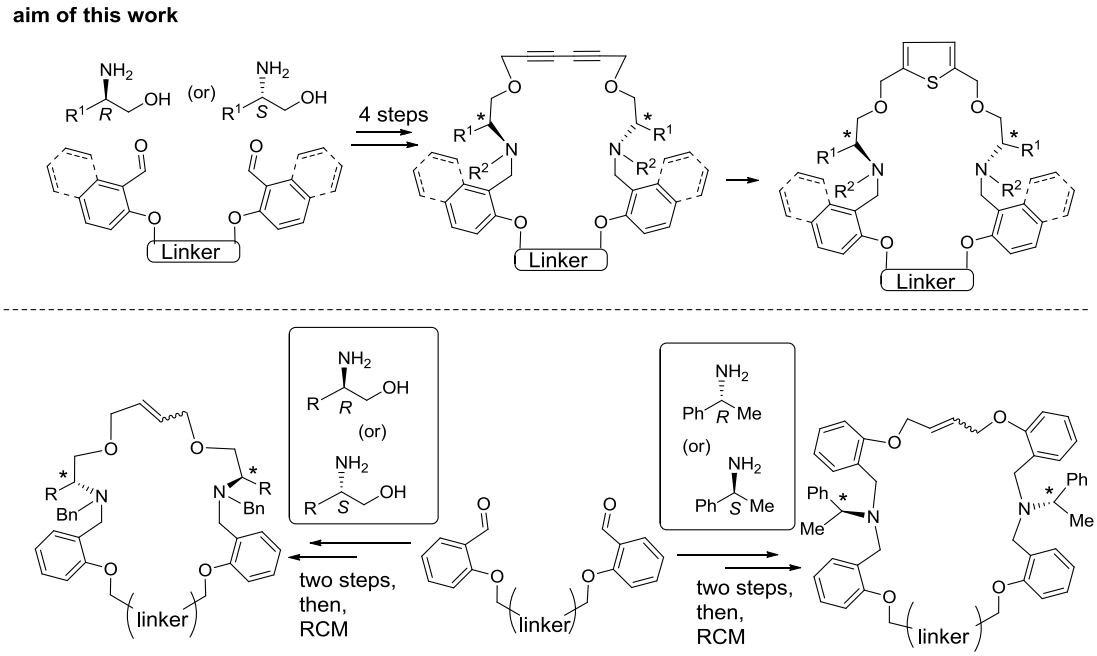
Objective 3 (Chapters 3a and 3b):

Alongside the classical polyether macrocycles, the synthesis of optically active oxo, aza, aza-oxo crown ethers/polyether macrocycles have received substantial attention. In general, optically active crown ethers/polyether macrocycles have found numerous applications in various branches of chemical sciences, e.g., host-guest chemistry due to their tendency to distinguish enantiomers and several optically active crown ethers have been used in the research area pertaining to analytical chemistry/chromatography and organic synthesis. Various

linkers/building blocks including enantiopure building blocks (e.g., amino acids, sugars, BINOL, amines and amino alcohols, etc) were employed for synthesizing the corresponding optically active polyether macrocycles by using the conventional macrocyclization approaches, such as, Williamson ether synthesis, peptide coupling, macrolactonization, macrolactamization and other standard macrocyclization methods.

Given the importance of optically active crown ether/polyether macrocycles in organic synthesis and research area pertaining to analytical chemistry and chromatography, the synthesis of a library of new classes of optically active crown ether/polyether macrocyclic systems and periphery modified polyether macrocyclic systems will be highly useful.

Accordingly, a part of this thesis work envisages to assemble the new classes of optically active crown ether/polyether macrocyclic systems and periphery modified polyether macrocyclic systems using chiral α-methylbenzylamine and amino alcohol building blocks *via* the ring closing metathesis (RCM) and Glaser-Eglinton-Hay-type strategies.

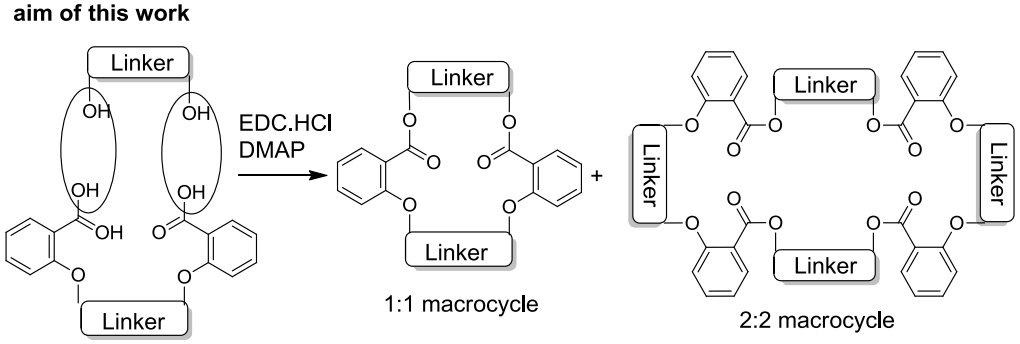


Objective 4 (Chapter 4):

Extra-large or large-cavity-based amide/lactone-based macrocycles has received a special significant attention because of their tendency to coordinate with more than one metal ions,

selectively bind a large range of metal and various other applications. There exist various exceptional reports dealing on the synthesis of different kinds of small macrocyclic di- and tetra-lactones via the intramolecular macrocyclization/macrolactonization methods. A literature survey revealed there exist only limited methods that deal on the direct synthesis of extra-large or large-cavity-based binuclear macrocycles (e.g., >20 atom-ring cycles, considering 18-crown analogue as standard macrocycle) via the intermolecular cyclization method (e.g., 1:1, 2:2 adduct formation) involving acyclic precursors.

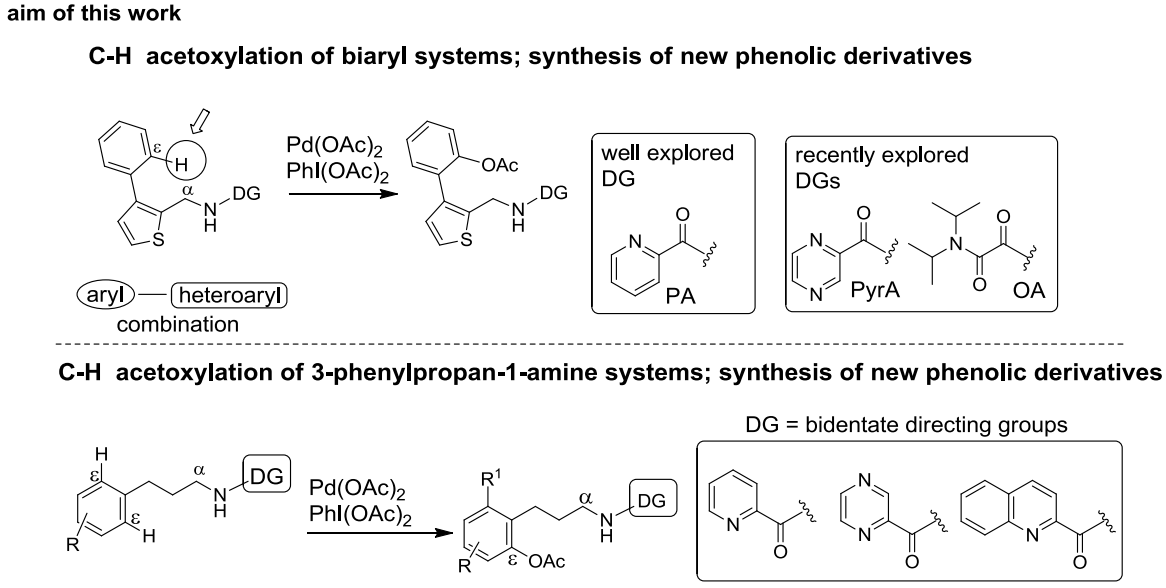
It is to be noted that reported methods dealing on the synthesis of large-cavity-based macrocyclic are not direct methods and require template and high dilution conditions. It was envisaged that developing a simple and straightforward method comprising direct condensation reactions of dicarboxylic acids with diols affording polyether macrocyclic di- and tetra-lactones would be highly appreciated. Taking an impetus from the papers dealing on the synthesis of large cavity-based extra-large macrocyclic macrocyclic systems, a part of this thesis work envisioned to investigate the direct condensation reactions of dicarboxylic acids with diols to afford polyether macrocyclic di- (small) and tetra-lactones (extra-large).



Objective 5 (Chapter 5a, *Miscellaneous Works*):

The Chapters 1-4 of this thesis envisaged to use the phenolic derivatives, such as, catechols and salicylic acids as the building blocks for the synthesis of a wide range of polyether macrocyclic compounds. Given the importance of phenolic compounds in various areas of chemical and biological sciences, development of simple and convenient methods for the construction of C-O bonds in arene systems (phenolic compounds) are highly desirable. A part of

this thesis work envisioned to investigate the construction of new phenolic derivatives via the Pd-catalyzed, C-H acetoxylation reaction. Accordingly, it was planned to carry out the Pd(II)-catalyzed, directing group-aided, C-H acetoxylation of heteroaryl-aryl-based, biaryl and 3-phenylpropan-1-amine systems.

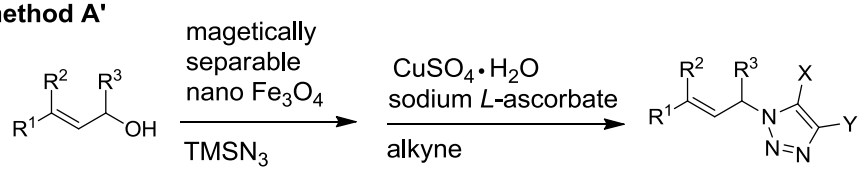


Objective 5 (Chapter 5b, *Miscellaneous Works*):

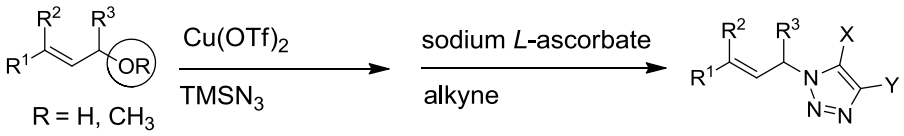
Allylic/benzylic azides have been used as synthetic building blocks for synthesizing a wide range of heterocyclic compounds, natural products and biologically active triazole molecules involving the click reaction. The conventional methods involving the synthesis benzylic and allylic azides from alcohols generally require two steps. First an alcohol is converted in to the respective halide or sulfonate and then, the corresponding halide/sulfonate is converted into an azide *via* the nucleophilic substitution reaction. A part of this thesis envisaged to assemble 1,2,3 triazoles without isolating the azide and the direct azidation of various allylic/benzylic alcohols with $TMSN_3$ using magnetically separable nano Fe_3O_4 as a heterogeneous catalyst. Accordingly, it was planned to investigate the direct azidation of various allylic/benzylic alcohols and their ethers with $TMSN_3$ using magnetically separable nano Fe_3O_4 as a heterogeneous catalyst followed by the Cu-catalyzed click reaction of azides with alkynes.

aim of this work

'method A'



'method B'



Chapter 1: Ring-closing metathesis reaction-based synthesis of new classes of polyether macrocyclic systems derived from 2-hydroxy benzaldehydes.

Introduction

Macrocyclic systems are ubiquitous structural motifs in Nature and the unique properties of different types of macrocyclic systems have been well exploited in chemical[1-3] and biological sciences and industry.[4] Since the Pederson's discovery[1] of crown ether macrocyclic system in 1967, crown ether/polyether macrocycles have been considered as imperative classes of macrocyclic systems in supramolecular chemistry due to their ability to encapsulate metal cations to form inclusion complexes.[1-3] Alongside their capability to encapsulate metal cations to form inclusion complexes, polyether macrocycles are well known for their unique properties in chemical industries. Crown ether/polyether macrocycles exhibit several important applications/properties in various research areas of chemical and biological sciences,[2-4] such as, in molecular recognition, as sensors,[2h] for selective ion separation and detection,[2i-j] in phase transfer catalysis,[2k] as synthetic building blocks (e.g., ring-opening polymerization),[2l] in electrochemical processes[2m] and as the model systems for mimicking some biological processes.[2n] Furthermore, polyether macrocycles have been found to exhibit various biological activites[4] and notably, some of the polyether macrocycles are reported to exhibit the anticancer and DNA interaction activities.[4]

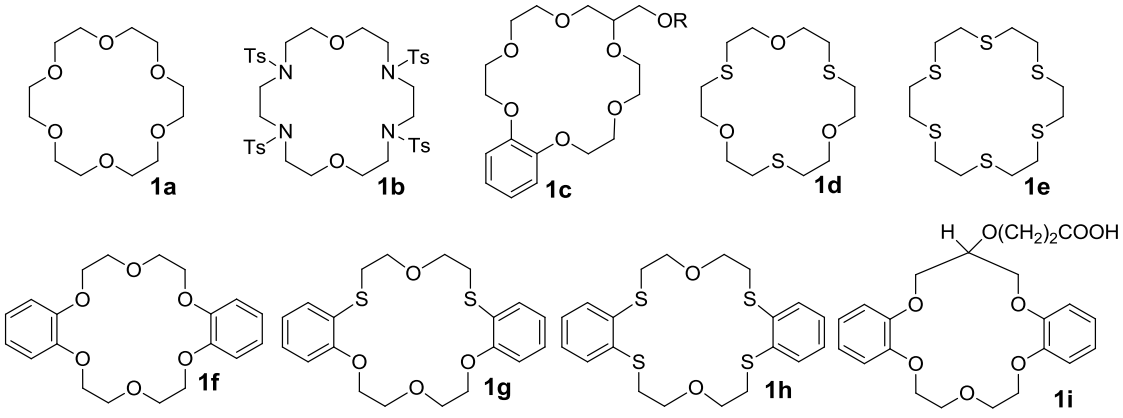


Figure 1. Representative examples of well-known examples of polyether macrocycles.

The importance of crown ether/polyether macrocyclic systems in various branches of chemical and biological and material sciences has inspired the chemists to synthesize a widespread examples of derivatized versions of archetypal (classical) crown ether systems (e.g., 18-crown-6 and dibenzo 18-crown-6 system, Figure 1). Accordingly, extensive studies have been carried out with regard to the synthesis of modified crown ether/polyether macrocyclic systems to enhance their cation-complexing properties and selectivity.[5] Some of these modifications involve the use of sulfur atoms[5a,b] and/or nitrogen substituted[5c-e] for oxygen in the macro-ring and alkyl substituents,[5f-g] aromatic sub-cyclic units changes[5h] which provide crown ether/polyether macrocyclic systems (Figure 1) with unique complexing properties. Furthermore, in recent years, the functional group modification at the periphery[6] and derivatization of crown ethers/polyethers before or after the ring-closure reaction has received considerable attention.[6] Along this line, there have been various impressive efforts, which revealed the synthesis of new symmetrical and less symmetrical crown ether/polyether macrocyclic systems. In general, a wide variety of synthetic strategies are available for the synthesis of macrocycles and crown ether/polyether macrocyclic systems. Notably, macrocycles other than crown ether/polyether macrocyclic systems have been synthesized by using the standard peptide coupling, Yamaguchi lactonization,[7a] Williamson ether synthesis, ring closing metathesis (RCM) and other techniques.[7b-d,8-11]

While there have been various exceptional reports with regard to the synthesis of new symmetrical and less symmetrical crown ether/polyether macrocyclic systems and the range of synthetic methods developed for the preparation of crown ether/polyether macrocyclic systems is broad.[1-7] In line with the objective of this thesis work, in the following section only the literature works that deal on the synthesis of new symmetrical and less symmetrical crown ether/polyether macrocyclic systems *via* the ring closing metathesis (RCM) are described.

Ring closing metathesis-based synthesis of macrocyclic systems.

Olefin metathesis considered as a preferential method for achieving cyclization due to the catalytic conditions, wide functional-group tolerance and mild reaction conditions.[8-12] Ring closure metathesis (RCM) reaction is a versatile technique mainly applied for the synthesis of a variety of five-, six- and seven- membered synthetic building blocks.[8] Notably, various

biologically relevant scaffolds and natural products were synthesized *via* ring closing metathesis reactions[9] (Figure 2) in the presence of a Grubbs's ruthenium carbene catalyst (Figure 3).[9a]

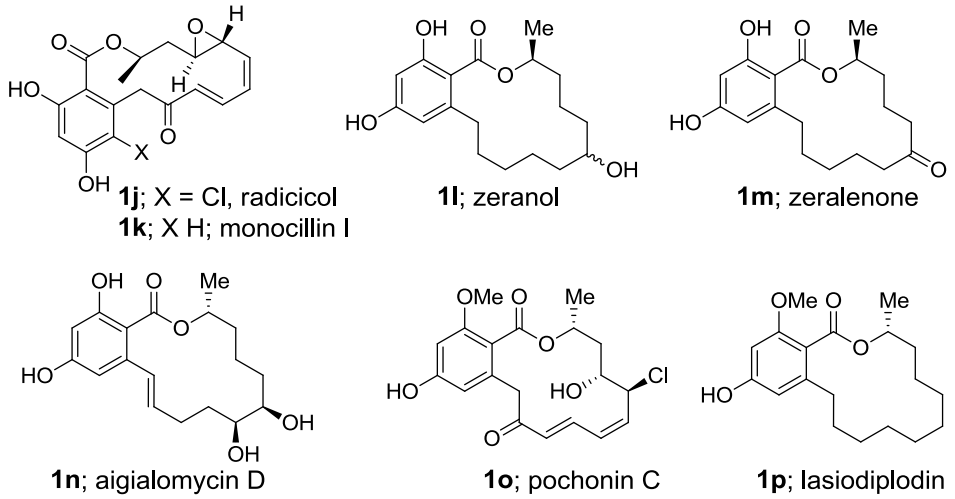


Figure 2. Representative examples of natural products accomplished by ring closing meathesis (RCM) technique.

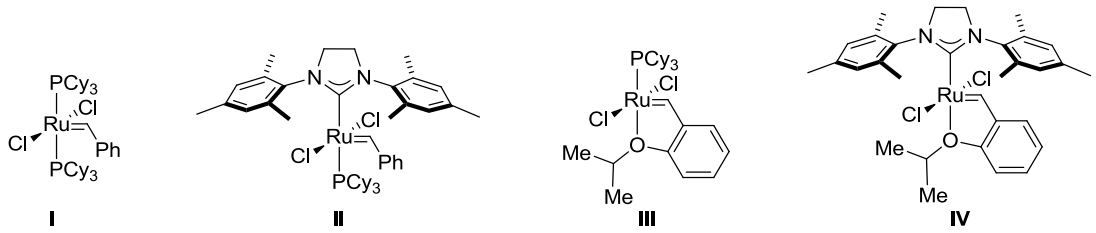


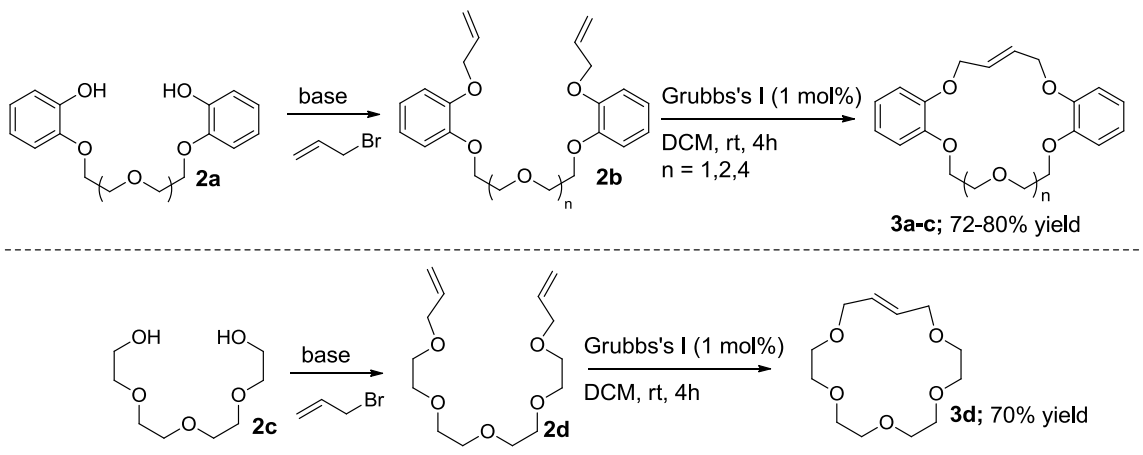
Figure 3. Ru-catalysts used for performing the ring closing metathesis (RCM): I generation Grubbs's catalyst (**I**), II generation Grubbs's catalyst (**I**), I generation Hoveyda Grubbs's catalyst (**III**) and II generation Hoveyda Grubbs's catalyst (**IV**).

Apart from the synthesis of small and medium sized rings, it is worth to mention that the ring closing metathesis methodology/technique has been extensively used for synthesizing several macrocycles (>10 atom ring containing cyclic compounds) as well as a variety of mechanically interlocked macrocyclic compounds (e.g., catenanes and rotaxanes, etc).[10,11] In addition to their good tolerance of normally employed reaction conditions and a wide range of functional groups, Grubbs's catalyst-catalyzed ring closing metathesis methodology/technique was also used for the synthesis of crown ether/polyether macrocyclic systems; e.g., crown ether and aza-crown

ether types macrocycles and amide functionality incorporated and lactone-based polyether macrocycles.[12-14]

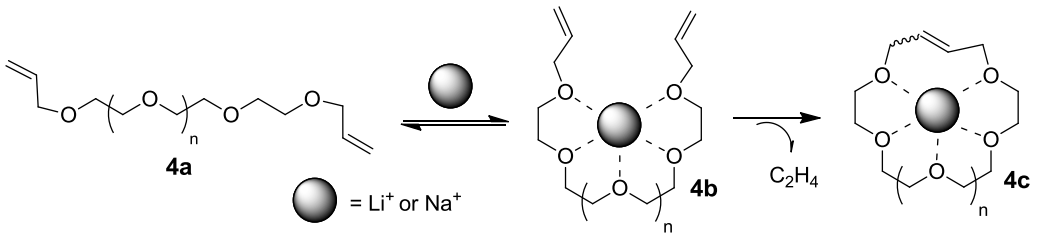
Representative literature reports dealing on the synthesis of crown ether/polyether macrocyclic systems *via* ring closing metathesis (RCM) strategy.

While the ring-closing metathesis (RCM) technique was used for the construction of various biologically relevant scaffolds and natural products (Figure 2) including small/medium/large ring compounds.[9d-h] A literature survey revealed that in spite of the existing developments in the research area pertaining to the ring-closing metathesis (RCM) reactions, there exist only limited reports that reveal the synthesis of crown ethers/polyether macrocycles *via* the ring-closing metathesis (RCM) reaction. In the following section the literature works that deal on the synthesis of crown ether/polyether macrocyclic systems *via* the ring closing metathesis (RCM) are described.



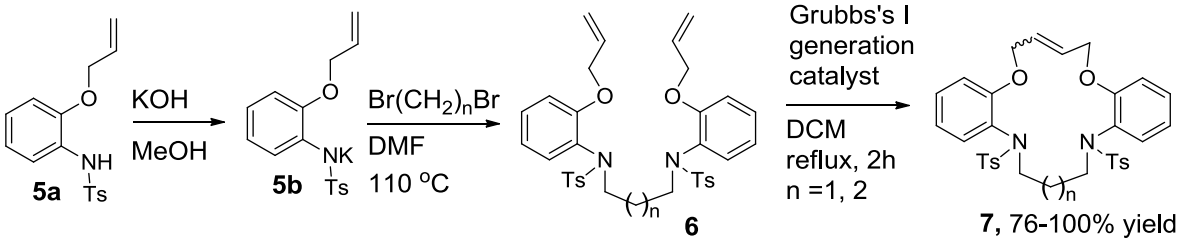
Scheme 1. Synthesis of crown ether/polyether macrocycles **33a-d** *via* ruthenium-catalyzed ring closing metathesis.

In 1996, König and coworkers[13a] reported a new and efficient route for the synthesis of medium to large size polyethers macrocyclic systems **3a-c** using acyclic bis-allyl precursors **2b**/**2d** which were assembled by alkylation of corresponding diols **2a**/**2c** with allyl bromide. Ring closing metathesis with substrate **2b**/**2d** in the presence of Grubbs's I generation catalyst in DCM afforded the corresponding polyether macrocyclic systems **3a-c** and **3d** having *trans* geometry (Scheme 1).



Scheme 2. Template-directed synthesis of crown ether/polyether macrocycles from liner acyclic polyether precursors *via* ring closing metathesis (RCM).

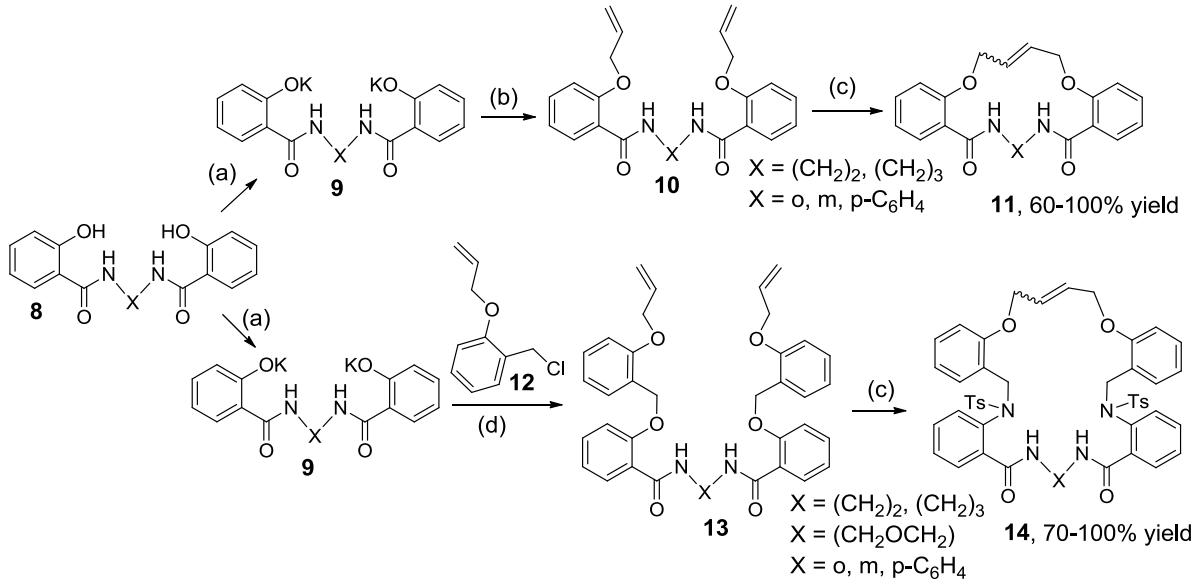
In 1997 Grubbs's *et al.* reported[13b] template-directed synthesis of polyether macrocycles **4c** from linear acyclic polyethers having terminal olefins in the presence of appropriate metal ions (Scheme 2). The ring closing metathesis (RCM) of **4a** was found to be favored in the presence of appropriate metal ions due to preorganization of linear polyethers **4a** (having terminal olefins) around a suitable complementary metal as shown in Scheme 2.



Scheme 3. Synthesis of diazapolyoxa crown ether/polyether macrocycles **7** *via* RCM.

Ibrahim and coworkers reported[13c] the synthesis of medium to extra-large diazapolyoxa crown ether/polyether macrocycles **7** (17-28 membered macrocycles, having aliphatic chain as linkers) using ring closing metathesis (RCM) technique (Scheme 3). The synthesis of macrocylic aza crown **7** started with the treatment of compound **5a** with methanolic KOH which afforded compound **5b**. Then, the compound **5b** was treated with di-bromo compounds in DMF to afford RCM precursor **6**. Then, the ring closing metathesis was carried out in the presence of Grubbs's I generation catalyst (1.25-5 mol%), which furnished the macrocyclic compounds **7** in 76-100% yield as a mixture of *E/Z* isomers, having aliphatic chain as linkers (scheme 3).

Ibrahim *et al.* reported[13d] an efficient synthesis of macrocyclic crown amides **11** and **14** (having aliphatic chain, polyether chain and aromatic ring as linkers) from acyclic bis-allyl precursors **10** /**13** using ring closing metathesis (RCM) technique (Scheme 4). Precursors **10** and **13** were assembled from the diol compound **8** (Scheme 4). The potassium salt **9** was converted into the desired dienes **10** and **13** upon treatment with the appropriate alkyl halides (allyl bromide and *o*-allyloxybenzyl chloride **12**) (Scheme 4). Then, the ring closing metathesis (RCM) of **10** and **13** in the presence of Grubbs's catalyst gave the macrocyclic crown amides **11** (as a mixture of *E/Z* isomers) in 60-100% yield and crown amides **14** (as a mixture of *E/Z* isomers) in 70-100% yield (Scheme 4).

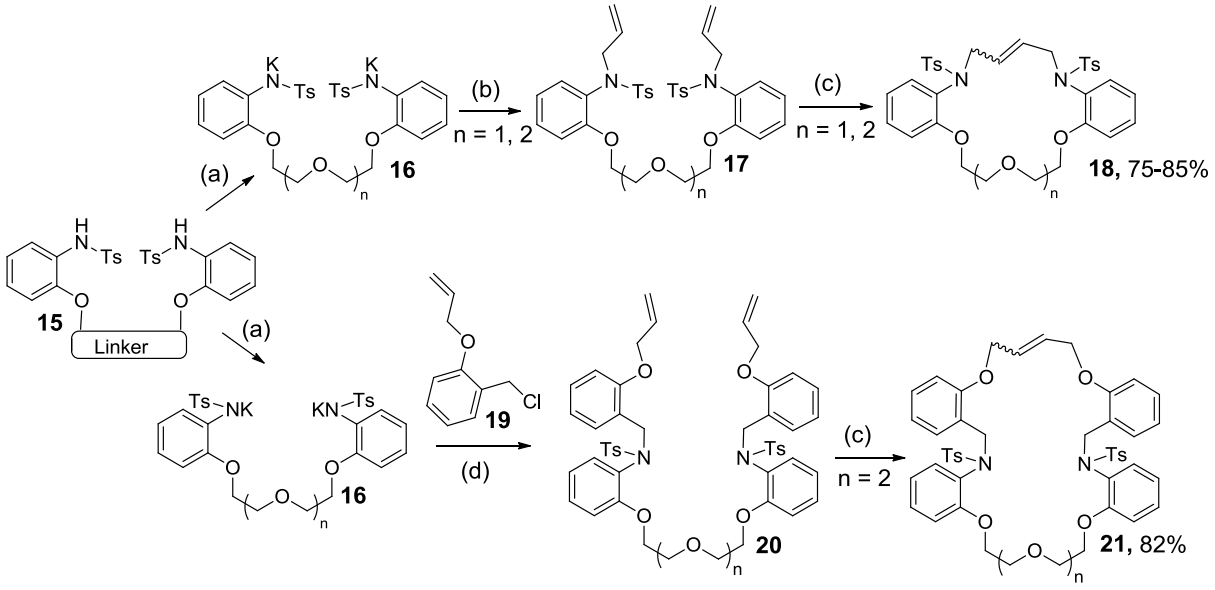


Reaction condition and reagents: (a) KOH, MeOH or K_2CO_3, DMF (b) allyl bromide, DMF, reflux (c) Grubbs's catalyst (1.5-5 mol%), DCM, reflux (d) *o*-allyloxybenzyl chloride, DMF, reflux.

Scheme 4. Synthesis of macrocyclic crown amides **11** and **14** *via* ring closing metathesis.

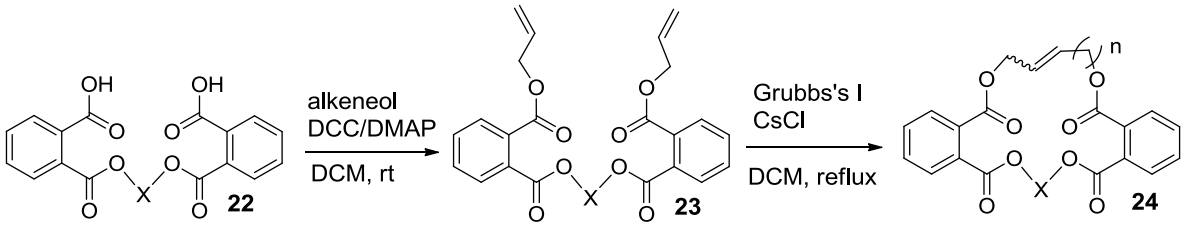
Subsequently, Ibrahim *et al.* reported[14a] the synthesis of aza-oxo polyether macrocycles **18** and **21** (having polyether chain as linkers). The bis-tosylamides **15** were converted into potassium salts **16**. Then the potassium salts **16** were treated with allyl bromide or *o*-allyloxybenzyl chloride **19**, to afford the corresponding diene precursors **17** and **20** (Scheme 5). Then, the ring closing metathesis of these dienes (**17**/**20**) in the presence of 1.5-5 mol% of Grubbs's I

generation catalyst in DCM gave the corresponding aza-crown ether macrocycles **18** and **21** (a mixture of *E/Z* isomers) in excellent yields (Scheme 5).



Reaction condition and reagents: (a) KOH, MeOH or K_2CO_3, DMF (b) allyl bromide, DMF, reflux (c) Grubbs's (1.5-5 mol%), DCM, reflux (d) *o*-allyloxybenzyl chloride, DMF, reflux.

Scheme 5. Synthesis of aza-oxo polyether macrocycles **18**/**21** *via* ring closing metathesis.

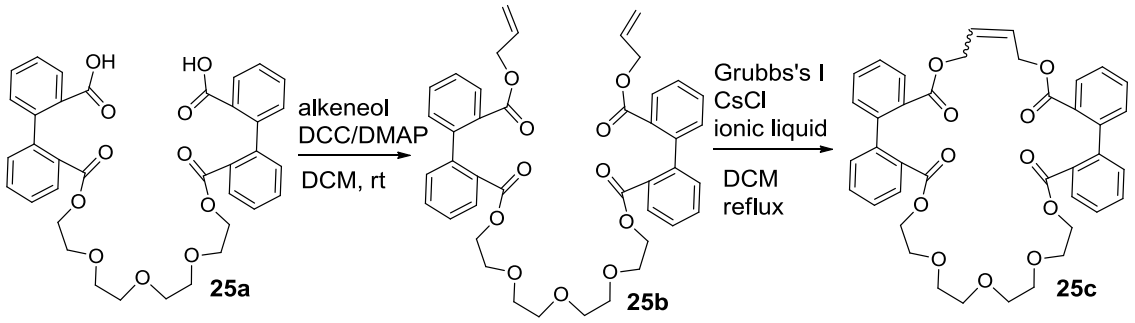


Scheme 6. Synthesis of the macrocyclic tetralactones **24** *via* ring closing metathesis.

In 2006, Muthusamy *et al.* reported[14b] the synthesis of macrocyclic tetralactones **24** (21 to 31-membered) *via* the ring closing metathesis reactions using Grubbs's catalyst (Scheme 6). The required diene precursors **23** were synthesized by alkylation of dicarboxylic acids **22** or DCC/DCMAP-mediated coupling of allyl alcohols with dicarboxylic acids (Scheme 6). Accordingly, alkenylation of dicarboxylic acids **22** with alkenyl bromide in the presence of K_2CO_3 and catalytic amount of tetrabutylammonium iodide (TBAI) afforded the required

precursors **23**. Then, the ring closing metathesis reactions of the diallyl compounds **23** using Grubbs's I generation catalyst and 2 equiv of CsCl afforded 21-31membered macrocyclic tetralactone **24** (having aliphatic, polyether and aromatic ring as linkers) in 64 to 88% yield, as a mixture of *E/Z* isomers (Scheme 6).

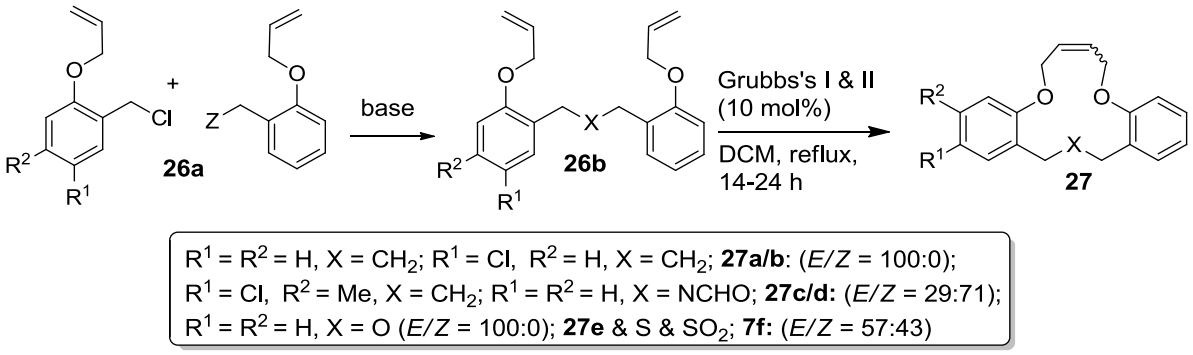
Table 1. Recovery of the Grubbs's catalyst and usage of ionic liquid (mmim)(PF_6) in ring closing metathesis reaction of **25b**.



Entry	Ionic liquid or solvent	Time (min)	Yield (%) of **25c**	
			without Cscl	with Cscl
1	[bmim] [PF_6]	8	86	87
2	[bmim] [BF_4]	24	53	56
3	[bmim] [NO_3]	24	20	22
4	[bmim] [HSO_4]	24	-	-
5	[mmim] [BF_4]	24	59	61
6	[mmim] [PF_6]	8	90	93
7	[mmim] [NO_3]	24	21	26
8	DCM	24	65	90
9	DCE	24	65	89
10	Toluene	24	72	86

Recently Muthusamy *et al.* demonstrated[14c] the synthesis of 19 to 31 membered macrocyclic tetralactones **25c** *via* the ring closing metathesis reaction in the presence of the Grubbs's catalyst using several ionic liquids (Table 1). The ring closing metathesis reactions of diolefinic compound **25b** were studied in various bmim or mmim ionic liquids have PF_6, BF_4, NO_2 and HSO_4 as counter anions (Table 1). It was found that the reaction of **25b** in [mmim][PF_6] ionic

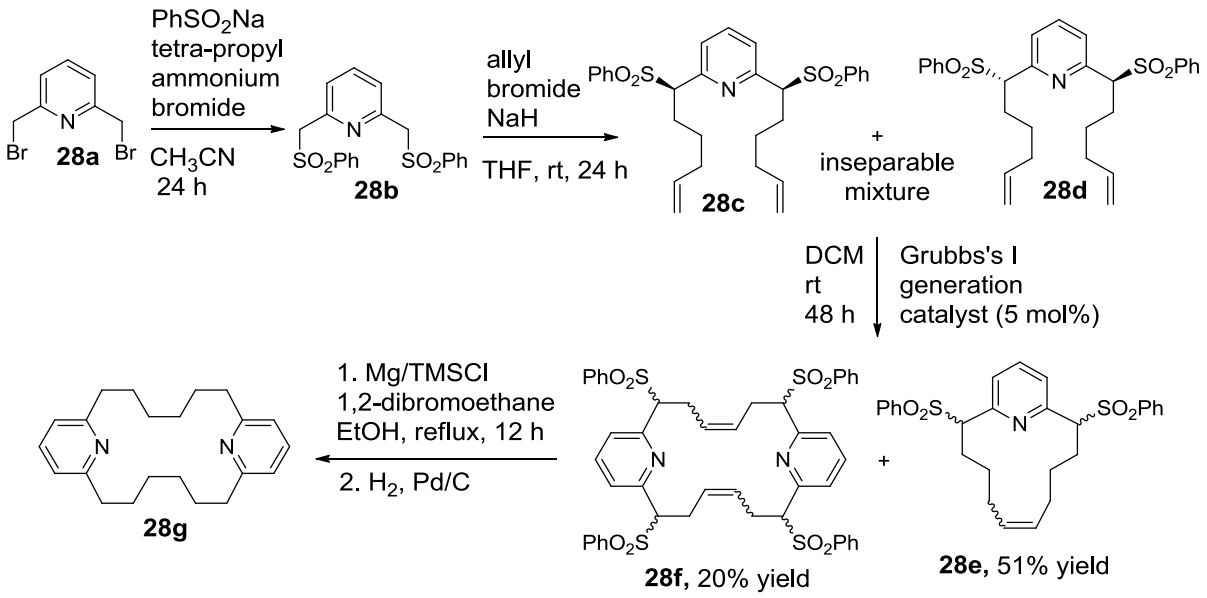
liquid afforded the product **25c** in high yield (Table 1). It was also found that anions play an important role in RCM reaction (Table 1). Notably, the reaction of diallyl precursor **25b** in different organic solvents, such as dichloromethane, dichloroethane or toluene afforded the corresponding macrocyclic compound **25c** in only moderate yield (Table 1). Furthermore, the authors successfully recovered the Grubbs's catalyst and used up to 5th cycle without losing the yield.



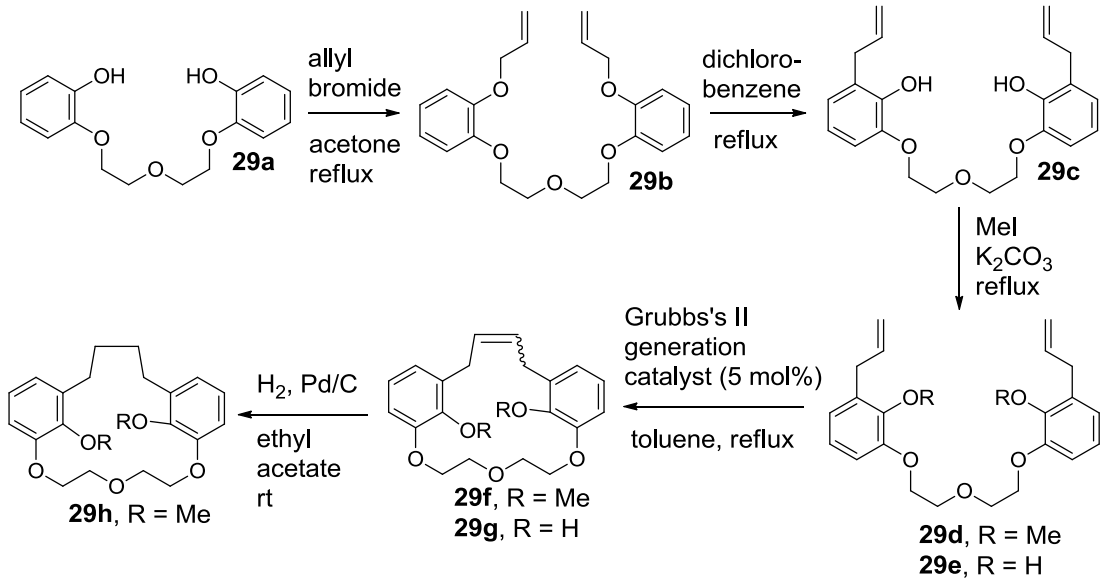
Scheme 7. Synthesis of the macrocyclic carbocyclic/heterocyclic ring systems **27** *via* ring closing metathesis (RCM).

In 2012, Rao *et al*. reported[14d] the synthesis of a new family of 13-membered carbocyclic /heterocyclic macrocyclic compounds **27** analogous to manzamine alkaloids *via* ring closing metathesis reaction using Grubbs's I and II generation catalysts. The study showed that the RCM reaction is kinetically controlled and the remote hetero atoms (N, O, S) found to influence the stereochemistry of double bond of macrocyclic compounds **27** (Scheme 7).

Recently, Kotha and coworkers[15a] used the ring-closing metathesis technique for the synthesis of new analogues of normuscopyridine **28g** (Scheme 8). Required precursors **28c/d** have been assembled as mixture of inseparable mixture of *cis* and *trans* isomers in 2 steps from 2,6-lutidine dibromide **28a**. Then, the ring closing metathesis reaction **28c/d** in the presence of Grubbs's I generation catalyst afforded monomeric and dimeric cyclophanes **28e** and **28f**, respectively (Scheme 8). Next, macrocyclic bisulfone **28f** was subjected to the reduction in the presence of Mg/TMSCl and 1,2-dibromoethane in ethanol followed by catalytic hydrogenation to afford the macrocyclic normuscopyridine **28g** (Scheme 8).



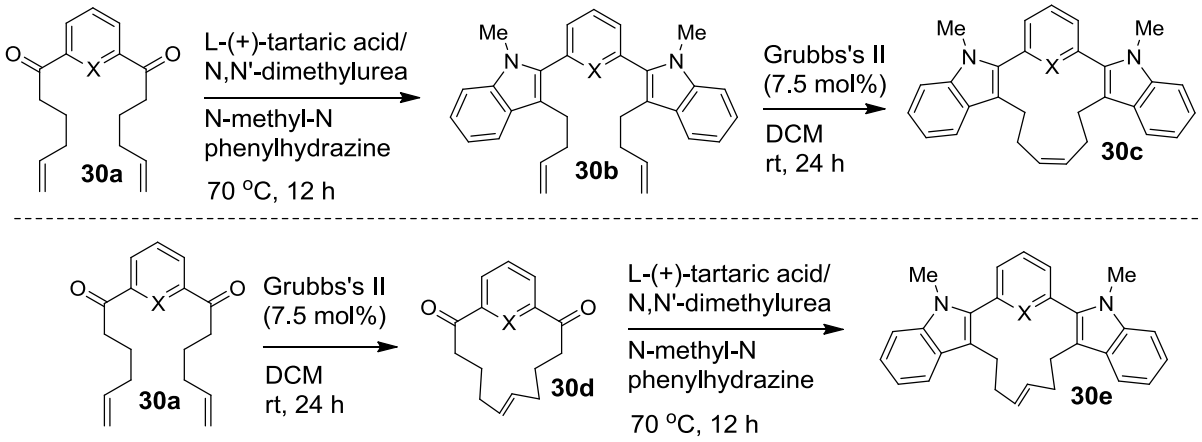
Scheme 8. Preparation of *meta*-pyridinophane derivatives **28f/e/g**.



Scheme 9. Preparation of cyclophane derivatives **29f-h** using Claisen rearrangement and ring closing metathesis reaction.

Kotha and coworkers reported[15b] the synthesis of new classes of cyclophane derivative **29h** using Claisen rearrangement and ring-closing metathesis reactions as steps (Scheme 9). The ring closing metathesis of **29d** in the presence of Grubbs's I or II generation catalyst followed by

catalytic hydrogenation process gave the cyclophane derivative **29h** (Scheme 9). It was reported that the product **29g** was formed in low yield when the RCM reaction was carried out with precursor **29e** having free OH, which perhaps inhibited the RCM process. However, the RCM reaction of **29d** in which the OH groups were protected, afforded the product **29f** in good yields.



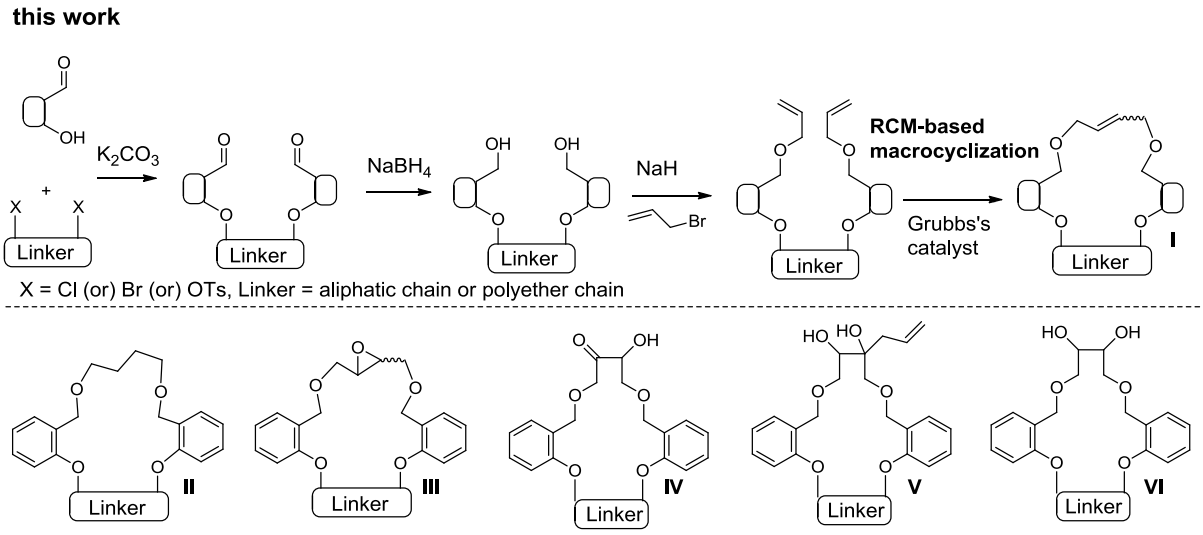
Scheme 10. Synthesis of macrocyclic cyclophane derivatives **30c** and **30e**.

Recently, Kotha *et al.* demonstrated[15c] an outstanding route for the synthesis of macrocyclic cyclophanes systems **30c** and **30e** using Fischer indolization and ring-closing metathesis (RCM) as the key steps. It was reported that depending on the order of synthetic sequence used, the geometry of the olefin unit that was formed in the RCM reaction found to change (Scheme 10). Accordingly, the Fischer indolization followed by RCM afforded the cis (*Z*) isomer **30c** (Scheme 10), whereas the RCM followed by Fischer indolization afforded the trans (*E*) isomer **30e** (Scheme 10).

Result and discussion

While the ring closing metathesis (RCM) technique was largely/widely used for the synthesis of numerous biologically relevant scaffolds and natural products;[8,9] the introduction part of this Chapter 1 revealed some of the contributions with regard to the use of ring closing metathesis (RCM) technique for the synthesis of crown ether/polyether macrocycles and related systems.

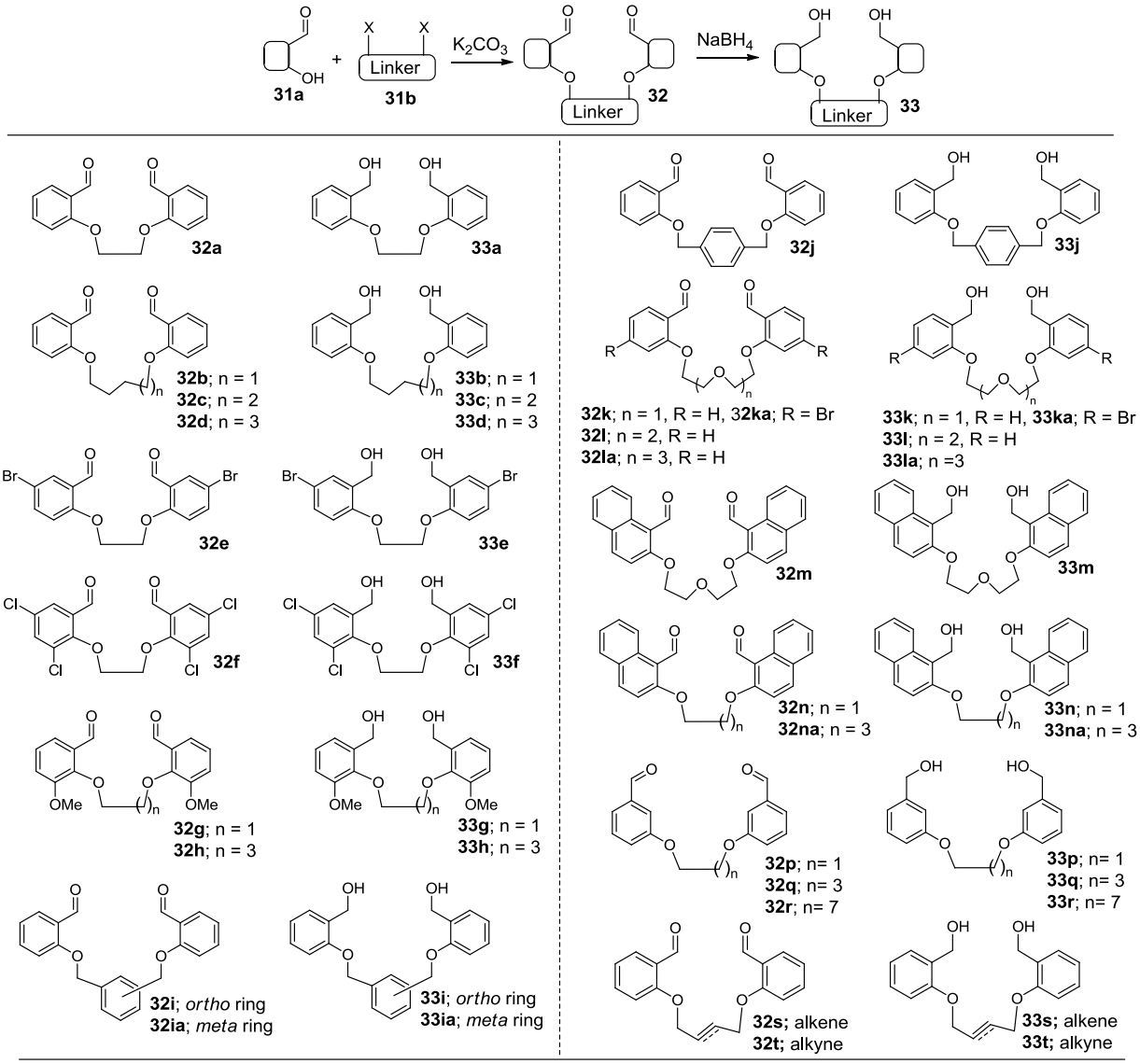
Given the importance derivatized versions of archetypal (classical) crown ether systems (e.g., 18-crown-6 and dibenzo 18-crown-6 system) in various areas of biology, chemistry and material science; the synthesis of a library of new symmetrical and less symmetrical crown ether/polyether macrocyclic systems and periphery modified polyether macrocyclic systems will be highly useful. Accordingly, in line with the objective of this thesis and taking an impetus from the papers dealing on the celebrated ring closing metathesis reactions and polyether macrocyclic systems, a part of this thesis report the investigations on the synthesis of new classes crown ether/polyether macrocyclic molecules starting from simple starting materials, such as, 2-hydroxy benzaldehydes and the post ring-closure functional derivatization and periphery modification of polyether macrocycles (Scheme 11).



Scheme 11. Generalized scheme revealing the synthesis of starting materials and periphery modified polyether macrocycles by exploiting the ring closing metathesis technique.

This chapter presents a comprehensive synthetic work encompassing, (i) the construction of 16-30 membered polyether macrocycles, macrocycles having nitrogen and sulphur heteroatoms in their linker part, *bis* aza-polyether macrocycles and dilactone moiety embedded polyether macrocycles (macrolides), large cavity containing polyether macrocycles by exploiting the RCM reaction, (ii) the construction of periphery modified polyether macrocycles, installed with epoxide, α-hydroxy ketone, 1,2-diol units and (iii) the construction of lactone ring appended and homoallyl alcohol moiety containing polyether macrocycles from the α-hydroxy ketone

functionality installed polyether macrocycles, involving the indium-based allylation and Reformatsky-type reaction processes (Scheme 11).



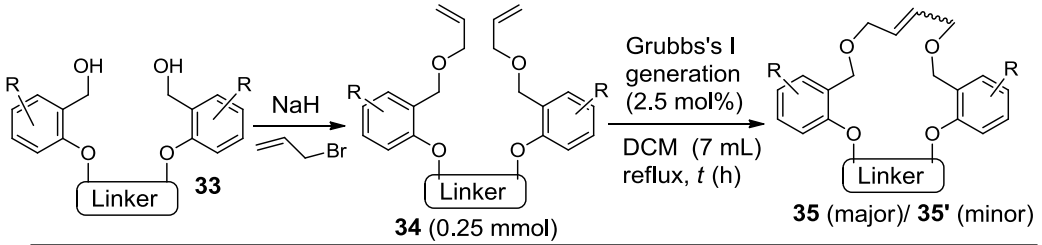
Scheme 12. Assembling required starting materials **32** and **33** from 2-hydroxy benzaldehydes and different linkers.

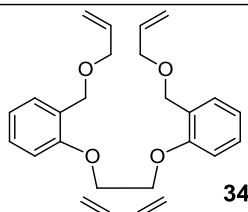
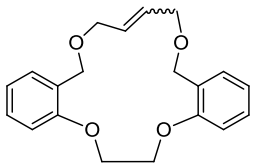
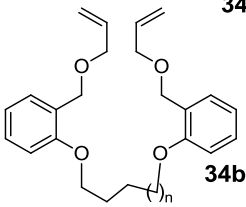
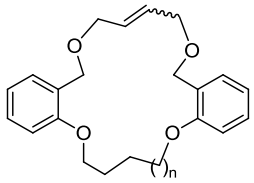
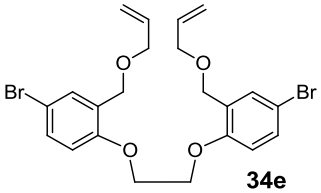
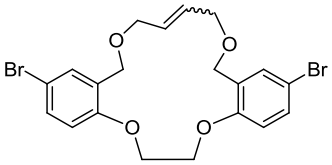
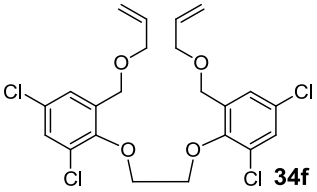
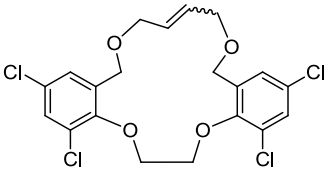
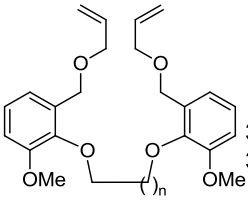
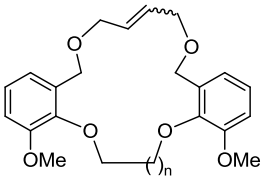
To begin with the synthesis of a library of crown ethers/polyether macrocycles by using the ring closing metathesis reaction, we prepared the necessary starting materials having a generalized structure **34** (Table 2) starting from *2*-hydroxy benzaldehydes and various linkers comprising aliphatic- or polyether chains (Table 2). Various *2*-hydroxy benzaldehydes **31a** were reacted with different linkers/spacers **31b** under standard reaction conditions reported in the literature, which

afforded a wide range of *bis*-aldehydes **32** (generalized structure) connected through various linkers (Scheme 12). Next, the *bis*-aldehydes **32** were treated with $NaBH_4$ to afford the corresponding *bis*-alcohols **33** (Scheme 12). Then, the base-mediated *O*-allylation of **33** afforded several RCM precursors **34** containing terminal olefins (Table 2), which are suitable for the ring closing metathesis reaction.

After assembling the required RCM precursors **34** containing terminal olefins, we performed the ring closing metathesis of the substrates **34**. In an initial trial reaction comprising the ring closing metathesis of **34a** in the presence of 2.5 mol% Grubbs's I generation catalyst afforded a 16-membered macrocyclic olefin **35a** as a mixture of *E/Z* diastereomers (*dr* = **35aA**:**35aB** = 70:30) in 87% yield (entry 1, Table 2). Next, the ring closing metathesis of the RCM precursors **34b-d**, which were prepared using the aliphatic chain-based linkers were performed to afford the corresponding macrocyclic olefins **35b** (18-membered macrocycle), **35c** (19-membered macrocycle), and **35d** (20-membered macrocycle) in 78, 71 and 73% yields, (*E/Z* ratio up to 86:14, entries 2-4, Table 2). Further, the ring closing metathesis of the RCM precursors **34e-h** having various substituents (e.g., Br, Cl and OMe) in the aromatic ring were carried out to afford the corresponding functionalized macrocycles **35e** (16-membered macrocycle), **35f** (16-membered macrocycle), **35g** (16-membered macrocycle), and **35h** (18-membered macrocycle) in 55-80% yields (*E/Z* ratio up to 87:13, entries 5-8, Table 2). Subsequently, the ring closing metathesis of the RCM precursor **34i** which was derived using aromatic ring-based linkers was performed to afford the polyether macrocyclic olefin **35i** (19-membered macrocycle, *E/Z* = 70:30, entry 9, Table 2). Then, the ring closing metathesis of the RCM precursor **34j** which was derived using aromatic ring-based linker was carried out to afford the macrocyclic olefin **35jA** (*E*-isomer, 20-membered polyether) as the major isomer and **35jB** (*Z*-isomer, 20-membered polyether) as the minor isomer (*E/Z* ratio = 80:20, entry 10, Table 2). The macrocyclic olefins **35jA** (*E*-isomer, major isomer) and **35jB** (*Z*-isomer, minor isomer) were isolated in pure forms by column chromatography purification.

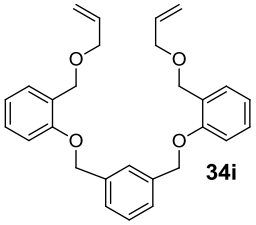
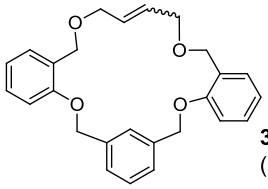
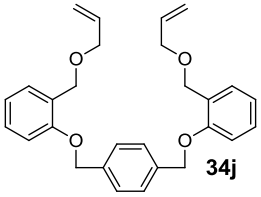
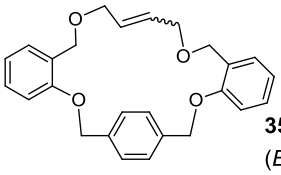
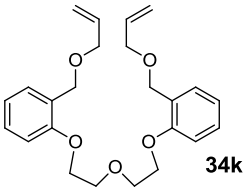
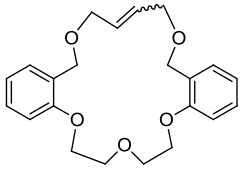
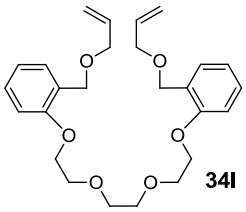
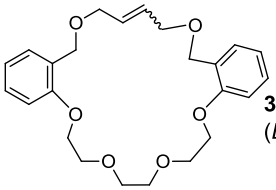
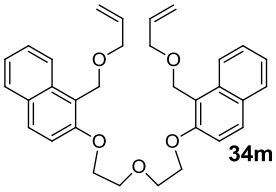
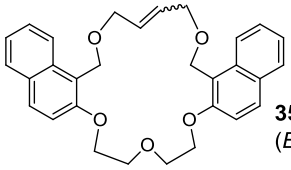
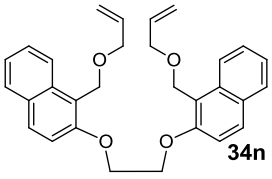
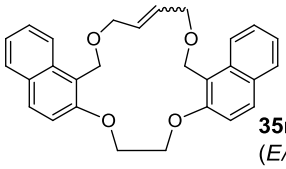
Table 2. RCM-based synthesis of polyether macrocyclic olefins **35a-n**.[a]



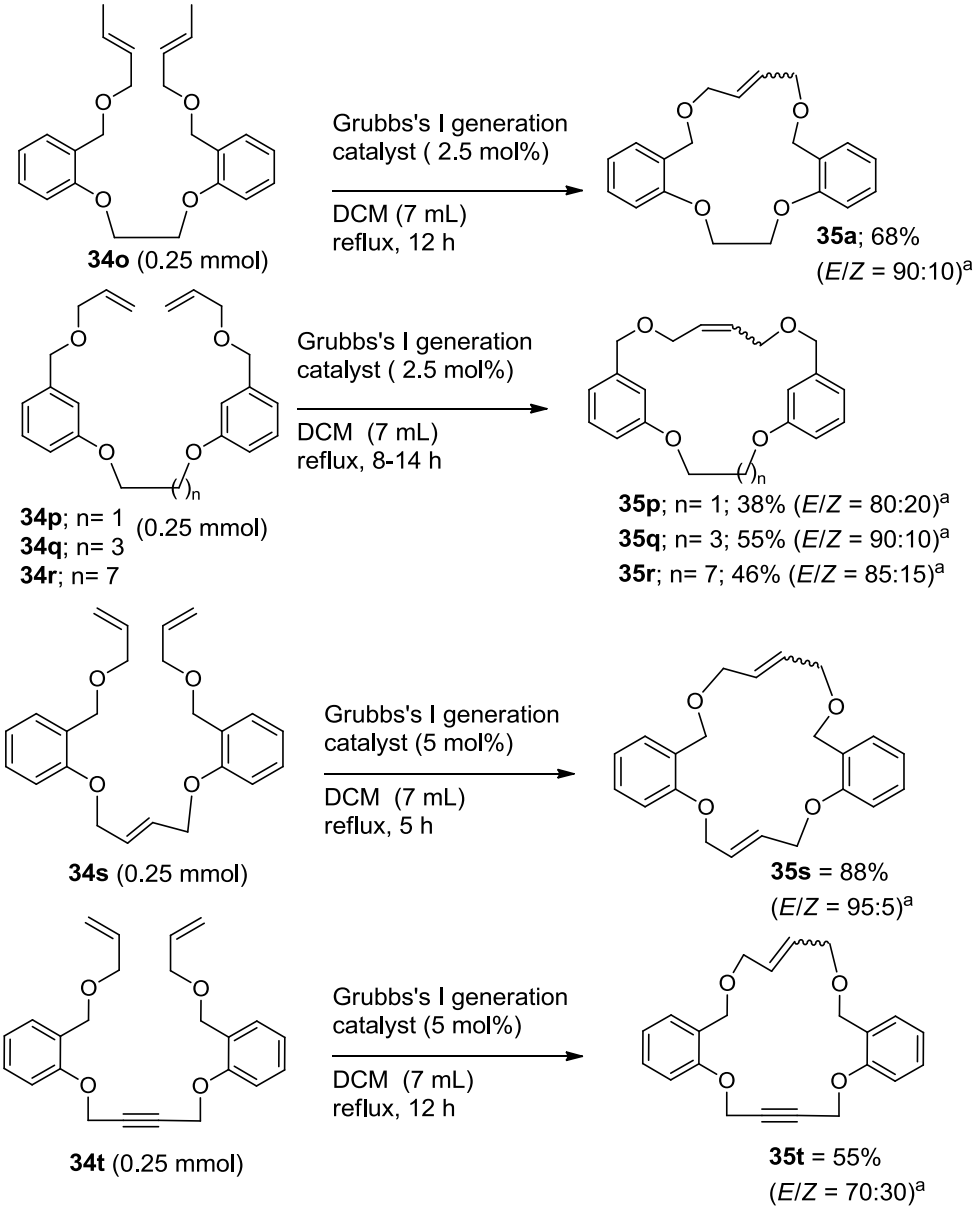
Entry	Substrate **34**	*t* (h)	Macrocyclic olefin **35**	Yield (%) (*E*/*Z* = ***35***/***35'***)
1	 **34a**	12		**35a**; 87 (*E*/*Z* = 70:30)
2	 **34b**; n = 1	14		**35b**; n = 1; 78 (*E*/*Z* = 86:14)
3	**34c**; n = 2	10		**35c**; n = 2; 71 (*E*/*Z* = 80:20)
4	**34d**; n = 3	10		**35d**; n = 3; 73 (*E*/*Z* = 80:20)
5	 **34e**	16		**35e**; 55 (*E*/*Z* = 80:20)
6	 **34f**	10		**35f**; 77 (*E*/*Z* = 87:13)
7	 **34g**; n = 1	10		**35g**; n = 1; 80 (*E*/*Z* = 65:35)
8	**34h**; n = 3	4		**35h**; n = 3; 78 (*E*/*Z* = 85:15)

[a] Based on the X-ray structures of **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and **47a** (major, *E*-isomer, Figure 6 and 7) and in concurrence with the literature reports,[10d-i,12,13] it is proposed that the major isomers (**35a-h**) formed in the RCM reactions of the substrates **34a-h** to have the *E*-geometry.

Table 2 (Continued). Synthesis of polyether macrocyclic olefins **35a-n**.[a]

Entry	Substrate **34**	t (h)	Macrocyclic olefin **35**	Yield (%) (*E*/*Z* = ***35/35'***)
9	 **34i**	14		**35i**; 50 (*E*/*Z* = 70:30)
10	 **34j**	4		**35j**; 67 (*E*/*Z* = 80:20)[a] **35jA** (major) **35jB** (minor)
11	 **34k**	17		**35k**; 75 (*E*/*Z* = 67:33)
12	 **34l**	15		**35l**; 80 (*E*/*Z* = 83:17)
13	 **34m**	4		**35m**; 87 (*E*/*Z* = 74:26)
14	 **34n**	14		**35n**; 85 (*E*/*Z* = 90:10)

[a] Based on the X-ray structures of **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and **47a** (major, *E*-isomer, Figure 6 and 7) and in concurrence with the literature reports, [10d-i,12,13] it is proposed that the major isomers (**35i-n**) formed in the RCM reactions of the substrates **34i-n** to have the *E*-geometry.



[a] Based on the X-ray structures of **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and **47a** (major, *E*-isomer, Figure 6 and 7) and in concurrence with the literature reports, [10d-i,12,13] it is proposed that the major isomers (**35a** and **35p-t**) formed in the RCM reactions of the substrates **34o-t** to have the *E*-geometry.

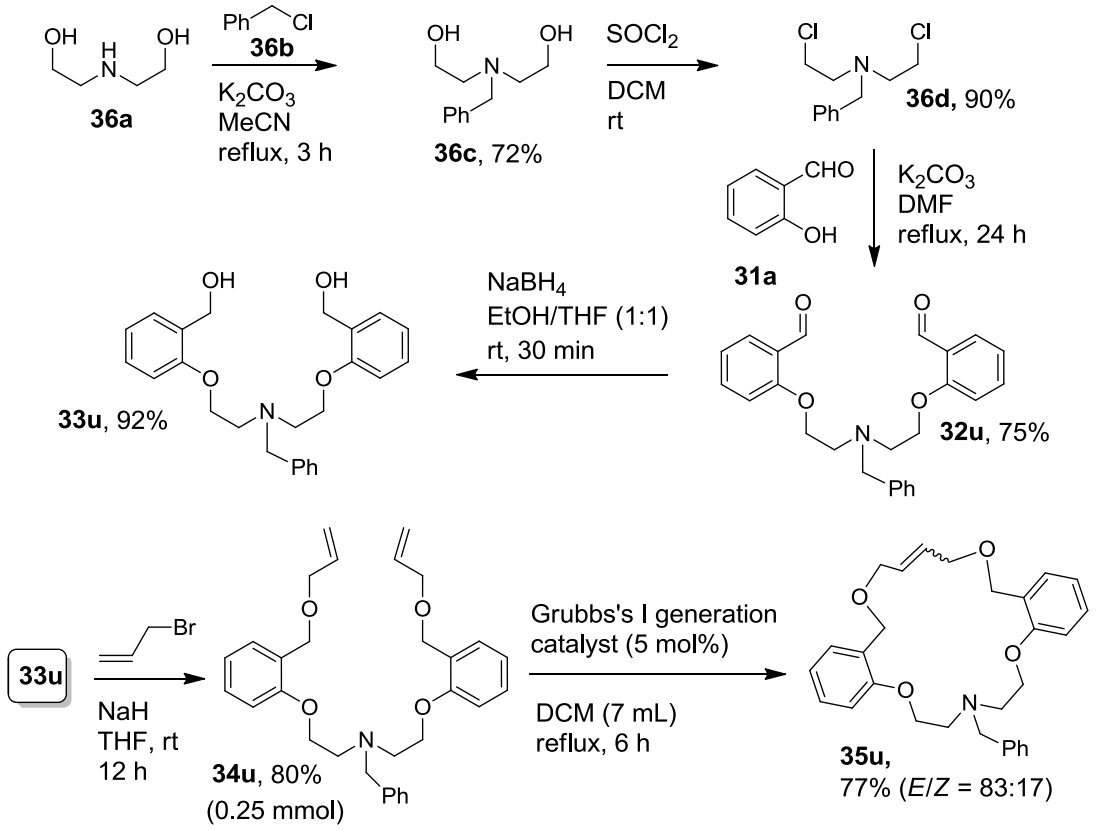
Scheme 13. Synthesis of polyether macrocyclic olefins **35a** and **35p-t**.

Successively, the RCM precursors **34k,l**, which were derived from 2-hydroxy benzaldehyde and the oxygen-based linkers were subjected to the ring closing metathesis reaction in the presence of

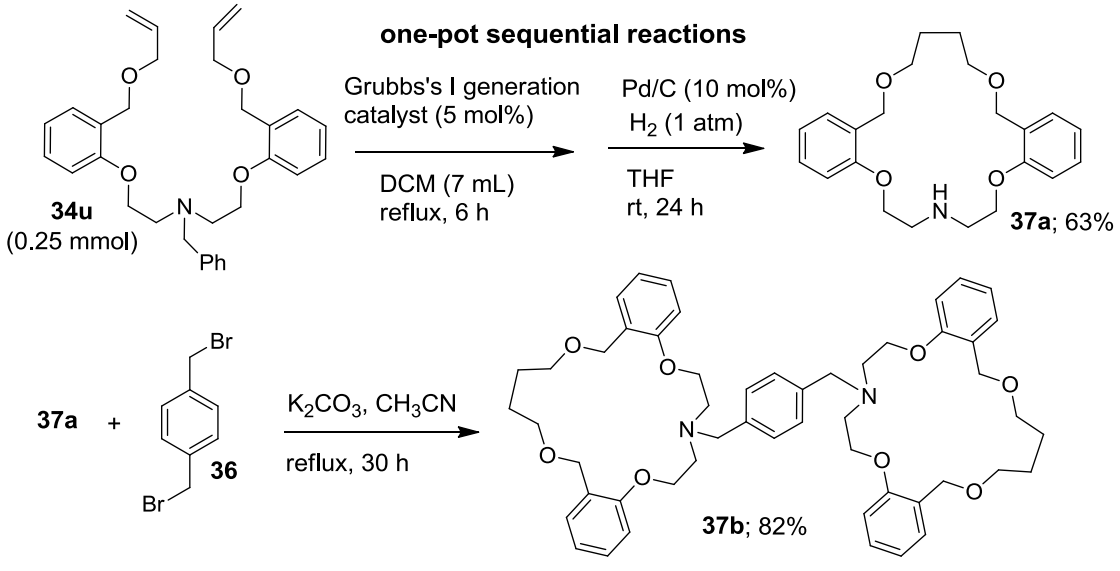
the Grubbs's I generation catalyst. These reactions which afforded the corresponding polyether macrocyclic olefins **35k** (19-membered macrocycle) and **35l** (22-membered macrocycle) in 75 and 80% yields (*E/Z* ratio up to 83:17, entries 11 and 12, Table 2). Further, the RCM reactions of the RCM precursors **34m,n**,which were derived from 2-hydroxy-1-naphthalaldehyde also afforded the corresponding macrocyclic olefins **35m** (19-membered macrocycle) and **35n** (16-membered macrocycle) in 87 and 85% yields (*E/Z* ratio up to 90:10, entries 13 and 14, Table 2).

Next, the RCM reaction of the RCM precursor **34o** having substituted terminal olefin units was performed to afford the 19-membered macrocyclic olefin **35a** (*E/Z* = 90:10). Subsequently, the ring closing metathesis reactions of the RCM precursors **34p-r** having two terminal olefins, which were derived from *m*-hydroxy benzaldehyde were performed in the presence of the Grubbs's catalyst to afford the corresponding polyether macrocyclic olefins **35p** (18-membered macrocycle), **35q** (20-membered macrocycle) and **35r** (24-membered macrocycle) in 38-55% yields (*E/Z* ratio up to 90:10, Scheme 13). Then, the ring closing metathesis reactions of the RCM precursors **34s,t**, which were prepared using *trans* alkene and alkyne units based rigid linkers were performed to afford the corresponding macrocyclic olefins **35s** (18-membered macrocycle) and **35t** (18-membered macrocycle) in 88 and 55% yields (*E/Z* ratio up to 95:5, Scheme 13).

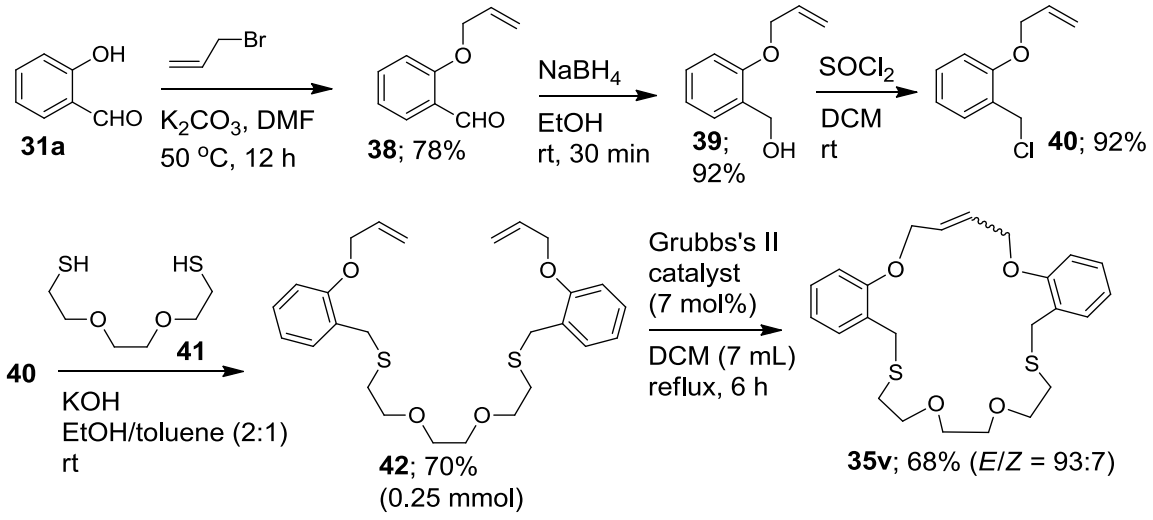
In line with the objective of enriching the library of crown ethers/polyether macrocycles, it was envisaged to prepare the aza-polyether macrocyclic olefin **35u**. Accordingly, the RCM precursor **34u** (Scheme 14) having terminal olefins and containing a nitrogen heteroatom in the linker part was assembled. The treatment of 2,2'-azanediyldiethanol (**36a**) with BnCl afforded the 2,2'-(benzylazanediyl)diethanol (**36c**). Next, the reaction of **36c** with thionyl chloride furnished *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine (**36d**). Then, **36d** was treated with 2-hydroxybenzaldehyde (**31a**) in the presence of K_2CO_3 to give the *bis*-aldehyde **32u** having a nitrogen atom in the linker part. Then, the reduction of aldehyde group of **32u** with $NaBH_4$ gave the *bis*-alcohol **33u**. Next, the NaH-mediated *O*-allylation of the *bis*-alcohol **33u** with allyl bromide afforded the RCM precursor **34u** having terminal olefins and containing a nitrogen heteroatom in the linker part. Next, the ring closing metathesis of RCM precursor **34u** in the presence of the Grubbs's I generation catalyst (5 mol%) afforded the expected aza-polyether macrocyclic olefin **35u** in 77% yield (*E/Z* = 83:17, Scheme 14).



Scheme 14.[16b] Synthesis of aza-polyether macrocyclic olefin **35u**.



Scheme 15. Synthesis of novel bis-aza-polyether macrocycle **37b**.

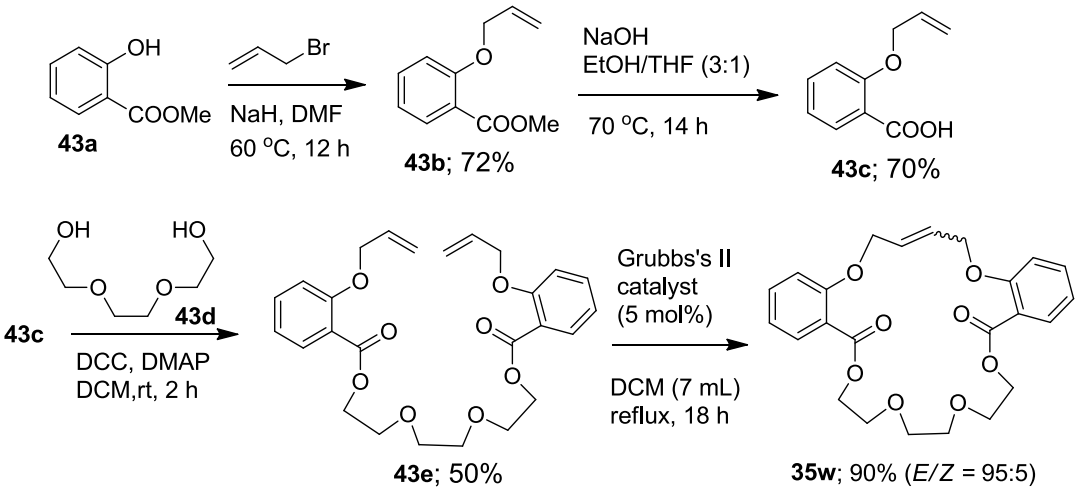


Scheme 16.[16b] Synthesis of thia polyether macrocyclic olefin **35v**.

After synthesizing the macrocyclic olefin **35u**, it was planned to reveal the synthetic utility of the aza-polyether macrocycle **35u** by synthesizing the *bis* aza-polyether macrocycle **37b** involving ring closing metathesis and hydrogenation reaction processes starting from **34u** (Scheme 15). Accordingly, the RCM precursor **34u** was treated with Grubbs's I generation catalyst for 6 h. After this period, the crude reaction mixture was directly subjected to the catalytic hydrogenation process under standard reaction conditions. These reaction processes gave the de-benzylated polyether macrocycle **37a** having a free secondary amine group in the macrocyclic core. Next, the reaction of two equiv of the compound **37a** with one equiv of 1,4- bis(bromomethyl)benzene (**36**) in the presence of K_2CO_3 in refluxing MeCN afforded the desired *bis* aza-polyether macrocycle **37b** in 82% yield (Scheme 15).

With an objective to further elaborate the generality of this method, the RCM precursor **42** having two sulphur heteroatoms in the linker was assembled starting from salicylaldehyde and 2,2 (ethylenedioxy)diethanethiol. Accordingly, the RCM precursor **42** was assembled by employing the standard synthetic procedures as described in Scheme 16. Then, the ring closing metathesis reaction of the RCM precursor **42** having two sulphur heteroatoms in the linker part was performed in the presence of Grubb's II generation catalyst (7 mol%). This reaction successfully afforded the 22-membered thia-polyether macrocyclic olefin **35v** in 68% yield (*E/Z*

= 93:7, Scheme 16). Furthermore, the RCM precursor **43e** was also assembled by employing the standard synthetic procedures as described in Scheme 17. Then, the ring closing metathesis reaction of the RCM precursor **43e** was performed in the presence of Grubb's II generation catalyst to afford the dilactone-based macrocyclic olefin **35w** (Scheme 17).

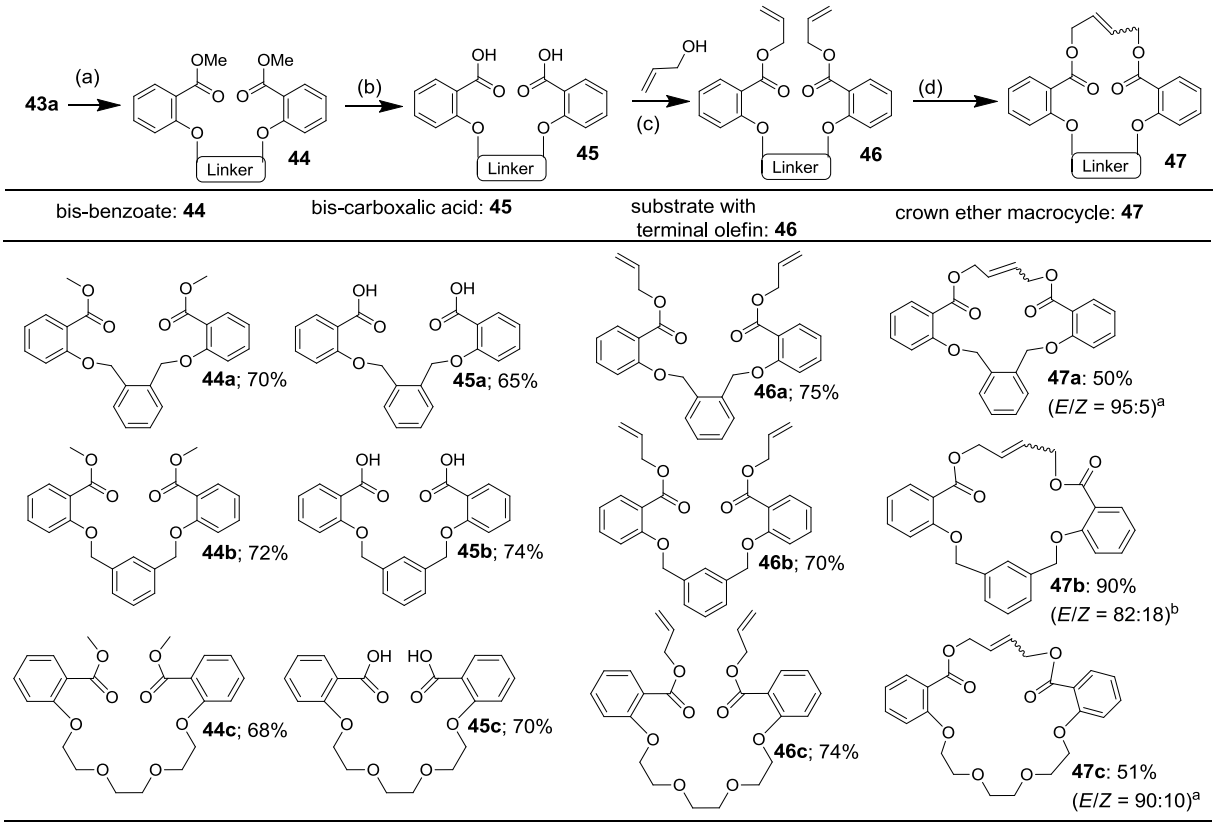


Scheme 17.[16b] Synthesis of dilactone macrocyclic olefin **35w**.

While a wide range of macrocyclic systems are known which include the esteemed crown ethers/polyether macrocycles compounds and amide-based macrocycles and macrolides (macrocyclic lactones). Apart from the well-known crown ethers/polyether macrocycles, macrocyclic lactones have also been attractive molecules due to their remarkable properties. Of special interest, dilactone macrocyclides[17] were reported to have ability to form metal encapsulated complexes with metal cations and act as ion carriers. A literature survey revealed that there are only limited numbers of methods available for synthesizing macrocyclic dilactones. Consequently, with an objective to elaborate the generality of the ring closing metathesis technique-based synthesis of crown ethers/polyether macrocycles, a part of this Chapter 1 aimed to synthesize new dilactone polyethers macrocycles. In this regard, different types of RCM precursors, such as *bis* allyl benzoate derivatives **46a-c** (Table 3) having terminal olefins were assembled from *bis*-carboxylic acids **45a-c** and allyl alcohol involving the DCC/DMAP coupling reaction (Table 3). Then, the ring closing metathesis reactions of the *bis* allyl benzoate derivatives **46a-c** were performed in the presence of Grubbs's catalyst to afford the corresponding dilactone polyether macrocyclic olefins **47a** (18-membered macrocycle), **47b** (19-

membered macrocycle) and **47c** (22-membered macrocycle) in 50-90% yields (*E/Z* ratio up to 95:5, Table 3).

Table 3. Synthesis of 18-22 membered dilactone crown ether/polyether (macrolides) macrocyclic olefins **47a-c** *via* RCM.[a]

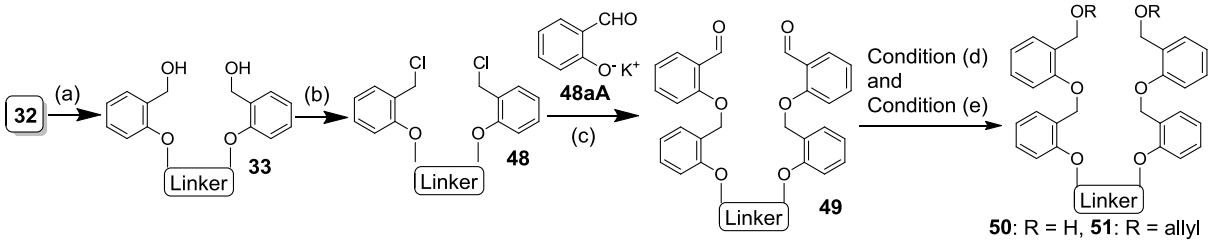


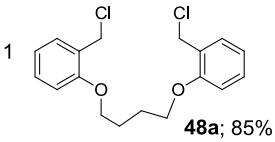
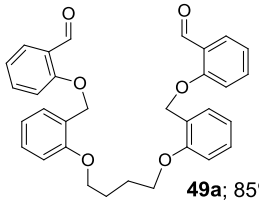
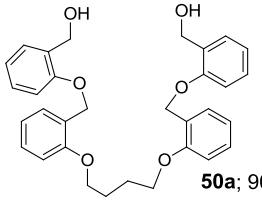
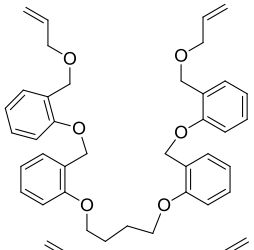
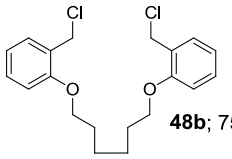
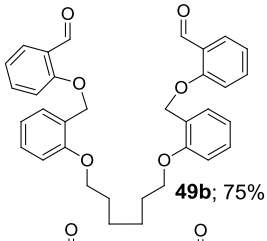
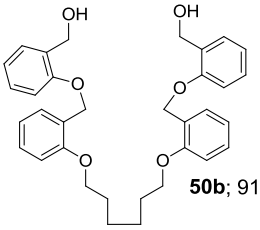
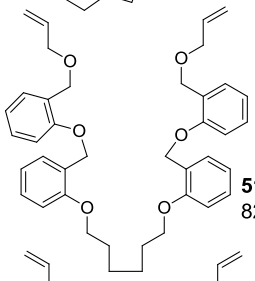
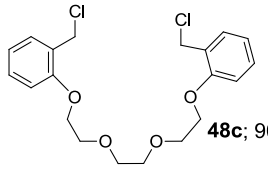
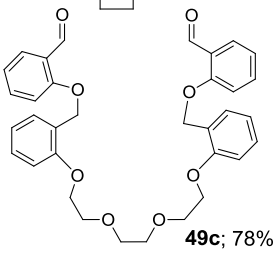
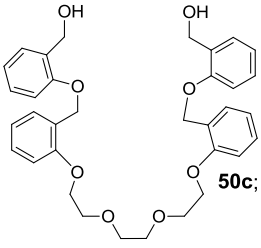
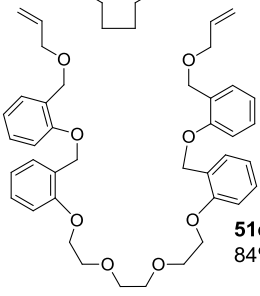
[a] RCM reaction was performed with Grubbs's II generation catalyst. [b] RCM reaction was performed with Grubbs's I generation catalyst. Reaction Condition: (a) K_2CO_3, NaI, MeCN, reflux, 24 h. (b) KOH, EtOH, reflux, 2 h. (c) DCC, DMAP, DCM, RT. (d) Grubbs's catalyst (5 mol%), DCM (7 mL), reflux, 3-15 h.

Next, with the purpose of increasing the ring size of polyether macrocyclic olefins, it was planned to construct various RCM precursors **51a-c** (Table 4). In this regard, initially, the *bis* benzyl chlorides **48a-c** were prepared from the reaction of $SOCl_2$ with the corresponding *bis* benzyl alcohols **33** (entries 1-3, Table 4). Next, the treatment of *bis* benzyl chlorides **48a-c** (with the potassium salt of salicylaldehyde **48aA**, which was derived from salicylaldehyde with methanolic KOH, afforded the corresponding *bis* aldehydes **49a-c**. Then, the reduction of *bis*

aldehydes **49a-c** with $NaBH_4$ gave the corresponding *bis* benzyl alcohols **50a-c**. Further, treatment of the *bis* benzyl alcohols **50a-c** with NaH and allyl bromide furnished the corresponding *O*-allylated RCM precursors **51a-c** having two terminal olefins. The RCM precursors **51a-c** are having extended chain lengths when compared to the RCM precursors shown in Tables 2 and 3 and Schemes 13-17.

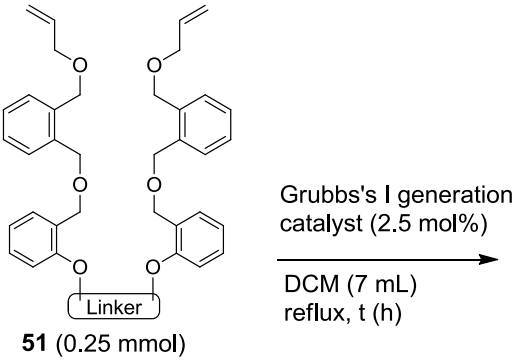
Table 4. Assembling of starting materials **51a-c** having two terminal olefins from *bis*-benzyl chlorides.[a]

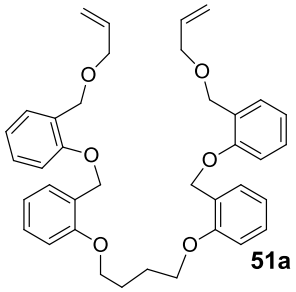
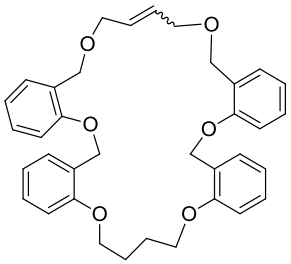
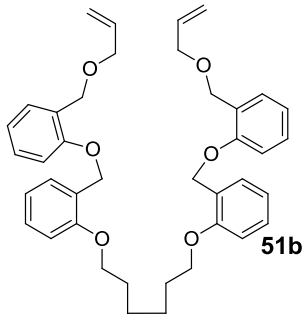
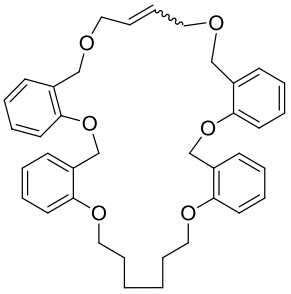
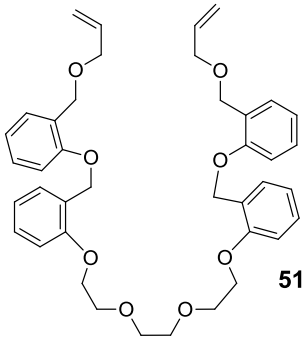
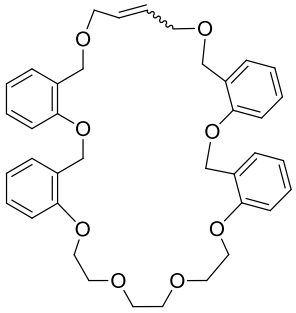


Entry	Substrate: **48**	Substrate: **49**	Substrate: **50**	Substrate: **51**
1	 **48a**; 85%	 **49a**; 85%	 **50a**; 90%	 **51a**; 85%
2	 **48b**; 75%	 **49b**; 75%	 **50b**; 91%	 **51b**; 82%
3	 **48c**; 90%	 **49c**; 78%	 **50c**; 74%	 **51c**; 84%

[a] Reaction conditions: (a) $NaBH_4$, EtOH, 30 min, rt. (b) $SOCl_2$, DCM, rt. (c) DMF, 110 ^oC, 12 h. (d) $NaBH_4$, EtOH, 30 min, rt. (e) NaH, allyl bromide, THF, rt, 12 h.

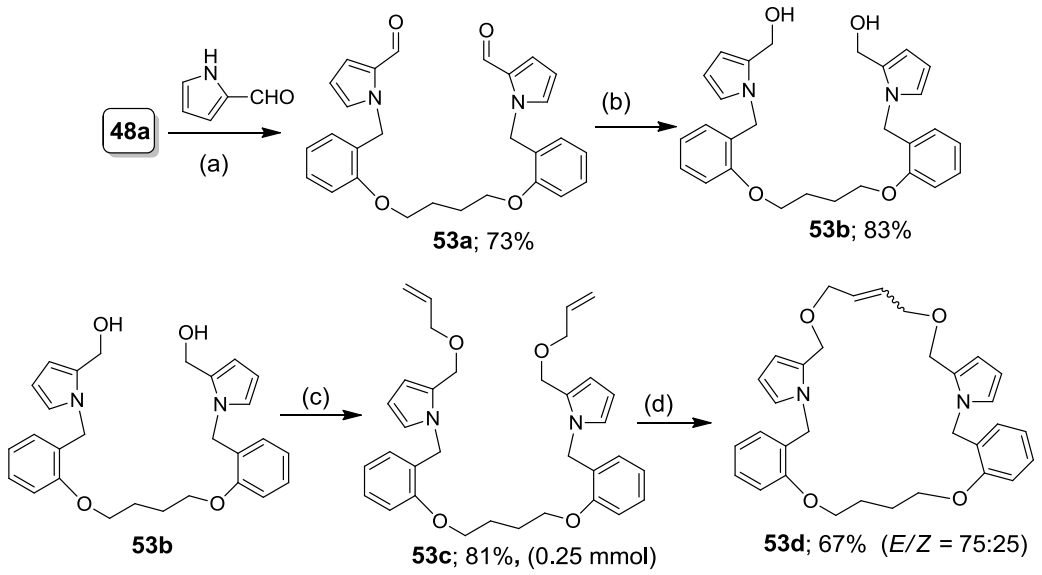
Table 5. Synthesis of 26-30 membered large sized polyether macrocyclic olefins **52a-c**, *via* the RCM reaction.[a]



Entry	Substrate: **51**	*t* (h)	Macrocylic olefin: **52**	Yield (%)
1	 **51a**	11		**52a**; 52 (*E*/*Z* = 75:25)
2	 **51b**	11		**52b**; 62 (*E*/*Z* = 80:20)
3	 **51c**	11		**52c**; 60 (*E*/*Z* = 90:10)

[a] Based on the X-ray structures of **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and **47a** (major, *E*-isomer, Figure 6 and 7), the major isomers (**52a-c**) are proposed to have the *E*-geometry in occurrence with the literature. [10d-i,12,13,16b]

Having synthesized RCM precursors **51a-c** are having extended chain lengths when compared to the RCM precursors shown in Tables 2 and 3 and Schemes 13-17, we then performed the ring closing metathesis reaction of the RCM precursors **51a-c** in the presence of the Grubbs's I generation catalyst. These reactions afforded the corresponding 26-30-membered crown ether/polyether macrocyclic olefins **52a** (26-membered macrocycle), **52b** (28-membered macrocycle) and **52c** (30-membered macrocycle) in 52-62% yields (*E/Z* ratio up to 90:10, Table 5).



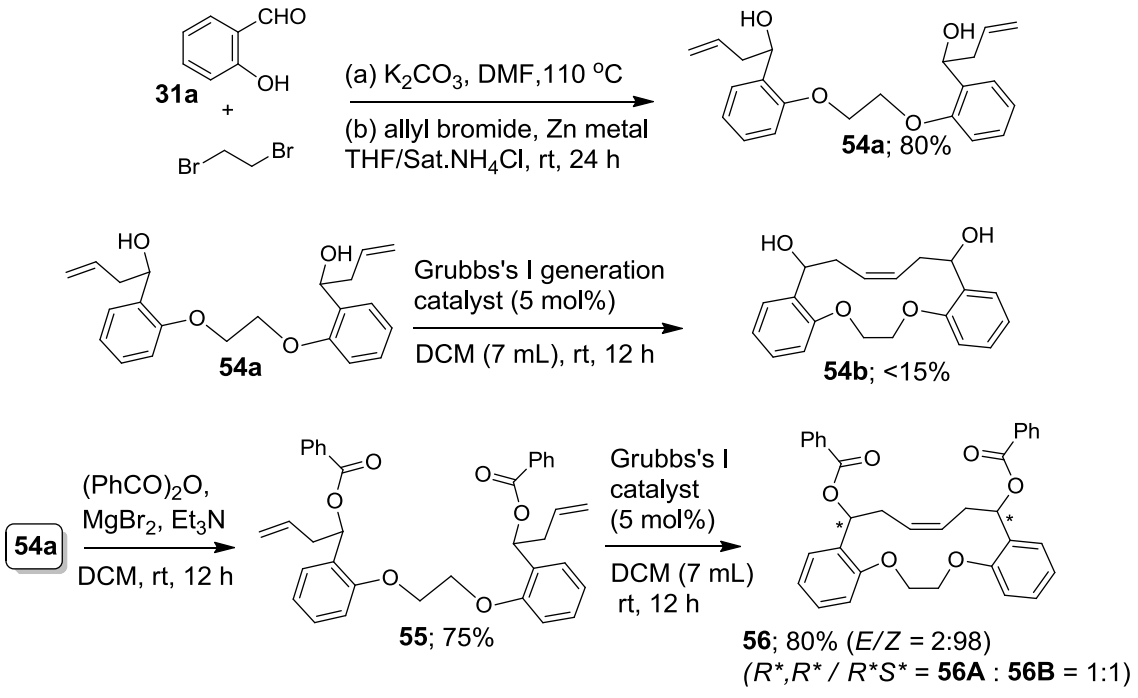
Reaction Conditions: (a) NaH, DMF, rt, 20 h. (b) $NaBH_4$, EtOH, 30 min, rt. (c) NaH, allyl bromide, THF, rt, 12 h. (d) Grubbs's I generation catalyst (2.5 mol%), DCM (7 mL), reflux, 10 h.

Scheme 18.[16b] Synthesis of pyrrole ring-based polyether macrocyclic olefins **53d**.

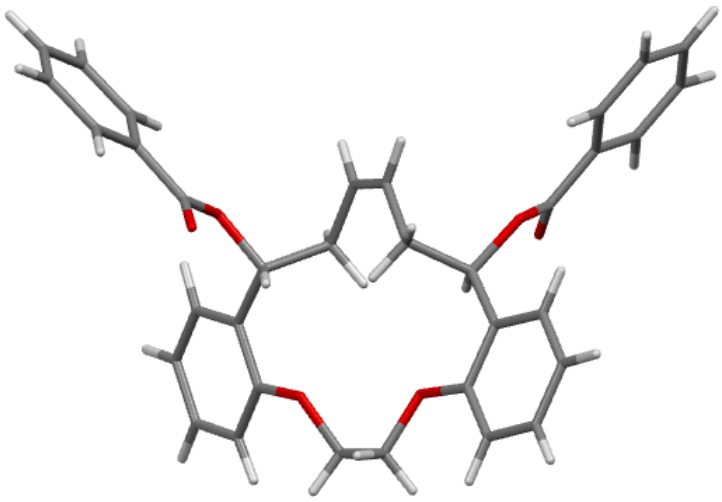
Subsequently, it was envisaged to assemble pyrrole ring-based polyether macrocyclic olefin and the necessary RCM precursor **53c** having two terminal olefins (Scheme 18). Accordingly, the treatment of *bis* benzyl chloride **48a** with pyrrole-2-carboxyldehyde in the presence of NaH furnished the *bis* aldehyde **53a**. Next, the reduction of *bis* aldehydes **53a** with $NaBH_4$ afforded the *bis* benzyl alcohol **53b**. The reaction of the *bis* benzyl alcohol **53b** and allyl bromide in the presence of NaH afforded the RCM precursor, *O*-allylated substrate **53c** having the two terminal olefins connected to pyrrole moiety. Then, the ring closing metathesis of the RCM precursor **53c**

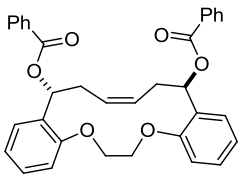
in the presence of the Grubbs's I generation catalyst was performed to give the pyrrole ring-based polyether macrocyclic olefins **53d** in 67% yield (*E/Z* ratio 75:25, Scheme 18).

Finally, it was planned to attempt the ring closing metathesis of the homoallyl alcohol substrate **54a**. The RCM precursor **54a** containing free OH groups were assembled from salicylaldehyde **31a** and 1,2-dibromoethane (Scheme 19). Then, the ring closing metathesis of the homoallyl alcohol substrate **54a** was performed. This reaction gave the macrocyclic olefin **54b** having two free OH groups in only <15% yield as a mixture of isomers (Scheme 19). Dissatisfied with this observation, the OH groups of substrate **54a** were protected to afford the substrate **55** (Scheme 19). Then, the ring closing metathesis of the homoallyl alcohol substrate **54a** was performed, which successfully gave the macrocyclic olefin **56** having *Z*-geometry as the major isomer. Since this compound has two chiral centers, the macrocycle **56** was obtained as mixture of diastereomers (*R*,R** / *R*,S** = **56A**:**56B** = 1:1) having *Z*-geometry. The structure and olefin geometry of both the macrocyclic olefin diastereomers **56A** and **56B** were characterized by X-ray structure analysis (Figure 4).

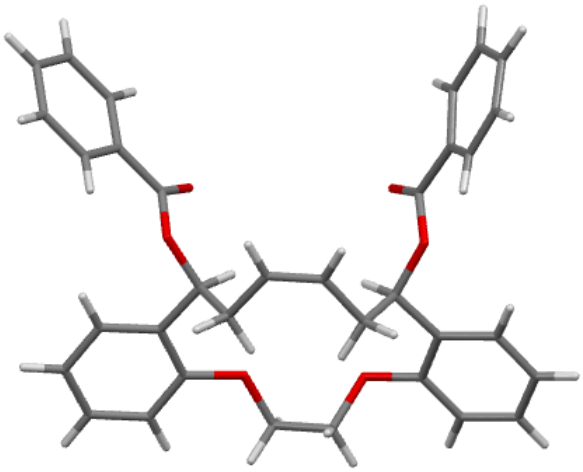


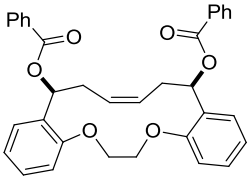
Scheme 19.[16b] Synthesis of macrocyclic olefin diastereomers **56A** and **56B**.





56A; R,R (or) S,S





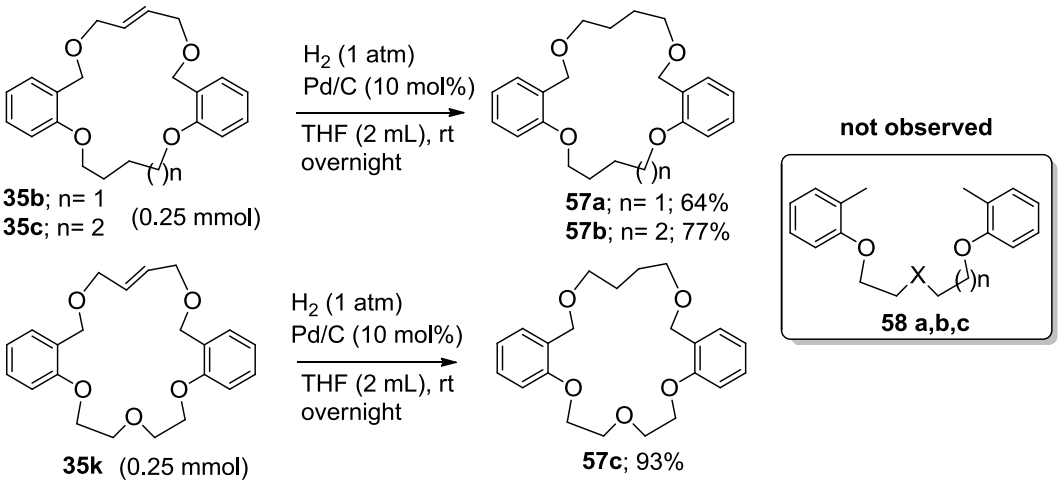
56B; R,S (or) S,R

Figure 4.[20] X-ray (capped sticks model) structures of **56A** (*Z*-isomer, *R**,*R**), **56B** (*Z*-isomer, *R**,*S**).

Synthesis of periphery modified polyether macrocycles.

Having done the assembling a library of polyether macrocyclic olefin *via* the ring closing metathesis reaction, it was envisaged to perform the post ring-closure functional derivatization of polyether macrocyclic olefins obtained from the ring closing metathesis reactions. In this regard, the polyether macrocyclic olefins **35b,c** obtained from the ring closing metathesis of the RCM precursors **34b,c** were subjected to the Pd-catalyzed hydrogenation reactions. These reactions

afforded the corresponding polyether macrocycles **57a** (18-membered macrocycle) and **57b** (19-membered macrocycle) in 64 and 77% yields (Scheme 20). Similarly, the catalytic hydrogenation of polyether macrocyclic olefin **35k** also furnished the 19-membered macrocycle polyether macrocycle **57c** having an oxygen-based linker (Scheme 20). It is to be noted the macrocyclic compounds **57a-c** appear to be stable under the catalytic hydrogenation reaction conditions and any of the corresponding compounds resulting from the cleavage of the benzyloxy functional group present in the macrocyclic systems **35b,c,k** were not observed (Scheme 20).

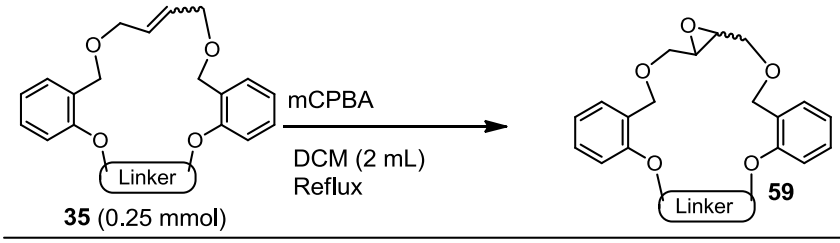


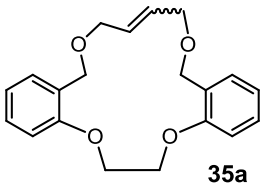
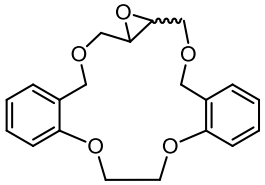
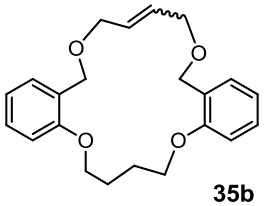
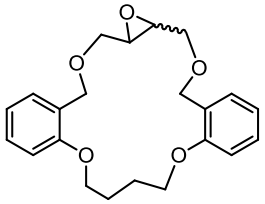
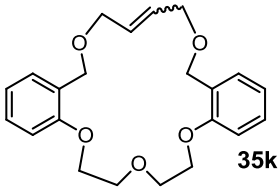
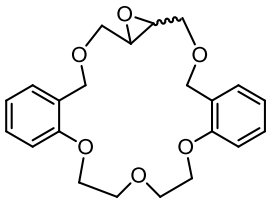
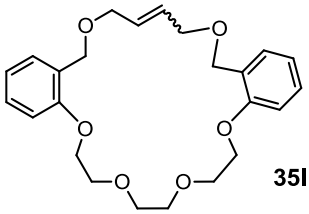
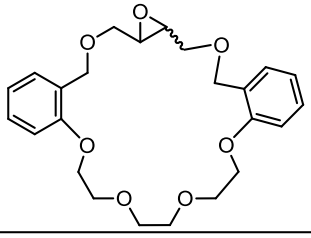
Scheme 20. Catalytic hydrogenation of polyether macrocyclic olefins **35b,c,k** and assembling of crown ether/polyether macrocyclic systems **57a-c**.

Next, the polyether macrocyclic olefins **35a,b,k,l** (mixture of *E/Z* diastereomers) which were obtained from the RCM reaction of the corresponding RCM precursors **34a,b,k,l** were subjected to the standard epoxidation reaction conditions. Accordingly, the reactions of the polyether macrocyclic olefins **35a,b,k,l** with mCPBA were performed to afford the corresponding epoxide functionality installed polyether macrocyclic systems **59a-d** (Table 6). It is to be noted that this process has given an easy way for assembling new epoxide functionality installed polyether macrocyclic systems, starting from simple starting materials, such as 2-hydroxy benzaldehydes. Since the macrocyclic olefin **35a** was isolated as a mixture of diastereomers (entry 1, Table 2), the mCPBA-mediated epoxidation of the macrocyclic olefin **35a** gave the epoxide macrocycle **59a** as a mixture diastereomers (*dr* = 70:30). Along this line, epoxide macrocycles **59b-d** were

also synthesized from the epoxidation of the corresponding polyether macrocyclic olefins (Table 6).

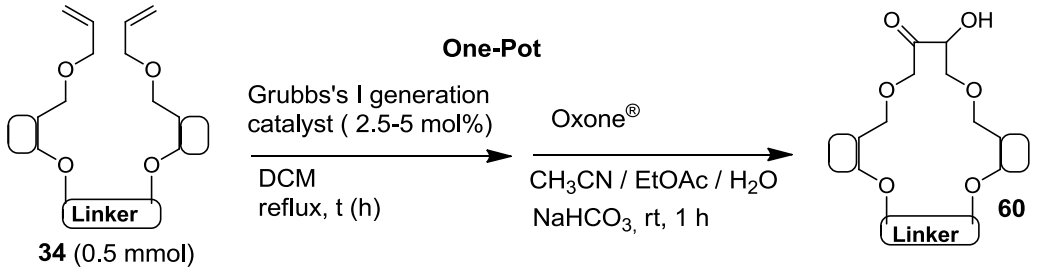
Table 6. Assembling of epoxide moiety installed polyether macrocycles **59a-d**.



Entry	Substrate **35**	t (h)	Epoxide Functionality Appended Macrocycle **59**	Yield (%)
1	 **35a**	14		**59a**; 52 (*dr* = 70:30) **59aA** (major) **59aB** (minor)
2	 **35b**	14		**59b**; 53 (*dr* = 86:14)
3	 **35k**	4 d		**59c**; 45 (*dr* = 67:33)
4	 **35l**	22		**59d**; 62 (*dr* = 85:15)

To elaborate the scope of the post ring-closure functional derivatization of polyether macrocyclic olefins, it was envisaged to synthesize the α-hydroxy ketone functionality installed polyether macrocyclic systems **60** (Table 7, Scheme 21; generalized scheme). It is worth to mention here that a literature survey revealed that there exists no report on the synthesis of the α-hydroxy ketone functionality installed polyether macrocyclic systems. The synthesis of the α-hydroxy

ketone functionality installed polyether macrocyclic systems was carried out in a one-pot reaction strategy comprising the ring closing metathesis of RCM precursor **34** followed by oxidation of the macrocyclic olefin formed in the RCM step.



Scheme 21: Generalized scheme for the synthesis of the α-hydroxy ketone functionality installed polyether macrocycles **60** from one pot RCM and oxone mediated oxidation reactions.

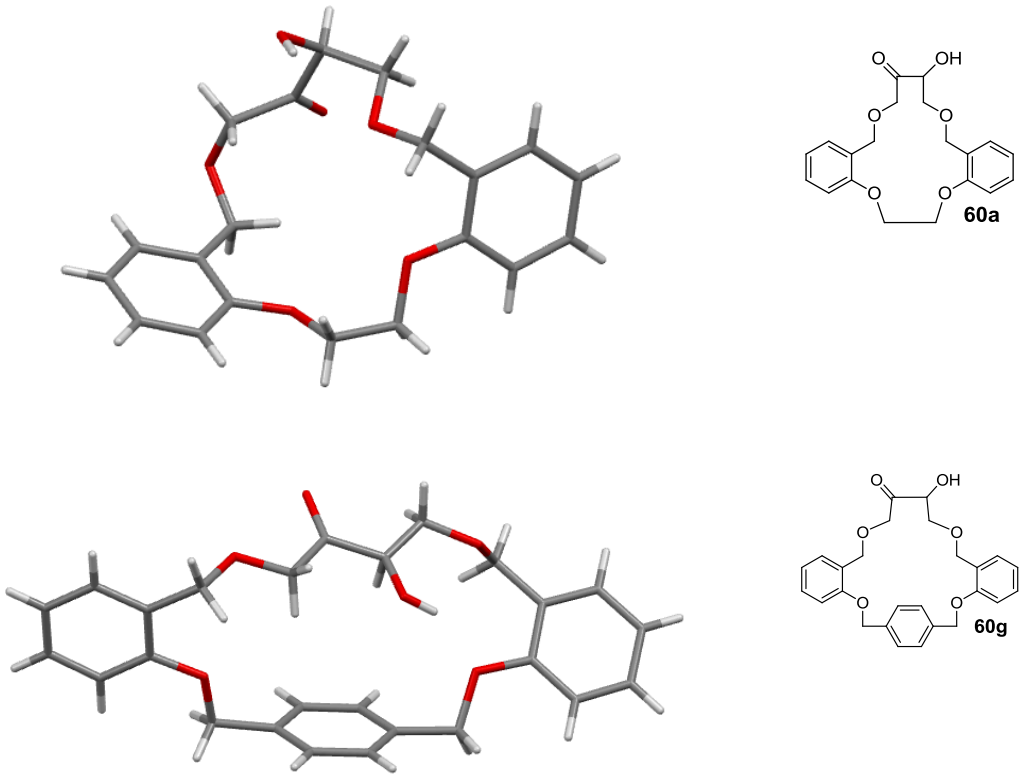
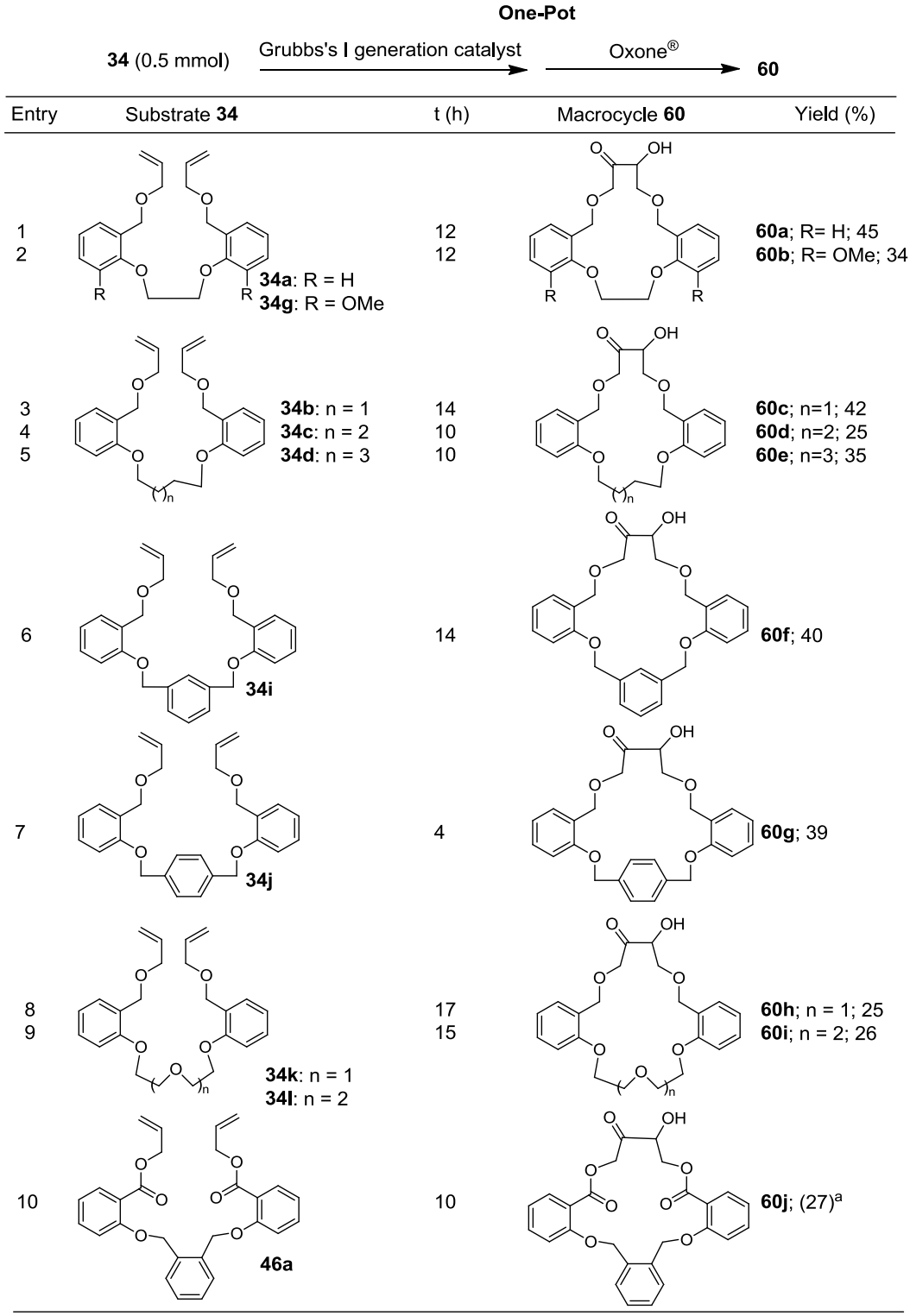


Figure 5. [20] X-ray (capped sticks model) structures of **60a** and **60g**.

Table 7. Synthesis of the α-hydroxy ketone functionality installed polyether macrocycles **60a-j** *via* one-pot RCM and oxone-mediated oxidation sequential reactions.

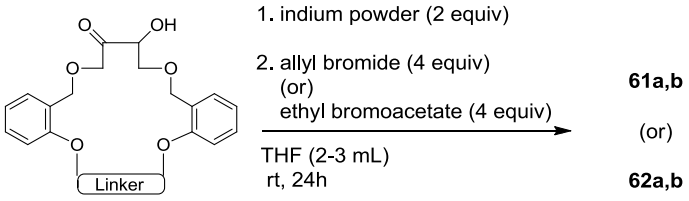


[a] In this reaction Grubbs's II generation catalyst was used

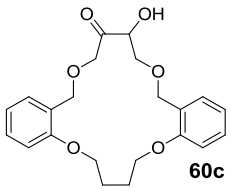
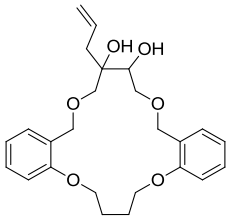
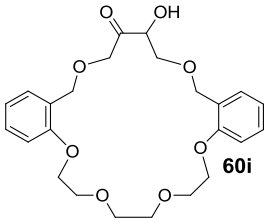
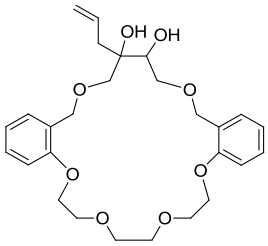
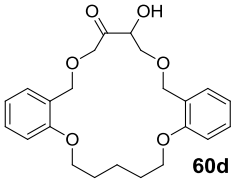
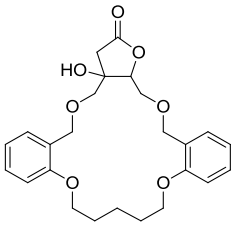
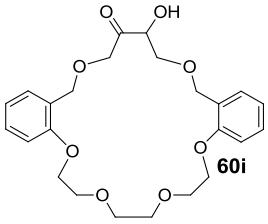
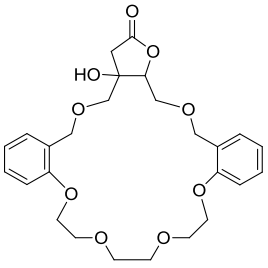
Initially, the RCM precursors **34a-d** and **34g**, which were assembled from the aliphatic chain-based linkers were treated with Grubbs's I generation catalyst for 10-14 h. After this period, the oxone®-mediated oxidation reaction[18] of the resulting macrocyclic olefins were performed without performing the isolation of the macrocyclic olefins. These sequential reaction processes gave the corresponding α-hydroxy ketone functionality installed polyether macrocyclic compounds **60a-e** in 25-45% yields (Table 7, entries 1-5). Further, the one-pot RCM followed by the oxone®-mediated oxidation reactions of the RCM precursors **34i,j**, which were assembled from the aromatic chain-based linkers afforded the corresponding α-hydroxy ketone functionality appended polyether macrocyclic compounds **60f,g** in 40 and 39% yields (Table 7, entries 6 and 7). Next, the one-pot RCM followed by the oxone®-mediated oxidation reactions of the RCM precursors containing terminal olefins **34k,l** and **46a**, which were assembled from the oxygen-based and aromatic ring-based linkers also afforded the corresponding α-hydroxy ketone functionality appended polyether macrocyclic compounds **60h-j** in 25-27% yields, (Table 7, entries 8-10).

Subsequently, it was envisioned to test the utility of the α-hydroxy ketone functionality installed polyether macrocycles **60c,i** by preparing their corresponding polyether macrocycles having a C-pivotal allyl group as a free handle. Accordingly, it was envisaged to treat the α-hydroxy ketone functionality installed polyether macrocycles **60c,i** with allyl bromide in the presence of indium powder in anhydrous THF. The indium-mediate allylation[19] of **60c,i** afforded the corresponding polyether/crown ether macrocycles **61a** (63%) and **61b** (60%) as a mixture of diastereomers having a C-pivotal allyl group as a free handle (Table 8, entries 1 and 2). Attempts were made to separate the corresponding diastereomers of **61a** and **61b**, however, the attempts were failed. Then, it was envisaged to perform the indium-mediated Reformatsky reaction[19] by using the α-hydroxy ketone functionality installed polyether macrocycles **60d,i**. Accordingly, the reaction of **60d,i** with ethyl bromoacetate and indium in THF was performed to afford the corresponding lactone moiety appended polyether/crown ether macrocycles **62a** (30%) and **62b** (23%) (Table 8, entries 3 and 4).

Table 8. Indium-mediated allylation of α-hydroxy ketone functionality installed polyether macrocycles **60c-d** and **60i**.

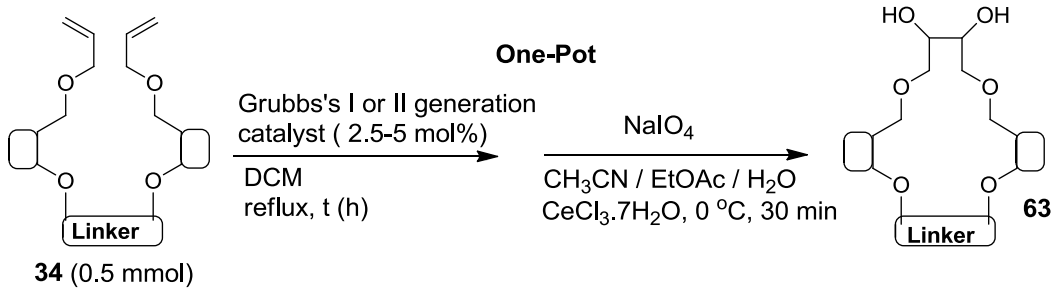


60 (0.12 mmol)

Entry	Substrate **60**	Dihydroxy group (or) lactone appendend macrocycles **61**/**62**	Yield (%)
1	 **60c**		**61a**; 63 *dr* = 65:35
2	 **60i**		**61b**; 60 *dr* = 80:20
3	 **60d**		**62a**; 30
4	 **60i**		**62b**; 23

To further extend the scope of the post ring-closure functional derivatization of polyether macrocyclic olefins, it was envisaged to modify the periphery of the polyether macrocyclic olefins by installing the 1,2-diol functionality *via* a one pot sequential RCM reaction followed by

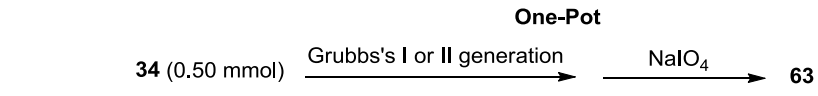
syn dihydroxylation starting from the RCM precursors **34** (generalized structure, Scheme 22. The corresponding the RCM precursor **34** was first treated with the Grubbs's catalyst for the required reaction period and then, the crude reaction mixture was dissolved in EtOAc. Then, this EtOAc solution was added slowly to a suspension of preformed Ce(IV)-periodate complex. These reaction sequences afforded the corresponding 1,2-diol functionality installed polyether macrocyclic system **38** as mixture of diastereomers (because both *E* and *Z* isomers are forming during the RCM reaction).

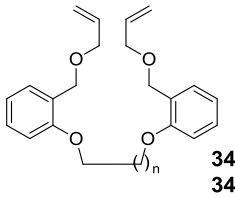
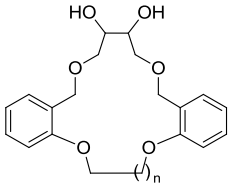
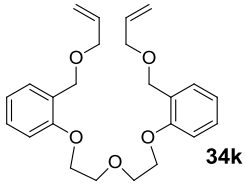
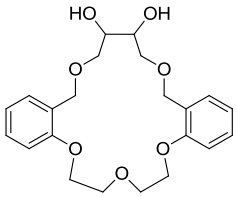
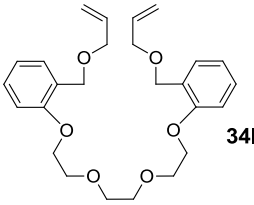
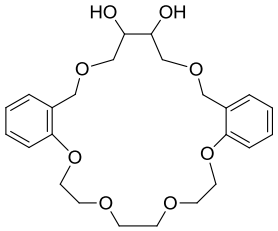
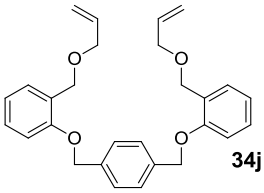
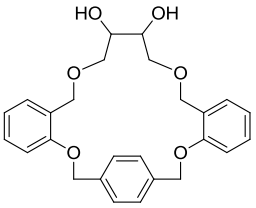
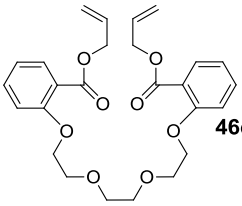
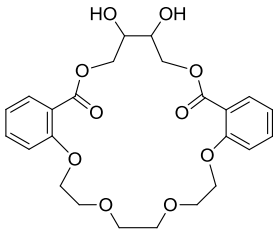
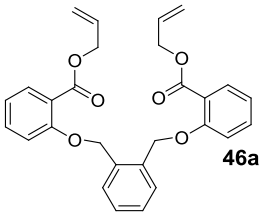
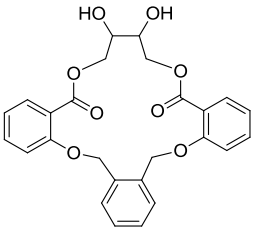


Scheme 22. Generalized scheme for the synthesis of 1,2-diol functionality installed polyether macrocycles **63** in one-pot RCM and *syn*-dihydroxylation oxidation reactions.

Accordingly, the polyether macrocycles **63a** and **63b** having aliphatic linkers were synthesized from the RCM precursors **34a** and **34d** in 23 and 30% yields, respectively (entries 1 and 2, Table 9). Similarly, the RCM precursors **34k** and **34l**, which were prepared using oxygen-based linkers afforded the corresponding 1,2-diol functionality installed crown ether-type macrocycles **63c** and **63d** in 32 and 25% yields (entries 3 and 4, Table 9). The synthesis of 1,2-diol functionality installed polyether macrocycles **63e** (43%) was also accomplished starting from the RCM precursor **4j** in one-pot sequential RCM and *syn* dihydroxylation oxidation reaction sequences (entry 5, Table 9). The RCM/oxidation sequential reactions were also performed by using the RCM/dilactone precursors **46c** and **46a**. These reactions also furnished the corresponding 1,2-diol functionality installed dilactone polyether macrocycles **63f** (45%) and **63g** (41%) (entries 6 and 7, Table 9). All the 1,2-diol functionality installed macrocycles **63a-g** were isolated as a mixture of diastereomers and the separation of diastereomers of **63a-g** was not easy and all the attempts to separate the diastereomers failed.

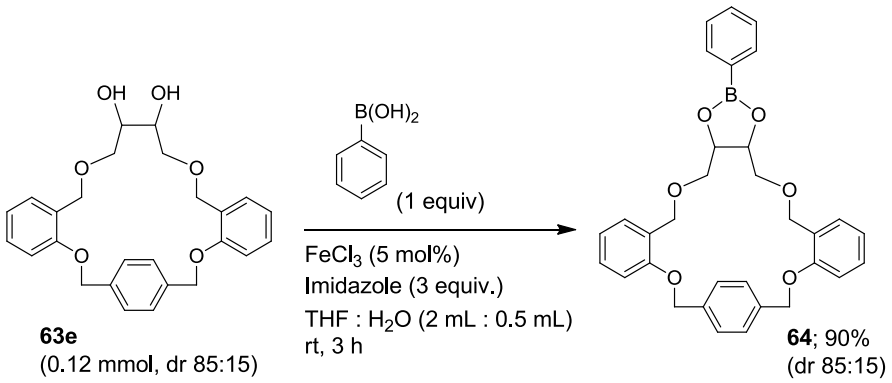
Table 9. Synthesis of 16-22 membered, 1,2-diol functionality installed polyether macrocycles **63a-g** *via* one-pot RCM and *syn* dihydroxylation oxidation reaction sequences.



Entry	Substrate **34**	*t* (h)	1,2-diol installed macrocycle **63**	Yield (%)
1 2	 **34a,** n =1 **34d,** n =5	12 10		**63a**; n = 1; 23 (*dr* =70:30)[a] **63b**; n = 5; 30 (*dr* = 80:20)[a]
3	 **34k**	17		**63c**, 32 (*dr* = 67:33)[a]
4	 **34l**	15		**63d**; 25 (*dr* =87:17)[a]
5	 **34j**	4		**63e**; 43 (*dr* = 80:20)[a]
6	 **46c**	12		**63f**; 45 (*dr* = 90:10)[b]
7	 **46a**	10		**63g**; 41 (*dr* = 95:10)[b]

[a] Grubbs's I generation catalyst was used. [b] Grubbs's II generation catalyst was used

Finally, it was decided to describe the utility of the 1,2-diol functionality installed crown polyether macrocycle by synthesizing the boronate ester-based polyether macrocyclic system **64** (Scheme 7). Accordingly, the $FeCl_3$-catalyzed esterification of boronic acid with the polyether macrocycle **63e** afforded the boronate ester-based polyether macrocyclic system **64** in 90% yield as a mixture of diastereomers (*dr* 85:15, Scheme 23).



Scheme 23. Synthesis of boronate ester-based polyether macrocyclic system **64**.

Stereochemistry of polyether macrocyclic olefins (Tables 2,3 and 5 and Schemes 13-18).

After the ring closing metathesis reactions, the respective crude reaction mixtures were purified by column chromatography. Based on all our trials to obtain the corresponding *E/Z* diastereomers (geometrical isomers) in pure forms, it was found that separating the *E/Z* diastereomers (geometrical isomers) obtained from the ring closing metathesis reaction was not an easy work. Further, a survey of literature also revealed that the purification of polyether macrocyclic compounds, especially, the macrocyclic olefins, was reported to be a difficult task.[6g-l,10] Isolation of both the *E*-isomer and *Z*-isomer formed from the RCM precursor was need to assign the geometry of the major isomer. After a few attempts, the macrocyclic olefins **35jA** (major isomer), **35jB** (minor isomer) and **47a** (major isomer) were successfully isolated in pure forms when the mixture of diastereomers was subjected to repetitive column chromatographic purification. Having isolated the macrocyclic olefins **35jA** (major isomer), **35jB** (minor isomer), these compounds were crystalized and then, their X-ray structures were obtained. Accordingly, the stereochemistry of the macrocyclic olefins **35jA** (*E*-isomer), **35jB** (*Z*-isomer) and **47a** (*E*-isomer), was clearly ascertained based on their X-ray structures (Figure 6).

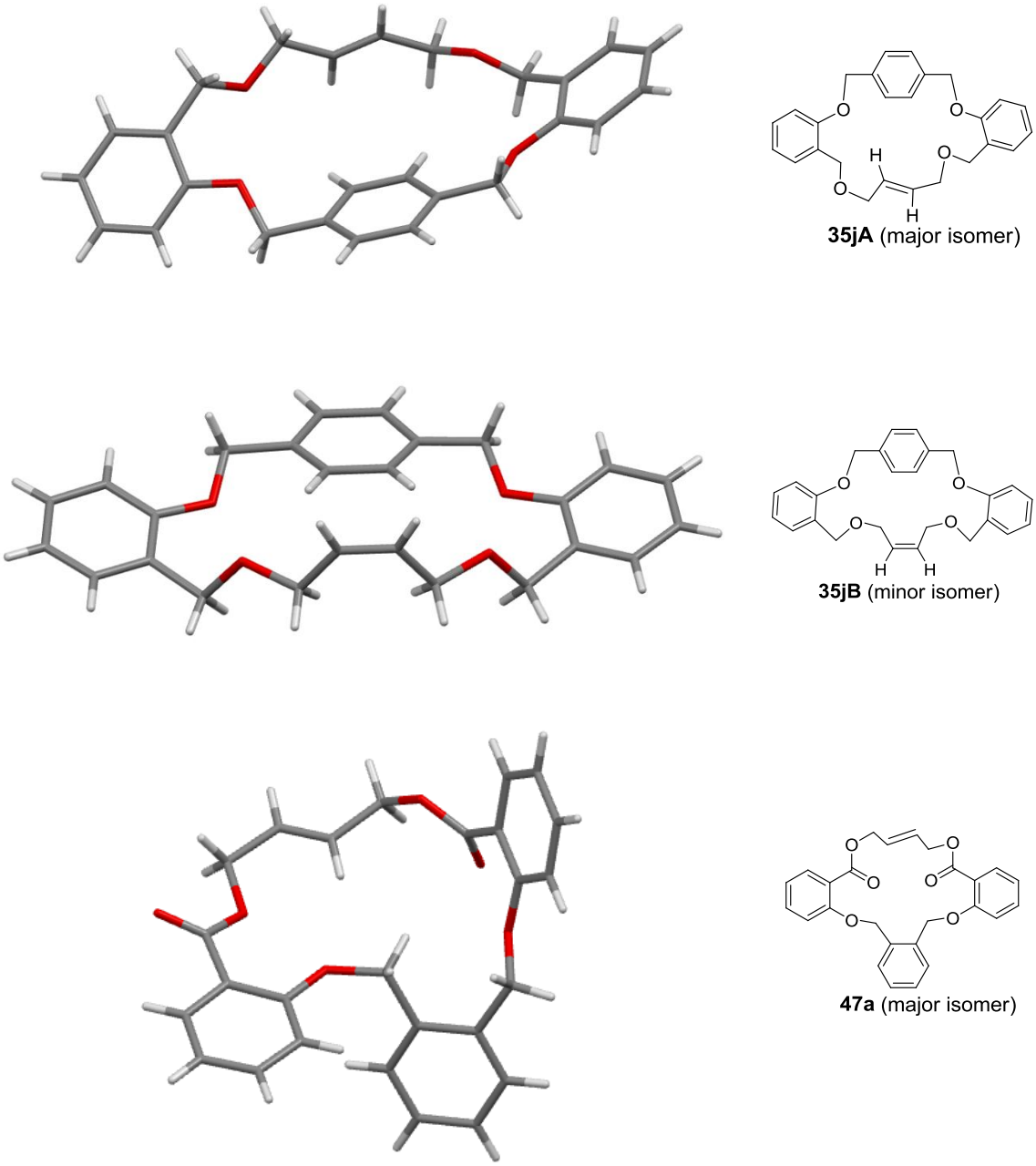


Figure 6.[20] X-ray (capped sticks model) structures of **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and X-ray (capped sticks model) structures of **47a** (major, *E*-isomer).

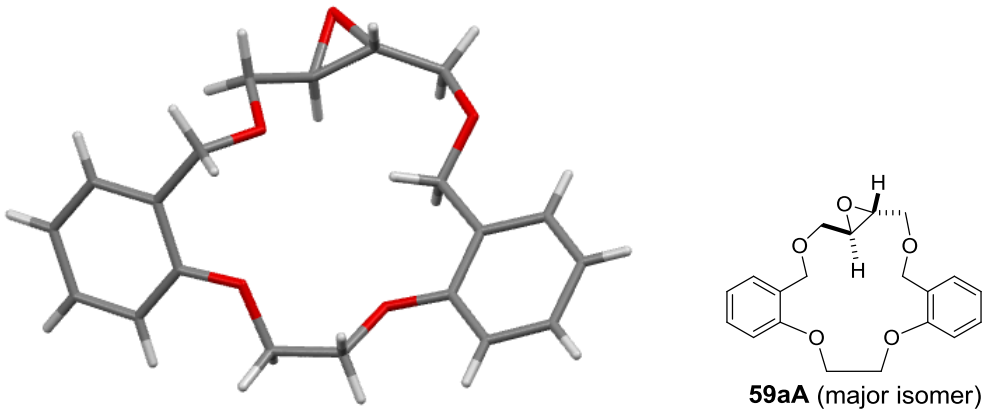


Figure 7.[20] X-ray (capped sticks model) structures of **59aA** (major isomer).

Additionally, the major isomer of the epoxide functionality installed polyether macrocyclic system **59aA** was also isolated in pure form and the major isomer **59aA** was crystalized and then, its X-ray structure was obtained. The X-ray structure of the epoxide functionality installed polyether macrocyclic system **59aA** (major isomer) is shown in Figure 7. The X-ray structure of the epoxide functionality appended polyether macrocycle **59aA** clearly revealed the major diastereomer to have a *R,R* (or *S,S*) configuration at C4 and C5 stereocenters. Further, the corresponding macrocyclic olefin **35a** (major compound **35a**) was assigned to have the *E*-geometry. Along this line, the stereochemistry of the major isomer of the macrocyclic olefin **47a** (*E*-isomer) was also clearly ascertained based on its X-ray structure (Figure 7).

While the stereochemistry of compounds **35jA**/**35jB** was clearly ascertained based on their X-ray structures, the proton and carbon signal assignment of some of the other compounds, such as, **35a**, **35e** and **35f** (which were obtained as a mixture of *E*/*Z* diastereomers) was also done using the ^{1}H, ^{13}C, H,H-COSY, HMQC NMR techniques. The characteristic ^{13}C signal of the OCH_2 group (of the -OCH_2CH=$CHCH_2O$- moiety) in the compounds **35a**, **35e** and **35f** (major isomers) appeared at δ 69.7, 70.0 and 69.6 ppm, respectively. Furthermore, the ^{1}H and ^{13}C signal assignments of the distinctly isolated diastereomers **35jA** and **35jB** were also done using the ^{1}H, ^{13}C, H,H-COSY, HMQC NMR techniques. The characteristic ^{13}C signal of the OCH_2 group (of the -OCH_2CH=$CHCH_2O$- moiety) in the compound **35jA** (major compound having the *E*-geometry) and **35jB** (minor compound having the *Z*-geometry) appeared at δ 70.9 and 67.1, respectively. These carbon NMR values indicated that the major and minor compounds to have the *E*- and *Z*-geometry, respectively, in all the ring closing metathesis reactions performed in this

work. The characteristic ^{13}C signal of the OCH_2 group (of the -OCH_2CH=$CHCH_2O$- moiety) of the compound **35jB** (minor compound having the *Z*-geometry) appeared at up field when compared to the ^{13}C signal of the OCH_2 group (of the -OCH_2CH=$CHCH_2O$- moiety) of the compound **35jA** (major compound having the *E*-geometry). These observations are in resemblance with the assignments made by Ibrahim and Rao based[13c,d,14d] on the NMR spectral values of the OCH_2 group (-OCH_2CH=$CHCH_2O$- moiety) present in crown formazans and related compounds having the *Z- or E*-geometry. On the basis of these deliberations and the X-ray structures of the macrocyclic olefins **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and the derivative **59aA** (major isomer) and **47a** (major, *E*-isomer), it is proposed that the corresponding major isomers of the compounds **35a-w**, **47a-c**, **52a-c** and **53d** formed in the RCM reactions of the corresponding substrates **34a-u**, **42**, **43e**, **46a-c**, **51a-c** and **53c** could have the *E*-geometry in concurrence with the literature reports[10d-i,12,13] (Tables 2,3 and 5 and Schemes 13-18). Additionally, the stereochemistry of macrocycles **56A** (*Z*-isomer, *R*,R**) and **56B** (*Z*-isomer, *R*,S**) and their Z-geometry was also clearly confirmed from the X-ray structure analysis.

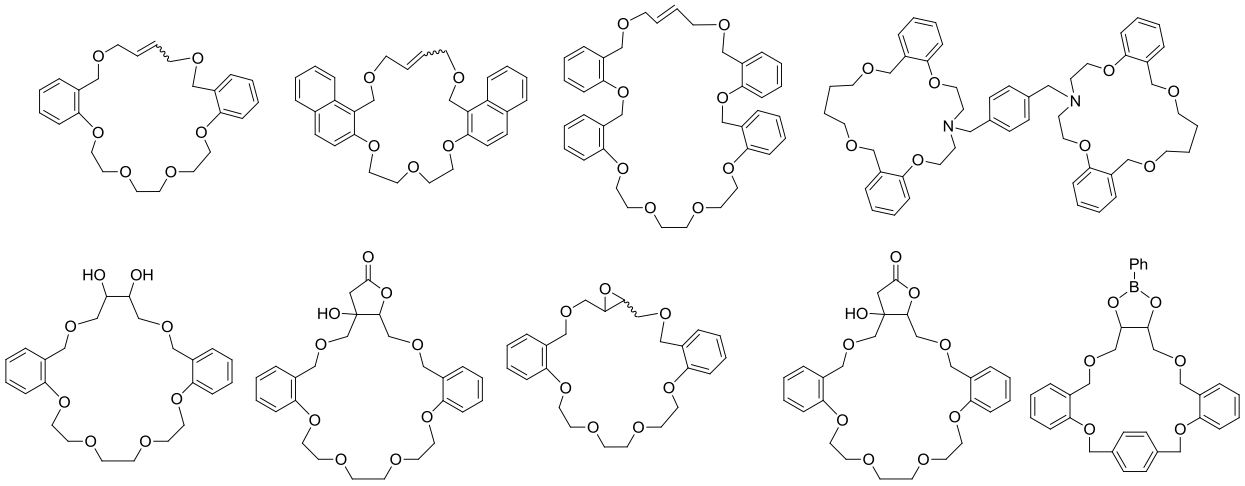
Conclusions

In summary the Chapter 1 described the synthesis of a library of new classes of crown ether-type polyether and aza-polyether macrocycles through the ring closing metathesis (RCM) reactions of suitable RCM precursors, which were assembled from various linkers/spacers and 2-hydroxy benzaldehydes.

The Chapter 1 described the modification of the olefinic unit present at the periphery of the crown ether/polyether macrocyclic systems obtained from the RCM reactions, using various others well-known synthetic transformations, such as epoxidation, oxidation and catalytic hydrogenation. Accordingly, the synthesis of a variety of polyether macrocycles possessing epoxide or α-hydroxy ketone or 1,2-diol functionalities at the periphery has been accomplished.
Furthermore, the Chapter 1 described the synthesis of homoallyl alcohol moiety-based and lactone-appended polyether macrocycles from the synthesized α-hydroxy ketone functionality installed polyether macrocycles involving the indium-mediated allylation and Reformatsky type reactions.

Overall, given the importance of the polyether macrocycles in various fields of biology and chemistry, the Chapter 1 reported the synthesis of several new functionally modified polyether macrocycles in good yields by involving simple starting materials and synthetic procedures. Currently our laboratory is in the process of exploring the applications of the synthesized functionalized crown ether-type polyether and aza-polyether macrocycles and further, the method investigated here is expected to be used by various research groups for synthesizing different classes of new polyether macrocycles.

Synthesis of periphery modified polyether macrocycles by exploiting the ring closing metathesis technique



All the compounds included in the Chapter 1 of this thesis are characterized by various characterization techniques including ^{1}H and ^{13}C NMR, IR, X-ray diffraction and HRMS. The structure and observed *E/Z* stereoselectivity of representative major/minor products were established from the single crystal X-ray structure analyses. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

Experimental Section

General. IR spectra of compounds were recorded as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of compounds were recorded on 400 MHz and100 MHz spectrometers, respectively, using TMS as an internal standard. Column chromatography was carried out on silica gel (100-200 mesh) or neutral Al_2O_3. Reactions were carried out in anhydrous solvents under a nitrogen atmosphere wherever required. Solutions were dried using anhydrous Na_2SO_4. Reagents/solvents were added to the reaction flask with the help of a syringe. Thin layer chromatography (TLC

analysis) was performed on silica plates or neutral Al_2O_3 plates and components were visualized by observation under iodine. Isolated yields of all the products were reported (yields were not optimized). The ring closing metathesis products were isolated as a mixture of *E*/Z diastereomers and $^1H/^{13}C$ data given here for the major isomer present in the mixture (selectively picked up) and in some cases, the $^1H/^{13}C$ data given for both the diastereomers. Ratios of diastereomers were determined from the ^1H and ^{13}C NMR spectra of crude reaction mixtures or after isolation. Compounds **32a**,**b**,[21a] **32c**,**d**,[21b] **32i**,**ia**,[21c], **32j**,[21d] **32k**,[22a] **32l**,[22b] **32la**,[22c] **32m**,[23a] **32n**,[23b] **32na**,[23c] **32p**,[23d] **32q**,**r**[23e] **32s**,[24a] **32t**,[24b] **33q**,**r**,[24c] **44a**,**b**,[24d,e] **45a**,**b**, [24d,e] **44c**,[24f] **45c**,[24f] **48a,b**,[25a] are reported in the literature.

General Procedure for Synthesis of *bis*-aldehydes 32. To a round-bottom flask was added the corresponding phenol derivative (12 mmol) in anhydrous DMF (20 mL) followed by anhydrous K_2CO_3 (20 mmol, 2.78 g) and the RB flask was dipped in to a preheated oil bath (80 ^oC) and stirred at 80 ^oC for15 min. After 15 min, the temperature of the oil bath was raised to 110 ^oC. Then, to the hot reaction mixture, alkyl dibromide or alkyl dichloride (5mmol) was added in one portion. The resulting reaction mixture was stirred at 110 ^oC for 12 h and after this period the RB flask was allowed to cool to rt. Next the reaction mixture was poured on to crushed ice (50-75 g). Then, the solid compound (*bis*-aldehyde) that formed is filtered through a filtration funnel and used without further purification (in case, if *bis*-aldehyde is liquid; then, the mixture (after adding water) was extracted by using ethyl acetate (3 X 10 mL) and the combined organic layers were concentrated and the crude reaction mixture was used after purification by column chromatography on silica gel (EtOAc/Hexanes) in the next step).

General procedure for the synthesis of *bis*-alcohols 33a-u, 50a-c and 53b. To a mixture of the corresponding *bis*-aldehyde (3 mmol) in ethanol (7 mL) was added $NaBH_4$ (10 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 30 min. After this period, the reaction mixture was poured on to cold water (20 mL) or crushed ice. Then, the solid compound (*bis*-alcohol) is filtered through a filtration funnel and used without further purification. (In case, if the corresponding *bis*-alcohol product is liquid; the mixture (after adding water) was extracted by using ethyl acetate (3 X10 mL) and the combined organic layers were concentrated and crude reaction mixture was used as such in the next step without further purification.

General procedure for the synthesis of compounds 34a-u, 51a-c and 53c. To a mixture of the corresponding diol compound (1 mmol) in dry THF (3 mL) was added NaH (4 mmol, 55-60% suspension in mineral oil) at room temperature. The mixture was stirred at room temperature for 10 min and then, allyl bromide (5 mmol) was added. The resulting mixture was stirred for 20 h at room temperature. After this period, few drops of EtOH was added and stirred for 10 min and then, the resulting mixture was poured on to water (20 mL) and was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated and the resulting crude reaction mixture was purified by silica gel column chromatography by using EtOAc/Hexanes to afford the corresponding *O*-allylated product.

General procedure for the synthesis of compounds 49a-c. The potassium salt of salicylaldehyde **48aA** (30 mmol) was dissolved in dry DMF (30 mL) and then, to this DMF solution, an appropriate alkyl halide **48** was added. Then, the reaction mixture was heated at 110 ^oC for 12 h. After this period, the reaction mixture was cooled to room temperature, and the reaction mixture was poured on to crushed ice. Then, the solid compound was filtered through a filtration funnel and used without further purification. (In case, if the *bis*-aldehyde is liquid; the mixture was extracted with ethyl acetate (3 X 10 mL) and used in the next step after purification by column chromatography on silica gel (EtOAc/Hexanes).

General procedure for the synthesis of compounds 46a-c. To a solution of allyl alcohol (1.5 mmol), dicarboxylic acid **45** (0.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.80 mmol) in CH_2Cl_2 (2.5 mL) was added 1,3-dicyclohexylcarbodiimide (1.5 mmol) in small fractions. The reaction mixture was stirred at room temperature for 2 h. The resulting pale yellow suspension was filtered through filtration funnel. The filtrate was concentrated and purified by silica gel column chromatography (20% EtOAc/Hexanes) to give the desired product **46**.

General procedure for the ring closing metathesis (RCM) reaction and synthesis of macrocycles 35a-w, 47a-c, 52a-c, 53d and 56. A solution of the corresponding substrate having two terminal olefins (0.25 mmol) in anhydrous CH_2Cl_2 (7 mL) and Grubbs's catalyst (1^{st} or 2^{nd} generation, 2.5-5 mol%)) was refluxed for the time indicated in the Tables/Schemes. Then, the mixture was concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (Hexanes/EtOAc) to afford the corresponding macrocyclic compound as a

mixture of *E*/*Z* isomers (ring closing metathesis product, see the corresponding Tables/Schemes for specific entries).

General procedure for the hydrogenation reaction and the synthesis of macrocycles 57a-c. To the solution of RCM products (**35b,c,k**) in anhydrous THF (2 mL) was added Pd/C (10 mol%). The reaction mixture was stirred at room temperature overnight under H_2 atmosphere (1 atm). After completion of the reaction, the reaction mixture was filtered by using a layer of celite pad and the filtrate was evaporated under vacuum and the resulting crude reaction mixture was purified by silica gel column chromatography, which gave the compounds **57a-c**, respectively.

General procedure for the synthesis of epoxide functionality appended macrocyclic systems 59a-d. 70 % *m*CPBA was added to the solution of substrate **35** (0.25 mmol) in CH_2Cl_2 (2 mL) and the reaction mixture was refluxed for the required time (see the corresponding Table/Scheme for the specific entries) and then, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4. Removal of solvent in vacuum followed by silica gel column chromatography gave the compound **59a-d** in pure form as a mixture of diastereomers.

General procedure for α-hydroxy ketone functionality appended macrocyclic systems 60a-j. A solution of the corresponding substrate having two terminal olefins **34/46** (0.5 mmol) in CH_2Cl_2 (14 mL) and Grubbs's catalyst (I or II generation, 2.5-5 mol%) was refluxed for appropriate time (see the corresponding Table/Scheme for the specific entries). Then, the solvent was removed under vacuum and to the resulting crude mixture was added EtOAc (3 mL), CH_3CN (3 mL) and H_2O (1 mL) followed by oxone® (5 equiv) and $NaHCO_3$ (2.5 equiv). Next, the reaction mixture was stirred at rt for 1 h and after this period, the reaction mixture was diluted with water and extracted with EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuum and the crude mixture was purified by silica gel column chromatography (EtOAc/Hexanes), to afford the corresponding α-hydroxy ketone functionality appended macrocycle (see the corresponding Table/Scheme for the specific entries).

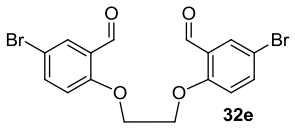
Procedure for the synthesis of macrocyclic systems 61a,b. To a solution of the corresponding substrate **60** (0.12 mmol) in anhydrous THF (2 mL) was added allyl bromide (4 equiv) followed by indium metal powder (2 equiv) with vigorous stirring. The reaction mixture was stirred at rt

for 24 h. After this period, the reaction mixture was diluted with water and extracted with EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuum and purification of the crude reaction mixture by silica gel column chromatography (EtOAc/Hexanes) afforded the corresponding allylated compound as a mixture of diastereomers (see the corresponding Table/Scheme for the specific entries).

Procedure for the synthesis of lactone appended macrocyclic systems 62a,b. To a solution of the corresponding substrate **60** (0.12 mmol) in dry THF (2 mL) was added ethyl bromoacetate (4 equiv) followed by indium powder (2 equiv) with vigorous stirring. The reaction mixture was stirred at rt for 24 h. After this period, the reaction mixture was diluted by adding water and extracted with EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuum and the crude mixture was purified by silica gel column chromatography (EtOAc/Hexanes), which afforded the corresponding compound **62** (see the corresponding Table/Scheme for the specific entries).

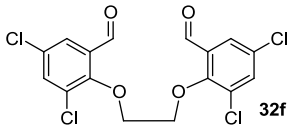
General procedure for the synthesis of macrocyclic systems 63a-g having *syn*-1,2-dihydroxy functionality. A solution of the corresponding substrate having two terminal olefins **34/46** (0.50 mmol) in CH_2Cl_2 (14 mL) and Grubbs's catalyst (I or II generation, 2.5-5 mol %) was refluxed for an appropriate time (see the Table/Scheme for specific entry). Then, the solvent was removed under vacuum and the resultant crude reaction mixture (macrocyclic olefin) was used as such for the next step. Subsequently, in a another RB flask, a suspension of $NaIO_4$ (1.5 equiv) in H_2O (0.3 mL) was treated with $CeCl_3 \bullet 7H_2O$ (0.1 equiv) and heated gently until the reaction colour was bright yellow, at this point the suspension was diluted with MeCN (3 mL) and cooled to 0 °C. Then, to this yellow suspension was added the macrocyclic olefin obtained in the first step prepared as a solution (in 3 mL of EtOAc). Then, the combined organic reaction mixture was stirred at 0 °C until the oxidation reaction was complete (approximately 30 min). After this, the reaction was quenched with the addition of solid Na_2SO_3 and Na_2SO_4 and stirred for 10 min. Then, the solution was filtered through filtration funnel and the filtrate was dried over anhydrous Na_2SO_4, concentrated under vacuum and the crude mixture was purified by silica gel column chromatography (EtOAc/Hexanes), to afford the corresponding macrocyclic system **63** as a mixture of diastereomers (see the corresponding Table/Scheme for the specific entries).

6,6'-(Ethane-1,2-diylbis(oxy))bis(3-bromobenzaldehyde) (32e): Following the general procedure, **32e** was obtained as a brown solid (3.83 g, 75%); mp 176-178 ^{o}C; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2921, 2879, 1677, 1589, 1474 and 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6): δ_H 10.20 (2 H, s), 7.77 (2 H, s), 7.56-7.52 (2 H, m), 6.88 (2 H, dd, J_1 = 8.4, J_2 = 1.4 Hz), 4.39 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ_C 187.7, 159.5, 138.3, 131.0, 126.2, 114.8, 114.1, 67.1; HRMS (ESI): MNa^+, found 448.8981. $C_{16}H_{12}Br_2NaO_4$ requires 448.9000.



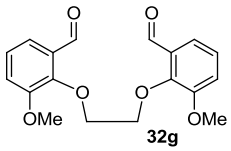
32e

2,2'-(Ethane-1,2-diylbis(oxy))bis(3,5-dichlorobenzaldehyde) (32f): Following the general procedure, **32f** was obtained as a brown solid (4.13 g, 85%); mp 162-164 ^{o}C; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2965, 1688, 1585, 1482 and 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.41 (2 H, s), 7.74 (2 H, d, J = 2.6 Hz), 7.65 (2 H, d, J = 2.6 Hz), 4.51 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 187.8, 155.9, 135.8, 131.4, 131.0, 129.7, 127.3, 74.1; HRMS (ESI): MNa^+, found 428.9215. $C_{16}H_{10}Cl_4NaO_4$ requires 428.9231.



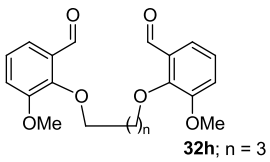
32f

2,2'-(Ethane-1,2-diylbis(oxy))bis(3-methoxybenzaldehyde) (32g): Following the general procedure, **32g** was obtained as a brown solid (2.97 g, 75%); mp 118-120 ^{o}C; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2966, 2839, 1687, 1586, 1482 and 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.53 (2 H, s), 7.44 (2 H, t, J = 4.7 Hz), 7.17 (4 H, d, J = 4.5 Hz), 4.51 (4 H, s), 3.89 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.5, 152.8, 151.1, 130.0, 124.3, 119.2, 117.9, 73.1, 56.0; HRMS (ESI): MNa^+, found 353.0990. $C_{18}H_{18}NaO_6$ requires 353.1001.



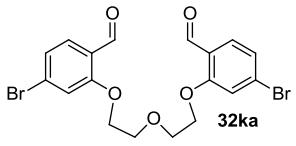
32g

2,2'-(Butane-1,4-diylbis(oxy))bis(3-methoxybenzaldehyde) (32h): Following the general procedure, **32h** was obtained as a brown solid (3.52 g, 82%); mp 115-117 ^{o}C; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2974, 2853, 1686, 1668, 1484 and 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.47 (2 H, s), 7.44-7.42 (2 H, m), 7.16-7.14 (4 H, m), 4.22 (4 H, s), 3.90 (6 H, s), 2.05 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.3, 153.0, 151.8, 130.0, 124.1, 119.1, 118.0, 74.5, 56.0, 26.7; HRMS (ESI): MNa^+, found 381.1304. $C_{20}H_{22}NaO_6$ requires 381.1314.

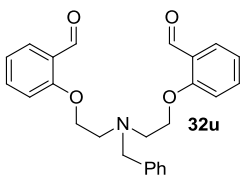


32h; n = 3

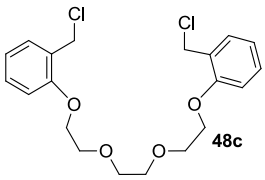
6,6'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(3-bromobenzaldehyde) (32ka): Following the general procedure A, **32ka** was obtained after filtration through a filtration funnel as a brown solid (4.127 g, 88%); mp: 141-143 ^{o}C; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2949, 1681, 1591, 1478, 1241, 1123, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (2 H, s), 7.93 (2 H, d, *J* = 2.6 Hz), 7.62 (2 H, dd, *J* = 6.24, 2.6 Hz), 6.91 (2 H, d, *J* = 8.8 Hz), 4.27 (4 H, t, *J* = 5.5 Hz), 3.99 (4 , t, *J* = 4.56 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 159.9, 138.3, 131.1, 126.3, 114.9, 114.0, 69.8, 68.6; HRMS (ESI): MNa^+, found 492.9256. $C_{18}H_{16}Br_2O_5Na$ requires 492.9262.



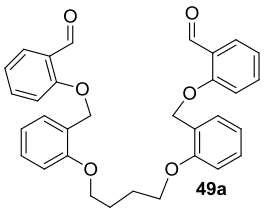
2,2'-(((Benzylazanediyl)bis(ethane-2,1-diyl))bis(oxy))dibenzaldehyde (32u): Following the general procedure, **32u** was obtained as a colourless liquid (3.63 g, 75%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2942, 2863, 1685, 1598 and 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.47 (2 H, s), 7.83 (2 H, dd, J_1 = 5.9, J_2 = 1.8 Hz), 7.52 (2 H, t, *J* = 7.3 Hz), 7.38-7.27 (5 H, m), 7.03 (2 H, t, *J* = 7.5 Hz), 6.92 (2 H, d, *J* = 8.3 Hz), 4.18 (4 H, t, *J* = 5.7 Hz), 3.87 (2 H, s), 3.15 (4 H, t, *J* = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 189.7, 161.0, 139.1, 136.0, 128.6, 128.5, 128.5, 127.3, 124.9, 120.8, 112.4, 67.3, 60.1, 53.5; HRMS (ESI): MH^+, found 404.1866. $C_{25}H_{26}NO_4$ requires 404.1862.



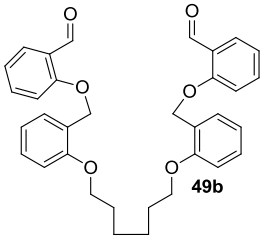
Procedure for the synthesis of 1,2-bis(2-(2-(chloromethyl)phenoxy)ethoxy)ethane (48c): To a solution of ((((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (5 mmol) in dry DCM (15 mL) was added $SOCl_2$ (10 mmol) drop wise at room temperature and the reaction mixture was stirred for 3 h. Then, the mixture was concentrated in vacuum and used as such (without further purification) in the next step. The compound **48c** was obtained as a brown colour liquid (1.79 g, 90%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2923, 2873, 1602, 1453 and 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33 (2 H, dd, J_1 = 7.1, J_2 = 1.5 Hz), 7.27-7.23 (2 H, m), 6.92 (2 H, t, *J* = 7.5 Hz), 6.86 (2 H, d, *J* = 8.1 Hz), 4.65 (4 H, s), 4.17 (4 H, t, *J* = 5.0 Hz), 3.89 (4 H, t, *J* = 4.7 Hz), 3.76 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.6, 130.6, 130.0, 126.2, 121.0, 112.1, 71.1, 69.7, 68.2, 41.7; HRMS (ESI): MNa^+, found 421.0944. $C_{20}H_{24}Cl_2NaO_4$ requires 421.0949.



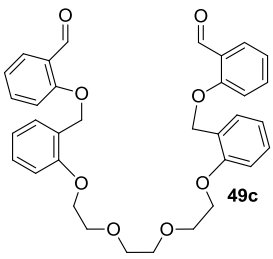
2,2'-((((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methylene))bis(oxy)) dibenzaldehyde (49a): Following the general procedure, **49a** was obtained as a brown solid (2.16 g, 85%); mp 154-156 ^{o}C; R_f (20% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 2864, 1686, 1598, 1482, 1379 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.54 (2 H, s), 7.83 (2 H, d, J = 7.6 Hz), 7.49 (2 H, t, J = 8.3 Hz), 7.43 (2 H, d, J = 7.1 Hz), 7.29 (2 H, t, J = 7.6 Hz), 7.06-6.95 (6 H, m), 6.88 (2 H, d, J = 8.2 Hz), 5.19 (4 H, s), 4.06 (4 H, s), 1.94 (4 H, s);^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.0, 161.4, 156.2, 135.9, 129.4, 128.8, 128.3, 125.2, 124.4, 120.9, 120.7, 113.3, 111.1, 67.4, 66.1, 26.0; HRMS (ESI): MNa^+, found 533.1934. $C_{32}H_{30}NaO_6$ requires 533.1940.



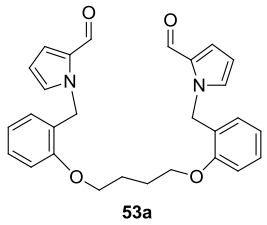
2,2'-((((Hexanes-1,6-diylbis(oxy))bis(2,1-phenylene))bis(methylene))bis(oxy)) dibenzaldehyde (49b): Following the general procedure, **49b** was obtained as brown solid (2.02 g, 75%); mp 117-119 ^{o}C; R_f (20% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 2921, 2864, 1686, 1598, 1482 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.55 (2 H, s), 7.83 (2 H, d, J = 7.6 Hz), 7.50 (2 H, t, J = 7.1 Hz), 7.42 (2 H, d, J = 7.1 Hz), 7.30 (2 H, t, J = 7.9 Hz), 7.07 (2 H, d, J = 8.3 Hz), 7.02-6.59 (4 H, m), 6.89 (2 H, d, J = 8.1 Hz), 5.21 (4 H, s), 3.99 (4 H, t, J = 6.3 Hz), 1.77-1.74 (4 H, m), 1.49-1.47 (4H, m);^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.0, 161.5, 156.4, 135.9, 129.4, 128.7, 128.3, 125.2, 124.5, 120.8, 120.5, 113.3, 111.2, 67.8, 66.1, 29.1, 25.9; HRMS (ESI): MNa^+, found 561.2249. $C_{34}H_{34}NaO_6$ requires 561.2253.



2,2'-((((((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(methylene))bis(oxy))dibenzaldehyde (49c): Following the general procedure, **49c** was obtained as a brown solid (2.22 g, 78%); mp 58-60 ^{o}C; R_f (20% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 2932, 1688, 1598, 1456 and 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.55 (2 H, s), 7.84 (2 H, dd, J_1 = 6.2, J_2 = 1.8 Hz), 7.53-7.49 (2 H, m), 7.43 (2 H, d, J = 7.6 Hz), 7.32-7.28 (2 H, m), 7.10 (2 H, d, J = 8.2 Hz), 7.03-6.98 (4 H, m), 6.90 (2 H, d, J = 8.2 Hz), 5.24 (4 H, s), 4.17 (4 H, t, J = 4.6 Hz), 3.83 (4 H, t, J = 4.9 Hz), 3.65 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.0, 161.4, 156.1, 135.9, 129.4, 128.7, 128.2, 125.2, 124.7, 121.0, 120.8, 113.4, 111.6, 70.9, 69.7, 67.8, 65.9; HRMS (ESI): MNa^+, found 593.2158. $C_{34}H_{34}NaO_8$ requires 593.2151.

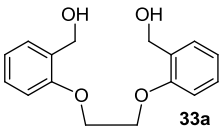


Procedure for the synthesis of compound 53a. To a mixture of **48a** (1 mmol) in dry DMF (2 mL) was added NaH (4 mmol, 55-60 % suspension in mineral oil) at room temperature. The mixture was stirred at room temperature for 15 min and then, 1*H*-pyrrole-2-carbaldehyde (2 mmol) was added to the reaction mixture. Next, the resulting mixture was stirred for 20 h at room temperature. After this period, few drops of EtOH was added and stirred for 10 min and then, the reaction mixture was poured on to water (20 mL) and extracted with ethyl acetate (3 X 10 mL).The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated and the crude reaction mixture was purified by silica gel column chromatography (30% EtOAc /Hexanes) to afford the compound **53a**, as a colourless solid (322 mg, 73%); mp 125-127 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2924, 2854, 1663, 1604, 1452 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.58 (2 H, s), 7.28-7.24 (3 H, m), 6.98-6.86 (9 H, m), 6.25-6.23 (2 H, m), 5.59 (4 H, s), 4.09 (4 H, br. s), 2.00 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 179.4, 156.2, 131.7, 129.1, 128.8, 126.0, 124.5, 120.7, 111.0, 109.8, 67.4, 47.2, 26.0; HRMS (ESI): MH^+, found 457.2126. $C_{28}H_{29}N_2O_4$ requires 457.2127.



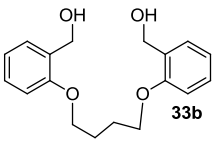
53a

((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))dimethanol (33a): Following the general procedure, **33a** was obtained after filtration through a filtration funnel as a white solid, (0.674 g, 82%); mp: 125-127 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3399, 2233, 1600, 1490, 1028 and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.36-7.32 (2 H, m), 7.24-7.19 (2 H, m), 6.98-6.87 (4 H, m), 4.61 (4 H, s), 4.34 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 155.9, 130.2, 128.5, 128.3, 121.0, 111.4, 67.7, 60.2; HRMS (ESI): MNa^+, found 297.1115. $C_{16}H_{18}O_4Na$ requires 297.1103. (In ^1H NMR OH protons could not be detected).



33a

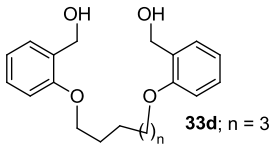
((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (33b): Following the general procedure, **33b** was obtained after filtration through a filtration funnel as a white solid, (1.11 g, 92%); mp: 91-93 ^oC ; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3398, 2231, 1601, 1491, 1027 and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.22 (4 H, m), 6.93 (2 H, t, J = 7.3 Hz), 6.86 (2 H, d, J = 8.1 Hz), 4.65 (4 H, s), 4.09 (4 H, s), 2.49 (2 H, br s), 2.01 (4 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7,



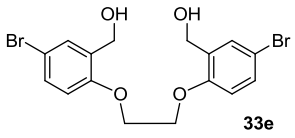
33b

129.2, 128.9, 128.8, 120.8, 111.1, 67.4, 61.9, 26.2; HRMS (ESI): MNa^+, found 325.1427. $C_{18}H_{22}O_4Na$ requires 325.1416.

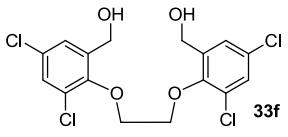
((Hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol (33d): Following the general procedure, **33d** was obtained after filtration through filtration funnel as a brown solid, (1.036 g, 80%); mp: 60-62 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3396, 2231, 1602, 1493, 1030 and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26-7.22 (4 H, m), 6.91 (2 H, t, J = 7.4 Hz), 6.85 (2 H, d, J = 8.1 Hz), 4.65 (4 H, s), 4.02 (4 H, t, J = 6.2 Hz), 2.44 (2 H, br s), 1.86-1.83 (4 H, m), 1.57-1.54 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 129.2, 128.9, 128.7, 120.6, 111.1, 67.7, 62.2, 29.2, 25.9; HRMS (ESI): MNa^+, found 353.1737. $C_{20}H_{26}O_4Na$ requires 353.1729.



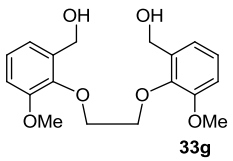
((Ethane-1,2-diylbis(oxy))bis(4-bromo-2,1-phenylene))dimethanol (33e): Following the general procedure, **33e** was obtained as a brown solid (955 mg, 74%); mp 155-157 ^oC; R_f (30% EtOAc/Hexanes) 0.52; IR (thin film): ν_{max} 3301, 2922, 2852, 1484 and 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.43 (2 H, s), 7.34 (2 H, d, J = 7.9 Hz), 6.94 (2 H, d, J = 8.6 Hz), 4.43 (4 H, s), 4.26 (4 H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 154.6, 133.6, 130.5, 129.6, 114.2, 112.8, 67.3, 57.8; HRMS (ESI): MNa^+, found 452.9300. $C_{16}H_{16}Br_2NaO_4$ requires 452.9313. Two OH protons were not appeared in the ^1H NMR.



((Ethane-1,2-diylbis(oxy))bis(3,5-dichloro-2,1-phenylene))dimethanol (33f): Following the general procedure, **33f** was obtained as a brown solid (903 mg, 70%); mp 139-141 ^oC; R_f (30% EtOAc/Hexanes) 0.52; IR (thin film): ν_{max} 3409, 2234, 1636, 1442 and 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ_H 7.38 (2 H, br. s), 7.30 (2 H, br. s), 4.73 (4 H, s), 4.58 (2 H, br. s), 4.35 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ_C 150.9, 138.4, 129.7, 128.7, 128.0, 127.6, 72.5, 59.4; HRMS (ESI): MNa^+, found 432.9522. $C_{16}H_{14}Cl_4NaO_4$ requires 432.9544.

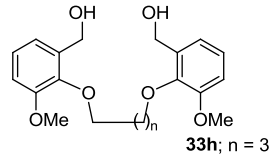


((Ethane-1,2-diylbis(oxy))bis(3-methoxy-2,1-phenylene))dimethanol (33g): Following the general procedure, **33g** was obtained as a brown colour solid (841 mg, 85%); mp 58-60 ^oC; R_f (30% EtOAc/Hexanes) 0.52; IR (CH_2Cl_2): ν_{max} 3401, 2936, 1586, 1480 and 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.06-7.03 (2 H,



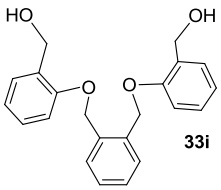
m), 6.93-6.88 (4 H, m), 4.68 (4 H, s), 4.41 (4 H, s), 3.85 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.4, 145.8, 134.8, 124.4, 121.8, 112.3, 72.6, 61.4, 55.8; m/z (CI) 334 (40, M^+).

((Butane-1,4-diylbis(oxy))bis(3-methoxy-2,1-phenylene))dimethanol (33h): Following the general procedure, **33h** was obtained as a brown solid (773 mg, 72%); mp 110-112 ^oC; R_f (30% EtOAc/Hexanes) 0.52; IR (CH_2Cl_2): ν_{max} 3335, 2869, 1471, 1455 and 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.06 (2 H, t, J = 7.9 Hz), 6.96-6.88 (4 H, m), 4.72 (4 H, d, J = 5.9 Hz), 4.14 (4 H, t, J = 5.8 Hz), 3.86 (6 H, s), 2.61 (2 H, t, J = 6.1 Hz), 2.03-2.01 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.5, 146.1, 134.7, 124.1, 120.8, 112.2, 73.0, 61.5, 55.8, 27.0; m/z (CI) 362 (25, M^+).



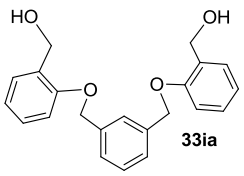
33h; n = 3

(((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (33i): Following the general procedure, **33i** was obtained after filtration through a filtration funnel as a brown solid, (0.903 g, 88%); mp: 95-97 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3364, 3067, 2877, 1602, 1589 and 730 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.52-7.50 (2 H, m), 7.38-7.36 (4 H, m), 7.22 (2 H, t, J = 7.7 Hz), 6.97-6.92 (4 H, m), 5.19 (4 H, s), 4.66 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 155.9, 134.9, 129.9, 128.9, 128.5, 128.4, 120.9, 111.4, 67.8, 60.5. HRMS (ESI): MH^+, found 351.1602. $C_{22}H_{23}O_4$ requires 351.1596. (In ^{1}H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).



33i

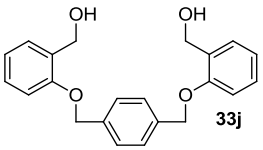
(((1,3-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (33ia): Following the general procedure, **33ia** was obtained after filtration through a filtration funnel as a brown solid, (0.882 g, 84%); mp: 82-84 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3364, 2921, 1602, 1589, 1128, 1491 and 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1 H, s), 7.40-7.30 (5 H, m), 7.26-7.22 (2 H, m), 6.97-6.90 (4 H, m), 5.12 (4 H, s), 4.71 (4 H, s), 2.69 (2 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 137.4, 129.4, 128.9, 128.9, 126.8, 125.7, 121.1, 111.6, 69.7, 61.8; HRMS (ESI): MNa^+, found 373.1425. $C_{22}H_{22}O_4Na$ requires 373.1416.



33ia

(((1,4-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (33j): Following the general procedure, **33j** was obtained as a colourless solid (865 mg, 82%); mp 134-136 ^oC; R_f

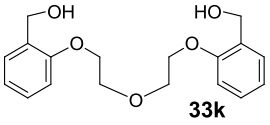
(30% EtOAc/Hexanes) 0.52; IR (thin film): ν_{max} 3332, 2922, 1602, 1453 and 750 cm^{-1}; ^1H NMR



33j

(400 MHz, $CDCl_3$ + DMSO-d_6): δ_H 7.40-7.17 (8 H, m), 6.94-6.86 (4 H, m), 5.07 (4 H, br. s), 4.68 (4 H, br. s), 3.16 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ_C 156.1, 136.7, 129.8, 128.5, 128.4, 127.5, 120.9, 111.5, 69.6, 61.1; HRMS (ESI): MNa^+, found 373.1404. $C_{22}H_{22}NaO_4$ requires 373.1416.

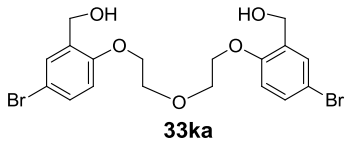
(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (33k): Following the general procedure, **33k** was obtained after filtration through a filtration funnel as a brown solid,



33k

(0.858 g, 90%); mp: 52-54 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3405, 2939, 2365, 1687, 1492 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25-7.20 (4 H, m), 6.92 (2 H, t, J = 7.4 Hz), 6.84 (2 H, d, J = 8.8 Hz), 4.61 (4 H, s), 4.20-4.18 (4 H, m), 4.03 (2 H, br s), 3.89-3.86 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 130.2, 129.7, 129.0, 121.3, 112.2, 69.8, 67.8, 61.8. HRMS (ESI): MNa^+, found 341.1374. $C_{18}H_{22}O_5Na$ requires 341.1365.

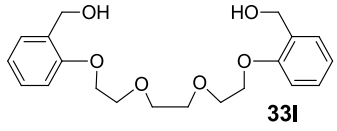
(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(3-bromo-6,1-phenylene))dimethanol (33ka): Following the general procedure, **33ka** was obtained after filtration through a filtration funnel as a brown solid, (1.248 g, 88%); mp: 88-90 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max}



33ka

3401, 2931, 1453, 1242, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.28-7.12 (4 H, m), 6.59-6.54 (2 H, m), 4.42 (4 H, s), 4.10 (2 H, s), 3.98 (4 H, s), 3.72 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 155.4, 132.6, 131.4, 130.9, 113.6, 113.3, 69.6, 67.9, 60.2; HRMS (ESI): MNa^+, found 496.9576. $C_{18}H_{20}Br_2O_5Na$ requires 496.9575. (In ^1H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).

((((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (33l): Following the general procedure, **33l** was obtained after purification by column

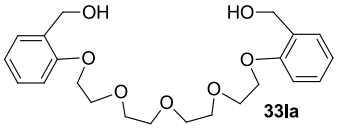


33l

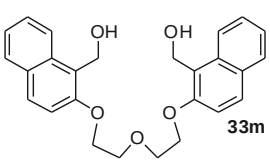
chromatography on silica gel (EtOAc:Hexanes = 40:60) as colourless liquid; (0.955 g, 88%); R_f (40% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3414, 2874, 1602, 1492 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (4 H, m), 6.95 (2 H, t, J = 7.4 Hz), 6.88 (2 H, d, J = 8.4 Hz), 4.64 (4 H, s), 4.20-4.18 (4 H, m), 3.87-3.85 (4 H, m), 3.73 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1,

130.2, 129.3, 128.9, 121.2, 112.3, 70.7, 69.6, 67.8, 62.1; HRMS (ESI): MNa^+, found 385.1639. $C_{20}H_{26}O_6Na$ requires 385.1627. (In ^1H NMR OH protons could not be detected).

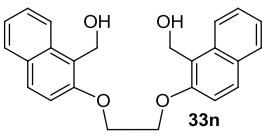
(((((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (33la): Following the general procedure, **33la** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a colorless liquid; (1.12 g, 92%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3402, 2935, 1455, 1242, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (4 H, m), 6.97-6.87 (4 H, m), 4.65 (4 H, s), 4.20-4.18 (4 H, m), 3.86-3.84 (4 H, m), 3.72-3.66 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 130.2, 129.3, 128.9, 121.2, 112.2, 70.6, 70.5, 69.6, 67.8, 61.9; HRMS (ESI): MNa^+, found 429.1894. $C_{22}H_{30}O_7Na$ requires 429.1889. (In ^1H NMR OH protons could not be detected).



(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(naphthalene-2,1-diyl))dimethanol (33m): Following the general procedure, **33m** was obtained after filtration through a filtration funnel as a brown solid, (1.065 g, 85%); mp: 124-126 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3401, 2934, 1454, 1240, and 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 8.11 (2 H, d, J = 8.5 Hz), 7.77 (4 H, d, J = 9.1 Hz), 7.48 (2 H, t, J = 8.1 Hz), 7.35 (2 H, t, J = 7.8 Hz), 7.21 (2 H, d, J = 9.1 Hz), 5.11 (4 H, s), 4.35-4.33 (4 H, m), 3.95-3.93 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 154.2, 132.8, 129.8, 129.6, 128.3, 126.9, 123.9, 123.4, 123.3, 114.9, 70.1, 69.1, 55.1; HRMS (ESI): MNa^+, found 441.1680. $C_{26}H_{26}O_5Na$ requires 441.1678. (In ^1H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).

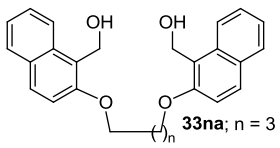


((Ethane-1,2-diylbis(oxy))bis(naphthalene-2,1-diyl))dimethanol (33n): Following the general procedure, **33n** was obtained as a brown solid (863 mg, 77%); mp 182-184 ^oC; R_f (30% EtOAc/Hexanes) 0.52; IR (thin film): ν_{max} 3325, 2923, 2354, 1592, 1446 and 749 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 8.09 (2 H, d, J = 8.6 Hz), 7.88 (2 H, d, J = 9.1 Hz), 7.84 (2 H, d, J = 8.1 Hz), 7.50 (2 H, t, J = 7.9 Hz), 7.45 (2 H, d, J = 9.1 Hz), 7.36 (2 H, t, J = 7.5 Hz), 4.95 (4 H, s), 4.47 (4 H, s), 2.51 (2 H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 154.1, 133.4, 130.1, 129.4, 128.6, 127.0, 124.4,

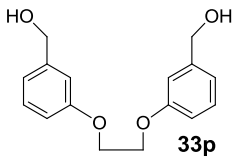


124.2, 122.9, 116.2, 69.2, 53.7; HRMS (ESI): MNa^+, found 397.1408. $C_{24}H_{22}NaO_4$ requires 397.1416.

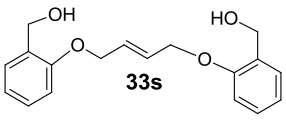
((Butane-1,4-diylbis(oxy))bis(naphthalene-2,1-diyl))dimethanol (3na): Following the general procedure, **33na** was obtained after filtration through a filtration funnel as a brown solid, (1.025 g, 85%); mp: 161-163 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3364, 2921, 1602, 1589, 1128, 1491 and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 8.17 (2 H, s), 7.97 (4H, s), 7.50-7.28 (6 H, m), 5.14 (4 H, s), 4.24 (4 H, s), 2.12 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 154.2, 133.1, 129.6, 129.0, 128.1, 126.6, 123.6, 123.5, 122.1, 114.7, 69.2, 54.8, 26.3. HRMS (ESI): MNa^+, found 425.1734. $C_{26}H_{26}O_4Na$ requires 425.1729. (In ^1H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).



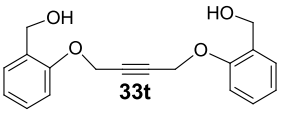
((Ethane-1,2-diylbis(oxy))bis(3,1-phenylene))dimethanol (33p): Following the general procedure, **33p** was obtained after filtration through filtration a funnel as a brown solid, (0.674 g, 82%); mp: 128-130 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3398, 2231, 1601, 1491, 1027 and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.29-6.74 (8 H, m), 4.54 (4 H, s), 4.25 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 158.7, 143.5, 129.3, 119.4, 113.5, 112.8, 66.4, 64.3; HRMS (ESI): MNa^+, found 297.1111. $C_{16}H_{18}O_4Na$ requires 297.1103. (In ^1H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).



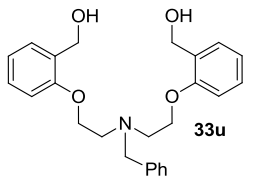
(*E*)-((But-2-ene-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (33s): Following the general procedure, **33s** was obtained after filtration through a filtration funnel as a brown solid, (0.774 g, 86%); mp: 95-96 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3353, 2918, 1602, 1489 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.37-6.82 (8 H, m), 6.05 (2 H, s), 4.62 (8 H, d, J = 3.1 Hz), 3.98 (2 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 160.4, 135.0, 132.9, 132.8, 132.7, 125.5, 116.1, 72.4, 64.8; HRMS (ESI): MNa^+, found 323.1270. $C_{18}H_{20}O_4Na$ requires 323.1259. (In ^1H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).



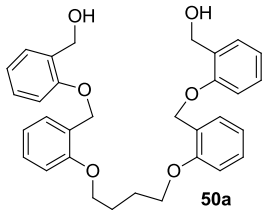
((But-2-yne-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (33t): Following the general procedure, **33t** was obtained after filtration through a filtration funnel as a brown solid, (0.795 g, 89%); mp: 96-98 ^{o}C; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3381, 2926, 1622, 1465 and 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.24 (2 H, d, J = 7.3 Hz), 7.12 (2 H, t, J = 7.8 Hz), 6.89 (2 H, t, J = 7.4 Hz), 6.81 (2 H, d, J = 8.6 Hz), 4.66 (4 H, s), 4.57 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 155.2, 130.0, 128.8, 128.6, 121.6, 111.9, 82.4, 61.2, 56.2; HRMS (ESI): MNa^+, found 321.1103. $C_{18}H_{18}O_4Na$ requires 321.1117. (In ^{1}H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).



Procedure for the synthesis of ((((benzylazanediyl)bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (33u): To a mixture of *bis*-aldehyde **32u** (1 mmol) in ethanol/THF (3 mL and 3 mL) was added $NaBH_4$ (10 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 min. After this period, the reaction mixture was poured on to cold water (20 mL). Then, the mixture was extracted using ethyl acetate (3 X 10 mL) and was purified by silica gel column chromatography by using (30% EtOAc/Hexanes) as a colourless liquid (930 mg, 92%); R_f (30% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 3381, 2922, 1602, 1492 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40-7.22 (9 H, m), 6.94 (2 H, t, J = 7.5 Hz), 6.84 (2 H, d, J = 8.1 Hz), 4.58 (4 H, s), 4.15 (4 H, t, J = 5.2 Hz), 3.81 (2 H, s), 3.01 (4 H, t, J = 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 137.5, 130.0, 129.4, 129.3, 129.0, 128.5, 127.4, 121.0, 111.8, 65.9, 61.9, 59.7, 53.7; HRMS (ESI): MH^+, found 408.2178. $C_{25}H_{30}NO_4$ requires 408.2175. Two OH protons were not appeared in the ^{1}H NMR.

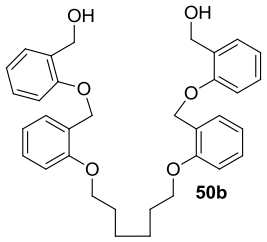


(((((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (50a): Following the general procedure, **50a** was obtained as a brown colour solid (1.38 g, 90%); mp 111-113 ^{o}C; R_f (30% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 3395, 2924, 1603, 1589, 1454 and 751cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42-7.26 (8 H, m), 7.01-6.89 (8 H, m), 5.13 (4 H, br. s), 4.69 (4 H, br. s), 4.07 (4 H, br. s), 2.77 (2 H, br. s), 1.95 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.6, 129.6, 129.5, 129.2,

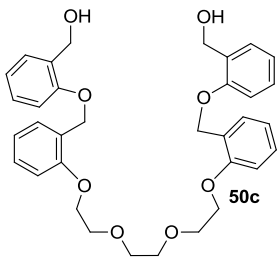


128.9, 128.8, 124.9, 120.8, 120.7, 111.7, 111.4, 67.7, 65.9, 62.5, 25.9; HRMS (ESI): MNa^+, found 537.2247. $C_{32}H_{34}NaO_6$ requires 537.2253.

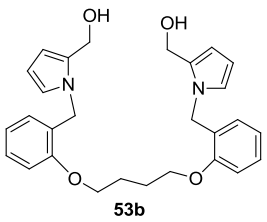
(((((Hexanes-1,6-diylbis(oxy))bis(2,1-phenylene))bis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (50b): Following the general procedure, **50b** was obtained as a brown colour solid (1.47 g, 91%); mp 74-76 ^oC; R_f (30% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 3401, 2927, 1603, 1589, 1454 and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.45-7.27 (8 H, m), 7.03-6.93 (8 H, m), 5.17 (4 H, br. s), 4.73 (4 H, br. s), 4.03 (4 H, br. s), 2.96 (2 H, br. s), 1.80 (4 H, br. s), 1.50 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.8, 129.7, 129.5, 129.2, 128.9, 128.8, 125.1, 120.8, 120.6, 111.7, 111.5, 68.1, 65.9, 62.4, 29.1, 25.8; HRMS (ESI): MH^+, found 543.2736. $C_{34}H_{39}O_6$ requires 543.2747.



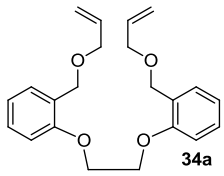
(((((((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (50c): Following the general procedure, **50c** was obtained as a colourless liquid (1.47 g, 74%); R_f (30% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 3401, 2927, 1589, 1288 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.42-7.25 (8 H, m), 7.02-6.91 (8 H, m), 5.15 (4 H, br. s), 4.69 (4 H, br. s), 4.16 (4 H, t, J = 5.1 Hz), 3.80 (4 H, t, J = 4.9 Hz), 3.59 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 156.6, 129.8, 129.5, 129.3, 128.8, 128.8, 125.3, 121.0, 120.8, 111.8, 111.8, 70.8, 69.6, 68.0, 65.9, 62.2; HRMS (ESI): MH^+, found 575.2634. $C_{34}H_{39}O_8$ requires 575.2645. Two OH protons were not appeared in the ^1H NMR.



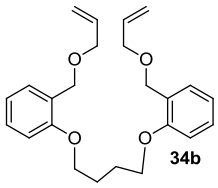
(1,1'-(((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methylene))bis(*1H*-pyrrole-2,1-diyl))dimethanol (53b): Following the general procedure, **53b** was obtained as a colourless solid (1.18 g, 83%); mp 113-115 ^oC; R_f (30% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 3388, 2924, 1601, 1493 and 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.28-7.24 (2 H, m), 6.91-6.86 (4 H, m), 6.68-6.65 (4 H, m), 6.17-6.11 (4 H, m), 5.21 (4 H, s), 4.52 (4 H s), 4.11 (4 H, s), 2.03 (4 H, br. s), 1.85 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.8, 131.9, 128.7, 127.7, 126.8, 123.2, 120.8, 110.9, 109.1, 107.1, 67.5, 56.7, 45.7, 26.1; HRMS (ESI): MNa^+, found 483.2256. $C_{28}H_{32}N_2NaO_4$ requires 483.2260.



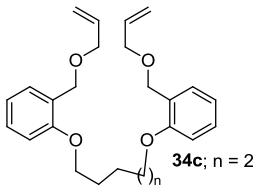
1,2-Bis(2-((allyloxy)methyl)phenoxy)ethane (34a): Following the general procedure, **34a** was obtained after as a colourless liquid (300 mg, 85%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2862, 1586, 1489, 1447 and 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (2 H, d, J = 7.0 Hz), 7.25 (2 H, t, J = 7.9 Hz), 6.98 (2 H, t, J = 7.3 Hz), 6.92 (2 H, d, J = 8.2 Hz), 5.98-5.88 (2 H, m), 5.31-5.12 (4 H, m), 4.55 (4 H, s), 4.34 (4 H, s), 4.05-4.02 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.1, 135.0, 128.9, 128.5, 127.4, 121.0, 116.8, 115.5, 71.5, 66.9, 66.9; HRMS (ESI): MNa^+, found 377.1723. $C_{22}H_{26}NaO_4$ requires 377.1729.



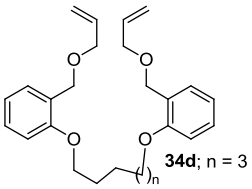
1,4-Bis(2-((allyloxy)methyl)phenoxy)butane (34b): Following the general procedure, **34b** was obtained as a colourless liquid (309 mg, 81%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2927, 1603, 1590, 1470 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.40 (2 H, d, J = 6.8 Hz), 7.23 (2 H, t, J = 8 Hz), 6.94 (2 H, t, J = 7.3 Hz), 6.84 (2 H, d, J = 8.2 Hz), 6.00-5.93 (2 H, m), 5.32 (2 H, dd, J_1 = 16.6, J_2 = 1.7 Hz), 5.18 (2 H, dd, J_1 = 9.8, J_2 = 1.5 Hz), 4.57 (4 H, s), 4.07-4.03 (8 H, m), 2.01-1.98 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.4, 135.1, 128.9, 128.6, 126.9, 120.5, 116.8, 111.1, 71.5, 67.5, 67.0, 26.2; HRMS (ESI): MNa^+, found 405.2029. $C_{24}H_{30}NaO_4$ requires 405.2042.



1,5-Bis(2-((allyloxy)methyl)phenoxy)pentane (34c): Following the general procedure, **34c** was obtained as a colourless liquid (340 mg, 86%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 1688, 1601, 1452 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.39 (2 H, d, J = 8 Hz), 7.23 (2 H, t, J = 5.9 Hz), 6.94 (2 H, t, J = 7.5 Hz), 6.84 (2 H, d, J = 8.1 Hz), 6.00-5.93 (2 H, m), 5.31 (2 H, dd, J_1 = 17.1, J_2 = 1.7 Hz), 5.17 (2 H, dd, J_1 = 10.2, J_2 = 1.6 Hz), 4.57 (4 H, s), 4.06 (4 H, td, J_1 = 5.6, J_2 = 1.45 Hz), 4.00 (4 H, t, J = 6.3 Hz), 1.89-1.84 (4 H, m), 1.71-1.64 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.5, 135.1, 128.9, 128.5, 127.0, 120.4, 116.8, 111.1, 71.5, 67.8. 67.0, 29.1, 22.9; HRMS (ESI): MNa^+, found 419.2194. $C_{25}H_{32}NaO_4$ requires 419.2198.

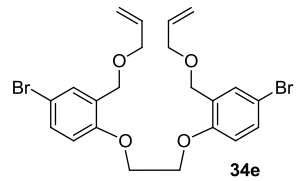


1,6-Bis(2-((allyloxy)methyl)phenoxy)Hexanes (34d): Following the general procedure, **34d** was obtained as a colourless liquid (348 mg, 85%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2938, 1603, 1455, 1242 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.39 (2 H, d, J = 7.4 Hz), 7.22 (2 H, t, J = 7.4 Hz), 6.93 (2 H, t, J = 7.4 Hz), 6.83 (2 H, d, J = 8.2 Hz), 5.99-5.93 (2 H,

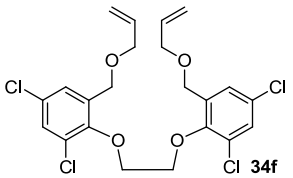


m), 5.33 (2 H, dd, J_1 = 17.2, J_2 = 1.7 Hz), 5.17 (2 H, dd, J_1 = 10.2, J_2 = 1.6 Hz), 4.56 (4 H, s), 4.06 (4 H, td, J_1 = 5.4, J_2 = 1.4 Hz), 3.97 (4 H, t, J = 6.4 Hz), 1.82 (4 H, t, J = 6.4 Hz), 1.56-1.52 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.6, 135.1, 128.9, 128.5, 127.0, 120.4, 116.8, 111.1, 71.5, 67.8, 67.0, 29.3, 26.0; HRMS (ESI): MNa^+, found 433.2353. $C_{26}H_{34}NaO_4$ requires 433.2355.

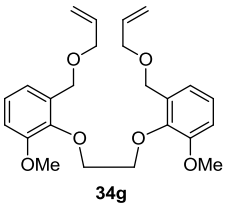
1,2-Bis(2-((allyloxy)methyl)-4-bromophenoxy)ethane (34e): Following the general procedure, **34e** was obtained as a brown solid (372 mg, 73%); mp 100-102 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2911, 2949, 2361, 1485 and 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47 (2 H, d, J = 2.5 Hz), 7.27 (2 H, dd, J_1 = 7.5, J_2 = 2.5 Hz), 6.69 (2 H, d, J = 8.7 Hz), 5.90-5.80 (2 H, m), 5.22 (2 H, dd, J_1 = 17.2, J_2 = 1.7 Hz), 5.10 (2 H, dd, J_1 = 10.3, J_2 = 1.5 Hz), 4.39 (4 H, s), 4.23 (4 H, s), 3.96 (4 H, td, J_1 = 5.6, J_2 = 1.4 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.9, 134.6, 131.3, 130.9, 129.7, 117.2, 113.6, 113.1, 71.7, 67.1, 66.2; HRMS (ESI): MNa^+, found 532.9930. $C_{22}H_{24}Br_2NaO_4$ requires 532.9939.



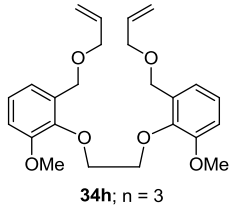
1,2-Bis(2-((allyloxy)methyl)-4,6-dichlorophenoxy)ethane (34f): Following the general procedure, **34f** was obtained as a colourless liquid (367 mg, 75%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2927, 2855, 1636, 1446, 1250 and 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35 (2 H, d, J = 2.6 Hz), 7.32 (2 H, d, J = 2.6 Hz), 5.95-5.88 (2 H, m), 5.27 (2 H, dd, J_1 = 17.1, J_2 = 1.7 Hz), 5.17 (2 H, dd, J_1 = 10.4, J_2 = 1.5 Hz), 4.59 (4 H, s), 4.29 (4 H, s), 4.04 (4 H, td, J_1 = 5.6, J_2 = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 151.4, 135.3, 134.2, 129.8, 129.3, 128.4, 127.9, 117.5, 72.7, 71.8, 66.6; m/z (CI) 492 (100, M^+).



1,2-Bis(2-((allyloxy)methyl)-6-methoxyphenoxy)ethane (34g): Following the general procedure, **34g** was as a colourless liquid (351 mg, 85%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2934, 1587, 1479, 1356 and 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.06-7.03 (4 H, m), 6.87-6.84 (2 H, m), 5.97-5.89 (2 H, m), 5.28 (2 H, dd, J_1 = 17.1, J_2 = 1.7 Hz), 5.14 (2 H, dd, J_1 = 10.4, J_2 = 1.7 Hz), 4.67 (4 H, s), 4.30 (4 H, s), 4.02 (4 H, td, J_1 = 5.6, J_2 = 1.4 Hz), 3.83 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.4, 145.9, 134.9, 132.6, 123.9, 120.9, 116.8, 111.7, 72.4, 71.4, 67.1, 55.8; HRMS (ESI): MNa^+, found 437.1938. $C_{24}H_{30}NaO_6$ requires 437.1940.

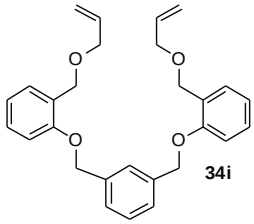


1,4-Bis(2-((allyloxy)methyl)-6-methoxyphenoxy)butane (34h): Following the general procedure, **34h** was obtained as a colourless liquid (344 mg, 78%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2853, 2838, 1475, 1455, 1274 and 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.01-6.99 (4 H, m), 6.83-6.81 (2 H, m), 5.97-5.90 (2 H, m), 5.29 (2 H, dd, J_1 = 17.2, J_2 = 1.7 Hz), 5.15 (2 H, dd, J_1 = 10.5, J_2 = 1.7 Hz), 4.57 (4 H, s), 4.03 (8 H, td, J_1 = 5.7, J_2 = 1.3 Hz), 3.79 (6 H, s), 1.98-1.95 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.7, 146.3, 134.9, 132.4, 123.9, 121.2, 116.9, 111.8, 73.1, 71.4, 67.1, 55.7, 27.0; HRMS (ESI): MNa^+, found 465.2243. $C_{26}H_{34}NaO_6$ requires 465.2253.

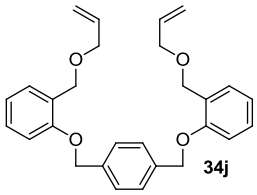


34h; n = 3

1,3-Bis((2-((allyloxy)methyl)phenoxy)methyl)benzene (34i): Following the general procedure, **34i** was obtained as a colourless liquid (339 mg, 79%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2855, 1602, 1493, 1286 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.44-7.35 (6 H, m), 7.19 (2 H, t, J = 7.4 Hz), 6.94 (2 H, t, J = 7.3 Hz), 6.86 (2 H, d, J = 1.7 Hz), 5.95-5.89 (2 H, m), 5.27 (2 H, d, J = 17.1 Hz), 5.12 (2 H, d, J = 10.2 Hz), 5.04 (4 H, s), 4.60 (4 H, s), 4.03 (4 H, d, J = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.2, 137.7, 135.1, 129.1, 128.9, 128.7, 127.3, 126.8, 126.0, 121.0, 116.8, 111.7, 71.6, 69.9, 67.2; m/z (CI): 430 (20, M^+), 431 (35, MH^+).

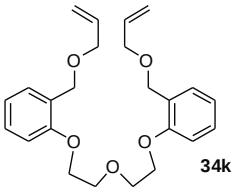

34i

1,4-Bis((2-((allyloxy)methyl)phenoxy)methyl)benzene (34j): Following the general procedure, **34j** was obtained as a colourless liquid (344 mg, 80%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3046, 2856, 1590, 1492, 1376 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.43 (6 H, s), 7.22 (2 H, t, J = 7.2 Hz), 6.96 (2 H, t, J = 7.4 Hz), 6.90 (2 H, d, J = 8.2 Hz), 6.00-5.90 (2 H, m), 5.30 (2 H, dd, J_1 = 17.3, J_2 = 1.4 Hz), 5.16 (2 H, dd, J_1 = 10.7, J_2 = 1.3 Hz), 5.07 (4 H, s), 4.62 (4 H, s), 4.07 (4 H, d, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.2, 136.9, 135.0, 129.1, 128.7, 127.4, 127.3, 120.9, 116.9, 111.7, 71.6, 69.7, 67.2; HRMS (ESI): MNa^+, found 453.2032. $C_{28}H_{30}NaO_4$ requires 453.2042.

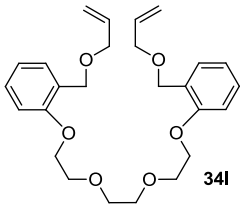

34j

2,2'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(((allyloxy)methyl)benzene) (34k): Following the general procedure, **34k** was obtained as a colourless liquid (326 mg, 82%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 2858, 1603, 1454 and 753 cm^{-1}; ^1H NMR (400

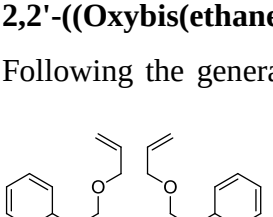
MHz, $CDCl_3$): δ_H 7.38 (2 H, d, J = 6.7 Hz), 7.21 (2 H, t, J = 8.5 Hz), 6.94 (2 H, t, J = 7.4 Hz), 6.84 (2 H, d, J = 8.2 Hz), 5.98-5.89 (2 H, m), 5.28 (2 H, dd, J_1 = 17.2, J_2 = 1.5 Hz), 5.15 (2 H, d, J = 10.5 Hz), 4.56 (4 H, s), 4.14 (4 H, t, J = 4.9 Hz), 4.03 (4 H, d, J = 5.5 Hz), 3.91 (4 H, t, J = 4.8 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.3, 135.0, 128.9, 128.6, 127.2, 120.9, 116.8, 111.5, 71.5, 70.0, 67.9, 67.0; HRMS (ESI): MNa^+, found 421.2004. $C_{24}H_{30}NaO_5$ requires 421.1991.


34k

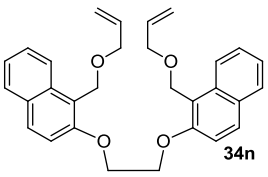
1,2-Bis(2-(2-((allyloxy)methyl)phenoxy)ethoxy)ethane (34l): Following the general procedure, **34l** was obtained as a colourless liquid (371 mg, 84%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 1688, 1601, 1452 and 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.36 (2 H, d, J = 6 Hz), 7.19 (2 H, t, J = 7.8 Hz), 6.92 (2 H, t, J = 7.4 Hz), 6.81 (2 H, d, J = 8.2 Hz), 5.98-5.88 (2 H, m), 5.28 (2 H, dd, J_1 = 17.4, J_2 = 1.7 Hz), 5.15 (2 H, dd, J_1 = 10.4, J_2 = 1.5 Hz), 4.54 (4 H, s), 4.10 (4 H, t, J = 5.0 Hz), 4.03 (4 H, td, J_1 = 5.5, J_2 = 1.4 Hz), 3.83 (4 H, t, J = 5.0 Hz), 3.71 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.3, 135.1, 128.9, 128.5, 127.1, 120.8, 116.8, 111.5, 71.5, 71.0, 69.9, 67.8, 67.0; HRMS (ESI): MNa^+, found 465.2250. $C_{26}H_{34}NaO_6$ requires 465.2253.


34l

2,2'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(1-((allyloxy)methyl)naphthalene) (34m): Following the general procedure, **34m** was obtained as a colourless liquid (383 mg, 77%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2930, 2854, 1585, 1468 and 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.11 (2 H, d, J = 8.6 Hz), 7.76 (4 H, t, J = 6.4 Hz), 7.50 (2 H, t, J = 7.0 Hz), 7.35 (2 H, t, J = 6.9 Hz), 7.25 (2 H, d, J = 9.1 Hz), 6.01-5.91 (2 H, m), 5.28 (2 H, dd, J_1 = 17.2, J_2 = 1.7 Hz), 5.14 (2 H, dd, J_1 = 10.2, J_2 = 1.7 Hz), 5.04 (4 H, s), 4.30 (4 H, t, J = 4.8 Hz), 4.07 (4 H, td, J_1 = 5.7, J_2 = 1.4 Hz), 3.97 (4 H, t, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.8, 135.2, 133.8, 130.3, 129.5, 128.2, 126.8, 124.1, 123.9, 119.7, 117.0, 115.1, 71.2, 70.3, 69.7, 62.3; HRMS (ESI): MNa^+, found 521.2301. $C_{32}H_{34}NaO_5$ requires 521.2304.

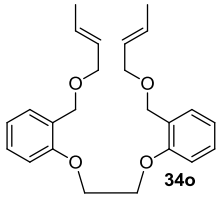

34m

1,2-Bis((1-((allyloxy)methyl)naphthalen-2-yl)oxy)ethane (34n): Following the general procedure, **34n** was obtained as a brown semi-solid (340 mg, 75%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2922, 1594, 1463, 1449 and 806 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.13 (2 H, d, J = 8.6 Hz), 7.84-7.80 (4 H, m), 7.52 (2 H, t, J = 8.0 Hz), 7.37 (2 H, t, J = 7.8 Hz), 7.30 (2

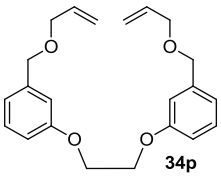

34n

H, d, J = 9.0 Hz), 5.96-5.90 (2 H, m), 5.25 (2 H, d, J = 17.2 Hz), 5.11 (2 H, d, J = 10.4 Hz), 5.03 (4 H, s), 4.49 (4 H, s), 4.04 (4 H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.7, 135.1, 133.9, 130.4, 129.6, 128.2, 126.9, 124.1, 124.0, 119.9, 117.1, 115.0, 71.2, 69.0, 62.3; HRMS (ESI): MNa^+, found 477.2031. $C_{30}H_{30}NaO_4$ requires 477.2042.

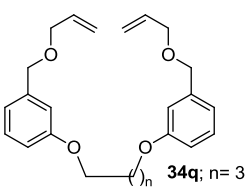
1,2-Bis(2-(but-2-en-1-yloxy)methyl)phenoxy)ethane (34o): Following the general procedure, **34o** was obtained as a colourless liquid (324 mg, 85%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2930, 2854, 1601, 1488 and 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.46 (2 H, d, J = 7.5 Hz), 7.31-7.27 (2 H, m), 7.02 (2 H, t, J = 7.4 Hz), 6.95 (2 H, d, J = 7.5 Hz), 5.80-5.62 (4 H, m), 4.57 (4 H, s), 4.38 (4 H, s), 4.01 (4 H, d, J = 6.1 Hz), 1.73 (6 H, dd, J_1 = 6.1, J_2 = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.2, 156.1, 129.3, 129.0, 128.5, 128.5, 127.8, 127.7, 127.6, 127.67, 127.2, 121.0, 111.5, 71.3, 66.9, 66.9, 66.7, 65.9, 17.8, 13.2; HRMS (ESI): MNa^+, found 405.2048. $C_{24}H_{30}NaO_4$ requires 405.2042. This compound was isolated as a mixture of *E* and *Z* isomers and ^{1}H and ^{13}C values corresponding to both isomers.



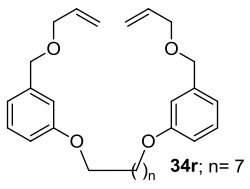
1,2-Bis(3-((allyloxy)methyl)phenoxy)ethane (34p): Following the general procedure, **34p** was obtained as a colourless liquid (297 mg, 84%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2855, 2360, 1599, 1488, 1261 and 784 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.26 (2 H, t, J = 7.8 Hz), 6.96-6.86 (6 H, m), 6.00-5.90 (2 H, m), 5.31 (2 H, d, J = 15.8 Hz), 5.20 (2 H, d, J = 9.4 Hz), 4.50 (4 H, s), 4.32 (4 H, s), 4.02 (4 H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 158.8, 140.0, 134.7, 129.5, 120.3, 117.2, 114.0, 113.8, 71.9, 71.2, 66.5; m/z (CI): 354 (10, M^+), 355 (15, MH^+).



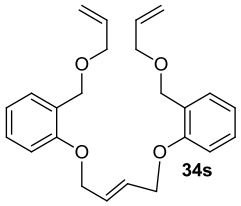
1,4-Bis(3-((allyloxy)methyl)phenoxy)butane (34q): Following the general procedure, **34q** was obtained as a colourless liquid (309 mg, 81%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2927, 2855, 1601, 1585, 1386 and 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.23 (2 H, t, J = 7.9 Hz), 6.91-6.80 (6 H, m), 5.99-5.90 (2 H, m), 5.30 (2 H, d, J = 17.2 Hz), 5.20 (2 H, d, J = 10.4 Hz), 4.48 (4 H, s), 4.02 (4 H, br. s), 4.01 (4 H, br. s), 1.96 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.1, 139.9, 134.8, 129.4, 119.9, 117.2, 113.8, 113.6, 72.0, 71.2, 67.4, 26.0; HRMS (ESI): MNa^+, found 405.2033. $C_{24}H_{30}NaO_4$ requires 405.2042.



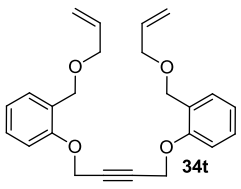
1,8-Bis(3-((allyloxy)methyl)phenoxy)octane (34r): Following the general procedure, **34r** was obtained as a colourless liquid (350 mg, 80%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2854, 1601, 1488, 1468, 1265 and 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.21 (2 H, t, J = 8.1 Hz), 6.89-6.78 (6 H, m), 5.98-5.88 (2 H, m), 5.28 (2 H, dd, J_1 = 17.2, J_2 = 1.7 Hz), 5.18 (2 H, dd, J_1 = 10.4, J_2 = 1.6 Hz), 4.47 (4 H, s), 4.01 (4 H, td, J_1 = 5.6, J_2 = 1.4 Hz), 3.93 (4 H, t, J = 6.5 Hz), 1.79-1.72 (4 H, m), 1.35-1.46 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.3, 139.9, 134.8, 129.4, 119.8, 117.2, 113.8, 113.6, 72.0, 71.1, 67.9, 29.4, 29.3, 26.0; HRMS (ESI): MNa^+, found 461.2653. $C_{28}H_{38}NaO_4$ requires 461.2668.



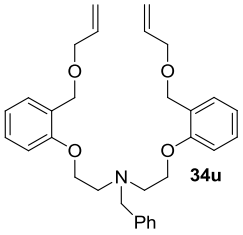
(*E*)-1,4-Bis(2-((allyloxy)methyl)phenoxy)but-2-ene (34s): Following the general procedure, **34s** was obtained as a colourless liquid (396 mg, 78%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 2869, 1688, 1601, 1452 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (2 H, d, J = 8.8 Hz), 7.29-7.25 (2 H, m), 7.00 (2 H, t, J = 9.3 Hz), 6.88 (2 H, d, J = 9.3 Hz), 6.10 (2 H, t, J = 2.7 Hz), 6.05-5.98 (2 H, m), 5.39-5.21 (4 H, m), 4.64 (8 H, br. s), 4.13-4.11 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.0, 135.0, 129.0, 128.5, 128.0, 127.1, 120.8, 116.9, 111.6, 71.5, 67.8, 67.0; HRMS (ESI): MNa^+, found 403.1873. $C_{24}H_{28}NaO_4$ requires 403.1885.



1,4-Bis(2-((allyloxy)methyl)phenoxy)but-2-yne (34t): Following the general procedure, **34t** was obtained as a colourless liquid (313 mg, 83%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2859, 1602, 1492, 1260 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (2 H, d, J = 7.4 Hz), 7.25 (2 H, t, J = 7.9 Hz), 7.03 (2 H, t, J = 7.4 Hz), 6.95 (2 H, d, J = 8.1 Hz), 6.04-5.96 (2 H, m), 5.39-5.34 (2 H, m), 5.25-5.22 (2 H, m), 4.77 (4 H, s), 4.60 (4 H, s), 4.10 (4 H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.0, 135.0, 129.0, 128.5, 127.5, 121.4, 116.9, 112.0, 82.4, 71.5, 66.8, 56.3; HRMS (ESI): MNa^+, found 401.1717. $C_{24}H_{26}NaO_4$ requires 401.1729.

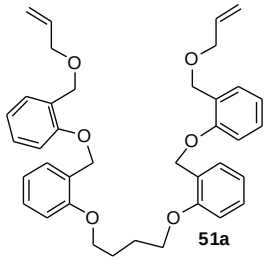


2-(2-((Allyloxy)methyl)phenoxy)-*N*-(2-(2-((allyloxy)methyl)phenoxy)ethyl)-*N*-benzylethanamine (34u):Following the general procedure, **34u** was obtained as a colourless liquid (389 mg, 80%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 2855, 1603, 1490 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (4 H, t, J = 6.8 Hz), 7.34 (2 H, t, J = 7.1 Hz), 7.30-7.22 (3 H, m), 6.98 (2 H, t, J = 6.7 Hz), 6.83 (2 H, d, J = 7.8 Hz), 6.00-5.92 (2 H, m), 5.31

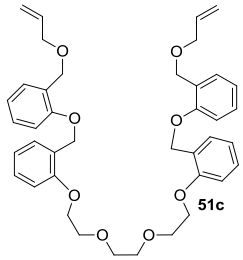


(2 H, dd, J_1 = 17.2, J_2 = 1.7 Hz), 5.19 (2 H, dd, J_1 = 10.4, J_2 = 1.7 Hz), 4.58 (4 H, s), 4.11 (4 H, t, J = 5.8 Hz), 4.05 (4 H, td, J_1 = 5.5, J_2 = 1.4 Hz), 3.89 (2 H, s), 3.10 (4 H, t, J = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.2, 139.6, 135.0, 128.7, 128.7, 128.5, 128.3, 127.1, 126.9, 120.5, 116.8, 110.9, 71.5, 67.0, 66.8, 60.0, 53.4; HRMS (ESI): MH^+, found 488.2812. $C_{31}H_{38}NO_4$ requires 488.2801.

1,4-Bis(2-((2-((allyloxy)methyl)phenoxy)methyl)phenoxy)butane (51a): Following the general procedure, **51a** was obtained as a colourless liquid (504 mg, 85%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3067, 2937, 1590, 1604 and 1751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58-7.52 (4 H, m), 7.37-7.28 (4 H, m), 7.08-6.95 (8 H, m), 6.11-6.02 (2 H, m), 5.44-5.39 (2 H, m), 5.29-5.25 (2 H, m), 5.23 (4 H, br. s), 4.75 (4 H, br. s), 4.18-4.15 (8 H, m), 2.08-2.06 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.4, 156.0, 135.1, 128.8, 128.8, 128.6, 128.3, 127.3, 125.8, 120.7, 120.6, 116.9, 111.8, 111.0, 71.6, 67.5, 67.2, 65.2, 26.2; HRMS (ESI): MNa^+, found 617.2888. $C_{38}H_{42}NaO_6$ requires 617.2879.



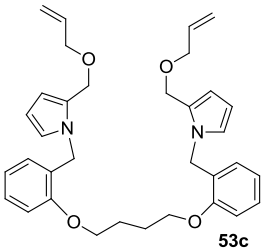
1,6-Bis(2-((2-((allyloxy)methyl)phenoxy)methyl)phenoxy)Hexanes (51b): Following the general procedure, **51b** was obtained as a colourless liquid (510 mg, 82%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3067, 2859, 1604, 1454 and 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54-7.48 (4 H, m), 7.34-725 (4 H, m), 7.04-6.92 (8 H, m), 6.05-6.01 (2 H, m), 5.41-5.36 (2 H, m), 5.26-5.21 (2 H, m), 5.21 (4 H, br. s), 4.73 (4 H, br. s), 4.16-4.14 (4 H, m), 4.06 (4 H, t, J = 12.5 Hz), 1.87 (4 H, br. s), 1.59 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.4, 156.1, 135.1, 128.8, 128.7, 128.5, 128.1, 127.2, 125.8, 120.6, 120.5, 116.8, 111.7, 111.0, 71.5, 67.9, 67.2, 65.1, 29.3, 26.0; HRMS (ESI): MNa^+, found 645.3185. $C_{40}H_{46}NaO_6$ requires 645.3192.



1,2-Bis(2-(2-((2-((allyloxy)methyl)phenoxy)methyl)phenoxy)ethoxy)ethane (51c): Following the general procedure, **51c** was obtained as a colourless liquid (549 mg, 84%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2924, 2856, 1604, 1452 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.49-7.43 (4 H, m), 7.28-7.23 (4 H, m), 7.02-6.95 (6 H, m), 6.90 (2 H, d, J = 8.1 Hz), 6.03-5.95 (2 H, m),

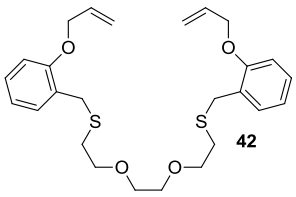
5.37-5.31 (2 H, m), 5.22-5.18 (6 H, m), 4.67 (4 H, br. s), 4.18 (4 H, t, J = 4.7 Hz), 4.12-4.09 (4 H, m), 3.86 (4 H, t, J = 4.8 Hz), 3.70 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.3, 155.8, 135.0, 128.8, 128.7, 128.5, 128.2, 127.2, 126.0, 120.9, 120.6, 116.8, 111.7, 111.4, 71.5, 71.0, 69.8, 67.8, 67.1, 65.0; HRMS (ESI): MNa^+, found 677.3100. $C_{40}H_{46}NaO_8$ requires 677.3090.

1,4-Bis(2-((2-((allyloxy)methyl)-1*H*-pyrrol-1-yl)methyl)phenoxy)butane (53c): Following the general procedure, **53c** was obtained as a colourless solid (437 mg, 81%); mp 60-62 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2924, 2853, 1602, 1493, 1259 and 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.24 (2 H, t, J = 7.4 Hz), 6.90-6.85 (4 H, m), 6.72-6.63 (4 H, m), 6.21-6.12 (4 H, m), 5.90-5.80 (2 H, m), 5.27-5.13 (8 H, m), 4.43 (4 H, s), 4.11 (4 H, br. s), 3.94 (4 H, td, J_1 = 5.6, J_2 = 1.5 Hz), 2.03 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.8, 134.8, 128.8, 128.4, 127.7, 127.0, 123.3, 120.6, 117.0, 110.7, 110.5, 106.9, 69.9, 67.3, 63.5, 45.7, 26.1; HRMS (ESI): MNa^+, found 563.2880. $C_{34}H_{40}N_2NaO_4$ requires 563.2886.



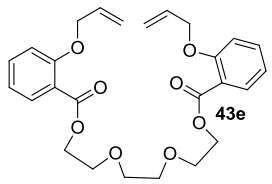
53c

Procedure for the synthesis of 1,12-bis(2-(allyloxy)phenyl)-5,8-dioxa-2,11-dithiadodecane (42): To a suspension of 2,2'-(ethane-1,2-diylbis(oxy))diethanethiol **41** (2 mmol) in ethanol (10 mL) at room temperature was added KOH (4 mmol). The reaction was stirred at room temperature for 1 h. Then, to this solution, a solution of 1-(allyloxy)-2-(chloromethyl)benzene **40** (4 mmol) in toluene (5 mL) was added drop wise. The resulting mixture was stirred for additional 1h and then, the reaction mixture was filtered. Filtrate was added to the DCM (20 mL) and washed with H_2O (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated, and the resulting crude reaction mixture was purified by silica gel column chromatography (20% EtOAc/Hexanes) to give the desired product **42** as a colourless liquid (663 mg, 70%); R_f (20% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 2923, 1745, 1384, 1260 and 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.30-7.19 (4 H, m), 6.92 (2 H, t, J = 7.44 Hz), 6.87 (2 H, d, J = 8.2 Hz), 6.12-6.04 (2 H, m), 5.48-5.43 (2 H, m), 5.31-5.28 (2 H, m), 4.59 (4 H, td, J_1 = 5.1, J_2 = 1.5 Hz), 3.82 (4 H, s), 3.63 (4 H, t, J = 7.1 Hz), 3.60 (4 H, s), 2.69 (4 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.2, 133.3, 130.4, 128.2, 127.3, 120.6, 117.2, 111.9, 70.9, 70.2, 68.8, 30.9, 30.7; HRMS (ESI): MNa^+, found 497.1804. $C_{26}H_{34}NaO_4S_2$ requires 497.1796.

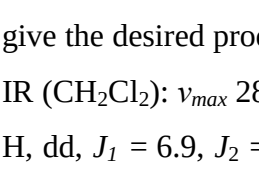


42

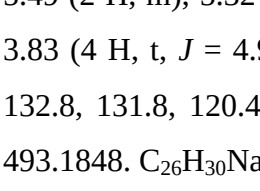
General procedure for the synthesis of compound 43e. To a solution of 2-(allyloxy)benzoic acid **43c** (1 mmol), 2,2'-(ethane-1,2-diylbis(oxy))diethanol **43d** (0.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 1 mmol) in CH_2Cl_2 (2.5 mL) was added 1,3-dicyclohexylcarbodiimide (1.5 mmol) in small fractions. The reaction mixture was stirred at room temperature for 2 h. The resulting pale yellow suspension was filtered through filtration funnel. The filtrate was concentrated and purified by silica gel column chromatography (20% EtOAc/Hexanes) to give the desired product **43e** as a colourless liquid (117 mg, 50%); R_f (20% EtOAc/Hexanes) 0.6; IR (CH_2Cl_2): ν_{max} 2872, 1726, 1600, 1450 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2 H, dd, J_1 = 6.9, J_2 = 1.8 Hz), 7.47-7.42 (2 H, m), 7.00-6.95 (4 H, m), 6.11-6.04 (2 H, m), 5.54-5.49 (2 H, m), 5.32-5.29 (2 H, m), 4.64 (4 H, td, J_1 = 4.9, J_2 = 1.6 Hz), 4.46 (4 H, t, J = 5 Hz), 3.83 (4 H, t, J = 4.9 Hz), 3.72 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 158.2, 133.4, 132.8, 131.8, 120.4, 120.4, 117.5, 113.6, 70.6, 69.5, 69.3, 63.9 ; HRMS (ESI): MNa^+, found 493.1848. $C_{26}H_{30}NaO_8$ requires 493.1838.



Diallyl 2,2'-((1,2-phenylenebis(methylene))bis(oxy))dibenzoate (46a): Following the general procedure, **46a** was obtained as a colourless liquid (171 mg, 75%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3079, 2942, 1723, 1449 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (2 H, dd, J_1 = 6.9, J_2 = 1.8 Hz), 7.66-7.64 (2 H, m), 7.48-7.37 (4 H, m), 7.10 (2 H, d, J = 8.4 Hz), 7.01 (2 H, t, J = 7.8 Hz), 6.02-5.92 (2 H, m), 5.37-5.32 (6 H, m), 5.23-5.19 (2 H, m), 4.78 (4 H, td, J_1 = 5.7, J_2 = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.9, 158.1, 134.6, 133.6, 132.2, 131.9, 128.6, 128.2, 120.5, 120.3, 118.3, 113.5, 68.8, 65.5; HRMS (ESI): MNa^+, found 481.1632. $C_{28}H_{26}NaO_6$ requires 481.1627.

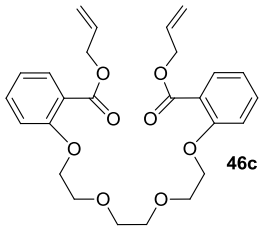


Diallyl 2,2'-((1,3-phenylenebis(methylene))bis(oxy))dibenzoate (46b): Following the general procedure, **46b** was obtained as a colourless liquid (160 mg, 70%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3087, 2934, 1715, 1599 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.88 (2 H, dd, J_1 = 7.1, J_2 = 1.9 Hz), 7.57 (1 H, s), 7.51-7.43 (5 H, m), 7.04-7.00 (4 H, m), 6.05-5.98 (2 H, m), 5.42-5.22 (8 H, m), 4.83 (4 H, td, J_1 = 5.1, J_2 = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.0, 158.1, 137.0, 133.5, 132.3, 131.9, 128.9, 126.5, 125.4, 120.7,

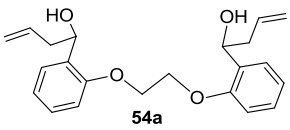


120.7, 118.1, 113.8, 70.5, 65.6; HRMS (ESI): MNa^+, found 481.1625. $C_{28}H_{26}NaO_6$ requires 481.1627.

Diallyl 2,2'-(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))dibenzoate (46c): Following the general procedure, **46c** was obtained as a colourless liquid (169 mg, 74%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2925, 1727, 1601, 1491, 1260 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 7.3, J_2 = 1.8 Hz), 7.47-7.43 (2 H, m), 7.01-6.98 (4 H, m), 6.05-5.98 (2 H, m), 5.45-5.25 (4 H, m), 4.80 (4 H, td, J_1 = 5.2, J_2 = 1.4 Hz), 4.21 (4 H, t, J = 5.2 Hz), 3.91 (4 H, t, J = 5.1 Hz), 3.78 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.0, 158.4, 133.5, 132.4, 131.7, 120.5, 120.5, 118.0, 113.6, 71.1, 69.6, 68.8, 65.4; HRMS (ESI): MNa^+, found 493.1842. $C_{26}H_{30}NaO_8$ requires 493.1838.

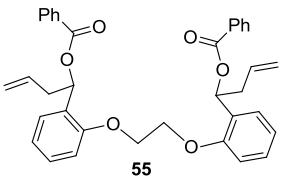


General procedure for the syntheses of 1,1'-((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) (54a): To a mixture of corresponding *bis*-aldehyde **32a** (3 mmol) and allyl bromide (7 equiv) in THF (7 mL) was added saturated NH_4Cl solution (18 mL) and Zn metal (5 equiv) successively at room temperature. The resulting mixture was stirred at room temperature for 30 h. After this period, the reaction mixture was extracted by using ethyl acetate (3 X 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the organic phase was concentrated and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc : hexanes = 30:70) which afforded the corresponding products **54a** as a white solid, (0.849 g, 80%); mp: 66-68 ^oC; R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3413, 2937, 1600, 1453 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (2 H, m), 7.24 (2 H, t, J = 7.8 Hz), 6.99 (2 H, t, J = 7.5 Hz), 6.91 (2 H, d, J = 8.2 Hz), 5.81-5.71 (2 H, m), 5.08-4.96 (6 H, m), 4.40-4.38 (4 H, m), 2.90 (2 H, br s), 2.58-2.46 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 135.1, 132.4, 128.3, 127.1, 121.4, 117.7, 111.5, 68.7, 66.9, 41.7; HRMS (ESI): MNa^+, found 377.1740. $C_{22}H_{26}O_4Na$ requires 377.1729. (Isolated as a 1:1 mixture of diastereomers and ^{13}C values given here for one isomer).

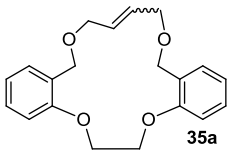


Procedure for the synthesis of ((ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl) dibenzoate (55): To a suspension of 1,1'-((ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) **54a** (1 mmol) in DCM (4 mL) at room temperature was added

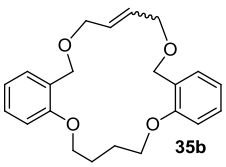
$MgBr_2$ (2.5 equiv), Et_3N (4 equiv) and $(PhCO)_2O$ (3 equiv). The reaction was stirred at room temperature for 12 h, after this period, the reaction mixture was diluted with DCM and washed with sat. solution of $NaHCO_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated, and the resulting crude reaction mixture was purified by silica gel column chromatography (20% EtOAc/Hexanes) to give the desired product **55** as a colourless liquid (421 mg, 75%); R_f (20% EtOAc/Hexanes) 0.65; IR (CH_2Cl_2): ν_{max} 2931, 1720, 1602, 1452, 1275 and 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.08 (4 H, d, J = 7.1 Hz), 7.53 (2 H, t, J = 6.8 Hz), 7.42 (6 H, t, J = 7.7 Hz), 7.27 (2 H, t, J = 7.7 Hz), 6.98 (4 H, d, J = 7.9 Hz), 6.48 (2 H, q, J = 7.2 Hz), 5.85-5.77 (2 H, m), 5.06-4.97 (4 H, m), 4.51 (1 H, d, J = 6.4 Hz), 4.45 (2 H, s), 4.38 (1 H, d, J = 6.3 Hz), 2.73-2.69 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.6, 165.5, 155.2, 133.7, 132.9, 130.6, 130.6, 129.6, 129.2, 129.2, 128.8, 128.4, 126.6, 126.5, 121.1, 117.7, 117.7, 112.0, 112.0, 70.6, 70.5, 67.1, 67.0, 39.7; HRMS (ESI): MNa^+, found 585.2258. $C_{36}H_{34}NaO_6$ requires 585.2253. Isolated as a mixture of diastereomers (50:50) and ^1H and ^{13}C NMR values corresponding to both isomers.



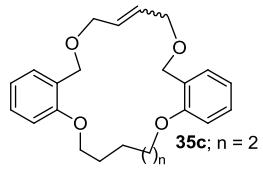
Compound 35a. Following the general procedure, **35a** was obtained as a colourless solid (70 mg, 87%) (*E/Z* = 70:30); mp 95-97 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2929, 2851, 1602, 1492 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.47 (2 H, d, J = 8.0 Hz), 7.24 (2 H, t, J = 7.8 Hz), 7.01 (2 H, t, J = 7.8 Hz), 6.89 (2 H, d, J = 8.0 Hz), 5.83-5.81 (2 H, m), 4.14-4.12 (4 H, m), 4.63 (4 H, s), 4.28 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.8, 131.8, 128.6, 128.3, 127.7, 121.4, 111.8, 69.7, 66.8, 64.0; HRMS (ESI): MNa^+, found 349.1400. $C_{20}H_{22}NaO_4$ requires 349.1415.



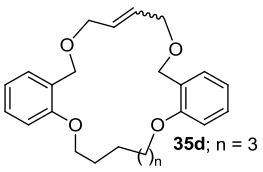
Compound 35b. Following the general procedure, **35b** was obtained as a colourless liquid (69 mg, 78%); (*E/Z* = 86:14); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2939, 2365, 1687, 1492 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.36 (2 H, d, J = 8.1 Hz), 7.23 (2 H, t, J = 7.6 Hz), 6.92 (2 H, t, J = 7.6 Hz), 6.83 (2 H, d, J = 8.1 Hz), 5.92-5.90 (2 H, m), 4.55 (4 H, s), 4.24-4.12 (4 H, m), 4.02 (4 H, br. s), 2.01-1.97 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 130.2, 129.8, 128.9, 126.9, 120.4, 111.2, 70.4, 67.5, 66.5, 26.4; HRMS (ESI): MNa^+, found 377.1730. $C_{22}H_{26}NaO_4$ requires 377.1723.



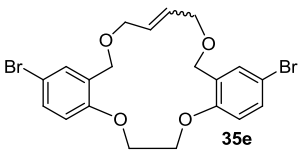
Compound 35c. Following the general procedure, **35c** was obtained as a colourless liquid (65 mg, 71%); (*E/Z* = 80:20); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 1602, 1494, 1242 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.39 (2 H, d, *J* = 8.1 Hz), 7.21 (2 H, t, *J* = 7.3 Hz), 6.92 (2 H, t, *J* = 7.3 Hz), 6.81 (2 H, d, *J* = 8.1 Hz), 5.88 (2 H, br. s), 4.54 (4 H, s), 4.16 (4 H, br. s), 3.98 (4 H, t, *J* = 4.5 Hz), 1.83 (4 H, br. s), 1.74 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.5, 130.4, 128.6, 128.5, 127.2, 120.4, 110.9, 70.7, 68.0, 66.1, 29.6, 24.4; HRMS (ESI): MNa^+, found 391.1886. $C_{23}H_{28}NaO_4$ requires 391.1879.



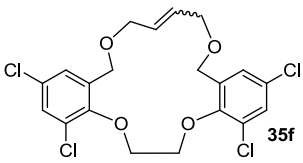
Compound 35d. Following the general procedure, **35d** was obtained as a colourless liquid (69 mg, 73%); (*E/Z* = 80:20); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1603, 1456, 1248 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31 (2 H, d, *J* = 8.1 Hz), 7.23 (2 H, t, *J* = 7.7 Hz), 6.90 (2 H, t, *J* = 7.7 Hz), 6.84 (2 H, d, *J* = 8.1 Hz), 5.88-5.86 (2 H, m), 4.50 (4 H, s), 4.12-4.10 (4 H, m), 3.99 (4 H, t, *J* = 5.7 Hz), 1.82-1.79 (4 H, m), 1.61-1.58 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.3, 130.3, 130.1, 129.1, 126.9, 120.4, 111.8, 70.7, 67.9, 67.3, 29.4, 26.0; HRMS (ESI): MNa^+, found 405.2028. $C_{24}H_{30}NaO_4$ requires 405.2041.



Compound 35e. Following the general procedure, **35e** was obtained as a colourless solid (66 mg, 55%) (*E/Z* = 80:20); mp 143-145 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2931, 1628, 1486,1367, 1184 and 657cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (2 H, d, *J* = 2.4 Hz), 7.29 (2 H, dd, J_1 = 8.6, J_2 = 2.5 Hz), 6.71 (2 H, d, *J* = 8.6 Hz), 5.77-5.74 (2 H, m), 4.51 (4 H, s), 4.20 (4 H, s), 4.12-4.11 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.4, 132.0, 130.9, 130.7, 130.1, 114.0, 113.3, 70.0, 66.8, 63.4; HRMS (ESI): MH^+, found 482.9796. $C_{20}H_{21}Br_2O_4$ requires 482.9806.

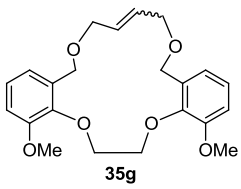


Compound 35f. Following the general procedure, **35f** was obtained after as a colourless solid (88 mg, 77%) (*E/Z* = 87:13); mp 118-120 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2927, 2852, 1629, 1446,1360 and 740cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.41 (2 H, d, *J* = 2.5 Hz), 7.32 (2 H, d, *J* = 2.5 Hz), 5.86-5.83 (2 H, m), 4.65 (4 H, s), 4.28 (4 H, s), 4.10-4.08 (4



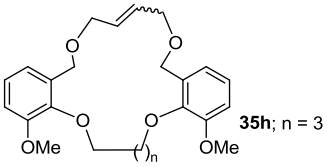
H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 151.5, 134.8, 131.7, 129.9, 129.4, 128.1, 73.1, 69.6, 63.6; HRMS (ESI): MH^+, found 463.0037. $C_{20}H_{19}Cl_4O_4$ requires 463.0037.

Compound 35g. Following the general procedure, **35g** was obtained as a colourless solid (77 mg, 80%) (*E/Z* = 65:35); mp 126-128 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2936, 2360, 1588, 1479 and 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.06 (4 H, d, *J* = 5.2 Hz), 6.85 (2 H, t, *J* = 4.8 Hz), 5.90-5.87 (2 H, m), 4.68 (4 H, s), 4.28 (4 H, s), 4.07-4.05 (4 H, m), 3.82 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.4, 146.2, 132.1, 131.4, 124.1, 121.8, 111.8,.69.4, 64.1, 55.8; HRMS (ESI): MNa^+, found 409.1612. $C_{22}H_{26}NaO_6$ requires 409.1627.



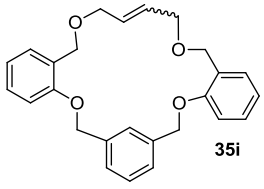
35g

Compound 35h. Following the general procedure, **35h** was obtained as a colourless solid (80 mg, 78%) (*E/Z* = 85:15); mp 111-112 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2936, 1587, 1479, 1276 and 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.06-7.00 (4 H, m), 6.86 (2 H, d, *J* = 7.5 Hz), 5.90 (2 H, br. s), 4.57 (4 H, s), 4.14 (4 H, s), 4.05 (4 H, br. s), 3.84 (6 H, s), 1.93 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 152.6, 146.5, 132.2, 130.2, 123.8, 121.5, 112.0, 73.4, 70.3, 66.6, 55.8, 26.9; HRMS (ESI): MNa^+, found 437.1950. $C_{24}H_{30}NaO_6$ requires 437.1940.



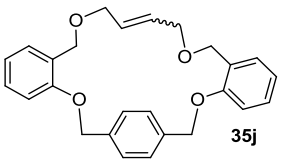
35h; n = 3

Compound 35i. Following the general procedure, **35i** was obtained as a colourless solid (50 mg, 50%) (*E/Z* = 70:30); mp 149-151 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2921, 2854, 1598, 1493, 1238 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (1 H, s), 7.74-7.26 (7 H, m), 7.03-6.97 (4 H, m) 5.87-5.84 (2 H, m), 5.12 (4 H, s), 4.64 (4 H, s), 4.17-4.16 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.0, 137.7, 130.5, 128.6, 128.5, 128.2, 127.4, 127.1, 126.4, 120.9, 111.5, 70.3, 69.7, 66.0; HRMS (ESI): MNa^+, found 425.1738. $C_{26}H_{26}NaO_4$ requires 425.1728.

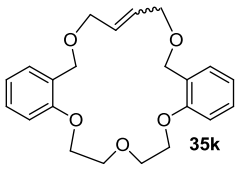

35i

Compound 35j. Following the general procedure, **35j** (major isomer, *E*) was obtained as a colourless solid (67 mg, 67% combined yield of **35j**/**35j′**) (*E/Z* = 80:20); mp 170-172 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2935, 2857, 1602, 1454, 1249 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (4 H, s), 7.34-7.28 (4 H, m), 7.05 (2 H, d, *J* = 7.9 Hz), 6.97 (2

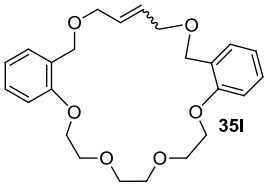
H, t, *J* = 7.4 Hz), 5.63-5.61 (2 H, m), 5.13 (4 H, s), 4.47 (4 H, s), 3.92-3.91 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 136.9, 131.5, 130.0, 129.7, 128.5, 127.1, 120.9, 112.4, 70.9, 70.2, 67.8; HRMS (ESI): MNa^+, found 425.1740. $C_{26}H_{26}NaO_4$ requires 425.1728. Data given here for the major (*E*) isomer and the ^{1}H and ^{13}C NMR spectrum contain traces of minor isomer **5j′**. The minor isomer **5j′** (*Z*) was isolated in very less quantity <6 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.41 (4 H, s), 7.24-7.21 (4 H, m), 6.94-6.88 (4 H, m), 5.63-5.62 (2 H, m), 5.02 (4 H, s), 4.38 (4 H, s), 3.90-3.89 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 130.8, 129.7, 128.5, 128.6, 120.9, 112.8, 70.5, 69.1, 67.1, since the compound was isolated in <6 mg, few signals corresponding to the quaternary carbons were not appeared in the ^{13}C spectrum.



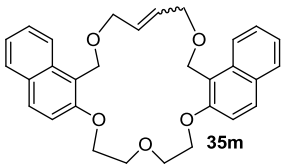
Compound 35k. Following the general procedure, **35k** was obtained as a colourless liquid (69 mg, 75%) (*E/Z* = 67:33); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 2364, 1603, 1494, 1246 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.41-7.37 (2 H, m), 7.24 (2 H, t, *J* = 7.6 Hz), 6.95 (2 H, t, *J* = 7.6 Hz), 6.83 (2 H, d, *J* = 8.2 Hz), 5.90-5.88 (2 H, m), 4.57 (4 H, s), 4.17-4.13 (8 H, m), 3.96 (4 H, t, *J* = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.3, 130.4, 129.2, 128.7, 127.1, 120.8, 111.1, 70.5, 70.1, 68.1, 66.2; HRMS (ESI): MNa^+, found 393.1665. $C_{22}H_{26}NaO_5$ requires 393.1677.



Compound 35l. Following the general procedure, **35l** was obtained after as a colourless liquid (82 mg, 80%) (*E/Z* = 83:17); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 2867, 1601, 1493, 1248 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.34 (2 H, d, *J* = 7.8 Hz), 7.27-7.23 (2 H, m), 6.96-6.92 (2 H, m), 6.83 (2 H, d, *J* = 7.8 Hz), 5.86-5.84 (2 H, m), 4.53 (4 H, s), 4.19-4.09 (8 H, m), 3.93-3.90 (4 H, m), 3.83 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 130.2, 129.9, 129.1, 126.8, 120.7, 111.2, 71.5, 70.4, 69.9, 68.7, 67.1; HRMS (ESI): MNa^+, found 437.1929. $C_{24}H_{30}NaO_6$ requires 437.1940.

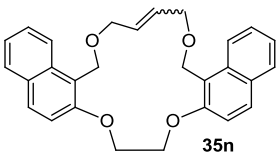


Compound 35m. Following the general procedure, **35m** was obtained as a colourless solid (102 mg, 87%) (*E/Z* = 74:26); mp 164-166 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2929, 1625, 1453, 1240 and 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.10 (2H, d, *J* = 8.5), 7.81-7.74 (4 H, m), 7.52-7.47 (2 H, m), 7.36-7.32 (2 H, m), 7.25-7.21 (2 H, m), 6.01-6.00 (2 H, m), 5.05 (4

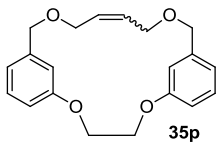


H, s), 4.31-4.18 (8 H, m), 4.06-4.03 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.8, 133.8, 130.4, 130.3, 129.5, 128.3, 126.9, 123.8, 123.8, 119.8, 114.8, 70.5, 70.2, 70.1, 61.5; HRMS (ESI): MNa^+, found 493.2008. $C_{30}H_{30}NaO_5$ requires 493.1990.

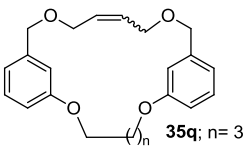
Compound 35n. Following the general procedure, **35n** was obtained as a colourless solid (90 mg, 85%) (*E/Z* = 90:10); mp 158-160 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2911, 1594, 1347, 1239 and 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.25 (2 H, d, *J* = 8.8 Hz), 7.90-7.84 (4 H, m), 7.59 (2 H, t, *J* = 7.6 Hz), 7.44 (2 H, t, *J* = 7.6 Hz), 7.33 (2 H, d, *J* = 8.8 Hz), 6.12-6.10 (2 H, m), 5.23 (4 H, s), 4.50 (4 H, s), 4.18-4.17 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.8, 134.0, 130.7, 130.5, 129.9, 128.3, 126.9, 124.4, 124.2, 120.5, 115.8, 70.1, 68.9, 60.3; HRMS (ESI): MNa^+, found 449.1710. $C_{28}H_{26}NaO_4$ requires 449.1728.

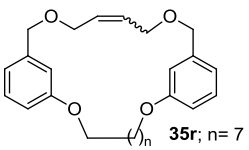


Compound 35p. Following the general procedure, **35p** was obtained as a colourless liquid (30 mg, 38%) (*E/Z* = 80:20); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 1600, 1449, 1263 and 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.24-7.16 (4 H, m), 6.85-6.82 (4 H, m), 5.80-5.78 (2 H, m), 4.51 (4 H, s), 4.38 (4 H, s), 4.01-4.00 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.1, 140.3, 129.9, 129.4, 120.6, 115.4, 115.0, 114.6, 71.6, 69.7, 67.5; HRMS (ESI): MH^+, found 327.1596. $C_{20}H_{23}O_4$ requires 327.1596.



Compound 35q. Following the general procedure, **35q** was obtained as a colourless liquid (48 mg, 55%) (*E/Z* = 90:10); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2941, 2855, 1600, 1488 and 783 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.21 (2 H, t, *J* = 7.9 Hz), 7.03 (2 H, s), 6.81 (4 H, t, *J* = 7.9 Hz), 5.89-5.88 (2 H, m), 4.51 (4 H, s), 4.11 (4 H, br. s), 4.05-4.04 (4 H, m), 2.01-1.98 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.2, 140.1, 129.5, 129.3, 119.6, 114.4, 112.7, 71.2, 69.3, 67.9, 26.4; HRMS (ESI): MH^+, found 355.1896. $C_{22}H_{27}O_4$ requires 355.1909.

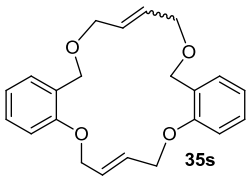




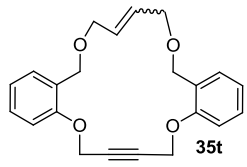
Compound 35r. Following the general procedure, **35r** was obtained as a colourless liquid (47 mg, 46%) (*E/Z* = 85:15); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 1726, 1455, 1384 and 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.24-7.19 (2 H, m), 7.00 (2 H, br. s), 6.81 (4 H, t, *J* = 8.5 Hz), 5.91-5.89

(2 H, m), 4.49 (4 H, s), 4.04-4.03 (4 H, m), 3.97 (4 H, t, J = 6.1 Hz), 1.79-1.72 (4 H, m), 1.53-1.46 (4 H, m), 1.41-1.36 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 159.5, 139.9, 129.3, 129.2, 119.6, 114.1, 113.3, 72.1, 67.7, 28.9, 28.5, 25.5; HRMS (ESI): MNa^+, found 433.2374. $C_{26}H_{34}NaO_4$ requires 433.2354.

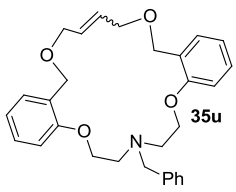
Compound 35s. Following the general procedure, **35s** was obtained as a colourless liquid (77 mg, 88%) (*E*/Z = 95:5); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2851, 1589, 1493, 1452 and 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.38 (2 H, dd, J_1 = 8.6, J_2 = 1.6 Hz), 7.30 (2 H, dt, J_1 = 7.1, J_2 = 1.4 Hz), 6.98 (2 H, dt, J_1 = 7.4, J_2 = 0.9 Hz), 6.89 (2 H, dd, J_1 = 8.5, J_2 = 0.6 Hz), 6.17 (2 H, t, J = 2.2 Hz), 5.99-5.97 (2 H, m), 4.63-4.62 (4 H, m), 4.61 (4 H, s), 4.18-4.17 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 130.4, 130.0, 129.2, 127.5, 126.9, 120.7, 111.6, 70.4, 67.5, 67.3; HRMS (ESI): MNa^+, found 375.1573. $C_{22}H_{24}NaO_4$ requires 375.1572.



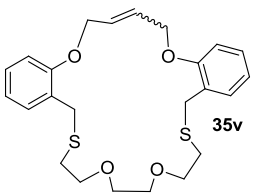
Compound 35t. Following the general procedure, **35t** was obtained as a colourless liquid (48 mg, 55%) (*E*/Z = 70:30); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2921, 1603, 1492, 1454 and 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.40-7.26 (4 H, m), 7.04-6.99 (2 H, m), 6.88 (2 H, t, J = 7.8 Hz), 5.94-5.91 (2 H, m), 4.75 (4 H, s), 4.58 (4 H, s), 4.16-4.08 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.8, 155.7, 130.5, 130.5, 130.3, 129.9, 129.1, 128.9, 128.1, 127.8, 121.8, 121.7, 112.7, 112.6, 81.9, 81.8, 70.3, 66.9, 66.5, 65.6, 56.9, 56.8; HRMS (ESI): MNa^+, found 373.1418. $C_{22}H_{22}NaO_4$ requires 373.1416.



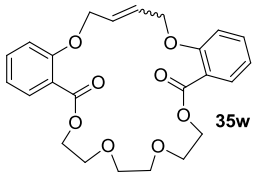
Compound 35u. Following the general procedure, **35u** was obtained as a colourless liquid (88 mg, 77%) (*E*/Z = 83:17); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 2850, 1603, 1453 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.41-7.24 (9 H, m), 6.98 (2 H, t, J = 7.4 Hz), 6.84 (2 H, d, J = 8.2 Hz), 5.94-5.92 (2 H, m), 4.60 (4 H, s), 4.19-4.18 (4 H, m), 4.13 (4 H, t, J = 5.9 Hz), 3.85 (2 H, s), 3.20 (4 H, t, J = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.5, 130.1, 129.5, 128.8, 128.7, 128.7, 128.4, 127.2, 126.9, 120.6, 111.2, 70.4, 67.2, 66.3, 58.7, 53.5; HRMS (ESI): MH^+, found 460.2485. $C_{29}H_{34}NO_4$ requires 460.2488.



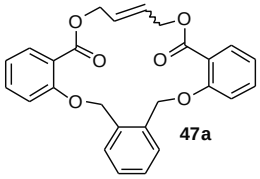
Compound 35v. Following the general procedure, **35v** was obtained as a colourless solid (75 mg, 68%) (*E*/Z = 93:7); mp 80-82 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2916, 2860, 1598, 1491 and 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35 (2 H, dd, J_1 = 8.5, J_2 = 1.6 Hz), 7.23 (2 H, dt, J_1 = 7.8, J_2 = 1.7 Hz), 6.96 (2 H, dt, J_1 = 7.1, J_2 = 1.5 Hz), 6.89 (2 H, d, J = 8.2 Hz), 6.21-6.20 (2 H, m), 4.63-4.62 (4 H, m), 3.87 (4 H, s), 3.67 (4 H, t, J = 6.8 Hz), 3.60 (4 H, s), 2.70 (4 H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.2, 130.6, 128.4, 128.2, 127.8, 121.1, 111.8, 70.9, 70.4, 68.0, 31.2, 30.3; HRMS (ESI): MNa^+, found 469.1479. $C_{24}H_{30}NaO_4S_2$ requires 469.1483.



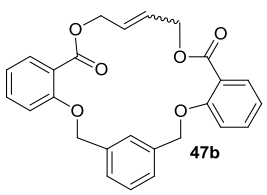
Compound 35w. Following the general procedure, **35w** was obtained as a brown solid (99 mg, 90%) (*E*/Z = 95:5); mp 107-109 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2918, 1724, 1600, 1451 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (2 H, dd, J_1 = 8.1, J_2 = 1.7 Hz), 7.45 (2 H, t, J = 7.2 Hz), 7.02 (2 H, t, J = 7.3 Hz), 6.97 (2 H, d, J = 8.4 Hz), 6.20 (2 H, s), 4.67 (4 H, br. s), 4.48-4.45 (4 H, m), 3.84-3.82 (4 H, m), 3.73 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.2, 157.7, 133.4, 132.0, 128.0, 121.2, 120.9, 114.2, 70.7, 69.3, 68.9, 64.5; HRMS (ESI): MNa^+, found 465.1513. $C_{24}H_{26}NaO_8$ requires 465.1525.



Compound 47a. Following the general procedure, **47a** was obtained as colourless solid (53 mg, 50%) (*E*/Z = 95:5); mp 181-183 ^{o}C; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1708, 1600, 1451, 1300 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2 H, dd, J_1 = 8.2, J_2 = 1.8 Hz), 7.47-7.35 (6 H, m), 7.04 (2 H, dt, J_1 = 7.6, J_2 = 0.9 Hz), 6.99 (2 H, d, J = 8.3 Hz), 6.12-6.10 (2 H, m), 5.38 (4 H, s), 4.85-4.84 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.0, 157.9, 134.8, 133.2, 131.7, 128.7, 128.2, 127.5, 121.8, 121.2, 114.7, 69.9, 64.3; HRMS (ESI): MH^+, found 431.1487. $C_{26}H_{23}O_6$ requires 431.1495.

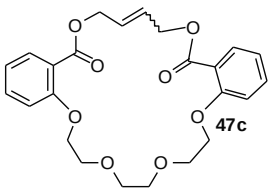


Compound 47b. Following the general procedure, **47b** was obtained as a colourless liquid (96 mg, 90%) (*E*/Z = 82:18); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2927, 1704, 1599, 1451 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.86-7.82 (3 H, m), 7.47-7.34 (5 H, m), 7.06-7.00 (4 H, m), 6.16-5.66 (2 H, m), 5.18 (4 H, s), 4.87-4.85 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C

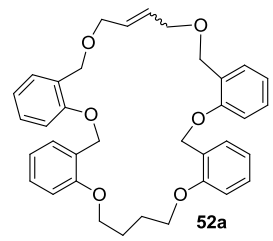


167.2, 157.8, 137.4, 133.5, 132.3, 128.4, 127.5, 127.4, 126.8, 121.1, 120.8, 113.9, 70.9, 64.5; HRMS (ESI): MNa^+, found 453.1319. $C_{26}H_{22}NaO_6$ requires 453.1314.

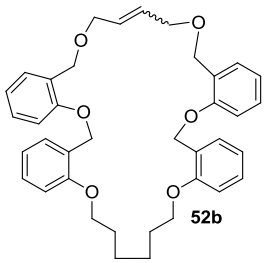
Compound 47c. Following the general procedure, **47c** was obtained as a colourless liquid (56 mg, 51%) (*E*/Z = 90:10); R_f (20% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 2933, 2870, 1699, 1490 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (2 H, dd, J_1 = 7.9, J_2 = 1.8 Hz), 7.45 (2 H, t, J = 7 Hz), 7.01 (2 H, t, J = 7.5 Hz), 6.93 (2 H, d, J = 8.2 Hz), 6.08-6.07 (2 H, m), 4.88-4.87 (4 H, m), 4.19 (4 H, t, J = 4.1 Hz), 3.93 (4 H, t, J = 4.1 Hz), 3.84 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.1, 157.9, 133.5, 132.0, 128.1, 120.5, 120.5, 112.8, 71.5, 69.5, 64.5; HRMS (ESI): MNa^+, found 465.1532. $C_{24}H_{26}NaO_8$ requires 465.1525.



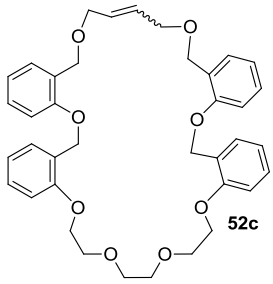
Compound 52a. Following the general procedure, **52a** was obtained as a colourless liquid (73 mg, 52%) (*E*/Z = 75:25); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2937, 2860, 1589, 1494 and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.41-7.34 (4 H, m), 7.28-7.16 (4 H, m), 7.01-6.80 (8 H, m), 5.77-5.75 (2 H, m), 4.93 (4 H, s), 4.52 (4 H, m), 4.02-4.00 (8 H, m), 1.87 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 156.7, 156.6, 130.0, 129.8, 129.6, 129.3, 129.2, 129.1, 128.9, 128.5, 128.4, 127.4, 125.6, 120.7, 120.6, 120.4, 120.3, 112.1, 111.3, 111.2, 70.3, 67.7, 67.5, 66.6, 66.4, 66.4, 66.3, 65.7, 26.2, 26.0; HRMS (ESI): MNa^+, found 589.2566. $C_{36}H_{38}NaO_6$ requires 589.2566.



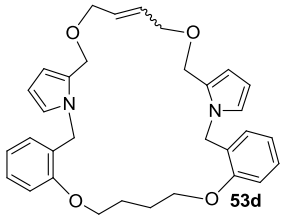
Compound 52b. Following the general procedure, **52b** was obtained as a colourless liquid (92 mg, 62%) (*E*/Z = 80:20); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2935, 2858, 1602, 1485 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.40-7.24 (4 H, m), 7.23-7.20 (4 H, m), 6.98-6.83 (8 H, m), 5.81-5.79 (2 H, m), 5.02 (4 H, s), 4.56 (4 H, s), 4.05-4.04 (4 H, m), 3.97 (4H, t, J = 6.1 Hz), 1.72 (4 H, br. s), 1.47 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 156.8, 156.7, 156.7, 129.9, 129.7, 129.4, 129.2, 129.1, 129.0, 128.8, 128.5, 128.4, 127.5, 125.6, 125.6, 120.6, 120.6, 120.4, 120.3, 120.3, 112.2, 112.1, 111.4, 111.3, 70.3, 67.9, 67.7, 66.7, 66.6, 66.3, 66.2, 65.8, 29.1, 29.1, 26.0, 25.8; HRMS (ESI): MNa^+, found 617.2878. $C_{38}H_{42}NaO_6$ requires 617.2879.



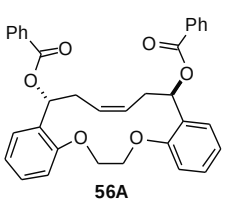
Compound 52c. Following the general procedure, **52c** was obtained as a colourless liquid (93 mg, 60%) (*E*/Z = 90:10); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2939, 2861, 1599, 1485 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.38 (4 H, t, J = 7 Hz), 7.23 (4 H, t, J = 7.4 Hz), 6.96-6.91 (6 H, m), 6.82 (2 H, d, J = 7.96 Hz), 5.76-5.75 (2 H, m), 5.09 (4 H, s), 4.51 (4 H, m), 4.07 (4 H, t, J = 4.6 Hz), 4.01-3.99 (4 H, m), 3.76 (4 H, t, J = 4.7 Hz), 3.59 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 156.3, 129.9, 129.3, 129.0, 129.0, 128.6, 127.4, 125.9, 120.8, 120.6, 112.1, 111.8, 71.0, 70.2, 69.7, 68.1, 66.5, 65.9; HRMS (ESI): MNa^+, found 649.2763. $C_{38}H_{42}NaO_8$ requires 649.2777.



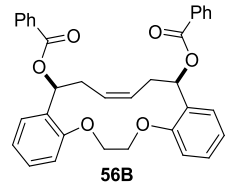
Compound 53d. Following the general procedure, **53d** was obtained as a colourless liquid (76 mg, 62%) (*E*/Z = 75:25); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 2854, 1602, 1493, 1260 and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.25 (2 H, t, J = 7.5 Hz), 6.92 (2 H, d, J = 8.1 Hz), 6.88 (2 H, t, J = 7.8 Hz), 6.76-6.74 (2 H, m), 6.41 (2 H, d, J = 7.4 Hz), 6.24-6.16 (4 H, m), 5.80 (2 H, br. s), 5.29 (4 H, s), 4.38 (4 H, s), 4.15-4.13 (4 H, m), 3.90-3.89 (4 H, m), 2.12-2.10 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.4, 128.8, 128.1, 127.6, 126.4, 123.6, 120.8, 110.6, 110.5, 107.0, 69.0, 67.9, 64.2, 45.8, 26.6; HRMS (ESI): MH^+, found 513.2738. $C_{32}H_{37}N_2O_4$ requires 513.2753.



Following the general procedure, the ring closing metathesis of substrate **55** and column chromatographic purification afforded the diastereomers **56A** and **56B**, (106 mg, 80%, combined yield of diastereomers). **Characterization data for the compound 56A.** Colourless solid, mp 167-169 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2930, 1717, 1602, 1490, 1274 and 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.12 (4 H, d, J = 7.1 Hz), 7.57-7.53 (2 H, m), 7.44 (4 H, t, J = 7.6 Hz), 7.35 (2 H, dd, J_1 = 7.6, J_2 = 1.4 Hz), 7.28-7.23 (2 H, m), 7.00-6.94 (4 H, m), 6.34 (2 H, dd, J_1 = 7.9, J_2 = 3.4 Hz), 5.70 (2 H, t, J = 5 Hz), 4.46 (4 H, s), 3.04-2.98 (2 H, m), 2.84-2.76 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 155.2, 132.9, 130.4, 129.7, 128.7, 128.4, 128.2, 126.0, 121.6, 113.0, 73.3, 67.4, 32.9; HRMS (ESI): MNa^+, found 557.1955. $C_{34}H_{30}NaO_6$ requires 557.1940.

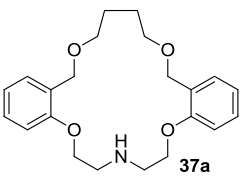


Characterization data for the compound 56B. Colourless solid, mp 153-155 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2957, 2853, 1721, 1602, 1451, 1273 and 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.11-8.09 (4 H, m), 7.56-7.51 (2 H, m), 7.42 (4 H, t, J = 7.6 Hz), 7.34 (2 H, dd, J_1 = 7.2, J_2 = 1.4 Hz), 7.26-7.22 (2 H, m), 6.98-6.93 (4 H, m), 6.30 (2 H, dd, J_1 = 8.5, J_2 = 1.4 Hz), 5.77 (2 H, t, J = 5.1 Hz), 4.52-4.45 (4 H, m), 3.03-2.98 (2 H, m), 2.67-2.59 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 155.0, 132.9, 131.1, 130.5, 129.7, 128.6, 128.4, 128.3, 125.9, 121.8, 113.3, 73.9, 67.5, 33.6; HRMS (ESI): MNa^+, found 557.1947. $C_{34}H_{30}NaO_6$ requires 557.1940.



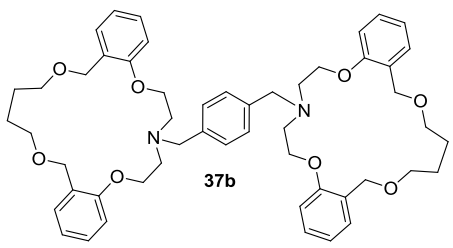
56B

Procedure for the synthesis of compound 37a from 34u. A solution of the substrate **34u** (0.25 mmol) in CH_2Cl_2 (7 mL) and Grubbs's catalyst (I generation, 5 mol%) was refluxed for 6 h. Then, the mixture was concentrated in vacuum and to the resulting crude mixture was added dry THF (2 mL) and Pd/C (10 mol%). Then, the reaction mixture was stirred at room temperature overnight under H_2 atm (1 atm). Next, the reaction mixture was filtered by using a layer of celite pad and the filtrate was evaporated under vacuum and the resulting crude reaction mixture was purified by silica gel column chromatography to afford the compound **37a** as a colourless liquid (58 mg, 63%) R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 2856, 1590, 1366 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.31-7.26 (4 H, m), 6.97-6.91 (4 H, m), 4.54 (4 H, s), 4.24 (4 H, t, J = 4.6 Hz), 3.55-3.53 (4 H, m), 3.21 (4 H, t, J = 4.6 Hz), 1.71-1.69 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 131.0, 129.5, 126.4, 120.8, 111.9, 69.5, 68.1, 67.5, 49.0, 25.9; HRMS (ESI): MH^+, found 372.2179. $C_{22}H_{30}NO_4$ requires 372.2175. The NH proton was not visible in the ^{1}H NMR spectrum.



37a

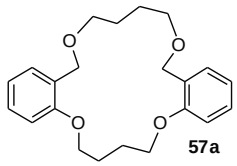
Procedure for the synthesis of compound 37b from 37a. A solution of the substrate **37a** (0.08 mmol), 1,4-bis(bromomethyl)benzene (0.04 mmol), anhydrous K_2CO_3 (0.10 mmol) in dry CH_3CN was refluxed for 30 h. After this period, the reaction mixture was allowed to cool at room temperature and this solution was added to H_2O (5 mL). Then, the mixture was extracted with ethyl acetate (3 X 10 mL), the combined organic layers were dried over anhydrous sodium



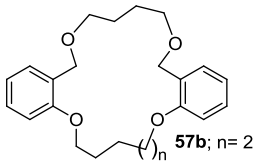
37b

sulphate and concentrated. Purification of the crude reaction mixture by silica gel column chromatography (40% EtOAc/Hexanes) afforded the compound **37b** as a colourless liquid (55 mg, 82%); R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3040, 2925, 2855, 1603, 1494 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.37 (4 H, s), 7.34 (4 H, dd, J_1 = 8.3, J_2 = 1.6 Hz), 7.29-7.24 (4 H, m), 6.95 (4 H, t, J = 7.4 Hz), 6.86 (4 H, d, J = 8.1 Hz), 4.53 (8 H, s), 4.13 (8 H, t, J = 5.9 Hz), 3.86 (4 H, s), 3.59 (8 H, t, J = 6.1 Hz), 3.24 (8 H, t, J = 5.9 Hz), 1.75-1.74 (8 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 138.5, 130.7, 129.2, 128.7, 126.7, 120.5, 111.3, 70.1, 68.1, 67.2, 58.5, 53.6, 26.0; HRMS (ESI): MH^+, found 845.4746. $C_{52}H_{65}N_2O_8$ requires 845.4741.

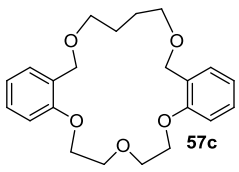
Compound 57a. Following the general procedure, **57a** was as a colourless liquid (56 mg, 64%); R_f (20% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2927, 2827, 1600, 1453, 1247 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.29-7.24 (4 H, m), 6.88-6.92 (4 H, m), 4.48 (4 H, s), 4.07 (4 H, br. s), 3.54 (4 H, t, J = 6.0 Hz), 2.04 (4 H, br. s), 1.71 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.6, 131.4, 129.5, 126.6, 120.3, 111.4, 70.0, 68.3, 67.6, 26.3, 26.0; HRMS (ESI): MNa^+, found 379.1883. $C_{22}H_{28}NaO_4$ requires 379.1885.


57a

Compound 57b. Following the general procedure, **57b** was obtained as a colourless liquid (71 mg, 77%); R_f (20% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2928, 2829, 1601, 1452, 1248 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31 (2 H, d, J = 8.1 Hz) 7.24 (2 H, t, J = 7.5 Hz), 6.91 (2 H, t, J = 7.5 Hz), 6.86 (2 H, d, J = 8.2 Hz), 4.52 (4 H, s), 4.01 (4 H, t, J = 5.5 Hz), 3.54 (4 H, t, J = 6.0 Hz), 1.92-1.86 (4 H, m), 1.78-1.67 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.5, 130.8, 129.2, 126.9, 120.5, 111.8, 69.8, 68.7, 67.7, 29.8, 25.9, 24.5; HRMS (ESI): MNa^+, found 393.2035. $C_{23}H_{30}NaO_4$ requires 393.2041.

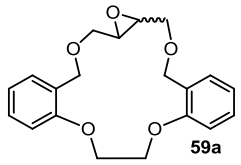

57b; n= 2

Compound 57c. Following the general procedure, **57c** was obtained as a colourless solid (86 mg, 93%); mp 64-66 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2928, 2829, 1601, 1452, 1248 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.24 (4 H, m), 6.94 (2 H, t, J = 7.8 Hz), 6.87 (2 H, d, J = 8.0 Hz), 4.51 (4 H, s), 4.16 (4 H, t, J = 4.9 Hz), 4.03 (4 H, t, J = 4.9 Hz), 3.55 (4 H, t, J =


57c

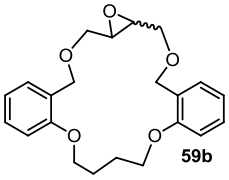
6.1 Hz), 1.71-1.68 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 131.0, 129.3, 126.9, 120.9, 111.9, 70.3, 69.9, 68.5, 67.9, 25.8; HRMS (ESI): MNa^+, found 395.1826. $C_{22}H_{28}NaO_5$ requires 395.1834.

Compound 59a. Following the general procedure, **59a** was obtained as a mixture of diastereomers (44 mg, 52%, *dr* = 70:30) after purification by column chromatography on silica gel (30% EtOAc/Hexanes). However, repetitive column purification of the mixture of

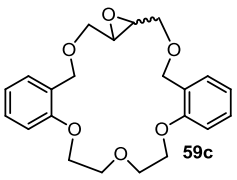


diastereomers gave the major diastereomer **59aA** in pure form and the ^{1}H/^{13}C data given here is for the major diastereomer **59aA**; colourless solid, mp 126-128 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2925, 1602, 1494, 1249 and 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.36 (2 H, d, *J* = 7.5 Hz), 7.29 (2 H, t, *J* = 7.8 Hz), 6.98 (2 H, t, *J* = 7.4 Hz), 6.91 (2 H, d, *J* = 7.9 Hz), 4.67 (4 H, s), 4.39-4.32 (4 H, m), 3.87 (2 H, dd, J_1 = 8.9, J_2 = 3.1 Hz), 3.38 (2 H, dd, J_1 = 7.4, J_2 = 5.7 Hz), 3.15-3.13 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 130.5, 129.3, 126.3, 121.1, 111.4, 68.7, 67.1, 66.8, 55.4; HRMS (ESI): MNa^+, found 365.1355. $C_{20}H_{22}NaO_5$ requires 365.1364.

Compound 59b. Following the general procedure, **59b** was obtained as a colourless liquid (49 mg, 53%) (*dr* = 86:14); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2922, 1602, 1455,



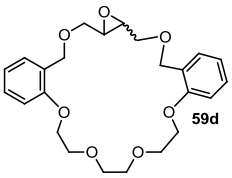
1368, 1240 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.21-7.17 (4 H m), 6.84 (2 H, t, *J* = 7.5 Hz), 6.79 (2 H, d, *J* = 8.4 Hz), 4.55-4.47 (4 H, m) 3.99 (4 H, s) 3.61-3.60 (4 H, m), 3.12 (2 H, t, *J* = 3.6 Hz), 1.98-1.96 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 131.1, 129.7, 126.0, 120.3, 111.2, 69.8, 69.0, 67.5, 54.7, 26.2; HRMS (ESI): MNa^+, found 393.1670. $C_{22}H_{26}NaO_5$ requires 393.1677.



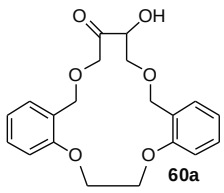
Compound 59c. Following the general procedure, **59c** was obtained as a colourless solid (43 mg, 45%) (*dr* = 67:33); mp 76-78 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (thin film): ν_{max} 2926, 1602, 1494, 1363, 1248 and 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32-7.24 (4 H, m), 6.97-6.92 (2 H, m), 6.86 (2 H, d, *J* = 8.2 Hz), 4.67-4.54 (4 H, m), 4.16 (4 H, t, *J* = 4.7 Hz), 4.03-3.97 (4 H, m), 3.67 (4 H, d, *J* = 4.0 Hz), 3.14 (2 H, t, *J* = 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9,

130.7, 129.4, 126.4, 120.9, 111.6, 70.3, 69.6, 68.4, 68.1, 54.7; HRMS (ESI): MNa^+, found 409.1613. $C_{22}H_{26}NaO_6$ requires 409.1627.

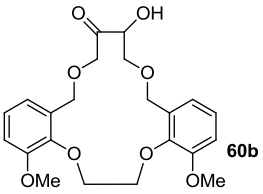
Compound 59d. Following the general procedure, **59d** was obtained as a colourless solid (66 mg, 62%) (*dr* = 85:15); mp 115-117 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2925, 1635, 1456, 1240 and 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31 (2 H, d, *J* = 7.8 Hz), 7.24 (2 H, s), 6.92 (2 H, t, *J* = 7.3 Hz), 6.82 (2 H, d, *J* = 7.8 Hz), 4.66 (2 H, d, *J* = 11.6 Hz), 4.58 (2 H, d, *J* = 11.6 Hz) 4.13 (4 H, br. s), 3.90 (4 H, br. s), 3.83 (6 H, s), 3.50-3.46 (2 H, m), 3.06 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 130.0, 129.2, 126.5, 120.7, 111.3, 71.4, 70.3, 69.9, 68.7, 68.3, 54.4; HRMS (ESI): MNa^+, found 453.1881. $C_{24}H_{30}NaO_7$ requires 453.1889.



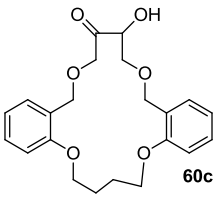
Compound 60a. Following the general procedure, **60a** was obtained as a colourless solid (40 mg, 45%), mp:116-117 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 3449, 2928, 1728, 1600, 1493 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.35-7.26 (4 H, m), 7.01-6.90 (4 H, m) 4.60 (3 H, dd, J_1 = 15.4, J_2 = 11.2 Hz), 4.46-4.41 (3 H, m), 4.39-4.29 (4 H, m), 4.24 (1 H d, *J* = 17.3 Hz), 3.90 (1 H, dd, J_1 = 6.6, J_2 = 4.0 Hz), 3.67 (1 H, dd, J_1 = 6.7, J_2 = 4.0 Hz), 3.52 (1 H, d, *J* = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.2, 157.2, 157.0, 132.0, 131.8, 129.9, 125.7, 125.6, 121.2, 120.9, 111.2, 111.1, 74.7, 73.4, 71.4, 69.1, 68.2, 66.7, 66.4; HRMS (ESI): MNa^+, found 381.1310. $C_{20}H_{22}NaO_6$ requires 381.1314.



Compound 60b. Following the general procedure, **60b** was obtained as a colourless liquid (71 mg, 34%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3470, 2942, 2839, 1731, 1588, 1481, 1281 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.03-6.91 (3 H, m), 6.88-6.87 (3 H, m), 4.73 (1 H, d, *J* = 10.9 Hz), 4.57 (2 H, t, *J* = 10.3 Hz), 4.46-4.16 (8 H, m), 4.01 (1 H, dd, J_1 = 10.1, J_2 = 3.4 Hz), 3.70 (1 H, dd, J_1 = 10.1, J_2 = 3.45 Hz), 3.81 (3 H, s), 3.78 (3 H, s), 3.53 (1H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.4, 152.8, 152.7, 146.8, 146.7, 131.3, 131.1, 124.3, 124.0, 123.3, 122.6, 112.9, 112.6, 74.9, 74.4, 72.9, 72.4, 72.0, 69.1, 68.8, 55.8; HRMS (ESI): MNa^+, found 441.1531. $C_{22}H_{26}NaO_8$ requires 441.1525.

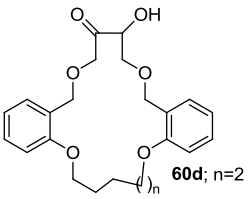


Compound 60c. Following the general procedure, **60c** was obtained as a colourless liquid (40 mg, 42%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3446, 2927, 1727, 1602, 1494, 1248 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31-7.24 (4 H, m), 6.93-6.85 (4 H, m), 4.58-4.41 (5 H, m), 4.31 (1 H, d, J = 16.9 Hz), 4.16-4.11 (3 H, m), 4.07-4.02 (2 H, m), 3.89 (1 H, dd, J_1 = 6.6, J_2 = 3.8 Hz), 3.74 (1 H, dd, J_1 = 6.2, J_2 = 3.8 Hz), 3.50 (1 H, d, J = 6.2 Hz), 2.10-1.99 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.5, 157.5, 157.4, 131.8, 131.6, 130.1, 129.9, 125.6, 125.3, 120.6, 120.5, 111.5, 111.4, 75.1, 74.1, 70.6, 69.3, 68.9, 67.8, 67.3, 26.6, 26.1; HRMS (ESI): MNa^+, found 409.1618. $C_{22}H_{26}NaO_6$ requires 409.1627.



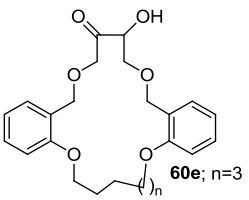
60c

Compound 60d. Following the general procedure, **60d** was obtained as a colourless liquid (50 mg, 25%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3470, 2938, 1731, 1602, 1590, 1454 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.27 (4 H, m), 6.99-6.89 (4 H, m), 4.73-4.31 (6 H, m), 4.09-4.05 (4 H, m), 3.94 (1 H, dd, J_1 = 6.7, J_2 = 3.4 Hz), 3.74 (1 H, dd, J_1 = 6.2, J_2 = 3.9 Hz), 3.56 (1 H, d, J = 6.5 Hz), 1.96-1.82 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 209.0, 157.2, 157.2, 130.8, 130.8, 129.6, 129.5, 125.5, 125.3, 120.5, 120.5, 111.4, 111.2, 75.0, 74.2, 71.0, 69.0, 68.8, 68.3, 68.2, 29.5, 29.5, 24.6; HRMS (ESI): MNa^+, found 423.1786. $C_{23}H_{28}NaO_6$ requires 423.1784. The OH proton was not visible in the ^1H NMR spectrum.



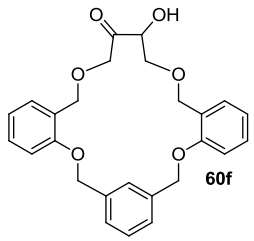
60d; n=2

Compound 60e. Following the general procedure, **60e** was obtained as a colourless liquid (72 mg, 35%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3450, 2933, 1731, 1602, 1244 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.34-7.28 (4 H, m), 6.97-6.89 (4 H, m), 4.66-4.34 (6 H, m), 4.09-4.05 (4 H, m), 3.82-3.61 (4 H, m), 1.89-1.57 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.4, 157.5, 157.4, 131.0, 130.9, 129.8, 129.8, 125.6, 125.5, 120.5, 120.4, 111.6, 111.5, 75.1, 74.1, 70.9, 69.2, 67.8, 67.8, 29.1, 29.0, 26.1, 26.0; HRMS (ESI): MNa^+, found 437.1936. $C_{24}H_{30}NaO_6$ requires 437.1940.



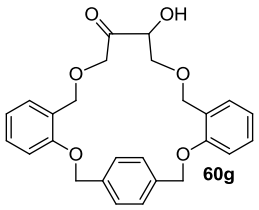
60e; n=3

Compound 60f. Following the general procedure, **60f** was obtained as a colourless liquid (43 mg, 40%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3436, 2925, 1728, 1666, 1600, 1494, 1240 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (1 H, s), 7.42-7.28 (7 H, m), 6.97 (4 H, t, J = 7.6 Hz), 5.14-5.06 (4 H, m), 4.67-4.50 (4 H, m), 4.39-4.37 (1 H, m) 4.28 (2 H, dd, J_1



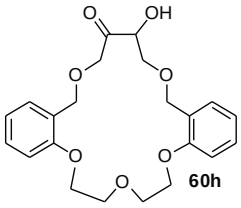
= 23.1, J_2 = 17.5 Hz), 3.87 (1 H, dd, J_1 = 6.6, J_2 = 3.6 Hz), 3.68 (1 H, dd, J_1 = 6.6, J_2 = 3.6 Hz), 3.54 (1 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.9, 157.0, 156.9, 137.6, 137.5, 131.0, 130.9, 129.8, 129.6, 128.5, 127.2, 126.6, 126.0, 125.7, 121.1, 121.0, 112.2, 111.9, 75.1, 74.2, 70.9, 70.4, 70.2, 69.0, 68.9; HRMS (ESI): MNa^+, found 457.1620. $C_{26}H_{26}NaO_6$ requires 457.1627.

Compound 60g. Following the general procedure, **60g** was obtained as a colourless solid (42 mg, 39%), mp 134-136 ^oC; R_f (50% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 3446, 2925, 1728, 1601, 1455, 1248 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (4 H, d, J = 1.6 Hz), 7.35-

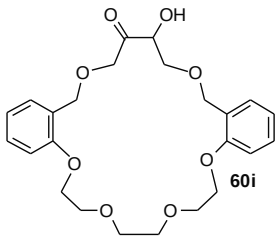


7.31 (2 H, m), 7.27-7.24 (2 H, m), 7.07 (2 H, d, J = 8.2 Hz), 6.99-6.95 (2 H, m), 5.05 (4 H, d, J = 7.9 Hz), 4.52-4.43 (2 H, m), 4.41-4.33 (2 H, m), 4.18 (2 H, d, J = 18.4 Hz), 3.99 (1 H, d, J = 18.4 Hz), 3.57 (1 H, dd, J_1 = 6.8, J_2 = 3.3 Hz), 3.34 (1 H, dd, J_1 = 6.9, J_2 = 3.3 Hz), 3.09 (1 H, d, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.2, 157.3, 157.2, 137.1, 136.7, 130.9, 130.8, 129.9, 129.8, 129.6, 129.5, 127.1, 126.6, 121.4, 121.3, 113.0, 112.8, 74.9, 74.6, 71.3, 71.1, 71.0, 69.5, 69.4; HRMS (ESI): MNa^+, found 457.1621. $C_{26}H_{26}NaO_6$ requires 457.1627.

Compound 60h. Following the general procedure, **60h** was obtained as a colourless liquid (50 mg, 25%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3415, 2927, 2874, 1728, 1601 and



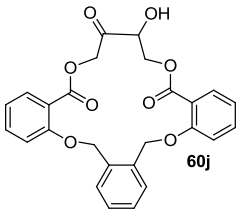
754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.26 (2 H, d, J = 7.8 Hz), 7.21 (2 H, d, J = 8.6 Hz), 6.91-6.87 (2 H, m), 6.82 (2 H, d, J = 8.1 Hz), 4.61-3.28 (8 H, m), 4.27-3.85 (9 H, m), 3.70-3.67 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.9, 157.1, 156.9, 131.0, 131.0, 129.7, 129.6, 125.9, 125.7, 121.0, 120.9, 111.8, 111.6, 75.0, 74.1, 71.0, 70.1, 70.1, 69.0, 69.0, 68.2, 68.2; HRMS (ESI): MNa^+, found 425.1571. $C_{22}H_{26}NaO_7$ requires 425.1576.



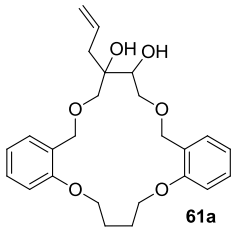
Compound 60i. Following the general procedure, **60i** was obtained as a colourless liquid (57 mg, 26%); R_f (50% EtOAc/Hexanes) 0.35; IR (CH_2Cl_2): ν_{max} 3441, 2926, 1730, 1602, 1494 and 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.24-7.17 (4 H, m), 6.89-6.77 (4 H, m), 4.58-4.33 (6 H, m), 4.10-4.06 (4 H, m), 3.84-3.70 (12 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 208.9, 157.0, 130.8, 130.7, 129.7, 129.5, 125.9, 125.8, 120.9, 120.8, 111.6, 111.6,

75.0, 74.0, 71.0, 70.9, 69.9, 68.9, 68.8, 68.0, 68.0; HRMS (ESI): MNa^+, found 469.1835. $C_{24}H_{30}NaO_8$ requires 469.1838.

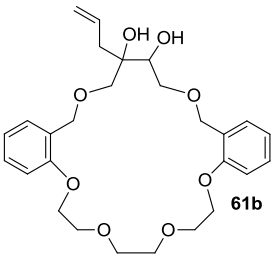
Compound 60j. Following the general procedure, **60j** was obtained as a colourless liquid (62 mg, 27%); R_f (50% EtOAc/Hexanes) 0.35; IR (CH_2Cl_2): ν_{max} 3425, 2953, 1716, 1600 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.91 (1 H, d, J = 7.7 Hz), 7.84 (1 H, d, J = 7.6 Hz), 7.56-7.33 (6 H, m), 7.15-6.99 (4 H, m), 5.60-5.13 (6 H, m), 4.72-4.52 (3 H, m), 3.41 (1 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 203.0, 167.3, 166.2, 158.5, 158.2, 135.9, 134.3, 133.9, 133.4, 132.9, 132.2, 129.6, 128.9, 128.1, 127.9, 121.3, 121.2, 120.4, 119.7, 114.4, 114.1, 73.7, 69.4, 69.2, 67.0, 66.0; HRMS (ESI): MNa^+, found 485.1221. $C_{26}H_{22}NaO_8$ requires 485.1212.



Compound 61a. Following the general procedure, **61a** was obtained (as a mixture of diastereomers) after purification by column chromatography as a colourless liquid (32 mg, 63%) (*dr* = 65:35); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3469, 2919, 2873, 1589, 1603 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.25-7.17 (4 H, m), 6.88-6.79 (4 H, m), 5.85-5.76 (1 H, m), 5.05-4.97 (2 H, m), 4.54-4.01 (8 H, m), 3.73-3.31 (5 H, m), 3.04 (2 H, br. s), 2.35-1.94 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.6, 157.6, 157.5, 133.8, 133.5, 132.0, 131.9, 131.8, 131.6, 130.0, 129.9, 129.8, 125.9, 125.8, 125.6, 125.5, 120.5, 120.5, 120.4, 118.1, 117.8, 111.5, 111.3, 111.3, 111.1, 74.9, 74.4, 73.8, 73.3, 72.7, 72.5, 72.0, 71.7, 69.4, 69.2, 69.1, 68.9, 67.8, 67.6, 67.4, 39.6, 38.5, 26.5, 26.5, 26.2; HRMS (ESI): MNa^+, found 451.2115. $C_{25}H_{32}NaO_6$ requires 451.2097.

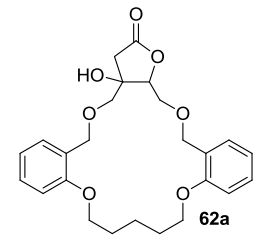


Compound 61b. Following the general procedure, **61b** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a colourless liquid (35 mg, 60%) (*dr* = 80:20); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3464, 2923, 2855, 1639, 1494 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.33-7.26 (4 H, m), 6.99-6.95 (2 H, m), 6.89-6.86 (2 H, m), 5.94-5.86 (1 H, m), 5.10-5.06 (2 H, m), 4.65-4.53 (4 H, m), 4.19-4.16 (4 H, m), 3.94-3.45 (13 H, m), 2.40 (2 H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.8, 135.5, 133.7, 132.4, 130.3, 130.1, 129.4, 129.2, 127.3, 126.6, 126.4, 120.8, 117.9, 117.1, 111.7, 111.6, 74.7, 73.3, 72.8, 71.7, 71.2, 71.1, 70.7, 69.9, 69.8, 69.7,

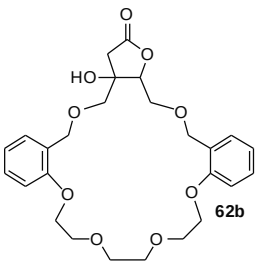


69.0, 68.8, 68.4, 68.2, 38.6; HRMS (ESI): MNa^+, found 511.2318. $C_{27}H_{36}NaO_8$ requires 511.2308. The OH protons were not visible in the ^1H NMR spectrum.

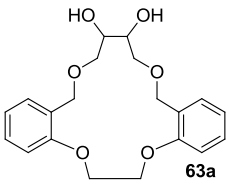
Compound 62a. Following the general procedure, **62a** was obtained as a colourless liquid (16 mg, 30%, single isomer); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3460, 2934, 1783, 1455 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.35-7.27 (4 H, m), 6.99-6.91 (4 H, m), 4.76 (2 H, dd, J_1 = 7.9, J_2 = 3.3 Hz), 4.61-4.46 (3 H, m), 4.12-4.01 (5 H, m), 3.87-3.81 (2 H, m), 3.57 (2 H, d, J= 4.6 Hz), 2.75 (1 H, d, J = 17.8 Hz), 2.44 (1 H, d, J = 17.8 Hz), 1.97-1.84 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.7, 157.7, 157.6, 131.5, 131.4, 130.2, 129.8, 125.6, 124.9, 120.7, 120.6, 111.9, 111.4, 80.8, 77.5, 72.8, 69.5, 69.0, 68.8, 68.3, 67.2, 39.8, 29.7, 29.6, 24.7; HRMS (ESI): MH^+, found 443.2068. $C_{25}H_{31}O_7$ requires 443.2070.



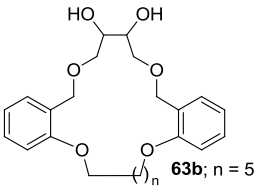
Compound 62b. Following the general procedure, **62b** was obtained as a colourless liquid (30 mg, 23%, single isomer); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3421, 2917, 2874, 1737, 1781, 1494 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.32-7.25 (4 H, m), 6.97 (2 H, t, J = 7.4 Hz), 6.89 (2 H, dd, J_1 = 7.1, J_2 = 3.2 Hz), 4.70-4.46 (4 H, m), 4.25-4.08 (4 H, m), 3.93-3.53 (14 H, m), 2.75 (1 H, d, J = 17.8 Hz), 2.58 (1 H, d, J = 17.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.9, 157.3, 157.2, 131.3, 131.0, 130.0, 129.8, 125.9, 125.5, 120.9, 120.8, 111.8, 111.6, 81.6, 77.4, 72.9, 71.1, 71.0, 69.9, 69.6, 69.4, 68.2, 68.1, 68.0, 40.2; HRMS (ESI): MNa^+, found 511.1944. $C_{26}H_{32}NaO_9$ requires 511.1944.



Compound 63a. Following the general procedure, **63a** was obtained (as a mixture of diastereomers) after purification by column chromatography as a colourless liquid (41 mg, 23%) (*dr* = 70:30); R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3412, 2924, 1602, 1494, 1258 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.27-7.22 (4 H, m), 6.90 (2 H, dt, J_1 = 7.8, J_2 = 0.9 Hz), 6.88-6.84 (2 H, m), 4.53-4.44 (4 H, m), 4.32-4.29 (4 H, m), 3.74-3.72 (2 H, m), 3.59-3.51 (4 H, m), 2.81 (1 H, br. s), 2.70 (1 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.3, 157.1, 132.0, 131.8, 129.9, 129.8, 126.3, 121.0, 121.0, 111.3, 111.2, 71.4, 71.3, 70.9, 68.5, 68.0, 66.9, 66.8; HRMS (ESI): MNa^+, found 383.1473. $C_{20}H_{24}NaO_6$ requires 383.1471.

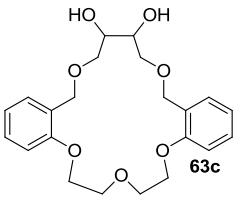


Compound 63b. Following the general procedure, **63b** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a colourless liquid



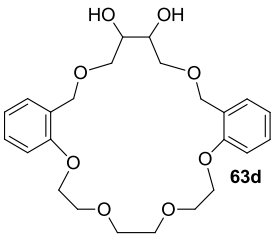
(62 mg, 30%) (*dr* = 80:20); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3456, 2936, 2866, 1602, 1454 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.33-7.29 (4 H, m), 6.96-6.90 (4 H, m), 4.61-4.48 (4 H, m), 4.06 (4 H, t, J = 5.8 Hz), 3.89-3.60 (6 H, m), 3.05-3.03 (2 H, m), 1.89-1.88 (4 H, m), 1.65-1.63 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.7, 131.3, 129.8, 126.1, 120.4, 111.6, 72.0, 70.2, 69.2, 67.8, 29.2, 25.9; HRMS (ESI): MNa^+, found 439.2116. $C_{24}H_{32}NaO_6$ requires 439.2097.

Compound 63c. Following the general procedure, **63c** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a colourless liquid



(64 mg, 32%) (*dr* = 80:20); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3445, 2926, 2873, 1590, 1452 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.33-7.28 (4 H, m), 6.97 (2 H, dt, J_1 = 7.1, J_2 = 0.94 Hz), 6.92 (2 H, d, J = 8.6 Hz), 4.69-4.50 (5 H, m), 4.21-3.91 (9 H, m), 3.71-3.66 (4 H, m), 2.99 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 131.4, 131.4, 129.8, 126.3, 126.3, 121.0, 112.0, 71.5, 71.4, 70.8, 70.2, 70.0, 69.0, 68.9, 68.5, 68.4; HRMS (ESI): MNa^+, found 427.1730. $C_{22}H_{28}NaO_7$ requires 427.1733.

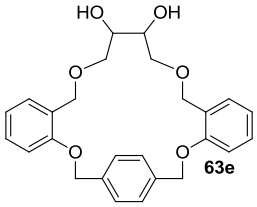
Compound 63d. Following the general procedure, **63d** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a colourless liquid



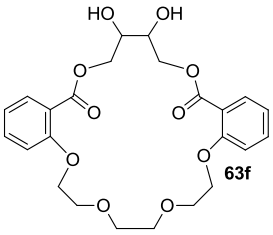
(56 mg, 25%) (*dr* = 87:17); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3412, 2924, 1602, 1494, 1258 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31-7.27 (4 H, m), 6.95 (2 H, dt, J_1 = 7.4, J_2 = 0.9 Hz), 6.88 (2 H, d, J = 8.5 Hz), 4.60 (2 H, s), 4.19-4.17 (5 H, m), 3.94-3.73 (16 H, m), 3.02 (1 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 131.0, 129.6, 126.3, 120.8, 111.6, 71.7, 71.1, 70.9, 70.0, 69.1, 68.2; HRMS (ESI): MNa^+, found 471.1998. $C_{24}H_{32}NaO_8$ requires 471.1995.

Compound 63e. Following the general procedure, **63e** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a colourless solid (93 mg, 43%) (*dr* = 80:20); mp 161-163 ^oC; R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max}

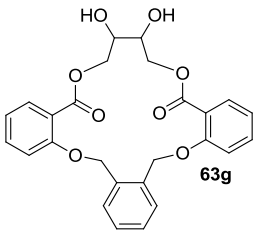
3450, 2929, 1460, 1490 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.48 (4 H, s), 7.38-7.28 (4 H, m), 7.10 (2 H, d, J = 7.9 Hz), 6.99 (2 H, t, J = 7.4 Hz), 5.10 (4 H, d, J = 1.9 Hz), 4.48 (4 H, s), 3.50-3.30 (6 H, m), 2.67 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 136.9, 131.1, 129.8, 129.1, 127.0, 121.2, 112.7, 72.7, 70.7, 69.9, 69.4; HRMS (ESI): MNa^+, found 459.1790. $C_{26}H_{28}NaO_6$ requires 459.1784.



Compound 63f. Following the general procedure, **63f** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a colourless liquid (107 mg, 45%) (*dr* = 80:20); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3448, 2928, 1699, 1490 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (2 H, d, J = 7 Hz), 7.45 (2 H, t, J = 7.6 Hz), 7.01 (2 H, t, J = 7.4 Hz), 6.92 (2 H, d, J = 8.4 Hz), 4.47-4.43 (4 H, m), 4.19-4.14 (6 H, m), 3.93-3.74 (10 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.4, 157.7, 133.6, 132.3, 120.7, 120.5, 112.8, 71.4, 69.9, 68.6, 68.4, 65.8; HRMS (ESI): MNa^+, found 499.1590. $C_{24}H_{28}NaO_{10}$ requires 499.1580.

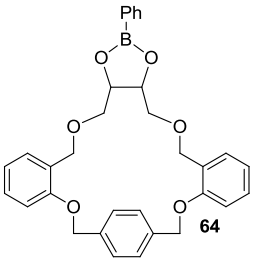


Compound 63g. Following the general procedure, **63g** was obtained (as a mixture of diastereomers) after purification by column chromatography on silica gel as a brown solid (95 mg, 41%) (*dr* = 90:10); mp 174-176 ^oC; IR R_f (50% EtOAc/Hexanes) 0.45; (CH_2Cl_2): ν_{max} 3386, 2923, 1704, 1600, 1453, 1260 and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (2 H, dd, J_1 = 6.1, J_2 = 1.8 Hz), 7.53-7.42 (6 H, m), 7.08-7.04 (4 H, m), 5.31 (4 H, dd, J_1 = 13.8, J_2 = 11.8 Hz), 4.40-4.30 (4 H, m), 3.99-3.97 (2 H, m), 2.29-2.28 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 157.7, 134.7, 133.5, 132.0, 129.7, 128.9, 121.3, 121.2, 113.9, 68.9, 68.9, 65.5; HRMS (ESI): MH^+, found 465.1546. $C_{26}H_{25}O_8$ requires 465.1549.



Procedure for the synthesis of pinacol boronate moiety installed macrocyclic crownophane 64.[25b] To a solution of aryl boronic acid (0.12 mmol) in anhydrous THF (2 mL) was sequentially added a solution of $FeCl_3$ (5 mol%) in H_2O (0.5 mL), imidazole (0.36 mmol) and the diol substrate **63e** (0.12 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 8 mL). The combined organic extracts were dried over Na_2SO_4 and solvent was evaporated under vacuum.

The resulting oil was then purified by a filtration through a silica gel plug (eluting with Et_2O) to afford the macrocyclic compound **64** as a mixture of diastereomers (*dr* = 85:15); colourless



liquid (56 mg, 90%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2922, 1603, 1493, 1455, 1259, 1091 and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.90 (2 H, dd, J_1 = 6.7, J_2 = 1.3 Hz), 7.48 (4 H, s), 7.44-7.32 (7 H, m), 7.08 (2 H, d, J = 7.7 Hz), 6.99 (2 H, t, J = 6.3 Hz), 5.14 (4 H, s), 4.57 (4 H, dd, J_1 = 18.4, J_2 = 10.8 Hz), 4.24-4.22 (2 H, m), 3.42-3.35 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 137.0, 135.1, 131.5, 131.4, 129.7, 128.8, 127.7, 127.0, 121.1, 112.8, 78.6, 72.6, 70.4, 69.2; HRMS (ESI): MNa^+, found 545.2128. $C_{32}H_{31}BNaO_6$ requires 545.2111.

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16. (a) Umemiya, T.; Takeuchi, D.; Osakada, K. *J. Organomet. Chem.* **2006**, *691*, 5260 (b) See the foot note of Table 2 and based on the X-ray structures of **35jA** (major, *E*-isomer), **35jB** (minor, *Z*-isomer) and **47a** (major, *E*-isomer, Figure 3) and in concurrence with the literature reports, see ref. [10d-i,12,13], the major isomers formed in the RCM reactions of substrates **34a-u**, **42**, **43e**, **46a-c**, **51a-c** and **53c** are proposed to have the *E*-geometry. (c) The stereochemistry of the macrocyclic olefin **30b** was not determined as the RCM reaction of the substrate **30a** gave the macrocyclic olefin **54b** in <15% yield as an impure mixture and the compound **54b** could not be isolated in pure form. (d) When compared to the other substrates, the RCM reaction of the substrate **55** gave the macrocyclic olefin **56** with *Z*-stereochemistry as the major product. Though an exact reason is not clear at this stage, presumably, the protected homoallyl alcohol group (OCOPh) directing or imposing the RCM reaction of the substrate **55** to give the macrocyclic olefins **56** with Z-stereochemistry.
17. For selected papers dealing on crown ether-type macrocyclic lactones, see: (a) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981,** *103*, 5183. (b) Galli, C.; Mandolini, L. *J. Org. Chem.* **1991**, *56*, 3045. (c) Vujasinović, I.; Veljković, J.; Mlinarić-Majerski, K.; Molčanov, K.; Kojić-Prodić, B. *Tetrahedron* **2006**, *62*, 2868. (d) Ertul, S.; Bayrakci, M.; Yilmaz, M. *Separ. Sci. Technol.* **2011**, *46*, 625. (e) Ertul, S.; Bedük, A. D.; Bayrakci, M.; Güler, E. *Chem. Pap.* **2008**, *62*, 589.

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20. Crystallographic data of X-ray crystal structures of the compounds **35jA** (major, *E*-isomer, CCDC 921754), **35jB** (minor, *Z*-isomer, CCDC 921753), **47a** (CCDC 1056418), **56A** (*R*,R**, CCDC 1056420), **56B** (*R*,S**, CCDC 1056417), **59aA** (major isomer, CCDC 908393), **60a** (CCDC 1056419) and **60g** (CCDC 910641) have been deposited with the Cambridge Crystallographic Data Centre.
21. (a) Xia, Y.; Liu, Z.; Xiao, Q.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J.; *Angew. Chem. Inl. Ed.* **2012**, *51*, 5714. (b) Zhou, Z.; Cao, C.; Liu, Q.; Jiang, R.; *Org. Lett.* **2010**, *12*, 1780. (c) Purushothaman, S; Raghunathan, R.; *Tetrahedron. Lett.* **2009**, *50*, 6848. (d) Arumugam, N.; Raghunathan, R. *Tetrahedron Lett*. **2006**, *47*, 8855.
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23. (a) Quinn, T. P.; Atwood, P. D.; Tanski, J. M.; Moore, T. F.; Folmer-Andersen, J. F.; *J. Org. Chem.* **2011**, *76*, 10020. (b) Azadbakht, R.; Parviz, M.; Tamari, E.; Keypour, H.; Golbedaghi, R. *Spectrachimica Acta Part A* **2011**, *82*, 200 (c) Singh, P.; R. Verma, V.; Singh, M. S.; *Tetrahedron Lett.*, **2011**, *52*, 3818. (d) Kamal, A.; Malik, M. S.; Bajee, S.; Azeeza, S.; Faazil, S.; Ramakrishna, S.; Naidu, V.G.M.; Vishnuwardhan, M.V.P.S. *Eur. J. Med. Chem*. **2011**, *46*, 3274. (e) Mayence, A.; Eynde, J. J. V.; Kaiser, M.; Brun, R.; Yarlett, N.; Huang, T. L. *Bioorg. Med. Chem.* **2011**, *19*, 7493.
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Chapter 2: Glaser-Eglinton-Hay sp-sp coupling and macrocyclization: construction of new classes of polyether macrocycles having a 1,3-diyne or triazole unit and thia-polyether macrocycles.

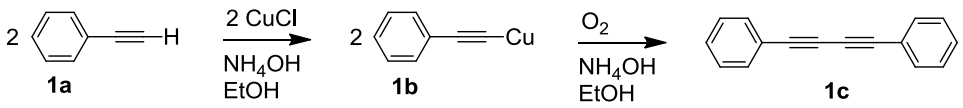
Introduction

Macrocycles are broadly distributed in nature and are common synthetic targets in organic and medicinal chemistry research.[1-2] Some representative examples of macrocycles include the antibiotics valinomycin and gramicidin S, the macrolide nonactin, cyclic DNA and plasmids. Of a particular interest, rigidified macrocycles are fascinating molecular frameworks.[3-4] The construction of rigidified macrocycles (e.g., diyne unit-based rigidified macrocycles) considered as one of the interesting chemical transformations. Because of their shape persistent skeletons and distinctive properties, rigidified and strained macrocycles have found significant applications in various research areas of chemical sciences.[1-4] Notably, diyne unit-based molecules/macrocycles are key building blocks in industrial and synthetic chemistry and electronic/optical materials.[3,4] The incorporation of a diyne unit in the molecular frameworks is considered as an important molecular tool to constrain the molecular conformation.[5-7] Accordingly, the inherent rigidity and directionally defined precise cylindrical symmetry of diyne units have been well exploited in different areas of chemical science. Diverse family of diyne unit-based rigidified shape persistent macrocyclic systems *e.g.* annulenes, rotaxanes, cyclophanes, cage compounds and artificial receptors have been constructed using Cu or Pd-based Glaser-Eglinton-Hay-type strategy.[5-7]

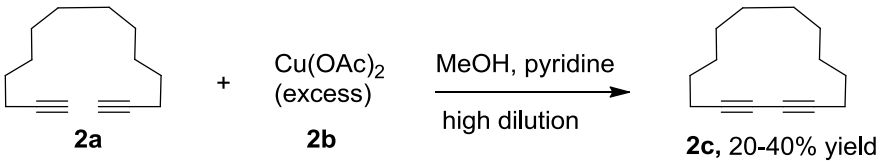
Since the Pederson's discovery of first macrocyclic crown ether in 1967, crown ether/polyether molecules have been considered as imperative classes of macrocyclic systems in supramolecular chemistry.[8a] A wide range of methods were employed for the synthesis of different classes of crown ether-type macrocycles and the functional derivatization or periphery modification of crown ether-type macrocycles.[9] However, the synthesis of crown ether-type macrocycles having a diyne unit-based cylindrical rigid backbone has not been well explored. The incorporation of a diyne unit as a part of crown ether/polyether macrocycles could provide directionally precise rigidity to polyether macrocycles and perhaps, new insights on their supramolecular chemistry. In line with the objective of the this thesis work, in the following section some of the literature

works that deal on the synthesis of diyne unit-based rigidified shape persistent macrocyclic systems *via* Glaser-Eglinton-Hay-type strategy are described.

History of Glaser coupling reaction and synthesis of macrocyclic systems using this technique.

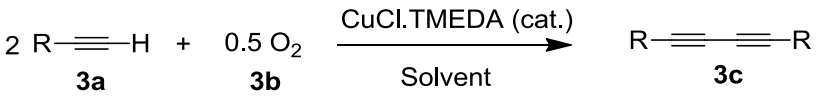


Scheme 1. The first acetylenic coupling described by Glaser.



Scheme 2. Acetylenic coupling described by Eglinton and Galbraith with copper(II) salt.

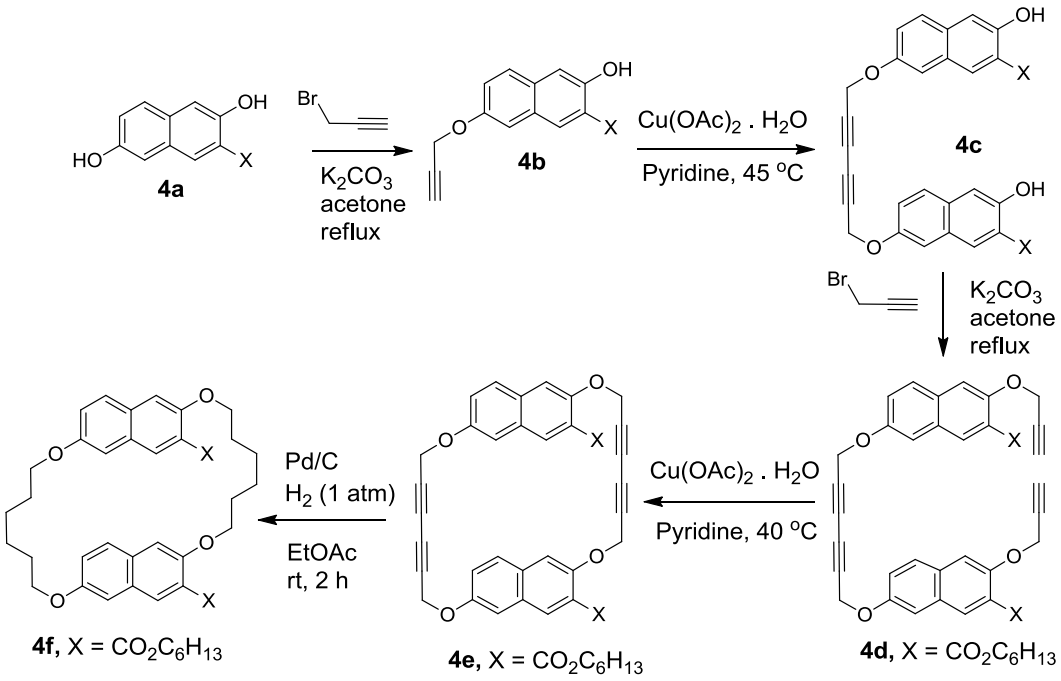
Carl Glaser[7a-b] in 1869 at the University of the Bonn, discovered the acetylenic coupling when phenyl acetylene **1a** treated with copper (I) catalyst in open air (Scheme 1). The acetylenic coupling method reported by Glaser failed to see a broad application due to the failed attempts of the isolation of potentially explosive copper acetylide intermediate. A further milestone in acetylenic coupling was reported by Eglinton and Galbraith in 1956.[7c] They revealed the use of a copper(II) salt catalyst for the oxidation in methanolic pyridine solution. The method described by Eglinton and Galbraith proved to be great for the synthesis of new unsaturated macrocycles in the upcoming years.



Scheme 3. Oxidative acetylenic coupling described by Hay.

Another important modification was reported by Hay[7d] in 1960, who performed the acetylenic coupling reaction with O_2 using catalytic amounts of *N,N,N',N'*-tetrmethylethylenediamine (TMEDA) as bidentate ligand and copper(I) chloride (Scheme 3).

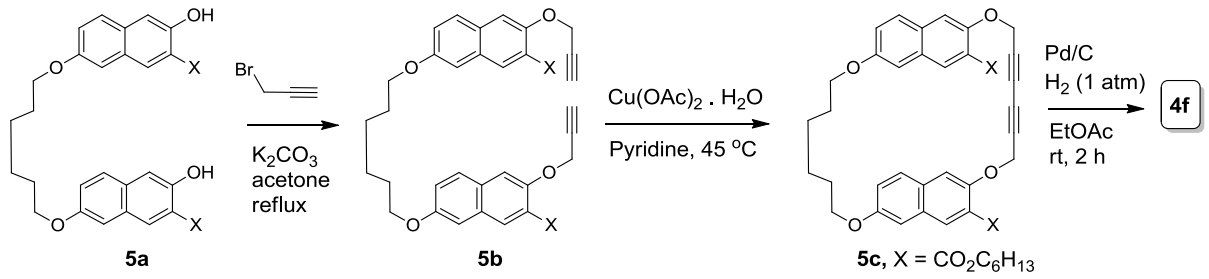
Modification by Eglinton and Galbraith opened a new route for the synthesis of novel class of rigidified macrocycles having a 1,3-dialkyne unit using copper (II) salt. Whitlock, Jr. reported[10a] the synthesis a series of rigid alkyne-alkyne unit based cyclophane **4e** *via* oxidative acetylic cyclization of **4d** in the presence of copper (II) acetate and pyridine as a solvent (Scheme 4). They described the synthesis of naphthalenophane **4f** *via* two different routes. In an initial route, naphthalenophane **4f** was prepared from starting material **4b** (Scheme 4). Cupric acetate-based coupling of **4b** in pyridine afforded **4c**, which was propargylated to afford **4d** (Scheme 4). Cyclization of **4d** (ca. 0.05 M) in pyridine with cupric acetate gave naphthalenophane **4e** in 49% yield. Then, the Pd-catalyzed hydrogenation reaction gave the corresponding macrocyclic naphthalenophane **4f**.



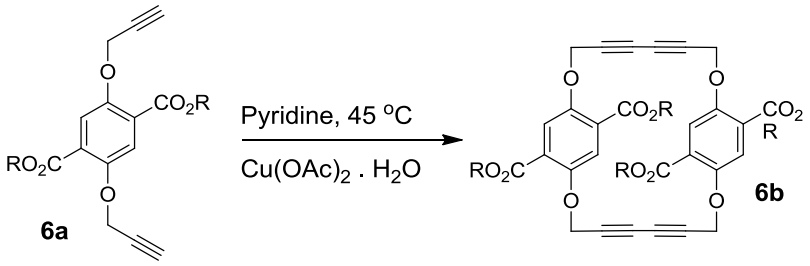
Scheme 4. Synthesis of naphthalenophane macrocycle **4f** *via* oxidative acetylenic coupling.

The other route included the catalytic hydrogenation of compound **4c** to afford **5a**. Then, **5a** was subjected to propargylation to afford **5b**. Next, the compound **5b** was subjected to the Cu-based intramolecular coupling to afford **5c**. Then, the Pd-catalyzed hydrogenation of **5c** gave the corresponding macrocyclic naphthalenophane macrocycle **4f** (Scheme 5). Whitlock, Jr. also reported[10b] the synthesis a series of rigid ω-phenylalkyl esters cyclophane **6b** having the cavity

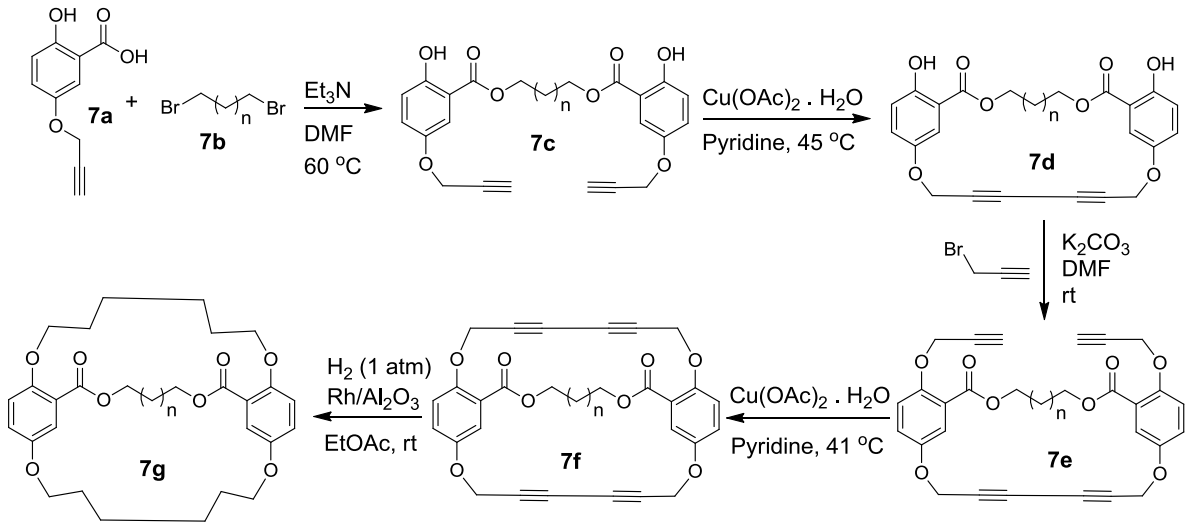
ca. 4.5 Å by 6 Å *via* an oxidative cyclodimerization of substrate **6a** in the presence of copper(II) acetate and pyridine as a solvent (Scheme 6).



Scheme 5. Synthesis of naphthalenophane **4f** *via* oxidative acetylenic coupling.

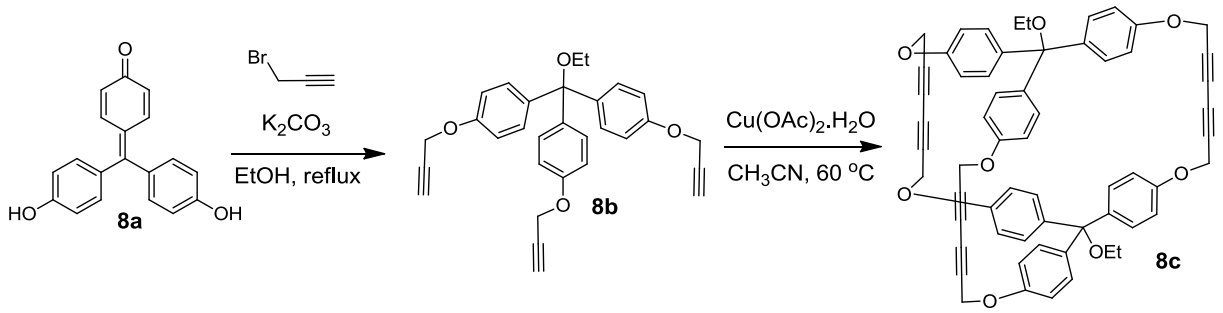


Scheme 6. Synthesis of rigid diyne bridge containing cyclophane macrocycle **6b**.



Scheme 7. Synthesis of tribridged cyclophatetrayne macrocycles **7f//7g** *via* oxidative acetylenic coupling.

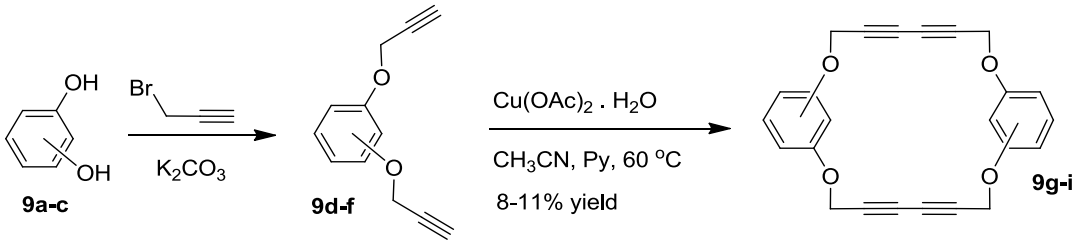
Brown and coworkers demonstrated[10c] the synthesis of tribridged cyclophanes **7f** by oxidative cyclization in 3 steps starting from the precursor **7c** (Scheme 7). Starting material **7c** was prepared by treating di-akylbromides with 2-hydroxy-5-(prop-2-yn-1-yloxy)benzoic acid **7a**. Then, the copper(II) aceate-based oxidative cyclization of **7c** in the presence of pyridine solvent afforded the macrocycle **7d** (Scheme 7). Next, the propargylation of free hydroxyl group of **7d** followed by oxidative coupling afforded **7f**. Further, the rhodium-catalyzed hydrogenation of macrocycle **7f** gave the macrocyclic skeleton **7g** (Scheme 7).



Scheme 8. Synthesis of triply bridged large cavity containing rigid macrocycle **8c** *via* Eglinton oxidative coupling.

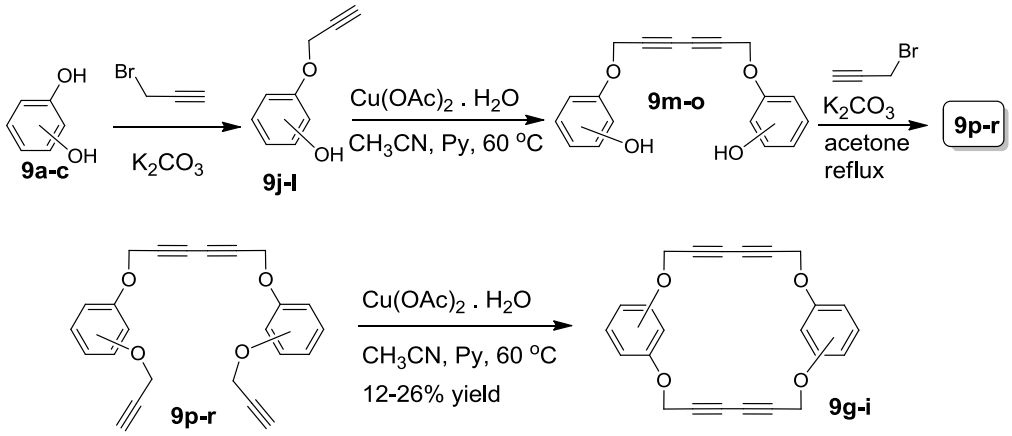
Vogtle *et al.* reported[10d] triply bridged concave dyestuffs bearing a large rigid cavity containing macrocyclic systems **8c** *via* the Eglinton oxidative coupling cyclodimerization process by using copper(II) acetate in pure acetonitrile (Scheme 8). The X-ray structure analysis proved that acetonitrile was enclosed inside the cavity. Possibly the "half cavity" starting material **8b** has the tendency to complex with acetonitrile, which might lead to a preorganization of alkyne units and which also could favor the oxidative cyclodimerization to afford bicyclic macrocyclic compound **8c** (Scheme 8).

Sankararaman and co-workers reported[11a] the synthesis of *ortho*, *meta*, and *para* isomers of shape-persistent [8.8]cyclophanes **9g-i** bearing rigid cavities of 1,6-dioxahexa-2,4-diyne bridges using modified Eglinton coupling in the presence of $Cu(OAc)_2.H_2O$ in CH_3CN and pyridine (Scheme 9). Acetylenic units as bridges impart rigidity to the cyclophanes, and the size of the cavity possessed by cyclophane was controlled by the number of acetylenic units in the bridge and its (*ortho*, *meta*, and *para*) connectivity to the arene units. The isomeric [8.8]-cyclophanes **9g-i** were synthesized from the corresponding benzenediols **9a-c** (Scheme 9).



Scheme 9. Syntheses of [8.8]Cyclophanes (**9g-i**) using Eglinton coupling.

In an attempt to improve the overall yield, an alternative route involving the stepwise construction of the bridges was attempted (Scheme 10). The benzenediols **9a-c** were first converted into the monopropargyl ethers **9j-l**, which were then subjected to the Eglington coupling to give the singly bridged precursors **9m-o** (Scheme 10). Next, the propargylation of free OH groups of **9m-o** afforded the compounds **9p-r**, which were then subjected to the Eglington coupling to give the isomeric cyclophanes **9g-i** in slightly improved yields (Scheme 10).

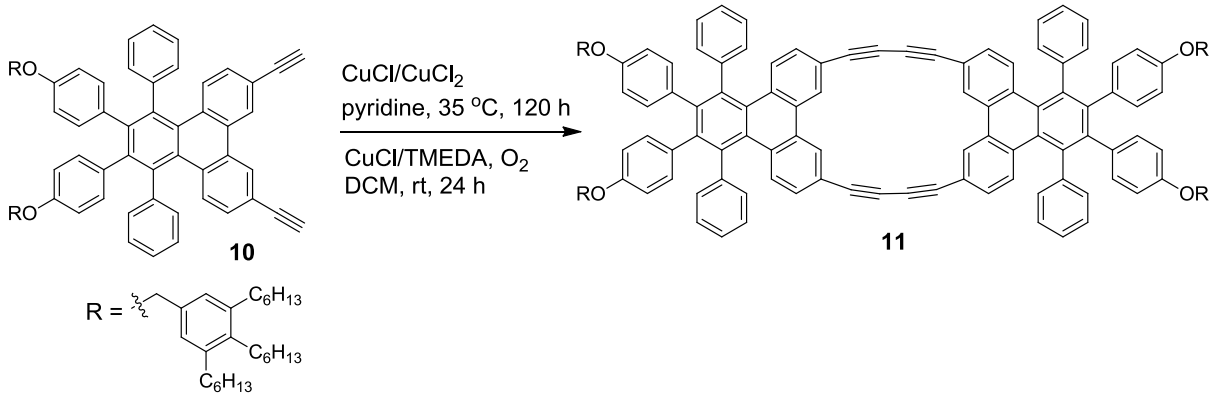


Scheme 10. Syntheses of [8.8]cyclophanes **9g-i** using Eglinton coupling.

In recent years, several shape persistent macrocycles/annulene and tubular or more complex molecular structures were synthesized *via* efficient oxidative dimerization of two acetylene-terminated precursors under pseudo high-dilution conditions, using CuCl or $Cu(OAc)_2$ and pyridine. These rigid macrocyclic skeletons have found interesting photophysical, light harvesting and material properties.[11b-d] Further, nano-sized shape persistent macrocycles containing appropriate functional groups in intra-annular sites can also act as biological

receptors.[11b-d] Some of the representative works dealing on the synthesis of shape persistent macrocycles/annulene and tubular or more complex molecular structures are described in the following section.

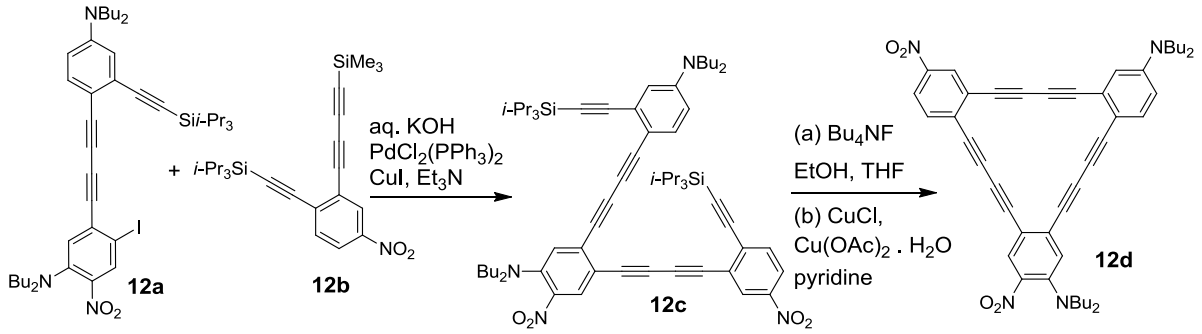
Recently, Höger group[12a] reported the synthesis and characterization of a shape-persistent triphenylene-butadiynylene macrocycle **11** (Scheme 11). The Glaser-Eglinton oxidative coupling of bisacetylenes **10** using $CuCl/CuCl_2$ (catalyst) and pyridine/TMEDA (ligand) in dichloromethane (DCM) solvent at rt afforded various shape-persistent triphenylene-butadiynylene macrocycles **11** (Scheme 11).



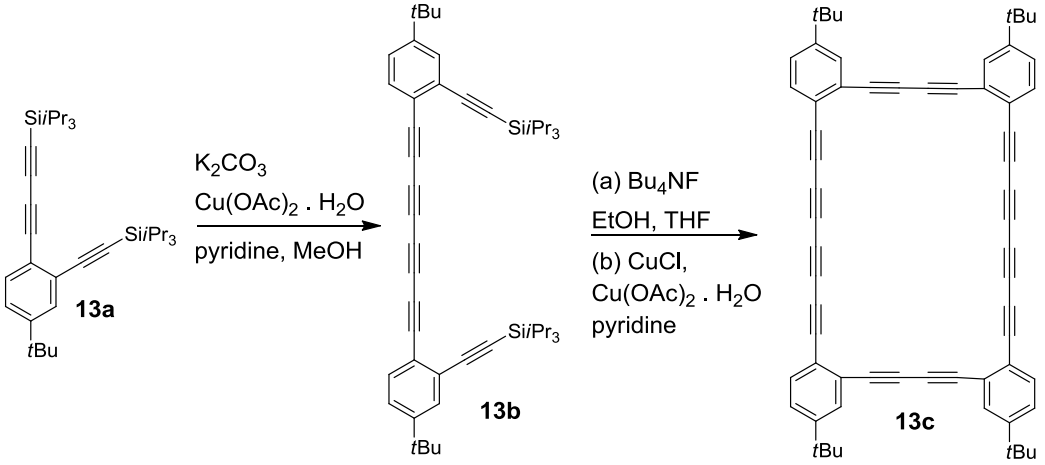
Scheme 11. Synthesis of shape persistence triphenylene-butadiynylene macrocycle **11**.

Haley and co-workers[12b,c] revealed an interesting synthesis of dehydrobenzo[18]annulenes **12d** *via* intramolecular oxidative coupling of **12c** by using excess of both CuCl and $Cu(OAc)_2$ in pyridine (Scheme 12).

Haley and co-workers showed the intermolecular coupling of **13a**, involving the selective deprotection of trimethylsilyl-protected alkyene **13a** followed by $Cu(OAc)_2$-promoted coupling afforded the compound **13b**. Then, the treatment of **13b** with Bu_4NF and then with CuCl and $Cu(OAc)_2$ in pyridine under pseudo-high dilution condition afforded the dehydrobenzo[32]annulenes **13c** (Scheme 13).

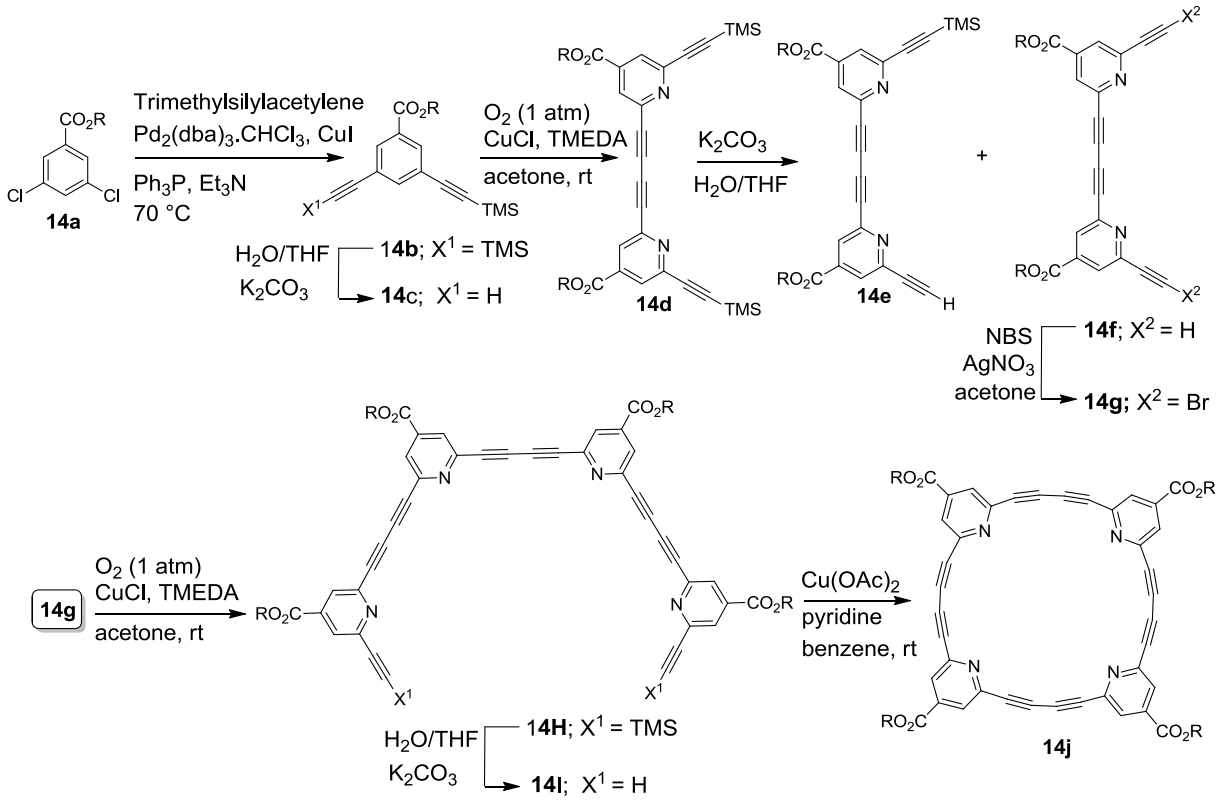


Scheme 12. Synthesis of functionalized dehydrobenzo[18]annulenes **12c** using CuCl and $Cu(OAc)_2$.

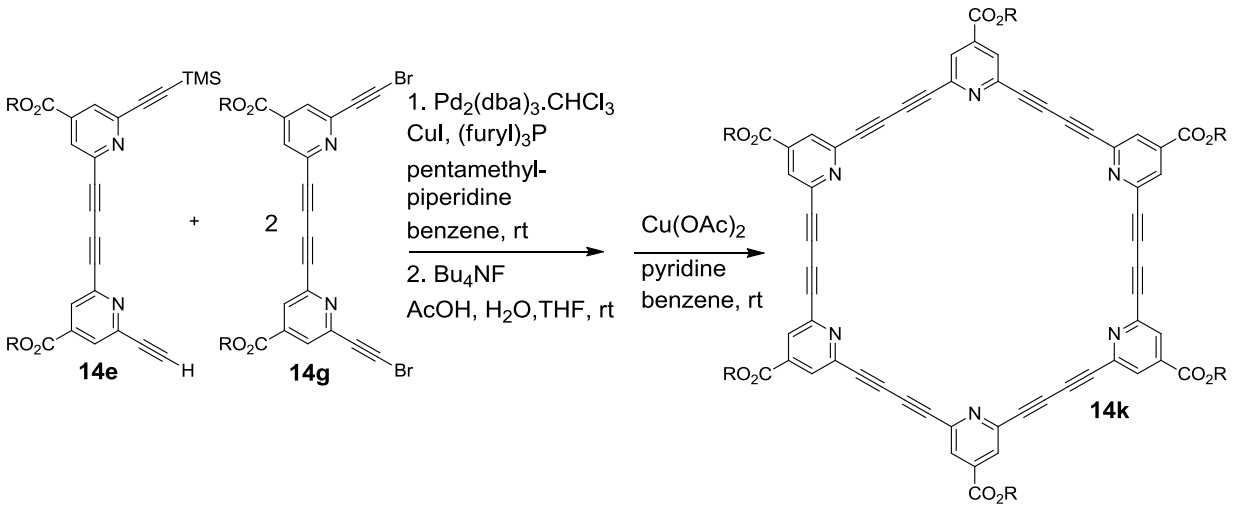


Scheme 13. Synthesis of functionalized dehydrobenzo[32]annulenes **13c** using CuCl and $Cu(OAc)_2$.

Tobe group reported[12d] the synthesis of butadiyne-bridged [4_4](2,6)pyridinophane **14j** and [4_6](2,6)pyridinophane **14k** derivatives (Schemes 14 and 15). The macrocycles [4_4] (2,6)-pyridinophane **14j** and [4_6] (2,6)-pyridinophane **14k** were synthesized starting from the compound **14a** involving copper-based acetylic coupling as one of the key steps and the overall synthetic steps involved are outlined in the corresponding Schemes 14 and 15. The pyridyl moiety was oriented endocyclic and exocyclic with respect to the macrocyclic core and adopted a nearly planar conformation in the solid state without any ring strain. These molecules were found to readily function as the macrocyclic analogues of bipyridines and self-assemble into highly ordered systems and have the tendency to coordinate selectively with organic cations.



Scheme 14. Synthesis of [4_4] (2,6)-pyridinophane **14j**.

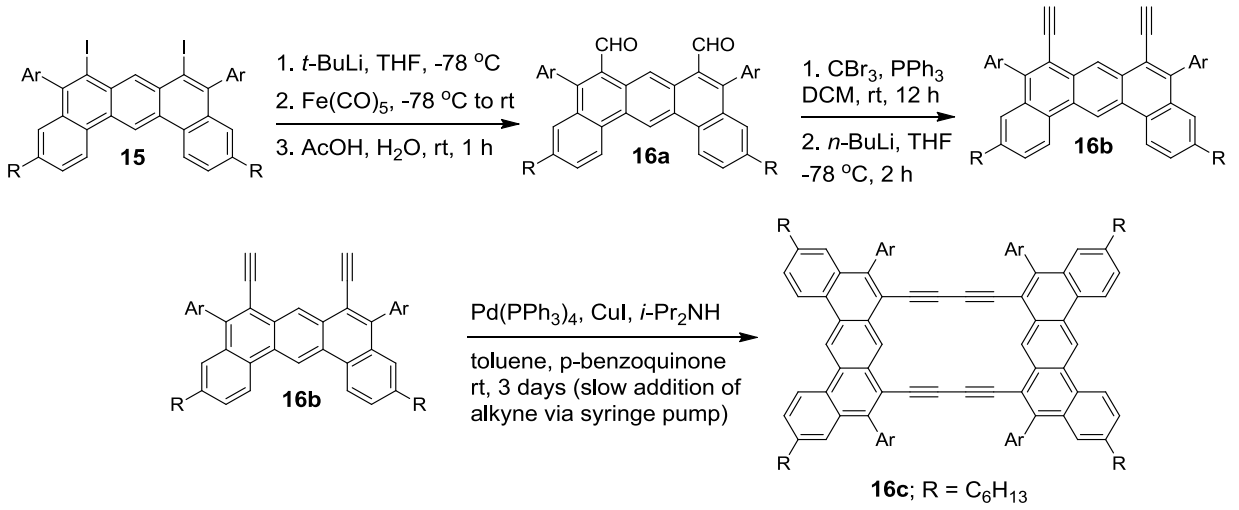


Scheme 15. Synthesis of [4_6] (2,6)-pyridinophane **14k**.

Further, Tobe group studied the binding ability of pyridinophanes **14j** and **14k** with the large organic cations, such as tropylium ion by using the NMR spectroscopy. It was observed that the tropylium cation was slightly larger than the cavity of pyridinophanes **14j** but was too small to fit

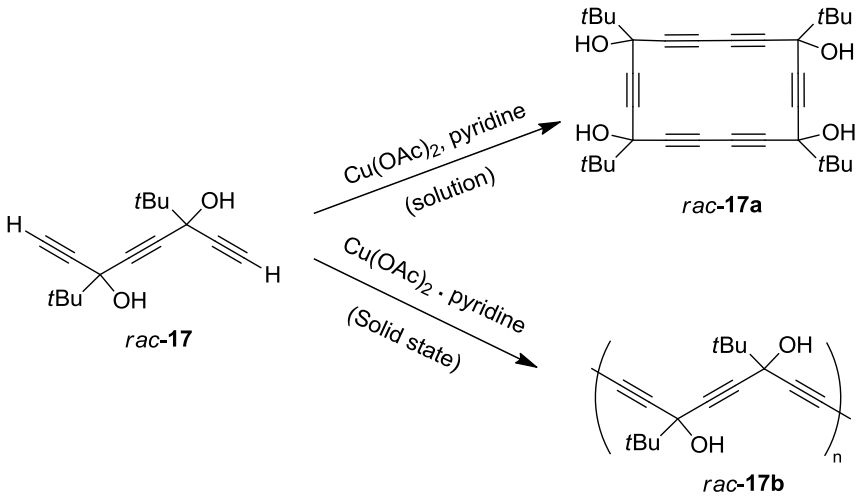
in the cavity of pyridinophanes **14k**. The chemical shift change of the aromatic protons of pyridinophanes **14j** and **14k** on titration with tropylium tetrafluoroborate in $CDCl_3/CD_3CN$ proved that macrocycles **14j** and **14k** form not only 1:1 but also 2:1 complexes with large tropylium cation.

Swager and co-workers reported[13a] the synthesis of several shape persistence fluorescent macrocycles based on 1,3-butadiyne-bridged dibenz[*a*,*j*]anthracene subunits **16c** *via* Glaser-the Eglinton oxidative coupling. These compounds displayed amazing photophysical properties and found applications in optoelectronic devices (Scheme 16). Functionalized dibenz[*a*,*j*]anthracene units with alkyne substituents **16c** were prepared in several steps involving Glaser coupling as one of the key steps (Scheme 16).



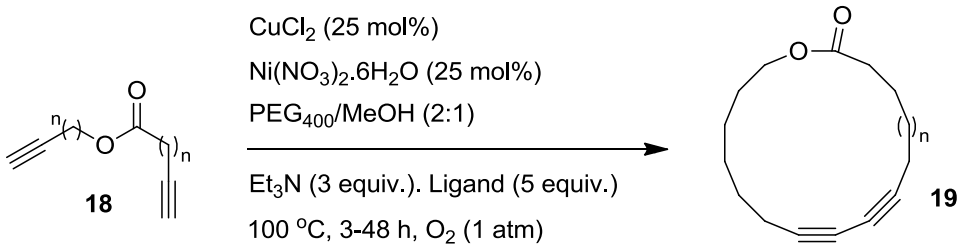
Scheme 16. Synthesis of shape persistence fluorescent macrocycles based on 1,3-butadiyne-bridged dibenz[*a*,*j*]anthracene subunits **16c** .

Copper-mediated oxidative coupling reactions are not limited to homogenous solutions, there are few reports in which alkyne-alkyne coupling was carried out in solid state by mixing of terminal alkyne substrates and copper catalyst.[13b] Although, the reaction rate is slow in solid state than in solution, however, different types of product were observed in some cases as reported by Toda and Tokumaru.[13b] For example, the Eglinton reaction was carried out with *rac*-**17** in the presence of $Cu(OAc)_2$. The solid state reaction exclusively gave the liner coupling product *rac*-**17b**, whereas in pyridine the cyclic product *rac*-**17a** was obtained (Scheme 17).



Scheme 17. Oxidative coupling under Eglinton conditions in solution and the solid state.

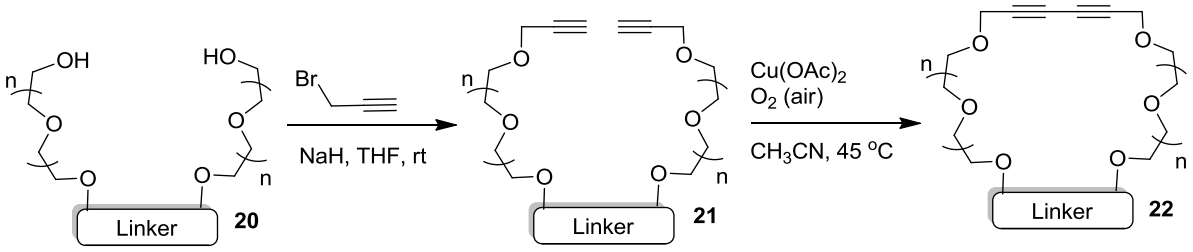
In recent years numerous macrocycles have been synthesized using biphasic conditions to control the pseudo-dilution of the precursors, allowing the use of relatively high concentrations of substrates in the organic phase. In this regard, Collins and co-workers developed[13c,d] a Glaser-Hay coupling method under biphasic conditions to obtain a wide range of industrially important macrocycles **19** (Scheme 18). Detailed investigations for the mechanism of Glaser-Hay coupling demonstrated that acetylenic subunits seemed to be coordinated with same copper center and an efficient macrocyclization due to aggregates of PEG_{400} that mimic phase separation (Scheme 18). The use of PEG_{400}/MeOH solvent mixtures allowed obtaining high macrocyclization yields at concentrations up to 0.1 M (Scheme 18). The use of flow chemistry allowed using concentrations up to 30 mM improving the yield with regard to the batch conditions.



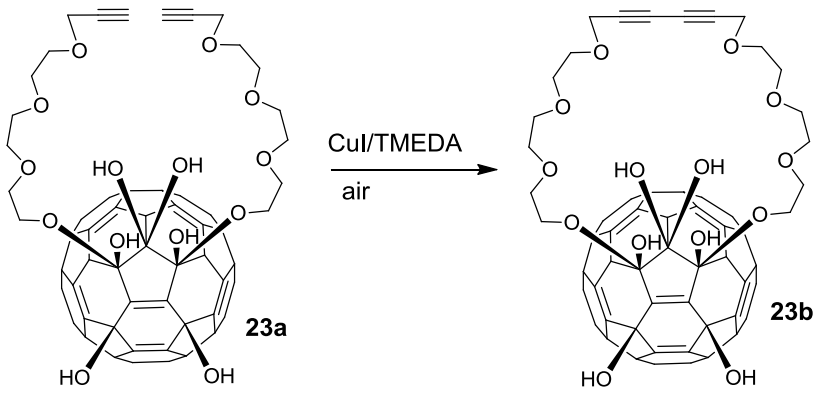
Scheme 18. Macrocyclization using the Glaser-Hay coupling in two phases.

Literature reports for the synthesis of macrocyclic polyethers *via* Glaser-Eglinton-Hay coupling.

Jiang, L. *et. al.* reported[14a] the synthesis of a series of 1,3-butadiyne unit containing crown ethers/polyether macrocycles **22** *via* the $Cu(OAc)_2$ promoted Eglinton coupling reaction using substrate **21**. The required terminal alkyne unit containing substrates **21** were prepared by base-mediated propargylation of the two arms of diol **20** (Scheme 19). These new macrocycles have the tendency to bind a paraquat guest such as (mono)pyridinium cations to form [2]pseudorotaxane-like complexes (tetraethylene glycol chains/linker based macrocycles) and [3]pseudorotaxane-like complexes (triethylene glycol chains/linker based macrocycles) in solution and in the solid state.



Scheme 19. Synthesis of 1,3-dialkyne-unit containing polyether macrocycles **22**.

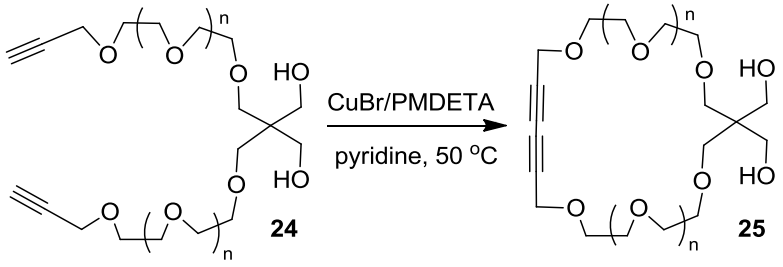


Scheme 20. Glaser-Hay coupling for the synthesis of fullerenyl crown ethers **23b**.

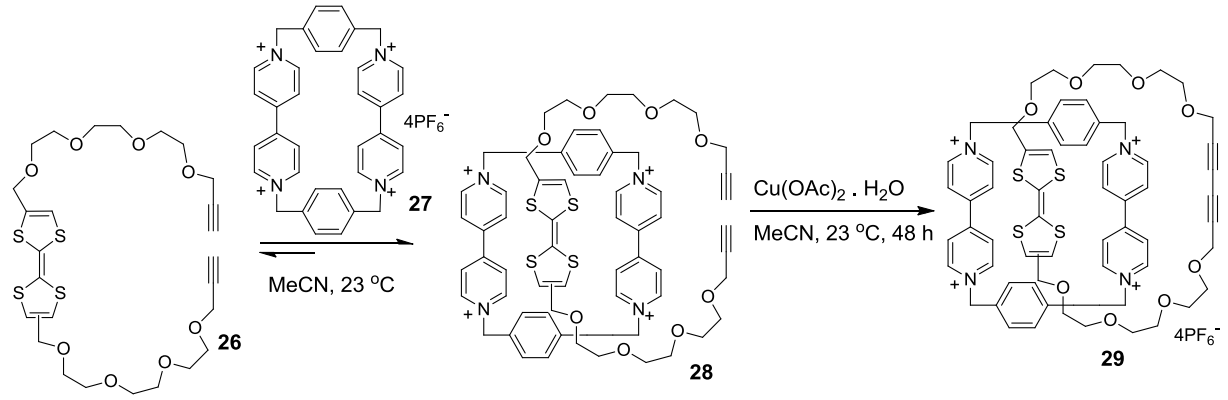
Recently, Gan and co-workers[14b] used Glaser-Hay coupling the synthesis of fullerene derivative **23b** having a 1,3-dialkyne unit rigid backbone (Scheme 20). Intramolecular oxidative coupling of fullerenol derivatives having terminal alkynes **23a** was carried out in the presence of cuprous iodide and TMEDA, which afforded a new class of fullerenyl crown ether derivative **23b** with a

crown size comparable to that of 24-crown-8 (Scheme 20). To avoid the intermolecular coupling, the concentration of the reaction mixture was kept at around 1 mg/3 mL in $CHCl_3$.

Huang *et al.* reported[14c] the synthesis of cyclic poly(ethylene oxide) **25** having two hydroxyl groups in the middle of the chain by oxidative cyclization of α, ω-dialkyne poly(ethylene oxide) **24** containing two hydroxyl groups in the presence of CuBr/PMDETA systems, which afforded the rigid backbone containing macrocyclic poly(ethylene oxide) **25** (Scheme 21) and intermolecular by-products were not observed during oxidative cyclization. the macrocylic poly(ethylene oxide) product was used in the synthesis of biocompatible tadpole shaped copolymer and (Scheme 21).



Scheme 21. Synthesis of hydroxyl groups containing crown ethers/polyether macrocycles **25** using Glaser-Hay coupling.



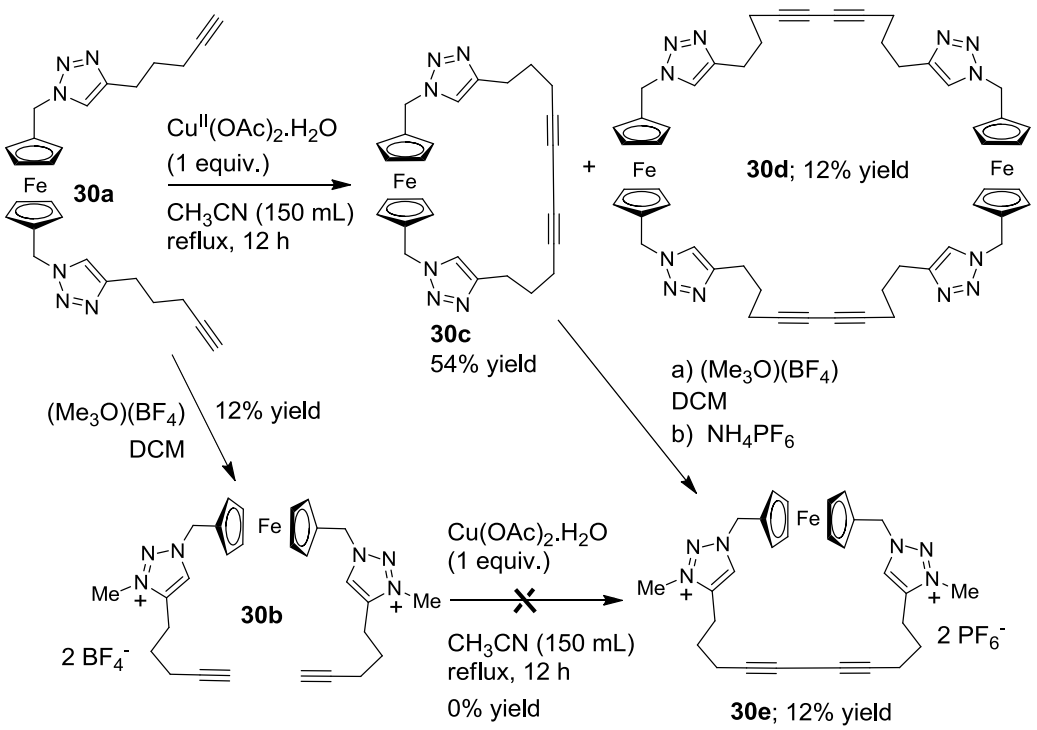
Scheme 22. Synthesis of single-station mechanically switchable hetero [2]catenane **29** *via* Copper-catalyzed Eglinton coupling.

Copper-catalyzed Eglinton coupling was used as a new route for the synthesis of single-station mechanically switchable hetero[2]catenane **29** by Stoddart and co-workers[14d] *via* threading-followed-by-clipping" approach (Scheme 22). When π-electron-rich TTF derivative **26** and CBPQT· $4PF_6$ **26** were mixed in a 2:1 molar ratio in MeCN, the solution became an intense emerald-green as a consequence of the formation of pseudorotaxane [**28**∩CBPQT]·4PF6 (Scheme 22). Then treatment of **28** with $Cu(OAc)_2 \cdot H_2O$ at 23 °C for 2 days effected the desired Eglinton coupling to afford the [2]catenane **29**·$4PF_6$ in 64% yield (Scheme 22). The facile synthesis of tetrathiafulvalene-based catenane utilizing a "threading-followed-by-clipping" protocol resulted in a mechanically interlocked molecule as a perfect molecular switch, most readily described as a "push-button" switch, whereby two discrete and fully occupied translational states are toggled electrochemically at incredibly high rates.

Literature reports for the synthesis of triazole moiety-installed macrocyclic systems *via* Glaser-Eglinton-Hay coupling.

Beer and co-workers[14e] described the preparation of *bis*-1,2,3-triazole unit incorporated different ferrocene macrocyclic structures **30c-e** *via* the $Cu(OAc)_2.H_2O$-catalyzed intramolecular Eglinton oxidative coupling of the acyclic *bis*-(alkyne) substrate **30a** (Scheme 23). Beer group observed that under the reported reaction conditions, it is possible to obtain the monomeric macrocyclic product **30c** ([1 + 1] adduct) in 54% yield along with larger dimeric product **30d** ([2 + 2] adduct) in 12% yield. While methylation of the macrocyclic structure afforded the corresponding *bis*-(triazolium) structures **30e**. The compound **30e** found to be efficient receptors for benzoate and chloride ions in acetonitrile and all attempts to cyclize the open-chain *bis*-(triazolium) **30b** system failed (Scheme 23).

The X-ray structure of small macrocyclic system **30c** showed that 1,3-diyne unit enforce a reasonably rigid geometry on the macrocycle **30c** due to its sterically demanding nature, which may help to constrain the anion binding cleft and led to selective anion binding. In contrast, the larger cavity containing macrocycle **30d** has a much more open structure as compared to small macrocycle, having a diameter of approximately 17 Å. The X-ray structure proved that larger macrocycle **30d** being tightly packed due to a series of intermolecular hydrogen bonds between triazole C-H donors and triazole N-acceptors on adjacent molecules and no solvent co-crystallizes with the macrocycle, despite this open structure of large macrocycle.



Scheme 23. Synthesis of *bis*-1,2,3-triazole unit incorporated ferrocene-based macrocycles **30c-e** by Eglinton coupling.

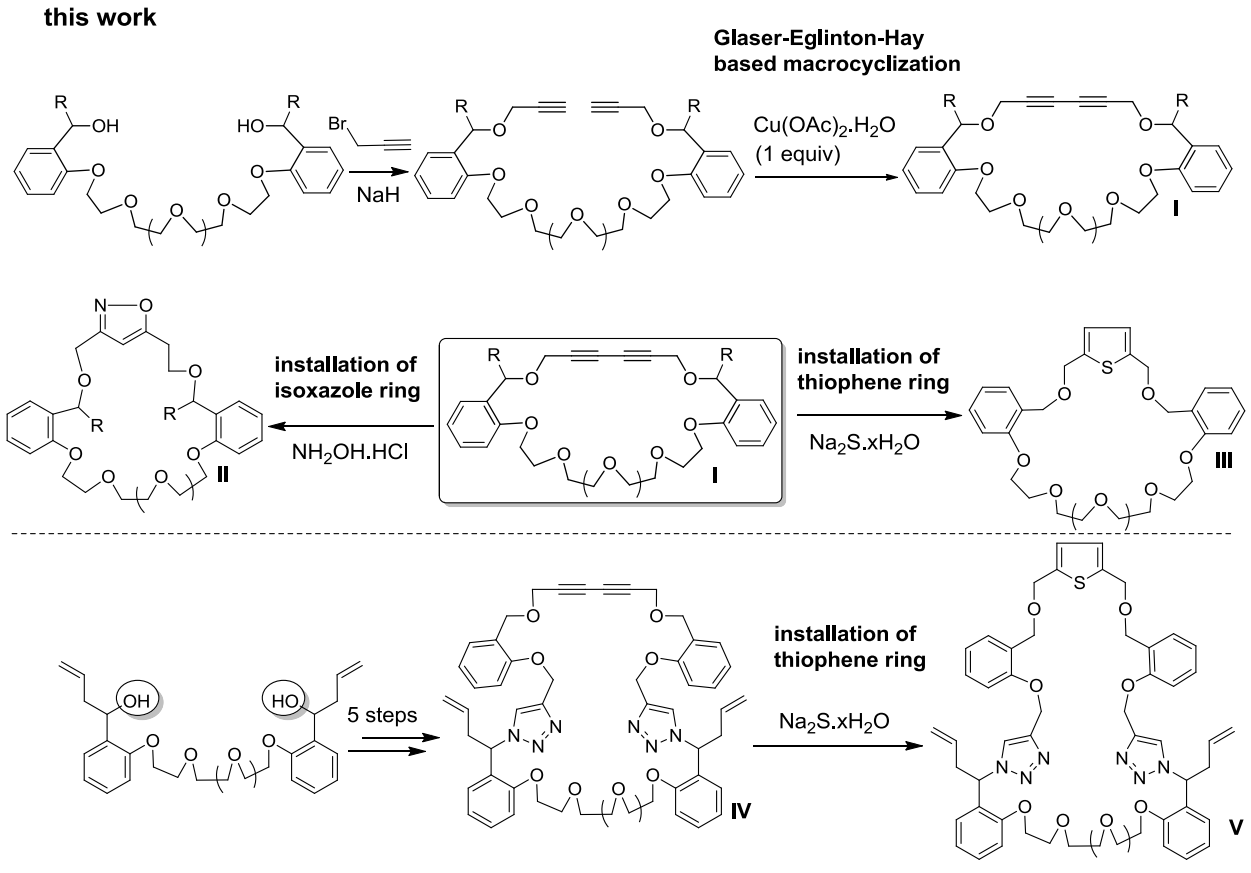
Result and discussion

While the Glaser-Eglinton-Hay-type strategy was largely used for the synthesis/constructions of diyne unit-based rigidified shape persistent macrocyclic systems, the introduction part of this Chapter 2 revealed some of the contributions with regard to the use of the Glaser-Eglinton-Hay-type strategy for the synthesis of crown ether/polyether macrocycles and related systems. Given the importance derivatized versions of archetypal (classical) crown ether systems (e.g., 18-crown-6 and dibenzo 18-crown-6 system) in various areas of biology, chemistry and material sciences, the synthesis of a library of new classes of crown ether/polyether macrocyclic systems and periphery modified polyether macrocyclic systems will be highly useful. It is believed that the incorporation of a 1,3-diyne unit as a part of crown ether/polyether macrocycles could provide directionally precise rigidity to polyether macrocycles and perhaps, new insights on their supramolecular chemistry.

A survey of literature revealed that the synthesis of crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone has not been explored well. Accordingly, in line with

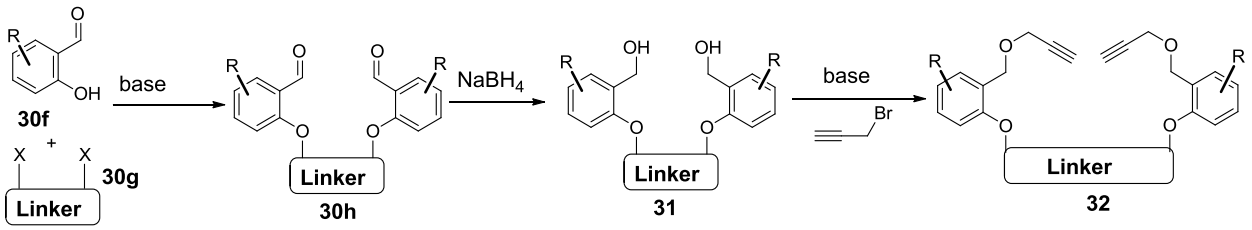
the objective of this thesis and taking an impetus from the papers dealing on the celebrated Glaser-Eglinton-Hay coupling reactions, a part of this thesis report the investigations on the synthesis of new classes of 18-40 membered crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone *via* the Glaser-Eglinton-Hay macrocyclization.

This Chapter presents a comprehensive synthetic work comprising, (i) the synthesis of new classes of 18-40 membered crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone *via* Glaser-Eglinton-Hay macrocyclization involving different linkers/spacers, (ii) the synthesis of periphery modified polyether macrocycles installed with thiophene and isoxazole functionalities from crown ether-type macrocycles having a 1,3-diyne unit, which were assembled *via* the Glaser-Eglinton-Hay macrocyclization and (iii) the synthesis of *bis*-1,2,3-triazoles appended polyether macrocycles having a 1,3-diyne unit using Glaser-Eglinton-Hay macrocyclization strategy (Scheme 24).



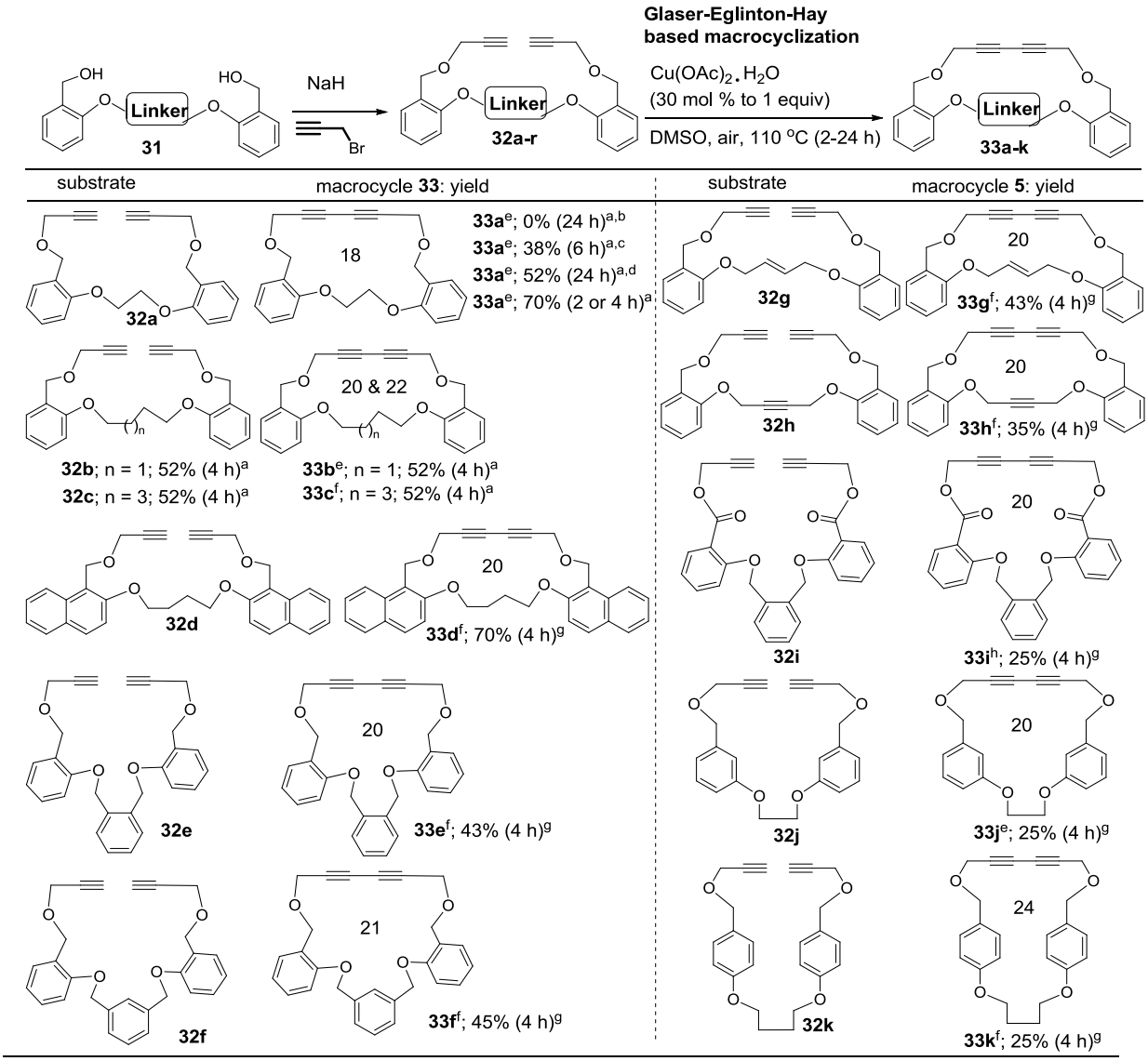
Scheme 24. The synthesis of crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone by exploiting the Glaser-Eglinton-Hay coupling reaction.

To begin the synthesis of polyether macrocycles having a 1,3-diyne unit-based rigid backbone **33** from dialkyne precurors **32** *via* alkyne-alkyne coupling. Initaily, dialkyne precurors **32** were assembled in three stepes from various 2-hydroxy benzaldehydes **30f** (Scheme 25). Reaction of 2-hydroxy benzaldehydes with various types of linkers/spacers **30g** using standard procedures afforded several *bis*-aldehydes **30h** (as discussed in the Chapter 1). Next, the $NaBH_4$-based reduction of the *bis*-aldehydes **30h** afforded the *bis*-alcohols **31**, which were subjected to the base-mediated *O*-propargylation to afford a variety of Glaser-Eglinton-Hay coupling precursors **32** containing two terminal alkyne units (Scheme 25).



Scheme 25. Generalized scheme for assembling the Glaser-Eglinton-Hay coupling precursors **32**, having the terminal alkyne units.

After assembling the required Glaser-Eglinton-Hay coupling precursors **32** having the terminal alkyne units, the sp–sp C–C bond forming intramolecular macrocyclization of the substrates **32a-r** were attempted under Glaser-Eglinton-Hay coupling reaction conditions (Scheme 26, Table 2). Initially, the macrocyclization reaction was attempted by using the Glaser-Eglinton-Hay coupling precursor **32a** in the presence of $Cu(OAc)_2 \cdot H_2O$ in various solvents to find out a suitable reaction condition. The Glaser-Eglinton-Hay-type macrocyclization reaction of the precursor **32a** in the presence of $Cu(OAc)_2 \cdot H_2O$ in refluxing toluene under an open-air atmosphere did not afford the expected polyether macrocycle **33a** (Scheme 26). Similarly, the Glaser-Eglinton-Hay-type macrocyclization reaction of the precursor **32a** in refluxing 1,4-dioxane failed to give the expected polyether macrocycle **33a** (Scheme 26).



[a] 1 Equiv of $Cu(OAc)_2 \cdot H_2O$ was used. [b] The reaction was done in toluene or 1,4-dioxane (100 mM) at refluxing temperature. [c] The reaction was done in DMF (100 mM) at 110 °C. [d] The reaction was done in refluxing MeCN (100 mM). [e] The reaction was performed using 0.25 mmol of the starting material. [f] The reaction was performed using 0.5 mmol of the starting material. [g] 30 mol% of catalyst was used. [h] The reaction was performed using 0.12 mmol of starting material.

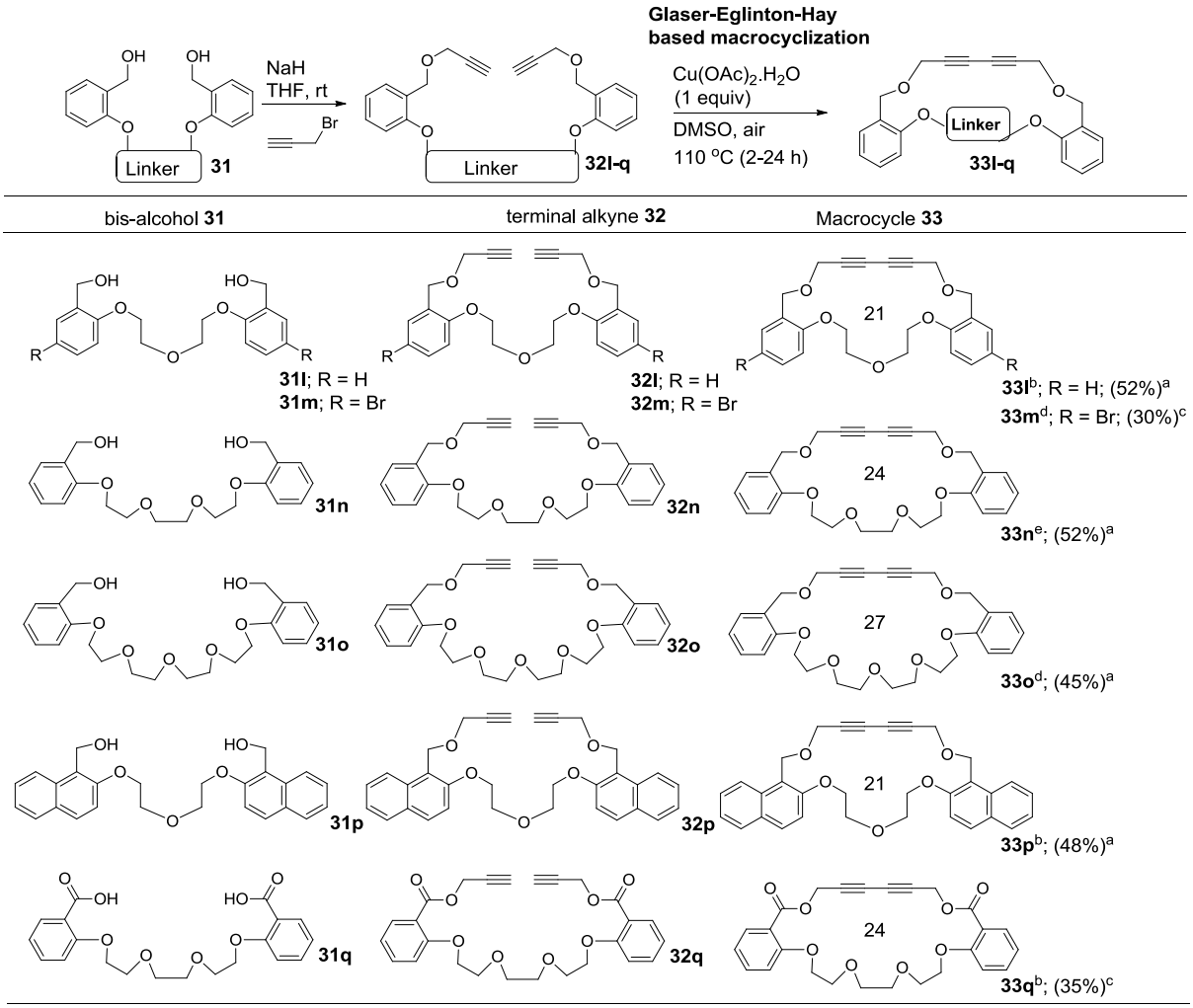
Scheme 26. Synthesis of 18-24-membered, crown ether/polyether-type macrocycles having a 1,3-diyne unit-based rigid backbone *via* the Glaser-Eglinton-Hay coupling.[16c]

Successively, the Glaser-Eglinton-Hay-type macrocyclization of the precursor **32a** in DMF at 110 ^{o}C furnished the polyether macrocycle **33a** possessing a 1,3-diyne unit-based rigid backbone in 38% yield (Scheme 26). Further, the polyether macrocycle **33a** was obtained with an improved yield of 52% when the Glaser-Eglinton-Hay-type macrocyclization of the precursor **32a** was performed in refluxing MeCN (Scheme 26). Successively, the Glaser-Eglinton-Hay-type macrocyclization of the precursor **32a** was performed in the presence of $Cu(OAc)_2 \cdot H_2O$ in DMSO at 110 ^{o}C under an open-air atmosphere, which afforded the polyether macrocycle **33a** in 70% yield (Scheme 26). Similarly, the Glaser-Eglinton-Hay-type macrocyclization of the precursors containing two terminal alkynes **32b-f**, which were derived from different aliphatic- and benzylic chain linkers/spacers afforded the corresponding polyether macrocycles **33b-f** having a 1,3-diyne unit-based rigid backbone in 43-70% yields (Scheme 26).

Subsequently, the substrates **32g** and **32h**, which were derived from the linkers containing an unsaturated backbone were subjected to the Glaser-Eglinton-Hay coupling reactions to afford the corresponding macrocycles **33g** (43%) and **33h** (35%) having a 1,3-diyne unit-based rigid backbone. Then, the Glaser-Eglinton-Hay coupling reaction of the benzoate derivative **32i** in the presence $Cu(OAc)_2 \cdot H_2O$ gave the polyether macrocycle **33i** having a 1,3-diyne unit-based rigid backbone in 25% yield. Next, the Glaser-Eglinton-Hay coupling reactions of the precursors **33j** and **33k**, which were derived from *meta*- and *para*-hydroxy benzaldehydes furnished the respective polyether macrocycles **33j** and **33k** having a 1,3-diyne unit-based rigid backbone in 25% yield (Scheme 26).

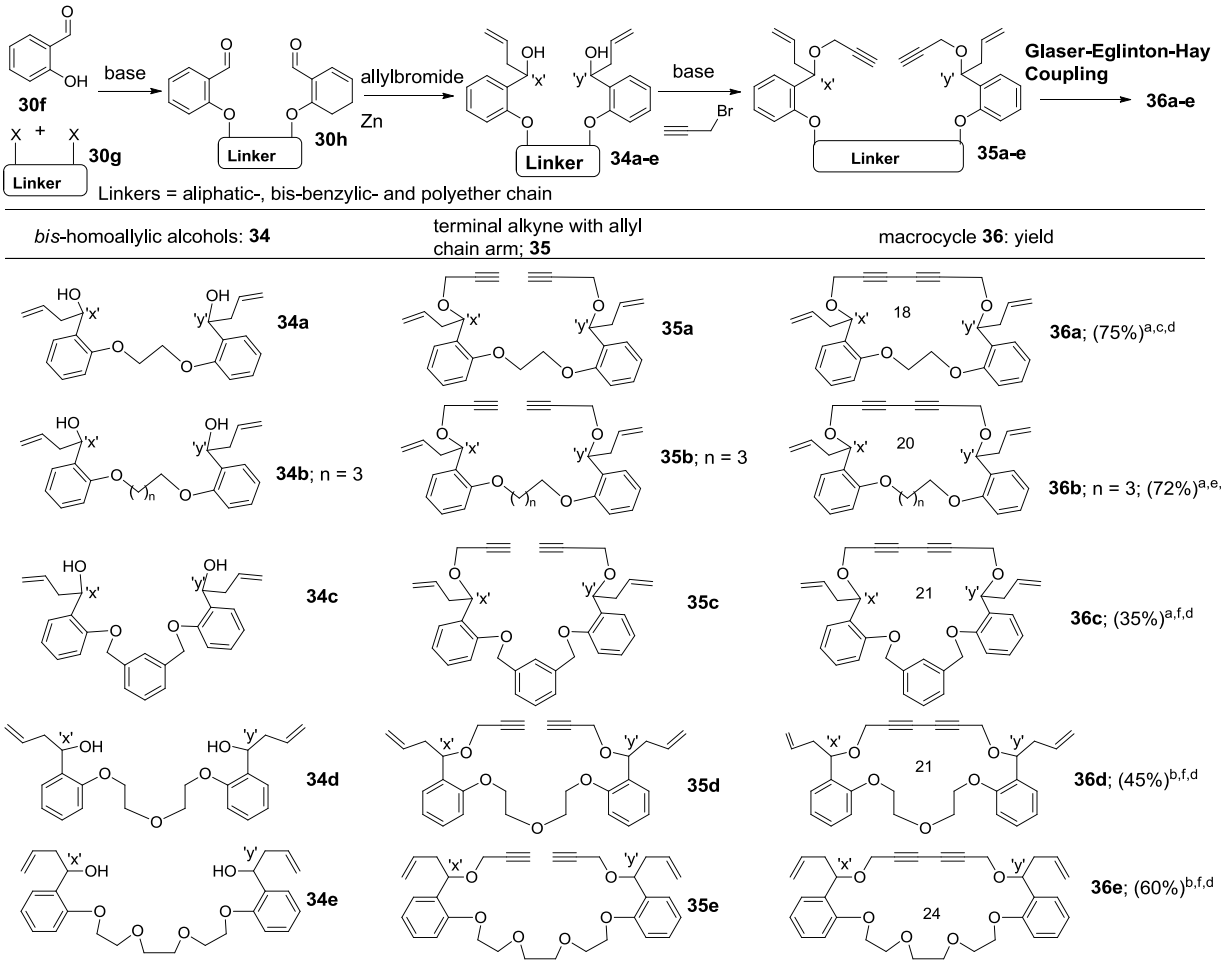
To show the scope and generality of this Glaser-Eglinton-Hay coupling protocol, the precursors **32l–p** having two terminal alkyne units were assembled from various polyether units-based linkers (Scheme 27). Then, the Glaser-Eglinton-Hay coupling reactions of the precursors **32l–p** were performed in the presence of $Cu(OAc)_2.H_2O$ in DMSO at 110 ^{o}C under an open-air atmosphere. These reactions afforded the corresponding crown ether/polyether macrocycles **33l-p** having a 1,3-diyne unit-based rigid backbone in 30-52% yields (Scheme 27). Similarly, the Glaser-Eglinton-Hay coupling reaction of the benzoate derivative **32q** possessing two terminal

alkyne units also afforded the crown-type macrocycle **33q** having a 1,3-diyne unit-based rigid backbone in 35% yield (Scheme 27).



[a] Reaction condition A:[16a] $Cu(OAc)_2.H_2O$ (30 mol%), DMSO (100 mM), 110 °C, 4 h and open air atm. [b] The reaction was done using 0.3 mmol of the corresponding starting material. [c] Reaction condition B:[16b] $Cu(OAc)_2.H_2O$ (1 equiv.), DMSO (100 mM), 110 °C, 4 h and open-air atm. [d] The reaction was done using 0.5 mmol of the corresponding starting material. [e] The reaction was done using 0.2 mmol of the respective starting material.

Scheme 27. Synthesis of 18-24-membered, crown ether/polyether-type macrocycles having a 1,3-diyne unit-based rigid backbone *via* the Glaser-Eglinton-Hay coupling.[16c]



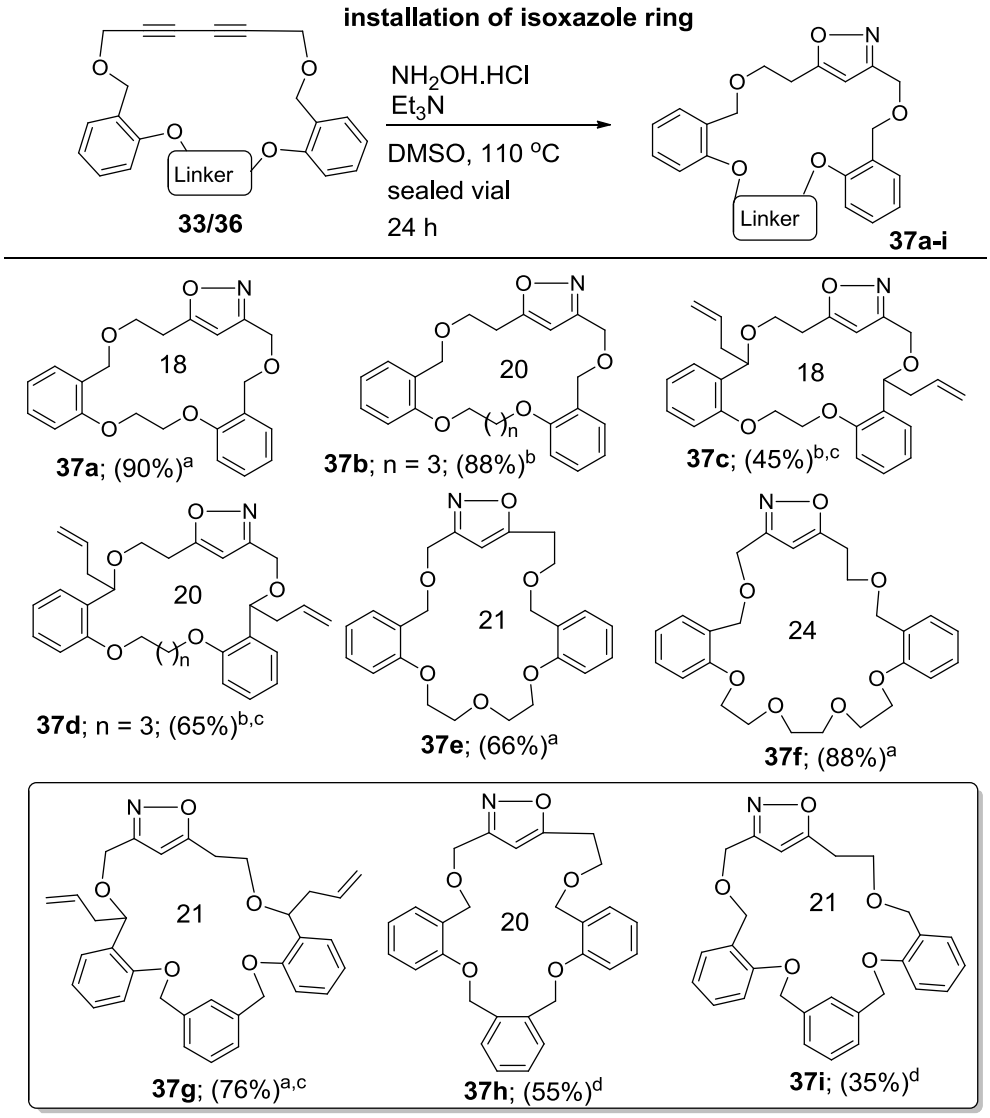
[a] Reaction condition A:[16a] $Cu(OAc)_2.H_2O$ (30 mol%), DMSO (100 mM), 110 ^oC, 4 h and open-air atm. [b] Reaction condition B:[16b] [c] The reaction was done using 0.4 mmol of the respective starting material. [d] The observed *dr* = 60 : 40. [e] The reaction was done using 1 mmol of the respective starting material. [f] The reaction was done using 0.2 mmol of the respective starting material.

Scheme 28. Synthesis of 18-24-membered, crown ether/polyether-type macrocycles having a 1,3-diyne unit-based rigid backbone *via* the Glaser-Eglinton-Hay coupling.[16c]

Next, to elaborate the substrate scope and generality, it was planned to prepare Glaser-Eglinton-Hay coupling precursors containing two terminal alkyne units starting from *bis*-homoallylic alcohol systems which can be assembled *via* the Zn mediated allylation strategy (Scheme 28). Accordingly, salicylaldehyde was treated with a variety of linkers using standard procedures to afford the corresponding *bis*-aldehydes **30**, which were subsequently treated with allyl bromide

and zinc dust. The Zn-mediated allylation of *bis*-aldehydes **30** gave different *bis*-homoallylic alcohols **34a-e** as a mixture of diastereomers (*dr* 1:1). Then, the base-mediated *O*-propargylation of the *bis*-homoallylic alcohols **34a-e** afforded a variety of Glaser-Eglinton-Hay coupling precursors containing of two terminal alkyne units **35a-e** incorporated with the allylic chains as the side-arms (Scheme 28). Before discussing the Glaser-Eglinton-Hay macrocyclization of the precursors **35a-e**, it is to be noted here that in some of the crown ethers/polyether macrocycles reported in the literature, the incorporation of an allylic chain as a sidearm was found to be important to induce an effective encapsulation of metals.[15a,b] For example, Gokel *et al.* reported a solid state evidence that neutral double bonds attached to flexible side-arm of a lariat crown ether, served as the intramolecular π-donors for a ring bound Na^+ cation. Taking an impetus from the Gokel's substrate,[15b] the substrates **35a-e** were subjected to the Glaser-Eglinton-Hay coupling reaction conditions. Accordingly, the reactions of the substrates **35a-e** in the presence of $Cu(OAc)_2.H_2O$ in DMSO at 110 ^oC under an open-air atm, led to the construction of structurally interesting C-pivot lariat crown ether/polyether-type macrocycles **36a-e** (Scheme 28). **36a-e** having a 1,3-diyne unit in 35-75% yields, respectively (Scheme 28). Since the Glaser-Eglinton-Hay coupling precursors **35a-e** were isolated as a mixture of diastereomers (*dr* 1:1, Scheme 28) in the previous step, the Glaser-Eglinton-Hay macrocyclization of the precursors **35a-e** afforded the corresponding polyether macrocycles **36a-e** as a mixture of diastereomers (*dr* 60:40) and having two remote stereocenters ('x' and 'y'). Unfortunately, all the attempts to separate the diastereomers of the respective polyether macrocycles **36a-e** were not successful (Scheme 28).

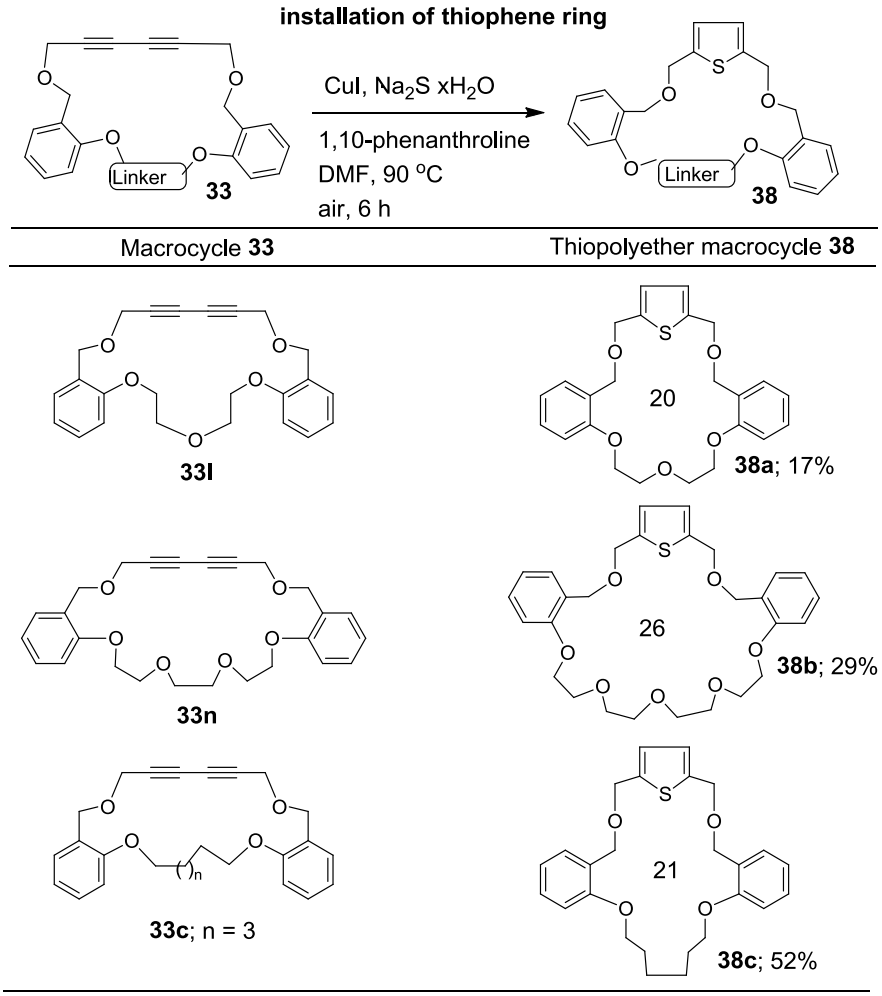
Next, to execute the utility of the macrocyclic compounds possessing the 1,3-diyne units and as a part of the objective of this chapter, attention was paid to execute the post ring-closure functional derivatization of the polyether macrocycles obtained from Glaser-Eglinton-Hay coupling reactions. Recently, Yu and Bao reported an efficient method for the synthesis of 3,5-disubstituted isoxazoles *via* the Cope-type hydroamination of the 1,3-dialkyne units.[16d] Taking an impetus from the Yu and Bao strategy, some of the 1,3-diyne units containing polyether macrocycles, which prepared *via* the Glaser-Eglinton-Hay macrocyclization were subjected to the post ring-closure functional derivatization to afford a variety of new examples of isoxazole appended crown ether-type macrocycles by using the literature procedures.[16d]



[a] The reaction was done using 0.18 mmol of the corresponding starting material. [b] The reaction was done using 0.25 mmol of the corresponding starting material. [c] *dr* = 60 : 40. The reaction was done using the corresponding mixture of diastereomers **36a-c**. [d] The reaction was done using 0.12 mmol of the corresponding starting material.

Scheme 29. Synthesis of isoxazole ring-appended 18-24-membered, crown ether-type macrocycles *via* the Cope-type hydroamination of the Glaser-Eglinton-Hay coupling products **33/36.**

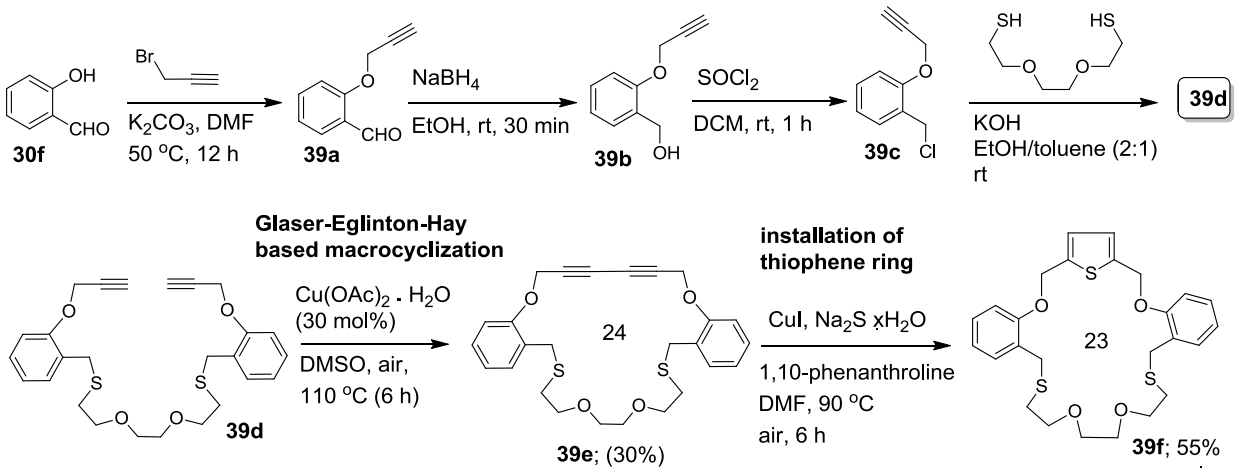
Accordingly, the reaction of the Glaser-Eglinton-Hay coupling products **33a**, **33b**, **33e**, **33f**, **33l**, **33n** and **36a-c** having a 1,3-diyne unit with $NH_2OH{\cdot}HCl$ and Et_3N gave the corresponding isoxazole moiety appended crown ether-type macrocycles **37a-i** in satisfactory yields. It is noteworthy to mention here that the isoxazole is an important structural unit, present in several bioactive molecules and natural products.[17] In this context the macrocycles **37a-i** obtained in this work are new classes of 18-21-membered isoxazole moiety appended crown ether-type macrocycles and can be considered as crownophane-type macrocyclic systems (Scheme 29).



[a] The reactions were done using the corresponding starting materials as given in the parenthesis, (for **38a**; 0.25 mmol of **33l**) (for **38b**; 0.39 mmol of **33n**) (for **38c**; 0.3 mmol of **33c**).

Scheme 30. Synthesis of thiophene ring appended 20-26-membered crown ether-type macrocycles from the Glaser-Eglinton-Hay coupling products **33**.

Inspired by a another work reported by the Jiang and co-workers, which deals on the Cu(I)-catalyzed synthesis of 2,5-disubstituted thiophenes from the 1,3-diyne units, it was envisaged to examine the construction of thiophene ring appended crown ether-type macrocycles from the from the Glaser-Eglinton-Hay coupling products **33** having the 1,3-diyne unit, which were prepared in this work. Accordingly, some of the Glaser-Eglinton-Hay coupling products **33** having the 1,3-diyne units were subjected to the reaction conditions reported by the Jiang's group.[16e] The macrocycles **33c**, **33l** and **33n** were treated with $Na_2S{\cdot}xH_2O$ in the presence of 1,10-phenanthroline and CuI in DMF at 90 ^oC under an open-air atmosphere. These reactions gave the corresponding thiophene moiety appended 20-26-membered, crown ether-type macrocycles **9a-c** in 17-52% yields (Scheme 30).

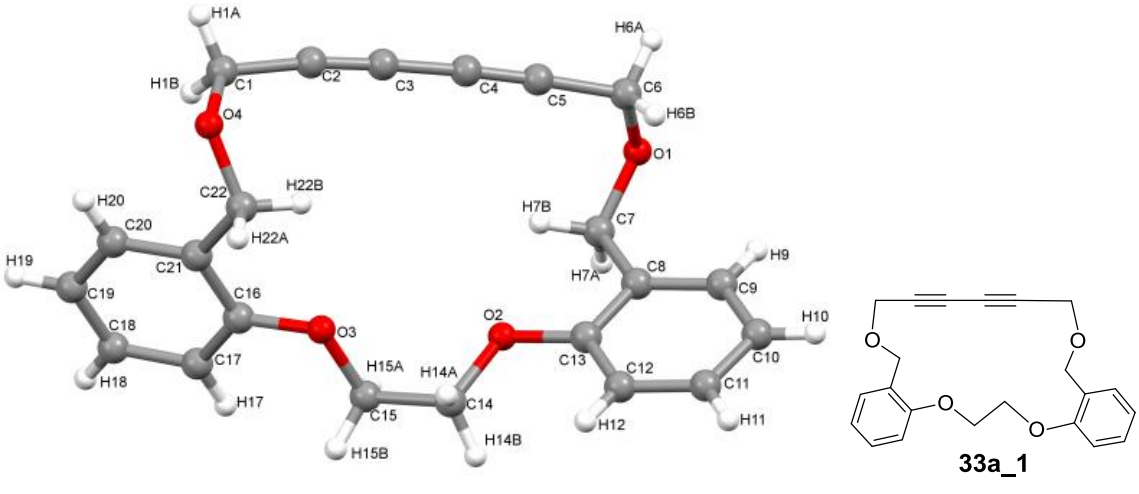


Scheme 31. Thiophene ring appended 23-membered thia-crown ether-type macrocycle **39f**.

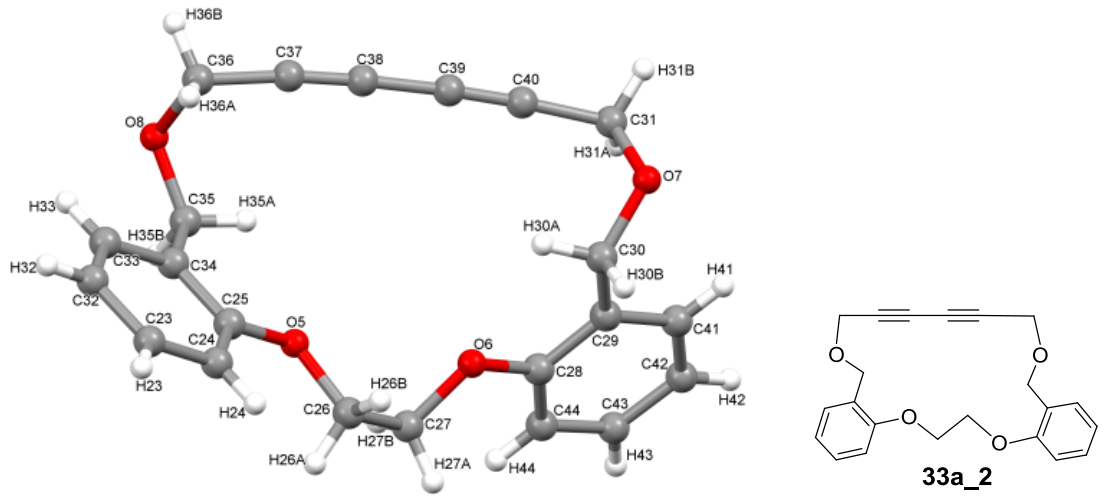
Along this line, the substrate **39d** having two sulphur heteroatoms in the linker was prepared starting from salicylaldehyde **30f** and 2,2 (ethylenedioxy)diethanethiol by employing the standard synthetic procedures (Scheme 31). Then, Glaser-Eglinton-Hay macrocyclization of the substrate **39d** in the presence of $Cu(OAc)_2.H_2O$ (30 mol%) in DMSO at 110 ^oC under an open-air atmosphere afforded the macrocycle **39e** having the 1,3-diyne unit and sulphur heteroatoms in the linker part. Next, treatment of the macrocycle **39e** with $Na_2S.xH_2O$ in the presence of 1,10-

phenanthroline and CuI in DMF at 90 ^{o}C under an open-air atmosphere afforded the thiophene ring installed thia-crown ether system **39f** in 55% yield (Scheme 31).

Discussion on the crystal structures of representative crown ether/polyether macrocycles containing a 1,3-diyne unit prepared from the Glaser-Eglinton-Hay coupling.



(a)

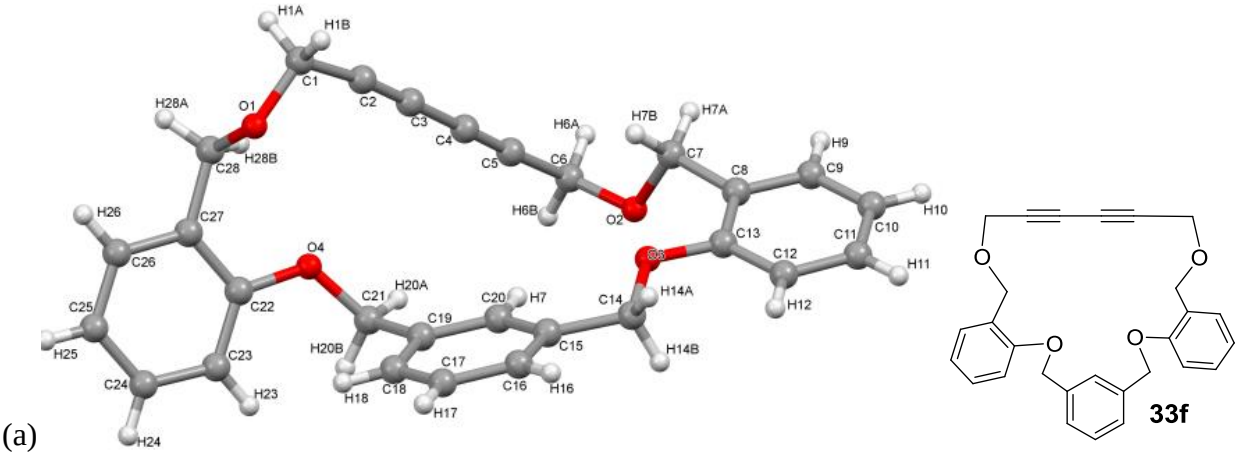


(b)

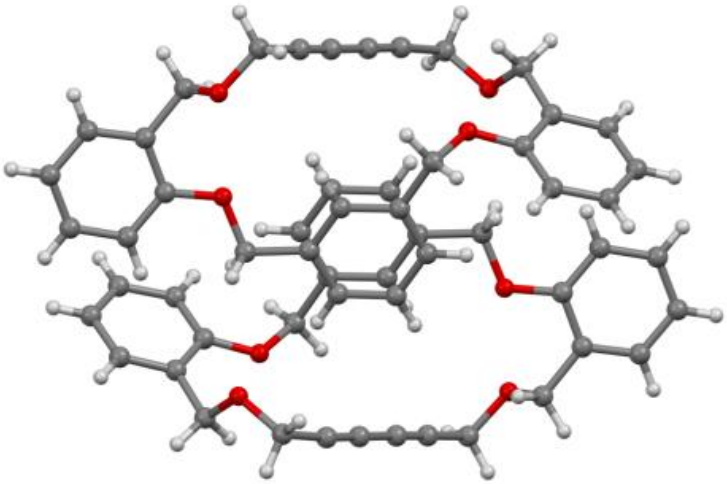
Figure 1. (a) Ball and stick model (X-ray structure) of **33a_1** and (b) Ball and stick model (X-ray structure) of **33a_2** were drawn at 0.15 times to atomic van der Waals radius.

The single crystal X-ray diffraction study revealed that the polyether macrocycle **33a** containing a 1,3-diyne unit was found to crystallize in the space group $P2_1/c$ with two independent 18-membered macrocyclic molecules in the asymmetric unit (Figure 1). In each molecule, the two phenyl rings have been found to be inclined at an angle of ~90^{o} to each other and both the

conformers majorly differ with respect to the torsion angles of the 1,3-diyne linkage, which is about <1° and ~7° respectively. The distance between phenyl rings in the both the conformations was same (~8 Å) and in each conformer the 1,3-diyne linkage has been found to be bent with an angle of ~15°.



(a)



(b)

Figure 2. (a) Ball and stick model (X-ray structure) of **33f** was drawn at 0.15 times to atomic van der Waals radius. (b) π···π Stacking between the phenyl rings which act as the linker in the compound **33f**.

The single crystal X-ray structure revealed that the polyether macrocycle **33f** containing a 1,3-diyne unit was found to crystallize in the space group $P2_1/c$ with one 21-membered macrocyclic molecule in the asymmetric unit (Figure 2). In contrast to the polyether macrocycle **33a** containing a 1,3-diyne unit, with the incorporation of the benzene ring in to the linker, the distance between the phenyal rings has increased by ~3 Å and the bending angle of the 1,3-

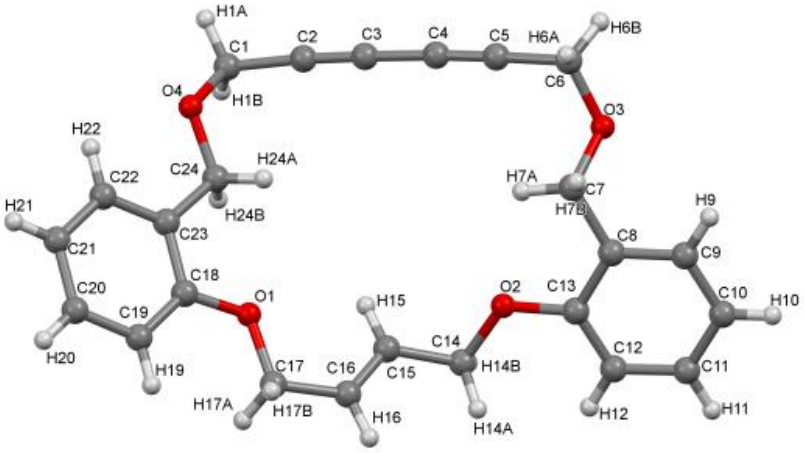
diyne unit was found to be ~11 °. The interplanar angles between the linker phenyl group (having substitutions at the 1,3-positions) and the two phenyl rings (having substitutions at the 1,2-positions) was ~21° and ~77°, respectively. The two phenyl rings (having substitutions at the 1,2-positions) have been found to be inclined at an angle of ~56°. Whereas, the torsion angle for the 1,3-diyne unit was ~13°. Interestingly, the phenyl ring, which act as a linker, has been found to be involved in π···π stacking (Figure 2).

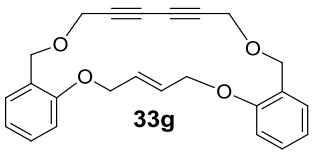
The X-ray structure analysis revealed that the polyether macrocycle **33g** containing a 1,3-diyne unit was found to crystallize in the space group $P2_1/c$ with one 20-membered macrocyclic molecule in the asymetric unit (Figure 3). With reference to the polyether macrocycle **33a** containing a 1,3-diyne unit, the incorporation of an extra *trans* alkene (ethylene) linkage led the distance between the phenyl rings to increase by ~2 Å. The bending and torsion angles of the 1,3-diyne linkage were found to be ~14° and ~11°, respectively. The interplanar angle between the two phenyl rings was found to be ~53°.

The single crystal X-ray diffraction study revealed that the polyether macrocycle **33h** containing a 1,3-diyne unit was found to crystallize in the space group $P2_1/c$ with one 20-membered macrocyclic molecule (Figure 3). With reference to the polyether macrocycle **33a** containing a 1,3-diyne unit, the incorporation of the alkyne (acetylenic, (C15 and C16)) group in to the linkage led the distance between the phenyl rings to increase by ~3Å. The bending and torsion angles of the 1,3-diyne linkage were found to be ~8° and ~115°, respectively. Two phenyl rings are inclined at an angle of ~61°. The bending angle of the (mono) acetylenic unit was found to be ~11°.

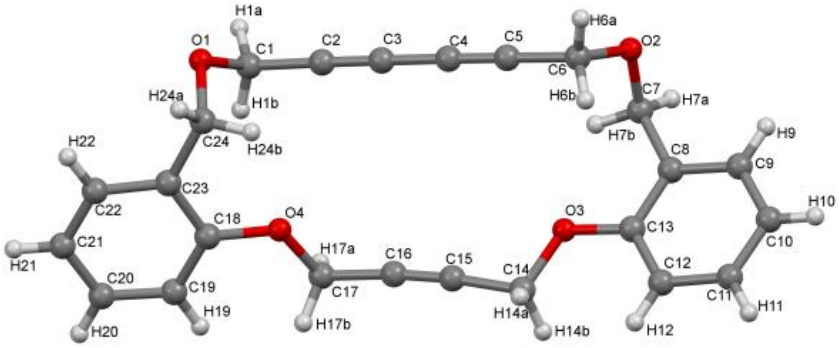
The X-ray structure analysis showed that the polyether macrocycle **33i** containing a 1,3-diyne unit contains a 20-membered macrocyclic ring and was found to crystallize in the space group $P2_1/c$ with one molecule in the asymmetric unit. In this molecule, two phenyl groups (having substitutions at 1,2-positions such as C8/C13 and C22/C27) have been found to be inclined at an angle of ~73°. The interplanar angles between the phenyl rings having substitutions at 1,2-positions and the phenyl group (C15 to C20), which acts as a linker were found to be ~86° and ~47° (Figure 3). The torsion angle for the 1,3-diyne unit is ~10°. The 1,3-diyne unit found to be not linear, the bending angle was found to be ~17°.

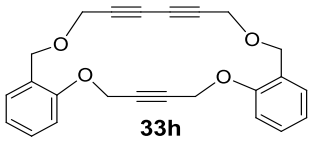
(a)



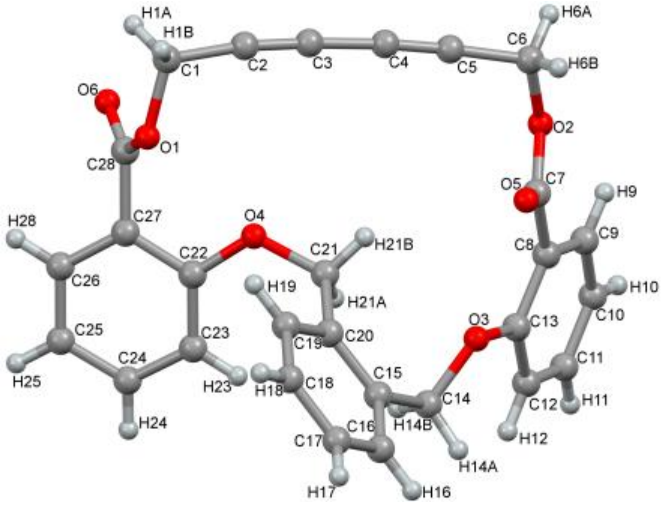


(b)





(c)



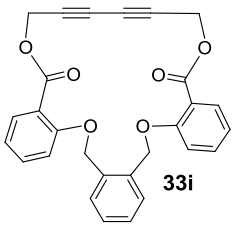
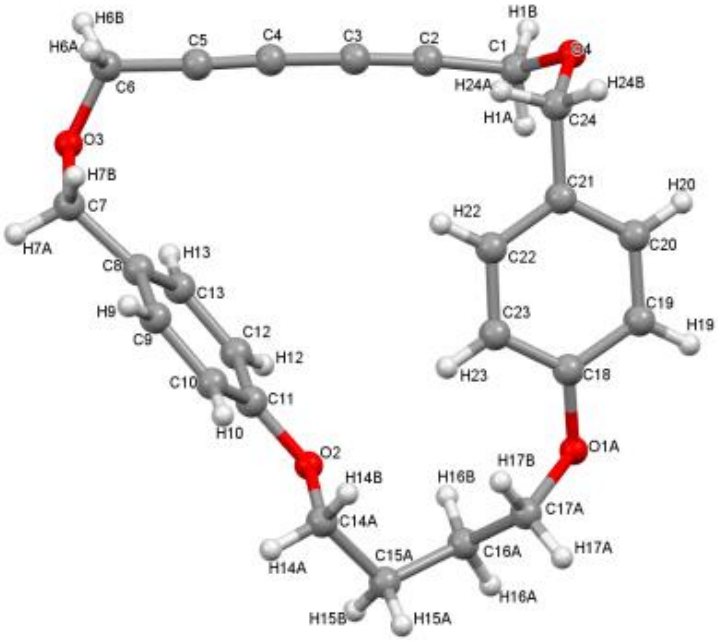


Figure 3. Ball and stick model (X-ray structure **33g-i**) was drawn at 0.15 times to atomic van der walls radius; (a) **33g** (b) **33h** (c) **33i**.

The single crystal X-ray diffraction study revealed that the polyether macrocycle **33k** containing a 1,3-diyne unit was found to crystallize in the space group $P\ \bar{1}$ with one 24-membered macrocyclic molecule (Figure 4) and this compound was prepared using 4-hydroxybenzaldehyde. When compared to the polyether macrocycle **33a** containing a 1,3-diyne unit (which was prepared from 2-hydroxybenzaldehyde) in this structure, the distance between the phenyl rings was found to decrease by ~2 Å and the bending and torsion angles of the 1,3-diyne unit were found to be ~16° and ~15°, respectively. The interplanar angle between the two phenyl rings has been found to be ~70°.



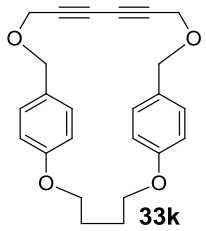


Figure 4. Ball and stick model (X-ray structures **33k**) was drawn at 0.15 times to atomic van der Waals radius.

The single crystal X-ray diffraction study revealed that the polyether macrocycle **33l** containing a 1,3-diyne unit was found to crystallize in the space group $P2_1/c$ with one 21-membered macrocyclic molecule in the asymetric unit (Figure 5). The incorporation of an oxygen atom at the center of the butyl linkage led the distance between the phenyl rings to increase by ~2 Å (with respect to **33a**). The bending and torsion angles of the 1,3-diyne linkage were found to be

~12° and ~19°, respectively. The inerplanar angle between two phenyl rings was found to be ~41°.

Preliminary single crystal X-ray diffraction study of the 24-membered polyether macrocycle **33n** containing a 1,3-diyne unit indicated that only half of the molecule is present in the asymmetric unit due to crystallographic imposed two fold symmetry and the structure having a center of inversion symmetry (Figure 5). The 1,3-diyne unit between the two phenyl groups was found to be bent and the bending angle was found to be ~19^{o} and the angle between the phenyl rings was found to be ~56^{o}. The distance between the phenyl rings is ~13 Å.

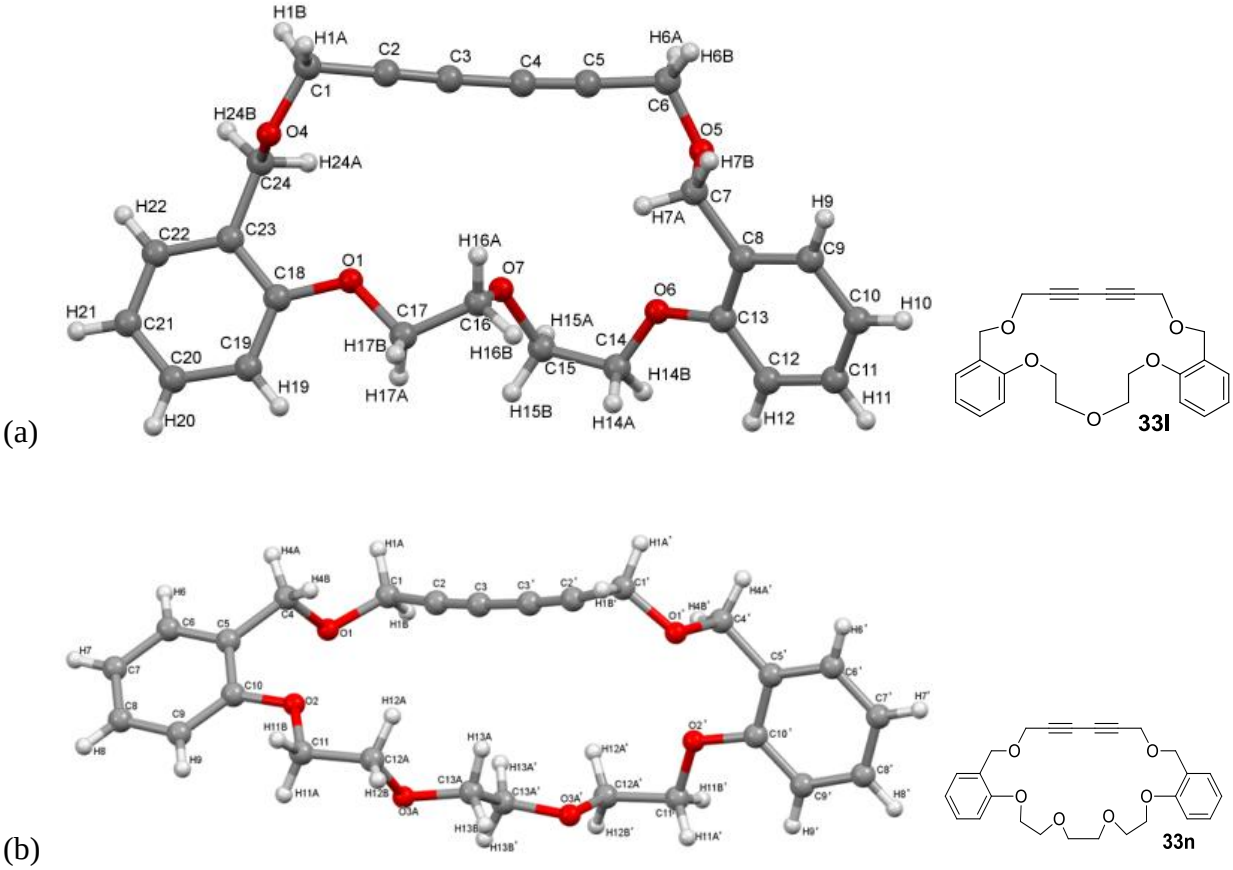


Figure 5. Ball and stick model (X-ray structures **33l** and **33n**) was drawn at 0.15 times to atomic van der Waals radius; (a) **33l** (b) **33n**. Only half of the molecule is present in the asymmetric unit of the X-ray structure of the compound **33n**. Therefore, the atoms at the right hand side of X-ray structure of **33n** (shown with a prime (‘) label) are at equivalent position (1-x, y, ½-z) with respect to the atoms on the left hand side.

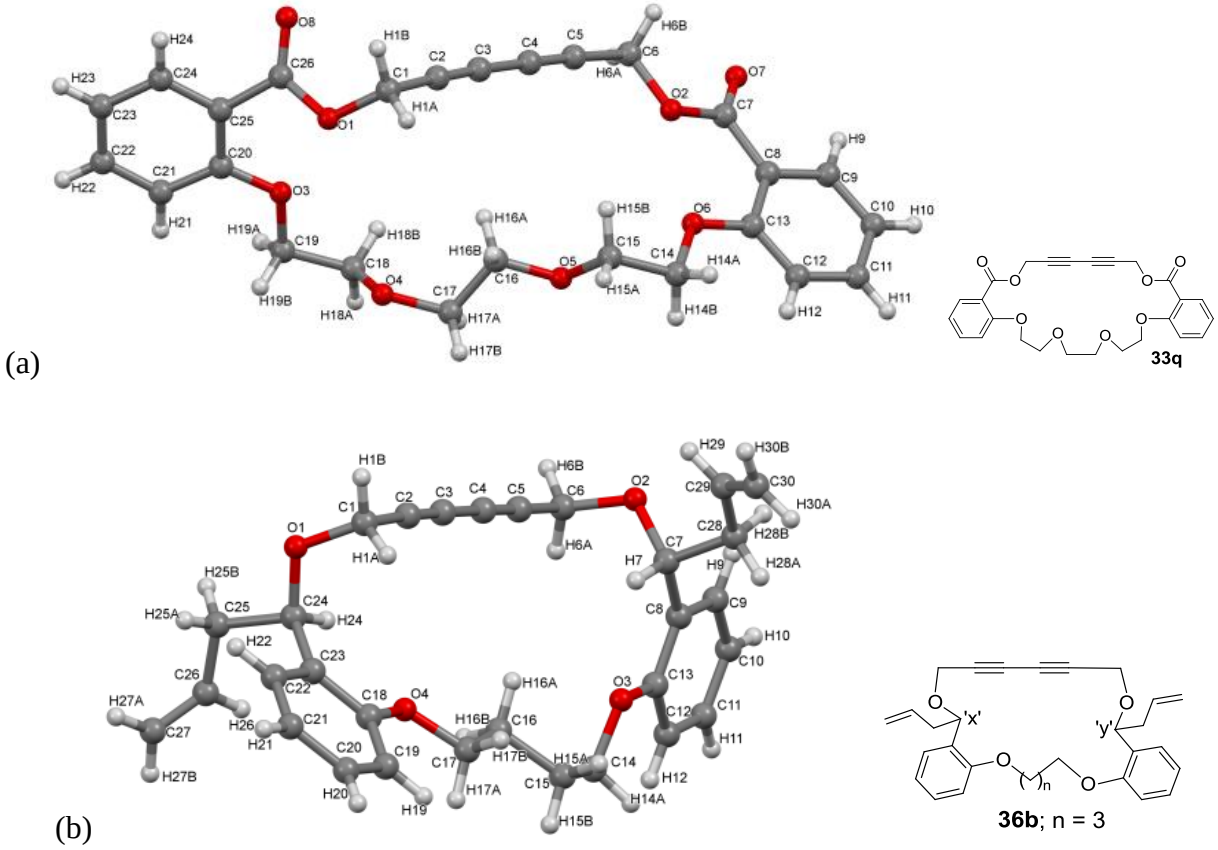
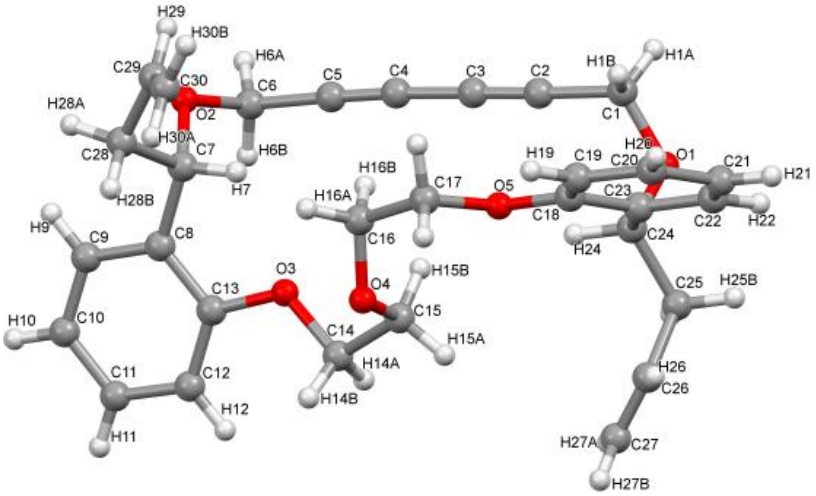


Figure 6. Ball and stick model (X-ray structures **33q** and **36b**) was drawn at 0.15 times to atomic van der Waals radius; (a) **33q** (b) **36b**.

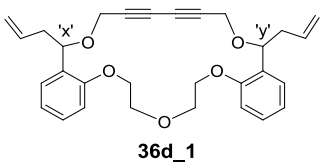
The polyether macrocycle **33q** containing a 1,3-diyne unit doesn't have any center of symmetry and one full molecule was found to be present in the asymmetric unit as a 24-membered macrocyclic ring (Figure 6). The bending angle of the 1,3-diyne unit was found to be ~11^{o}. The interplanar angle between two phenyl rings was found to be ~73^{o} and those rings are ~13 Å distance apart from each other, which is similar to the polyether macrocycle **33n** containing a 1,3-diyne unit. Out of two ester groups, one carbonyl group (C26/O8) was found to be in-plane to benzene ring whereas the other group was found to be out of the plane by an angle of ~36^{o}, which has led the molecule to be in an unsymmetrical form.

The 20-membered polyether macrocycle **36b** containing a 1,3-diyne unit, doesn't have any center of inversion symmetry and one full molecule was found to be present in the asymmetric unit (Figure 6). This molecule contains a flexible sidearm group (allyl chain) at the benzylic

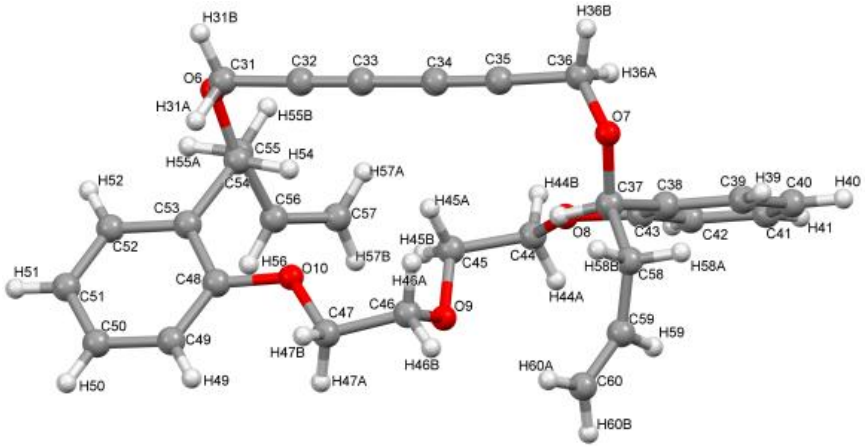
carbons (C7 and C24) and the bending angle of the 1,3-diyne unit was found to be ~5^{o} and the inter-planer angle between the two phenyl rings was found to be ~57^{o}.



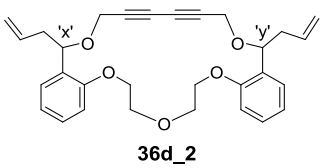
(a)



36d_1



(b)

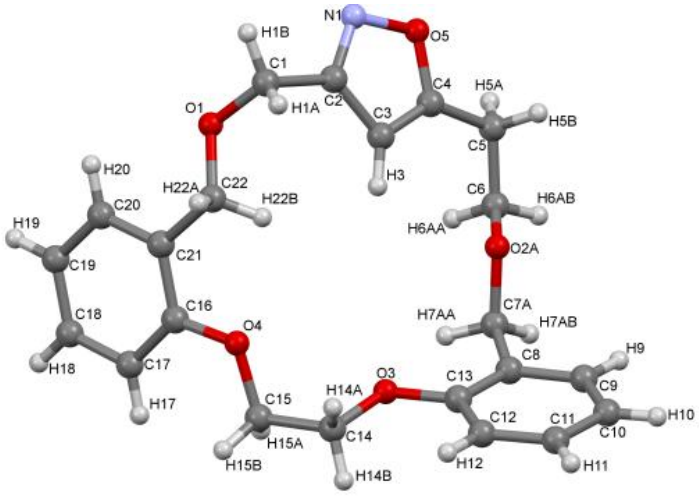


36d_2

Figure 7. (a) Ball and stick model (X-ray structure) **36d_1** and (b) Ball and stick model (X-ray structure) of **36d_2** was drawn at 0.15 times to atomic van der Waals radius.

The single crystal X-ray diffraction study revealed that the polyether macrocycle **36d** containing a 1,3-diyne unit was found to crystallize in $P\ \bar{1}$ space group and asymmetric unit was found to contain two independent molecules (Figure 7). In the molecule **36d_1**, the bending angle of the 1,3-diyne unit was found to be ~12^{o}, however, in the case of **36d_2** the bending angle of the 1,3-diyne unit was found to be ~7^{o}. The interplanar angle between two phenyl rings of the conformers **36d_1** and **36d_2** were found to be ~64^{o} and ~66^{o}, respectively. Two different

conformations were found in the crystal packing and the interplanar angles between phenyl rings were almost same.



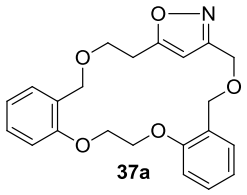


Figure 8. Ball and stick model (X-ray structures **37a**) was drawn at 0.15 times to atomic van der Waals radius.

The single crystal X-ray structure analysis showed that the 18-membered macrocyclic compound **37a** was found to crystallize in the $P2_1/c$ space group and the asymmetric unit contained one full molecule (Figure 8). The interplanar angle between two phenyl rings was found to be ~76^o and the interplanar angle between phenyl and isoxazole rings was found to be ~61 ^{o} and ~73^o (with respect to each phenyl ring), respectively. The distance between the phenyl rings was found to be ~8 Å and the distances between phenyl and isoxazole ring were found to be ~6 Å and ~7 Å (with respect to each phenyl ring), respectively.

Preliminary single crystal X-ray diffraction study revealed that the 20-memberd macrocyclic compound **38a** was found to crystallize in the *Pnma* space group with half the molecule in the asymmetric unit. The molecule has a crystallographically-imposed mirror symmetry which leads to the appearance of the half of the molecule in the asymmetric unit (Figure 9). The both the methoxymethyl linkages connecting the thiophene and phenyl ring were found to be in the same plane. The interplanar angle between the two phenyl rings was found to be ~77^o and the interplanar angle between the phenyl and thiophene rings was found to be ~77^o.

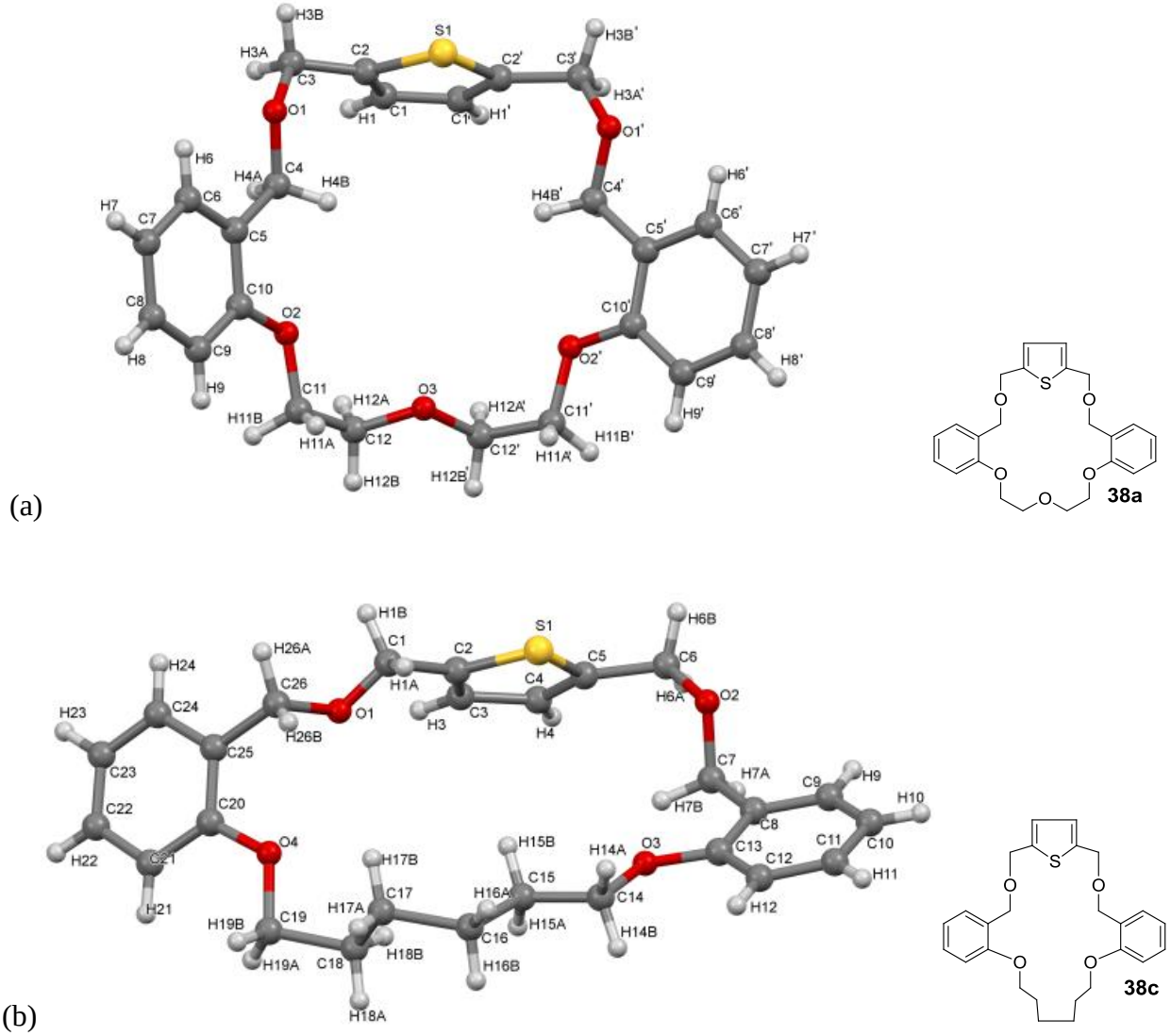


Figure 9. Ball and stick model (X-ray structures **38a** and **38c**) was drawn at 0.15 times to atomic van der Waals radius; (a) **38a** (b) **38c**. Only half of the molecule is present in the asymmetric unit of the X-ray structure of the compound **38a**. Therefore, the atoms at the right hand side of X-ray structure of **38a** (shown with a prime (‘) label) are at equivalent position (x, 3/2-y, z) with respect to the atoms on the left hand side.

The single crystal X-ray structure analysis revealed that the 21-membered macrocyclic compound **38c** was found to pack in $P\ \bar{1}$ space group and one full molecule was found in the asymmetric unit (Figure 9). While considering that the methoxymethyl thiophene linkage

between the phenyl rings is same in the structures **38c** and **38a**, however, the change of linker from polyether unit-based linker (**38a**) in to a flexible alkyl chain-based linker (**38c**) has led to increase the distance between two phenyl rings (centriods) by ~2 Å and the interplanar angle between two phenyl rings was reduced to ~42^{o}. This increment has led desymetrizitation in the molecule.

Subsequently, the cavity dimensions were calculated from the in the X-ray structures of representative crown ether/polyether macrocycles obtained in this work. The cavities in the X-ray structure of representative crown ether/polyether macrocycles can be approximated to be a rectangular box and the cavity dimensions are mentioned in Table 1.[16f,g] From all the above deliberations about the X-ray structures of representative macrocycles presented in this work, it was observed that in these set of molecules the 1,3-diyne unit was not able to hold the linearity. It seems that the substituents attached to the benzylic carbon, size and nature of the linkers are playing some significant roles to control the conformation including the shape of the 1,3-diyne unit of the macrocycles synthesized in this work. Along this line, some of the X-ray structures were further scrutinized and compared to find out the effect of the substituents attached to the benzylic carbon, size and nature of the linkers on the conformation of macrocycles having the 1,3-diyne units.

Effect of the ring size and the nature of the linkers on the conformation/shape/bending of the 1,3-diyne unit of macrocycles.

First of all, to see the effect of the substituent on the benzylic carbon and on the bending angle of the 1,3-diyne unit, we have compared the structures of the compounds **33l** and **36d**, in which the ring size molecules (entries 8,12 and 13, Table 1) as well as on the bending angles of the 1,3-diyne unit (bending angle ~12° in **36d** and bending angle = ~12° in **33l**). Thus, apparently the allyl group was not playing any role in controlling the strain, cavity size or the bending angle of the 1,3-diyne unit and the conformation of the molecule **36d**.

Table 1. Cavity dimensions (in Å) of crown ethers/polyethers macrocycles from their X-ray structures.

entry	compound	ring size	approximate cavity dimensions (m[a] x n[b] in Å) from X-ray structure[c,d]	approximate bend angle of 1,3-diyne unit /[a]
1	**33a_1**	18	4 x 7	15
2	**33a_2**	18	4 x 7	15
3	**33f***	21	4 x 8	11
4	**33g**	20	5 x 7	14
5	**33h**	20	3 x 8	8
6	**33i**	20	4 x 7	17
7	**33k**	24	6 x 8	16
8	**33l**	21	4 x 8	12
9	**33n***	24	4 x 8	18
10	**33q***	24	4 x 8	11
11	**36b**	20	4 x 8	5
12	**36d_1**	21	4 x 8	12
13	**36d_2**	21	4 x 8	7
14	**37a**	18	4 x 6	-
15	**38a**	20	6 x 6	-
16	**38c**	21	5 x 8	-

[a] Center to center distance between the 1,3-diyne bridges and the linkers. [b] Center to center distance between two benzylic carbons, except the compounds **33f, 33n,** and **33q**. [c] In all the compounds, the cavity dimensions are calculated from the center to center distance between the 1,3-diyne bridges and the linkers as well as the center to center distance between two benzylic carbons, except the compounds **33f, 33n,** and **33q**. [d] In the cases of the compounds **33f, 33n,** and **33q**, the cavity dimensions are calculated from the center to center distance between the 1,3-diyne bridges and the linkers as well as the distance between the two oxygen atoms, which are attached to the benzylic carbons.

Then, to study the effect of the size or nature of the linkers on the bending angle of the 1,3-diyne unit, the X-ray structures of **33a** and **36b**, which have different linkers were compared. In the compound **33a**, the linker is an ethyl group (–CH_2–CH_2–), while butyl group acts as a linker in the case of **36b** (–CH_2–CH_2–CH_2–CH_2–). Compound **36b** contains the allyl groups at the benzylic carbons, which is not there in the compound **33a**. It has already been discussed that the allyl group was not playing any role in altering the cavity size and bending angle of the 1,3-dialkyne unit and hence, it was envisaged to compare the structures of both the macrocycles (**33a** and **36b**) on the basis of ring size. It has been found that with the increase in the size of the ring from 18-membered (structure **33a**) to 20-membered (structure **36b**), the cavity size has increased (entries 1,2 and 11, Table 1). Consequently, there is a decrease in the bending angle of the 1,3-dialkyne unit in **36b** (bending angle ~5°) by ~10° when compared to **33a** (bending angle = ~15°).

Increase in the size of the macrocyclic ring from 20-membered (structure **36b**) to 21-membered (compound **33l**) by the incorporation of an oxygen atom in the linker of **33l** (–CH_2–CH_2–O–CH_2–CH_2–) has resulted a decrease in the cavity size in the structure of **33l** (entries 8 and 11, Table 1) and as a result the bending angle of the 1,3-dialkyne unit has increased by ~7° in the structure of **33l** (bending angle ~12°) when compared to the structure of **36b** (bending angle ~5°).

When the size of the macrocyclic ring was increased from 21-membered (compound **33l**) to 24-membered (compound **33n**) by the incorporation of another –CH_2–O–CH_2– group in the linker of **33l**, surprisingly the cavity size has not increased (entries 8 and 9, Table 1) and it is expected that the bending angle of the 1,3-dialkyne unit in the structure **33n** has to decrease when compared to the structure **33l**. However, the bending angle of the 1,3-dialkyne unit in the macrocycle **33n** (bending angle ~18°) was found to increase by ~6° when compared to the structure of **33l** (bending angle = ~12°).

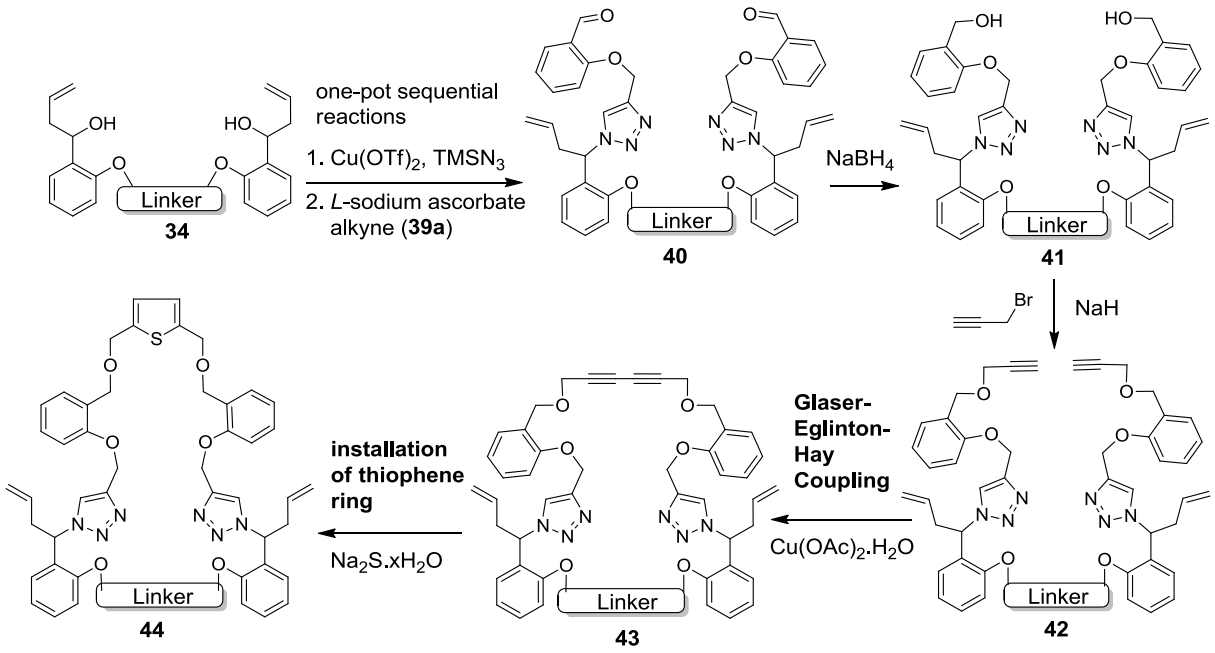
In the compounds **33q** and **33n** the ring size is same (24-membered) and in the compound **33n** the 1,3-diyne unit is connected *via* the benzylic carbons (C4 carbon, (Ph–CH_2–O unit)) while in the compound **33q**, the 1,3-diyne unit is connected *via* the Ph–COO (benzoyl carboxyl) groups (C7 and C24). In the case of the compound **33q** the carbonyl group has been found to play an important role in controlling the bending of the 1,3-diyne unit; though the ring size is same in the

compounds **33q** and **33n** (entries 9 and 10, Table 1). However, the incorporation of the –COO (benzoyl carboxyl) group has altered the cavity size of **33q**. Furthermore, the bending angle of the 1,3-dialkyne unit in the macrocycle **33q** (bending angle ~11°) was found to decrease by ~7° when compared to the structure of **33n** (bending angle = ~18°).

Additionally, to explore the effect of the nature of the linker by keeping the ring size constant, we have compared the structures of **36b**, **33g** and **33h**. In the structure **36b**, where the linker is the butyl group (–CH_2–CH_2–CH_2–CH_2– (C14 to C17 unit)), the bending angle of the 1,3-dialkyne unit was found to be ~5°. Varying the linker from butyl group (see compound **36b**) in to the 2,3-*trans* butenyl group (–CH_2– CH=CH–CH_2– (C14 to C17 unit), see the compound **33g**), the cavity size of the macrocyclic ring **33g** was found to be larger when compared to the structure of **36b** (entries 4 and 11, Table 1), consequently, the ring strain is expected to increase. Hence, the bend angle of the 1,3-dialkyne unit in the macrocycle **33g** (bend angle ~14°) was found to increase by ~9° when compared to the structure **36b** (bend angle ~5°). Similarly, varying the linker from the 2,3-*trans* butenyl group (–CH_2–CH=CH–CH_2– (C14 to C17 unit), see the compound **33g**) in to the –CH_2–C≡C–CH_2– group (C14 to C17 unit), see the compound **33h**), the cavity size of the macrocyclic ring **33h** was found to be smaller when compared to the structure of **33g** (entries 4 and 5, Table 1). Surprisingly, the bending angle of the 1,3-dialkyne unit in the macrocycle **33h** (bending angle ~8°) did not increase more than the bending angle of the 1,3-dialkyne unit of the macrocycle **33g** (bending angle ~14°). On the other hand, interestingly, the mono acetylenic unit linker (C14 to C17 unit) present in the structure **33h** was found to be bent and the bending angle of the mono acetylenic unit linker was found to be ~11°, which indicated that in order to accommodate the ring strain, the (mono) acetylenic unit, which act as a linker (C14 to C17 unit) is also bending. From the preliminary analysis of the X-ray structures of representative macrocycles, it has been found that the ring size and the nature of the linkers have been found to play vital role to accommodate the ring strain and control the conformation including the shape of the 1,3-diyne unit of macrocycles.

Investigations on the synthesis of new classes of 1,2,3-triazole moiety embedded polyether macrocycles *via* the Glaser-Eglinton-Hay coupling strategy.

The copper(I)-catalyzed cycloaddition (click) reactions of alkynes and azides affording the 1,2,3-triazoles have been well exploited in organic synthesis[18,19] 1,2,3-Triazole units offer various supramolecular interactions, ranging from anion complexation *via* (charge-assisted) hydrogen and halogen bonds and metal coordination by anionic, neutral, or cationic nitrogen donors as well as carbanionic and mesoionic carbine donors.[20,21] Several seminal studies have demonstrated the ability of acyclic and macrocyclic *bis*- and poly triazole unit containing systems to bind anions in organic solvents through triazole C–H···anion interactions.[21] A wide range of macrocyclic ligand architectures based on 1,2,3-triazoles are available and also numerous applications of the triazole's coordination chemistry have been reported, covering metal ion sensing, medicinal chemistry, catalysis, magnetic materials, and photovoltaic as well as electroluminescent devices.[20,21]

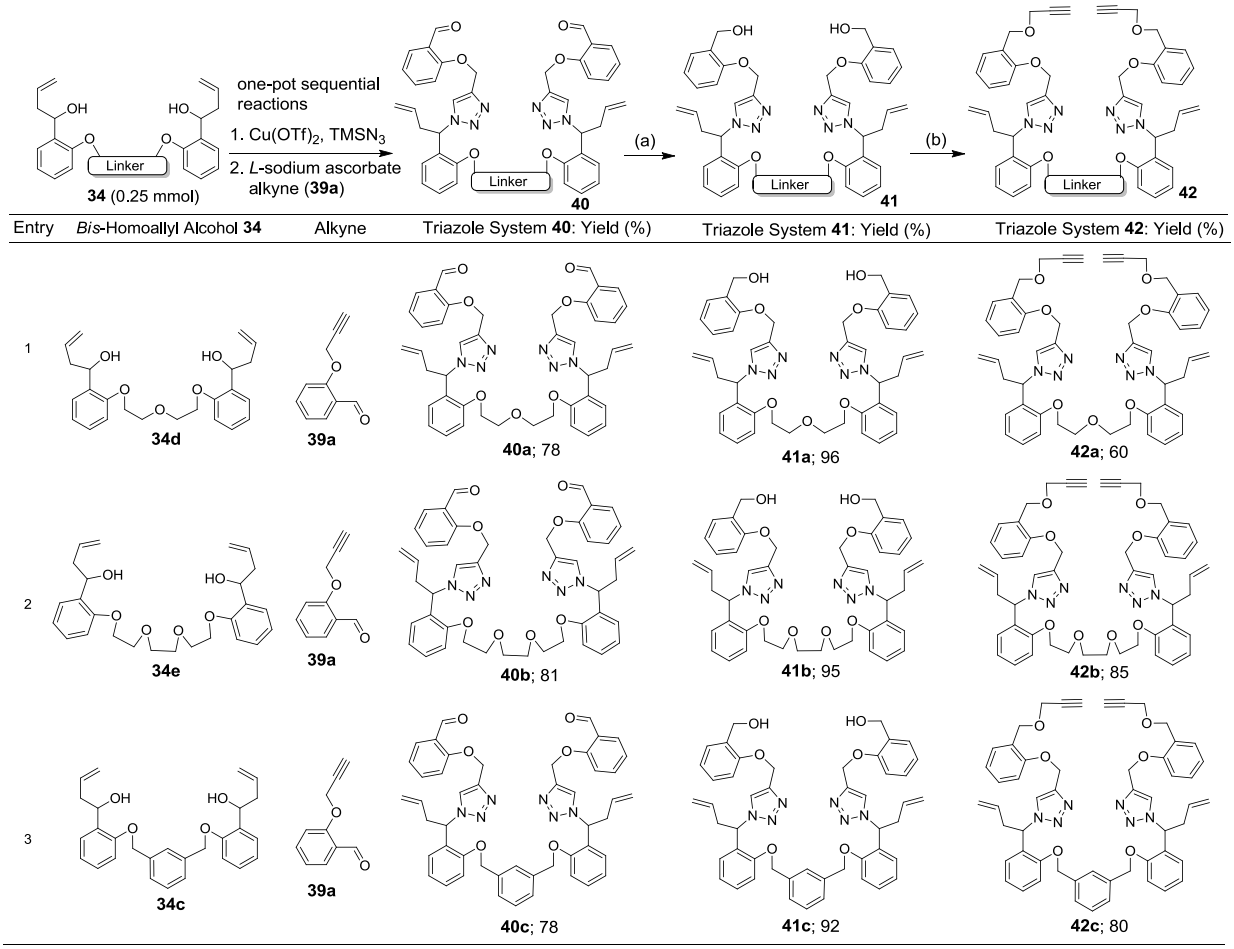


Scheme 32. Generalized scheme for the synthesis of triazole incorporated macrocycle synthesis.

In line with the objective of this thesis and taking an impetus from the papers dealing on the celebrated Glaser-Eglinton-Hay coupling reactions, a part of this thesis report the synthesis of *bis*-1,2,3-triazoles appended polyether macrocycles having a 1,3-diyne unit using Glaser-Eglinton-Hay macrocyclization strategy. Further, the 1,3-diyne unit of the *bis*-1,2,3-triazoles

appended polyether macrocycles were converted into thiophene ring to afford new classes of thiophene ring and *bis*-1,2,3-triazole unit appended polyether macrocycles (Scheme 32).

Table 2. Synthesis of Glaser-Eglinton-Hay coupling precursors **42a-c** having terminal alkyne units incorporated with 1,2,3-trizole moieties **40, 41** and **42**.

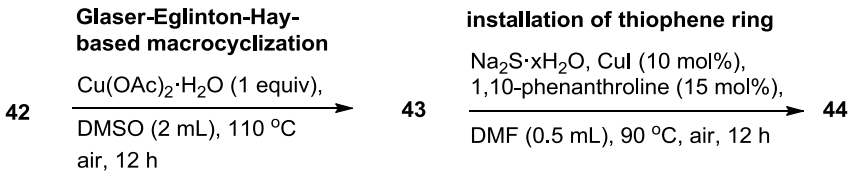


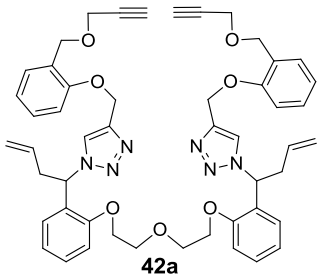
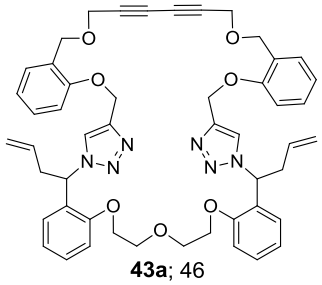
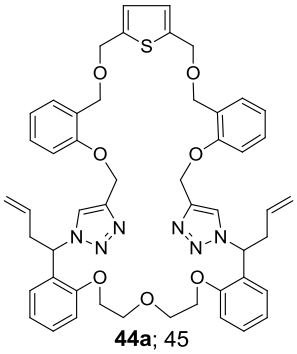
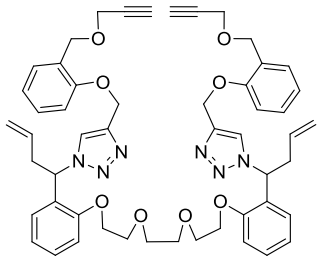
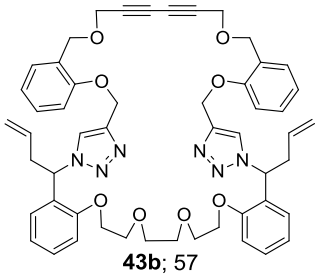
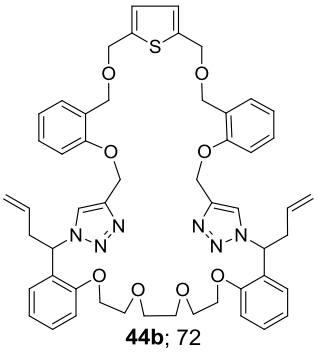
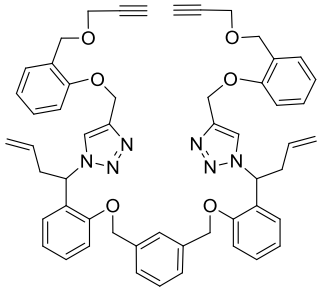
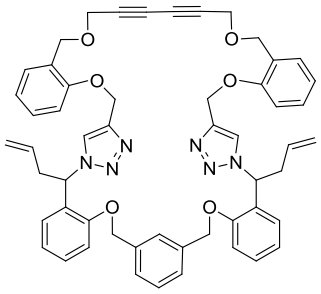
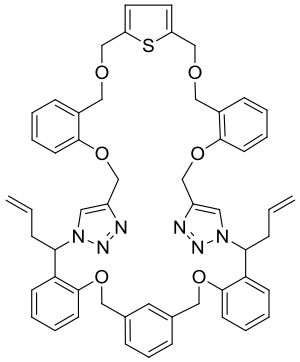
[a] Reagents and Conditions: The direct azidation of substrate **34** was carried out using $Cu(OTf)_2$ (10 mol%), $TMSN_3$ (3 equiv) in DCM (3 mL) at rt for 3 h and the solvent was evaporated in vacuum. Then, the click reaction was carried out using alkyne (5 equiv) in THF (2 mL) and water (2 mL) in the presence of *L*-sodium ascorbate (100 mol%) at rt for 20 h. (a) $NaBH_4$ (4 equiv), THF (3 mL) and EtOH (7 mL), 1 h, r.t. (b) NaH (4 equiv), propargyl bromide (5 equiv), THF (3 mL), 20 h, r.t.

To being with the synthesis of *bis*-1,2,3-triazole appended polyether macrocycles having a 1,3-diyne unit (Scheme 32), initially, the required Glaser-Eglinton-Hay coupling precursors **42a-c** having terminal alkyne units incorporated with 1,2,3-trizole moieties were assembled from *bis*-homoallylic alcohol **34d,e** and **34c** in multiple steps as shown in Table 2. The *bis*-homoallylic alcohol **34d,e** and **34c** connected *via* polyether linkers and aromatic linkers were treated with $TMSN_3$ (3 equiv) in the presence of $Cu(OTf)_2$ (10 mol%) at rt in DCM for 3 h and after this period, the solvent was evaporated (Table 2, entries 1, 2 and 3). Then, the resulted crude reaction mixture containing the corresponding azides was subjected to the click reaction with 2-(prop-2-yn-1-yloxy)benzaldehyde **39a** to afford the corresponding *bis*-triazole systems **40a-c** linked through suitable linkers in 78-81% yield (entries 1-3, Table 2). Next, the compounds **40a,b** and the compound **40c** were treated with $NaBH_4$ to afford *bis*-triazole systems **41a-c** linked through suitable linkers (entries 1-3, Table 2). Then, compounds **41a-c** were treated with propargyl bromide in the presence of NaH to give the required dialkyne precursors **42a-c** (entries 1-3, Table 2). Next, the Glaser-Eglinton-Hay-type cyclization with **42a-c** precursors having terminal alkyne units incorporated with 1,2,3-triazole moieties were attempted (entries 1-3, Table 2).

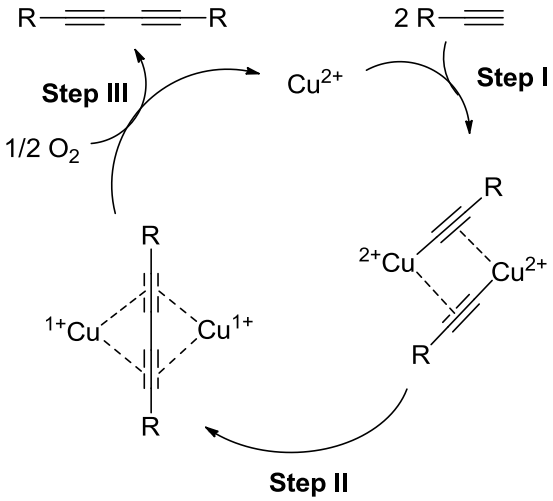
Accordingly the reactions of **42a-c** in the presence of $Cu(OAc)_2.H_2O$ in DMSO at 110 ^oC under an open-air atmosphere gave new classes of polyether macrocyclic systems **43a-c** embedded with 1,2,3-triazole moieties and the 1,3-diyne unit (entries 1-3, Table 3). Consequently, it was planned to convert the 1,3-diyne unit present in the compounds **43a-c** into a thiophene ring, to synthesize thiophene ring and *bis*-1,2,3-triazole unit appended polyether macrocycles **44a-c**. Accordingly, the reactions of macrocycles **43a-c** with $Na_2S.xH_2O$ in the presence of catalytic amount of 1,10-phenanthroline and CuI in DMF at 90^oC under an open-air atmosphere were performed to afford new classes of thiophene ring and *bis*-1,2,3-triazole unit appended polyether macrocycles **44a-c** in 45-72% yield (entries 1-3, Table 3).

Table 3. Synthesis of *bis*-1,2,3-triazole units incorporated polyether macrocycles **43** *via* the Glaser-Eglinton-Hay coupling and thiophene ring and *bis*-1,2,3-triazole unit appended polyether macrocycles **44**.



Entry	Triazole System **42**	Macrocycle **43**: Yield (%)	Macrocycle **44**: Yield (%)
1	 **42a**	 **43a**; 46	 **44a**; 45
2	 **42b**	 **43b**; 57	 **44b**; 72
3	 **42c**	 **43c**; 42	 **44c**; 69

Accordingly, in concurrence with the literature reports,[22,23] a plausible mechanism is proposed for the oxidative homocoupling of terminal alkynes into 1,3-diyne derivatives using Cu(II) catalyst (Scheme 33). In the initial step, the formation of a di-copper(II)- alkynyl intermediate takes place by the reaction of Cu^{2+} with 2 moles of terminal alkynes, which readily reduced to a Cu^{1+} species in step II. In step III, the desired diyne product formation and re-oxidation of the reduced Cu^{1+} species into Cu^{2+} occurs simultaneously *via* the O_2 supplied during the reaction from air or open atmosphere.



Scheme 33. Plausible mechanism for the homocoupling of alkynes to 1,3-diynes.

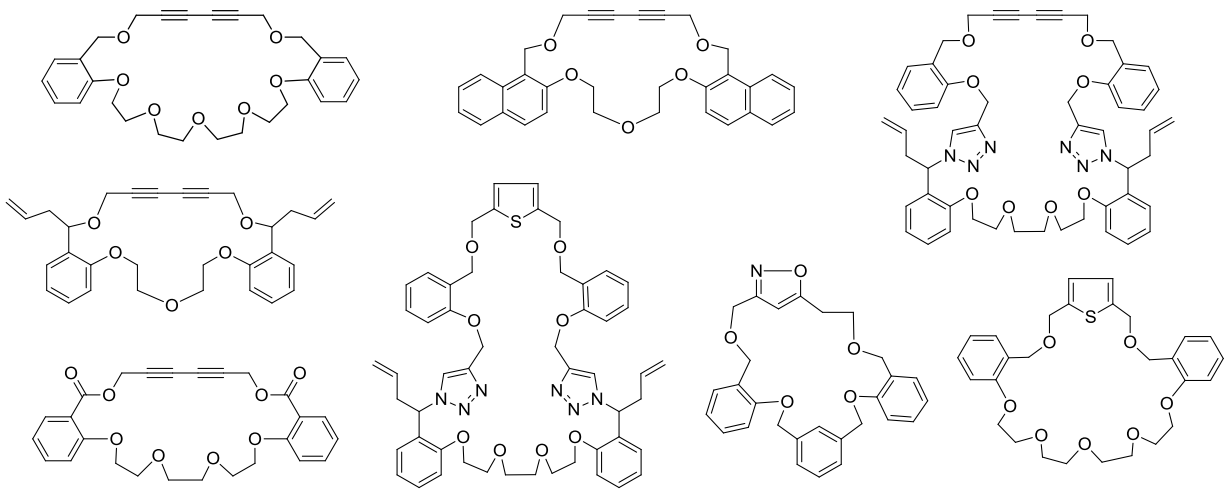
Conclusions

In summary, the Chapter 2 revealed a comprehensive synthetic work comprising the synthesis of new classes of crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone and different linkers/spacers by exploiting the Glaser-Eglinton-Hay macrocyclization route.

Next, a part of the Chapter 2 revealed the utility of polyether macrocycles possessing the 1,3-diyne units by incorporating the isoxazole and thiophene moieties in the macrocycles. Accordingly, the synthesis of periphery modified polyether macrocycles installed with thiophene and isoxazole functionalities from the crown ether-type macrocycles having a 1,3-diyne unit were shown.

Further, a part of the Chapter 2 revealed synthesis of *bis*-1,2,3-triazoles appended polyether macrocycles having a 1,3-diyne unit using Glaser-Eglinton-Hay macrocyclization strategy. Then, the utility of *bis*-1,2,3-triazoles appended polyether macrocycles having a 1,3-diyne unit was shown by incorporating a thiophene ring to afford thiophene ring and *bis*-1,2,3-triazole unit appended polyether macrocycles.

Assembling rigidified crown ether/polyether macrocycles *via* Glaser-Eglinton-Hay macrocyclization



The structures of selected crown ether/polyether-type macrocycles were unambiguously confirmed from the single crystal X-ray analyses of representative compounds. It has been found that in the crystal structures of representative macrocyclic compounds, the cylindrical backbone comprising a 1,3-diyne unit is not linear and the 1,3-diyne unit has been found to be bent.

Overall, given the importance of the polyether macrocycles in various fields of biology and chemistry, the Chapter 2 reported the synthesis of crown ether-type macrocycles having a 1,3-diyne unit-based rigid cylindrical backbone, *bis*-1,2,3-triazoles appended polyether macrocycles having a 1,3-diyne unit and polyether macrocycles installed with 1,2,3-triazole, thiophene and isoxazole functionalities in good yields by involving simple starting materials and synthetic procedures. Currently our laboratory is in the process of exploring the applications of the polyether macrocycles synthesized in the Chapter 2.

All the compounds included in the Chapter 2 of this thesis are characterized by various characterization techniques including ^{1}H and ^{13}C NMR, IR, X-ray diffraction and HRMS. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

Experimental Section

General: IR spectra were recorded as thin films or KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively using TMS as an internal standard. Compounds were purified by column chromatography using silica gel (100-200 mesh). Reactions were carried out in anhydrous solvent and under a nitrogen atm, wherever necessary. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analysis was performed on silica gel plates and the components were visualized by observation under iodine. Isolated yields of products were reported and yields were not optimized

Typical procedure for the synthesis of *bis*-aldehydes 30 (Procedure A). To a flame dried round-bottom flask was sequentially added the corresponding phenol derivative (12 mmol) dry DMF (20 mL), and anhydrous K_2CO_3 (20 mmol, 2.780 g). The reaction mixture was stirred at 80 ^{o}C for 15 min. After 15 min, the temperature of the reaction bath was increased to 110 ^{o}C and the corresponding alkyl dibromide or alkyl dichloride (5 mmol) was added in one portion to the hot reaction mixture. The resulting reaction mixture was stirred at 110 ^{o}C for 12 h and after this period, the reaction mixture was allowed to attain the room temperature, which was then added to ice flakes (15-25 g). The resulting solid compound (*bis*-aldehyde) was filtered through a filtration funnel and used in the next step without further purification. In case, if the *bis*-aldehyde is liquid; then the reaction mixture (after the treatment with ice flakes/cold water) was extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated under vacuum and used as such (without further purification) in the next step.

General procedure for the synthesis of *bis*-alcohols 31k (Procedure B). To a mixture of *bis*-aldehyde **30k** (3 mmol) in ethanol (7 mL) was added $NaBH_4$ (10 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 min. After this period, the reaction mixture was poured on to cold water (20 mL) or crushed ice (20 g). Then, the resulting solid compound was filtered through a filtration funnel and used without further purification. In case, if the *bis*-alcohol **31k** is liquid; then the reaction mixture (after the treatment with ice flakes/cold water) was extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried

over anhydrous Na_2SO_4, evaporated under vacuum and used as such (without further purification) in the next step.

General procedure for the syntheses of *bis*-alcohols 34a-e (Procedure C). To a mixture of corresponding *bis*-aldehyde **30** (3 mmol) and allyl bromide (7 equiv) in THF (7 mL) was added saturated NH_4Cl solution (18 mL) and Zn metal (5 equiv) successively at room temperature. The resulting mixture was stirred at room temperature for 30 h. After this period, the reaction mixture was extracted by using ethyl acetate (3 X 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the organic phase was concentrated and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc : hexanes = 30:70) which afforded the corresponding products **34a-e**.

General procedure for the syntheses of compounds 32a-h, 32j-p and 35a-e (Procedure D). To a solution of corresponding *bis*-alcohol **31** (1 mmol) (synthesized in the previous steps by using the procedure B or C) in dry THF (3 mL) was added NaH (4 mmol, 55-60 % suspension in mineral oil) at room temperature. The mixture was stirred at room temperature for 10 min and then propargyl bromide (5 mmol, 80 wt% in toluene) was added. The resulting mixture was stirred for 20 h at room temperature. After this period, few drops of EtOH was added and stirred for 10 min and then the resulting mixture was poured on to water (20 mL) and was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc : Hexanes = 20:80) to give the corresponding product **32**.

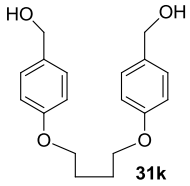
General procedure for the syntheses of macrocycles 33a-q, 36a-e and 39e (Procedure E). A mixture of **32a** (0.20 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mol% or 1 equiv as mentioned the respective Scheme/Table/Fig.) and DMSO (2 mL) was taken in a vial (10 mL capacity) or round bottom flask (10 or 20 mL capacity). The reaction mixture was stirred at 110 °C under open air atmosphere for 4 h. After this period, the resulting mixture was cooled to room temperature and diluted with water (4 mL). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 x 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed

under reduced pressure and the residue was purified by silica gel chromatography (EtOAc : Hexane) which gave the crown/polyether-type macrocycles **33a-q, 36a-e and 39e**.

General procedure for the syntheses of macrocycles 37a-i (Procedure F). A mixture of **33** (0.20 mmol), $NH_2OH{\cdot}HCl$ (5 equiv), Et_3N (6 equiv) and DMSO (1 mL) was taken in a vial (10 mL capacity). The reaction mixture was sealed using a vial cap and stirred at 110 °C for 24 h. After this period, the vial was cooled to room temperature. Then the resulting mixture was diluted with water (4 ml). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 x 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc : Hexane) which gave the crown/polyether macrocycle **37a-i**.

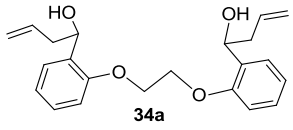
General procedure for the syntheses of macrocycles 38a-c and 39f (Procedure G). A mixture of **6f** (0.06 mmol), $Na_2S.xH_2O$ (70 mg), CuI (10 mol%), 1,10-phen (15 mol%) and DMF (0.5 mL) was stirred at 90 ^oC for 6h under open air atmosphere. After this period, the vial was cooled to room temperature. Then the resulting mixture was diluted with water (4 ml). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 x 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc : Hexane) which gave the crown/polyether macrocycle **38/39**.

((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))dimethanol (31k): Following the general procedure B, **31k** was obtained after filtration through a filtration funnel as a brown solid, (1.063 g, 88%); mp: 160-162 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3398, 2231, 1601, 1491, 1027 and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ and DMSO): δ 7.15 (4 H, d, *J* = 8.5 Hz), 6.73 (4 H, d, *J* = 8.5 Hz), 4.44 (4 H, d, *J* = 5.1Hz), 3.90 (4 H, s), 3.82 (2 H, t, *J* = 5.5 Hz), 1.84-1.82 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$ and DMSO): δ 158.1, 133.9, 128.4, 114.2, 67.4, 64.1, 25.9; HRMS (ESI): MNa^+, found 325.1428. $C_{18}H_{22}O_4Na$ requires 325.1416. (In ^1H NMR OH protons could not be detected may be it is merged with the residual DMSO signal).

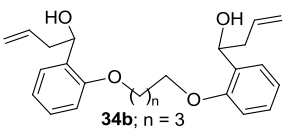


31k

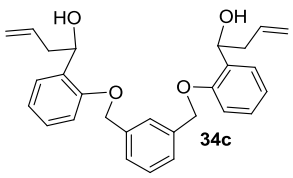
1,1'-((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) (34a): Following the general procedure C, **34a** was obtained after purification by column chromatography on silica gel as a white solid, (0.849 g, 80%); mp: 66-68 ^{o}C; R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3413, 2937, 1600, 1453 and 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (2 H, m), 7.24 (2 H, t, *J* = 7.8 Hz), 6.99 (2 H, t, *J* = 7.5 Hz), 6.91 (2 H, d, *J* = 8.2 Hz), 5.81-5.71 (2 H, m), 5.08-4.96 (6 H, m), 4.40-4.38 (4 H, m), 2.90 (2 H, br s), 2.58-2.46 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 135.1, 132.4, 128.3, 127.1, 121.4, 117.7, 111.5, 68.7, 66.9, 41.7; HRMS (ESI): MNa^+, found 377.1740. $C_{22}H_{26}O_4Na$ requires 377.1729. (Isolated as a 1:1 mixture of diastereomers and ^{13}C values given here for one isomer).



1,1'-((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) (34b): Following the general procedure C, **34b** was obtained after purification by column chromatography on silica gel as a white solid, (1.008 g, 88%); mp: 57-59 ^{o}C; R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3413, 3073, 2875, 1588 and 754 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (2 H, dd, *J* = 5.9, 1.56 Hz), 7.23-7.19 (2 H, m), 6.95 (2 H, t, *J* = 7.4 Hz), 6.85 (2 H, d, *J* = 7.6 Hz), 5.86-5.75 (2 H, m), 5.14-5.06 (4 H, m), 4.99-4.96 (2 H, m), 4.09-4.07 (4 H, m), 2.57-2.47 (6 H, m), 2.02-1.99 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 135.2, 131.9, 128.3, 126.8, 120.8, 117.6, 111.1, 69.4, 67.3, 42.0, 26.3; HRMS (ESI): MNa^+, found 405.2043. $C_{24}H_{30}O_4Na$ requires 405.2042. (In ^{1}H NMR OH protons could not be detected. This compound was isolated as a 1:1 mixture of diastereomers and ^{13}C values given here for one isomer).

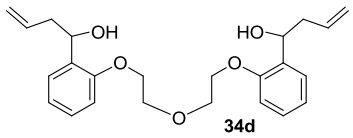


1,1'-(((1,3-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) (34c): Following the general procedure C, **34c** was obtained after purification by column chromatography on silica gel as a brown liquid; (1.057 g, 82%); R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3397, 3073, 2917, 1640, and 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1 H, s), 7.47-7.41 (5 H, m), 7.26 (2 H, t, *J* = 7.6 Hz), 7.04-6.94 (4 H, m), 5.89-5.85 (2 H, m), 5.30-5.09 (12 H, m), 2.92 (2 H, br s), 2.66-2.53 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2,

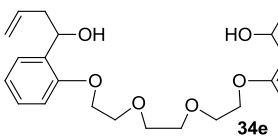


137.5, 135.2, 132.3, 129.1, 128.3, 126.9, 126.9, 126.7, 125.7, 121.1, 117.7, 111.7, 69.7, 69.1, 42.1; HRMS (ESI): MNa^+, found 453.2044. $C_{28}H_{30}O_4Na$ requires 453.2041. (Isolated as a 1:1 mixture of diastereomers and ^{13}C values given here for one isomer).

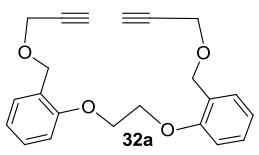
1,1'-(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) (34d): Following the general procedure C, **34d** was obtained after purification by column chromatography on silica gel as a colourless liquid; (Yield: 0.955 g, 80%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3416, 3073, 1640, 1601 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.17 (4 H, m), 6.94 (2 H, t, *J* = 7.4 Hz), 6.86 (2 H, d, *J* = 8.1 Hz), 5.82-5.71 (2 H, m), 5.07-4.99 (4 H, m), 4.92-4.87 (2 H, m), 4.21-4.15 (4 H, m), 3.90 (4 H, t, *J* = 4.5 Hz), 3.33 (2 H, t, *J* = 5.1 Hz), 2.57-2.53 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 135.4, 132.3, 128.3, 127.3, 121.2, 117.2, 112.1, 70.3, 69.8, 67.6, 41.5; HRMS (ESI): MNa^+, found 421.1997. $C_{24}H_{30}O_5Na$ requires 421.1991. (In ^1H NMR OH protons could not be detected. This compound was isolated as a 1:1 mixture of diastereomers and ^{13}C values given here for one isomer).



1,1'-((((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(but-3-en-1-ol) (34e): Following the general procedure C, **34e** was obtained after purification by column chromatography on silica gel as a colourless liquid; (1.169 g, 82%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3416, 2876, 1640, 1587 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.23 (4H, m), 6.97-6.87 (4 H, m), 5.90-5.79 (2 H, m), 5.13-5.05 (4 H, m), 4.92-4.88 (2 H, m), 4.19-4.17 (4 H, m), 3.88-3.85 (4 H, m), 3.73 (4 H, s), 3.39 (2 H, br s), 2.63-2.59 (4 H, m);^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 135.2, 132.4, 132.3, 128.3, 127.3, 121.1, 117.1, 112.2, 112.2, 70.8, 70.6, 69.7, 67.7, 67.6, 41.5; HRMS (ESI): MNa^+, found 465.2257. $C_{26}H_{34}O_6Na$ requires 465.2253. (This compound was isolated as a 1:1 mixture of diastereomers and ^{13}C values given here for one isomer).

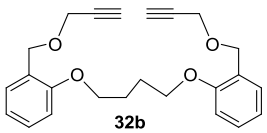


1,2-Bis(2-((prop-2-yn-1-yloxy)methyl)phenoxy)ethane (32a): Following the general procedure D, **32a** was obtained after purification by column chromatography on silica gel as a white solid, (0.262 g, 75%); mp: 64-66 ^oC; R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2943, 2883, 1602, 1493,1241,1081 and 754 cm^{-1}; ^1H NMR

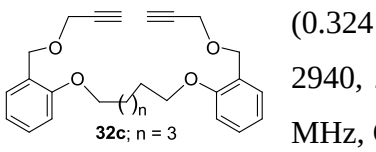


(400 MHz, $CDCl_3$): δ 7.42 (2 H, d, *J* =7.4 Hz), 7.31 (2 H, t, *J* = 8 Hz), 7.01 (2 H, t, *J* = 7.4 Hz), 6.96 (2 H, d, *J* = 8.2 Hz), 4.66 (4 H, s), 4.40 (4 H, s), 4.21 (4 H, d, *J* = 2.4 Hz), 2.38 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 129.5, 129.0, 126.3, 121.0, 111.6, 79.9, 74.3, 66.9, 66.6, 57.5. HRMS (ESI): MNa^+, found 373.1425. $C_{22}H_{22}O_4Na$ requires 373.1416.

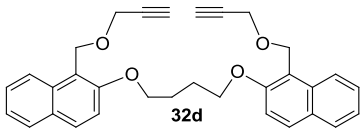
1,4-Bis(2-((prop-2-yn-1-yloxy)methyl)phenoxy)butane (32b): Following the general procedure D, **32b** was obtained after purification by column chromatography on silica gel as a red liquid; (0.321 g, 85%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2943, 2883, 1602, 1493, 1241, 1081and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (2 H, d, *J* =7.4 Hz), 7.29 (2 H, t, *J* = 7.8 Hz), 6.98 (2 H, t, *J* = 7.8 Hz), 6.90 (2 H, d, *J* = 8.0 Hz), 4.68 (4 H, s), 4.24 (4 H, d, *J* = 2.4 Hz), 4.09 (4 H, br s), 2.48 (2 H, t, *J* = 2.4 Hz), 2.07-2.04 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 129.6, 129.1,125.8, 120.4, 111.2, 80.0, 74.4, 67.5, 66.6, 57.5, 26.1; HRMS (ESI): MNa^+, found 401.1736. $C_{24}H_{26}O_4Na$ requires 401.1729.



1,6-Bis(2-((prop-2-yn-1-yloxy)methyl)phenoxy)hexane (32c): Following the general procedure D, **32c** was obtained after purification by column chromatography on silica gel as a brown liquid; (0.324 g, 80%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3291, 2940, 2862, 1602, 1590, 1494, 1455, 1048 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (2 H, d, *J* =7.4 Hz), 7.24 (2 H, t, *J* = 7.8 Hz), 6.92 (2 H, t, *J* = 7.4 Hz), 6.85 (2 H, d, *J* = 8.2 Hz), 4.64 (4 H, s), 4.20 (4 H, d, *J* = 2.3 Hz), 3.98 (4 H, t, *J* = 6.3 Hz), 2.43 (2 H, t, *J* = 2.3 Hz), 1.83 (4 H, t, *J* = 6.3 Hz), 1.57-1.53 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 129.5, 129.0, 125.9, 120.3, 111.3, 80.1, 74.3, 67.9, 66.7, 57.5, 29.3, 25.9; HRMS (ESI): MNa^+, found 429.2048. $C_{26}H_{30}O_4Na$ requires 429.2042.

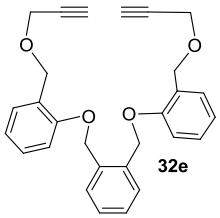


1,4-Bis((1-((prop-2-yn-1-yloxy)methyl)naphthalen-2-yl)oxy)butane (32d): Following the general procedure D, **32d** was obtained after purification by column chromatography on silica gel as a brown solid, (0.429 g, 92%); mp: 86-88 ^oC; R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2946, 1513, 1464, 1264, 1023 and 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (2 H, d, *J* = 8.4 Hz), 7.81-7.75 (4 H, m), 7.50 (2 H, t, *J* = 7.7 Hz), 7.34 (2 H, t, *J* = 7.4 Hz), 7.24 (2 H, d, *J* = 9.1 Hz), 5.14 (4 H, s), 4.22-4.18 (8 H, m), 2.49 (2 H, t, *J* = 2.3 Hz), 2.10 (4 H, t, *J* = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 133.9, 130.7, 129.2, 128.3, 127.0, 123.8, 118.1, 114.4,



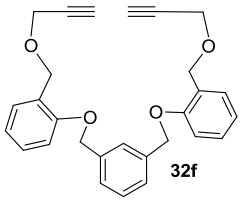
80.4, 74.4, 69.2, 61.9, 57.3, 26.5; HRMS (ESI): MNa^+, found 501.2037. $C_{32}H_{30}O_4Na$ requires 501.2042.

1,2-Bis((2-((prop-2-yn-1-yloxy)methyl)phenoxy)methyl)benzene (32e): Following the general procedure D, **32e** was obtained after purification by column chromatography on silica gel as a



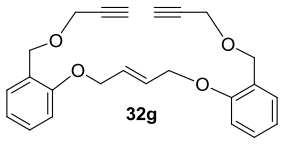
colourless liquid; (0.319 g, 75%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 2851, 1603, 1590, 1493 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58-7.56 (2 H, m), 7.41-7.37 (4 H, m), 7.29-7.24 (2 H, m), 7.01-6.95 (4 H, m), 5.22 (4 H, s), 4.68 (4 H, s), 4.16 (4 H, d, *J* = 2.4 Hz), 2.38 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 135.1, 129.7, 129.2, 128.7, 128.3, 126.1, 120.9, 111.7, 79.9, 74.5, 68.0, 66.7, 57.5; HRMS (ESI): MNa^+, found 449.1731. $C_{28}H_{26}O_4Na$ requires 449.1729.

1,3-Bis((2-((prop-2-yn-1-yloxy)methyl)phenoxy)methyl)benzene (32f): Following the general procedure D, **32f** was obtained after purification by column chromatography on silica gel as a



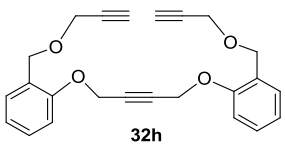
white solid, (0.332 g, 78%); mp: 62-64 ^oC; R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 2851, 1603, 1590, 1493 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (1 H, s), 7.45 (5 H, s), 7.29 (2 H, t, *J* = 7.7 Hz), 7.03-6.95 (4 H, m), 5.16 (4 H, s), 4.76 (4 H, s), 4.24 (4 H, s), 2.44 (2 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 137.5, 129.6, 129.1, 128.8, 128.8, 126.8, 126.2, 126.0, 120.9, 111.9, 80.0, 74.5, 69.9, 66.8, 57.6; HRMS (ESI): MNa^+, found 449.1724. $C_{28}H_{26}O_4Na$ requires 449.1729.

(*E*)-1,4-Bis(2-((prop-2-yn-1-yloxy)methyl)phenoxy)but-2-ene (32g): Following the general procedure D, **32g** was obtained after purification by column chromatography on silica gel as a

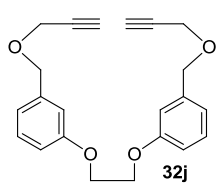


red solid, (0.263 g, 70%) mp: 73-75 ^oC; R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 1625, 1595, 1513, 1148 and 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (2 H, d, *J* = 7.4 Hz), 7.19 (2 H, t, *J* = 7.8 Hz), 6.91 (2 H, t, *J* = 7.4 Hz), 6.81 (2 H, d, *J* = 8.2 Hz), 6.05-6.04 (2 H, m), 4.63 (4 H, s), 4.56-4.55 (4 H, m), 4.16 (4 H, d, *J* = 2.4 Hz), 2.40 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 129.6, 129.6, 127.9, 126.2, 120.8, 111.7, 80.0, 74.5, 67.9, 66.6, 57.5; HRMS (ESI): MNa^+, found 399.1578. $C_{24}H_{24}O_4Na$ requires 399.1572.

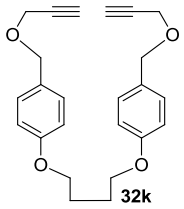
1,4-Bis(2-((prop-2-yn-1-yloxy)methyl)phenoxy)but-2-yne (32h): Following the general procedure D, **32h** was obtained after purification by column chromatography on silica gel as red a liquid; (0.187 g, 50%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 1625, 1595, 1513, 1148 and 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (2 H, d, *J* = 7.4 Hz), 7.19-7.14 (2 H, m), 6.93 (2 H, t, *J* = 7.4 Hz), 6.86 (2 H, d, *J* = 8.2 Hz), 4.68 (4 H, s), 4.58 (4 H, s), 4.14 (4 H, d, *J* = 2.4 Hz), 2.39 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 129.6, 128.9, 126.5, 121.5, 112.2, 82.4, 79.9, 74.4, 65.5, 57.5, 56.3; MS (CI): *m/z* (%) 374 ([M]$^+$, 20).



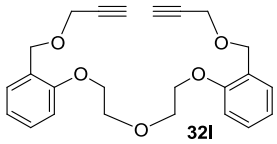
1,2-Bis(3-((prop-2-yn-1-yloxy)methyl)phenoxy)ethane (32j): Following the general procedure D, **32j** was obtained after purification by column chromatography on silica gel as a red liquid; (0.175 g, 50%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 2851, 1602, 1492 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (2 H, t, *J* = 7.7 Hz), 7.0-6.92 (6 H, m), 4.62 (4 H, s), 4.35 (4 H, s), 4.20 (4 H, d, *J* = 2.4 Hz), 2.50 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 138.9, 129.5, 120.7, 114.4, 114.1, 79.6, 74.7, 71.3, 66.5, 57.1; HRMS (ESI): MNa^+, found 373.1427. $C_{22}H_{22}O_4Na$ requires 373.1416.



1,4-Bis(4-((prop-2-yn-1-yloxy)methyl)phenoxy)butane (32k): Following the general procedure D, **32k** was obtained after purification by column chromatography on silica gel as a white solid; (0.189 g, 50%); mp: 86-88 ^oC; R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2920, 2851, 1611, 1584, 1454 and 818 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (4 H, d, *J* = 8.6 Hz), 6.90 (4 H, d, *J* = 8.6 Hz), 4.56 (4 H, s), 4.16 (4 H, d, *J* = 2.4 Hz), 4.05 (4 H, br s), 2.49 (2 H, t, *J* = 2.4 Hz), 2.01-1.98 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 129.9, 129.2, 114.4, 79.8, 74.5, 71.2, 67.5, 56.7, 25.9. HRMS (ESI): MNa^+, found 401.1735. $C_{24}H_{26}O_4Na$ requires 401.1729.

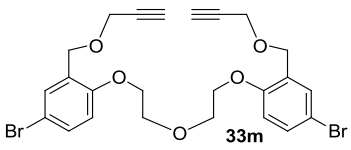


2,2'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(((prop-2-yn-1-yloxy)methyl)benzene) (32l): Following the general procedure D, **32l** was obtained after purification by column chromatography on silica gel as a red liquid; (0.275 g, 70%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2930, 2875, 1603, 1494, 1083 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (2 H, d, *J* = 7.4 Hz), 7.26 (2 H, t, *J* = 7.8

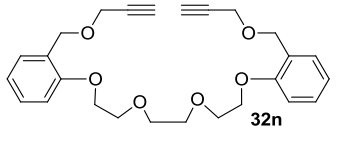


Hz), 6.97 (2 H, t, *J* = 7.4 Hz), 6.88 (2 H, d, *J* = 7.6 Hz), 4.66 (4 H, s), 4.20-4.17 (8 H, m), 3.98-3.95 (4 H, m), 2.44 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 129.6, 129.0, 126.2, 120.9, 111.6, 80.1, 74.4, 70.0, 68.0, 66.7, 57.5; HRMS (ESI): MNa^+, found 417.1689. $C_{24}H_{26}O_5Na$ requires 417.1678.

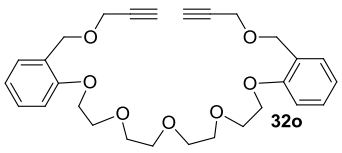
4,4'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(1-bromo-3-((prop-2-yn-1-yloxy)methyl)benzene) (32m): Following the general procedure D, **32m** was obtained after purification by column chromatography on silica gel as a red liquid; (0.247 g, 45%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2931, 2874, 1603, 1590, 1494, 1288, 1083 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (2 H, d, *J* = 2.5 Hz), 7.26 (2 H, dd, *J* = 6.2, 2.5 Hz), 6.67 (2 H, d, *J* = 8.7 Hz), 4.52 (4 H, s), 4.12 (4 H, d, *J* = 2.3 Hz), 4.06 (4 H, t, *J* = 4.7 Hz), 3.86-3.83 (4 H, m), 2.37 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 131.8, 131.4, 128.6, 113.3, 113.3, 79.7, 74.6, 69.9, 68.3, 66.0, 57.8; HRMS (ESI): MNa^+, found 572.9886. $C_{24}H_{24}Br_2O_5Na$ requires 572.9888.



1,2-Bis(2-(2-((prop-2-yn-1-yloxy)methyl)phenoxy)ethoxy)ethane (32n): Following the general procedure D, **32n** was obtained after purification by column chromatography on silica gel as a red liquid; (0.35 g, 80%); R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2926, 2874, 1590, 1494, 1247and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (2 H, d, *J* = 7.4 Hz), 7.24 (2 H, t, *J* = 7.9 Hz), 6.94 (2 H, t, *J* = 7.4 Hz), 6.85 (2 H, d, *J* = 8.1 Hz), 4.65 (4 H, s), 4.20 (4 H, d, *J* = 2.3 Hz), 4.14 (4 H, t, *J* = 4.9 Hz), 3.87 (4 H, t, *J* = 4.9 Hz), 3.75 (4 H, s), 2.46 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 129.5, 129.0, 126.1, 120.8, 111.6, 80.1, 74.4, 71.0, 69.8, 67.9, 66.7, 57.5; HRMS (ESI): MNa^+, found 461.1949. $C_{26}H_{30}O_6Na$ requires 461.1940.

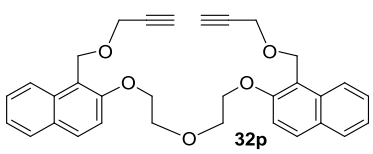


2,2'-((((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(((prop-2-yn-1-yloxy)methyl)benzene) (32o): Following the general procedure D, **32o** was obtained after purification by column chromatography on silica gel as a colourless liquid; (0.462 g, 96%); R_f (40% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2874, 1603, 1590, 1494, 1121 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (2 H, d, *J* = 7.4 Hz), 7.24 (2 H, t, *J* = 7 Hz), 6.95 (2 H, t, *J* = 7.4 Hz), 6.84 (2 H, d, *J* = 7.9 Hz), 4.65 (4 H, s), 4.21 (4 H, d, *J* = 2.4 Hz), 4.14 (4 H, d, *J* = 4.9 Hz), 3.86 (4 H,

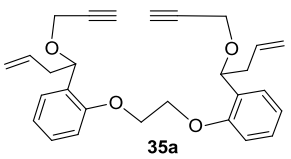


t, *J* = 4.9 Hz), 3.75-3.72 (4 H, m), 3.69-3.66 (4 H, m), 2.47 (2 H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 129.5, 129.0, 126.1, 120.7, 111.6, 80.1, 74.4, 70.9, 70.7, 69.7, 67.8, 66.6, 57.5; HRMS (ESI): MNa^+, found 505.2206. $C_{28}H_{34}O_7Na$ requires 505.2202.

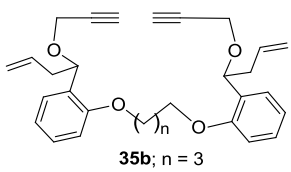
2,2'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(1-((prop-2-yn-1-yloxy)methyl)naphthalene) (32p): Following the general procedure D, **32p** was obtained after purification by column chromatography on silica gel as a colourless liquid; (0.395 g, 80%); R_f (20% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2879, 1596, 1513, 1135, 1074 and 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (2 H, d, *J* = 8.5 Hz), 7.85-7.80 (4 H, m), 7.55 (2 H, t, *J* = 8.4 Hz), 7.40 (2H, t, *J* = 8.1 Hz), 7.30 (2 H, d, *J* = 8.9 Hz), 5.1 (4 H, s), 4.35 (4 H, t, *J* = 4.8 Hz), 4.25 (4 H, d, *J* = 2.4 Hz), 4.04 (4 H, t, *J* = 4.8 Hz), 2.51 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 133.8, 130.7, 129.5, 128.3, 127.1, 123.9, 123.9, 118.7, 115.0, 80.5, 74.4, 70.3, 69.7, 62.0, 57.3; HRMS (ESI): MNa^+, found 517.1992. $C_{32}H_{30}O_5Na$ requires 517.1991.



1,2-Bis(2-(1-(prop-2-yn-1-yloxy)but-3-en-1-yl)phenoxy)ethane (35a): Following the general procedure described above, **35a** was obtained after purification by column chromatography on silica gel as a red liquid; (0.352 g, 82%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 2851, 1602, 1492 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.27 (4 H, m), 7.04 (2 H, t, *J* = 7.2 Hz), 6.96 (2 H, d, *J* = 8.2 Hz), 5.86-5.79 (2 H, m), 5.07-4.98 (6 H, m), 4.36 (4 H, s), 4.14 (1 H, d, *J* = 2.4 Hz), 4.10 (1 H, d, *J* = 2.4 Hz), 3.95-3.90 (2 H, m), 2.53-2.49 (4 H, m), 2.36 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 134.8, 129.4, 128.5, 127.0, 121.3, 116.7, 111.5, 80.2, 74.1, 73.9, 66.9, 56.0, 40.8; HRMS (ESI): MNa^+, found 453.2051. $C_{28}H_{30}O_4Na$ requires 453.2042.

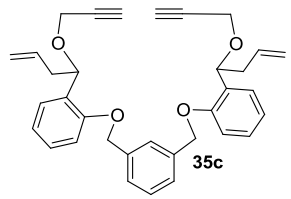


1,4-Bis(2-(1-(prop-2-yn-1-yloxy)but-3-en-1-yl)phenoxy)butane (35b): Following the general procedure D, **35b** was obtained after purification by column chromatography on silica gel as a white solid, (0.389 g, 85%); mp: 85-87 ^{o}C; R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2929, 2851, 1602, 1492 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (2 H, dd, *J* = 5.8, 1.6 Hz), 7.28-7.24 (2 H, m), 7.01 (2 H, t, *J* = 7.4 Hz), 6.90 (2 H, d, *J* = 8.2 Hz), 5.92-5.82 (2 H, m), 5.11-5.02 (6 H, m), 4.17-3.92 (8 H, m), 2.54-2.49 (4 H, m), 2.40-2.39 (2 H, m) 2.05 (2 H, t, *J* = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 135.1, 129.1, 128.5, 126.7, 120.7, 116.6,

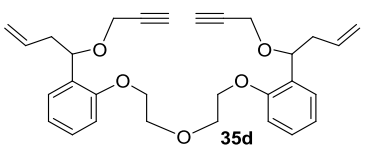


111.1, 80.2, 74.1, 73.9, 67.4, 55.9, 40.9, 26.2; HRMS (ESI): MNa^+, found 481.2364. $C_{30}H_{34}O_4Na$ requires 481.2355.

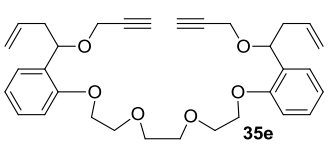
1,3-Bis((2-(1-(prop-2-yn-1-yloxy)but-3-en-1-yl)phenoxy)methyl)benzene (35c): Following the general procedure D, **35c** was obtained after purification by column chromatography on silica gel as a colourless liquid; (0.253 g, 50%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 3073, 2924, 2855, 1601, 1588, 1048 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (1 H, s), 7.44-7.42 (5 H, m), 7.28-7.24 (2 H, m), 7.03 (2 H, t, *J* = 7.2 Hz), 6.95 (4 H, d, *J* = 8.1 Hz), 5.92-5.85 (2 H, m), 5.15 (6 H, s), 5.10-5.02 (4 H, m), 3.97 (1 H, d, *J* = 2.3 Hz), 3.93 (1 H, d, *J* = 2.3 Hz), 2.57-2.53 (4 H, m), 2.38-2.37 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 137.5, 135.0, 129.5, 128.8, 128.5, 126.9, 126.6, 125.7, 121.2, 116.6, 111.9, 80.2, 74.3, 73.9, 69.8, 56.0, 41.0; HRMS (ESI): MNa^+, found 529.2357. $C_{34}H_{34}O_4Na$ requires 529.2355.



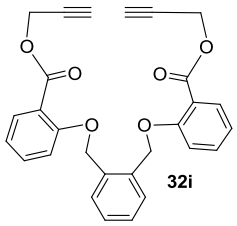
2,2'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis((1-(prop-2-yn-1-yloxy)but-3-en-1-yl)benzene) (35d): Following the general procedure D, **35d** was obtained after purification by column chromatography on silica gel as a red liquid; (0.402 g, 85%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2927, 1600, 1588,1489, 1285, 1241, 1082 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.24 (4 H, m), 7.02-6.89 (4 H, m), 5.93-5.83 (2 H, m), 5.10-5.01 (6 H, m), 4.20-3.93 (12 H, m), 2.55-2.53 (4 H, m), 2.38 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 135.1, 129.4, 128.5, 126.8, 121.1, 116.5, 111.6, 80.3, 74.4, 74.3, 73.8, 70.1, 67.9, 50.0, 40.9; HRMS (ESI): MNa^+, found 497.2318. $C_{30}H_{34}O_5Na$ requires 497.2304.



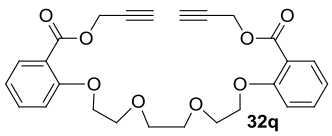
1,2-Bis(2-(2-(1-(prop-2-yn-1-yloxy)but-3-en-1-yl)phenoxy)ethoxy)ethane (35e): Following the general procedure D, **35e** was obtained after purification by column chromatography on silica gel as a red liquid; (0.450 g, 87%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2927, 1600, 1588, 1489, 1285, 1241, 1082 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.23 (4 H, m), 7.01-6.87 (4 H, m), 5.92-5.83 (2 H, m), 5.11-5.02 (6 H, m), 4.18-3.88 (12 H, m), 3.77 (4 H, s), 2.54-2.51 (4 H, m), 2.41 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 135.1, 129.3, 128.5, 126.8, 121.0, 116.5, 111.6, 80.3, 74.3, 73.9, 71.0, 69.9, 67.7, 56.0, 40.8; HRMS (ESI): MNa^+, found 541.2567. $C_{32}H_{38}O_6Na$ requires 541.2566.



Di(prop-2-yn-1-yl) 2,2'-((1,2-phenylenebis(methylene))bis(oxy))dibenzoate (32i): To a solution of propargyl alcohol (1.5 mmol), 2,2'-((1,2-phenylenebis(methylene))bis(oxy))dibenzoic acid (0.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.80 mmol) in CH_2Cl_2 (2.5 mL) was added 1,3-dicyclohexylcarbodiimide (1.5 mmol) in small fractions. The reaction mixture was stirred at room temperature for 2 h. The resulting pale yellow suspension was filtered through filtration funnel. The filtrate was concentrated and purified by silica gel column chromatography which afforded the product **32i** as a red solid, (0.181 g, 80%); mp: 104-106 ^oC; R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2933, 1782, 1600, 1489, 1244 and 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90-7.87 (2 H, m), 7.69-7.67 (2 H, m), 7.51-7.39 (4 H, m), 7.14-6.99 (4 H, m), 5.37 (4 H, s), 4.88 (4 H, m), 2.49 (2 H, t, J = 2.4 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 158.3, 134.5, 134.1, 132.2, 128.6, 128.3, 120.5, 119.3, 113.5, 77.8, 75.0, 68.9, 52.3; HRMS (ESI): MNa^+, found 477.1311. $C_{28}H_{22}O_6Na$ requires 477.1314.

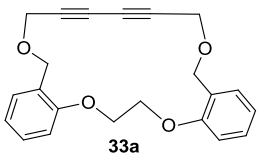


Di(prop-2-yn-1-yl) 2,2'-(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))dibenzoate (32q): To a solution of propargyl alcohol (1.5 mmol), 2,2'-(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))dibenzoic acid (0.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 0.80 mmol) in CH_2Cl_2 (2.5 mL) was added 1,3-dicyclohexylcarbodiimide (1.5 mmol) in small fractions. The reaction mixture was stirred at room temperature for 2 h. The resulting pale yellow suspension was filtered through filtration funnel. The filtrate was concentrated and purified by silica gel column chromatography which afforded the product **32q** as red sticky liquid; (0.202 g, 87%); R_f (10% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2): ν_{max} 2935, 2876, 1590, 1603, 1494, 1248 and 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86-7.83 (2 H, m), 7.48-7.44 (2 H, m), 6.99 (4 H, d, J = 8 Hz), 4.88 (4 H, d, J = 2.4 Hz), 4.21 (4 H, t, J = 4.7 Hz), 3.93 (4 H, t, J = 5.16 Hz), 3.81 (4 H, s), 2.53 (2 H, t, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 158.7, 133.9, 131.9, 120.5, 119.6, 113.7, 77.9, 74.9, 71.2, 69.5, 68.9, 52.2; HRMS (ESI): MNa^+, found 489.1530. $C_{26}H_{26}O_8Na$ requires 489.1525.



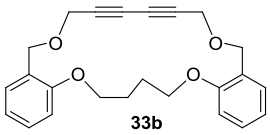
33a: Following the general procedure E, **33a** was obtained after purification by column chromatography on silica gel as a white solid (0.061 g, 70%); mp: 142-144 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3031, 1702, 1599, 1486 and 1027 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$): δ 7.37 (2 H, d, *J* = 5.8 Hz), 7.26 (2 H, t, *J* = 6.9 Hz), 6.98 (2 H, t, *J* = 7.0 Hz), 6.88 (2 H, d, *J* = 7.6 Hz), 4.81 (4 H, s), 4.41 (4 H, s), 4.28 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$):


33a

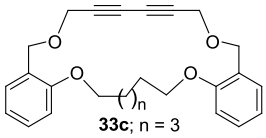
δ 156.6, 129.3, 128.9, 126.1, 121.1, 111.7, 76.5, 72.1, 67.6, 64.5, 57.3; HRMS (ESI): MNa^+, found 371.1263. $C_{20}H_{20}O_4Na$ requires 371.1259. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.

33b: Following the general procedure E, **33b** was obtained after purification by column chromatography on silica gel as a white solid (0.049 g, 52%); mp: 131-133 ^oC; R_f (10%


33b

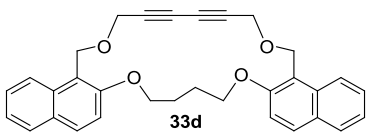
EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2942, 2883, 1599, 1343 and 891 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (2 H, d, *J* = 5.9 Hz), 7.29-7.26 (2 H, m), 6.96 (2 H, t, *J* = 7.0 Hz), 6.89 (2 H, d, *J* = 8.1 Hz), 4.76 (4 H, s), 4.27 (4 H, s), 4.05(4 H, br s), 2.06 (4 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 129.6,129.1, 125.7, 120.7, 111.4, 75.4, 70.9, 68.4, 64.9, 57.2, 26.5; HRMS (ESI): MH^+, found 377.1729. $C_{24}H_{25}O_4$ requires 377.1752.

33c: Following the general procedure E, **33c** was obtained after purification by column


33c; n = 3

chromatography on silica gel as a white solid (0.105 g, 52%); mp: 134-136 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2936, 1602, 1424, 1248 and 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (4 H, m), 6.91 (2 H, t, *J* =7.0 Hz), 6.85 (2 H, d, *J* = 8.2 Hz), 4.65 (4 H, s), 4.27 (4 H, s), 3.99 (4 H, t, *J* = 5.9 Hz), 1.89-1.86 (4 H, m), 1.66-1.62(4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 130.5, 129.5, 125.7, 120.4, 111.4, 75.6, 70.3, 68.3, 66.3, 57.6, 29.6, 26.7; HRMS (ESI): MNa^+, found 427.1899. $C_{26}H_{28}O_4Na$ requires 427.1885.

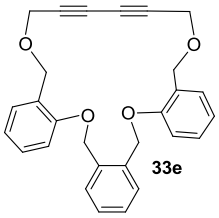
33d: Following the general procedure E, **33d** was obtained after purification by column chromatography on silica gel as a white solid (0.167 g, 70%); mp: 185-187 ^oC; R_f (20%


33d

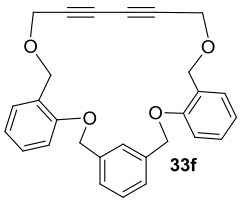
EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 2867, 1601, 1493, 1248 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (2 H, d, *J* = 8.2 Hz), 7.83 (2 H, d, *J* = 9 Hz), 7.78 (2 H, d, *J* = 8 Hz), 7.51 (2 H, t, *J* = 7 Hz), 7.37 (2 H, t, *J* = 6.9 Hz), 7.30 (2 H, d, *J* = 9.0 Hz), 5.28 (4 H, s), 4.21-4.19 (8 H, m), 2.22-2.20 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 133.8, 130.7, 129.4, 128.3, 126.9,

124.0, 123.9, 117.9, 115.0, 75.8, 70.9, 70.4, 60.8, 56.2, 27.3; HRMS (ESI): MH^+, found 477.2058. $C_{32}H_{29}O_4$ requires 477.2066.

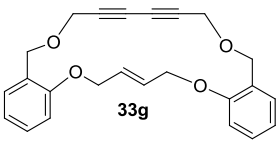
33e: Following the general procedure E, **33e** was obtained after purification by column chromatography on silica gel as a white solid (0.091 g, 43%); mp: 95-97 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2873, 1603, 1344, 1492 and 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.45 (2 H, m), 7.36-7.29 (4 H, m), 7.21 (2 H, t, *J* = 7.8 Hz), 6.94 (2 H, t, *J* = 6.9 Hz), 6.80 (2 H, d, *J* = 7.8 Hz), 5.34 (4 H, s), 4.75 (4 H, s), 4.27 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 135.1, 129.6, 129.2, 128.4, 128.2, 126.1, 120.9, 111.6, 75.7, 70.8, 68.1, 66.2, 57.8; HRMS (ESI): MH^+, found 425.1747. $C_{28}H_{25}O_4$ requires 425.1753.



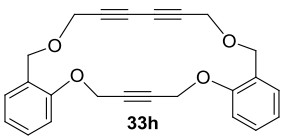
33f: Following the general procedure E, **33f** was obtained after purification by column chromatography on silica gel as a white solid (0.095 g, 45%); mp: 92-94 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3048, 2872, 1590, 1373 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (1 H, s), 7.35-7.29 (5 H, m), 7.24-7.17 (2 H, m), 6.96-6.91 (4 H, m), 5.01 (4 H, s), 4.64 (4 H, s), 4.22 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 137.4, 129.2, 129.0, 128.6,128.3, 128.1, 126.6, 121.2, 112.4, 75.4, 70.9, 70.7, 65.9, 57.8; HRMS (ESI): MH^+, found 425.1749. $C_{28}H_{25}O_4$ requires 425.1753. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.



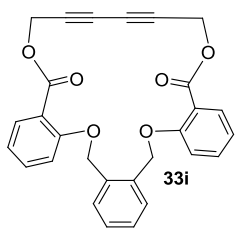
33g: Following the general procedure E, **33g** was obtained after purification by column chromatography on silica gel as a white solid (0.081 g, 43%); mp: 110-112 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2878, 1602, 1493, 1239 and 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (2 H, d, *J* = 7.4 Hz), 7.20 (2 H, t, *J* = 7.9 Hz), 6.92 (2 H, t, *J* = 7.3 Hz), 6.83 (2 H, d, *J* = 7.8 Hz), 6.15 (2 H, s), 4.74 (4 H, s), 4.51 (4 H, s), 4.21 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 129.4, 129.0, 127.7, 125.9, 121.1, 111.7, 75.4, 71.0, 68.2, 64.8, 57.3; HRMS (ESI): MNa^+, found 397.1409. $C_{24}H_{22}O_4Na$ requires 397.1416. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.



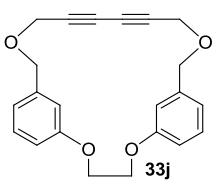
33h: Following the general procedure E, **33h** was obtained after purification by column chromatography on silica gel as a white solid (0.065 g, 35%); mp: 145-147 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2943, 1600, 1493, 1061 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (2 H, d, J = 7.4 Hz), 7.31-7.27 (2 H, m), 7.04 (2 H, t, J = 7 Hz), 6.89 (2 H, d, J = 8.2 Hz), 4.79 (4 H, s), 4.78 (4 H, s), 4.33 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 129.4, 128.9, 126.8, 121.8, 112.3, 81.7, 75.3, 71.0, 65.4, 57.6, 57.2; HRMS (ESI): MNa^+, found 395.1253. $C_{24}H_{20}O_4Na$ requires 395.1259. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.



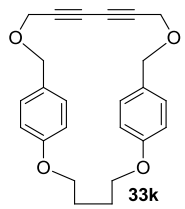
33i: Following the general procedure E, **33i** was obtained after purification by column chromatography on silica gel as a white solid (0.014 g, 25%); mp: 215-217 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2929, 1732, 1600, 1297 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (2 H, dd, J = 5.8, 1.7 Hz), 7.52-7.50 (2 H, m), 7.42-7.34 (4 H, m), 6.99 (2 H, t, J = 5.5 Hz), 6.85 (2 H, d, J = 8 0 Hz), 5.33 (4 H, s), 4.92 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 157.3, 134.4, 133.2, 130.6, 128.4, 128.3, 120.6, 113.0, 74.7, 70.7, 68.5, 52.8. HRMS (ESI): MNa^+, found 475.1156. $C_{28}H_{20}O_6$ requires 475.1158. This compound was crystallized using a mixture of DCM and Hexanes and confirmed by single crystal X-ray structure analysis.



33j: Following the general procedure E, **33j** was obtained after purification by column chromatography on silica gel as a white solid (0.022 g, 25%); mp: 120-122 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (KBr): ν_{max} 2925, 2851, 1731, 1595 and 786 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (2 H, m), 7.14 (2 H, s), 6.97-6.93 (4 H, m), 4.67 (4 H, s), 4.45 (4 H, s), 4.24 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 138.7, 129.7, 120.9, 116.1, 114.8, 75.9, 71.3, 70.9, 67.3, 57.3; HRMS (ESI): MH^+, found 349.1434. $C_{22}H_{21}O_4$ requires 349.1439.

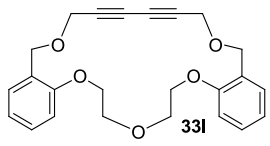


33k: Following the general procedure E, **33k** was obtained after purification by column chromatography on silica gel as a white solid (0.047 g, 25%); mp: 83-85 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2920, 2851, 1611, 1584, 1454 and 818 cm^{-1}; ^{1}H NMR

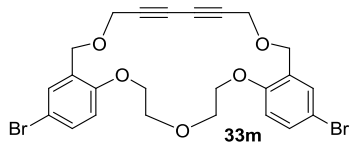


(400 MHz, $CDCl_3$): δ 7.30 (4 H, d, *J* = 8.6 Hz), 6.89 (4 H, d, *J* = 8.6 Hz), 4.63 (4 H, s), 4.24 (4 H, s), 4.17 (4 H, br s), 1.96 (4 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 129.9, 129.6, 114.6, 76.3, 71.7, 67.1, 57.9, 24.4; HRMS (ESI): MH^+, found 377.1747. $C_{24}H_{25}O_4$ requires 377.1752. This compound was crystallized using a mixture of DCM and Hexanes and confirmed by single crystal X-ray structure analysis.

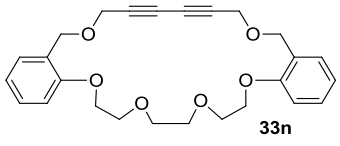
33l: Following the general procedure E, **33l** was obtained after purification by column chromatography on silica gel as a white solid (0.061 g, 52%); mp: 99-101 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2935, 2876, 1603, 1494, 1246 and 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (2 H, d, *J* = 5.8 Hz), 7.29-7.25 (2 H, m), 6.96 (2 H, t, *J* = 7.0 Hz), 6.89 (2 H, d, *J* = 8.2 Hz), 4.73 (4 H, s), 4.27 (4 H, s), 4.18-4.09 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 130.5, 129.5, 125.9, 121.1,112.2, 75.8, 70.9, 70.6, 69.1, 65.7, 57.4; HRMS (ESI): MNa^+, found 415.1557. $C_{24}H_{24}O_5Na$ requires 415.1521. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.



33m: Following the general procedure E, **33m** was obtained after purification by column chromatography on silica gel as a white solid (0.082 g, 30%); mp: 132-134 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 2874, 1603, 1454, 1249 and 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (2 H, d, *J* = 2.5 Hz), 7.40-7.37 (2 H, m), 6.79 (2 H, d, *J* = 8.7 Hz), 4.70 (4 H, s), 4.31 (4 H, s), 4.18-4.16 (4 H, m), 4.09-4.06 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 132.6, 131.9, 128.3, 113.8, 113.4, 75.5, 70.9, 70.7, 69.3, 65.1, 57.6; HRMS (ESI): MNa^+, found 570.9714. $C_{24}H_{22}Br_2O_5Na$ requires 570.9731.

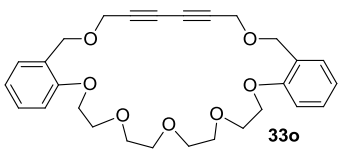


33n: Following the general procedure E, **33n** was obtained after purification by column chromatography on silica gel as a white solid (0.045 g, 52%); mp:131-133 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2938, 1624, 1512, 1435, 1246 and 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (2 H, d, *J* = 7.4 Hz), 7.31-7.27 (2 H, m), 6.98 (2 H, t, *J* = 7.4 Hz), 6.88 (2 H, d, *J* = 7.9 Hz), 4.69 (4 H, s), 4.35 (4 H, s), 4.20-4.18 (4 H, m), 3.99-3.97 (4 H, m), 3.92 (4 H, s); ^{13}C

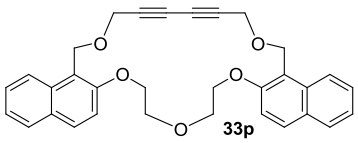


NMR (100 MHz, $CDCl_3$): δ 156.7, 130.1, 129.4, 125.9, 120.8, 111.5, 75.9, 71.4, 70.4, 69.9, 68.7, 66.7, 58.0; HRMS (ESI): MNa^+, found 459.1794. $C_{26}H_{28}O_6Na$ requires 459.1783.

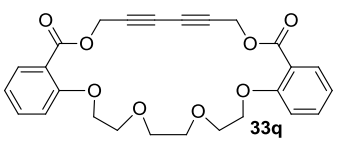
33o: Following the general procedure E, **33o** was obtained after purification by column chromatography on silica gel as a colourless liquid (0.108 g, 45%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2874, 1603, 1590, 1494, 1288 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (2 H, d, *J* = 7.4 Hz), 7.25 (2 H, t, *J* = 6.9 Hz), 6.94 (2 H, t, *J* = 7.4 Hz), 6.84 (2 H, d, *J* = 8.1 Hz), 4.65 (4 H, s), 4.31 (4 H, s), 4.14-4.12 (4 H, m), 3.90-3.72 (12 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 130.1, 129.3, 126.0, 111.6, 75.9, 71.1, 70.7, 70.4, 69.7, 68.2, 66.9, 58.1; HRMS (ESI): MNa^+, found 503.2032. $C_{28}H_{32}O_7Na$ requires 503.2046.



33p: Following the general procedure E, **33p** was obtained after purification by column chromatography on silica gel as a white solid (0.071 g, 48%); mp: 163-165 ^oC; R_f (20% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2874, 1623, 1590, 1345, 1288 and 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (2 H, d, *J* = 8.4 Hz), 7.84 (2 H, d, *J* = 9 0 Hz), 7.79 (2 H, d, *J* = 8.1 Hz), 7.51 (2 H, t, *J* = 7.1 Hz), 7.37 (2 H, t, *J* = 7 0 Hz), 7.28-7.24 (2 H, m), 5.27 (4 H, s), 4.33-4.25 (8 H, m), 4.24 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 133.8, 130.8, 129.4, 128.4, 127.1, 123.9, 123.8, 117.7, 114.4, 76.3, 71.5, 70.5, 70.4, 61.1, 56.6; HRMS (ESI): MNa^+, found 515.1853. $C_{32}H_{28}O_5Na$ requires 515.1834. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.

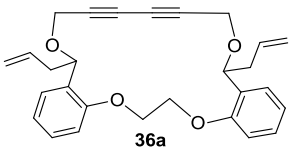


33q: Following the general procedure E, **33q** was obtained after purification by column chromatography on silica gel as a white solid (0.049 g, 35%); mp: 157-159 ^oC; R_f (60% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2935, 2876, 1590, 1603, 1494, 1248 and 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (2 H, dd, *J* = 5.96, 1.76 Hz), 7.51-7.47 (2 H, m), 7.01 (2 H, t, *J* = 7.8 Hz), 6.95 (2 H, d, *J* = 8.4 Hz), 5.01 (4 H, s), 4.23-4.21(4 H, m), 4.01-3.98 (4 H, m), 3.95 (4 H, s), ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 158.4, 134.2, 132.4, 120.5, 119.1, 112.9, 73.9, 71.6, 70.4, 69.6, 69.5, 52.8; HRMS (ESI): MH^+, found 465.1541. $C_{26}H_{25}O_8$ requires 465.1549. This

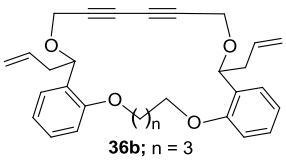


compound was crystallized using a mixture of DCM and Hexanes and confirmed by single crystal X-ray structure analysis.

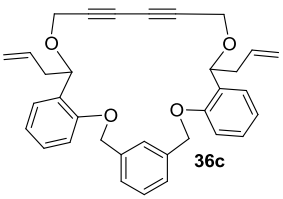
36a: Following the general procedure E, **36a** was obtained after purification by column chromatography on silica gel as a semi solid (0.322 g, 75%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2931, 1718, 1599, 1489 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.22 (4 H, m), 7.04-6.87 (4 H, m), 5.87-5.74 (2 H, m), 5.59-5.51 (2 H, m), 5.10-4.98 (4 H, m), 4.49-4.07 (8 H, m), 2.57-2.44 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 156.5, 134.8, 134.6, 129.2, 128.5, 128.5, 128.4, 127.1, 126.8, 121.3, 121.3, 116.8, 116.7, 112.3, 111.8, 75.5, 75.3, 71.1, 71.9, 70.9, 70.4, 68.1, 67.5, 55.3, 55.1, 41.5, 41.6; HRMS (ESI): MNa^+, found 451.1868. $C_{28}H_{28}O_4Na$ requires 451.1885. Isolated as a mixture of isomers (*dr* = 60:40) and NMR values given for both the isomers.



36b: Following the general procedure E, **36b** was obtained after purification by column chromatography on silica gel as white solid (0.329 g, 72%); mp: 110-112 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2953, 2876, 1602, 1491 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (2 H, d, *J* = 5.8 Hz), 7.25-7.21 (2 H, m), 6.96 (2 H, t, *J* = 7.2 Hz), 6.86 (2 H, d, *J* = 7.6 Hz), 5.82-5.76 (2 H, m), 5.45-5.42 (2 H, m), 5.06-4.97 (4 H, m), 4.24 (2 H, d, *J* = 16.56 Hz), 4.04 (4 H, t, *J* = 5.82 Hz), 3.94 (2 H, d, *J* = 16.6 Hz), 2.48-2.42 (4 H, m), 2.10-1.98 (4 H, m);^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 134.8, 128.6, 128.5, 126.5, 120.8, 116.6, 110.9, 75.3, 70.9, 70.6, 67.9, 55.4, 41.2, 26.7; HRMS (ESI): MH^+, found 457.2365. $C_{30}H_{33}O_4$ requires 457.2378. This reaction gave a mixture of isomers (*dr* = 60:40) however, we got one of the isomer in pure form and NMR values given for one of the pure isomers. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.

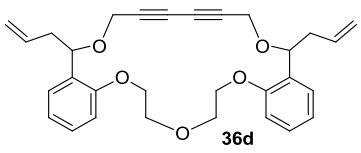


36c: Following the general procedure E, **36c** was obtained after purification by column chromatography on silica gel as a semi solid (0.035 g, 35%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2874, 1488, 1248, 1017 and 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (1 H, s), 7.39-7.28 (7 H, m), 7.13-7.05 (4 H, m), 5.84-5.38 (2 H, m), 5.38-5.15 (2 H, m), 5.15-5.01 (8 H, m), 4.31-4.27 (2 H, m), 4.08-4.01 (2 H, m), 2.52-2.48 (4 H, m); ^{13}C NMR (100 MHz,

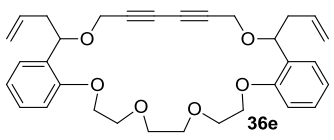


$CDCl_3$): δ 156.7, 156.6, 137.6, 137.4, 134.9, 134.8, 129.6, 129.5, 128.7, 128.6, 128.6, 128.5, 128.4, 127.5, 126.9, 126.8, 126.6, 121.5, 121.4, 116.7, 116.6, 112.8, 112.6, 75.4, 75.2, 72.2, 71.1, 71.0, 70.5, 70.3, 55.7, 55.6, 41.1, 40.9; HRMS (ESI): MNa^+, found 527.2189. $C_{34}H_{32}O_4Na$ requires 527.2198. Isolated as a mixture of isomers (*dr* = 60:40) and NMR values given for both the isomers.

36d: Following the general procedure E, **36d** was obtained after purification by column chromatography on silica gel as a white solid (0.042 g, 45%); mp: 82-84 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2930, 1641, 1600, 1489 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (4 H, m), 7.06-6.91 (4 H, m), 5.92-5.42 (2 H, m), 5.18-5.13 (2 H, m), 5.12-5.07 (4 H, m), 4.31-3.96 (12 H, m), 2.57-2.54 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 156.7, 134.9, 134.9, 129.3, 128.8, 128.7, 128.6, 126.8, 126.8, 121.5, 121.3, 116.7, 116.6, 112.7, 111.6, 75.5, 75.4, 72.1, 71.7, 71.1, 70.6, 70.3, 69.9, 69.4, 55.6, 55.4, 41.0, 41.0; HRMS (ESI): M Na^+, found 495.2139. $C_{30}H_{32}O_5Na$ requires 495.2147. Isolated as a mixture of isomers (*dr* = 60:40) and NMR values given for both the isomers. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.

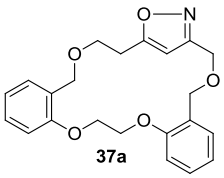


36e: Following the general procedure E, **36e** was obtained after purification by column chromatography on silica gel as a colourless liquid (0.061 g, 60%); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3076, 2870, 1598, 1489 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (4 H, m), 7.03-6.87 (4 H, m), 5.87-5.83 (2 H, m), 5.27-5.24 (2 H, m), 5.13-5.03 (4 H, m), 4.33-4.17 (6 H, m), 4.02-3.86 (10 H, m), 2.53-2.51 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 134.9, 129.1, 128.7, 126.8, 121.1, 116.6, 111.4, 75.8, 72.8, 71.5, 69.9, 69.8, 68.8, 56.1, 40.8; HRMS (ESI): MNa^+, found 539.2404. $C_{32}H_{36}O_6Na$ requires 539.2409. This reaction gave a mixture of isomers (*dr* = 60:40) however, we got one of the isomer in pure form and NMR values given for one of the pure isomer.

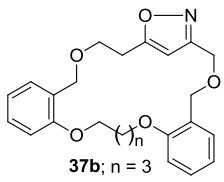


37a: Following the general procedure F, **37a** was obtained after purification by column chromatography on silica gel as a white solid (0.062 g, 90%); mp: 141-143 ^oC; R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2925, 2875, 1603, 1495 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.33 (1 H, m), 7.28-7.21 (3 H, m), 6.95-6.89 (2 H, m), 6.86-6.83 (2 H, m),

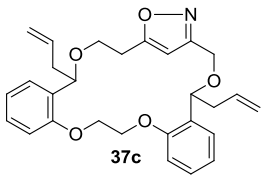
6.30 (1 H, s), 4.60 (2 H, s), 4.50 (2 H, s), 4.54 (2 H, s), 4.33-4.27 (4 H, m), 3.79 (2 H, t, *J* = 5.08 Hz), 2.92 (2 H, t, *J* = 5.20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 161.9, 156.9, 156.6, 130.9, 129.9, 129.5, 129.2, 126.6, 126.2, 121.2, 120.9, 111.0, 111.8, 101.5, 69.0, 67.6, 67.5, 67.3, 67.2, 63.5, 28.1; HRMS (ESI): MNa^+, found 404.1483. $C_{22}H_{23}NO_5Na$ requires 404.1474. This compound was crystallized using a mixture of MeOH, DCM and Hexanes and confirmed by single crystal X-ray structure analysis.



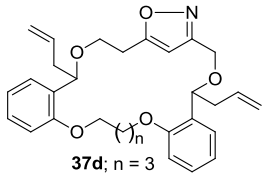
37b: Following the general procedure F, **37b** was obtained after purification by column chromatography on silica gel as a white solid (0.089 g, 88%); mp: 120-121 ^oC; R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2943, 2884, 1599, 1470 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.25 (4 H, m), 6.95-6.85 (4 H, m), 6.34 (1 H, s), 4.62 (2 H, s), 4.54 (4 H, d, *J* = 2.6 Hz), 4.08-4.04 (4 H, m), 3.81 (2 H, t, *J* = 5.9 Hz), 2.99 (2 H, t, *J* = 5.8 Hz), 2.09-1.97 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 161.6, 157.5, 157.4, 131.7, 131.1, 129.8, 129.7, 125.7, 125.5, 120.5, 120.4, 111.4, 111.1, 101.1, 68.9, 68.9, 67.9, 67.4, 67.1, 64.1, 27.8, 26.4, 26.1; HRMS (ESI): MNa^+, found 432.1769. $C_{24}H_{27}NO_5Na$ requires 432.1769.



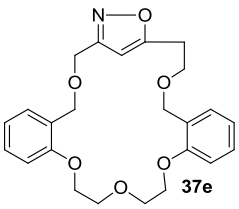
37c: Following the general procedure F, **37c** was obtained after purification by column chromatography on silica gel as a white solid (0.051 g, 45%); mp: 77-79 ^oC; R_f (50% EtOAc/Hexanes) 0.50; IR (KBr): ν_{max} 2923, 2865, 1604, 1495 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.37 (2 H, m), 7.31-7.26 (2 H, m), 7.15-7.03 (2 H, m), 6.92-6.88 (2 H, m), 6.16 (1 H, s), 5.82-5.71 (2 H, m), 5.01-4.90 (5 H, m), 4.69-4.24 (7 H, m), 3.99-3.87 (1 H, m), 3.66-3.38 (1 H, m), 3.14-2.81 (2 H, m), 2.53-2.47 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 171.8, 161.9, 161.7, 156.9, 156.2, 156.1, 155.9, 135.0, 134.9, 134.5, 133.9, 130.6, 130.3, 129.9, 128.7, 128.4, 128.3, 128.3, 127.5, 127.4, 127.3, 126.8, 122.5, 121.3, 121.2, 120.8, 117.1, 116.8, 116.7, 116.4, 115.2, 112.7, 111.1, 110.8, 102.2, 100.6, 72.5, 71.1, 69.3, 67.9, 67.6, 66.6, 66.6, 65.7, 60.8, 60.1, 41.5, 40.9, 40.9, 40.3, 29.4, 28.9; HRMS (ESI): MNa^+, found 484.2092. $C_{28}H_{31}NO_5Na$ requires 484.2099. Reaction was carried out from mixture of isomers of **36a** (*dr* = 60:40) and the compound **37c** was isolated as a mixture of isomers (*dr* = 60:40) and ^{13}C NMR values given for both the isomers. ^{1}H NMR values given for one of the isomer.



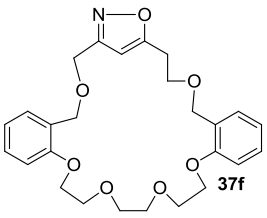
37d: Following the general procedure F, **37d** was obtained after purification by column chromatography on silica gel as a white solid (0.079 g, 65%); mp: 92-94 ^{o}C; R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2938, 2873, 1600, 1490 and 804 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (1 H, d, *J* = 7.56 Hz), 7.30 (1 H, d, *J* = 7.30 Hz),7.19-7.16 (2 H, m), 6.92 (2 H, q, *J*= 7.60 Hz), 6.79 (2 H, t, *J* = 7.02 Hz), 6.17 (1 H, s), 5.69-5.60 (2 H, m), 4.97-4.87 (5 H, m), 4.71 (1 H, t, *J* = 6.38 Hz), 4.56-4.52 (1 H, m), 4.32-4.22 (1 H, m), 3.98-3.90 (4 H, m), 3.76-3.71 (1 H, m), 3.49-3.42 (1 H, m), 3.03-2.96 (1 H, m), 2.79-2.74 (1 H, m), 2.52-2.36 (4 H, m), 1.91-1.82 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 171.2, 161.8, 161.6, 156.9, 156.3, 135.2, 134.9, 134.5, 129.6, 129.6, 128.7, 128.6, 128.5, 128.5, 127.5, 127.4, 127.3, 127.2, 120.8, 120.7, 120.6, 120.5, 116.8, 116.7, 116.6, 116.4, 111.4, 111.1, 110.9, 101.8, 100.9, 75.5, 73.2, 72.1, 67.8, 67.6, 67.5, 67.1, 66.1, 60.5, 42.4, 41.2, 41.0, 40.8, 29.7, 28.5, 28.3, 26.9, 26.7, 26.7; HRMS (ESI): MH^+, found 490.2581. $C_{30}H_{36}NO_5$ requires 490.2593. Reaction was carried out from mixture of isomers of **36b** (*dr* = 60:40) the compound **37d** was isolated as a mixture of isomers (*dr* = 60:40) and ^{13}C NMR values given for both the isomers. ^{1}H NMR values given for one of the isomer.



37e: Following the general procedure F, **37e** was obtained after purification by column chromatography on silica gel as a colourless liquid (0.05 g, 66%); R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2926, 2871, 1602, 1453 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (4 H, m), 7.00-6.96 (2 H, m), 6.90 (2 H, t, *J* = 8.8 Hz), 6.35 (1 H, s), 4.66 (2 H, s), 4.60 (2 H, s), 4.56 (2 H, s), 4.20-4.12 (4 H, m), 4.0-3.97 (4 H, m), 3.83 (2 H, t, *J* = 6.1 Hz), 3.03 (2 H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 161.9, 157.4, 156.9, 131.2, 130.9, 129.7, 129.6, 126.4, 126.1, 121.0, 120.9, 112.5, 111.9, 101.3, 70.3, 70.2, 68.6, 68.5, 68.3, 68.1, 66.9, 63.9, 27.7; HRMS (ESI): MH^+, found 426.1933. $C_{24}H_{28}NO_6$ requires 426.1916.

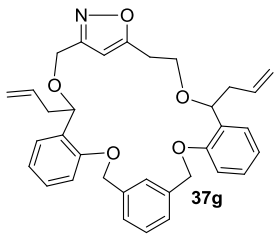


37f: Following the general procedure F, **37f** was obtained after purification by column chromatography on silica gel as a colourless liquid (0.074 g, 88%); R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 3042, 2871, 1603, 1494 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.18 (4 H, m), 6.92-6.86 (2 H, m), 6.82 (2 H, d, *J* = 8.1 Hz), 6.18 (1 H, s), 4.57 (2 H, s), 4.52 (2 H, s), 4.51 (2 H, s), 4.06 (4 H, t, *J* = 4.3 Hz), 3.79-3.73 (6 H, m), 3.64 (4 H, s), 3.01 (2 H, t, *J*

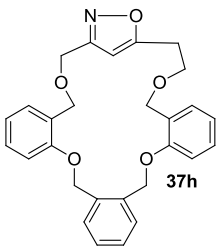


= 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 161.9, 157.1, 156.9, 130.7, 130.6, 129.5, 129.4, 126.3, 126.0, 120.9, 120.8, 111.9, 111.6, 101.2, 70.9, 70.8, 69.8, 69.7, 68.3, 68.0, 67.6, 67.1, 63.6, 27.5; HRMS (ESI): MNa^+, found 492.2006. $C_{26}H_{31}NO_7Na$ requires 492.1998.

37g: Following the general procedure F, **37g** was obtained after purification by column chromatography on silica gel as a colourless liquid (0.073 g, 76%); R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 3076, 2865, 1600, 1484 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (1 H, s), 7.47-7.23 (8 H, m), 7.11-6.92 (3 H, m), 5.91 (1 H, s), 5.17-4.77 (10 H, m), 4.60-4.49 (1 H, m), 4.34 (1 H, d, *J* = 13.9 Hz), 4.54-3.42 (1 H, m), 3.32-3.26 (1 H, m), 2.93-2.74 (2 H, m), 2.62-2.40 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.5, 161.5, 161.5, 156.6, 156.3, 156.3, 137.6, 137.4, 137.3, 137.2, 135.2, 135.0, 134.7, 130.8, 130.4, 129.7, 129.6, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.2, 127.8, 127.8, 127.8, 127.4, 127.4, 127.3, 127.2, 126.8, 121.8, 121.7, 121.5, 116.8, 116.7, 116.7, 116.6, 113.8, 112.9, 112.8, 112.5, 101.2, 100.9, 74.7, 74.6, 73.8, 73.8, 71.6, 71.1, 70.8, 70.4, 66.1, 65.7, 61.1, 60.9, 40.8, 40.7, 40.6, 40.6, 27.5, 27.4; HRMS (ESI): MH^+, found 538.2596. $C_{34}H_{36}NO_5$ requires 538.2593. Reaction was carried out from mixture of isomers of **7c** (*dr* = 60:40) and the compound **37g** was isolated as a mixture of isomers (*dr* = 60:40) and ^{13}C NMR values given for both the isomers. ^{1}H NMR values given for one of the isomer.

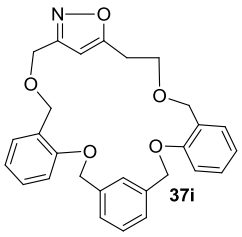


37h: Following the general procedure F, **37h** was obtained after purification by column chromatography on silica gel as a white solid (0.028 g, 55 %); mp: 150-152 ^{o}C; R_f (50% EtOAc/Hexanes) 0.50; IR (KBr): ν_{max} 2929, 2851, 1602, 1492 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.20 (7 H, m), 7.09-7.05 (1 H, m), 6.92-6.78 (3 H, m), 6.62-6.54 (1 H, m), 6.28 (1 H, s), 5.38 (2 H, s), 5.15 (2 H, s), 4.53 (4 H, d, *J* = 6.5 Hz), 4.41 (2 H, s), 3.72 (2 H, t, *J* = 5.4 Hz), 2.89 (2 H, t, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 161.8, 156.9, 137.2, 133.1, 132.1, 131.7, 130.0, 129.9, 129.4, 128.9, 127.3, 126.8, 125.6, 125.3, 120.7, 120.4, 112.0, 111.4, 101.2, 69.7, 69.4, 69.2, 66.9, 66.8, 64.0, 27.5; HRMS (ESI): MNa^+, found 480.1816. $C_{28}H_{27}NO_5Na$ requires 480.1787.

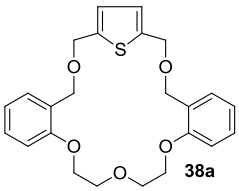


37i: Following the general procedure F, **37i** was obtained after purification by column chromatography on silica gel as a colourless liquid (0.017 g, 35 %); R_f (50% EtOAc/Hexanes)

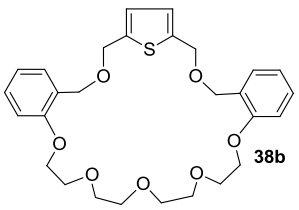
0.50; IR (KBr): ν_{max} 2929, 2856, 1602, 1495 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (1 H, s), 7.37-7.22 (7 H, m), 6.95-6.90 (4 H, m), 5.85 (1 H, s), 5.01 (2 H, s), 4.97 (2 H, s), 4.52 (2 H, s), 4.47 (4 H, d, *J* = 7.1 Hz), 3.59 (2 H, t, *J* = 6.6 Hz), 2.77 (2 H, t, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 161.8, 157.4, 157.1, 137.5, 137.4, 131.0, 130.9, 129.7, 129.6, 128.8, 128.1, 127.8, 127.5, 127.1, 126.7, 126.3, 121.2, 121.1, 112.6, 112.3, 101.0, 71.0, 70.4, 68.4, 68.3, 67.3, 63.9, 27.5; HRMS (ESI): MH^+, found 458.1961. $C_{28}H_{28}NO_5$ requires 458.1967.



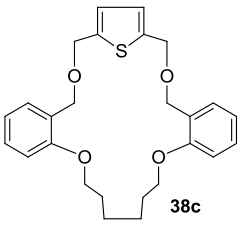
38a: Following the general procedure G, **38a** was obtained after purification by column chromatography on silica gel as a white solid (0.018 g, 17%); mp: 90-92 ^oC; R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2872, 1602, 1493,1358 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (2 H, d, *J* = 7.5 Hz), 7.14 (2 H, t, *J* = 7.3 Hz), 6.90 (2 H, t, *J* = 7.4 Hz), 6.80 (2 H, s), 6.76 (2 H, d, *J* = 8.2 Hz), 4.67 (4 H, s), 4.47 (4 H, s), 4.01 (4 H, t, *J* = 4.7 Hz), 3.82 (4 H, t, *J* = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 141.6, 129.6, 128.9,126.8, 126.5, 121.1, 111.9, 70.5, 68.8, 66.6, 65.8; HRMS (ESI): MNa^+, found 449.1408. $C_{24}H_{26}O_5SNa$ requires 449.1399. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.



38b: Following the general procedure G, **38b** was obtained after purification by column chromatography on silica gel as a colourless (0.058 g, 29%); R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2871, 1602, 1493, 1248 and 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (2 H, d, *J* = 7.4 Hz), 7.19 (2 H, t, *J* = 7.8 Hz), 6.90 (2 H, t, *J* = 7.4 Hz), 6.83 (2 H, s), 6.78 (2 H, d, *J* = 8.1 Hz), 4.66 (4 H, s), 4.55 (4 H, s), 4.06 (4 H, t, *J* = 4.3 Hz), 3.76 (4 H, t, *J* = 4.3 Hz), 3.61-3.59 (4 H, m), 3.53-3.51 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 141.8, 130.0, 129.0, 126.8, 126.1, 120.8, 111.6, 70.9, 70.7, 69.7, 68.2, 66.9, 66.6; HRMS (ESI): MNa^+, found 537.1927. $C_{28}H_{34}O_7SNa$ requires 537.1923.



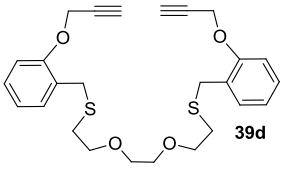
38c: Following the general procedure G, **38c** was obtained after purification by column chromatography on silica gel as a white solid (0.068 g, 52%); mp: 84-86 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2936, 2858, 1603, 1494, 1248 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (2 H, d, *J* = 7.4 Hz), 7.28 (2 H, dd, *J* = 13.9, 1.7 Hz), 6.95 (2 H, t, *J* =



38c

7.3Hz), 6.90 (2 H, s), 6.88 (2 H, d, *J* = 7.7 Hz), 4.74 (4 H, s), 4.60 (4 H, s), 4.01 (4 H, t, *J* = 5.98 Hz), 1.84-1.80 (4 H, m), 1.59-1.55 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 141.7, 130.4, 129.2, 126.4, 126.0, 120.3, 111.6, 67.9, 67.2, 67.1, 29.3, 25.9; HRMS (ESI): MNa^+, found 461.1765. $C_{26}H_{30}O_4SNa$ requires 461.1762. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by single crystal X-ray structure analysis.

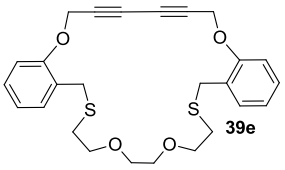
1,12-Bis(2-(prop-2-yn-1-yloxy)phenyl)-5,8-dioxa-2,11-dithiadodecane (39d): To a suspension of 2,2'-(ethane-1,2-diylbis(oxy))diethanethiol (2 mmol) in ethanol (10 mL) at room temperature



39d

was added KOH (4mmol) and the reaction mixture was stirred at room temperature for 1 h. Then, to this solution, a solution of 1-(chloromethyl)-2-(prop-2-yn-1-yloxy)benzene(4 mmol) in benzene (5 mL) was added drop wise. The resulting mixture was stirred for an additional 1 h and then the reaction mixture was filtered. The resulted filtrate was added with DCM (20 mL) and the combined layers were washed with H_2O (3 X 10 mL). After this, the organic were dried over anhydrous Na_2SO_4, concentrated under vacuum and the resulting crude reaction mixture was purified by silica gel column chromatography, which afforded the product **39d** as a pale yellow solid, (0.705 g, 75%); mp: 76-78 ^oC; R_f (10% EtOAc/Hexanes) 0.45; IR ν_{max} (CH_2Cl_2): 2929, 1732, 1600, 1297 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.15 (4 H, m), 6.94-6.88 (4 H, m), 4.69 (2 H, d, *J* = 2.4 Hz), 3.74 (4 H, s), 3.57 (4 H, t, *J* = 7 Hz), 3.54 (4 H, s), 2.62 (4 H, t, *J* = 7 Hz), 2.47 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 130.6, 128.2, 127.7, 121.5, 112.3, 78.7, 75.6, 70.8, 70.2, 56.1, 30.8, 30.5; HRMS (ESI): MH^+, found 471.1659. $C_{26}H_{32}O_4S_2$ requires 471.1664.

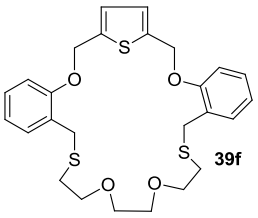
39e: Following the general procedure E, **39e** was obtained after purification by column chromatography on silica gel as a white solid (0.028 g, 30%); mp: 119-121 ^oC; R_f (20%



39e

EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2929, 1732, 1600, 1297 and 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (2 H, d, *J* = 6.2 Hz), 7.24 (2 H, t, *J* = 7.2 Hz), 7.02 (2 H, t, *J* = 7.4 Hz), 6.89 (2 H, d, *J* = 7.8 Hz), 4.81 (4 H, s), 3.80 (4 H, s), 3.63-3.59(8 H, m), 2.65 (4 H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 131.1, 128.2, 128.1, 122.2, 111.6, 74.6, 70.9, 70.8, 70.1, 56.5, 30.1, 29.3; HRMS (ESI): MNa^+, found 491.1361. $C_{26}H_{28}O_4S_2Na$ requires 491.1327.

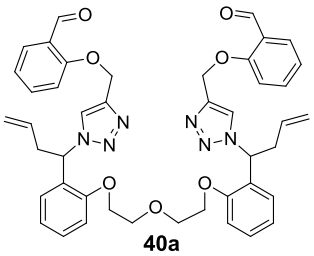
39f: Following the general procedure G, **39f** was obtained after purification by column chromatography on silica gel as a yellow liquid (0.017 g, 55%); R_f (50% EtOAc/Hexanes) 0.50; IR (CH_2Cl_2): ν_{max} 2918, 1599, 1453, 1290 and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (2 H, d, *J* = 6.2 Hz), 7.30 (2 H, s), 7.25 (2 H, t, *J* = 7.8 Hz), 7.03-6.97 (4 H, m), 5.25 (4 H, s), 3.87 (4 H, s), 3.66 (4 H, t, *J* = 6.6 Hz), 3.56 (4 H, s), 2.70 (4 H, t, *J* = 6.6 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 140.5, 130.7, 128.2, 128.0, 125.9, 121.5, 112.1, 70.9, 70.3, 65.8, 31.4, 30.4; HRMS (ESI): MNa^+, found 525.1196. $C_{26}H_{30}O_4S_3Na$ requires 525.1203.



39f

General procedure for the one-pot synthesis of 1,2,3-triazoles 40a-c directly from bis-homoallylic alcohols 34. A solution of the corresponding *bis*-homoallylic alcohol **34** (0.5 mmol) and $TMSN_3$ (1.5 mmol, 3 equiv) and copper(II) triflate (10 mol%) in DCM (5.0 mL) was stirred at rt for 3 h under an inert atmosphere. After this period, the solvent was evaporated. Then, to the resulting reaction mixture THF (2-3 mL), water (2-3 mL), alkyne (2.5 mmol, 5 equiv) and sodium *L*-ascorbate (100 mol%) were added and stirred at rt for 20 h. Then, the reaction mixture was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated, and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc/Hexanes) to give the desired 1,2,3-*bis*-triazole product **40** (see the corresponding Tables/Schemes for specific entries).

2,2'-(((1,1'-((((Oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis(oxy))dibenzaldehyde (40a):

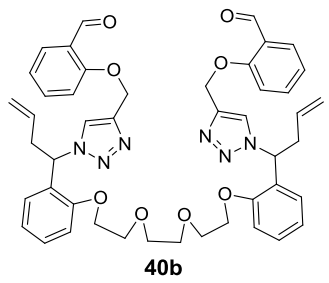


40a

Following the general procedure, **40a** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (299 mg, 78%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2976, 1686, 1599, 1483and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.41 (2 H, s), 7.79 (2 H, dd, J_1 = 7.6 Hz, J_2 = 1.1 Hz), 7.73 (2 H, s), 7.52 (2 H, td, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.30-7.24 (4 H, m), 7.10 (2 H, d, *J* = 8.4 Hz), 7.02 (2 H, t, *J* = 7.6 Hz), 6.96 (2 H, t, *J* = 7.5 Hz), 6.85 (2 H, d, *J* = 8.2 Hz), 6.10-6.06 (2 H, m), 5.69-5.62 (2 H, m), 5.22 (4 H, d, *J* = 3.9 Hz), 5.05 (2 H, d, *J* = 17.1 Hz), 4.96 (2 H, d, *J* = 10.2 Hz), 4.17-4.06 (4 H, m), 3.88-3.84 (4 H, m), 3.25-3.17 (2 H, m), 3.07-3.02 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 160.5, 155.8, 142.5, 136.0, 133.3,

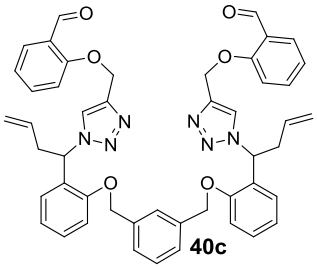
130.0, 128.5, 127.7, 126.5, 125.0, 122.9, 121.3, 121.2, 118.5, 113.1, 112.0, 69.7, 67.7, 62.7, 62.7, 59.1, 59.0, 38.0 ppm; HRMS (ESI): MNa^+, found 791.3150. $C_{44}H_{44}N_6NaO_7$ requires 791.3169. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.

2,2'-(((1,1'-(((((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1*H*-1,2,3-triazole-4,1 diyl))bis(methylene))bis(oxy))dibenzaldehyde (40b). Following the general procedure, **40b**



was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (163 mg, 81%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2875, 1687, 1599, 1493 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.39 (2 H, s), 7.82 (2 H, s), 7.77-7.75 (2 H, m), 7.50-7.46 (2 H, m), 7.28-7.21 (4 H, m), 7.12 (2 H, d, *J* = 8.4 Hz), 7.00-6.90 (4 H, m), 6.81 (2 H, d, *J* = 8.1 Hz), 6.06 (2 H, t, *J* = 6.8 Hz), 5.69-5.62 (2 H, m), 5.25 (4 H, s), 5.07-4.93 (4 H, m), 4.10-4.00 (4 H, m), 3.78-3.76 (4 H, m), 3.69 (4 H, br. s), 3.25-3.18 (2 H, m), 3.04-3.00 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 189.7, 160.6, 155.7, 142.4, 136.0, 133.4, 129.9, 128.4, 127.7, 126.6, 125.0, 123.3, 121.2, 121.2, 118.5, 113.2, 112.0, 70.6, 69.5, 67.6, 62.6, 59.2, 37.9 ppm; HRMS (ESI): MNa^+, found 835.3456. $C_{46}H_{48}N_6NaO_8$ requires 835.3431. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.

2,2'-(((1,1'-((((1,3-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis(oxy))dibenzaldehyde (40c):

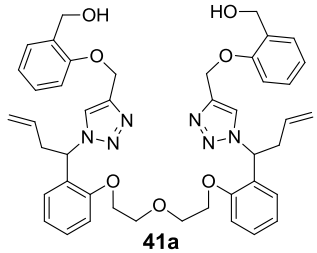


Following the general procedure, **40c** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (312 mg, 78%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2976, 1686, 1462, 1194 and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.37 (2 H, s), 7.79 (2 H, dd, J_1 = 7.4 Hz, J_2 = 0.9 Hz), 7.62 (2 H, s), 7.51 (2 H, td, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 7.37-7.26 (8 H, m), 7.10 (2 H, d, *J* = 8.4 Hz), 7.03-6.96 (6 H, m), 6.16-6.12 (2 H, m), 5.73-5.62 (2 H, m), 5.24 (4 H, s), 5.12-4.97 (8 H, m), 3.26-3.18 (2 H, m), 3.07-3.00 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 189.6, 160.5, 155.6, 142.5, 137.0, 136.0, 133.2, 130.0, 129.1, 128.5, 127.6, 127.1, 126.5, 126.2, 125.0, 123.0, 121.3, 121.2, 118.7, 113.1, 112.2, 70.0, 62.6, 58.9, 38.3 ppm; HRMS

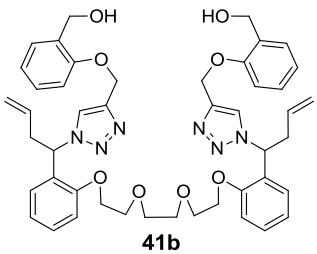
(ESI): MNa^+, found 823.3250. $C_{48}H_{44}N_6NaO_6$ requires 823.3220. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.

Procedure for the synthesis of *bis*-alcohol 41. $NaBH_4$ (4 mmol) was added to a mixture of *bis*-aldehyde **40** (1 mmol) in THF (3 mL) and ethanol (7 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h. After this period, the reaction mixture was poured on to cold water (5 mL). Then, extracted by using ethyl acetate (3 X 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc : Hexanes) to give the desired compound **41.**

Compound 41a: Following the general procedure, **41a** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 60:40) as a colorless liquid (741 mg, 96%); R_f (60% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 3402, 2936, 1601, 1455and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (2 H, s), 7.31-7.20 (8 H, m), 6.99-6.89 (6 H, m), 6.84 (2 H, d, *J* = 8.2 Hz), 6.05-6.01 (2 H, m), 5.69-5.62 (2 H, m), 5.10-4.96 (8 H, m), 4.62 (4 H, s), 4.15-4.03 (4 H, m), 3.85-3.80 (4 H, m), 3.23-3.19 (2 H, m), 3.05-3.02 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.9, 155.8, 143.2, 143.2, 133.3, 133.3, 130.0, 129.9, 129.0, 129.0, 128.8, 127.8, 127.8, 126.4, 126.4, 122.7, 122.6, 121.3, 121.3, 118.5, 112.0, 69.8, 67.7, 62.3, 61.3, 59.1, 37.9, 37.8 ppm; HRMS (ESI): MNa^+, found 795.3467. $C_{44}H_{48}N_6NaO_7$ requires 795.3482. The OH protons could not be detected.

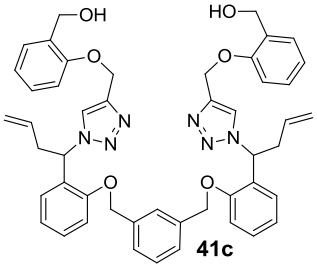


Compound 41b: Following the general procedure, **41b** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (709 mg, 95%); R_f (60% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 3412, 2876, 1589, 1602, 1454 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (2 H, s), 7.32-7.19 (8 H, m), 6.98-6.91 (6 H, m), 6.83 (2 H, d, *J* = 8.2 Hz), 6.05 (2 H, t, *J* = 7.7 Hz), 5.71-5.64 (2 H, m), 5.16 (4 H, s), 5.10-4.97 (4 H, m), 4.63 (4 H, s), 4.08-3.98 (4 H, m), 3.75 (4 H, t, *J* = 4.8 Hz), 3.69 (4 H, br. s), 3.25-3.19 (2 H, m), 3.08-3.03 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.8, 143.1, 133.4, 130.0, 129.9, 128.9, 128.7, 127.9, 126.5, 122.9, 121.3, 121.2, 118.5,



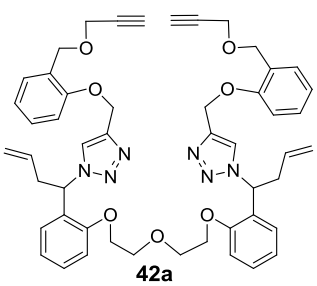
112.0, 112.0, 70.6, 69.5, 67.5, 62.4, 61.1, 59.2, 37.9 ppm; HRMS (ESI): MNa^+, found 839.3761. $C_{46}H_{52}N_6NaO_8$ requires 839.3744. The OH protons could not be detected.

Compound 41c: Following the general procedure, **41c** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 60:40) as a colorless liquid (739 mg, 92%); R_f (60% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 3345, 1601, 1492, 1243 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.52 (2 H, s), 7.41 (2 H, t, J = 8.2 Hz), 7.30 (8 H, m), 7.22 (2 H, t, J = 8.0 Hz), 7.01-6.92 (8 H, m), 6.13-6.09 (2 H, m), 5.72-5.62 (2 H, m), 5.15-4.98 (12 H, m), 4.62 (4 H, s), 3.25-3.18 (2 H, m), 3.07-3.00 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.6, 143.2, 137.0, 133.2, 130.0, 129.9, 129.1, 128.9, 128.8, 127.6, 127.1, 127.1, 126.6, 126.6, 126.3, 126.3, 122.6, 122.6, 121.4, 118.6, 112.2, 112.0, 70.0, 62.4, 61.4, 58.9, 58.9, 38.2 ppm; HRMS (ESI): MH^+, found 805.3755. $C_{48}H_{49}N_6O_6$ requires 805.3714. The OH protons could not be detected.



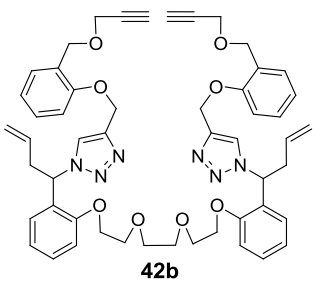
Procedure for the syntheses of compounds 42. To a mixture of the diol compound **41** (0.5 mmol) in dry THF (3 mL) was added NaH (4 mmol, 55-60 % suspension in mineral oil) at rt. The mixture was stirred at room temperature for 10 min and then, propargyl bromide (5 mmol, 80 wt% in toluene) was added. The resulting mixture was stirred for 20 h at rt. After this period, few drops of EtOH was added and stirred for 10 min and then, the resulting mixture was poured on to water (20 mL) and was extracted by using ethyl acetate (3 X 10 mL).The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated, and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc/ Hexanes) to give the desired product **42**.

Compound 42a: Following the general procedure, **42a** was obtained after purification by silica gel column chromatography as colorless liquid (254 mg, 60%); R_f (40% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 3288, 2976, 1602, 1455 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2 H, s), 7.36 (2 H, dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz), 7.29-7.24 (6 H, m), 6.99-6.95 (6 H, m), 6.86 (2 H, d, J = 8.6 Hz), 6.11-6.06 (2 H, m), 5.71-5.64 (2 H, m), 5.18 (4 H, s), 5.07 (2 H, d, J = 17.1 Hz), 4.99 (2 H, d, J = 10.1 Hz), 4.61 (4 H, s), 4.16-4.08 (8 H, m), 3.88-3.84 (4 H, m), 3.22-3.17 (2 H, m), 3.07-2.99 (2 H, m), 2.37 (2 H,



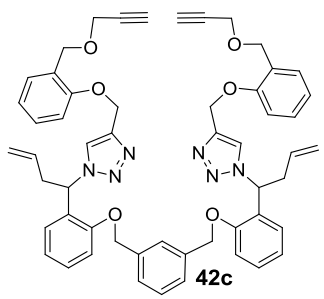
m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.7, 143.6, 133.4, 129.9, 129.8, 129.2, 127.6, 126.7, 126.1, 122.6, 122.6, 121.2, 121.1, 118.4, 112.1, 112.0, 80.0, 74.5, 69.8, 67.8, 66.7, 62.6, 58.9, 57.4, 38.1 ppm; HRMS (ESI): MH^+, found 849.3996. $C_{50}H_{53}N_6O_7$ requires 849.3976.

Compound 42b: Following the general procedure, **42b** was obtained after purification by silica gel column chromatography as colorless liquid (379 mg, 85%); R_f (40% EtOAc/Hexanes) 0.42;



IR (CH_2Cl_2) ν_{max} 2875, 1602, 1493, 1454, 1247 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (2 H, s), 7.37 (2 H, dd, J_1 = 7.4 Hz, J_2 = 1.5 Hz), 7.29-7.24 (6 H, m), 7.00-6.94 (6 H, m), 6.85 (2 H, d, J = 8.2 Hz), 6.11-6.07 (2 H, m), 5.73-5.67 (2 H, m), 5.21 (4 H, s), 5.11-5.98 (4 H, m), 4.61 (4 H, s), 4.14-4.03 (8 H, m), 3.79 (4 H, t, J = 4.8 Hz), 3.71 (4 H, s), 3.24-3.19 (2 H, m), 3.07-2.99 (2 H, m), 2.38 (2 H, t, J = 2.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.7, 143.5, 133.5, 129.8, 129.7, 129.2, 127.6, 126.9, 126.1, 122.9, 121.2, 121.1, 118.4, 112.1, 112.0, 80.0, 74.5, 70.7, 69.6, 67.6, 66.7, 62.6, 59.0, 57.4, 38.1 ppm; HRMS (ESI): MH^+, found 893.4271. $C_{52}H_{57}N_6O_8$ requires 893.4238.

Compound 42c: Following the general procedure, **42c** was obtained after purification by silica gel column chromatography as colorless liquid (352 mg, 80%); R_f (40% EtOAc/Hexanes) 0.42;

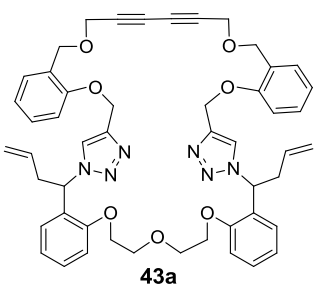


IR (CH_2Cl_2) ν_{max} 2973, 1603, 1461, 1249 and 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58 (2 H, s), 7.43-7.23 (12 H, m), 7.01-6.95 (8 H, m), 6.14 (2 H, t, J = 7.1 Hz), 5.74-5.64 (2 H, m), 5.20 (4 H, m), 5.13-4.99 (8 H, m), 4.60 (4 H, s), 4.12-4.10 (4 H, m), 3.26-3.18 (2 H, m), 3.07-3.00 (2 H, m), 2.31 (2 H, t, J = 2.3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.5, 143.6, 137.0, 133.3, 129.9, 129.8, 129.2, 129.1, 127.5, 127.1, 126.8, 126.2, 126.1, 122.6, 121.3, 121.1, 118.6, 112.2, 112.1, 80.0, 74.5, 70.0, 66.7, 62.7, 58.8, 57.4, 38.4 ppm; HRMS (ESI): MNa^+, found 903.3871. $C_{54}H_{52}N_6NaO_6$ requires 903.3846.

Procedure for the synthesis of macrocyclic bis-triazole polyether 43. A mixture of **42** (0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (100 mol%) and DMSO (2 mL) was taken in a 10 ml round bottom flask. The reaction mixture was stirred at 110 °C under open air atmosphere for 12 h. After this period, the resulting mixture was cooled to rt and diluted with water (4 mL). The mixture was filtered

through a filtration funnel and then washed with ethyl acetate (4 times, using 5 mL of EtOAc) and extracted using EtOAc (3 X 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/Hexanes) which gave the macrocyclic bis-triazole polyether **43.**

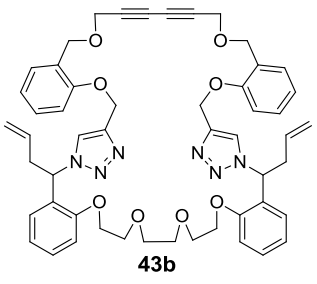
Compound 43a: Following the general procedure, **43a** was obtained after purification by silica gel column chromatography as colorless liquid (194 mg, 46%); R_f (40% EtOAc/Hexanes) 0.42;



43a

IR (CH_2Cl_2) ν_{max} 2973, 1601, 1459, 1368 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (2 H, s), 7.38 (2 H, dt, J_1 = 7.7 Hz, J_2 = 1.9 Hz), 7.33 (2 H, dd, J_1 = 7.3 Hz, J_2= 1.6 Hz), 7.29-7.22 (4 H, m), 7.00-6.95 (6 H, m), 6.82-6.79 (2 H, m), 6.04-5.99 (2 H, m), 5.70-5.63 (2 H, m), 5.22-5.15 (4 H, m), 5.07 (2 H, m), 5.00-4.96 (2 H, m), 4.60 (4 H, s), 4.23 (4 H, s), 4.16-4.06 (4 H, m), 3.88-3.81 (4 H, m), 3.31-3.28 (2 H, m), 3.10-3.05 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.0, 155.9, 143.4, 133.4, 130.0, 129.2, 129.2, 128.2, 128.2, 126.5, 125.8, 123.1, 123.0, 121.2, 121.0, 118.4, 112.0, 111.9, 76.0, 70.3, 69.7, 69.7, 67.6, 67.6, 67.1, 62.7, 62.6, 59.3, 58.1, 37.7 ppm; HRMS (ESI): MH^+, found 847.3850. $C_{50}H_{51}N_6O_7$ requires 847.3819.

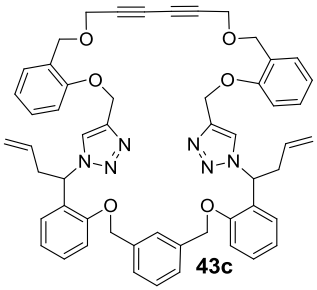
Compound 43b: Following the general procedure, **43b** was obtained after purification by silica gel column chromatography as colorless liquid (259 mg, 57%); R_f (40% EtOAc/Hexanes) 0.42;



43b

IR (CH_2Cl_2) ν_{max} 2926, 1603, 1493, 1454, 1247 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.88 (2 H, s), 7.38-7.24 (8 H, m), 7.03-6.95 (6 H, m), 6.81 (2 H, d, J = 8.2 Hz), 6.05-6.01 (2 H, m), 5.74-5.64 (2 H, m), 5.22 (4 H, t, J = 3.6 Hz), 5.11-5.07 (2 H, m), 5.00-4.98 (2 H, m), 4.61 (4 H, s), 4.24 (4 H, s), 4.05-4.00 (4 H, m), 3.75-3.71 (8 H, m), 3.35-3.27 (2 H, m), 3.12-3.05 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.0, 155.8, 143.3, 133.5, 129.8, 129.2, 129.2, 128.1, 128.1, 126.8, 126.8, 125.9, 123.5, 121.2, 121.0, 118.4, 111.9, 111.9, 75.9, 70.6, 70.3, 69.5, 67.5, 67.5, 67.1, 62.6, 59.3, 59.3, 58.1, 37.7 ppm; HRMS (ESI): MH^+, found 891.4110. $C_{52}H_{55}N_6O_8$ requires 891.4081. This compound contains traces of residual DMSO signal.

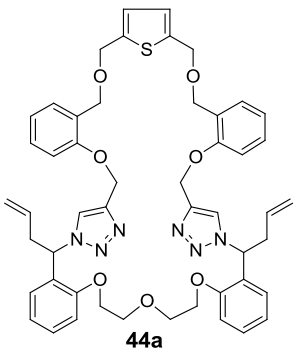
Compound 43c: Following the general procedure, **43c** was obtained after purification by silica gel column chromatography as colorless liquid (184 mg, 42%); R_f (40% EtOAc/Hexanes) 0.42;



IR (CH_2Cl_2) ν_{max} 2975, 1602, 1493, 1244 and 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.55 (2 H, s), 7.41-7.26 (12 H, m), 7.02-6.92 (8 H, m), 6.07-6.02 (2 H, m), 5.73-5.65 (2 H, m), 5.23-4.98 (12 H, m), 4.53 (4 H, s), 4.09-4.06 (4 H, m), 3.32-3.25 (2 H, m), 3.09-3.03 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 156.0, 155.7, 155.7, 143.4, 143.4, 137.0, 133.4, 133.4, 129.9, 129.5, 129.3, 129.1, 127.9, 127.4, 127.3, 126.6, 126.6, 125.8, 125.8, 123.1, 121.3, 121.1, 118.6, 112.1, 112.1, 111.9, 111.9, 75.8, 75.8, 70.3, 70.1, 70.0, 67.0, 62.7, 62.6, 59.0, 58.9, 57.9, 38.0, 38.0 ppm; HRMS (ESI): MH^+, found 879.3891. $C_{54}H_{51}N_6O_6$ requires 879.3870.

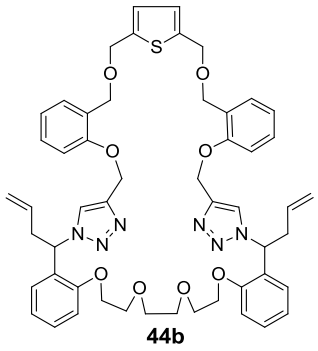
Procedure for the synthesis of macrocycle 44. A mixture of **43** (0.1 mmol), $Na_2S.xH_2O$ (70 mg), CuI (10 mol%), 1,10-phen (15 mol%) in DMF (0.5 mL) was stirred at 90 ^oC for 12 h under open air atmosphere. After this period, the reaction mixture was cooled to room temperature. Then, the resulting mixture was diluted with water (4 mL). The mixture was filtered through a filtration funnel and then washed with ethyl acetate (4 times, using 5 mL of EtOAc) and extracted using ethyl acetate (3 X 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/Hexanes) which gave the desired macrocyclic polyether **44**.

Compound 44a: Following the general procedure, **44a** was obtained after purification by silica gel column chromatography as yellow color liquid (39 mg, 45%); R_f (40% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2975, 1721, 1602, 1457 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2 H, s), 7.40-7.33 (4 H, m), 7.26-7.20 (4 H, m), 7.00-6.94 (6 H, m), 6.76-6.74 (4 H, m), 5.99-5.93 (2 H, m), 5.69-5.60 (2 H, m), 5.18 (4 H, br. s), 5.08-4.94 (4 H, m), 4.60 (4 H, d, J = 4.8 Hz), 4.56 (4 H, d, J = 4.7 Hz), 4.06-3.93 (4 H, m), 3.74-3.65 (4 H, m), 3.29-3.23 (2 H, m), 3.08-3.01 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.8, 155.8, 143.4, 141.7, 133.5, 129.9, 129.6, 129.0, 128.2, 128.1, 126.5, 126.4, 125.9, 123.0, 121.2, 121.0, 118.4, 111.9, 69.6, 69.5, 67.5, 67.5, 67.0,



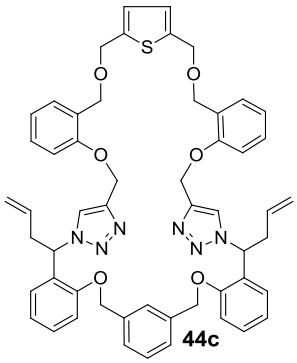
67.0, 66.9, 66.9, 62.6, 62.6, 59.5, 59.3, 37.7, 37.7 ppm; HRMS (ESI): MNa^+, found 903.3545. $C_{50}H_{52}N_6NaO_7S$ requires 903.3516.

Compound 44b: Following the general procedure, **44b** was obtained after purification by silica gel column chromatography as yellow color liquid (66 mg, 72%); R_f (40% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2926, 1600, 1493, 1454, 1247 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (2 H, s), 7.39 (2 H, d, J = 7.4 Hz), 7.31 (2 H, dt, J_1 = 7.7 Hz, J_2 = 1.8 Hz), 7.27-7.23 (4 H, m), 7.01-6.94 (6 H, m), 6.79 (2 H, d, J = 8.7 Hz), 6.78 (1 H, s), 6.76 (1 H, s), 5.99 (2 H, t, J = 8.2 Hz), 5.70-5.62 (2 H, m), 5.20 (4 H, br. s), 5.08-4.96 (4 H, m), 4.62 (4 H, s), 4.58 (4 H, s), 4.02-3.94 (4 H, m), 3.67-3.64 (4 H, m), 3.59 (4 H, s), 3.29-3.24 (2 H, m), 3.08-3.04 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1, 155.7, 143.4, 141.7, 133.5, 129.8, 129.5, 128.9, 128.1, 128.0, 126.9, 126.8, 126.7, 125.9, 123.4, 123.4, 121.2, 121.2, 121.0, 118.4, 112.0, 111.9, 70.6, 70.5, 69.4, 67.5, 67.5, 67.0, 66.9, 66.9, 62.6, 59.4, 59.3, 37.7 ppm; HRMS (ESI): MH^+, found 925.3987. $C_{52}H_{57}N_6O_8S$ requires 925.3959.



44b

Compound 44c: Following the general procedure, **44c** was obtained after purification by silica gel column chromatography as yellow color liquid (62 mg, 69%); R_f (40% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2971, 1603, 1495, 1243 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (2 H, s), 7.38-7.32 (4 H, m), 7.28-7.20 (8 H, m), 7.00-6.95 (6 H, m), 6.90 (2 H, d, J = 8.3 Hz), 6.65 (1 H, s), 6.60 (1 H, s), 6.63-5.97 (2 H, m), 5.71-5.62 (2 H, m), 5.23-5.15 (4 H, m), 5.09-4.95 (8 H, m), 4.50-4.67 (8 H, m), 3.28-3.21 (2 H, m), 3.07-2.99 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.0, 155.6, 155.6, 143.5, 143.4, 141.6, 137.0, 133.4, 129.9, 129.9, 129.5, 129.2, 129.1, 129.0, 127.9, 127.8, 127.2, 126.6, 126.6, 126.6, 126.6, 126.4, 126.3, 125.8, 125.8, 123.1, 123.0, 121.3, 121.3, 121.1, 118.5, 112.1, 111.9, 69.9, 69.9, 66.8, 66.8, 66.7, 62.6, 62.6, 59.2, 58.9, 38.1, 38.0 ppm; HRMS (ESI): MH^+, found 913.3716. $C_{54}H_{53}N_6O_6S$ requires 913.3747.



44c

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33h (CCDC 970705), **33q** (CCDC 970706), **36b** (CCDC 970707), **36d** (CCDC 970708) **37a** (CCDC 970709), **38a** (CCDC 970710), and **38c** (CCDC 970711) have been deposited with the Cambridge Crystallographic Data Centre. (g) For a some selected papers describing the X-ray structural properties of 1,3-diyene units, see ref., Zhou, Q.; Carroll, P. J.; Swager, T. M. *J. Org. Chem.* **1994**, *59*, 1294. (h) Collins, S. K.; Yap, G. P. A.; Fallis, A. G.; *Angew. Chem. Int. Ed.* **2000**, *39*, 385. (i) Srinivasan, M.; Sankararaman, S.; Hopf, H.; Dix, I.; Jones, P. G. *J. Org. Chem.* **2001**, *66*, 4299.

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Chapter 3: Exploitation of Glaser-Eglinton-Hay and ring closing metathesis-based strategies for the synthesis of new classes of optically active aza-oxo-thia polyether macrocycles from chiral amino alcohol and α-methylbenzylamine building blocks

Introduction

Alongside the well celebrated oxo-aza-thia crown ethers/polyether macrocycles, optically active crown ethers/polyether macrocycles possessing ability to recognize chiral small molecules has been explored extensively.[1-5] In general, optically active crown ethers/polyether macrocycles have found numerous applications in various branches of chemical sciences, e.g., host-guest chemistry due to their tendency to distinguish enantiomers and several optically active crown ethers have been used in the research area pertaining to analytical chemistry/chromatography and organic synthesis.[4] One of the advantages of optically active crown ethers/polyether macrocycles containing chiral building blocks is, it is easy to modify their chiral cavity in order to improve their tendency or selectivity to distinguish enantiomers.[5] Cram and coworkers made the first advancement in the research area pertaining to the preparation of optically active crown ethers/polyether macrocycles by incorporating binaphthyl subunits in the polyether macrocyclic ring (Figure 1).[5a-c] Since their studies on the discrimination between enantiomers of amine by binaphthyl-containing macrocycles in early 1970, several enantiopure synthetic building blocks (e.g., amino acids, sugars, BINOL, amines and amino alcohols etc) and asymmetric routes were exploited for synthesizing optically active crown ethers/polyether macrocycles.[6-9]

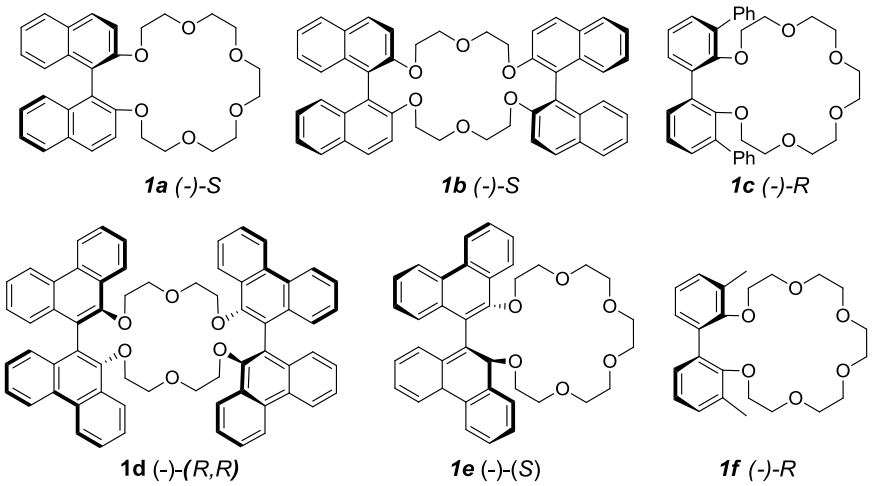
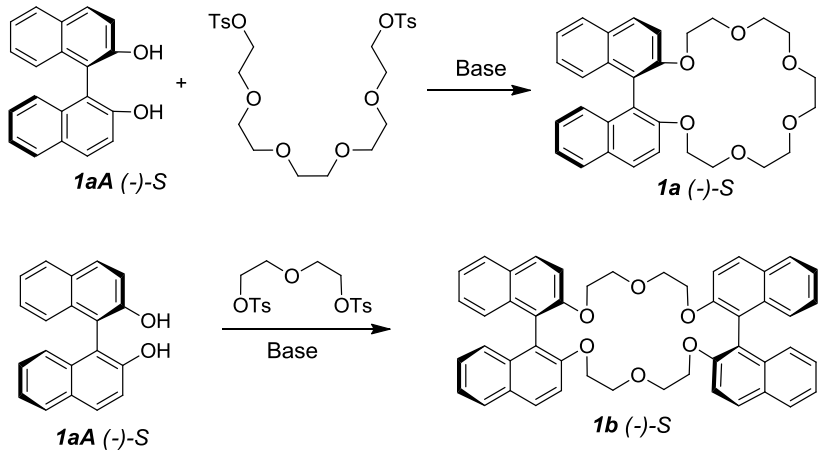


Figure 1. Examples of some classical optically active crown ethers.[5a-c]

Literature reports on the synthesis optically active crown ethers/polyether macrocycles based on enantiopure BINOL-type building blocks.

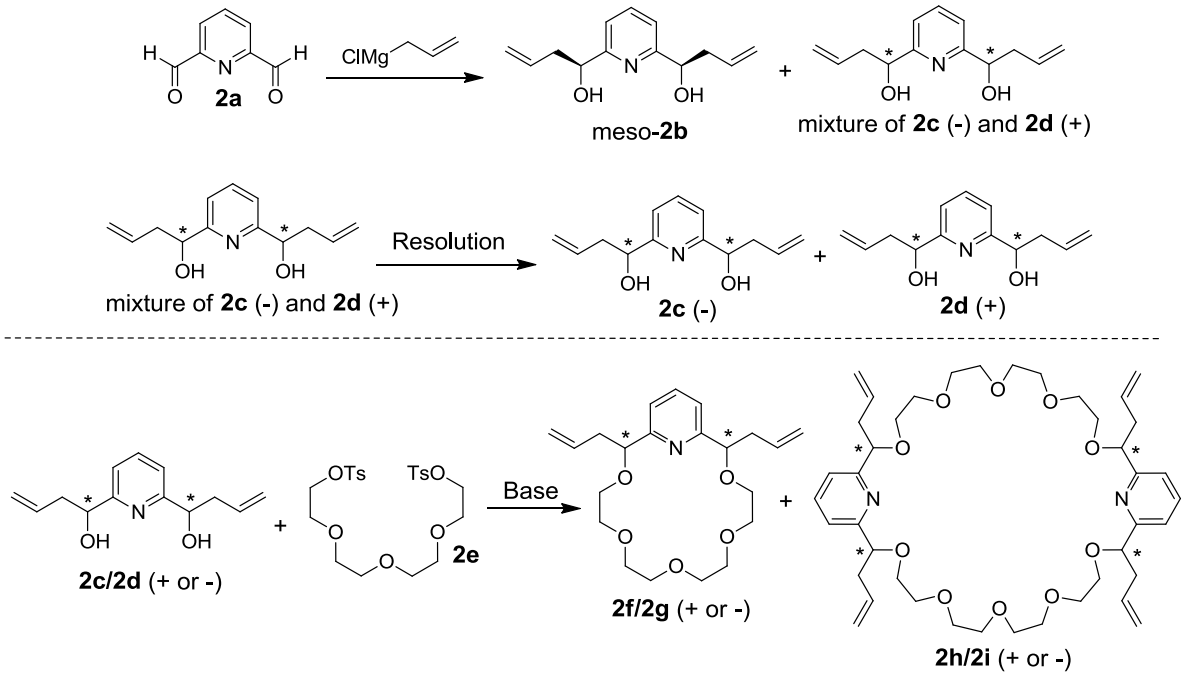
Cram and coworkers reported the preparation of optically active crown ethers/polyether macrocycles by incorporating binaphthyl subunits in the polyether macrocyclic ring (Scheme 1). Macrocycles **1a** and **1b** were assembled from **1aA** in a single step and these polyether macrocycles on interaction with racemic amine salts showed high ability to discriminate the enantiomers. Chiral recognition/discrimination of enantiomers of this type provides basis for the designing new hosts for recognizing amino acids and their esters. Markedly, numerous chiral macrocyclic polyethers having biphenanthryl and bisphenanthryl units (Figure 1) have been reported by Cram and different research groups. Further, the optically active crown ethers/polyether macrocycles shown in Figure 1 were derived from enantiopure building blocks such as biphenanthryl and bisphenanthryl have been successfully tested for chiral recognition/discrimination of enantiomers different salts of amines.



Scheme 1. Enantiopure binaphthyl unit based optically active crown ethers/polyether macrocycles.

Chirality also has been introduced into crown ethers/polyether macrocycles hosts using optically active functional groups other than bi-naphthol. Accordingly, sugar, amino acids, amino alcohols and α-methylbenzylamine were used as building blocks to assemble several optically active crown ethers/polyether macrocycles hosts, which have been found to exhibit varying degrees of chiral recognition towards a range of guests. [10-14]

Bradshaw *et al.* reported[10a] the synthesis of optically active crown ethers/polyether macrocycles **2f/2g** analogous to classical 18-crown-6 (Scheme 2). Chiral 2,16-diallyl-, 2,16-dimethyl-pyridino-18-crown-6 have been prepared by treating the appropriate chiral α,α'-disubstituted pyridinedimethanol with tetraethylene glycol ditosylate in the presence of base to complete the synthesis of chiral crown ethers **2f/2g** (1:1 adduct). In these reactions; chiral 2:2 dimers **2h/2i** (dipyridin-36-crown-12 derivatives) were also obtained along with **2f/2g** (Scheme 2).

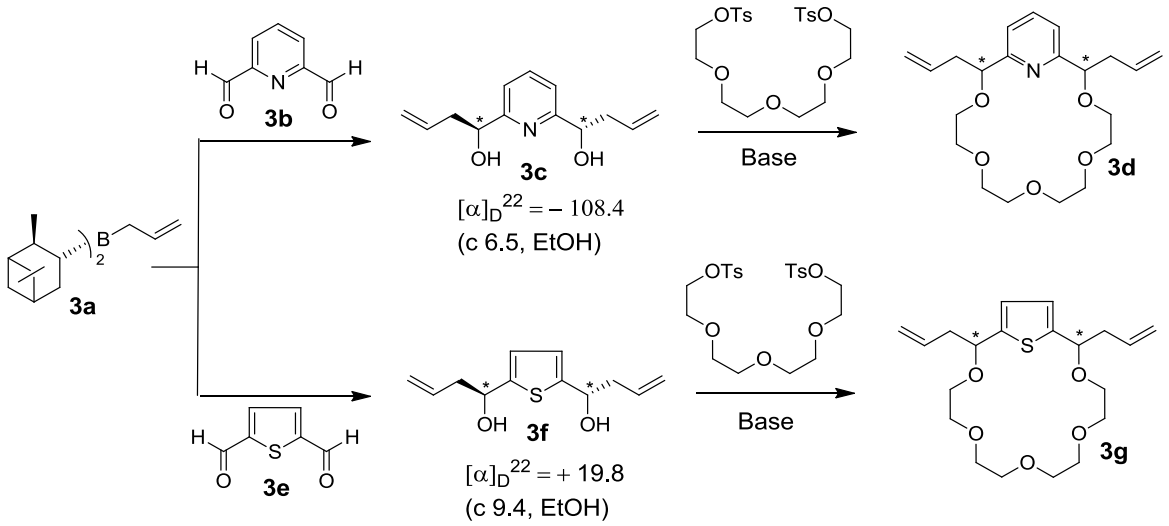


Scheme 2. Preparation of chiral pyridino-18-crown-6 **2f/2g** and dipyridino-36-crown-12 **2h/2i**.

The log *K* values for the interaction of these optically active crown ethers/polyether macrocycles with the enantiomers of (*R*-phenylethyl)ammonium perchlorate and (*R*-(1-naphthyl)ethyl)-ammonium perchlorate were measured via the ^{1}H NMR titration method in a $CDCl_3$:CD_3OD (1:1) solvent mixture. The log *K* values indicated that these chiral pyridino-18-crown-6 ligands have high complexing abilities and some enantiomeric recognition for the chiral organic ammonium perchlorates.

Brown *et al.* reported[10b] the synthesis of chiral pyridino and thiopheno-18-crown-6 crown ethers/polyethers **3d/3g** *via* asymmetric allylboration method. Asymmetric allylboration of 2,6-pyridinedicarboxaldehyde **3b** and 2,5-thiophenedicarboxaldehyde **3e** provided the corresponding

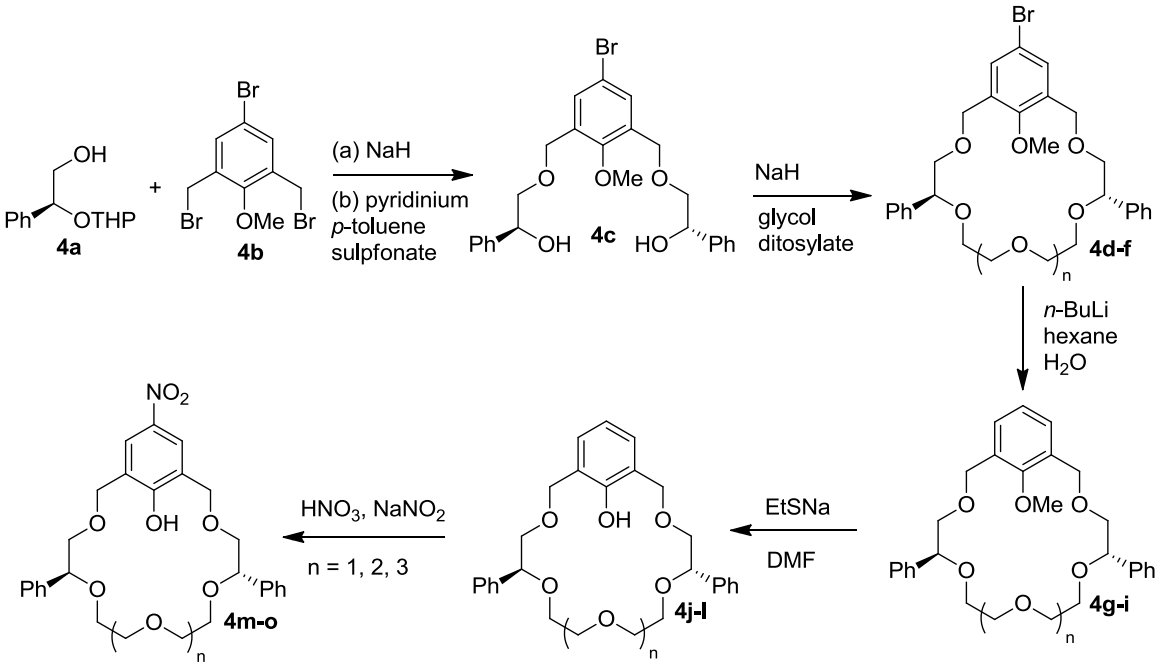
bishomoallylic alcohols **3d/3g** in very high de and ee (Scheme 3). These optically pure diols were converted to the disodium or dipotassium salts and subsequently treated with tetra(ethylene glycol) ditosylate to obtain the corresponding chiral pyridine- and thiopheno-18-crown-6 ligands **3d/3g** (Scheme 3).



Scheme 3. Preparation of optically active crown ethers/polyether macrocycles **3d/3g**.

Hirose *et al* reported[11a] the synthesis of optically active phenolic crown ethers/polyether macrocycles **4d-o** using (*S*)-(+)-mandelic acid derivatives as the source of the chiral building block. Chiral recognition of secondary amines was studied by using these optically active phenolic crown ethers/polyether macrocycles. The synthesis started with condensation of 2 equiv of mandelic acid derivative **4a** with 5-bromo-1,3-bis(bromomethyl)-2-methoxybenzene (**4b**) in the presence of NaH followed by the deprotection of THP groups with pyridinium *p*-toluenesulfonate, which afforded the chiral acyclic diol-podand **4c** (Scheme 4). Then, the acyclic diol-podand **4c** was reacted with different di(*p*-toluenesulfonate) ethylene glycols under high dilution conditions in the presence of NaH to form *p*-methoxy aryl bromide crown ethers **4d-f** (Scheme 4). Further steps were performed to remove bromine substituting at the *para*-position of the aromatic ring of **4d-f** by reaction with *n*-BuLi and demethylation of OMe group with sodium ethanethiolate in DMF, which afforded optically active phenolic crown ethers/polyether macrocycles **4j-l** (Scheme 4). Finally, the nitro group was introduced at the *para* position in **4j-l** *via* nitration reaction using a $HNO_3/NaNO_2$ mixture (Scheme 4). Hirose *et al.* studied the binding

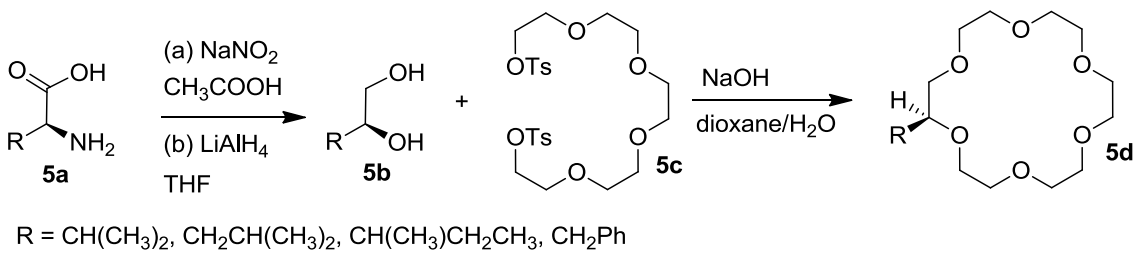
ability of these optically active macrocyclic crown ethers with primary and secondary amines. They have observed that among all the macrocyclic compounds reported *p*-nitro phenolic crown ethers **4m-o** showed the promising results as chiral hosts for secondary amines.



Scheme 4. Synthesis of optically active phenolic crown ethers/polyether macrocycles using (*S*)-(+)-mandelic acid derivatives.

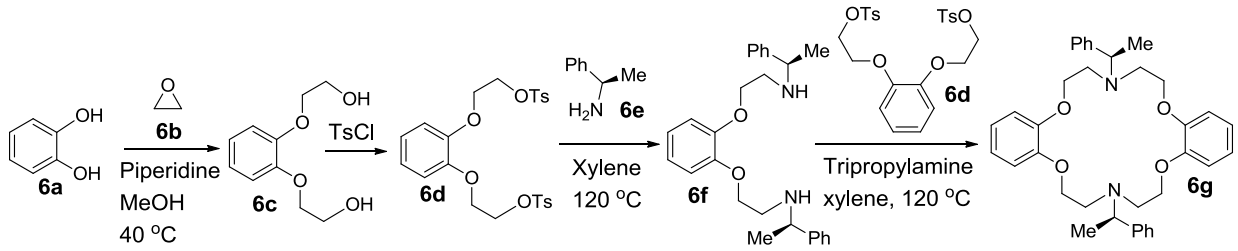
Literature reports on the synthesis chiral macrocycles based on enantiopure amino acids, amino alcohol and α-methylbenzylamine building blocks.

α-Amino acids such as L-valine, L-leucine, L-isoleucine and L-phenylalanine have been used to create optically active crown ethers **5d** containing amino acid-derived chiral building blocks in their macrocyclic core (Scheme 5). Firstly, α-amino acids **5a** were converted into the corresponding chiral glycols **5b**, then **5b** were reacted with pentaethylene glycol ditosylate **5c** to afford the corresponding chiral crown ethers (Scheme 5).[11b,c]



Scheme 5. Synthesis of optically active phenolic crown ethers/polyether macrocycles from α-Amino acids.

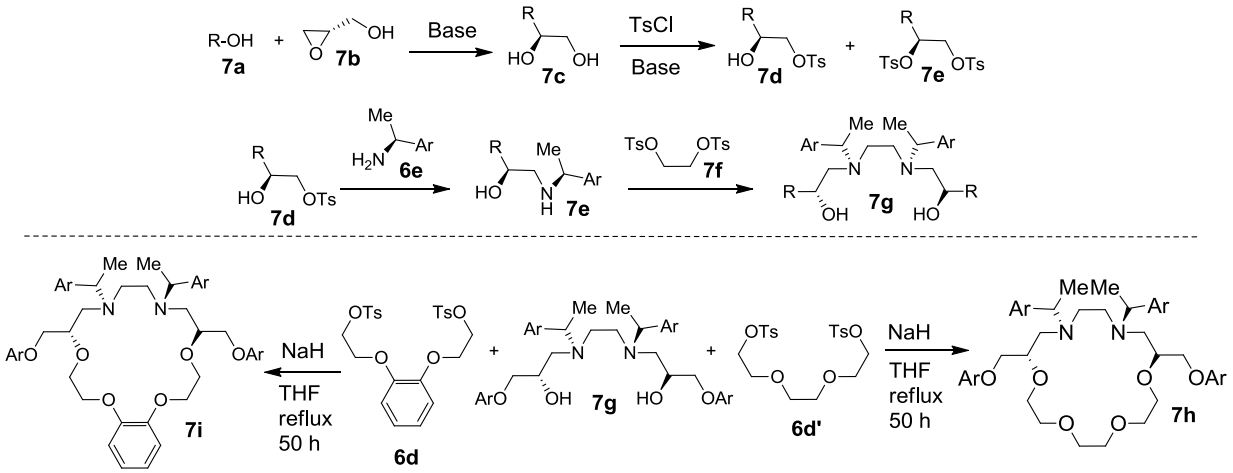
Demirel reported[12a] the synthesis of chiral oxo-aza polyether macrocycle **6g** (18-crown-6) by using α-methylbenzylamine as the chiral building block (Scheme 6). The epoxide opening reaction between ethylene oxide **6** and catechol **6a** afforded the diol compound **6c** (having two free hydroxyl group), which was converted into ditosylate compound **6d** (Scheme 6). Next, nucleophilic substitution reaction of ditosylate compound **6d** with chiral α-methylbenzylamine **6e** afforded the diamine **6f** (Scheme 6). Finally, the reaction between ditosylate **6d** and diamine **6f** afforded chiral oxo-aza polyether macrocycle **6g** (Scheme 6).



Scheme 6. Synthesis of chiral oxo-aza polyether macrocycle using α-methylbenzylamine as the chiral building block.

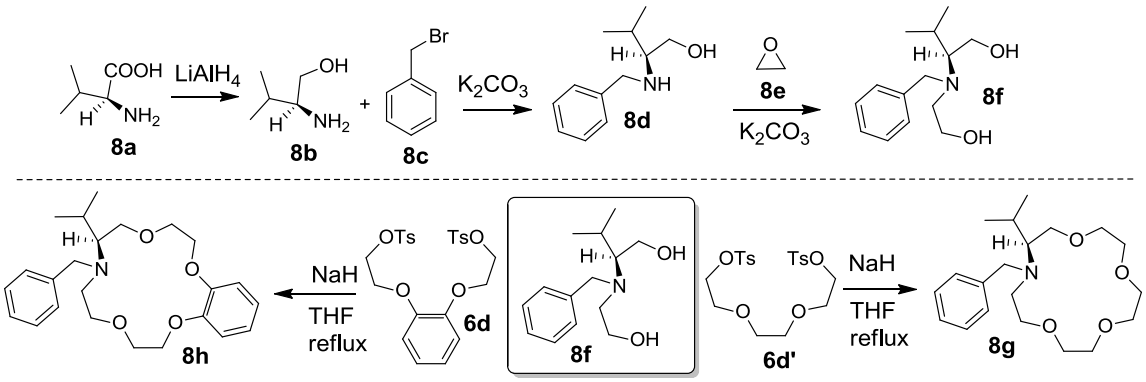
Turgut *et al.*[12b] reported the synthesis of C_2-symmetric chiral oxo-aza crown ether macrocycles **7h** and **7i** from reaction between diol **7g** and the corresponding ditosylates **6d** and **6d'**. Diol **7g** was assembled from alcohol **7a** *via* a series of reactions. Initially the reaction of **7a** with (*S*)-glycidol **7b** in the presence of base afforded the diol **7c**, which was tosylated to generate **7d** and **7e** (Scheme 7). Next, the compound **7d** was reacted with excess (*S*)-α-phenyl ethylamine to obtain **7e**, which was treated with ethane-1,2-diyl bis(4-methylbenzenesulfonate) **7f** to afford the diol **7g** (Scheme 7). Finally, C_2-symmetric chiral oxo-aza-18-crown-6 **7h**/**7i** were synthesized

from the reaction of **7g** with the corresponding ditosylates **6d** and **6d'** (Scheme 7). The chiral oxoa-aza-18-crown-6 systems **7h** and **7i** were tested for recognition of amino acid ester derivatives. These optically active macrocyclic polyethers **7h** and **7i** have shown strong complexing ability for D-enantiomer of phenylalanine methyl ester hydrochloride.



Scheme 7. Synthesis of chiral crown macrocycles 18-crown-6 **7h** and **7i**.

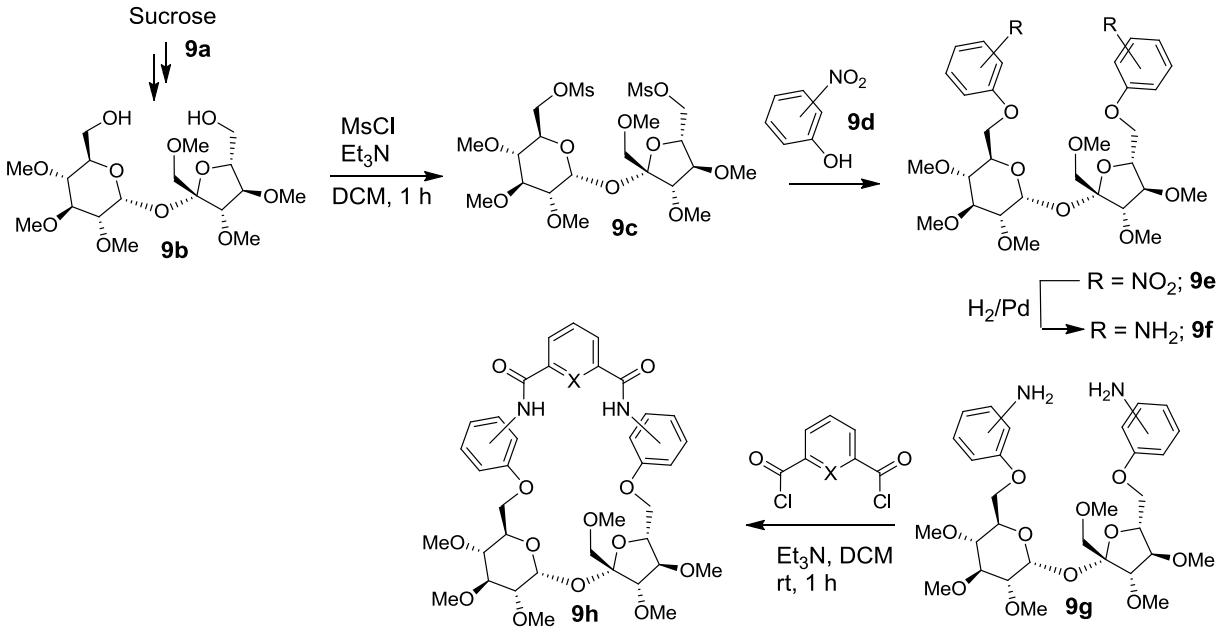
Turgut *et al.* reported[12c] the synthesis of chiral oxo-aza macrocycles **8g** and **8h** (15-crown-5) using L-valinol as a chiral building block (Scheme 8). The synthesis began with the reduction of L-valine (**8a**) to L-valinol (**8b**) which was then benzylated to afford the *N*-benzyl amino alcohol **8d** (Scheme 8). Then, the reaction of **8d** with ethylene oxide (**8e**) afforded the diol **8f**. Next, the reaction 8f with the corresponding ditosylates **6d** and **6d'** afforded the corresponding chiral oxo-aza macrocycles **8g** and **8h**.



Scheme 8. Synthesis of chiral oxo-aza 15-crown-5 using amino alcohol as chiral building block.

Literature reports on the synthesis chiral macrocycles based on sugar building blocks.

Jarosz *et al.* reported[12d] a convenient route to macrocyclic diamide-linked macrocyclic derivatives having sucrose scaffold (Scheme 9). Reaction of sucrose based *ortho*- and *meta*-amines **9g** (which were assembled from sucrose **9a**, in 6 steps as shown in Scheme 9) with acid dichlorides afforded the monomeric chiral sucrose based macrocycles **9h**, while reaction of the *para*-amines **9g** provided the corresponding dimeric macrocyclic products (Scheme 9).



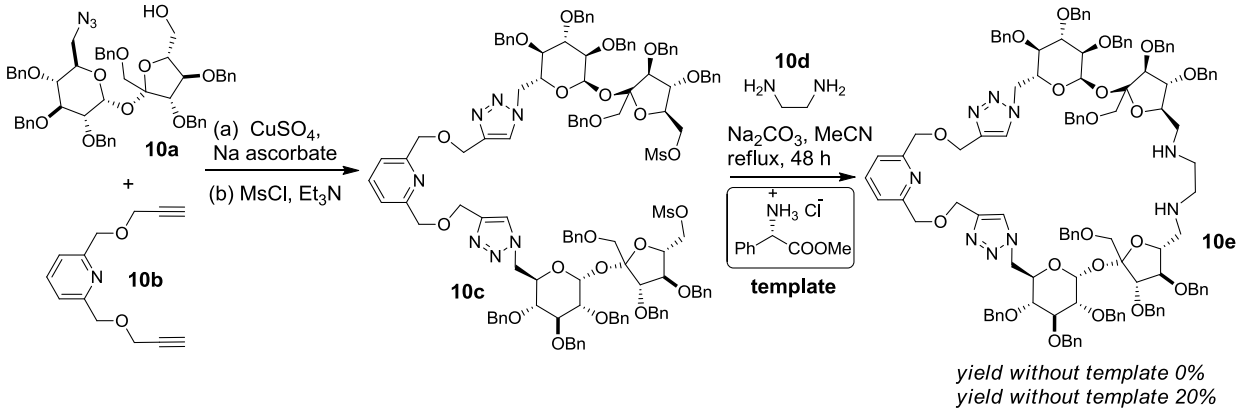
Scheme 9. Sucrose scaffold based chiral macrocyclic diamide macrocycles.

Literature reports on the synthesis of peptide/amino acids/sugar based chiral macrocyclic polyethers formed *via* click reaction.

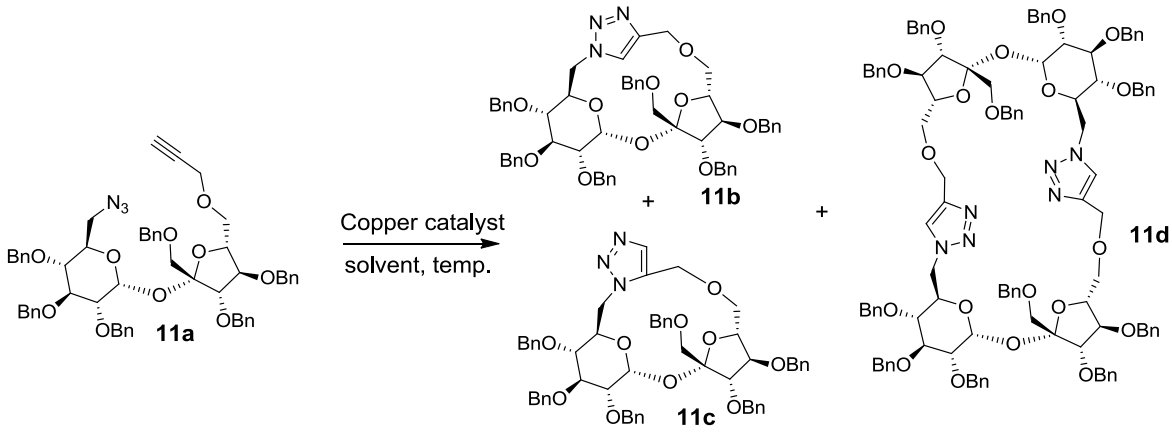
1,2,3-Triazole heterocyclic scaffold containing macrocyclic systems have found several applications in supramolecular and coordination chemistry as discussed in Chapter 2.[18] The synthesis of macrocyclic compounds containing 1,2,3-triazole involving the click chemistry has attracted the interest of the chemical community because of their usefulness in supramolecular/host-guest chemistry, organic synthesis and drug discovery.[18] Selected reports dealing on the synthesis of bis-1,2,3-triazole appended polyether macrocycles *via* the click reaction was described in Chapter 2. Some of the literature reports dealing on the synthesis of

peptide/amino acids/sugar based optically active macrocyclic polyethers embedded with 1,2,3-triazole units involving the click reaction are described in this section.

Jarosz *et al.* reported[13a] the synthesis of sugar based optically active macrocyclic polyether **10e** embedded with 1,2,3-triazole units *via* amino acid templated macrocyclization. The copper catalyzed 'click reaction' of sucrose-based azide precursor **10a** and 2,6-bis((prop-2-yn-1-yloxy)methyl)pyridine **10b** led to the formation of **10c** (Scheme 10). Then, the reaction of **10c** with ethylenediamine (**10d**) led to the formation of C_2-symmetrical sugar based optically active macrocyclic polyether **10e** embedded with 1,2,3-triazole units.



Scheme 10. Synthesis of C_2-symmetrical sugar based optically active macrocyclic polyether **10e** embedded with 1,2,3-triazole units.



Scheme 11. Synthesis of sugar based optically active macrocyclic polyethers **11b-d** embedded with 1,2,3-triazole units.

Jarosz *et al.* reported[13b] the synthesis of sugar based optically active macrocyclic polyether **11b-d** embedded with 1,2,3-triazole units. The synthesis of macrocyclic polyether **11b,c** was accomplished *via* the copper catalyzed intramolecular 'click reaction' of sugar-based azide precursor **11a** (Scheme 11). The macrocyclic polyether **11d** was obtained *via* the copper catalyzed intermolecular 'click reaction' of sugar-based azide precursor **11a** (Scheme 11).

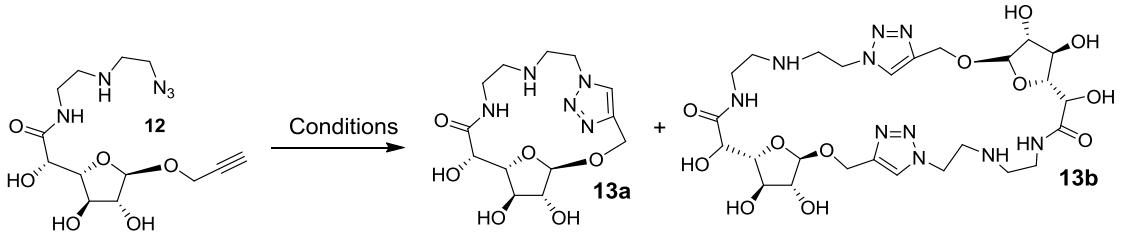
solvent (mmol/L)	Copper catalyst	temp.	yield **11b/11c** (%)	yield **11d** (%)
CH_3CN (4.23)	CuI	r.t.	40	5
CH_3CN (16.93)	CuI	r.t.	23	trace
CH_3CN (2.12)	CuI	r.t.	48	3
toluene (3.81)	none	80 °C	trace	45
toluene (3.97)	CuI	80 °C	25	10

Scheme 12. Effect of solvent and catalyst on alkyne-azide cycloaddition (click reaction) of **11a**.

Jarosz and coworkers[13b] observed that the ratio of these macrocyclic products depends on nature of solvent, copper catalyst and dilution conditions used for performing the click reaction of **11a** (Scheme 12). For example formation of triazole based macrocycle with CuI as the catalyst in CH_3CN solvent at room temperature yielded **11b**/**11c** in 48% and traces amount of **11d** (Scheme 12). Whereas, when reaction was carried out in toluene without using any catalyst resulted the macrocyclic product **11d** in 45% and macrocyclic products **11b**/**11c** in traces (Scheme 12).

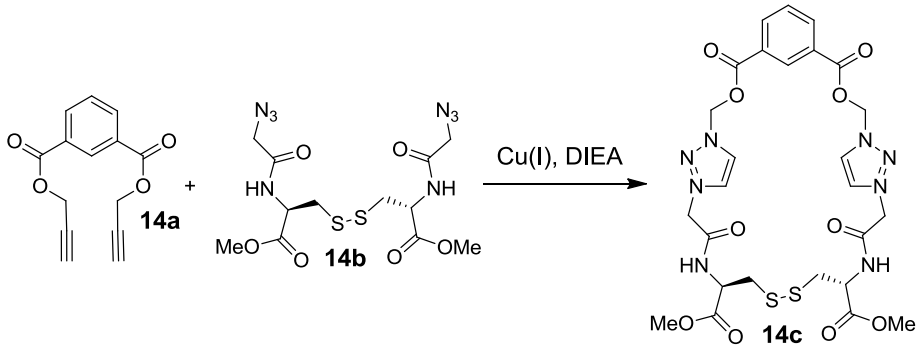
Plantier-Royon and coworkers also reported[14a] a convenient approach for construction of triazole-ring containing macrocycles **13a/13b** (Scheme 13). The ratio of macrocycle **13a/13b** was found to change depending on the reaction conditions used. The macrocycles **13a/13b** formed in a ratio of 80:20 and 84% yield by using the conditions of method as shown in Scheme 13. When the reaction was performed in the presence of copper(I) iodide in THF/acetonitrile (3:1) and a large excess of diisopropylethylamine (method 2, Scheme 13), a similar result was

obtained (ratio of **13a**/**13b** = 70:30). By using the same conditions but in water (method 3, Scheme 13), the reaction was completely selective, and only the C_2-symmetric dimeric macrocycle **13b** was isolated in 55% yield (Scheme 13).

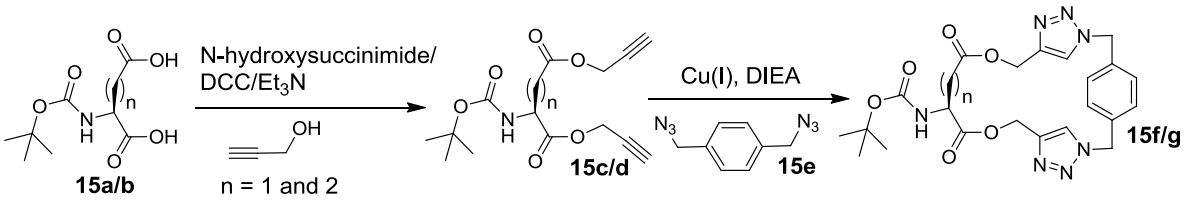


Method 1: $CuSO_4$, Na ascorbate, H_2O, rt	80%	20%
Method 2: CuI, THF/CH_3CN, DIEA, rt	70%	30%
Method 3: CuI, H_2O, DIEA, rt	0%	100%

Scheme 13. Synthesis of optically active triazole unit-based macrocycle *via* click reactions.



Scheme 14. Synthesis of cystine unit containing triazolophane **14c**.



Scheme 15. Synthesis of amino acid (Asp and Glu) based triazolophanes.

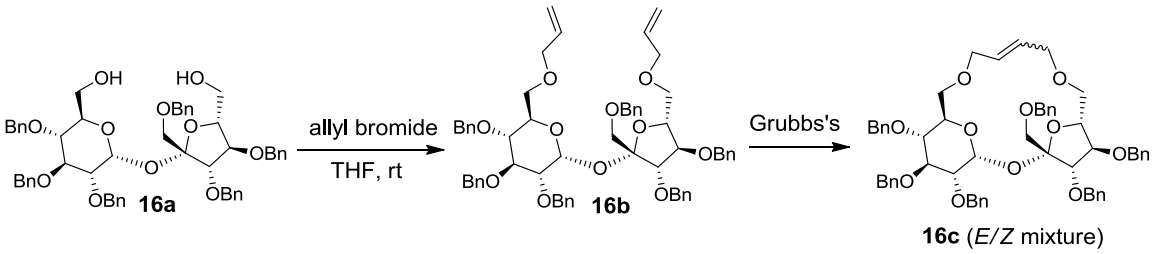
Haridas *et al.* reported[14b] an efficient synthesis of peptidic backbone containing macrocyclic system *via* click reaction (Scheme 14). The cystine derived diazide **14b**, which was synthesized from cystine methyl ester and azidoacetyl chloride was reacted with dialkyne **14a** to afford the

27-membered 1,2,3-triazole ring containing optically active macrocycle **14c** (Scheme 14). Further, Haridas group assembled chiral amino acids (Asp and Glu) derived dialkynes **15c-d** and treated them with *p*-xylyldiazide xylyldiazide **15e** in the presence of Cu(I) to afford the 20- and 21-membered optically macrocyclic triazolophanes **15f-g** (Scheme 15).

Literature reports for the synthesis of chiral macrocycles *via* the ring closing metathesis (RCM) reaction.

Selected reports dealing on the synthesis of polyether macrocycles *via* the ring closing metathesis (RCM) reaction was described in Chapter 1. Some of the literature reports dealing on the synthesis of optically active macrocyclic polyethers involving the ring closing metathesis (RCM) reaction are described in this section.

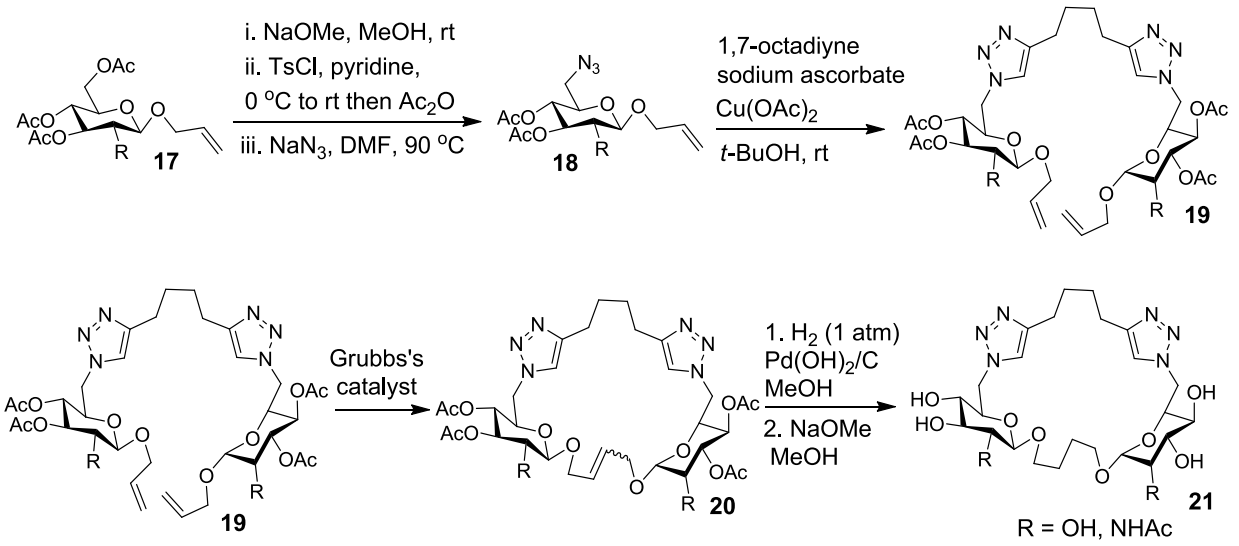
Jarosz *et al.* used[14d] the ring closing metathesis (RCM) strategy for the synthesis of chiral macrocyclic polyether **16c** using sucrose scaffold 16a. The sucrose scaffold **16a** was first converted into the RCM precursor diallyl ether **16b** *via* allylation of free hydroxyl groups. Then the RCM precursor diallyl ether 16b was subjected to metathesis reaction with the Grubbs's catalyst to afford the optically active macrocyclic olefin **16c** as a cis/trans mixture (Scheme 16).



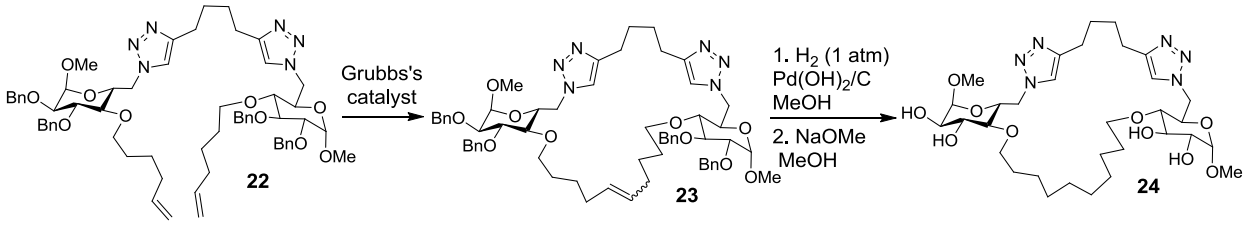
Scheme 16. Synthesis of optically active macrocyclic olefin **16c** based on sucrose scaffold *via* ring closing metathesis strategy.

Westermann and coworkers reported[14d] a facile approach for the preparation of macrocyclic systems containing different carbohydrate moieties *via* ring-closing metathesis technique (Scheme 17). The di-olefin precursors **20** and **23** were prepared starting from glucose and glucosamine (**17**) in good yields (17). Then, the RCM precursors **19** were reacted with Grubbs's I generation catalyst in a 2 mM dichloromethane solution at 40 ^{o}C to afford the sugar scaffold-

installed macrocyclic polyether **20** as a mixture of *E/Z* olefins. Next, the products **20** were subjected to the catalytic hydrogenation using palladium(II) hydroxide on charcoal followed by deprotection of OAc afforded the optically active macrocyclic polyethers **21** (Scheme 17). Similarly, the ring closing metathesis of sugar-derived di-olefin precursors **22** were performed in the presence of Grubbs's I generation to afford the sugar scaffold-installed macrocyclic polyether **23** as a mixture of *E/Z* olefins (Scheme 18). Next, the products **23** were subjected to the catalytic hydrogenation using palladium(II) hydroxide on charcoal followed by deprotection of OAc afforded the optically active macrocyclic polyethers **24** (Scheme 18).

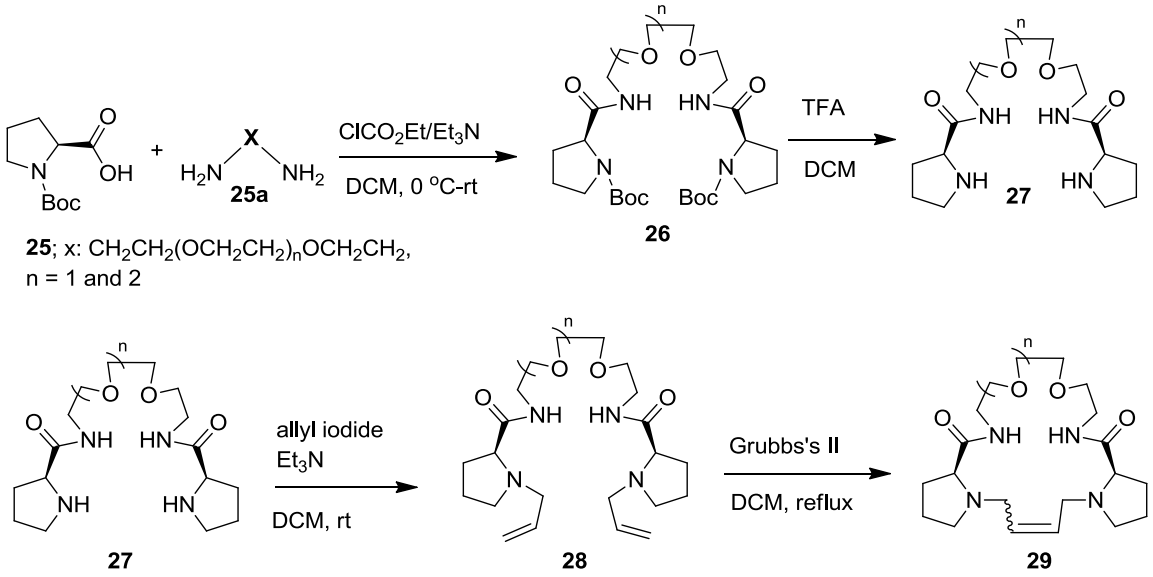


Scheme 17. Preparation of macrocycles **20**/**21** based on glucose and glucosamine scaffolds *via* the RCM reaction.



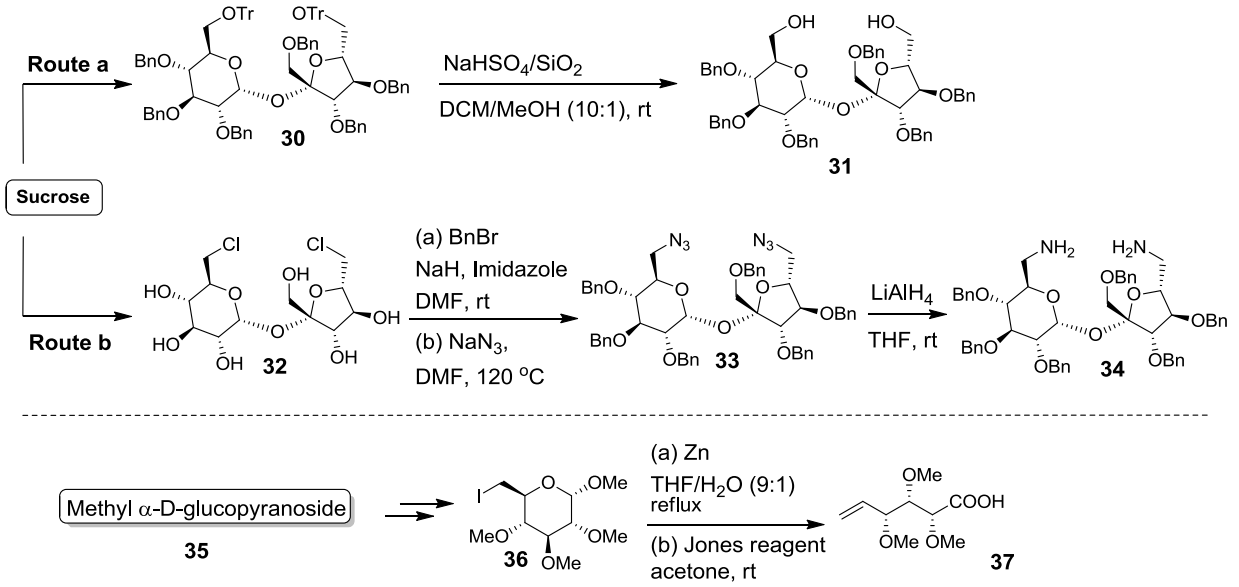
Scheme 18. Preparation of macrocycles **23**/**24** based on glucose and glucosamine scaffolds *via* the RCM reaction.

Recently, Al-Azemi *et al.* reported[14e] the synthesis of optically active macrocyclic compounds **29** using L-proline as chiral building blocks *via* ring closing metathesis (RCM) technique as a key step (Scheme 19). The reaction of *N*-Boc protected L-proline **25** with various diamine linkers **25a** followed by Boc deprotection afforded the precursor **27**. Next, allylation of free amine of **27** in the presence of triethylamine and allyl iodide gave the RCM precursors **28**. Then, the RCM precursors **28** were subjected to the ring closing metathesis in the presence of the Grubbs's II catalyst (5 mol%) under high dilution condition to afford the optically active macrocycles **29** (Scheme 19).

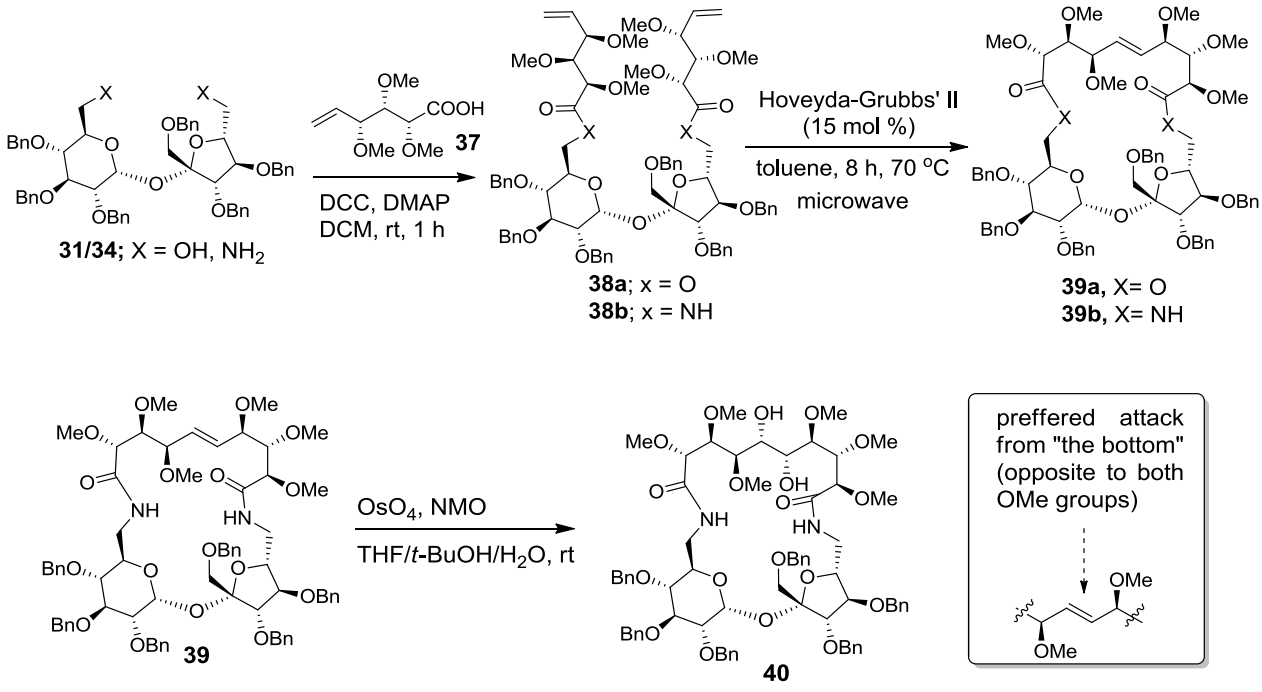


Scheme 19. Synthesis of optically active macrocyclic compounds **29** using L-proline as the building block *via* RCM reaction.

Jarosz *et al.* reported[14f] the synthesis of optically active 21-membered macrocyclic di-lactone **39a** and di-lactam **39b** having *E*-geometry *via* the ring closing metathesis of di-allyl precursor **38** using sucrose scaffold (Scheme 21). The required diol **31** was prepared by deprotection of di-tritylated sucrose derivative **30** (*route a*, Scheme 20) and di-amine **34** from di-chlorosucrose derivative **32** (*route b*, Scheme 20). Then, the required olefin unit **37** was prepared by a reductive dehalogenation (commonly known as the Vasella reaction) of iodosugar **36**, which was prepared from methyl α-D-glucopyranoside **35** (Scheme 20). The esterification of acid **37** with diol **31** afforded di-ester **38a** (Scheme 21). The analogous reaction of acid **37** with di-amine **34** gave the di-amide **38b** (Scheme 21).



Scheme 20. Synthesis of hexa-*O*-benzyl-6,6'-diolsucrose **31** and hexa-*O*-benzyl-6,6'-diaminosucrose **34** and preparation of the olefin unit **37**.



Scheme 21. Preparation of sucrose based macrocyclic di-lactone **39a** and di-amide **39b** *via* the ring closing metathesis strategy.

Finally, the ring closing metathesis of **38a/38b** using Hoveyda-Grubbs's II generation catalyst (15 mol%) under MW irradiation at 90 ^{o}C in perfluorotoluene gave desired sucrose containing macrocyclic polyethers **39a** and **39b** (Scheme 21). Furthermore, Jarosz *et al.* carried out the *syn*-dihydroxylation of the *E*-olefin unit of macrocyclic di-lactone **39a** and di-amide **39b** using OsO_4 (cat.) and NMO in THF/^{t}BuOH/H_2O mixture (Scheme 21). Macrocycle di-ester **39a** did not provide the expected diol(s). However, the macrocycle di-amide **39b** afforded the required periphery functionalized macrocycle **40** having *syn*-diol unit (Scheme 21).

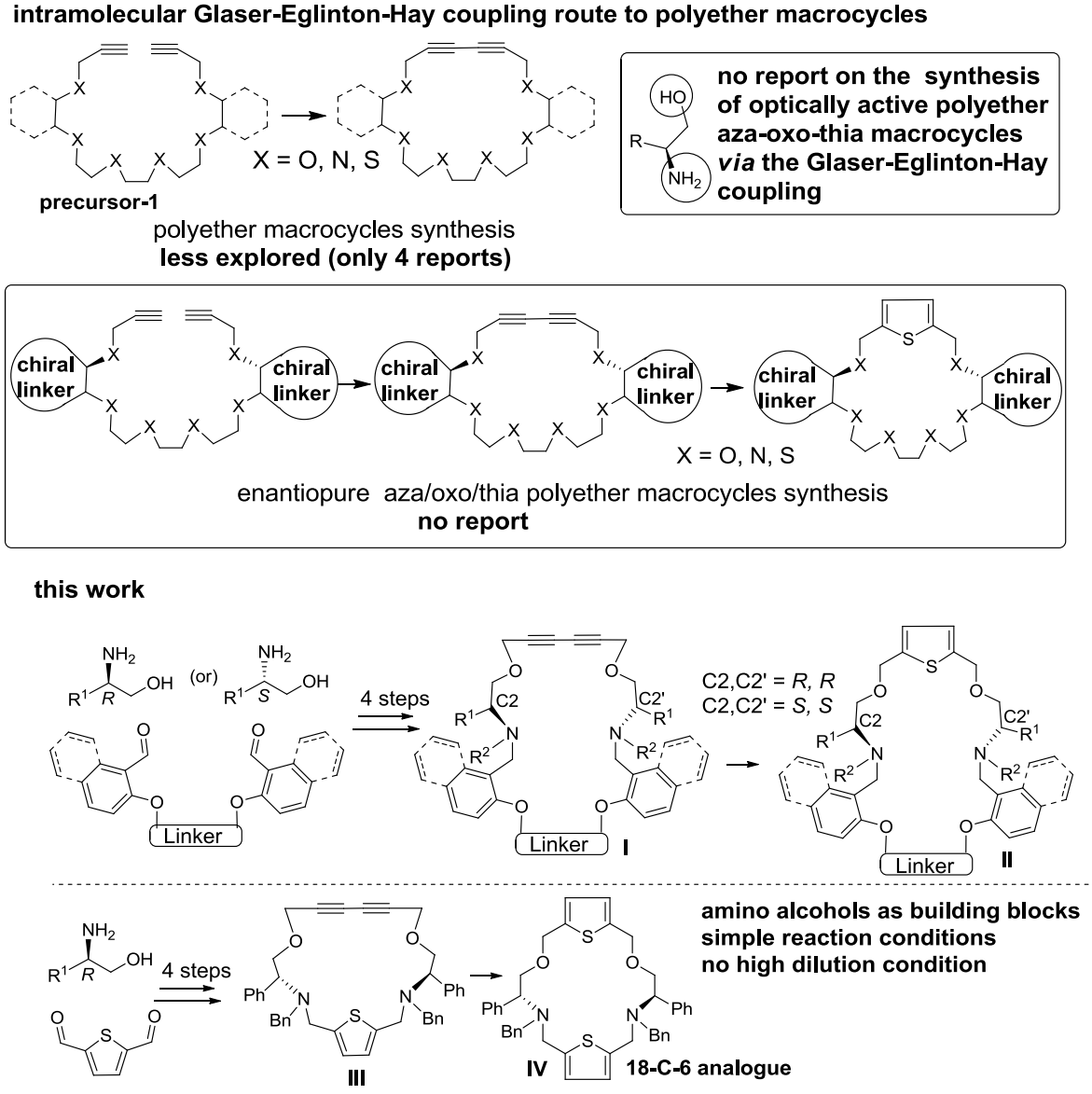
Result and discussion

Chapter 3a: Exploitation of Glaser-Eglinton-Hay coupling strategy for the synthesis of new classes of optically active aza-oxo-thia polyether macrocycles from chiral amino alcohol building blocks.

The synthesis of polyether macrocycles is a well explored research area. Numerous methods were developed for the synthesis of polyether macrocycles. Polyether macrocycle synthesis was investigated by using a wide range of linkers/building blocks, e.g., alkyl chain, polyether and aromatic linkers. Further, polyether macrocycle synthesis was investigated by using various types of enantiopure synthetic building blocks, e.g., amino acids, sugars, BINOL, amines and amino alcohols.

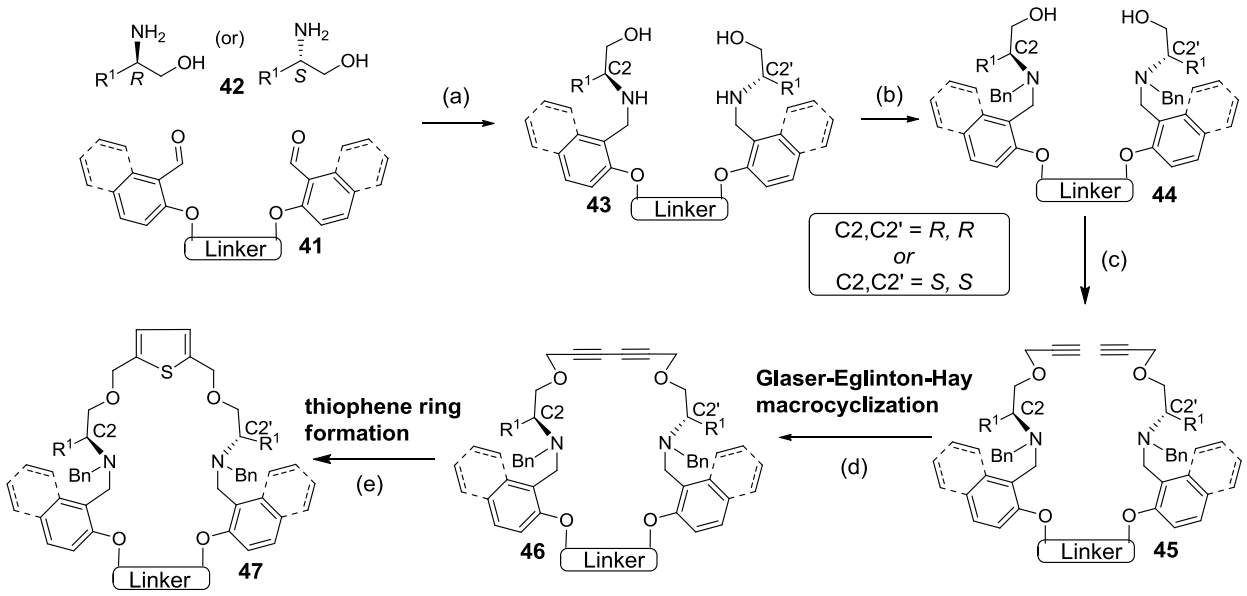
The general chemical transformations used to accomplish the polyether macrocycle synthesis are, the standard peptide coupling, Yamaguchi lactonization, ring closing metathesis, Williamson ether synthesis, Glaser-Eglinton-Hay and some other methods.[1-9] Of special interest, while the Glaser-Eglinton-Hay reaction was used for synthesizing several 1,3-diyne-based shape persistent linear and macrocyclic molecules;[15,16] however, a literature survey revealed that there exist only two reports by other groups[17a,b] and two reports by our group[17c,d] dealing on the synthesis of 1,3-diyne unit containing polyether macrocycles. Furthermore, there exists no report that deals on the synthesis of optically active polyether macrocycles *via* the intramolecular Glaser-Eglinton-Hay-type cross-coupling reaction.

The introduction part of this Chapter 3 revealed some of the contributions with regard to the synthesis of optically active crown ether/polyether macrocycles and related systems. Given the importance of optically active crown ether/polyether macrocycles in organic synthesis and research area pertaining to analytical chemistry and chromatography, the synthesis of a library of new classes of optically active crown ether/polyether macrocyclic systems and periphery modified polyether macrocyclic systems will be highly useful.



Scheme 22. literature on the Glaser-Eglinton-Hay macrocyclization and synthesis of aza-oxo-thia polyether macrocycles *via* the Glaser-Eglinton-Hay coupling.

Accordingly, in line with the objective of this thesis, a part of this thesis report the investigations on the synthesis of optically active aza-oxo polyether macrocycles having 1,3-diyne unit from amino alcohol building blocks and suitable linkers by exploiting the intramolecular Glaser-Eglinton-Hay macrocyclization as the key step (Scheme 23). Furthermore, the conversion of 1,3-diyne unit of aza-oxo polyether macrocycles into a thiophene ring has led to the assembling of optically active aza-oxa-thia heterotopic-type polyether macrocycles and some examples similar to classical 18-C-6 and 18-C-5 systems (Scheme 23).

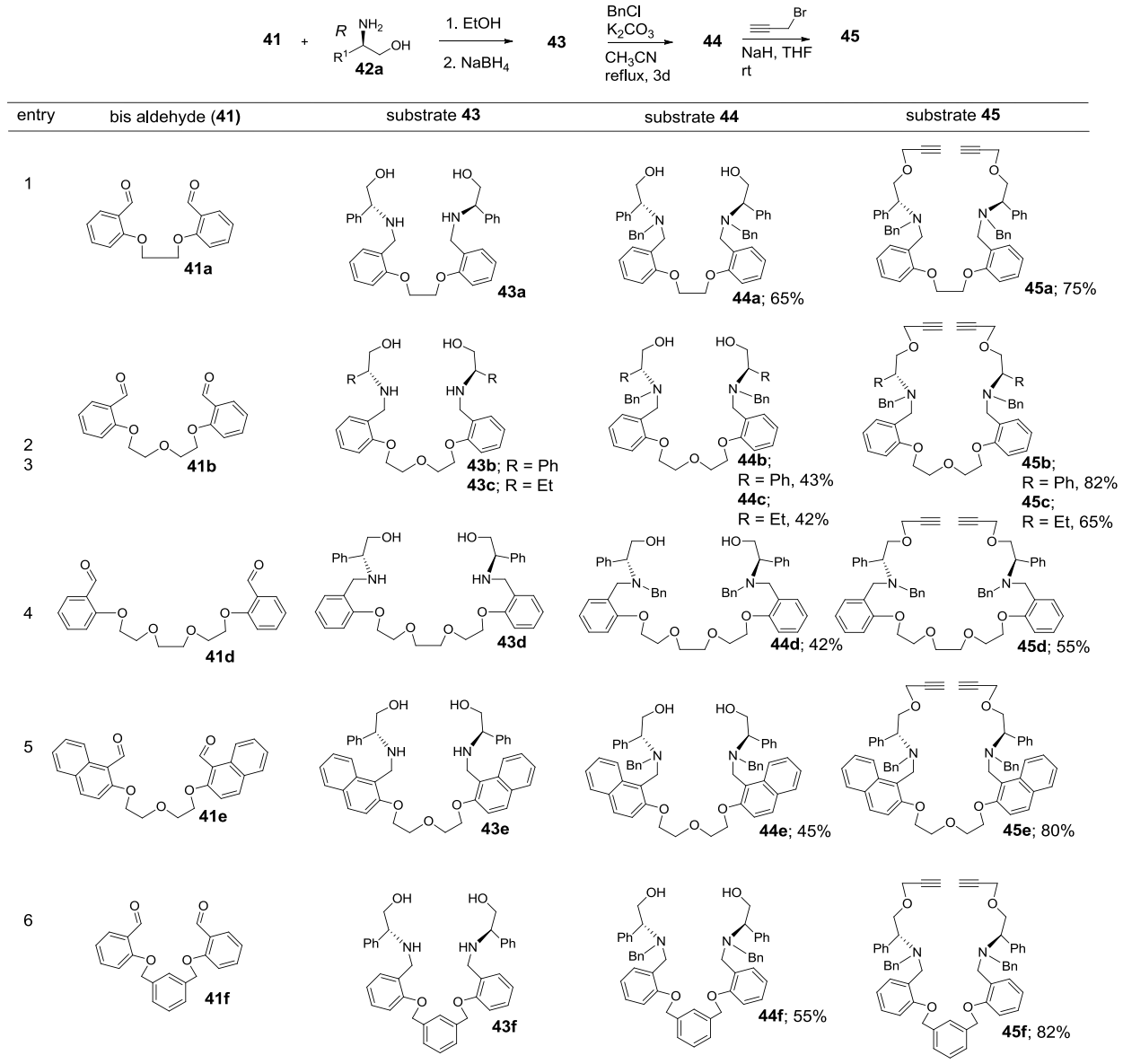


Reaction Conditions: (a) EtOH, reflux, 12 h, then, $NaBH_4$, reflux, 12 h. (b) BnCl, K_2CO_3, MeCN, reflux, 72 h, (c) propargyl bromide, NaH, THF, rt. (d) $Cu(OAc)_2 \cdot H_2O$, DMSO, 110 ^oC, air, 6 h. (e) $Na_2S \cdot xH_2O$, CuI, 1,10-phenanthroline, DMF, 90 ^oC, air, 9 h.

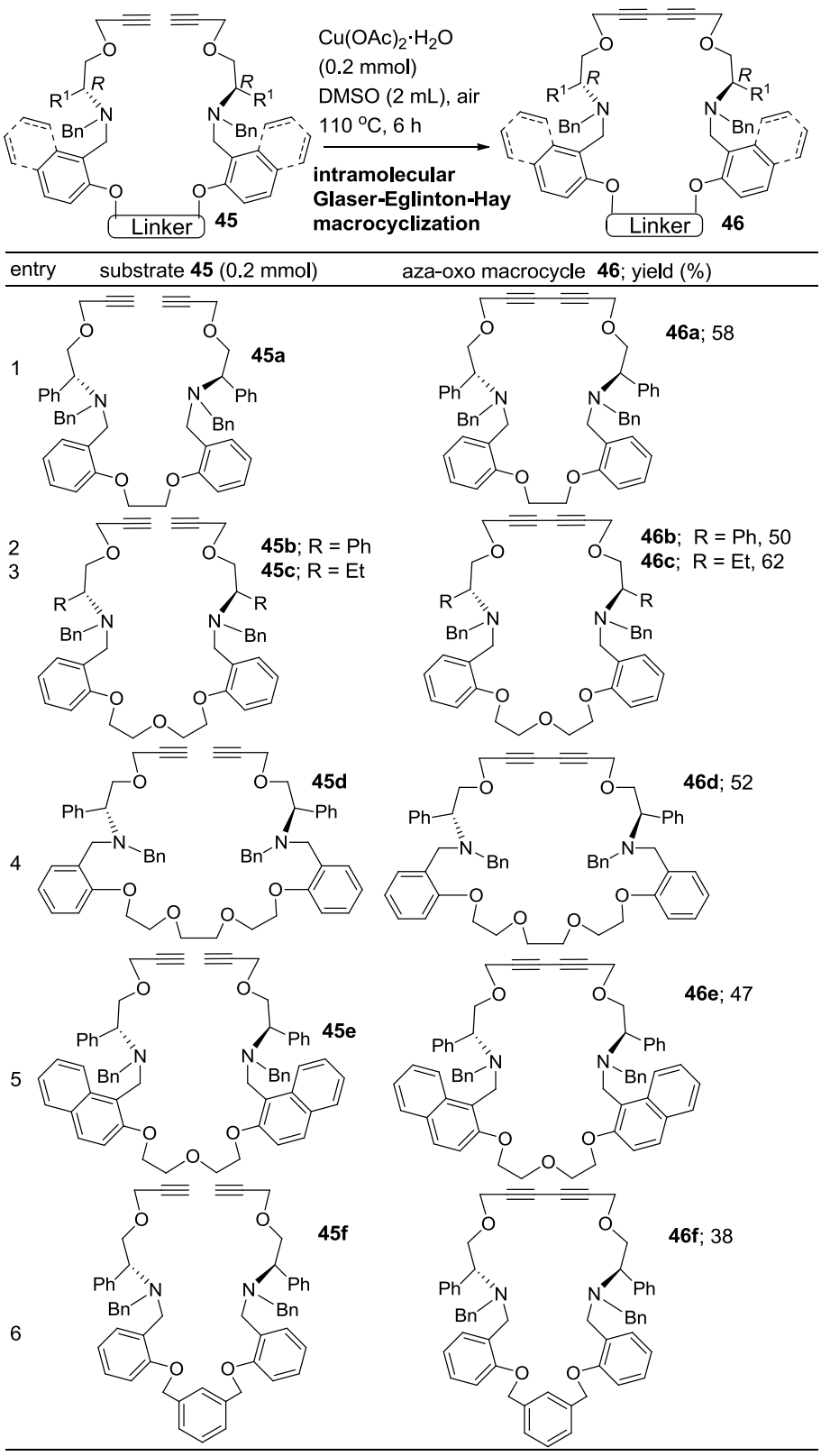
Scheme 23. Generalized strategy of the synthesis of Glaser-Eglinton-Hay coupling precursors **45** and optically active aza-oxo-thia polyether macrocycles **46**/**47**.

The generalized strategy to execute the intramolecular Glaser-Eglinton-Hay macrocyclization-based synthesis of optically active aza-oxo-thia polyether macrocycles from amino alcohols is shown in Scheme 23. At first, several bis aldehydes having the generalized structure **41** were prepared from the corresponding 2-hydroxy benzaldehydes and a variety of linkers as discussed in Chapter 1 and 2. Next, the treatment of *R* or *S* amino alcohol **42** with bis aldehydes **41**, followed by the addition of $NaBH_4$ afforded the corresponding bis alcohol precursors **43**. Then,

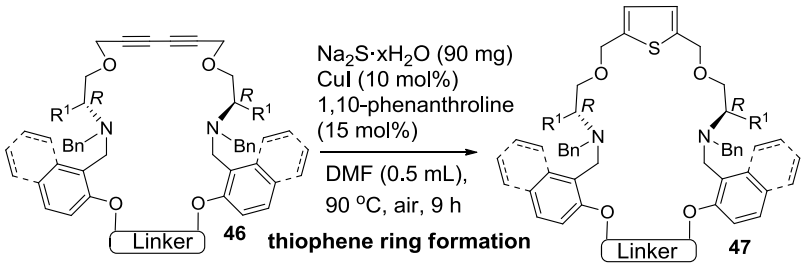
the *N*-benzylation followed by *O*-propargylation of the amino alcohol moieties of bis alcohol precursors **43** were carried out. These reaction sequences afforded the corresponding optically active Glaser-Eglinton-Hay coupling precursors **45** having two terminal alkyne units, comprising different aliphatic, polyether and aromatic linkers (Schemes 24).

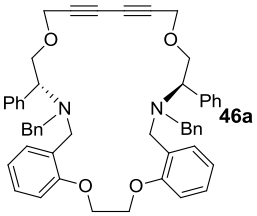
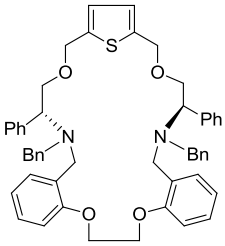
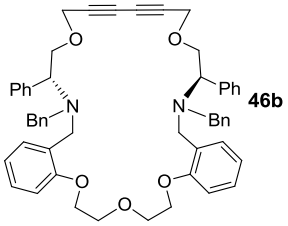
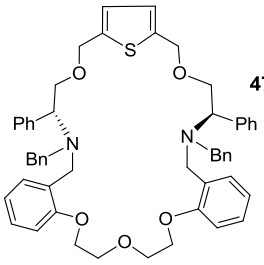
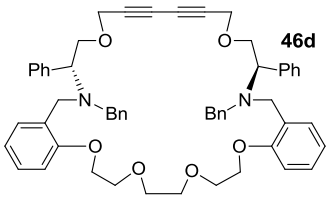
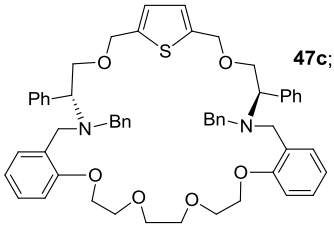
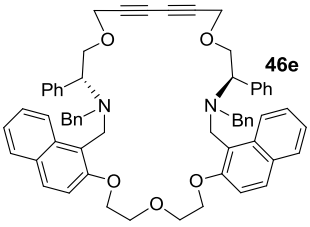
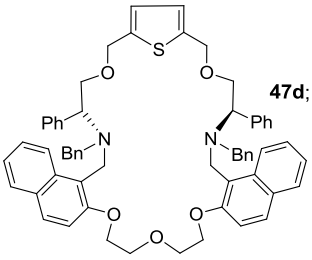
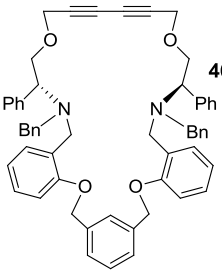
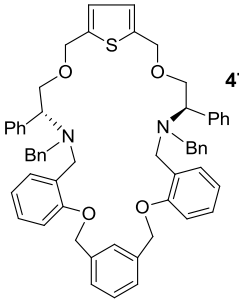


Scheme 24. Assembling of the (*R*,*R*) optically active precursors **43a-f**, **44a-f** and **45a-f**.



Scheme 25. Synthesis of optically active aza-oxo macrocycles **46a-f** *via* the Glaser-Eglinton-Hay-type macrocyclization.



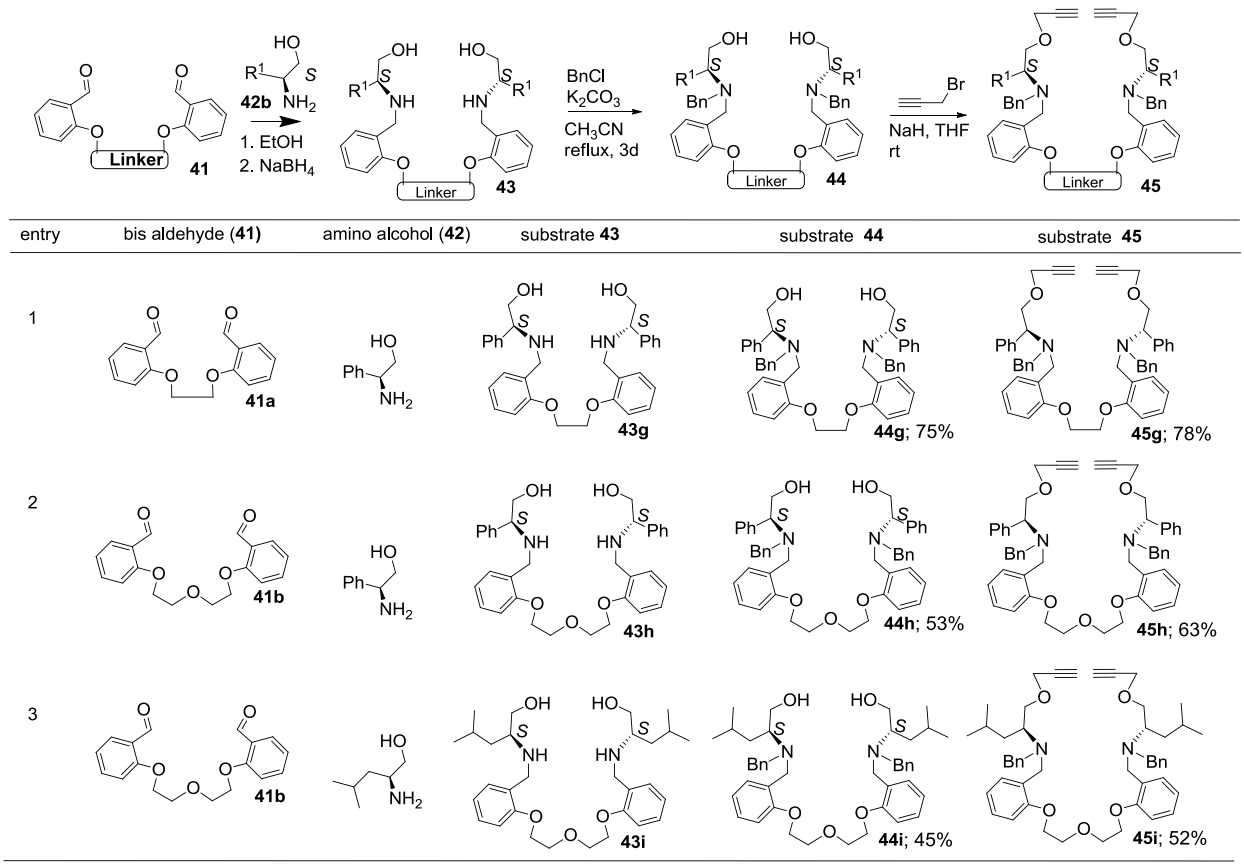
entry	aza-oxo macrocycle **46** (0.1 mmol)	aza-oxo-thia macrocycle **47**; yield (%)
1	 **46a**	 **47a**; 42
2	 **46b**	 **47b**; 62
3	 **46d**	 **47c**; 43
4	 **46e**	 **47d**; 58
5	 **46f**	 **47e**; 50

Scheme 26. Synthesis of optically active thiophene ring-installed, aza-oxa-thia macrocycles **47a-e**.

Then, investigations were carried out on the intramolecular sp-sp carbon-carbon bond forming Glaser-Eglinton-Hay-type macrocyclization by using the assembled optically active Glaser-Eglinton-Hay coupling precursors **45** (generalized structure) possessing two terminal alkyne units. Initially, the Glaser-Eglinton-Hay macrocyclization reactions were attempted using the optically active Glaser-Eglinton-Hay coupling precursors **45a-f**, which were derived from the corresponding *R*-amino alcohols (Scheme 24). The reaction of the optically active Glaser-Eglinton-Hay coupling precursor **45a** in the presence of $Cu(OAc)_2.H_2O$ in DMSO at 110 ^oC under aerobic condition afforded the optically active aza-oxo polyether macrocycle **46a** containing a 1,3-diyne unit in 58% yield (Scheme 25). Next, to elaborate the substrate scope, various optically active Glaser-Eglinton-Hay coupling precursors **45b-f**, which were prepared using various polyether unit-based linkers, were subjected to the intramolecular coupling. Accordingly, the Cu-promoted Glaser-Eglinton-Hay macrocyclization of the substrates **45b-f** gave the optically active aza-oxo polyether macrocycles **46b-f** in 38-62% yields, respectively (Scheme 25).

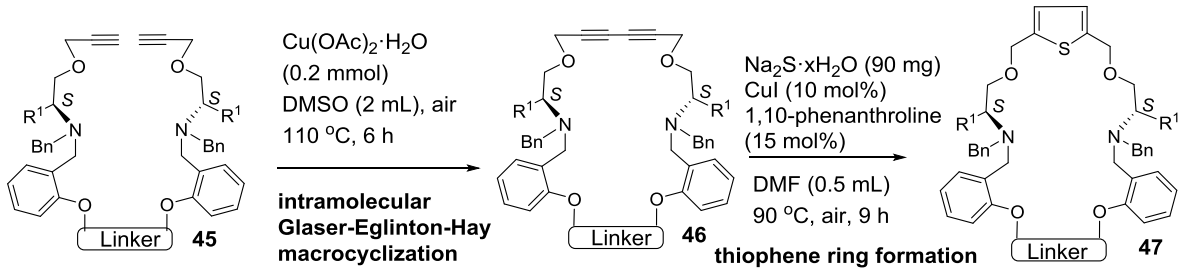
Then, it was envisaged to assemble optically active aza-oxa-thia polyether macrocycles from **46a,b,d-f** by converting the 1,3-diyne unit of aza-oxo polyether macrocycles **46a,b,d-f** into a thiophene ring.[17c-e] In this regard, initially the macrocycle **46a** was treated with $Na_2S.xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 ^oC, which gave the thiophene ring-installed, optically active aza-oxa-thia (heterotopic-type) polyether macrocycle **47a** in 42% yield (Scheme 25). Similarly, the various other macrocycles **46b,d-f** possessing the 1,3-diyne unit were treated with $Na_2S.xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 ^oC to afford the corresponding thiophene ring-installed, optically active aza-oxa-thia (heterotopic-type) polyether macrocycles **47b-e** having different polyether linkers in 43-58 % yields (Scheme 26).

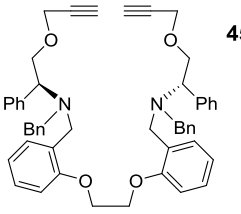
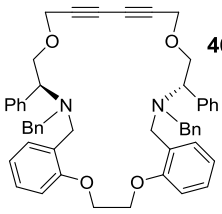
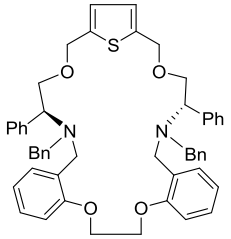
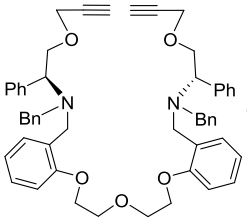
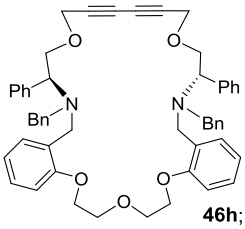
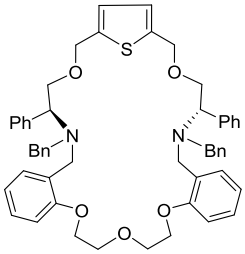
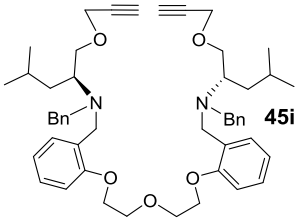
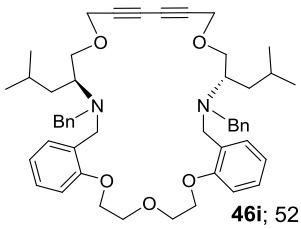
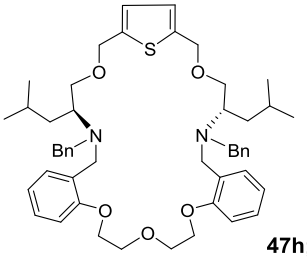
Next, to further elaborate the generality of this protocol, Glaser-Eglinton-Hay macrocyclization reactions were attempted using of the optically active Glaser-Eglinton-Hay coupling precursors **45g-i**, which were derived from the corresponding *S*-amino alcohols (Scheme 27).



Scheme 27. Assembling of the (*S*,*S*)- optically active precursors **43g-i**, **44g-i** and **45g-i**.

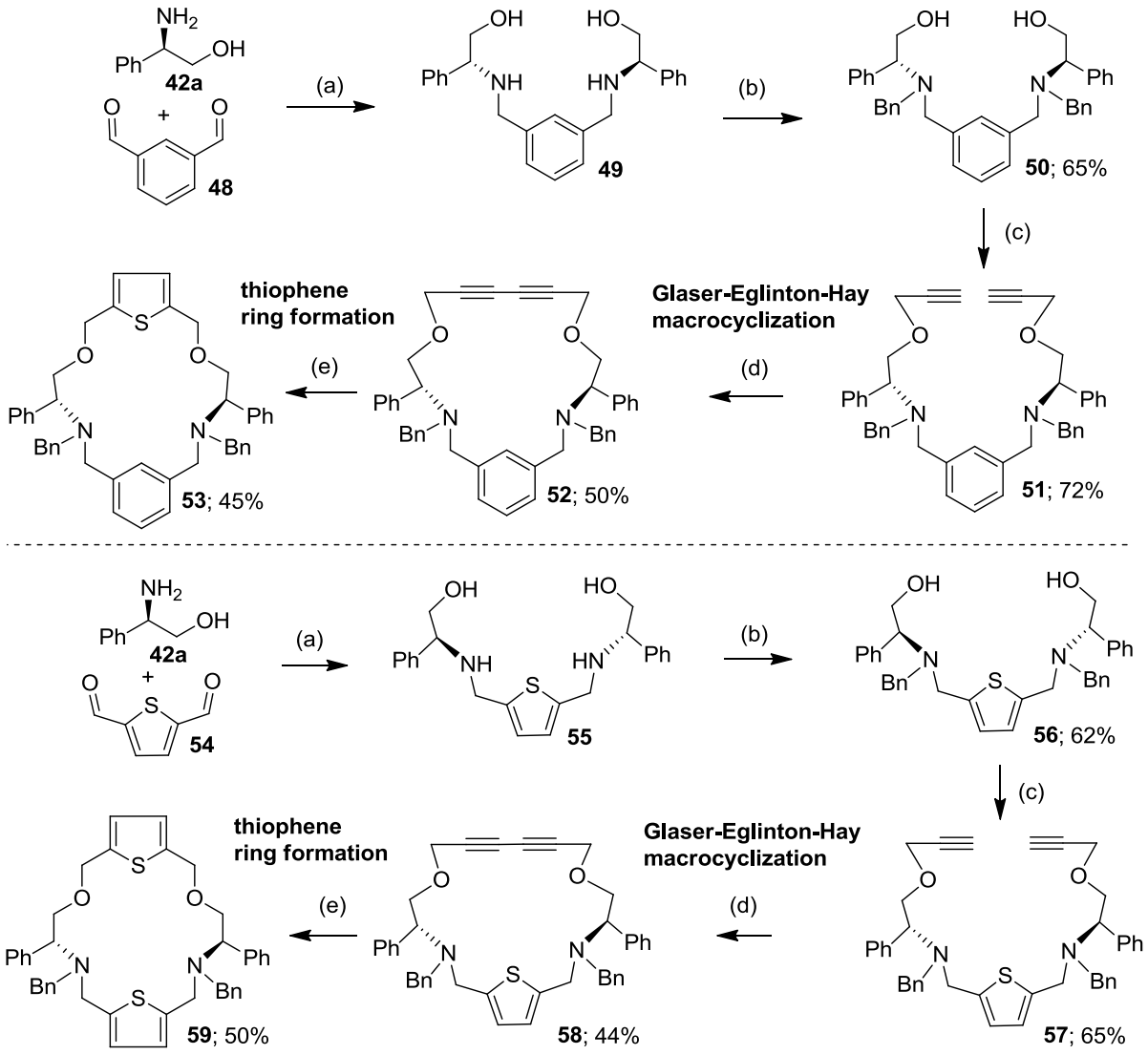
Accordingly, the optically active Glaser-Eglinton-Hay coupling precursors **45g-i** were subjected to the intramolecular coupling reaction to afford the corresponding the optically active aza-oxo polyether macrocycles **46g-i** in 45-53% yields (Scheme 28). Subsequently, it was envisaged to assemble optically active aza-oxa-thia polyether macrocycles **47f-h** from **46g-i** by converting the 1,3-diyne unit of aza-oxo polyether macrocycles **46g-i** into a thiophene ring.[17c-e]. Accordingly, the reaction macrocycles of **46g-i** possessing the 1,3-diyne unit were treated with $Na_2S.xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 ^oC to give the thiophene ring-installed, optically active aza-oxa-thia (heterotopic-type) polyether macrocycles **47f-h** in 52-65 % yields, respectively (Scheme 28).



entry	substrate **45** (0.2 mmol)	aza-oxo macrocycle **46**; yield (%)	aza-oxo-thia macrocycle **47**; yield (%)
1	 **45g**	 **46g**; 53	 **47f**; 62
2	 **45h**	 **46h**; 45	 **47g**; 65
3	 **45i**	 **46i**; 52	 **47h**; 52

Scheme 28. Synthesis of optically active aza-oxo macrocycles **46g-i** *via* the Glaser-Eglinton-Hay macrocyclization and thiophene ring-installed, aza-oxa-thia macrocycles **47f-h**.

Subsequently, it was envisaged to apply the above described synthetic methodology for the synthesis of optically active heterotopic aza-oxa-thia polyether macrocycles **53** and **59** that are analogous to classical 18-C-5 and 18-C-6 systems (Scheme 29). At first, the required starting materials were assembled to synthesize the macrocycles **53** and **59**. Accordingly, *R* amino alcohol **42a** was heated with isophthalaldehyde **48** or thiophene-2,5-dicarbaldehyde **54** in refluxing ethanol for 12 h. Then to the reaction mixture was added $NaBH_4$ and the reaction mixture was heated for 12 h to afford the corresponding bis alcohol precursors **49** and **55**.



(a) **48**/**54** (3 mmol), **42a** (2 equiv.), EtOH (10 mL), reflux, 12 h, then, $NaBH_4$ (4 equiv) reflux 12 h. (b) **49**/**55** (crude from previous step), BnCl (4 equiv), K_2CO_3 (4 equiv), CH_3CN (10 mL), reflux, 72 h (c) **50**/**56** (1 mmol), NaH (4 equiv), propargyl bromide (5 equiv), THF (3 mL), 20 h, rt. (d) **51**/**57** (0.25 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol), DMSO (2 mL), 110 ^oC, air, 6 h. (e) **52**/**58** (0.1 mmol) $Na_2S \cdot xH_2O$ (90 mg), CuI (10 mol%), 1,10-phenanthroline (15 mol%), DMF (0.5 mL), 90 ^oC, air, 9 h.

Scheme 29. Synthesis of aza-oxo-thia macrocycles **53** and **59**.

Then, the *N*-benzylation followed by the *O*-propargylation of the amino alcohol moieties of **49** and **55** afforded optically active Glaser-Eglinton-Hay coupling precursors **51** and **57** possessing

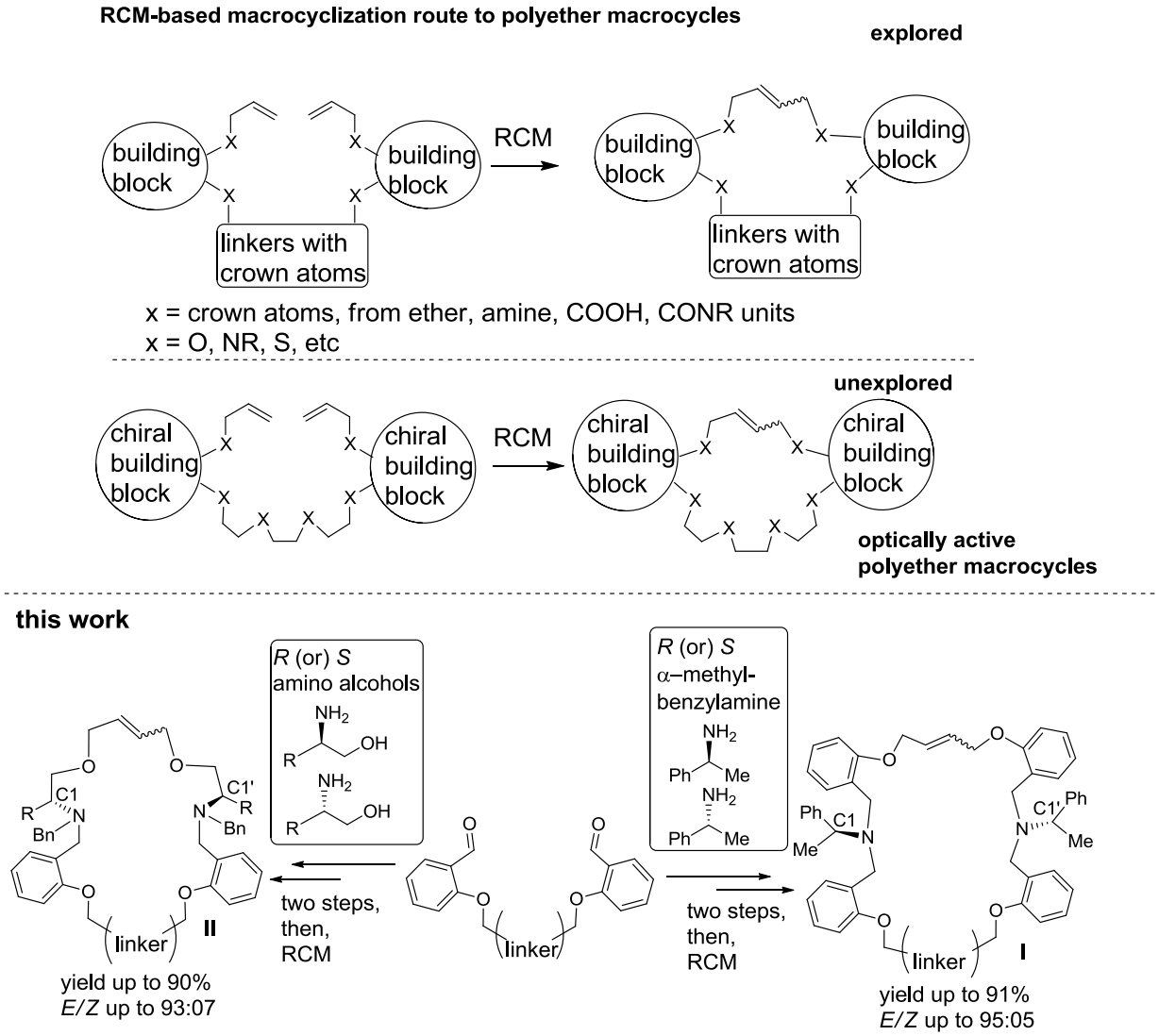
two terminal alkyne units (Scheme 29). Next, the optically active Glaser-Eglinton-Hay coupling precursors **51** and **57** were subjected to the Cu-promoted Glaser-Eglinton-Hay macrocyclization reaction conditions to afford the corresponding optically active aza-oxo polyether macrocycles **52** and **58** possessing the 1,3-diyne unit in 44-50% yields (Scheme 29). Subsequently, aza-oxo polyether macrocycles **52** and **58** possessing the 1,3-diyne unit were treated with $Na_2S.xH_2O$ in the presence of catalytic amounts of CuI and 1,10-phenanthroline in DMF at 90 ^oC to afford the corresponding thiophene ring-installed, optically active aza-oxa-thia polyether macrocycles **53** and **59** in 45 and 50% yields, respectively (Scheme 29). It is to be noted that the conversion of 1,3-diyne unit of aza-oxo polyether macrocycles **52** and **58** into a thiophene ring has led to the assembling of 18-atom ring-based optically active aza-oxa-thia polyether macrocycles **53** and **59** that are analogous to classical 18-C-5 and 18-C-6 systems (Scheme 29).

Chapter 3b: Exploitation of ring closing metathesis-based strategy for the synthesis of new classes of optically active aza-oxo polyether macrocycles from chiral amino alcohol and α-methylbenzylamine building blocks.

The general chemical transformations used to accomplish the polyether macrocycle synthesis are, the standard peptide coupling, Yamaguchi lactonization, ring closing metathesis, Williamson ether synthesis, Glaser-Eglinton-Hay, RCM and some other methods.[1-9] while various periphery modified oxo and aza-oxo polyether macrocycles and a variety of mechanically interlocked macrocyclic compounds (e.g., catenanes and rotaxanes, etc) were synthesized using different methods; the olefin unit of polyether macrocycles constructed *via* RCM-based macrocyclization technique was found to be very useful for performing the periphery modifications in the polyether macrocycles.[18] Chapter 1 of this thesis also described the RCM-based macrocyclization route to new classes of polyether macrocycles starting from simple starting materials.

While the RCM technique was extensively used for synthesizing numerous racemic and optically active small, medium and large-sized cyclic olefins and natural products;[19] however, only some handful reports are available in the literature that deal on the synthesis of macrocyclic polyethers involving the ring closing metathesis strategy. Furthermore, a literature survey revealed that the

synthesis of optically active polyether macrocycles was not explored using the ring closing metathesis strategy. Especially, there exist no reports dealing on the synthesis of optically active aza-oxo polyethers *via* the RCM strategy by using amino alcohols and α-methylbenzylamine as chiral building blocks (Scheme 30).



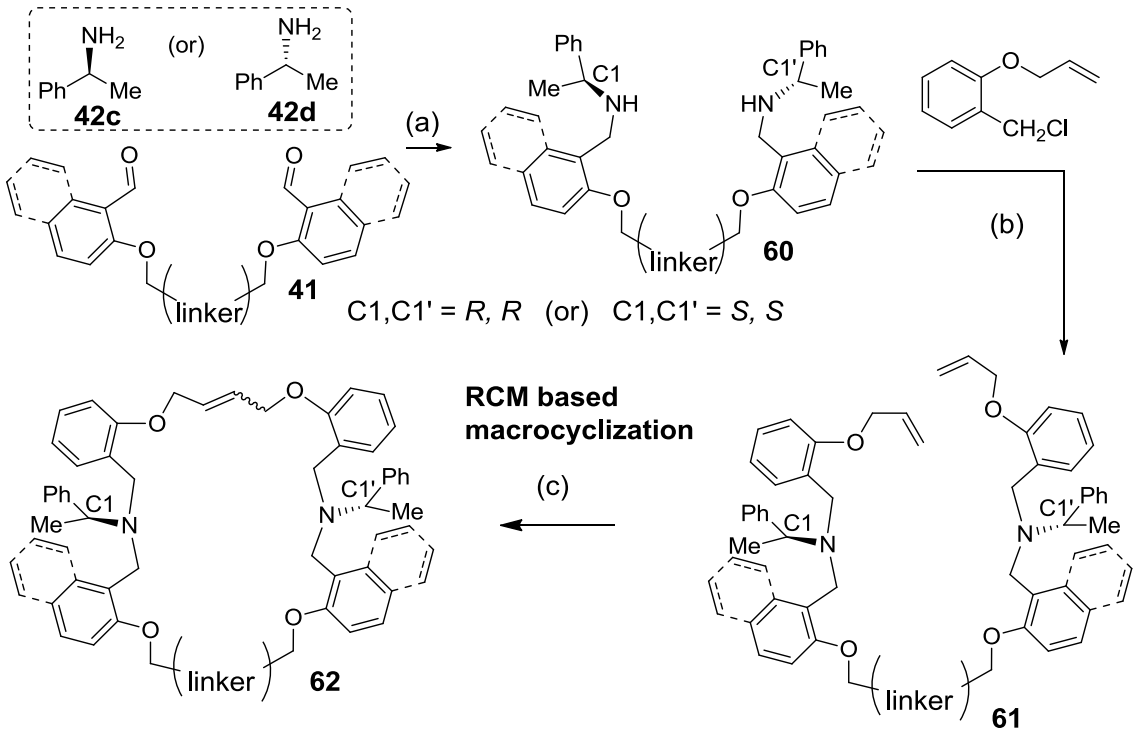
Scheme 30. Synthesis of aza-oxo polyether macrocycles *via* the ring closing metathesis (RCM) technique.

Given the importance of optically active crown ether/polyether macrocycles in organic synthesis and research area pertaining to analytical chemistry and chromatography, the synthesis of a

library of new classes of optically active crown ether/polyether macrocyclic systems *via* the RCM strategy will be very useful.

Accordingly, given the efficiency and usefulness of the RCM strategy in organic synthesis[18,19] and in line with the objective of this thesis, a part of this thesis report the investigations on the synthesis of optically active aza-oxo polyether macrocycles *via* the RCM strategy by using amino alcohols and α-methylbenzylamine as chiral building blocks (Scheme 30).

Result and discussion



Reaction conditions: (a) EtOH, 80 ^{o}C, 12 h, then, $NaBH_4$, 80 ^{o}C, 12 h. (b) K_2CO_3, CH_3CN, 80 ^{o}C, 3 d. (c) Grubbs's catalyst I, DCM, reflux, 24 h.

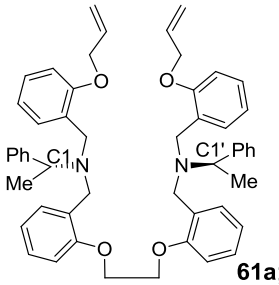
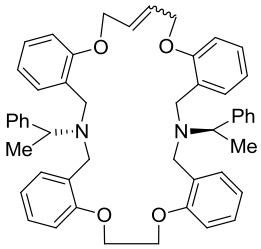
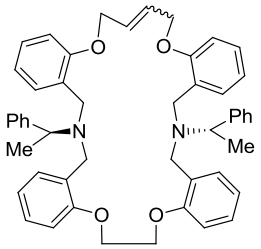
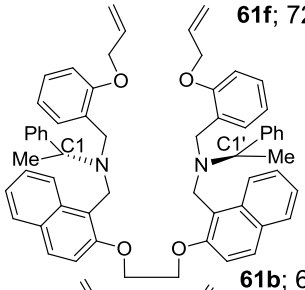
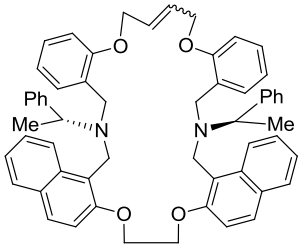
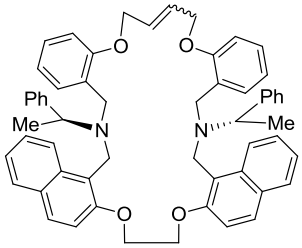
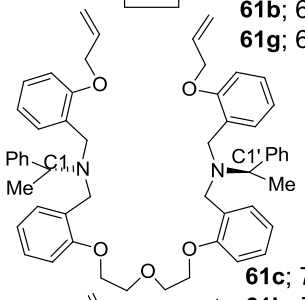
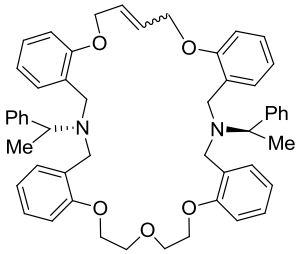
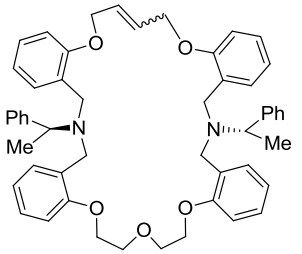
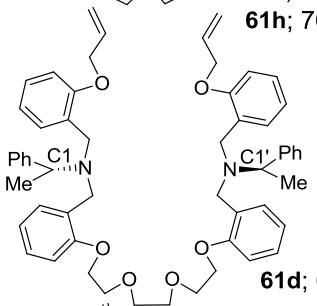
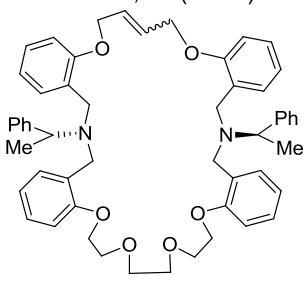
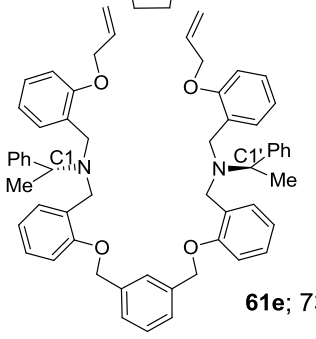
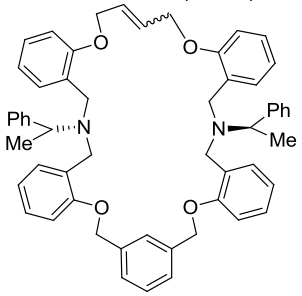
Scheme 31. Generalized scheme describing the synthesis of RCM precursors **61** and aza-oxo polyether macrocycles **62**.

To execute the synthesis of optically active aza-oxo polyether macrocycles *via* RCM method; at first various optically active RCM precursors were assembled using different linkers and *R* or *S*

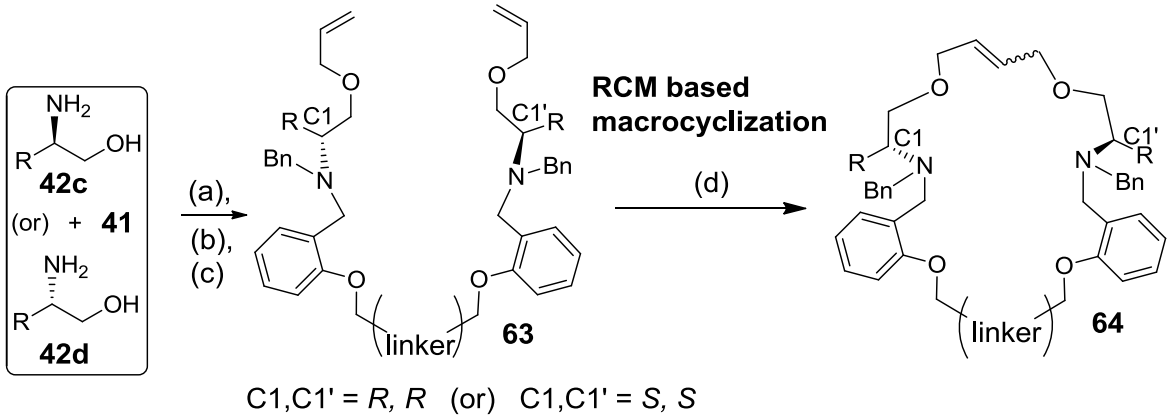
α-methylbenzylamines and Scheme 31 describes the generalized strategy used to assemble the require starting materials. Initially, various bis aldehydes **41** were prepared from the corresponding 2-hydroxyl benzaldehydes and different linkers by using the standard synthetic procedures (as described in Chapter 1). Next, the treatment of *R* and *S* α-methylbenzylamines **42c/42d** with **41** followed by the addition of $NaBH_4$ afforded the corresponding optically active bis amines **60**. Then, the *N*-benzylation of **60** with 1-(allyloxy)-2-(chloromethyl)benzene afforded the corresponding optically active RCM precursors **61** encompassing various aliphatic, polyether and aromatic ring-based linkers (Scheme 31). Then, RCM reaction was attempted by using the assembled optically active RCM precursors **61** (Scheme 31) using Grubbs's I generation catalyst to afford the optically active aza-oxo polyether macrocyclic olefins **62** (Scheme 31).

To begin with the synthesis of optically active aza-oxo polyether macrocycles *via* the RCM-based macrocyclization, initially, the RCM-based macrocyclization reactions were attempted using the RCM precursors **61a-e** which were prepared from (*R*)-α-methylbenzylamine. Accordingly, the reaction of the RCM precursor **61a** was performed in the presence of 5 mol% of the Grubbs's I generation catalyst, which gave the optically active aza-oxo polyether macrocyclic olefin **62a** in 80% yield (*E/Z* = 90:10, Table 1). Then, the RCM reaction of the precursor **61b** was performed to afford the optically active aza-oxo polyether macrocyclic olefin **62b** in 91% yield (*E/Z* = 80:20, Table 1). Next, the RCM precursors **61c-e** were subjected to the RCM reaction in the presence of the Grubbs's I generation catalyst. These reactions gave the corresponding optically active aza-oxo polyether macrocyclic olefins **62c-e** in 75-82% yields (*E/Z* ratio up to 87:13, Table 1). Subsequently, the RCM-based macrocyclization reactions were attempted using the RCM precursors **61f-h**, which were prepared from (*S*)-α-methylbenzylamine. Accordingly, the RCM-based macrocyclization of the RCM precursors **61f-h** in the presence of the Grubbs's I generation catalyst afforded the corresponding optically active aza-oxo polyether macrocyclic olefins **62f-h** in 72-82% yields (*E/Z* ratio up to 95:05, Table 1).

Table 1. Synthesis of optically active aza-oxo polyether macrocycles **62a-h** *via* the RCM-based macrocyclization of **61a-h**.

substrate **61a-e**: C1,C1' = *R, R* **61f-h**: C1,C1' = *S, S*	macrocycle **62a-e** from **61a-e**: yield (%, *E*/*Z*)	macrocycle **62f-h** from **61f-h**: yield (%, *E*/*Z*)
 **61a**; 78%/ **61f**; 72%	 **62a**; 80 (90:10)	 **62f**; 72 (95:05)
 **61b**; 68%/ **61g**; 65%	 **62b**; 91 (80:20)	 **62g**; 78 (75:25)
 **61c**; 78%/ **61h**; 76%	 **62c**; 78 (80:20)	 **62h**; 82 (75:25)
 **61d**; 69%	 **62d**; 75 (78:22)	—
 **61e**; 73%	 **62e**; 82 (87:13)	—

Having done the synthesis of optically active aza-oxo polyether macrocycles **62a-h**, which were prepared from *R* and *S* α-methylbenzylamines; then, it was envisaged to increase the scope and generality of this method by using *R* and *S* amino alcohols as chiral building blocks. Accordingly, the required optically active RCM precursors **63a-g** (Scheme 32) were prepared. At first, several bis aldehydes having the generalized structure **41** as shown in Schemes 24 were prepared from the corresponding 2-hydroxy benzaldehydes and a variety of linkers as discussed in Chapter 1 and 2. Next, the treatment of *R* or *S* amino alcohol **42** with bis aldehydes **41**, followed by the addition of $NaBH_4$ afforded the corresponding bis alcohol precursors **43**. Then, the *N*-benzylation followed by *O*-allylation of the amino alcohol moieties of bis alcohol precursors **43** were carried out to afford the optically active RCM precursors **63a-g** encompassing various aliphatic, polyether and aromatic linkers (Scheme 32).

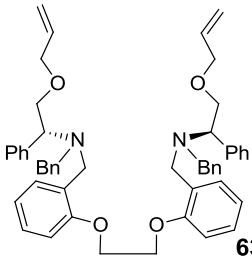
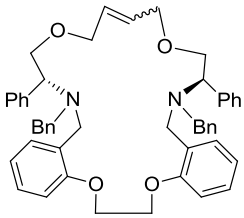
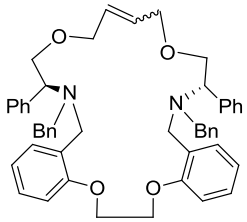
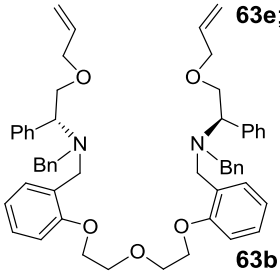
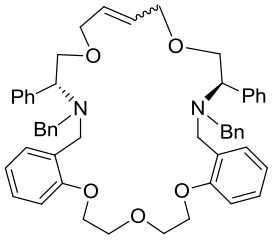
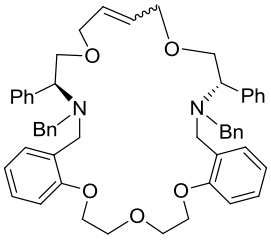
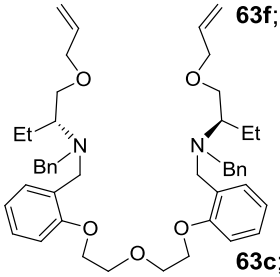
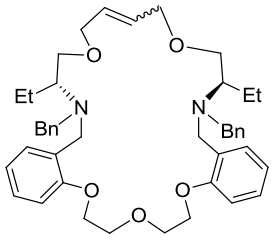
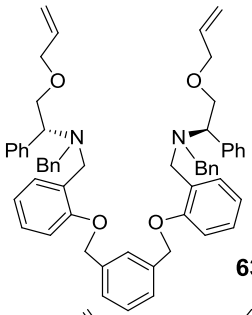
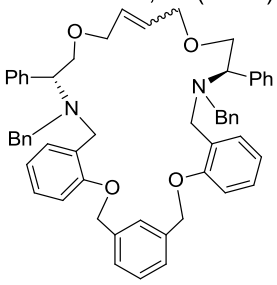
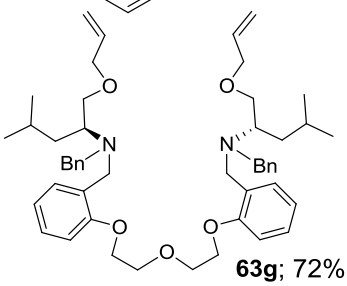
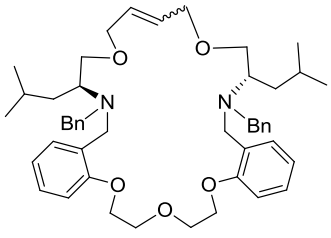


Reaction conditions: (a) EtOH, 80 ^{o}C, 12 h, then, $NaBH_4$ (b) BnBr, K_2CO_3, CH_3CN, 80 ^{o}C, 3 d. (c) allyl bromide, NaH, THF, rt. (d) Grubbs's catalyst I, DCM, reflux, 24 h.

Scheme 32. Generalized scheme comprising assembling of RCM precursors **63** and aza-oxo polyether macrocycles **64** using chiral amino alcohol building blocks.

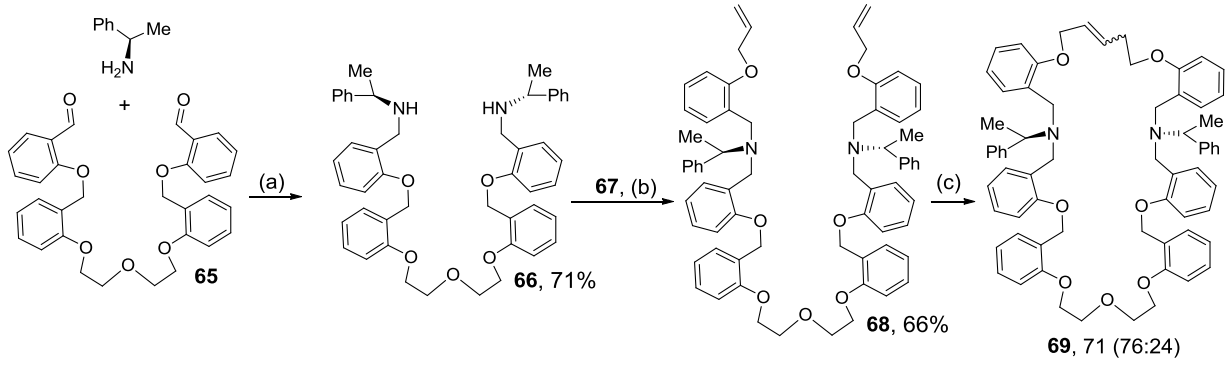
After assembling the optically active RCM precursors **63a-g**, these compound were subjected to the RCM-based macrocyclization. At first, the RCM reactions were attempted using the optically active RCM precursors **63a**,**b**,**d**, which were prepared from (*R*)-2-amino-2-phenylethanol and different linkers (Table 2). Accordingly, the RCM reactions of **63a**,**b**,**d** in the presence of the Grubbs's I generation catalyst gave the corresponding optically active aza-oxo polyether macrocyclic olefins **64a**,**b**,**d** in 80-90% yields (*E/Z* ratio up to 93:07, Table 2).

Table 2. Assembling of RCM precursors **63a-g** from α-amino alcohols and synthesis of optically active aza-oxo polyether macrocycles **64a-g** *via* the RCM-based macrocyclization.

substrate **63a-d**: C1,C1' = *R, R* **63e-g**: C1,C1' = *S, S*	macrocycle **64a-d** from **63a-d**: yield (%, *E*/*Z*)	macrocycle **64e-g** from **63e-g**: yield (%, *E*/*Z*)
 **63a**; 86%/ **63e**; 80%	 **64a**; 90 (93:07)	 **64e**; 72 (82:18)
 **63b**; 76%/ **63f**; 78%	 **64b**; 80 (80:20)	 **64f**; 74 (78:22)
 **63c**; 78%	 **64c**; 85 (81:19)	—
 **63d**; 75%	 **64d**; 82 (85:15)	—
 **63g**; 72%	—	 **64g**; 88 (80:20)

Similarly, the RCM reaction of the optically active RCM precursor **63c**, which was prepared from (*R*)-2-aminobutan-1-ol, afforded the optically active aza-oxo polyether macrocyclic olefin **64c** in 85% yield (*E/Z* = 81:19, Table 2). Having done the synthesis of aza-oxo polyether macrocycles **64a-d** based on the (*R*)-α-amino alcohols; subsequently, the RCM reactions were attempted using the optically active RCM precursors **63e-g** which were prepared from (*S*)-*α*-amino alcohols and different linkers. Accordingly, the RCM reactions of **63e-g** in the presence of the Grubbs's I generation catalyst afforded the corresponding optically active aza-oxo polyether macrocyclic olefins **64e-g** in 72-88% yields (*E/Z* ratio up to 82:18, Table 2).

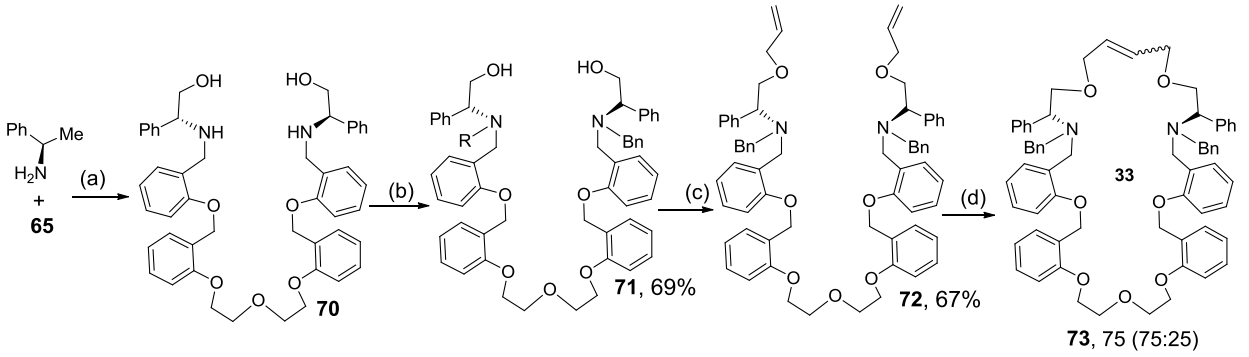
Finally it was envisaged to further elaborate the generality of this method by synthesizing large cavity-based, optically active polyether macrocycles **69** and **73**. In this regard, at first the required optically active RCM precursors **68** and **72** were assembled (Schemes 33 and 34). The bis aldehyde **65** was synthesized by using the same synthetic procedures as discussed in chapter 1.[18f,g] Next, the reductive amination of (*R*)-α-methylbenzylamine (**42c**) with bis aldehyde **65** gave the optically active bis amine **66** (Scheme 33). Further, the *N*-benzylation of **66** with 1-(allyloxy)-2-(chloromethyl)benzene (**67**) gave the optically active RCM precursor **68** (Scheme 33). Then, the optically active RCM precursor **68** was subjected to RCM reaction conditions using the Grubbs's I generation catalyst. This reaction successfully afforded the optically active aza-oxo polyether macrocycle **69** in 71% yield (*E/Z* = 76:24, Scheme 33).



Reaction conditions: (a) EtOH, 80 ^{o}C, 12 h, then, $NaBH_4$, 80 ^{o}C, 12 h. (b) 1-(allyloxy)-2-(chloromethyl)benzene (**67**), K_2CO_3, CH_3CN, 80 ^{o}C, 3 d. (c) Grubbs's catalyst I, DCM, reflux, 20 h.

Scheme 33. Synthesis of optically active aza-oxo polyether macrocycles **69** *via* RCM reaction

Subsequently, it was envisaged to prepare an amino alcohol building block-based optically active polyether macrocycle **73**. In this regard, at first the RCM precursor **72** was assembled from (*R*)-2-amino-2-phenylethanol **42a** and **65** involving the reductive amination, *N*-benzylation and *O*-allylation steps as shown in Scheme 34. Then, the optically active RCM precursor **72** was subjected to RCM reaction conditions using the Grubbs's I generation catalyst. This reaction successfully afforded the optically active aza-oxo polyether macrocycle **73** in 75% yield (*E/Z* = 75:25, Scheme 34).



Reaction conditions: (a) EtOH, 80 ^{o}C, 12 h, then, $NaBH_4$ (b) BnCl, K_2CO_3, CH_3CN, 80 ^{o}C, 3 d. (c) allyl bromide, NaH, THF, rt. (d) Grubbs's catalyst I, DCM, reflux, 24 h.

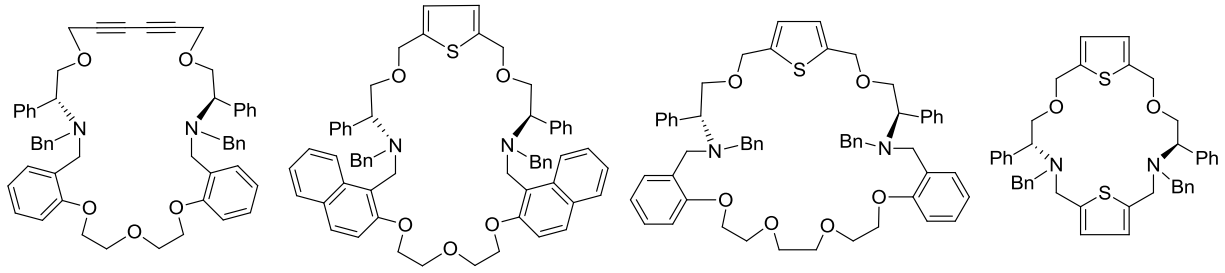
Scheme 34. Synthesis of optically active aza-oxo polyether macrocycles **73**.

Conclusions

In summary, the Chapter 3a reported the investigations on the synthesis of optically active aza-oxo polyether macrocycles having 1,3-diyne unit from amino alcohol building blocks and suitable linkers by exploiting the intramolecular Glaser-Eglinton-Hay macrocyclization as the key step under simple macrocyclization reaction conditions.

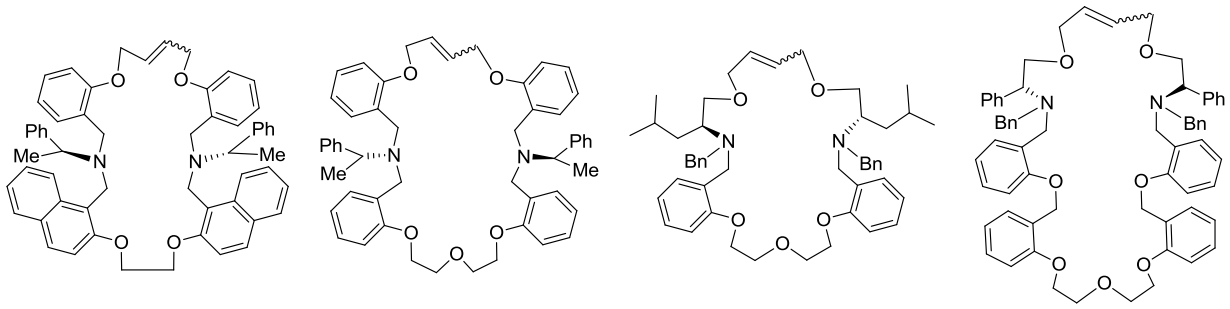
Then, the Chapter 3a also reported the conversion of 1,3-diyne unit of aza-oxo polyether macrocycles obtained from Glaser-Eglinton-Hay reaction into a thiophene ring has led to the assembling of optically active aza-oxa-thia heterotopic-type polyether macrocycles and some examples similar to classical 18-C-6 and 18-C-5 systems.

Synthesis of aza-oxa-thia heterotopic-type polyether macrocycles *via* Glaser-Eglinton-Hay macrocyclization



Furthermore, the Chapter 3b reported the exploitation of ring closing metathesis (RCM) macrocyclization technique for the synthesis of new classes of optically active aza/oxo polyether macrocycles from optically active amino alcohol and α-methylbenzylamine building blocks.

Synthesis of aza-oxa heterotopic-type polyether macrocycles *via* ring closing metathesis (RCM) technique



Overall, given the importance of optically active crown ether/polyether macrocycles in organic synthesis and research area pertaining to analytical chemistry and chromatography, the synthesis of a library of new classes of optically active crown ether/polyether macrocyclic systems and periphery modified polyether macrocyclic systems will be highly useful. Furthermore, the synthesis of optically active polyether macrocycles *via* the intramolecular Glaser-Eglinton-Hay was not reported in the literature, the Chapter 3a revealed an easy way for synthesizing optically active aza-oxo polyether macrocycles having 1,3-diyne unit. Currently our laboratory is in the process of exploring the applications of the synthesized optically active crown ether-type polyether and aza-polyether macrocycles.

All the compounds included in the Chapters 3a and 3b of this thesis are characterized by various characterization techniques including ^{1}H and ^{13}C NMR, IR and HRMS. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

Experimental Section

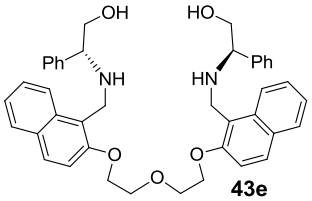
General. FT-IR spectra were recorded as thin films or KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively using TMS as an internal standard. Compounds were purified by column chromatography using silica gel (100-200 mesh) or neutral alumina. Reactions were carried out in anhydrous solvent and under a nitrogen atm, wherever necessary. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analysis was performed on silica gel/alumina plates and the components were visualized by observation under iodine. Isolated yields of products were reported and yields were not optimized.

Typical procedure for the synthesis of bis-aldehydes 41 (Procedure A). To a flame dried round-bottom flask was sequentially added the corresponding phenol derivative (12 mmol) dry DMF (20 mL) and anhydrous K_2CO_3 (20 mmol). The reaction mixture was stirred at 80 ^{o}C for 15 min. After 15 min, the temperature of the reaction bath was increased to 110 ^{o}C and the corresponding alkyl dibromide or alkyl dichloride (6-7 mmol) was added in one portion to the hot reaction mixture. The resulting reaction mixture was stirred at 110 ^{o}C for 12 h and after this period, the reaction mixture was allowed to attain the room temperature, which was then added to ice flakes (15-25 g). The resulting solid compound (*bis*-aldehyde) was filtered through a filtration funnel and used in the next step without further purification. In case, if the *bis*-aldehyde is liquid; then the reaction mixture (after the treatment with ice flakes/cold water) was extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, evaporated in *vacuo* to afford the corresponding crude residue, which was used as such (without further purification) in the next step.

Typical procedure for the synthesis of bis-alcohols 43 (Procedure B). To a round-bottom flask was sequentially added the corresponding *bis*-aldehyde derivative (**41**, 1 mmol), chiral amino alcohol (2 equiv) in EtOH (5-10 mL). The reaction mixture was refluxed for 12 h and after this period, the reaction mixture was allowed to attain the room temperature and in the same reaction mixture was added $NaBH_4$ (4 equiv) portion wise at room temperature. Then, again the reaction mixture was refluxed for 12 h. After this period, the resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture was purified by Al_2O_3 gel

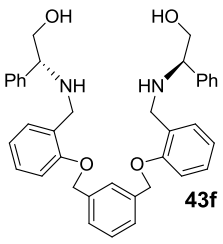
column chromatography (EtOAc/Hexanes) to give the corresponding product **43** (in some cases crude reaction mixture of bis-alcohols was used as such for the next step due to instability of the product (Note: After preparing the *bis*-alcohols **43,** they were immediately subjected to the next step and it was found the colour of **43** was changing into black and perhaps they were decomposing and in some cases, we could not isolate the corresponding *bis*-alcohols **43** in pure form (**43a**, **43b, 43c, 43d** and **43i**) and the corresponding crude reaction mixture was used as such in the next step).

Compound 43e. Following the general procedure, **43e** was obtained as a colourless liquid (262 mg, 40%); R_f (60% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3395, 2931, 1595, 1514 and 1266 cm^{-1}; $[\alpha]^{25}_D$ – 26.97 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (4 H, t, J = 9.1 Hz), 7.74 (2 H, d, J = 8.5 Hz), 7.45-7.33 (14 H, m), 7.26 (2 H, d, J = 9.0 Hz), 4.32-4.30 (4 H, m), 4.21 (2 H, d, J = 12.5 Hz), 4.14 (2 H, d, J = 12.5 Hz), 3.99-3.97 (4 H, m), 3.80 (2 H, dd, J_1 = 8.8 Hz, J_2 = 4 Hz), 3.59 (2 H, dd, J_1 = 7.9 Hz, J_2 = 4.1 Hz), 3.51-3.46 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.6, 140.8, 133.3, 129.4, 129.3, 128.5, 127.7, 127.5, 126.7, 123.6, 123.2, 121.4, 114.3, 70.3, 69.0, 66.7, 64.6, 41.4; HRMS (ESI): MH^+, found 657.3344. $C_{42}H_{45}N_2O_5$ requires 657.3328. Perhaps due to fast exchange, the NH and OH protons could not be precisely located in the ^1H NMR spectrum.



43e

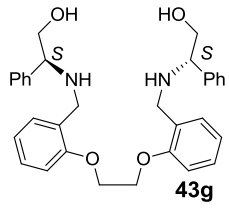
Compound 43f. Following the general procedure, **43f** was obtained as a colourless liquid (352 mg, 60%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3387, 2925, 1601, 1493 and 1237 cm^{-1}; $[\alpha]^{25}_D$ – 87.91 (c 0.04, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (1 H, s), 7.44-7.24 (15 H, m), 7.04 (2 H, dd, J_1 = 7.4 Hz, J_2 = 1.6 Hz), 6.98 (2 H, d, J = 8.2 Hz), 6.91 (2 H, td, J_1 = 7.3 Hz, J_2 = 0.8 Hz), 5.17 (2 H, d, J = 11.6 Hz), 5.11 (2 H, d, J = 11.6 Hz), 3.94 (2 H, d, J = 13.0 Hz), 3.77-3.51 (12 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 139.5, 137.5, 130.8, 128.9, 128.8, 128.6, 127.7, 127.6, 127.4, 127.2, 126.6, 120.8, 111.8, 70.1, 66.4, 63.2, 47.1; HRMS (ESI): MH^+, found 589.3045. $C_{38}H_{41}N_2O_4$ requires 589.3066. Perhaps due to fast exchange, either two NH or OH protons could not be precisely located in the ^1H NMR spectrum.



43f

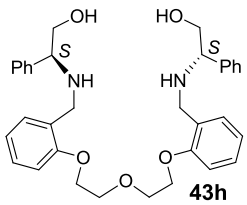
Compound 43g. Following the general procedure, **43g** was obtained as a colourless liquid (384 mg, 75%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3314, 2927, 1595, 1514 and 1247

cm^{-1}; $[\alpha]^{25}_D$ + 17.12 (c 0.07, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.43-7.32 (12 H, m), 7.01 (2 H, d, *J* = 8.1 Hz), 6.97-6.90 (4 H, m), 4.55 (2 H, d, *J* = 8.0 Hz), 4.43 (2 H, d, *J* = 8.0 Hz), 4.12 (2 H, d, *J* = 13.5 Hz), 3.83-3.70 (6 H, m), 3.39 (2 H, d, *J* = 13.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 139.1, 131.1, 129.0, 128.9, 128.0, 127.7, 126.7, 120.5, 110.5, 66.9, 66.0, 62.2, 46.0; HRMS (ESI): MNa^+, found 535.2557. $C_{32}H_{36}N_2NaO_4$ requires 535.2573. Perhaps due to fast exchange, two NH and OH protons could not be precisely located in the ^{1}H NMR spectrum.



43g

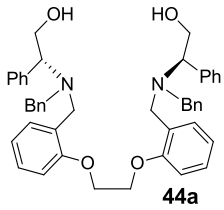
Compound 43h. Following the general procedure, **43h** was obtained as a colourless liquid (389 mg, 70%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3319, 3055, 1453, 1265 and 1160 cm^{-1}; $[\alpha]^{25}_D$ + 47.70 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.23 (12 H, m), 6.95 (2 H, dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz), 6.90-6.86 (4 H, m), 4.24-4.22 (4 H, m), 4.10-4.06 (4 H, m), 3.99 (2 H, d, *J* = 13.3 Hz), 3.71 (2 H, dd, J_1 = 9.2 Hz, J_2 = 4.1 Hz), 3.60 (2 H, dd, J_1 = 11.3 Hz, J_2 = 4.9 Hz), 3.54-3.46 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 140.1, 130.9, 128.6, 128.5, 127.8, 127.6, 127.4, 120.7, 111.3, 70.3, 68.1, 66.8, 63.2, 47.5; HRMS (ESI): MH^+, found 557.3026. $C_{34}H_{41}N_2O_5$ requires 557.3015. Perhaps due to fast exchange, two NH and OH protons could not be precisely located in the ^{1}H NMR spectrum.



43h

Typical procedure for the synthesis of *bis*-alcohols 44 (Procedure C). To a flame dried round-bottom flask was sequentially added the corresponding alcohol derivative (**43**, 1 mmol), benzyl chloride (4 equiv.) and anhydrous K_2CO_3 (3.5-4 equiv) in dry CH_3CN (6-10 mL). The reaction mixture was stirred at 80 ^oC for 48-72 h and after this period, the reaction mixture was allowed to attain the room temperature. The resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture was purified by Al_2O_3 gel column chromatography (EtOAc/Hexanes) to give the corresponding product **44**.

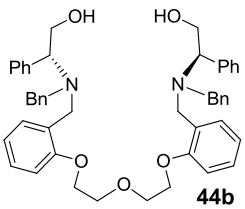
Compound 44a. Following the general procedure, **44a** was obtained as a colourless liquid (449 mg, 65%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3400, 2928, 1601, 1493 and 1265 cm^{-1}; $[\alpha]^{25}_D$ – 141.88 (c 0.10, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.32-7.21 (20 H, m), 7.09-7.07 (6 H, m), 6.97 (2 H, td, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 4.71 (2 H, t, *J* = 6.6 Hz), 4.54 (2 H, d, *J* = 6.9 Hz), 4.08 (2 H, d, *J* = 12.7 Hz), 3.93 (2 H, t, *J* = 10.8 Hz), 3.86-3.83 (4 H, m), 3.34 (2 H, dd,



44a

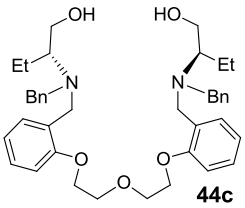
J_1 = 10 Hz, J_2 = 5.4 Hz), 3.16 (2 H, d, J = 13.6 Hz), 3.02 (2 H, d, J = 12.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.6, 139.4, 135.2, 131.8, 129.2, 129.0, 128.9, 128.3, 128.1, 127.7, 127.3, 127.0, 120.9, 112.7, 67.7, 62.9, 60.0, 53.6, 48.5; HRMS (ESI): MH^+, found 693.3674. $C_{46}H_{49}N_2O_4$ requires 693.3692. Perhaps due to fast exchange, two OH protons could not be precisely located in the ^{1}H NMR spectrum.

Compound 44b. Following the general procedure, **44b** was obtained as a colourless liquid (316 mg, 43%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3490, 3055, 1494, 1265, and 778 cm^{-1}; $[\alpha]^{25}_D$ – 220.41 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.43-7.19 (24 H, m), 6.98-6.93 (4 H, m), 4.36-4.19 (8 H, m), 4.05-3.94 (6 H, m), 3.85 (2 H, d, J = 13.8 Hz), 3.57 (2 H, dd, J_1 = 10.8 Hz, J_2 = 4.8 Hz), 3.20 (4 H, dd, J_1 = 13.8 Hz, J_2 = 4.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 139.6, 135.5, 132.0, 129.4, 129.0, 128.7, 128.4, 128.2, 127.8, 127.0, 126.9, 120.7, 112.0, 69.5, 67.9, 63.2, 60.4, 53.5, 48.8; HRMS (ESI): MH^+, found 737.3977. $C_{48}H_{53}N_2O_5$ requires 737.3954. Perhaps due to fast exchange, two OH protons could not be precisely located in the ^{1}H NMR spectrum.

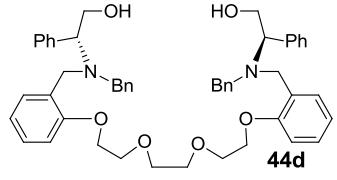


44b

Compound 44c. Following the general procedure, **44c** was obtained as a colourless liquid (289 mg, 42%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3433, 2931, 1601, 1494, 1453 and 1276 cm^{-1}; $[\alpha]^{25}_D$ – 75.89 (c 0.15, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.39-7.38 (4 H, m), 7.30-7.23 (10 H, m), 6.98-6.90 (4 H, m), 4.68 (2 H, s), 4.24-4.14 (4 H, m), 3.96-3.84 (8 H, m), 3.54-3.43 (8 H, m), 2.73-2.67 (2 H, m), 1.82-1.78 (2 H, m), 1.27-1.19 (2 H, m), 0.91 (6 H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.3, 141.2, 139.9, 131.7, 129.0, 128.6, 128.5, 128.3, 127.5, 127.4, 126.9, 126.9, 120.7, 111.8, 69.6, 67.6, 65.1, 61.0, 60.6, 53.4, 48.1, 17.8, 11.8; HRMS (ESI): MH^+, found 641.3933. $C_{40}H_{53}N_2O_5$ requires 641.3954.



44c

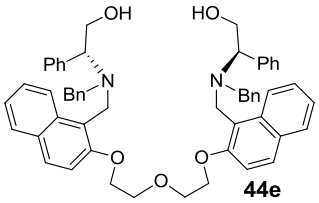


44d

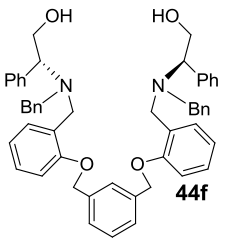
Compound 44d. Following the general procedure, **44d** was obtained as a colourless liquid (327 mg, 42%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3480, 2927, 1601, 1494 and 1288 cm^{-1}; $[\alpha]^{25}_D$ – 171.73 (c 0.11, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.48-7.26 (24 H, m), 6.99-6.97 (4 H, m), 4.35-4.20 (8 H, m), 4.00-3.84 (12 H, m), 3.64-3.62 (2

H, m), 3.27-3.23 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 139.7, 135.6, 131.8, 129.4, 129.0, 128.7, 128.4, 128.3, 127.8, 127.2, 127.0, 120.8, 112.0, 70.8, 69.6, 67.8, 63.3, 60.4, 53.7, 48.8; HRMS (ESI): MH^+, found 781.4235. $C_{50}H_{57}N_2O_6$ requires 781.4217. Perhaps due to fast exchange, two OH protons could not be precisely located in the ^{1}H NMR spectrum.

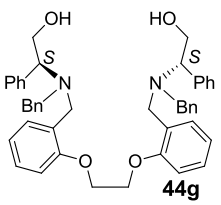
Compound 44e. Following the general procedure, **44e** was obtained as a colourless liquid (376 mg, 45%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3490, 3050, 1422, 1265 and 741 cm^{-1}; $[\alpha]^{25}_D$ – 186.47 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78-7.66 (6 H, m), 7.39-7.20 (26 H, m), 4.40-4.27 (9 H, m), 4.08-4.00 (6 H, m), 3.91 (2 H, dd, J_1 = 10.3 Hz, J_2 = 5.2 Hz), 3.73 (2 H, d, J = 13.3 Hz), 3.60 (2 H, dd, J_1 = 10.8 Hz, J_2 = 5.1 Hz), 3.26 (3 H, d, J = 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.2, 139.6, 136.5, 134.0, 129.7, 129.4, 129.4, 129.3, 128.5, 128.2, 128.1, 127.6, 127.0, 126.5, 123.6, 123.6, 119.7, 114.4, 70.0, 69.1, 63.1, 60.4, 53.8, 43.5; HRMS (ESI): MH^+, found 837.4246. $C_{56}H_{57}N_2O_5$ requires 837.4267.



Compound 44f. Following the general procedure, **44f** was obtained as a colourless liquid (422 mg, 55%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3488, 3029, 1601, 1493, and 1233 cm^{-1}; $[\alpha]^{25}_D$ –171.86 (c 0.10, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50-7.20 (28 H, m), 7.02-6.98 (4 H, m), 5.24 (4 H, s), 4.23 (2 H, t, J = 10.4 Hz), 4.07-3.93 (6 H, m), 3.60 (2 H, br s), 3.45 (2 H, d, J = 13.0 Hz), 3.19 (2 H, d, J = 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 139.4, 137.5, 135.4, 131.5, 129.4, 129.1, 129.0, 128.6, 128.5, 128.3, 127.9, 127.4, 127.1, 126.4, 121.1, 112.5, 70.2, 63.2, 60.5, 53.8, 48.4; HRMS (ESI): MH^+, found 769.4002. $C_{52}H_{53}N_2O_4$ requires 769.4005. Perhaps due to fast exchange, two OH protons could not be precisely located in the ^{1}H NMR spectrum.

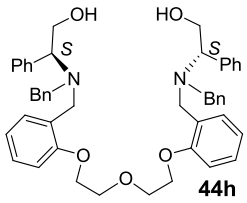


Compound 44g. Following the general procedure, **44g** was obtained as a colourless liquid (519 mg, 75%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3495, 2928, 1601, 1493 and 1265 cm^{-1}; $[\alpha]^{25}_D$ + 151.66 (c 0.11, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.41-7.22 (21 H m), 7.12-7.11 (5 H, m), 7.00 (2 H, t, J = 7.6 Hz), 4.74 (2 H, t, J = 7.6 Hz), 4.58 (2 H, dd, J_1 = 9.2 Hz, J_2 = 2.3 Hz), 4.12 (2 H, d, J = 12.4 Hz), 3.96 (2 H, t, J = 9.6 Hz), 3.88 (4 H, d, J = 12.9 Hz), 3.38-3.35 (2 H, m), 3.20 (2 H, d, J = 13.6 Hz), 3.03 (2 H, d, J = 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.7, 139.4,

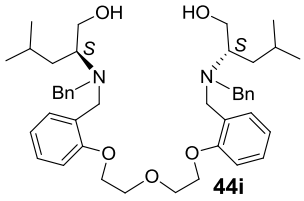


135.2, 131.9, 129.3, 129.1, 129.0, 128.4, 128.2, 127.8, 127.3, 127.0, 121.0, 112.8, 67.8, 62.9, 59.9, 53.6, 48.5; HRMS (ESI): MH^+, found 693.3705. $C_{46}H_{49}N_2O_4$ requires 693.3692. Perhaps due to fast exchange, two OH protons could not be precisely located in the ^1H NMR spectrum.

Compound 44h. Following the general procedure, **44h** was obtained as a colourless liquid (390 mg, 53%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3499, 3055, 1601, 1494, 1452, 1265 and 1134 cm^{-1}; $[\alpha]^{25}_D$ + 197.88 (c 0.0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.43-7.17 (24 H, m), 6.98-6.92 (4 H, m), 4.36-4.18 (8 H, m), 4.05-4.02 (4 H, m), 3.96-3.92 (2 H, m), 3.84 (2 H, d, J = 13.8 Hz), 3.56 (2 H, dd, J_1 = 6.1 Hz, J_2 = 4.8 Hz), 3.20 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.4, 139.6, 135.4, 132.0, 129.4, 129.0, 128.8, 128.4, 128.2, 127.8, 127.0, 126.9, 120.7, 112.0, 69.5, 67.9, 63.2, 60.3, 53.5, 48.8; HRMS (ESI): MH^+, found 737.3937. $C_{48}H_{53}N_2O_5$ requires 737.3954. Perhaps due to fast exchange, two OH protons could not be precisely located in the ^1H NMR spectrum.



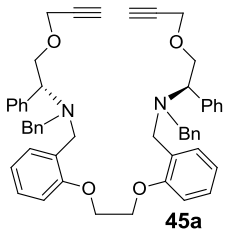
Compound 44i. Following the general procedure, **44i** was obtained as a colourless liquid (313 mg, 45%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3480, 2953, 1601, 1494, 1453 and 1247 cm^{-1}; $[\alpha]^{25}_D$ + 90.61 (c 0.14, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.29-7.17 (14 H, m), 6.96-6.90 (4 H, m), 4.28-4.23 (2 H, m), 4.18-4.13 (2 H, m), 3.96-3.92 (6 H, m), 3.82 (2 H, d, J = 13.5 Hz), 3.63 (2 H, br. s), 3.53-3.41 (8 H, m), 2.38 (2 H, br. s), 1.53-1.49 (4 H, m), 1.14 (2 H, t, J = 9.2 Hz), 0.91 (6 H, d, J = 6.0 Hz), 0.85 (6 H, d, J = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.3, 140.0, 131.7, 129.0, 128.6, 128.2, 127.4, 126.9, 111.8, 69.5, 67.5, 61.3, 57.2, 53.4, 48.0, 33.9, 25.4, 24.0, 22.2; HRMS (ESI): MH^+, found 697.4565. $C_{44}H_{61}N_2O_5$ requires 697.4580.



General procedure for the syntheses of compounds 45 (Procedure D). To a solution of corresponding *bis*-alcohol **44** (1 mmol) in dry THF (3 mL) was added NaH (4 mmol, 55-60 % suspension in mineral oil) at room temperature. The mixture was stirred at room temperature for 10 min and then propargyl bromide (5 mmol, 80 wt% in toluene) was added. The resulting mixture was stirred for 12 h at room temperature. After every 12 h another lot NaH (2 mmol) and propargyl bromide (2.5 mmol) were added until starting material completely finished according to the TLC, and after this period, few drops of EtOH were added and stirred for 10 min and then

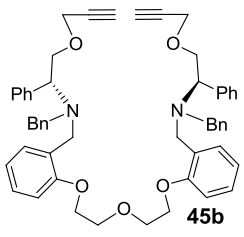
the resulting mixture was poured on to water (20 mL) and was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated and the resulting crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc : Hexanes = 20:80) to give the corresponding product **45**.

Compound 45a. Following the general procedure, **45a** was obtained as a colourless liquid (576 mg, 75%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 1600, 1452, 1421 and 1262 cm^{-1}; $[\alpha]^{25}_D$ – 94.08 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.62 (2 H, d, J = 7.5 Hz), 7.40-7.19 (22 H, m), 7.01 (2 H, t, J = 7.4 Hz), 6.90 (2 H, d, J = 8.2 Hz), 4.32 (4 H, s), 4.04-4.01 (8 H, m), 4.00 (2 H, d, J = 10.3 Hz), 3.78 (4 H, d, J = 14.3 Hz), 3.59 (2 H, d, J = 14.5 Hz), 3.46 (2 H, d, J = 14.0 Hz), 2.37 (2 H, t, J = 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.4, 138.7, 130.3, 128.7, 128.6, 128.6, 128.2, 128.0, 127.6, 127.1, 126.7, 121.0, 111.6, 79.9, 74.5, 69.5, 66.9, 61.1, 58.1, 54.6, 47.7; HRMS (ESI): MH^+, found 769.3987. $C_{52}H_{53}N_2O_4$ requires 769.4005.



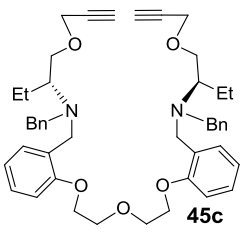
45a

Compound 45b. Following the general procedure, **45b** was obtained as a colourless liquid (665 mg, 82%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3289, 2873, 1600, 1493, 1452 and 1100 cm^{-1}; $[\alpha]^{25}_D$ – 68.23 (c 0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (2 H, d, J = 7.5 Hz), 7.45-7.20 (22 H, m), 7.03 (2 H, t, J = 7.4 Hz), 6.86 (2 H, d, J = 8.2 Hz), 4.14-4.06 (14 H, m), 3.92-3.83 (8 H, m), 3.67 (2 H, d, J = 14.7 Hz), 3.50 (2 H, d, J = 14.1 Hz), 2.44 (2 H, t, J = 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 140.4, 138.5, 130.0, 128.9, 128.7, 128.5, 128.2, 128.0, 127.6, 127.1, 126.8, 121.0, 111.6, 79.9, 74.6, 70.1, 69.6, 67.8, 61.2, 58.2, 54.7, 47.7; HRMS (ESI): MH^+, found 813.4283. $C_{54}H_{57}N_2O_5$ requires 813.4267.



45b

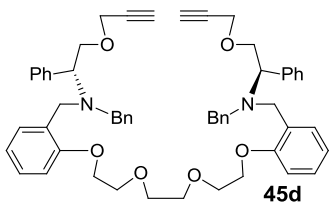
Compound 45c. Following the general procedure, **45c** was obtained as a colourless liquid (538 mg, 65%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 2987, 1601, 1422, and 1263 cm^{-1}; $[\alpha]^{25}_D$ + 62.49 (c 0.18, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.62 (2 H, d, J = 7.4 Hz), 7.43 (4 H, d, J = 7.6 Hz), 7.31 (4 H, t, J = 7.4 Hz), 7.25-7.18 (4 H, m), 7.00 (2 H, t, J = 7.4 Hz), 6.87 (2 H, d, J = 8.2 Hz), 4.18-4.14 (8 H, m), 3.98-3.96 (4 H, m), 3.87-3.71 (10 H, m), 3.61-3.57 (2 H, m), 2.77-2.74 (2 H, m), 2.45 (2 H, br. s), 1.66-1.50 (4 H, m), 0.95 (6 H, t, J = 7.4



45c

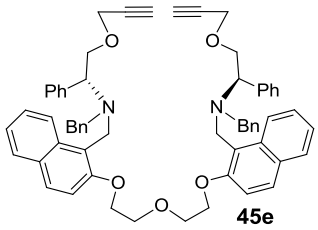
Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 140.9, 130.1, 129.0, 128.8, 128.1, 127.4, 126.6, 120.8, 111.5, 80.2, 74.2, 70.3, 70.1, 67.8, 58.8, 58.2, 54.6, 47.3, 21.9, 11.8; HRMS (ESI): MH^+, found 717.4247. $C_{46}H_{57}N_2O_5$ requires 717.4267.

Compound 45d. Following the general procedure, **45d** was obtained as a colourless liquid (470 mg, 55%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2874, 1600, 1493, 1452, 1243 and 1102 cm^{-1}; $[\alpha]^{25}_D$ – 50.82 (c 0.16, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (2 H, d, J = 7.4 Hz), 7.47-7.39 (12 H, m), 7.36-7.30 (6 H, m), 7.28-7.20 (4 H, m), 7.03 (2 H, t, J = 7.4 Hz), 6.87 (2 H, d, J = 8.0 Hz), 4.16-4.08 (14 H, m), 3.90-3.84 (8 H, m), 3.74 (4 H, s), 3.68 (2 H, d, J = 14.6 Hz), 3.52 (2 H, d, J = 14.7 Hz), 2.48 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 140.4, 138.6, 130.0, 128.9, 128.7, 128.5, 128.2, 128.1, 127.6, 127.1, 126.8, 120.9, 111.5, 79.9, 74.6, 71.0, 69.9, 69.7, 67.7, 61.2, 58.2, 54.8, 47.7; HRMS (ESI): MH^+, found 857.4520. $C_{56}H_{61}N_2O_6$ requires 857.4530.



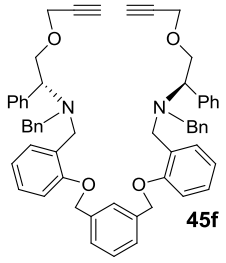
45d

Compound 45e. Following the general procedure, **45e** was obtained as a colourless liquid (729 mg, 80%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): 3054, 2987, 1422, 1267 and 896 cm^{-1}; $[\alpha]^{25}_D$ – 62.73 (c 0.10, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.00 (2 H, d, J = 8.2 Hz), 7.78-7.75 (4 H, m), 7.40-7.37 (12 H, m), 7.28-7.20 (14 H, m), 4.39 (2 H, d, J = 12.1 Hz), 4.31-4.25 (6 H, m), 4.21-4.07 (10 H, m), 3.97-3.96 (4 H, m), 3.68 (2 H, d, J = 13.7 Hz), 3.59 (2 H, d, J = 13.6 Hz), 2.49 (2 H, t, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.1, 140.5, 138.8, 134.2, 129.5, 129.4, 129.3, 129.3, 127.9, 127.9, 127.0, 126.7, 125.9, 125.5, 123.7, 120.3, 114.5, 80.0, 74.6, 70.4, 69.3, 68.2, 60.9, 58.2, 54.3, 44.1; HRMS (ESI): MH^+, found 913.4565. $C_{62}H_{61}N_2O_5$ requires 913.4580.



45e

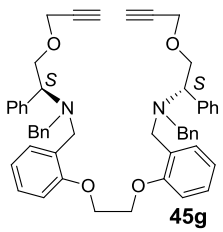
Compound 45f. Following the general procedure, **45f** was obtained as a colourless liquid (692 mg, 82%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3289, 2923, 1600, 1493, 1453 and 1234 cm^{-1}; $[\alpha]^{25}_D$ – 148.25 (c 0.0.5, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (2 H, d, J = 7.4 Hz), 7.43-7.18 (26 H, m), 7.02 (2 H, t, J = 7.4 Hz), 6.90 (2 H, d, J = 8.1 Hz), 5.08 (4 H, s), 4.09-4.02 (10 H, m), 3.86 (2 H, d, J = 8.6 Hz), 3.83 (2 H, d, J = 6 Hz), 3.70 (2 H, d, J = 14.6 Hz), 3.47 (2 H, d, J = 14.1 Hz), 2.38 (2 H, t, J = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7,



45f

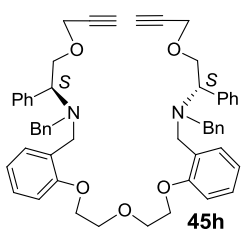
140.3, 138.4, 137.7, 130.1, 128.8, 128.7, 128.5, 128.2, 128.0, 127.6, 127.1, 126.7, 126.7, 125.9, 121.0, 111.7, 79.8, 74.5, 69.9, 69.6, 61.1, 58.1, 54.7, 47.7; HRMS (ESI): MH^+, found 845.4297 $C_{58}H_{57}N_2O_4$ requires 845.4318.

Compound 45g. Following the general procedure, **45g** was obtained as a colourless liquid (599 mg, 78%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3292, 3059, 1600, 1452 and 1100 cm^{-1}; $[\alpha]^{25}_D$ + 49.15 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.63 (2 H, d, J = 7.3 Hz), 7.42-7.21 (22 H, m), 7.04 (2 H, t, J = 7.3 Hz), 6.92 (2 H, d, J = 8.1 Hz), 4.34 (4 H, s), 4.06-4.01 (10 H, m), 3.81 (4 H, d, J = 14.3 Hz), 3.61 (2 H, d, J = 14.4 Hz), 3.48 (2 H, d, J = 14.0 Hz), 2.39 (2 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.4, 138.7, 130.3, 128.8, 128.7, 128.6, 128.2, 128.0, 127.7, 127.1, 126.7, 121.1, 111.6, 79.9, 74.5, 69.5, 66.9, 61.2, 58.1, 54.7, 47.7; HRMS (ESI): MH^+, found 769.4021. $C_{52}H_{53}N_2O_4$ requires 769.4005.



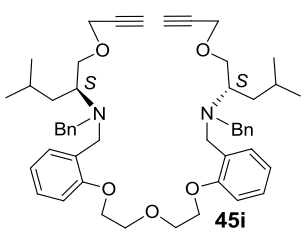
45g

Compound 45h. Following the general procedure, **45h** was obtained as a colourless liquid (511 mg, 63%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3287, 2873, 1600, 1493, 1242 and 1100 cm^{-1}; $[\alpha]^{25}_D$ + 55.69 (c 0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (2 H, d, J = 7.5 Hz), 7.45-7.20 (22 H, m), 7.03 (2 H, t, J = 7.4 Hz), 6.86 (2 H, d, J = 8.1 Hz), 4.14-4.05 (14 H, m), 3.92-3.83 (8 H, m), 3.66 (2 H, d, J = 14.7 Hz), 3.48 (2 H, d, J = 14.7 Hz), 2.44 (2 H, t, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 140.4, 138.5, 130.0, 128.9, 128.7, 128.5, 128.2, 128.0, 127.6, 127.1, 126.8, 121.0, 111.5, 79.9, 74.6, 70.1, 69.6, 67.8, 61.2, 58.2, 54.7, 47.7; HRMS (ESI): MH^+, found 813.4257. $C_{54}H_{57}N_2O_5$ requires 813.4267.



45h

Compound 45i. Following the general procedure, **45i** was obtained as a colourless liquid (540 mg, 52%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2953, 1600, 1452, 1240 and 1100 cm^{-1}; $[\alpha]^{25}_D$ – 94.30 (c 0.05, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.56 (2 H, dd, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 7.40 (4 H, d, J = 7.3 Hz), 7.32-7.28 (4 H, m), 7.23-7.16 (4 H, m), 6.98 (2 H, t, J = 7.4 Hz), 6.86 (2 H, d, J = 8.1 Hz), 4.18-4.13 (8 H, m), 3.97-3.94 (4 H, m), 3.87-3.76 (6 H, m), 3.68 (4 H, t, J = 13.8 Hz), 3.56 (2 H, dd, J_1 = 9.6 Hz, J_2 = 5.3 Hz), 2.91-2.88 (2 H, m), 2.44 (2 H, t, J = 2.3 Hz), 1.82-1.77 (2 H, m), 1.55-1.48 (2 H, m), 1.23-1.16 (2 H, m), 0.83 (6 H, d, J = 6.6 Hz), 0.64 (6 H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C

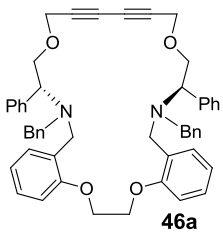


45i

156.9, 140.9, 130.3, 129.0, 128.9, 128.0, 127.4, 126.6, 120.9, 111.5, 80.3, 74.2, 70.7, 70.0, 67.8, 58.2, 54.6, 54.5, 47.1, 38.5, 24.7, 23.4, 22.2; HRMS (ESI): MH^+, found 773.4880. $C_{50}H_{65}N_2O_5$ requires 773.4893.

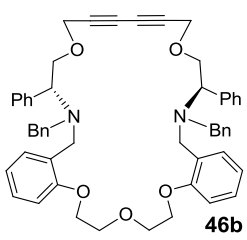
General procedure for the syntheses of macrocycles 46 (Procedure E). A mixture of **45** (0.2 mmol), $Cu(OAc)_2.H_2O$ (1 equiv.) and DMSO (2 mL) was taken in a vial (10 mL capacity) or round bottom flask (10 or 20 mL capacity). The reaction mixture was stirred at 110 °C for 6 h in air. After this period, the resulting mixture was cooled to room temperature and diluted with water (4 mL). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 times, using 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by Al_2O_3 column chromatography (EtOAc : Hexane) to give the polyether macrocycles **46**.

Compound 46a. Following the general procedure, **46a** was obtained as a colourless liquid (88 mg, 58%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3028, 1600, 1493, 1452 and 1237 cm^{-1}; $[\alpha]^{25}_D$ – 47.57 (c 0.14, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.64 (2 H, d, J = 8.7 Hz), 7.47-7.43 (8 H, m), 7.38-7.32 (8 H, m), 7.30-7.23 (6 H, m), 7.04 (2 H, t, J = 7.4 Hz), 6.95 (2 H, d, J = 8.2 Hz), 4.46-4.44 (4 H, m), 4.27-3.92 (12 H, m), 3.79 (2 H, d, J = 13.8 Hz), 3.64 (2 H, d, J = 14.5 Hz), 3.58 (2 H, d, J = 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.6, 140.2, 139.6, 130.3, 129.0, 128.7, 128.5, 128.2, 128.2, 127.7, 127.2, 126.8, 120.9, 111.6, 75.7, 70.5, 69.7, 66.4, 62.3, 58.7, 55.5, 47.9; HRMS (ESI): MH^+, found 767.3861. $C_{52}H_{51}N_2O_4$ requires 767.3849.



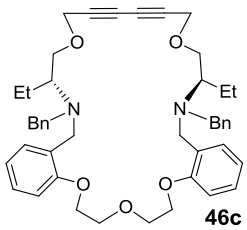
46a

Compound 46b. Following the general procedure, **46b** was obtained as a colourless liquid (80 mg, 50%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2927, 1601, 1493, 1452 and 1099 cm^{-1}; $[\alpha]^{25}_D$ – 21.81 (c 0.12, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.53-7.24 (24 H, m), 7.02 (2 H, t, J = 7.4 Hz), 6.94 (2 H, d, J = 8.2 Hz), 4.37-4.11 (20 H, m), 3.82 (2 H, d, J = 14.0 Hz), 3.73 (2 H, d, J = 13.9 Hz), 3.53 (2 H, d, J = 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 140.4, 139.6, 130.5, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 127.1, 126.8, 120.8, 111.6, 75.9, 70.7, 70.3, 69.3, 68.0, 61.0, 58.9, 54.8, 48.0; HRMS (ESI): MH^+, found 811.4108. $C_{54}H_{55}N_2O_5$ requires 811.4111.



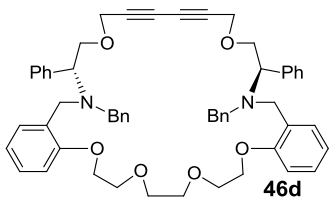
46b

Compound 46c. Following the general procedure, **46c** was obtained as a colourless liquid (102 mg, 62%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2960, 1600, 1493, 1452 and 1276 cm^{-1}; $[\alpha]^{25}_D$ + 99.90 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.53 (2 H, d, J = 7.4 Hz), 7.47 (4 H, d, J = 7.5 Hz), 7.35 (4 H, t, J = 7.4 Hz), 7.28-7.19 (4 H, m), 6.99 (2 H, d, J = 7.3 Hz), 6.89 (2 H, d, J = 8.1 Hz), 4.34-4.08 (14 H, m), 3.96 (2 H, d, J = 13.9 Hz), 3.90-3.87 (2 H, m), 3.68-3.56 (6 H, m), 2.75-2.71 (2 H, m), 1.61-1.51 (4 H, m), 0.96 (6 H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 141.0, 130.3, 128.9, 128.7, 128.1, 127.5, 126.6, 120.8, 111.6, 76.0, 70.4, 70.2, 68.0, 58.9, 58.5, 54.2, 46.9, 22.8, 11.7; HRMS (ESI): MH^+, found 715.4116. $C_{46}H_{55}N_2O_5$ requires 715.4111.



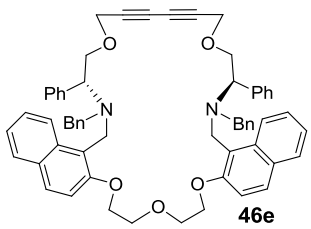
46c

Compound 46d. Following the general procedure, **46d** was obtained as a colourless liquid (88 mg, 52%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2872, 1605, 1499, 1241 and 1103 cm^{-1}; $[\alpha]^{25}_D$ – 29.00 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.51-7.49 (6 H, m), 7.45-7.21 (18 H, m), 6.99 (2 H, t, J = 7.2 Hz), 6.89 (2 H, d, J = 8.2 Hz), 4.34-4.28 (4 H, m), 4.23-4.10 (12 H, m), 4.04-4.02 (4 H, m), 3.93 (4 H, br. s), 3.80 (2 H, d, J = 13.8 Hz), 3.72 (2 H, d, J = 13.7 Hz), 3.53 (2 H, d, J = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 140.4, 139.7, 130.3, 128.7, 128.5, 128.4, 128.3, 128.1, 127.8, 127.0, 126.8, 120.8, 111.5, 75.9, 71.1, 70.6, 70.0, 69.3, 67.9, 61.0, 58.8, 54.8, 48.0; HRMS (ESI): MH^+, found 855.4378. $C_{56}H_{59}N_2O_6$ requires 855.4373.



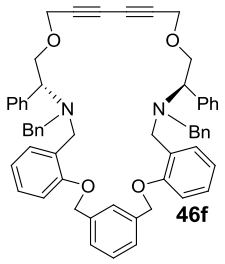
46d

Compound 46e. Following the general procedure, **46e** was obtained as a colourless liquid (85 mg, 47%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1600, 1492, 1238 and 1094 cm^{-1}; $[\alpha]^{25}_D$ + 31.68 (c 0.07, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.78-7.74 (4 H, m), 7.58 (2 H, d, J = 8.5 Hz), 7.36-7.24 (26 H, m), 4.60-4.37 (12 H, m), 4.30-4.25 (6 H, m), 4.03-3.99 (4 H, m), 3.88 (2 H, d, J = 13.0 Hz), 3.65 (2 H, d, J = 13.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.3, 140.6, 140.2, 134.0, 129.7, 129.4, 129.4, 128.8, 128.0, 127.9, 127.0, 126.8, 125.8, 125.2, 123.6, 120.2, 114.4, 76.2, 71.0, 70.4, 69.1, 67.1, 59.5, 59.1, 54.5, 43.6; HRMS (ESI): M^+, found 911.4429. $C_{62}H_{59}N_2O_5$ requires 911.4424.

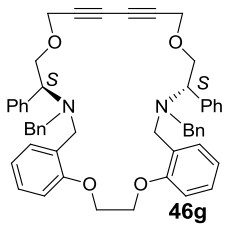


46e

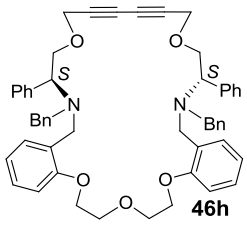
Compound 46f. Following the general procedure, **46f** was obtained as a colourless liquid (63 mg, 38%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1493, 1452, 1238 and 1095 cm^{-1}; $[\alpha]^{25}_D$ – 50.60 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.58 (1 H, s), 7.53-7.19 (27 H, m), 6.98 (2 H, t, J = 7.3 Hz), 6.93 (2 H, d, J = 8.0 Hz), 5.22 (4 H, s), 4.20 (2 H, d, J = 13.9 Hz), 4.14-3.98 (10 H, m), 3.77 (2 H, d, J = 13.9 Hz), 3.63 (2 H, d, J = 13.9 Hz), 3.50 (2 H, d, J = 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 140.4, 139.4, 137.9, 130.6, 128.9, 128.7, 128.6, 128.2, 128.1, 127.9, 127.0, 126.9, 126.8, 126.1, 120.8, 111.9, 75.6, 70.5, 70.1, 69.4, 61.3, 58.7, 54.9, 48.2; HRMS (ESI): MH^+, found 843.4160. $C_{58}H_{55}N_2O_4$ requires 843.4162.



Compound 46g. Following the general procedure, **46g** was obtained as a colourless liquid (81 mg, 53%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 2985, 1600, 1493, 1452 and 1262 cm^{-1}; $[\alpha]^{25}_D$ + 55.29 (c 0.14, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.64 (2 H, dd, J_1 = 6.0 Hz, J_2 = 1.4 Hz), 7.47-7.42 (8 H, m), 7.38-7.23 (14 H, m), 7.04 (2 H, t, J = 7.4 Hz), 6.94 (2 H, d, J = 8.2 Hz), 4.46-4.44 (4 H, m), 4.23 (2 H, d, J = 16.3 Hz), 4.16-3.93 (10 H, m), 3.79 (2 H, d, J = 13.8 Hz), 3.64 (2 H, d, J = 14.5 Hz), 3.58 (2 H, d, J = 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.6, 140.2, 139.6, 130.3, 128.9, 128.7, 128.5, 128.2, 128.2, 127.7, 127.2, 126.8, 120.9, 111.6, 75.7, 70.5, 69.7, 66.3, 62.3, 58.6, 55.5, 47.9; HRMS (ESI): MH^+, found 767.3856. $C_{52}H_{51}N_2O_4$ requires 767.3849.

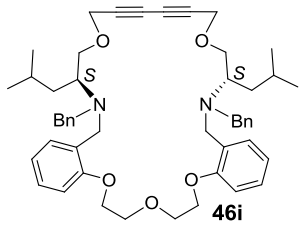


Compound 46h. Following the general procedure, **46h** was obtained as a colourless liquid (73 mg, 45%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2871, 1493, 1452, 1244 and 1098 cm^{-1}; $[\alpha]^{25}_D$ + 35.96 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.52-7.24 (24 H, m), 7.01 (2 H, t, J = 7.4 Hz), 6.93 (2 H, d, J = 8.2 Hz), 4.35 (2 H, d, J = 16.3 Hz), 4.28-4.00 (18 H, m), 3.80 (2 H, d, J = 14.0 Hz), 3.72 (2 H, d, J = 13.9 Hz), 3.51 (2 H, d, J = 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 140.4, 139.5, 130.4, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 127.1, 126.8, 120.8, 111.6, 75.9, 70.7, 70.3, 69.3, 68.0, 60.9, 58.8, 58.9, 54.7, 48.0; HRMS (ESI): MH^+, found 811.4112. $C_{54}H_{55}N_2O_5$ requires 811.4111.



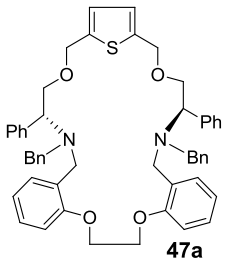
Compound 46i. Following the general procedure, **46i** was obtained as a colourless liquid (80 mg, 52%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2952, 1600, 1493, 1452, 1242 and

1097 cm^{-1}; $[\alpha]^{25}_D$ – 93.33 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45-7.42 (6 H, m), 7.35-7.24 (4 H, m), 7.22-7.20 (2 H, m), 7.19 (2 H, td, J_1 = 8.1 Hz, J_2 = 1.8 Hz), 6.96 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.8 Hz), 6.87 (2 H, d, J = 8.2 Hz), 4.34 (2 H, d, J = 16.3 Hz), 4.24 (2 H, d, J = 16.3 Hz), 4.22-4.17 (4 H, m), 4.10-4.05 (6 H, m), 3.93 (2 H, d, J = 13.8 Hz), 3.88 (2 H, dd, J_1 = 9.4 Hz, J_2 = 5.1 Hz), 3.61-3.56 (4 H, m), 3.50 (2 H, d, J = 14.0 Hz), 2.86-2.82 (2 H, m), 1.88-1.82 (2 H, m), 1.58-1.51 (2 H, m), 1.15-1.09 (2 H, m), 0.84 (6 H, d, J = 6.7 Hz), 0.54 (6 H, d, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 141.0, 130.6, 128.9, 128.8, 128.1, 127.6, 126.6, 120.9, 111.6, 76.0, 70.7, 70.4, 70.2, 67.9, 59.0, 54.2, 54.1, 46.7, 39.4, 24.3, 23.7, 21.6; HRMS (ESI): MH^+, found 771.4740. $C_{50}H_{63}N_2O_5$ requires 771.4737.

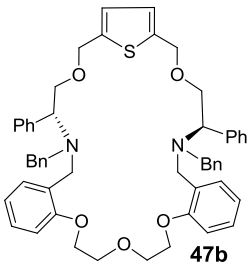


General procedure for the syntheses of macrocycles 47 (Procedure F). A mixture of **46** (0.10 mmol), $Na_2S.xH_2O$ (90 mg), CuI (10 mol%), 1,10-phen (15 mol%) and DMF (1 mL) was stirred at 90 ^oC for 9 h in air. After this period, the vial was cooled to room temperature. Then the resulting mixture was diluted with water (4 mL). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 times, using 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc:Hexane) to give the polyether macrocycle **47**.

Compound 47a. Following the general procedure, **47a** was obtained as a pale yellow liquid (33 mg, 42%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1600, 1493, 1452 and 1259 cm^{-1}; $[\alpha]^{25}_D$ – 29.08 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.58 (2 H, dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz), 7.41-7.37 (8 H, m), 7.31-7.27 (8 H, m), 7.24-7.19 (6 H, m), 7.00 (2 H, t, J = 7.4 Hz), 6.85 (2 H, dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz), 6.77 (2 H, s), 4.65 (2 H, d, J = 12.8 Hz), 4.50 (2 H, d, J = 12.8 Hz), 4.26-4.24 (4 H, m), 4.07-3.89 (8 H, m), 3.73 (2 H, d, J = 14.0 Hz), 3.55 (4 H, dd, J_1 = 13.9 Hz, J_2 = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 141.5, 140.4, 139.8, 130.3, 129.0, 128.7, 128.5, 128.2, 128.0, 127.6, 126.9, 126.7, 126.0, 120.8, 111.6, 69.4, 67.7, 66.4, 61.9, 55.1, 47.8; HRMS (ESI): MH^+, found 801.3734. $C_{52}H_{53}N_2O_4S$ requires 801.3726.

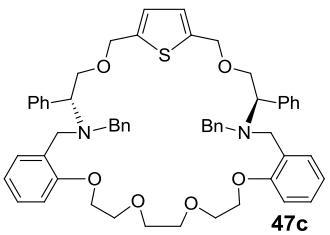


Compound 47b. Following the general procedure, **47b** was obtained as a pale yellow liquid (52 mg, 62%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2866, 1600, 1493, 1452 and 1083 cm^{-1}; $[\alpha]^{25}_D$ – 40.95 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.49-7.17 (24 H, m), 6.95 (2 H, t, J = 7.4 Hz), 6.85-6.82 (4 H, m), 4.66 (2 H, d, J = 12.6 Hz), 4.57 (2 H, d, J = 12.6 Hz), 4.17-4.02 (12 H, m), 3.94 (4 H, t, J = 4.8 Hz), 3.79 (2 H, d, J = 14.0 Hz), 3.68 (2 H, d, J = 14.0 Hz), 3.51 (2 H, d, J = 14.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 141.6, 140.5, 140.0, 130.1, 128.7, 128.7, 128.5, 128.2, 128.1, 127.6, 126.9, 126.7, 125.7, 120.7, 111.4, 70.2, 69.8, 68.0, 67.9, 61.2, 54.8, 48.2; HRMS (ESI): MH^+, found 845.4003. $C_{54}H_{57}N_2O_5S$ requires 845.3988.



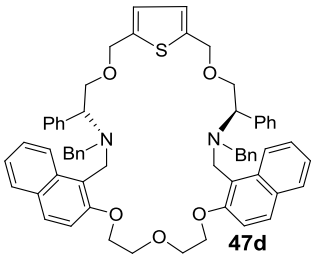
47b

Compound 47c. Following the general procedure, **47c** was obtained as a pale yellow liquid (38 mg, 43%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2961, 1600, 1493, 1452, 1259and 1099 cm^{-1}; $[\alpha]^{25}_D$ – 44.49 (c 0.07, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.50-7.15 (24 H, m), 6.94 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.8 Hz), 6.83-6.81 (4 H, m), 4.65-4.58 (4 H, m), 4.15-3.99 (12 H, m), 3.87 (4 H, t, J = 4.2 Hz), 3.80-3.75 (6 H, m), 3.67 (2 H, d, J = 14.0 Hz), 3.55 (2 H, d, J = 14.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 141.6, 140.5, 140.1, 130.0, 128.7, 128.6, 128.5, 128.2, 128.0, 127.5, 126.9, 126.7, 125.7, 120.7, 111.3, 71.0, 69.9, 69.7, 67.9, 67.8, 61.4, 54.9, 48.1; HRMS (ESI): MH^+, found 889.4256. $C_{56}H_{61}N_2O_6S$ requires 889.4250.



47c

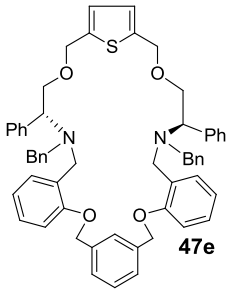
Compound 47d. Following the general procedure, **47d** was obtained as a pale yellow liquid (54 mg, 58%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2918, 1595, 1494, 1267 and 1087 cm^{-1}; $[\alpha]^{25}_D$ + 48.35 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.72 (4 H, d, J = 8.8 Hz), 7.53 (2 H, d, J = 8.5 Hz), 7.34-7.32 (10 H, m), 7.30-7.20 (16 H, m), 7.01 (2 H, s), 4.86 (2 H, d, J = 12.6 Hz), 4.75 (2 H, d, J = 12.6 Hz), 4.53 (2 H, d, J = 12.3 Hz), 4.46 (2 H, dd, J_1 = 9.6 Hz, J_2 = 5.4 Hz), 4.34-4.30 (4 H, m), 4.22-4.18 (2 H, m), 4.10-4.01 (8 H, m), 3.85 (2 H, d, J = 13.2 Hz), 3.74 (2 H, d, J = 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 155.2, 141.6, 140.7, 140.6, 134.0, 129.5, 129.4, 129.3, 128.9, 127.9, 127.9, 127.8,



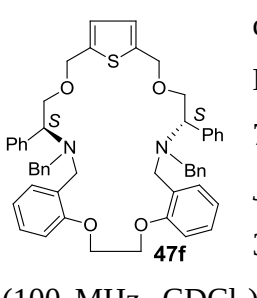
47d

126.8, 126.7, 125.8, 125.7, 125.2, 123.5, 120.5, 111.4, 70.4, 69.1, 68.2, 68.0, 60.1, 54.6, 43.6; HRMS (ESI): MH^+, found 945.4310. $C_{62}H_{61}N_2O_5S$ requires 945.4301.

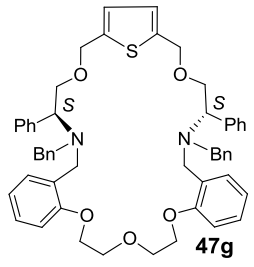
Compound 47e. Following the general procedure, **47e** was obtained as a pale yellow liquid (44 mg, 50%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2854, 1600, 1493, 1452 and 1027 cm^{-1}; $[\alpha]^{25}_D$ – 37.58 (c 0.10, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.51-7.50 (3 H, m), 7.45-7.37 (11 H, m), 7.34-7.28 (8 H, m), 7.25-7.18 (6 H, m), 6.98 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.8 Hz), 6.91 (2 H, d, J = 8.1 Hz), 6.66 (2 H, s), 5.08 (4 H, s), 4.46 (2 H, d, J = 12.6 Hz), 4.40 (2 H, d, J = 12.6 Hz), 4.16 (2 H, d, J = 14.3 Hz), 4.09-4.06 (2 H, m), 4.01-3.91 (4 H, m), 3.76 (2 H, d, J = 14.0 Hz), 3.64 (2 H, d, J = 14.0 Hz), 3.54 (2 H, d, J = 14.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 141.3, 140.5, 139.9, 137.8, 130.3, 128.9, 128.8, 128.7, 128.6, 128.2, 128.0, 127.7, 126.9, 126.8, 126.7, 126.1, 125.6, 120.8, 111.8, 70.0, 69.8, 67.7, 61.4, 54.9, 48.2; HRMS (ESI): MH^+, found 877.4043. $C_{58}H_{57}N_2O_4S$ requires 877.4039.



Compound 47f. Following the general procedure, **47f** was obtained as a pale yellow liquid (50 mg, 62%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1595, 1465, 1268 and 1087 cm^{-1}; $[\alpha]^{25}_D$ + 26.44 (c 0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.59 (2 H, d, J = 7.4 Hz), 7.43-7.38 (8 H, m), 7.33-7.28 (8 H, m), 7.25-7.20 (6 H, m), 7.02 (2 H, t, J = 7.4 Hz), 6.86 (2 H, d, J = 8.1 Hz), 6.78 (2 H, s), 4.66 (2 H, d, J = 12.8 Hz), 4.51 (2 H, d, J = 12.8 Hz), 4.26 (4 H, s), 4.08-3.91 (8 H, m), 3.74 (2 H, d, J = 14.0 Hz), 3.56 (4 H, dd, J_1 = 13.9 Hz, J_2 = 9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 141.5, 140.4, 139.8, 130.3, 129.0, 128.7, 128.5, 128.2, 128.0, 127.6, 127.0, 126.7, 126.1, 120.8, 111.6, 69.4, 67.7, 66.5, 61.9, 55.1, 47.8; HRMS (ESI): MH^+, found 801.3736. $C_{52}H_{53}N_2O_4S$ requires 801.3726.

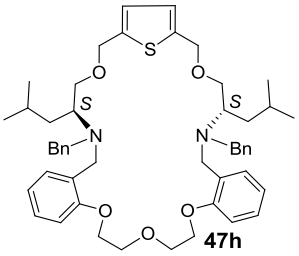


Compound 47g. Following the general procedure, **47g** was obtained as a pale yellow liquid (54 mg, 65%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2866, 1600, 1493, 1452 and 1093 cm^{-1}; $[\alpha]^{25}_D$ + 52.70 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.50-7.18 (24 H, m), 6.96 (2 H, t, J = 6.7 Hz), 6.84 (2 H, d, J = 7.7 Hz), 6.82 (2 H, s), 4.66 (2 H, d, J = 12.6 Hz), 4.58 (2 H, d, J = 12.6 Hz), 4.18-4.11 (10 H, m), 4.05-3.93 (6 H, m), 3.80 (2 H, d, J = 14.0 Hz), 3.69 (2 H, d, J = 14.1 Hz), 3.52 (2 H, d, J = 14.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C



157.0, 141.6, 140.5, 140.0, 130.1, 128.8, 128.7, 128.5, 128.2, 128.1, 127.6, 126.9, 126.7, 125.7, 120.7, 111.5, 70.2, 69.9, 68.0, 67.9, 61.2, 54.8, 48.2; HRMS (ESI): MH^+, found 845.3998. $C_{54}H_{57}N_2O_5S$ requires 845.3988.

Compound 47h. Following the general procedure, **47h** was obtained as a pale yellow liquid (39 mg, 52%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2952, 2863, 1601, 1492, 1451 and 1087 cm^{-1}; $[\alpha]^{25}_D$ – 36.34 (c 0.11, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50 (2 H, dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.40 (4 H, d, J = 7.2 Hz), 7.32-7.28 (4 H, m), 7.23 (2 H, d, J = 7.2 Hz), 7.20-7.15 (2 H, m), 6.97 (2 H, td, J_1 = 7.2 Hz, J_2 = 0.8 Hz), 6.92 (2 H, s), 6.83 (2 H, d, J = 8.2 Hz), 4.73 (2 H, d, J = 12.5 Hz), 4.63 (2 H, d, J = 12.5 Hz), 4.14-4.07 (6 H, m), 3.97-3.94 (4 H, m), 3.88 (2 H, d, J = 13.7 Hz), 3.78 (2 H, dd, J_1 = 9.7 Hz, J_2 = 6.1 Hz), 3.65 (2 H, d, J = 13.7 Hz), 3.58-3.55 (4 H, dd), 2.97-2.94 (2 H, m), 1.88-1.81 (2 H, m), 1.56-1.49 (2 H, m), 1.19-1.12 (2 H, m), 0.85 (6 H, d, J = 6.7 Hz), 0.59 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 141.9, 141.1, 130.3, 129.3, 129.0, 128.0, 127.4, 126.6, 125.3, 120.8, 111.5, 71.2, 70.3, 68.3, 68.1, 54.6, 54.3, 47.0, 39.5, 24.5, 23.6, 21.9; HRMS (ESI): MH^+, found 805.4622. $C_{50}H_{65}N_2O_5S$ requires 805.4614.



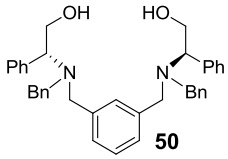
47h

General procedure for the synthesis of *bis*-alcohols 49 and **55 (Procedure B).** To a round-bottom flask was sequentially added the corresponding *bis*-aldehyde (**48** or **54,** 3 mmol), *R*-phenyl glycinol (2 equiv) in EtOH (10 mL). The reaction mixture was refluxed for 12 h and after this period, the reaction mixture was allowed to attain the room temperature and in the same reaction mixture was added $NaBH_4$ (4 equiv) portion wise at room temperature. Then again reaction mixture was refluxed for 12 h. After this period, the resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture bis-alcohols were used as such for the next step due to instability of the product **49** and **55**.

Typical procedure for the synthesis of *bis*-alcohols 50 and **56 (Procedure C).** To a flame dried round-bottom flask was sequentially added the corresponding alcohol derivative (**49** or **55,** crude mixture, 1 equiv), benzyl chloride (4 equiv) and anhydrous K2CO3 (3.5-4 equiv) in dry CH_3CN (10 mL). The reaction mixture was stirred at 80 ^oC for 72 h and after this period, the reaction mixture was allowed to attain the room temperature. The resulting reaction mixture was added

into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc : Hexanes = 40:60) to give the corresponding product **50** and **56**.

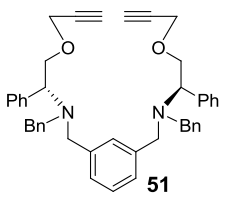
Compound 50. Following the general procedure, **50** was obtained as a pale yellow liquid (361 mg, 65%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3435, 3028, 1493, 1452 and 1265 cm^{-1}; $[\alpha]^{25}_D$ – 137.40 (c 0.22, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.50-7.27 (24 H, m), 4.20 (2 H, t, J = 10.6 Hz), 4.02-3.95 (6 H, m), 3.69-3.65 (2 H, m), 3.23-3.19 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 139.6, 139.1, 135.1, 129.4, 129.3, 129.0, 128.8, 128.6, 128.5, 128.1, 127.9, 127.3, 63.2, 60.5, 53.7, 53.5; HRMS (ESI): MH^+, found 557.3182. $C_{38}H_{41}N_2O_2$ requires 557.3168.



50

General procedure for the syntheses of compounds 51 and **57 (Procedure D).** To a solution of corresponding *bis*-alcohol **50**/**56** (1 mmol) (synthesized in the previous steps by using the procedure) in dry THF (3 mL) was added NaH (4 mmol, 55-60 % suspension in mineral oil) at room temperature. The mixture was stirred at room temperature for 10 min and then propargyl bromide (5 mmol, 80 wt% in toluene) was added. The resulting mixture was stirred for 12 h at room temperature. After every 12 h another lot NaH (2 mmol) and propargyl bromide (2.5 mmol) were added until starting material completely finished according to the TLC, and after this period, few drops of EtOH were added and stirred for 10 min and then the resulting mixture was poured on to water (10-20 mL) and was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated and the resulting crude reaction mixture was purified by Al_2O_3 gel column chromatography (EtOAc : Hexanes = 20:80) to give the corresponding product **51**/**57**.

Compound 51. Following the general procedure, **51** was obtained as a pale yellow liquid (455 mg, 72%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3290, 3028, 1602, 1494, 1261 and 1100 cm^{-1}; $[\alpha]^{25}_D$ – 72.59 (c 0.06, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (1 H, s), 7.47 (4 H, d, J = 7.2 Hz), 7.43-7.41 (9 H, m), 7.36-7.33 (6 H, m), 7.30-7.27 (4 H, m), 4.15 (4 H, d, J = 2.3 Hz), 4.14-4.05 (6 H, m), 3.86 (4 H, dd, J_1 = 13.9 Hz, J_2 = 9.3 Hz), 3.49 (4 H, d, J = 13.8 Hz), 2.45 (2 H, t, J = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 140.2, 140.1, 138.4, 129.1, 128.8, 128.8, 128.3,

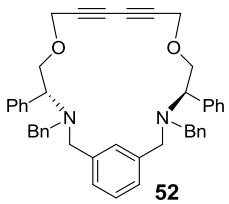


51

128.1, 127.5, 127.2, 126.8, 79.8, 74.6, 69.5, 60.6, 58.2, 54.4; HRMS (ESI): MH^+, found 633.3495. $C_{44}H_{45}N_2O_2$ requires 633.3481.

General procedure for the syntheses of macrocycles 52 and **58 (Procedure E).** A mixture of **51/57** (0.25 mmol), $Cu(OAc)_2.H_2O$ (1 equiv) and DMSO (2.5 mL) was taken in a vial (10 mL capacity) or round bottom flask (10 or 20 mL capacity). The reaction mixture was stirred at 110 °C for 6 h in air. After this period, the resulting mixture was cooled to room temperature and diluted with water (4 mL). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 times, using 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by Al_2O_3 gel column chromatography (EtOAc:Hexane) which gave the crown/polyether-type macrocycles **52** and **58**.

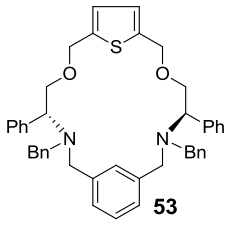
Compound 52. Following the general procedure, **52** was obtained as a pale yellow liquid (63 mg, 50%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3060, 2924, 1494, 1452 and 1092 cm^{-1}; $[\alpha]^{25}_D$ – 72.62 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (1 H, s), 7.43-7.39 (12 H, m), 7.35-7.30 (6 H, m), 7.29-7.24 (5 H, m), 4.38-4.24 (4 H, m), 4.20 (2 H, d, J = 16.3 Hz), 4.12 (2 H, t, J = 6.2 Hz), 4.07-4.01 (4 H, m), 3.83 (2 H, d, J = 13.8 Hz), 3.61 (2 H, d, J = 13.8 Hz), 3.51 (2 H, d, J = 13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 140.2, 140.1, 138.7, 129.5, 128.8, 128.8, 128.2, 128.1, 128.1, 127.3, 127.2, 126.8, 76.2, 71.1, 69.8, 60.4, 58.6, 54.7, 54.1; HRMS (ESI): MH^+, found 631.3340. $C_{40}H_{43}N_2O_2$ requires 631.3325.



52

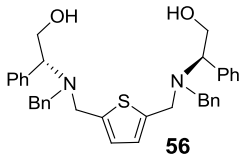
General procedure for the syntheses of macrocycles 53 and **59 (Procedure F).** A mixture of **52/58** (0.1 mmol), $Na_2S.xH_2O$ (90 mg), CuI (10 mol%), 1,10-phen (15 mol%) and DMF (1 mL) was stirred at 90 ^oC for 9 h in air. After this period, the vial was cooled to room temperature. Then the resulting mixture was diluted with water (4 ml). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 times, using 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc : Hexane) which gave the crown/polyether macrocycle **53** and **59**.

Compound 53. Following the general procedure, **53** was obtained as a pale yellow liquid (30 mg, 45%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3028, 2854, 1602, 1493, 1452 and 1083 cm^{-1}; $[\alpha]^{25}_D$ – 68.62 (c 0.06, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (1 H, s), 7.40-7.27 (19 H, m), 7.22-7.13 (4 H, m), 6.94 (2 H, s), 4.84 (2 H, d, *J* = 12.4 Hz), 4.64 (2 H, d, *J* = 12.4 Hz), 4.21 (2 H, t, *J* = 9.3 Hz), 4.13-4.10 (2 H, m), 3.89-3.81 (6 H, m), 3.49 (2 H, d, *J* = 13.7 Hz), 3.41 (2 H, d, *J* = 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.3, 140.5, 140.1, 138.7, 130.2, 128.7, 128.6, 128.1, 128.1, 127.7, 127.1, 127.0, 126.6, 126.0, 69.5, 67.8, 60.5, 54.0, 53.8; HRMS (ESI): MH^+, found 665.3202. $C_{44}H_{45}N_2O_2S$ requires 665.3202.



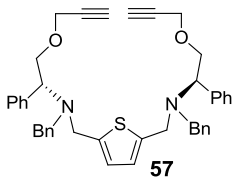
53

Compound 56. Following the general procedure, **56** was obtained as a pale yellow liquid (348 mg, 62%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3428, 2891, 1667, 1494, 1453 and 1027 cm^{-1}; $[\alpha]^{25}_D$ – 186.14 (c 0.06, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.47-7.38 (14 H, m), 7.33-7.27 (6 H, m), 6.77 (2 H, s), 4.17 (2 H, t, *J* = 10.5 Hz), 4.06-3.99 (6 H, m), 3.68-3.66 (2 H, m), 3.47 (2 H, d, *J* = 14.2 Hz), 3.21 (2 H, d, *J* = 13.6 Hz), 2.93 (2 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 143.2, 138.9, 135.1, 129.2, 128.9, 128.6, 128.5, 128.1, 127.4, 125.6, 63.2, 60.7, 53.5, 48.9; HRMS (ESI): MH^+, found 563.2745. $C_{36}H_{39}N_2O_2S$ requires 563.2732.



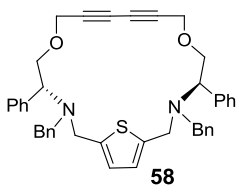
56

Compound 57. Following the general procedure, **57** was obtained as a pale yellow liquid (414 mg, 65%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3290, 2848, 1494, 1358 and 1099 cm^{-1}; $[\alpha]^{25}_D$ – 39.29 (c 0.06, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.50 (4 H, d, *J* = 7.2 Hz), 7.46-7.25 (16 H, m), 6.74 (2 H, s), 4.18 (4 H, d, *J* = 2.3 Hz), 4.16-4.05 (6 H, m), 3.96 (2 H, d, *J* = 14.4 Hz), 3.86 (2 H, d, *J* = 14.0 Hz), 3.66 (2 H, d, *J* = 14.4 Hz), 3.56 (2 H, d, *J* = 14.0 Hz), 2.46 (2 H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 143.5, 140.0, 138.6, 128.7, 128.7, 128.3, 128.2, 127.3, 126.9, 124.6, 79.8, 74.6, 69.8, 60.8, 58.3, 54.2, 49.6; HRMS (ESI): MH^+, found 639.3068. $C_{42}H_{43}N_2O_2S$ requires 639.3045.



57

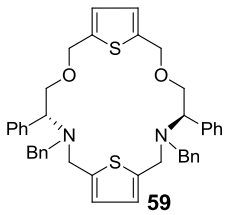
Compound 58. Following the general procedure, **58** was obtained as a pale yellow liquid (56 mg, 44%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 2986, 1493, 1422 and 1265 cm^{-1}; $[\alpha]^{25}_D$ – 42.47 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.49 (4 H, d, *J* = 7.2 Hz), 7.45-7.34 (14 H, m), 7.28 (2 H, t, *J* = 7.3 Hz), 6.76 (2 H, s), 4.30-4.26 (4 H, m), 4.19-4.10 (6 H,



58

m), 4.06 (2 H, d, *J* = 2.3 Hz), 3.87 (2 H, d, *J* = 13.4 Hz), 3.68 (2 H, t, *J* = 14.6 Hz), 3.18 (2 H, d, *J* = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 143.5, 139.6, 137.2, 129.2, 128.7, 128.3, 128.2, 127.5, 126.9, 124.9, 75.7, 71.5, 70.8, 61.4, 58.5, 54.5, 49.6; HRMS (ESI): MH^+, found 637.2877. $C_{42}H_{41}N_2O_2S$ requires 637.2889.

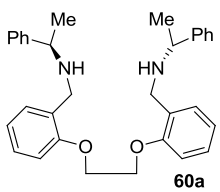
Compound 59. Following the general procedure, **59** was obtained as a pale yellow liquid (33 mg, 50%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3921, 1493, 1453, 1261 and 1090 cm^{-1}; $[\alpha]^{25}_D$ – 25.23 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (4 H, d, *J* = 7.3 Hz), 7.45-7.27 (16 H, m), 6.90 (2 H, s), 6.63 (2 H, s), 4.78 (2 H, d, *J* = 12.7 Hz), 4.61 (2 H, d, *J* = 12.7 Hz), 4.14-4.09 (4 H, m), 4.01 (2 H, d, *J* = 14.4 Hz), 3.90 (2 H, d, *J* = 14.2 Hz), 3.84-3.81 (2 H, m), 3.59 (2 H, d, *J* = 14.5 Hz), 3.13 (2 H, d, *J* = 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 144.0, 142.1, 140.0, 129.1, 128.7, 128.2, 127.4, 126.8, 125.5, 124.0, 70.9, 67.8, 61.8, 54.0, 49.9; HRMS (ESI): MH^+, found 671.2759. $C_{42}H_{43}N_2O_2S_2$ requires 671.2766.



59

General procedure for the synthesis of *bis* amine 60 (Procedure G). To a round-bottom flask was sequentially added the corresponding *bis* aldehyde derivative (**41,** 1 mmol), *R* or *S* α-methylbenzylamines (2 equiv) in EtOH (10 mL). The reaction mixture was refluxed for 12 h and after this period, the reaction mixture was allowed to attain the room temperature and in the same reaction mixture was added $NaBH_4$ (4 equiv) portion wise at room temperature. Then, again the reaction mixture was refluxed for 12 h. After this period, the resulting reaction mixture was added into water and extracted using EtOAc (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in *vacuo* and the crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc/Hexanes) to give the corresponding product **60**.

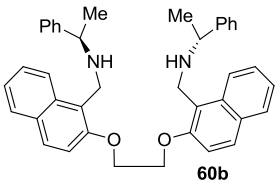
Compound 60a. Following the general procedure, **60a** was obtained as a brown coloured solid (268 mg, 70%); mp 87-89 ^oC; R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2965, 1492, 1451, 1238 and 1113 cm^{-1}; $[\alpha]^{25}_D$ + 51.45 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.19 (14 H, m), 6.97 (2 H, td, J_1 = 7.3 Hz, J_2 = 0.8 Hz), 6.92 (2 H, d, *J* = 8.2 Hz), 4.37-4.29 (4 H, m), 3.78-3.56 (6 H, m), 1.31 (6 H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 145.3, 130.4, 128.6, 128.4,



60a

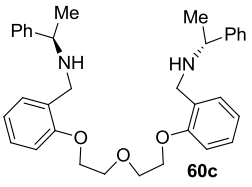
128.3, 126.9, 126.8, 121.0, 111.4, 66.7, 57.4, 47.1, 24.4; HRMS (ESI): MNa^+, found 503.1137. $C_{32}H_{36}N_2NaO_2$ requires 503.2674. Two NH protons could not be detected in the proton NMR spectra.

Compound 60b. Following the general procedure, **60b** was obtained as a brown coloured solid (435 mg, 75%); mp 103-105 ^oC; R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): 2923, 1595, 1513, 1452 and 1094 cm^{-1}; $[\alpha]^{25}_D$ + 32.97 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86-7.81 (6 H, m), 7.48 (2 H, t, J = 7.3 Hz), 7.40-7.36 (6 H, m), 7.32-7.26 (6 H, m), 7.19 (2 H, t, J = 7.9 Hz), 4.47-4.25 (4 H, m), 4.09 (2 H, d, J = 12 Hz), 4.02 (2 H, d, J = 12 Hz), 3.81 (2 H, q, J = 6.6 Hz), 1.76 (2 H, br. s), 1.29 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 154.2, 145.9, 133.5, 129.7, 129.1, 128.5, 128.4, 126.9, 126.8, 123.8, 123.5, 122.5, 114.8, 68.5, 58.5, 41.8, 24.8; HRMS (ESI): MH^+, found 581.3160. $C_{40}H_{40}N_2O_2$ requires 581.3168.



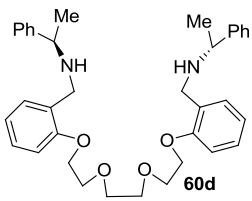
60b

Compound 60c. Following the general procedure, **60c** was obtained as a brown coloured liquid (340 mg, 67%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 1600, 1492, 1451 and 1130 cm^{-1}; $[\alpha]^{25}_D$ + 51.20 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.32 (8 H, m), 7.28-7.24 (4 H, m), 7.16 (2 H, dd, J_1 = 7.3 Hz, J_2 = 1.6 Hz), 6.93 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.9 Hz), 6.86 (2 H, d, J = 8.2 Hz), 4.15-4.11 (4 H, m), 3.89-3.75 (8 H, m), 3.57 (2 H, d, J = 13.3 Hz), 2.18 (2 H, br. s), 1.34 (6 H, d, J = 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 145.7, 130.3, 128.7, 128.4, 128.2, 126.9, 126.8, 120.7, 111.4, 69.9, 67.5, 57.0, 47.5, 24.6; HRMS (ESI): MH^+, found 525.3104. $C_{34}H_{41}N_2O_3$ requires 525.3117.



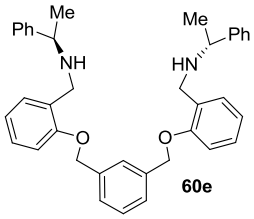
60c

Compound 60d. Following the general procedure, **60d** was obtained as a brown coloured liquid (408 mg, 72%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1601, 1492, 1451 and 1243 cm^{-1}; $[\alpha]^{25}_D$ + 43.58 (c 0.16, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.40-7.34 (8 H, m), 7.29-7.21 (4 H, m), 7.15 (2 H, dd, J_1 = 7.3 Hz, J_2 = 1.4 Hz), 6.92 (2 H, t, J = 7.4 Hz), 6.86 (2 H, d, J = 8.2 Hz), 4.18-4.12 (4 H, m), 3.87-3.74 (8 H, m), 3.69 (4 H, s), 3.56 (2 H, d, J = 13.2 Hz), 2.12 (2 H, br. s), 1.36 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 145.8, 130.3, 128.7, 128.4, 128.2, 126.9, 126.8, 120.6, 111.3, 70.9, 69.8, 67.3, 57.0, 47.5, 24.7; HRMS (ESI): MH^+, found 569.3369. $C_{36}H_{45}N_2O_4$ requires 569.3379.



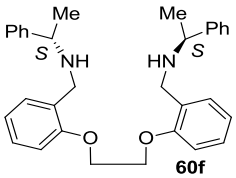
60d

Compound 60e. Following the general procedure, **60e** was obtained as a colourless liquid (389 mg, 70%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2962, 1601, 1492, 1452 and 1025 cm^{-1}; $[\alpha]^{25}_D$ + 48.16 (c 0.19, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.48-7.44 (4 H, m), 7.35-7.25 (14 H, m), 7.01-6.97 (4 H, m), 5.13 (4 H, s), 3.85-3.81 (4 H, m), 3.68 (2 H, d, J = 13.1 Hz), 2.15 (2 H, br. s), 1.36 (6 H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 145.7, 137.5, 130.3, 129.1, 128.9, 128.4, 128.3, 127.0, 126.9, 126.8, 126.3, 120.9, 111.7, 69.8, 57.3, 47.6, 24.6; HRMS (ESI): MH$^+$, found 557.3178. $C_{38}H_{41}N_2O_2$ requires 557.3168.



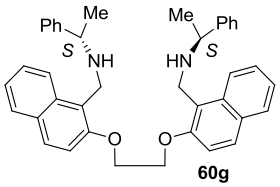
60e

Compound 60f. Following the general procedure, **60f** was obtained as a colourless solid (326 mg, 70%); mp 82-84 ^{o}C; R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2961, 1492, 1451, 1238 and 1056 cm^{-1}; $[\alpha]^{25}_D$ – 65.68 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35-7.22 (14 H, m), 6.99 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.9 Hz), 6.93 (2 H, dd, J_1 = 8.1 Hz, J_2 = 0.7 Hz), 4.38-4.30 (4 H, m), 3.76 (2 H, d, J = 6.5 Hz), 3.72 (2 H, d, J = 13.1 Hz), 3.58 (2 H, d, J = 13.1 Hz), 1.96 (2 H, s), 1.31 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 145.7, 130.3, 129.0, 128.4, 128.2, 126.8, 126.8, 121.0, 111.4, 66.7, 57.4, 47.2, 24.6; HRMS (ESI): MH$^+$, found 481.2865. $C_{32}H_{37}N_2O_2$ requires 481.2855.



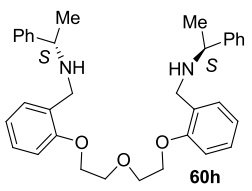
60f

Compound 60g. Following the general procedure, **60g** was obtained as a reddish brown coloured solid (417 mg, 72%); mp 101-103 ^{o}C; R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3055, 2965, 1624, 1595 and 1265 cm^{-1}; $[\alpha]^{25}_D$ – 25.08 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.88-7.83 (6 H, m), 7.52-7.48 (2 H, m), 7.42-7.37 (6 H, m), 7.33-7.28 (6 H, m), 7.22-7.18 (2 H, m), 4.48-4.42 (4 H, m), 4.11 (2 H, d, J = 11.9 Hz), 4.03 (2 H, d, J = 11.9 Hz), 3.86-3.80 (2 H, m), 1.31 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.2, 145.9, 133.4, 129.7, 129.1, 128.5, 128.3, 126.9, 126.7, 123.7, 123.5, 122.4, 114.7, 68.5, 58.5, 41.7, 24.7; HRMS (ESI): MH$^+$, found 581.3176. $C_{40}H_{41}N_2O_2$ requires 581.3168.



60g

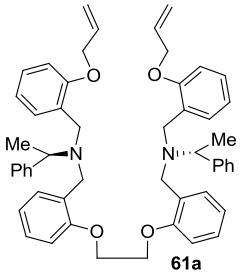
Compound 60h. Following the general procedure, **60h** was obtained as a brown coloured liquid (372 mg, 71%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924, 1600, 1492, 1451 and 1130 cm^{-1}; $[\alpha]^{25}_D$ – 57.94 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42-7.36 (8 H, m), 7.30-7.25 (4 H, m), 7.19 (2 H, d, J = 7.3 Hz), 6.96 (2 H, t, J = 7.4 Hz), 6.88 (2 H, d, J = 8.2 Hz),



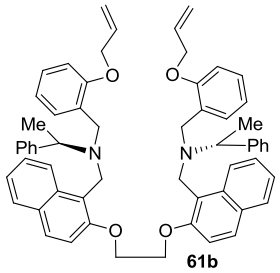
4.19-4.11 (4 H, m), 3.92-3.76 (8 H, m), 3.61 (2 H, d, J = 13.2 Hz), 2.32 (2 H, br. s), 1.37 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 145.8, 130.3, 128.7, 128.4, 128.2, 126.9, 126.9, 120.7, 111.4, 69.9, 67.5, 57.0, 47.5, 24.7; HRMS (ESI): MH^+, found 525.3102. $C_{34}H_{41}N_2O_3$ requires 525.3117.

Typical procedure for the synthesis of *bis*-allyl substrates 61 (Procedure H). To a flame dried round-bottom flask was sequentially added the corresponding *bis*-amine derivative (**60,** 0.5 mmol), 1-(allyloxy)-2-(chloromethyl)benzene (3 equiv) and anhydrous K_2CO_3 (3.5 equiv) in dry CH_3CN (5 mL). The reaction mixture was stirred at 80 ^oC for 48-72 h and after this period, the reaction mixture was allowed to attain the room temperature. The resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc/Hexanes) to give the corresponding product **61**.

Compound 61a. Following the general procedure, **61a** was obtained as a brown coloured liquid (301 mg, 78%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2971, 1600, 1490, 1452 and 1236 cm^{-1}; $[\alpha]^{25}_D$ + 48.62 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.69 (2 H, d, J = 7.5 Hz), 7.66 (2 H, d, J = 7.5 Hz), 7.46 (4 H, d, J = 7.6 Hz), 7.31-7.27 (4 H, m), 7.22-7.14 (6 H , m), 7.00 (2 H, t, J = 7.5 Hz), 6.95 (2 H, t, J = 7.5 Hz), 6.89 (2 H, d, J = 8.2 Hz), 6.81 (2 H, d, J = 8.2 Hz), 6.09-6.02 (2 H, m), 5.40 (2 H, d, J = 17.2 Hz), 5.26 (2 H, d, J = 10.5 Hz), 4.51 (4 H, d, J = 5.1 Hz), 4.30 (4 H, s), 3.98 (2 H, q, J = 6.7 Hz), 3.83 (4 H, dd, J_1 = 15.1 Hz, J_2 = 3.5 Hz), 3.56 (4 H, dd, J_1 = 14.9 Hz, J_2 = 10.2 Hz), 1.43 (6 H, d, J = 6.8Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 156.6, 143.9, 133.7, 129.8, 129.6, 129.2, 129.1, 127.9, 127.8, 127.3, 127.1, 126.4, 120.9, 120.6, 117.0, 111.4, 111.3, 68.8, 66.8, 57.2, 47.5, 47.5, 13.8; HRMS (ESI): MH^+, found 773.4330. $C_{52}H_{57}N_2O_4$ requires 773.4318.



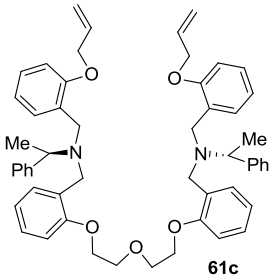
Compound 61b. Following the general procedure, **61b** was obtained as a brown coloured liquid (296 mg, 68%); mp 109-111 ^oC; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3055, 1596, 1491, 1451 and 1265 cm^{-1}; $[\alpha]^{25}_D$ – 13.24 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79-7.73 (6 H, m), 7.35-7.11 (20 H, m), 6.83 (2 H, t, J = 7.3 Hz), 6.77 (2 H, d, J = 7.1 Hz), 5.97-5.87 (2 H, m), 5.33 (2 H, dd, J_1 = 17.2 Hz, J_2 = 1.1 Hz), 5.15 (4 H, dd, J_1 = 10.5 Hz, J_2 = 0.8 Hz), 4.49



61b

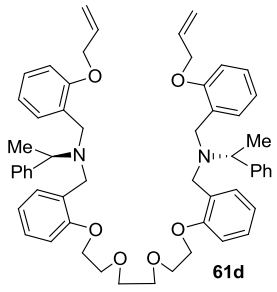
(4 H, s), 4.40 (4 H, d, *J* = 4.9 Hz), 4.28 (2 H, d, *J* = 12.4 Hz), 3.91-3.88 (4 H, m), 3.79 (2 H, d, *J* = 13.4 Hz), 3.47 (2 H, d, *J* = 13.5 Hz), 1.48 (6 H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 155.1, 143.8, 134.4, 133.8, 131.6, 129.6, 129.1, 129.0, 128.7, 127.8, 127.6, 127.5, 126.4, 125.7, 125.7, 123.6, 121.4, 120.4, 116.8, 114.6, 111.5, 68.8, 68.6, 56.8, 46.5, 43.6, 11.5; HRMS (ESI): MH^+, found 873.4647. $C_{60}H_{61}N_2O_4$ requires 873.4631.

Compound 61c. Following the general procedure, **61c** was obtained as a brown coloured liquid (318 mg, 78%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 1600, 1490, 1451 and 1265 cm^{-1}; $[\alpha]^{25}_D$ + 55.69 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (4 H, d, *J* = 7.1 Hz), 7.53 (4 H, d, *J* = 7.7 Hz), 7.36 (4 H, t, *J* = 7.4 Hz), 7.28-7.20 (6 H, m), 7.06-7.01 (4 H, m), 6.87 (4 H, t, *J* = 7.9 Hz), 6.13-6.06 (2 H, m), 5.46 (2 H, d, *J* = 17.2 Hz), 5.31 (2 H, d, *J* = 10.5 Hz), 4.56 (4 H, d, *J* = 4.4 Hz), 4.18-4.15 (4 H, m), 4.06-3.88 (10 H, m), 3.63 (4 H, t, *J* = 14.5 Hz), 1.54 (6 H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.6, 143.7, 133.7, 129.7, 129.7, 129.2, 129.1, 128.0, 127.9, 127.3, 127.2, 126.5, 120.9, 120.7, 117.1, 111.4, 111.3, 70.1, 68.8, 67.8, 57.1, 47.5, 47.5, 14.0; HRMS (ESI): MH^+, found 817.4596. $C_{54}H_{61}N_2O_5$ requires 817.4580.



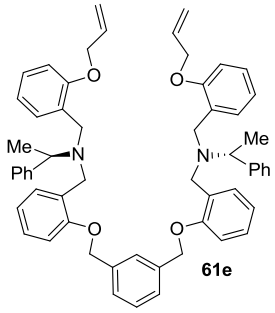
61c

Compound 61d. Following the general procedure, **61d** was obtained as a brown coloured liquid (296 mg, 69%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2872, 1600, 1490, 1452 and 1048 cm^{-1}; $[\alpha]^{25}_D$ + 51.95 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (4 H, d, *J* = 7.4 Hz), 7.53 (4 H, d, *J* = 7.5 Hz), 7.37 (4 H, t, *J* = 7.3 Hz), 7.28-7.19 (6 H, m), 7.02 (4 H, td, J_1 = 7.1 Hz, J_2 = 0.9 Hz), 8.87 (4 H, dd, J_1 = 8.1 Hz, J_2 = 3.8 Hz), 6.16-6.06 (2 H, m), 5.48-5.44 (2 H, m), 5.32 (2 H, dd, J_1 = 10.5 Hz, J_2 = 1.4 Hz), 4.57-4.56 (4 H, m), 4.16 (4 H, t, *J* = 4.8 Hz), 4.08-4.03 (2 H, m), 3.92-3.88 (8 H, m), 3.77 (4 H, s), 3.62 (4 H, t, *J* = 15.2 Hz), 1.54 (6 H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.6, 143.7, 133.7, 129.6, 129.1, 128.0, 127.9, 127.3, 127.2, 126.5, 120.8, 120.7, 117.0, 111.3, 71.0, 69.9, 68.8, 67.7, 57.1, 47.5, 47.5, 14.0; HRMS (ESI): MH^+, found 861.4868. $C_{56}H_{65}N_2O_6$ requires 861.4843.



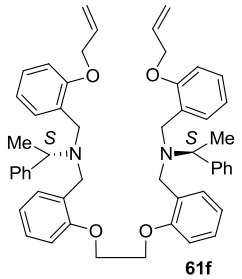
61d

Compound 61e. Following the general procedure, **61e** was obtained as a brown coloured liquid (309 mg, 73%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2969, 1600, 1490, 1452, 1235 and 1104 cm^{-1}; $[\alpha]^{25}_D$ + 48.70 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.73 (2 H, d, J = 7.2 Hz), 7.70 (2 H, d, J = 7.3 Hz), 7.49 (4 H, d, J = 7.6 Hz), 7.44-7.43 (4 H, m), 7.32 (4 H, t, J = 7.4 Hz), 7.24-7.16 (6 H, m), 7.01 (2 H, t, J = 7.4 Hz), 6.96 (2 H, t, J = 7.4 Hz), 6.89 (2 H, d, J = 8.2 Hz), 6.83 (2 H, d, J = 8.2 Hz), 6.02-6.01 (2 H, m), 5.41 (2 H, dd, J_1 = 17.2 Hz, J_2 = 1.1 Hz), 5.27 (2 H, d, J = 10.6 Hz), 5.09 (4 H, s), 4.53 (4 H, d, J = 5.0 Hz), 4.03 (2 H, q, J = 6.7 Hz), 3.89 (4 H, t, J = 14.9 Hz), 3.62 (4 H, dd, J_1 = 15.0 Hz, J_2 = 8.9 Hz), 1.48 (6 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.7, 143.7, 137.8, 133.7, 129.8, 129.7, 129.3, 129.1, 128.9, 128.1, 128.0, 127.4, 127.3, 126.7, 126.6, 126.0, 121.0, 120.8, 117.1, 111.7, 111.4, 70.0, 68.8, 57.3, 47.7, 47.6, 14.2; HRMS (ESI): MH^+, found 849.4649. $C_{58}H_{60}N_2O_4$ requires 849.4631.



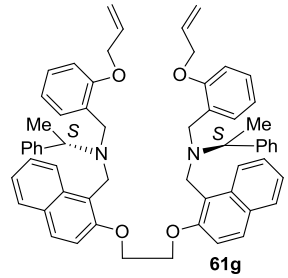
61e

Compound 61f. Following the general procedure, **61f** was obtained as a brown coloured liquid (227 mg, 72%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2970, 1600, 1587, 1452, 1236 and 1024 cm^{-1}; $[\alpha]^{25}_D$ – 59.94 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (2 H, d, J = 7.4 Hz), 7.67 (2 H, d, J = 7.4 Hz), 7.46 (4 H, d, J = 7.5 Hz), 7.29 (4 H, t, J = 7.4 Hz), 7.22-7.14 (6 H , m), 7.00 (2 H, t, J = 7.4 Hz), 6.95 (2 H, t, J = 7.5 Hz), 6.89 (2 H, d, J = 8.1 Hz), 6.81 (2 H, d, J = 8.1 Hz), 6.09-6.01 (2 H, m), 5.40 (2 H, dd, J_1 = 17.4 Hz, J_2 = 1.4 Hz), 5.26 (2 H, dd, J_1 = 10.5 Hz, J_2 = 1.2 Hz), 4.51 (4 H, d, J = 5.0 Hz), 4.30 (4 H, s), 3.98 (2 H, q, J = 6.8 Hz), 3.82 (4 H, dd, J_1 = 15 Hz, J_2 = 3.3 Hz), 3.57 (4 H, dd, J_1 = 14.9 Hz, J_2 = 10.2 Hz), 1.44 (6 H, d, J = 6.8Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 156.6, 143.9, 133.7, 129.8, 129.6, 129.2, 129.1, 127.9, 127.8, 127.3, 127.1, 126.4, 120.9, 120.6, 117.0, 111.4, 111.3, 68.8, 66.8, 57.2, 47.5, 47.5, 13.8; HRMS (ESI): MH^+, found 773.4335. $C_{52}H_{57}N_2O_4$ requires 773.4318.



61f

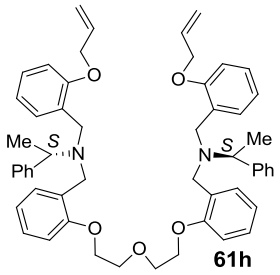
Compound 61g. Following the general procedure, **61g** was obtained as a colourless solid (227 mg, 65%); mp 119-121 ^oC; R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3055, 1591, 1491, 1451, 1265 and 747 cm^{-1}; $[\alpha]^{25}_D$ + 7.78 (c 0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84-7.78 (6 H, m), 7.39-7.15 (20 H, m), 6.87 (2 H, t, J = 7.4 Hz), 6.80 (2 H, d, J = 6.2 Hz), 5.99-5.91



61g

(2 H, m), 5.40-5.35 (2 H, m), 5.20-5.17 (2 H, m), 4.52 (4 H, s), 4.43 (4 H, d, *J* = 4.9 Hz), 4.32 (2 H, d, *J* = 12.4 Hz), 3.95-3.92 (4 H, m), 3.84 (2 H, d, *J* = 13.5 Hz), 3.52 (2 H, d, *J* = 13.4 Hz), 1.53 (6 H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 155.0, 143.7, 134.4, 133.8, 131.6, 129.6, 129.1, 129.0, 128.6, 127.8, 127.6, 127.5, 126.4, 125.7, 125.7, 123.6, 121.4, 120.4, 116.8, 114.6, 111.5, 68.8, 68.6, 56.7, 46.5, 43.6, 11.5; HRMS (ESI): MH^+, found 873.4605. $C_{60}H_{61}N_2O_4$ requires 873.4631.

Compound 61h. Following the general procedure, **61h** was obtained as a brown coloured liquid (310 mg, 76%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 1600, 1490, 1451 and 1265 cm^{-1}; $[\alpha]^{25}_D$ – 55.94 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (4 H, d, *J* = 7.3 Hz), 7.49 (4 H, d, *J* = 7.7 Hz), 7.33 (4 H, t, *J* = 7.4 Hz), 7.24-7.17 (6 H, m), 7.02-6.97 (4 H, m), 6.84 (4 H, t, *J* = 7.3 Hz), 6.08-6.03 (2 H, m), 5.43 (2 H, dd, J_1 = 17.2 Hz, J_2 = 1.4 Hz), 5.28 (2 H, dd, *J* = 10.5 Hz, J_2 = 1.2 Hz), 4.54-4.53 (4 H, m), 4.13 (4 H, t, *J* = 4.8 Hz), 4.04-3.99 (2 H, m), 3.92-3.84 (8 H, m), 3.59 (4 H, t, *J* = 14.3 Hz), 1.50 (6 H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 156.6, 143.7, 133.7, 129.7, 129.7, 129.1, 129.1, 127.9, 127.9, 127.3, 127.2, 126.4, 120.9, 120.7, 117.0, 111.4, 111.3, 70.1, 68.8, 67.8, 57.1, 47.5, 47.4, 14.0; HRMS (ESI): MH^+, found 817.4564. $C_{54}H_{61}N_2O_5$ requires 817.4580.

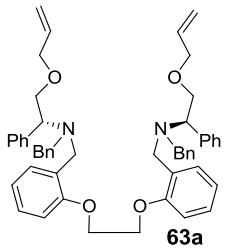


61h

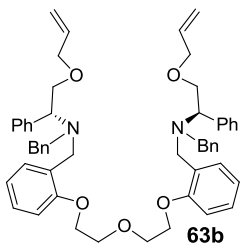
General procedure for the synthesis of compounds 63 (Procedure I). To a mixture of the corresponding diol compound **44** (0.5 mmol) in dry THF (3 mL) was added NaH (4 mmol, 55-60% suspension in mineral oil) rt. Then, the mixture was stirred at rt for 10 min and then, allyl bromide (5 mmol) was added. The resulting mixture was stirred for 30 h at rt. After this period, few drops of EtOH was added and stirred for 10 min and then, the resulting mixture was poured on to water (20 mL) and was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated in *vacuo* and the resulting crude reaction mixture was purified by neutral Al_2O_3 chromatography (EtOAc/Hexanes) to afford the corresponding *O*-allylated products **63**.

Compound 63a. Following the general procedure, **63a** was obtained as a brown coloured liquid (331 mg, 86%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3029, 2859, 1493, 1452 and

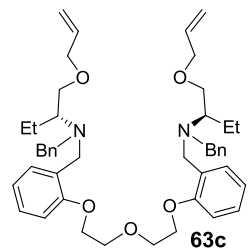
1236 cm^{-1}; $[\alpha]^{25}_D$ – 76.25 (c 0.12, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.68 (2 H, d, *J* = 7.4 Hz), 7.44-7.21 (22 H, m), 7.04 (2 H, t, *J* = 7.3 Hz), 6.91 (2 H, d, *J* = 8.1 Hz), 5.91-5.84 (2 H, m), 5.26-5.21 (2 H, m), 5.15 (2 H, d, *J* = 10.4 Hz) 4.32 (4 H, s), 4.08 (2 H, t, *J* = 6.2 Hz), 4.01-3.97 (2 H, m), 3.93-3.80 (10 H, m), 3.64 (2 H, d, *J* = 14.6 Hz), 3.50 (2 H, d, *J* = 14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.5, 139.1, 134.9, 130.2, 128.8, 128.7, 128.6, 128.2, 128.0, 127.6, 127.0, 126.7, 121.0, 116.7, 111.6, 71.9, 70.1, 66.9, 61.6, 54.8, 47.8; HRMS (ESI): MH^+, found 773.4339. $C_{52}H_{57}N_2O_4$ requires 773.4318.



Compound 63b. Following the general procedure, **63b** was obtained as a brown coloured liquid (310 mg, 76%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2868, 1600, 1493, 1452 and 1240 cm^{-1}; $[\alpha]^{25}_D$ – 76.05 (c 0.15, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (2 H, d, *J* = 7.5 Hz), 7.44-7.10 (22 H, m), 7.02 (2 H, t, *J* = 7.4 Hz), 6.84 (2 H, d, *J* = 8.2 Hz), 5.94-5.85 (2 H, m), 5.28-5.23 (2 H, m), 5.19-5.15 (2 H, m), 4.12-3.80 (22 H, m), 3.67 (2 H, d, *J* = 14.1 Hz), 3.48 (2 H, d, *J* = 14.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.5, 138.9, 134.9, 129.9, 128.9, 128.6, 128.2, 128.0, 127.5, 127.0, 126.7, 120.9, 116.7, 111.5, 72.0, 70.3, 70.1, 67.8, 61.5, 54.8, 47.7; HRMS (ESI): MH^+, found 817.4594. $C_{54}H_{61}N_2O_5$ requires 817.4580.

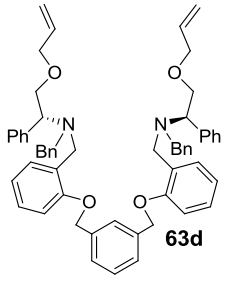


Compound 63c. Following the general procedure, **63c** was obtained as a brown coloured liquid (288 mg, 80%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2872, 1600, 1492, 1452, 1239 and 1096 cm^{-1}; $[\alpha]^{25}_D$ + 8.21 (c 0.09, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.69 (2 H, d, *J* = 7.5 Hz), 7.47 (4 H, d, *J* = 7.6 Hz), 7.34 (4 H, t, *J* = 7.4 Hz), 7.27-7.21 (4 H, m), 7.03 (2 H, t, *J* = 7.5 Hz) 6.89 (2 H, d, *J* = 8.2 Hz), 6.00-5.93 (2 H, m), 5.35 (2 H, d, *J* = 17.2 Hz), 5.22 (2 H, d, *J* = 10.4 Hz), 4.20 (4 H, t, *J* = 4.9 Hz), 4.01-3.97 (8 H, m), 3.90-3.71 (10 H, m), 3.52 (2 H, dd, J_1 = 9.3 Hz, J_2 = 5.2 Hz), 2.83-2.77 (2 H, m), 1.71-1.52 (4 H, m), 1.00 (6 H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 141.1, 135.3, 130.0, 129.2, 128.8, 128.1, 127.4, 126.6, 120.9, 116.4, 111.5, 72.0, 70.7, 70.1, 67.8, 59.0, 54.7, 47.3, 22.0, 12.0; HRMS (ESI): MH^+, found 721.4597. $C_{46}H_{61}N_2O_5$ requires 721.4580.

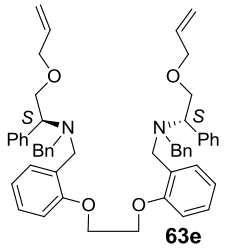


Compound 63d. Following the general procedure, **63d** was obtained as a brown coloured liquid (318 mg, 75%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3028, 2857, 1600, 1493, 1452

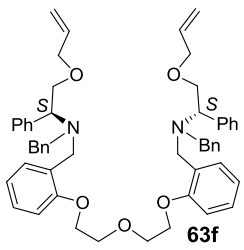
and 1232 cm^{-1}; $[\alpha]^{25}_D$ – 62.09 (c 0.13, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.73 (2 H, d, *J* = 7.4 Hz), 7.47-7.20 (26 H, m), 7.04 (2 H, t, *J* = 7.4 Hz), 6.92 (2 H, d, *J* = 8.2 Hz), 5.93-5.84 (2 H, m), 5.25 (2 H, dd, J_1 = 17.2 Hz, J_2 = 1.5 Hz), 5.16 (2 H, dd, J_1 = 10.4 Hz, J_2 = 2.7 Hz), 5.10 (4 H, s), 4.12 (2 H, t, J = 6.6 Hz), 4.01 (2 H, dd, J_1 = 9.9 Hz, J_2 = 6.0 Hz), 3.99-3.87 (10 H, m), 3.75 (2 H, d, *J* = 14.7 Hz), 3.50 (2 H, d, *J* = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.5, 138.8, 137.7, 134.9, 130.1, 128.9, 128.8, 128.7, 128.7, 128.2, 128.0, 127.5, 127.0, 126.7, 126.6, 125.8, 121.0, 116.7, 111.7, 72.0, 70.3, 69.9, 61.6, 54.8, 47.8; HRMS (ESI): MH^+, found 849.1176. $C_{58}H_{61}N_2O_4$ requires 849.4631.



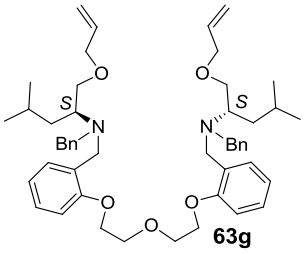
Compound 63e. Following the general procedure, **63e** was obtained as a brown coloured liquid (308 mg, 80%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3096, 2861, 1493, 1452 and 1103 cm^{-1}; $[\alpha]^{25}_D$ + 62.09 (c 0.13, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.67 (2 H, d, *J* = 6.8 Hz), 7.43-7.21 (22 H, m), 7.04 (2 H, t, *J* = 7.4 Hz), 6.91 (2 H, d, *J* = 8.1 Hz), 5.90-5.82 (2 H, m), 5.23 (2 H, dd, J_1 = 17.2 Hz, J_2 = 1.4 Hz), 5.15 (2 H, dd, J_1 = 10.4 Hz, J_2 = 0.9 Hz), 4.32 (4 H, s), 4.07 (2 H, t, *J* = 6.4 Hz), 4.01-3.97 (2 H, m), 3.92-3.79 (10 H, m), 3.64 (2 H, d, *J* = 14.6 Hz), 3.49 (2 H, d, *J* = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.5, 139.1, 134.9, 130.2, 128.8, 128.7, 128.6, 128.2, 128.0, 127.6, 127.0, 126.7, 121.0, 116.6, 111.6, 71.9, 70.1, 66.9, 61.6, 54.8, 47.8; HRMS (ESI): MH^+, found 773.4335. $C_{52}H_{57}N_2O_4$ requires 773.4318.



Compound 63f. Following the general procedure, **63f** was obtained as a brown coloured liquid (318 mg, 78%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2868, 1600, 1493, 1452, 1240, 1104 and 752 cm^{-1}; $[\alpha]^{25}_D$ + 31.14 (c 0.17, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.70 (2 H, d, *J* = 7.4 Hz), 7.45-7.20 (22 H, m), 7.03 (2 H, t, *J* = 7.4 Hz), 6.85 (2 H, d, *J* = 8.1 Hz), 5.95-5.86 (2 H, m), 5.29-5.24 (2 H, m), 5.18 (2 H, dd, J_1 = 10.4 Hz, J_2 = 1.3 Hz), 4.13-3.82 (22 H, m), 3.68 (2 H, d, *J* = 14.8 Hz), 3.49 (2 H, d, *J* = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.5, 138.9, 135.0, 129.9, 128.9, 128.6, 128.6, 128.2, 128.0, 127.5, 127.0, 126.7, 120.9, 116.7, 111.5, 72.0, 70.3, 70.1, 67.8, 61.6, 54.8, 47.7; HRMS (ESI): MH^+, found 817.4558. $C_{54}H_{61}N_2O_5$ requires 817.4580.

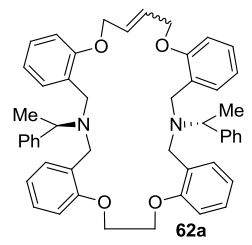


Compound 63g. Following the general procedure, **63g** was obtained as a brown coloured liquid (279 mg, 72%); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2953, 1600, 1452, 1243 and 919 cm^{-1}; $[\alpha]^{25}_D$ – 87.91 (c 0.07, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (2 H, dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.41 (4 H, d, J = 7.1 Hz), 7.32-7.28 (4 H, m), 7.23-7.16 (4 H, m), 6.99 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.7 Hz), 6.85 (2 H, d, J = 8.1 Hz), 5.98-5.90 (2 H, m), 5.34-5.29 (2 H, m), 5.21-5.17 (2 H, m), 4.15 (4 H, t, J = 5.1 Hz), 3.98-3.93 (8 H, m), 3.86-3.80 (4 H, m), 3.74-3.66 (6 H, m), 3.46 (2 H, dd, J_1 = 9.8 Hz, J_2 = 5.4 Hz), 2.92-2.89 (2 H, m), 1.82-1.79 (2 H, m), 1.55-1.48 (2 H, m), 1.23-1.16 (2 H, m), 0.84 (6 H, d, J = 6.7 Hz), 0.66 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 141.0, 135.3, 130.2, 129.2, 128.9, 128.0, 127.4, 126.5, 120.8, 116.2, 111.5, 72.0, 71.1, 70.0, 67.7, 54.8, 54.6, 47.1, 38.6, 24.8, 23.4, 22.3; HRMS (ESI): MH^+, found 777.5190. $C_{50}H_{69}N_2O_5$ requires 777.5206.

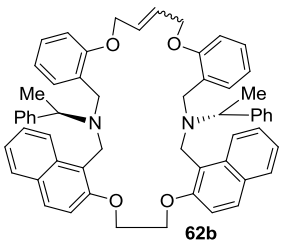


General procedure for the ring closing metathesis (RCM) reaction and synthesis of macrocycles 62a-h and 64a-g (Procedure J). A solution of the corresponding RCM precursor (0.1 mmol) in anhydrous DCM (7 mL) and Grubbs's I generation (5 mol%)) was refluxed for 20-24 h. Then, the mixture was concentrated in *vacuo*. The resulting residue was purified by neutral Al_2O_3 chromatography (Hexanes/EtOAc) to afford the corresponding macrocyclic olefin (**62a-h** and **64a-g**, see the corresponding Tables/Schemes for specific entries).

Compound 62a. Following the general procedure, **62a** was obtained as a colourless solid (59 mg, 80%, *E/Z* = 90:10); mp 158-160 ^oC; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2971,1600, 1588, 1490, 1452 and 1236 cm^{-1}; $[\alpha]^{25}_D$ + 64.11 (c 0.13, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (4 H, t, J = 6.1 Hz), 7.52 (4 H, d, J = 7.6 Hz), 7.29-7.17 (10 H , m), 7.07-7.02 (4 H, m), 6.86 (4 H, t, J = 8.4 Hz), 6.16 (2 H, s), 4.55 (4 H, br. s), 4.30-4.28 (4 H, m), 4.05 (2 H, q, J = 6.8 Hz,), 3.96 (4 H, dd, J_1 = 15.6 Hz, J_2 = 6.7 Hz), 3.59 (4 H, t, J = 17.9 Hz), 1.49 (6 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 156.4, 144.5, 129.4, 129.3, 129.2, 129.1, 127.9, 127.6, 127.4, 127.1, 127.1, 126.3, 121.1, 120.9, 111.1, 111.0, 67.4, 67.0, 56.5, 47.3, 47.1, 12.5; HRMS (ESI): MH^+, found 745.4016. $C_{50}H_{53}N_2O_4$ requires 745.4005. Data given here corresponds to the major isomer.

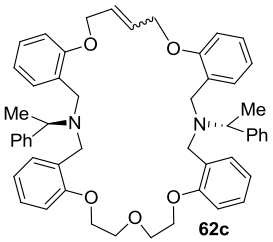


Compound 62b. Following the general procedure, **62b** was obtained as a colourless solid (76 mg, 91%, *E/Z* = 80:20); mp 257-259 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2967, 2857, 1596, 1510, 1492, 1451 and 1239 cm^{-1}; $[\alpha]^{25}_{D}$ – 15.56 (c 0.14, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75 (4 H, dd, J_1 = 9.0 Hz, J_2 = 3.7 Hz), 7.54 (2 H, d, J = 8.5 Hz), 7.36-7.13 (20 H , m), 6.93 (2 H, t, J = 7.4 Hz), 6.88 (2 H, d, J = 8.0 Hz), 6.25 (2 H, br. s), 4.55-4.43 (10 H, m), 4.05-3.99 (6 H, m), 3.42 (2 H, d, J = 13.3 Hz), 1.66 (6 H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 155.1, 144.4, 134.3, 132.2, 129.5, 129.2, 128.6, 127.8, 127.7, 127.6, 127.6, 126.4, 125.8, 125.5, 123.5, 121.6, 120.7, 114.3, 111.1, 68.8, 67.9, 56.5, 45.3, 43.6, 10.6; HRMS (ESI): MH^+, found 845.4307. $C_{58}H_{57}N_2O_4$ requires 845.4318. Data given here corresponds to the major isomer.



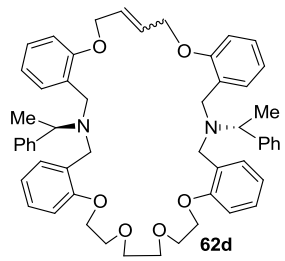
62b

Compound 62c. Following the general procedure, **62c** was obtained as a reddish coloured solid (61 mg, 78%, *E/Z* = 80:20); mp 162-164 ^{o}C; R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 1600, 1490, 1451, 1265 and 740 cm^{-1}; $[\alpha]^{25}_{D}$ + 64.21 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (4 H, d, J = 7.4 Hz), 7.54 (4 H, d, J = 7.7 Hz), 7.33 (4 H, t, J = 7.5 Hz), 7.26-7.20 (6 H, m), 7.08 (4 H, t, J = 6.9 Hz), 6.88 (4 H, d, J = 8.2 Hz), 6.15 (2 H, br. s), 4.58 (4 H, s), 4.15-3.94 (14 H, m), 3.65 (4 H, t, J = 16.3 Hz), 1.54 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.5, 144.1, 129.6, 129.5, 129.3, 129.3, 127.9, 127.8, 127.3, 126.4, 121.0, 121.0, 111.4, 111.1, 70.6, 68.4, 67.8, 57.0, 47.2, 47.2, 13.5; HRMS (ESI): MH^+, found 789.4261. $C_{52}H_{57}N_2O_5$ requires 789.4267. The compound was isolated with minor isomer and the ^{13}C NMR data given here corresponds to the major isomer.



62c

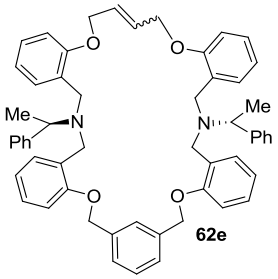
Compound 62d. Following the general procedure, **62d** was obtained as a brown coloured liquid (62 mg, 75%, *E/Z* = 78:22); R_f (15% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2873, 1600, 1491, 1452, 1237 and 1106 cm^{-1}; $[\alpha]^{25}_{D}$ + 47.40 (c 0.07, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78-7.68 (4 H, m), 7.51-7.48 (4 H, m), 7.34-7.16 (10 H, m), 7.04-6.98 (4 H, m), 6.86-6.80 (4 H, m), 6.10 (2 H, br. s), 4.71-4.56 (6 H, m), 4.13-3.57 (20 H, m), 1.51 (6 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 156.5, 156.4, 143.9, 130.0, 129.8, 129.6, 129.6, 129.4, 129.4, 129.2, 129.2, 129.1, 128.5, 128.0, 127.9, 127.8, 127.2, 126.5, 126.4, 121.0,



62d

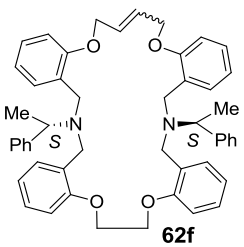
120.9, 111.3, 111.3, 111.2, 111.1, 71.1, 71.0, 69.9, 69.9, 68.1, 68.0, 68.0, 67.9, 64.2, 56.9, 47.2, 47.1, 47.0, 41.7, 14.0, 13.6; HRMS (ESI): MH^+, found 833.4536. $C_{54}H_{61}N_2O_6$ requires 833.4530. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.

Compound 62e. Following the general procedure, **62e** was obtained as a brown coloured solid (67 mg, 82%, *E/Z* = 87:13); mp 81-83 ^oC; R_f (15% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2895, 1599, 1490, 1452, 1232 and 1105 cm^{-1}; $[\alpha]^{25}_D$ + 47.48 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (4 H, td, J_1 = 7.4 Hz, J_2 = 1.4 Hz), 7.57-6.96 (24 H , m), 6.82 (2 H, d, J = 8.2 Hz), 6.05 (2 H, t, J = 2.1 Hz), 5.04 (4 H, s), 4.51 (4 H, s), 4.01 (2 H, q, J = 6.7 Hz), 3.88 (4 H, d, J = 15.2 Hz), 3.58 (4 H, dd, J_1 = 15.3 Hz, J_2 = 3.7 Hz), 1.44 (6 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.5, 144.0, 137.6, 129.6, 129.5, 129.3, 129.2, 128.6, 127.9, 127.8, 127.8, 127.8, 127.7, 127.5, 127.2, 127.1, 126.4, 121.1, 120.9, 111.7, 111.1, 70.4, 67.7, 60.4, 57.0, 47.2, 47.2, 14.2, 13.8; HRMS (ESI): MH^+, found 821.4316. $C_{56}H_{57}N_2O_4$ requires 821.4318. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.



62e

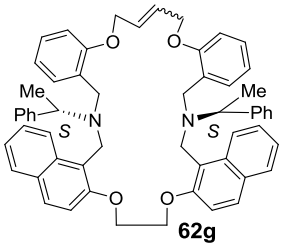
Compound 62f. Following the general procedure, **62f** was obtained as a colourless solid (56 mg, 72%, *E/Z* = 95:05); mp 148-150 ^oC; R_f (15% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2971, 1600, 1490, 1452 and 1284 cm^{-1}; $[\alpha]^{25}_D$ – 60.57 (c 0.13, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.87 (4 H, t, J = 6.8 Hz), 7.56 (4 H, d, J = 7.6 Hz), 7.32-7.17 (10 H , m), 7.10-7.04 (4 H, m), 6.88 (4 H, t, J = 8.3 Hz), 6.18 (2 H, br. s), 4.56 (4 H, br. s), 4.34-4.27 (4 H, m), 4.08 (2 H, q, J = 6.8 Hz,), 3.99 (4 H, dd, J_1 = 15.6 Hz, J_2 = 6.8 Hz), 3.62 (4 H, t, J = 17.9 Hz), 1.52 (6 H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.7, 156.4, 144.5, 129.4, 129.3, 129.2, 129.1, 127.9, 127.6, 127.4, 127.2, 127.1, 126.3, 121.1, 120.9, 111.0, 110.9, 67.4, 66.9, 56.5, 47.3, 47.1, 12.5; HRMS (ESI): MH^+, found 745.4011. $C_{50}H_{53}N_2O_4$ requires 745.4005. Data given here corresponds to the major isomer.



62f

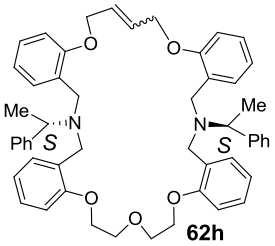
Compound 62g. Following the general procedure, **62g** was obtained as a colourless solid (65 mg, 78%, *E/Z* = 75:25); mp 236-238 ^oC; R_f (15% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3967, 1596, 1492, 1451 and 1239 cm^{-1}; $[\alpha]^{25}_D$ + 13.99 (c 0.14, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H

7.76 (4 H, d, *J* = 9.2 Hz), 7.54 (2 H, d, *J* = 8.5 Hz), 7.35-7.13 (20 H , m), 6.93 (2 H, t, *J* = 7.3 Hz), 6.88 (2 H, d, *J* = 8.2 Hz), 6.25 (2 H, br. s), 4.60-4.43 (10 H, m), 4.02 (6 H, t, *J* = 12.0 Hz), 3.42 (2 H, d, *J* = 13.3 Hz), 1.66 (6 H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 155.1, 144.4, 134.4, 132.2, 129.5, 129.2, 129.2, 128.6, 127.8, 127.7, 127.6, 127.6, 126.4, 125.8, 125.5, 123.5, 121.6, 120.7, 114.3, 111.1, 68.8, 67.9, 56.5, 45.3, 43.6, 10.6; HRMS (ESI): MH^+, found 845.4315. $C_{58}H_{57}N_2O_4$ requires 845.4318. Data given here corresponds to the major isomer.



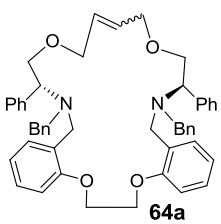
62g

Compound 62h. Following the general procedure, **62h** was obtained as a colourless solid (64 mg, 82%, *E/Z* = 75:25); mp 134-136 ^oC; R_f (18% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3054, 1600, 1490, 1451, 1265 and 1239 cm^{-1}; $[\alpha]^{25}_D$ – 63.46 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (4 H, d, *J* = 7.4 Hz), 7.49 (4 H, d, *J* = 7.6 Hz), 7.33-7.13 (10 H , m), 7.05-6.98 (4 H, m), 6.85 (4 H, d, *J* = 8.2 Hz), 6.12 (2 H, br. s), 4.56 (4 H, br. s), 4.17-3.82 (14 H, m), 3.64-3.54 (4 H, m), 1.50 (6 H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 156.5, 156.4, 144.1, 129.9, 129.8, 129.5, 129.4, 129.3, 129.2, 129.2, 128.5, 127.9, 127.9, 127.8, 127.2, 127.2, 126.4, 121.0, 120.9, 111.5, 111.3, 111.1, 70.5, 70.2, 68.4, 68.2, 67.7, 64.3, 57.2, 56.9, 47.2, 47.1, 13.9, 13.4; HRMS (ESI): MH^+, found 789.4280. $C_{52}H_{57}N_2O_5$ requires 789.4267. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.



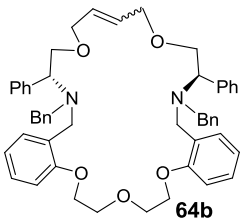
62h

Compound 64a. Following the general procedure, **64a** was obtained as a brown coloured liquid (67 mg, 90%, *E/Z* = 93:07); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 2856, 1492, 1452 and 1236 cm^{-1}; $[\alpha]^{25}_D$ – 58.52 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.66 (2 H, d, *J* = 7.5 Hz), 7.45-7.22 (22 H, m), 7.05 (2 H, t, *J* = 7.3 Hz), 6.91 (2 H, d, *J* = 8.1 Hz), 5.72 (2 H, br. s), 4.41-4.36 (4 H, m), 4.13-3.90 (12 H, m), 3.78 (2 H, d, *J* = 14.0 Hz), 3.62 (4 H, t, *J* = 13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.8, 140.4, 139.8, 130.2, 129.8, 129.0, 128.7, 128.5, 128.2, 128.1, 127.6, 127.0, 126.7, 120.9, 111.4, 70.9, 69.6, 66.7, 61.9, 55.1, 47.8; HRMS (ESI): MH^+, found 745.4022. $C_{50}H_{53}N_2O_4$ requires 745.4005. The data given here corresponds to the major isomer.

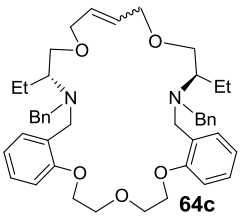


64a

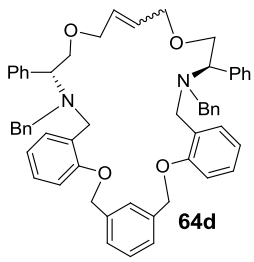
Compound 64b. Following the general procedure, **64b** was obtained as a colourless liquid (63 mg, 80%, *E/Z* = 80:20); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 2863, 1493, 1452 and 1243 cm^{-1}; $[\alpha]^{25}_D$ – 55.74 (c 0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.52-7.19 (24 H, m), 6.98 (2 H, t, *J* = 7.3 Hz), 6.86 (2 H, d, *J* = 8.1 Hz), 5.82 (2 H, br. s), 4.22-3.94 (20 H, m), 3.79-3.55 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 140.5, 140.4, 130.2, 129.2, 128.8, 128.6, 128.6, 128.4, 128.2, 128.0, 127.6, 126.8, 126.7, 120.8, 111.4, 71.1, 70.2, 69.9, 69.4, 67.9, 66.8, 61.2, 61.0, 61.0, 54.7, 48.1, 47.8; HRMS (ESI): MH^+, found 789.4269. $C_{52}H_{57}N_2O_5$ requires 789.4267. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.



Compound 64c. Following the general procedure, **64c** was obtained as a colourless liquid (59 mg, 85%, *E/Z* = 81:19); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 1600, 1490, 1451 and 1246 cm^{-1}; $[\alpha]^{25}_D$ + 88.34 (c 0.05, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.57 (2 H, d, *J* = 7.4 Hz), 7.45 (4 H, d, *J* = 7.3 Hz), 7.33 (4 H, t, *J* = 7.3 Hz), 7.26-7.18 (4 H, m), 6.99 (2 H, t, *J* = 7.2 Hz), 6.86 (2 H, d, *J* = 8.0 Hz), 5.91 (2 H, t, *J* = 2.6 Hz), 4.21-3.92 (16 H, m), 3.78 (2 H, dd, J_1 = 9.8 Hz, J_2 = 5.4 Hz), 3.68-3.59 (4 H, m), 3.50 (2 H, dd, J_1 = 9.8 Hz, J_2 = 5.4 Hz), 2.80-2.75 (2 H, m), 1.62-1.48 (4 H, m), 0.96 (6 H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 141.1, 130.1, 129.3, 129.2, 128.8, 128.1, 127.3, 126.6, 120.8, 111.4, 71.2, 70.7, 70.4, 68.1, 58.7, 54.1, 47.1, 22.9, 11.7; HRMS (ESI): MH^+, found 693.4283. $C_{44}H_{57}N_2O_5$ requires 693.4267. The compound was isolated with minor isomer and the ^{13}C NMR data given here corresponds to the major isomer.

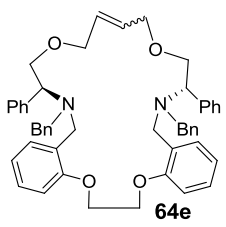


Compound 64d. Following the general procedure, **64d** was obtained as a colourless liquid (67 mg, 82%, *E/Z* = 85:15); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3028, 2857, 1600, 1493, 1452 and 1232 cm^{-1}; $[\alpha]^{25}_D$ – 65.95 (c 0.06, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (1 H, s), 7.53-7.52 (4 H, m), 7.44-7.38 (8 H, m), 7.35-7.22 (15 H, m), 7.02-6.96 (4 H, m), 5.58 (2 H, br. s), 5.15 (4 H, s), 4.20 (2 H, d, *J* = 14.1 Hz), 4.04 (2 H, t, *J* = 6.4 Hz), 3.91-3.84 (4 H, m), 3.77-3.55 (10 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 140.5, 140.1, 139.8, 137.8, 130.5, 129.3, 128.9, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.0, 126.8, 126.7, 126.7,



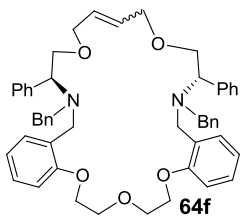
126.4, 120.9, 111.7, 70.9, 70.2, 70.0, 69.8, 66.6, 61.4, 60.9, 54.7, 54.6, 48.3, 47.8; HRMS (ESI): MH^+, found 821.4322. $C_{56}H_{57}N_2O_4$ requires 821.4318. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.

Compound 64e. Following the general procedure, **64e** was obtained as a colourless liquid (53 mg, 72%, *E/Z* = 82:18); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3025, 2855, 1492, 1452, 1236 and 1103 cm^{-1}; $[\alpha]^{25}_D$ + 57.46 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.66 (2 H, d, *J* = 7.5 Hz), 7.45-7.43 (8 H, m), 7.36-7.24 (14 H, m), 7.06 (2 H, t, *J* = 7.4 Hz), 6.92 (2 H, d, *J* = 8.1 Hz), 5.72 (2 H, br. s), 4.41-4.36 (4 H, m), 4.13-3.87 (12 H, m), 3.79 (2 H, d, *J* = 14.0 Hz), 3.62 (4 H, t, *J* = 14.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 140.4, 139.8, 130.2, 129.9, 129.0, 128.7, 128.5, 128.2, 128.1, 127.6, 127.0, 126.7, 120.9, 111.4, 70.9, 69.6, 66.7, 61.9, 55.1, 47.8; HRMS (ESI): MH^+, found 745.4014. $C_{50}H_{53}N_2O_4$ requires 745.4005. The data given here corresponds to the major isomer.



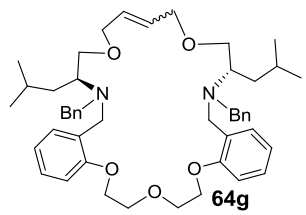
64e

Compound 64f. Following the general procedure, **64f** was obtained as a colourless liquid (58 mg, 74%, *E/Z* = 78:22); R_f (20% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2855, 1492, 1452, 1236 and 1103 cm^{-1}; $[\alpha]^{25}_D$ + 55.74 (c 0.09, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.54-7.49 (6 H, m), 7.43 (4 H, d, *J* = 7.3 Hz), 7.39-7.21 (14 H, m), 7.00 (2 H, t, *J* = 7.3 Hz), 6.89 (2 H, d, *J* = 8.2 Hz), 5.84 (2 H, br. s), 4.24-3.96 (20 H, m), 3.76 (4 H, q, *J* = 14.2 Hz), 3.59 (2 H, d, *J* = 14.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 140.5, 140.4, 130.2, 129.3, 128.8, 128.7, 128.5, 128.2, 128.1, 127.7, 126.9, 126.7, 120.8, 111.4, 71.1, 70.2, 69.9, 67.9, 61.2, 54.8, 48.1; HRMS (ESI): MH^+, found 789.4279. $C_{52}H_{57}N_2O_5$ requires 789.4267. The data given here corresponds to the major isomer.



64f

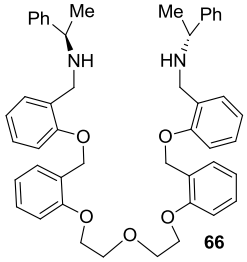
Compound 64g. Following the general procedure, **64g** was obtained as a colourless liquid (65 mg, 88%, *E/Z* = 80:20); R_f (10% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2952, 1491, 1452, 1238 and 1125 cm^{-1}; $[\alpha]^{25}_D$ – 56.29 (c 0.06, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.54-7.49 (2 H, m), 7.42 (4 H, d, *J* = 7.0 Hz), 7.34-7.17 (8 H, m), 7.01-6.96 (2 H, m), 6.87 (2 H, t, *J* = 7.7 Hz), 5.93 (2 H, t, *J* = 2.7 Hz), 4.21-4.01 (14 H, m), 3.92 (2 H, d, *J* = 13.6 Hz), 3.79-3.69 (2 H, m), 3.63 (2 H, dd, J_1 = 9.6 Hz, J_2 = 5.4 Hz), 3.56 (2 H, dd, J_1 = 14.2 Hz, J_2 = 4.1 Hz),



64g

3.49 (2 H, dd, J_1 = 14.2 Hz, J_2 = 4.1 Hz), 2.95-2.90 (2 H, m), 1.90-1.83 (2 H, m), 1.56-1.49 (2 H, m), 1.19-1.12 (2 H, m), 0.86 (6 H, d, J = 6.7 Hz), 0.59 (6 H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.1, 157.0, 141.1, 141.1, 141.0, 130.4, 130.3, 129.7, 129.2, 129.1, 129.1, 129.0, 128.9, 128.1, 127.4, 126.6, 121.0, 120.8, 111.5, 111.4, 71.3, 71.2, 70.8, 70.4, 70.4, 68.1, 68.1, 67.0, 54.6, 54.5, 54.4, 54.2, 47.0, 46.8, 39.6, 39.5, 24.5, 24.4, 23.7, 21.8; HRMS (ESI): MH^+, found 749.4872. $C_{48}H_{65}N_2O_5$ requires 749.4893. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.

Typical procedure for the synthesis of *bis*-amine 66 (Procedure K). To a round-bottom flask was sequentially added the *bis*-aldehyde derivative (**65**, 1 mmol), (*R*)-benzyl amine (2 equiv) in

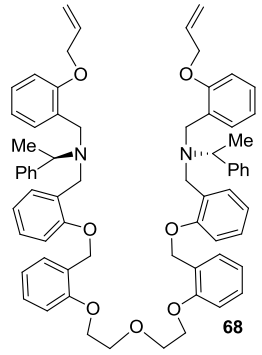


66

EtOH (10 mL). The reaction mixture was refluxed for 12 h and after this period, the reaction mixture was allowed to attain rt and in the same reaction mixture was added $NaBH_4$ (4 equiv) portion wise at rt. Then again reaction mixture was refluxed for 12 h. After this period, the resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc/Hexanes) to give the product **66** as a brown coloured liquid (515 mg, 71%); R_f (60% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 1603, 1494, 1451 and 1242 cm^{-1}; $[\alpha]^{25}_D$ + 57.94 (c 0.08, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.42-7.17 (18 H, m), 7.02 (2 H, t, J = 7.4 Hz), 6.96-6.90 (6 H, m), 5.18-5.10 (4 H, m), 4.12 (4 H, t, J = 4.6 Hz), 3.85 (4 H, t, J = 5.1 Hz), 3.81-3.76 (4 H, m), 3.60 (2 H, d, J = 13 Hz), 2.24 (2 H, br. s), 1.32 (6 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.2, 156.2, 145.6, 130.3, 129.1, 128.8, 128.6, 128.4, 128.2, 126.8, 126.8, 125.8, 121.1, 120.5, 111.7, 111.6, 69.9, 68.0, 65.1, 57.4, 47.8, 24.5; HRMS (ESI): MH^+, found 737.3968. $C_{48}H_{53}N_2O_5$ requires 737.3954.

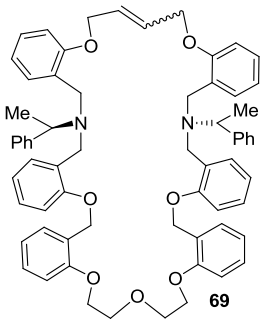
Typical procedure for the synthesis of *bis*-allyl substrate 68 (Procedure L). To a flame dried round-bottom flask was sequentially added the corresponding *bis*-amine derivative (**66**, 0.5 mmol), 1-(allyloxy)-2-(chloromethyl)benzene (3 equiv) and anhydrous K2CO3 (3.5 equiv) in dry CH_3CN (5 mL). The reaction mixture was stirred at 80 ^{o}C for 72 h and after this period, the reaction mixture was allowed to attain the room temperature. The resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers

were dried over anhydrous Na_2SO_4, and crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc/Hexanes) to give the product **68** as a brown coloured liquid (308 mg, 60%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2877, 1601, 1492, 1452, 1239 and 933 cm^{-1}; $[\alpha]^{25}_D$ + 33.60 (c 0.11, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.71 (4 H, d, J = 7.3 Hz), 7.50-7.45 (6 H, m), 7.33-7.10 (12 H, m), 7.01-6.94 (6 H, m), 6.88 (4 H, d, J = 8.1 Hz), 6.82 (2 H, d, J = 8.2 Hz), 6.11-6.02 (2 H, m), 5.41 (2 H, d, J = 17.3 Hz), 5.28 (2 H, d, J = 10.6 Hz), 5.13 (4 H, br. s), 4.54-4.52 (4 H, m), 4.14 (4 H, t, J = 4.4 Hz), 4.01 (2 H, q, J = 6.4 Hz), 3.92-3.83 (8 H, m), 3.60 (4 H, dd, J_1 = 15.0 Hz, J_2 = 8.9 Hz), 1.47 (6 H, d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.6, 155.8, 143.6, 133.6, 129.6, 129.5, 129.1, 129.1, 128.6, 128.3, 128.0, 127.9, 127.2, 127.1, 126.4, 126.2, 121.0, 120.7, 120.6, 117.0, 111.6, 111.4, 111.3, 70.0, 68.8, 67.9, 65.0, 57.1, 47.5, 47.5, 14.1; HRMS (ESI): MH^+, found 1029.5436. $C_{68}H_{73}N_2O_7$ requires 1029.5418.



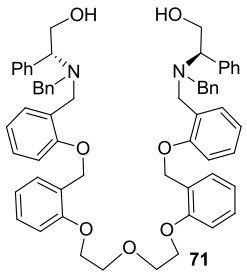
68

Typical procedure for the ring closing metathesis-based synthesis of macrocycle 69 (Procedure M). A solution of **68** (0.1 mmol) in anhydrous CH_2Cl_2 (7 mL) and Grubbs's I generation (5 mol%) was refluxed for 20 h. Then, the mixture was concentrated in *vacuo*. The resulting residue was purified by neutral Al_2O_3 chromatography (Hexanes/EtOAc) to afford the macrocyclic compound **69** as a brown coloured liquid (71 mg, 71%, *E/Z* = 76:24); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2861, 1493, 1452, 1236 and 1103 cm^{-1}; $[\alpha]^{25}_D$ + 37.41 (c 0.07, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.70-7.67 (4 H, m), 7.47 (4 H, d, J = 7.4 Hz), 7.35-7.14 (12 H, m), 7.06 (2 H, td, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 6.99-6.88 (8 H, m), 6.80 (4 H, d, J = 8.2 Hz), 6.04 (2 H, s), 5.03 (4 H, s), 4.49 (4 H, br. s), 4.11-3.79 (14 H, m), 3.57 (4 H, t, J = 12.2 Hz), 1.42 (6 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 156.6, 155.9, 143.9, 129.8, 129.4, 129.2, 129.1, 128.6, 128.4, 128.0, 127.9, 127.8, 127.2, 127.1, 126.3, 126.3, 120.9, 120.8, 120.6, 111.7, 111.6, 111.3, 69.9, 68.2, 67.9, 65.3, 57.2, 47.6, 47.1, 13.9; HRMS (ESI): MH^+, found 1001.5136. $C_{66}H_{69}N_2O_7$ requires 1001.5105. The compound was isolated with minor isomer and the NMR data given here corresponds to both the isomers.



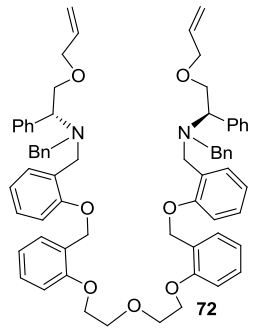
69

Typical procedure for the synthesis of N-protected *bis*-alcohol 71 (Procedure N). Step 1. To a round-bottom flask was sequentially added the corresponding *bis*-aldehyde derivative (**65**, 1 mmol), (*R*)-phenyl glycinol (2 equiv) in EtOH (10 mL). The reaction mixture was refluxed for 12 h and after this period, the reaction mixture was allowed to attain rt and in the same reaction mixture was added $NaBH_4$ (4 equiv) portion wise at rt. Then again reaction mixture was refluxed for 12 h. After this period, the resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and crude reaction mixture was immediately used as such for the next step due to unstable nature of unprotected *bis*-alcohols **70**. **Step 2.** To a flame dried round-bottom flask was sequentially added the crude reaction mixture of alcohol derivative **70**, benzyl chloride (4 equiv) and anhydrous K_2CO_3 (3.5 equiv) in dry CH_3CN (10 mL). The reaction mixture was stirred at 80 ^oC for 72 h and after this period, the reaction mixture was allowed to attain rt. The resulting reaction mixture was added into water and extracted using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in *vacuo* crude reaction mixture was purified by Al_2O_3 column chromatography (EtOAc/Hexanes) to give the product **71** as a brown coloured liquid (507 mg, 69%); R_f (60% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 1602, 1493, 1452, 1244 and 1027 cm^{-1}; $[\alpha]^{25}_D$ – 183.47 (c 0.06, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.44 (2 H, d, J = 7.5 Hz), 7.38-7.25 (24 H, m), 7.19 (2 H, t, J = 8.1 Hz), 7.04-6.99 (4 H, m), 6.96-6.92 (4 H, m), 5.34-5.24 (4 H, m), 4.25-3.91 (18 H, m), 3.61-3.57 (2 H, m), 3.43 (2 H, d, J = 13.0 Hz), 3.17 (2 H, d, J = 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.3, 156.0, 139.5, 135.4, 131.2, 129.4, 129.0, 129.0, 128.7, 128.6, 128.4, 128.2, 127.8, 127.2, 127.0, 125.7, 121.0, 120.8, 112.5, 111.6, 70.0, 68.0, 65.4, 63.1, 60.5, 53.7, 48.2; HRMS (ESI): MH^+, found 949.4782. $C_{62}H_{65}N_2O_7$ requires 949.4792.

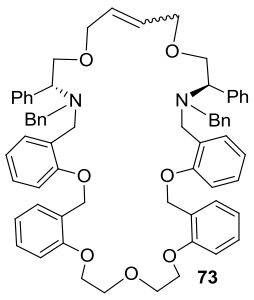


General procedure for the synthesis of compounds 72 (Procedure O). To a mixture of the diol compound **71** (0.5 mmol) in dry THF (3 mL) was added NaH (4 mmol, 55-60% suspension in mineral oil) at rt. The mixture was stirred at rt for 10 min and then, allyl bromide (5 mmol) was added. The resulting mixture was stirred for 30 h at rt. After this period, few drops of EtOH was added and stirred for 10 min and then, the resulting mixture was poured on to water (20 mL) and was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated in *vacuo* and the resulting crude

reaction mixture was purified by neutral Al_2O_3 chromatography by using EtOAc/Hexanes to afford the corresponding *O*-allylated products **72** as a brown coloured liquid (344 mg, 67%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2872, 1602, 1493, 1452, 1029 and 923 cm^{-1}; $[\alpha]^{25}_D$ – 94.40 (c 0.08, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.01 (2 H, dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.47-7.22 (24 H, m), 7.14 (2 H, td, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 7.02-6.96 (4 H, m), 6.92-6.88 (4 H, m), 5.91-5.84 (2 H, m), 5.27-5.14 (8 H, m), 4.16-3.85 (22 H, m), 3.72 (2 H, d, J = 14.8 Hz), 3.47 (2 H, d, J = 14.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 156.9, 155.8, 140.5, 138.7, 134.9, 129.8, 128.9, 128.6, 128.6, 128.6, 128.2, 128.2, 128.0, 127.5, 127.0, 126.7, 126.2, 121.0, 120.7, 116.8, 111.7, 111.4, 72.0, 70.2, 70.0, 67.9, 65.0, 61.5, 54.8, 47.7; HRMS (ESI): MH^+, found 1029.5418. $C_{68}H_{73}N_2O_7$ requires 1029.5418.



Typical procedure for the ring closing metathesis-based synthesis of macrocycle 73 (Procedure P). A solution of the **72** (0.1 mmol) in anhydrous CH_2Cl_2 (7 mL) and Grubbs's I generation (5 mol%)) was refluxed for 20 h. Then, the mixture was concentrated in *vacuo*. The resulting residue was purified by neutral Al_2O_3 chromatography (Hexanes/EtOAc) to afford the corresponding macrocyclic compound **73** as a colourless liquid (75 mg, 75%, *E/Z* = 75:25); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2900, 1600, 1494, 1452 and 1243 cm^{-1}; $[\alpha]^{25}_D$ – 46.25 (c 0.07, DCM); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.58 (2 H, d, J = 7.4 Hz), 7.44-7.20 (24 H, m), 7.12-7.08 (2 H, m), 6.99 (2 H, t, J = 7.3 Hz), 6.93 (2 H, t, J = 7.4 Hz), 6.88 (4 H, dd, J_1 = 7.8 Hz, J_2 = 5.1 Hz), 5.57 (2 H, t, J = 2.8 Hz), 5.13-5.11 (4 H, m), 4.15-4.11 (4 H, m), 4.01 (2 H, t, J = 6.9 Hz), 3.92-3.75 (16 H, m), 3.63 (2 H, d, J = 14.8 Hz), 3.45 (2 H, d, J = 14.0 Hz);^{13}C NMR (100 MHz, $CDCl_3$): δ_C 157.0, 156.0, 140.5, 139.2, 130.0, 129.3, 128.8, 128.8, 128.7, 128.7, 128.6, 128.2, 127.9, 127.5, 126.9, 126.7, 126.2, 121.0, 120.6, 111.7, 111.7, 70.9, 70.0, 69.9, 68.2, 65.2, 61.4, 54.9, 47.7; HRMS (ESI): MH^+, found 1001.5128. $C_{66}H_{69}N_2O_7$ requires 1001.5105. The compound was isolated with traces of minor isomer and the NMR data given here corresponds to major isomer.



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Chapter 4: EDC/DMAP-Mediated direct condensation of dicarboxylic acids and diols: A concise synthesis of extra-large polyether macrocyclic lactones and their X-ray structures.

Introduction

Macrocyclic compounds are synthesized using a variety of chemical reactions and some of the transformations used are, amide/peptide coupling, lactonization/esterification, Williamson ether synthesis, RCM (ring closing metathesis) and Glaser-Hay-Eglington reactions and other types of transformation.[1-4] Depending on the macrocyclic compound to be synthesized, selecting an appropriate ring-closing method to achieve the macrocyclization is a crucial step for obtaining macrocyclic compounds.

While a wide range of macrocyclic systems are known, which include the esteemed crown-type/polyether macrocycles, [1-4] amide-based macrocycles,[5a-c] macrocyclic di- and tetralactones (macrolides) and cyclophanes etc.[5d-g,6,7,11] of particular interest, macrocyclic lactones (e.g., macrocyclic di- and tetralactones) have been attractive molecules due to their remarkable biological activities (Figure 1) and ability to complex and transport alkali metal cations and application in various research fields pertaining to chemical/biological sciences and industry.[8]

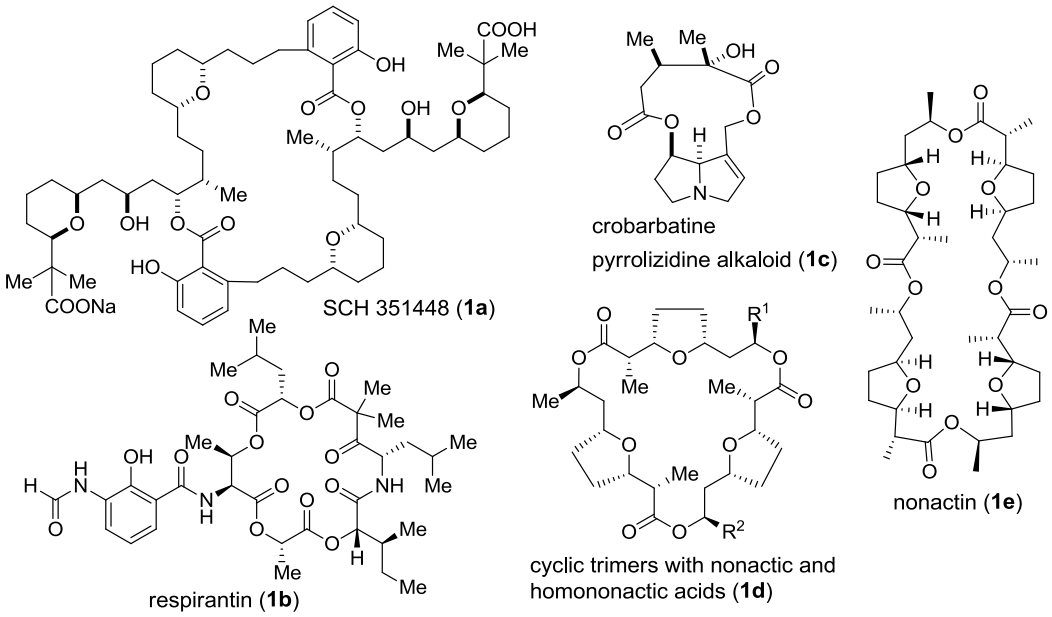


Figure 1. Representative examples of naturally occurring and bioactive macrocyclic lactones.

A literature survey revealed that the synthesis of macrocyclic dilactones have been carried out using various common methods which are; (i) enzymatic reaction of diol with anhydride/dicarboxylic acid,[9a,b] (ii) reactions of alkali metal dicarboxylates with alkyl dibromides,[9c,d,10a-c] and (iii) cyclization of (ω-carboxyalkyl)diphenylsulfonium salts.[10d] Recently, macrocyclic dilactone, (+)-SCH 351448[10e] (Figure 1) was synthesized *via* an intramolecular nucleophilic attack by a phenoxide ion on benzodioxinone system. Representative methods used for the synthesis of macrocyclic tetralactones are; (i) tin template-based synthesis[11a,b] (ii) $CuSO_4$-based intramolecular lactonization,[11c] (iii) RCM-based ring closure,[11d] (iv) Desymmetrization of cyclic anhydrides using diols,[11e] (v) dibutylstannylene acetal of sugar derivative with dicarboxylic acid chlorides,[11f] and (vi) [2+2] photocycloaddition reactions of di-2-pyrones with α,ω-diolefins.[11g] It is to be noted that some of the reported methods dealing on the synthesis of macrocyclic di- and tetralactones are not direct methods and require pre-assembling of alkali metal salts or dicarboxylic acid chlorides and alkyl dibromides or sulfonium salts or a template.

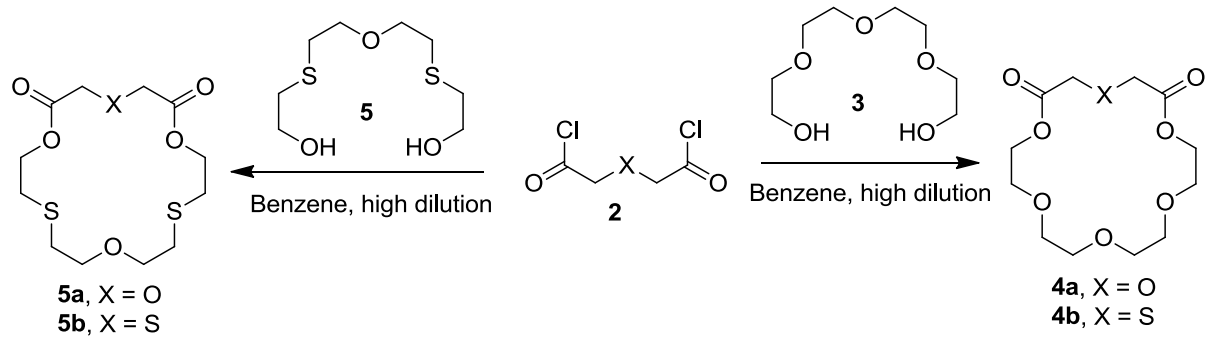
Considering the fact that due to their unique properties macrocyclic systems, continuous attention was paid to develop new methods for obtaining different classes of macrocyclic systems. In recent years, attention was devoted to the synthesis of extra-large or large-cavity-based binuclear macrocycles (e.g., >20 atom-ring cycles, considering 18-crown analogue as standard macrocycle). Especially, extra-large or large-cavity-based amide or lactone-based macrocycles has received a special significant attention because of their tendency to coordinate with more than one metal ions, selectively bind a large range of metal.[12] Some of the extra-large or large-cavity-based macrocycles have been used to understand certain biological process.[13] Traditionally small or medium size macrocyclic systems have been used as receptors and sensors for small organic molecules. Large and conformationally stable macrocyclic systems are proposed to form organic tubular scaffolds by supramolecular association of the subunits *via* covalent and other interactions. Substantial amount of efforts have been devoted for the synthesis of complex macrocyclic models that would permit the reliable simulation of enzyme behaviors experimentally to better understand their function.[13b]

There have been various reports with regard to the synthesis of various types of macrocyclic lactones (e.g., macrocyclic di- and tetralactones) and lactone-based polyether macrocyclic systems and the range of synthetic methods developed for the preparation of macrocyclic lactones (e.g., macrocyclic di- and tetralactones) and lactone-based polyether macrocyclic

systems is broad.[14-20] In line with the objective of the this thesis work, in the following section some of the representative literature works that deal on the synthesis of macrocyclic lactones (e.g., macrocyclic di- and tetralactones) and lactone-based polyether macrocyclic systems are described.

Literature reports on the synthesis of macrocyclic dilactone systems.

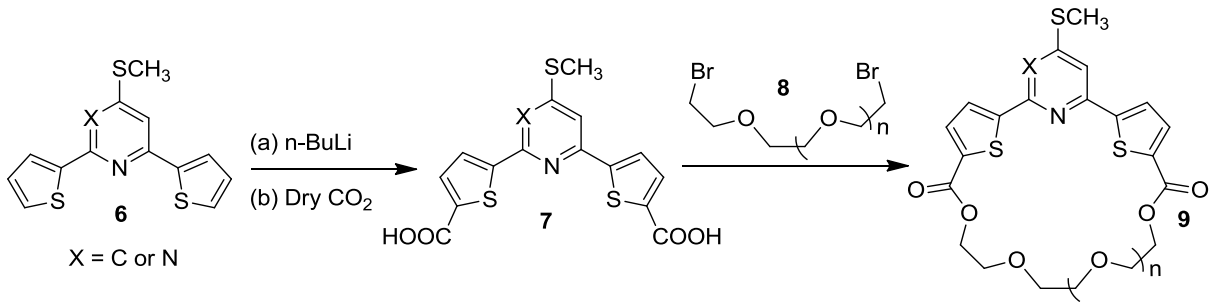
Bradshaw *et al.* reported[14a] the synthesis of a series of macrocyclic polyether-dilactones in which the carbonyl groups are available for cation complexation in a manner similar to valinomycin (a cyclic antibiotic which shows selectivity for potassium over barium in methanol). Macrocyclic polyether-dilactones **4**/**5** were obtained on treatment of various oligoethylene glycols and sulfur-containing oligoethylene glycols with diglycolyl and thiodiglycolyl dichlorides under high-dilution conditions by simultaneously dripping each of the reactants into a large volume of benzene that was being stirred rapidly. Calorimetric titration of the different cations (Ba^{2+}, K^{+}, and Na^{+}) with macrocycle **4a** and 18-crown-6 in methanol were carried out, which proved the effect of the ester moieties on the cation complexing properties of macrocyclic di-lactone systems. A comparison between log *K* values for these cations showed that log *K* values are much smaller in the case of di-lactone macrocycle **4a**. The decreased stabilities of the cation complexes of **4a** are primarily a result of smaller ΔH values, as opposed to the TΔS values which favor complexation of **4a** relative to 18-crown-6 (Scheme 1).



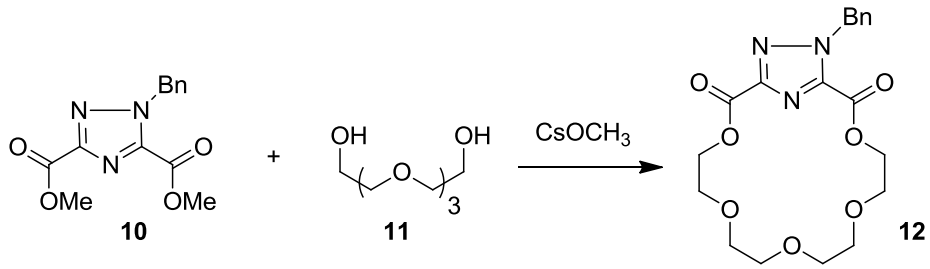
Scheme 1. Synthesis of macrocyclic di-lactones **4**/**5**.

Potts *et al.* reported[14b] the synthesis a variety of polyether diester macrocyclic systems **9** having rigid 2,6-bis(2-thienyl)-4-(methylthio)pyridine subcyclic unit. The reaction of cesium salts of

2,2'-difuryl- and 2,2'-dithienyl-5,5'-dicarboxylic acids **7** (which was assembled from 2,6-bis(2-thienyl)-4-(methylthio) pyridine **6**) with α,ω-dibromopolyethyl ethers **8** in DMF (Scheme 2). Further, utility of the rigid unit based macrocyclic di-lactones have been reported by forming 1:1 complexes with potassium thiocyanate.



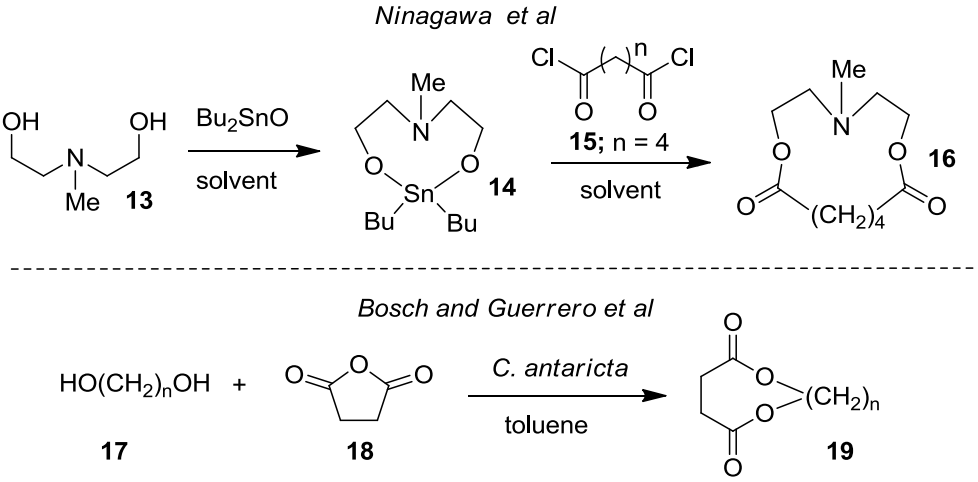
Scheme 2. Synthesis of macrocyclic di-lactone polyether system **9**.



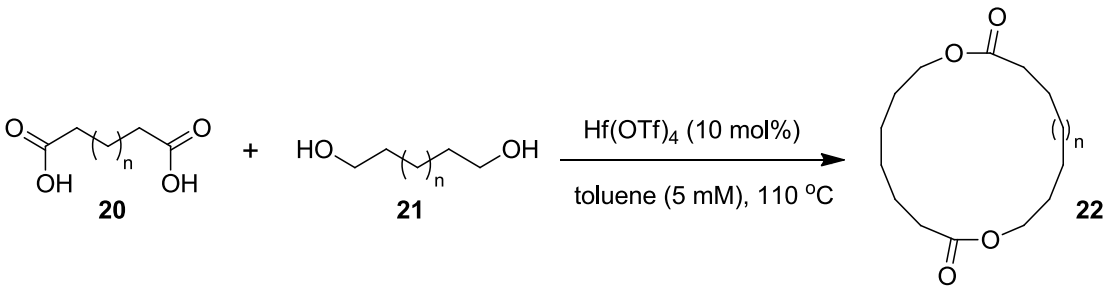
Scheme 3. Synthesis of triazole installed macrocyclic di-lactone **12**.

Dalley and Izatt *et al.* reported[14c] a concise synthesis of proton-ionizable triazole subcyclic unit containing macrocyclic polyether-dilactone systems **12** *via* trans-esterification reaction of dimethyl ester **10** and the appropriate glycol **11** using cesium methoxide as a catalyst (Scheme 3). The crystal structure of one of macrocyclic polyether-dilactone system showed that it forms a hydrate complex with the water molecule, which was located in the macrocyclic cavity. The water is coordinated by hydrogen bonding to two oxygen atoms of the macrocycle and to the N atom of the triazole moiety. Further they studied that, these macrocyclic di-lactone polyethers also formed complexes with amines. These amine complexes are kinetically more stable than complexes formed by the triazole ligands with the corresponding alkylammonium perchlorate salts.

Ninagawa and co-workers reported[15a] tin template-based synthesis of macrocyclic aza-oxo-di-lactones **16**. The direct reaction of diacid chloride **15** with tin template diol intermediate **14**, which was assembled by the treatment of diol **13** with Bu_2SnO, afforded a macrocyclic aza-oxo-di-lactones **16** (Scheme 4). Bosch and Guerrero *et al.* reported[9a] an efficient method to prepare macrocyclic dilactones **19** *via* biocatalytic condensation reaction of diols **17** and succinic anhydride **18** in the presence of *Candida Antarctica B lipase* under mild conditions (Scheme 4).



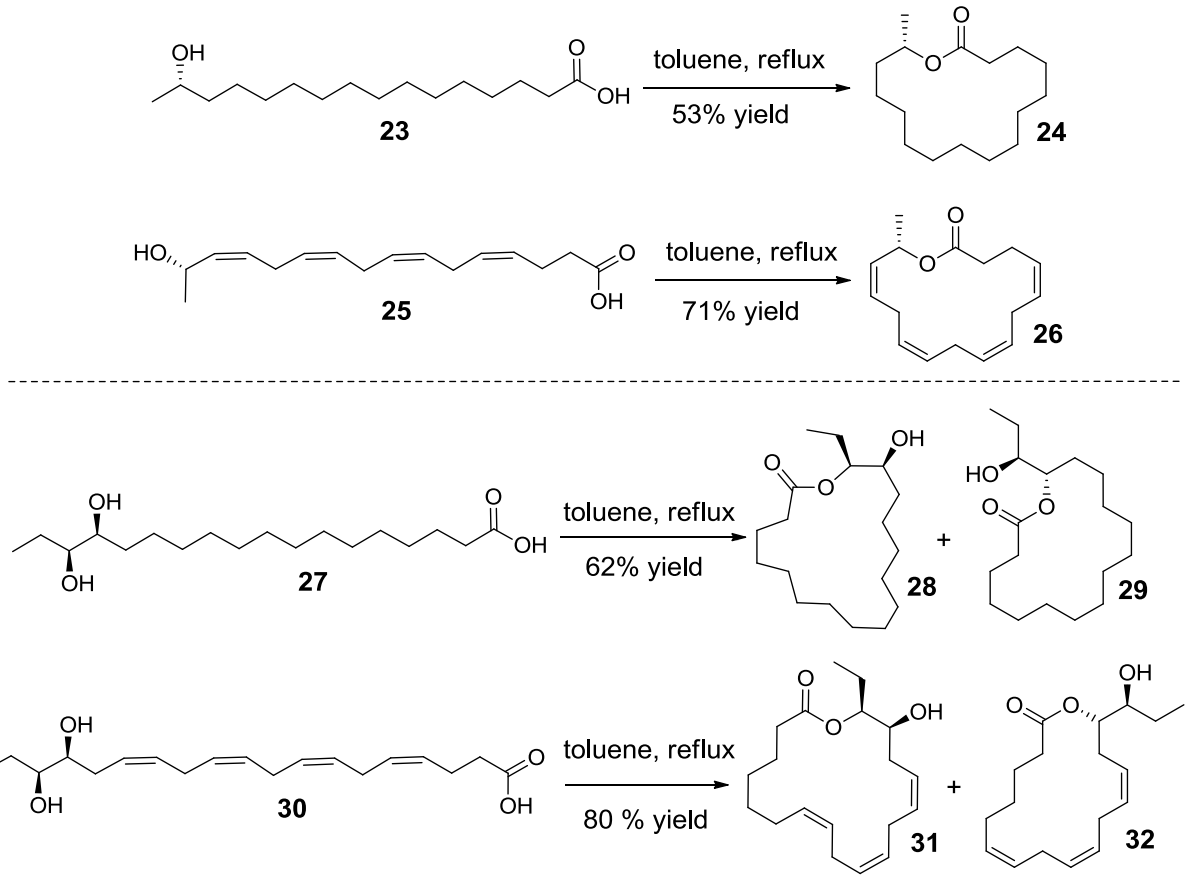
Scheme 4. Tin template-based and lipase-catalyzed synthesis of macrocyclic di-lactones **16** and **19**.



Scheme 5. $Hf(OTf)_4$-catalyzed macrodiolide synthesis.

Recently, Collins group[15b] reported an operationally simple protocol for the synthesis of macrodiolides using commercially available $Hf(OTf)_4$ catalyst. The $Hf(OTf)_4$-catalyzed reactions of equimolar mixtures of diols **21** and dicarboxylic acids (seco acids) **20** led to the synthesis of macrodiolides **22** (Scheme 5).

In the case of macrocyclizations involving rigid building blocks, the geometry of these blocks essentially determines the feasibility of the macrocyclization reaction. Components containing properly substituted aromatic rings, acetylenic units, and allenic subunits and olefin units play a role in the synthesis of shape persistent macrocycles (SPMs). Spinella and Monaco[15c] investigated the influence of the unsaturation on the macrolactonization of different hydroxyl fatty acids **23**/**25** and **27**/**30** (Scheme 6). They found an influence of the olefin units on the macrocyclization yield (53/71% to 62/82%) and the macrolactonization yield was found to be higher for the unsaturated compounds **25** and **30** (Scheme 6).

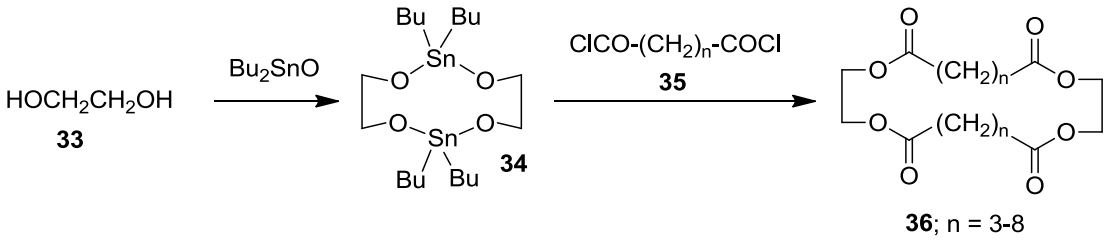


Scheme 6. Hydroxy fatty acids based macrocyclic di-lactone.

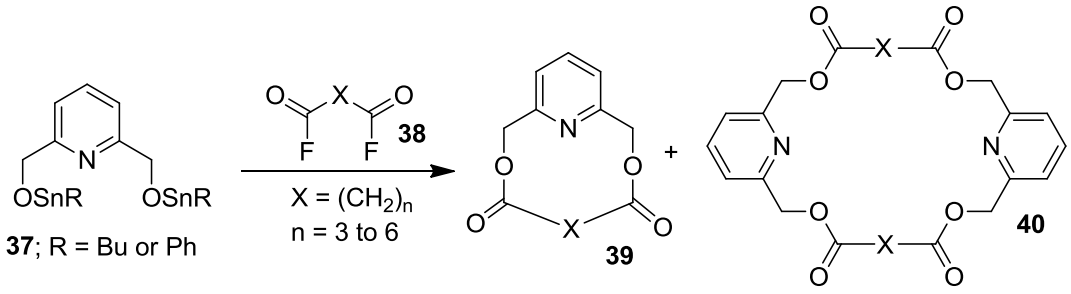
Literature reports on the synthesis of large cavity-based extra-large tetralactone and other macrocyclic systems.

Shanzer and co-workers described[15d,e] a tin template-based preparation of macrocyclic lactones *via* the condensation of acyclic diols and diacyl halides in refluxing chloroform to selectively

provide a large cavity-based 2:2 macrocyclic tetralactones **36** as the sole ring products (Scheme 7). Cyclic stannoxanes are expected to condense efficiently with bifunctional organic substrates such as diols, dicarboxylic acids and diacid chlorides to provide ring products. The usefulness of the method is demonstrated by the preparation of a series of symmetric and mixed tetralactones **36** in high yields. The formation of 2:2 macrocyclic tetralactone as the predominant compound than 1:1 macrocyclic dilactone is due to the occurrence of a stepwise condensation reaction between a cyclic stannoxane and acyl halide (Scheme 7).[15d,e]



Scheme 7. Selective synthesis of large cavity based extra-large 2:2 macrocyclic tetralactones **36**.

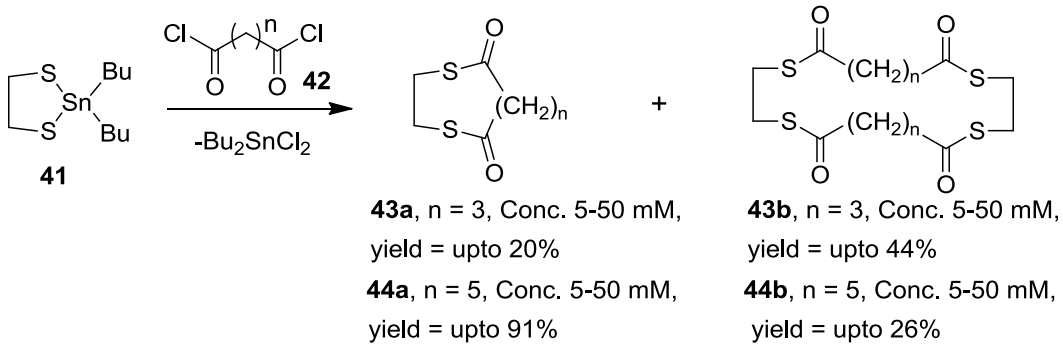


Scheme 8. Synthesis of dilactone **39** and large cavity based extra-large 2:2 macrocyclic tetralactones **40**.

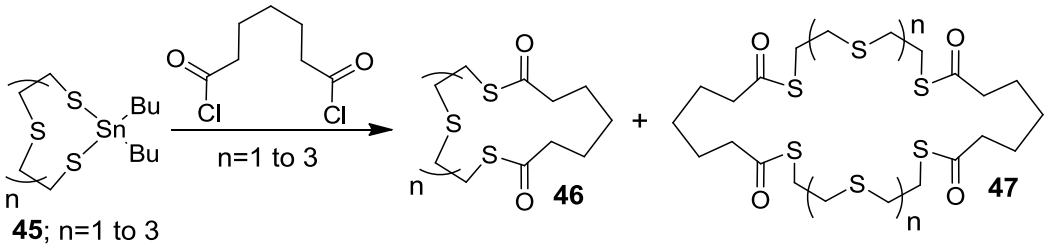
Times and co-workers also reported[15f] the tin template-based synthesis of macrocyclic di- and tetralactones **39**/**40** having a pyridine unit (Scheme 8). On treatment of the diacid fluoride **38** with a tin derivative of 2,6-pyridinedimethanol **37** led to the formation of both dilactone **39** and large cavity based extra-large 2:2 macrocyclic tetralactones **40**.

Dalla Cort *et al*.[15g] studied the synthesis of large cavity-based 2:2 macrocyclic poly(thiolactones) **43/44**. Influenced by the tin template-based approach reported by Shanzer and co-workers, Dalla Cort *et al*. studied the reaction of stannadithiane **41** and diacyl chlorides **42** in refluxing $CHCl_3$ (Scheme 9). The yields of the 1:1 macrocyclic dilactones **43a/44a** and large cavity containing 2:2

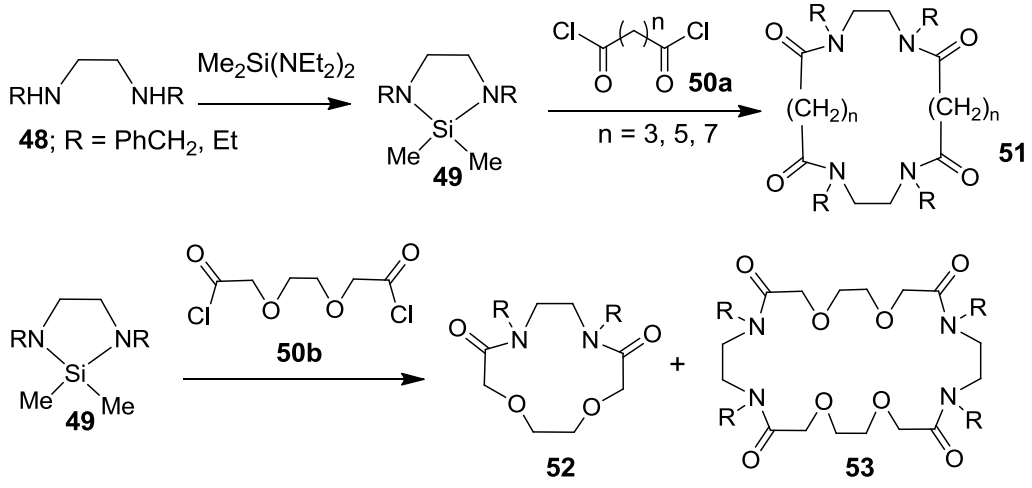
macrocyclic tetralactone **43b/44b** were found to change depending on the concentration of the corresponding reactants and chain length of diacyl chlorides **42** used. Higher concentrations led to decrease in the overall yield of the process due to oligomerization reactions.



Scheme 9. Synthesis of 1:1 macrocyclic dilactones **43a/44a** and large cavity containing 2:2 macrocyclic tetralactone **43b/44b**.



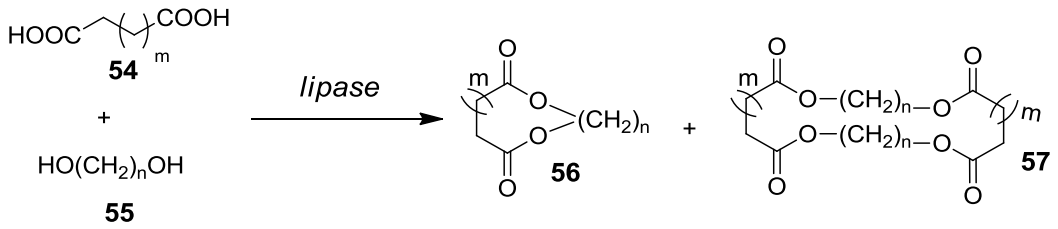
Scheme 10. 1:1 macrocyclic thiolactones **46** and large cavity containing 2:2 macrocyclic thiolactones **47**.



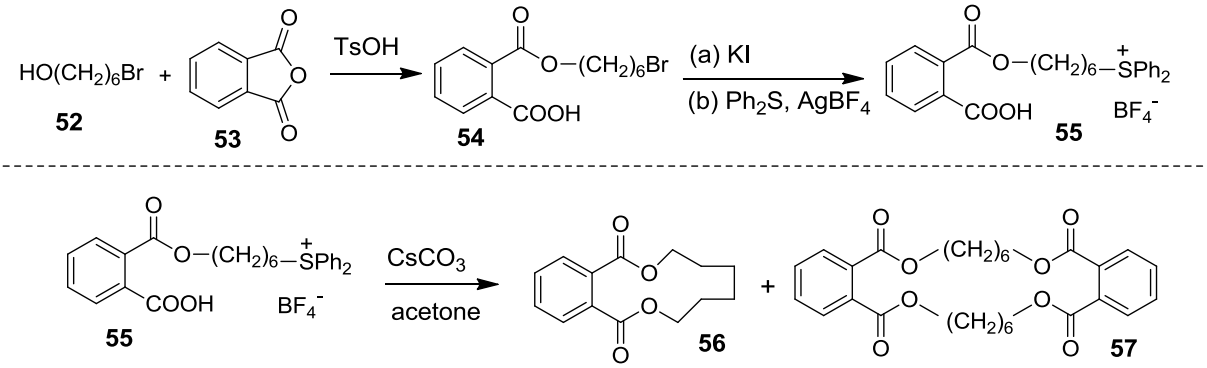
Scheme 11. Silicon templates synthesis of macrocyclic di- and tetra-amide.

Vujasinović and co-workers reported[15h] the synthesis of macrocyclic polythiolactones **46/47** using stannathianes **45**. The reaction of stannathianes **45** with pimeloyl dichloride afforded a mixture of 1:1 macrocyclic lactones **46** and large cavity containing 2:2 macrocyclic lactones **47** (Scheme 10).

Schwartz *et al.* developed[16a] the preparation of cyclic tetraamides **51** (Scheme 11). At first, the preparation of 1,3,2-diazasilolidine intermediate **49** was carried out by treating diamine **48** with dimethylbis(diethy1amino)silane (Scheme 11). Then, the intermediate **49** was reacted with a diacid chloride **50a** to afford the macrocyclic tetraamide **51**. Further, this procedure was used to prepare macrocyclic di- and tetra-amides **52/53** by treating 1,3,2-diazasilolidine intermediate **49** with diacid chloride **50b** (Scheme 11).[16b]



Scheme 12. Biocatalytic synthesis of macrocyclic lactones *via* the condensation of diacids with diols.

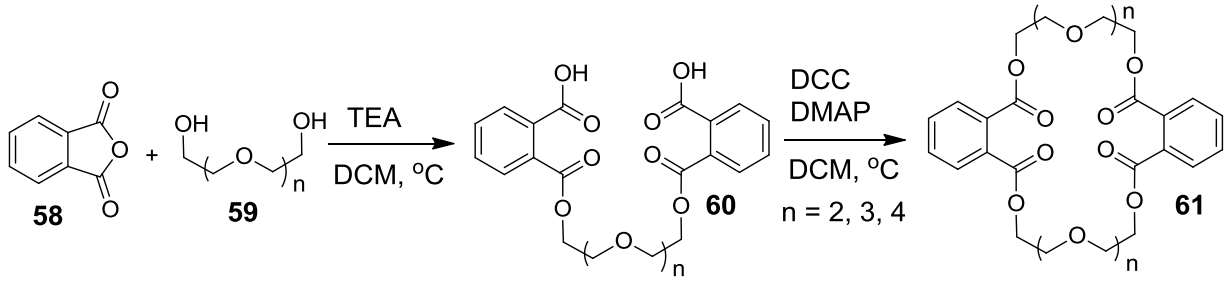


Scheme 13. Synthesis of macrocyclic lactones from sulfonium salt **55**.

Sih *et al*. disclosed[16c] a method for the construction of macrocyclic lactones. Lipase-catalyzed direct condensation of diacids **54** with diols **55** gave a mixture of di-lactone **56** and tetra-lactone **57** in 5-19% yields (Scheme 12). The yield of the macrocyclic lactones found to change depending on the reaction conditions used. In general, nonpolar organic solvents such as

anhydrous isooctane, hexane, cyclohexane and carbon tetrachloride found to be the most suitable solvents.

Matauyama *et al.* described[17a] an efficient method for the synthesis of macrocyclic lactones **56/57** *via* the cyclization of (ω-carboxyalky1)diphenylsulfonium salts **55**, which were prepared from phthalic anhydride **53** (Scheme 13). On treatment of **55** with $CsCO_3$ in acetone afforded the 1:1 macrocyclic dilactones **56** (major product) and large cavity containing 2:2 macrocyclic tetralactones **57** (minor product and sometime obtained in traces). In order to obtain large cavity-based macrocycle **57** in good yield, sulfonium salt **55** was cyclized in the presence of various carbonates, such as Na_2CO_3, K_2CO_3 and $CsCO_3$ under high-dilution conditions. The use of cesium carbonate afforded the macrocycle **57** in considerably good yield (Scheme 13).

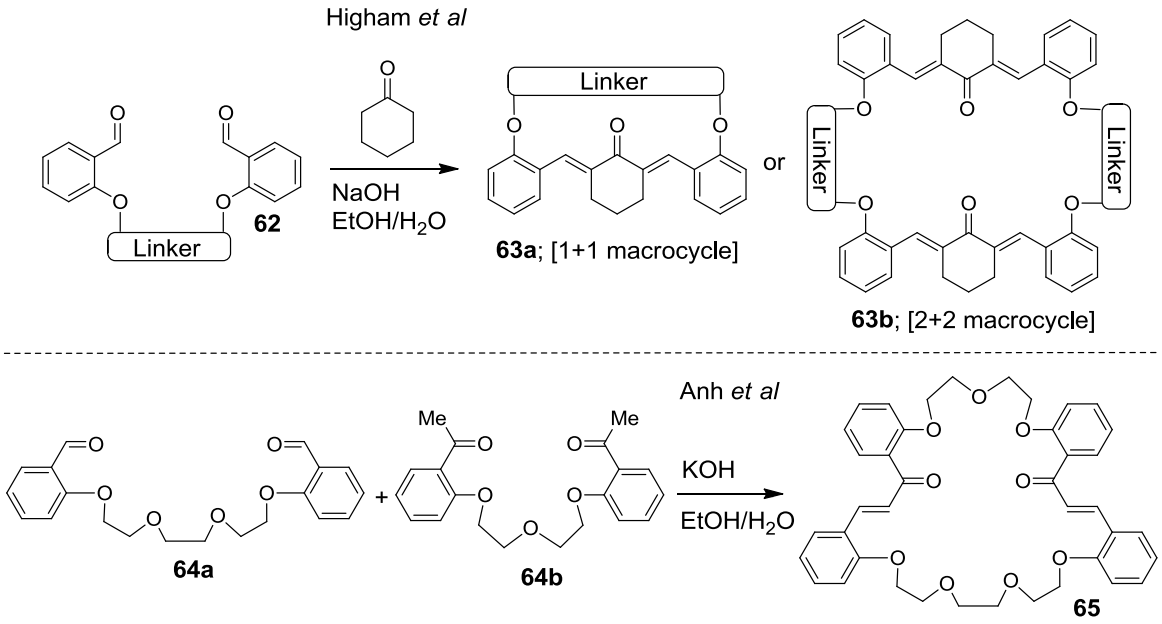


Scheme 14. Synthesis of the macrocyclic tetralactones **61** *via* DCC/DMAP cyclization.

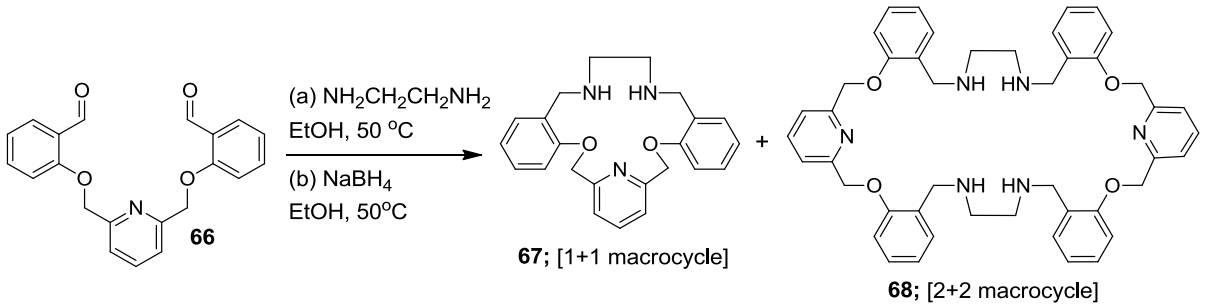
Muthusamy *et al*. reported[17b] the synthesis of 20-34 membered macrocyclic tetralactones **61** from bis-carboxylic acid **60** (Scheme 14). The desymmetrization of cyclic anhydrides **58** using bis alcohols led to the formation of **60**, which was further treated with various bis alcohols in the presence of excess of DCC and catalytic amount of DMAP in DCM at 0 ^oC to furnish large symmetrical and unsymmetrical macrocyclic tetralactones **61** (Scheme 14).

Recently, Higham *et al*. reported[18a] a sequential Claisen-Schmidt/aldol condensations strategy for the synthesis of extra-large cavity containing 2:2 macrocyclic system **63b** in a single step. The condensation of bis-aldehyde **62** and cyclohexanone in the presence of NaOH in refluxing $EtOH/H_2O$ led to the construction of 1:1 and 2:2 macrocyclic products depending on the length of the spacer present in bis-aldehyde precursors **62** (Scheme 15). When the spacer unit contained seven or more atoms afforded the 1:1 macrocyclic product **63a**. In cases where the spacer unit contained fewer than seven atoms, 2:2 macrocyclic products **63b** were obtained (Scheme 15).

Anh and co-workers,[18b] reported the synthesis of 31-crown-7-ether macrocyclic system **65**, involving aldol condensation of bis(2-formylphenoxy)-3,6-dioxaoctane **64a** and bis(2-acetylphenoxy)-3-oxapentane **64b** (Scheme 15).



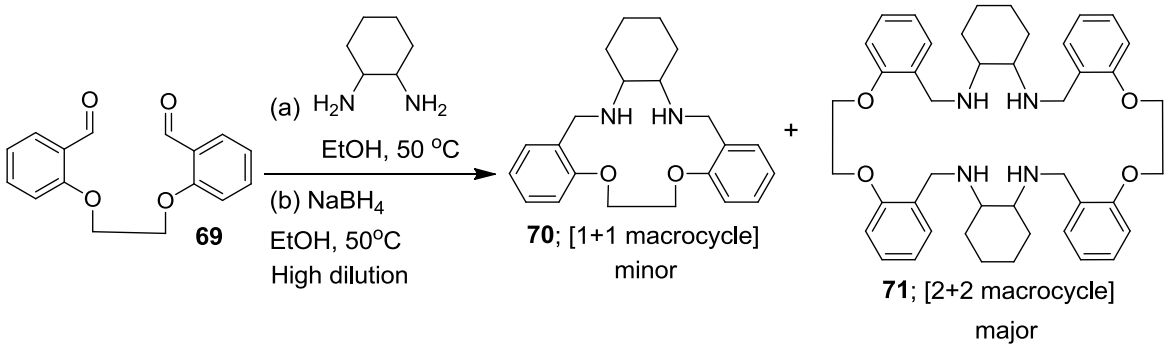
Scheme 15. Synthesis of extra-large macrocycles by sequential Claisen-Schmidt and aldol condensations.



Scheme 16. Synthesis of 18-membered small 1:1 macrocycle **67** and 36-membered large 2:2 macrocycle **68**.

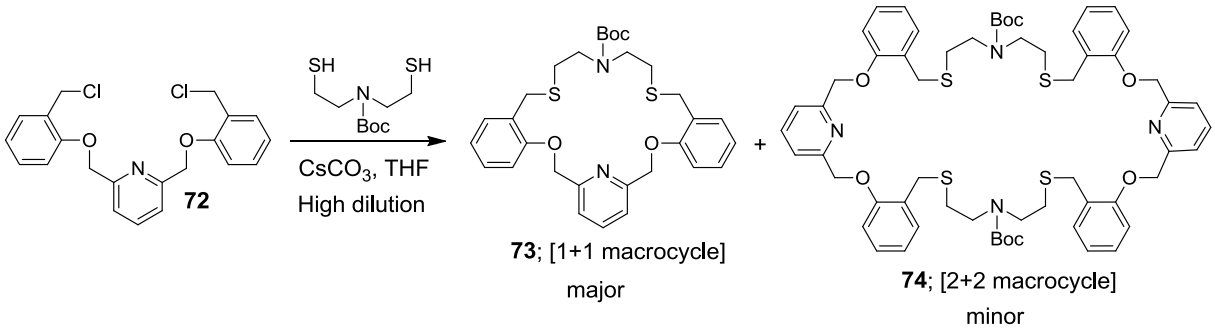
Lindoy *et al.* reported[19a] the synthesis of large cavity containing macrocycle **68** using reductive amination strategy (Scheme 16). The reaction of bis-aldehyde **66** with ethane-1,2-diamine, under very high dilution condition gave a mixture of 18-membered small 1:1 macrocycle **67** and 36-membered large 2:2 macrocycle **68** (Scheme 16). Macrocycle **67** was found to be the major

product in the presence of manganese (II) as a templating ion. When reaction was performed in the absence of metal template and under higher dilution conditions, the 2:2 macrocycle **68** was found to be the major product. Further they have explored the utility of large polyaza-macrocycle **68** in solvent extraction studies due to their tendency for selectively binding with large metal cations (due the large cavity size of **68**).



Scheme 17. Synthesis of 1:1 macrocycle **70** and 2:2 macrocycle **71**.

Matarranz and co-workers[19b] reported the synthesis of macrocyclic systems **70/71** using the procedure described by Lindoy *et al.* (Scheme 17). Reductive amination of reaction of bis-aldehyde **69** with cis-1,2-diaminocyclohexane in the presence of $NaBH_4$ afforded a mixture of the 1:1 macrocycle **70** and 2:2 macrocycle **71**. Repetitive washing and recrystallization processes led to the separation of the 1:1 macrocycle **70** and 2:2 macrocycle **71**. The extra-large 28-membered macrocyclic system **71** was found to have the tendency to form dinuclear complexes with hydrated nitrate and perchlorate salts of transition Co(II) and Cu(II) metal ions.



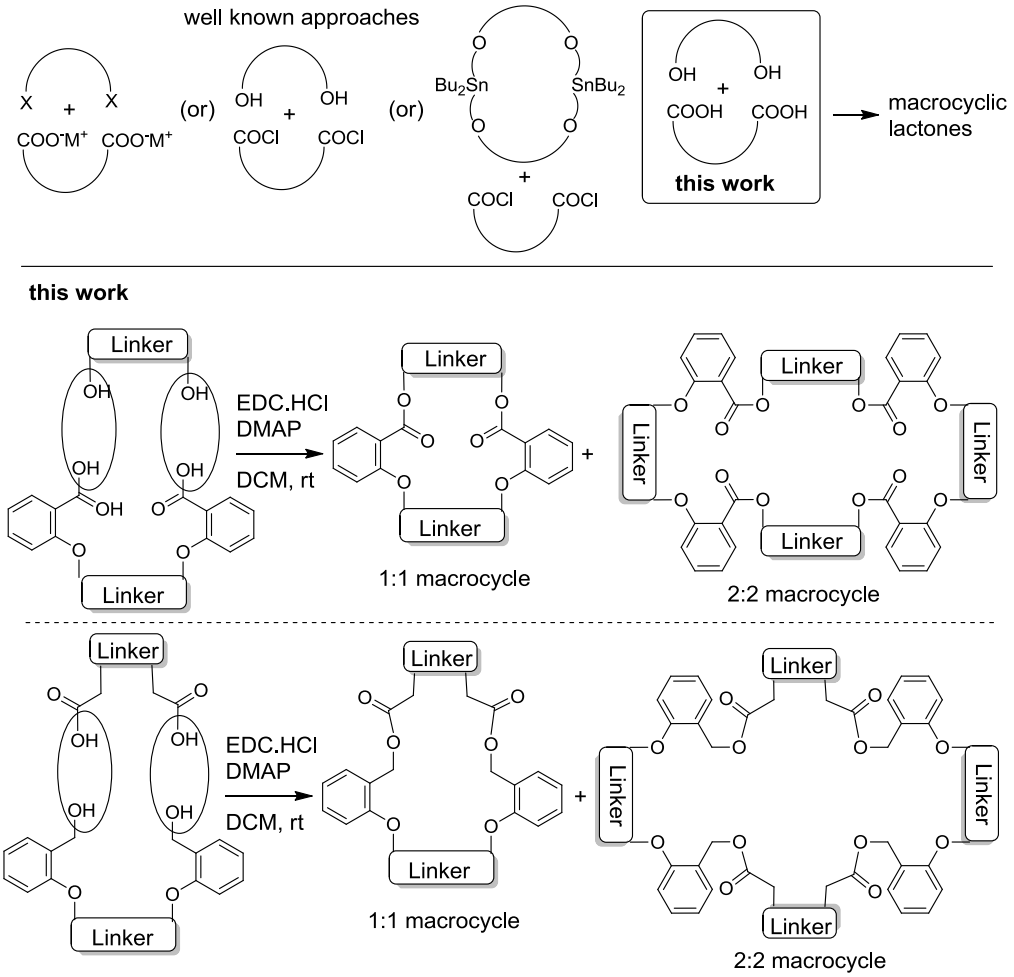
Scheme 18. Synthesis of 1:1 macrocycle **73** and 2:2 macrocycle **74**.

Lee and co-workers, observed[20] the unexpected formation of extra-large cavity containing, 40-membered macrocycle **74** through a 2:2 cyclization of the corresponding *N*-Boc dithiol and dichloride **72** in 17% yield along with the expected 20-membered, 1:1 macrocyclic product **73** in 83% (Scheme 18). The extra-large 40-membered macrocyclic system **74** was found to have the tendency to form dimercury(II) complex, whereas the 20 membered macrocycle **73** formed monomercury(II) complex with mercury (II) metal (Scheme 18).

Result and discussion

Especially, extra-large or large-cavity-based amide or lactone-based macrocycles has received a special significant attention because of their tendency to coordinate with more than one metal ions, selectively bind a large range of metal and various other applications. The introduction part of this Chapter 1 revealed some of the contributions with regard to the synthesis of various types of macrocyclic lactones (e.g., macrocyclic di- and tetralactones) and lactone-based polyether macrocyclic systems. There exist various exceptional reports dealing on the synthesis of different kinds of macrocyclic di- and tetra-lactones.[14-20] It is to be noted that some of the reported methods dealing on the synthesis of macrocyclic di- and tetralactones are not direct methods and require pre-assembling of alkali metal salts or dicarboxylic acid chlorides and alkyl dibromides or sulfonium salts or a template.[14-20] It is also to be noted that a literature survey revealed there exist only limited methods that deal on the direct synthesis of extra-large or large-cavity-based binuclear macrocycles (e.g., >20 atom-ring cycles, considering 18-crown analogue as standard macrocycle) involving the 2:2 and 3:3 cyclization of acyclic precursors.[18-20]

Detailed literature survey reveals that in case of macrocyclizations rigid building blocks, essentially determines the feasibility of the macrocyclization reactions.[15c] Components containing properly substituted aromatic rings, acetylenic units and olefin units play a role in the synthesis of macrocycles but as per our literature survey there exist no report that reveals the effect of rigid building blocks on 2:2 macrocyclization.

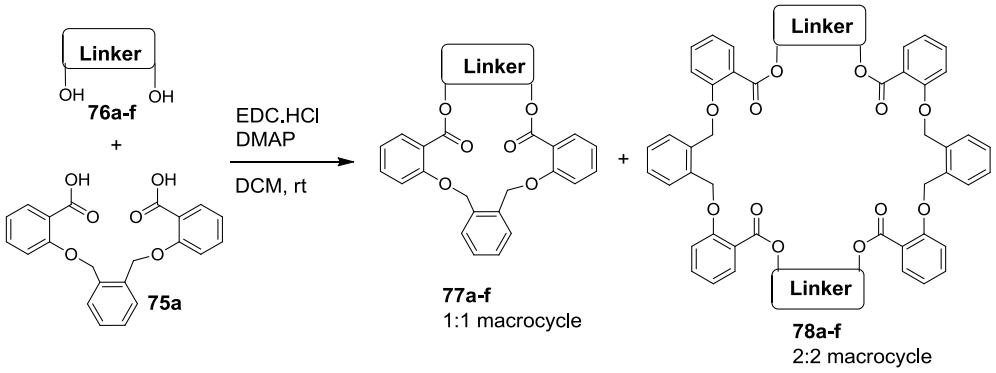


Scheme 19. Direct condensation of dicarboxylic acids and diols mediated by EDC-DMAP.

Given the importance derivatized versions of archetypal (classical) crown ether systems (e.g., 18-crown-6 and dibenzo 18-crown-6 system) and extra-large macrocycles in various areas of biology, chemistry and material science; the synthesis of a library of new classes of large cavity-based extra-large polyether macrocyclic lactones will be highly useful. Particularly, developing a simple and straightforward method comprising direct condensation reactions of dicarboxylic acids with diols affording polyether macrocyclic di- and tetralactones would be highly appreciated.

In line with the objective of this thesis and taking an impetus from the papers dealing on the synthesis of large cavity-based extra-large macrocyclic macrocyclic systems, a part of this thesis envisaged the synthesis of a library of new classes of large cavity-based, extra-large polyether macrocyclic di- and tetralactones. Accordingly, this Chapter 4, reports the investigations on the

direct condensation reactions of a wide range of dicarboxylic acids with various diols mediated by EDC.HCl/DMAP and the synthesis of 18-58 membered, polyether macrocyclic di-/tetralactones and effect of different rigid/flexible linkers/spacers on 2:2 macrocyclization were studied (Scheme 19).



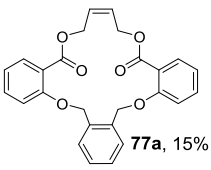
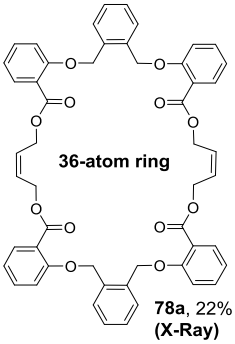
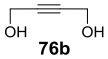
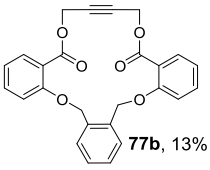
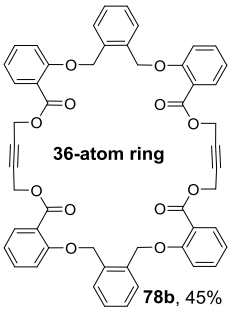
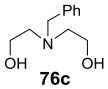
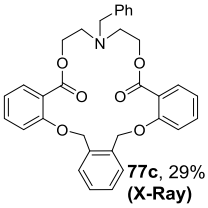
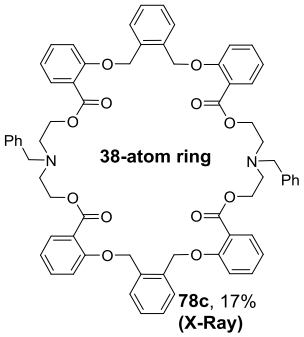
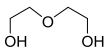
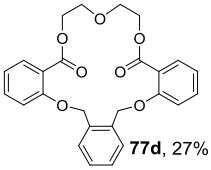
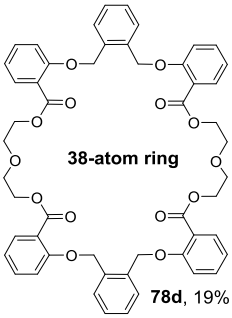
Scheme 20. Generalized scheme for the direct condensation of dicarboxylic acid **75a** and diols **76a-f**. Synthesis of macrocyclic lactones **77a-f** (small) and **78a-f** (extra-large).

To begin with the synthesis of new classes of extra-large polyether macrocyclic tetralactones *via* the direct reactions of dicarboxylic acids and diols, initially the dicarboxylic acid **75a** was assembled from salicylic acid and *o*-xylylene dibromide (Scheme 20). The dicarboxylic acid **75a** (0.25 mmol, 1 equiv) was treated with a various diol systems **76a-f** in the presence of DMAP (1 equiv) and EDC.HCl (2.5 equiv) in DCM (15 mL) to afford the corresponding macrocyclic lactones **77** (1:1 cyclization) and **78** (2:2 cyclization) as shown in Scheme 20 (generalized scheme). In an initial attempt, the dicarboxylic acid **75a** was treated diol **76a** ((*Z*)-but-2-ene-1,4-diol, 1 equiv) in the presence of DMAP (1 equiv) and EDC.HCl (2.5 equiv) in DCM (15 mL). Then, the solvent was removed to afford a crude reaction mixture, which was subjected to the column chromatographic purification, which afforded the macrocyclic lactone **77a** (18-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78a** (36-membered, 2:2 cyclization adduct) in 15 and 37% yields, respectively (Table 1). Similarly, the EDC/DMAP-mediated reaction of **75a** with a rigid diol system **76b** furnished the macrocyclic lactone **77b** (18-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78b** (36-membered, 2:2 cyclization adduct) in 13 and 45% yields, respectively (Table 1).

Next, the EDC/DMAP-mediated condensation reaction of **75a** with a flexible diethanolamine system **76c** was performed. This reaction furnished the expected macrocyclic lactone **77c** (19-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78c** (38-membered, 2:2 cyclization adduct) in 29 and 17% yields, respectively (Table 1). Similarly, the EDC/DMAP-mediated condensation reaction of **75a** with a flexible diethylene glycol system **76d** was performed, which also gave the macrocyclic lactone **77d** (19-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78d** (38-membered, 2:2 cyclization adduct) in 27 and 19% yields, respectively (Table 1). In this reaction, along with **77d** and **78d** a 3:3 cyclization adduct **79d** was also obtained in 5% yield (Scheme 21). Next, the condensation reaction of **75a** with a flexible 2,2'-thiodiethanol system **76e** afforded the macrocyclic lactone **77e** (19-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78e** (38-membered, 2:2 cyclization adduct) in 15 and 12% yields, respectively (Table 1). In this reaction, along with **77e** and **78e** a 3:3 cyclization adduct **79e** was also obtained in 9% yield (Scheme 21).

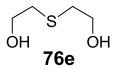
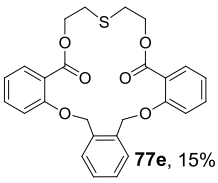
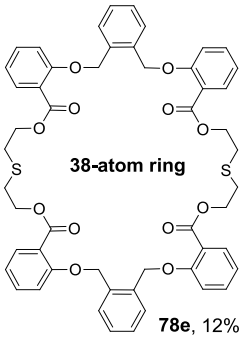
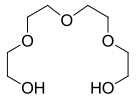
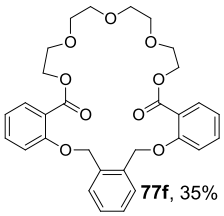
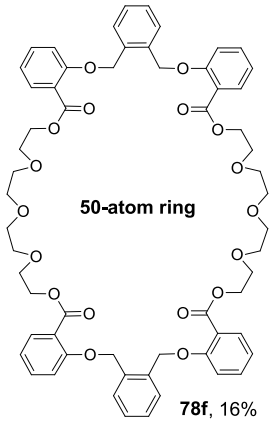
Condensation reaction of polyether diol **76f** having long chain length when compared diol linkers **77a-e** with dicarboxylic acid **75a** afforded macrocyclic lactones **77f** (25-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78f** (50-membered, 2:2 cyclization adduct) in 35 and 16% yields, respectively (Table 1). It is to be noted that the 2:2 cyclization adducts **78a** and **78b** were obtained as the major isomers when the macrocyclization reactions were carried out by using rigid diol systems **76a** and **76b**. On the other hand, 1:1 cyclization adducts **78c-f** were obtained as the major isomers when the macrocyclization reactions were carried out by using flexible diol systems **76c-f** (Table 1).

Table 1. Direct condensation of dicarboxylic acids **75a** and diols **76a-f**. Synthesis of macrocyclic lactones **77a-f** (small) and **78a-f** (extra-large).[a]

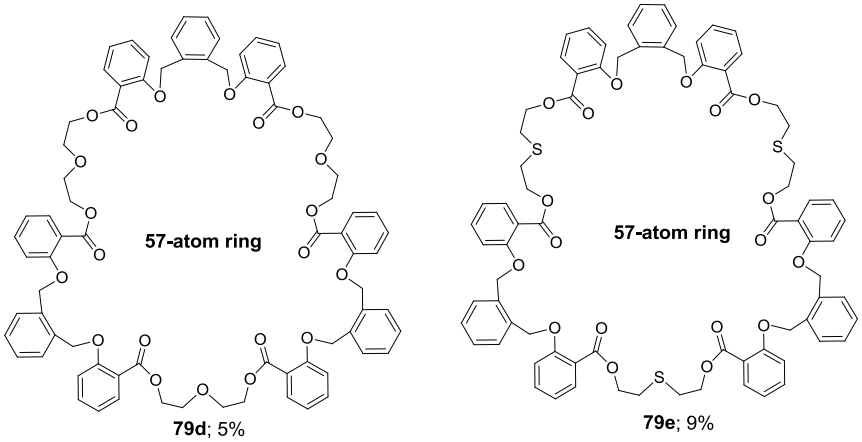
Entry	Diol (**76**)	t (h)	Macrocyclic Diactones (**77**)	Macrocyclic Tetralactones (**78**)	Total yield
1	 **76a**	14	**18-atom ring**  **77a**, 15%	 **36-atom ring** **78a**, 22% **(X-Ray)**	37
2	 **76b**	20	**18-atom ring**  **77b**, 13%	 **36-atom ring** **78b**, 45%	58
3	 **76c**	17	**19-atom ring**  **77c**, 29% **(X-Ray)**	 **38-atom ring** **78c**, 17% **(X-Ray)**	46
4	 **76d**	5	**19-atom ring**  **77d**, 27%	 **38-atom ring** **78d**, 19%	51

[a] Reagents: **75** (0.5 mmol), **76** (0.5 mmol), DCM (15 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).

Table 1 (Continued). Direct condensation of dicarboxylic acids **75a** and diols **76a-f**. Synthesis of macrocyclic lactones **77a-f** (small) and **78a-f** (extra-large).[a]

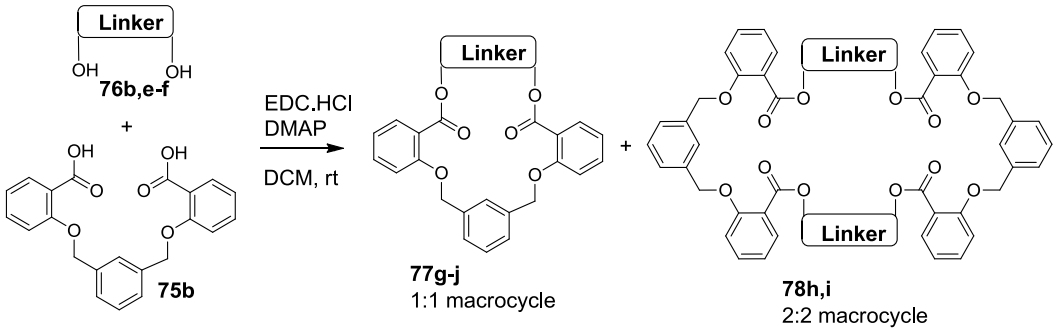
Entry	Diol (**76**)	t (h)	Macrocyclic Diactones (**77**)	Macrocyclic Tetralactones (**78**)	Total yield
5	 **76e**	5	**19-atom ring**  **77e**, 15%	 **38-atom ring** **78e**, 12%	36
6	 **76f**	10	**25-atom ring**  **77f**, 35%	 **50-atom ring** **78f**, 16%	51

[a] Reagents: **75** (0.5 mmol), **76** (0.5 mmol), DCM (15 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).



79d; 5% **79e**; 9%

Scheme 21. 57-Membered extra-large macrocyclic lactones **79d**,**e**.



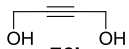
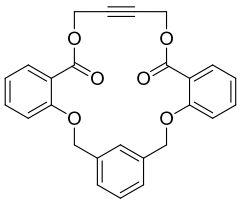
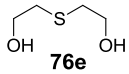
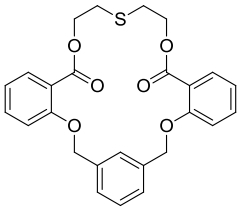
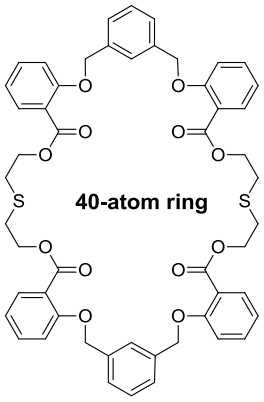
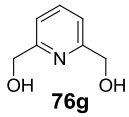
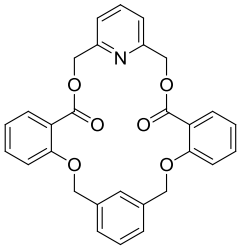
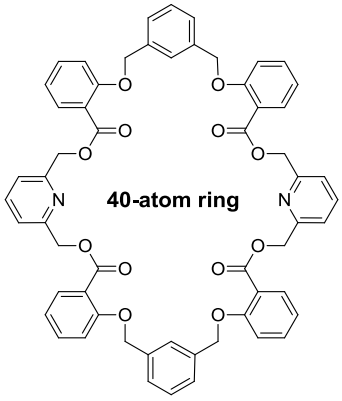
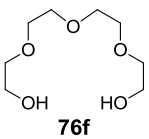
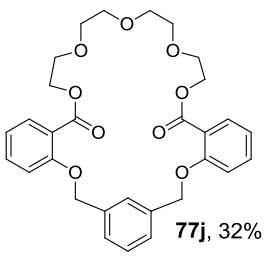
Scheme 22. Generalized scheme for the direct condensation of dicarboxylic acid **75b** and diols **76b,e-f**. Synthesis of macrocyclic lactones **77g-j** (small) and **78h,i** (extra-large).

To elaborate the substrate scope, the dicarboxylic acid **75b** was assembled from salicylic acid and *m*-xylylene dibromide (Scheme 22, generalized scheme). The dicarboxylic acid **75b** (0.25 mmol, 1 equiv) was treated with a various diol system **76b** and **76e-g** in the presence of DMAP (1 equiv) and EDC.HCl (2.5 equiv) in DCM (15 mL) to afford the corresponding macrocyclic lactones **77** (1:1 cyclization) and **78** (2:2 cyclization) as shown in Scheme 22 (generalized scheme). In an initial reaction, the EDC/DMAP-mediated condensation reaction of **75b** with a rigid diol system **76b** afforded only the 1:1 cyclization adduct **77g** (19-membered) in 38% and the corresponding 2:2 cyclization adduct was not obtained (Table 2). Subsequently, the EDC/DMAP-mediated condensation reaction of **75b** and a flexible diol system **76e** was performed. This reaction furnished the macrocyclic lactone **77h** (20-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78h** (40-membered, 2:2 cyclization adduct) in 38 and 9% yields, respectively (Table 2).

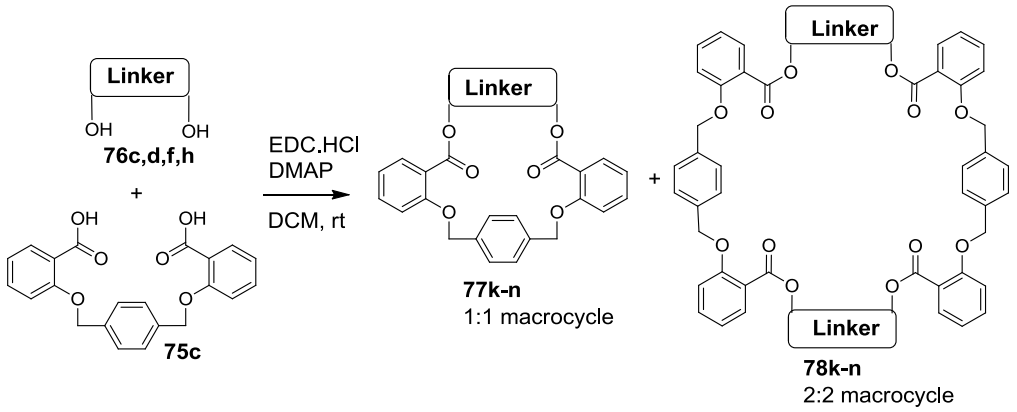
The EDC/DMAP-mediated condensation of **76g** and **75b** also furnished the macrocyclic lactone **77i** (20-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78i** (40-membered, 2:2 cyclization adduct) in 52 and 4% yields, respectively (Table 2). Next, the EDC/DMAP-mediated condensation of **76f** and **75b** furnished only the macrocyclic lactone **77j** (26-membered, 1:1 cyclization adduct) in 32% yield and in this case, the corresponding 2:2 cyclization adduct was not observed (Table 2). It is to be noted that, when compared to the substrate **75a**, the reaction of substrate **75b** with **76b** afforded only a 1:1 cyclization adduct **77g** and an exact reason is not clear to us at this stage. Similarly, the reaction of **75b** with flexible

diol systems **76e/76g** afforded 2:2 cyclization adducts **78h/78i** as the minor product similar to the products **76c-f**.

Table 2. Direct condensation of dicarboxylic acids **75a** and diols **76b,e,g,f**. Synthesis of macrocyclic lactones **77g-j** (small) and **78h,i** (extra-large).[a]

Entry	diol (**76**)	*t* (h)	macrocyclic dilactones (**77**)	macrocyclic tetralactones (**78**)	total yield
1	 **76b**	10	**19-atom ring**  **77g**, 38%	ND	38%
2	 **76e**	16	**20-atom ring**  **77h**, 38%	 **40-atom ring** **78h**, 9%	47%
3	 **76g**	10	**20-atom ring**  **77i**, 52%	 **40-atom ring** **78i**, 4%	56%
4	 **76f**	16	**26-atom ring**  **77j**, 32%	ND	32%

[a] Reagents: **75** (0.5 mmol), **76** (0.5 mmol), DCM (15 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).

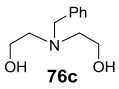
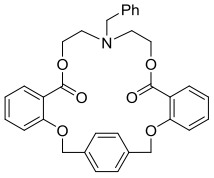
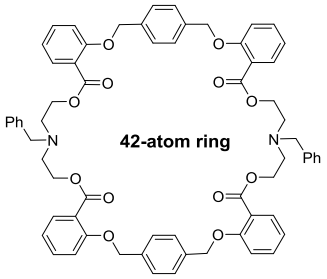
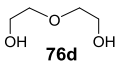
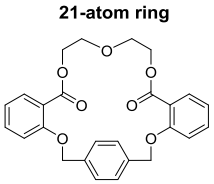
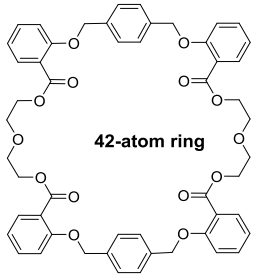
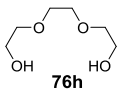
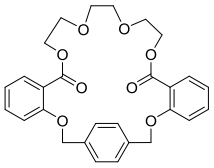
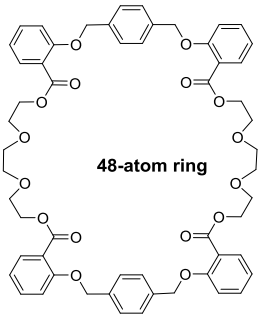
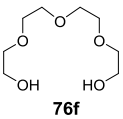
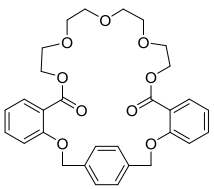
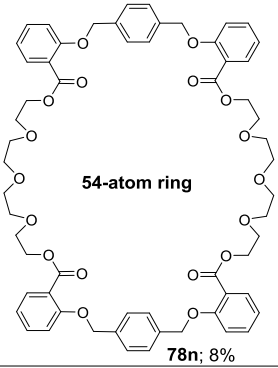


Scheme 23. Generalized scheme for the direct condensation of dicarboxylic acids **75c** and diols **76c,d,h,f.** Synthesis of macrocyclic lactones **77k-n** (small) and **78k-n** (extra-large).

Next, the dicarboxylic acid **75c** was assembled from salicylic acid and *p*-xylylene dibromide (Scheme 23, generalized structures). The dicarboxylic acid **75c** (0.25 mmol, 1 equiv) was treated with a various diol systems **76c,d,f,h** in the presence of DMAP (1 equiv) and EDC.HCl (2.5 equiv) in DCM (15 mL) to afford the corresponding macrocyclic lactones **77** (1:1 cyclization) and **78** (2:2 cyclization) as shown in Scheme 23 (generalized scheme).

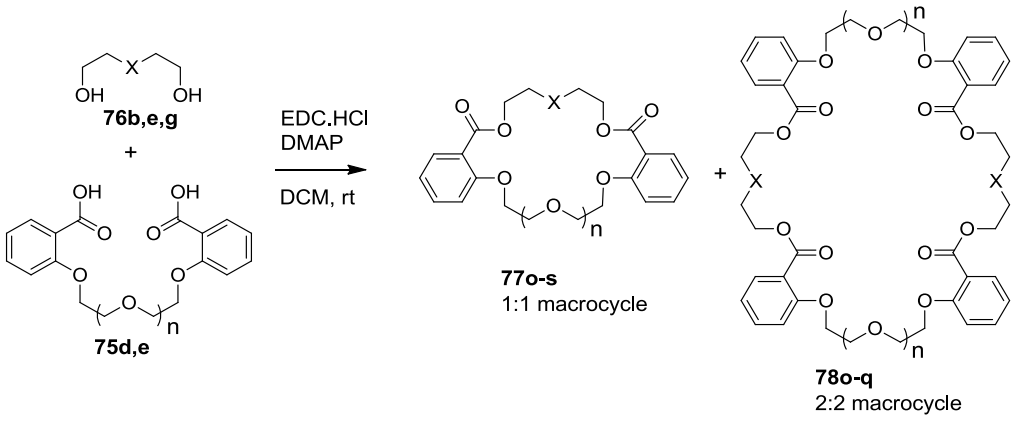
In an initial reaction, the EDC/DMAP-mediated condensation reaction of **75c** with flexible diethanolamine system **76c** successfully afforded the macrocyclic lactone **77k** (21-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78k** (42-membered, 2:2 cyclization adduct) in 13 and 29% yields, respectively (Table 3). Similarly, the EDC/DMAP-mediated condensation reaction of **75c** with other flexible diol systems **76d,h,f** furnished the corresponding macrocyclic lactone **77l-n** (21-27-membered, 1:1 cyclization adduct) in 5-15% yields and extra-large macrocyclic lactone **78l-n** (42-54-membered, 2:2 cyclization adduct) in 23-27% yields, respectively (Table 3). It is to be noted that when compared to the substrate **75a** the reaction of substrate **75c** with diols **76c,d** afforded 2:2 cyclization adducts **78k,l** as the major products, while the 2:2 cyclization adducts **78c,d** were obtained as the minor product from the substrate **75a**). Based results observed in Tables 1-3, it is predicted that the ratio/yield of 1:1 and 2:2 cyclization adducts depends on the nature and flexibility of diols **76a-h** and dicarboxylic acid systems **75a-c**, in which the dicarboxylic acid units are connected *via* a rigid aromatic spacer.

Table 3. Direct condensation of dicarboxylic acids **75c** and diols **76c,d,h,f**. Synthesis of macrocyclic lactones **77k-n** (small) and **78k-n** (extra-large).[a]

Entry	Diol (**76**)	t (h)	Macrocyclic Diactones (**77**)	Macrocyclic Tetralactones (**78**)	Total yield
1	 **76c**	18	**21-atom ring**  **77k**; 13%	 **42-atom ring** **78k**; 29%	42%
2	 **76d**	4	**21-atom ring**  **77l**; 5%	 **42-atom ring** **78l**; 22% **(X-Ray)**	27%
3	 **76h**	12	**24-atom ring**  **77m**; 12%	 **48-atom ring** **78m**; 14%	26%
4	 **76f**	4	**27-atom ring**  **77n**; 15%	 **54-atom ring** **78n**; 8%	23%

[a] Reagents: **75** (0.5 mmol), **76** (0.5 mmol), DCM (15 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).

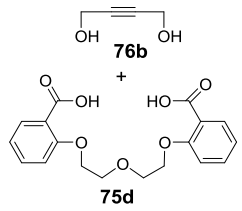
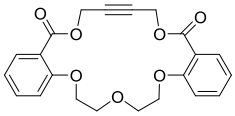
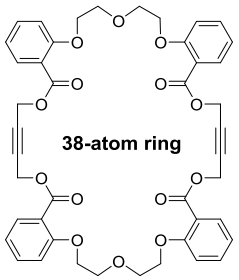
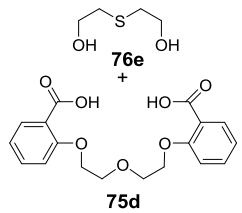
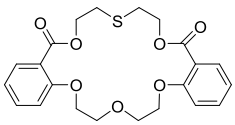
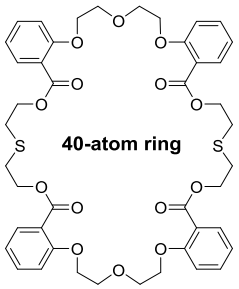
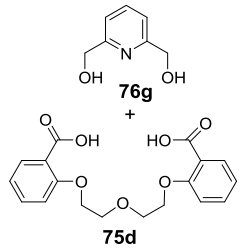
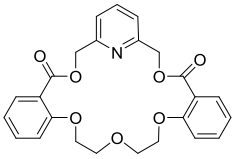
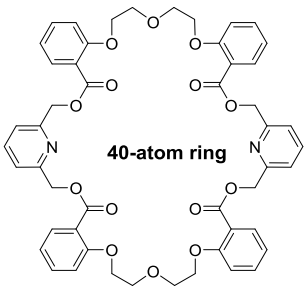
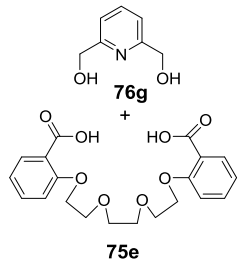
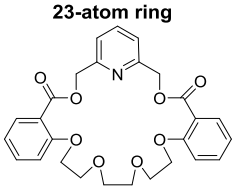
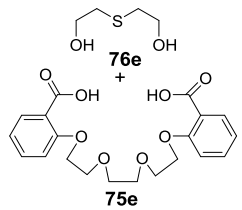
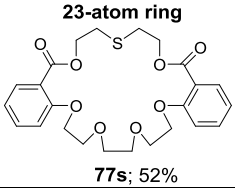
Having done the condensation of diols **76a-h** and dicarboxylic acid systems **75a-c**, in which the dicarboxylic acid units are connected *via* a rigid aromatic spacer; next it was envisaged to perform the condensation of diols **76b,e,g** and dicarboxylic acid systems **75d,e**, in which the dicarboxylic acid units are connected *via* flexible polyether-based linkers/spacers (Scheme 24, generalized structure).



Scheme 24. Generalized scheme for the direct condensation of dicarboxylic acids **75d,e** and diols **76b,e,g**. Synthesis of macrocyclic lactones **77o-s** (small) and **78o-q** (extra-large).

In an initial reaction, the EDC/DMAP-mediated condensation reaction of **75d** with a rigid diol system **76b** afforded the macrocyclic lactone **77o** (19-membered, 1:1 cyclization adduct) and extra-large macrocyclic lactone **78o** (38-membered, 2:2 cyclization adduct) in 45 and 18% yields, respectively (Table 4). Next, the condensation reactions of **75d** with flexible diol systems **76e,g** were performed. These reactions afforded the corresponding macrocyclic lactones **77p,q** (20-membered, 1:1 cyclization adduct) in 25-55% yields and extra-large macrocyclic lactone **78p,q** (40-membered, 2:2 cyclization adduct) in 8% yield (Table 4). Successively, the EDC/DMAP-mediated condensation reactions of the dicarboxylic acid **75e** having more flexible spacer with diol systems **76g**,**e** were performed. These reactions afforded only the corresponding 1:1 cyclization macrocyclic lactones **77r**,**s** in 42 and 55% yields (Table 4). It is to be noted that the 2:2 cyclization macrocyclic lactones **78o-q** were as the minor products in only 8-18% yields from the dicarboxylic acid **75e**.

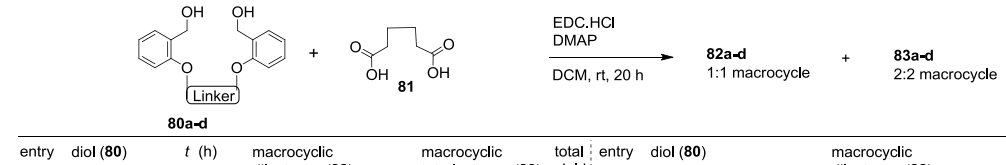
Table 4. Direct condensation of dicarboxylic acids **75d,e** and diols **76b,e,g**. Synthesis of macrocyclic lactones **77o-s** (small) and **78o-q** (extra-large).[a]

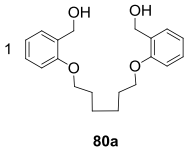
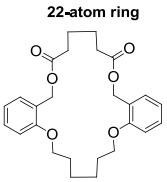
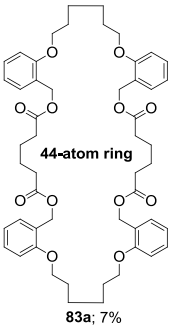
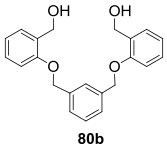
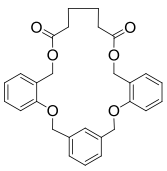
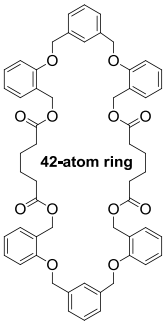
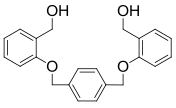
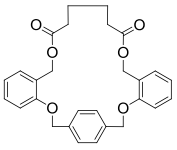
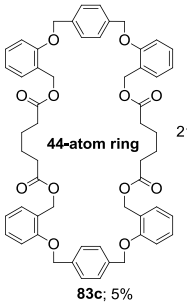
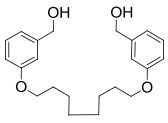
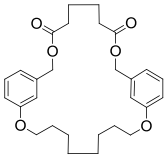
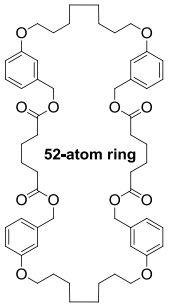
entry	diol (**76**) dicarboxylic acid (**75**)	*t* (h)	macrocyclic dilactones (**77**)	macrocyclic tetralactones (**78**)	total yield
1	 **76b** + **75d**	12	**19-atom ring**  **77o**; 45%	 **38-atom ring** **78o**; 18%	63%
2	 **76e** + **75d**	12	**20-atom ring**  **77p**; 55%	 **40-atom ring** **78p**; 8%	63%
3	 **76g** + **75d**	6	**20-atom ring**  **77q**; 25%	 **40-atom ring** **78q**; 8%	33%
4	 **76g** + **75e**	10	**23-atom ring**  **77r**; 42%	ND	42%
5	 **76e** + **75e**	10	**23-atom ring**  **77s**; 52%	ND	52%

[a] Reagents: **75** (0.5 mmol), **76** (0.5 mmol), DCM (15 mL) DMAP (1 equiv), EDC.HCl (2.5 equiv).

When compared to the dicarboxylic acid **75d**, the dicarboxylic acid **75e** is having more flexible and relatively longer chain length-based spacer and hence, the 1:1 cyclization macrocyclic lactones **77r**,**s** were preferably formed and their corresponding 2:2 cyclization macrocyclic lactones were not obtained from **75e**.

Table 5. Direct condensation of dicarboxylic acid **81** and diols **80a-d**. Synthesis of macrocyclic lactones **82a-d** (small) and **83a-d** (extra-large).[a]



entry	diol (**80**)	*t* (h)	macrocyclic dilactones (**82**)	macrocyclic tetralactones (**83**)	total yield
1	 **80a**		 **82a**; 22%	 **83a**; 7%	29%
2	 **80b**		 **82b**; 17%	 **83b**; 13%	30%
3	 **80c**		 **82c**; 16%	 **83c**; 5%	21%
4	 **80d**		 **82d**; 12%	 **83d**; 9%	21%

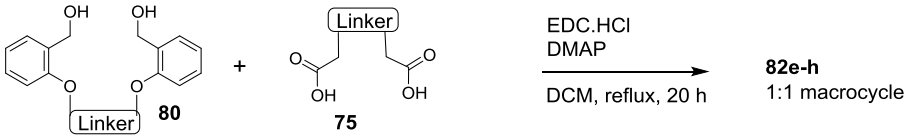
[a] Reagents: **80a-d** (0.5 mmol), **81** (0.5 mmol), DCM (15 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).

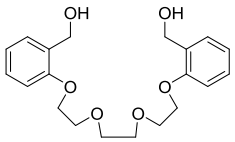
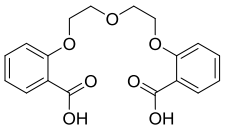
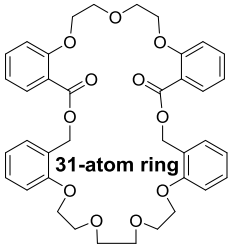
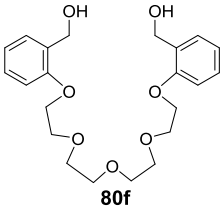
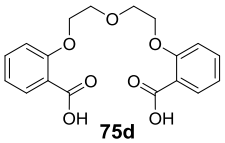
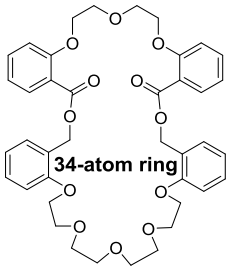
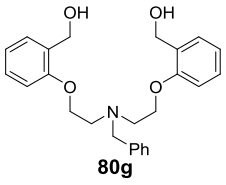
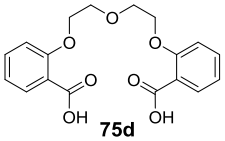
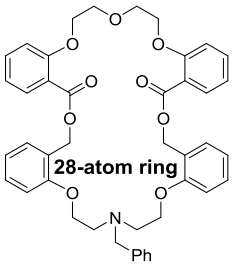
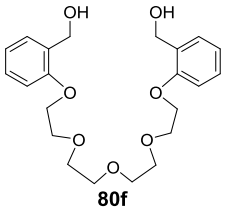
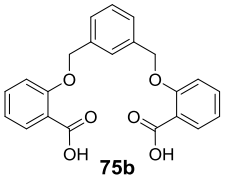
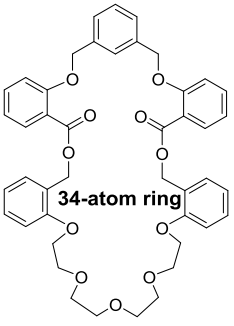
Having shown the condensation of various linear diols **76a-h** with carboxylic acids **75a-e**, it was envisaged to perform the condensation reactions of adipic acid **81** with various diols **80a-d**, which were assembled from salicylaldehyde (Table 5). The condensation reactions of diols **80a,d** having alkyl linker chain spacers/linkers with adipic acid **81** were performed in the presence of EDC.HCl/DMAP, which afforded the corresponding macrocyclic lactones **82a,d** (22 and 26-

membered, 1:1 cyclization adduct) in 12-22% yields and extra-large macrocyclic lactones **83a,d** (44 and 56-membered, 2:2 cyclization adduct) in 7-9% yields (Table 5). Next, the condensation reaction of diols **80b**,**c** having aromatic linker spacer/linker with **81** furnished the corresponding macrocyclic lactones **82b**,**c** (21 and 22-membered, 1:1 cyclization adduct) in 17-16% yields and extra-large macrocyclic lactones **83b**,**c** (42 and 44-membered, 2:2 cyclization adduct) in 5-13% yields (Table 5).

Subsequently, it was envisaged to perform the condensation reactions using the dicarboxylic acid systems **75a,b,d** and various diols **80b,c** and **80e-j** (Table 6). It is to be noted that in the dicarboxylic acid systems **75d** and **75a,b** the dicarboxylic acid units are connected *via* flexible polyether-based linker/spacer and rigid aromatic spacers, respectively. Similarly, in the diol systems **80e-g** and **80b,c/80h-j** the diol units are connected *via* flexible polyether-based linkers/spacers and rigid aromatic spacer, respectively. At first, the reactions of the diols **80b,e-g** having flexible polyether-based linkers/spacers and dicarboxylic acids **75a,b,d** were performed in the presence of EDC.HCl/DMAP. These condensation reactions afforded the corresponding polyether macrocyclic lactones **82e-i** (28-34-membered, 1:1 cyclization adduct) in 32-50% yields (Table 6). Next, the reactions of the diol **80b** having rigid aromatic linker/spacer and dicarboxylic acids **75a,b,d** were performed in the presence of EDC.HCl/DMAP. These condensation reactions also afforded the corresponding polyether macrocyclic lactones **82j-l** (27-28-membered, 1:1 cyclization adduct) in 28-48% yields (Table 6). Along this line, the reactions of the diols **80c/80h-j** having rigid aromatic linker/spacer and dicarboxylic acids **75a,b** were performed in the presence of EDC.HCl/DMAP. These condensation reactions gave the corresponding polyether macrocyclic lactones **82m-p** (26-29-membered, 1:1 cyclization adduct) in 42-55% yields (Table 6). Notably, the column chromatography purification of the crude reaction mixture of the corresponding condensation reactions using the dicarboxylic acid systems **75a,b,d** and various diols **80b,c** and **80e-j** afforded the corresponding 1:1 cyclization adducts **82e-p** as the major compounds and did not yield any of their corresponding 2:2 cyclization adducts in characterizable amounts.

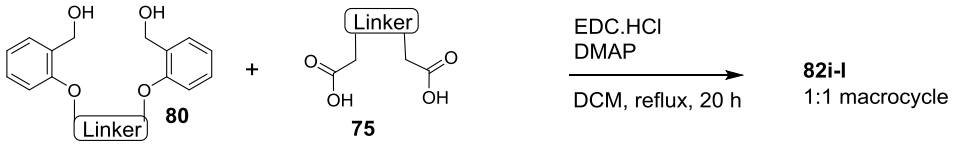
Table 6. Direct condensation of dicarboxylic acids **75b,d** and diols **80e-g**. Synthesis of macrocyclic lactones **82e-h**.[a]

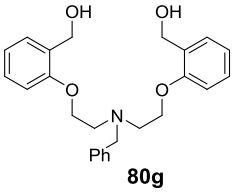
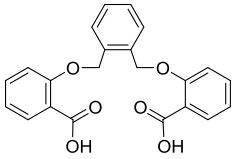
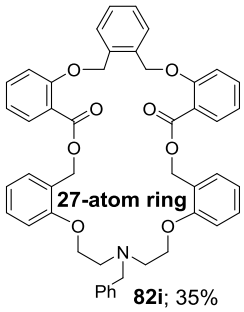
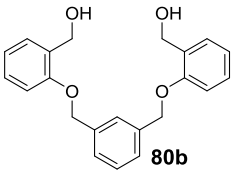
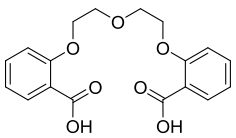
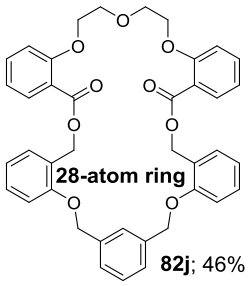
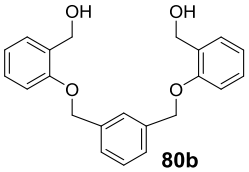
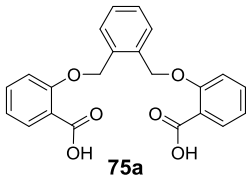
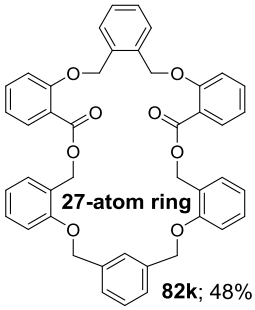
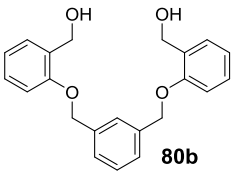
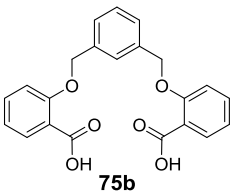
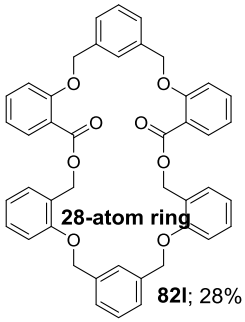


entry	diol (**80**)	dicarboxylic acid (**75**)	macrocyclic dilactones (**82**)
1	 **80e**	 **75d**	 **31-atom ring** **82e**; 50%
2	 **80f**	 **75d**	 **34-atom ring** **82f**; 40%
3	 **80g**	 **75d**	 **28-atom ring** **82g**; 32%
4	 **80f**	 **75b**	 **34-atom ring** **82h**; 42%

[a] Reagents: **80** (0.25 mmol), **75** (0.25 mmol), DCM (3 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).

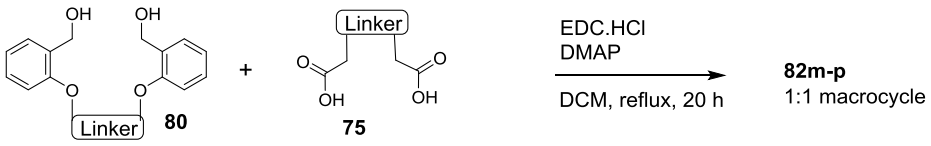
Table 6 (Continued). Direct condensation of dicarboxylic acids **75a**,**b**,**d** and diols **80b,g**. Synthesis of macrocyclic lactones **82i-l**.[a]

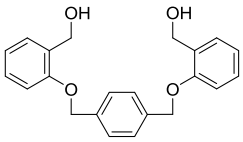
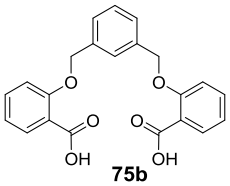
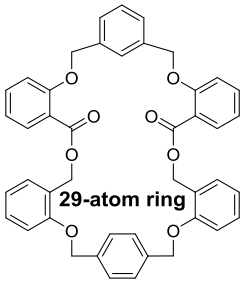
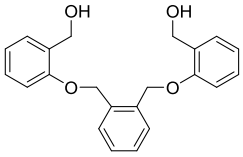
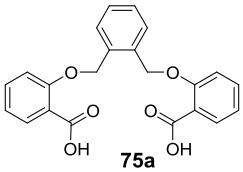
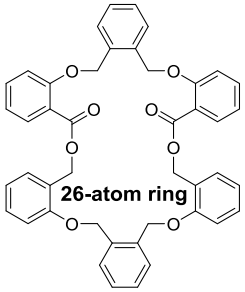
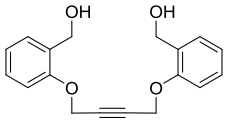
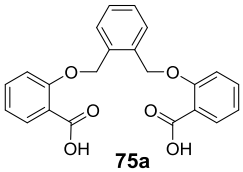
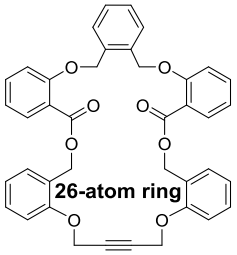
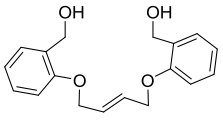
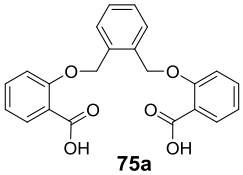
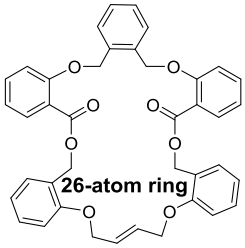


entry	diol (**80**)	dicarboxylic acid (**75**)	macrocyclic dilactones (**82**)
5	 **80g**	 **75a**	 **27-atom ring** **82i**; 35%
6	 **80b**	 **75d**	 **28-atom ring** **82j**; 46%
7	 **80b**	 **75a**	 **27-atom ring** **82k**; 48%
8	 **80b**	 **75b**	 **28-atom ring** **82l**; 28%

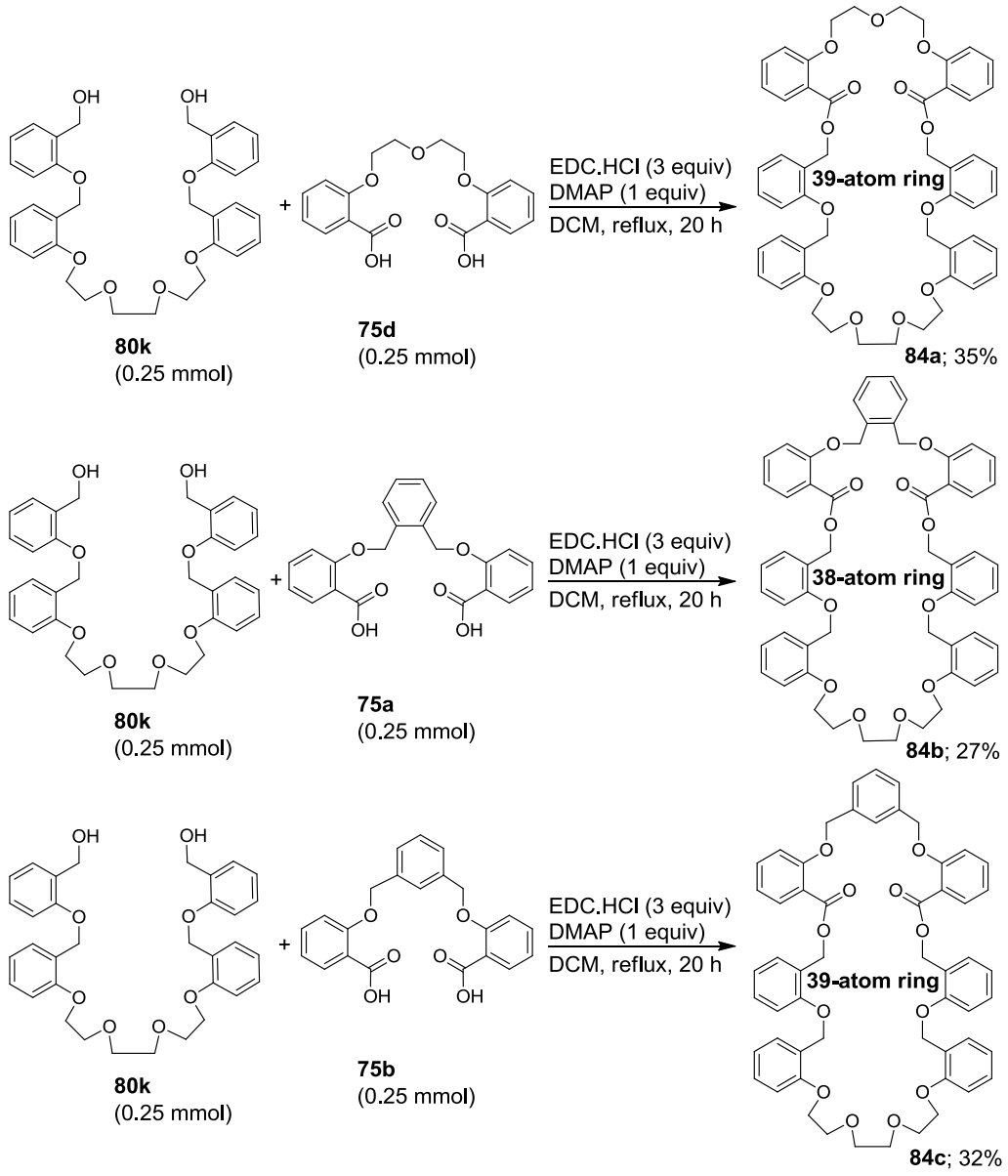
[a] Reagents: **80** (0.25 mmol), **75** (0.25 mmol), DCM (3 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).

Table 6. (Continued). Direct condensation of dicarboxylic acids **75a**,**b** and diols **80c**/**80h-j**. Synthesis of macrocyclic lactones **82m-p**.[a]



entry	diol (**80**)	dicarboxylic acid (**75**)	macrocyclic dilactones (**82**)
9	 **80c**	 **75b**	 **82m**; 55%
10	 **80h**	 **75a**	 **82n**; 45%
11	 **80i**	 **75a**	 **82o**; 42
12	 **80j**	 **75a**	 **82p**; 45

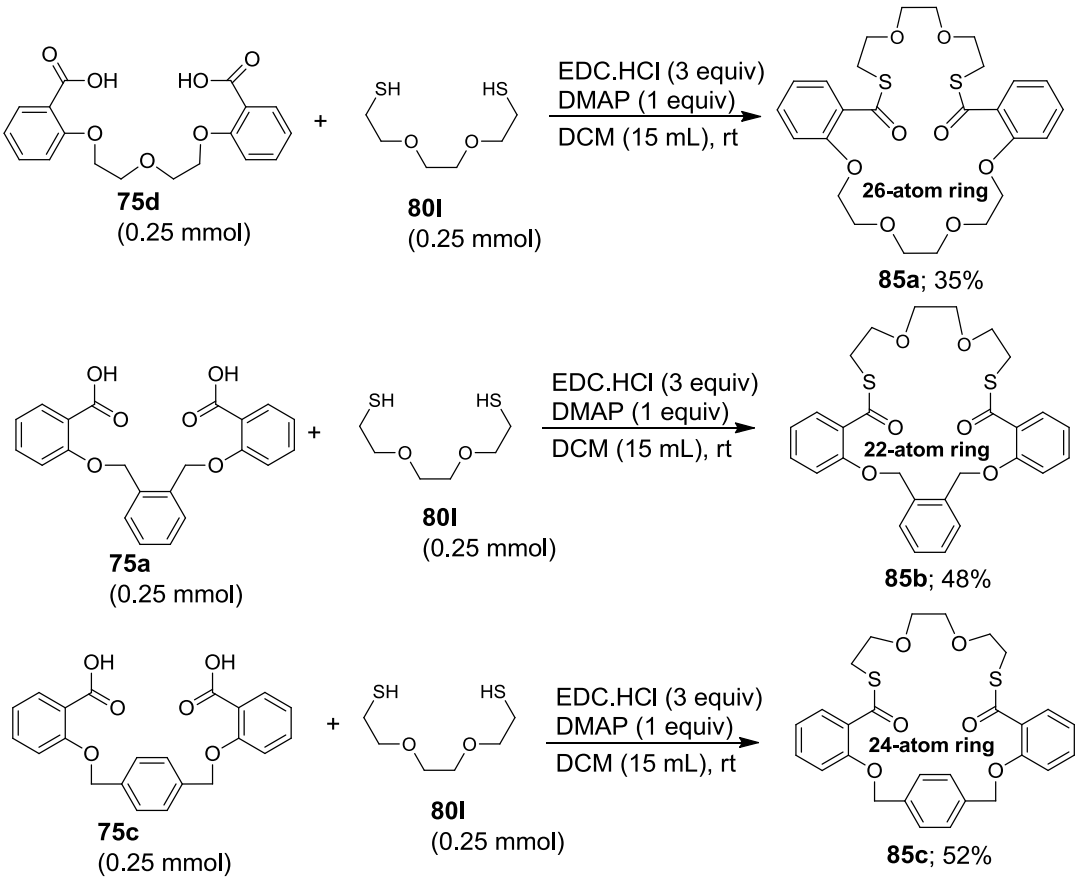
[a] Reagents: **80** (0.25 mmol), **75** (0.25 mmol), DCM (3 mL), DMAP (1 equiv), EDC.HCl (2.5 equiv).



Scheme 25. Direct condensation of dicarboxylic acids **75a,b,d** and diol **80k**. Synthesis of extra-large macrocyclic lactones **84a-c**.

Next, elaborate the generality of this method, it was envisaged to perform the condensation reactions using the dicarboxylic acid systems **75a,b,d** and diol system **80k** (Scheme 25). It is to be noted that in the diol system **80k** the diol units are connected *via* flexible polyether-based linker/spacer having relatively large chain length than the diols **75a,b,d**, which were used in the reactions shown Table 6. The condensation reactions of the diol **80k** and dicarboxylic acids **75a,b,d** were performed in the presence of EDC.HCl/DMAP. These reactions afforded the

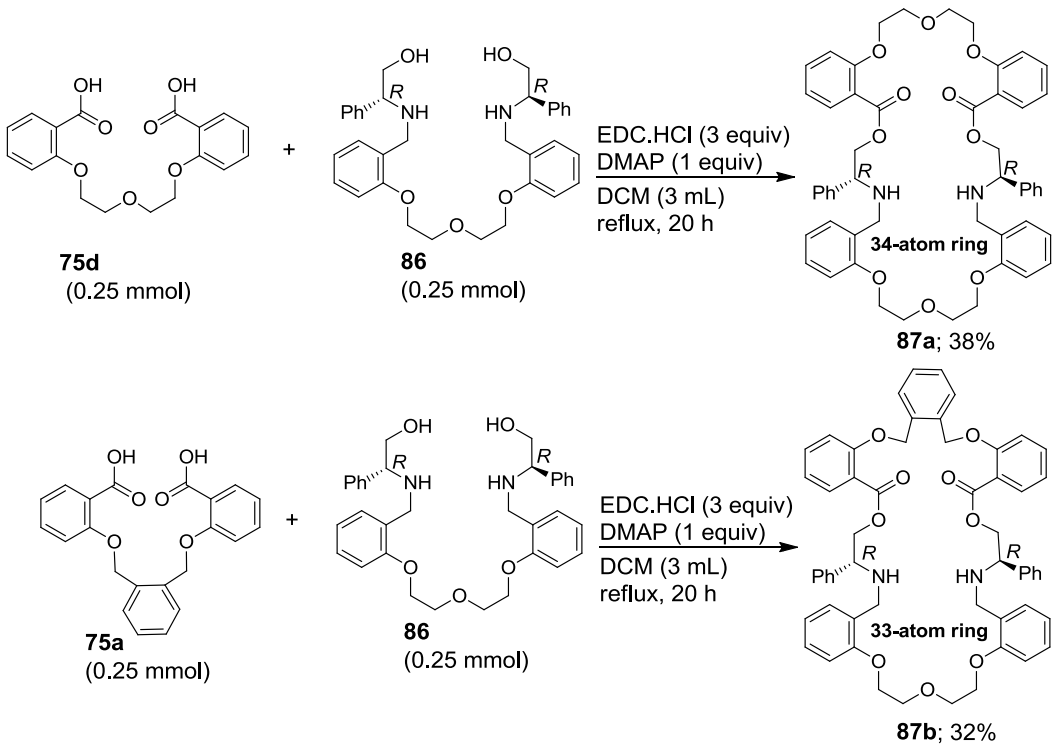
corresponding extra-large polyether macrocyclic lactones **84a-c** (38-39-membered, 1:1 cyclization adduct) in 27-35% yields (Scheme 25). Notably, the column chromatography purification of the crude reaction mixture of the corresponding condensation reactions using the dicarboxylic acid systems **75a,b,d** and various diol **80k** gave the corresponding 1:1 cyclization adducts **84a-c** as the major compounds and did not yield any of their corresponding 2:2 cyclization adducts in characterizable amounts.



Scheme 26. Direct condensation of dicarboxylic acids **75** and dithiol system **80l**. Synthesis of thiolactone macrocycles **85a-c**.

Having done the direct condensation of various dicarboxylic acids **75** and diols **80**, to extend the substrate scope and generality of this work, it was envisaged to perform the direct condensation of dicarboxylic acid with dithiol system **80l** instead of diol (Scheme 26) to obtain thiolactone macrocycles. It is to be noted that there exists only limited reports that deal on the synthesis of thiolactone macrocycles. The condensation reaction of the dithiol system **80l** and dicarboxylic

acids **75d** and **75a,c** having flexible polyether-based linker/spacer and rigid aromatic spacers were performed in the presence of EDC.HCl/DMAP. These reactions afforded the corresponding thiolactone macrocycles **85a-c** (22-26-membered, 1:1 cyclization adduct) in 35-52% yields (Scheme 26). Notably, the column chromatography purification of the crude reaction mixture of the corresponding condensation reactions using the dicarboxylic acid systems **75a,c,d** and dithiol system **80l** gave the corresponding 1:1 cyclization adducts **85a-c** as the major compounds and did not yield any of their corresponding 2:2 cyclization adducts in characterizable amounts.



Scheme 27. Direct condensation of dicarboxylic acids **75a,d** and diol **86**. Synthesis of macrocyclic lactones **87a,b** (small).

Finally, it was planned to extend the utility of this method by synthesizing the optically pure macrocyclic lactones *via* the direct condensation of dicarboxylic acid and optically pure diol systems. In this regard, the condensation reaction of the optically pure diol system **86** (which was assembled from corresponding bis-aldehyde as discussed in Chapter 3). In an initial trial, the condensation reaction of the optically pure diol system **86** and dicarboxylic acid **75d** having flexible polyether-based linker/spacer was performed in the presence of EDC.HCl/DMAP. This reaction afforded the optically pure macrocyclic lactone **87a** (34-membered, 1:1 cyclization

adduct) in 38% yield (Scheme 27). Similarly, the EDC.HCl/DMAP-mediated condensation reaction of the optically pure diol system **86** and dicarboxylic acid **75a** having rigid aromatic spacer was performed to afford the optically pure macrocyclic lactone **87b** (33-membered, 1:1 cyclization adduct) in 32% yield (Scheme 27).

All the macrocyclic lactones **77-79**, **82-85** and **87** reported in this Chapter 4, were isolated by column chromatography and characterized by NMR and HRMS analyses. Furthermore, the macrocyclic lactone **77c** (19-membered), and extra-large macrocyclic lactones **78a** (36-membered), **78c** (38-membered), **78g** (42-membered) and **78l** (42-membered) were characterized by X-ray structure analysis (Figures 2-6).[21]

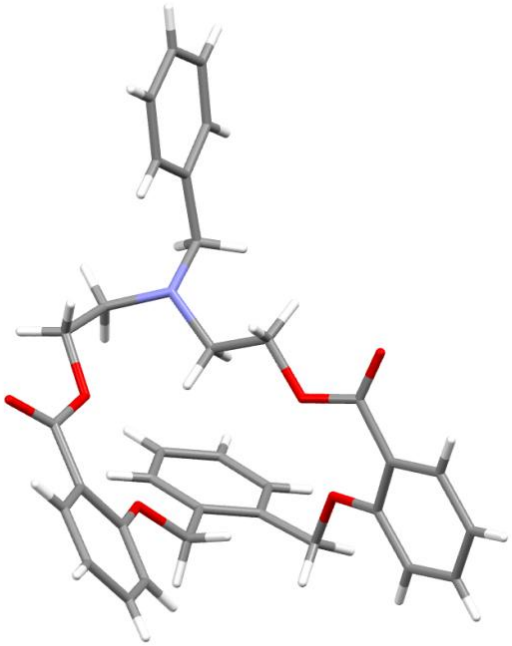


Figure 2.[21] X-ray structures of macrocyclic lactones **77c**.

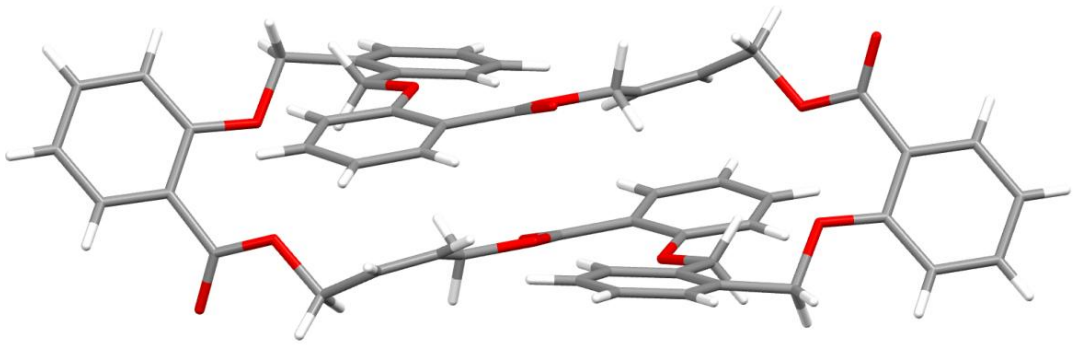


Figure 3.[21] X-ray structures of macrocyclic lactones **78a**.

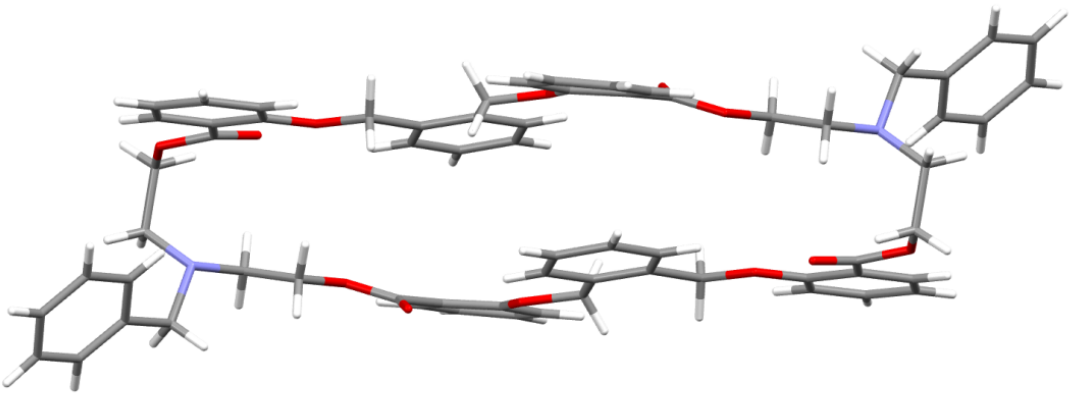


Figure 4.[21] X-ray structure of macrocyclic lactone **78c**.

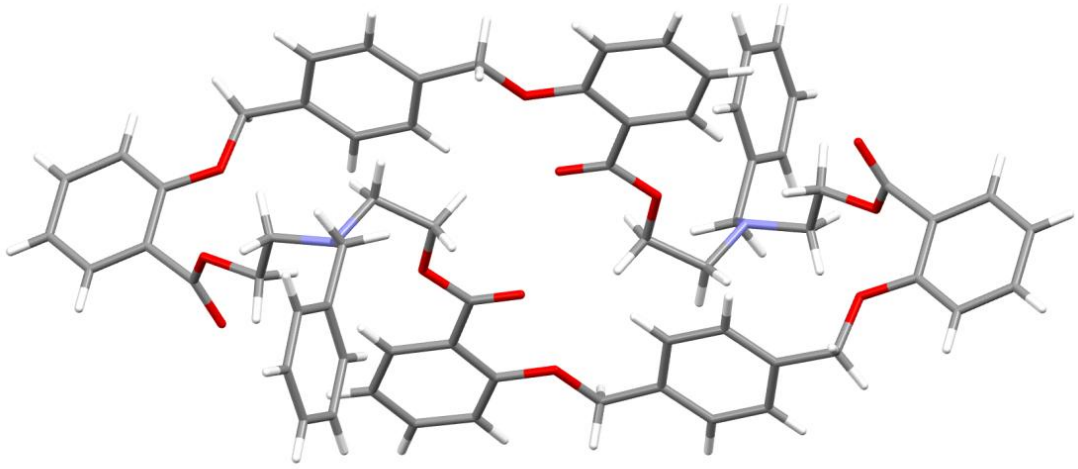


Figure 5.[21] X-ray structure of macrocyclic lactone **78k**.

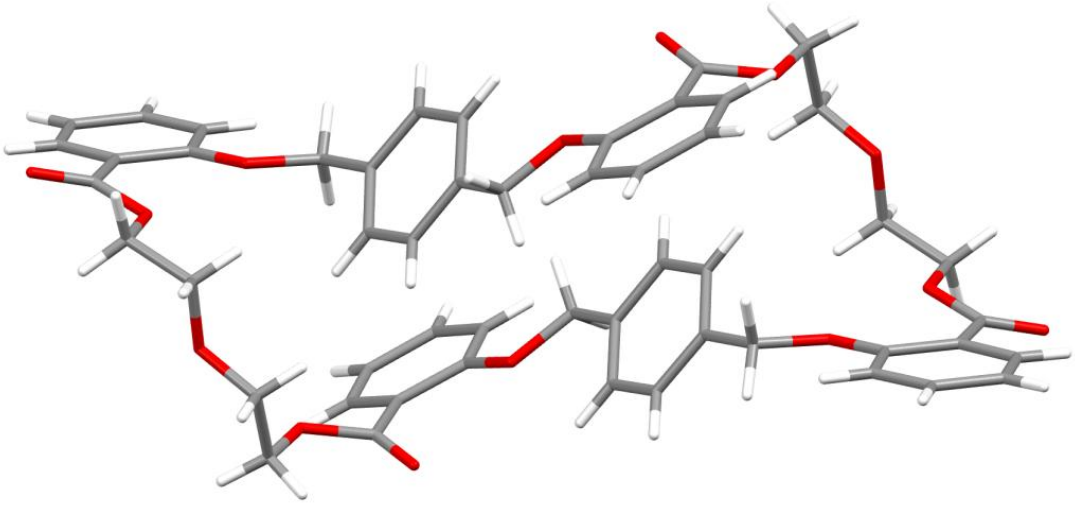


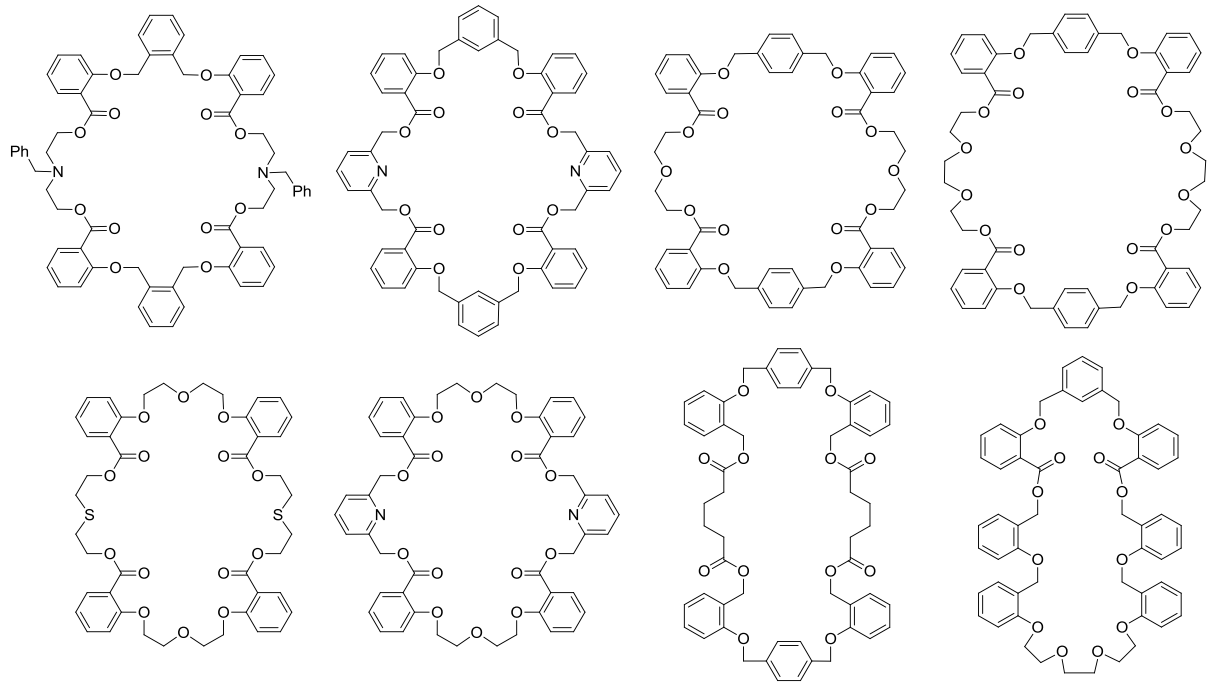
Figure 6.[21] X-ray structure of macrocyclic lactone **78l**.

Conclusions

In summary, Chapter 4 revealed the direct condensation reactions of a wide range of dicarboxylic acids with various diols mediated by EDC/DMAP. The EDC/DMAP-mediated

direct condensation reactions of dicarboxylic acids with diols have led to the synthesis of a library of new classes of medium to extra-large polyether macrocyclic di- and tetralactones. The methodology was well executed by using various dicarboxylic acids and diols having different types of flexible and rigid linkers/spacers and relatively simple reaction conditions. Depending on the nature of the linkers/spacers present in the dicarboxylic acids and diols, 1:1 and 2:2 cyclizations occurred to afford the corresponding medium to extra-large polyether macrocyclic di- and tetralactones.

Synthesis of extra-large macrocyclic tetra-lactones



Given that some of the reported methods dealing on the synthesis of macrocyclic di- and tetra-lactones are not direct methods and require pre-assembling of alkali metal salts or dicarboxylic acid chlorides and alkyl dibromides or sulfonium salts or a template; the Chapter 4 revealed the synthesis of medium to extra-large polyether macrocyclic di- and tetralactones by using various dicarboxylic acids and diols under relatively simple reaction conditions.

Further, given the importance to crown ether/polyether macrocycles and macrocyclic lactones in organic synthesis and research area pertaining to analytical chemistry and chromatography, the synthetic work shown in Chapter 4, pertaining to the assembling of a library of new classes of polyether macrocyclic di- and tetralactones will be highly useful.

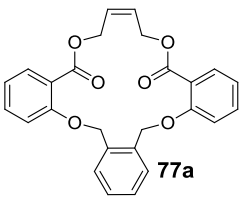
All the compounds included in the Chapter 4 of this thesis are characterized by various characterization techniques including ^{1}H and ^{13}C NMR, IR, X-ray diffraction and HRMS. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

Experimental section

General. FT-IR spectra were recorded as thin films or KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively using TMS as an internal standard. Compounds were purified by column chromatography using silica gel (100-200 mesh) or neutral alumina. Reactions were carried out in anhydrous solvent and under a nitrogen atm, wherever necessary. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analysis was performed on silica gel/alumina plates and the components were visualized by observation under iodine. Isolated yields of products were reported and yields were not optimized.

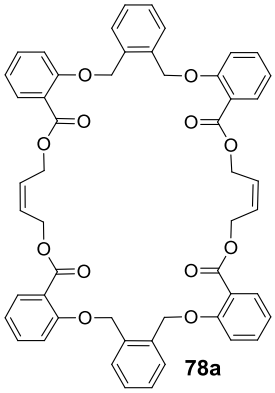
General procedure for the syntheses of macrocyclic lactones 77a-s and 78a-q. To a solution of dicarboxylic acid **75** (0.25 mmol) and diol **76** (0.25 mmol) in CH_2Cl_2 (15 mL) was added DMAP (1 equiv) followed by EDC.HCl (2.5 equiv). The reaction mixture was stirred at room temperature for 4-20 h. After this period, the resulting crude reaction mixture was washed with 2 N HCl (2 X 5 mL). The solvent was removed under reduced pressure and the residue was purified by using neutral alumina/silica gel column chromatography (EtOAc/Hexanes) to give the corresponding macrocyclic lactones **77a-s** and **78a-s** (see the respective Tables for specific entries).

Compound 77a: Following the general procedure, **77a** was obtained after purification by column chromatography as a colourless solid (16 mg, 15%); mp: 126-128 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1712, 1601, 1486 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (2 H, dd, J_1 = 5.92 Hz, J_2 = 1.76 Hz), 7.55-7.52 (2 H, m), 7.47-7.38 (4 H, m), 7.09-7.04 (4 H, m), 5.74 (2 H, t, J = 4.7 Hz), 5.21 (4 H, s), 4.90 (4 H, d, J = 3.1 Hz); ^{13}C NMR (100 MHz,

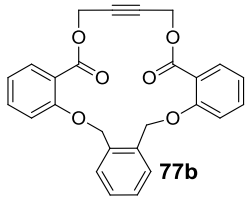


$CDCl_3$): δ_C 167.0, 158.1, 135.1, 133.4, 131.7, 128.6, 128.6, 128.1, 122.5, 121.9, 116.7, 70.9, 59.5; HRMS (ESI): MNa^+, found 453.1293. $C_{26}H_{22}NaO_6$ requires 453.1314.

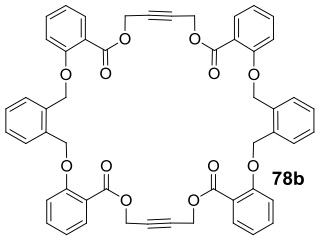
Compound 78a: Following the general procedure, **78a** was obtained after purification by column chromatography as a colourless solid (23 mg, 22%); mp: 162-164 ^oC; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 1722, 1600, 1489 and 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (4 H, dd, J_1 = 5.92 Hz, J_2 = 1.76 Hz), 7.63-7.61 (4 H, m), 7.47-7.43 (4 H, m), 7.32-7.28 (4 H, m), 7.03-6.97 (8 H, m), 5.68 (4 H, t, J = 4.2 Hz), 5.27 (8 H, s), 4.77 (8 H, d, J = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.3, 157.8, 134.4, 133.6, 132.1, 128.4, 128.3, 128.1, 120.6, 120.4, 113.2, 68.6, 60.4; HRMS (ESI): MNa^+, found 883.2765. $C_{52}H_{44}NaO_{12}$ requires 883.2730.


78a

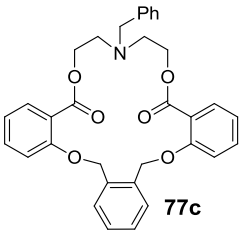
Compound 77b: Following the general procedure, **77b** was obtained after purification by column chromatography as a colourless liquid, (14 mg, 13%); R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1731, 1600, 1486, 1451, 1298 and 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (2 H, dd, J_1 = 5.96 Hz, J_2 = 1.76 Hz), 7.51-7.49 (2 H, m), 7.45-7.36 (4 H, m), 7.05 (2 H, t, J = 7.5 Hz), 6.97 (2 H, d, J = 8.4 Hz), 5.35 (4 H, s), 4.92 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 158.5, 135.1, 133.6, 131.7, 128.9, 128.2, 121.5, 121.3, 116.2, 80.6, 71.0, 52.6; HRMS (ESI): MNa^+, found 451.1142. $C_{26}H_{20}NaO_6$ requires 451.1158.


77b

Compound 78b: Following the general procedure, **78b** was obtained after purification by column chromatography as a colourless solid, (48 mg, 45%); mp: 197-199 ^oC; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2927, 1726, 1600, 1450, 1299 and 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (4 H, dd, J_1 = 6.0 Hz, J_2 = 1.7 Hz), 7.66-7.64 (4 H, m), 7.47 (4 H, t, J = 6.7 Hz), 7.28 (4 H, t, J = 5.2 Hz), 7.06 (4 H, d, J = 8.2 Hz), 6.98 (4 H, t, J = 7.4 Hz), 5.28 (8 H, s), 4.83 (8 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.6, 158.1, 134.4, 134.0, 132.4, 128.3, 128.2, 120.5, 119.3, 113.4, 81.0, 68.8, 52.7; HRMS (ESI): MNa^+, found 879.2415. $C_{52}H_{40}NaO_{12}$ requires 879.2417.

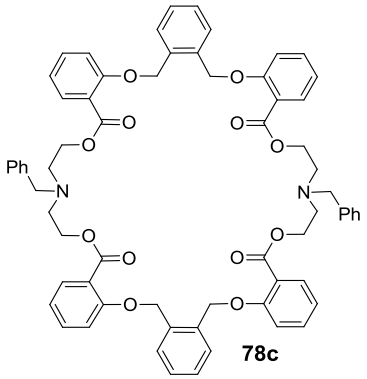

78b

Compound 77c: Following the general procedure, **77c** was obtained after purification by column chromatography as a colourless solid, (38 mg, 29%); mp: 131-133 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1699, 1601, 1452 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 5.92 Hz, J_2 = 1.76 Hz), 7.54-7.52 (2 H, m), 7.48-7.40 (4 H, m), 7.29-7.28 (5 H, m), 7.06-6.99 (4 H, m), 5.33 (4 H, s), 4.33 (4 H, t, J = 6.2 Hz), 3.63 (2 H, s), 2.88 (4 H, t, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 157.6, 139.2, 134.6, 133.4, 132.4, 128.6, 128.6, 128.3, 128.3, 127.1, 121.0, 120.9, 113.2, 68.5, 64.1, 58.3, 52.6; HRMS (ESI): MNa^+, found 560.2066. $C_{33}H_{31}NNaO_6$ requires 560.2049.



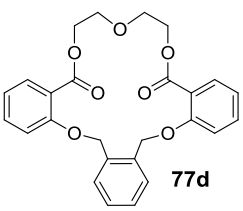
77c

Compound 78c: Following the general procedure, **78c** was obtained after purification by column chromatography as a colourless solid, (23 mg, 17%); mp: 160-162 ^{o}C; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 1723, 1600, 1490 and 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.74 (4 H, dd, J_1 = 6.01 Hz, J_2 = 1.72 Hz), 7.60-7.58 (4 H, m), 7.40-7.35 (4 H, m), 7.31-7.21 (14 H, m), 7.01 (4 H, d, J = 8.3 Hz), 6.88 (4 H, t, J = 7.4 Hz), 5.27 (8 H, s), 4.26 (8 H, t, J = 6.0 Hz), 3.65 (4 H, s), 2.79 (8 H, t, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.9, 157.9, 139.2, 134.6, 133.4, 131.9, 128.7, 128.5, 128.2, 127.0, 120.4, 120.3, 113.3, 68.6, 62.7, 59.1, 52.4; HRMS (ESI): MNa^+, found 1097.4220. $C_{66}H_{62}N_2NaO_{12}$ requires 1097.4200.



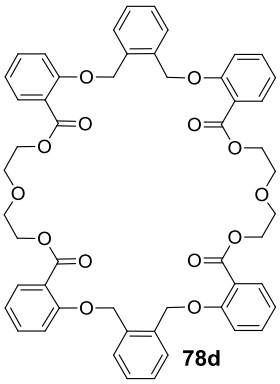
78c

Compound 77d: Following the general procedure, **77d** was obtained after purification by column chromatography as a colourless solid, (30 mg, 27%); mp: 137-139 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2949, 1704, 1601, 1487 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 5.92 Hz, J_2 = 1.8 Hz), 7.55-7.53 (2 H, m), 7.46-7.39 (4 H, m), 7.04 (2 H, t, J = 7.6 Hz), 6.99 (2 H, d, J = 8.4 Hz), 5.30 (4 H, s), 4.42 (4 H, t, J = 4.8 Hz), 3.67 (4 H, t, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 157.8, 134.9, 133.5, 132.3, 128.5, 128.2, 121.5, 121.3, 114.7, 69.5, 69.3, 64.9; HRMS (ESI): MNa^+, found 471.1419. $C_{26}H_{24}NaO_7$ requires 471.1420.

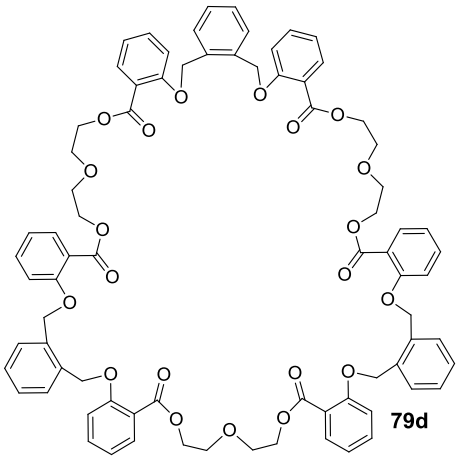


77d

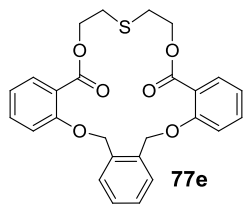
Compound 78d: Following the general procedure, **78d** was obtained after purification by column chromatography as a colourless solid, (21 mg, 19%); mp: 141-143 ^{o}C; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2930, 1723, 1600, 1492 and 1081 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (4 H, dd, J_1 = 5.9 Hz, J_1 = 1.8 Hz), 7.59-7.57 (4 H, m), 7.39-7.35 (4 H, m), 7.31-7.28 (4 H, m), 6.99 (4 H, d, J = 8.1 Hz), 6.86 (4 H, t, J = 7.6 Hz), 5.24 (8 H, s), 4.33 (8 H, t, J = 4.8 Hz), 3.63 (8 H, t, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.3, 157.9, 134.6, 133.5, 131.9, 128.6, 128.2, 120.4, 120.2, 113.4, 68.9, 68.7, 63.9; HRMS (ESI): MNa^+, found 919.2963. $C_{52}H_{48}NaO_{14}$ requires 919.2942.



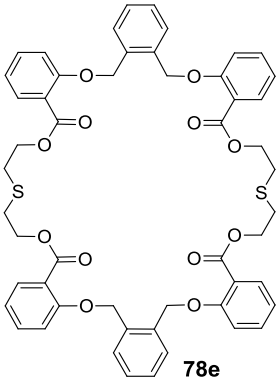
Compound 79d: Following the general procedure, **79d** was obtained after purification by column chromatography as a colourless liquid, (6 mg, 5%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2919, 1723, 1600, 1490 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 (6 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.60-7.58 (6 H, m), 7.39-7.35 (6 H, m), 7.31-7.29 (6 H, m), 7.02 (6 H, d, J = 8.4 Hz), 6.87 (6 H, t, J = 6.9 Hz), 5.25 (12 H, s), 4.32 (12 H, t, J = 4.8 Hz), 3.62 (12 H, t, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.0, 158.0, 134.6, 133.5, 131.9, 128.5, 128.2, 120.4, 120.2, 113.4, 69.0, 68.7, 63.9; HRMS (ESI): MNa^+, found 1367.4496. $C_{78}H_{72}NaO_{21}$ requires 1367.4464.



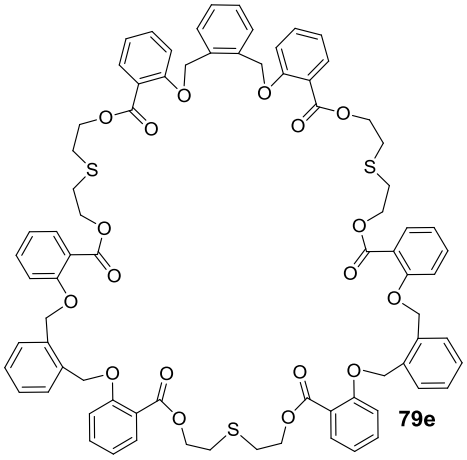
Compound 77e: Following the general procedure, **77e** was obtained after purification by column chromatography as a colourless solid (17 mg, 15%); mp: 123-125 ^{o}C; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1712, 1601, 1486 and 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.87 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.54-7.39 (6 H, m), 7.04 (2 H, t, J = 7.5 Hz), 7.01 (2 H, d, J = 8.4 Hz), 5.33 (4 H, s), 4.42 (4 H, t, J = 6.7 Hz), 2.84 (4 H, t, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.4, 157.5, 134.5, 133.6, 132.5, 128.5, 128.4, 120.9, 120.6, 113.0, 68.3, 65.9, 31.5; HRMS (ESI): MNa^+, found 487.1191. $C_{26}H_{24}NaO_6S$ requires 487.1191.



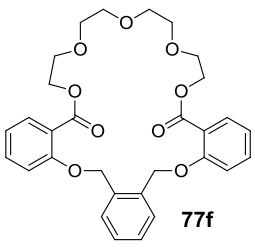
Compound 78e: Following the general procedure, **78e** was obtained after purification by column chromatography as a colourless solid (13 mg, 12%); mp: 146-148 ^{o}C; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1723, 1600, 1450 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (4 H, dd, J_1 = 6.0 Hz, J_2 = 1.8 Hz), 7.62-7.59 (4 H, m), 7.45-7.41 (4 H, m), 7.34-7.32 (4 H, m), 7.04 (4 H, d, J = 8.1 Hz), 6.96 (4 H, t, J = 7.7 Hz), 5.30 (8 H, s), 4.32 (8 H, t, J = 6.9 Hz), 2.71 (8 H, t, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.9, 158.0, 134.5, 133.6, 131.9, 128.6, 128.3, 120.6, 120.3, 113.5, 68.8, 63.8, 30.5; HRMS (ESI): MNa^+, found 951.2522. $C_{52}H_{48}NaO_{12}S_2$ requires 951.2485.


78e

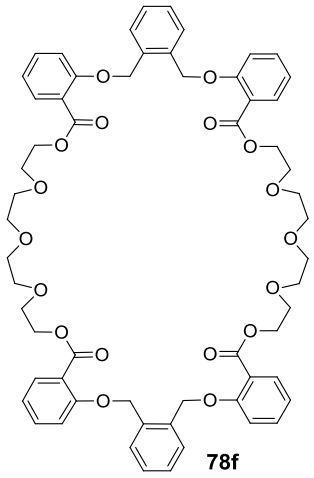
Compound 79e: Following the general procedure, **79e** was obtained after purification by column chromatography as a colourless liquid (10 mg, 9%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1723, 1600, 1450 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (6 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.61-7.58 (6 H, m), 7.43-7.39 (6 H, m), 7.33-7.31 (6 H, m), 7.05 (6 H, d, J = 8.3 Hz), 6.94 (6 H, t, J = 7.3 Hz), 5.29 (12 H, s), 4.33 (12 H, t, J = 6.8 Hz), 2.74 (12 H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 158.1, 134.6, 133.7, 131.9, 128.6, 128.3, 120.5, 120.1, 113.5, 68.8, 63.7, 30.6; HRMS (ESI): MNa^+, found 1415.3737. $C_{78}H_{72}NaO_{18}S_3$ requires 1415.3778.


79e

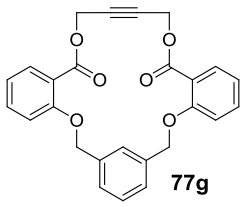
Compound 77f: Following the general procedure, **77f** was obtained after purification by column chromatography as a colourless liquid (46 mg, 35%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2873, 1723, 1600, 1490 and 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (2 H, dd, J_1 = 6.0 Hz, J_2 = 1.9 Hz), 7.70-7.68 (2 H, m), 7.47-7.39 (4 H, m), 7.05-7.01 (4 H, m), 5.33 (4 H, s), 4.41 (4 H, t, J = 4.8 Hz), 3.65 (4 H, t, J = 4.7 Hz), 3.53-3.50 (4 H, m), 3.47-3.45 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.0, 157.7, 134.7, 133.5, 132.1, 128.7, 128.2, 120.9, 120.7, 113.7, 70.8, 70.5, 69.0, 68.9, 64.2; HRMS (ESI): MNa^+, found 559.1954. $C_{30}H_{32}NaO_9$ requires 559.1944.


77f

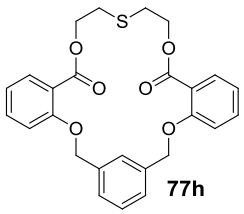
Compound 78f: Following the general procedure, **78f** was obtained after purification by column chromatography on silica gel as colourless liquid (21 mg, 16%); R_f (45% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2877, 1723, 1600, 1450 and 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (4 H, dd, J_1 = 6.0 Hz, J_2 = 1.8 Hz), 7.64.-7.62 (4 H, m), 7.43-7.34 (8 H, m), 7.06 (4 H, d, J = 8.4 Hz), 6.96 (4 H, t, J = 7.5 Hz), 5.31 (8 H, s), 4.37 (8 H, t, J = 4.8 Hz), 3.67 (8 H, t, J = 4.8 Hz), 3.53 (16 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 158.0, 134.7, 133.6, 131.9, 128.6, 128.3, 120.4, 113.5, 70.6, 70.5, 69.0, 68.8, 63.9; HRMS (ESI): MNa^+, found 1095.4041. $C_{60}H_{64}NaO_{18}$ requires 1095.3990.


78f

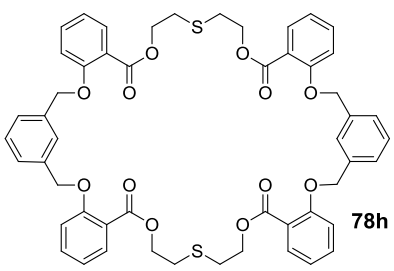
Compound 77g: Following the general procedure, **77g** was obtained after purification by column chromatography as a colourless solid, (40 mg, 38%); mp: 152-155 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2936, 1732, 1600, 1453 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (1 H, s), 7.83 (2 H dd, J_1 = 5.9 Hz, J_2 = 1.7 Hz), 7.50-7.40 (5 H, m), 7.11 (2 H, d, J = 8.2 Hz), 7.05 (2 H, t, J = 7.5 Hz), 5.20 (4 H, s), 4.96 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.4, 158.2, 137.3, 133.8, 132.0, 128.3, 127.5, 127.1, 121.2, 121.0, 115.5, 81.1, 71.9, 52.7; HRMS (ESI): MNa^+, found 451.1144. $C_{26}H_{20}NaO_6$ requires 451.1158.


77g

Compound 77h: Following the general procedure, **77h** was obtained after purification by column chromatography as a colourless solid, (44 mg, 38%); mp: 89-91 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2932, 1704, 1600, 1489 and 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.81 (2 H, dd, J_1 = 5.9 Hz, J_2 =1.7 Hz), 7.78 (1 H, br. s), 747-7.37 (5 H, m), 7.03 (4 H, t, J = 7.9 Hz), 5.15 (4 H, s), 4.44 (4 H, t, J = 6.6 Hz), 2.81 (4 H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.0, 158.0, 137.2, 133.4, 131.9, 128.5, 127.6, 127.4, 121.1, 120.9, 114.1, 71.2, 64.4, 31.0; HRMS (ESI): MNa^+, found 487.1189. $C_{26}H_{24}NaO_6S$ requires 487.1191.

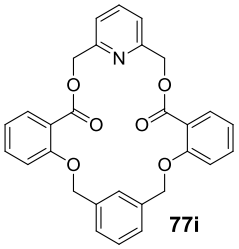

77h

Compound 78h: Following the general procedure, **78h** was obtained after purification by column chromatography as a colourless solid, (10 mg, 9%); mp: 160-162 ^oC; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2919, 1724, 1492, 1453, 1248 and 755 cm^{-1}; ^1H NMR

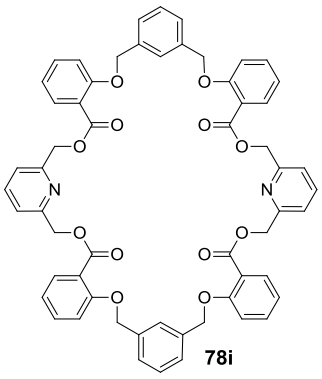


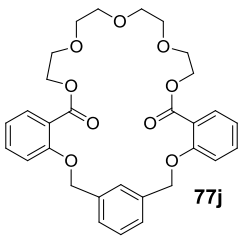
(400 MHz, $CDCl_3$): δ_H 7.80 (4 H, dd, J_1 = 6.2 Hz, J_2 = 1.7 Hz), 7.54 (2 H, br s), 7.43-7.38 (10 H, m), 6.98-6.95 (8 H, m), 5.12 (8 H, s), 4.38 (8 H, t, J = 7 Hz), 2.79 (8 H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 158.0, 137.0, 133.5, 131.9, 128.8, 126.8, 125.9, 120.6, 120.5, 113.7, 70.5, 63.9, 30.5; HRMS (ESI): MH^+, found 929.2675. $C_{52}H_{49}O_{12}S_2$ requires 929.2665.

Compound 77i: Following the general procedure, **77i** was obtained after purification by column chromatography on silica gel as white solid (62 mg, 52%); mp: 201-203 ^oC; R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 1705, 1601, 1489, 1453 and 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.89 (2 H, dd, J_1 = 6.3 Hz, J_2 = 1.8 Hz), 7.51-7.46 (2 H, m), 7.41 (1 H, t, J = 7.8 Hz), 7.32-7.28 (4 H, m), 7.24 (2 H, d, J = 7.7 Hz), 7.10-7.06 (4 H, m), 5.41 (4 H, s), 4.97 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.2, 158.2, 154.9, 137.0, 136.8, 133.5, 131.9, 128.3, 127.2, 127.0, 122.3, 121.6, 121.4, 115.4, 71.9, 67.5; HRMS (ESI): MNa^+, found 504.1434. $C_{29}H_{23}NNaO_6$ requires 504.1423.



Compound 78i: Following the general procedure, **78i** was obtained after purification by column chromatography as a colourless liquid (5 mg, 4%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2929, 1730, 1599, 1244 and 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.88 (4 H, dd, J_1 = 6.2 Hz, J_2 = 1.9 Hz), 7.50 (2 H, br. s), 7.44-7.36 (8 H, m), 7.28-7.15 (8 H, m), 7.00-6.95 (8 H, m), 5.38 (8 H, s), 5.07 (8 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.0, 158.1, 155.6, 136.8, 133.7, 132.1, 132.1, 128.9, 126.8, 120.7, 120.7, 120.3, 120.2, 113.6, 70.4, 66.9; HRMS (ESI): MH^+, found 963.3115. $C_{58}H_{47}N_2O_{12}$ requires 963.3129.

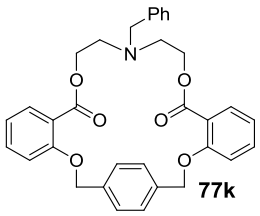




Compound 77j: Following the general procedure, **77j** was obtained after purification by column chromatography on as a colourless liquid (39 mg, 32%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2877, 1704, 1601, 1452 and 1251 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 8.0 Hz, J_2 = 6.1 Hz), 7.58 (1 H, br. s), 7.53-7.43 (5 H, m), 7.03 (4 H, t, J = 7.7

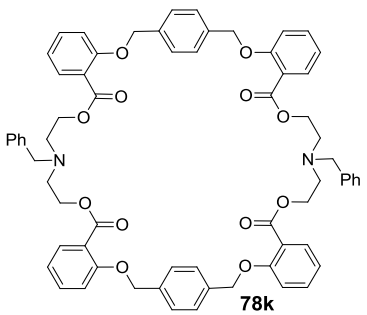
Hz), 4.48 (4 H, t, J = 4.6 Hz), 3.70 (4 H, t, J = 4.6 Hz), 3.52-3.45 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 157.9, 137.1, 133.4, 132.0, 128.9, 126.8, 125.7, 121.3, 120.8, 114.0, 70.7, 70.6, 70.5, 69.1, 64.4; HRMS (ESI): MNa^+, found 515.8217. $C_{28}H_{28}NaO_8$ requires 515.1682.

Compound 77k: Following the general procedure, **77k** was obtained after purification by column chromatography as a colourless solid, (17 mg, 13%); mp: 167-169 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2925, 1704, 1601, 1489 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.55-7.50 (6 H, m), 7.28-7.27 (5 H, m), 7.11 (2 H, d, J = 8.1 Hz), 7.06 (2 H, t, J = 7.6 Hz), 5.10 (4 H, s), 4.32 (4 H, t, J = 7.3 Hz), 3.69 (2 H, s), 2.80 (4 H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 157.6, 136.5, 133.3, 131.7, 128.7, 128.4, 128.3, 127.2, 121.4, 120.8, 112.9, 70.6, 62.1, 58.8, 52.4; HRMS (ESI): MH^+, found 538.2231. $C_{33}H_{32}NO_6$ requires 538.2230.



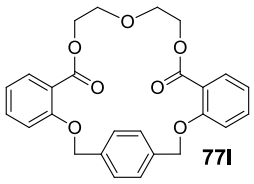
77k

Compound 78k: Following the general procedure, **78k** was obtained after purification by column chromatography as a colourless solid, (38 mg, 29%); mp: 116-118 ^oC; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1723, 1600, 1452 and 1132 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.77 (4 H dd, J_1 = 6.0 Hz, J_2 = 1.7 Hz), 7.43 (8 H, m), 7.39-7.35 (4 H, m), 7.31-7.28 (4 H, m), 7.23-7.20 (6 H, m), 6.97-6.90 (8 H, m), 5.05 (8 H, s), 4.33 (8 H, t, J = 6.2 Hz), 3.69 (4 H, s), 2.84 (8 H, t, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.5, 157.9, 139.3, 136.3, 133.3, 131.8, 128.7, 128.2, 127.3, 127.0, 120.8, 120.4, 113.4, 70.2, 62.8, 59.1, 52.3; HRMS (ESI): MH^+, found1075.4390. $C_{66}H_{63}N_2O_{12}$ requires 1075.4381.



78k

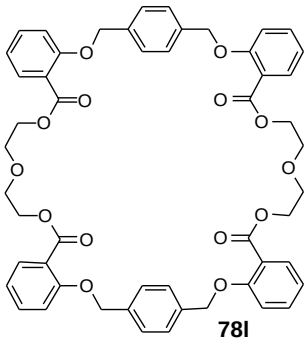
Compound 77l: Following the general procedure, **77l** was obtained after purification by column chromatography as a colourless solid, (6 mg, 5%); mp: 160-162 ^oC; R_f (30% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2968, 1698, 1602, 1492 and 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.59 (4 H, s), 7.54-7.50 (2 H, m), 7.11 (2 H, d, J = 7.8 Hz), 7.06 (2 H, td, J_1= 7.5 Hz, J_2 = 0.9 Hz), 5.13 (4 H, s), 4.42 (4 H, t, J = 5.1 Hz), 3.57 (4 H, t, J = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.9, 157.8, 136.4, 133.4, 132.0, 128.3,



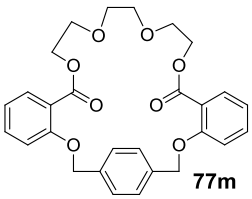
77l

121.1, 120.8, 113.1, 70.6, 69.1, 64.0; HRMS (ESI): MNa^+, found 471.1427. $C_{26}H_{24}NaO_7$ requires 471.1420.

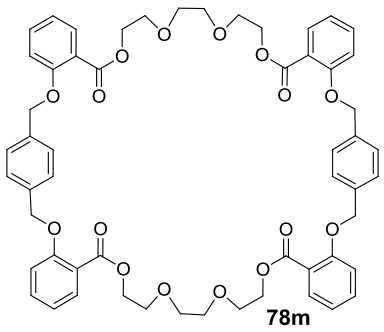
Compound 78l: Following the general procedure, **78l** was obtained after purification by column chromatography as a colourless solid (25 mg, 22%); mp: 161-163 ^oC; R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2923, 1711, 1600, 1453, 1375 and 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (4 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.49 (8 H, s), 7.44-7.40 (4 H, m), 6.97-6.93 (8 H, m), 5.07 (8 H, s), 4.40 (8 H, t, J = 4.8 Hz), 3.69 (8 H, t, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.6, 158.0, 136.3, 133.4, 132.0, 127.4, 120.6, 120.5, 113.4, 70.1, 69.0, 64.1; HRMS (ESI): MNa^+, found 919.2969. $C_{52}H_{48}NaO_{14}$ requires 919.2942.


78l

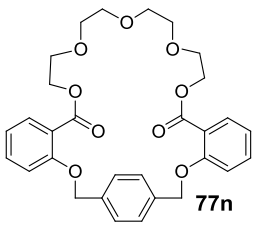
Compound 77m: Following the general procedure, **77m** was obtained after purification by column chromatography as a colourless liquid (14 mg, 12%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2869, 1702, 1601, 1452 and 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.60 (4 H, s), 7.51-7.47 (2 H, m), 7.08 (2 H, d, J = 8.4 Hz), 7.04 (2 H, td, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 5.17 (4 H, s), 4.50-4.49 (4 H, t, J = 4.5 Hz), 3.76 (4 H, m), 3.56 (4 H, t, J = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.7, 157.7, 136.4, 133.4, 132.2, 127.5, 121.0, 120.7, 113.2, 70.4, 70.2, 69.3, 64.4; HRMS (ESI): MH^+, found 493.1880. $C_{28}H_{29}O_8$ requires 493.1862.


77m

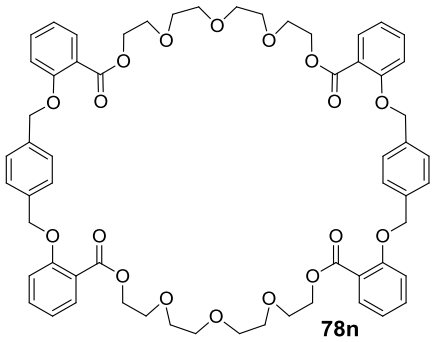
Compound 78m: Following the general procedure, **78m** was obtained after purification by column chromatography as a colourless liquid (17 mg, 14%); R_f (45% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2873, 1725, 1601, 1490 and 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (4 H, dd, J_1 = 6.5 Hz, J_2 = 1.8 Hz), 7.50 (8 H, s), 7.43-7.38 (4 H, m), 6.99-6.96 (8 H, m), 5.13 (8 H, s), 4.40 (8 H, t, J = 4.9 Hz), 3.71 (8 H, t, J = 4.9 Hz), 3.57 (8 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.4, 158.0, 136.4, 133.4, 131.9, 127.2, 120.7, 120.6, 113.7, 70.5, 70.2, 69.1, 64.0; HRMS (ESI): MNa^+, found 1007.3497. $C_{56}H_{56}NaO_{16}$ requires 1007.3466.


78m

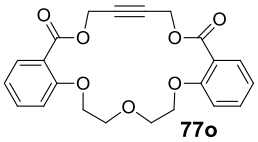
Compound 77n: Following the general procedure, **77n** was obtained after purification by column chromatography as a colourless solid (20 mg, 15%); mp: 130-132 ^{o}C; R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2870, 1704, 1600, 1489 and 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 6.2 Hz, J_2 = 1.9 Hz), 7.55 (4 H, s), 7.50-7.44 (4 H, m), 7.04 (2 H, d, J = 7.8 Hz), 5.19 (4 H, s), 4.47 (4 H, t, J = 4.7 Hz), 3.76 (4 H, t, J = 4.7 Hz), 3.59-3.52 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.2, 157.8, 136.5, 133.4, 132.1, 127.6, 121.1, 120.7, 113.7, 70.7, 70.6, 70.5, 69.1, 64.3; HRMS (ESI): MNa^+, found 559.1945. $C_{30}H_{32}NaO_9$ requires 559.1944.


77n

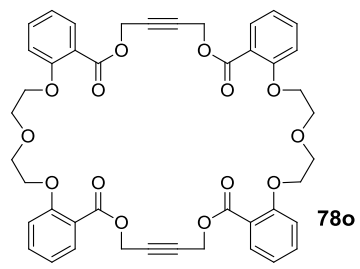
Compound 78n: Following the general procedure, **78n** was obtained after purification by column chromatography as a colourless liquid (11 mg, 8%); R_f (45% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2873, 1703, 1601, 1452 and 1253 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (4 H, dd, J_1 = 6.8 Hz, J_2 = 1.8 Hz), 7.50 (8 H, s), 7.43-7.39 (4 H, m), 7.00-6.97 (8 H, m), 5.15 (8 H, s), 4.42 (8 H, t, J = 4.8 Hz), 3.72 (8 H, t, J = 4.9 Hz), 3.57 (16 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.3, 158.0, 136.4, 133.4, 131.9, 127.2, 120.7, 120.6, 113.7, 70.6, 70.6, 70.3, 69.1, 64.0; HRMS (ESI): MNa^+, found 1095.4006. $C_{60}H_{64}NaO_{18}$ requires 1095.3990.


78n

Compound 77o: Following the general procedure, **77o** was obtained after purification by column chromatography as a colourless liquid, (44 mg, 45%); R_f (35% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2954, 1695, 1602, 1490 and 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 5.9 Hz, J_2 =1.8 Hz), 7.51-7.47 (2 H, m), 7.06-6.99 (4 H, m), 4.99 (4 H, s), 4.23-4.20 (4 H, m), 4.17-4.14 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.6, 158.4, 133.9, 132.2, 121.0, 120.2, 114.3, 81.1, 70.7, 70.3, 52.7; HRMS (ESI): MNa^+, found 419.1097. $C_{22}H_{20}NaO_7$ requires 419.1107.

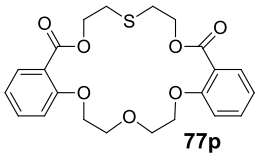

77o

Compound 78o: Following the general procedure, **78o** was obtained after purification by column chromatography as a colourless liquid, (18 mg, 18%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2936, 1732, 1600, 1453 and 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80


78o

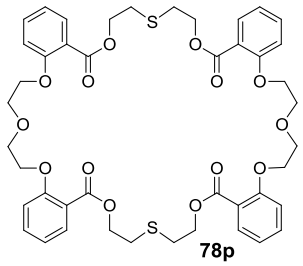
(4 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.45-7.40 (4 H, m), 6.97 (4 H, td, J_1 = 6.8 Hz, J_2 =0.9 Hz), 6.93 (4 H d, J = 8.4 Hz), 4.96 (8 H, s), 4.16 (8 H, t, J = 4.7 Hz), 4.04 (8 H, t, J = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 158.5, 133.9, 132.0, 120.5, 119.7, 113.7, 81.1, 70.2, 69.2, 52.5; HRMS (ESI): MNa^+, found 815.2300. $C_{44}H_{40}NaO_{14}$ requires 815.2316.

Compound 77p: Following the general procedure, **77p** was obtained after purification by column chromatography as a colourless liquid (59 mg, 55%); R_f (40% EtOAc/Hexanes) 0.55; IR


77p

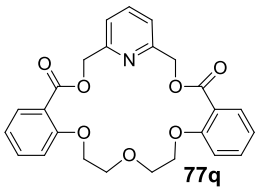
(CH_2Cl_2): ν_{max} 2916, 1725, 1601, 1490 and 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.82 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.48-7.44 (2 H, m), 7.02 (2 H, dt, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 6.97 (2 H, d, J = 8.5 Hz), 4.52 (4 H, t, J = 6.4 Hz), 4.22 (4 H, t, J = 4.7 Hz), 4.11 (4 H, t, J = 4.7 Hz), 3.03 (4 H, t, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.0, 158.1, 133.5, 131.9, 120.7, 113.4, 70.3, 69.5, 64.7, 31.3; HRMS (ESI): MH^+, found 433.1316. $C_{22}H_{25}O_7S$ requires 433.1321.

Compound 78p: Following the general procedure, **78p** was obtained after purification by column chromatography as a colourless liquid (9 mg, 8%); R_f (45% EtOAc/Hexanes) 0.55; IR


78p

(CH_2Cl_2): ν_{max} 2920, 1724, 1450 and 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (4 H, dd, J_1 = 6.1 Hz, J_2 = 1.8 Hz), 7.45-7.40 (4 H, m), 6.99-6.96 (8 H, m), 4.42 (8 H, t, J = 6.8 Hz), 4.20 (8 H, t, J = 4.8 Hz), 4.01 (8 H, t, J = 4.8 Hz), 2.93 (8 H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 158.3, 133.5, 131.7, 120.5, 113.7, 70.0, 69.0, 63.8, 30.7; HRMS (ESI): MNa^+, found 887.2388. $C_{44}H_{48}NaO_{14}S_2$ requires 887.2383.

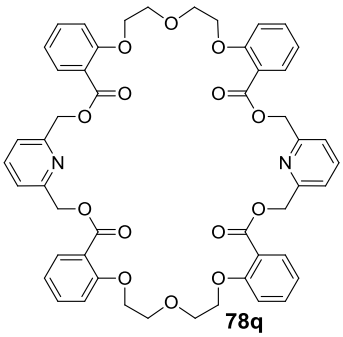
Compound 77q: Following the general procedure, **77q** was obtained after purification by column chromatography as a colourless liquid (28 mg, 25%); R_f (45% EtOAc/Hexanes) 0.55; IR


77q

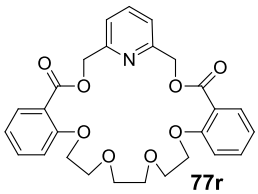
(CH_2Cl_2): ν_{max} 2934, 1699, 1489, 1451 and 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.90 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.6 Hz), 7.79 (1 H, t, J = 7.6 Hz), 7.49 (2 H, d, J = 7.7 Hz), 7.46 (2 H, td , J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.04 (2 H, t, J = 7.5 Hz), 6.94 (2 H, d, J = 8.3 Hz), 5.46 (4 H, s), 4.03 (4 H, t, J = 4.4 Hz), 3.55 (4 H, t, J = 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 158.3, 155.6,

137.4, 133.7, 132.2, 123.4, 121.1, 120.9, 114.6, 70.1, 70.0, 68.0; HRMS (ESI): MNa^+, found 472.1376. $C_{25}H_{23}NNaO_7$ requires 472.1372.

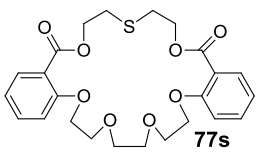
Compound 78q: Following the general procedure, **78q** was obtained after purification by column chromatography on silica gel as colourless liquid (9 mg, 8%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2919, 1694, 1599, 1491 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (4 H, dd, J_1 = 6.0 Hz, J_2 = 1.7 Hz), 7.64 (2 H, t, J = 7.6 Hz), 7.47-7.43 (4 H, m), 7.37 (4 H, d, J = 7.8 Hz), 7.02-6.95 (8 H, m), 5.40 (8 H, s), 4.14 (8 H, t, J = 4.7 Hz), 3.85 (8 H, t, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 158.3, 155.9, 137.4, 133.7, 132.0, 120.7, 120.6, 120.3, 113.6, 69.8, 68.8, 67.0; HRMS (ESI): MNa^+, found 921.2854. $C_{50}H_{46}N_2NaO_{14}$ requires 921.2847.



Compound 77r: Following the general procedure, **77**was obtained after purification by column chromatography as a colourless solid (52 mg, 42%); R_f (45% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2937, 1704, 1601, 1301 and 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.92 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz,), 7.77 (1 H, t, J = 7.7 Hz), 7.50-7.46 (4 H, m), 7.04 (2 H, t, J = 7.7 Hz), 6.93 (2 H, d, J = 8.2 Hz), 5.50 (4 H, s), 4.12 (4 H, t, J = 4.2 Hz), 3.72 (4 H, t, J = 4.2 Hz), 3.25 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.1, 158.2, 155.9, 137.3, 133.7, 132.3, 121.6, 120.6, 120.3, 113.6, 70.6, 69.4, 69.2, 67.5; HRMS (ESI): MH^+, found 516.1621. $C_{27}H_{27}NNaO_8$ requires 516.1634.

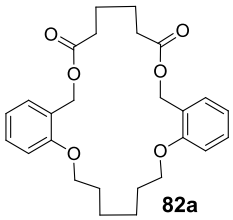


Compound 77s: Following the general procedure, **77s** was obtained after purification by column chromatography on silica gel as colourless liquid (61 mg, 52%); R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2927, 1601, 1726, 1450 and 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.47-7.42 (2H, m), 6.99 (2 H, t, J = 7.5 Hz), 6.93 (2 H, d, J = 8.4 Hz), 4.49 (4 H, t, J = 7.1 Hz), 4.19 (4 H, t, J = 4.4 Hz), 3.95 (4 H, t, J = 4.2 Hz), 3.86 (4 H, s), 2.98 (4 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.7, 158.1, 133.5, 131.7, 120.5, 120.5, 112.9, 71.2, 69.6, 69.1, 63.6, 30.4; HRMS (ESI): MNa^+, found 499.1390. $C_{24}H_{28}NaO_8S$ requires 499.1403.

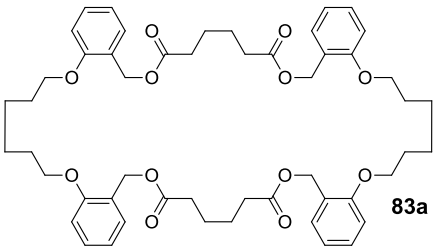


General procedure for the syntheses of macrocyclic lactones 82a-d and 83a-d. To a solution of dicarboxylic acid **81** (0.25 mmol) and diol **80** (0.25 mmol) in CH_2Cl_2 (15 mL) was added DMAP (1 equiv) followed by EDC.HCl (2.5 equiv). The reaction mixture was stirred at room temperature for 20 h. After this period, the resulting crude reaction mixture was washed with 2 N HCl (2 X 5 mL). The solvent was removed under reduced pressure and the residue was purified by using neutral alumina/silica gel column chromatography (EtOAc/Hexanes) to give the corresponding macrocyclic lactones **82a-d** and **83a-d** (see the respective Tables for specific entries).

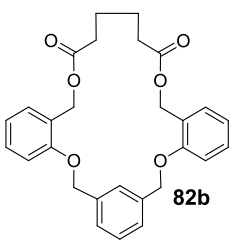
Compound 82a. Following the general procedure, **82a** was obtained after purification by column chromatography as a colourless solid (24 mg, 22%); mp: 117-119 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2941, 1732, 1497, 1457 and 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.36-7.30 (4 H, m), 6.94 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.9 Hz), 6.90 (2 H, d, J = 8.2 Hz), 5.13 (4 H, s), 4.02 (4 H, t, J = 6.1 Hz), 2.34 (4 H, br. s), 1.84-1.81 (4 H, m), 1.71-1.67 (4 H, m), 1.59-1.56 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2, 158.0, 131.7, 130.4, 123.9, 120.1, 111.3, 67.7, 62.9, 34.0, 29.3, 25.9, 24.5; HRMS (ESI): MNa^+, found 463.2103. $C_{26}H_{32}NaO_6$ requires 463.2097.



Compound 83a. Following the general procedure, **83a** was obtained after purification by column chromatography as a colourless solid (18 mg, 7%); mp: 100-102 ^oC, R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 1733, 1602, 1496, 1456 and 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31-7.27 (8 H, m), 6.93 (4 H, td, J_1 = 7.4 Hz, J_2 = 0.9 Hz), 6.87 (4 H, d, J = 8.0 Hz), 5.16 (8 H, s), 3.99 (8 H, t, J = 6.3 Hz), 2.35 (8 H, br. s), 1.83-1.80 (8 H, m), 1.69-1.64 (8 H, m), 1.56-1.52 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2, 157.1, 129.9, 129.6, 124.3, 120.2, 111.3, 67.8, 61.9, 33.9, 29.2, 25.9, 24.4; HRMS (ESI): MNa^+, found 903.4300. $C_{52}H_{64}NaO_{12}$ requires 903.4295.

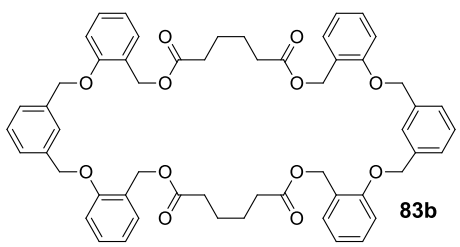


Compound 82b. Following the general procedure, **82b** was obtained after purification by column chromatography as a colorless liquid (19 mg, 17%); R_f (40% EtOAc/Hexanes) 0.55; IR

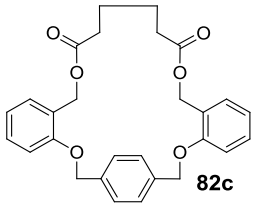


(CH_2Cl_2): ν_{max} 2941, 1730, 1602, 1456 and 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.57 (1 H, br. s), 7.43-7.34 (7 H, m), 7.06 (2 H, d, J = 7.9 Hz), 7.01 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.8 Hz), 5.18 (4 H, s), 5.12 (4 H, s), 2.13 (4 H, t, J = 6.6 Hz), 1.46-1.42 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.3, 157.7, 137.2, 131.4, 130.4, 128.6, 127.0, 126.4, 124.7, 120.9, 112.3, 70.2, 62.7, 33.9, 24.3; HRMS (ESI): MNa^+, found 483.1786. $C_{28}H_{28}NaO_6$ requires 483.1784.

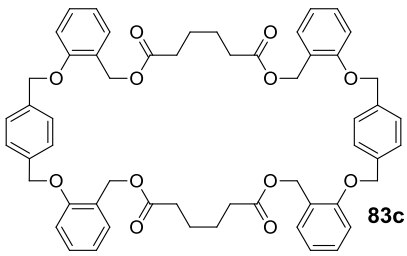
Compound 83b. Following the general procedure, **83b** was obtained after purification by column chromatography as a colourless solid (14 mg, 13%); mp: 139-141 ^oC, R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 1731, 1606, 1496, 1246 and 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.48 (2 H, br. s), 7.38-7.26 (14 H, m), 6.95 (8 H, t, J = 9.2 Hz), 5.19 (8 H, s), 5.11 (8 H, s), 2.25 (8 H, t, J = 6.9 Hz), 1.57-1.54 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2, 156.7, 137.3, 130.2, 129.7, 128.8, 126.6, 125.7, 124.6, 120.8, 111.9, 69.7, 62.0, 33.9, 24.3; HRMS (ESI): MNa^+, found 943.3668. $C_{56}H_{56}NaO_{12}$ requires 943.3669.



Compound 82c. Following the general procedure, **82c** was obtained after purification by column chromatography as a colourless solid (20 mg, 18%); mp: 155-157 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2941, 1730, 1496, 1254 and 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.47 (4 H, s), 7.41-7.35 (4 H, m), 7.02-6.97 (4 H, m), 5.19 (4 H, s), 5.14 (4 H, s), 2.37-2.33 (4 H, m), 1.68-1.65 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2, 157.6, 136.5, 132.0, 130.6, 126.9, 124.1, 120.7, 111.5, 69.0, 63.3, 34.0, 24.5; HRMS (ESI): MNa^+, found 483.1776. $C_{28}H_{28}NaO_6$ requires 483.1784.

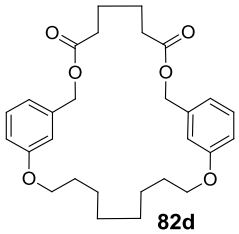


Compound 82c. Following the general procedure, **82c** was obtained after purification by column chromatography as a colourless solid (9 mg, 8%); mp: 168-170 ^oC, R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2926, 1733, 1496, 1456 and 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.42 (8 H, s), 7.34-7.27 (8 H, m), 6.98-6.93 (8 H, m), 5.20 (8 H, s), 5.08 (8 H, s), 2.30 (8 H, t, J = 5.9 Hz), 1.63-1.60 (8 H,

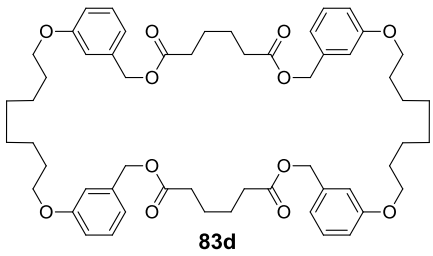


m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.2, 156.7, 136.6, 130.2, 129.7, 127.3, 124.6, 120.7, 111.8, 69.5, 62.0, 33.0, 24.4; HRMS (ESI): MNa^+, found 943.3669. $C_{56}H_{56}NaO_{12}$ requires 943.3669.

Compound 82d. Following the general procedure, **82d** was obtained after purification by column chromatography as a semi solid (14 mg, 12%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2935, 1737, 1453, 1267 and 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.25 (2 H, d, J = 7.9 Hz), 6.94 (2 H, t, J = 1.8 Hz), 6.89-6.85 (4 H, m), 5.10 (4 H, s), 4.00 (4 H, t, J = 6.2 Hz), 2.43-2.40 (4 H, m), 1.84-1.77 (4 H, m), 1.75-1.71 (4 H, m), 1.54-1.49 (4 H, m), 1.44-1.40 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.0, 159.4, 137.4, 129.5, 120.1, 114.2, 113.9, 67.7, 66.0, 33.8, 29.0, 28.9, 25.7, 24.2; HRMS (ESI): MNa^+, found 491.2419. $C_{28}H_{36}NaO_6$ requires 491.2410.

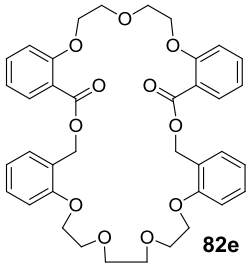

82d

Compound 83d. Following the general procedure, **83d** was obtained after purification by column chromatography as a colourless solid (21 mg, 12%); mp: 76-78 ^{o}C, R_f (50% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2934, 1736, 1603, 1586 and 1262 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.25 (4 H, d, J = 7.6 Hz), 6.92-6.84 (12 H, m), 5.08 (8 H, s), 3.96 (8 H, t, J = 6.4 Hz), 2.41-2.37 (8 H, m), 1.82-1.75 (8 H, m), 1.72-1.68 (8 H, m), 1.50-1.47 (8 H, m), 1.41-1.39 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 173.1, 159.3, 137.4, 129.6, 129.6, 120.2, 114.3, 114.2, 67.9, 66.1, 33.9, 29.3, 29.2, 26.0, 24.3; HRMS (ESI): MNa^+, found 959.4922. $C_{56}H_{72}NaO_{12}$ requires 959.4921.

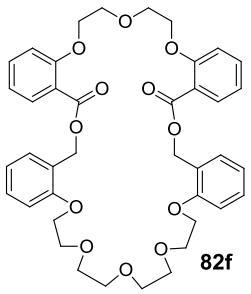

83d

General procedure for the syntheses of macrocyclic lactones 82e-s and 84a-c. To a solution of dicarboxylic acid **75** (0.25 mmol) and diol **80** (0.25 mmol) in CH_2Cl_2 (3 mL) was added DMAP (1 equiv) followed by EDC.HCl (2.5 equiv). The reaction mixture was refluxed for 20 h. After this period, the resulting crude reaction mixture was washed with 2 N HCl (2 X 5 mL). The solvent was removed under reduced pressure and the residue was purified by using neutral alumina/silica gel column chromatography (EtOAc/Hexanes) to give the corresponding macrocyclic di-lactones **82e-s** and **84a-c** (see the respective Tables for specific entries).

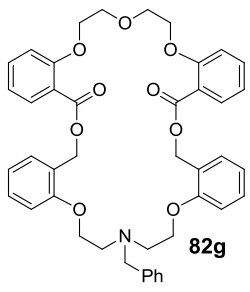
Compound 82e. Following the general procedure, **82e** was obtained after purification by column chromatography as a colorless liquid (84 mg, 50%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2937, 1723, 1602, 1451 and 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.8 Hz), 7.44-7.40 (4 H, m), 7.24 (2 H, t, J = 7.7 Hz), 7.01-6.93 (6 H, m), 6.86 (2 H, d, J = 8.2 Hz), 5.41 (4 H, s), 4.13 (4 H, t, J = 4.4 Hz), 4.08 (4 H, t, J = 4.6 Hz), 3.83-3.79 (8 H, m), 3.60 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 158.5, 156.8, 133.3, 131.8, 129.6, 129.3, 124.9, 121.0, 120.6, 114.1, 111.6, 71.0, 69.8, 69.6, 69.3, 68.3, 62.2; HRMS (ESI): MNa^+, found 695.2456. $C_{38}H_{40}NaO_{11}$ requires 695.2468.



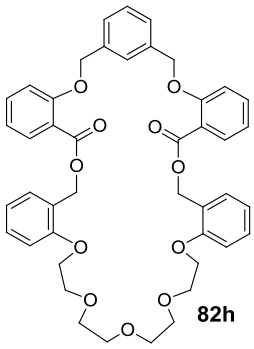
Compound 82f. Following the general procedure, **82f** was obtained after purification by column chromatography as a colorless liquid (72 mg, 40%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2939, 1725, 1601, 1452 and 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1= 6.2 Hz, J_2 = 1.9 Hz), 7.45-7.41 (4 H, m), 7.28-7.24 (2 H, m), 7.01-6.94 (6 H, m), 6.87 (2 H, d, J = 8.2 Hz), 5.41 (4 H, s), 4.14 (8 H, q, J = 4.5 Hz), 3.86-3.81 (8 H, m), 3.67-3.65 (4 H, m), 3.54-3.51 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 158.5, 156.7, 133.4, 131.8, 129.6, 129.3, 124.9, 120.9, 120.6, 120.6, 114.0, 111.6, 70.9, 70.6, 69.8, 69.6, 69.2, 68.2, 62.1; HRMS (ESI): MNa^+, found 739.2735. $C_{40}H_{44}NaO_{12}$ requires 739.2730.



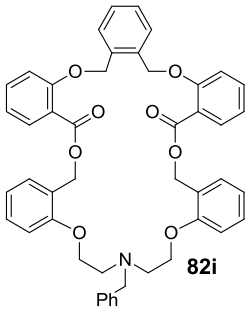
Compound 82g. Following the general procedure, **82g** was obtained after purification by column chromatography as a colorless liquid (57 mg, 32%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2937, 1732, 1605, 1495 and 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, d, J = 6.1 Hz), 7.44-7.21 (11 H, m), 6.99 (2 H, t, J = 7.3 Hz), 6.94-6.87 (4 H, m), 6.78 (2 H, d, J = 8.2 Hz), 5.39 (4 H, s), 4.03 (4 H, t, J = 4.7 Hz), 3.97 (4 H, t, J = 4.7 Hz), 3.75 (2 H, s), 3.71 (4 H, t, J = 4.8 Hz), 3.04 (4 H, t, J = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.5, 158.4, 156.9, 133.3, 131.9, 130.0, 129.4, 128.6, 128.3, 124.6, 121.0, 120.5, 120.3, 113.9, 111.4, 69.8, 69.3, 67.2, 62.3, 59.7, 53.3; HRMS (ESI): MNa^+, found 740.2820. $C_{43}H_{43}NNaO_9$ requires 740.2836.



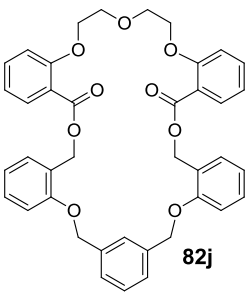
Compound 82h. Following the general procedure, **82h** was obtained after purification by column chromatography as a colourless liquid (78 mg, 42%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2920, 1723, 1601, 1299 and 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.87 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.9 Hz), 7.60 (1 H, s), 7.46-7.37 (6 H, m), 7.30-7.24 (3 H, m), 7.02-6.99 (4 H, m), 6.93 (2 H, t, J = 7.5 Hz), 6.85 (2 H, d, J = 7.7 Hz), 5.43 (4 H, s), 5.11 (4 H, s), 4.08 (4 H, t, J = 4.7 Hz), 3.76 (4 H, t, J = 4.7 Hz), 3.60-3.57 (4 H, m), 3.46-3.43 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 158.1, 156.8, 137.0, 133.4, 131.9, 129.7, 129.4, 128.8, 126.5, 125.7, 124.8, 121.1, 120.6, 114.0, 111.6, 70.8, 70.5, 70.4, 69.6, 68.2, 62.3; HRMS (ESI): MNa^+, found 771.2826. $C_{44}H_{44}NaO_{11}$ requires 771.2781.



Compound 82i. Following the general procedure, **82i** was obtained after purification by column chromatography as a colorless liquid (65 mg, 35%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2920, 1721, 1601, 1452 and 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.8 Hz), 7.48-7.46 (2 H, m), 7.37-7.18 (13 H, m), 6.96-6.88 (6 H, m), 6.75 (2 H, d, J = 8.1 Hz), 5.35 (4 H, s), 5.19 (4 H, s), 3.94 (4 H, br. s), 3.67 (2 H, s), 2.90 (4 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.7, 157.7, 157.2, 134.5, 133.3, 132.0, 130.8, 129.8, 128.6, 128.4, 128.2, 128.1, 126.9, 124.3, 120.9, 120.5, 120.4, 120.4, 113.6, 111.6, 68.8, 67.1, 62.7, 59.3, 53.1; HRMS (ESI): MH^+, found 750.3065. $C_{47}H_{44}NO_8$ requires 750.3067.

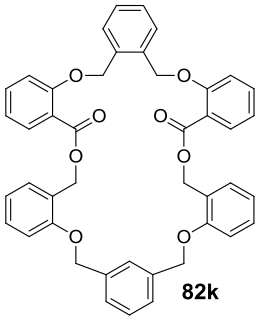


Compound 82j. Following the general procedure, **82j** was obtained after purification by column chromatography as a colourless solid (76 mg, 46%); mp: 132-134 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2924,1722, 1602, 1493 and 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.56 (1 H, br. s), 7.45-7.38 (4 H, m), 7.29-7.24 (5 H, m), 6.97 (4 H, t, J = 7.4 Hz), 6.89 (4 H, dd, J_1 = 6.8 Hz, J_2 = 1.7 Hz), 5.43 (4 H, s), 5.06 (4 H, s), 3.99 (4 H, t, J = 4.9 Hz), 3.70 (4 H, t, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.4, 158.4, 156.7, 137.4, 133.3, 131.8, 130.4, 129.5, 128.5, 126.4, 125.9,

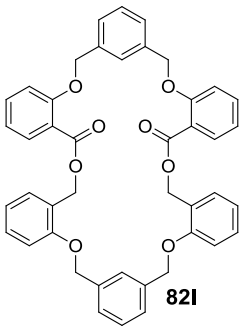


125.0, 121.0, 120.7, 120.5, 114.0, 112.0, 69.7, 69.5, 69.2, 62.2; HRMS (ESI): MNa^+, found 683.2257. $C_{40}H_{36}NaO_9$ requires 683.2257.

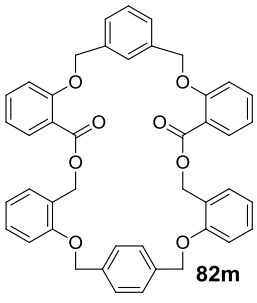
Compound 82k. Following the general procedure, **82k** was obtained after purification by column chromatography as a colorless liquid (83 mg, 48%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2920, 1725, 1601, 1494, 1452 and 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.87 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.8 Hz), 4.47-7.39 (4 H, m), 7.29-7.17 (10 H, m), 6.97-6.89 (6 H, m), 6.84 (2 H, d, J = 8.1 Hz), 5.40 (4 H, s), 5.10 (4 H, s), 4.84 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.6, 157.9, 157.0, 137.3, 134.5, 133.5, 132.1, 130.7, 129.8, 128.4, 128.4, 128.1, 126.6, 126.2, 124.7, 120.8, 120.7, 120.5, 113.8, 112.3, 69.7, 69.0, 62.7; HRMS (ESI): MNa^+, found 715.2293. $C_{44}H_{36}NaO_8$ requires 715.2308.



Compound 82l. Following the general procedure, **82l** was obtained after purification by column chromatography on silica gel as a white solid (48 mg, 28%); mp: 186-188 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 1716, 1698, 1601, 1493 and 1299 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.55 (1 H, s), 7.45 (1 H, s), 7.43-7.39 (4 H, m), 7.27-7.15 (8 H, m), 6.98 (2 H, t, J = 7.4 Hz), 6.93-6.89 (4 H, m), 6.79 (2 H, d, J = 8.1 Hz), 5.43 (4 H, s), 4.93 (4 H, s), 4.87 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.6, 157.9, 156.6, 137.3, 137.0, 133.2, 132.0, 130.0, 129.4, 128.4, 128.3, 126.3, 126.3, 126.0, 125.8, 124.9, 121.2, 120.6, 120.5, 113.9, 111.7, 70.4, 69.3, 62.7; HRMS (ESI): MNa^+, found 715.2333. $C_{44}H_{36}NaO_8$ requires 715.2308.

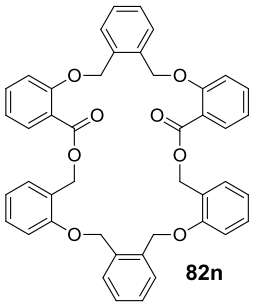


Compound 82m. Following the general procedure, **82m** was obtained after purification by column chromatography as a colourless solid (95 mg, 55%); mp: 165-167 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2916, 1722, 1602, 1493 and 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.49 (2 H, dd, J_1 = 5.8 Hz, J_2 = 1.6 Hz), 7.45-7.40 (2 H, m), 7.37 (1 H, s), 7.33-7.25 (4 H, m), 7.18 (4 H, s), 7.12 (1 H, t, J = 7.7 Hz), 7.02-6.91 (8 H, m), 5.49 (4 H, s), 4.96 (4 H, s), 4.95 (4 H, s); ^{13}C

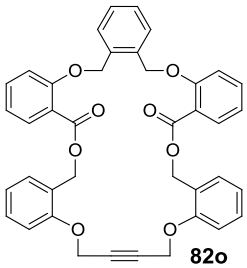


NMR (100 MHz, $CDCl_3$): δ_C 166.8, 157.8, 156.9, 137.0, 136.4, 133.1, 131.6, 130.5, 129.7, 128.6, 127.1, 126.1, 125.3, 124.8, 121.5, 120.7, 120.6, 113.9, 111.9, 70.3, 69.5, 62.7; HRMS (ESI): MNa^+, found 715.2293. $C_{44}H_{36}NaO_8$ requires 715.2308.

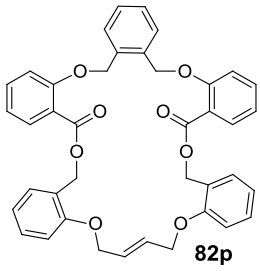
Compound 82n. Following the general procedure, **82n** was obtained after purification by column chromatography as a colourless solid (77 mg, 55%); mp: 145-147 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2920, 1699, 1601, 1494 and 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.46 (2 H, dd, J_1 = 5.7 Hz, J_2 = 1.7 Hz), 7.39-7.37 (2 H, m), 7.34-7.25 (4 H, m), 7.09-7.05 (4 H, m), 6.97 (2 H, t, J = 7.6 Hz), 6.89-6.82 (6 H, m), 6.76 (2 H, d, J = 8.2 Hz), 5.45 (4 H, s), 5.17 (4 H, s), 5.10 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.7, 157.2, 157.0, 134.6, 133.4, 132.3, 132.1, 130.3, 127.8, 127.8, 127.8, 127.7, 123.8, 120.9, 120.5, 120.3, 112.8, 111.4, 68.5, 67.8, 62.7; HRMS (ESI): MNa^+, found 715.2309. $C_{44}H_{36}NaO_8$ requires 715.2308.



Compound 82o. Following the general procedure, **82o** was obtained after purification by column chromatography as a colourless solid (67 mg, 42%); mp: 161-163 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 1722, 1601, 1452, 1300 and 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.87 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.9 Hz), 7.50-7.48 (2 H, m), 7.40-7.36 (4 H, m), 7.26-7.19 (4 H, m), 7.01-6.97 (4 H, m), 6.91 (2 H, t, J = 7.5 Hz), 6.83 (2 H, d, J = 8.2 Hz), 5.33 (4 H, s), 5.24 (4 H, s), 4.48 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.9, 157.8, 156.1, 134.7, 133.3, 132.0, 130.8, 129.6, 128.5, 128.1, 125.2, 121.4, 121.2, 120.7, 114.0, 112.7, 82.1, 69.1, 62.6, 56.4; HRMS (ESI): MNa^+, found 663.1988. $C_{40}H_{32}NaO_8$ requires 663.1995.

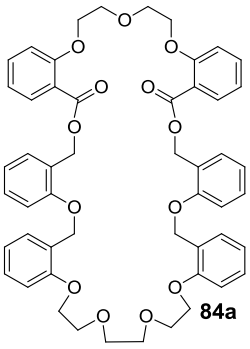


Compound 82p. Following the general procedure, **82p** was obtained after purification by column chromatography as a colourless solid (72 mg, 42%); mp: 145-147 ^oC, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 1722, 1601, 1494, 1299 and 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.86 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.7 Hz), 7.50-7.48 (2 H, m), 7.39 (2 H, d, J = 7.4 Hz), 7.35-7.27 (4 H, m), 7.17-7.15 (2 H, m), 7.00-6.93 (6 H, m), 6.80 (2 H, d, J = 8.2

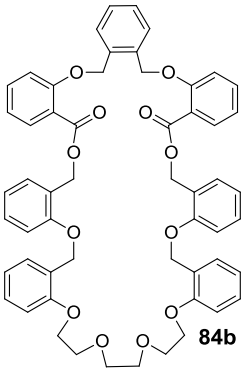


Hz), 5.96 (2 H, s), 5.34 (4 H, s), 5.27 (4 H, s), 4.37 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.7, 157.7, 157.0, 134.6, 133.3, 131.9, 130.7, 129.7, 128.4, 128.1, 127.7, 124.7, 121.1, 120.7, 120.6, 113.8, 112.1, 69.1, 67.6, 62.7; HRMS (ESI): MNa^+, found 665.2143. $C_{40}H_{34}NaO_8$ requires 665.2151.

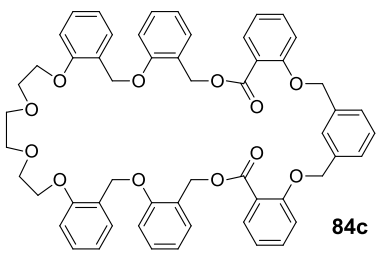
Compound 84a. Following the general procedure, **84a** was obtained after purification by column chromatography as a colorless liquid (77 mg, 35%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2933, 1725, 1603, 1300 and 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.45-7.39 (6 H, m), 7.25-7.15 (4 H, m), 7.00-6.82 (12 H, m), 5.44 (4 H, s), 5.13 (4 H, s), 4.11 (4 H, t, J = 4.8 Hz), 4.02 (4 H, t, J = 5.2 Hz), 3.78 (4 H, t, J = 4.5 Hz), 3.66 (4 H, t, J = 4.9 Hz), 3.61 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.7, 158.3, 156.7, 156.0, 133.3, 131.9, 129.4, 129.3, 128.9, 128.7, 125.7, 124.9, 121.0, 120.9, 120.6, 120.5, 113.8, 112.0, 111.5, 70.9, 69.7, 69.6, 68.8, 68.1, 65.4, 62.3; HRMS (ESI): MNa^+, found 907.3305. $C_{52}H_{52}NaO_{13}$ requires 907.3306.



Compound 84b. Following the general procedure, **84b** was obtained after purification by column chromatography as a colorless liquid (61 mg, 27%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2929, 1722, 1601, 1494 and 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.40-7.15 (16 H, m), 6.93 (2 H, t, J = 7.6 Hz), 6.86 (4 H, t, J = 8.6 Hz), 6.81-6.75 (4 H, m), 5.38 (4 H, s), 4.99 (4 H, s), 4.95 (4 H, s), 4.08 (4 H, t, J = 4.5 Hz), 3.76 (4 H, t, J = 4.6 Hz), 3.59 (4 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.8, 157.8, 156.9, 156.0, 134.5, 133.3, 132.0, 130.0, 129.5, 128.7, 128.5, 128.1, 125.7, 124.5, 120.8, 120.6, 120.5, 120.3, 113.1, 112.1, 111.4, 70.9, 69.7, 68.6, 68.0, 65.3, 62.6; HRMS (ESI): MNa^+, found 939.3370. $C_{56}H_{52}NaO_{12}$ requires 939.3356.



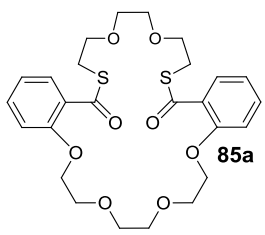
Compound 84c. Following the general procedure, **84c** was obtained after purification by column chromatography as a colorless liquid (73 mg, 27%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2929, 1722, 1602, 1493 and 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.40 (6 H, t, J = 7.4 Hz), 7.35 (1 H, s), 7.30-7.28 (2 H, m), 7.23-7.15 (5 H, m), 6.99 (2 H, t, J = 7.4 Hz), 6.94-6.80 (10 H, m), 5.48 (4 H, s), 5.08 (4 H, s), 4.98 (4 H, s), 4.08



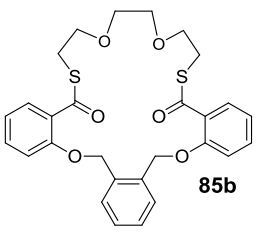
(4 H, t, *J* = 4.8 Hz), 3.74 (4 H, t, *J* = 4.7 Hz), 3.58 (4 H, t, *J* = 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.8, 157.8, 156.9, 156.0, 136.8, 133.3, 131.9, 129.4, 129.2, 128.6, 128.7, 128.7, 126.3, 125.7, 125.4, 124.8, 12.1.3, 120.8, 120.6, 120.5, 113.8, 112.0, 111.5, 70.9, 70.3, 69.6, 68.0, 65.4, 62.5; HRMS (ESI): MNa^+, found 939.3358. $C_{56}H_{52}NaO_{12}$ requires 939.3356.

General procedure for the syntheses of macrocyclic lactones 85a-c. To a solution of dicarboxylic acid **75** (0.25 mmol) and dithiol **80l** (0.25 mmol) in CH_2Cl_2 (15 mL) was added DMAP (1 equiv) followed by EDC.HCl (2.5 equiv). The reaction mixture stirred at room temperature for 20 h. After this period, the resulting crude reaction mixture was washed with 2 N HCl (2 X 5 mL). The solvent was removed under reduced pressure and the residue was purified by using neutral alumina/silica gel column chromatography (EtOAc/Hexanes) to give the corresponding macrocyclic di-thio-lactones **85a-c** (see the respective Tables for specific entries).

Compound 85a. Following the general procedure, **85a** was obtained after purification by column chromatography as a colorless liquid (47 mg, 35%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2865, 1674, 1632, 1595 and 1285 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (2 H, dd, J_1 = 6.1 Hz, J_2 = 1.7 Hz,), 7.47-7.43 (2 H, m), 7.00 (2 H, t, *J* = 7.7 Hz), 6.95 (2 H, d, *J* = 8.2 Hz), 4.25 (4 H, t, *J* = 4.5 Hz), 4.01 (4 H, t, *J* = 4.5 Hz), 3.88 (4 H, s), 3.77 (4 H, t, *J* = 6.0 Hz), 3.68 (4 H, s), 3.27 (4 H, t, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 190.8, 157.5, 133.7, 129.6, 126.8, 120.6, 112.8, 71.3, 70.4, 70.1, 69.5, 69.1, 29.5; HRMS (ESI): MNa^+, found 559.1442. $C_{26}H_{32}NaO_8S_2$ requires 559.1436.

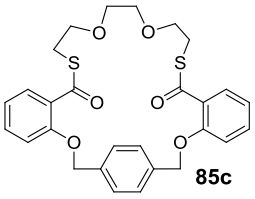


Compound 85b. Following the general procedure, **85b** was obtained after purification by column chromatography as a colourless solid (62 mg, 48%); mp: 158-160 ^{o}C, R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2929, 1670, 1633, 1595, 1478 and 1286 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80 (2 H, dd, J_1 = 6.0 Hz, J_2 = 1.7 Hz), 7.53-7.51 (2 H, m), 7.42-7.35 (4 H, m), 7.02 (2 H, t, *J* = 7.7 Hz), 6.92 (2 H, d, *J* = 8.3 Hz), 5.44 (4 H, s), 3.76 (4 H, t, *J* = 6.1 Hz), 3.65 (4 H, s), 3.25 (4 H, t, *J* = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.0, 156.9,



134.4, 133.5, 129.6, 128.5, 128.4, 127.3, 120.9, 113.4, 70.8, 69.8, 69.2, 29.7; HRMS (ESI): MNa^+, found 547.1216. $C_{28}H_{28}NaO_6S_2$ requires 547.1225.

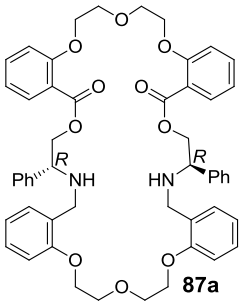
Compound 85c. Following the general procedure, **85c** was obtained after purification by column chromatography as a colorless liquid (69 mg, 52%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 2865, 1632, 1564, 1445 and 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.79 (2 H, dd, J_1 = 6.6 Hz, J_2 = 1.7 Hz), 7.62 (4 H, s), 7.51-7.47 (2 H, m), 7.10 (2 H, d, J = 7.2 Hz), 7.05 (2 H, td, J_1 = 7.4 Hz, J_2 = 0.8 Hz), 5.23 (4 H, s), 3.78 (4 H, t, J = 6.1 Hz), 3.70 (4 H, s), 3.27 (4 H, t, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 191.1, 156.7, 135.9, 133.4, 129.5, 127.7, 127.5, 120.9, 113.3, 70.4, 69.9, 29.5; HRMS (ESI): MNa^+, found 547.1212. $C_{28}H_{28}NaO_6S_2$ requires 547.1225.



85c

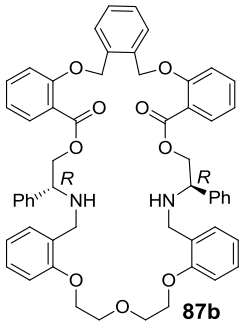
General procedure for the syntheses of macrocyclic lactones 87a,b. To a solution of diol **86** (0.25 mmol) and dicarboxylic acid **75** (0.25 mmol) in CH_2Cl_2 (3 mL) was added DMAP (1 equiv) followed by EDC.HCl (2.5equiv). The reaction mixture was refluxed for 20 h. After this period, the resulting crude reaction mixture was washed with 2 N HCl (2 X 5 mL). The solvent was removed under reduced pressure and the residue was purified by neutral alumina column chromatography (EtOAc/Hexanes) to give the desired macrocyclic di-lactones **87a,b.**

Compound 87a. Following the general procedure, **87a** was obtained after purification by column chromatography as a colorless liquid (71 mg, 38%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3293, 2952, 1739, 1600, and 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.50-7.33 (14 H, m), 7.22 (2 H, t, J = 7.4 Hz), 7.10 (2 H, dd, J_1 = 5.7 Hz, J_2 = 1.6 Hz), 7.03-6.96 (4 H, m), 6.90 (2 H, t, J = 7.4 Hz), 6.81 (2 H, d, J = 7.7 Hz), 4.42 (2 H, dd, J_1 = 6.8 Hz, J_2 = 4.3 Hz), 4.29-4.15 (6 H, m), 4.06-3.90 (4 H, m), 3.92 (2 H, d, J = 13.8 Hz), 3.84-3.79 (6 H, m), 3.61 (4 H, t, J = 4.8 Hz), 3.52 (2 H, d, J = 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 158.3, 157.0, 133.5, 131.8, 130.8, 128.6 ,128.4, 128.3, 128.1, 127.8, 120.6, 120.5, 120.4, 113.6, 111.4, 69.6, 69.6, 69.1, 68.7, 67.3, 60.2, 47.1; HRMS (ESI): MH^+, found 867.3839. $C_{52}H_{55}N_2O_{10}$ requires 867.3857.



87a

Compound 87b. Following the general procedure, **87b** was obtained after purification by column chromatography as a colorless liquid (82 mg, 38%); R_f (40% EtOAc/Hexanes) 0.55; IR (CH_2Cl_2): ν_{max} 3344, 3046, 1722, 1600 and 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (2 H, dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 7.55-7.34 (14 H, m), 7.29-7.27 (2 H, m), 7.17-7.09 (4 H, m), 7.01-6.95 (4 H, m), 6.83 (2 H, t, J = 7.4 Hz), 6.73 (2 H, d, J = 7.8 Hz), 5.33 (4 H, s), 4.35 (4 H, d, J = 6.3 Hz), 4.02-3.94 (4 H, m), 3.89 (2 H, d, J = 13.5 Hz), 3.81-3.76 (2 H, m), 3.53-3.49 (4 H, m), 3.43 (4 H, d, J = 13.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.7, 158.0, 157.1, 139.9, 134.4, 133.7, 131.8, 130.5, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 120.4, 120.4, 120.3, 113.4, 111.36, 69.6, 69.2, 68.9, 67.1, 59.9, 47.4; HRMS (ESI): MH^+, found 899.3867. $C_{56}H_{55}N_2O_9$ requires 899.3908.



87b

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Chapter 5: Miscellaneous Works.

Chapter 5a: Pd(II)-Catalyzed, substrate design-facilitated chemo- and regioselective acetoxylation over cyclization of remote ε-C(sp^2)-H bonds in heteroaryl-aryl-based biaryl and 3-phenylpropan-1-amine systems.

Introduction

In recent years, the transition metal-catalyzed sp^2/sp^3 C-H activation/functionalization has emerged as one of the remarkable synthetic transformations in organic synthesis.[1-3] The sp^2/sp^3 C-H activation/functionalization can be accomplished with or without the help of directing groups. While the directing group-free sp^2/sp^3 C-H activation/functionalization is well recognized, on the other hand, the directing group-aided sp^2/sp^3 C-H activation/functionalization considered as a reliable and powerful synthetic strategy for accomplishing the site-selective sp^2/sp^3 C-H activation/functionalization.[1-3] While the construction of C-C, C-N and C-O bonds are equally important, of a particular interest, the directing-group-aided, transition-metal-catalyzed C-H oxidations of the C(sp^2)-H bonds of arenes comprising the C-O bond forming reactions have been considered as a versatile technique for synthesizing of phenolic compounds.[4] Accordingly, given the importance of phenolic compounds in academia and industry, the transition metal catalyzed C-H oxidations of the C(sp^2)-H bonds of arene systems have been actively pursued.[4] It is worth to mention several medicinal compounds contain the phenolic core unit.[5] Phenolic compounds are key structural motifs in numerous drugs, carbohydrates and natural products (Figure 1).[5] Additionally, phenolic compounds are versatile building blocks in organic synthesis and medicinal chemistry research.

It is to be noted that the Chapters 1-4 of this thesis, used the phenolic derivatives, such as, catechols and salicylic acids as the building blocks for the synthesis of a wide range of polyether macrocyclic compounds. Given the importance of phenolic compounds in various areas of chemical and biological sciences, development of simple and convenient methods for the construction of C-O bonds in arene systems (phenolic compounds) are highly desirable.[5]

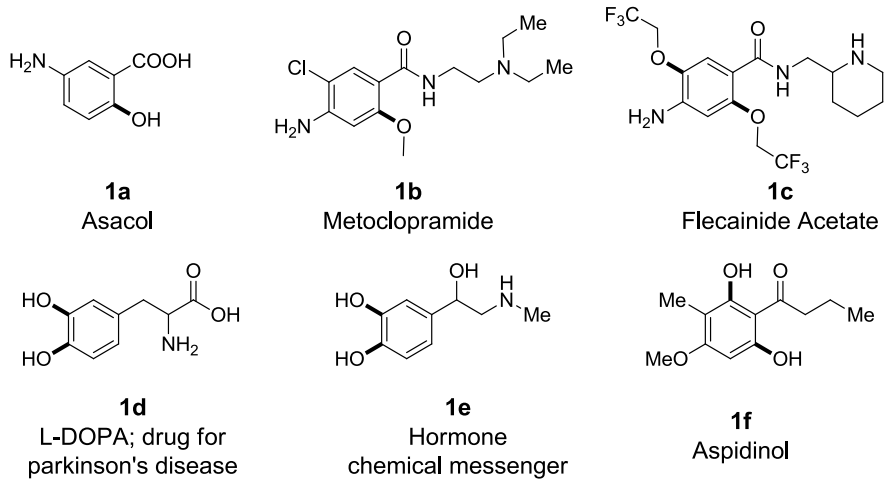


Figure 1: Biologically active molecules containing C-O bonds phenolic motif.

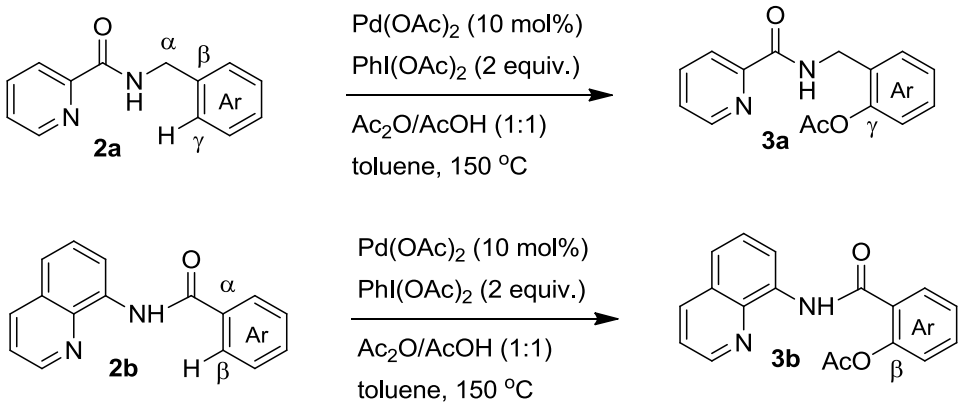
In the research area pertaining to the transition-metal-catalyzed C-H oxidations of the C(sp^2)-H bonds of arenes comprising the C-O bond forming reactions; especially, the acetoxylation of sp^2 C-H bonds of arenes using bidentate directing groups (BDGs), such as 8-aminoquinoline (8AQ)-type and picolinamide (PA) considered as the direct and efficient method for synthesizing phenolic compounds. In general, the BDG-directed acetoxylation of sp^2 C-H bonds of arenes have been performed using a Pd(II)-catalyst and $PhI(OAc)_2$ as an oxidant.[6-10] The 8-aminoquinoline (8AQ)-type BDGs have preferentially assisted the functionalization of the sp^2/sp^3 β-C-H bonds of carboxylic acid substrates.[8] Picolinamide (PA)-type BDGs have assisted the functionalization of the sp^2/sp^3 γ- and δ-C-H bonds of amine systems.[9,10,15a] The BDG-aided functionalization of the sp^2/sp^3 β- and γ-C-H bonds of appropriate carboxamide systems are well documented.[1-4,6-10] A literature survey revealed that there exist only rare reports dealing on the BDG-aided functionalization of remote sp^2/sp^3 ε-C-H bonds.[11]

A literature survey revealed that the attempts on the Pd(II)-catalyzed, BDG-aided functionalization of remote δ- or ε-C(sp^2)-H bonds with $PhI(OAc)_2$ generally gave the cyclized products.[12] Apart from the well-known classical methods dealing on the synthesis of phenolic compounds,[5] there have been various exceptional reports with regard to the synthesis of phenolic compounds *via* C-H activation technique. A part of this thesis aimed to synthesize new phenolic derivatives using heteroaryl-aryl-based biaryl and 3-phenylpropan-1-amine systems *via* the Pd(II)-Catalyzed, acetoxylation of remote ε-C(sp^2)-H bonds in heteroaryl-aryl-based biaryl and 3-phenylpropan-1-amine systems. Accordingly, in line with the objective of the this thesis work,

in the following section some representative literature works that deal on the synthesis of phenolic systems *via* the transition-metal-catalyzed C-H oxidations of the C(sp^2)-H bonds of arylalkylamines/carboxylic acids comprising the C-O bond forming reactions are presented.

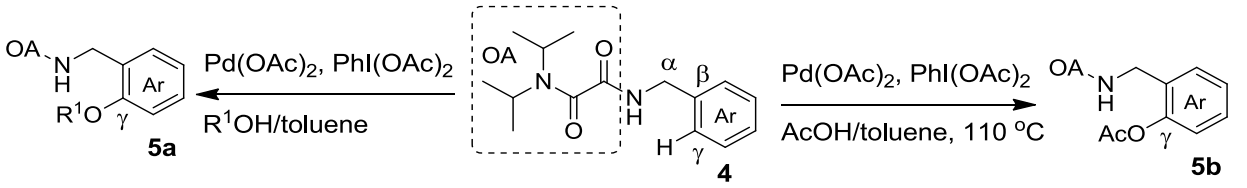
Literature reports dealing on the synthesis of phenolic derivatives *via* the palladium-catalyzed bidentate-directing group directed site-selective sp^2 C-H activation/oxidation of arylalkylamine derivatives.

The successful demonstration of transition-metal-catalyzed monodentate ligands assisted C-H oxidation[13,14] of arenes with different oxidants inspired the researcher examining the effect of easily available bidentate ligands as directing groups for the C(sp^2)-H acetoxylation, some of the notable strategies are sketched herewith. In 2009, Liang *et al.*[15a] employed N,N-bidentate i.e. picolinamide **2a** (attached with various benzyl amines) and 8-aminoquinoline **2b** (attached with various benzoic acids) as directing groups for the regioselective *ortho*-C-H acetoxylation reaction at the corresponding γ- and β positions **2a** and **2b** using $Pd(OAc)_2$ the catalyst and $PhI(OAc)_2$ as an oxidant in toluene at 150 ^oC (Scheme 1).



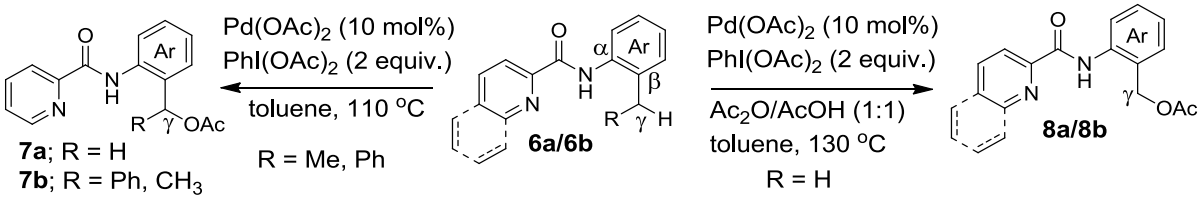
Scheme 1. Pd-catalyzed acetoxylation using picolinamide and 8-aminoquinoline bidentate directing groups.

Recently, Zhao and Shi *et al.* reported[15b] a practical palladium-catalyzed, oxalyl amide-assisted alkoxylation and acetoxylation of the γ-C(sp^2)-H of benzyl amine **4** in the presence $PhI(OAc)_2$ as an oxidant to afford **5a/5b** (Scheme 2).



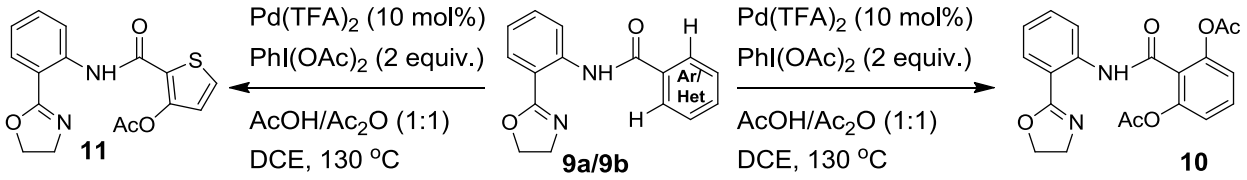
Scheme 2. Oxalyl amide-assisted alkoxylation and acetoxylation of the γ-C(sp^2)-H of benzyl amine **4**.

Zhang *et al.* disclosed[15c] the $Pd(OAc)_2$-catalyzed acetoxylation of benzylic γ-C(sp^3)-H bonds utilizing a bidentate systems, such as picolinamide **6a/6b** and quinoline-2-carboxamide, which afforded benzylic C-H acetoxylation products **8a/8b** (Scheme 3). Huang and co-workers[15d] also reported the same strategy comprising the $Pd(OAc)_2$-catalyzed acetoxylation of benzylic γ-C(sp^3)-H bonds of **6a/6b** to get the acetoxylated products **7a/7b** using picolinamide directing group (Scheme 3).



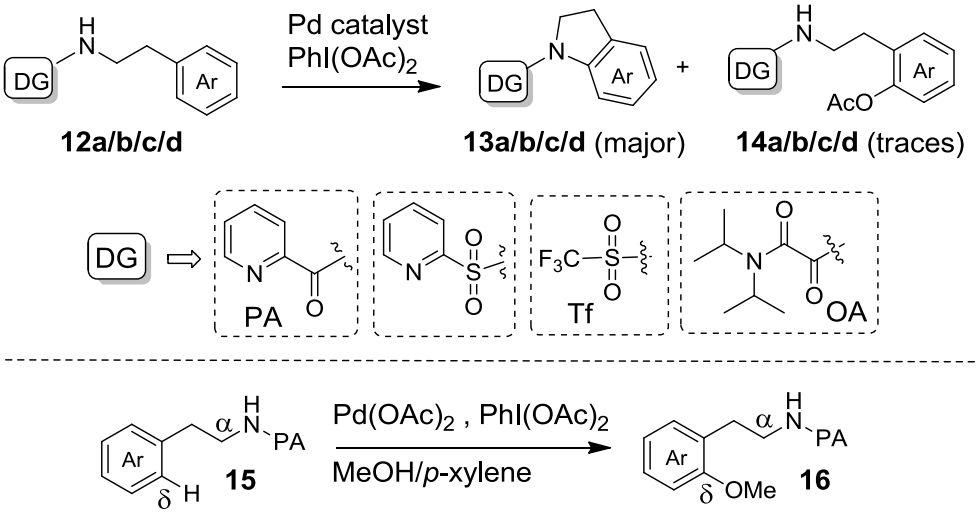
Scheme 3. Pd-catalyzed bidentate ligand acetoxylation of benzylic C-H Bonds.

Recently, Li and co-workers[15e] reported, Pd-catalyzed *ortho*-acetoxylation of arenes **9a** and hetero-arene **9b** using amide-oxazoline as the directing group (Scheme 4). The approach provides general and straightforward access to wide range of phenol esters of aryls **10** and heteroaryls **11** (Scheme 4).



Scheme 4. Oxazoline-amide directing acetoxylation *via* six-membered bidentate complex.

Chen *et al*. demonstrated[15f] δ-C(sp^2-H) bond activation using picolinamides **12a** of 2-phenylethanamine substrates (Scheme 5). Reaction of substrate **12a**, which was assembled from 2-phenylethanamine and picolinic acid with $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ oxidant in toluene preferentially afforded the cyclized product **13a** as the major product over the expected δ-C(sp^2-H) acetoxylation product **14a** (minor product, Scheme 5).



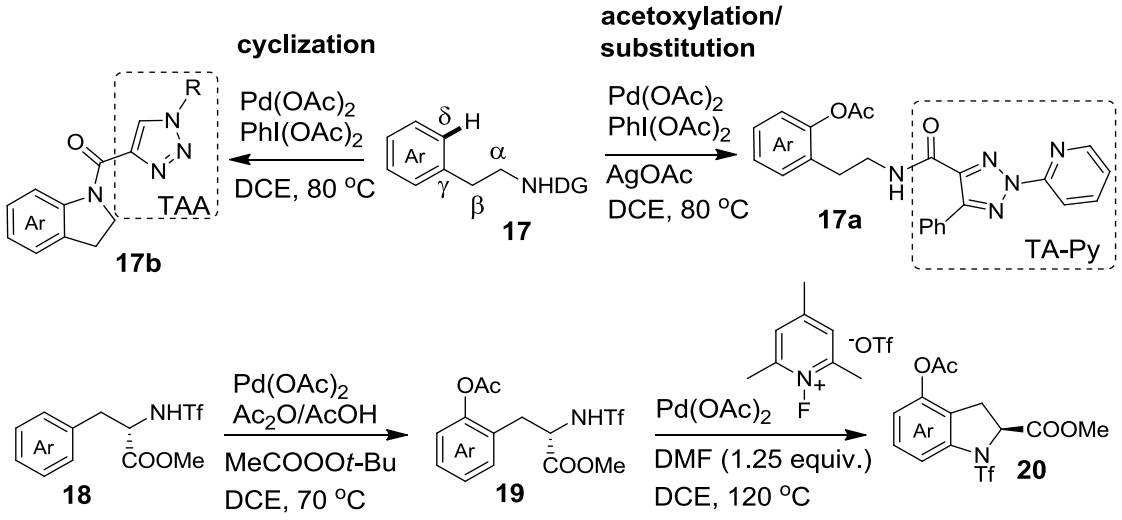
Scheme 5. Bidenate ligand picolinamide-directed δ-C(sp^2-H) bond activation and acetoxylation/alkoxylation. Cyclization or acetoxylation/alkoxylation process.

Further, triflamide of 2-phenylethanamine **12b** (Yu *et al*),[15g] 2-pyridylsulfonylamide of 2-phenylethanamine **12c** (Shi *et al*)[15h] and oxalyl amide of 2-phenylethanamine **12d** (*Zhao et al*)[15i] were subjected to the δ-C(sp^2-H) bond activation/acetoxylation in the presence the $Pd(OAc)_2$ catalyst. In many of these investigations, the corresponding cyclized product **13** were obtained as the major product over the expected δ-C(sp^2-H) acetoxylation product **14** (Scheme 5).

Recently Chen *et al.* revealed[16a] the use of alcohols as the co-solvents to promote the C-H oxygenation/alkoxylation over the cyclization using picolinamide systems and accordingly, several picolinamide systems were alkoxylated using the $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ oxidant in *para*-xylene along with methanol as a co-solvent (Scheme 5).

In 2013, Shi and co-workers reported[16b] directing group controlled selective acetoxylation or cyclization of **17** to afford the acetoxylated compound **17a** and cyclized product **17b** *via* the

remote δ-C(sp^2)-H activation using tridentate Py-TA and triazole based TAA directing groups (Scheme 6).

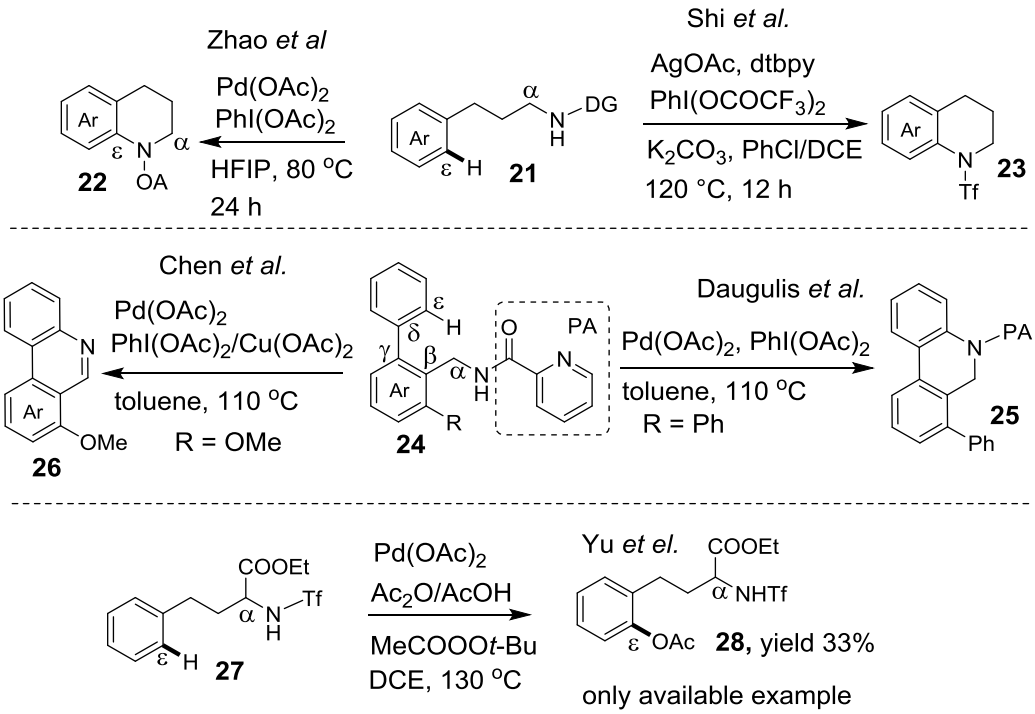


Scheme 6. TA-Py directed δ-C(sp^2)-H bond acetoxylation and TAA-directed cyclization *via* δ-C(sp^2)-H bond activation and δ-C(sp^2)-H bond acetoxylation of **18**.

Yu *et al.* reported[16c] Pd(II)-catalyzed ortho δ-C(sp^2)-H acetoxylation of triflate protected phenethylamines **18** with *tert*-butyl peroxyacetate as the stoichiometric oxidant and either DMF or CH_3CN solvent, which acted as the promoter to afford the acetoxylation product at remote δ position (Scheme 6). The reaction was found to tolerate a large variety of functional groups and could be combined with subsequent intramolecular amination to afford functionalized indoline derivatives.

With regard to the available examples of palladium-catalyzed bidentate-directing group directed site-selective ε-C(sp^2)-H activation/oxidation of arylalkylamine derivatives; a literature survey revealed that the attempts on the remote ε-C(sp^2)-H activation/oxidation of arylalkylamine systems have led to the formation of cyclized products **22**, **23**, **25** and **26** (Scheme 7). Treatment of triflamide system **21** with $PhI(OCOCF_3)_2$catalyzed in the presence of silver salts led to the intramolecular amination to form six-membered heterocyclic ring **23** (Scheme 7).[17] Zhao *et al.* explored[18a] oxalyl amide as the directing group for intramolecular amination at remote ε-C(sp^2-H) position of **21** using only 1 mol% of $Pd(OAc)_2$ (Scheme 7). Pd-catalyzed picolinamide-directed ε-C(sp^2-H) bond functionalization of bi-aryl systems **24** in the presence of $PhI(OAc)_2$

oxidant in toluene at 110 ^{o}C led to the intramolecular amination to form six-membered heterocyclic ring **25** (Scheme 7).[18b] Similarly, Chen *et al.*[18c] also reported the Pd-catalyzed picolinamide-directed ε-C(sp^2-H) bond functionalization of bi-aryl systems **24** in the presence of $PhI(OAc)_2/Cu(OAc)_2$ oxidant system, which led to the intramolecular amination to form six-membered heterocyclic ring **26** (Scheme 7). Yu *et al.* revealed[16c] an example of remote ε-C(sp^2-H) acetoxylation of phenylpropylamine system protected with triflate using *tert*-butyl peroxyacetate as an oxidant in the presence of CH_3CN solvent, which afforded the ε-C(sp^2)-H acetoxylated product **28** in only 33% yield (Scheme 7).



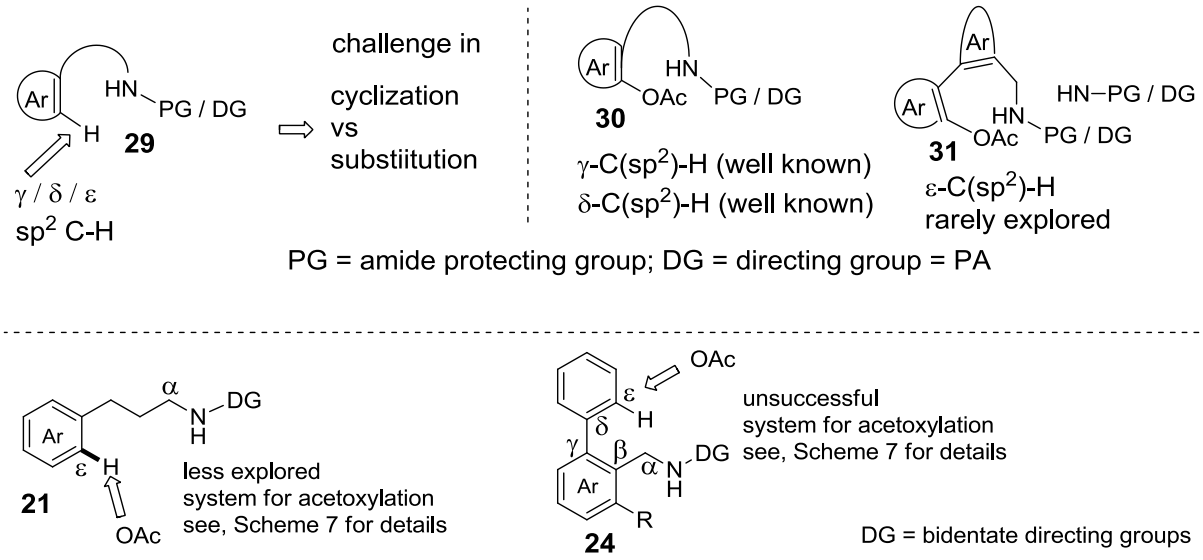
Scheme 7. Bidenate ligand/amide-directed ε-C(sp^2-H) bond activation and acetoxylation/alkoxylation. Cyclization or acetoxylation/alkoxylation process.

Result and discussion

The introduction part of Chapter 5a revealed some representative literature works that deal on the synthesis of phenolic systems *via* the transition-metal-catalyzed C-H oxidations of the C(sp^2)-H bonds of arylalkylamines/carboxylic acids comprising the C-O bond forming reactions. In the research area pertaining to the transition-metal-catalyzed C-H oxidations of the C(sp^2)-H bonds

of arenes comprising the C-O bond forming reactions; the BDG-aided acetoxylation of the sp^2/sp^3 β- and γ-C-H bonds of appropriate carboxamide systems were well documented.[2-4,6-11]

Further, a literature survey revealed that the attempts on the Pd(II)-catalyzed, BDG-aided functionalization of remote δ- or ε-C(sp^2)-H bonds with $PhI(OAc)_2$ generally gave the cyclized products.[12,16-18] Notably, the Pd(II)-catalyzed, BDG-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond over cyclization has not been reported. Additionally, a survey of the literature reports revealed that obtaining the control on the acetoxylation/substitution over cyclization and chemoselectivity in the BDG-aided functionalization of remote ε-C-H bond of a suitable substrate considered as a challenging task (Scheme 8).

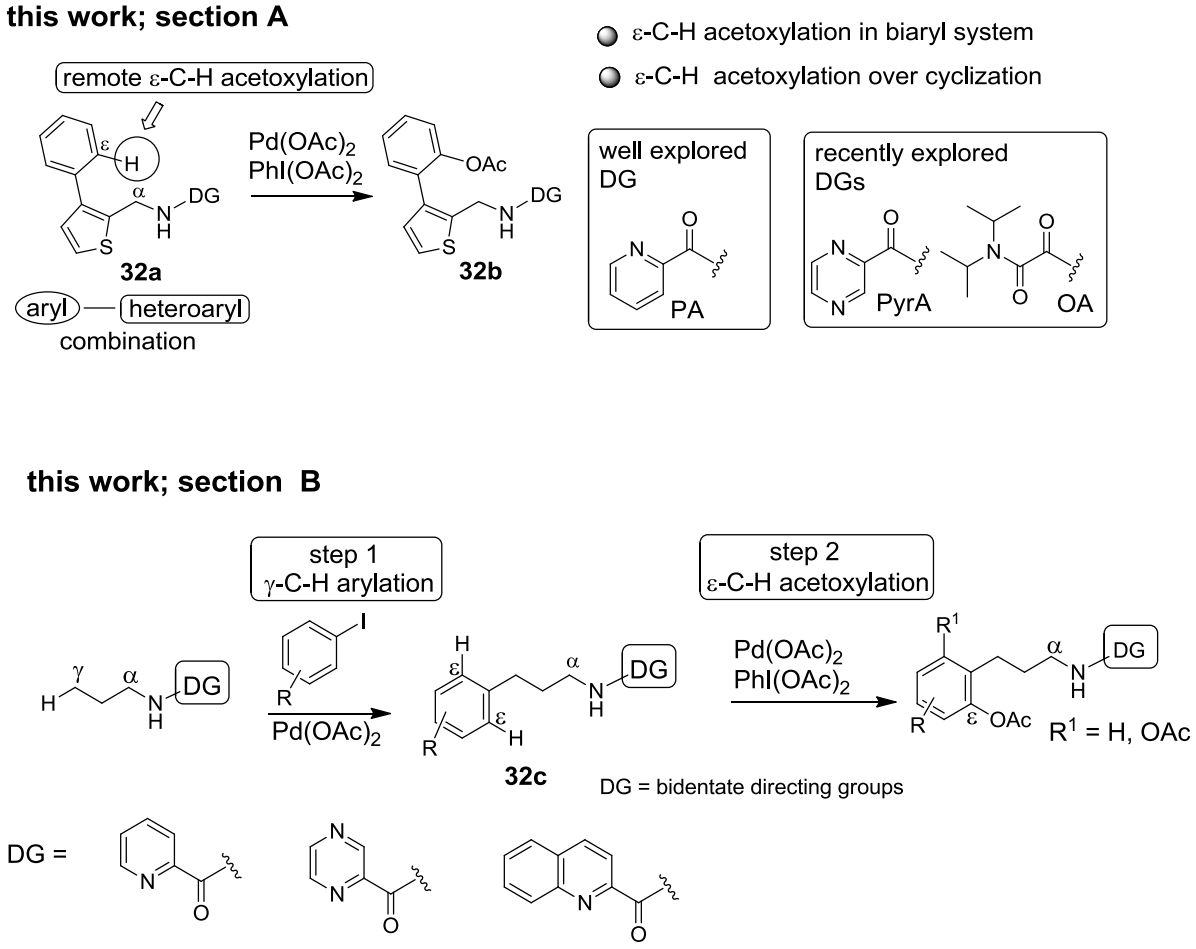


Scheme 8. Typical systems for acetoxylation of the ε-C(sp^2)-H bonds.

In general, the C-H functionalization processes are substrate specific; however, it is possible to achieve the chemoselective acetoxylation/substitution or cyclization by using suitably modified substrates[7] or changing the reaction conditions[16a] or directing groups.[16b] Taking an impetus from the existing developments with regard to the site-selective acetoxylation of C-H bonds of arene systems, a part of this thesis envisaged to study the prevailing subject comprising dominant cyclization over acetoxylation/substitution in the Pd(II)-catalyzed, bidentate ligand picolinamide (PA)-aided functionalization of ε-C(sp^2)-H bond by using an appropriate substrate.

Accordingly, Chapter 5a and section A of this thesis reports the investigations on the Pd(II)-catalyzed, picolinamide and substrate design-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond by using the heteroaryl-aryl-based biaryl system **32a** (Scheme 9).

Further, Chapter 5a and section B of this thesis also reports the investigations on the Pd(II)-catalyzed, picolinamide-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond of less explored phenylpropylamine systems **32c** (Scheme 9).



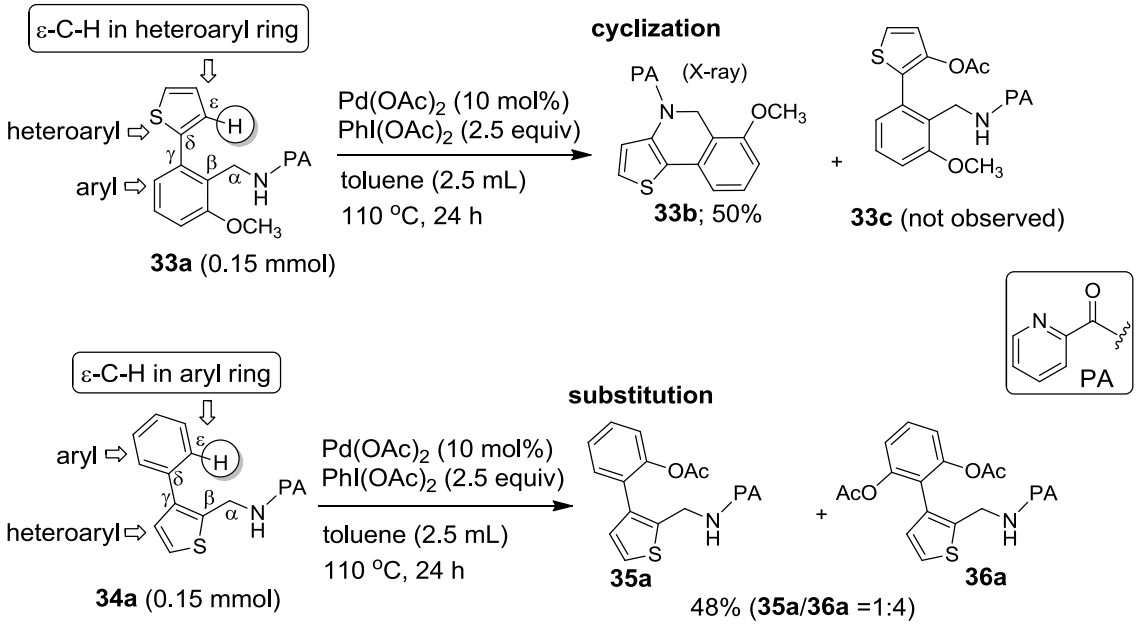
Scheme 9. Bidentate directing groups-aided Selective acetoxylation of the ε-C(sp^2)-H bonds of heteroaryl-aryl-based biaryl system **32a**. Bidentate directing groups-aided acetoxylation of the ε-C(sp^2)-H bonds of heteroaryl-aryl-based biaryl system **32c**.

Section A: Investigations on the Pd(II)-catalyzed, picolinamide and substrate design-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond by using the heteroaryl-aryl-based biaryl system 32a.

The suitable types of systems for attempting the Pd(II)-catalyzed, BDG-aided acetoxylation of remote ε-C(sp^2)-H bond is either 3-phenylpropan-1-amine-type system **21** or the biaryl-type system **24** (Schemes 8/9). Nevertheless, the Pd(II)-catalyzed, BDG-aided ε-C(sp^2)-H bond activation reactions of **21** and **24** with $PhI(OAc)_2$ were reported to give the corresponding cyclized products (Schemes 8/9). Therefore, it was envisaged to attempt the chemoselective acetoxylation of remote ε-C(sp^2)-H bonds, by using biaryl systems other than **24** and also having a combination of heteroaryl-aryl rings, such as thiophene-phenyl and furan-phenyl biaryl systems.[19] It was envisioned that given their peculiar planarity,[19a] the furan and thiophene heteroaryl rings might be behaving differently than simple aryl rings in a given biaryl system having a combination of heteroaryl-aryl rings. A support for this proposal can be drawn from a literature paper, which described on the characterization of biaryl torsional energetics.[19a] In this work, the authors[19a] stated that "the biaryls investigated with two hydrogen or other atoms attached to the ortho positions on both rings are nonplanar. This can be attributed to steric clashes between the ortho groups that are relieved upon rotation to nonplanar geometries. The preference is stronger for 6:6 systems than for 6:5 ones owing to the increased bond angles to the 5-membered ring". Therefore, the chemoselective acetoxylation of remote ε-C(sp^2)-H bond was expected over cyclization in the biaryl system having a combination of heteroaryl-aryl rings (e.g. **33a**/**34a**, Scheme 10).[19b]

To begin the investigations on the Pd(II)-catalyzed directing group-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond, at first, the picolinamide substrates **33a** and **34a** were assembled (Scheme 10). Then, the functionalization of the ε-C-H bond of the thiophene ring of **33a** was attempted by using $PhI(OAc)_2$ as an oxidant. This attempt afforded the cyclized product **33b** in 50% yield rather than the expected ε-C-H acetoxylated product **33c** (Scheme 10). Next, the Pd(II)-catalyzed functionalization of the ε-C-H bond of the phenyl ring of **34a** was attempted. Fortunately, this reaction gave the ε-C-H acetoxylated products **35a** (mono OAc) and the product **36a** (di OAc). Markedly, these reactions implied that the substrate **34a** was found to be an

appropriate design for the ε-C-H acetoxylation and the substrate **33a** was not a suitable design for the ε-C-H acetoxylation.



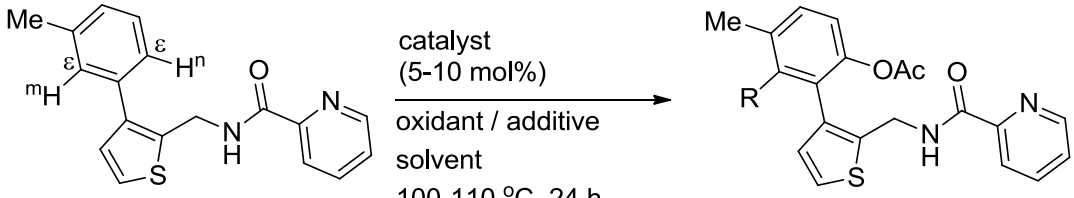
Scheme 10. Substrate design-facilitated chemoselective cyclization and acetoxylation of remote ε-C(sp^2)-H bonds of **33a**/**34a**.

Encouraged by the successful attempt of ε-C-H acetoxylation by using the biaryl system **34a** (Scheme 10); next, the optimization of reaction conditions were performed to obtain the best reaction conditions (Table 1). The ε-C-H acetoxylation of the picolinamide derivative **34b** were performed in the presence of various oxidants or additives and palladium catalysts. The reaction of the substrate **34b** with 2 equiv of $PhI(OAc)_2$ and 10 mol% of the $Pd(OAc)_2$ catalyst in toluene solvent at 110 ^oC for 24 h was found to give the mono ε-C-H acetoxylated product **35b** in a maximum yield of 80% (entry 4, Table 1).

It is to be noted that in the substrate **34b** the ε-C-H^n bond was selectively acetoxylated over the ε-C-H^m bond affording the mono acetoxylated product **35b** and the bis acetoxylated product **36b** was not observed. This is because, the methyl group present at the *ortho*-position with respect to the ε-C-H^m bond in the substrate **34b** perhaps hinders the acetoxylation of the ε-C-H^m bond in the substrate **34b**. However, the preliminary acetoxylation reaction of **34a** which is not having

any substituent at the *ortho*-position with respect to the ε-C-$H^{m/n}$ bond gave the acetoxylated products **35a** (mono OAc) and **36a** (di OAc, Scheme 3).

Table 1. Optimization of reaction conditions. Picolinamide-aided ε-C-H acetoxylation.[20-22]



34b
(0.1 mmol)

35b; R=H,
36b; R=OAc

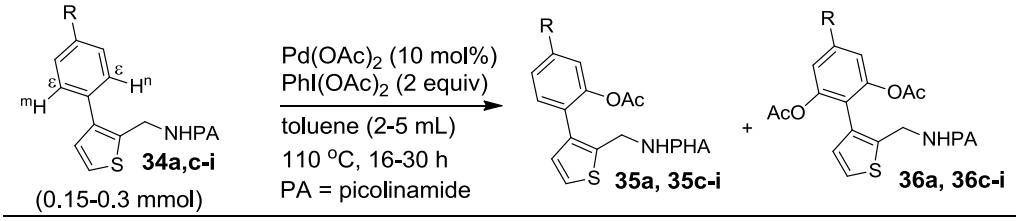
entry	catalyst (mol%)	oxidant / additive (equiv)	solvent (mL)	**35b**: yield (%)
1	nil	$PhI(OAc)_2$ (2.0)	toluene (2)	0
2	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.0)	toluene (2)	70
3	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (1.5)	toluene (2)	75
4	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	toluene (2)	80
5	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3.0)	toluene (2)	62
6	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)-AcOH (1)/Ac_2O (1)	toluene (2)	64
7	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0) AgOAc (1)	toluene (2)	42
8	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)-oxone (1)	toluene (2)	40
9	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2.0)	AcOH (2)	0
10	$Pd(OAc)_2$ (10)	AgOAc (2.0)	toluene (2)	0
11	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2.0)	toluene (2)	0
12	$Pd(TFA)_2$ (10)	$PhI(OAc)_2$ (2.0)	toluene (2)	41
13	$Pd(PPh_3)_2Cl_2$ (10)	$PhI(OAc)_2$ (2.0)	toluene (2)	45

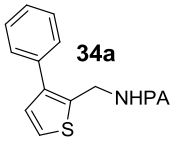
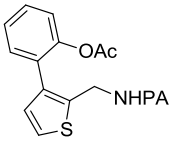
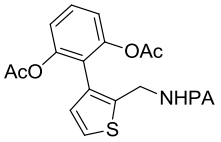
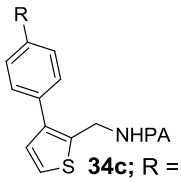
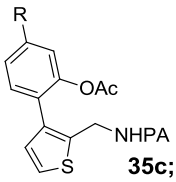
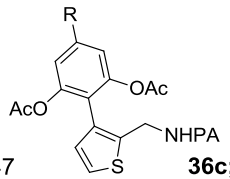
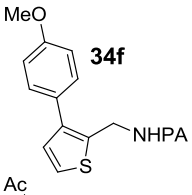
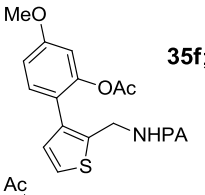
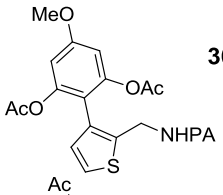
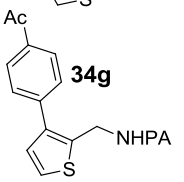
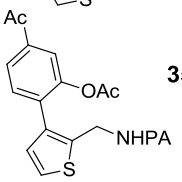
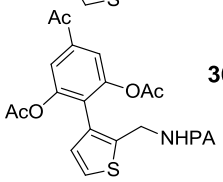
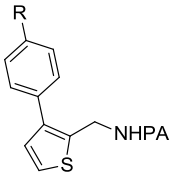
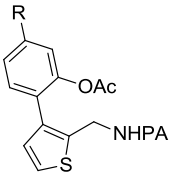
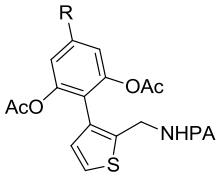
Accordingly, it was decided to reexamine the scope of the reaction of the substrate **34a** by using different equiv of $PhI(OAc)_2$ to selectively obtain either the acetoxylated product **35a** (mono OAc) or the acetoxylated product **36a** (di OAc). The reaction of the substrate **34a** with 1.1 equiv of $PhI(OAc)_2$ gave only traces of the acetoxylated products **35a** and **36a** (entry 1, Table 2). The reaction of the substrate **34a** with 2 equiv of $PhI(OAc)_2$ gave the corresponding acetoxylated products **35a** and **36a** in 45 and 16% yields (entry 2, Table 2). The reaction of the substrate **34a** with 3 equiv of $PhI(OAc)_2$ afforded only the acetoxylated product **36a** (di OAc) in 45% yield (entry 3, Table 2). This reaction suggested that it is possible to selectively obtain the bis acetoxylated product **36a** by using excess of $PhI(OAc)_2$. As a part of optimization reaction, the Pd(II)-catalyzed acetoxylation of the substrate **34a** was also performed in a gram scale, which gave the corresponding acetoxylated products **35a** and **36a** in 42 and 14% yields (Table 2).

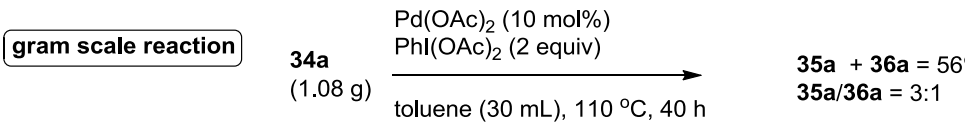
Next, to elaborate the generality substrate and scope of this protocol, various other substrates **34c-i** containing different substituents at the *meta*-position with respect to the ε-C-$H^{m/n}$ bond were assembled. Then, these substrates were subjected to the Pd(II)-catalyzed, ε-C-H acetoxylation with $PhI(OAc)_2$ (Table 2). Except for one of the case as shown in entry 6, Table 2, irrespective of the substituents present in the aryl rings of the substrates **34c-i**, the acetoxylation reactions furnished the corresponding acetoxylated products **35c-i** (mono OAc) and **36c-i** (di OAc) in 52-72% yields (combined yields of **35** and **36**).

Notably, an interesting trend was observed in entries 4-6 (Table 2), which indicated that the mono/bis selectivity with regard to the mono/bis acetoxylation reaction was found to be dependent on the nature of the alkyl substituents present at the *meta*-position with respect to the ε-C-$H^{m/n}$ bond in the respective substrates **34c-e**. The substrate **34c** containing a methyl group in the aryl ring gave the corresponding acetoxylated products **35c** (mono OAc, 47%) and **36c** (di OAc, 25%). The substrate **34d** with an ethyl group in the aryl ring afforded the corresponding acetoxylated products **34d** (mono OAc, 24%) and **36d** (di OAc, 44%).

Table 2. Picolinamide-aided ε-C-H acetoxylation reactions.[21,22]

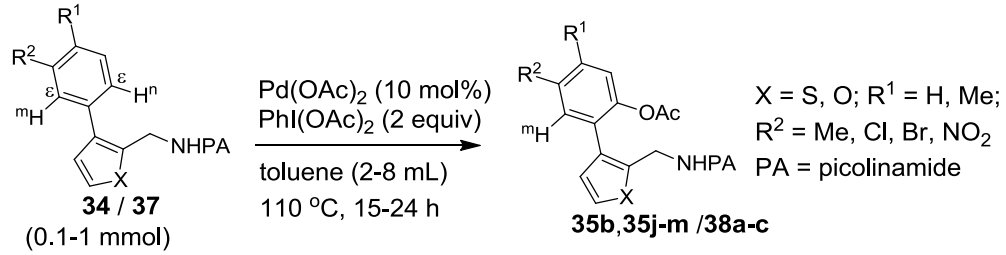


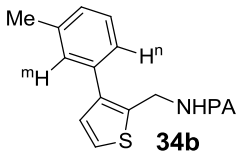
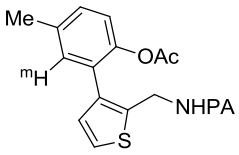
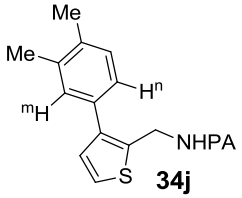
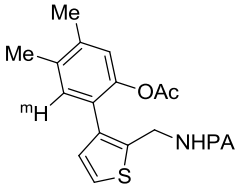
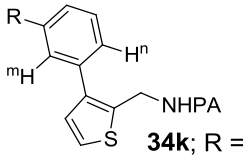
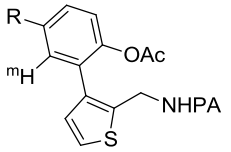
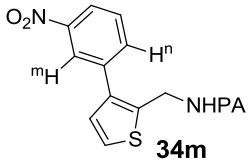
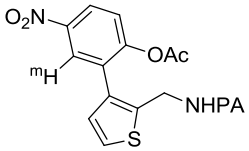
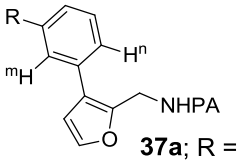
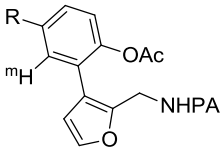
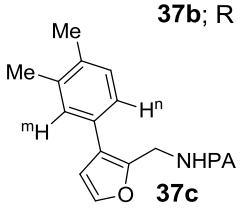
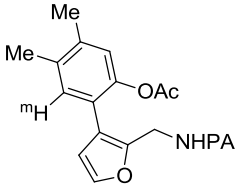
entry	substrate (**34**)	*t* (h)	**35**: yield (%) (mono OAc)	**36**: yield (%) (di OAc)	**35** + **36**: yield (%)
1[a,b]	 **34a**	30	 **35a**; 0	 **36a**; 0	0
2[a,c]		30	**35a**; 45	**36a**; 16	61
3[a,d]		30	**35a**; 0	**36a**; 45	45
4[e]	 **34c;** R = CH_3	24	 **35c;** R = CH_3; 47	 **36c;** R = CH_3; 25	72
5[e]	**34d**; R = Et	18	**35d**; R = Et; 24	**36d**; R = Et; 44	68
6[f]	**34e**; R = i-Pr	16	**35e**; R = i-Pr; 0	**36e**; R = i-Pr; 55	55
7[g]	 **34f**	24	 **35f**; 35	 **36f**; 27	62
8[e,h]	 **34g**	17	 **35g**; 26	 **36g**; 26	52
9[a]	 **34h;** R = Cl	18	 **35h;** R = Cl; 36	 **36h;** R = Cl; 19	55
10[f]	**34i**; R = Br	17	**35i**; R = Br; 37	**36i**; R = Br; 25	62



[a] 0.3 mmol of **34a**/**34h** was used. [b] 1.1 Equiv of $PhI(OAc)_2$ was used. [c] 2 Equiv of $PhI(OAc)_2$ was used. [d] 3 Equiv of $PhI(OAc)_2$ was used. [e] 0.2 mmol of **34c**/**34d**/**34g** was used. [f] 0.24 mmol of **34e**/**34i** was used. [g] 0.15 mmol of **34f** was used. [h] Isolated as a mixture of **35g** and **36g**.

Table 2 (Continued). Picolinamide-aided ε-C-H acetoxylation reactions.[21,22]

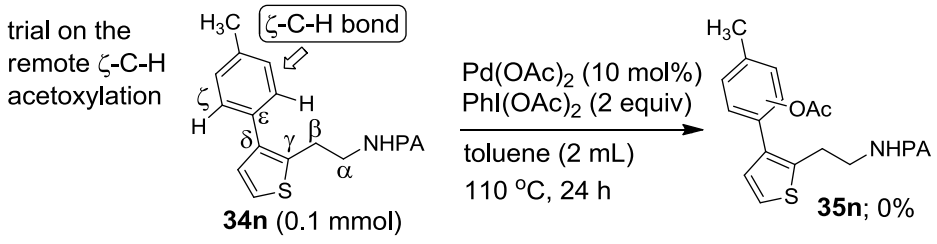


entry	biaryl system (**34/37**)	*t* (h)	product (**35/38**)	**35** / **38**: yield (%)
11[i]	 **34b**	24		**35b**; 80
12[j]	 **34j**	18		**35j**; 60
13[k] 14[k]	 **34k**; R = Cl **34l**; R = Br	16 15		**35k**; R = Cl; 40 **35l**; R = Br; 46
15[k]	 **34m**	24		**35m**; 32
16[j] 17[g]	 **37a**; R = Me **37b**; R = Br	18 24		**38a**; R = Me; 53 **38b**; R = Br; 32
18[e]	 **37c**	16		**38c**; 35

[e] 0.2 mmol of **37c** was used. [g] 0.15 mmol of **37a,b** was used. [i] 1 mmol of **34b** was used. [j] 0.18 mmol of **34j**/**37a** was used. [k] 0.12 mmol of **34k**/**34l**/**34m** was used.

The substrate **34e** with an isopropyl group in the aryl ring selectively gave the acetoxylated product **36e** (di OAc, 55%) and the corresponding product **35e** (mono OAc) was not. These observations indicated that yield of the bis acetoxylation product gradually increased when the alkyl substituent was changed from Me to Et and then to isopropyl. While an exact reason for this trend was not clear at this stage; however, an inductive effect might be operational in **34c-e**. Next, the substrates **34f-i** containing substituents e.g., OMe, Ac, Cl and Br in the aryl ring afforded the corresponding mono acetoxylated products, e.g., **35f**, **35g, 35h** and **35i** as the major products over the corresponding bis acetoxylated products, e.g., **36f**, **35g, 36h** and **36i** (Table 2, entries 7-10).

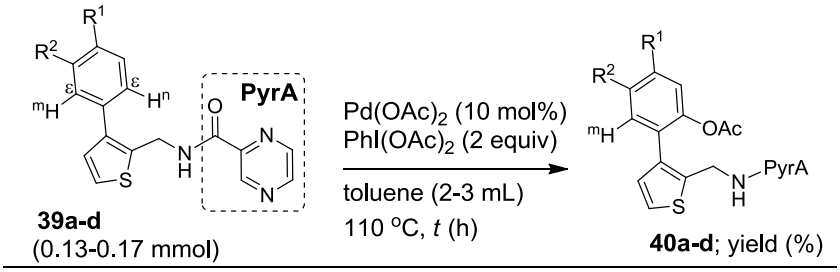
To extend the substrate scope and generality of this work, the biaryl substrates **34j-m** and **37a-c** (Table 2, entries 11-18), having different substituents at the *para*-position with respect to the ε-C-H^n bond (or substituents at the *ortho*-position with respect to the ε-C-H^m bond) were prepared. Initially, the Pd(II)-catalyzed, ε-C-H acetoxylation of the substrates **34j-m** were performed to afford the corresponding acetoxylated products **35j-m** in 32-60% yields (Table 2, entries 12-15). The Pd(II)-catalyzed, ε-C-H acetoxylation of the substrates **37a-c** with $PhI(OAc)_2$ were carried out, which gave the corresponding acetoxylated products **38a-c** in 32-53% yields (Table 2, entries 16-18). In the substrates **34j-m** and **37a-c** the ε-C-H^n bonds were selectively acetoxylated over the ε-C-H^m bonds. This is because, in **34j-m** the respective substituents present at the *ortho*-positions with respect to the ε-C-H^m bonds perhaps hinder the acetoxylation of the ε-C-H^m bonds. Therefore, the corresponding ε-C-H^n acetoxylated products **35j-m** and **38a-c** were obtained as the major compounds. The low yields of the acetoxylated products **35k-m** may be due to the electron-withdrawing groups (e.g., Cl, Br and NO_2) present at the *para*-position with respect to the ε-C-H^n bond in **34k-m** (Table 2, entries 13-15).

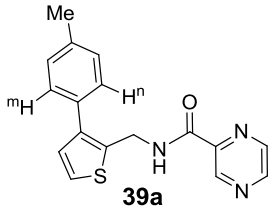
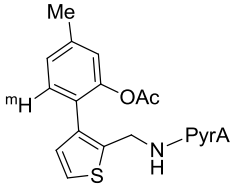
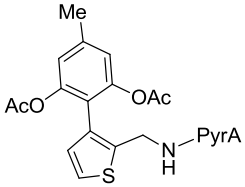
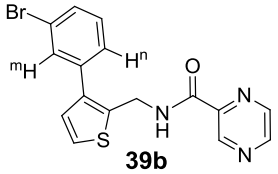
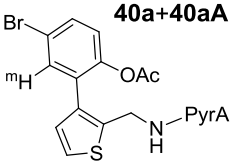
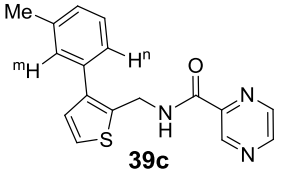
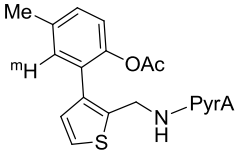
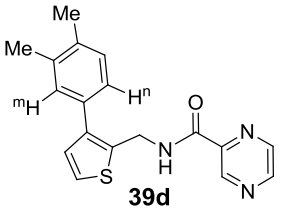
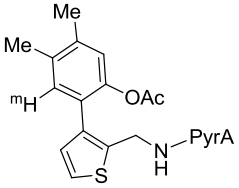


Scheme 11. and Pd(II)-catalyzed acetoxylation of the ζ-C-H bond.

Then, taking an inspiration from the successful attempts of the Pd(II)-catalyzed acetoxylation of the ε-C-H bonds of **34**/**37**, the Pd(II)-catalyzed acetoxylation of the ζ-C-H bond was attempted using the substrate **34n**. However, the reaction of the Pd(II)-catalyzed acetoxylation substrate **34n** with $PhI(OAc)_2$ failed to give any acetoxylated product (Scheme 11).

Table 3. Pyrazine-2-carboxamide-aided ε-C-H acetoxylation.[21,22]



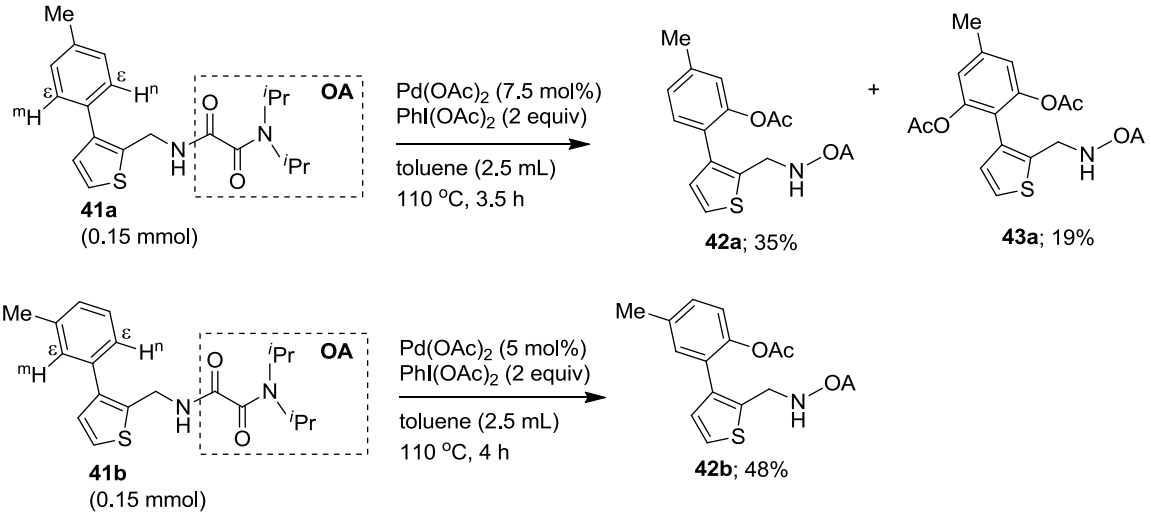
substrate (**39**)	product **40**: yield (%)
 **39a**	 **40a**; 39  **40aA**; 13 **40a**+**40aA** = 52 (18 h)[a]
 **39b**	 **40b**; 44 (24 h)[b]
 **39c**	 **40c**; 57 (13 h)[c]
 **39d**	 **40d**; 50 (24 h)[a]

[a] 0.13 mmol of **40a**/**40d** was used. [b] 0.15 mmol of **40b** was used. [c] 0.17 mmol of **40c** was used.

Having done the Pd(II)-catalyzed chemoselective ε-C-H acetoxylation by using the bidentate directing group picolinamide (PA) installed biaryl systems, then, it was planned to perform the

ε-C-H acetoxylation reactions by using other bidentate directing groups, e.g., pyrazine-2-carboxamide (PyrA)[3h] and oxalylamide (OA).[3i]

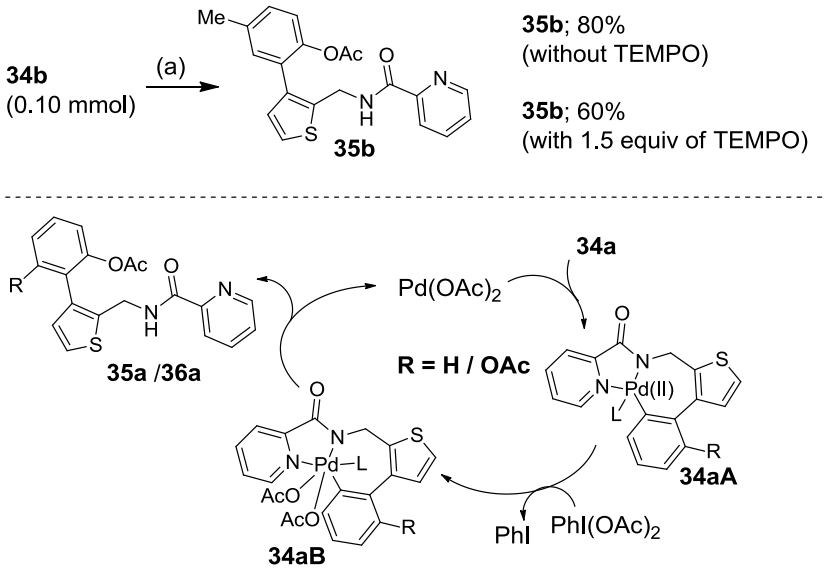
Along this line, initially, the pyrazine-2-carboxamide derivatives **39a-d** were subjected to the Pd(II)-catalyzed acetoxylation reaction conditions using $PhI(OAc)_2$. These reactions gave the corresponding acetoxylated products **40a-d** in 44-57% yields, respectively (Table 3). Similar to the picolinamide-directed acetoxylation of **34a** which gave both the mono and bis acetoxylation products **35a** and **36a**, the PyrA-directed acetoxylation of **39a** also gave both the mono and bis acetoxylation products **40a** and **40aA**. Further, the yields obtained for the picolinamide-directed acetoxylation of **34b**,**j**,**l** (46-80%, Table 2) were slightly higher than the yields obtained for the PyrA-directed acetoxylation of **39b-d** (44-57%, Table 3). Recently, Yu *et al.* stated[23] that in the directing group-based C-H activation reactions, strongly coordinating N/ S/ P heteroatoms present in the substrates investigated often outcompete the directing groups for catalyst binding, thus preventing the C-H activation/functionalization process. In the present case, it seems that the presence of an extra nitrogen atom in the PyrA-BDG did not interfere with the acetoxylation process. Thus, the efficiency of the bidentate directing group pyrazine-2-carboxamide (PyrA) was more or less same as the bidentate directing group picolinamide (PA).



Scheme 12. Oxalylamide-aided ε-C-H acetoxylation.[21,22]

Subsequently, the ε-C-H acetoxylation was attempted by using the biaryl substrates **41a**,**b** containing the oxalylamide (OA) as the directing group (Scheme 12). The Pd(II)-catalyzed

acetoxylation of the oxalylamide derivative **41a** with $PhI(OAc)_2$ led to the formation of the expected ε-C-H mono-acetoxylated product **42a** in 35% yield along with di-acetoxylated product **43a** in 19% yield. Similarly, the Pd(II)-catalyzed acetoxylation of the oxalylamide derivative **41b** with $PhI(OAc)_2$ led to the formation of the expected ε-C-H mono-acetoxylated product **42b** in 48% yield (Scheme 12). It is to be noted that the C(2)-H and C(5)-H bonds of thiophene ring are susceptible for the direct C-H functionalization. Notably, the direct functionalization/arylation of the C(2)-H and C(5)-H bonds of the thiophene/furan systems has been well documented in the literature.[24] In the present work dealing on the ε-C-H acetoxylation of the thiophene-based biaryl systems **34a-m/39a-d/41a**,**b** and furan-based biaryl systems **37a-c** selectively gave the corresponding ε-C-H acetoxylated products **35a-m/40a-d/42a,b**/**43a** and **38a-c**. In these cases, the corresponding bidentate directing groups, such as PA and PyrA have effectively directed the ε-C-H acetoxylation of the substrates **34a-m/39a-d/41a**,**b** to afford the corresponding ε-C-H acetoxylated products **35a-m/40a-d/42a,b**/**43a** and **38a-c** and the formation of any thiophene/furan C5-acetoxylated products as the by-products was not observed.



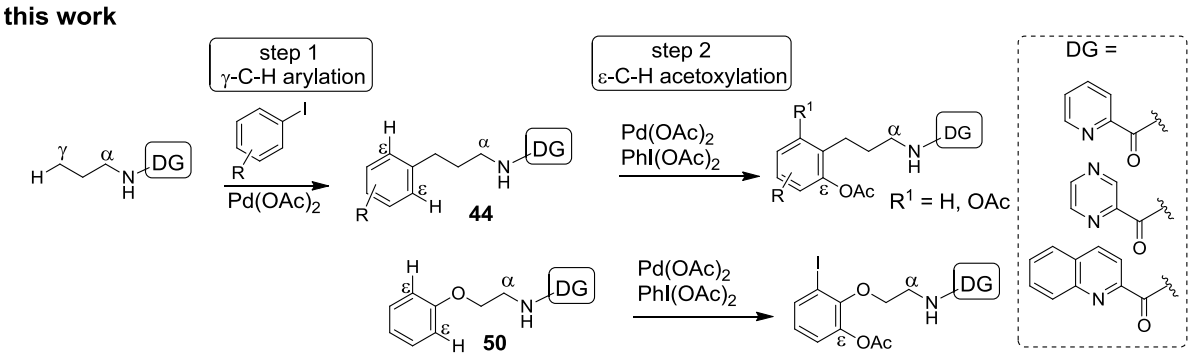
Reagents and conditions: (a) **34b** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2 equiv), toluene (2 mL), 110 ^oC, 24 h.

Scheme 13. Plausible mechanism for the ε-C-H acetoxylation of **34a**.

A literature survey revealed that it is debated that the C-H acetoxylation might occur *via* an oxidative radical mechanism when $PhI(OAc)_2$ is used as an oxidant.[6-10] However, it was found that the acetoxylation reaction of the substrate **34b** with $PhI(OAc)_2$ in the presence of TEMPO reagent still afforded the acetoxylated product **35b** in 60% yield. This observation suggested that perhaps the ε-C-H acetoxylation of the biaryl substrates investigated in this work does not follow the single electron transfer (SET) or free radical mechanism. Accordingly, in concurrence with the literature reports,[4,6-10] a plausible mechanism is proposed for the chemoselective ε-C-H acetoxylation of a typical compound **34a** involving the plausible 7-membered palladacycle **34aA**. It is proposed that **34aA** is formed after an initial co-ordination followed by the ε-C-H activation in the presence of the Pd(II) catalyst. Then, an oxidative addition of the intermediate **34aA** with $PhI(OAc)_2$ followed by the reductive elimination results the acetoxylated products **35a**/**36a** (Scheme 13).

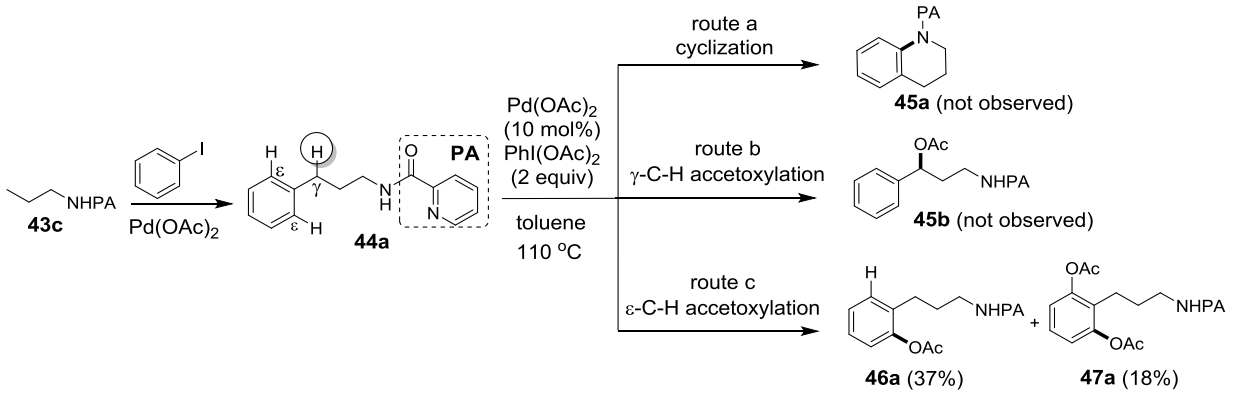
Section B: Motivation and designed plan for the regioselective ε-C(sp^2)-H acetoxylation of phenylpropylamine systems.

While the acetoxylation of ε-C(sp^2)-H bonds was successfully achieved as described in Section A of Chapter 5a, however, the investigations were done using a less common and specifically designed biaryl systems (Tables 1-3/Schemes 10-13). Notably, the *ortho* acetoxylation of remote ε-C(sp^2)-H bond using phenylpropylamine systems will be more useful and the literature survey as shown in Scheme 7 revealed that the Pd(II)-catalyzed, bidentate directing group-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond of phenylpropylamine systems **44** are less common.



Scheme 14. Palladium catalyzed directing groups assisted chemo- and regioselective acetoxylation of the ε-C(sp^2)-H bonds with phenylpropylamine systems.

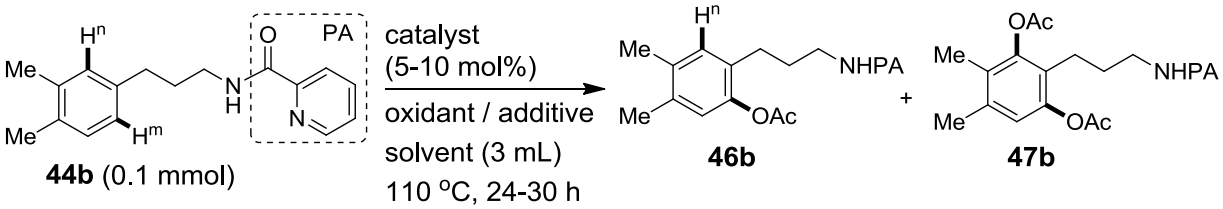
Accordingly, Chapter 5a of this thesis also reports the investigations on the Pd(II)-catalyzed, bidentate directing group-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond of phenylpropylamine systems **44** (Scheme 14).



Scheme 15. Initial attempt on the Pd(II)-catalyzed, PA-directed *ortho* acetoxylation of remote ε-C(sp^2)-H of **44a**.

To begin the investigation on the *ortho* acetoxylation of remote ε-C(sp^2)-H bond of phenylpropylamine systems, initially, the acetoxylation of the picolinamide substrate **44a** was attempted in the presence of the $Pd(OAc)_2$ and $PhI(OAc)_2$ in refluxing toluene. This reaction successfully afforded the corresponding ε-C(sp^2)-H acetoxylation products **46a** (mono OAc) and **47a** (di OAc) in 55% (total yield of **46a** and **47a**, Scheme 15). It was reported[18a] that the oxalylamide-directed ε-C(sp^2)-H functionalization of the substrate type **44a** afforded the corresponding cyclized product (Scheme 7 and Scheme 15). In the present case, the picolinamide-directed ε-C(sp^2)-H functionalization of **44a** in the presence of the $Pd(OAc)_2$ and $PhI(OAc)_2$ did not give the cyclized product **45a** (Scheme 15). Similarly, the Pd(II)-catalyzed picolinamide-directed functionalization of the substrate **44a** did not give the benzylic γ-C(sp^3)-H acetoxylated product **45b** as reported by Huang *et al.*[15d]

Table 4. Pd(II)-catalyzed picolinamide directed acetoxylation of remote ε-C(sp^2)-H bonds.[25,26]



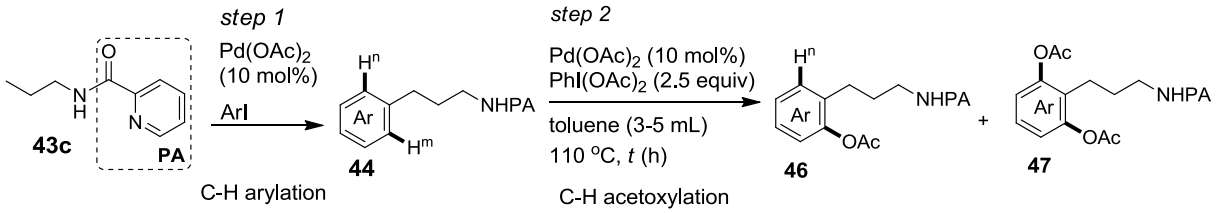
entry	catalyst	oxidant/additive (equiv)	solvent	**46b**: yield (%)
1	–	$PhI(OAc)_2$ (2.0)	toluene	–
2	$Pd(OAc)_2$	–	toluene	–
3	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.5)	toluene	40[a]
4	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5)	toluene	19
5	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.0)	toluene	40
6	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.5)	toluene	55, 47[b]
7	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.5)	toluene	49[c]
8	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.5)	toluene	41[d], 38[e]
9	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.5)	AcOH	–[f]
10	$Pd(OAc)_2$	$Cu(OAc)_2$ (2.5)	toluene	–
11	$Pd(OAc)_2$	AgOAc (2.5)	toluene	–
12	$Pd(TFA)_2$	$PhI(OAc)_2$ (2.5)	toluene	20
13	$Pd(PPh_3)_2Cl_2$	$PhI(OAc)_2$ (2.5)	toluene	traces

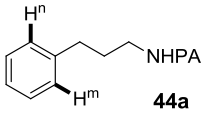
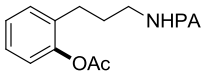
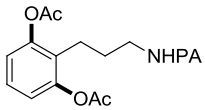
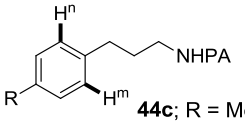
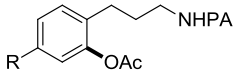
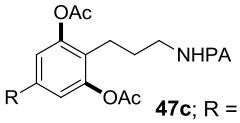
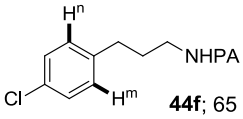
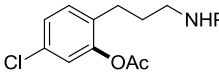
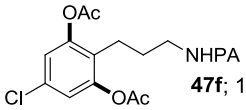
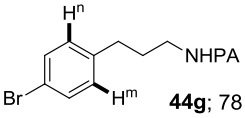
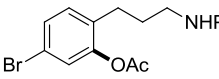
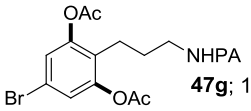
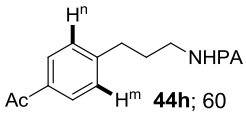
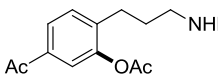
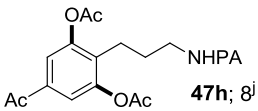
[a] 5 mol% of $Pd(OAc)_2$ was used. [b] 3 Equiv of $PhI(OAc)_2$ was used. [c] AcOH and Ac_2O (1:1 equiv) were used. [d] 1 Equiv of AgOAc was used. [e] 1 Equiv of oxone was used. [f] The reaction was carried out at reflux temp by using AcOH (3 mL).

Having done a successful attempt of the Pd(II)-catalyzed, picolinamide-directed *ortho* acetoxylation of remote ε-C(sp^2)-H bond of substrate **44a**; then, the optimization of reaction conditions were performed. Table 4 shows the Pd(II)-catalyzed, picolinamide-directed *ortho* acetoxylation of remote ε-C(sp^2)-H bond of the substrate **44b** in the presence of different palladium catalysts, oxidants and additives. The control experiments carried out with the substrate shown in entries 1 and 2 (Table 4) did not give any product in characterizable amounts. The C-H acetoxylation of the substrate **44b** in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and 2.5 equiv of $PhI(OAc)_2$ furnished the acetoxylated product **46b** in 40% yield (entry 3, Table 4). Next, the C-H acetoxylation of the substrate **44b** was attempted by using 10 mol% of the $Pd(OAc)_2$ catalyst and different equiv of $PhI(OAc)_2$ (entries 4-6, Table 4). The C-H acetoxylation reaction of the substrate **44b** with 2.5 equiv of $PhI(OAc)_2$ and 10 mol% of the $Pd(OAc)_2$ catalyst found to afford the product **46b** in a maximum of 55% yield (entry 6, Table 4). The Pd(II)-catalyzed C-H acetoxylation reaction of **44b** with $PhI(OAc)_2$ along with AcOH and Ac_2O as the additives did not improve the yield of the C-H acetoxylation product **46b** (entry 7, Table 4). The Pd(II)-catalyzed C-H acetoxylation reaction of the substrate **44b** with $PhI(OAc)_2$ along with AgOAc and oxone as the additives also did not improve the yield of the C-H acetoxylation **46b** (entry 8, Table 4). Various other optimization reactions were also attempted to improve the yield of the ε-C(sp^2)-H acetoxylated product **46b** (entries 9-13, Table 4). However, the attempts to improve the yield of the *ortho* acetoxylation of remote ε-C(sp^2)-H of the substrate **44b** by using different catalysts, oxidants/additives were not productive (entries 9-13, Table 4).

It is to be noted that in the phenylpropylamine system **44b** the ε-C-H^m bond was selectively acetoxylated over the ε-C-H^n bond to afford the mono acetoxylated product **46b** and the corresponding bis acetoxylated product **47b** was not obtained. In the substrate **44b**, the methyl group present at the *ortho*-position with respect to the ε-C-H^n bond, perhaps hinders the acetoxylation of the ε-C-H^n bond. Thus the formation of the bis acetoxylated product **47b** seems to be a less facile process. On the other hand, the acetoxylation of the substrate **44a** having no substituent at the *ortho*-position with respect to the ε-C-$H^{m/n}$ bonds gave both the acetoxylated products **46a** (mono OAc) and **47a** (di OAc, Scheme 15 and Table 5).

Table 5. Substrate scope investigation. Picolinamide-directed regioselective acetoxylation of remote ε-C(sp^2)-H bonds of **44a**, **44c-h**.[25,26]



entry	*step 1:* arylation product **44**: yield (%)	*step 2:* ε-C-H acetoxylation product **46**/**47**		**46**+**47** yield (%) *t* (h)
		46 (mono OAc): yield (%)	**47** (di OAc): yield (%)	
1[f]	 **44a**	 **46a**; 35[a]	 **47a**; 14[a]	49 (24 h)[a]
2[f]		**46a**; 37[b]	**47a**; 18[b]	55 (24 h)[b]
3[f]		**46a**; 40[c]	**47a**; 32[c]	72 (24 h)[c]
4[f]		**46a**; 35[d]	**47a**; 30[d]	65 (24 h)[d]
5[f]		**46a**; 8[e]	**47a**; 22[e]	30 (24 h)[e]
6	 **44c**; R = Me, 65	 **46c**; R = Me, 43	 **47c**; R = Me, 12	55 (24 h)[g]
7	**44d**; R = Et, 64	**46d**; R = Et, 16	**47d**; R = Et, 44	62 (17 h)[g]
8	**44e**; R = OMe, 59	**46e**; R = OMe, 49	**47e**; R = OMe, 12	64 (24 h)[h]
9	 **44f**; 65	 **46f**; 42	 **47f**; 16	58 (24 h)[i]
10	 **44g**; 78	 **46g**; 44	 **47g**; 11	55 (24 h)[f]
11	 **44h**; 60	 **46h**; 42	 **47h**; 8[j]	50 (34 h)[k]

[a] 1.5 Equiv. of $PhI(OAc)_2$ was used [b] 2 Equiv. of $PhI(OAc)_2$ was used. [c] 2.5 Equiv. of $PhI(OAc)_2$ was used. [d] 2.5 Equiv. of $PhI(OAc)_2$ and 1:1 equiv of $AcOH/Ac_2O$ were used. [e] 5 Equiv. of $PhI(OAc)_2$ was used. [f] The reaction was performed using 0.3 mmol of **44a**/**44g**. [g] The reaction was performed using 0.38 mmol **44c**/**44d**. [h] The reaction was performed using 0.23 mmol of **44e**. [i] The reaction was performed using 0.59 mmol **44f**. [j] The NMR spectrum of **47h** contains traces of **46h**. [k] The reaction was performed using 0.36 mmol of **44h**.

Therefore, further other optimization reactions were performed to improve the yield/selectivity of the ε-C(sp^2)-H acetoxylated product **46a** and **47a**. However, the attempts to improve the ratio of the mono and bis *ortho* acetoxylation of the substrate **44a** (entries 1-5, Table 5) were not productive. Notably, all the reactions afforded both the products **46a** (mono OAc) and **47a** (di OAc) in 30-72% yields (total yield of acetoxylated products **46a** and **47a**).

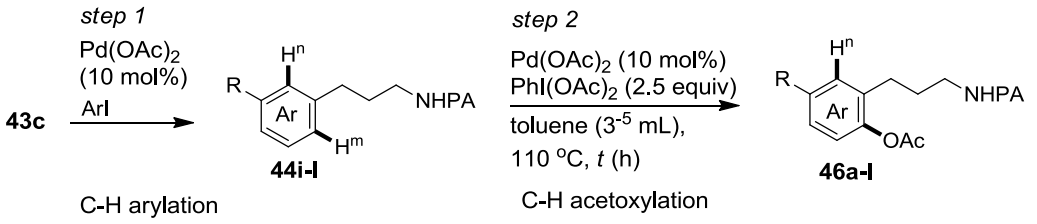
Then, it was envisaged to reveal the substrate scope and generality of the picolinamide-directed ε-C(sp^2)-H acetoxylation of by using phenylpropylamine systems. In this regard, initially various phenylpropylamine systems **44c-h** having different substituents at the *meta*-position with respect to the ε-C-$H^{m/n}$ bonds were assembled *via* the Pd(II)-catalyzed, picolinamide-directed γ-C-H arylation of the propyl amine system **43c** with corresponding aryl iodides.

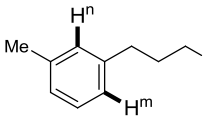
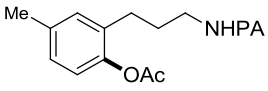
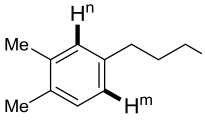
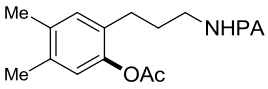
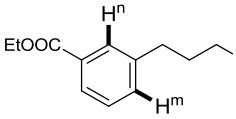
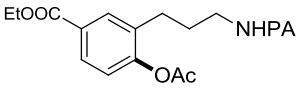
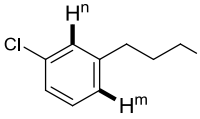
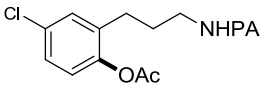
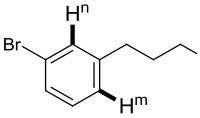
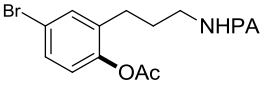
Afterwards, the Pd(II)-catalyzed, picolinamide-directed *ortho* acetoxylation of remote ε-C(sp^2)-H bonds of the substrates **44c-h** were performed. These C-H acetoxylation reactions gave the corresponding mono ε-C-H acetoxylated products **46c-h** and bis ε-C-H acetoxylated products **47c-h** in 50-64% yields (total yield of **46** and **47**, Table 5). The selectivity and ratio of mono/bis acetoxylation was found to be dependent on the nature of the substituents present at the *meta*-position with respect to the ε-C-$H^{m/n}$ bonds of the corresponding substrates **44c-h**.

The substrate **44c** with a methyl group in the aryl ring gave the corresponding C-H acetoxylated products **46c** (mono OAc, 43%) and **47c** (di OAc, 12%). The substrate **44d** with an ethyl group in the aryl ring gave the corresponding C-H acetoxylated products **46d** (mono OAc, 16%) and **47d** (di OAc, 44%). The yield of the bis acetoxylation product relatively increased when the alkyl substituent was changed from Me to Et (entries 6 and 7, Table 5).

The substrates **44e-h** containing OMe, Cl, Br and Ac substituents in the aryl ring gave the corresponding mono C-H acetoxylated products **46e-h** as the predominant compounds over the corresponding bis C-H acetoxylated products **47e-h** (entries 8-11, Table 5). The above observations revealed that perhaps the C-H acetoxylations of the substrates **44c-h** are perhaps controlled by the inductive effect of the corresponding substituents present in the aryl rings of the substrates **44c-h**.

Table 6. Substrate scope investigation. Picolinamide-directed regioselective acetoxylation of remote ε-C(sp^2)-H bonds of **44i-l**.[25,26]



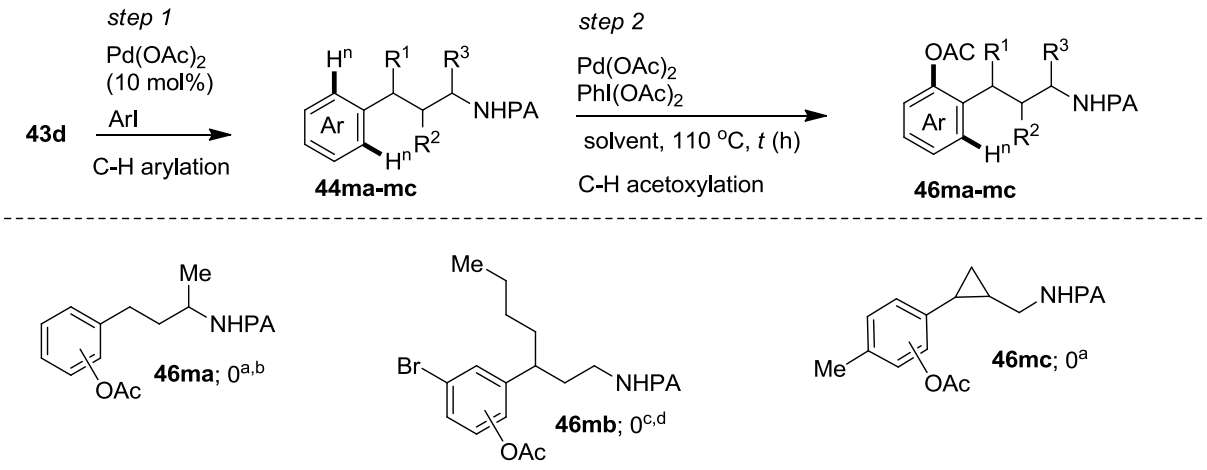
entry	*step 1:* arylation product **44i-l**: yield (%)	**46a-l** (mono OAc): yield (%)
1	 **44i**; 55	 **46i**; 56 (30 h)[a]
2	 **44b**; 72	 **46b**; 54 (25 h)[a]
3	 **44j**; 69	 **46j**; 45 (24 h)[a]
4	 **44k**; 60	 **46k**; 37 (23 h)[b]
5	 **44l**; 68	 **46l**; 43 (24 h)[c]

[a] The reaction was performed using 0.31 mmol of **44b**,**i**,**j**. [b] The reaction was performed using 0.37 mmol of **44k**. [c] The reaction was performed using 0.26 mmol of **44l**.

To extend the substrate scope, the substrates **44i-l** containing different substituents at the *ortho*-position with respect to the ε-C-H^n bond (*para*-position with respect to the ε-C-H^m bond) were also assembled *via* the Pd(II)-catalyzed, γ-C-H arylation of phenyl amine system **43c** with corresponding aryl iodides. Then, the acetoxylation of the substrates **44b** and **44i-l** were performed in the presence of the Pd(II) catalyst and $PhI(OAc)_2$, which afforded the corresponding mono ε-C-H acetoxylated products **46b** and **46i-l** in 37-56% yields (Table 6).

In the substrates **44b** and **44i-l** the ε-C-H^m bonds were selectively acetoxylated over the ε-C-H^n bonds to afford the corresponding mono acetoxylated products **46b** and **46i-l**. Apparently, the corresponding substituent present at the ortho-position with respect to the ε-C-Hn bond perhaps hinders the acetoxylation of the ε-C-H^n bonds of the substrates **44b** and **44i-l**.

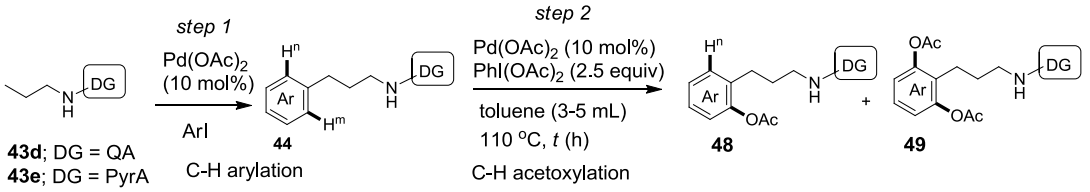
Thus, the acetoxylations of the ε-C-H^n bonds of the substrates **44b** and **44i-l** appear to be a less facile process. Further trials on the Pd(II)-catalyzed, picolinamide-directed acetoxylation reactions of other substrates **44ma**, **44mb** and **44mc** containing substituents in the alkyl chain failed to give the corresponding ε-C-H acetoxylated products **46ma**, **46mb** and **46mc** (Scheme 16). While an exact reason for the failure of these reactions is not clear at this stage. However, perhaps the substituents in the alkyl chain seem to interfere with the C-H activation/acetoxylation process.

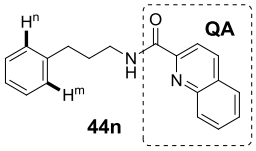
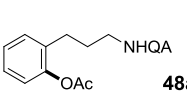
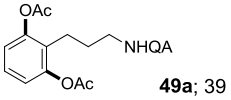
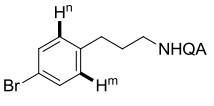
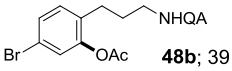
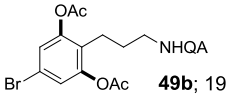
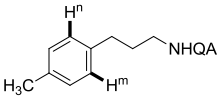
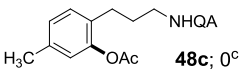
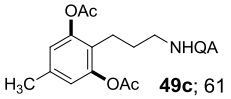
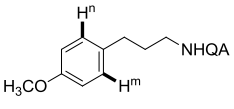
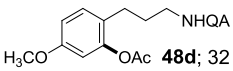
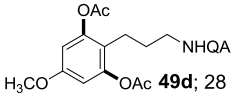
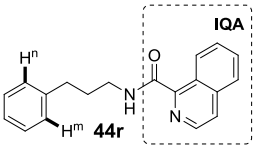
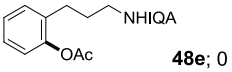
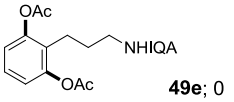
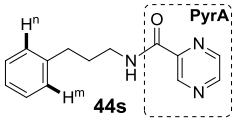
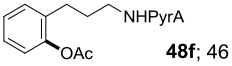
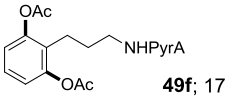
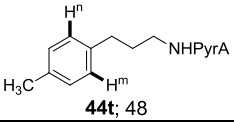
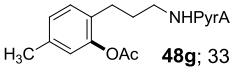
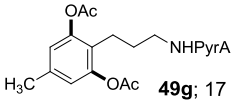


[a] $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv), toluene (4 mL), 110 °C, 48 h and this reaction afforded a complex mixture. [b] $Pd(TFA)_2$ (15 mol%), oxone (2.5 equiv) and Ac_2O (6 equiv), MeCN/DCE (4 mL), 85 °C, 24 h. In this reaction, the starting material was recovered. [c] $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv), toluene (4 mL), 110 °C, 24 h. [d] $Pd(OAc)_2$ (30 mol%), $PhI(OAc)_2$ (2.5 equiv), toluene (4 mL), 110 °C, 72 h. The reactions involving preparation of **46ma**, **46mb** and **46mc** were attempted by using their corresponding starting materials **44ma**, **44mb** and **44mc**.

Scheme 16. Substrate scope investigation.

Table 7. Quinolinamide and pyrazinamide-directed remote ε-C(sp^2)-H acetoxylation.[25,26]



entry	*step 1:* arylation product **44**: yield (%)	*step 2:* ε-C-H acetoxylation product **48/49**		**48**+**49** yield (%) *t* (h)
		48 (mono OAc): yield (%)	**49** (di OAc): yield (%)	
1	 **44n**	 **48a**; 31	 **49a**; 39	
2	 **44o**; 48	 **48b**; 39	 **49b**; 19	58 (24 h)[b]
3	 **44p**; 41	 **48c**; 0[c]	 **49c**; 61	61 (24 h)[d]
4	 **44q**; 40	 **48d**; 32	 **49d**; 28	60 (18 h)[a]
5	 **44r**	 **48e**; 0	 **49e**; 0	0 (45 h)[e]
6	 **44s**	 **48f**; 46	 **49f**; 17	63 (20 h)[a]
7	 **44t**; 48	 **48g**; 33	 **49g**; 17	50 (24 h)[f]

[a] The reaction was performed using 0.22 mmol of **44n**,**q**,**s**. [b] The reaction was performed using 0.40 mmol of **44o**. [c] mono acetoxylated product was not formed under the given reaction condition. [d] The reaction was performed using 0.46 mmol of **44p**. [e] The reaction was performed using 0.20 mmol of **44r**. [f] The reaction was performed using 0.50 mmol of **44t**. Note: The compounds **44n**,**r**,**s** were not assembled *via* the Pd-catalyzed arylation method.

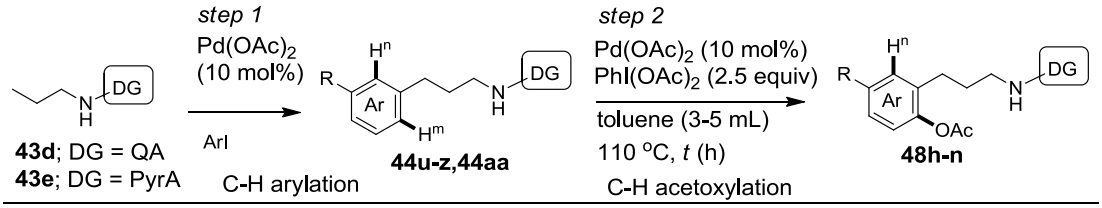
The reactions shown in Tables 4-6 revealed the successful attempts on the ε-C-H acetoxylation of phenylpropylamine systems **44a-l** by using picolinamide as the bidentate directing group. Then, it was envisaged to alter the ratio of the mono/bis ε-C-H acetoxylation of phenylpropylamine systems by using other bidentate directing groups, e.g., quinoline-2-carboxamide (QA), isoquinoline-1-carboxamide (IQA) and pyrazine-2-carboxamide (PyrA). In this regard, initially we various quinoline-2-carboxamide systems **44n-q** containing different substituents at the *meta*-position with respect to the ε-C-$H^{m/n}$ bonds were assembled.

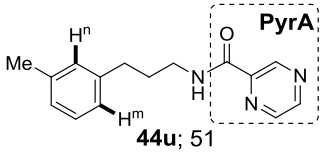
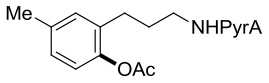
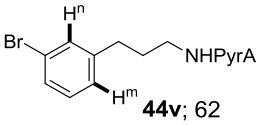
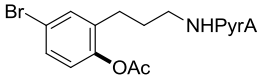
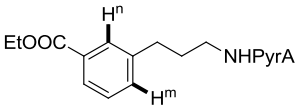
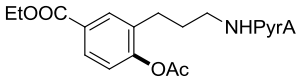
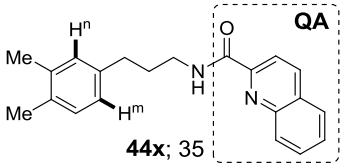
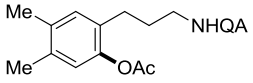
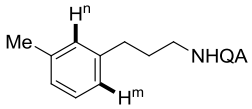
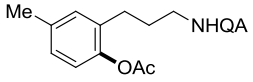
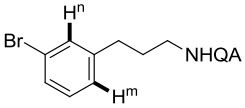
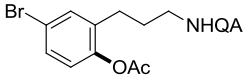
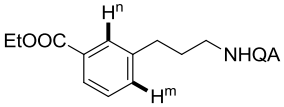
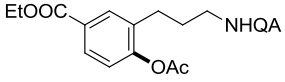
Then, QA-directed *ortho* acetoxylation of remote ε-C(sp^2)-H bonds of the substrates **44n-q** were attempted in the presence of Pd(II) catalyst to afford the corresponding mono ε-C-H acetoxylated products **48a,b,d** and bis ε-C-H acetoxylated products **49a-d** in 58-70% yields (total yield of **48** and **49**, Table 7). Only the substrate **44p** having a methyl group in the aryl ring afforded the bis ε-C-H acetoxylated product **49c** as the predominant compound. The other substrates **44n,o,q** afforded both the mono/bis C-H acetoxylation products in comparable yields (entries 1-4, Table 7). Next, the isoquinoline-2-carboxamide system **44r** was prepared and this substrate was subjected to the Pd(II)-catalyzed C-H acetoxylation reaction conditions. The acetoxylation of the substrate **44r** involving isoquinoline-2-carboxamide as the directing group failed to give the corresponding C-H acetoxylated products **48e** and **49e** (entry, 5, Table 7). This reaction revealed that isoquinoline-2-carboxamide is not assisting the ε-C-H acetoxylation process.

Next, the pyrazine-2-carboxamide systems **44s,t** were assembled and these substrates were subjected to the Pd(II)-catalyzed acetoxylation reaction conditions to afford the corresponding mono ε-C-H acetoxylated products **48f,g** and bis ε-C-H acetoxylated products **49f,g** in 50-63% yields (total yield of **48** and **49**, Table 7). The substrates **44s,t** gave the corresponding mono acetoxylated products **48f,g** as the predominant compounds over the corresponding bis acetoxylated products **49f,g** (entries 6 and 7, Table 7).

Furthermore, it was envisaged to examine the efficiency of quinoline-2-carboxamide (QA) and pyrazine-2-carboxamide (PyrA) for the acetoxylation of the ε-C-H bonds of substrates **44u-z** and **44aa** containing different substituents at the *ortho*-position with respect to the ε-C-H^n bond (*para*-position with respect to the ε-C-H^m bond). Thus, the required substrates **44u-z** and **44aa** were assembled *via* the Pd(II)-catalyzed, γ-C-H arylation of **43d,e** with corresponding aryl iodides (Table 8).

Table 8. Quinolinamide and Pyrazinamide-directed remote ε-C(sp^2)-H acetoxylation.[25,26]



entry	*step 1:* arylation product **44u-z,44aa**: yield (%)	**48h-n** (mono OAc): yield (%)
1	 **44u**; 51	 **48h**; 40 (30 h)[a]
2	 **44v**; 62	 **48i**; 33 (24 h)[b] **48i**; 27 (48 h)[c]
3	 **44w**; 65	 **48j**; 35 (20 h)[b]
4	 **44x**; 35	 **48k**; 53 (20 h)[b]
5	 **44y**; 35	 **48l**; 58 (10 h)[b]
6	 **44z**; 45	 **48m**; 50 (24 h)[d]
7	 **44aa**; 45	 **48n**; 55 (18 h)[b]

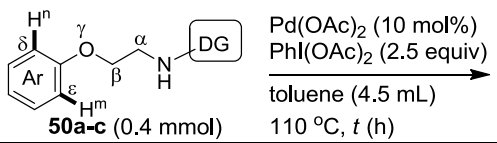
[a] The reaction was performed using 0.40 mmol of **44u**. [b] The reaction was performed using 0.30 mmol of **44v-y,44aa**. [c] The reaction was performed using 0.15 mmol of **44v**. [d] The reaction was performed using 0.22 mmol of **44z**. The starting material **44y** was not isolated in pure form and the corresponding crude reaction mixture after a quick pass through column was used for the acetoxylation reaction.

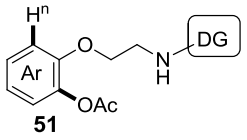
Then, the Pd(II)-catalyzed, acetoxylation of the pyrazine-2-carboxamide substrates **44u-w** were performed using $PhI(OAc)_2$ to afford the corresponding mono ε-C-H acetoxylated products **48h-j** in 27-40% yields (Table 8). The Pd(II)-catalyzed, acetoxylation of the quinoline-2-carboxamide substrates **44x-z** and **44aa** with $PhI(OAc)_2$ also afforded the corresponding mono ε-C-H acetoxylated products **48k-n** in 50-58% yields (Table 8). Based on the observed yields of the products **48h-n**, it is evident that there was no major change in the yields of the products, irrespective of the nature of the substituent present at the *ortho*-position with respect to the ε-C-H^n bond (*para*-position with respect to the ε-C-H^m bond). Further, the C-H acetoxylation of the substrates **44u-z** and **44aa** also afforded the corresponding mono ε-C-H^m acetoxylated products as the predominant compounds. The corresponding bis acetoxylated products from the substrates **44u-z** and **44aa** were not obtained. Apparently, the corresponding substituent present at the *ortho*-position with respect to the ε-C-H^n bond, perhaps hinders the acetoxylation of the ε-C-H^n bonds of the substrates **44u-z** and **44aa**. Thus, the C-H acetoxylation of ε-C-H^n bonds of **44u-z** and **44aa** appear to be a less facile process.

After completing investigations on the acetoxylation of remote ε-C(sp^2)-H bond of by using various phenylpropylamine systems, then the acetoxylation of remote ε-C(sp^2)-H bond of 2-phenoxyethanamine system **50** was attempted. In this regard, at first the bidentate ligand possessing phenoxyethanamine systems **50a-c** installed with the bidentate directing groups such as, PA, PyrA and QA were assembled (Table 9). Then, the Pd(II)-catalyzed, acetoxylation of the phenoxyethanamine systems **50a,b** were performed using $PhI(OAc)_2$. The Pd(II)-catalyzed, PA- and PyrA-directed C-H acetoxylation reactions of the substrates **50a,b** with $PhI(OAc)_2$ afforded the corresponding ε-C-H acetoxylated and the ε-C-H iodinated products **52a,b** in 30-40% yields (entries 1 and 2, Table 9). Similarly, the Pd(II)-catalyzed, QA-directed reaction of the substrate **50c** in the presence of $PhI(OAc)_2$ gave the ε-C-H acetoxylated and ε-C-H iodinated product **52c** in 33% yield. In this reaction, the mono ε-C-H acetoxylated product **51c** was also obtained 13% yield (entry 3, Table 9). In these reactions the expected products are mono/bis ε-C-H acetoxylated products; however, the C-H acetoxylation reactions of the phenoxyethanamine systems **50a-c** using $PhI(OAc)_2$ gave the corresponding ε-C-H iodinated products **52a-c** along with the expected C-H acetoxylated products.[27] It is to be noted that the reactions of phenylpropylamine systems **44a-z** and **44aa** with $PhI(OAc)_2$ did not give any ε-C-H iodinated products. While, at this stage a clear reason is not known that why the ε-C-H iodination occurred

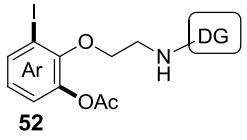
in the substrates **50a-c** but not in the phenylpropylamine systems **44a-z** and **44aa**. However, it seemed that the second ε-C-H^n acetoxylation is a facile process in the substrates **44a-z** and **44aa** and not in the in the phenoxyethanamine systems **50a-c**. Further, based on the isolated product **51c**, it is expected that the substrates **50a-c** undergo either C-H acetoxylation or C-H iodination of the ε-C-H^m bond to afford the ε-C-H acetoxylated product **51c** and ε-C-H iodinated product **52c′**. Considering the mechanism that is operating in these reactions, it is assumed that after the Pd(II)-catalyzed ε-C-H activation, the transfer of either iodide unit or OAc unit occurs in the reductive elimination step to afford the ε-C-H iodinated products **52a-c** along and/or the expected C-H acetoxylated products.[27]

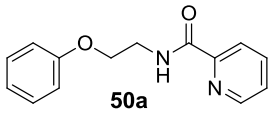
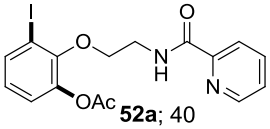
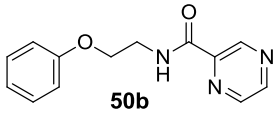
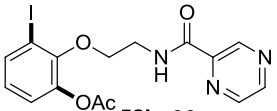
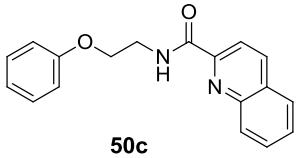
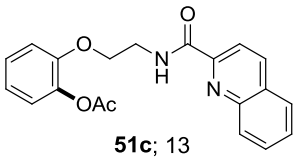
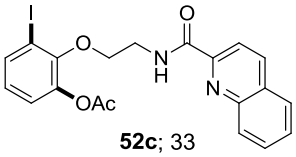
Table 9. Substrate scope investigation. Pd(II)-catalyzed, $PhI(OAc)_2$-promoted remote ε-C(sp^2-H) acetoxylation and iodination of **50a-c**.[25,26]





+



entry	substrate **50**	**51**: yield (%)	**52**: yield (%)	**51**+**52**: yield (%) *t* (h)
1	 **50a**	–[a]	 **52a**; 40	40 (28 h)
2	 **50b**	–[a]	 **52b**; 30	30 (30 h)
3	 **50c**	 **51c**; 13	 **52c**; 33	46 (22 h)[b]

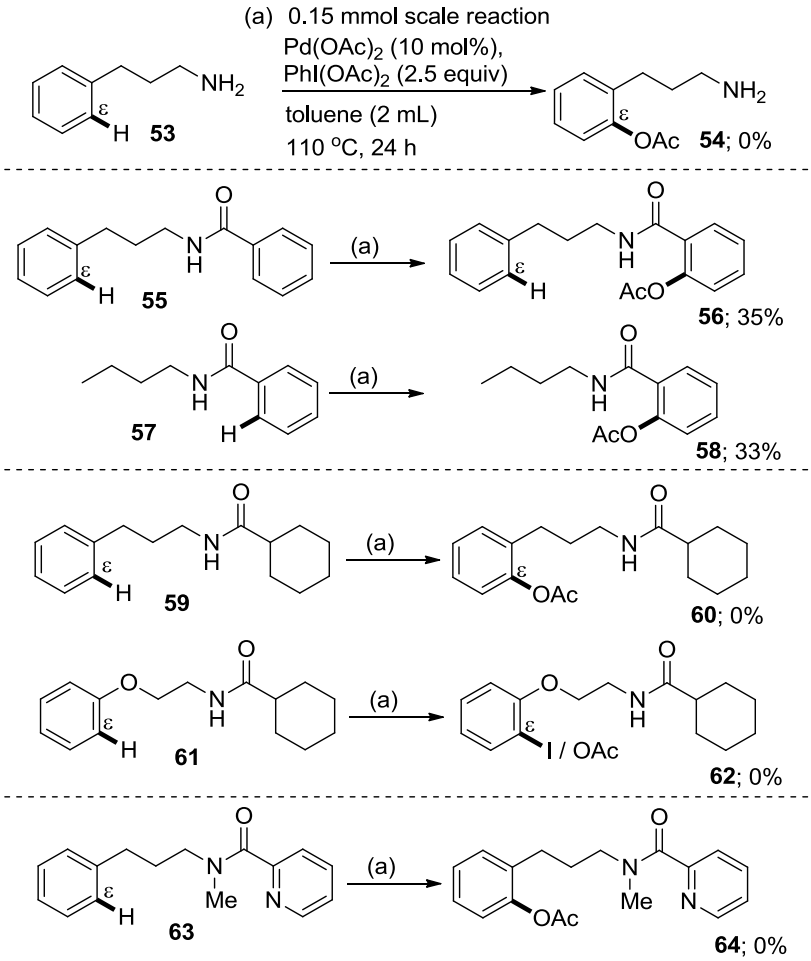
[a] The corresponding mono acetoxylation product was not obtained. [b] 10% *ortho*-mono-iodination product **52c′** was also isolated in this case.

Overall the efficiency of the bidentate directing groups e.g., PA, QA and PyrA, which were used for the *ortho* acetoxylation and ε-C(sp^2)-H bonds was comparable and a brief discussion with regard to their efficiency regard is presented here. The picolinamide-directed C-H acetoxylation

of the substrates **44a,c-h** gave the corresponding C-H acetoxylated products **46a,c-h** (mono OAc) and **47a,c-h** (di OAc) in 50-72% yields (total yield of **46** and **47**, Table 5). The QA-directed C-H acetoxylation of the substrates **44n-q** gave the corresponding C-H acetoxylated products **48a-d** (mono OAc) and **49a-d** (di OAc) in 58-70% yields (total yield of **48** and **49**, Table 7). Then, the PyrA-directed C-H acetoxylation of the substrates **44s,t** gave the corresponding C-H acetoxylated products **48f,g** (mono OAc) and **49f,g** (di OAc) in 50-63% (total yield of **48** and **49**, Table 7). In general, except for some cases, e.g., the substrates **44d** and **44p**, irrespective of the directing group, the C-H acetoxylation of phenylpropylamine systems having different substituents at the *meta*-position with respect to the ε-C-$H^{m/n}$ bonds of the aryl rings gave the corresponding mono C-H acetoxylated products as the major compounds (Tables 5 and 7).

The picolinamide-directed C-H acetoxylation of the substrates **44b,i-l** having different substituents at the *ortho*-position with respect to the ε-C-H^{n} bond afforded the corresponding acetoxylated products **46b,i-l** in 37-56% yields (Table 6). The PyrA-directed C-H acetoxylation of the substrates **44u-w** gave the products **48h-j** in 27-40% yields, respectively (Table 8). The QA-directed acetoxylation of the substrates **44x-z,44aa** gave the corresponding products **48k-n** in 50-58% yields, respectively (Table 8). These results indicated that the bidentate ligand QA is relatively efficient than the ligands PA and PyrA for the acetoxylation of the substrates having different substituents at the *ortho*-position with respect to the ε-C-H^{n} bond (Tables 6 and 8).

It was desired to substantiate the role of the bidentate directing groups in the C-H acetoxylation of remote ε-C(sp^2)-H bond of phenylpropylamine systems **44a-z**, **44aa** and phenoxyethanamine systems **50a-c**. In this regard, the ε-C(sp^2)-H acetoxylation of the substrate **53**, which is not having any directing group was attempted. This reaction did not give the expected ε-C-H acetoxylated product **54** (Scheme 17). The trial reaction comprising the ε-C-H acetoxylation by using the phenylpropyl-benzamide system **55** indicated the occurrence of *ortho* acetoxylation in the aryl ring of the benzamide unit of **55** instead of in the aryl ring of phenylpropyl unit of **55** (Scheme 17). Thus, the C-H acetoxylated product **56** was obtained in 35% yield. To further confirm this process, a another control reaction was carried out using the *N*-butylbenzamide **57**, which also suggested the occurrence of *ortho* acetoxylation in the aryl ring of the benzamide unit of **57**. Thus, the C-H acetoxylated product **58** was obtained in 33% yield (Scheme 17).



Scheme 17. Control experiments revealing the role of directing groups.

Further, some control experiments comprising the acetoxylation of remote ε-C(sp^2)-H bond of phenylpropyl-cyclohexylcarboxamide **59** and phenoxyethyl-cyclohexylcarboxamide **61** were also performed (Scheme 17). These reactions did not give the expected ε-C-H acetoxylated product **60** and ε-C-H acetoxylated/iodinated product **62** (Scheme 17). Additionally, based on the results obtained from the corresponding substrates **53**,**55**,**57**,**59** and **61** and the results of Tables 4-9; it is obvious that the bidentate directing groups, e.g., PA, QA, PyrA have directed the C-H acetoxylation to occur at the ε-C-H position in the substrates **44a-z**, **44aa** and **50a-c**. An additional trial comprising the C-H acetoxylation of *N*-methylated picolinamide derivative **63** also did not give the expected ε-C-H acetoxylated product **64** (Scheme 17). This reaction suggested that a free N-H group is essential for producing the preliminary Pd(II)-picolinamide coordination complex, which subsequently enables the ε-C-H activation followed by acetoxylation processes.

Chapter 5b: Direct azidation of allylic/benzylic alcohols and ethers followed by the click reaction: one-pot synthesis of 1,2,3-triazoles.

Allylic/benzylic azides have been used as synthetic building blocks[28-30] for synthesizing a wide range of heterocyclic compounds, natural products and biologically active triazole molecules involving the click reaction (Figure 2). The azide moiety is reported to be a key component of the HIV/AIDS drug, zidovudine. Benzylic and allylic azides are useful building blocks for the synthesis of triazole-installed macrocyclic compounds as discussed in Chapter 3.[28-30]

The conventional methods involving the synthesis benzylic and allylic azides from alcohols generally require two steps. First an alcohol is converted in to the respective halide[31] or sulfonate and then, the corresponding halide/sulfonate[31] is converted into an azide *via* the nucleophilic substitution reaction. Owing to the importance of carbon-nitrogen (C-N) bonds and their construction, the direct catalytic substitution of OH group of alcohols with nitrogen-based nucleophiles would be an ideal and simple synthetic procedure for obtaining allylic/benzylic azides and other related nitrogenous compounds.[32-34]

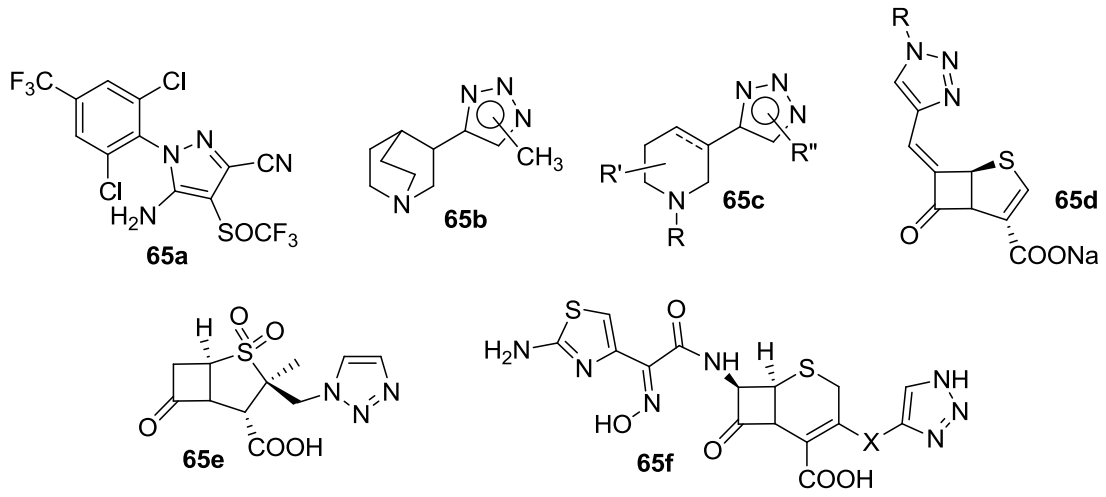


Figure 2. Biologically active molecules containing triazole motif.

The direct conversion of alcohols into azides has been reported in the literature and the regents of some of the reports methods are; NaN_3/CCl_4-DMF,[32a] TsIm/TBAI/NaN_3,[32b] 2,4,6-trichloro[1,3,5]triazine/*n*-Bu_4NN_3,[32c] $NaN_3/BF_3{\cdot}OEt_2$,[32d] 2-azido-1,3 dimethylimidazolinium hexafluorophosphate (2-ADMP)/DBU[32e] and NaN_3/ionic liquid [H-NMP]HSO_4,[32f] NaN_3/amphiphilic resin-supported palladium phosphine complex[32g] and NaN_3/triphosgene.[32h]

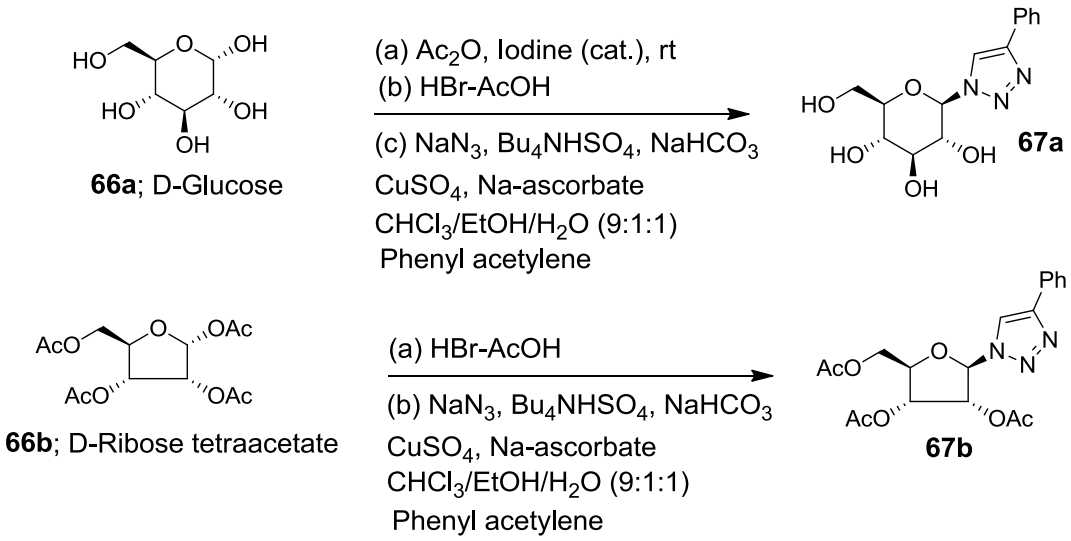
Especially, the direct azidation of allylic and benzylic alcohols with $TMSN_3$ as an azide reagent has been accomplished in the presence of various catalysts/promoters, e.g., AgOTf,[33a] $Cu(ClO_4)_2 \cdot 6H_2O$,[33b] $Cu(OTf)_2$[33c] and $BF_3 \cdot OEt_2$.[33d]

The well-established method for the synthesis of 1,2,3-triazoles is Huisgen's [3+2] cycloaddition between an alkyne and an organic azides.[34] Notably, the synthesis of 1,2,3-triazoles compounds has gained significant attention in the fields of chemistry, biology and materials science.[34] One-pot synthesis of 1,2,3-triazoles involving sequential reactions starting from organic halide/pseudo halide, sodium azide reagent and alkyne are well explored; but synthesis of 1,2,3-triazoles in one pot directly from allylic/benzylic alcohols has not been explored well.

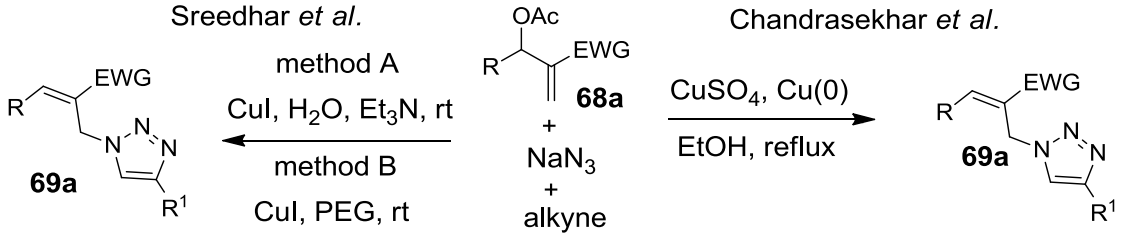
The Chapters 1-4 revealed the usage of various bis benzylic alcohols connectd *via* polyether linkers/spacers as the starting materials for the synthesis of new classes of polyether macrocycles. It was envisaged to develop a method to accomplish the substitution of OH group of alcohols with azide nucleophile for obtaining allylic/benzylic azides and execute the synthesis bis benzylic azides connectd *via* polyether linkers/spacers starting from bis benzylic alcohols connectd *via* polyether linkers/spacer. Further it was envisaged to use bis benzylic azides connectd *via* polyether linkers/spacers for synthesizing new classes of 1,2,3-triazole rings-appended polyether macrocycles as discussed in Chapter 2. Along this line, some of literature works dealing on the synthesis of azides from alcohols and also 1,2,3-triazole from allylic/benzylic azides involving click reaction starting from alcohols or alcohol derivatives in one-pot method.

Literature reports on the one-pot method-based synthesis of 1,2,3-triazoles by direct azidation of allylic/benzylic alcohols or other starting materials.

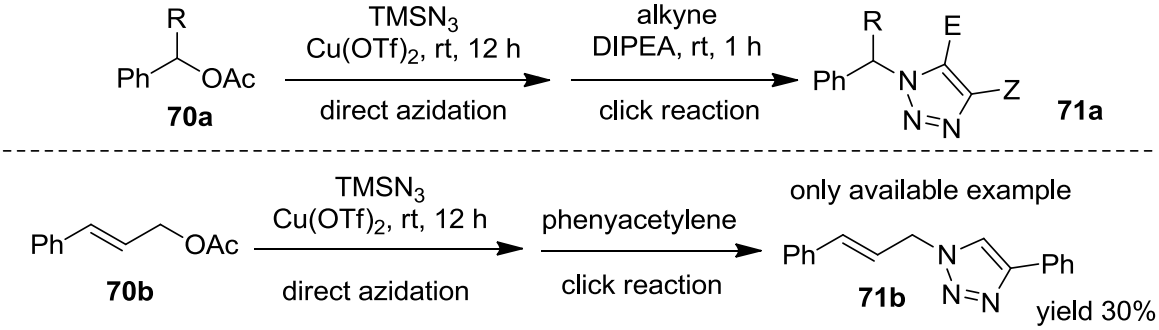
Wang *et al*. reported[35] efficient or convenient route to prepare 1,2,3-triazole-linked neoglycoconjugates from unprotected saccharides or peracetylated saccharides involving a Cu(I) catalyzed 1,3-dipolar cycloaddition in one-pot (Scheme 18). Unprotected D-glucose **66a** was acetylated with acetic anhydride, followed by brominolysis of the anomeric acetate. After removal of all volatiles, azide preparation followed by Cu(I) catalyzed 1,3-dipolar cycloaddition reaction afforded triazolylglycoside **67a** (Scheme 18). Same strategy was applied for the synthesis of triazole-linked neoglycoconjugates **67b** derived from saccharide acetates **66b** (Scheme 18).



Scheme 18. One-pot synthesis of triazolylglycosides from unprotected monosaccharides.



Scheme 19. One pot synthesis of 1,4-disubstituted 1,2,3-triazoles from Baylis-Hillman acetates.



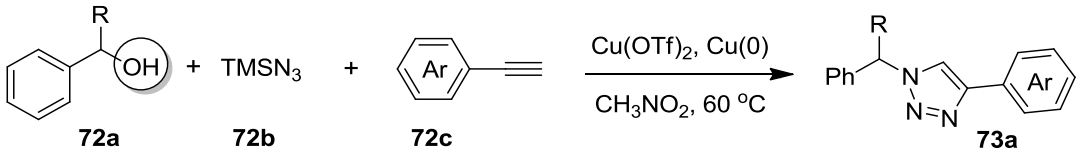
Scheme 20. One-pot synthesis of 1,2,3-triazoles from benzyl and allylic acetates-catalyzed by $Cu(OTf)_2$.

In 2006, Chandrasekhar and co-workers reported[36a] a copper catalyzed one-pot reaction to prepare a series of multi-functional 1,4-disubstituted-1,2,3-triazoles from the corresponding

acetylated Baylis-Hillman adducts **68a**, sodium azide and terminal alkynes (Scheme 19). Sreedhar and co-workers described[36b] an operationally simple and environmentally benign method for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles **69a** comprising a one-pot three-component coupling method by using a variety of aryl and alkyl-substituted Baylis–Hillman acetates and terminal alkynes with sodium azide using CuI as a catalyst (Scheme 19).

Fukuzawa *et al.* described[36c] a one-pot procedure for the preparation of 1,4-disubstituted 1,2,3-triazoles **71a/71b** from the easily accessible benzylic acetates **70a** without isolating an organic azide using copper(II) triflate as a single catalyst for substitution of acetates by $TMSN_3$ and the subsequent 1,3-dipolar addition with an alkyne (Scheme 20). The sequential reaction with allyl acetate **70b** proceeded to give 1,4-disubstituted cinnamyl triazole **71b** in moderate 30% yield (Scheme 20).

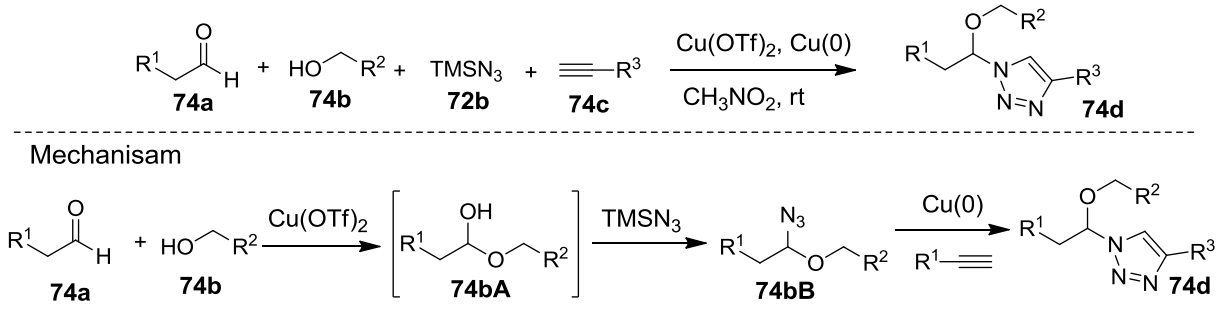
Sreedhar and co-workers reported[36d] the synthesis of 1,2,3-triazoles **73a** directly from secondary benzyl alcohols **72a**, $TMSN_3$ **72b** and terminal alkynes **72c** in the presence of a catalytic amount of a $Cu(OTf)_2$ and Cu powder. Yadav *et al.* reported[37] a convenient route to prepare a wide range of α-alkoxytriazoles **74d** from aldehydes (**74a**), alcohols (**74b**), azides (**72b**), and alkynes (**74c**) *via* a four-component reaction (Scheme 22).



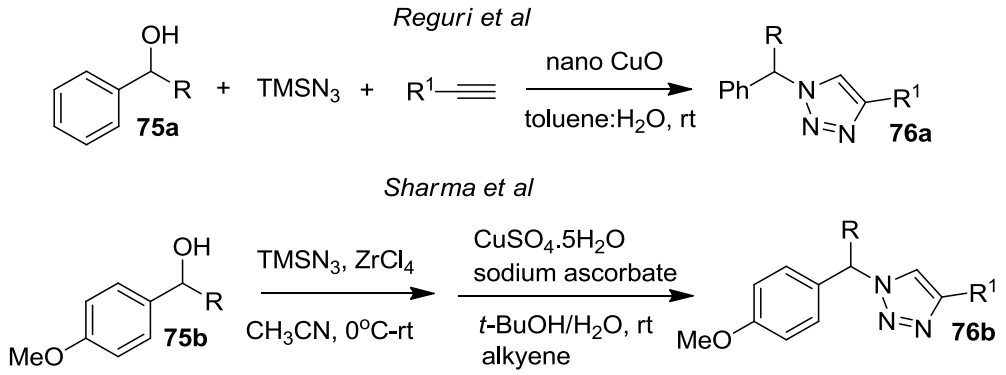
Scheme 21. Synthesis of triazoles *via* the three-component reaction of various secondary alcohols, alkynes and $TMSN_3$ catalyzed by $Cu(OTf)_2$ and Cu powder.

Reguri *et el.* demonstrated[38a] a one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles **76a** from benzyl alcohols **75a** by nucleophilic substitution of alcohols with $TMSN_3$, followed by azide-alkyne cycloaddition using copper oxide nanoparticles (nano CuO) in toluene (Scheme 23). Similarly, Sharma and co-workers[38b] reported $ZrCl_4$-catalyzed efficient protocol for the synthesis of benzyl azides directly from benzyl alcohols **75b**. Then, click reaction was performed without

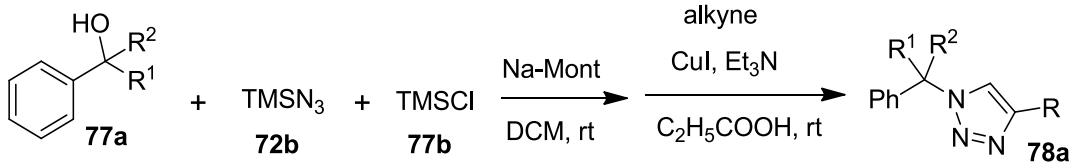
isolating the azides and this process afforded the 1,4-disubstituted 1,2,3-triazoles **76b** (Scheme 23).



Scheme 22. One-pot synthesis of α-alkoxytriazoles.



Scheme 23: One-pot direct azidation of benzylic alcohols followed by the click reaction.

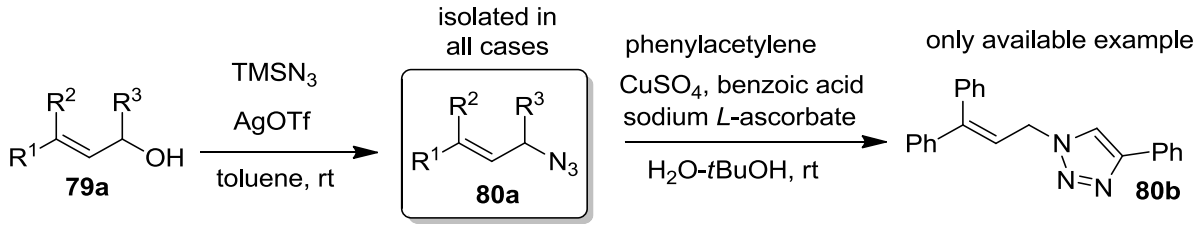


Scheme 24. One-pot synthesis of 1,2,3-triazoles from alcohols catalyzed by natural montmorillonite and TMSCl.

Onaka and co-workers developed[38c] a new and practical method for the one-pot synthesis of 1,2,3-triazole derivatives **78a** from various benzylic and allylic alcohols using natural montmorillonite and catalytic amount of TMSCl **77b** (Scheme 24). The acidic montmorillonite effectively catalyzed the azidation of various benzylic alcohols with $TMSN_3$, which afforded the

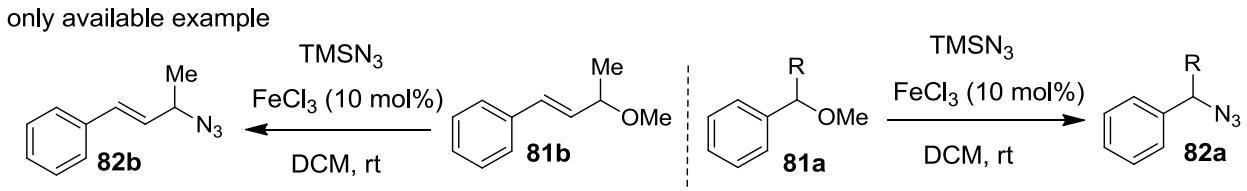
corresponding azides. Then a subsequent CuI-catalyzed click reaction afforded 1,2,3-triazole derivatives **78a** (Scheme 24).

Rueping *et al.* demonstrated[38d] silver triflate (AgOTf)-catalyzed, direct azidation of primary, secondary, and tertiary allylic alcohols (Scheme 25). Rueping *et al.* demonstrated the synthesis of several allylic azides and primary amines or 1,2,3-triazole derivatives. The authors showed a one-pot synthesis of 1,2,3-triazole **80b** through azidation of the corresponding 3,3-diphenylprop-2-en-1-ol **79a** and 1,3-cycloaddition (Scheme 25).



Scheme 25. Direct catalytic azidation of allylic alcohols.

Recently, Sawama *et al.* reported[38e] the direct azidation of chemically stable methyl protected benzyl ethers **81a** (Scheme 26). Similarly, direct azidation of methyl protected (*E*)-4-phenylbut-3-en-2-ol **81b** also led to the synthesis of allylic azide **82b** (Scheme 26).



Scheme 26. Direct azidation of methyl protected benzyl alcohols.

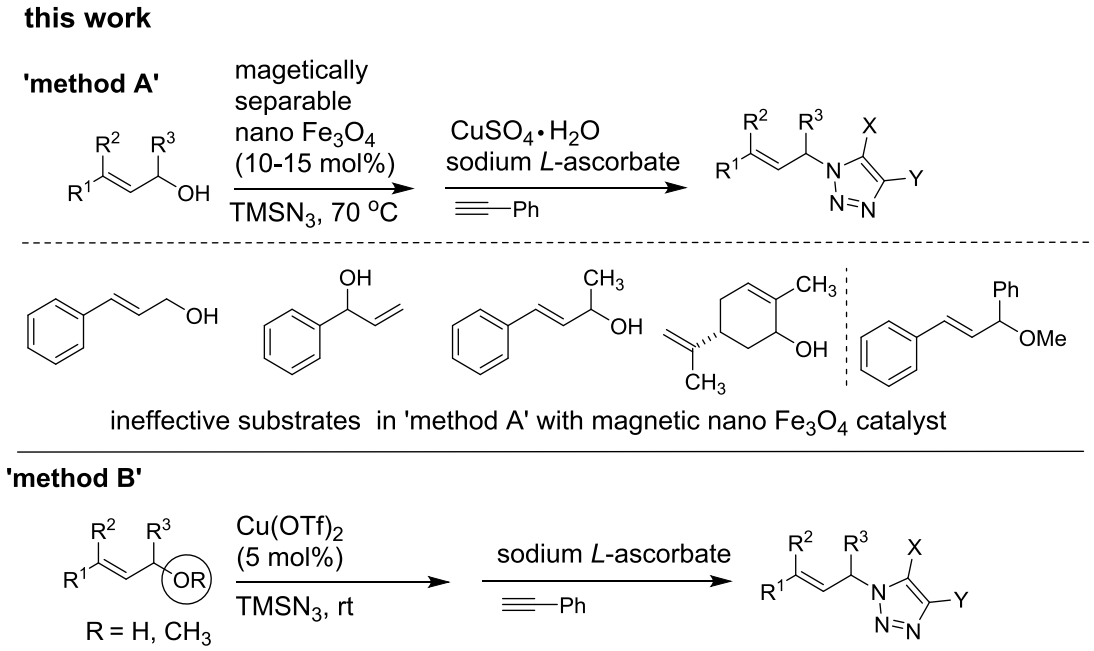
Result and discussion

While methods for the direct conversion of alcohols into azides are well documented; however, one-pot sequential processes comprising the direct azidation of allylic/benzylic alcohols followed by the Cu-catalyzed click reaction of the corresponding azides with alkynes are limited and not explored well. Particularly, a literature survey revealed that in most of the cases, the azides were

synthesized and isolated before performing the click reaction and the azidation reactions were not performed using easily separable heterogeneous catalyst. Taking the impetus from the literature, it was envisaged to develop simple methods for synthesizing substituted 1,2,3-triazoles starting from allylic/benzylic alcohols.

Accordingly, this chapter 5b of this thesis envisaged the direct azidation of various allylic/benzylic alcohols with $TMSN_3$ using magnetically separable nano Fe_3O_4 as a heterogeneous catalyst, followed by the Cu-catalyzed click reaction of azides with alkynes. In this process the synthesis of 1,2,3-triazoles can be accomplished without isolating the azide.

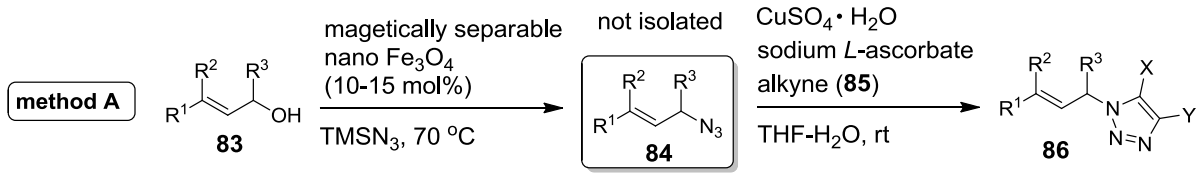
Further, this chapter 5b of this thesis envisaged the direct azidation of various allylic/benzylic alcohols with $TMSN_3$ using $Cu(OTf)_2$ catalyst, followed by the click reaction of azides with alkynes. In this process the synthesis of 1,2,3-triazoles can be accomplished without isolating the azide. Furthermore, in this method, $Cu(OTf)_2$ is expected to serve as a single catalyst for both the azidation of alcohol and click reaction steps.



Scheme 27. One-pot direct azidation of allylic/benzylic alcohols and ethers followed by the click reaction.

Developing heterogeneous catalytic methods with clean recovery of the catalyst after the reaction and efficient recyclability of the catalyst have been actively practiced by the synthetic chemists. Along this line, organic transformations catalyzed by magnetic nanoparticles have attracted the

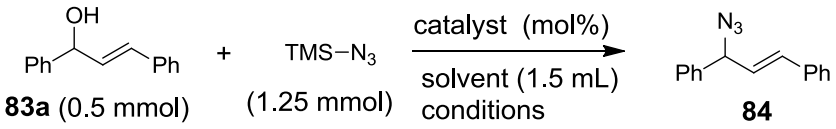
attention of the synthetic chemists.[41,42] Notably, the direct catalytic azidation of allylic and benzylic alcohols has not been explored using magnetically separable heterogeneous catalysts. Accordingly, Chapter 5b reports sequential processes comprising the magnetic nano Fe_3O_4 catalyzed direct azidation of allylic and benzylic alcohols, followed by the copper-catalyzed click reaction of the corresponding azides with alkynes affording several new 1,2,3-triazoles (Scheme 28).



Scheme 28. One-pot direct azidation of allylic/benzylic alcohols using heterogeneous nano Fe_3O_4 catalyst followed by the copper catalyzed click reaction.

To accomplish the envisaged method A, initially, various optimization reactions were performed to find out the suitable reaction conditions for the direct azidation of allylic alcohol **83a** with $TMSN_3$ by using magnetically separable nano Fe_3O_4 catalyst (particle size = < 50 nm). Two best reaction conditions were found for the conversion of alcohol **83a** into the corresponding azide **84**. The azide substrate **84** was obtained in 89% yield when the azidation of the substrate **83a** (1 equiv) was performed with $TMSN_3$ (2.5 equiv) by using 15 mol% of nano Fe_3O_4 in 1,2-DCE at rt (entry 2, Table 10). The azide **84** was obtained in 98% yield when the azidation of the substrate **83a** (1 equiv) was performed with $TMSN_3$ (2.5 equiv) by using nano Fe_3O_4 (15 mol%) in 1,2-DCE at 70 °C (entry 5, Table 10). The conversion of alcohol **83a** into azide **84** was not effective when the reaction was performed in solvents, such as 1,4-dioxane, MeCN, MeOH, acetone, THF and toluene. Similarly, other catalysts, e.g. nano Fe_2O_3 or powder Fe_3O_4 were not effective for the direct azidation. The recyclability of the magnetic nano Fe_3O_4 catalyst was also checked and accordingly, the direct azidation of allylic alcohol **83a** with $TMSN_3$ gave **84** in 95% yield in the 7th run. The recovered nano Fe_3O_4 catalyst after the usage at different runs was analyzed by IR and HRTEM techniques. The IR spectra and HRTEM analysis of the fresh and recovered magnetic nano Fe_3O_4 catalyst showed no characteristic changes.

Table 10. Nano Fe_3O_4-catalyzed reaction **83a** with $TMSN_3$.



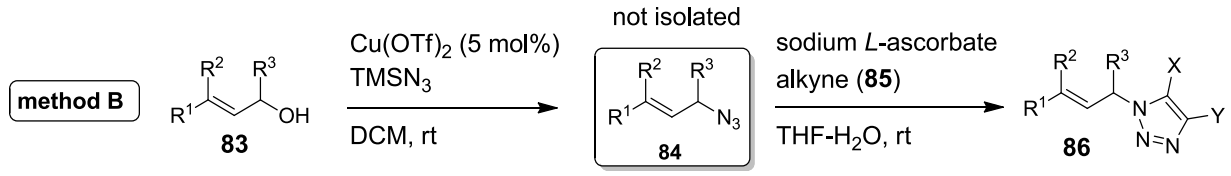
83a (0.5 mmol) (1.25 mmol) **84**

Entry	Catalyst (mol %)	Solvent	Reaction Condition	Yield of azide **84** (%)
1	nil	1,2-DCE	70 °C, 40 h	0
2	nano Fe_3O_4 (15)	1,2-DCE	rt, 15 h	89
3	nano Fe_3O_4 (15)	1,2-DCE	rt, 15 h	80[a]
4	nano Fe_3O_4 (15)	1,2-DCE	rt, 15 h	83[b]
5	nano Fe_3O_4 (15)	1,2-DCE	70 °C, 6 h	98
6	nano Fe_3O_4 (15)	1,2-DCE	70 °C, 6 h	85[a]
7	nano Fe_3O_4 (15)	1,2-DCE	70 °C, 6 h	89[b]
8	nano Fe_3O_4 (15)	DCM	rt, 10 h	85
9	nano Fe_3O_4 (15)	DCM	reflux, 8 h	92
10	nano Fe_3O_4 (15)	1,4-dioxane	rt, 30 h	0
11	nano Fe_3O_4 (15)	MeCN	rt, 30 h	0
12	nano Fe_3O_4 (15)	MeOH	rt, 30 h	0
13	nano Fe_3O_4 (15)	acetone	rt, 30 h	23
14	nano Fe_3O_4 (15)	THF	rt, 30 h	20
15	nano Fe_3O_4 (15)	toluene	rt, 30 h	55
16	nano Fe_3O_4 (10)	1,2-DCE	70 °C, 16 h	92
17	nano Fe_2O_3 (15)	1,2-DCE	70 °C, 30 h	<5
18	powder Fe_3O_4 (15)	1,2-DCE	70 °C, 48 h	35

[a] In this case, 0.55 mmol of $TMSN_3$ was used. [b] In this case, 0.75 mmol of $TMSN_3$ was used

Next, attention was paid to execute a one-pot method A for synthesizing 1,2,3 triazole derivatives starting from allylic and benzylic alcohols. Having the best reaction condition for the direct azidation of **83a** with $TMSN_3$ by using nano Fe_3O_4 catalyst (entry 5, Table 10), then, it was decided to perform the Cu-catalyzed click reaction of **84** in the same RBF (Round bottle flask) without isolating **84**. Accordingly, the direct azidation of allylic alcohol **83a** was performed followed by the copper-catalyzed click reaction of the azide **84** with ethyl propiolate,

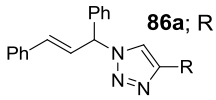
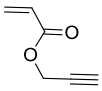
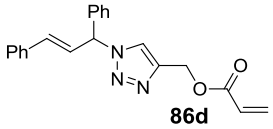
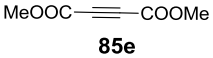
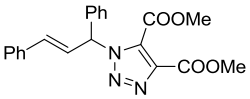
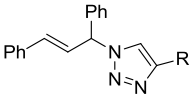
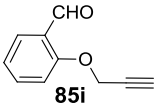
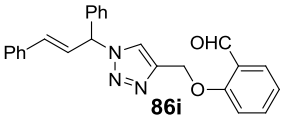
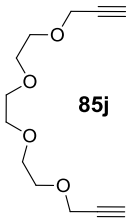
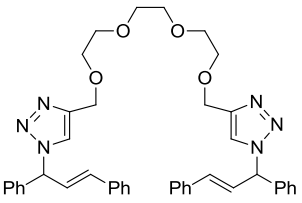
which afforded the 1,2,3-triazole derivative **86a** in 86% yield (entry 1, method A, Table 11). Successively, the one-pot direct azidation of substrate **83a** followed by the copper-catalyzed click reaction of **84** with various alkynes **85b-e**, **85g-j** gave the corresponding substituted 1,2,3-triazoles **86b-e**, **86g-j** in 75-93% yields (method A, Table 11). Method A involves nano Fe_3O_4-catalyzed direct azidation of the substrate **83a** with $TMSN_3$ as the first step, followed by the Cu-catalyzed click reaction of the corresponding azides with alkynes as the second step. Then, it was envisaged to simplify the reaction procedure of the method A by using a single catalyst to perform the direct azidation of **83a** with $TMSN_3$ followed by the click reaction of the corresponding azides with alkynes.



Scheme 29. Copper catalyzed one-pot direct azidation of allylic alcohols followed by the catalyzed click reaction using single catalyst.

Then, the method B procedure was thought of, in which the direct azidation of substrate **83a** with $TMSN_3$ followed by the click reaction of the product **84** with various alkynes can be attempted in the same RBF (Round bottle flask) by using $Cu(OTf)_2$ catalyst (Scheme 29). In this regard, initially, the optimizations of the reactions were performed to find out the best reaction conditions for the method B. The direct azidation of the **83a** with $TMSN_3$ in the presence of 5 mol% of $Cu(OTf)_2$ followed by the click reaction of **84** with **85a** without any additive in the click reaction step did not give the expected 1,2,3-triazole **86a** (entry 1, method B, Table 11). When DIPEA or *L*-ascorbic acid was used as an additive, the 1,2,3-triazole **86a** was obtained in 10-20% yields (entry 1, method B, Table 11). The use of sodium *L*-ascorbate as an additive for the click reaction step afforded the 1,2,3-triazole **86a** in 87% yield (entry 1, method B, Table 11). Then, using the same reaction conditions, the direct azidation of substrate **83a** followed by the click reaction of the product **84** with various alkynes **85b-I** were performed to afford the corresponding substituted 1,2,3-triazole derivatives **86b-i** in 72-98% yields (method B, Table 11).

Table 11. One-Pot direct azidation of allylic alcohol **83a** followed by the click reaction with **85a-j**. Synthesis of substituted 1,2,3-triazoles **86a-j**.[a]

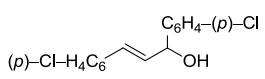
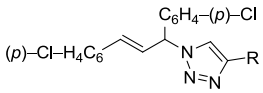
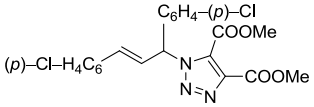
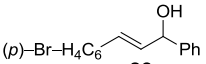
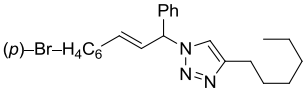
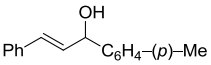
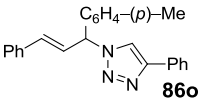
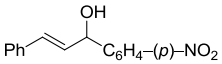
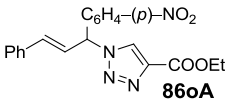
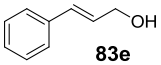
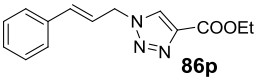
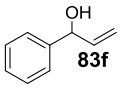
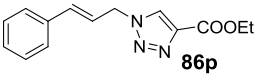
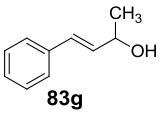
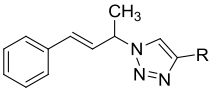
Entry	Alkyne	Triazole	Yield (%) Method A	Yield (%) Method B
1	**85a**; R = COOEt	 **86a**; R = COOEt	86	(0),[b] (10),[c] (20),[d] (60),[e] (81),[f] (87)[g]
2	**85b**; R = -CH_2OH	**86b**; R = -CH_2OH	82	75
3	**85c**; R = Ph	**86c**; R = Ph	90	97
4	 **85d**	 **86d**	93	96
5	 **85e**	 **86e**	86	72
				
6	**85f**; R = Bu	**86f**; R = Bu	-[h]	98
7	**85g;** R = hex	**86g**; R = hex	85	97
8	**85h**; R = oct	**86h**; R = oct	92	93
9	 **85i**	 **86i**	85	89
10	 **85j**	 **86j**	75	-[h]

[a] In method A, 0.5 mmol of **83a** and 1.5 mmol of $TMSN_3$ were used. In method B, 0.5 mmol of **83a** and 0.75 mmol of $TMSN_3$ were used. In both the methods, initially, the azidation of **83a** was carried out with $TMSN_3$ and after the reaction period the solvent was evaporated. Then, the click reaction was carried out. [b] The reaction was carried out without sodium *L*-ascorbate. [c] DIPEA (50 mol%) was used instead of sodium *L*-ascorbate. [d] *L*-Ascorbic acid (50 mol%) was used instead of sodium *L*-ascorbate. [e] CuCl (60 mol%) was used instead of sodium *L*-ascorbate. [f] Sodium *L*-ascorbate (30 mol%) was used. [g] Sodium *L*-ascorbate (50 mol%) was used. [h] The reaction was not performed.

Next, it was planned to explore the direct conversion of various allylic alcohols **83b-g** (Table 12) into the corresponding substituted 1,2,3-triazole derivatives using either method A or method B procedure. The 1,2,3-triazole derivatives **86k** (75%) and **86l** (60%) were synthesized from **84b** using the method B procedure involving $Cu(OTf)_2$ catalyst (entries 1 and 2, Table 12). Then, the 1,2,3-triazole derivatives **86m-o** and **86oA** were synthesized from the corresponding alcohols **83b-d** and **83dA** using the method A or B procedures (entries 3-6, Table 12). It is to be noted that the products **86n,o** and **86oA** were obtained as a mixture of regioisomers since the corresponding allylic alcohols **83c,d** and **83dA** underwent an allylic rearrangement under the experimental condition, thereby led to the formation of the corresponding regioisomers. The allylic alcohols **83e-g** failed to afford corresponding 1,2,3-triazole derivatives **86p** and **86q** when the direct azidation of **83e-g** followed by the click reaction were performed using method A procedure (Starting material was recovered). This is perhaps because the nano Fe_3O_4-catalyzed conversion of allylic alcohols **83e-g** into the corresponding azides did not occur in the first step, as a result the subsequent click reaction failed to afford the 1,2,3-triazole derivatives **86p** and **86q** under the method A procedure (entries 7-9, method A, Table 12, starting material was recovered). However, the allylic alcohols **83e-g** successfully afforded the corresponding 1,2,3-triazole derivatives **86p** (70-80%) and **86q** (76%) when the direct azidation of allylic alcohols **83e-g** followed by the click reaction were performed using the method B procedure (entries 7-9, method B, Table 12). Similarly, the 1,2,3-triazole derivatives **86r** was obtained in 85% yield from **83g** using the method B procedure (entry 10, method B Table 12).

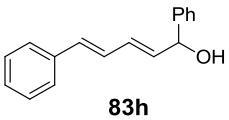
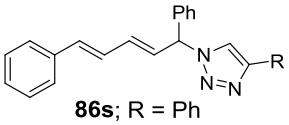
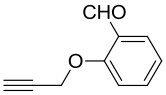
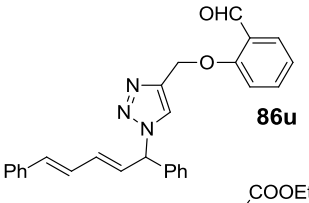
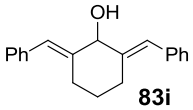
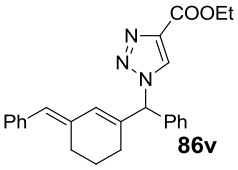
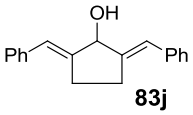
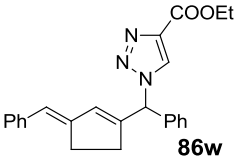
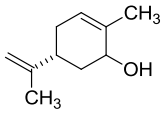
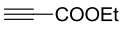
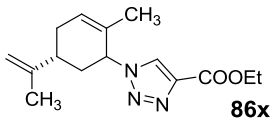
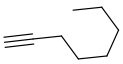
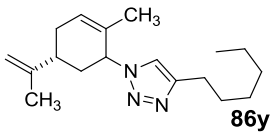
Subsequently, it was planned to carry out the conversion of the conjugated and cyclic allylic alcohols **83h-k** (Table 13) into the corresponding 1,2,3-triazole derivatives using the reaction conditions of either method A or method B procedure. The direct azidation of **83h** followed by the click reaction with **85c** using the method A and method B procedures gave the 1,2,3-triazole derivative **86s** in 62-68% yields. The azidation of **83h** followed by the click reaction with different alkynes **85a** and **85i** gave the corresponding 1,2,3-triazole derivatives **86t** (73% yield in method B) and **86u** (57% yield in method A). Then, the 1,2,3-triazole derivatives **86v** (62%), and **86w** (45%) were synthesized from the corresponding allylic alcohols **83i** and **83j** using the method A procedure (entries 4 and 5, Table 13).

Table 12. One-Pot direct azidation of various allylic alcohols **83b-g** followed by the click reaction with alkynes. Synthesis of substituted 1,2,3-triazoles **86k-r**.[a]

Entry	Alcohol	Alkyne	Triazole	Yield (%) Method A	Yield (%) Method B[b]
1	 **83b**	 **85c**; R = Ph	 **86k**; R = Ph	-[c]	75
2	**83b**	**85a**; R = COOEt	**86l**; R = COOEt	-[c]	60
3	**83b**	 **85e**	 **86m**	52 (14 h)[d]	50
4	 **83c**	 **85g**	 **86n**	82 (12 h)[d] (50:50)[e]	70 (50:50)[e]
5	 **83d**	 **85c**	 **86o**	72 (15 h)[d] (50:50)[e]	64 (50:50)[e]
6	 **83dA**	 **85a**	 **86oA**	-[c]	68 (50:50)[e]
7	 **83e**	 **85a**	 **86p**	0	70
8	 **83f**	 **85a**	 **86p**	0	80
9	 **83g**	 **85a**; R = COOEt	 **86q**; R = COOEt	0	76
10	**83g**	**85g**; R = hex	**86r**; R = hex	-[c]	85

[a] In both the methods, initially, the azidation of **83** was carried out with $TMSN_3$ and after the reaction period the solvent was evaporated. Then, the click reaction was carried out. [b] In method B, for all the reactions, 0.5 mmol of **83** and 0.75 mmol of $TMSN_3$ were used. [c] The reaction was not performed. [d] In this reaction, 1 mmol of alcohol and 3 mmol of $TMSN_3$ were used and the reaction time indicated in the parenthesis corresponds to azidation reaction. [e] Products were obtained as a mixture of regioisomers due to an allylic rearrangement under the experimental condition.

Table 13. One-Pot direct azidation of conjugated and cyclic allylic alcohols **83h-k** followed by the click reaction with alkynes. Synthesis of substituted 1,2,3-triazoles **86s-y**.[a]

Entry	Alcohol	Alkyne	Triazole	Yield (%) Method A	Yield (%) Method B[b]
1	 **83h**	 **85c**; R = Ph	 **86s**; R = Ph	62 (18 h)[c]	68
2	**83h**	**85a**; R = COOEt	**86t**; R = COOEt	-[d]	73
3	**83h**	 **85i**	 **86u**	57 (18 h)[c]	42
4	 **83i**	 **85a**	 **86v**	62 (30 h)[c] (76:24)[e]	<5[f]
5	 **83j**	 **85a**	 **86w**	45 (24 h)[c] (88:12)[e]	<5[f]
6	 **83k** (60:40)	 **85a**	 **86x**	0 (24 h)[c]	80 (86:14)[g]
7	**83k** (60:40)	 **85g**	 **86y**	-[d]	87 (86:14)[g]

[a] In both the methods, initially, the azidation of **83** was carried out with $TMSN_3$ and after the reaction period the solvent was evaporated. Then, the click reaction was carried out. [b] In method B, for all the reactions, 0.5 mmol of **83** and 0.75 mmol of $TMSN_3$ were used. [c] In this reaction, 1 mmol of alcohol and 3 mmol of $TMSN_3$ were used and the reaction time indicated in the parenthesis corresponds to azidation reaction. [d] The reaction was not performed. [e] Products were obtained as a mixture of regioisomers due to an allylic rearrangement under the experimental condition. [f] In this case, the reaction gave a mixture of compounds and the expected product could not be isolated in pure form. [g] The products **86x,y** were obtained as a mixture of diastereomers as the starting material **83k** was used as diastereomers

The products **86v** and **86w** were obtained as a mixture of regioisomers since the corresponding allylic alcohols **83i** and **83j** underwent an allylic rearrangement under the experimental condition, thereby led to the formation of their corresponding regioisomers. The cyclic allylic alcohol **83k** failed to afford corresponding 1,2,3-triazole **86x** when the direct azidation of **83k** followed by the click reaction with **85a** was performed using the method A procedure (Starting material was recovered). This is perhaps because, the nano Fe_3O_4-catalyzed conversion of **83k** into the corresponding azides did not occur in the first step and as a result, the subsequent click reaction failed to afford **86x** (entry 6, method A, Table 13, starting material was recovered). However, the cyclic allylic alcohol **83k** successfully afforded the corresponding 1,2,3-triazole **86x** (80%) when the direct azidation of **83k** followed by the click reaction was performed using the method B procedure (entry 6, method B, Table 13). Similarly, the 1,2,3-triazole **86y** (87%) was obtained from **83k** using the method B procedure (entry 7, method B Table 13). Since, the alcohol **83k** was used as a mixture of diastereomers (*dr* 60:40), the corresponding 1,2,3-triazoles **86x** and **86y** were obtained as diastereomers with improved diastereoselectivity (*dr* 86:14) under the experimental condition. The efforts to isolate the respective major isomers of **86x** and **86y** were not fruitful and hence, the stereochemistry of the major/minor diastereomers was not ascertained.

To elaborate the substrate scope and generality of this protocol, it was envisaged to examine the direct conversion of the benzylic alcohols **87a,c,e,g** and methyl ethers **87b,d,f,h** prepared from their corresponding alcohols (Table 14) into the corresponding 1,2,3-triazoles by using either the method A or method B procedure. The direct azidation of the benzylic alcohol **87a** followed by the click reaction with **85a** under the method A procedure gave the 1,2,3-triazole derivative **88a** in 71% yield (entry 1, method A, Table 14). On the other hand, the direct azidation of the ether **87b** followed by the click reaction with **85a** under the method A procedure failed to give the 1,2,3-triazole **88a** (entry 2, method A, Table 14). However, the direct azidation of **87b** followed by the click reaction with **85a** under the method B procedure successfully gave the product **88a** in 75% yield (entry 2, method B, Table 14). Similarly, various 1,2,3-triazoles **88b-f** were prepared in 35-87% yields starting from the corresponding benzylic alcohols or their corresponding methyl ethers **87b-h** (entries 3-9, Table 14).

Table 14. One-pot synthesis of 1,2,3-triazoles **88a-f** and **86a,q,x** from allylic ethers **87i-k** and benzylic alcohols/ethers **87a-h**.[a,b]

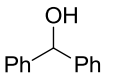
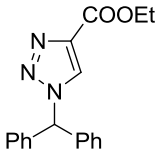
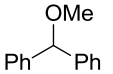
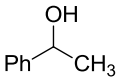
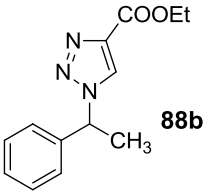
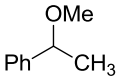
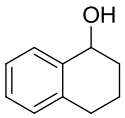
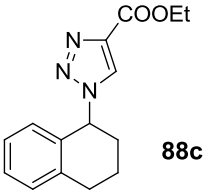
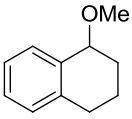
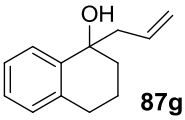
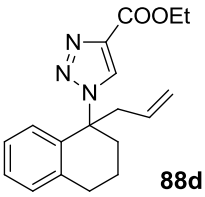
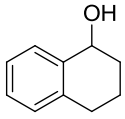
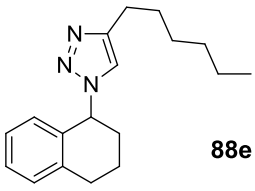
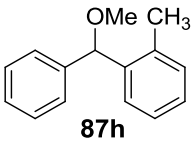
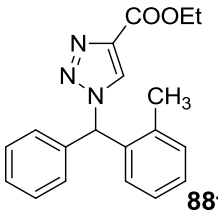
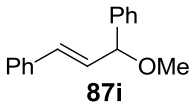
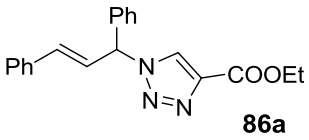
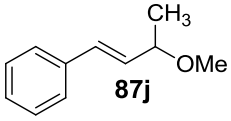
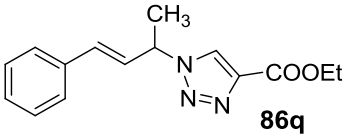
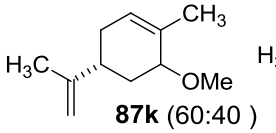
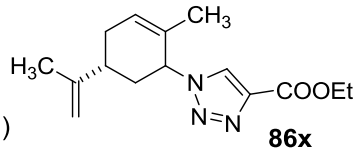
Entry	Ether Substrate	Triazole	Yield (%) Method A	Yield (%) Method B
1	 **87a**	 **88a**	71	-[d]
2	 **87b**	**88a**	0	75
3	 **87c**	 **88b**	35	-[d]
4	 **87d**	**88b**	-[d]	50
5	 **87e**	 **88c**	70	-[d]
6	 **87f**	**88c**	-[d]	70
7	 **87g**	 **88d**	52	-[d]
8[c]	 **87e**	 **88e**	70	-[d]

Table 14 (continued). One-pot synthesis of 1,2,3-triazoles **88a-f** and **86a,q,x** from allylic ethers and benzylic alcohols/ethers **87a-k**.[a,b]

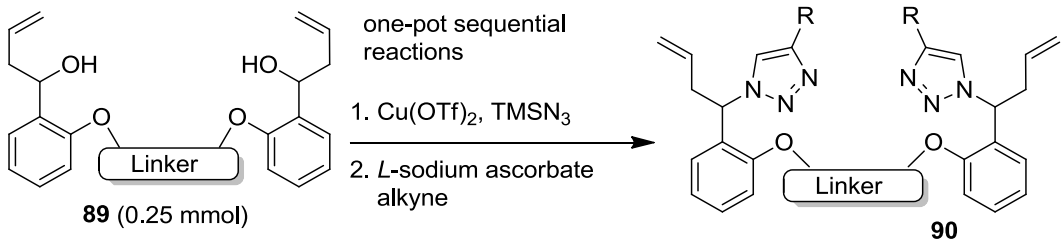
Entry	Ether Substrate	Triazole	Yield (%) Method A	Yield (%) Method B
9	 **87h**	 **88f**	-[d]	87
10	 **87i**	 **86a**	0	80
11	 **87j**	 **86q**	-[d]	72
12	 **87k** (60:40)	 **86x**	-[d]	70 (84:16)[e]

[a] Reaction condition for method A: The reaction was performed using **87** (1 mmol), $TMSN_3$ (3 mmol) and nano Fe_3O_4 (15 mol%) in 1,2-DCE (3 mL) at 70 ^oC for 14-20 h and the solvent was evaporated and then, the click reaction was carried out using ethyl propiolate (**85a**, 2 mmol) in THF (3 mL) and water (3 mL) in the presence of $CuSO_4 \cdot 5H_2O$ (30 mol%) and sodium *L*-ascorbate (30 mol%) at rt for 12 h. [b] Reaction condition for method B: The reaction was performed using **87** (0.5 mmol), $TMSN_3$ (0.75 mmol) and $Cu(OTf)_2$ (5 mol%) in DCM (3 mL) at rt for 3 h and the solvent was evaporated and then, the click reaction was carried out using ethyl propiolate (**85a**, 1.25 mmol) in THF (2 mL) and water (2 mL) in the presence sodium *L*-ascorbate (50 mol%) at rt for 20 h. [c] In this case, alkyne **85g** was used instead of **85a**. [d] The reaction was not performed. [e] Product was obtained as a mixture of diastereomers as the starting material **87k** was used as diastereomers.

Additionally, the azidation of methyl ethers **87i-k**, which were prepared from of their corresponding allylic alcohols followed by the click reaction with ethyl propiolate under the

method B procedure successfully gave the corresponding 1,2,3-triazoles **86a** (80%), **86q** (72%) and **86x** (70%, *dr* 84:16, entries 10-12, Table 14).

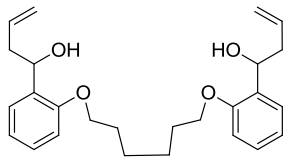
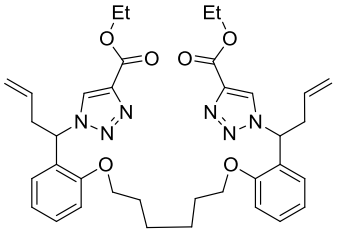
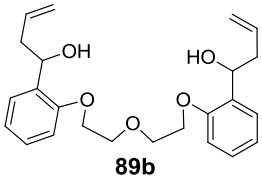
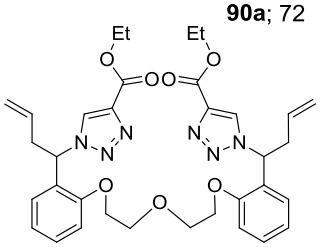
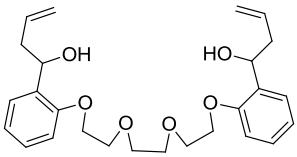
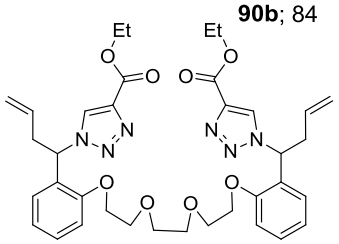
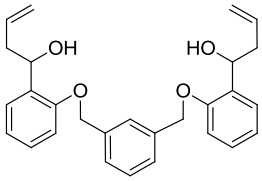
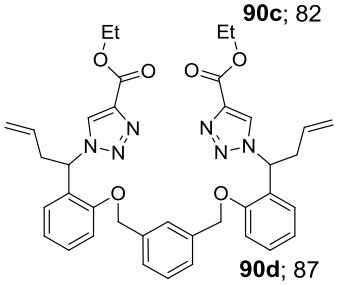
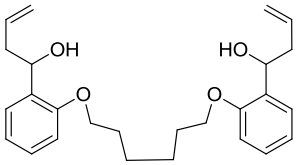
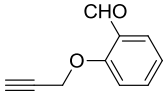
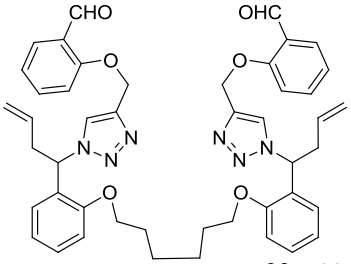
Finally, it was envisaged to elaborate the scope of this work by synthesizing acyclic polyethers embedded with bis-triazole moieties **90** (Scheme 28, generalized structure). In this regard, at first, the bis-homoallylic alcohols **89a-d** were subjected to the azide formation and click reaction sequences as discussed in the Tables 10-14. Notably, the substrates **89a-d** were obtained from the Zn-mediated allylation of their corresponding bis-aldehydes as discussed in Chapters 1 and 2.



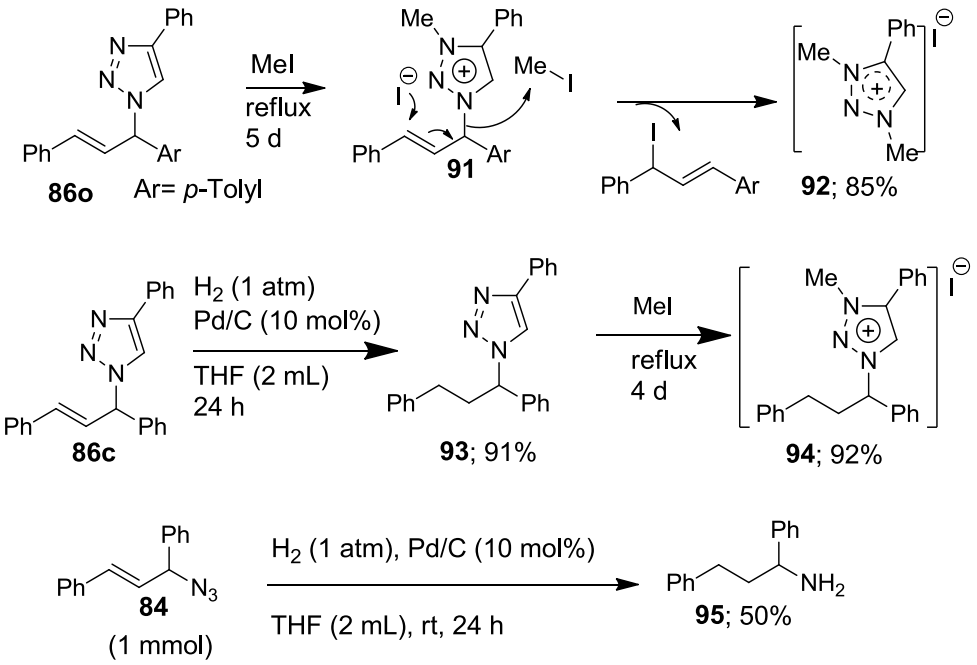
Scheme 28. $Cu(OTf)_2$-catalyzed one-pot synthesis of *bis*-1,2,3-triazoles **90** from *bis*-homoallyl alcohols **89**.

The *bis*-homoallylic alcohols having aliphatic linker **89a**, polyether linker **89b,c** and aromatic linker **89d** were treated with $TMSN_3$ (3 equiv) in the presence of $Cu(OTf)_2$ (10 mol%) at rt in DCM for 3 h. After this period, the solvent was evaporated and the corresponding azides were not isolated and subjected to the click reaction with ethyl propiolate. These reaction sequences gave the corresponding compounds **90a-d** with *bis*-triazole moieties linked through suitable linkers in 72-87% yields, (entries 1-4, Table 15). Similarly, the compound **90e** with *bis*-triazole moieties linked through suitable linkers was obtained in 68% yield from the direct azidation of the corresponding *bis*-homoallylic alcohol **89a** followed by the click reaction with **85i** (entries 5, Table 15).

Table 15. Cu(OTf)$_2$-catalyzed one-pot synthesis of *bis*-1,2,3-triazoles **90a-f** from *bis*-homoallyl alcohols.[a]

Entry	*Bis*-Homoallyl Alcohol	Alkyne	Triazole System **8**: Yield (%)
1	 **89a**	 **85a**	 **90a**; 72
2	 **89b**	**85a**	 **90b**; 84
3	 **89c**	**85a**	 **90c**; 82
4	 **89d**	**85a**	 **90d**; 87
5	 **89a**	 **85i**	 **90e**; 68

[a] Reagents and Conditions: The direct azidation of substrate **89** was carried out using Cu(OTf)$_2$ (10 mol%), $TMSN_3$ (3 equiv) in DCM (3 mL) at rt for 3 h and the solvent was evaporated in vacuum. Then, the click reaction was carried out using alkyne (5 equiv) in THF (2 mL) and water (2 mL) in the presence of *L*-sodium ascorbate (100 mol%) at rt for 20 h.



Scheme 29. Synthetic transformations of 1,2,3-triazole derivative **86c** and conversion of azide **84** into **95**.

In order to reveal the synthetic utility of representative 1,2,3-triazoles, in an initial reaction MeI was treated with the 1,2,3-triazole **86o**. This reaction led to the formation of an ionic liquid-type product **92**. Presumably, in the reaction of MeI with **86o**, the product **92** was formed *via* the loss of the allylic moiety present in the 1,2,3-triazole system **86o** (Scheme 29). To avoid the elimination of the allylic moiety present in the 1,2,3-triazole system, in a succeeding attempt, at first the hydrogenation of the olefin moiety present in the 1,2,3-triazole system **86c** was carried out, which gave the 1,2,3-triazole system **93**. Then, the reaction of the 1,2,3-triazole **93** with MeI gave an ionic liquid-type product **94** (Scheme 29). Further, the hydrogenation of a representative azide compound **84** successfully gave the benzylamine system **95** (1,3-diphenylpropan-1-amine) in 50% yield (Scheme 29).

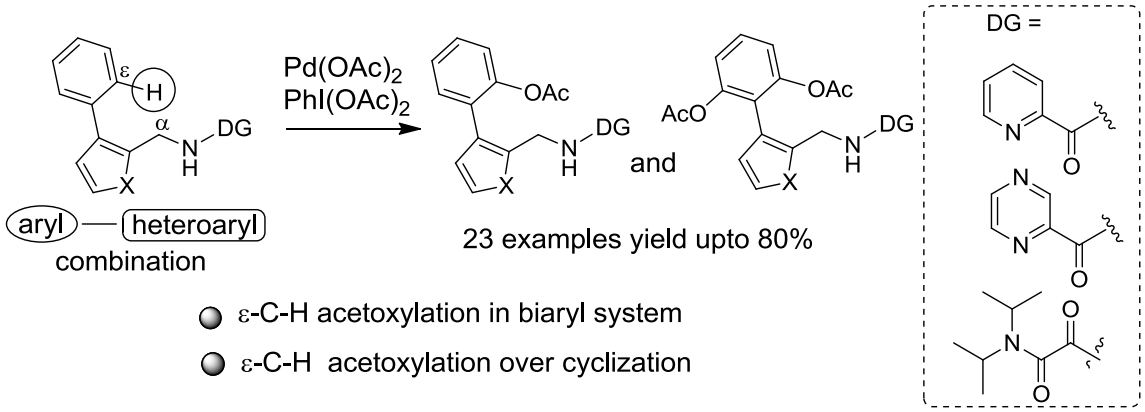
Conclusions

In summary, the Chapter 5a revealed the successful attempts of the Pd(II)-catalyzed, bidentate directing group-aided, chemoselective acetoxylation of remote the ε-C(sp^2)-H bonds over cyclization by using heteroaryl-aryl-based biaryl systems and phenylpropylamine systems.

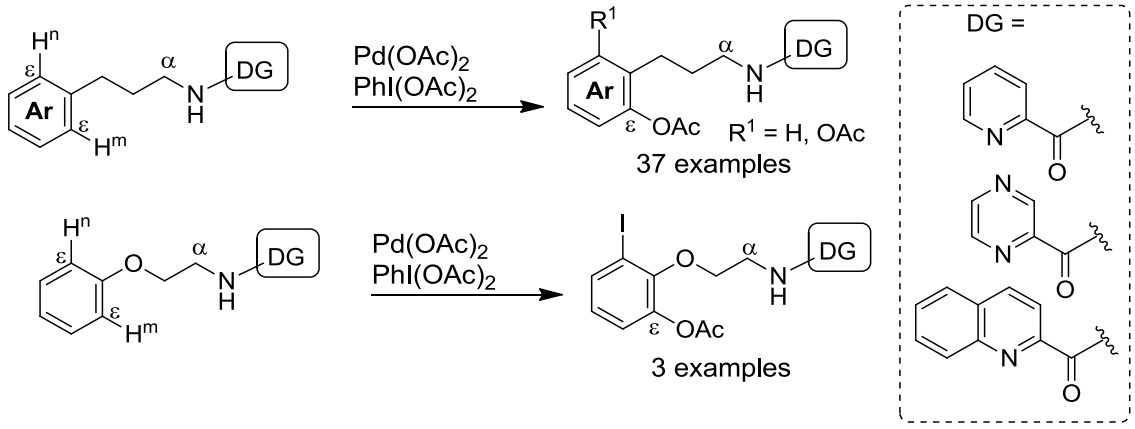
The investigations shown in Chapter 5a and section A, of this thesis revealed that the chemoselective acetoxylation of ε-C-H bond was possible and facilitated by the biaryl substrate design **34**/**37**/**39**/**41** than the biaryl substrate design **33a**.

Given the importance of biaryl systems in medicinal chemistry research, the present work comprising the functionalization of remote ε-C-H bond in biaryl systems will be a contribution towards the enrichment of the library of biaryl systems with the functionalized heteroaryl-aryl-based biaryl systems prepared in this work.

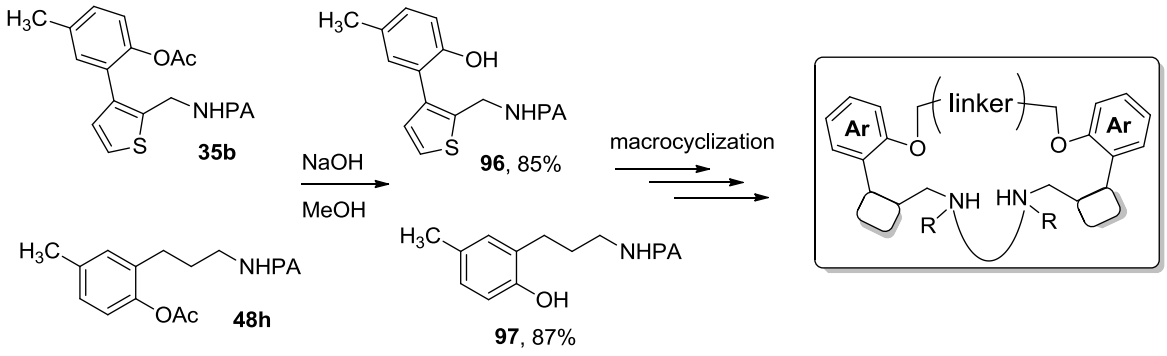
Further, Chapter 5a and section B of this thesis revealed the investigations on the Pd(II)-catalyzed, picolinamide-aided chemoselective acetoxylation of remote ε-C(sp^2)-H bond of phenylpropylamine systems.



The Chapter 5a and section A, revealed the successful attempts on the Pd(II)-catalyzed, bidentate directing group-enabled, chemoselective *ortho* and remote ε-C(sp^2)-H acetoxylation of various 3-phenylpropan-1-amine and 2-phenoxyethanamine systems. Treatment of various 3-phenylpropan-1-amine and 2-phenoxyethanamine systems possessing the bidentate directing groups with $PhI(OAc)_2$ afforded the acetoxylation products over the intramolecular cyclized products. The efficiency of the bidentate directing groups, e.g., PA, QA and PyrA used for the acetoxylation of remote ε-C(sp^2)-H bonds of phenylpropylamine systems was found to be comparable. While the 3-phenylpropan-1-amine systems selectively afforded the corresponding mono/bis ε-C-H acetoxylated products, 2-phenoxyethanamine systems afforded the ε-C-H acetoxylated and iodinated *via* the double ε-C-H functionalization.



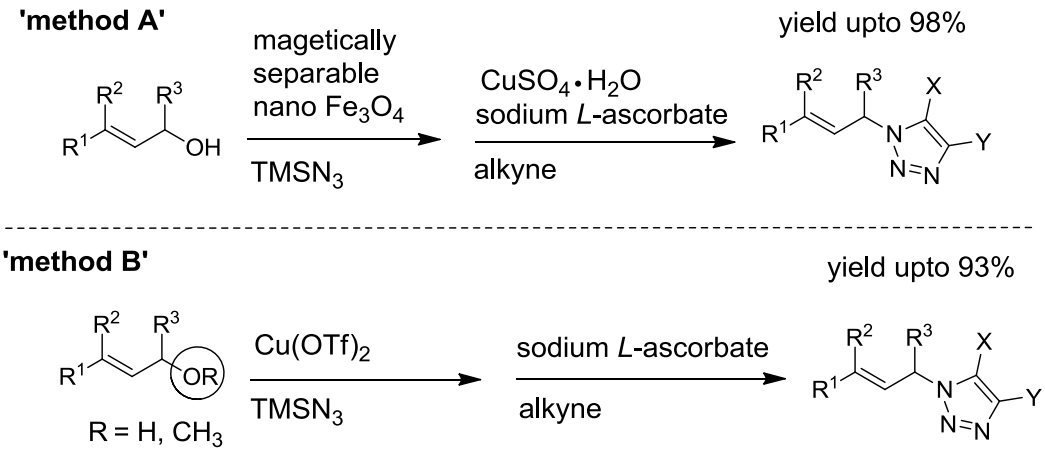
Chapters 1, 2 and 3 revealed the synthesis of macrocyclic crown ether/polyether molecules starting from various hydroxy benzaldehydes. Accordingly, a part of the Chapter 5a of this Thesis intended to synthesize phenolic compounds *via* C-H activation strategy as our group engaged in the development of the C-H activation based strategies.



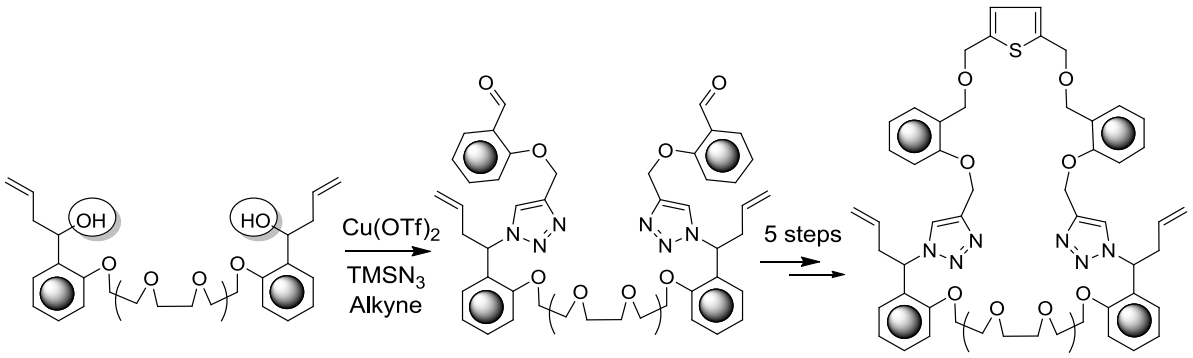
Accordingly, the Chapter 5a showed the successful chemo- and regioselective synthesis of *ortho* C-H acetoxylated 3-phenylpropan-1-amine, 2-phenoxyethanamine systems and heteroaryl-aryl-based biaryl systems *via* the remote ε-C(sp^2)-H functionalization and few of the acetoxylated products (**35b** and **48h**) converted into phenolic compounds (**96** and **97**) *via* the hydrolysis of acetate group. These new classes of hetero-biaryl/aryl phenolic compounds can be used further for the synthesis of macrocyclic molecules.

Finally, the Chapter 5b revealed the investigations on the one-pot direct azidation of allylic alcohols/ethers followed by click reaction. Two different procedures were developed for synthesizing various 1,2,3-triazole derivatives directly from various allylic/benzylic alcohols without isolating the corresponding azides. The first method (Method A) involved magnetic nano Fe_3O_4-catalylzed direct azidation of allylic/benzylic alcohols with $TMSN_3$ as the first step

followed by the Cu-catalyzed click reaction of the corresponding azides with alkynes as the second step. The second method (Method B) involved the $Cu(OTf)_2$-catalyzed direct azidation of various allylic/benzylic alcohols and methyl ethers of allylic/benzylic alcohols with $TMSN_3$ as the first step followed by the click reaction of the corresponding azides with alkynes as the second step. In the second method, $Cu(OTf)_2$ served as a single catalyst for azidation of alcohol and click reaction steps.



The Chapters 1-4 revealed the usage of various bis benzylic alcohols connectd *via* polyether linkers/spacers as the starting materials for the synthesis of new classes of polyether macrocycles. In connection to the works described in Chapters 1-4, Chapter 5b revealed the synthesis bis benzylic azides connectd *via* polyether linkers/spacers starting from bis benzylic alcohols connectd *via* polyether linkers/spacer. Further the bis benzylic azides connectd *via* polyether linkers/spacers were used for synthesizing new classes of 1,2,3-triazole rings-appended polyether chains **90**. 1,2,3-Triazole rings-appended polyether chains were used for the synthesis of new class of polyethers macrocycles embedded with triazole moieties *via* the Glaser-Eglinton-Hay coupling and this part was discussed in Chapter 2.



All the compounds included in the Chapter 5a of this thesis are characterized by various characterization techniques including ^{1}H and ^{13}C NMR, IR and HRMS. The relevant characterization data of all the compounds and complete experimental details are given in the experimental section.

Experimental section

General: IR spectra of compounds were recorded as neat or thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra of all compounds were recorded in 400 and 100 MHz spectrometers, respectively, by using TMS as an internal standard. The HRMS measurements were obtained from QTOF mass analyzer using electrospray ionization (ESI) method. Column chromatography purification was carried out on silica gel (100–200 mesh). Reactions were conducted in anhydrous solvents under a nitrogen atmosphere wherever required. Organic layers obtained after work up were dried using anhydrous Na_2SO_4. Reagents were added to the reaction flask by using a syringe. Thin layer chromatography (TLC) analysis was performed on alumina plates and components were visualized by observation under iodine vapour. Isolated yields of all the products are reported and yields were not optimized. In all the cases, after the Pd(II)-catalyzed acetoxylation reactions, the respective crude reaction mixtures were subjected to column chromatographic purification method. Then, the fractions were collected according to the TLC and in all the cases we focused to isolate the corresponding acetoxylation products reported here to the best of our effort and the column chromatographic purification of the respective crude reaction mixtures did not give and we could not detect any of the corresponding cyclized products in characterizable amount. The starting materials **34a-m/37a-c/39a-d/41a,b** used in this work are known compounds.[3h]

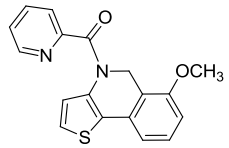
General procedure for assembling the biaryl starting materials 34a-m/37a-c/39a-d *via* the Pd(II)-promoted DG-enabled C-H arylation of the C-3 position of the corresponding 2- or 3-(aminoalkyl)-thiophene and furfurylamine derivatives.[3h] A mixture of appropriate 2- or 3-(aminoalkyl)-thiophene and furfurylamine carboxamides (1 equiv, 0.25 mmol), $Pd(OAc)_2$ (10-30 mol%, 5.5-16.7 mg), AgOAc (1-2.2 equiv, 41-82 mg) or Ag_2CO_3 (2.2-4 equiv, 150-273 mg) and appropriate ArI (3-4 equiv, 0.75-1 mmol) in anhydrous toluene (2.5 mL) was heated at 110 °C for 24–72 h under a nitrogen atm. Then, the reaction mixture was concentrated in vacuo and

purification of the reaction mixture by silica gel column chromatography gave the corresponding C3-arylated compounds **34a-m/37a-c/39a-d**.

General procedure for obtaining the biaryl scaffolds 41a,b *via* the Pd(II)-promoted DG-enabled C-H arylation of the C-3 position of the corresponding 2-(aminoalkyl)-thiophene derivatives.[3h] A mixture of appropriate 2-(aminoalkyl)-thiophene oxalylamide (1 equiv, 0.25 mmol), $Pd(OAc)_2$ (10 mol%, 5.5 mg), AgOAc (1.2-2.2 equiv, 41-82 mg) and ArI (3-4 equiv, 0.75-1 mmol) in anhydrous toluene (1.5 mL) was heated at 110 °C for 2-8 h under a nitrogen atm. Then, the reaction mixture was concentrated in vacuum and purification of the reaction mixture by silica gel column chromatography gave the corresponding C3-arylated compounds **41a,b**.

General procedure for the Pd(II)-catalyzed acetoxylation of remote ε-C(sp^2)-H bond of biaryl systems 33a/34/37/39/41. In a dry 10 mL RB flask containing a mixture of an appropriate biaryl carboxamide **33a/34/37/39/41** (0.15 mmol), $Pd(OAc)_2$ (10 mol%, 3.4 mg) and $PhI(OAc)_2$ (2 equiv, 96.3 mg) in anhydrous toluene (2-2.5 mL) was heated at 110 ^oC for 24 h. After this period, reaction mixture was cooled to rt, and concentrated under vacuo. The resulting residue was purified by silica gel flash chromatography gave the corresponding ε-C-H acetoxylated products (See the corresponding Tables/Schemes for specific entries and conditions).

(6-Methoxythieno[3,2-*c*]isoquinolin-4(5*H*)-yl)(pyridin-2-yl)methanone (33b): The compound

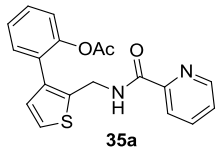


33b

33b was isolated a dark brown colored solid (24 mg, 50%); IR (KBR): ν_{max} 2925, 1651, 1475 and 1266 cm^{-1}; ^1H NMR (CD_3CN, 400 MHz, 70 ^oC): δ 8.59 (1 H, br.s), 7.93-7.89 (1 H, m), 7.64 (1 H, d, J = 7.7 Hz), 7.50-7.47 (1 H, m), 7.36-7.20 (3 H, m), 7.08 (1 H, d, J = 7.3 Hz), 6.95 (1 H, d, J = 8.0 Hz), 5.04 (1 H, br.s), 3.85 (3 H, s); HRMS (ESI): MH^+, found 323.0861. $C_{18}H_{15}N_2O_2S$ requires 323.0854. This compound seems to exist as amide rotomers and we tried to record the NMR for this compound at 70 ^oC. We did not get all the peaks in ^{13}C NMR and a representable ^{13}C NMR spectrum even after 1200 scans and hence, the ^{13}C NMR data is not provided. However, this compound was also characterized by the X-ray structure analysis.

2-(2-(Picolinamidomethyl)thiophen-3-yl)phenyl acetate (35a): The compound **35a** was isolated as a yellow coloured liquid (47 mg, 45%); IR (CH_2Cl_2): ν_{max} 2927, 1767, 1673, 1518,

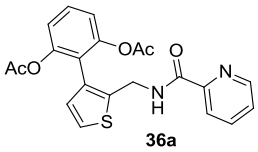
1458 and 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (1 H, d, *J* = 4.6 Hz), 8.45 (1 H, br. s), 8.24 (1 H, d, *J* = 7.8 Hz), 7.86 (1 H, t, *J* = 7.7 Hz), 7.45-7.38 (3 H, m), 7.33 (1 H, t, *J* = 7.4 Hz),



35a

7.27 (1 H, d, *J* = 5.2 Hz), 7.17 (1 H, d, *J* = 7.9 Hz), 6.93 (1 H, d, *J* = 5.2 Hz), 4.71 (2 H, d, *J* = 6.1 Hz), 2.10 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 164.1, 149.7, 148.6, 148.1, 137.7, 137.3, 135.3, 131.3, 129.5, 129.1, 129.0, 126.3, 126.3, 124.1, 122.7, 122.4, 36.8, 20.7; HRMS (ESI): MNa^+, found 375.0769. $C_{19}H_{16}N_2NaO_3S$ requires 375.0779.

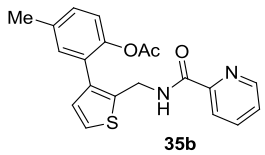
2-(2-(Picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36a): The compound **36a** was isolated as a yellow coloured liquid (20 mg, 16%); IR (CH_2Cl_2): ν_{max} 2931, 1768, 1674,



36a

1518, 1458 and 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (1 H, d, *J* = 4.8 Hz), 8.55 (1 H, br. s), 8.25 (1 H, d, *J* = 7.8 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.6 Hz), 7.47-7.42 (2 H, m), 7.25 (1 H, d, *J* = 5.2 Hz), 7.11 (2 H, d, *J* = 8.2 Hz), 6.83 (1 H, d, *J* = 5.2 Hz), 4.62 (2 H, d, *J* = 6.3 Hz), 2.04 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 164.2, 149.9, 149.8, 148.1, 139.5, 137.3, 129.5, 129.4, 128.7, 126.2, 124.3, 124.0, 122.5, 120.4, 36.5, 20.5; HRMS (ESI): MH^+, found 411.1031. $C_{21}H_{19}N_2O_5S$ requires 411.1015.

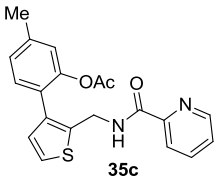
4-Methyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35b): The compound **35b**



35b

was isolated as a yellow coloured liquid (311 mg, 80%); IR (CH_2Cl_2): ν_{max} 2923, 1761, 1675, 1517 and 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.45 (1 H, br. s), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 7.25 (1 H, d, *J* = 5.2 Hz), 7.21 (1 H, dd, J_1 = 8.1 Hz, J_2 = 1.6 Hz), 7.17 (1 H, d, *J* = 1.5 Hz), 7.05 (1 H, d, *J* = 8.1 Hz), 6.92 (1 H, d, *J* = 5.1 Hz), 4.71 (2 H, d, *J* = 6.1 Hz), 2.39 (3 H, s), 2.09 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 164.1, 149.7, 148.1, 146.3, 137.5, 137.3, 136.0, 135.4, 131.8, 129.7, 129.1, 129.1, 126.2, 124.1, 122.4, 122.3, 36.8, 20.9, 20.7; HRMS (ESI): MNa^+, found 389.0952. $C_{20}H_{18}N_2NaO_3S$ requires 389.0936.

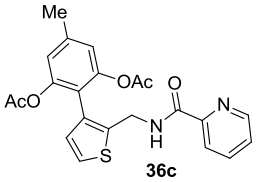
5-Methyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35c): The compound **35c** was isolated as a yellow coloured liquid (34 mg, 47%); IR (CH_2Cl_2): ν_{max} 3055, 2923, 1766, 1675, 1517 and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (1 H, m), 8.44 (1 H, br. s), 8.24 (1 H, d, *J* = 7.8 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz), 7.44 (1 H, dd, J_1 = 7.5 Hz, J_2 =



35c

4.7 Hz), 7.28-7.24 (2 H, m), 7.14 (1 H, d, *J* = 7.7 Hz), 6.99 (1 H, s), 6.92 (1 H, d, *J* = 5.1 Hz), 4.71 (2 H, d, *J* = 6.1 Hz), 2.41 (3 H, s), 2.10 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.1, 149.7, 148.4, 148.1, 139.5, 137.5, 137.3, 135.4, 131.0, 129.1, 127.1, 126.4, 126.2, 124.0, 123.2, 122.4, 36.8, 21.2, 20.7; HRMS (ESI): MH^+, found 367.1130. $C_{20}H_{19}N_2O_3S$ requires 367.1116.

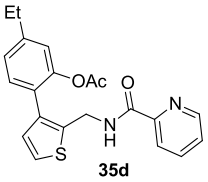
5-Methyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36c): The Compound **36c** was isolated as a yellow coloured liquid (21 mg, 25%); IR (CH_2Cl_2): ν_{max} 2931,



36c

1770, 1675, 1464 and 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (2 H, m), 8.25 (1 H, d, *J* = 7.8 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1 H, m), 7.24 (1 H, d, *J* = 5.2 Hz), 6.92 (2 H, d, *J* = 0.9 Hz), 6.81 (1 H, d, *J* = 5.2 Hz), 4.61 (2 H, d, *J* = 6.3 Hz), 2.42 (3 H, s), 2.02 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.1, 149.8, 149.5, 148.1, 140.0, 139.3, 137.3, 129.6, 128.9, 126.2, 124.2, 122.5, 121.0, 120.8, 36.5, 21.3, 20.5; HRMS (ESI): MH^+, found 425.1188. $C_{22}H_{21}N_2O_5S$ requires 425.1171.

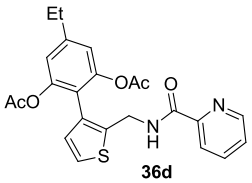
5-Ethyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35d): The compound **35d** was isolated as a yellow coloured liquid (18 mg, 24%); IR (CH_2Cl_2): ν_{max} 2969, 1769, 1676,



35d

1518 and 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.44 (1 H, br. s), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 2 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.44 (1 H, m), 7.29 (1 H, d, *J* = 7.8 Hz), 7.25 (1 H, d, *J* = 5.1 Hz), 7.17 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 7.0 (1 H, d, *J* = 1.5 Hz), 6.93 (1 H, d, *J* = 5.1 Hz), 4.71 (2 H, d, *J* = 6.1 Hz), 2.72 (2 H, q, *J* = 7.6 Hz), 2.10 (3 H, s), 1.29 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.1, 149.7, 148.5, 148.1, 145.7, 137.5, 137.3, 135.4, 131.0, 129.1, 126.6, 126.2, 125.9, 124.0, 122.4, 121.9, 36.8, 28.4, 20.7, 15.1; HRMS (ESI): MH^+, found 381.1292. $C_{21}H_{21}N_2O_3S$ requires 381.1273.

5-Ethyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36d): The

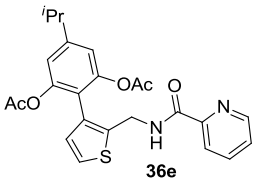


36d

compound **36d** was isolated as a yellow coloured liquid (38 mg, 44%); IR (CH_2Cl_2): ν_{max} 2978, 1764, 1677, 1449 and 1200 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (2 H, m), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1 H, m), 7.24 (1 H, d, *J* = 5.2 Hz), 6.94 (2 H, s), 6.82 (1 H, d, *J* = 5.1 Hz), 4.62 (2 H, d, *J* = 6.3 Hz), 2.73 (2H, q, *J* = 7.6 Hz),

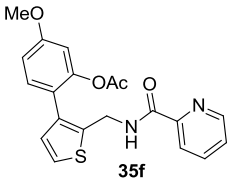
2.03 (6 H, s), 1.30 (3 H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.1, 149.8, 149.6, 148.1, 146.3, 139.3, 137.3, 129.7, 128.9, 126.2, 124.2, 122.4, 120.9, 119.7, 36.5, 28.4, 20.5, 14.7; HRMS (ESI): MH^+, found 439.1350. $C_{23}H_{23}N_2O_5S$ requires 439.1328.

5-Isopropyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36e): The compound **36e** was isolated as a yellow coloured liquid (52 mg, 55%); IR (CH_2Cl_2): ν_{max} 2964, 1770, 1676, 1518 and 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.53 (2 H, m), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1 H, m), 7.24 (1 H, d, J = 5.2 Hz), 6.96 (2 H, s), 6.82 (1 H, d, J = 5.2 Hz), 4.62 (2 H, d, J = 6.3 Hz), 3.00-2.93 (1 H, m), 2.03 (6 H, s), 1.30 (6 H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.2, 151.0, 149.8, 149.6, 148.1, 139.3, 137.3, 129.8, 128.9, 126.2, 124.2, 122.5, 121.0, 118.4, 36.6, 33.8, 23.6, 20.5; HRMS (ESI): MNa^+, found 475.1290. $C_{24}H_{24}N_2NaO_5S$ requires 475.1304.



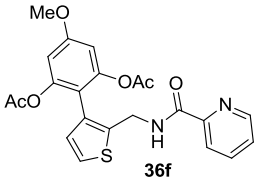
36e

5-Methoxy-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35f): The compound **35f** was isolated as a yellow coloured liquid (21 mg, 35%); IR (CH_2Cl_2): ν_{max} 2937, 1769, 1672, 1518 and 1191 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (1 H, d, J = 4.8 Hz), 8.43 (1 H, br. s), 8.23 (1 H, d, J = 7.8 Hz), 7.86 (1 H, t, J = 7.7 Hz), 7.45-7.42 (1 H, m), 7.28 (1 H, d, J = 8.4 Hz), 7.25 (1 H, d, J = 5.1 Hz), 6.91 (1 H, d, J = 5.2 Hz), 6.90-6.87 (1 H, m), 6.72 (1 H, d, J = 2.4 Hz), 4.70 (2 H, d, J = 6.0 Hz), 3.85 (3 H, s), 2.09 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.1, 160.1, 149.7, 149.4, 148.1, 137.4, 137.3, 135.2, 131.7, 129.2, 126.2, 124.0, 122.4, 121.6, 112.1, 108.4, 55.6, 36.8, 20.7; HRMS (ESI): MNa^+, found 405.0870. $C_{20}H_{18}N_2NaO_4S$ requires 405.0885.



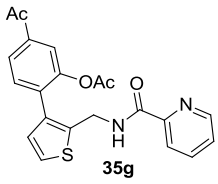
35f

5-Methoxy-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36f): The compound **36f** was isolated as a yellow coloured liquid (18 mg, 27%); IR (CH_2Cl_2): ν_{max} 2935, 1770, 1674, 1518 and 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (2 H, m), 8.26-8.24 (1 H, m), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1 H, m), 7.23 (1 H, d, J = 5.2 Hz), 6.81 (1 H, d, J = 5.2 Hz), 6.66 (2 H, s), 4.62 (2 H, d, J = 6.3 Hz), 3.84 (3 H, s), 2.02 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.2, 160.3, 150.4, 149.8, 148.1, 139.4, 137.3, 129.5, 129.1, 126.2, 124.1, 122.5, 116.0, 106.6, 55.7, 36.5, 20.5; HRMS (ESI): MH^+, found 441.1142. $C_{22}H_{21}N_2O_6S$ requires 441.1120.

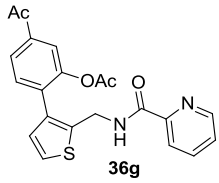


36f

5-Acetyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35g) and 5-acetyl-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36g): The compounds **35g/36g** were isolated as a mixture and yellow coloured liquid (41 mg, 50%). The column chromatographic purification gave the compound **35g/36g** as an inseparable mixture, because both compounds have the same R_f values; repetitive column chromatographic purification of the mixture of compounds **35g/36g** failed to give the corresponding compounds as a pure compounds. Because of mixture of compounds with similar structure, it was difficult to assign the number of protons; hence, we could not provide the proton and carbon NMR data, however, copies of proton/carbon spectra were included in the NMR spectra section. The NMR spectra of the pure sample containing the mixture of compounds **35g/36g** showed the signature peaks corresponding to **35g/36g**. Further, the HRMS analysis of the pure sample containing the mixture of compounds **35g/36g** confirmed the presence of **35g** and **36g** in the mixture. **35g**. HRMS (ESI): MNa^+, found 417.0908. $C_{21}H_{18}N_2NaO_4S$ requires 417.0885; **36g**. HRMS (ESI): MNa^+, found 475.0922. $C_{23}H_{20}N_2NaO_6S$ requires 475.0940.

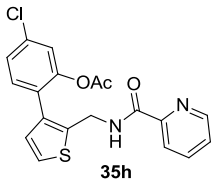


35g



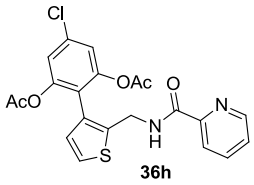
36g

5-Chloro-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35h): The compound **35h** was isolated as a yellow coloured liquid (41 mg, 36%); IR (CH_2Cl_2): ν_{max} 2928, 1770, 1674, 1518 and 1188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.43 (1 H, s), 8.23 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.32-7.31 (2 H, m), 7.27 (1 H, d, J = 5.2 Hz,), 7.20 (1 H, dd, J_1 = 1.6 Hz, J_2 = 0.7 Hz), 6.90 (1 H, d, J = 5.2 Hz), 4.69 (2 H, d, J = 6.1 Hz), 2.10 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.1, 149.6, 149.0, 148.1, 138.1, 137.4, 134.2, 134.1, 132.0, 128.8, 128.2, 126.6, 126.3, 124.4, 123.3, 122.4, 36.8, 20.6; HRMS (ESI): MNa^+, found 409.0388. $C_{19}H_{15}ClN_2NaO_3S$ requires 409.0390.



35h

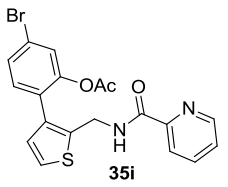
5-Chloro-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36h): The compound **36h** was isolated as a yellow coloured liquid (25 mg, 19%); IR (CH_2Cl_2): ν_{max} 2931, 1773, 1676, 1518 and 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (2 H, m), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.42 (1 H, m), 7.26 (1 H, d, J = 5.2



36h

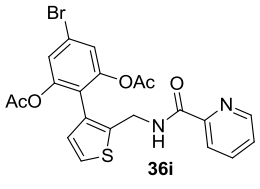
Hz), 7.13 (2 H, s), 6.80 (1 H, d, J = 5.2 Hz), 4.61 (2 H, d, J = 6.3 Hz), 2.03 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 164.2, 150.1, 149.7, 148.1, 139.8, 137.3, 134.4, 128.6, 128.5, 126.3, 124.6, 122.9, 122.5, 121.1, 36.5, 20.4; HRMS (ESI): MH^+, found 445.0646. $C_{21}H_{18}ClN_2O_5S$ requires 445.0625.

5-Bromo-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35i): The compound **35i** was isolated as a yellow coloured liquid (38 mg, 37%); IR (CH_2Cl_2): ν_{max} 2923, 1768, 1672, 1516 and 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.43 (1 H, br. s), 8.23 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.42 (2 H, m), 7.36 (1 H, d, J = 1.9 Hz), 7.28-7.25 (2 H, m), 6.90 (1 H, d, J = 5.2 Hz), 4.69 (2 H, d, J = 6.1 Hz), 2.09 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 164.1, 149.6, 149.0, 148.1, 138.1, 137.4, 134.1, 132.3, 129.5, 128.8, 128.7, 126.3, 126.1, 124.4, 122.4, 121.8, 36.8, 20.6; HRMS (ESI): MH^+, found 431.0051. $C_{19}H_{16}BrN_2O_3S$ requires 431.0065.



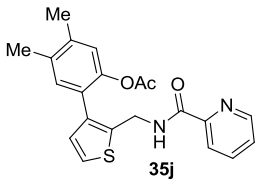
35i

5-Bromo-2-(2-(picolinamidomethyl)thiophen-3-yl)-1,3-phenylene diacetate (36i): The compound **36i** was isolated as a yellow coloured liquid (29 mg, 25%); IR (CH_2Cl_2): ν_{max} 1772, 1674, 1518, and 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (2 H, m), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.42 (1 H, m), 7.28 (2 H, s) 7.25 (1 H, d, J = 5.2 Hz), 6.79 (1 H, d, J = 5.2 Hz), 4.60 (2 H, d, J = 6.1 Hz), 2.03 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 164.2, 150.2, 149.7, 148.1, 139.8, 137.3, 128.6, 128.5, 126.3, 124.6, 124.0, 123.5, 122.5, 121.6, 36.5, 20.4; HRMS (ESI): MNa^+, found 510.9930. $C_{21}H_{17}BrN_2NaO_5S$ requires 510.9939.



36i

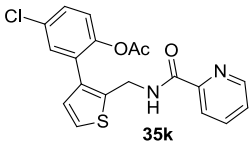
4,5-Dimethyl-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35j): The compound **35j** was isolated as a yellow coloured liquid (41 mg, 60%); IR (CH_2Cl_2): ν_{max} 2973, 1766, 1675, 1636 and 1193 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.45 (1 H, br s), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.41 (1 H, m), 7.23 (1 H, d, J = 5.1 Hz), 7.13 (1 H, s), 6.94 (1 H, s), 6.92 (1 H, d, J = 5.2 Hz), 4.71 (2 H, d, J = 6.1 Hz), 2.30 (3 H, s), 2.28 (3 H, s), 2.09 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 164.0, 149.7,



35j

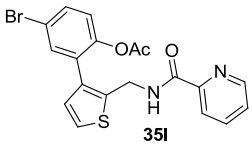
148.1, 146.3, 137.8, 137.3, 137.2, 135.5, 134.7, 132.2, 129.2, 126.4, 126.2, 124.0, 123.4, 122.4, 36.8, 20.7, 19.7, 19.2; HRMS (ESI): MNa^+, found 403.1110. $C_{21}H_{20}N_2NaO_3S$ requires 403.1092.

4-Chloro-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35k): The compound **35k** was isolated as a yellow coloured liquid (18 mg, 40%); IR (CH_2Cl_2): ν_{max} 1767, 1675, 1639, 1517 and 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.45 (1 H, br. s), 8.23 (1 H, dt, J_1 = 7.9 Hz, J_2 = 1.1 Hz), 7.87 (1 H, td, J_1 = 7.3 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.39-7.36 (2 H, m), 7.27 (1 H, d, J = 5.2 Hz), 7.12-7.10 (1 H, m), 6.91 (1 H, d, J = 5.2 Hz), 4.71 (2 H, d, J = 6.1 Hz), 2.1 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.1, 149.6, 148.1, 147.1, 138.3, 137.4, 133.8, 131.6, 131.2, 131.1, 129.0, 128.8, 126.3, 124.5, 124.0, 122.4, 36.7, 20.6; HRMS (ESI): MH^+, found 387.0575. $C_{19}H_{16}ClN_2O_3S$ requires 387.0570.



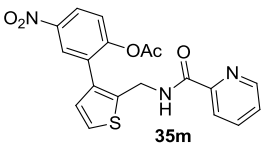
35k

4-Bromo-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35l): The compound **35l** was isolated as a yellow coloured liquid (23 mg, 46%); IR (CH_2Cl_2): ν_{max} 3363, 1762, 1675, 1517 and 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.44 (1 H, br. s), 8.24 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz,), 7.53-7.50 (2 H, m), 7.46-7.43 (1 H, m), 7.26 (1 H, d, J = 5.2 Hz), 7.06-7.04 (1 H, m), 6.90 (1 H, d, J = 5.2 Hz), 4.70 (2 H, d, J = 6.1 Hz), 2.10 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 164.1, 149.6, 148.1, 147.7, 138.3, 137.4, 134.0, 133.7, 132.0, 131.6, 128.8, 126.3, 124.5, 124.4, 122.4, 119.3, 36.7, 20.6; HRMS (ESI): MH^+, found 431.0078. $C_{19}H_{16}BrN_2O_3S$ requires 431.0065.



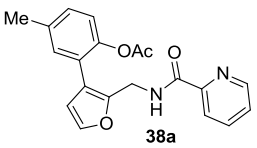
35l

4-Nitro-2-(2-(picolinamidomethyl)thiophen-3-yl)phenyl acetate (35m): The compound **35m** was isolated as a yellow coloured liquid (15 mg, 32%); IR (CH_2Cl_2): ν_{max} 2940, 1769, 1674, 1520 and 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.43 (1 H, br. s), 8.29-8.26 (2 H, m), 8.21 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1 H, m), 7.37-7.34 (1 H, m), 7.33 (1 H, d, J = 5.2 Hz), 6.95 (1 H, d, J = 5.2 Hz), 4.71 (2 H, d, J = 6.1 Hz), 2.15 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 164.1, 153.4, 149.4, 148.1, 145.6, 139.0, 137.4, 132.8, 131.2, 128.7, 126.8, 126.4, 124.9, 124.4, 123.9, 122.4, 36.7, 20.6; HRMS (ESI): MH^+, found 398.0826. $C_{19}H_{16}N_3O_5S$ requires 398.0811.



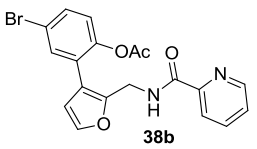
35m

4-Methyl-2-(2-(picolinamidomethyl)furan-3-yl)phenyl acetate (38a): The compound **38a** was isolated as a yellow coloured liquid (33 mg, 53%); IR (CH_2Cl_2): ν_{max} 1762, 1676, 1521, 1435 and 1194 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.35 (1 H, br. s), 8.24-8.22 (1 H, m),7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (2 H, m), 7.20 (1 H, d, J = 1.9 Hz), 7.16 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 7.02 (1 H, d, J = 8.2 Hz), 6.43 (1 H, d, J = 1.8 Hz), 4.68 (2H, d, J = 5.8 Hz), 2.36 (3 H, s), 2.18 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.1, 149.7, 148.1, 147.5, 146.2, 141.9, 137.3, 136.1, 131.7, 129.5, 126.2, 125.9, 122.4, 119.0, 112.2, 35.3, 20.9; HRMS (ESI): MH^+, found 351.1349. $C_{20}H_{19}N_2O_4$ requires 351.1345.



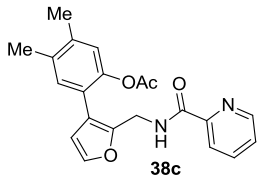
38a

4-Bromo-2-(2-(picolinamidomethyl)furan-3-yl)phenyl acetate (38b): The compound **38b** was isolated as a yellow coloured liquid (19 mg, 32%); IR (CH_2Cl_2): ν_{max} 2928, 1764, 1674, 1521 and 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.34 (1 H, br. s), 8.23 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.56 (1 H, d, J = 2.4 Hz), 7.47-7.42 (3 H, m), 7.02 (1 H, d, J = 8.6 Hz), 6.41 (1 H, d, J = 1.9 Hz), 4.68 (2 H, d, J = 5.8 Hz), 2.18 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.2, 149.6, 148.1, 148.0, 147.5, 142.1, 137.3, 133.8, 131.7, 128.5, 126.3, 124.4, 122.4, 119.3, 117.7, 112.0, 35.3, 20.8; HRMS (ESI): MNa^+, found 437.0100. $C_{19}H_{15}BrN_2NaO_4$ requires 437.0113.



38b

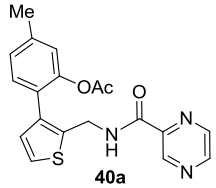
4,5-Dimethyl-2-(2-(picolinamidomethyl)furan-3-yl)phenyl acetate (38c): The compound **38c** was isolated as a yellow coloured liquid (25 mg, 35%); IR (CH_2Cl_2): ν_{max} 2919, 1761, 1674, 1519 and 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.34 (1 H, br. s), 8.23 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.43 (1 H, m), 7.42 (1 H, d, J = 1.8 Hz), 7.15 (1 H, s), 6.91 (1 H, s), 6.41 (1 H, d, J = 1.8 Hz), 4.68 (2 H, d, J = 5.7 Hz), 2.27 (3 H, s), 2.26 (3 H, s), 2.17 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 164.1, 149.7, 148.1, 147.3, 146.2, 141.8, 137.6, 137.3, 134.8, 132.0, 126.2, 123.5, 123.2, 122.4, 118.9, 112.3, 35.3, 20.9, 19.6, 19.2; HRMS (ESI): MNa^+, found 387.1309. $C_{21}H_{20}N_2NaO_4$ requires 387.1321.



38c

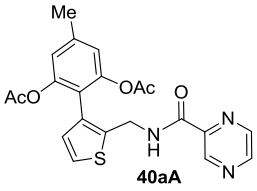
5-Methyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (40a): The compound **40a** was isolated as a yellow coloured liquid (15 g, 39%); IR (CH_2Cl_2): ν_{max} 2969, 1766, 1676, 1521 and 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (1 H, d, J = 1.4 Hz), 8.75

(1 H, d, *J* = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.4 Hz), 8.19 (1 H, br. s), 7.26 (1 H, d, *J* = 5.2 Hz), 7.24 (1 H, d, *J* = 7.7 Hz), 7.14 (1 H, dd, J_1 = 7.7 Hz, J_2 = 0.8 Hz), 6.98 (1 H, s), 6.92 (1 H, d, *J* = 5.2 Hz), 4.72 (2 H, d, *J* = 6.1 Hz), 2.41 (3 H, s), 2.07 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 162.7, 148.4, 147.3, 144.6, 144.4, 142.6, 139.6, 136.8, 135.7, 130.9, 129.2, 127.2, 126.3, 124.2, 123.1, 36.7, 21.2, 20.7; HRMS (ESI): MNa^+, found 390.0875. $C_{19}H_{17}N_3NaO_3S$ requires 390.0888.



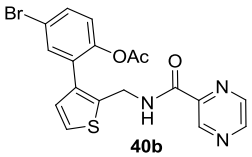
40a

5-Methyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)-1,3-phenylene diacetate (40aA): The compound **40aA** was isolated as a yellow coloured liquid (7 mg, 13%); IR (CH_2Cl_2): ν_{max} 2927, 1761, 1677, 1520 and 1179 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (1 H, s), 8.74 (1 H, d, *J* = 2.4 Hz), 8.52 (1 H, s), 8.32 (1 H, br. s), 7.25 (1 H, d, *J* = 5.2 Hz), 6.91 (2 H, s), 6.82 (1 H, d, *J* = 5.2 Hz), 4.63 (2 H, d, *J* = 6.2 Hz), 2.42 (3 H, s), 2.01 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 162.8, 149.5, 147.2, 144.6, 144.6, 142.6, 140.3, 138.7, 129.9, 129.0, 124.5, 121.0, 120.8, 36.5, 21.3, 20.5; HRMS (ESI): MNa^+, found 448.0929. $C_{21}H_{19}N_3NaO_5S$ requires 448.0943.



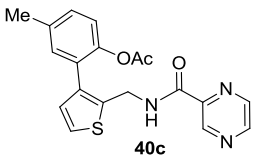
40aA

4-Bromo-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (40b): The compound **40b** was isolated as a yellow coloured liquid (28 mg, 44%); IR (CH_2Cl_2): ν_{max} 2927, 1762, 1676, 152, 1477 and 1190 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (1 H, d, *J* = 1.4 Hz), 8.76 (1 H, d, *J* = 2.4 Hz), 8.53-8.52 (1 H, m), 8.19 (1 H, br. s), 7.53-7.50 (2 H, m), 7.28 (1 H, d, *J* = 5.2 Hz), 7.05-7.03 (1 H, m), 6.91 (1 H, d, *J* = 5.2 Hz), 4.73 (2 H, d, *J* = 6.1 Hz), 2.07 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 162.8, 147.7, 147.4, 144.6, 144.2, 142.6, 137.7, 134.0, 134.0, 132.1, 131.6, 128.8, 124.6, 124.3, 119.3, 36.6, 20.6; HRMS (ESI): MNa^+, found 453.9820. $C_{18}H_{14}BrN_3NaO_3S$ requires 453.9837.



40b

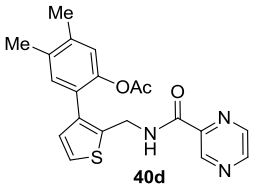
4-Methyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (40c): The compound **40c** was isolated as a coloured less liquid (35 mg, 57%); IR (CH_2Cl_2): ν_{max} 2931, 1762, 1677, 1522 and 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (1 H, d, *J* = 1.2 Hz), 8.75 (1 H, d, *J* = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.3 Hz, J_2 = 1.5 Hz), 8.21 (1 H, br. s), 7.26 (1 H, d, *J* = 5.2 Hz), 7.20 (1 H, dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz), 7.16 (1 H, d, *J* = 1.9 Hz), 7.03 (1 H, d, *J* = 8.2



40c

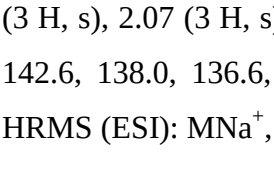
Hz), 6.93 (1 H, d, *J* = 5.2 Hz), 4.74 (2 H, d, *J* = 6.1 Hz), 2.38 (3 H, s), 2.07 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 162.7, 147.3, 146.3, 144.6, 144.4, 142.6, 136.8, 136.1, 135.7, 131.7, 129.8, 129.1, 129.0, 124.2, 122.3, 36.7, 20.9, 20.7; HRMS (ESI): MH^+, found 368.1072. $C_{19}H_{18}N_3O_3S$ requires 368.1069.

4,5-Dimethyl-2-(2-((pyrazine-2-carboxamido)methyl)thiophen-3-yl)phenyl acetate (40d): The compound **40d** was isolated as a colourless liquid (24 mg, 50%); IR (CH_2Cl_2): ν_{max} 2927, 1760, 1676, 1521 and 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (1 H, d, *J* = 1.2 Hz), 8.75 (1 H, d, *J* = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz), 8.20 (1 H, br. s,), 7.25 (1 H, d, *J* = 5.2 Hz), 7.11 (1 H, br. s), 6.94 (1 H, s), 6.92 (1 H, d, *J* = 5.2 Hz), 4.73 (2 H, d, *J* = 6.0 Hz,), 2.30 (3 H, s), 2.28 (3 H, s), 2.07 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.7, 147.3, 146.3, 144.6, 144.4, 142.6, 138.0, 136.6, 135.8, 134.7, 132.1, 129.2, 126.4, 124.1, 123.4, 36.7, 20.7, 19.7, 19.2; HRMS (ESI): MNa^+, found 404.1031. $C_{20}H_{19}N_3NaO_3S$ requires 404.1045.



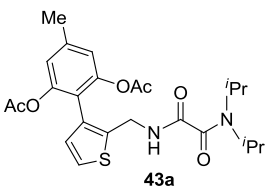
40d

2-(2-((2-(diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-5-methylphenyl acetate (42a): The compound **42a** was isolated as a yellow coloured liquid (22 mg, 35%); IR (CH_2Cl_2): ν_{max} 2925, 1767, 1676, 1633, 1446 and 1203 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 5.1 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.14-7.12 (m, 2H), 6.96 (br s, 1H), 6.90 (d, *J* = 5.1 Hz, 1H), 4.62-4.56 (m, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.53-3.46 (m, 1H), 2.41 (s, 3H), 2.05 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 163.0, 162.9, 148.4, 139.6, 136.3, 135.8, 130.8, 129.1, 127.2, 126.2, 124.2, 123.1, 46.7, 46.4, 36.2, 21.2, 20.8, 20.7, 20.0; HRMS (ESI): *m/z* $[M + Na]^+$calcd for $C_{22}H_{28}N_2NaO_4S$: 439.1667; found 439.1649.



42a

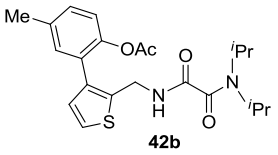
2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-5-methyl-1,3-phenylene diacetate (43a): The compound **43a** was isolated as a yellow coloured liquid (23 mg, 33%); IR (CH_2Cl_2): ν_{max} 2973, 1771, 1638, 1368 and 1193 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (1 H, d, *J* = 5.3 Hz), 6.90 (2 H, s), 6.81 (1 H, d, *J* = 5.3 Hz), 4.57-4.51 (1 H, m), 4.44 (2 H, d, *J* = 6.1 Hz), 3.53-3.46 (1 H, m), 2.42 (3 H, s), 2.00 (6 H, s), 1.42 (6 H, d, *J* = 6.8 Hz), 1.21 (6H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 163.3, 163.1, 149.4, 140.3, 138.1, 130.0, 129.0,



43a

124.5, 121.0, 120.6, 49.7, 46.3, 36.1, 21.3, 20.8, 20.4, 20.0; HRMS (ESI): MH^+, found 475.1903. $C_{24}H_{31}N_2O_6S$ requires 475.1898.

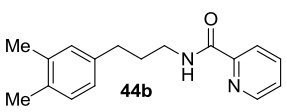
2-(2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl)-4-methylphenyl acetate (42b): The compound **42b** was isolated as a yellow coloured liquid (9 mg, 15%); IR (CH_2Cl_2): ν_{max} 2973, 1766, 1636 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (1 H, d, *J* = 5.1 Hz), 7.21-7.19 (2 H, m), 7.13 (1 H, d, *J* = 1.9 Hz), 7.02 (1 H, d, *J* = 8.2 Hz), 6.91 (1 H, d, *J* = 5.2 Hz), 4.62-4.56 (1 H, m), 4.53 (2 H, d, *J* = 5.9 Hz), 3.54-3.47 (1 H, m), 2.39 (3 H, s), 2.05 (3 H, s), 1.42 (6 H, d, *J* = 6.8 Hz), 1.22 (6 H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 163.0, 162.9, 146.3, 136.4, 136.1, 135.9, 131.6, 129.8, 129.1, 128.9, 124.3, 122.3, 49.7, 46.4, 36.3, 20.9, 20.8, 20.6, 20.0; HRMS (ESI): MNa^+, found 439.1652. $C_{22}H_{28}N_2NaO_4S$ requires 439.1667.



42b

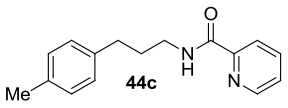
General procedure for the preparation of 44b-z and **44aa *via* Pd(II)-catalyzed arylation of *N*-alkylamide 43c-e.**[20j] An appropriate *N*-alkylamide **43** (1 mmol, 1 equiv), $Pd(OAc)_2$ (10-15 mol%, 22.3-33.5 mg), an appropriate iodo compound (4.0 equiv), AgOAc (1.2 mmol, 198 mg) was heated at 150 ^oC, for 72 h under a nitrogen atmosphere. After the reaction period, the reaction was cooled to rt and concentrated in vacuum and purification of the resulting crude reaction mixture by column chromatography on silica gel furnished the corresponding γ-arylated *N*-alkylamide **44b-z** and **44aa** (see Tables/Schemes for specific examples).

***N*-(3-(3,4-Dimethylphenyl)propyl)picolinamide (44b).** Brown colour liquid (192 mg, 72%); IR (CH_2Cl_2): ν_{max} 2928, 1674, 1501, 1427 and 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.55 (1 H, m), 8.21 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.12 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 7.07 (1 H, d, *J* = 7.6 Hz), 7.01 (1 H, s), 6.97 (1 H, d, *J* = 7.6 Hz), 3.53 (2 H, q, *J* = 6.9 Hz), 2.69 (2 H, t, *J* = 7.9 Hz), 2.25 (3 H, s), 2.44 (3 H, s), 2.01-1.94 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.0, 148.0, 138.9, 137.4, 136.5, 134.0, 129.8, 129.7, 126.1, 125.7, 122.2, 39.1, 32.8, 31.4, 19.8, 19.3; HRMS (ESI): MH^+, found 269.1661. $C_{17}H_{21}N_2O$ requires 269.1654.



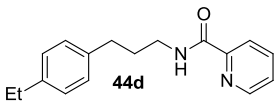
44b

***N*-(3-(*p*-Tolyl)propyl)picolinamide (44c).** Brown colour liquid (165 mg, 65%); IR (CH_2Cl_2): ν_{max} 2927, 1674, 1527, 1464 and 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.12 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz),

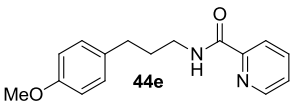


7.45-7.42 (1 H, m), 7.12 (4 H, s), 3.53 (2 H, q, *J* = 6.9 Hz), 2.71 (2 H, t, *J* = 7.4 Hz), 2.33 (3 H, s), 2.01-1.94 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.0, 148.0, 138.3, 137.4, 135.4, 129.1, 128.3, 126.1, 122.2, 39.0, 32.8, 31.4, 21.0; HRMS (ESI): MH^+, found 255.1491. $C_{16}H_{19}N_2O$ requires 255.1497.

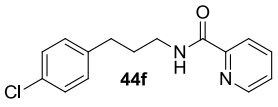
***N*-(3-(4-Ethylphenyl)propyl)picolinamide (44d).** Brown colour liquid (171 mg, 64%); IR (CH_2Cl_2): ν_{max} 2963, 1674, 1527, 1464 and 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (1 H, m), 8.23 (1 H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 8.12 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 7.15 (4 H, s), 3.53 (2 H, q, *J* = 6.9 Hz), 2.72 (2 H, t, *J* = 7.4 Hz), 2.63 (2 H, q, *J* = 7.5 Hz), 2.05-1.95 (2 H, m), 1.24 (3 H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.0, 148.0, 141.8, 138.6, 137.4, 128.3, 127.9, 126.1, 122.2, 39.0, 32.8, 31.3, 28.4, 15.7; HRMS (ESI): MH^+, found 269.1661. $C_{17}H_{21}N_2O$ requires 269.1654.



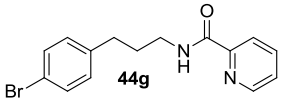
***N*-(3-(4-Methoxyphenyl)propyl)picolinamide (44e).** Brown colour liquid (159 mg, 59%); IR (CH_2Cl_2): ν_{max} 3057, 1673, 1527, and 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.55 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.11 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 7.15 (2 H, d, *J* = 8.6 Hz), 6.85 (2 H, d, *J* = 8.7 Hz), 3.80 (3 H, s), 3.51 (2 H, q, *J* = 7.0 Hz), 2.69 (2 H, t, *J* = 7.5 Hz), 2.00-1.93 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 157.9, 150.0, 148.0, 137.4, 133.5, 129.3, 126.1, 122.2, 113.9, 52.3, 39.0, 32.4, 31.5; HRMS (ESI): MH^+, found 271.1451. $C_{16}H_{19}N_2O_2$ requires 271.1447.



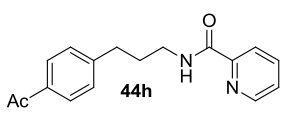
***N*-(3-(4-Chlorophenyl)propyl)picolinamide (44f).** Brown colour liquid (178 mg, 65%); IR (CH_2Cl_2): ν_{max} 2933, 1673, 1528, 1492 and 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.21 (1 H, d, *J* = 7.8 Hz), 8.11 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 7.25 (2 H, d, *J* = 8.4 Hz), 7.15 (2 H, d, *J* = 8.4 Hz), 3.51 (2 H, q, *J* = 6.9 Hz), 2.70 (2 H, t, *J* = 7.5 Hz), 2.00-1.92 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.8, 148.0, 139.9, 137.4, 131.7, 129.8, 128.5, 126.2, 122.2, 38.9, 32.7, 31.2; HRMS (ESI): MH^+, found 275.0960. $C_{15}H_{16}ClN_2O$ requires 275.0951.



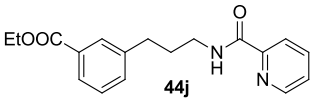
***N*-(3-(4-Bromophenyl)propyl)picolinamide (44g).** Brown colour liquid (248 mg, 78%); IR (CH_2Cl_2): ν_{max} 2926, 1672, 1527, 1488 and 1433 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.55 (1 H, m), 8.21 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.10 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.40 (3 H, m), 7.10 (2 H, d, J = 8.4 Hz), 3.52 (2 H, q, J = 6.9 Hz), 2.70 (2 H, t, J = 7.5 Hz), 2.01-1.93 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 149.9, 148.0, 140.4, 137.4, 131.5, 130.2, 126.2, 122.2, 119.7, 38.9, 32.7, 31.1; HRMS (ESI): MH^+, found 319.0434. $C_{15}H_{16}BrN_2O$ requires 319.0446.



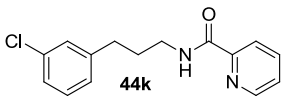
***N*-(3-(4-Acetylphenyl)propyl)picolinamide (44h).** Brown colour liquid (169 mg, 60%); IR (CH_2Cl_2): ν_{max} 2930, 1678, 1606, 1528 and 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (1 H, m), 8.20-8.17 (1 H, m), 8.13 (1 H, br. s), 7.88-7.82 (3 H, m), 7.44-7.40 (1 H, m), 7.30 (2 H, d, J = 8.1 Hz), 3.52 (2 H, q, J = 6.7 Hz), 2.78 (2 H, t, J = 7.9 Hz), 2.57 (3 H, s), 2.00-1.96 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 164.4, 149.8, 148.0, 147.3, 137.4, 135.1, 128.6, 126.2, 122.2, 38.9, 33.3, 30.9, 26.6; HRMS (ESI): MH^+, found 283.1451. $C_{17}H_{19}N_2O_2$ requires 283.1447.



Ethyl 3-(3-(picolinamido)propyl)benzoate (44j). Brown colour liquid (215 mg, 69%); IR (CH_2Cl_2): ν_{max} 2939, 1716, 1674, 1527 and 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.20 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.13 (1 H, br. s), 7.91-7.84 (3 H, m), 7.46-7.38 (2 H, m), 7.36 (1 H, t, J = 7.6 Hz), 4.38 (2 H, q, J = 7.2 Hz), 3.54 (2 H, q, J = 6.9 Hz), 2.80 (2 H, t, J = 7.5 Hz), 2.06-1.98 (2 H, m,), 1.41 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 164.3, 149.9, 148.0, 141.7, 137.4, 133.0, 130.6, 129.4, 128.5, 127.3, 126.1, 122.2, 61.0, 39.0, 33.1, 31.2, 14.4; HRMS (ESI): MH^+, found 313.1563. $C_{18}H_{21}N_2O_3$ requires 313.1552.

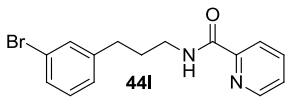


***N*-(3-(3-Chlorophenyl)propyl)picolinamide (44k).** Brown colour liquid (164 mg, 60%); IR (CH_2Cl_2): ν_{max} 2928, 1674, 1501 and 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (1 H, d, J = 4.5 Hz), 8.20 (1 H, d, J = 8.9 Hz), 8.13 (1 H, br. s), 7.85 (1 H, td, J_1 = 9.3 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1 H, m), 7.23-7.14 (3 H, m), 7.09 (1 H, d, J = 7.4 Hz), 3.52 (2 H, q, J = 6.9 Hz), 2.71 (2 H, t, J = 7.5 Hz), 2.01-1.93 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.0, 148.0, 143.5, 137.4, 134.2, 129.7,



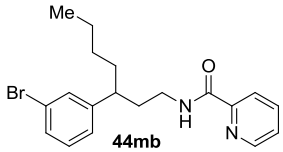
128.5, 126.6, 126.1, 122.2, 38.9, 33.0, 31.1; HRMS (ESI): MH^+, found 275.0940. $C_{15}H_{16}ClN_2O$ requires 275.0951.

***N*-(3-(3-Bromophenyl)propyl)picolinamide (44l).** Brown colour liquid (216 mg, 68%); IR (CH_2Cl_2): ν_{max} 2932, 1673, 1527, 1434 and 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.20 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.13 (1 H, br. s), 7.85 (1 H, td, J_1 = 9.4 Hz, J_2 = 1.7 Hz), 7.44-7.41 (1 H, m), 7.36 (1 H, d, J = 0.7 Hz), 7.33-7.29 (1 H, m), 7.15-7.13 (2 H, m), 3.52 (2 H, q, J = 6.9 Hz), 2.70 (2 H, t, J = 7.5 Hz), 2.01-1.93 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 149.9, 148.0, 143.8, 137.4, 131.4, 130.0, 129.1, 127.1, 126.2, 122.5, 122.2, 38.9, 33.0, 31.1; HRMS (ESI): MH^+, found 319.0455. $C_{15}H_{16}BrN_2O$ requires 319.0446.



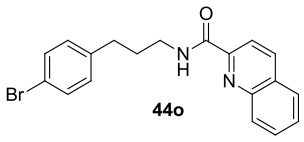
44l

***N*-(3-(3-Bromophenyl)heptyl)picolinamide (44mb).** Yellow colour liquid (86 mg, 25%); IR (CH_2Cl_2): ν_{max} 2928, 1676, 1568, 1527 and 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.52 (1 H, m), 8.17 (1 H, d, J = 7.8 Hz), 7.97 (1 H, br. s), 7.83 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.43-7.40 (1 H, m), 7.34-7.30 (2 H, m), 7.18-7.11 (2 H, m), 3.37-3.28 (2 H, m), 2.63-2.57 (1 H, m), 2.05-2.02 (1 H, m), 1.89-1.84 (1 H, m), 1.66-1.62 (1 H, m), 1.59-1.55 (1 H, m), 1.31-1.69 (4 H, m), 0.83 (3 H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 149.9, 148.0, 147.5, 137.3, 130.5, 130.1, 129.3, 126.4, 126.1, 122.7, 122.1, 43.9, 37.9, 36.6, 36.3, 29.6, 22.7, 14.0; HRMS (ESI): MH^+, found 375.1065. $C_{19}H_{24}BrN_2O$ requires 375.1072.



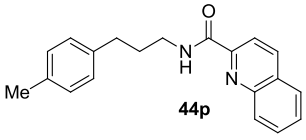
44mb

***N*-(3-(4-Bromophenyl)propyl)quinoline-2-carboxamide (44o).** Brown colour liquid (176 mg, 48%); IR (CH_2Cl_2): ν_{max} 2934, 1674, 1529, 1501, 1426 and 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (1 H, br. s), 8.32 (2 H, s), 8.11 (1 H, d, J = 8.4 Hz), 7.90 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.81-7.76 (1 H, m), 7.65-7.61 (1 H, m), 7.42 (2 H, dd, J = 6.5 Hz, J_2 = 1.8 Hz), 7.12 (2 H, d, J = 8.4 Hz), 3.59 (2 H, q, J = 6.9 Hz), 2.73 (2 H, t, J = 7.4 Hz), 2.06-1.99 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 149.7, 146.5, 140.5, 137.5, 131.5, 130.2, 130.1, 129.7, 129.3, 127.9, 127.8, 119.7, 118.8, 39.1, 32.8, 31.2; HRMS (ESI): MH^+, found 369.0617. $C_{19}H_{18}BrN_2O$ requires 369.0603.



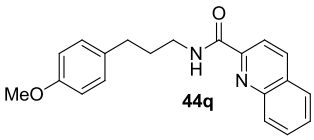
44o

***N*-(3-(*p*-Tolyl)propyl)quinoline-2-carboxamide (44p).** Brown colour liquid (124 mg, 41%); IR (CH_2Cl_2): ν_{max} 2933, 1674, 1528, 1465 and 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34-8.33 (3 H, m), 8.12 (1 H, d, *J* = 8.5 Hz), 7.89 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz), 7.81-7.76 (1 H, m), 7.65-7.61 (1 H, m), 7.16-7.11 (4 H, m), 3.60 (2 H, q, *J* = 6.9 Hz), 2.75 (2 H, t, *J* = 7.5 Hz), 2.32 (3 H, s), 2.08-2.01 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 149.9, 146.5, 138.4, 137.5, 135.4, 130.1, 129.7, 129.3, 129.2, 128.3, 127.8, 127.8, 118.9, 39.2, 32.9, 31.4, 21.0; HRMS (ESI): MH^+, found 305.1656. $C_{20}H_{21}N_2O$ requires 305.1654.



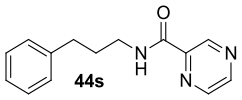
44p

***N*-(3-(4-Methoxyphenyl)propyl)quinoline-2-carboxamide (44q).** Brown colour liquid (128 mg, 40%); IR (CH_2Cl_2): ν_{max} 2933, 1672, 1533, 1400 and 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33-8.31 (3 H, m), 8.12 (1 H, d, *J* = 8.4 Hz), 7.90 (1 H, d, *J* = 8.1 Hz), 7.79 (1 H, t, *J* = 7.9 Hz), 7.64 (1 H, t, *J* = 7.7 Hz), 7.18 (2 H, d, *J* = 8.4 Hz), 6.86 (2 H, d, *J* = 8.5 Hz), 3.79 (3 H, s), 3.59 (2 H, q, *J* = 6.8 Hz), 2.73 (2 H, t, *J* = 7.5 Hz), 2.07-1.99 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 157.9, 149.9, 146.5, 137.5, 133.5, 130.1, 129.7, 129.3, 129.3, 127.8, 127.8, 118.8, 113.9, 55.2, 39.2, 32.5, 31.5; HRMS (ESI): MH^+, found 321.1591. $C_{20}H_{21}N_2O_2$ requires 321.1603.



44q

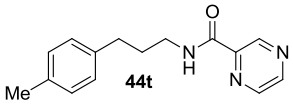
Procedure for the synthesis of *N*-(3-phenylpropyl)pyrazine-2-carboxamide (44s). To a round bottom flask, pyrazine-2-carboxylic acid (2 mmol, 246 mg), DMF (2-3 drops) and DCM (12 mL) were added under a nitrogen atmosphere. Then, to the reaction mixture was added oxalyl chloride (3 mmol, 378 mg) dropwise at 0 °C. The mixture was stirred at rt for 12 h, and then the solvent was removed in vacuum. To another round bottom flask an appropriate alkyl amine (1.8 mmol), Et_3N (1.5-2 mmol, 152-203 mg), DMAP (0.1 mmol, 12 mg) and DCM (12 mL) were added. A solution of the acid chloride in DCM (5 mL) (prepared in the previous step) was added dropwise to the solution containing alkyl amine at 0 °C. Then, the resulting reaction mixture was warmed to rt and stirred at rt for overnight. After this period, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were dried over anhydrous MgSO4, and evaporated in vacuum. The crude reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc = 70:30) to afford the corresponding product **44s** as



44s

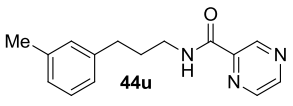
a colourless solid (261 mg, 60%); mp: 88-90 ^{o}C; IR (CH_2Cl_2): ν_{max} 2950, 1667, 1533, 1248 and 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (1 H, d, J = 1.5 Hz), 8.76 (1 H, d, J = 2.4 Hz), 8.52 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz), 7.85 (1 H, br. s), 7.32-7.18 (2 H, m), 7.23-7.18 (3 H, m), 3.55 (2 H, q, J = 6.9 Hz), 2.75 (2 H, t, J = 7.4 Hz), 2.04-1.97 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 147.2, 144.5, 144.4, 142.5, 141.2, 128.5, 128.4, 126.0, 39.0, 33.3, 31.1; HRMS (ESI): MH^+, found 242.1282. $C_{14}H_{16}N_3O$ requires 242.1293.

***N*-(3-(*p*-Tolyl)propyl)pyrazine-2-carboxamide (44t).** Brown colour liquid (122 mg, 48%); IR (CH_2Cl_2): ν_{max} 2933, 1668, 1533, 1457 and 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (1 H, d, J = 1.5 Hz), 8.75 (1 H, d, J = 2.5 Hz), 8.52 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz), 7.86 (1 H, br. s), 7.11 (4 H, s), 3.53 (2 H, q, J = 6.9 Hz), 2.70 (2 H, t, J = 7.5 Hz), 2.32 (3 H, s), 2.01-1.94 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 147.2, 144.5, 144.4, 142.5, 138.1, 135.5, 129.2, 128.3, 39.0, 32.8, 31.2, 21.0; HRMS (ESI): MH^+ found 256.1439. $C_{15}H_{18}N_3O$ requires 256.1450.



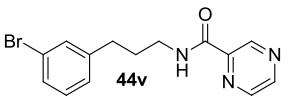
44t

***N*-(3-(*m*-Tolyl)propyl)pyrazine-2-carboxamide (44u).** Brown colour liquid (130 mg, 51%); IR (CH_2Cl_2): ν_{max} 1672, 1533, 1400 and 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (1 H, d, J = 1.4 Hz), 8.74 (1 H, d, J = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.4 Hz), 7.88 (1 H, br. s), 7.18 (1 H, t, J = 7.5 Hz), 7.02-7.00 (3 H, m), 3.53 (2 H, q, J = 6.9 Hz), 2.70 (2 H, t, J = 7.4 Hz), 2.32 (3 H, s), 2.02-1.94 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 147.2, 144.5, 144.3, 142.5, 141.2, 138.0, 129.2, 128.4, 126.8, 125.4, 39.1, 33.2, 31.1, 21.4; HRMS (ESI): MH^+, found 256.1440. $C_{15}H_{18}N_3O$ requires 256.1450.



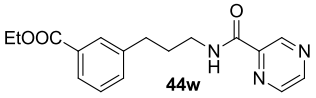
44u

***N*-(3-(3-Bromophenyl)propyl)pyrazine-2-carboxamide (44v).** Brown colour liquid (197 mg, 62%); IR (CH_2Cl_2): ν_{max} 2938, 1672, 1533, 1401 and 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (1 H, d, J = 1.5 Hz), 8.74 (1 H, d, J = 2.5 Hz), 8.51 (1 H, dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz), 7.86 (1 H, br. s), 7.35 (1 H, s), 7.32-7.29 (1 H, m), 7.16-7.13 (2 H, m), 3.53 (2 H, q, J = 6.9 Hz), 2.70 (2 H, t, J = 7.4 Hz), 2.01-1.94 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 147.2, 144.4, 144.4, 143.6, 142.5, 131.4, 130.0, 129.1, 127.1, 122.5, 39.0, 32.9, 30.9; HRMS (ESI): MH^+, found 320.0401. $C_{14}H_{15}BrN_3O$ requires 320.0398.



44v

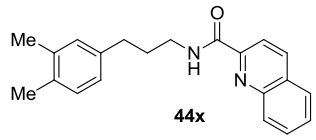
Ethyl 3-(3-(pyrazine-2-carboxamido)propyl)benzoate (44w). Brown colour liquid (203 mg, 65%); IR (CH_2Cl_2): ν_{max} 2937, 1715, 1674, 1532 and 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ



44w

9.40 (1 H, d, *J* = 1.4 Hz), 8.74 (1 H, d, *J* = 2.5 Hz), 8.50 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.4 Hz), 7.88-7.85 (3 H, m), 7.41-7.39 (1 H, m), 7.36-7.32 (1 H, m), 4.36 (2 H, q, *J* = 7.1 Hz), 3.53 (2 H, q, *J* = 6.9 Hz), 2.78 (2 H, t, *J* = 7.9 Hz), 2.04-1.97 (2 H, m), 1.31 (3 H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 163.0, 147.2, 144.4, 144.3, 142.5, 141.5, 132.9, 130.6, 129.4, 128.5, 127.3, 61.0, 39.0, 33.1, 31.1, 14.3; HRMS (ESI): MNa^+, found 336.1330. $C_{17}H_{19}N_3NaO_3$ requires 336.1324.

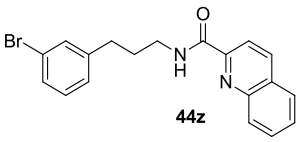
***N*-(3-(3,4-Dimethylphenyl)propyl)quinoline-2-carboxamide (44x).** Brown colour liquid (111



44x

mg, 35%); IR (CH_2Cl_2): ν_{max} 2929, 1674, 1528 and 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34-8.33 (3 H, m), 8.12 (1 H, d, *J* = 8.0 Hz), 7.90 (1 H, dd, J_1 = 8.1 Hz, J_2 = 0.7 Hz), 7.81-7.76 (1 H, m), 7.66-7.61 (1 H, m), 7.09-6.98 (3 H, m), 3.58 (2 H, q, *J* = 6.9 Hz), 2.73 (2 H, t, *J* = 7.8 Hz), 2.25 (3 H, s), 2.23 (3 H, s), 2.08-2.02 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 149.9, 146.5, 138.9, 137.5, 136.5, 134.0, 130.1, 129.8, 129.7, 129.7, 129.3, 127.8, 127.8, 125.8, 118.9, 39.3, 32.9, 31.4, 19.8, 19.3; HRMS (ESI): MH^+, found 319.1819. $C_{21}H_{23}N_2O$ requires 319.1810.

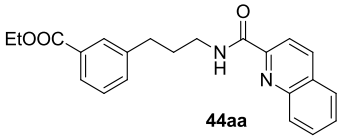
***N*-(3-(3-Bromophenyl)propyl)quinoline-2-carboxamide (44z).** Brown colour liquid (165 mg, 45%); IR (CH_2Cl_2): ν_{max} 2938, 1673, 1529, 1501 and 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ



44z

8.33 (3 H, s), 8.12 (1 H, d, *J* = 8.5 Hz), 7.90 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m,), 7.41 (1 H, d, *J* = 1.3 Hz), 7.34-7.31 (1 H, m), 7.18-7.16 (2 H, m), 3.59 (2 H, q, *J* = 6.9 Hz), 2.75 (2 H, t, *J* = 8.0 Hz), 2.08-2.01 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 149.7, 146.5, 143.9, 137.5, 131.5, 130.1, 130.0, 129.7, 129.3, 129.1, 127.9, 127.8, 127.1, 122.5, 118.8, 30.1, 33.0, 31.0; HRMS (ESI): MH^+, found 369.0595. $C_{19}H_{18}BrN_2O$ requires 369.0603.

Ethyl 3-(3-(quinoline-2-carboxamido)propyl)benzoate (44aa). Brown colour liquid (162 mg, 45%); IR (CH_2Cl_2): ν_{max} 2926, 1738, 1673, 1566, 1489 and 1398 cm^{-1}; ^1H NMR (400 MHz,



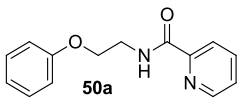
44aa

$CDCl_3$): δ 8.35 (1 H, br. s), 8.33 (2 H, s), 8.12 (1 H, d, *J* = 8.5 Hz), 7.94 (1 H, s), 7.91-7.88 (2 H, m), 7.79 (1 H, t, *J* = 7.4 Hz), 7.64 (1 H, t, *J* = 7.3 Hz), 7.45 (1 H, d, *J* = 7.6 Hz), 7.37 (1 H, t, *J* = 7.6 Hz), 4.38 (2 H, q, *J* = 7.1 Hz), 3.60 (2 H, q, *J* = 6.7 Hz), 2.84 (2 H, t, *J* = 7.6 Hz), 2.12-2.05 (2 H, m),

1.41 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 164.5, 149.8, 146.5, 141.8, 137.5, 133.0, 130.6, 130.1, 129.7, 129.4, 129.3, 128.5, 127.9, 127.8, 127.3, 118.8, 61.0, 39.1, 33.2, 31.3, 14.4; HRMS (ESI): MH^+, found 363.1696. $C_{22}H_{23}N_2O_3$ requires 363.1709.

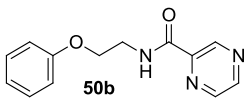
General procedure for the synthesis of compounds 50a-c. To a round bottom flask, picolinic acid or pyrazine-2-carboxylic acid or quinoline-2-carboxylic acid (2 mmol), DMF (2-3 drops) and DCM (12 mL) were added under a nitrogen atmosphere. Then, to the reaction mixture was added oxalyl chloride (3 mmol, 378 mg) dropwise at 0 °C. The mixture was stirred at rt for 12 h, and then the solvent was removed in vacuum. To another round bottom flask 2-phenoxyethanamine (1.8 mmol), Et_3N (1.5-2 mmol, 152-203 mg), DMAP (0.1 mmol, 12 mg) and DCM (12 mL) were added. A solution of the acid chloride in DCM (5 mL) (prepared in the previous step) was added dropwise to the solution containing alkyl amine at 0 °C. Then, the resulting reaction mixture was warmed to rt and stirred at rt for overnight. After this period, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were dried over anhydrous MgSO4, and evaporated in vacuum. The crude reaction mixture was purified by column chromatography on silica gel (hexane/EtOAc = 70:30) to afford the corresponding product **50**.

***N*-(2-Phenoxyethyl)picolinamide (50a).** Colourless liquid (145 mg, 60%); IR (CH_2Cl_2): ν_{max} 2941, 1675, 1525, 1497 and 1244 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58-8.57 (1 H, m), 8.49 (1 H, br. s), 8.21 (1 H, dt, J_1 = 8.0 Hz, J_2 = 0.9 Hz), 7.86 (1 H, td, J_1 = 9.4 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.33-7.29 (2 H, m), 7.00-6.97 (3 H, m), 4.18 (2 H, t, J = 5.3 Hz), 3.92 (2 H, q, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.6, 149.7, 148.2, 137.3, 129.5, 126.3, 122.3, 121.1, 114.5, 66.7, 39.0; HRMS (ESI): MH^+, found 243.1141. $C_{14}H_{15}N_2O_2$ requires 243.1134.



50a

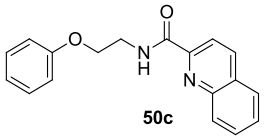
***N*-(2-Phenoxyethyl)pyrazine-2-carboxamide (50b).** Colorless solid (165 mg, 68%); mp: 114-116 ^{o}C; IR (CH_2Cl_2): ν_{max} 2950, 1669, 1532, 1248 and 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (1 H, d, J = 1.4 Hz), 8.77 (1 H, d, J = 2.5 Hz), 8.56 (1 H, dd, J_1 = 2.5 Hz, J_2 = 1.4 Hz), 8.27 (1 H, br. s), 7.34-7.29 (2 H, m), 7.01-6.94 (3 H, m), 4.18 (2 H, t, J = 5.1 Hz), 3.93 (2 H, q, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 158.4,



50b

147.4, 144.4, 144.3, 142.6, 129.6, 121.2, 114.5, 66.5, 39.0; HRMS (ESI): MH^+, found 244.1079. $C_{13}H_{14}N_3O_2$ requires 244.1086.

***N*-(2-Phenoxyethyl)quinoline-2-carboxamide (50c).** Colourless solid (204 mg, 70%); mp: 90-92 ^oC; IR (CH_2Cl_2): ν_{max} 2937, 1675, 1598, 1528 and 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

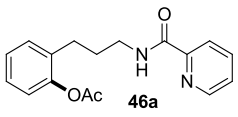


50c

8.17 (1 H, br. s), 8.33 (2 H, s), 8.14 (1 H, d, J = 8.5 Hz), 7.90 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.9 Hz), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m), 7.35-7.31 (2 H, m), 7.01-6.98 (3 H, m), 4.24 (2 H, t, J = 5.2 Hz), 3.99 (2 H, q, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 158.6, 149.6, 146.5, 137.5, 130.1, 129.8, 129.6, 129.3, 128.0, 127.8, 121.1, 118.8, 114.6, 66.8, 39.1; HRMS (ESI): MH^+, found 293.1295. $C_{18}H_{17}N_2O_2$ requires 293.1290.

General procedure for Pd(II)-catalyzed remote ε-C(sp^2)-H acetoxylation of 44a-z, 44aa and 50a-c and preparation of 46/4748/49/51/52. A mixture of an appropriate starting compound **44a-z, 44aa** and **50a-c** (0.15-0.40 mmol, 1 equiv), $Pd(OAc)_2$ (0.1 equiv, 10 mol%, 3.3-13.4 mg) and $PhI(OAc)_2$ (0.38-1 mmol, 2.5 equiv, 122-321 mg) in anhydrous toluene (3-5 mL) in a 10 mL round bottom flask was heated at 110 ^oC for 17-48 h. After this period, reaction mixture was cooled to rt, and concentrated in vacuum. The resulting residue was purified by flash chromatography on silica gel to give the corresponding products **46/4748/49/51/52** (see the respective Schemes/Tables for specific examples).

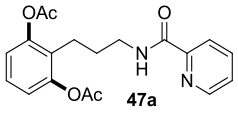
2-(3-(Picolinamido)propyl)phenyl acetate (46a). Yellow colour liquid (35 mg, 40%); IR (CH_2Cl_2): ν_{max} 2933, 1766, 1672, 1528 and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (1



46a

H, d, J = 4.7 Hz), 8.22 (1 H, d, J = 7.8 Hz), 8.16 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.31-7.18 (3 H, m), 7.04 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 3.51 (2 H, q, J = 6.7 Hz), 2.65 (2 H, t, J = 7.7 Hz), 2.34 (3 H, s), 1.98-1.91 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 164.3, 149.9, 149.0, 148.0, 137.4, 133.2, 130.2, 127.3, 126.3, 126.1, 122.4, 122.2, 38.9, 30.0, 27.5, 20.9; HRMS (ESI): MH^+, found 299.1408. $C_{17}H_{19}N_2O_3$ requires 299.1396.

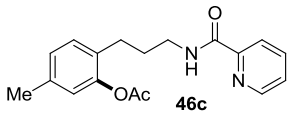
2-(3-(Picolinamido)propyl)-1,3-phenylene diacetate (47a). Yellow colour liquid (34 mg, 32%); IR (CH_2Cl_2): ν_{max} 2929, 1755, 1666, 1530 and 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.22 (1 H, d, J = 7.8 Hz), 8.17 (1 H, br. s), 7.88 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1 H, m), 7.26 (1 H, t, J = 8.1 Hz), 6.98 (2 H, d, J = 8.2 Hz), 3.50 (2 H, q, J = 6.7



47a

Hz), 2.58 (2 H, t, *J* = 7.6 Hz,), 2.33 (6 H, s,), 1.88-1.80 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 164.3, 149.9, 149.8, 147.9, 137.5, 127.0, 126.4, 126.2, 122.2, 120.2, 38.9, 29.0, 22.2, 20.9; HRMS (ESI): MH^+, found 357.1461. $C_{19}H_{21}N_2O_5$ requires 357.1450.

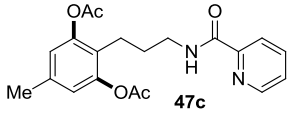
5-Methyl-2-(3-(picolinamido)propyl)phenyl acetate (46c). Colourless liquid (51 mg, 43%); IR (CH_2Cl_2): ν_{max} 2935, 1766, 1673, 1527 and 1212 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54



46c

(1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.15 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.8 Hz), 7.46-7.43 (1 H, m), 7.17 (1 H, d, *J* = 7.7 Hz), 7.01 (1 H, dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz), 6.85 (1 H, d, *J* = 0.8 Hz), 3.50 (2 H, q, *J* = 6.8 Hz), 2.60 (2 H, t, *J* = 7.4 Hz), 2.33 (3 H, s), 2.32 (3 H, s), 1.96-1.88 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 164.3, 149.9, 148.7, 148.0, 137.4, 137.3, 130.0, 127.1, 126.2, 122.8, 122.2, 38.9, 30.1, 27.1, 20.9, 20.9; HRMS (ESI): MNa^+, found 335.1389. $C_{18}H_{20}N_2NaO_3$ requires 335.1372.

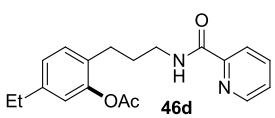
5-Methyl-2-(3-(picolinamido)propyl)-1,3-phenylene diacetate (47c). Colourless liquid (16 mg, 12%); IR (CH_2Cl_2): ν_{max} 2932, 1764, 1674, 1528 and 1202 cm^{-1}; ^{1}H NMR (400 MHz,



47c

$CDCl_3$): δ 8.55-8.53 (1 H, m), 8.23 (1 H, dt, J_1 = 7.9 Hz, J_2 = 1.1 Hz), 8.16 (1 H, br. s), 7.88 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.43 (1 H, m), 6.80 (2 H, d, *J* = 0.3 Hz), 3.49 (2 H, q, *J* = 6.6 Hz), 2.52 (2 H, t, *J* = 7.9 Hz), 2.33 (3 H, s), 2.32 (6 H, s), 1.85-1.81 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.3, 149.9, 149.5, 147.9, 137.4, 126.2, 123.1, 122.2, 120.9, 38.9, 29.1, 22.0, 21.1, 20.9; HRMS (ESI): MNa^+, found 393.1420. $C_{20}H_{22}N_2NaO_5$ requires 393.1426.

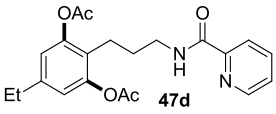
5-Ethyl-2-(3-(picolinamido)propyl)phenyl acetate (46d). Yellow colour liquid (20 mg, 16%); IR (CH_2Cl_2): ν_{max} 2935, 1758, 1673, 1529 and 1501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-



46d

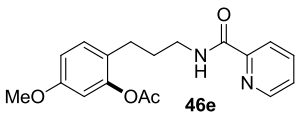
8.54 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 8.14 (1 H, br. s), 7.88 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.20 (1 H, d, *J* = 7.8 Hz), 7.04 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 6.87 (1 H, d, *J* = 1.6 Hz), 3.50 (2 H, q, *J* = 6.8 Hz), 2.67-2.59 (4 H, m), 2.33 (3 H, s), 1.97-1.89 (2 H, m), 1.23 (3 H, t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 164.3, 150.0, 148.9, 148.0, 143.7, 137.4, 130.2, 130.0, 126.1, 125.8, 122.2, 121.6, 38.9, 30.0, 28.2, 27.1, 20.9, 15.2; HRMS (ESI): MNa^+, found 349.1515. $C_{19}H_{22}N_2NaO_3$ requires 349.1528.

5-Ethyl-2-(3-(picolinamido)propyl)-1,3-phenylene diacetate (47d). Yellow colour liquid (63 mg, 44%); IR (CH_2Cl_2): ν_{max} 2932, 1765, 1674, 1570 and 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54-8.52 (1 H, m), 8.21 (1 H, dt, J_1 = 7.9 Hz, J_2 = 1.1 Hz), 8.16 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 6.81 (2 H, s), 3.48 (2 H, q, J = 6.6 Hz), 2.65 (2 H, q, J = 7.6 Hz), 2.52 (2 H, t, J = 7.6 Hz), 2.31 (3 H, s), 1.85-1.78 (2 H, m), 1.23 (3 H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.3, 149.9, 149.6, 147.9, 143.6, 137.4, 126.2, 123.3, 122.2, 119.6, 38.9, 29.1, 28.2, 22.1, 20.9, 14.7; HRMS (ESI): MNa^+, found 407.1576. $C_{21}H_{24}N_2NaO_5$requires 407.1583.



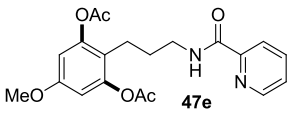
47d

5-Methoxy-2-(3-(picolinamido)propyl)phenyl acetate (46e). Yellow colour liquid (37 mg, 49%); IR (CH_2Cl_2): ν_{max} 2941, 1761, 1673, 1528, 1212 and 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.21 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.14 (1 H br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 7.18 (1 H, d, J = 8.5 Hz), 6.76 (1 H, dd, J_1 = 8.5 Hz, J_2 = 2.6 Hz), 6.60 (1 H, d, J = 2.6 Hz), 3.78 (3 H, s), 3.49 (2 H, q, J = 6.8 Hz), 2.57 (2 H, t, J = 7.6 Hz) 2.32 (3 H, s), 1.94-1.87 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.3, 158.7, 149.9, 149.5, 148.0, 137.4, 130.6, 126.1, 125.1, 122.2, 112.2, 108.1, 55.4, 38.8, 30.1, 26.8, 20.9;
HRMS (ESI): MH^+, found 329.1490. $C_{18}H_{21}N_2O_4$ requires 329.1501.



46e

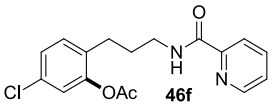
5-Methoxy-2-(3-(picolinamido)propyl)-1,3-phenylene diacetate (47e). Yellow colour liquid (11 mg, 12%); IR (CH_2Cl_2): ν_{max} 2937, 1767, 1673, 1527 and 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.15 (1 H, br. s), 7.88 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1 H, m), 6.56 (2 H, s), 3.77 (3 H s), 3.48 (2 H q, J = 6.4 Hz), 2.49 (2 H, t, J = 7.6 Hz), 2.32 (6 H, s), 1.84-1.80 (2 H m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.3, 158.3, 150.2, 147.9, 137.4, 126.2, 122.2, 118.3, 106.6, 55.6, 38.8, 29.2, 21.8, 20.9; HRMS (ESI): MNa^+, found 409.1373. $C_{20}H_{22}N_2NaO_6$ requires 409.1376.



47e

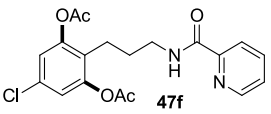
5-Chloro-2-(3-(picolinamido)propyl)phenyl acetate (46f). Brown colour liquid (82 mg, 42%); IR (CH_2Cl_2): ν_{max} 2939, 1771, 1673, 1604 and 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.54 (1 H, m), 8.21 (1 H, d, J = 7.8 Hz), 8.14 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.2 Hz),

7.46-7.43 (1 H, m), 7.20 (1 H, d, J = 8.2 Hz), 7.17 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz), 7.08 (1 H, d, J = 1.8 Hz), 3.50 (2 H, q, J = 6.6 Hz), 2.61 (2 H, t, J = 7.6 Hz) 2.32 (3 H s), 1.95-1.88 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.4, 149.8, 149.2, 148.0, 137.4, 132.1, 132.0, 131.0, 126.5, 126.2, 122.9, 122.2, 38.8, 29.9, 27.1, 20.8; HRMS (ESI): MNa^+, found 355.0817. $C_{17}H_{17}ClN_2NaO_3$ requires 355.0825.



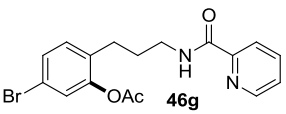
46f

5-Chloro-2-(3-(picolinamido)propyl)-1,3-phenylene diacetate (47f). Brown colour liquid (36 mg, 16%); IR (CH_2Cl_2): ν_{max} 2939, 1766, 1673, 1528 and 1501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 8.15 (1 H, br. s), 7.88 (1H td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1 H, m), 7.02 (2 H, s), 3.49 (2 H, q, J = 6.6 Hz), 2.54 (2 H t, J = 7.7 Hz), 2.32 (3 H, s), 1.85-1.78 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 164.4, 149.9, 148.0, 137.5, 131.9, 126.3, 125.3, 122.2, 120.9, 38.8, 28.9, 22.1, 20.8; HRMS (ESI): MNa^+, found 413.0877. $C_{19}H_{19}ClN_2NaO_5$ requires 413.0880.



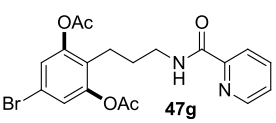
47f

5-Bromo-2-(3-(picolinamido)propyl)phenyl acetate (46g). Brown colour liquid (49 mg, 44%); IR (CH_2Cl_2): ν_{max} 2963, 1772, 1642, 1594 and 1197 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.21 (1 H, td, J = 7.9 Hz, J_2 = 1.2 Hz), 8.14 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.32 (1 H, dd, J_1 = 8.1 Hz, J_2 = 2.0 Hz), 7.22 (1 H, d, J = 2.0 Hz), 7.17 (1 H, d, J = 8.2 Hz), 3.50 (2 H, q, J = 6.7 Hz), 2.60 (2 H, t, J = 7.6 Hz), 2.32 (3 H, s), 1.95-1.88 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.4, 149.8, 149.4, 148.0, 137.4, 132.5, 131.4, 129.4, 126.2, 125.7, 122.2, 119.7, 38.8, 29.8, 27.2, 20.8; HRMS (ESI): MH^+, found 377.0493. $C_{17}H_{18}BrN_2O_3$ requires 377.0501.



46g

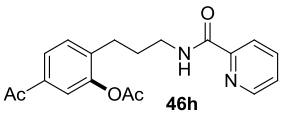
5-Bromo-2-(3-(picolinamido)propyl)-1,3-phenylene diacetate (47g). Brown colour liquid (14 mg, 11%); IR (CH_2Cl_2): ν_{max} 2939, 1766, 1673, 1258 and 1202 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 8.15 (1 H, br. s), 7.88 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.47-7.44 (1 H, m), 7.17 (2 H, s), 3.49 (2 H, q, J = 6.6 Hz), 2.53 (2 H, t, J = 7.6 Hz), 2.32 (6 H, s), 1.85-1.80 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 164.3, 150.1, 149.8, 148.0, 137.5, 126.3, 125.9, 123.7, 122.2, 119.0, 38.8, 28.8, 22.2, 20.8;



47g

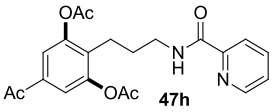
HRMS (ESI): MNa^+, found 457.0367. $C_{19}H_{19}BrN_2NaO_5$ requires 457.0375.

5-Acetyl-2-(3-(picolinamido)propyl)phenyl acetate (46h). Brown colour liquid (54 mg, 42%); IR (CH_2Cl_2): ν_{max} 2930, 1768, 1672, 1501 and 1204 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54-8.53 (1 H, m), 8.21 (1 H, d, J = 7.8 Hz), 8.16 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.78 (1 H, dd, J = 7.8 Hz, J_2 = 1.6 Hz), 7.62 (1 H, d, J = 1.5 Hz), 7.45 (1 H, dd, J_1 = 7.1 Hz, J_2 = 4.5 Hz), 7.39 (1 H, d, J = 7.9 Hz), 3.52 (2 H, q, J = 6.7 Hz), 2.69 (2 H, t, J = 7.4 Hz), 2.57 (3 H, s), 2.34 (3 H, s), 1.99-1.92 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 169.5, 164.4, 149.8, 149.1, 148.0, 139.2, 137.5, 136.6, 130.4, 126.2, 126.2, 122.4, 122.2, 38.8, 29.7, 27.7, 26.6, 20.8; HRMS (ESI): MNa^+, found 363.1310. $C_{19}H_{20}N_2NaO_4$ requires 363.1321.



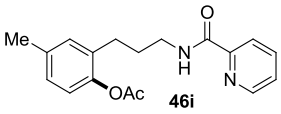
46h

5-Acetyl-2-(3-(picolinamido)propyl)-1,3-phenylene diacetate (47h). Brown colour liquid (11 mg, 8%); IR (CH_2Cl_2): ν_{max} 2935, 1768, 1688, 1465, 1398 and 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.23-8.17 (2 H, m), 7.90-7.86 (1 H, m), 7.56 (2 H, s), 7.47-7.44 (1 H, m), 3.50 (2 H, q, J = 6.4 Hz), 2.63-2.58 (2 H, m), 2.57 (3 H, s), 2.35 (6 H, s), 1.88-1.84 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 169.1, 164.4, 149.9, 149.8, 148.0, 137.5, 136.2, 132.2, 126.3, 122.3, 120.2, 38.9, 28.8, 26.5, 22.6, 20.8; HRMS (ESI): MNa^+, found 421.1371. $C_{21}H_{22}N_2NaO_6$ requires 421.1376.



47h

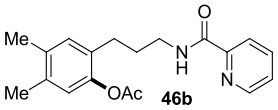
4-Methyl-2-(3-(picolinamido)propyl)phenyl acetate (46i). Brown colour liquid (54 mg, 56%); IR (CH_2Cl_2): ν_{max} 2929, 1759, 1673, 1528 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.23 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.15 (1 H, br. s), 7.87 (1 H, td, J = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.09 (1 H, d, J = 1.8 Hz), 7.03 (1 H, dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz), 6.91 (1 H, d, J = 8.1 Hz), 3.51 (2 H, q, J = 6.8 Hz), 2.60 (2 H, t, J = 7.5 Hz), 2.32 (3 H, s), 2.32 (3 H, s), 1.97-1.90 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 164.3, 149.9, 148.0, 146.7, 137.4, 135.9, 132.8, 130.8, 127.9, 126.1, 122.2, 122.0, 38.9, 30.0, 27.5, 20.9, 20.9; HRMS (ESI): MH^+, found 313.1559. $C_{18}H_{21}N_2O_3$ requires 313.1552.



46i

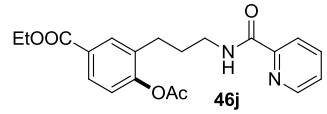
4,5-Dimethyl-2-(3-(picolinamido)propyl)phenyl acetate (46b). Colourless liquid (54 mg, 54%); IR (CH_2Cl_2): ν_{max} 2929, 1757, 1673, 1527 and 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

8.568.54 (1 H, m), 8.22 (1 H, dt, J_1 = 7.8 Hz, J_2 = 1.1 Hz), 8.15 (1 H, br. s), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.42 (1 H, m), 7.04 (1 H, s), 6.80 (1 H, s), 3.50 (2 H, q, J = 6.8 Hz), 2.57 (2 H, t, J = 7.4 Hz), 2.31 (3 H, s), 2.22 (6 H, s), 1.95-1.88 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 164.3, 150.0, 148.0, 146.7, 137.4, 135.7, 134.6, 131.3, 130.1, 126.1, 123.1, 122.2, 38.9, 30.1, 27.1, 20.9, 19.4, 19.2; HRMS (ESI): MNa^+, found 349.1530. $C_{19}H_{22}N_2NaO_3$ requires 349.1528.



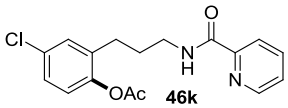
46b

Ethyl 4-acetoxy-3-(3-(picolinamido)propyl)benzoate (46j). Colourless liquid (51 mg, 45%); IR (CH_2Cl_2): ν_{max} 2932, 1717, 1674, 1527 and 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.53 (1 H, m), 8.21 (1 H, dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz), 8.16 (1 H, br. s), 7.98 (1 H, d, J = 2.1 Hz), 7.91 (1 H, dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 7.86 (1 H, td, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.46-7.42 (1 H, m), 7.12 (1 H, d, J = 8.4 Hz), 4.37 (2 H, q, J = 7.1 Hz), 3.52 (2 H, q, J = 6.7 Hz), 2.69 (2 H, t, J = 7.6 Hz), 2.33 (3 H, s), 1.98-1.93 (2 H, m), 1.39 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 165.9, 164.4, 152.5, 149.8, 148.0, 137.4, 133.6, 131.7, 128.8, 128.4, 126.2, 122.5, 122.2, 61.1, 38.9, 29.9, 27.5, 20.9, 14.3; HRMS (ESI): MH^+, found 371.1605. $C_{20}H_{23}N_2O_5$ requires 371.1607.



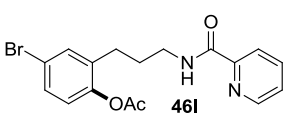
46j

4-Chloro-2-(3-(picolinamido)propyl)phenyl acetate (46k). Colourless liquid (45 mg, 37%); IR (CH_2Cl_2): ν_{max} 2937, 1761, 1673, 1569 and 1210 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.21 (1 H, dt, J_1 = 7.9 Hz, J_2 = 1.0 Hz), 8.16 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.27 (1 H, d, J = 2.5 Hz), 7.20 (1 H, dd, J_1 = 8.6 Hz, J_2 = 2.5 Hz), 6.98 (1 H, d, J = 8.6 Hz), 3.51 (2 H, q, J = 6.7 Hz), 2.61 (2 H, t, J = 7.6 Hz), 2.31 (3 H, s), 1.97-1.89 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.4, 149.8, 148.0, 147.4, 137.4, 135.2, 131.4, 130.0, 127.3, 126.2, 123.7, 122.2, 38.8, 29.8, 27.4, 20.8; HRMS (ESI): MNa^+, found 355.0827. $C_{17}H_{17}ClN_2NaO_3$ requires 355.0825.



46k

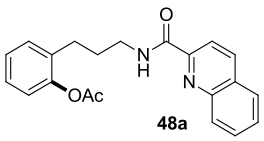
4-Bromo-2-(3-(picolinamido)propyl)phenyl acetate (46l). Colourless liquid (42 mg, 43%); IR (CH_2Cl_2): ν_{max} 2928, 1760, 1672, 1527 and 1208 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.22 (1 H, dd, J_1 = 7.1 Hz, J_2 = 0.8 Hz), 8.16 (1 H, br. s), 7.87 (1 H, td, J_1 = 7.6 Hz, J_2 = 1.7 Hz), 7.46-7.43 (1 H, m), 7.42 (1 H, d, J = 2.4 Hz), 7.34 (1 H, dd, J_1 = 8.5 Hz, J_2 = 2.4 Hz), 6.92 (1 H, d, J = 8.5 Hz), 3.51 (2 H, q, J = 6.7 Hz), 2.61 (2 H, t, J = 7.6 Hz), 2.31 (3 H, s), 1.97-1.89 (2 H, m); ^{13}C



46l

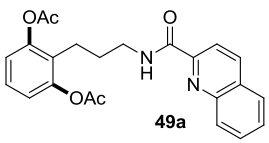
NMR (100 MHz, $CDCl_3$): δ 169.3, 164.4, 149.8, 148.0, 148.0, 137.4, 135.7, 133.0, 130.3, 126.2, 124.1, 122.2, 119.3, 38.8, 29.9, 27.4, 20.8; HRMS (ESI): MH^+, found 377.0507. $C_{17}H_{18}BrN_2O_3$ requires 377.0501.

2-(3-(Quinoline-2-carboxamido)propyl)phenyl acetate (48a). Colourless liquid (24 mg, 31%); IR (CH_2Cl_2): ν_{max} 2989, 1759, 1673, 1463 and 1425 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (3 H, s), 8.11 (1 H, d, J = 8.4 Hz), 7.92-7.90 (1 H, m), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m), 7.33 (1 H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.25-7.20 (2 H, m), 7.06 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz), 3.59 (2 H, q, J = 6.9 Hz), 2.69 (2 H, t, J = 7.5 Hz), 2.32 (3 H, s), 2.05-1.98 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 164.5, 149.8, 149.0, 146.5, 137.5, 133.3, 130.3, 130.1, 129.6, 129.3, 127.9, 127.8, 127.3, 126.3, 122.4, 118.8, 39.2, 30.0, 27.6, 20.9; HRMS (ESI): MH^+, found 349.1563. $C_{21}H_{21}N_2O_3$requires 349.1552.



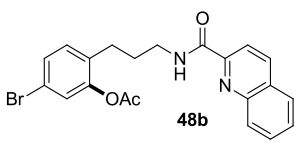
48a

2-(3-(Quinoline-2-carboxamido)propyl)-1,3-phenylene diacetate (49a). Red colour liquid (34 mg, 39%); IR (CH_2Cl_2): ν_{max} 2939, 1766, 1673, 1528, 1501 and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (3 H, s), 8.09 (1 H, d, J = 8.5 Hz), 7.92-7.90 (1 H, m), 7.81-7.77 (1 H, m), 7.67-7.63 (1 H, m), 7.26 (1 H, d, J = 8.1 Hz), 6.99 (2 H, d, J = 8.1 Hz), 3.58 (2 H, q, J = 6.7 Hz), 2.62 (2 H, t, J = 7.7 Hz), 2.31 (6 H, s), 1.92-1.89 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 164.6, 149.8, 149.8, 146.4, 137.6, 130.2, 129.5, 129.3, 127.9, 127.8, 127.0, 126.5, 120.2, 118.9, 39.2, 29.2, 22.4, 20.9; HRMS (ESI): MH^+, found 407.1603. $C_{23}H_{23}N_2O_5$requires 407.1607.



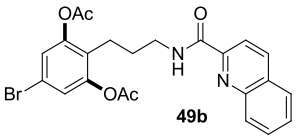
49a

5-Bromo-2-(3-(quinoline-2-carboxamido)propyl)phenyl acetate (48b). Red colour liquid (66 mg, 39%); IR (CH_2Cl_2): ν_{max} 2930, 1768, 1672, 1501 and 1204 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (1 H, br. s), 8.33 (2 H, s), 8.10 (1 H, d, J = 8.5 Hz), 7.90 (1 H, d, J = 8.2 Hz), 7.79 (1 H, t, J = 7.3 Hz), 7.64 (1 H, t, J = 7.6 Hz), 7.32 (1 H, d, J = 8.2 Hz), 7.23-7.18 (2 H, m), 3.57 (2 H, q, J = 6.7 Hz), 2.63 (2 H, t, J = 7.5 Hz), 2.31 (3 H, s), 2.00-1.96 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.6, 149.7, 149.4, 146.4, 137.6, 132.6, 131.4, 130.2, 129.6, 129.4, 129.3, 127.9, 127.8, 125.7, 119.7, 118.8, 39.1, 29.8, 27.3, 20.8; HRMS (ESI): MH^+, found 449.0476. $C_{21}H_{19}BrN_2NaO_3$ requires 449.0477.



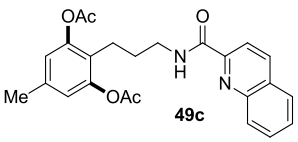
48b

5-Bromo-2-(3-(quinoline-2-carboxamido)propyl)-1,3-phenylene diacetate (49b). Red colour liquid (36 mg, 19%); IR (CH_2Cl_2): ν_{max} 2930, 1770, 1673, 1501 and 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (1 H, br. s), 8.34 (2 H, s), 8.09 (1 H, d, J = 8.6 Hz), 7.91 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.82-7.77 (1 H, m), 7.67-7.63 (1 H, m), 7.17 (2 H, s), 3.57 (2 H, q, J = 6.6 Hz), 2.56 (2 H, t, J = 7.7 Hz), 2.30 (6 H, s), 1.89-1.85 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.6, 150.1, 149.7, 146.4, 137.6, 130.3, 129.5, 129.3, 128.0, 127.9, 126.0, 123.7, 119.0, 118.8, 39.1, 29.0, 22.3, 20.8; HRMS (ESI): MH^+, found 485.0723. $C_{23}H_{22}BrN_2O_5$ requires 485.0712.



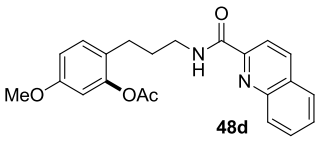
49b

5-Methyl-2-(3-(quinoline-2-carboxamido)propyl)-1,3-phenylene diacetate (49c). Colourless liquid (112 mg, 61%); IR (CH_2Cl_2): ν_{max} 2932, 1763, 1673, 1501 and 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (1 H, br. s), 8.33 (2 H, s), 8.09 (1 H, d, J = 8.5 Hz), 7.90 (1 H, d, J = 8.2 Hz), 7.78 (1 H, t, J = 8.2 Hz), 7.63 (1 H, t, J = 7.3 Hz), 6.80 (2 H, s), 3.56 (2 H, q, J = 6.6 Hz), 2.56 (2 H, t, J = 7.1 Hz), 2.31 (3 H, s), 2.29 (6 H, s), 1.90-1.84 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 164.5, 149.8, 149.5, 146.4, 137.6, 137.4, 130.2, 129.5, 129.3, 127.9, 127.8, 123.3, 120.9, 118.8, 39.2, 29.2, 22.2, 21.0, 20.9; HRMS (ESI): MH^+, found 443.1589. $C_{24}H_{24}N_2NaO_5$requires 443.1583.



49c

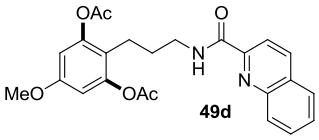
5-Methoxy-2-(3-(quinoline-2-carboxamido)propyl)phenyl acetate (48d). Brown colour liquid (26 mg, 32%); IR (CH_2Cl_2): ν_{max} 2930, 1760, 1673, 1620 and 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (3 H, s), 8.11 (1 H, d, J = 8.4 Hz), 7.90 (1 H, d, J = 8.2 Hz), 7.79 (1 H, t, J = 7.1 Hz), 7.64 (1 H, t, J = 7.4 Hz), 7.21 (1 H, d, J = 8.4 Hz), 6.77 (1 H, dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz), 6.61 (1 H, s), 3.77 (3 H, s), 3.57 (2 H, q, J = 6.6 Hz), 2.62 (2 H, t, J = 7.5 Hz), 2.31 (3 H, s), 2.01-1.94 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 164.5, 158.7, 149.8, 149.5, 146.5, 137.5, 130.6, 130.1, 129.6, 129.3, 127.9, 127.8, 125.2, 118.8, 112.2, 108.1, 55.4, 39.1, 30.2, 27.0, 20.9; HRMS (ESI): MH^+, found 379.1646. $C_{22}H_{23}N_2O_4$requires 379.1658.



48d

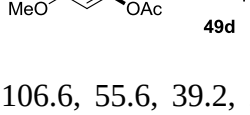
5-Methoxy-2-(3-(quinoline-2-carboxamido)propyl)-1,3-phenylene diacetate (49d). Brown colour liquid (26 mg, 28%); IR (CH_2Cl_2): ν_{max} 2940, 1767, 1674, 1529, 1501 and 1133 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (2 H, s), 8.32 (1 H, s), 8.09 (1 H, d, J = 8.5 Hz), 7.91 (1 H, d, J

= 8.1 Hz), 7.79 (1 H, t, *J* = 7.3 Hz), 7.64 (1 H, t, *J* = 7.7 Hz), 6.56 (2 H, s), 3.75 (3 H, s), 3.56 (2 H, q, *J* = 6.4 Hz), 2.53 (2 H, t, *J* = 7.4 Hz), 2.30 (6 H, s), 1.91-1.83 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 164.5, 158.3, 150.2, 149.8, 146.4, 137.6, 130.2, 129.5, 129.3, 127.9, 127.8, 118.9, 118.4, 106.6, 55.6, 39.2, 29.3, 22.0, 20.9; HRMS (ESI): MH^+, found 437.1723. $C_{24}H_{25}N_2O_6$requires 437.1713.



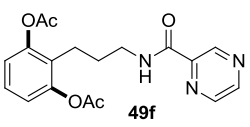
49d

2-(3-(Pyrazine-2-carboxamido)propyl)phenyl acetate (48f). Colourless liquid (30 mg, 46%); IR (CH_2Cl_2): ν_{max} 2932, 1758, 1673, 1532 and 1211 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (1 H d, *J* = 1.4 Hz), 8.76 (1 H, d, *J* = 2.5 Hz), 8.50 (1 H, dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz), 7.89 (1 H, br. s), 7.29-7.16 (3 H, m), 7.03 (1 H, dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 3.51 (2 H, q, *J* = 6.9 Hz), 2.64 (2 H, t, *J* = 7.3 Hz), 2.33 (3 H, s), 1.99-1.92 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 163.0, 148.9, 147.2, 144.5, 144.4, 142.4, 133.0, 130.2, 127.3, 126.3, 122.4, 39.0, 29.7, 27.4, 20.9; HRMS (ESI): MNa^+, found 322.1161. $C_{16}H_{17}N_3NaO_3$ requires 322.1168.



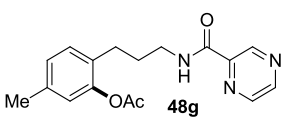
48f

2-(3-(Pyrazine-2-carboxamido)propyl)-1,3-phenylene diacetate (49f). Colourless liquid (13 mg, 17%); IR (CH_2Cl_2): ν_{max} 2932, 1765, 1672, 1532, 1370 and 1202 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (1 H, d, *J* = 1.5 Hz), 8.77 (1 H, d, *J* = 2.5 Hz), 8.50 (1 H, dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz), 7.89 (1 H, br. s), 7.25 (1 H, d, *J* = 8.3 Hz), 6.98 (2 H, d, *J* = 8.2 Hz), 3.50 (2 H, q, *J* = 6.8 Hz), 2.58 (2 H, t, *J* = 7.5 Hz), 2.34 (6 H, s), 1.89-1.82 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 163.0, 149.8, 147.3, 144.5, 144.4, 142.4, 127.1, 126.2, 120.2, 39.0, 28.8, 22.2, 20.9; HRMS (ESI): MNa^+, found 380.1212. $C_{18}H_{19}N_3NaO_5$ requires 380.1222.



49f

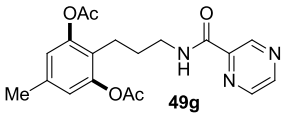
5-Methyl-2-(3-(pyrazine-2-carboxamido)propyl)phenyl acetate (48g). Brown colour liquid (51 mg, 33%); IR (CH_2Cl_2): ν_{max} 2932, 1759, 1674, 1532 and 1212 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (1 H, d, *J* = 1.4 Hz), 8.75 (1 H, d, *J* = 2.5 Hz), 8.51 (1 H, dd, J_1 = 2.5 Hz, J_2 = 1.5 Hz), 7.88 (1 H, br. s), 7.16 (1 H, d, *J* = 7.6 Hz), 7.00 (1 H, dd, J_1 = 7.7 Hz, J_2 = 0.9 Hz), 6.85 (1 H, s), 3.51 (2 H, q, *J* = 6.9 Hz), 2.60 (2 H, t, *J* = 7.4 Hz), 2.32 (3 H, s), 2.32 (3 H, s), 1.96-1.89 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 163.0, 148.7, 147.2, 144.5, 144.4, 142.4, 137.4, 129.9, 129.8, 127.2,



48g

122.9, 39.0, 29.8, 27.1, 20.9, 20.9; HRMS (ESI): MNa^+, found 336.1310. $C_{17}H_{19}N_3NaO_3$ requires 336.1324.

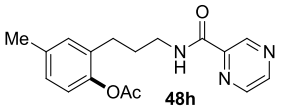
5-Methyl-2-(3-(pyrazine-2-carboxamido)propyl)-1,3-phenylene diacetate (49g). Brown colour liquid (31 mg, 17%); IR (CH_2Cl_2): ν_{max} 2937, 1764, 1675, 1532 and 1202 cm^{-1}; ^1H NMR



49g

(400 MHz, $CDCl_3$): δ 9.43 (1 H, d, J = 1.4 Hz), 8.77 (1 H, d, J = 2.5 Hz), 8.52 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz), 7.89 (1 H, br. s), 6.80 (2 H, s), 3.48 (2 H, q, J = 6.9 Hz), 2.53 (2 H, t, J = 7.4 Hz), 2.33 (9 H, s), 1.87-1.79 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 163.0, 149.5, 147.3, 144.5, 144.4, 142.4, 137.6, 122.9, 120.9, 39.0, 28.9, 22.0, 21.1, 20.9; HRMS (ESI): MNa^+, found 394.1380. $C_{19}H_{21}N_3NaO_5$ requires 394.1379.

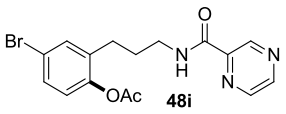
4-Methyl-2-(3-(pyrazine-2-carboxamido)propyl)phenyl acetate (48h). Brown colour liquid



48h

(50 mg, 40%); IR (CH_2Cl_2): ν_{max} 2933, 1758, 1673, 15332 and 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.42 (1 H, d, J = 1.3 Hz), 8.75 (1 H, d, J = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.2 Hz, J_2 = 1.6 Hz), 7.89 (1 H, br. s), 7.07 (1 H, s), 7.02 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 6.90 (1 H, d, J = 8.2 Hz), 3.51 (2 H, q, J = 6.8 Hz), 2.59 (2 H, t, J = 7.9 Hz), 2.32 (3 H, s), 2.30 (3 H, s), 1.97-1.92 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 163.0, 147.2, 146.7, 144.5, 144.4, 142.5, 135.9, 132.6, 130.7, 127.9, 122.1, 39.0, 29.8, 27.4, 20.9; HRMS (ESI): MNa^+, found 336.1312. $C_{17}H_{19}N_3NaO_3$ requires 336.1324.

4-Bromo-2-(3-(pyrazine-2-carboxamido)propyl)phenyl acetate (48i). Brown colour liquid (37 mg, 33%); IR (CH_2Cl_2): ν_{max} 2937, 1760, 1673, 1532, 1481 and 1208 cm^{-1}; ^1H NMR (400 MHz,

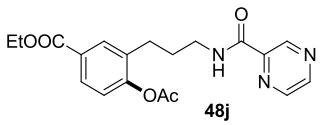


48i

$CDCl_3$): δ 9.42 (1 H, d, J = 1.2 Hz), 8.76 (1 H, d, J = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz), 7.88 (1 H, br. s), 7.42 (1 H, d, J = 2.4 Hz), 7.33 (1 H, dd, J_1 = 8.6 Hz, J_2 = 2.4 Hz), 6.92 (1 H, d, J = 8.6 Hz), 3.52 (2 H, q, J = 6.8 Hz), 2.61 (2 H, t, J = 7.5 Hz), 2.32 (3 H, s), 1.98-1.90 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 163.0, 148.0, 147.3, 144.4, 144.4, 142.4, 135.4, 132.9, 130.3, 124.2, 119.3, 38.9, 29.6, 27.4, 20.8; HRMS (ESI): MNa^+, found 400.0280. $C_{16}H_{16}BrN_3NaO_3$ requires 400.0273.

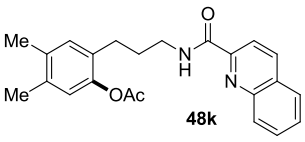
Ethyl 4-acetoxy-3-(3-(pyrazine-2-carboxamido)propyl)benzoate (48j). Brown colour liquid (38 mg, 35%); IR (CH_2Cl_2): ν_{max} 2937, 1763, 1716, 1675, 1532 and 1207 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$): δ 9.42 (1 H, d, J = 1.4 Hz), 8.76 (1 H, d, J = 2.4 Hz), 8.51 (1 H, dd, J_1 = 2.4 Hz, J_2 = 1.4 Hz), 7.98 (1 H, d, J = 2.0 Hz), 7.92 (1 H, dd, J_1 = 8.4 Hz, J_2 = 2.1Hz), 7.90 (1 H, br. s), 7.12 (1 H, d, J = 8.4 Hz), 4.37 (2 H, q, J = 7.1 Hz), 3.53 (2 H, q, J = 6.5 Hz), 2.69 (2 H, t, J = 7.9 Hz), 2.35 (3 H, s), 2.01-1.94 (2 H, m), 1.39 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 165.9, 163.0, 152.5, 147.3, 144.4, 142.5, 133.4, 131.6, 128.9, 128.4, 122.6, 61.1, 39.0, 29.7, 27.5, 20.9, 14.3; HRMS (ESI): MH^+, found 372.1551. $C_{19}H_{22}N_3O_5$ requires 372.1559.



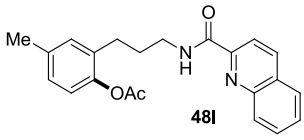
48j

4,5-Dimethyl-2-(3-(quinoline-2-carboxamido)propyl)phenyl acetate (48k). Colourless liquid (59 mg, 53%); IR (CH_2Cl_2): ν_{max} 2928, 1756, 1673, 1502 and 1217 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (3 H, s), 8.10 (1 H, d, J = 8.4 Hz), 7.90 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m), 7.06 (1 H, s), 6.81 (1 H, s), 3.57 (2 H, q, J = 6.8 Hz), 2.61 (2 H, t, J = 7.5 Hz), 2.30 (3 H, s), 2.21 (3 H, s), 2.20 (3 H, s), 2.02-1.95 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 164.5, 149.8, 146.7, 146.4, 137.5, 134.6, 131.3, 130.1, 129.6, 129.3, 127.9, 127.8, 123.1, 118.8, 39.2, 30.1, 27.2, 20.9, 19.4, 19.2; HRMS (ESI): MH^+, found 399.1684. $C_{23}H_{24}N_2NaO_3$ requires 399.1685.



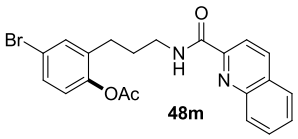
48k

4-Methyl-2-(3-(quinoline-2-carboxamido)propyl)phenyl acetate (48l). Colourless liquid (62 mg, 58%); IR (CH_2Cl_2): ν_{max} 2935, 1758, 1673, 1501 and 1193 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (3 H, br. s), 8.33 (2 H, s), 8.11 (1 H, d, J = 8.4 Hz), 7.90 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m), 7.11 (1 H, d, J = 1.7 Hz), 7.03 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.7 Hz), 6.92 (1 H, d, J = 8.2 Hz), 3.58 (2 H, q, J = 6.8 Hz), 2.64 (2 H, t, J = 7.5 Hz), 2.32 (3 H, s), 2.30 (3 H, s), 2.04-1.96 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 164.5, 149.8, 146.7, 146.5, 137.5, 135.9, 132.9, 130.9, 130.1, 129.6, 129.3, 127.9, 127.8, 122.0, 118.8, 39.2, 30.1, 27.6, 20.9, 20.9; HRMS (ESI): MH^+, found 363.1723. $C_{22}H_{23}N_2O_3$ requires 363.1709.



48l

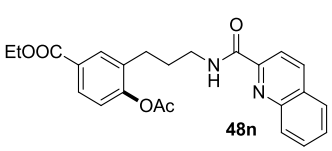
4-Bromo-2-(3-(quinoline-2-carboxamido)propyl)phenyl acetate (48m). Colourless liquid (46 mg, 50%); IR (CH_2Cl_2): ν_{max} 2937, 1760, 1673, 1501 and 1208 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (1 H, br. s), 8.34 (2 H, br. s), 8.11 (1 H, d, J = 8.5 Hz), 7.90 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m), 7.45 (1 H, d, J = 2.4 Hz), 7.34 (1 H, dd, J_1 = 8.6 Hz, J_2 = 2.4 Hz), 6.93(1 H, d, J = 8.6 Hz), 3.59 (2 H, q, J = 6.8 Hz), 2.65 (2 H, t, J = 7.5



48m

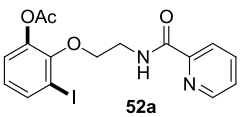
Hz), 2.30 (3 H, s), 2.01-1.98 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 164.6, 149.7, 148.0, 146.4, 137.6, 135.7, 133.0, 130.3, 130.2, 129.6, 129.3, 127.9, 127.8, 124.1, 119.3, 118.8, 39.1, 29.9, 27.5, 20.9; HRMS (ESI): MH^+, found 449.0489. $C_{21}H_{19}BrN_2NaO_3$ requires 449.0477.

Ethyl 4-acetoxy-3-(3-(quinoline-2-carboxamido)propyl)benzoate (48n). Brown colour liquid (69 mg, 55%); IR (CH_2Cl_2): ν_{max} 3387, 2229, 1763, 1716, 1673 and 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (1 H, br. s), 8.34 (2 H, br. s), 8.11 (1 H, d, J = 8.5 Hz), 8.02 (1 H, s), 7.91 (2 H, t, J = 8.7 Hz), 7.79 (1 H, t, J = 7.4 Hz), 7.64 (1 H, t, J = 7.5 Hz), 7.13 (1 H, d, J = 8.4 Hz), 4.38 (2 H, q, J = 7.1 Hz), 3.61 (2 H, q, J = 6.7 Hz), 2.73 (2 H, t, J = 7.5 Hz), 2.32 (3 H, s), 2.07-2.00 (2 H, m), 1.40 (3 H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 165.9, 164.6, 152.5, 149.7, 146.5, 137.5, 133.6, 131.7, 130.1, 129.6, 129.3, 128.8, 128.4, 127.9, 127.8, 122.5, 118.8, 61.1, 39.2, 30.0, 27.6, 20.9, 14.4; HRMS (ESI): MH^+, found 421.1774. $C_{24}H_{25}N_2O_5$ requires 421.1763.



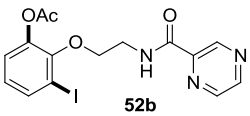
48n

3-Iodo-2-(2-(picolinamido)ethoxy)phenyl acetate (52a). Brown colour liquid (68 mg, 40%); IR (CH_2Cl_2): ν_{max} 2963, 1772, 1642, 1594 and 1197 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (br. s, 1H), 8.59-8.57 (m, 1H), 8.22 (dt, J = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.87 (td, J = 7.6 Hz, J_2 = 1.7 Hz, 1H), 7.66 (dd, J = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.47-7.43 (m, 1H), 7.08 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 6.89 (t, J = 8.0 Hz, 1H), 4.16 (t, J = 4.9 Hz, 2H), 3.92 (q, J = 5.4 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 164.5, 150.3, 149.7, 148.2, 143.6, 137.3, 136.8, 126.3, 124.2, 122.2, 92.5, 72.5, 39.6, 20.6; HRMS (ESI): MNa^+, found 448.9963. $C_{16}H_{15}IN_2NaO_4$ requires 448.9974.



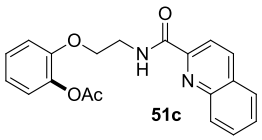
52a

3-Iodo-2-(2-(pyrazine-2-carboxamido)ethoxy)phenyl acetate (52b). Brown colour liquid (51 mg, 30%); IR (CH_2Cl_2): ν_{max} 1769, 1676, 1530, 1454 and 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (1 H, d, J = 1.2 Hz), 8.78 (1 H, d, J = 2.4 Hz), 8.57 (1 H, t, J = 1.8 Hz), 8.48 (1 H, br. s), 7.66 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz), 7.09 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz), 6.90 (1 H, t, J = 8.0 Hz), 4.17 (2 H, t, J = 8.0 Hz), 3.92 (2 H, q, J = 5.5 Hz), 2.26 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 163.2, 150.1, 147.7, 144.4, 144.3, 143.5, 142.7, 136.8, 126.4, 124.2, 92.4, 72.2, 39.7, 20.7; HRMS (ESI): MNa^+, found 449.9913. $C_{15}H_{14}IN_3NaO_4$ requires 449.9927.



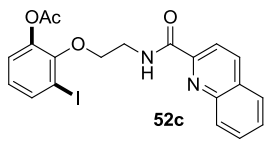
52b

2-(2-(Quinoline-2-carboxamido)ethoxy)phenyl acetate (51c). Brown colour liquid (18 mg, 13%); IR (CH_2Cl_2): ν_{max} 2932, 1767, 1676, 1528, 1500 and 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (1 H, br. s), 8.34-8.33 (2 H, m), 8.19 (1 H, d, J = 8.6 Hz), 7.90 (1 H, dd, J_1 = 8.1 Hz, J_2 = 0.8 Hz), 7.81-7.77 (1 H, m), 7.66-7.62 (1 H, m), 7.24-7.19 (1 H, m), 7.10-6.97 (3 H, m), 4.29 (2 H, t, J = 5.2 Hz), 3.95 (2 H, q, J = 5.5 Hz), 2.35 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 164.8, 150.0, 149.5, 146.6, 140.2, 137.5, 130.1, 129.8, 129.3, 128.0, 127.7, 127.0, 122.9, 121.5, 118.8, 113.8, 67.6, 39.0, 20.7; HRMS (ESI): MH^+, found 351.1338. $C_{20}H_{19}N_2O_4$ requires 351.1345.



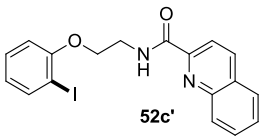
51c

3-Iodo-2-(2-(quinoline-2-carboxamido)ethoxy)phenyl acetate (52c). Brown colour liquid (62 mg, 33%); IR (CH_2Cl_2): ν_{max} 2941, 1769, 1676, 1526, 1501 and 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.97 (1 H, br. s), 8.34 (2 H, s), 8.16 (1 H, d, J = 8.4 Hz), 7.92-7.90 (1 H, m), 7.82-7.78 (1 H, m), 7.68 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 7.67-7.63 (1 H, m), 7.10 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 6.91 (1 H, t, J = 8.0 Hz), 4.21 (2 H, t, J = 4.8 Hz), 4.00 (2 H, q, J = 5.4 Hz), 2.21 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 164.7, 150.3, 149.5, 146.5, 143.7, 137.5, 136.8, 130.3, 129.8, 129.3, 128.0, 127.8, 126.4, 124.2, 118.8, 92.6, 72.6, 39.7, 20.7; HRMS (ESI): MH^+, found 477.0326. $C_{20}H_{18}IN_2O_4$ requires 477.0311.



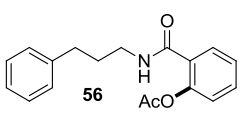
52c

***N*-(2-(2-Iodophenoxy)ethyl)quinoline-2-carboxamide (52c′).** Colourless liquid (16 mg, 10%); IR (CH_2Cl_2): ν_{max} 2878, 1676, 1527, 1427 and 1277 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (1 H, br. s), 8.33 (2 H, s), 8.17 (1 H, d, J = 8.4 Hz), 7.89 (1 H, dd, J_1 = 8.2 Hz, J_2 = 0.8 Hz), 7.82-7.76 (2 H, m), 7.66-7.62 (1 H, m), 7.34-7.30 (1 H, m), 6.89 (1 H, dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 6.75 (1 H, td, J_1 = 7.6 Hz, J_2 = 1.3 Hz), 4.27 (2 H, t, J = 5.1 Hz), 4.04 (2 H, q, J = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 157.0, 149.5, 146.6, 139.4, 137.5, 130.1, 129.9, 129.6, 129.3, 128.0, 127.7, 123.1, 112.5, 86.9, 68.3, 38.8; HRMS (ESI): MH^+, found 419.0270. $C_{20}H_{18}IN_2O_4$ requires 419.0256.



52c'

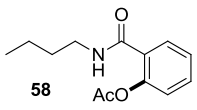
2-((3-Phenylpropyl)carbamoyl)phenyl acetate (56). Yellow colour liquid (15 mg, 35%); IR (CH_2Cl_2): ν_{max} 2933, 1764, 1642, 1593, 1452 and 1198 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (1 H, dd, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.50-7.45 (1 H, m), 7.33-7.29 (3 H, m), 7.23-7.20 (3 H, m), 7.11 (1 H, dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz), 6.20 (1 H, br s), 3.49-3.44 (2 H, m), 2.73 (2 H, t, J = 7.6 Hz), 2.33 (3 H, s), 1.98-1.90 (2 H,



56

m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 165.9, 147.9, 141.3, 131.7, 129.4, 128.8, 128.5, 128.4, 126.3, 126.1, 123.2, 39.6, 33.3, 31.3, 21.1; HRMS (ESI): MNa^+, found 320.1251. $C_{18}H_{19}NNaO_3$ requires 320.1263.

2-(Butylcarbamoyl)phenyl acetate (58). Yellow colour liquid (11 mg, 33%); IR (CH_2Cl_2): ν_{max} 2966, 1772, 1642, 1594 and 1197 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (1 H, d, *J* = 7.7 Hz), 7.48-7.44 (1 H, m), 7.32-7.28 (1 H, m), 7.10 (1 H, d, *J* = 8.1 Hz), 6.26 (1 H, br. s), 3.42 (2 H, q, *J* = 6.7 Hz), 2.33 (3 H, s), 1.61-1.54 (2 H, m), 1.46-1.37 (2 H, m), 0.97 (3 H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 165.7, 147.8, 131.6, 129.6, 128.7, 126.3, 123.1, 39.6, 31.7, 21.0, 20.1, 13.8; HRMS (ESI): MNa^+, found 258.1100. $C_{13}H_{17}NNaO_3$ requires 258.1106.



58

General procedure for the magnetic nano Fe_3O_4-catalyzed direct azidation of allylic/benzylic alcohol, Step '1'. A round-bottom flask containing a mixture of the corresponding allylic/benzylic alcohol **83** (0.5 mmol, 1 equiv), trimethylsilyl azide (1.25-1.5 mmol, 2.5-3 equiv) and magnetic nano Fe_3O_4 (particle size < 50 nm, 15 mol% and the Fe_3O_4 nanoparticles can be handled using a Teflon spatula) in 1,2-dichloroethane (1.5-3 mL) was stirred at 70 ^oC for 6 h. The purification of the corresponding azide product **84** and recovery of the catalyst (Fe_3O_4 nanoparticles) were performed as stated in Step '2'. **Step '2'.** After the reaction time, a magnet was externally appended to the RB flask, the magnetic Fe_3O_4 nanoparticles were gathered at the walls of the RB flask and the resulting clear solution of the reaction mixture was transferred in to an another RB flask with the help of a dropper. Then, the catalyst (Fe_3O_4 nanoparticles) was washed again using EtOAc (2 mL). The RB flask containing Fe_3O_4 nanoparticles was heated in an oven (at 100-110 ^oC, overnight) and the catalyst was reused in the next cycle. The combined organic layers were evaporated under vacuum and purified by column chromatography to give the corresponding azide product **84**.

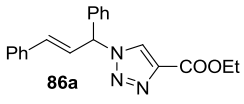
General procedure (Method A) for the one-pot magnetic nano Fe_3O_4-catalyzed direct azidation of allylic alcohols and click reaction, Step '3'. The direct azidation of the corresponding allylic/benzylic alcohol **83** (0.5 mmol, 1 equiv) was carried out using the step '1' procedure. Next, the catalyst (Fe_3O_4 nanoparticles) was removed using an external magnet and the solvent was evaporated. Then, to the crude reaction mixture obtained in the step '1' procedure, THF (3 mL), water (3 mL), alkyne (1-1.2 mmol), $CuSO_4.5H_2O$ (30 mol%) and

sodium *L*-ascorbate (30 mol%) were sequentially added. Then, the reaction mixture was stirred at rt for 12 h, then, was extracted using EtOAc and the combined organic layers were concentrated and the resulting crude reaction mixture was purified by column chromatography (50% EtOAc/Hexanes), to afford the corresponding 1,2,3-triazole product **86**/**88** (see the corresponding Tables/Schemes for specific entries).

General procedure for the copper(II) triflate-catalyzed one-pot direct azidation of alcohol followed by click reaction (Method B): A solution of allylic alcohol **83** (0.5 mmol) and $TMSN_3$ (0.75 mmol, 1.5 equiv) and copper(II) triflate (5 mol%) in DCM (3 mL) was stirred at rt for 3 h under an inert atmosphere. Then, DCM was removed under reduced pressure. After this, to the resulting crude reaction mixture THF (2-3 mL), water (2-3 mL), alkyne (1-1.25 mmol) and sodium *L*-ascorbate (50 mol%) were added and the reaction mixture was stirred at rt for 20 h. Then, the reaction mixture was extracted using EtOAc and the combined organic layers were evaporated and the resulting reaction mixture was purified by silica gel column chromatography to afford the triazole product **86**/**88** (See the corresponding Tables/Schemes for specific entries).

General procedure for the copper(II) triflate-catalyzed one-pot direct azidation of allylic and benzylic methyl ethers followed by click reaction (Method B): A solution of allyl methyl ether **87** (0.5 mmol) and $TMSN_3$ (0.75 mmol, 1.5 equiv) and copper(II) triflate (5 mol%) in DCM (3 mL) was stirred at rt for 3 h under an inert atmosphere. After this period, the solvent was evaporated. Then, to the resulting reaction mixture THF (2 mL), water (2 mL), alkyne (1.25 mmol, 2.5 equiv) and sodium *L*-ascorbate (50 mol%) were added and the reaction mixture was stirred at rt for 20 h. Then, the reaction mixture was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc/Hexanes) to give the desired 1,2,3-trizole product **86**/**88** (see the corresponding Tables/Schemes for specific entries).

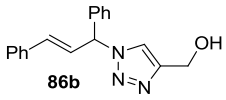
(*E*)-Ethyl 1-(1,3-diphenylallyl)-1*H*-1,2,3-triazole-4-carboxylate (86a). Following the general procedure, **86a** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a brown solid (286 mg, 86%); R_f (30% EtOAc/Hexanes) 0.42; mp 123-125 °C; IR (thin film): ν_{max} 2982, 1727, 1449, 1202 and 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (1 H, s), 7.42-7.29 (10 H,



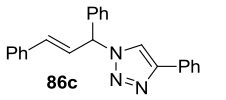
86a

m), 6.70 (1 H, dd, J_1 = 15.7 Hz, J_2 = 6.8 Hz), 6.58 (1 H, d, J = 6.8 Hz), 6.50 (1 H, d, J = 15.7 Hz), 4.42 (2 H, q, J = 7.1 Hz), 1.40 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.8, 140.3, 137.1, 135.3, 135.2, 129.3, 129.1, 128.8, 127.5, 126.9, 124.9, 66.7, 61.4, 14.3 ppm; HRMS (ESI): MNa^+, found 356.1385. $C_{20}H_{19}N_3NaO_2$ requires 356.1375.

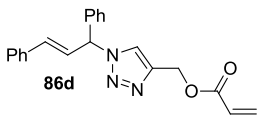
(*E*)-(1-(1,3-Diphenylallyl)-1*H*-1,2,3-triazol-4-yl)methanol (86b). Following the general procedure, **86b** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (238 mg, 82%); R_f (50% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 3375, 2954, 1731, 1450, 1223 and 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 (1 H, s), 7.41-7.28 (10 H, m), 6.70 (1 H, dd, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 6.52-6.47 (2 H, m), 4.79 (2 H, s) , 3.36 (1 H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.8, 137.7, 135.5, 134.7, 129.2, 128.8, 128.7, 128.6, 127.5, 126.9, 125.5, 121.2, 66.5, 56.4; HRMS (ESI): MNa^+, found 314.1254. $C_{18}H_{17}N_3ONa$ requires 314.1269.



(*E*)-1-(1,3-Diphenylallyl)-4-phenyl-1*H*-1,2,3-triazole (86c). Following the general procedure, **86c** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (303 mg, 90%); R_f (30% EtOAc/Hexanes) 0.42; mp 178-179 °C; IR (thin film) ν_{max} 2925, 1724, 1450, 1226 and 970 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.86 (2 H, d, J = 7.1 Hz), 7.79 (1 H, s), 7.45-7.31 (13 H, m), 6.77 (1 H, dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz), 6.59-6.53 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.9, 137.9, 135.6, 134.7, 130.5, 129.2, 128.8, 128.8, 128.6, 128.2, 127.5, 126.9, 125.8, 125.6, 118.9, 66.4 ppm; HRMS (ESI): MH^+, found 338.1642. $C_{23}H_{20}N_3$ requires 338.1657.

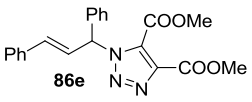


(*E*)-(1-(1,3-Diphenylallyl)-1*H*-1,2,3-triazol-4-yl)methyl acrylate (86d). Following the general procedure, **86d** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (321 mg, 93%); R_f (30% EtOAc/Hexanes) 0.42; mp 112-114 °C; IR (thin film) ν_{max} 2926, 1495, 1454 and 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (1 H, s), 7.43-7.29 (10 H, m), 6.72 (1 H, dd, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 6.54-6.42 (3 H, m), 6.15 (1 H, dd, J_1 = 17.3 Hz, J_2 = 10.4 Hz), 5.87 (1 H, d, J = 10.4 Hz), 5.33 (2 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.0, 142.8, 137.7, 135.5, 134.9, 131.6, 129.2, 128.9, 128.7, 128.6, 128.0, 127.4,



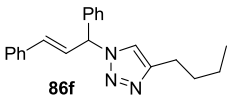
126.9, 125.5, 123.1, 66.6, 57.8 ppm; HRMS (ESI): MH^+, found 346.1555. $C_{21}H_{20}N_3O_2$ requires 346.1556.

(*E*)-Dimethyl 1-(1,3-diphenylallyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (86e). Following the general procedure, **86e** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as yellow liquid (324 mg, 86%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2950, 1735, 1485, 1210 and 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.45-7.28 (10 H, m), 6.96 (1 H, dd, J_1 = 15.7 Hz, J_2 = 8.0 Hz), 6.81 (1 H, d, J = 8.0 Hz), 6.64 (1 H, d, J = 15.7 Hz), 3.97 (3 H, s), 3.85 (3 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.6, 159.3, 139.8, 137.3, 135.5, 135.1, 130.2, 129.0, 128.8, 128.7, 128.6, 127.4, 127.0, 125.1, 67.1, 53.4, 52.7 ppm; HRMS (ESI): MNa^+, found 400.1285. $C_{21}H_{19}N_3NaO_4$ requires 400.1273.



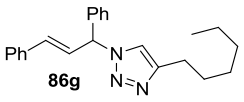
86e

(*E*)-4-Butyl-1-(1,3-diphenylallyl)-1*H*-1,2,3-triazole (86f). Following the general procedure, **86f** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (154 mg, 98%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 2927, 1495, 1451,1215 and 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.43-7.28 (11 H, m), 6.72 (1 H, dd, J_1 = 16.1 Hz, J_2 = 6.6 Hz), 6.51 (1 H, d, J = 4.58 Hz), 6.48 (1 H, d, J = 2.8 Hz), 2.74 (2 H, t, J = 7.6 Hz), 1.71-1.63 (2 H, m), 1.42-1.35 (2 H, m), 0.94 (3 H, t, J = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.2, 135.6, 134.4, 129.1, 128.7, 128.6, 128.5, 127.4, 126.8, 125.9, 119.8, 66.2, 31.6, 25.5, 22.4, 13.9 ppm; HRMS (ESI): MNa^+, found 340.1773. $C_{21}H_{23}N_3Na$ requires 340.1790.



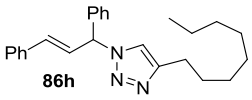
86f

(*E*)-1-(1,3-Diphenylallyl)-4-hexyl-1*H*-1,2,3-triazole (86g). Following the general procedure, **86g** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (293 mg, 85%); R_f (30% EtOAc/Hexanes) 0.42; mp 98-100 °C; IR (thin film) ν_{max} 2928, 1495, 1454 and 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.42-7.28 (11 H, m), 6.73 (1 H, dd, J_1 = 16.1 Hz, J_2 = 6.5 Hz), 6.51-6.48 (2 H, m), 2.74 (2 H, t, J = 7.6 Hz), 1.72-1.67 (2 H, m), 1.39-1.29 (6 H, m), 0.89 (3 H, t, J = 6.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.6, 138.2, 135.7, 134.4, 129.1, 128.7, 128.6, 128.5, 127.4, 126.8, 126.0, 119.9, 66.2, 31.6, 29.4, 29.0, 25.9, 22.6, 14.1 ppm; HRMS (ESI): MH^+, found 346.2294. $C_{23}H_{28}N_3$ requires 346.2283.

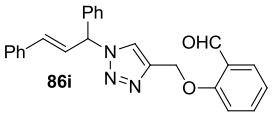


86g

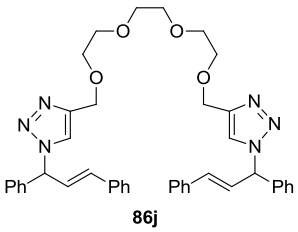
(*E*)-1-(1,3-Diphenylallyl)-4-octyl-1*H*-1,2,3-triazole (86h). Following the general procedure, **86h** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (343 mg, 92%); R_f (30% EtOAc/Hexanes) 0.42; mp 99-101 °C; IR (thin film) ν_{max} 2926, 1495, 1454 and 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.43-7.28 (11 H, m), 6.72 (1 H, dd, J_1 = 16.1 Hz, J_2 = 6.6 Hz), 6.49 (2 H, dd, J_1 = 12.0 Hz, J_2 = 4.4 Hz), 2.73 (2 H, t, J = 7.7 Hz), 1.71-1.64 (2 H, m), 1.38-1.27 (10 H, m), 0.89 (3 H, t, J = 6.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.6, 138.2, 135.7, 134.4, 129.1, 128.7, 128.6, 128.5, 127.4, 126.8, 126.0, 119.8, 66.2, 31.9, 29.5, 29.3, 29.2, 25.8, 22.7, 14.1 ppm; HRMS (ESI): MH^+, found 374.2591. $C_{25}H_{32}N_3$ requires 374.2596.



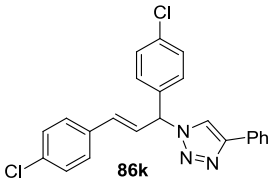
(*E*)-2-((1-(1,3-Diphenylallyl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde (86i). Following the general procedure, **86i** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 27:73) as a red colored solid (336 mg, 85%); R_f (30% EtOAc/Hexanes) 0.55; mp 111-113 °C; IR (thin film) ν_{max} 3030, 1663, 1598, 1456 and 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.44 (1 H, s), 7.82 (1 H, d, J = 7.6 Hz), 7.75 (1 H, br. s), 7.54 (1 H, t, J = 7.4 Hz), 7.42-7.27 (10 H, m), 7.17 (1 H, d, J = 8.5 Hz), 7.03 (1 H, t, J = 7.6 Hz), 6.74 (1 H, dd, J_1 = 16.1 Hz, J_2 = 6.8 Hz), 6.51 (2 H, dd, J_1 = 12.0 Hz, J_2 = 4.4 Hz), 5.33 (2 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 189.7, 160.5, 143.3, 137.7, 136.1, 135.4, 134.9, 129.2, 128.9, 128.8, 128.7, 128.6, 127.4, 126.9, 125.4, 125.0, 122.5, 121.3, 113.1, 66.7, 62.6 ppm; HRMS (ESI): MH^+, found 396.1702. $C_{25}H_{22}N_3O_2$ requires 396.1712.



1,12-Bis(1-((*E*)-1,3-diphenylallyl)-1*H*-1,2,3-triazol-4-yl)-2,5,8,11-tetraoxadodecane (86j). Following the general procedure, **86j** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as colorless liquid (522 mg, 75%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2869, 1495, 1450 and 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2 H, s), 7.41-7.28 (20 H, m), 6.71 (2 H, dd, J_1 = 15.6 Hz, J_2 = 7.2 Hz), 6.52-6.47 (4 H, m), 4.69 (4 H, s), 3.70-3.62 (8 H, m), 3.60 (4 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.2, 137.9, 135.5, 134.7, 129.1, 128.8, 128.7, 128.5, 127.5, 126.8, 125.7, 121.9, 70.5, 70.5, 69.8, 66.4, 64.8 ppm; HRMS (ESI): MH^+, found 697.3505. $C_{42}H_{45}N_6O_4$ requires 697.3502.

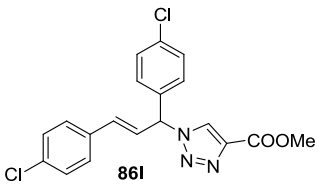


(*E*)-1-(1,3-Bis(4-chlorophenyl)allyl)-4-phenyl-1*H*-1,2,3-triazole (86k). Following the general procedure, **86k** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless solid (151 mg, 75%); R_f (30% EtOAc/Hexanes) 0.52; mp: 88-90 ^oC; IR (CH_2Cl_2) ν_{max} 2928, 1595, 1491, 1407 and 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (2 H, dd, J_1 = 7.1 Hz, J_2 = 1.4 Hz), 7.79 (1 H, s), 7.45-7.25 (11 H, m), 6.71 (1 H, dd, J_1 = 15.8 Hz, J_2 = 6.8 Hz), 6.50-6.45 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.0, 136.2, 134.9, 134.4, 133.8, 133.8, 130.3, 129.4, 129.0, 128.9, 128.8, 128.4, 128.1 125.8, 125.7, 118.9, 65.7 ppm; HRMS (ESI): MNa^+, found 428.0672. $C_{23}H_{17}Cl_2N_3Na$ requires 428.0697.



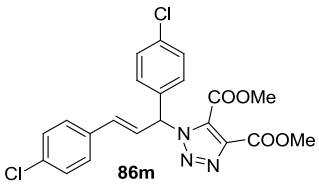
86k

(*E*)-Ethyl 1-(1,3-bis(4-chlorophenyl)allyl)-1*H*-1,2,3-triazole-4-carboxylate (86l). Following the general procedure, **86l** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (120 mg, 60%); R_f (30% EtOAc/Hexanes) 0.48; IR (CH_2Cl_2) ν_{max} 2983, 1731, 1594, 1492, 1093 and 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.10 (1 H, s), 7.39 (2 H, d, J = 8.5 Hz), 7.32 (4 H, s), 7.23 (2 H, d, J = 8.4 Hz), 6.65 (1 H, dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz), 6.54 (1 H, d, J = 6.9 Hz), 6.46 (1 H, dd, J_1= 15.8 Hz, J_2= 1.1 Hz), 4.42 (2H, q, J = 7.1 Hz), 1.40 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.6, 140.4, 135.4, 135.3, 134.7, 134.4, 133.5, 129.6, 129.0, 128.8, 128.1, 126.8, 125.0, 66.0, 61.5, 14.3 ppm; HRMS (ESI): MNa^+, found 424.0578. $C_{20}H_{17}Cl_2N_3NaO_2$ requires 424.0596.



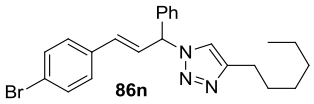
86l

(*E*)-Dimethyl 1-(1,3-bis(4-chlorophenyl)allyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate (86m). Following the general procedure, **86m** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a yellow liquid (232 mg, 52%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film): ν_{max} 2954, 1732, 1491, 1224 and 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.37-7.26 (8 H, m), 6.88 (1 H, dd, J_1 = 15.6 Hz, J_2 = 7.7 Hz), 6.80 (1 H, d, J = 7.8 Hz), 6.56 (1 H, d, J = 15.6 Hz), 3.98 (3 H, s), 3.90 (3 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.5, 159.2, 140.1, 135.6, 135.0, 134.5, 134.1, 133.8, 129.6, 129.3, 129.0, 128.9, 128.2, 125.4, 66.1, 53.5, 52.8 ppm; HRMS (ESI): MNa^+, found 468.0487. $C_{21}H_{17}Cl_2N_3NaO_4$ requires 468.0494.

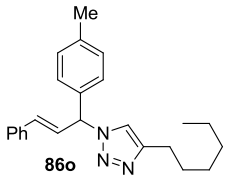


86m

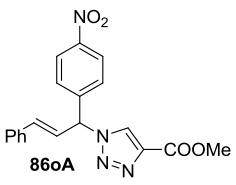
(*E*)-1-(3-(4-Bromophenyl)-1-phenylallyl)-4-hexyl-1*H*-1,2,3-triazole (86n). Following the general procedure, **86n** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as colorless liquid (346 mg, 82%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2927, 2857, 1588, 1488 and 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.53-7.13 (10 H, m), 6.75-6.64 (1 H, m), 6.51-6.38 (2 H, m), 2.75-2.70 (2 H, m), 1.69-1.65 (2 H, m), 1.38-1.28 (6 H, m), 0.88 (3 H, t, J = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.8, 148.7, 137.9, 137.3, 135.4, 134.9, 134.6, 133.1, 132.2, 131.8, 129.1, 129.1, 128.8, 128.7, 128.3, 127.4, 126.9, 126.9, 125.3, 122.7, 122.3, 119.9, 119.8, 66.1, 65.6, 31.5, 29.4, 29.0, 25.8, 22.6, 14.1 ppm; HRMS (ESI): MH^+, found 424.1386. $C_{23}H_{27}BrN_3$ requires 424.1388. Isolated as a mixture of regioisomers and NMR values given for both isomers.



(*E*)-4-Phenyl-1-(3-phenyl-1-(*p*-tolyl)allyl)-1*H*-1,2,3-triazole (86o). Following the general procedure, **86o** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as colorless solid (253 mg, 72%); R_f (30% EtOAc/Hexanes) 0.42; mp 134-136 °C; IR (thin film) ν_{max} 2930, 1482, 1456, 1224 and 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.87 (2 H, d, J = 7.5 Hz), 7.82 (1 H, s), 7.55-7.19 (12 H, m), 6.85-6.33 (3 H, m), 2.32 (3 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.9, 147.6, 138.1, 136.7, 136.0, 135.7, 135.6, 134.8, 133.8, 132.8, 131.3, 130.6, 130.5, 129.2, 128.9, 128.5, 128.2, 127.4, 127.3, 127.0, 126.8, 126.8, 126.3, 126.0, 125.8, 125.7, 119.2, 118.8, 66.6, 63.0, 19.8, 19.2 ppm; HRMS (ESI): MH^+, found 352.1807. $C_{24}H_{22}N_3$ requires 352.1814. Isolated as a mixture of regioisomers and NMR values given for both isomers.

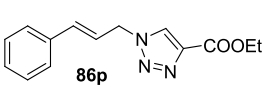


(*E*)-Ethyl 1-(1-(4-nitrophenyl)-3-phenylallyl)-1*H*-1,2,3-triazole-4-carboxylate (86oA). Following the general procedure, **86oA** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as light yellow colour liquid (128 mg, 68%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2979, 1731, 1519, 1344 and 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.28-8.19 (2 H, m), 8.06 (1 H, s), 7.57-7.28 (7 H, m), 6.92 (1 H, dd, J_1 = 15.9 Hz, J_2 = 6.5 Hz), 6.66-6.48 (2 H, m), 4.43 (2 H, q, J = 7.1 Hz), 1.40 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.7, 147.6, 141.6, 140.4, 137.1, 136.1, 132.5, 129.8, 129.6, 129.6, 129.3,



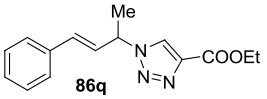
128.9, 128.2, 127.7, 127.7, 127.5, 127.0, 127.0, 126.9, 124.4, 124.1, 123.0, 66.5, 66.0, 61.6, 61.5, 14.3 ppm; HRMS (ESI): MNa^+, found 401.1239. $C_{20}H_{18}N_4NaO_4$ requires 401.1226. Isolated as a mixture of regioisomers and NMR values given for both isomers.

Ethyl 1-cinnamyl-1*H*-1,2,3-triazole-4-carboxylate (86p). Following the general procedure, **86p** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless solid (89 mg, 70%); R_f (30% EtOAc/Hexanes) 0.42; mp: 87-89 ^oC; IR (CH_2Cl_2) ν_{max} 3139, 2983, 1731, 1450 and 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (1 H, s), 7.39-7.28 (5 H, m), 6.69 (1 H, d, J = 15.8 Hz), 6.36-6.29 (1 H, m), 5.18 (2 H, d, J = 6.7 Hz), 4.39 (2 H, q, J = 7.1 Hz), 1.38 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.7, 140.7, 136.2, 135.2, 128.8, 127.3, 126.8, 120.9, 61.3, 52.6, 14.3 ppm; HRMS (ESI): MNa^+, found 280.1059. $C_{14}H_{15}N_3NaO_2$ requires 280.1062.



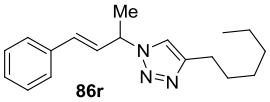
86p

(*E*)-Ethyl 1-(4-phenylbut-3-en-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (86q). Following the general procedure, **86q** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless solid (102 mg, 76%); R_f (30% EtOAc/Hexanes) 0.50; mp: 77-79 ^oC; IR (CH_2Cl_2) ν_{max} 2984, 1738, 1494, 1376 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.16 (1 H, s), 7.37-7.24 (5 H, m), 6.59 (1 H, d, J = 15.9 Hz), 6.35 (1 H, dd, J_1 = 15.9 Hz, J_2 = 6.9 Hz), 5.49-5.44 (1 H, m), 4.39 (2 H, q, J = 7.1 Hz), 1.80 (3 H, d, J = 6.9 Hz), 1.37 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.8, 140.1, 135.3, 133.5, 128.7, 128.6, 126.8, 126.7, 125.9, 61.2, 59.0, 20.9, 14.3 ppm; HRMS (ESI): MNa^+, found 294.1208. $C_{15}H_{17}N_3NaO_2$ requires 294.1218.



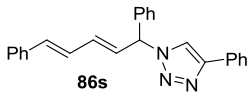
86q

(*E*)-4-Hexyl-1-(4-phenylbut-3-en-2-yl)-1*H*-1,2,3-triazole (86r). Following the general procedure, **86r** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (120 mg, 85%); R_f (30% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2) ν_{max} 3028, 1482, 1448, 1178 and 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.36-7.20 (6 H, m), 6.52 (1 H, d, J = 16.0 Hz), 6.35 (1 H, dd, J_1 = 15.9 Hz, J_2 = 6.6 Hz), 5.38-5.31 (1 H, m), 2.70 (2 H, t, J = 7.9 Hz), 1.75 (3 H, d, J = 6.9 Hz), 1.69-1.62 (2 H, m), 1.36-1.22 (6 H, m), 0.86 (3 H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.4, 135.7, 132.4, 128.7, 128.3, 128.1, 126.6, 118.9, 58.2, 31.6, 29.5, 29.0, 25.8, 22.6, 20.8, 14.1 ppm; HRMS (ESI): MH^+, found 284.2115. $C_{18}H_{26}N_3$ requires 284.2127.



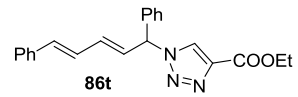
86r

1-((*2E,4E*)-1,5-Diphenylpenta-2,4-dien-1-yl)-4-phenyl-1*H*-1,2,3-triazole (86s). Following the general procedure, **86s** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (225 mg, 62%); R_f (30% EtOAc/Hexanes) 0.42; mp 131-133 °C; IR (thin film) ν_{max} 3028, 1494, 1449 and 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.87 (2 H, d, J = 8.4 Hz), 7.77 (1 H, s), 7.47-7.26 (13 H, m), 6.88 (1 H, dd, J_1 = 15.6 Hz, J_2 = 8.4 Hz), 6.60 (1 H, d, J = 15.6 Hz), 6.52 (1 H, d, J = 5.6 Hz), 6.40-6.28 (2 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.8, 137.8, 136.6, 135.1, 134.9, 130.6, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 128.2, 128.1, 127.5, 127.0, 126.6, 125.8, 118.9, 66.2 ppm; HRMS (ESI): MNa^+, found 386.1622. $C_{25}H_{21}N_3Na$ requires 386.1633.



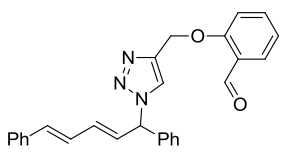
86s

Ethyl 1-((*2E,4E*)-1,5-diphenylpenta-2,4-dien-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (86t). Following the general procedure, **86t** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (131 mg, 73%); R_f (30% EtOAc/Hexanes) 0.32; IR (CH_2Cl_2) ν_{max} 2983, 1731, 1449, 1377 and 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.10 (1 H, s), 7.41-7.38 (5 H, m), 7.33 (2 H, t, J = 7.5 Hz), 7.29-7.26 (3 H, m), 6.87-6.81 (1 H, m), 6.59 (1 H, d, J = 15.7 Hz), 6.51 (1 H, d, J = 5.3 Hz), 6.29-6.26 (2 H, m), 4.42 (2 H, q, J = 7.2 Hz), 1.40 (3 H, t, J = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.8, 140.2, 137.1, 136.5, 135.5, 135.4, 129.3, 129.1, 128.7, 128.2, 128.2, 127.5, 126.9, 126.7, 126.6, 66.5, 61.4, 14.4 ppm; HRMS (ESI): MNa^+, found 382.1522. $C_{22}H_{21}N_3NaO_2$ requires 382.1531.



86t

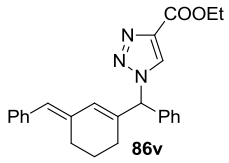
2-((1-((*2E,4E*)-1,5-Diphenylpenta-2,4-dien-1-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde (86u). Following the general procedure, **86u** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as yellow liquid (240 mg, 57%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 3030, 1663, 1598, 1456 and 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.46 (1 H, s), 7.85 (1 H, d, J = 7.5 Hz), 7.67 (1 H, s), 7.57 (1 H, t, J = 8.5 Hz), 7.42-7.26 (10 H, m), 7.19 (1 H, d, J = 8.4 Hz), 7.08 (1 H, t, J = 7.5 Hz), 6.86 (1 H, dd, J_1 = 15.6 Hz, J_2 = 9.4 Hz), 6.57 (1 H, d, J = 15.6 Hz), 6.46 (1 H, d, J = 5.7 Hz), 6.36-6.24 (2 H, m), 5.36 (2 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 189.7, 160.5, 143.4, 137.6, 136.5, 136.1, 135.2, 135.2, 129.2, 128.9, 128.7, 128.7, 128.6, 128.2, 127.4, 126.9, 126.6,



86u

125.1, 122.2, 121.4, 113.1, 66.5, 62.7 ppm; HRMS (ESI): MH^+, found 422.1858. $C_{27}H_{24}N_3O_2$ requires 422.1869.

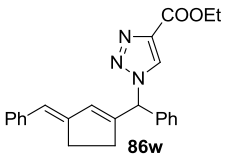
(*E*)-Ethyl 1-((3-benzylidenecyclohex-1-en-1-yl)(phenyl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (86v). Following the general procedure, **86v** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (247 mg, 62%);



86v

R_f (30% EtOAc/Hexanes) 0.42; mp 135-137 °C; IR (thin film) ν_{max} 2936, 1722, 1447, 1224 and 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.01/7.90* (1 H, s), 7.44-7.20 (9 H, m), 7.04 (1 H, d, J = 7.2 Hz), 6.48/6.35* (1 H, s), 6.25/6.17* (1 H, s), 5.74 (1 H, s), 4.44 (2 H, q, J = 7.2 Hz), 2.68-2.65/2.48-2.45* (2 H, m), 2.12 (2 H, t, J = 5.8 Hz), 1.88-1.85*/1.80-1.73 (2 H, m), 1.42 (3 H, t, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.9, 139.9, 138.5, 137.2, 136.6, 135.7, 135.6, 134.3, 131.4, 129.4, 129.3, 129.3, 129.2, 129.1, 128.9, 128.3, 128.2, 128.2, 128.1, 127.5, 127.1, 126.7, 126.6, 125.3, 70.1, 70.0, 61.4, 61.3, 31.9, 28.0, 27.6, 26.4, 22.9, 22.5, 14.4 ppm; HRMS (ESI): MNa^+, found 422.1844. $C_{25}H_{25}N_3NaO_2$ requires 422.1844. Isolated as a mixture of regioisomers and the characterization data given correspond to both isomers and *corresponds to the minor isomer in the ^1H NMR.

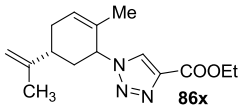
(*E*)-Ethyl 1-((3-benzylidenecyclopent-1-en-1-yl)(phenyl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (86w). Following the general procedure, **86w** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (173 mg, 45%);



86w

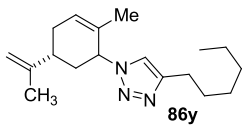
R_f (30% EtOAc/Hexanes) 0.42; mp 153-155 °C; IR (thin film) ν_{max} 2926, 1724, 1448, 1202 and 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.05/8.00* (1 H, s), 7.45-7.43 (3 H, m), 7.34 (5 H, d, J = 4.4 Hz), 7.22-7.17 (1 H, m), 6.61 (1 H, s), 6.35 (1 H, s), 5.90 (1 H, s), 4.44 (2 H, q, J = 7.1 Hz), 3.02-2.99 (2 H, m), 2.63-2.60 (2 H, m), 1.42 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.8, 160.8, 150.7, 147.0, 145.8, 146.4, 140.1, 140.0, 138.1, 137.9, 136.7, 135.6, 135.4, 130.6, 129.4, 128.5, 128.1, 128.0, 128.0, 127.8, 127.0, 126.3, 126.3, 122.3, 120.7, 66.4, 66.2, 61.4, 34.0, 31.9, 31.5, 29.5, 14.4 ppm; HRMS (ESI): MNa^+, found 408.1696. $C_{24}H_{23}N_3NaO_2$ requires 408.1688. Isolated as a mixture of regioisomers and the characterization data given correspond to both isomers and *corresponds to the minor isomer in the ^1H NMR.

Ethyl 1-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (86x). Following the general procedure, **86x** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (110 mg, 80%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 3132, 2977, 1731, 1645, 1538 and 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.02*/8.01 (1 H, s), 5.92 (1 H, br. s), 5.12 (1 H, br. s), 4.64 (1 H, s), 4.57 (1 H, s), 4.34 (2 H, q, J = 7.0 Hz), 2.29-1.89 (5 H, m), 1.58 (6 H, s), 1.32 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.9, 160.8, 147.2, 147.0, 140.2, 139.6, 130.4, 130.0, 128.2, 127.7, 126.7, 126.0, 109.9, 109.9, 62.5, 61.2, 61.2, 60.0, 40.4, 36.5, 34.8, 34.6, 30.5, 30.3, 20.8, 20.7, 20.6, 20.5, 18.8, 14.3 ppm; HRMS (ESI): MNa^+, found 298.1519. $C_{15}H_{21}N_3NaO_2$ requires 298.1531. Isolated as a mixture of diastereomers and the characterization data given correspond to both isomers and *corresponds to the minor isomer in the ^1H NMR.



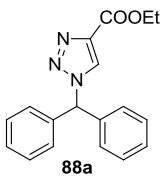
86x

4-Hexyl-1-(2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-1*H*-1,2,3-triazole (86y). Following the general procedure, **86y** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (124 mg, 87%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2): ν_{max} 3131, 2926, 2857, 1548, 1377 and 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.25 (1 H, s), 5.90 (1 H, br. s), 5.08 (1 H, br. s), 4.72 (1 H, s), 4.65 (1 H, s), 2.70 (2 H, t, J = 7.8 Hz), 2.34-1.90 (5 H, m), 1.66-1.62 (8 H, m), 1.35-1.25 (6 H, m), 0.86 (3 H, t, J = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 148.6, 147.8, 147.7, 147.5, 131.2, 129.1, 128.9, 127.1, 119.7, 118.8, 109.7, 61.8, 59.2, 40.7, 36.5, 35.3, 34.9, 31.5, 30.6, 30.4, 29.4, 28.9, 25.8, 25.7, 22.5, 20.8, 20.7, 20.5, 18.9, 14.0 ppm; HRMS (ESI): MH^+, found 288.2436. $C_{18}H_{30}N_3$ requires 288.2440. Isolated as a mixture of diastereomers and the characterization data given correspond to both isomers.



86y

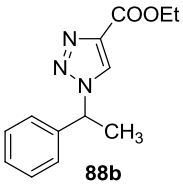
Ethyl 1-benzhydryl-1*H*-1,2,3-triazole-4-carboxylate (88a). Following the general procedure, **88a** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (218 mg, 71%); R_f (30% EtOAc/Hexanes) 0.42; mp 146-148 °C; IR (thin film) ν_{max} 2983, 1722, 1453, 1207 and 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.94 (1 H, s), 7.39-7.37 (6 H, m), 7.18 (1 H, s), 7.12-7.10 (4 H, m), 4.40 (2 H, q, J = 7.1 Hz), 1.39 (3 H, t, J = 7.1 Hz) ppm; ^{13}C



88a

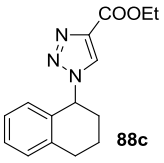
NMR (100 MHz, $CDCl_3$) δ_C 160.8, 140.0, 137.4, 129.1, 128.9, 128.0, 127.7, 68.4, 61.4, 14.3 ppm; HRMS (ESI): MH^+, found 308.1398. $C_{18}H_{18}N_3O_2$ requires 308.1399.

Ethyl 1-(1-phenylethyl)-1*H*-1,2,3-triazole-4-carboxylate (88b). Following the general procedure, **88b** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as yellow liquid (87 mg, 35%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2926, 1731, 1375, 1220 and 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.97 (1 H, s), 7.43-7.37 (3 H, m), 7.31-7.29 (2 H, m), 5.90 (1 H, q, J = 7.1 Hz), 4.41 (2 H, q, J = 7.1 Hz), 2.02 (3 H, d, J = 7.1 Hz), 1.40 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.9, 140.2, 138.9, 129.2, 129.0, 126.6, 126.2, 61.3, 60.7, 21.2, 14.3 ppm; HRMS (ESI): MH^+, found 246.1252. $C_{13}H_{16}N_3O_2$ requires 246.1243.



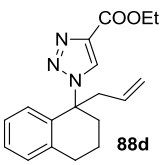
88b

Ethyl 1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (88c). Following the general procedure, **88c** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless solid (190 mg, 70%); R_f (30% EtOAc/Hexanes) 0.42; mp 86-88 °C; IR (thin film) ν_{max} 2939, 1721, 1452, 1198 and 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (1 H, s), 7.26-7.10 (3 H, m), 6.89 (1 H, d, J = 7.6 Hz), 5.95 (1 H, t, J = 5.1 Hz), 4.31 (2 H, q, J = 7.1 Hz), 2.93-2.78 (2 H, m), 2.31-2.26 (2 H, m), 1.89-1.81 (1 H, m), 1.74-1.68 (1 H, m), 1.32 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.8, 139.7, 137.9, 131.6, 129.8, 129.1,128.9, 127.1, 126.8, 61.2, 59.4, 30.9, 28.6, 18.9, 14.3 ppm; HRMS (ESI): MH^+, found 272.1390. $C_{15}H_{18}N_3O_2$ requires 272.1399.



88c

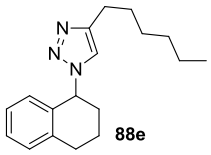
Ethyl 1-(1-allyl-1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (88d). Following the general procedure, **88d** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as a colorless liquid (162 mg, 52%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2939, 1739, 1319, 1221 and 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.52 (1 H, s), 7.34-7.21 (4 H, m), 5.59-5.48 (1 H, m), 5.24-5.07 (2 H, m), 4.36 (2 H, q, J = 7.1 Hz), 3.52 (1 H, dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz), 3.24-3.19 (1 H, m), 2.84-2.80 (2 H, m), 2.56-2.51 (1 H, m), 2.32-2.24 (1 H, m), 1.85-1.78 (1 H, m), 1.35 (3 H, t, J = 7.1 Hz), 1.38-1.34 (1 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.1, 138.7, 138.6, 134.0, 132.5, 130.2, 129.0, 128.3, 127.8, 127.0, 120.0,



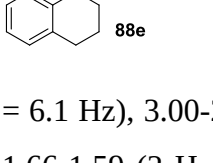
88d

66.1, 61.2, 45.0, 35.1, 29.5, 18.2, 14.3 ppm; HRMS (ESI): MH^+, found 312.1704. $C_{18}H_{22}N_3O_2$ requires 312.1712.

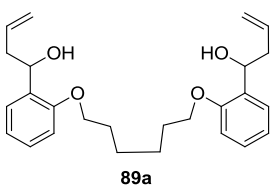
4-Hexyl-1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1*H*-1,2,3-triazole (88e). Following the general procedure, **88e** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 30:70) as yellow liquid (198 mg, 70%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2928, 1454, 1219 and 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.28 (1 H, t, J = 7.7 Hz), 7.21 (1 H, d, J = 6.1 Hz), 7.15 (1 H, t, J = 7.7 Hz), 6.95 (1 H, s), 6.91 (1 H, d, J = 7.7 Hz), 5.93 (1 H, t, J = 6.1 Hz), 3.00-2.83 (2 H, m), 2.67 (2 H, t, J = 7.5 Hz), 2.35-2.24 (2 H, m), 1.92-1.84 (2 H, m), 1.66-1.59 (2 H, m), 1.35-1.27 (6 H, m), 0.87 (3 H, t, J = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.2, 137.7, 133.1, 129.5, 128.9, 128.3, 126.6, 119.8, 58.9, 31.5, 31.3, 29.4, 28.9, 25.8, 22.5, 19.7, 14.0 ppm; HRMS (ESI): MH^+, found 284.2118. $C_{18}H_{26}N_3$ requires 284.2127.



Ethyl 1-(phenyl(*o*-tolyl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (88f). Following the general procedure, **88f** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (139 mg, 87%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2985, 1738, 1491, 1375 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (1 H, s), 7.35-7.25 (3 H, m), 7.30 (1 H, s), 7.23-7.13 (3 H, m), 7.03-7.02 (2 H, m), 6.66 (1 H, d, J = 7.7 Hz), 4.37 (2 H, q, J = 7.0 Hz), 2.16 (3 H, s), 1.33 (3 H, t, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.8, 139.7, 136.8, 136.3, 135.7, 131.2, 129.2, 128.9, 128.9, 128.0, 128.0, 127.3, 126.6, 65.6, 61.3, 19.2, 14.3 ppm; HRMS (ESI): MNa^+, found 344.1366. $C_{19}H_{19}N_3NaO_2$ requires 344.1375.



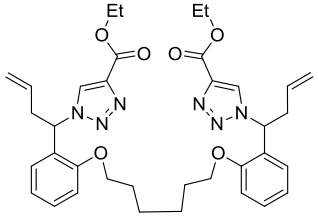
General procedure for the synthesis of *bis*-alcohols 89a. To a mixture of corresponding *bis*-aldehyde (3 mmol), allyl bromide (7 equiv) in THF (7 mL) were sequentially added sat. NH_4Cl (18 mL) and Zn metal (5 equiv) at rt. The resulting mixture was stirred at rt for 30 h. After this period, the reaction mixture was extracted by using ethyl acetate (3 X 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated, and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc/hexanes) to give the desired products **89a** as a colorless liquid (885 mg, 72%); R_f (30% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 3413, 2937, 1600, 1453 and 751 cm^{-1}; ^1H NMR (400



MHz, $CDCl_3$) δ_H 7.32 (2 H, d, *J* = 7.2 Hz), 7.19 (2 H, t, *J* = 7.4 Hz), 6.92 (2 H, t, *J* = 7.4 Hz), 6.82 (2 H, d, *J* = 8.1 Hz), 5.87-5.77 (2 H, m), 5.11-5.04 (4 H, m) 4.95 (2 H, br. s), 3.98-3.96 (4 H, m), 2.86 (2 H, s), 2.57-2.42 (4 H, m), 1.83-1.81 (4 H, m), 1.56-1.54 (4 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.7, 135.4, 132.1, 128.2, 126.8, 120.6, 117.4, 111.2, 69.6, 67.6, 42.1, 29.3, 26.0 ppm; HRMS (ESI): MNa^+, found 433.2357. $C_{26}H_{34}NaO_4$ requires 433.2355. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.

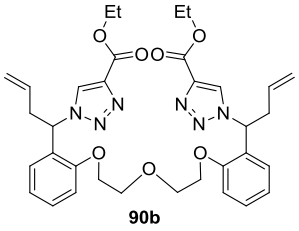
General procedure for the one-pot synthesis of 1,2,3-triazoles 90a-e directly from bis-homoallylic alcohols 89a-e. A solution of the corresponding *bis*-homoallylic alcohol **89** (0.5 mmol) and $TMSN_3$ (1.5 mmol, 3 equiv) and copper(II) triflate (10 mol%) in DCM (5.0 mL) was stirred at rt for 3 h under an inert atmosphere. After this period, the solvent was evaporated. Then, to the resulting reaction mixture THF (2-3 mL), water (2-3 mL), alkyne (2.5 mmol, 5 equiv) and sodium *L*-ascorbate (100 mol%) were added and stirred at rt for 20 h. Then, the reaction mixture was extracted by using ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated, and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc/Hexanes) to give the desired 1,2,3-*bis*-triazole product **90** (see the corresponding Tables/Schemes for specific entries).

Diethyl 1,1'-(((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1*H*-1,2,3-triazole-4-carboxylate) (90a). Following the general procedure, **90a** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a red color liquid (117 mg, 72%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2) ν_{max} 2939, 1738, 1602, 1542, 1494 and 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.04 (2 H, s), 7.34-7.28 (4 H, m), 6.97 (2 H, t, *J* = 7.5 Hz), 6.91 (2 H, d, *J* = 8.6 Hz), 6.14 (2 H, t, *J* = 7.1 Hz), 5.74-5.70 (2 H, m), 5.14-5.02 (4 H, m), 4.38 (4 H, q, *J* = 7.2 Hz), 4.02-3.93 (4 H, m), 3.24-3.18 (2 H, m), 3.06-3.02 (2 H, m), 1.82-1.79 (4 H, m), 1.47-1.44 (4 H, m), 1.37 (6 H, t, *J* = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.0, 156.1, 139.5, 132.9, 130.2, 127.5, 127.2, 127.2, 125.4, 120.7, 118.9, 111.7, 67.9, 61.2, 59.2, 59.2, 38.1, 29.0, 25.8, 14.3 ppm; HRMS (ESI): MNa^+, found 679.3224. $C_{36}H_{44}N_6NaO_6$ requires 679.3220. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.



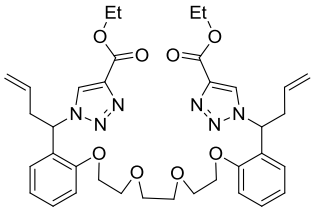
90a

Diethyl 1,1'-((((oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1*H*-1,2,3-triazole-4-carboxylate) (90b). Following the general procedure, **90b** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (135 mg, 84%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2) ν_{max} 2939, 1731, 1642, 1542, and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.18 (2 H, s), 7.36-7.28 (4 H, m), 6.97 (2 H, t, *J* = 7.5 Hz), 6.92 (2 H, d, *J* = 8.2 Hz), 6.12-6.07 (2 H, m), 5.67-5.60 (2 H, m), 5.08-4.97 (4 H, m), 4.34 (4 H, q, *J* = 7.1 Hz), 4.21-4.09 (4 H, m), 3.89 (4 H, t, *J* = 4.6 Hz), 3.26-3.19 (2 H, m), 3.08-3.01 (2 H, m), 1.34 (6 H, t, *J* = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.0, 156.0, 139.5, 132.9, 130.3, 127.8, 127.6, 127.5, 125.6, 125.6, 121.2, 118.9, 112.0, 69.7, 69.7, 67.6, 61.2, 59.5, 59.5, 37.7, 14.3 ppm; HRMS (ESI): MNa^+, found 667.2863. $C_{34}H_{40}N_6NaO_7$ requires 667.2856. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.



90b

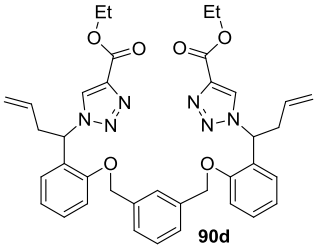
Diethyl 1,1'-(((((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1*H*-1,2,3-triazole-4-carboxylate) (90c). Following the general procedure, **90c** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (141 mg, 82%); R_f (50% EtOAc/Hexanes) 0.45; IR (CH_2Cl_2) ν_{max} 2933, 1737, 1602, 1494, and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (2 H, s), 7.33 (2 H, d, *J* = 7.5 Hz), 7.28 (2 H, t, *J* = 7.8 Hz), 6.96 (2 H, t, *J* = 7.5 Hz), 6.85 (2 H, d, *J* = 8.2 Hz), 6.10 (2 H, t, *J* = 7.7 Hz), 5.70-5.63 (2 H, m), 5.11-4.97 (4 H, m), 4.37 (4 H, q, *J* = 7.1 Hz), 4.14-4.05 (4 H, m), 3.84 (4 H, t, *J* = 5.5 Hz), 3.77 (4 H, br. s), 3.29-3.21 (2 H, m), 3.09-3.02 (2 H, m), 1.36 (6 H, t, *J* = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.0, 155.9, 139.4, 133.0, 130.2, 127.8, 127.8, 125.9, 121.2, 118.9, 112.0, 70.7, 69.4, 67.5, 61.1, 59.6, 37.7, 14.3 ppm; HRMS (ESI): MNa^+, found 711.3135. $C_{36}H_{44}N_6NaO_8$ requires 711.3118. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.



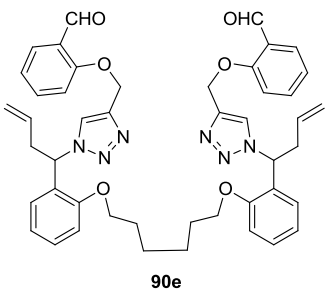
90c

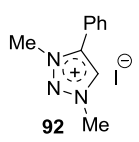
Diethyl 1,1'-((((1,3-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1*H*-1,2,3-triazole-4-carboxylate) (90d). Following the general procedure, **90d** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a

colorless liquid (147 mg, 87%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2982, 1732, 1493, 1227, 1041 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.90 (2 H, s), 7.44 (4 H, s), 7.37-7.28 (4 H, m), 7.04-6.91 (4 H, m), 6.10-6.05 (2 H, m), 5.65-5.58 (2 H, m), 5.06-4.95 (8 H, m), 4.41-4.35 (4 H, m), 3.21-3.12 (2 H, m), 3.10-2.95 (2 H, m), 1.40-1.38 (6 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 160.9, 155.7, 155.7, 139.5, 134.5, 134.4, 132.6, 132.6, 130.4, 129.8, 129.7, 129.1, 127.7, 127.6, 127.2, 127.2, 125.7, 125.6, 121.5, 121.5, 119.1, 119.1, 112.3, 112.2, 68.2, 68.1, 61.2, 59.0, 58.8, 38.1, 14.3 ppm; HRMS (ESI): MNa^+, found 699.2918. $C_{38}H_{40}N_6NaO_6$ requires 699.2907. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.



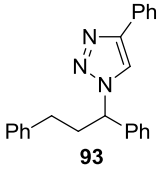
2,2'-(((1,1'-(((Hexane-1,6-diylbis(oxy))bis(2,1-phenylene))bis(but-3-ene-1,1-diyl))bis(1*H*-1,2,3-triazole-4,1-diyl))bis(methylene))bis(oxy))dibenzaldehyde (90e). Following the general procedure, **90e** was obtained after purification by silica gel column chromatography (EtOAc:Hexanes = 50:50) as a colorless liquid (131 mg, 68%); R_f (50% EtOAc/Hexanes) 0.42; IR (CH_2Cl_2) ν_{max} 2940, 1687, 1599, 1456 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 10.42 (2 H, s), 7.80 (2 H, dd, J_1 = 5.8 Hz, J_2 = 1.8 Hz), 7.65 (2 H, s), 7.52 (2 H, t, J = 8.8 Hz), 7.31-7.26 (4 H, m), 7.13 (2 H, d, J = 8.4 Hz), 7.02 (2 H, t, J = 7.4 Hz), 6.95 (2 H, t, J = 8.2 Hz), 6.89 (2 H, d, J = 8.0 Hz), 6.11 (2 H, t, J = 8.7 Hz), 5.75-5.65 (2 H, m), 5.29 (4 H, s), 5.10-4.99 (4 H, m), 4.00-3.93 (4 H, m), 3.25-3.18 (2 H, m), 3.06-2.99 (2 H, m), 1.80-1.77 (4 H, m), 1.49-1.47 (4 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 189.6, 160.6, 156.0, 142.5, 136.0, 133.3, 129.9, 128.5, 127.4, 126.2, 125.0, 122.8, 121.2, 120.7, 118.5, 113.1, 111.6, 67.9, 62.7, 59.0, 38.3, 29.1, 25.8 ppm; HRMS (ESI): MNa^+, found 803.3548. $C_{46}H_{48}N_6NaO_6$ requires 803.3533. Isolated as a mixture of diastereomers (*dr* = 50:50) and NMR values given for both isomers.





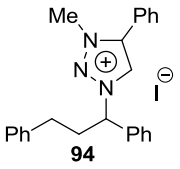
Preparation of the compound 10.[43] A solution of (*E*)-4-phenyl-1-(3-phenyl-1-(*p*-tolyl)allyl)-1*H*-1,2,3-triazole (**86o**) in MeI (5 mL) was refluxed for 5 d. After this period, excess of MeI was removed under vacuum and the resulting crude reaction mixture was washed with Hexanes and ether which gave the compound **92**.

1-(1,3-Diphenylpropyl)-4-phenyl-1*H*-1,2,3-triazole (93). To the solution of (*E*)-1-(1,3-diphenylallyl)-4-phenyl-1*H*-1,2,3-triazole (**86c**, 1 mmol) in THF (2 mL) was added Pd/C (10 mol%). The reaction mixture was stirred at room temperature for 24 h, under H_2 atm (1 atm). After completion of the reaction, the reaction mixture was filtered by using a layer of celite pad and the filtrate was evaporated under vacuum and the resulting crude reaction mixture was purified by silica gel column chromatography (EtOAc : Hexanes = 30 : 70) which gave the compound **93** as a colorless solid (311 mg, 91%); R_f (30% EtOAc/Hexanes) 0.42; mp 110-112 °C; IR (thin film) ν_{max} 3062, 3028, 1603, 1454 and 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (2 H, d, J = 7.1 Hz), 7.71 (1 H, s), 7.45-7.22 (11 H, m), 7.19 (2 H, d, J = 7.1 Hz), 5.61 (1 H, dd, J_1 = 9.2 Hz, J_2 = 6.2 Hz), 2.95-2.88 (1 H, m), 2.70-2.66 (3 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.8,140.3, 138.8, 130.6, 129.1, 128.8, 128.7, 128.7, 128.5, 128.2, 127.0, 126.4, 125.7, 118.8, 64.4, 36.6, 32.3 ppm; HRMS (ESI): MH^+, found 340.1806. $C_{23}H_{22}N_3$ requires 340.1814.



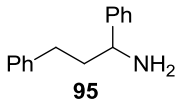
93

Preparation of the compound 94. A solution of (1-(1,3-diphenylpropyl)-4-phenyl-1*H*-1,2,3-triazole (**93**, 0.25 mmol) in MeI (5 mL) was refluxed for 4 d. After this period, excess of MeI was removed under vacuum and the resulting crude reaction mixture was washed with Hexanes and ether which gave the compound **94** as a semi solid (110 mg, 92%); R_f (30% EtOAc/Hexanes) 0.42; IR (thin film) ν_{max} 2928, 1603, 1494, 1454, 1384 and 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 9.45 (1 H, s), 7.72 (2 H, d, J = 8.0 Hz), 7.61 (2 H, d, J = 8.0 Hz), 7.53-7.45 (3 H, m), 7.42-7.37 (3 H, m), 7.18 (4 H, d, J = 4.3 Hz), 7.13-7.08 (1 H, m), 6.54 (1 H, t, J = 7.6 Hz), 4.20 (3 H, s), 3.12-3.03 (1 H, m), 2.81-2.69 (3 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.8, 139.7, 135.5, 132.0, 130.0, 129.7, 129.5, 129.5, 128.9, 128.6, 128.4, 128.2, 126.3, 121.5, 68.9, 39.7, 35.6, 32.3 ppm; HRMS (ESI): $M\text{-}IH^+$, found 355.1996. $C_{24}H_{25}N_3$ requires 355.2048.



94

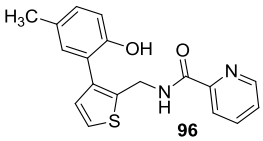
Preparation of the compound 95. To a solution of (*E*)-(3-azidoprop-1-ene-1,3-diyl)dibenzene (**84**, 1 mmol) in THF (2 mL) was added Pd/C (10 mol%). The reaction mixture was stirred at room temperature for 24 h under H_2 atm (1 atm). After completion of the reaction, the reaction mixture was filtered by using a layer of celite pad and the filtrate was evaporated under vacuum and the resulting crude reaction mixture was transferred into a separating funnel with DCM and extracted twice with 1 N HCl (4 mL). The



95

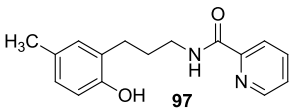
acidic aqueous layer was washed 2 times with EtOAc (5 mL). The aqueous phase was then made basic (pH: 10-11) with 2 N NaOH and extracted with DCM (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the organic phase was concentrated to afford the compound **95** as colorless liquid (105 mg, 50%); IR (Thin film) ν_{max} 3026, 1602, 1453 and 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.39-7.18 (10 H, m), 3.93 (1 H, t, J = 6.8 Hz), 2.70-2.55 (2 H, m), 2.07-2.01 (2 H, m), 1.73 (2 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 146.2, 141.9, 128.6, 128.4, 127.1, 126.4, 125.8, 55.8, 41.0, 32.8 ppm; HRMS (ESI): MH^+, found 212.1441. $C_{15}H_{18}N$ requires 212.1439.

Compound 96: A mixture of picolinamide **35b** (0.2 mmol) and NaOH (2 equiv) in MeOH (2 mL) were stirred at rt for 2 h. The reaction mixture was concentrated under high vacuo. The resulting crude residue was purified by silica gel flash chromatography to give the product **95** as colourless liquid (37 mg, 85%); IR (CH_2Cl_2): ν_{max} 3240, 1662, 1525, 1276 and 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (1 H, br s), 8.55 (1 H, d, J = 4.2 Hz), 8.20 (1 H, d, J = 7.8 Hz), 7.86 (1 H, td, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 7.47-7.44 (1 H, m), 7.33 (1 H, d, J = 5.1 Hz), 7.09 (1 H, dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz), 7.00 (1 H, d, J = 1.9 Hz), 6.97-6.94 (2 H, m), 6.68 (1 H, br s), 4.66 (2 H, d, J = 8.0 Hz), 2.32 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 150.9, 149.3, 148.2, 138.0, 137.4, 135.5, 131.2, 130.1, 129.6, 129.5, 126.5, 124.8, 122.4, 122.1, 116.5, 37.9, 20.5; HRMS (ESI): MNa^+, found 347.0818. $C_{18}H_{16}N_2NaO_2S$ requires 347.0830.



96

Compound 97. Brown colour liquid (35mg, 87%); IR (CH_2Cl_2): ν_{max} 3326, 2935, 1659, 1569, 1537 and 1262 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (1 H, m), 8.36 (1 H, br s), 8.25-8.22 (1 H, m), 7.86 (1 H, td, J_1 = 7.7 Hz, J_2 = 1.7 Hz), 7.45-7.42 (1 H, m), 6.94 (1 H, d, J = 1.9 Hz), 6.88 (1 H, dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz), 6.77 (1 H, d, J = 8.0 Hz), 3.50 (2 H, q, J = 6.5 Hz), 2.73 (2 H, t, J = 7.2 Hz), 2.26 (3 H, s), 2.02-1.95 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 152.0, 149.8, 148.1, 137.5, 131.0, 129.6, 127.7, 127.5, 126.2, 122.4, 115.8, 38.8, 30.7, 27.1, 20.5; HRMS (ESI): MH^+ found 271.1441. $C_{16}H_{19}N_2O_2$ requires 271.1147.



97

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20. The column chromatographic purification of the respective crude reaction mixtures gave the mono-OAc product **35b** and the di-OAc product **36b** was not obtained.
21. The regioselectivity/chemoselectivity of the process comprising the Pd(II)-catalyzed acetoxylation of ε-C-H bonds of aryl rings of **34a-m**/**37a-c**/**39a-d**/**41a,b** and the regiochemistry of the aryl rings of structures of the compounds **35a-m**, **36a-i**, **38a-c**, **40a-d**, **42a,b** and **43a,b** were assigned based on the similarity in their ^{1}H NMR spectral pattern and coupling constant values/splitting pattern of the aryl ring that is subjected to the mono/bis ε-

C-H acetoxylation. For example, the proton NMR of the compound **35j** (or **38c** or **40d**) revealed the presence of two singlet peaks for the respective *para* protons of the aryl ring after the ε-C-H acetoxylation of **34j** (or **37c** or **39d**). This observation confirmed that in the substrates **34j** (or **37c** or **39d**), the ε-C-H^n bond was selectively acetoxylated over the ε-C-H^m bond to afford the corresponding mono ε-C-H acetoxylation products (**35a-m**, **38a-c**, **40a-d**, **42b** and **43b**). Similarly, the double ε-C-H acetoxylation products **36a-i**/**40aA**/**42a** and **43a** were assigned based on the similarity in their ^{1}H NMR spectral pattern and coupling constant values/splitting pattern of the aryl ring that is subjected to ε-C-H acetoxylation. For example, the proton NMR of the compound **36a** revealed the presence of a doublet peak for the respective *para* protons of the aryl ring after the double ε-C-H acetoxylation of **34a**. This observation confirmed that in the substrate **34a**, both the ε-C-H^n and ε-C-H^m bonds were selectively acetoxylated. In an another example, the proton NMR of the compound **36c** revealed the presence of a singlet peak for the respective *para* protons of the aryl ring after the double ε-C-H acetoxylation of **34c**. This confirmed that in the substrate **34c**, both the ε-C-H^n and ε-C-H^m bonds were selectively acetoxylated.

22. In addition to the discussion given in the ref.16; in all the thiophene-based products **35a-m/36a-i/40a-d**/**42a,b**, except for **43a,b** the thiophene C4 and C5 protons respectively gave two doublets with a coupling constant (*J*) value in the range of 5.2 Hz as usually reported in the literature. This indicated that the thiophene C4 and C5-protons are intact in the cases of the products **35a-m/36a-i /40a-d /42a,b**. Similarly, in all the furan-based products **38a-c**, the furan C4 and C5 protons respectively gave two doublets with a coupling constant (*J*) value in the range of 1.8 Hz as usually reported in the literature. This indicated that the furan C4 and C5-protons are intact in the cases of the products **38a-c**.
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25. The regioselectivity and chemoselectivity of the reactions involving the acetoxylation of ε-C(sp^2)-H bonds of **44a-l**, **44n-z**, **44aa** and **50a-c** and the regiochemistry of the ε-C(sp^2)-H acetoxylated aryl rings of **46a-l**, **48a-n**, **51c** (mono OAc) and **46a-h**, **49a-g** (di OAc) and **52a-c** (iodinated and acetoxylated compounds) were assigned based on the similarity in their ^{1}H NMR spectral pattern and coupling constant values/splitting pattern of the aryl ring. For example, the proton NMR of the mono acetoxylated compound **46b** revealed the presence of two singlet peaks at δ 7.04 (1H) and 6.80 (1H) for the respective *para* protons of aryl ring after the ε-C-H acetoxylation of **44b**.This observation confirmed that in the substrates **44b,x** the ε-C-H^m bond was selectively acetoxylated over the ε-C-H^n bond to furnish the corresponding mono ε-C-H acetoxylation products **46b** (Table 6) and **48k** (Table 8). Notably, the proton NMR spectral pattern of aryl ring of **46b** (Table 6) and **48k** (Table 8) endorsed that the acetoxylation has occurred at the *ortho* ε-C(sp^2)-H bonds of phenylpropylamines and also the assignment of the regiochemistry of the acetoxylated aryl rings of phenylpropylamines investigated in this work. the proton NMR of the mono acetoxylated compound **46d** (Table 5) revealed the corresponding signature peaks for the tri substituted aryl ring after the mono *ortho* ε-C-H^m acetoxylation of **44d**. Accordingly, a doublet at δ 7.20 (J = 7.8 Hz, 1H), a doublet of doublet at δ 7.04 (J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H) and a doublet at δ 6.87 (J = 1.6 Hz, 1H) confirmed the regiochemistry of the mono ε-C(sp^2)-H^m acetoxylated aryl ring of **46d**. Almost a similar proton NMR spectral pattern were observed for the other mono acetoxylated compounds **46c,e** and **46f-h** (Table 5) and **48b,d,g** (Table 7). Next, the proton NMR of the bis acetoxylated compound **47d** revealed the presence of a singlet peak at δ 6.81 (2H), for the respective *para* protons of the aryl ring of **47d** after the double ε-C-H acetoxylation of **44d**. This observation confirmed that in the substrate **44d**, both the ε-C-H^n and ε-C-H^m bonds were acetoxylated. Almost a similar proton NMR spectral pattern were observed for the other bis acetoxylated compounds **47c,e** and **47f-h** (Table 5) and **49b,c,d,g** (Table 7).

26. (a) In continuation of the deliberations given in Refs. 21, the proton NMR of the mono acetoxylated compound **46i** (Table 6) revealed the corresponding signature peaks for the tri substituted aryl ring after the mono *ortho* ε-C-H^m acetoxylation of **44i**. Accordingly, a doublet at δ 7.09 (J = 1.8 Hz, 1H), a doublet of doublet at δ 7.03 (J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H) and a doublet at δ 6.91 (J = 8.1 Hz, 1H), confirmed the regiochemistry of the mono ε-

$C(sp^2)$-H^m acetoxylated aryl ring of **46i**. Almost a similar proton NMR spectral pattern were observed for the other mono acetoxylated compounds **46i-l, 46b** (Table 6) and **48h-n** (Table 7). The proton NMR of the mono acetoxylated compound **46a** (Table 5) revealed the corresponding signature peaks for the di substituted aryl ring after the mono *ortho* ε-C-H^m acetoxylation of **43a**. Accordingly, a multiplet for three arying ring protons at δ 7.31-7.18 and a doublet of doublet for one of the aryl ring proton at δ 7.04 (J_1 = 7.8 Hz, J_2 = 1.5 Hz), confirmed the regiochemistry of the mono ε-$C(sp^2)$-H^m acetoxylated aryl ring of **46a**. Almost a similar proton NMR spectral pattern was observed for the other mono acetoxylated compound **48a** (Table 7). Furthermore, the proton NMR of the bis acetoxylated compound **47a** (Table 5) revealed the corresponding signature peaks for the tri substituted aryl ring after the bis *ortho* ε-C-H acetoxylation of **44a**. Accordingly, a triplet at δ 7.26 (J = 8.1 Hz, 1H) and a doublet at δ 6.98 (J = 8.2 Hz, 2H), confirmed the regiochemistry of the bis ε-$C(sp^2)$-H^m acetoxylated aryl ring of **47a**. Almost a similar proton NMR spectral pattern were observed for the other bis acetoxylated compounds **49a,f** (Table 7). (b) The proton NMR spectral patterns of picolinamide, pyrazine2-carboxamide and quinoline-2-carboxamide moieties were noticeably different than the aryl rings of corresponding starting materials **44a-l**, **44n-z**, **44aa** and **50a-c** and the products shown in Tables 4-9. This observation guided the assignment of regiochemistry after the C-H acetoxylation of the products shown in Tables 4-9. **(**i) Based on the literature works and our observation, generally, the proton NMR signals for picolinamide moiety approximately appears between δ 8.6 and 7.4. A typical proton NMR spectral pattern for picolinamide moiety of compound **44d** is given here; δ 8.57-8.55 (m, 1H), 8.23 (dt, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 8.12 (br. s, 1H), 7.86 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 7.45-7.42 (m, 1H). (ii) Based on the literature works and our observation, generally, the proton NMR signals for pyrazine-2-carboxamide moiety approximately appears between δ 9.4 and 7.8. A typical proton NMR spectral pattern for picolinamide moiety of compound **44t** is given here; δ 9.42 (d, J = 1.5 Hz, 1H), 8.75 (d, J = 2.5 Hz, 1H), 8.52 (dd, J_1 = 2.4 Hz, J_2 = 1.5 Hz, 1H), 7.86 (br. s, 1H). (iii) Based on the literature works and our observation, generally, the proton NMR signals for quinoline-2-carboxamide moiety approximately appears between δ 8.3 and 7.6. A typical proton NMR spectral pattern for picolinamide moiety of compound

44q is given here; δ 8.33-8.31 (m, 3H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H).

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