Studies on the Stereo- and Regioselective Synthesis of New Sets of Functionalized Pyrrolidine, Spiro- Pyrrolidine / Pyrrolizidine, Furfurylamine and 2-/3-(Aminoalkyl)-Thiophene Scaffolds *via* the Azomethine Ylide Cycloaddition and C-H Functionalization Methods

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

By

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May 2016

DEDICATED to

MY BELOVED PARENTS

BROTHER AND SISTER

Declaration

I hereby declare that the matter embodied in this thesis entitled "*Studies on the Stereo- and Regioselective Synthesis of New Sets of Functionalized Pyrrolidine, Spiro- Pyrrolidine / Pyrrolizidine, Furfurylamine and 2-/3-(Aminoalkyl)-Thiophene Scaffolds via the Azomethine Ylide Cycloaddition and C-H Functionalization Methods*" 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.

Vadla Rajkumar

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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Place:

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List of publications from the thesis work

1) **Rajkumar**, **V**.; Aslam, N. A.; Reddy, C.; Babu, S. A.* *Synlett* **2012**, 549.

Title: Unactivated norbornenes in [3+2] cycloadditions: Remarkably stereocontrolled entry into norbornane-fused spirooxindolopyrrolidines, spiro-1,3-indandionolylpyrrolidines and spirooxindolopyrrolizidines.

2) **Rajkumar**, **V**.; Babu, S. A.* *Indian Journal of Chemistry* **2013**, *52A,* 1113 (Invited article).

Title: Diastereoselective construction of new class of nicotine analogues having contiguous stereocenters *via* 1,3- dipolar cycloaddition of azomethine ylides.

3) **Rajkumar**, **V**.; Babu, S. A.* *Synlett* **2014**, 2629.

Title: Regio- and diastereoselective cycloaddition of azomethine ylides with benzylidenemalononitrile: Assembly of a new set of multisubstituted 4,4-dicyanopyrrolidine-2-carboxylate and nornicotine scaffolds.

4) **Rajkumar**, **V**.; Naveen.; Babu, S. A.* *ChemistrySelect* **2016**, 1207.

Title: Pd(II)-Promoted directing group-enabled regioselective C-H arylations of the C-3 position of furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives.

5) **Rajkumar**, **V**.; Babu, S. A.;* Padmavathi, R. *Tetrahedron* **2016**, *72,* 5578.

Title: Regio- and diastereoselective construction of a new set of functionalized pyrrolidine, spiropyrrolidine and spiropyrrolizidine scaffolds appended with aryl- and heteroaryl moieties *via* the azomethine ylide cycloadditions.

6) **Rajkumar**, **V**.; Naveen.; Babu, S. A.* *Manuscript under preparation.*

Title*:* Pd(II)-catalyzed acetoxylation of the *ortho* C-H bond of benzyl amines, γ and remote δ C(3)-H bond of 2-/3-(aminoalkyl)-thiophenes using pyrazine- or quinoline-2-carboxamide as the directing groups.

List of publications as a co-author

1) Aslam, N. A.; **Rajkumar**, **V**.; Reddy, C**.**; Yasuda, M.; Baba, A.; Babu, S. A.* *Eur. J. Org. Chem.* **2012**, 4395.

Title: Indium-mediated addition of γ-substituted allylic halides to *N*-aryl α-imino esters: Diastereoselective production of β,β'-disubstituted α-amino acid derivatives with two contiguous stereocenters.

2**)** Reddy, C.; Babu, S. A.;* Aslam, N. A.; **Rajkumar**, **V**. *Eur. J. Org. Chem.* **2013**, 2362.

Title: Construction of functionalized carbocycles having contiguous tertiary carbinol and all-carbon stereogenic centers.

3) Babu, S. A.;* Padmavathi, R.; Aslam, N. A.; **Rajkumar, V**. *Studies in Natural Products Chemistry* **2015**, *46*, 227 (Book chapter).

Title: Recent developments on the synthesis and applications of natural products-inspired spirooxindole frameworks.

Patent application filed

Inventors: Srinivasarao Arulananda Babu and **Vadla Rajkumar**, Patent Application No. 1102/DEL/2013, Date: 12th April, 2013 entitled "Novel nicotine analogues/2-pyridylpyrrolidine derivatives and the process of preparation thereof".

Conferences/Symposia

Oral presentation entitled "Approach towards natural product –like bioactive molecules: Remarkably stereocontrolled entry into norbornane-fused spiro-1,3-indandionolylpyrrolidines, spirooxindolopyrrolidines and pyrrolizidines" **V. Rajkumar,** N. A. Aslam, C. K. Reddy, S. A. Babu at the *7th Junior National Organic Symposium (J-NOST)* held at the Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (14-17 December, 2011).

Presented poster entitled "Palladium-catalyzed regiocontrolled C(sp^2)-H arylation of C-3 position of 2-thiophenemethylamine and furfurylamine**"** **V. Rajkumar**, Naveen and S. A. Babu at the *18th CRSI National Symposium in Chemistry* held at the Institute of Nano Science and Technology and Panjab University, India (5-7 February, 2016).

Preamble.

Heterocyclic chemistry is one of the fascinating sub-fields in organic chemistry dealing on the synthesis, properties and applications of heterocycles and recognized as disciplines of general importance that covers several aspects other branches of science, such as, biochemistry and medicinal chemistry.

In general, heterocyclic compounds are very important class of organic molecules with high degree of structural diversity and approximately two thirds of organic compounds are heterocycles. Heterocyclic compounds are cyclic molecules with at least one atom of carbon and one element other than carbon, such as, oxygen, nitrogen or sulfur within a ring structure. Heterocyclic skeleton present in a wide range of vital molecules, such as, alkaloids, vitamins, drugs, many natural products, agrochemicals, biomolecules etc. Numerous heterocyclic derivatives are useful as therapeutic agents like antibacterial, antifungal, antidiabetic, antiviral, antitumor, antibiotic, antimalarial, antimicrobial, antidepressant, anti-inflammatory, anti-HIV, fungicidal, herbicidal and insecticidal agents. Furthermore, most of the heterocyclic compounds exhibit vital applications in materials science (e.g. heterocyclic framework forms the central unit of various sensors, plastics, dyestuff, semiconductors, liquid crystalline compounds), polymer chemistry and supra molecular chemistry. Notably, many heterocyclic compounds were used as organocatalysts, chiral auxiliaries, protecting groups and synthetic intermediates in organic chemistry.

Given the importance of heterocyclic compounds, chemists have special interest for the synthesis of heterocyclic compounds because of their numerous applications across various branches of science. Hence, a special attention is always taken to build up efficient new methods to synthesize new heterocyclic molecules that are expected to play an important role in human life. For example, pyrrolidine-, pyrrolizidine- and spirooxindole alkaloids have significantly attracted the attention of organic and medicinal chemists due to their promising biological activities and candidature as drugs. Similarly, multisubstituted furans and thiophenes considered as important heterocyclic building blocks in organic synthesis, materials chemistry and medicinal chemistry.

Thus, this thesis work envisages to enrich the library of (a) pyrrolidines, spiro-pyrrolidines/pyrrolizidines *via*the stereo- and regioselective azomethine ylide cycloaddition reactions, and (b) C3-arylated/heteroarylated/acetoxylated furfurylamine and 2-/3-(aminoalkyl)-thiophene scaffolds *via* C-H activation/functionalization routes.

Accordingly, this thesis entitled "*Studies on the Stereo- and Regioselective Synthesis of New Sets of Functionalized Pyrrolidine, Spiro- Pyrrolidine / Pyrrolizidine, Furfurylamine and 2-/3-(Aminoalkyl)-Thiophene Scaffolds via the Azomethine Ylide Cycloaddition and C-H Functionalization Methods*"consists of the following **three chapters** along with objectives of the thesis work. Individual chapters contain the sub-sections, such as, introduction, results and discussion and conclusions, experimental section and references.

Chapter 1: *Regio- and diastereoselective cycloaddition of azomethine ylides with dipolarophiles to give a new set of pyrrolidine-2-carboxylic acid and nicotine analogues.*

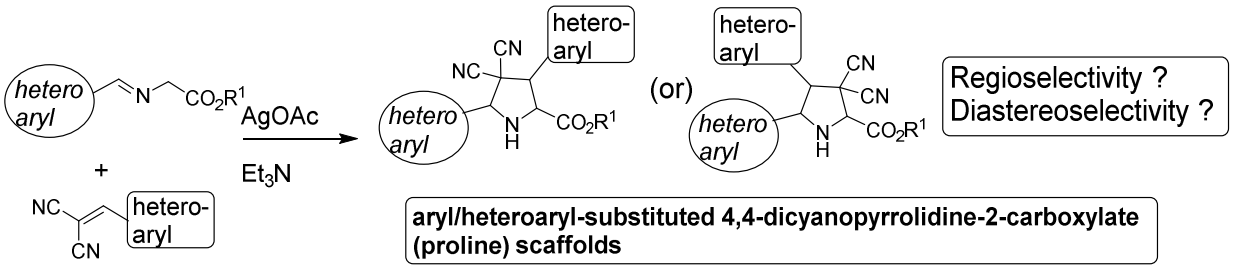
Chapter 2: *Highly Regio- and diastereoselective construction of densely functionalized spirooxindolo-pyrrolidine / pyrrolizidine, spiro-1,3-indandionolylpyrrolidine and spiroacenaphthylenolyl- pyrrolidine / pyrrolizidine derivatives.*

Chapter 3: *Regioselective construction of C-3 arylated furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives via the Pd(II)-catalyzed directing group-aided C-H arylation/acetoxylation reactions*.

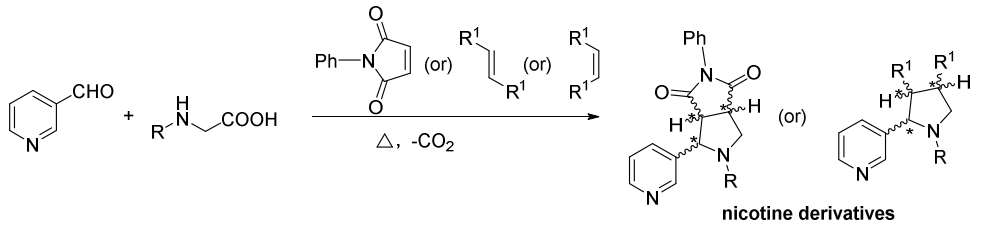
Objectives.

The research work carried out is mainly focused on accomplishing the stereo- and regioselective synthesis of new sets of *functionalized heterocyclic compounds,* such as, arylated pyrrolidines, spirooxindolopyrrolidines/pyrrolizidines and spiro-pyrrolidines/pyrrolizidines, arylated/acetoxylated furfurylamines and 2-/3-(aminoalkyl)-thiophenes.

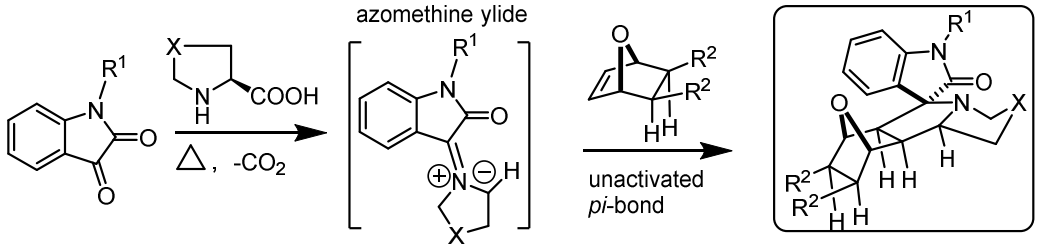
Objective 1a (Chapter 1a): Multisubstituted pyrrolidines exhibit a range of biological activities, in particular, pyrrolidine carboxylic acid (proline) derivatives having aryl/heteroaryl groups show promising biological activities. In the context of enriching the library of functionalized pyrrolidines, a part of this thesis envisages to investigate the Ag-catalyzed cycloaddition of azomethine ylides with arylidene / heteroarylidenemalononitriles for the construction of new sets of C2,C5-arylated 4,4-dicyanopyrrolidine-2-carboxylates and nornicotine derivatives.



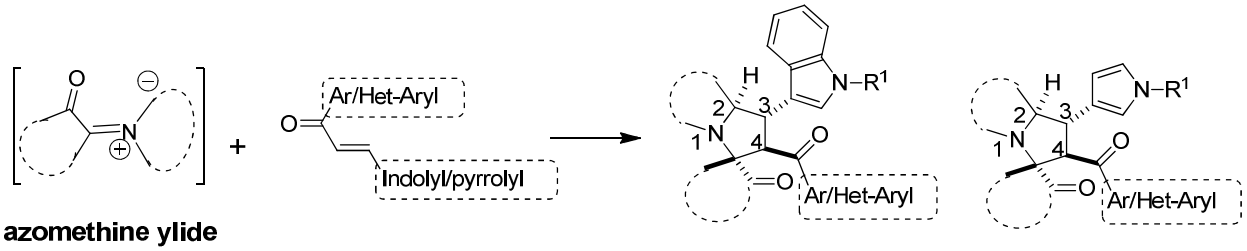
Objective 1b (Chapter 1b): Nicotine and nicotine analogues found to be important drug molecules for treating central nervous system (CNS) disorders as well as other ailments. However, nicotine molecule reported to offer no selectivity or a lack of high degree of selective coordination with the nAChRs. In the context of finding new nicotine analogues that are efficient and selective in their biological activities, nicotine analogues were prepared by various research groups. A part of this thesis envisages the synthesis of new class of nicotine derivatives having contiguous stereocenters *via* the cycloaddition of azomethine ylides derived from the decarboxylative reactions of nicotinaldehyde and α-amino acids with various symmetrical dipolarophiles.



Objective 2a (Chapter 2a): Due to the bountiful biological activities exhibited by the spirooxindolopyrrolidine alkaloids, synthetic chemists synthesized several spirooxindolopyrrolidines/pyrrolizidines and some of them found to exhibit promising biological activities. In the context of enriching the library of functionalized spirooxindolopyrrolidines/pyrrolizidines and spiro-pyrrolidines/pyrrolizidines, a part of this thesis envisaged to investigate the cycloaddition of azomethine ylides with unactivated norbornene-type dipolarophiles and synthesize norbornane-fused- spirooxindolopyrrolidines/pyrrolizidines and spiro-pyrrolidines/pyrrolizidines.



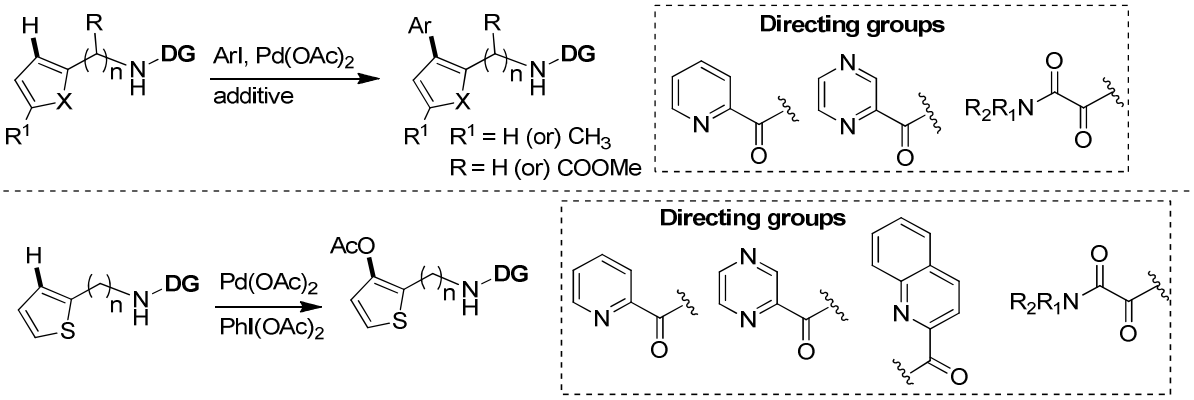
Objective 2b (Chapter 2b): Various research groups are interested in preparing new libraries of spirooxindolopyrrolidine and spiro-pyrrolidines/pyrrolizidine appended with medicinally important functional groups and sub-units. Given the importance of indole moieties containing pyrrolidines and spiro-pyrrolidines/pyrrolizidines; a part of this thesis work envisages to assemble spirooxindolopyrrolidine and spiro-pyrrolidines/pyrrolizidine scaffolds directly connected with the indolyl or pyrrolyl moieties *via* the azomethine ylide cycloaddition route.



azomethine ylide

Objectives 3a and 3b(Chapters 3a and 3b): Substituted furan/thiophene derivatives are important class of aromatic compounds and several furan/thiophene-based biaryl derivatives were reported to be biologically active compounds. In the broad family of furan/thiophene-based biaryl derivatives, the C3- or C5-arylated furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives were found to show promising biological activities.A part of this thesis work envisioned to apply the bidentate

ligand directed, Pd-catalyzed, regioselective *ortho*C-H functionalization strategy for assembling the C3 arylated furfurylamine and 2- or 3-(aminoalkyl)-thiophene scaffolds. Along this line, the final part of this thesis work envisioned to investigate the bidentate ligand directed, Pd-catalyzed, C-H oxidation/acetoxylation strategy for assembling the C3 acetoxylated thiophene scaffolds.



Chapter 1*: *Regio- and diastereoselective cycloaddition of azomethine ylides with dipolarophiles to give a new set of pyrrolidine-2-carboxylic acid and nicotine analogues.

Introduction.

Pyrrolidine framework is a privileged structural unit frequently found in a variety of natural products (e.g. alkaloids) and synthetically derived biologically active compounds.[1] Several substituted pyrrolidine derivatives reveal a wide range of biological activites[2] and act as robust organocatalysts in organic chemistry.[3] In particular,the construction of pyrrolidine carboxylic acid (proline) derivatives remains an active research field because of their numerous applications in synthetic organic, medicinal chemistry and biochemistry etc.[1b,1c,2b,3,4] Amongst the α-amino acids (α-AAs), proline is one of the very useful molecules for designing biologically active peptides[5] and its derivatives. Further, proline is an efficient organocatalyst for many asymmetric transformations[3] and important building block for synthesizing drug molecules.[1b] There exist various methods to synthesize proline derivatives,[4d,5,6,10i] including (a) functionalization of L-proline itself or other related derivatives, (b) intramolecular cyclizations of chiral amino acids and (c) synthesis of pyrrolidine rings (proline derivatives) *via* the 1,3-dipolar cycloaddition of azomethine ylides. Specifically, the azomethine ylidecycloaddition reaction considered as one of most simple routes for assembling substituted prolines.

The 1,3-dipolar cycloaddition[7] reaction is an extremely powerful method to construct five-membered heterocyclic compounds with high degree of stereocontrol. Amongst, the 1,3-dipoles used for carrying out 1,3-dipolar cycloaddition reaction, the azomethine ylides[8] found to be highly important 1,3-dipole systems and their reaction with 2π components considered as a straightforward method to assemble pyrrolidine-based natural products and synthetic molecules. Even thoughmany methods are known for the generation of azomethine ylides, two methods are popularly used; (a) the construction of metallo-dipoles (azomethine ylides) from *N*-benzylideneiminoglycinates (b) generation of azomethine ylides from the decarboxylative reactions of 1,2-dicarbonyl compounds and α-amino acids. With a perspective of finding new drug molecules, several pyrrolidine carboxylic acids or proline molecules were constructed through the 1,3-dipolar cycloaddition of azomethine ylides with various electron-deficient 2π components with high degree of regio-, diastereo- and enantiocontrol.[4,8,9,10]

While there are several substituted pyrrolidine derivatives[11-17] exhibit a wide range of biological activities, in particular, pyrrolidine carboxylic acid (proline) frameworks having aryl or heteroaryl groups show promising biological activities (Figure 1).[11-15] For example, Abbott Laboratories[11a] discovered a drug molecule ABT-627 (2,4-diarylpyrrolidine-3-carboxylic acid derivative) as a potent and selective molecule for the ET_A receptor subtype. Wang *et al.*[12a] discovered the 3,4-disubstituted pyrrolidines as a novel class of monoamine transporter inhibitors. Some of the pyrrolidine carboxylic acid natural products, [13a,b] e.g., (-) kainic acid[13a] possess neuro-excitatory action (Figure 1). Further, functionalized pyrrolidine scaffolds obtained from the azomethine ylide cycloaddition reaction found to show potential activity against the hepatitis C virus.[14]In addition, functionalized pyrrolidine scaffolds were also found to exhibit promising glucosidase inhibitory activity, potent antiviral, antidiabetic, antibacterial and anticancer activities.[15]

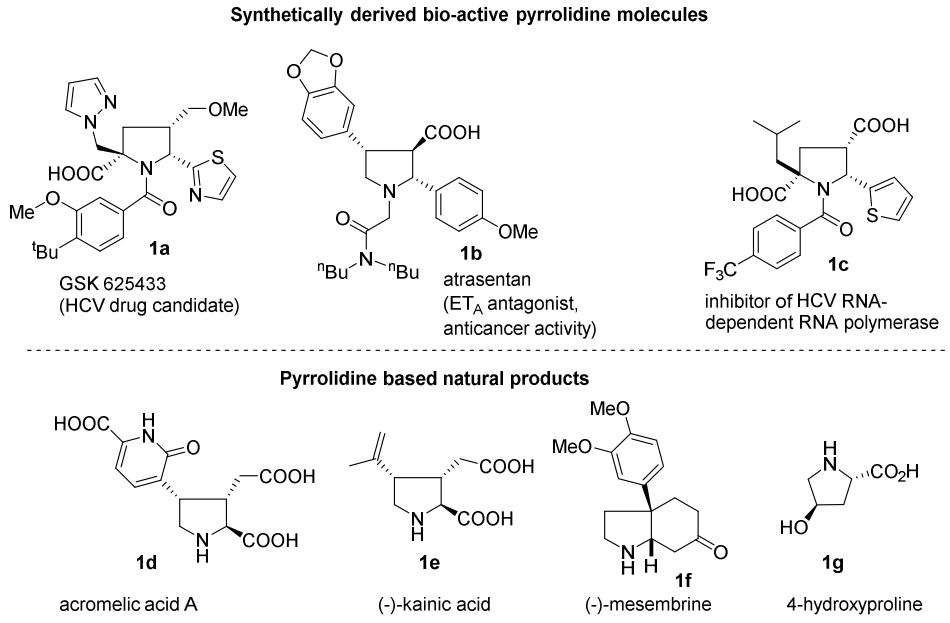


Figure 1.Biologically active pyrrolidine molecules.

Along this line, the pyrrolidine alkaloid, (*S*)-nicotine is the most abundant alkaloid (tobacco products) and it was isolated from genus *Nicotiana* plant.[20-24] Nicotine was first isolated by Posselt and Reimann in 1828.[20] In 1843 Melsens proposed its first chemical empirical formula. The correct structure of nicotine is suggested by Pinner in 1893.[21] In 1904, the first synthesis of nicotine was reported by Pictet and Rotshy.[22] Pitner recognized the spatial orientation of (*S*)-

nicotine in 1978. The fresh *N. tabacum* contains[23] 93% of (*S*)-nicotine **2a**, 3.9% of (*S*)-anatabine **2b**, 2.4% of (*S*)-nornicotine **2c**, 0.5% (*S*)-anabasine **2d** (Figure 2). Annually 2800 tons of (*S*)-nicotine used as a crop protectant and it is used as an insecticide in a bulk manner.[25,26] Nicotine molecule has significantly attracted the attention of the medicinal chemists, because of its potential role as a drug molecule for treating central nervous system (CNS) disorders. Nicotine mainly binds with the neuronal nicotinic receptors (nAChRs) in the body[27] and principally, (*S*)-nicotine plays a key role in the treatment of Parkinson's disease (PD), Alzheimer's disease (AD), Tourette's syndrome, attention-deficit hyperactivity disorder (ADHD), smoking cessation, depression, and other CNS disorders.[28] Nicotine is used as a therapeutic agent in smaller doses, if it is used in higher doses, it can cause the seizures, neuromuscular effects and sleep disturbance etc.[29] These side effects due to a subtype selectivity or a lack of coordination among the nAChRs.[30]

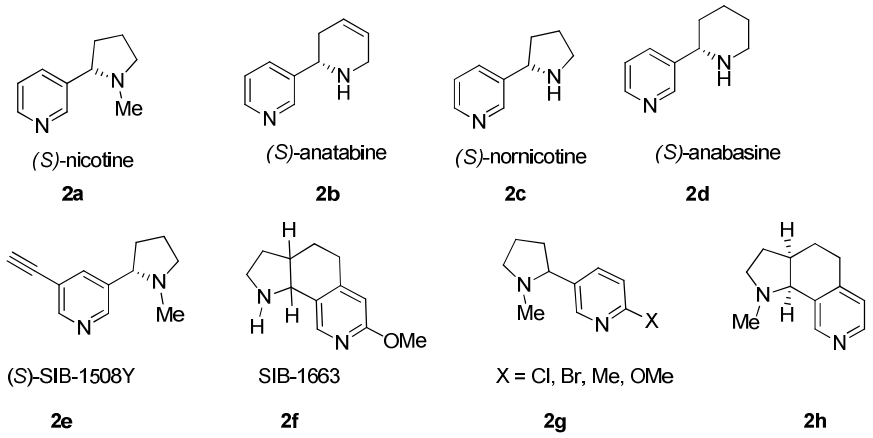


Figure 2. Pyrrolidine/piperidine natural products and synthetically derived nicotine molecules.

The medicinal chemists are aiming to synthesize nicotine derivatives that are only selective in binding to ACh sites to reduce the side effects (Figure 2).For instance, the synthetic molecule, SIB-1508Y ((*S*)-(-)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate **2e**, was discovered as a potential nicotine-based drug by SIBIA Neurosciences Inc.[32] This molecule acts as an agonist of human neuronal nAChRs. Preclinical studies showed that **2e** is used for treatment of Parkinson's disease. Likewise, the synthetic molecule SIB-1663 ([(+) and (-)]-7-methoxy-2,3,3a,4,5,6,9b-hexahydro-1*H*-pyrrolo-[3,2*h*]-isoquinoline **2f**, produces ipsilateral turning in unilaterally 6-hydroxydopamine-lesioned rats, an animal model of Parkinson's disease.[33]

Synthesis of pyrrolidine and nicotine skeletons (arylated pyrrolidine frameworks).

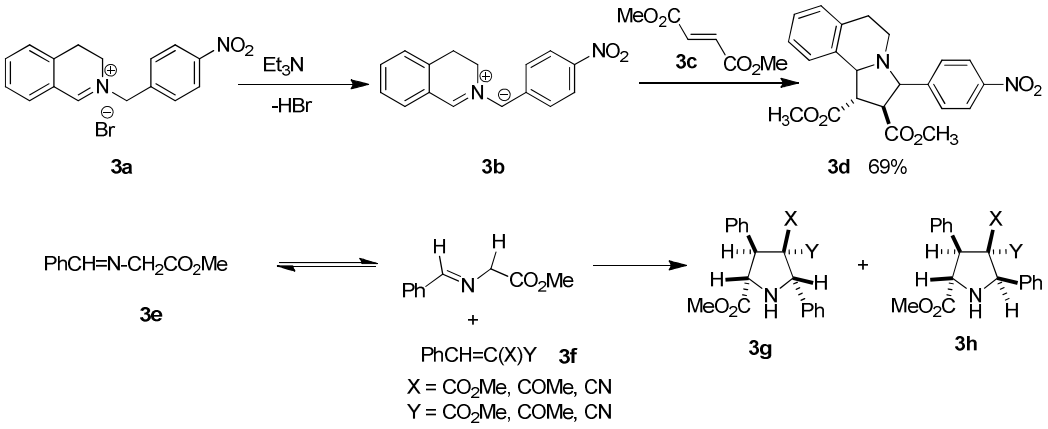
Given that the pyrrolidine framework is a privileged structural unit frequently found in a variety of natural products, synthetically derived biologically active compounds and drugs; several arylated pyrrolidine derivatives including nicotine derivatives were prepared in view of enriching the library of pyrrolidine and nicotine skeletons.

Accordingly, in the following sections some of the literature papers dealing on the azomethine cycloaddition-based synthesis of arylated pyrrolidine derivatives including nicotine derivatives prepared in view of enriching the library of pyrrolidine and nicotine skeletons are presented.

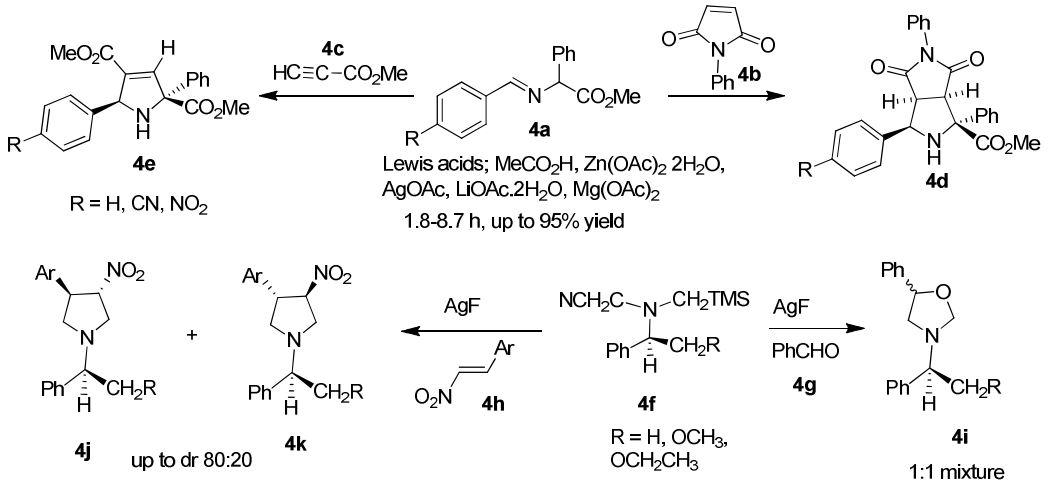
Huisgen*et al.*[36] first reported the generation of azomethine ylide **3b** from *N-(p*-nitrobenzyl)-3,4-dihydroisoquinoliniumbromide **3a** with triethylamine in hot pyridine and it was further reacted with dimethyl fumarate **3c** to give the pyrrolidine-fused tricyclic skeleton **3d** in 69% yield. Hamelin *et al.* [37] reported the first synthesis of pyrrolidines **3g** and **3h**by using Knöevenagel adducts **3f** as the dipolarophiles in the 1,3-dipolar cycloaddition with the azomethine ylides derived from the imine ester **3e** (Scheme 1).

Grigg *et al*.[38] reported the first synthesis of substituted pyrrolidine 2-carboxylic acids **4d** and **4e** through the 1,3-dipolar cycloaddition of azomethine ylides with *N*-phenyl maleimide **4b** and methyl propiolate **4c** with arylidene imines **4a** in the presence of the Bronsted and Lewis acids (Scheme 2). After the first report published by Grigg *et al*. several reports appeared in the literature, which revealed the Lewis acid-catalyzed synthesis of proline molecules (or) pyrrolidine-2-carboxylic acid derivatives. Padwa *et al*.[39] first reported the diastereoselective synthesis of chiral pyrrolidines **4i**, **4j** and **4k** from optically active *α*-cyanoaminosilanes **4f** with *β*-nitrostyrenes **4h** or aldehyde **4g** in presence of AgF (Scheme 2).

Grigg *et al*.[40] reported the first asymmetric synthesis of chiral prolines **5d** by using stoichiometric amounts of chiral bases or chiral metal complexes. In 2002, Zhang and co-workers[41] reported the first substoichiometric catalytic enantioselective synthesis of chiral prolines **6c***via* the asymmetric azomethine ylide cycloaddition in the presence of chiral diphosphane / silver (I) complex (Scheme 3). After this report, various research groups revealed the enantioselective synthesis of proline molecules.



Scheme 1. Synthesis of pyrrolidine derivatives **3d**, **3g** and **3h**.

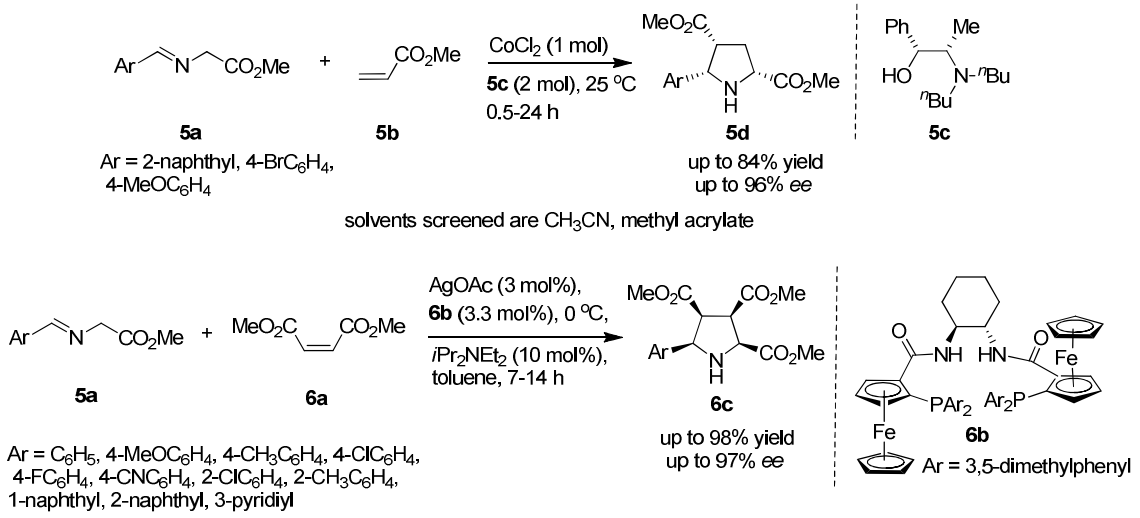


Scheme 2. Construction of pyrrolidines**4d**, **4i,4j** and **4k** and 3-pyrrolines **4e**.

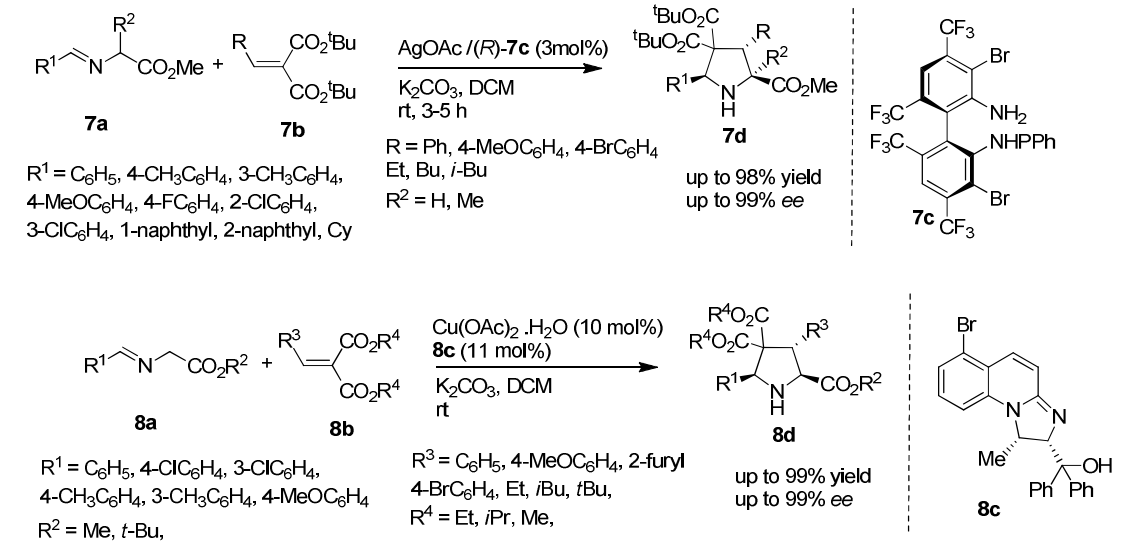
Wang *et al.*[42a] reported the asymmetric azomethine ylide cycloaddition with alkylidene malonates **7b** in presence of chiral ligand TF-BiphamPhos **7c** gave polysubstituted pyrrolidine derivatives **7d** with high enantioselectivity (Scheme 4). Deng and co-workers[42b] reported the enantioselective azomethine ylide cycloaddition for the preparation of highly functionalized pyrrolidines **8d** in presence of the chiral ligand **8c** and $Cu(OAc)_2$ (Scheme 4).

Fukuzawa *et al.*[43a]revealed enantioselective synthesis of proline ester derivatives **9d** through the catalytic asymmetric azomethine ylide cycloaddition with alkylidene malonates **9b** in presence of the bifunctional AgOAc/thioclickferrophos complex (Scheme 5). Subsequently, Zhou and co-workers[43b] described an efficient enantioselective of synthesis pyrrolidine-2,4,4-tricarboxylate

derivatives **10d** by azomethine ylide cycloaddition in presence of Cu^{II}-N,P oxazolinylferrocene ligand complex (Scheme 5).



Scheme 3. Enantioselective synthesis of pyrrolidines **5d** and **6c**.

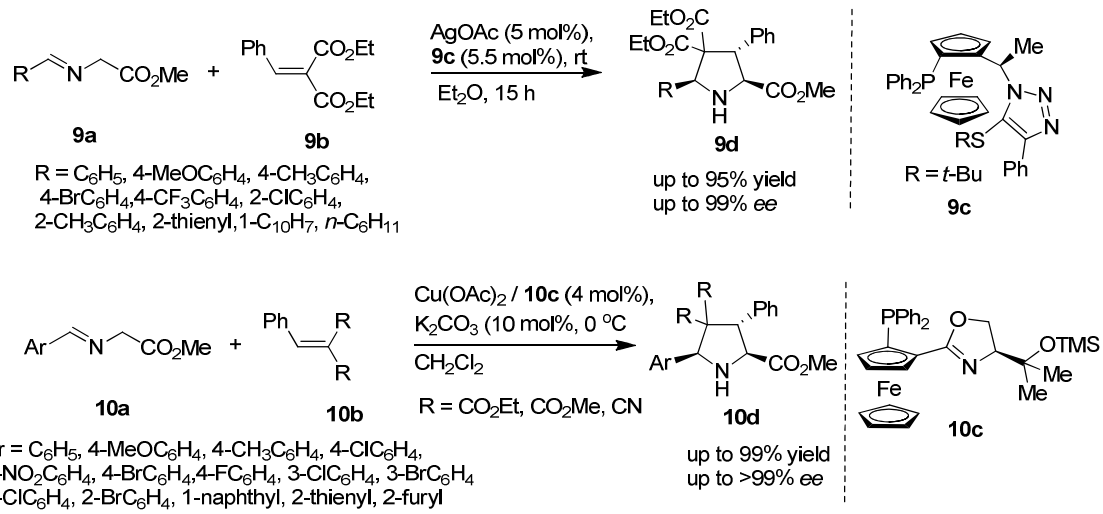


Scheme 4. Enantioselective construction of proline molecules **7d** and **8d**.

Representative methods dealing on the synthesis of cyano group containing spiropyrrolidines and spiropyrrolizidines.

El-Ahl[44] first reported the synthesis of spirooxindoles **11d** involving the 1,3-dipolar cycloaddition of azomethine ylide generated *via* the decarboxylative reaction of isatin **11a** and secondary amino acid **11b** with arylidenemalonitrile **11c** as a 2π system (Scheme 6). After this

report, various groups worked on the synthesis of spiro-pyrrolidines and pyrrolizidines*via* theazomethine cycloaddition reaction by using arylidenemalonitriles as a dipolarophile.



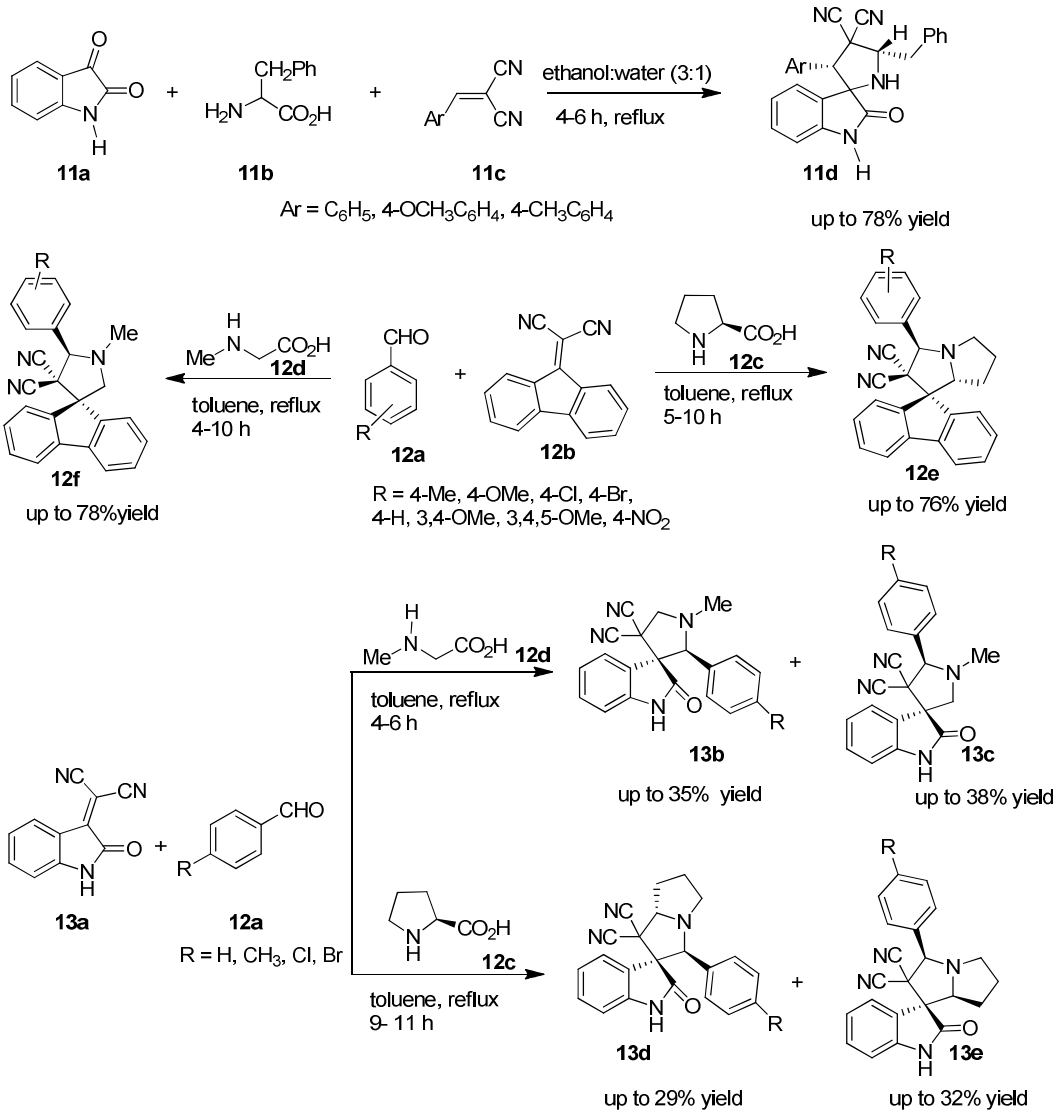
Scheme 5. Enantioselective synthesis of proline derivatives **9d** and **10d**.

Ghandi *et al.*[45] reported the synthesis of cyano group containing spiropyrrolizidines **12e** and spiropyrrolidines **12f** involving the 1,3-dipolar cycloaddition of the azomethine ylides generated *via* the decarboxylative reaction of aldehydes **12a** and amino acids **12c** and **12d** with the Knöevenagel adduct of 9-fluorenone-malononitrile **12b** (Scheme 6). The same group[46] reported the synthesis of cyano group containing spiropyrrolidine oxindoles and spiropyrrolizidines oxindoles **13b**-**e**, respectively, involving the 1,3-dipolar cycloaddition of azomethine ylides generated *via* a one pot reaction of sarcosine / proline with aromatic aldehydes **12a** and **13a** (Scheme 6).

Perumal and coworkers[47] reported the synthesis of a series of cyano group containing dispiropyrrolidine bisoxindoles **14f** and dispiropyrrolidine oxindoles **14e** (Scheme 7) involving the 1,3-dipolar cycloaddition of azomethine ylide with isatylidene malononitrile **14d** and 2-(1,3-dioxo-indan-2-ylidene)-malononitrile **14c**, respectively. Shi *et al.*[48] reported the synthesis of cyano group containing dispiropyrrolidine bisoxindoles **15b** and **16b***via* the 1,3-dipolar cycloaddition of azomethine ylides through a muticomponent reaction method (Scheme 7).

Nabid *et al.*[49] reported the synthesis of dicyano functionalized spiropyrrolidines and spiropyrrolizidines **17g** from the 1,3-dipolar cycloaddition of arylidenemalononitrile Knöevenagel adducts **17f** with non-stabilized azomethine ylides generated from isatin **17a** / acenaphthenequinone **17b** and sarcosine or *N*-phenylglycine or proline. Dandia *et al.*[50] reported

the synthesis of cyano group containing dispiro pyrrolidines **17k** and **17l** from 2-oxo-(2*H*)-acenaphthylen-1-ylidene-malononitrile and 2-fluoren-9-ylidene-malononitriles **17j** and **17i** (Scheme 8).

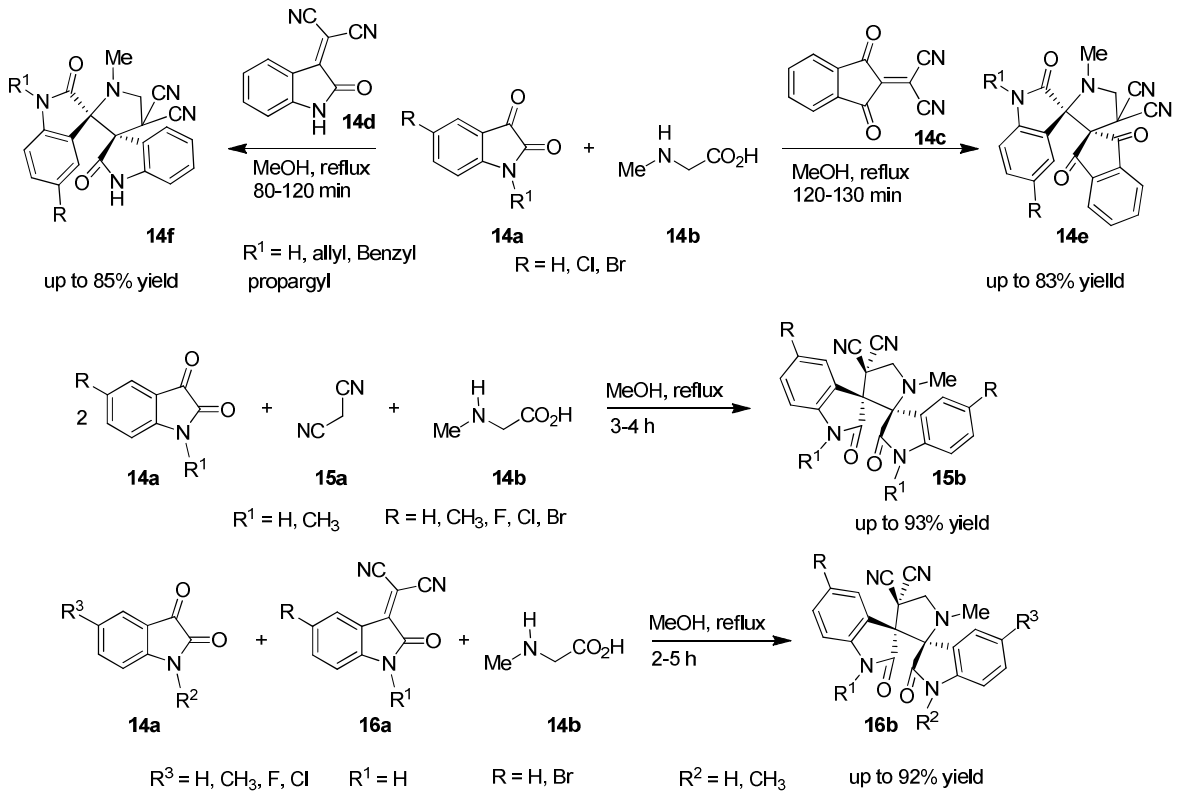


Scheme 6. Construction of cyano group containing spiropyrrolidines **11d**, **12f** and **13b,c** and **12e** **13d**,**e**.

Representative methods dealing on the synthesis of nicotine derivatives (α-heteroarylated pyrrolidine derivatives).

Ishar *et al.*[51] reported the regio- and stereoselective synthesis of mono- and bicyclic-isoxazolidine-based nicotine analogues **18f-j** from the reaction of α-(3-pyridyl)-*N*-phenylnitrone **18c** with variety of dipolarophiles **18d** and **18e** (Scheme 9). Ishar *et al.*[52] achieved the regio

selective synthesis of norbornane fused bis-isoxazolidine-based nicotine analogues **19b-d** from the reaction of α-(3-pyridyl)-*N*-phenylnitrone (**18c**) with norbornadiene **19a** (Scheme 10).

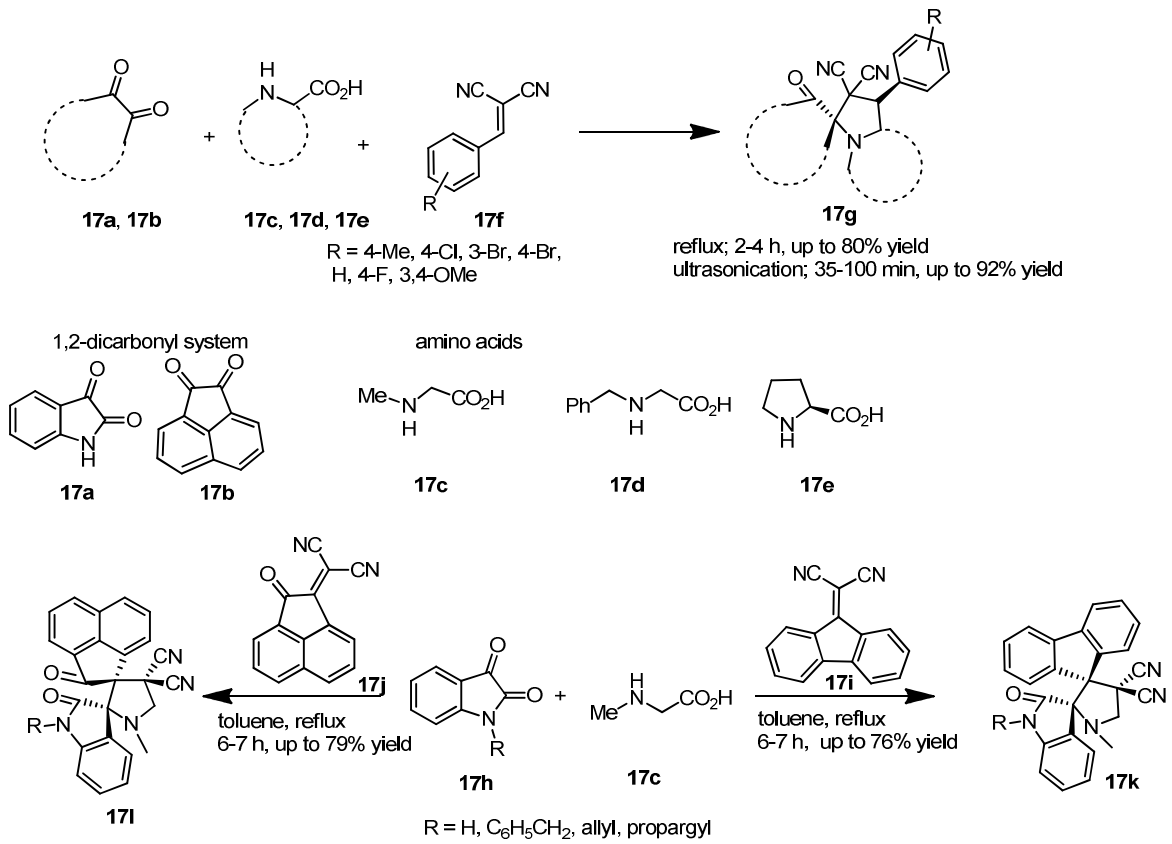


Scheme 7. Construction of cyano group containing dispiropyrrolidine bisoxindoles **14f**, **15b** and **16b** and dispiropyrrolidine oxindoles **14e**.

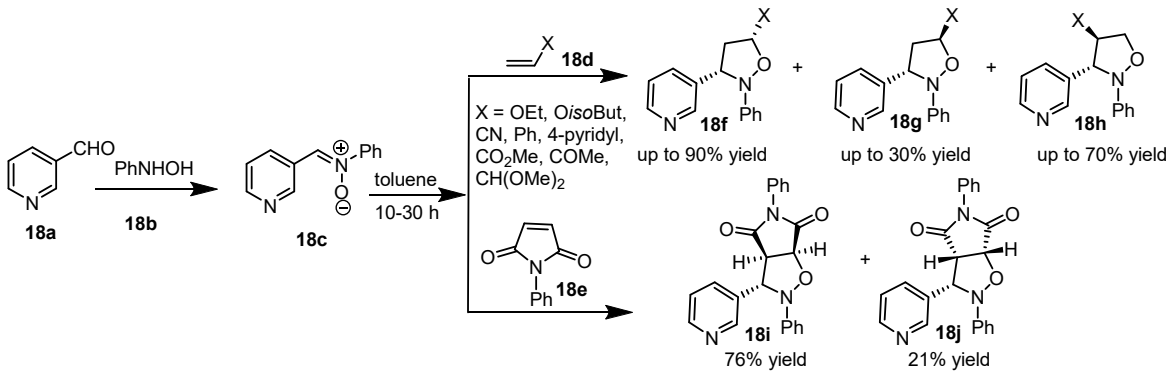
Zhai *et al.*[53a,b,c] reported the synthesis of conformationally locked nicotine analogue **20i** from 3-bromopyridine (**20a**) *via* the intramolecular azomethine ylide cycloaddition as a key step, which afforded the compounds **20g** and **20h** with dr ratio 58:42 (Scheme 11). Zhai *et al.* also[53a] reported the synthesis of conformationally locked nicotine analogues **20m** and **20q** involving the azomethine ylide cycloaddition as a key strategy (Schemes 12 and 13) and further, they also[54] revealed the synthesis of fluorinated tricyclic nicotine analogue **20u***via* theintramolecular azomethine ylide cycloaddition as a key step (Scheme 14).

Bashiardes *et al.*[55] reported the synthesis of nicotine analogues **23***via* the intramolecular cycloaddition of azomethine ylide generated from nicotinaldehyde **22** and secondary amino acids **22** (Scheme 15). Ghandi *et al.*[56] also reported the synthesis of some nicotine derivatives from the

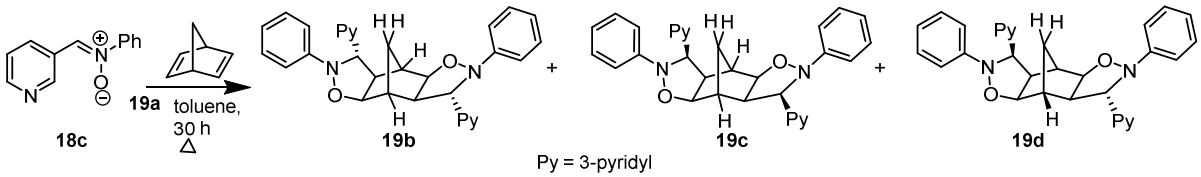
1,3-dipolar cycloaddition of azomethine ylide generated from pyridine-3-carbaldehyde and sarcosine with Knöevenagel adducts as the dipolarophiles.



Scheme 8. Regioselective synthesis of cyano group containing spiro- dispiro-based pyrrolidines and pyrrolizidines (**17g**, **17k** and **17l**).

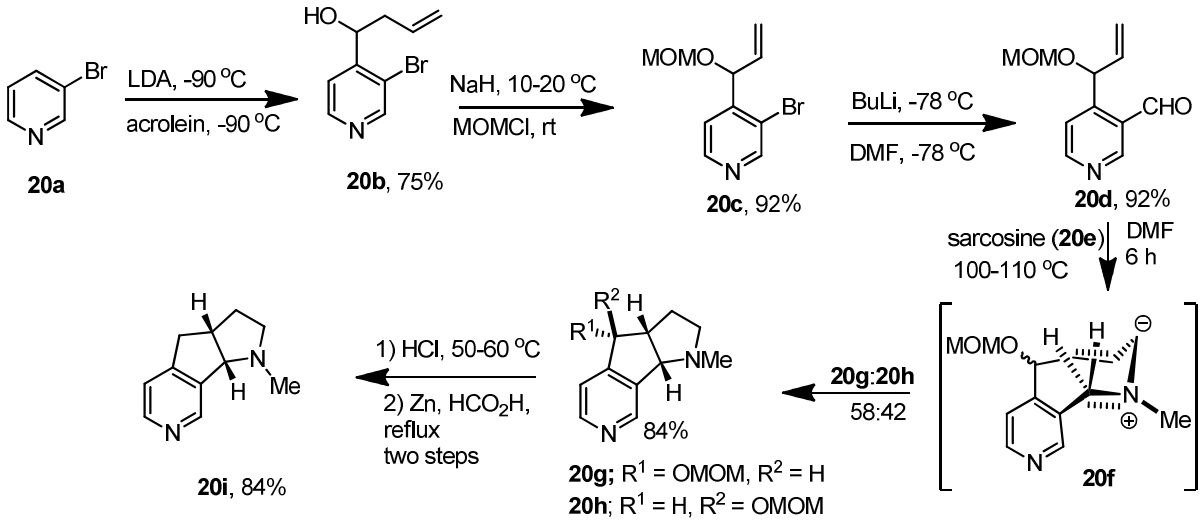


Scheme9. Synthesis of isoxazolidine-based nicotine analogues **18f-j**.

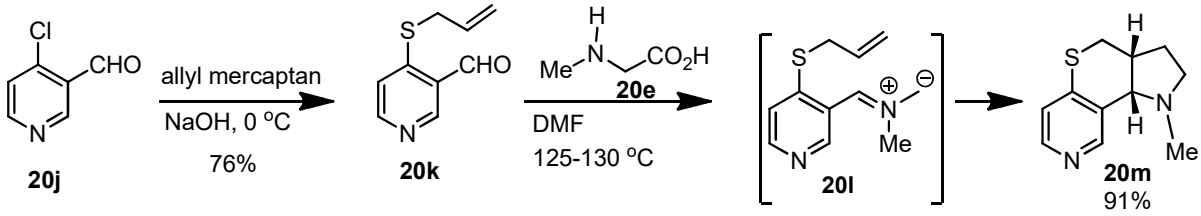


Scheme10. Synthesis of isoxazolidine-based nicotine analogues **19b-d**.

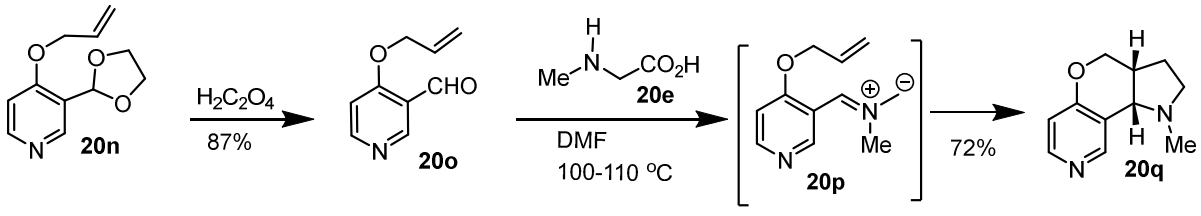
Padwa *et al*.[57] reported the synthesis of nicotine analogue **26** through the cycloaddition of azomethine ylide with vinyl sulfone as a dipolarophile (Scheme 16).



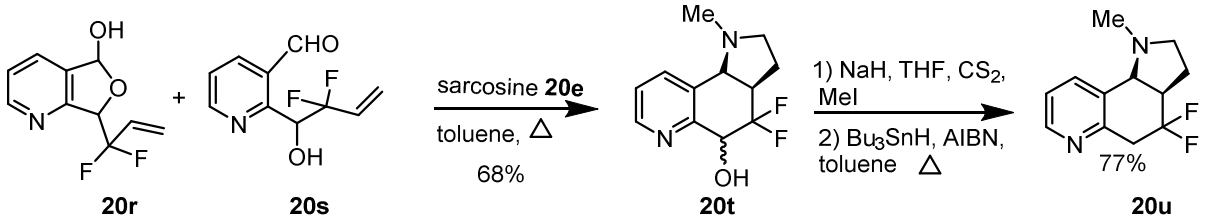
Scheme 11. Synthesis of conformationally locked nicotine analogue **20i**.



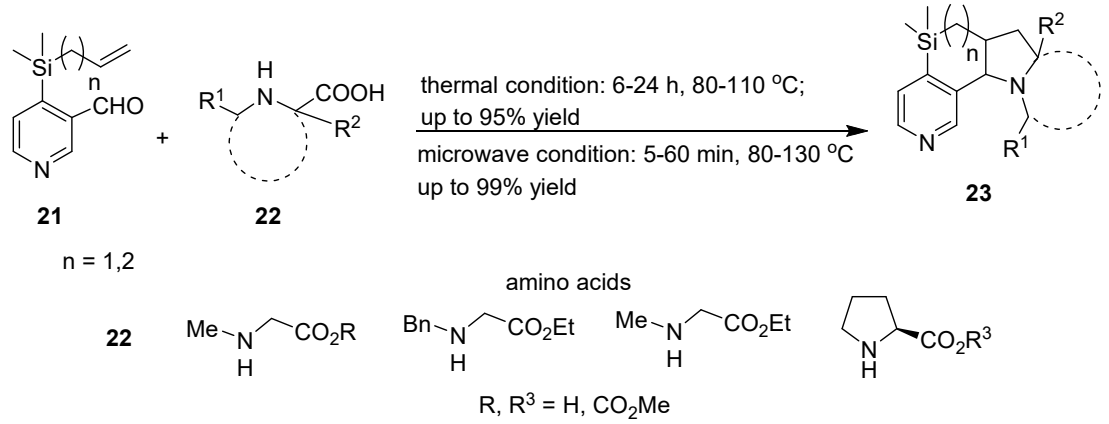
Scheme 12. Synthesis of conformationally locked nicotine analogue **20m**.



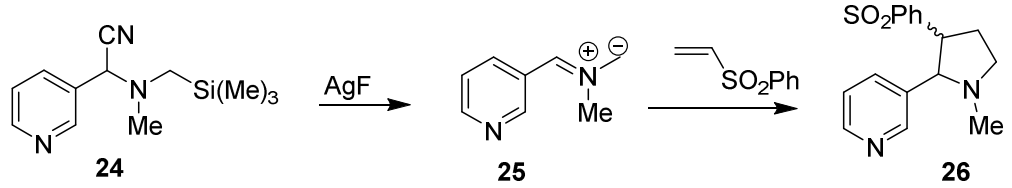
Scheme 13. Construction of conformationally locked nicotine analogue **20q**.



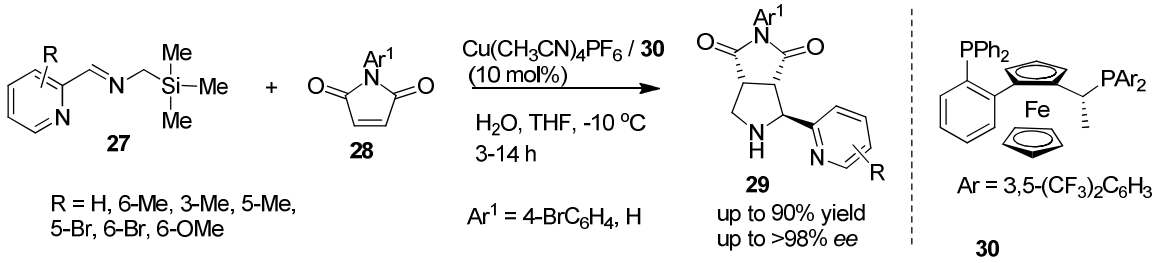
Scheme 14. Synthesis of conformationally locked nicotine analogue **20u**.



Scheme 15. Construction of silicon based restricted nicotine **23**.



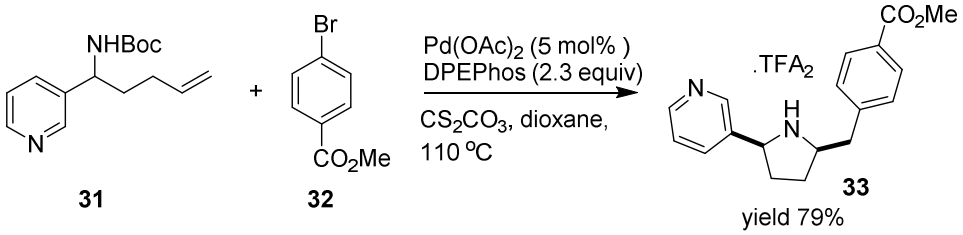
Scheme 16. Synthesis of heteroarylated-pyrrolidine molecule **26**.



Scheme 17. Synthesis of chiral heteroarylated-pyrrolidine molecule **29**.

Carretero *et al.*[58a] revealed the synthesis of α-heteroarylpyrrolidines **29***via* theazomethine ylide cycloaddition between silylimines **27** and activated olefins **28** in presence of $Cu(CH_3CN)_4PF_6$ /

Walphos **30**(Scheme 17). Nelson and co-workers[58b] reported the synthesis of nornicotine scaffold **33** *via* the Pd-catalyzed aminoarylation (Scheme 18).



Scheme 18. Construction of heteroarylated-pyrrolidine molecule **33**.

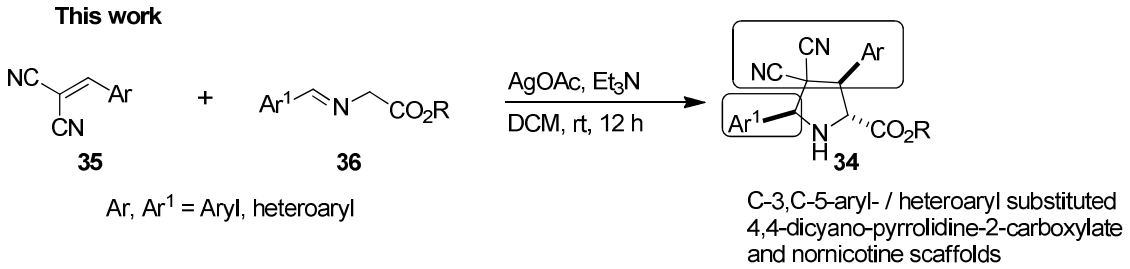
Results and discussion.

Chapter 1a: C-3,C-5-Aryl- / heteroaryl substituted 4,4-dicyano-pyrrolidine-2-carboxylate and nornicotine scaffolds (proline derivatives).

Given the pyrrolidine framework is a privileged structural unit frequently found in a variety of natural products, synthetically derived biologically active compounds and drugs;[1-16]categorically, in the context of finding new lead bio-active molecules exhibiting promising biological activities and for finding potential drug candidates, there have been bestowed interests and continuous efforts for preparing new libraries of multi substituted pyrrolidines. In particular, pyrrolidine carboxylic acid (proline) frameworks having aryl or heteroaryl groups show promising biological activity.

There exist various reports dealing on the synthesis of substituted pyrrolidine scaffolds *via* the azomethine cycloaddition method as discussed above.[4,8,10] The key to assemble new class of a library of diversely functionalized pyrrolidines has been to use different 2π components (dipolarophiles) in the azomethine ylide cycloaddition reaction. It was envisaged to use the arylidene / heteroarylidenemalononitriles **35** as the 2π components in the Ag-catalyzed azomethine ylide cycloaddition reactions. A literature survey revealed that the Ag-catalyzed generation of azomethine ylides from *N*-benzylideneiminoglycinates[17-19] and their 1,3-dipolar cycloaddition reaction with benzylidenemalononitriles (Knöevenagel adducts)[59] has not been well explored.[4,8,10] In the context of enriching the library of functionalized pyrrolidines,

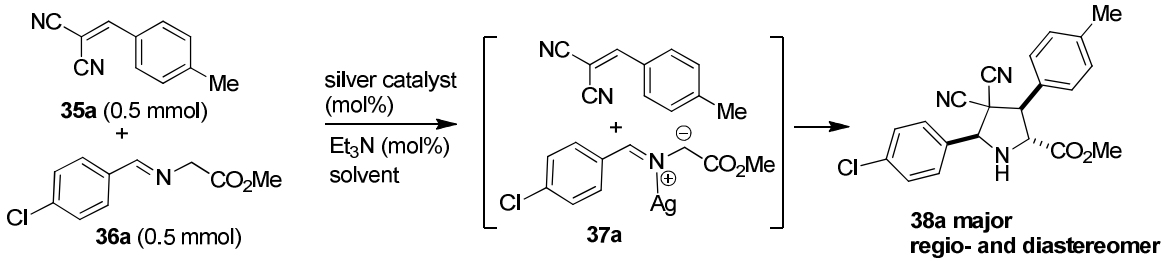
especially, pyrrolidine carboxylic acid (proline) frameworks having aryl or heteroaryl groups and as a part of this thesis, it was envisaged to investigate the regio- and diastereoselective cycloaddition of azomethine ylides with arylidene / heteroarylidenemalononitriles **35** for the construction of a new set of substituted pyrrolidine scaffolds, mainly, pyrrolidines-appended with different aryl- / heteroaryl moieties. Accordingly, the synthesis of several C-3,C-5-aryl- / heteroaryl substituted 4,4-dicyano-pyrrolidine-2-carboxylate and nornicotine scaffolds (proline derivatives) was accomplished and the results obtained are discussed here (Scheme 19).



Scheme 19. Regio- and diastereoselective cycloaddition of azomethine ylides with benzylidenemalononitriles: Synthesis of a new set of 4,4-dicyanopyrrolidine-2-carboxylate derivatives.

At the outset, we investigated the 1,3-dipolar cycloaddition reaction of azomethine ylides derived from *N*-benzylideneiminoglycinates in the presence of a silver salt with benzylidenemalononitriles (Knöevenagel adducts) to obtain multisubstituted 4,4-dicyanopyrrolidine-2-carboxylate and nornicotine derivatives and we performed several reactions to find out the best reaction conditions and solvents. Table 1 comprises of the silver-catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylide derived from *N*-benzylideneiminoglycinate (**36a**) with benzylidenemalononitrile (**35a**). The reaction of *N*-benzylideneiminoglycinate (**36a**) with benzylidenemalononitrile (**35a**) in the presence of catalytic amount of $AgClO_4$ (5-20 mol%) and Et_3N (10 mol%) in a nonpolar solvent, such as, toluene at rt gave the product **38a** (3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylate)as the major regio- and diastereomer in 71-74% yields with good diastereoselectivity (entries 1-3, Table 1).

Table 1. Optimization reactions: 1,3-Dipolar cycloaddition of azomethine ylide with benzylidenemalononitrile **35a**.



entry	Ag catalyst (mol%)	Et_3N (mol%)	solvent (mL)	*T* (°C)	time (h)	yield (%)	dr
1	$AgClO_4$ (5)	10	toluene (5)	r.t.	48	71	>90:10
2	$AgClO_4$ (10)	10	toluene (5)	r.t.	48	74	>90:10
3	$AgClO_4$ (20)	10	toluene (5)	r.t.	48	74	>75:25
4	$AgClO_4$ (10)	40	toluene (5)	0	12	83	>90:10
5	$AgClO_4$ (10)	40	THF (5)	r.t.	12	93	>90:10
6	$AgClO_4$ (10)	40	DCM (5)	r.t.	12	87	>90:10
7	$AgClO_4$ (10)	40	DCM (5)	r.t.	24	93	>90:10
8	AgOAc (10)	10	toluene (5)	r.t.	48	69	>90:10
9	AgOAc (10)	40	toluene (5)	r.t.	48	77	>90:10
10	AgOAc (10)	40	THF (5)	0	12	83	>90:10
11	AgOAc (10)	10	DCM (5)	r.t.	24	79	>90:10
12	AgOAc (10)	40	DCM (5)	r.t.	12	96	>90:10
13	AgOAc (10)	40	DCM (5)	0	12	87	>85:15

[a] The diastereomeric ratio dr 90:10 refers to the major isomer **38a** is 90% (isolated in pure form in all cases) and the remaining 10% could be any other minor isomers which were not isolated pure form as the quantity was very less.

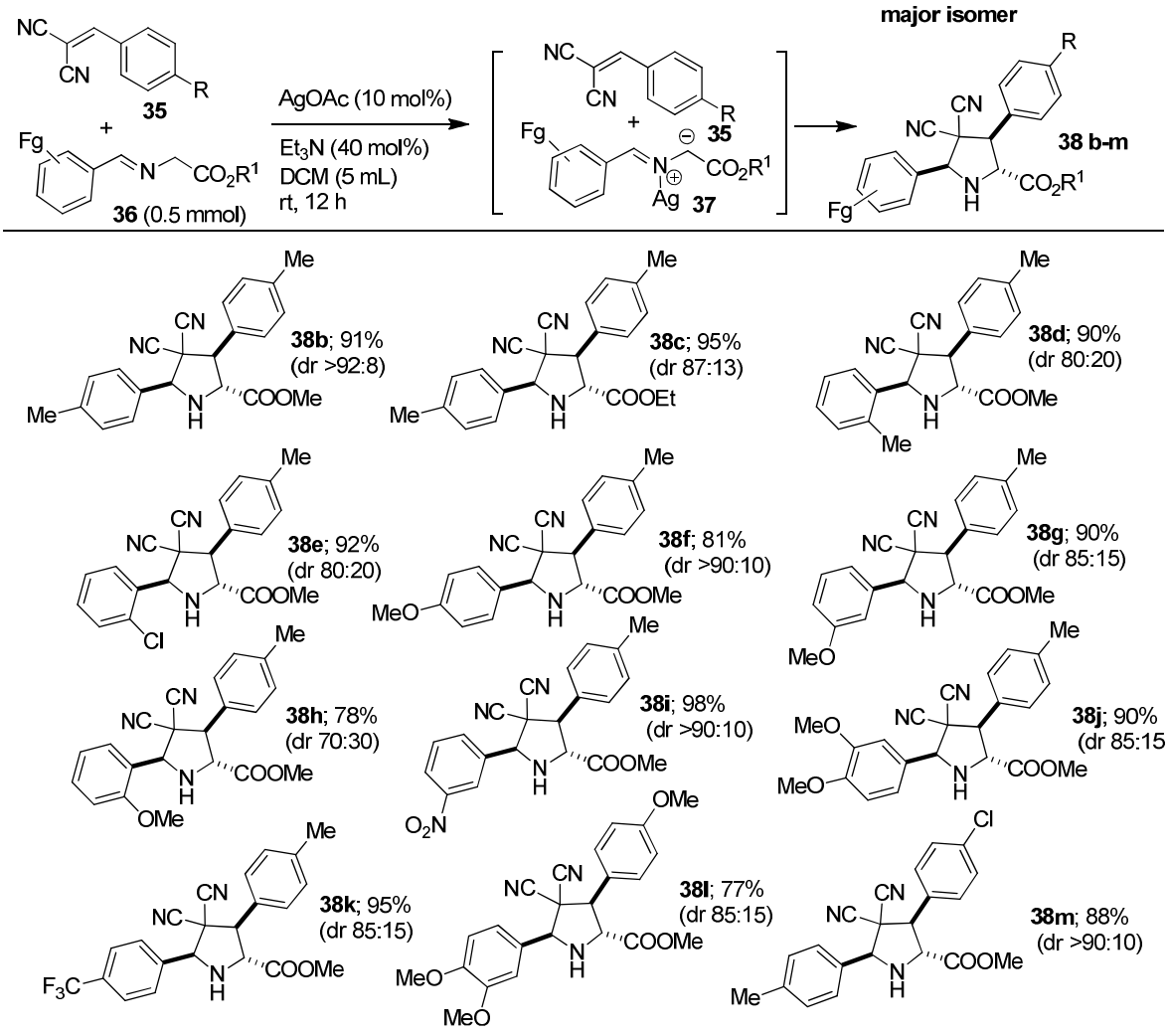
The reaction of *N*-benzylideneiminoglycinate (**36a**) with benzylidenemalononitrile **35a** in the presence of catalytic amount of $AgClO_4$ at 0 °C afforded the product **38a** possessing three stereocenters as the major isomer in 83% yield with very good diastereoselectivity (entry 4, Table 1). Next, we tried the $AgClO_4$-catalyzed cycloaddition of azomethine ylide derived from *N*-benzylideneiminoglycinate (**36a**) with benzylidenemalononitrile **35a** inpolar solvents, such as, tetrahydrofuran anddichloromethane, which furnished the cycloadduct **38a** as the major isomer in improved yields (87-93%) with very high diastereoselectivity (entries 5-7, Table 1).

The yields and diastereoselectivity in the 1,3-dipolar cycloaddition reaction azomethine ylide generated from *N*-benzylideneiminoglycinate (**36a**) with benzylidenemalononitrile **35a** in the presence of catalytic amount of AgOAc (10 mol%) in toluene or tetrahydrofuran were comparable with the yields obtained when $AgClO_4$ was used as the catalyst (entries 2,5 and 8,10 Table 1). The 1,3-dipolar cycloaddition reaction azomethine ylide generated from *N*-benzylideneiminoglycinate (**36a**) with benzylidenemalononitrile **35a** in the presence of catalytic amount of AgOAc (10 mol%) and Et_3N (10 or 40 mol%) in dichloromethane furnished the cycloadduct **38a** as the major isomer in 79-96% yields with very high diastereoselectivity (entries 11-13, Table 1).In all these reactions (entries 1-13, Table 1), we obtained the diastereomer having the core structure of the cycloadduct **38a** the major regio-and diastereomerpossessing three stereocenters. Further, in all of the above reactions (entries 1-13, Table 1), the regioselectivity and diastereoselectivity of the 1,3-dipolar cycloaddition and structure of the cycloadduct **38a** were ascertained based on the similarity in the $^{1}H/^{13}C$ NMR spectral pattern of **38a** obtained in all these reactions. Further the stereochemistry of the major diastereomer **38a** was assigned based on an analogous cycloadduct **40b** that was characterized bythe single crystal X-ray structure analysis and similarity in their NMR spectral pattern.

Having done the optimization reactions, to reveal the generality of this Ag-catalyzed 1,3-dipolar cycloaddition of azomethine ylide with benzylidenemalononitrile, several *N*-benzylideneiminoglycinates **36b-m** were prepared from a variety of aromatic aldehydes or ethyl glycinate or methyl glycinate and then, the compounds **36b-m** were used to assemble various 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylates **38b-m** (Scheme 20). Consequently, the 1,3-dipolar cycloaddition reactions of azomethine ylides derived from the respective *N*-benzylideneiminoglycinates **36b-m** with the benzylidenemalononitrile **35** in the presence of catalytic amount of AgOAc (10 mol%) and Et_3N (40 mol%) in dichloromethane furnished various 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylate derivatives **38b-m** possessing three stereocenters as the major regio- and diastereomers in 77-98% yields with very high regio- and diastereoselectivity (Scheme 20).

Along this line, to further extend the substrate scope, it was planned to synthesize thiophene- or furan- or pyridine substituted 4,4-dicyanopyrrolidine-2-carboxylates(proline) scaffolds possessing three stereocenters (Scheme 21 and 22). Accordingly, various substituted 4,4-dicyanopyrrolidine-2-carboxylates(proline) scaffolds **39a-e** and **39f-i** possessing three

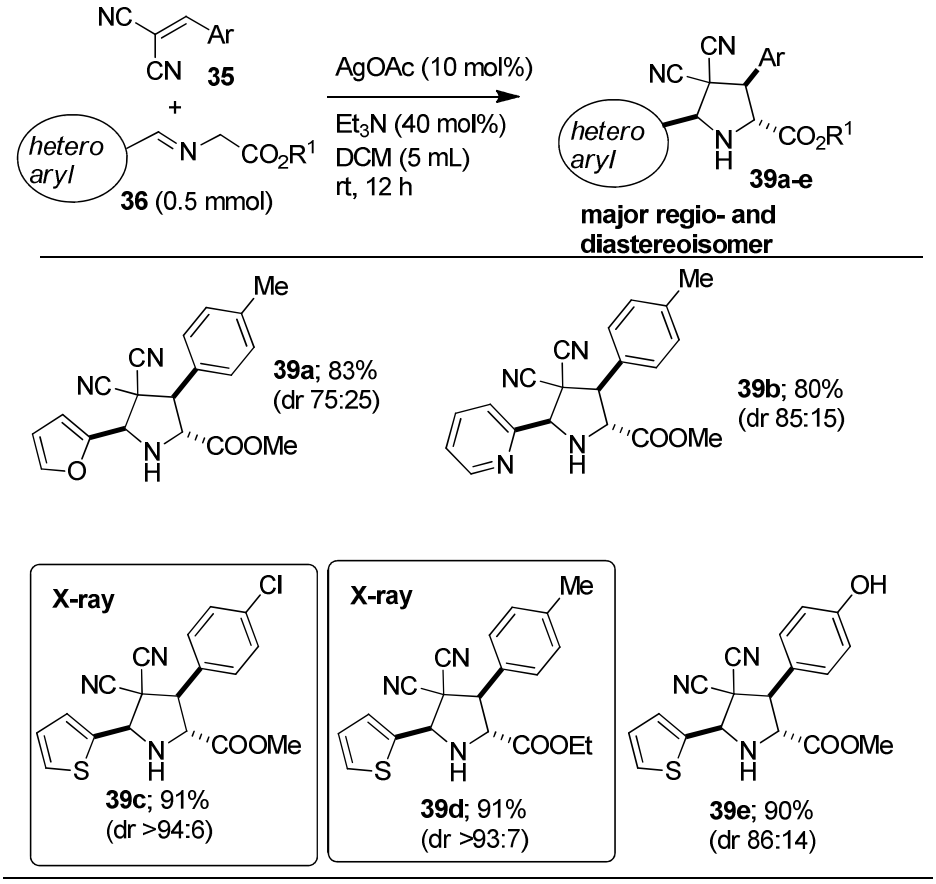
stereocenters were synthesized from the 1,3-dipolar cycloaddition reaction of azomethine ylides derived from the respective *N*-arylideneiminoglycinates with the corresponding arylidenemalononitriles in the presence of catalytic amount of AgOAc (10 mol%) and Et_3N (40 mol%) in dichloromethane at rt.



Scheme 20. Stereo and regioselective synthesis of 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylates possessing three stereocenters.

Next, it was planned to assemble nornicotine analogues **40a-c** possessing three stereocenters. Accordingly, by using the optimized reaction condition the nornicotine analogues possessing three stereocenters **40a-c** (Scheme 23) were synthesized *via* the Ag-catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides derived from the corresponding *N*-

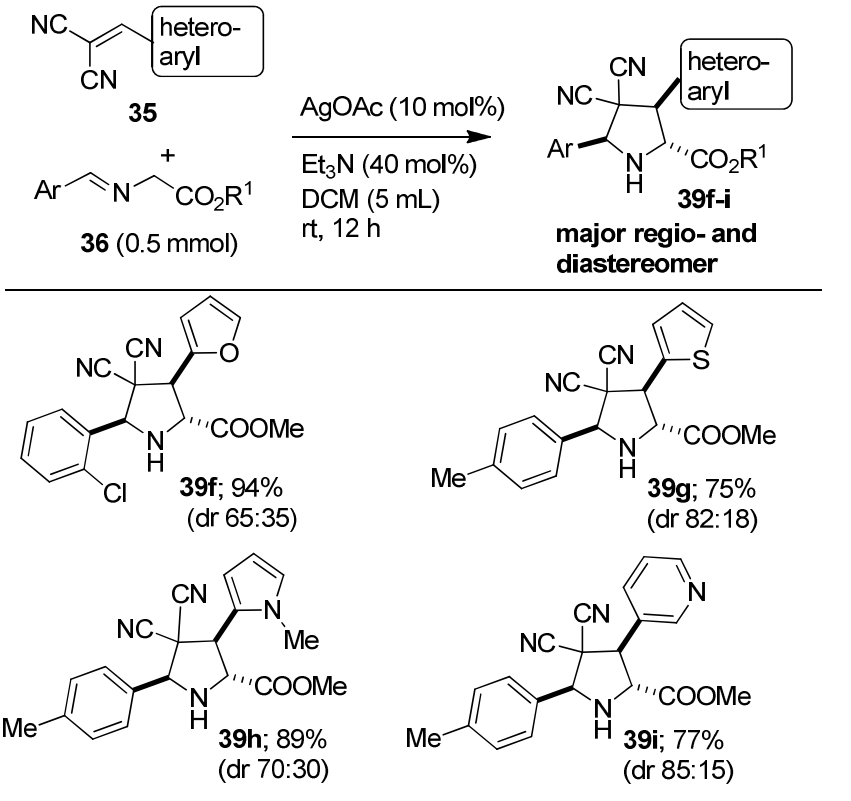
arylideneiminoglycinates with arylidene-malononitriles. In all these reactions, the thiophene- or furan- or pyridine substituted 4,4-dicyanopyrrolidine-2-carboxylates(proline) scaffolds **39a-e** (Scheme 21), **39f-i** (Scheme 22) and nornicotine derivatives **40a-c** (Scheme 23) were obtained in good yields with high regio- and diastereoselectivity.



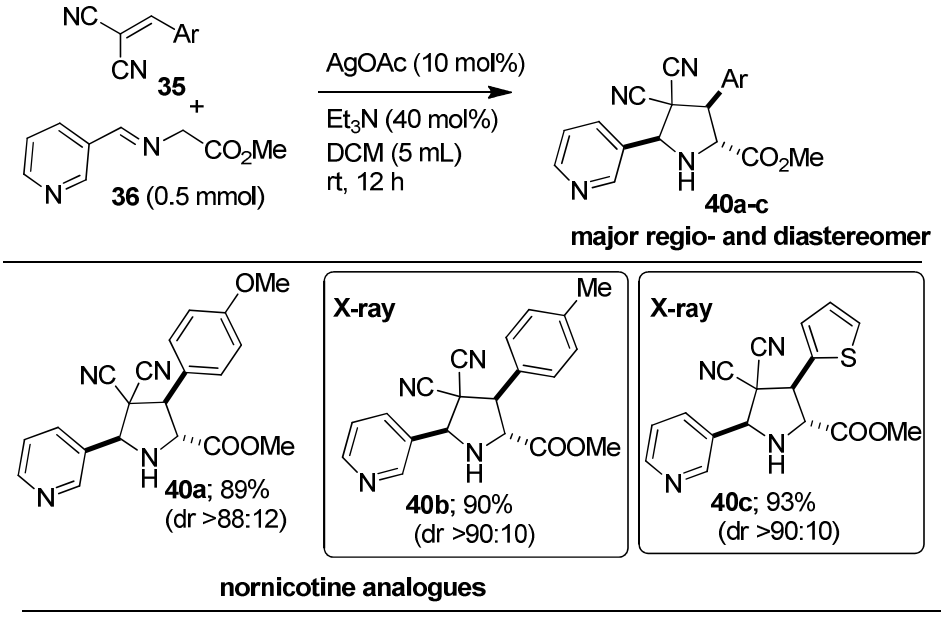
Scheme 21. Diastereoselective synthesis of 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylates consisting of three stereocenters.

Then, to further increase the scope and synthetic utility of this method, it was planned to assemble the *N*-acrylated pyrrolidine derivatives **42a,b** by reacting acryloyl chloride with the pyrrolidine derivatives **38a,b** which were obtained from the Ag-catalyzed azomethine cycloaddition reaction. Then, it was planned to use the *N*-acrylated pyrrolidine derivatives **42a,b** as the 2π component in the [3+2] cycloaddition reaction of the azomethine ylides to assemble the 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylate (proline) scaffolds **45a,b** and **46a,b**.

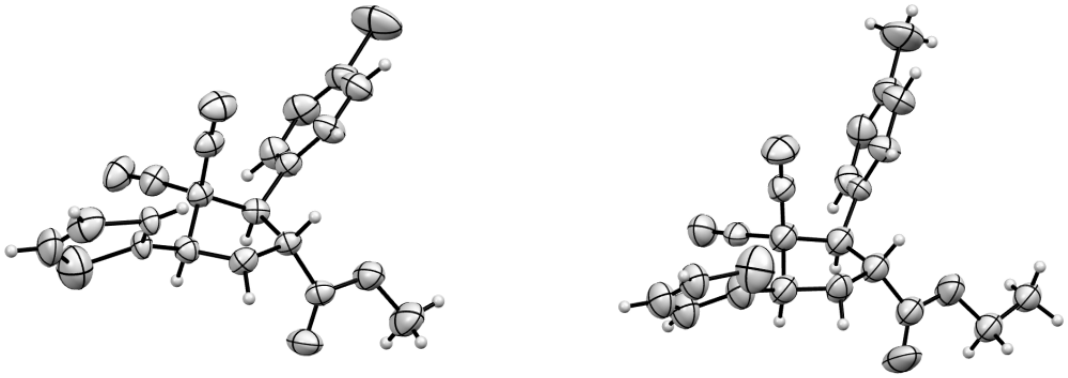
Accordingly, the three component [3+2] cycloaddition reactions of the azomethine ylides derived from the decarboxylative reactions of formaldehyde with sarcosine or *N*-benzyl glycine hydrochloride with the *N*-acrylated pyrrolidine derivatives **42a,b** as the 2π components (dipolarophile) have led to the synthesis of 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylate (proline) scaffolds **45a,b** and **46a,b** (Scheme 24). The cycloaddition reaction of azomethine ylides with the compounds **42a,b** gave the respective single isomers **45a,b** and **46a,b**. At this stage, we could not assign the stereochemistry of the newly formed C3-center in the compounds **45a,b** and **46a,b**. The diastereomeric ratios given for the compounds **45a,b** and **46a,b** are based on their respective starting materials **42a,b** obtained from the respective compounds **38a,b**.



Scheme 22. Diastereoselective construction of 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylates having three stereocenters.



Scheme 23. Construction of nornicotine analogues.

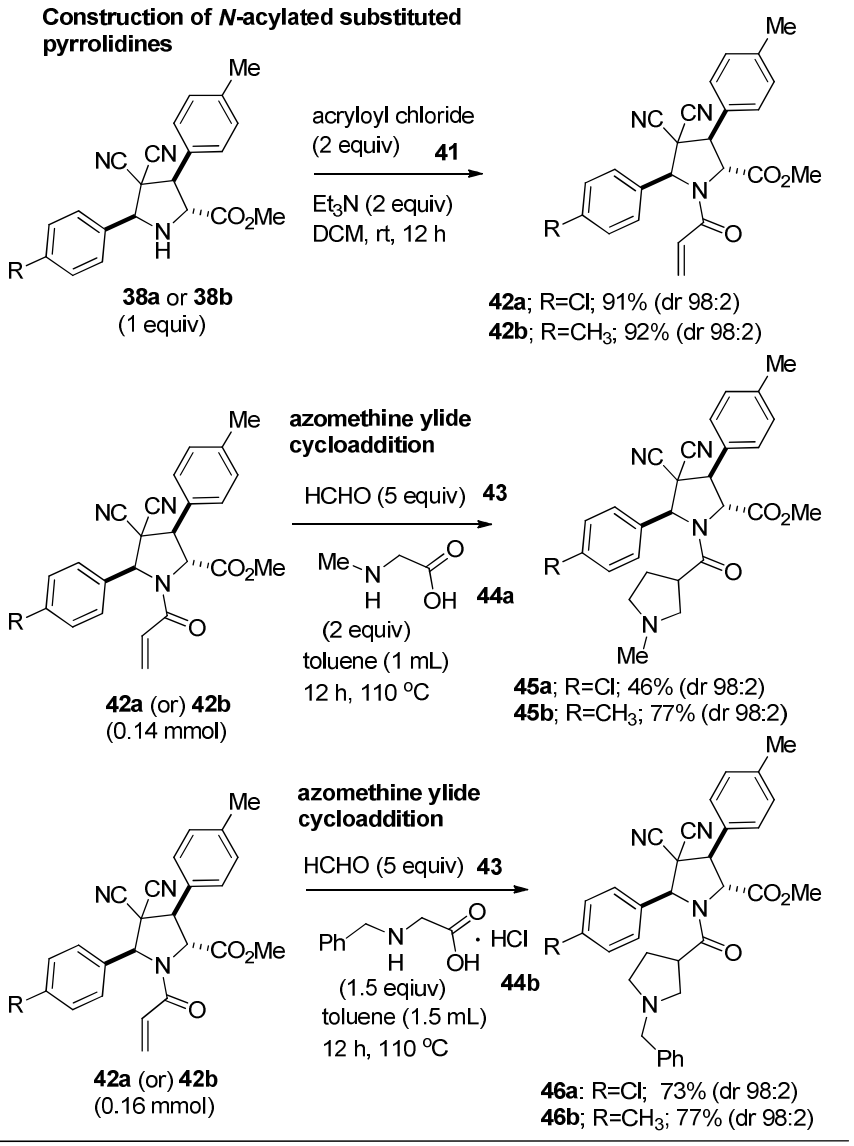


39c **39d**

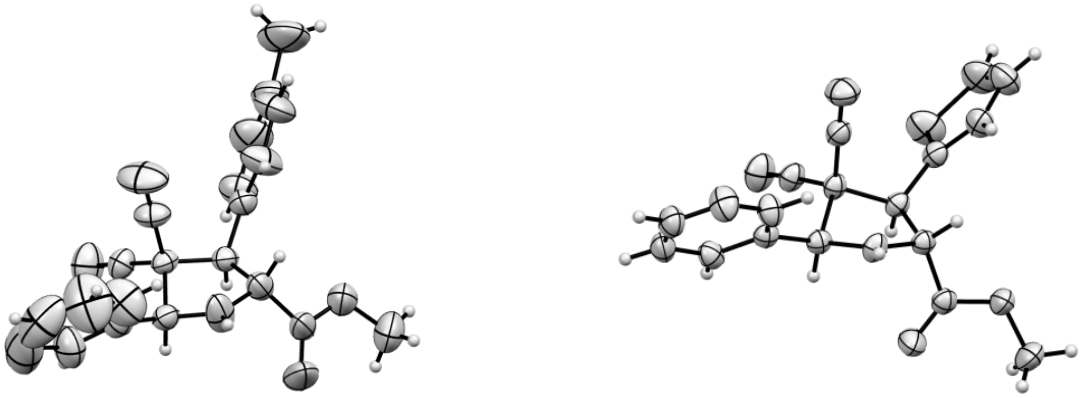
Figure 3. X-ray structures of **39c** and **39d.**

Generally, in all the above described 1,3-dipolar cycloaddition reactions of azomethine ylides derived from *N*-benzylideneiminoglycinates with benzylidenemalononitriles (Knöevenagel adducts), the respective diastereomers having the core structure of the regioisomers **38a-m** (Table 1 and Scheme 20), **39a-e** (Scheme 21), **39f-i** (Scheme 22) and **40a-c** (Scheme 23) were

obtained. The regioselectivity and diastereoselectivity of the products **38a-m** (Table 1 and Scheme 20), **39a-e** (Scheme 21), **39f-i** (Scheme 22) and **40a-c** (Scheme 23) discussed in this work were ascertained based on the similarity in their NMR spectral pattern. Furthermore, the structure and stereochemistry of the aryl substituted 4,4-dicyanopyrrolidine-2-carboxylate (proline) and nicotine scaffolds (major regio- and diastereomers) were unequivocally assigned from the single crystal X-ray structure analyses of the compounds **39c,d** and **40b,c** (Figures 3 and 4).



Scheme 24. Construction of 3,5-aryl-substituted 4,4-dicyanopyrrolidine-2-carboxylate (proline) scaffolds connected to another pyrrolidine unit.



40b **40c**

Figure 4. X-ray structures of the products **40b** and **40c.**

Finally, a preliminary level density functional calculations for geometry optimizations were performed to have an idea regarding the observed regiochemisty in the [3+2] cycloaddition reaction of azomethine ylide derived from the *N*-benzylideneiminoglycinate **36a** with benzylidenemalononitrile **35a** (Figure 5). Density functional calculations for geometry optimizations were done at the 6-311++g (2d,2p) basis set using Becke-3 parameter exchange and the Lee-Yang-Parr correlation (B3LYP) functional in the G'09 suite of programs. The calculations indicate that the experimentally observed major regioisomer **38** comes through a reaction pathway that has a barrier of 28.88 kcal/mol. In comparison with this, the minor regioisomer **38′** comes through a reaction pathway that involves a higher barrier of magnitude 35.99 kcal/mol. The barriers have been calculated from the identified transition states (TS), and the imaginary frequency corresponding to the transition state was examined to make sure that the TS's are indeed the ones that connect reactants with the products. The sum of energies of reactants was taken to 0 kcal/mol in the barrier calculation. Further from the optimized geometries of the products, it was seen that the major product **38** is also thermodynamically favored with an electronic energy stabilization of -5.92 kcal/mol relative to the reactants **35a** and **36a**. The minimal nature of the reactants and products and the saddle point character of the TS have been confirmed with Hessian evaluations at the optimized geometry. Nevertheless, we have done only preliminary level density functional calculations for geometry optimizations to support

the observed regiochemisty. However, a completely detailed theoretical study on the observed diastereoseltivity and regioselectivity in the [3+2] cycloaddition reaction of azomethine ylide derived from *N*-benzylideneiminoglycinates with benzylidenemalononitriles needs to be done and further work is in progress in this regard.

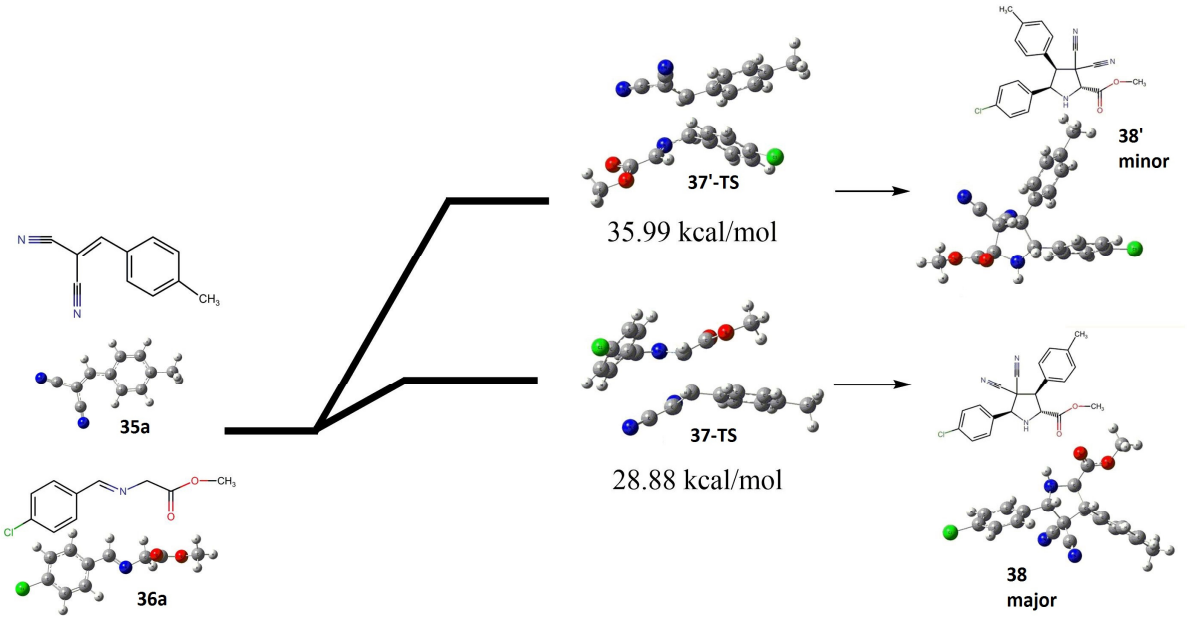


Figure 5. Preliminary level density functional calculations for geometry optimizations for the [3+2] cycloaddition reaction of azomethine ylide derived from the *N*-benzylideneiminoglycinate **36a** with benzylidenemalononitrile **35a**.

Chapter 1b: Synthesis of new class of nicotine analogues*via* theazomethine ylide cycloaddition.

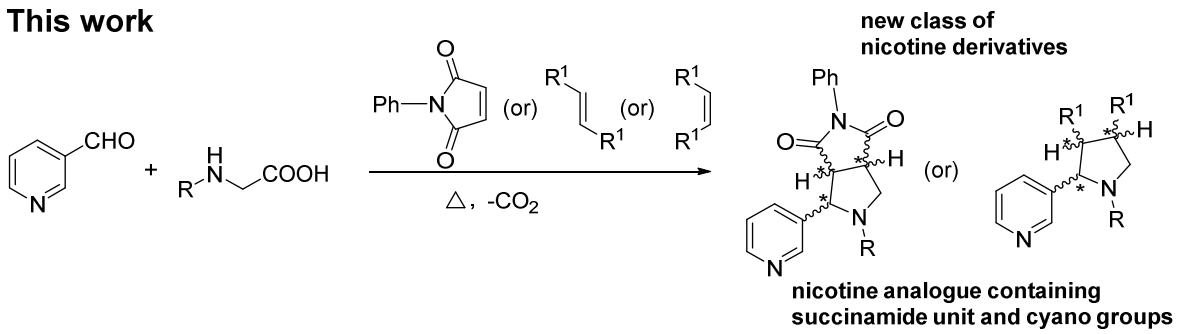
Nicotine and various nicotine analogues found to function as drug molecule for treating central nervous system (CNS) disorders. (*S*)-nicotine plays a key role in the treatment of Parkinson's disease, Alzheimer's disease, Tourette's syndrome, attention-deficit hyperactivity disorder, smoking cessation, depression, and other CNS disorders.[28] While nicotine molecule has been proven to be an important drug molecule, however, there are some limitations. In general, nicotine is used as a therapeutic agent in smaller doses, if it is used in higher doses, it can cause the seizures, neuromuscular effects and sleep disturbance etc.[29] These side effects are due to a

poor selectivity or a lack of high degree of selective coordination with the nAChRs.[30] Hence, the medicinal chemists are aiming to synthesize nicotine derivatives that are only selective in binding to nACh sites to reduce the side effects. Accordingly, different nicotine analogues (Figure 2) were prepared by various research groups. Among various methods, the 1,3-dipolar azomethine ylide cycloaddition reaction[51-58] is one of the methods used to construct nicotine analogues (C-2 heteroarylated pyrrolidine skeletons) with high stereoselectivity.

Various conformationally locked nicotine analogues and annulated nicotine analogues have been prepared *via* the intramolecular cycloaddition and annulation reactions. However, a literature survey revealed[51-58] that there exist only limited reports dealing on the synthesis of nicotine derivatives *via* the intermolecular cycloaddition of azomethine ylides with electron-deficient olefins as dipolarophiles. Considering the importance of nicotine and nicotine analogues as nAChR modulators[28-33] and drug molecules and insecticides; as a part of the objective of the thesis it was envisaged to further investigate the 1,3-dipolar azomethine ylide cycloaddition reaction with readily available symmetrical dipolarophiles such as, maleimides to construct a new class of nicotine analogues (C-2 heteroarylated pyrrolidine skeletons) appended with succinamide unit. It is worth to mention that maleimide derivatives were found to exhibit a range of biological activities, such as antifungal, cytotoxic and evaluation as 5-HT_6 receptor.[34]

Hence, it was envisaged that the preparation of nicotine analogues (C-2 heteroarylated pyrrolidine skeletons) appended with succinamide unit will be helpful to enrich the library of bio-active nicotine analogues. Accordingly, a part of this thesis report the synthesis of various nicotine derivatives having contiguous stereocenters *via* the intermolecular 1,3-dipolar cycloaddition of azomethine ylides derived from the decarboxylative/condensation reactions of nicotinaldehyde and α-amino acids with symmetrical dipolarophiles, e.g. maleimides, dialkyl fumarates, dialkyl maleates and fumaronitrile (Scheme 25).

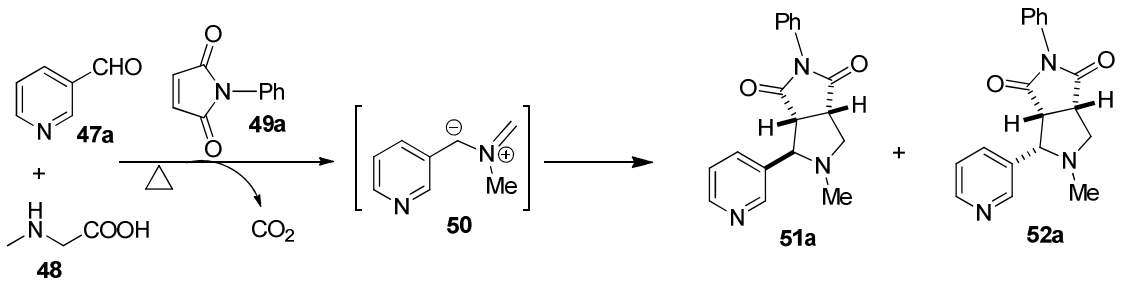
To start with the synthesis of various nicotine derivatives appended with succinamide moiety and having contiguous stereocenters. Initially, we carried out the intermolecular 1,3-dipolar cycloaddition of azomethine ylides derived from the decarboxylative/condensation reaction of nicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a**under various reaction conditions to get the cycloadducts **51a** and **52a** in good yields(Table 2).



Scheme 25. Synthesis of new class of nicotine analogues.

The one pot reaction ofnicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in 1,4-dioxane at 100 °C for 3 h gave the nicotine analogues **51a** and **52a** having three stereocentersin 57%yield (dr = 65:35, Table 2, entry 1). The reaction of nicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in 1,4-dioxane at 100 °C for 6 h or 12 h afforded the nicotine analogues **51a** and **52a** in very good yields (86%, dr = 65:35, Table 2, entries 2 and 3). Further, the multicomponent reaction ofnicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in 1,4-dioxane at 80 °C or 60 °C for 6 h, which furnished the nicotine analogues **51a** and **52a** in30%(dr = 65:35) and**<**10%yields, respectively (Table 2, entries 4 and 5). These results indicated that lowering the reaction temperatures gave relatively low yields of the nicotine analogues **51a** and **52a** but the diastereoselectivity was unaffected (Table 2, entry 4). The multicomponent reaction ofnicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in acetonitrile gave the nicotine analogues **51a** and **52a** in good yields (75% yield, dr = 65:35, Table 2, entry 6).The azomethine ylide generated from nicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in a nonpolar solvent, e.g. toluene, gave the nicotine analogues **51a** and **52a** in only35% yields (dr = 66:34, Table 2, entry 7). The low yields in these reactions are perhaps due to the low solubility of the starting materials in toluene. Further, we also performed the reaction of nicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in EtOH at 78 °C and MeOH at 64 °C, which gave nicotine analogues **51a** and **52a** in 55% (dr = 60:40) and 20% (dr = 60:40) yields, respectively (Table 2, entries 8 and 9). The low yields in these cases may be due to the effect of temperature as the decarboxylative reactions of nicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** were carried out at the refluxing temperatures of the corresponding solvents, such as, EtOH and MeOH.

Table 2. Optimization reactions: Multicomponent cycloaddition reaction of **47a**and **48** with**49a**.[a]



entry	solvent	t (°C)	t (h)	yield[b] (%)	dr = **51a**:**52a**
1	1,4-dioxane (5 mL)	100	3	57	65:35
2	1,4-dioxane (5 mL)	100	6	86	65:35
3	1,4-dioxane (5 mL)	100	12	86	65:35
4	1,4-dioxane (5 mL)	80	6	30	65:35
5	1,4-dioxane (5 mL)	60	6	<10	N.D.[c]
6	MeCN (5 mL)	82	6	75	65:35
7	toluene (5 mL)	100	6	35	66:34
8	EtOH (5 mL)	78	6	55	60:40
9	MeOH (5 mL)	64	6	20	60:40

[a] All the reactions were carried out using **47a** (0.5 mmol), **48** (0.6 mmol) and **49a** (0.5 mmol). [b] Isolated yields. [c] N.D. = Not Determined.

These results are comparable with the results obtained when the reactions of nicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** were performed in 1,4-dioxane at 80 °C or 60 °C for 6 h instead of 100 °C (Table 2, entries 4 and 5). Hence, we found that the decarboxylative reaction ofnicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** in 1,4-dioxane at 100 °C for 6 h as the best reaction condition, which gave the nicotine analogues **51a**and **52a**in good yields (Table 2, entry 2). Since the core structure of nicotine analogue **51a/52a** contain three stereocenters, the one pot azomethine cycloaddition reaction ofnicotinaldehyde **47a** and sarcosine **48** with *N*-phenylmaleimide **49a** is expected to afford only two diastereomers as the stereochemistry of *N*-phenylmaleimide **49a** (dipolarophile)is*cis* andthe maximum diastereomeric ratio obtained is 65:35 (**51a**and **52a**).

Subsequently, it was envisaged to examine the substrate scope and generality of this approach comprising the synthesis of nicotine analogues having contiguous stereocenters *via* the

intermolecular 1,3-dipolar cycloaddition of azomethine ylides derived from decarboxylative/condensation reactions of nicotinaldehyde and α-amino acids with various symmetrical dipolarophiles. The intermolecular cycloaddition reactions of azomethine ylide derived from the condensation reaction of nicotinaldehyde **47a** and *N*-methyl glycine **48** with several symmetrical dipolarophiles **49b-i** were carried outin 1,4 dioxane at 100 °C, which afforded several new nicotine derivatives **51** and **52** in very good yields (Table 3). Representatively, the stereochemistry of the nicotine analogue (**51b**) was unambiguously assigned from the X-ray structure analysis (Figure 6). The compound **51b** was found to be major compound and in this compound **51b** the stereochemistry of pyridyl ring and amide carbonyls was found to be *trans*. Based on the X-ray structure of the compound **51b** (major isomer) and coupled with the similarity in ^{1}H /^{13}C NMR spectral patterns of the compounds **51a-i**, the stereochemistry of other products **51a/51c-i** (major isomers) was assigned. Subsequently, after assigning the stereochemistry of the compounds **51a-i** (major isomers), the stereochemistry of other diastereomers **52a-i** (minor isomers) was assigned based on the similarity in their ^{1}H /^{13}C NMR spectral patterns.

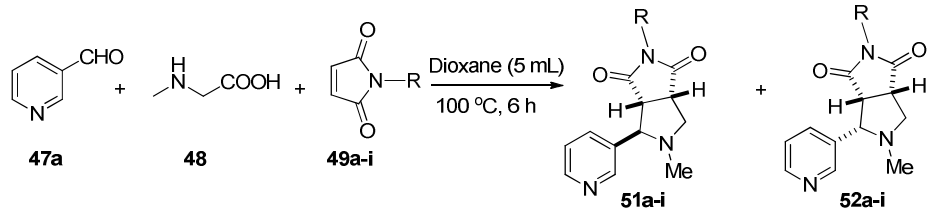
Then, we also carried out the intermolecular cycloaddition of azomethine ylide derived from the decarboxylative/condensation reaction of picolinaldehyde **47b** or isonicotinaldehyde **47c** and *N*-methyl glycine **48** with *N*-phenylmaleimide **49a** to get the pyrrolidine derivatives **53-5**6 (Scheme 26), which are structurally similar to the nicotine derivatives **51/52**. The reaction of picolinaldehyde **47b** or isonicotinaldehyde **47c** and *N*-methyl glycine with *N*-phenylmaleimide in 1,4-dioxane at 100 °C gave the corresponding functionalized pyrrolidine derivatives **53/54** and **55/56**, which are analogous to the compounds **51/52**. The compound **53** was characterized by ^{1}H and ^{13}C NMR spectroscopy/mass analysis and the stereochemistry of pyrrolidine derivative **53** (major diastereomer) was clearly established from the X-ray structure analysis (Figure 6). Notably, like in major diastereomer **51b**, the stereochemistry of pyridyl ring and amide carbonyls was found to be *trans* in the major diastereomer **53**. After assigning the stereochemistry of the compound **53**, the stereochemistry of minor diastereomer **54** was assigned. The compounds **55/56** were found to have same $R_f$values and hence, our trials to separate the compounds **55/56** by the column chromatographic purification were failed and the compounds **55/56** wereisolated as a mixture of isomers.

Further, we carried out the cycloadditions of azomethine ylide with diethyl fumarate **57a** or dimethyl fumarate **57b** in 1,4-dioxane at 100 °C to synthesize the functionalized nicotine derivatives having three contiguous stereocenters in the pyrrolidine ring. The intermolecular cycloaddition reaction of the corresponding azomethine ylide generated from nicotinaldehyde **47a** with diethyl fumarate **57a** or dimethyl fumarate **57b** gave the corresponding nicotine analogues **58a,b** and **59a,b** in good yields (Scheme 27). The nicotine analogues **58a,b** and **59a,b** were characterized by $^{1}H/^{13}C$ NMR spectroscopy/mass analysis.[60]

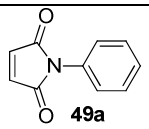
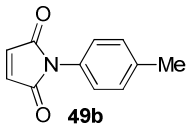
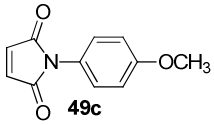
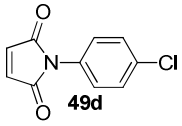
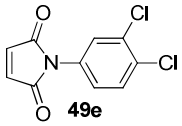
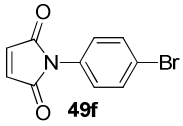
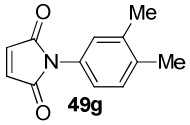
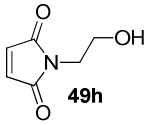
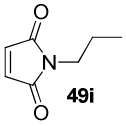
Afterwards, we carried out the reactions of picolinaldehyde (**47b**) or isonicotinaldehyde (**47c**) and *N*-methyl glycine with diethyl fumarate (**57a**) and dimethyl fumarate (**57b**) in 1,4-dioxane at 100 °C, which gave the corresponding functionalized 2-pyridylpyrrolidine derivatives **60-65** analogous to the compounds **58/59** (Scheme 28). The compounds **60-62** were isolated in pure form, however, the compounds **64/65** could not be separated by column chromatographic purification and isolated as a mixture isomers. Then, we performed the one pot cycloaddition reaction of the azomethine ylide generated from nicotinaldehyde **47a** and sarcosine **48** with diethyl maleate **57c**, which furnished the nicotine derivatives **58a** (37%) and **59a** (46%) instead of the expected nicotine analogues **66a** and **67a** (Scheme 29). The $^{1}H/^{13}C$ NMR spectra of the nicotine derivatives **58a** and **59a** obtained in this reaction were same as the products obtained in the azomethine ylide cycloaddition reaction of azomethine ylide generated from nicotinaldehyde **47a** and sarcosine **48** with diethyl fumarate **57a** (Scheme 27).

Similarly, we also observed the same reactivity pattern as the multicomponent azomethine ylide cycloaddition reaction of the azomethine ylide generated from nicotinaldehyde **47a** and sarcosine **48** with dimethyl maleate **57d** gave the corresponding products **58b** and **59b** (Scheme 27) instead of the compounds **66b/67b** (Scheme 29). This is because, at higher temperatures, the dipolarophiles **57c,d** (*cis* geometry) underwent *cis* to *trans* isomerization, generating the corresponding dipolarophiles **57a,b** (*trans* geometry), which further reacted with the azomethine ylide to give the respective products **58a,b** and **59a,b** (Scheme 29).

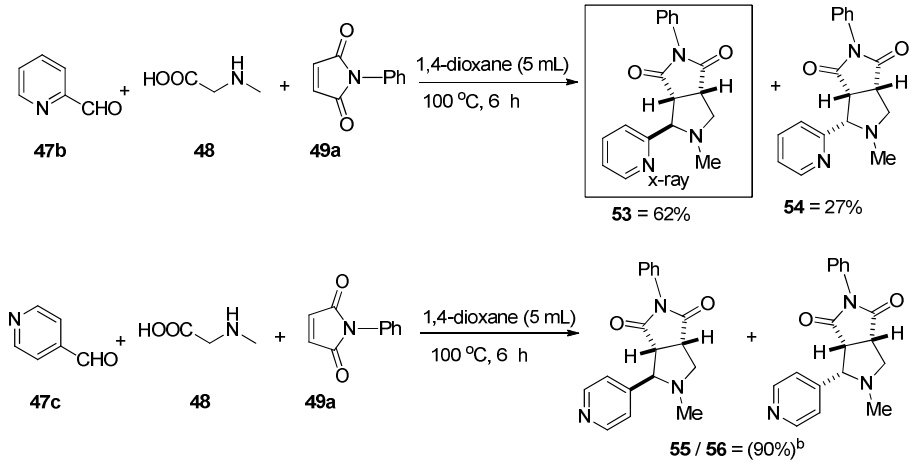
Table 3: Synthesis of nicotine analogues **51/52**[a]



47a **48** **49a-i** **51a-i** **52a-i**

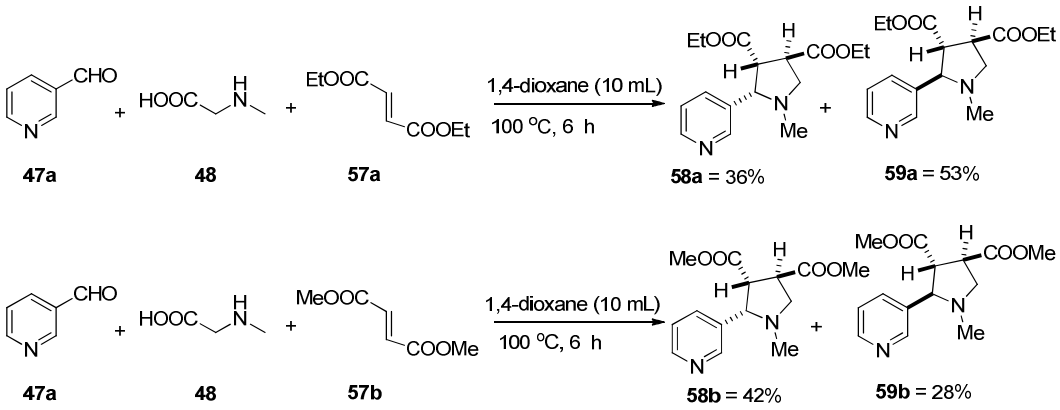
entry	dipolarophile (**49a-i**)	**51**:**52** yield (%)	dr = **51**:**52**
1	 **49a**	**51a/52a** = 93	65:35
2	 **49b**	**51b/52b** = 78 **51b** (x-ray)	60:40
3	 **49c**	**51c/52c** = 85[b]	56:44
4	 **49d**	**51d/52d** = 85[b]	55:45
5	 **49e**	**51e/52e** = 86[b]	60:40
6	 **49f**	**51f/52f** = 87[b]	56:44
7	 **49g**	**51g/52g** = 89	57:43
8	 **49h**	**51h/52h** = 83	52:48
9[c]	 **49i**	**51i/52i** = 87	54:46

[a] All the reactions were doneby using **47a** (0.75 mmol), **48** (1 mmol) and **49** (0.5 mmol). Isolated yields are given. [b] The reactions were carried out for 12 h. [c] The reaction was carried out using **47a** (0.5 mmol), **48** (0.6 mmol) and **49** (0.5 mmol).



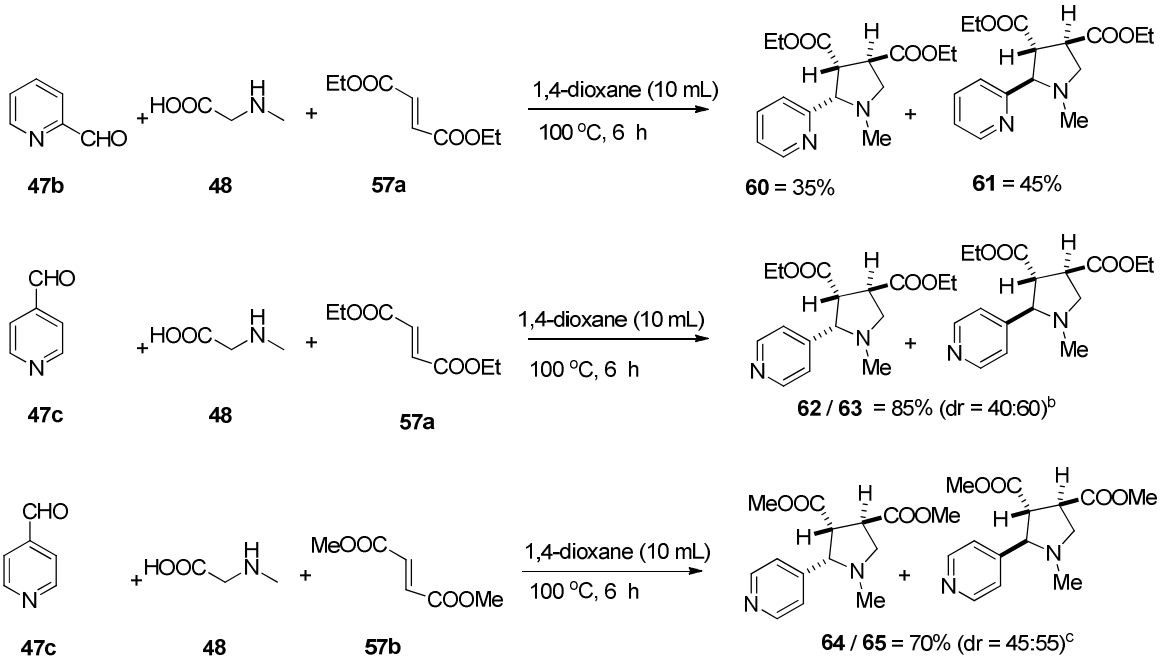
[a] The reactions were carried out using **47** (0.75 mmol), **48** (1 mmol) and **49a** (0.5 mmol). Isolated yields are given. [b] The compounds **55/56** could not be separated and were isolated as a mixture of isomers.

Scheme 26. Synthesis of pyrrolidine derivatives **53-56** analogous to nicotine derivatives.



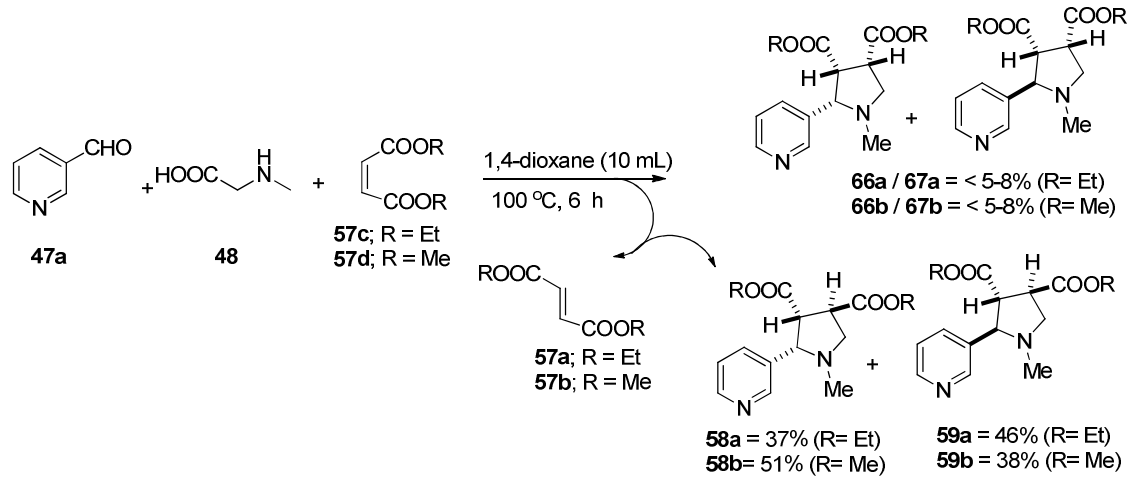
[a]All the reactions were doneby using **47a** (1 mmol), **48** (1.2 mmol) and **57a-b** (1 mmol). Isolated yields are given.

Scheme 27. Synthesis of nicotine analogues **58a,b** and **59a,b**[a].



[a]The reactions were carried out using **47** (1 mmol), **48** (1.2 mmol) as well as**57** (1 mmol). Isolated yields are given. [b] In this case, the compound **62** was isolated in pure form. However, the compound **63** could not be separated from the other isomer **62**. [c] Compounds **64/65** could not be separated and isolated as a mixture of isomers.

Scheme 28. Synthesis of pyrrolidine derivatives **60-65**.[a]

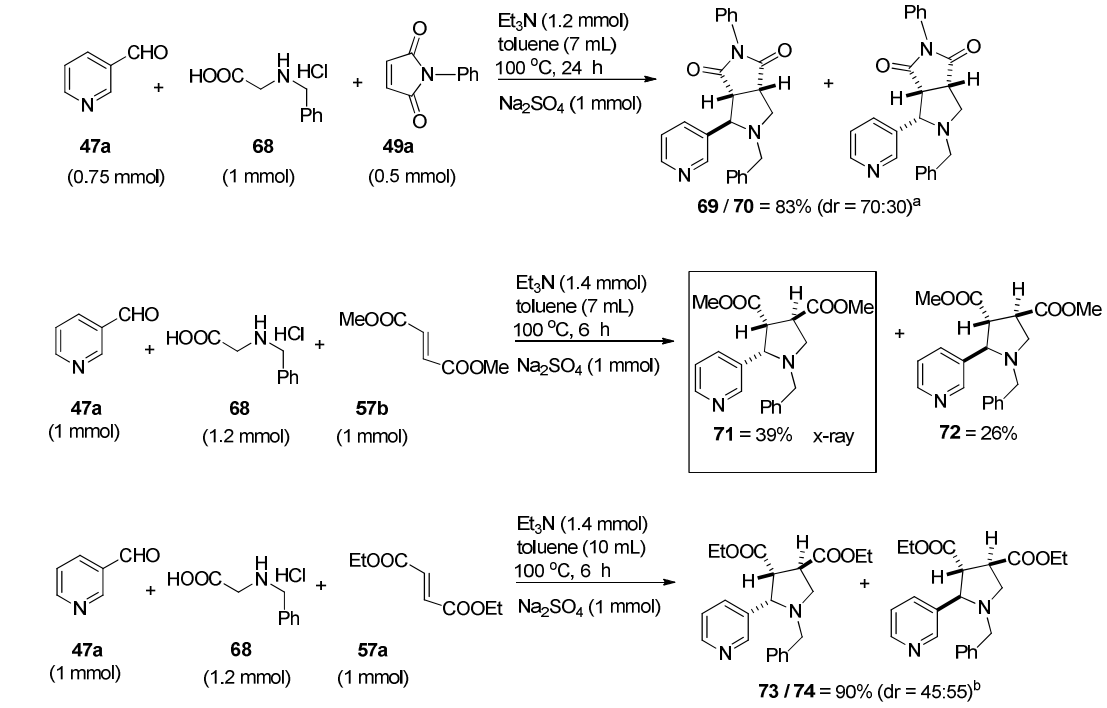


[a] All the reactions were carried out using **47a** (1 mmol), **48** (1.2 mmol) and **57** (1 mmol). Isolated yields are given.

Scheme 29. Azomethine ylide cycloaddition of nicotinaldehyde with dialkyl maleates **57c,d**.[a]

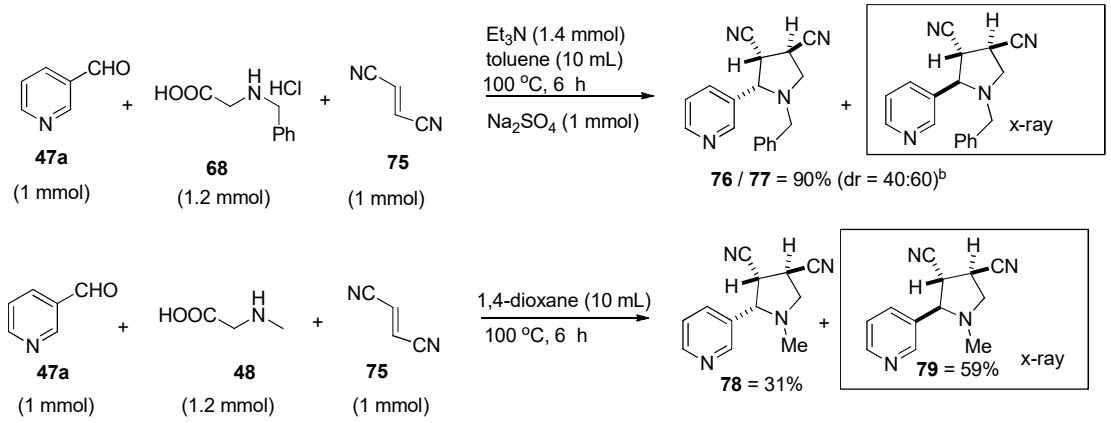
Furthermore, the cycloaddition reaction of azomethine ylide derived from the condensation of nicotinaldehyde **47a** and *N*-benzyl glycine hydrochloride **68** with *N*-phenylmaleimide **49a** and dialkyl fumarates **57a,b** was investigated (Scheme 30). The multicomponent azomethine ylide cycloaddition reaction of azomethine ylide with dipolarophile *N*-phenylmaleimide **49a** in toluene at 100 °C gave the new nicotine analogues **69/70** in 83% yield. Similarly, the multicomponent cycloaddition reaction of azomethine ylide generated from **47a** and *N*-benzyl glycine hydrochloride with dialkyl fumarates **57a,b** furnished the corresponding nicotine analogues **71-74** in very good yields (Scheme 30). The compounds **71** and **72** were isolated in pure form, however, the nicotine analogues **70**, **73** and **74** could not be separated from their corresponding isomers by column chromatographic purification and isolated as a mixture isomers (Scheme 30). The nicotine derivative **71** was characterized by $^{1}H/^{13}C$ NMR spectroscopy/mass analysis and the stereochemistry of nicotine analogue **71** was unequivocally assigned from the X-ray structure analysis (Figure 7). After assigning the stereochemistry of the nicotine analogue **71**, the stereochemistry of its corresponding diastereomer **72** was assigned.

Finally, we carried out the one pot cycloaddition reaction of azomethine ylide generated from nicotinaldehyde **47a** and *N*-benzyl glycine hydrochloride **68** with fumaronitrile **75** in toluene at 100 °C, which gave the new class of nicotine analogues **76/77** possessing cyano groups in the pyrrolidine ringin 90% yield (Scheme 31). Similarly, the nicotine analogues **78** (31% yield) and **79** (59% yield) possessing cyano groups in the pyrrolidine ringwere obtained from the multicomponent azomethine ylide cycloaddition reaction of azomethine ylide generated from nicotinaldehyde **47a** and sarcosine **48** with fumaronitrile **75** (Scheme 31). The nicotine derivatives **76, 78** and **79** were characterized by $^{1}H/^{13}C$ NMR spectroscopy/mas analysis and the stereochemistry of nicotine analogues **77** and **79** was unequivocally assigned from the X-ray structure analysis (Figure 7). After assigning the stereochemistry of nicotine analogues **77/79**, the stereochemistry of nicotine analogue **78** was assigned.



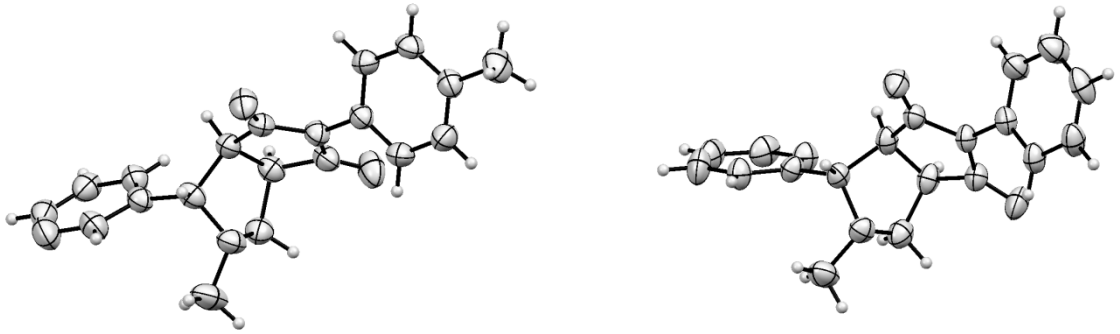
[a] In this case, the compound **69** was isolated in pure form. However, the compound **70** could not be separated from the other isomer **69**. [b] Compounds **73/74** could not be separated and isolated as a mixture of isomers.

Scheme 30. Generation ofazomethine ylide from nicotinaldehyde and *N*-benzyl glycine and construction of nicotine analogues.



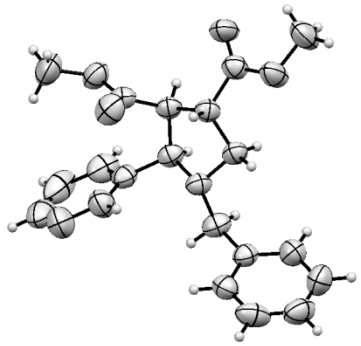
[a]Isolated yields are given.[b] In this case, the compound **77** was isolated in pure form. However, the compound **76** could not be separated from the other isomer **77**.

Scheme 31. Construction of nicotine analogues **76-79**.[a]

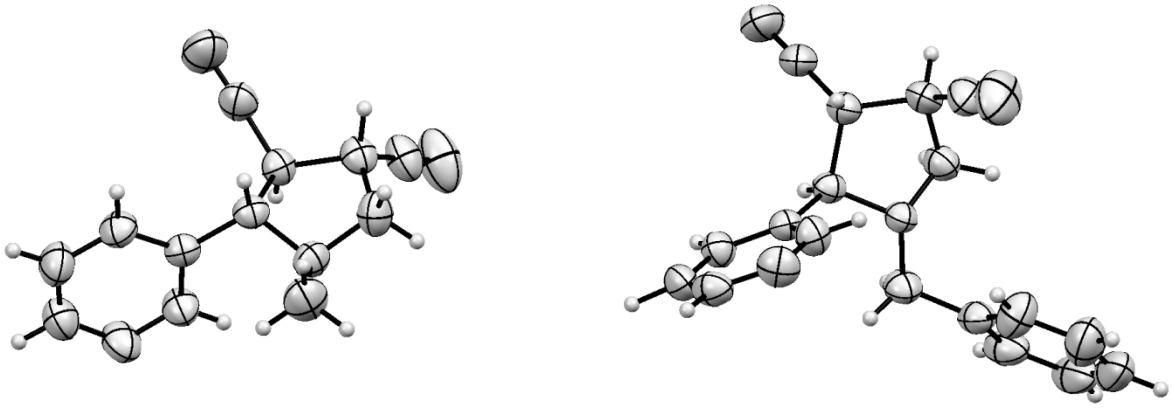


51b **53**

Figure 6. X-ray structure (ORTEP) of nicotine derivatives **51b** and **53**.



71



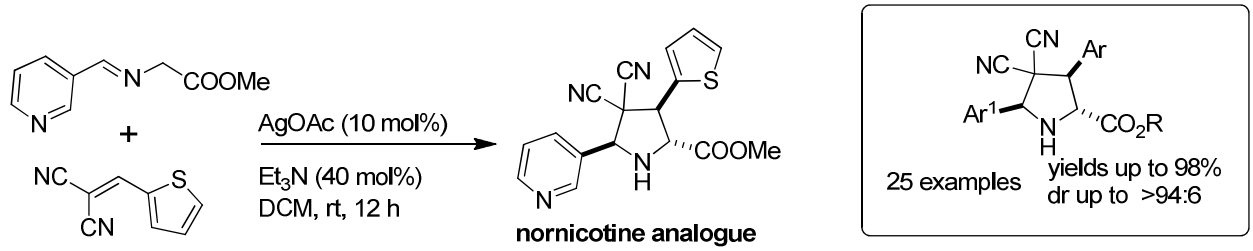
77 **79**

Figure 7. X-ray structures (ORTEP diagrams) of the compounds **71**, **77** and **79**.

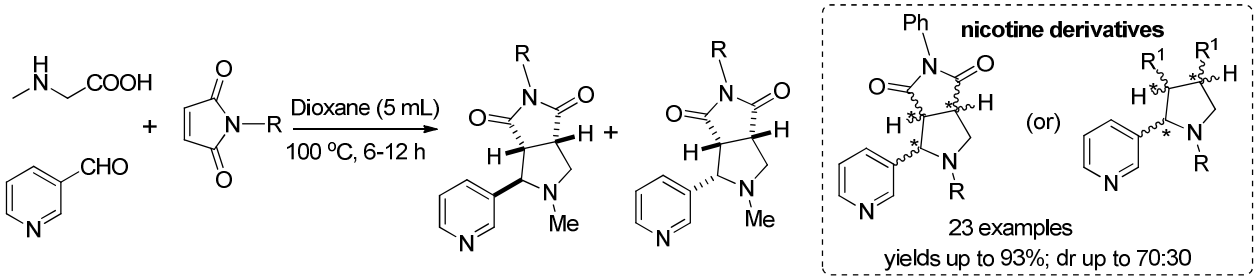
Conclusions.

In summary, the Chapter 1a revealed the regio- and diastereoselective cycloaddition of azomethine ylides with arylidene / heteroarylidenemalononitriles for the construction of a new set of pyrrolidines-appended with different aryl- / heteroaryl moieties. Diastereoselective synthesis of several C-3,C-5-aryl- / heteroaryl substituted 4,4-dicyano-pyrrolidine-2-carboxylate and nornicotine scaffolds (proline derivatives) was accomplished. Given that in the literature, several substituted pyrrolidine derivatives are bio-active molecules and in particular, pyrrolidine carboxylic acid (proline) frameworks having aryl or heteroaryl groups were reported to be promising biological activities; this work contributed for enriching the library of pyrrolidine carboxylic acid derivatives.

Diastereo- and regioselective synthesis of C3,C5 arylated 4,4-dicyanopyrrolidine-2-carboxylates



Further, the Chapter 1b revealed the diastereoselective construction of several new nicotine analogues (C-2 heteroarylated pyrrolidine skeletons) *via* the multicomponent1,3-dipolar cycloaddition of azomethine ylides derived from the decarboxylative reactions of nicotinaldehyde and α-amino acids with symmetrical dipolarophiles. Given the importance of nicotine and nicotine analogues as nAChR modulators, drug molecules and insecticides; this work contributed in enriching the library of nicotine analogues.



All the cycloaddition reactions were stereoselective and 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 stereochemistry of representative products was 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. The synthesized molecules will be screened for their biological activities in collaboration with a medicinal chemistry lab and further work is in progress in this direction as well as synthesizing the optically pure C-3,C-5-aryl- / heteroaryl substituted 4,4-dicyano-pyrrolidine-2-carboxylate, nornicotine and nicotine scaffolds.

Experimental section.

General: Melting points are uncorrected. IR spectra were recorded as neat or thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with 400 and 100 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 conducted in anhydrous solvent under nitrogen atmosphere where required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask by using a syringe. Thin layer chromatography (TLC) was performed on silica plates or neutral Al_2O_3 and components were visualized by observation under iodine. Isolated yields of all the products are reported (yields were not optimized). Ratios of diastereomers were determined from the ^{1}H (or) ^{13}C spectra of crude reaction mixture. The stereochemistry of the products were assigned based on the X-ray structure analysis of representative compounds. Good quality single crystals were grown by using a combination of dichloromethane or hexanes or methanol or acetone by slow solvent evaporation technique at 25 °C and the single crystal X-ray diffraction data for all the compounds was collected using four circle CCD diffractometer (monochromatic Mo Kα radiation). Data collection and unit cell refinement for the data sets were done using APEX-II suit. The crystal structures were solved using Olex2 or WinGx packages using SHELXS97, and the structures were refined using SHELXL97. All the hydrogen atoms have been fixed at their geometrically ideal positions and refined using the riding model available within SHELXS97. All figures have been generated using Mercury.

Procedure A for catalytic 1, 3-dipolar cycloaddition of azomethine ylides with benzylidenemalononitrile: Under a nitrogen atmosphere AgOAc (10 mol%) in anhydrous DCM (1 mL) was stirred for 30 min; to this mixture were sequentially added a solution of *N*-benzylideneiminoglycinates (0.5 mmol) and benzylidenemalononitrile (0.5 mmol) in 4 mL DCM and Et_3N (40 mol%) and stirred for 12 h in the absence of light at r.t. The reaction mixture was filtered through a celite pad. The filtrate was directly evaporated and the residue was purified by column chromatography.

Procedure B for the preparation of 42a and **42b**:Cycloadducts **38a** or **38b** (1 mmol) in DCM (5 mL)was stirred for 5 min, and then triethyl amine (2 mmol) was added followed by acryloyl chloride (2 mmol) drop wise with cooling. Further, the reaction mixture was stirred for overnight under nitrogen atmosphere. After this period, the reaction mixture was quenched with water and extracted using DCM, combined the organic layers evaporated and the resulting crude mixture was subjected to column chromatography which gave the compounds **42a** and **42b.**

Procedure C for the preparation of 45a,b or **46a,b**:A mixture of pyrrolidine derivative **42a** or **42b** (0.14 mmol), glycine **44a** (0.28 mmol) or **44b** *N*-benzyl glycine hydrochloride (0.21 mmol) and paraformaldehyde **43** (0.70 mmol) in toluene (1 mL) was heated at 110 ^{o}C for 12 h under nitrogen atmosphere. After this period, the reaction mixture was evaporated and the resulting crude reaction mixture was purified through chromatography which afforded the corresponding products **45a,b** or **46a,b.**

Procedure D for the preparation of nicotine analogues 51a-i and 52a-i: A dry flask containing nicotinaldehyde **47a**, sarcosine **48** and *N*–phenyl malemide derivatives **49a-i** in 1,4-dioxane (5 mL) was heated to the appropriate temperature and time as shown in the respective Tables/Schemes. Then the reaction mixture was cooled to rt and subjected to the rotary evaporation, which afforded a crude mixture. Purification of the curde reaction mixture through alumina column choromatography (EtOAc/Hexane = 75:25) afforded the nicotine derivatives **51a-i** and **52a-i** (see the respective Tables/Schemes for appropriate or exact amount of solvent/reagents).

Procedure E for the synthesis of nicotine analogues 53-56: A dry flask containing picolinaldehyde or isonicotinaldehyde **47b/c** (0.75 mmol), sarcosine **48** (1 mmol) and *N*-phenyl

malemide **49a** (0.5 mmol) in 1,4-dioxane (5 mL) was heated to the appropriate temperature and time as shown in the respective Tables/Schemes. Then the reaction mixture was cooled to rt and subjected to the rotary evaporation, which afforded a crude mixture. Purification of the curde reaction mixture through alumina column choromatography (EtOAc/Hexane = 75:25) afforded the nicotine derivatives **53**-**56** (see the coressponding Tables/Schemes for appropriate or exact amount of solvent/reagents).

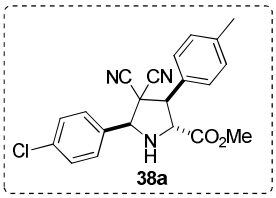
Procedure F for the synthesis of nicotine derivatives 58/59 and 78/79: A dry flask containing nicotinaldehyde **47a** (1 mmol), sarcosine **48** (1.2 mmol) and diethyl fumarate **57a** or dimethyl fumarate **57b** or fumaronitrile **75**(1 mmol) in 1,4-dioxane (10 mL) was heated to the appropriate temperature and time as shown in the respective Tables/Schemes. Then the reaction mixture was cooled to rt and subjected to rotary evaporation which afforded a crude mixture. Purification of the curde reaction mixture through silica column choromatography (EtOAc) afforded nicotine derivatives **58/59** and **78/79** (see the coressponding Tables/Schemes for appropriate or exact amount of solvent/reagents).

Procedure G for the synthesis of pyrrolidines 60-65: A dry flask containing picolinaldehyde **47b** or isonicotinaldehyde **47c** (1 mmol), sarcosine **48** (1.2 mmol) and diethyl fumarate **57a** or dimethyl fumarate **57b**(1 mmol) in 1,4-dioxane (10 mL) was heated to the appropriate temperature and time as shown in the respective Tables/Schemes. Then the reaction mixture was cooled to rt and subjected to the rotary evaporation, which afforded a crude mixture. Purification of the curde reaction mixture through silica column choromatography (EtOAc/Hexane = 75:25) afforded pyrrolidines **60-65**

Procedure H for the synthesis of nicotine derivatives 69-77: A dry flask containing *N*-benzyl glycine hydrochloride **68**, triethyl amine and Na_2SO_4 in toluene (7-10 mL) was stirred for 1 h, then to the falsk add nicotinaldehyde **47a** and *N*-phenyl malemide **49a** or diethyl fumarate **57a** or dimethyl fumarate **57b** or fumaronitrile **75** was heated to an appropriate temperature and time as shown in the respective Tables/Schemes. Then the reaction mixture was cooled to rt and subjected to the rotary evaporation, which afforded a crude mixture. Purification of the curde reaction mixture through silica column choromatography (EtOAc/Hexane = 70:30) afforded

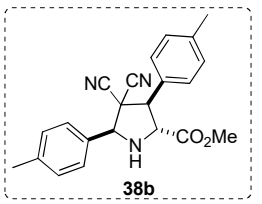
nicotine derivatives **69-77** (see coressponding Tables/Schemes for appropriate or exact amount of solvent/reagents).

(2R*,3R*,5S*)-Methyl 5-(4-chlorophenyl)-4,4-dicyano-3-(p-tolyl)pyrrolidine-2-carboxylate (**38a**): Following the general procedure described above **38a** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (182 mg, 96%), mp: 156-158 ^{o}C; FT-IR (KBr): 3341, 2954, 1737 and 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, 2H, J = 8.1 Hz), 7.46 (d, 4H, J = 8.1 Hz), 7.30 (d, 2H, J = 8.1 Hz), 4.94 (s, 1H), 4.51 (d, 1H, J = 8.1 Hz), 4.14 (d, 1H, J = 8.1 Hz), 3.75 (s, 3H), 2.99 (br. s,1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 139.8, 136.0, 132.3, 130.0, 129.4, 129.2, 128.7, 128.2, 113.5, 111.4, 69.7, 60.9, 58.0, 53.2, 50.8, 21.3; HRMS (ESI) calcd for $C_{21}H_{19}ClN_3O_2$ $[M+H]^+$ 380.1166 found $[M+H]^+$ 380.1171.



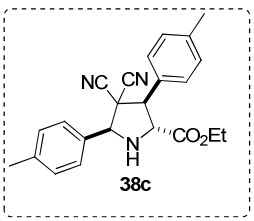
38a

(2R*,3R*,5S*)-Methyl 4,4-dicyano-3,5-di-p-tolylpyrrolidine-2-carboxylate (**38b**): Following the general procedure described above **38b** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (163 mg, 91%), mp:170-172 ^{o}C; FT-IR (KBr): 3343, 2902, 1737 and 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, 2H, J= 8.1 Hz),7.46 (d, 2H, J= 8.1 Hz), 7.31-7.27 (m, 4H), 4.92 (s, 1H), 4.51 (d, 1H, J= 8.1 Hz), 4.15 (d, 1H, J= 8.1 Hz), 3.76 (s, 3H), 2.97 (br. s, 1H), 2.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 140.1, 139.6, 130.6, 130.0, 129.7, 129.6, 128.3. 127.2, 113.8, 111.7, 70.4, 61.0, 58.1, 53.1, 50.9, 21.3, 21.2; HRMS (ESI) calcd for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1712 found $[M+H]^+$ 360.1716.



38b

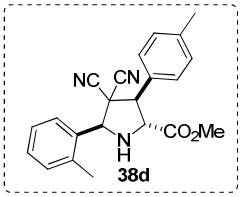
(2R*,3R*,5S*)-Ethyl 4,4-dicyano-3,5-di-p-tolylpyrrolidine-2-carboxylate (**38c**): Following the general procedure described above **38c** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (177 mg, 95%), mp: 99-101 ^{o}C; FT-IR (KBr): 3345, 2983, 1731 and 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.1 Hz), 7.30-7.27 (m, 4H), 4.93 (s, 1H), 4.47 (d, 1H, J = 8.1 Hz), 4.26-4.16 (m, 2H), 4.13 (d, 1H, J = 8.1 Hz), 2.96 (br. s, 1H), 2.41 (s, 6H), 1.21 (t, 3H, J = 7.1 Hz); ^{13}C NMR



38c

($CDCl_3$, 100 MHz): δ 172.8, 140.0, 139.5, 130.7, 129.9, 129.8, 129.6, 128.3, 127.2, 113.9, 111.7, 70.4, 62.2, 61.2, 58.2, 50.9, 21.3, 21.3, 14.1; HRMS (ESI) calcd for $C_{23}H_{24}N_3O_2$ $[M+H]^+$ 374.1869 found $[M+H]^+$ 374.1873.

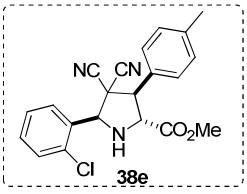
(2R*,3R*,5S*)-Methyl 4,4-dicyano-5-(o-tolyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**38d**):



38d

Following the general procedure described above **38d** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (179 mg, 90%), mp:146-148 ^oC; FT-IR (KBr): 3339, 2954, 1736 and 1221 cm^-1; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.97 (m, 1H), 7.48 (d, 2H, J = 8.1 Hz), 7.35-7.27 (m, 5H), 5.33 (s, 1H), 4.51 (d, 1H, J = 7.9 Hz), 4.20 (d, 1H, J = 7.9 Hz), 3.77 (s, 3H), 2.86 (br. s, 1H), 2.58 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 139.7, 136.9, 131.7, 131.1, 130.0, 129.7, 129.6, 128.4, 127.5, 126.5, 114.2, 111.8, 65.5, 60.8, 58.7, 53.1, 49.5, 21.3, 19.8; HRMS (ESI) calcd for $C_{22}H_{22}N_3O_2$ $[M+H]^+$ 360.1712 found $[M+H]^+$ 360.1711.

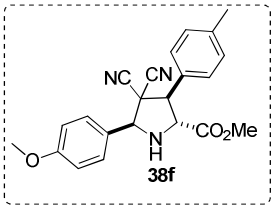
(2R*,3R*,5R*)-Methyl 5-(2-chlorophenyl)-4,4-dicyano-3-(p-tolyl)pyrrolidine-2-carboxylate



38e

(**38e**): Following the general procedure described above **38e** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (174 mg, 92%), mp:153-155 ^oC; FT-IR (KBr): 3346, 2954, 1737 and 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.05 (dd, 1H, J_1 = 7.9, J_2 = 2.0 Hz), 7.49-7.46 (m, 3H), 7.44-7.36 (m, 2H), 7.30 (d, 2H, J = 7.9 Hz), 5.61 (s, 1H), 4.51 (d, 1H, J = 8.1 Hz), 4.20 (d, 1H, J = 8.1 Hz), 3.77 (s, 3H), 2.93 (br. s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 173.1, 139.7, 134.2, 131.6, 130.9, 130.0, 130.0, 129.5, 129.5, 128.4, 127.3, 113.4, 111.6, 64.9, 60.7, 58.7, 53.2, 49.2, 21.3; HRMS (ESI) calcd for $C_{21}H_{19}ClN_3O_2$ $[M+H]^+$ 380.1166 found $[M+H]^+$ 380.1167.

(2R*,3R*,5S*)-Methyl 4,4-dicyano-5-(4-methoxyphenyl)-3-(p-tolyl)pyrrolidine-2-carboxylate

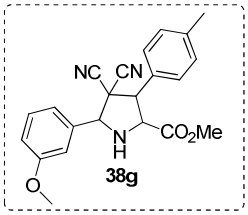


38f

(**38f**): Following the general procedure described above **38f** was obtained after purification by silica column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (152 mg, 81%), mp:140-142 ^oC; FT-IR (KBr): 3345, 2955, 1737 and 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 2H, J = 8.7 Hz), 7.46 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 6.99 (d, 2H, J = 8.7

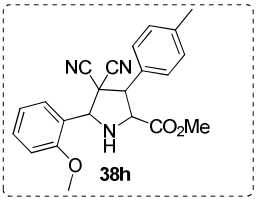
Hz), 4.90 (d, 1H, *J* = 3.8 Hz), 4.50 (d, 1H, *J* = 8.0 Hz), 4.14 (d, 1H, *J* = 8.0 Hz), 3.85 (s, 3H), 3.75 (s, 3H), 2.95 (br. s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 160.9, 139.6, 130.0, 130.0, 128.6, 128.3, 125.4, 114.3, 113.8, 111.7, 70.2, 60.9, 57.9, 55.4, 53.1, 51.0, 21.3; HRMS (ESI) calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$ 376.1661 found $[M+H]^+$ 376.1668.

Methyl 4,4-dicyano-5-(3-methoxyphenyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**38g**): Following



the general procedure described above **38g** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless semi solid (169 mg, 90%), FT-IR (DCM): 3343, 2955, 1738 and 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-6.99 (m, 8H), 4.95 (s, 1H), 4.53 (d, 1H, *J*= 8.1 Hz), 4.18 (d, 1H, *J*= 8.1 Hz), 3.86 (s, 3H), 3.74 (s, 3H), 2.41 (s, 3H). (The ^{1}H NMR given here for major isomer); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 171.4, 160.0, 159.9, 139.7, 139.6, 135.3, 130.9, 130.1, 130.0, 129.7, 129.6, 128.6, 128.3, 119.6, 119.4, 115.9, 115.7, 113.8, 113.8, 112.8, 112.5, 111.7, 70.5, 70.2, 60.9, 60.5, 58.1, 57.7, 55.4, 55.3, 53.1, 53.0, 50.8, 48.9, 21.3, 21.1 (The ^{13}C NMR given here for mixture of isomers); HRMS (ESI) calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$ 376.1661 found $[M+H]^+$ 376.3090.

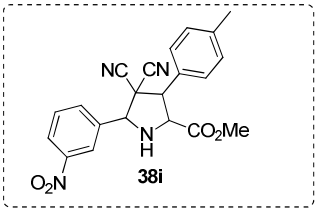
Methyl 4,4-dicyano-5-(2-methoxyphenyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**38h**): Following



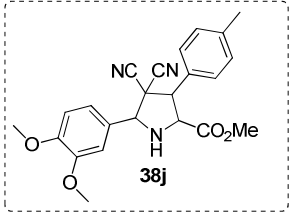
the general procedure described above **38h** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (146 mg, 78%), mp:138-140 ^{o}C; FT-IR (KBr): 3340, 2955, 1737 and 1247 cm^{-1}; ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.85 (dd, 1H, J_1 = 7.7, J_2 = 1.4 Hz), 7.47-6.95 (m, 7H), 5.46 (s, 1H), 4.46 (d, 1H, *J* = 8.0 Hz), 4.18 (d, 1H, *J* = 8.0 Hz), 3.90 (s, 3H), 3.75 (s, 3H), 2.40 (s, 3H). (The ^{1}H NMR given here for major isomer); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 171.0, 157.3, 157.0, 139.5, 139.4, 130.8, 130.6, 130.0, 129.9, 128.8, 128.6, 128.4, 128.0, 127.8, 123.9, 122.6, 121.0, 120.8, 114.5, 114.2, 114.0, 112.2, 110.8, 110.5, 67.1, 63.7, 63.1, 61.3, 59.1, 58.4, 55.1, 55.1, 53.0, 52.9, 49.4, 48.8, 21.3 (The ^{13}C NMR given here for mixture of isomers); HRMS (ESI) calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$ 376.1661 found $[M+H]^+$ 376.1667.

Methyl 4,4-dicyano-5-(3-nitrophenyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**38i**): Following the general procedure described above **38i** (mixture of isomers) was obtained after purification by

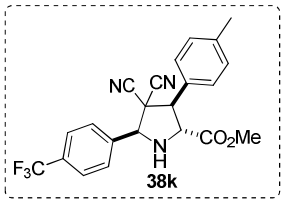
silica column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (191 mg, 98%), mp: compound decomposes after 128°C; FT-IR (KBr): 3340, 2956, 1738 and 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.63-8.62 (m, 1H), 8.33 (d, 1H, *J*= 7.9 Hz), 8.03 (d, 1H, *J*= 7.9 Hz), 7.68 (t, 1H, *J*= 8.1 Hz), 7.47 (d, 2H, *J*= 8.1 Hz), 7.34-7.28 (m, 2H), 5.09 (s, 1H), 4.57 (d, 1H, *J*= 8.2 Hz), 4.16 (d, 1H, *J*= 8.2 Hz), 3.76 (s, 3H), 3.13 (br. s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 148.6, 140.0, 136.4, 133.5, 130.2, 130.1, 129.1, 128.5, 128.2, 125.0, 122.5, 113.2, 111.1, 69.2, 60.9, 57.9, 53.3, 50.6, 21.3 (The ^1H and ^{13}C NMR given here for major isomer); HRMS (ESI) calcd for $C_{21}H_{19}N_4O_4$ $[M+H]^+$ 391.1406 found $[M+H]^+$ 391.1416.



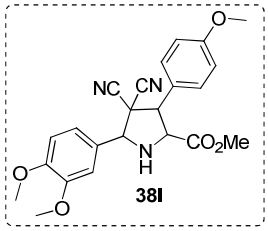
Methyl 4,4-dicyano-5-(3,4-dimethoxyphenyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**38j**): Following the general procedure described above **38j** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane =50:50); as a colorless semi solid (182 mg, 90%), FT-IR (DCM): 3345, 2960, 1736 and 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, 2H, *J*= 8.2 Hz), 7.30-7.27 (m, 3H), 7.20 (dd, 1H, J_1 = 8.4, J_2 = 2.1 Hz), 6.93 (d, 1H, *J*= 8.4 Hz), 4.90 (s, 1H), 4.50 (d, 1H, *J*= 8.4 Hz), 4.13 (d, 1H, *J*= 8.4 Hz), 3.94 (s, 3H), 3.91 (s, 3H), 3.74 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 150.3, 149.2, 139.6, 129.9, 129.7, 128.3, 125.9, 120.0, 113.9, 111.9, 111.1, 109.9, 70.4, 60.8, 57.9, 56.0, 53.1,50.9, 21.2 (The^1H and ^{13}C NMR given here for major isomer); HRMS (ESI) calcd for $C_{23}H_{24}N_3O_4$ $[M+H]^+$ 406.1767 found $[M+H]^+$ 406.1772.



(***2R*,3R*,5S*)-Methyl 4,4-dicyano-3-(p-tolyl)-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate*** (**38k**): Following the general procedure described above **38k** was obtained after purification by silica column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (196 mg, 95%), mp:144-146 °C; FT-IR (KBr): 3346, 2958, 1738 and 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, 2H, *J* = 8.2 Hz), 7.75 (d, 2H, *J* = 8.2 Hz), 7.46 (d, 2H, *J* = 8.1 Hz), 7.32-7.28 (m, 2H), 5.02 (s, 1H), 4.54 (d, 1H, *J* = 8.2 Hz), 4.15 (d, 1H, *J* = 8.2 Hz), 3.77 (s, 3H), 3.02 (br. s, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 139.9, 137.8, 132.2 (d, J_{C-F} = 33 Hz), 130.1, 129.2, 128.2, 127.9, 126.0 (q, 2H, *J* = 14.6 Hz), 113.4, 111.2, 69.6, 60.9, 58.1, 53.2, 50.6, 21.3; HRMS (ESI) calcd for $C_{22}H_{19}F_3N_3O_2$ $[M+H]^+$ 414.1429 found $[M+H]^+$ 414.1432.



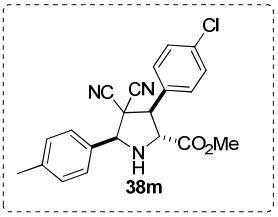
Methyl 4,4-dicyano-5-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)pyrrolidine-2-carboxylate(**38l**): Following the general procedure described above **38l** (mixture of isomers) was



38l

obtained after purification by silica column chromatography (EtOAc:Hexane = 55:45); as a colorless semi solid (162 mg, 77%), FT-IR (DCM): 3336, 2956, 1738 and 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, 2H, J = 8.7 Hz), 7.27 (d, 1H, J = 2.0 Hz), 7.20 (dd, 1H, J_1 = 8.7, J_2 = 2.0 Hz), 7.00 (d, 2H, J = 8.3 Hz), 6.93 (d, 1H, J = 8.3 Hz), 4.89 (s, 1H), 4.47 (d, 1H, J= 8.2 Hz), 4.12 (d, 1H, J= 8.2 Hz), 3.95 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.75 (s, 3H), 2.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 160.5, 150.3, 149.2, 129.9, 129.6, 125.9, 124.5, 119.9, 114.6, 113.9, 111.9, 111.1, 110.0, 70.3, 61.0, 57.7, 56.0, 55.9, 55.3, 53.1, 51.1 (The ^1H and ^{13}C NMR given here for major isomer); HRMS (ESI) calcd for $C_{23}H_{24}N_3O_5$ $[M+H]^+$ 422.1716 found $[M+H]^+$ 422.1721.

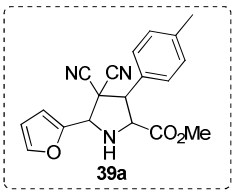
(2R*,3R*,5S*)-Methyl 3-(4-chlorophenyl)-4,4-dicyano-5-(p-tolyl)pyrrolidine-2-carboxylate (**38m**): Following the general procedure described above **38m** was



38m

obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (166 mg, 88%), mp: 148-150 ^oC; FT-IR (KBr): 3345, 2955, 1738 and 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.46 (m, 6H), 7.29-7.27 (m, 2H), 4.92 (s, 1H), 4.46 (d, 1H, J = 8.0 Hz), 4.16 (d, 1H, J = 8.0 Hz), 3.71 (s, 3H), 2.98 (br. s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9,140.2, 135.8, 131.3, 130.3, 129.8, 129.7, 129.6, 127.1, 113.5, 111.5, 70.4, 61.0, 57.6, 53.2, 50.7, 21.3; HRMS (ESI) calcd for $C_{21}H_{19}ClN_3O_2$ $[M+H]^+$ 380.1166 found $[M+H]^+$ 380.1167.

Methyl 4,4-dicyano-5-(furan-2-yl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**39a**): Following the

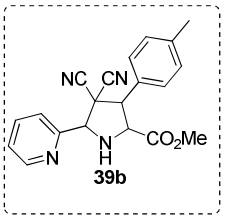


39a

general procedure described above **39a** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless semi solid (139 mg, 83%), FT-IR (DCM): 3338, 2955, 1737 and 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (dd, 1H, J_1 = 1.8, J_2 = 0.7 Hz), 7.44 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 6.70 (d, 1H, J = 3.4 Hz), 6.48-6.47 (m, 1H), 5.04 (s, 1H), 4.51 (d, 1H, J = 8.7 Hz), 4.18 (d, 1H, J = 8.7 Hz), 3.74 (s, 3H), 2.41 (s, 3H) (The ^1H NMR given here for major isomer); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 171.4, 148.1, 147.0, 144.1, 144.0, 139.8, 139.7, 130.0, 129.6, 129.2, 128.8, 128.5, 128.3, 113.3,

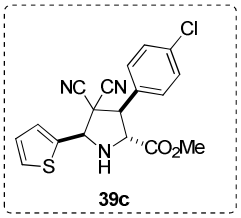
113.1, 113.0, 111.6, 111.0, 110.9, 110.5, 110.0, 65.5, 65.1, 63.3, 61.0, 58.2, 57.6, 53.2, 53.1, 49.4, 48.0, 21.3 (The ^{13}C NMR values given here for mixture of isomers); HRMS (ESI) calcd for $C_{19}H_{18}N_3O_3$ $[M+H]^+$ 336.1348 found $[M+H]^+$ 336.1359.

Methyl 4,4-dicyano-5-(pyridin-2-yl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**39b**): Following the general procedure described above **39b** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 90:10); as a colorless semi solid (138 mg, 80%), FT-IR (DCM): 3321, 2954, 1738 and 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.70 (d, 1H, J = 4.8 Hz), 7.84-7.80 (m, 1H), 7.60 (d, 1H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz), 7.41-7.36 (m, 1H), 7.30-7.27 (m, 2H), 5.11 (s, 1H), 4.65 (d, 1H, J = 9.4 Hz), 4.40 (d, 1H, J = 9.4 Hz), 3.74 (s, 3H), 2.39 (s, 3H) (The ^1H NMR given here for major isomer); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 171.1, 153.1, 151.9, 149.9, 149.6, 139.7, 139.5, 137.4, 130.0, 129.2, 128.7, 128.5, 128.4, 124.7, 124.7, 122.9, 122.5, 113.8, 113.7, 113.3, 111.3, 71.7, 71.3, 64.6, 61.8, 59.6, 59.2, 53.1, 53.0, 50.4, 48.6, 21.2 (The ^{13}C NMR values given here for mixture of isomers); HRMS (ESI) calcd for $C_{20}H_{19}N_4O_2$ $[M+H]^+$ 347.1508 found $[M+H]^+$ 347.1518.



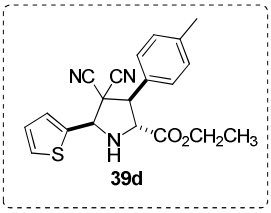
39b

(2R*,3R*,5R*)-Methyl 3-(4-chlorophenyl)-4,4-dicyano-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (**39c**): Following the general procedure described above **39c** was obtained after purification by silica column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (169 mg, 91%), mp:154-156 ^oC; FT-IR (KBr): 3338, 2955, 1738 and 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.39 (m, 6H), 7.13 (dd, 1H, J_1 = 4.9, J_2 = 3.7 Hz), 5.26 (d, 1H, J= 4.9 Hz), 4.47 (dd, 1H, J_1 = 8.4, J_2 = 1.4Hz), 4.12 (d, 1H, J= 8.4 Hz), 3.75 (s, 3H), 3.26 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 136.5, 135.9, 130.8, 130.0, 129.6, 127.5, 126.9, 126.8, 113.2, 111.3, 66.9, 60.8, 57.4, 53.3, 51.0; HRMS (ESI) calcd for $C_{18}H_{15}N_3O_2S$ $[M+H]^+$ 372.0573 found $[M+H]^+$ 372.0578.



39c

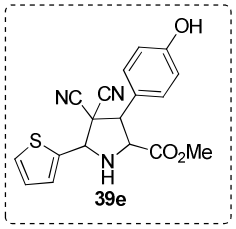
(2R*,3R*,5R*)-Ethyl 4,4-dicyano-5-(thiophen-2-yl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**39d**): Following the general procedure described above **39d** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (166 mg, 91%), mp: 153-155 ^oC; FT-IR (KBr): 3346, 2984, 1731and 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d,



39d

2H, J = 8.1 Hz), 7.42 (dd, 1H, J_1 = 5.1, J_2 = 1.2 Hz), 7.40 (dd, 1H, J_1 = 3.7, J_2 = 0.7 Hz), 7.29 (d, 2H, J = 8.1 Hz), 7.13 (dd, 1H, J_1 = 5.1, J_2 = 3.6 Hz), 5.26 (d, 1H, J = 2.9 Hz), 4.47 (d, 1H, J = 8.5 Hz), 4.21 (q, 2H, J = 7.2 Hz), 4.09 (d, 1H, J = 8.5 Hz), 3.23 (br. s, 1H), 2.41 (s, 3H), 1.19 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 139.7, 136.9, 130.0, 129.3, 128.2, 127.5, 126.8, 126.6, 113.5, 111.5, 66.9, 62.3, 60.9, 58.1, 51.2, 21.3, 14.1; HRMS (ESI) calcd for $C_{20}H_{20}N_3O_2S$ $[M+H]^+$ 366.1276 found $[M+H]^+$ 366.1281.

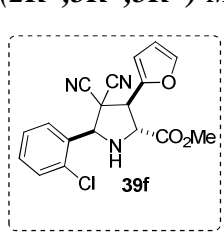
Methyl 4,4-dicyano-3-(4-hydroxyphenyl)-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (**39e**):



39e

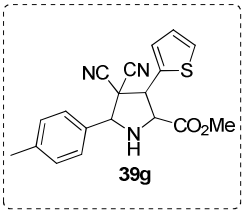
Following the general procedure described above **39e** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 35:65); as a colorless semi solid (159 mg, 90%), FT-IR (DCM): 3351, 2971, 1736 and 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 1H, J = 8.6 Hz), 7.41-7.36 (m, 4H), 7.11 (dd, 1H, J_1 = 5.0, J_2 = 3.6 Hz), 6.92 (d, 2H, J= 8.6 Hz), 5.24 (s, 1H), 4.45 (d, 1H, J= 8.5 Hz), 4.10 (d, 1H, J= 8.5 Hz), 3.72 (s, 3H) (The ^{1}H NMR values given here for major isomer); ^{13}C NMR ($CDCl_3$ + DMSO, 100 MHz): δ 173.1, 171.2, 159.4, 158.4, 137.0, 135.3, 133.9, 132.3, 129.9, 129.6, 128.4, 127.4, 126.7, 126.6, 126.5, 122.7, 117.0, 116.4, 116.3, 116.1, 113.6, 111.7, 66.7, 66.2, 63.6, 60.9, 57.7, 55.7, 53.1, 51.4, 49.5 (The ^{13}CNMR values given here for mixture of isomers); HRMS (ESI) calcd for $C_{18}H_{16}N_3O_3S[M+H]^+$ 354.0912 found $[M+H]^+$ 354.0916.

(2R*,3R*,5R*)-Methyl 5-(2-chlorophenyl)-4,4-dicyano-3-(furan-2-yl)pyrrolidine-2-carboxylate (**39f**): Following the general procedure described above **39f** was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (167 mg, 94%), mp:120-122 ^{o}C; FT-IR (KBr): 3345, 2960, 1738 and 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ8.00 (dd, 1H, J_1 = 9.5, J_2 = 2.2 Hz), 7.56 (dd, 1H, J_1 = 1.8, J_2 = 0.6 Hz), 7.49-7.36 (m, 3H), 6.63 (d, 1H, J = 3.4 Hz), 6.49 (dd, 1H, J_1 = 3.4, J_2 = 1.8 Hz), 5.56 (d, 1H, J = 5.0 Hz), 4.56 (dd, 1H, J_1 = 8.1, J_2 = 2.2 Hz), 4.40 (d, 1H, J = 8.1 Hz), 3.83 (s, 3H), 2.91 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100MHz): δ 172.6, 146.4, 144.2, 134.2, 131.1, 131.0, 130.0, 129.4, 127.4, 113.0, 111.2, 111.0, 110.3, 64.5, 59.3, 53.4, 52.5, 47.3; HRMS (ESI) calcd for $C_{18}H_{15}ClN_3O_3$ $[M+H]^+$ 356.0802 found $[M+H]^+$ 356.0802.



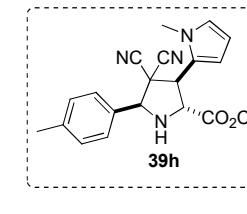
39f

Methyl 4,4-dicyano-3-(thiophen-2-yl)-5-(p-tolyl)pyrrolidine-2-carboxylate (**39g**): Following the general procedure described above **39g** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 30:70); as a colorless semi solid (132 mg, 75%), FT-IR (DCM): 3344, 2953, 1741 and 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, 2H, J = 8.1 Hz),7.42 (dd, 1H, J_1 = 5.2, J_2 = 1.1 Hz),7.36 (dd, 1H, J = 3.6 Hz), 7.28 (d, 2H, J = 7.8 Hz), 7.15-7.13 (m, 1H), 4.92 (s, 1H), 4.51 (s, 2H), 3.79 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 140.2, 134.8, 130.3, 129.7, 127.8, 127.1, 127.6, 126.6, 113.5, 114.4, 70.1, 62.5, 53.7, 53.3, 51.3, 21.3 (The ^1H and ^{13}CNMR values given here for major isomers); HRMS (ESI) calcd for $C_{19}H_{18}N_3O_2S[M+H]^+$ 352.1120 found $[M+H]^+$ 352.1130.



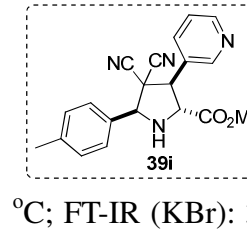
39g

(2R*,3R*,5S*)-Methyl 4,4-dicyano-3-(1-methyl-1H-pyrrol-2-yl)-5-(p-tolyl)pyrrolidine-2-carboxylate (**39h**): Following the general procedure described above **39h** was obtained after purification by silica column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (155 mg, 89%), mp:144-146 ^oC; FT-IR (KBr): 3345, 2953, 1737 and 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, 2H, J= 8.1Hz), 7.28 (d, 2H, J= 8.1Hz), 6.71 (dd, 1H, J_1 = 2.5, J_2 = 1.8 Hz), 6.55 (dd, 1H, J_1 = 3.8, J_2 = 1.8 Hz), 6.21 (dd, 1H, J_1 = 3.8, J_2 = 2.5 Hz), 4.90 (d, 1H, J= 5.0 Hz), 4.49 (d, 1H, J= 8.0 Hz), 4.39 (d, 1H, J= 8.0 Hz), 3.79 (s, 6H), 2.93 (br. s, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9, 140.2, 130.3, 129.7, 127.0, 124.7, 124.3, 114.3, 115.6, 109.9, 108.0, 70.7, 63.1, 53.2, 50.4, 49.7, 34.2, 21.3; HRMS (ESI) calcd for $C_{20}H_{21}N_4O_2$ $[M+H]^+$ 349.1665 found $[M+H]^+$ 349.1674.



39h

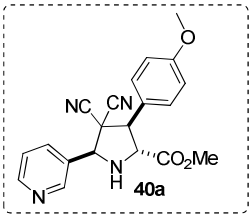
(2S*,4R*,5S*)-5-Methyl-4-(pyridin-3-yl)-2-(p-tolyl)pyrrolidine-3,3-dicarbonitrile (**39i**): Following the general procedure described above **39i** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a colorless solid (133 mg, 77%), mp:138-140 ^oC; FT-IR (KBr): 3338, 2954, 1738 and 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.79 (d, 1H, J= 1.9 Hz), 8.73 (dd, 1H, J_1 = 4.8, J_2 = 1.3 Hz), 7.99-7.28 (m, 6H), 4.94 (s, 1H), 4.48 (d, 1H, J= 7.9 Hz), 4.21 (d, 1H, J= 7.9 Hz), 3.77 (s, 3H), 3.03 (br. s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$+DMSO, 100 MHz): δ 172.6, 150.8, 149.9, 140.1, 135.7, 130.2, 129.6, 129.1, 127.1,



39i

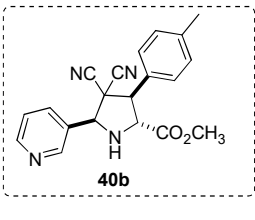
124.0, 113.3, 111.5, 70.4, 60.9, 55.5, 53.2, 50.5, 21.3; HRMS (ESI) calcd for $C_{20}H_{19}N_4O_2$ $[M+H]^+$ 347.1508 found $[M+H]^+$ 347.1508.

(2R*,3R*,5S*)-Methyl 4,4-dicyano-3-(4-methoxyphenyl)-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (**40a**): Following the general procedure described above **40a** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a colorless solid (162 mg, 89%), mp:132-134 ^oC; FT-IR (KBr): 3338, 2955, 1738 and 1253 $cm^{-1;1}H$ NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, 1H, J = 2.1 Hz), 8.73 (dd, 1H, J_1 = 4.8, J_2 = 1.4 Hz), 8.11-8.08 (m, 1H), 7.50 (d, 2H, J = 8.8 Hz), 7.44 (dd, 1H, J_1 = 7.9, J_2 = 4.8 Hz), 7.01 (d, 2H, J = 8.8 Hz), 4.99 (s, 1H), 4.50 (d, 1H, J = 8.2 Hz), 4.14 (d, 1H, J = 8.2 Hz), 3.86 (s, 3H), 3.76 (s, 3H), 3.03 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 160.6, 151.4, 148.9, 135.2, 130.0, 129.6, 124.0, 123.9, 114.7, 113.2, 111.3, 68.1, 61.0, 57.8, 55.4, 53.3, 50.8; HRMS (ESI) calcd for $C_{20}H_{19}N_4O_3$ $[M+H]^+$ 363.1457 found $[M+H]^+$ 363.1460.



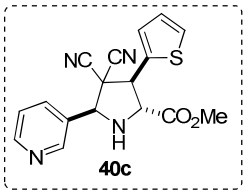
40a

(2R*,3R*,5S*)-Methyl 4,4-dicyano-5-(pyridin-3-yl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**40b**): Following the general procedure described above **40b** was obtained after purification by silica column chromatography (EtOAc:Hexane = 90:10); as a colorless solid (156 mg, 90%), mp: 157-159 ^oC; FT-IR (KBr): 3348, 2955, 2210, 1734 and 1220 $cm^{-1;}H$ NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, 1H, J = 1.9 Hz), 8.73 (dd, 1H, J_1 = 4.8, J_2 = 1.3 Hz), 8.09 (d, 1H, J = 8.0 Hz), 7.47- 7.42 (m, 3H), 7.29 (d, 2H, J = 8.0 Hz), 5.00 (s, 1H), 4.54 (d, 1H, J = 8.2 Hz), 4.15 (d, 1H, J = 8.2 Hz), 3.76 (s, 3H), 3.06 (br. s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 151.3, 148.8, 139.9, 135.3, 130.1, 129.9, 129.2, 128.2, 123.9, 113.2, 111.2, 68.2, 60.9, 58.0, 53.3, 50.7, 21.3; HRMS (ESI) calcd for $C_{20}H_{19}N_4O_2$ $[M+H]^+$ 347.1508 found $[M+H]^+$ 347.1501.



40b

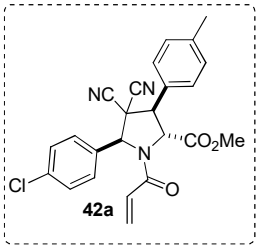
(2R*,3R*,5S*)-Methyl 4,4-dicyano-5-(pyridin-3-yl)-3-(thiophen-2-yl)pyrrolidine-2-carboxylate (**40c**): Following the general procedure described above **40c** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a colorless solid (158 mg, 93%), mp:152-154 ^oC; FT-IR (KBr): 3337, 2957, 1738 and 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, 1H, J = 2.2 Hz), 8.74 (dd, 1H, J_1 = 4.9, J_2 = 1.7 Hz), 8.09-8.07 (m, 1H), 7.45-



40c

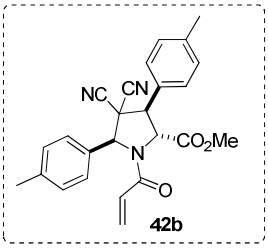
7.36 (m, 3H), 7.15 (dd, 1H, J_1 = 5.1, J_2 = 3.7 Hz), 5.00 (d, 1H, J = 3.9 Hz), 4.54-4.49 (m, 2H), 3.81 (s, 3H), 3.03 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 151.6, 149.0, 135.1, 134.3, 129.5, 127.9, 127.8, 126.9, 123.9, 112.9, 110.9, 67.9, 62.3, 53.7, 53.4, 51.0; HRMS (ESI) calcd for $C_{17}H_{15}N_4O_2S[M+H]^+$ 339.0916 found $[M+H]^+$ 339.0911.

(2R*,3R*,5S*)-Methyl 1-acryloyl-5-(4-chlorophenyl)-4,4-dicyano-3-(p-tolyl)pyrrolidine-2-carboxylate (**42a**): Following the general procedure described above **42a** was obtained after purification by silica column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (395 mg, 91%), mp:222-224 ^oC; FT-IR (KBr):, 2958, 1738, 1675, 1416 and 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51-7.44 (m, 6H), 7.30 (d, 2H, J = 8.0 Hz), 6.30 (d, 1H, J = 16.4 Hz), 5.78-5.70 (m, 2H), 5.48 (d, 1H, J = 10.5 Hz), 5.28 (d, 1H, J = 10.5 Hz), 4.15-4.10 (m, 1H), 3.72 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 165.3, 140.7, 137.0, 132.0, 130.0, 128.5, 127.4, 125.3, 112.0, 110.4, 69.2, 62.9, 54.3, 53.3, 52.0, 21.3; HRMS (ESI) calcd for $C_{24}H_{21}ClN_3O_3$ $[M+H]^+$ 434.1271 found $[M+H]^+$ 434.1247.



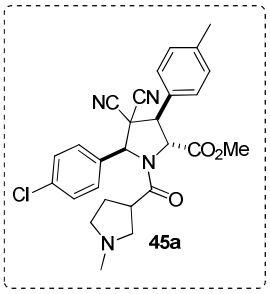
42a

(2R*,3R*,5S*)-Methyl 1-acryloyl-4,4-dicyano-3,5-di-p-tolylpyrrolidine-2-carboxylate (**42b**): Following the general procedure described above **42b** was obtained after purification by silica column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (380 mg, 92%), mp:198-200 ^oC; FT-IR (KBr): 2954, 1738, 1655, 1416 and 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, 2H, J = 8.1 Hz), 7.39 (d, 2H, J = 8.1 Hz), 7.31-7.28 (m, 4H), 6.28 (dd, 1H, J_1 = 16.6, J_2 = 1.3 Hz), 5.78 (dd, 1H, J_1 = 16.6, J_2 = 10.4 Hz), 5.68 (s, 1H), 5.43 (dd, 1H, J_1 = 10.4, J_2 = 1.3 Hz), 5.30 (d, 1H, J = 11.2 Hz), 4.10 (d, 1H, J = 11.2 Hz), 3.71 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 165.5, 141.0, 140.5, 130.4, 130.3, 130.2, 129.4, 128.3, 127.6, 127.0, 125.6, 112.2, 110.6, 69.8, 62.9, 54.3, 53.2, 52.3, 21.4, 21.3; HRMS (ESI) calcd for $C_{25}H_{23}N_3NaO_3$ $[M+Na]^+$ 436.1637 found $[M+Na]^+$ 436.1624.



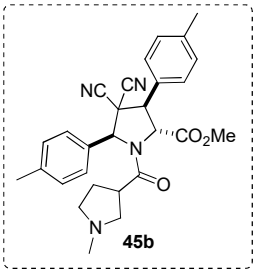
42b

(2R*,3R*,5S*)-Methyl 5-(4-chlorophenyl)-4,4-dicyano-1-(1-methylpyrrolidine-3-carbonyl)-3-(p-tolyl)pyrrolidine-2-carboxylate (**45a**): Following the general procedure described above **45a** was obtained after purification by alumina column chromatography (EtOAc:Hexane = 45:55); as a colorless solid (33 mg, 46%), mp:218-220 ^oC; FT-IR (KBr): 2952, 1750, 1662, 1411 and 1218

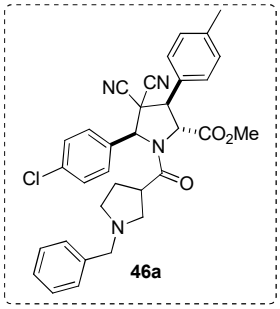


cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.28 (m, 8H), 5.61 (s, 1H), 5.24 (d, 1H, J = 11.2 Hz), 4.06 (d, 1H, J = 11.2 Hz), 3.68 (s, 3H), 2.89 (t, 1H, J = 8.1 Hz), 2.64-2.58 (m, 2H), 2.40 (s, 3H), 2.36-2.32 (m, 3H), 2.30 (s, 3H), 1.93-1.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.8, 169.6, 140.6, 137.0, 132.1, 130.2, 130.1, 128.2, 125.3, 112.0, 110.4, 69.4, 63.1, 60.1, 55.9, 54.3, 53.2, 52.0, 42.7, 41.5, 28.5, 21.3; HRMS (ESI) calcd for $C_{27}H_{28}ClN_4O_3$ $[M+H]^+$ 491.1850 found $[M+H]^+$ 491.1852.

(2R*,3R*,5S*)-Methyl 4,4-dicyano-1-(1-methylpyrrolidine-3-carbonyl)-3,5-di-p-tolylpyrrolidine-2-carboxylate(**45b**): Following the general procedure described above **45b** was

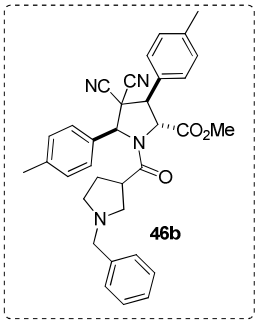


obtained after purification by alumina column chromatography (EtOAc:Hexane = 45:55); as a colorless solid (51 mg, 77%), mp:190-192 ^{o}C; FT-IR (KBr): 2954, 1753, 1649, 1449 and 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.27 (m, 8H), 5.59 (s, 1H), 5.24 (d, 1H, J = 11.2 Hz), 4.04 (d, 1H, J = 11.2 Hz), 3.68 (s, 3H), 2.87 (t, 1H, J = 8.8 Hz), 2.73-2.55 (m, 3H), 2.40 (s, 3H), 2.39 (s, 3H), 2.37-2.32 (m, 2H), 2.29 (s, 3H), 1.93-1.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0, 169.8, 141.0, 140.4, 130.5, 130.4, 130.1, 128.3, 126.9, 125.6, 112.3, 110.6, 69.9, 63.0, 60.1, 56.0, 54.2, 53.1, 52.2, 42.6, 41.5, 28.5, 21.3, 21.3; HRMS (ESI) calcd for $C_{28}H_{31}N_4O_3$ $[M+H]^+$ 471.2396 found $[M+H]^+$ 471.2411.



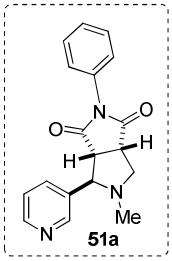
(2R*,3R*,5S*)-Methyl 1-(1-benzylpyrrolidine-3-carbonyl)-5-(4-chlorophenyl)-4,4-dicyano-3-(p-tolyl)pyrrolidine-2-carboxylate (**46a**): Following the general procedure described above **46a** was obtained after purification by silica column chromatography (EtOAc:Hexane = 65:35); as a colorless semi solid (58 mg, 73%), FT-IR (DCM): 2953, 1749, 1661, 1409 and 1218 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53-7.28 (m, 13H), 5.59 (s, 1H), 5.22 (d, 1H, J = 11.2 Hz), 4.03(d, 1H, J = 11.2 Hz), 3.69 (s, 3H), 3.60 (s, 2H), 3.02 (t, 1H, J = 8.0 Hz), 2.77-2.62 (m, 2H), 2.40 (s, 3H), 2.39-2.34 (m, 3H), 1.94-1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.7, 169.5, 140.6, 138.2, 130.2, 130.2, 130.1, 128.9, 128.4, 128.2, 127.3, 125.3, 112.0, 110.4, 69.3, 63.1, 59.8, 57.9, 54.2, 53.8, 53.2, 52.0, 42.2, 27.8, 21.3; HRMS (ESI) calcd for $C_{33}H_{32}ClN_4O_3$ $[M+H]^+$ 567.2163 found $[M+H]^+$ 567.2175.

(2R*,3R*,5S*)-Methyl 1-(1-benzylpyrrolidine-3-carbonyl)-4,4-dicyano-3,5-di-p-tolylpyrrolidine-2-carboxylate (**46b**): Following the general procedure described above **46b** was

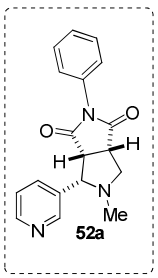


obtained after purification by silica column chromatography (EtOAc:Hexane = 65:35); as a colorless semi solid (59 mg, 77%), FT-IR (DCM): 2952, 1749, 1660, 1411 and 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.26 (m, 13H), 5.56 (s, 1H), 5.23 (d, 1H, J = 11.2 Hz), 4.03 (d, 1H, J = 11.2 Hz), 3.69 (s, 3H), 3.58 (s, 2H), 2.99 (t, 1H, J = 8.5 Hz), 2.72-2.67 (m, 2H), 2.40 (s, 3H), 2.40 (s, 3H), 2.37-2.31 (m, 3H), 1.95-1.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.0, 169.7, 141.0, 140.4, 138.6, 130.5, 130.4, 130.1, 128.9, 128.3, 128.3, 127.1, 127.0, 125.6, 112.3, 110.6, 69.8, 63.1, 60.0, 58.0, 54.2, 53.9, 53.1, 52.3, 42.1, 27.9, 21.3, 21.3; HRMS (ESI) calcd for $C_{34}H_{35}N_4O_3$ $[M+H]^+$ 547.2709 found $[M+H]^+$ 547.2719.

(3aR*,4R*,6aS*)-5-Methyl-2-phenyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**51a*****):*** Following the general procedure described above **51a** was obtained



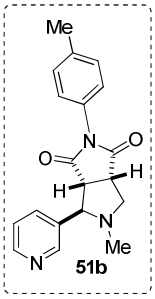
after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (100 mg, 60%), mp:124-126 ^oC; FT-IR (KBr): 2974, 2777, 1702, 1494, 1167, cm^{-1}; ^1H NMR (400 MHz , $CDCl_3$): δ 8.65 (d, 1H, J = 1.5 Hz), 8.59 (dd, 1H, J_1 = 4.7, J_2 = 1.5 Hz), 7.71 (d, 1H, J = 7.8 Hz), 7.50-7.30 (m, 6H), 3.66 (t, 2H, J = 6.4 Hz), 3.60 (t, 1H, J = 6.4 Hz), 3.41 (dd, 1H, J_1 = 8.8, J_2 = 6.3 Hz), 2.74 (dd, 1H, J_1 = 9.5, J_2 = 6.3 Hz), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 176.0, 149.6, 149.4, 135.6, 134.5, 131.6, 129.2, 128.8, 126.4, 123.8, 70.5, 57.5, 53.5, 44.1, 38.8; HRMS (ESI): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1399 found 308.1393.



(3aR*,4S*,6aS*)-5-Methyl-2-phenyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**52a**)*:* Following the general procedure described above **52a** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (54 mg, 33%), mp: 168-170 ^oC; FT-IR (KBr): 2923, 2848, 1707, 1387, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.53 (d, 1H, J = 3.6 Hz), 7.59 (d, 1H, J = 7.8 Hz), 7.43-7.18 (m, 6H), 3.72 (d, 1H, J = 9.7 Hz), 3.63 (d, 1H, J = 8.5 Hz), 3.54 (t, 1H, J = 8.5 Hz), 3.40 (t, 1H, J = 7.1 Hz), 2.67 (dd, 1H, J_1 = 9.7, J_2 = 7.1 Hz), 2.19 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 178.0, 174.6, 149.6, 135.7, 132.4, 131.8, 129.2, 128.6, 126.2, 123.5, 71.0, 58.5, 50.5, 44.4, 39.7; HRMS (ESI): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1399 found 308.1403.

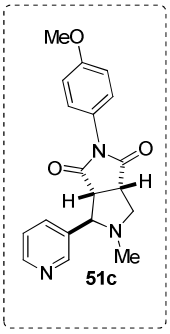
(3aR*,4R*,6aS*)-5-Methyl-4-(pyridin-3-yl)-2-(p-tolyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione(**51b**): Following the general procedure described above **51b** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (96 mg, 47%), mp: 174-176 ^oC; FT-IR (KBr): 2923, 2835, 1708, 1512, 1169 cm^{-1};



51b

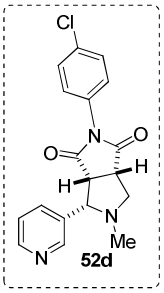
^1H NMR (400 MHz, $CDCl_3$): δ8.66 (d, 1H, J = 1.7 Hz), 8.60 (dd, 1H, J_1 = 4.8, J_2 = 1.3 Hz), 7.73-7.70 (m, 1H), 7.35-7.18 (m, 5H), 3.66 (t, 2H, J = 6.1 Hz), 3.60 (t, 1H, J = 8.8 Hz), 3.40 (dd, 1H, J_1 = 8.8, J_2 = 6.3 Hz), 2.74 (dd, 1H, J_1 = 9.4, J_2 =6.3 Hz), 2.39 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 176.1, 149.6, 149.4, 138.9, 135.5, 134.6, 129.9, 128.9, 126.2, 123.7, 70.5, 57.5, 53.5, 44.1, 38.8, 21.3; HRMS (ESI): calcd for $C_{19}H_{20}N_3O_2$ $[M+H]^+$ 322.1551 found 322.1550. The corresponding isomer (**52b**) could not be separated in pure form as both isomers have similar R_f values.

(3aR*,4R*,6aS*)-2-(4-Methoxyphenyl)-5-methyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione(**51c**): Following the general procedure described above**51c** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (95 mg, 48%), mp: 174-176 ^oC; FT-IR (KBr): 2941, 2786, 1708, 1515, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.65-8.59 (m, 2H), 7.72 (d, 1H, J = 7.8 Hz), 7.34 (dd, 1H, J_1 = 7.8, J_2 = 4.9 Hz), 7.23 (d, 2H, J = 8.9 Hz), 6.99 (d, 2H, J = 8.9 Hz), 3.83 (s, 3H), 3.59 (t, 1H, J = 8.7 Hz), 3.64 (t, 2H, J = 6.5 Hz), 3.39 (dd, 1H, J_1 = 8.7, J_2 = 6.5 Hz), 2.73 (dd, 1H, J_1 = 9.4, J_2 = 6.6 Hz), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 176.3, 159.6, 149.6, 149.4, 135.5, 134.6, 127.7, 124.2, 123.7, 114.5, 70.4, 57.5, 55.5, 53.5, 44.0, 38.8; HRMS (ESI): calcd for $C_{19}H_{20}N_3O_3$ $[M+H]^+$ 338.1504 found 338.1510. The corresponding isomer (**52c**) could not be separated in pure form as both isomers have similar R_f values.



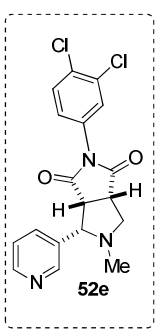
51c

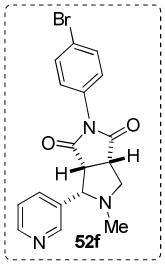
(3aR*,4S*,6aS*)-2-(4-Chlorophenyl)-5-methyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**52d**): Following the general procedure described above**52d** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (77 mg, 38%), mp: 198-200 ^oC; FT-IR (KBr): 2949, 2821, 1706, 1492, 1196,



cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.53 (m, 2H), 7.58-7.55 (m, 1H), 7.40-7.16 (m, 5H), 3.72 (d, 1H, J = 9.8 Hz), 3.63 (d, 1H, J = 8.7 Hz), 3.54 (t, 1H, J = 8.7 Hz), 3.40 (t, 1H, J = 7.2 Hz), 2.68 (dd, 1H, J_1 = 9.8, J_2 = 7.2 Hz), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 174.3, 149.7, 149.6, 135.7, 134.3, 132.3, 130.2, 129.4, 127.4, 123.5, 71.0, 58.4, 50.5, 44.3, 39.7; HRMS (ESI): calcd for $C_{18}H_{17}N_3O_2Cl$ $[M+H]^+$ 342.1009 found 342.1024. The corresponding isomer (**51d**) could not be separated in pure form as both isomers have similar R_f values.

(3aR*,4S*,6aS*)-2-(3,4-Dichlorophenyl)-5-methyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**52e**): Following the general procedure described above**52e** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (75 mg, 34%), mp: 190-192 ^{o}C; FT-IR (KBr): 2920, 2824, 1711, 1474, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 2H),7.56 (d, 1H, J = 7.8 Hz), 7.49 (d, 1H, J = 8.6 Hz), 7.38 (d, 1H, J = 2.3 Hz), 7.29 (dd, 1H, J_1 = 7.8, J_2 = 7.0 Hz), 7.12 (dd, 1H, J_1= 8.6, J_2 = 2.3 Hz), 3.72 (d, 1H, J = 9.8 Hz), 3.64 (d, 1H, J = 8.6 Hz), 3.55 (t, 1H, J = 8.6 Hz), 3.40 (t, 1H, J = 7.3 Hz), 2.69 (dd, 1H, J_1 = 9.8, J_2 = 7.3 Hz), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 174.0, 149.7, 149.5, 135.6, 133.0, 132.7, 132.2, 130.9, 130.8, 128.0, 125.4, 123.5, 70.9, 58.5, 50.5, 44.3, 39.6; HRMS (ESI): calcd for $C_{18}H_{16}N_3O_2Cl_2$ $[M+H]^+$ 376.0619 found 376.0634. The corresponding isomer (**51e**) could not be separated in pure form as both isomers have similar R_f values.

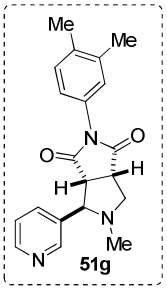




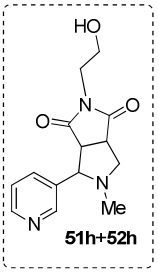
(3aR*,4S*,6aS*)-2-(4-Bromophenyl)-5-methyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione(**52f**): Following the general procedure described above**52f** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (85 mg, 38%), mp: 184-186 ^{o}C; FT-IR (KBr): 2927, 2821, 1705, 1489, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.55 (m, 2H), 7.59-7.11 (m, 6H), 3.72 (d, 1H, J = 9.7 Hz), 3.64 (d, 1H, J = 8.2 Hz), 3.54 (t, 1H, J = 8.2 Hz), 3.40 (t, 1H, J = 7.2 Hz), 2.69 (dd, 1H, J_1 = 9.7, J_2 = 7.2 Hz), 2.21 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 174.3, 149.7, 149.6, 135.6, 132.3, 132.2, 130.7, 127.7, 123.5, 122.4, 71.0, 58.4, 50.5, 44.3, 39.7; HRMS (ESI): calcd for

$C_{18}H_{17}N_3O_2Br$ $[M+H]^+$ 386.0504 found 386.0489. The corresponding isomer (**51f**) could not be separated in pure form as both isomers have similar R_f values.

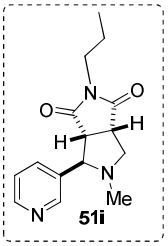
(3aR*,4R*,6aS*)-2-(3,4-Dimethylphenyl)-5-methyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**51g**): Following the general procedure described above**51g** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless viscous liquid (95 mg, 51%), FT-IR (DCM): 2924, 2791, 1712, 1504, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.59 (d, 1H, J = 3.7 Hz), 7.71 (d, 1H, J = 7.8 Hz), 7.32 (dd, 1H, J_1 = 7.8, J_2 = 4.7 Hz), 7.23 (d, 1H, J = 7.9 Hz), 7.04 (d, 1H, J = 2.0 Hz), 7.01 (dd, 1H, J_1 = 7.9, J_2 = 2.0 Hz), 3.66-3.62 (m, 2H), 3.59 (t, 1H, J = 8.9 Hz), 3.38 (dd, 1H, J_1 = 8.9, J_2 = 6.4 Hz), 2.73 (dd, 1H, J_1= 9.3, J_2 = 6.4 Hz), 2.28 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 176.2, 149.6, 149.4, 137.9, 137.7, 135.6, 134.6, 130.4, 129.1, 127.4, 123.9, 123.7, 70.5, 57.6, 53.6, 44.1, 38.8, 19.9, 19.6; HRMS (ESI): Calcd for $C_{20}H_{22}N_3O_2$ $[M+H]^+$ 336.1712, found 336.1727. The corresponding isomer (**52g**) could not be separated in pure form as both isomers have similar R_f values.



2-(2-Hydroxyethyl)-5-methyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione **(51h/52h):**Following the general procedure described above**51h/52h** **(**mixture of isomers) was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 90:10); as a yellow colored viscous liquid (114 mg, 83%), FT-IR (DCM): 3405, 2953, 1698, 1401, 1181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64-8.57 (m, 2H), 7.69-7.55 (m, 1H), 7.33-7.24 (m, 1H), 3.79-3.37 (m, 8H), 3.25-3.22 (m, 1H), 2.61-2.57 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 178.2, 177.6, 176.2, 149.5, 149.3, 149.2, 149.1, 136.1, 135.8, 134.7, 132.7, 123.8, 123.5, 70.6, 70.0, 59.4, 58.1, 57.1, 53.4, 50.4, 44.1, 44.0, 41.7, 41.6, 39.6, 38.7 (The ^{13}C NMR given here for mixture of isomers); HRMS (ESI): calcd for $C_{14}H_{18}N_3O_3$ $[M+H]^+$ 276.1348 found 276.1467. The compounds (**51h**) and (**52h**) could not be separated in pure form as both isomers have similar R_f values.

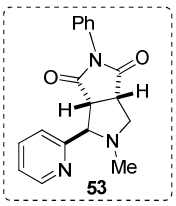


(3aR*,4R*,6aS*)-5-Methyl-2-propyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione(**51i**): Following the general procedure described above**51i** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless



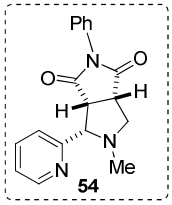
viscous liquid (74 mg, 47%), FT-IR (DCM): 2965, 1712, 1401, 1139, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 1H, J = 1.9 Hz), 8.50 (dd, 1H, J_1 = 4.8, J_2 = 1.9 Hz), 7.62-7.59 (m, 1H), 7.26-7.22 (m, 1H), 3.44-3.37 (m, 5H), 3.15 (dd, 1H, J_1 = 8.7, J_2 = 6.3 Hz), 2.48 (dd, 1H, J_1 = 8.7, J_2 = 5.6 Hz), 2.05 (s, 3H), 1.54 (dd, 2H, J_1 = 14.9, J_2 = 7.4 Hz), 0.83 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 177.0, 149.4, 149.3, 135.6, 134.7, 123.7, 70.3, 57.4, 53.5, 44.0, 40.4, 38.8, 21.0, 11.2; HRMS (ESI): calcd for $C_{15}H_{20}N_3O_2$ $[M+H]^+$ 274.1556 found 274.1592.

(3aR*,4S*,6aS*)-5-Methyl-2-propyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**52i**): Following the general procedure described above **52i** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless viscous liquid (63 mg, 40%), FT-IR (DCM): 2965, 1699, 1403, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, 1H, J_1 = 4.8, J_2 = 1.9 Hz), 8.41 (d, 1H, J = 1.9 Hz), 7.44-7.41 (m, 1H), 7.21-7.17 (m, 1H), 3.55 (d, 1H, J = 9.6 Hz), 3.45 (d, 1H, J = 8.5 Hz), 3.32- 3.29 (m, 2H), 3.28 (d, 1H, J = 1.3 Hz), 3.14 (t, 1H, J = 7.4 Hz), 2.51 (dd, 1H, J_1 = 9.6, J_2 = 7.4 Hz), 2.07 (s, 3H), 1.48 (dd, 1H, J_1 = 7.4, J_2 = 1.8 Hz), 1.45 (dd, 1H, J_1 = 7.4, J_2 = 2.0 Hz), 0.81 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 175.6, 149.6, 149.5, 135.7, 132.4, 123.3, 70.7, 58.3, 50.4, 44.0, 40.6, 39.7, 21.1, 11.3; HRMS (ESI): calcd for $C_{15}H_{20}N_3O_2$ $[M+H]^+$ 274.1556 found 274.1550.

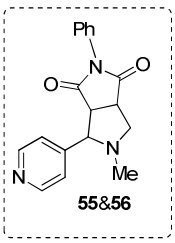


(3aR*,4R*,6aS*)-5-Methyl-2-phenyl-4-(pyridin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione(**53**): Following the general procedure described above**53** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (95 mg, 62%), mp: 159-161 ^oC; FT-IR (KBr): 2918, 2793, 1702, 1381, 1198 cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ8.66 (dd, 1H, J_1 = 4.8, J_2 = 0.8 Hz), 7.72-7.68 (m, 1H), 7.51-7.23 (m, 7H), 4.13 (d, 1H, J = 3.6 Hz), 3.84 (dd, 1H, J_1 = 8.7, J_2 =3.6 Hz), 3.79-3.74 (m, 1H), 3.50-3.45 (m, 1H), 3.01 (dd, 1H, J_1 = 9.6, J_2 = 4.2 Hz), 2.17 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 177.6, 157.2, 149.9, 136.3, 132.0, 129.1, 128.6, 126.5, 123.9, 122.9, 72.1, 56.7, 51.5, 45.1, 37.9; HRMS (ESI): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1399 found 308.1407.

(3aR*,4S*,6aS*)-5-Methyl-2-phenyl-4-(pyridin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**54**):Following the general procedure described above**54** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (42 mg, 27%), mp: 146-148 ^{o}C; FT-IR (KBr): 2925, 2852, 1709, 1384, 1192 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ8.62-8.60 (m, 1H), 7.69-7.65 (m, 1H), 7.41-7.19 (m, 7H), 3.82 (d, 1H, J = 8.8 Hz), 3.74-3.68 (m, 2H), 3.42 (t, 1H, J = 7.2 Hz), 2.72 (dd, 1H, J_1 = 9.6, J_2 = 7.2 Hz), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 174.9, 157.1, 149.4, 136.7, 131.9, 129.1, 128.5, 126.3, 123.1, 122.1, 74.6, 58.5, 50.1, 44.5, 39.9; HRMS (ESI): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1399 found 308.1393.

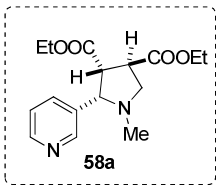


5-Methyl-2-phenyl-4-(pyridin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione **(55**&**56):**Following the general procedure described above**55/56** (mixture of isomers) was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 75:25); as a colorless solid (138 mg, 90%), mp: compound decomposes after 170 ^{o}C; FT-IR (KBr): 2945, 2779, 1703, 1496, 1185 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64-8.59 (m, 2H), 7.52-7.19 (m, 7H), 3.75-3.56 (m, 3H), 3.41-3.34 (m, 1H), 2.75-2.68 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 176.4, 175.9, 174.2, 150.3, 150.0, 148.3, 146.2, 131.8, 131.6, 129.2, 129.1, 128.8, 128.6, 126.4, 126.1, 123.1, 122.7, 72.1, 71.4, 58.4, 57.6, 53.4, 50.4, 44.5, 44.1, 39.7, 39.0 (The ^{13}C NMR given here for mixture of isomers); HRMS (ESI): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1399 found 308.1413. The compounds (**55/56**) could not be separated in pure form as the isomers have similar R_f values.



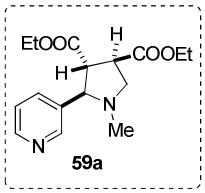
(2S*,3R*,4R*)-Diethyl 1-methyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate (**58a**):

Following the general procedure described above**58a** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (110 mg, 36%), FT-IR (DCM): 2981, 2936, 1731, 1320, 1187 cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$): δ 8.54-8.51 (m, 2H), 7.67 (d, 1H, J = 7.9 Hz), 7.28-7.24 (m, 1H), 4.19 (q, 2H, J = 7.1 Hz), 3.77-3.56 (m, 5H), 3.48 (dd, 1H, J_1 = 10.8, J_2 = 7.1 Hz), 2.54 (t, 1H, J = 9.8 Hz), 2.19 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 0.76 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 171.5, 150.2, 149.1, 135.8, 134.3, 123.3,



70.2, 61.1, 60.8, 58.5, 52.4, 44.6, 39.9, 14.2, 13.5; MS (CI): m/z (%) 308 ($[M+2]^+$, 20), 307 ($[M+1]^+$, 100), 293 (10) and 261 (10).

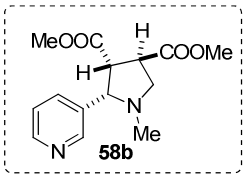
(2R*,3R*,4R*)-Diethyl 1-methyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate (**59a**):Following



59a

the general procedure described above**59a** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (162 mg, 53%), FT-IR (DCM): 2984, 2931, 1734, 1458, 1183, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 2H, J = 2.6 Hz), 7.80-7.77 (m, 1H), 7.29 (dd, 1H, J_1 = 7.8, J_2 = 4.8 Hz), 4.24-4.04 (m, 4H), 3.52 (dd, 1H, J_1 = 9.7, J_2 = 1.6 Hz), 3.43 (dd, 1H, J_1 = 8.6, J_2 = 5.2 Hz), 3.39-3.36 (m, 1H), 3.29 (d, 1H, J = 8.6 Hz), 2.69 (dd, 1H, J_1 = 9.7, J_2 = 8.6 Hz), 2.09 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.15 (t, 3H, J = 7.1 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.6, 150.0, 149.4, 136.2, 135.5, 123.8, 72.0, 61.4, 61.2, 58.9, 54.8, 44.9, 39.6, 14.2, 14.1; MS (CI): m/z (%) 307 ($[M+1]^+$, 100), 304 (10) and 259 (5).

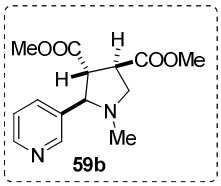
(2S*,3R*,4R*)-Dimethyl 1-methyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate (**58b**):



58b

Following the general procedure described above**58b** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (117 mg, 42%), FT-IR (DCM): 2981, 2789, 1736, 1435, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, 2H, J = 0.8 Hz), 7.54 (dd, 1H, J_1 = 7.9, J_2 = 1.4 Hz), 7.15 (dd, 1H, J_1 = 7.9, J_2 = 4.8 Hz), 3.67-3.64 (m, 1H), 3.60 (s, 3H), 3.57-3.49 (m, 2H), 3.46 (t, 1H, J = 8.8 Hz), 3.00 (s, 3H), 2.44 (t, 1H, J = 9.2 Hz), 2.07 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 171.8, 150.0, 149.1, 135.7, 134.1, 123.2, 70.2, 58.5, 52.5, 52.2, 51.6, 44.3, 39.9; MS (CI): m/z (%) 280 ($[M+2]^+$, 20), 279 ($[M+1]^+$, 100), 247 (12) and 217 (8).

(2R*,3R*,4R*)-Dimethyl 1-methyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate (**59b**):

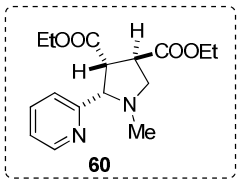


59b

Following the general procedure described above**59b** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (78 mg, 28%), FT-IR (DCM): 2923, 2800, 1734, 1456, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 2H, J = 1.7 Hz), 7.78 (dd, 1H, J_1 = 7.9, J_2 = 1.7 Hz), 7.30 (dd, 1H, J_1 = 7.9, J_2 = 4.8 Hz), 3.76 (s, 3H), 3.64 (s, 3H), 3.52 (dd, 1H, J_1 = 9.7, J_2 = 1.2 Hz), 3.48 (dd, 1H, J_1 = 8.6, J_2 = 5.1 Hz), 3.40-3.36 (m, 1H), 3.31 (d, 1H, J = 8.6 Hz), 2.69 (t, 1H, J = 8.6 Hz), 2.09 (s, 3H), ^{13}C NMR (100 MHz,

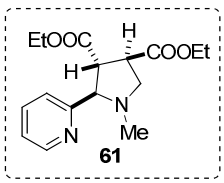
$CDCl_3$): δ 173.9, 173.1, 149.8, 149.4, 136.1, 135.5, 123.9, 71.8, 58.9, 54.6, 52.6, 52.3, 44.9, 39.5; MS (CI): m/z (%) 279 ($[M+1]^+$, 15), 277 (50), 267 (14) and 262 (50).

(2S*,3R*,4R*)-Diethyl 1-methyl-2-(pyridin-2-yl)pyrrolidine-3,4-dicarboxylate **(60)**: Following the general procedure described above**60** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (107 mg, 35%), FT-IR (DCM): 2980, 2778, 1733, 1589, 1178, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53-8.51 (m, 1H), 7.65-7.60 (m, 1H), 7.35 (d, 1H, J = 7.9 Hz), 7.17-7.13 (m, 1H), 4.15 (dd, 1H, J_1 = 7.1, J_2 = 0.9 Hz), 4.12 (dd, 1H, J_1 = 7.1, J_2 = 0.9 Hz), 3.88 (d, 1H, J = 9.6 Hz), 3.79-3.66 (m, 3H), 3.53 (dd, 1H, J_1 = 8.9, J_2 = 7.9 Hz), 3.46 (dd, 1H, J_1 = 10.8, J_2 = 7.2 Hz), 2.58 (t, 1H, J = 9.6 Hz), 2.18 (s, 3H), 1.23 (t, 3H, J = 7.2 Hz), 0.73 (t, 3H, J = 7.2 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 171.7, 158.8, 148.9, 136.5, 122.6, 122.5, 73.7, 61.0, 60.6, 58.3, 51.7, 44.7, 40.0, 14.2, 13.6; HRMS (ESI): calcd for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 307.1658 found 307.1699.



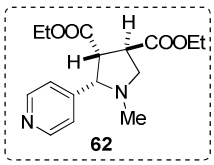
60

(2R*,3R*,4R*)-Diethyl 1-methyl-2-(pyridin-2-yl)pyrrolidine-3,4-dicarboxylate (**61**): Following the general procedure described above**61** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (138 mg, 45%), FT-IR (DCM): 2975, 2782, 1734, 1585, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56-8.54 (m, 1H), 7.67-7.63(m, 1H), 7.41 (d, 1H, J = 7.8 Hz), 7.19-7.15 (m, 1H), 4.19 (dd, 1H, J_1 = 7.2, J_2 = 1.9 Hz), 4.16 (dd, 1H, J_1 = 7.2, J_2 = 1.9 Hz), 4.10-3.99 (m, 2H), 3.64 (dd, 1H, J_1 = 8.9, J_2 = 5.9 Hz), 3.54 (dd, 1H, J_1 = 9.4, J_2 = 2.3 Hz), 3.47 (d, 1H, J = 8.9 Hz), 3.42-3.37 (m, 1H), 2.74 (t, 1H, J = 9.4 Hz), 2.13 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.08 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.8, 159.7, 149.3, 136.7, 122.8, 122.5, 75.7, 61.3, 61.0, 58.6, 53.7, 44.9, 39.8, 14.2, 14.0; HRMS (ESI): calcd for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 307.1658 found 307.1652.



61

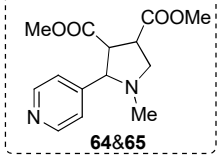
(2S*,3R*,4R*)-Diethyl 1-methyl-2-(pyridin-4-yl)pyrrolidine-3,4-dicarboxylate **(62)**: Following the general procedure described above**62** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (122 mg, 34%), FT-IR (DCM): 2980, 2927, 1733, 1603, 1192, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, 2H, J_1 = 4.6, J_2 = 1.4 Hz), 7.25 (dd, 2H, J_1 = 4.6, J_2 = 1.4 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.75-3.63 (m, 2H), 3.61-3.53 (m,



62

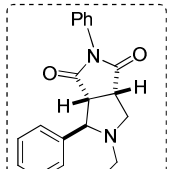
3H), 3.47-3.41 (m, 1H), 2.50 (dd, 1H, J_1 = 10.2, J_2 = 9.1 Hz), 2.16 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 0.74 (t, 3H, J = 7.1 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 171.3, 149.5, 148.0, 123.6, 71.7, 61.1, 60.8, 58.5, 52.3, 44.6, 40.0, 14.2, 13.5; HRMS (ESI): calcd for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 307.1658 found 307.1670.

Dimethyl 1-methyl-2-(pyridin-4-yl)pyrrolidine-3,4-dicarboxylate **(64&65):** Following the general procedure described above**64&65** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a yellow colored viscous liquid (195 mg, 70%), FT-IR (DCM):2952, 2792, 1736, 1600, 1204, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56-8.51 (m, 4H), 7.32-7.21 (m, 4H), 3.75 (s, 3H), 3.70 (s, 4H), 3.64-3.62 (m, 5H), 3.55-3.49 (m, 2H), 3.44 (dd, 1H, J_1 = 8.5, J_2 =5.1 Hz), 3.32 (s, 1H), 3.10 (s, 4H), 2.69 (dd, 1H, J_1 = 9.1, J_2 =8.5 Hz), 2.53 (dd, 1H, J_1 = 10.4, J_2 = 9.1 Hz), 2.17 (s, 4H), 2.10 (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 173.0, 172.9, 171.5, 150.0, 149.9, 149.6, 147.8, 123.3, 123.0, 73.0, 71.6, 58.8, 58.5, 54.5, 52.5, 52.2, 51.5, 45.1, 44.4, 39.9, 39.6 (The ^{1}H NMR and ^{13}C NMR is given here for mixture of isomers); HRMS (ESI): calcd for $C_{14}H_{19}N_2O_4$ $[M+H]^+$ 279.1345 found 279.1377.



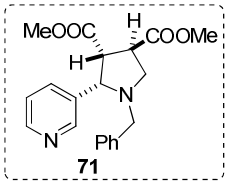
64&65

(3aR*,4R*,6aS*)-5-Benzyl-2-phenyl-4-(pyridin-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione **(69)**: Following the general procedure described above**69** was obtained after purification by silica column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (134 mg, 70%), mp: 70-72 ^{o}C; FT-IR (KBr): 2981, 2811, 1713, 1496, 1183, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, 1H, J = 1.9 Hz), 8.59 (dd, 1H, J_1 = 4.8, J_2 = 1.5 Hz), 7.73-7.70 (m, 1H), 7.48-7.19 (m, 11H), 3.98 (d, 1H, J = 5.5 Hz), 3.66 (d, 1H, J = 13.3 Hz), 3.61-3.55 (m, 1H), 3.45-3.39 (m, 2H), 3.22 (d, 1H, J = 13.3 Hz), 2.74 (dd, 1H, J_1 = 10.0, J_2 = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 176.2, 149.7, 149.5, 137.2, 135.7, 134.5, 131.6, 129.3, 128.8, 128.6, 128.4, 127.6, 126.4, 123.8, 68.2, 55.9, 54.4, 53.0, 43.8; HRMS (ESI): calcd for $C_{24}H_{22}O_2N_3$ $[M+H]^+$ 384.1706 found 384.1698.



69

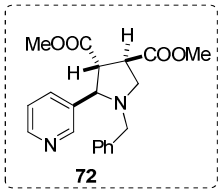
(2S*,3R*,4R*)-Dimethyl 1-benzyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate **(71)**: Following the general procedure described above**71** was obtained after purification by silica column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (138 mg, 39%), mp: 67-69 ^{o}C; FT-IR (KBr):



71

2924, 1735, 1435, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, 1H, J = 1.8 Hz), 8.52 (dd, 1H, J_1 = 4.8, J_2 = 1.8 Hz), 7.80-7.77 (m, 1H), 7.29-7.22 (m, 6H), 4.00 (d, 1H, J = 10.0 Hz), 3.77 (d, 1H, J = 13.2 Hz), 3.73 (dd, 1H, J_1 = 7.7, J_2 = 2.5 Hz), 3.68 (d, 1H, J = 6.2 Hz), 3.66 (s, 3H), 3.43 (dd, 1H, J_1 = 9.0, J_2 = 7.3 Hz), 3.16 (d, 1H, J = 13.2 Hz), 3.12 (s, 3H), 2.45 (dd, 1H, J_1 = 10.0, J_2 = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.7, 150.4, 149.4, 137.6, 135.8, 134.5, 128.6, 128.4, 127.3, 123.3, 67.8, 57.3, 55.0, 52.2, 51.9, 51.6, 44.2; HRMS (ESI): calcd for $C_{20}H_{23}O_4N_2$ $[M+H]^+$ 355.1658 found 355.1646.

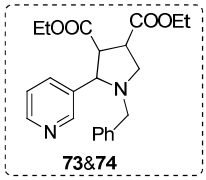
***(2R*,3R*,4R*)-Dimethyl 1-benzyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate* (72)**:



72

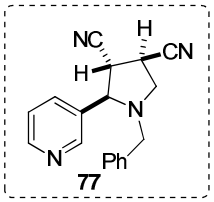
Following the general procedure described above**72** was obtained after purification by silica column chromatography (EtOAc:Hexane = 70:30); as a colorless viscous liquid (92 mg, 26%), FT-IR (DCM): 2953, 1735, 1435, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 1H, J = 1.6 Hz), 8.55 (dd, 1H, J_1 = 4.7, J_2 = 1.4 Hz), 7.92-7.89 (m, 1H), 7.33-7.19 (m, 6H), 3.72-3.64 (m, 2H), 3.71 (s, 3H), 3.65 (s, 3H), 3.48 (dd, 1H, J_1 = 8.5, J_2 = 5.4 Hz), 3.39 (t, 1H, J = 2.1 Hz), 3.37 (br. s, 1H), 3.10 (d, 1H, J = 13.4 Hz), 2.63 (dd, 1H, J_1 = 9.9, J_2 = 9.4 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 173.0, 150.0, 149.5, 137.9, 136.4, 135.5, 128.3, 127.2, 123.9, 69.6, 56.7, 55.3, 54.5, 52.5, 52.3, 44.7; HRMS (ESI): calcd for $C_{20}H_{23}N_2O_4$ $[M+H]^+$ 355.1658 found 355.1652.

***Diethyl 1-benzyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarboxylate* (73/74):** Following the general procedure described above **73/74** (mixture of isomers) was obtained after purification by silica column chromatography (EtOAc:Hexane = 70:30); as a colorless viscous liquid (344 mg, 90%), FT-IR (DCM):2981, 1731, 1372, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 1H, J = 1.8 Hz), 8.53 (dd, 1H, J_1 = 4.8, J_2 = 1.6 Hz), 7.95-7.81 (m, 1H), 7.39-7.24 (m, 6H), 4.26-4.02 (m, 3H), 3.84-3.64 (m, 3H), 3.52-3.36 (m, 2H), 3.18 (d, 1H, J = 13.4 Hz), 2.46 (dd, 1H, J_1 = 10.1, J_2 = 9.2 Hz), 1.27-1.18 (m, 4H), 0.79 (t, 3H, J = 7.1 Hz) (The ^1H NMR is given here for major isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 172.6, 172.5, 171.3, 150.5, 150.1, 149.4, 149.3, 138.1, 137.8, 136.5, 136.0, 135.5, 134.8, 128.6, 128.4, 128.3, 128.2, 127.3, 127.1, 123.8, 123.3, 69.8, 67.8, 61.2, 61.1, 61.0, 60.8, 57.3, 56.6, 55.3, 55.1, 54.6, 51.8, 44.8, 44.4, 14.2, 14.1, 13.6 (The ^{13}C NMR is given here for mixture of isomers); HRMS (ESI): calcd for $C_{22}H_{27}N_2O_4$ $[M+H]^+$ 383.1965 found 383.1969.



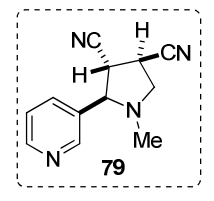
73&74

(2R*,3R*,4R*)-1-Benzyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarbonitrile **(77)**: Following the general procedure described above**77** was obtained after purification by silica column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (173 mg, 54%) mp: 130-132 ^{o}C; FT-IR (KBr): 2929, 2820, 2364, 2247, 1430, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, 1H, J = 1.5 Hz), 8.70-8.69 (m, 1H), 7.95-7.92 (m, 1H), 7.45 (dd, 1H, J_1 = 7.8, J_2= 4.8 Hz), 7.37-7.22 (m, 3H), 7.24-7.22 (m, 2H), 3.85 (d, 1H, J = 13.6 Hz), 3.74 (d, 1H, J = 8.6 Hz), 3.46 (dd, 1H, J_1 = 10.2, J_2 = 2.0 Hz), 3.42-3.38 (m, 1H), 3.25 (d, 1H, J = 13.6 Hz), 3.22 (dd, 1H, J_1 = 8.6, J_2 = 5.6 Hz), 2.82 (dd, 1H, J_1 = 10.2, J_2 = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 149.4, 135.8, 135.1, 132.4, 128.8, 128.4, 127.9, 124.5, 119.2, 117.2, 69.8, 55.8, 55.1, 42.0, 30.9; HRMS (ESI): calcd for $C_{18}H_{17}N_4$ $[M+H]^+$ 289.1447 found 289.1445.



77

(2S*,3R*,4R*)-1-Methyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarbonitrile **(78)**: Following the general procedure described above**78** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a colorless solid (66 mg, 31%), mp: 122-124 ^{o}C; FT-IR (KBr): 2925, 2853, 2364, 2245, 1443, 1182 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (dd, 1H, J_1 = 4.8, J_2 = 2.0 Hz), 8.59 (d, 1H, J = 2.0 Hz), 7.81-7.78 (m, 1H), 7.38 (dd, 1H, J_1 = 7.8, J_2 = 4.8 Hz), 3.71-3.67 (m, 2H), 3.62 (dd, 1H, J_1 = 7.6, J_2 = 5.4 Hz), 3.50-3.45 (m, 1H), 2.66 (t, 1H, J = 9.3 Hz), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 149.9, 136.0, 131.0, 123.9, 118.1, 117.1, 68.5, 58.2, 40.7, 39.1, 31.1; HRMS (ESI): calcd for $C_{12}H_{13}N_4$ $[M+H]^+$ 213.1140 found 213.1134.



78

(2R*,3R*,4R*)-1-Methyl-2-(pyridin-3-yl)pyrrolidine-3,4-dicarbonitrile **(79):**Following the general procedure described above**79** was obtained after purification by silica column chromatography (EtOAc:Hexane = 100:0); as a colorless solid (125 mg, 59%), mp: 124-126 ^{o}C; FT-IR (KBr): 2954, 2850, 2247, 1432, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.56 (m, 2H), 7.71-7.68 (m, 1H), 7.30 (dd, 1H, J_1 = 7.8, J_2 = 4.8 Hz), 3.50 (dd, 1H, J_1 = 10.0, J_2 = 1.7 Hz), 3.36-3.31 (m, 2H), 3.06 (dd, 1H, J_1 = 8.7, J_2 = 5.4 Hz), 2.78 (dd, 1H, J_1 = 10.0, J_2 = 8.7 Hz), 2.14 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 150.9, 149.3, 135.0, 132.2, 124.3, 119.4, 117.3, 71.9, 58.4, 42.2, 38.8, 31.0; HRMS (ESI): calcd for $C_{12}H_{13}N_4$ $[M+H]^+$ 213.1140 found 213.1133.

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(60) The ^{1}H /^{13}C NMR spectral patterns of the compounds **58a** and **58b** were similar.Likewise,the ^{1}H /^{13}C NMR spectral patterns of the compounds **59a** and **59b** were similar. On the basis of the X-ray structure of the nicotine analogue **71** (Figure 7) and the similarity in the ^{1}H /^{13}C NMR spectral patterns of the respective compounds **58a** and **58b**, with the compounds **71** and **73**, the stereochemistry of the products **58a,b** and **59a,b** was assigned.

(61) Generally, in the major compounds **59a**, **61** and **63**, it has been noticed that the stereochemistry is *trans* with respect to the aryl and ethyl ester moieties (1,2-positions) which may be due to steric interactions. Contrary to this observation, we obtained the compounds **59b** and **72** as the minor isomers having *trans* stereochemistry with respect to the aryl and methyl ester moieties (while using dimethyl fumarate) and at this stage, an exact reason is not clear to us for this.

Chapter 2: Highly Regio- and diastereoselective construction of densely functionalized spirooxindolo-pyrrolidine / pyrrolizidine, spiro-1,3-indandionolylpyrrolidine and spiroacenaphthylenolyl- pyrrolidine / pyrrolizidine derivatives.

Introduction.

Multicomponent reactions (MCRs) provides an easy access to combinatorial libraries of compounds having interesting physical, chemical or biological properties.[1] The stereoselective construction of multiple stereocenters containing molecule in a single step reaction would be an interesting and step-economical method.

The regio- and stereoselective 1,3-dipolar cycloaddition[1c,2] reaction is one of the powerful methods for the construction of naturally occurring and synthetic five-membered heterocyclic compounds. Among the diverse 1,3-dipoles engaged for the synthesis of five-membered heterocyclic compounds *via* the 1,3-dipolar cycloaddition reactions, the azomethine ylides (as a 1,3-dipoles)[2b,3] received special attention due to the following reasons; (a) the cycloaddition reaction of azomethine ylides with electron-deficient olefins is an stupendous method for the regio- and stereoselective preparation of pyrrolidine-based nitrogen heterocycles, which are often found in natural alkaloids and subunits of bioactive alkaloids, and (b) the construction of up to four new stereocenters in a pyrrolidine ring can be accomplished with high degree of regio- and stereocontrol. Although numerous methods are known for the generation of azomethine ylides, two of the azomethine cycloaddition methods are very popularly studied; (a) the construction of metallo-1,3-dipoles (azomethine ylides) from *N*-benzylideneiminoglycinates and their cycloaddition with electron-deficient olefins (b) the generation of azomethine ylides in multicomponent reactions *via* the decarboxylative reactions of 1,2-dicarbonyl compounds and α-amino acids with electron-deficient olefins.

Spiro compounds have significantly attracted the attention of organic- and medicinal chemists due to their potential biological properties. Further, the stereoselective construction of the spiro unity of a given molecule considered as interesting and challenging task. Some of the important natural products possessing spiro linkage are shown in Figure 1.[4] Amongst the spiro compounds, naturally occurring spirooxindole alkaloids and synthetically derived spirooxindoles have attracted the attention towards synthetic, medicinal chemists and chemical biologists.[5,6] The

spirooxindole alkaloids were first isolated from plants of the *Apocynaceae* and *Rubiacae* families.[5] The oxindole and spirooxindole skeleton having a tetra-substituted carbon stereocenter at the 3-position found to be the core structural unit of a large family of bio-active natural / unnatural spirooxindole molecules (Figure 2).[6-10]

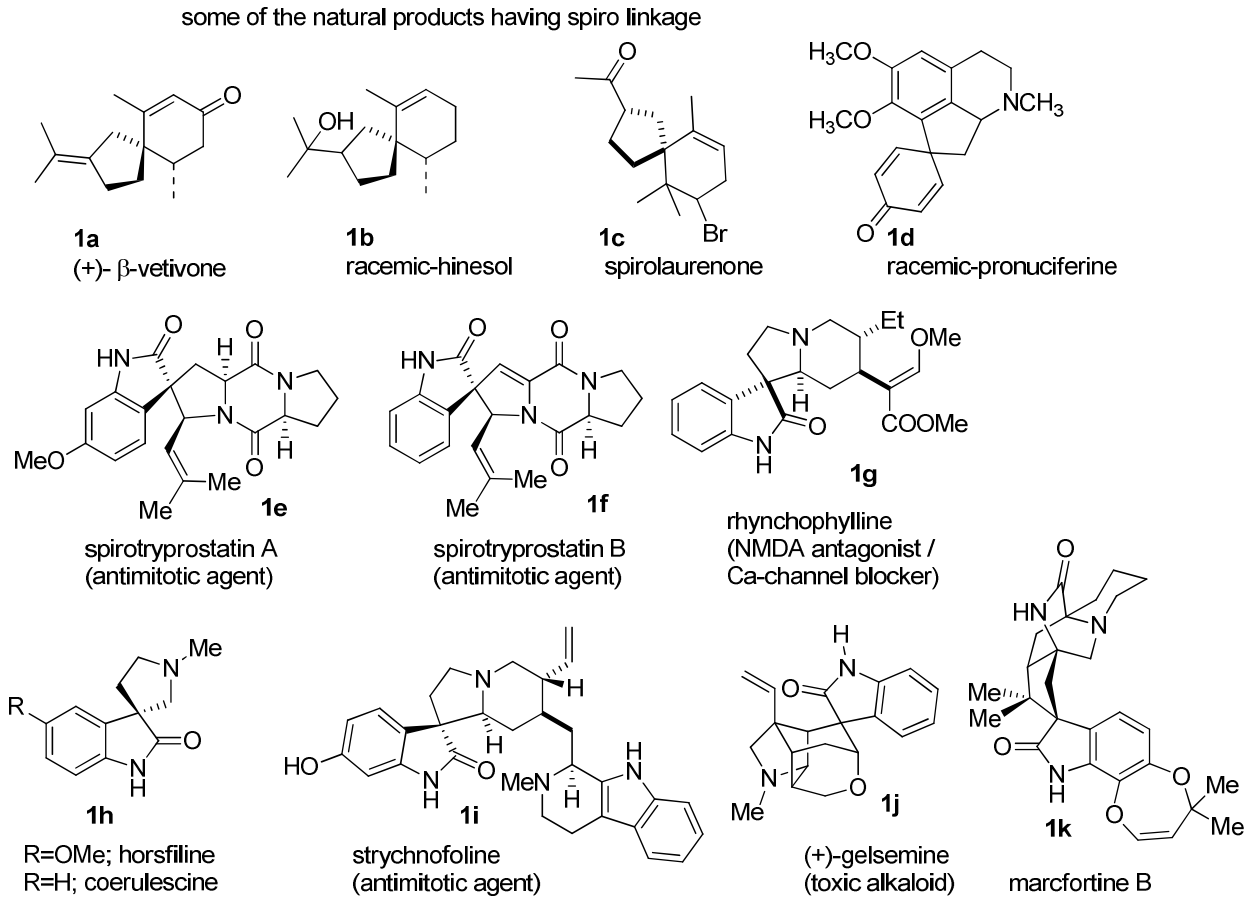


Figure 1. Spiro compounds and biologically active naturally occurring spirooxindole molecules.

For example, spirooxindoles spirotryprostatins A and B[7] isolated from fermentation broth of *Aspergillus fumigatus* were found to completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations in excess of 12.5 mgmL. Spirooxindole rhynchophylline found in certain *uncaria* species, especially *uncaria rhynchophylla* and *uncaria tomentosa*. Spirooxindole rhynchophylline was useful in the treatment of cardiovascular and central nervous system diseases.[8] Spirooxindole coerulescine was isolated from the *phalaris coerulescens* species, such as *blue canary grass,* found to show analgesic effect. Spirooxindole strychnofoline isolated from

the leaves of *strychnos usambarensis* found to exhibit antimitotic activity against cultures of mouse melanoma and Ehrlich tumor cells.[10]

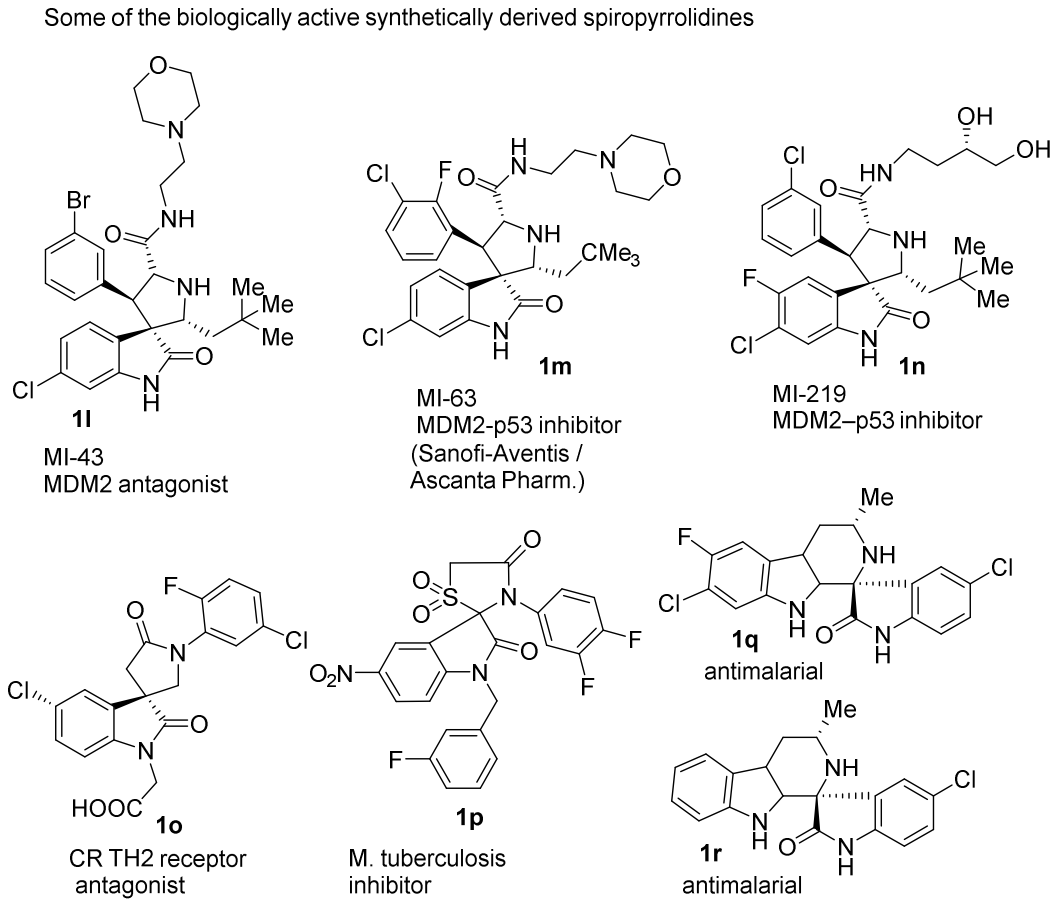


Figure 2. Synthetically derived biologically active spirooxindole molecules.

Due to their bountiful applications of naturally occurring spirooxindole alkaloids in chemical biology, organic synthesis and medicinal chemistry research, synthetic and medicinal chemists are inspired to design and synthesize libraries of new classes spirooxindole scaffolds, which are analogues to naturally occurring spirooxindole molecules (Figure 2).[5,6d,11,12] Several synthetic spirooxindoles display a wide range of biological activities. For example, Wang *et al.*[13] revealed MI-43 as inhibitor of the MDM2-p53 interaction and their study suggested that p53 activation by a potent and specific spirooxindole MDM2 antagonist and this result found to be a potential therapeutic approach for the treatment of colon cancer. Gal *et al.*[14] reported spirooxindole SR 121463A as a highly potent and selective nonpeptide vasopressin V_2 receptor antagonist. Waldmann *et al.*[15] achieved the synthesis of indolin-2-on-3-spirothiazolidinones and they act as

potent and selective inhibitors of the *mycobacterium tuberculosis* protein tyrosine phosphatase B. Yeung *et al*.[16] reported the synthesis of spiroindolones and these compounds were found to be effective in the treatment of malaria.

Furthermore, several synthetically derived spirooxindolo-pyrrolidine / pyrrolizidine scaffolds were found to act as poliovirus, aldose reductase, rhinovirus 3C-proteinase inhibitors.[17] Apart from the potential biological activities exhibited by the synthetically derived spirooxindole scaffolds, various spirooxindole scaffolds act as potential synthetic intermediates to synthesize spirooxindole natural products.[5,6d,11-16]

The promising biological activities showed by natural and unnatural spirooxindole scaffolds have raised the interests of synthetic and medicinal chemists. Notably, in the past few years, there have been rapid developments in the research area pertaining to the stereoselective synthesis and application of spirooxindole-based molecules. Accordingly, a wide range of synthetic strategies were developed for assembling architecturally complex spirooxindole molecules.[6d] Predominantly, the cycloaddition method has served as one of the important methods for the stereoselective construction of spirooxindole frameworks. Amongst the cycloaddition routes, the multicomponent azomethine ylide 1,3-dipolar cycloaddition reactions[6d,11e,18,19] represent the most attractive strategy to generate spirooxindole moieties.[6d] Accordingly, in the context of finding new lead molecules with biological activities and for finding potential drug candidates there have been continuous efforts for preparing new libraries of multi substituted spiro-oxindoles / pyrrolizidines / pyrrolidines appended with various medicinally important functional groups and sub-units, such as,cyano, aryl- / heteroaryl moieties *via* the multicomponent reaction-based 1,3-dipolar cycloadditions of azomethine ylides with suitable dipolarophiles and other methods.[6d,11e,18-21] Especially, some of the C-3-indole moiety substituted pyrrolidines (e.g., eletriptan) and spiro-oxindoles / pyrrolizidines / pyrrolidines appended with medicinally important and sub-units, such as,indole moieties were found to be important class of molecules with promising biological activities (Figure 3). It was apparent that a literature survey revealed that there exist few reports dealing on the cycloadditions of azomethine ylides with nitroolefin-based dipolarophiles as the route for synthesis of C-3-indole moiety substituted pyrrolidines,[20] apart from cycloaddition, other mehods also provide an access to synthesize C-3-indole moiety substituted pyrrolidines.[21] However, there exist only some rare reports dealing on the azomethine ylide cycloaddition-based construction of spiro-oxindoles /

pyrrolizidines / pyrrolidines connected with an indolecarbonyl unit.[41] Further a literature survey revealed that, there exist no reports on the azomethine ylide cycloaddition-based synthesis of spiro-oxindole- / pyrrolizidine- / pyrrolidine scaffolds directly appended with the indolyl or pyrrolyl moieties.[5,6,21]

In analogy to the importance of synthetically derived spirooxindole scaffolds,[5,6,21] several spiroacenaphthylenolyl-pyrrolidines / pyrrolizidines[22a,b] and spiro-1,3-indandionolyl-pyrrolidines / pyrrolizidines[22c-f] are also considered as distinguished heterocyclic compounds with potential biological activities[6] (Figure 3).

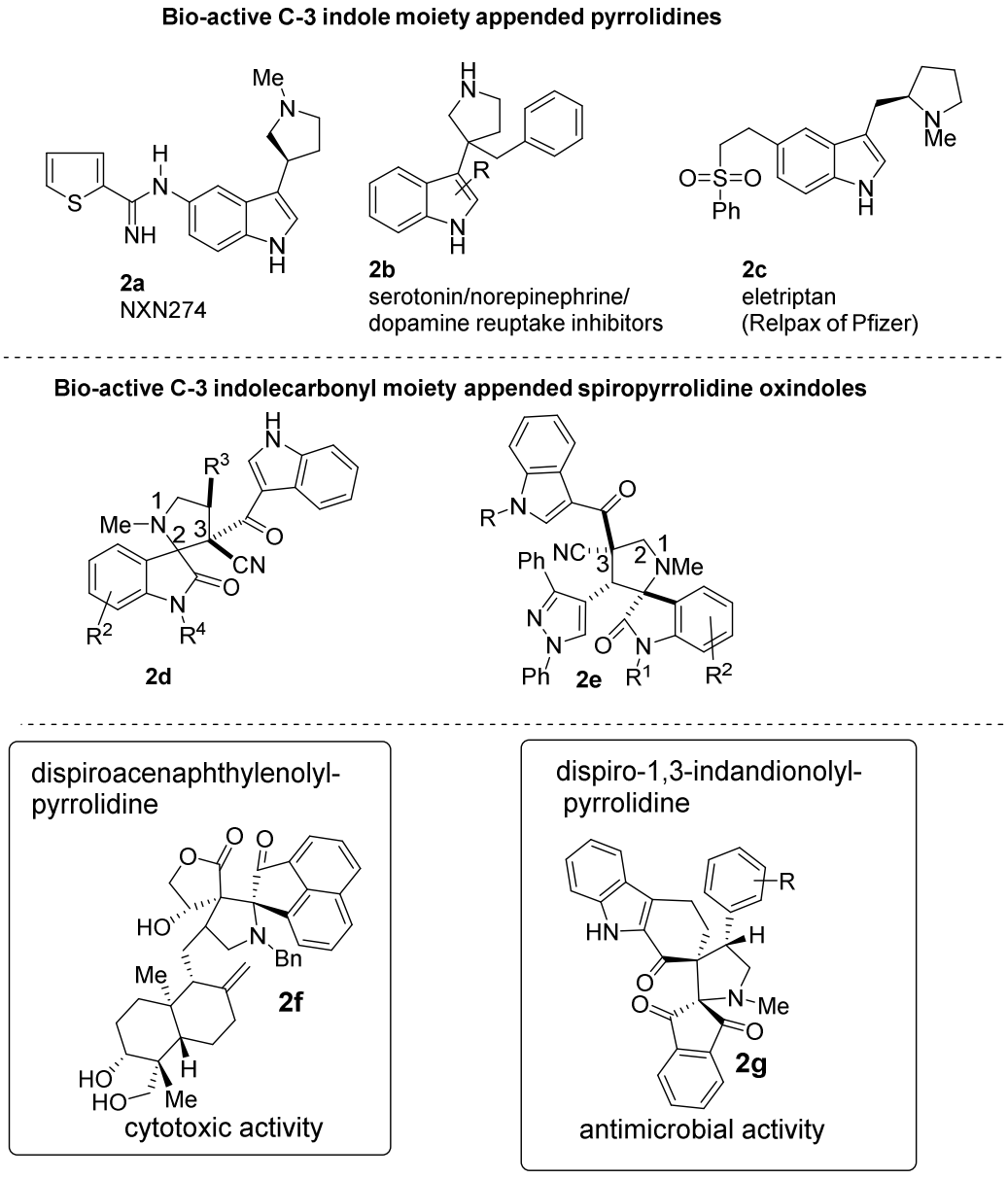


Figure 3. Bio-active indole moieties containing pyrrolidines, spiropyrrolidines, spiroacenaphthylenolylpyrrolidines as well as spiro-1,3-indandionolylpyrrolidines.

Representative papers dealing on the spirooxindole natural product-inspired synthesis of complex spiro-oxindole and spiro-pyrrolidine/pyrrolizidine scaffolds and biologically activities.

Given that the spiro-oxindole / pyrrolizidine / pyrrolidine frameworks considered as privileged frameworks found in a variety of natural products, synthetically derived biologically active compounds and drug molecules; several functionalized spiro-oxindole / pyrrolizidine / pyrrolidine frameworks and spiroacenaphthylenolyl-pyrrolidines / pyrrolizidines and spiro-1,3-indandionolyl-pyrrolidines / pyrrolizidines were prepared in view of enriching the library of spiro-oxindole and spiropyrrolidine frameworks. Accordingly, several methods were also developed for preparing spiro-oxindole / pyrrolizidine / pyrrolidine frameworks, which includes; cycloaddition reactions, organocatalyzed transformations, metal-catalyzed cyclization reaction, multicomponent reactions, etc. Particularly, the cycloaddition protocol considered as one of the important methods for stereoselective construction of spirooxindole frameworks. Amongst the cycloaddition routes, the multicomponent azomethine ylide cycloaddition reactions[6d,11e,18,19] found to be the robust method to generate spirooxindole moieties.[5,6]

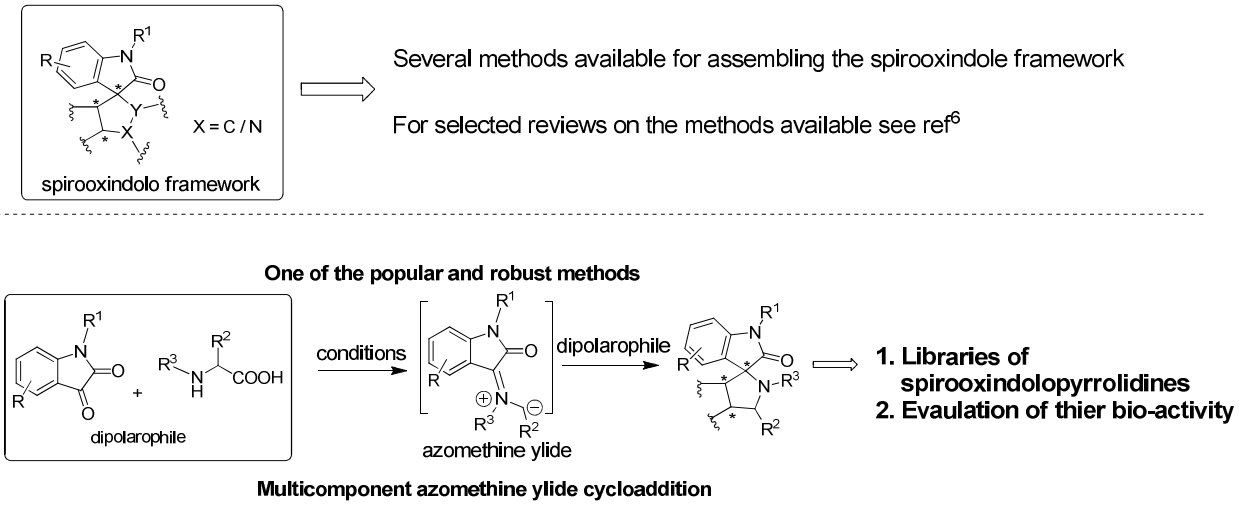
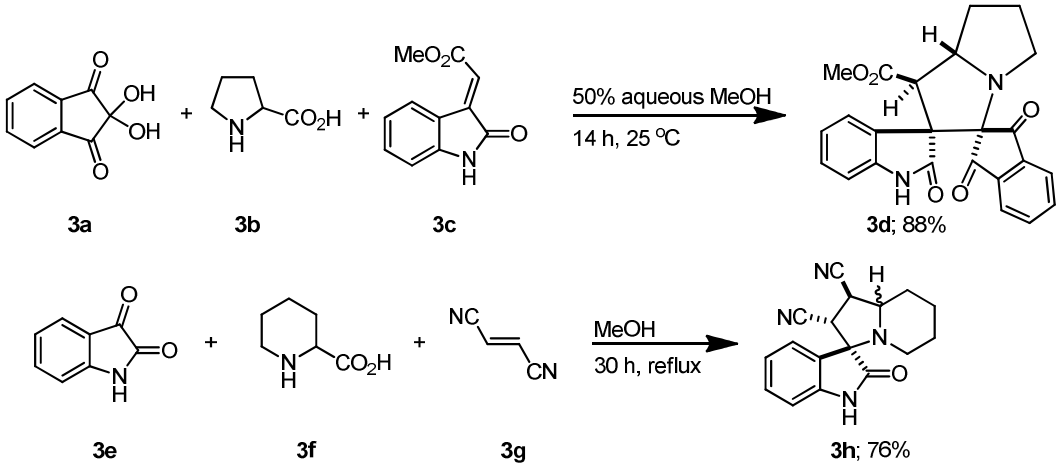


Figure 4. Preparation of spirooxindole skeleton *via* azomethine ylide cycloaddition.

In the following section some of the literature reports dealing on the synthesis of functionalized spiro-oxindole and spiropyrrolidine frameworks involving the multicomponent 1,3-dipolar cycloadditions of azomethine ylides are represented.

Grigg's group[23a] was one of the first groups successfully synthesize spiro[pyrrolidine-3,3-oxindole] framework *via* the generation of azomethine ylide from the decarboxylative reactions of 1,2-dicarbonyl compound and α-amino acid followed by the cycloaddition with electron-deficient olefin. The reaction of ninhydrin **3a** and proline **3b** with oxindole **3c** in 50% aqueous methanol at 25 ^{o}C for 14 h yielded the spiro[pyrrolidine-3,3-oxindole] framework **3d** in 88% yield with high degree of stereocontrol (Scheme 1). Similarly, the reaction of isatin **3e** and pipecolic acid **3f** with fumaronitrile **3g** in refluxing methanol gave the spiro[pyrrolidine-3,3-oxindole] framework **3h** in 76% yield (Scheme 1). After the report by Grigg *et al.* various other research groups achieved the synthesis of spiro[pyrrolidine-3,'3-oxindole] skeletons with interesting medicinal properties *via* the 1,3-dipolar cycloaddition of azomethine ylide with different olefin dipolarophiles.

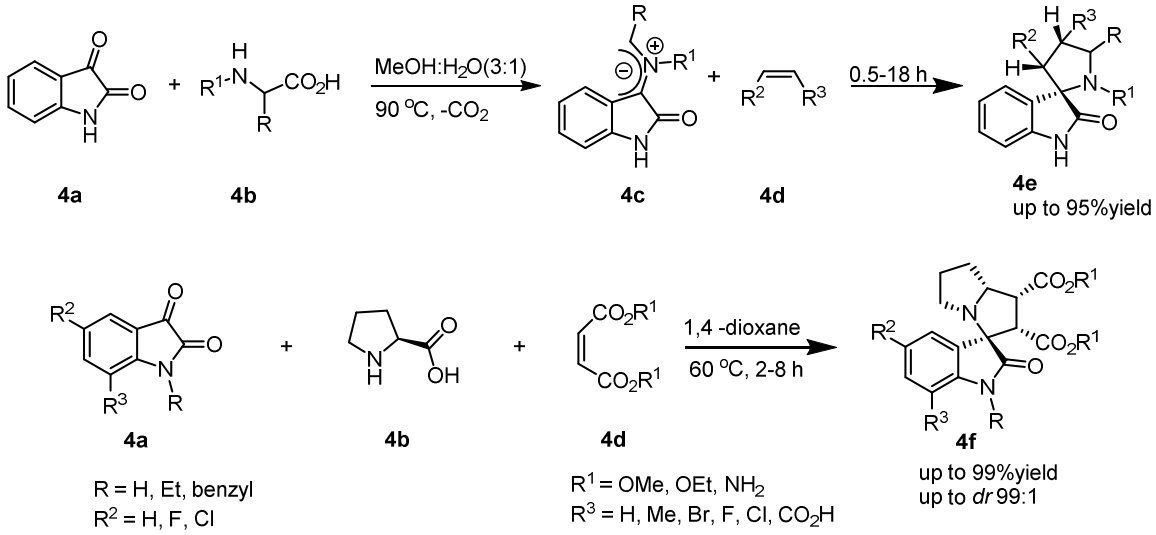


Scheme 1. Synthesis of spirooxindoles **3d** and **3h** *via* the azomethine cycloaddition reaction.

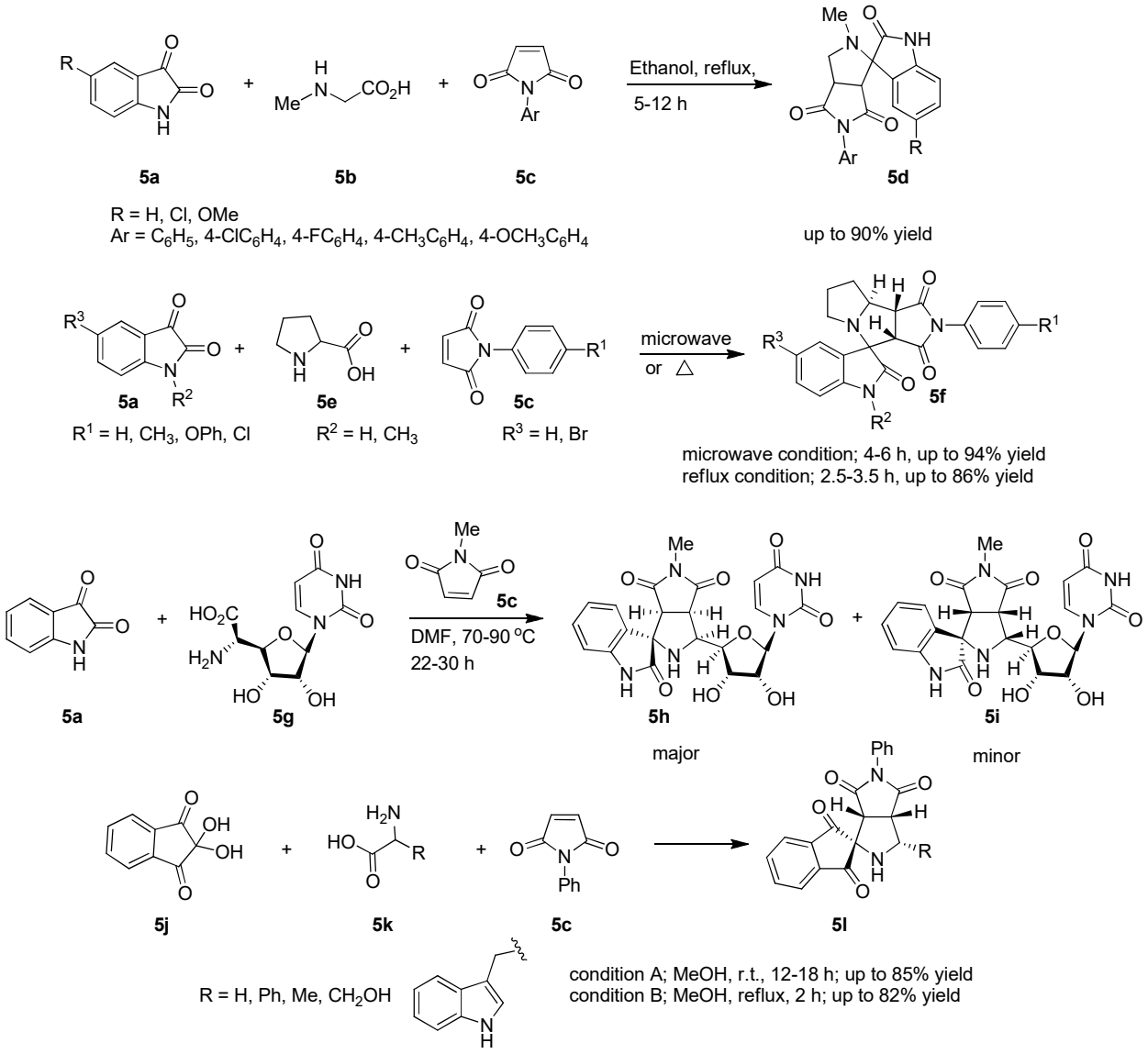
Bergman and co-workers[23b] reported the efficient synthesis of spiro[pyrrolidine-3,3'-oxindole] **4e** from the cycloaddition reaction of azomethine ylide **4c** generated from isatin **4a** and variety of amino acids **4b** with activated dipolarophiles **4d** (Scheme 2). Kang *et al.*[24] reported the one-pot stereoselective synthesis of spiropyrrolizidine oxindoles **4f** from the cycloaddition reaction of azomethine ylide generated from the decarboxylative reaction of 1,2-dicarbonyl compound and α-amino acid with maleates and maleimides **4d** as dipolarophiles (Scheme 2).

Girgis and Stawinski[25a] reported the generation of azomethine ylide in one pot involving the decarboxylative reaction of 1,2-dicarbonyl compound and α-amino acid **5b** followed by cycloaddition of azomethine ylide with 1-aryl-1*H*-pyrrole-2,5-diones (maleimides) **5c**, which gave various spirooxindole molecules **5d** (Scheme 3). Girgis and Stawinski[25a] revealed that one of the compound from the series of spirooxindole molecules **5d** exhibited anti-tumor activity against liver cancer HepG2 cell line. Lipson*et al.*[25b] alsoreported the synthesis of spirooxindoles **5d** (Scheme 3) *via* the generation of azomethine ylide from the decarboxylative reaction of 1,2-dicarbonyl compound and various α-amino acids followed by cycloaddition of azomethine ylide with maleimide **5c**. Azizian *et al.*[25c] reported the synthesis of spirooxindolopyrrolizidines **5f** (Scheme 3) involving the generation of azomethine ylide from decarboxylative reaction of 1,2-dicarbonyl compound and α-amino acid followed by cycloaddition with **5c** under thermal and microwave conditions.

Grigg *et al.*[25d] reported the synthesis of spirooxindole derivatives **5h** and **5i** (Scheme 3) involving the generation of azomethine ylide in one pot manner *via* the decarboxylative reaction of 1,2-dicarbonyl compound and α-amino acid followed by cycloaddition with **5c**. Grigg *et al*. also achieved[25e] the synthesis of spiro-1,3-indandionolylpyrrolidines **5l** involving the generation of azomethine ylide in the multicomponent reactionof 1,2-dicarbonyl compound and α-amino acid followed by cycloaddition with **5c** (Scheme 3).



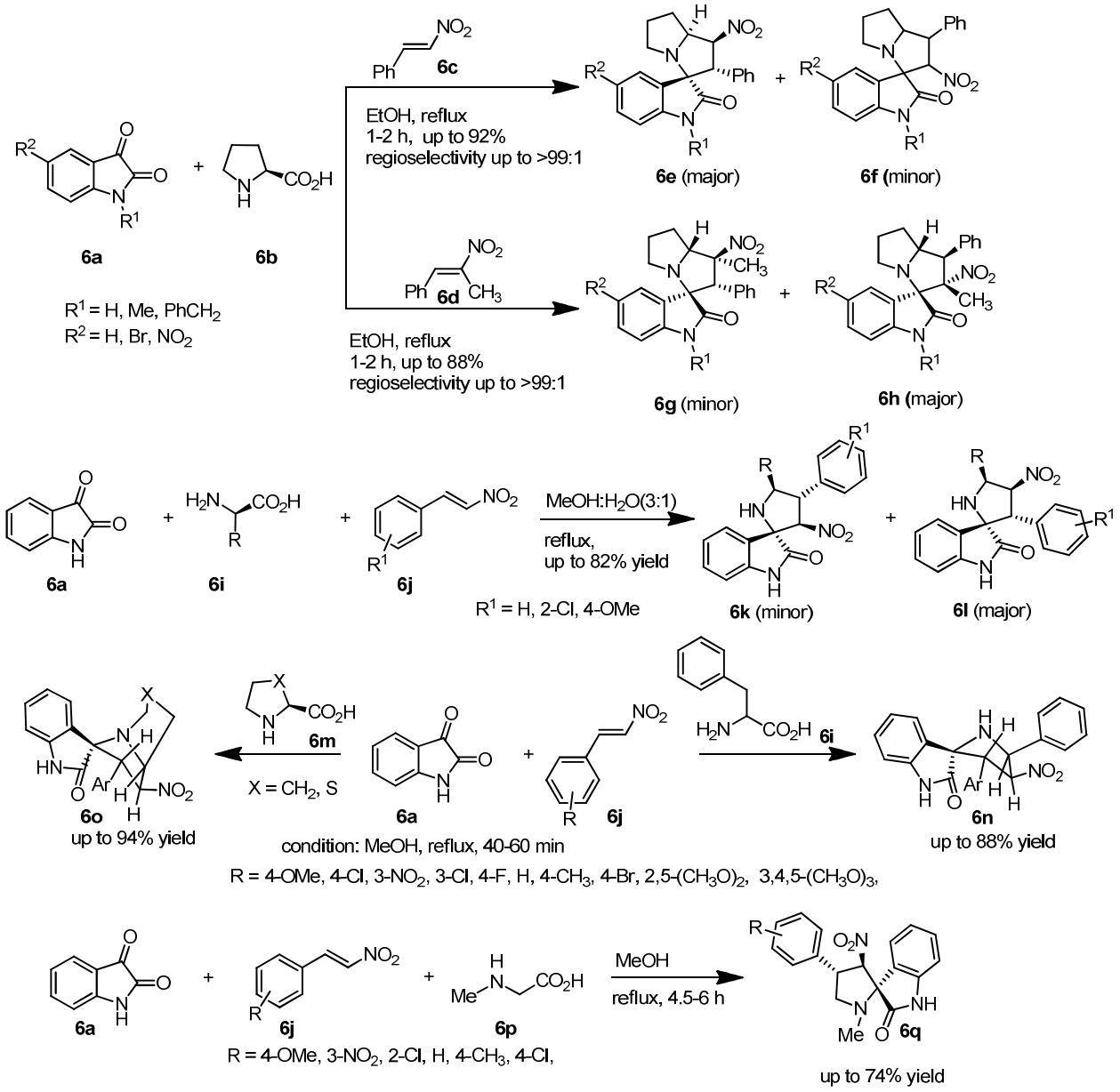
Scheme 2. Synthesis of spirooxindoles **4e**-**f** *via* the azomethine cycloaddition reaction.



Scheme 3. Synthesis of spirooxindoles **5d**, **5f**, **5h** and **5i** and spiro-1,3-indandionolylpyrrolidines **5l.**

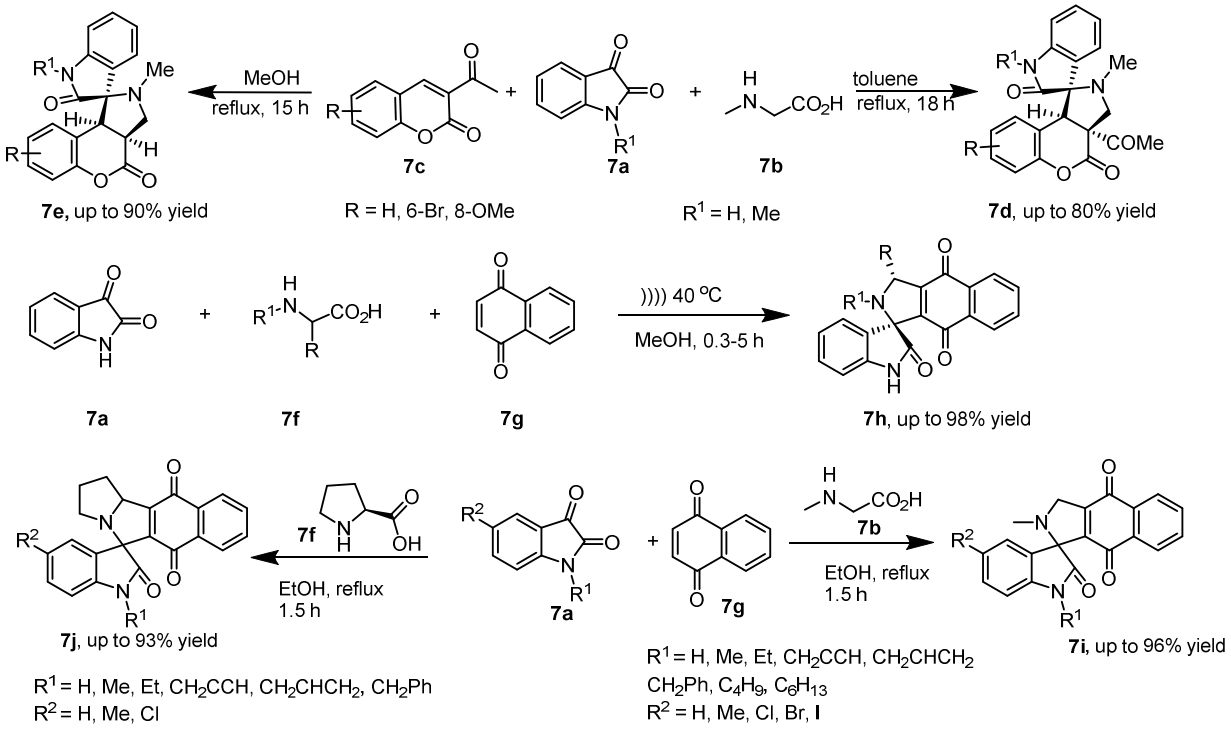
Sarrafi and co-workers[26a] reported the regio- and stereoselective synthesis of spirooxindoles **6e-h** involving the generation of azomethine ylide from the decarboxylative reaction of 1,2-dicarbonyl compound **6a** and α-amino acid **6b** followed by cycloaddition with (*E*)-β-nitrostyrene **6c** and (*E*)-1-phenyl-2-nitropropene **6d** (Scheme 4). While the cycloaddition of azomethine ylide with *β*-nitrostyrene **6c** gave the spirooxindoles **6e** (major regioisomer) and **6f** (minor regioisomer); in the cycloaddition of azomethine ylide with *β*-nitrostyrene **6d** reversal of the regioselectivity was observed and the reaction gave the spirooxindoles **6g** (minor regioisomer) and **6h** (major

regioisomer). In a related study, Chen *et al.*[26b] achieved the regioselective synthesis of spirooxindoles **6k** (minor regioisomer) and **6l** (major regioisomer) involving the generation of azomethine ylides in multicomponent reactions *via* the decarboxylative reaction of 1,2-dicarbonyl compound **6a** and various α-amino acids **6i** followed by cycloaddition with **6j** (Scheme 4).



Scheme 4. Regioselective synthesis of spirooxindolo-pyrrolidine, pyrrolizine and pyrrolothiazole scaffolds **6e**-**h**, **6k**-**l**, **6n**-**o** and **6q** containing nitro moiety *via* the azomethine cycloaddition reaction.

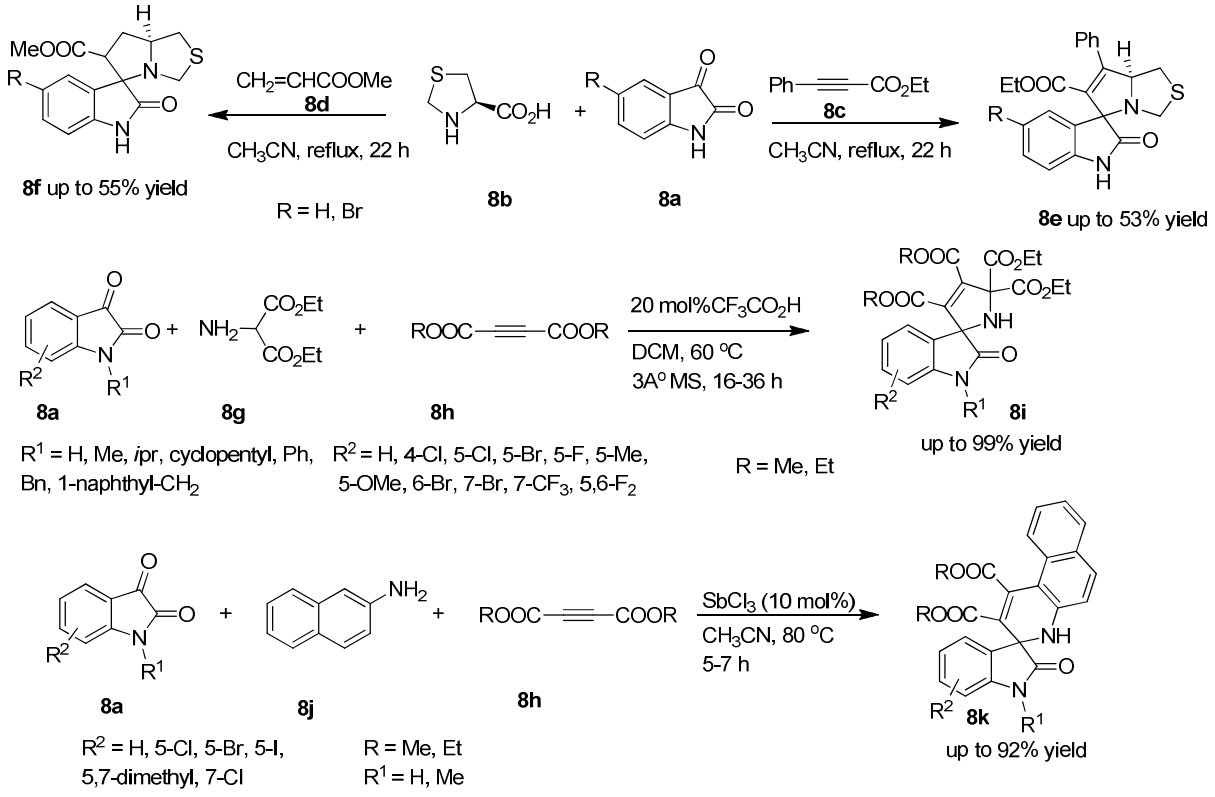
Perumal *et al.*[26c] reported the synthesis of a series of spirooxindolo-pyrrolidine, pyrrolizine and pyrrolothiazole scaffolds **6n** and **6o** involving the generation of azomethine ylides in one pot reactions *via* the decarboxylative reaction of 1,2-dicarbonyl compound and various α-amino acids followed by cycloaddition with **6j**.(Scheme 4). The compounds spirooxindolo-pyrrolidine, pyrrolizine and pyrrolothiazole scaffolds **6n** and **6o** showed *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB). Raghunathan *et al.*[26d] also reported the synthesis of a series of spirooxindolo-pyrrolidines **6q** involving the generation of azomethine ylide *via* the decarboxylative reaction of 1,2-dicarbonyl compound and α-amino acid followed by cycloaddition with **6j** (Scheme 4).



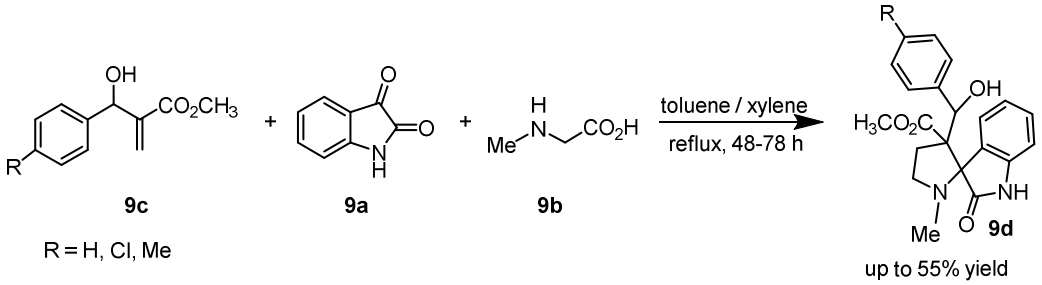
Scheme 5. Synthesis of spirooxindoles **7d-e**, **7h** and **7i-j** *via* the azomethine cycloaddition reaction.

Ghandi and co-workers[27a] reported the synthesis of spirooxindoles **7d** by using 3-acetylcoumarins **7c** as dipolarophiles in azomethine ylide cycloaddition reaction. Notably, the azomethine cycloaddition reaction in MeOH gave the deacetylated product **7e** (Scheme 5). Ji *et al.*[27b] reported the synthesis of 3-spiro[pyrrolidino-oxindoles] **7h** involving generation of

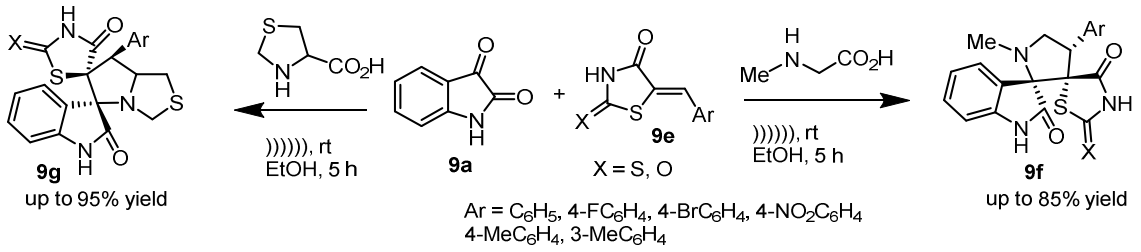
azomethine ylide *via* the decarboxylative reaction of 1,2-dicarbonyl compound and various α-amino acid followed by cycloaddition with **7g** in methanol at 40 ^{o}C under ultrasonic irradiation (Scheme 5). In a related study, Perumal *et al.*[27c] achieved the synthesis of a series of spirooxindoles **7i** and **7j** by using **7g** as a dipolarophile. The synthesized spirooxindoles **7i** and **7j** were tested for their antimicrobial activity (Scheme 5).



Scheme 6. Construction of spirooxindoles **8e**, **8f**, **8i** and **8k** *via* the azomethine ylide 1,3 dipolar cycloaddition reaction.



Scheme 7. Synthesis of spirooxindoles **9d** *via* the azomethine cycloaddition reaction.



Scheme 8. Synthesis of spirooxindoles **9f** and **9g** *via* the [3+2] dipolar cycloaddition reaction.

Pardasani and co-workers[28a] revealed the synthesis of spirooxindoles **8e** and **8f** involving the generation of azomethine ylides from 1,2-dicarbonyl compounds and various α-amino acids followed by cycloaddition reactions with dipolarophiles **8c** and **8d** (Scheme 6). Furthermore, Shi *et al*.[28b] reported the cycloaddition of isatin derived azomethine ylide with electron deficient alkynes **8h** to give spirooxindole derivatives **8i**. The synthesized spirooxindole derivatives **8i** were found to exhibit promising cytotoxicity to MCF-7 cells. Maiti *et al*. [28c] reported the $SbCl_3$–catalyzed one-pot synthesis of benzoquinolinespirooxindoles **8k** (Scheme 6).

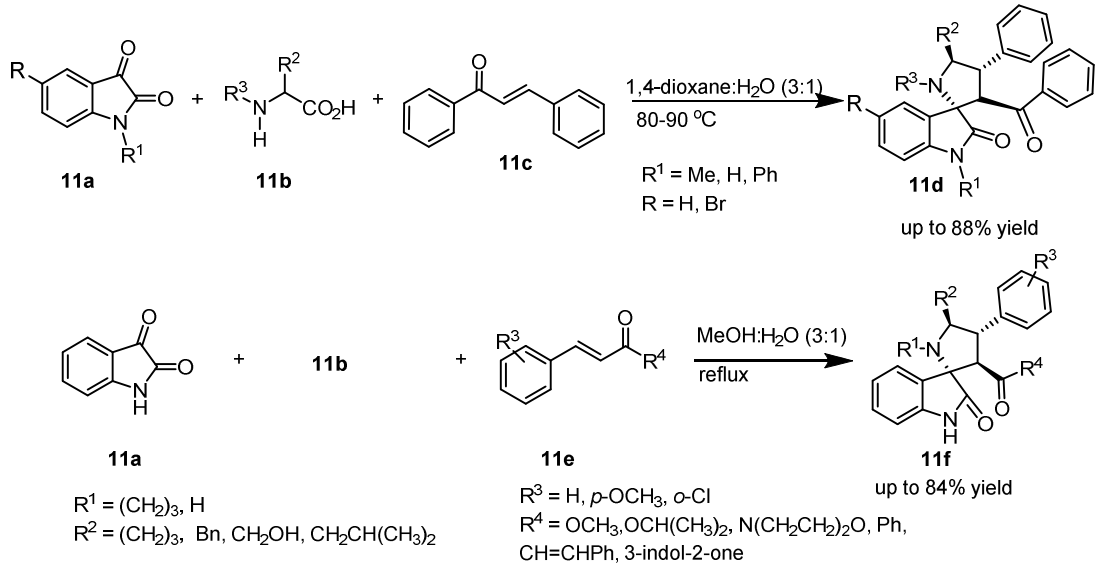
Raghunathan *et.al*[29] reported the synthesis of spiropyrrolidines **9d** by using Baylis-Hillman adducts **9c** as a dipolarophiles in the multicomponent azomethine ylide cycloaddition reaction (Scheme 7). Shi and co-workers[30] reported the one pot synthesis of dispirooxindolothiazolidine derivatives **9f** and **9g** by using **9e** as a dipolarophile in the azomethine ylide cycloaddition reaction under ultrasonic irradiation without any catalyst (Scheme 8).

Fokas *et al*.[32a] prepared combinatorial library of spiro[pyrrolidine-2,3'-oxindoles) **11d** by using chalcones[31]**11c** as dipolarophiles in the multicomponent 1,3-dipolar azomethine ylide cycloaddition reaction (Scheme 9). Moreover, Hao *et al*. [32b] prepared a series of spiro[pyrrolidine-2,3'-oxindoles) **11f** (Scheme 9) and these compounds were found to exhibit antitumor activities on A549 and P388 cell lines.

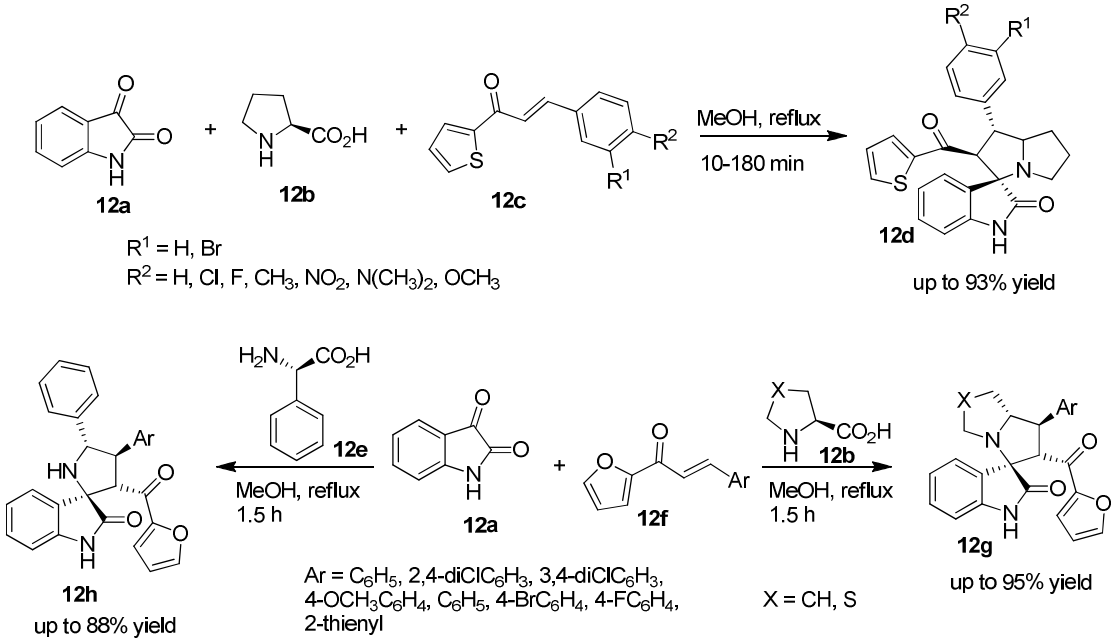
Thangamani[33a] prepared spirooxindolopyrrolizidines **12d** by using (*E*)-3-aryl-1-(thiophen-2-yl)prop-2-en-1-ones **12c** as a dipolarophile in the multicomponent azomethine ylide cycloaddition reaction (Scheme 10). The spirooxindolopyrrolizidines **12d** were screened for their antibacterial and antifungal activities against a range of microbial organisms.

Ouyang and He *et al.*[33b] prepared a series of functionalized spirooxindolo-pyrrolidines, pyrrolizidines, and pyrrolothiazoles **12g** and **12h***via* the multicomponent reactions (Scheme 10). Notably, the compounds **12g** and **12h** contain heteroaryl rings as substituents in the pyrrolizidine

ring (connected *via* a carbonyl linkage) and these compounds were tested for their antimicrobial activities and one of the compounds from the series **12g** and **12h** showed potential antimicrobial activity against drug-resistant bacteria.



Scheme 9. Synthesis of **11d** and **11f** *via* the azomethine cycloaddition reaction.

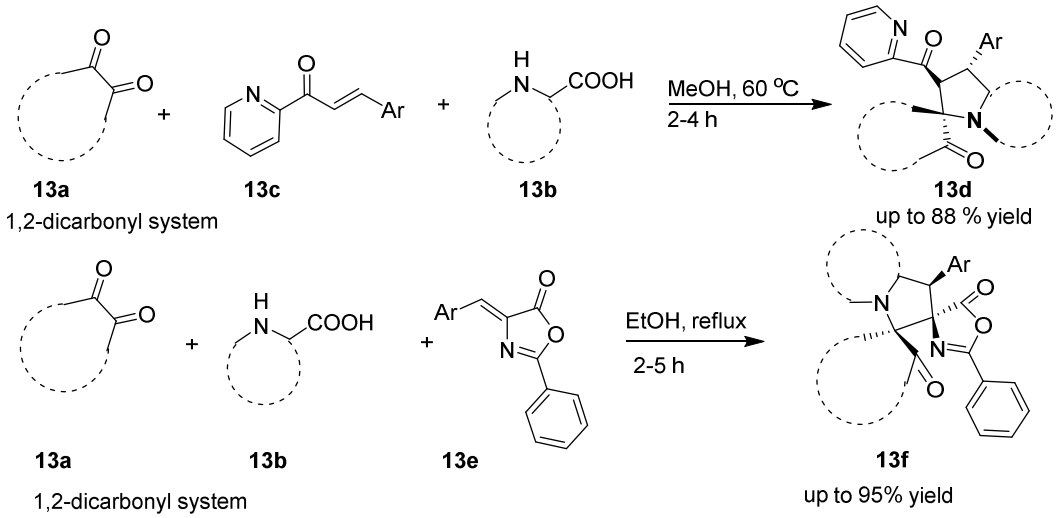


Scheme 10. Synthesis of spirooxindoles **12d 12g** and **12h** containing heteroaryl moieties in the pyrrolizidine ring.

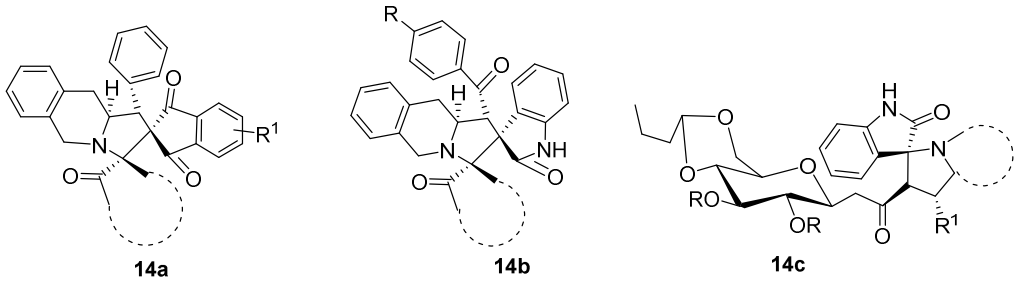
Zhu *et al.*[34a] reported a series of functionalized spirooxindole-pyrrolidine / pyrrolizidine / pyrrolothiazole molecules **13d** containing heteroaryl moieties in the pyrrolidine/pyrrolizidine ring through the 1,3-dipolar cycloaddition of azomethine ylides generated from isatin or acenaphthenequinone **13a** and α-amino acids with 3-aryl-1-(pyridin-2-yl)-prop-2-en-1-one **13c** as a dipolarophile (Scheme 11).

Shi *et al.*[34b] reported the regioselective synthesis of functionalized dispiropyrrolizidine molecules **13f** by using (*Z*)-4-benzylidene-2-phenyloxazol-5(4H)-ones **13e** as a dipolarophiles in the 1,3-dipolar cycloaddition reactions and the compounds **13f** were tested for their antiproliferative properties against cancer cells (Scheme 11).

Raghunathan *et al.*[35a] achieved the regioselective synthesis of novel dispiroheterocyclic frameworks **14a** and **14b** *via* the TiO_2-silica-catalyzed azomethine ylide cycloaddition. Das and co-workers[35b] revealed the synthesis of sugar based spirooxindole-pyrrolidine and pyrrolizidines **14c** by using α-β- unsaturated β-C-glycosidic ketone as a dipolarophile in the azomethine ylide cycloaddition reaction (Scheme 12).

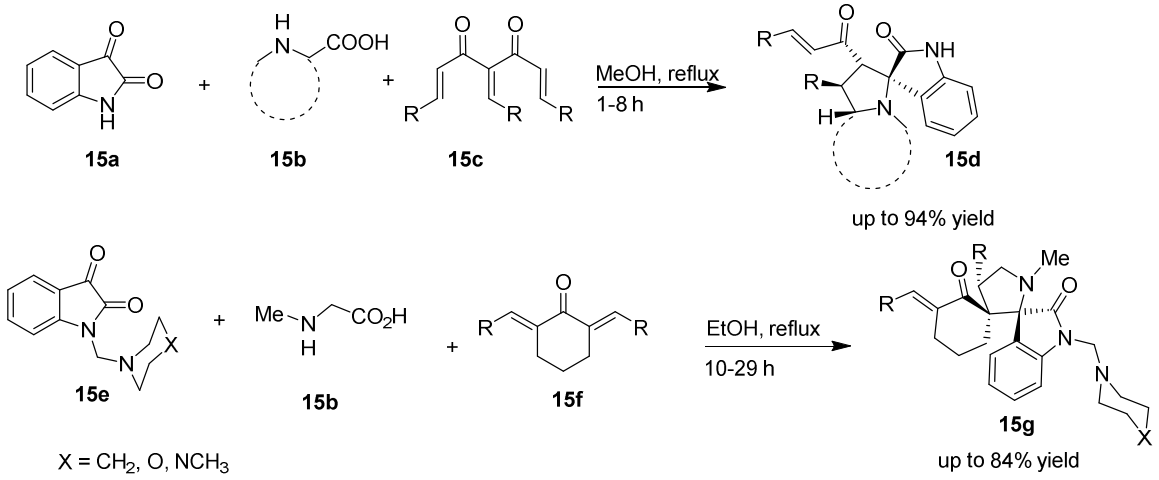


Scheme 11. Synthesis of spirooxindoles and spiro-pyrrolidines/pyrrolizidines **13d** and **13f** containing aryl/heteroaryl moieties in the pyrrolidine and pyrrolizidine rings *via* the azomethine ylide 1,3-dipolar cycloaddition reaction.



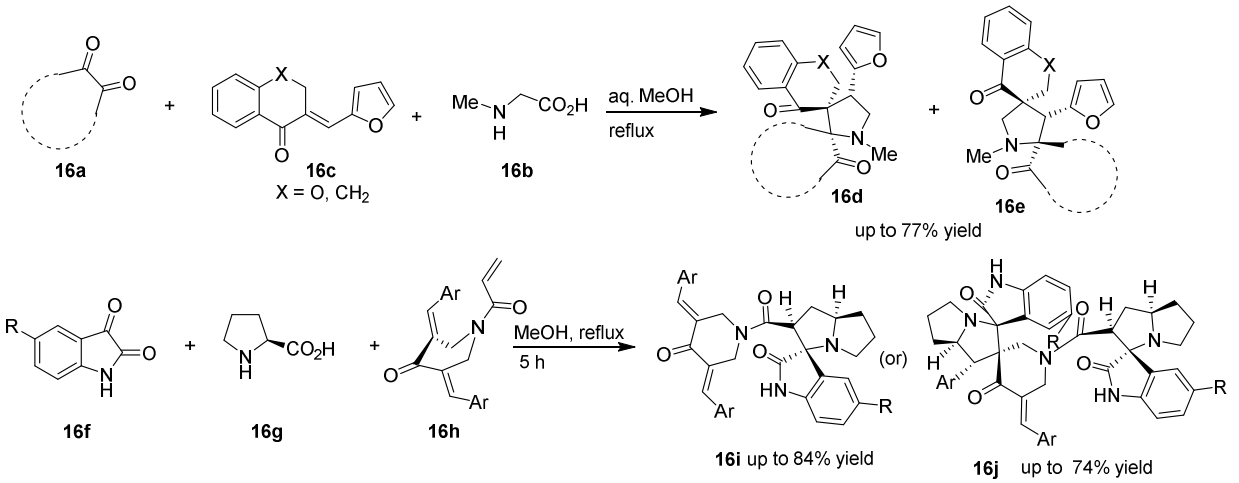
Scheme 12. Spiro- and dispiro- pyrrolidine/pyrrolizidines **14a-c** synthesized *via* the azomethine cycloaddition reaction.

Narayanan *et al*.[36a] reported the regioselective synthesis of spiroheterocycles **15d** by using tris benzylidene acetylacetone **15c** as an unusual dipolarophile in the azomethine ylide cycloaddition reaction (Scheme 13). Stawinski and Girgis *et al*.[36b] reported the synthesis of dispiroindoles **15g** (Scheme 13) by using 2*E*, 6*E*-bis (arylidene)-1-cyclohexanones **15f** as a dipolarophiles and these compounds were screened for their antitumor properties against HEPG2 (liver), HELA (cervical) and PC3 (prostate) human tumor cell lines.

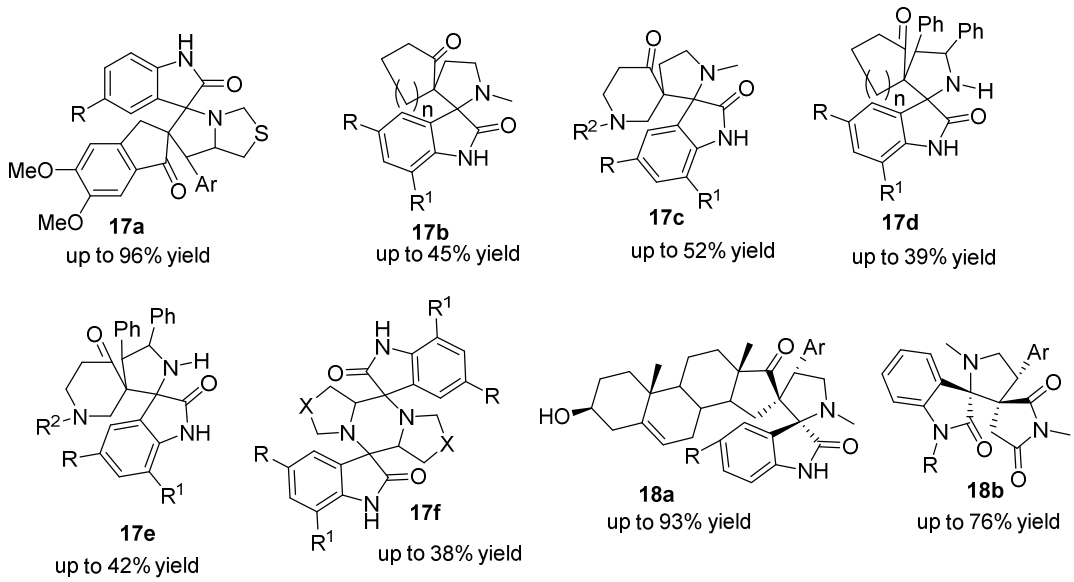


Scheme 13. Spiro-pyrrolidine/pyrrolizidines **15d** and **15g** synthesized *via* the azomethine cycloaddition reaction.

Raghunathan *et al*.[37] described an efficient synthesis of spiropyrrolo-bicyclo [2.2.1]heptanes **16d** and **16e***via* theazomethine ylide cycloaddition reaction (Scheme 14). Osman and Kumar[38a,b] reported the synthesis of mono and bis spiroheterocyclic frameworks **16i** and **16j** (Scheme 14) and these spiro compounds were found to act as potent cholinesterase inhibitors.



Scheme 14. Construction of spiro-pyrrolidine/pyrrolizidines **16d, 16e, 16i** and **16j** *via* the azomethine cycloaddition reaction.

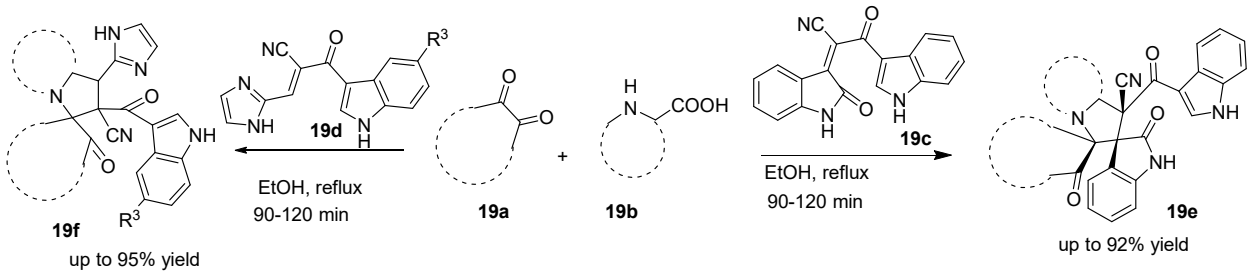


Scheme 15. Construction of bis-spirooxindoles **17a-f** and **18a**,as well as**18b**.

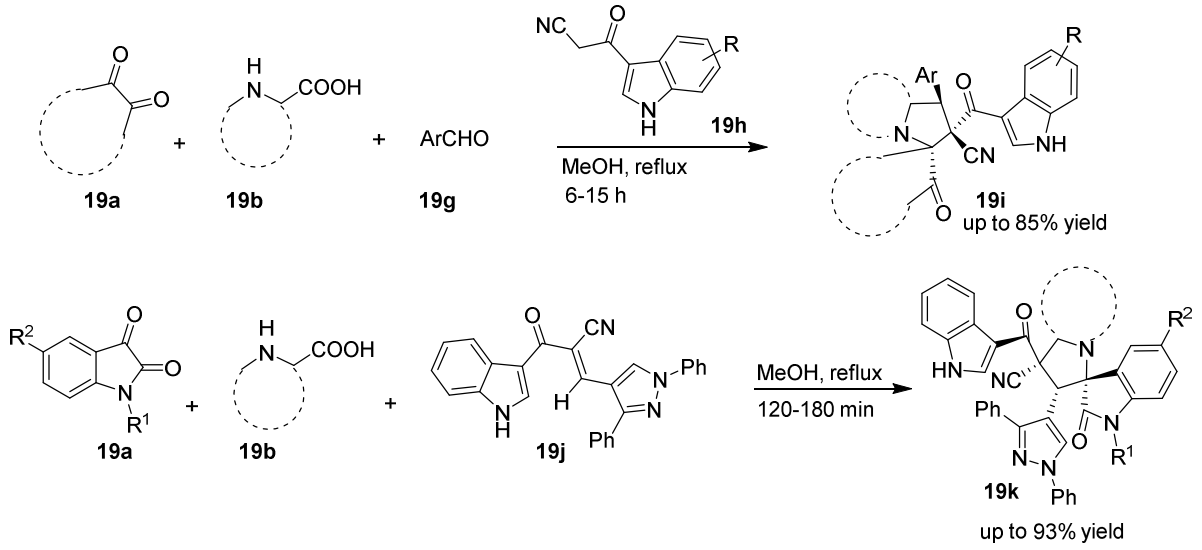
Ali *et al.* [39a] reported series of spiropyrrolothiazolyloxindoles **17a**(Scheme 15) from the cycloaddition of corresponding azomethine yilde with 5,6-dimethoxy-2-[(*E*)-1-arylmethylidene]-1-indanones as a dipolarophiles and the synthesized compounds **17a** were tested for their cholinesterase inhibition activity. Perumal *et al.*[39b] reported synthesis of dispirooxindoles **17b-f** (Scheme 15) from the cycloaddition of corresponding azomethine yilde with cyclic ketones andthese compounds evaluated for their *Mycobacterium tuberculosis* H37Rv inhibition activity.

Yu *et al.*[40a] reported the regioselective synthesis of steroidal pyrrolidine spirooxindoles **18a** (Scheme 15) from the cycloaddition of corresponding azomethine yilde with (*E*)-3β-hydroxy-5-ene-16-arylidene-17-ketosteroids as a dipolarophiles and the synthesized compounds **18a** (Scheme 15) were tested for their anticancer activities.Perumal *et al.*[40b] reported the synthesis of dispiropyrrolidines **18b** (Scheme 15) from the cycloaddition of corresponding azomethine yilde with 3-benzylidene-1-methyl-pyrrolidine-2,5-dione andthese compounds evaluated for their antibacterial activity.

Perumal and co-workers[41a] reported the synthesis of dispirooxindolopyrrolidines **19e** and **19f** (Scheme 16) from the multicomponent cycloaddition of azomethine yilde with indole-based dipolarophiles. The compounds **19e** and **19f** were evaluated for their anticancer activity on A549 human lung adenocarcinoma cancer cell lines.



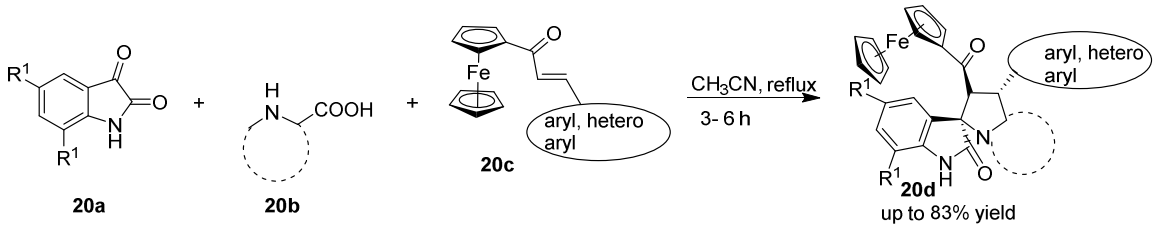
Scheme 16. Construction of dispirooxindolopyrrolidines **19e** and **19f**.



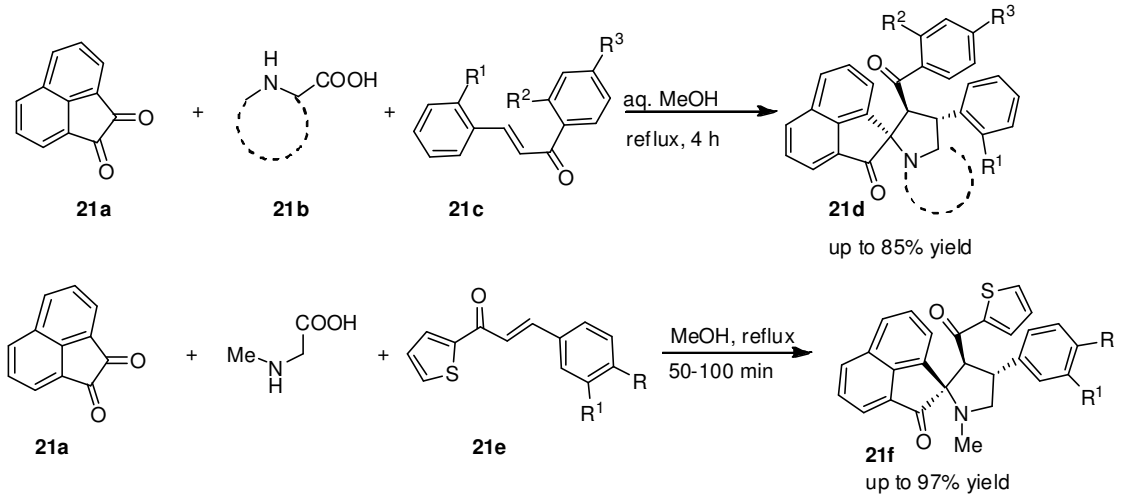
Scheme 17. Synthesis of spirooxindolo-pyrrolidines / pyrrolizidines **19i** and **19k** appended with the indolecarbonyl moiety.

Ji *et al.*[41c]reported the synthesis of spirooxindolo-pyrrolidines / pyrrolizidines **19i** appended with the indolecarbonyl moiety(Scheme 17) from the one pot cycloaddition of corresponding azomethine yilde generated from isatin / acenaphthenequinone and amino acids with the corresponding indole-based dipolarophiles. In addition, Reddy *et al.*[41d] reported the diastereoselective synthesis of spirooxindolo-pyrrolidines / pyrrolizidines **19k** (Scheme 17) and the compounds **19k** were evaluated for their antimicrobial activity.

Raghunathan *et al.*[42a,b] reported the synthesis of ferrocenyl moiety attached spirooxindolo-pyrrolidines and pyrrolizidines **20d** (Scheme 18) from the one pot cycloaddition of corresponding azomethine yilde generated from isatin / acenaphthenequinone and amino acids with the corresponding ferrocene-based dipolarophiles.



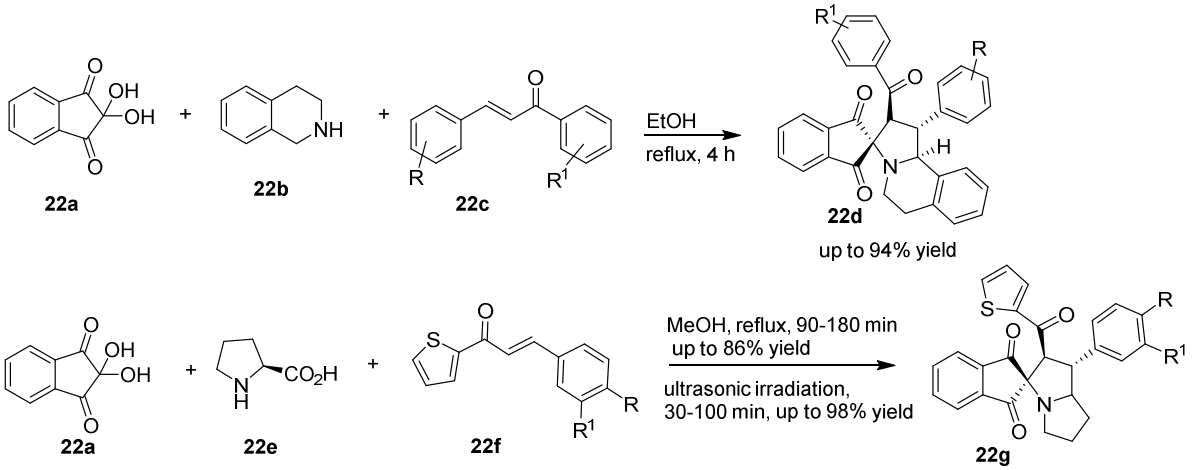
Scheme 18. Synthesis of ferrocenyl moiety attached spirooxindolo-pyrrolidines and pyrrolizidines **20d**.



Scheme 19. Synthesis of spiroacenaphthylenolyl-pyrrolidines / pyrrolizidines appended with heteroaryl moieties.

Ignacimuthu *et al.*[43a] reported the synthesis of spiroacenaphthylenolyl-pyrrolidines / pyrrolizidines**21d**(Scheme 19) appended with heteroaryl moieties from the multicomponent

cycloaddition of azomethine yilde generated from acenaphthenequinone and amino acids withdipolarophile **21c**. Thangamani *et al.*[43b] reported synthesis of spiroacenaphthylenolylpyrrolidines **21f**appended with heteroaryl moieties (Scheme 19). Sarrafi *et al.*[44a] reported the regioselective synthesis of spiro-1,3-indandionolylpyrrolizidines **22d** (Scheme 20) from the multicomponent cycloaddition of corresponding azomethine yilde generated from ninhydrin and 1,2,3,4-tetrahydroisoquinoline **22b** with the corresponding chalcones as a dipolarophiles. Finally, Thangamani *et al.*[44b] reported the synthesis of spiro-1,3-indandionolylpyrrolizidines **22g** (Scheme 20) from the multicomponent cycloaddition of azomethine yilde generated from ninhydrin and L-proline with chalcones as dipolarophiles.



Scheme 20. Synthesis of spiro-1,3-indandionolylpyrrolizidines **22d** and **22g**.

Results and discussion.

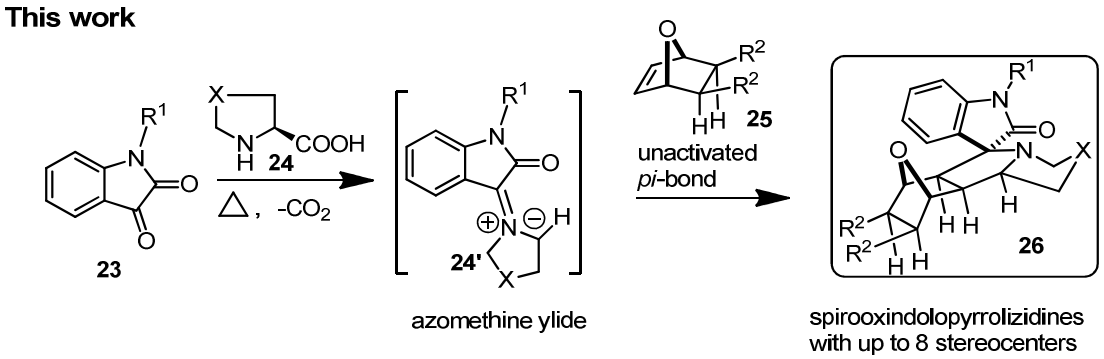
Due to the importance of spiro-pyrrolidine- / pyrrolizidine derivatives in organic synthesis and medicinal chemistry and drug discovery research, several research labs including our lab are interested in enriching the library of medicinally important spirooxindole, spiro-pyrrolidine- / pyrrolizidine scaffolds.[1-6] Categorically, in the context of finding new lead compounds with promising biological activities and for finding potential drug candidates there have been vested interests and continuous efforts for preparing new libraries of multi substituted or highly functionalized spiro-oxindoles / pyrrolizidines / pyrrolidines appended with medicinally important functional groups and sub-units, such as,aryl- / heteroaryl moieties *via* the azomethine ylide 1,3-dipolar cycloaddition route.[6] There exist various reports dealing on the synthesis of

biologically active spirooxindole, spiro-pyrrolidine- / pyrrolizidine scaffolds *via* the azomethine cycloaddition method. The key to assemble new class of a library of diversely functionalized spiro-oxindoles / pyrrolizidines / pyrrolidines appended with medicinally important functional groups and sub-units has been to use different 2π components (dipolarophiles) in the azomethine ylide cycloaddition.

Chapter 2a: Stereocontrolled entry into norbornane-fused- spirooxindolopyrrolidines, spiro-1,3-indandionolylpyrrolidines and spirooxindolopyrrolizidines.

Although there exist various reports dealing on the synthesis of biologically active spirooxindole, spiro-pyrrolidine- / pyrrolizidine scaffolds *via* the azomethine cycloaddition method; generally, electron-deficient dipolarophiles have been used in the intermolecular [3+2] cycloaddition reactions of azomethine ylides for the synthesis of spiro-oxindoles / pyrrolizidines / pyrrolidines derivatives.[6]

A part of this thesis work envisaged that an azomethine ylide (which can be derived from the condensation of isatin and L-proline) could serve as one partner as, while an unactivated norbornene could serve as the other partner (dipolarophile) to effect the stereoselective synthesis of a new class of norbornane-fused spirooxindolopyrrolizidines. It is worth to mention that unactivated norbornenes have been used as dipolarophiles in the block coupling methodology.[45a] Further, the reaction of carbonyl ylides with unactivated oxanorbornene dipolarophiles was found to afford *syn*-facially bridged norbornane scaffolds.[45b] Additionally, Deloisy and co-workers[45c,d] reported the synthesis of norbornane-fused pyrrolidines *via* the cycloaddition of azomethine ylides generated from imine esters with norbornenes.

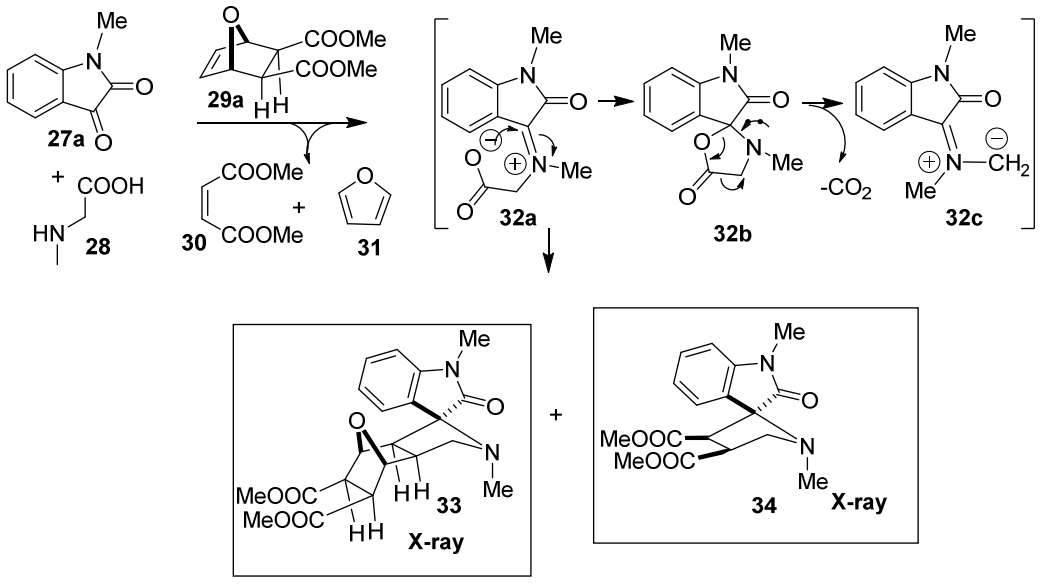


Scheme 21. 1,3-Dipolar cycloaddition of azomethine ylide with unactivated π bond and stereoselective synthesis of complex norbornane-fused spirooxindolopyrrolizidines.

At the outset, various reactions were performed to arrive at the best reaction conditions and solvents to synthesize complex norbornane-fused spirooxindolopyrrolidine *via* the 1,3-dipolar cycloaddition of azomethine ylides with unactivated norbornene dipolarophiles. Scheme 22 and Table 1 demonstrate the investigation of the multicomponent reaction of a mixture of *N*-methylisatin **27a** and sarcosine **28** with dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **29a**. The 1,3-dipolar cycloaddition of azomethine ylide generated from *N*-methylisatin **27a** and sarcosine **28** with dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **29a** is expected to afford the norbornane-fused spirooxindolopyrrolidine **33** (Table 1 and Scheme 22). The multicomponent reaction of a mixture of *N*-methylisatin **27a** and sarcosine **28** with dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **29a** was carried out in different solvents at various reaction temperatures. Of the reaction conditions investigated (entries 1-12, Table 1), it was observed that the 1,3-dipolar cycloaddition reaction of the azomethine ylide **32c** generated from **27a** and **28** with **29a** in EtOH at 80 ^{o}C furnished the norbornane-fused spirooxindolopyrrolidine **33** as a single isomer in a maximum yield of 55% (entry 11, Table 1). The structure and stereochemistry of the norbornane-fused spirooxindolopyrrolidine **33** was unambiguously assigned on the basis of the X-ray structure analysis (Figure 5).

The reactivity pattern and limitations of the usage of norbornene dipolarophile in the 1,3-dipoloar cycloaddition was further investigated, because only a moderate yield for the norbornane-fused spirooxindolopyrrolidine **33** was obtained. The multicomponent reaction of **27a** and sarcosine **28** with **29a** in 1,4-dioxane at 101 ^{o}C gave the spirooxindolopyrrolidine **34**

(65%) instead of the norbornane-fused spirooxindolopyrrolidine **33**. This is because, at higher temperatures, the dipolarophile **29a** underwent the retro Diels-Alder reaction, generating furan **31** and the dipolarophile **30** and **t**he dipolarophile **30** reacted with the azomethine ylide **32c** to furnish the spirooxindolopyrrolidine **34** (entry l2, Table 1). The structure and stereochemistry of spirooxindolopyrrolidine **34** was unambiguously assigned on the basis of the X-ray structure analysis (Figure 5). However, heating the norbornane-fused spirooxindolopyrrolidine **33** in 1,4-dioxane at 101 ^{o}C for 2 h confirmed that the norbornane-fused spirooxindolopyrrolidine **33** is stable under the present experimental condition (eq 1, Scheme 23). Next, in an another trial involving the reaction of **29b** (which contains both the unactivated as well as activated 2π components) with the azomethine ylide generated from isatin **27b** and sarcosine **28** gave the spirooxindolopyrrolidine **35c** instead of the expected norbornane-fused spirooxindolopyrrolidines **35a** or **35b** (Scheme 23, eq 2).[45d] This reaction clearly indicated that the norbornene dipolarophile **29b**[45d] is sensitive to heat and underwent the retro Diels-Alder reaction to produce DMAD **29b′** that trapped the azomethine ylide resulting from isatin **27b** and sarcosine **28**. Finally, to understand the reactivity pattern of norbornene **29a** at rt,. The silver-catalyzed 1,3-dipoloar cycloaddition of iminoester **36** with norbornene dipolarophile **29a** was performed, which did not give the expected product **37** (eq 3, Scheme 23).



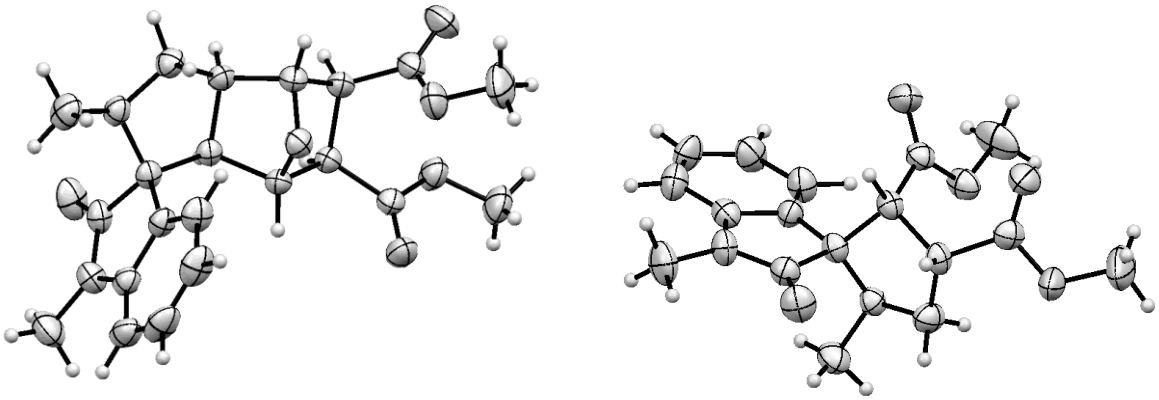
Scheme 22. Multicomponent reaction of a mixture of *N*-methylisatin **27a** and sarcosine **28** with dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **29a**.

Table 1. Optimization of the reaction condition.

entry	solvent (mL)	*T* (°C)	*t* (h)	**29a** (%)	yield **33** (%)[a]
1	EtOH (3)	60	24	78	18
2	MeOH (3)	70	6	68	24
3	MeCN (3)	90	6	51	27
4	MeOH (1.5)/MeCN (1.5)	80	15	79	21
5	MeOH (1.5)/1,4-dioxane (1.5)	90	6	64	35
6	EtOH (1.5)/MeCN (1.5)	90	6	59	32
7	EtOH (1.5)/1,4-dioxane (1.5)	80	6	33	43
8	EtOH (1.5)/1,4-dioxane (1.5)	80	12	20	43
9	EtOH (1.5)/H_2O (1.5)	95	6	50	<5
10	EtOH (3)	80	6	50	29[b]
11	EtOH (3)	80	20	16	55[b]
12	1,4-dioxane (3)	101	17	<5	<5 (**34**[c]: 65)

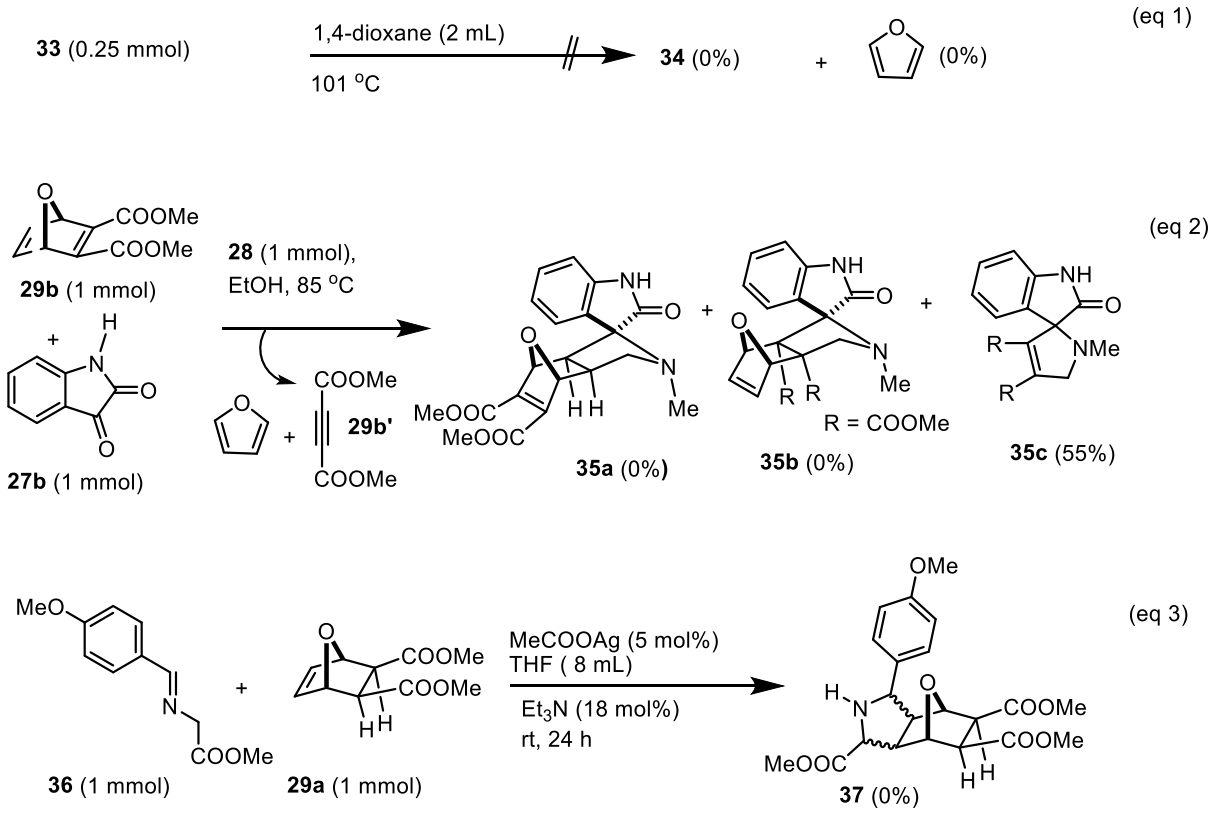
[a] The reactions were done on a 0. 5 mmol scale. [b] The reactions were done on a 1 mmol scale.

[c] A mixture of diastereomers (**34**:**34'**, dr 90:10) was obtained.



33 **34**

Figure 5. X-ray structures of the compounds **33** and **34**.

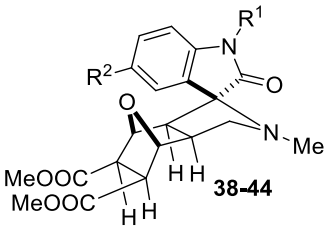


Scheme 23. Investigation on the reactivity pattern of norbornene dipolarophiles.

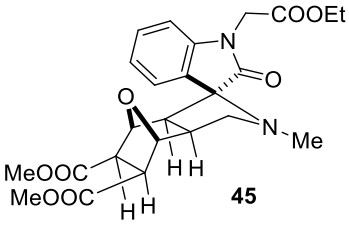
Then, it was envisaged to demonstrate the generality of this methodology for assembling a variety of norbornane-fused spirooxindolopyrrolidines (Table 2). The norbornane-fused spirooxindolopyrrolidines **38** was obtained in 47% yield as a single stereoisomer from the multicomponent azomethine ylide cycloaddition of the corresponding isatin**27b**, sarcosine **28**and norbornene dipolarophile **29a** (entry 1, Table 2). The diastereoselective one pot cycloaddition reactions of 5-fluoroisatin **27c** and 5-fluoro-1-methylisatin **27d** and sarcosine **28** with **29a** also yielded the respective norbornane-fused spirooxindolopyrrolidines **39** and **40** (entry 2 and 3, Table 2). Similarly, the cycloaddition reactions of 5-chloroisatin **27e**, 5-chloro-1-methylisatin **27f**, 5-bromoisatin **27g**, 5-bromo-1-methylisatin **27h** and sarcosine **28** with **29a** furnished the respective norbornane-fused spirooxindolopyrrolidines **41-44** (entries 4-7, Table 2). The multicomponent cycloaddition reaction of azomethine ylide generated from ethyl (2,3-dioxo-2,3-dihydroindol-1-yl)-acetate **27i** and *N*-benzylisatin **27j** and sarcosine **28** with norbornene dipolarophile **29a** gave the corresponding norbornane-fused spirooxindolopyrrolidines **45** and **46**

(entries 8 and 9, Table 2). The structure and stereochemistry of the norbornane-fused spirooxindolopyrrolidines **33** and **39** wereassignedbased on their X-ray structures; then, the stereochemistry of other norbornane-fused spirooxindolopyrrolidines shown in Table 2 was assigned (Figures 5 and 6).

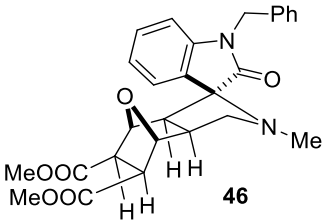
Table 2.Scope and generality: Diastereoslective synthesis of norbornane-fused spirooxindolo-pyrrolidines **38**-**46**.



38-44



45



46

entry	solvent (mL)	*T* (°C)	*t* (h)	recovery of **29a** (%)	yield (%)
1	EtOH (6)	80	12	32	**38**: R^1=H, R^2=H; 47[a]
2	EtOH (2) / 1,4-dioxane (2)	82	6	26	**39**: R^1=H, R^2=F; 45[b] **(x-ray)**
3	EtOH (2) / 1,4-dioxane (2)	82	6	25	**40**: R^1=Me, R^2=F; 44
4	EtOH (3)	80	3	40	**41**: R^1=H, R^2=Cl; 45[c]
5	EtOH (3)	80	5	26	**42**: R^1=Me, R^2=Cl; 40[c]
6	EtOH (1.5) / 1,4-dioxane (1.5)	82	12	21	**43**: R^1=H, R^2=Br; 50[c]
7	EtOH (6)	82	10	10	**44**: R^1=Me, R^2=Br; 45[b]
8	EtOH (3) / 1,4-dioxane (3)	82	6	25	**45**: 49[a]
9	EtOH (3) / 1,4-dioxane (3)	82	6	35	**46**: 50[b]

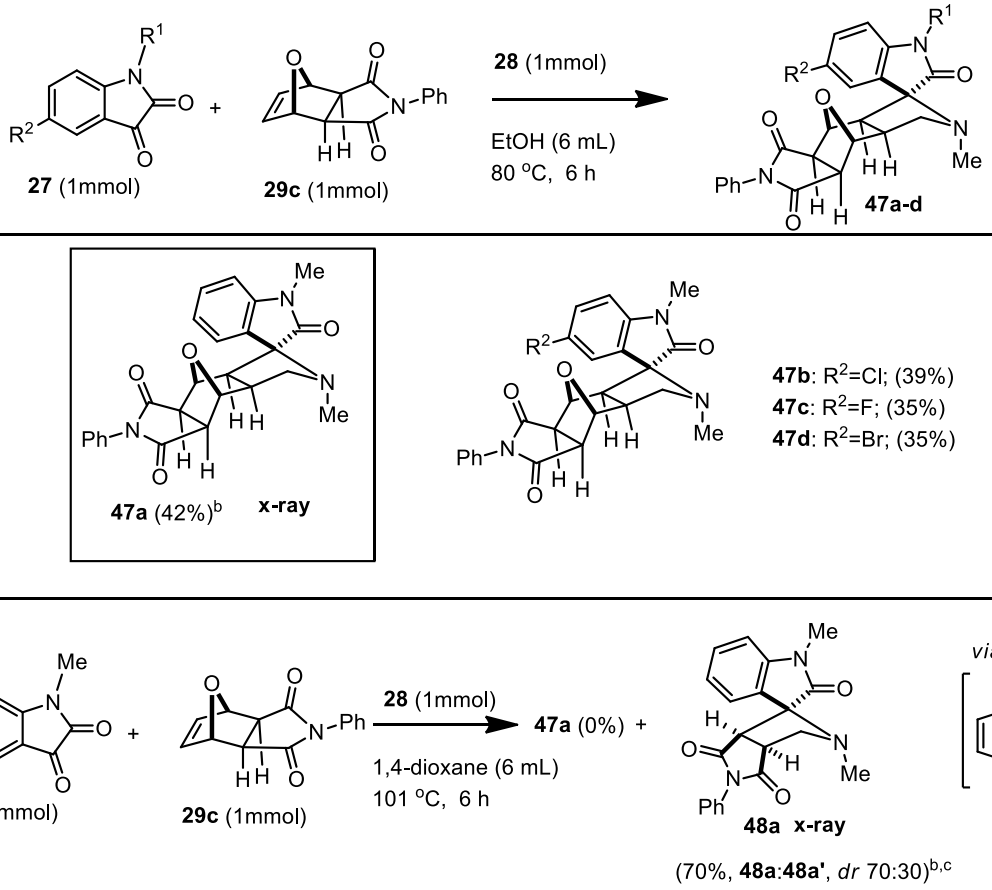
[a] The reactions were done on a 1 mmol scale. [b] The reactions were done on a 2 mmol scale.

[c] The reactions were done on a 0.5 mmol scale.

Furthermore, the cycloaddition reaction of azomethine ylide generated from isatin **27a** and sarcosine **28** was investigated by using the norbornene dipolarophile **29c**.Accordingly, the reaction of isatin **27a** and sarcosine **28** with **29c** gave the norbornane-fused spirooxindolopyrrolidine **47a** (42%, Table 3). Along this line, various norbornane-fused spirooxindolopyrrolidines **47b-d** were synthesized from the corresponding cycloaddition reactions by using **29c**. The structure and stereochemistry of norbornane-fused

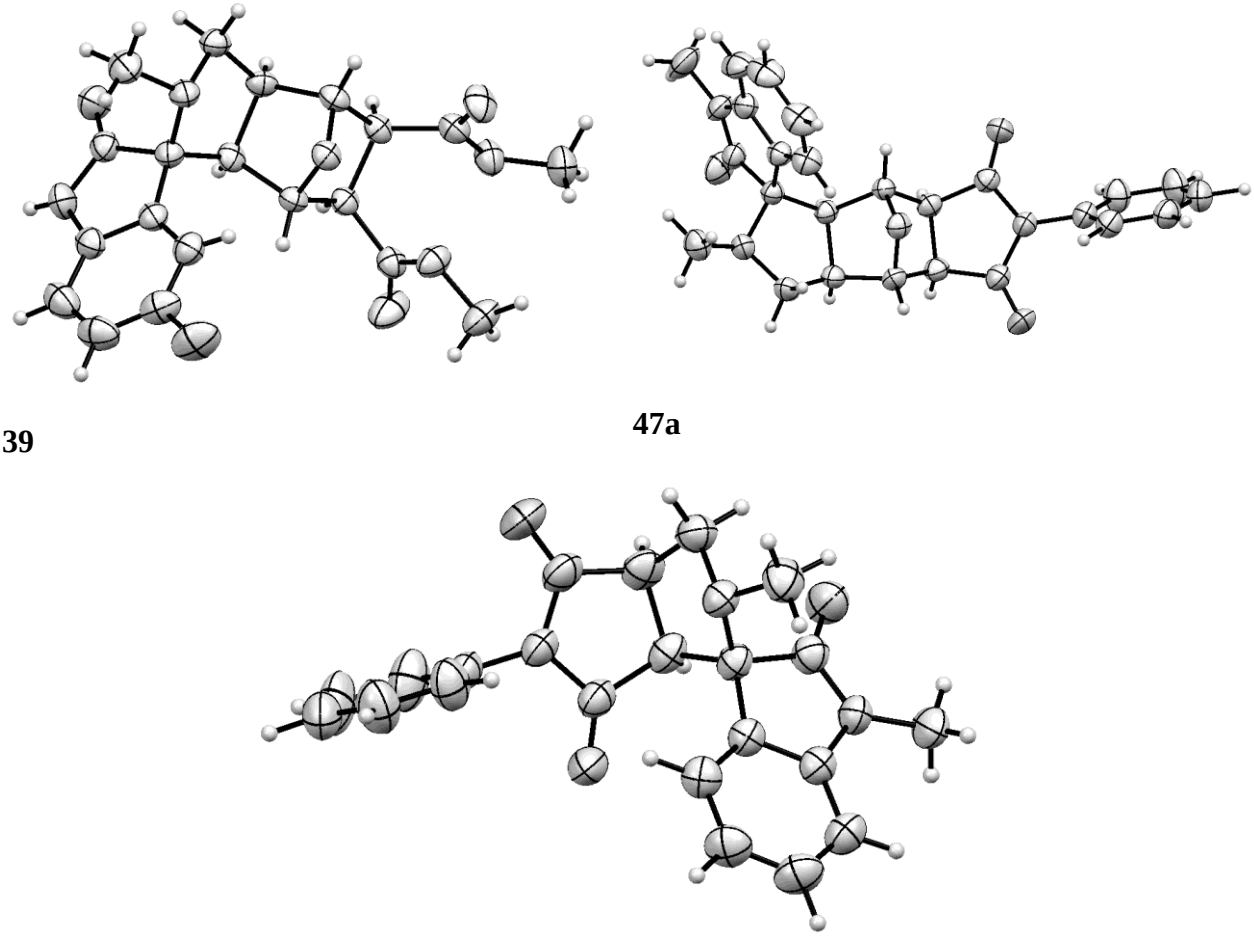
spirooxindolopyrrolidine **47a** wereassignedbased on its X-ray structure; then, the stereochemistry of other norbornane-fused spirooxindolopyrrolidines **47b-d** shown in Table 3 was assigned (Figure 6). Trials were carried out to improve the yield of **47a** by varying the solvents or increasing the reaction temperature, however, the attempts were not fruitful. Notably, the reaction of **27** and sarcosine **28** with **29c** in 1,4-dioxane at higher temperature (101 ^{o}C) furnished the spirooxindolopyrrolidine**48a** (dr 70:30) instead of the norbornane-fused spirooxindolopyrrolidine**47a***via* the retro Diels-Alder reaction similar to the case that was shown in Scheme 22 and Table 1.

Table 3:Scope and generality: Stereoslective synthesis of norbornane-fused spirooxindolo-pyrrolidines **47a-d**.



[a] The reactions were done on a 1 mmol scale. In all the reactions recovery of **29c** (23-28%) was observed.

[b] The reaction was done on a 0.5 mmol scale. [c] Diastereomers were obtained.

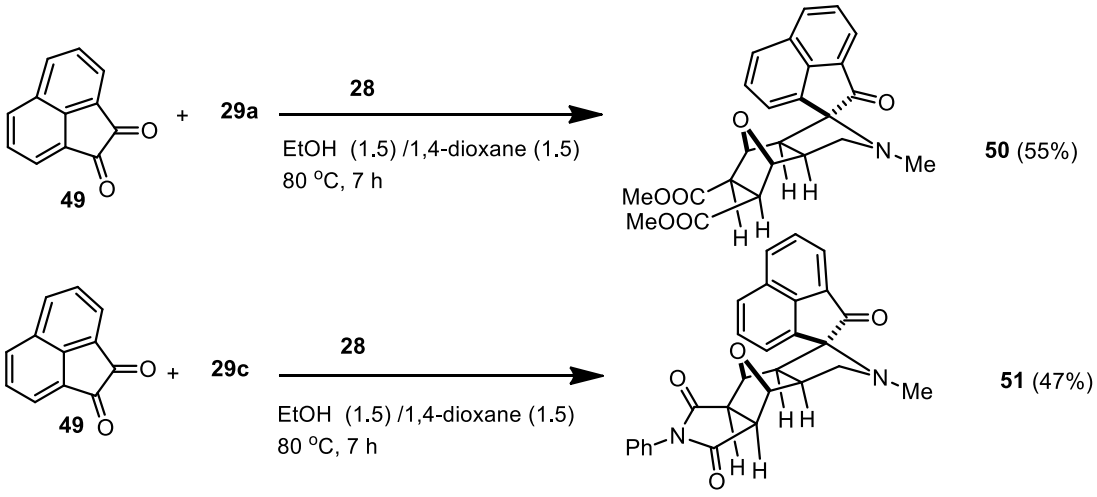


39 **47a**

48a

Figure 6. X-ray structures of the representative compounds **39**, **47a** and **48a**.

Successively, it was envisaged to investigate the multicomponent cycloaddition reaction of azomethine ylide generated from acenaphthenequinone **49** and sarcosine **28** with **29a** and **29c** to obtain norbornane-fused spiroacenaphthylenolylpyrrolidines. Accordingly, the multicomponent cycloaddition reaction of azomethine ylide generated from acenaphthenequinone **49** and sarcosine **28** with **29a** afforded the norbornane-fused spiroacenaphthylenolylpyrrolidine **50** as a single diastereomer (Scheme 24). Similarly, the cycloaddition reaction of azomethine ylide generated from acenaphthenequinone **49** and sarcosine **28** with **29c** afforded the norbornane-fused spiroacenaphthylenolylpyrrolidine **51** with very high diastereoselectivity (Scheme 24). The structure and stereochemistry of norbornane-fused spiroacenaphthylenolylpyrrolidines **50** and **51** were assigned based on their X-ray structures (Figure 7).



Scheme 24.Diastereoslective synthesis of norbornane-fused spiroacenaphthylenolyl-pyrrolidines.

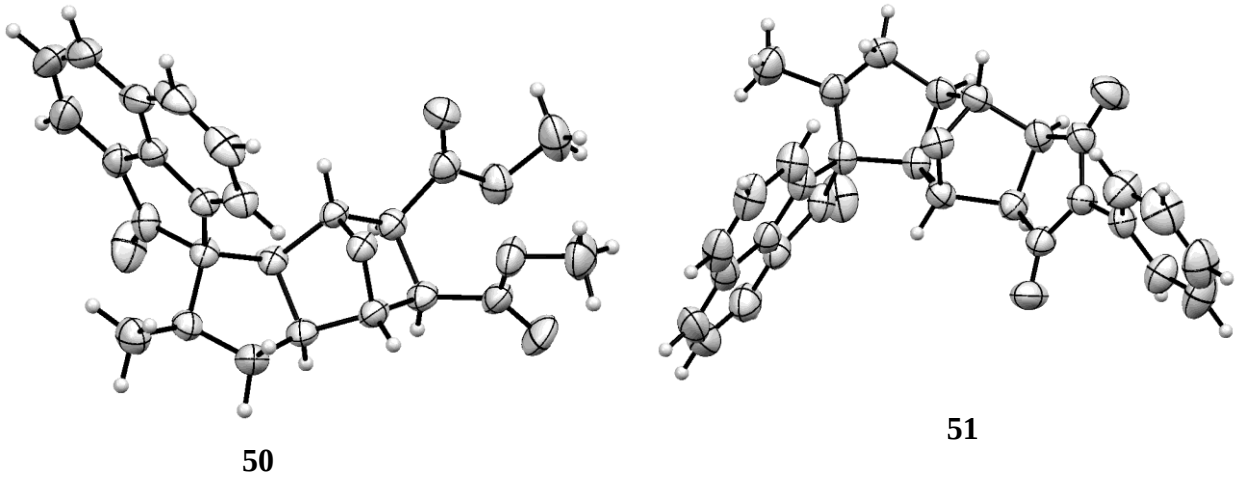


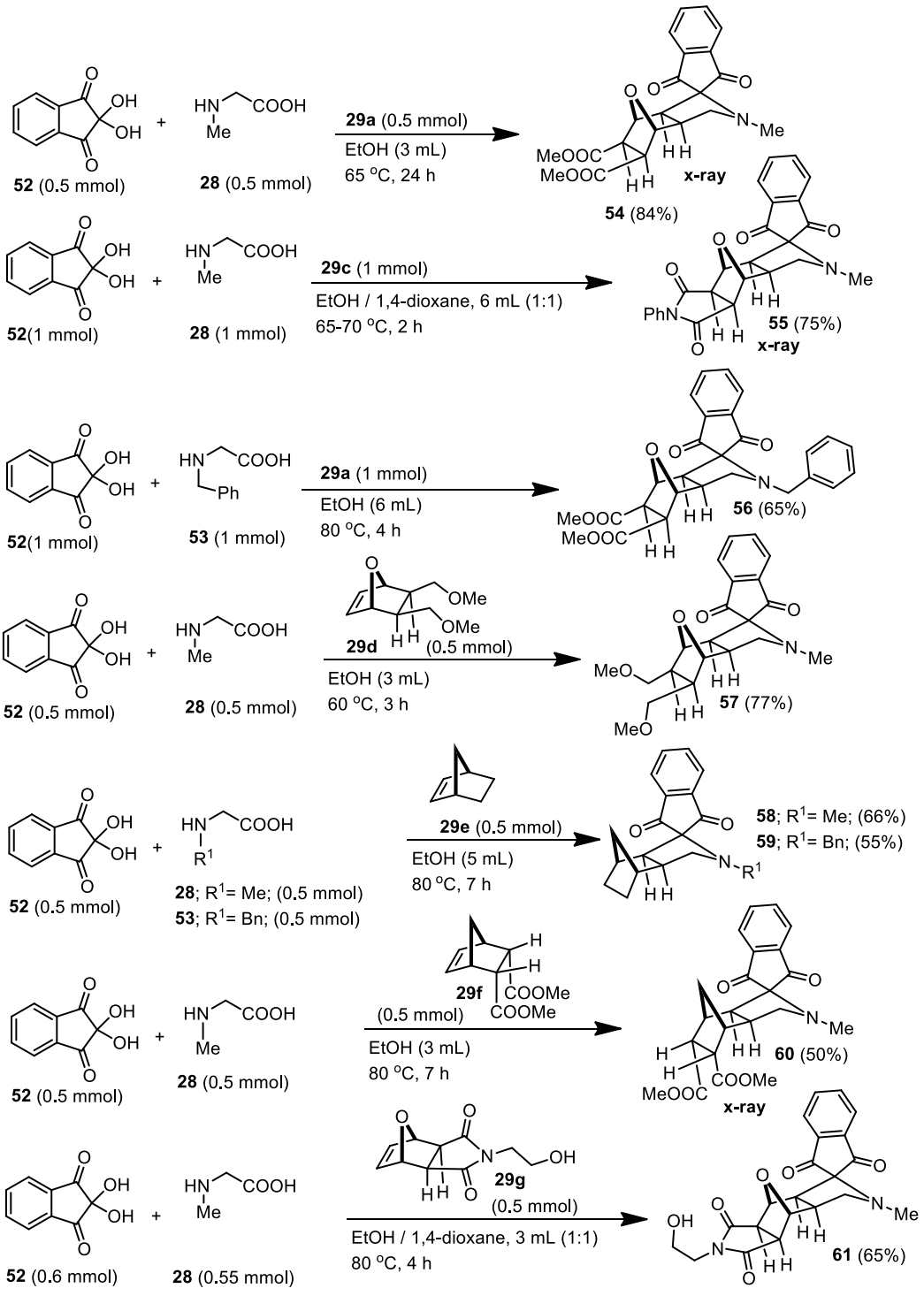
Figure 7. X-ray structures of the compounds **50** and **51**.

Next, it was envisaged to explore the multicomponent cycloaddition reaction of azomethine ylide generated from ninhydrin **52** and sarcosine **28** with dipolarophiles **29** to obtain norbornane-fused spiro-1,3-indandionolylpyrrolidines.In this regard,Scheme 25 illustrates the construction of a variety of norbornane-fused spiro-1,3-indandionolylpyrrolidine derivatives **54-61**. The multicomponent cycloaddition reactions of ninhydrin **52** and sarcosine **28** with oxanorbornene dipolarophiles **29a** or **29c** gave the respective spiro-1,3-indandionolylpyrrolidines **54, 55** and **56**

as single diastereomers with high degree of stereocontrol. The one pot cycloaddition reaction of azomethine ylide generated from ninhydrin **52** and sarcosine **28** withoxanorbornene dipolarophile **29d** and various other norbornene dipolarophiles **29e-g** furnished the corresponding norbornane-fused spiro-1,3-indandionolylpyrrolidines **57-61** as single isomers with high degree of stereocontrol (Scheme 25). The structure and stereochemistry of the norbornane-fused spiro-1,3-indandionolylpyrrolidines **54**, **55** and **60** wereassignedbased on their X-ray structures (Figure 8).

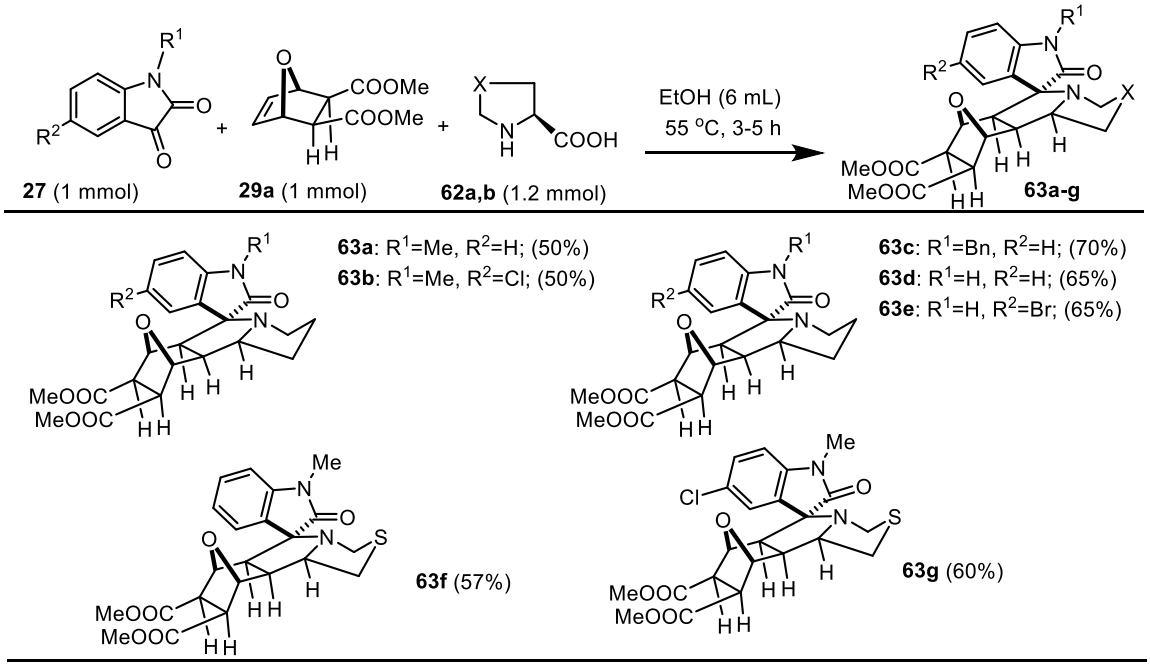
Finally, it was envisaged to expand the substrate scope and generality of this methodology for assembling a variety of norbornane-fused spirooxindolopyrrolizidines by using L-proline **62a** and L-thiaproline **62b** to generate and trap the corresponding azomethine ylides with norbornene dipolarophile. Accordingly, the multicomponent cycloaddition reaction of azomethine ylides derived from the condensation of isatins **27** and L-proline **62a** or L-thiaproline **62b** with norbornene dipolarophile **29a** proceeded with a very high degree of stereocontrol and gave the respective norbornane-fused spirooxindolopyrrolizidines **63a-g** as single diastereomers (Table 4). It is worth to mention here that these three component reactions gave a variety of novel and complex norbornane-fused spirooxindolopyrrolizidines **63a-g** possessing eight stereocenters.

In the multicomponent cycloaddition reaction involving norbornene dipolarophiles, some of the norbornane-fused spirooxindoles and spiropyrrolidines/pyrrolizidines were obtained in moderate yields. The moderate to good yields of norbornane-fused spirooxindoles and spiropyrrolidines/pyrrolizidines in all the above reactions could be explained based on the optimization reactions shown in (Table 1 & Scheme 23), which indicated the tricky nature of the methodology and sensitivity of norbornene dipolarophiles at high reaction temperatures. Consequently, the reaction temperature was controlled to suppress the retro-Diels-Alder reaction[45d] of norbornene dipolarophiles and to carefully preserve the norbornane fusion intact in all the spirocompounds shown in this work, so that the synthesis of novel and complex norbornane-fused spirooxindoles and spiropyrrolidines could be successfully accomplished.



Scheme 25. Synthesis of spiro-1,3-indandionolylpyrrolidines **54-61**.

Table 4. Norbornane-fused spirooxindolopyrrolizidines.



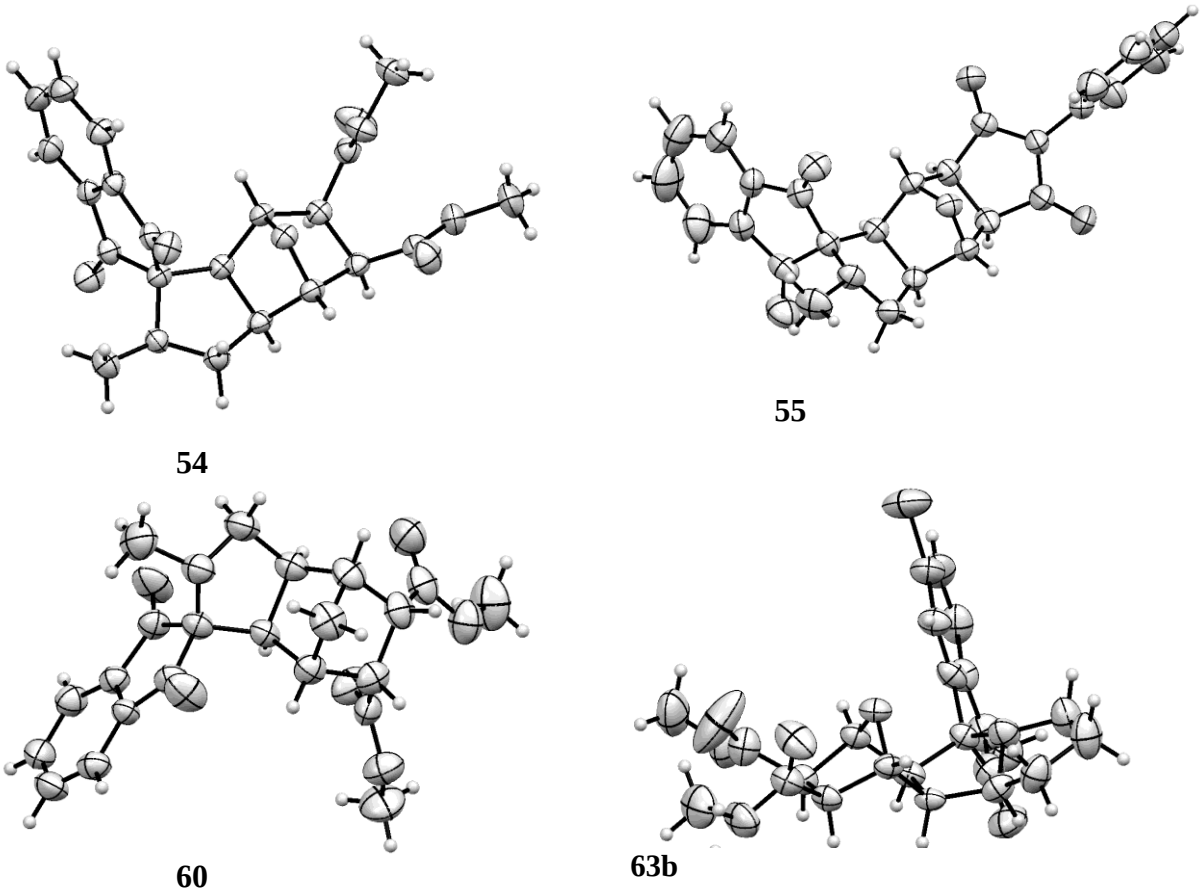


Figure 8. X-ray structures of the compounds **54**, **55**, **60** and **63b**.

Chapter 2b: Diastereoselective construction ofspiro-pyrrolidine / pyrrolizidine oxindole, spiroacenaphthylenolyl- pyrrolidine / pyrrolizidine and spiro-1,3-indandionolyl-pyrrolidine scaffolds appended with indole and pyrrole moieties.

While several types of multi substituted spiro-oxindoles / pyrrolizidines / pyrrolidines appended with medicinally important functional groups and sub-units, such as,cyano-, aryl- / heteroaryl moieties considered as lead compounds with potential biological activities;[6d,11e,18-22] pyrrolidines containing an indole moiety at the C-3 position (e.g., eletriptan) and spiro-oxindoles / pyrrolizidines / pyrrolidines appended with indole moieties were found to be important class of bio-active molecules (Figure 9). While there exist few reports dealing on the synthesis of pyrrolidines containing an indole moiety at the C-3 position;[20] however, there exist only rare reports dealing on the construction of spiro-oxindoles / pyrrolizidines / pyrrolidines connected with an indole-carbonyl unit.[21] Further a literature survey revealed that there exist no reports dealing on synthesis of spiro-oxindole- / pyrrolizidine- / pyrrolidine scaffolds directly connected with the indolyl or pyrrolyl moieties.[5,6,41]

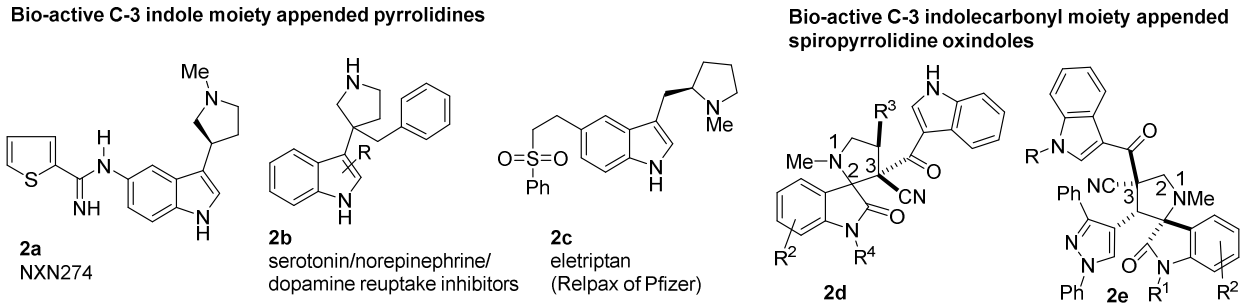
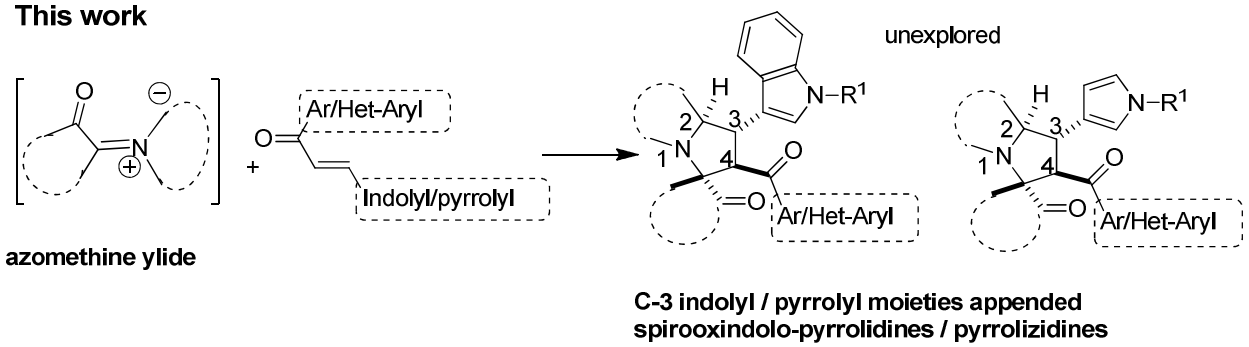


Figure 9. Biologically active indole moieties containing pyrrolidines and spiropyrrolidines.

Given that several research groups are interested in finding new lead compounds with promising biological activities by preparing new libraries of spiro-oxindoles / pyrrolizidines / pyrrolidines appended with medicinally important functional groups and sub-units, such as,aryl- / heteroaryl moieties *via* the azomethine ylide cycloaddition route;[6] and given the importance of indole moieties containing pyrrolidines and spiro-pyrrolidines/pyrrolizidines found to be with promising biological activities (Figure 9), a part of this thesis work envisaged to assemble spiro-oxindole- / pyrrolizidine- / pyrrolidine scaffolds directly connected with the indolyl or pyrrolyl moieties. Accordingly it was envisaged to use the azomethine ylide cycloaddition route for the

construction of a new set of spiro-pyrrolidine- / pyrrolizidine oxindole, spiroacenaphthylenolyl-pyrrolidine / pyrrolizidine and spiro-1,3-indandionolyl- pyrrolizidine scaffolds appended with the indolyl or pyrrolyl moieties (Scheme 26).



Scheme 26. Regio-and stereoselective synthesis of a new set ofC-3,C4- aryl- / heteroaryl spiro-pyrrolidines / pyrrolizidines.

The key to assemble new class of diversely functionalized spiro-oxindoles / pyrrolizidines / pyrrolidines appended with medicinally important functional groups and sub-units has been to use diverse 2π components (dipolarophiles) in the azomethine ylide cycloaddition. Accordingly, to prepare to assemble the spiro-pyrrolidine / pyrrolizidine oxindole, spiroacenaphthylenolyl-pyrrolidine / pyrrolizidine and spiro-1,3-indandionolyl- pyrrolidine scaffolds directly appended with the indolyl- or pyrrolyl moieties at the pyrrolidine / pyrrolizidine rings; initially, various indole- and pyrrole-based dipolarophiles **64a-n** were assembled (Figure 10). Then, the indole- and pyrrole-based compounds **64a-n** were used as dipolarophiles for the 1,3-dipolar cycloadditions with the azomethine ylides than can be generated from the decarboxylative reactions of dicarbonyl compounds (e.g., isatin, acenaphthoquinone and ninhydrin) and α-amino acids (e.g., sarcosine and proline). Initially, the optimization reactions comprising the multicomponent cycloaddition reaction of azomethine ylide derived from the decarboxylative reaction of isatin **65a** and proline **66a** with the indole-based dipolarophile **64a** (Table 5) were carried out. The multicomponent cycloaddition of azomethine ylide derived from isatin **65a** and proline **66a** with the indole-based dipolarophile **64a** in toluene at 80 ^{o}C gave the spirooxindolopyrrolizidine scaffold **67a** appended with an indolyl moiety as the single diastereomer in 36% yield (dr >95:5, entry 1, Table 5). The multicomponent cycloaddition of

azomethine ylide derived from isatin **65a** and proline **66a** with the indole-based dipolarophile **64a** in MeCN or 1,4-dioxane provided the spirooxindolopyrrolizidine scaffold **67a** with an improved yields (59% and 75%, dr >95:5, entries 2 and 3, Table 5). Similarly, the three component 1,3-dipolar cycloaddition of azomethine ylide derived from isatin **65a** and proline **66a** with **64a** in EtOH at 80 ^{o}C furnished the spirooxindolopyrrolizidine scaffold **67a** in 80% yield (dr >95:5, entry 4, Table 5). The yield of the spirooxindolopyrrolizidine scaffold **67a** slightly decreased to 69% when the multicomponent cycloaddition reaction of isatin **65a** and proline **66a** with the dipolarophile **64a** was performed in EtOH/1,4-dioxane mixture (entry 5, Table 5).

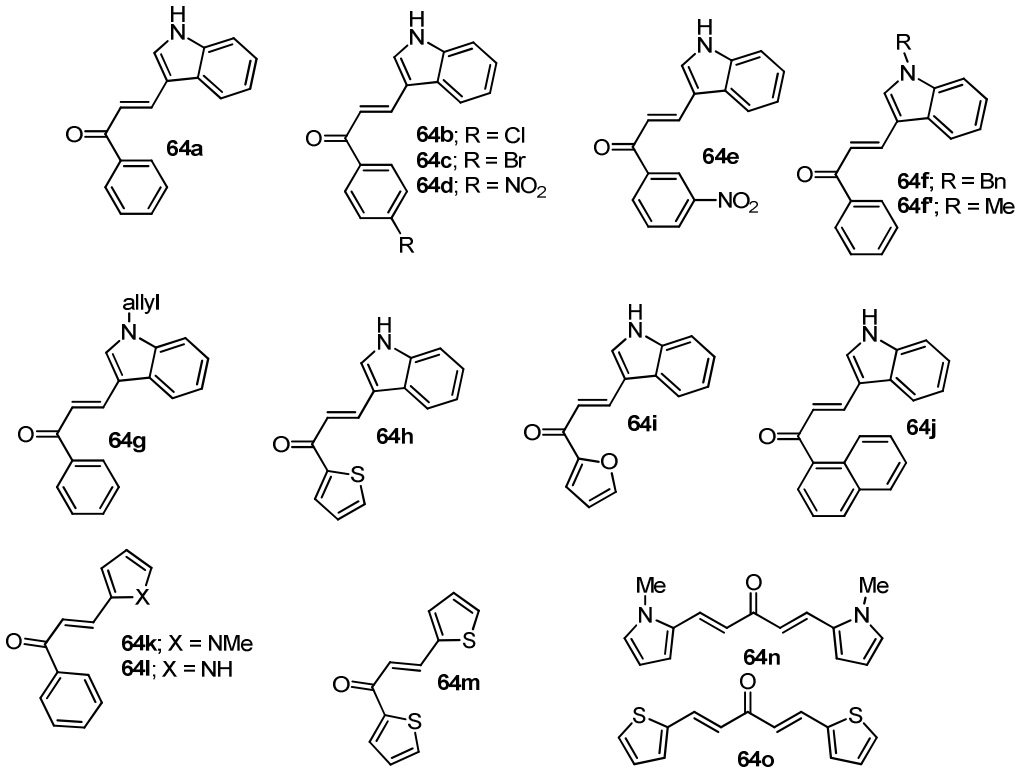
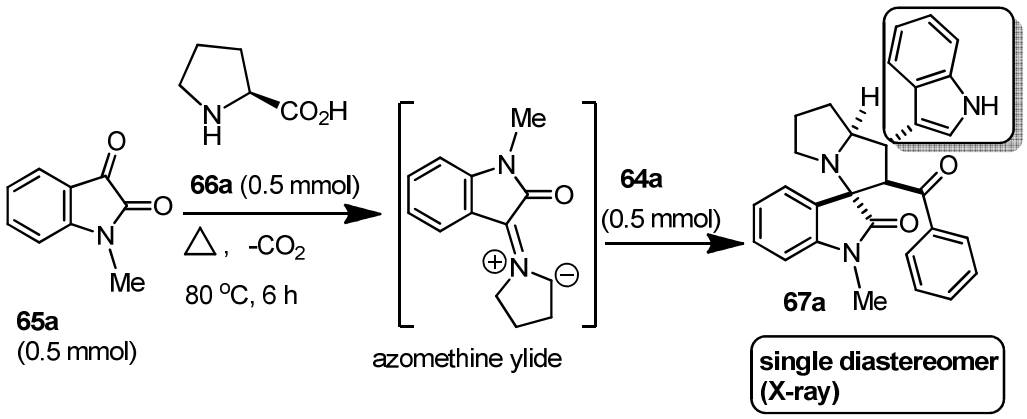


Figure 10. Indole / pyrrole -based dipolarophiles used for the construction of spiro-pyrrolidines / spiro-pyrrolizidines appended with the indole or pyrrole moieties.

Table 5. Optimization reactions: Diastereoselective synthesis of spiropyrrolizidine oxindole scaffold **67a** appended with an indolyl moiety.

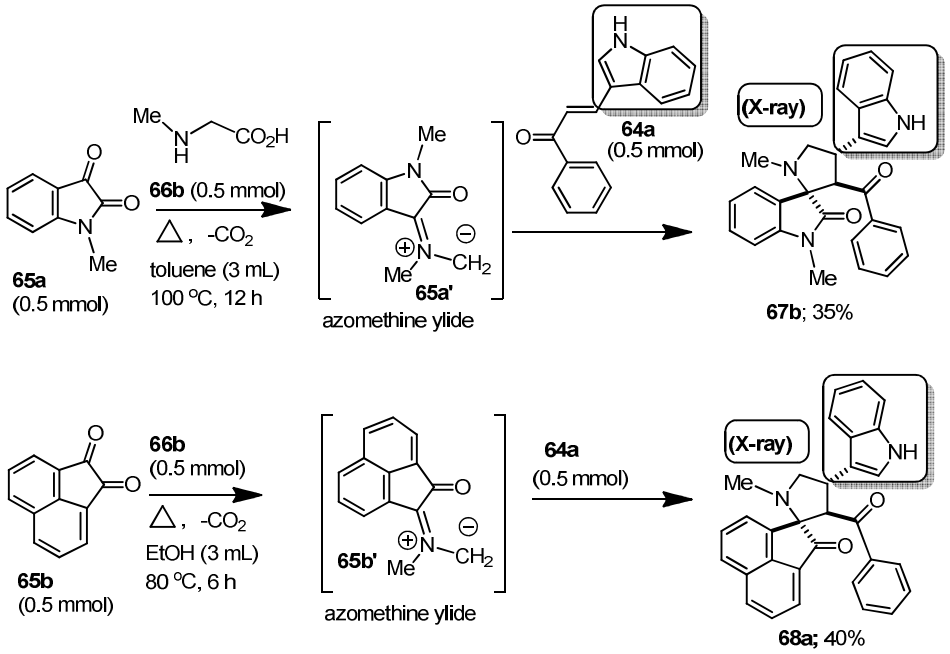


entry	solvent	**67a**: yield	*dr*
1	toluene (3 mL)	36	>95:5
2	MeCN (3 mL)	59	>95:5
3	1,4-dioxane (3 mL)	75	>95:5
4	EtOH (3 mL)	80	>95:5
5	EtOH/1,4-dioxane (1.5 : 1.5 mL)	69	>95:5

Then, by using the optimized reaction conditions of Table 5, the multicomponent 1,3-dipolar cycloaddition reaction of azomethine ylide derived from the decarboxylative reaction *N*-methyl isatin **65a** and sarcosine **66b** with indole-based dipolarophile **64a** was carried out. This reaction afforded the spirooxindolopyrrolidine scaffold **67b** appended with an indolyl moiety in 35% yield as a single diastereomer with very high diastereoselectivity (Scheme 27). Next we carried out the cycloaddition reaction of decarboxylative reaction of acenaphthoquinone **65b,** sarcosine **66b** with the indole-based dipolarophile **64a** gave the spiroacenaphthylenolylpyrrolidine scaffold **68a** appended with an indolyl moiety in 40% yield as a single diastereomer with high diastereoselectivity (Scheme 27).

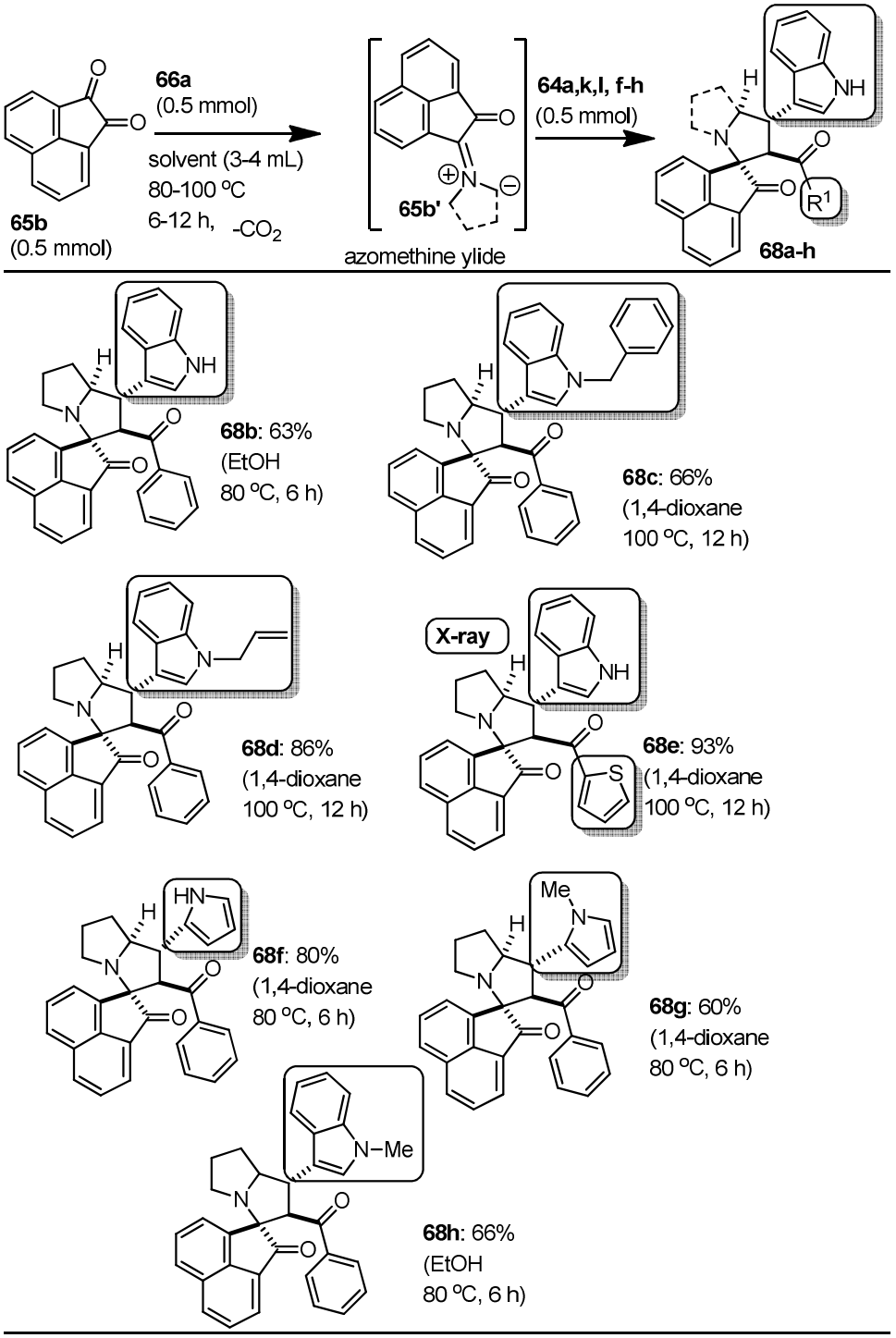
Subsequently, to increase substrate scope and enrich the library of spiro-pyrrolizidine appended with the indolyl-, pyrrolyl moieties at the spiropyrrolizidine ring, the multicomponent cycloaddition reactions of azomethine ylide derived from the decarboxylative reaction of acenaphthoquinone **65b** and proline **66a** with the corresponding indole-based dipolarophiles **64a**, **64f-h** and **64f′** were performed. These reactions afforded the spiroacenaphthylenolylpyrrolizidine

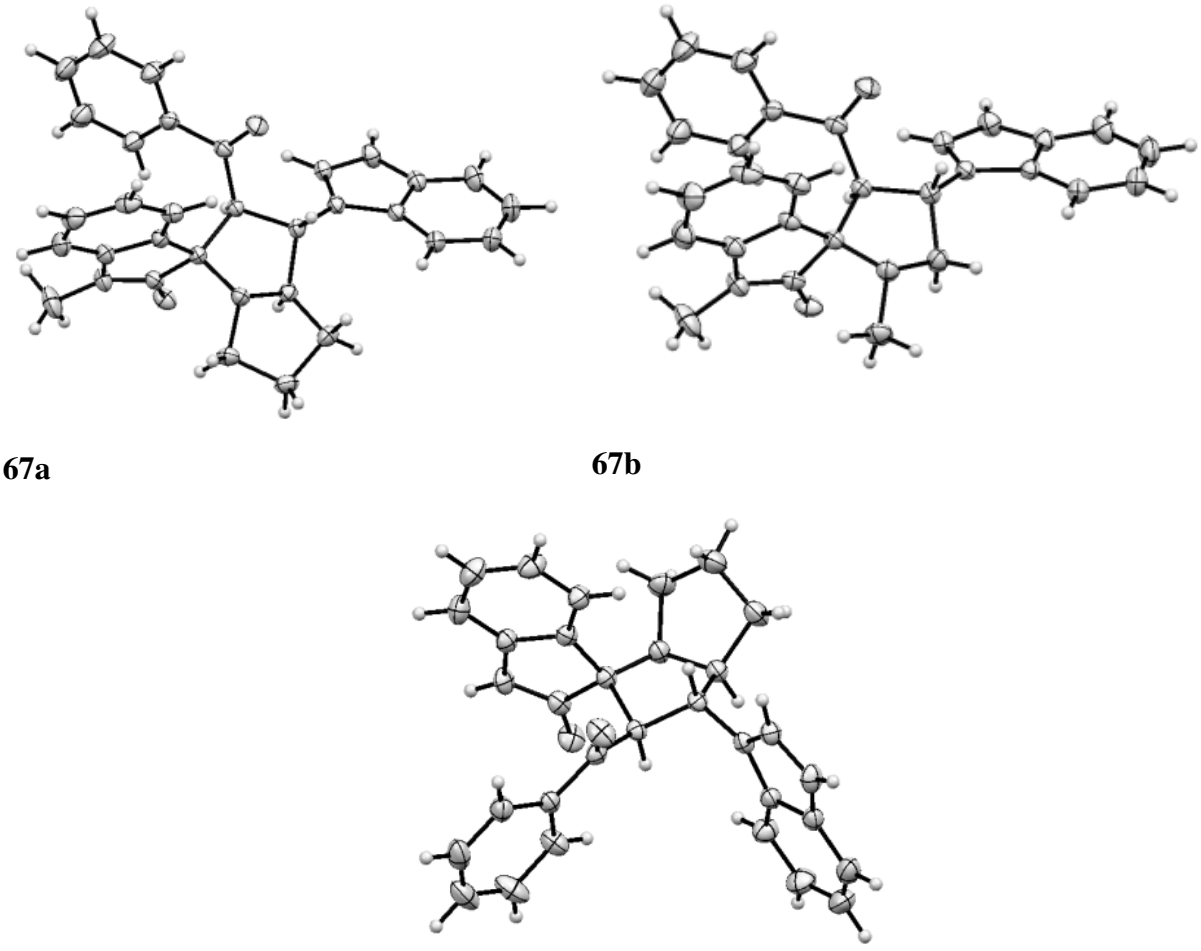
scaffolds **68b-e** and **68h** containing an indolyl moiety at the pyrrolizidine ring in 63-93% yields, respectively (Table 6). Likewise, the one pot cycloaddition reactions of azomethine ylide derived from the decarboxylative reaction of acenaphthoquinone **65b** and proline **66a** with the pyrrole-based dipolarophiles **64l,k** successfully afforded thecorrespondingspiroacenaphthylenolylpyrrolizidine derivatives **68f** and **68g** possessing a pyrrole moiety at the pyrrolizidine ring in 80 and 60% yields (Table 6). All these cycloaddition reactions shown in Table 6 afforded the spiroacenaphthylenolylpyrrolizidine derivatives **68b-h** as the major regio- and diastereomers with very good selectivity. Afterwards, the reactions of azomethine ylide derived from the decarboxylative reaction of acenaphthoquinone **65b** and proline **66a** with dipolarophiles **64n** and **64o** containing two 2π units were carried out. These reactions furnished thecorrespondingspiroacenaphthylenolylpyrrolizidine derivatives **68i** and **68j** in 80 and 64% yields (Scheme 28). Notably, in these reactions, the azomethine ylide cycloaddition underwent selectively with one of the 2π units of the respective dipolarophiles **64n** and **64o** to give the corresponding spiroacenaphthylenolylpyrrolizidine scaffolds **68i** and **68j** containing the pyrrole / thienyl and the α,β-unsaturated unit with high regioselectivity (Scheme 28).



Scheme 27. Diastereoselective synthesis of spiropyrrolidine scaffolds **67b** and **68a** appended with an indolyl moiety.

Table 6. Synthesis of spiroacenaphthylenolylpyrrolizidine scaffolds **68a-h** appended with the indolyl and pyrrolyl moieties.





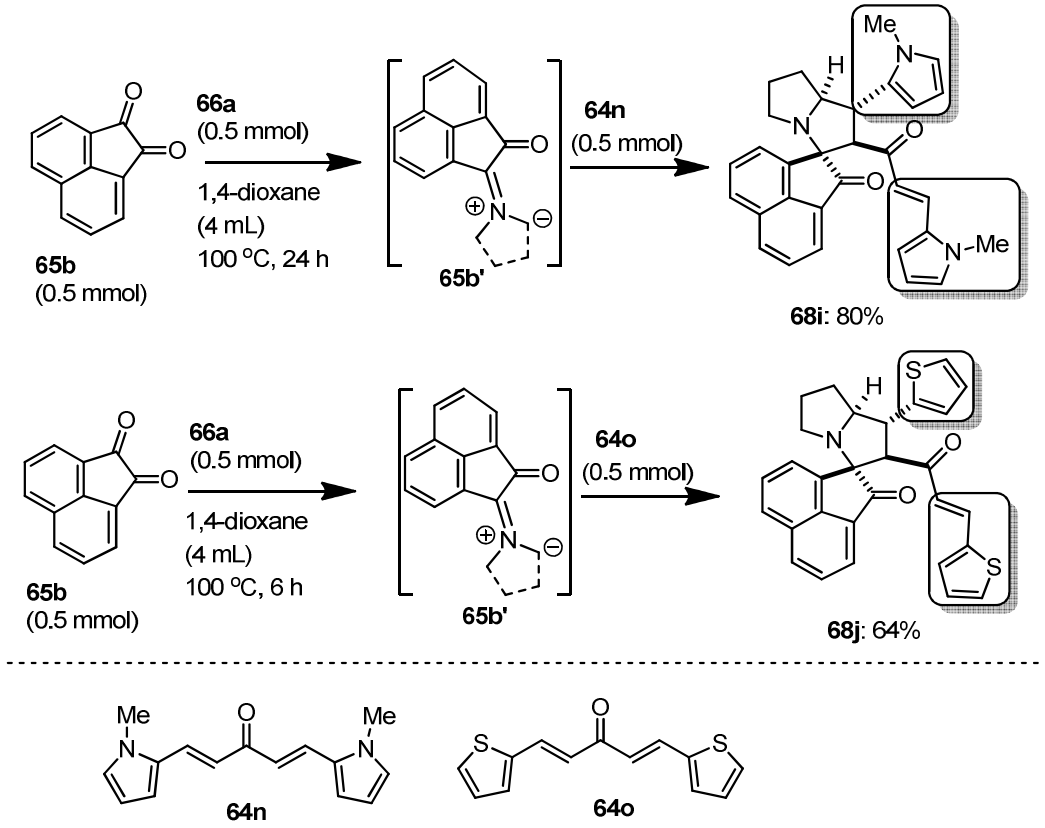
67a **67b**

67c

Figure 11. X-ray (ORTEP diagram) structures of the compounds **67a**, **67b** and **67c**.

Additionally, to enrich the library of spiropyrrolidines appended with indolyl-, pyrrolyl moieties at the spiro-pyrrolidine ring, the one pot 1,3-dipolar cycloaddition reaction of azomethine ylide derived from the decarboxylative reaction of ninhydrin **65c** and sarcosine **66b** with the indole-based dipolarophiles **64a-c** were also performed. These reactions afforded the corresponding spiro-1,3-indandionolylpyrrolidines **69a-c** appended with an indolyl moiety in 40-60% yields with very high diastereoselectivity (Scheme 29). Further, the [3+2] cycloaddition of azomethine

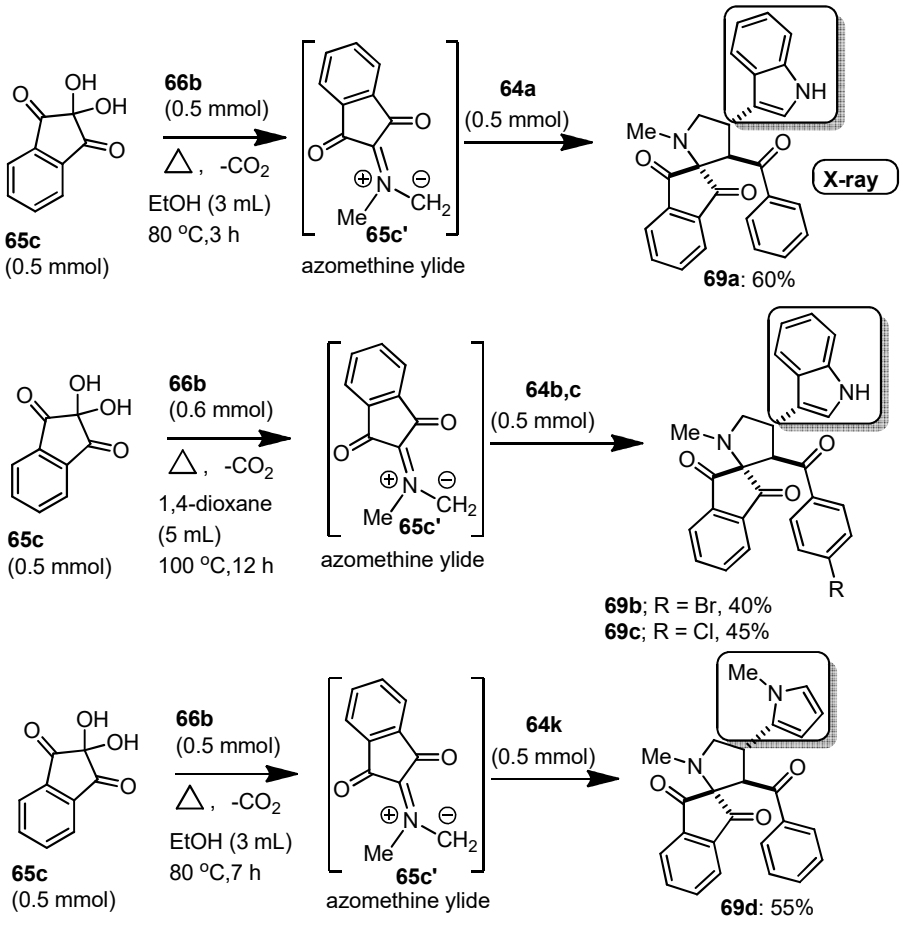
generated from **65c** and **66b** with **64k** gave the spiro-1,3-indandionolylpyrrolidine **69d** appended with a pyrrole moiety in 55% yield with high diastereoselectivity (Scheme 29).



Scheme 28. Stereoselective synthesis of spiroacenaphthylenolylpyrrolizidine derivatives **68i** and **68j** appended with the pyrrolyl and thienyl moieties.

Finally, to further extend the substrate scope and enrich the library of spiropyrrolizidine oxindoles with new examples of spiropyrrolizidine oxindole scaffolds appended with the indolyl-, pyrrolyl moieties at the pyrrolizidine ring, the three component 1,3-dipolar cycloaddition reactions of azomethine ylides derived from the decarboxylative reaction of various isatin derivatives **65d-f** and proline **66** with the indole-based dipolarophile **64a** were carried out. These reactions furnished the corresponding spiropyrrolizidine oxindole scaffolds **67c-e** appended with an indole moiety in 73-75% yields with very high diastereoselectivity (Table 7). Then, several other indole-based dipolarophiles **64b-e** and **64h-j** were used in the three component 1,3-dipolar cycloaddition reaction of azomethine ylide derived from the decarboxylative reactions of various isatin derivatives **65a** and **65d-i** and proline **66a** to give a variety of spiropyrrolizidine oxindole

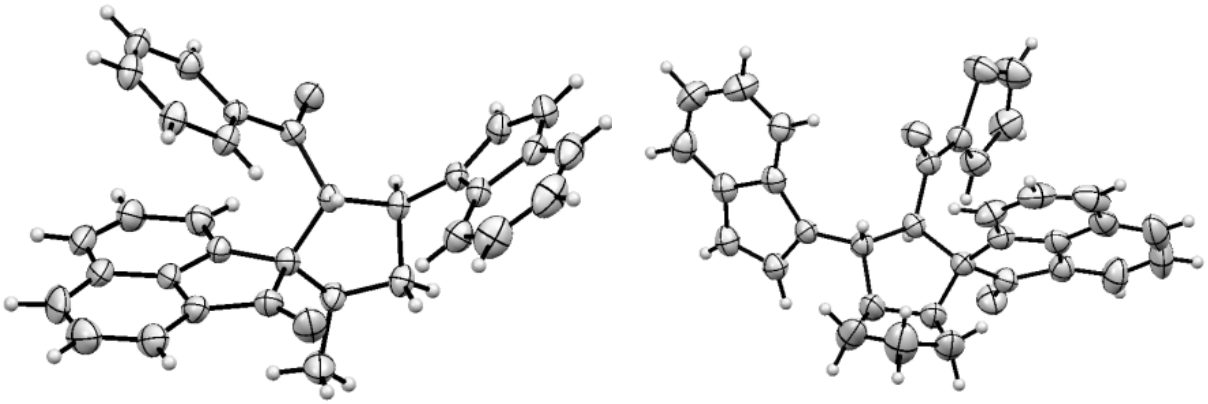
scaffolds **67f-n** appended with an indole moiety in 45-80% yields with very high diastereoselectivity (Table 7).



Scheme 29. Stereoselective construction of spiro-1,3-indandionolylpyrrolidines (**69a-d**) appended with the indolyl moieties.

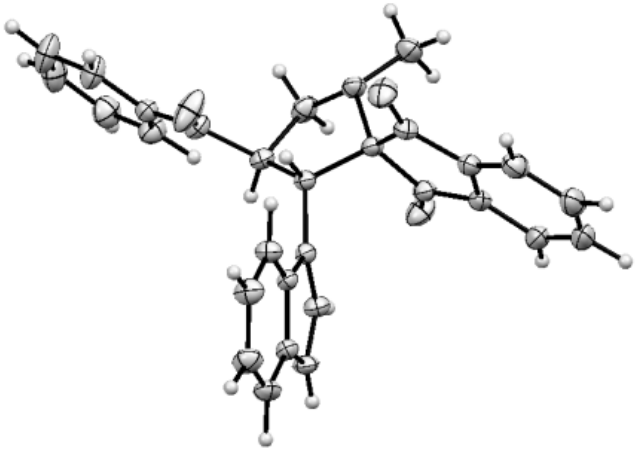
All the above described multicomponent cycloaddition reactions of azomethine ylides derived from the decarboxylative reactions of the corresponding dicarbonyl compounds (e.g., isatin, acenaphthoquinone and ninhydrin) and α-amino acids (e.g., sarcosine and proline) with indole / pyrrole-based dipolarophiles afforded the corresponding spiro-pyrrolidines / pyrrolizidines **67a-n**, **68a-j** and **69a-d** (major isomers) containing indole / pyrrole units with high regio- and diastereoselectivity. The structure and stereochemistry of representative spiro-pyrrolidines / pyrrolizidines **67a**, **67b**, **67c**, **68a**, **68e** and **69a** (major isomers) were unambiguously assigned from their respective X-ray structures (Figures 11 and 12). After assigning the stereochemistry of

representative spiro-pyrrolidines / pyrrolizidines **67a**, **67b**, **67c**, **68a**, **68e** and **69a** (major isomers), the regio- and diastereoselectivity and the stereochemistry of the other major isomers of the respective series of the compounds **67a-n**, **68a-j**, and **69a-d** (major isomers) were assigned based on the similarity in their NMR spectral pattern in conjunction with the X-ray structures of the corresponding spiro-pyrrolidines / pyrrolizidines **67a**, **67b**, **67c**, **68a**, **68e**, and **69a** (major isomers).



68a

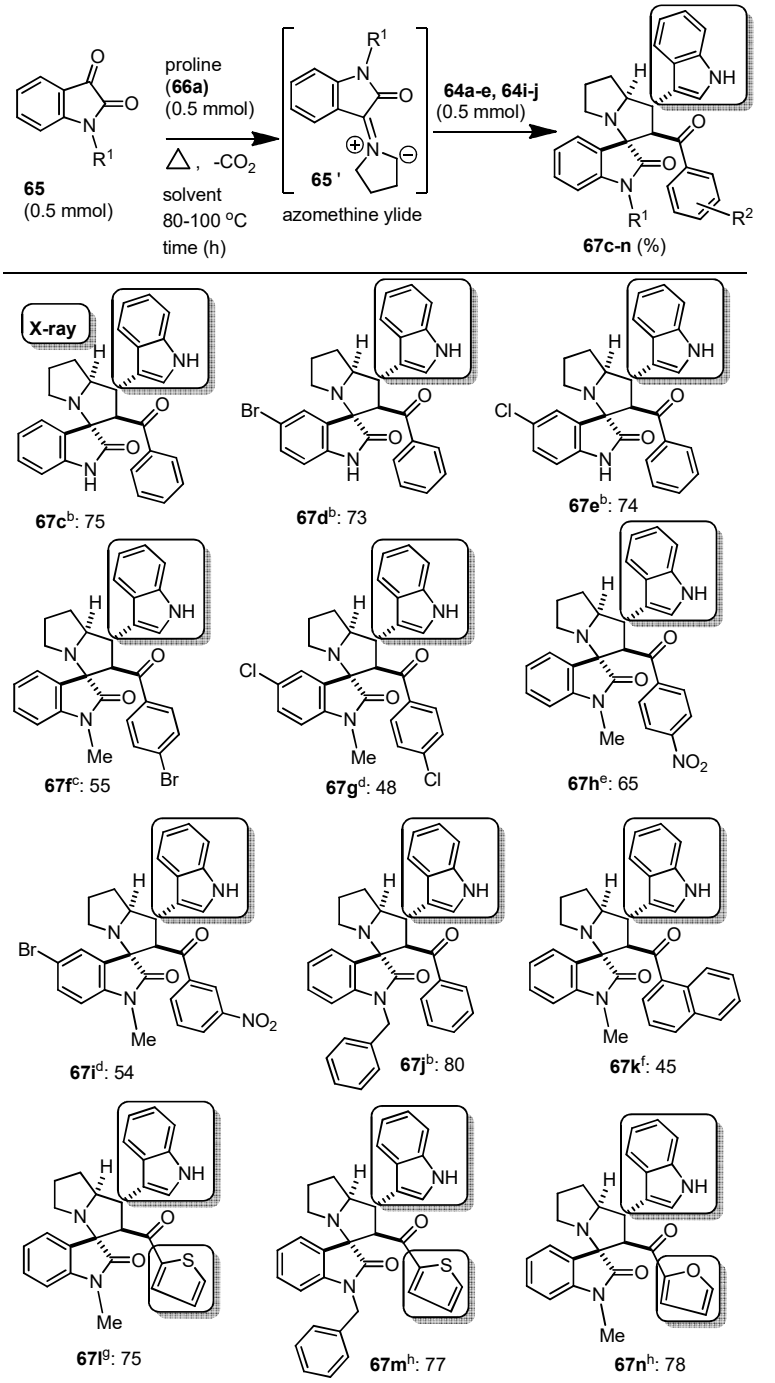
68e



69a

Figure 12. X-ray (ORTEP diagram) structures of the compounds **68a**, **68e** and **69a**.

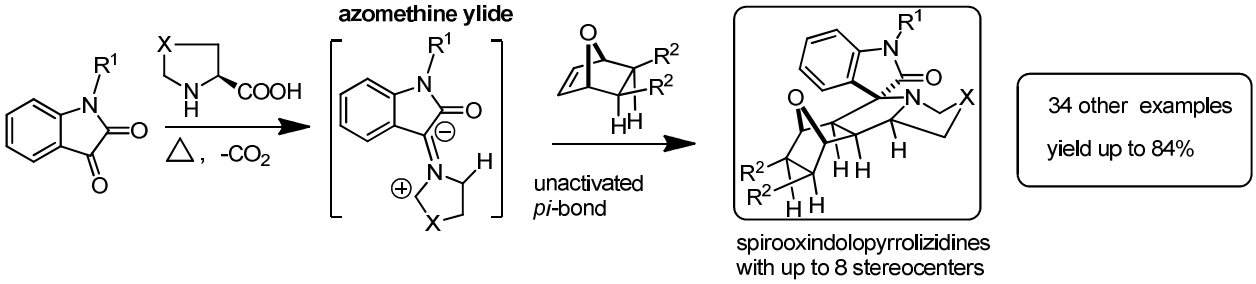
Table 7: Stereoselective synthesis of oxindole scaffolds **67c-n** appended with an indolyl moiety.[a]



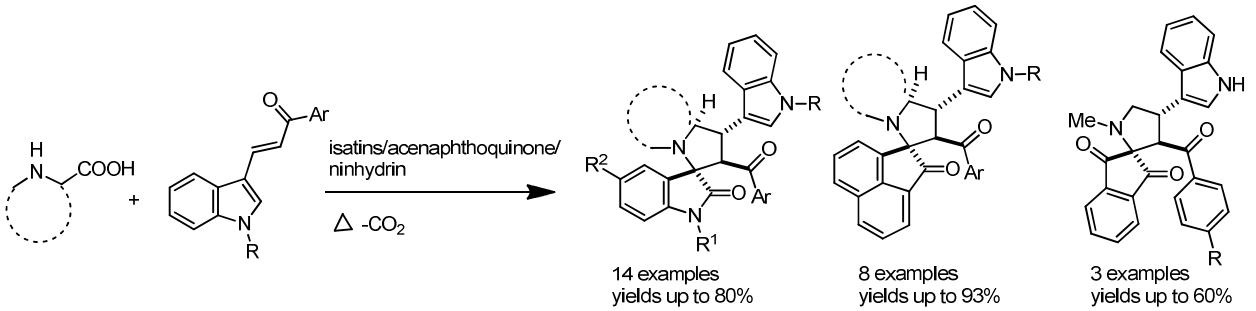
[a]**65a**: *N*-methyl isatin, **65d**: isatin, **65e**: 5-bromoisatin, **65f**: 5-chloroisatin, **65g**: *N*-methyl 5-chloroisatin, **65h**: *N*-methyl 5-bromoisatin, **65i**: *N*-benzyl isatin. [b] EtOH (3 mL) at 80 °C, 6 h. [c] 1,4-Dioxane (4 mL) at 80 °C, 14 h. [d] 1,4-Dioxane (4 mL) at 100 °C, 18 h. [e] 1,4-Dioxane (4 mL) at 100 °C, 6 h. [f] 1,4-Dioxane (4 mL) at 80 °C, 24 h. [g] EtOH (3 mL) at 80 °C, 9 h. [h] 1,4-Dioxane (5 mL) at 100 °C, 12 h.

Conclusions.

In summary, the chapter 2a revealed; (a) the highly diastereoselective one pot 1,3-dipolar cycloaddition reaction of azomethine ylides generated from the decarboxylative reactions of 1,2-dicarbonyl compounds and α-amino acids with various unactivated norbornene-type dipolarophiles, (b) the scope and generality of the diastereoselective 1,3-dipolar cycloaddition reaction of azomethine ylides with various unactivated norbornene-type dipolarophiles by synthesizing several novel norbornane-fused- spirooxindolopyrrolidines, spiroacenaphthylenolyl-pyrrolidines, spiro-1,3-indandionolylpyrrolidines and spirooxindolopyrrolizidines having a fascinating architecture consisting of an array of stereocenters with an excellent degree of stereocontrol, (c) the 1,3-dipolar cycloaddition reaction of azomethine ylides generated from isatin and proline with norbornene dipolarophiles led to construction of spirooxindolopyrrolizidines containing eight stereocenters in a single step reaction.



Further, the chapter 2b revealed the highly regio- and diastereoselective 1,3-dipolar cycloaddition reaction of azomethine ylides with various indole and pyrrole-based dipolarophiles, which has led to construction of a new set of spirooxindolo-pyrrolidine/pyrrolizidine, spiroacenaphthylenolyl- pyrrolidine / pyrrolizidine and spiro-1,3-indandionolyl- pyrrolidine / pyrrolizidine scaffolds appended with indolyl or pyrrolyl moieties.



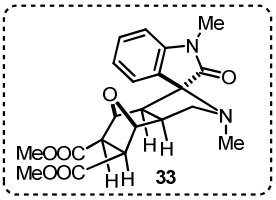
All the cycloaddition reactions were stereoselective and all the compounds included in the chapter 2 of this thesis are characterized by various characterization techniques including ^{1}H and ^{13}C NMR, IR, X-ray diffraction and HRMS. The stereochemistry of representative products was established from 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. The norbornane-fused and indole/pyrrole containing spirooxindolo-pyrrolidine / pyrrolizidine, spiro-1,3-indandionolylpyrrolidine and spiroacenaphthylenolyl- pyrrolidine / pyrrolizidine derivatives will be screened for their biological activities in collaboration with a medicinal chemistry lab and further work is in progress in this direction.

Experimental section.

General: Melting points are uncorrected. IR spectra were recorded as neat or thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with 400 and 100 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 conducted in anhydrous solvent under nitrogen atmosphere where required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask by using a syringe. Thin layer chromatography (TLC) was performed on silica plates or neutral Al_2O_3 and components were visualized by observation under iodine. Isolated yields of all the products are reported (yields were not optimized). Ratios of diastereomers were determined from the ^{1}H (or) ^{13}C spectra of crude reaction mixture. The stereochemistry of the products were assigned based on the X-ray structure analysis of representative compounds. Good quality single crystals were grown by using a combination of dichloromethane or hexanes or methanol or acetone by slow solvent evaporation technique at 25 °C and the single crystal X-ray diffraction data for all the compounds was collected using four circle CCD diffractometer (monochromatic Mo Kα radiation). Data collection and unit cell refinement for the data sets were done using APEX-II suit. The crystal structures were solved using Olex2 or WinGx packages using SHELXS97, and the structures were refined using SHELXL97. All the hydrogen atoms have been fixed at their geometrically ideal positions and refined using the riding model available within SHELXS97. All figures have been generated using Mercury.

Procedure A for synthesis of spiropyrrolidines and pyrrolizidines by using norbornene dipolarophile: A dry flask containing isatin or acenaphthenequinone or ninhydrin (2, 1, 0.5 mmol), sarcosine or *N*-benzylglycine hydrochloride or L-proline or L-thiaproline (1.0-1.1 equiv) and norbornene dipolarophile (1 equiv) in dry solvent (3-12 mL) was heated to the appropriate temperature and time as shown in the respective Tables/Schemes. After the completion of reaction (monitored by TLC), the reaction mixture was cooled to rt and subjected to rotary evaporation which afforded a crude mixture. Purification of the crude reaction mixture through neutral alumina or silica gel column choromatography afforded the respective norbornane-fused-spirooxindolopyrrolidines or spiroacenaphthylenolylpyrrolidines or spiro-1,3-indandionolylpyrrolidines or spiro-oxindolopyrrolizidines (see the coressponding Tables/Schemes for the appropriate or exact amount of solvent/reagents).

Procedure B for the preparation of the spiro-pyrrolidine/pyrrolizidines containing heteroaryl moieties 67/68/69: A oven dried flask containing an appropriate dicarbonyl compound **65** (isatin or acenaphthoquinone or ninhydrin, 0.5 mmol), an appropriate α-amino acid **66** (sarcosine or L-proline, 0.6 mmol) and an appropriate dipolarophile **64**(0.5 mmol) in an appropriate dry solvent (3-5 mL) was heated (see the respective Tables/Schemes for time/temperature). Then, the reaction mixture was cooled to rt and solvent was evaporated, which afforded a crude reaction mixture. Then, the crude mixture was subjected to the column chromatography purification, which gave the corresponding spiro-pyrrolidine/pyrrolizidines containing heteroaryl moieties **67/68/69** (see the corresponding Tables/Schemes for specific entries).

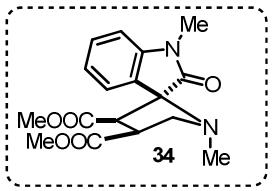


33

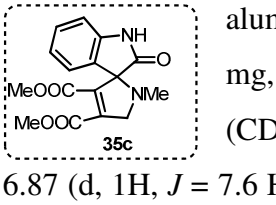
(1S*,3aS*,5R*,6S*)-Dimethyl 1',2-dimethyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate (**33**): Following the general procedure described above **33** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 60:40); as a colorless solid (220 mg, 55%), mp: 223-225 ^{o}C (MeOH:hexane = 1:1); FT-IR (KBR): 2948, 2906, 1750, 1717, 1606, 1467, 1437, 1279 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, 1H, *J* = 7.6 Hz), 7.34 (t, 1H, *J*= 7.6 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), 6.85 (d, 1H, *J* = 7.6 Hz), 4.88 (s, 1H), 4.56 (s, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.47 (t, 1H, *J* = 8.2 Hz), 3.20 (s, 3H), 3.08 (d, 1H, *J* = 9.6 Hz), 3.01-2.98 (m, 1H), 2.87 (d, 1H, *J*= 9.6 Hz), 2.89-2.85 (m, 1H), 2.65 (d, 1H, *J* = 8.2 Hz), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.2, 171.1, 144.0, 129.4, 127.8,

126.1, 122.7, 108.3, 82.1, 80.4, 74.2, 58.4, 55.8, 52.2, 52.1, 51.5, 50.7, 47.5, 35.1, 26.3; MS (CI): m/z (%) 402 ([M+2]$^+$, 401 ([M+1]$^+$, 100), 30) 195 (8), 175 (7), 111 (30), 79 (15); HRMS (ESI) calcd for $C_{21}H_{24}N_2O_6Na$ [M+Na]$^+$ 423.1532 found 423.1532.

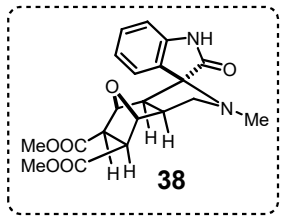
(2'S*,3'R*,4'S*)-Dimethyl 1,1'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidine]-3',4'-dicarboxylate(**34**): Following the general procedure described above **34** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 40:60); as a colorless solid (216mg, 65%); mp: 149-151 ^oC (MeOH:hexane = 1:1); FT-IR (KBR): 2954, 2864, 1732, 1699, 1613, 1474, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.25 (m, 2H), 7.04 (t, 1H, *J* = 7.6 Hz), 6.82 (d, 1H, *J* = 7.6 Hz), 4.02-3.99 (m, 1H), 3.78-3.74 (m, 1H), 3.70 (s, 3H), 3.55 (d, 1H, *J* = 8.9 Hz), 3.42 (s, 3H), 3.38 (d, 1H, *J* = 8.9 Hz), 3.19 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.8, 172.6, 170.4, 144.0, 129.6, 125.4, 125.4, 122.8, 108.1, 73.7, 54.4, 53.6, 52.0, 51.6, 43.0, 35.3, 26.1; MS (CI): m/z (%) 334 ([M+2]$^+$, 20), 333 ([M+1]$^+$, 100), 305 (13), 270 (14), 258 (17), 241 (9), 212 (7); HRMS (ESI) calcd for $C_{17}H_{21}N_2O_5$ [M+H]$^+$ 333.1450 found 333.1450.



Dimethyl 1'-methyl-2-oxo-1',5'-dihydrospiro[indoline-3,2'-pyrrole]-3',4'-dicarboxylate (**35c**): Following the general procedure described above **35c** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 60:40); as a semisolid (174 mg, 55%); FT-IR (DCM): 3443, 1722, 1620, 1470, 1276 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (s, 1H), 7.26-7.21 (m, 2H), 7.02 (t, 1H, *J* = 7.6 Hz), 6.87 (d, 1H, *J* = 7.6 Hz), 4.23 (d, 1H, *J* = 15.0 Hz), 4.14 (d, 1H, *J* = 15.0 Hz), 3.81 (s, 3H), 3.52 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3, 163.3, 162.4, 141.7, 141.3, 138.5, 130.0, 127.1, 125.4, 122.9, 110.4, 79.5, 60.5, 52.4, 52.2, 34.5; MS (CI): m/z (%) 317 ([M+1]$^+$, 11), 289 (5), 271 (15), 258 (16), 257 (100), 243 (18), 239 (4); HRMS (ESI) calcd for $C_{16}H_{17}N_2O_5$ [M+H]$^+$ 317.1137 found 317.1137.

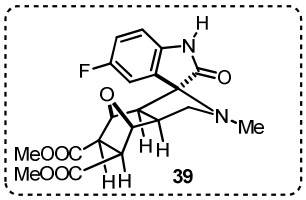


(1S*,3aS*,6S*)-Dimethyl 2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate(**38**): Following the general procedure described above **38** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 65:35); as a colorless solid (181 mg,



47%); mp: 234-236 ^{o}C; FT-IR (KBR): 3202, 2949, 1740, 1712, 1619, 1468, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (s, 1H), 7.53 (d, 1H, J = 7.6 Hz), 7.22 (t, 1H, J = 7.6 Hz), 7.05 (t, 1H, J = 7.6 Hz), 6.89 (d, 1H, J = 7.6 Hz), 4.88 (s, 1H), 4.55 (s, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.45 (t, 1H, J = 8.2 Hz), 3.07 (d, 1H, J = 9.6 Hz), 2.98-2.95 (m, 1H), 2.89 (d, 1H, J = 9.6 Hz), 2.88-2.84 (m, 1H), 2.71 (d, 1H, J = 8.24 Hz), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.5, 171.2, 171.1, 141.1, 129.1, 128.2, 126.4, 122.8, 110.1, 81.7, 80.0, 74.6, 58.5, 55.8, 52.2, 52.1, 51.4, 50.6, 47.6, 35.1; MS (CI): m/z (%) 388 ([M+2]$^{+}$, 20), 387 ([M+1]$^{+}$, 100), 355 (13), 327 (4), 284 (2), 252 (3); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_6Na$ [M+Na]$^{+}$ 409.1376 found 409.1375.

(1S*,3aS*,5R*,6S*)-Dimethyl 5'-fluoro-2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate **(39):** Following the general procedure described above **39** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 65:35); as a colorless solid (364 mg, 45%); mp: 207-209 ^{o}C (MeOH:hexane = 1:1); FT-IR (KBR): 3223, 2856, 1746, 1719, 1489, 1473, 1287 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (s, 1H), 7.30 (dd, 1H, J_1 = 8.4, J_2 = 2.6 Hz), 6.95 (dt, 1H, J_1 = 8.4, J_2 = 2.6 Hz), 6.84 (dd, 1H, J_1 = 8.5, J_2 = 4.1 Hz), 4.85 (s, 1H), 4.52 (s, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.43 (t, 1H, J = 8.0 Hz), 3.07 (d, 1H, J = 9.6 Hz), 2.93-2.85 (m, 2H), 2.90 (d, 1H, J = 9.6), 2.73 (d, 1H, J = 8.0 Hz), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.9, 171.2, 171.1, 158.9 (d, $J_{C\text{-}F}$ = 240.0 Hz), 137.2 (d, $J_{C\text{-}F}$ = 2.0 Hz), 128.0 (d, $J_{C\text{-}F}$ = 8.0 Hz), 116.0 (d, $J_{C\text{-}F}$ = 27.0 Hz), 115.8 (d, $J_{C\text{-}F}$ = 26.0 Hz), 110.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 81.5, 79.9, 75.1, 58.5, 56.0, 52.3, 52.3, 51.3, 50.6, 47.8, 35.1; MS (CI): m/z (%) 405 ([M+1]$^{+}$, 2), 404 ([M]$^{+}$, 20), 403 (100); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_6F$ [M+H]$^{+}$ 405.1462 found 405.1461.



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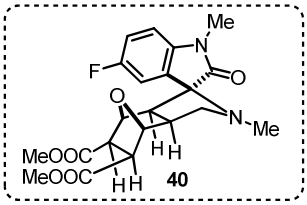
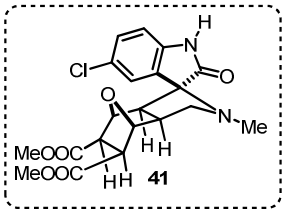
(1S*,3aS*,5R*,6S*)-Dimethyl 5'-fluoro-1',2-dimethyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate(**40**): Following the general procedure described above **40** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 60:40); as a colorless solid (184 mg, 44%); mp: 177-179 ^{o}C; FT-IR (KBR): 2956, 1749, 1699, 1619, 1496 1202 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (dd, 1H, J_1 = 8.4, J_2 = 2.6 Hz), 7.03 (dt, 1H, J_1= 8.4, J_2 = 2.6 Hz), 6.77 (dd, 1H, J_1 = 8.5, J_2 = 4.1 Hz), 4.86 (s, 1H), 4.54 (s, 1H), 3.68 (s,



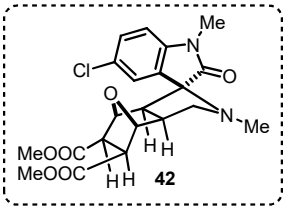
40

3H), 3.61 (s, 3H), 3.45 (t, 1H, J = 8.0 Hz), 3.18 (s, 3H), 3.08 (d, 1H, J = 9.5 Hz), 2.96-2.93 (m, 1H), 2.88 (d, 1H, J = 9.5 Hz), 2.86-2.85 (m, 1H), 2.68 (d, 1H, J = 8.0 Hz), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.9, 171.1, 171.0, 159.2 (d, $J_{C\text{-}F}$ = 241.0 Hz), 140.0 (d, $J_{C\text{-}F}$ = 2.0 Hz), 127.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 115.8 (d, $J_{C\text{-}F}$ = 36.0 Hz), 115.6 (d, $J_{C\text{-}F}$ = 36.0 Hz), 108.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 81.9, 79.9, 74.5, 58.5, 55.9, 52.2, 52.2, 51.4, 50.6, 47.6, 35.0, 26.2; MS (CI): m/z (%) 421 ([M+3]$^+$, 4), 420 ([M+2]$^+$, 40), 419 ([M+1]$^+$, 100), 341 (2), 195 (2), 163 (2), 97 (12), 79 (5), 65(5); HRMS (ESI) calcd for $C_{21}H_{24}N_2O_6F$ [M+H]$^+$ 419.1618 found 419.1620.

(1S*,3aS*,6S*)-Dimethyl 5'-chloro-2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate (**41**): Following the general procedure described above **41** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 65:35); as a colorless solid (95 mg, 45%); mp: 240-242 ^{o}C; FT-IR (KBR): 3448, 2957, 2867, 1736, 1724, 1467, 1283 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 10.24 (s, 1H), 7.39 (s, 1H), 7.20 (d, 1H, J = 8.2 Hz), 6.82 (d, 1H, J = 8.2 Hz), 4.79 (s, 1H), 4.52 (s, 1H), 3.64 (s, 3H), 3.58 (s, 3H), 3.41 (t, 1H, J = 8.3 Hz), 3.14 (d, 1H, J = 9.5 Hz), 2.94 (d, 1H, J = 9.5 Hz), 2.94-2.92 (m, 1H), 2.82-2.80 (m, 1H), 2.66 (d, 1H, J = 8.3 Hz), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 184.4, 175.9, 146.3, 133.7, 133.5, 132.1, 131.5, 115.9, 87.1, 84.6, 79.3, 63.2, 60.0, 56.7, 56.6, 55.9, 54.9, 51.9, 39.9; MS (CI): m/z (%) 421 ([M+1]$^+$, 25), 420 ([M]$^+$, 20), 419 (100); HRMS (ESI) calcd for $C_{20}H_{21}N_2O_6NaCl$ [M+Na]$^+$ 443.0986 found 443.0985.

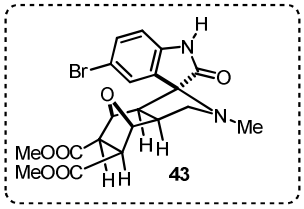


(1S*,3aS*,6S*)-Dimethyl 5'-chloro-1',2-dimethyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate **(42):** Following the general procedure described above **42** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 60:40); as a colorless solid (87 mg, 40%); mp: 112-114 ^{o}C; FT-IR (KBR): 2948, 1741, 1715, 1607, 1437, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, 1H, J = 2.1 Hz), 7.30 (dd, 1H, J_1= 8.3, J_2= 2.1 Hz), 6.77 (d, 1H, J= 8.3 Hz), 4.87 (s, 1H), 4.56 (s, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.45 (t, 1H, J = 8.2 Hz), 3.18 (s, 3H), 3.08 (d, 1H, J = 9.5 Hz), 3.00-2.96 (m, 1H), 2.87 (d, 1H, J = 9.5 Hz), 2.86-2.84 (m, 1H), 2.65 (d, 1H, J = 8.2 Hz), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.8, 171.1, 171.0, 142.6, 129.2, 128.5, 127.9, 127.7, 109.0, 82.1,

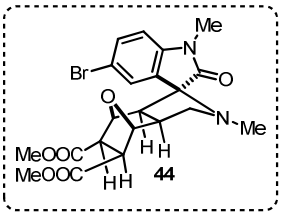


79.9, 74.3, 58.4, 55.9, 52.2, 51.4, 50.6, 47.5, 35.1, 26.1; MS (CI): m/z (%) 437 ($[M+3]^+$, 50), 436 ($[M+2]^+$, 40), 435 ($[M+1]^+$, 100), 357 (2), 209 (3), 195 (5), 163 (2%); HRMS (ESI) calcd for $C_{21}H_{24}N_2O_6Cl$ $[M+H]^+$ 435.1323 found 435.1322.

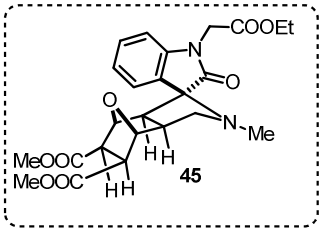
(1S*,3aS*,6S*)-Dimethyl 5'-bromo-2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate **(43):** Following the general procedure described above **43** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 65:35); as a colorless solid (116 mg, 50%); mp: 250-252 ^oC; FT-IR (KBR): 3426, 2956, 2866, 1722, 1615, 1437, 1279cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 10.11 (s, 1H), 7.53 (s, 1H), 7.32 (d, 1H, J = 8.1 Hz), 6.76 (d, 1H, J = 8.1 Hz), 4.79 (s, 1H), 4.53 (s, 1H), 3.63 (s, 3H), 3.58 (s, 3H), 3.40 (t, 1H, J = 8.1 Hz), 3.08 (d, 1H, J = 9.4 Hz), 3.00-2.79 (m, 3H), 2.63 (d, 1H, J = 8.1 Hz), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 184.4, 175.9, 175.8, 146.5, 136.6, 134.8, 133.7, 119.3, 116.4, 87.0, 84.5, 79.3, 63.1, 60.2, 56.8, 56.7, 56.0, 55.1, 52.0 39.9; MS (CI): m/z (%) 467 ($[M+3]^+$, 100), 466 ($[M+2]^+$, 40), 465 ($[M+1]^+$, 100), 387 (20), 359 (5), 195 (15); HRMS (ESI) calcd for $C_{20}H_{21}N_2O_6NaBr$ $[M+Na]^+$ 487.0481 found 487.0480.

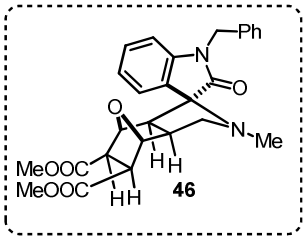


(1S*,3aS*,6S*)-Dimethyl 5'-bromo-1',2-dimethyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate **(44):** Following the general procedure described above **44** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 60:40); as a colorless solid (430 mg, 45%); mp: 103-105 ^oC; FT-IR (KBR): 2946, 2829, 1741, 1606, 1486, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, 1H, J = 2.0 Hz), 7.45 (dd, 1H, J_1= 8.2, J_2 = 2.0 Hz), 6.71 (d, 1H, J= 8.2 Hz), 4.85 (s, 1H), 4.56 (s, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 3.43 (t, 1H, J = 8.0 Hz), 3.15 (s, 3H), 3.06 (d, 1H, J = 9.5 Hz), 2.98-2.94 (m, 1H), 2.85 (d, 1H, J = 9.5 Hz), 2.84-2.82 (m, 1H), 2.62 (d, 1H, J = 8.0 Hz), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.7, 171.1, 171.0, 143.1, 132.2, 130.3, 128.3, 115.9, 109.5, 82.2, 79.9, 74.3, 58.4, 55.9, 52.2, 52.2, 51.4, 50.6, 47.5, 35.1, 26.1; MS (CI): m/z (%) 481 ($[M+3]^+$, 100), 479 ($[M+1]^+$, 100), 401 (30), 195(10), 163 (5); HRMS (ESI) calcd for $C_{21}H_{24}N_2O_6Br$ $[M+H]^+$ 479.0818 found 479.0817.



***(1S*,3aS*,5R*,6S*)-Dimethyl 1'-(2-ethoxy-2-oxoethyl)-2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate* (45):** Following the general procedure described above **45** was obtained after purification by neutral alumina column chromatography(EtOAc:Hexane = 65:35); as a colorless solid (231 mg, 49%); mp: 120-122 ^{o}C; FT-IR (KBR): 2948, 2823, 1745, 1701, 1610, 1466, 1208 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, 1H, *J* = 6.7 Hz), 7.28 (t, 1H, *J*= 6.7 Hz), 7.10 (t, 1H, *J*= 6.7 Hz), 6.70 (d, 1H, *J* = 6.7 Hz), 4.86 (s, 1H), 4.59 (s, 1H), 4.52 (d, 1H, *J* = 17.5 Hz), 4.30 (d, 1H, *J* = 17.5 Hz), 4.15 (q, 2H, *J* = 7.2 Hz), 3.66 (s, 3H), 3.58 (s, 3H), 3.45 (t, 1H, *J* = 8.1 Hz), 3.06 (d, 1H, *J* = 9.5 Hz), 3.01-2.98 (m, 1H), 2.86 (d, 1H, *J* = 9.5 Hz), 2.85-2.83 (m, 1H), 2.64 (d, 1H, *J* = 8.1 Hz), 1.99 (s, 3H), 1.22 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1, 171.2, 171.1, 167.4, 142.8, 129.3, 128.0, 125.8, 123.1, 108.0, 82.2, 80.1, 74.0, 61.7, 58.5, 55.8, 52.1, 52.0, 51.4, 50.6, 47.4, 41.0, 35.1, 14.0; MS (CI): m/z (%) 474 ([M+2]$^{+}$, 30), 473 ([M+1]$^{+}$, 100), 463 (10), 369 (2), 94 (2); HRMS (ESI) calcd for $C_{24}H_{28}N_2O_8Na$ [M+Na]$^{+}$ 495.1743 found 495.1745.

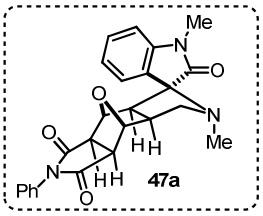




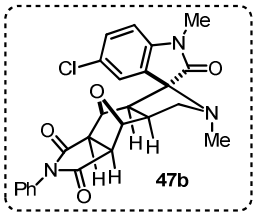
***(1S*,3aS*,5R*,6S*)-Dimethyl 1'-benzyl-2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,3'-indoline]-5,6-dicarboxylate* (46):** Following the general procedure described above **46** was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 60:40); as a colorless solid (476 mg, 50%); mp: 178-180 ^{o}C; FT-IR (KBR): 2948, 2842, 1743, 1704, 1609, 1462, 1362, 1174 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, 1H, *J* = 7.5 Hz), 7.31-7.17 (m, 5H), 7.19 (t, 1H, *J*= 7.5 Hz), 7.06 (t, 1H, *J*= 7.5 Hz), 6.72 (d, 1H, *J*= 7.5 Hz), 4.98 (d, 1H, *J* = 15.5 Hz), 4.88 (s, 1H), 4.73 (d, 1H, *J* = 15.5 Hz), 4.64 (s, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.49 (t, 1H, *J* = 8.1 Hz), 3.08 (d, 1H, *J* = 9.5 Hz), 3.04-3.01 (m, 1H), 2.87 (d, 1H, *J* = 9.5 Hz), 2.86-2.85 (m, 1H), 2.65 (d, 1H, *J* = 8.1 Hz), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.3, 171.2, 171.1, 143.2, 135.8, 129.0, 128.8, 127.7, 127.3, 126.2, 123.0, 109.1, 82.5, 80.0, 74.2, 58.5, 55.6, 52.2, 52.1, 51.5, 50.7, 47.3, 43.6, 35.3; MS (CI): m/z (%) 477 ([M+1]$^{+}$, 4), 476 ([M]$^{+}$, 30), 475 (100), 461 (50), 457 (10), 414 (10), 237 (15); HRMS (ESI) calcd for $C_{27}H_{29}N_2O_6$ [M+H]$^{+}$ 477.2026 found 477.2025.

***(1S*,3aS*,4aR*,7aS*)-1',2-Dimethyl-6-phenyl-3,3a,4,4a,8,8a-hexahydro-2H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,3'-indoline]-2',5,7(6H,7aH)-trione* (47a):** Following the general

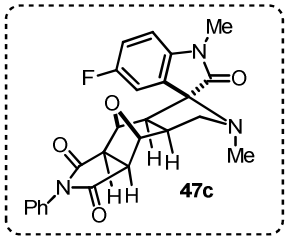
procedure described above **47a**was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (90 mg, 42%); mp: 221-223 ^{o}C (acetone:hexane = 1:1); FT-IR (KBR): 2937, 1710, 1612, 1494, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (m, 5H), 7.22 (d, 2H, J = 7.5 Hz), 7.12 (t, 1H, J = 7.5 Hz), 6.85 (d, 1H, J = 7.5 Hz), 4.97 (s, 1H), 4.77 (s, 1H), 3.56 (t, 1H, J = 8.1 Hz), 3.19 (s, 3H), 3.14 (d, 1H, J = 7.0 Hz), 3.10-3.07 (m, 1H), 3.00-2.92 (m, 2H), 2.69 (d, 1H, J = 8.1 Hz), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.0, 175.9, 175.8, 144.2, 131.6, 129.5, 129.2, 128.9, 127.0, 126.5, 125.9, 123.0, 108.3, 83.9, 81.1, 74.2, 58.2, 55.1, 49.6, 48.9, 47.0, 35.3, 25.9; MS (CI): m/z (%) 431 ([M+2]$^{+}$, 30), 430 ([M+1]$^{+}$, 70), 429 ([M]$^{+}$, 100), 415(20), 401 (70); HRMS (ESI) calcd for $C_{25}H_{24}N_3O_4$ [M+H]$^{+}$ 430.1767 found 430.1766.



(1S*,3aS*,4aR*,7aS*)-5'-Chloro-1',2-dimethyl-6-phenyl-3,3a,4,4a,8,8a-hexahydro-2H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,3'-indoline]-2',5,7(6H,7aH)-trione **(47b):** Following the general procedure described above **47b**was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (181 mg, 39%); mp: 229-231 ^{o}C; FT-IR (KBR): 2920, 1708, 1609, 1389, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.34 (m, 4H), 7.33 (d, 1H, J = 8.3 Hz), 7.25 (d, 2H, J = 7.3 Hz), 6.79 (d, 1H, J = 8.3 Hz), 4.98 (s, 1H), 4.69 (s, 1H), 3.54 (t, 1H, J = 8.1 Hz), 3.19 (s, 3H), 3.15 (d, 1H, J = 7.1 Hz), 3.06-2.95 (m, 3H), 2.74 (d, 1H, J = 8.1 Hz), 1.99 (s, 3H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 177.6, 175.8, 175.6, 142.7, 131.5, 129.5, 129.2, 128.9, 128.5, 127.6, 127.3, 126.5, 109.3, 83.4, 80.0, 74.2, 58.2, 55.4, 49.5, 48.8, 47.2, 35.2, 26.2; MS (CI): m/z (%) 466 ([M+3]$^{+}$, 50), 465 ([M+2]$^{+}$, 40), 464 ([M+1]$^{+}$, 100), 195 (4); HRMS (ESI) calcd for $C_{25}H_{23}N_3O_4Cl$ [M+H]$^{+}$ 464.1377 found 464.1379.

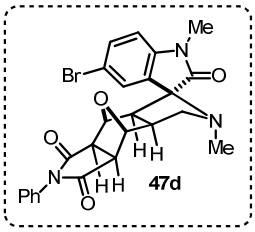


(1S*,3aS*,4aR*,7aS*)-5'-Fluoro-1',2-dimethyl-6-phenyl-3,3a,4,4a,8,8a-hexahydro-2H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,3'-indoline]-2',5,7(6H,7aH)-trione **(47c):** Following the general procedure described above **47c**was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (157 mg, 35%); mp: 268-270 ^{o}C; FT-IR (KBR): 2928, 1703, 1622, 1389, 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (m, 3H), 7.23 (m, 3H), 7.05 (m, 1H), 6.78 (m, 1H), 4.97 (s, 1H), 4.69

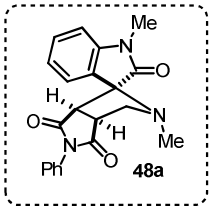


(s, 1H), 3.54 (t, 1H, J = 8.1 Hz), 3.19 (s, 3H), 3.15 (d, 1H, J = 7.0 Hz), 3.05-2.95 (m, 3H), 2.75 (d, 1H, J = 8.1 Hz), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.8, 175.8, 175.6, 159.3 (d, $J_{C\text{-}F}$ = 240.0 Hz), 140.1 (d, $J_{C\text{-}F}$ = 2.0 Hz), 131.6, 129.2, 128.9, 127.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.5, 115.8 (d, $J_{C\text{-}F}$ = 24.0 Hz), 115.3 (d, $J_{C\text{-}F}$ = 24.0 Hz), 108.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 83.4, 81.0, 74.4, 58.3, 55.4, 49.6, 48.8, 47.2, 35.2, 26.2; MS (CI): m/z (%) 450 ([M+3]$^+$, 5), 449 ([M+2]$^+$, 30), 448 ([M+1]$^+$, 100), 278 (4), 179 (5); HRMS (ESI) calcd for $C_{25}H_{23}N_3O_4F$ [M+H]$^+$ 448.1673 found 448.1672.

(1S*,3aS*,4aR*,7aS*)-5'-Bromo-1',2-dimethyl-6-phenyl-3,3a,4,4a,8,8a-hexahydro-2H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,3'-indoline]-2',5,7(6H,7aH)-trione **(47d):** Following



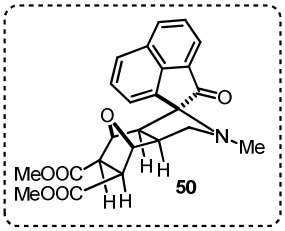
the general procedure described above **47d**was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (178 mg, 35%); mp 240-242 ^{o}C; FT-IR (KBR): 2931, 1714, 1606, 1190, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (s, 1H), 7.50-7.46 (m, 4H), 7.27-7.26 (m, 2H), 6.75 (d, 1H, J = 8.3 Hz), 5.00 (s, 1H), 4.71 (s, 1H), 3.55 (t, 1H, J = 8.1 Hz), 3.19 (s, 3H), 3.16 (d, 1H, J = 7.1 Hz), 3.10-3.00 (m, 2H), 2.96 (d, 1H, J = 7.1 Hz), 2.74 (d, 1H, J = 8.1 Hz), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.5, 175.8, 175.6, 143.3, 132.5, 130.0, 129.2, 128.9, 128.0, 126.5, 115.9, 109.8, 83.5, 80.9, 74.3, 58.3, 55.5, 49.6, 48.9, 47.2, 35.3, 26.2; MS (CI): m/z (%) 510 ([M+3]$^+$, 100), 509 ([M+2]$^+$, 30), 508 ([M+1]$^+$, 100), 430 (40), 241 (10), 194 (5); HRMS (ESI) calcd for $C_{25}H_{23}N_3O_4Br$ [M+H]$^+$ 508.0872, found 508.0871.



(1'S*,3a'S*,6a'R*)-1,2'-Dimethyl-5'-phenyl-3',3a'-dihydro-2'H-spiro[indoline-3,1'-pyrrolo[3,4-c]pyrrole]-2,4',6'(5'H,6a'H)-trione **(48a):** Following the general procedure described above **48a**was obtained after purification by neutral alumina column chromatography (EtOAc:Hexane = 40:60); as a colorless solid (127 mg, 70%); mp: 202-204 ^{o}C (MeOH:hexane = 1:1); FT-IR (KBR): 2942, 1700, 1606, 1461, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (t, 2H, J = 7.2 Hz), 7.42-7.31 (m, 4H), 7.05 (t, 1H, J = 7.5 Hz), 6.99 (d, 1H, J = 7.5 Hz), 6.83 (d, 1H, J = 7.80 Hz), 3.85 (dd, 1H, J_1 = 9.2, J_2 = 7.6 Hz), 3.70 (t, 1H, J = 8.4 Hz), 3.58 (d, 1H, J = 9.2 Hz), 3.57 (d, 1H, J = 8.2 Hz), 3.19 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.0, 176.6, 174.1, 144.2, 131.9, 130.0, 129.2, 128.7, 126.3, 126.1, 124.3, 122.9, 108.4, 72.8, 54.9, 52.0, 44.6,

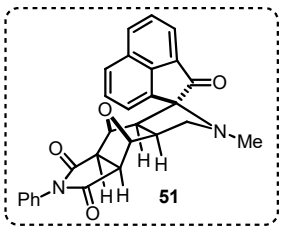
34.6, 25.8; MS (CI): m/z (%) 363 ($[M+2]^+$, 5), 362 ($[M+1]^+$, 30), 361 ($[M]^+$, 30), 330 (10), 241 (74), 207 (59), 159 (22); HRMS (ESI) calcd for $C_{21}H_{20}N_3O_3$ $[M+H]^+$ 362.1505 found 362.1504.

***(1S*,3aS*,5R*,6S*)-Dimethyl 2-methyl-2'-oxo-2,3,3a,4,5,6,7,7a-octahydro-2'H-spiro[4,7-epoxyisoindole-1,1'-acenaphthylene]-5,6-dicarboxylate*(50):** Following the general procedure described above **50**was obtained after purification by neutral alumina column chromatography

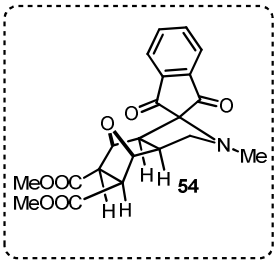


(EtOAc:Hexane = 60:40); as a yellow colored solid (232 mg, 55%); mp: 236-238 ^oC (acetone:hexane = 1:1); FT-IR (KBR): 2950, 1749, 1724, 1437, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 1H, J = 8.1 Hz), 7.93-7.84 (m, 3H), 7.74-7.67 (m, 2H), 4.90 (s, 1H), 4.41 (s, 1H), 3.67 (s, 3H), 3.53 (s, 3H), 3.53 (t, 1H, J = 8.1 Hz), 3.09 (d, 1H, J = 9.5 Hz), 3.05-3.02 (m, 1H), 2.93-2.91 (m, 1H), 2.84 (d, 1H, J = 9.5 Hz), 2.71 (d, 1H, J = 8.1 Hz), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.4, 171.2, 171.1, 142.6, 135.6, 132.2, 131.4, 130.8, 128.8, 127.9, 125.0, 124.9, 121.2, 81.5, 80.3, 78.2, 59.2, 56.1, 52.2, 52.0, 51.4, 50.6, 48.0, 35.5; MS (CI): m/z (%) 424 ($[M+3]^+$, 5), 423 ($[M+2]^+$, 30), 422 ($[M+1]^+$, 100), 390 (2), 196 (2); HRMS (ESI) calcd for $C_{24}H_{23}NO_6Na$ $[M+Na]^+$ 444.1423 found 444.1425.

***(1S*,3aS*,4aR*,7aS*)-2-Methyl-6-phenyl-3,3a,4,4a,8,8a-hexahydro-2H,2'H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,1'-acenaphthylene]-2',5,7(6H,7aH)-trione* (51):** Following the general procedure described above **51**was obtained after purification by silica column chromatography (EtOAc:Hexane = 65:35); as a yellow colored solid (211 mg, 47%); mp: 236-

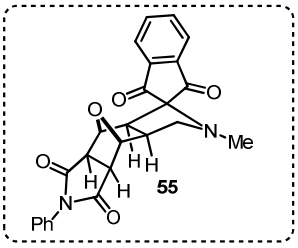


238 ^oC (MeOH:hexane = 1:1); FT-IR (KBR): 2927, 2852, 1710, 1595, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, 1H, J = 8.1 Hz), 7.93-7.90 (m, 2H), 7.77-7.71 (m, 3H), 7.44 (t, 2H, J = 7.2 Hz), 7.37 (t, 1H, J = 7.2 Hz), 7.21 (d, 2H, J = 7.4 Hz), 5.03 (s, 1H), 4.70 (s, 1H), 3.64 (t, 1H, J = 8.1 Hz), 3.17 (d, 1H, J = 7.0 Hz), 3.17-3.14 (m, 1H), 3.08-3.03 (m, 1H), 2.90 (d, 1H, J = 7.0 Hz), 2.75 (d, 1H, J = 8.1 Hz), 2.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.5, 175.9, 175.8, 142.6, 135.9, 132.3, 131.6, 131.1, 130.8, 129.2, 128.8, 128.7, 128.2, 126.5, 125.3, 124.0, 121.3, 83.6, 81.4, 78.2, 58.9, 55.4, 49.6, 48.9, 47.5, 35.3; MS (CI): m/z (%) 453 ($[M+3]^+$, 10), 452 ($[M+2]^+$, 50), 451 ($[M+1]^+$, 100), 196 (2); HRMS (ESI) calcd for $C_{28}H_{23}N_2O_4$ $[M+H]^+$ 451.1658 found 451.1657.

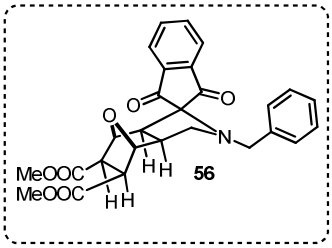


(3aS*,5R*,6S*)-Dimethyl 2-methyl-1',3'-dioxo-1',2,3,3a,3',4,5,6,7,7a-decahydrospiro[4,7-epoxyisoindole-1,2'-indene]-5,6-dicarboxylate (**54**): Following the general procedure described above **54**was obtained after purification by silica column chromatography (EtOAc:Hexane = 85:15); as a yellow colored solid (168 mg, 84%); mp: 188-190 ^{o}C (MeOH:hexane = 1:1); FT-IR (KBR): 2945, 1739, 1704, 1592, 1268 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, 1H, J = 7.2 Hz), 7.97 (d, 1H, J = 7.2 Hz), 7.92-7.88 (m, 2H), 4.84 (s, 1H), 4.66 (s, 1H), 3.64 (s, 3H), 3.58 (s, 3H), 3.41 (t, 1H, J = 8.1 Hz), 3.24 (dd, 1H, J_1 = 9.1, J_2 = 5.4 Hz), 2.96 (d, 1H, J = 9.1 Hz), 2.83-2.79 (m, 1H), 2.76 (d, 1H, J = 9.1 Hz), 2.48 (d, 1H, J = 8.1 Hz), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.9, 199.4, 170.8, 170.7, 141.8, 140.1, 136.6, 136.2, 123.4, 123.2, 81.6, 78.7, 59.2, 56.7, 52.1, 51.2, 51.0, 48.4, 35.3; MS (CI): m/z (%) 402 ([M+3]$^+$, 10), 401 ([M+2]$^+$, 40), 400 ([M+1]$^+$, 100), 195 (2); HRMS (ESI) calcd for $C_{21}H_{22}NO_7$ [M+H]$^+$ 400.1396 found 400.1396.

(3aS*,4aR*,7aS*)-2-Methyl-6-phenyl-3,3a,4,4a,8,8a-hexahydro-2H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,2'-indene]-1',3',5,7(6H,7aH)-tetraone **(55):** Following the general procedure described above **55**was obtained after purification by silica column chromatography (EtOAc:Hexane = 90:10); as an orange colored solid (321 mg, 75%); mp: 264-266 ^{o}C (MeOH:hexane = 1:1); FT-IR (KBR): 2933, 1741, 1714, 1592, 1392, 1198 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05-8.02 (m, 1H), 7.99-7.97 (m, 1H), 7.94-7.92 (m, 2H), 7.44 (t, 2H, J = 7.1 Hz), 7.40-7.38 (m, 1H), 7.20-7.14 (m, 2H), 4.94 (s, 1H), 4.84 (s, 1H), 3.51 (t, 1H, J = 8.1 Hz), 3.27 (dd, 1H, J_1 = 9.3, J_2 = 4.7 Hz), 3.09 (d, 1H, J = 7.0 Hz), 2.98-2.94 (m, 1H), 2.87 (d, 1H, J = 7.0 Hz), 2.62 (d, 1H, J = 8.1 Hz), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.9, 199.7, 175.5, 175.5, 141.7, 140.0, 136.8, 136.6, 131.5, 129.2, 128.9, 126.5, 123.5, 123.3, 83.1, 79.9, 76.3, 59.1, 55.8, 49.2, 49.1, 47.9, 35.6; MS (CI): m/z (%) 431 ([M+3]$^+$, 5), 430 ([M+2]$^+$, 25), 429 ([M+1]$^+$,100), 414 (15), 257 (15); HRMS (ESI) calcd for $C_{25}H_{21}N_2O_5$ [M+H]$^+$ 429.1450 found 429.1450.

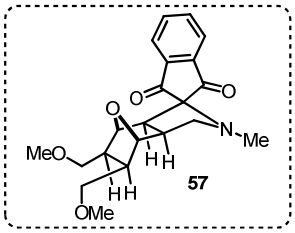


(3aS*,5R*,6S*)-Dimethyl 2-benzyl-1',3'-dioxo-1',2,3,3a,3',4,5,6,7,7a-decahydrospiro[4,7-epoxyisoindole-1,2'-indene]-5,6-dicarboxylate **(56):** Following the general procedure described above **56**was obtained after purification by silica column chromatography(EtOAc:Hexane =

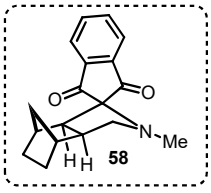


85:15); as a brown colored solid (309 mg, 65%); mp: 188-190 ^{o}C; FT-IR (KBR): 2998, 1726, 1704, 1595, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, 1H, J = 7.2 Hz), 7.90-7.84 (m, 3H), 7.20-7.13 (m, 5H), 4.77 (s, 1H), 4.66 (s, 1H), 3.66 (d, 1H, J = 12.9 Hz), 3.63 (s, 3H), 3.58 (s, 3H), 3.47 (d, 1H, J = 12.9 Hz), 3.34 (t, 1H, J = 8.2 Hz), 3.13 (dd, 1H, J_1 = 9.0, J_2 = 6.1 Hz), 2.96 (d, 1H, J = 9.0 Hz), 2.79-2.77 (m, 2H), 2.52 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.6, 199.4, 170.9, 170.7, 141.6, 140.1, 137.7, 136.5, 136.0, 129.1, 128.0, 127.3, 123.3, 123.2, 81.2, 78.6, 76.2, 56.6, 56.5, 54.0, 52.2, 51.3, 50.9, 48.1; MS (CI): m/z (%) 478 ([M+3]$^+$, 5), 477 ([M+2]$^+$, 25), 476 ([M+1]$^+$,100), 444 (7), 385 (15), 264 (7), 210 (4), 91 (15); HRMS (ESI) calcd for $C_{27}H_{26}NO_7$ [M+H]$^+$ 476.1709 found 476.1709.

(3aS*,5S*,6R*)-5,6-Bis(methoxymethyl)-2-methyl-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-epoxyisoindole-1,2'-indene]-1',3'-dione **(57):** Following the general procedure described above **57**was obtained after purification by silica column chromatography(EtOAc:Hexane = 85:15); as



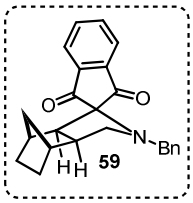
a semi solid (143 mg, 77%); FT-IR (DCM): 2927, 1702, 1592, 1456 and 1259 cm^{-1}, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.97 (m, 1H), 7.93-7.91 (m, 1H), 7.88-7.84 (m, 2H), 4.32 (s, 1H), 4.17 (s, 1H), 3.38 (t, 1H, J = 8.5 Hz), 3.29 (s, 3H), 3.28-3.16 (m, 4H), 3.17 (s, 3H), 3.10 (t, 1H, J = 8.5 Hz), 2.78-2.72 (m, 1H), 2.47 (d, 1H, J = 8.1 Hz), 2.21 (s, 3H), 2.10-2.01 (m, 1H), 1.89-1.86 (m, 1H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 203.5, 200.3, 141.8, 140.1, 136.3, 136.1, 123.2, 123.1, 82.6, 79.3, 70.7, 70.4, 59.7, 58.8, 58.7, 56.9, 48.6, 45.0, 44.7, 35.7; MS (CI): m/z (%) 374 ([M+3]$^+$, 5), 373 ([M+2]$^+$, 25), 372 ([M+1]$^+$,100), 340 (5), 240 (15), 188 (5); HRMS (ESI) calcd for $C_{21}H_{26}NO_5$ [M+H]$^+$ 372.1811 found 372.1810.



(3aS*)-2-Methyl-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-methanoisoindole-1,2'-indene]-1',3'-dione (**58**): Following the general procedure described above **58**was obtained after purification by silica column chromatography (EtOAc:Hexane = 25:75); as a yellow colored solid (93 mg, 66%); mp: 169-171 ^{o}C; FT-IR (KBR): 2868, 1681, 1503 and 1297 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.96 (m, 1H), 7.95-7.92 (m, 1H), 7.86-7.84 (m, 2H), 3.45 (t, 1H, J = 9.2 Hz), 2.96 (dd, 1H, J_1 = 9.2, J_2 = 4.4 Hz), 2.50-2.41 (m, 1H), 2.26 (s, 3H), 2.20-2.16 (m, 2H), 2.11 (d, 1H, J = 8.0 Hz),

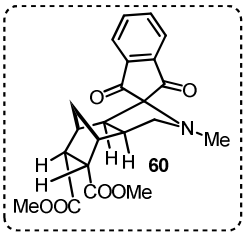
1.92 (d, 1H, J = 4.4 Hz), 1.47-1.37 (m, 2H), 1.11-1.08 (m, 2H), 0.92-0.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.9, 200.9, 141.9, 139.9, 136.0, 123.0, 79.7, 61.0, 57.5, 48.2, 41.1, 38.7, 35.8, 34.4, 28.8, 28.3; MS (CI): m/z (%) 283 ($[M+2]^+$, 24), 282 ($[M+1]^+$, 90), 281 ($[M]^+$,100), 280 (34), 252(10), 224(20), HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ 282.1494 found 282.1502.

(3aS*)-2-Benzyl-2,3,3a,4,5,6,7,7a-octahydrospiro[4,7-methanoisoindole-1,2'-indene]-1',3'-dione **(59):** Following the general procedure described above **59**was obtained after purification

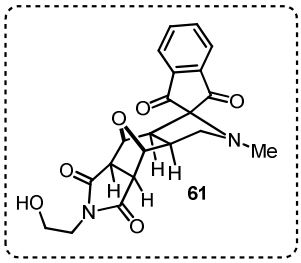


by silica column chromatography (EtOAc:Hexane = 35:65); as an orange red colored solid (99 mg, 55%); mp: 150-152 ^{o}C; FT-IR (KBR): 2919, 1742, 1597 and 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98- 7.91(m, 2H), 7.88-7.85 (m, 2H), 7.32 (d, 2H, J = 7.0 Hz), 7.26-7.18 (m, 3H), 3.65 (d, 1H, J = 12.9 Hz), 3.52 (d, 1H, J = 12.9 Hz), 3.38 (t, 1H, J = 8.9 Hz), 2.84 (dd, 1H, J_1 = 9.2, J_2 = 3.6 Hz), 2.49-2.44 (m, 1H), 2.34 (d, 1H, J = 9.8 Hz), 2.16-2.13 (m, 2H), 2.01 (d, 1H, J = 3.6 Hz), 1.47-1.35 (m, 2H), 1.16-1.09 (m, 2H), 0.95-0.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.0, 200.6, 142.0, 139.7, 139.0, 135.8, 128.7, 128.0, 127.0, 123.0, 79.6, 58.1, 56.7, 54.7, 47.7, 41.5, 38.9, 34.5, 28.7, 28.3; HRMS (ESI) calcd for $C_{24}H_{24}NO_2$ $[M+H]^+$ 358.1807 found 358.1794.

(3aS*,5R*,6S*)-Dimethyl 2-methyl-1',3'-dioxo-1',2,3,3a,3',4,5,6,7,7a-decahydrospiro[4,7-methanoisoindole-1,2'-indene]-5,6-dicarboxylate **(60):** Following the general procedure described above **60**was obtained after purification by silica column

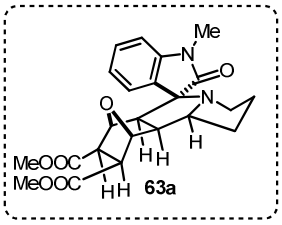


chromatography(EtOAc:Hexane = 35:65); as a yellow colored solid (100 mg, 50%); mp: 172-174 ^{o}C; FT-IR (KBR): 2951, 1732, 1699, 1435 and 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99-7.92 (m, 2H), 7.87-7.84 (m, 2H), 3.64 (s, 3H), 3.52 (t, 1H, J = 9.1 Hz), 3.44 (s, 3H), 3.10 (dd, 1H, J_1 = 11.1, J_2 = 4.4 Hz), 2.98 (d, 1H, J = 7.7 Hz), 2.90 (dd, 1H, J_1 = 9.3, J_2 = 2.8 Hz), 2.78-2.73 (m, 2H), 2.59-2.55 (m, 2H), 2.37 (d, 1H, J = 2.8 Hz), 2.24 (s, 3H), 1.28 (d, 1H, J = 11.1 Hz); ^{13}C NMR($CDCl_3$, 100 MHz): δ 203.2, 200.9, 172.3, 141.8, 139.7, 136.1, 135.8, 123.1, 79.0, 60.8, 51.6, 51.1, 49.8, 46.0, 42.2, 41.9, 35.8; MS (CI): m/z (%) 399 ($[M+2]^+$, 24), 398 ($[M+1]^+$, 90), 397 ($[M]^+$,100), 396 (34), 340 (19); HRMS (ESI) calcd for $C_{22}H_{24}NO_6$ $[M+H]^+$ 398.1603 found 398.1591.

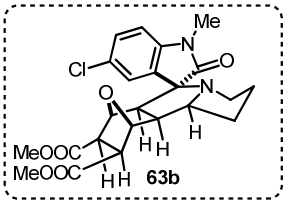


(3aS*,4aR*,7aS*)-6-(2-hydroxyethyl)-2-methyl-3,3a,4,4a,8,8a-hexahydro-2H-spiro[4,8-epoxypyrrolo[3,4-f]isoindole-1,2'-indene]-1',3',5,7(6H,7aH)-tetraone **(61):** Following the general procedure described above **61**was obtained after purification by silica column chromatography (EtOAc:Hexane = 80:20); as a yellow colored solid (129 mg, 65%); mp: 223-225 ^{o}C; FT-IR (KBR): 3486, 2846, 1704, 1424 and 1176 cm^{-1}; ^{1}H NMR (CDCl$_3$+DMSO-d_6, 400 MHz): δ 8.0-7.92 (m, 4H), 4.78 (s, 1H), 4.68 (s, 1H), 3.89 (s, 1H), 3.70-3.57 (m, 4H), 3.46 (t, 1H, J = 8.7 Hz), 3.22-3.19 (m, 1H), 2.97 (d, 1H, J = 6.7 Hz), 2.94-2.87 (m, 1H), 2.80-2.70 (m, 1H), 2.59 (d, 1H, J = 7.9 Hz), 2.22 (s, 3H); ^{13}C NMR (CDCl$_3$+DMSO-d_6, 100 MHz): δ 207.5, 204.6, 181.5, 146.4, 144.6, 141.5, 128.0, 127.9, 87.5, 84.1, 81.0, 63.9, 63.1, 60.1, 53.7, 52.8, 46.2, 40.4, 34.3; MS (CI): m/z (%) 398([M+2]$^+$, 10), 397 ([M+1]$^+$, 35), 396 ([M]$^+$, 90), 86 (55), 85 (100); HRMS (ESI) calcd for $C_{21}H_{21}N_2O_6$ [M+H]$^+$ 397.1399 found 397.1390.

(3'S*,5aS*,7S*,8R*,9aS*,9bS*)-dimethyl 1'-methyl-2'-oxo-1,2,3,5a,6,7,8,9,9a,9b-decahydrospiro[6,9-epoxypyrrolo[2,1-a]isoindole-5,3'-indoline]-7,8-dicarboxylate **(63a):**



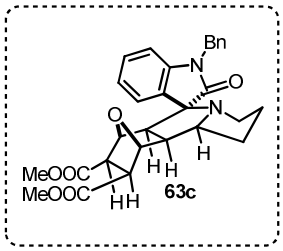
Following the general procedure described above **63a**was obtained after purification by neutral alumina column chromatography(EtOAc:Hexane = 60:40); as a colorless solid (213 mg, 50%); mp: 195-197 ^{o}C; FT-IR (KBR): 2925, 1749, 1610, 1473 and 1250 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.53 (d, 1H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.6 Hz), 7.09 (t, 1H, J = 7.6 Hz), 6.83 (d, 1H, J = 7.6 Hz), 5.01 (s, 1H), 4.71 (s, 1H), 4.22 (q, 1H, J = 7.4 Hz), 3.69 (s, 3H), 3.61 (s, 3H), 3.16 (s, 3H), 3.06 (d, 1H, J = 9.6 Hz), 2.92 (d, 1H, J = 9.6 Hz), 2.86-2.72 (m, 3H), 2.38 (t, 1H, J = 9.0 Hz), 1.94-1.72 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 179.5, 171.4, 144.5, 129.3, 128.4, 125.9. 122.5, 108.2, 79.5, 71.9, 66.8, 58.3, 52.2, 51.8, 50.8, 49.8, 46.8, 26.5, 26.1, 25.4; MS (CI): m/z (%) 429 ([M+3]$^+$, 65), 428([M+2]$^+$, 45), 427 ([M+1]$^+$, 100), 425 (55), 397 (45), 396 (40), 215 (26); HRMS (ESI) calcd for $C_{23}H_{26}N_2O_6Na$ [M+Na]$^+$ 449.1688 found 449.1676.



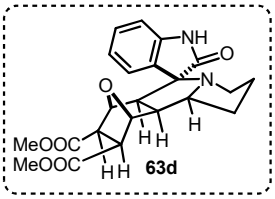
(3'S*,5aS*,7S*,8R*,9aS*,9bS*)-Dimethyl 5'-chloro-1'-methyl-2'-oxo-1,2,3,5a,6,7,8,9,9a,9b-decahydrospiro[6,9-epoxypyrrolo[2,1-a]isoindole-5,3'-indoline]-7,8-dicarboxylate **(63b):** Following the general procedure described above **63b**was obtained after purification

by neutral alumina column chromatograph (EtOAc:Hexane = 60:40); as a colorless solid (230 mg, 50%); mp 210-212 ^{o}C; FT-IR (KBR): 2951, 1741, 1608, 1488 and 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (s, 1H), 7.33 (d, 1H, J = 8.2 Hz), 6.76 (d, 1H, J = 8.2 Hz), 5.03 (s, 1H), 4.72 (s, 1H), 4.21 (q, 1H, J = 7.4 Hz), 3.71 (s, 3H), 3.63 (s, 3H), 3.15 (s, 3H), 3.07 (d, 1H, J = 9.6 Hz), 2.94 (d, 1H, J = 9.6 Hz), 2.82-2.70 (m, 3H), 2.39-2.36 (m, 1H), 1.97-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.0, 171.3, 143.1, 129.4, 128.3, 128.1, 127.7, 109.0, 79.4, 71.6, 66.8, 58.7, 52.3, 51.7, 50.8, 49.5, 46.3, 26.5, 26.1, 25.1; MS (CI): m/z (%) 463 ([M+3]$^{+}$, 28), 462 ([M+2]$^{+}$, 30), 461 ([M+1]$^{+}$, 80), 398 (100), 397 (45), 396 (40), 358 (20); HRMS (ESI) calcd for $C_{23}H_{25}N_2O_6NaCl$ [M+Na]$^{+}$ 483.1298 found 483.1277.

***(3'S*,5aS*,7S*,8R*,9aS*,9bS*)-Dimethyl 1'-benzyl-2'-oxo-1,2,3,5a,6,7,8,9,9a,9b-decahydrospiro[6,9-epoxypyrrolo[2,1-a]isoindole-5,3'-indoline]-7,8-dicarboxylate* (63c):**



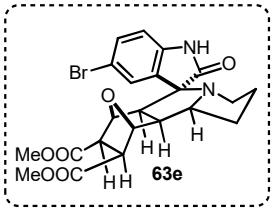
Following the general procedure described above **63c**was obtained after purification by neutral alumina column chromatograph (EtOAc:Hexane = 60:40); as a colorless solid (352 mg, 70%); mp: 174-176 ^{o}C; FT-IR (KBR): 2950, 1738, 1610, 1467 and 1181 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, 1H, J = 7.0 Hz), 7.33-7.17 (m, 6H), 7.03 (t, 1H, J = 7.6 Hz), 6.71 (d, 1H, J = 7.6 Hz), 5.02 (s, 1H), 4.87 (d, 1H, J = 15.7 Hz), 4.81 (d, 1H, J = 15.7 Hz), 4.74 (s, 1H), 4.23 (d, 1H, J = 7.4 Hz), 3.69 (s, 3H), 3.61 (s, 3H), 3.07 (d, 1H, J = 9.5 Hz), 2.94 (d, 1H, J = 9.5 Hz), 2.84 (d, 1H, J = 8.0 Hz), 2.83-2.73 (m, 2H), 2.45-2.35 (m, 1H), 1.95-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.6, 171.3, 143.6, 135.8, 129.2, 128.8, 128.5, 127.6, 127.2, 126.0, 122.6, 109.2, 79.6, 79.3, 71.6, 66.9, 58.6, 52.2, 51.8, 50.8, 49.5, 46.3, 43.6, 26.6, 25.2; MS (CI): m/z (%) 504 ([M+2]$^{+}$, 20), 502 ([M]$^{+}$, 70), 501 (55), 399 (90), 288 (62), 220 (78), 91 (100); HRMS (ESI) calcd for $C_{29}H_{31}N_2O_6$ [M+H]$^{+}$ 503.2182 found 503.2159.



***(3'S*,5aS*,7S*,8R*,9aS*,9bS*)-Dimethyl 2'-oxo-1,2,3,5a,6,7,8,9,9a,9b-decahydrospiro[6,9-epoxypyrrolo[2,1-a]isoindole-5,3'-indoline]-7,8-dicarboxylate* (63d):** Following the general procedure described above **63d**was obtained after purification by neutral alumina column chromatograph (EtOAc:Hexane = 60:40); as a colorless solid (268 mg, 65%); mp: 239-241 ^{o}C; FT-IR (KBR): 2956, 1731, 1619, 1438 and 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (s, 1H), 7.49 (d, 1H, J = 7.2 Hz), 7.25 (t, 1H, J = 7.6 Hz), 7.03 (t, 1H,

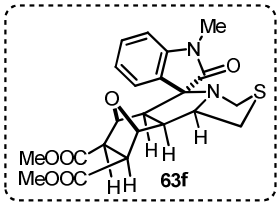
J = 7.6 Hz), 6.87 (d, 1H, *J* = 7.6 Hz), 5.00 (s, 1H), 4.66 (s, 1H), 4.16 (q, 1H, *J* = 7.7 Hz), 3.68 (s, 3H), 3.60 (s, 3H), 3.05 (d, 1H, *J* = 9.6 Hz), 2.93 (d, 1H, *J* = 9.6 Hz), 2.85 (d, 1H, *J* = 8.2 Hz), 2.76 (q, 2H, *J* = 8.2 Hz), 2.46-2.41 (m, 1H), 1.91-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.1, 171.3, 141.7, 129.2, 128.8, 126.4, 122.5, 110.2, 79.4, 72.7, 67.3, 58.4, 52.2, 51.7, 50.8, 49.5, 46.6, 29.7, 26.5, 25.5; MS (CI): m/z (%) 413 ($[M+1]^+$, 20), 412 ($[M]^+$, 75), 309 (55), 211 (70), 209 (100); HRMS (ESI) calcd for $C_{22}H_{24}N_2O_6Na$ $[M+Na]^+$ 435.1532 found 435.1525.

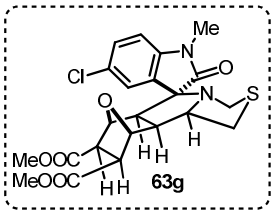
(3'S*,5aS*,7S*,8R*,9aS*,9bS*)-Dimethyl 5'-bromo-2'-oxo-1,2,3,5a,6,7,8,9,9a,9b-decahydrospiro[6,9-epoxypyrrolo[2,1-a]isoindole-5,3'-indoline]-7,8-dicarboxylate **(63e):**



Following the general procedure described above **63e**was obtained after purification by neutral alumina column chromatograph (EtOAc:Hexane = 60:40); as a colorless solid (319 mg, 65%); mp: 164 ^{o}C (decomposed); FT-IR (KBR): 3434, 2955, 1729, 1615, 1471 and 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (s, 1H), 7.62 (s, 1H), 7.41 (d, 1H, *J* = 8.0 Hz), 6.80 (d, 1H, *J* = 8.0 Hz), 5.02 (s, 1H), 4.69 (s, 1H), 4.15 (q, 1H, *J* = 7.5 Hz), 3.71 (s, 3H), 3.65 (s, 3H), 3.07 (d, 1H, *J* = 9.5 Hz), 2.96 (d, 1H, *J* = 9.5 Hz), 2.86 (d, 1H, *J* = 8.0 Hz), 2.74 (m, 2H), 2.45-2.42 (m, 1H), 2.00-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.5, 171.3, 140.8, 132.3, 131.2, 128.6, 115.4, 111.6, 79.3, 72.4, 67.1, 58.7, 52.3, 51.7, 50.8, 49.2, 46.1, 26.5, 25.2; MS (CI): m/z (%) 493 ($[M+3]^+$, 20), 491($[M+1]^+$, 65), 490 ($[M]^+$, 85), 291 (55), 288 (100), 287 (60); HRMS (ESI) calcd for $C_{22}H_{23}N_2O_6NaBr$ $[M+Na]^+$ 513.0637 found 513.0627.

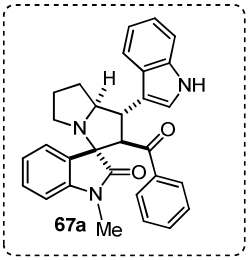
(3'S*,5aS*,7S*,8R*,9aS*,9bR*)-Dimethyl 1'-methyl-2'-oxo-3,5a,6,7,8,9,9a,9b-octahydro-1H-spiro[6,9-epoxythiazolo[4,3-a]isoindole-5,3'-indoline]-7,8-dicarboxylate **(63f):** Following the general procedure described above **63f**was obtained after purification by neutral alumina column chromatograph (EtOAc:Hexane = 80:20); as a colorless solid (254 mg, 57%); mp: 87-89^{o}C; FT-IR (KBR): 2950, 1740, 1609, 1380 and 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, *J* =7.5 Hz), 7.35 (t, 1H, *J* =7.5 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 6.85 (d, 1H, *J* =7.5 Hz), 4.97 (s, 1H), 4.31 (s, 1H), 4.18 (q, 1H, *J* = 9.2 Hz), 3.87 (d, 1H, *J* = 8.5 Hz), 3.69 (s, 3H), 3.59 (s, 3H), 3.21 (s, 3H), 3.21-2.88 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.7, 170.9, 144.1, 129.8, 128.8, 123.5, 123.1, 108.1, 79.1, 73.2, 71.9, 58.4, 52.3, 51.5, 50.6, 50.3, 48.5, 31.7, 29.7, 26.5; MS (CI): m/z (%) 446 ($[M+2]^+$, 15), 445 ($[M+1]^+$, 25), 444 ($[M]^+$, 100), 443 (35), 264 (95).



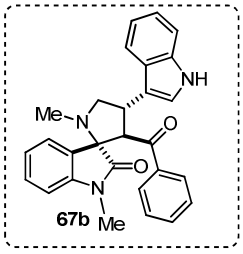


(3'S*,5aS*,7S*,8R*,9aS*,9bR*)-Dimethyl 5'-chloro-1'-methyl-2'-oxo-3,5a,6,7,8,9,9a,9b-octahydro-1H-spiro[6,9-epoxythiazolo[4,3-a]isoindole-5,3'-indoline]-7,8-dicarboxylate **(63g):** Following the general procedure described above **63g**was obtained after purification by neutral alumina column chromatograph (EtOAc:Hexane = 80:20); as a colorless solid (287 mg, 60%); mp: 248-250 ^{o}C; FT-IR (KBR): 2952, 1732, 1606, 1485 and 1207 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (s, 1H), 7.33 (d, 1H, J = 8.3 Hz), 6.79 (d, 1H, J = 8.3 Hz), 4.98 (s, 1H), 4.36 (s, 1H), 4.21-4.14 (m, 1H), 3.81 (d, 1H, J = 8.4 Hz), 3.70 (s, 3H), 3.61 (s, 3H), 3.19 (s, 3H), 3.19-2.89 (m, 7H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 178.1, 170.9, 142.7, 129.9, 128.8, 128.5, 125.3, 109.0, 79.1, 78.9, 72.9, 71.6, 58.7, 52.3, 51.4, 50.5, 49.8, 48.2, 31.5, 26.6; MS (CI): m/z (%) 479 ([M+1]$^{+}$, 28), 478 ([M]$^{+}$, 25), 461 (50), 460 (70), 360 (90), 329 (88) 316 (100); HRMS (ESI) calcd for $C_{22}H_{23}N_2O_6NaSCl$ [M+Na]$^{+}$ 501.0863 found 501.0841.

(1'S*,2'R*,3S*,7a'S*)-2'-Benzoyl-1'-(1H-indol-3-yl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67a):** Following the general procedure described above **67a** was obtained after purification by silica gel column chromatography



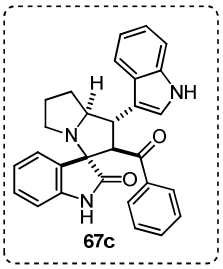
(EtOAc:Hexane = 70:30); as a colorless solid (184 mg, 80%); mp: 192-194 ^{o}C; FT-IR (KBR): 3314, 2972, 1683, 1613 and 747cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.64 (br s, 1H), 8.18-8.15 (m, 1H), 7.35-7.33 (m, 1H), 7.26-7.10 (m, 10H), 7.06-7.02 (m, 1H), 6.39 (d, 1H, J = 7.7 Hz), 5.17 (d, 1H, J = 11.5 Hz), 4.56-4.51 (m, 1H), 4.15 (dd, 1H, J_1 = 11.4, J_2 = 9.9 Hz), 2.77 (s, 3H), 2.72-2.68 (m, 1H), 2.64-2.58 (m, 1H), 2.06-2.01 (m, 2H), 1.95-1.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 179.0, 143.4, 137.4, 136.7, 132.4, 129.3, 127.8, 127.7, 127.1, 126.4, 125.0, 122.4, 122.2, 122.0, 120.0, 119.6, 114.3, 111.4, 108.0, 73.7, 70.7, 64.0, 48.5, 45.0, 31.4, 27.3, 26.0; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_2$ [M+H]$^{+}$ 462.2182 found 462.2182.



(2'S*,3'R*,4'S*)-3'-Benzoyl-4'-(1H-indol-3-yl)-1,1'-dimethylspiro[indoline-3,2'-pyrrolidin]-2-one **(67b):** Following the general procedure described above **67b** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (76 mg, 35%); mp: 226-228 ^{o}C; FT-IR (KBR): 3317, 2929, 1682, 1612 and 467 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-8.21 (m,1H), 8.13 (br s, 1H), 7.37-7.35

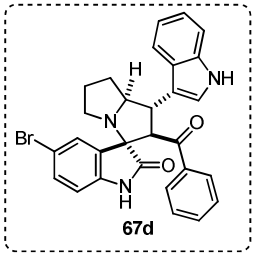
(m, 1H), 7.29-7.25 (m, 4H), 7.23-7.20 (m, 3H), 7.12-7.04 (m, 3H), 7.01-6.97 (m, 1H), 6.34 (d, 1H, *J* = 7.5 Hz), 4.83-4.80 (m, 2H), 3.92-3.87 (m, 1H), 3.52-3.48 (m, 1H), 3.01 (s, 3H), 2.22 (s, 3H);^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 178.1, 143.2, 137.4, 136.6, 132.4, 129.0, 127.8, 127.6, 127.0, 126.6, 126.3, 123.0, 122.2, 122.0, 120.1, 119.6, 115.7, 111.2, 107.3, 73.5, 61.9, 59.6, 36.6, 35.2, 25.9; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_2$ $[M+H]^+$ 436.2025 found 436.2008.

(1'S*,2'R*,3S*,7a'S*)-2'-Benzoyl-1'-(1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67c):** Following the general procedure described above **67c** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 85:15); as a colorless solid (168 mg, 75%); mp: 212-214 ^{o}C; FT-IR (KBR): 3283, 2985, 1723, 1663, 1471 and 1184 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.80 (br s, 1H), 10.17 (br s, 1H), 7.86 (d, 1H, *J* = 7.2 Hz), 7.35-7.15 (m, 8H), 7.01-6.93 (m, 3H), 6.86-6.85 (m, 1H), 6.44 (d, 1H, *J* = 7.2 Hz), 5.01 (d, 1H, *J* = 10.5 Hz), 4.05-4.02 (m, 2H), 2.56-2.50 (m, 1H), 2.29-2.25 (m, 1H), 1.81-1.60 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 197.5, 180.2, 142.3, 137.3, 137.0, 133.5, 129.6, 128.8, 128.0, 127.8, 126.8, 125.5, 123.0, 121.5, 121.5, 119.5, 118.9, 113.3, 112.2, 110.0, 73.1, 70.7, 62.2, 48.0, 45.3, 30.7, 27.2; HRMS (ESI) calcd for $C_{29}H_{26}N_3O_2$ $[M+H]^+$ 448.2025 found 448.2014.

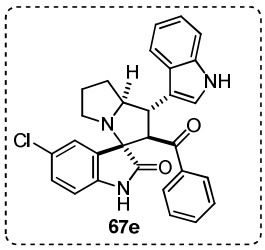


67c

(1'S*,2'R*,3S*,7a'S*)-2'-Benzoyl-5-bromo-1'-(1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67d):**Following the general procedure described above **67d** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 85:15); as a colorless solid (191 mg, 73%); mp: compound decomposes after 110 ^{o}C; FT-IR (KBR): 3308, 2956, 1719, 1683 and 1223 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 9.25 (br s, 1H), 9.07 (br s, 1H), 8.11 (d, 1H, *J* = 2.8 Hz), 7.44-7.31 (m, 5H), 7.25-7.14 (m, 6H), 6.44-6.41 (m, 1H), 5.22-5.18 (m, 1H), 4.52-4.49 (m, 1H), 4.17-4.10 (m, 1H), 2.73-2.61 (m, 2H), 2.05-1.86 (m, 3H), 1.78-1.73 (m, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 197.3, 180.4, 140.5, 137.2, 136.7, 132.7, 132.0, 130.4, 128.1, 127.9, 127.7, 126.3, 122.6, 121.7, 119.8, 119.3, 114.3, 113.5, 111.5, 111.4, 73.6, 70.3, 62.8, 48.2, 45.5, 31.0, 27.3; HRMS (ESI) calcd for $C_{29}H_{25}BrN_3O_2$ $[M+H]^+$ 526.1130 found 526.1114.



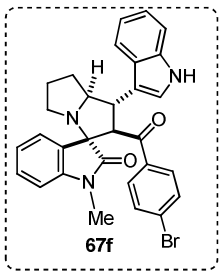
67d



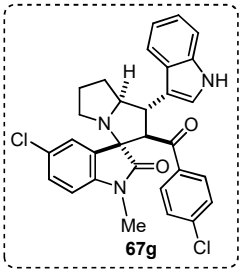
67e

***(1'S*,2'R*,3S*,7a'S*)-2'-Benzoyl-5-chloro-1'-(1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one* (67e):** Following the general procedure described above **67e** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 85:15); as a colorless solid (178 mg, 74%); mp: 160-162 ^{o}C; FT-IR (KBR): 3406, 2960, 1718, 1702, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 9.48 (br s, 1H), 9.37 (br s, 1H), 8.10-8.08 (m, 1H), 7.43-7.23 (m, 6H), 7.17-7.12 (m, 4H), 7.05-7.03 (m, 1H), 6.47 (d, 1H, *J*= 8.2 Hz), 5.19 (d, 1H, *J*= 11.4 Hz), 4.51-4.47 (m, 1H), 4.16-4.11 (m, 1H), 2.74- 2.62 (m, 2H), 2.04-1.86 (m, 3H), 1.79-1.73 (m, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 197.3, 180.5, 140.2, 137.2, 136.8, 132.7, 129.1, 128.1, 127.9, 127.5, 127.2, 126.8, 126.3, 122.6, 121.5, 119.7, 119.1, 113.3, 111.6, 111.0, 73.7, 70.4, 62.7, 48.2, 45.5, 31.1, 27.2; HRMS (ESI) calcd for $C_{28}H_{25}N_3ClO_2$ $[M+H]^+$ 482.1635 found 482.1636.

***(1'S*,2'R*,3S*,7a'S*)-2'-(4-Bromobenzoyl)-1'-(1H-indol-3-yl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one*(67f):** Following the general procedure described above **67f** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (148 mg, 55%); mp: 212-214 ^{o}C; FT-IR(KBr): 3307, 2867, 1716, 1610 and 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (br s, 1H), 8.11 (m, 1H), 7.32-7.14 (m, 8H), 7.05- 7.01 (m, 3H), 6.43 (d, 1H, *J*= 7.7 Hz), 5.08 (d, 1H, *J*= 11.5 Hz), 4.52-4.46 (m, 1H), 4.12 (t, 1H, *J*= 10.5 Hz), 2.81 (s, 3H), 2.71-2.57 (m, 2H) 2.02-1.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.8, 179.0, 143.2, 136.7, 136.0, 131.1, 129.5, 129.3, 127.5, 127.2, 126.4, 124.8, 122.4, 122.4, 122.0, 119.8, 119.6, 114.0, 111.5, 108.2, 73.7, 70.7, 64.1, 48.5, 45.0, 31.4, 27.3, 26.2; HRMS (ESI) calcd for $C_{30}H_{27}BrN_3O_2$ $[M+H]^+$ 540.1287 found 540.1276.



67f

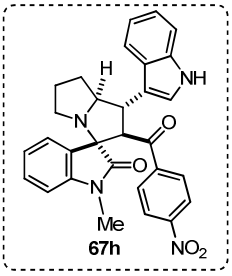


67g

***(1'S*,2'R*,3S*,7a'S*)-5-Chloro-2'-(4-chlorobenzoyl)-1'-(1H-indol-3-yl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one*(67g):** Following the general procedure described above **67g** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 65:35); as a colorless solid (127 mg, 48%); mp: 116-118 ^{o}C; FT-IR (KBR): 3398, 2924, 1718, 1607 and 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (br s, 1H), 8.14-8.12 (m, 1H), 7.35-7.33 (m, 1H), 7.25-7.17 (m, 7H), 7.10 (d, 2H, *J* = 8.4 Hz),

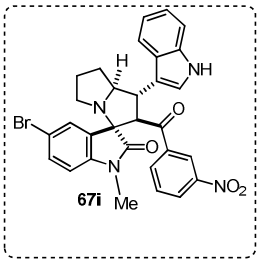
6.38 (d, 1H, *J* = 8.2 Hz), 5.12 (d, 1H, *J* = 11.4 Hz), 4.56-4.51 (m, 1H), 4.09 (t, 1H, *J* = 10.6 Hz), 2.83 (s, 3H), 2.68-2.61 (m, 2H); 2.05-1.88 (m, 3H), 1.77-1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.1, 178.6, 141.8, 139.1, 136.7, 135.5, 129.4, 129.2, 128.3, 127.9, 127.4, 126.7, 126.2, 122.5, 122.1, 119.9, 119.7, 113.7, 111.5, 109.0, 73.5, 70.5, 63.9, 48.4, 45.1, 31.3, 27.5, 26.3; HRMS (ESI) calcd for $C_{30}H_{26}Cl_2N_3O_2$ $[M+H]^+$ 530.1402 found 530.1402.

(1'S*,2'R*,3S*,7a'S*)-1'-(1H-Indol-3-yl)-1-methyl-2'-(4-nitrobenzoyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67h):**Following the general procedure described above **67h** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 70:30); as a brownish blue colored solid (164 mg, 65%); mp: 154-156 ^{o}C; FT-IR (KBR): 3292, 1715, 1609, and 1343 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (br s, 1H), 8.14-8.12 (m, 1H), 7.92 (d, 2H, *J* = 8.6 Hz), 7.35-7.15 (m, 8H), 7.06-7.03 (m, 1H), 6.40 (d, 1H, *J* = 7.7 Hz), 5.13 (d, 1H, *J* = 11.3 Hz), 4.56-4.51 (m, 1H), 4.11 (dd, 1H, J_1 = 11.3, J_2 = 10.1 Hz), 2.79 (s, 3H), 2.70-2.56 (m, 2H), 2.04-1.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 178.8, 149.6, 143.2, 141.8, 136.6, 129.8, 128.7, 127.2, 126.3, 124.5, 123.0, 122.6, 122.5, 122.2, 119.8, 119.7, 113.8, 111.5, 108.3, 73.4, 70.6, 64.5, 48.5, 45.1, 31.2, 27.2, 26.2; HRMS (ESI) calcd for $C_{30}H_{27}N_4O_4$ $[M+H]^+$ 507.2032 found 507.2026.

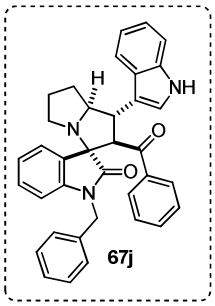


67h

(1'S*,2'R*,3S*,7a'S*)-5-Bromo-1'-(1H-indol-3-yl)-1-methyl-2'-(3-nitrobenzoyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67i):**Following the general procedure described above **67i** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (158 mg, 54%); mp: compound decomposes after 90 ^{o}C; FT-IR (KBR): 3400, 2924, 1717, 1606 and 1248 cm^{-1}, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (br s, 1H), 8.11 (d, 2H, *J* = 6.2 Hz), 7.95 (br s, 1H), 7.66 (d, 1H, *J* = 7.4 Hz), 7.34-7.17 (m, 7H), 6.32 (d, 1H, *J* = 8.1 Hz), 5.08 (d, 1H, *J* = 11.0 Hz), 4.59-4.57 (m, 1H), 4.14 (t, 1H, *J* = 10.5 Hz), 2.87 (s, 3H), 2.75-2.63 (m, 2H), 2.05-1.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.6, 178.3, 147.9, 142.3, 138.4, 136.6, 133.3, 132.6, 130.2, 129.2, 126.9, 126.7, 126.2, 122.7, 122.5, 122.2, 119.8, 115.4, 113.5, 111.5, 109.5, 73.0, 70.1, 64.3, 48.5, 45.1, 30.6, 27.1, 26.3; HRMS (ESI) calcd for $C_{30}H_{26}BrN_4O_4$ $[M+H]^+$ 585.1137 found 585.1137.

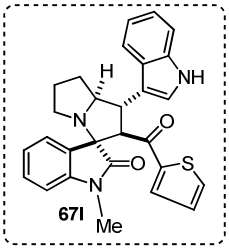


67i



(1'S*,2'R*,3S*,7a'S*)-2'-Benzoyl-1-benzyl-1'-(1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67j):**Following the general procedure described above **67j** was obtained after purification by silica gel column chromatography(EtOAc:Hexane = 75:25); as a colorless solid (214 mg, 80%); mp: 188-190 ^{o}C; FT-IR (KBR): 3377, 2922, 1695, 1605 and 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (br s, 2H), 7.34-7.10 (m, 13H), 7.03-7.00 (m, 4H), 6.31 (d, 1H, J = 7.0 Hz), 5.29 (d, 1H, J = 11.4 Hz), 4.87 (d, 1H, J = 15.7 Hz), 4.61-4.56 (m, 1H), 4.22 (t, 1H, J = 11.4 Hz), 4.14 (d, 1H, J = 15.7 Hz), 2.70-2.61 (m, 2H), 2.06-1.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 179.2, 142.6, 137.3, 136.7, 135.5, 132.6, 129.2, 128.7, 128.1, 128.0, 127.5, 127.4, 127.0, 126.4, 125.0, 122.4, 122.3, 122.0, 120.0, 119.6, 114.3, 111.4, 109.2, 73.5, 70.6, 63.1, 48.4, 45.5, 43.8, 31.4, 27.3; HRMS (ESI) calcd for $C_{36}H_{32}N_3O_2$ $[M+H]^+$ 538.2495 found 538.2494.

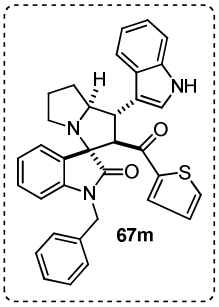
(1'S*,2'R*,3S*,7a'S*)-2'-(1-Naphthoyl)-1'-(1H-indol-3-yl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67k):** Following the general procedure described above **67k** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 70:30); as a colorless solid (115 mg, 45%); mp 206-208 ^{o}C; FT-IR (KBR): 3338, 2926, 1708, 1609 and 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (br s, 1H), 8.19 (d, 1H, J = 7.1 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.49 (d, 1H, J = 6.9 Hz), 7.43 (d, 1H, J = 7.1 Hz), 7.29-7.17 (m, 7H), 7.12-7.06 (m, 2H), 7.00-6.96 (m, 1H), 5.98 (d, 1H, J = 7.6 Hz), 5.34 (d, 1H, J = 11.6 Hz), 4.50 (dd, 1H, J_1 = 14.9, J_2 = 6.6 Hz), 4.21 (t, 1H, J = 10.8 Hz), 2.58-2.53 (m, 2H), 2.33 (s, 3H), 2.08-1.72 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.3, 178.4, 143.3, 136.7, 134.8, 132.9, 132.4, 129.6, 129.5, 128.2, 127.5, 127.1, 126.8, 126.4, 125.9, 125.1, 124.8, 124.0, 122.4, 122.3, 121.9, 119.8, 119.6, 114.4, 111.5, 108.4, 73.9, 71.2, 66.0, 47.9, 44.6, 32.2, 28.0, 25.7; HRMS (ESI) calcd for $C_{34}H_{30}N_3O_2$ $[M+H]^+$ 512.2338 found 512.2338.



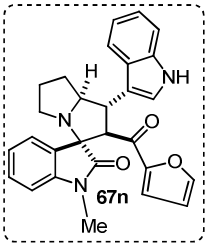
(1'S*,2'R*,3S*,7a'S*)-1'-(1H-Indol-3-yl)-1-methyl-2'-(thiophene-2-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67l):** Following the general procedure described above **67l** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 85:15); as a colorless solid (175 mg, 75%); mp: 210-212 ^{o}C; FT-IR (KBR):

3304, 2963, 1713, 1657 and 1260 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 8.82 (br s, 1H), 8.09-8.07 (m, 1H), 7.39-7.38 (m, 1H), 7.34-7.31 (m, 3H), 7.20-7.03 (m, 5H), 6.86-6.83 (m, 1H), 6.54-6.52 (m, 1H), 4.99 (dd, 1H, J_1 = 11.6, J_2 = 3.2 Hz), 4.51-4.49 (m, 1H), 4.15 (t, 1H, J = 10.0 Hz), 2.96 (s, 3H), 2.80-2.55 (m, 2H), 2.06-1.73 (m, 4H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 189.1, 179.2, 144.5, 143.2, 136.7, 134.0, 131.9, 129.4, 127.5, 127.4, 126.4, 124.8, 122.5, 122.4, 121.7, 119.9, 119.3, 113.6, 111.4, 108.0, 74.2, 70.6, 64.5, 48.5, 44.9, 31.2, 27.3, 26.2; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_2S[M+H]^+$ 468.1746 found 468.1730.

(1'S*,2'R*,3S*,7a'S*)-1-Benzyl-1'-(1H-indol-3-yl)-2'-(thiophene-2-carbonyl)-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67m):** Following the general procedure described above **67m** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 85:15); as a colorless solid (209 mg, 77%); mp: 188-190 ^oC; FT-IR(KBr): 3308, 2960, 1713, 1656 and 1358 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 8.73 (br s, 1H), 8.12-8.09 (m, 1H), 7.50-7.49 (m, 1H), 7.43-7.41 (m, 1H), 7.38 (dd, 1H, J_1 = 4.9, J_2 = 3.2 Hz), 7.34-7.32 (m, 1H), 7.21-7.14 (m, 6H), 7.11-7.02 (m, 4H), 6.78 (dd, 1H, J_1 = 4.8, J_2 = 4.0 Hz), 6.48 (d, 1H, J= 7.8 Hz), 5.17 (d, 1H, J= 11.7 Hz), 4.86 (d, 1H, J= 15.8 Hz), 4.64 (d, 1H, J= 15.8 Hz), 4.57-4.51 (m, 1H), 4.25 (dd, 1H, J_1 = 11.6, J_2 = 10.0 Hz), 2.74-2.62 (m, 2H), 2.07-1.76 (m, 4H); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 189.1, 179.3, 144.7, 142.5, 136.7, 135.4, 134.3, 132.6, 129.3, 128.7, 128.0, 127.7, 127.5, 127.0, 126.5, 124.9, 122.4, 121.8, 119.8, 119.4, 113.6, 111.5, 109.3, 74.1, 70.6, 63.7, 48.3, 45.5, 44.0, 31.3, 27.4; HRMS (ESI) calcd for $C_{34}H_{30}N_3O_2S[M+H]^+$ 544.2059 found 544.2042.

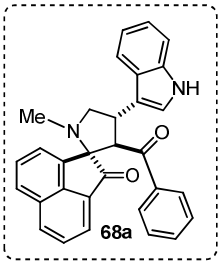


(1'S*,2'R*,3S*,7a'S*)-2'-(Furan-2-carbonyl)-1'-(1H-indol-3-yl)-1-methyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one **(67n):** Following the general procedure described above **67n** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 85:15); as a colorless solid (176 mg, 78%); mp: 196-198 ^oC; FT-IR (KBR): 3333, 2928, 1713, 1668 and 1026 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 9.00 (br s, 1H), 8.07-8.05 (m, 1H), 7.31-7.23 (m, 3H), 7.18-7.07 (m, 4H), 7.01-6.99 (m, 1H), 6.83 (d, 1H, J= 3.5 Hz), 6.59 (d, 1H, J= 7.8 Hz), 6.20-6.19 (m, 1H),4.86 (d, 1H, J= 11.6 Hz), 4.50-4.46 (m, 1H), 4.13 (t, 1H, J= 11.3 Hz), 3.06 (s, 3H), 2.77-2.71 (m, 1H), 2.59-2.53 (m, 1H), 2.00-1.71 (m, 4H);

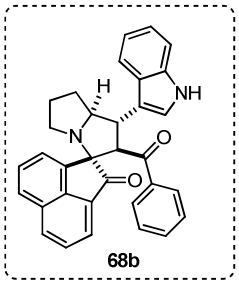


^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 184.7, 179.2, 152.4, 146.4, 143.3, 136.7, 129.4, 127.3, 126.4, 124.8, 122.6, 122.3, 121.6, 119.9, 119.2, 117.7, 113.4, 111.9, 111.4, 108.0, 73.7, 70.2, 63.3, 48.5, 44.5, 30.8, 27.0, 26.3; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_3$ $[M+H]^+$ 452.1974 found 452.1960.

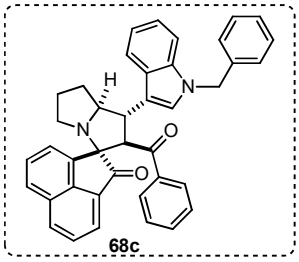
(1S*,3'R*,4'S*)-3'-Benzoyl-4'-(1H-indol-3-yl)-1'-methyl-2H-spiro[acenaphthylene-1,2'-pyrrolidin]-2-one **(68a):**Following the general procedure described above **68a** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 40:60); as a yellow colored solid (91 mg, 40%); mp: 194-196 ^oC; FT-IR(KBr): 3375, 2923, 1708, 1673 and 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (dd, 1H, J_1= 6.3, J_2= 2.1 Hz), 8.15 (br s,1H), 7.86 (d, 1H, J = 8.0 Hz), 7.81 (d, 1H, J = 6.8 Hz), 7.61 (dd, 1H, J_1= 7.0, J_2= 2.3 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.57-7.51 (m, 2H), 7.35-7.33 (m, 1H), 7.31-7.30 (m, 1H), 7.21-7.18 (m, 2H), 7.05-7.02 (m, 2H), 6.94-6.90 (m, 1H), 6.72 (t, 2H, J = 7.9 Hz), 4.98-4.91 (m, 1H), 4.85 (d, 1H, J = 9.4 Hz), 3.98 (t, 1H, J = 9.4 Hz), 3.57 (dd, 1H, J = 8.8, J_2= 7.4 Hz), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.0, 198.6, 142.2, 137.1, 137.0, 136.6, 132.0, 131.8, 129.9, 128.6, 127.7, 127.5, 127.3, 126.6, 124.7, 123.7, 122.3, 122.0, 120.7, 120.1, 119.7, 116.0, 111.2, 61.7, 60.1, 37.0, 35.3; HRMS (ESI) calcd for $C_{31}H_{25}N_2O_2$ $[M+H]^+$ 457.1916 found 457.1897.



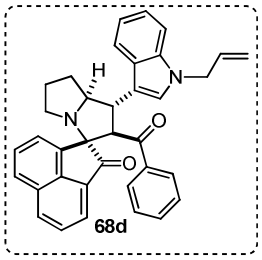
(1S*,1'S*,2'R*,7a'S*)-2'-Benzoyl-1'-(1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68b):**Following the general procedure described above **68b** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 45:55); as a yellow colored solid (151 mg, 63%); mp: 154-156 ^oC; FT-IR (KBR): 3360, 2921, 1716, 1653 and 1233 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28-8.27 (m, 1H), 8.18 (br s, 1H), 7.91 (d, 1H, J = 7.4 Hz), 7.77-7.52 (m, 5H), 7.35-7.21 (m, 4H), 7.07-7.00 (m, 3H), 6.84 (d, 2H, J = 6.3 Hz), 5.34-5.30 (m, 1H), 4.62-4.61 (m, 1H), 4.37-4.32 (m, 1H), 2.81-2.79 (m, 1H), 2.51-2.49 (m, 1H), 2.08-1.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.7, 198.8, 141.9, 137.2, 136.7, 135.0, 132.2, 131.6, 131.5, 130.4, 127.9, 127.8, 127.7, 127.4, 126.6, 125.1, 124.5, 122.4, 122.0, 121.8, 120.1, 119.6, 114.4, 111.4, 70.5, 62.9, 48.9, 45.9, 30.8, 26.9; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_2$ $[M+H]^+$ 483.2073 found 483.2076.



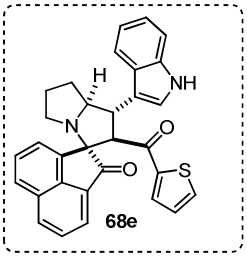
(1S*,1'S*,2'R*,7a'S*)-2'-Benzoyl-1'-(1-benzyl-1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68c):**Following the general procedure described above **68c** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 30:70); as a yellow colored solid (190 mg, 66%); mp: 170-172 ^{o}C; FT-IR (KBR): 2944, 1721, 1678, 1597 and 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, 1H, J = 7.5 Hz), 7.93 (d, 1H, J = 8.1 Hz), 7.79 (d, 1H, J = 7.0 Hz), 7.76 (dd, 1H, J_1 = 7.2 Hz, J_2= 1.8 Hz), 7.64-7.59 (m, 2H), 7.57-7.53 (m, 1H), 7.29-7.19 (m, 7H), 7.14-7.08 (m, 4H), 7.04 (t, 1H, J = 7.5 Hz), 6.86 (t, 2H, J = 7.8 Hz), 5.34 (d, 1H, J = 11.2 Hz), 5.28 (br s, 2H), 4.68-4.62 (m, 1H), 4.37 (t, 1H, J = 10.5 Hz), 2.85-2.79 (m, 1H), 2.54-2.49 (m, 1H), 2.14-1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.6, 198.7, 141.9, 137.4, 137.3, 137.1, 135.1, 132.1, 131.6, 131.5, 130.4, 128.8, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 126.9, 126.6, 125.1, 124.5, 121.8, 121.7, 120.3, 119.4, 113.6, 109.9, 70.6, 62.9, 50.1, 48.9, 46.0, 30.7, 26.8; HRMS (ESI) calcd for $C_{40}H_{33}N_2O_2$ $[M+H]^+$ 573.2542 found 573.2526.



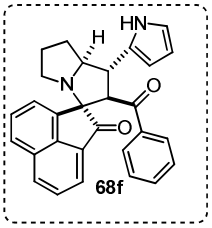
(1S*,1'S*,2'R*,7a'S*)-1'-(1-Allyl-1H-indol-3-yl)-2'-benzoyl-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68d):** Following the general procedure described above **68d** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 30:70); as a yellow colored solid (225 mg, 86%); mp: 162-164 ^{o}C; FT-IR (KBR): 2971, 1721, 1678, 1597 and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33-8.31 (m, 1H), 7.92 (d, 1H, J = 8.1 Hz), 7.81 (d, 1H, J = 7.0 Hz), 7.75 (dd, 1H, J_1 = 5.7, J_2 = 3.4 Hz), 7.63-7.61 (m, 2H), 7.54 (dd, 1H, J_1 = 8.0, J_2 = 7.2 Hz), 7.33-7.30 (m, 1H), 7.28-7.24 (m, 3H), 7.11 (s, 1H), 7.09 (s, 1H), 7.02 (t, 1H, J = 7.4 Hz), 6.85 (t, 2H, J = 7.6 Hz), 6.04-5.94 (m, 1H), 5.35 (d, 1H, J = 11.2 Hz), 5.20 (dd, 1H, J_1 = 10.0, J_2 = 1.2 Hz), 5.13 (dd, 1H, J_1 = 17.0, J_2 = 1.3 Hz), 4.69-4.64 (m, 3H), 4.37 (t, 1H, J = 10.8 Hz), 2.88-2.81 (m, 1H), 2.56-2.51 (m, 1H), 2.14-1.87 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.6, 198.8, 141.9, 137.3, 136.8, 135.0, 133.5, 132.2, 131.6, 131.5, 130.4, 127.9, 127.8, 127.7, 127.4, 127.2, 126.1, 125.1, 124.5, 121.8, 121.6, 120.3, 119.3, 117.5, 113.3, 109.8, 77.3, 70.5, 62.9, 49.0, 48.8, 45.9, 30.7, 26.8; HRMS (ESI) calcd for $C_{36}H_{31}N_2O_2$ $[M+H]^+$ 523.2386 found 523.2370.



(1S*,1'S*,2'R*,7a'S*)-1'-(1H-Indol-3-yl)-2'-(thiophene-2-carbonyl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68e):** Following the general procedure described above **68e** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 30:70); as a yellow colored solid (227 mg, 93%); mp: 173-175 ^{o}C; FT-IR (KBR): 2965, 1720, 1650, 1412 and 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, 1H, J = 6.7 Hz), 7.99 (d, 1H, J = 7.2 Hz), 7.91 (d, 1H, J = 5.9 Hz), 7.78 (d, 1H, J = 7.2 Hz), 7.69-7.60 (m, 3H), 7.36-7.34 (m, 1H), 7.28-7.11 (m, 5H), 6.58-6.56 (m, 1H), 5.19 (d, 1H, J = 11.3 Hz), 4.60-4.58 (m, 1H), 4.40-4.35 (m, 1H), 2.86-2.82 (m, 1H), 2.50-2.49 (m, 1H), 2.07-1.85 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.4, 190.4, 144.5, 142.0, 136.7, 134.8, 133.8, 131.9, 131.8, 131.4, 130.5, 128.1, 127.9, 127.6, 126.6, 125.2, 124.8, 122.5, 121.9, 120.0, 119.5, 111.5, 111.4, 77.6, 70.3, 63.4, 49.0, 46.0, 30.5, 26.7; HRMS (ESI) calcd for $C_{31}H_{25}N_2O_2S[M+H]^+$ 489.1637 found 489.1623.

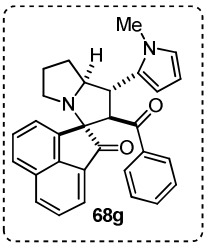


(1S*,1'R*,2'R*,7a'S*)-2'-Benzoyl-1'-(1H-pyrrol-2-yl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68f):** Following the general procedure described above **68f** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 50:50); as a yellow colored solid (172 mg, 80%); mp: compound decomposes after 160 ^{o}C; FT-IR (KBR): 3437, 1724, 1664 and 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (br s, 1H), 7.89 (d, 1H, J = 8.0 Hz), 7.75 (d, 1H, J = 8.3 Hz), 7.66 (d, 1H, J = 6.9 Hz),7.58 (t, 1H, J = 7.9 Hz), 7.50-7.43 (m, 2H), 7.02 (t, 1H, J = 7.1 Hz), 6.96 (d, 2H, J = 7.4 Hz), 6.83 (d, 2H, J = 7.7 Hz), 6.71 (br s, 1H), 6.20 (br s, 1H), 6.17 (d, 1H, J = 2.4 Hz), 4.78 (d, 1H, J = 10.4 Hz), 4.56-4.50 (m, 1H), 4.06 (t, 1H, J = 10.4 Hz), 2.67-2.61 (m, 1H), 2.48-2.43 (m, 1H), 2.25-2.19 (m, 1H), 1.94-1.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.5, 201.5, 141.7, 137.1, 134.7, 132.4, 131.5, 131.5, 130.6, 130.3, 127.8, 127.7, 127.3, 125.3, 123.9, 121.8, 117.5, 107.9, 104.9, 68.5, 65.3, 48.5, 45.8, 30.9, 27.2; HRMS (ESI) calcd for $C_{29}H_{25}N_2O_2$ $[M+H]^+$ 433.1916 found 433.1916.

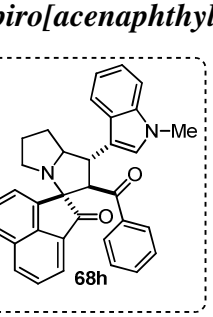


(1S*,1'R*,2'R*,7a'S*)-2'-Benzoyl-1'-(1-methyl-1H-pyrrol-2-yl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68g):** Following the general procedure described above **68g** was obtained after purification by silica gel column chromatography

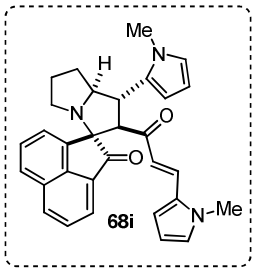
(EtOAc:Hexane = 35:65); as a yellow colored solid (134 mg, 60%); mp: 138-140 ^{o}C; FT-IR (KBR): 2955, 1727, 1676 and 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, 1H, J = 7.1 Hz), 7.73-7.48 (m, 5H), 7.03-6.85 (m, 5H), 6.49 (br s, 1H), 6.35 (br s, 1H), 6.09 (br s, 1H), 5.01 (d, 1H, J = 10.4 Hz), 4.30-4.29 (m, 1H), 4.11 (t, 1H, J = 9.4 Hz), 3.83 (s, 3H), 2.69-2.67 (m, 1H), 2.45-2.45 (m, 1H), 2.14-2.13 (m, 1H), 1.93-1.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.2, 198.7, 141.7, 137.0, 134.9, 132.3, 132.3, 131.5, 131.4, 130.3, 127.8, 1278, 127.4, 125.2, 124.1, 121.7, 121.7, 107.1, 105.3, 72.4, 65.6, 48.4, 44.3, 34.2, 30.8, 27.2; HRMS (ESI) calcd for $C_{30}H_{27}N_2O_2$ $[M+H]^+$ 447.2073 found 447.2080.



(1S*,1'S*,2'R*)-2'-Benzoyl-1'-(1-methyl-1H-indol-3-yl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68h):** Following the general procedure described **68h**was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 30:70); as a yellow colored solid (149 mg, 66%); mp: 174-176 ^{o}C; FT-IR (KBR): 2964, 1722, 1675, 1597 and 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29-8.27 (m, 1H), 7.93 (d, 1H, J = 8.2 Hz), 7.80 (d, 1H, J = 7.1 Hz), 7.76 (dd, 1H, J_1= 7.4, J_2= 1.6 Hz), 7.64-7.60 (m, 2H), 7.57-7.54 (m, 1H), 7.32-7.29 (m, 1H), 7.26-7.24 (m, 2H), 7.20 (s, 1H), 7.10-7.08 (m, 2H), 7.04-7.00 (m, 1H), 6.87-6.83 (m, 2H), 5.32 (d, 1H, J = 11.2 Hz), 4.67-4.62 (m, 1H), 4.37 (t, 1H, J = 10.9 Hz), 3.76 (s, 3H), 2.86-2.80 (m, 1H), 2.54-2.49 (m, 1H), 2.12-2.06 (m, 1H), 2.02-1.96 (m, 1H), 1.91-1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.5, 198.8, 141.9, 137.4, 137.3, 135.0, 132.2, 131.6, 131.5, 130.4, 127.9, 127.8, 127.7, 127.4, 127.1, 127.0, 125.2, 124.6, 121.8, 121.6, 120.2, 119.1, 112.9, 109.5, 77.2, 70.5, 62.9, 49.0, 46.0, 32.7, 30.6, 26.8. HRMS (ESI) calcd for $C_{34}H_{29}N_2O_2$ $[M+H]^+$ 497.2290 found 497.2209.

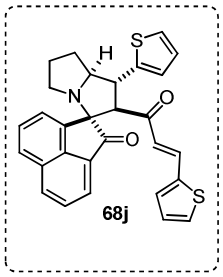


(1S*,1'R*,2'R*,7a'S*)-1'-(1-Methyl-1H-pyrrol-2-yl)-2'-((E)-3-(1-methyl-1H-pyrrol-2-yl)acryloyl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68i):** Following the general procedure described above **68i** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 40:60); as a yellow colored solid (187 mg, 80%); mp: compound decomposes after 65 ^{o}C; FT-IR (KBR): 2925, 1716, 1585 and 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, 1H, J = 8.0 Hz), 7.95 (d, 1H, J = 7.0 Hz),

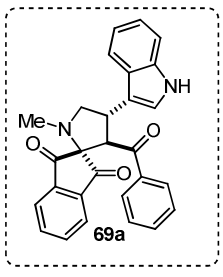


7.80 (d, 1H, *J* = 8.0 Hz), 7.63 (t, 2H, *J* = 6.5 Hz), 7.57 (d, 1H, *J* = 7.0 Hz), 6.87 (d, 1H, *J* = 15.7 Hz), 6.58 (br s, 1H), 6.49 (br s, 1H), 6.26 (br s, 1H), 6.14 (d, 1H, *J* = 2.7 Hz), 6.08 (br s, 1H), 5.95 (br s, 1H), 5.70 (d, 1H, *J* = 15.7 Hz), 4.56 (d, 1H, *J* = 11.2 Hz), 4.23-4.21 (m, 1H), 4.03 (t, 1H, *J* = 11.2 Hz), 3.80 (s, 3H), 3.39 (s, 3H), 2.53-2.46 (m, 2H), 1.92-1.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.8, 195.4, 142.0, 135.4, 132.4, 132.1, 131.7, 130.7, 129.1, 128.1, 128.0, 127.8, 125.2, 124.0, 121.7, 121.6, 120.5, 112.8, 109.5, 107.1, 105.1, 72.6, 67.1, 48.0, 44.1, 34.2, 34.1, 31.2, 27.6; HRMS (ESI) calcd for $C_{31}H_{30}N_3O_2$ $[M+H]^+$ 476.2338 found 476.2333.

(1S*,1'R*,2'R*,7a'S*)-1'-(Thiophen-2-yl)-2'-((E)-3-(thiophen-2-yl)acryloyl)-1',2',5',6',7',7a'-hexahydro-2H-spiro[acenaphthylene-1,3'-pyrrolizin]-2-one **(68j):**Following the general procedure described above **68j** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 30:70); as a yellow colored solid (154 mg, 64%); mp: 126-128 ^{o}C; FT-IR (KBR): 2963, 1718, 1706, 1590 and 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, 1H, *J* = 8.0 Hz), 7.97 (d, 1H, *J* = 8.0 Hz), 7.79 (d, 1H, *J* = 8.2 Hz), 7.63-7.58 (m, 2H), 7.52 (d, 1H, *J* = 6.9 Hz), 7.18 (d, 1H, *J* = 5.0 Hz), 7.15 (dd, 1H, J_1 = 5.0, J_2 = 1.0 Hz), 7.04-7.00 (m, 2H), 6.93 (dd, 1H, J_1 = 5.0, J_2 = 3.5 Hz), 6.88 (d, 1H, *J* = 3.5 Hz), 6.83 (dd, 1H, J_1 = 4.9, J_2 = 3.7 Hz), 5.77 (d, 1H, *J* = 15.6 Hz), 4.48 (d, 1H, *J* = 11.8 Hz), 4.31-4.26 (m, 1H), 4.22 (t, 1H, *J* = 11.8 Hz), 2.61-2.55 (m, 1H), 2.49-2.44 (m, 1H), 1.94-1.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.6, 195.1, 143.2, 142.0, 139.3, 135.4, 134.7, 132.2, 131.8, 131.5, 130.7, 129.0, 128.1, 128.0, 127.0, 125.4, 124.7, 124.1, 124.0, 123.7, 122.1, 72.5, 67.5, 48.4, 48.0, 30.7, 27.3; HRMS (ESI) calcd for $C_{29}H_{24}NO_2S_2$ $[M+H]^+$ 482.1248 found 482.1243.

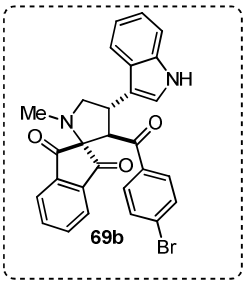


(3'R*,4'S*)-3'-Benzoyl-4'-(1H-indol-3-yl)-1'-methylspiro[indene-2,2'-pyrrolidine]-1,3-dione**(69a):**Following the general procedure described above **69a** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 50:50); as a yellow colored solid (130 mg, 60%); mp: 207-209 ^{o}C; FT-IR (KBR): 3168, 2853, 1738, 1703 and 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 8.65 (br s, 1H), 7.96 (d, 2H, *J* = 7.3 Hz), 7.74-7.72 (m, 1H), 7.56-7.43 (m, 7H), 7.04-7.02 (m, 1H), 6.96-6.91 (m, 3H), 4.99 (d, 1H, *J* = 10.5 Hz), 4.91-4.84 (m, 1H), 3.92 (t, 1H, *J* = 9.0 Hz), 3.52 (dd, 1H, J_1 = 9.0, J_2 = 6.6 Hz), 2.38 (s, 3H), ^{13}C NMR ($CDCl_3$+DMSO-d_6, 100 MHz): δ 204.9, 201.9, 197.7, 142.1, 140.8, 136.6,

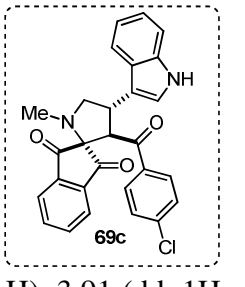


135.8, 135.6, 135.5, 133.2, 128.7, 128.5, 126.8, 122.9, 122.6, 122.1, 121.8, 119.7, 119.5, 110.8, 110.5, 79.7, 57.7, 50.4, 47.0, 36.7, 29.7; HRMS (ESI) calcd for $C_{28}H_{23}N_2O_3$ $[M+H]^+$ 435.1709 found 435.1693.

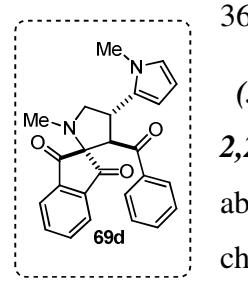
(3'R*,4'S*)-3'-(4-Bromobenzoyl)-4'-(1H-indol-3-yl)-1'-methylspiro[indene-2,2'-pyrrolidine]-1,3-dione **(69b):** Following the general procedure described above **69b** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 50:50); as a yellow colored solid (103 mg, 40%); mp: 210-212 ^oC; FT-IR (KBR): 3749, 2863, 1736, 1702 and 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (br s, 1H), 7.87 (d, 2H, J = 8.6 Hz), 7.77-7.74 (m, 1H), 7.55-7.49 (m, 4H), 7.38 (d, 2H, J = 8.6 Hz), 7.07-7.05 (m, 1H), 7.01-6.93 (m, 3H), 4.98 (d, 1H, J = 10.5 Hz), 4.83-4.76 (m, 1H), 3.90 (dd, 1H, J_1 = 10.5, J_2 = 9.1 Hz), 3.53 (dd, 1H, J_1 = 9.1, J_2 = 6.6 Hz), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.9, 201.8, 196.7, 142.0, 140.7, 139.7, 135.9, 135.6, 134.8, 129.9, 129.0, 126.7, 122.9, 122.6, 122.2, 121.8, 119.7, 119.4, 110.6, 79.5, 57.6, 50.6, 47.0, 36.7; HRMS (ESI) calcd for $C_{28}H_{22}BrN_2O_3$ $[M+H]^+$ 513.0814 found 513.0795.



(3'R*,4'S*)-3'-(4-Chlorobenzoyl)-4'-(1H-indol-3-yl)-1'-methylspiro[indene-2,2'-pyrrolidine]-1,3-dione **(69c):** Following the general procedure described above **69c** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 50:50); as a pale yellow colored solid (105 mg, 45%); mp: 203-205 ^oC; FT-IR (KBR): 3668, 2927, 1705, 1587 and 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.93 (br s, 1H), 7.82 (d, 2H, J = 8.6 Hz), 7.78-7.75 (m, 1H), 7.59-7.50 (m, 6H), 7.06-6.93 (m, 4H), 4.97 (d, 1H, J = 10.5 Hz), 4.84-4.77 (m, 1H), 3.91 (dd, 1H, J_1 = 10.5, J_2 = 9.1 Hz), 3.54 (dd, 1H, J_1 = 9.1, J_2 = 6.6 Hz), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.9, 201.7, 196.8, 142.0, 140.7, 137.5, 135.8, 135.5, 135.3, 132.0, 130.0, 128.5, 126.7, 122.9, 122.5, 122.2, 121.8, 119.8, 119.4, 110.7, 110.6, 79.5, 57.5, 50.6, 47.0, 36.7; HRMS (ESI) calcd for $C_{28}H_{22}ClN_2O_3$ $[M+H]^+$ 469.1319 found 469.1303.



(3'R*,4'R*)-3'-Benzoyl-1'-methyl-4'-(1-methyl-1H-pyrrol-2-yl)spiro[indene-2,2'-pyrrolidine]-1,3-dione **(69d):**Following the general procedure described above **69d** was obtained after purification by silica gel column chromatography (EtOAc:Hexane = 45:55); as a yellow colored solid (109 mg,



55%); mp: 184-186 ^{o}C; FT-IR (KBR): 2857,1735, 1704, 1608 and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94-7.73 (m, 7H), 7.55 (t, 1H, J = 7.3 Hz), 7.45 (t, 2H, J = 7.4 Hz), 6.11 (br s, 1H), 5.90 (d, 1H, J = 2.0 Hz), 5.70 (t, 1H, J = 3.0 Hz), 4.70-4.68 (m, 2H), 3.92-3.88 (m, 1H), 3.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.0, 201.7, 197.7, 141.6, 141.2, 136.5, 136.3, 135.7, 133.4, 128.7, 128.5, 126.5, 122.6, 122.5, 122.3, 108.1, 106.9, 79.3, 57.0, 52.0, 46.1, 36.5, 33.5; HRMS (ESI) calcd for $C_{25}H_{23}N_2O_3$ $[M+H]^+$ 399.1709 found 399.1711.

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Chapter 3:Regioselective construction of C-3 arylated furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives via* the *Pd(II)-catalyzed directing group-aided C-H arylation/acetoxylation reactions.

General introduction. Pd(II)-catalyzed direct C(sp^2)-H arylation of heteroarenes and synthesis of functionalized heteroarenes.

Arylated heteroarenes (heterobiaryls) belong to an important class of aromatic compounds and there exist numerous arylated heteroarenes-based natural products, synthetically derived biologically active moleculesand organic materials.[1,2] Particularly, several furan/thiophene-based biaryl derivatives were reported to show a range of biological activities and considered as medicinally important compounds. Further, furan/thiophene-based biaryl derivatives are used as building blocks in organic materials and organic synthesis.[1,2] In the broad family of furan/thiophene-based biaryl derivatives, the C3-arylated furan/thiophene-2-carboxamides,[1,2] and the C3- or C5-arylated furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives[3] were found to show promising various biological activities (Figure 1).

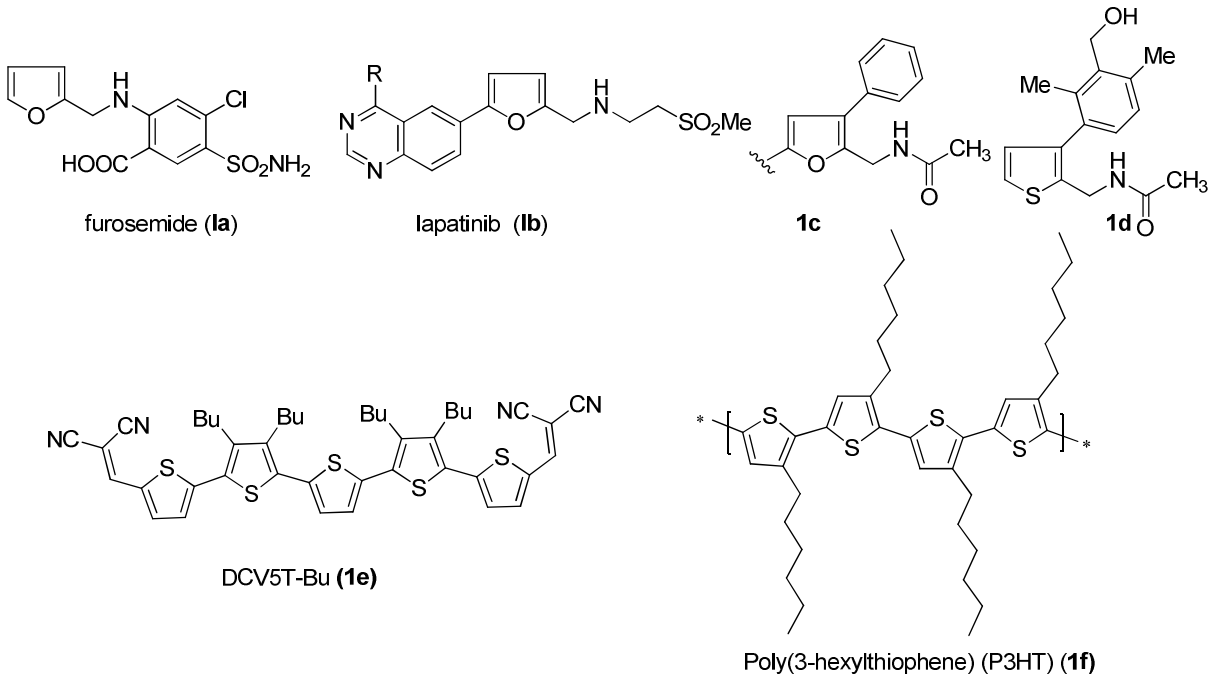


Figure 1. Biologically active and organic material molecules-based on thiophene and furan.

Given the importance of heterobiaryl compounds, the introduction of aryl/heteroaryl groups onto furan and thiophene rings is an essential task. In general, the well-known transition–metal-catalyzed cross-coupling reactions (e.g. Heck, Negishi, Suzuki, Kumada coupling and Stille reactions) were efficiently employed for the construction of functionalized furan/thiophene heterobiaryl molecules.[4a-d]

Nevertheless, the traditional cross-coupling reactions (e.g. Heck, Negishi, Suzuki, Kumada coupling and Stille reactions) are associated with some unavoidable limitations, e.g.; (a) there is a need for assembling of organometallic reagents prior to the traditional cross-coupling reactions, (b) there is a need for expensive and bulky ligands to accomplish the cross-coupling reactions, and (c) production of stoichiometric quantity of hazardous acidic or basic or metallic waste in the traditional cross-coupling reactions. Therefore, development of a method that avoids the above said limitations is always attractive. Accordingly, alternative methods involving the preparation of heterobiaryl molecules *via* the direct functionalization C-H bonds were developed.

Over the past few years, the transition metal-catalyzed C-H activation/functionalization reactions have received special attention because it allows a facile construction of carbon-carbon and carbon-heteroatom bonds.[4e-p,5] Many research groups are successful in achieving the transition metal-catalyzed direct coupling of C-H bonds of heteroaromatics with arenes (heteroarenes) or aryl (heteroaryl) halides by using the C-H activation/functionalization strategy, without any preactivation of one or both coupling partners.[4e-p,5,6] The Pd based catalysts and a variety of other transition metal catalysts (e.g. Ru[5d,5n,7], Rh[8], Cu[9] and Ir[10]) were used for achieving the coupling of C-H bonds of heteroaromatics with arenes/heteroarenes or aryl-/heteroaryl halides.

Accordingly, the transition metal-catalyzed direct C-H arylation of furans and thiophenes with aryl halides by using the C-H activation/functionalization strategy has been well explored and there exists only rare reports dealing on the C-H arylation at the C-3 or C-4 position of thiophenes and furans.[6,11,12] There are some shortcomings by using this strategy for selectively synthesizing the arylated furans and thiophene and a literature survey revealed the following shortcomings; (a) in most of the cases, the C-H arylation of thiophenes and furans selectively occurs at the more reactive C-2 and C-5 positions under the Pd catalysis,[6,11-14] (b) the arylation of less reactive C-3 and C-4 positions of thiophene or furan can be achieved by using pre-assembled aryl boron or aryl triflate as one of the coupling partners, (c) arylation of the C-3 or C-4 position of thiophene or furan systems done if C-2 and C-5 positions are already

substituted,[14,15a,b] and (d) under certain conditions, the arylation of thiophene or furan system occurs at multiple positions.[15c-e]

Recently, the directing group-assisted regioselective functionalization (arylation/alkylation) of the *ortho* C-H bonds of aromatic carboxylic acid derivatives found to be efficient approach for functionalizing aromatic carboxamides and the construction of C-C bonds.[4e-p,5] A range of functional groups such as, amides, esters, ketones, oxazoline and pyridines were found to function as the directing groups to selectively functionalize the C-H bonds of organic molecules. Accordingly, the transition metal catalyzed C-C bond construction *via* the arylation and alkylation of the *ortho* sp^2 C-H bonds of aromatic carboxylic acid derivatives have been well studied.

General introduction. Pd-catalyzed direct C(sp^2)-H oxidation/acetoxylation of arenes and synthesis of functionalized arenes.

Similar to the concept pertaining to the transition metal catalyzed C-C bond construction *via* the arylation and alkylation of the *ortho* sp^2 C-H bonds of aromatic carboxylic acid derivatives, the directing group-assisted regioselective acetoxylation/alkoxylation of sp^2 *ortho* C-H bonds of aromatic carboxylic acid derivatives found to be an efficient approach for functionalizing the aromatic carboxamides and construction of C-O bonds.[4e-p,5,16,17e-h] While the construction of C-C, C-N and C-O bonds are equally important, in particular, the directing-group-aided, transition-metal-catalyzed C-H oxidation of the C(sp^2)-H bonds of arenes involving the C-O bond forming reactions is a straightforward approach for the synthesis of phenol derivatives. It is well known and also a survey revealed phenolic compounds are very important class of organic molecules exhibiting a wide range of biological activities (Figure 2).[17a-d] Sanford's group first reported the Pd-catalyzed pyridine-directed acetoxylation of the sp^2 C–H bond. Subsequently, Yu *et al.*, Chen *et al.* and Sahoo *et al.* and other research groups reported the directing group-aided acetoxylation/alkoxylation of C–H bond bonds of organic molecules.[4e-p,5,16,17e-h]

General introduction. Pd(II)-catalyzed C(sp^2)-H arylation and cyclization route to heterocycles.

While the concept pertaining to the directing group-assisted transition metal-catalyzed sp^2 C-H activation followed by C-C, C-N and C-O bonds has been well explored, there have been efforts to assemble *N*-heterocycles *via* the directing group-assisted C-H activation followed by intramolecular C-C or C-N bond formation route. Needless to mention that *N*-heterocycles are backbone of various branches of science, including organic chemistry, medicinal chemistry and biochemistry. Among the various important classes of *N*-heterocycles, phenanthridine derivatives are a class of structures found in a variety of natural products and a wide range of pharmacologically active compounds.[18] Apart from the biological properties, phenanthridine derivatives are reported to exhibit luminescence properties (Figure 2).

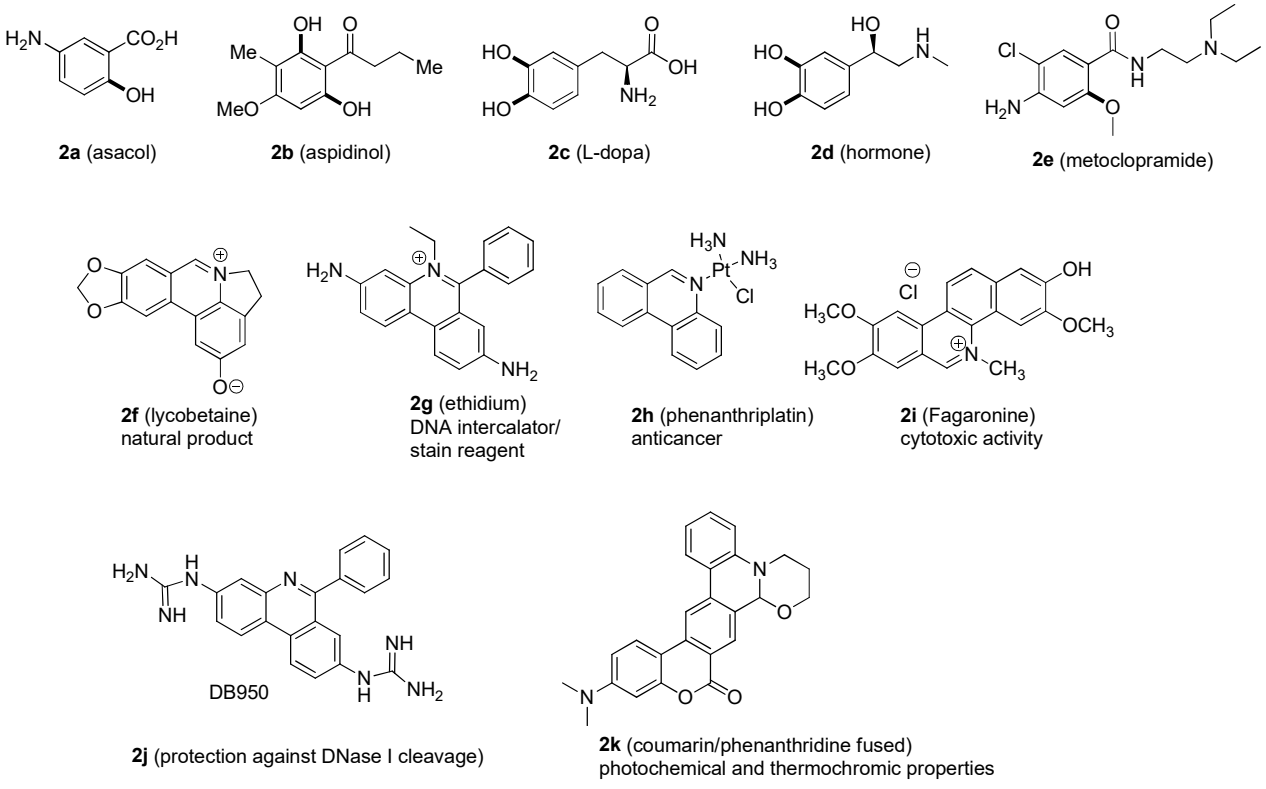


Figure 2. Representative bio-active phenolic compounds and phenanthridines.

Given the importance of the heterobiaryl compounds,[1-3] especially, arylated or heteroarylated furans and thiophenes in various branches of chemical science, the preparation of arylated or heteroarylated furans and thiophenes *via* the introduction of aryl/heteroaryl groups onto furan and thiophene rings is an essential task. While this can be achieved *via* the transition metal-catalyzed functionalization of C-H bonds can be achieved without any directing group as well as by using a suitable directing group; however, a literature survey indicated that there exist only limited reports dealing on the direct and regioselective C3 arylations of furan and thiophene systems with high regiocontrol.

While the transition-metal catalyzed C-H arylations of various thiophene/furan substrates were investigated in the literature, especially a literature survey indicated that there exists no report dealing on the direct and regioselective C3 arylations of furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives with aryl halides as coupling partners (Figure 3).[1-3]

To give a glimpse on the existing literature papers dealing on the preparation of arylated or heteroarylated furans and thiophenes involving various thiophene/furan substrates and arylating agents *via* the transition-metal catalyzed C-H activation[4e-p,5,16] based introduction of aryl/heteroaryl groups onto the furan and thiophene rings involving are presented below.

Representative papers dealing on the transition metal-catalyzed, directing group-free, direct arylation of the C-3 and C-4 positions of thiophene and furan systems involving different arylating agents.

Itami *et al*.[19a] reported the Pd-catalyzed regioselective synthesis of C-4 substituted thiophenes **3d** by using arylboronic acids **3b** as a coupling partner (Scheme 1). Next, the same group[14b] reported the *β*-selective arylation of thiophene derivatives **3a** with iodoarenes **3e** involving $PdCl_2$ / $P[OCH(CF_3)_2]_3$ / Ag_2CO_3 catalytic system (Scheme 1). Further they also[19b] revealed the synthesis of C-3 substituted thiophenes **3h** and **3i** from thiophenes **3a** with arylboronic acids **3b** in presence of Pd(II)-sulfoxide-oxazoline (sox) ligand **3g** and iron-phthalocyanine. Subsequently,

Itami *et al.*[19c] achieved the synthesis of sterically hindered heterobiaryls **3k** in presence of $Pd(OAc)_2$/bisoxazoline/TEMPO catalytic system by using arylboronic acids **3b** (Scheme 1).

Glorius *et al.*[20] reported the regioselective direct C-H functionalization of benzo[*b*]thiophenes **4a** with arylchlorides **4b** in the presence of dual catalytic system (Pd/C and CuCl). Further, Glorius's group[14c] reported the synthesis of functionalizationalized thiophenes **4f** and **4g** *via* the direct C-H arylation route involving the Pd/C catalytic system (Scheme 2).

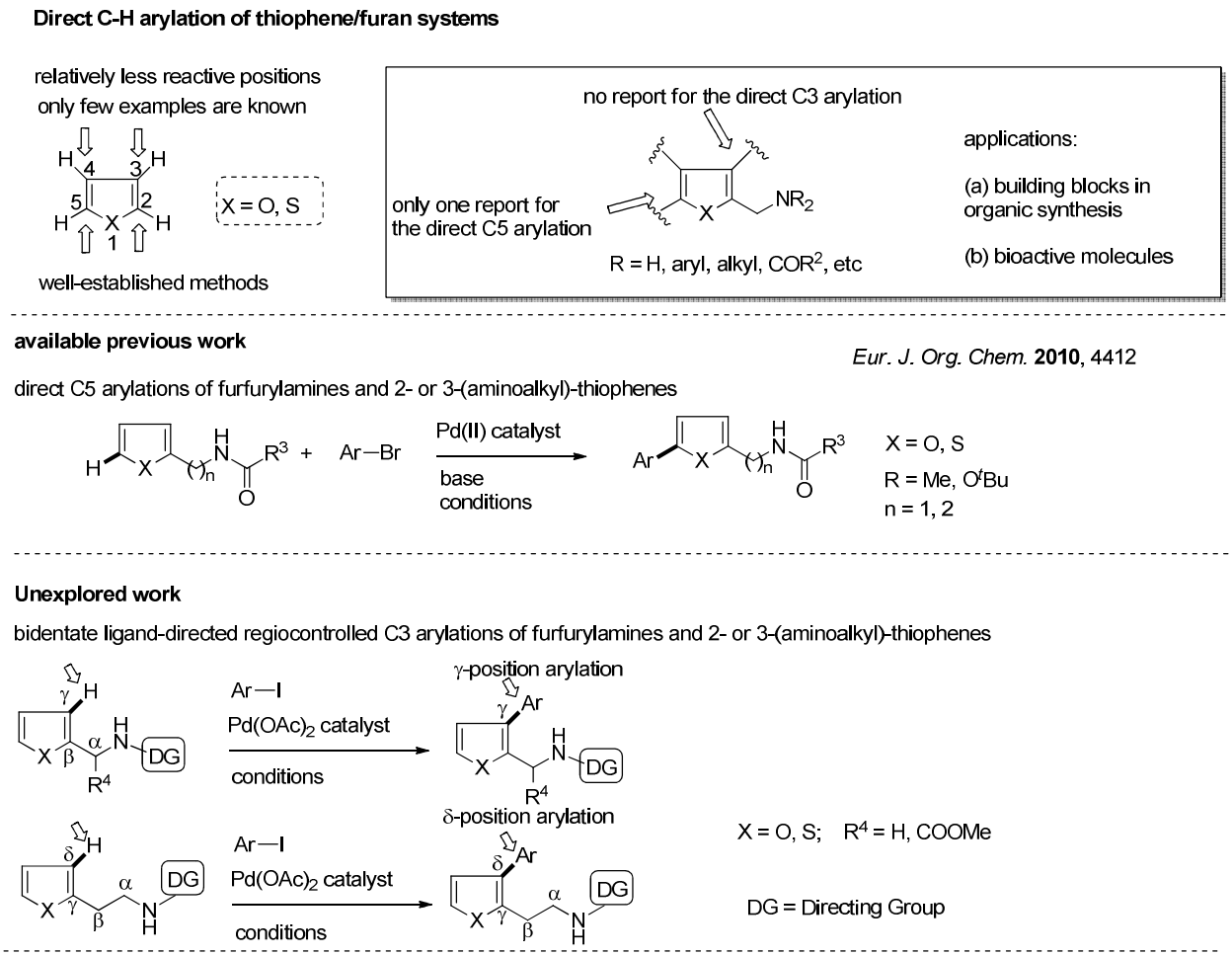
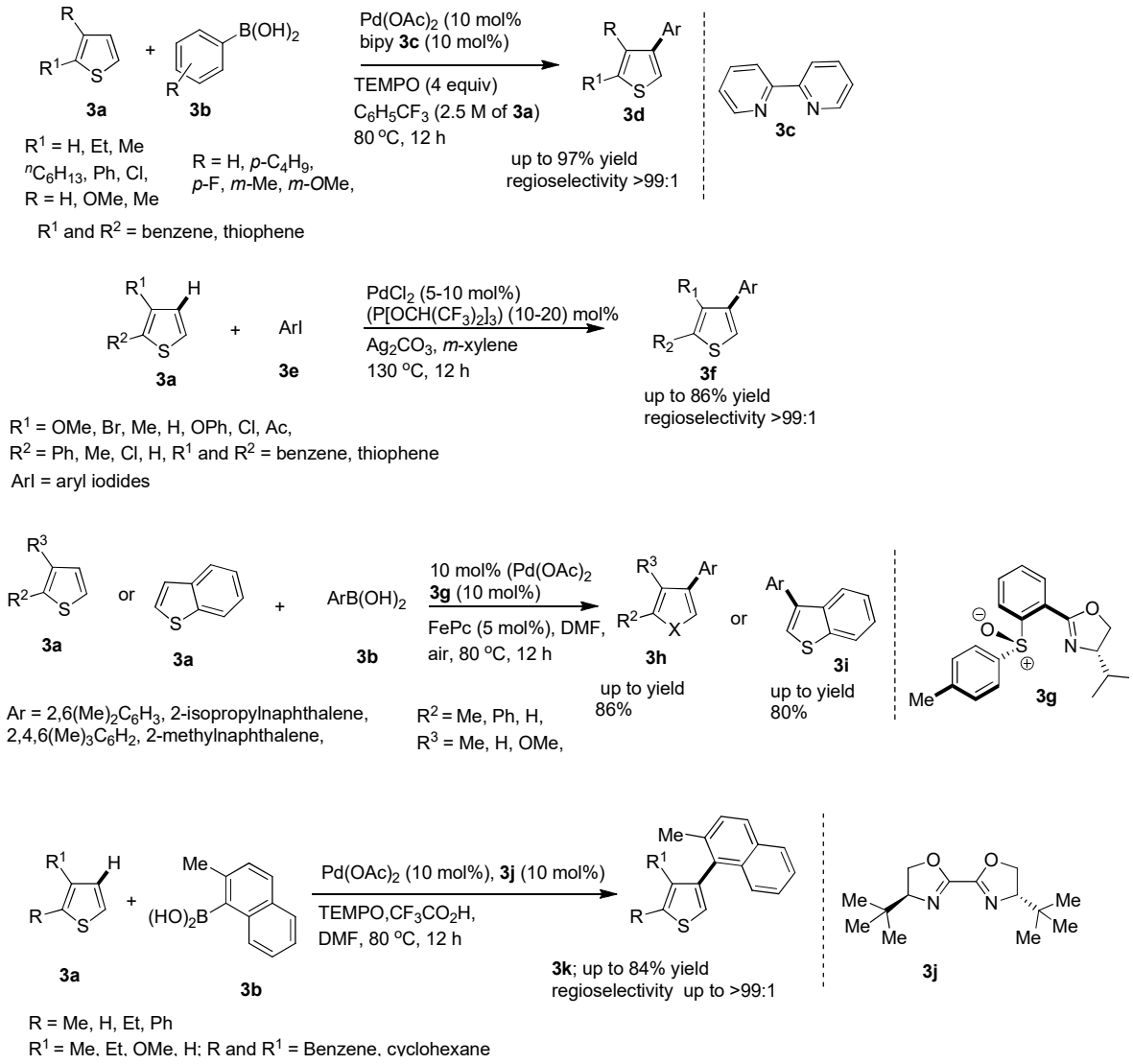


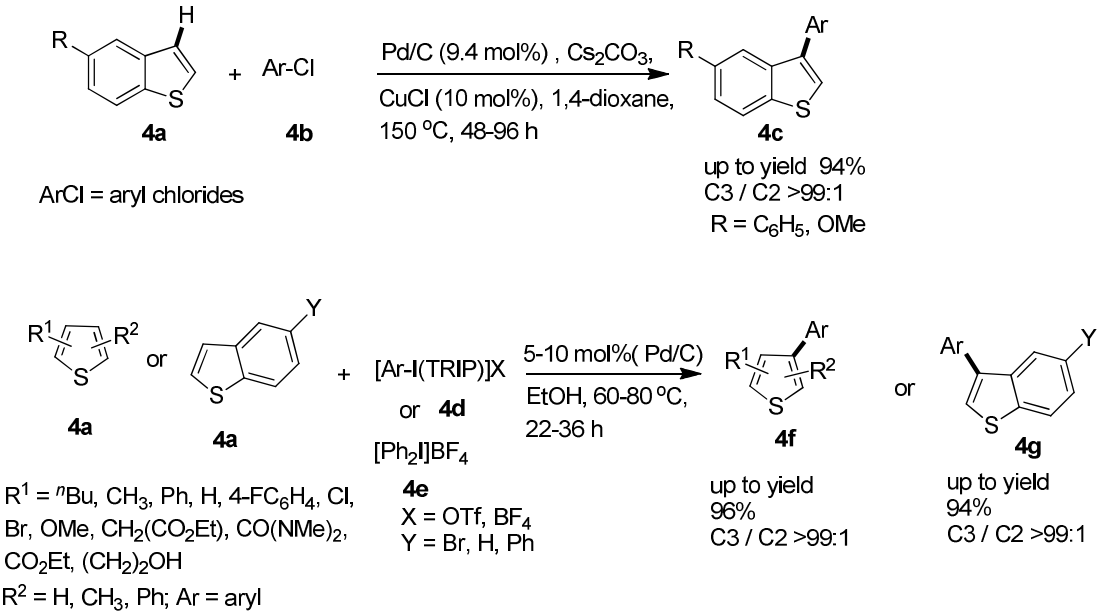
Figure 3. C3 arylations of furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives.



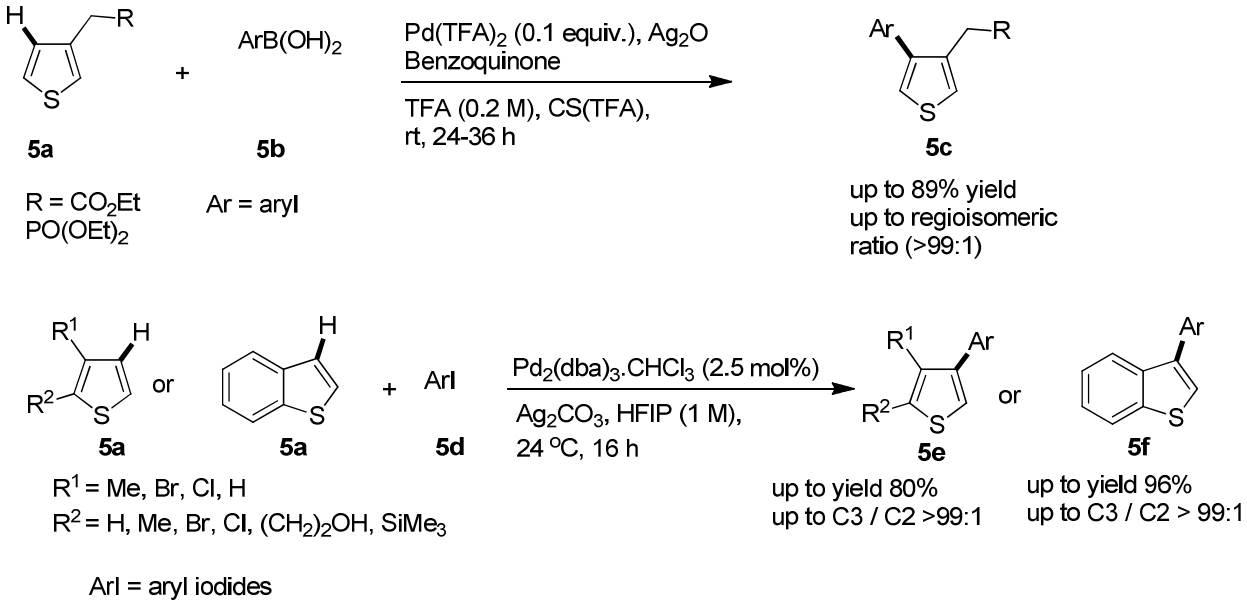
Scheme 1. C-H arylation of C-3 position of substituted thiophenes involving different coupling partners.

Bach *et al.*[21a] reported the synthesis of 4-substituted thiophenes **5c** in presence of $Pd(TFA)_2$ by using various aryl boronic acids **5b** (Scheme 3). Recently, Larrosa *et al.*[21b] reported the Pd-catalyzed direct *β*-arylation of thiophenes **5a** and benzo[*b*]thiophenes **5a**(Scheme 3). In addition, Oi *et al.*[21c] reported the synthesis of arylated thiophene **5h** and **5i***via* the Pd-catalyzed direct *β*-arylation of thiophenes **5a** and benzothiophenes **5a** with aryltrimethylsilanes **5g** in presence of $CuCl_2$(Scheme 4). Huang and Wu *et al.*[21d] reported the direct C-H arylation of benzothiophenes **5a** involving MIDA boronates **5j** in presence of a palladium catalyst afforded the arylated benzo[*b*]thiophenes **5k**(Scheme 4). Tsukada *et al.*[21e] reported the β-arylation of thiophenes **5a**

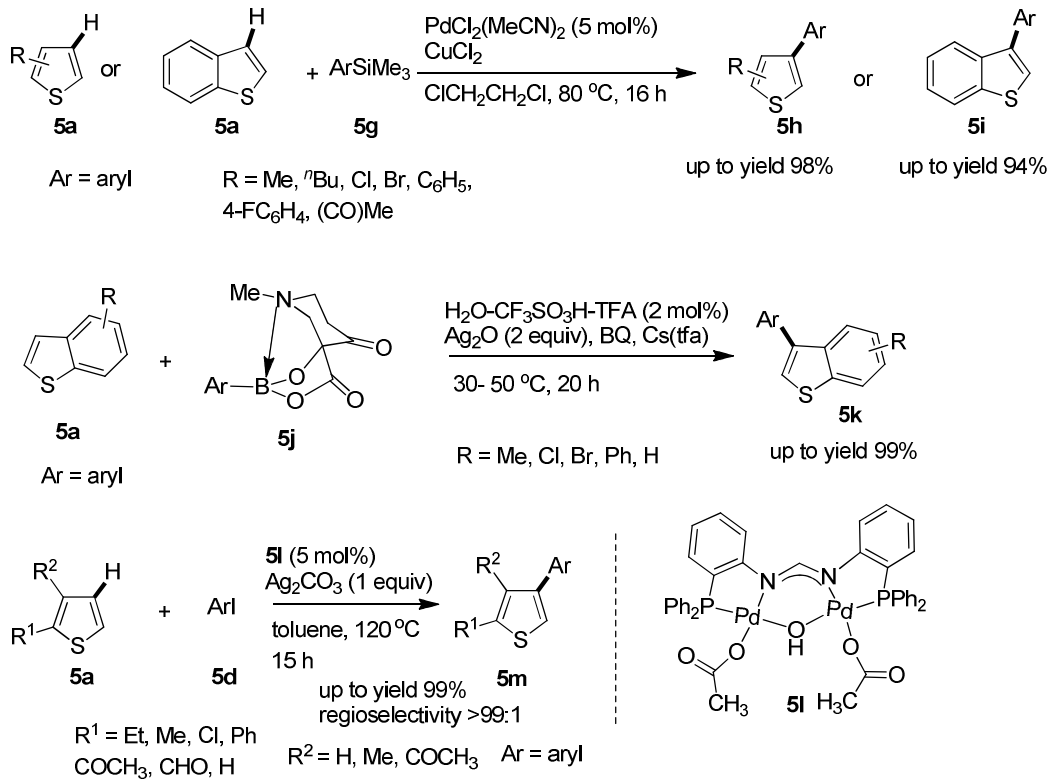
with aryl iodides **5d** catalyzed by dinuclear palladium carboxylate complex gave the arylated thiophens **5m** (Scheme 4).



Scheme 2. Synthesis of C-3 substituted thiophenes **4f** and benzo[*b*]thiophenes **4c** and **4g**.



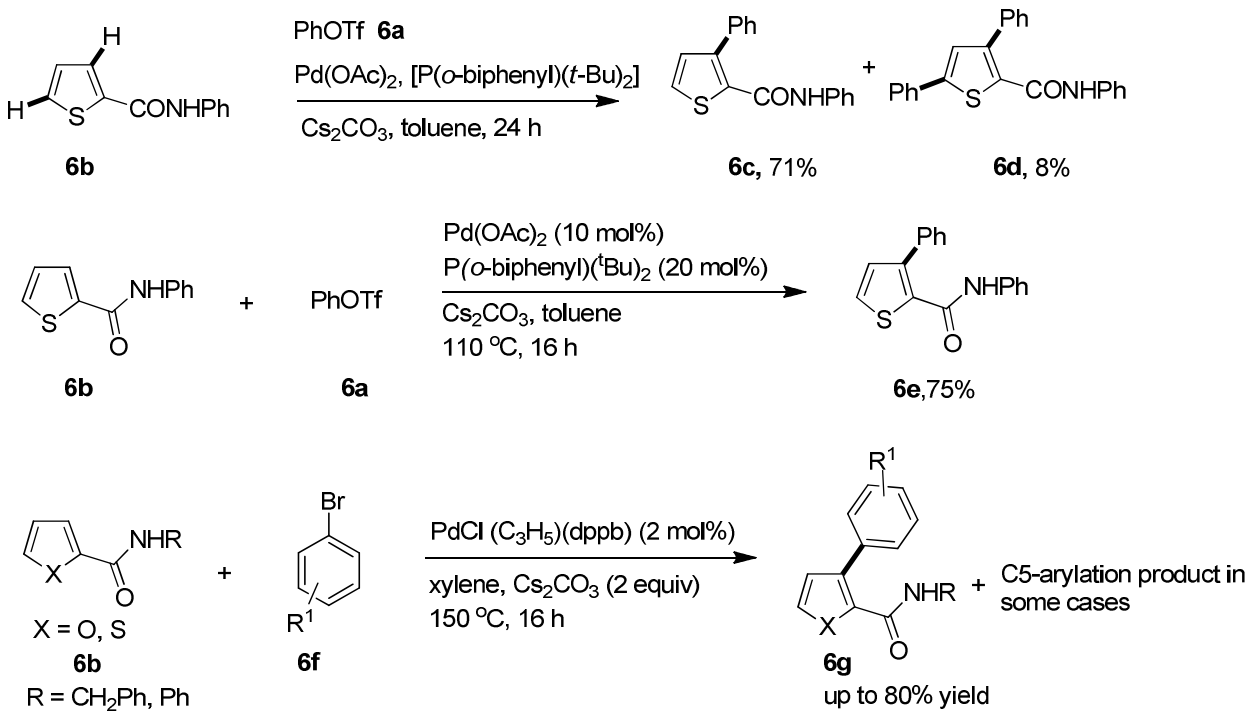
Scheme 3. Construction of C-3 substituted thiophenes **5c** and **5e** and benzo[*b*]thiophenes **5f**.



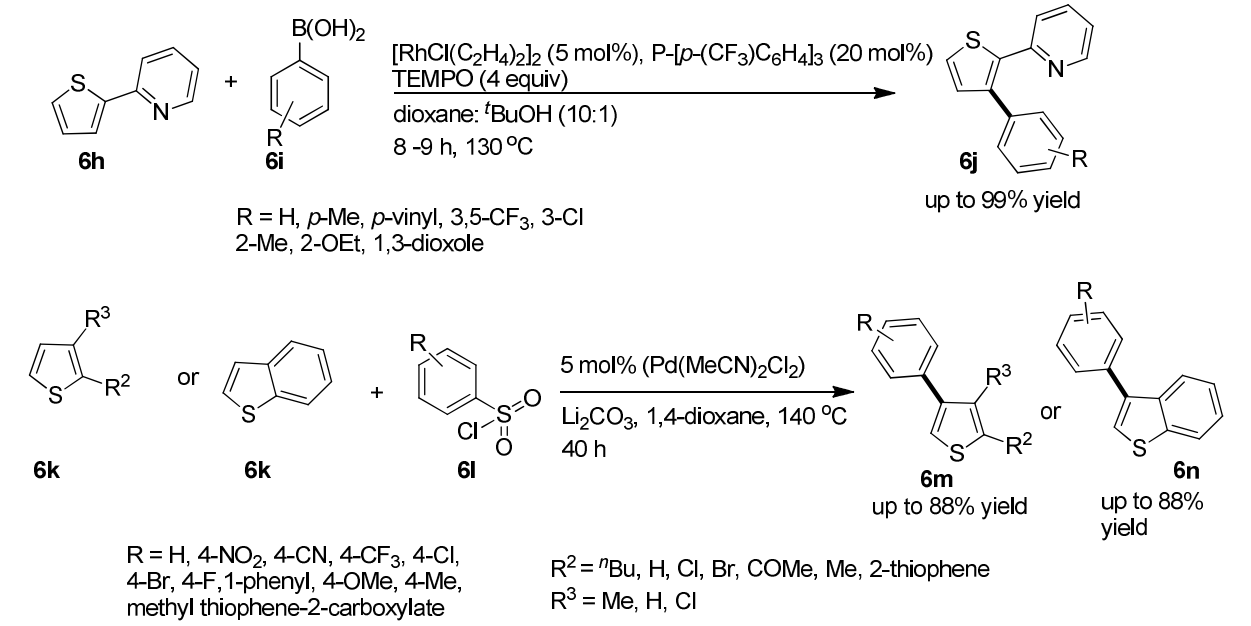
Scheme 4. Synthesis of C-3 substituted thiophenes **5h** and **5m**and benzo[*b*]thiophenes **5k**.

Miura and co-workers[22a] prepared C-3 substituted thiophene-2-carboxamide **6c** along with C-3and C-5 substituted thiophene-2-carboxamide **6d***via* the C-H arylation of **6b** with PhOTf **6a** in the presence of $Pd(OAc)_2$ as the catalyst and [P(*o*-biphenyl)(*t*Bu)$_2$] as the ligand (Scheme 5). Moreover, Doucet *et al.*[11h] reported the synthesis C-3 substituted thiophene-2-carboxamides **6e** from the Pd-catalyzed reaction of **6b** with PhOTf. Further, Doucet *et al.*[22b] reported the synthesis of C-3 arylated furan- and thiophene-2-carboxamides **6g** from the Pd-catalyzed reaction of C-2 substituted furan- and thiophene-2-carboxamides **6b** with substituted aryl bromides **6f** (Scheme 5).

Studer *et al.*[22c] reported the synthesis of C-3 substituted thiophenes **6j** from the reaction of 2-pyridyl thiophene **6h** with arylboronic acid **6i** in presence of $[RhCl(C_2H_4)_2]_2$ and P[*p*-$(CF_3)C_6H_4]_3$ (Scheme 6). Doucet *et al.*[22d] reported the regioselective synthesis of *β*-arylated thiophenes **6m** and **6n** from the Pd-catalyzed reaction of thiophene derivatives **6k** with benzenesulfonyl chlorides **6l** (Scheme 6).



Scheme 5. C-H arylation of C-3 position of substituted thiophenes involving different coupling partners.

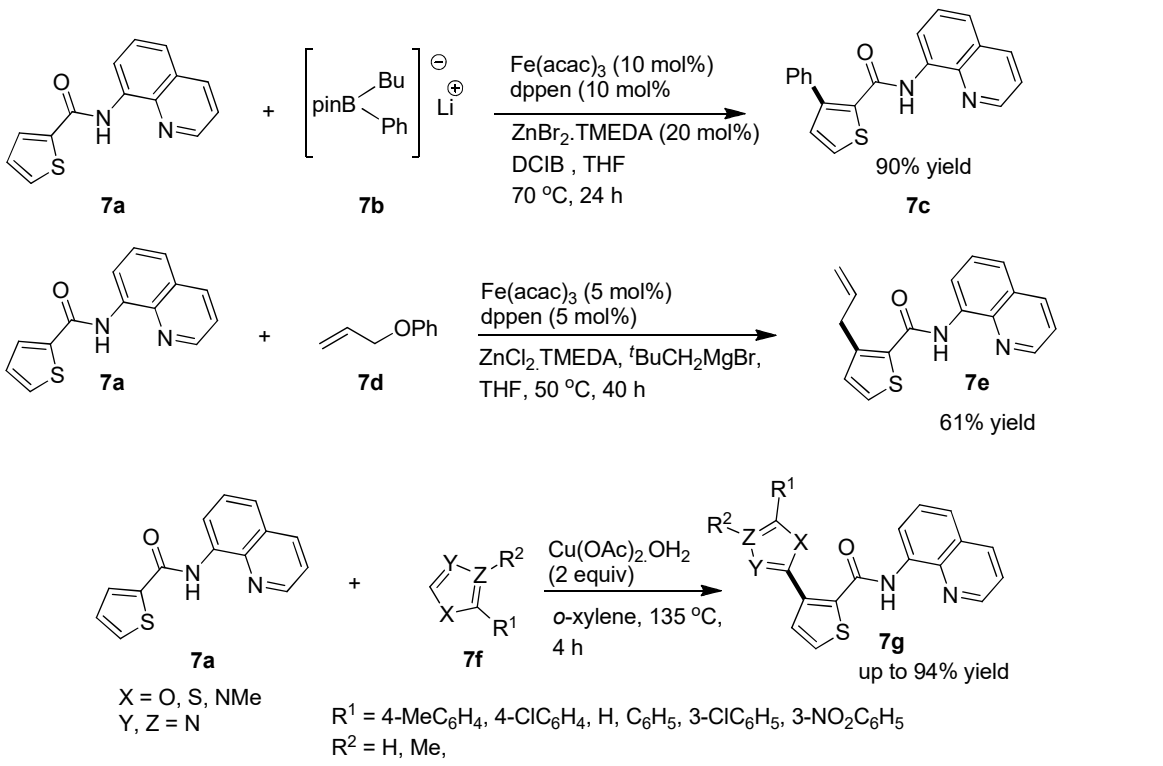


Scheme 6. C-H arylation of C-3 position of substituted thiophenesinvolving different coupling partners.

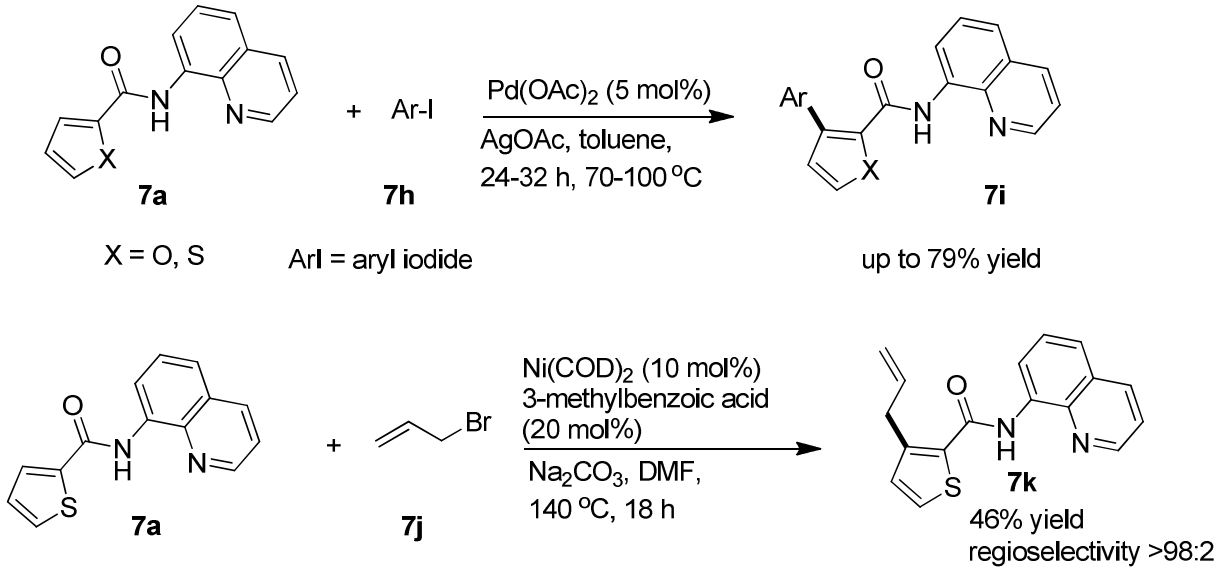
Representative papers dealing on the transition metal-catalyzed, directing group 8-aminoquinoline-aided, direct arylation of the C-3 and C-4 positions of thiophene and furan systems involving different arylating agents and other reagents.

Recently, the directing group-assisted regioselective functionalization (arylation/alkylation) of the *ortho* C-H bonds of aromatic carboxylic acid derivatives found to be efficient approach for functionalizing the aromatic carboxamides and the construction of C-C bonds. [4e-p,5]Ater the seminal paper published by Daugulis, which revealed the bidentate ligand 8-aminoquinoline provided support to selectively activate/functionalize the *ortho* C-H bonds of aromatic carboxylic acid derivatives; several research groups employed the bidentate ligand 8-aminoquinoline as the ligand to functionalize various carboxylic acid derivatives. In this line, Nakamura *et al.*[23a] achieved the synthesis of C-3 arylated thiophene **7c***via* the iron-catalyzed bidentate ligand 8-aminoquinoline-directd C3-arylation of **7a** (Scheme 7). Nakamura *et al.*also[23b] reported the bidentate ligand 8-aminoquinoline-directd *ortho*-allylation of thiophene-2-carboxamide **7a** with allyl ether **7d** in presence of an iron catalyst (Scheme 7). Miura *et al.*[23c] reported the synthesis of C-3 substituted thiophene-2-carboxamides **7g***via* thecopper-mediated C-H/C-H biaryl coupling of carboxylic acid derivatives **7a** and 1,3-azoles **7f** (Scheme 7). Recently our group[23d] reported the bidentate ligand 8-aminoquinoline-assisted, $Pd(OAc)_2$/AgOAc-catalytic system-based regioselective C-H arylation of C-3 position of thiophene and furan-2-carboxamides **7a** with variety of aryl iodides **7h**, which gave several C-3 substituted thiophene and furan-2-carboxamides **7i**(Scheme 8). Recently, Sundararaju and co-workers[23e] revealed the Ni-catalyzed synthesis of C-3 allylated thiophenes **7k** (Scheme 8).

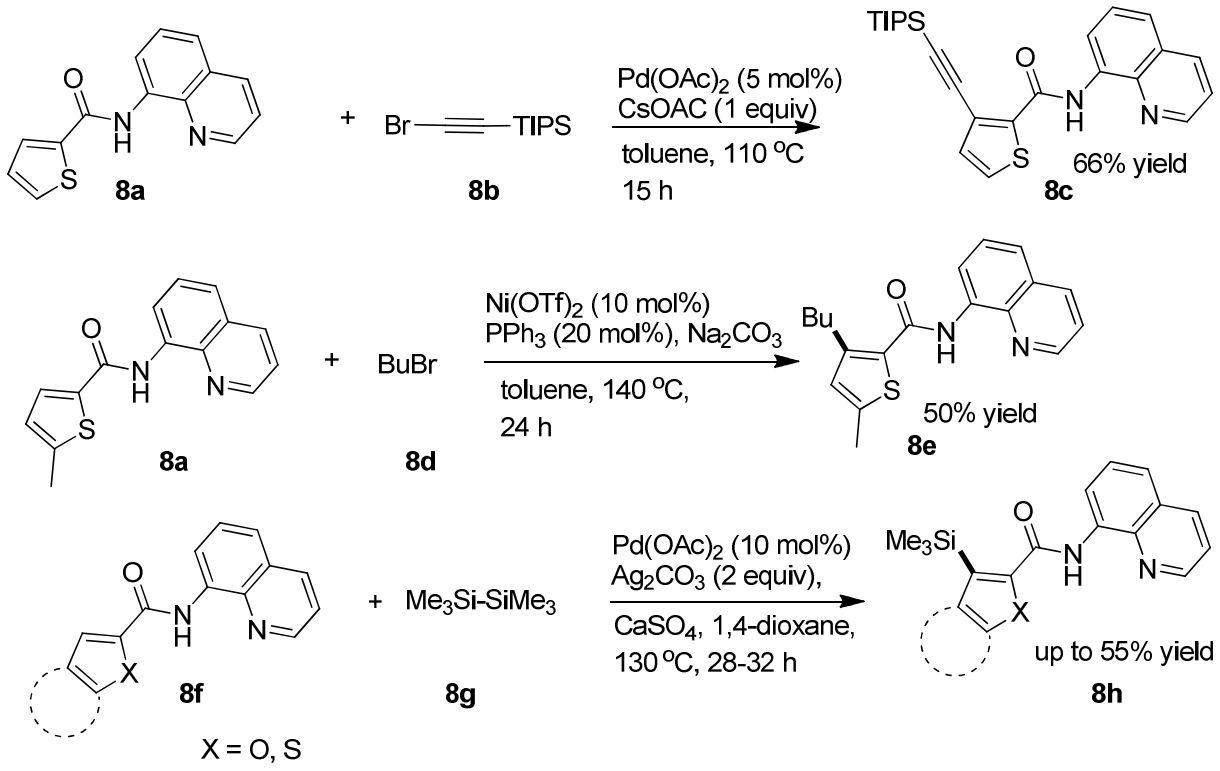
Chatani *et al.*[23f] reported the bidentate ligand 8-aminoquinoline-assisted, Pd-catalyzed regioselective C-H alkynylation of C-3 position of thiophene-2-carboxamides **8a** which gave C-3 alkynylated thiophene **8c** (Scheme 9). The same group revealed the synthesis of C-3 alkylated thiophene **8e***via* the bidentate ligand 8-aminoquinoline-assisted, Ni-catalyzed regioselective C-H alkylation of C-3 position of thiophene-2-carboxamides **8a** (Scheme 9). Additionally, Kanai *et al.*[23h] reported the regioselective synthesis of C-3 silylated thiophene-2-carboxamides **8h***via* the bidentate ligand 8-aminoquinoline-direced Pd-catalyzed silylation (Scheme 9).



Scheme 7. Bidentate ligand 8-aminoquinoline directed synthesis of C-3 substituted thiophene-2-carboxamides **7c**, **7e** and **7g**.



Scheme 8. Bidentate ligand 8-aminoquinoline directed synthesis of C-3 substituted furan/thiophene-2-carboxamides **7i** and **7k**.

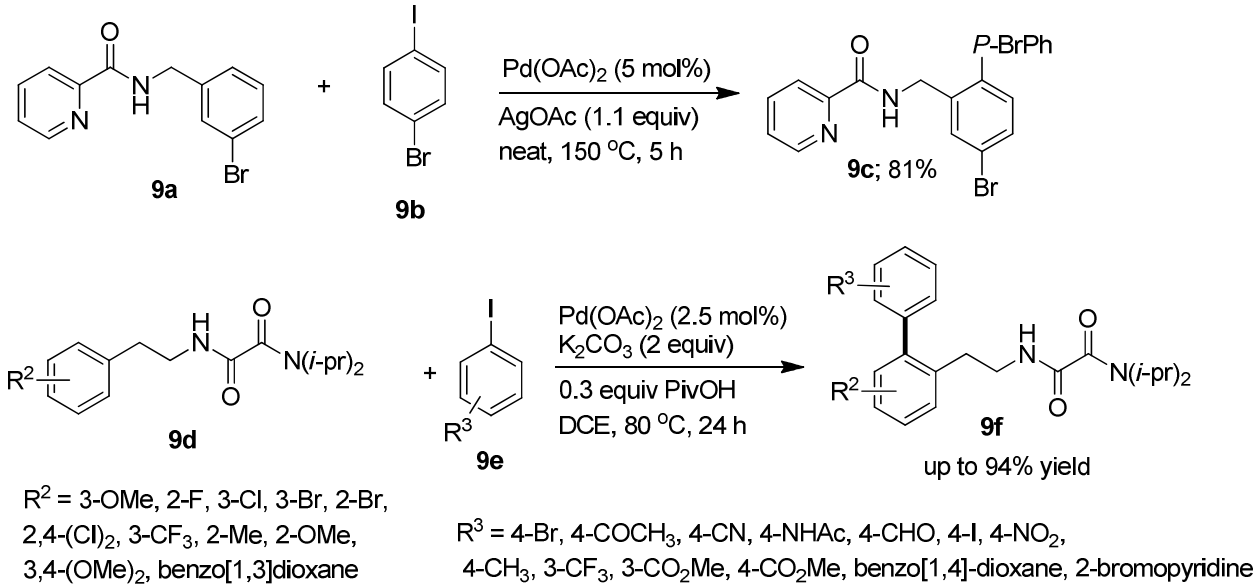


Scheme 9. 8-Aminoquinoline-directed synthesis of C-3 substituted furan/thiophene-2-carboxamides **8c**, **8e** and **8h**.

Representative papers dealing on the transition metal-catalyzed, directing group picolinamide- or oxalylamide-aided, direct arylation and acetoxylation of the *ortho* sp^2 C-H bonds of aromatic carboxamides.

Alongside the popularity of the bidentate ligand 8-aminoquinoline,[5] which provided the support to selectively activate/functionalize the *ortho* C-H bonds of aromatic carboxylic acid derivatives; Daugulis *et al.*[24a] reported the bidentate directing group picolinamide as an efficient ligand for the direct arylation of the *ortho* sp^2 C-H bonds of aromatic amines, such as benzylamine systems. For example, the direct arylation of the *ortho* sp^2 C-H bonds of aromatic carboxamides **9a** prepared from picolinic acid and 3-bromobenzylamine gave the *ortho* C-H arylated benzylamine system **9c** (Scheme 10). After this initial result, many groups used picolinamide as a directing group in various synthetic transformations pertaining to the C-H functionalization of organic molecules.[4e-p,5] Recently, Zhao *et al.*[24b] reported the oxalylamide-directed direct arylation of the

ortho sp^2 C-H bonds of aromatic carboxamides **9d** gave the *ortho* C-H arylated β-arylethylmines **9f** (Scheme 10).

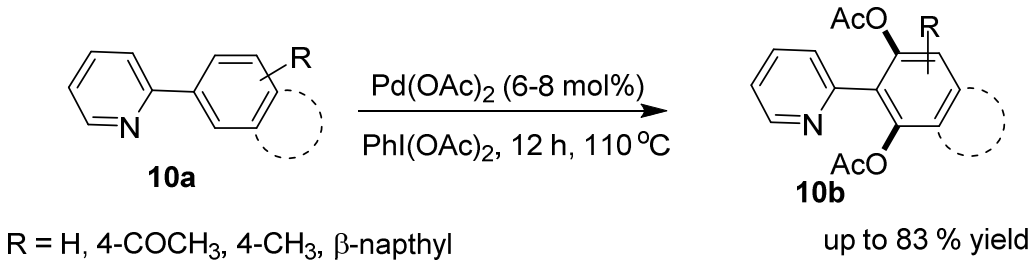


Scheme 10. Picolinamide- and oxalylamide-directed arylation of the *ortho* sp^2 C-H bonds of aromatic carboxamides at γ and δ positions.

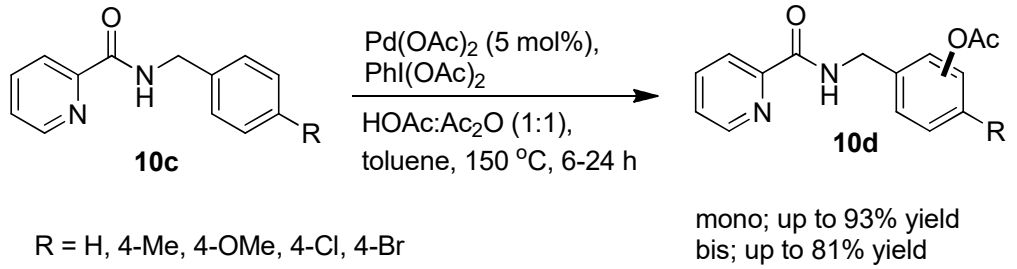
Similar to the concept pertaining to the bidentate ligand-aided transition metal catalyzed C-C bond construction, the directing group-assisted regioselective C-H oxidation or acetoxylation of the sp^2*ortho* C-H bonds of aromatic compounds found to be an efficient approach for functionalizing the aromatic carboxamides and the construction of C-O bonds. [4e-p,5,16,17e-i]

In particular, the directing-group-aided, transition-metal-catalyzed C-H oxidation of the C(sp^2)-H bonds of arenes involving the C-O bond forming reactions is a straightforward approach for the synthesis of phenol derivatives. Sanford's group[25a] first reported the Pd-catalyzed pyridine-directed acetoxylation of the sp^2 C–H bond (Scheme 11). Subsequently, Yu *et al.*, Chen *et al.* and Sahoo *et al.* and other research groups reported the directing group-aided acetoxylation of C–H bond bonds of organic molecules.[4e-p,5,16,17e-h] The regioselective C-H oxidation or acetoxylation of the sp^2*ortho* C-H bonds of aromatic compounds were accomplished with the help of bidentate directing groups such as 8-aminoquinoline and picolinamide. Liang *et al.*[25b] first reported the Pd-catalyzed bidentate ligand picolinamide-directed acetoxylation of the compound **10c** prepared

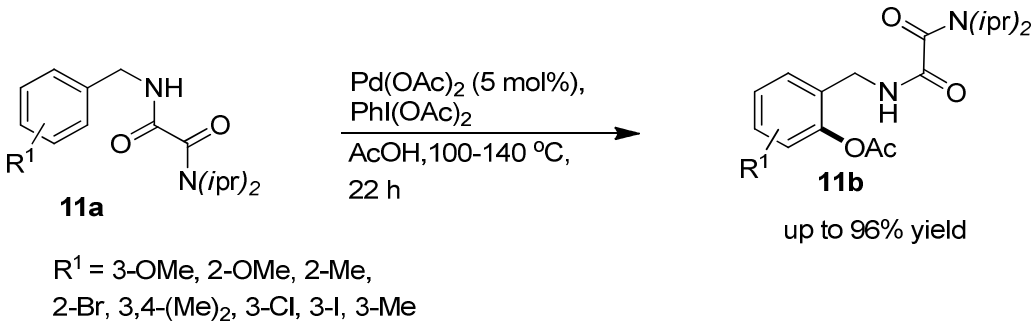
from picolinic acid and benzylamine (Scheme 12). Recently, Zhao *et al.*[25c] reported the Pd-catalyzed bidentate ligand oxalylamide-directed acetoxylation of the compound **11a** prepared from oxalyl chloride and benzylamine (Scheme 13).



Scheme 11. Pyridine-directed direct C-H acetoxylation of the sp^2 C-H bond.



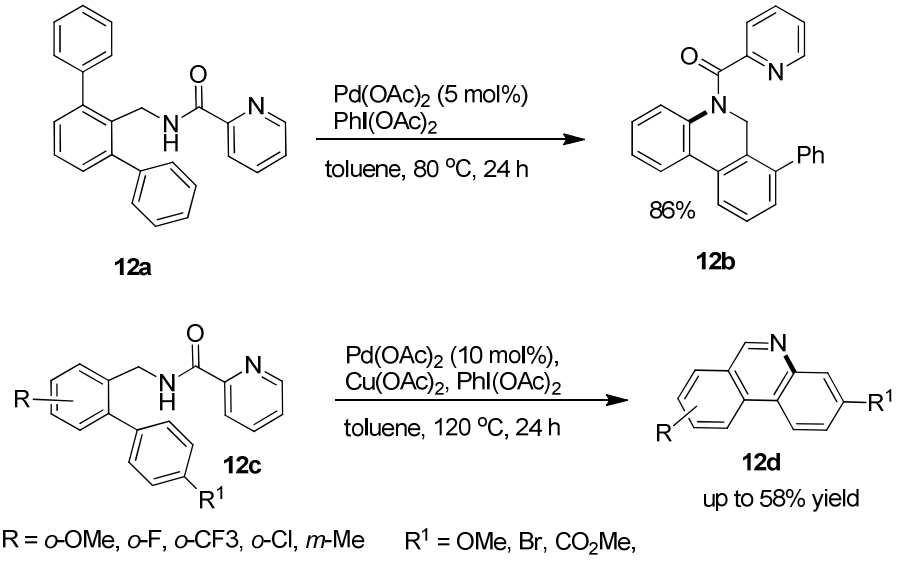
Scheme 12. Bidentate ligand picolinamide-directed C-H acetoxylation of the sp^2 C-H bond at γ position.



Scheme 13. Bidentate ligand oxalylamide-assisted C-H acetoxylation of the sp^2 C-H bond.

Representative papers dealing on the transition metal-catalyzed, directing group picolinamide-aided, intramolecular C-N formation and synthesis of heterocycles.

Alongside the directing group-assisted transition metal-catalyzed sp^2 C-H activation followed by C-C, C-N and C-O bonds, there have been efforts to assemble *N*-heterocycles *via* the directing group-assisted C-H activation followed by intramolecular C-N bond formation. Various groups revealed the synthesis of *N*-heterocycles, such as, phenanthridine and isoindoline/isoindolinone derivatives *via* the directing group-assisted C-H activation followed by intramolecular C-N bond formation.[4e-p,5,26] Representative papers dealing on the synthesis of *N*-heterocycles *via* the directing group-assisted C-H activation followed by intramolecular C-N bond formation are; (a) Daugulis *et al.*[26a] reported thepalladium-catalyzed C–H/N–H coupling and synthesis of six-membered heterocyclic compound, dihydrophenanthridine **12b** from the benzylamine system **12a** linked with the bidentate ligand picolinamide (Scheme 14), (b) Chen *et al.* [26b] achieved the synthesis of phenanthridine molecules **12d** involving $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$, $Cu(OAc)_2$ as oxidants (Scheme 14).



Scheme 14. Bidentate ligand -assisted C-H activation followed by intramolecular C-N bond formation and synthesis of phenanthridine derivatives **12b**, **12d**

Results and discussion.

Chapter 3a: Pd(II)-based bidentate directing group-aided regioselective C-H arylations of the C-3 position of 2- or 3-(aminoalkyl)-thiophene and furfurylamine derivatives.

Given that the thiophene and furan systems considered as a important class of heteroaromatic substrates and versatile building blocks in organic synthesis, materials- and medicinal chemistry, categorically, in the context of finding new lead bio-active thiophene- and furan-based carboxamides exhibiting promising biological activities and for finding potential drug candidates, there have been bestowed interests and continuous efforts for preparing new libraries of thiophene- and furan-based carboxamides (Figure 4).

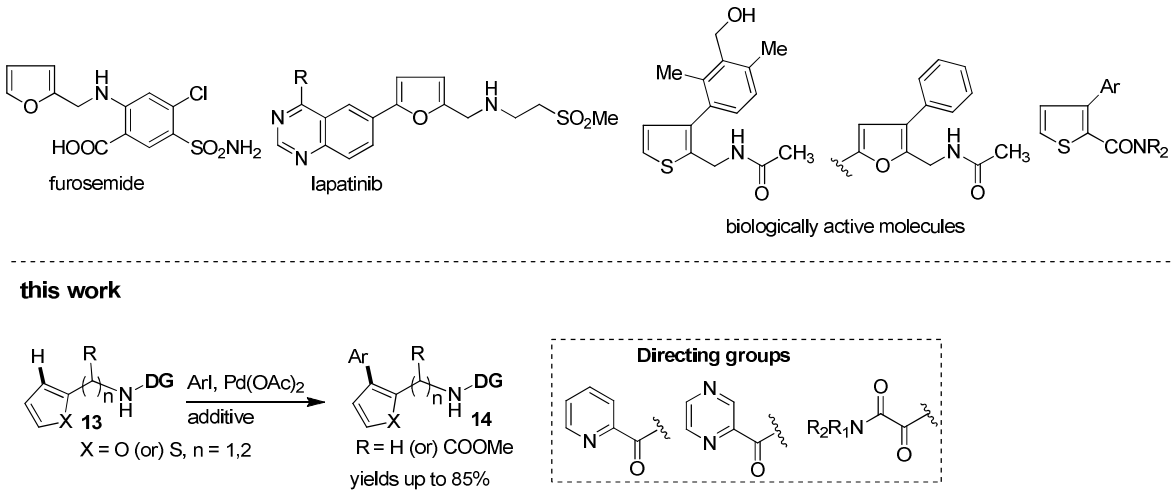


Figure 4. Bio-active thiophene- and furan-based carboxamides and topic of this work.

While the transition-metal catalyzed C-H arylations of various thiophene/furan substrates were investigated in the literature, especially a literature survey indicated that there exists no report dealing on the direct and regioselective C3 arylations of furfurylamine and 2- or 3-(aminoalkyl)-thiophene derivatives with aryl halides as the coupling partners (Figure 3). It is worth to mention here, in 2010 Doucet *et al.* investigated[27] the Pd-catalyzed arylation of the C-H bonds furfurylamine and 2-(aminomethyl)-thiophene derivatives. Understandably, the arylations

occurred only at the relatively more reactive C(2)-H and C(5)-H positions of furfurylamine and 2-(aminomethyl)-thiophene derivatives (Figure 3).

Given the importance of C3 or C5-arylated 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives as promising biologically active compounds (e.g., furosemide and lapatinib, Figure 4)and versatile synthetic intermediates, devising a C-H functionalization method for assembling of C3 arylated 2-/3-(aminoalkyl)-thiophene and furfurylamine scaffolds will be very useful. A literature survey indicated that the regioselective C3 arylations of 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives were not explored *via* the C-H bond activation route. Thus, a part of the thesis work envisioned to apply the bidentate ligand directed, Pd-catalyzed, regioselective *ortho* C-H functionalization strategy for assembling C3 arylated furfurylamine and 2- or 3-(aminoalkyl)-thiophene scaffolds with regiocontrol. Accordingly, a part of this thesis work report the $Pd(OAc)_2$/AgOAc catalytic system-based, bidentate ligand-directed, highly regioselective mono C-H arylation of the C3-position of the 2-/3-(aminoalkyl)-thiophene and furfurylamine derived amides (Figure 4).

At the outset, for investigating regioselective C3 arylations of 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives *via* the C-H activation route, at first, the required 2-/3-(aminoalkyl)-thiophene and furfurylamine derived amides **15a-h**, **16a-c**, **17** and **18** (Figure 5)were assembledby linking 2-3-(aminoalkyl)-thiophene and furfurylamine with the corresponding acid chlorides. Similarly, the 2-(aminomethyl)-thiophene substrates **15a,d,e** and **15f-h** were prepared from the corresponding bidentate ligand units, such as, picolinamide, quinoline-2-carboxamide, pyrazine-2-carboxamide and oxalylamide. Then, the 2-(aminomethyl)-thiophene substrates **15b,c** were prepared from benzoyl chloride and butanoyl chloride, respectively. Next, the 2- or 3-(aminoalkyl)-thiophene derivatives **16a-c** containing picolinamide and oxalylamide directing groups were prepared from the corresponding starting materials, such as, DL-α-amino-2-thiopheneacetic acid methyl ester hydrochloride and 3-(aminoethyl)thiophene. To further elaborate the substrate scope, the furfurylamine substrates **17** and **18** possessing the picolinamide directing group were also synthesized (Figure 5).

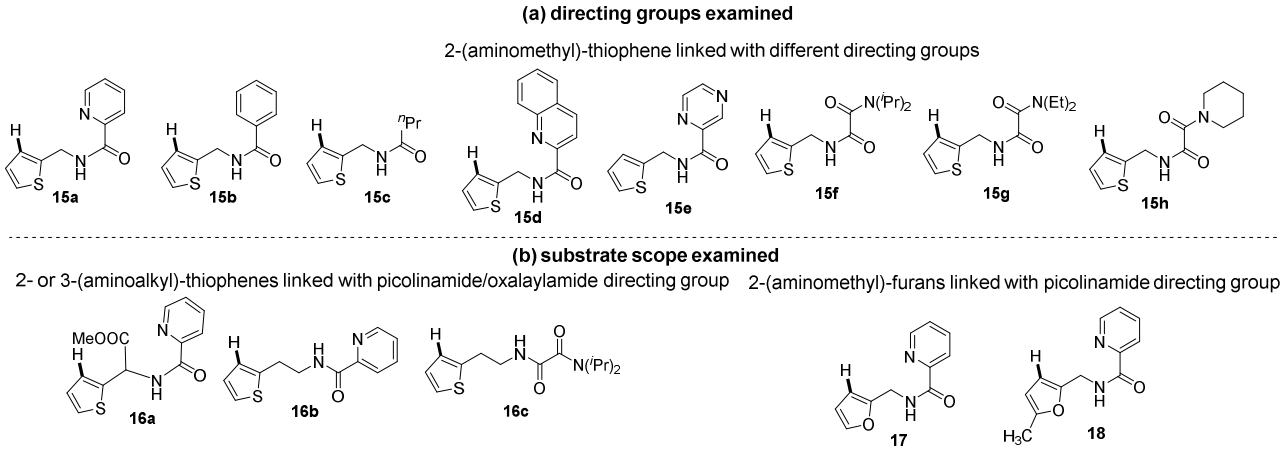
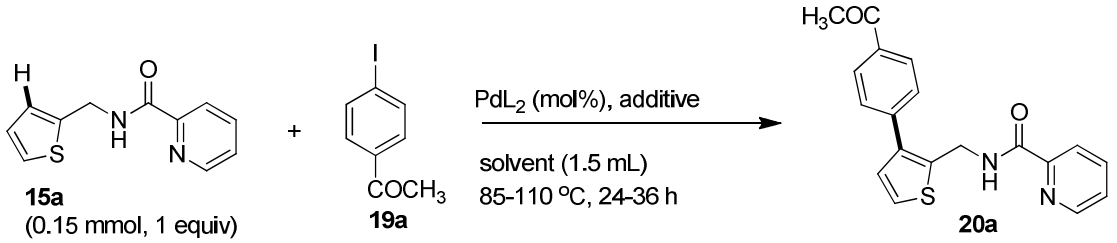


Figure 5. Substrates and directing groups employed in this work.

To start the investigation for achieving the direct arylation at C3-position of 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives; initially, various optimization reactions were carried out to find the suitable reaction conditions obtaining C(3)-H arylated2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives. Table 1 comprised of the bidentate ligand-assisted Pd(II)-catalyzed C-H arylation reaction of 2-(aminomethyl)-thiophene derivative **15a** containing the picolinamide as the directing group[28] with an aryl iodide **19a** (1-(4-iodophenyl)ethan-1-one). The reaction of a mixture of 2-(aminomethyl)-thiophene derivative **15a** (1 equiv), 1-(4-iodophenyl)ethan-1-one **19a** (4 equiv) and AgOAc additive (2.2 equiv) in the absence of any palladium catalyst in toluene at 110 ^{o}C for 24 h did not give any C-H arylated thiophene derivatives (entry 1, Table 1). Then, under the similar reaction conditions, the C-H arylation reaction of the 2-(aminomethyl)-thiophene derivative **15a** with **19a** (1-(4-iodophenyl)ethan-1-one) in the presence of 10 mol% of the $Pd(OAc)_2$ catalyst without any additives, furnished the C(3)-H arylated thiophene derivative **20a** in 11% yield (entry 2, Table 1). Next, the C-H arylation reaction of the 2-(aminomethyl)-thiophene derivative **15a** with **19a** (1-(4-iodophenyl)ethan-1-one) in the presence of 5 mol% of the $Pd(OAc)_2$ catalyst and 2.2 equiv of AgOAc additive in toluene at 110 ^{o}C for 36 h was performed. This reaction gave the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in 78% yield with an excellent regioselectivity (entry 3, Table 1). Then, the C-H arylation of thiophene system **15a** with **19a** in the presence of 10 mol% of the $Pd(OAc)_2$ catalyst and only one equiv of AgOAc additive gave the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in 74% yield (entry 4, Table 1). Then, it was envisioned to vary the equivalents of **19a** for obtaining **20a** with an improved yield.

Thus, the C(3)-H arylation of **15a** was carried out by using different equivalents of **19a** (1-4 equiv) in the presence of $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc (2.2 equiv) in toluene for 24 h or 36 h (entries 5-9, Table 1).

Table 1. Optimization reactions: Bidentate ligand picolinamide-directed C(3)-H arylation of 2-(aminomethyl)-thiophene **15a**.



entry	PdL_2 (mol %)	additive (equiv)	**19a** (equiv)	solvent	t (°C)	time (h)	**20a**: yield (%)
1	nil	AgOAc (2.2)	4	toluene	110	24	0
2	$Pd(OAc)_2$ (10)	nil	4	toluene	110	36	11
3	$Pd(OAc)_2$ (5)	AgOAc (2.2)	4	toluene	110	36	78
4	$Pd(OAc)_2$ (10)	AgOAc (1)	4	toluene	110	36	74
5	$Pd(OAc)_2$ (10)	AgOAc (2.2)	1	toluene	110	36	34
6	$Pd(OAc)_2$ (10)	AgOAc (2.2)	2	toluene	110	36	50
7	$Pd(OAc)_2$ (10)	AgOAc (2.2)	3	toluene	110	36	74
8	$Pd(OAc)_2$ (10)	AgOAc(2.2)	4	toluene	110	24	65
9	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	toluene	110	36	85
10	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	1,2-DCE	85	36	7
11	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	1,4-dioxane	100	36	59
12	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	*t*-amylOH	100	36	77
13	$Pd(OAc)_2$ (10)	KOAc (2.2)	4	toluene	110	36	25
14	$Pd(OAc)_2$ (10)	K_2CO_3 (2.2)	4	toluene	110	36	33
15	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.2)	4	toluene	110	36	70
16	$PdCl_2$ (10)	AgOAc (2.2)	4	toluene	110	36	79
17	$Pd(TFA)_2$ (10)	AgOAc (2.2)	4	toluene	110	36	22

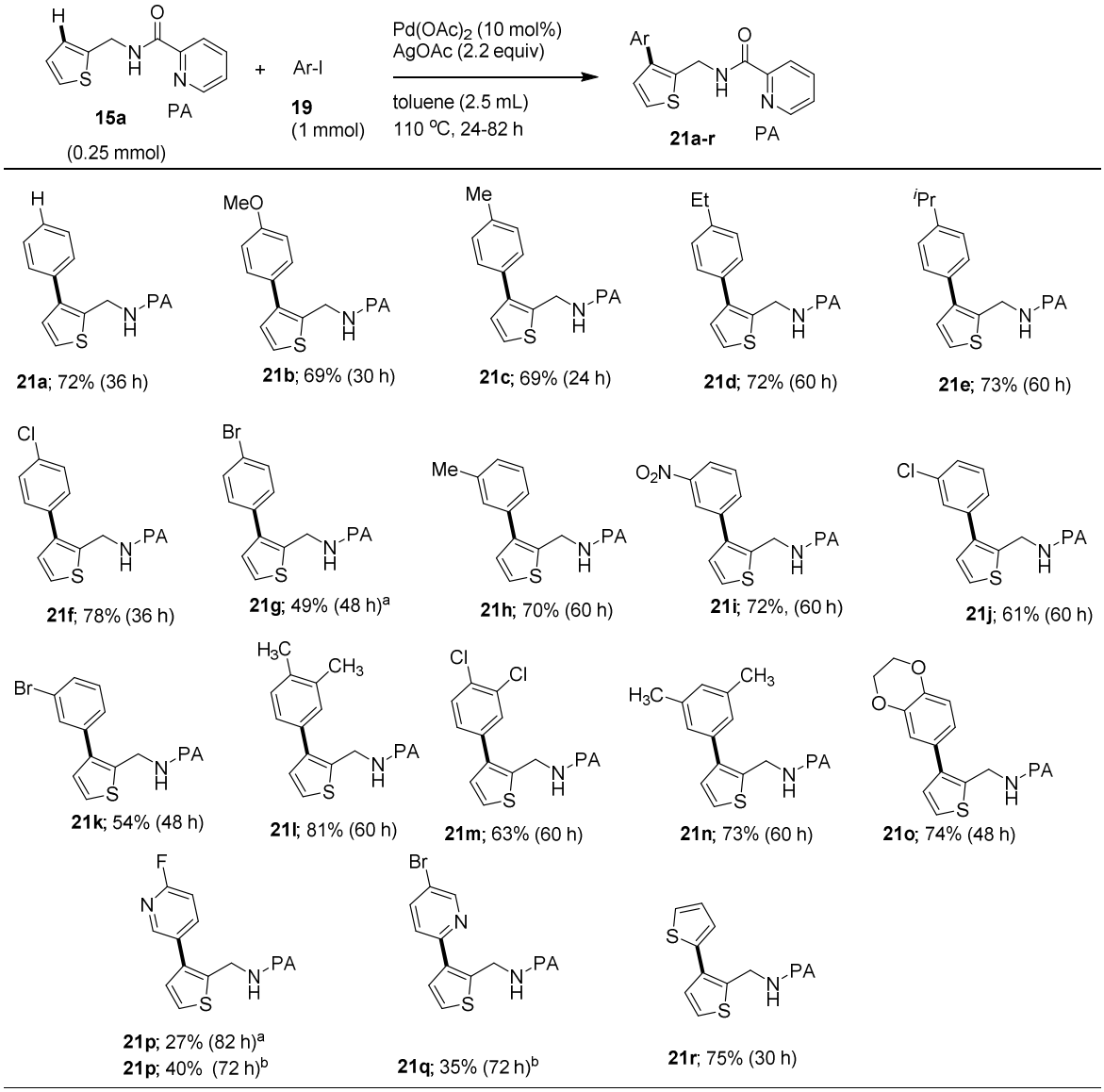
Further optimization reactions were also carried out for obtaining **20a** with an improved yield. The C(3)-H arylation of **15a** with **19a** (4 equiv) in the presence of 10 mol% of $Pd(OAc)_2$ catalyst and AgOAc additive (2.2 equiv) in toluene at 110 ^oC for 36 h found to afford the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in a maximum yield of 85% (entry 9, Table 1). Additionally, the C(3)-H arylation of **15a** with **19a** in other solvents, such as 1,2-DCE or 1,4-dioxane or *t*-amylOH afforded the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in 7-77% yields (entries 10-12, Table 1). The Pd(II)-catalyzed C(3)-H arylation reaction of **15a**

with **19a** in the presence other additives, such as, KOAc or K_2CO_3 or Ag_2CO_3 furnished the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in 25-70% yields (entries 13-15, Table 1). Finally, the C(3)-H arylation reaction of **15a** with **19a** in the presence of other Pd catalysts, such as, $PdCl_2$ or $Pd(TFA)_2$ gave the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in 79 and 22%, respectively (entries 16 and 17, Table 1).

Having found the optimized reaction condition which gave the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **20a** in high yield (entry 9, Table 1); next, it was envisaged to investigate the generality and scope of this protocol encompassing the bidentate ligand, picolinamide directed Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15a**. Thus, the bidentate ligand, picolinamide directed Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15a**with different *para*-substituted aryl iodides having electron-donating/withdrawing substituents furnished several C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **21a-g** in 49-78% yields, respectively (Scheme 15).

Similarly, the bidentate ligand, picolinamide directed Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15a**with *meta*-substituted aryl iodides having electron-donating/withdrawing substituents also furnished the respective C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **21h-k** in 54-72% yields (Scheme 15). Additionally, the bidentate ligand, picolinamide directed Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15a** with the corresponding di-substituted aryl iodides afforded the C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **21l-o** in 63-81% yields (Scheme 15). Furthermore, the bidentate ligand, picolinamide directed Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15a** with heteroaryl iodides successfully afforded the C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **21p-r** in 27-75% yields (Scheme 15). It is worth to mention that all the reactions of Scheme 15 comprising the Pd-catalyzed C-H arylation of **15a** were regioselective and gave the corresponding biaryl derivatives **21a-r** with an excellent regioselectivity. The Pd(II)-catalyzed C-H arylation reactions involving iodopyridines afforded the corresponding products **21p** and **21q** in poor yields when compared to the Pd(II)-catalyzed C-H arylation reactions involving iodobenzenes. Notably, our group previously reported a

similar trend in the Pd(II)-catalyzed C(3)-H arylation reactions involving furan- and thiophene-2-carboxamides.[23d]

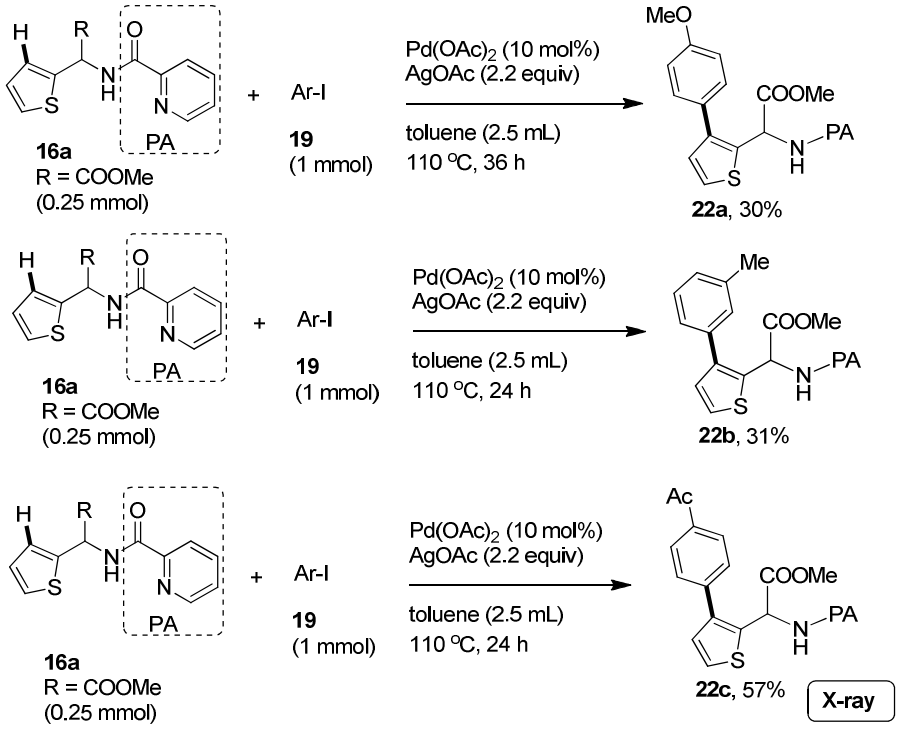


[a] 20 mol% of $Pd(OAc)_2$ was used. [b] 30 mol% of $Pd(OAc)_2$ was used.

Scheme 15. Scope and generality. Bidentate ligand picolinamide-directed C(3)-H arylation of 2-(aminomethyl)-thiophene **15a**.

Successively, to increase the substrate scope and generality, it was envisaged to use the substrate thiophene derivative **16a** containing picolinamide directing group (which was obtained from DL-α-amino-2-thiopheneacetic acid methyl ester hydrochloride, Scheme 16). Thus, the direct C(3)-H

arylation of thiophene derivative **16a**with different aryl iodides in the presence of $Pd(OAc)_2$ catalyst and AgOAc additive gave the corresponding C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **22a-c** in 30-57% yields (Scheme 16). Notably, the Pd(II)-catalyzed direct C(3)-H arylation of thiophene derivative **16a**with different aryl iodides were regioselective and the observed regioselectivity for products **22a-c** was confirmed on the basis of the X-ray structure of a representative C(3)-H arylated 2-(aminomethyl)-thiophene derivative **22c** (Figure 6).

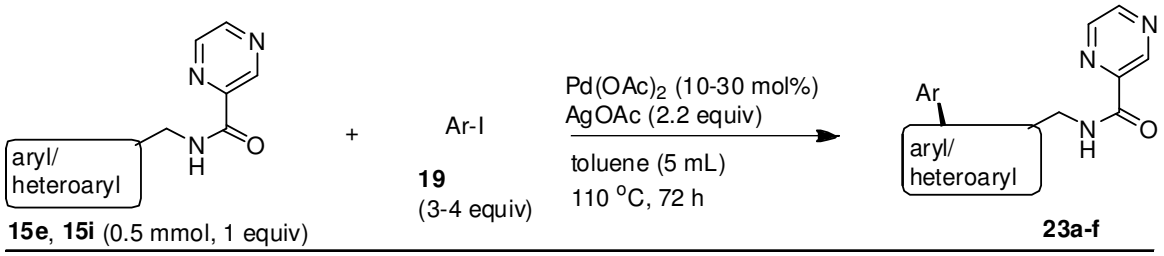


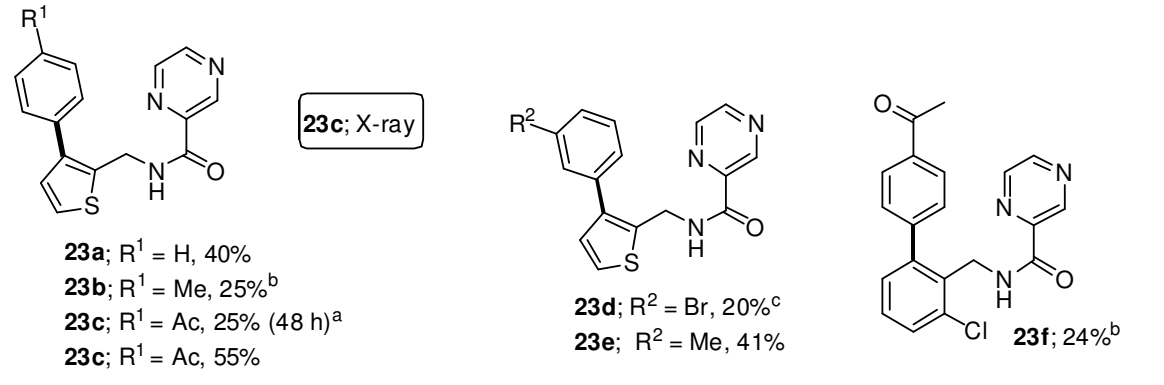
Scheme 16. Scope and generality: Bidentate ligand picolinamide-directed C(3)-H arylation of 2-(aminomethyl)-thiophene **16a**.

After examining the bidentate ligand picolinamide-directed Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivatives **15a** and **16a**, it was envisaged to examine the scope of the Pd(II)-catalyzed C-H arylation of 2-(aminomethyl)-thiophene derivative **15e** which contains the pyrazine-2-carboxamide unit as the directing group (Scheme 17). Notably, the 2-(aminomethyl)-thiophene derivative **15e** which contains the pyrazine-2-carboxamide as the directing group, which is structurally similar to picolinamide ligand (substrates **15a** and **16a**). Thus, it was envisaged that the C(3)-H arylation of the 2-(aminomethyl)-thiophene derivative **15e** will also be efficient. Accordingly, the direct C(3)-H arylation of the 2-(aminomethyl)-

thiophene **15e** was carried out with different aryl iodides containing electron-donating/withdrawing substituents in the presence of $Pd(OAc)_2$ catalyst and AgOAc additive, which gave the corresponding C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **23a-e** in low to moderate yields (20-55%) with high regioselectivity (Scheme 17).

When compared to the yields obtained in C(3)-H arylation reactions of **15a**, the C(3)-H arylation of **15e**gave the corresponding C(3)-H arylated 2-(aminomethyl)-thiophene derivatives **23a-e** in relatively lower yields. It was envisaged to check the efficiency of pyrazine-2-carboxamide by using a benzene derivative **15i,** which contains the pyrazine-2-carboxamide ligand. Accordingly, the Pd(II)-catalyzed C-H arylation of **15i** also gave product **23f** in low yield (24%). The low yield obtained in the arylation reaction of **15i** containing pyrazine-2-carboxamide ligand was comparable with the yield obtained in the arylation of thiophene system **15e** containing same pyrazine-2-carboxamide ligand. Notably, the Pd(II)-catalyzed direct C(3)-H arylation of 2-(aminomethyl)-thiophene **15e** was regioselective and the observed regioselectivity was confirmed based on the X-ray structure of a representative C(3)-H arylated 2-(aminomethyl)-thiophene derivative **23c** (Figure 6).

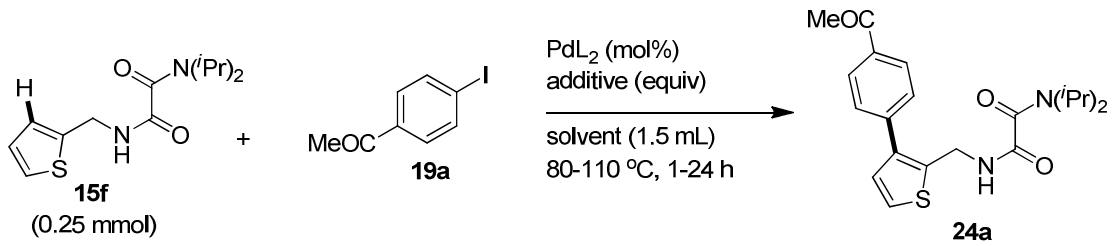




[a] 10 Mol% of $Pd(OAc)_2$ was used. [b] 20 Mol% of $Pd(OAc)_2$ was used. [c] 3 Equiv of ArI was used.

Scheme 17. 2-Pyrazine carboxamide-directed C(3)-H arylation of 2-thiomethylamine **15e** and **15i**.

Table 2. Optimization reactions. Oxalylamide-directed, C(3)-H arylation of the 2-(aminomethyl)-thiophene derivative **15f**.

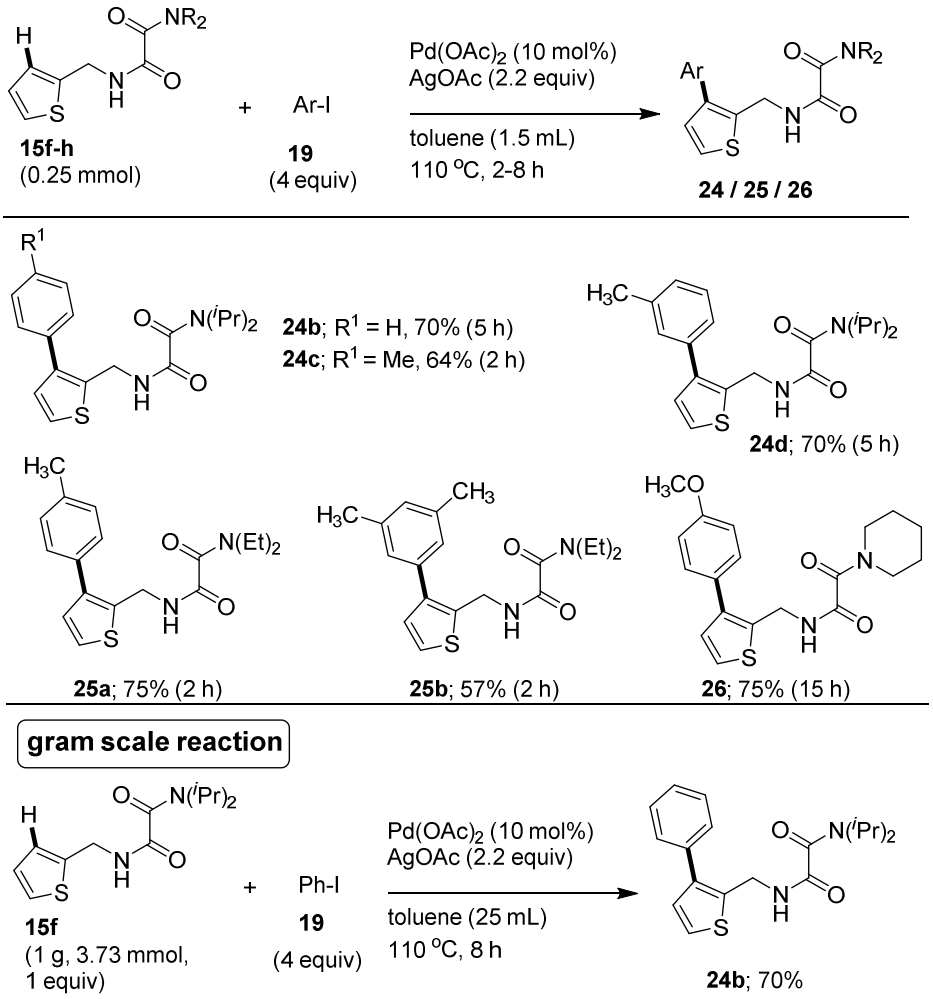


entry	PdL_2 (mol%)	additive (equiv)	**19a** (equiv)	solvent	t (°C)	time (h)	**24a**; yield (%)
1	$Pd(OAc)_2$ (5)	AgOAc (1.2)	2	toluene	110	2	47
2	$Pd(OAc)_2$ (10)	AgOAc (1.2)	2	toluene	110	2	60
3	$Pd(OAc)_2$ (10)	AgOAc (1.2)	4	toluene	110	1	59
4	$Pd(OAc)_2$ (10)	AgOAc (2.2)	2	toluene	110	2	55
5	$Pd(OAc)_2$ (10)	AgOAc (2.2)	3	toluene	110	2	59
6	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	toluene	80	3	29
7	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	toluene	110	2	69
8	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	toluene	110	5	54
9	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	toluene	110	10	50
10	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.2)	4	toluene	110	2	53
11	$Pd(OAc)_2$ (2.5)	K_2CO_3 (2.0)	1.5	DCE	80	24	15[a]
12	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	*t*-amylOH	110	2	18
13	$Pd(OAc)_2$ (10)	AgOAc (2.2)	4	toluene	110	2	46[b]

[a] The reaction was carried out in presence of 0.3 equiv of pivalic acid. [b] This reaction was performed under open atm.

Furthermore, along the line of inspection of the ligand scope (Schemes 16 and 17) and to improve the efficiency of the Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivatives, it was envisagedto investigate the Pd(II)-catalyzed regisoselective C(3)-H arylation of 2-(aminomethyl)-thiophene derivatives **15f-h,** which are possessing oxalylamide unit as a directing group[29] (Table 2, Scheme 18). To begin with, various optimization reactions were carried out to find the suitable reaction conditions as shown in Table 2. Table 2 comprises of the Pd(II)-catalyzed regioselective C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15f**containing oxalylamide unit as the directing groupwith an aryl iodide **19a** (1-(4-iodophenyl)ethan-1-one). The C-H arylation reaction of 2-(aminomethyl)-thiophene derivative **15f** with **19a** (1-(4-iodophenyl)ethan-1-one), 4 equiv) in the presence of $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive (2.2 equiv) in toluene at 110 °C for 2 h gave the C(3)-H arylated 2-

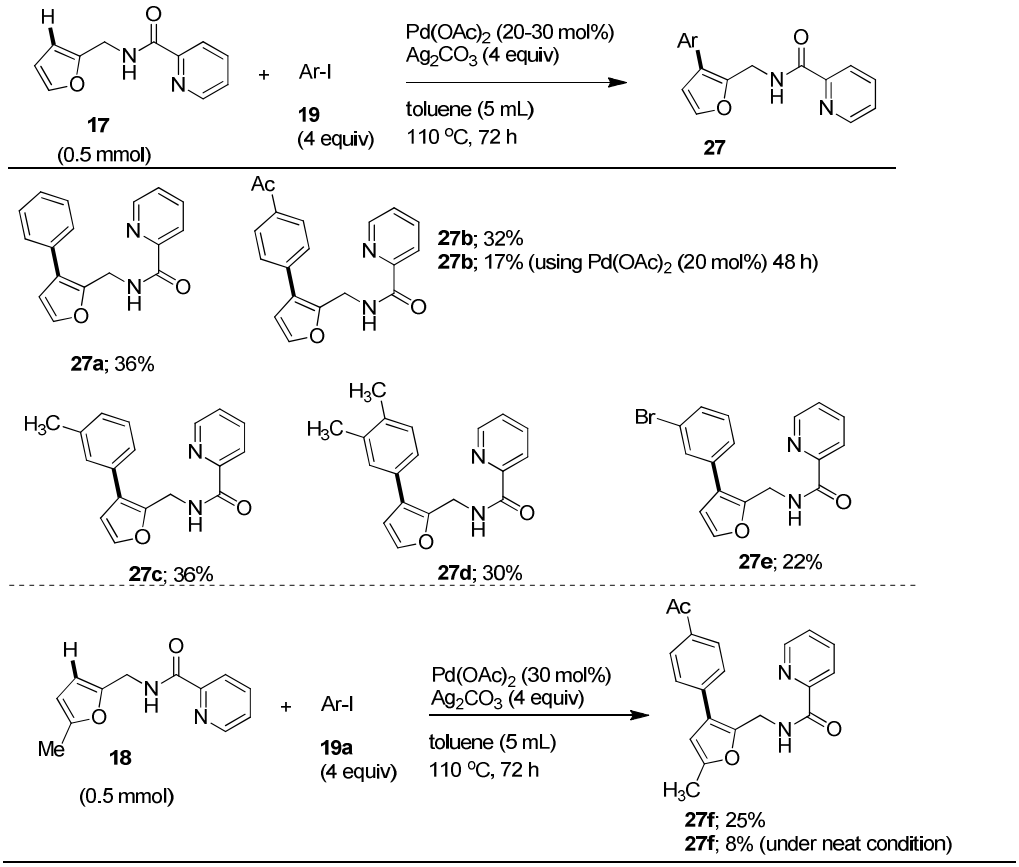
(aminomethyl)-thiophene derivative **24a** in a maximum yield of 69% with an excellent regioselectivity (entry 7, Table 2). Various other optimization reactions were carried out to improve the yield of the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **24a** by varying the amounts of $Pd(OAc)_2$ catalyst or equivalents of **19a** (1-(4-iodophenyl)ethan-1-one) or reaction temperature/time. Nevertheless, there was no further significant improvement in the yield of the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **24a** (entries 1-6, 8 and 9, Table 2). In the reaction involving the Pd(II)-catalyzed C(3)-H arylation of **15f** with **19a**;(a) the use of additives, such as, Ag_2CO_3 or K_2CO_3 instead of AgOAc, (b) the reaction in other solvents, such as, 1,2-DCE or *t*-amylOH instead of toluene, and (c) under open atm, did not help to improve the yield of the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **24a** (entries 10-13, Table 2).



Scheme 18. Oxalylamide-assisted, C(3)-H arylation of 2-(aminomethyl)-thiophene derivatives**15f-h**.

Afterwards, having the optimized reaction condition in hand (entry 7, Table 2), it was envisaged to explore the generality of the Pd(II)-catalyzed regioselective C(3)-H arylation of **15f** by using different aryl iodides. Accordingly, the Pd(II)-catalyzed regioselective C(3)-H arylation of **15f** with various aryl iodides successfully afforded the C(3)-H arylated 2-(aminomethyl)-thiophene derivatives**24b-d** in 64-70% yields, respectively (Scheme 18). Then, a gram scale reaction involving the Pd(II)-catalyzed direct C-H arylation of **15f** with iodobenzenealso was performed to afford the C(3)-H arylated 2-(aminomethyl)-thiophene derivative **24b** in 70% yield (Scheme 18). Furthermore, in analogy to the 2-(aminomethyl)-thiophene derivative **15f**, the Pd(II)-catalyzed direct C(3)-H arylation of other 2-(aminomethyl)-thiophene derivatives **15g** and **15h** containing the oxalylamide unit as the directing group, successfully furnished the corresponding products **25a,b** and **26** in 57-75% yields, respectively, with an excellent regioselectivity (Scheme 18).

Consecutively, it was envisaged to extend the substrate scope and to study the regioselective direct C(3)-H arylation furfurylamine system. Accordingly, Scheme 19 shows the investigations on the Pd(II)-based C(3)-H arylation of furfurylamine derivatives **17** and **18** containing the picolinamide unit as a directing group. The C(3)-H arylation reaction of furfurylamine derivative **17** with PhI (4 equiv) in the presence of the $Pd(OAc)_2$ (30 mol%) and Ag_2CO_3 additive (4 equiv) in toluene at 110 ^oC for 72 h gave the C(3)-H arylated furfurylamine system **27a** in a maximum yield of 36% with an excellent regioselectivity (Scheme 19). Similarly, the Pd(II)-promoted C(3)-H arylation of furfurylamine system **17**with various aryl iodides finished the corresponding C(3)-H arylated furfurylamine systems **27b-e** in 22-36% yields (Scheme 19). The usage of lesser amounts of Pd catalyst furnished the C(3)-arylated product in low yields. For example, the C(3)-H arylation reaction of furfurylamine system **17** in the presence of $Pd(OAc)_2$ (20 mol%) gave the C(3)-H arylated furfurylamine system **27b** only in 17% yield. In analogy to furfurylamine system **17** the Pd(II)-based regioselective direct C-H arylation of furfurylamine system **18** furnished the C(3)-H arylated furfurylamine system **27f** in 25% yield with high regioselectivity (Scheme 19). In fact, the C(3)-H arylation of furfurylamine system **17** was carried out under variousreactions conditions; however, our efforts to improve the yield of C(3)-H arylation of furfurylamine derivative **17** were not productive. Further, our trials to use lesser amounts of the Pd catalyst loadings were also not fruitful.



Scheme 19. Pd(II)-based picolinamide-assisted C(3)-H arylation of furfurylamine derivatives **17** and **18**.

Having investigated the Pd(II)-catalyzed C(3)-H arylation of 2-(aminomethyl)-thiophene derivatives **15a**, **15e-h** and **16a** containing the respective bidentate ligands; then, it was envisaged to further extend the importance and substrate scope this method. Consequently, the 3-(aminoethyl)-thiophene systems **16b** and **16c** were assembled and subjected to the Pd(II)-catalyzed C(3)-H arylation reaction conditions. It is to be noted that the C(3)-H bond that is arylated in 2-(aminomethyl)-thiophene derivatives **15a**, **15e-h** and **16a**, is located at the γ position with respect to the amide nitrogen.

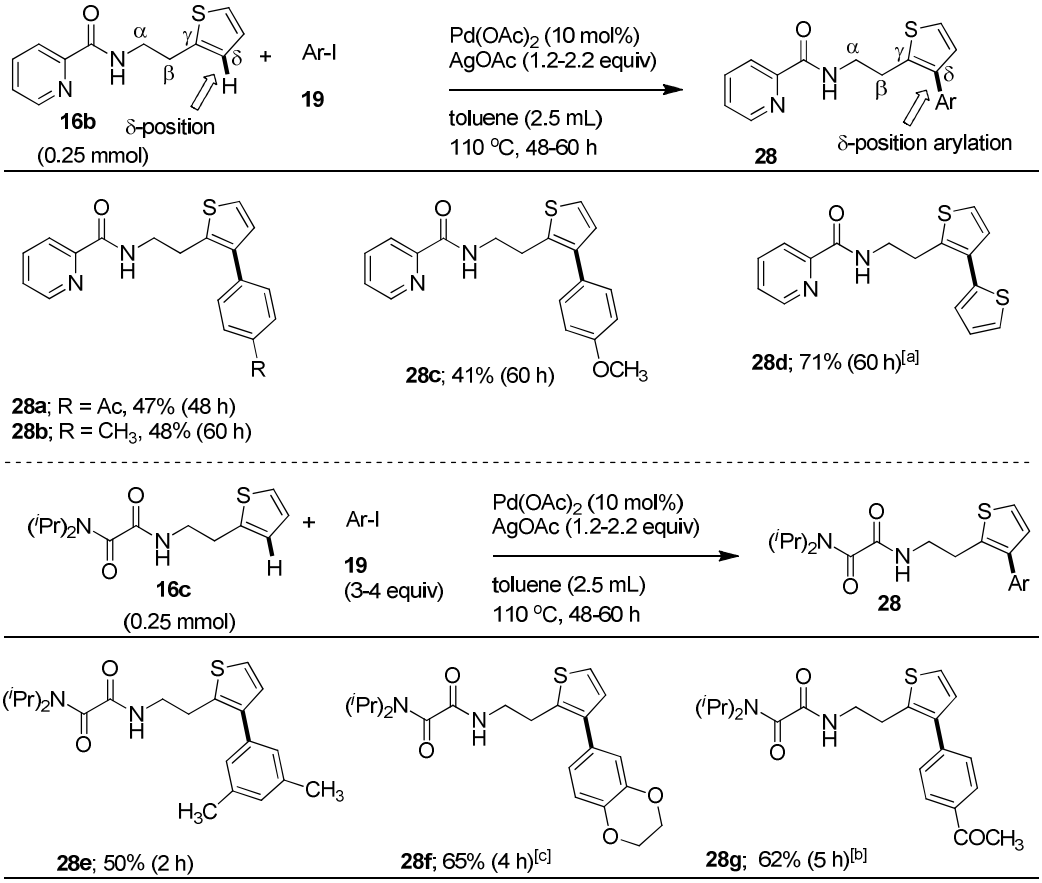
In general, the sp^2 C-H arylations of the γ-C-H bond located at γ position with respect to the amide nitrogen or *ortho* C-H bond of amides (benzylamine systems) prepared from bidentate ligands and benzylamines have been well explored.[4e-p,5,23-29] On the other hand, the sp^2 C-H

arylation of thje remote δ C-H bond located at the δ position with respect to the amide nitrogen or *ortho* C-H bond of amides prepared from the bidentate ligands and alkyl amines, e.g., β-arylethylamine have not been explored well.

Thus, it is to be noted that in 3-(aminoethyl)-thiophene derivatives **16b** and **16c**, which arecontaining picolinamide and oxalylamide as a directing groups,the C(3)-H bond that is to be arylated is located at δ the position with respect to the amide nitrogen.Scheme 20 shows the studies carried out on the Pd(II)-catalyzed C(3)-H arylation of 3-(aminoethyl)-thiophene systems **16b** and **16c** containing picolinamide and oxalylamide directing groups, respectively. The C(3)-H arylation reaction of 3-(aminoethyl)-thiophene derivative **16b** with an aryl iodide **19a** (1-(4-iodophenyl)ethan-1-one) in the presence of $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive in toluene at 110 ^oC for 48 h furnished the C(3)-H arylated 3-(aminoethyl)-thiophene derivative **28a** in 47% yield with an excellent regioselectivity (Scheme 20). Similarly, the C(3)-H arylation reaction of 3-(aminoethyl)-thiophene derivative **16b** with different aryl iodides gave the C3-arylated 3-(aminoethyl)-thiophene derivatives **28b-d** in 41-71% yields, respectively (Scheme 20). In analogy to 3-(aminoethyl)-thiophene derivative **16b**, the Pd(II)-catalyzed C-H arylations of 2-(aminomethyl)-thiophene derivative **16c** having the oxalylamide as a directing group with various aryl iodides successfully furnished the corresponding C(3)-H arylated 3-(aminoethyl)-thiophene derivatives **28e-g** in 50-62% yields with high regioselectivity (Scheme 20).

Discussion with regard to the role and efficiency of bidentate ligands and the substrate scope/reactivity. Having described the Pd(II)-based C(3)-H arylation of 2-(aminomethyl)-thiophene derivatives **15a/15e-h/16a-c** and furfurylamine derivatives **17/18** possessing the respective bidentate directing groups, it was envisaged to substantiate the role of bidentate ligand for the Pd(II)-catalyzed regioselective C(3)-H arylation of the substrates **15a**, **15e-h**, **16a-c**, **17** and **18**. Thus, the thiophene derivative **15b** having the benzoyl group was assembled. Then, the C-H arylation reaction of **15b** with an aryl iodide (4 equiv) was carried out in the presence of $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive (2.2 equiv) in toluene at 110 ^oC for 24 h. This reaction gave mixture of compounds without any selectivity and the column chromatographic purification of the crude reaction mixture was unsuccessful and the expected product **29a** was not obtained (Scheme 21). Next, the C-H arylation of thiophene system **15c** with **19a** (4 equiv)

was performed in the presence of $Pd(OAc)_2$ catalyst (10 mol%) and AgOAc additive (2.2 equiv) in toluene at 110 ^oC for 36 h. This reaction also gave a mixture compounds which was purified to furnish the di-arylated product **29b** in low yield 22% along with some inseparable complex mixture of compounds (Scheme 21). These reactions revealed that the bidentate ligands are essential for achieving the C-H arylation of C(3)-H bond of thiophene derivatives **15a**, **15e-h**,and **16a-c** as well as furfurylamine derivatives **17** and **18** with an excellent regioselectivity (Tables 1,2 and Schemes 15-20).

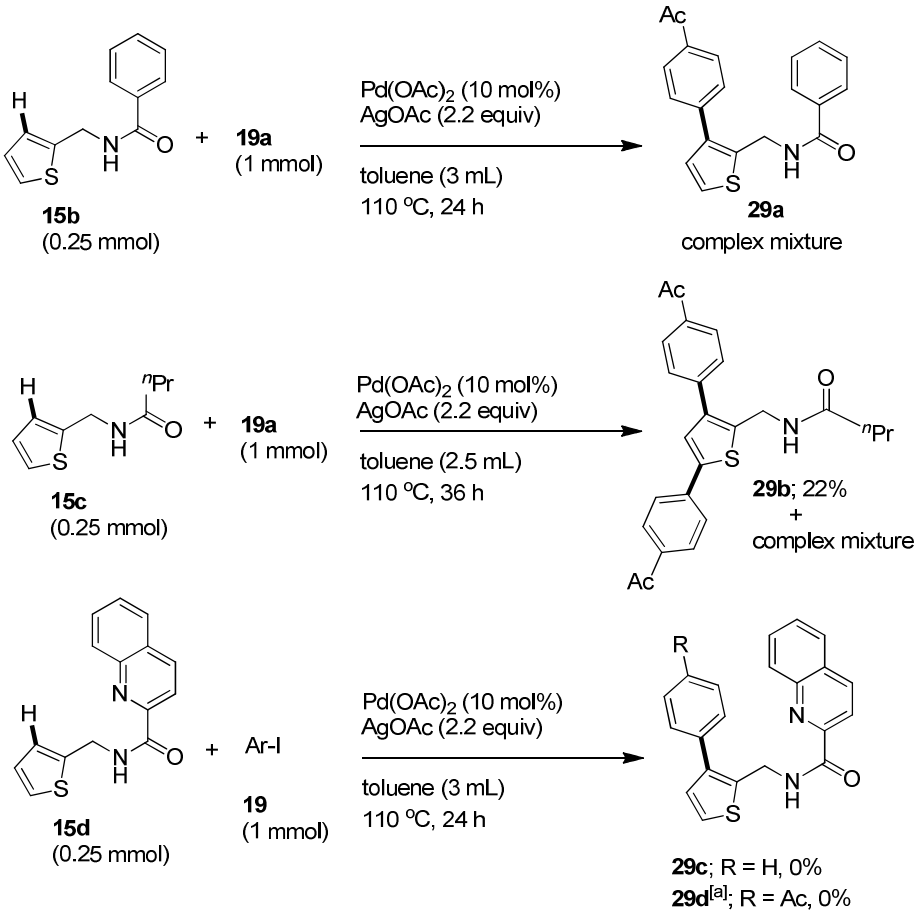


[a] 2.2 Equiv of Ag_2CO_3 was used. [b] 1.2 Equiv of AgOAc was used. [c] 3 Equiv of aryl iodide was used.

Scheme 20. Pd(II)-based picolinamide/oxalylamide-directed C(3)-H arylation 3-(aminoethyl)-thiophenes **16b**,**c**.

The investigation to find out the efficiency of bidentate ligands in the Pd-based C(3)-H arylations of thiophene/furan derivatives **15a**, **15e-h**, **16a-c**, **17** and **18** containing the respective bidentate

ligands, revealed that picolinamide was the better bidentate directing group. Correspondingly, the picolinamide-aided C(3)-H arylation afforded the C-H arylated product **20a** in a maximum yield of 85%. On other hand, the efficiency of oxalylamide ligand was comparable with picolinamide ligand. The oxalylamide-aided C(3)-H arylation gave the products **25a** or **26** in a maximum yield of 75%. The efficiency of pyrazine-2-carboxamide ligand found to be moderate and pyrazine-2-carboxamide-aided C(3)-H arylation afforded the product **23c** in a maximum yield of 55%. It is to be noted a literature survey revealed that generally, the bidentate ligand, picolinamide has been well exploited to accomplish the C-H functionalization of a variety of carboxamide derivatives.[4e-p,5,23-29]



[a] Ag_2CO_3 (2.2 equiv) was used instead of AgOAc.

Scheme 21. Role of directing groups in the Pd(II)-catalyzed direct arylations.

Though, the pyrazine-2-carboxamide ligand is structurally similar to picolinamide ligand,[28] the C-H functionalization reactions have not been studied by using bidentate ligand pyrazine-2-carboxamide. Further, it is to be noted that only recently, the bidentate ligand, oxalylamide was found to assist the C-H functionalization of carboxamide derivatives.[29] Additionally, the Pd-catalyzed C-H arylation of thiophene derivative **15d** containing quinoline-2-carboxamide as a directing group failed to furnish the corresponding C-H arylated products **29c** or **29d** (Scheme 21). Although, the compound **15d** contains bidentate ligand that is similar to the **15a**, at this stage, an exact reason for the failure of our trials to get the corresponding C-H arylated products **29c** or **29d** is not clear (Scheme 21). Apparently, in these cases, a rigid palladacycle TS might have not formed due to the steric hindrance provided by quinoline-2-carboxamide unit and this could be a plausible reason due to which the C-H arylated products **29c** or **29d** did not form.

With regard to thiophene/furan derivatives investigated in this work, though the bidentate directing group is same in furan/thiophene substrates **15a**, **17** and **18**, the reactivity of furfurylamine derivatives **17** and **18** was relatively lesser than 2-(aminomethyl)-thiophene derivative **15a**. For example, the Pd-catalyzed picolinamide-directed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15a** gave the C(3)-H arylated product **20a** in a maximum yield of 85%. Similarly, the oxalylamide-directed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15f** gave the C(3)-H arylated product **25a** in a maximum yield of 75% and the pyrazine-2-carboxamide ligand-directed C(3)-H arylation of 2-(aminomethyl)-thiophene derivative **15e** afforded the C(3)-H arylated compound **23c** in maximum of yield 55%. However the picolinamide-directed C-H arylation of furfurylamine derivative **17** furnished the C3-arylated products **27a/27c** in a maximum yield of only 36%. Notably, the remote C(δ)-H arylation of picolinamide/oxalylamide-based 3-(aminoethyl)-thiophene derivatives **16b** and **16c** having an increased alkyl chain length (when compared to **15a**) afforded the corresponding C(3)-H arylated3-(aminoethyl)-thiophene derivatives **28a-g** in moderate to good yields.

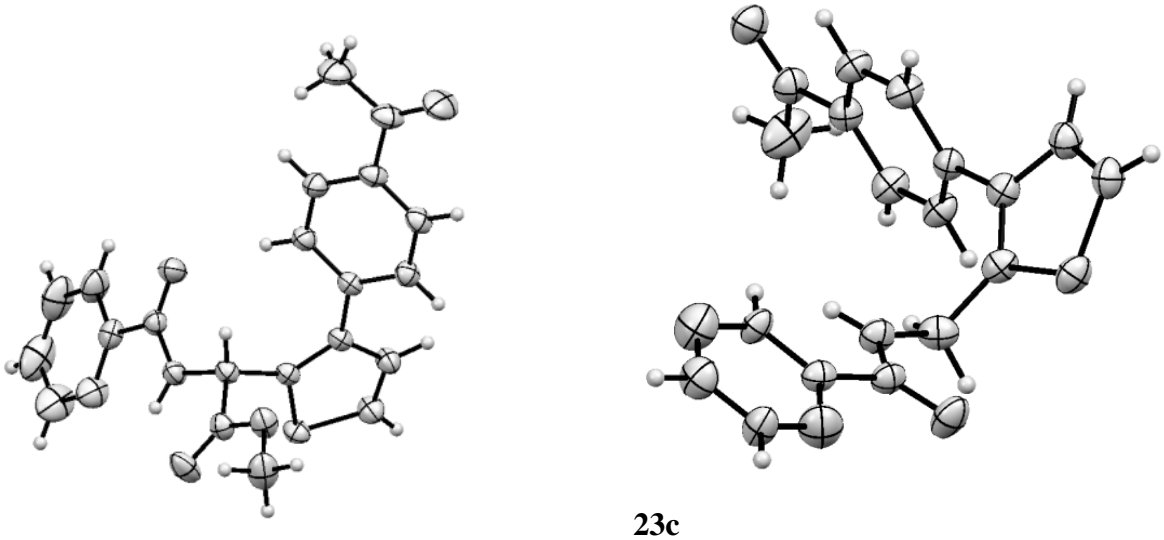
Furthermore, looking at the reactivity pattern of different aryl iodides (iodobenzenes) employed in this work, aryl iodides containing electron withdrawing- or donating groups gave the corresponding C(3)-H-arylated 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives in comparable yields (e.g., products **20a** and **21a-r**, Tables 1 and 2). However, when compared to

iodobenzenes, iodopyridines gave the corresponding products **21p** and **21q** in poor yields. The following assumption may be one of the possible reasons for the poor yields in products **21p** and **21q**. Apparently, the complete process comprising the C-H arylation of **15a** with iodopyridines includes a number of coordinating sites containing substrates that might be deterring the entire Pd(II)-based C-H arylation process. In this regard, Yu *et al.* stated[30] that in directing group-aided C-H activation reactions, strongly coordinating N / S/ P heteroatoms frequently outcompete the directing groups for catalyst binding, thus, preventing the main C-H activation process.

As described in the introduction part, there are only inadequate reports dealing on the arylations of C(3)-H and C(4)-H bonds of different kinds of thiophene and furan derivatives with aryl iodides as coupling partners involving exceptional reaction conditions. Prior to this work, in 2005 Doucet's group[27] reported that the Pd-catalyzed C-H arylation of furfurylamine and 2-(aminomethyl)-thiophene derivatives regioselectively occurred at the relatively more reactive C(5)-H bond. On the other hand, a part of this thesis work report the bidentate ligand-aided regioselective arylation at the C(3)-H bond of 2/3-(aminoalkyl)-thiophene and furfurylamine derivatives with various aryl-/heteroaryl iodides. In concurrence with the literature works,[4e-p,5,23-30] and the present investigation with regard to the C-H arylation of 2/3-(aminoalkyl)-thiophene and furfurylamine derivatives has revealed that the bidentate ligands are essential for achieving regioselective direct arylation at the C(3)-H bond of2/3-(aminoalkyl)-thiophene derivatives **15a**, **15e-h** and **16a-c** and furfurylamine systems **17** and **18** (Tables 1,2 and Schemes 15-20).

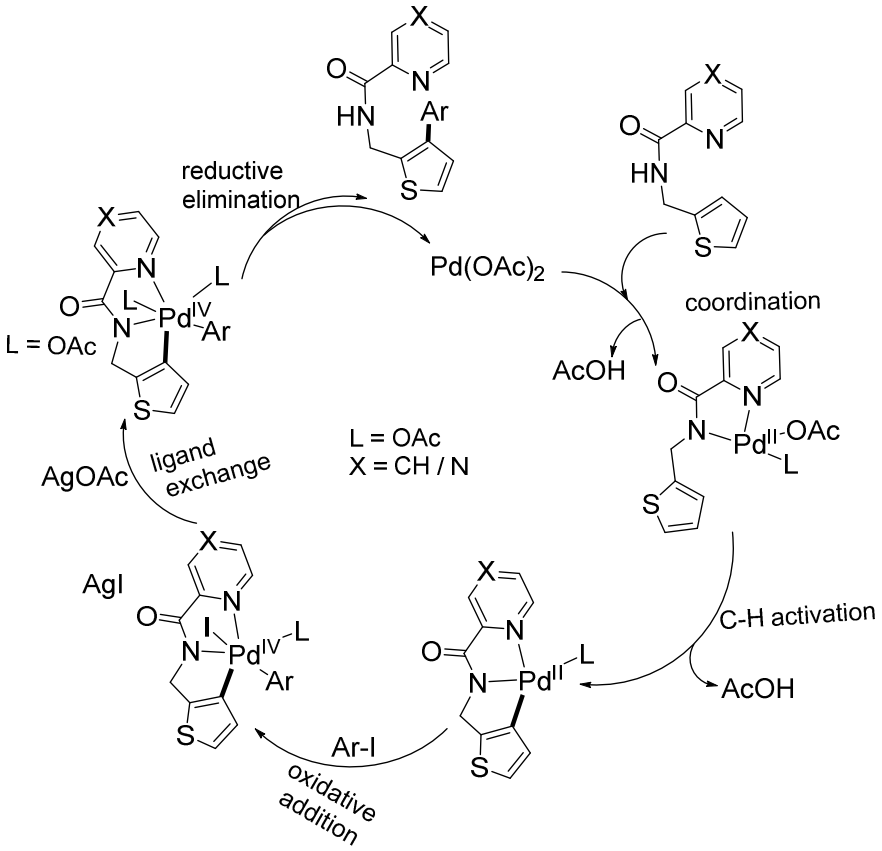
Discussion with regard to the observed regioselectivity in the Pd(II)-based C(3)-H arylation of furans/thiophenes. The observed regioselectivities in the Pd(II)-based, bidentate ligand-directed, C-H arylation of 2- or 3-(aminoalkyl)-thiophene derived amides and the structure of **20a**, **21a-r**, **22a-c**, **23a-e**, **24a-d**, **25a,b**, **26** and **28a-g** were assigned on the basis of the coupling constant (*J*) values of doublet peaks of the C4 and C5 protons of thiophene ring in **20a**, **21a-r**, **22a-c**, **23a-e**, **24a-d**, **25a,b**, **26** and **28a-g**, which were found to be around 5 Hz in concurrence with the literature reports. Likewise, the observed regioselectivities in the Pd(II)-based, bidentate ligand-directed, C-H arylation of furfurylamine derived amides and the structure of regioisomers **27a-e** were assigned on the basis of coupling constant (*J*) values of the doublet peaks of the C4 and C5 protons of furan ring in **27a-e**, which were found to be around 1.8 Hz in concurrence with the literature reports. Additionally, the observed regioselectivity in the directing-group

enabled Pd(II)-based direct *ortho* C(3)-H arylation of 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives and the structures of representative regioisomers **22c** and **23c** were explicitly determined from the single-crystal X-ray structure analyses (Figure 6). Having the results in the hand pertaining to the bidentate ligand-directed Pd(II)-based C(3)-H arylation of 2-/3-(aminoalkyl)-thiophene and furfurylamine derivatives; the observed *ortho* selective C-H arylation of 2-/3-(aminoalkyl)-thiophene and furfurylamine derived amides linked with the bidentate ligand (e.g., picolinamide) can be explained *via* a plausible chelation-assisted reaction pathway in concurrence with the generally proposed Pd(II/IV) catalytic cycle mechanism.[4e-p,5,23-30] In this Pd(II)/AgOAc catalytic system-based C-H activation of carboxamides aided by the bidentate ligands, the $Pd(OAc)_2$ functions as a catalyst and AgOAc works as an additive to regenerate $Pd(OAc)_2$ catalyst (Scheme 22).



22c **23c**

Figure 6. Confirmation of the observed regioselectivity from the X-ray structures (ORTEP diagrams) of the representative compounds **22c** and **23c**.



Scheme 22. Plausible mechanism (in concurrence with the literature works[4e-p,5,23-29]). Regioselective C(3)-H arylation 2- or 3-(aminoalkyl) thiophenes directed by the 2-picolinamide and pyrazine-2-carboxamide ligands.

Chapter 3b: Pd(II)-catalyzed acetoxylation of the *ortho* C–H bond of benzyl amines, γ and remote δ C(3)–H bond of 2-/3-(aminoalkyl)-thiophenes.

Substituted thiophenes are important synthetic building blocks in the research areas of materials and organic chemistry, medicinal chemistry and drug development.[17] Various thiophene based molecules were found to be biologically active compounds.[17,18] Though the Pd-catalyzed direct introduction of aryl groups or alkyl groups at the C-H bonds of furan- and thiophene-based systems was explored well,[19-22] the direct C-H oxygenation of C-H bonds furan-and thiophene-based systems is not explored well.[17,18] For example, the direct C-H acetoxylation of

furan/thiophene system will afford the corresponding C-H acetoxylated furan/thiophene systems (Figure 7).

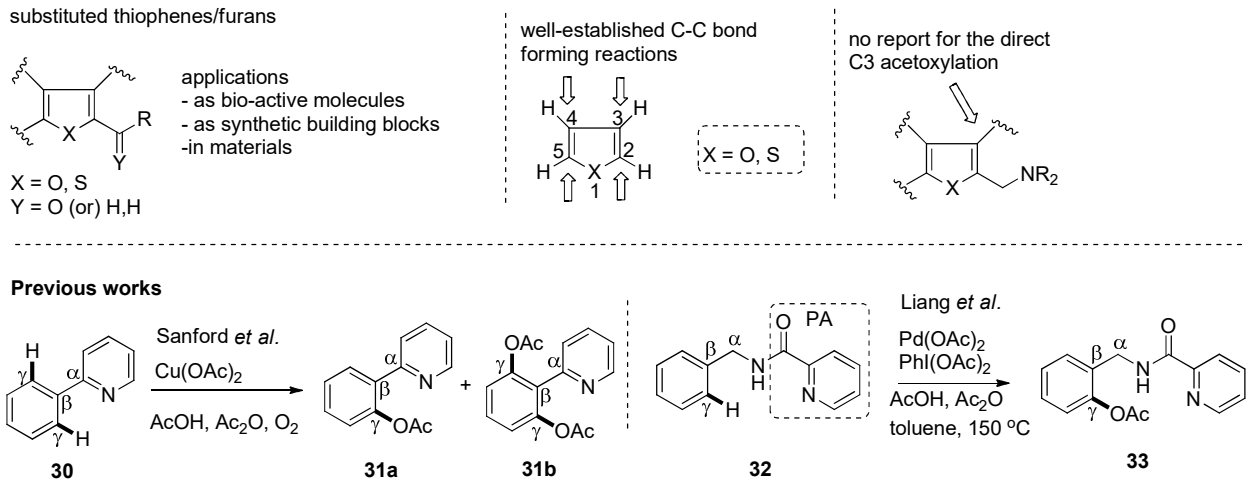


Figure 7. Assembling of functionalized thiophenes and literatures works related to C-H acetoxylations.

Although, there exist some exceptional papers dealing with the direct C-H activation/arylation of the C3 or C4 positions of thiophene, the direct C-H activation/arylation of the C2 or C5 positions of thiophenes and related heteroaromatic substrates have received much attention.[20-23] Various research groups including our group reported the regioselective C3 arylation/functionalization of thiophenes/furans involving the bidentate ligand-directed regioselective C-H activation/functionalization route.[1-6,23-25]

Given the noteworthy progress that has been made with regard to the oxygenation C-H bonds of aryl systems (e.g., aromatic carboxamides, aryl amines and benzylamines) by using various directing groups; however, the direct C-H oxygenation of C-H bonds of thiophene compounds has been not explored well.

Given the importance of functionalized furans/thiophenes in various research areas, studying the regioselective acetoxylations of C(sp^2)–H of furans/thiophene systems using directing groups will be very useful (Figures 7 and 8). Accordingly, with a desire to foster the regioselective C3 functionalization of thiophenes and in continuation of our lab's interest on the C-H activation reactions and finding new directing groups, a part of this thesis envisages to examine the Pd-catalyzed highly regioselective C-H acetoxylation of the C3-position of the 2- 3-(aminoalkyl)-thiophene derived amides by using the unexplored/less explored directing groups, such as, pyrazine- or quinoline-2-carboxamides. Further, these directing groups were also examined to perform the acetoxylation of the *ortho* C–H bond of benzyl amines under simple reaction conditions and short reaction period (toluene at 110 ^{o}C for 3-15 h).

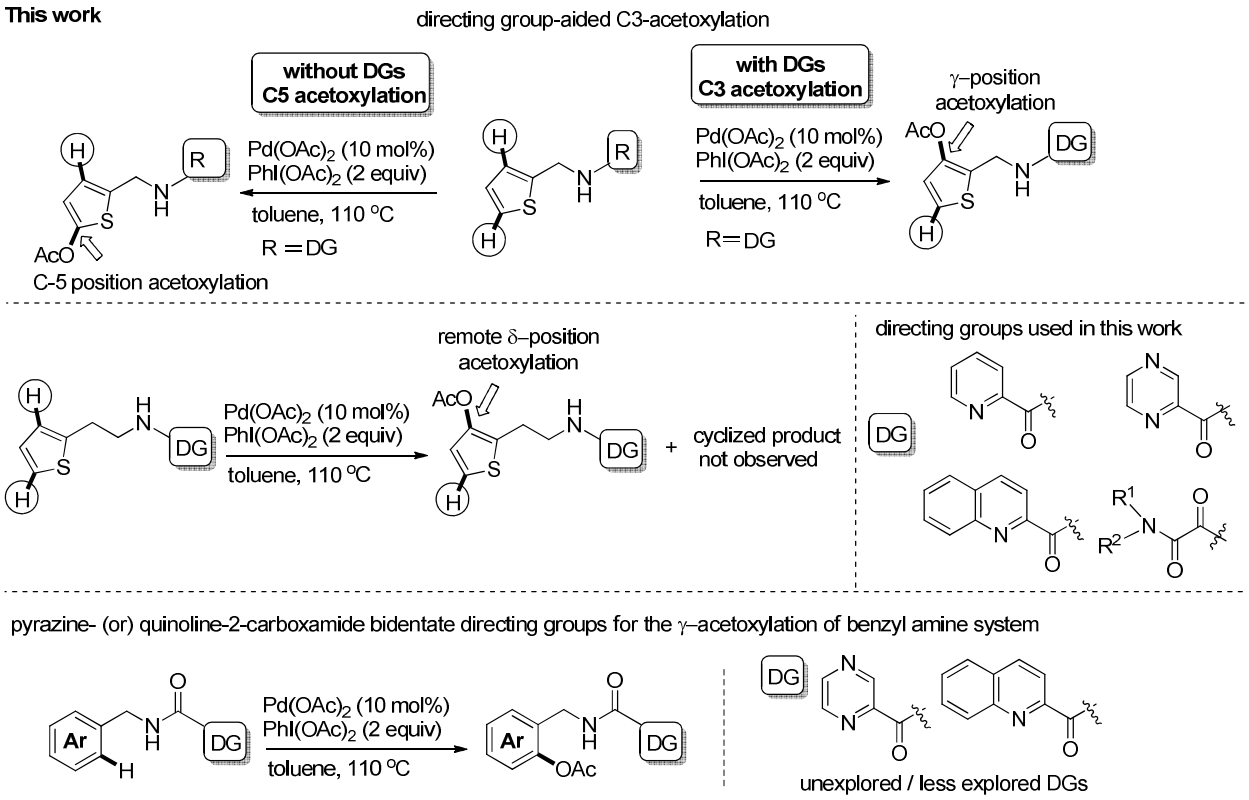
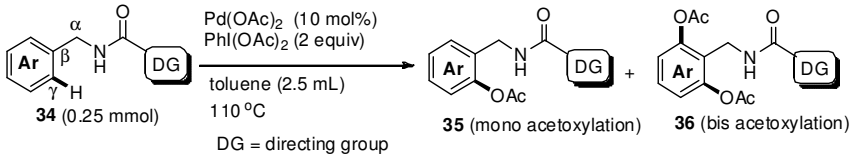
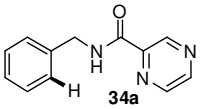
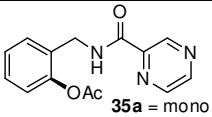
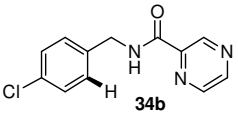
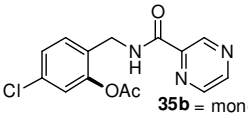
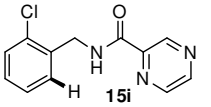
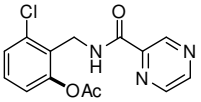
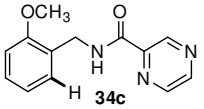
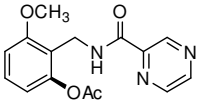
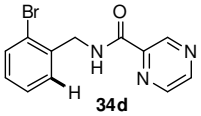
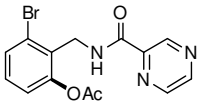
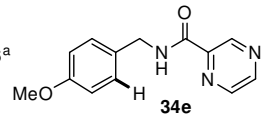
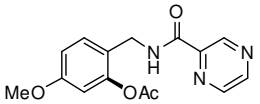


Figure 8. Topic of this work.

To begin with the investigations on the regioselective C3 acetoxylation of thiophene system*via* the C-H bond activation method, at first, to find out the suitable directing group and reaction conditions, various optimization reactions comprising the acetoxylation of the *ortho* C–H bond of benzyl amines. Though the reaction conditions for performing the acetoxylation of the *ortho* C–H bond of benzyl amines systems are known, which involves picolinamide as a directing group and the reaction was performed in toluene in the presence of $AcOH/Ac_2O$ at 150 ^oC (Figure 7).[25b]

Table 3. C–H Acetoxylation of benzyl amines using pyrazine-2-carboxamide as the directing group.

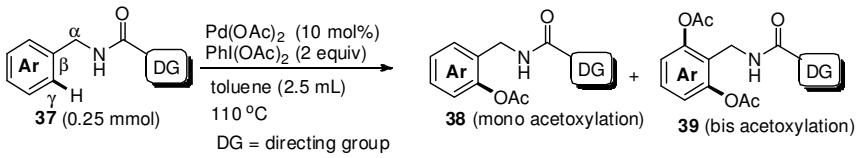


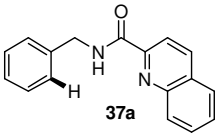
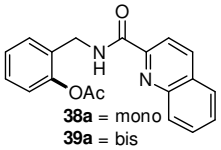
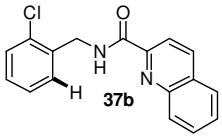
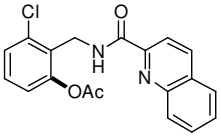
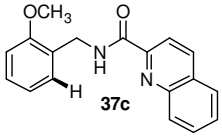
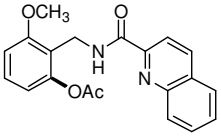
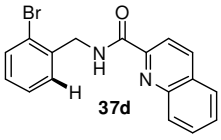
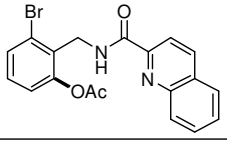
entry	substrate	acetoxylation product	time (h)	yield (%)
1	 **34a**	 **35a** = mono **36a** = bis	6	**35a** + **36a** 50 (1.2:1)
2	 **34b**	 **35b** = mono **36b** = bis	6	**35b** + **36b** 49 (1.5:1)
3	 **15i**		9	**35c**; 73
4	 **34c**		5	**35d**; 64
5	 **34d**		6	**35e**; 56
6[a]	 **34e**	 **35f** = mono **36f** = bis	15	**35f** + **36f** 45 (2:3)

[a] 3 Equiv of $PhI(OAc)_2$ was used.

In the present investigation it was found that the acetoxylation of the *ortho* C–H bond of benzyl amine system **34a** by using less explored pyrazine-2-carboxamide ligand in the presence of $PhI(OAc)_2$ as an acetate source and $Pd(OAc)_2$ (10 mol%) as the catalyst in toluene at 110 ^oC, afforded the mono acetoxylated product **35a** and bis acetoxylated product **36a** (50% yield, 1.2:1 ratio of **35a**:**36a**) (Table 3). Similarly, the acetoxylation of **34b** containing pyrazine-2-carboxamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst gave the mono acetoxylated product **35b** and bis acetoxylated product **36b** (50% yield with 1.5:1 ratio of **35b**:**36b**) (Table 3). Next, the C-H acetoxylation of benzyl amine systems **15i**, **34c-e** containing pyrazine-2-carboxamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC afforded the mono acetoxylated products **35c-f** in 15-73% yields, respectively (Table 3).

Table 4. C–H Acetoxylation of benzyl amines using quinoline-2-carboxamide as the directing group.



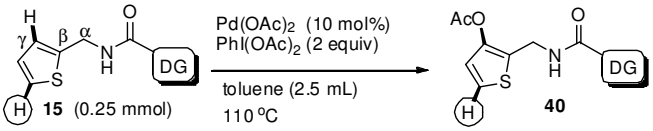
entry	substrate	acetoxylation product	time (h)	yield (%)
1	 **37a**	 **38a** = mono **39a** = bis	3	**38a** + **39a** 50 (1:3)
2	 **37b**		3	**38b**; 71
3	 **37c**		3	**38c**; 66
4	 **37d**		3	**38d**; 73

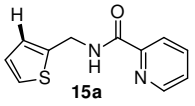
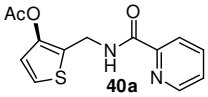
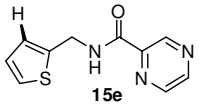
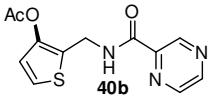
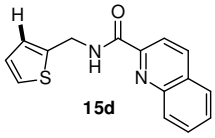
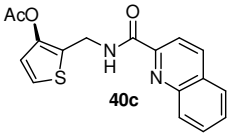
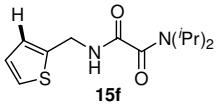
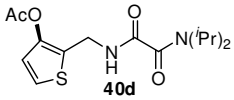
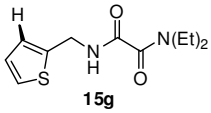
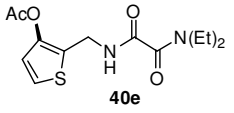
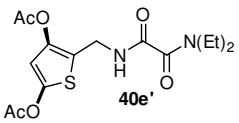
The acetoxylation of the *ortho* C–H bond of benzyl amine system **37a** containing quinoline-2-carboxamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC furnished the mono acetoxylated product **38a** and bis acetoxylated product **39a** (50% yield, **38a**:**39a** (1:3), Table 4). Subsequently, the acetoxylation of *ortho* C–H bond of benzyl amine systems **37b-d** containing quinoline-2-carboxamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst afforded the mono acetoxylated products **38b-d** in 66-73% yields, respectively (Table 4). The yields obtained for the *ortho* C–H acetoxylation of the substrates **34** and **37** having the corresponding bidentate ligands, such as, pyrazine-2-carboxamide and quinoline-2-carboxamide were comparable.

Having found suitable reaction conditions for the acetoxylation of the *ortho* C–H bond of benzyl amine systems (Tables 3 and 4) with the help of the corresponding directing groups; next, the 2-(aminomethyl)-thiophene systems **15a, 15d-g**were assembledbylinking 2-(aminomethyl)-thiophene with the corresponding directing groups, such as, picolinamide, pyrazine-2-carboxamide, quinoline-2-carboxamide and oxalylamide (Table 5). The acetoxylation of C(3)–H bond of 2-(aminomethyl)-thiophene system**15a** containing the picolinamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC afforded the C3-acetoxylated 2-(aminomethyl)-thiophene system**40a** in 56% with high regioselectivity. Similarly, the Pd(II)-catalyzed C(3)–H acetoxylation of 2-(aminomethyl)-thiophene systems **15e** and **15d** containing other bidentate ligands, such as, pyrazine-2-carboxamide and quinoline-2-carboxamide also furnished the corresponding C3-acetoxylated 2-(aminomethyl)-thiophene systems**40b** and **40c** in 61 and 78% yields with high regioselectivity. Then, the Pd(II)-catalyzed acetoxylation of 2-(aminomethyl)-thiophene systems **15f** and **15g** containing the oxalylamide directing groups furnished the corresponding C3-acetoxylated 2-(aminomethyl)-thiophene systems **40d** and **40e** in 48 and 57% yields, respectively. In the case of the acetoxylation of 2-(aminomethyl)-thiophene system **15g**, along with C3-acetoxylated 2-(aminomethyl)-thiophene system **40e** C3 and C5-acetoxylated 2-(aminomethyl)-thiophene system **40e′** was also obtained in 17% yield and the product **40e′** might have formed after the C3-acetoxylation of 2-(aminomethyl)-thiophene system **40e** (Table 5).

A literature survey revealed that generally, the C(3)-H and C(4)-H bonds of thiophene system are relatively less reactive when compared to C(2)-H and C(5)-H bonds and the direct arylation/functionalization of the C(2)-H and C(5)-H bonds of thiophenes is well documented. [6,11-15] In the present case, the C-H acetoxylations of thiophene compounds **15** (Table 5) selectively occurred at the C(3)-H bond with the help of the corresponding bidentate directing groups.

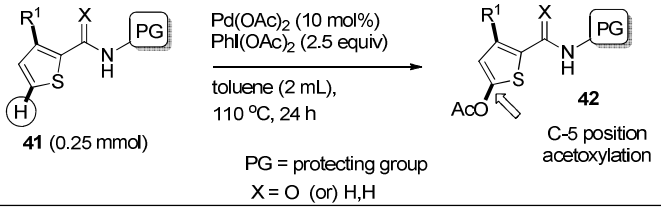
Table5. Bidentate directing group-enabled regioselective C(3)–H acetoxylation of 2-(aminomethyl)-thiophenes.

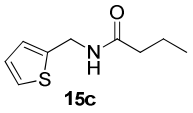
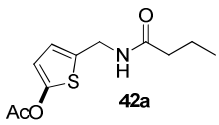
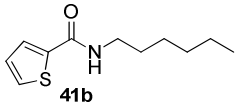
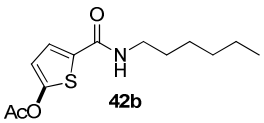
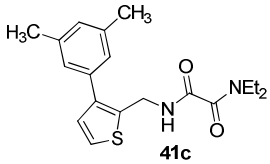
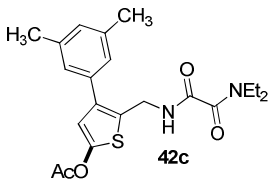
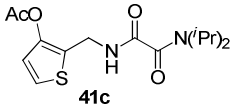
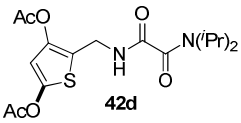


entry	substrate	acetoxylation product	time (h)	yield (%)
1	 **15a**	 **40a**	12	56[a]
2	 **15e**	 **40b** **X-ray**	6	61[a]
3	 **15d**	 **40c**	3	78
4	 **15f**	 **40d**	2	48
5	 **15g**	 **40e** +  **40e'**	2	**40e**; 57 & **40e'**; 17 **40e** + **40e'** = 74

[a] The reaction was carried out by using 1:1 Gla.AcOH and Ac_2O.

Table 6. Directing group free regioselective C(5)–H acetoxylation of various thiophene systems.



entry	substrate	acetoxylation product	yeld (%)
1	 **15c**	 **42a**	40
2	 **41b**	 **42b**	0
3	 **41c**	 **42c**	40
4	 **41c**	 **42d**	35

Having observed the formation of the C3 and C5-acetoxylated product **40e′** (Table 5) that might have formed after the C3-acetoxylation of 2-(aminomethyl)-thiophene system **40e**, then, it was envisaged to investigate the selective C5-acetoxylation of 2-(aminomethyl)-thiophene system. In this regard, the 2-(aminomethyl)-thiophene systems that are not having any directing groups **15c**, **41b** or thiophene systems **41c,d** having a substitution at the C3-positionwere assembled(Table 6). The C-H acetoxylation of the 2-(aminomethyl)-thiophene system**15c** in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC gave the C5-acetoxylated thiophene system **42a** in 40% yield (Table 6). On the other hand, the C-H acetoxylation reaction of thiophene-2-carboxamide **41b** in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst failed to give the corresponding C5-acetoxylated thiophene compound **42b**. Though the substrates **15c** and **41b** are structurally similar, however, at this stage, an explanation for the failure of the acetoxylation of the substrate **41b** is not known. Along the same line, the acetoxylation reaction of thiophene

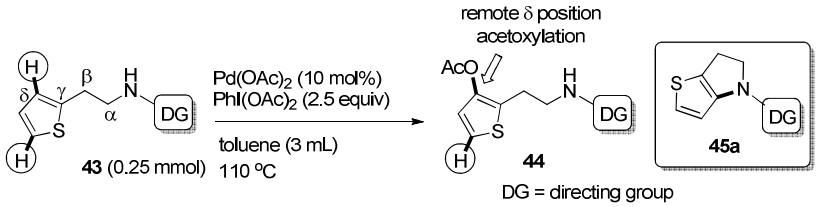
systems **41c** and **41d** having a substitution at the C3-position in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC gave the corresponding C5-acetoxylated thiophene systems **42c** and **42d** in 40 and 35% yields (Table 6).

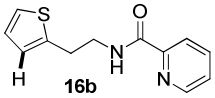
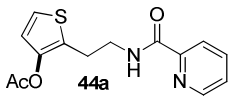
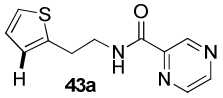
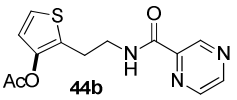
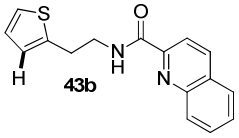
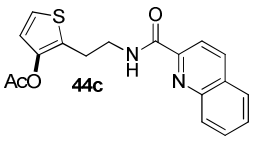
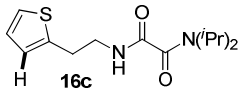
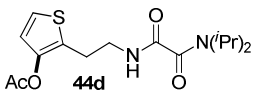
Subsequently, it was envisaged to further expand the substrate scope and the significance of this method comprising Pd-catalyzed C-H acetoxylation of thiophene systems. In this regard, the 2-(aminoethyl)-thiophene systems **16b-c** and **43a-b** were preparedbylinking 2-(aminoethyl)-thiophene with the corresponding directing groups, such as, picolinamide, pyrazine-2-carboxamide, quinoline-2-carboxamide and oxalylamide (Table 7). It is to be noted that in the thiophene-based amides **15a**, **15d-g** shown in Table 5, with respect to amide nitrogen the C(3)-H bond of thiophene ring is located at the γ-position. However, in the thiophene-based amides **16b-c** and **43a-b** (Table 7), with respect to amide nitrogen the C(3)-H bond of thiophene ring is located at the δ-position. It is worth to mention here that a literature survey revealed that the C-H acetoxylation of the sp^2 C-H bond at γ-position of a designed carboxamide is explored well.[4e-p,5,16,17e-h] On the other hand, the sp^2 C-H acetoxylation of the sp^2 C-H bond at δ-position of a designed carboxamide is rarely examined. Accordingly, it was envisaged to study the C-H acetoxylation of thiophene systems **16b,c, 43a,b** (Table 7) which contain the sp^2 C-H bond at the δ-position.

The sp^2 C-H acetoxylation of the sp^2 C-H bond at the δ-position of 2-(aminoethyl)-thiophene system**16b** containing picolinamide ligand in the presence of $PhI(OAc)_2$ and $Pd(OAc)_2$ catalyst in toluene at 110 ^oC gave the C3-acetoxylated thiophene system **44a** in 27% yield along with the cyclized product **45a** in 20% yield. Similarly, the Pd(II)-catalyzed acetoxylation of 2-(aminoethyl)-thiophene systems **43a** and **43b** containing the bidentate ligands, such as, pyrazine-2-carboxamide and quinoline-2-carboxamide furnished the corresponding C3-acetoxylated thiophenes **44b** and **44c** in 52 and 43% yields. Then, the Pd(II)-catalyzed C-H acetoxylation of 2-(aminoethyl)-thiophene system **16c** containing oxalylamide as adirecting group failed to give the corresponding C3-acetoxylated products **44d** and the reaction afforded a complex mixture (Table 7). An exact reason is not clear for the failure of C-H acetoxylation of **16c**; nevertheless, when compared to the other directing groups used for the C-H acetoxylation of thiophene system shown in Table 7, the oxalylamide directing group may be a weak directing group to assist the acetoxylation at the remote δ-C-H bond of the thiophene system **16c**. Except in one case, where

the cyclized products **45a** was obtained under the present experimental condition, in other reactions the corresponding cyclized products were not observed under the experimental condition (Table 7).

Table 7: Regioselective C(3)–H acetoxylation of 2-(aminoethyl)-thiophene systems by using various bidentate directing groups.

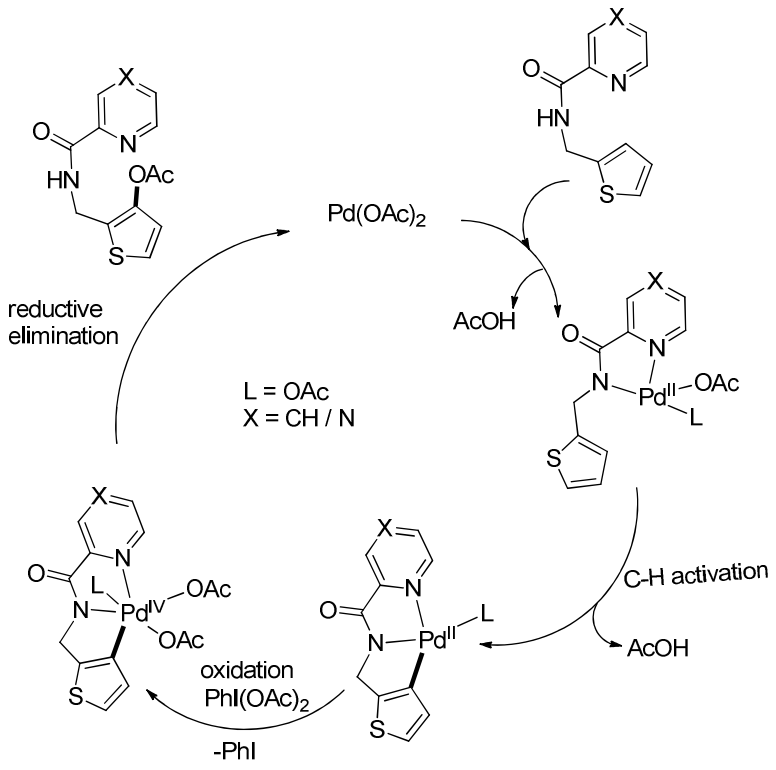


entry	substrate	acetoxylation product	time (h)	yield (%)
1[a]	 **16b**	 **44a**	8	47 **44a**; 27 **45a**; 20
2	 **43a**	 **44b**	72	52
3	 **43b**	 **44c**	48	43
4[b]	 **16c**	 **44d**	3	mixture of compounds

[a] 1.5 Equiv of $PhI(OAc)_2$ was used. [b] This reaction was performed with 2 equiv of $PhI(OAc)_2$ and the reaction afforded a complex inseparable mixture of compounds.

The observed regioselectivities in the Pd(II)-catalyzed, bidentate ligand-directed, selective C(3)-H acetoxylation of 2- or 3-(aminoalkyl)-thiophenes **15a**, **15d-g**, **16b-c** and **43a-b** and the structure of the regioisomers **40** and **44** were assigned based on the coupling constant (*J*) of values of the doublet peaks of the C4 and C5 protons of thiophene ring, which were found to be around 5 Hz as reported in the literature. Furthermore, the observed regioselectivity in the directing-group aided Pd(II)-catalyzed direct C(3)-H acetoxylation of 2- or 3-(aminoalkyl)-

thiophenes and the structures of the representative regioisomer **40b** was unequivocally determined from the single-crystal X-ray structure (Figure 9). The observed *ortho* selective C(3)-H-acetoxylation of 2- or 3-(aminoalkyl)-thiophene derived amides linked with the respective bidentate ligands (e.g., picolinamide) can be exemplified *via* a generally proposed chelation-assisted mechanism comprising the Pd(II/IV) catalytic cycle.[4e-p,5,17,23-29]



Scheme 24. Proposed mechanism (in concurrence generally proposed mechanism[4e-p,5,17,23-29]) for the regioselective C3-acetoxylation of thiophene system.

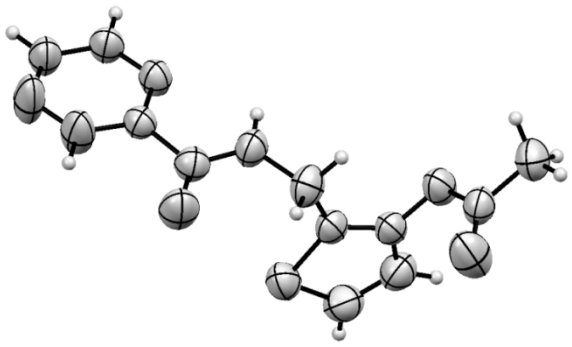
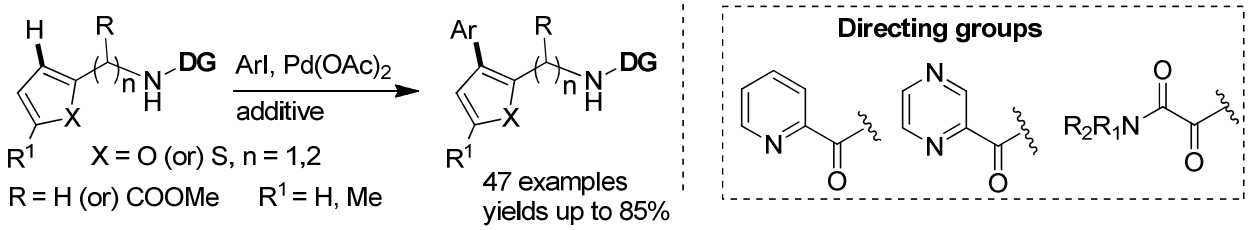


Figure 9. X-ray (ORTEP diagram) of the compound **40b**.

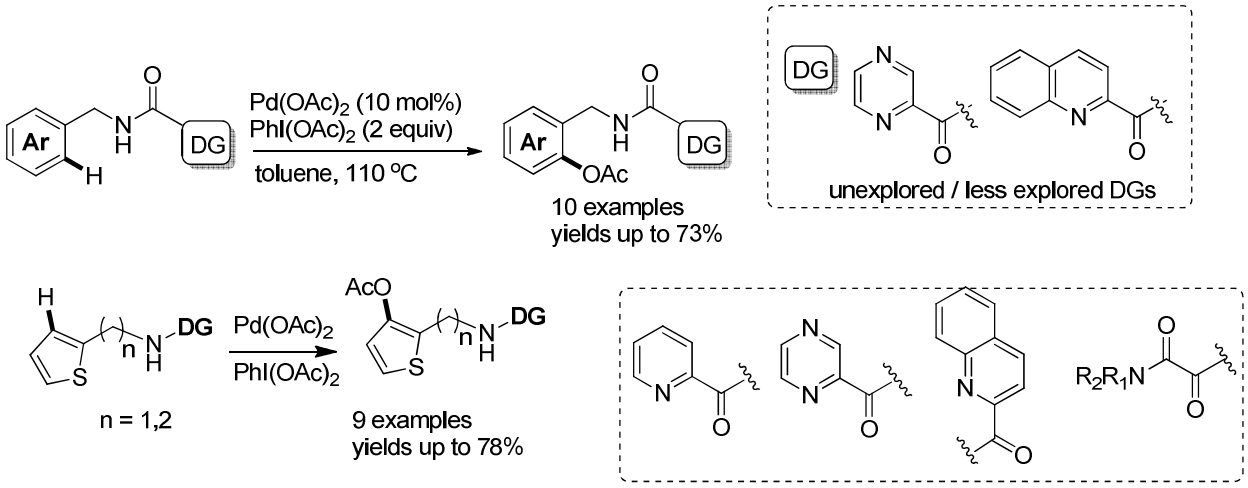
Conclusions.

In summary, chapter 3a revealed (a) a resourceful synthetic protocol comprising the Pd(II)-based, bidentate ligand-directed, highly regioselective mono C-H arylation of the C3-position of 2- or 3-(aminoalkyl)-thiophene and furfurylamine derived amides, (b) investigations on the efficiency and role of bidentate ligands in the Pd(II)-based C(3)-H arylations of 2- or 3-(aminoalkyl)-thiophene and furfurylamine derived amidesand screening of the substrate scope and generality.



Given that a survey of the literature revealed several arylated thiophene/furan-based carboxamide derivativesare biologically active compounds; and given that there exists no report dealing on the regioselective arylations of the C(3)-H bonds of 2-/3-(aminoalkyl)-thiophene and furfurylamine derived amides; it is believed that this method comprising the $Pd(OAc)_2$-promoted C(3)-H arylation of 2- or 3-(aminoalkyl)-thiophene and furfurylamine derived amides will be very helpful for assembling several heteroaromatic carboxamide scaffolds based on C(3)-H-arylated 2-/3-(aminoalkyl)-thiophene or furfurylamine and different carboxylic acid units (bidentate ligands).

Further, the chapter 3b revealed, (a) the sp^2 C-H acetoxylation of the *ortho* C–H bond of benzyl amines under improved reaction conditions and short reaction period (toluene at 110 ^oC for 3-15 h) with the help of the directing groups, such as, pyrazine- or quinoline-2-carboxamides, (b) then, by using these reaction conditions found for the sp^2 C-H acetoxylation of the *ortho* C–H bond of benzyl amines, the regioselective sp^2C-H acetoxylation of the C3-position of 2- or 3-(aminoalkyl)-thiophene derived amides was accomplished by using the directing groups, such as, picolinamide, pyrazine- and quinoline-2-carboxamides.



Given the importance of functionalized thiophenes, this work dealing on the regioselective C-H acetoxylation of 2- or 3-(aminoalkyl)-thiophene systems will be a very useful method to obtain C3-acetoxylated thiophene systems.

All the C-H arylation/acetoxylation reactions were regioselective and all compounds included in the chapter 3 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 regioselectivity of representative 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. The synthesized molecules will be screened for their biological activities in collaboration with a medicinal chemistry lab and further work is in progress in this direction.

Experimental section.

General: Melting points are uncorrected. IR spectra were recorded as neat or thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with 400 and 100 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 conducted in anhydrous solvent under nitrogen atmosphere where required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask by using a syringe. Thin layer chromatography (TLC)

was performed on silica plates or neutral Al_2O_3 and components were visualized by observation under iodine. Isolated yields of all the products are reported (yields were not optimized). Ratios of regioisomers were determined from the ^1H (or) ^{13}C spectra of crude reaction mixture. The regioselectivity of the products were assigned based on the X-ray structure analysis of representative compounds. Good quality single crystals were grown by using a combination of dichloromethane or hexanes or methanol or acetone by slow solvent evaporation technique at 25 °C and the single crystal X-ray diffraction data for all the compounds was collected using four circle CCD diffractometer (monochromatic Mo Kα radiation). Data collection and unit cell refinement for the data sets were done using APEX-II suit. The crystal structures were solved using Olex2 or WinGx packages using SHELXS97, and the structures were refined using SHELXL97. All the hydrogen atoms have been fixed at their geometrically ideal positions and refined using the riding model available within SHELXS97. All figures have been generated using Mercury.

General procedure A for the synthesis of carboxamides (15a-e, **15i**, **16b**, **17 and 18):** The corresponding carboxylic acid (6 mmol) was dissolved in dry DCM (25 mL) by adding 2 to 3 drops of dry DMF. To this reaction mixture oxalyl chloride (1.5 equiv.) was added at 0 ^oC slowly and the resultant reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period, the reaction mixture was concentrated in vacuum to remove excess oxalyl chloride and solvent. The resultant acid chloride was dissolved in DCM (25 mL) and this reaction mixture was added to a separate flask which contained the corresponding amine (5 mmol), Et_3N (1.5 equiv, 9 mmol) in DCM (5 mL) at 0 ^oC and the resultant reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period, the reaction mixture was diluted with DCM and then washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification of the resulting reaction mixture by column chromatography furnished the corresponding carboxamides **15a-e**, **15i**, **16b**, **17** and **18**.

Typical procedure B for the synthesis of methyl 2-(picolinamido)-2-(thiophen-2-yl)acetate (16a): The corresponding carboxylic acid (2 mmol) was dissolved in dry DCM (15 mL) by adding 2 to 3 drops of dry DMF followed by Et_3N (1.5 equiv) the reaction mixture was stirred at rt for 2 h. To this reaction mixture oxalyl chloride (1.5 equiv) was added at 0 ^oC slowly and the

reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period, the reaction mixture was concentrated in vacuum to remove excess oxalyl chloride and solvent. The resultant acid chloride was dissolved in DCM (10 mL), this reaction mixture was added to a separate flask which contained corresponding amine (1 mmol), Et_3N (1.5 equiv, 1.5 mmol) in DCM (5 mL) at 0 ^oC and the resultant reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period of time, the reaction mixture was diluted with dichloromethane and then washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification of the resulting reaction mixture by column chromatography furnished the carboxamide **16a**.

General procedure C for the synthesis of carboxamides 15f-h and 16c: To a solution of the corresponding 2º amine (6 mmol) dissolved in dry DCM (25 mL) was added oxalyl chloride (1.5 equiv) was added drop wise at 0 ^oC slowly, then, the reaction mixture was stirred at rt for 30 min, then, Et_3N (1.2 equiv) was added drop wise at 0 °C. The resultant reaction mixture was stirred at rt for 6 h under a nitrogen atm. The excess oxalyl chloride and the solvent were removed under reduce pressure**.** The resultant crude product was dissolved in 20 mL DCM at 0 °C, to this solution was added the corresponding 1º amine(5 mmol) followed by Et_3N (1.2 equiv) drop wise at 0 °C. Then, the reaction mixture was stirred at rt for 6 h under a nitrogen atm and then, the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The resulting reaction mixture was purified by column chromatography on silica gel to give the corresponding carboxamides **15f-h** and **16c**.

General procedure D for the synthesis of amides 15b and 15c: The corresponding amine (5 mmol), Et_3N (1.5 equiv) dissolved in dry DCM (25 mL). To this reaction mixture acid chloride (6 mmol) was added drop wise at 0 ^oC. Then, the reaction mixture was stirred at rt for 6-8 h under a nitrogen atm. After this period of time, the reaction mixture was diluted with dichloromethane and then, washed with water followed by saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification of the resulting reaction mixture by column chromatography furnished the carboxamides **15b** and **15c**.

General procedure E for the synthesis of carboxamides (34, 37 and 43): The corresponding carboxylic acid (4 mmol) was dissolved in dry DCM (15 mL) by adding 2 to 3 drops of dry DMF. To this reaction mixture oxalyl chloride (1.5 equiv) was added at 0 ^{o}C slowly and the reaction mixture was stirred for 6-8 h under a nitrogen atmosphere. After this period, the reaction mixture was concentrated in vacuo to remove the excess oxalyl chloride and solvent. The acid chloride was dissolved in DCM (15 mL), this reaction mixture was added to a separate flask which contained the corresponding amine (3 mmol), Et_3N (1.5 equiv) in DCM (5 mL) at 0 ^{o}C and the reaction mixture was stirred for 6-8 h. After this period of time, the reaction mixture was diluted with dichloromethane and then, washed with water followed by a saturated aqueous $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the resulting reaction mixture by silica column chromatography furnished the corresponding carboxamides.

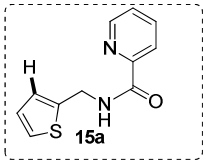
General procedure F for the regioselective arylation of sp^2 C(3)–H bond directed by 2-picolinamide and pyrazine-2-carboxamide: A mixture of the corresponding heterocyclic carboxamides (1 equiv), $Pd(OAc)_2$ (10-30 mol%), AgOAc (1-2.2 equiv) or Ag_2CO_3 (2.2-4 equiv) and ArI (3-4 equiv) in anhydrous toluene was heated at 110 °C for 24–72 h under a nitrogen atm. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the reaction mixture by silica gel column chromatography gave the corresponding C3-arylated compounds (see the corresponding Tables/Schemes for specific details).

General procedure G for the regioselective arylation of sp^2 C(3)–H bond directed by oxalylamide: A mixture of the corresponding heterocyclic carboxamides (1 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (1.2-2.2 equiv) and ArI (3-4 equiv) in anhydrous toluene was heated at 110 °C for 2-8 h under a nitrogen atm. After the reaction period, the reaction mixture was concentrated in vacuum and purification of the reaction mixture by silica gel column chromatography gave the corresponding C3-arylated compounds (see the corresponding Tables/Schemes for specific details).

General procedure H for the regioselective acetoxylation of compounds: A mixture of the corresponding heterocyclic carboxamides (0.25 mmol), $Pd(OAc)_2$ (10 mol%) and $PhI(OAc)_2$ (2-3 equiv) in anhydrous toluene was heated at 110-130 °C for 2–72 h under a nitrogen atmosphere. After the reaction period, the reaction mixture was concentrated in vacuum and purification of

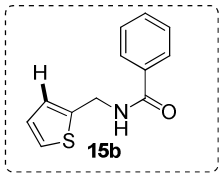
the reaction mixture by silica gel column chromatography gave the corresponding acetoxylated products (see the respective Schemes/Tables for specific entries).

N-(Thiophen-2-ylmethyl)picolinamide **(15a):** Following the general procedure described above



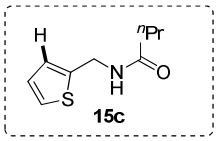
15a was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored solid (654 mg, 60%); mp: 103-105 ^{o}C; FT-IR (KBr): 3320, 3058, 1652, 1524, 1292, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56-8.54 (m, 1H), 8.41 (br s, 1H), 8.25 (dt, 1H, J_1 =7.8, J_2 = 1.0 Hz), 7.88 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.46-7.42 (m, 1H), 7.25 (dd, 1H, J_1 = 5.1, J_2 = 1.2 Hz), 7.08-7.06 (m, 1H), 6.98 (dd, 1H, J_1 = 5.1, J_2 = 3.5 Hz), 4.86 (dd, 2H, J_1 = 6.0, J_2 = 0.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.1, 140.8, 137.4, 126.9, 126.3, 126.2, 125.2, 122.4, 38.2; HRMS (ESI) calcd for $C_{11}H_{11}N_2OS$ $[M+H]^+$ 219.0592 found 219.0582.

N-(Thiophen-2-ylmethyl)benzamide **(15b):** Following the general procedure described above



15b was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (918 mg, 85%); mp: 120-122 ^{o}C; FT-IR (KBr): 3300, 3054, 1682, 1421, 1264, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.79 (m, 2H), 7.54-7.50 (m, 1H), 7.46-7.42 (m, 2H), 7.27 (dd, 1H, J_1 = 5.1, J_2 = 1.2 Hz), 7.06-7.05 (m, 1H), 6.99 (dd, 1H, J_1 = 5.1, J_2 = 3.5 Hz), 6.58 (br s, 1H), 4.83 (dd, 2H, J_1 = 5.5, J_2 = 0.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 140.8, 134.1, 131.7, 128.6, 127.0, 127.0, 126.3, 125.4, 38.9; HRMS (ESI) calcd for $C_{12}H_{12}NOS$ $[M+H]^+$ 218.0640 found 218.0643.

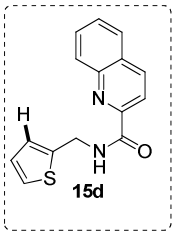
N-(Thiophen-2-ylmethyl)butyramide**(15c):** Following the general procedure described above **15c** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (750 mg, 82%); mp: 55-57 ^{o}C; FT-IR (KBr): 3399,
2961, 1635, 1548, 1222, 831 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, 1H, J = 4.8 Hz), 6.97-



6.95 (m, 2H), 5.93 (br s, 1H), 4.62 (d, 2H, J = 5.6 Hz), 2.19 (t, 2H, J = 7.4 Hz), 1.74-1.65 (m, 2H), 0.96 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 141.2, 126.9, 125.9, 125.2, 38.6, 38.2, 19.1, 13.8; HRMS (ESI) calcd for $C_9H_{14}NOS$ $[M+H]^+$ 184.0796 found 184.0790.

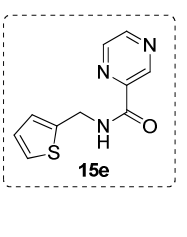
N-(Thiophen-2-ylmethyl)quinoline-2-carboxamide **(15d):** Following the general procedure described above **15d** was obtained after purification by column chromatography (EtOAc:Hexane

= 25:75); as a colorless solid (1.1 g, 83%); mp: 99-101 ^{o}C; FT-IR (KBr): 3392, 3115, 1673, 1519, 1218, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (br s, 1H), 8.37-8.31 (m, 2H), 8.09 (d, 1H, J = 8.4 Hz). 7.89 (d, 1H, J = 8.2 Hz), 7.78-7.74 (m, 1H), 7.65-7.61 (m, 1H), 7.27 (dd, 1H, J_1 = 5.1, J_2 = 1.1 Hz), 7.12 (d, 1H, J = 2.6 Hz), 7.01 (dd, 1H, J_1 = 5.1, J_2 = 3.5 Hz), 4.93 (d, 2H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 149.5, 146.5, 140.9, 137.6, 130.2, 129.7, 129.4, 128.0, 127.8, 127.0, 126.2, 125.3, 118.9, 38.3; HRMS (ESI) calcd for $C_{15}H_{13}N_2OS$ $[M+H]^+$ 269.0749 found 269.0756.

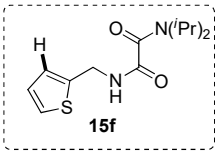


15d

N-(Thiophen-2-ylmethyl)pyrazine-2-carboxamide **(15e):** Following the general procedure described above **15e** was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a yellow colored solid (403 mg, 37%); mp: 118-120 ^{o}C; FT-IR (KBr): 3380, 3085, 1666, 1522, 1265, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.46 (d, 1H, J = 1.2 Hz), 8.77 (d, 1H, J = 2.4 Hz), 8.53 (t, 1H, J = 1.7 Hz), 8.16 (br s, 1H), 7.27 (s, 1H), 7.09 (d, 1H, J = 3.4 Hz), 7.00 (dd, 1H, J_1= 5.0, J_2= 3.4 Hz), 4.87 (d, 2H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 147.4, 144.6, 144.2, 142.6, 140.2, 127.0, 126.4, 125.5, 38.2; HRMS (ESI) calcd for $C_{10}H_{10}N_3OS$ $[M+H]^+$ 220.0545 found 220.0541.

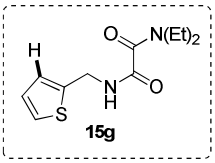


15e



15f

N^1,N^1-Diisopropyl-N^2-(thiophen-2-ylmethyl)oxalamide **(15f)**: Following the general procedure described above **15f** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a yellow colored solid (1.27 g, 95%); mp: 124-126 ^{o}C; FT-IR (KBr): 3323, 2973, 1662, 1633, 1522, 1250, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (br s, 1H), 7.22 (dd, 1H, J_1 = 5.1, J_2 =1.2 Hz), 7.00 (dd, 1H, J_1 = 3.4, J_2 =0.9 Hz), 6.95 (dd, 1H, J_1 = 5.1, J_2 = 3.4 Hz), 4.71-4.64 (m, 1H), 4.60 (d, 2H, J = 6.0 Hz), 3.54-3.47 (m, 1H), 1.40 (d, 6H, J = 6.8 Hz), 1.23 (d, 6H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 162.9, 140.0, 126.9, 126.3, 125.3, 49.7, 46.5, 37.9, 20.8, 20.0; HRMS (ESI) calcd for $C_{13}H_{20}N_2NaO_2S$ $[M+Na]^+$ 291.1143 found 291.1130.

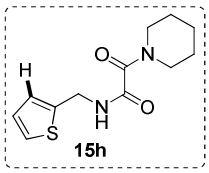


15g

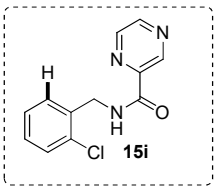
N^1,N^1-Diethyl-N^2-(thiophen-2-ylmethyl)oxalamide **(15g):** Following the general procedure described above **15g** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (660 mg, 55%); FT-IR (DCM): 3296, 2980, 1680, 1632, 1520, 1266, 736 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz): δ 7.82 (br s, 1H), 7.23 (dd, 1H, J_1 = 5.1, J_2 =1.0 Hz), 7.00 (d, 1H, J = 2.6 Hz), 6.95 (dd, 1H, J_1 = 5.1, J_2 = 3.6 Hz), 4.63 (d, 2H, J = 6.0 Hz), 3.77 (q, 2H, J = 7.0 Hz), 3.41 (q, 2H, J = 7.0 Hz), 1.28 (t, 3H, J = 7.0 Hz), 1.16 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7, 161.2, 140.0, 126.9, 126.3, 125.3, 43.3, 42.0, 37.9, 14.7, 12.5; HRMS (ESI) calcd for $C_{11}H_{16}N_2NaO_2S$ $[M+Na]^+$ 263.0830 found 263.0826.

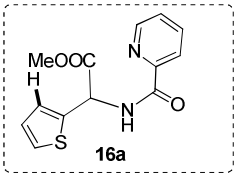
2-Oxo-2-(piperidin-1-yl)-N-(thiophen-2-ylmethyl)acetamide **(15h):** Following the general procedure described above **15h** was obtained after purification by column chromatography (EtOAc:Hexane = 60:40); as a brown colored solid (756 mg, 60%); mp: 57-59 ^{o}C; FT-IR (KBr): 3291, 2943, 1678, 1631, 1447, 1265, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (br s, 1H), 7.26 (dd, 1H, J_1 = 5.0, J_2 = 1.0 Hz), 7.02 (d, 1H, J = 3.0 Hz), 6.97 (dd, 1H, J_1 = 5.0, J_2 = 3.5 Hz), 4.66 (d, 2H, J = 6.0 Hz), 4.00-3.98 (m, 2H), 3.60-3.58 (m, 2H), 1.68-1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 161.0, 139.9, 126.9, 126.3, 125.4, 47.5, 44.2, 38.0, 26.7, 25.7, 24.5; HRMS (ESI) calcd for $C_{12}H_{16}N_2NaO_2S$ $[M+Na]^+$ 275.0830 found 275.0838.



N-(2-Chlorobenzyl)pyrazine-2-carboxamide **(15i):** Following the general procedure described above **15i** was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a colorless solid (743 mg, 60%); mp: 103-105 ^{o}C; FT-IR (KBr): 3380, 3053, 1665, 1525, 1265, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.43 (d, 1H, J = 1.3 Hz), 8.76 (d, 1H, J = 2.4 Hz), 8.54 (dd, 1H, J_1 = 2.4, J_2 = 1.5 Hz), 8.29 (br s, 1H), 7.48-7.46 (m, 1H), 7.41-7.39 (m, 1H), 7.28-7.25 (m, 2H), 4.78 (d, 2H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 147.4, 144.5, 144.3, 142.6, 135.2, 133.8, 130.3, 129.7, 129.2, 127.2, 41.5; HRMS (ESI) calcd for $C_{12}H_{11}ClN_3O$ $[M+H]^+$ 248.0591 found 248.0585.

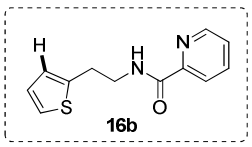


Methyl 2-(picolinamido)-2-(thiophen-2-yl)acetate **(16a):**Following the general procedure described above **16a** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored solid (139 mg, 50%); mp: 83-85 ^{o}C;FT-IR (KBr): 3380, 2956, 1750, 1674, 1513, 1220, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.91 (d, 1H, J = 7.4 Hz), 8.62 (d, 1H, J = 4.6 Hz), 8.20 (d, 1H, J = 7.8 Hz), 7.87 (td, 1H, J_1 = 7.8, J_2 = 1.7 Hz), 7.49-7.45 (m, 1H), 7.31 (dd, 1H, J_1 = 5.1, J_2 = 1.0 Hz), 7.18 (d, 1H, J = 3.6 Hz), 7.02 (dd, 1H, J_1 = 5.1, J_2 = 3.6 Hz), 6.09



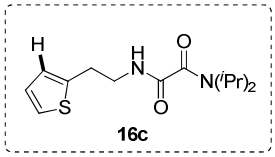
(d, 1H, J = 7.8 Hz), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 163.8, 149.0, 148.4, 138.4, 137.4, 127.1, 126.6, 126.5, 126.0, 122.4, 53.1, 52.0; HRMS (ESI) calcd for $C_{13}H_{12}N_2NaO_3S$ $[M+Na]^+$ 299.0466 found 299.0471.

N-(2-(Thiophen-2-yl)ethyl)picolinamide **(16b):** Following the general procedure described above **16b** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (672 mg, 58%); FT-IR (DCM): 3374, 2929, 1670, 1527, 1248, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, 1H, J= 4.5 Hz), 8.26 (br s, 1H), 8.22 (d, 1H, J = 7.8 Hz), 7.86 (td, 1H, J_1 = 7.8, J_2 = 1.6 Hz), 7.43 (dd, 1H, J_1 = 6.8, J_2 = 5.0 Hz), 7.19 (d, 1H, J= 4.7 Hz), 6.98-6.96 (m, 1H), 6.91 (d, 1H, J = 3.0 Hz), 3.78 (q, 2H, J = 6.9 Hz), 3.18 (t, 2H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4, 149.8, 148.1, 141.3, 137.3, 127.0, 126.2, 125.3, 123.9, 122.2, 40.9, 30.1; HRMS (ESI) calcd for $C_{12}H_{13}N_2OS$ $[M+H]^+$ 233.0749 found 233.0739.



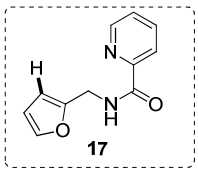
16b

N^1,N^1-Diisopropyl-N^2-(2-(thiophen-2-yl)ethyl)oxalamide (**16c**): Following the general procedure described above **16c** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a light yellow colored solid (1.1 g, 81%); mp: 71-73 ^{o}C; FT-IR (DCM): 3285, 2973, 1672, 1628, 1448, 1259, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (br s, 1H), 7.16 (dd, 1H, J_1 = 5.1, J_2 = 1.1 Hz), 6.94 (dd, 1H, J_1 = 5.1, J_2 = 3.4 Hz), 6.88-6.87 (m, 1H), 4.60-4.54 (m, 1H), 3.58 (q, 2H, J = 6.8 Hz), 3.53-3.46 (m, 1H), 3.08 (t, 2H, J = 6.8 Hz), 1.41 (d, 6H, J = 6.8 Hz), 1.21 (d, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 163.4, 140.9, 127.0, 125.4, 123.9, 49.8, 46.4, 40.6, 29.6, 20.8, 20.1; HRMS (ESI) calcd for $C_{14}H_{22}N_2NaO_2S$ $[M+Na]^+$ 305.1300 found 305.1393.



16c

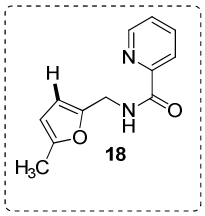
N-(Furan-2-ylmethyl)picolinamide **(17):** Following the general procedure described above **17** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a black colored solid (798 mg, 79%); mp: 93-95 ^{o}C; FT-IR (KBr): 3345, 3108, 1663, 1524, 1165, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.54 (m, 1H), 8.37 (br s, 1H), 8.22 (dd, 1H, J_1 = 7.8, J_2 =0.9 Hz), 7.85 (td, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.44-7.41 (m, 1H), 7.38 (dd, 1H, J_1 = 1.8, J_2 = 0.8 Hz), 6.34 (dd, 1H, J_1 =



17

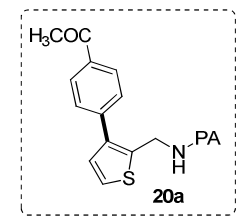
3.2, J_2 = 1.8 Hz), 6.30 (dd, 1H, J_1 = 3.2, J_2 = 0.6 Hz), 4.67 (d, 2H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 151.3, 150.0, 148.1, 142.3, 137.4, 126.3, 122.4, 110.4, 107.5, 36.4; HRMS (ESI) calcd for $C_{11}H_{10}N_2NaO_2$ $[M+Na]^+$ 225.0640 found 225.0648.

N-((5-Methylfuran-2-yl)methyl)picolinamide **(18):** Following the general procedure described above **18** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a dark brown colored semi solid (735 mg, 68%); FT-IR (DCM): 3341, 2923, 1677, 1524, 1189 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, 1H, J = 4.7 Hz), 8.32 (br s, 1H), 8.19 (d, 1H, J = 7.8 Hz), 7.81 (t, 1H, J = 7.7 Hz), 7.40-7.37 (m, 1H), 6.15 (d, 1H, J = 2.7 Hz), 5.87 (s, 1H), 4.58 (d, 2H, J = 5.8 Hz), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 152.0, 149.7, 149.3, 148.1, 137.3, 126.2, 122.3, 108.4, 106.3, 36.5, 13.6; HRMS (ESI) calcd for $C_{12}H_{12}N_2NaO_2$ $[M+Na]^+$ 239.0796 found 239.0789.



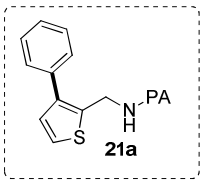
18

N-((3-(4-Acetylphenyl)thiophen-2-yl)methyl)picolinamide **(20a):** Following the general procedure described above **20a**was obtained after purification by column chromatography (EtOAc:Hexane = 60:40); as a brown colored solid (42 mg, 85%); mp: 112-114 °C**;** FT-IR (KBr): 3363, 3059, 1677, 1604, 1519, 1267, 749 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53-8.51 (m, 1H), 8.38 (br s, 1H), 8.22 (dt, 1H, J_1 = 7.8, J_2 =1.0 Hz), 8.02 (d, 2H, J = 8.5 Hz), 7.86 (td, 1H, J_1 = 7.8, J_2 = 1.7 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.45-7.42 (m, 1H), 7.31 (d, 1H, J = 5.2 Hz), 7.09 (d, 1H, J = 5.2 Hz), 4.88 (d, 2H, J = 5.8 Hz), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 164.1, 149.4, 148.2, 140.7, 139.2, 137.4, 136.9, 135.8, 129.0, 128.9, 128.8, 126.4, 124.6, 122.4, 37.1, 26.7; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_2S$ $[M+H]^+$ 337.1011 found 337.1005.



20a

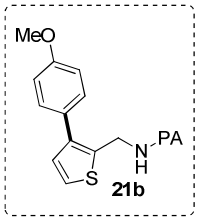
N-((3-Phenylthiophen-2-yl)methyl)picolinamide **(21a)**: Following the general procedure described above **21a**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (52 mg, 72%); FT-IR (DCM): 3390, 3020, 1674, 1520, 1265, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (br s, 1H), 8.60 (d, 1H, J = 4.3 Hz), 8.36 (d, 1H, J = 7.8 Hz), 8.02 (td, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.59-7.56 (m, 1H), 7.46-7.45 (m, 4H), 7.38-7.35 (m, 1H), 7.28 (d, 1H, J = 5.2 Hz), 7.08 (d, 1H, J = 5.2 Hz), 4.89 (d, 2H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ



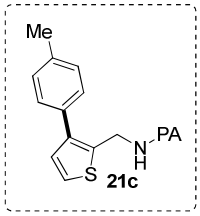
21a

162.8, 148.5, 146.7, 140.7, 139.1, 135.9, 135.3, 129.2, 128.9, 128.7, 127.3, 126.8, 124.2, 123.6, 37.3; HRMS (ESI) calcd for $C_{17}H_{14}N_2NaOS$ $[M+Na]^+$ 317.0725 found 317.0715.

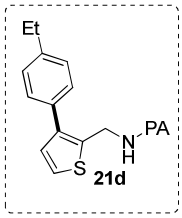
N-((3-(4-Methoxyphenyl)thiophen-2-yl)methyl)picolinamide **(21b):** Following the general procedure described above **21b**was obtained after purification by column chromatography (EtOAc:Hexane = 40:60); as a brown colored solid (56 mg, 69%); mp: 65-67 ^oC; FT-IR (KBr): 3379, 3057, 1674, 1506, 1247, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, 1H, J = 4.7 Hz), 8.39 (br s, 1H), 8.24 (dt, 1H, J_1 = 7.8, J_2 = 0.9 Hz), 7.85 (td, 1H, J_1 = 7.8, J_2 = 1.6 Hz), 7.43-7.40 (m, 1H), 7.36 (d, 2H, J = 8.8 Hz), 7.26 (d, 1H, J = 5.2 Hz), 7.05 (d, 1H, J = 5.2 Hz), 6.98 (d, 2H, J = 8.8 Hz), 4.87 (d, 2H, J = 5.8 Hz), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 158.9, 149.6, 148.2, 140.2, 137.4, 134.8, 129.9, 129.3, 128.4, 126.3, 124.0, 122.4, 114.1, 55.3, 37.2; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_2S$ $[M+Na]^+$ 347.0830 found 347.0817.



N-((3-(p-Tolyl)thiophen-2-yl)methyl)picolinamide **(21c)**: Following the general procedure described above **21c**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (53 mg, 69%); FT-IR (DCM): 3381, 3055, 1673, 1515, 1288, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54-8.52 (m, 1H), 8.40 (br s, 1H), 8.25 (d, 1H, J = 7.8 Hz), 7.87 (dt, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.44-7.41 (m, 1H), 7.33 (d, 2H, J = 8.0 Hz), 7.28-7.25 (m, 3H), 7.07 (d, 1H, J = 5.2 Hz), 4.89 (d, 2H, J = 5.8 Hz), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.2, 140.6, 137.4, 137.1, 135.2, 133.0, 129.4, 129.3, 128.7, 126.3, 124.1, 122.4, 37.1, 21.3; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaOS$ $[M+Na]^+$ 331.0881 found 331.0875.

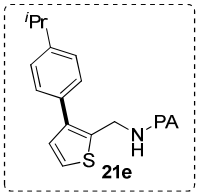


N-((3-(4-Ethylphenyl)thiophen-2-yl)methyl)picolinamide **(21d):** Following the general procedure described above **21d**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (58 mg, 72%); FT-IR (DCM): 3380, 2964, 1676, 1517, 1288, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, 1H, J = 4.5 Hz), 8.38 (br s, 1H), 8.25 (d, 1H, J = 7.8 Hz), 7.87 (td, 1H, J_1 = 7.7, J_2 = 1.4 Hz), 7.45-7.42 (m, 1H), 7.36 (d, 2H, J = 8.0 Hz), 7.30-7.28 (m, 3H), 7.09 (d, 1H, J = 5.1 Hz), 4.89 (d, 2H, J = 5.8 Hz), 2.71 (q, 2H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.1, 143.4, 140.6, 137.4, 135.2,



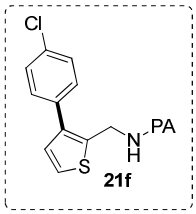
133.3, 129.3, 128.8, 128.2, 126.3, 124.0, 122.4, 37.2, 28.6, 15.6; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaOS$ $[M+Na]^+$ 345.1038 found 345.1025.

N-((3-(4-Isopropylphenyl)thiophen-2-yl)methyl)picolinamide **(21e):** Following the general procedure described above **21e**was obtained after purification by column chromatography



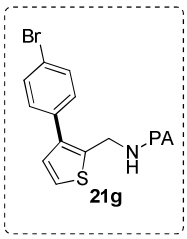
(EtOAc:Hexane = 30:70); as a yellowish brown colored semi solid (61 mg, 73%); FT-IR (DCM): 3386, 2954, 1675, 1517, 1290, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.38 (br s, 1H), 8.26-8.24 (m, 1H), 7.87 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 7.37 (d, 2H, J = 8.3 Hz), 7.31 (d, 2H, J = 8.3 Hz), 7.28 (d, 1H, J = 5.2 Hz), 7.09 (d, 1H, J = 5.2 Hz), 4.90 (d, 2H, J = 5.8 Hz), 3.00-2.93 (m, 1H), 1.31 (d, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.1, 148.0, 140.6, 137.4, 135.1, 133.4, 129.3, 128.7, 126.7, 126.3, 124.0, 122.4, 37.2, 33.9, 24.0; HRMS (ESI) calcd for $C_{20}H_{20}N_2NaOS$ $[M+Na]^+$ 359.1194 found 359.1182.

N-((3-(4-Chlorophenyl)thiophen-2-yl)methyl)picolinamide **(21f):**Following the general procedure described above **21f**was obtained after purification by column



chromatography (EtOAc:Hexane = 30:70); as a brown colored solid (64 mg, 78%); mp:92-94 ^oC; FT-IR (KBr): 3378, 3059, 1674, 1518, 1092, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56-8.54 (m, 1H), 8.36 (br s, 1H), 8.25 (dt, 1H, J_1 = 7.8, J_2 = 0.9 Hz), 7.88 (td, 1H, J_1 = 7.8, J_2 = 1.7 Hz), 7.47-7.44 (m, 1H), 7.42 (d, 2H, J = 8.6 Hz), 7.37 (d, 2H, J = 8.6 Hz), 7.30 (d, 1H, J = 5.2 Hz), 7.06 (d, 1H, J = 5.2 Hz), 4.86 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.5, 148.2, 139.2, 137.4, 136.0, 134.4, 133.3, 130.1, 129.1, 128.8, 126.4, 124.4, 122.4, 37.0; HRMS (ESI) calcd for $C_{17}H_{14}ClN_2OS$ $[M+H]^+$ 329.0515 found 329.0513.

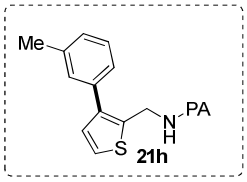
N-((3-(4-Bromophenyl)thiophen-2-yl)methyl)picolinamide **(21g):** Following the general procedure described above **21g**was obtained after purification by column



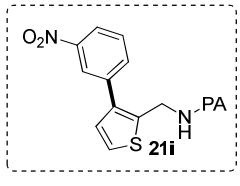
chromatography (EtOAc:Hexane = 30:70); as a grey colored solid (46 mg, 49%); mp: 97-99 ^oC; FT-IR (KBr): 3274, 3059, 1674, 1518, 1226, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, 1H, J = 4.4 Hz), 8.37 (br s, 1H), 8.24 (d, 1H, J = 7.8 Hz), 7.88 (td, 1H, J_1 = 7.8, J_2 = 1.7 Hz), 7.57 (d, 2H, J = 8.5 Hz), 7.47-7.43 (m, 1H), 7.31 (d, 2H, J = 8.5 Hz), 7.29 (d, 1H, J = 5.2 Hz), 7.05 (d, 1H, J = 5.2 Hz), 4.85 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.5, 148.2,

139.2, 137.4, 136.0, 134.9, 131.8, 130.4, 129.0, 126.4, 124.4, 122.4, 121.5, 37.1; HRMS (ESI) calcd for $C_{17}H_{13}BrN_2NaOS$ $[M+Na]^+$ 394.9830 found 394.9820.

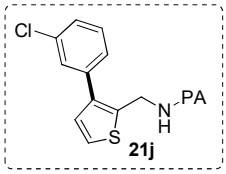
N-((3-(m-Tolyl)thiophen-2-yl)methyl)picolinamide **(21h)**:Following the general procedure described above **21h**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (54 mg, 70%); FT-IR (DCM): 3380, 3056, 1676, 1518, 1288, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, 1H, J = 4.4 Hz), 8.40 (br s, 1H), 8.25 (d, 1H, J = 7.8 Hz), 7.87 (t, 1H, J = 7.8 Hz), 7.45-7.42 (m, 1H), 7.34 (t, 1H, J = 7.5 Hz), 7.28 (d, 1H, J = 5.1 Hz), 7.24-7.23 (m, 2H), 7.18 (d, 1H, J = 7.5 Hz), 7.08 (d, 1H, J = 5.1 Hz), 4.90 (d, 2H, J = 5.8 Hz), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.2, 140.7, 138.3, 137.4, 135.9, 135.5, 129.6, 129.3, 128.5, 128.1, 126.3, 125.9, 124.0, 122.4, 37.1, 21.5; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaOS$ $[M+Na]^+$ 331.0881 found 331.0873.



N-((3-(3-Nitrophenyl)thiophen-2-yl)methyl)picolinamide **(21i):** Following the general procedure described above **21i**was obtained after purification by column chromatography (EtOAc:Hexane = 45:55); as a pale yellow colored solid (60 mg, 72%); mp: 117-119 ^oC; FT-IR (KBr): 3376, 3082, 1673, 1521, 1289,713 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, 1H, J = 4.7 Hz), 8.43 (br s, 1H), 8.29 (br s, 1H), 8.22-8.18 (m, 2H), 7.87 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.79 (d, 1H, J = 7.7 Hz), 7.62 (t, 1H, J = 8.0 Hz), 7.46-7.43 (m, 1H), 7.35 (d, 1H, J = 5.2 Hz), 7.11 (d, 1H, J = 5.2 Hz), 4.87 (d, 2H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.3, 148.4, 148.2, 137.8, 137.6, 137.5, 137.3, 134.8, 129.6, 128.9, 126.5, 124.9, 123.6, 122.4, 122.2, 37.0; HRMS (ESI) calcd for $C_{17}H_{13}N_3NaO_3S$ $[M+Na]^+$ 362.0575 found 362.0564.

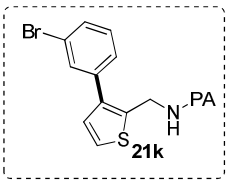


N-((3-(3-Chlorophenyl)thiophen-2-yl)methyl)picolinamide **(21j):** Following the general procedure described above **21j**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (50 mg, 61%); FT-IR (DCM): 3376, 3055, 1673, 1518, 1289, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.54 (m, 1H), 8.39 (br s, 1H), 8.24 (dt, 1H, J_1 = 7.8, J_2 = 0.9 Hz), 7.87 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.46-7.41 (m, 2H), 7.38-7.34 (m, 1H), 7.34-7.31 (m, 2H), 7.30 (d, 1H, J = 5.2 Hz), 7.06 (d, 1H, J = 5.2 Hz), 4.87 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.4, 148.1, 139.0, 137.7, 137.5, 136.4, 134.5,

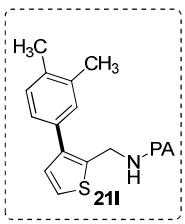


129.9, 129.0, 128.9, 127.5, 127.0, 126.4, 124.4, 122.5, 37.0; HRMS (ESI) calcd for $C_{17}H_{14}ClN_2OS$ $[M+H]^+$ 329.0515 found 329.0518.

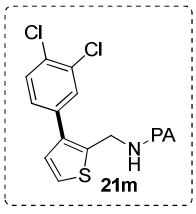
N-((3-(3-Bromophenyl)thiophen-2-yl)methyl)picolinamide **(21k):** Following the general procedure described above **21k**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (50 mg, 54%); FT-IR (DCM): 3385, 3055, 1677, 1518, 1265, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, 1H, J = 4.6 Hz), 8.38 (br s, 1H), 8.24 (d, 1H, J = 7.8 Hz), 7.89-7.85 (m, 1H), 7.58 (br s, 1H), 7.50-7.43 (m, 2H), 7.38-7.31 (m, 2H), 7.30 (d, 1H, J = 5.1 Hz), 7.05 (d, 1H, J = 5.1 Hz), 4.87 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.5, 148.2, 138.9, 138.0, 137.4, 136.5, 131.8, 130.4, 130.2, 129.0, 127.4, 126.4, 124.4, 122.7, 122.4, 37.0; HRMS (ESI) calcd for $C_{17}H_{13}BrN_2NaOS$ $[M+Na]^+$ 394.9830 found 394.9832.



N-((3-(3,4-Dimethylphenyl)thiophen-2-yl)methyl)picolinamide **(21l):**Following the general procedure described above **21l**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (65 mg, 81%); FT-IR (DCM): 3381, 2919, 1675, 1517, 1287, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.36 (br s, 1H), 8.25 (d, 1H, J = 7.8 Hz), 7.89-7.85 (m, 1H), 7.46-7.42 (m, 1H), 7.28 (d, 1H, J = 5.2 Hz), 7.23-7.16 (m, 3H), 7.07 (d, 1H, J = 5.2 Hz), 4.89 (d, 2H, J = 5.8 Hz), 2.33 (s, 3H), 2.32 (s, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.7, 148.1, 140.7, 137.3, 136.8, 135.8, 135.1, 133.5, 130.1, 129.9, 129.4, 126.3, 126.2, 123.9, 122.4, 37.1, 19.9, 19.5; HRMS (ESI) calcd for $C_{19}H_{19}N_2OS$ $[M+H]^+$ 323.1218 found 323.1226.

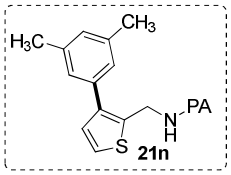


N-((3-(3,4-Dichlorophenyl)thiophen-2-yl)methyl)picolinamide **(21m):** Following the general procedure described above **21m**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a pale yellow colored solid (57 mg, 63%); mp: 108-110 ^oC; FT-IR (KBr): 3378, 3058, 1674, 1518, 1135, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.54 (m, 1H), 8.37 (br s, 1H), 8.23 (d, 1H, J = 7.8 Hz), 7.88 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.53-7.50 (m, 2H), 7.47-7.44 (m, 1H), 7.31 (d, 1H, J = 5.3 Hz), 7.29-7.27 (m, 1H), 7.04 (d, 1H, J = 5.3 Hz), 4.85 (d, 2H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.4, 148.2, 137.9, 137.4, 136.8, 135.9,

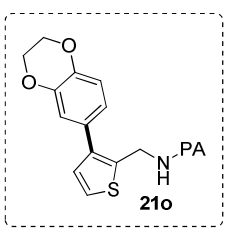


132.7, 131.5, 130.6, 130.6, 128.9, 128.1, 126.4, 124.6, 122.4, 37.0; HRMS (ESI) calcd for $C_{17}H_{13}Cl_2N_2OS$ $[M+H]^+$ 363.0126 found 363.0138.

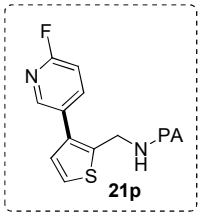
N-((3-(3,5-Dimethylphenyl)thiophen-2-yl)methyl)picolinamide **(21n)**: Following the general procedure described above **21n**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (58 mg, 73%); FT-IR (DCM): 3390, 3051, 1677, 1517, 1265, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.54 (m, 1H), 8.37 (br s, 1H), 8.25 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.87 (td, 1H, J_1 = 7.8, J_2 = 1.7 Hz), 7.46-7.42 (m, 1H), 7.27 (d, 1H, J = 5.1 Hz), 7.07 (d, 1H, J = 5.1 Hz), 7.04 (br s, 2H), 7.01 (br s, 1H), 4.90 (d, 2H, J = 5.8 Hz), 2.38 (br s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 149.6, 148.1, 140.8, 138.1, 137.4, 135.9, 135.3, 129.4, 129.0, 126.7, 126.3, 123.9, 122.4, 37.1, 21.4; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaOS$ $[M+Na]^+$ 345.1038 found 345.1046.



N-((3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)methyl)picolinamide **(21o):** Following the general procedure described above **21o**was obtained after purification by column chromatography (EtOAc:Hexane = 45:55); as a brown colored semi solid (65 mg, 74%); FT-IR (DCM): 3378, 3056, 1674, 1506, 1286, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.42 (d, 1H, J = 4.2 Hz), 8.27 (br s, 1H), 8.13 (d, 1H, J = 7.8 Hz), 7.75 (td, 1H, J_1 = 7.7, J_2 = 1.5 Hz), 7.34-7.31 (m, 1H), 7.15 (d, 1H, J = 5.2 Hz), 6.92 (d, 1H, J = 5.2 Hz), 6.84 (d, 1H, J = 1.8 Hz), 6.82-6.78 (m, 2H), 4.77 (d, 2H, J = 5.8 Hz), 4.19 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.6, 148.1, 143.5, 143.0, 140.0, 137.4, 135.1, 129.3, 129.2, 126.3, 124.0, 122.4, 122.0, 117.6, 117.4, 64.4, 64.4, 37.1; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_3S$ $[M+H]^+$ 353.0960 found 353.0951.

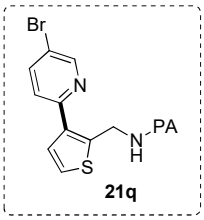


N-((3-(6-Fluoropyridin-3-yl)thiophen-2-yl)methyl)picolinamide **(21p):** Following the general procedure described above **21p**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown colored semi solid (31 mg, 40%); FT-IR (DCM): 3372, 3059, 1672, 1519, 1253, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.41 (br s, 1H), 8.30-8.29 (m, 1H), 8.22 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.92-7.86 (m, 2H), 7.48-7.44 (m, 1H), 7.35 (d, 1H, J = 5.2 Hz), 7.06 (d, 1H, J = 5.2 Hz), 7.04-7.01 (m, 1H), 4.83 (d, 2H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 162.8 (d, J_{C-F} = 238.5 Hz), 149.3, 148.2, 147.2 (d, J_{C-F} = 14.6 Hz), 141.4 (d,

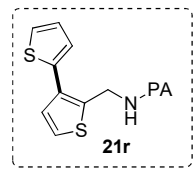


J_{C-F} = 7.8 Hz), 137.5, 137.2, 135.4, 129.8 (d, J_{C-F} = 4.3 Hz), 128.8, 126.5, 125.0, 122.4, 109.5 (d, J_{C-F} = 37.2 Hz), 36.9; HRMS (ESI) calcd for $C_{16}H_{13}FN_3OS$ $[M+H]^+$ 314.0763 found 314.0753.

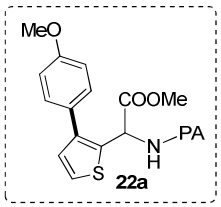
N-((3-(5-Bromopyridin-2-yl)thiophen-2-yl)methyl)picolinamide **(21q):** Following the general procedure described above **21q**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a colorless solid (32 mg, 35%); mp: 112-114 ^oC; FT-IR (KBr): 3390, 3054, 1671, 1515, 1265, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.34 (br s, 1H), 8.84 (s, 1H), 8.58-8.57 (m, 1H), 8.23 (d, 1H, J = 7.8 Hz), 7.90-7.82 (m, 2H), 7.50 (d, 1H, J = 8.5 Hz), 7.42-7.39 (m, 1H), 7.31-7.23 (m, 2H), 5.00 (d, 2H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 152.9, 150.5, 150.2, 148.3, 139.8, 139.5, 137.2, 136.9, 127.7, 126.1, 124.0, 123.4, 122.5, 118.6, 36.7; HRMS (ESI) calcd for $C_{16}H_{13}BrN_3OS$ $[M+H]^+$ 373.9963 found 373.9948.



N-([2,3'-Bithiophen]-2'-ylmethyl)picolinamide **(21r):** Following the general procedure described above **21r**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (56 mg, 75%); FT-IR (DCM): 3380, 3104, 1673, 1518, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, 1H, J = 4.7 Hz), 8.44 (br s, 1H), 8.25 (d, 1H, J = 7.8 Hz), 7.86 (t, 1H, J = 7.8 Hz), 7.43 (dd, 1H, J_1 = 7.6, J_2 = 4.8 Hz), 7.33 (d, 1H, J = 5.2 Hz), 7.25 (d, 1H, J = 5.2 Hz), 7.17 (d, 2H, J = 4.5 Hz), 7.10 (t, 1H, J = 4.5 Hz), 4.98 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.5, 148.2, 137.4, 137.4, 135.5, 132.6, 129.2, 127.7, 126.4, 125.7, 125.1, 124.2, 122.4, 37.2; HRMS (ESI) calcd for $C_{15}H_{12}N_2NaOS_2$ $[M+Na]^+$ 323.0289 found 323.0280.

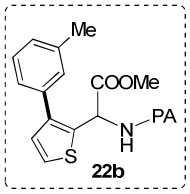


Methyl 2-(3-(4-methoxyphenyl)thiophen-2-yl)-2-(picolinamido)acetate **(22a):** Following the general procedure described above **22a**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown colored solid (28 mg, 30%); mp: 141-143 ^oC; FT-IR (KBr): 3383, 2950, 1746, 1681, 1506, 1248, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.79 (d, 1H, J = 6.4 Hz), 8.60 (d, 1H, J = 4.6 Hz), 8.16 (d, 1H, J = 7.8 Hz), 7.85 (td, 1H, J_1 = 7.7, J_2 = 1.1 Hz), 7.48 (d, 2H, J = 8.6 Hz), 7.46-7.44 (m, 1H), 7.35 (d, 1H, J = 5.2 Hz), 7.06 (d, 1H, J = 5.2 Hz), 7.00 (d, 2H, J = 8.6 Hz), 6.09 (d, 1H, J = 6.8 Hz), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 163.8, 159.2, 149.0, 148.3, 142.4, 137.3, 132.1, 130.1, 129.8, 127.9, 126.5, 125.0, 122.4,



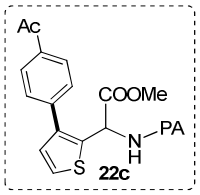
114.2, 55.3, 53.1, 51.2; HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_4S$ $[M+Na]^+$ 405.0885 found 405.0900.

Methyl 2-(picolinamido)-2-(3-(m-tolyl)thiophen-2-yl)acetate **(22b):** Following the general procedure described above **22b**was obtained after purification by column chromatography

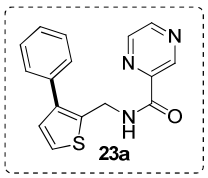


(EtOAc:Hexane = 35:65); as a pale yellow colored solid (28 mg, 31%); mp: 84-86 ^oC; FT-IR (KBr): 3381, 3056, 1746, 1679, 1505, 1265, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.79 (d, 1H, J = 6.6 Hz), 8.60-8.59 (m, 1H), 8.17 (d, 1H, J = 7.8 Hz), 7.85 (td, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.47-7.44 (m, 1H), 7.36-7.34 (m, 4H), 7.21-7.19 (m, 1H), 7.08 (d, 1H, J = 5.2 Hz), 6.10 (d, 1H, J = 6.8 Hz), 3.77 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 163.7, 149.0, 148.3, 142.8, 138.3, 137.3, 135.4, 132.6, 129.8, 128.6, 128.5, 126.5, 126.0, 125.1, 122.4, 53.0, 51.2, 21.5; HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_3S$ $[M+Na]^+$ 389.0936 found 389.0923.

Methyl 2-(3-(4-acetylphenyl)thiophen-2-yl)-2-(picolinamido)acetate **(22c):** Following the general procedure described above **22c**was obtained after purification by column chromatography (EtOAc:Hexane = 60:40); as a brown colored solid (50 mg, 57%); mp: 154-156 ^oC; FT-IR (KBr): 3377, 2954, 1746, 1681, 1505, 1268, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, 1H, J = 6.8 Hz), 8.61-8.59 (m, 1H), 8.14 (d, 1H, J = 7.7 Hz), 8.07 (d, 2H, J = 8.4 Hz), 7.85 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.69 (d, 2H, J = 8.4 Hz), 7.48-7.44 (m, 1H), 7.39 (d, 1H, J = 5.2 Hz), 7.09 (d, 1H, J = 5.2 Hz), 6.11 (d, 1H, J = 7.0 Hz), 3.77 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.8, 170.4, 163.8, 148.9, 148.4, 141.4, 140.4, 137.4, 136.1, 134.3, 129.3, 129.2, 128.8, 126.7, 125.5, 122.4, 53.2, 51.1, 26.7; HRMS (ESI) calcd for $C_{21}H_{19}N_2O_4S$ $[M+H]^+$ 395.1066 found 395.1076.



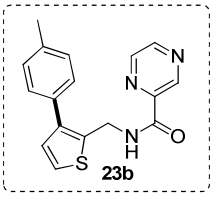
N-((3-Phenylthiophen-2-yl)methyl)pyrazine-2-carboxamide **(23a)**: Following the general procedure described above **23a**was obtained after purification by column chromatography



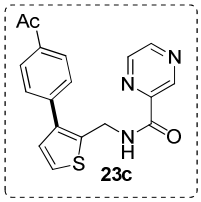
(EtOAc:Hexane = 55:45); as a brown colored semi solid (59 mg, 40%); FT-IR (DCM): 3391, 3059, 1678, 1522, 1265, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, 1H, J = 1.3 Hz), 8.76 (d, 1H, J = 2.4 Hz), 8.51-8.50 (m, 1H), 8.11 (br s, 1H), 7.47-7.34 (m, 5H), 7.30 (d, 1H, J = 5.1 Hz), 7.09 (d, 1H, J =

5.1 Hz), 4.90 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 147.4, 144.5, 144.2, 142.6, 140.8, 135.8, 134.9, 129.4, 128.8, 128.7, 127.5, 124.3, 37.1; HRMS (ESI) calcd for $C_{16}H_{14}N_3OS$ $[M+H]^+$ 296.0858 found 296.0870.

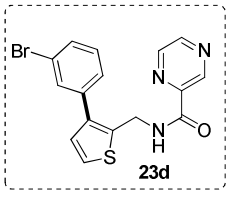
N-((3-(p-Tolyl)thiophen-2-yl)methyl)pyrazine-2-carboxamide **(23b):** Following the general procedure described above **23b**was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a colorless solid (38 mg, 25%); mp: 122-124 ^{o}C; FT-IR (KBr): 3386, 2922, 1674, 1506, 1198, 821cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, 1H, J = 1.4 Hz), 8.76 (d, 1H, J = 2.5 Hz), 8.51 (dd, 1H, J_1 = 2.5, J_2 = 1.4 Hz), 8.11 (br s, 1H), 7.32-7.25 (m, 5H), 7.08 (d, 1H, J = 5.2 Hz), 4.89 (d, 2H, J = 5.8 Hz), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 147.4, 144.5, 144.2, 143.0, 140.9, 137.2, 134.4, 132.9, 129.4, 129.4, 128.6, 124.2, 37.1, 21.2; HRMS (ESI) calcd for $C_{17}H_{16}N_3OS$ $[M+H]^+$ 310.1014 found 310.1021.



N-((3-(4-Acetylphenyl)thiophen-2-yl)methyl)pyrazine-2-carboxamide **(23c):** Following the general procedure described above **23c**was obtained after purification by column chromatography (EtOAc:Hexane = 80:20); as a brown colored solid (37 mg, 55%); mp: 150-152 ^{o}C; FT-IR (KBr): 3390, 3055, 1673, 1523, 1265, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.44 (d, 1H, J = 1.5 Hz), 8.77 (d, 1H, J = 2.4 Hz), 8.52 (dd, 1H, J_1 = 2.4, J_2 = 1.5 Hz), 8.15 (br s, 1H), 8.04 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.34 (d, 1H, J = 5.2 Hz), 7.11 (d, 1H, J = 5.2 Hz), 4.90 (d, 2H, J = 5.8 Hz), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 162.7, 147.5, 144.5, 144.0, 142.6, 140.6, 139.5, 136.2, 135.9, 129.1, 128.9, 128.8, 124.8, 37.1, 26.7; HRMS (ESI) calcd for $C_{18}H_{15}N_3NaO_2S$ $[M+Na]^+$ 360.0783 found 360.0793.

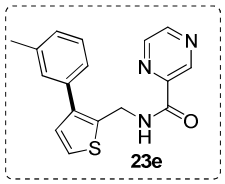


N-((3-(3-Bromophenyl)thiophen-2-yl)methyl)pyrazine-2-carboxamide **(23d):** Following the general procedure described above **23d**was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a brown colored semi solid (37 mg, 20%); FT-IR (DCM): 3311, 2924, 1675, 1520, 1265, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, 1H, J = 1.3 Hz), 8.78 (d, 1H, J = 2.3 Hz), 8.53 (dd, 1H, J_1 = 2.3, J_2 =1.6 Hz), 8.10 (br s, 1H), 7.56-7.55 (m, 1H), 7.50 (dt, 1H, J_1 = 7.5, J_2 = 1.6 Hz), 7.36-7.30 (m, 3H), 7.06 (d, 1H, J = 5.2 Hz), 4.88 (d, 2H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 147.5, 144.5, 144.1, 142.6, 139.2, 137.9, 135.7,

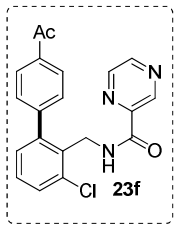


131.8, 130.5, 130.2, 129.1, 127.4, 124.6, 122.7, 37.0; HRMS (ESI) calcd for $C_{16}H_{13}BrN_3OS$ $[M+H]^+$ 373.9963 found 373.9960.

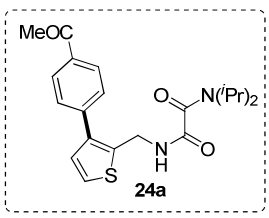
N-((3-(m-Tolyl)thiophen-2-yl)methyl)pyrazine-2-carboxamide **(23e):** Following the general procedure described above **23e**was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a brown colored solid (63 mg, 41%); mp: 69-71 ^oC; FT-IR (KBr): 3360, 3053, 1675, 1522, 1020, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, 1H, J = 1.5 Hz), 8.75 (d, 1H, J = 2.2 Hz), 8.51-8.50 (m, 1H), 8.11 (br s, 1H), 7.33 (t, 1H, J = 7.4 Hz), 7.29 (d, 1H, J = 5.4 Hz), 7.22-7.16 (m, 3H), 7.08 (d, 1H, J = 5.4 Hz), 4.89 (d, 2H, J = 5.8 Hz), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 147.4, 144.5, 144.2, 142.6, 141.0, 138.3, 135.8, 134.7, 129.5, 129.4, 128.6, 128.2, 125.8, 124.2, 37.1, 21.5; HRMS (ESI) calcd for $C_{17}H_{16}N_3OS$ $[M+H]^+$ 310.1014 found 310.1000.



N-((4'-Acetyl-3-chloro-[1,1'-biphenyl]-2-yl)methyl)pyrazine-2-carboxamide **(23f):** Following the general procedure described above **23f**was obtained after purification by column chromatography (EtOAc:Hexane = 80:20); as a brown colored solid (44 mg, 24%); mp: 114-116 ^oC; FT-IR (KBr): 3397, 2928, 1682, 1522, 1266, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.37 (d, 1H, J = 1.3 Hz), 8.75 (d, 1H, J = 2.4 Hz), 8.51 (dd, 1H, J_1 = 2.2, J_2 = 1.6 Hz), 8.03 (d, 2H, J = 8.2 Hz), 7.51 (dd, 1H, J_1 = 8.0, J_2 = 1.3 Hz), 7.44 (d, 2H, J = 8.2 Hz), 7.36 (t, 1H, J = 8.0 Hz), 7.23 (dd, 1H, J_1 = 7.6, J_2 = 1.2 Hz), 4.70 (d, 2H, J = 5.4 Hz), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 162.2, 147.3, 144.8, 144.4, 144.3, 144.0, 142.6, 136.4, 136.0, 132.4, 129.7, 129.4, 129.1, 128.9, 128.5, 39.4, 26.8; HRMS (ESI) calcd for $C_{20}H_{16}ClN_3NaO_2$ $[M+Na]^+$ 388.0829 found 388.0819.

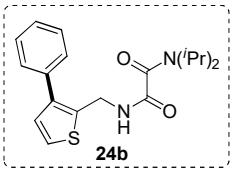


N^1-((3-(4-Acetylphenyl)thiophen-2-yl)methyl)-N^2,N^2-diisopropyloxalamide **(24a):** Following the general procedure described above **24a**was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as a brown colored solid (66 mg, 69%); mp: 120-122 ^oC; FT-IR (KBr): 3276, 2974, 1679, 1633, 1447, 1266, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, 2H, J = 8.3 Hz), 7.62 (br s, 1H), 7.48 (d, 2H, J = 8.3 Hz), 7.29 (d, 1H, J = 5.2 Hz), 7.06 (d, 1H, J = 5.2 Hz), 4.67-4.62 (m, 1H), 4.66 (d, 2H, J = 5.8 Hz), 3.54-3.47 (m, 1H), 2.63 (s, 3H), 1.39 (d, 6H, J = 6.8 Hz), 1.23 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$,

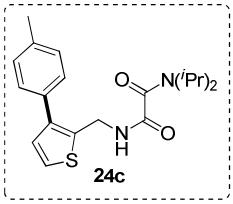


100 MHz): δ 197.8, 163.0, 162.9, 140.6, 139.4, 136.1, 135.8, 129.0, 128.9, 128.7, 124.7, 49.8, 46.5, 36.8, 26.7, 20.9, 20.0; HRMS (ESI) calcd for $C_{21}H_{26}N_2NaO_3S$ $[M+Na]^+$ 409.1562 found 409.1544.

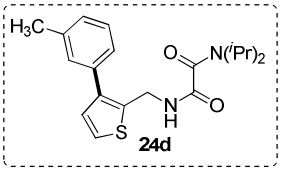
N^1,N^1-Diisopropyl-N^2-((3-phenylthiophen-2-yl)methyl)oxalamide **(24b):** Following the general procedure described above **24b**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (870 mg, 70%); FT-IR (DCM): 3272, 2972, 1673, 1624, 1448, 1257, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.19 (m, 6H), 7.06 (d, 1H, J = 5.2 Hz), 4.76-4.56 (m, 1H), 4.68 (d, 2H, J = 5.8 Hz), 3.56-3.49 (m, 1H), 1.43 (d, 6H, J = 6.8 Hz), 1.25 (d, 6H, J = 6.7 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 162.7, 140.8, 135.8, 134.5, 130.2, 129.3, 128.7, 128.7, 127.4, 124.3, 49.7, 46.6, 36.8, 20.9, 20.1; HRMS (ESI) calcd for $C_{19}H_{24}N_2NaO_2S$ $[M+Na]^+$ 367.1456 found 367.1442.



N^1,N^1-Diisopropyl-N^2-((3-(p-tolyl)thiophen-2-yl)methyl)oxalamide **(24c):** Following the general procedure described above **24c**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (57 mg, 64%); FT-IR (DCM): 3273, 2971, 1675, 1624, 1447, 1254, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.23 (m, 5H), 7.05 (d, 1H, J = 5.2 Hz), 4.77-4.70 (m, 1H), 4.67 (d, 2H, J = 5.8 Hz), 3.56-3.49 (m, 1H), 2.40 (s, 3H), 1.43 (d, 6H, J = 6.8 Hz), 1.25 (d, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 162.7, 140.8, 137.2, 134.1, 132.8, 129.4, 128.6, 124.2, 49.7, 46.6, 36.8, 21.2, 20.9, 20.1; HRMS (ESI) calcd for $C_{20}H_{26}N_2NaO_2S$ $[M+Na]^+$ 381.1613 found 381.1602.

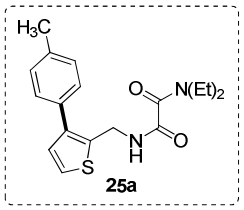


N^1,N^1-Diisopropyl-N^2-((3-(m-tolyl)thiophen-2-yl)methyl)oxalamide **(24d):** Following the general procedure described above **24d**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (62 mg, 70%); FT-IR (DCM): 3271, 2968, 1673, 1623, 1448, 1256, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (t, 1H, J = 7.2 Hz), 7.27 (d, 1H, J = 5.2 Hz), 7.18 (br s, 2H), 7.16 (br s, 1H), 7.05 (d, 1H, J = 5.2 Hz), 4.76-4.71 (m, 1H), 4.69 (d, 2H, J = 5.8 Hz), 3.56-3.49 (m, 1H), 2.41 (s, 3H), 1.43 (d,

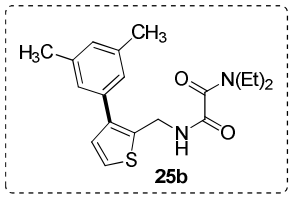


6H, *J* = 6.8 Hz), 1.25 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 162.7, 141.0, 138.3, 135.7, 134.3, 129.5, 129.4, 128.5, 128.2, 125.8, 124.2, 49.7, 46.6, 36.8, 21.5, 20.9, 20.1; HRMS (ESI) calcd for $C_{20}H_{26}N_2NaO_2S$ $[M+Na]^+$ 381.1613 found 381.1600.

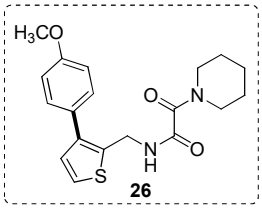
N^1,N^1-Diethyl-N^2-((3-(p-tolyl)thiophen-2-yl)methyl)oxalamide **(25a):** Following the general procedure described above **25a**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored solid (66 mg, 75%); mp: 104-106 ^{o}C; FT-IR (KBr): 3287, 2976, 1680, 1630, 1507, 1245, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (br s, 1H), 7.28-7.23 (m, 5H), 7.04 (d, 1H, *J* = 5.2 Hz), 4.67 (d, 2H, *J* = 5.8 Hz), 3.78 (q, 2H, *J* = 7.0 Hz), 3.41 (q, 2H, *J* = 7.0 Hz), 2.41 (s, 3H), 1.29 (t, 3H, *J* = 7.0 Hz), 1.18 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 161.0, 140.8, 137.2, 134.1, 132.9, 129.4, 129.4, 128.6, 124.2, 43.3, 42.1, 36.8, 21.2, 14.8, 12.5; HRMS (ESI) calcd for $C_{18}H_{22}N_2NaO_2S$ $[M+Na]^+$ 353.1300 found 353.1290.



N^1-((3-(3,5-Dimethylphenyl)thiophen-2-yl)methyl)-N^2,N^2-diethyloxalamide**(25b)**: Following the general procedure described above **25b**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (49 mg, 57%); FT-IR (DCM): 3281, 2931, 1679, 1629, 1460, 1245, 732 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (br s, 1H), 7.27 (d, 1H, *J* = 5.2 Hz), 7.04 (d, 1H, *J* = 5.2 Hz), 7.01 (br s, 1H), 6.98 (br s, 2H), 4.69 (d, 2H, *J* = 5.8 Hz), 3.78 (q, 2H, *J* = 7.0 Hz), 3.42 (q, 2H, *J* = 7.0 Hz), 2.37 (s, 6H), 1.30 (t, 3H, *J* = 7.0 Hz), 1.19 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 161.0, 141.1, 138.2, 135.7, 134.2, 129.4, 129.1, 126.6, 124.1, 43.3, 42.1, 36.8, 21.4, 14.8, 12.5; HRMS (ESI) calcd for $C_{19}H_{24}N_2NaO_2S$ $[M+Na]^+$ 367.1456 found 367.1444.

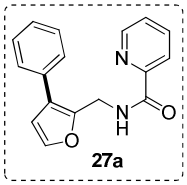


N-((3-(4-Methoxyphenyl)thiophen-2-yl)methyl)-2-oxo-2-(piperidin-1-yl)acetamide **(26):** Following the general procedure described above **26**was obtained after purification by column chromatography (EtOAc:Hexane = 65:35); as a colorless solid (67 mg, 75%); mp: 141-143 ^{o}C; FT-IR (KBr): 3296, 2938, 1678, 1631, 1506, 1247, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (br s, 1H), 7.30 (d, 2H, *J* = 8.7 Hz), 7.26 (d, 1H, *J* = 5.2 Hz), 7.03 (d, 1H, *J* = 5.2 Hz), 6.97 (d, 2H, *J* = 8.7 Hz), 4.66 (d, 2H, *J* = 5.8 Hz), 3.96-3.93 (m, 2H), 3.86 (s, 3H), 3.58-3.56 (m, 2H), 1.68-1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 160.8, 159.0, 140.6,



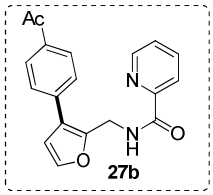
133.6, 129.8, 129.4, 128.2, 124.1, 114.1, 55.4, 47.4, 44.3, 36.9, 26.8, 25.7, 24.5; HRMS (ESI) calcd for $C_{19}H_{22}N_2NaO_3S$ $[M+Na]^+$ 381.1249 found 381.1236.

N-((3-Phenylfuran-2-yl)methyl)picolinamide **(27a):** Following the general procedure described above **27a**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70);



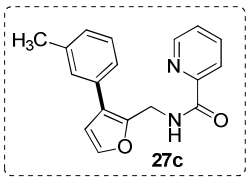
as a green colored solid (50 mg, 36%); mp: 85-87 °C**;** FT-IR (KBr): 3391, 3055, 1677, 1521, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57-8.55 (m, 1H), 8.39 (br s, 1H), 8.25 (dt, 1H, J_1 = 7.8, J_2 =1.0 Hz), 7.87 (td, 1H, J_1 = 7.7, J_2 =1.7 Hz), 7.50-7.42 (m, 6H), 7.34-7.30 (m, 1H), 6.58 (d, 1H, J = 1.8 Hz), 4.84 (d, 2H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 149.7, 148.1, 146.1, 142.1, 137.4, 132.9, 128.8, 128.0, 127.1, 126.3, 123.8, 122.4, 111.6, 35.6; HRMS (ESI) calcd for $C_{17}H_{14}N_2NaO_2$ $[M+Na]^+$ 301.0953 found 301.0947.

N-((3-(4-Acetylphenyl)furan-2-yl)methyl)picolinamide **(27b):** Following the general procedure



described above **27b**was obtained after purification by column chromatography (EtOAc:Hexane = 60:40); as a dark brown colored solid (48 mg, 32%); mp: compound decomposed after 50 ^oC; FT-IR (KBr): 3363, 3059, 1679, 1523, 1270, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56-8.55 (m, 1H), 8.44 (br s, 1H), 8.24 (d, 1H, J = 7.7 Hz), 8.02 (d, 2H, J = 8.3 Hz), 7.88 (td, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.60 (d, 2H, J = 8.3 Hz), 7.48 (d, 1H, J = 1.8 Hz), 7.47-7.43 (m, 1H), 6.61 (d, 1H, J = 1.8 Hz), 4.85 (d, 2H, J = 5.7 Hz), 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 164.2, 149.5, 148.2, 147.1, 142.5, 137.8, 137.4, 135.6, 128.9, 127.9, 126.4, 122.8, 122.4, 111.3, 35.7, 26.7; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ 321.1239 found 321.1233.

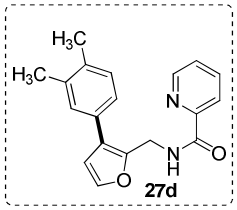
N-((3-(m-Tolyl)furan-2-yl)methyl)picolinamide **(27c):** Following the general procedure



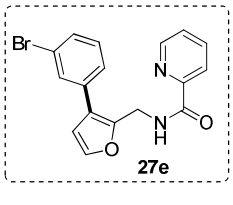
described above **27c**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a green colored solid (52 mg, 36%); mp: 74-76 °C**;** FT-IR (KBr): 3386, 2924, 1676, 1521, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56-8.54 (m, 1H), 8.37 (br s, 1H), 8.26 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.87 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.46 (d, 1H, J = 1.8 Hz*)*, 7.44-7.42 (m, 1H), 7.35-7.28 (m, 3H), 7.14 (d, 1H, J = 7.2 Hz), 6.57 (d, 1H, J = 1.9 Hz*),* 4.84 (d, 2H, J = 5.6 Hz), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.7, 148.1, 146.1, 142.0, 138.4,

137.4, 132.8, 128.7, 127.9, 126.3, 125.0, 123.9, 122.4, 111.6, 35.6, 21.5; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_2$ $[M+Na]^+$ 315.1109 found 315.1117.

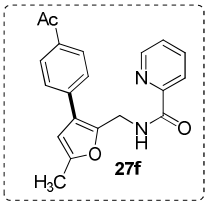
N-((3-(3,4-Dimethylphenyl)furan-2-yl)methyl)picolinamide **(27d):** Following the general procedure described above **27d**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a dark green colored semi solid (46 mg, 30%); FT-IR (DCM): 3360, 3021, 1670, 1524, 1110, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56-8.55 (m, 1H), 8.36 (br s, 1H), 8.25 (d, 1H, J = 7.8 Hz), 7.87 (td, 1H, J_1 = 7.7, J_2 = 1.8 Hz), 7.46-7.43 (m, 2H), 7.24 (br s, 1H), 7.21-7.20 (m, 2H), 6.56 (d, 1H, J = 1.9 Hz), 4.83 (d, 2H, J = 5.6 Hz), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 149.7, 148.1, 145.8, 142.0, 137.4, 137.0, 135.6, 130.4, 130.1, 129.2, 126.3, 125.3, 123.8, 122.4, 111.7, 35.6, 19.9, 19.5; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_2$ $[M+Na]^+$ 329.1266 found 329.1251.



N-((3-(3-Bromophenyl)furan-2-yl)methyl)picolinamide **(27e):** Following the general procedure described above **27e** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a dark green colored semi solid (39 mg, 22%); FT-IR (DCM): 3382, 3063, 1674, 1522, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57-8.55 (m, 1H), 8.39 (br s, 1H), 8.25 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.88 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.62 (t, 1H, J = 1.8 Hz), 7.47-7.43 (m, 4H), 7.31 (d, 1H, J = 7.6 Hz), 6.55 (d, 1H, J = 1.9 Hz), 4.82 (d, 2H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 149.6, 148.1, 146.7, 142.3, 137.4, 135.1, 130.9, 130.3, 130.1, 126.6, 126.4, 122.8, 122.5, 122.4, 111.4, 35.5; HRMS (ESI) calcd for $C_{17}H_{13}BrN_2NaO_2$ $[M+Na]^+$ 379.0058 found 379.0051.

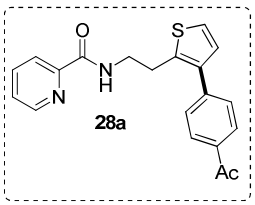


N-((3-(4-Acetylphenyl)-5-methylfuran-2-yl)methyl)picolinamide **(27f):** Following the general procedure described above **27f** was obtained after purification by column chromatography (EtOAc:Hexane = 65:35); as a dark green colored semi solid (42 mg, 25%); FT-IR (DCM): 3382, 3056, 1676, 1605, 1267, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57-8.56 (m, 1H), 8.38 (br s, 1H), 8.25 (dt, 1H, J_1 = 7.8, J_2 = 1.8 Hz), 8.01 (d, 2H, J = 8.5 Hz), 7.88 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.57 (d, 2H, J = 8.5 Hz), 7.47-7.44 (m, 1H), 6.21 (s, 1H), 4.79 (d, 2H, J = 5.6 Hz), 2.62 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 164.1, 152.3, 149.6, 148.1, 145.2, 138.2, 137.4, 135.4,

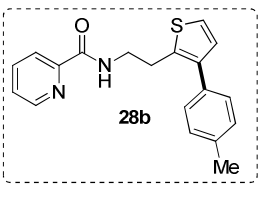


128.9, 127.8, 126.4, 123.7, 122.4, 107.2, 35.8, 26.6, 13.6; HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_3$ $[M+Na]^+$ 357.1215 found 357.1225.

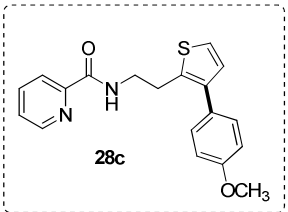
N-(2-(3-(4-Acetylphenyl)thiophen-2-yl)ethyl)picolinamide **(28a):** Following the general procedure described above **28a** was obtained after purification by column chromatography (EtOAc:Hexane = 60:40); as a brown colored semi solid (41 mg, 47%); FT-IR (DCM): 3380, 3055, 1676, 1603, 1524, 1269, 748 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, 1H, J = 4.9 Hz), 8.18 (br s, 1H), 8.13 (d, 1H, J = 7.8 Hz), 7.94 (d, 2H, J = 8.2 Hz), 7.83 (td, 1H, J_1 = 7.8, J_2 = 1.4 Hz), 7.46 (d, 2H, J = 8.2 Hz), 7.44-7.41 (m, 1H), 7.25 (d, 1H, J = 5.4 Hz), 7.06 (d, 1H, J = 5.4 Hz), 3.72 (q, 2H, J = 6.8 Hz), 3.25 (t, 2H, J = 6.8 Hz), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 164.3, 149.6, 148.0, 141.4, 138.8, 137.4, 137.3, 135.5, 129.2, 128.9, 128.6, 126.2, 123.3, 122.2, 41.1, 28.5, 26.7; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_2S$ $[M+H]^+$ 351.1167 found 351.1176.



N-(2-(3-(p-Tolyl)thiophen-2-yl)ethyl)picolinamide **(28b):** Following the general procedure described above **28b** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored semi solid (38 mg, 48%); FT-IR (DCM): 3378, 3055, 1674, 1524, 1244, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54-8.53 (m, 1H), 8.19-8.17 (m, 2H), 7.84 (td, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.44-7.41 (m, 1H), 7.28 (d, 2H, J = 8.0 Hz), 7.21 (d, 1H, J = 5.2 Hz), 7.19 (d, 2H, J = 8.0 Hz), 7.04 (d, 1H, J = 5.2 Hz), 3.73 (q, 2H, J = 7.0 Hz), 3.23 (t, 2H, J = 7.0 Hz), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 149.8, 148.0, 140.0, 137.3, 136.6, 135.7, 133.7, 129.6, 129.2, 128.7, 126.1, 122.6, 122.2, 41.0, 28.5, 21.2; HRMS (ESI) calcd for $C_{19}H_{19}N_2OS$ $[M+H]^+$ 323.1218 found 323.1223.

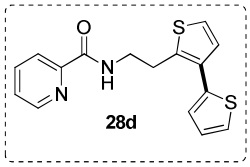


N-(2-(3-(4-Methoxyphenyl)thiophen-2-yl)ethyl)picolinamide **(28c):** Following the general procedure described above **28c** was obtained after purification by column chromatography (EtOAc:Hexane = 40:60); as a brown colored semi solid (34 mg, 41%); FT-IR (DCM): 3384, 3055, 1674, 1526, 1246, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, 1H, J = 4.6 Hz), 8.18 (d, 1H, J = 7.8 Hz), 8.18 (br s, 1H), 7.86 (td, 1H, J_1 = 7.8, J_2 = 1.7 Hz), 7.45-7.42 (m, 1H), 7.30 (d, 2H, J = 8.8 Hz), 7.21 (d, 1H, J = 5.1 Hz), 7.02 (d, 1H, J = 5.1 Hz), 6.91 (d, 2H, J = 8.8 Hz), 3.83 (s, 3H), 3.73 (q, 2H, J = 7.0 Hz), 3.22 (t, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 158.6,



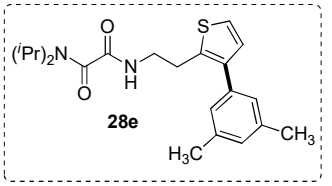
149.8, 148.0, 139.6, 137.3, 135.4, 129.9, 129.6, 129.0, 126.2, 122.6, 122.2, 113.9, 55.3, 41.0, 28.5; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2S$ $[M+H]^+$ 339.1167 found 339.1178.

N-(2-([2,3'-Bithiophen]-2'-yl)ethyl)picolinamide **(28d):**Following the general procedure described above **28d** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a dark green colored semi solid (55 mg, 71%); FT-IR (DCM): 3380, 3010, 1673, 1526, 1216, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.28 (br s, 1H), 8.21 (d, 1H, J = 7.7 Hz), 7.86 (td, 1H, J_1 = 7.7, J_2 = 1.4 Hz), 7.45-7.42 (m, 1H), 7.28 (d, 1H, J = 4.4 Hz), 7.19 (d, 1H, J = 5.2 Hz), 7.15 (d, 2H, J = 5.0 Hz), 7.07 (dd, 1H, J_1 = 5.0, J_2 = 3.6 Hz), 3.80 (q, 2H, J = 6.8 Hz), 3.34 (t, 2H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4, 149.7, 148.1, 138.0, 137.3, 136.3, 132.0, 129.4, 127.5, 126.2, 125.4, 124.7, 122.9, 122.2, 40.6, 28.9; HRMS (ESI) calcd for $C_{16}H_{15}N_2OS_2$ $[M+H]^+$ 315.0626 found 315.0634.

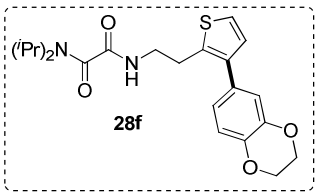


N^1-(2-(3-(3,5-Dimethylphenyl)thiophen-2-yl)ethyl)-N^2,N^2-diisopropyloxalamide

(28e): Following the general procedure described above **28e** was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown colored semi solid (48 mg, 50%); FT-IR (DCM): 3286, 2971, 1675, 1624, 1447, 1253, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, 1H, J = 5.2 Hz), 7.04-6.99 (m, 5H), 4.74-4.68 (m, 1H), 3.57-3.48 (m, 3H), 3.13 (t, 2H, J = 7.0 Hz), 2.37 (br s, 6H), 1.43 (d, 6H, J = 6.8 Hz), 1.22 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 162.9, 140.3, 138.1, 136.4, 135.3, 129.7, 128.8, 126.7, 122.6, 49.6, 46.5, 40.7, 28.1, 21.4, 20.9, 20.1; HRMS (ESI) calcd for $C_{22}H_{30}N_2NaO_2S$ $[M+Na]^+$ 409.1926 found 409.1918.

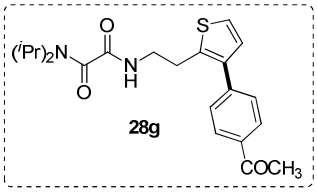


N^1-(2-(3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)ethyl)-N^2,N^2-diisopropyloxalamide **(28f):** Following the general procedure described above **28f** was obtained after purification by column chromatography (EtOAc:Hexane = 40:60); as a brown colored semi solid (67 mg, 65%); FT-IR (DCM): 3303, 2974, 1670, 1627, 1503, 1245, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, 1H, J = 5.2 Hz), 6.99 (d, 1H, J = 5.2 Hz), 6.97 (br s, 1H), 6.91 (d, 1H, J = 8.2 Hz),6.87-6.82 (m, 2H), 4.75-4.68 (m, 1H), 4.31 (s, 4H), 3.55-3.48 (m, 3H), 3.13 (t, 2H, J = 7.0 Hz), 1.43 (d, 6H, J = 6.8 Hz), 1.22 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$,



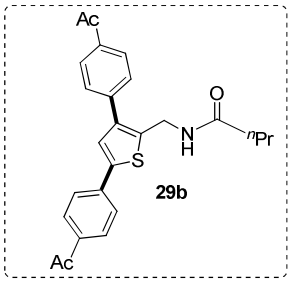
100 MHz): δ 163.2, 162.9, 143.4, 142.8, 139.4, 135.1, 129.8, 129.6, 122.6, 121.9, 117.5, 117.3, 64.4, 64.4, 49.6, 46.5, 40.6, 28.0, 20.9, 20.0; HRMS (ESI) calcd for $C_{22}H_{28}N_2NaO_4S$ $[M+Na]^+$ 439.1667 found 439.1654.

N^1-(2-(3-(4-Acetylphenyl)thiophen-2-yl)ethyl)-N^2,N^2-diisopropyloxalamide **(28g):** Following

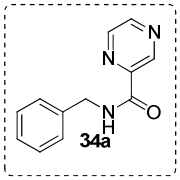


the general procedure described above **28g** was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as a brown colored solid (62 mg, 62%); mp: 94-96 ^oC; FT-IR (KBr): 3416, 3055, 1681, 1635, 1422, 1265, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, 2H, J = 8.3 Hz), 7.47 (d, 2H, J = 8.3 Hz), 7.24 (d, 1H, J = 5.2 Hz), 7.05 (d, 1H, J = 5.2 Hz), 4.68-4.61 (m, 1H), 3.56-3.48 (m, 3H), 3.15 (t, 2H, J = 7.1 Hz), 2.64 (s, 3H), 1.40 (d, 6H, J = 6.8 Hz), 1.21 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 163.2, 162.9, 141.3, 138.8, 136.8, 135.6, 129.2, 128.9, 128.7, 123.3, 49.6, 46.5, 40.6, 28.2, 26.7, 20.8, 20.0; HRMS (ESI) calcd for $C_{22}H_{28}N_2NaO_3S$ $[M+Na]^+$ 423.1718 found 423.1706.

N-((3,5-Bis(4-acetylphenyl)thiophen-2-yl)methyl)butyramide **(29b):** Following the general procedure described above **29b** was obtained after purification by column chromatography



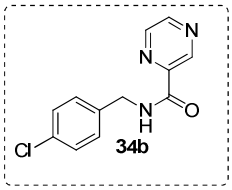
(EtOAc:Hexane = 80:20); as a brown colored solid (23 mg, 22%); FT-IR (KBr): 3326, 2926, 1679, 1602, 1268, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, 2H, J = 8.3 Hz), 7.85 (d, 2H, J = 8.3 Hz), 7.33 (d, 4H, J = 8.2 Hz), 7.07 (br s, 1H), 4.66 (d, 2H, J = 5.8 Hz), 2.61 (s, 3H), 2.60 (s, 3H), 2.25 (t, 2H, J = 7.4 Hz), 1.76-1.70 (m, 3H), 0.99 (t, 3H, J = 7.4 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 197.5, 173.0, 142.0, 140.8, 138.6, 138.0, 137.6, 136.0, 135.8, 129.2, 129.2, 129.0, 128.7, 128.7, 38.5, 38.3, 26.7, 19.1, 13.8; HRMS (ESI) calcd for $C_{25}H_{25}NNaO_3S$ $[M+Na]^+$ 442.1453 found 442.1449. The purity of this sample is about 95% and our trials to improve the purity of this sample were not fruitful as the compound **29b** was isolated from a complex mixture.



N-Benzylpyrazine-2-carboxamide **(34a):** Following the general procedure described above **34a** was obtained after purification by column chromatography (EtOAc:Hexane = 50:50); as a colorless solid (299 mg, 47%); mp: 117-119 °C; FT-IR (KBr): 3378, 2933, 1670, 1524, 1026 and 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.47 (d, 1H, J = 1.0 Hz), 8.77 (d, 1H, J = 2.3 Hz), 8.52 (br. s, 1H), 8.15 (br. s, 1H),

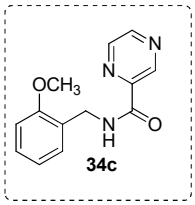
7.39-7.31 (m, 5H), 4.70 (d, 2H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 147.4, 144.6, 144.4, 142.6, 137.7, 128.8, 127.9, 127.7, 43.5; HRMS (ESI) calcd for $C_{12}H_{12}N_3O$ $[M+H]^+$ 214.0980 found 214.0972.

N-(4-Chlorobenzyl)pyrazine-2-carboxamide **(34b):** Following the general procedure described above **34b** was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a colorless solid (504 mg, 68%); mp: 138-140 °C; FT-IR (KBr): 3361, 2939, 1661, 1528, 1025 and 797 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.45 (br. s, 1H), 8.78 (d, 1H, J = 2.4 Hz), 8.53 (d, 1H, J = 1.5 Hz), 8.16 (br. s, 1H), 7.35-7.28 (m, 4H), 4.66 (d, 2H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 147.5, 144.6, 144.2, 142.6, 136.3, 133.5, 129.2, 128.9, 42.8; HRMS (ESI) calcd for $C_{12}H_{11}ClN_3O$ $[M+H]^+$ 248.0591 found 248.0584.



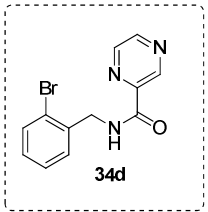
34b

N-(2-Methoxybenzyl)pyrazine-2-carboxamide **(34c):** Following the general procedure described above **34c** was obtained after purification by column chromatography (EtOAc:Hexane = 60:40); as a colorless solid (269 mg, 37%); mp: 104-106 °C; FT-IR (KBr): 3341, 2939, 1674, 1529, 1020 and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.43 (d, 1H, J = 1.4 Hz), 8.73 (d, 1H, J = 2.5 Hz), 8.52-8.51 (m, 1H), 8.28 (br. s, 1H), 7.36 (dd, 1H, J_1 = 7.4, J_2 = 1.4 Hz), 7.32-7.27 (m, 1H), 6.96 (d, 1H, J = 7.4 Hz), 6.92 (d, 1H, J = 8.2 Hz), 4.69 (d, 2H, J = 6.2 Hz), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 157.7, 147.1, 144.8, 144.5, 142.5, 129.8, 129.1, 125.8, 120.7, 110.4, 55.4, 39.3; HRMS (ESI) calcd for $C_{13}H_{14}N_3O_2$ $[M+H]^+$ 244.1086 found 244.1080.



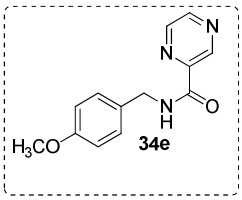
34c

N-(2-Bromobenzyl)pyrazine-2-carboxamide **(34d):** Following the general procedure described above **34d** was obtained after purification by column chromatography (EtOAc:Hexane = 55:45); as a colorless solid (331 mg, 38%); mp: 105-107 °C; FT-IR (KBr): 3378, 3057, 1674, 1526, 1021 and 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.44 (d, 1H, J = 1.4 Hz), 8.77 (d, 1H, J = 2.5 Hz), 8.55 (dd, 1H, J_1 = 2.4, J_2 = 1.6 Hz), 8.31 (br. s, 1H), 7.60 (dd, 1H, J_1 = 8.0, J_2 = 1.0 Hz), 7.48 (dd, 1H, J_1 = 7.6, J_2 = 1.5 Hz), 7.31 (td, 1H, J_1 = 7.5, J_2 = 1.1 Hz), 7.19 (td, 1H, J_1 = 7.8, J_2 = 1.6 Hz), 4.78 (d, 2H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 147.4, 144.5, 144.3, 142.6, 136.8, 132.9, 130.4, 129.4, 127.8, 123.9, 43.8; HRMS (ESI) calcd for $C_{12}H_{11}BrN_3O$ $[M+H]^+$ 292.0085 found 292.0078.

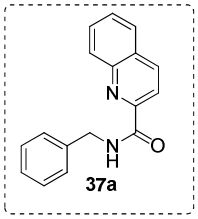


34d

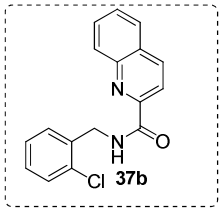
N-(4-Methoxybenzyl)pyrazine-2-carboxamide (**34e**)**:**Following the general procedure described above **34e** was obtained after purification by column chromatography (EtOAc:Hexane = 50:50); as a colorless solid (294 mg, 40%); mp: 126-128 °C; FT-IR (KBr): 3312, 3007, 1660, 1509 and 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.46 (br. s, 1H), 8.76 (d, 1H, J = 2.4 Hz), 8.51 (t, 1H, J = 1.6 Hz), 8.07 (br. s, 1H), 7.31 (d, 2H, J = 8.6 Hz), 6.91 (d, 2H, J = 8.6 Hz), 4.63 (d, 2H, J = 6.0 Hz), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 159.2, 147.3, 144.5, 144.5, 142.5, 129.8, 129.3, 114.2, 55.3, 43.0; HRMS (ESI) calcd for $C_{13}H_{14}N_3O_2$ $[M+H]^+$ 244.1086 found 244.1078.



N-Benzylquinoline-2-carboxamide **(37a):** Following the general procedure described above **37a** was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (259 mg, 48%); mp: 117-119 °C; FT-IR (KBr): 3385, 3065, 1673, 1528 and 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.64 (br. s, 1H), 8.38 (d, 1H, J = 8.5 Hz), 8.34 (d, 1H, J = 8.6 Hz), 8.09 (d, 1H, J = 8.5 Hz), 7.90 (dd, 1H, J_1 = 8.1, J_2 = 0.7 Hz), 7.79-7.75 (m, 1H), 7.66-7.62 (m, 1H), 7.46-7.44 (m, 2H), 7.41-7.38 (m, 2H), 7.35-7.31 (m, 1H), 4.77 (d, 2H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 149.7, 146.5, 138.3, 137.5, 130.1, 129.7, 129.4, 128.8, 127.9, 127.9, 127.8, 127.5, 119.0, 43.6; HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$ 263.1184 found 263.1178.

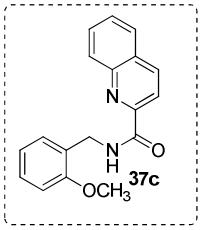


N-(2-Chlorobenzyl)quinoline-2-carboxamide **(37b):** Following the general procedure described above **37b** was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (408 mg, 46%); mp: 119-121 °C; FT-IR (KBr): 3387, 3055, 1675, 1525 and 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.76 (br. s, 1H), 8.35 (d, 1H, J = 8.5 Hz), 8.32 (d, 1H, J = 8.6 Hz), 8.12 (d, 1H, J = 8.5 Hz), 7.89 (dd, 1H, J_1 = 8.2, J_2 = 0.8 Hz), 7.79-7.75 (m, 1H), 7.65-7.61 (m, 1H), 7.53-7.50 (m, 1H), 7.43-7.40 (m, 1H), 7.28-7.24 (m, 2H), 4.86 (d, 2H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6, 149.6, 146.5, 137.5, 135.7, 133.7, 130.1, 129.9, 129.8, 129.6, 129.4, 128.9, 128.0, 127.8, 127.1, 118.9, 41.4; HRMS (ESI) calcd for $C_{17}H_{14}ClN_2O$ $[M+H]^+$ 297.0795 found 297.0785.

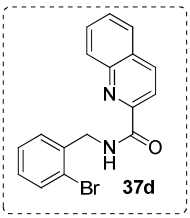


N-(2-Methoxybenzyl)quinoline-2-carboxamide **(37c):** Following the general procedure described above **37c** was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a colorless solid (394 mg, 45%); mp: 89-91 °C; FT-IR (KBr): 3393, 3055, 1674,

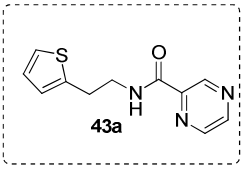
1527 and 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.75 (br. s, 1H), 8.35 (d, 1H, J = 8.5 Hz), 8.31 (d, 1H, J = 8.5 Hz), 8.10 (d, 1H, J = 8.5 Hz), 7.88 (d, 1H, J = 8.1 Hz), 7.78-7.74 (m, 1H), 7.63-7.60 (m, 1H), 7.42 (d, 1H, J = 7.4 Hz), 7.32-7.28 (m, 1H), 6.97 (d, 1H, J = 7.4 Hz), 6.94 (d, 1H, J = 8.0 Hz), 4.77 (d, 2H, J = 6.2 Hz), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.3, 157.7, 150.0, 146.5, 137.4, 130.0, 129.7, 129.6, 129.3, 128.8, 127.8, 127.8, 126.3, 120.7, 119.0, 110.4, 55.4, 39.2; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_2$ $[M+Na]^+$ 315.1109 found 315.1100.



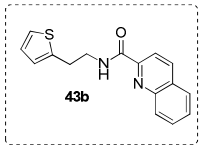
N-(2-Bromobenzyl)quinoline-2-carboxamide **(37d):** Following the general procedure described above **37d** was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (450 mg, 44%); mp: 126-128 °C; FT-IR (KBr): 3385, 3065, 1674, 1525 and 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.78 (br. s, 1H), 8.34 (br. s, 2H), 8.13 (d, 1H, J = 8.5 Hz), 7.90 (dd, 1H, J_1 = 8.2, J_2 = 0.8 Hz), 7.80-7.76 (m, 1H), 7.66-7.63 (m, 1H), 7.61 (dd, 1H, J_1 = 8.0, J_2 = 1.0 Hz), 7.52 (dd, 1H, J_1 = 7.6, J_2 = 1.5 Hz), 7.32 (td, 1H, J_1 = 7.5, J_2 = 1.1 Hz), 7.18 (td, 1H, J_1 = 7.8, J_2 = 1.6 Hz), 4.84 (d, 2H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 149.5, 146.5, 137.5, 137.3, 132.9, 130.1, 130.0, 129.8, 129.4, 129.1, 128.0, 127.8, 123.8, 118.9, 43.8; HRMS (ESI) calcd for $C_{17}H_{14}BrN_2O$ $[M+H]^+$ 341.0290 found 341.0300.



N-(2-(Thiophen-2-yl)ethyl)pyrazine-2-carboxamide**(43a):** Following the general procedure described above **43a** was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (720 mg, 62%); mp: 89-91 °C; FT-IR (KBr): 3357, 2926, 1670, 1530 and 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.43 (d, 1H, J = 1.5 Hz), 8.77 (d, 1H, J = 2.5 Hz), 8.52 (dd, 1H, J_1 = 2.5, J_2 = 1.5 Hz), 8.00 (br. s, 1H), 7.20 (dd, 1H, J_1 = 5.1, J_2 = 1.1 Hz), 6.98 (dd, 1H, J_1 = 5.1, J_2 = 3.4 Hz), 6.90 (dd, 1H, J_1 = 3.4, J_2 = 0.9 Hz), 3.80 (q, 2H, J = 6.7 Hz), 3.19 (t, 2H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 147.3, 144.4, 144.4, 142.6, 141.0, 127.1, 125.5, 124.1, 40.8, 30.0; HRMS (ESI) calcd for $C_{11}H_{12}N_3OS$ $[M+H]^+$ 234.0701 found 234.0696.

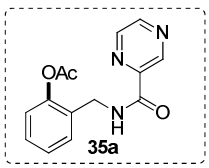


N-(2-(Thiophen-2-yl)ethyl)quinoline-2-carboxamide**(43b):** Following the general procedure described above **43b** was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless solid (1.04 g, 74%)**;** mp: 67-69 °C; FT-IR (KBr): 3385, 2926, 1673, 1527

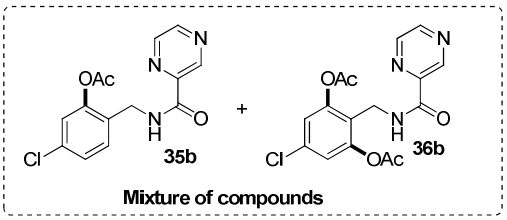


and 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.50 (br. s, 1H), 8.34 (s, 2 H), 8.10 (d, 1H, J = 8.5 Hz), 7.92-7.89 (m, 1H), 7.80-7.76 (m, 1H), 766-7.62 (m, 1H), 7.22 (dd, 1H, J_1 = 5.1, J_2 = 1.2 Hz), 7.00 (dd, 1H, J_1 = 5.1, J_2 = 3.4 Hz), 6.95 (dd, 1H, J_1 = 3.4, J_2 = 0.9 Hz), 3.85 (q, 2H, J = 6.9 Hz), 2.25 (t, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 149.7, 146.5, 141.3, 137.5, 130.1, 129.7, 129.3, 127.9, 127.8, 127.1, 125.4, 124.0, 118.8, 41.0, 31.2; HRMS (ESI) calcd for $C_{16}H_{15}N_2OS$ $[M+H]^+$ 283.0905 found 283.0897.

2-((Pyrazine-2-carboxamido)methyl)phenyl acetate **(35a):** Following the general procedure described above **35a**was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as a brown colored solid (17 mg, 24%); mp: 143-145 ^oC; FT-IR (KBr): 3392, 3055, 1762, 1678, 1527 and 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.44 (d, 1H, J = 1.3 Hz), 8.76 (d, 1H, J = 2.4 Hz), 8.52 (dd, 1H, J_1 = 2.3, J_2 = 1.6 Hz), 8.08 (br. s, 1H), 7.45 (dd, 1H, J_1 = 7.6, J_2 = 1.5 Hz), 7.36 (td, 1H, J_1 = 7.7, J_2 = 1.6 Hz), 7.28-7.24 (m, 1H), 7.11 (dd, 1H, J_1 = 8.0, J_2 = 1.0 Hz), 4.64 (d, 2H, J = 6.0 Hz), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 162.7, 149.1, 147.4, 144.4, 144.3, 142.7, 130.2, 129.7, 129.2, 126.6, 122.7, 38.6, 21.0; HRMS (ESI) calcd for $C_{14}H_{13}N_3NaO_3$ $[M+Na]^+$ 294.0855 found 294.0846.



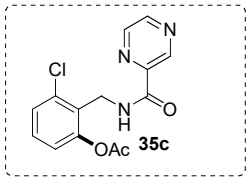
2-((Pyrazine-2-carboxamido)methyl)-1,3-phenylene diacetate **(36a):** Following the general procedure described above **36a**was obtained after purification by column chromatography (EtOAc:Hexane = 75:25); as a brown colored solid (21 mg, 26%); mp: 146-148 ^oC; FT-IR (KBr): 3399, 3055, 1767, 1680, 1527 and 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.40 (d, 1H, J = 1.4 Hz), 8.73 (d, 1H, J = 2.4 Hz), 8.52 (dd, 1H, J_1 = 2.4, J_2 = 1.5 Hz), 7.98 (br. s, 1H), 7.39 (t, 1H, J = 8.2 Hz), 7.04 (d, 2H, J = 8.2 Hz), 4.58 (d, 2H, J = 5.8 Hz), 2.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 162.4, 150.3, 147.2, 144.4, 144.3, 142.8, 129.4, 123.1, 120.5, 32.9, 21.0; HRMS (ESI) calcd for $C_{16}H_{15}N_3NaO_5$ $[M+Na]^+$ 352.0909 found 352.0921.



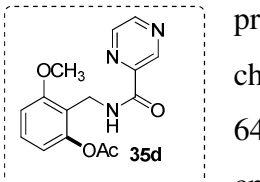
***5-Chloro-2-((pyrazine-2-carboxamido)methyl)phenyl acetate (35b) and 5-chloro-2-((pyrazine-2-carboxamido)methyl)-1,3-phenylene diacetate (36b)*:**Following the general procedure described

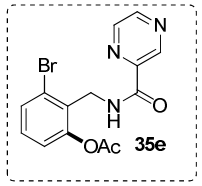
above **35b/36b**was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as an inseparable vicous liquid mixture of containing the compounds **35b/36b** in49% yield. Since these compounds were not separable it was not possible to obtain the data for the corresponding compounds.

3-Chloro-2-((pyrazine-2-carboxamido)methyl)phenyl acetate **(35c):** Following the general procedure described above **35c**was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as a brown colored solid (55 mg, 73%); mp: 130-132 ^{o}C; FT-IR (KBr): 3395, 2930, 1768, 1681, 1525 and 1194 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.41 (d, 1H, J = 1.4 Hz), 8.74 (d, 1H, J = 2.4 Hz), 8.51 (dd, 1H, J_1 = 2.2, J_2 = 1.6 Hz), 8.08 (br. s, 1H), 7.36-7.28 (m, 2H), 7.05 (dd, 1H, J_1 = 7.8, J_2 = 1.4 Hz), 4.80 (d, 2H, J = 6.0 Hz), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 162.5, 150.3, 147.3, 144.4, 144.3, 142.6, 135.9, 129.6, 128.3, 127.5, 121.8, 35.5, 20.9; HRMS (ESI) calcd for $C_{14}H_{12}ClN_3NaO_3$ $[M+Na]^+$ 328.0465 found 328.0456.



3-Methoxy-2-((pyrazine-2-carboxamido)methyl)phenyl acetate **(35d):** Following the general procedure described above **35d**was obtained after purification by column chromatography (EtOAc:Hexane = 75:25); as a brown colored solid (48 mg, 64%); mp: 129-131 ^{o}C; FT-IR (KBr): 3405, 2945, 1766, 1679, 1526 and 1206 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.41 (d, 1H, J = 1.4 Hz), 8.71 (d, 1H, J = 2.5 Hz), 8.49 (dd, 1H, J_1 = 2.3, J_2 = 1.6 Hz), 8.07 (br. s, 1H), 7.31(t, 1H, J = 8.2 Hz), 6.83 (d, 1H, J = 8.3 Hz), 6.73 (d, 1H, J = 8.2 Hz), 4.67 (d, 2H, J = 6.0 Hz), 3.92 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 162.4, 159.0, 149.8, 147.1, 144.7, 144.4, 142.6, 129.3, 118.5, 115.1, 108.3, 56.0, 32.6, 21.0; HRMS (ESI) calcd for $C_{15}H_{15}N_3NaO_4$ $[M+Na]^+$ 324.0960 found 324.0948.

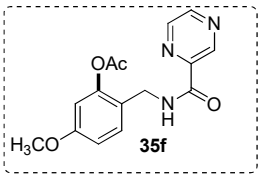




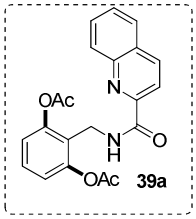
3-Bromo-2-((pyrazine-2-carboxamido)methyl)phenyl acetate **(35e):** Following the general procedure described above **35e**was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as a brown colored solid (49 mg, 56%); mp: 126-128 ^{o}C; FT-IR (KBr): 3397, 3055, 1767, 1680, 1526 and 1194 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.41 (d, 1H, J = 1.3 Hz), 8.74 (d, 1H, J = 2.4 Hz), 8.52 (dd, 1H, J_1 = 2.3, J_2 = 1.5 Hz), 8.11 (br. s, 1H), 7.53 (dd, 1H, J_1 = 8.0, J_2 = 0.8 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.09 (d, 1H, J = 8.1 Hz), 4.81 (d, 2H, J = 6.0 Hz), 2.41 (s, 3H); ^{13}C NMR

($CDCl_3$, 100 MHz): δ 169.8, 162.5, 150.2, 147.3, 144.4, 144.3, 142.7, 130.7, 130.1, 129.9, 125.9, 122.5, 37.9, 21.0; HRMS (ESI) calcd for $C_{14}H_{13}BrN_3O_3$ $[M+H]^+$ 350.0140 found 350.0148.

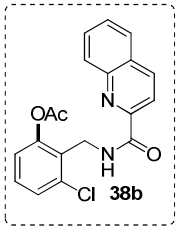
***5-Methoxy-2-((pyrazine-2-carboxamido)methyl)phenyl acetate*(35f)**: Following the general procedure described above **35f**was obtained after purification by column chromatography (EtOAc:Hexane = 75:25); as a brown colored thick liquid (11 mg, 15%); FT-IR (DCM): 3396, 2928, 1766, 1677, 1527 and 1206 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.43 (d, 1H, J = 1.4 Hz), 8.75 (d, 1H, J = 2.4 Hz), 8.52-8.51 (m, 1H), 8.00 (br. s, 1H), 7.36 (d, 1H, J = 8.5 Hz), 6.81 (dd, 1H, J_1 = 8.5, J_2 = 2.6 Hz), 6.66 (d, 1H, J = 8.5 Hz), 4.56 (d, 2H, J = 5.9 Hz), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 162.6, 160.2, 149.9, 147.3, 144.4, 142.7, 131.1, 121.7, 112.3, 108.5, 55.6, 38.2, 21.0; HRMS (ESI) calcd for $C_{15}H_{15}N_3NaO_4$ $[M+H]^+$ 324.0960 found 324.0947.



***2-((Quinoline-2-carboxamido)methyl)-1,3-phenylene diacetate* (39a):** Following the general procedure described above **39a**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a light yellow colored solid (66 mg, 76%); mp: 107-109 ^oC; FT-IR (KBr): 3382, 2925, 1768, 1677, 1527 and 1191 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (br. s, 1H), 8.31 (s, 2H), 8.10 (d, 1H, J= 8.5 Hz), 7.87 (d, 1H, J= 8.1 Hz), 7.76-7.72 (m, 1H), 7.63-7.59 (m, 1H), 7.39 (t, 1H, J= 8.2 Hz), 7.07 (d, 2H, J= 8.2 Hz), 4.66 (d, 2H, J= 5.8 Hz), 2.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 164.0, 150.4, 149.5, 146.5, 137.4, 130.0, 130.0, 129.3, 129.1, 127.9, 127.6, 123.3, 120.5, 118.7, 33.2, 21.0; HRMS (ESI) calcd for $C_{21}H_{19}N_2O_5$ $[M+H]^+$ 379.1294 found 379.1281. The corresponding mono acetoxylated compound **38a** could not be isolated in pure form.



***3-Chloro-2-((quinoline-2-carboxamido)methyl)phenyl acetate* (38b):** Following the general procedure described above **38b**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a light yellow colored solid (63 mg, 71%); mp: 123-125 ^oC; FT-IR (KBr): 3389, 2937, 1767, 1678, 1525 and 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.56 (br. s, 1H), 8.31 (br. s, 2H), 8.10 (d, 1H, J= 8.5 Hz), 7.87 (d, 1H, J= 8.2 Hz), 7.75 (td, 1H, J_1 = 7.0, J_2 = 1.2 Hz), 7.63-7.59 (m, 1H), 7.36 (dd, 1H, J_1 = 8.1, J_2 = 1.0 Hz), 7.32-7.28 (m, 1H), 7.06 (d, 1H, J= 8.0



Hz), 4.87 (d, 2H, *J*= 6.0 Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 164.0, 150.4, 149.5, 146.5, 137.5, 135.9, 130.0, 129.9, 129.4, 129.3, 128.7, 127.9, 127.7, 127.4, 121.8, 118.9, 35.7, 21.1; HRMS (ESI) calcd for $C_{19}H_{16}ClN_2O_3$ $[M+H]^+$ 355.0849 found 355.0838.

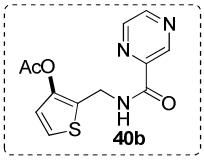
3-Methoxy-2-((quinoline-2-carboxamido)methyl)phenyl acetate **(38c):** Following the general procedure described above **38c**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown colored solid (57 mg, 66%); mp: 111-113 ^{o}C; FT-IR (KBr): 3399, 3055, 1766, 1678, 1527 and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (br. s, 1H), 8.33 (d, 1H, *J*= 8.5 Hz), 8.29 (d, 1H, *J*= 8.6 Hz), 8.09 (d, 1H, *J*= 8.4 Hz), 7.87 (dd, 1H, J_1 = 8.2, J_2 = 0.8 Hz),7.77-7.72 (m, 1H), 7.62-7.58 (m, 1H), 7.32 (t, 1H, *J* = 8.2 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 6.76 (dd, 1H, J_1 = 8.2, J_2 = 0.6 Hz), 4.75 (d, 2H, *J* = 6.0 Hz), 3.97 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 164.0, 159.1, 150.0, 149.9, 146.5, 137.3, 129.9, 129.8, 129.2, 129.1, 127.8, 127.7, 119.0, 118.9, 115.1, 108.4, 56.0, 32.8, 21.1; HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_4$ $[M+Na]^+$ 373.1164 found 373.1151.

3-Bromo-2-((quinoline-2-carboxamido)methyl)phenyl acetate **(38d):** Following the general procedure described above **38d**was obtained after purification by column chromatography (EtOAc:Hexane = 30:70); as a brown colored solid (72 mg, 73%); mp: 122-124 ^{o}C; FT-IR (KBr): 3055, 2987, 1768, 1680, 1526 and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.59 (br. s, 1H), 8.31 (s, 2H), 8.11 (d, 1H, *J*= 8.5 Hz), 7.87 (dd, 1H, J_1 = 8.2, J_2 = 0.6 Hz), 7.77-7.73 (m, 1H), 7.63-7.59 (m, 1H), 7.55 (dd, 1H, J_1 = 8.0, J_2 = 0.9 Hz), 7.24 (t, 1H, *J* = 8.1 Hz), 7.11 (dd, 1H, J_1 = 8.2, J_2 = 0.8 Hz), 4.88 (d, 2H, *J*= 6.0 Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 163.9, 150.3, 149.5, 146.5, 137.5, 130.7, 130.3, 130.0, 129.9, 129.8, 129.3, 127.9, 127.7, 125.9, 122.5, 118.9, 38.2, 21.1; HRMS (ESI) calcd for $C_{19}H_{16}BrN_2O_3$ $[M+H]^+$ 399.0344 found 399.0330.

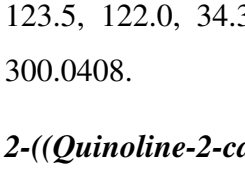
2-(Picolinamidomethyl)thiophen-3-yl acetate **(40a):** Following the general procedure described above **40a**was obtained after purification by column chromatography (EtOAc:Hexane = 45:55); as a dark brown colored semi-solid (39 mg, 56%); FT-IR (DCM): 3380, 3058, 1766, 1673, 1520, 1204, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.40 (br. s, 1H), 8.22 (dt, 1H, J_1 = 7.8, J_2 = 1.0 Hz), 7.85 (td, 1H, J_1 = 7.7, J_2 = 1.7 Hz), 7.44-7.41 (m, 1H), 7.19

(d, 1H, *J* = 5.5 Hz), 6.87 (d, 1H, *J* = 5.5 Hz), 4.70 (d, 2H, *J* = 6.0 Hz), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 164.1, 149.5, 148.2, 144.4, 137.4, 126.3, 125.5, 123.2, 122.4, 121.9, 34.4, 20.8; HRMS (ESI) calcd for $C_{13}H_{12}N_2NaO_3S$ $[M+Na]^+$ 299.0466 found 299.0465.

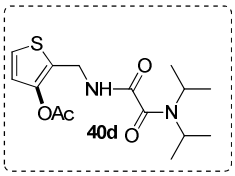
2-((Pyrazine-2-carboxamido)methyl)thiophen-3-yl acetate **(40b):** Following the general procedure described above **40b**was obtained after purification by column chromatography (EtOAc:Hexane = 70:30); as a brown colored solid (42 mg, 61%); FT-IR (KBr): 3369, 2931, 1764, 1673, 1525, 1204, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.44 (br. s, 1H), 8.76 (d, 1H, *J* = 2.4 Hz), 8.54 (d, 1H, *J* = 1.5 Hz), 8.16 (br. s, 1H), 7.22 (d, 1H, *J* = 5.5 Hz), 6.87 (d, 1H, *J* = 5.5 Hz), 4.71 (d, 2H, *J* = 6.0 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 162.8, 147.4, 144.6, 144.4, 144.2, 142.7, 125.0, 123.5, 122.0, 34.3, 20.8; HRMS (ESI) calcd for $C_{12}H_{11}N_3NaO_3S$ $[M+Na]^+$ 300.0419 found 300.0408.



2-((Quinoline-2-carboxamido)methyl)thiophen-3-yl acetate **(40c):** Following the general procedure described above **40c**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown colored solid (63 mg, 78%); mp: 102-104 ^oC; FT-IR (KBr): 3386, 2923, 1767, 1675, 1500, 1204, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (br. s, 1H), 8.32 (d, 2H, *J* = 1.9 Hz), 8.10 (d, 1H, *J* = 8.5 Hz), 7.88-7.86 (m, 1H), 7.77-7.73 (m, 1H), 7.61 (td,1H, J_1 = 8.1, J_2 = 1.1 Hz), 7.21 (d, 1H, *J* = 5.5 Hz), 6.89 (d, 1H, *J* = 5.5 Hz), 4.78 (d, 2H, *J* = 6.0 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 164.3, 149.4, 146.5, 144.4, 137.5, 130.1, 129.8, 129.4, 128.0, 127.7, 125.6, 123.2, 122.0, 118.9, 34.6, 20.8; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_3S$ $[M+H]^+$ 327.0803 found 327.0809.

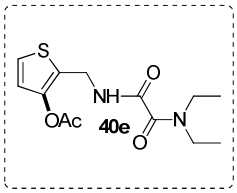


2-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophen-3-yl acetate **(40d):** Following the general procedure described above **40d**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown color solid (42 mg, 48%); mp: 94-96 °C**;** FT-IR (KBr): 3275, 2923, 1673, 1631, 1448, 1206, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, 1H, *J* = 5.5 Hz), 6.86 (d, 1H, *J* = 5.5 Hz), 4.72-4.65 (m, 1H), 4.49 (d, 2H, *J* = 6.0 Hz), 3.55-3.48 (m,

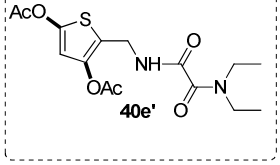


1H), 2.31 (s, 3H), 1.42 (d, 6H, *J* = 6.8 Hz), 1.24 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 162.9, 162.7, 144.5, 124.7, 123.3, 121.9, 49.7, 46.6, 34.1, 20.9, 20.0; HRMS (ESI) calcd for $C_{15}H_{22}N_2NaO_4S$ $[M+Na]^+$ 349.1198 found 349.1183.

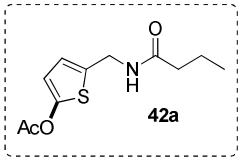
2-((2-(Diethylamino)-2-oxoacetamido)methyl)thiophen-3-yl acetate **(40e):** Following the general procedure described above **40e**was obtained after purification by column chromatography (EtOAc:Hexane = 35:65); as a brown colored thick liquid (43 mg, 57%); FT-IR (DCM): 3300, 2930, 1767, 1633, 1487 and 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (br. s, 1H), 7.18 (d, 1H, *J*= 5.5 Hz), 6.85 (d, 1H, *J*= 5.5 Hz), 4.49 (d, 2H, *J*= 6.1 Hz), 3.73 (q, 2H, *J*= 7.0 Hz), 3.40 (q, 2H, *J*= 7.1 Hz), 2.31 (s, 3H), 1.27 (t, 3H, *J*= 7.0 Hz), 1.16 (t, 3H, *J*= 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 161.4, 161.2, 144.5, 124.7, 123.3, 122.0, 43.3, 42.0, 34.1, 20.8, 14.7, 12.5; HRMS (ESI) calcd for $C_{13}H_{18}N_2NaO_4S$ $[M+Na]^+$ 321.0885 found 321.0873.



5-((2-(Diethylamino)-2-oxoacetamido)methyl)thiophene-2,4-diyl diacetate **(40e'):** Following the general procedure described above **40e'**was obtained after purification by column chromatography (EtOAc:Hexane = 40:60); as a brown colored solid (15 mg, 17%); mp: 155-157 °C**;** FT-IR (KBr): 3400, 3055, 1766, 1680, 1527 and 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (br. s, 1H), 6.51 (s, 1H), 4.43 (d, 2H, *J* = 6.0 Hz), 3.74 (q, 2H, *J* = 7.0 Hz), 3.41 (q, 2H, *J* = 7.1 Hz), 2.30 (s, 3H), 2.29 (s, 3H), 1.27 (t, 3H, *J* = 7.0 Hz), 1.17 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.7, 167.2, 161.2, 161.1, 148.9, 140.5, 116.7, 108.3, 43.3, 42.1, 33.8, 20.7, 20.7, 14.8, 12.4; HRMS (ESI) calcd for $C_{15}H_{20}N_2NaO_6S$ $[M+Na]^+$ 379.0940 found 379.0927.



5-(Butyramidomethyl)thiophen-2-yl acetate **(42a):** Following the general procedure described above **42a**was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless liquid (24 mg, 40%); FT-IR (DCM): 3301, 2923, 1656, 1539 and 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.70 (d, 1H, *J* = 3.8 Hz), 6.52 (d, 1H, *J* = 3.8 Hz), 5.85 (br. s, 1H), 4.52 (d, 2H, *J* = 5.6 Hz), 2.30 (s, 3H), 2.18 (t, 2H, *J* = 7.3 Hz),1.69 (q, 2H, *J* = 7.4 Hz), 0.96 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 167.6, 151.0, 133.4, 122.3, 113.2, 38.7, 38.5, 20.8, 19.1, 13.8; HRMS (ESI) calcd for $C_{11}H_{15}NNaO_3S$ $[M+Na]^+$ 264.0670 found 264.0664.



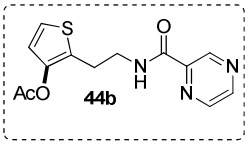
5-((2-(Diethylamino)-2-oxoacetamido)methyl)-4-(3,5-dimethylphenyl)thiophen-2-yl acetate **(42c):** Following the general procedure described above **42c**was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless liquid (40 mg, 40%); FT-IR (DCM): 3273, 2920, 1682, 1634, 1275 and 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (br. s, 1H), 6.99 (s, 1H), 6.95 (s, 2H), 6.64 (s, 1H), 4.60 (d, 2H, J = 5.8 Hz), 3.77 (q, 2H, J = 7.1 Hz), 3.42 (q, 2H, J = 7.1 Hz), 2.36 (s, 6H), 2.32 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 161.2, 160.9, 150.0, 138.2, 137.4, 135.3, 129.2, 126.5, 126.3, 115.5, 43.3, 42.2, 36.7, 21.4, 20.8, 14.8, 12.5; HRMS (ESI) calcd for $C_{21}H_{26}N_2NaO_4S$ $[M+Na]^+$ 425.1511 found 425.1496.

5-((2-(Diisopropylamino)-2-oxoacetamido)methyl)thiophene-2,4-diyl diacetate **(42d):** Following the general procedure described above **42d**was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless liquid (34 mg, 35%)**;** FT-IR (DCM): 3277, 2926, 1771, 1627 and 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (br. s, 1H), 6.51 (s, 1H), 4.73-4.66 (m, 1H), 4.42 (d, 2H, J = 5.9 Hz), 3.55-3.48 (m, 1H), 2.30 (s, 6H), 1.42 (d, 6H, J = 6.8 Hz), 1.24 (d, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.7, 167.1, 162.9, 162.5, 149.0, 140.5, 116.7, 108.3, 49.7, 46.6, 33.7, 20.9, 20.7, 20.0; HRMS (ESI) calcd for $C_{17}H_{24}N_2NaO_6S$ $[M+Na]^+$ 407.1253 found 407.1257.

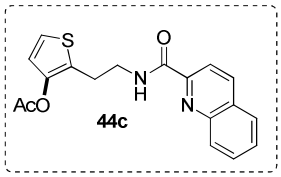
2-(2-(Picolinamido)ethyl)thiophen-3-yl acetate **(44a):** Following the general procedure described above **44a**was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a brown coloured semisolid (37 mg, 27%)**;** FT-IR (DCM): 3382, 2926, 1767, 1672, 1526 and 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.55-8.54 (m, 1H), 8.28 (br. s, 1H), 8.21 (d, 1H, J = 7.8 Hz), 7.88-7.83 (m, 1H), 7.45-7.42 (m, 1H), 7.12 (dd, 1H, J_1 = 5.5, J_2 = 0.7 Hz), 6.88 (d, 1H, J = 5.5 Hz), 3.69 (d, 2H, J = 6.8 Hz), 3.02 (t, 2H, J = 6.8 Hz), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 164.5, 149.8, 148.1, 143.9, 137.4, 126.2, 126.0, 122.2, 122.0, 121.7, 40.1, 26.3, 20.7; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_3S$ $[M+H]^+$ 291.0803 found 291.0812.

2-(2-(Pyrazine-2-carboxamido)ethyl)thiophen-3-yl acetate**(44b):** Following the general procedure described above **44b**was obtained after purification by column chromatography

(EtOAc:Hexane = 25:75); as a colorless liquid (37 mg, 52%)**;** FT-IR (DCM): 3378, 2930, 1768, 1673, 1530 and 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.41 (d, 1H, J = 1.5 Hz), 8.75 (d, 1H, J = 2.5 Hz), 8.52 (dd, 1H, J_1 = 2.5, J_2 = 1.5 Hz), 8.03 (br. s, 1H), 7.12 (d, 1H, J = 5.5 Hz), 6.86 (d, 1H, J = 5.5 Hz), 3.71 (q, 2H, J = 6.6 Hz), 3.03 (t, 2H, J = 6.7 Hz), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 163.2, 147.3, 144.4, 144.3, 144.0, 142.6, 125.7, 122.1, 121.9, 40.1, 26.1, 20.7; HRMS (ESI) calcd for $C_{13}H_{13}N_3NaO_3S$ $[M+Na]^+$ 314.0575 found 314.0583.



2-(2-(Quinoline-2-carboxamido)ethyl)thiophen-3-yl acetate **(44c):** Following the general procedure described above **44c**was obtained after purification by column chromatography (EtOAc:Hexane = 25:75); as a colorless liquid (37 mg, 43%)**;** FT-IR (DCM): 3378, 2926, 1767, 1673, 1528 and 1203 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.51 (br. s, 1H), 8.32 (s, 2H), 8.11 (d, 1H, J = 8.4 Hz), 7.89 (dd, 1H, J_1= 7.7, J_2 = 0.8 Hz), 7.80-7.75 (m, 1H), 7.65-7.61 (m, 1H), 7.14 (d, 1H, J = 5.5 Hz), 6.90 (d, 1H, J= 5.4 Hz), 3.77 (q, 2H, J = 6.9 Hz), 3.09 (t, 2H, J = 6.8 Hz), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 164.7, 149.6, 146.5, 143.9, 137.5, 130.1, 129.7, 129.3, 127.9, 127.8, 126.0, 122.1, 121.8, 118.7, 40.2, 26.3, 20.8; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_3S$ $[M+H]^+$ 341.0960 found 341.00967.



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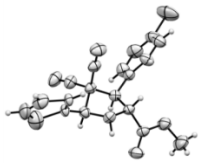
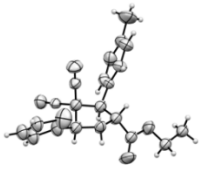
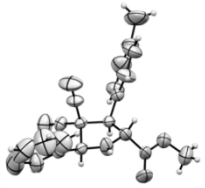
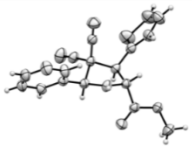
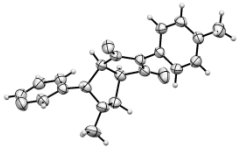
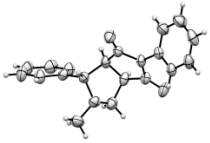
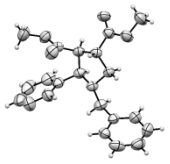
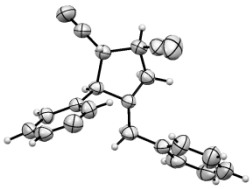
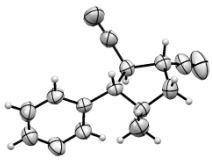
Appendix Section

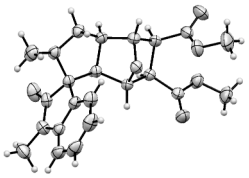
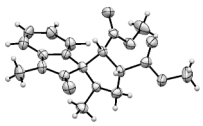
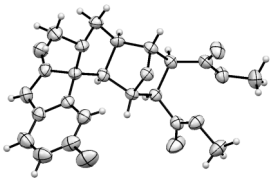
Brief single crystal X-ray structure analysis data of compounds.

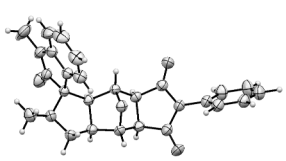
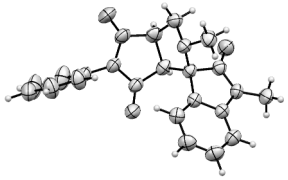
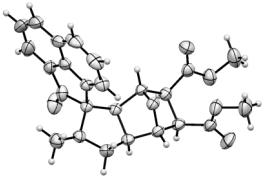
Proton/Carbon NMR spectra of representative compounds.

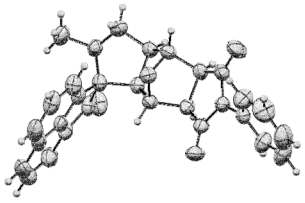
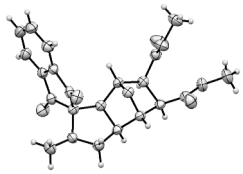
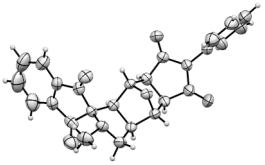
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 1)			
X-ray Structure			
Compound	**39c**	**39d**	**40b**
CCDC No.	CCDC 1011746	CCDC 1011747	CCDC 1011745
Empirical formula	$C_{18}H_{14}ClN_3O_2S$	$C_{20}H_{19}N_3O_2S$	$C_{20}H_{18}N_4O_2$
Formula weight	371.83	365.44	346.38
Temperature / K	1385.6	571.15	571.15
Crystal system	triclinic	monoclinic	monoclinic
Space group	P-1	$P2_1/n$	$P2_1/c$
a / Å, b / Å, c / Å	7.9737(9), 10.6719(13), 11.1080(12)	6.1500(6), 20.407(2), 15.7035(16)	6.1848(4), 14.5904(8), 20.7597(12)
α/°, β/°, γ/°	81.44(2), 86.04(2), 75.606(19)	90, 97.229(7), 90	90, 96.743(3), 90
Volume / $Å^3$	904.9(2)	1955.2(3)	1860.37(19)
Z	2	4	4
ρ_{calc} / mg mm^{-3}	1.365	1.241	1.237
μ / mm^{-1}	0.342	0.184	0.083
F(000)	384	768	728
Crystal size / mm^3	0.2 × 0.2 × 0.2	0.3 × 0.3 × 0.2	0.3 × 0.2 × 0.2
2Θ range for data collection	6.35 to 54.956°	3.288 to 50.054°	3.42 to 50.06°
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 13$, $-14 \le l \le 14$	$-7 \le h \le 7$, $-24 \le k \le 24$, $-17 \le l \le 18$	$-5 \le h \le 7$, $-16 \le k \le 17$, $-24 \le l \le 24$
Reflections collected	9761	13268	12614
Independent reflections	4124[R(int) = 0.0697]	3461[R(int) = 0.0492]	3273[R(int) = 0.0465]
Data/restraints/ parameters	4124/7/225	3461/3/187	3273/0/238
Goodness-of-fit on F^2	1.588	1.563	1.014
Final R indexes [I>2σ (I)]	R_1 = 0.1289, wR_2 = 0.3849	R_1 = 0.1367, wR_2 = 0.4071	R_1 = 0.0648, wR_2 = 0.1713
Final R indexes [all data]	R_1 = 0.1501, wR_2 = 0.4225	R_1 = 0.2097, wR_2 = 0.4577	R_1 = 0.1226, wR_2 = 0.2055
Largest diff. peak/hole / e $Å^{-3}$	2.855/-1.057	1.466/-1.373	0.304/-0.273

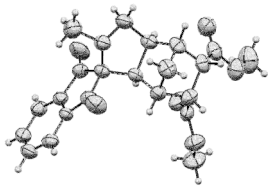
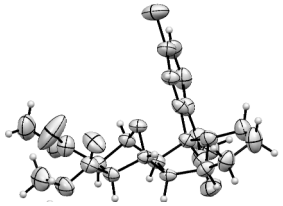
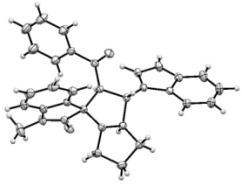
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 1)			
X-ray Structure			
Compound	**40c**	**51b**	**53**
CCDC No.	CCDC 1011744	CCDC 931881	CCDC 931882
Empirical Formula	$C_{17}H_{14}N_4O_2S$	$C_{19}H_{19}N_3O_2$	$C_{18}H_{17}N_3O_2$
Formula weight	338.38	321.37	308.35
Temperature / K	571.15	569(2)	571.15
Crystal system	triclinic	monoclinic	monoclinic
Space group	P-1	$P2_1/c$	$P2_1/n$
a / Å, b / Å, c / Å	7.7513(5), 8.2188(5), 13.0693(11)	12.725(2), 9.4250(14), 13.450(2)	11.741(12), 8.048(10), 16.74(2)
α/°, β/°, γ/°	81.785(15), 78.243(16), 79.153(16)	90, 101.637(2), 90	90, 97.135(18), 90
Volume / $Å^3$	795.82(12)	1580.0(4)	1569(3)
Z	2	4	4
ρ_{calc} / mg mm^{-3}	1.412	1.351	1.305
μ / mm^{-1}	0.221	0.09	0.087
F(000)	352	680	652
Crystal size / mm^3	0.2 × 0.2 × 0.2	0.3 × 0.2 × 0.2	0.3 × 0.2 × 0.1
2Θ range for data collection	6.292 to 54.962°	3.26 to 50.04°	4.02 to 50.24°
Index ranges	$-10 \le h \le 10$, $-10 \le k \le 10$, $-16 \le l \le 16$	$-14 \le h \le 15$, $-11 \le k \le 5$, $-15 \le l \le 16$	$-5 \le h \le 13$, $-9 \le k \le 8$, $-19 \le l \le 19$
Reflections collected	10902	6349	4831
Independent reflections	3628[R(int) = 0.0284]	2768[R(int) = 0.0366]	2588[R(int) = 0.0601]
Data/restraints/ parameters	3628/0/217	2768/0/219	2588/0/210
Goodness-of-fit on F^2	1.071	1.039	1.058
Final R indexes [I>2σ (I)]	R_1 = 0.0613, wR_2 = 0.1831	R_1 = 0.0419, wR_2 = 0.1152	R_1 = 0.0821, wR_2 = 0.227
Final R indexes [all data]	R_1 = 0.0729, wR_2 = 0.198	R_1 = 0.0545, wR_2 = 0.1227	R_1 = 0.1339, wR_2 = 0.2595
Largest diff. peak/hole / e $Å^{-3}$	0.581/-0.518	0.165/-0.174	0.304/-0.273

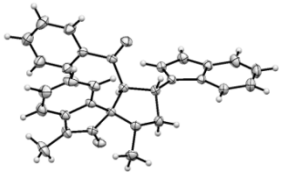
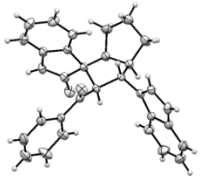
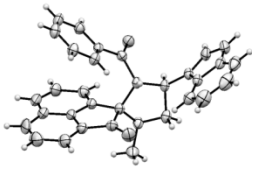
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 1)			
X-ray Structure			
Compound	**71**	**77**	**79**
CCDC No.	CCDC 931884	CCDC 932693	CCDC 931883
Empirical formula	$C_{20}H_{22}N_2O_4$	$C_{18}H_{16}N_4$	$C_{12}H_{12}N_4$
Formula weight	354.4	288.35	213.26
Temperature / K	569(2)	571.15	571.15
Crystal system	monoclinic	orthorhombic	orthorhombic
Space group	$P2_1/c$	Fdd2	$P2_12_12_1$
a / Å, b / Å, c / Å	19.2090(13), 6.1778(5), 16.3757(11)	17.767(9), 56.77(3), 6.166(3)	7.3502(5), 8.4518(6), 18.6480(13)
α/°, β/°, γ/°	90, 106.529(4), 90	90, 90, 90	90, 90, 90
Volume / $Å^3$	1863.0(2)	6219(5)	1158.46(14)
Z	4	16	4
ρ_{calc} / mg mm^{-3}	1.264	1.232	1.223
μ / mm^{-1}	0.089	0.076	0.078
F(000)	752	2432	452
Crystal size / mm^3	0.3 × 0.2 × 0.2	0.3 × 0.3 × 0.3	0.3 × 0.2 × 0.2
2Θ range for data collection	2.22 to 50.26°	2.86 to 61.14°	4.36 to 50.04°
Index ranges	$-21 \le h \le 22$, $-7 \le k \le 7$, $-19 \le l \le 18$	$-23 \le h \le 23$, $-74 \le k \le 80$, $-6 \le l \le 7$	$-7 \le h \le 8$, $-10 \le k \le 10$, $-22 \le l \le 17$
Reflections collected	8722	8792	5911
Independent reflections	3299[R(int) = 0.0632]	3086[R(int) = 0.0502]	2031[R(int) = 0.0262]
Data/restraints/ parameters	3299/0/238	3086/1/207	2031/0/147
Goodness-of-fit on F^2	1.055	1.016	1.081
Final R indexes [I>2σ (I)]	R_1 = 0.0635, wR_2 = 0.197	R_1 = 0.0426, wR_2 = 0.104	R_1 = 0.0346, wR_2 = 0.0818
Final R indexes [all data]	R_1 = 0.0935, wR_2 = 0.226	R_1 = 0.0565, wR_2 = 0.1133	R_1 = 0.0424, wR_2 = 0.0869
Largest diff. peak/hole / e $Å^{-3}$	0.336/-0.236	0.148/-0.173	0.104/-0.107

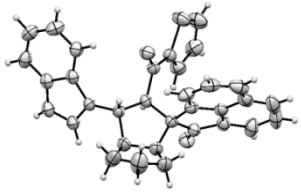
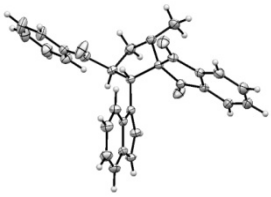
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 2)			
X-ray Structure			
Compound	**33**	**34**	**39**
CCDC No.	CCDC 847073	CCDC 847074	CCDC 847075
Empirical formula	$C_{21}H_{24}N_2O_6$	$C_{17}H_{20}N_2O_5$	$C_{20}H_{21}FN_2O_6$
Formula weight	400.42	332.35	404.39
Temperature / K	569.15	569.15	571.15
Crystal system	monoclinic	monoclinic	triclinic
Space group	C2/c	$P2_1/n$	P-1
a / Å, b / Å, c / Å	21.9132(7), 10.7761(3), 16.6742(5)	9.4307(9), 7.7612(9), 22.764(2)	6.5931(13), 10.063(2), 14.260(3)
α/°, β/°, γ/°	90, 99.612(2), 90	90, 93.340(7), 90	92.373(11), 99.725(12), 99.565(11)
Volume / $Å^3$	3882.1(2)	1663.4(3)	917.1(3)
Z	8	4	2
ρ_{calc} / mg mm^{-3}	1.37	1.327	1.464
μ / mm^{-1}	0.101	0.099	0.115
F(000)	1696	704	424
Crystal size / mm^3	0.2 × 0.2 × 0.1	0.2 × 0.2 × 0.1	0.3 × 0.2 × 0.2
2Θ range for data collection	4.22 to 56.56°	3.58 to 50.06°	4.12 to 47.06°
Index ranges	$-28 \le h \le 29$, $-12 \le k \le 14$, $-22 \le l \le 22$	$-11 \le h \le 10$, $-9 \le k \le 9$, $-27 \le l \le 26$	$-7 \le h \le 7$, $-9 \le k \le 11$, $-15 \le l \le 15$
Reflections collected	36652	10343	6280
Independent reflections	4818[R(int) = 0.0293]	2938[R(int) = 0.134]	2714[R(int) = 0.0643]
Data/restraints/ parameters	4818/0/266	2938/0/265	2714/0/347
Goodness-of-fit on F^2	1.092	0.955	1.028
Final R indexes [I>2σ (I)]	R_1 = 0.0433, wR_2 = 0.1261	R_1 = 0.0816, wR_2 = 0.2074	R_1 = 0.0571, wR_2 = 0.1516
Final R indexes [all data]	R_1 = 0.0658, wR_2 = 0.1491	R_1 = 0.1465, wR_2 = 0.241	R_1 = 0.0668, wR_2 = 0.1612
Largest diff. peak/hole / e $Å^{-3}$	0.535/-0.446	0.517/-0.418	0.284/-0.249

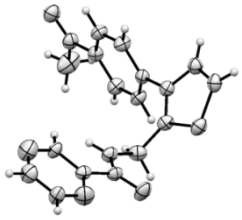
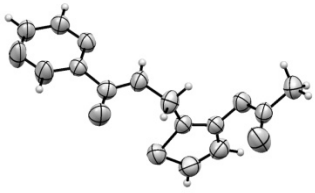
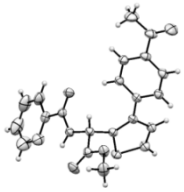
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 2)			
X-ray Structure			
Compound	**47a**	**48a**	**50**
CCDC No.	CCDC 847076	CCDC 847077	CCDC 847078
Empirical formula	$C_{25}H_{23}N_3O_4$	$C_{21}H_{19}N_3O_3$	$C_{24}H_{23}No_6$
Formula weight	429.47	361.39	421.43
Temperature / K	571.15	571.15	563.15
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	C2/c
a / Å, b / Å, c / Å	12.9718(6), 6.9048(3), 26.2625(12)	8.801(3), 20.946(6), 9.974(3)	22.2874(3), 10.7589(2), 17.0986(2)
α/°, β/°, γ/°	90, 100.4240(10), 90	90, 97.905(14), 90	90, 95.5070(10), 90
Volume / $Å^3$	2313.45(18)	1821.3(9)	4081.11(11)
Z	4	4	8
ρ_{calc} / mg mm^{-3}	1.313	1.318	1.372
μ / mm^{-1}	0.092	0.09	0.099
F(000)	960	760	1776
Crystal size / mm^3	0.2 × 0.2 × 0.1	0.2 × 0.2 × 0.2	0.2 × 0.1 × 0.1
2Θ range for data collection	3.16 to 53.46°	3.88 to 58.46°	3.68 to 51.36°
Index ranges	-16 ≤ h ≤ 16, -8 ≤ k ≤ 7, -33 ≤ l ≤ 33	-9 ≤ h ≤ 11, -19 ≤ k ≤ 28, -13 ≤ l ≤ 13	-26 ≤ h ≤ 27, -13 ≤ k ≤ 13, -20 ≤ l ≤ 20
Reflections collected	22883	12244	20843
Independent reflections	4919[R(int) = 0.0264]	4581[R(int) = 0.044]	3853[R(int) = 0.019]
Data/restraints/ parameters	4919/0/392	4581/0/321	3853/0/372
Goodness-of-fit on F^2	1.143	1.03	1.08
Final R indexes [I>2σ (I)]	R_1 = 0.062, wR_2 = 0.1606	R_1 = 0.0533, wR_2 = 0.1225	R_1 = 0.0376, wR_2 = 0.1057
Final R indexes [all data]	R_1 = 0.0869, wR_2 = 0.189	R_1 = 0.1045, wR_2 = 0.1444	R_1 = 0.046, wR_2 = 0.1195
Largest diff. peak/hole / e $Å^{-3}$	0.826/-0.851	0.196/-0.187	0.23/-0.179

Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 2)			
X-ray Structure			
Compound	**51**	**54**	**55**
CCDC No.	CCDC 847079	CCDC 847080	CCDC 847081
Empirical formula	$C_{28}H_{22}N_2O_4$	$C_{21}H_{21}NO_7$	$C_{25}H_{20}N_2O_5$
Formula weight	450.48	399.39	428.43
Temperature / K	563.15	571.15	571.15
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/c$	C2/c	Pbca
a / Å, b / Å, c / Å	13.6139(12), 11.2334(10), 16.8670(14)	25.0264(8), 7.7155(3), 19.4079(7)	14.4264(7), 10.7925(4), 54.837(2)
α/°, β/°, γ/°	90, 112.459(3), 90	90, 98.967(2), 90	90, 90, 90
Volume / $Å^3$	2383.8(4)	3701.7(2)	8537.9(6)
Z	4	8	16
ρ_{calc} / mg mm^{-3}	1.342	1.491	1.333
μ / mm^{-1}	0.092	0.115	0.094
F(000)	1012	1744	3584
Crystal size / mm^3	0.2 × 0.2 × 0.1	0.1 × 0.1 × 0.1	0.2 × 0.2 × 0.15
2Θ range for data collection	3.24 to 50.06°	4.24 to 54.2°	3.2 to 54.2°
Index ranges	$-16 \le h \le 14$, $-13 \le k \le 10$, $-19 \le l \le 20$	$-32 \le h \le 31$, $-9 \le k \le 9$, $-24 \le l \le 24$	$-18 \le h \le 17$, $-13 \le k \le 13$, $-70 \le l \le 68$
Reflections collected	14720	20286	93815
Independent reflections	4208[R(int) = 0.0299]	4079[R(int) = 0.0485]	9411[R(int) = 0.1255]
Data/restraints/ parameters	4208/0/327	4079/0/342	9411/0/715
Goodness-of-fit on F^2	1.044	1.019	1.006
Final R indexes [I>2σ (I)]	R_1 = 0.0539, wR_2 = 0.1531	R_1 = 0.0421, wR_2 = 0.0882	R_1 = 0.0629, wR_2 = 0.1193
Final R indexes [all data]	R_1 = 0.0807, wR_2 = 0.1763	R_1 = 0.0779, wR_2 = 0.1025	R_1 = 0.1713, wR_2 = 0.1572
Largest diff. peak/hole / e $Å^{-3}$	0.395/-0.269	0.191/-0.186	0.489/-0.319

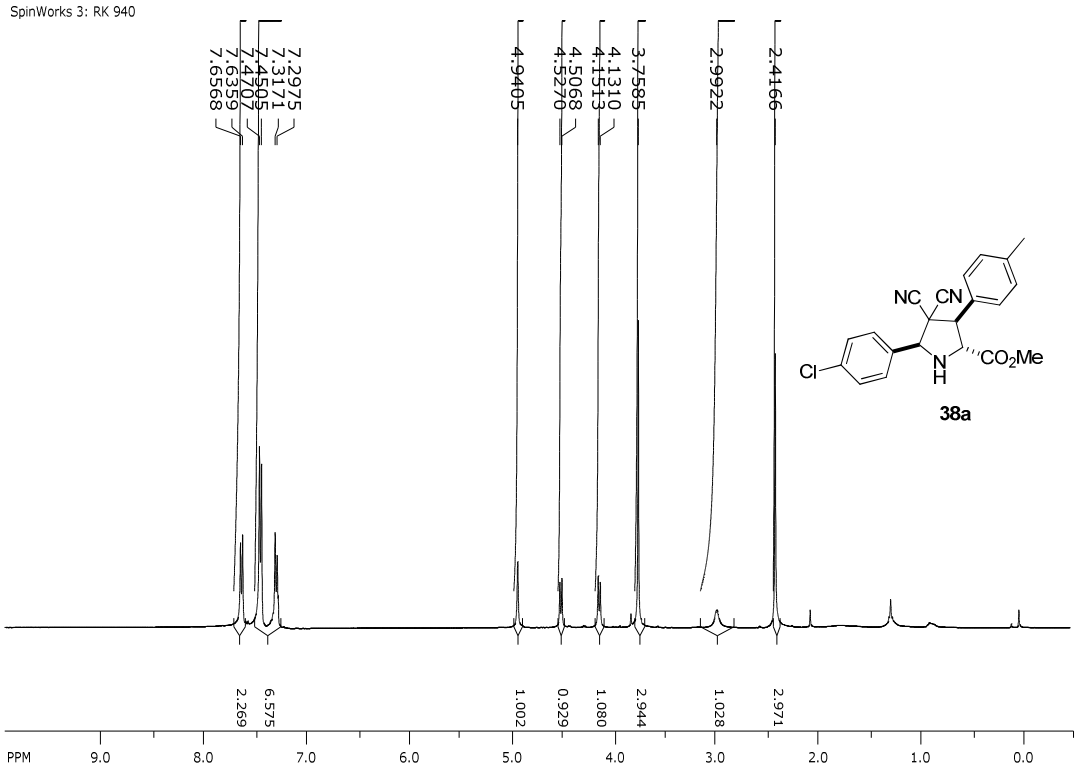
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 2)			
X-ray Structure			
Compound	**60**	**63b**	**67a**
CCDC No.	CCDC 847082	CCDC 847083	CCDC 1447111
Empirical formula	$C_{22}H_{23}No_6$	$C_{23}H_{22}ClN_2O_6$	$C_{30}H_{27}N_3O_2$
Formula weight	397.41	457.88	461.55
Temperature / K	563.15	569.15	569(2)
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	P-1	$P2_1/c$
a / Å, b / Å, c / Å	7.8690(6), 24.188(2), 12.5034(10)	10.378(2), 12.316(3), 18.342(5)	12.473(4), 10.220(4), 19.035(6)
α/°, β/°, γ/°	90, 125.238(5), 90	87.581(12), 80.085(12), 75.464(17)	90, 92.846(18), 90
Volume / $Å^3$	1943.7(3)	2235.5(9)	2423.5(15)
Z	4	4	4
ρ_{calc} / mg mm^{-3}	1.358	1.36	1.265
μ / mm^{-1}	0.099	0.213	0.08
F(000)	840	956	976
Crystal size / mm^3	0.2 × 0.2 × 0.1	0.5 × 0.4 × 0.2	0.2 × 0.2 × 0.2
2Θ range for data collection	3.36 to 50.04°	2.26 to 50.06°	4.28 to 50.06°
Index ranges	$-9 \le h \le 9$, $-28 \le k \le 27$, $-14 \le l \le 14$	$-11 \le h \le 12$, $-14 \le k \le 14$, $-21 \le l \le 21$	$-12 \le h \le 14$, $-5 \le k \le 12$, $-22 \le l \le 22$
Reflections collected	10053	11266	13685
Independent reflections	3421[R(int) = 0.0971]	7786[R(int) = 0.0391]	4281[R(int) = 0.0424]
Data/restraints/ parameters	3421/0/266	7786/0/581	4281/0/425
Goodness-of-fit on F^2	0.93	0.999	1.038
Final R indexes [I>2σ (I)]	R_1 = 0.0608, wR_2 = 0.1202	R_1 = 0.102, wR_2 = 0.2838	R_1 = 0.0385, wR_2 = 0.0946
Final R indexes [all data]	R_1 = 0.1532, wR_2 = 0.1585	R_1 = 0.1816, wR_2 = 0.3393	R_1 = 0.0464, wR_2 = 0.1004
Largest diff. peak/hole / e $Å^{-3}$	0.172/-0.184	0.95/-0.4	0.216/-0.146

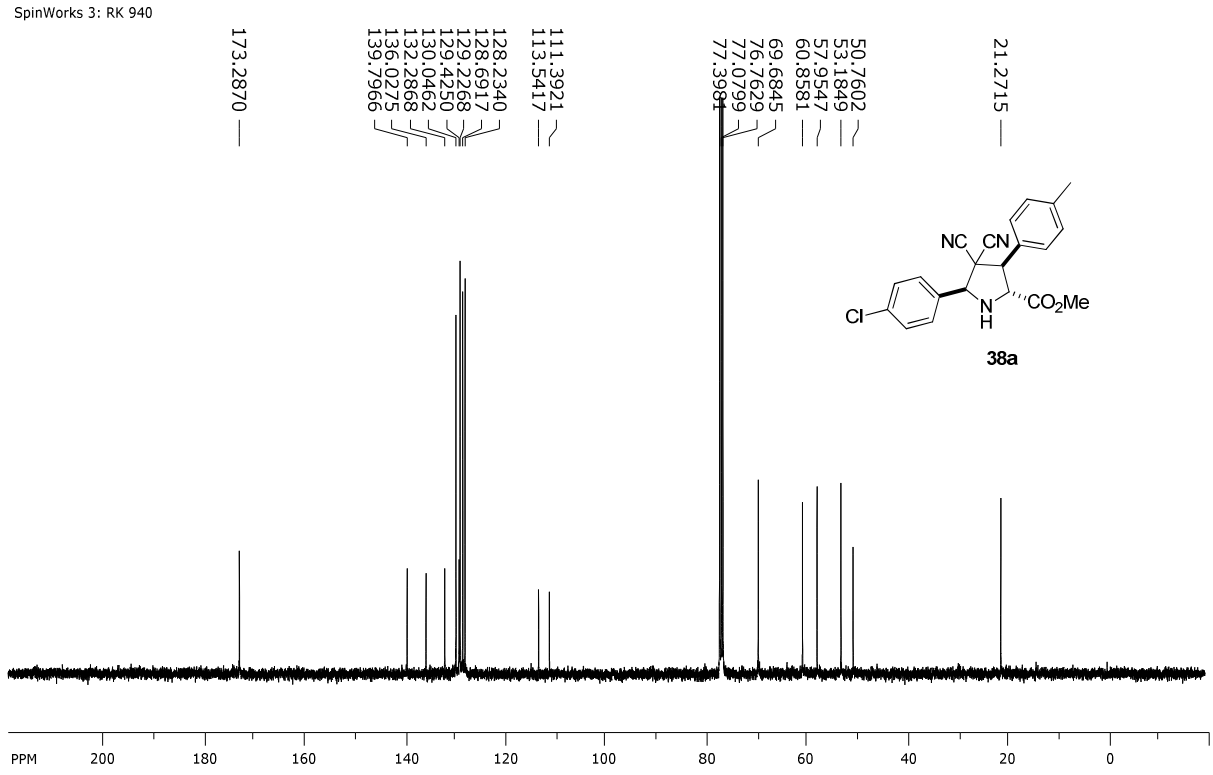
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 2)			
X-ray Structure			
Compound	**67b**	**67c**	**68a**
CCDC No.	CCDC 1447112	CCDC 1447113	CCDC 1447114
Empirical formula	$C_{28}H_{25}N_3O_2$	$C_{29}H_{25}N_3O_2$	$C_{31}H_{24}N_2O_2$
Formula weight	435.51	447.53	456.52
Temperature / K	569(2)	569(2)	571.15
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a / Å, b / Å, c / Å	12.067(4), 9.931(3), 19.084(6)	8.2811(3), 10.3853(4), 28.6276(10)	26.7123(17), 9.0358(6), 20.6366(11)
α/°, β/°, γ/°	90, 91.770(10), 90	90, 93.263(2), 90	90, 105.941(4), 90
Volume / $Å^3$	2285.9(13)	2458.03(16)	4789.4(5)
Z	4	4	8
ρ_{calc} / mg mm^{-3}	1.265	1.296	1.266
μ / mm^{-1}	0.081	0.085	0.079
F(000)	920	1016	1920
Crystal size / mm^3	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.2	0.3 × 0.3 × 0.2
2Θ range for data collection	4.28 to 50.04°	2.84 to 50.06°	1.58 to 50.06°
Index ranges	$-14 \le h \le 10$, $-10 \le k \le 11$, $-22 \le l \le 15$	$-8 \le h \le 9$, $-10 \le k \le 12$, $-29 \le l \le 33$	$-31 \le h \le 31$, $-8 \le k \le 10$, $-22 \le l \le 24$
Reflections collected	11441	12723	17904
Independent reflections	4026[R(int) = 0.0667]	4253[R(int) = 0.0515]	8448[R(int) = 0.0567]
Data/restraints/ parameters	4026/0/399	4253/0/328	8448/0/633
Goodness-of-fit on F^2	1.029	0.904	1.015
Final R indexes [I>2σ (I)]	R_1 = 0.0484, wR_2 = 0.1249	R_1 = 0.0425, wR_2 = 0.1145	R_1 = 0.0798, wR_2 = 0.1902
Final R indexes [all data]	R_1 = 0.0622, wR_2 = 0.1364	R_1 = 0.0622, wR_2 = 0.1319	R_1 = 0.183, wR_2 = 0.2384
Largest diff. peak/hole / e $Å^{-3}$	0.199/-0.173	0.268/-0.236	0.456/-0.426

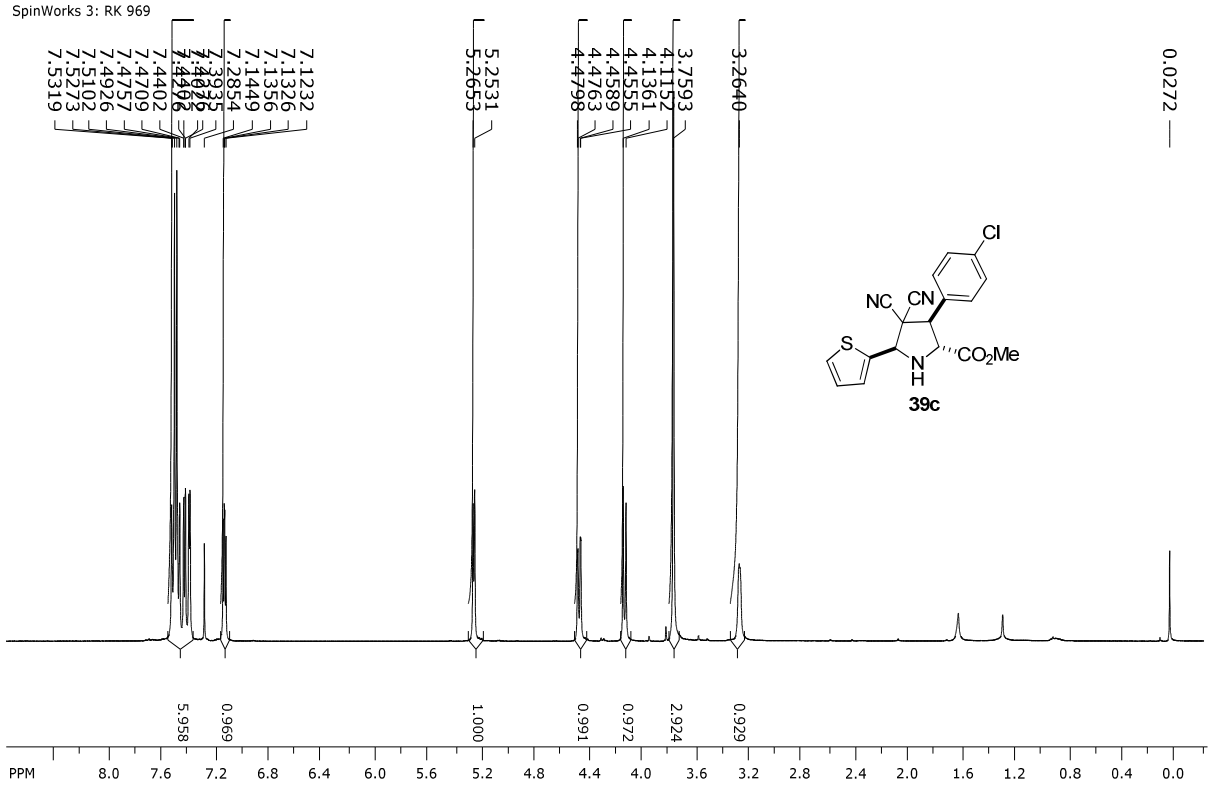
Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 2)		
X-ray Structure		
Compound	**68e**	**69a**
CCDC No.	CCDC 1447115	CCDC 1447116
Empirical formula	$C_{31}H_{24}N_2O_2S$	$C_{28}H_{22}N_2O_3$
Formula weight	488.58	434.48
Temperature / K	569(2)	569(2)
Crystal system	monoclinic	triclinic
Space group	$P2_1/n$	P-1
a / Å, b / Å, c / Å	13.432(2), 11.286(3), 17.177(3)	7.8078(7), 8.2532(7), 17.4961(14)
α/°, β/°, γ/°	90, 107.131(13), 90	77.066(5), 89.137(6), 86.562(5)
Volume / $Å^3$	2488.6(8)	1096.85(16)
Z	4	2
ρ_{calc} / mg mm^{-3}	1.304	1.316
μ / mm^{-1}	0.162	0.086
F(000)	1024	456
Crystal size / mm^3	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.2
2Θ range for data collection	6.138 to 50.722°	4.78 to 50.06°
Index ranges	$-16 \le h \le 16$, $-13 \le k \le 13$, $-20 \le l \le 20$	$-9 \le h \le 9$, $-9 \le k \le 6$, $-20 \le l \le 20$
Reflections collected	21715	10250
Independent reflections	4555[R(int) = 0.0996]	3859[R(int) = 0.0567]
Data/restraints/ parameters	4555/0/329	3859/0/386
Goodness-of-fit on F^2	1.095	1.05
Final R indexes [I>2σ (I)]	R_1 = 0.0911, wR_2 = 0.2641	R_1 = 0.0503, wR_2 = 0.1269
Final R indexes [all data]	R_1 = 0.1355, wR_2 = 0.3225	R_1 = 0.0678, wR_2 = 0.1403
Largest diff. peak/hole / e $Å^{-3}$	0.312/-0.381	0.165/-0.237

Appendix Section(Brief single crystal X-ray structure analysis data of compounds of Chapter 3)			
X-ray Structure			
Compound	**23c**	**40b**	**22c**
CCDC No.	CCDC 1453197	CCDC 1478597	CCDC 1453197
Empirical formula	$C_{18}H_{15}N_3O_2S$	$C_{12}H_{11}N_3O_3S$	$C_{21}H_{18}N_2O_4S$
Formula weight	337.39	276.29	394.43
Temperature / K	566(2)	293.0	566(2)
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/n$	$P2_1/n$	Pbca
a / Å, b / Å, c / Å	9.2816(8), 14.2096(13), 12.6958(13)	7.7742(12), 5.5689(6), 29.240(4)	9.9923(7), 17.0592(10), 22.9867(14)
α/°, β/°, γ/°	90, 96.382(5), 90	90, 94.235(6), 90	90, 90, 90
Volume / $Å^3$	1664.0(3)	1262.4(3)	3918.3(4)
Z	4	4	8
ρ_{calc} / mg mm^{-3}	1.347	1.459	1.337
μ / mm^{-1}	0.21	0.264	0.195
F(000)	704	576	1648
Crystal size / mm^3	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.2
2Θ range for data collection	6.428 to 50.054°	6.476 to 54.988°	6.526 to 54.98°
Index ranges	$-11 \le h \le 11$, $-16 \le k \le 16$, $-15 \le l \le 15$	$-10 \le h \le 10$, $-7 \le k \le 7$, $-37 \le l \le 37$	$-12 \le h \le 12$, $-22 \le k \le 22$, $-29 \le l \le 29$
Reflections collected	9605	12287	39982
Independent reflections	2929[R(int) = 0.0498]	2885[R(int) = 0.0385]	4483[R(int) = 0.0776]
Data/restraints/ parameters	2929/0/218	2885/0/173	4483/0/255
Goodness-of-fit on F^2	1.066	1.124	1.153
Final R indexes [I>2σ (I)]	R_1 = 0.0718, wR_2 = 0.2152	R_1 = 0.0715, wR_2 = 0.1951	R_1 = 0.0635, wR_2 = 0.1719
Final R indexes [all data]	R_1 = 0.0838, wR_2 = 0.233	R_1 = 0.0978, wR_2 = 0.2167	R_1 = 0.075, wR_2 = 0.1825
Largest diff. peak/hole / e $Å^{-3}$	0.583/-0.53	0.788/-0.24	0.437/-0.176

Appendix Section. Representative NMR-spectra.



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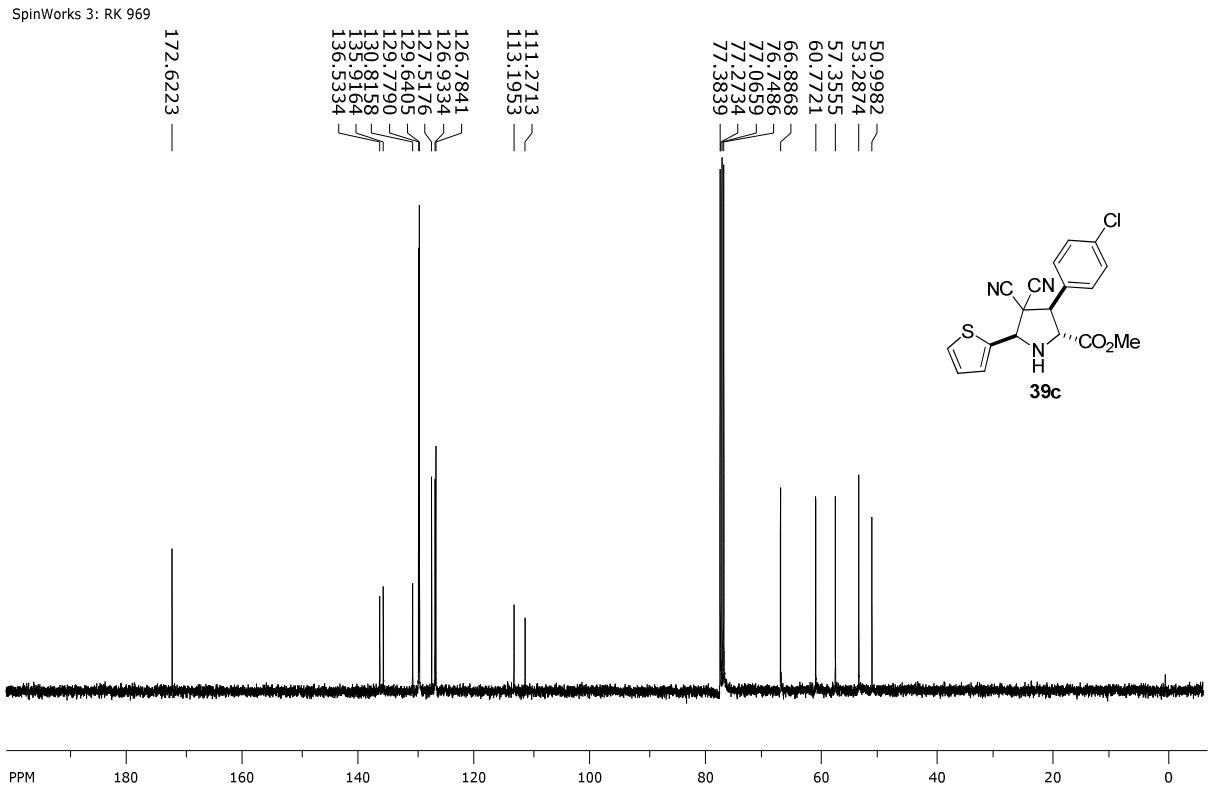
7.4926
7.4757
7.4709
7.4402
7.2854
7.1449
7.1356
7.1326
7.1232
5.2653
5.2531
4.4798
4.4763
4.4589
4.4555
4.1361
4.1152
3.7593
3.2640
0.0272
Cl
NC
CN
S
N
H
CO2Me
39c
5.958
0.969
1.000
0.991
0.972
2.924
0.929
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0


SpinWorks 3: RK 969
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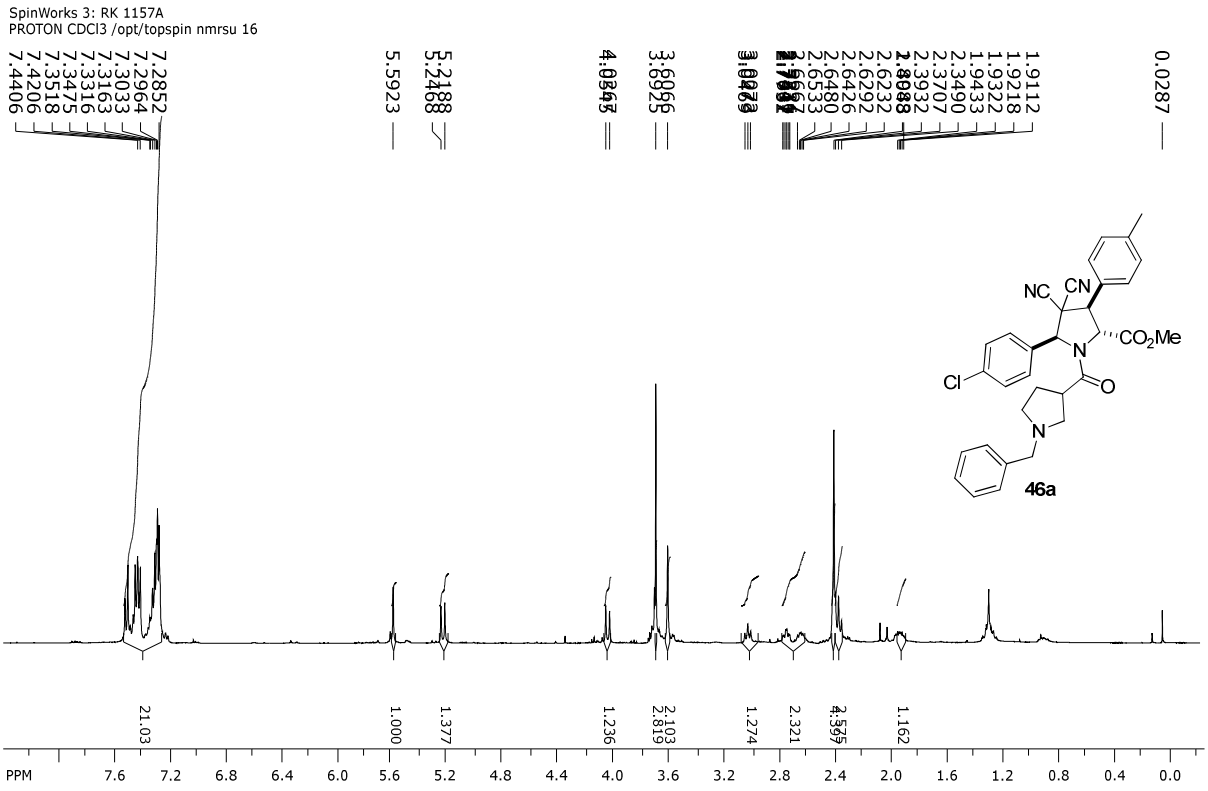
136.5334
135.9164
130.8158
129.7790
129.6405
127.5176
126.9334
126.7841
113.1953
111.2713
77.3839
77.2734
77.0659
76.7486
66.8868
60.7721
57.3555
53.2874
50.9982
Cl
NC
CN
S
N
H
CO2Me
39c
PPM
180
160
140
120
100
80
60
40
20
0


SpinWorks 3: RK 1157A
PROTON CDCl3 /opt/topspin nmrsu 16
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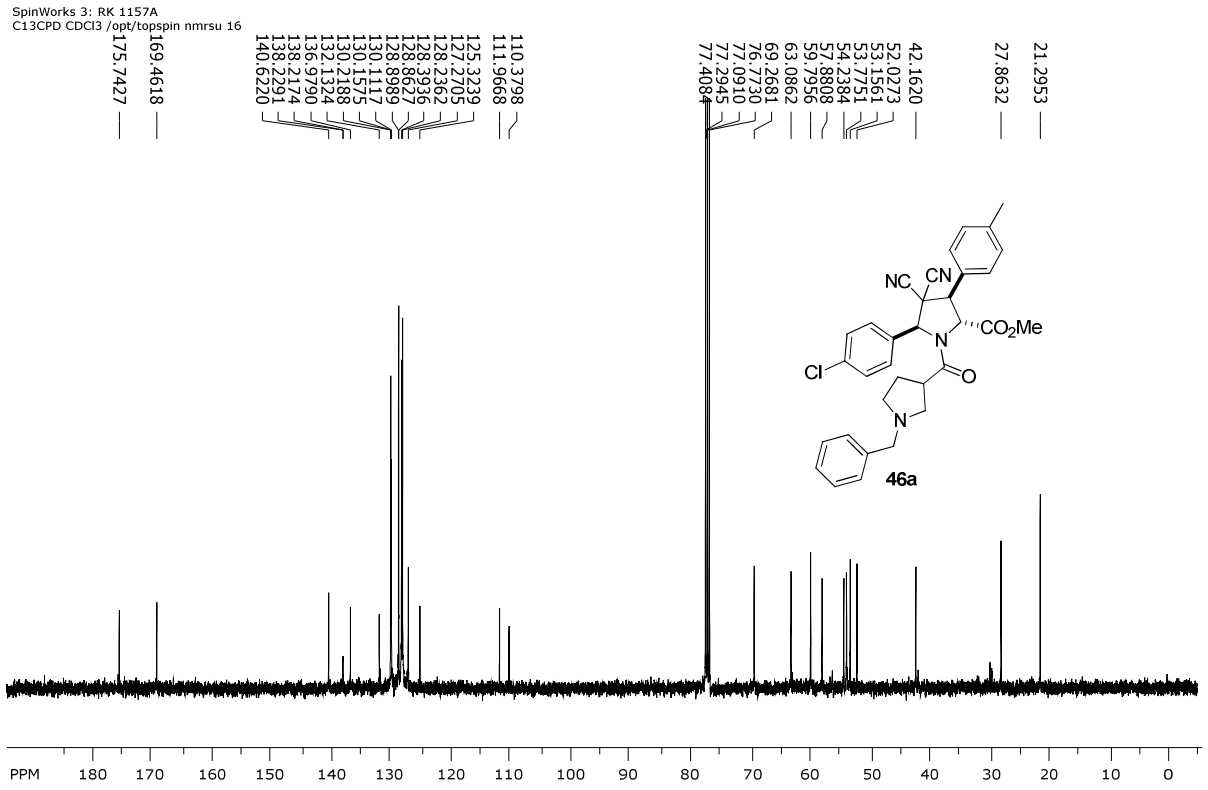
7.4206
7.3518
7.3475
7.3316
7.3163
7.3033
7.2964
7.2852
5.5923
5.2188
4.0947
3.6925
1.9112
1.9218
1.9322
1.9433
2.3490
2.3707
2.3932
2.6232
2.6292
2.6426
2.6480
2.6533
0.0287
21.03
1.000
1.377
1.236
2.103
2.819
1.274
2.321
4.397
1.162
PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0
NC
CN
CO2Me
N
O
Cl
N
46a


SpinWorks 3: RK 1157A
C13CPD CDCl3 /opt/topspin nmrsu 16
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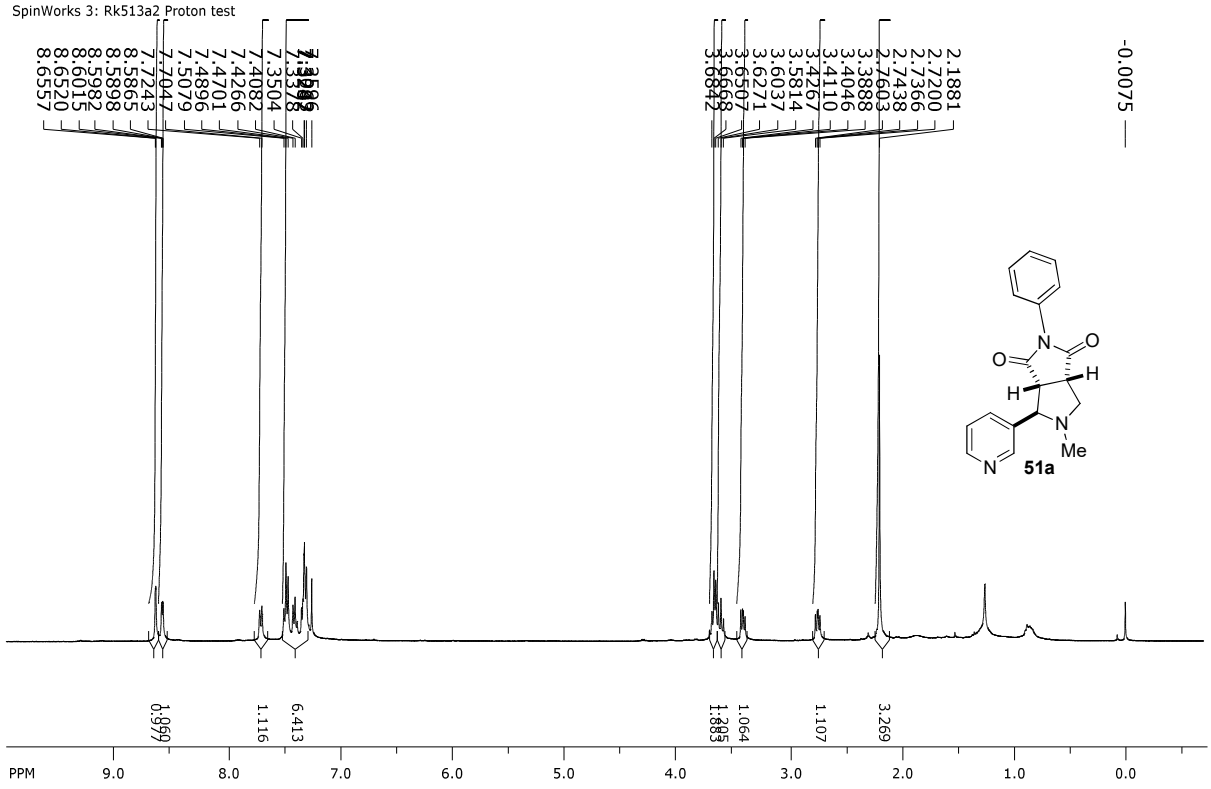
169.4618
140.6220
138.2291
138.2174
136.9790
132.1324
130.2188
130.1575
130.1117
128.8989
128.8627
128.3936
128.2362
127.2705
125.3239
111.9668
110.3798
77.4084
77.2945
77.0910
76.7730
69.2681
63.0862
59.7956
57.8808
54.2384
53.1751
53.1561
52.0273
42.1620
27.8632
21.2953
PPM
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
NC
CN
CO2Me
N
O
Cl
N
46a


SpinWorks 3: Rk513a2 Proton test
8.6557
8.6520
8.6015
8.5982
8.5898
8.5865
7.7243
7.7047
7.5079
7.4896
7.4701
7.4266
7.4082
7.3504
3.6842
3.6668
3.6507
3.6271
3.6037
3.5814
3.4267
3.4110
3.4046
3.3888
2.7603
2.7438
2.7366
2.7200
2.1881
-0.0075
1.069
0.977
1.116
6.413
1.885
1.064
1.107
3.269
PPM
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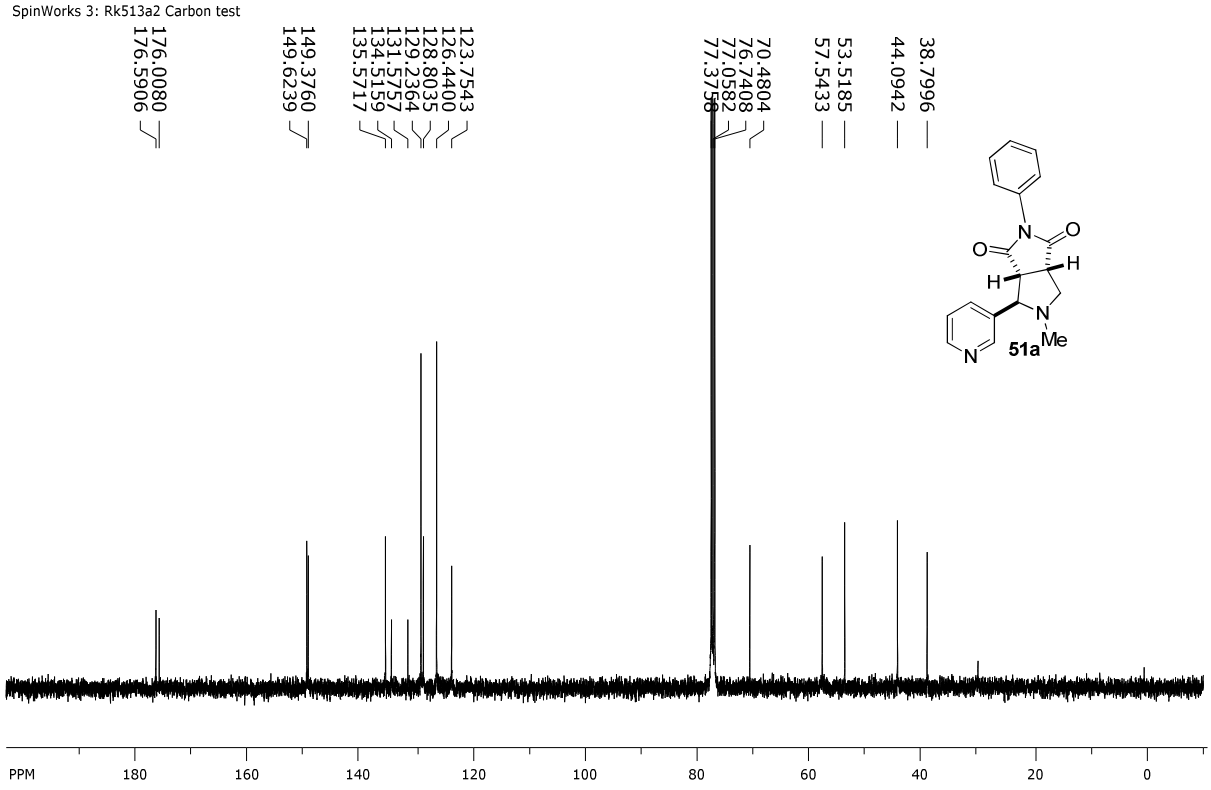
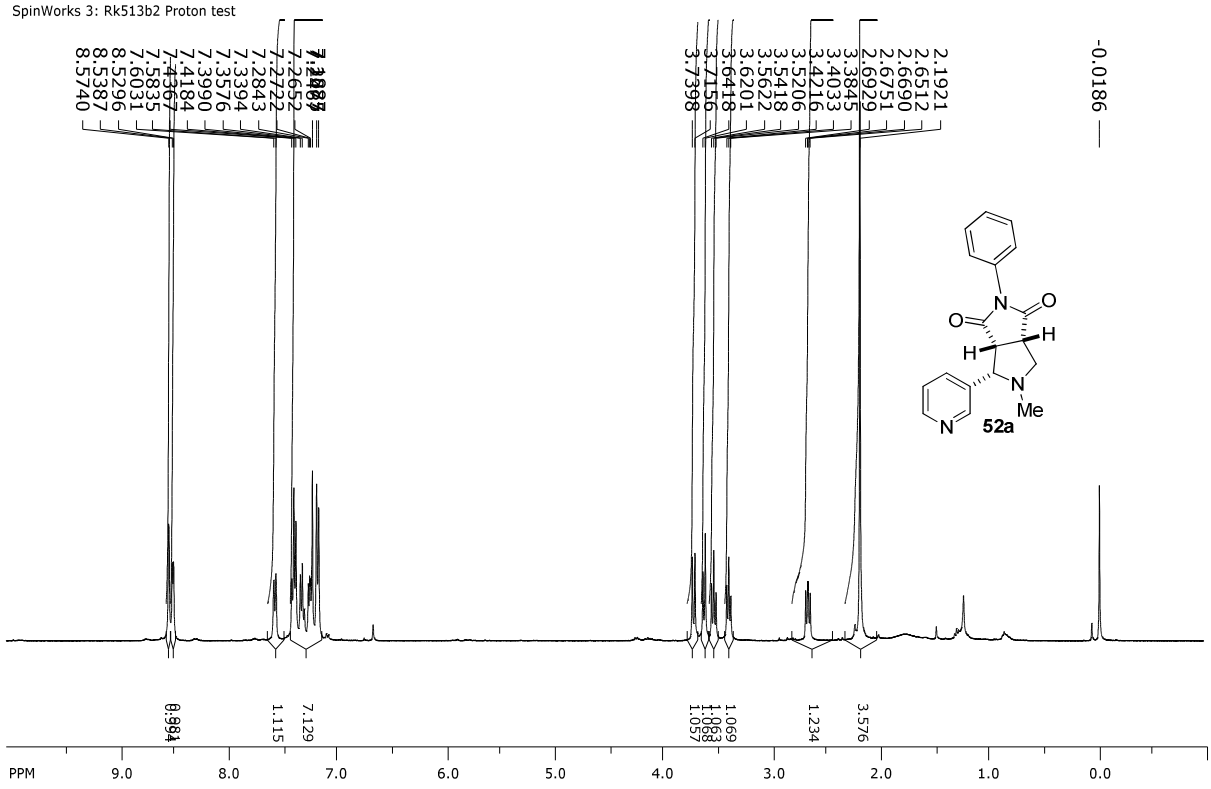
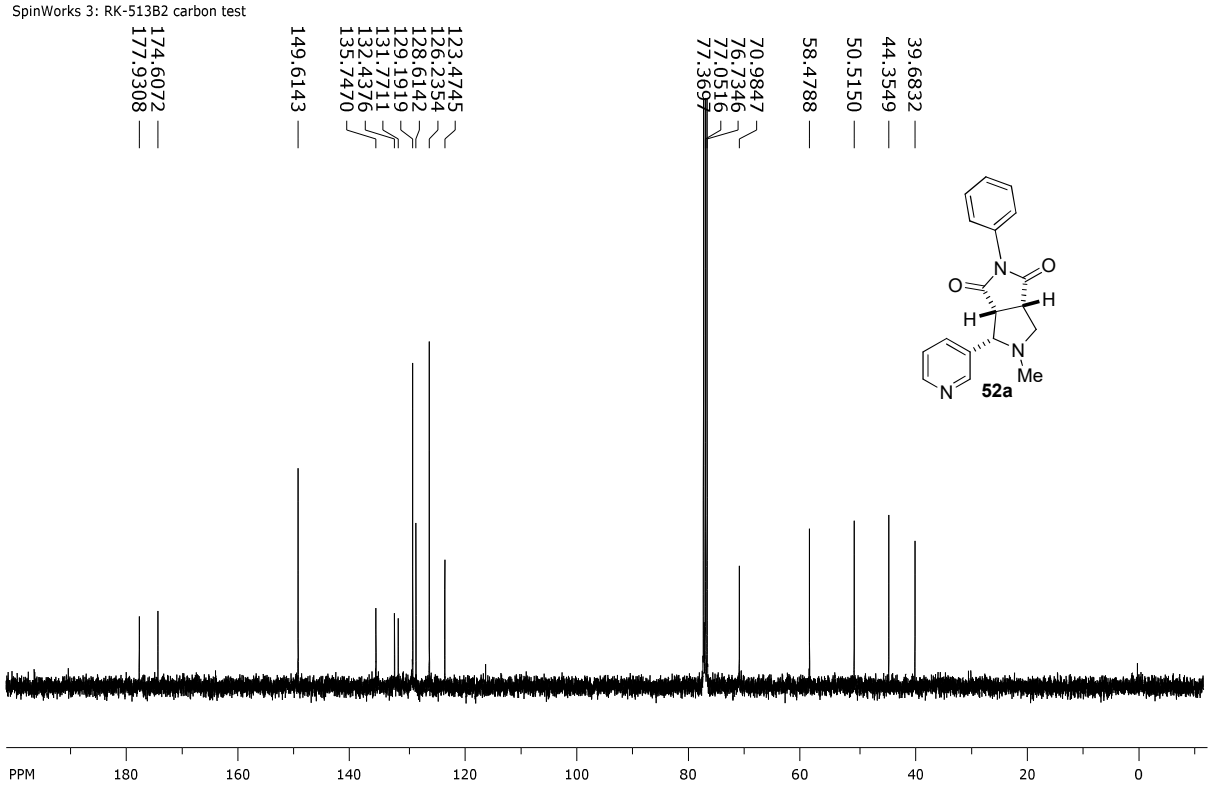
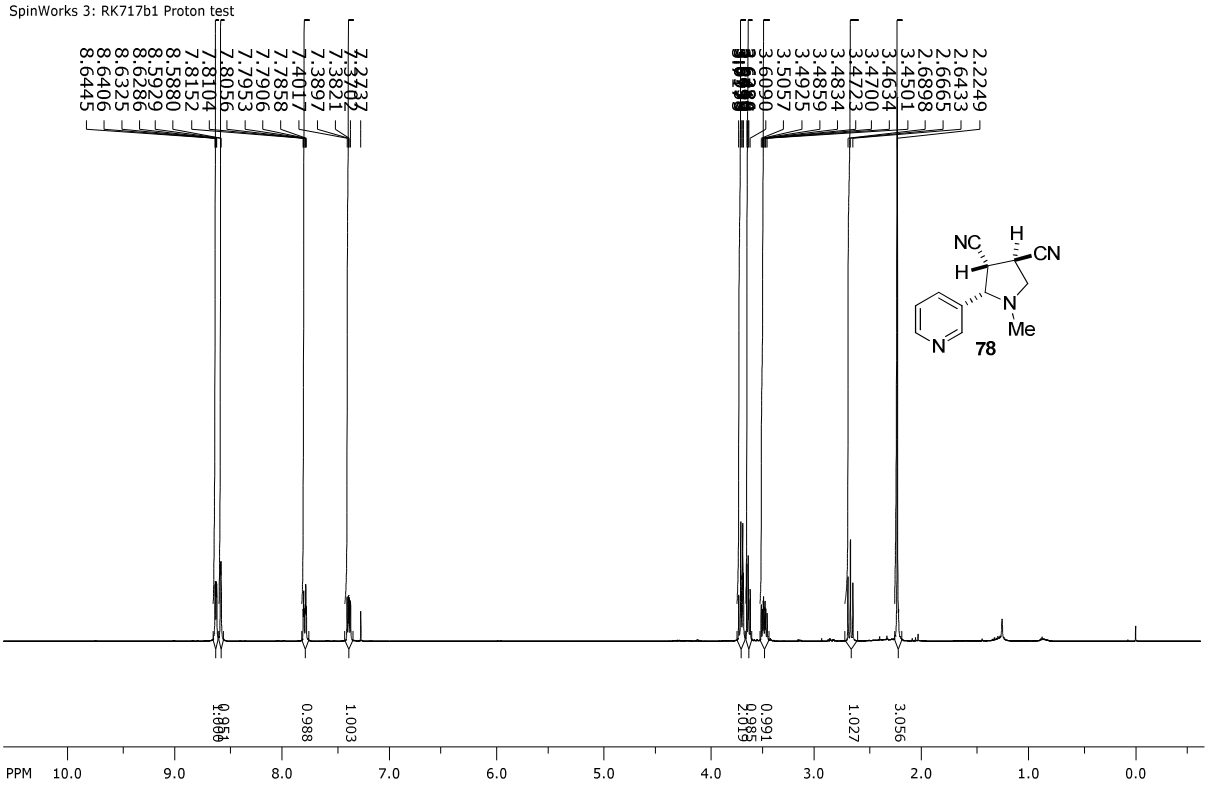
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
51a


SpinWorks 3: Rk513a2 Carbon test
176.0080
176.5906
149.3760
149.6239
135.5717
134.5159
131.5757
129.2364
128.8035
126.4400
123.7543
77.3756
76.7408
70.4804
57.5433
53.5185
44.0942
38.7996
PPM
180
160
140
120
100
80
60
40
20
0
51a


SpinWorks 3: Rk513b2 Proton test
8.5740
8.5387
8.5296
7.6031
7.5835
7.4367
7.4184
7.3990
7.3576
7.3394
7.2843
7.2722
7.2652
3.7398
3.7156
3.6418
3.6201
3.5622
3.5418
3.5206
3.4216
3.4033
3.3845
2.6929
2.6751
2.6690
2.6512
2.1921
-0.0186
0.994
1.115
7.129
1.057
1.069
1.234
3.576
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
N
O
O
H
H
N
Me
N
52a


SpinWorks 3: RK-513B2 carbon test
177.9308
174.6072
149.6143
135.7470
132.4376
131.7711
129.1919
128.6142
126.2354
123.4745
77.3697
77.0516
76.7346
70.9847
58.4788
50.5150
44.3549
39.6832
PPM
180
160
140
120
100
80
60
40
20
0
N
O
O
H
H
N
Me
N
52a


SpinWorks 3: RK717b1 Proton test
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8.6406
8.6325
8.6286
8.5929
8.5880
7.8152
7.8104
7.8056
7.7953
7.7906
7.7858
7.4017
7.3897
7.3821
7.3737
2.2249
2.6433
2.6665
2.6898
3.4501
3.4634
3.4700
3.4723
3.4834
3.4859
3.4925
3.5057
3.6090
0.851
0.988
1.003
0.991
1.027
3.056
NC
H
CN
H
N
Me
N
78
PPM
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8.0
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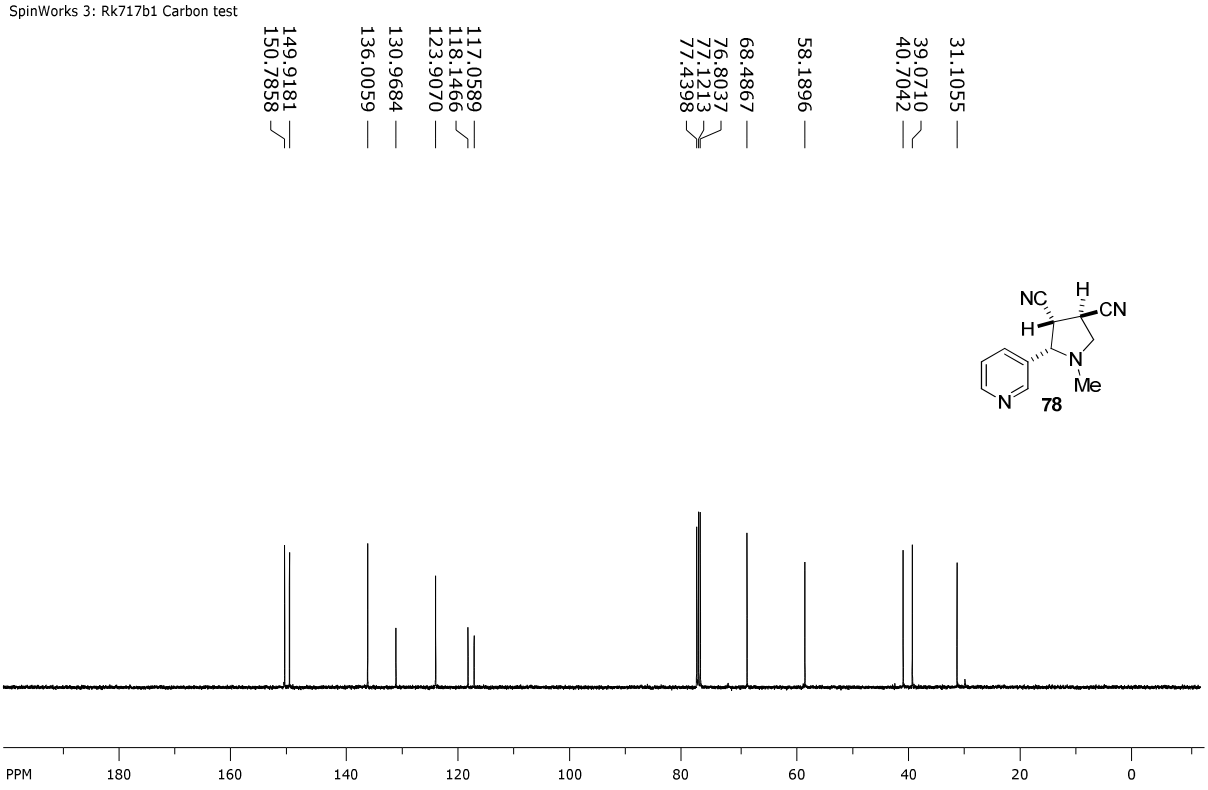
6.0
5.0
4.0
3.0
2.0
1.0
0.0


SpinWorks 3: Rk717b1 Carbon test
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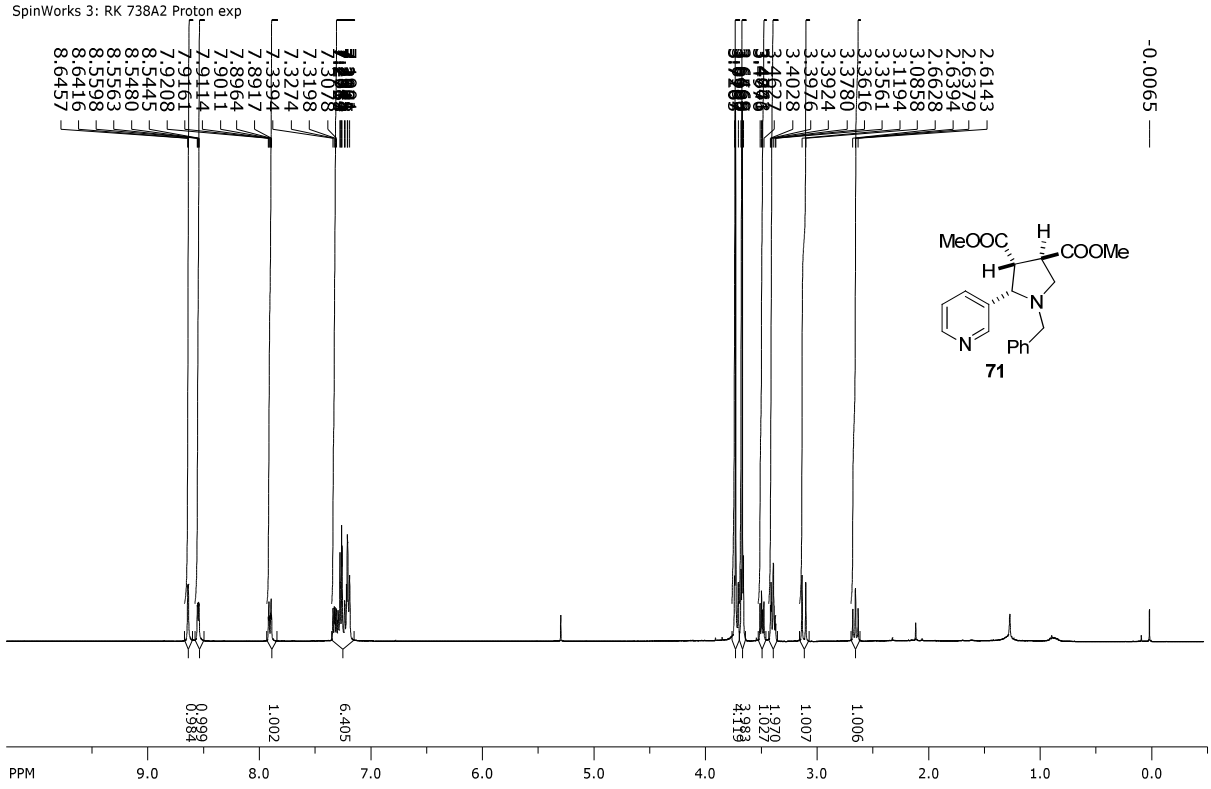
150.7858
136.0059
130.9684
123.9070
117.0589
118.1466
77.4398
77.1213
76.8037
68.4867
58.1896
39.0710
40.7042
31.1055
NC
H
CN
H
N
Me
N
78
PPM
180
160
140
120
100
80
60
40
20
0


SpinWorks 3: RK 738A2 Proton exp
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8.6416
8.5598
8.5563
8.5480
8.5445
7.9208
7.9161
7.9114
7.9011
7.8964
7.8917
7.3394
7.3274
7.3198
7.3098
2.6143
2.6379
2.6394
2.6628
3.0858
3.1194
3.3561
3.3616
3.3780
3.3924
3.3976
3.4028
-0.0065
MeOOC
H
COOMe
N
Ph
71
0.999
0.984
1.002
6.405
3.983
1.970
1.027
1.007
1.006
PPM
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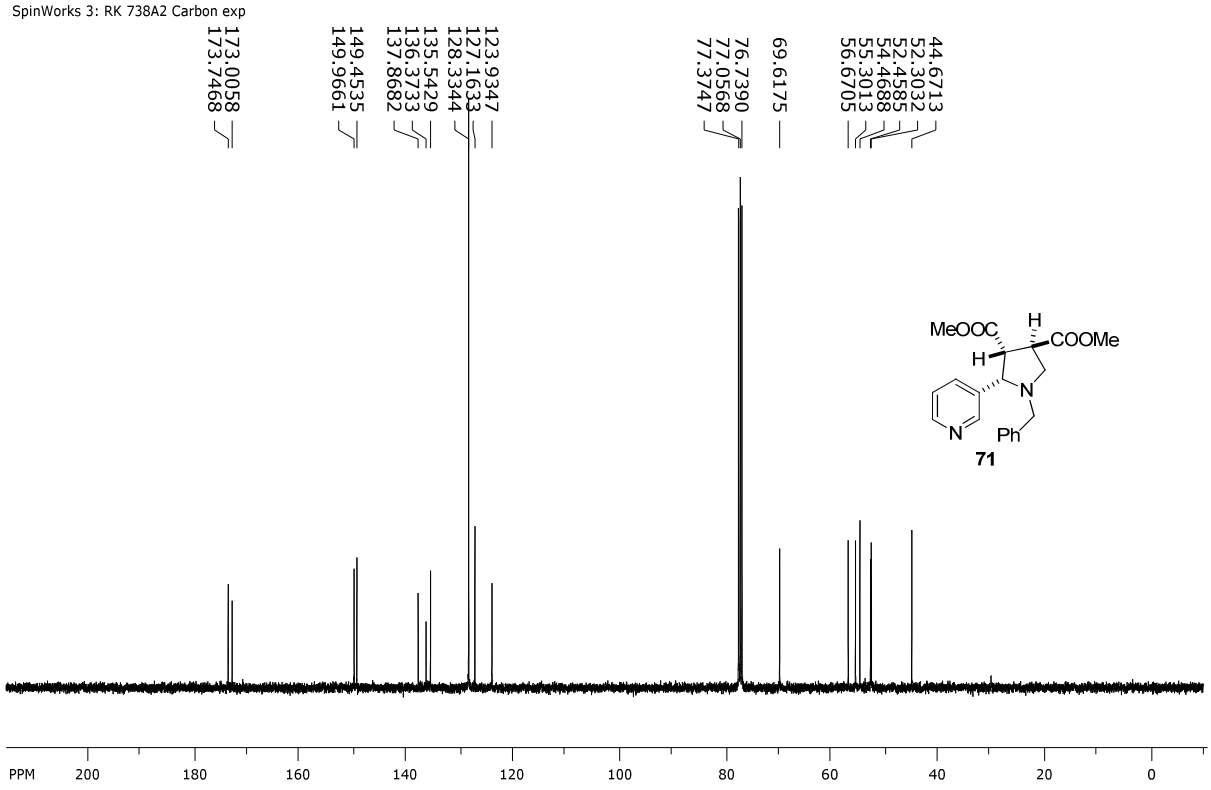
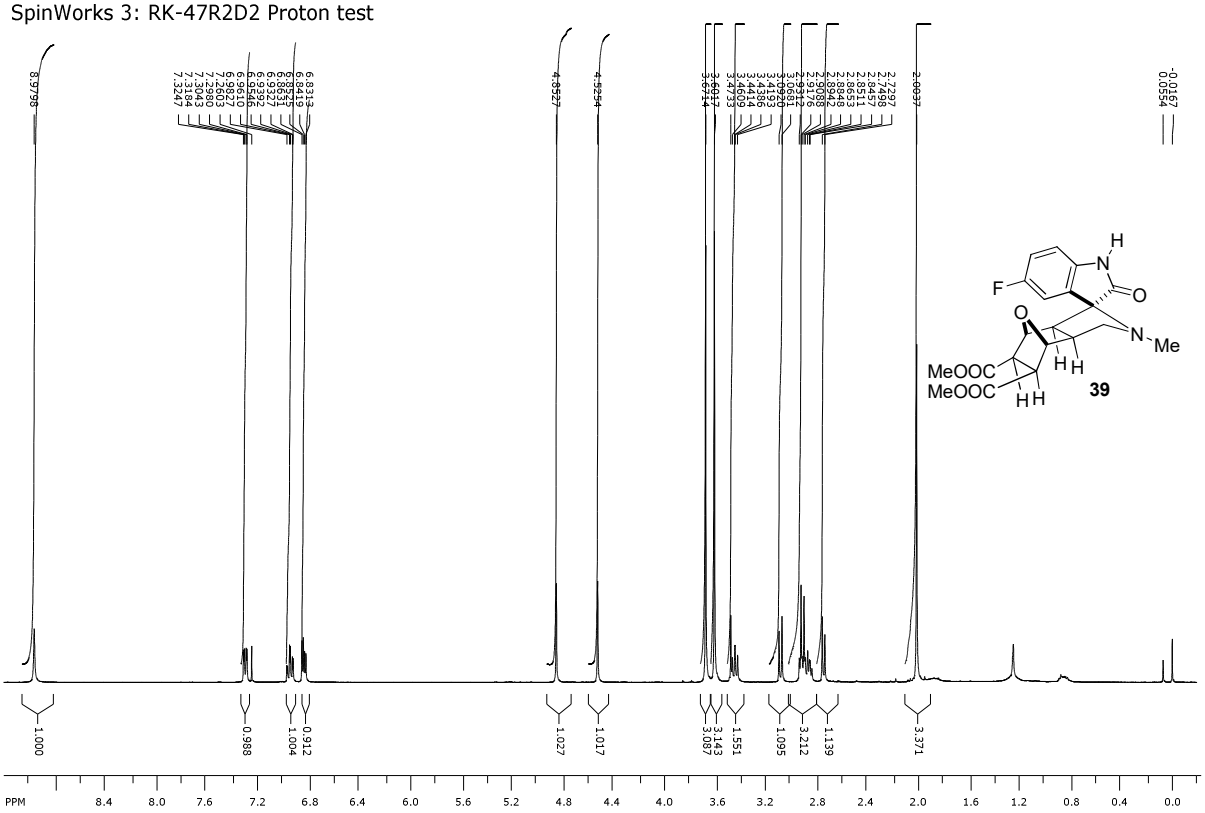
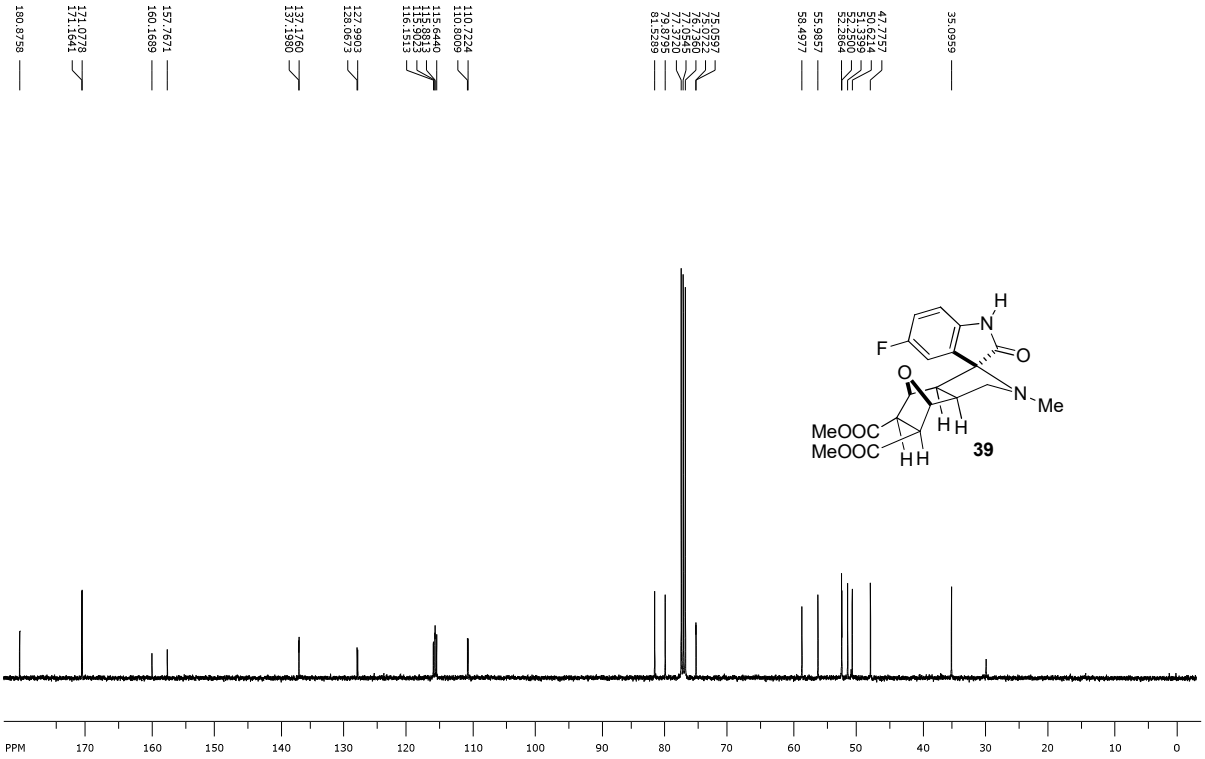
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


SpinWorks 3: RK 738A2 Carbon exp
173.0058
173.7468
149.4535
149.9661
137.8682
136.3733
135.5429
128.3344
127.1633
123.9347
77.3747
77.0568
76.7390
69.6175
56.6705
55.3013
54.4688
52.4585
52.3032
44.6713
MeOOC
H
COOMe
N
Ph
71
PPM
200
180
160
140
120
100
80
60
40
20
0

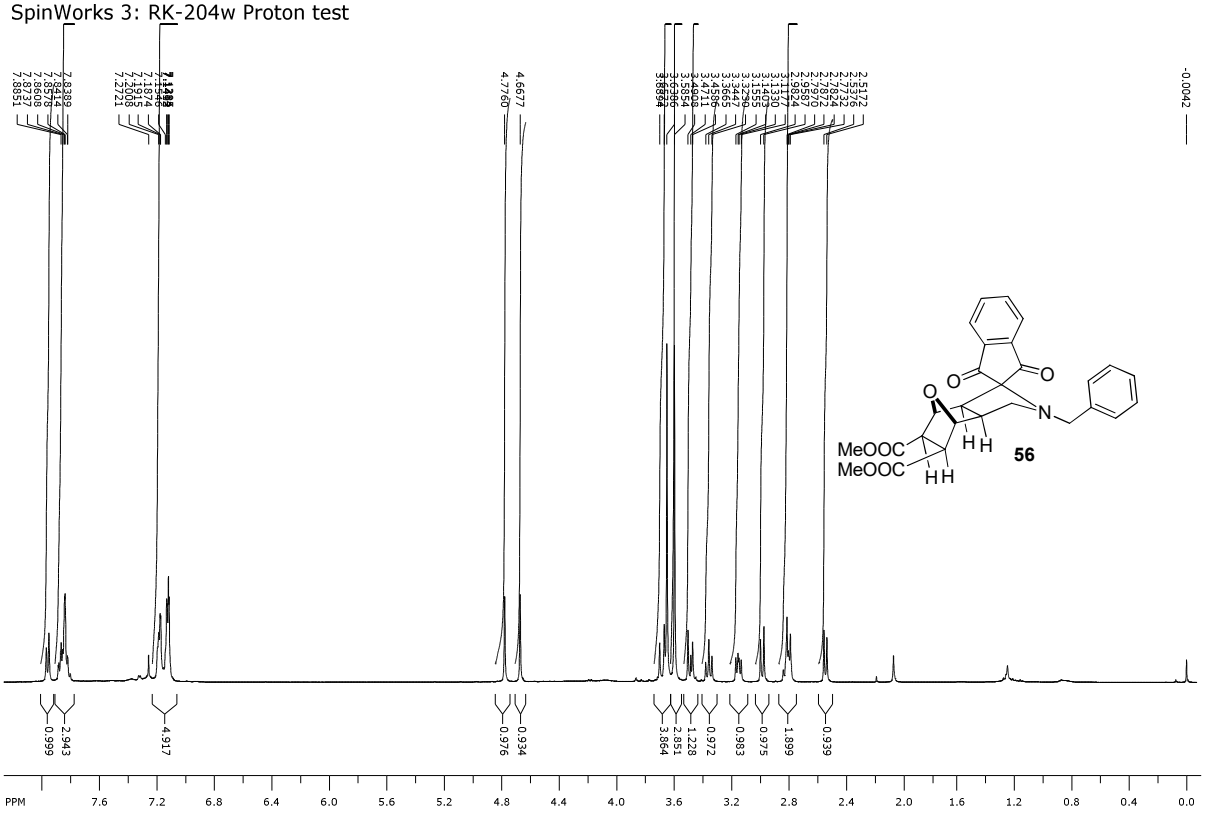
SpinWorks 3: RK-47R2D2 Proton test



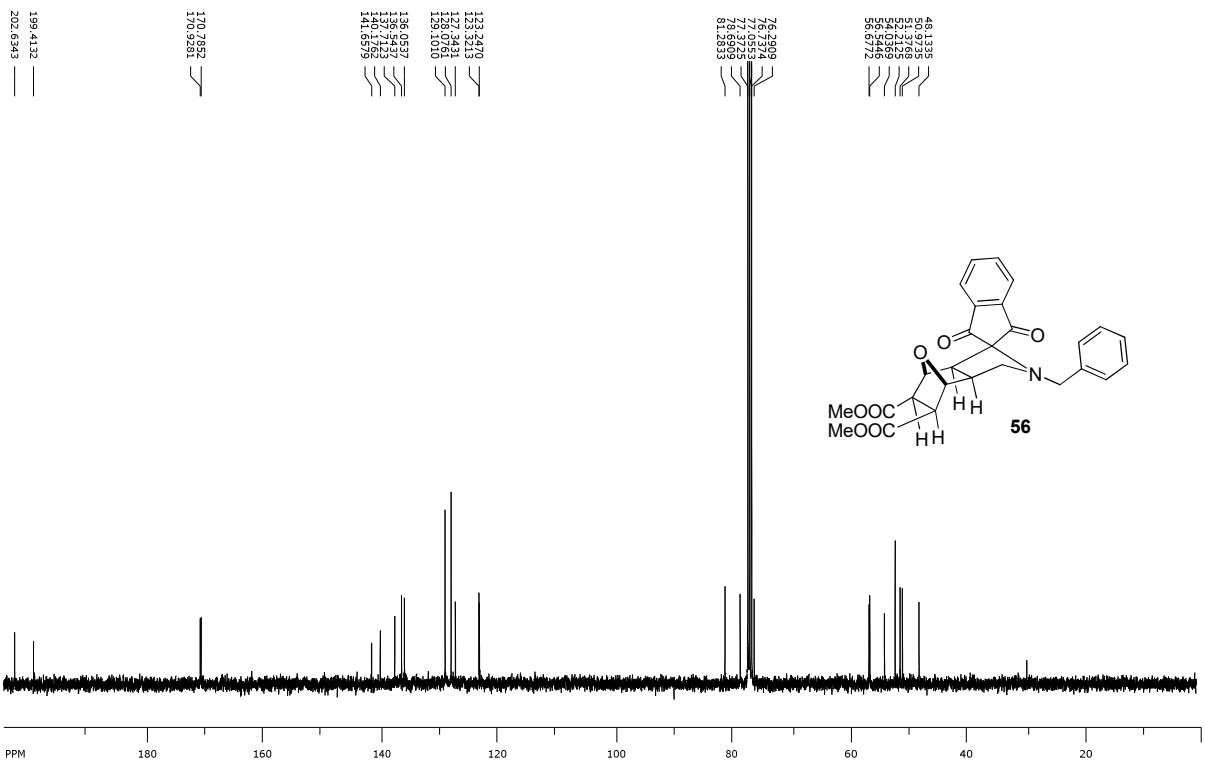
SpinWorks 3: RK-47R2D2 Carbon test



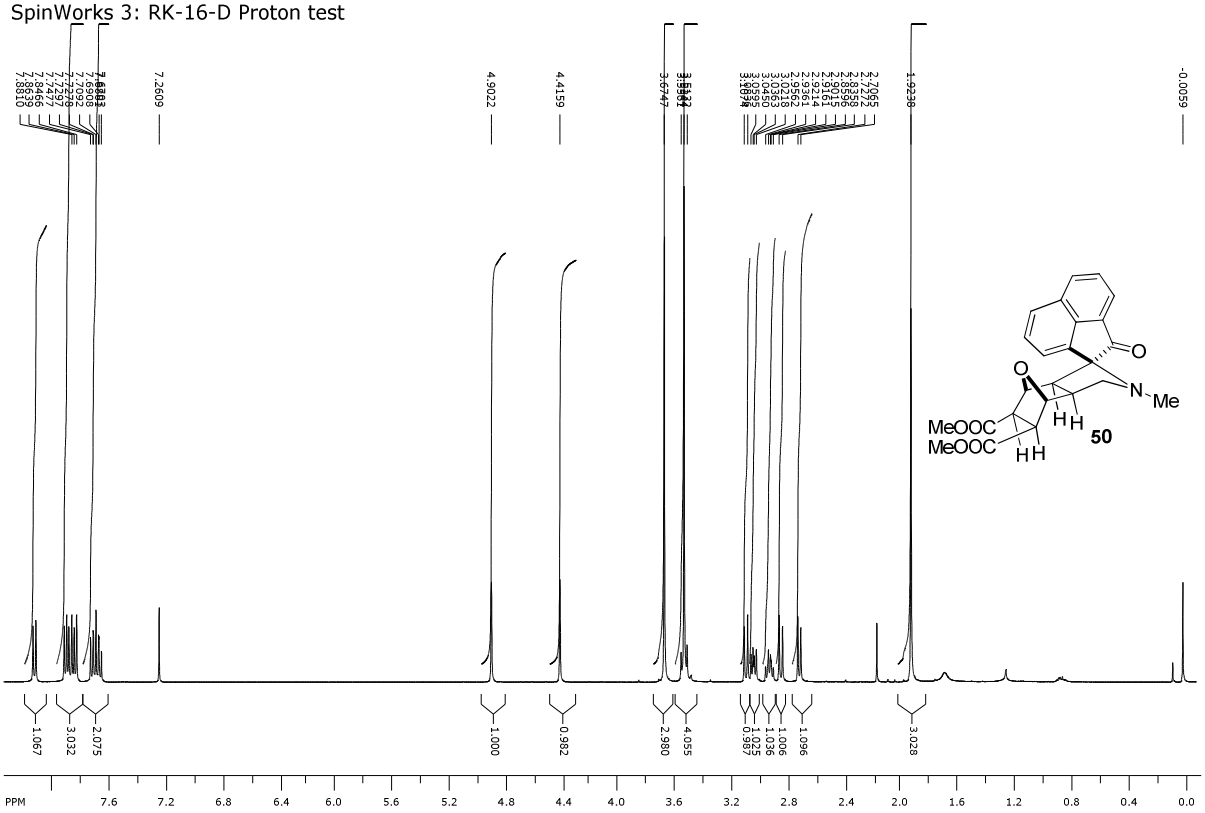
SpinWorks 3: RK-204w Proton test



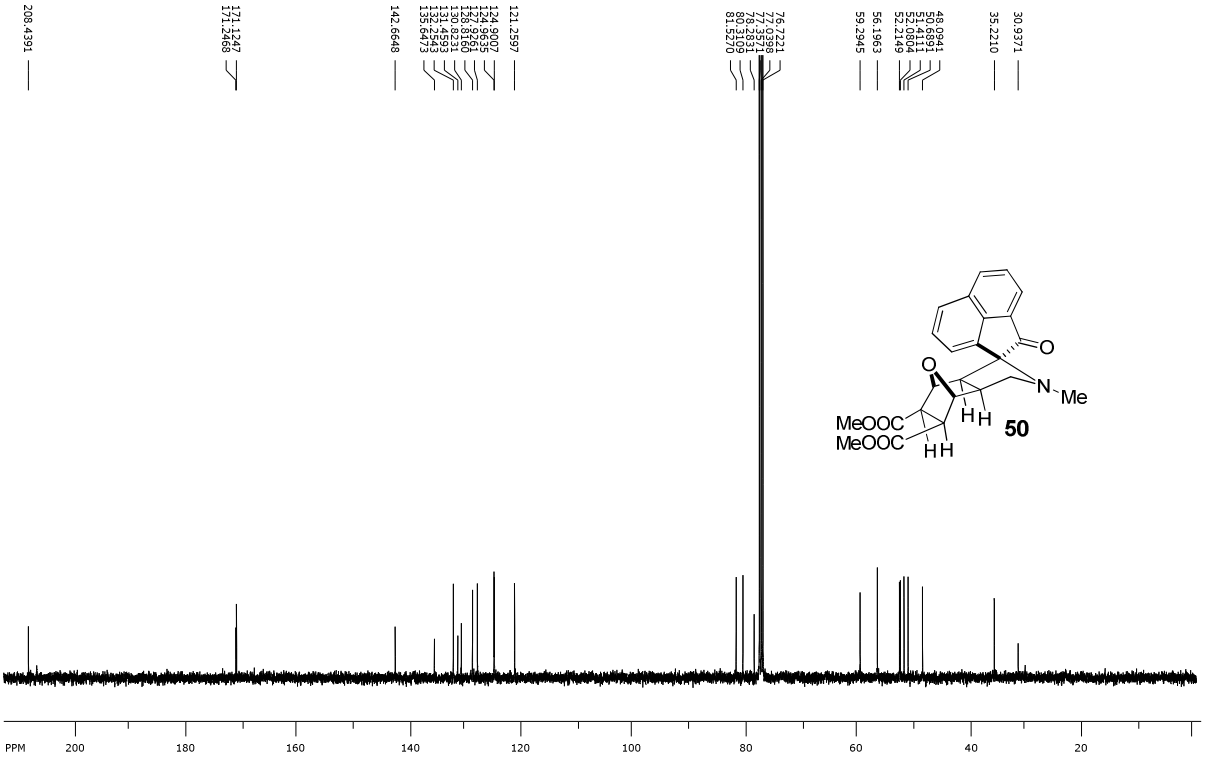
SpinWorks 3: RK-204W Carbon test

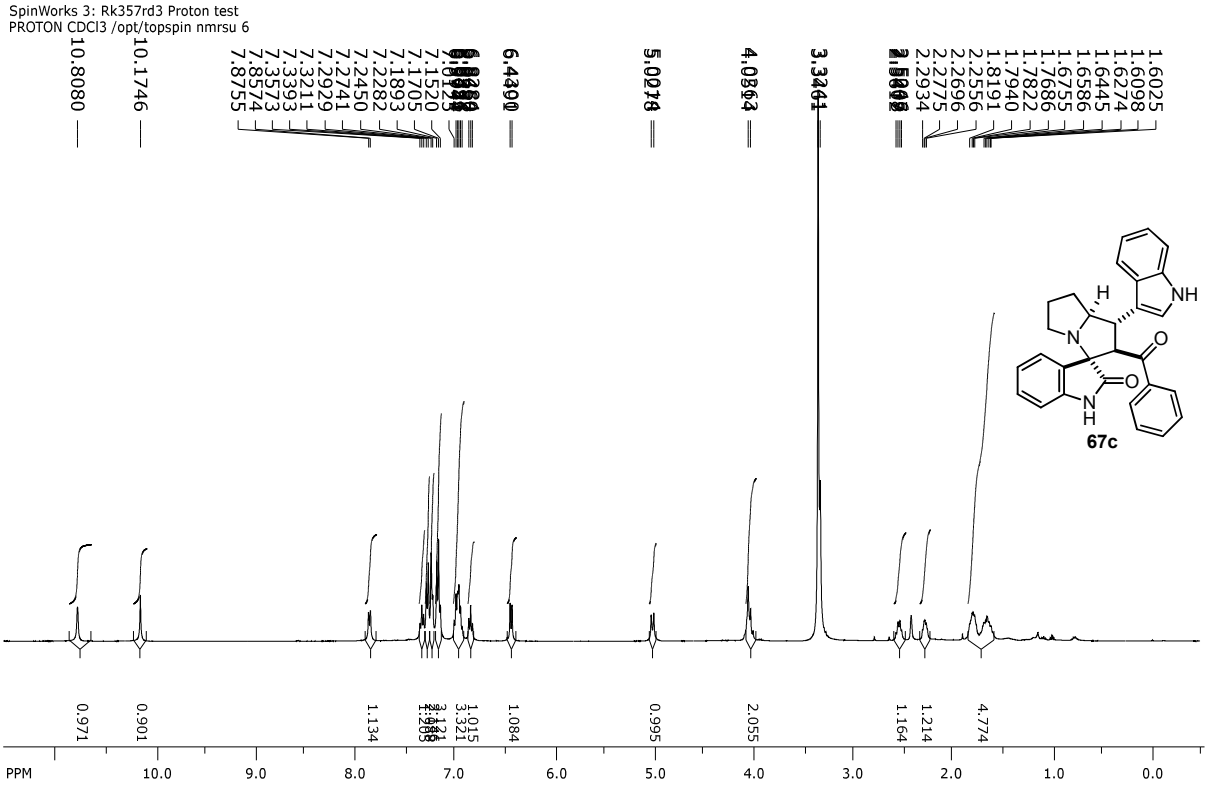


SpinWorks 3: RK-16-D Proton test



SpinWorks 3: RK-16D Carbon test




SpinWorks 3: Rk357rd3 Proton test
PROTON CDCl3 /opt/topspin nmrsu 6
10.8080
10.1746
7.8755
7.8574
7.3573
7.3393
7.3211
7.2929
7.2741
7.2450
7.2282
7.1893
7.1705
7.1520
6.4490
5.0278
4.0364
3.3401
2.2934
2.2775
2.2696
2.2556
1.8191
1.7940
1.7822
1.7686
1.7555
1.6586
1.6445
1.6274
1.6098
1.6025
0.971
0.901
1.134
1.015
3.321
1.084
0.995
2.055
1.164
1.214
4.774
PPM
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8.0
7.0
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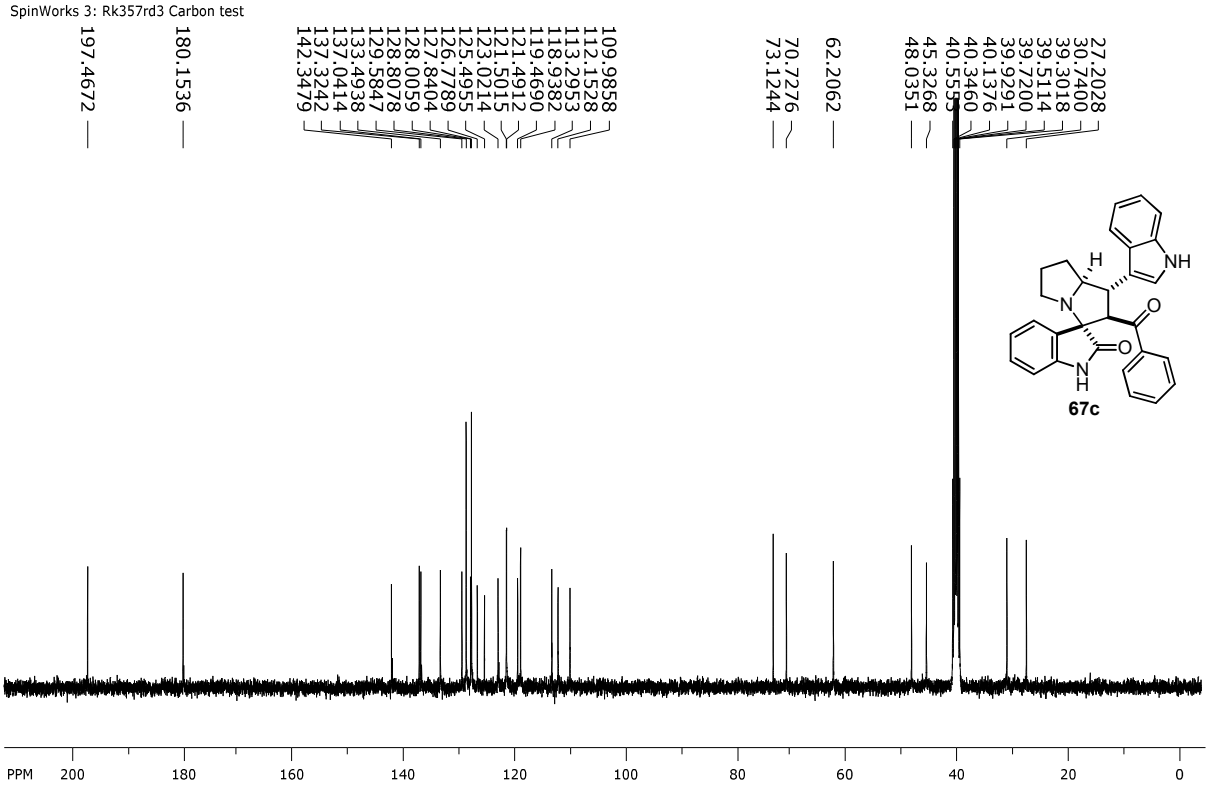
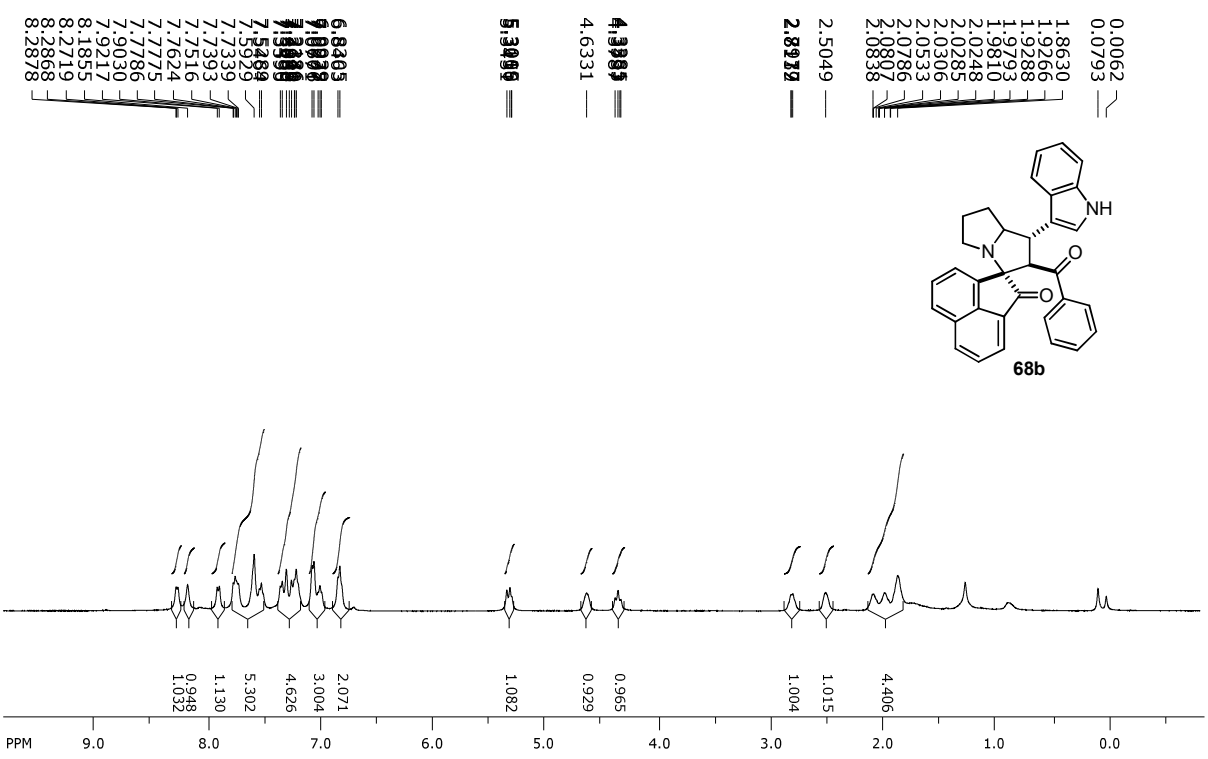
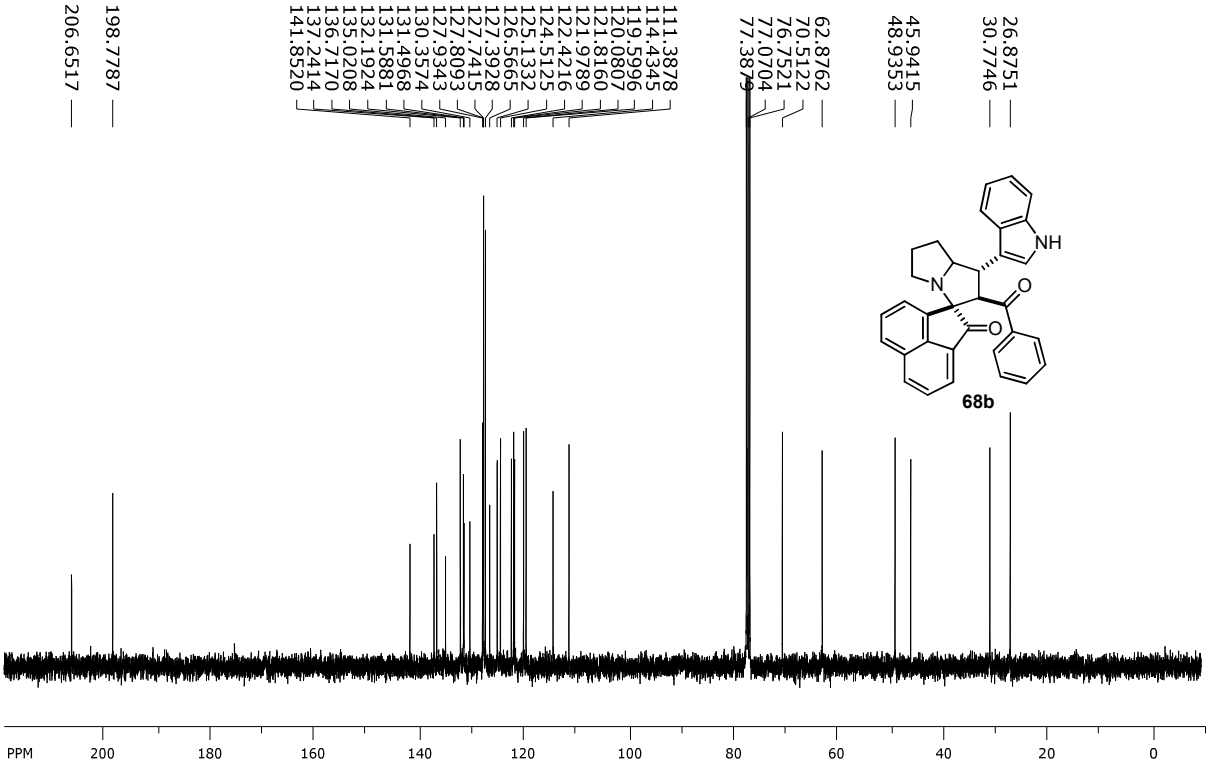
5.0
4.0
3.0
2.0
1.0
0.0
67c


SpinWorks 3: Rk357rd3 Carbon test
197.4672
180.1536
142.3479
137.3242
137.0414
133.4938
129.5847
128.8078
128.0059
127.8404
126.7789
125.4955
123.0214
121.5015
121.4912
119.4690
118.9382
113.2953
112.1528
109.9858
73.1244
70.7276
62.2062
48.0351
45.3268
40.5595
40.3460
40.1376
39.9291
39.7200
39.5114
39.3018
30.7400
27.2028
PPM
200
180
160
140
120
100
80
60
40
20
0
67c

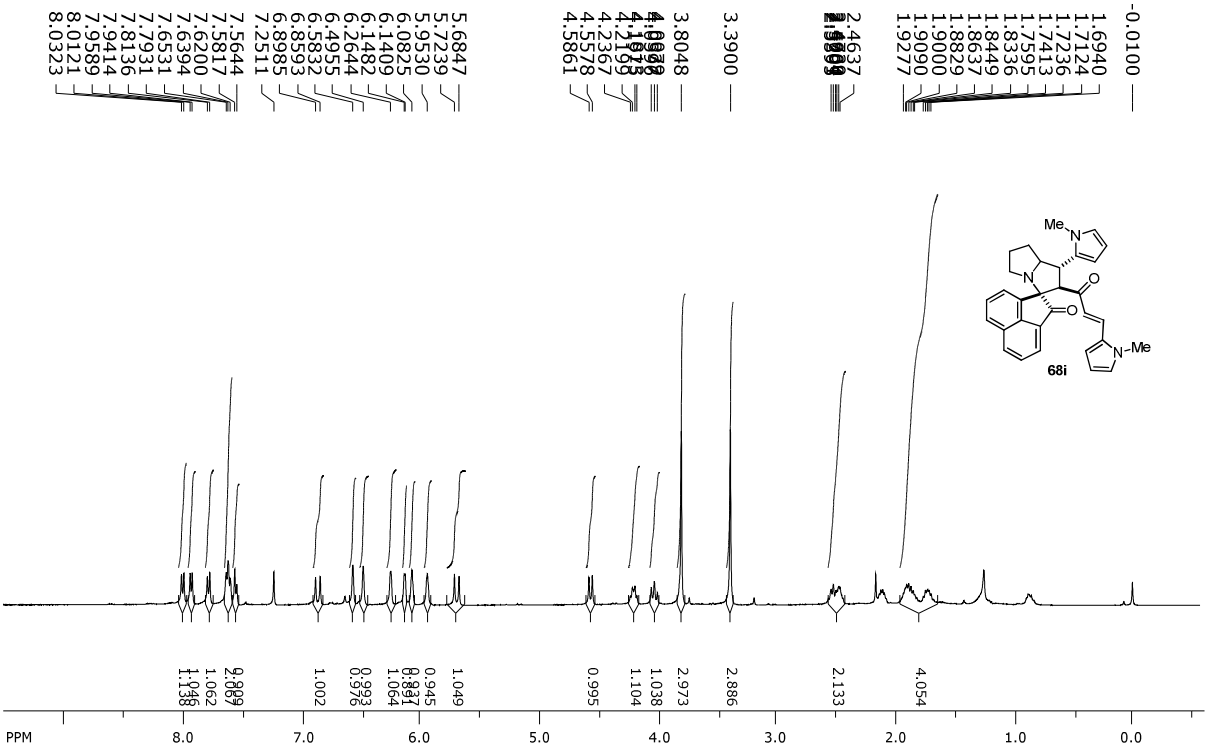
SpinWorks 3: Rk359r2c2 Proton test



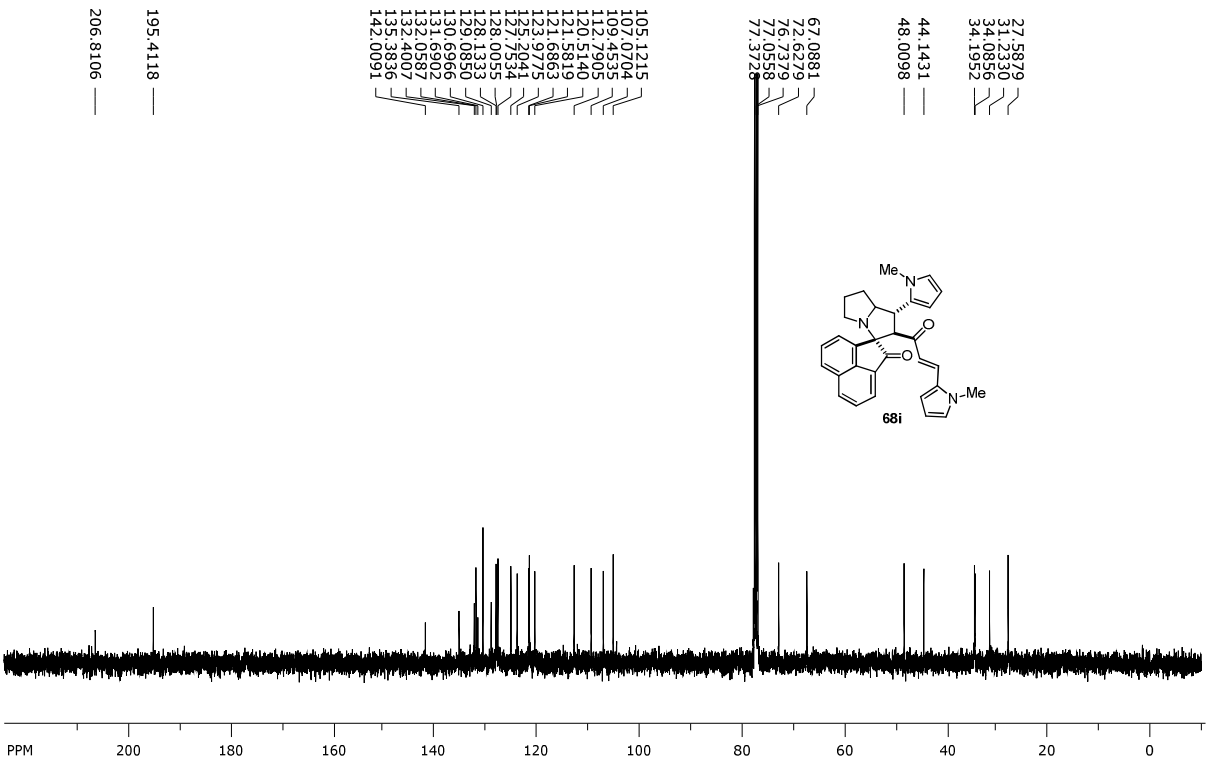
SpinWorks 3: RK359rc3 Carbon test

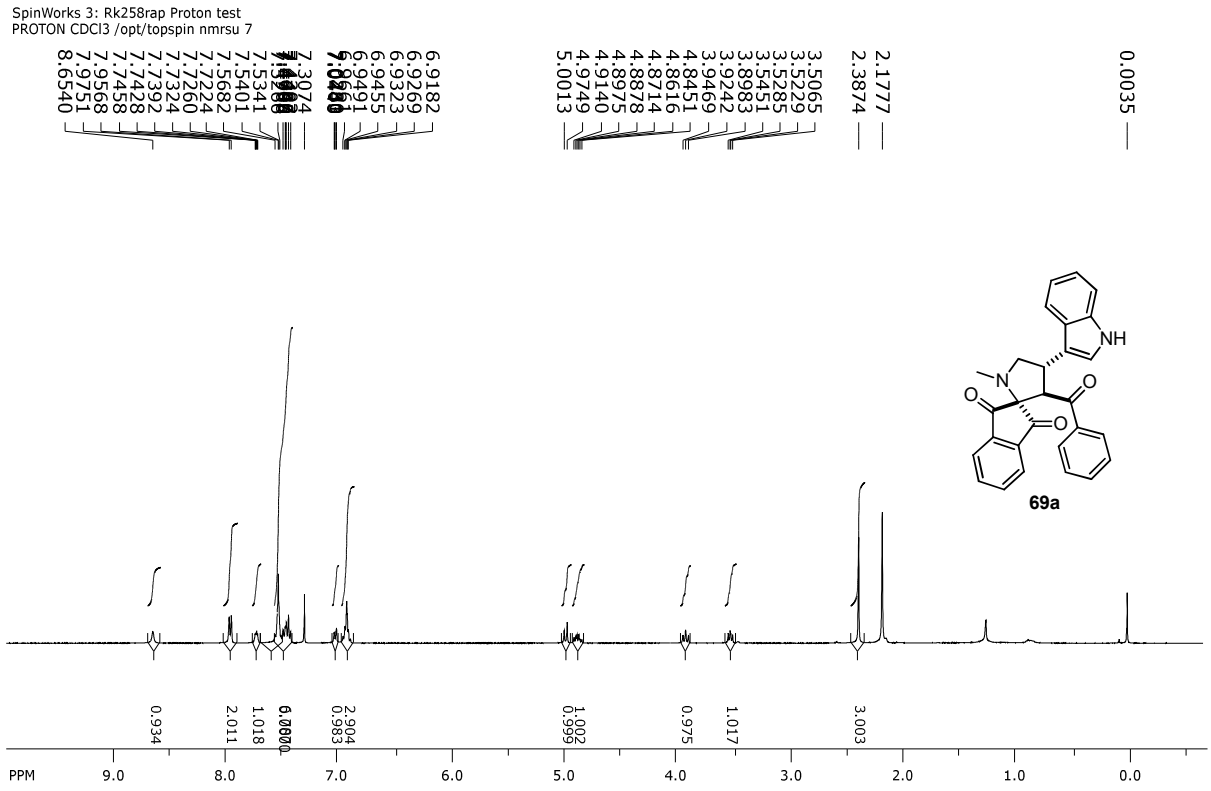


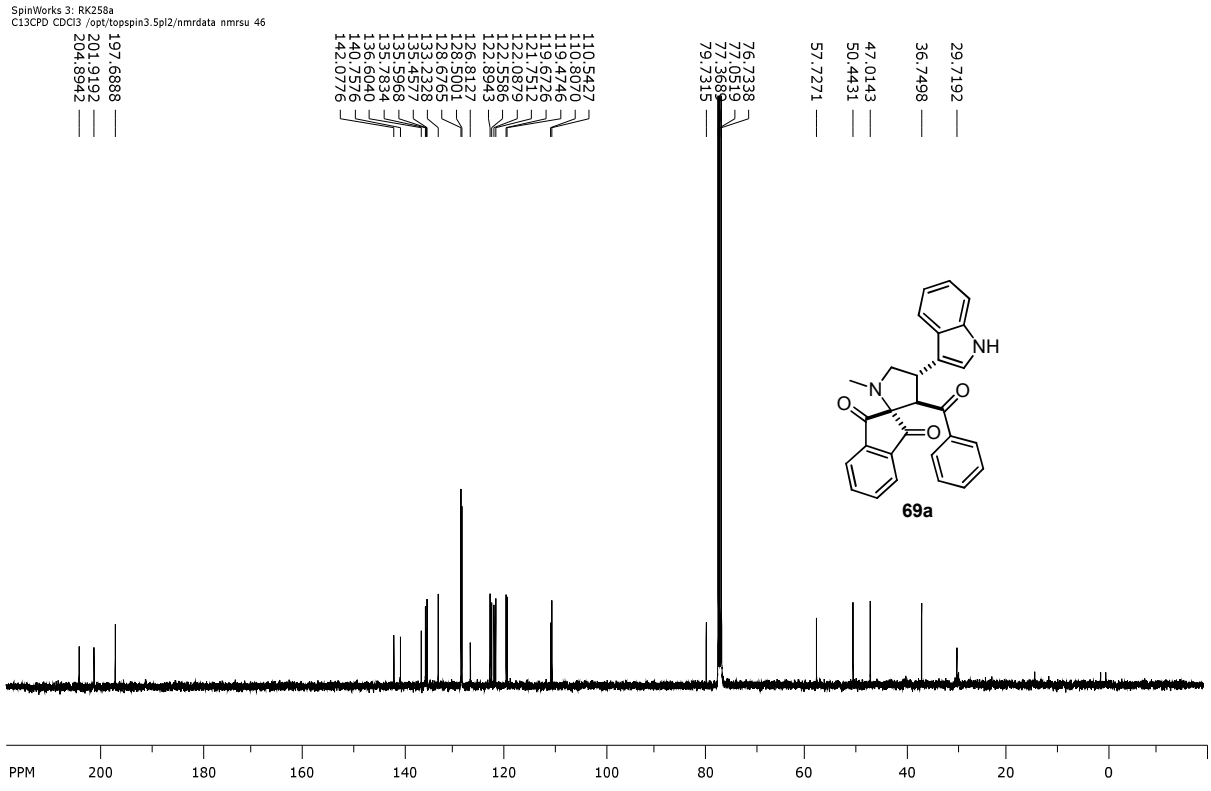
SpinWorks 3: Rk442a1 Proton test

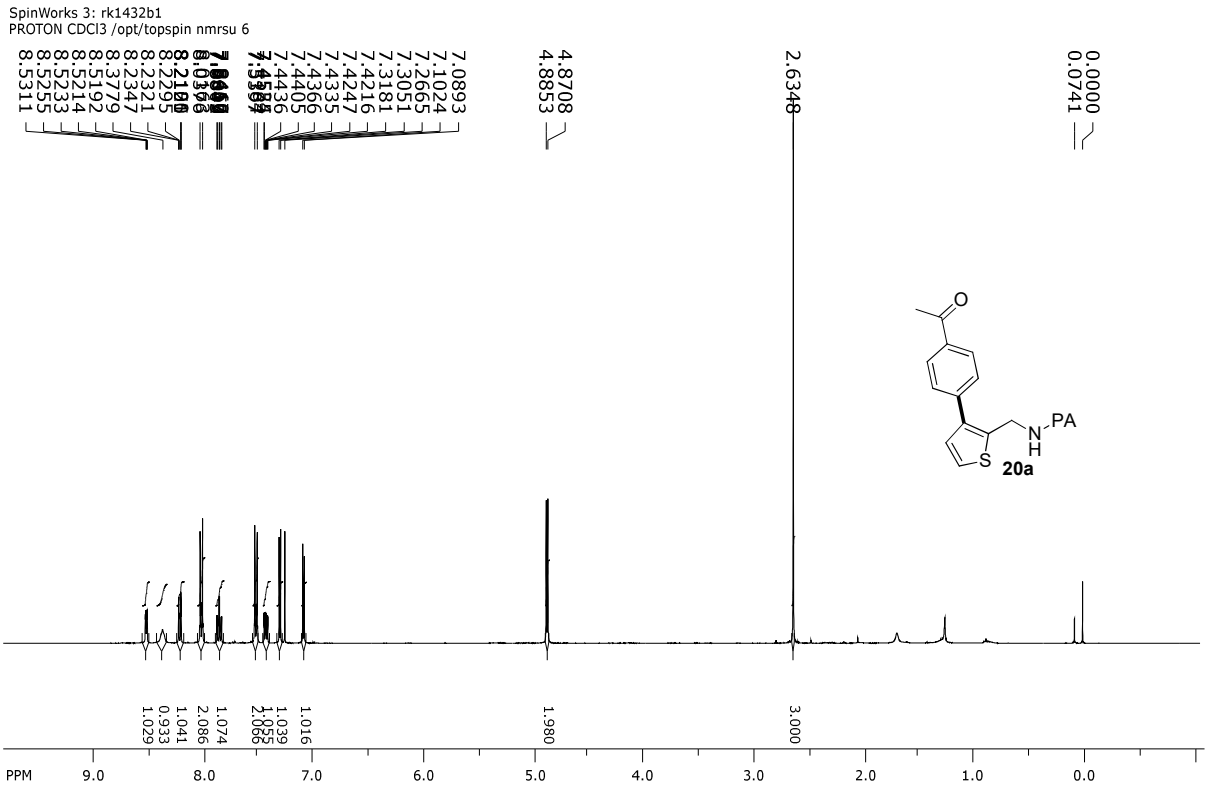


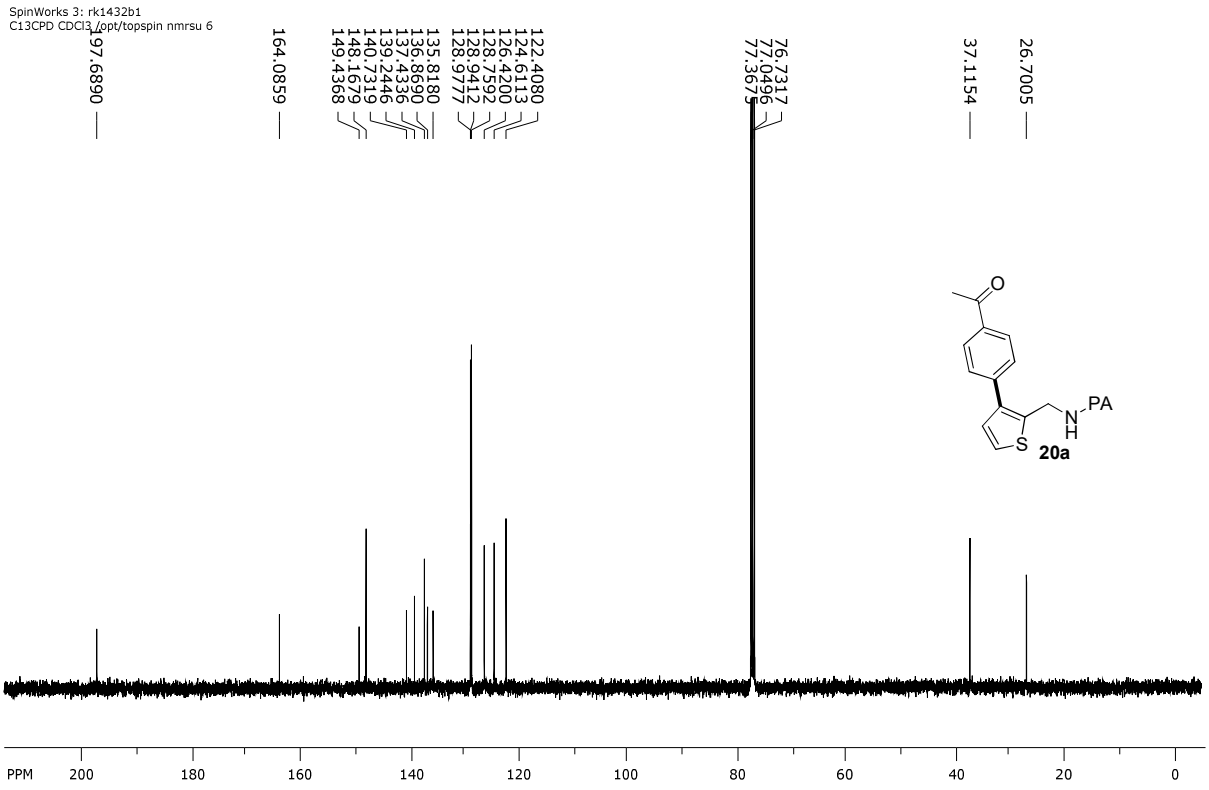
SpinWorks 3: RK442a1 Carbon test



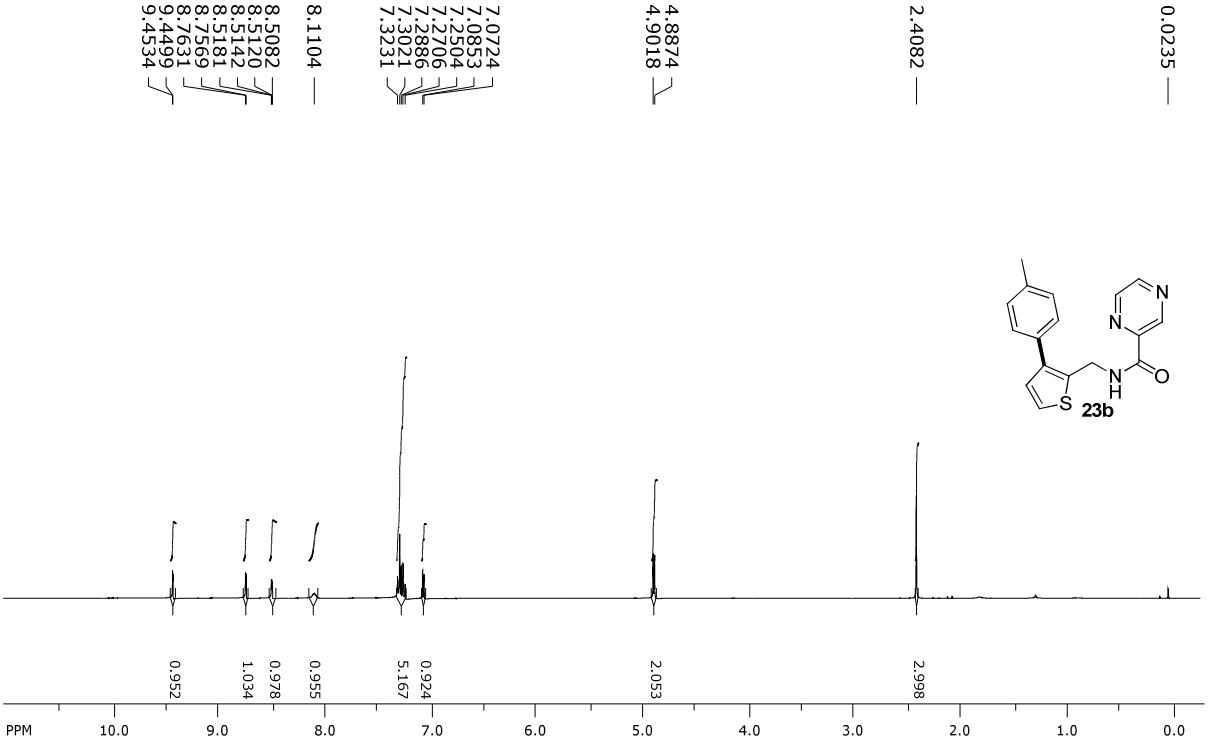

SpinWorks 3: Rk258rap Proton test
PROTON CDCl3 /opt/topspin nmrsu 7
69a
PPM


SpinWorks 3: RK258a
C13CPD CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 46
69a
PPM

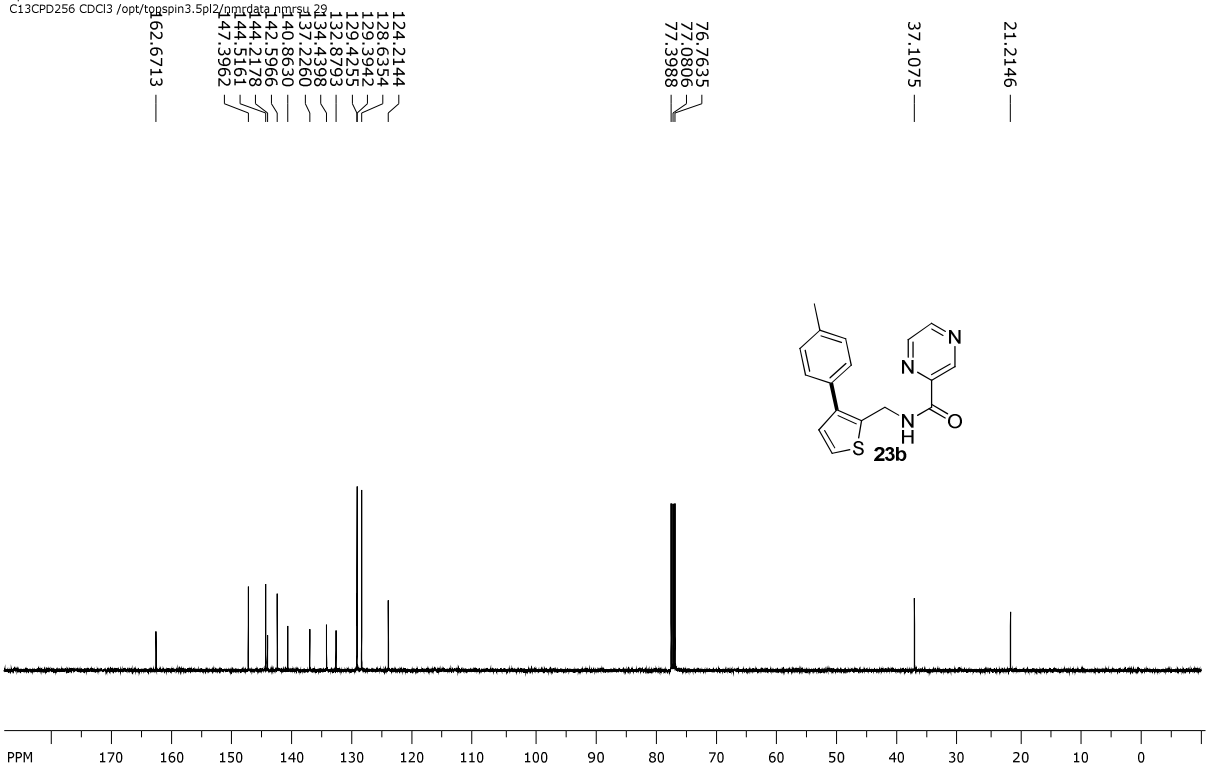

SpinWorks 3: rk1432b1
PROTON CDCl3 /opt/topspin nmrsu 6
8.5311
8.5255
8.5233
8.5214
8.5192
8.3779
8.2347
8.2321
8.2295
7.1024
7.0893
7.2665
7.3051
7.3181
7.4216
7.4247
7.4335
7.4366
7.4405
7.4436
4.8853
4.8708
2.6348
0.0741
0.0000
1.029
0.933
1.041
2.086
1.074
2.068
1.055
1.039
1.016
1.980
3.000
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
O
PA
N
H
S
20a

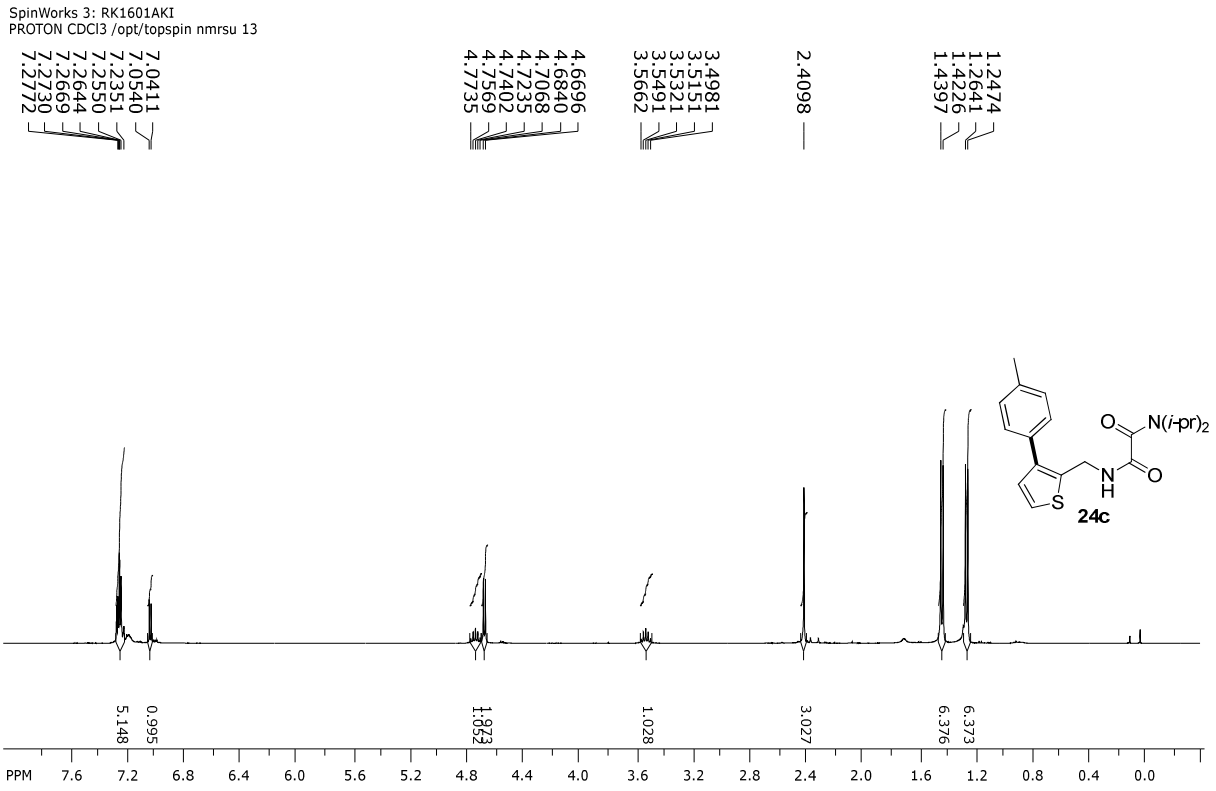

SpinWorks 3: rk1432b1
C13CPD CDCl3 /opt/topspin nmrsu 6
97.6890
164.0859
149.4368
148.1679
140.7319
139.2446
137.4336
136.8690
135.8180
128.9777
128.9412
128.7592
126.4200
124.6113
122.4080
77.3675
77.0496
76.7317
37.1154
26.7005
PPM
200
180
160
140
120
100
80
60
40
20
0
O
PA
N
H
S
20a

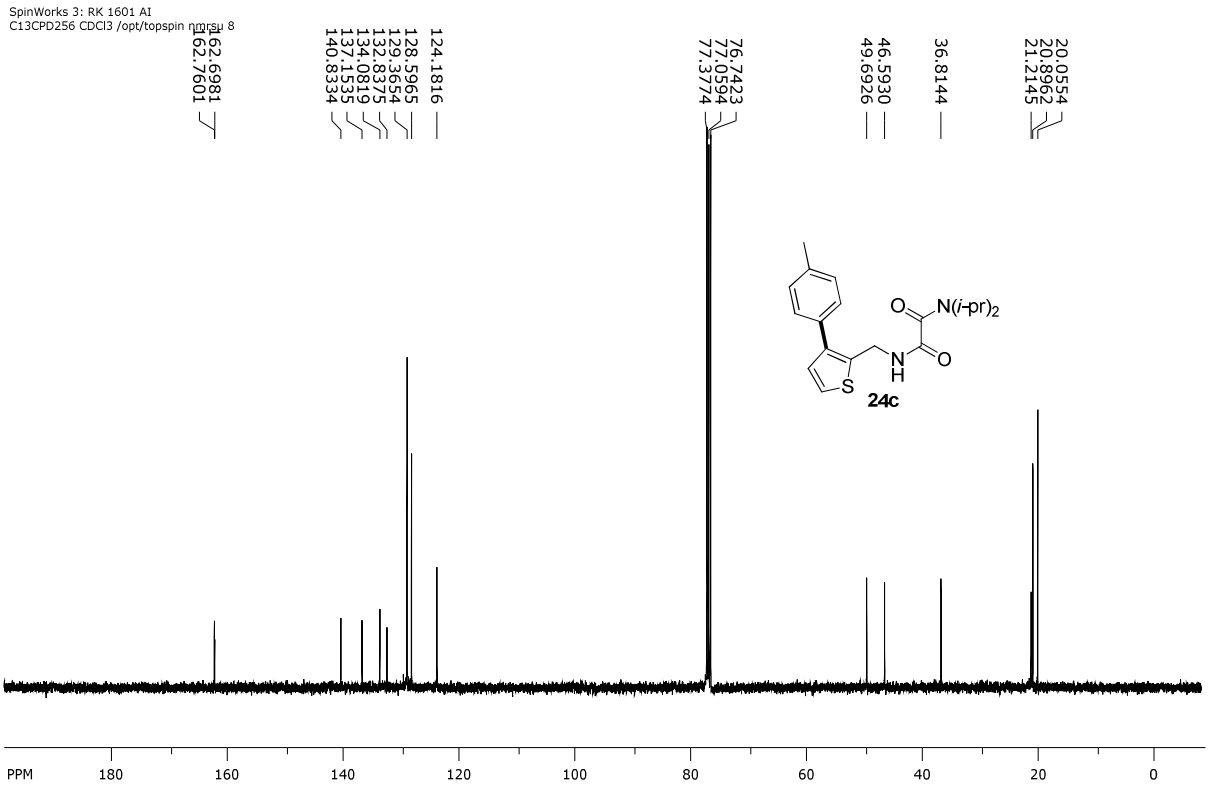
SpinWorks 3: RK 1641 A
PROTON CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 29



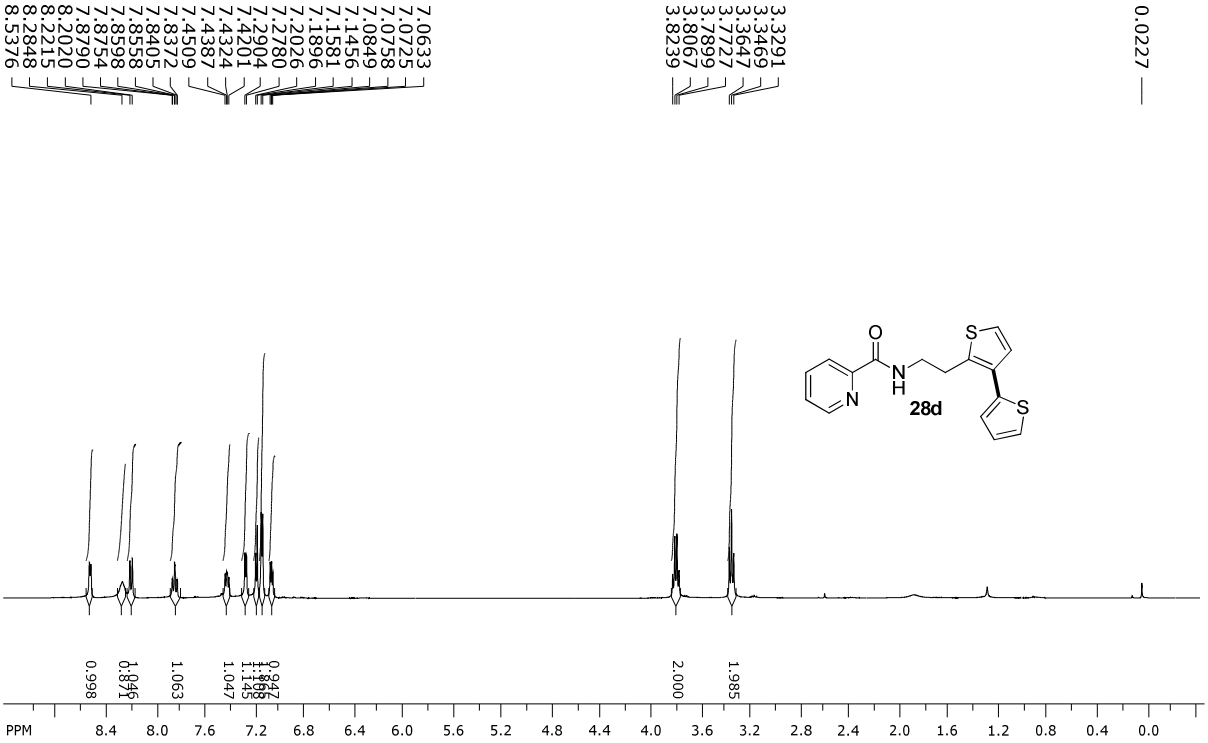
SpinWorks 3: RK 1641 A
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 29



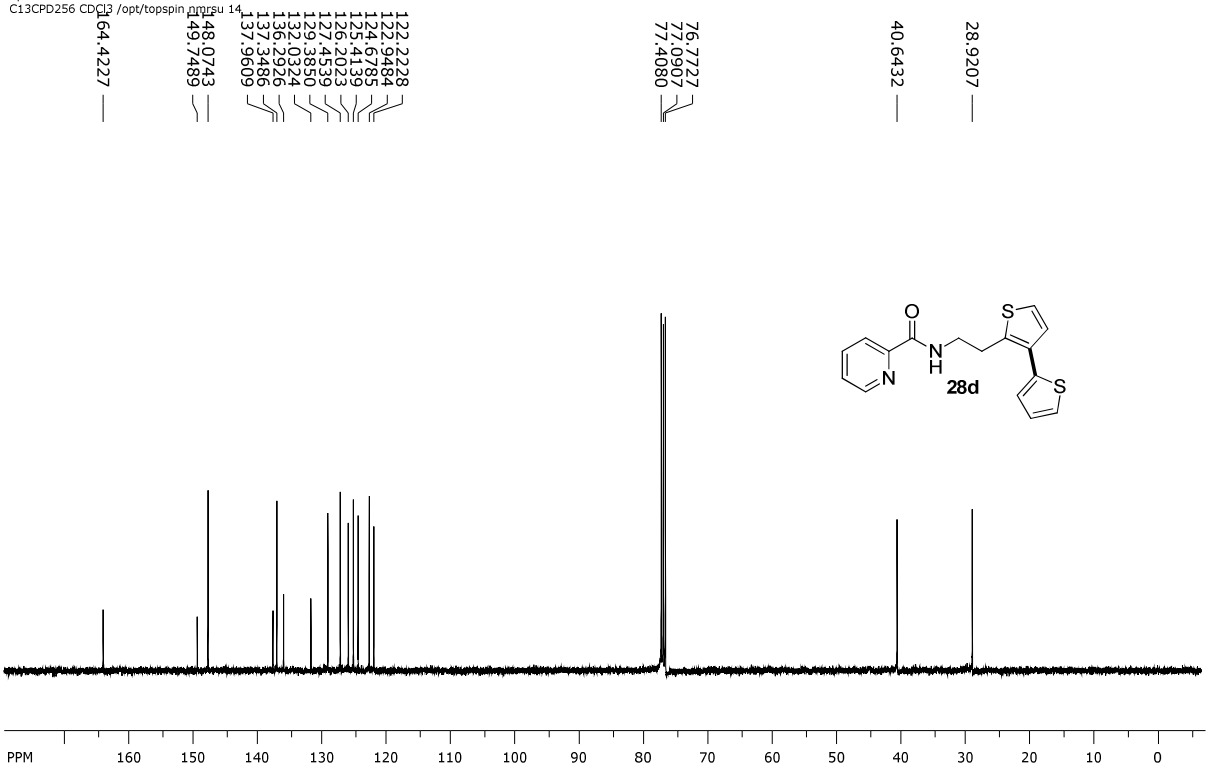

SpinWorks 3: RK1601AKI
PROTON CDCl3 /opt/topspin nmrsu 13
7.2772
7.2730
7.2669
7.2644
7.2550
7.2351
7.0540
7.0411
4.7735
4.7569
4.7402
4.7235
4.7068
4.6840
4.6696
3.5662
3.5491
3.5321
3.5151
3.4981
2.4098
1.4397
1.4226
1.2641
1.2474
5.148
0.995
1.052
1.028
3.027
6.376
6.373
PPM
24c


SpinWorks 3: RK 1601 AI
C13CPD256 CDCl3 /opt/topspin nmrsu 8
162.7601
162.6981
140.8334
137.1535
134.0819
132.8375
129.3654
128.5965
124.1816
77.3774
77.0594
76.7423
49.6926
46.5930
36.8144
21.2145
20.8962
20.0554
PPM
24c

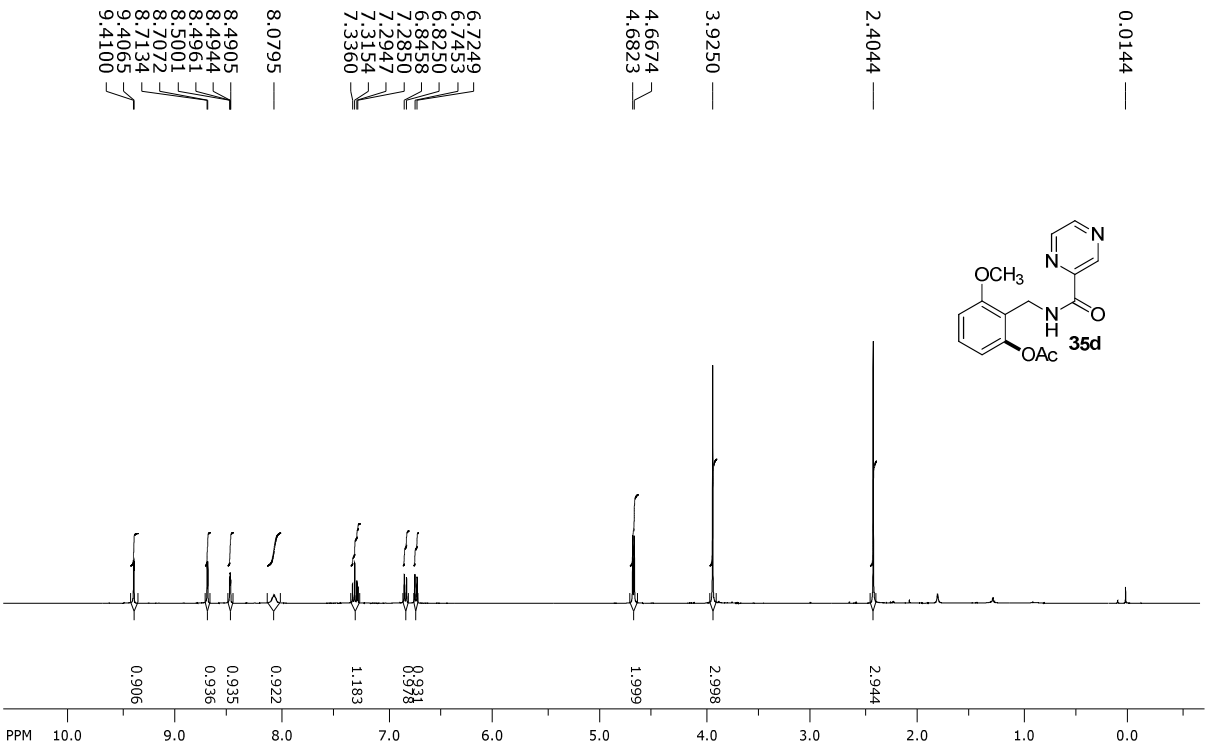
SpinWorks 3: RK-1589 A1



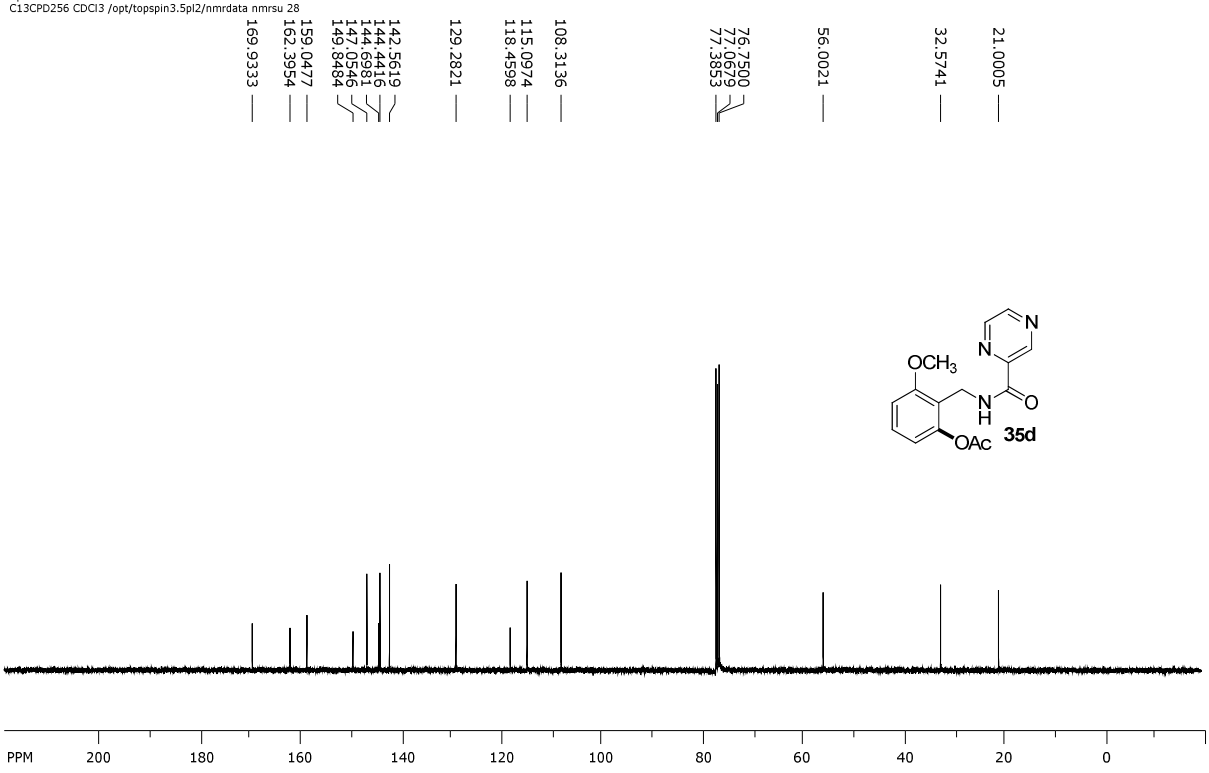
SpinWorks 3: RK 1589 A1
C13CPD256 CDCl3 /opt/topspin nmrsu 14



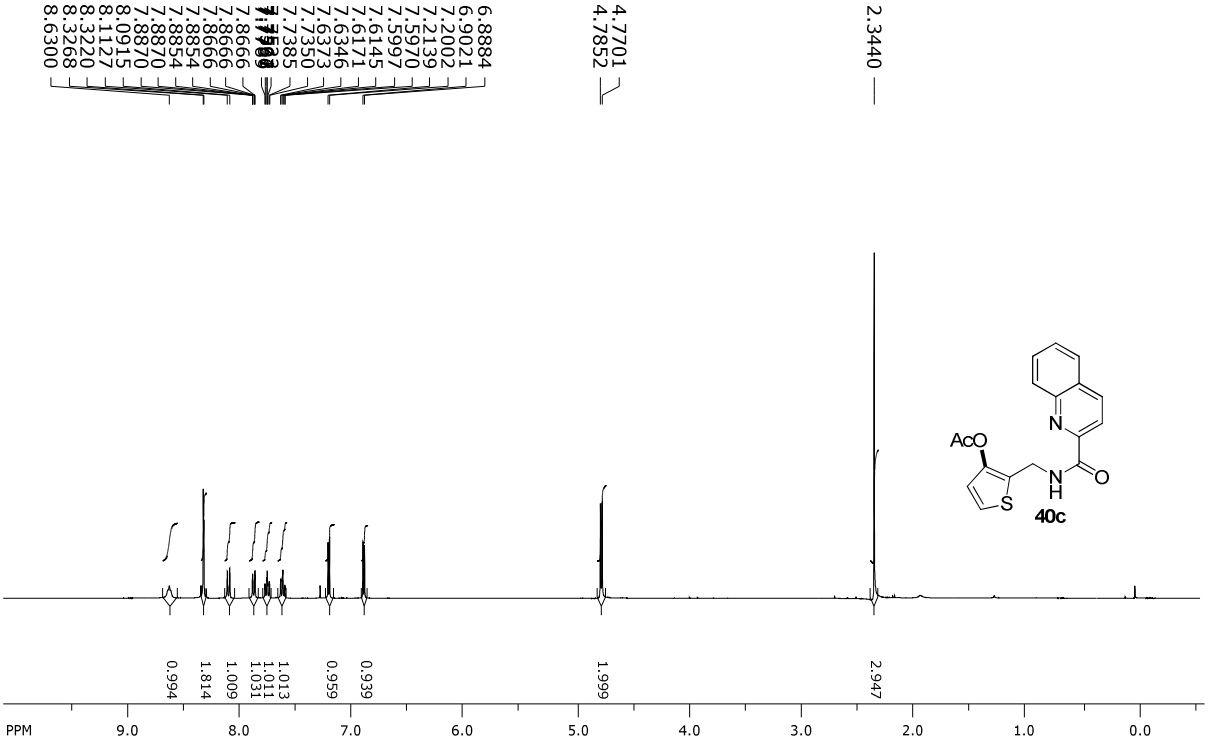
SpinWorks 3: rk-1687-b



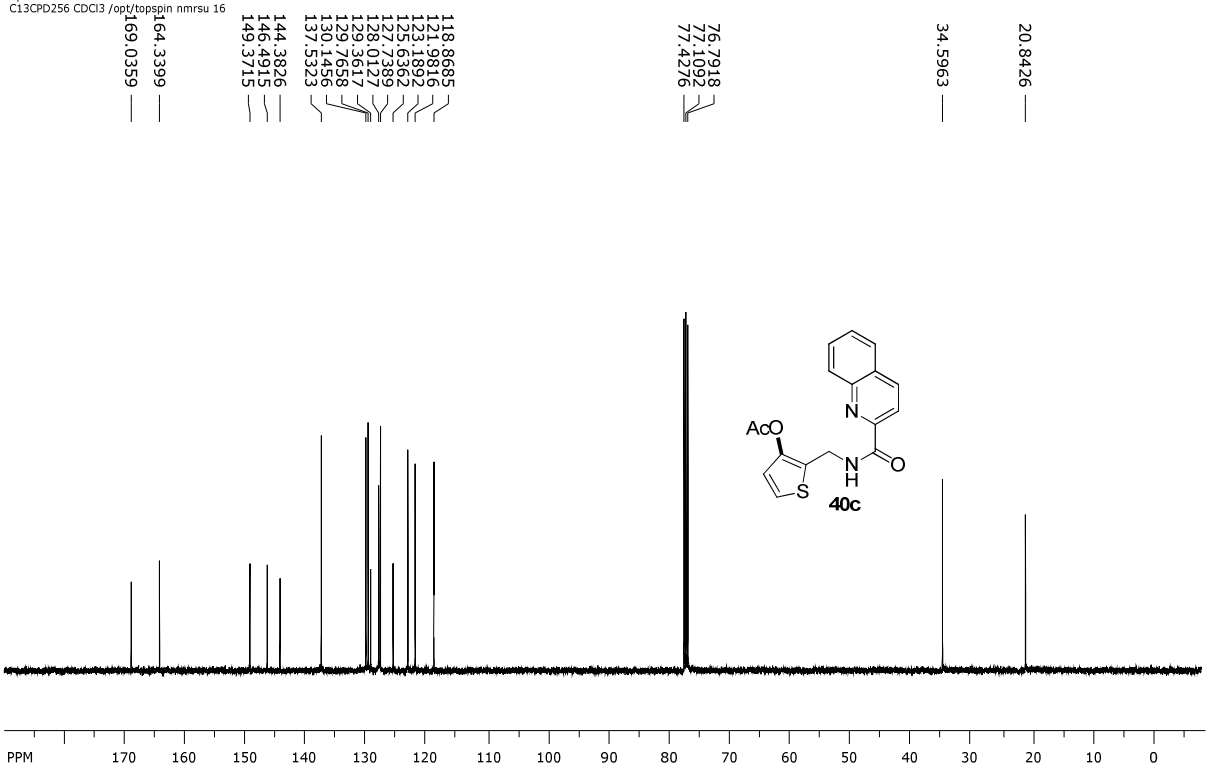
SpinWorks 3: rk 1687 b
C13CPD256 CDCl3 /opt/topspin3.5pl2/nmrdata nmrsu 28



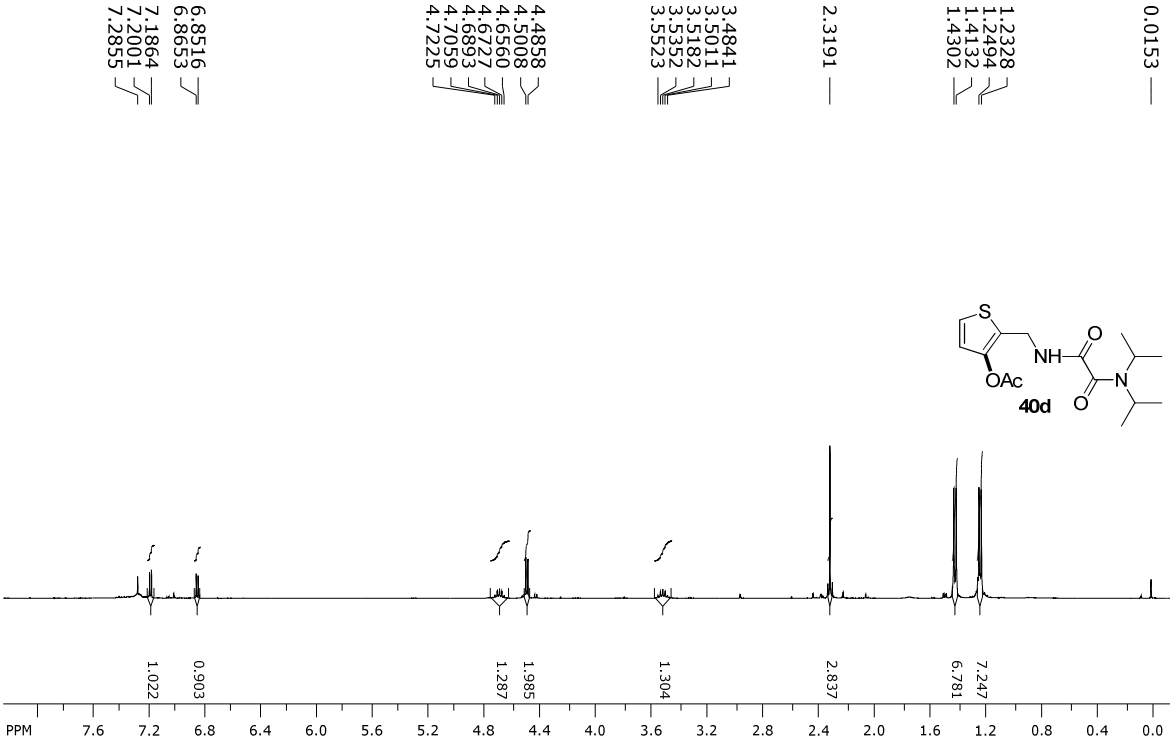
SpinWorks 3: RK 1586 B
PROTON CDCl3 /opt/topspin nmrsu 16



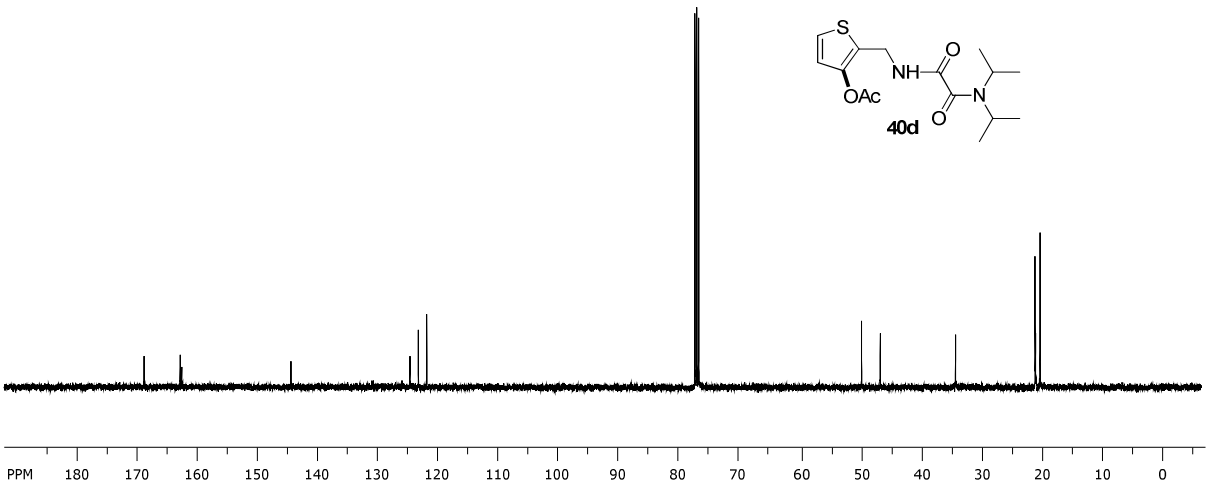
SpinWorks 3: RK 1586 B
C13CPD256 CDCl3 /opt/topspin nmrsu 16



SpinWorks 3: RK 1560/ 1560 A
PROTON CDCl3 /opt/topspin nmrsu 6

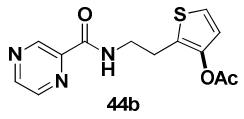


SpinWorks 3: RK 1560 A
C13CPD256 CDCl3 /opt/topspin nmrsu 6

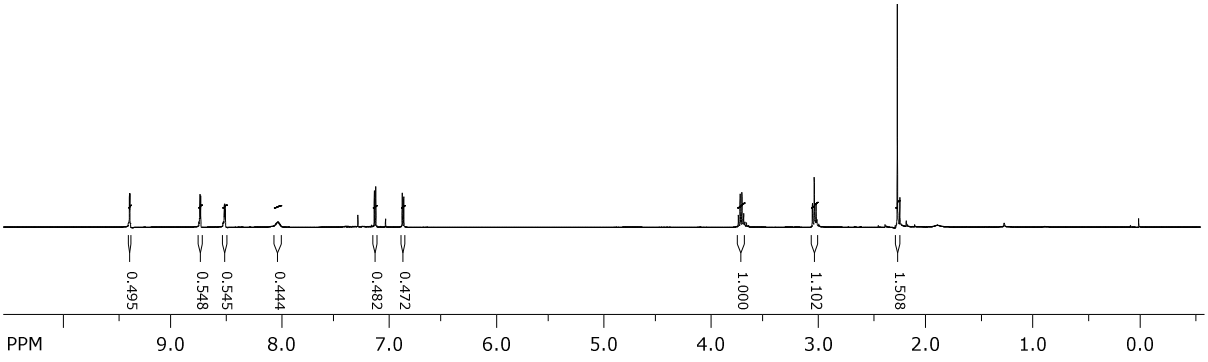


SpinWorks 3: NM 2244 B

9.4144
9.4107
8.7571
8.7509
8.5306
8.5268
8.5245
8.5207
8.0338
7.1318
7.1181
6.8711
6.8574
3.7376
3.7210
3.7049
3.6884
3.0473
3.0305
3.0136
2.2559

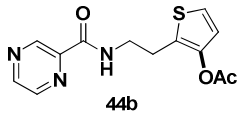


44b



SpinWorks 3: NM 2244 B

169.0136
163.1767
147.3150
144.3771
144.2971
144.0264
142.6270
125.7051
122.1076
121.8900
77.4099
77.0924
76.7739
40.0680
26.0633
20.7252



44b