Synthesis of biologically relevant molecules *via* organometallic methodologies

Akshey Sandhu

A dissertation submitted for the partial fulfilment of BS-MS dual degree in Science

Department of Chemical Sciences,
Indian Institute of Science Education and Research Mohali
April 2016

DEDICATED TO MY BELOVED PARENTS

Certificate of Examination

This is to certify that the dissertation titled "***Synthesis of biologically relevant molecules via organometallic methodologies***" submitted by Mr. Akshey Sandhu (Reg. No. MS11024) for the partial fulfillment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

Dr. Sugumar Venkataramani	Dr. Sripada S. V. Ramasastry	Dr. S. Arulananda Babu
Assistant Professor	Assistant Professor	Associate Professor
IISER Mohali	IISER Mohali	IISER Mohali
		(Supervisor)

Dated : April 22, 2016

Declaration

The work presented in this dissertation has been carried out by me under the guidance of **Dr. S. Arulananda Babu** at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Akshey Sandhu
(Candidate)
Dated : April 22,2016

In my capacity as the supervisor of the candidate's project work, I certify that the above statement by the candidate is true to the best of my knowledge.

Dr. S. Arulananda Babu
(Supervisor)

Acknowledgment

It is my privilege to express my sincere gratitude to my supervisor, **Dr. S. Arulananda Babu** for his invaluable discussion, guidance and supervision throughout the work. The confidence and dynamism with which he guided the work requires no elaboration. Additionally, I am very thankful to him for exposing me to this interesting field of research. Without his guidance, compiling the project report in this form would have been impossible.

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Akshey Sandhu

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Notations and Abbreviations

TLC	Thin layer chromatography
NMR	Nuclear magnetic resonance
δ	Chemical shift in ppm
ppm	Parts per million
MeCN	Acetonitrile
EtOAc	Ethyl acetate
IR	Infra-red
s	Singlet
d	Doublet
t	triplet
m	multiplet
br s	Broad singlet
dd	Doublet of doublet
dt	Doublet of triplet
td	Triplet of doublet
mp	Melting point
MS	Mass spectrometry
ESI	Electron spray ionization

Contents

Abstract

Efforts toward developing various examples of agrochemically active or biologically relevant molecules via organometallic methodologies where a variety of cinnamamide based molecules have been synthesized via the Mizoroki–Heck Cross-Coupling Reaction. Alongside, the synthesis of β-nitrile equipped *N*-arylated amino acid derivatives via nucleophilic addition of bromoacetonitrile or 2-bromopropanenitrile to α-imino esters followed by hydrolysis and dipeptides composed of nitrile attached unnatural α-amino acid were also synthesized.

Chapter 1

Introduction

Work A

Amino acids are vital to life and building blocks of peptides, proteins and a number of natural products. Natural as well as unnatural amino acids serve as intermediates in biological synthesis and as a core of many natural products. Amino acids are used as additives in agrochemicals, pharmaceuticals and food products. Especially, amino acids comprise an important class of molecules which serve as synthetic reagents, catalysts in chemical sciences. The fundamental building blocks of proteins and peptides are a small number of proteinogenic amino acids. To study the chemistry of proteins and peptides, in the past decades, a huge amount of synthetic work dealing with the synthesis of unnatural amino acids has been reported. In addition to the synthetically derived unnatural amino acid derivatives, several non-proteinogenic amino acids called as unusual amino acids are also found in the nature. However, they are not naturally encoded or found in the genetic code of organisms. Some of the unusual amino acids are produced by microorganisms and have evolved to interfere with biochemical pathways of other organisms. [2] Thus, despite of not being encoded by the genetic code as proteinogenic amino acids, many non-standard amino acids are found in proteins (see Figure 1 for representative examples of structurally modified unusual amino acids).

The unusual amino acids which are formed by post translational modifications, are often essential for the function or regulation of a protein.[8] For example, carboxyglutamic acid[8a] (**1a**, Figure 1) formed by carboxylation of glutamate provides better binding ability to calcium ions in gamma-carboxy glutamate. In the case of 4-hydroxyproline[8b] (**1b**, Figure 1), the hydroxyl group is critical for proline to stabilize the triple helical structure of collagen through additional water mediated hydrogen bonds, which in turn helps to maintain the connective tissues. Certain amino acid analogues prop up translational errors that result in irregular protein synthesis and have been used to understand the effects of protein misfolding in a variety of physiological and pathological situations. For example, canavanine (**1g**,

Figure 1) and azatidine-2-carboxylic acid (**1h**, Figure 1) exhibit greater degree of dose dependent toxicity to primary rat neurons culture as compared to astrocytes. [9a]

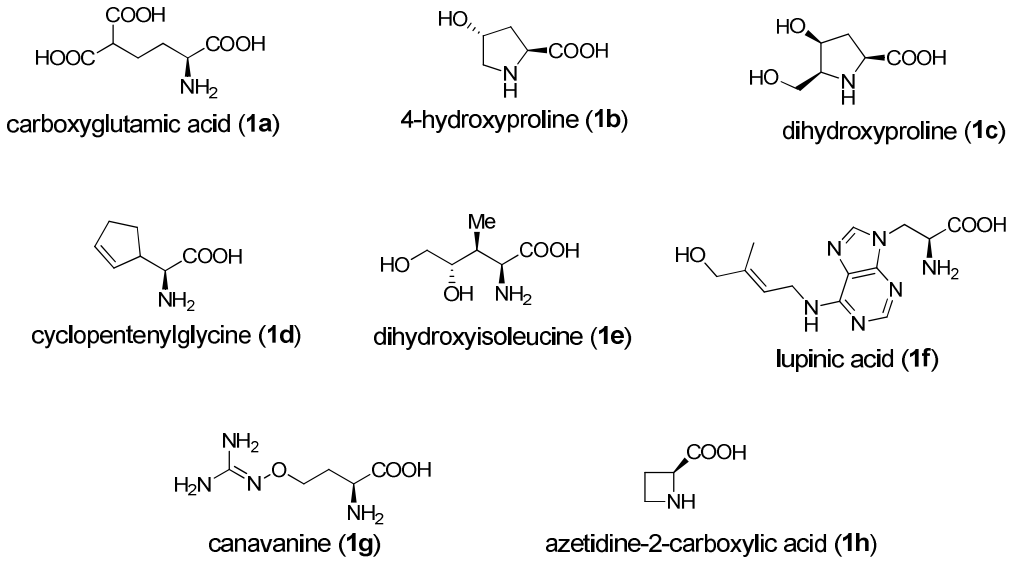


Figure 1. Structurally modified amino acids.

In particular, amongst the families of structurally modified amino acids, the β, β'-disubstituted α-amino acid family is relatively well known.[13a] The β, β'-disubstituted α-amino acids are also one of the prevalent substructures found in a large number of natural products; e.g., halipeptins (**2a**), celogentin, nikkomycins (**2b**), lysobactin, papuamides, tamandarin B, salinosporamide A (**2c**), cyclomarine C (**2d**) (Figures 2). Several β, β'-disubstituted α-amino acids are found to exhibit a wide range of biological activities (e.g. anti-HIV, antiviral, cytotoxic, antidiabetic, proteasome inhibition, etc).

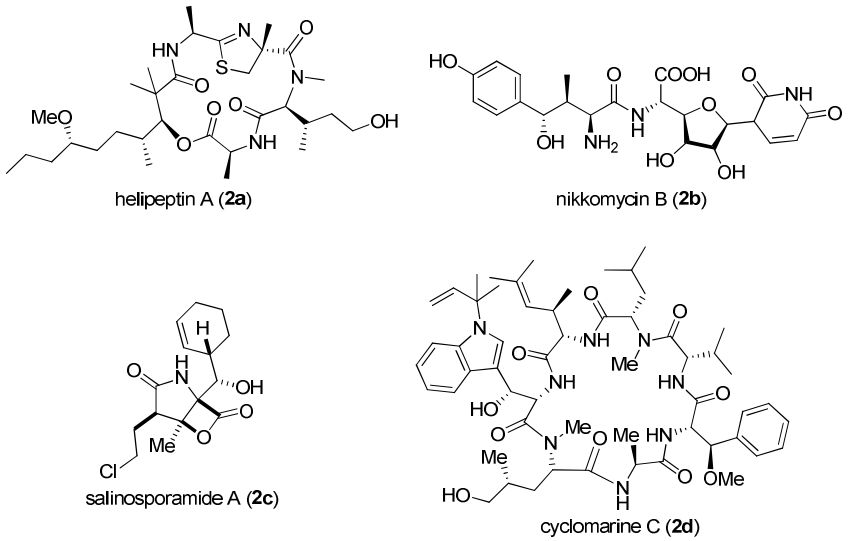


Figure 2. Natural products with unnatural amino acid component as the substructural unit.

Further, the functions and properties of native peptides vary from highly specific antibiotics or cytotoxic antitumor drugs to hormones, immunomodulators, neurotransmitters, etc. For example, cecropin-melittin hybrid peptide, protect fish against infection caused by the fish pathogen *Vibrio anguillarum*. Aside from this, *N*-protected α-amino acids containing peptides, isolated from a variety of sources and secondary metabolites of these peptides[13a] (e.g., vancomycin, cyclosporin, actinomycin D) have gained pharmaceutical importance due to the physical properties and chemical stability added by the *N*-protected α-amino acids present in their structures. Additionally, the *N*-protected α-amino acids also form the core framework of various medicinal agents. Many of the *N*-protected α-amino acid derivatives are reported to display promising biological activities, e.g. opaviraline (**2e**) acts as the non-nucleoside reverse transcriptase inhibitor, farglitazar (**2f**) function as the insulin sensitizer, lotrafiban (SB-214857; **2g**) acts as anticoagulant factor Xa inhibitor and platelet aggregation inhibitor GP IIb/IIIa antagonist (Figure 3).

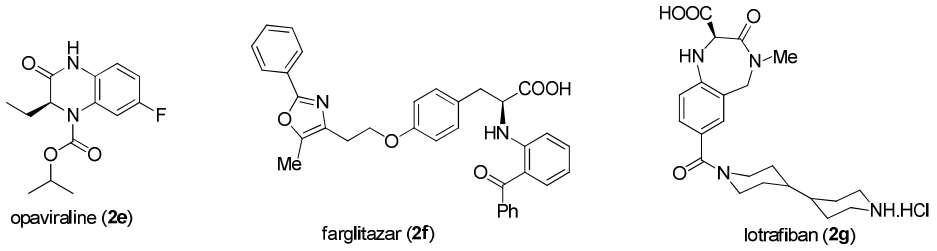
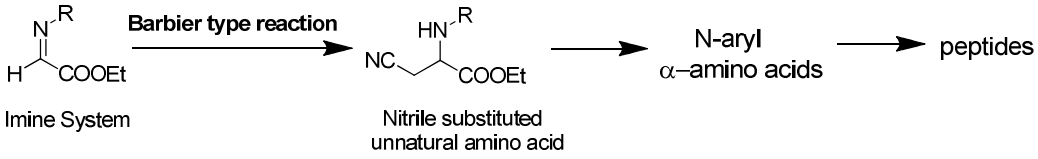


Figure 3. *N*-Aryl-α-amino acids as part of potential biologically important molecules.

Specifically, *N*-aryl-α-amino acids constitute the common core structural unit for a number of synthetically challenging and medicinally important agents. Due to the versatile use of unnatural amino acids in pharmaceuticals, synthetic/medicinal chemists have taken keen interest in developing new routes for the synthesis of unnatural amino acids having biological importance. [10] Additionally, nitriles possess various applications in pharmaceuticals. 30 Nitrile containing pharmaceuticals have been marketed for various medical indications and also about 2 are under clinical developmental studies. In some cases, it increases water solubility or decreases susceptibility to metabolism inside body or as a substrate for enzymes. As a result, we focussed our attention to develop a methodology for the synthesis of nitrile substituted unnatural α-amino acid derivatives (masked aspartic acid derivatives)

that combine the importance of gifted nitrile group with that of unnatural amino acids.

Nucleophilic addition of carbon nucleophiles to imines to achieve C-C bond formation is an important tool to synthesize nitrogen containing biologically relevant molecules. Barbier type nucleophilic addition reaction has been known for many years and has been well investigated as these reactions can be carried out with relatively inexpensive metals like zinc, tin, bismuth etc. Nucleophilic addition reaction of bromoacetonitrile to carbonyl compounds and imine systems has been already reported.[10] Glyoxalate imines are well studied as starting material for the synthesis of natural/unnatural α- amino acids and its derivatives or related compounds via ene reaction or cycloaddition or nucleophilic addition of organometallic compounds. We have also chosen metal mediated Barbier type nucleophilic addition reaction of bromoacetonitrile to glyoxalate imine systems to synthesize nitrile substituted unnatural amino acid derivatives. Barbier type nucleophilic addition to glyoxalate imines results in *N*-substituted α-amino acid derivatives under mild reaction conditions and in good yields.



Scheme 1. Theme of the work: Synthesis of nitrile equipped *N*-aryl α-amino acids and peptides.

Work B

Palladium catalyzed coupling reactions have been generally used in the synthesis of various organic compounds starting from natural products to photo-electronic materials. These reactions, normally performed with 1–5 mol% of Palladium catalyst along with equal or higher mole amounts of phosphine ligands and there are various problems that still needs to be solved, like expensive nature of the catalyst and contamination of the product by Palladium often has to be well taken care of. Many phosphine ligands are very much expensive than Palladium, and they are not comfortable to work with, because of many reasons like, their poisonous, air sensitive nature, etc. In this regard, a result is to come up with high turnover-number catalysts. Recently, scientists have reported various numbers of phosphine free catalysts for Palladium catalysed Heck reaction. In these catalysts the ligands are either nitrogen-containing compounds or heterocyclic carbenes.[19] Heterocycles, where the coordinating atom is oxygen or nitrogen like 1, 3-dicarbonyl compounds, N,N-Dimethyl-β-alanine can also be used as ligand.[19] 1,3-dicarbonyl compounds were discovered in 2002 by Song and co-workers to be useful ligands for Cu-catalyzed Ullmann diaryl ether synthesis. More recently Buchwald and Shafir discovered that a 1, 3-dicarbonyl ligand could facilitate Cu-catalyzed C–N coupling reactions. Recently, it's also reported that 1,3-dicarbonyl compounds can also be used as phosphine free ligands for Palladium catalyzed Heck reactions.

Arylation of alkenes *via* Heck coupling pathway is an important tool to synthesize cinnamamide bases biologically relevant molecules.[23] Cinnamamide derivatives exemplify an important class of agrochemicals, and several cinnamamide derivatives[23] (e.g., Dimethomorph (**3a**), Flumorph (**3b**), and Pyrimorph (**3c**), Figure 1) exhibit fungicidal , herbicidal activities and a wide range of biological activities, [20] such as anticonvulsant, antituberculosis, antidepressant, analgesic, antifungal, and antiestrogenic agents,[21] and function as 5 KCNQ2 potassium channel openers, mPTP inhibitors, and vanilloid receptor-1 antagonists. Cinnamamide derivatives were also used as starting materials for assembling heterocyclic compounds (e.g., quinolones). Generally, cinnamamide derivatives (β-arylated acrylamide derivatives) were prepared using the traditional synthetic methods or the Pd-catalyzed Mizoroki−Heck reaction of acrylic acid based substrates with a suitable coupling partner.

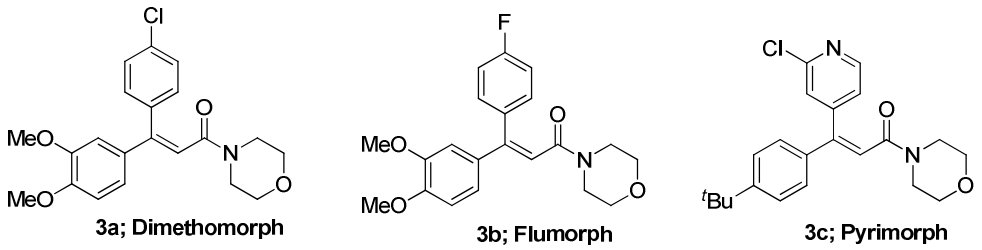
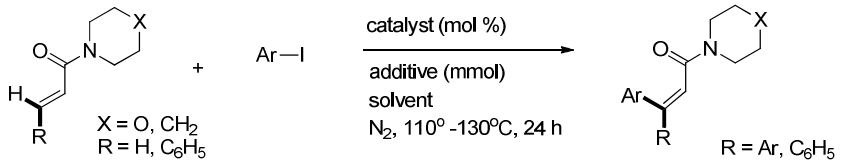


Figure 4. Examples of cinnamamide-based agrochemicals.

We have chosen phosphine free ligands i.e 1, 3-dicarbonyl compounds to synthesize a class of cinnamamide derivatives under mild reaction conditions and in good yields.



Scheme 2. Theme of the work: Synthesis of cinnamamide derivatives followed via the Mizoroki–Heck Cross-Coupling reaction.

Chapter2

Experimental

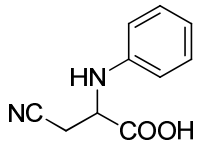
General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers respectively with TMS as an internal or external standard. IR spectra were recorded as KBr pellets or thin films. Column chromatography was carried out on silica gel. Reactions were carried out in dry solvent under nitrogen atmosphere wherever required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask with the help of syringe. Thin layer chromatography (TLC) was performed on silica plates or and components were visualized by observation under iodine. Isolated yields of all the products were reported (yields were not optimized). Ratios of diastereomers were determined from the ^{1}H and ^{13}C NMR spectra of crude reaction mixtures or after isolation.

Procedure A: Base mediated hydrolysis of nitrile containing α-amino esters (4). The compound **4** (0.4 mmol) was dissolved in a mixture of THF/MeOH/H_2O = 3/1/1 (5 mL), and LiOH (1.2 mmol) was added at 0 ^{o}C. The mixture was allowed to stir for 12 h and then acidified with 1N aqueous HCl to pH = 2 and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. Then the solvent was evaporated under vacuum that gave the product **5**.

Procedure B: Synthesis of peptides of nitrile containing α-amino acids (6). The respective compound **6** (0.4 mmol) was dissolved in dry DCM (5 mL) and phenylalanine methyl ester hydrochloride (**7a**; 0.8 mmol) or glycine ethyl ester hydrochloride (**7b**; 0.8 mmol), EDCI (0.8 mmol), HOBt.xH_2O (0.8 mmol), DIPEA (0.8 mmol) were added and the reaction mixture was allowed to stir at room temperature. After 12 h, the reaction mixture was washed with water and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and purification of resulting crude reaction mixture by column

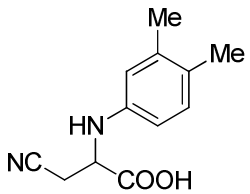
chromatography on silica gel (EtOAc:Hexane = 70:30) gave the respective products **8.**

Procedure C: Arylation on acrylamides to generate a class of cinnamamides. The compound **9a** (0.25 mmol) was taken and Pd-acetate (5 mol %), Potassium carbonate (0.5 mmol), benzoylacetone (5 mol %) *p*-iodoanisole (0.5) and DMF (1 mL) were added and the reaction mixture was allowed to stir at 130 ^{o}C. After 24 h, the reaction mixture was washed with water, ether and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and purification of resulting crude reaction mixture by column chromatography on silica gel (EtOAc:Hexane = 75:25) gave the respective products **10a'.**



5a

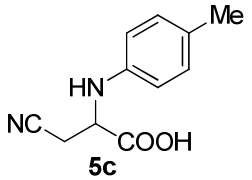
3-Cyano-2-(phenylamino)propanoic acid (5a): Following the general procedure A described above, **5a** was obtained as light yellowish solid (31 mg, 81.6%): mp 91-93 ^{o}C; R_f = 0.60 (30% EtOAc/Hexane); IR (thin film): υ_{max} 3382, 2923, 1498, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ 7.18 (dd, *J* = 8.6, 7.4 Hz, 2 H), 6.78-6.64 (m, 1 H), 6.66-6.64 (m, 2 H), 4.35 (t, *J* = 5.4 Hz, 1 H), 2.94 (t, *J* = 5.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ 172.1, 145.3, 129.4, 119.0, 116.8, 113.6, 52.9, 21.4; HRMS (ESI): calcd. for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 191.0821; found 191.0831.



5b

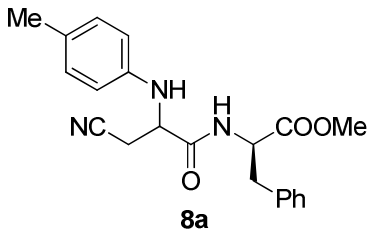
3-Cyano-2-((3,4-dimethylphenyl)amino)propanoic acid (5b): Following the general procedure A described above, **5b** was obtained as brownish semisolid (21 mg, 57%): R_f = 0.60 (30% EtOAc/Hexane); IR (thin film): υ_{max} 3382, 2922, 1646, 1583,

1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CD_3OD): δ 6.94 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 3.6 Hz, 1H), 6.43 (dd, *J* = 8.1, 2.6 Hz, 1H), 4.33 (t, *J* = 5.7 Hz, 1H), 2.95 (d, *J* = 5.7 Hz, 1H), 2.93 (d, *J* = 5.5 Hz, 1H), 2.18 (s, 3H). 2.13 (s, 3H)); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ 172.3, 143.6, 137.6, 130.6, 127.2, 116.9, 115.7, 111.2, 53.3, 21.3, 19.6, 18.4; HRMS (ESI): calcd. for $C_{12}H_{15}N_2O_2$ $[M + H]^+$ 219.1134; found 219.1144.



5c

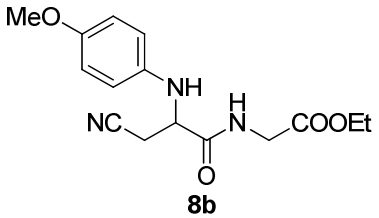
3-Cyano-2-(*p*-tolylamino)propanoic acid (5c): Following the general procedure A described above, **5c** was obtained as brown colored semisolid (16mg, 62%): R_f = 0.60 (30% EtOAc/Hexane); IR (thin film): υ_{max} 3371, 2921, 1643, 1590, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+CD_3OD): δ 6.99 (d, *J* = 8.0 Hz, 2 H), 6.56 (d, *J* = 8.0 Hz, 2 H), 4.30 (t, *J* = 5.4 Hz, 1 H), 2.91 (dd, *J* = 5.4, 4.8 Hz, 2 H), 2.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ 172.2, 142.9, 129.9, 128.5, 116.8, 114.0, 53.3, 21.4, 20.2; HRMS (ESI): calcd. for $C_{11}H_{13}N_2O_2$ $[M + H]^+$ 205.0977; found 203.0811.



8a

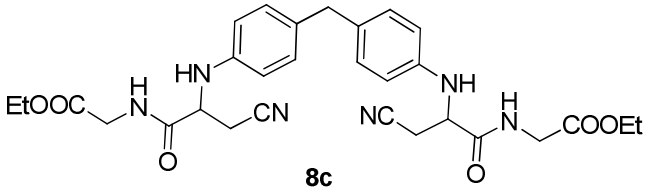
Methyl 2-(3-cyano-2-(*p*-tolylamino)propanamido)-3-phenylpropanoate (8a): Following the general procedure B described above, **8a** was obtained as brown colored semisolid (70mg, 32%): R_f = 0.60 (30% EtOAc/Hexane); IR (thin film): υ_{max} 3350, 2958, 1743, 1671, 1520. 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.16 (m, 3 H), 7.07-7.03 (m, 4 H), 6.96-6.94 (m, *2*H), 4.91-4.88 (m, 1 H), 4.13-4.06 (m, 1 H), 3.74 (s, 3 H), 3.18-3.07 (m, 2 H), 2.93-2.90 (m, 2 H), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 171.3, 169.7, 169.5, 142.4,142.2, 135.5, 135.4, 130.1, 129.2, 129.1, 128.7, 128.7, 127.3, 127.2, 115.1, 114.7, 55.6, 55.6, 53.3, 53.1, 52.5, 52.4,

37.7, 37.6, 20.8, 20.5, 20.1; HRMS (ESI): calcd. for $C_{21}H_{24}N_3O_3$ $[M + H]^+$ 366.1818; found 366.1812.



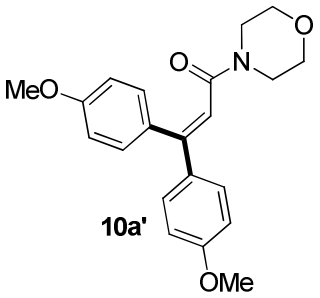
8b

Ethyl 2-(3-cyano-2-((4-methoxyphenyl)amino)propanamido)acetate (8b): Following the general procedure B described above, **8b** was obtained as brown colored semisolid (32 mg, 25%): R_f = 0.60 (30% EtOAc/Hexane); IR (thin film): υ_{max} 3352, 1926, 1741, 1668, 1513, 1239, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 9.0 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.13-4.11 (m, 1H), 4.05 (t, *J* = 5.6 Hz, 2H), 3.76 (s, 3H), 2.98 (t, *J* = 6.08 Hz, 2H), 1.27 (t, *J* = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 169.3, 154.2, 138.5, 116.9, 116.5, 115.0, 61.8, 56.3, 55.7, 41.4, 20.4, 14.1; HRMS (ESI): calcd. for $C_{15}H_{20}N_3O_4$ $[M + H]^+$ 306.1454; found 306.1440.



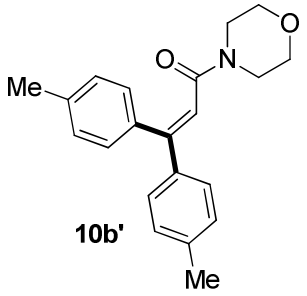
8c

Diethyl 2,2'-((2,2'-((methylenebis(4,1-phenylene))bis(azanediyl))bis(3-cyanopropanoyl))bis(azanediyl))diacetate (8c): Following the general procedure B described above, **8c** was obtained as brown colored semisolid (49 mg, 50%): R_f = 0.60 (30% EtOAc/Hexane); IR (thin film): υ_{max} 3375, 1742, 1670, 1518, 1411 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 2H), 7.05 (d, *J* = 8.5 Hz, 4H), 6.63 (d, *J* = 8.5 Hz, 4H), 4.29 (d, *J* = 7.5 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 6H), 4.04 (dd, *J* = 12.0, 5.8 Hz, 3H), 3.80 (s, 2H), 2.98 (t, *J* = 6.2 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.3, 43.0, 133.6, 130.0, 117.0, 114.8, 61.7, 55.4, 41.4, 40.1, 20.6, 14.1; HRMS (ESI): calcd. for $C_{29}H_{35}N_6O_6$ $[M + H]^+$ 563.2618; found 563.2617.



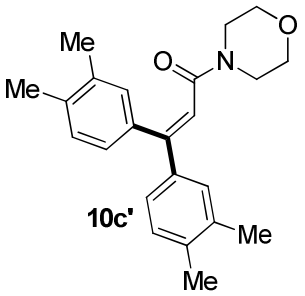
10a'

3,3-Bis(4-methoxypheny0l)-1-morpholinoprop-2-en-1-one (10a'): Following the general procedure C described above, **10a'** was obtained as brown colored semisolid (67 mg, 76%): R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2962, 16.5, 1512, 1248, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.2 Hz, 2 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.14 (s, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.56-3.48 (m, 4 H), 3.26-3.24 (m, 2 H), 3.11-3.09 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 160.0, 159.9, 147.1, 133.5, 131.3, 130.9, 129.5, 117.7, 113.7, 113.7, 66.4, 66.3, 55.3, 55.3, 46.7, 41.5; HRMS (ESI): calcd. for $C_{21}H_{24}NO_4$ $[M + H]^+$ 354.1705; found 354.1698.

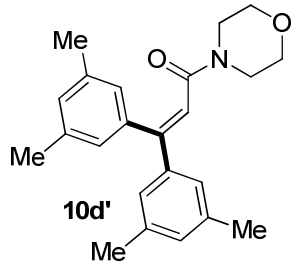


10b'

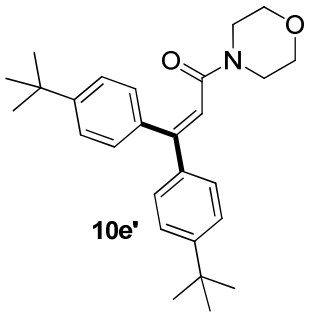
1-Morpholino-3,3-di-p-tolylprop-2-en-1-one (10b'): Following the general procedure C described above, **10b'** was obtained as colorless solid (75 mg, 85%): mp 87-89 ^oC; R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2921, 1632, 1432, 1245, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.13 (m, 8 H), 6.23 (s, 1 H), 3.55-3.50 (m, 4 H), 3.25 (t, *J* = 4.4 Hz, 2 H), 3.08 (t, *J* = 4.6 Hz, 2H), 2.39 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 147.7, 138.6, 138.6, 138.1, 136.0, 129.4, 129.0, 128.0, 119.0, 66.3, 66.3, 46.7, 41.5, 21.4, 21.2; HRMS (ESI): calcd. for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1807; found 322.1802.



3,3-Bis(3,4-dimethylphenyl)-1-morpholinoprop-2-en-1-one (10c'): Following the general procedure C described above, **10c'** was obtained as brown colored solid (81mg, 93%): mp 95-97 ^{o}C; R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2920, 1631, 1432, 1273, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 - 7.09 (m, 3 H), 7.04 – 6.99 (m, 3 H), 6.19 (s, 3 H), 3.55 (dd, J_1, J_2= 4.8, 4.8 Hz, 4 H), 3.26 (t, J = 4.3 Hz, 2 H), 3.06 (t, J = 4.6 Hz, 2H), 2.30 (s, 3 H), 2.29 (s, 3 H), 2.25 (s, 6 H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 148.0, 138.7, 137.2, 137.2, 136.5, 130.5, 129.5, 129.3, 127.0, 125.8, 118.9, 66.3, 66.2, 46.7, 41.5, 19.8, 19.7, 19.7, 19.6; HRMS (ESI): calcd. for $C_{23}H_{28}NO_2$ $[M + H]^+$ 350.2120; found 350.2131.

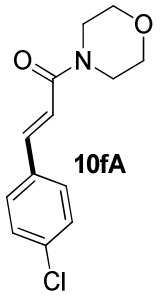


3,3-Bis(3,5-dimethylphenyl)-1-morpholinoprop-2-en-1-one (10d'): Following the general procedure C described above, **10d'** was obtained as brown colored solid (76 mg, 87%): mp 142-144^{o}C; R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2917, 1631, 1435, 1244, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, J = 7.3 Hz, 2 H), 6.90 (d, J = 9.4 Hz, 4 H), 6.20 (s, 1 H), 3.55 (t, J = 4.0 Hz, 2 H), 3.47 (t, J = 4.3 Hz, 2 H), 3.26 (t, J = 4.4 Hz, 2 H), 2.99 (t, J = 4.6 Hz, 2 H), 2.31 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 148.1, 141.1, 138.9, 137.8, 137.8, 130.3, 130.3, 127.1, 126.1, 119.8, 66.3, 66.1, 46.7, 41.5, 21.3; HRMS (ESI): calcd. for $C_{23}H_{28}NO_2$ $[M + H]^+$ 350.2120; found 350.2132.



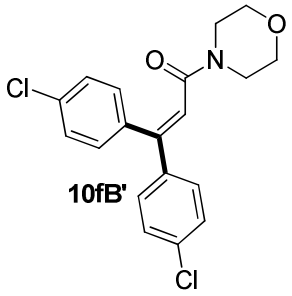
10e'

3,3-Bis(4-(tert-butyl)phenyl)-1-morpholinoprop-2-en-1-one (10e'): Following the general procedure C described above, **10e'** was obtained as light yellowish solid (48 mg, 40%): mp 149-151 ^{o}C; R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 3429, 2962, 1632, 1272, 1113 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.5 Hz, 2 H-), 7.36 (d, *J* = 8.6 Hz, 2 H), 7.26 (d, *J* = 8.6 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 6.25 (s, 1 H), 3.54 (t, *J* = 4.4 Hz, 2 H), 3.44 (t, *J* = 5.0 Hz, 2 H), 3.25 (t, *J* = 4.5 Hz, 2 H), 2.92 (t, *J* = 4.8 Hz, 2 H), 1.35 (s, 9 H), 1.34 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 151.9, 151.8, 147.3, 137.8, 135.8, 129.3, 127.9, 125.2, 125.2, 119.1, 66.2, 66.1, 46.7, 41.5, 34.7, 34.6, 31.3, 31.3; HRMS (ESI): calcd. for $C_{27}H_{36}NO_2$ [M + H] $^{+}$ 406.2746; found 406.2731.

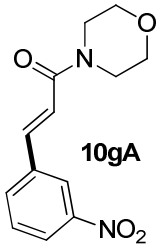


10fA

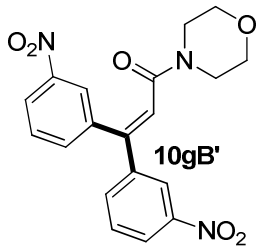
(*E*)-3-(4-Chlorophenyl)-1-morpholinoprop-2-en-1-one (10fA): Following the general procedure C described above, **10fA** was obtained as light yellow colored solid (29 mg, 34%): mp 141-143 ^{o}C; R_f = 0.40 (80% EtOAc/Hexane); IR (thin film): υ_{max} 2861, 1611, 1494, 1113, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 15.4 Hz, 1 H), 7.47 (d, *J* = 8.2 Hz, 2 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 6.84 (d, *J* = 15.4 Hz, 1 H), 3.75-3.68 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 141.9, 135.6, 133.6, 129.1, 129.0, 117.1, 66.8; HRMS (ESI): calcd. for $C_{13}H_{15}ClNO_2$ [M + H] $^{+}$252.0791; found 252.0783.



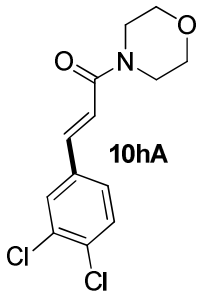
3,3-Bis(4-chlorophenyl)-1-morpholinoprop-2-en-1-one (10fB'): Following the general procedure C described above, **10fB'** was obtained as yellow colored semisolid (27 mg, 25%): R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1632, 1492, 1114, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 4 H), 7.21 (d, *J* = 8.2 Hz, 4 H), 6.33 (s, 1 H), 3.55 (s, 4 H), 3.29-3.24 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 145.6, 138.8, 136.7, 135.0, 135.0, 130.7, 129.3, 128.8, 128.8, 121.0, 66.4, 66.4, 46.6, 41.5; HRMS (ESI): calcd. for $C_{19}H_{18}Cl_2NO_2$ $[M + H]^+$ 362.0715; found 362.0726.



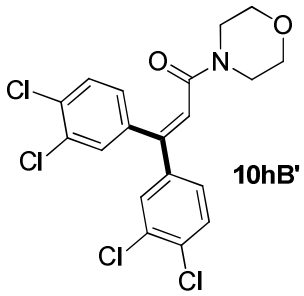
(*E*)-1-Morpholino-3-(3-nitrophenyl)prop-2-en-1-one (10gA): Following the general procedure C described above, **10gA** was obtained as yellow reddish colored solid (44 mg, 42%): mp 165-167 °C; R_f = 0.40 (80% EtOAc/Hexane); IR (thin film): υ_{max} 2865, 1652, 1529, 1352, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1 H), 8.21 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 7.7 Hz, 1 H), 7.74 (d, *J* = 15.4 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 15.4 Hz, 1 H), 3.77-3.71 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 148.6, 140.4, 136.9, 134.1, 130.0, 124.1, 121.6, 119.7, 66.8, 46.3, 42.6, 42.6; HRMS (ESI): calcd. for $C_{13}H_{15}N_2O_4$ $[M + H]^+$ 263.1032; found 263.1024.



1-Morpholino-3,3-bis(3-nitrophenyl)prop-2-en-1-one (10gB'): Following the general procedure C described above, **10gB'** was obtained as light yellow colored solid (20 mg, 12%): mp 158-160 ^{o}C; R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1633, 1530, 1348, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32-8.27 (m, 2 H), 8.19 (s, 1 H), 8.13 (s, 1 H), 7.65-7.64 (m, 2 H), 7.60-7.59 (m, 2 H), 7.29 (s, 1 H), 6.65 (s, 1 H), 3.62-3.58 (m, 4 H), 3.50-3.47 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 148.6, 148.4, 144.2, 141.4, 139.2, 135.3, 133.8, 130.0, 130.0, 124.8, 124.0, 124.0, 123.9, 122.7, 66.5, 66.5, 46.6, 41.7; HRMS (ESI): calcd. for $C_{19}H_{18}N_3O_6$ $[M + H]^+$ 384.1196; found 384.1186.

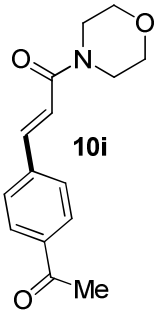


(*E*)-3-(3,4-Dichlorophenyl)-1-morpholinoprop-2-en-1-one (10hA): Following the general procedure C described above, **10hA** was obtained as brown colored solid (13 mg, 23%): R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2854, 1651, 1434, 1116, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 15.5 Hz, 2 H), 7.47 (d, J = 8.3 Hz, 1 H), 7.35 (dd, J_1 = 8.3, J_2 = 1.9, Hz, 1 H), 6.85 (d, J = 15.5 Hz, 1 H), 3.75-3.68 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 140.6, 135.2, 133.6, 133.1, 130.8, 129.1, 127.1, 118.3, 66.8; HRMS (ESI): calcd. for $C_{13}H_{14}Cl_2NO_2$ $[M + H]^+$ 286.0402; found 286.0394.



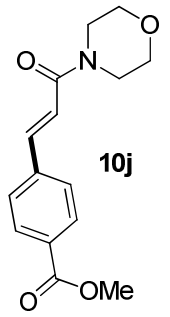
10hB'

3,3-Bis(3,4-dichlorophenyl)-1-morpholinoprop-2-en-1-one (10hB'): Following the general procedure C described above, **10hB'**was obtained as brown colored solid (30 mg, 16%): R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1650, 1473, 1229, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 15.1 Hz, 2 H), 7.49-7.43 (m, 2 H), 7.37-7.33 (m, 2 H), 7.09 (dt, J_1 = 8.8, J_2 = 2.0, Hz, 1 H), 6.85 (d, J = 15.4 Hz, 1 H), 3.75-3.67 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 164.9, 143.6, 140.6, 139.8, 137.6, 135.2, 133.6, 133.1, 130.9, 130.8, 130.7, 130.7, 129.7, 129.1, 128.6, 127.2, 127.1, 122.9, 118.3, 66.8, 66.8, 66.5, 66.4; HRMS (ESI): calcd. for $C_{19}H_{16}Cl_4NO_2$ $[M + H]^+$ 429.9935; found 429.9919.

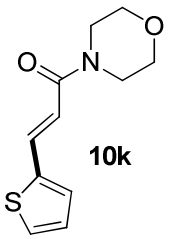


10i

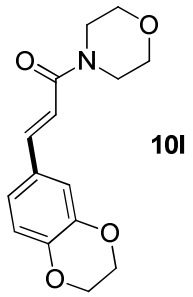
(*E*)-3-(4-Acetylphenyl)-1-morpholinoprop-2-en-1-one (10i): Following the general procedure C described above, **10i** was obtained as colorless solid (35 mg, 41%): mp 137-139 ^oC; R_f = 0.60 (75% EtOAc/Hexane); IR (thin film): υ_{max} 2861, 1678, 1267, 1114, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.3 Hz, 2 H), 7.73 (d, J = 15.4 Hz, 1 H), 7.62 (d, J = 8.3 Hz, 2 H), 6.96 (d, J = 15.4 Hz, 2 H), 3.76-3.69 (m, 8 H), 2.63 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 165.0, 141.7, 139.5, 137.6, 128.9, 127.9, 119.1, 66.9, 26.7; HRMS (ESI): calcd. for $C_{15}H_{18}NO_3$ $[M + H]^+$ 260.1287; found 260.1280.



(*E*)-3-(4-Acetylphenyl)-1-morpholinoprop-2-en-1-one (10j): Following the general procedure C described above, **10j** was obtained as brownish solid (42 mg, 50%): mp 122-124 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1719, 1436, 1278, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.3 Hz, 2 H), 7.72 (d, *J* = 15.5 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 15.5 Hz, 2 H), 3.95 (s, 3 H), 3.76-3.69 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 165.1, 141.9, 139.4, 130.9, 130.1, 127.7, 118.9, 66.8, 66.8, 52.3; HRMS (ESI): calcd. for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.1236; found 276.1229.

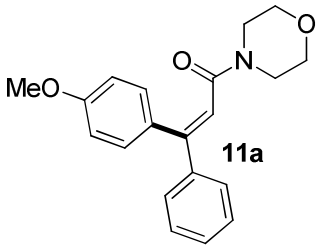


(*E*)-1-Morpholino-3-(thiophen-2-yl)prop-2-en-1-one (10k): Following the general procedure C described above, **10k** was obtained as yellow brownish solid (45 mg, 72%): mp 118-120 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1640, 1598, 1237, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 15.0 Hz, 1 H), 7.34 (d, *J* = 4.9 Hz, 1 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 7.06 (t, *J* = 4.3 Hz, 1 H), 6.65 (d, *J* = 15.0 Hz, 1 H), 3.74-3.66 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 140.3, 136.1, 130.5, 128.1, 127.4, 115.2, 66.9; HRMS (ESI): calcd. for $C_{11}H_{14}NO_2S$ $[M + H]^+$ 224.0745; found 224.0739.



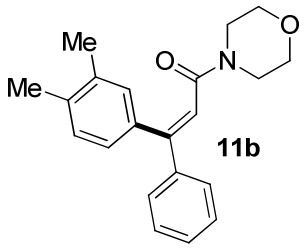
10l

(*E*)-3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-morpholinoprop-2-en-1-one (10l): Following the general procedure C described above, **10l** was obtained as brown colored solid (30 mg, 40%): mp 141-143 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 3477, 2857, 1645, 1508, 1282 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 15.3 Hz, 1 H), 7.07–7.03 (m, 2 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 6.70 (d, *J* = 15.3 Hz, 1 H), 4.29-4.28 (m, 4 H), 3.73–3.67 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 145.2, 143.7, 142.8, 128.8, 121.7, 117.6, 116.3, 114.6, 66.9, 64.5, 64.3; HRMS (ESI): calcd. for $C_{15}H_{18}NO_4$ $[M + H]^+$ 276.1236; found 276.1228.



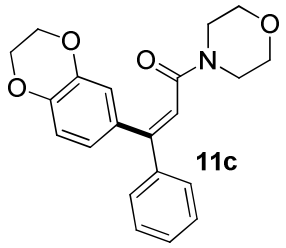
11a

(*E*)-3-(4-Methoxyphenyl)-1-morpholino-3-phenylprop-2-en-1-one (11a): Following the general procedure C described above, **11a** was obtained as colourless brown colored solid (84 mg, 87%): mp 138-140 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1630, 1248, 1113, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 3 H), 7.31-7.28 (m, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.24 (s, 1 H), 3.84 (s, 3 H), 3.53 (t, *J* = 4.3 Hz, 2 H), 3.46 (t, *J* = 5.0 Hz, 2 H), 3.25 (t, *J* = 4.5 Hz, 2 H), 3.03 (t, *J* = 5.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 160.1, 147.2, 139.0, 133.1, 129.5, 129.4, 128.7, 128.4, 118.6, 113.7, 66.3, 66.2, 55.3, 46.7, 41.5; HRMS (ESI): calcd. for $C_{20}H_{22}NO_3$ $[M + H]^+$ 324.1600; found 324.1588.



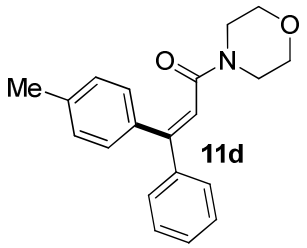
11b

(*E*)-3-(3,4-Dimethylphenyl)-1-morpholino-3-phenylprop-2-en-1-one (11b): Following the general procedure C described above, **11b** was obtained as light yellowish solid (90 mg, 94%): mp 106-108 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2856, 1632, 1433, 1273, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 3 H), 7.30-7.28 (m, 2 H), 7.11-7.08 (m, 2 H), 7.02 (dd, J_1, J_2 = 7.7, 1.8 Hz, 1 H), 6.27 (s, 1 H), 3.54 (t, J = 4.3 Hz, 2 H), 3.47 (t, J = 4.9 Hz, 2 H), 3.26 (t, J = 4.7 Hz, 2 H), 3.03 (t, J = 5.0 Hz, 2 H), 2.29 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 147.7, 139.0, 138.3, 137.4, 136.6, 129.6, 129.5, 129.2, 128.7, 128.3, 125.7, 119.4, 66.3, 66.2, 46.7, 41.5, 19.8, 19.6 ; HRMS (ESI): calcd. for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1807; found 322.1795.

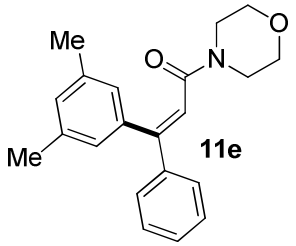


11c

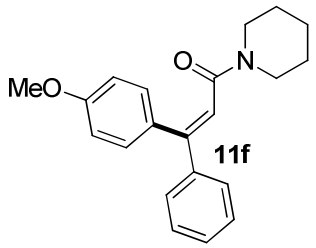
(*E*)-3-(2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)-1-morpholino-3-phenylprop-2-en-1-one (11c): Following the general procedure C described above, **11c** was obtained as brownish solid (89 mg, 86%): mp 130-133 ^{o}C; R_f = 0.60 (70% E-tOAc/Hexane); IR (thin film): υ_{max} 2854, 1629, 1506, 1287, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.36 (m, 3 H), 7.29-7.27 (m, 2 H), 6.83-6.81 (m, 2 H), 6.78 (dd, J_1, J_2 = 8.5, 1.6 Hz, 1 H), 6.23 (s, 1 H), 4.28-4.25 (m, 4 H), 3.51 (t, J = 4.2 Hz, 2 H), 3.45 (t, J = 5.0 Hz, 2 H), 3.23 (t, J = 4.6 Hz, 2 H), 3.02 (t, J = 4.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 147.0, 144.2, 143.2, 138.7, 134.2, 129.5, 128.7, 128.4, 121.4, 118.9, 117.1, 117.1, 66.3, 66.2, 64.5, 64.3, 46.7, 41.5; HRMS (ESI): calcd. for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.1549; found 352.1536.



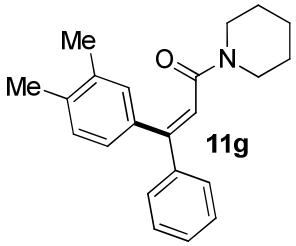
(*E*)-1-Morpholino-3-phenyl-3-(p-tolyl)prop-2-en-1-one (11d): Following the general procedure C described above, **11d** was obtained as brown colored solid (50 mg, 60%): mp 130-132 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2857, 1632, 1433, 1113, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 3 H), 7.30-7.28 (m, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 6.28 (s, 1 H), 3.54 (t, *J* = 4.2 Hz, 2 H), 3.47 (t, *J* = 5.0 Hz, 2 H), 3.26 (t, *J* = 4.6 Hz, 2 H), 3.03 (t, *J* = 4.9 Hz, 2 H), 2.38 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 147.5, 138.9, 138.7, 137.9, 129.5, 129.1, 128.7, 128.4, 128.0, 119.5, 66.3, 66.2, 46.7, 41.5, 21.2; HRMS (ESI): calcd. for $C_{20}H_{22}NO_2$ $[M + H]^+$ 308.1651; found 308.1641.



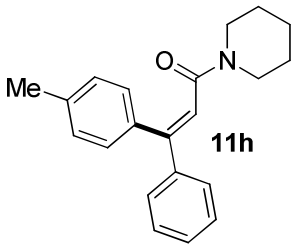
(E)-3-(3,5-dimethylphenyl)-1-morpholino-3-phenylprop-2-en-1-one (11e): Following the general procedure C described above, **11e** was obtained as brown colored solid (71 mg, 76%): mp 100-102 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2854, 1632, 1435, 1113, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 3 H), 7.30-7.28 (m, 2 H), 7.00 (s, 1 H), 6.91 (s, 2 H), 6.27 (s, 1 H), 3.54 (t, *J* = 4.0 Hz, 2 H), 3.47 (t, *J* = 4.9 Hz, 2 H), 3.26 (t, *J* = 4.6 Hz, 2 H), 3.03 (t, *J* = 5.0 Hz, 2 H), 2.31 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 147.8, 140.8, 139.0, 137.9, 130.4, 130.0, 129.5, 128.7, 128.3, 128.2, 127.2, 126.0, 120.0, 66.3, 66.2, 46.7, 41.5, 21.3; HRMS (ESI): calcd. for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1807; found 322.1795.



(*E*)-3-(4-Methoxyphenyl)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (11f): Following the general procedure C described above, **11f** was obtained as brown colored solid (80 mg, 78%): mp 100-102 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2939, 1626, 1441, 1254, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.33 (m, 3 H), 7.31-7.29 (m, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.27 (s, 1 H), 3.83 (s, 3 H), 3.47 (t, *J* = 5.6 Hz, 2 H), 3.24 (t, *J* = 5.6 Hz, 2 H), 1.45-1.39 (m, 4 H), 1.04 (t, *J* = 5.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 159.8, 146.1, 139.2, 133.7, 129.6, 129.4, 128.3, 128.1, 119.9, 113.6, 55.3, 47.3, 42.0, 25.7, 25.1, 24.4; HRMS (ESI): calcd. for $C_{21}H_{24}NO_2$ $[M + H]^+$ 322.1807; found 322.1818.

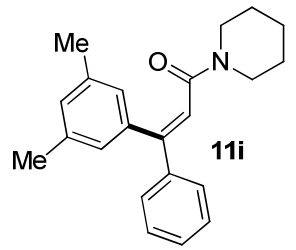


(*E*)-3-(3,4-Dimethylphenyl)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (11g): Following the general procedure C described above, **11g** was obtained as reddish brown colored solid (88 mg, 89%): mp 116-118 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2935, 1629, 1287, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.29 (m, 5 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 6.30 (s, 1 H), 3.48 (t, *J* = 5.6 Hz, 2 H), 3.25 (t, *J* = 5.6 Hz, 2 H), 2.29 (s, 3 H), 2.26 (s, 3 H), 1.46-1.40 (m, 4 H), 1.05 (t, *J* = 5.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 146.5, 139.2, 138.8, 137.0, 136.4, 129.6, 129.5, 129.3, 128.2, 128.1, 125.7, 120.7, 47.3, 42.0, 25.8, 25.1, 24.4, 19.8, 19.6; HRMS (ESI): calcd. for $C_{22}H_{26}NO$ $[M + H]^+$ 320.2014; found 320.2004.



11h

(*E*)-3-Phenyl-1-(piperidin-1-yl)-3-(p-tolyl)prop-2-en-1-one (11h): Following the general procedure C described above, **11h** was obtained as yellowish brown colored solid (32 mg, 47%): mp 122-124 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2936, 1606, 1441, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.29 (m, 5 H), 7.31-7.29 (m, 2 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 6.31 (s, 1 H), 3.48 (t, *J* = 5.6 Hz, 2 H), 3.24 (t, *J* = 5.6 Hz, 2 H), 2.38 (s, 3 H), 1.47-1.40 (m, 4 H), 1.04 (t, *J* = 5.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 146.4, 139.1, 138.3, 138.3, 129.6, 129.0, 128.3, 128.1, 128.0, 120.7, 47.3, 42.0, 25.7, 25.1, 24.4, 21.2; HRMS (ESI): calcd. for $C_{21}H_{24}NO$ $[M + H]^+$ 306.1858; found 306.1870.



11i

(*E*)-3-(3,5-Dimethylphenyl)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (11i): Following the general procedure C described above, **11i** was obtained as yellowish brown colored solid (43 mg, 54%): mp 94-96 ^{o}C; R_f = 0.60 (70% EtOAc/Hexane); IR (thin film): υ_{max} 2935, 1606, 1442, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.29 (m, 5 H), 7.31-7.29 (m, 2 H), 6.99 (s, 1 H), 6.92 (s, 2 H), 6.29 (s, 1 H), 3.48 (t, *J* = 5.6 Hz, 2 H), 3.25 (t, *J* = 5.6 Hz, 2 H), 2.31 (s, 6 H), 1.46-1.40 (m, 4 H), 1.04 (t, *J* = 4.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 146.7, 141.3, 139.1, 137.7, 130.1, 129.5, 128.2, 128.1, 126.0, 121.2, 47.3, 42.0, 25.7, 25.1, 24.4, 21.3; HRMS (ESI): calcd. for $C_{22}H_{26}NO$ $[M + H]^+$ 320.2014; found 320.2004.

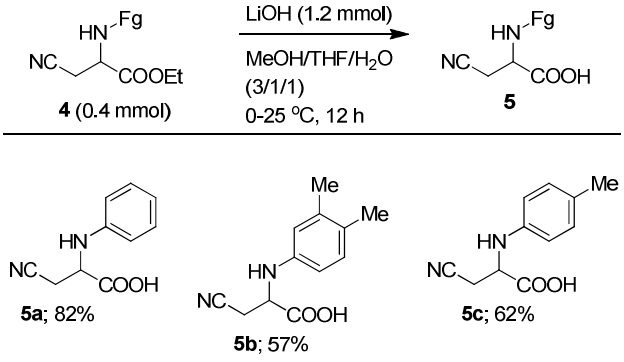
Chapter 3

Result and Discussion

Work A:

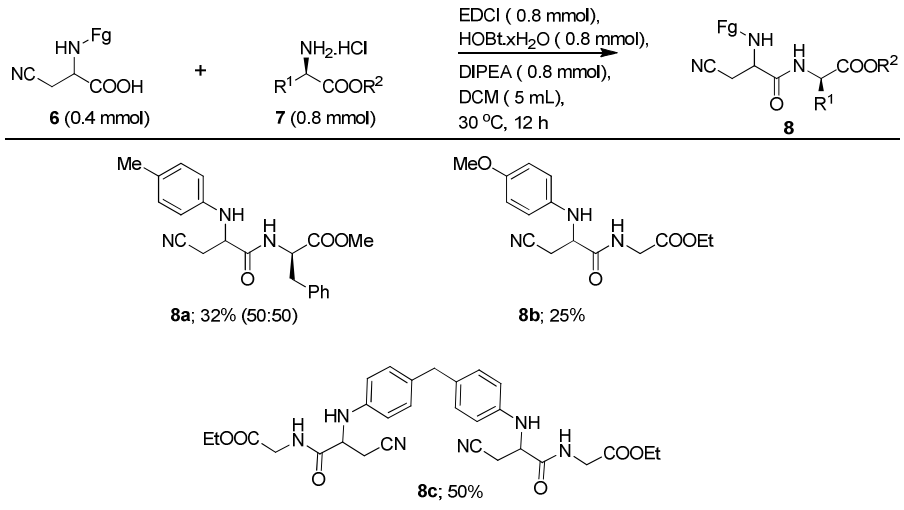
The selective lithium hydroxide mediated hydrolysis of nitrile containing α-amino esters (**4**) in the mixture of methanol-THF-water solvent at 0-25 °C resulted β-nitrile substituted *N*-protected α-amino acids (**5**) in very good yields.

Scheme 3. Synthesis of nitrile substituted *N*-protected α-amino acid **5**



Peptide formation is of the important fundamental reaction and amino acids are important synthetic building blocks for the peptide synthesis methodology. To explore the utility of the amino acid synthesized from our work in peptide chemistry, we carried out the coupling reaction of the nitrile substituted *N*-protected amino acid **5** with phenylalanine methyl ester hydrochloride or glycine ethyl ester hydrochloride which gave the dipeptides **8** in good yields.

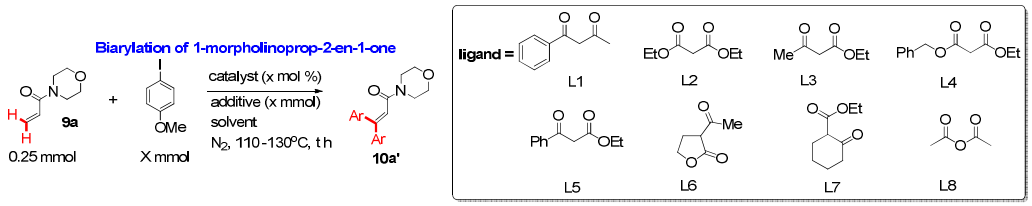
Scheme 4. Synthesis of peptides of nitrile containing α-amino acids **8**



Work B:

For the synthesis of cinnamamide derivatives, we have screened the various parameters such as solvents, ligands, additives and catalysts to find the best reaction condition for the arylation of 1-morpholinoprop-2-en-1-one. We started our optimization without ligands where the product is not obtained. Then we started screening various ligands based on a class of 1, 3 dicarbonyl compounds where the best condition is found out with benzoyl acetone (entry 7, **Table 1**). Pd-acetate in association with benzoyl acetone found out to be the best condition among all where potassium carbonate is used as base and DMF as a solvent at 130 ^{o}C for 24 hours.

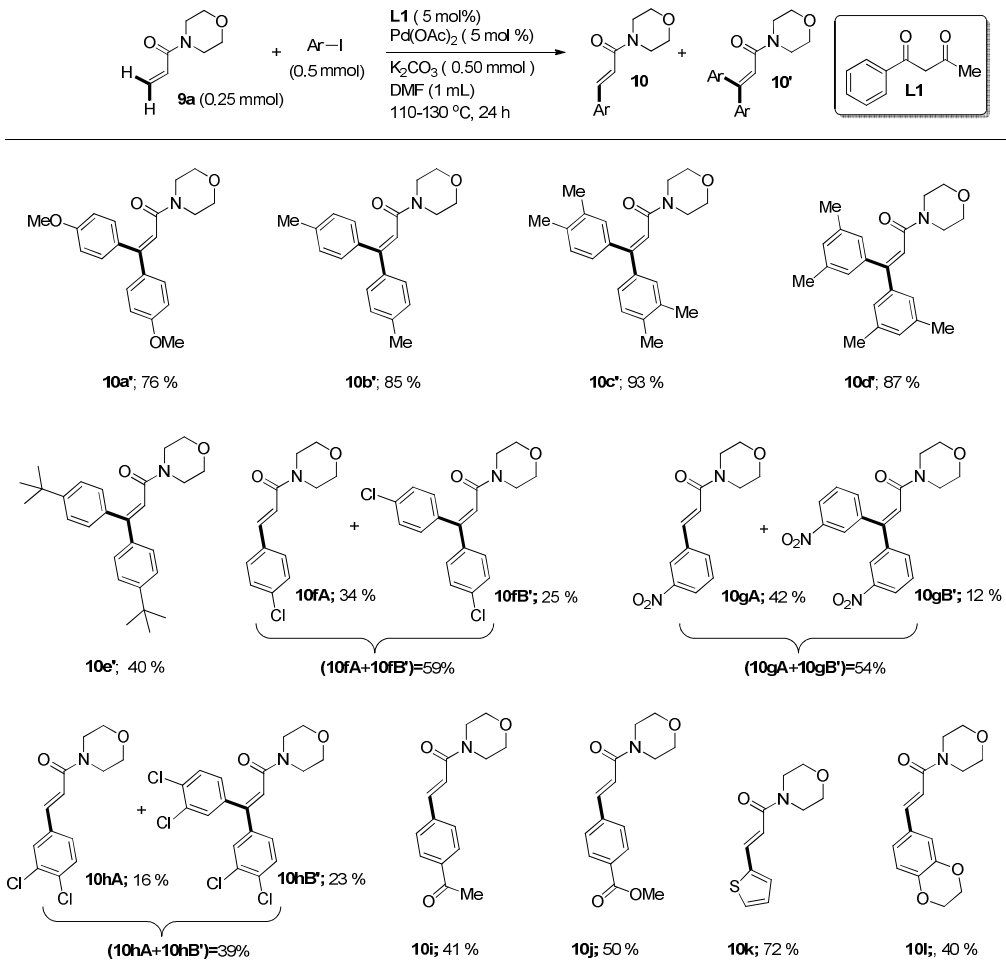
Table 1. Optimization for the best reaction condition.



entry	*p*-iodoanisole (mmol)	solvent (mL)	ligand (mol %)	catalyst (mol %)	additive (mmol/mL)	*t* (h)	yield (%)
1	1	toluene (3)	---	$Pd(OAc)_2$ (10)	AgOAc (0.55)	24	NR
2	1	toluene (3)	---	$Pd(OAc)_2$ (10)	AcOH (0.50 mL)	24	NR
3	1	toluene (3)	---	$Pd(PPh_3)_4$ (10)	AgOAc (0.55)	24	traces
4	1	*t*-amyl alcohol (3)	---	$Pd(OAc)_2$ (10)	K_2CO_3 (1.50)	20	NR
5	1	neat	---	$Pd(OAc)_2$ (10)	NEt_3 (0.70 mL)	24	NR
6	1	DMF (1)	---	$Pd(PPh_3)_4$ (10)	Cs_2CO_3 (0.50)	24	NR
7	**0.5**	**DMF (1)**	L1	**$Pd(OAc)_2$ (5)**	**K_2CO_3 (0.50)**	**24**	**76**
8	0.5	DMF (1)	L2	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	73
9	0.5	DMF (1)	L3	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	65
10	0.5	DMF (1)	L4	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	60
11	0.5	DMF (1)	L5	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	62
12	0.5	DMF (1)	L6	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	NR
13	0.5	DMF (1)	L7	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	73
14	0.5	DMF (1)	L1	$Pd(OTf)_2$	K_2CO_3 (0.50)	24	NR
15	0.5	DMF (1)	L1	$Pd(dba)_2$	K_2CO_3 (0.50)	24	NR
16	0.5	DMF (1)	L1	$PdCl_2(CH_3CN)_2$	K_2CO_3 (0.50)	24	50
17	0.5	1,4-dioxane (4)	L1	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	NR
18	0.5	ethanol (3)	L1	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	NR
19	0.5	1,2-DCE (3)	L1	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	NR
20	0.5	DMF (1)	L8	$Pd(OAc)_2$ (5)	K_2CO_3 (0.50)	24	73

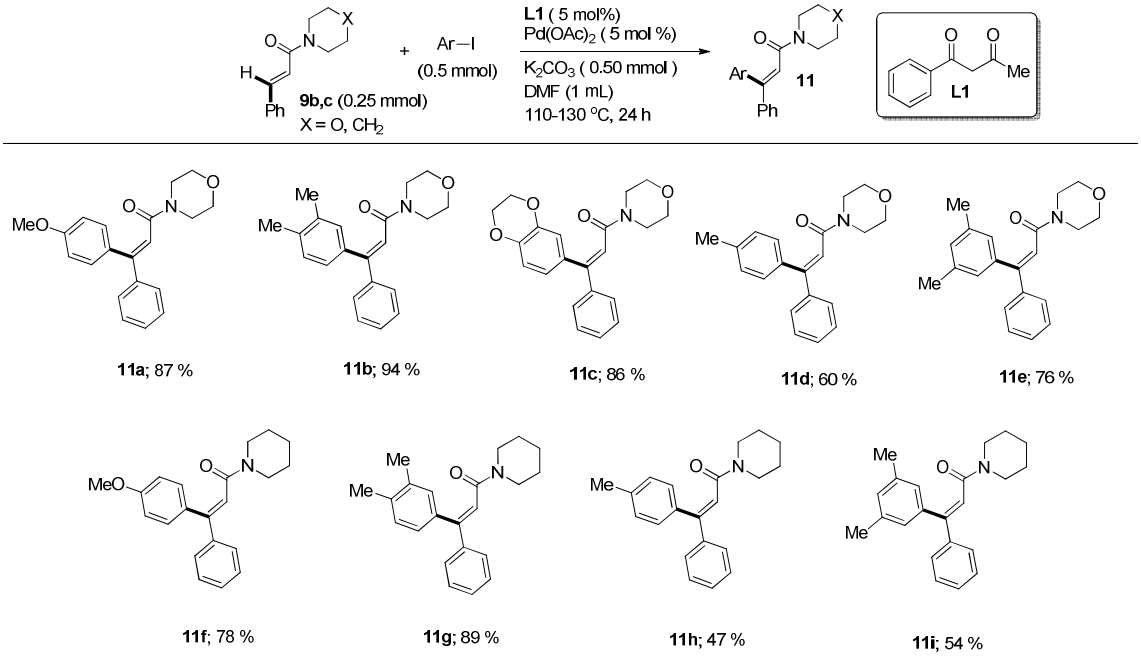
After achieving the best reaction condition (entry 7, **Table 1**), various aryl iodides have been used to make a class of derivatives from moderate to good yields.

Scheme 5. Construction of mono and bis acrylamide derivatives **10, 10'**



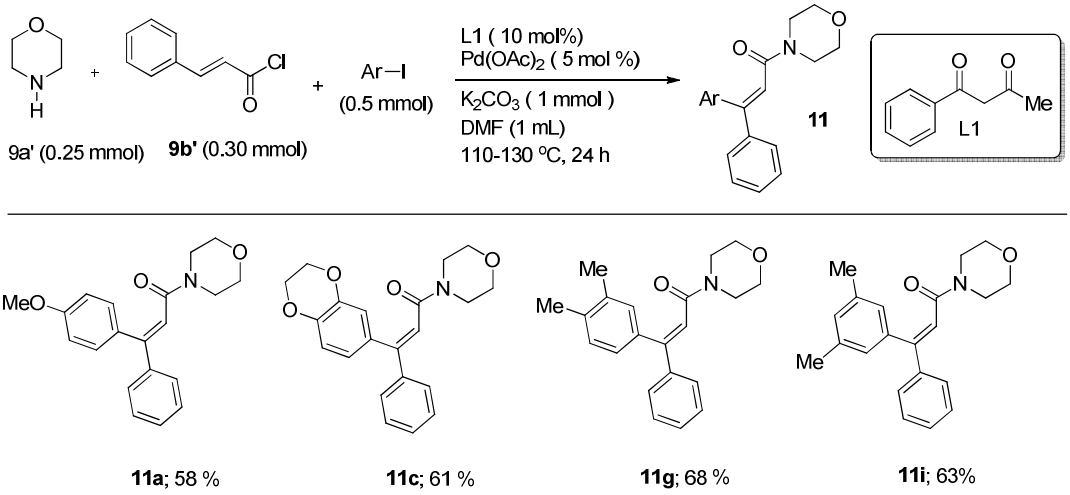
Then, we explored this methodology by using cinnmamides as our starting materials where we used various aryl iodide source to construct various unsymmetrical bis-arylated cinnamamide derivatives.

Scheme 6. Construction of cinnamamide derivatives **11**



Further, an attempt has been made to reduce the synthetic pathways to get the cinnamamide derivatives where we achieved the construction of cinnamamides in 'one pot' manner.

Scheme 7. One pot synthesis of cinnamamide derivatives **11**



Summary

In summary, we have explored a variety of biologically relevant molecules which includes the synthesis of nitrile equipped *N*-aryl α-amino acid derivatives were achieved via nucleophilic addition of bromoacetonitrile to α-imino acids followed by hydrolysis and further, dipeptide derivatives of the nitrile equipped unnatural amino acid were also synthesized. Along this line, a part of the thesis involves the synthesis of various substituted cinnamamide derivatives via Mizoroki–Heck Cross-Coupling reaction have been achieved.

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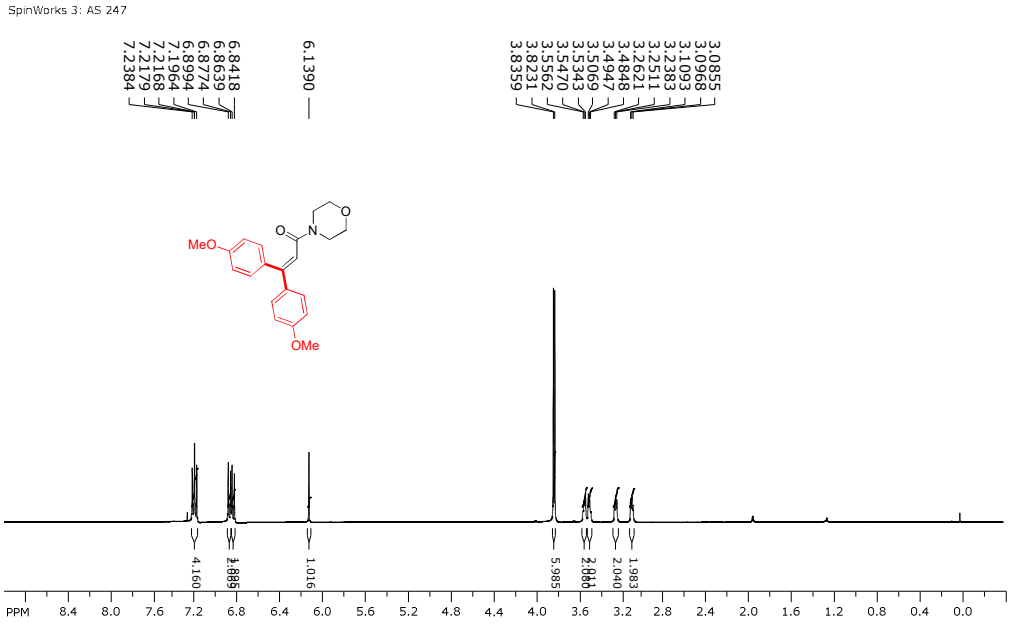
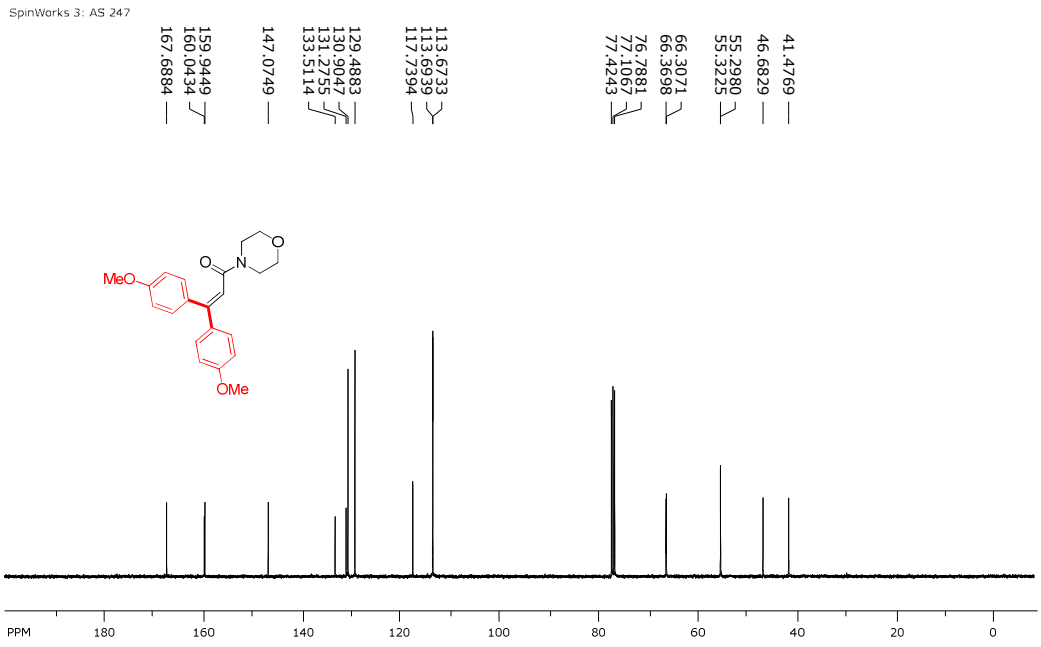
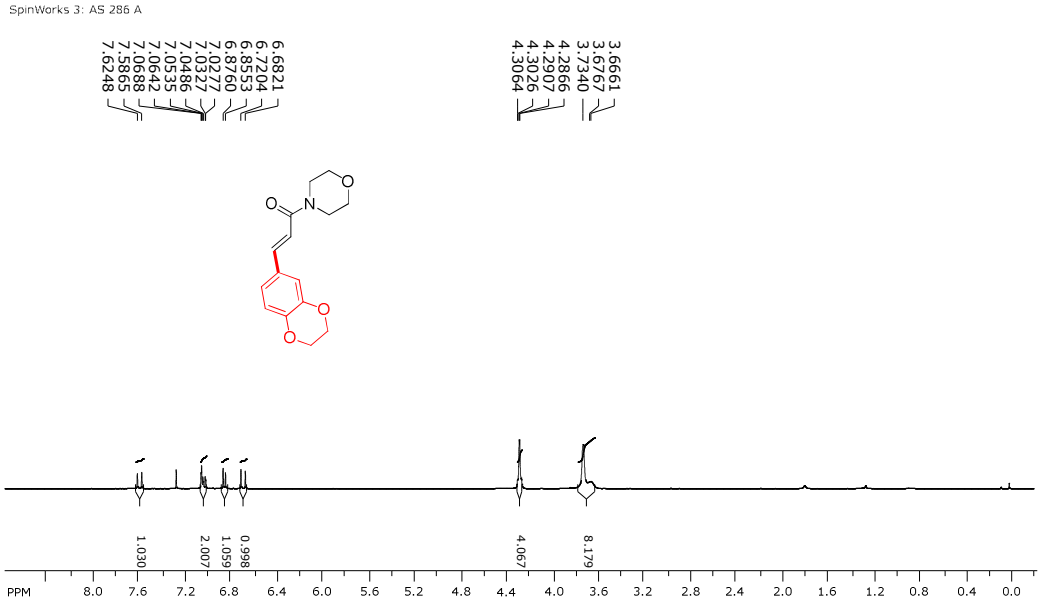
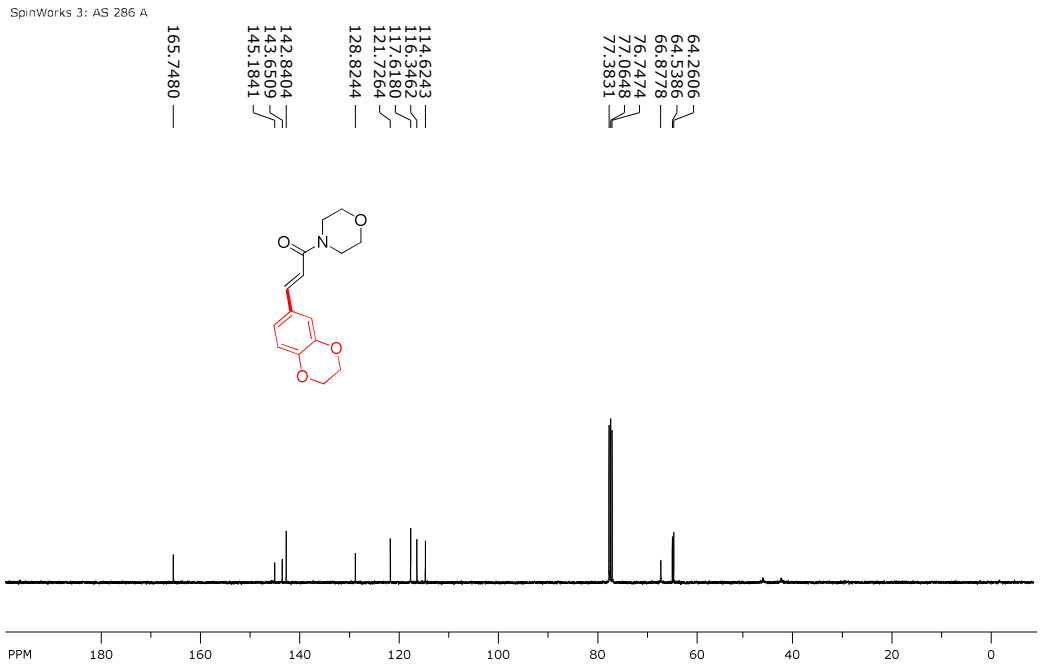
Appendix

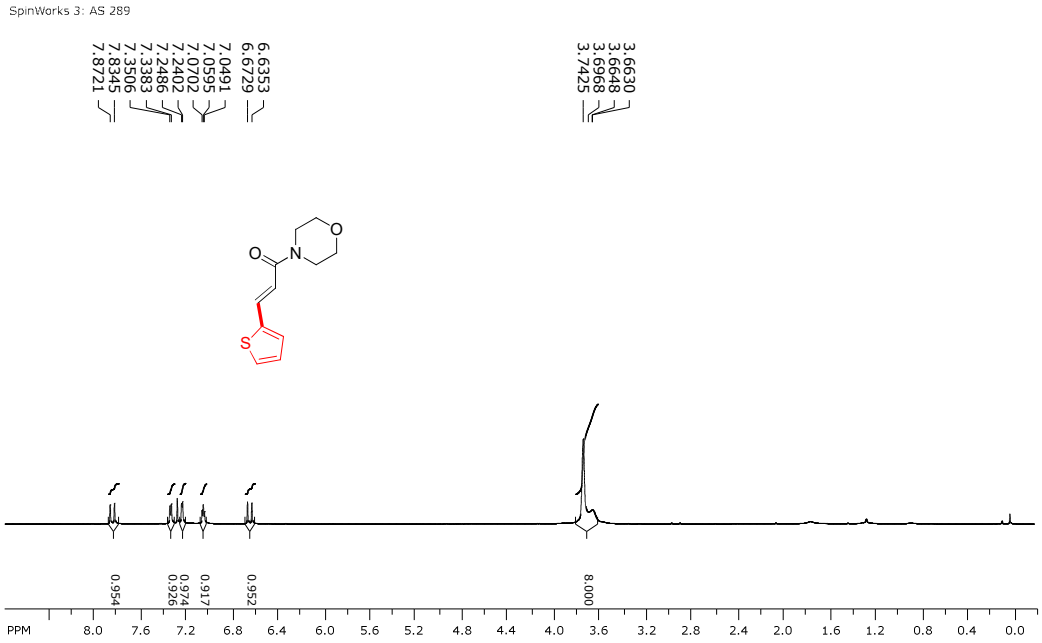
NMR Spectra of Representative Compounds

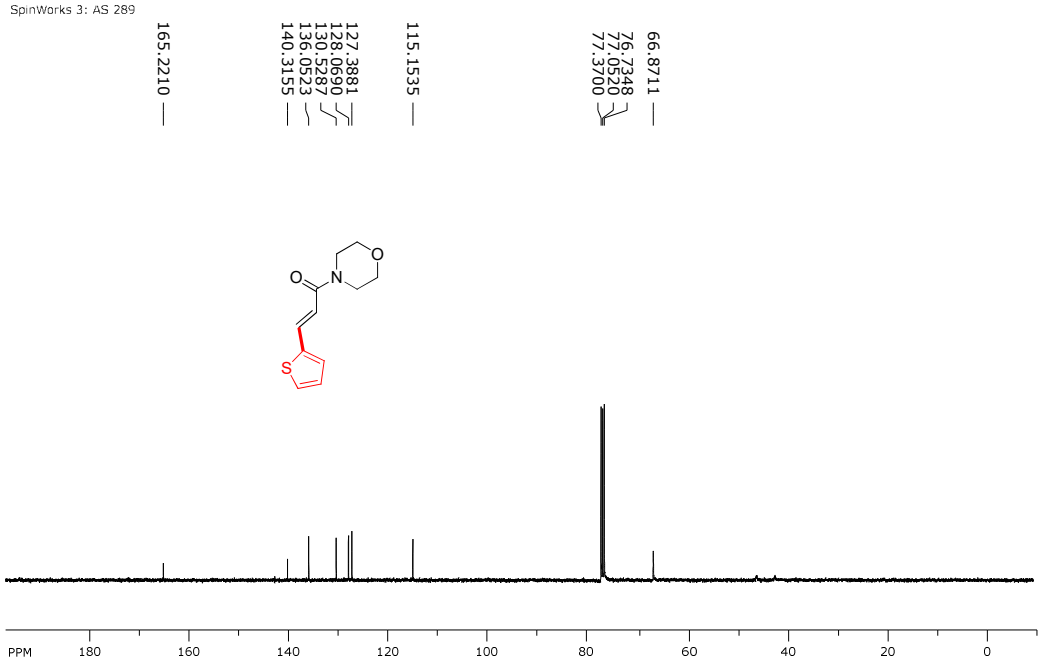


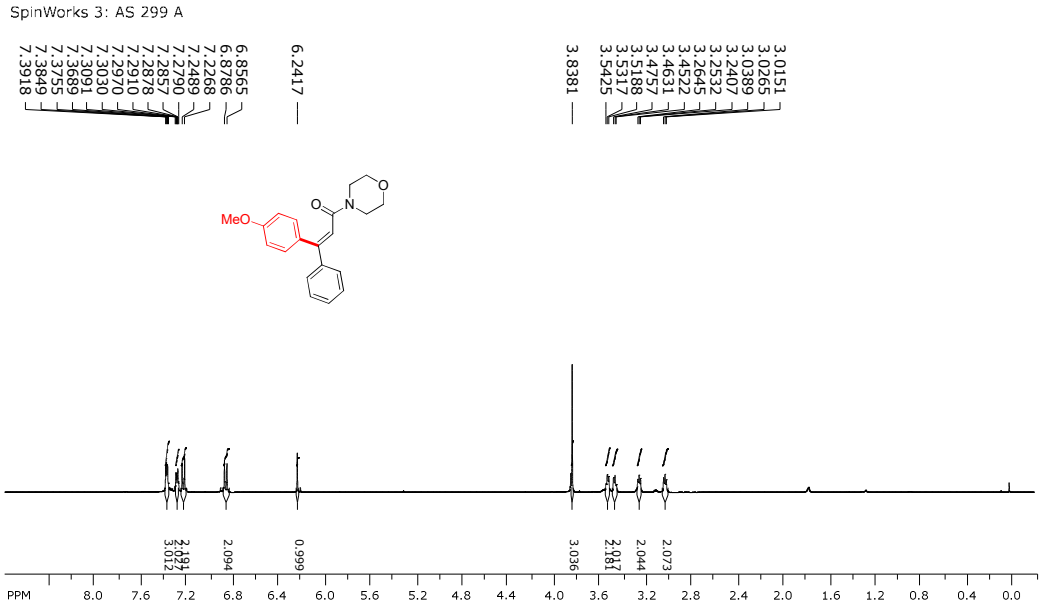


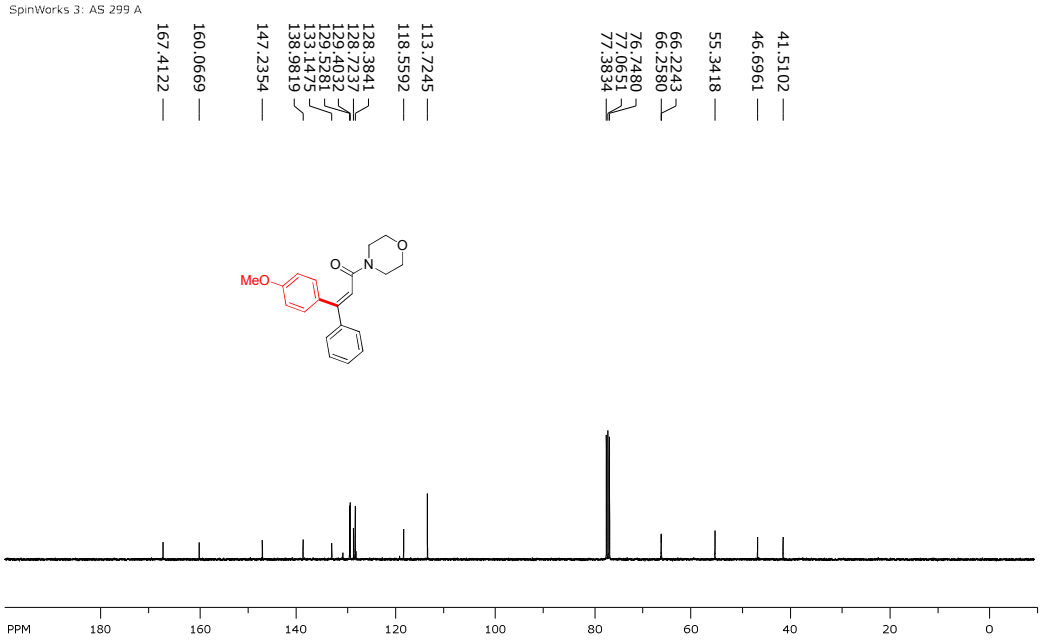

SpinWorks 3: AS 286 A
7.6248
7.5865
7.0688
7.0642
7.0535
7.0486
7.0327
7.0277
6.8760
6.8553
6.7204
6.6821
4.3064
4.3026
4.2907
4.2866
3.7340
3.6767
3.6661
O
N
O
O
O
1.030
2.007
1.059
0.998
4.067
8.179
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0

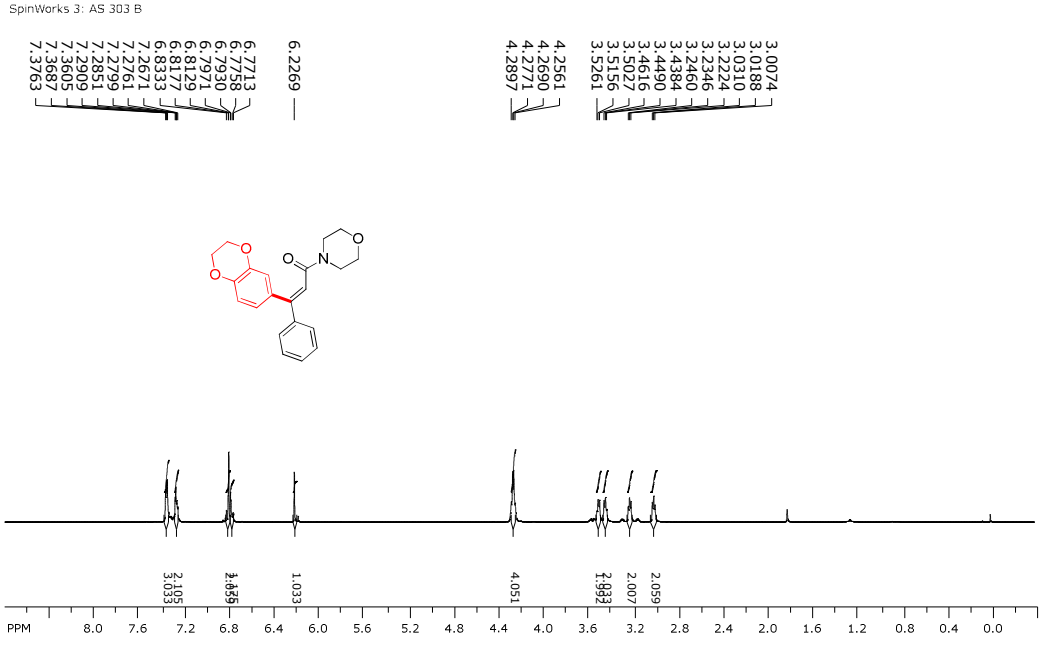

SpinWorks 3: AS 286 A
165.7480
145.1841
143.6509
142.8404
128.8244
121.7264
117.6180
116.3462
114.6243
77.3831
77.0648
76.7474
66.8778
64.5386
64.2606
O
N
O
O
O
PPM
180
160
140
120
100
80
60
40
20
0

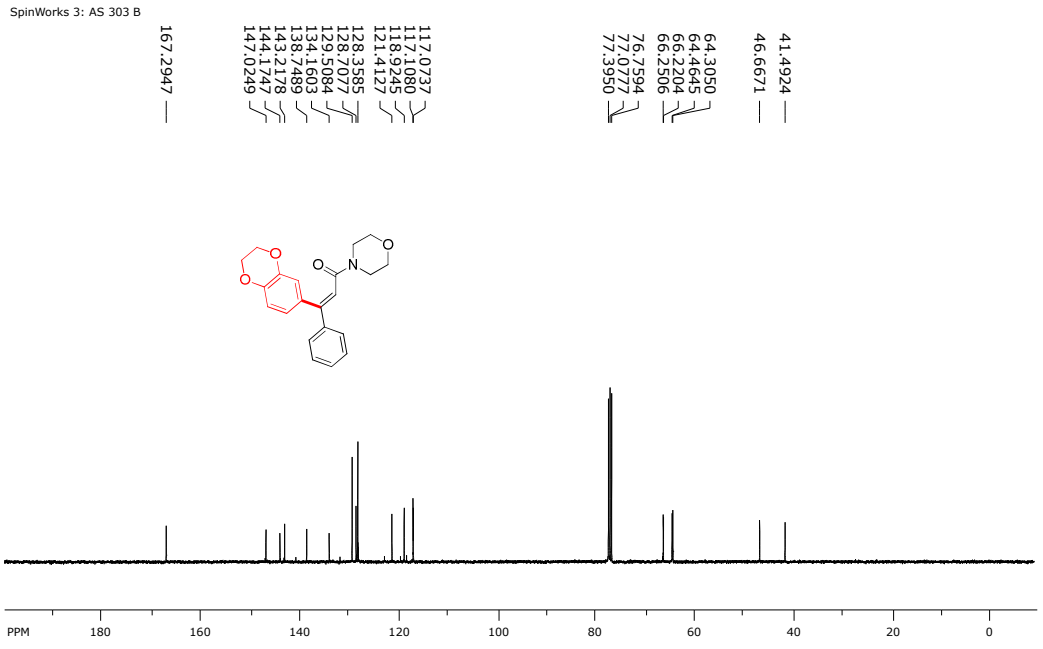

SpinWorks 3: AS 289
7.8721
7.8345
7.3506
7.3383
7.2486
7.2402
7.0702
7.0595
7.0491
6.6729
6.6353
3.7425
3.6968
3.6648
3.6630
O
N
O
S
0.954
0.926
0.974
0.917
0.952
8.000
PPM
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0


SpinWorks 3: AS 289
165.2210
140.3155
136.0523
130.5287
128.0690
127.3881
115.1535
77.3700
77.0520
76.7348
66.8711
O
N
O
S
PPM
180
160
140
120
100
80
60
40
20
0


SpinWorks 3: AS 299 A
7.3918
7.3849
7.3755
7.3689
7.3091
7.3030
7.2970
7.2910
7.2878
7.2857
7.2790
7.2489
7.2268
6.8786
6.8565
6.2417
3.8381
3.5425
3.5317
3.5188
3.4757
3.4631
3.4522
3.2645
3.2532
3.2407
3.0389
3.0265
3.0151
MeO
O
N
O
3.012
2.092
2.091
2.094
0.999
3.036
2.187
2.044
2.073
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: AS 299 A
167.4122
160.0669
147.2354
138.9819
133.1475
129.5281
129.4032
128.7237
128.3841
118.5592
113.7245
77.3834
77.0651
76.7480
66.2580
66.2243
55.3418
46.6961
41.5102
MeO
O
N
O
PPM
180
160
140
120
100
80
60
40
20
0


SpinWorks 3: AS 303 B
7.3763
7.3687
7.3605
7.2909
7.2851
7.2799
7.2761
7.2671
6.8333
6.8177
6.8129
6.7971
6.7930
6.7758
6.7713
6.2269
4.2897
4.2771
4.2690
4.2561
3.5261
3.5156
3.5027
3.4616
3.4490
3.4384
3.2460
3.2346
3.2224
3.0310
3.0188
3.0074
O
N
O
O
3.033
2.105
1.859
1.033
4.051
1.992
2.007
2.059
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: AS 303 B
167.2947
147.0249
144.1747
143.2178
138.7489
134.1603
129.5084
128.7077
128.3585
121.4127
118.9245
117.1080
117.0737
77.3950
77.0777
76.7594
66.2506
66.2204
64.4645
64.3050
46.6671
41.4924
O
N
O
O
PPM
180
160
140
120
100
80
60
40
20
0