Design and Development of New Synthetic Methods for Biologically Important Five Membered Heterocycles via Novel Organosulfur Synthons

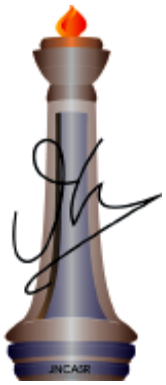
A Thesis

Submitted for the Degree of

Doctor of Philosophy

By

S. Vijay Kumar



New Chemistry Unit

Jawaharlal Nehru Centre for Advanced Scientific Research

(*A Deemed University*)

Jakkur, Bengaluru-560064

India

November- 2015

Declaration

I hereby declare that the entire work embodied in this thesis entitled "***Design and Development of New Synthetic Methods for Biologically Important Five Membered Heterocycles via Novel Organosulfur Synthons***" is the result of investigations carried out by me in the *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore, India* under the guidance of **Prof. H. Ila**, and it has not been submitted elsewhere for any degree or diploma.

In keeping with general practice, due acknowledgements have been made wherever the work described is based on findings of other investigators. Any omissions that might have occurred due to oversight or error in judgment are regretted.

November, 2015 **S. Vijay Kumar**

Bangalore (Research Scholar)

Certificate

I hereby certify that the entire work embodied in this thesis entitled "***Design and Development of New Synthetic Methods for Biologically Important Five Membered Heterocycles via Novel Organosulfur Synthons***" has been carried out by **Mr. S. Vijay Kumar** under my supervision in the *New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore, India* and that no part of it has been submitted elsewhere for any degree or diploma.

November, 2015
Bangalore

Prof. H. Ila
(Research Supervisor)
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Dedicated to…..

Prof. H. Ila and Prof. H. Junjappa

Acknowledgement

*First and foremost, I would like to express my sincere gratitude to my research supervisor **Prof. H. Ila**, Synthetic Organic Chemistry Lab, New Chemistry Unit, JNCASR, for her continued support, motivation, patience and guidance throughout my PhD career. It has been a great privilege and honor to be associated with her.*

*I would like to thank **Prof. C. N. R. Rao**, FRS, Chairman, New Chemistry Unit, JNCASR for being the constant source of inspiration, support and encouragement throughout my stay in JNCASR. I also thank him for providing excellent facilities and infrastructure to carry out my research work.*

*I would like to thank **Prof. H. Junjappa** for his discussions over a wide range of interesting topics, apart from chemistry, educated us about a number of things going around in the world. Also, the Diwali dinner parties heartily arranged by sir and madam at their home will ever be remembered.*

I am thankful to Prof. H. Ila, Prof. Jayanta Haldar and Prof. Sridhar Rajaram of JNCASR and Prof. P. Balaram and Prof. Siddhartha P. Sarma of IISc for teaching me during my course work. Also I would like to thank all NCU faculty for their support.

I am thankful to my seniors Dr. Vijayalaxmi, Dr Aravind, Dr. Parameshwarappa for their timely help and moral support. Especially I would like to thank Dr. Vijayalaxmi for helping in lab setup. I extend my heartfelt gratitude to my colleagues Dr. Vibha Gautham, Dr. Saidulu, Yugandar, Anand, Saraiah for their constant support and help not only during my thesis preparation work but also during my whole stay at JNCASR. I would also like to thank Yoginath Reddy (POCE) and Priyadarshini (SRF) for their help in the laboratory.

I sincerely thank Mahesh, Vasu and Shiva for recording the NMR, IR and HRMS spectra for my samples.

I would like to thank Academic, Administration, Purchase, Stores, and NCU Office staff for their constant help.

I thank JNCASR Library, Comp Lab, Hostel, Gym and Health Center for providing and maintaining the various facilities that have helped me immensely.

This is the best time to say "Thank You" to all my respected teachers who taught me at different levels. I am grateful to my teacher B. Rajendra Prasad (late), Pragathi Vidyalayam, Aler where I started my journey of education. Special thanks to my school teachers S. Haragopal, S. Sudhakar Reddy, S. Mallesham, Somaraju (late), Radhakrishna Sharma. I thank my Intermediate lecturers K.L.N. Cahri, Bhavani, Bhrahmeshwari. I am also very much thankful to my graduation teachers Ravi Kumar, Shanthikala, Jyothi, Dr. Chandraiah (NCC).

I sincerely thank Surender Reddy Sir, J. P Sir, Ashok Sir, Udaya Kumari Madam, Dr. Sridevi Madam, Dr, Bhavani Madam, Viritha Madam from Osmania University for their support and encouragement throughout my life.

I specially thank all my friends from school, intermediate, B.Sc, M.Sc and JNCASR friends for their unforgettable company throughout my academic life. Especially Prashanth, Saidulu, Venu, Rambabu, Uday Bhanu, Sandeep, Srinu 11, Laxman, Harinath, Farooq, Sharma, Shalini, Rohini, Naveen, Sathish, Shiva, Jyothi, kranthi, Ravi Nimma. I cannot imagine my life without their support and encouragement. Thank you all.

I am obliged to Fellowship (JRF & SRF) from CSIR, New Delhi and the infrastructural facilities and financial assistance of JNCASR and express the sincere thanks for the same.

I thank Jubilant Biosys Drug Discovery, Bangalore, India where I learnt all experimental techniques.

Finally and most importantly, I am grateful to my family, especially my father, brother and sister for their love, moral support and constant encouragement throughout my life. They always sacrificed their own wishes and happiness just for betterment of my career. Without their love, care, support, sacrifice, prayers, wishes, motivation, it would have been impossible to imagine my present position in my life. Also I thank my uncle and aunt (Shad Nagar) for their financial support for my education.

Finally I would like to thank everybody who was important to the successful realization of thesis, as well as expressing my apology that I could not mention personally one by one.

S. Vijay Kumar

Synopsis

Title of Thesis: "***Design and Development of New Synthetic Methods for Biologically Important Five Membered Heterocycles via Organosulfur Synthons***"

Submitted by: Mr. S. Vijay Kumar, New Chemistry Unit, JNCASR, Bangalore-64, India

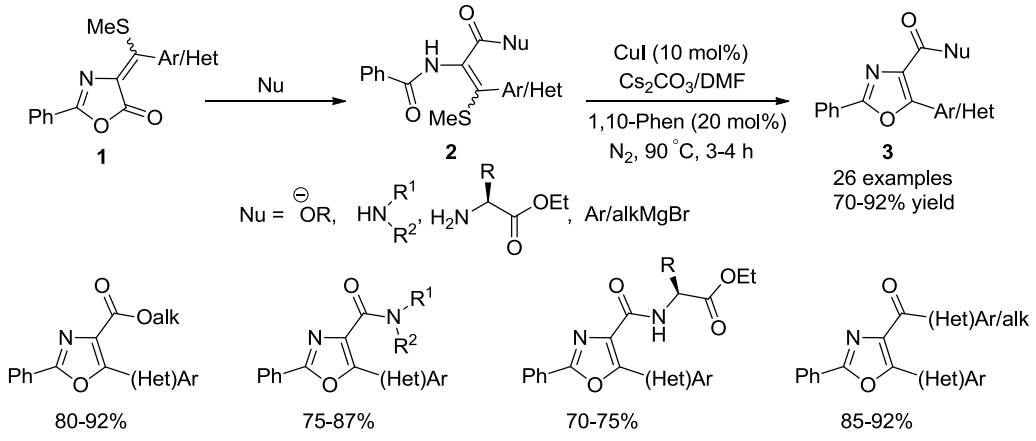
The above thesis is divided into six chapters:

Chapter 1: "*Organosulfur Based Synthons and Reactive Intermediates: An Introduction*"

The present chapter gives a brief account of synthetic versatility of polarized ketene dithioacetals and its variants i.e., β-(methylthio)methylene ketones/acrylonitriles, previously reported from our laboratory and other research groups.

Chapter 2: "*An Efficient Synthesis of 2,4,5-Trisubstituted Oxazoles by Cu-Catalyzed Intramolecular Cyclization of Highly Functionalized Enamides*"

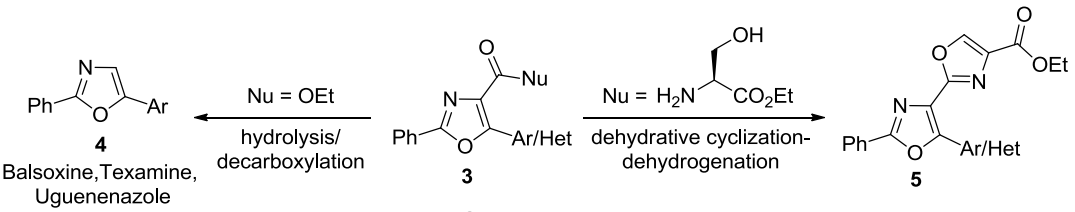
The chapter 2 of the thesis describes the synthesis of 2-phenyl-4,5-substituted oxazoles **3** involving intramolecular copper-catalyzed cyclization of novel, highly functionalized β-(methylthio) enamides **2**, which are readily accessible in high yields, by nucleophilic ring opening of a number of 4-[(methylthio)-(het)arylmethylene]-5-oxazolones **1** with various alkoxides, primary and seconadary aliphatic/aromatic amines, amino acid esters and Grignard reagents (Scheme 1).



Scheme 1

Synthesis of few naturally occurring 2,5-diaryloxazoles **4** such as balsoxine, texamine and uguenenazole has also been described. Few of the serine-derived oxazole-4-

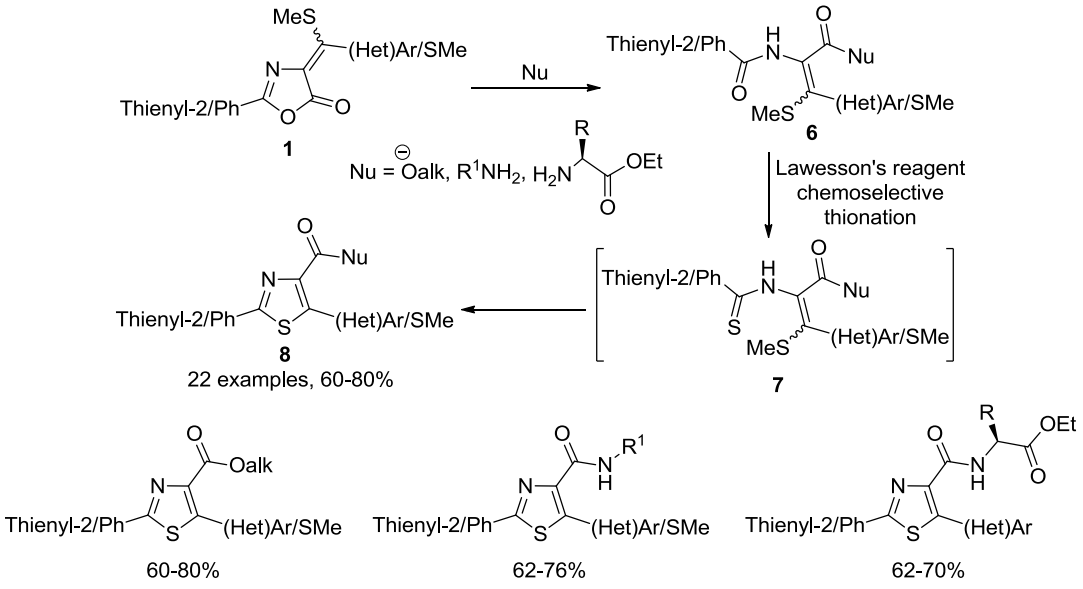
carboxamides **3** were transformed into novel trisubstituted 4,2′-bisoxazoles **5** through DAST/DBU-mediated cyclodehydration-dehydrohalogenation (Scheme 2).



Scheme 2

Chapter 3: "*Synthesis of 2,4,5-Trisubstituted Thiazoles via Lawesson's Reagent Mediated Chemoselective Thionation-Cyclization of Functionalized Enamides*"

The chapter 3 of the thesis describes a highly regio- and chemoselective synthesis of 2,4,5-trisubstituted thiazoles such as **8** *via* one step thionation-intramolecular cyclization of functionalized enamide precursors **6** in the presence of Lawesson's reagent, offering wide range of functional group diversity at 2,4 and 5-positions of the product thiazoles (Scheme 3).

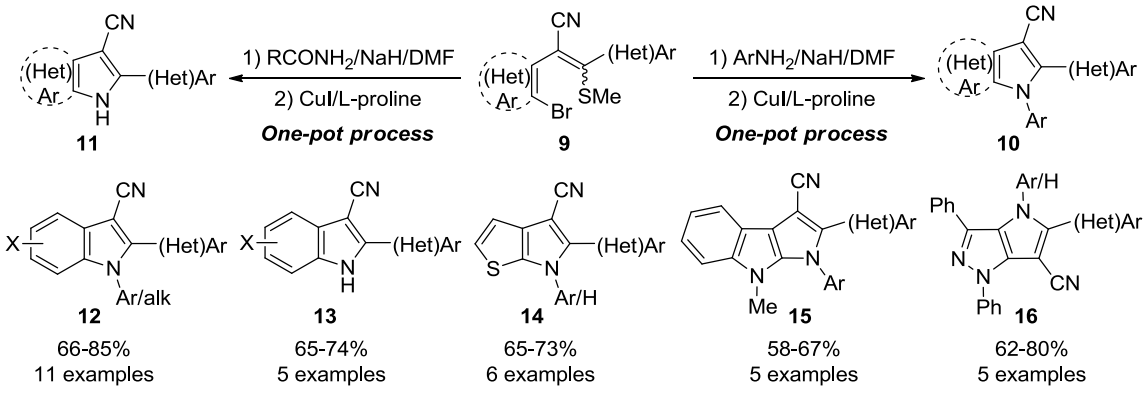


Scheme 3

Chapter 4: "*Synthesis of Multisubstituted Indoles and Heterofused Pyrroles via Sequential One-Pot Base Mediated and Copper Catalyzed Inter- and Intramolecular Amination of 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitriles*"

The chapter 4 of the thesis deals with a novel, one-pot, two step synthesis of substituted 1-*N*-(het)aryl-2-(het)aryl-3-cyanoindoles and the related pyrrolo fused heterocycles **10** such as thienopyrroles **14**, pyrroloindoles **15** and pyrazolopyrroles **16** via

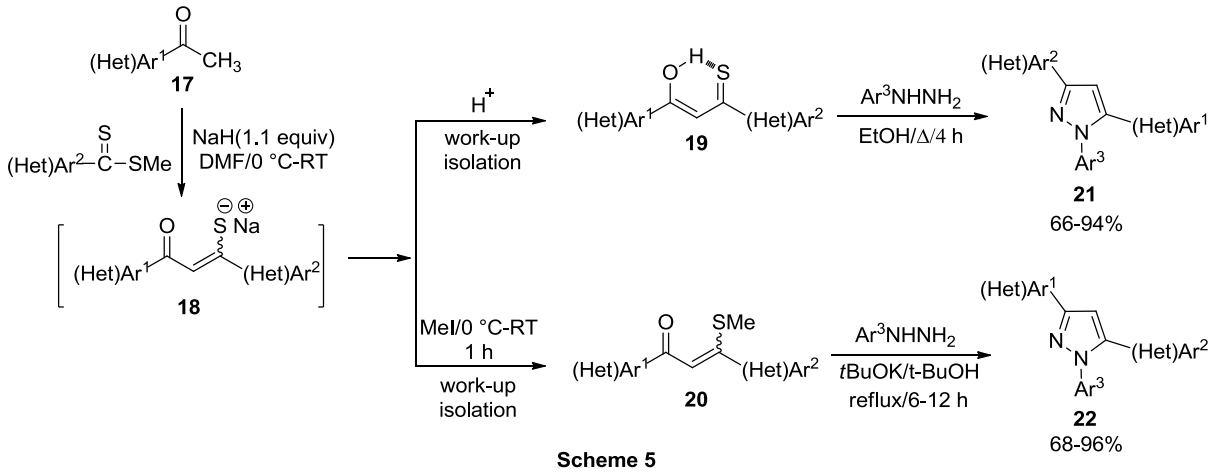
copper catalyzed intramolecular C-N bond formation of functionalized enaminonitriles, generated in situ by base mediated displacement on 2-[2-bromo(het)aryl]-3-(het)aryl-3-(methylthio) acrylonitrile **9** with various (het)aryl amines. The broad scope of the methodology was further illustrated with the synthesis of *NH*-indoles **13** by employing primary amides as coupling partners in this sequential one-pot C-N bond-forming reaction (Scheme 4).



Scheme 4

Chapter 5: "*Cyclocondensation of Arylhydrazines with 1,3-Bis(het)arylmonothio-1,3-diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 1-Aryl-3,5-bis(het) aryl pyrazoles with Complementary Regioselectivity*"

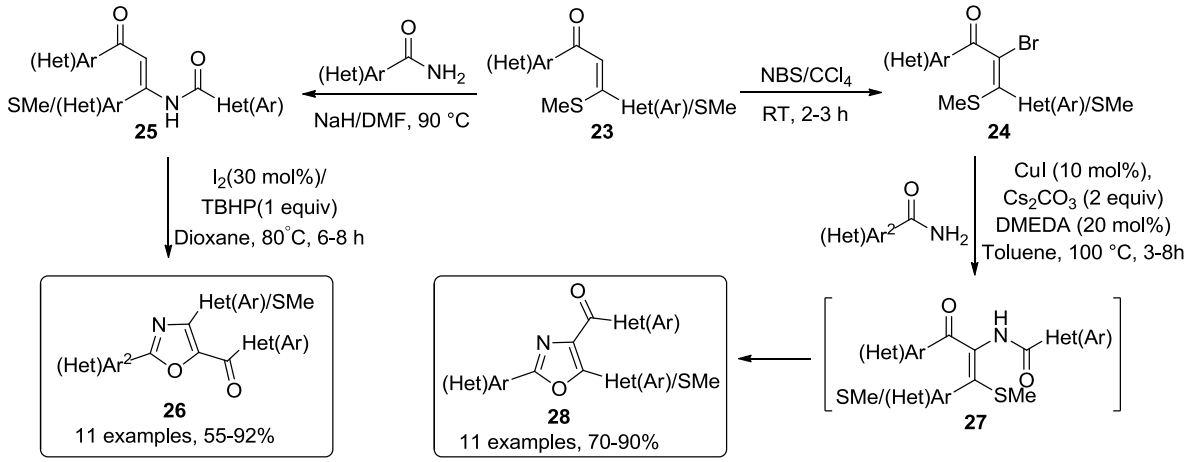
The chapter 5 of the thesis describes two efficient highly regioselective routes for the synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles **21** and **22** with complementary regioselectivity starting from active methylene ketones **17**. In the first protocol, the newly synthesized 1,3-bis(het)aryl-monothio-1,3-diketone precursors **19** [prepared by condensation of active methylene ketones **17** with het(aryl) dithioesters in the presence of sodium hydride] were reacted with arylhydrazines in refluxing ethanol under neutral conditions, furnishing 1-aryl-3,5-bis(het)arylpyrazoles **21**, in which the het(aryl) moiety attached to the thiocarbonyl group of monothio-1,3-diketones is installed at 3-position. In the second method, the corresponding 3-(methylthio)-1,3-bis(het)aryl-2-propenones **20** (prepared *in situ* by base induced alkylation of 1,3-monothiodiketones) were condensed with arylhydrazines in the presence of potassium-*t*-butoxide in refluxing *t*-butanol yielding 1-aryl-3,5-bis(het)arylpyrazoles **22** with complementary regioselectivity (Scheme 5).



Scheme 5

Chapter 6: Regioselective *Synthesis of 2,4,5-Trisubstituted Oxazoles from α-Oxoketene Dithioacetals and β-(methylthio)-β-(Het/Aryl)-2-propenones*"

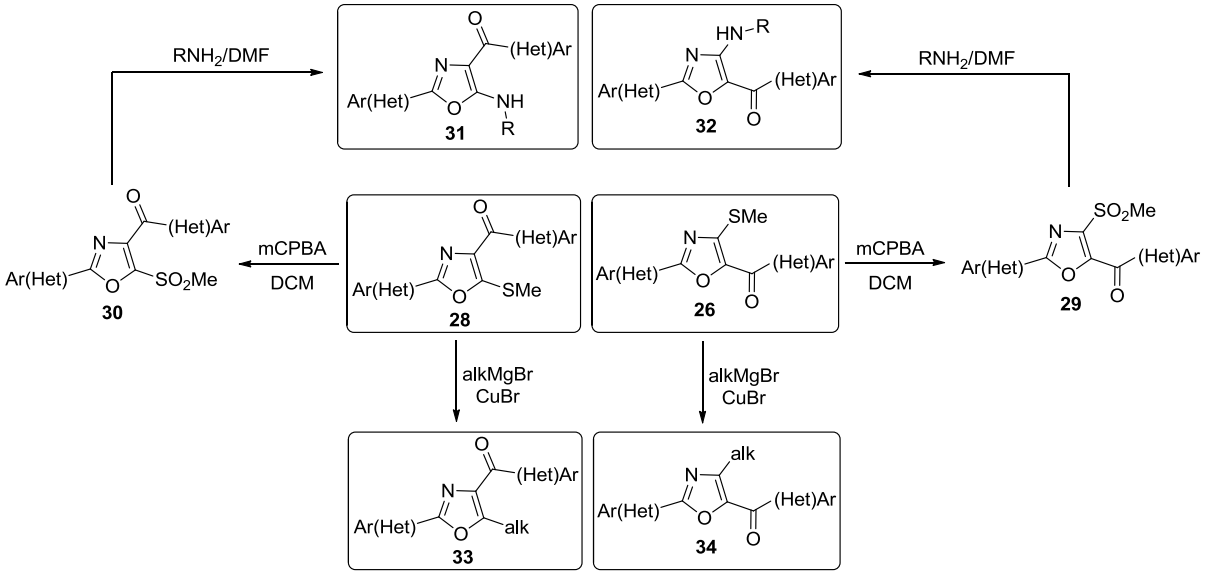
This chapter describes a regioselective synthesis of 2,5 substituted 4-acyl oxazoles **28** and 2,4 substituted 5-acyl oxazoles **26** with complementary substituents from α-oxo ketenedithioacetal/1,3-bis(het)aryl-3-(methylthio)-2-propenones **23** by using two synthetic strategies. In the first case, these intermediates were converted to α-bromo derivatives **24** by treatment with NBS followed by intermolecular copper-catalyzed cross coupling with primary amides. In the second case, these intermediates were first subjected to base mediated conjugate addition with amides to furnish regioisomeric enamides **25**, which on intramolecular iodine catalyzed oxidative cyclization afforded the other regioisomeric oxazoles **26** (Scheme 6).



Scheme 6

These newly synthesized 4/5–(methylthio)oxazoles **26/28** were subsequently transformed into the corresponding 4/5-amino and 4/5-alkyloxazoles **31/32** and **33/34** by

oxidation of SMe group to SO_2Me (*m*-CPBA) followed by replacement with primary and secondary amines and by replacement of alkylthio group by Grignard reagents in presence of CuBr (Scheme 7).



Scheme 7

Table of Content

List of Abbreviations

NMR	:	Nuclear magnetic resonance
IR	:	Infrared spectroscopy
TMS	:	Tetramethylsilane
m.p.	:	Melting point
DMF	:	*N*,*N*-Dimethyl formamide
DMSO	:	Dimethyl sulfoxide
THF	:	Tetrahydrofuran
EtOAc	:	Ethyl acetate
DCM	:	Dichloromethane
DCE	:	Dichloroethane
DMA	:	*N*,*N*-Dimethylacetamide
CS_2	:	Carbon disulfide
NaH	:	Sodium hydride
LDA	:	Lithium diisopropylamide
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
PPA	:	Polyphosphoric acid
TFA	:	Trifluroacetic acid
m-CPBA	:	*m*-Chloroperbenzoic acid
NBS	:	N-Bromosuccinimide
TLC	:	Thin layer chromatography
Ts	:	Tosyl
Nu	:	Nucleophile
Bn	:	Benzyl

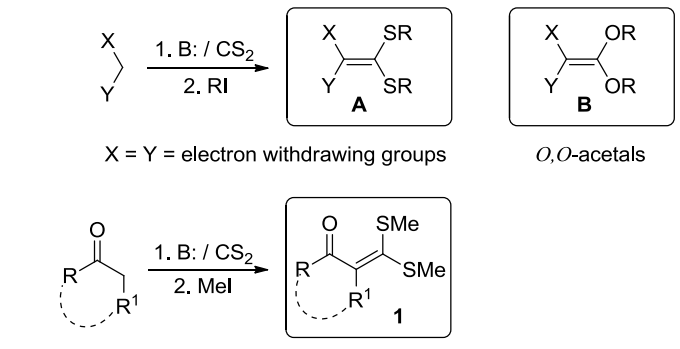
Equiv	:	Equivalent
RT	:	Room temperature
EWG	:	Electron withdrawing group
PMB	:	*p*-Methoxy benzyl
TBHP	:	*t*-Butyl hydroperoxide
DMEDA	:	*N,N′*-Dimethylethylenediamine
DIPEA	:	*N,N*-Diisopropylethylamine
TMSE	:	Trimethylsilylethyl
PIDA	:	Phenyliodine diacetate
DAST	:	Diethylaminosulphur trifluoride
LR	:	Lawesson's reagent
CuTC	:	Copper(I)-thiophene-2-carboxylate
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
LiHMDS	:	Lithium bis(trimethylsilyl)amide
NMI	:	1-Methylimidazole

Chapter 1

Introduction: Polarized Ketene Dithioacetals and Other Organosulfur Building Blocks: A Short Survey

1.1 Polarized ketene dithioacetals

The versatile synthon family of polarized ketene dithioacetals of the general structure **A** has been proven to be among the simplest and useful synthetic building blocks in various organic transformations.[1] Among them, the corresponding α-oxoketene dithioacetals have been extensively studied by our research group. These organosulfur synthons can easily be prepared by the reaction of CS_2 with various active methylene ketones in the presence of base followed by alkylation in one-pot reaction (Scheme 1).



Scheme 1

1.2 *α*-Oxoketene dithioacetals: A brief survey

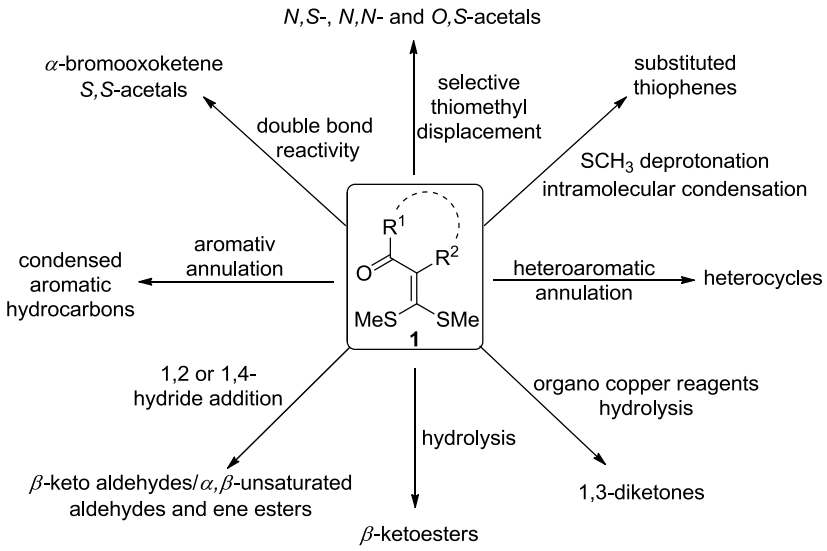
The *α*-oxoketene dithioacetals are generally crystalline solids or distillable liquids and exhibit prolonged shelf-life. They are stable at room temperature and reasonably stable to mild acidic and basic conditions. On the other hand, the corresponding *O,O*-acetals **B** are moisture sensitive and are susceptible for hydrolysis even under mild conditions. Although few of *α*-oxoketene dithioacetals were reported in 1910[2] and later on by Thuillier and co-workers,[3] no systematic investigation on the reactivity and synthetic applications of these versatile synthons was undertaken until mid 1970's when Junjappa and Ila's group extensively explored the synthetic utility of these compounds and developed new general methods for various heterocycles and carbocycles based on these intermediates. This work has been highlighted in several reviews.[1]

1.2.1 Reactivity profile

Scheme 2 explains various reactivity profiles of *α*-oxoketene dithioacetals of the general structure **1**. The *α*-oxoketene dithioacetals can be visualized as masked *β*-ketoesters, as the ketene dithioacetal can be readily converted to an ester group. Alternatively, they may be considered as *α,β*-unsaturated ketones containing a highly functionalized *β*-carbon. The *α*-oxoketene dithioacetals have been shown to be excellent three carbon fragments possessing 1,3-electrophilic centers exhibiting different electrophilicity. These intermediates possess considerable potential for regioselective construction of new C-C or C-heteroatom bonds by 1,2-nucleophilic addition to carbonyl carbon or 1,4-conjugate addition to *β*-carbon of enone system. The hydrides, organomagnesium or organolithium compounds and organocopper reagents give either 1,2- or 1,4-addition products characteristic of *α,β*-enone functionality which can be suitably manipulated by the reagents and reaction conditions.[4-6] The differential electrophilicity at 1,3-carbon of the *α*-oxoketene dithioacetals has been utilized for the regioselective synthesis of substituted five- and six-membered heterocycles and carbocycles by reacting **1** with symmetrical and unsymmetrical 1,2- and 1,3-binucleophiles. The enolate anion formed by deprotonation of *α*-oxoketene dithioacetals (R^1 = Me, Et *etc.*) can undergo condensation with aldehydes to give *α*-enoylketene dithioacetals.[7]

The *α*-oxoketene dithioacetals **1** are shown to undergo facile displacement with either one or two equivalent of primary or secondary amines to give the corresponding

N,S- and *N,N*-acetals, a new series of synthons which can be viewed as either 1,3-electrophiles with amino functionality or functionalized enaminones or enaminonitriles.[1c,9-10] The reactivity of the mercapto double bond has also been explored with electrophiles. Thus, α-oxoketene dithioacetals **1** undergo bromination at α-position with *N*-bromosuccinimide.[8]



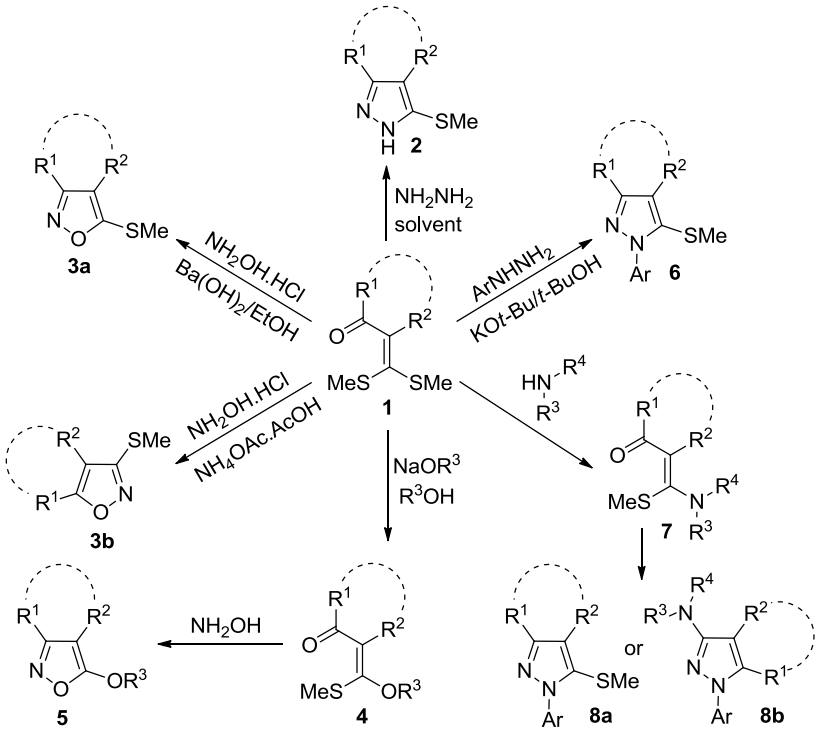
Scheme 2

The preparation of *O,S*-acetals is accomplished through displacement by an oxygen nucleophile on the *S,S*-sulfonium salt of the corresponding α-oxoketene dithioacetals.[11-12]

1.2.2 Synthesis of five membered heterocycles from α-oxoketene dithioacetals

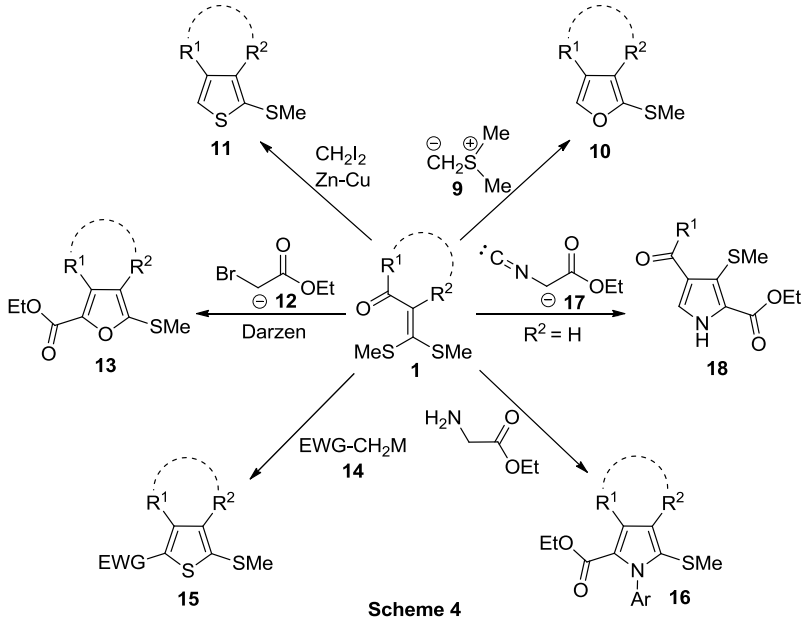
Our research group has developed new general routes for the synthesis of wide range of biologically important five membered heterocycles by utilizing α-oxoketene dithioacetals **1** as three carbon 1,3-bielectrophilic synthons and by reacting them with symmetrical and unsymmetrical bifunctional heteronucleophiles such as hydrazine and hydroxyl amine (Scheme 3).[13] Thus, 5-(3-methylthio)pyrazoles **2** were obtained by the treatment of α-oxoketene dithioacetals **1** with hydrazine hydrate or phenylhydrazine.[13] The reaction of hydroxylamine with α-oxoketene dithioacetals **1** was investigated under different reaction conditions to give highly regioselective synthesis of 3- or 5-(methylthio)isoxazoles **3a** or **3b** (Scheme 3).[14a-b] 5-Alkoxyisoxazoles **5** were synthesized from these α-oxoketene dithioacetals **1** via *O,S*-acetals **4**.[14c] These reactive intermediates were also utilized for the highly efficient and regioselective synthesis of 1-aryl-3,4-disubstituted/annulated-5-(methylthio)pyrazoles **6**.[15a] Similarly, α-oxoketene dithioacetals

1 were transformed into 1,3-diaryl (or 1-aryl-3-alkyl) 1,5-diaryl (or 1-aryl-5-alkyl)-5-(or 3)(*N*-cycloamino)pyrazoles **8a** and **8b** respectively, *via N,S*-acetals **7** in highly regio controlled manner (Scheme3).[15b]



Scheme 3

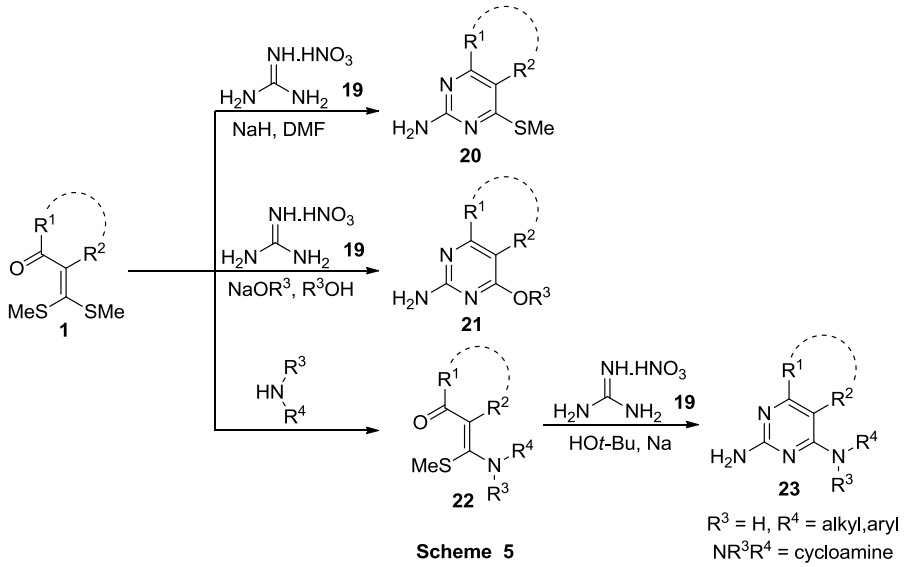
Treatment of sulfonium ylide **9** with **1** followed by acidic treatment afforded substituted or annulated 2-(methylthio)furans **10** (Scheme 4).[16] Our research group has also reported the synthesis of 3,4-substituted and annulated thiophenes **11** *via* intramolecular Aldol condensation of *in situ* generated sulfonium ylide intermediates under Simmon's Smith reaction conditions (Scheme 4).[17] α-Oxoketene dithioacetals **1** have also shown to undergo Darzen's glycidic ester condensation yielding substituted and annulated furan-2-carboxylates **13** in good yields. (Scheme 4).[18] In a further studies, α-oxoketene dithioacetals **1** were utilized for the synthesis of pyrroles **16** by 1,4-addition followed by intramolecular cyclocondensation with ethyl glycinate.[19a] Furthermore, **1** underwent 1,3-dipolar cycloaddition with carbanions derived from activated methylene isocyanides **17** afford 2,3,4-substituted pyrroles **18**.[19c]



Scheme 4

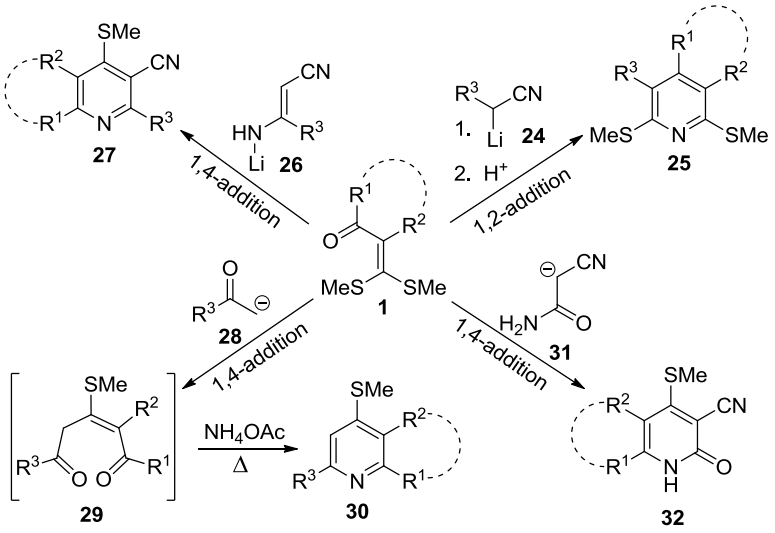
1.2.3 Synthesis of six-membered heterocycles

α-Oxoketene dithioacetals **1** were successfully converted to substituted pyrimidines upon treatment with guanidine nitrate in basic medium (Scheme 5).[20] Thus synthesis of 2-amino-4-(methylthio)pyrimidines **20** was accomplished by the reaction of **1** with guanidine nitrate in the presence of NaH (Scheme 5).[20a] Similarly the reaction of **1** with guanidine nitrate **19** in the presence of sodium alkoxides afforded the corresponding 2-amino-4-(alkoxy)pyrimides **21** (Scheme 5).[20b] Furthermore, synthesis of 2-amino-5,6-substituted-4-N-alkyl/N-aryl/N-azacyclo-aminopyrimidines **23** was achieved from the corresponding *N,S*-acetals **22** by treatment with guanidine nitrate (Scheme 5).[20d]



Scheme 5

The reaction of **1** with lithioacetonitrile or it's higher analogs followed by acid treatment resulted a novel route for the synthesis of substituted and fused 2,6-bis(methylthio)pyridines **25** (Scheme 6).[23a] In an extension of the above approach, cyclocondensation of α-oxoketene dithioacetals **1** with β-lithioamino-β-substituted acrylonitriles **26** afforded access to 2,6-disubstituted and 5,6-annulated 3-cyano-4-methylthiopyridines **27** (Scheme 6).[21b] Potts and co-workers have reported a general synthesis of substituted and annulated pyridines **30** by subjecting α-oxoketene dithioacetals **1** to conjugate addition-elimination with enolates of various active methylene ketones followed by intramolecular heterocyclization of resulting adducts with ammonium acetate.[22a] A general synthesis of 5,6-substituted/annulated 3-cyano-4-methylthiopyridin-2-ones of the type **32** had been developed previously in our laboratory by cyclocondensation of cyanoacetamide derived carbanion.[23]

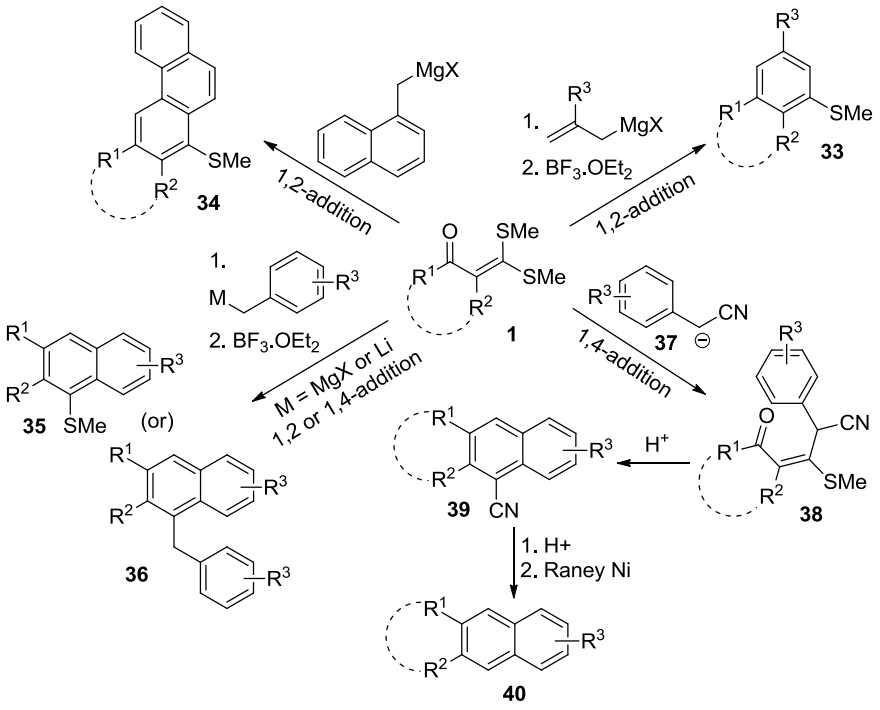


Scheme 6

1.2.4 Aromatic annulations *via* α-oxoketene dithioacetals

Aromatic annulation strategy, developed in our laboratory in 1984, has emerged as an area of great synthetic potential.[1] The reaction, now known as Junjappa-Ila (JI) aromatic and heteroaromatic annulation, involves an unprecedented protocol for the construction of substituted aromatic ring *via* [3+3] annulation of α-oxoketene dithioacetals (1,3-bielectrophilic components) with a three-carbon 1,3-binucleophilic component (usually allylic or benzylic anions). Some of the examples of the synthesis of few aromatic hydrocarbons using this strategy are shown in Scheme 7.

Interestingly, various allyl anions displayed different regiocontrolled addition pattern with **1** yielding either 1,2-adduct or sequential 1,4-followed by 1,2-addition. Thus, the allyl or methyl Grignard reagents[19b,24] generally followed 1,2-addition pathway to **1** whereas benzyl magnesium halides[19b,25a] followed 1,4- and 1,2-addition mode yielding the corresponding benzyl substituted carbanions which upon acid-induced cyclization furnished methylthio and benzyl substituted aromatics **33** and **35-36** respectively, (Scheme 7). Furthermore, when **1** was subjected to addition-cycloaromatization with 1-(naphthylmethyl) Grignard reagent, the formation of only methylthio substituted phenanthrenes **34** was observed thus demonstrating exclusively 1,2-addition mode in the first addition step (Scheme 7).[25b] When lithiomethyl benzenes, instead of benzyl magnesium chlorides, was reacted with **1**, surprisingly the reaction followed exclusively 1,2-addition mode to afford the corresponding carbinol acetals which upon acid-induced cyclization yielded methylthionaphthalenes **35** in good yields (Scheme 7).[25c] On the otherhand, stabilized anions **37** derived from benzyl cyanides underwent exclusive 1,4-addition-elimination to **1** affording adducts **38** which upon acid-induced cyclization yielded the corresponding angularly substituted/annulated aromatic hydrocarbons **40** (Scheme 7).[26]



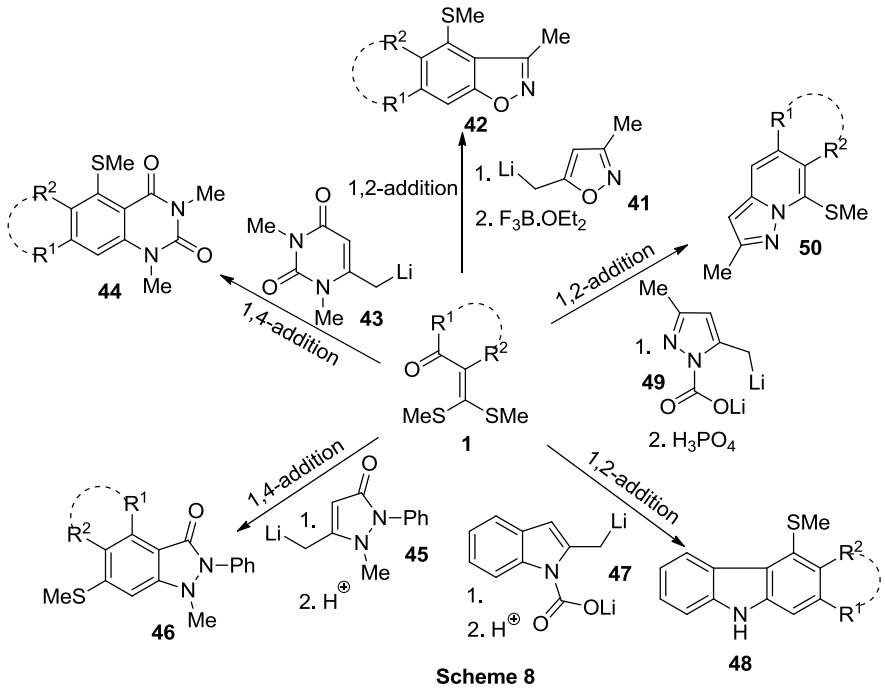
Scheme 7

1.2.5 Heteroaromatic annulation *via a*-oxoketene dithioacetals

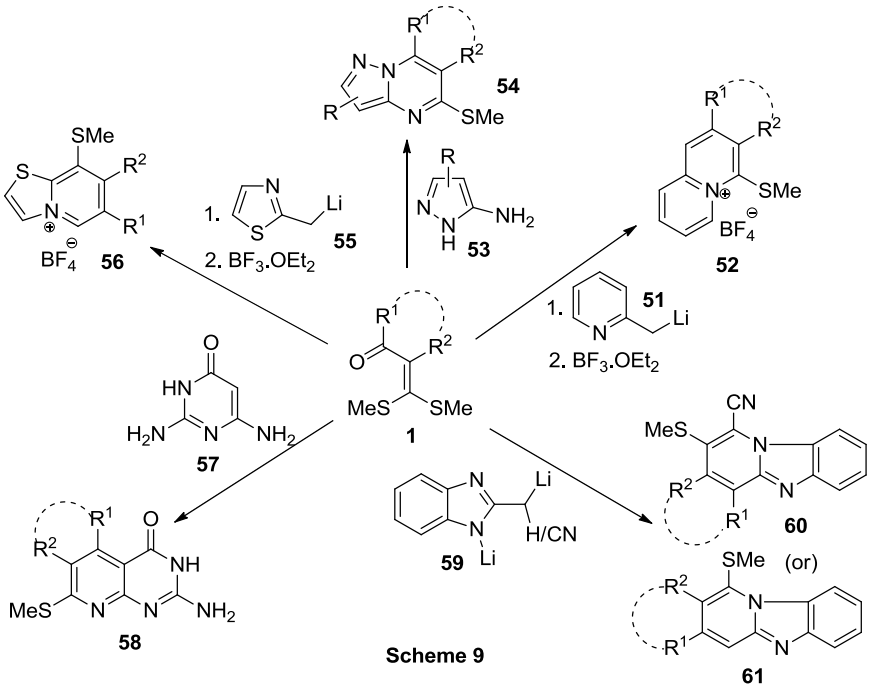
The versatile aromatic annulation strategy has also been extended for the synthesis of benzoheterocycles (heteroaromatic annulation), which represents reverse approach for the construction of benzoheterocycles. The classical methods for the synthesis of five- and six-membered benzoheterocycles generally involve sequential construction of heterocyclic ring over pre-constructed benzene precursors, which have to be synthesized *via* multi step processes. However, inverse approach i.e, construction of an aromatic ring over a pre-constructed heterocyclic framework are scant in the literature.[27] During the course of ongoing programme for benzoheterocycle synthesis from *a*-oxoketene dithioacetals **1**, our research group has developed a new regiospecific routes for a wide range of substituted and annulated benzoheterocycles employing our heteroaromatic annulation protocol.

Thus, heteroaromatic annulation of 5-lithiomethyl-3-methylisoxazole **41** with *a*-oxoketene dithioacetals **1** was first reported in 1988 from our laboratory (Scheme 8).[28a] Thus, the anion **41** was shown to add to *a*-oxoketene dithioacetals **1** in regiospecific 1,2-addition fashion to afford the carbinols which were smoothly transformed into the corresponding substituted and annulated 1,2- benzisoxazoles **42** in the presence of $BF_3 \cdot OEt_2$ (Scheme 8).[28a] In an another study, the anion **43** derived from 1,3,6-trimethyluracil (generated by regiospecific deprotonation of 1,3,6-trimethyluracil with LDA) was subjected to cycloaromatization with *a*-oxoketene dithioacetals of the type **1** affording the corresponding substituted and annulated quinazolones **44** in good yields (Scheme 8).[28b] These quinazolones **44** were formed by conjugate 1,4-addition-elimination of **43** to **1** followed by *in situ* intramolecular cyclocondensation of the 1,4-adducts under experimental conditions (Scheme 8). Similar trend was also observed when the 3-lithiomethyl-2-methyl-1-phenylpyrazolin-5-one **45** (generated by regiospecific deprotonation of antipyrine) was subjected to cycloaromatization with *a*-oxoketene dithioacetals **1** to yield the corresponding disubstituted indazolones and their condensed analogs **46** through 1,4-conjugate addition-elimination pathway (Scheme 8).[28c] On the other hand, 1-*N*-carboxy-2-metylindole dianion **47** (generated by Katrizky's method)[28d] underwent regioselective 1,2-addition with acyclic and cyclic *a*-oxoketene dithioacetals **1** affording the corresponding carbinol adducts, which upon cyloaromatization in the presence of H_3PO_4 yielded linearly substituted and annulated carbazoles **48** in good yields as shown in Scheme 8.[28e] The dianion **49**, prepared for the first time in our laboratory,

reacted with *a*-oxoketene dithioacetals **1** in 1,2-addition mode which upon subsequent phosphoric acid-mediated *N*-centered cyclization yielded substituted pyrazolopyridines **50** in good yield (Scheme 8).[28f]



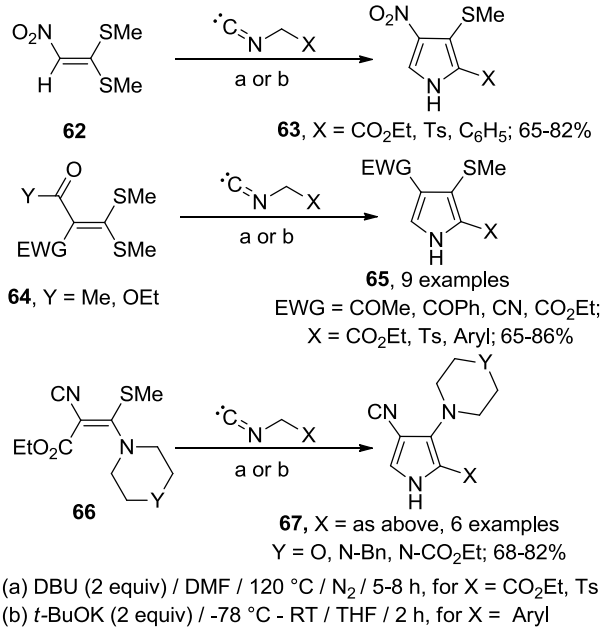
The 2-lithiomethyl pyridine **51** reacted with **1** to afford the corresponding carbinol acetals which upon subsequent cyclization in the presence of $BF_3{\cdot}OEt_2$ yielded quinolizinium fluoroborate salts **52** (Scheme 9).[29a] The 3-amino pyrazole **53** also underwent cyclocondensation with **1** to yield the corresponding pyrazolo[2,3-*a*]pyrimidines **54** in good yield (Scheme 9).[29b] When 2-lithiomethylthiazole **55** was treated with **1**, the corresponding thiazolopyridinium fluoroborate salts **56** were formed in good yields (Scheme 9).[29c] Cyclocondensation of 2,4-diaminopyrimidone **57** with *a*-oxoketene dithioacetals **1** furnished 5-deazapteridines **58** in moderate to excellent yields (Scheme 9).[29d] Similarly treatment of **1** with dianion **59** derived from 2-methyl or 2-cyanomethylbenzimidazoles provided novel regiospecific routes for the synthesis of linear or angularly substituted or annulated pyrido[1,2-*a*]benzimidazoles **60** and **61**, respectively in high yields (Scheme 9).[29e]



Scheme 9

1.2.6 Formal cycloaddition of polarized ketene dithioacetals with activated methylene isocyanide anions: Efficient synthesis of 2,3,4-trisubstituted pyrroles

The diverse reactivity pattern of polarized ketene dithioacetals was further demonstrated by designing an efficient and versatile protocol for regioselective synthesis of 2,3,4-trisubstituted pyrroles by base induced formal cycloaddition of activated double bonds of various polarized ketene S,S- and few N,S-acetals with activated methylene isocyanide anions (Scheme 10).[30] The methodology allows precise control over the

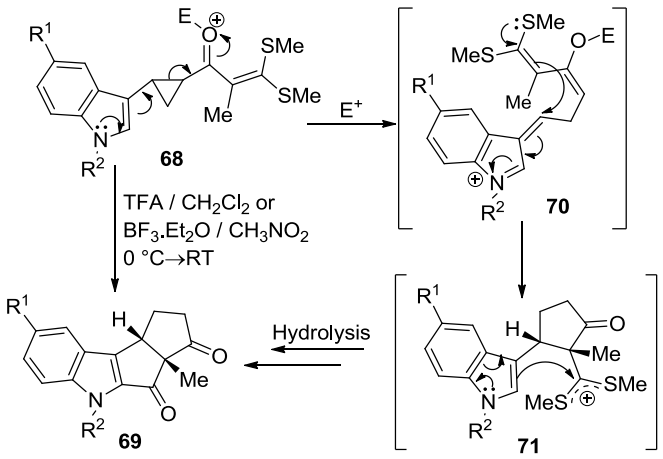


Scheme 10

introduction of a variety of substituents and functionalities (tosyl, carboalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines etc.) at the 3- and 5-positions of pyrrole ring. The reaction of nitroketene dithioacetal **62** with activated methylene isocyanides is particularly noteworthy, since the nitro group is retained in the 3- position of pyrroles **63** unlike in Barton-Zard reaction, where it acts as the leaving group (Scheme 10).[31]

1.2.7 Ketene dithioacetal functionality as cationic cyclization initiator/terminator in domino carbocationic rearrangements of *α*-[bis(methylthio)methylene]alkyl-2-het(aryl)cyclopropyl ketones

The ability of two sulfur atoms in ketene dithioacetal moiety to stabilize a positive charge makes it useful functionality as potential cationic cyclization initiator or terminator group in polyene cyclizations.[1c] Our group has demonstrated in earlier studies, that domino carbocationic rearrangements of newly designed het(aryl)cyclopropyl ketones bearing an *α*-bis(methylthio) methylene functionality allow construction of a variety of carbocyclic and heterocyclic scaffolds such as substituted cyclopentanones, cyclopenta[*b*]indanes, diquinanes, 1-arylindanes, bicyclo[3.2.1]octene, and other cyclopentano fused heterocycles.[32] In a recent paper, it was shown that carbocationic rearrangement of *α*-[bis(methylthio)methylene]alkyl-2-(3/2-indolyl)cyclopropyl ketones of the general structure **68** in the presence of trifluoroacetic acid or other Lewis acids provides a direct approach to pentaleno- fused indolodiketones such as **69** involving appendage of two cyclopentanone rings in a cascade process in one-pot reaction (Scheme 11).[32]

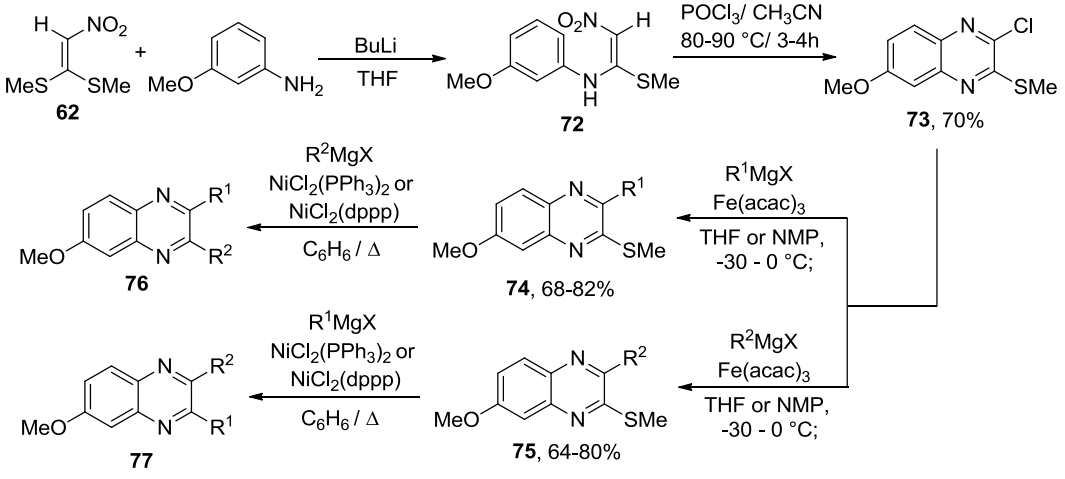


R^1 = H, MeO, Br; R^2 = Me, PMB; 64-72%, 6 examples

Scheme 11

1.3 Reactivity of polarized ketene *N,S*-acetals: A novel highly regioselective synthesis of unsymmetrical 2,3-substituted quinoxalines and imidazo[1,5-*a*]quinoxaline-3-carboxylates

The polarized ketene *N,S*- and *N,N*-acetals can be considered as second generation of reactive intermediates derived from polarized ketene dithioacetals via replacement of one or both methylthio groups by primary or seconadry aliphatic or aromatic amines. We have extensively explored these *N,S*-acetals in the past, for the synthesis of novel functionalized five and six membered heterocycles by making use of their diverse reactivity profile either as functionalized enamines or as three carbon 1,3 electrophilic fragments.[1b,1g,33] Few years back, our group has reported a novel general highly regioselective synthesis of unsymmetrically substituted 2-methylthio-3-chloroquinoxalines of the general structure **73** by $POCl_3$ mediated intramolecular cyclocondensation of a broad range of nitroketene *N,S*-arylaminoacetals **72** (Scheme 12).[33] The 2-methylthio- and 3-chloro functionalities in these quinoxalines could be further elaborated for the synthesis of regioisomeric unsymmetrically substituted 2,3-aryl/alkyl quinoxalines such as **76** and **77** by sequential iron or nickel catalyzed cross-coupling with various aryl/alkyl Grignard reagents in highly regiocontrolled fashion (Scheme 12),[33] thus overcoming regioselectivity problems encountered in previous syntheses (Hinsberg condensation) of unsymmetrically substituted quinoxalines.



62 → **72** → **73**, 70%

74, 68-82% → **76**

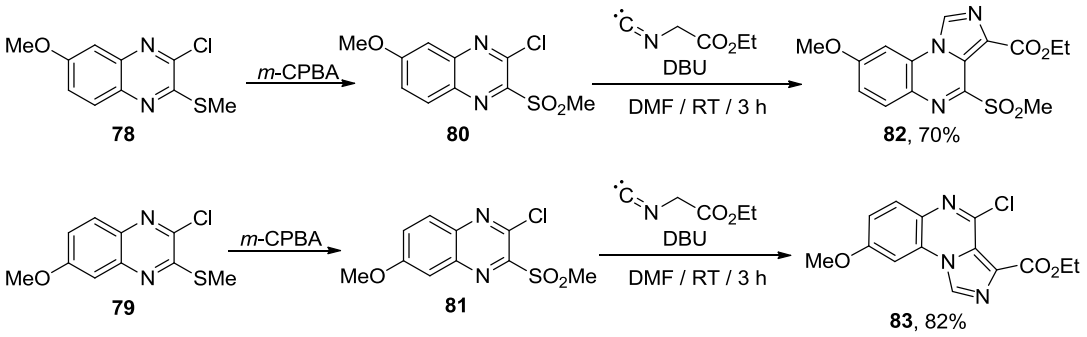
75, 64-80% → **77**

76, **77** R^1 = Me, R^2 = n-Bu; R^1 = Ph, R^2 = n-Bu; R^1 = C_6H_5, R^2 = 4-$OMeC_6H_4$; 68-89%

Scheme 12

In a subsequent studies, our group has also reported an efficient regio- and chemoselective synthesis of novel biologically relevent 3-(carboethoxy)imidazo[1,5-*a*]quinoxalines such as **82-83** by subjecting the unsymmetrically substituted 2-

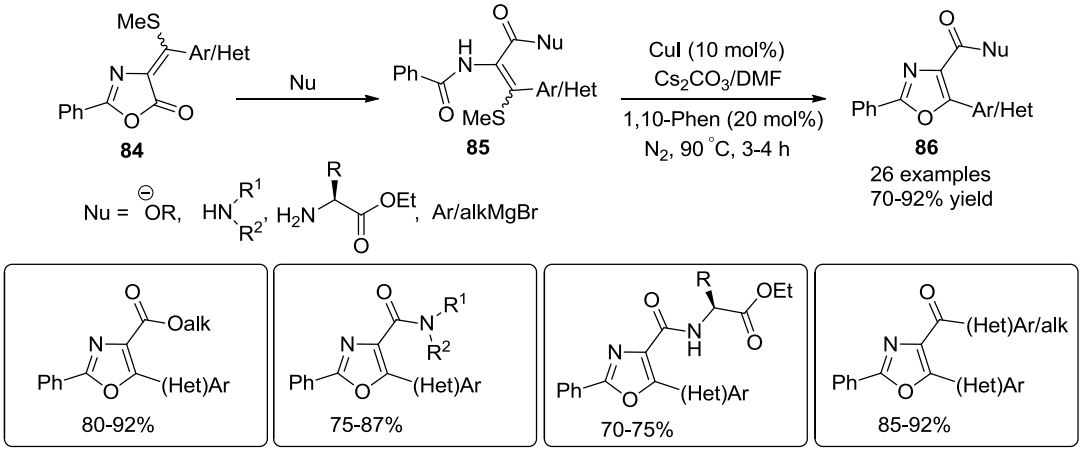
methylsulfonylquinoxalines **80-81** to base induced formal cycloaddition with ethyl isocyanoacetate on N=C bond (Scheme 13).[34]



Scheme 13

1.4 Present work

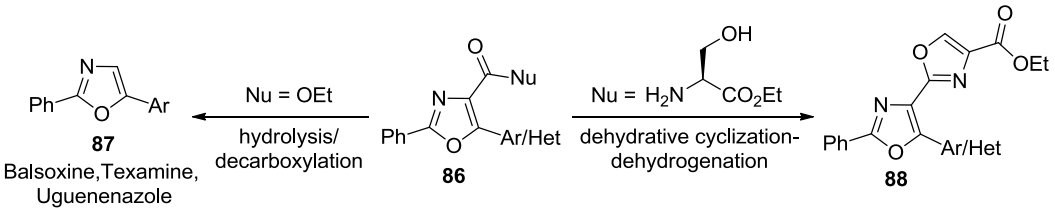
From the foregoing discussion, it is evident that polarized ketene dithioacetals and its variants i.e., *β*-(methylthio)methylene ketones/acrylonitriles are an important class of building blocks for the synthesis of 5- and 6-membered heterocycles and aromatic compounds. The present thesis is based on further synthetic elaboration of newly designed organo sulfur intermediated for designing new synthetic methods for five membered heterocycles. Thus, **chapter 2** of the thesis describes the synthesis of 2-phenyl-4,5-substituted oxazoles of type **86** involving intramolecular copper-catalyzed cyclization of novel, highly functionalized *β*-(methylthio)enamides **85**, which are readily accessible in high yields, by nucleophilic ring opening of a number of 4-[(methylthio)-(het)arylmethylene]-5-oxazolones **84** with various alkoxides, primary and seconadary aliphatic/aromatic amines, amino acid esters and Grignard reagents (Scheme 14).



Scheme 14

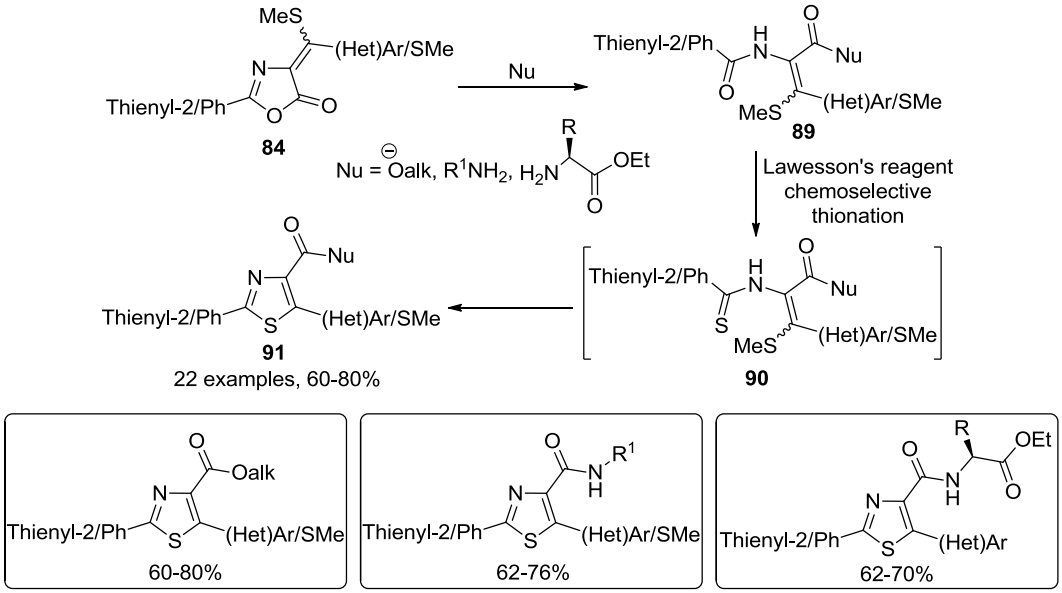
Synthesis of few naturally occurring 2,5-diaryloxazoles **87** such as balsoxine, texamine and uguenenazole has also been described. Few of the serine derived oxazole-4-

carboxamides **86** were transformed into novel trisubstituted 4,2′-bisoxazoles **88** through DAST/DBU-mediated cyclodehydration-dehydrohalogenation (Scheme 15).



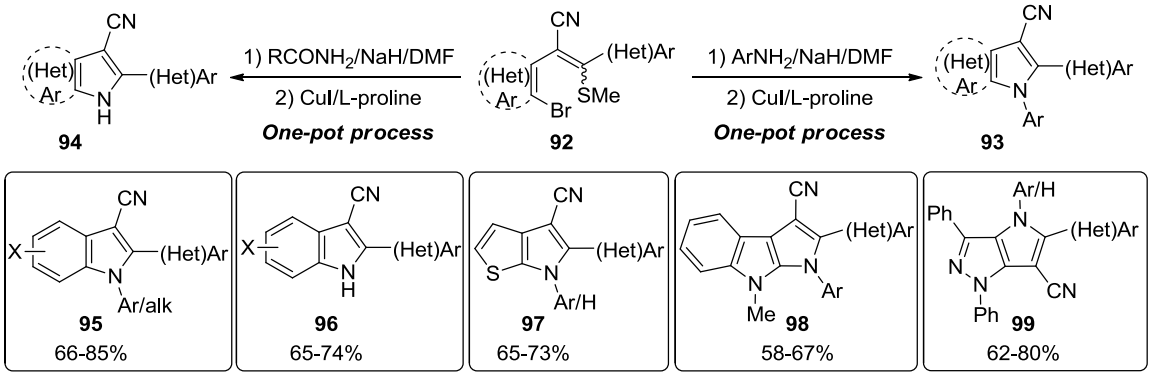
Scheme 15

The **chapter 3** of the thesis describes a highly regio- and chemoselective synthesis of 2,4,5-trisubstituted thiazoles such as **91** *via* one step thionation-intramolecular cyclization of functionalized enamide precursors **89** in the presence of Lawesson's reagent, offering wide range of functional group diversity at 2,4 and 5-positions of the product thiazoles (Scheme 16).



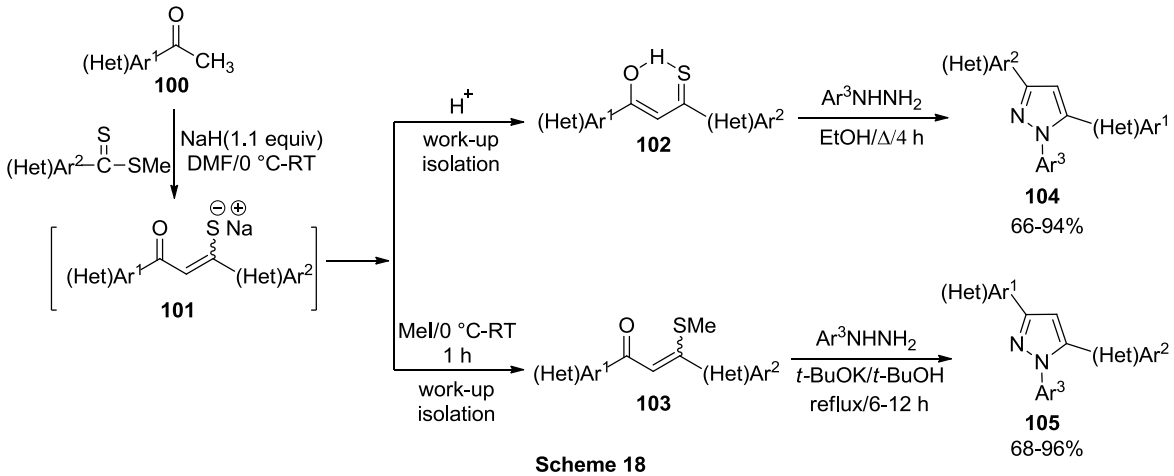
Scheme 16

The **chapter 4** of the thesis deals with a novel, one-pot, two step synthesis of substituted 1-*N*-(het)aryl-2-(het)aryl-3-cyanoindoles and the related pyrrolo fused heterocycles **93** such as thienopyrroles **97**, pyrroloindoles **98** and pyrazolopyrroles **99** *via* Cu-catalyzed intramolecular C-N bond formation of functionalized enaminonitriles, generated in situ by base mediated displacement on 2-[2-bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitrile **92** with various (het)aryl amines. The broad scope of the methodology was further illustrated with the synthesis of *NH*-indoles **94** by employing primary amides as coupling partners in this sequential one-pot C-N bond-forming reaction (Scheme 17).



Scheme 17

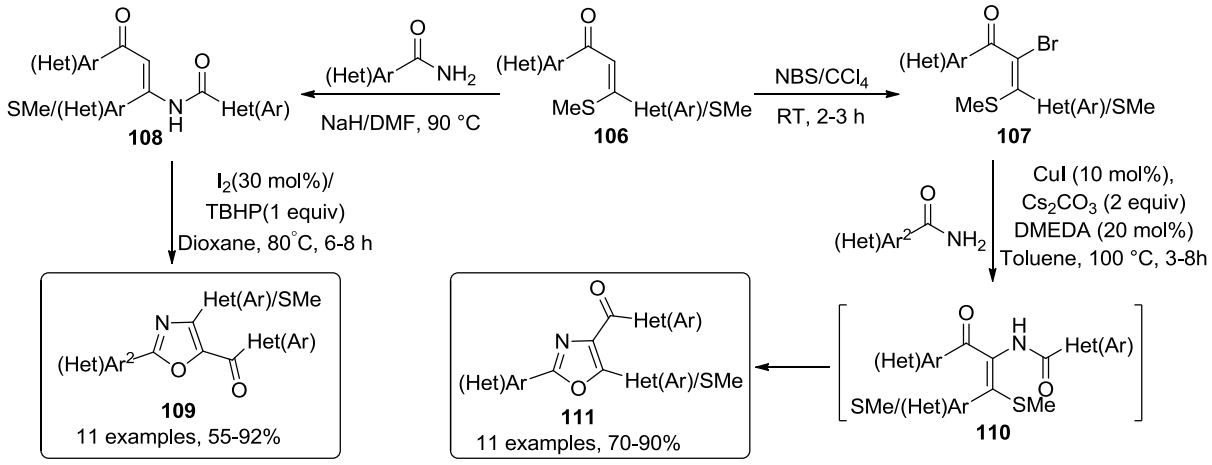
The **chapter 5** of the thesis describes two efficient highly regioselective routes for the synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles **104** and **105** with complementary regioselectivity starting from active methylene ketones **100**. In the first protocol, the newly synthesized 1,3-bis(het)aryl-monothio-1,3-diketone precursors **102** [prepared by condensation of active methylene ketones **100** with het(aryl) dithioesters in the presence of sodium hydride] were reacted with arylhydrazines in refluxing ethanol under neutral conditions, furnishing 1-aryl-3,5-bis(het)arylpyrazoles **104**, in which the het(aryl) moiety attached to the thiocarbonyl group of monothio-1,3-diketones is installed at 3-position. In the second method, the corresponding 3-(methylthio)-1,3-bis(het)aryl-2-propenones **103** (prepared *in situ* by base induced alkylation of 1,3-monothiodiketones) were condensed with arylhydrazines in the presence of potassium-*t*-butoxide in refluxing *t*-butanol yielding 1-aryl-3,5-bis(het)arylpyrazoles **105** with complementary regioselectivity in a one-pot process (Scheme 18).



Scheme 18

The **chapter 6** of the thesis describes a regioselective synthesis of 2,5-substituted 4-acyloxazoles **111** and 2,4-substituted 5-acyloxazoles **109** from *α*-oxoketene

dithioacetal/1,3-bis(het)aryl-3-(methylthio)-2-propenones **106** by using two synthetic strategies. In the first case, these intermediates were converted to α-bromo derivatives **107** by treatment with NBS followed by intermolecular Cu-catalyzed cross coupling with primary amides. In the second case, these intermediates were first subjected to base mediated conjugate addition with amides to furnish regioisomeric enamides **108**, which on intramolecular iodine catalyzed oxidative cyclization afforded the other regioisomeric oxazoles **109** (Scheme 19).



Scheme 19

1.5 References

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Chapter 2

*Synthesis of 2-Phenyl-4,5-Substituted Oxazoles by Copper-Catalyzed Intramolecular Cyclization of Highly Functionalized Enamides**

2.1 Introduction

Oxazole structural motifs have attracted considerable attention from both synthetic and medicinal chemists, because of their presence in a wide range of biologically important natural products[1] and their pivotal role as synthetic intermediates.[2] Also, 2,4- and 2,4,5-substituted oxazoles are frequently encountered structural motifs present in many pharmaceuticals, lead structures, optical materials as scintillant molecules and fluorescent dyes.[3]

A large number of oxazole containing natural products have been isolated from marine invertebrates and microorganisms, many of which exhibit potent biological activities.[1] A few of these common oxazole motifs, originate in nature from post-translational modifications of serine and threonine residues as components of complex peptide fragments.[4]

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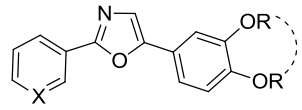
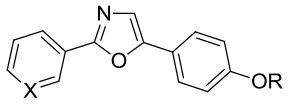
*The overall results of study described in this chapter have been published in *J. Org. Chem*. **2012**, *77*, 10752.

Naturally occurring oxazoles range in structure from relatively simple 2,5-disubstituted derivatives such as balsoxine[5] **1**, texamine[6,7] **2**, texaline[8] **3**, halfordinol[9] **4**, uguenenazole[10] **5**, annuloline[11] **6** or 5-(indole-3-yl)oxazole alkaloids such as **7-13** (Chart 1) to more complex compounds as shown in Chart 2. Balsoxine **1** and texamine **2** were isolated from *Amyris texana* in carribean,[5] with texamine **2** exhibiting antituberculosis activity against *M. avium* and *M. kansasii*.[7] Halfordinol[9] **4**, an oxazole alkaloid of Rutaceae family, was first isolated from the bark of *Halfordia scleroxyla* in 1963. Annuloline **6**, a 2-(3,4-dimethoxy) styryl derivative isolated from the roots of *Lolium multiflorum* displays brilliant fluorescence of rye grass.[11]

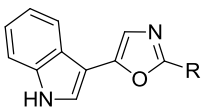
The most simple 5-(3-indolyl)oxazole, pimprinine **7** was isolated from *Streptovertes pimprina*, and is known to display monoamine oxidase (MAO) inhibitory activity having an antiepileptic effect.[12,13] The corresponding 2-(*n*-propyl)- and 2-(*n*-butyl)oxazole derivatives WS-30581A, **9** and WS-30581B, **10** were isolated from *Streptoverticillium waksmanii* and show potent inhibitory effect on platelet aggregation.[12,13] The corresponding pimprinaphine **11**, a 2-benzyloxazole derivative was isolated from *Streptoverticillum alovoreti* species. Recently, Pettit and coworkers have isolated new 3-(oxazolyl)indole alkaloids labradorin 1 **12** and labradorin 2 **13** from *Pseudonomous syringae* which were found to be potent inhibitor against human cancer cells (Chart 1).[14] A more complex marine natural product martefragin A **14,** containing a (3-indolyl)oxazole framework isolated from *Martensia fragilis*, was found to be strong inhibitor of lipid peroxidation, nearly 100 times more potent than α-tocopherol (Chart 1).[15]



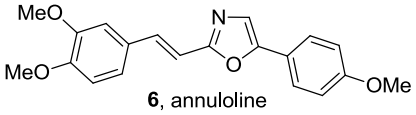
1, X = CH, R = CH_3, balsoxine
2, X = CH, R = CH_2, texamine
3, X = N, R = CH_2, texaline



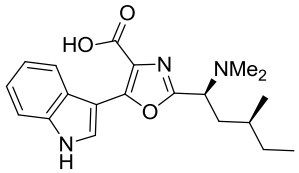
4, X = N, R = H, halfordinol
5, X = CH, R = Me, uguenenazole



7, R = Me, pimprinine
8, R = Et, pimprinethine
9, R = *n*-Pr, WS-30581 A
10, R = *n*-Butyl, WS-30581 B
11, R = $PhCH_2$, pimprinaphine
12, R = *i*-Butyl, labradorin 1
13, R = *n*-Pentyl, labradorin 2



6, annuloline



14, martefragine A

Chart 1

A wide variety of biologically important natural products containing a 2,4,5-trisubstituted oxazole moiety, display a range of biological activities such as antibacterial, antiviral, anticancer, antifungal, cytotoxicity. A few of them are shown in Chart 2. Thus phenoxan[16] **15** and tentazole[17] **16** are examples of more complex acyclic natural products containing one oxazole unit exhibits potent antiviral activity (Chart 2). The naturally occurring (−)-muscoride **17** a secondary metabolite of fresh water *Cyanobacterium muscorum* and (−)-hennoxazole A **18** isolated from *Polyfibrospongia* sponge having two contiguous oxazole rings in a acyclic framework, exhibit potent antibacterial[18] and strong antiviral activity against herpes simplex[19] (Chart 2).

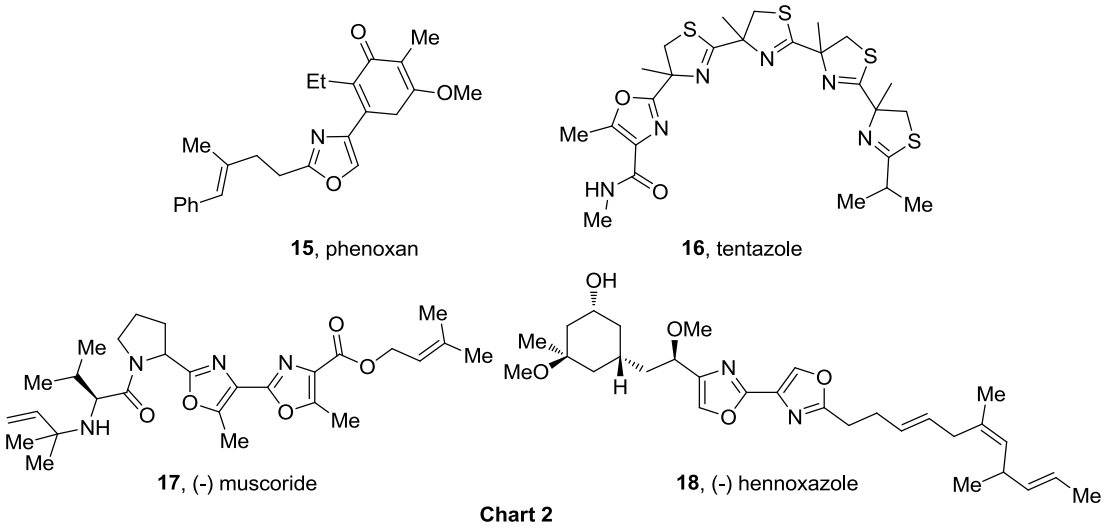
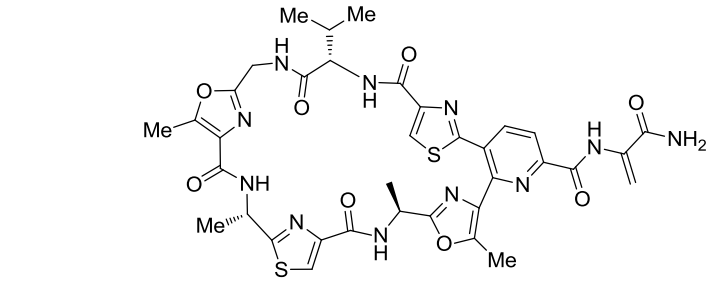


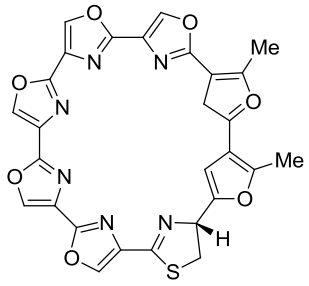
Chart 2

Telomestatin **19**,[20] a C2-C4 linked macrocyclic heptaoxazole isolated from *Streptomyces annalates* is shown to be a potent telomerase inhibitor which has found application in cancer chemotherapy.[20] Promothiocin **20**,[21] a member of thiopeptide family of antibiotics possess two isolated oxazole rings in a cyclic peptide, whereas diazonamide A **21**, a secondary metabolite of *Diazona chinensis* is relatively a rare example of cyclic peptide containing two trisubstituted oxazoles in contiguous fashion, displays a strong *in vivo* cytotoxic activity against human tumor cell lines HCT-116 (Chart 3).[22,23]

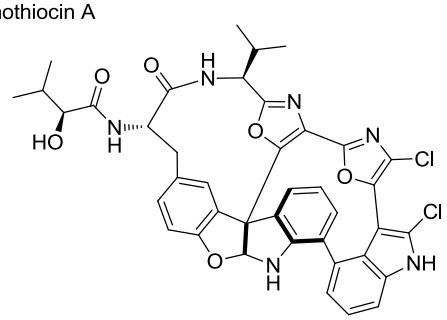
Oxazoles have also been used as primary scaffolds for the synthesis of several biologically important compounds. A number of oxazole benzenesulfonamides have recently been introduced as B-3 adrenergic receptor agonists.[24] Another recent example, explores dopamine receptor bonding profiles of a series of phenyloxazoles.[25]



20, promothiocin A



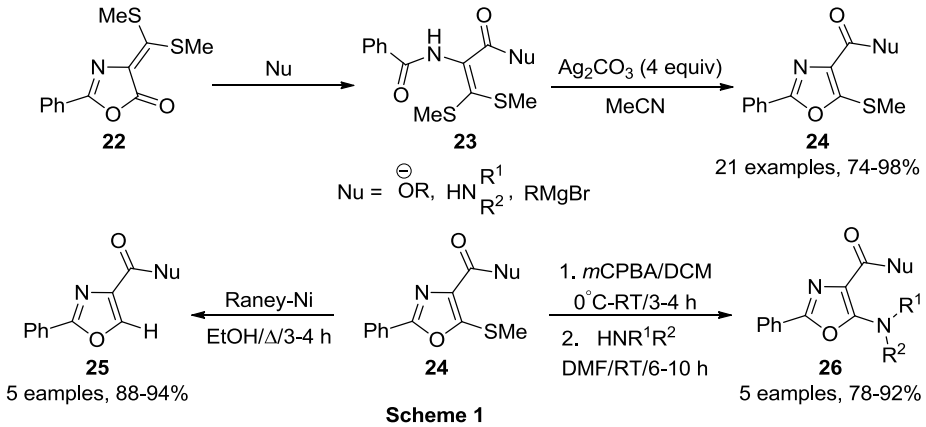
19, telomestatin



21, diazonamide A

Chart 3

The wide range of biological activity displayed by these oxazole containing compounds has stimulated renewed interest in the chemistry and synthesis of these important classes of heterocycles.[1] Earlier work from our laboratory has reported a new synthesis of 2-phenyl-4,5-functionalized oxazoles **24** involving silver carbonate mediated intramolecular 5-*endo* cyclization of functionalized enamides **23**, which were obtained by ring opening of 2-phenyl-4-bis(methylthio)methylene-5-oxazolone **22** by various oxygen, nitrogen and carbon nucleophiles (Scheme 1).[26]

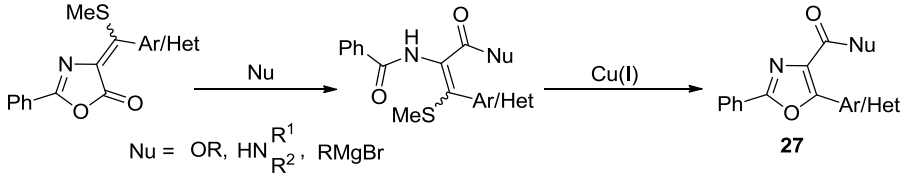


Scheme 1

The 5-(methylthio)oxazoles were either dethiomethylated with Raney Ni to 5-unsubstituted oxazoles **25** or transformed into 5-alkyl/arylaminooxazoles **26** in two steps involving peracid oxidation and replacement of 5-methylsulfonyl group by primary and secondary amines (Scheme 1).

In continuation of this work, we sought to explore possible utilization of this strategy for the synthesis of 4-substituted 2,5-di(het)aryloxazoles by installation of a (het)aryl group at 5-position of oxazoles (Scheme 2). Many of the naturally occurring 2,5-diaryloxazoles such as balsoxine **1**, texamine **2**, texaline **3**, halfordinol **4**, display broad range of biological activity (Chart 1).

We therefore envisaged a related transformation as depicted in Scheme 2 and successfully executed it to develop a general protocol for diversity oriented synthesis of 2-phenyl-5-(het)aryl-4-substituted oxazoles **27**.



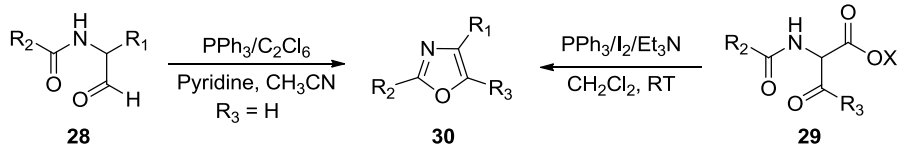
Scheme 2

Before discussing our results, a short survey of some recent methods for the synthesis of oxazoles has been described in the following section.

2.2 Synthesis of substituted oxazoles: A short literature survey

2.2.1 Synthesis of oxazoles via cyclization of acyclic precursors

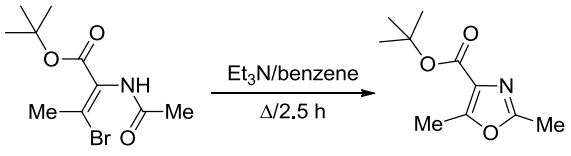
One of the oldest and most important methods for the preparation of 2,4,5-trisubstituted oxazoles is Robinson-Gabriel synthesis, involving cyclodehydration of *α*-acylaminoketones.[27] However this method requires harsh reaction conditions and gives poor yield. Several modified versions of Robinson–Gabriel synthesis have been developed for the preparation of substituted oxazoles from a broad range of *α*-acylaminocarbonyl compounds derivatives (Scheme 3).[28a-b]



Scheme 3

The other synthetic methods which fall under this category are Cornforth and Cornforth method,[29] improved by Yokoyama,[30] the biomimetic dehydrative cyclization of *β*-hydroxy amides to oxazolines and their oxidative dehydrogenation.[31a-f]

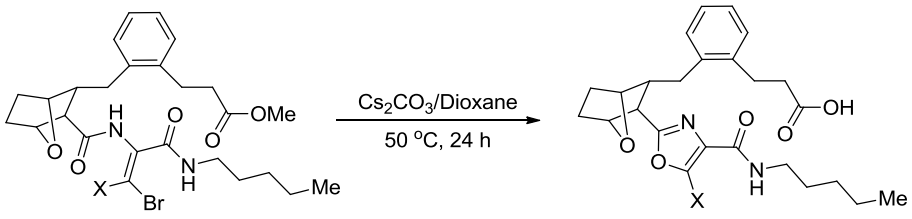
In a similar approach, Yoshimura and co-workers[32] reported a base catalyzed intramolecular cyclization-elimination of *t*-butyl 2-acetylamino-3-bromoalkenoates such as **31** to the corresponding oxazole **32** in moderate yields (Scheme 4).



31 **32,** 58%

Scheme 4

This methodology was successfully modified for the synthesis of potent and long active thromboxane receptor antagonists BMS180291 **35-36** by treatment of the acylaminovinyl bromides **33-34** with cesium carbonate (Scheme 5).[33]



33, X=H
34, X=Br

35, X=H, BMS180291
MeOH/NaOH **35**, X=H, 85%
$CuBr_2$/DBU/DCM **36**, X=Br, 65%

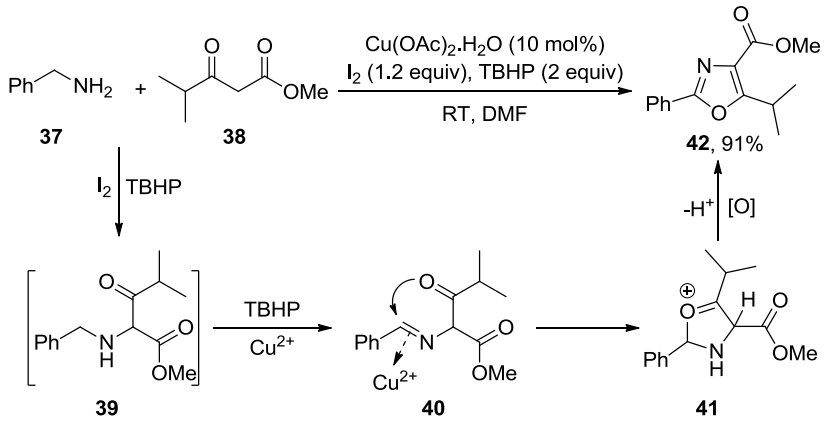
Scheme 5

All these methods have been elaborated earlier in a previous thesis from our laboratory.[34] Therefore only selected recent methods have been described here.

2.2.2 Recent developments in synthesis of substituted oxazoles

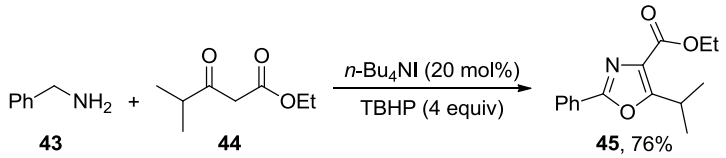
2.2.2.1 Oxazoles via oxidative cyclization of 1,3-dicarbonyl compounds and amines

Among recently reported methods, oxidative [3+2] coupling of a prefunctionalized ketones or aldehydes with benzylamine has been well studied as straightforward procedure. Thus Wang and co-workers[35] have developed a facile and efficient copper catalyzed synthesis of polysubstituted oxazoles such as **42** from readily available benzylamine **37** and *β*-ketoester **38** *via* a tandem oxidative cyclization (Scheme 6). The suggested mechanism of this transformation involving an oxidative C-N bond formation followed by intramolecular cyclization *via* intermediates **39-41** is shown in Scheme 6.



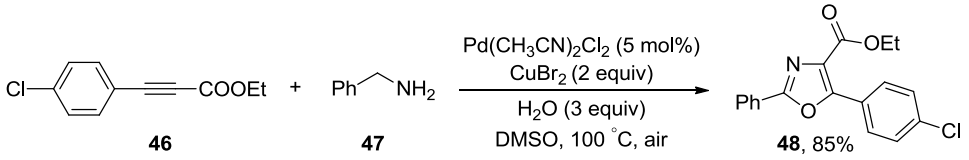
Scheme 6

Zhu and co-workers have described a one-pot organocatalytic metal-free cascade reaction for synthesis of trisubstituted oxazoles such as **45** via oxidative cyclization of benzyl amine and *β*-ketoesters in the presence of *n*-Bu_4NI and TBHP (Scheme 7).[36]



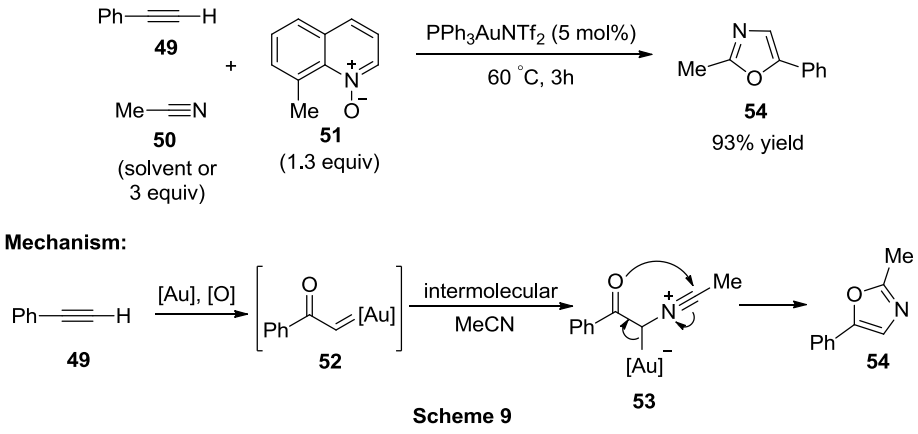
Scheme 7

Jiang and co-workers have recently reported a [2+2+1] approach for synthesis of oxazoles such as **48** by Pd-catalyzed and Cu-mediated cascade oxidative cyclization of aryl propiate and benzyl amine with water as source of oxygen.[37] In this protocol, four hydrogen atoms were removed and one oxygen atom was added from water (Scheme 8).



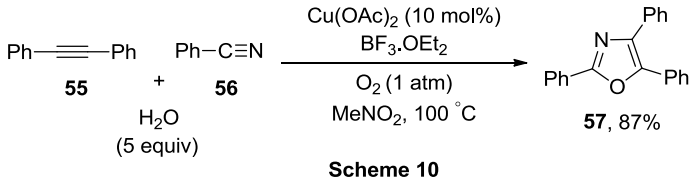
Scheme 8

In recent years many fragment assembling strategies involving [2+2+1] annulations have been developed. Thus, Zhang and co-workers have reported an efficient intermolecular cyclization of gold carbene complex (**52**, generated *via* gold catalyzed oxidation of alkyne) and nitrile to afford 2,5-disubstituted oxazoles in good yields (Scheme 9).[38]



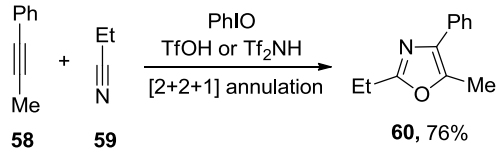
Scheme 9

Similarly Jiang and co-workers[39] have described an efficient synthesis of oxazoles such as **57** *via* copper-catalyzed [2+2+1] aerobic cyclization of internal alkynes and nitriles (Scheme 10).



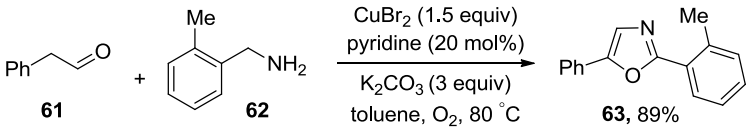
Scheme 10

Similarly Saito and co-workers have recently reported a metal-free [2+2+1] annulation of alkynes such as **58**, nitriles **59**, and O-atoms (derived from iodosobenzene) for the regioselective assembly of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles, using PhIO with TfOH or Tf_2NH (Scheme 11).[40]



Scheme 11

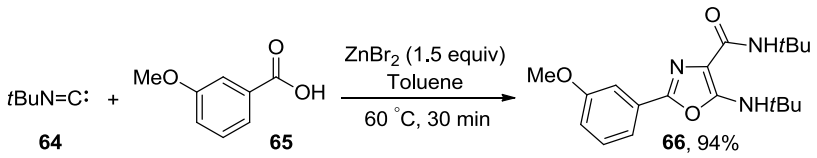
Other similar approaches include copper mediated aerobic oxidative dehydrogenative annulations and oxygenation of aldehydes and amines as demonstrated by Jiao and co-workers (Scheme 12).[41]



Scheme 12

2.2.2.2 Synthesis of oxazoles from isocyanides

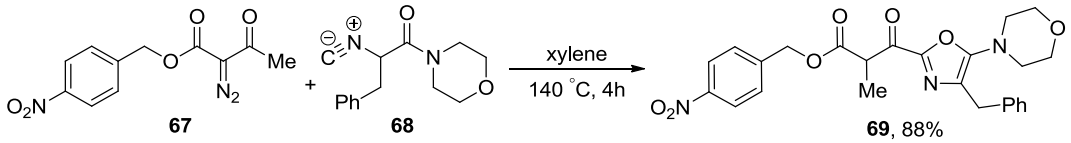
Due to their carbenoid nature, isocyanides are versatile reagents, which have been widely used in heterocyclic chemistry as important synthons.[42a-c] Thus Zhu and co-workers[42a] have developed an efficient synthesis of 2,4,5-trisubstituted oxazoles by zinc bromide mediated co-trimerization of isonitriles with carboxylic acids as shown in Scheme 13. A broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and α,β-unsaturated substrates were used in this reaction.



64 **65** **66**, 94%

Scheme 13

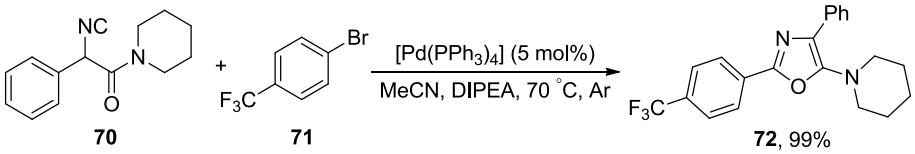
Oxazoles have also been synthesized from various α-isocyanoacetamides.[43a-c] Recently Yu and co-workers[43a] reported the efficient and atom economy synthesis of 2-keto-5-aminooxazoles such as **69** from α-diazocarbonyl esters and α-isocyanoacetamides (Scheme 14).



67 **68** **69**, 88%

Scheme 14

Recently Zhu and co-workers[44] have developed a novel procedure for the synthesis of C2-diversified oxazoles such as **72**, through palladium-catalyzed imidoylative cyclization of α-isocyanoacetamides with aryl, vinyl or alkynyl halides or triflates (Scheme 15).



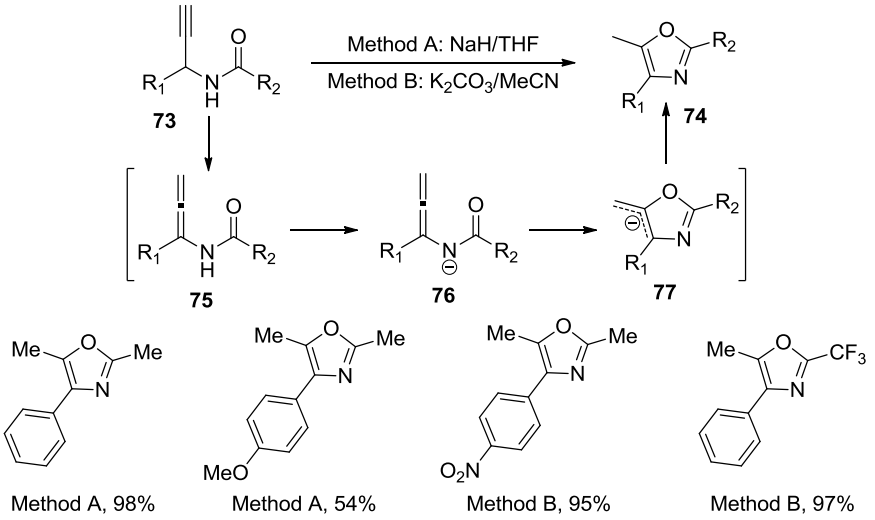
70 **71** **72**, 99%

Scheme 15

2.2.2.3 Synthesis of oxazoles via cycloisomerization of propargyl amides

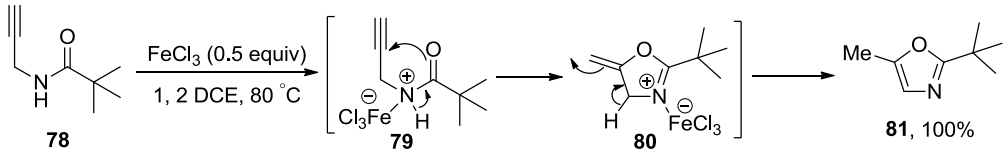
Cyclization reactions of propargylic amides have gained considerable attention in recent years due to their rapid assembly of structural complexity and good functional group compatibility.[45a]

One of the most popular methods for the synthesis of oxazoles was reported by Hacksell and co-workers a few years ago, involving base-induced cycloisomerization of propargyl amides **73** to oxazoles **74** (Scheme 16).[45b-c] The cycloisomerization is shown to proceed through intramolecular cyclization of allene intermediate such as 75.



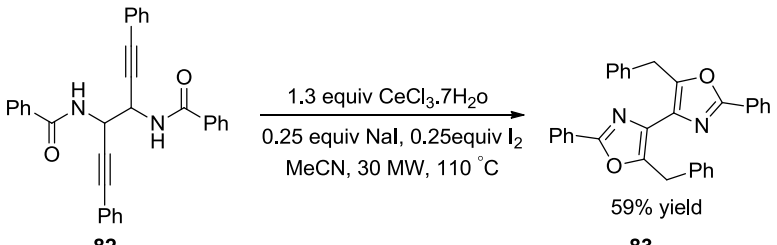
Scheme 16

In 2012, Wang and co-workers have recently developed a $FeCl_3$ promoted intramolecular cyclization of propargylic amides to oxazoles via C-O bond formation (Scheme 17).[46] The abundant, affordable and environmentally benign $FeCl_3$ acts as a Lewis acid in this reaction.



Scheme 17

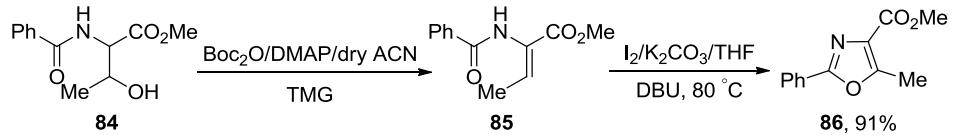
Giovannini and co-workers[47] have developed an efficient approach towards bisoxazoles such as **83** through 5-exo-dig cyclizations of propargyl amides mediated by $CeCl_3/NaI/I_2$ system under microwave irradiation (Scheme 18).



Scheme 18

2.2.2.4 Synthesis of oxazoles by base mediated cyclization of enamides containing leaving group at *β*-position

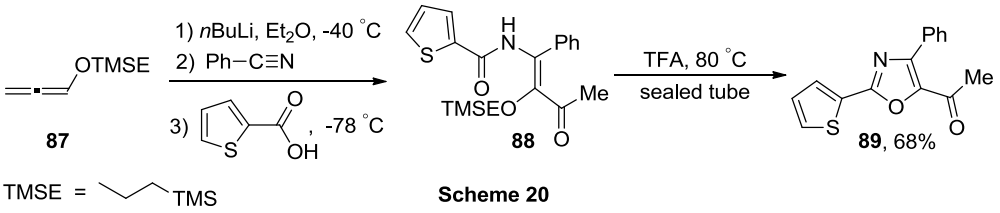
Among various methods for oxazole synthesis, intramolecular cyclization of enamides derivatives (carrying a leaving group at *β*-position) provides a convenient access to oxazoles through intramolecular carbon-oxygen bond formation. For example, enamides bearing the β-vinylic C-heteroatom bonds (C-Br, C-I, C-OMe) serve as stable easily accessible precursors, which are shown to undergo facile intramolecular cyclization-elimination in the presence of various organic or inorganic bases or acid providing a broad range of substituted oxazoles in good yields. These enamide precursors are generated in several ways. Thus, Ferreira and co-workers[48] have reported synthesis of *β*-halogen amides *via* sequential dehydration of *N*-acyl-*β*-hydroxy amino acids **84** and subsequent halogenations with NBS or iodine, followed by treatment with DBU in a stepwise or one-pot process to afford 2,5-disubstituted oxazole-4-carboxylates such as **86** (Scheme 19).



84 **85** **86**, 91%

Scheme 19

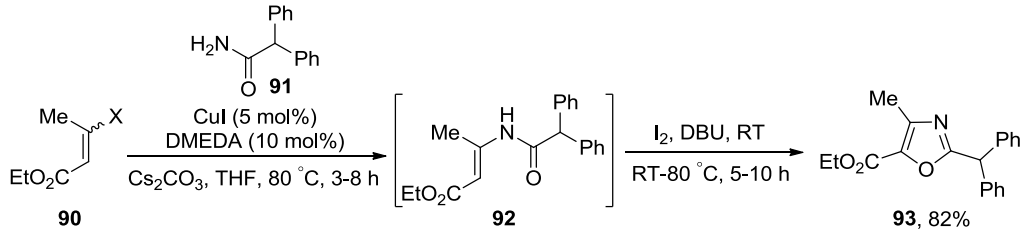
Reissig has developed an interesting mechanistically intriguing serendipitous synthesis of *β*-alkoxy-*β*-ketoenamides involving three component reaction between lithiated alkoxyallenes, nitriles and carboxylic acids.[49] These enamides undergo facile intramolecular cyclization in presence of trifluoroacetic acid to furnish 2,4-substituted 5-acetyloxazoles such as **89** in good yields (Scheme 20).



87 **88** **89**, 68%

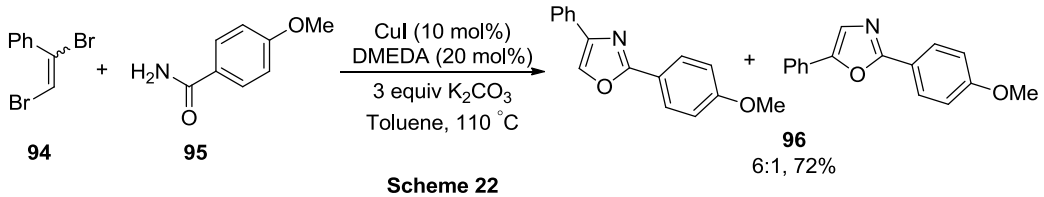
Scheme 20

Enamides have also been generated by copper catalyzed amidation of vinyl halides. Thus Buchwald and co-workers[50] have previously developed a sequential (two step one-pot) synthesis of 2,4,5-trisubstituted oxazoles *via* copper catalyzed amidation of vinyl halides to form enamides, followed by intramolecular cyclization promoted by iodine (Scheme 21).



Scheme 21

Glorious and co-workes[51] have developed a copper catalyzed synthesis of 2,5-disubstituted oxazoles from primary amides reacting with 1,2-dihaloalkenes which involves formation of halogen substituted enamides, however the reaction affords a regioisomeric mixture of 2,4- and 2,5 substituted oxazoles (Scheme 22).

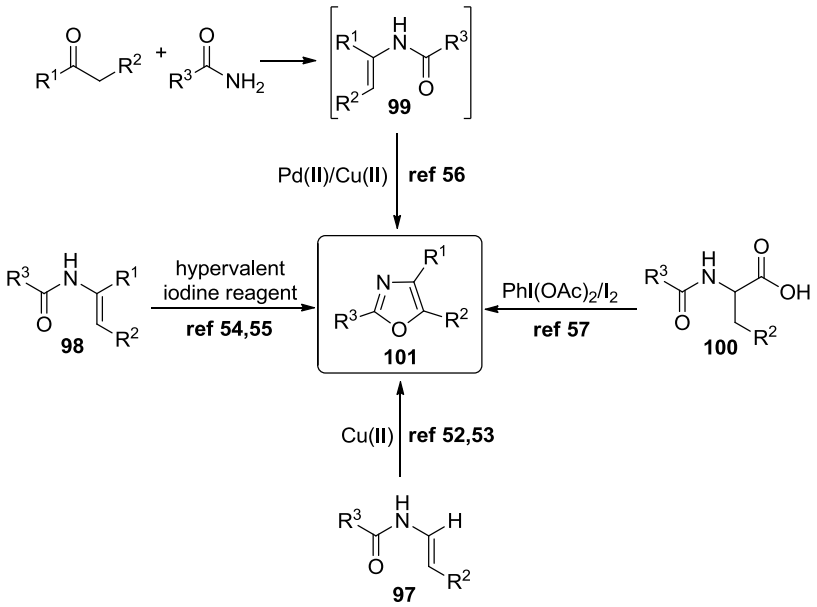


Scheme 22

2.2.2.5 Synthesis of oxazoles *via* vinylic C-H functionalization (C-O bond formation) of enamides

Recently several methods have been developed for the synthesis of substituted oxazoles from various enamides through intramolecular C-O bond formation reaction. Thus, Buchwald and co-workers[52] have developed a copper(II)-catalyzed oxidative cyclization of enamides to oxazoles via vinylic C−H bond functionalization at room temperature. With this method various 2,5-disubstituted oxazoles bearing aryl, vinyl, alkyl, and heteroaryl substituents could be synthesized in moderate to high yields (Scheme 23). Stahl et al.[53] have also reported a $CuCl_2$ mediated oxidative cyclization of enamides to oxazoles. These enamides were prepared from readily available simple amide and alkyne precursors (Scheme 23). Zhao and co-workers have demonstrated the synthesis of functionalized oxazoles from enamides via phenyliodine diacetate (PIDA)-mediated intramolecular cyclization. The main advantage of this method is broad substrate scope and heavy-metal-free C-O bond formation.[54] Another group Nachtsheim and co-workers[55] have reported a metal-free oxidative C-O bond-forming reaction for the synthesis of oxazoles, involving hypervalent iodine (PIFA) mediated oxidative cyclization of *N*-styrylbenzamides. By applying this mild reaction conditions, a variety of oxazoles bearing electron-poor or electron-rich aromatic substituents at the 5-position were obtained in good to high yields in short reaction time (Scheme 23). Jiang and co-

workers[56] have also reported the synthesis of oxazoles from simple amides and ketones via a Pd(II)-catalyzed sp^2 C-H activation pathway in one step.

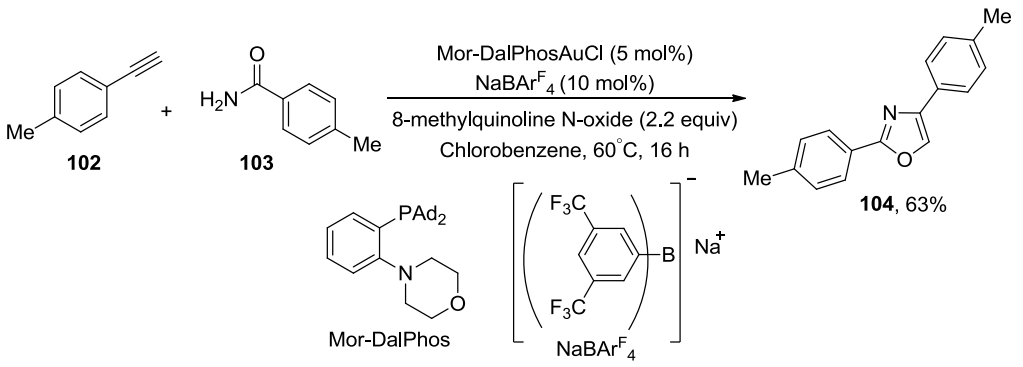


Scheme 23

The reaction proceeds through a C-N bond formation to form enamide, followed by a C-O bond formation (cyclization). Recently, Boto and co-workers[57] have reported that *N*-acylamino acids can be converted into 2,5-disubstituted oxazoles using a one-pot process in which a radical decarboxylation–oxidation–isomerization reaction generates an enamide intermediate, which then undergoes an iodine-promoted cyclization. No metals are needed to promote this cyclization (Scheme 23).

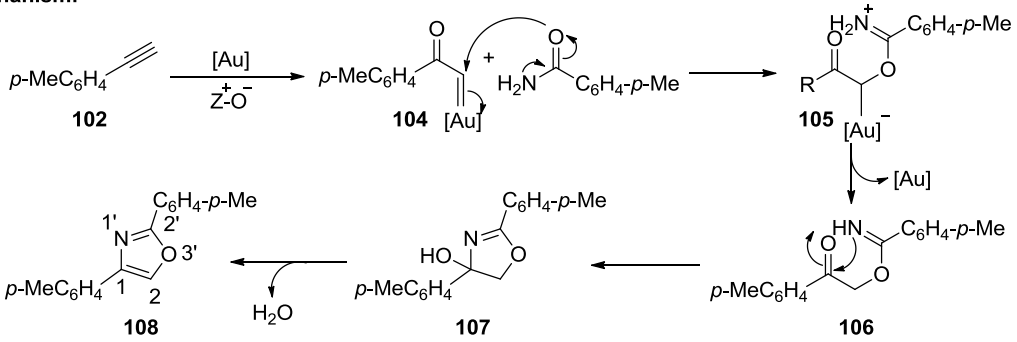
2.2.2.6 Miscellaneous approaches for the synthesis of oxazoles

Recently Zhang and co-workers[58] have developed a Au(I)-catalyzed modular synthesis of 2,4-disubstituted oxazoles via [3+2] annulations between readily available terminal alkynes and aromatic/alkenic carboxamides. The key reaction intermediate, an α-oxo gold carbene, is generated via gold-promoted oxidation of a terminal alkyne which is highly electrophilic, but the use of a P,N- or P,S-bidentate ligand, especially Mor-DalPhos, significantly tempers its reactivity, thereby permitting its efficient trapping by a carboxamide en route to the formation of the oxazole ring (Scheme 24).

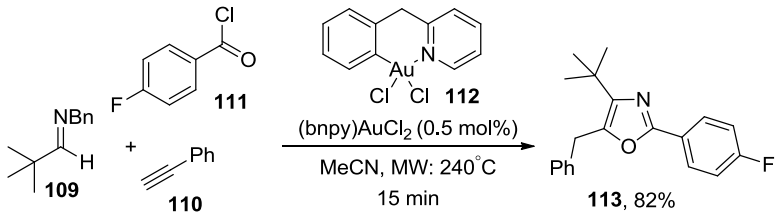


Scheme 24

Mechanism:



Cyclometallated aryl-pyridine Au(III) complex **112** has been shown to efficiently catalyze oxazole formation in a three-component reaction between *N*-Bn imine **109**, alkyne **110**, and acyl chloride **111** by Daniel Strand and co-workers (Scheme 25).[59]



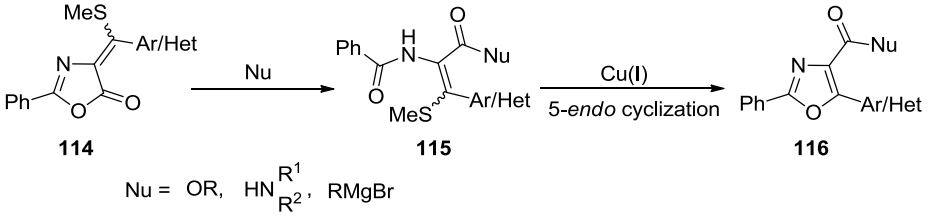
Scheme 25

Despite the availability of these above elegant methods, only a few reports deal with efficient and regioselective synthesis of 2,4,5-trisubstituted oxazoles with flexible substitution pattern at all positions.

2.3 Present work

2.3.1 Inrtoduction

We therefore developed a general protocol for diversity oriented synthesis of 2-phenyl-5-(het)aryl-4-substituted oxazoles **116** by a sequential nucleophilic ring opening of newly synthesized 4-[methylthio(aryl/heteroaryl)methylene]-2-phenyl-5-oxazolone precursors **114** followed by copper catalyzed intramolecular cyclization of the resulting highly functionalized enamide intermediates **115** (Scheme 26). Thus in the following section, we report the results of our studies based on above strategy leading to synthetic route for substituted oxazoles, along with the synthesis of three naturally occurring 2,5-diaryloxazoles, i.e. balsoxine, texamine and uguenenazole following this protocol.



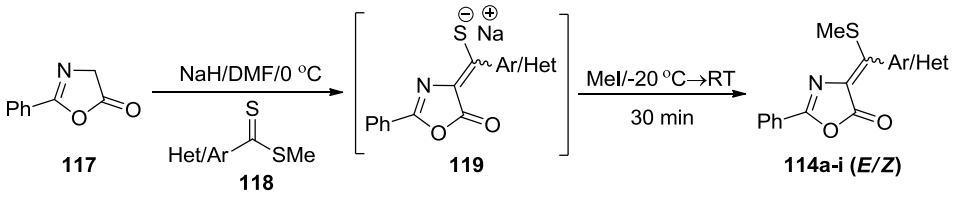
Scheme 26

2.3.2 Results and discussion

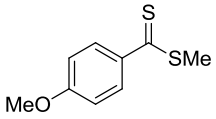
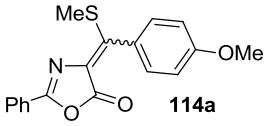
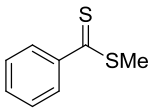
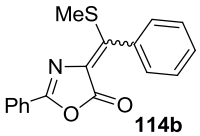
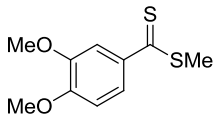
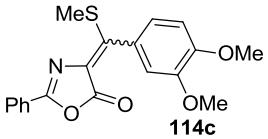
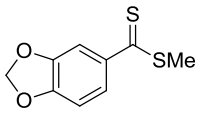
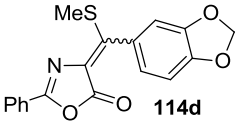
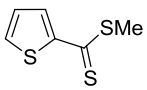
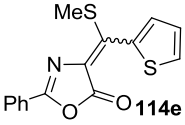
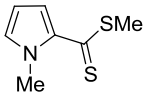
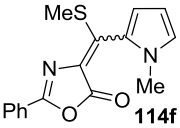
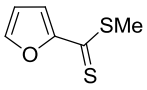
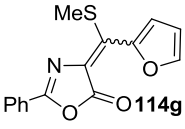
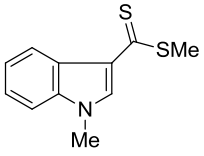
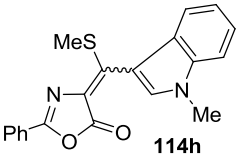
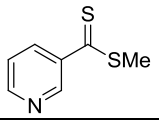
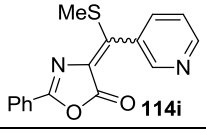
2.3.2.1 Synthesis of novel 2-phenyl-4-[methylthio(het)arylmethylene]-5-oxazolone precursors 114a-i

The desired 2-phenyl-4-[methylthio(aryl/heteroaryl)methylene]-5-oxazolones **114a-i** were synthesized in good yields by reacting 2-phenyl-5-oxazolone **117** with appropriate (het)aryl dithioesters **118** in the presence of sodium hydride in DMF followed by alkylation of the resulting thiolate salts **119** with methyl iodide (Scheme 27). The structures of all these newly synthesized 4-arylidene oxazolone precursors **114a-i** were established with the help of spectral and analytical data. The ^{1}H and ^{13}C NMR spectra of **114a-i** revealed that these compounds exist as mixture of *E*/*Z* stereoisomers (Scheme 27, Table 1).

Table 1. Synthesis of novel 2-phenyl-4-[methylthio(het)arylmethylene]-5-oxazolone precursors 114a-i



Scheme 27

Entry	Dithioester **118**	**114**	*E/Z* Ratio	% Yield **114**
1		 **114a**	60:40	80
2		 **114b**	55:45	75
3		 **114c**	63:37	78
4		 **114d**	52:48	72
5		 **114e**	55:45	70
6		 **114f**	75:25	75
7		 **114g**	55:45	70
8		 **114h**	64:36	78
9		 **114i**	57:43	60

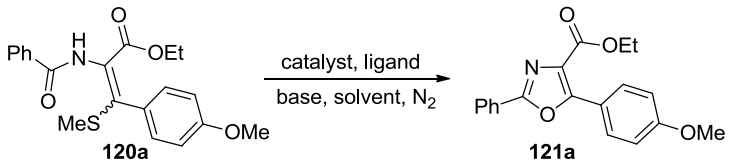
The oxazolone precursors **114a-i** were next subjected to nucleophilic ring opening in the presence of various alkoxides (Scheme 28). Thus **114a** was allowed to react with

sodium ethoxide in ethanol at room temperature for 2-3 h furnishing exclusively *α*-[(methylthio)(4-methoxyphenyl)methylene]-*N*-benzoylglycinate **120a** (Ar = 4-$MeOC_6H_4$, R^1 = Et) in 88% yield. Similarly the other substituted open chain ethyl- (**120b-f**), *n*-butyl-, benzyl- and *t*-butyl esters (**120g-i**) were obtained in high yields on treatment of the corresponding oxazolones **114** with either sodium ethoxide, *n*-butoxide, benzyloxide or *tert*-butoxide under identical conditions (Scheme 28).

Intramolecular 5-*endo* cyclization of the open-chain esters **120a-i** to the desired 2-phenyl-4-carboalkoxy-5-(het)aryloxazoles **121** was next examined under the influence of various cyclizing agents reported earlier.[26] Thus **120a** underwent facile cyclization in the presence of excess of silver carbonate (4 equiv) in refluxing acetonitrile yielding the corresponding ethyl 2-phenyl-5-(4-methoxyphenyl)oxazole-4-carboxylate **121a** in 85% yield (Table 2, entry 1). On the other hand, the yield of **121a** was drastically reduced (58%) when the reaction was performed with 2 equiv of silver carbonate under identical conditions even for prolonged time (Table 1, entry 2). The previously utilized cyclizing agents (Et_3N/C_6H_6, Cs_2CO_3/dioxane, $CuBr_2$/DBU, etc.)[26] were also not found to be much effective yielding **121a** in unsatisfactory yields (with maximum yield of 67% with Et_3N/C_6H_6). Therefore, in view of the large amount and high cost of silver carbonate employed in this cyclization, we envisaged a related transformation of these highly functionalized enamides **120** to oxazoles **121** by means of copper catalyzed cyclization reactions, which provide a promising alternative mainly due to their high efficiency, mild reaction conditions and low cost.[60] Over the past years, remarkable progress has been achieved in the synthesis of heterocycles by copper catalyzed C-C and C-heteroatom bond formations.[61-62]

For our studies, enamide **120a** was chosen as a model substrate for its cyclization to oxazole **121a** under copper catalysis (Table 2). Initial studies were performed by screening various copper catalysts (10 mol%) in the absence of base in DMF at 90 °C, affording the oxazole **121a** in maximum yield of 65% (Table 2, entries 3-5). However in the presence of Cs_2CO_3 as base (1 equiv), in the absence of any ligand, the oxazole **121a** was obtained in increased yields (Table 2, entries 6-9) and CuI proved to be best choice among catalysts investigated, yielding **121a** in 79% yield after 7 h (Table 2, entry 8). Subsequently our study focussed on cyclization of **120a** by testing various ligands (entries 10-13) and it was found that use of 1,10-phenanthroline as ligand significantly improved the catalyst efficiency affording **121a** in 92% yield within 3 h (Table 2, entry 13). Further

Table 2. Optimization of reaction conditions for the cyclization of enamide 120a to oxazole 121a



120a **121a**

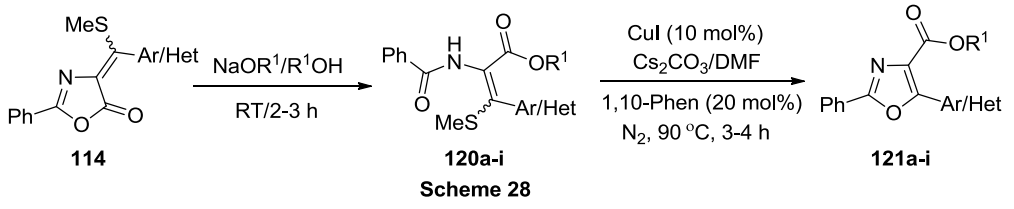
entry	Reagent/ catalyst	Base	solvent	Time(h)	%yield **121a**
1	Ag_2CO_3 (4 equiv)	-	CH_3CN	4	85
2	Ag_2CO_3 (2 equiv)	-	CH_3CN	12	58
3	Cu_2O	-	DMF	15	63
4	CuCl	-	DMF	15	62
5	CuI	-	DMF	15	65
6	CuCl	Cs_2CO_3	DMF	12	70
7	CuBr	Cs_2CO_3	DMF	12	71
8	CuI	Cs_2CO_3	DMF	7	79
9	Cu powder	Cs_2CO_3	DMF	12	69
10	CuI/L-proline	Cs_2CO_3	DMF	8	81
11	CuI/TMEDA	Cs_2CO_3	DMF	10	75
12	CuI/Py	Cs_2CO_3	DMF	10	78
13	**CuI/Phen**	**Cs_2CO_3**	**DMF**	**3**	**92**
14	CuI/Phen	K_2CO_3	DMF	10	79
15	CuI/Phen	tBuOK	DMF	10	81
16	CuI/Phen	tBuOLi	DMF	10	80
17	CuI/Phen	Cs_2CO_3	Toluene	10	71
18	CuI/Phen	Cs_2CO_3	DMA	10	70
19	CuI/Phen	Cs_2CO_3	DMSO	10	72
20	CuI(5 mol%)/Phen	Cs_2CO_3	DMF	10	85

screening of bases including K_2CO_3, *t*-BuOK or *t*-BuOLi revealed that no obvious improvement in yields was achieved and Cs_2CO_3 being the base of choice (Table 2, entries 14-16). Among solvent selection, DMF was clearly the best solvent than toluene, DMA or DMSO (Table 2, entries 13, 17-19). A low catalytic loading was not effective resulting in diminished yield of **121a** with prolonged reaction time (Table 2, entry 20). Further screening of reaction temperature or reaction time did not show any improvement in yield of **121a**, therefore CuI (10 mol%) in the presence of 1,10-phenanthroline (20 mol%) as ligand and Cs_2CO_3 (1equiv) as base in DMF at 90 $^{\circ}$C were used as optimal conditions (Table 2, entry 13) throughout our studies.

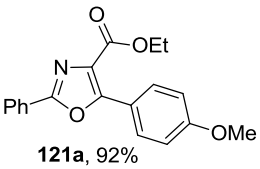
2.3.2.2 Synthesis of novel 2-phenyl-5-(het)aryloxazole-4-carboxylates

With an optimized catalytic system in hand, we next explored the generality of this copper catalyzed cyclization reaction with various open chain enamide esters **120b-i**

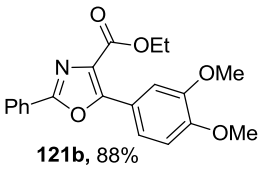
(Scheme 28). Thus acyclic ethyl esters bearing substituted aryl (**120b-c**), furyl (**120d**), 3-indolyl (**120e**) and 3-pyridyl (**120f**) moieties readily underwent cyclization under these optimized conditions providing the corresponding ethyl 2-phenyl-5-(het)aryloxazole-4-carboxylates **121b-f** in excellent overall yields (Scheme 28). Similarly the *n*-butyl and benzyl 2-phenyl-5-(3-indolyl)-oxozole-4-carboxylates **121g-h** could be obtained in excellent yields from the acyclic precursors **120g-h**.



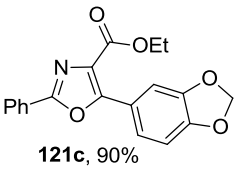
Scheme 28



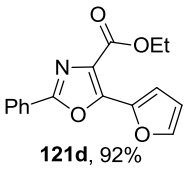
121a, 92%



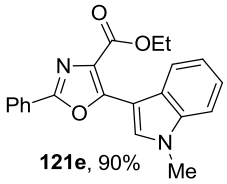
121b, 88%



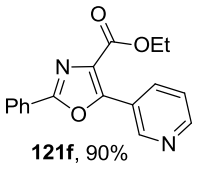
121c, 90%



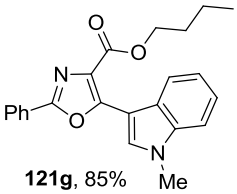
121d, 92%



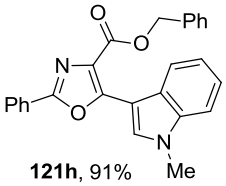
121e, 90%



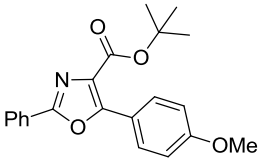
121f, 90%



121g, 85%



121h, 91%



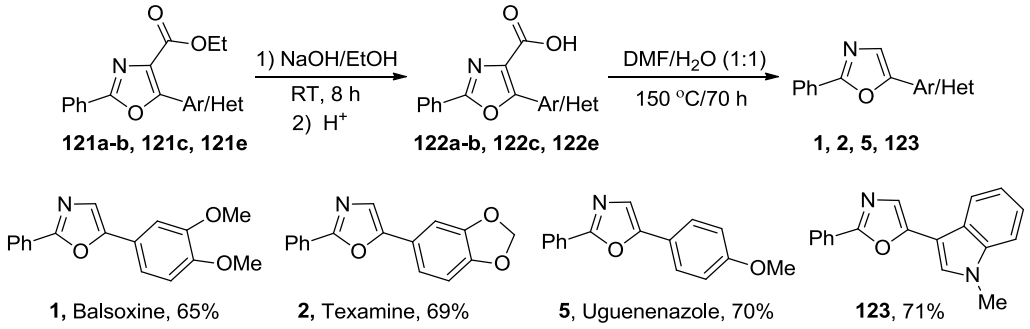
121i, 80%

Interestingly, the corresponding *t*-butyl 2,5-diaryloxazole-4-carboxylate **121i** could also be obtained in 80% yield from **120i**, without any side reactions under identical conditions (Scheme 28).

2.3.2.3 Synthesis of 2-phenyl-5-(het)aryloxazole natural products

Having established the facile ring closing copper catalyzed cyclization protocol for a broad range of 2,5-(het)aryloxozole-4-carboxylates **121a-i**, we exploited these newly synthesized oxozole-4-carboxylates as precursors for 2,5-di(het)aryloxazole natural products by removal of 4-ester functionality through two steps hydrolysis and decarboxylation protocol (Scheme 29). Hodgetts and Kershaw[63] have synthesised balsoxine **1** following this strategy from ethyl 2-phenyl-5-(3,4-bismethoxyphenyl) oxazole-4-carboxylate **121b**, which was obtained in six steps from ethyl 2-aminooxazole

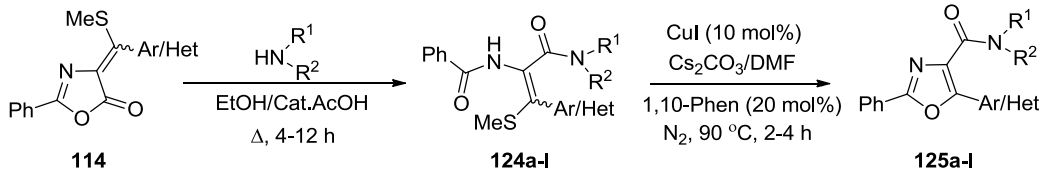
carboxylate in Suzuki-Miyaura approach. Hoarau and co-workers[64] have reported a five steps synthesis of balsoxine **1** and texaline **3** (Figure 1) and other 2,5-di(hetero)aryloxazoles by regiocontrolled palladium catalyzed 2- and 5-(het)arylation of oxazole-4-carboxylates and subsequent hydrolysis-decarboxylation (CuO) of the resulting 2,5-di(hetero)aryl-4-carboxylates. We undertook the synthesis of three natural products i.e., balsoxine **1**, texamine **2** (isolated from *Amyris texana*),[6,8,65a,65c,65e] uguenenazole **5** (recently isolated form *Vepris uguenensis*)[10,65c] and 2-phenyl-5-(3-indolyl)oxazole **123** from the respective 2,5-di(hetero)aryloxazole-4-carboxylates **121a-b**, **121c** and **121e** as shown in the Scheme 29. Thus the oxazole esters were subjected to hydrolysis in ethanolic NaOH furnishing the respective carboxylic acids **122** in nearly quantitative yields. Thermal decarboxylation of **122a-b**, **122c** and **122e** in H_2O/DMF (1:1) afforded balsoxine **1**, uguenenazole **5**, texamine **2**, and 2-phenyl-5-(3-indolyl)-oxazole **123** respectively in 65-71% overall yields in a four steps sequence (Scheme 29).



Scheme 29

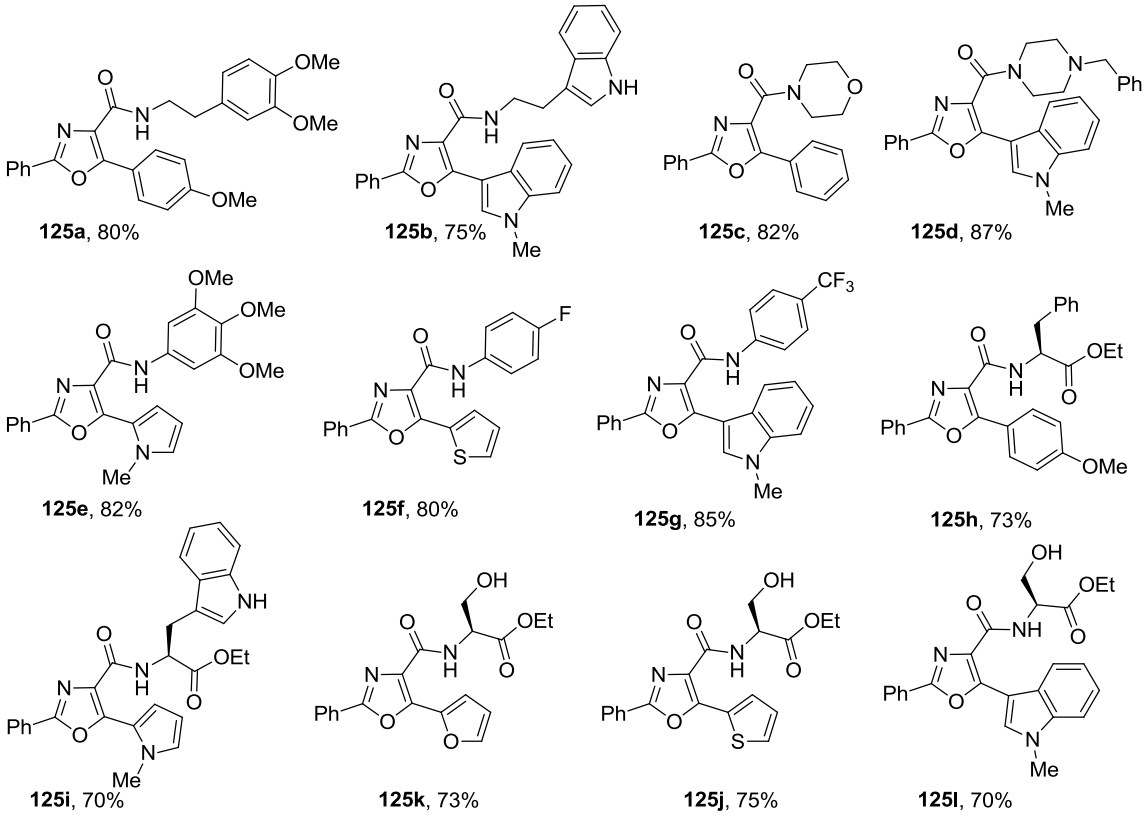
2.3.2.4 Synthesis of 2,5-di(het)aryloxazole-4-carboxamides

Having optimized the reaction conditions for copper catalyzed 5-*endo* cyclization of enamides bearing a carboxylate functionality, we next evaluated the scope of the reaction for the synthesis of 2,5-di(het)aryloxazole-4-carboxamides **125** by ring opening of **114** with various primary and secondary amines followed by copper catalyzed 5-*endo* cyclization of the resulting enamides **124** (Scheme 30). We were pleased to find that 4-(het)arylideneoxazolones **114a-b** and **114h** underwent smooth ring opening with primary and secondary aliphatic acyclic/cyclic amines to afford the corresponding open-chain adducts **124a-d** in excellent yields. Similarly, aromatic amines with both electron donating and withdrawing groups also reacted smoothly with few selected oxazolones (**114e-f**, **114h**) yielding acyclic precursors **124e-g** in good yields. The ring opening of **114**



114 **124a-l** **125a-l**

Scheme 30



125a, 80% **125b**, 75% **125c**, 82% **125d**, 87%

125e, 82% **125f**, 80% **125g**, 85% **125h**, 73%

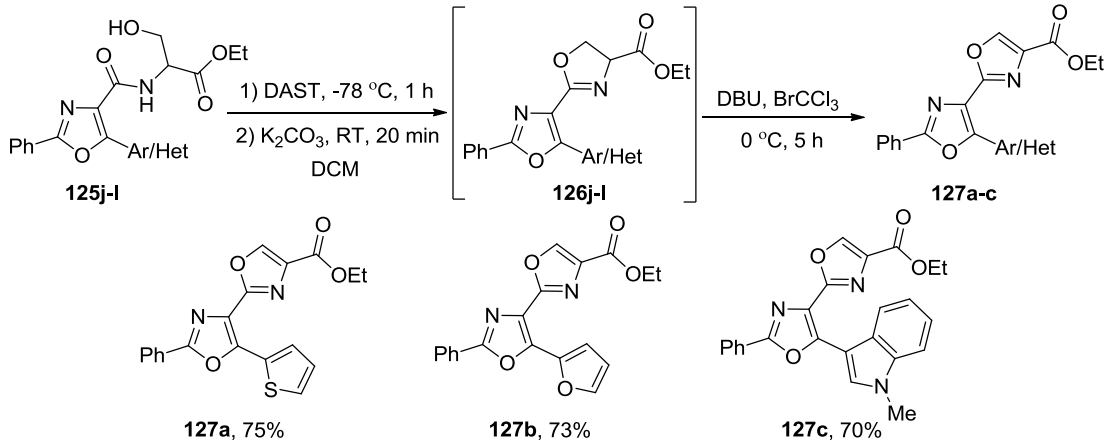
125i, 70% **125k**, 73% **125j**, 75% **125l**, 70%

was found to be equally facile with amino acid esters (phenylalanine, tryptophan and serine) leading to novel peptidomimetic motifs **124h-l** in moderate to good yields. Further, to our delight, the optimized copper catalyzed reaction conditions turned out to be equally successful for intramolecular cyclization of acyclic amide precursors **124a-l** furnishing the novel 2-phenyl-5-(het)aryloxazole-4-carboxamides **125a-l** in excellent yields (Scheme 30). Thus, a diverse range of 2,5-disubstituted oxazole-4-carboxamides derived from primary aliphatic/aromatic and cyclic secondary amines and amino acid derivatives **125a-l** could be readily synthesized in two steps from easily accessible precursors.

2.3.2.5 Synthesis of 2,5-substitued 4,2'-bisoxazole-4'-carboxylates

The newly synthesized serine derived 2,5-disubstitued oxazole-4-(*β*-hydroxy)amides **125j-l** were subjected to one-pot dehydrative cyclization-dehydrohalgenation by sequential treatment with DAST (diethylaminosulphur trifluoride)

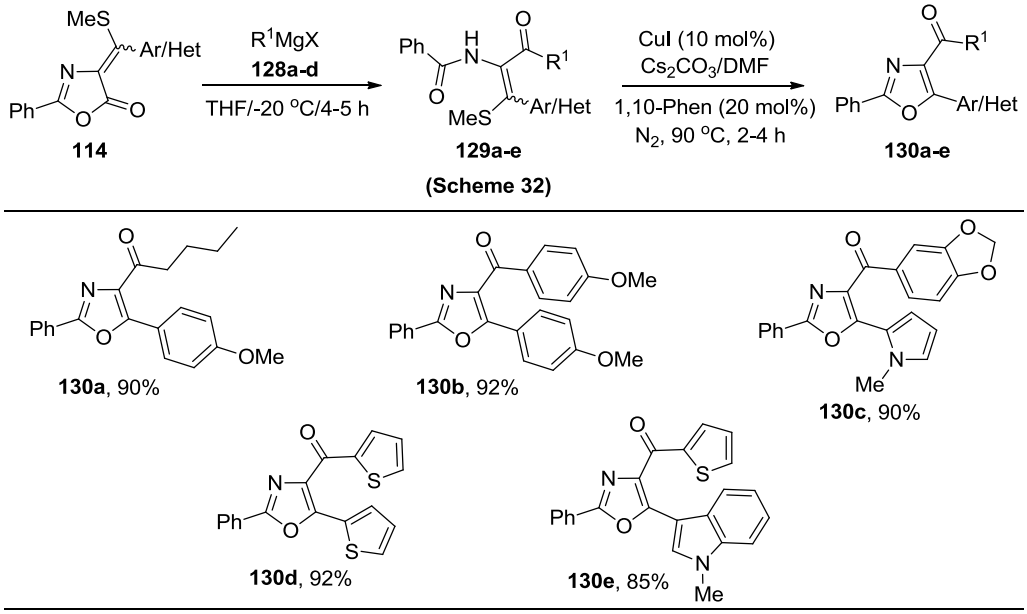
at -78 °C for 30 min and bromotrichloromethane/DBU to furnish 2,5-substitued 4,2'-bisoxazole-4'-carboxylates **127a-c** in 70-75% yields (Scheme 31).[66] The 4,2'-bisoxazoles are common motifs in many natural products (diazonamide, hennoxazole A, telomestatin) displaying broad range of biological activity.[1]



Scheme 31

2.3.2.6 Synthesis of 2,5-di(het)aryl-4-acyloxazoles

Finally, after successful implementation of this two steps protocol for the introduction of 4-carboxylate and 4-carboxamide functionalities in the trisubstituted oxazoles **121** and **125** (Scheme 28, 30), we next focussed our studies on the synthesis of 2,5-substituted 4-acyl(aroyl)oxazoles *via* ring opening of oxazolones **114** with alkyl/aryl Grignard reagents **128a-d** (Scheme 32). Thus, treatment of **114a** with *n*-butylmagnesium bromide **128a** gave the α-acylenamide **129a** (72%) exclusively with no trace of conjugate addition-elimination product. The enamide **129a** was subjected to copper catalyzed cyclization under optimized conditions to furnish the 2-phenyl-5-(4-methoxyphenyl)-4-(*n*-pentanoyl)oxazole **130a** in 90% yield. Similarly, the ring opening of **114a** and **114f** with aryl Grignard reagents **128b-c** also proceeded smoothly leading to 4-aroyloxazoles **130b-c** in excellent yields after subsequent cyclization of the resulting enamides **129b-c** under copper catalysis. The versatility of the methodology was further demonstrated by the synthesis of two 2-phenyl-5-(hetero)aryl-4-thienoyloxazoles **130d-e** in high yields under identical sequence by initial treatment of either **114e** or **114h** with 2-thienyl Grignard reagent **128d** (Scheme 32).



2.4 Conclusion

In the present chapter, we have developed an efficient two step synthesis of highly functionalized 2-phenyl-4,5-substitued oxazoles from readily available novel 4-[(methylthio)-het(aryl)-methylene]-2-phenyl-5-oxazolone precursors **114**. The overall process involves highly regioselective nucleophilic ring opening of **114** by oxygen, nitrogen and carbon nucleophiles and subsequent copper catalyzed intramolecular cyclization of the resulting functionalized *β*-[(methylthio)het(aryl)]enamides to 2-phenyl-4,5-substituted oxazoles as the key step. The protocol displays broad substrate scope and wide functional group compatibility with flexible substitution at 4,5-positions of oxazoles. The 4-carboxylate functionality can be easily removed to afford the corresponding 2,5-di(hetero)aryloxazoles and the method is applied for the synthesis of 2,5-di(het)aryloxazole natural products balsoxine **1**, texamine **2**, uguenenazole **5** and 2-phenyl-5-(3-indolyl) oxazole **123** in overall high yields (Scheme 29). Additionally, the amino acid derived enamides **124h-l** provide access to a range of chiral potentially biologically relevant oxazoles **125h-l** (Scheme 30). The ease of further elaboration was demonstrated by facile dehydrative cyclization-aromatization of serine derived oxazoles **125j-l** to 4,2'-bisoxazoles **127a-c** (Scheme 31), which are structural component of several biologically active bisoxazole containing natural products. The copper catalyzed cyclization of these highly functionalized *β*-(methylthio)enamides to oxazoles complements the growing collection of copper catalyzed heterocyclization reactions and provides practical and economical advantage over previously reported[26] silver carbonate

mediated cyclization (requiring 4 equiv of Ag_2CO_3) in terms of inexpensive copper catalyst and better yields. We believe that the present method is attractive for further library construction for diversity oriented synthesis of oxazoles as well as related natural products. The easy availability of starting materials along with the convenience and efficiency of the present method should make it useful complement to the existing methods for the synthesis of multisubstituted oxazoles.

2.5 Experimental section

2.5.1 General information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using TLC Silica gel plates and visualized with UV light. Flash chromatography was performed using silica gel (100-200 mesh). Optical rotations were obtained on a polarimeter. Nuclear magnetic resonance spectra were recorded on a (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$ (or) DMSO-d_6 as solvent. Chemical shifts were reported in δ ppm (parts per million) using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6 in ^{1}H-NMR, δ 77.16 for $CDCl_3$ and δ 39.5 for DMSO-d_6 in ^{13}C-NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (double doublet), dt (double triplet), sex (sextet), m (multiplet), br (broad). Infrared spectra were recorded on FTIR instrument and HRMS on Q-TOF spectrometer. Elemental analyses were carried out on a organic elemental analyzer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem*. **2012**, *77*, 10752.

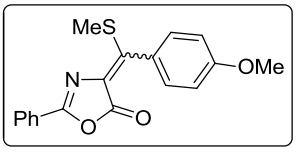
2.5.2 General procedure for the synthesis of 4-[(methylthio)(aryl/heteroaryl) methylene]-2-phenyloxazol-5-ones (114a-i).

To a stirred suspension of NaH (0.31 g, 7.8 mmol) and appropriate (het)aryl dithioester **118** (3.0 mmol) in DMF (10 mL), a solution of 2-phenyloxazol-5-one **117**[67] (0.5 g, 3.0 mmol) in DMF (10 mL) was added drop wise at 0 °C. The reaction mixture was stirred at room temperature for 0.5-1 hr, cooled to -20 °C, followed by addition of MeI (0.28 mL, 4.5 mmol) and further stirring at room temperature for 30 min. It was then poured into satd. NH_4Cl solution (100 mL), extracted with EtOAc (3 x 50 mL), washed

with water (2 x 50 mL), brine (1 x 50 mL), dried over Na_2SO_4 and solvent removed under reduced pressure to give crude products, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

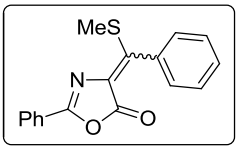
All oxazolones **114a-i** were obtained as mixture of *E*/*Z* stereoisomers. The *E*/*Z* stereochemistry of **114a-i** were established on the basis of chemical shift value of methylthio group, which appears at higher δ value in *E* isomer due to deshielding effect of *cis* carbonyl group of azalactone.

(*E*/*Z*) 4-[(4-Methoxyphenyl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one



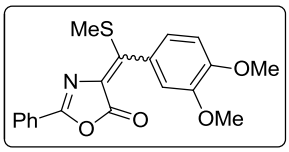
(114a). Obtained from oxazolone **117** and dithioester **118a**, (*E*:*Z* = 60:40), yellow solid (0.805 g, 80%); mp 134-136 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3076, 2959, 2928, 2834, 1768, 1627, 1502, 1298, 1251, 1173, 1008, 820, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.08 (m, 1.2H), 7.98-7.96 (m, 0.8H), 7.56-7.40 (m, 3.8H), 7.35-7.32 (m, 1.2H), 7.04-6.98 (m, 2H), 3.89 (s, 1.2H), 3.87 (s, 1.8H), 2.27 (s, 1.8H), 2.22 (s, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.6, 161.4, 161.2, 160.1, 159.1, 157.6, 156.9, 132.6, 132.3, 132.2, 131.0, 129.4, 128.9, 128.2, 128.1, 127.9, 127.7, 126.8, 126.3, 126.2, 124.9, 114.4, 114.1, 55.6, 55.5, 17.4, 16.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}NO_3S$ $[M + Na]^+$ 348.0670, found 348.0681.

(*E*/*Z*) 4-[Methylthio(phenyl)methylene]-2-phenyloxazol-5(4*H*)-one (114b). Obtained



from oxazolone **117** and dithioester **118b**, (*E*:*Z* = 55:45), yellow solid (0.69 g, 75%); mp 94-96 °C; R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 1760, 1627, 1327, 1207, 964, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 1.1H), 7.96-7.94 (m, 0.9H), 7.58-7.33 (m, 8H), 2.19 (s, 1.65H), 2.14 (s, 1.35H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.2, 160.6, 159.3, 156.9, 156.8, 134.4, 132.9, 132.7, 132.3, 130.1, 129.8, 129.7, 128.9, 128.8, 128.6, 128.4, 127.9, 127.8, 126.08, 126.06, 16.7, 16.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}NO_2S$ $[M + Na]^+$ 318.0565, found 318.0564.

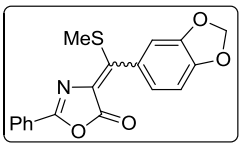
(*E*/*Z*) 4-[(3,4-Dimethoxyphenyl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one



(114c). Obtained from oxazolone **117** and dithioester **118c**, (*E*:*Z* = 63:37), yellow solid (0.86 g, 78%); mp 142-144 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2923, 1756, 1617, 1512, 1269, 1002, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1 (d, *J* = 7.6 Hz, 1.26H), 7.98 (d, *J* = 7.6 Hz,

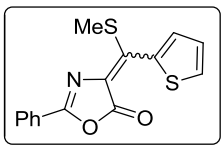
0.74H), 7.57-7.41 (m, 3H), 7.14-6.89 (m, 3H), 3.97 (s, 1.11H), 3.95 (s, 1.89H), 3.93 (s, 1.11H), 3.9 (s, 1.89H), 2.29 (s, 1.89H), 2.25 (s, 1.1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.5, 160.2, 159.2, 157.4, 156.7, 150.9, 150.8, 149.3, 148.9, 132.6, 132.3, 129.5, 128.93, 128.86, 128.2, 127.9, 127.7, 126.9, 126.2, 126.1, 125.2, 123.9, 122.6, 113.6, 112.5, 111.2, 110.9, 56.2, 56.1, 56.0, 17.5, 16.9; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NO_4S$ $[M + Na]^+$ 378.0776, found 378.0773.

(*E*/*Z*) 4-(Benzo[d][1,3]dioxol-5-yl(methylthio)methylene)-2-phenyloxazol-5(4*H*)-one



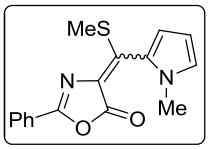
(114d). Obtained from oxazolone **117** and dithioester **118d**, (*E*:*Z* = 52:48), yellow solid (0.758 g, 72%); mp 100-104 °C; R_f 0.55 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2923, 1779, 1622, 1501, 1251, 1071, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 0.96H), 7.97 (d, *J* = 7.2 Hz, 1.04H), 7.56-7.40 (m, 3.2H), 7.03-6.83 (m, 2.8H), 6.06 (s, 1.04H), 6.04 (s, 0.96H), 2.28 (s, 1.56H), 2.23 (s, 1.44H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.4, 160.3, 159.3, 156.9, 156.3, 149.5, 149.3, 148.2, 148.0, 132.6, 132.3, 129.7, 128.9, 128.8, 128.4, 128.1, 127.9, 127.8, 126.4, 126.1, 126.08, 125.0, 123.7, 110.7, 109.5, 108.8, 108.5, 101.8, 17.3, 16.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{13}NO_4S$ $[M + Na]^+$ 362.0463, found 362.0463.

(*E*/*Z*) 4-[Methylthio(thiophen-2-yl)methylene]-2-phenyloxazol-5(4*H*)-one (114e).



Obtained from oxazolone **117** and dithioester **118e**, (*E*:*Z* = 55:45), yellow solid (0.65 g, 72%); mp 130-132 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2928, 1783, 1737, 1611, 1564, 1204, 1008, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.6 Hz, 2H), 8.0 (dd, *J* = 4.0 Hz, 1.2 Hz, 0.43H), 7.74 (dd, *J* = 5.2 Hz, 1.2 Hz, 0.43H), 7.60 (dd, *J* = 5.2 Hz, 1.2 Hz, 0.51H), 7.56 (t, *J* = 7.6 Hz, 1.1H), 7.51-7.47 (m, 2.1H), 7.42 (dd, *J* = 3.6 Hz, 1.2 Hz, 0.51H), 7.22 (dd, *J* = 4.8 Hz, 3.6 Hz, 0.48H), 7.18 (dd, *J* = 4.8 Hz, 3.6 Hz, 0.53H), 2.60 (s, 1.36H), 2.53 (s, 1.64H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 162.5, 160.2, 160.0, 148.3, 140.1, 134.6, 134.3, 132.8, 132.7, 131.3, 130.8, 129.1, 129.0, 128.2, 128.1, 128.0, 127.9, 126.0, 125.9, 19.8, 18.1; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}NO_2S_2$ $[M + Na]^+$ 324.0129, found 324.0132.

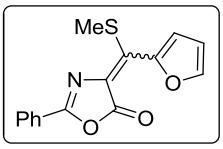
(*E*/*Z*) 4-[(1-Methyl-1*H*-pyrrol-2-yl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-



one (114f). Obtained from oxazolone **117** and dithioester **118f**, (*E*:*Z* = 75:25), reddish yellow solid (0.69 g, 75%); mp 78-80 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 1729, 1619, 1525, 1392, 1062, 734, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (m, 0.67H), 8.02-7.99 (m, 1.33H), 7.57-

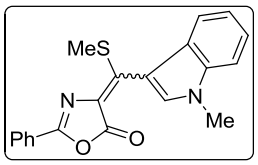
7.50 (m, 0.75H), 7.49-7.41 (m, 2.25H), 6.92 (dd, *J* = 2.6 Hz, 1.8 Hz, 0.75H), 6.90 (dd, *J* = 2.6 Hz, 1.6 Hz, 0.25H), 6.58 (dd, *J* = 3.8 Hz, 1.8 Hz 0.75H), 6.46 (dd, *J* = 4.0 Hz, 1.6 Hz, 0.25H), 6.31 (dd, *J* = 3.8 Hz, 2.6 Hz, 0.75H), 6.29 (dd, *J* = 4.0 Hz, 2.6 Hz, 0.25H), 3.63 (s, 2.25H), 3.59 (s, 0.75H), 2.38 (s, 0.75H), 2.35 (s, 2.25H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 160.2, 158.8, 147.6, 147.0, 132.6, 132.3, 129.0, 128.9, 128.4, 128.0, 127.8, 127.6, 127.1, 126.3, 126.2, 125.0, 117.1, 115.1, 109.6, 109.5, 35.8, 34.4, 18.0, 17.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}N_2O_2S$ $[M + Na]^+$ 321.0674, found 321.0672.

(*E*/*Z*) 4-[(Furan-2-yl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one (114g).



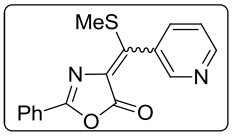
Obtained from oxazolone **117** and dithioester **118g**, (*E*:*Z* = 55:45), brown solid (0.62 g, 70%); mp 102-104 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2928, 1780, 1616, 1453, 1328, 882, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.06 (m, 2H), 7.72 (dd, *J* = 1.6 Hz, 0.8 Hz, 0.55H), 7.67 (dd, *J* = 1.6 Hz, 0.8 Hz, 0.45H), 7.58-7.46 (m, 3.55H), 7.13 (dd, *J* = 3.6 Hz, 0.8 Hz, 0.45H), 6.68 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.55H), 6.61 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.45H), 2.58 (s, 1.65H), 2.56 (s, 1.35H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.2, 160.3, 159.7, 149.4, 146.3, 146.0, 145.8, 142.7, 141.2, 132.8, 132.7, 129.0, 128.9, 128.5, 128.3, 127.94, 127.90, 126.03, 126.0, 120.1, 117.9, 113.3, 112.6, 18.4, 17.8; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}NO_3S$ $[M + Na]^+$ 308.0357, found 308.0359.

(*E*/*Z*) 4-[(1-Methyl-1*H*-indol-3-yl)(methylthio)methylene]-2-phenyloxazol-5(4*H*)-one



(114h). Obtained from oxazolone **117** and dithioester **118h**, (*E*:*Z* = 64:36), yellow solid (0.84 g, 78%); mp 186-188 °C; R_f 0.5 (1:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3106, 2927, 1767, 1727, 1619, 1522, 1325, 1131, 887, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 1.34H), 7.99-7.97 (m, 0.66H), 7.93 (d, *J* = 8 Hz, 0.33H), 7.73 (s, 0.33H), 7.71 (s, 0.67H), 7.56 (s, 1H), 7.53-7.42 (m, 3H), 7.40-7.37 (m, 1H), 7.33-7.31 (m, 1.34H), 7.27 (d, *J* = 1.2 Hz, 0.33H), 7.25-7.23 (m, 0.67H), 3.92 (s, 0.99H), 3.89 (s, 2.01H), 2.45 (s, 2.01H), 2.44 (s, 0.99H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.1, 158.3, 157.8, 151.8, 151.5, 138.0, 137.8, 135.2, 133.8, 132.1, 131.9, 128.9, 128.8, 127.6, 127.4, 126.7, 126.65, 126.59, 126.3, 123.2, 123.0, 122.0, 121.8, 121.7, 121.2, 111.6, 110.3, 110.2, 108.5, 33.73, 33.65, 18.7, 18.1; HRMS (ESI) *m/z* calcd for $C_{20}H_{16}N_2O_2S$ $[M + Na]^+$ 371.0830, found 371.0833.

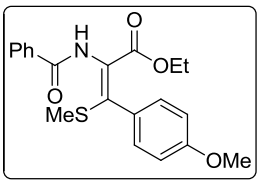
(*E*/*Z*) 4-[Methylthio(pyridin-3-yl)methylene]-2-phenyloxazol-5(4*H*)-one (114i).



Obtained from oxazolone **117** and dithioester **118i**, (*E*:*Z* = 57:43), yellow solid (0.55 g, 75%); mp 100-102 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 1760, 1619, 1572, 1008, 867, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72-8.71 (m, 1.14H), 8.62 (d, *J* = 1.6 Hz, 0.86H), 8.11-8.09 (m, 1.14H), 7.96-7.94 (m, 0.86H), 7.81 (dt, *J* = 7.6 Hz, 1.8 Hz, 0.43H), 7.71 (dt, *J* = 8 Hz, 1.8 Hz, 0.57H), 7.59-7.47 (m, 2.7H), 7.45-7.41 (m, 1.3H), 2.32 (s, 1.71H), 2.2 (s, 1.29H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.5, 161.5, 160.3, 152.0, 151.7, 151.1, 150.8, 150.6, 149.6, 137.7, 136.9, 133.2, 132.9, 131.1, 130.8, 129.6, 129.5, 129.12, 129.0, 128.2, 128.0, 125.9, 125.8, 123.6, 123.5, 17.1, 16.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}N_2O_2S$ $[M + H]^+$ 297.0698, found 297.0698.

2.5.3 Nucleophilic ring opening of 2-phenyl 4-[(methylthio)(hetero)arylidene]-oxazole-5-ones 114 with sodium alkoxides: General procedure for the Synthesis of α-[(methylthio)(het)arylidene]-*N*-benzoylglycinates 120a-i. To a stirred suspension of the corresponding sodium alkoxide [freshly prepared from sodium (20 mg, 1.0 mmol) in the respective alkanol (5 mL)], a solution of the appropriate 5-oxazolone **114** (0.325 g, 1.0 mmol) in 10 mL of alkanol was added dropwise and the reaction mixture was further stirred at room temperature for 2-3 h (monitored by TLC). It was then concentrated under reduced pressure, poured into water (100 mL), extracted with EtOAc (3 x 50 mL), washed with brine (1 x 50 mL), the organic layer dried (Na_2SO_4), and evaporated and the residue was triturated with diethyl ether to give open-chain esters **120a-i** as white solids. All the open-chain esters **120a-i** were found to be inseparable mixture of *E/Z* stereoisomers from their ^{1}H NMR spectra.

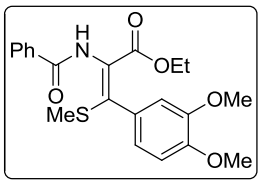
(*E*/*Z*) Ethyl 2-benzamido-3-(4-methoxyphenyl)-3-(methylthio)acrylate (120a).



Obtained from oxazolone **114a** and sodium ethoxide, (*E*:*Z* = 40:60), white solid (0.326 g, 88%); mp 146-148 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3326, 2983, 2926, 1715, 1658, 1511, 1467, 1288, 1244, 1028, 709; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.9 (s, 0.6H), 9.4 (s, 0.4H), 7.98 (d, *J* = 7.6 Hz, 1.2H), 7.60-7.57 (m, 1.2H), 7.53-7.48 (m, 1.8H), 7.40-7.36 (m, 0.8H), 7.19 (d, *J* = 8.8 Hz, 0.8H), 7.15 (d, *J* = 8.8 Hz, 1.2H), 7.0 (d, *J* = 8.8 Hz, 1.2H), 6.95 (d, *J* = 8.8 Hz, 0.8H), 4.15 (q, *J* = 7.2 Hz, 0.8H), 3.80 (q, *J* = 7.2 Hz, 1.2H), 3.79 (s, 1.8H), 3.72 (s, 1.2H), 1.9 (s, 1.8H), 1.78 (s, 1.2H), 1.18 (t, *J* = 7.2 Hz, 1.2H), 0.79 (t, *J* = 7.2 Hz, 1.8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ

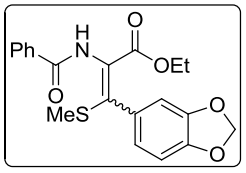
166.1, 165.3, 164.5, 163.7, 159.5, 158.9, 151.1, 144.3, 133.8, 133.2, 131.8, 131.4, 129.9, 129.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.3, 123.5, 120.7, 113.8, 113.7, 60.2, 59.9, 55.2, 55.1, 16.1, 14.9, 14.1, 13.5; Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.57; H, 5.67; N, 3.71.

(*E*/*Z*) Ethyl 2-benzamido-3-(3,4-dimethoxyphenyl)-3-(methylthio)acrylate (120b).

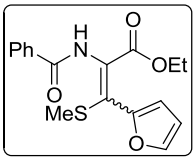


Obtained from oxazolone **114c** and sodium ethoxide, (*E*:*Z* = 55:45), white solid (0.300 g, 75%); mp 124-128 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3343, 2980, 2905, 1721, 1660, 1475, 1304, 1263, 1024, 713; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 0.54H), 7.9 (d, *J* = 7.2 Hz, 0.9H), 7.58-7.52 (m, 1.65H), 7.50-7.44 (m, 1.35H), 7.35 (t, *J* = 7.2 Hz, 1.1H), 7.25 (br s, 0.45H), 6.90-6.83 (m, 3H), 4.36 (q, *J* = 7.2 Hz, 1.1H), 4.02 (q, *J* = 7.2 Hz, 0.9H), 3.89 (s, 1.35H), 3.88 (s, 1.65H), 3.87 (s, 1.35H), 3.82 (s, 1.65H), 1.96 (s, 1.35H), 1.91 (s, 1.65H), 1.35 (t, *J* = 7.2 Hz, 1.65H), 0.96 (t, *J* = 7.2 Hz, 1.35H); ^{13}CNMR (100MHz, $CDCl_3$) δ 165.6, 165.0, 164.7, 164.5, 149.6, 149.5, 149.4, 149.2, 134.2, 133.6, 133.3, 132.4, 132.1, 128.9, 128.8, 128.0, 127.7, 127.6, 127.2, 126.5, 123.3, 122.0, 121.1, 112.2, 111.5, 111.4, 110.9, 61.6, 61.4, 56.19, 56.15, 56.06, 56.05, 16.5, 15.5, 14.3, 13.8 ; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}NO_5S$ $[M + H]^+$ 402.1375, found 402.1349.

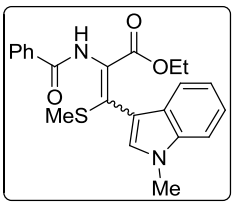
(*E*/*Z*) Ethyl 2-benzamido-3-(benzo[*d*][1,3]dioxol-5-yl)-3-(methylthio)acrylate (120c).



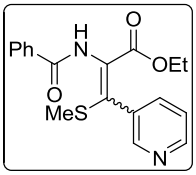
Obtained from oxazolone **114d** and sodium ethoxide, (*E*:*Z* = 84:16), white solid (0.288 g, 75%); mp 120-122 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3272, 3066, 2958, 1723, 1644, 1477, 1245, 1037, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 0.16H), 7.89 (d, *J* = 7.2 Hz, 0.32H), 7.56 (d, *J* = 7.2 Hz, 1.68H), 7.49-7.46 (m, 1.2H), 7.36 (t, *J* = 7.2 Hz, 1.68H), 7.24 (br s, 0.84H), 6.86-6.79 (m, 3.1H), 5.99 (s, 0.32H), 5.98 (s, 1.68H), 4.35 (q, *J* = 7.2 Hz, 1.68H), 4.06 (q, *J* = 7.2 Hz, 0.32H), 1.97 (s, 0.48H), 1.91 (s, 2.52H), 1.34 (t, *J* = 7.2 Hz, 2.52H), 1.00 (t, *J* = 7.2 Hz, 0.48H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 165.5, 164.6, 164.3, 148.5, 148.1, 148.0, 142.0, 133.7, 133.3, 132.3, 132.0, 129.3, 129.0, 128.9, 128.8, 127.6, 127.3, 123.3, 123.2, 122.2, 109.5, 108.94, 108.85, 108.3, 101.6, 101.5, 61.6, 61.4, 16.5, 15.5, 14.3, 13.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{20}NO_5S$ $[M + H]^+$ 386.1062, found 386.1042.

(*E*/*Z*) Ethyl 2-benzamido-3-(furan-2-yl)-3-(methylthio)acrylate (120d). Obtained 

from oxazolone **114g** and sodium ethoxide, (*E*:*Z* = 70:30), white solid (0.251 g, 75%); mp 68-70 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3413, 3345, 2983, 2918, 1727, 1677, 1461, 1326, 1180, 1015, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (br s, 0.7H), 8.39 (br s, 0.3H), 7.90-7.85 (m, 2H), 7.58-7.55 (m, 1.7H), 7.51-7.47 (m, 2.1H), 7.45 (dd, *J* = 2.0 Hz, 0.8 Hz, 0.3H), 6.84 (dd, *J* = 3.6 Hz, 0.8 Hz, 0.7H), 6.55-6.53 (m, 1H), 6.44 (dd, *J* = 3.6 Hz, 2.0 Hz, 0.3H), 4.46 (q, *J* = 7.2 Hz, 1.4H), 4.26 (q, *J* = 7.2 Hz, 0.6H), 2.28 (s, 2.1H), 2.18(s, 0.9H), 1.42 (t, *J* = 7.2 Hz, 2.1H), 1.20 (t, *J* = 7.2 Hz, 0.9H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 164.5, 164.4, 164.3, 163.6, 152.3, 148.7, 143.5, 143.2, 133.1, 132.9, 132.6, 132.1, 129.9, 129.1, 129.0, 127.6, 127.5, 117.5, 112.7, 112.3, 112.0, 111.6, 109.3, 62.0, 61.9, 19.5, 16.5, 14.2, 14.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}NO_4S$ $[M + Na]^+$ 354.0776, found 354.0769.

(*E*/*Z*) Ethyl 2-benzamido-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)acrylate (120e). 

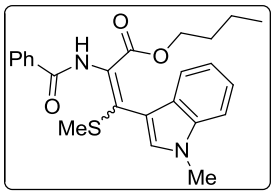
Obtained from oxazolone **114h** and sodium ethoxide, (*E*:*Z* = 35:65), off-white solid (0.334 g, 85%); mp 120-122 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3364, 2977, 2926, 1708, 1664, 1524, 1473, 1307, 1180, 741; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (br s, 0.65H), 9.49 (br s, 0.35H), 8.01 (d, *J* = 7.6 Hz, 1.25H), 7.65 (s, 0.35H), 7.59-7.49 (m, 3.85H), 7.47-7.40 (m, 1.9H), 7.33 (t, *J* = 7.2 Hz, 0.67H), 7.21 (t, *J* = 7.2 Hz, 0.73H), 7.14 (t, *J* = 7.2 Hz, 0.30H), 7.11 (t, *J* = 7.2 Hz, 0.60H), 6.98 (t, *J* = 7.2 Hz, 0.35H), 4.18 (q, *J* = 7.2 Hz, 0.7H), 3.83 (s, 1.95H), 3.82 (s, 1.05H), 3.73 (q, *J* = 7.2 Hz, 1.3H), 1.99 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 1.05H), 0.63 (t, *J* = 7.2 Hz, 1.95H); ^{13}CNMR (100 MHz, DMSO-d_6) δ 166.1, 165.2, 165.0, 164.3, 138.2, 136.9, 136.7, 135.6, 133.8, 133.4, 131.8, 131.7, 131.4, 130.5, 128.4, 128.1, 127.6, 127.5, 126.7, 125.6, 122.4, 122.3, 121.8, 121.7, 119.9, 119.8, 119.0, 110.3, 110.2, 109.4, 109.2, 60.1, 59.6, 32.7, 32.6, 16.6, 15.3, 14.1, 13.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}N_2O_3S$ $[M + H]^+$ 395.1429, found 395.1411.

(*E*/*Z*) Ethyl 2-benzamido-3-(methylthio)-3-(pyridin-3-yl)acrylate (120f). Obtained 

from oxazolone **114i** and sodium ethoxide, (*E*:*Z* = 35:65), off-white solid (0.273 g, 80%); mp 112-114 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3359, 2918, 1658, 1600, 1383, 1301, 1187, 715; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (d, *J* = 2.0 Hz, 0.35H), 8.43 (br d, *J* = 8.0 Hz, 0.43H), 8.32-8.29 (m, 1.45H), 8.16 (br d, *J* = 4.8 Hz, 0.45H), 8.04 (br t, *J* = 3.6 Hz, 1.34H), 7.96 (dd, *J* = 7.2 Hz, 3.6 Hz, 0.9H), 7.54 (br d, *J* = 8.0 Hz, 0.70H), 7.26-7.25 (m, 4.38H), 4.13 (q, *J* =

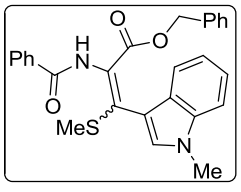
7.2 Hz, 0.7H), 3.72 (q, *J* = 7.2 Hz, 1.3H), 1.95 (s, 1.05H), 1.93 (s, 1.95H), 1.26 (t, *J* = 7.2 Hz, 1.05H), 0.78 (t, *J* = 7.2 Hz, 1.95H); ^{13}CNMR (100 MHz, DMSO-d_6) δ 168.0, 167.2, 150.8, 149.79, 149.76, 146.2, 144.2, 144.1, 141.3, 136.5, 136.4, 135.6, 128.5, 128.4, 128.3, 127.1, 126.93, 126.90, 126.87, 122.7, 122.2, 58.7, 58.6, 18.9, 15.6, 14.1, 13.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}N_2O_3S$ $[M + H]^+$ 343.1116, found 343.1123.

(*E*/*Z*) *n*-Butyl 2-benzamido-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)acrylate (120g).



Obtained from oxazolone **114h** and sodium *n*-butoxide, (*E*:*Z* = 45:55), white solid (0.290 g, 80%); mp 144-146 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3297, 2956, 2925, 1711, 1660, 1526, 1466, 1300, 1170, 742, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 0.55H), 7.93 (d, *J* = 7.2 Hz, 1H); 7.80 (d, *J* = 8 Hz, 0.55H), 7.62 (d, *J* = 8 Hz, 0.45H), 7.58-7.54 (m, 0.62H), 7.50-7.47 (m, 1.2H), 7.43-7.27 (m, 4.26H), 7.24-7.23 (m, 0.86H), 7.15 (td, *J* = 8 Hz, 0.8 Hz, 1H), 7.10 (s, 0.51H), 4.34 (t, *J* = 6.4 Hz, 0.9H), 3.90 (t, *J* = 6.4 Hz, 1.1H), 3.81 (s, 1.35H), 3.79 (s, 1.65), 2.0 (s, 1.35H), 1.98 (s, 1.65H), 1.74 (quin, *J* = 7.2 Hz, 0.9H), 1.45 (sex, *J* = 7.2 Hz, 0.9H), 1.14 (quin, *J* = 7.2 Hz, 1.1H). 0.94 (t, *J* = 7.2 Hz, 1.35H), 0.77 (sex, J = 7.2 Hz, 1.1H), 0.59 (t, *J* = 7.2 Hz, 1.65H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 164.8, 137.3, 137.2, 133.7, 133.4, 132.2, 131.8, 130.0, 129.5, 128.8, 128.6, 127.6, 127.4, 127.2, 125.9, 125.6, 124.1, 122.8, 122.6, 121.0, 120.5, 120.3, 120.2, 110.1, 109.7, 109.5, 65.4, 65.2, 33.3, 33.1, 30.7, 30.1, 19.4, 18.7, 17.0, 15.7, 13.9, 13.6; Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63. Found: C, 68.32; H, 6.17; N, 6.57.

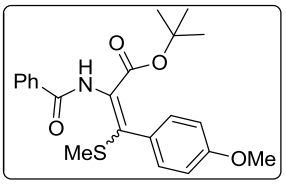
(*E*/*Z*) Benzyl 2-benzamido-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)acrylate (120h).



Obtained from oxazolone **114h** and sodium benzyloxide, (*E*:*Z* = 25:75), off-white solid (0.355 g, 80%); mp 138-140 °C; R_f 0.3 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3325, 3062, 2891, 1711, 1649, 1466, 1303, 1172, 720, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 0.73H), 7.94 (d, *J* = 7.2 Hz, 1.46H); 7.81 (d, *J* = 8 Hz, 0.73H), 7.62-7.55 (m, 1H), 7.55-7.45 (m, 2H), 7.42-7.26 (m, 4.72H), 7.18-7.027 (m, 1.71H), 7.05 (t, *J* = 7.6 Hz, 1.46H), 6.96 (s, 0.73H), 6.73 (d, *J* = 7.6 Hz, 1.46H), 5.38 (s, 0.54H), 4.97 (s, 1.46H), 3.8 (s, 0.81H), 3.58 (s, 2.19H), 1.98 (s, 0.81H), 1.97 (s, 2.19H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 164.8, 137.3, 137.2, 136.1, 135.6, 133.7, 133.5, 132.3, 131.8, 130.1, 129.7, 129.2, 128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 127.7, 127.6, 127.3, 127.2, 125.9, 124.8, 122.8, 122.6, 121.1, 120.6, 120.3, 120.1, 110.1, 109.7, 109.5, 109.4, 67.4, 66.9, 33.3, 33.0, 17.1,

15.7; Anal. Calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 70.77; H, 5.26; N, 6.24.

(*E*/*Z*) *t*-Butyl 2-benzamido-3-(4-methoxyphenyl)-3-(methylthio)acrylate (120i).



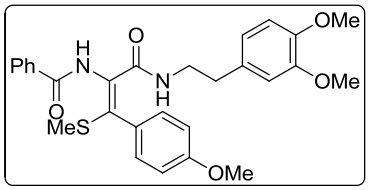
Obtained from oxazolone **114a** and sodium *t*-butoxide, (*E*:*Z* = 50:50), white solid (0.330 g, 90%); mp 165-167 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3212, 2977, 2925, 1689, 1646, 1506, 1256, 1160, 1021, 706; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 0.5H), 9.24 (s, 0.5H), 7.97 (d, *J* = 7.2 Hz, 1H); 7.59-7.56 (m, 1.5H), 7.52-7.45 (m, 1.5H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 1.5H), 3.73 (s, 1.5H), 1.87 (s, 1.5H), 1.77 (s, 1.5H), 1.43 (s, 4.5H), 1.09 (s, 4.5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 165.2, 163.6, 162.6, 159.4, 158.9, 149.3, 142.6, 134.1, 133.4, 131.8, 131.3, 130.1, 129.5, 128.4, 128.2, 128.1, 127.7, 127.67, 127.3, 124.9, 122.2, 113.8, 113.6, 80.4, 79.8, 55.3, 55.1, 27.8, 27.2, 16.1, 14.9; Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.15; H, 6.11; N, 3.71.

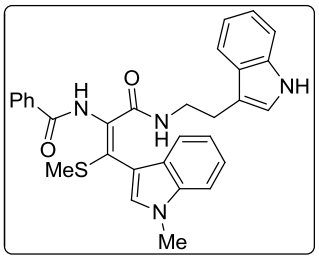
2.5.4 Nucleophilic ring opening of 2-phenyl 4-[(methylthio)(hetero)arylidene]-oxazole-5-ones 114 with amines and amino acid esters: General procedure for the synthesis of α-[(methylthio)(hetero)arylidene]-(*N*-benzoyl)-*N*-glycinamides 124a-l.

Procedure A: A solution of appropriate oxazolone **114** (0.9 mmol) and respective amine/amino acid ester (0.9 mmol) in EtOH (15 mL) was stirred at room temperature for 35-40 h (monitored by TLC). The ethanol was evaporated under reduced pressure, the residue triturated with diethyl ether to give **124** as white solids, which were filtered and crystallized (EtOAc) for characterization. The products **124a-d** and **124h** were obtained following this procedure either as pure stereoisomers or as *E/Z* mixtures. The product **124h** from oxazolone **114a** and phenylalanine ester was purified by column chromatography on silica gel to give single stereoisomer.

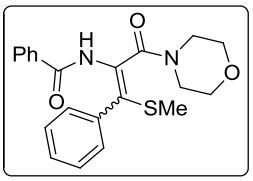
Procedure B: A solution of appropriate oxazolone **114** (0.9 mmol) and the corresponding amine/amino acid ester (0.9 mmol) in EtOH (15 mL) and trace of acetic acid (0.1 mL) was refluxed for 10-16 h (monitored by TLC) and worked up as in the procedure A. The product **124e** was separated as pure solid on trituration with diethyl ether, whereas products **124f-g**, **124i-k** were purified by column chromatography over silica gel using EtOAc:hexane as eluent. The open-chain precursor **124l** from oxazolone **124h** and serine

ethyl ester could not be purified by column chromatography and was used as such for Cu catalyzed cyclization without purification.

***N*-[1-(3,4-Dimethoxyphenethylamino)-3-(4-methoxyphenyl)-3-(methylthio)-1-oxoprop-2-en-2-yl]benzamide (124a).**  Obtained from the oxazolone **114a** and 3,4-dimethoxyphenylethylamine, (Procedure A) as single stereoisomer, white solid (0.373 g, 80%); mp 132-134 °C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3264, 2920, 1633, 1517, 1261, 1028, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 3H), 7.32-7.29 (m, 3H), 7.22 (d, *J* = 8.8 Hz, 2H); 6.87 (d, *J* = 8.8 Hz, 2H), 6.82-6.80 (br m, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 6.76 (dd, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.77 (s. 3H), 3.63 (q, *J* = 6.8 Hz, 2H), 2.87 (t, *J* = 6.8 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.4, 159.8, 149.1, 147.7, 141.5, 133.4, 132.0, 131.8, 129.9, 128.7, 127.6, 127.3, 125.4, 120.9, 114.5, 112.3, 111.5, 55.9, 55.4, 41.2, 35.2, 16.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{30}N_2O_5S$ $[M + H]^+$ 507.1954, found 507.1934.

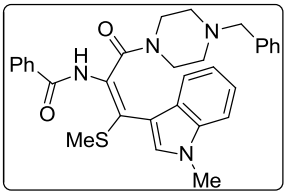
***N*-(1-(2-(1*H*-Indol-3-yl)ethylamino)-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)-1-oxoprop-2-en-2-yl)benzamide (124b).**  Obtained from oxazolone **114h** and tryptamine (Procedure A) as inseparable mixture of stereoisomers (*E*:*Z* = 55:45), pale yellow solid (0.402 g, 88%); mp 190-194 °C; R_f 0.4 (4:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3281, 2923, 2853, 1643, 1519, 1463, 1249, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 0.45H), 8.02 (br s, 0.55H), 7.95-7.92 (m, 0.9H), 7.88 (d, *J* = 7.6 Hz, 0.45H), 7.68 (d, *J* = 7.6 Hz, 0.55H), 7.59-7.45 (m, 2.0H), 7.37-7.25 (m, 4.8H), 7.25-7.01 (m, 6.85H), 6.76 (br t, J = 5.6 Hz, 0.55H), 6.02 (d, *J* = 2.4 Hz, 0.45H), 5.56 (br t, *J* = 5.6 Hz, 0.45H), 3.83 (q, *J* = 6.4 Hz, 1.1H), 3.76 (s, 1.65H), 3.51 (s, 1.45H), 3.43 (q, *J* = 6.4 Hz, 0.9H), 3.14 (t, *J* = 6.4 Hz, 1.1H), 2.49 (t, *J* = 6.4 Hz, 0.9H), 1.89 (s, 1.45H), 1.84 (s, 1.65H); ^{13}CNMR (100MHz, $CDCl_3$) δ 165.4, 164.9, 137.2, 137.1, 136.5, 136.4, 133.7, 133,6, 132.2, 131.8, 130.1, 129.8, 129.3, 128.8, 128.5, 127.7, 127.2, 127.1, 127.0, 122.7, 122.5, 122.1, 122.0, 121.9, 120.9, 120.5, 120.4, 120.2, 119.5, 119.3, 119.0, 118.6, 113.4, 112.3, 111.3, 110.1, 109.9, 109.7, 108.5, 40.2, 39.4, 33.3, 32.8, 25.1, 24.3, 16.8, 15.4; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_4O_2S$ $[M + H]^+$ 509.2011, found 509.2002.

***N*-(3-(Methylthio)-1-morpholino-1-oxo-3-phenylprop-2-en-2-yl)benzamide (124c).**



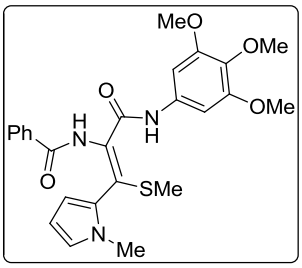
Obtained from oxazolone **114b** and morpholine (Procedure A) as inseparable mixture of stereoisomers (*E*:*Z* = 83:17), white solid (0.257 g, 75%); mp 186-188 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3256, 2921, 28.56, 1653, 1620, 1464, 1279, 1110, 1028, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 0.17H), 7.91 (d, *J* = 7.2 Hz, 0.34H), 7.54 (s, 0.83H), 7.52-7.32 (m, 9.66H), 3.88-3.78 (m, 8H), 1.99 (s, 0.51H), 1.93 (s, 2.49H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 164.2, 134.7, 133.0, 132.4, 132.3, 129.54, 129.49, 129.2, 128.9, 128.8, 128.7, 128.3, 127.60, 127.2, 125.6, 66.5, 66.4, 47.2, 42.1, 15.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{22}N_2O_3S$ $[M + Na]^+$ 405.1249, found 405.1220.

***N*-(1-(4-Benzylpiperazin-1-yl)-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)-1-oxoprop-2-en-2-yl)benzamide (124d).**



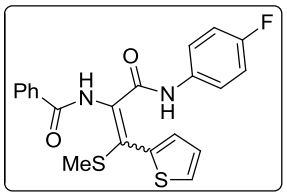
Obtained from oxazolone **114h** and N-benzylpiperazine (Procedure A) as single stereoisomer, white solid (0.384 g, 85%); mp 158-160 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3370, 2921, 2810, 1632, 1531, 1467, 1301, 741, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.94-7.92 (m, 3H), 7.56-7.46 (m, 3H), 7.36-7.28 (m, 2H), 7.18-7.14 (m, 5H); 7.11-7.09 (m, 2H), 3.78 (s, 3H), 3.54 (br s, 1H), 3.40 (br s. 2H), 3.19 (d, *J* = 12.4 Hz, 1H), 3.10 (d, *J* = 12.4 Hz, 1H), 3.01 (br s, 1H), 2.42 (br s, 1H), 2.13 (br s, 1H), 1.99 (s, 3H), 1.78 (br s, 1H), 1.09 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.3, 137.8, 137.2, 133.5, 132.1, 130.3, 129.2, 128.8, 128.3, 127.6, 127.2, 127.1, 122.6, 120.6, 120.2, 119.1, 109.7, 108.4, 62.9, 52.2, 51.8, 46.6, 41.4, 33.1, 15.6; Anal. Calcd for $C_{31}H_{32}N_4O_2S$: C, 70.96; H, 6.15; N, 10.68. Found: C, 71.04; H, 6.11; N, 10.63.

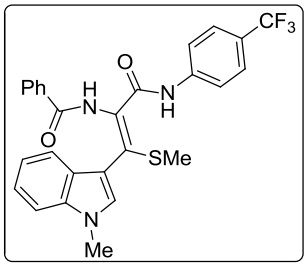
***N*-(3-(1-Methyl-1*H*-pyrrol-2-yl)-3-(methylthio)-1-oxo-1-(3,4,5 trimethoxyphenylamino) prop-2-en-2-yl)benzamide (124e).**

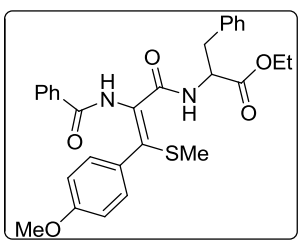


Obtained from oxazolone **114f** and 3,4,5-trimethoxyphenylamine (Procedure B) as single stereoisomer, white solid (0.387 g, 80%); mp 198-202 °C; R_f 0.4 (2:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3408, 3313, 2937, 1676, 1506, 1230, 1126, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 7.72 (br s, 1H), 7.53-7.51 (m, 2H), 7.49-7.45 (m, 1H), 7.36-7.33 (m, 2H); 6.9 (s, 2H), 6.68 (t, *J* = 2 Hz, 1H), 6.17 (d, *J* = 2 Hz, 2H), 3.82 (s, 6H), 3.79 (s, 3H), 3.52 (s. 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 162.9, 153.3, 134.9, 134.2, 132.9, 132.4, 128.8, 127.9, 127.8,

127.4, 125.1, 124.6, 110.6, 108.6, 97.9, 61.0, 56.2, 34.3, 15.83; HRMS (ESI) *m/z* calcd for $C_{25}H_{27}N_3O_5S$ $[M + H]^+$ 482.1750, found 482.1721.

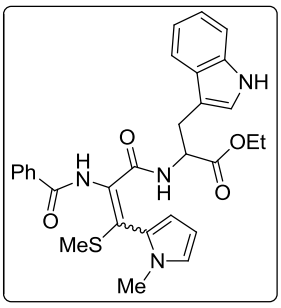
***N*-(1-(4-Fluorophenylamino)-3-(methylthio)-1-oxo-3-(thiophen-2-yl)prop-2-en-2-yl)benzamide (124f).**  Obtained from oxazolone **114e** and 4-fluorophenylamine (Procedure B) as inseparable mixture of stereoisomers (*E*:*Z* = 83:17), white solid (0.251 g, 68%); mp 178-180 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3257, 3069, 2923, 1649, 1620, 1508, 1479, 1211, 1096, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 0.76H), 8.27 (br s, 0.13H), 8.0 (s, 0.88H), 7.89 (d, *J* = 7.6 Hz, 0.3H), 7.67 (d, *J* = 7.6 Hz, 1.7H), 7.58 (dd, *J* = 8.4 Hz, 4.8 Hz, 1.8H), 7.51-7.48 (m, 1.3H), 7.4-7.36 (m, 2.9H), 7.16 (dd, *J* = 8.4 Hz, 4.8 Hz, 0.5H), 7.05 (dd, *J* = 5.2 Hz, 4.0 Hz, 0.95H), 6.99 (t, J = 8.8 Hz, 1.9H), 6.88 (t, J = 8.8 Hz, 0.34H), 2.14 (s, 2.5H), 2.12 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.2, 137.2, 132.5, 129.3, 128.8, 128.5, 128.4, 127.8, 127.7, 127.6, 127.4, 122.4, 122.3, 115.6, 115.4, 15.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}FN_2O_2S_2$ $[M + Na]^+$ 435.0613, found 435.0581.

***N*-(1-(1-Methyl-1*H*-indol-3-yl)-1-(methylthio)-3-oxo-3-(4-trifluoromethyl) phenylamino)prop-1-en-2-yl)benzamide (124g).**  Obtained from oxazolone **114h** and 4-(trifluoromethyl) phenylamine (Procedure B) as single stereoisomer, pale yellow solid (0.307 g, 70%); mp 210-212 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3249, 3065, 2927, 1646, 1543, 1322, 1116, 1066, 743; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.97-7.91 (m, 3H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.51-7.47 (m, 2H), 7.33-7.31 (m, 5H); 7.24 (s, 1H), 7.13 (s, 1H), 6.95 (br d, *J* = 8.0 Hz, 2H), 3.63 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 163.7, 140.9, 137.4, 133.2, 132.4, 130.0, 128.9, 128.6, 127.7, 127.6, 126.6, 125.9, 125.6, 123.3, 122.9, 121.3, 119.9, 119.2, 110.0, 108.2, 33.1, 15.5; Anal. Calcd for $C_{27}H_{22}F_3N_3O_2S$: C, 63.64; H, 4.35; N, 8.25. Found: C, 63.49; H, 4.25; N, 8.20.

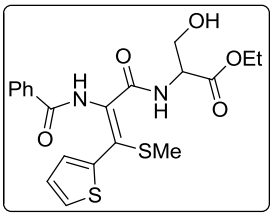
Ethyl 2-(2-benzamido-3-(4-methoxyphenyl)-3-(methylthio)acrylamido)-3-phenyl propanoate (124h).  Obtained from oxazolone **114a** and ethyl (α-benzyl)glycinate as (Procedure A) as single stereoisomer, white solid (0.382 g, 80%); mp 140-142 °C; R_f 0.3 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3440, 3195, 2975, 1731, 1642,

1504, 1244, 1076, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 3H), 7.35-7.31 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.21-7.16 (m, 6H), 7.10 (br s, 1H); 6.89 (d, J = 8.8 Hz, 2H), 5.0 (q, J = 6.0 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.22 (qd, J = 13.6 Hz, 6.4 Hz, 2H), 1.83 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 166.5, 164.5, 159.7, 143.8, 136.2, 133.5, 131.9, 129.7, 129.6, 128.6, 128.4, 127.7, 127.1, 126.9, 123.9, 114.4, 61.4, 55.3, 53.6, 38.1, 16.4, 14.0; Anal. Calcd for $C_{29}H_{30}N_2O_5S$: C, 67.16; H, 5.83; N, 5.40. Found: C, 67.0; H, 5.75; N, 5.49.

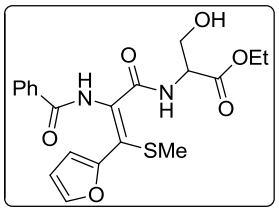
Ethyl 2-(2-benzamido-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)acrylamido)-3-(1*H*-indol-3-yl)propanoate (124i). Obtained from oxazolone **114f** and tryptophan ethyl ester (Procedure B) as inseparable mixture of stereoisomers (*E*:*Z* = 25:75), yellow solid (0.357 g, 75%); mp 84-86 °C; R_f 0.4 (4:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3325, 3056, 2924, 1734, 1648, 1508, 1472, 1304, 1198, 1096, 742, 712; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 0.75H), 8.04 (s, 0.75H), 7.90 (m, 1.5H), 7.58-7.44 (m, 3.6H), 7.40-7.27 (m, 2.5H), 7.16-6.97 (m, 3.4H), 6.64 (t, J = 2.0 Hz, 0.25H), 6.6 (br s, 0.75H), 6.09-6.03 (m, 2.5H), 5.06 (q, J = 5.6 Hz, 0.25H), 4.70 (q, J = 5.6 Hz, 0.75H), 4.15-3.89 (m, 2H), 3.52-3.42 (m, 3.5H), 3.07-3.05 (m, 1.5H), 1.83 (s, 2.25H), 1.77 (s, 0.75H), 1.16 (t, J = 7.2 Hz, 0.75H), 1.07 (t, J = 7.2Hz, 2.25H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 172.0, 171.7, 166.4, 165.1, 164.0, 163.4, 136.20, 136.16, 133.7, 133.5, 132.2, 132.1, 128.80, 128.78, 127.9, 127.7, 127.2, 126.3, 125.5, 124.7, 124.4, 124.2, 123.7, 123.2, 122.1, 122.0, 119.5, 118.9, 118.8, 112.2, 111.22, 111.18, 110.19, 110.15, 110.0, 108.4, 61.6, 61.4, 53.44, 53.40, 34.3, 34.1, 28.0, 27.7, 15.8, 14.8, 14.1, 14.0 ; HRMS (ESI) *m/z* calcd for $C_{29}H_{31}N_4O_4S$ $[M + H]^+$ 531.2066, found 531.2045.



Ethyl 2-(2-benzamido-3-(methylthio)-3-(thiophen-2-yl)acrylamido)-3-hydroxypropanoate (124j). Obtained from oxazolone **114e** and serine ethyl ester (Procedure B) as single stereoisomer, off-white solid (0.303 g, 70%); mp 100-102 °C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3403, 2977, 2918, 1735, 1640, 1518, 1467, 1283, 1193, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.52-7.51 (m, 1H), 7.46 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.39-7.36 (m, 2H), 7.28 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.11 (dd, J = 5.2 Hz, 3.6 Hz, 1H); 7.07 (br d, J = 6.8 Hz, 1H), 4.69 (ddd, J = 8 Hz, 3.2 Hz, 2,8 Hz, 1H), 4.42 (dd, J = 11.6 Hz, 2.8 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H),



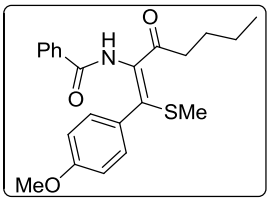
3.95 (br d, *J* = 11.6 Hz, 1H), 3.75 (br s, 1H), 2.17 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 165.1, 164.3, 138.3, 132.6, 132.4, 131.1, 129.3, 128.9, 128.7, 128.0, 127.6, 122.3, 62.2, 61.7, 56.0, 17.6, 14.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2O_5S_2$ $[M + H]^+$ 435.1048, found 435.1024.



Ethyl 2-(2-benzamido-3-(furan-2-yl)-3-(methylthio)acrylamido)-3-hydroxypropanoate (124k). Obtained from oxazolone **114g** and ethyl ester of serine (Procedure B) as single stereoisomer, off-white solid (0.308 g, 70%); mp 120-122 $^{\circ}$C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3411, 3307, 2918, 1734, 1653, 1513, 1271, 1013, 712; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (br s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.58-7.46 (m, 4H), 6.87 (d, *J* = 3.2 Hz, 1H), 6.83 (br d, *J* = 6.0 Hz, 1H), 6.56 (dd, *J* = 1.6 Hz, 1.2 Hz, 1H), 4.73 (dd, *J* = 3.0 Hz, 2.4 Hz, 1H), 4.54 (dd, *J* = 11.0 Hz, 2.4 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.96 (br d, *J* = 11.0 Hz, 1H), 3.83 (br s, 1H), 2.30 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 165.0, 164.4, 147.8, 144.0, 132.79, 132.75, 129.0, 128.9, 127.7, 127.6, 112.7, 111.7, 62.1, 61.7, 56.0, 16.1, 14.2; Anal. Calcd for $C_{20}H_{22}N_2O_6S$: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.52; H, 5.25; N, 6.63.

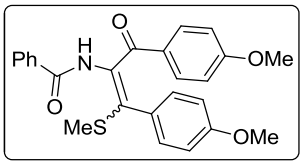
2.5.5 Nucleophilic ring opening of 2-phenyl 4-[(methylthio)(hetero)arylidene]-oxazole-5-ones 114 with Grignard reagents: General procedure for the synthesis of alkyl/(hetero)aryl-α-(N-benzoyl)-β-[(methylthio)(hetero)arylidene]ketones 129a-e. To a stirred, cooled (-20 $^{\circ}$C) solution of the corresponding 5-oxazolone **114** (2.0 mmol) in dry THF (10 mL), appropriate Grignard reagent (2.3 mmol) [freshly prepared from the corresponding alkyl/(hetero)aryl bromides (2.3 mmol) and magnesium metal (3.45 mmol) in 10 mL of THF] was added slowly with the help of syringe. The reaction mixture was further stirred for 2-3 h at -20 $^{\circ}$C (monitored by TLC), brought to room temperature and poured into satd. NH_4Cl solution (100 mL). It was then extracted with EtOAc (3 x 50 mL), washed with H_2O, brine (1 x 50 mL), the organic layer dried (Na_2SO_4) and evaporated under reduced pressure and the residue triturated with diethyl ether to give open-chain ketones **129a-e** as white solids.

***N*-(1-(4-Methoxyphenyl)-1-(methylthio)-3-oxohept-1-en-2-yl)benzamide (129a).**



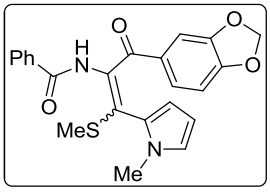
Obtained from oxazolone **114a** and *n*-butylmagnesium bromide as single stereoisomer, white solid (0.265 g, 75%); mp 150-152 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3307, 2956, 1651, 1466, 1250, 1034, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.57-7.54 (m, 1H), 7.51-7.46 (m, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 2.24 (t, *J* = 7.6 Hz, 2H), 1.95 (s, 3H), 1.43 (quin, *J* = 7.2 Hz, 2H), 1.08 (sex, *J* = 7.2 Hz, 2H), 0.719 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 160.5, 134.9, 133.2, 132.3, 131.4, 130.1, 128.9, 127.6, 127.3, 114.8, 114.5, 55.5, 42.1, 26.1, 22.2, 15.7, 13.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{25}NO_3S$ $[M + Na]^+$ 406.1453, found 406.1452.

***N*-[1,3-Bis(4-methoxyphenyl)-1-(methylthio)-3-oxoprop-1-en-2-yl]benzamide (129b).**



Obtained from oxazolone **114a** and (4-methoxyphenyl)magnesium bromide as inseparable mixture of *E/Z* stereoisomers (*E*:*Z* = 40:60), white solid (0.280 g, 70%); mp 82-84 °C; R_f 0.4 (5:5 EtOAc:hexane); IR (KBr, cm^{-1}) 3276, 2921, 2836, 1659, 1600, 1251, 1161, 1028, 837, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 0.4H), 8.15 (d, *J* = 8.8 Hz, 1.2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 0.8H), 7.75 (br s, 0.6H), 7.60-7.58 (m, 1.6H), 7.55 (d, *J* = 8.8 Hz, 1.2H), 7.49-7.44 (m, 1.2H), 7.35 (t, *J* = 7.6 Hz, 1.2H), 7.18 (d, *J* = 8.8 Hz, 0.8H), 7.01 (d, *J* = 8.8 Hz, 1.2H), 6.99 (d, *J* = 8.8 Hz, 1.2H), 6.70 (d, *J* = 8.8 Hz, 0.8H), 6.65 (d, *J* = 8.8 Hz, 0.8H), 3.88 (s, 2H), 3.87 (s, 2H), 3.7 (s, 1H), 3.69 (s, 1H), 2.0 (s, 1H), 1.74 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 163.3, 160.3, 159.8, 133.2, 132.6, 132.5, 132.3, 131.7, 131.6, 131.2, 131.1, 131.0, 128.9, 128.8, 127.7, 127.5, 126.9, 114.9, 113.9, 113.4, 55.6, 55.5, 55.4, 55.3, 16.1, 15.9; HRMS (ESI) *m/z* calcd for $C_{25}H_{23}NO_4S$ $[M + Na]^+$ 456.1245, found 456.1244.

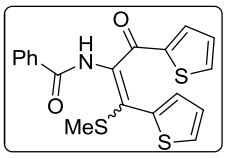
***N*-(1-(Benzo[d][1,3]dioxol-5-yl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)-1-oxoprop-2-en-2-yl)benzamide (129c).**



Obtained from oxazolone **114f** and 3,4-methylenedioxyphenylmagnesium bromide (*E*:*Z* = 86:14), off-white solid (0.688 g, 82%); mp 180-182 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3281, 3059, 2918, 2842, 1658, 1605, 1505, 1467, 1288, 1244, 703 ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 0.86H), 8.21 (s, 0.14H), 7.1-7.88 (m, 1.72H), 7.9 (dd, *J* = 8.0 Hz, 106 Hz, 0.14H), 7.60-7.58 (m, 0.6H), 7.55-7.53 (m, 0.75H), 7.49-7.45 (m, 1.93H), 7.41 (dd, *J* = 8.0 Hz, 1.6 Hz, 0.86H), 7.38-

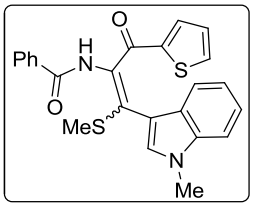
7.35 (m, 0.14H), 7.27 (d, *J* = 1.6 Hz, 0.86H), 6.88 (d, *J* = 8.0 Hz, 0.14H), 6.81 (dd, *J* = 2.0 Hz, 1.6 Hz, 0.14H), 6.69 (d, *J* = 8.0 Hz, 0.86H), 6.45 (dd, *J* = 2.4 Hz, 1.6 Hz, 0.86H), 6.39 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.14H), 6.25 (dd, *J* = 3.6 Hz, 2.4 Hz, 0.14H), 6.04 (s, 0.28H), 5.97 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.86H), 5.94 (s, 1.72H), 5.83 (dd, *J* = 3.6 Hz, 2.4 Hz, 0.86H), 3.72 (s, 0.42H), 3.59 (s, 2.58H), 1.95 (s, 2.58H), 1.81 (s, 0.42H); ^{13}CNMR (100MHz, $CDCl_3$) δ 190.2, 164.3, 163.3, 151.8, 151.0, 148.3, 147.5 , 135.7, 135.2, 132.8, 132.5, 132.4, 132.3, 128.9, 127.7, 127.5, 125.6, 125.3, 125.2, 125.1, 124.7, 121.2, 116.4, 116.2, 112.1, 108.7, 108.62, 108.58, 108.2, 108.1, 107.3, 101.9, 101.7, 35.0, 34.5, 16.3, 15.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_2O_4S$ $[M + H]^+$ 421.1222, found 421.1200.

***N*-(1-(Methylthio)-3-oxo-1,3-di(thiophen-2-yl)prop-1-en-2-yl)benzamide (129d).**



Obtained from oxazolone **114e** and (2-thienyl)magnesium bromide as inseparable mixture of *E*/*Z* stereoisomers (*E*:*Z* = 13:87), yellow solid (0.318 g, 83%); mp 162-164 $^{\circ}$C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3281, 3085, 2918, 1658, 1625, 1515, 1473, 1413, 1269, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 0.13H), 8.18 (br s, 0.87H), 7.91-7.88 (m, 0.26H), 7.86 (dd, *J* = 3.6 Hz, 1.2Hz, 0.87H), 7.72-7.70 (m, 1.74H), 7.64 (dd, J = 5.0 Hz, 1.2 Hz, 0.87H), 7.56-7.46 (m, 2.53H), 7.42-7.38 (m, 2.6H), 7.16 (dd, *J* = 4.2 Hz, 4.0 Hz, 0.87H), 7.14 (dd, *J* = 4.2 Hz, 3.6 Hz, 0.87H), 6.99 (dd, *J* = 3.6 Hz, 1.2 HZ, 0.13H), 6.91 (dd, *J* = 4.8 Hz, 4.0 Hz, 0.13H), 6.75 (dd, *J* = 5.0 Hz, 4.0 Hz, 0.13H), 2.71 (s, 0.39H), 1.98 (s, 2.61H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 164.0, 163.9, 144.7, 143.5, 138.8, 134.3, 133.8, 133.7, 133.2, 132.6, 132.5, 132.2, 130.5, 129.1, 128.9, 128.8, 128.7, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 119.9, 17.54, 16.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}NO_2S_3$ $[M + Na]^+$ 408.0163, found 408.0161.

***N*-[3-(1-Methyl-1*H*-indol-3-yl)-3-(methylthio)-1-oxo-1-(thiophen-2-yl)prop-2-en-2-yl] benzamide (129e).**

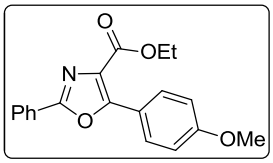


Obtained from oxazolone **114h** and 2-thienylmagnesium bromide (*E*:*Z* = 17:83), pale yellow solid (0.604 g, 70%); mp 160-163 $^{\circ}$C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 3364, 2918, 1660, 1632, 1530, 1464, 1303, 1263, 742, 708 ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 0.83H), 9.76 (s, 0.17H), 8.0 (d, *J* = 7.2 Hz, 1.66H), 7.85 (dd, *J* = 6.6 Hz, 4.8 Hz, 0.37H), 7.74 (d, *J* = 7.2 Hz, 1.06H), 7.60-7.57 (m, 1.3H), 7.53-7.42 (m, 4H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.22 (s, 0.83H), 7.19-7.15 (m, 1H), 7.08 (t, *J* = 7.2 Hz, 0.83H), 6.99 (t, *J* = 7.2 Hz, 0.17H), 6.68 (dd, *J* = 4.8 Hz, 4.0 Hz, 0.83H), 3.87 (s, 0.51H), 3.64 (s, 2.49H), 2.05 (s, 2.49H), 1.85 (s, 0.51H); ^{13}CNMR

(100MHz, DMSO-d_6) δ 184.6, 184.2, 165.3, 164.8, 145.5, 144.0, 137.3, 136.9, 135.2, 133.1, 133.0, 132.6, 132.4, 132.2, 131.9, 131.8, 131.5, 131.4, 131.3, 129.5, 129.1, 128.4, 128.1, 128.0, 127.69, 127.65, 127.6, 126.9, 126.3, 125.6, 122.0, 121.7, 120.1, 120.0, 119.9, 119.5, 110.4, 110.1, 109.6, 109.2, 32.8, 32.4, 16.2, 15.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}N_2O_2S_2$ $[M + Na]^+$ 455.0864, found 455.0862.

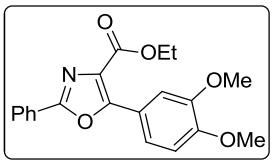
2.5.6 General procedure for copper catalyzed intramolecular cyclization of open-chain precursors 120a-i, 124a-l and 129a-e: Synthesis of 2-phenyl-5-(hetero)aryl-4-substituted oxazoles 121a-i, 125a-l and 130a-e. To a stirred solution of the corresponding open-chain precursors **120**, **124** or **129** (1.0 mmol) in DMF (3 mL) were added CuI (19 mg, 0.1 mmol), 1,10-phenanthroline (36 mg, 0.2 mmol) and Cs_2CO_3 (32 mg, 1.0 mmol) and the reaction mixture was heated at 90 °C with stirring for 2-3 h (monitored by TLC). It was then poured into ice-cold water (20 mL), extracted with EtOAc (3 x 10 mL), washed with brine (1 x 10 mL), dried over Na_2SO_4 followed by removal of the solvent to give crude oxazoles, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

Ethyl 5-(4-methoxyphenyl)-2-phenyloxazole-4-carboxylate (121a). Obtained from



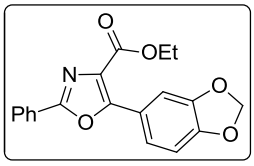
enamide **120a**, white solid (160 mg, 92%); mp 148-149 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1715, 1505, 1212, 1091, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.15 (m, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.49-7.48 (m, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.46 (q, *J* = 7.21 Hz, 2H), 3.87 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 161.3, 159.4, 155.6, 131.0,130.4, 128.9, 127.3, 126.9, 126.7, 119.9, 114.0, 61.5, 55.6, 14.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NO_4$ $[M + Na]^+$ 346.1055, found 346.1051.

Ethyl 5-(3,4-dimethoxyphenyl)-2-phenyloxazole-4-carboxylate (121b).[64] Obtained



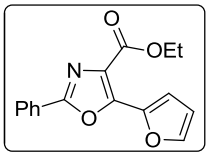
from enamide **120b**, white solid (154 mg, 88%); mp 165-166 °C (lit. 165-166 °C)[64]; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3030, 2836, 1711, 1513, 1259, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.14 (m, 2H), 7.88 (d, *J* = 2 Hz, 1H), 7.76 (dd, *J* = 8.6 Hz, 2 Hz, 1H), 7.49 (m, 3H), 6.98 (d, *J* = 8.6 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.1, 155.2, 150.8, 148.7, 130.9, 128.8, 127.3, 126.8, 126.5, 121.9, 119.9, 111.8, 110.8, 61.39, 56.12, 55.99, 14.39; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}NO_5$ $[M + Na]^+$ 376.1161, found 376.1161.

Ethyl 5-(benzo[d][1,3]dioxol-5-yl)-2-phenyloxazole-4-carboxylate (121c). Obtained



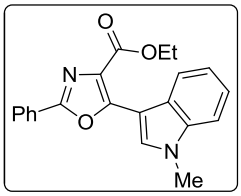
from enamide **120c**, pale yellow solid (157 mg, 90%); mp 168-170 °C; R_f 0.6 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 2982, 1711, 1493, 1252, 1211, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 7.73 (dd, J = 8.3 Hz, 1.6 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.49-7.48 (m, 3H), 6.93 (d, J = 8.3 Hz, 1H), 6.05 (s, 1H), 4.46 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 159.4, 155.1, 149.5, 147.8, 131.1, 128.9, 127.6, 126.9, 126.6, 123.7, 121.2, 108.9, 108.5, 101.8, 61.6, 14.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}NO_5$ $[M + Na]^+$ 360.0848, found 360.0849.

Ethyl 5-(furan-2-yl)-2-phenyloxazole-4-carboxylate (121d). Obtained from enamide



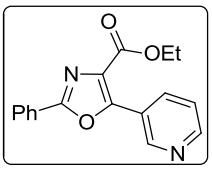
120d, white solid (157 mg, 92%); mp 136-138 °C; R_f 0.7 (1:5 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1715, 1339, 1256, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.16 (m, 2H), 7.66-7.64 (m, 2H), 7.50-7.47 (m, 3H), 6.61(dd, J = 3.6 Hz, 2 Hz, 1H), 4.49 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 159.7, 147.0, 144.6,142.5, 131.3, 128.9, 127.1, 126.9, 126.4, 115.6, 112.5, 61.6, 14.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}NO_4$ $[M + Na]^+$ 306.0742, found 306.0746.

Ethyl 5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxylate (121e). Obtained



from enamide **120e**, white solid (160 mg, 90%); mp 186-188 °C; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1708, 1570, 1218, 1085, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.34-8.31 (m, 1H), 8.22 (dd, J = 8 Hz, 1.6 Hz, 2H), 7.56-7.50 (m, 3H), 7.44-7.35 (m, 3H), 4.51(q, J = 6.8 Hz, 2H), 3.91 (s, 3H), 1.49 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 157.9, 154.9, 137.1, 134.2, 130.7, 128.9, 127.1, 126.8, 126.1, 124.4, 123.1, 121.7, 121.6, 110.1, 102.9, 61.2, 33.6, 14.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}N_2O_3$ $[M + Na]^+$ 369.1215, found 369.1216.

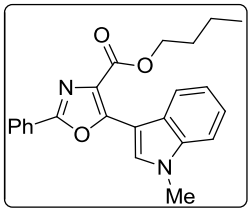
Ethyl 2-phenyl-5-(pyridin-3-yl)oxazole-4-carboxylate (121f). Obtained from enamide



120f, white solid (145 mg, 90%); mp 96-98 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 2983, 2926, 1715, 1218, 1098, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (br s, 1H), 8.71 (d, J = 2.4 Hz, 1H), 8.54 (d, J = 8 Hz, 1H), 8.18-8.16 (m, 2H), 7.53-7.49 (m, 3H), 7.48-7.45 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 160.9,

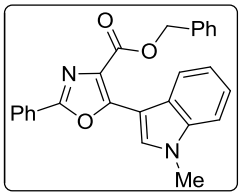
152.2, 151.1, 149.5, 136.2, 131.6, 130.0, 129.0, 127.2, 126.2, 124.0, 123.5, 61.9, 14.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N_2O_3$ $[M + Na]^+$ 317.0902, found 317.0903.

***n*-Butyl 5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxylate (121g).** Obtained



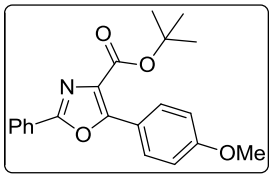
from enamide **120g**, white solid (160 mg, 90%); mp 144-145 °C; R_f 0.7 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2996, 2867, 1693, 1567, 1220, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.33-8.31 (m, 1H), 8.22 (d, J = 6.8 Hz, 2H), 7.55-7.49 (m, 3H), 7.42-7.35 (m, 3H), 4.44 (t, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.87 (quint, J = 7.2 Hz, 2H), 1.50 (quint, J = 7.2 Hz, 2H), 1.0 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 157.9, 154.8, 137.0, 134.1, 130.6, 128.9, 127.1, 126.7, 126.1, 124.5, 123.1, 121.7, 121.5, 110.1, 103.0, 65.1, 33.6, 31.1, 19.4, 13.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_2O_3$ $[M + Na]^+$ 397.1528, found 397.1529.

Benzyl 5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxylate (121h). Obtained



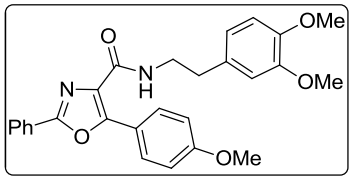
from enamide **120h**, white solid (160 mg, 91%); mp 178-180 °C; R_f 0.7 (1:2.3 EtOAc:hexane); IR (KBr, cm^{-1}) 2942, 1691, 1247, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.32-8.29 (m, 1H), 8.22 (d, J = 6.4 Hz, 2H), 7.54-7.49 (m, 5H), 7.42-7.34 (m, 6H), 5.50 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 158.0, 154.9, 136.9, 136.3, 134.2, 130.6, 128.9, 128.7, 128.5, 128.3, 127.0, 126.7, 126.1, 124.2, 123.1, 121.7, 121.5, 110.1, 102.8, 66.7, 33.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{20}N_2O_3$ $[M + Na]^+$ 431.1372, found 431.1373.

***t*-Butyl 5-(4-methoxyphenyl)-2-phenyloxazole-4-carboxylate (121i).** Obtained from



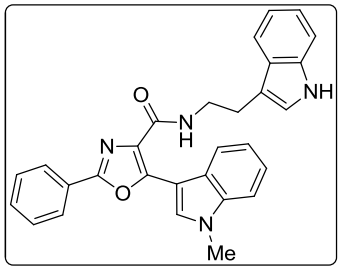
enamide **120i**, white solid (140 mg, 80%); mp 90-92 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2985, 1711, 1501, 1366, 1253, 837; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16-8.13 (m, 2H), 7.99 (d, J = 9.2 Hz, 2H), 7.49-7.47 (m, 3H), 7.01 (d, J = 9.2 Hz, 2H), 3.89 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 161.2, 159.4, 154.7, 131.1, 131.6, 128.9, 128.2, 126.9, 126.6, 119.9, 113.9, 82.7, 55.6, 28.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NO_4$ $[M + Na]^+$ 374.1368, found 374.1369.

***N*-(3,4-Dimethoxyphenethyl)-5-(4-methoxyphenyl)-2-phenyloxazole-4-carboxamide**



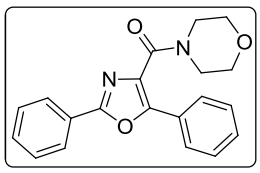
(125a). Obtained from enamide **124a**, white solid (140 mg, 80%); mp 138-140 °C; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3336, 2913, 2838, 1643, 1529, 1255, 836, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 2H), 8.06-8.04 (m, 2H), 7.53-7.48 (m, 4H), 7.01 (d, J = 10 Hz, 2H), 6.84-6.81 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.69 (q, J = 6.8, 2 Hz, 2H), 2.91 (t, J = 6.8 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.0, 157.9, 152,6, 149.2, 147.8, 131.8, 130.9, 130.1, 129.3, 129.0, 126.8, 126.6, 120.9, 120.1, 113.9, 112.2, 111.6, 56.1, 55.9, 55.5, 40.9, 35.8; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}N_2O_5$ $[M + Na]^+$ 481.1739, found 481.1738.

***N*-[2-(1*H*-indol-3-yl)ethyl]-5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxamide**

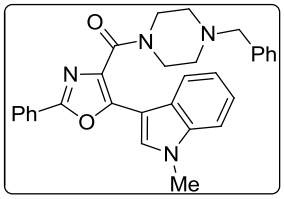


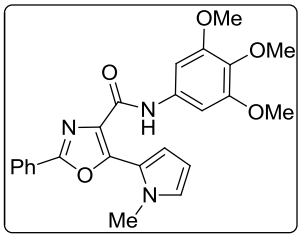
(125b). Obtained from enamide **124b**, grey solid (135 mg, 75%); mp 202-205 °C; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3395, 3260, 2925, 1637, 1504, 1583, 1290, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.34-8.32 (m, 1H), 8.10 (dd, J = 6.6 Hz, 1.2 Hz, 2H), 8.05 (br s, 1H), 7.72 (br d, J = 8 Hz, 1H), 7.55-7.47 (m, 4H), 7.42-7.38 (m, 2H), 7.35-7.33 (m, 2H), 7.24-7.21 (m, 1H), 7.18-7.14 (m, 2H), 3.9 (s, 3H), 3.84 (q, J = 7.2 Hz, 2H), 3.16 (t, J = 7.2 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 156.9, 151.5, 137.1, 136.5, 134.3, 130.4, 129.0, 128.7, 127.6, 127.3, 126.8, 126.4, 126.1, 122.8, 122.3, 122.2, 121.4, 121.3, 119.7, 119.1, 113.6, 111.3, 110.0, 39.8, 33.5, 25.9.; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_2$ $[M + Na]^+$ 483.1797, found 483.1798.

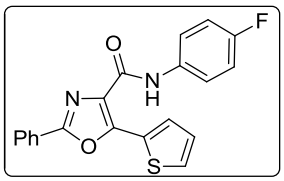
(2,5-Diphenyloxazol-4-yl)(morpholino)methanone (125c). Obtained from enamide

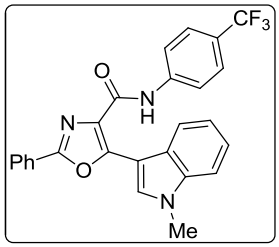


124c, white solid (143 mg, 82%); mp 152-154 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2956, 1639, 1492, 1231, 1110, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.10 (m, 2H), 7.89 (br d, J = 7.6 Hz, 2H), 7.50-7.38 (m, 6H), 3.83 (dd, J = 17.6 Hz, 4.8 Hz, 4H), 3.63 (d, J = 2.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 159.8, 150.1, 131.0, 130.5, 129.6, 129.0,127.3, 126.8, 126.7, 126.4, 67.1, 66.9, 47.7, 42.7; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2O_3$ $[M + Na]^+$ 357.1215, found 357.1217.

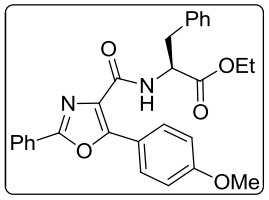
(4-Benzylpiperazin-1-yl)[5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazol-4-yl]methanone (125d).  Obtained from enamide **124d**, off-white solid (158 mg, 87%); mp 160-162 °C; R_f 0.45 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 2909, 2802, 1624, 1442, 1228, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.21 (d, J = 6.8 Hz, 1H), 8.14 (d, J = 6.8, Hz, 2H), 7.54-7.47 (m, 3H), 7.40-7.29 (m, 8H), 3.94 (br s, 2H), 3.87 (s, 3H), 3.85 (br s, 2H), 3.55 (s, 2H), 2.58 (br s, 2H), 2.52 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 157.3, 151.4, 137.9, 137.1, 132.1, 131.1, 130.4, 129.3, 129.0, 128.5, 127.6, 127.5, 127.4, 126.3, 126.0, 122.8, 121.2, 121.1, 109.9, 103.2, 63.1, 53.7, 53.1, 47.5, 42.7, 33.4; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_4O_2$ $[M + Na]^+$ 499.2110, found 499.2113.

5-(1-Methyl-1*H*-pyrrol-2-yl)-2-phenyl-*N*-(3,4,5-trimethoxyphenyl)oxazole-4-carboxamide (125e).  Obtained from enamide **124e**, white solid (147 mg, 82%); mp 198-200 °C; R_f 0.5 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3369, 2942, 1679, 1607, 1235, 1120, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (br s, 1H), 8.11-8.03 (m, 2H), 7.52 (m, 3H), 7.3 (dd, J = 4 Hz, 2 Hz 1H), 7.04 (s, 2H), 6.84 (dd, J = 2.8 Hz, 2 Hz, 1H), 6.16 (dd, J = 4 Hz, 2.8 Hz, 1H), 3.90 (s, 6H), 3.89 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.1, 153.5, 147.1, 134.8, 134.2, 131.2, 129.5, 129.2, 127.3, 126.6, 119.9, 116.8, 109.1, 97.7, 97.6, 61.1, 56.4, 36.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_3O_5$ $[M + Na]^+$ 456.1535, found 456.1532.

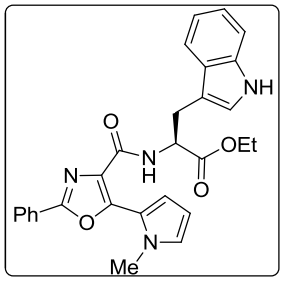
***N*-(4-Fluorophenyl)-2-phenyl-5-(thiophen-2-yl)oxazole-4-carboxamide (125f).**  Obtained from enamide **124f**, white solid (140 mg, 82%); mp 142-144 °C; R_f 0.6 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3355, 2924, 1725, 1538, 1217, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.29 (d, J = 3.6 Hz, 1H), 8.14-8.11 (m, 2H), 7.74-7.70 (m, 2H), 7.54 (m, Hz, 4H), 7.19 (t, J = 4.8 Hz, 1H), 7.08 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.84, 159.4, 158.4, 158.1, 149.3, 133.89, 133.86, 131.4, 130.3, 129.6, 129.2, 128.8, 128.1, 128.0, 126.9, 126.3, 121.9, 121.8, 116.0, 115.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{13}FN_2O_2S$ $[M + Na]^+$ 387.0579, found 387.0577.

5-(1-Methyl-1*H*-indol-3-yl)-2-phenyl-*N*-[4-(trifluoromethyl)phenyl]oxazole-4-carboxamide (125g). 

Obtained from enamide **124g**, white solid (153 mg, 85%); mp 258-260 °C; R_f 0.8 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3351, 2942, 1673, 1581, 1326, 1114, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 9.02 (s, 1H), 8.36-8.33 (m, 1H), 8.21 (m, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.59-7.54 (m, 3H), 7.45-7.36 (m, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 156.9, 153.1, 141.4, 137.2, 134.7, 130.8, 129.2, 126.9, 126.5, 126.46, 126.43, 126.39, 126.1, 125.9, 123.1, 121.7, 121.5, 119.5, 110.2, 102.9, 33.6; HRMS (ESI) *m/z* calcd for $C_{26}H_{18}F_3N_3O_2$ $[M + Na]^+$ 484.1249, found 484.1249.

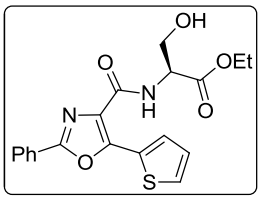
(2*S*)-Ethyl 2-[5-(4-Methoxyphenyl)-2-phenyloxazole-4-carboxamido]-3-phenylpropanoate (125h). 

Obtained from enamide **124h**, white solid (132 mg, 73%); mp 78-80 °C; R_f 0.5 (1:1 EtOAc:hexane); $[\alpha]_D^{25}$ = +29.5 (*c*, 0.40, $CHCl_3$); IR (KBr, cm^{-1}) 3403, 2926, 1735, 1665, 1511, 1256, 1180, 709; 1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 6.8 Hz 2H), 8.10-8.07 (m, 2H), 7.85 (br d, *J* = 8.0 Hz, 1H), 7.50-7.49 (m, 3H), 7.33-7.24 (m, 5H), 6.99 (d, *J* = 6.8 Hz, 2H), 5.04 (dt, *J* = 8.0 Hz, 6.0 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.27 (d, *J* = 6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 161.4, 161.1, 158.0, 152.9, 136.3, 132.4, 130.9, 130.1, 129.6, 128.9, 128.7, 127.2, 126.8, 126.7, 120,1, 114.0, 61.6, 55.5, 53.4, 38.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}N_2O_5$ $[M + Na]^+$ 493.1739, found 493.1736.

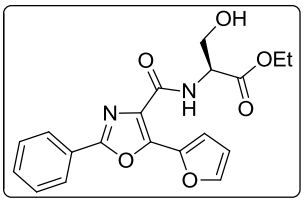
(2*S*)-Ethyl 3-(1*H*-indol-3-yl)-2-(5-(1-methyl-1*H*-pyrrol-2-yl)-2-phenyloxazole-4-carboxamido)propanoate (125i). 

Obtained from enamide **124i**, white solid (125 mg, 70%); mp 94-96 °C; R_f 0.5 (1:2 EtOAc:hexane); $[\alpha]_D^{25}$ = +31.4 (*c*, 0.58, $CHCl_3$); IR (KBr, cm^{-1}) 3385, 3268, 3056, 2926, 1736, 1661, 1529, 1235, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.96 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.48-7.45 (m, 3H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 4 Hz, 1.6 Hz, 1H), 7.20 (t, 7.2 Hz, 1H), 7.12-7,10 (m, 2H), 6.79 (dd, *J* = 2.8 Hz, 1.6 Hz, 1H), 6.24 (dd, J = 4 Hz, 2.8 Hz, 1H), 5.08 (dt, *J* = 8 Hz, 2.8 Hz, 1H), 4.18-4.10 (m, 2H), 3.82 (s, 3H), 3.43 (dd, *J* = 5.6 Hz, 2.0 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 160.9, 158.2, 146.5, 136.3, 130.9, 129.4, 128.9, 127.9, 126.9, 126.8, 126.6, 122.9, 122.3, 120.0, 119.8, 119.1, 116.4, 111.3, 110.6, 108.9, 61.6, 52.9,

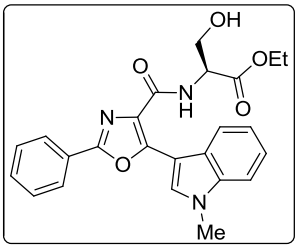
36.5, 28.1, 14.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}N_4O_4$ [M + H]$^+$ 483.2032, found 483.2033.

(2*S*)-Ethyl 3-hydroxy-2-[2-phenyl-5-(thiophen-2-yl)oxazole-4-carboxamido]propanoate (125j). 

Obtained from enamide **124j**, off-white solid (133 mg, 75%); mp 194-196 °C; R_f 0.55 (1:1 EtOAc:hexane); $[\alpha]_D^{25}$ = +20.0 (*c*, 0.55, $CHCl_3$); IR (KBr, cm^{-1}) 3384, 3332, 2956, 1740, 1640, 1531, 1269, 1058, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 4 Hz, 1.2 Hz, 1H), 8.13-8.06 (m, 2H), 8.07 (br d, *J* = 7.2 Hz, 1H), 7.52-7.50 (m, 4H), 7.16 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 4.88 (dt, 7.2 Hz, 4.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.11 (dd, *J* = 4.4 Hz, 4.0 Hz, 2H), 2.61 (br s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 161.9, 158.3, 149.0, 131.3, 130.1, 129.4, 129.1, 128.8, 127.9, 127.8, 126.8, 126.3, 63.9, 62.2, 55.0, 14.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2O_5S$ [M + Na]$^+$ 409.0834, found 409.0833.

(2*S*)-Ethyl 2-[5-(furan-2-yl)-2-phenyloxazole-4-carboxamido]-3-hydroxypropanoate (125k). 

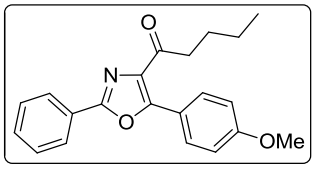
Obtained from enamide **124k**, off-white solid (129 mg, 73%); mp 166-168 °C; R_f 0.5 (1:1 EtOAc:hexane); $[\alpha]_D^{25}$ = +35.8 (*c*, 0.30, $CHCl_3$); IR (KBr, cm^{-1}) 3378, 3331, 2926, 1722, 1647, 1555, 1264, 1064, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 2H), 8.06 (br d, *J* = 7.2 Hz, 1H), 7.81 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 7.62 (dd, *J* = 2 Hz, 0.8 Hz, 1H), 7.51-7.49 (m, 3H), 6.51 (dd, *J* = 3.6 Hz, 2 Hz, 1H), 4.85 (dt, *J* = 7.6 Hz, 4 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.10 (d, *J* = 4.0 Hz, 2H), 2.63 (br s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 161.6, 158.8, 144.8, 144.4, 142.6, 131.3, 129.1, 128.5, 126.9, 126.4, 115.59, 112.6, 64.1, 62.2, 55.1, 14.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2O_6$ [M + Na]$^+$ 393.1063, found 393.1061.

(2*S*)-Ethyl 3-hydroxy-2-[5-(1-methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxamido]propanoate (125l). 

Obtained from enamide **124l**, off-white solid (125 mg, 70%); mp 184-186 °C; R_f 0.5 (1:1 EtOAc:hexane); $[\alpha]_D^{25}$ = -27.0 (*c*, 0.18, $CHCl_3$); IR (KBr, cm^{-1}) 3381, 3355, 2922, 1738, 1637, 1587, 1208, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.32-8.29 (m, *J* = 1H), 8.17 (dd, *J* = 8.2 Hz, 1.2 Hz, 2H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.56-7.45 (m, 3H), 7.41-7.38 (m, 3H), 4.88 (dt, *J* = 7.2 Hz, 4 Hz,1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.12-4.11 (dd, *J* = 3.6 Hz, 1.6 Hz, 2H), 3.89 (s, 3H), 2.95 (br s, 1H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

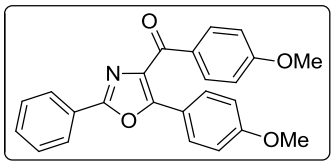
170.6, 163.0, 157.1, 152.3, 137.1, 134.4, 130.6, 129.6, 127.0, 126.5, 125.96, 125.93, 122.9, 121.51, 121.45, 110.1, 102.9, 64.3, 62.2, 55.2, 33.6, 14.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_3O_5$ $[M + Na]^+$ 456.1535, found 456.1533.

1-[5-(4-Methoxyphenyl)-2-phenyloxazol-4-yl]pentan-1-one (130a). Obtained from



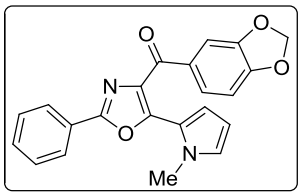
enamide **129a**, white solid (157 mg, 90%); mp 78-80 °C; R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2925, 1679, 1496, 1255, 830, 706; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.2 Hz, 2H), 8.14-8.11 (m, 2H), 7.51-7.49 (m, 3H), 7.01 (d, *J* = 9.2 Hz, 2H), 3.89 (s, 3H), 3.15 (t, J = 7.6 Hz, 2H), 1.78-1.70 (m, 2H), 1.49-1.40 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 161.5, 158.1, 153.5, 134.4, 130.9, 130.1, 129.0, 127.0, 126.7, 120.2, 114.0, 55.5, 40.7, 26.4, 22.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NO_3$ $[M + Na]^+$ 358.1419, found 358.1418.

(4-Methoxyphenyl)[5-(4-methoxyphenyl)-2-phenyloxazol-4-yl]methanone (130b).



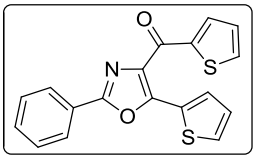
Obtained from enamide **129b**, white solid (163 mg, 92%); mp 114-116 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2967, 1648, 1579, 1240, 707; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 8.16-8.13 (m, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.49 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.3, 163.7, 161.2, 158.4, 154.7, 134.3, 133.2, 130.9, 130.7, 129.7, 129.0, 127.0, 126.8, 120.3, 114.1, 113.6, 55.6, 55.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{19}NO_4$ $[M + Na]^+$ 408.1212, found 408.1212.

Benzo[*d*][1,3]dioxol-5-yl[5-(*N*-methyl-1*H*-pyrrol-2-yl)-2-phenyloxazol-4-



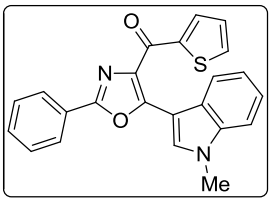
yl]methanone (130c). Obtained from enamide **129c**, brown solid (160 mg, 90%); mp 82-84 °C; R_f 0.6 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2918, 1646, 1613, 1486, 1250, 709; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11-8.10 (m, 2H), 7.95 (dd, *J* = 8.2 Hz, 1.6 Hz, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.50 (m, 3H), 7.15 (dd, *J* = 4 Hz, 2.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.84 (dd, *J* = 2.4 Hz, 1.2 Hz, 1H), 6.25 (dd, *J* = 4 Hz, 1.2 Hz, 1H), 6.06 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 158.3, 151.7, 149.0, 147.8, 134.8, 132.4, 131.0, 129.1, 127.4, 127.3, 127.0, 126.7, 120.5, 116.4, 110.5, 108.9, 107.9, 101.8, 36.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}N_2O_4$ $[M + Na]^+$ 395.1008, found 395.1007.

[2-Phenyl-5-(thiophen-2-yl)oxazol-4-yl](thiophen-2-yl)methanone (130d). Obtained



from enamide **129d**, yellow solid (160 mg, 92%); mp 164-166 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2918, 1613, 1410, 1047, 703; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, J = 4 Hz, 1.2 Hz, 1H), 8.29 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 8.19-8.16 (m, 2H), 7.74 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.56 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.54-7.52 (m, 3H), 7.23 (dd, J = 5.2 Hz, 4.0 Hz, 1H), 7.21 (dd, J = 4.8 Hz, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 158.2, 151.8, 143.2, 135.9, 135.1, 132.9, 131.2, 130.6, 130.2, 129.3, 129.1, 128.1, 128.0, 127.0, 126.5; HRMS (ESI) *m/z* calcd for $C_{18}H_{11}NO_2S_2$ $[M + Na]^+$ 360.0129, found 360.0133.

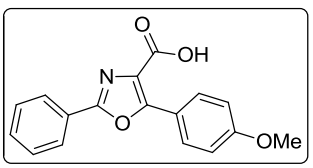
[5-(*N*-Methyl-1*H*-indol-3-yl)-2-phenyloxazol-4-yl](thiophen-2-yl)methanone (130e).



Obtained from enamide **129e**, yellow solid (150 mg, 85%); mp 214-218 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1631, 1539, 1388, 1231, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.86 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 8.40-8.36 (m, 1H), 8.25 (m, 2H), 7.72 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.59-7.50 (m, 3H), 7.43-7.36 (m, 3H), 7.24 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 156.9, 155.6, 144.2, 137.4, 135.4, 135.2, 134.2, 131.7, 130.6, 129.1, 128.0, 127.3, 126.6, 126.2, 123.2, 121.9, 121.8, 110.2, 103.8, 33.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{16}N_2O_2S$ $[M + Na]^+$ 407.0830, found 407.0831.

2.5.7 General procedure for the hydrolysis of esters 121a, 121c, 121e to 2-phenyl-5-(het)aryloxazole-4-carboxylic acids 122a, 122c, 122e. A solution of the corresponding 2-phenyl-5-(het)aryloxazole-4-carboxylate **121** (0.3 mmol) and NaOH (20 mg, 0.5 mmol) in EtOH (4 mL) was stirred at room temperature for 8 h. The solvent was removed under reduced pressure and and the residue diluted with H_2O (10 mL), acidified with dil. HCl (20 mL, 2 M), extracted with EtOAc (3 x 10 mL). The combined organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give carboxylic acids **122** as white solids, which were crystallized from EtOAc.

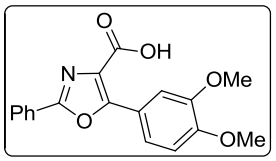
5-(4-Methoxyphenyl)-2-phenyloxazole-4-carboxylic acid (122a).[28b] Obtained from



ester **121a**, white solid (85 mg, 95%); mp 193-194 °C (lit. 192-194 °C) [28b]; R_f 0.3 (EtOAc); IR (KBr, cm^{-1}) 2933, 1690, 1513, 1256, 1183, 830, 706; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 2H), 8.13-8.10 (m, 2H), 7.53 (m, 3H), 7.03 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.7, 158.6, 155.8, 131.4, 130.3, 129.1, 126.9,

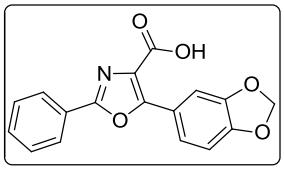
126.1, 125.8, 119.1, 114.3, 55.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}NO_4$ $[M + Na]^+$ 318.0742, found 318.0742.

5-(3,4-dimethoxyphenyl)-2-phenyloxazole-4-carboxylic acid (122b). Obtained from



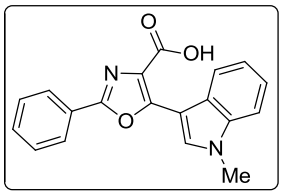
ester **121b**, white solid (87 mg, 95%); mp 165-167 °C; R_f 0.2 (EtOAc); IR (KBr, cm^{-1}) 3065, 2926, 1708, 1505, 1263, 709; ^1H NMR (400 MHz, DMSO-d_6) δ 8.11-8.08 (m, 2H), 7.86 (d, J = 1.6 Hz, 1H), 7.75 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.58 (t, J = 2.8 Hz, 3H), 7.12 (d, J = 8.8 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 158.0, 154.2, 150.5, 148.3, 131.1, 129.2, 127.4, 126.3, 126.1, 121.6, 119.2, 111.8, 111.5, 55.7, 55.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}NO_5$ $[M + Na]^+$ 348.0848, found 348.0849.

5-(Benzo[d][1,3]dioxol-5-yl)-2-phenyloxazole-4-carboxylic acid (122c). Obtained from



ester **121c**, white solid (87 mg, 95%); mp 205-206 °C; R_f 0.2 (EtOAc); IR (KBr, cm^{-1}) 2919, 2851, 1696, 1487, 1237, 707; ^1H NMR (400 MHz, DMSO-d_6) δ 13.17 (br s, 1H), 8.11-8.08 (m, 2H), 7.76 (d, J = 1.6 Hz, 1H), 7.73 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.59-7.57 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 6.14 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 158.0, 153.8, 148.9, 147.3, 131.1, 129.2, 127.6, 126.3, 126.0, 123.2, 120.5, 108.4, 101.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{11}NO_5$ $[M + Na]^+$ 332.0535, found 332.0534.

5-(1-Methyl-1*H*-indol-3-yl)-2-phenyloxazole-4-carboxylic acid (122e). Obtained from

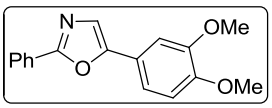


ester **121e**, white solid (87 mg, 95%); mp 220-221 °C; R_f 0.15 (EtOAc); IR (KBr, cm^{-1}) 2926, 2855, 1677, 1557, 1247, 737; ^1H NMR (400 MHz, DMSO-d_6) δ 12.9 (br s, 1H), 8.71 (s, 1H), 8.21 (m, 1H), 8.11 (d, J = 6.8 Hz, 2H), 7.64-7.56 (m, 4H), 7.35-7.32 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 156.5, 153.5, 136.6, 133.9, 130.7, 129.3, 126.4, 125.8, 125.1, 124.3, 122.7, 121.5, 120.7, 110.7, 101.6, 33.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}N_2O_3$ $[M + Na]^+$ 341.0902, found 341.0902.

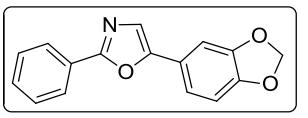
2.5.8 General procedure for decarboxylation of oxazole-4-carboxylic acids 122a-b, 122c and 122e to 2-phenyl-5-(het)aryloxazoles 1, 2, 5 and 123. A solution of the corresponding oxazole-4-carboxylic acid **122** (0.17 mmol) in DMF/H_2O (1:1, 4 mL) was refluxed at 150 °C for 70 h (monitored by TLC). The solvent was removed under reduced

pressure and the crude product was purified by column chromatography over silica gel using EtOAc-hexane as eluent to give 2-phenyl-5-(hetero)aryloxazoles **1**, **2**, **5** and **123**.

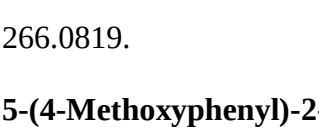
5-(3,4-Dimethoxyphenyl)-2-phenyloxazole (1) (Balsoxine). Obtained from carboxylic acid **122b**, white solid (31 mg, 70%); mp 96-98 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2931, 1507, 1259, 1016, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 7.50-7.45 (m, 3H), 7.31 (s, 1H), 7.24 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 149.7, 149.6, 130.3, 128.9, 127.7, 126.4, 122.4, 121.3, 117.5, 111.8, 107.8, 56.3, 56.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}NO_3$ $[M + H]^+$ 282.1130, found 282.1131.



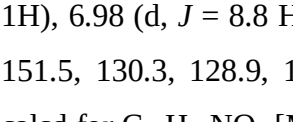
5-(Benzo[d][1,3]dioxol-5-yl)-2-phenyloxazole (2) (Texamine).[8] Obtained from carboxylic acid **122c**, white solid (29 mg, 70%); mp 135-137 °C (lit. 134-136.5 °C)[8]; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2906, 1479, 1231, 1036, 704; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 7.50-7.45 (m, 3H), 7.31 (s, 1H), 7.24 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 151.2, 148.2, 147.9, 130.2, 128.8, 127.5, 126.2, 122.4, 122.3, 118.4, 108.9, 104.9, 101.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}NO_3$ $[M + H]^+$ 266.0817, found 266.0819.



5-(4-Methoxyphenyl)-2-phenyloxazole (5) (Uguenenazole).[68] Obtained from carboxylic acid **122a**, white solid (30 mg, 70%); mp 134-135 °C (lit. 133-135 °C)[68]; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2957, 2831, 1507, 1255, 1022, 827, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 6.2 Hz, 1.2 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.51-7.45 (m, 3H), 7.33 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 160.0, 151.5, 130.3, 128.9, 127.7, 126.3, 125.9, 121.9, 121.0, 114.6, 55.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}NO_2$ $[M + H]^+$ 252.1025, found 252.1024.



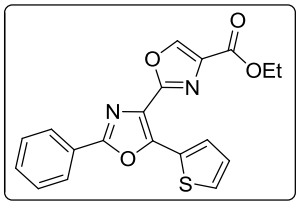
5-(1-Methyl-1*H*-indol-3-yl)-2-phenyloxazole (123). Obtained from carboxylic acid **122e**, white solid (30 mg, 70%); mp 111-112 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3053, 2926, 1626, 1467, 1333, 739, 708; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.51-7.44 (m, 4H), 7.40-7.28 (m, 4H), 3.88 (s, 3H); ^{13}C NMR (100 MHz,



$CDCl_3$) δ 159.5, 148.1, 137.4, 129.9, 128.9, 127.9, 126.6, 126.2, 124.9, 122.8, 121.3, 120.9, 120.4, 109.9, 104.4, 33.3; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}N_2O$ $[M + H]^+$ 275.1184, found 275.1186.

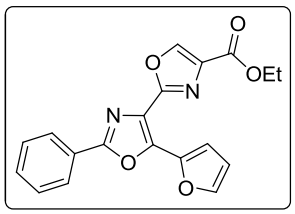
2.5.9 Cyclodehydration-dehydrohalogenation of oxazoles 125j-l: General procedure for the synthesis of ethyl 2,5-bis(het)aryl 4,2'-bisoxazole-4'-carboxylates 127a-c. To a stirred and cooled (-78 °C) solution of respective oxazole 4-carboxamides **125j-l** (0.15 mmol) in DCM (5 mL), a solution of diethylaminosulfur trifluride (DAST, 27 mg, 0.17 mmol) in 3 mL of DCM was added slowly under N_2 atmosphere and the reaction mixture was further stirred at -78 °C for 1 hr, followed by addition of K_2CO_3 (31 mg, 0.23 mmol, 1.5 equiv) and warming it to room temperature. It was then poured into 10% aq. $NaHCO_3$ solution (20 mL), extracted with DCM (2 x 10 mL), the organic layer washed with brine (1 x 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure and the residue was dissolved in DCM (3 mL), cooled to 0 °C, followed by sequential addition of a solution of DBU (45 mg, 0.30 mmol in 2 mL of DCM) and bromotrichloromethane (59 mg, 0.30 mmol). The reaction mixture was further stirred for 5 h at 0 °C, brought to room temperature and poured into 10% aq. $NaHCO_3$ solution (20 mL), extracted with DCM (2 x 10 mL), washed with brine (1 x 10 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give crude products, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

Ethyl 2-phenyl-5-(2-thienyl)-[4,2']bisoxazole-4'-carboxylate (127a). Obtained from



125j, off-white solid (35 mg, 75%); mp 135-136 °C; R_f 0.6 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2910, 1717, 1566, 1307, 1113, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 8.36 (s, 1H), 8.19-8.16 (m, 2H), 7.54-7.51 (m, 4H), 7.24 (dd, J = 4.8 Hz, 4.0 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.9, 156.5, 147.1, 143.6, 134.8, 131.3, 129.9, 129.1, 128.8, 128.7, 128.6, 126.9, 126.3, 123.3, 61.4, 14.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}N_2O_4S$ $[M + Na]^+$ 389.0572, found 389.0572.

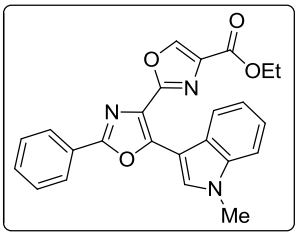
Ethyl 2-phenyl-5-(2-furyl)-[4,2']bisoxazole-4'-carboxylate (127b). Obtained from



125k, off-white solid (34 mg, 73%); mp 150-152 °C; R_f 0.55 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2921, 1728, 1118, 994, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.21-8.19 (m, 2H), 8.08

(d, J = 3.6 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H), 7.52-7.50 (m, 3H), 6.66 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 160.3, 156.2, 144.3, 143.6, 143.0, 142.3, 134.8, 131.3, 129.0, 127.0, 126.2, 123.4, 114.6, 112.7, 61.4, 14.4; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}N_2O_5$ $[M + Na]^+$ 373.0800, found 373.0800.

Ethyl 2-phenyl-5-(1-methyl-1*H*-indol-3-yl)-[4,2']bisoxazole-4'-carboxylate (127c).



Obtained from **125l**, brown solid (33 mg, 70%); mp 214-216 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 1717, 1577, 1307, 1113, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.36-8.35 (m, 1H), 8.34 (s, 1H), 8.25 (br d, J = 6.8 Hz, 2H), 7.57-7.51 (m, 3H), 7.45-7.36 (m, 3H), 4.45 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 158.8, 157.7, 150.4, 143.1, 137.2, 134.4, 133.8, 130.7, 129.1, 127.0, 126.6, 125.9, 123.1, 121.6, 121.5, 121.1, 110.1, 103.1, 61.3, 33.8, 14.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{19}N_3O_4$ $[M + Na]^+$ 436.1273, found 436.1272.

2.6 References

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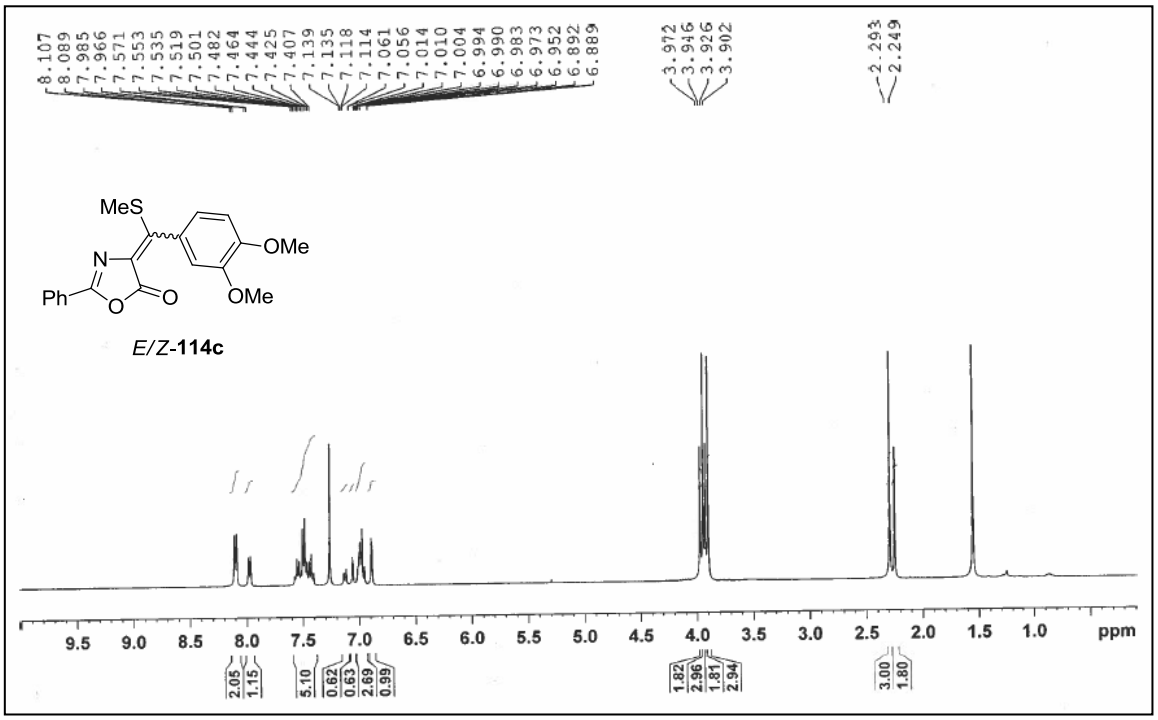
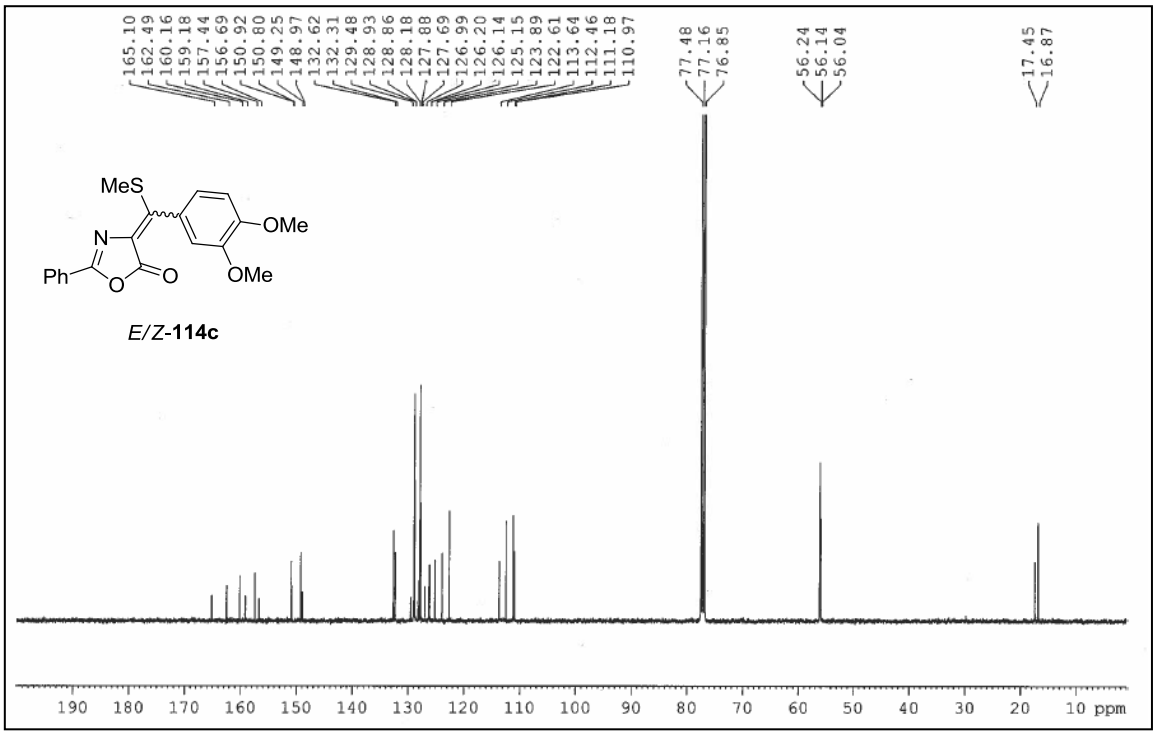
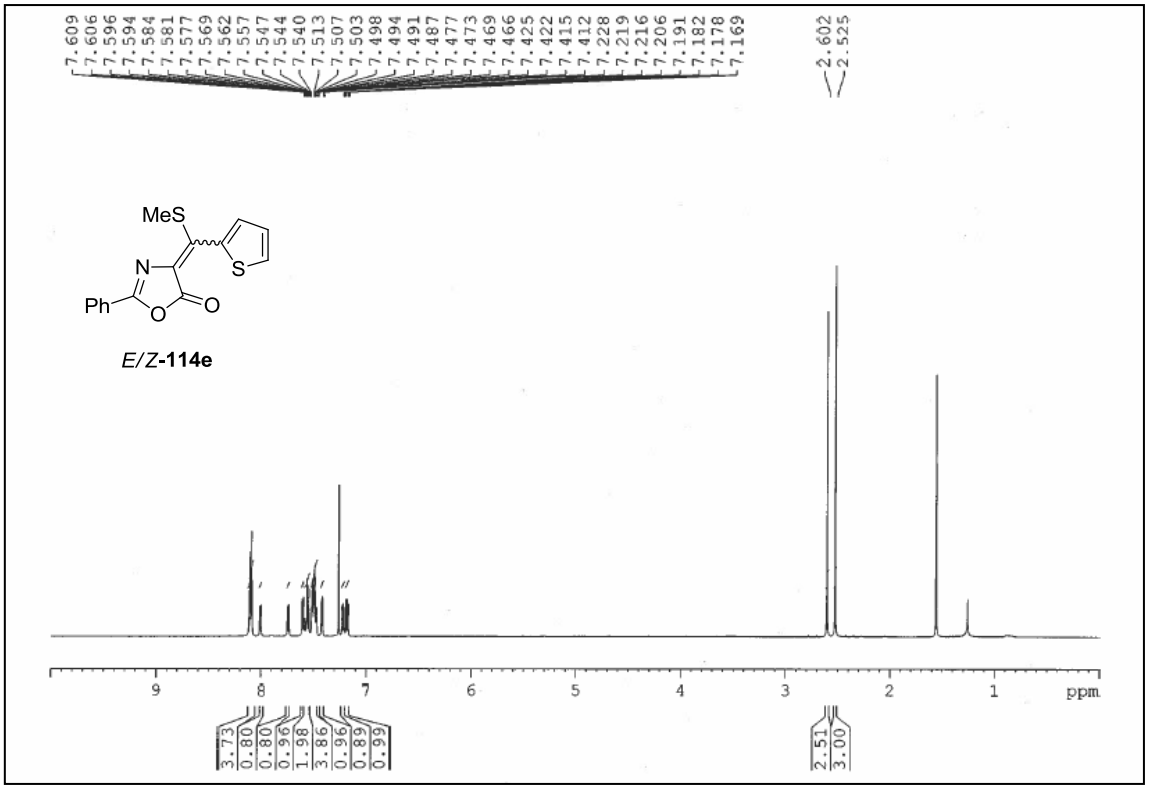
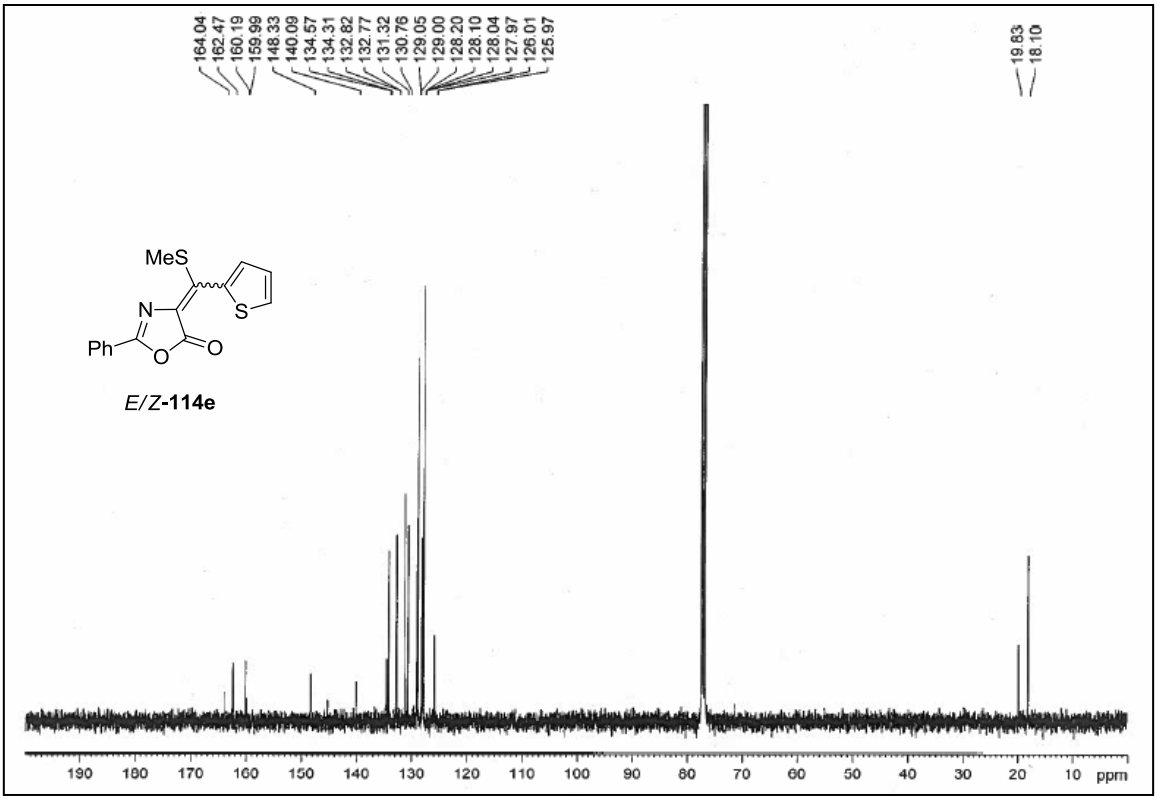
2.7 Representative spectra





^{1}H NMR and ^{13}C NMR Spectra for compound *E/Z*-**114c** in $CDCl_3$





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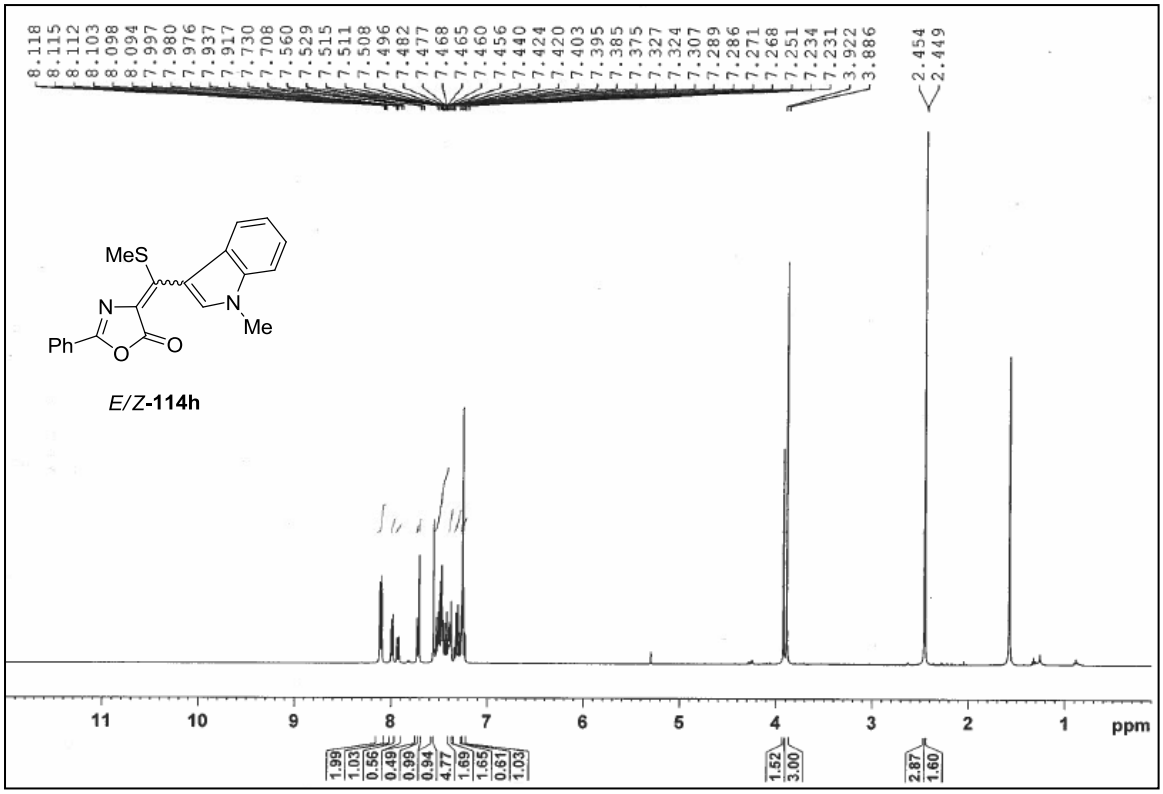

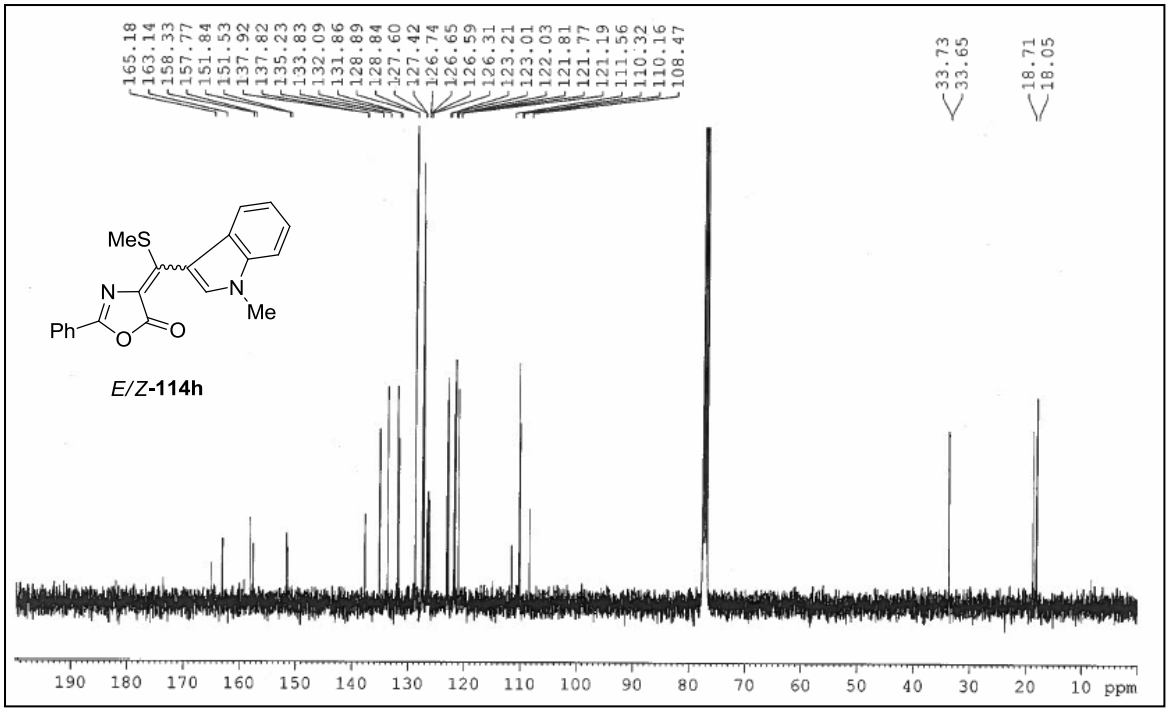

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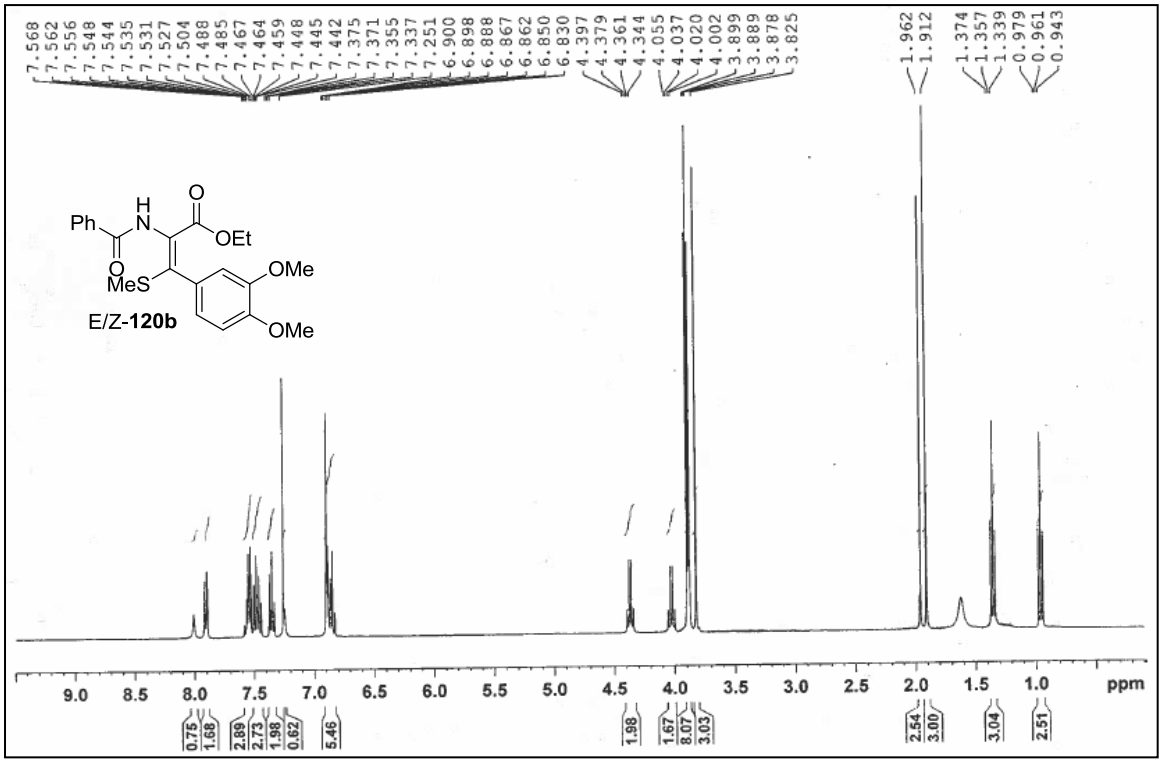

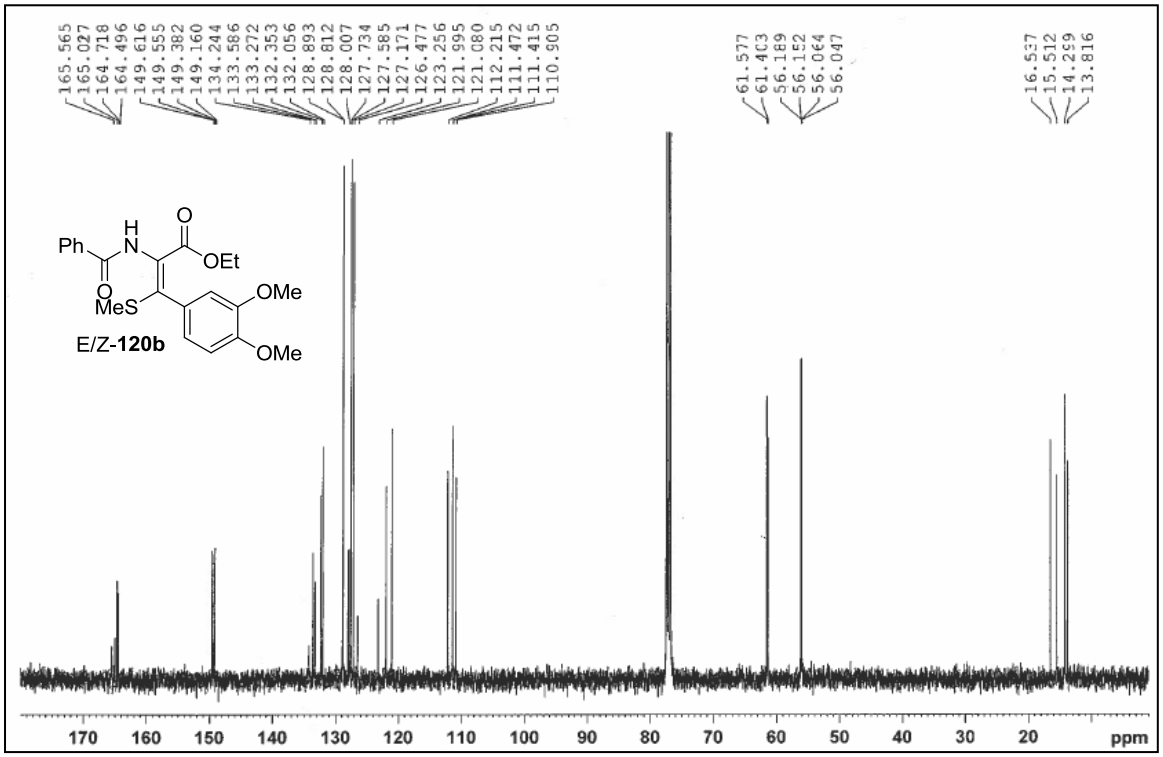

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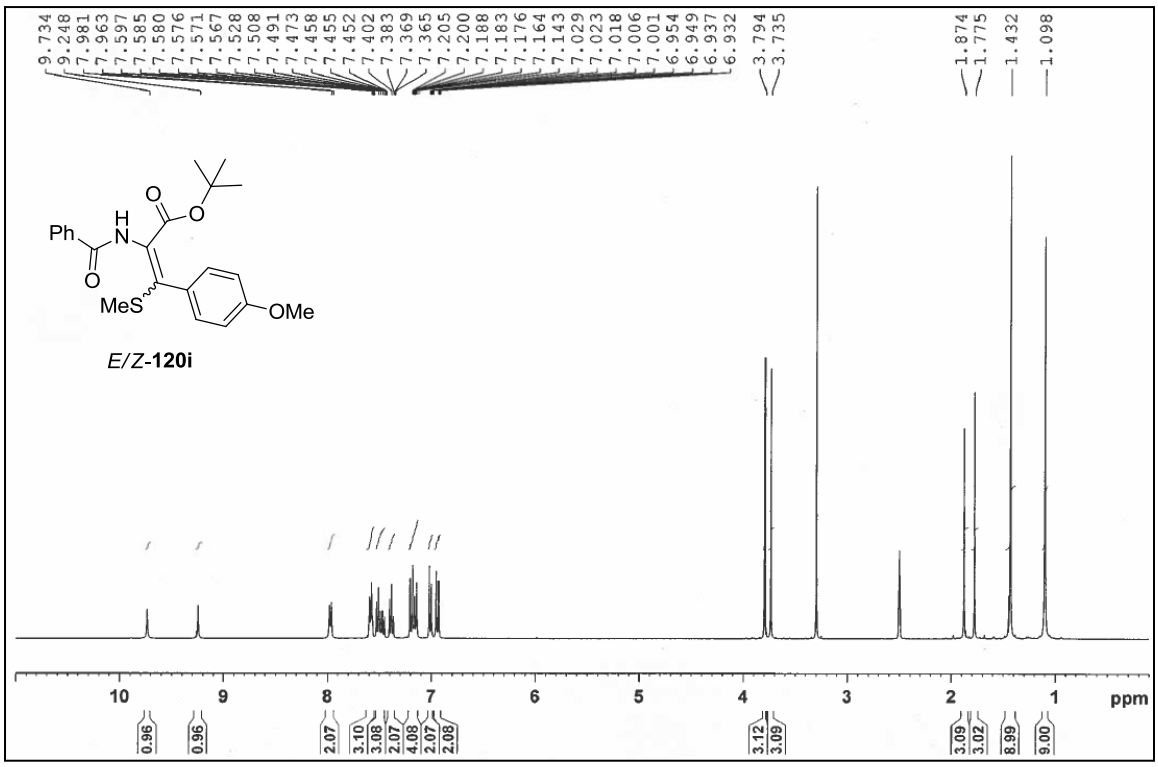
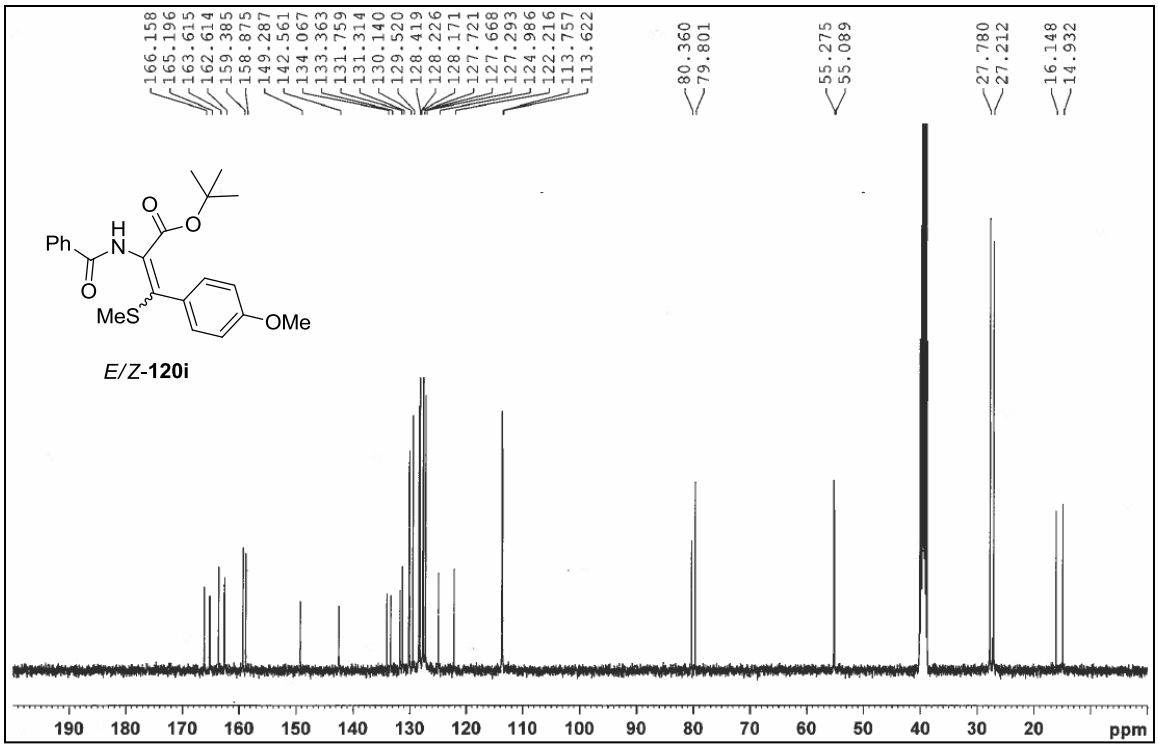
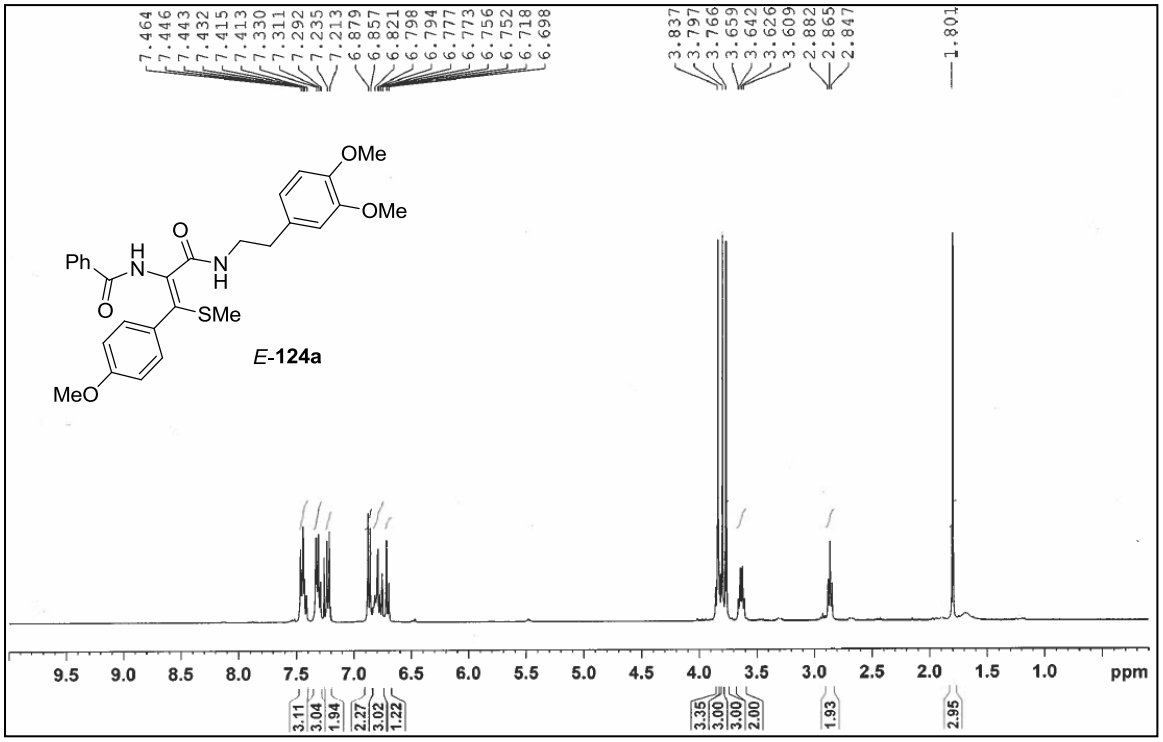
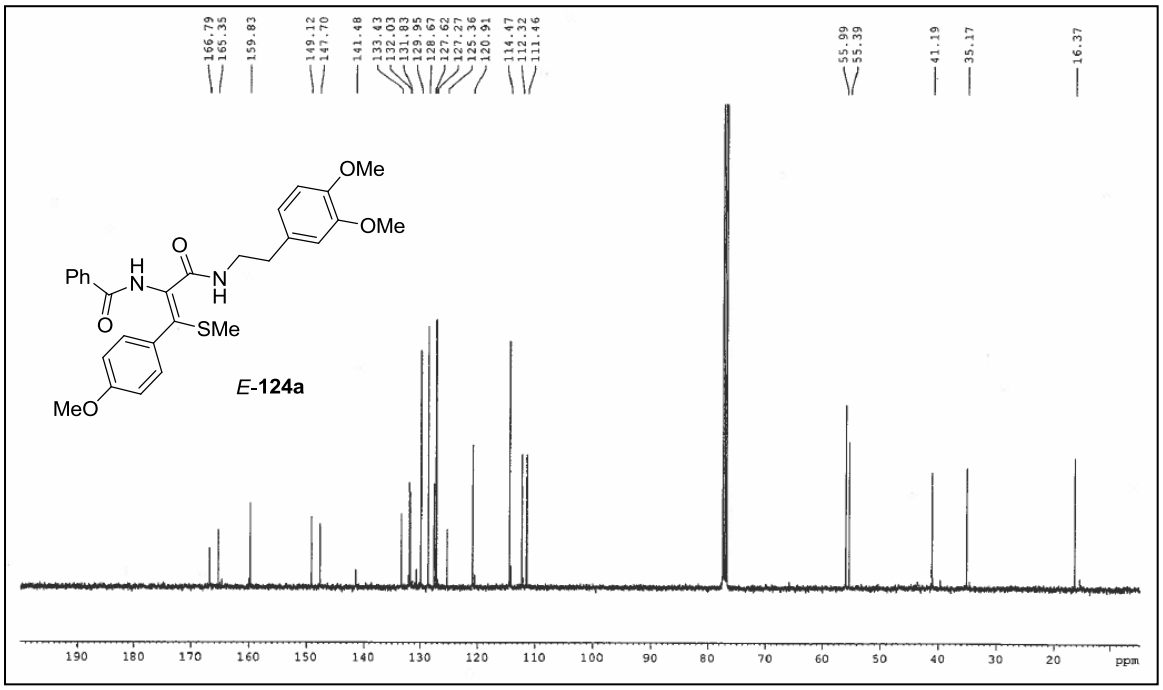


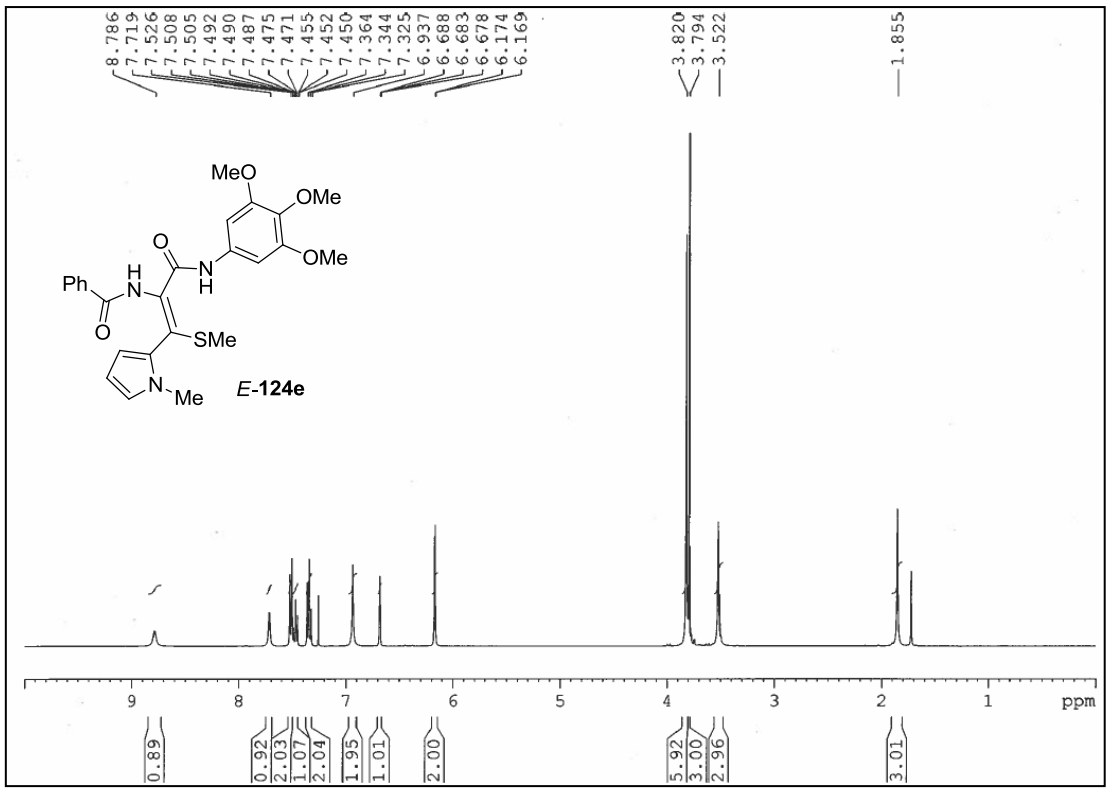


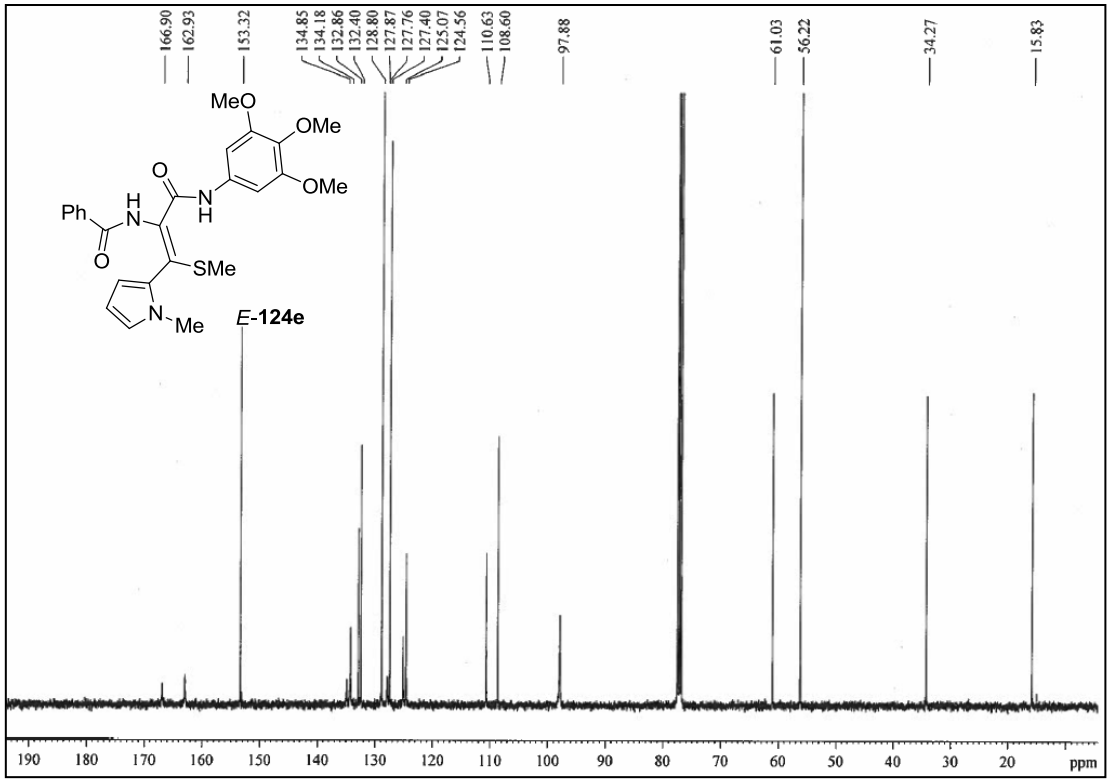
^{1}H NMR and ^{13}C NMR Spectra for compound *E/Z*-**120i** in DMSO-d_6





^{1}H NMR and ^{13}C NMR Spectra for compound *E*-**124a** in $CDCl_3$





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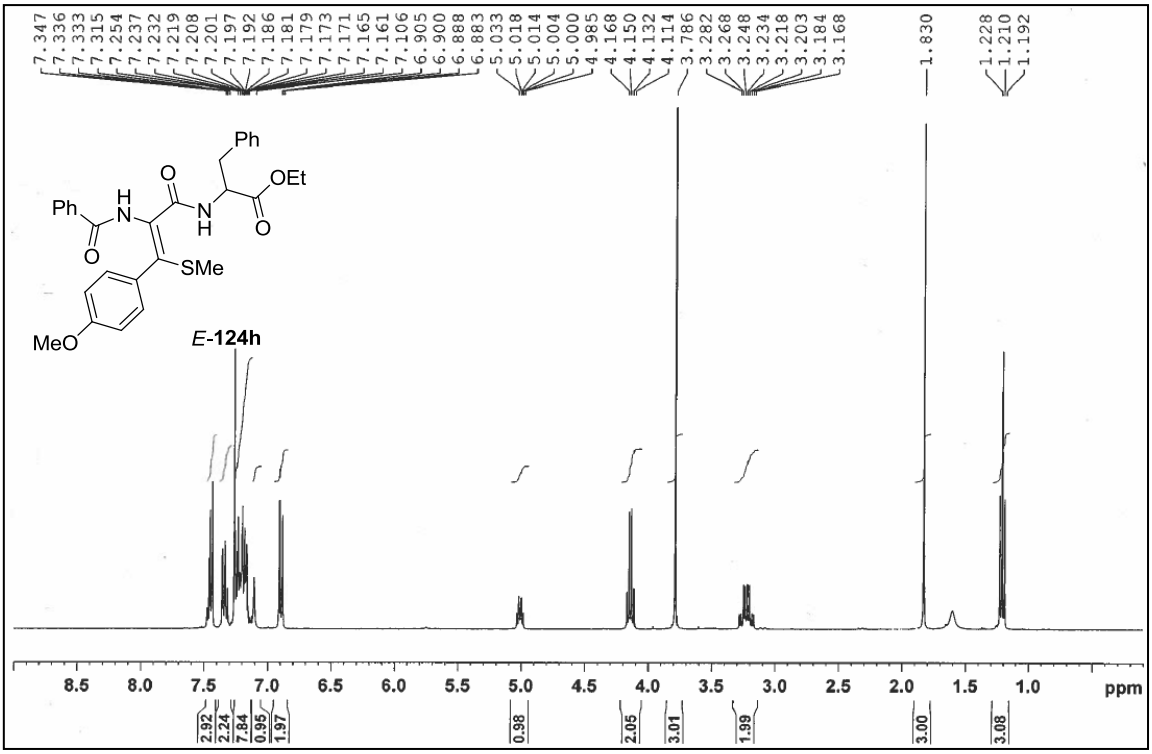

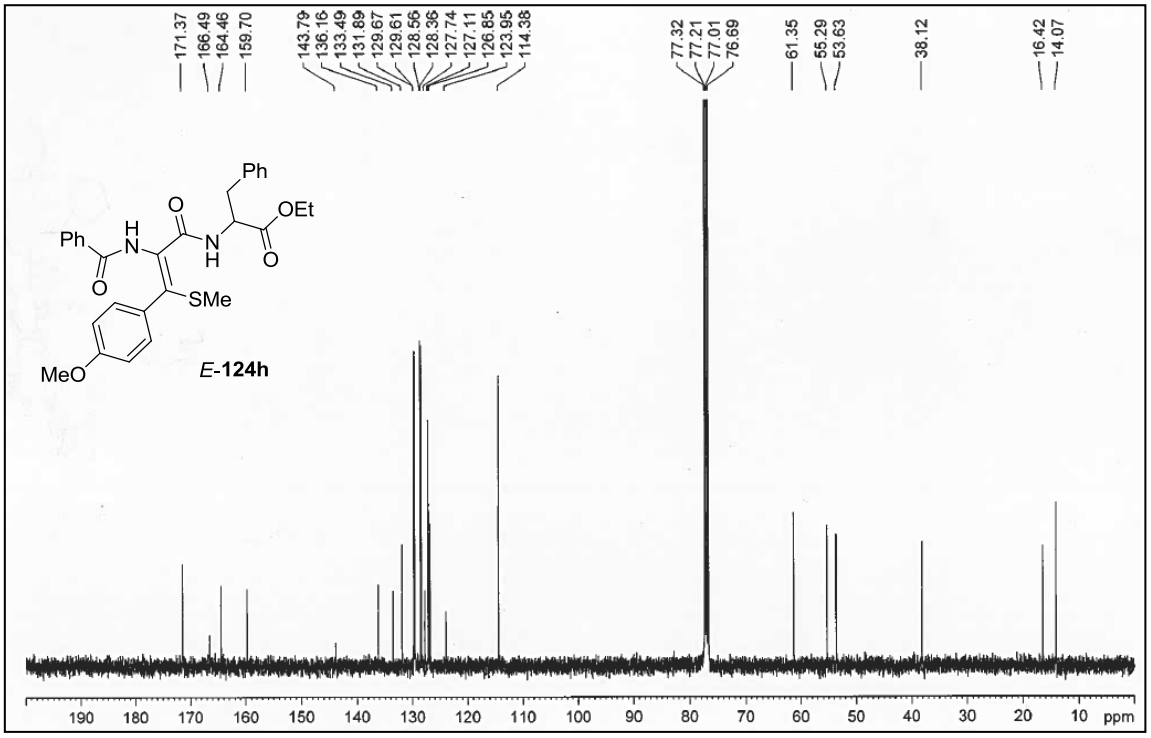

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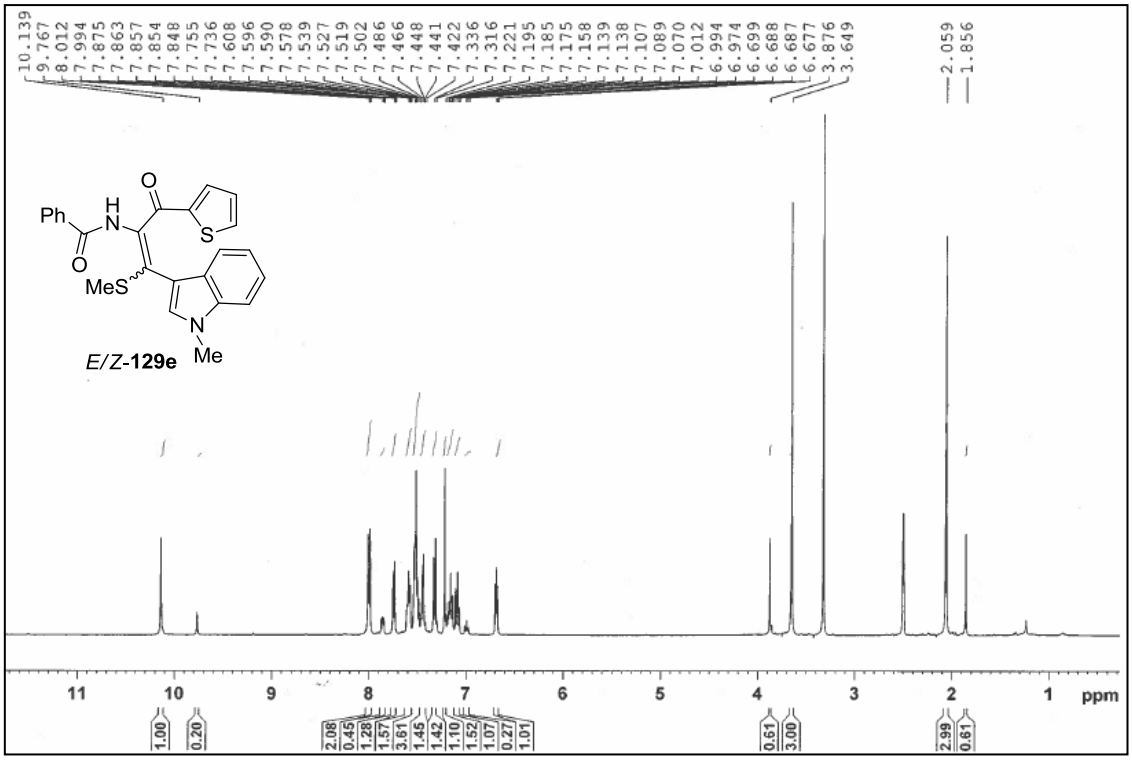

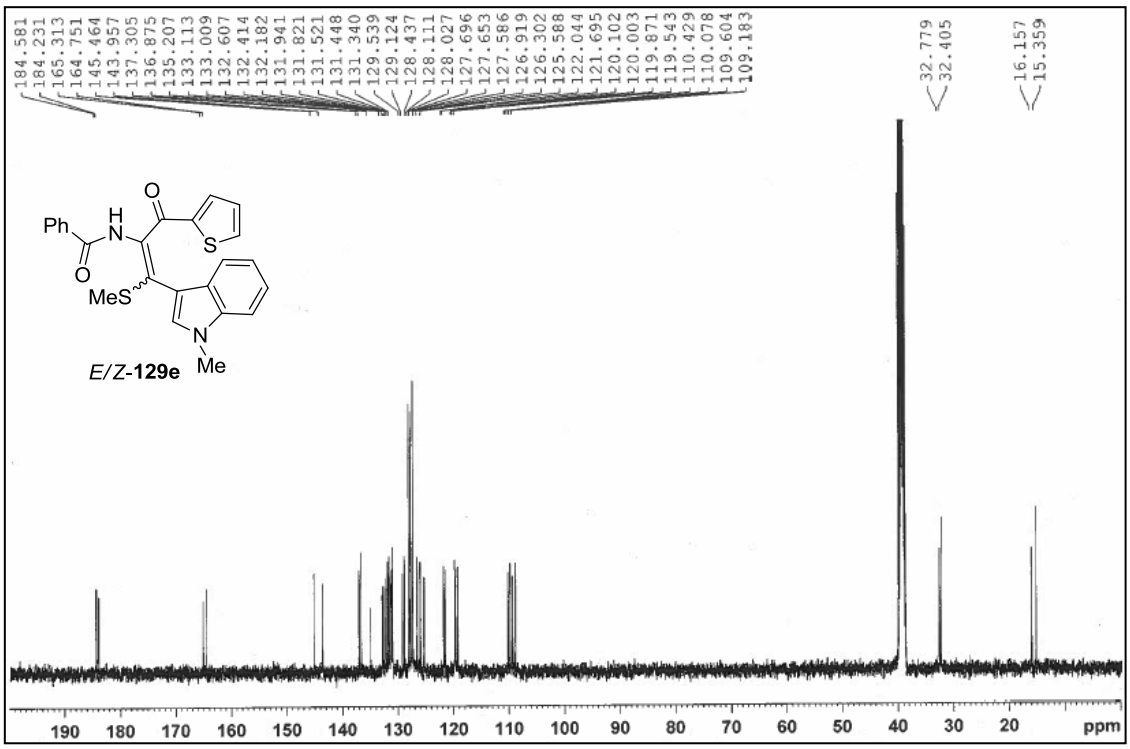

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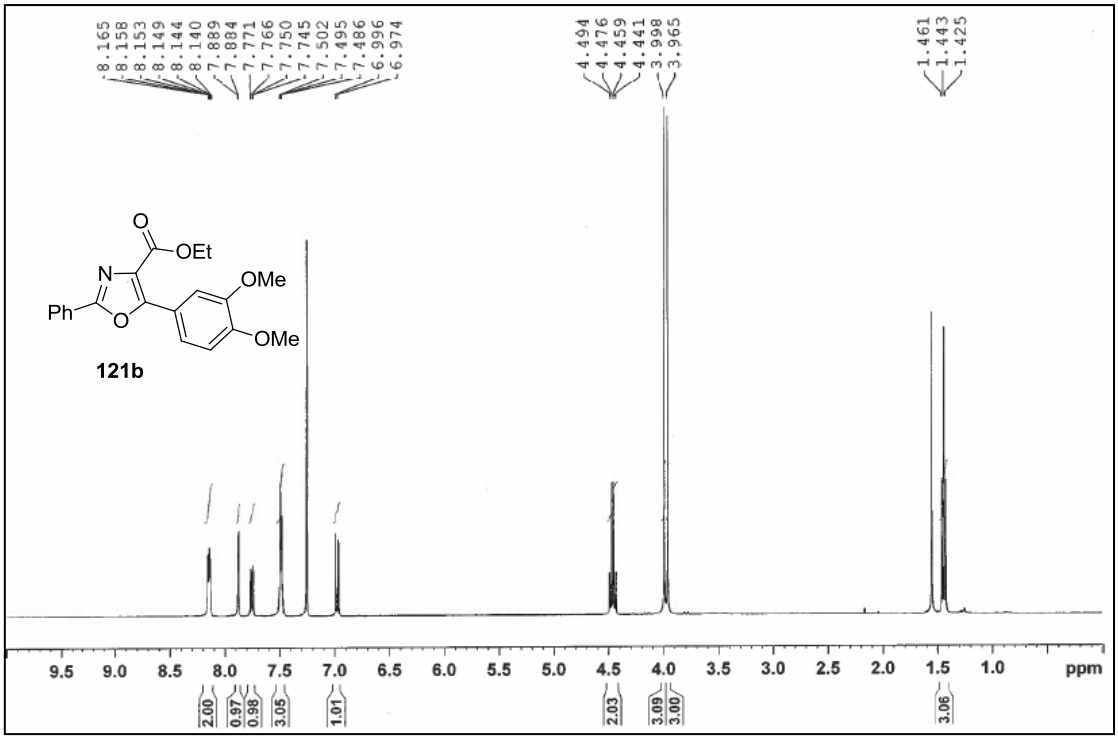
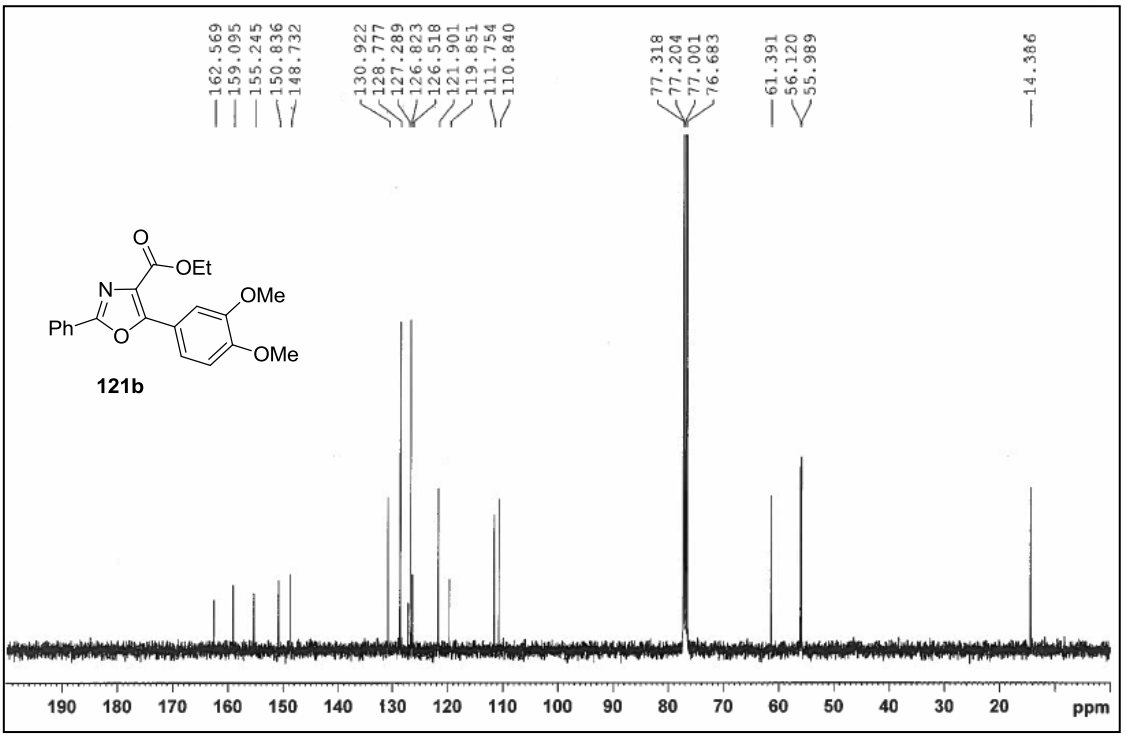
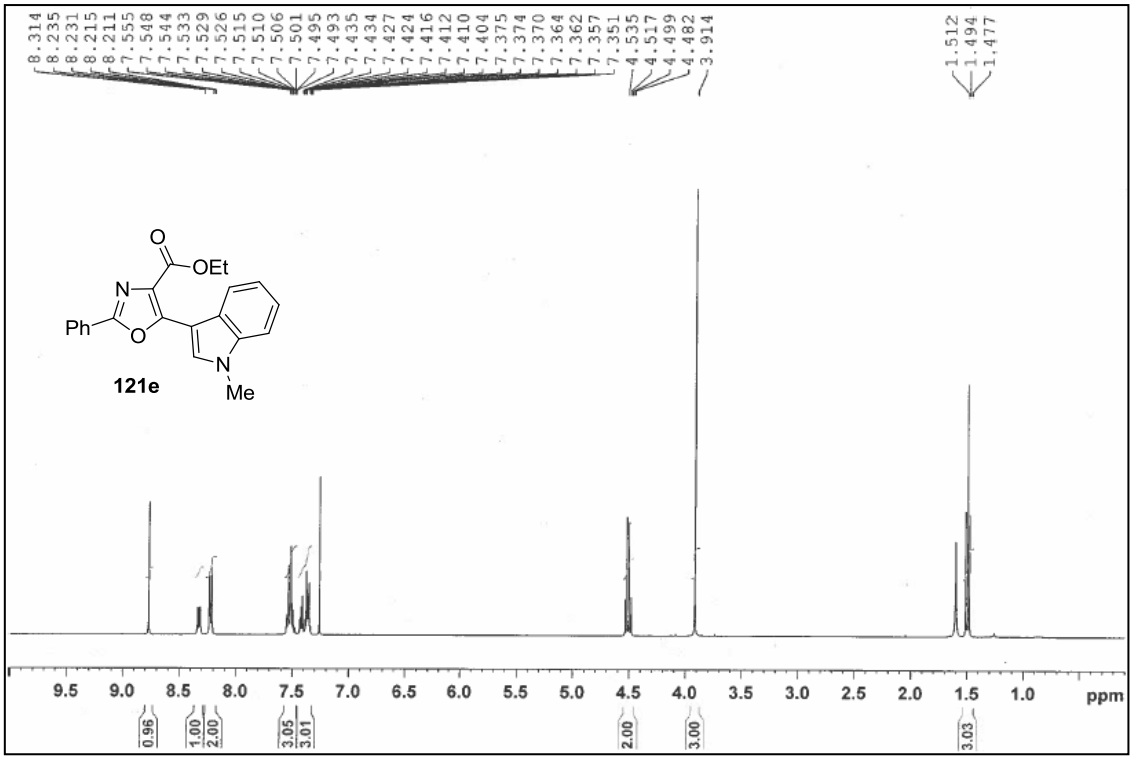
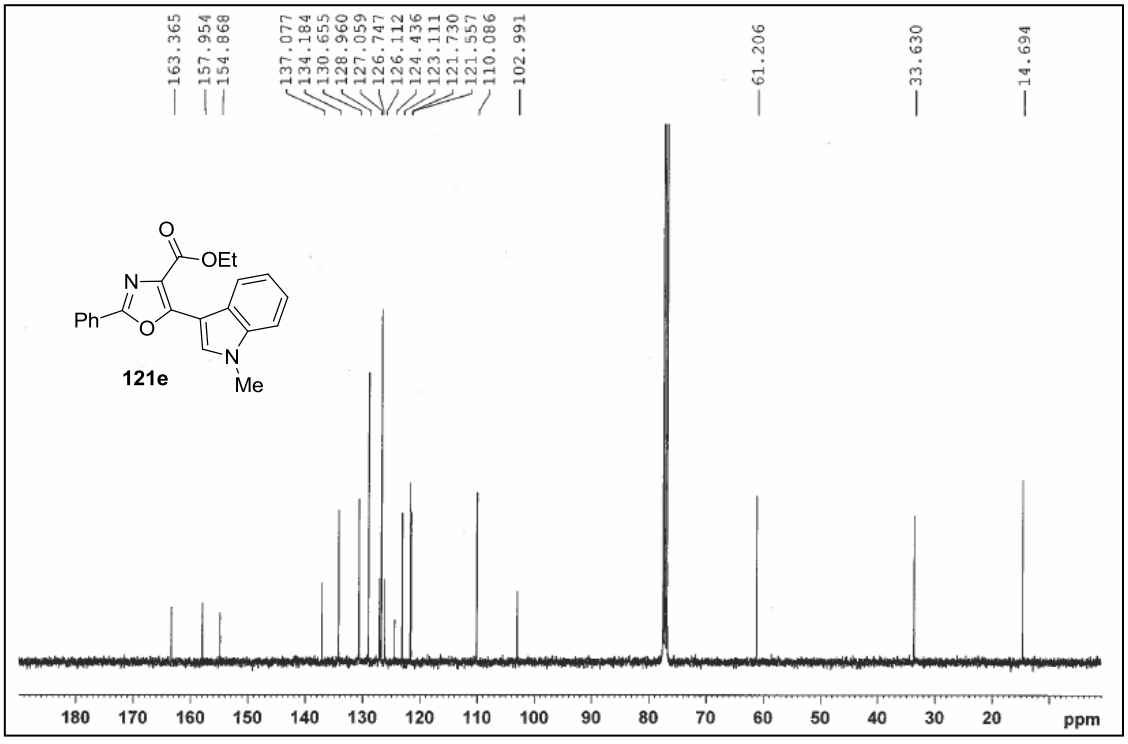


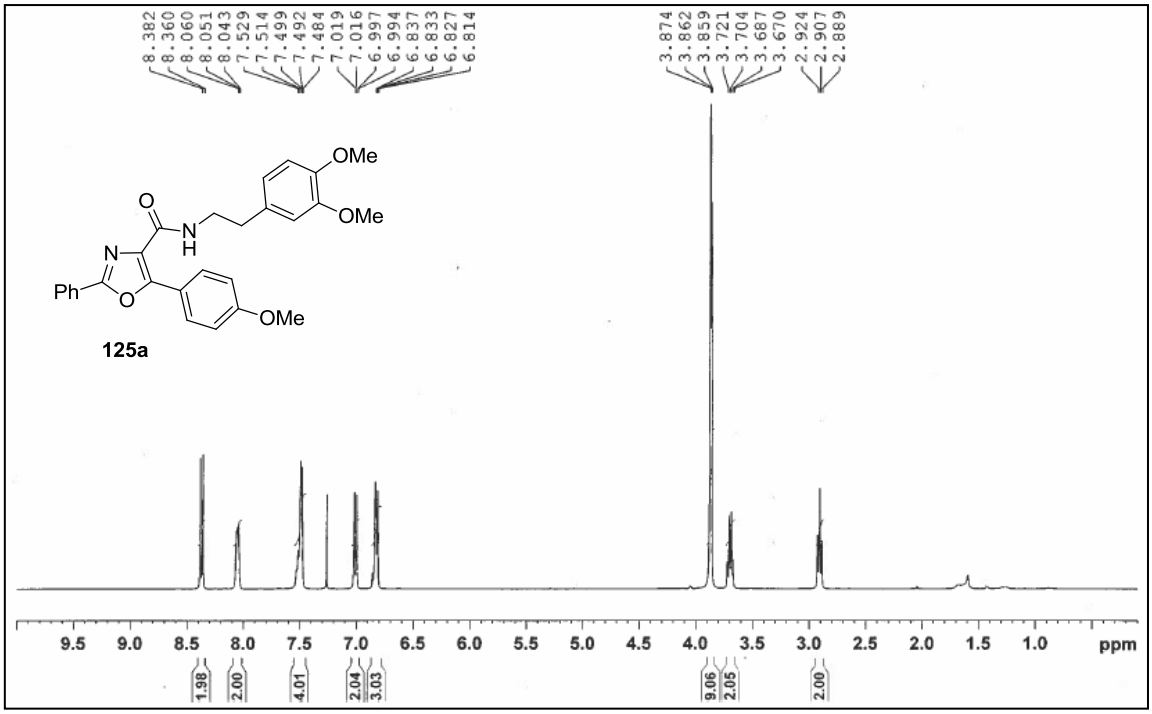


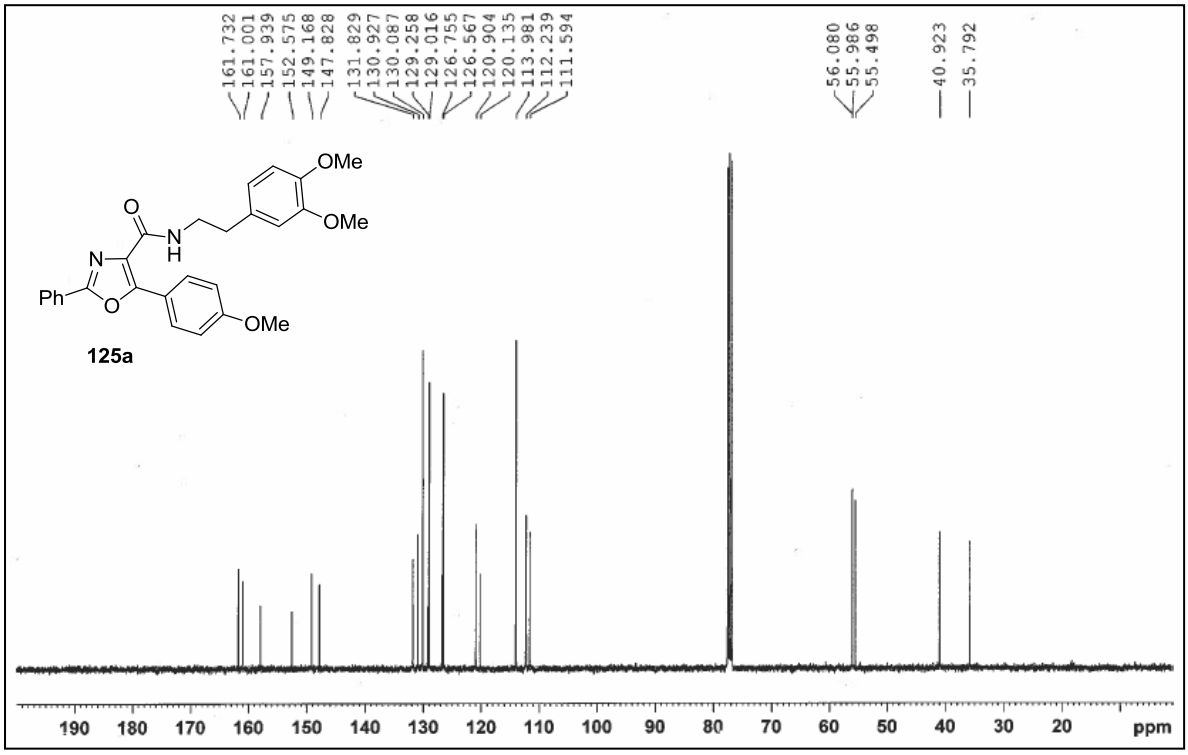
^{1}H NMR and ^{13}C NMR Spectra for compound **121b** in $CDCl_3$



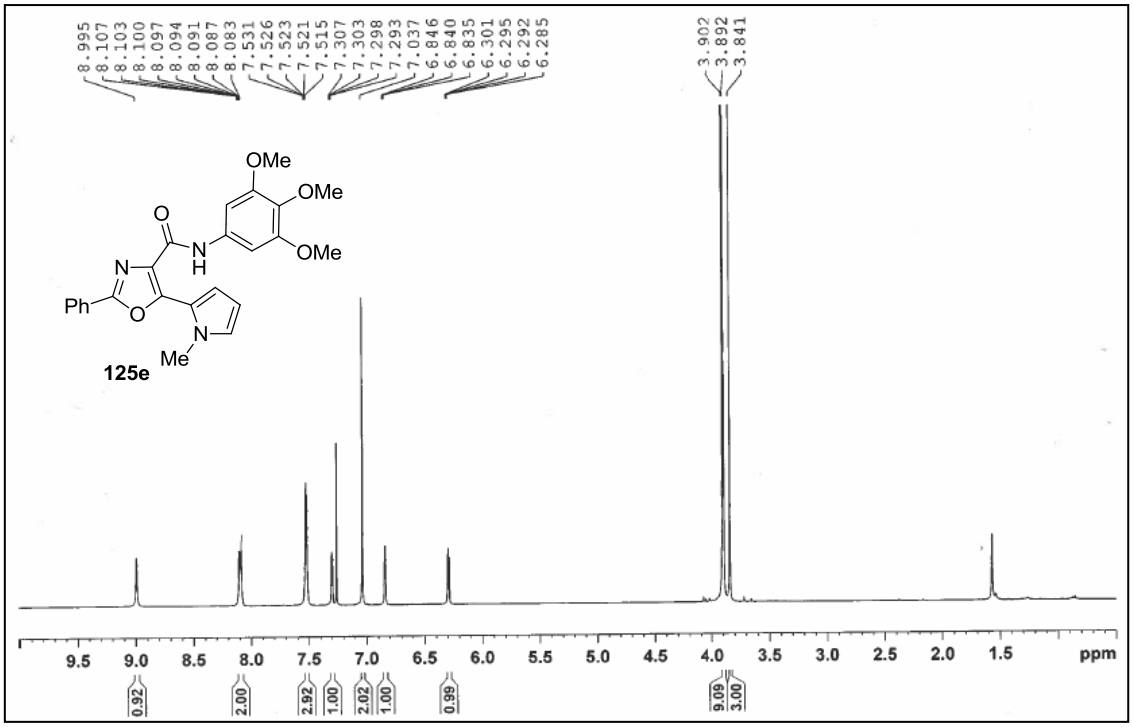


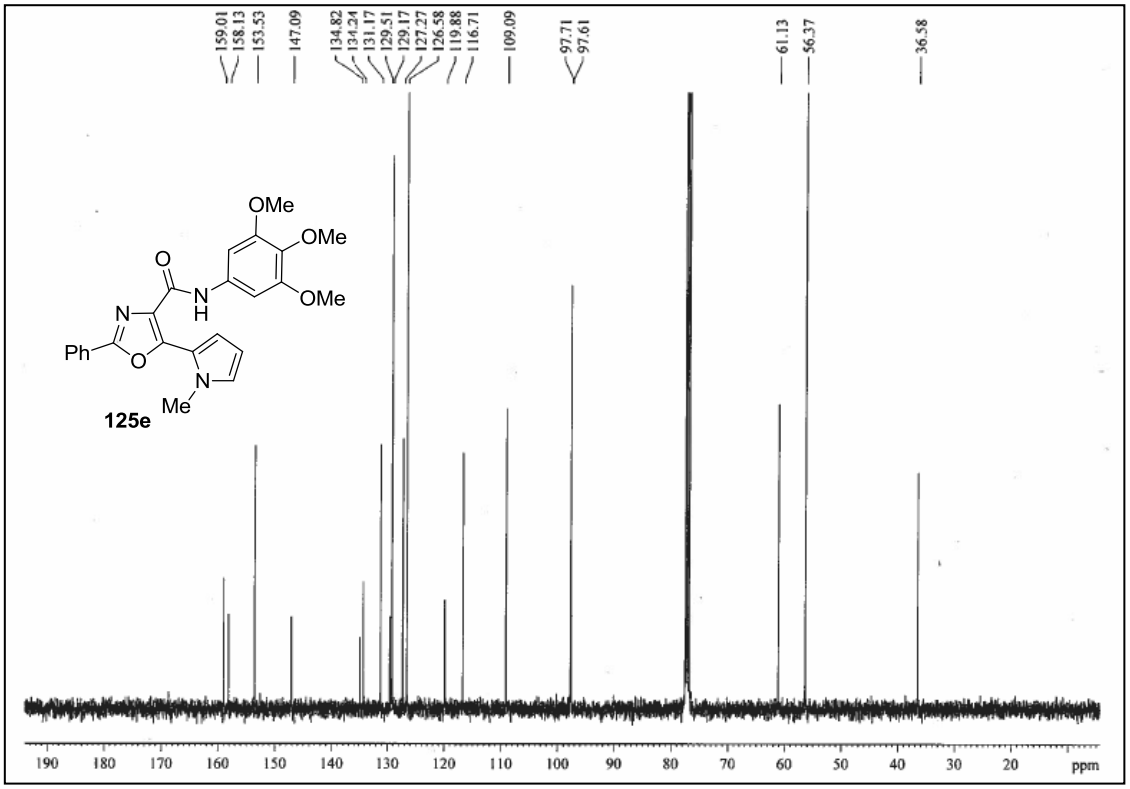
^{1}H NMR and ^{13}C NMR Spectra for compound **121e** in $CDCl_3$



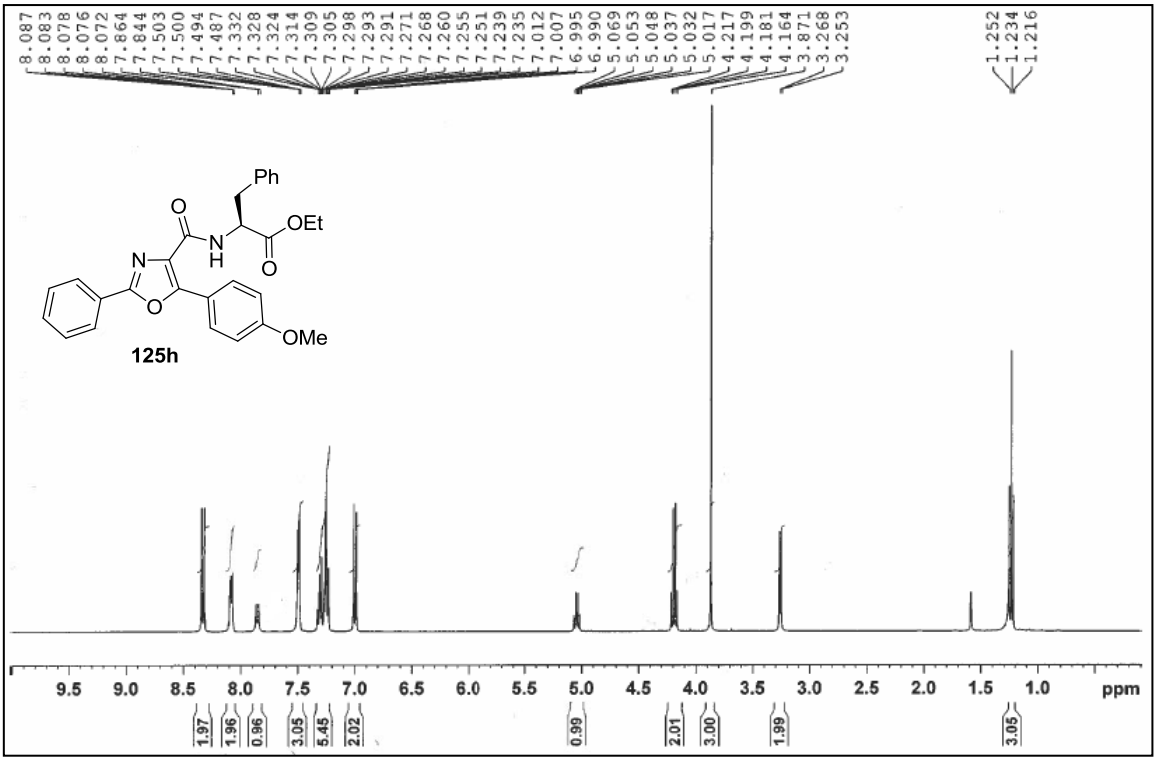


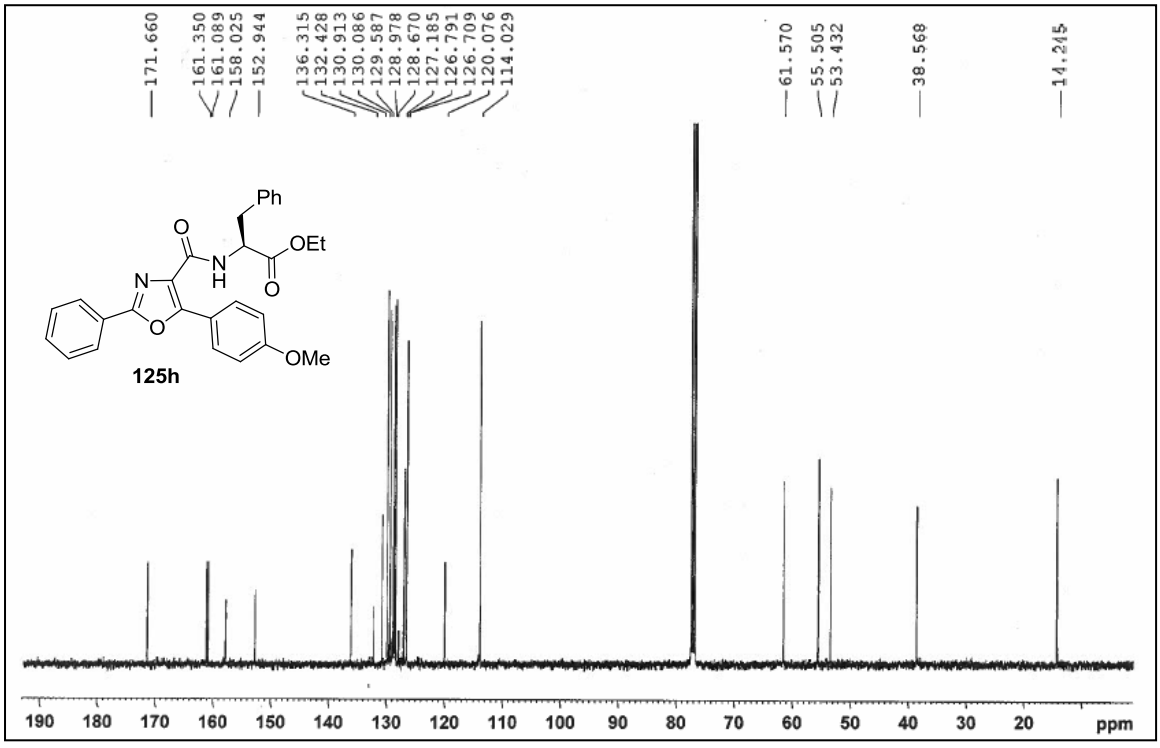
^{1}H NMR and ^{13}C NMR Spectra for compound **125a** in $CDCl_3$



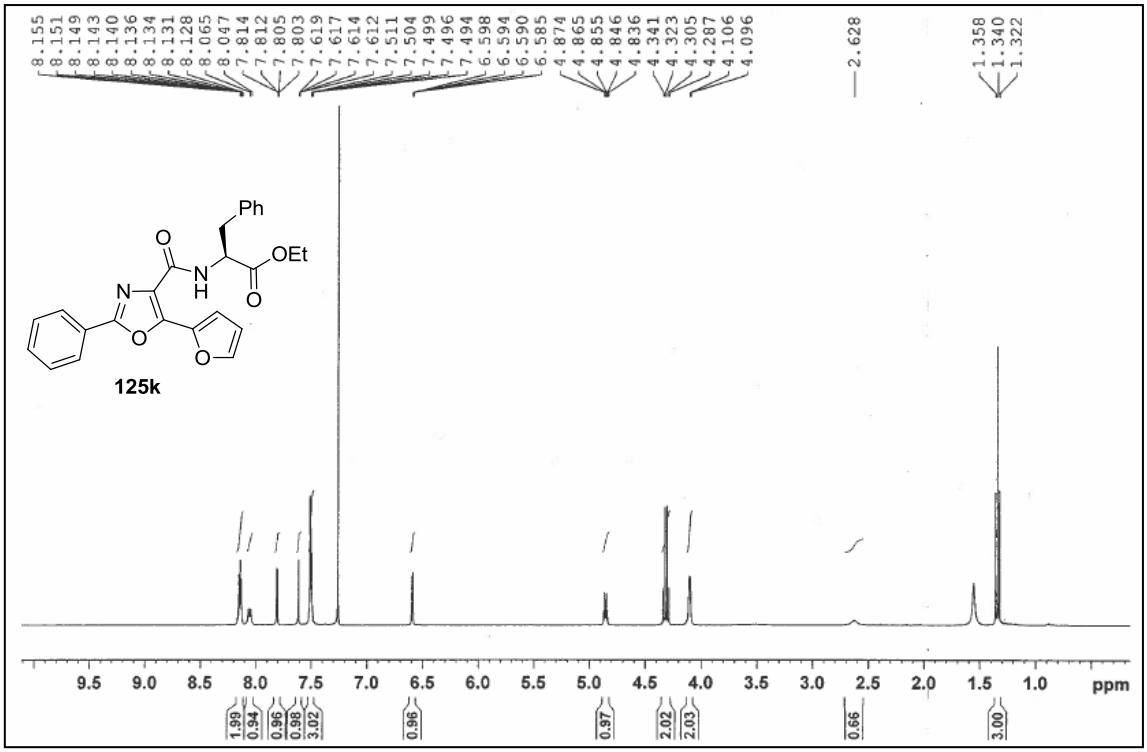


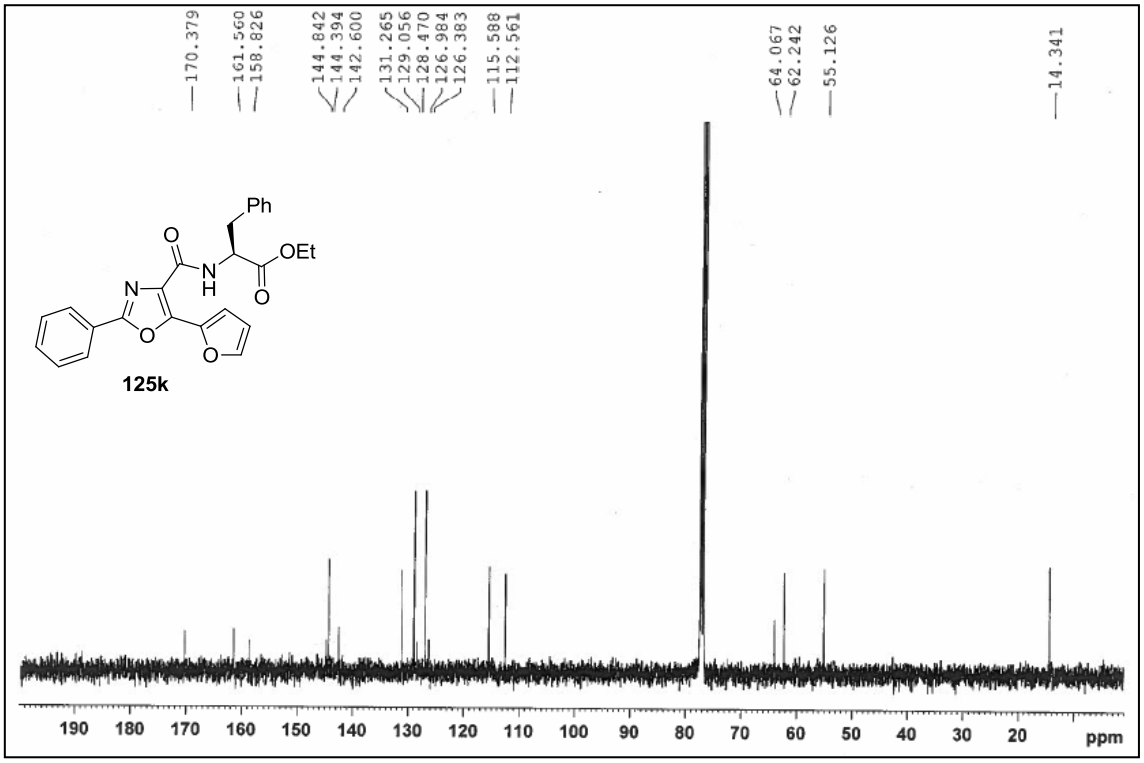
^{1}H NMR and ^{13}C NMR Spectra for compound **125e** in $CDCl_3$



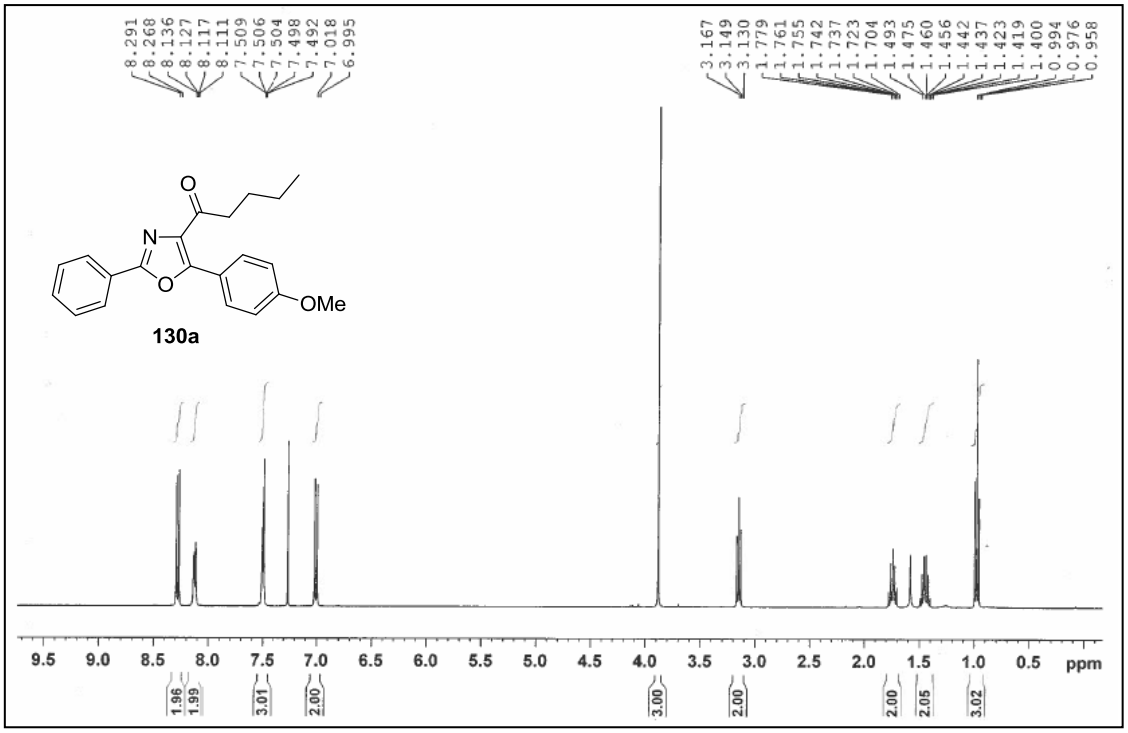


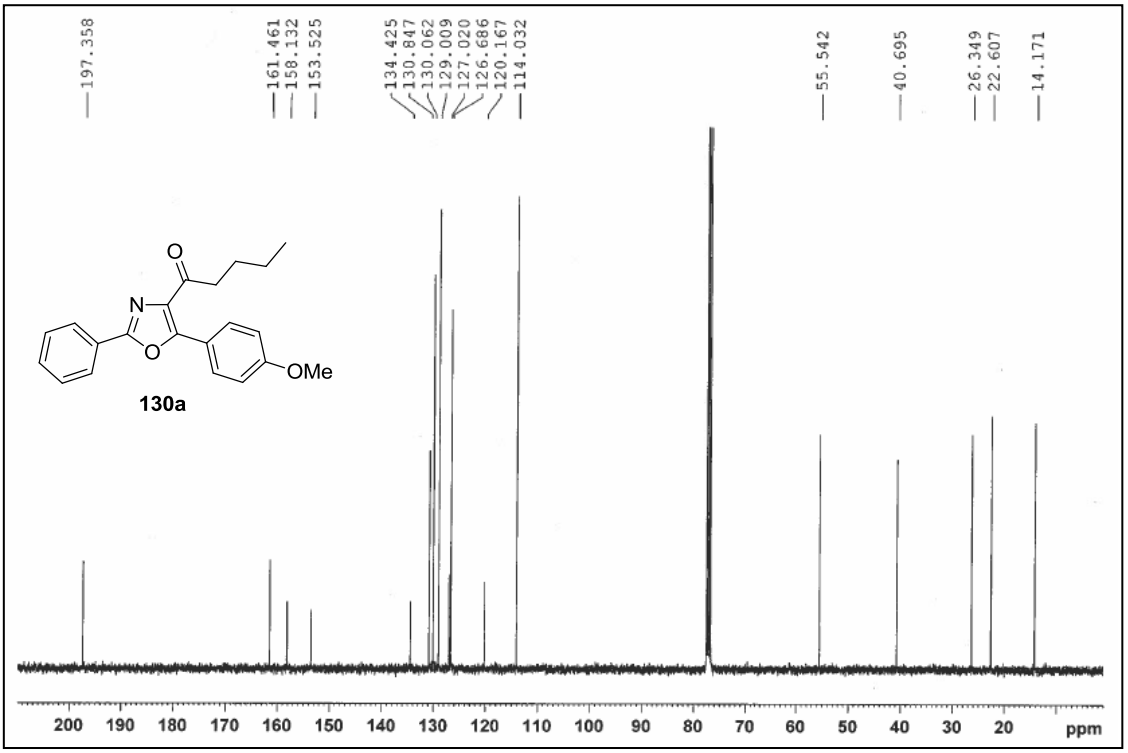
^{1}H NMR and ^{13}C NMR Spectra for compound **125h** in $CDCl_3$



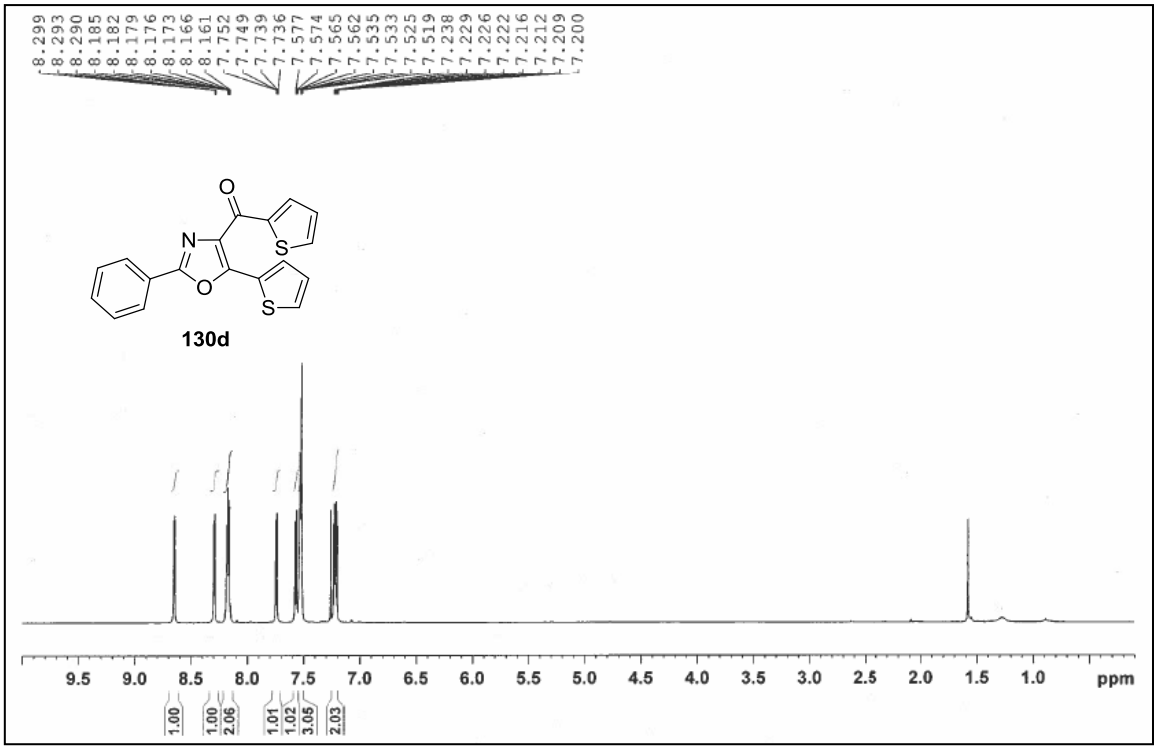


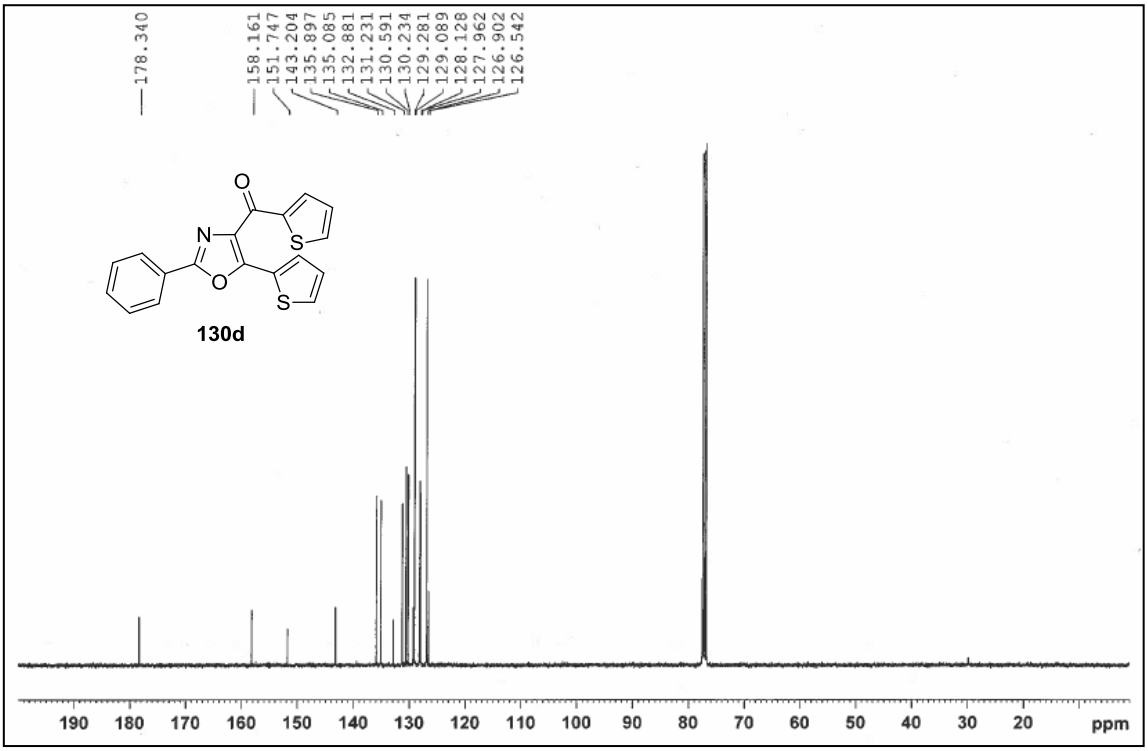
^{1}H NMR and ^{13}C NMR Spectra for compound **125k** in $CDCl_3$



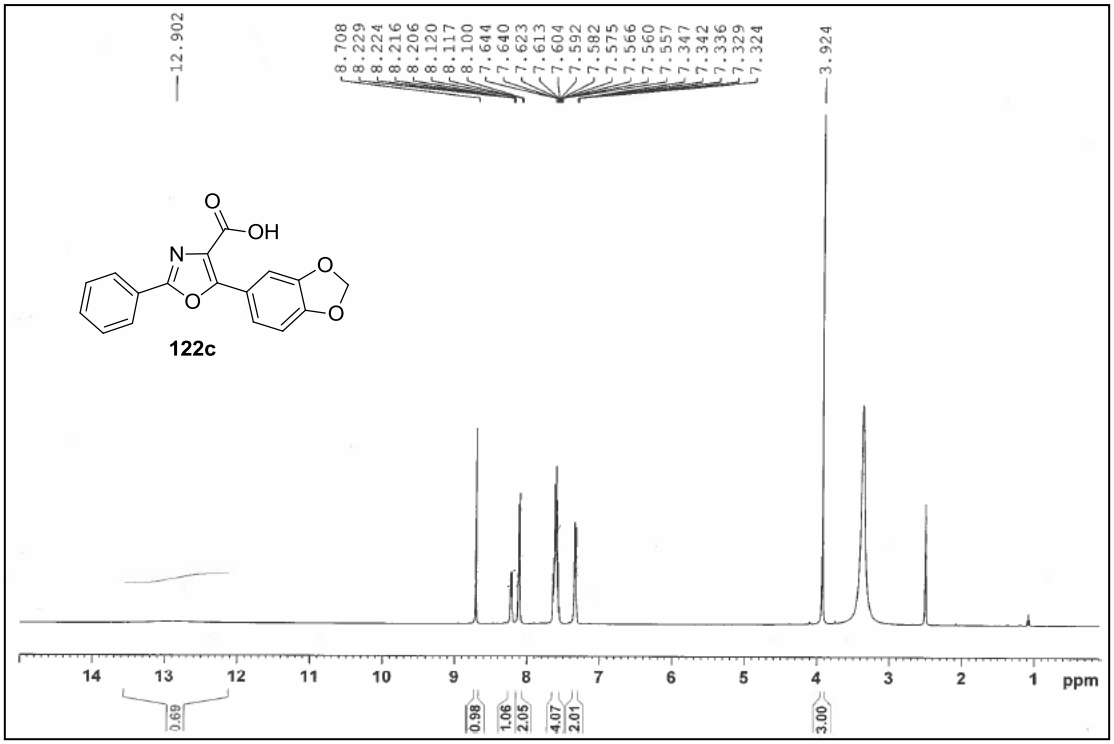


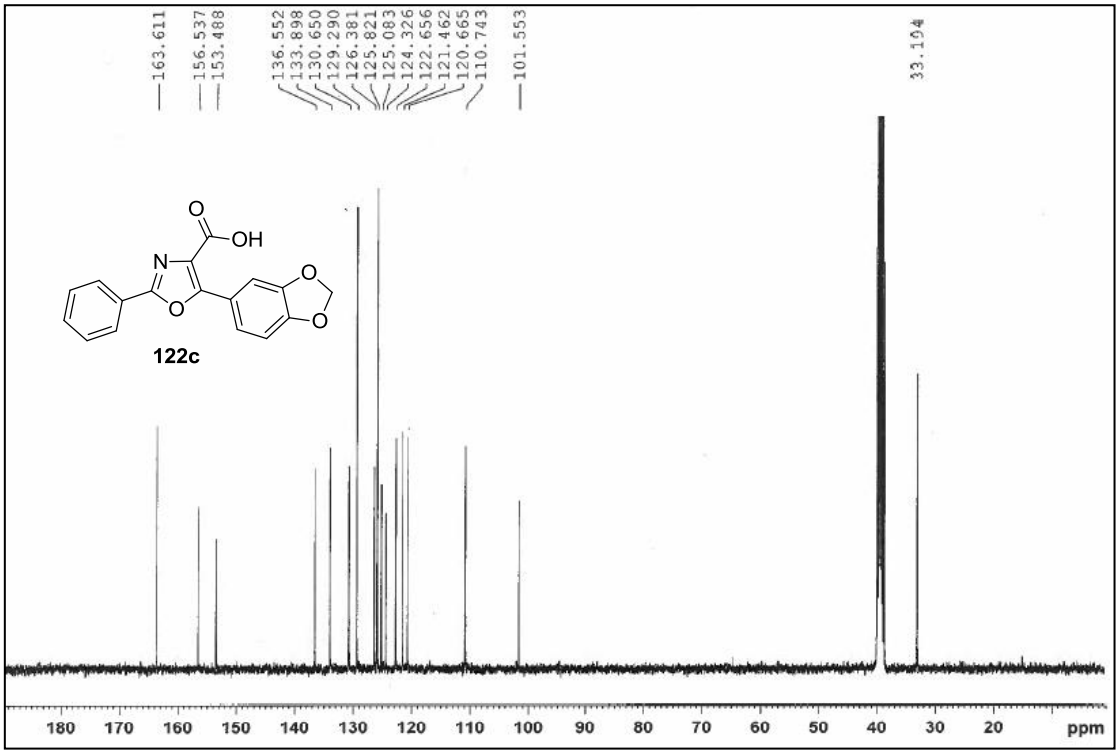
^{1}H NMR and ^{13}C NMR Spectra for compound **130a** in $CDCl_3$



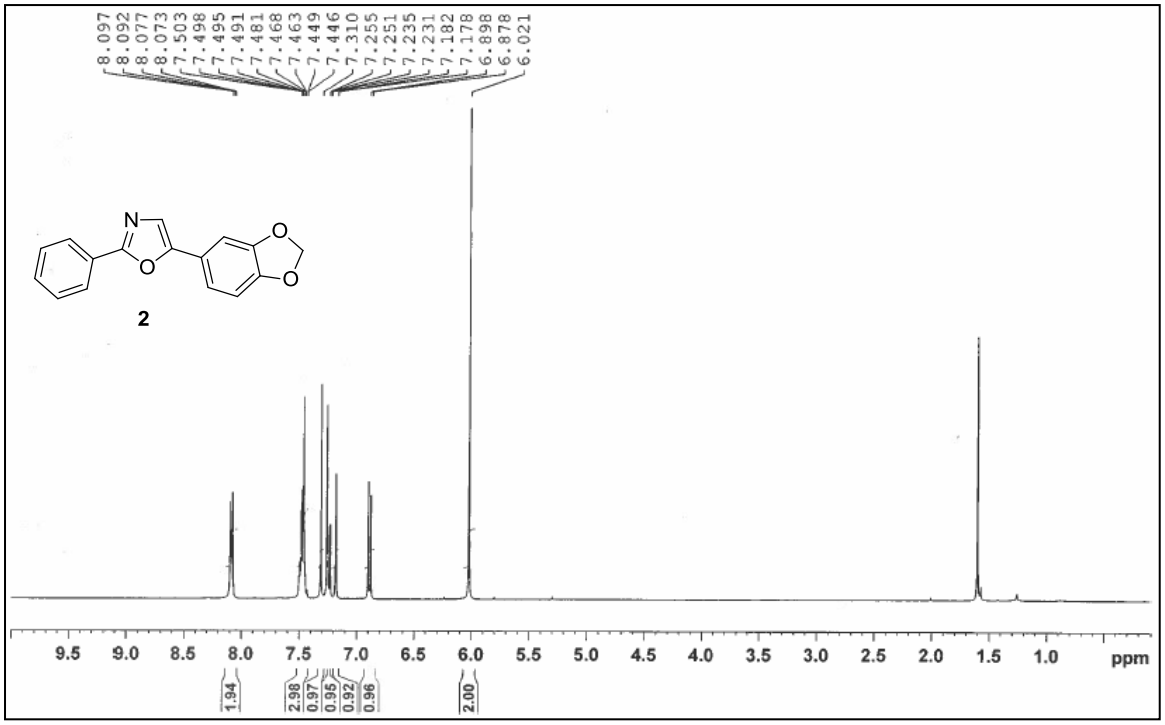


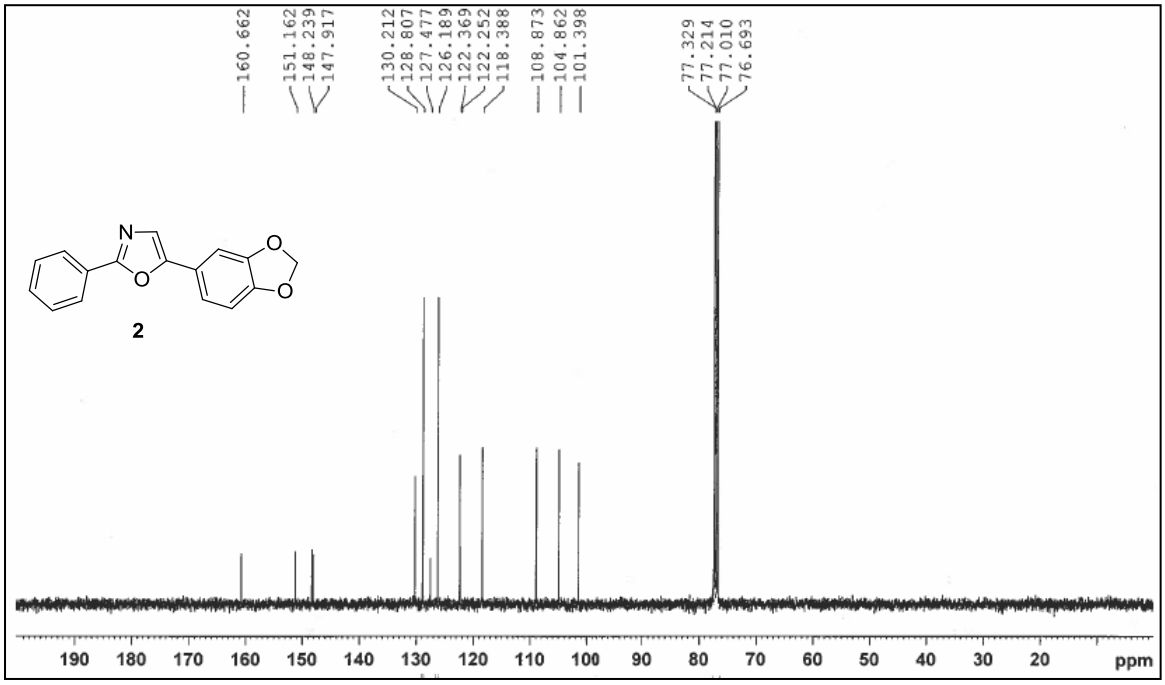
^{1}H NMR and ^{13}C NMR Spectra for compound **130d** in $CDCl_3$



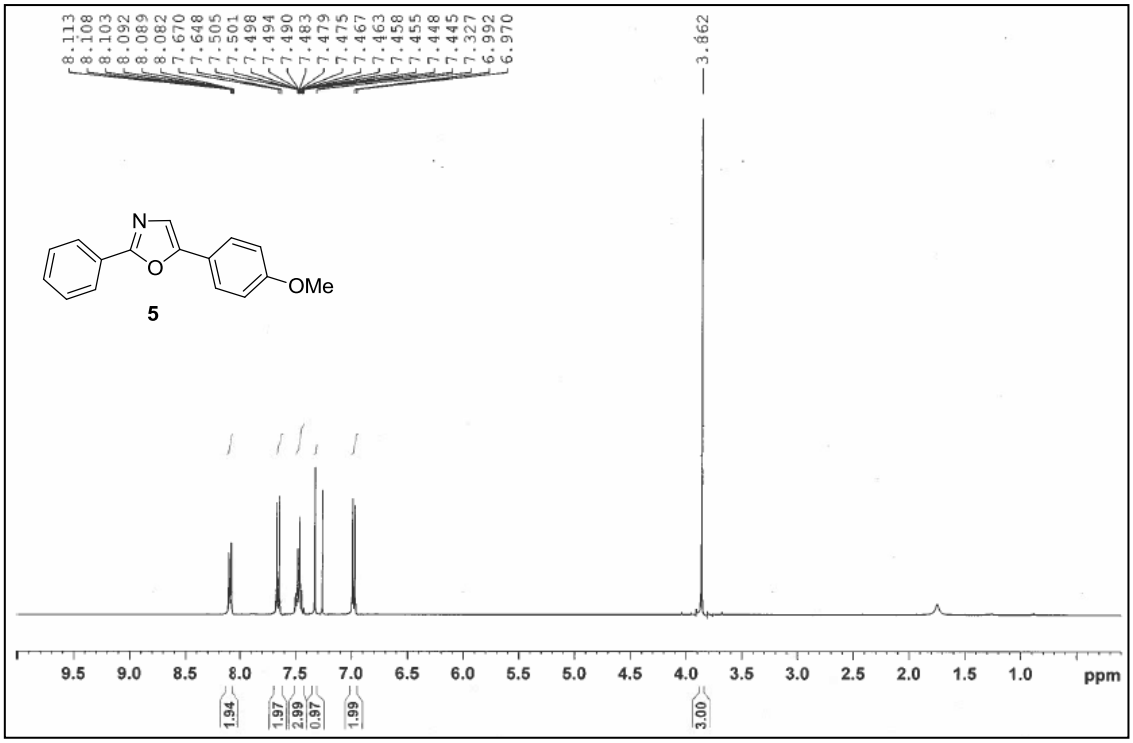


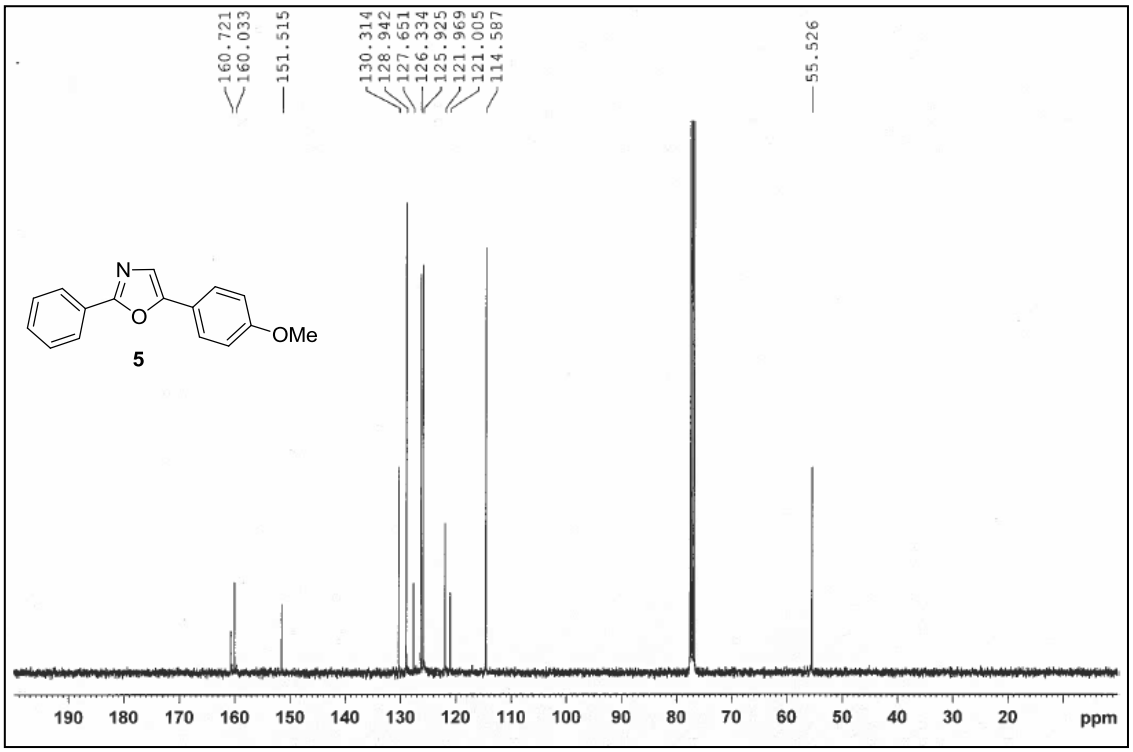
^{1}H NMR and ^{13}C NMR Spectra for compound **122c** in DMSO-d_6



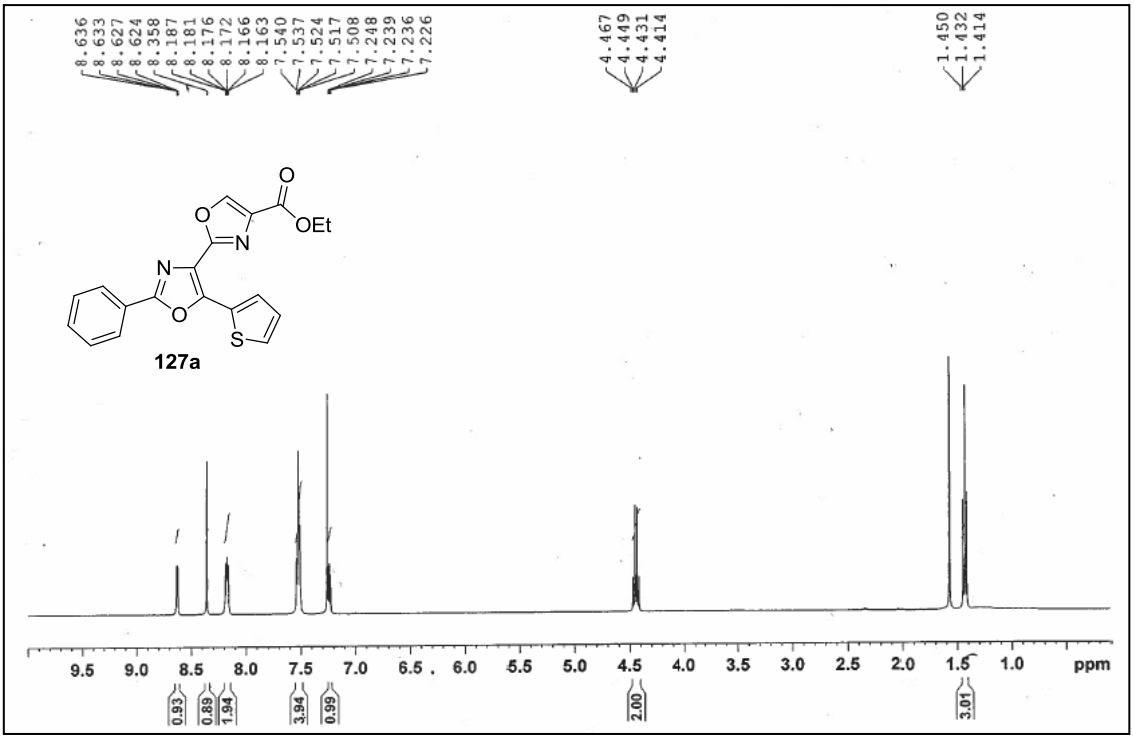


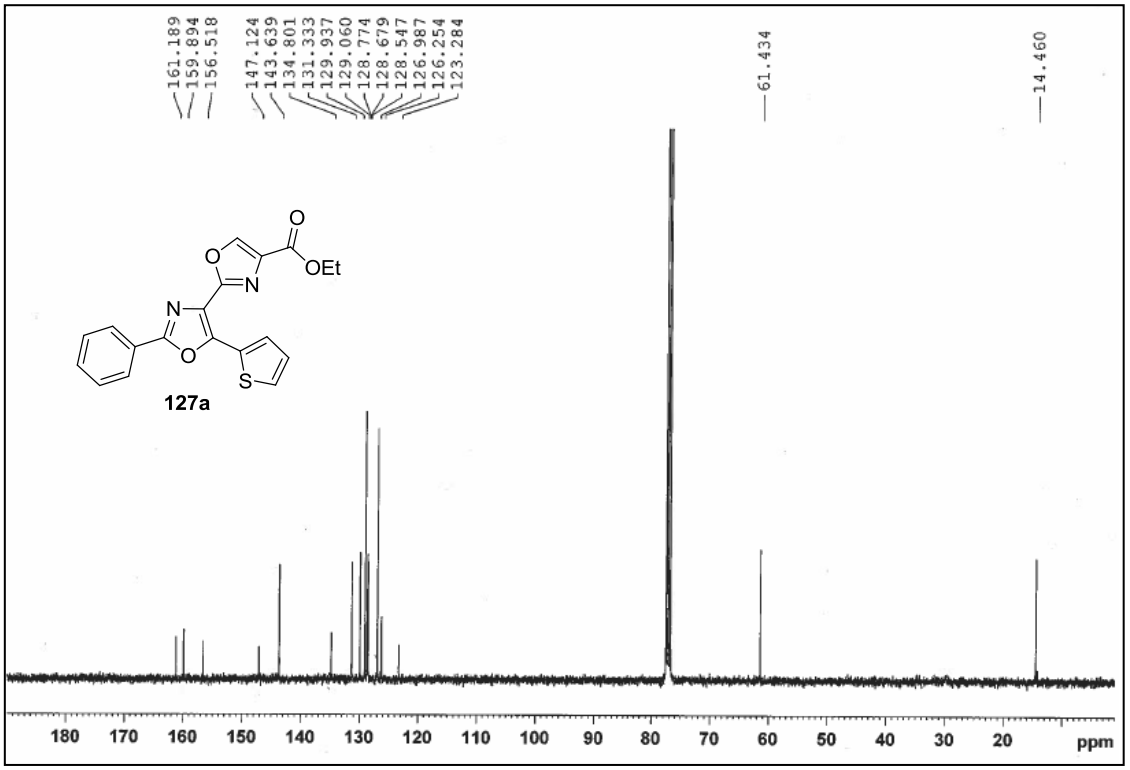
^{1}H NMR and ^{13}C NMR Spectra for compound **2** in $CDCl_3$



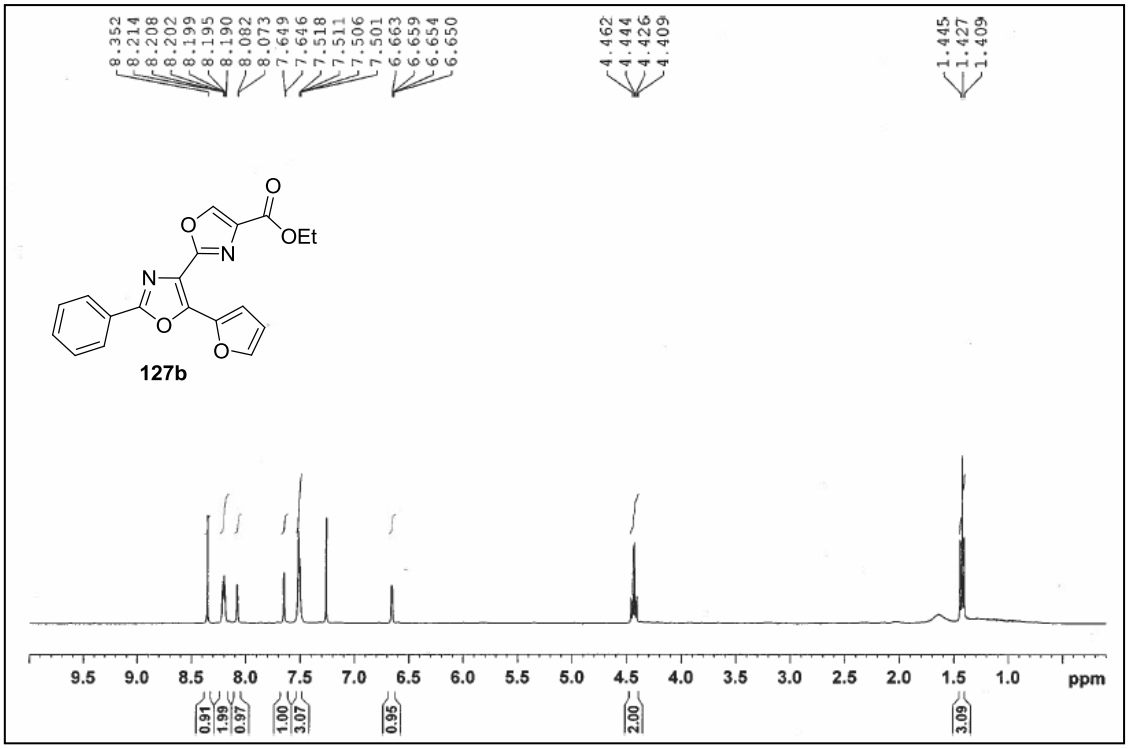


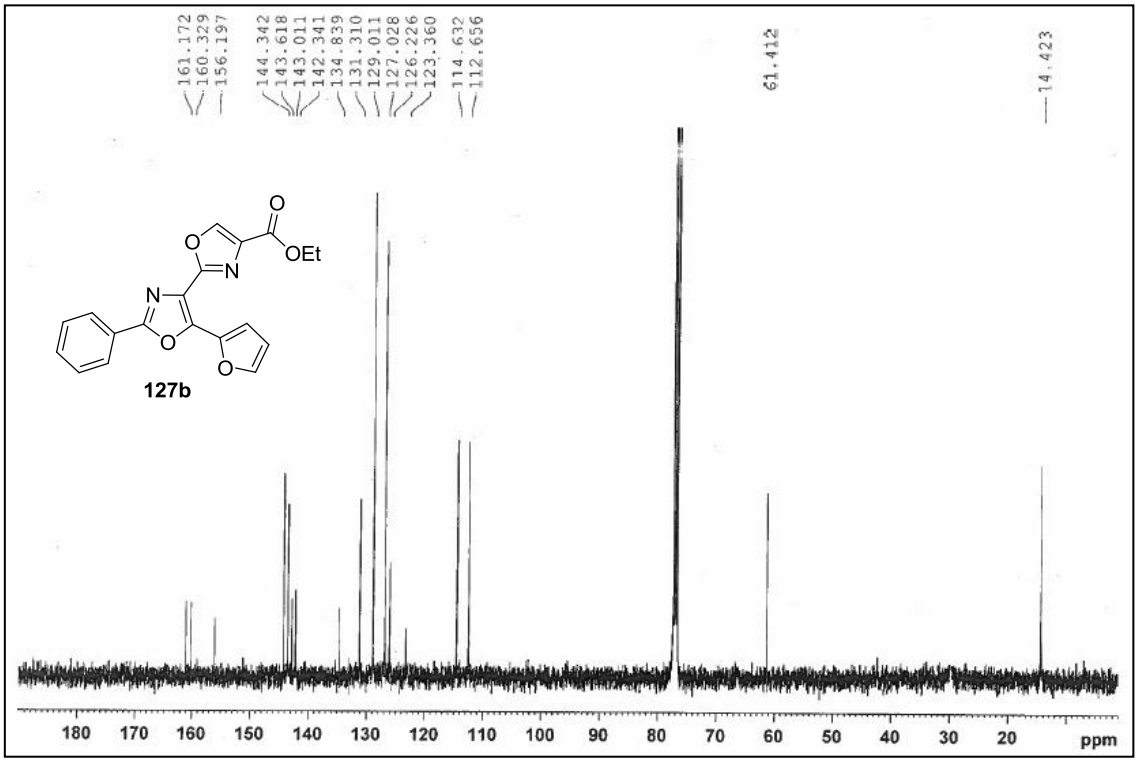
^{1}H NMR and ^{13}C NMR Spectra for compound **5** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **127a** in $CDCl_3$





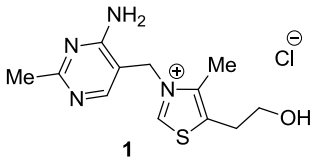
^{1}H NMR and ^{13}C NMR Spectra for compound **127b** in $CDCl_3$

Chapter 3

*Synthesis of 2,4,5-Trisubstituted Thiazoles via Lawesson's Reagent Mediated Chemoselective Thionation-Cyclization of Functionalized Enamides**

3.1 Introduction

Thiazoles[1] are one of the most commonly encountered heterocycles among the compounds of biological interest, as well as in bioactive natural products of microbial and marine origin (particularly non ribosomal peptides), exhibiting important biological activities,[1,2a] such as antitumor, antifungal, antibiotic, antiviral, antibacterial as well as peptidomimetic[2a-b] and enzyme inhibition.[2c-e] Thiazole ring plays a central role in the biochemistry of life, being incorporated into the structure of vitamin B1 (thiamine)[3] **1**, which is vital for natural function and the metabolism of carbohydrates.



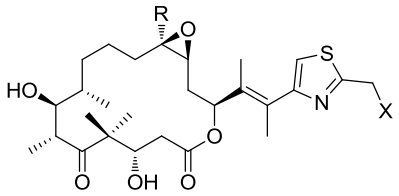
1

vitamine B1 (thiamine)

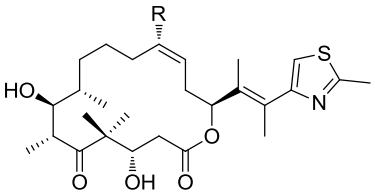
*The overall results of study described in this chapter have been published in *J. Org. Chem*. **2013**, *78*, 7362.

Substituted thiazoles are found in a number of natural products,[4] especially biologically active alkaloids,[5] and are increasingly being incorporated into pharmaceutical compounds,[6] They have also found applications in flavouring and perfume industries.[7] Major agrochemical compounds[8] have incorporated thiazole moiety for more than twenty years. Also, these class of compounds have found broad application as functional materials,[9a] due to their interesting electronic and optical properties.[10] They are used in liquid crystals for ferroelectric display[9b-c] and as cosmetic sunscreens.[9d-e] Synthetic thiazoles also occupy a prominent position in drug discovery process and this ring system is found in several marketed drugs.[11]

There are a number of different types of thiazole natural products, of which the most well known are the epothilones **2a-f**,[12,13] originally isolated from soil bacteria *Sorangium cellulosum*, exhibiting microtubule polymerization promoter activity similar to Taxol.[6f,14-16] Although structurally dissimilar, these compounds exhibit dramatically improved potency against multi-drug resistant tumour cell lines and thus have received considerable attention from medicinal chemists. Also in contrast to Taxol, multikilogram quantities of epithilones are available from fermentation which has allowed extensive biological studies of a number of its analogues.

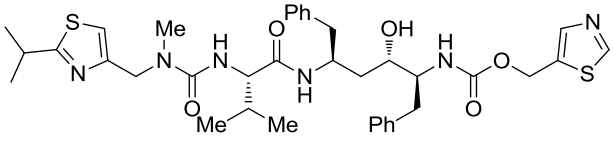


R = H, X = H, epothilone A, **2a**
R = Me, X = H, epothilone B, **2b**
R = H, X = OH, epothilone E, **2e**
R = Me, X = OH, epothilone F, **2f**



R = H, epothilone C, **2c**
R = Me, epothilone D, **2d**

Thiazoles are convenient bioisosteres for carbonyl or aromatic groups in the pharmaceutical industry.[17] Carbonyl and aromatic moieties can be quickly metabolized by the body, therefore, their replacement by thiazole analogue offers a better pharmacokinetic profile and increased concentration of drug reaching its point of action. Thiazole has been incorporated into ritonavir **3**, an HIV1 protease inhibitor,[18] which is perhaps the most well known drug containing two thiazole units.



3, ritonavir

It is common to utilize thiazoles in drug substances as can be seen in Chart 1. Meloxicam **4**, is a non-steroidal anti inflammatory compound (NSAID) developed by Boehringer Ingelheim for treatment in arthritis, dysmenorrheal and fever. It has a longer half-life *in vivo* than similar compounds, enabling it to be administered in a once daily dose.[19] Dasatinib **5**, was developed by Bristol Myers Squibb as an ABL/SCR family tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukaemia.[20] It is currently being

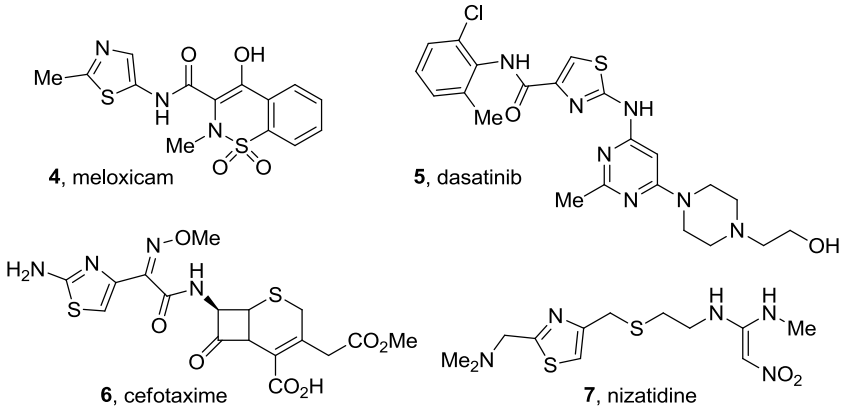


Chart 1: Thiazole pharmaceuticals

assessed for use in the treatment of metastatic melanoma also.[21] Cefotaxime, **6**, is a third generation cephalosporin antibiotic with broad spectrum activity against both gram positive and gram negative bacteria.[22] Nizatidine **7**, was developed by Eli Lilly, and is a histamine H_2 receptor antagonist, inhibiting the production of stomach acid,[23] thus used in the treatment of peptic ulcer and gastroesophageal reflux disease (Chart 1).

Many of the thiazole derivatives are used as agrochemicals as shown in Chart 2. Thiabendazole **8**, metsulfovax **9** and ethaboxam **10** are potent fungicides, whereas clothianidin **11** and thiamethoxam **12** are neonicotinoid insecticides,[8] used in seed treatment as well as for protection of juvenile and mature crops (Chart 2).

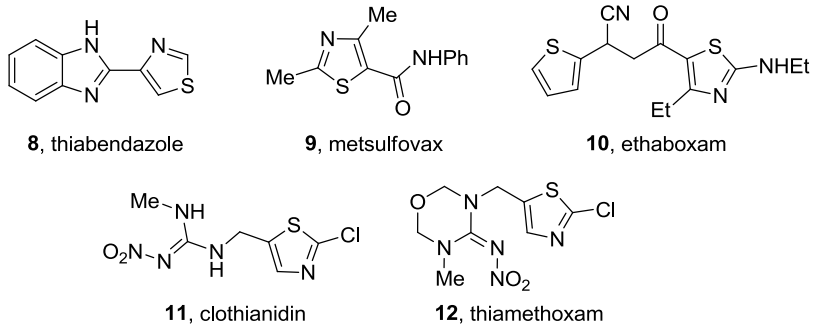


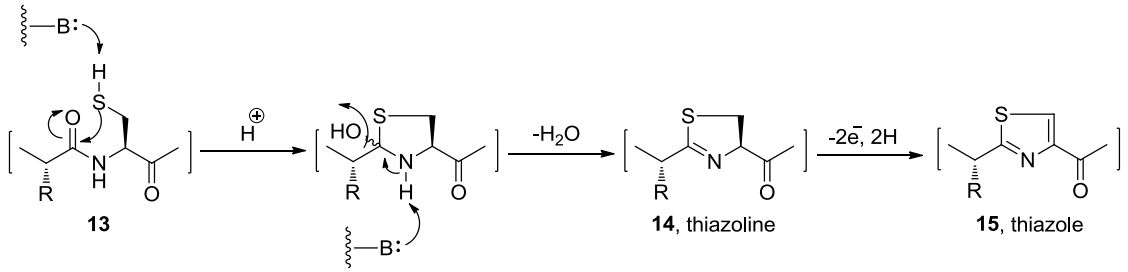
Chart 2. Thiazole agrochemicals

Therefore, in view of the structural diversity of the complex naturally occurring thiazoles along with their broad application in various fields, new methods continue to be developed for thiazole synthesis. Some of the recent important methods for thiazole syntheses are described in the following section.

3.2 Synthesis of substituted thiazoles: A short literature survey

3.2.1 Biosynthetic pathway

The thiazole ring is substituted in the C2 and C4 positions in natural products as a consequence of the biosynthesis of this ring. They originate from cysteine residues precursor **13** via enzymatic cyclization to thiazolines **14**, followed by their oxidation to thiazoles **15** (Scheme 1).[24]

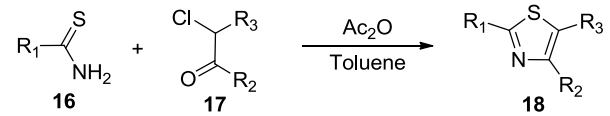


Scheme 1. Biosynthesis of thiazoles

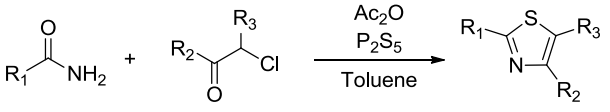
3.2.2 Chemical synthesis

3.2.2.1 Thiazoles from *α*-halocarbonyl compounds: *Hantzsch thiazole synthesis*

The most common method for synthesis of thiazoles was first developed by Hantzsch in 1889, involving cyclocondensation of *α*-haloketones **17** and thioamides **16** in a convergent manner (Scheme 2).[25] Its modified and improved version was developed by Erlenmeyer in 1947 which avoids the need to preform the thioamide and utilizes amides, which are in situ transformed into thioamides in the presence of P_2S_5 (Scheme 3).[26] However this method suffers from low to moderate yields.



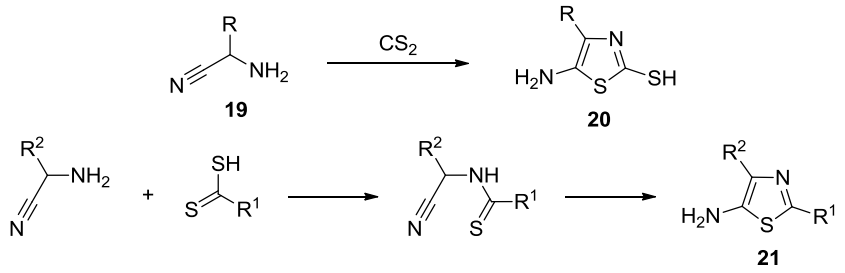
Scheme 2



Scheme 3

3.2.2.2 Thiazoles from *α*-aminonitriles: *Cook-Heilbron synthesis*

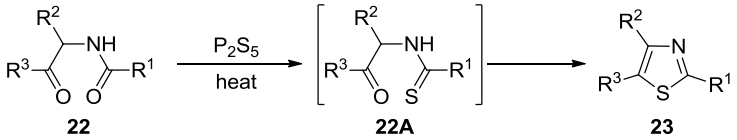
This type of synthesis, which was developed by Cook, Heilbron[27] and Takahashi involves condensation of *α*-aminonitrile with either CS_2, COS, salts and esters of dithiocarboxylic acids or isothiocyanates, furnishing 5-aminothiazoles **21** in good yields (Scheme 4).



Scheme 4

3.2.2.3 Thiazoles via intramolecular cyclization of *α*-acylaminocarbonyl compounds: *Gabriel Synthesis*

Intramolecular cyclization of *α*-acylamino ketones in presence of P_2S_5 via intermediacy of *α*-thioamidoketones **22A**, is a useful method for synthesis of 2,4,5-substituted thiazoles in good yields (Scheme 5).[28]



Scheme 5

To date, the majority of thiazoles are synthesized by the classical Hantzsch synthesis via intramolecular cyclocondensation of *α*-haloketones with thioamides. However, the synthesis of both *α*-haloketones and thioamides require several steps from commercially available compounds. To address this drawback, various methods for the synthesis of substituted thiazoles have been developed in recent years, some of which are shown in Chart 3. Thus, Wipf and co-workers have reported a novel thiazole synthesis based on the cyclocondensation of hypervalent alkynyliodonium salts **25** and thioamides.[29] Yields based on iodonium salts as limiting reagents range from 32 to 62%, and highly functionalized building blocks for natural product synthesis are readily prepared by this convergent, single-step process (Chart 3). Recently Moody and co-workers have developed a novel route to thiazoles involving cyclization of thiobenzamide with *α*-diazoketone **26** in presence of dirhodiumtetrakis catalyst.[30] Zhang and his group

have reported a novel synthesis of substituted thiazoles via AgOTf catalyzed cyclization of propargylic alcohols **27** with thioamides (Chart 3).[31] Donohoe and co-workers[32] have

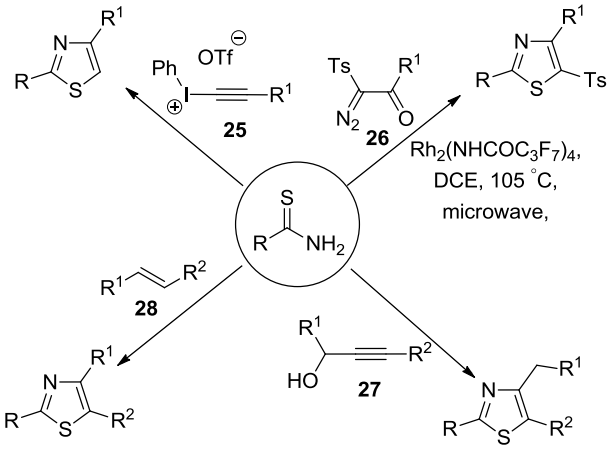
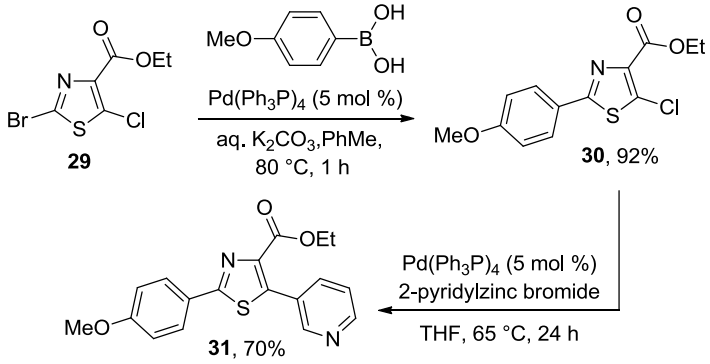


Chart 3

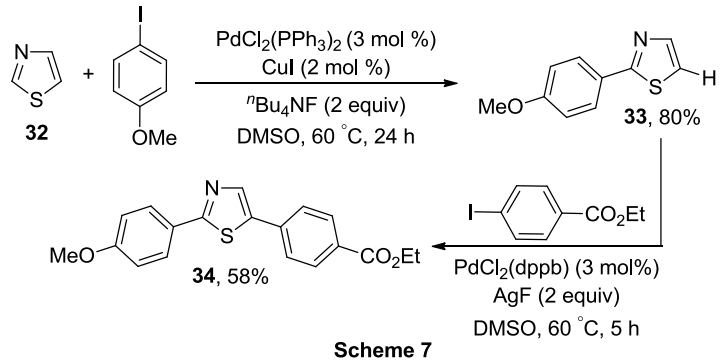
recently reported a novel approach to thiazoles via a two-step ketoiodination/cyclization of substituted olefins **28** with thioamides (Chart 3).

The most common approach for the synthesis of substituted thiazoles is functionalization of a pre-existing core. Thus, Hodgetts [33] reported a synthesis of 2,4,5-trisubstituted thiazoles such as **31** from ethyl 2-bromo-5-chloro-4-thiazolecarboxylate **29** using sequential Suzuki and Negishi coupling (Scheme 6).



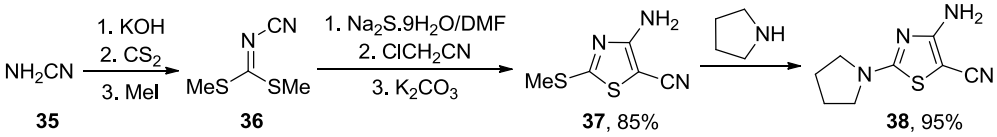
Scheme 6

Later, Mori and co-workers[34] developed the synthesis of 2,5-diarylthiazoles **34** from unsubstituted thiazole ring **32** using sequential palladium-catalyzed direct arylation protocol (Scheme 7). Since the preparation method is quite simple and practical, it would be suitable for the synthesis of a wide variety of related derivatives in a combinatorial manner.



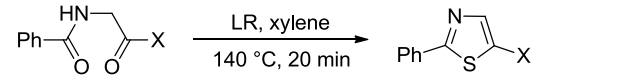
Scheme 7

Kirsch and co-workers[35] have reported the synthesis of 2,4,5-trisubstituted thiazoles in one-pot procedure from dimethyl cyanodithioimidocarbonate **36** which was prepared from cyanamide **35**. The compound **36** was reacted successively with sodium sulfide, chloroacetonitrile, and potassium carbonate to furnish 2-methylthio-3-amino-5-cyano thiazoles **37**. The nucleophilic substitution of 2-(methylthio) group in **37** with secondary amines allowed the formation of thiazoles **38** (Scheme 8).



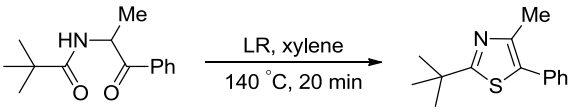
Scheme 8

There are several reports of the synthesis of thiazoles from *α*-acylamino ketones using Lawesson's reagent (LR).[36a-d] In 1983, Lawesson had demonstrated that the reaction of Lawesson's reagent with *N*-acylamino acid derivatives such as **39a-b** smoothly produces substituted thiazole **40**.[36a] Accordingly, 1-(*N*-benzoyl-glycyl)-ethyl ester **39a** and 1-(*N*-benzoyl-glycyl)-piperidine **39b** gave 2-phenyl-5-ethoxythiazole **40a** and 2-phenyl-5-piperidinothiazole **40b** in high yields (Scheme 9).



Scheme 9

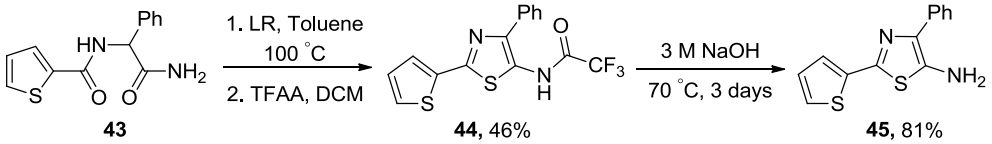
Nishio and co-workers have reported that, treatment of 2-acylamino ketones such as **41** with an equimolar amount of Lawesson's reagent in toluene at reflux temperature for 15 min, furnished exclusively thiazole derivatives **42** in good yield (Scheme 10).[36d] However, this method is not well explored, probably because of the lack of availability of structural variants of *α*-acylaminocarbonyl compounds.



41 **42,** 92%

Scheme 10

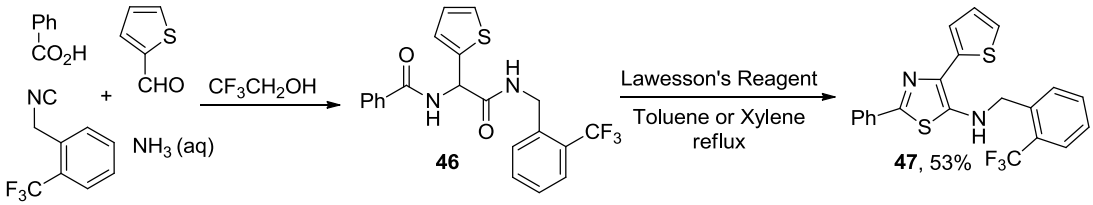
Recently, Chen and co-workers[37] have reported the synthesis of 2-substituted 4-phenyl-5-aminothiazoles such as **45** in moderate yield, involving the thionation of *α*-acylglycinamides **43** with Lawesson's reagent and subsequent TFAA mediated cyclization of thioamide intermediate followed by deprotection of the 5-*N*-trifluoroacetyl group (Scheme 11).



43 **44,** 46% **45,** 81%

Scheme 11

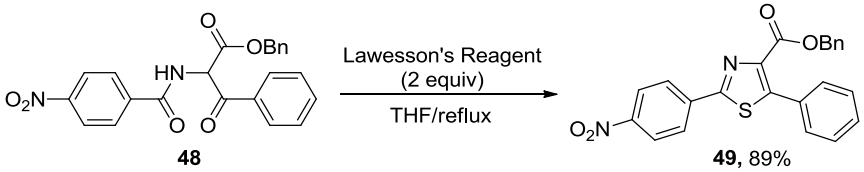
Later, the same group developed a four-component Ugi reaction using ammonia as the amine component, resulting in a simple one-step assembly of diamide precursors **46** that were transformed into a library of 2,4-substituted 5-primary or secondary aminothiazoles in moderate to low yields by thionation with Lawesson's reagent (Scheme 12).[38]



46 **47**, 53%

Scheme 12

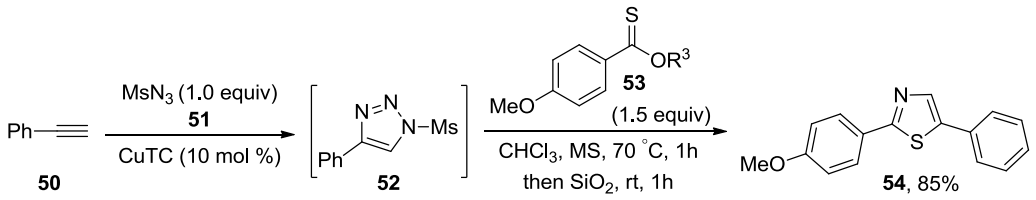
Sanz-Cervera and co-workers[39] have described the efficient fluorous and solution phase synthesis of a small library of 2,5-substituted thiazole-4-carboxylic esters as potential antibacterial compounds through the thionation and cyclization of *α*-amido-*β*-ketoesters with Lawesson's reagent (Scheme 13).



48 **49,** 89%

Scheme 13

Recently Miura and co-workers reported a sequential procedure for the synthesis of 2,5- disubstituted thiazoles from terminal alkynes, sulfonyl azides, and thionoesters.[40] A copper(I) catalyzed 1,3-dipolar cycloaddition of terminal alkynes **50** with sulfonyl azides affords 1-sulfonyl- 1,2,3-triazoles **52**, which then react with thionoesters in the presence of a rhodium (II) catalyst. The resulting 3-sulfonyl-4-thiazolines subsequently aromatize into the corresponding 2,5-disubstituted thiazoles **54** by elimination of the sulfonyl group (Scheme 14).

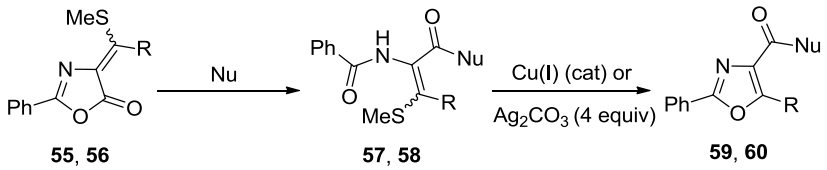


Scheme 14

3.3 Present work

3.3.1 Inrtoduction

Our own interest in thiazole synthesis derived from our earlier reported protocol for the efficient synthesis of 2-phenyl-5-(methylthio)/(het)aryl-4-functionlized oxazoles **59-60** from the common 2-phenyl-4-[(methylthio)-het(aryl)/bis(methylthio)methylene]-5-oxazolone precursors **55** and **56** (Scheme 15).[41,42] The oxazolones **55** and **56** were shown to undergo facile ring opening in the presence of various oxygen (alkoxides), nitrogen (primary/secondary amines) and carbon (Grignard reagents) nucleophiles, yielding functionalized enamide precursors such as **57** and **58**, which on subsequent copper catalyzed (for **57**) and silver carbonate mediated (for **58**) 5-*endo* cyclization, afford substituted oxazoles **59** and **60** respectively in high yields (Scheme 15).[41a,42a]

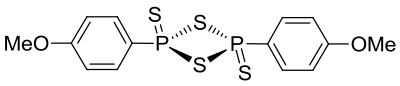


55, 57, 59, R= Substituted (het)aryl; **56, 58, 60,** R= SMe;
Nu = $\overset{\ominus}{O}$Alk, NH(R^1R^2), R^3MgX

Scheme 15

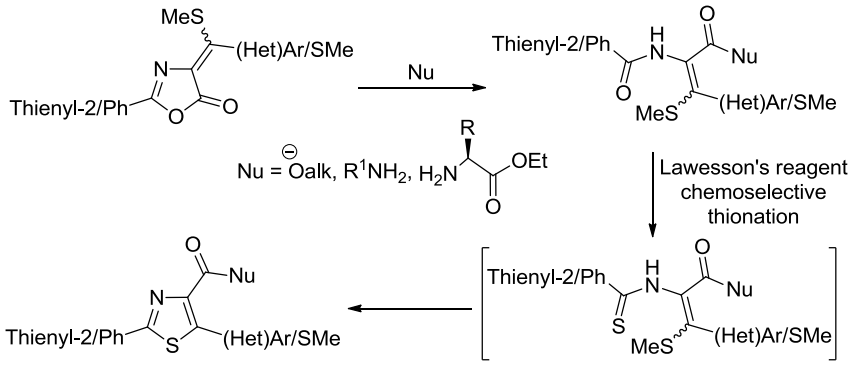
In continuation of this work, we further envisaged to utilize these enamide precursors **57** and **58** for the synthesis of 2,4,5-substituted thiazoles via thionation-

cyclization of these intermediates in the presence of Lawesson's reagent (Schemes 18 and 20).



Lawesson's Reagent (LR)

In the present chapter, we hereby report an efficient route to 2-phenyl/(2-thienyl)-5-(het)aryl/(methylthio)-4-functionalized thiazoles *via* one step chemoselective thionation-cyclization of highly functionalized enamides, mediated by Lawesson's reagent. These enamide precursors were obtained by nucleophilic ring opening of 2-phenyl/(2-thienyl)-4-[bis(methylthio)/(methylthio)(het)arylmethylene]-5-oxazolones with alkoxides and a variety of primary aromatic/aliphatic amines or amino acid esters, thus leading to the introduction of an ester, N-substituted carboxamide or peptide functionality in the 4-position of the product thiazoles (Scheme A). These results are described in the following section.

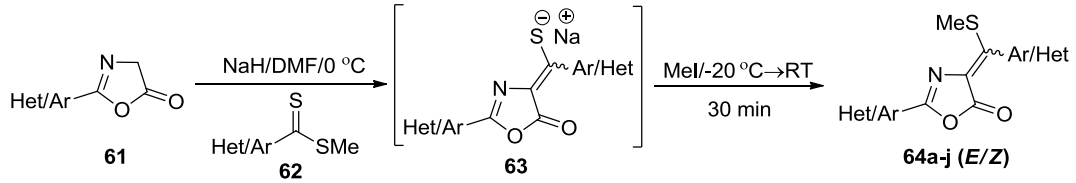


Scheme A

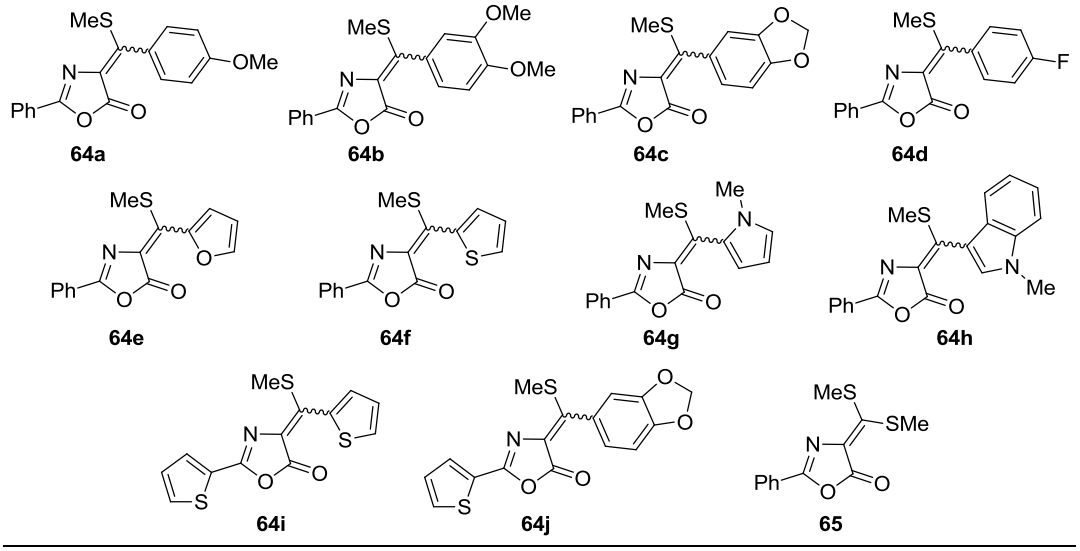
3.3.2 Results and discussion

3.3.2.1 Synthesis of 2-phenyl/thienyl-4-[(methylthio)-(het)aryl/bis(methylthio)-methylene]-5-oxazolone precursors 64a-j and 65

The desired 4-[(methylthio)-(het)arylmethylene]-2-phenyl/(2-thienyl)-5-oxazolones precursors **64a-j** or the corresponding 4-[bis(methylthio)methylene] derivative **65** (Scheme 16) were obtained in good yields according to the reported procedure.[41,42]

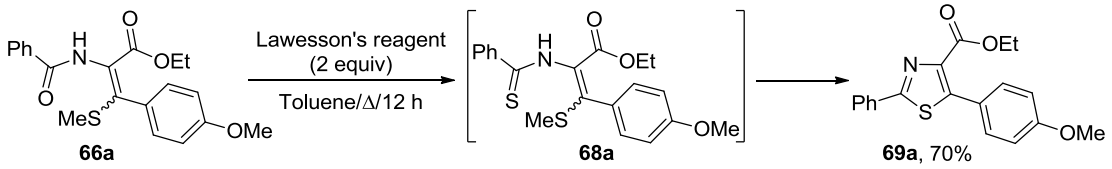


Scheme 16



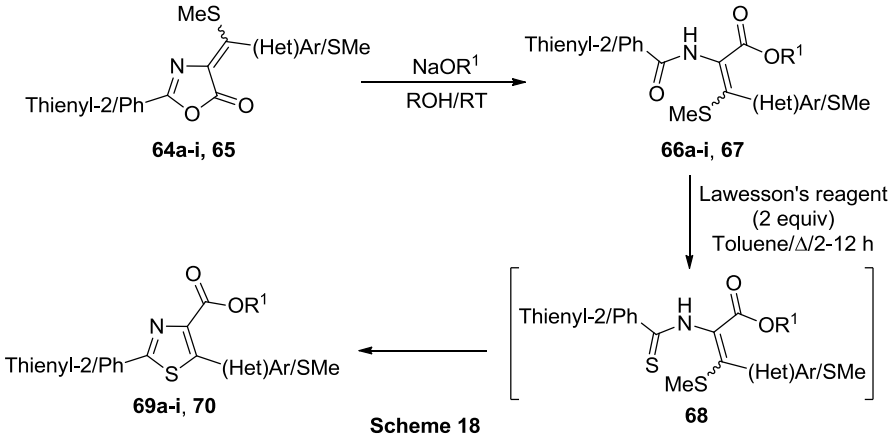
3.3.2.2 Synthesis of 2-phenyl/(2-thienyl)-5-(het)aryl/(methylthio)thiazole-4-carboxylates 69a-i and 70

We first examined the synthesis of 2-phenyl-5-(het)arylthiazole-4-carboxylates **69a-i** and the corresponding 5-(methylthio)thiazole-4-carboxylate **70** via thionation-cyclization of the enamino esters **66a-i** and **67** respectively, which were obtained in high yields by nucleophilic ring opening of the corresponding oxazolones **64** or **65** with various sodium alkoxides, as reported earlier (Scheme 17).[41a,42] Thionation-cyclization of the enamide ester **66a** to thiazole-4-carboxylate **69a** was first attempted, as a model substrate for optimization of reaction conditions. Thus, refluxing **66a** with 1 equiv of Lawesson's reagent in THF for prolonged time, yielded only unreacted starting material with no trace of thiazole **69a** (or thioamide **68a**). However we found, that higher temperature reflux in toluene for 12 h, resulted in efficient thionation as well as intramolecular cyclization of **66a**, furnishing ethyl 2-phenyl-4-(methoxyphenyl)thiazole-4-carboxylate **69a** in 68% yield. On the other hand, when **66a** was reacted with 2 equiv of Lawesson's reagent in refluxing toluene, reaction was complete within 2 h yielding **69a** in 70% yield (Scheme 17).

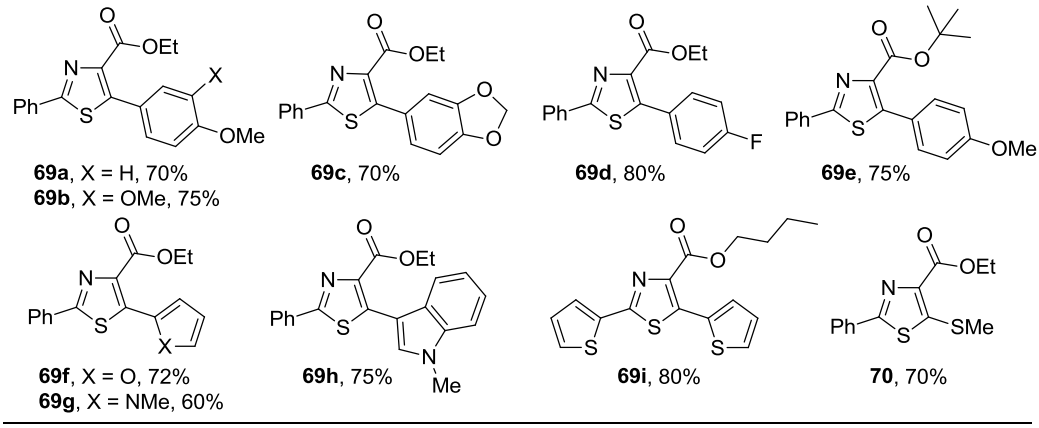


Scheme 17

Therefore this optimized protocol (with 2 equiv of Lawesson's reagent) for the conversion of **66a** to **69a** was used throughout for the synthesis of other 5-(het)arylthiazole-4-carboxylates **69b-i** as shown in the Scheme 18. Thus the reaction was equally facile for the synthesis of other 5-arylthiazole-4-carboxylates **69b-d** carrying both electron donating (**69b-c**) and electron withdrawing (**69d**) substituents on 5-aryl group. Interestingly, the thionation-cyclization of the enamide *t*-butyl carboxylate **66e**, also proceeded smoothly without any side reactions, yielding the corresponding *t*-butyl thiazole-4-carboxylate **69e** in 75% yield. Similarly, the enaminone carboxylic esters **66f-h** carrying various het(aryl) groups, were also converted into the corresponding 2-phenyl-5-(2-furyl)/(2-*N*-methylpyrrolyl)/(3-*N*-methylindolyl)thiazoles **69f-h** in good yields, under identical conditions, requiring prolonged refluxing (12 h) (Scheme 18). Further diversity at the 2 and 5 positions of the product thiazoles **69** could be achieved by synthesis of the corresponding *n*-butyl 2,5-bis(2-thienyl)thiazole-4-carboxylate **69i** in 80% yield by



Scheme 18



thionation-cyclization of enaminoester **66i** obtained by ring opening of 2-thienyl-4-[methylthio(2-thienyl)methylene]-5-oxazolone **64i** with sodium *n*-butoxide (Scheme 18).[42b] Extension of the protocol to bis(methylthio)enamide carboxylate **67** (obtained by ring opening of **65** with sodium ethoxide) also afforded the ethyl 2-phenyl-5-(methylthio)thiazole-4-carboxylate **70** in 70% yield (Scheme 18). The structures of all these newly synthesized thiazoles were confirmed with the help of spectral and analytical data and also by X-ray crystal structure analysis of thiazole ester **69b** (Figure 1).

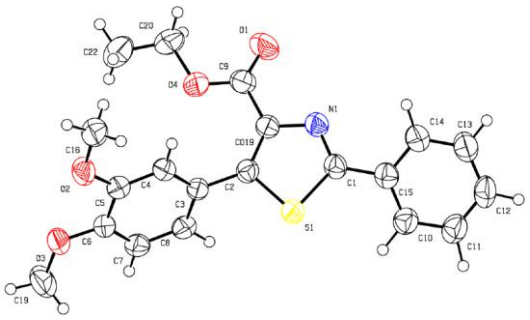


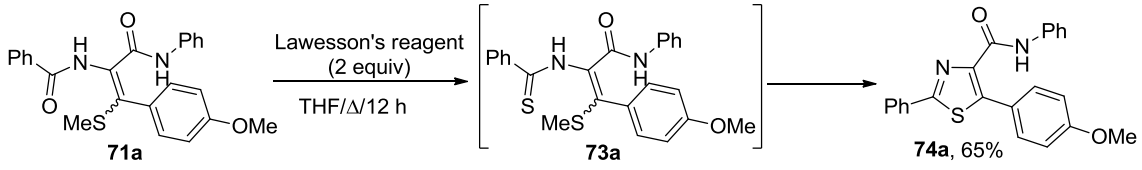
Figure 1. X-ray crystal structure of thiazole ester **69b**

3.3.2.3. Synthesis of N-substituted 2-phenyl/(2-Thienyl)-5- (het)aryl/(methylthio) thiazole-4-carboxamides 74a-k and 75

With successful synthesis of 2,5-(het)arylthiazole-4-carboxylates **69-70** in hand, we next investigated elaboration of this protocol, for the synthesis of 2,5-(het)arylthiazole-4-(N-aryl/alkyl)carboxamides **74a-k** and **75** by one step thionation-cyclization of the corresponding enamides **71a-k** or **72**, bearing a secondary amide functionality, which were readily accessible by ring opening of the corresponding oxazolones **64** or **65** with primary aliphatic, aromatic amines or amino acid esters as reported earlier (Scheme 15).[41,42] It should be noted, that these enamide-amide precursors **71-72** carry two secondary amide functionalities (though electronically different), and their transformation to the corresponding thiazole-4-(N-substituted)carboxamides **74-75** in the presence of Lawesson's reagent is more challenging, requiring chemoselective thionation of enamide benzoylamino group, leading to the enamide monothioamide intermediates **73**, which on intramolecular cyclization would afford the desired thiazoles **74-75** (Scheme 20).

We therefore selected enamide-anilide **71a** as the model substrate for evaluation of optimal conditions, for its chemoselective thionation-cyclization to the thiazole **74a** (Scheme 19). To begin with, the thionation-cyclization of **71a** was conducted in refluxing

toluene in the presence of 2 equivalents of Lawesson's reagent, under previously described conditions for the conversion of enamide carboxylates **66-67** to thiazole 4-carboxylates **69-70** (Scheme 18). However these enamide-amide intermediates **71-72** were found to be insoluble in toluene and attempted cyclization of **71a** to **74a** under toluene reflux for prolonged time (20 h) led only to the unreacted starting material. On the other hand, when **71a** was reacted with Lawesson's reagent (2 equiv) in refluxing THF for 12 h, analysis of reaction mixture revealed exclusive formation of only one product in reasonably good yield (65%), which to our delight, was found to be the desired 2-pheny-5-(4-methoxyphenyl)-thiazole-4-(N-phenyl)carboxamide **74a** on the basis of its spectral and analytical data (Scheme 19).

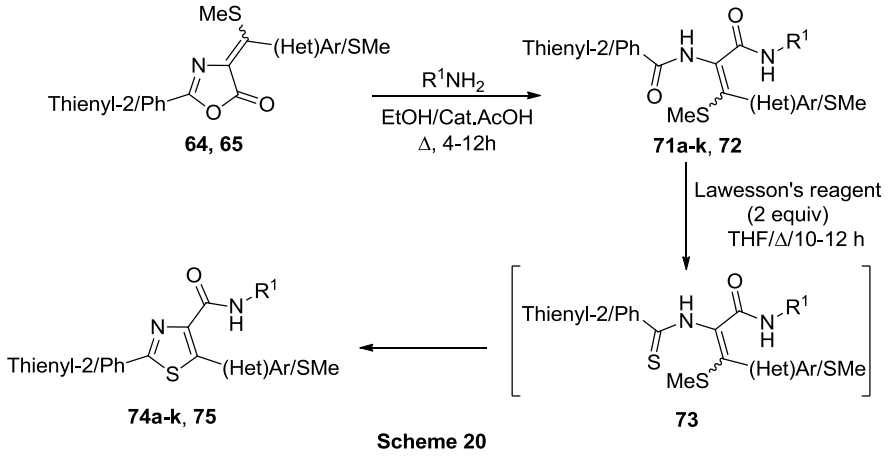


Scheme 19

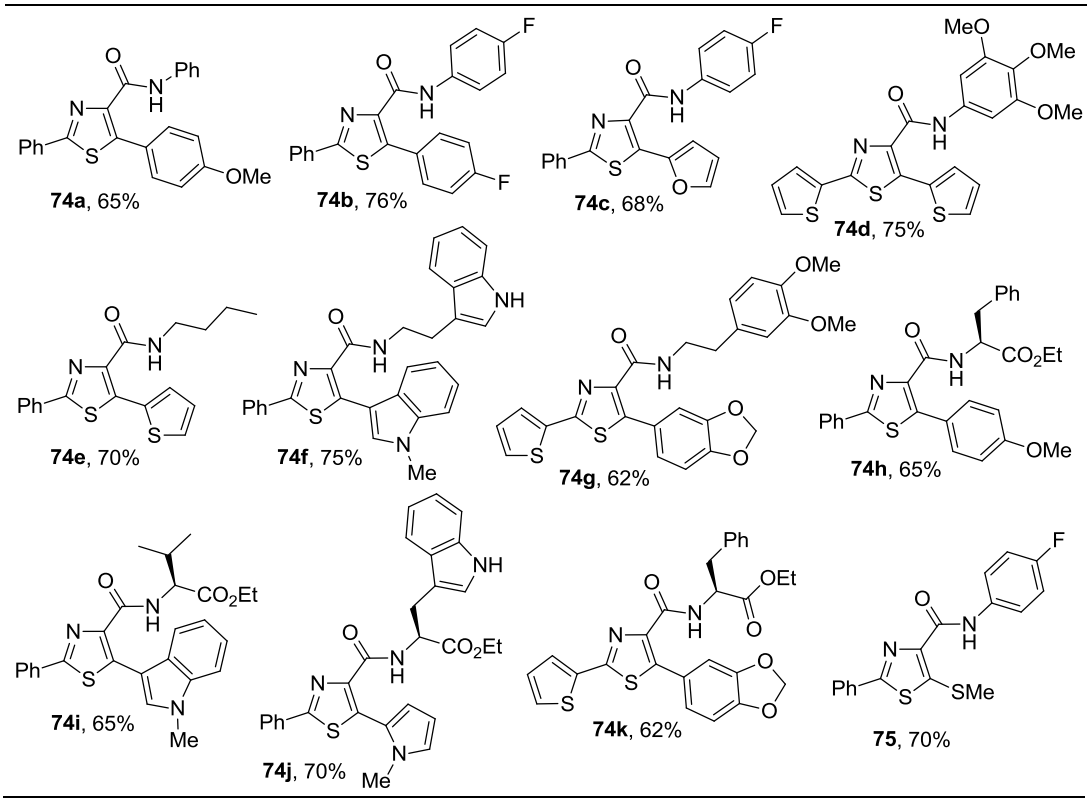
Similarly, the other enamide-anilide precursors **71b-c**, derived from ring opening of oxazolones **64d-e** with 4-fluoroaniline, also underwent facile chemoselective monothionation-cyclization in the presence of Lawesson's reagent, furnishing the corresponding 2-phenyl-5-(het)arylthiazole-4-carboxyanilides **74b-c** in good yields (Scheme 20). Similarly, the 2,5-bis(2-thienyl)thiazole-4-carboxyanilide **74d** could also be obtained in 75% yield, by thionation-cyclization of the enamide precursor **71d** (obtained by ring opening of 2-(2-thienyl)-4-[(methylthio)(2-thienyl)methylene]-5-oxazolone **64i** with 3,4,5-trimethoxyaniline). The versatility and the scope of this chemoselective monothionation-cyclization protocol was further demonstrated by efficient synthesis of 2-phenyl/(2-thienyl)-5-(het)arylthiazole-4-(*N*-alkyl)carboxamides **74e-g** in good yields from the respective enamide-*N*-(alkyl)amides **71e-g** under the identical conditions (Scheme 20).

With the successful implementation of this strategy for the synthesis of 2,5-(het)arylthiazole-4-(N-aryl/alkyl)carboxamides **74a-g**, we further envisaged interesting extension of this work for the synthesis of thiazole based peptidomimetics such as **74h-k**, which are known to display interesting biological activity.[2b-c] We were indeed delighted to find that open- chain peptidoenamide precursors **71h-k** (obtained by ring opening of **64** with various amino acid esters i.e., phenyalanine, valine and tryptophan) were smoothly

transformed into thiazole based peptidomimetics **74h-k**, with a range of 5-(het)aryl groups, in good yields, under these optimized reaction conditions (Scheme 20). Finally the corresponding bis[(methylthio)methylene]enamide anilide **72** (obtained by ring opening of 4-bis(methylthio)methyleneoxazolone **65** with 4-fluoroaniline) also afforded the corresponding 2-phenyl-5-(methylthio)thiazole-4-(*N*-4-flurophenyl)carboxyanilide **75** in 70% yield (Scheme 20).



Scheme 20



The structure of these thiazole carboxamides was further confirmed by X-ray crystal structure analysis of **74b** (Figure 2).

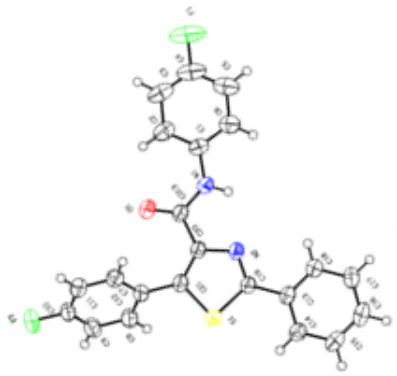
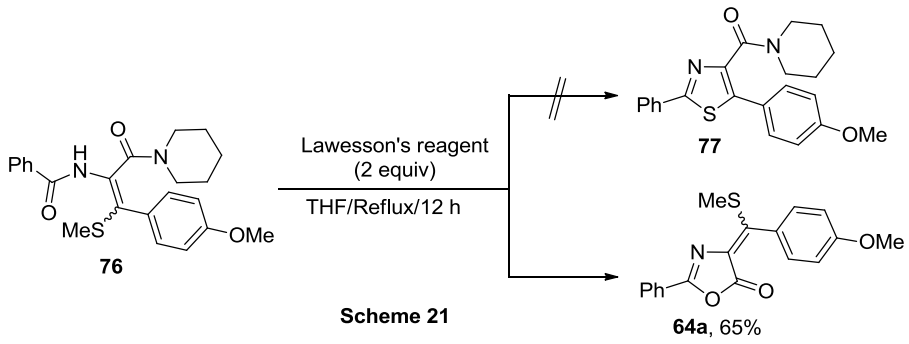


Figure 2. X-ray crystal structure of thiazole-4-carboxamide **74b**

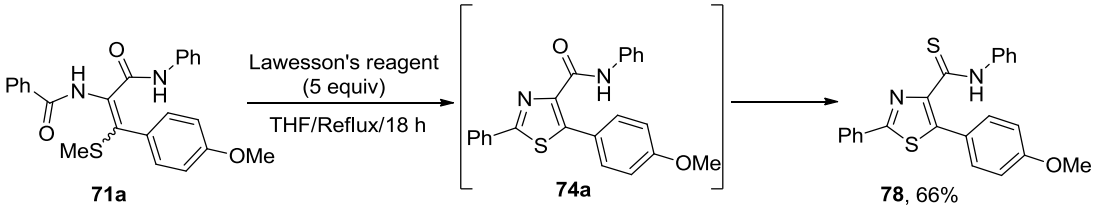
3.3.2.4 Thionation-cyclization of *N*-piperidino-enamide-amide 76

Interestingly, attempted thionation-cyclization of tertiary amide **76** (derived from ring opening of **64a** with piperidine, did not furnish the desired thiazole-5-tertiary-amide **77**. The product isolated was characterized as the 2-phenl-4-[(4-methoxyarylidene) (methylthio)]oxazolone **64a** formed by thermal eliminative cyclization of **76**, presumably due to the steric reasons (Scheme 21).



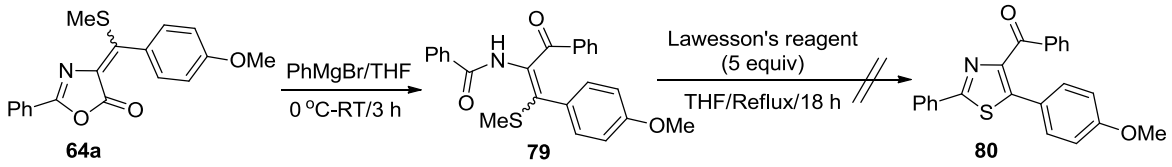
Scheme 21

When the enamide-anilide **71a** was reacted with excess of Lawesson's reagent (5 equiv) in refluxing THF for prolonged time (18 hr), monitoring of reaction showed initial formation of thiazole-4-anilide **74a**, which was slowly converted to the thiazole-4-thioanilide **78** in 66% yield. Similarly, when the thiazole **74a** was reacted with Lawesson's reagent (2 equiv) for 8 hr in refluxing THF, the thioanilide **78** was obtained in 65 % yield (Scheme 22).



Scheme 22

Finally, after successful implementation of this one step thionation-cyclization protocol for the synthesis of thiazole-4-carboxylates **69** and thiazole-4-carboxamides **74** (Scheme 18, 20), we next focussed our studies on the synthesis of 2,5-substituted 4-aroylthiazoles **80** via ring opening of oxazolones **64** with Grignard reagents (Scheme 23). Thus, treatment of **64a** with phenyl magnesium bromide gave the α-aroylenamide **79** (75%) exclusively with no trace of conjugate addition-elimination product. The enamide **79** was subjected to thionation-cyclization under optimized conditions to furnish the 2-phenyl-5-(4-methoxyphenyl)-4-(benzoyl)thiazole **80**, but we ended up with only polymeric mixture (Scheme 23).



Scheme 23

3.4 Conclusion

In this chapter, we have devised a highly regio- and chemoselective, useful protocol for the synthesis of 2,4,5-trisubstituted thiazoles via one step thionation-cyclization of functionalized enamide precursors in the presence of Lawesson's reagent. These enamide intermediates are readily available in high yields by nucleophilic ring opening of a number of 4-[(methylthio)-(het)arylmethylene]-5-oxazolones with alkoxides or a variety of primary aliphatic, aromatic amines and amino acid esters, offering a wide range of functional group diversity at 4- and 5-positions of the product thiazoles. Also, the remarkable chemoselectivity observed in the facile thionation of benzoylamino group (over the other secondary amide moiety) in enamides **71-72**, is particularly noteworthy, since, selective conversion of an amide to thioamide with various thionating agents is often not feasible for substrates, comprised of ketone, esters and amide moieties.[36a, 43] Additionally, thionation-cyclization of the aminoacid derived enamide precursors **71h-k**, provides an access to a range of potentially biologically relevant, thiazole based chiral peptidomimetics. The broad scope and operational simplicity of the reaction, along with the diversity of the compatible starting materials, makes this methodology attractive for the synthesis of biologically important thiazoles, with option for combinatorial synthesis.

Although it is not possible to give a definite explanation for the observed chemoselectivity in the thionation of enamide amides **71-72** with Lawesson's reagent,

however it appears that enamide carbonyl group is more electrophilic (because of the delocalization of the nitrogen lone pair on double bond), than the carbonyl group of the other secondary amide moiety, thus undergoing faster nucleophilic attack by the dissociated Lawesson's reagent, followed by facile intramolecular cyclization of the resulting thioamides to the corresponding thiazoles.[36a]

3.5 Experimental section

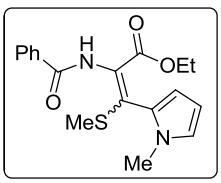
3.5.1 General information

The general experimental details were the same as those described in Chapter 2. X-ray single crystal data was collected on a diffractometer using MoK_α radiation (λ = 0.71073 Å), at room temperature. The structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares against F^2 using SHELXL-97 software.

The desired oxazolone precursors **64a-j** and **65** were prepared according to the reported procedure.[41-42] Similarly, all the starting enamide esters **66a-i** and **67** were obtained by ring opening of the corresponding oxazolones **64a-e**, **64g-i** or **65** with appropriate alkoxides in alkanols as reported,[41a,42a] whereas, the enamide amide precursors **71a-k** and **72** were prepared by ring opening of the respective oxazolones **64a,64d-j** or **65** with appropriate primary amines or amino acid esters.[41,42a] The known enamide esters **66a-c, 66e-f, 66h, 67** and the enamide amides **71f**, **71h**, **71j** and **72** were characterized by comparison of their spectral data with those reported,[41a,42a] whereas the spectral and analytical data of the unknown **66g, 66i, 71a-c**, **71g** and **71k** is given below. A few of the enamides (**66d**, **71d-e** and **71i**) were subjected to thionation-cyclization without further purification and characterization.

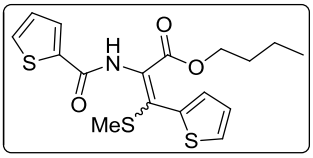
The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem*. **2013**, *78*, 7362.

(*E*) Ethyl 2-benzamido-3-(1-methyl-1*H*-pyrrol-2-yl)-3-(methylthio)acrylate (66g).



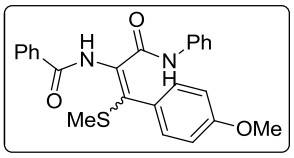
Brown semisolid (268 mg, 78%): R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3310, 1648, 1478, 1296; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.59-7.57 (m, 2H), 7.50-7.46 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 6.71 (t, *J* = 2.4 Hz, 1H), 6.19-6.17 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.59(s, 3H), 1.86 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 164.2, 133.5, 132.1, 130.5, 128.8, 127.3, 126.7, 124.9, 124.7, 110.5, 108.4, 61.7, 34.4, 15.9, 14.3; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2O_3S$ $[M + H]^+$ 345.1273, found 345.1256.

(*E*) Butyl 3-(methylthio)-3-(thiophen-2-yl)-2-(thiophene-2-carboxamido)acrylate



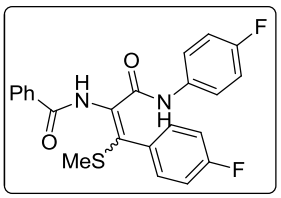
(66i). White solid (305 mg, 80%): mp 132-133 °C; R_f 0.5 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3312, 1712, 1650, 1511, 1244; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.51 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.46 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.41 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.27 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.11 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.05 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 4.32 (t, J = 6.8 Hz, 2H), 2.13 (s, 3H), 1.74 (quin, J = 6.8 Hz, 2H), 1.47 (sex, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.0, 138.7, 137.3, 131.7, 129.6, 128.8, 128.5, 128.2, 128.1, 128.0, 65.9, 30.6, 19.4, 17.6, 13.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_3S_3$ $[M + Na]^+$ 404.0425, found 404.0402.

(*E*) *N*-(1-(4-Methoxyphenyl)-1-(methylthio)-3-oxo-3-(phenylamino)prop-1-en-2-yl) benzamide (71a).



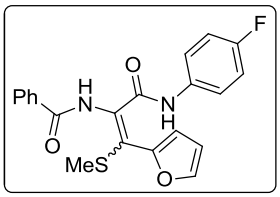
White solid (394 mg, 85%): mp 112-113 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3270, 1634, 1250; ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (br s, 1H), 9.53 (br s, 1H), 7.68 (t, J = 8.8 Hz, 4H), 7.49 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.35-7.29 (m, 4H), 7.05 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.74 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 164.3, 159.1, 139.5, 138.5, 133.6, 131.6, 130.5, 128.6, 128.3, 127.7, 127.6, 123.2, 119.8, 113.8, 55.2, 15.7; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}N_2O_3S$ $[M + H]^+$ 419.1429, found 419.1411.

(*E*/*Z*) *N*-(1-(4-Fluorophenyl)-3-(4-fluorophenylamino)-1-(methylthio)-3-oxoprop-1-en-2-yl) benzamide (71b).

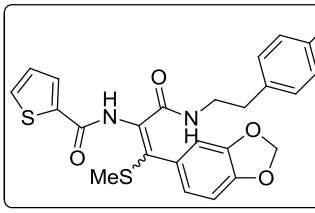


(*E*:*Z* = 50:50), white solid (400 mg, 85%): mp 224-225 °C; R_f 0.5 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3250, 1641, 1508; ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (br s, 0.5H), 9.86 (br s, 0.5H), 9.79 (br s, 0.5H), 9.58 (br s, 0.5H), 8.01 (d, J = 7.6 Hz, 1H), 7.73-7.59 (m, 3H), 7.55-7.48 (m, 1.5H), 7.42-7.40 (m, 2.5H), 7.32-7.14 (m, 4H), 7.00 (t, J = 8.8 Hz, 1H), 1.96 (s, 1.5H), 1.88 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.0, 164.0, 163.1, 162.9, 160.6, 160.5, 159.4, 157.0, 156.9, 138.7, 135.7, 135.4, 133.6, 133.5, 133.2, 132.1, 131.7, 131.53, 131.44, 131.2, 131.1, 130.8, 128.6, 128.3, 127.8, 127.7, 121.73, 121.66, 121.1, 121.0, 115.4, 115.3, 115.2, 115.1, 114.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}F_2N_2O_2S$ $[M + Na]^+$ 447.0955, found 447.0938.

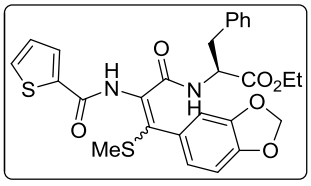
(*E*/*Z*) *N*-(3-(4-Fluorophenylamino)-1-(furan-2-yl)-1-(methylthio)-3-oxoprop-1-en-2-yl) benzamide (71c). (*E*:*Z* = 50:50), off-white solid (382 mg, 87%): mp 120-122 °C; R_f 0.5 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3268, 1634, 1509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (br s, 0.5H), 8.32 (br s, 0.5H), 8.17 (br s, 0.5H), 7.91-7.89 (m, 1H), 7.86-7.84 (m, 1H), 7.63-7.54 (m, 3H), 7.49-7.44 (m, 2H), 7.42 (dd, *J* = 2.0 Hz, 0.8 Hz, 0.5H), 7.33 (dd, *J* = 9.2 Hz, 4.8 Hz, 1H), 7.00 (t, *J* = 8.4 Hz, 1H), 6.92 (t, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 3.2 Hz, 0.5H), 6.56 (dd, *J* = 3.6 Hz, 0.4 Hz, 0.5H), 6.52 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.5H), 6.39 (dd, *J* = 3.6 Hz, 1.6 Hz, 0.5 H), 2.26 (s, 1.5H), 2.12 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.7, 162.7, 162.5, 161.0, 158.6, 151.5, 147.6, 144.3, 143.5, 133.9, 133.8, 133.6, 133.5, 133.4, 133.0, 132.9, 132.8, 132.68, 132.65, 129.0, 128.9, 127.8, 127.7, 122.5, 122.4, 122.3, 122.2, 118.2, 115.9, 115.73, 115.66, 115.5, 113.7, 113.6, 112.9, 112.3, 111.9, 19.3, 16.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{17}FN_2O_3S$ $[M + Na]^+$ 419.0842, found 419.0833.



(*E*) *N*-(3-(3,4-Dimethoxyphenethylamino)-1-(benzo[*d*][1,3]dioxol-5-yl)-1-(methylthio)-3-oxoprop-1-en-2-yl)thiophene-2-carboxamide (71g). White solid (467 mg, 80%): mp 184-185 °C; R_f 0.4 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3251, 1626, 1480, 1243; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.40 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.32 (d, *J* = 3.2 Hz, 1H), 6.95 (dd, *J* = 4.8 Hz, 3.6 Hz, 1H), 6.80-6.72 (m, 7H), 5.93 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.61 (q, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 161.2, 149.1, 148.3, 147.9, 147.7, 137.7, 131.8, 131.1, 129.5, 129.0, 127.9, 126.0, 122.6, 120.9, 112.3, 111.4, 109.1, 108.7, 101.5, 56.0, 41.3, 35.1, 16.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N_2O_6S_2$ $[M + H]^+$ 527.1311, found 527.1301



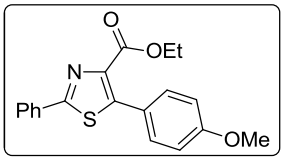
(*S*) Ethyl 2-(3-(benzo[*d*][1,3]dioxol-5-yl)-3-(methylthio)-2-(thiophene-2-carboxamido) acrylamido)-3-phenylpropanoate (71k). Off-white solid (449 mg, 75%): mp 184-185 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3403, 1735, 1665, 1511; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1H), 7.78-7.75 (m, 2H), 7.55 (d, *J* = 3.2 Hz, 1H), 7.14 (s, 5H), 7.09 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H), 4.57 (q, *J* = 6.8 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.03 (dd, *J* = 6.0 Hz, 4.0 Hz, 2H), 1.75 (s, 3H), 1.12 (t, *J* = 7.2



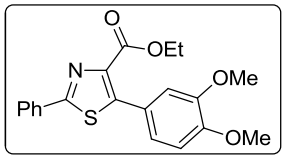
Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.6, 160.9, 146.9, 146.7, 138.8, 136.8, 131.4, 129.2, 129.1, 128.1, 127.8, 126.5, 122.6, 121.9, 108.6, 108.0, 101.1, 60.6, 53.5, 36.8, 15.9, 13.9; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}N_2O_6S_2$ $[M + H]^+$ 539.1311, found 539.1288**.**

3.5.2 General procedure for the synthesis of 2-phenyl/(2-thienyl)-5-(het)aryl/(methylthio) thiazole-4-carboxylates 69a-i and 70. To a solution of enamide ester **66** or **67** (0.5 mmol) in toluene (10 mL), Lawesson's reagent (0.4 g, 1.0 mmol) was added and the reaction mixture was refluxed with stirring for 2-3 (for **69a-e**) or 10-12 h (for **69f-i** and **70**) (monitored by TLC). It was then poured into ice-cold water (30 mL), extracted with EtOAc (3 x 30 mL), washed with brine (1 x 30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude thiazoles, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

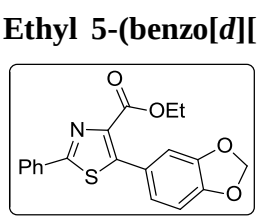
Ethyl 5-(4-methoxyphenyl)-2-phenylthiazole-4-carboxylate (69a). White solid (118 mg, 70%): mp 126-127 °C; R_f 0.45 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1720, 1247, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.46-7.44 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.6, 160.6, 146.2, 141.1,133.1, 131.5, 130.6, 129.1, 126.9, 122.8, 113.8, 61.4, 55.5, 14.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{17}NO_3S$ $[M + H]^+$ 340.1007, found 340.1008.



Ethyl 5-(3,4-dimethoxyphenyl)-2-phenylthiazole-4-carboxylate (69b). Pale yellow solid (138 mg, 75%): mp 140-141 °C; R_f 0.45 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1720, 1261, 1186; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.46-7.45 (m, 3H), 7.12 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.7, 150.1, 148.7, 146.0, 141.2, 133.0, 130.7, 129.1, 126.9, 123.0, 113.4, 110.9, 61.4, 56.2, 56.1, 14.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}NO_4S$ $[M + Na]^+$ 392.0932, found 392.0932.

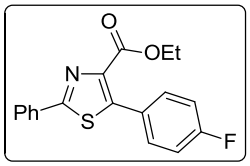


Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-phenylthiazole-4-carboxylate (69c). Pale yellow solid (124 mg, 70%): mp 139-140 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1720, 1477, 1240, 1187; ^{1}H NMR (400 MHz,

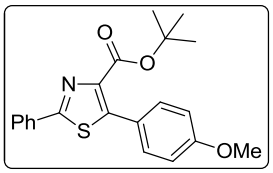


$CDCl_3$) δ 7.98-7.96 (m, 2H), 7.45-7.46 (m, 3H), 7.03-7.01 (m, 2H), 6.85 (dd, J = 6.8 Hz, 1.6 Hz, 1H), 6.03 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 162.5, 148.7, 147.7, 145.8, 141.4, 133.0, 130.7, 129.1, 126.9, 124.2, 124.1, 110.6, 108.3, 101.7, 61.5, 14.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}NO_4S$ [M + Na]$^+$ 376.0619, found 376.0618.

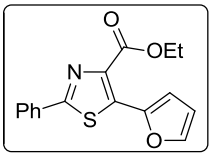
Ethyl 5-(4-fluorophenyl)-2-phenylthiazole-4-carboxylate (69d). White solid (130 mg, 80%): mp 158-160 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1716, 1195; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.51 (dd, J = 8.8 Hz, 5.2 Hz, 2H), 7.47-7.45 (m, 3H), 7.12 (t, J = 8.8 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 164.6, 162.3, 162.2, 144.9, 141.7, 132.8, 132.0, 131.9, 130.8, 129.1, 127.0, 126.63, 126.6, 115.6, 115.3, 61.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}FNO_2S$ [M + H]$^+$ 328.0808, found 328.0803.



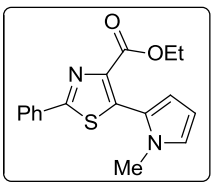
***t*-Butyl 5-(4-methoxyphenyl)-2-phenylthiazole-4-carboxylate (69e).** Pale yellow solid (138 mg, 75%): mp 99-100 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1718, 1251, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.98 (m, 2H), 7.45-7.41 (m, 5H), 6.95 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.8, 160.4, 144.5, 143.1, 133.1, 131.4, 130.5, 129.0, 126.9, 123.4, 113.8, 82.1, 55.6, 28.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NO_3S$ [M + H]$^+$ 368.1320, found 368.1312.



Ethyl 5-(furan-2-yl)-2-phenylthiazole-4-carboxylate (69f). Brown solid (108 mg, 72%): mp 69-70 °C; R_f 0.65 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1712, 1317, 1226, 1186; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.54 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.47-7.43 (m, 3H), 6.56 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.6, 145.6, 143.9, 139.1, 136.1, 132.9, 130.7, 129.1, 126.9, 114.1, 112.8, 61.7, 14.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}NO_3S$ [M + Na]$^+$ 322.0514, found 322.0508.

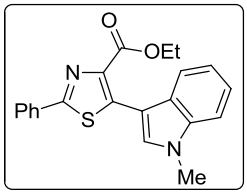


Ethyl 5-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylthiazole-4-carboxylate (69g). Brown semisolid (94 mg, 60%): R_f 0.6 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 1720, 1465, 1189; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 2H), 7.46-7.45 (m, 3H), 6.81 (dd, J = 2.4 Hz, 2.0 Hz, 1H), 6.34 (dd, J = 3.6



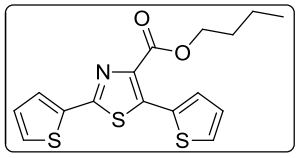
Hz, 2.0 Hz, 1H), 6.22 (dd, *J* = 3.6 Hz, 2.4 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 161.9, 143.9, 136.8, 133.0, 130.8, 129.1, 127.0, 124.8, 121.0, 112.8, 108.4, 61.4, 34.7, 14.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}N_2O_2S$ $[M + H]^+$ 313.1011, found 313.1005.

Ethyl 5-(1-methyl-1*H*-indol-3-yl)-2-phenylthiazole-4-carboxylate (69h). Yellow solid



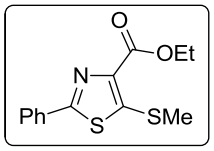
(135 mg, 75%): mp 96-98 °C; R_f 0.5 (1:5 EtOAc:hexane); IR (KBr, cm^{-1}) 1708, 1469, 1190; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.00 (m, 2H), 7.86-7.83 (m, 2H), 7.49-7.43 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.25-7.22 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.2, 140.5, 140.2, 137.1, 133.4, 131.9, 130.3, 129.1, 127.5, 126.9, 122.7, 120.9, 120.1, 109.9, 104.7, 61.4, 33.4, 14.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}N_2O_2S$ $[M + Na]^+$ 385.0987, found 385.0985.

Butyl 2,5-di(thiophen-2-yl)thiazole-4-carboxylate (69i). Yellow semisolid (140 mg,



80%): R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1716, 1464, 1186; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.47-7.43 (m, 3H), 7.09 (dd, *J* = 4.0 Hz, 2.4 Hz, 1H), 7.08 (dd, *J* = 3.6 Hz, 2.4 Hz, 1H), 4.33 (t, *J* = 6.8 Hz, 2H), 1.71 (quin, *J* = 6.8 Hz, 2H), 1.37 (sex, *J* = 7.6 Hz, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 159.0, 140.5, 137.9, 136.1, 130.5, 128.74, 128.69, 128.0, 127.6, 127.4, 65.5, 30.6, 19.1, 13.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}NO_2S_3$ $[M + H]^+$ 350.0343, found 350.0335.

Ethyl 5-(methylthio)-2-phenylthiazole-4-carboxylate (70). Yellow solid (98 mg, 70%):

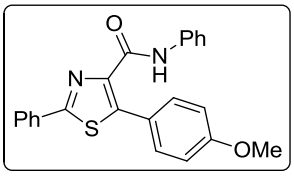


mp 82-83 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 1693, 1446, 1203, 1058; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.89 (m, 2H), 7.44-7.42 (m, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.66 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.6, 149.5, 139.4, 132.9, 130.4, 129.1, 126.6, 61.6, 20.3, 14.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}NO_2S_2$ $[M + Na]^+$ 302.0285, found 302.0288.

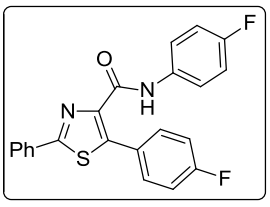
3.5.3 General procedure for the synthesis of N-substituted 2-(2-thienyl)/phenyl-5-(het)aryl/(methylthio)thiazole-4-carboxamides 74a-k and 75. To a solution of enamide-amide **71** or **72** (0.5 mmol) in THF (10 mL), Lawesson's reagent (0.4 g, 1.0 mmol) was added and the reaction mixture was refluxed with stirring for 10-12 h

(monitored by TLC). It was then concentrated under reduced pressure and the residue was diluted with water (30 mL), extracted with EtOAc (3 x 30 mL), washed with brine (1 x 30 mL), dried over Na_2SO_4, followed by removal of the solvent to give crude thiazoles, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

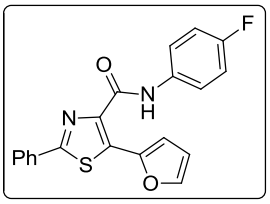
5-(4-Methoxyphenyl)-*N*,2-diphenylthiazole-4-carboxamide (74a). Yellow solid (125 mg, 65%): mp 167−168 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3362, 1681, 1602, 1516; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (br s, 1H), 7.99-7.97 (m, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.52-7.49 (m, 3H), 7.34 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 160.6, 159.7, 141.9, 138.2, 132.9, 131.9, 130.8, 129.3, 129.1, 126.6, 124.3, 123.4, 122.5, 120.1, 113.8, 55.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_2O_2S$ $[M + Na]^+$ 409.0987, found 409.0984.



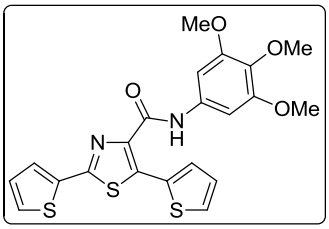
***N*,5-Bis(4-fluorophenyl)-2-phenylthiazole-4-carboxamide (74b).** Pale yellow solid (148 mg, 76%): mp 208-209 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3352, 1680, 1228; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 7.99-7.96 (m, 2H), 7.69-7.63 (m, 4H), 7.51 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 7.04 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.7, 162.2, 160.8, 159.4, 158.4, 143.5, 142.3, 134.0, 133.9, 132.6, 132.4, 132.3, 131.1, 129.3, 126.7, 126.19, 126.15, 121.9, 121.8, 115.9, 115.7, 115.6, 115.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{14}F_2N_2OS$ $[M + H]^+$ 393.0873, found 393.0854.



***N*-(4-Fluorophenyl)-5-(furan-2-yl)-2-phenylthiazole-4-carboxamide (74c).** Brown solid (123 mg, 68%): mp 120-122 °C; R_f 0.5 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3357, 1692, 1509, 1225; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (br s, 1H), 7.99-7.97 (m, 2H), 7.95 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.70 (dd, J = 8.8 Hz, 5.2 Hz, 2H), 7.52 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.51-7.48 (m, 3H), 7.09 (t, J = 8.8 Hz, 2H), 6.58 (dd, J = 3.6 Hz, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.1, 159.6, 147.9, 143.7, 134.73, 134.70, 132.4, 131.7, 131.1, 129.3, 129.0, 127.93, 127.90, 126.7, 125.74, 125.7, 116.0, 115.8, 114.0, 112.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{13}FN_2O_2S$ $[M + Na]^+$ 387.0579, found 387.0579.

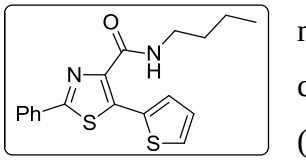


2,5-Di(thiophen-2-yl)-*N*-(3,4,5-trimethoxyphenyl)thiazole-4-carboxamide (74d).

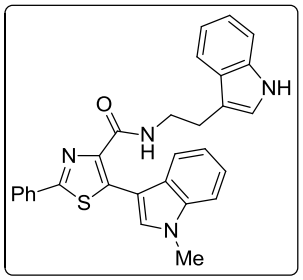


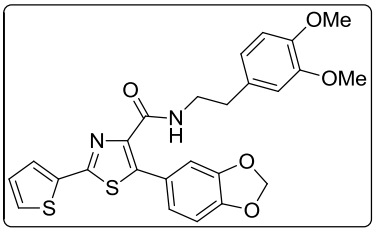
Yellow semisolid (172 mg, 75%): R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3412, 1671, 1507, 1128; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.71 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.54 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.48 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.46 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.13 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.09 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 6.98 (s, 2H), 3.89 (s, 6H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.4, 153.5, 140.9, 137.3, 135.9, 135.1, 134.0, 131.4, 130.8, 129.4, 128.9, 128.4, 128.0, 127.6, 98.2, 61.1, 56.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{18}N_2O_4S_3$ $[M + H]^+$ 459.0507, found 459.0495.

***N*-Butyl-2-phenyl-5-(thiophen-2-yl)thiazole-4-carboxamide (74e).** Brown solid (120 mg, 70%): mp 94-95 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3409, 1664, 1515; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.68 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.62 (br s, 1H), 7.48-7.46 (m, 3H), 7.43 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.06 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 3.46 (q, J = 7.2 Hz, 2H), 1.64 (quin, J = 7.2 Hz, 2H), 1.44 (sex, J = 7.6 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.9, 141.9, 136.9, 132.7, 131.4, 131.1, 130.8, 129.2, 129.1, 127.3, 126.6, 39.3, 32.0, 20.4, 14.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_2OS_2$ $[M + Na]^+$ 365.0758, found 365.0758.

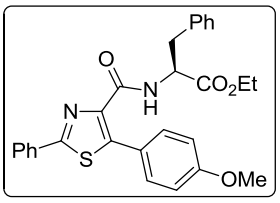


***N*-(2-(1*H*-Indol-3-yl)ethyl)-5-(1-methyl-1*H*-indol-3-yl)-2-phenylthiazole-4-carboxamide (74f).** Yellow solid (178 mg, 75%): mp 159-160 °C; R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3401, 3293, 1652, 1523; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.12 (br s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.87-7.85 (m, 3H), 7.70 (d, J = 8.0 Hz, 1H), 7.45-7.43 (m, 3H), 7.39-7.35 (m, 2H), 7.30 (td, J = 8.0 Hz, 0.8 Hz, 1H), 7.24-7.19 (m, 2H), 7.13 (td, J = 8.0 Hz, 0.8 Hz, 1H), 7.08 (s, 1H), 3.84 (s, 3H), 3.80 (q, J = 7.2 Hz, 2H), 3.12 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 161.8, 141.4, 137.9, 137.1, 136.5, 133.6, 133.2, 130.2, 129.1, 127.6, 127.5, 126.5, 122.4, 122.3, 122.2, 120.7, 120.0, 119.6, 119.0, 113.5, 111.3, 109.9, 104.4, 40.0, 33.3, 25.7; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4OS$ $[M + Na]^+$ 499.1569, found 499.1567.

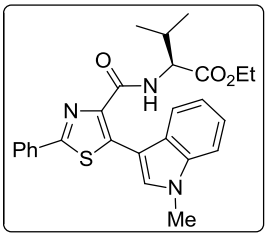


***N*-(3,4-Dimethoxyphenethyl)-5-(benzo[*d*][1,3]dioxol-5-yl)-2-(thiophen-2-yl)thiazole-4-carboxamide (74g).** 

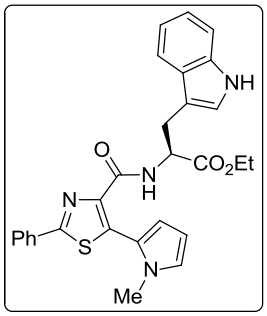
Yellow semisolid (153 mg, 62%); R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3406, 1665, 1507, 1236; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (br t, J = 6.0 Hz, 1H), 7.47 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.43 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.11-7.08 (m, 2H), 6.85-6.78 (m, 4H), 6.0 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.62 (q, J = 6.8 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.1, 149.2, 148.7, 147.8, 147.5, 142.6, 141.8, 136.5, 131.8, 128.5, 128.2, 127.4, 124.6, 123.6, 120.9, 112.2, 111.6, 111.1, 108.1, 101.6, 56.1, 56.0, 40.9, 35.7; HRMS (ESI) *m/z* calcd for $C_{25}H_{22}N_2O_5S_2$ $[M + H]^+$ 495.1048, found 495.1017.

(*S*)-Ethyl-2-(5-(4-methoxyphenyl)-2-phenylthiazole-4-carboxamido)-3-phenylpropanoate (74h). 

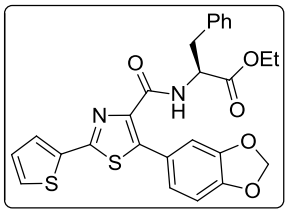
Yellow solid (158 mg, 65%): mp 88-89 °C; R_f 0.45 (1:4 EtOAc:hexane); $[\alpha]_{25}^{D}$ = +35.1 (*c*, 0.3, $CHCl_3$); IR (KBr, cm^{-1}) 3394, 1739, 1673, 1508; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (br d, J = 8.4 Hz, 1H), 7.92-7.89 (m, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.47-7.45 (m, 3H), 7.32-7.22 (m, 5H), 6.94 (d, J = 8.8 Hz, 2H), 4.99 (dt, J = 8.4 Hz, 6.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.23 (dd, J = 14.0 Hz, 6.0 Hz, 1H), 3.19 (dd, J = 14.0 Hz, 6.0 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 164.2, 161.3, 160.5, 144.1, 141.5, 136.3, 132.9, 131.8, 130.6, 129.7, 129.1, 128.7, 127.2, 126.6, 122.5, 113.7, 61.5, 55.5, 53.2, 38.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}N_2O_4S$ $[M + Na]^+$ 509.1511, found 509.1512.

(2*S*)-Ethyl-3-methyl-2-(5-(1-methyl-1*H*-indol-3-yl)-2-phenylthiazole-4-carboxamido) butanoate (74i). 

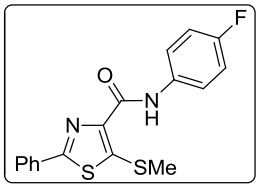
Yellow solid (150 mg, 65%): mp 79-80 °C; R_f 0.45 (1:4 EtOAc:hexane); $[\alpha]_{25}^{D}$ = +22.3 (*c*, 0.6, $CHCl_3$); IR (KBr, cm^{-1}) 3403, 1735, 1668, 1509; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.20 (br d, J = 8.8 Hz 1H), 8.01-7.97 (m, 3H), 7.50-7.45 (m, 3H), 7.37-7.35 (m, 1H), 7.29 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.24 (td, J = 8.0 Hz, 1.2 Hz, 1H), 4.70 (dd, J = 9.2 Hz, 5.2 Hz, 1H), 4.29-4.20 (m, 2H), 3.87 (s, 3H), 2.36-2.28 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.05 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 162.5, 161.9, 140.9, 138.5, 137.1, 133.6, 133.2, 130.3, 129.1, 127.5, 126.5, 122.4, 120.8, 120.0, 109.9, 104.4, 61.3, 57.4, 33.4, 31.7, 19.3, 18.3, 14.4; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_3O_3S$ $[M + Na]^+$ 484.1671, found 484.1670.

(2*S*)-Ethyl 3-(1*H*-indol-3-yl)-2-(5-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylthiazole-4-carboxamido)propanoate (74j). 

Brown solid (174 mg, 70%): mp 88-89 °C; R_f 0.45 (1:4 EtOAc:hexane); $[\alpha]_{25}^{D}$ = −6.0 (*c*, 0.3, $CHCl_3$); IR (KBr, cm^{-1}) 3376, 1735, 1664, 1517; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 8.03 (br d, *J* = 8.4 Hz 1H), 7.79-7.77 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.45-7.42 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.19 (dt, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.10-7.05 (m, 2H), 6.7 (dd, *J* = 2.8 Hz, 2.0 Hz, 1H), 6.34 (dd, *J* = 3.6 Hz, 2.0 Hz, 1H), 6.19 (dd, *J* = 3.6 Hz, 2.8 Hz, 1H), 5.03 (dt, *J* = 8.4 Hz, 5.6 Hz, 1H), 4.16-4.10 (m, 2H), 3.50 (s, 3H), 3.40 (dd, *J* = 5.6 Hz, 3.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 165.7, 160.9, 144.2, 136.3, 133.9, 132.8, 130.7, 129.1, 127.9, 126.7, 125.0, 123.0, 122.3, 121.0, 119.9, 119.0, 112.7, 111.3, 110.6, 108.2, 61.5, 53.2, 34.9, 28.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{26}N_4O_3S$ $[M + Na]^+$ 521.1623, found 521.1624.

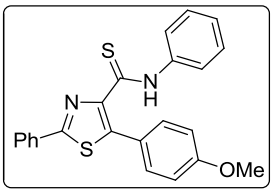
(2*S*)-Ethyl 2-(5-(benzo[*d*][1,3]dioxol-5-yl)-2-(thiophen-2-yl)thiazole-4-carboxamido)-3-phenylpropanoate (74k). 

Yellow semisolid (156 mg, 62%): R_f 0.45 (1:4 EtOAc:hexane); $[\alpha]_{25}^{D}$ = +47.2 (*c*, 0.3, $CHCl_3$); IR (KBr, cm^{-1}) 3391, 1737, 1672, 1502, 1250; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 7.44 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.34-7.30 (m, 2H), 7.27-7.22 (m, 3H), 7.12 (d, *J* = 1.6 Hz, 1H), 7.09 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.0 (s, 2H), 4.95 (dt, *J* = 8.4 Hz, 6.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.20 (dd, *J* = 6.0 Hz, 4.0 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 160.9, 158.2, 148.7, 147.5, 143.1, 141.2, 136.6, 136.2, 129.6, 128.8, 128.6, 128.1, 127.4, 127.2, 124.5, 123.5, 111.0, 108.1, 101.6, 61.5, 53.3, 38.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{26}H_{22}N_2O_5S_2$ $[M + H]^+$ 507.1048, found 507.1046.

***N*-(4-Fluorophenyl)-5-(methylthio)-2-phenylthiazole-4-carboxamide (75).** 

Off-white solid (120 mg, 70%): mp 185-186 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3374, 1664, 1509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.1 (br s, 1H), 7.89-7.87 (m, 2H), 7.69 (dd, *J* = 8.8 Hz, 4.8 Hz, 2H), 7.47-7.45 (m, 3H), 7.05 (dd, *J* = 8.6 Hz, 8.8 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.7, 160.3, 158.2, 146.1, 140.9, 134.1, 134.0, 132.7, 130.6, 129.3, 126.2, 121.5, 121.4, 115.9, 115.6, 20.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}FN_2OS_2$ $[M + Na]^+$ 367.0351, found 367.0354.

5-(4-Methoxyphenyl)-*N*,2-diphenylthiazole-4-carbothioamide (78). Red solid (132 mg, 66%): mp 130-132 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3440, 1594, 1550, 1244; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.85 (br s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.81-7.78 (m, 2H), 7.50-7.48 (m, 4H), 7.40-7.39 (m, 3H), 7.30-7.27 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 163.6, 161.5, 145.8, 141.7, 141.2, 140.2, 133.1, 131.8, 130.1, 130.0, 129.1, 126.7, 126.3, 121.4, 112.6, 55.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_2OS_2$ $[M + H]^+$ 403.0939, found 403.0920.



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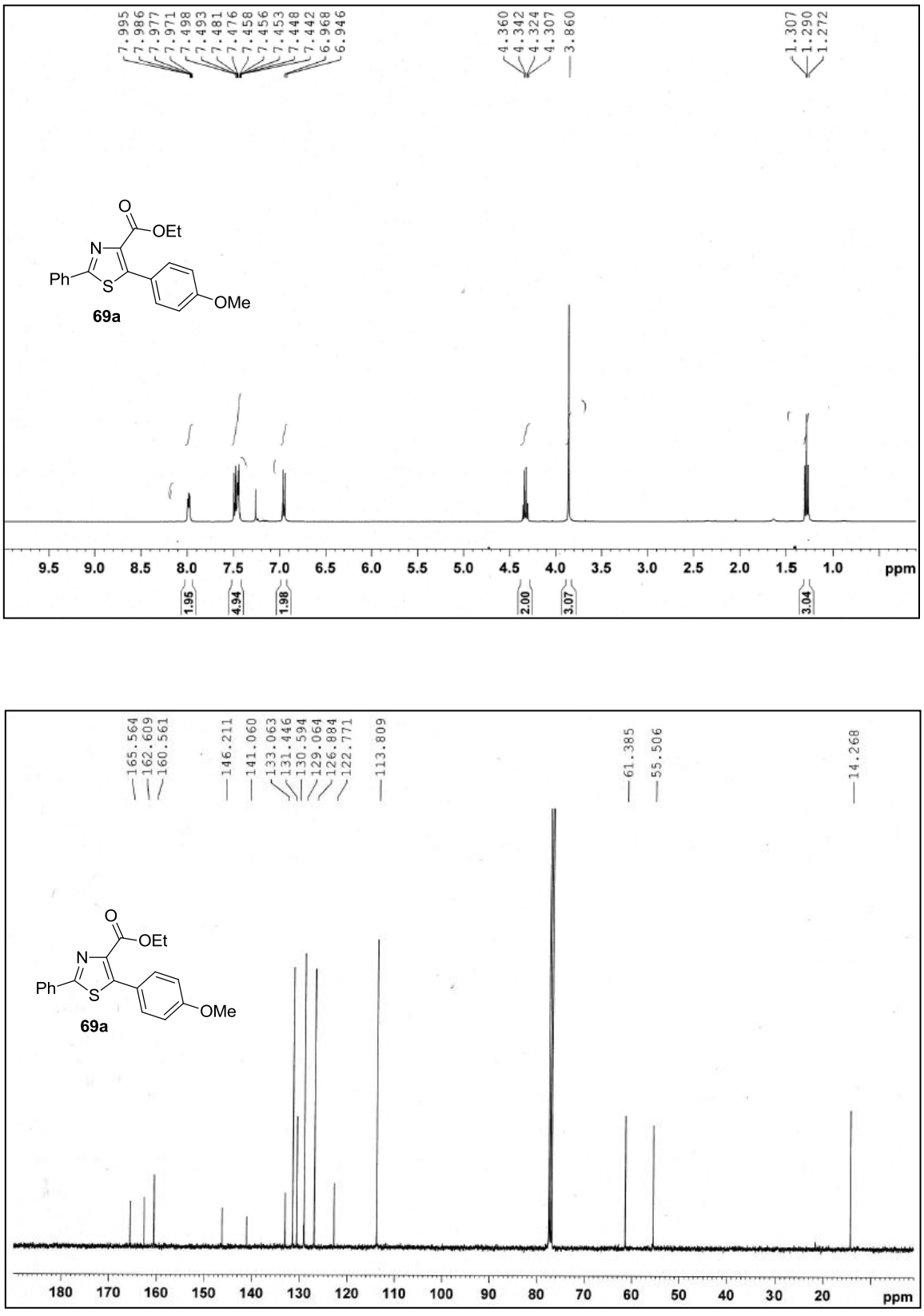
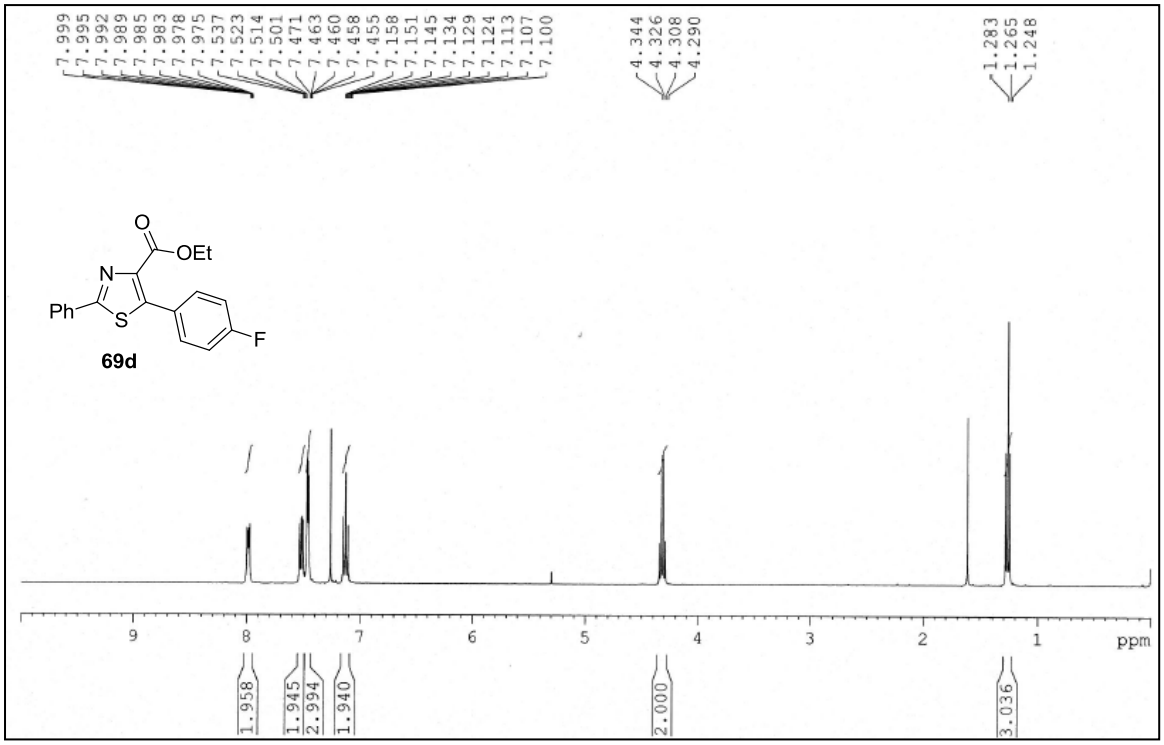
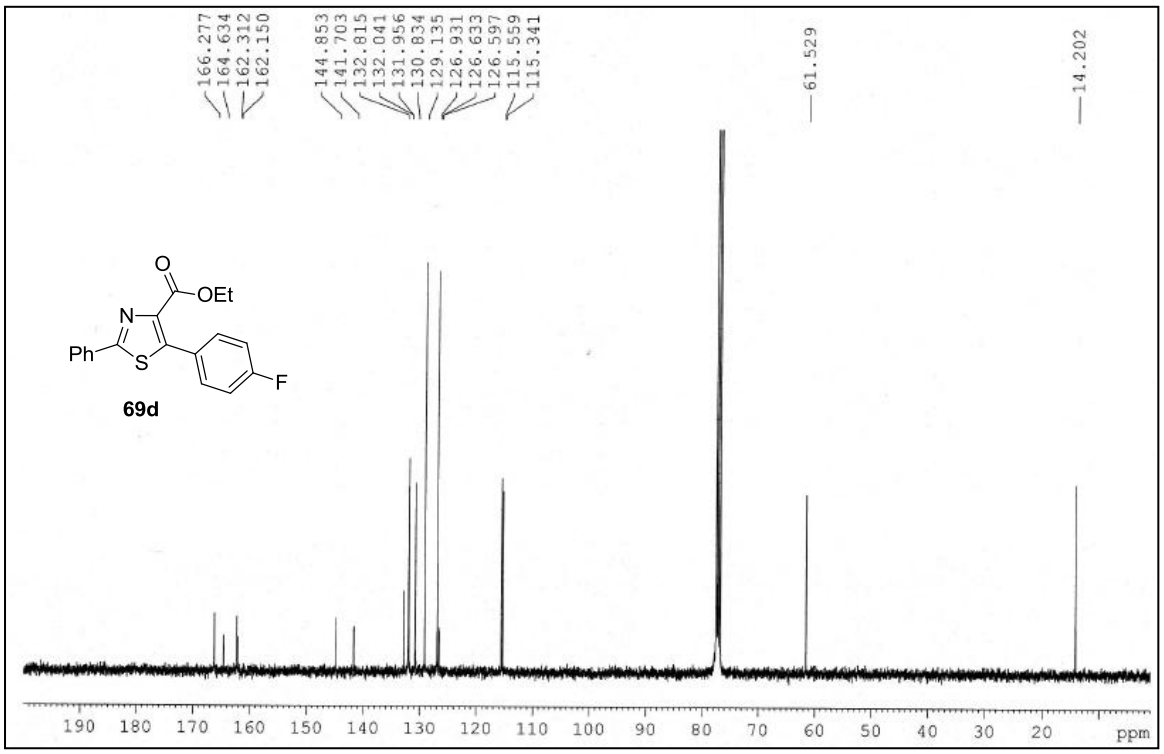
3.7 Representative spectra



^{1}H NMR and ^{13}C NMR Spectra for compound **69a** in $CDCl_3$





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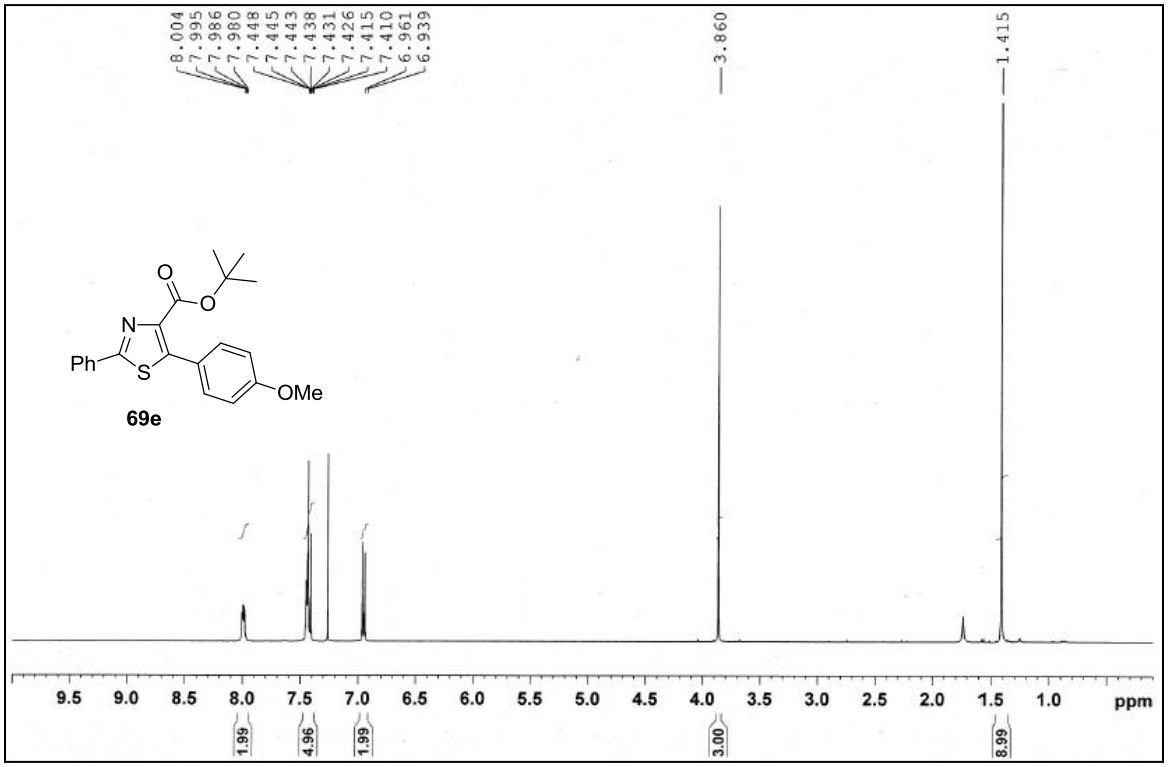
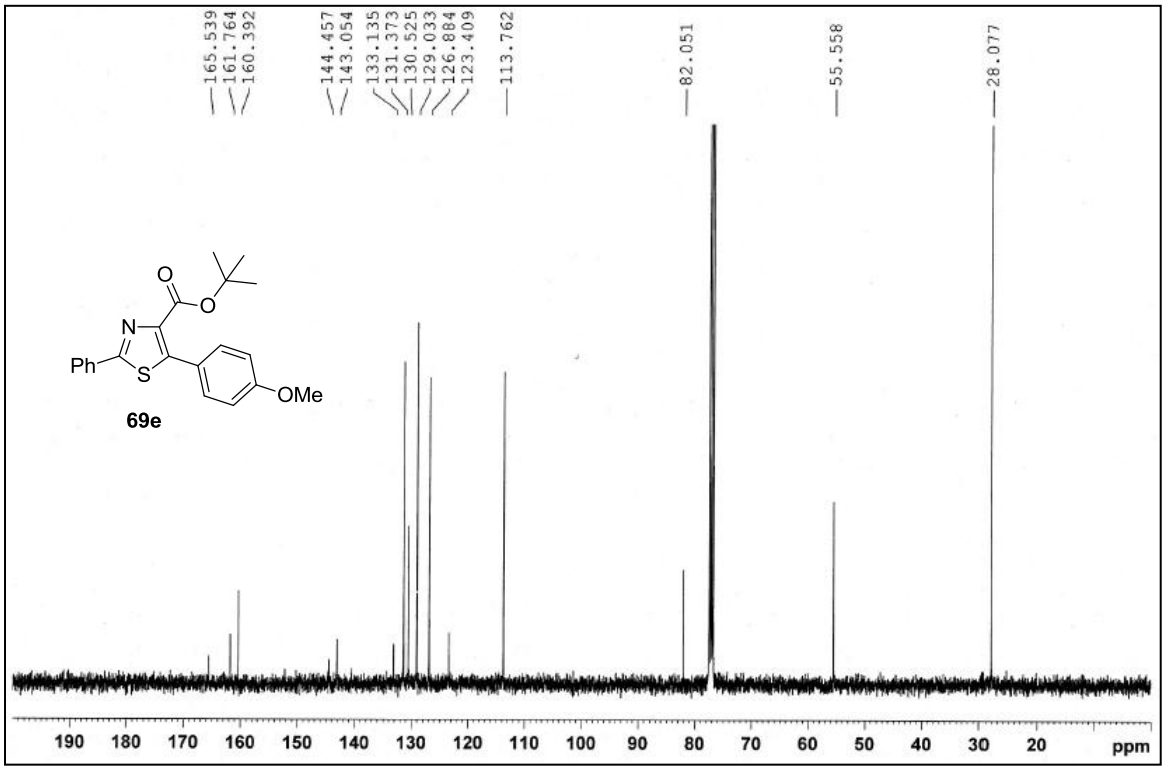
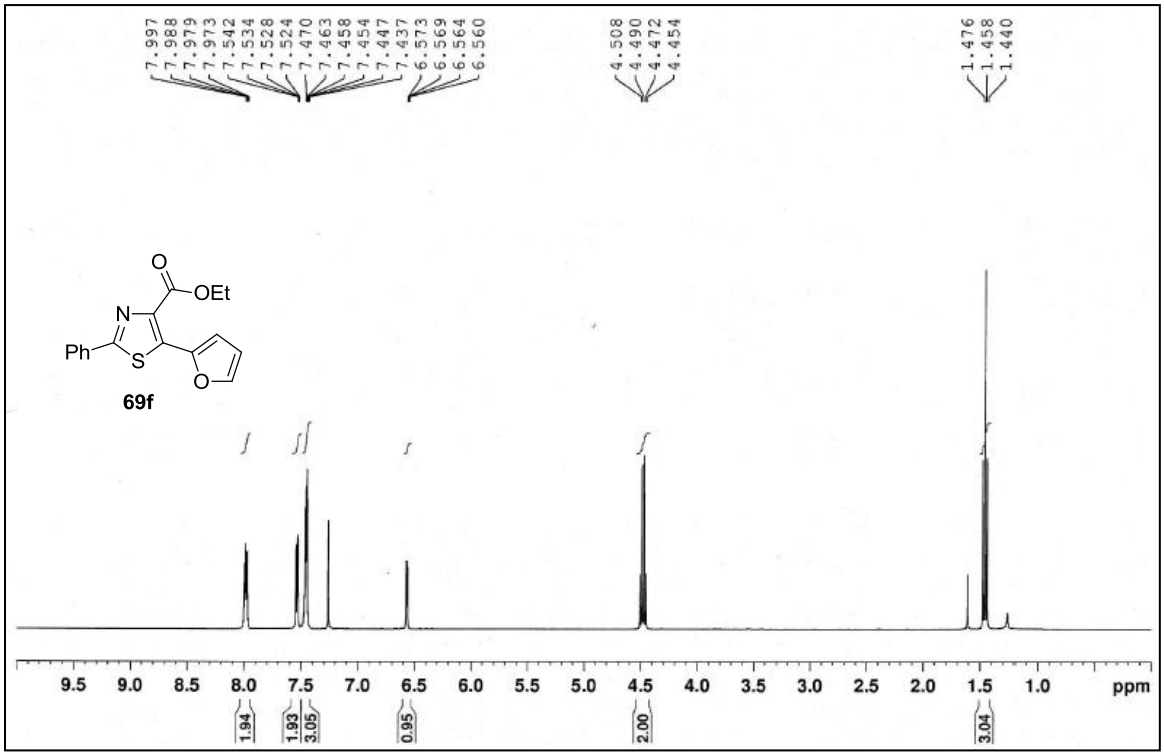
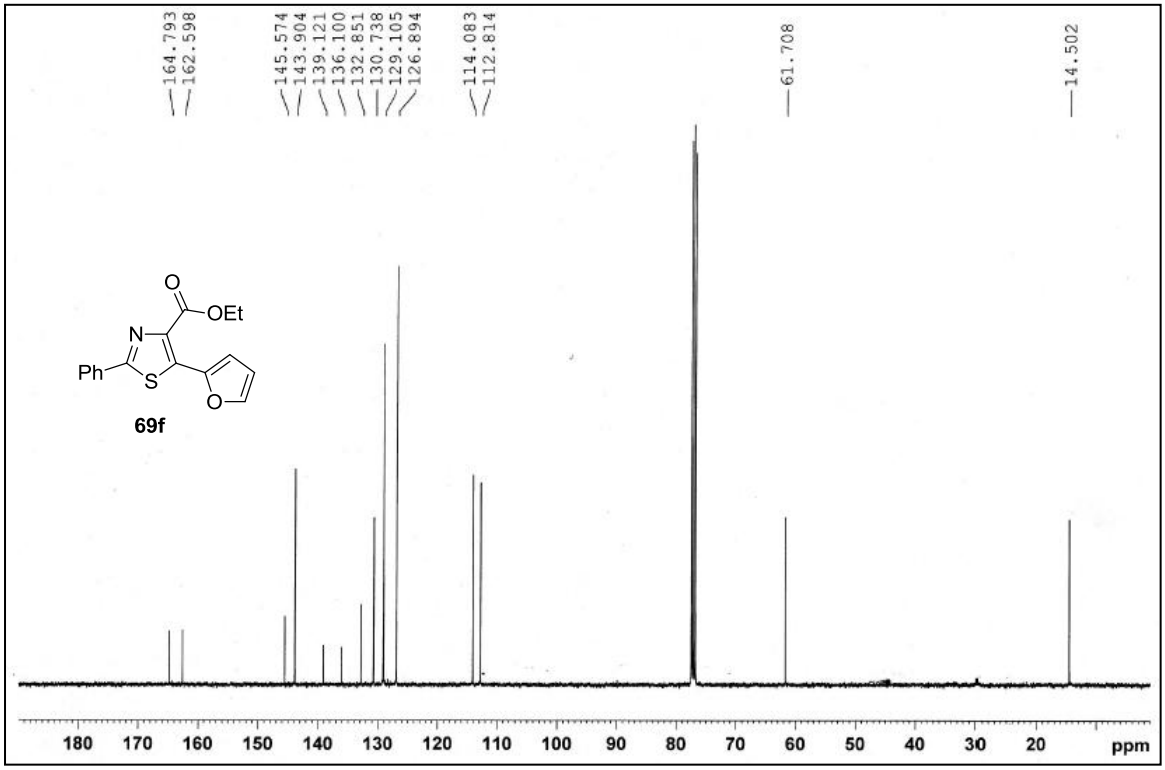


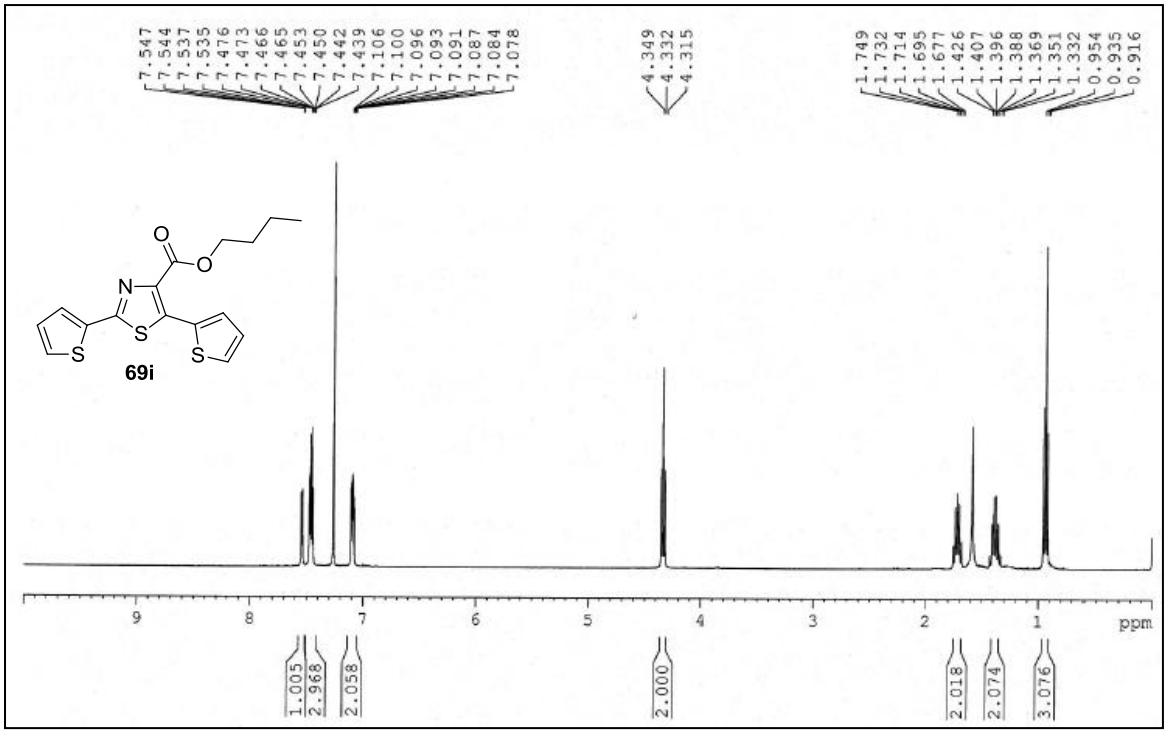


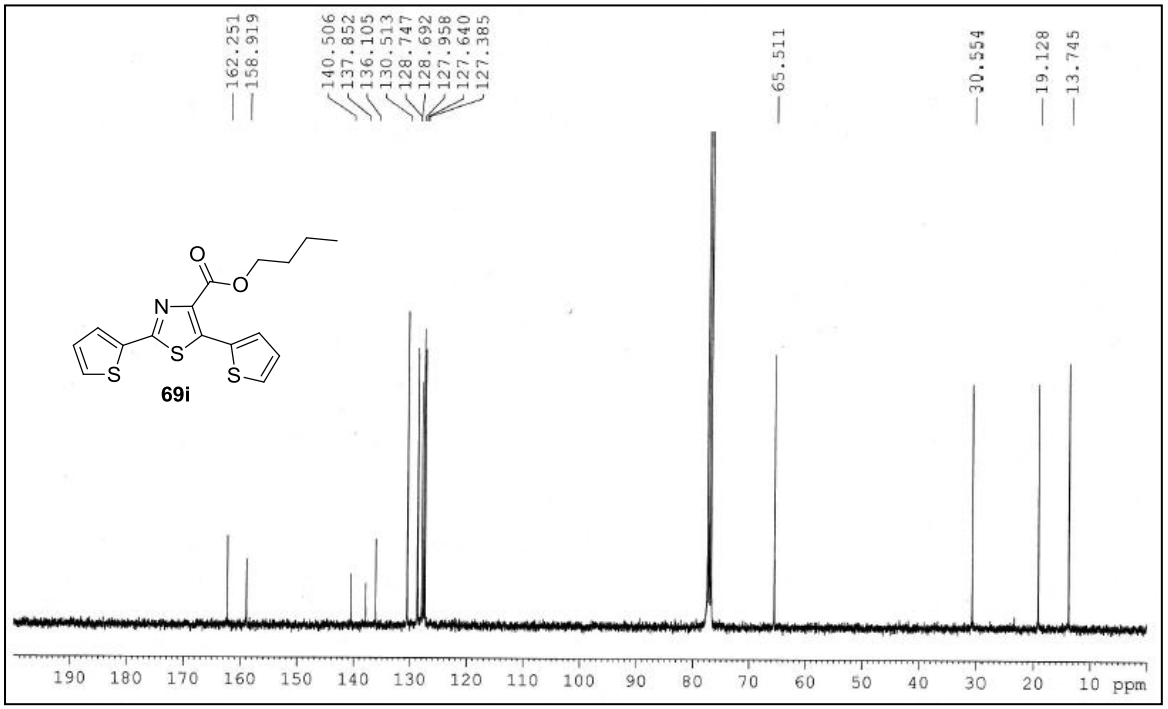
^{1}H NMR and ^{13}C NMR Spectra for compound **69e** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **69f** in $CDCl_3$





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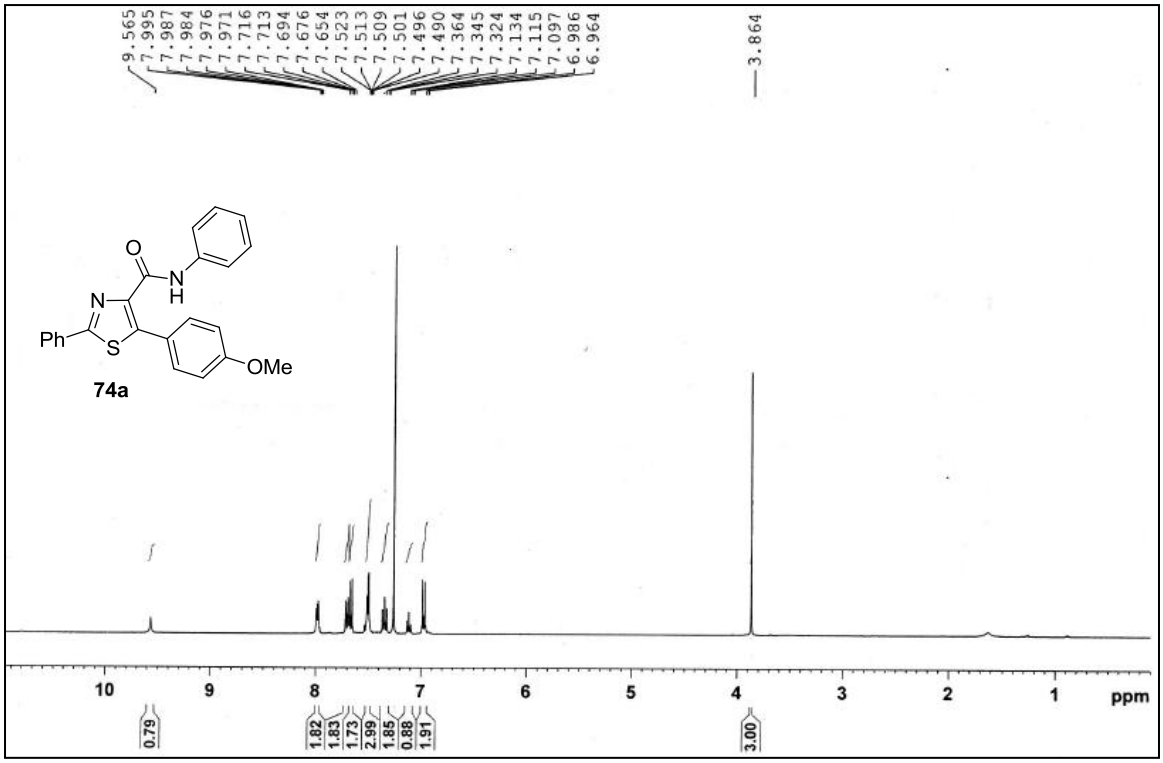

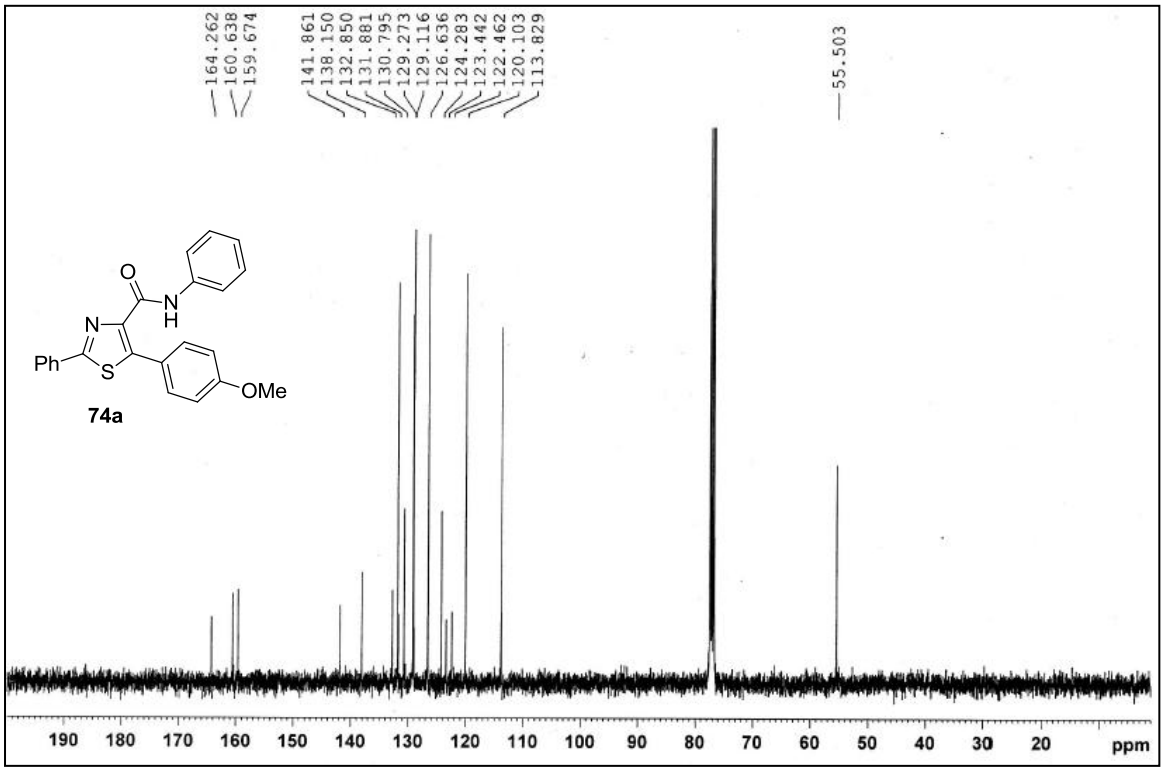

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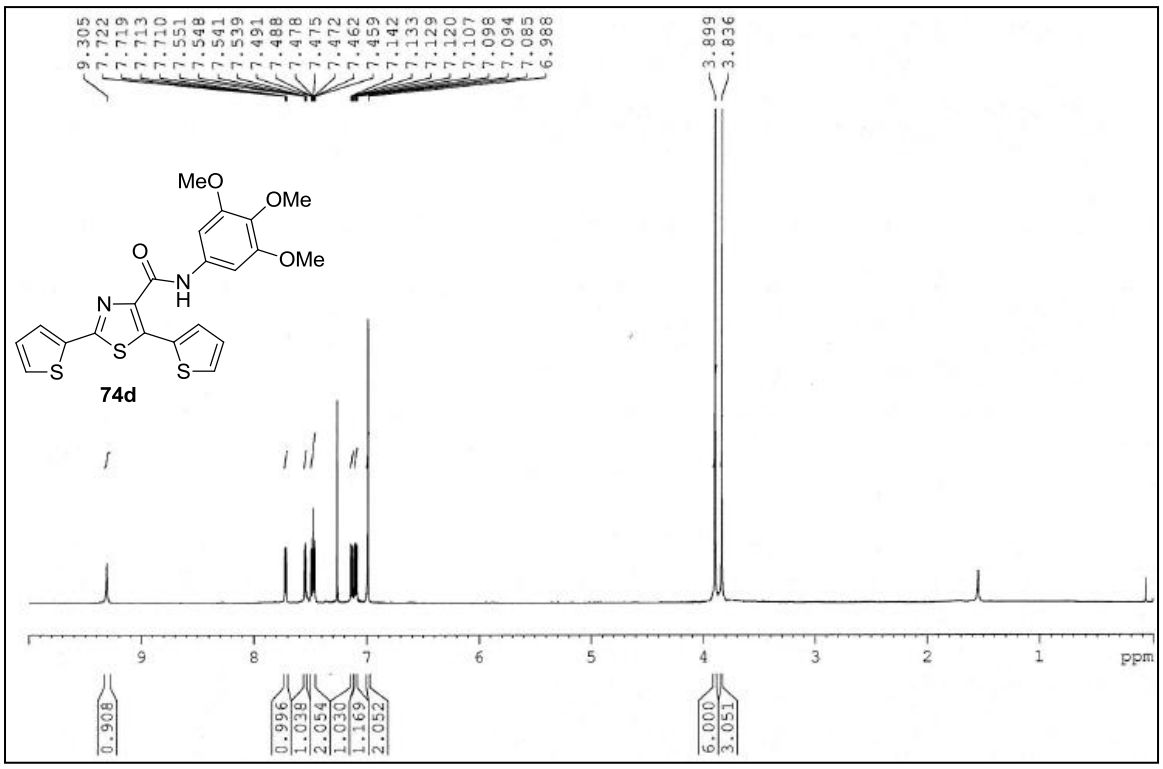

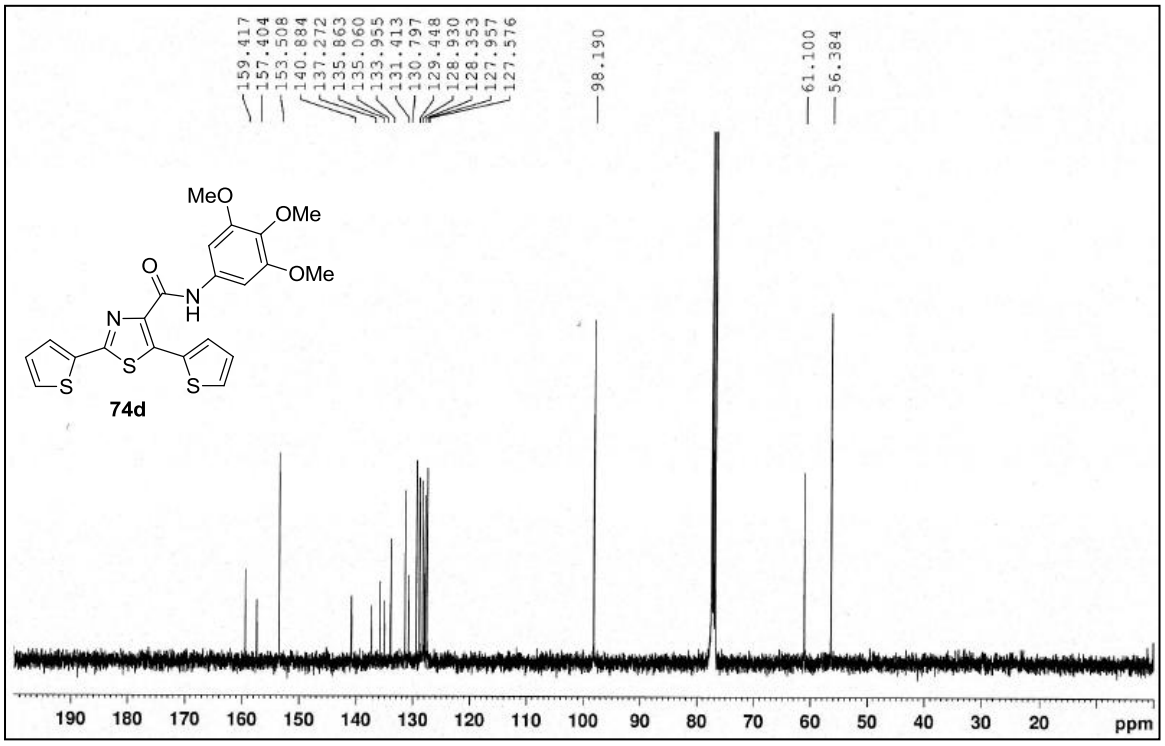

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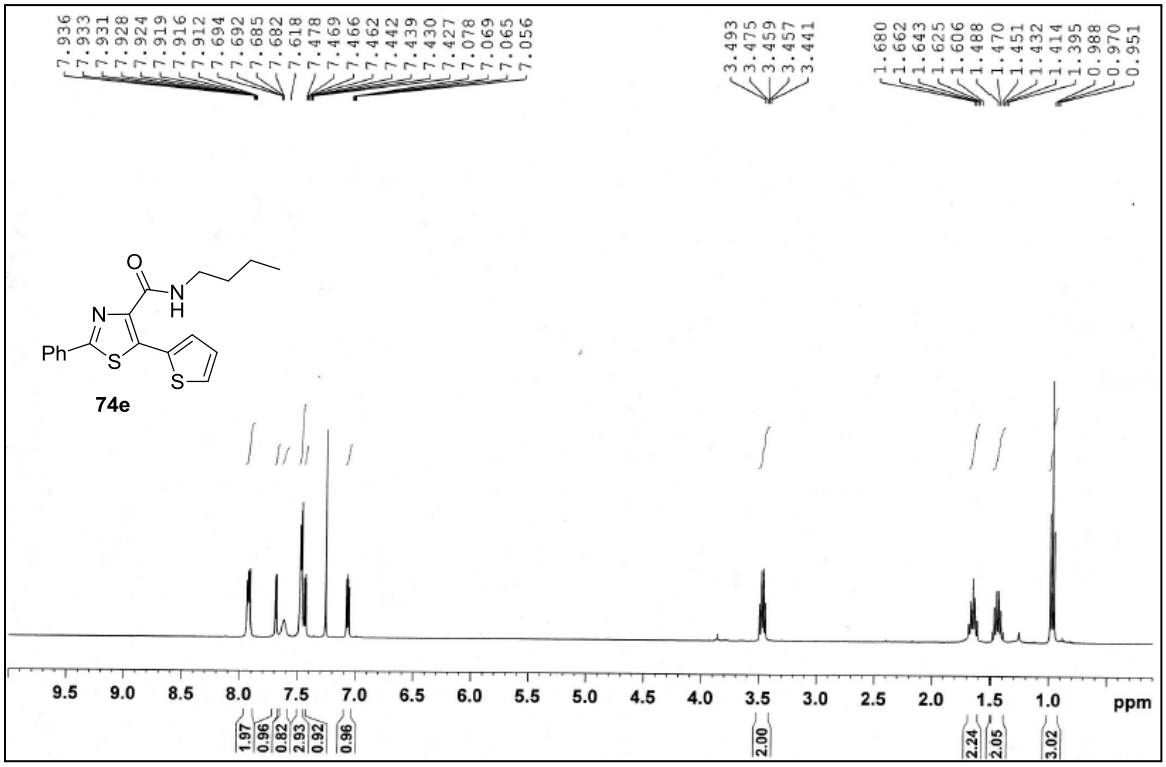

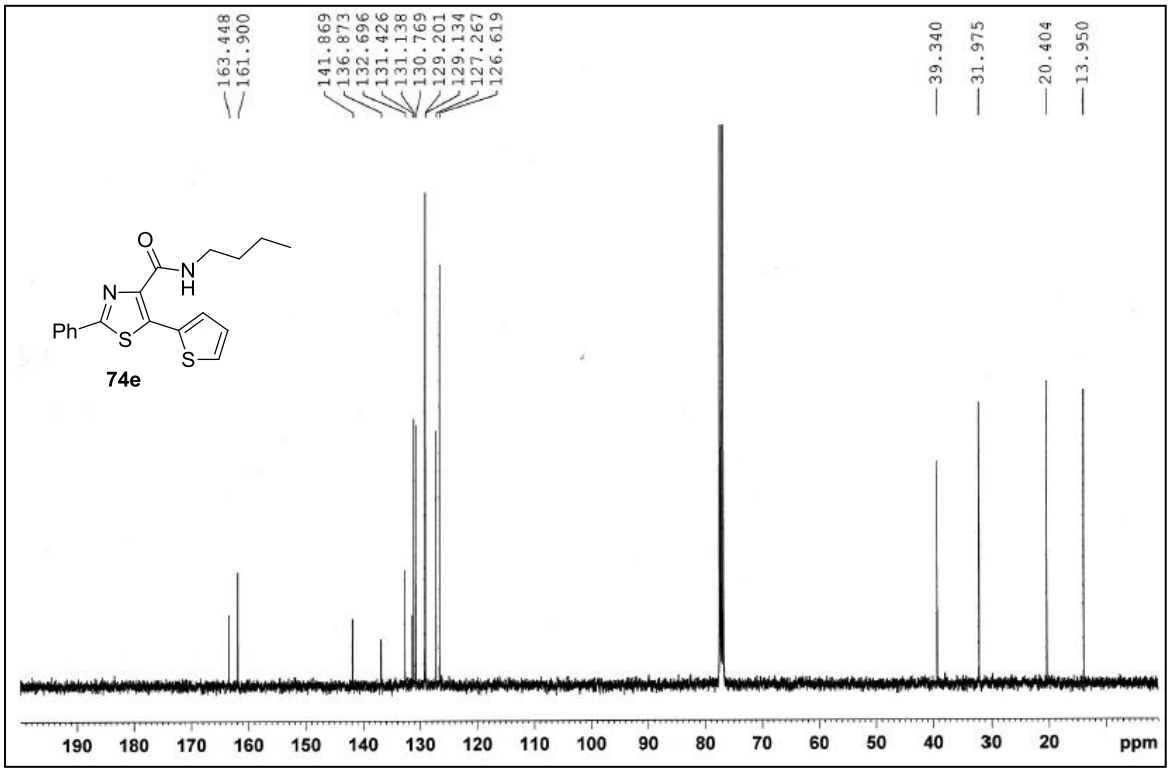

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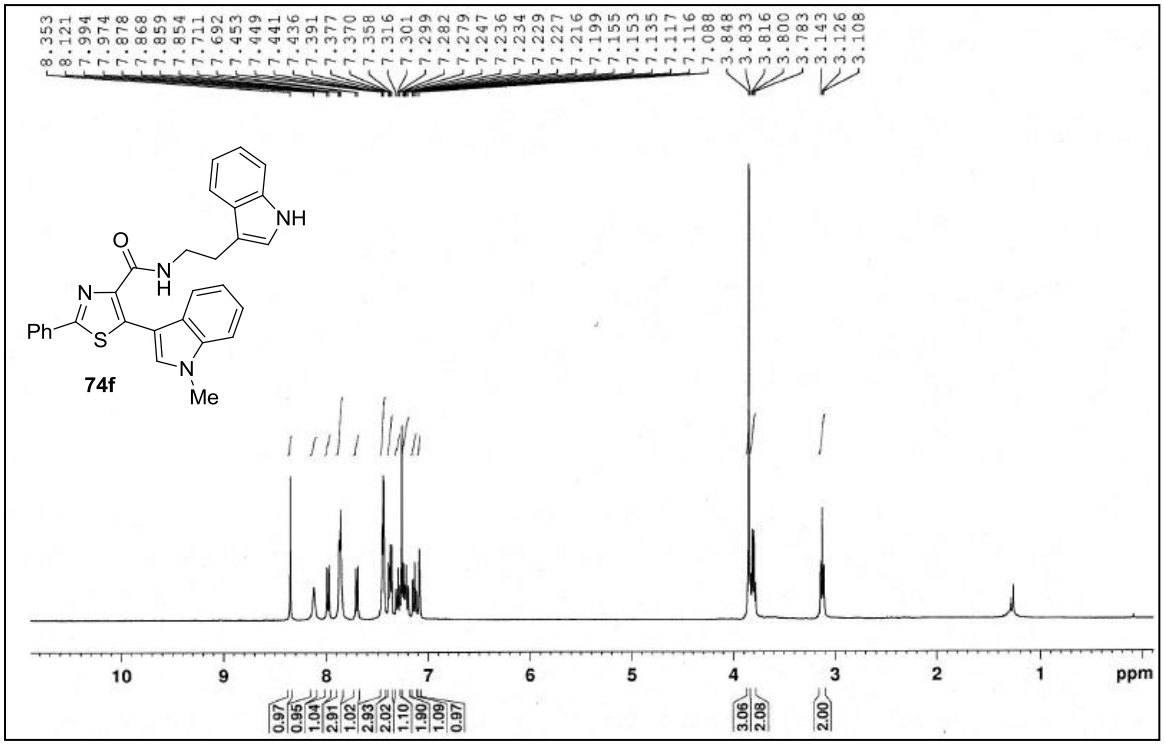

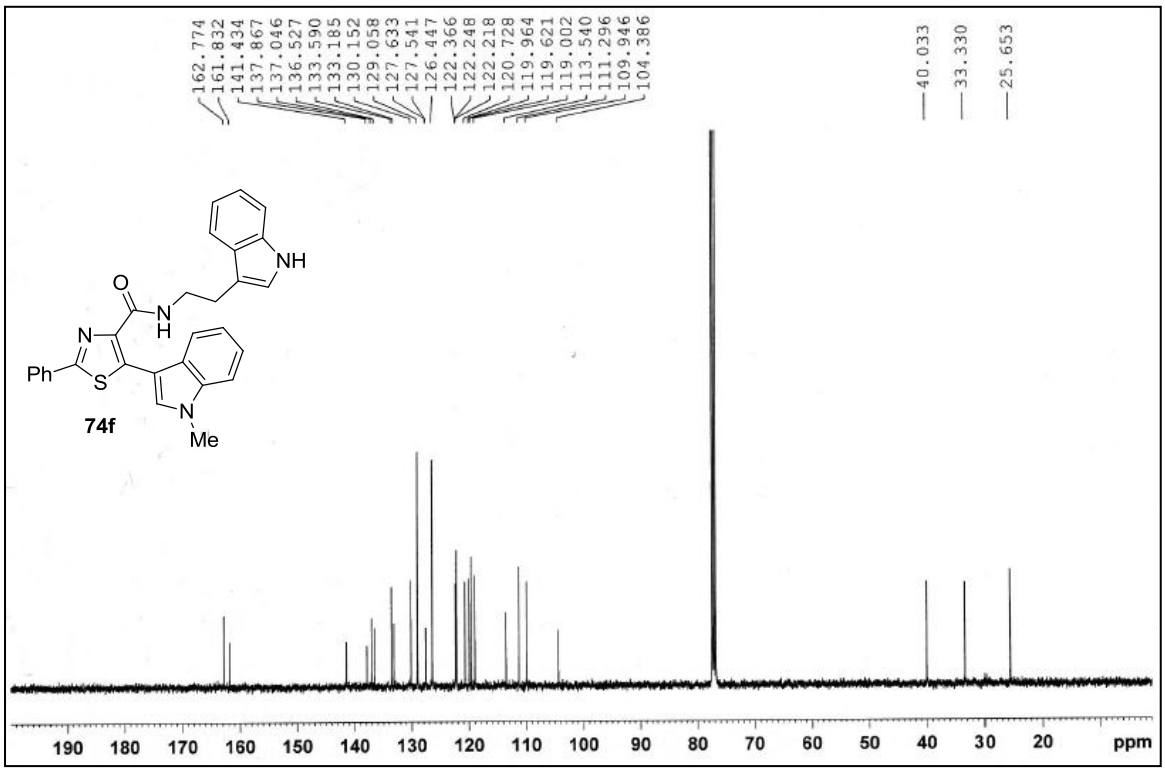

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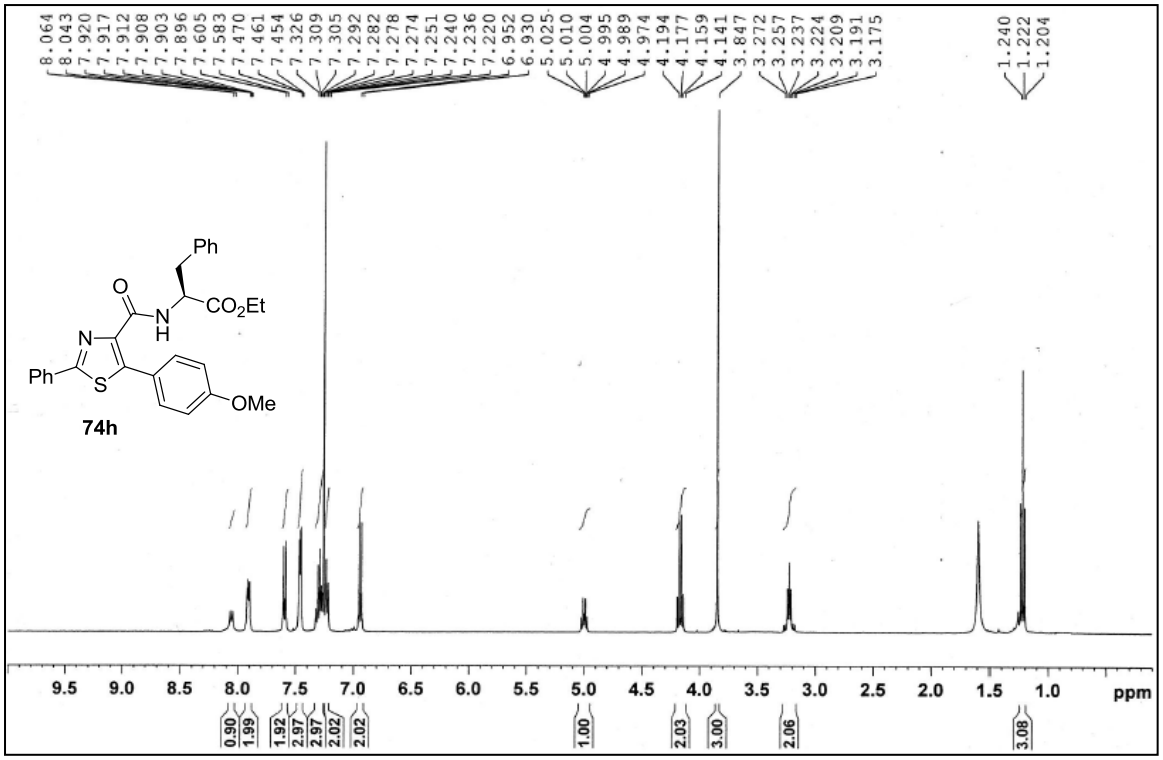

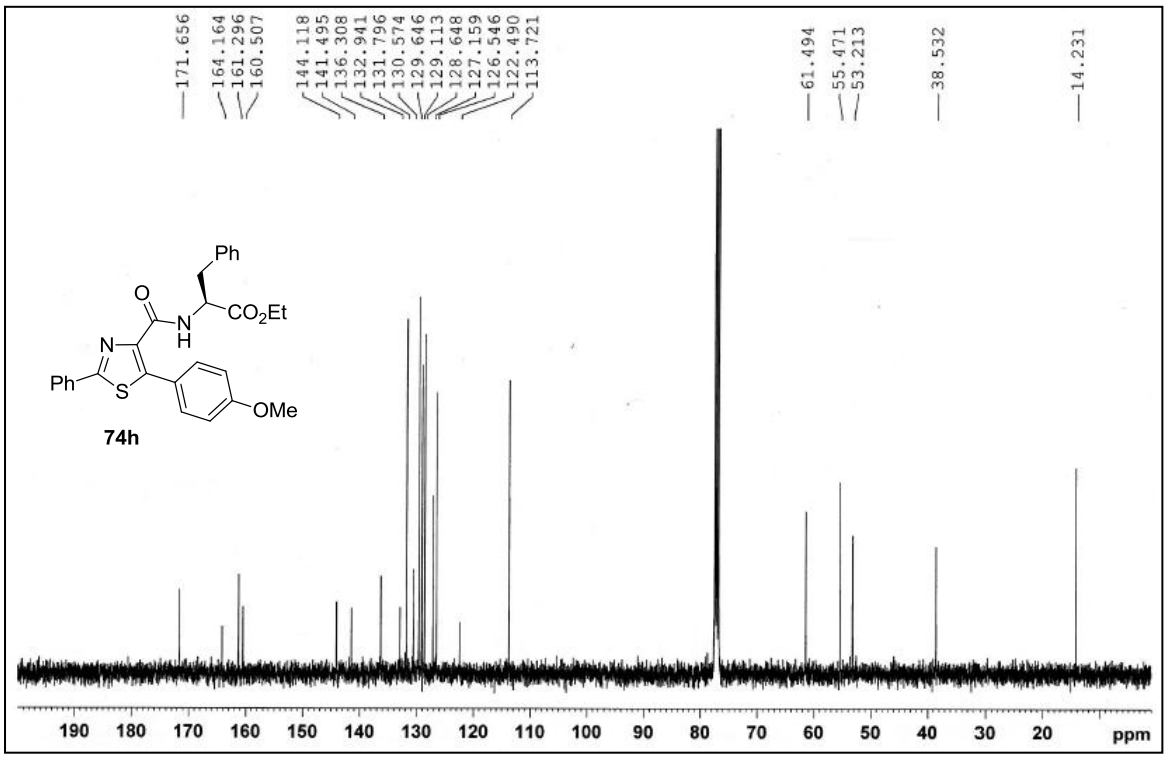

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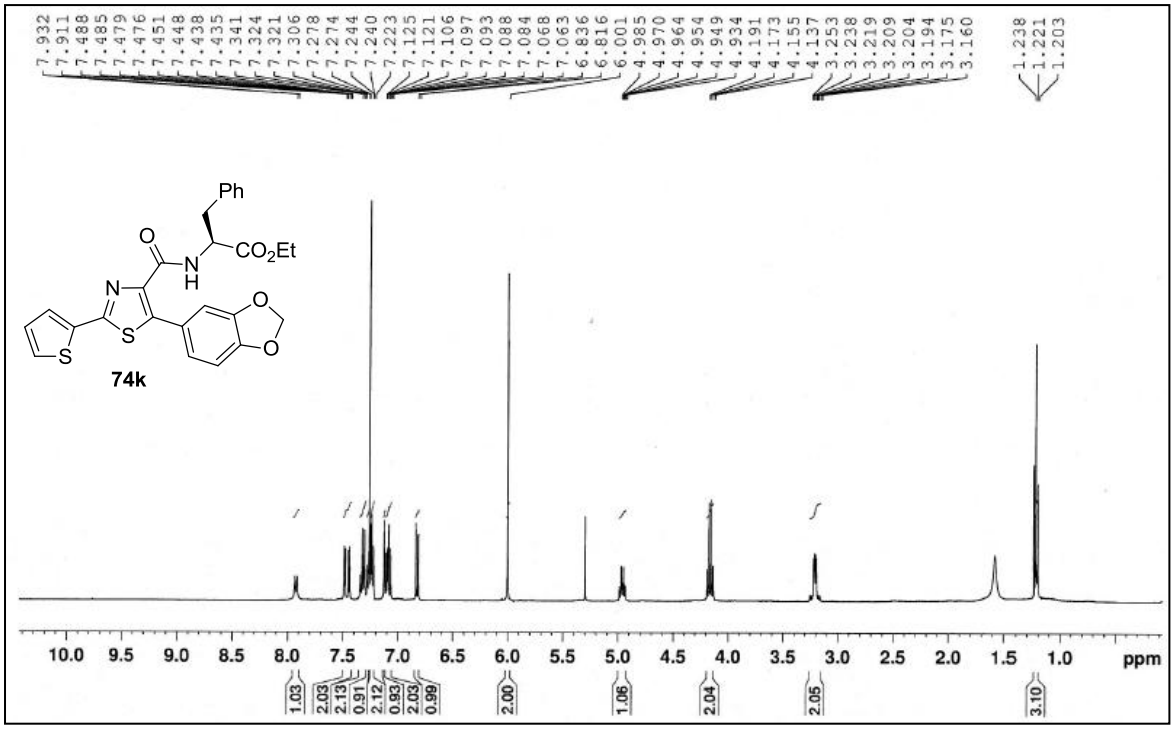
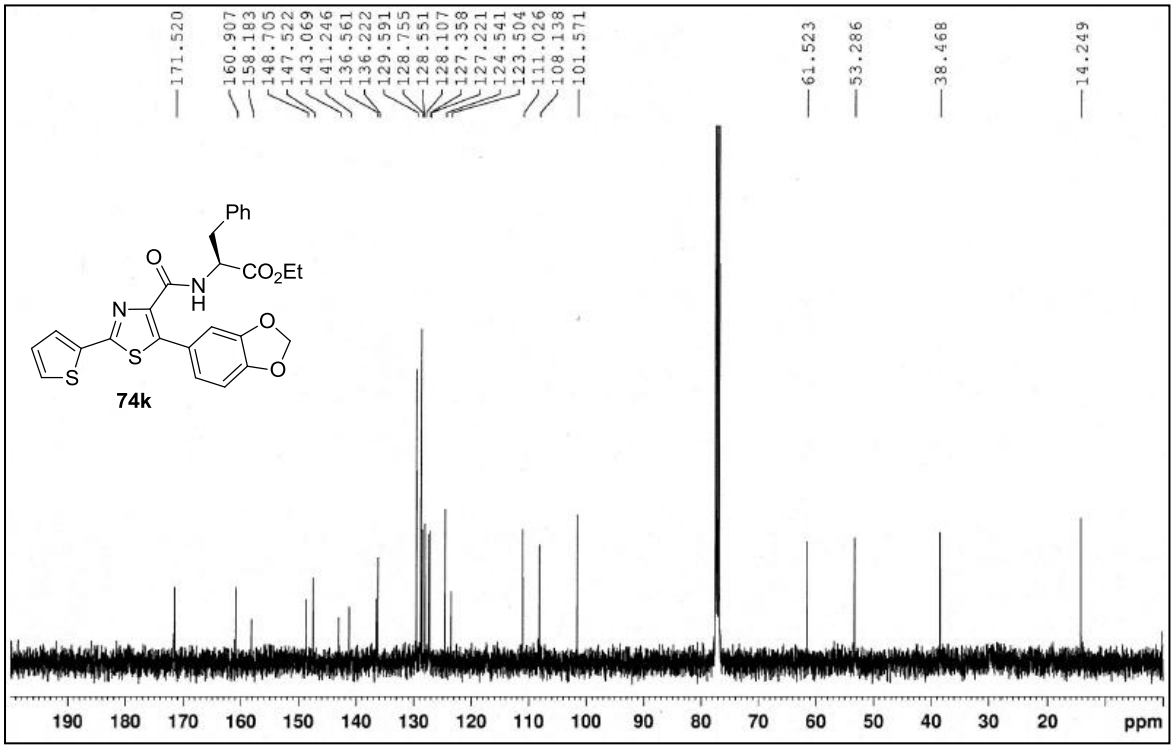
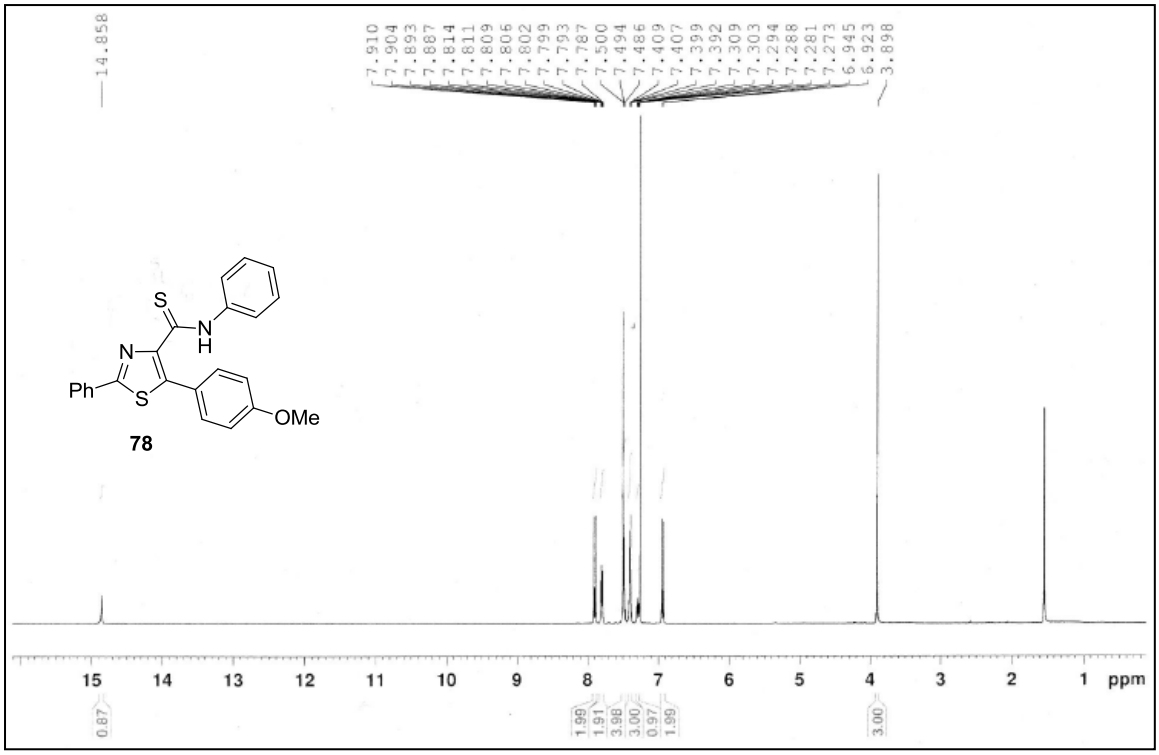
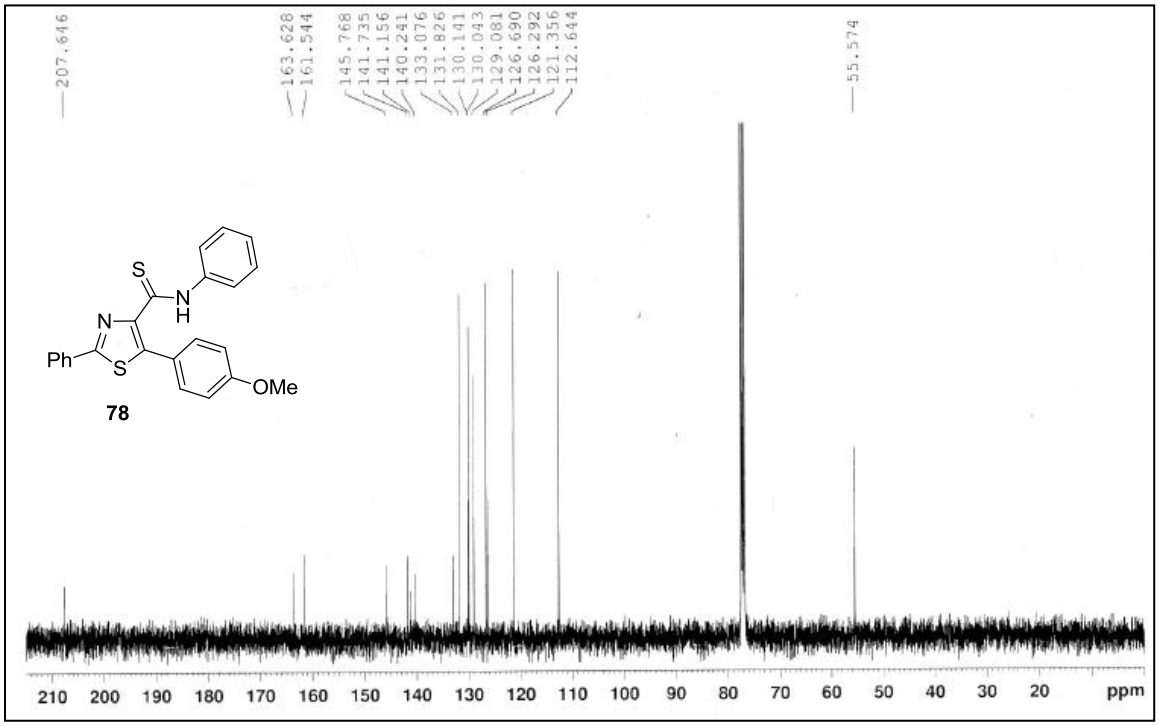




^{1}H NMR and ^{13}C NMR Spectra for compound **74k** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **78** in $CDCl_3$

Chapter 4

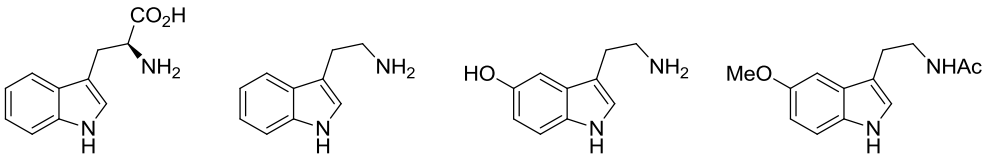
*Synthesis of N-Functionalized/NH Multisubstituted Indoles, Thienopyrroles, Pyrroloindoles and Pyrazolopyrroles via Sequential One-Pot Base Mediated and Copper Catalyzed Inter- and Intramolecular Amination of 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitriles**

4.1. Introduction

Indole structural motif has been generally recognized as a 'privileged structure' in medicinal chemistry, because of the presence of this heterocyclic scaffold in numerous therapeutic agents as well as in natural products displaying wide range of biological[1] and pharmacological activity.[2-3]

One of the most important indole derivatives is naturally occurring essential amino acid tryptophan **1**, which is a biochemical precursor to the family of triptamine **2**,[5] such as serotonin **3**, a key neuro-transmitter in the central nervous system, and melatonin **4**, a hormone that regulates function of smooth muscle in the cardiovascular and gastrointestinal systems. Tryptophan containing proteins have reducing effect on depression and insomnia related with hormonal functions[4] (Chart 1).

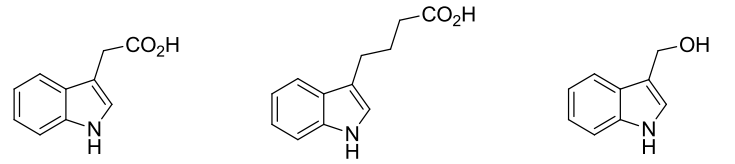
*The overall results of study described in this chapter have been published in *J. Org. Chem*. **2014**, *79*, 7961.



1, tryptophan **2,** tryptamine **3,** serotonin **4,** melatonin

Chart 1

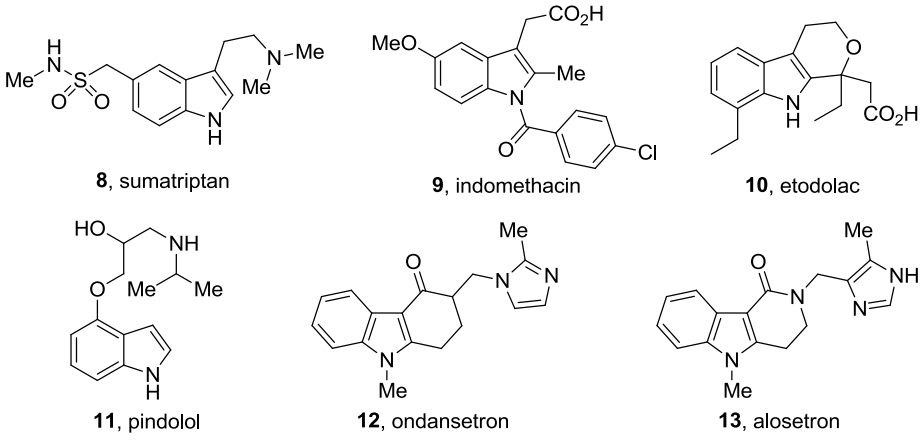
Beside tryptamines, indole moiety is also present in auxins (plant growth hormone) such as indole-3-acetic acid **5** and indole-3-butyric acid **6** (Chart 2).[6] Naturally occurring indole-3-carbinol **7** is known to prevent the binding of aflatoxin to DNA resulting in reduction of the carcinogenic effects of aflatoxins.[7-9] Indole-3-carbinol **7** is also found to be effective in the prevention of breast cancer[10] as well as in treatment of skin cancer[11] (Chart 2).



5, indole-3-acetic acid **6,** indole-3-butyric acid **7,** indole-3-carbinol

Chart 2

A few of the marketed drugs containing indole skeleton are shown in Chart 3. Thus, sumatriptan **8**, a tryptamine[12] derivative is used in the treatment of migraine headaches, whereas indomethacin **9** and etodolac **10**,[13] are well established non-steroidal anti-inflammatory drugs. Similarly, pindolol **11** is a β-adrenoceptor antagonist,[14] while ondansetron **12**[15] and alosetron **13**[16] are used for suppression of nausea and vomiting in cancer chemotherapy and in the treatment of irritable bowel syndrome respectively.



8, sumatriptan **9**, indomethacin **10**, etodolac

11, pindolol **12**, ondansetron **13**, alosetron

Chart 3

Several of the indole containing alkaloids display important biological activitiy. Thus, reserpine **14**, isolated from the dried root of *Rauwolfia serpentina* (sarpagandha), has been used earlier as powerful antihypertensive and antipsychotic drug.[17] Similarly, ellipticine **15**, a pyridocarbazole derivative, displays strong anti-tumor activity,[18] whereas, vincristine **16**, an anti-mitotic agent drug, is used in cancer chemotherapy.[19] Eudistalbin **17**, a β-carboline derivative isolated from marine organism, exhibit strong cytotoxic activity, while dihydroflustramine **18**, is a powerful antimicrobial and antiparasitic agent (Chart 4).[20]

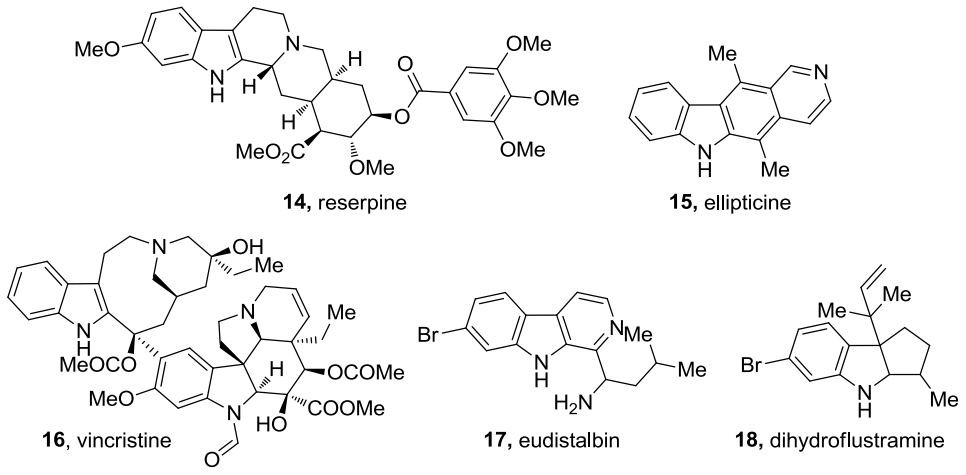


Chart 4

Several of the indole derivatives are known to display tubulin polymerization inhibitor activity (Chart 5).[21-22] Thus, indolyl-3-glyoxamide D-24851 **19** and the 2-aroylindole derivative **20**, discovered by Baxter Oncology, are found to be highly active against various tumors, including those resistant to drug paclitaxel.[23] Angerer and co-workers have demonstrated that 2-arylindole-3-aldehyde **21**, completely blocks microtubule assembly at a concentration of 40 μM.[24] Similarly, the compound **22**, a heterocombretastatin derivative,[25] developed by Medarde and co-workers and 2,3-diaryl/2-aryl-3-arylcarbonylindole derivatives **23** and **24** from Flynn and co-workers are known to display strong tubulin polymerization inhibitory activity (Chart 5).[26]

As is evident from the previous discussion, because of the presence of indole nucleus in several naturally occurring and synthetic bioactive compounds, synthesis of functionalized indoles has attracted considerable attention from synthetic and medicinal chemists over past several decades.[27] In the following section, a short survey of some of the recently developed important synthetic approaches for indole derivatives have been highlighted.

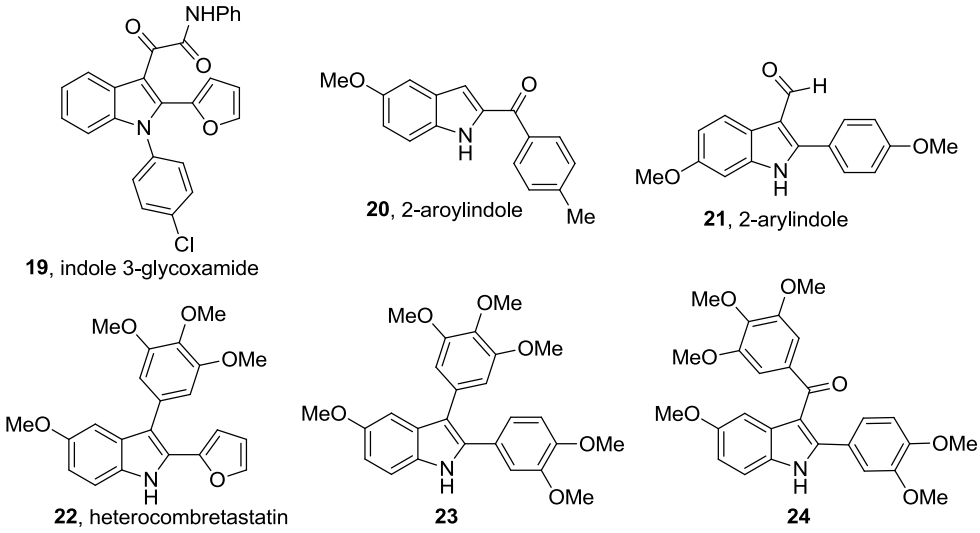
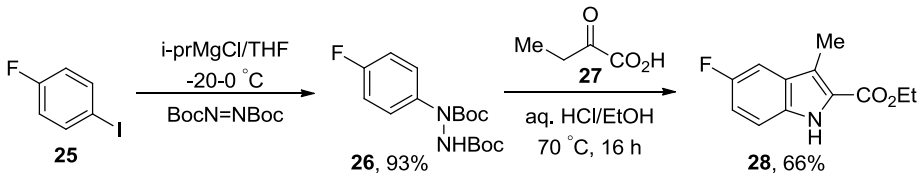


Chart 5

4.2 Synthesis of substituted indoles: A short literature survey

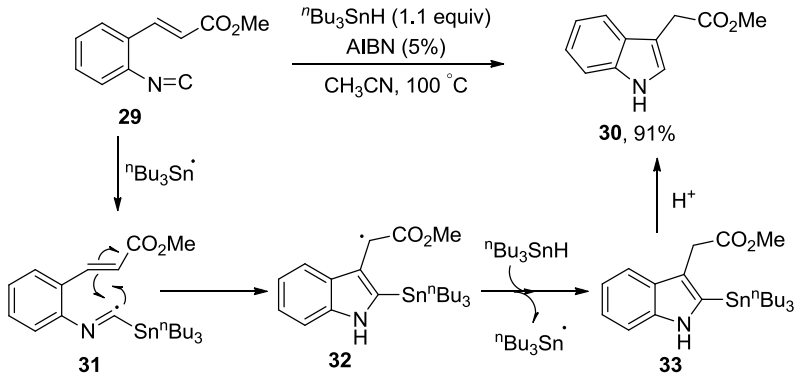
One of the most widely used methods for the synthesis of indoles is Fischer indole synthesis, involving acid induced rearrangement of arylhydrazones, which was discovered by a German chemist, Hermann Emil Fischer, in 1883.[28a]

Several modified methods of this Fischer indole synthesis have been developed for the preparation of substituted indoles. Thus, Moody and co-workers reported a new variation of Fischer indole synthesis, in which N-Boc protected arylhydrazines such as **26** are prepared by reaction of aryl Grignard regents with di-*tert*-butyl azodicarboxylate. These hydrazines **26** react with various ketones under acidic conditions to provide substituted indoles such as **28** in good yields (Scheme 1).[28b]



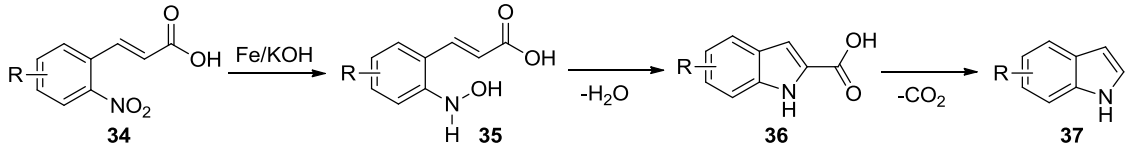
Scheme 1

Fukuyama and co-workers[29] have developed a radical mediated synthesis of 3-substituted indoles such as **30** by treatment of arylisocyanides **29** with tributyltinhydride (Scheme 2). The overall reaction involves intramolecular radical cyclization of the intermediate **31**, generated by treatment of **29** with tributuyltin radical, followed by reductive quenching of the resulting radical intermediates **32** and **33** (Scheme 2).



Scheme 2

The Baeyer-Emmerling indole synthesis involves intramolecular cyclization of *o*-nitrocinnamic acids **34** in presence of iron powder under basic medium to give indole 2-carboxylic acid **36** which undergoes decarboxylation to give indole **37** (Scheme 3).[30]

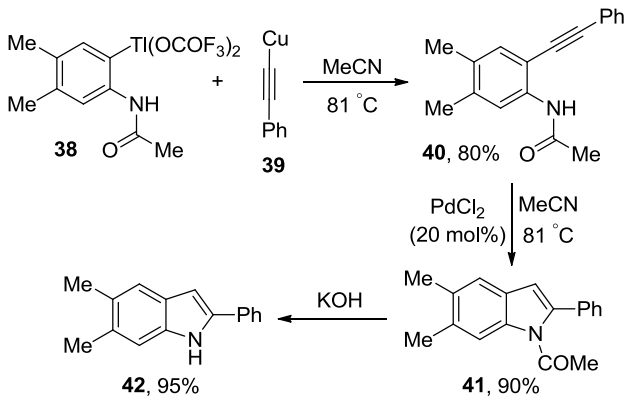


Scheme 3

4.2.1 Synthesis of indoles via palladium-catalyzed intramolecular cyclization of *o*-alkynylanilines and related compounds

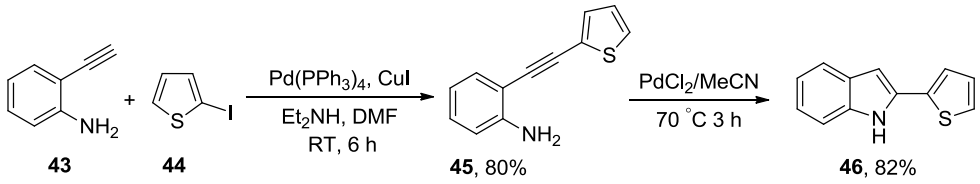
Transition metal catalyzed C−C and C−N bond-formation reactions have recently enabled the development of alternative methodologies toward modular indole synthesis.[31,32] In this context, palladium-catalyzed transformations for the synthesis of indole backbone starting from *o*-alkynylanilines and *o*-alkynylanilides[32,33] have been studied extensively.

The first example of palladium-catalyzed cyclization of *o*-alkynylanilides to indoles was reported by Taylor and McKillop (Scheme 4).[34] Their synthesis involves the coupling of the preformed Cu(I) salt of phenylacetylene with *o*-thallated anilides **38** in acetonitrile to give *o*-(phenylethynyl) acetanilides **40**, which on treatment with Pd(II) catalyst in acetonitrile results in smooth cyclization to *N*-acyl-2-phenylindoles **41**, from which free NH indoles **42** are obtained by deacylation with alcoholic KOH (Scheme 4).



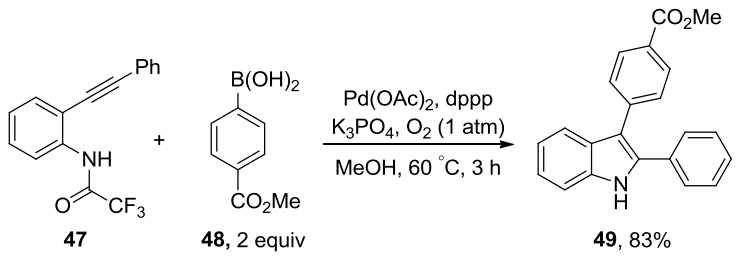
Scheme 4

Cacchi and coworkers have developed an alternative approach in which 2-substituted NH indoles such as **46** were synthesized by palladium catalyzed intramolecular cyclization of *o*-amino substituted internal alkynes **45**, obtained by Sonogashira coupling of *o*-ethynylaniline **43** with 2-iodothiophene **44** (Scheme 5).[35]



Scheme 5

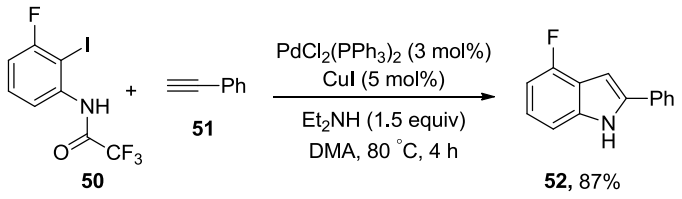
Recently same group has reported a synthesis of free NH 2-substituted 3-arylindoles such as **49** via tandem palladium catalyzed intramolecular cyclization of 2-alkynyltrifluoroacetanilides **47** followed by Suzuki cross-coupling with 4-substituted arylboronic acids such as **48** at 3-position of indole nucleus (Scheme 6).[36]



Scheme 6

The palladium catalyzed coupling of terminal alkynes with *o*-haloanilines or *o*-haloanilides followed by intramolecular cyclization of the resulting *o*-alkynylanilines either in a stepwise, one-pot, or domino process is also a very useful approach to the synthesis of 2-substituted indoles.[37] Thus, Sanz and co-workers[37b] have recently described a convenient route for accessing 2-substituted-1*H*-indoles such as **52** in high yields by

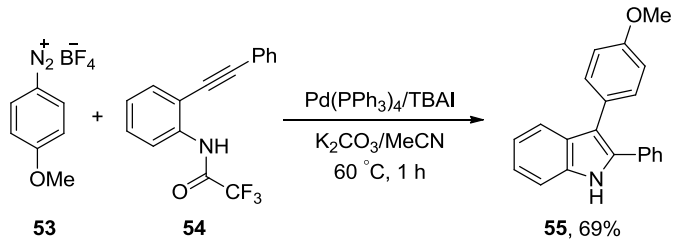
reaction of 3-fluoro-2-iodotrifluoroacetanilide **50** with terminal alkynes such as **51** through a domino Pd/Cu-catalyzed coupling-cyclization process (Scheme 7).



Scheme 7

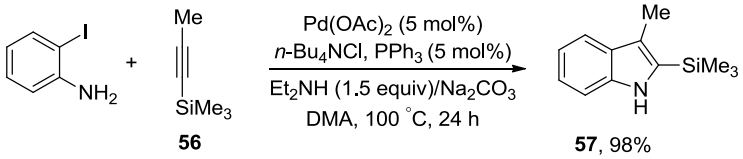
These methods generally afford 2-unsubstituted indoles, however, in some cases, subsequent functionalization of the 3-position can be performed in a one-pot manner, via either Pd-catalyzed arylation,[38] alkenylation,[39] alkylation,[40] or alkynation.[41]

Cacchi and co-workers have recently reported an efficient one- pot, two step protocol for the synthesis of free N-H 2,3-disubstituted indoles such as **55** by palladium catalyzed intramolecular cyclization of 2-alkynyltrifluoroacetanilides **54** followed by cross-coupling of aryldiazonium salt **53** at 3-position to give indole **55** in good yield as shown in the Scheme 8.[38a]



Scheme 8

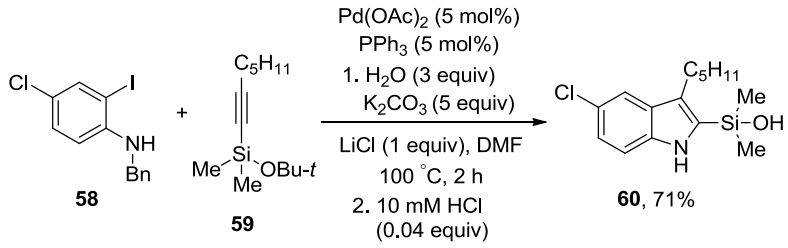
Larock has developed an efficient synthesis of 2,3-substituted indoles via palladium catalyzed intermolecular cross coupling-cyclization of *o*-iodoanilines or their *N*-methyl, *N*-acetyl, and *N*-tosyl derivatives with internal alkynes such as **56** to give indole **57** in good yields (Scheme 9).[42a]



Scheme 9

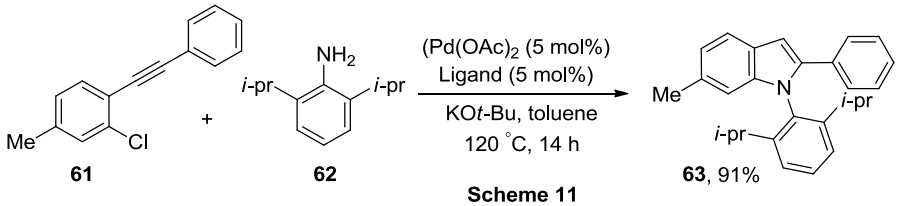
Recently, Denmark and co-workers replaced the simple trimethylsilyl group employed by Larock with a silylether such as **59** and showed that *N*-benzyl-2-iodoanilines **58** underwent palladium catalyzed cross coupling-cyclization with an alkynyldimethyl

silyl tert-butyl ether **59** to afford indole-2-silanols **60** after subsequent hydrolysis (Scheme 10).[42b]



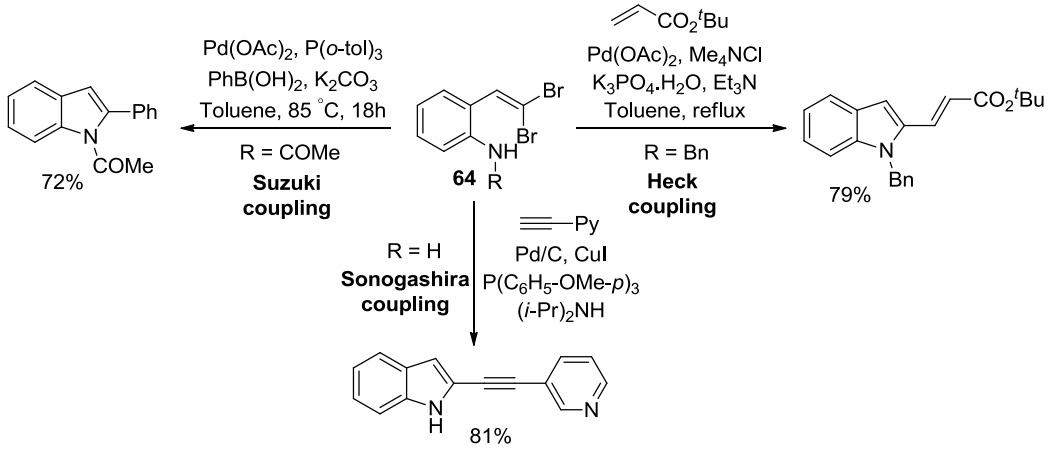
Scheme 10

Ackermann and co-workers have reported a useful route to N-arylindoles such as **63** *via* palladium-catalyzed tandem *N*-arylation-hydroamination of *o*-alkynylhaloarene precursors such as **61** (Scheme 11).[43]



Scheme 11

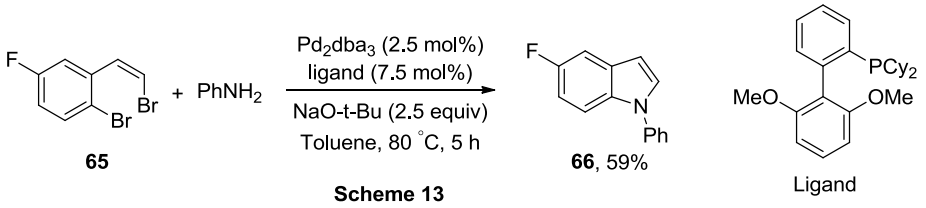
In a series of recent papers, Lautens and co-workers have described several strategies to synthesize indole derivatives from *o-gem*-dihalovinylanilines **64** based on palladium catalyzed domino C-N/Suzuki,[44a,b] C-N/Heck,[44c] and C-N/Sonogashira[44d] couplings initiated by intramolecular carbon-nitrogen coupling (Buchwald-Hartwig amination) followed by an intermolecular cross-coupling reaction (Scheme 12).



Scheme 12

Willis and co-workers[45] have recently reported an efficient route to *N*-functionalized indoles such as **66** via Pd-catalyzed inter- and intramolecular alkenyl-

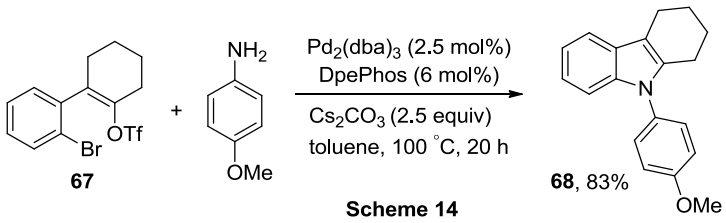
arylamination reaction of a broad range of 2-(2-haloalkenyl)aryl halides such as **65** with a variety of substituted anilines (Scheme 13).



65 **66**, 59%

Scheme 13

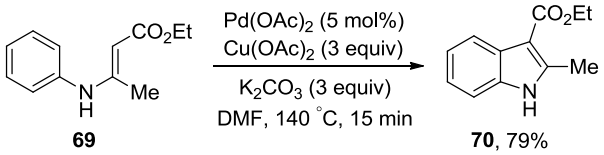
Same group has also extended this protocol to the corresponding 2-haloarylalkenyl triflate precursors such as **67** and subjected them to Pd-catalyzed inter and intramolecular aryl alkenyl amination with various substituted anilines and alkyl amines to furnish indoles such as **68** in good yields (Scheme 14).[46]



67 **68**, 83%

Scheme 14

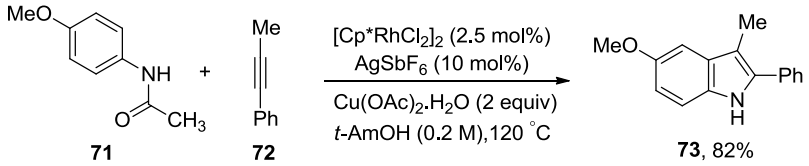
Significant breakthroughs have also been made in recent years by several research groups[47] for developing direct approaches for indole synthesis by transition-metal-catalyzed oxidative C−H activation. Thus, Glorius and co-workers[47a] have reported the direct Pd-catalyzed oxidative coupling of two C-H bonds of *N*-aryl-enamines such as **69** for the synthesis of substituted indoles **70** (Scheme 15). In this cross-dehydrogenative coupling, many different functional groups are tolerated and the starting *N*-arylenamino esters **69** can be easily prepared in one step from various commercially available anilines and *β*-ketoesters.



69 **70**, 79%

Scheme 15

Fagnou and his group has described a rhodium-catalyzed C-H bond functionalization strategy for the synthesis of substituted indoles such as **73** by insitu generation of enamines from N-acetylanilines **71** and substituted internal alkynes such as **72** using Rh complex $[Cp^*RhCl_2]_2$ and stoichiometric Cu(II) oxidant (Scheme 16).[47h]



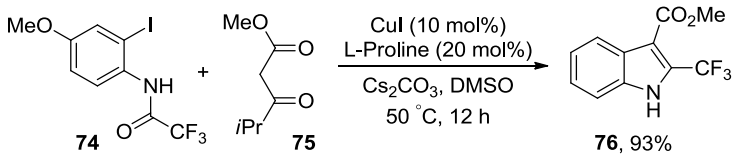
71 **72** **73**, 82%

Scheme 16

4.2.2 Copper-catalyzed synthesis of substituted indoles

With emerging interest in the Ullman-Goldberg reaction[48] and also due to the low cost of copper catalysts, several new efficient routes to indole synthesis have also been developed *via* copper-catalyzed reactions.[49]

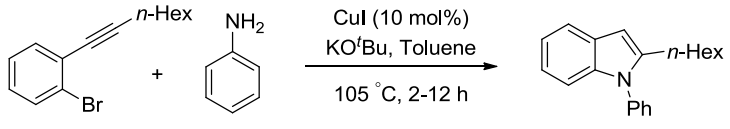
Thus, Ma and co-workers[49b] have reported a Cu-catalyzed coupling of 2-halotrifluoro acetanilides such as **74** with *β*-keto esters **75** in anhydrous DMSO in presence of Cs_2CO_3 at 40-80 °C yielding polysubstituted 2-(trifluoromethyl)indoles such as **76** in good to excellent yields via initial C-C bond formation and subsequent intramolecular condensation (Scheme 17).



74 **75** **76**, 93%

Scheme 17

The *N*-arylation of 2-haloarylalkynes represents a useful alternative for in situ generation of 2-alkynylanilines. This strategy has been successfully exploited by Ackermann and co-workers for the synthesis of indoles by copper catalyzed *N*-arylation of 2-haloarylalkynes followed by in situ intramolecular cyclization of the resulting 2-anilinoarylalkynes to substituted indoles such as **79** (Scheme 18).[50]



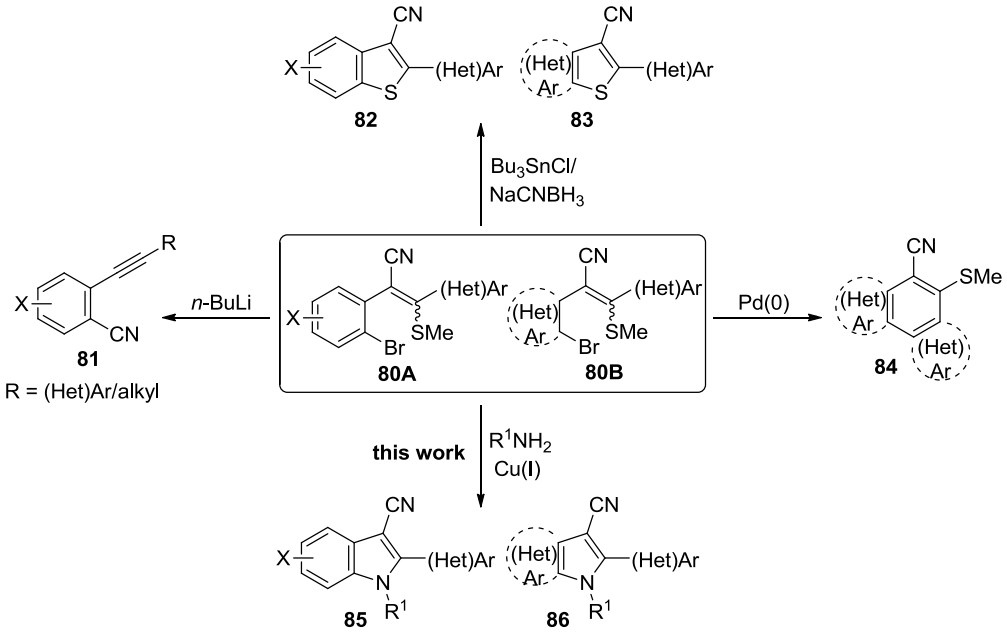
77 **78** **79**, 84%

Scheme 18

Despite these existing methods, synthesis of *N*-functionalized multisubstituted indoles has not received much attention.[42b,33f,47d,54]

As part of research efforts directed towards design and development of new synthetic methods for substituted and fused five and six membered heterocycles, utilizing polarized ketene dithoacetals and other newly developed organosulfur synthons,[51] earlier

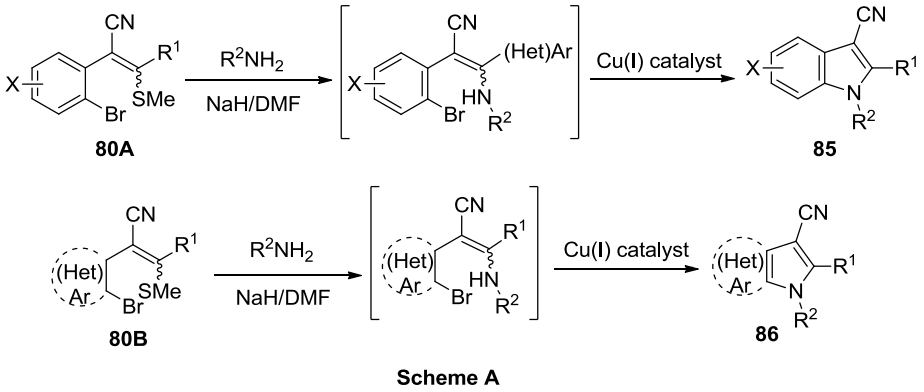
work from our laboratory has demonstrated design and development of a new class of organosulfur building blocks such as 2-[2-bromo(het)aryl]-3-(het)aryl/alkyl-3-(methylthio)acrylonitriles of the general structures **80A** and **80B** (Scheme 19).[52] Thus these intermediates (**80A**) have been shown undergo a novel unexpected anionic domino rearrangement in the presence of *n*-BuLi, leading to a general synthesis of 2-(het)aryl/alkyl-1-(*o*-cyano)acetylenes such as **81**.[52a] Also, our research group has reported an efficient route for the synthesis of 2-(het)aryl/alkyl-3-cyano-benzothiophenes **82**[52b] and the corresponding thieno fused heterocycles **83**[52c] by intramolecular radical cyclization of these intermediates (Scheme 19). It was further demonstrated, that Pd(0) catalyzed direct intramolecular (het)arylation of these intermediates provides a facile access to functionalized phenanthrenes, and a variety of novel angularly fused polycyclic heteroarenes such as **84**[52d] in good yields (Scheme 19).



Scheme 19

During the course of these studies, we became interested in employing these intermediates **80A** and **80B** in a cascade inter- and intramolecular C-N bond formation-cyclization process with various primary amines, with a view to develop a novel synthesis of substituted indoles **85** and hetero fused pyrroles **86** respectively (Scheme 19). We have successfully achieved this goal and herein describe a two step one-pot protocol, involving a base mediated intermolecular N(1)-C(2) and a Cu-catalyzed intramolecular N(1)-C(7a) bond formation with primary amines, that allows direct transformation of these easily

accessible intermediates **80A** and **80B** into a variey of N-functionalized/NH multisubstituted indoles and their hetero fused analogs (Scheme A).



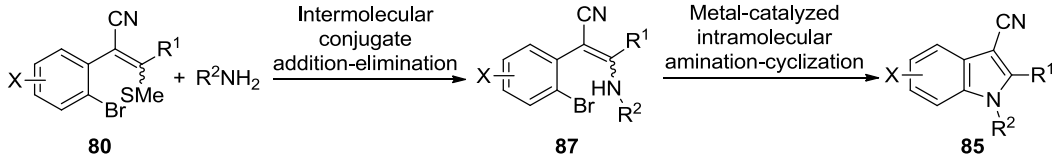
Scheme A

4.3 Results and discussion

4.3.1 Synthesis of 1-N-aryl/alkyl-2-(het)aryl/alkyl-3-cyanoindoles 85a-q

4.3.1.1 Designed strategy for the synthesis of indole 85 from 2-[2-bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitrile 80

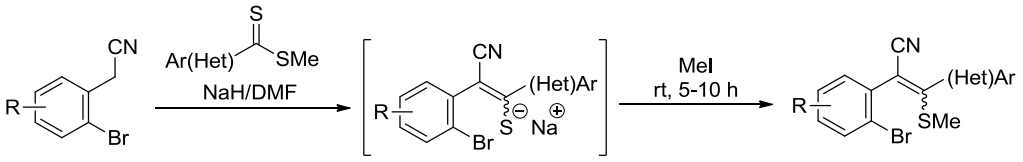
The general strategy for the one-pot indole synthes is from *β*-(methylthio)acrylonitrile precursors **80** is shown in the Scheme 20. The major expectation was, that treatment of **80** with primary amines will furnish under optimized conditions, the enaminonitriles **87** via conjugate addition-elimination of amine on activated *β*-(methylthio)acrylonitrile double bond of **80**. The *ortho* bromo substituent in benzene ring of **87** should offer the possibility to convert them (*in situ* or in two step) into indole **85** by copper (or palladium) catalyzed intramolecular N-arylamination-cyclization process.



Scheme 20

4.3.1.2 Synthesis of 2-[2-bromoaryl]-3-(het)aryl-3-(methylthio)acrylonitrile precursors 80a-l

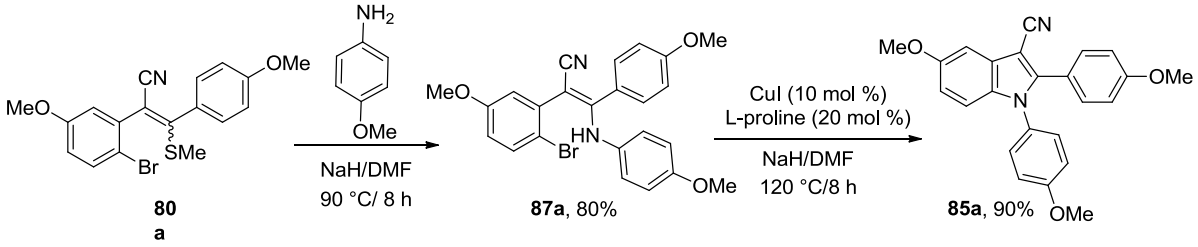
The desired 2-(2-bromoaryl)-3-(het)aryl-3-(methylthio)acrylonitrile precursors **80a-l** (Table 2) were prepared according to earlier reported method in our laboratory[52a-d] by base induced condensation of the corresponding 2-bromoarylacetonitriles with (het)aryl dithioesters, followed by *in situ S*-methylation of the resulting enethiolate intermediates (Scheme 21).



Scheme 21

4.3.1.3 Optimization of raction conditions for the synthesis of indole 85a from 80a via enaminonitrile 87a

The cyclization of the acrylonitrile **80a** with 4-methoxyaniline was selected as a test reaction for optimization of reaction conditions for the synthesis of indole **85a** (Scheme 22, Table 1). We first focused on devising reaction conditions for a two-step process, i.e., synthesis and isolation of enaminonitrile **87a** by conjugate addition-elimination on **80a** with 4-methoxyaniline and its subsequent Cu (or Pd) catalyzed intramolecular arylamination to indole **85a**. Thus optimization studies revealed that **80a** remained unaffected, when reacted with 4-methoxyaniline in the presences of bases like K_2CO_3 or Cs_2CO_3 in solvents like toluene, acetonitrile or DMF, even at higher temperature, whereas, with potassium *t*-butoxide in DMF at 120 °C, the enaminonitrle **87a** could be obtained in maximum yield of 35% only, on prolonged heating (24 h). On the other hand, employing sodium hydride as base in DMF at 90 °C, the reaction was complete within 8 h, furnishing the enaminonitrile **87a** in 80% yield (Scheme 22).



Scheme 22

The ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data of **87a** revealed that it exists as single (*E*) stereoisomer.

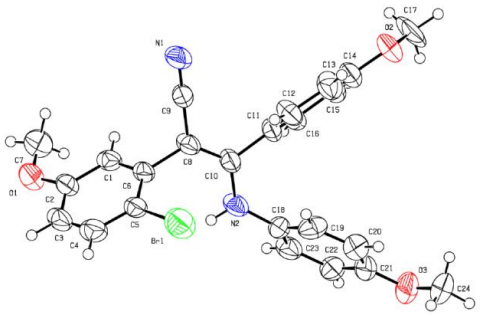
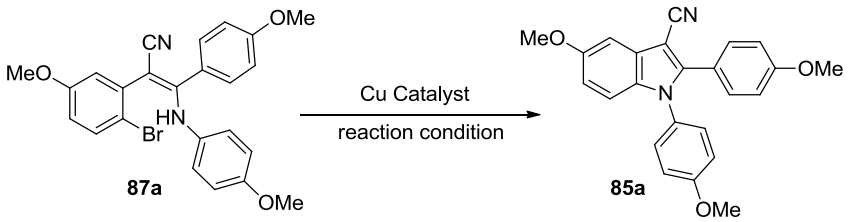


Figure 1. X-Ray crystal structure of **87a**

Having established reaction conditions for the formation of enaminonitrile **87a**, we next set out to examine its intramolecular arylamination-cross coupling to indole **85a** under influence of various catalysts and ligands. In view of the lower costs of copper salts and the related ligands, in comparison to palladium catalysts and phosphine ligands, we first evaluated copper catalyzed intramolecular cyclization[48,49,53,57b-c] of **87a** to indole **85a** and these results are summarized in the Table 1.

Copper catalyzed 'nitrogen ligand free' amination reactions are shown to proceed efficiently in the presence of *t*-BuOK as base.[50,55a] We therefore first explored the possibility of accomplishing intramolecular aminoarylation of **87a** with inexpensive CuI as catalyst under these conditions, which afforded the desired indole **85a** in 65% yield (Table 1, entry 1). On the other hand, promising results could be achieved with proline ligand affording indole **85a** in increased yield of 78%, under identical conditions (entry 2). Further, use of sodium hydride as base, was found to be superior, furnishing indole **85a** in 90% yield within 8 h (entry 3). Preliminary studies revealed that DMF, among a

Table 1. Optimization of reaction conditions for the synthesis of 85a from 87a

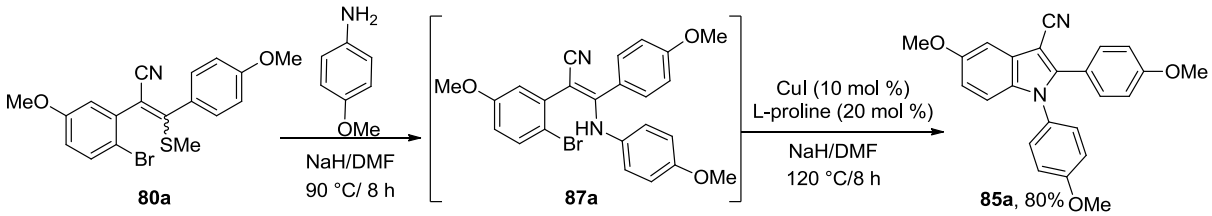


entry	Cu catalyst (10 mol %)	ligand (20 mol %)	base	solvent	temp/time °C/h	yield (%) **85a**
1	CuI	-	*t*-BuOK	DMF	120/12	65
2	CuI	L-proline	*t*-BuOK	DMF	120/10	78
3	**CuI**	**L-proline**	**NaH**	**DMF**	**120/8**	**90**
4	CuI	phenanthroline	NaH	DMF	120/9	78
5	CuI	DMEDA	NaH	DMF	120/10	73
6	CuI	cyclohexane 1,2-diamine	NaH	DMF	120/10	75
7	CuI	ethyleneglycol	K_3PO_4	2-propanol	80/12	68
8	CuI	ethylenegycol	K_3PO_4	DMF	120/10	78
9	CuI	L-proline	Cs_2CO_3	DMF	120/12	70
10	CuI	L-proline	K_2CO_3	DMF	120/12	55
11	CuBr	L-proline	NaH	DMF	120/10	78
12	CuOAc	L-proline	NaH	DMF	120/10	75
13	CuI (5 mol %)	L-proline	NaH	DMF	120/15	75

variety of other solvents (toluene, DMSO, acetonitrile, NMP, THF) proved to give rise to optimal results. Use of representative ligands (phenanthroline, DMEDA, cyclohexa-1,2-diamine), generally employed in Cu-catalyzed N-arylation, also furnished the indole **85a** in 73-78% yield (entries 4-6). Similarly, ethylene glycol in the presence of K_3PO_4 as base in either 2-propanol or DMF was also found to be effective[49c] providing **85a** in reasonably good yields (entries 7-8). Bases like Cs_2CO_3 and K_2CO_3 were found to be inferior in comparison to sodium hydride (entries 9-10), whereas alternative Cu sources could also be employed, with both CuBr and CuOAc, found to be effective, although with reduced efficiency compared to CuI (entries 11-12 vs entry 3). Reducing the catalytic loading (5 mole %) resulted in decreased yield of **85a** even after 15 h of heating (entry 13).

With optimized reaction conditions for the two step synthesis of indole **85a** from 2-(2-bromoaryl)acrylonitrile **80a** in hand (Table 1, entry 3), we next attempted one-pot sequence by subjecting *in situ* generated enaminonitrile **87a** to intramolecular arylamination by adding CuI (10 mol %) and proline (20 mol %) to the reaction mixture (from **80a** and 4-methoxyaniline in the presence of NaH in DMF) and further heating it at 120 °C (monitored by TLC). To our delight, the reaction was complete within 8 h and work-up of the reaction mixture afforded indole **85a** in 80% yield (Scheme 23). Despite the slightly reduced yield of indole **85a**, in comparison with the two step process, this sequential one-pot procedure was followed throughout our subsequent studies for the synthesis of 1-N-aryl-2-(het)arylindoles **85** (Table 2).

4.3.1.4 Synthesis of indole 85a from 80a in one-pot process

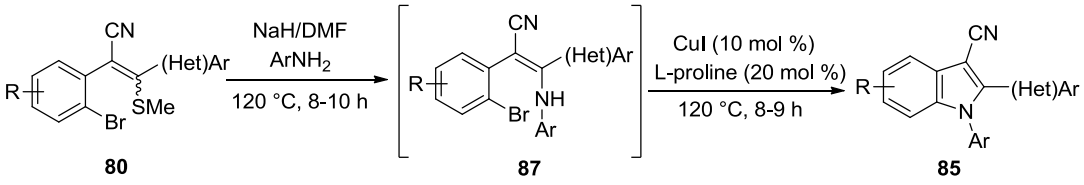


Scheme 23

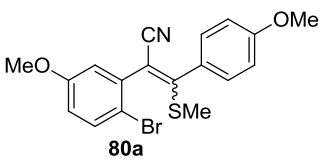
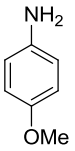
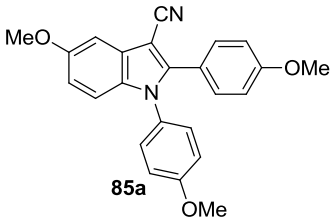
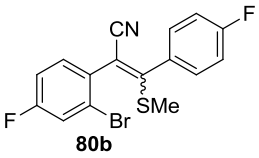
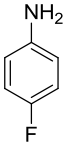
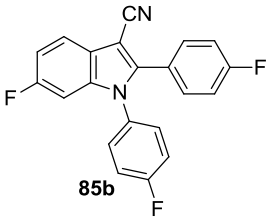
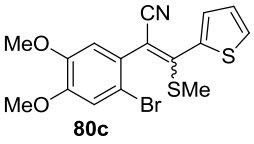
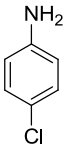
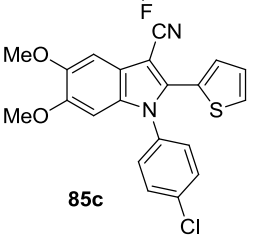
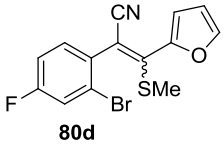
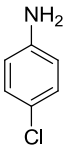
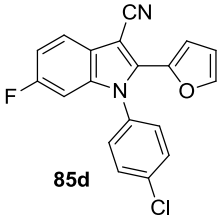
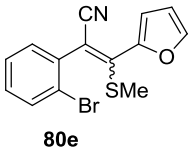
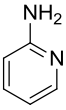
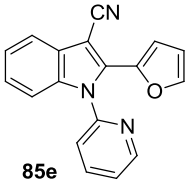
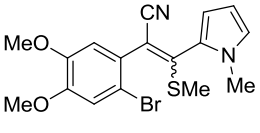
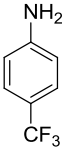
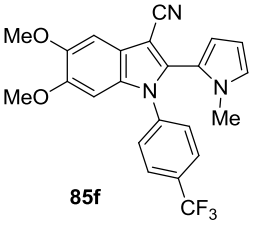
Having accomplished the optimal conditions for the two step one-pot base mediated amination-copper catalyzed intramolecular arylamination protocol, we set out to evaluate the scope and generality of this novel indole synthesis by varying the substituents on acrylonitrile precursors **80**, as well as on N-coupling partners i.e., anilines,

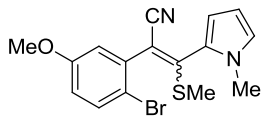
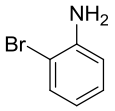
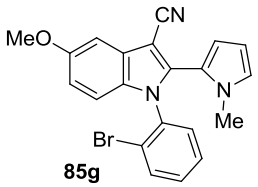
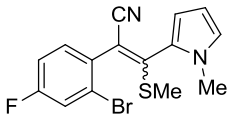
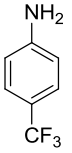
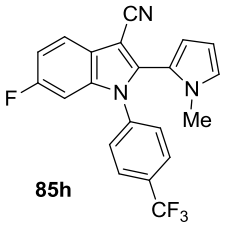
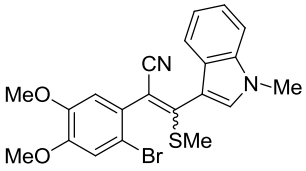
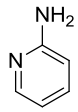
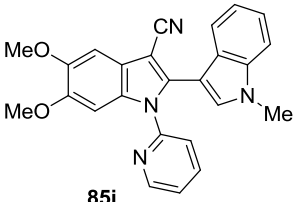
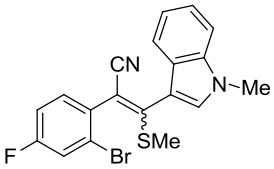
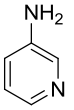
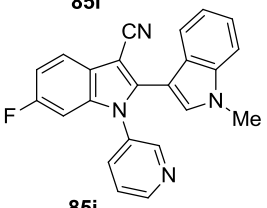
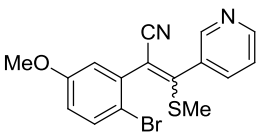
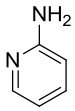
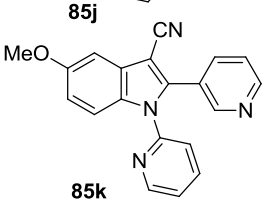
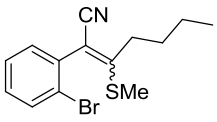
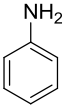
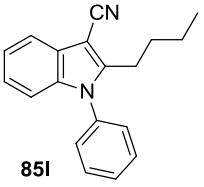
following these optimized reaction conditions (Table 2). Thus the reaction was equally facile with both electron donating as well as electron withdrawing substituents on aromatic ring of **80** (**80a-d**), yielding the indoles **85a-d** in high yields (Table 2, entries 1-4). Also by employing appropriate 3-(het)aryl substituted acrylonitrile precursors (**80c-k**),

Table 2. One-pot two step synthesis of 1,2,3-trisubstituted indoles 85 from 80



80 **87** **85**

entry	substrate	amine	product	yield (%)
1	 **80a**		 **85a**	80
2	 **80b**		 **85b**	85
3	 **80c**		 **85c**	74
4	 **80d**		 **85d**	75
5	 **80e**		 **85e**	75
6	 **80f**		 **85f**	68

entry	substrate	amine	product	yield (%)
7	 **80g**		 **85g**	78
8	 **80h**		 **85h**	71
9	 **80i**		 **85i**	75
10	 **80j**		 **85j**	78
11	 **80k**		 **85k**	66
12	 **80l**		 **85l**	0

the protocol could also be extended for the synthesis of 2-(het)arylindoles bearing (2-thienyl) (**85c**), (2-furyl) (**85d-e**), [2-(N-methylpyrrolyl)] (**85f-h**), [3-(N- methylindolyl)] (**85i-j**) and (3-pyridyl) (**85k**) moieties in good to excellent yields (entries 3-11). It should be noted that, despite the broad application of Pd (or Cu) catalyzed C-N cross coupling/cyclization protocol for the synthesis of 2-substituted indoles from the relevant acetylene precursors, not much attention has been paid for extending this methodology for the synthesis of biologically important 2 -(het)arylindoles from the corresponding *o*-halo(het)arylacetylene substrates.[55g,50] Also, extension of the reaction to a range of commercially available anilines, as N-coupling partners in the cyclization reaction, revealed, that a wide variety of substitution pattern and functionalities are tolerated as

shown in Table 2. Thus N-arylindoles containing both electron donating (**85a)** and electron withdrawing groups (**85b-d**, **85f** and **85h**; entries 1, 2-4, 6, 8) or bearing sterically constrained *o*-substituent (**85g**, entry 7) on N-aryl moiety, could be prepared efficiently in good yields following this procedure (Table 2). When the pyridyl-2 (or 3-) amines were used as the amine coupling partners, the corresponding N-pyridylindoles (**85e, 85i-k**; entries 5, 9-11) were also obtained in good yields (Table 2).

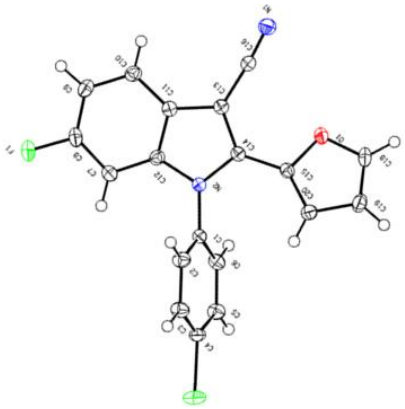
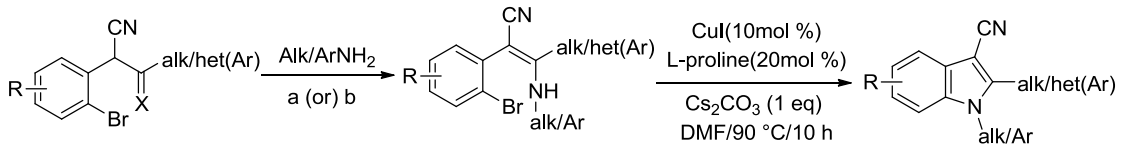


Figure 2. X-Ray crystal structure of **85d**

4.3.1.5 Synthesis of 3-cyano-2-alkyl-*N*-aryl indoles 85m-o and 3-cyano-2-(het)aryl-*N*-alkyl indoles 85p-q

Elaboration of the above methodology for the synthesis of 2-(alkyl)indole by treatment of 2-(2-bromophenyl)-3-(methylthio)hept-2-enenitrile (**80l)** with aniline under two step one-pot conditions (NaH/CuI/L-proline) did not yield the desired indole **85l**, furnishing only the intractable reaction mixture (Table 2, entry 12). We therefore synthesized few 2-alkyl- (**85m-o**) and 1-*N*-alkyl- (**85p-q**) indoles via two step procedure as depicted in the Table 3. Thus enaminonitriles **87m-q** were prepared by reaction of either α-ketonitriles[58] **88m** and **88o** or the corresponding thiocarbonyl analogs **88p-q** with appropriate primary amines under varying conditions (Table 3). However, enaminonitriles **87m-q** failed to yield indoles **85m-q**, when subjected to Cu catalyzed intramolecular aminoarylation under previously described conditions (NaH/CuI/L-proline/DMF) affording only complex mixture of products. Optimization of reaction conditions using weaker base such as Cs_2CO_3, instead of NaH in presence of CuI catalyst and proline as ligand, afforded the corresponding 2-alkyl (**85m-o**) and 1-*N*-alkyl (**85p-q**) indoles in moderate to good yields (Table 3, entries 1-5).

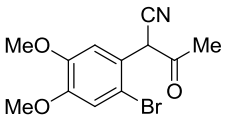
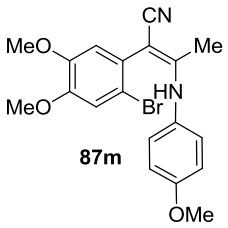
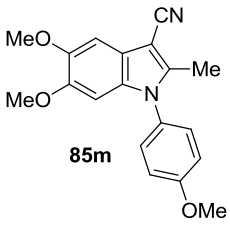
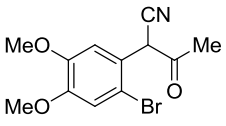
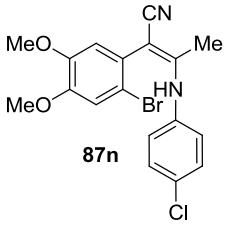
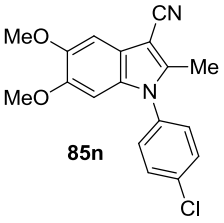
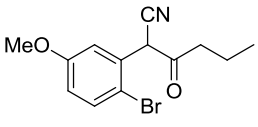
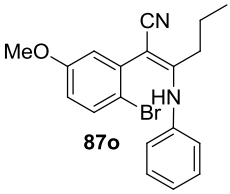
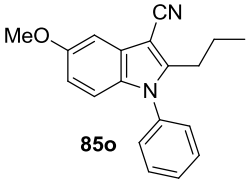
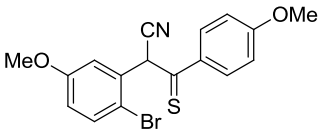
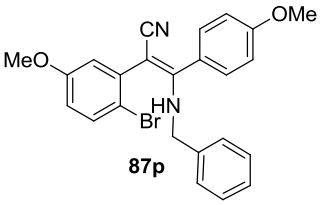
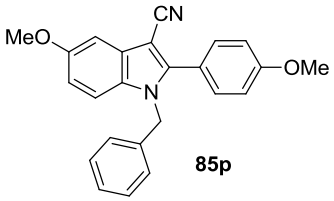
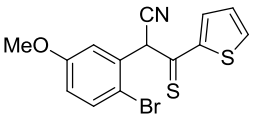
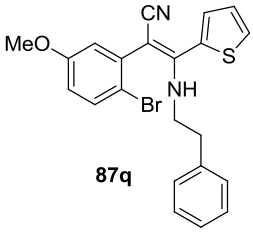
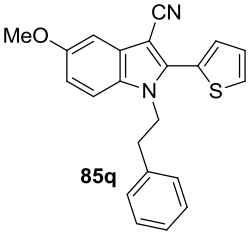
Table 3. Synthesis of 3-cyano-2-alkyl-N-aryl indoles 85m-o and 3-cyano-2-(het)aryl-N-alkyl indoles 85p-q



88m, **88o**, X = O
88p-q, X = S

87m-q

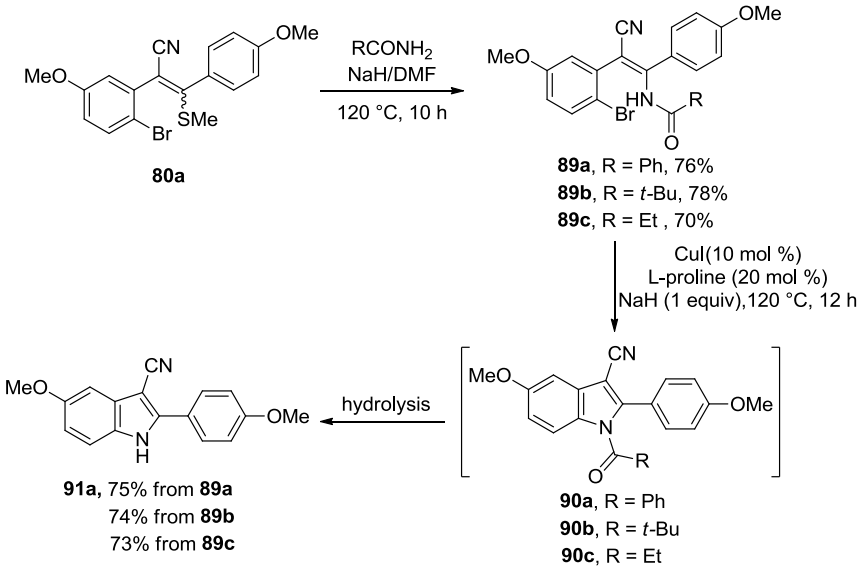
85m-q

entry	substrate **88**	substrate **87**	product[c]	yield (%)
1	 **88m**	 **87m**	 **85m**	80
2	 **88m**	 **87n**	 **85n**	78
3	 **88o**	 **87o**	 **85o**	60
4	 **88p**	 **87p**	 **85p**	55
5	 **88q**	 **87q**	 **85q**	55

4.3.1.6 Synthesis of substituted 2-(het)aryl-3-cyano-1-NH-indoles 91a-e

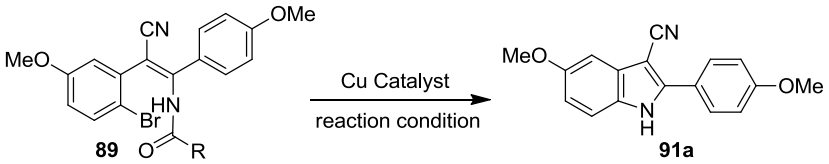
In view of the importance of free N-H indoles among biologically active compounds,[49b,59] besides ease with which less nucleophilic amides can be N-arylated under copper catalysis,[48a-c] we further conceived of extending this protocol for the synthesis of *N*-acylindoles **90** and their subsequent hydrolysis to the corresponding NH indoles **91** (Scheme 24 and Table 4).[50] Thus, the acrylonitrile substrate **80a** was reacted

with either benzamide, trimethylacetamide or propionamide in the presence of NaH/DMF (120 °C/10 h), yielding the corresponding *N*-acylenaminonitriles **89a-c** in good yields (Scheme 24). However, subsequent copper catalyzed intramolecular N-arylation of **89a-c** under earlier described reaction conditions (CuI/proline/NaH) did not provide the expected *N*-acylindoles **90a-c**, but the product isolated from all these reactions, was characterized as the hydrolyzed NH indole **91a** (Scheme 24). Attempted intramolecular *N*-arylation of *N*-acylenaminonitriles **89a-c** in the presence of various copper catalysts/ligands/bases under varying conditions also resulted in the formation of only NH



Scheme 24

Table 4. Intramolecular *N*-arylation of *N*-acylenaminonitriles 89

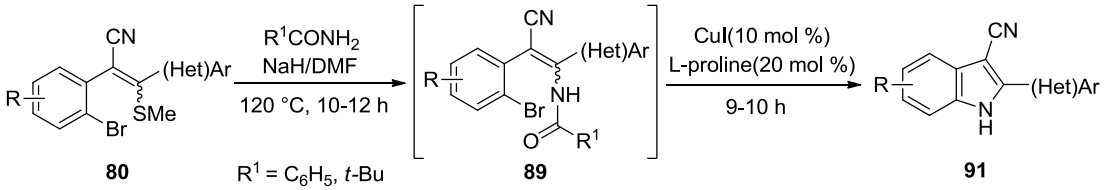


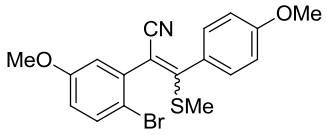
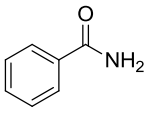
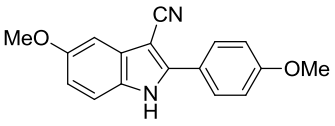
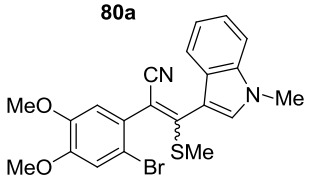
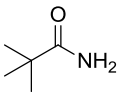
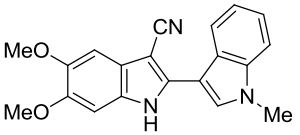
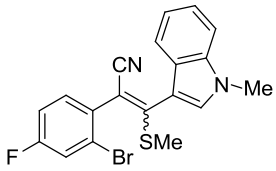
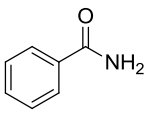
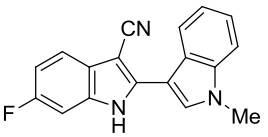
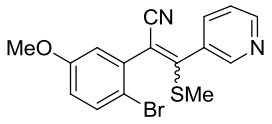
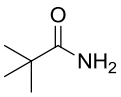
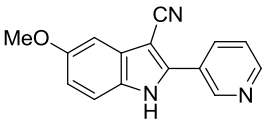
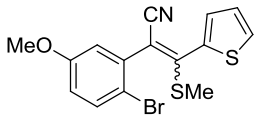
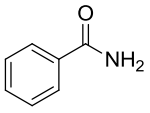
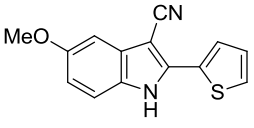
entry	substrate	Cu catalyst (10 mol %)	ligand (20 mol %)	base (equiv)	solvent	temp/time (°C/h)	yield (%) **91a**
1	**89a**	CuI	L-proline	NaH (1)	DMF	120/12	75
2	**89b**	CuI	L-proline	NaH (1)	DMF	120/12	74
3	**89a**	CuI	DMEDA	K_2CO_3 (2)	toluene	110/24	70
4	**89a**	CuI	DMEDA	K_2CO_3 (2)	THF	80/12	62
5	**89b**	CuI	DMEDA	K_2CO_3 (2)	toluene	110/12	66
6	**89a**	CuTC	DMEDA	K_2CO_3 (2)	toluene	110/12	70
7	**89b**	CuTC	DMEDA	K_2CO_3 (2)	toluene	110/12	68
8	**89c**	CuI	DMEDA	K_2CO_3 (2)	toluene	110/12	64

indole **91a**, without any trace of the corresponding N-acylindoles **90a-c** (Table 4, entries 1-8).

In view of our failure to isolate N-acylindoles **90**, we therefore focused our attention towards direct one-pot synthesis of N-unsubstituted-2-(het)arylindoles **91a-e**, by reacting the respective acrylonitrile precursors **80** with either benzamide or *t*-butylamide in the presence of sodium hydride in DMF, and subsequent *in situ* treatment of the resulting *N*-acylenaminonitrile intermediates **89a-e** with CuI/L-proline in one-pot procedure (Table 5). Following this protocol, 1-N-unsubstituted 3-cyanoindoles bearing various 2-(het)aryl moieties such as 2-(3-indolyl) (**91b-c**), 2-(3-pyridyl) (**91d**), and 2-(2-thienyl) (**91e**) groups, could be obtained in good to excellent overall yields (65-74%) (Table 5, entries 2-5).

Table 5. Synthesis of 3-cyano-2-(het)aryl-1-unsubstituted indoles 91a-e



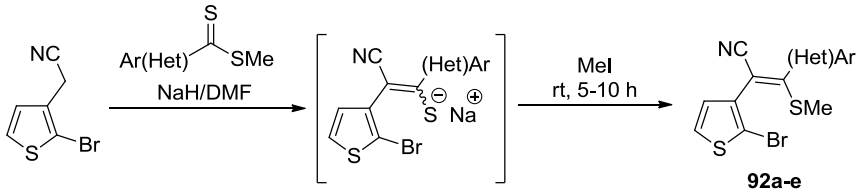
entry	substrate	amide	product	yield (%)
1	 **80a**		 **91a**	72
2	 **80i**		 **91b**	74
3	 **80j**		 **91c**	65
4	 **80k**		 **91d**	70
5	 **80m**		 **91e**	70

4.3.2 Synthesis of hetero fused pyrroles

With the successful synthesis of substituted indoles, we sought to extend our methodology to the synthesis of other hetero fused pyrroles such as thieno[2,3-*b*]pyrroles,[60] pyrrolo[2,3-*b*]indoles[61] and pyrazolo[3,2-*c*]pyrroles,[62] which have important optical and electronic properties.[63] Also, bioisosteric replacement of indole arene ring by other heteroarenes in these pyrrolo fused heterocycles, is known to alter their biological profile by changing the binding sites as well as their bioavailability.[60a,64] Thus thienopyrroles,[60a-b,64] and pyrazolopyrroles[62a] are known to display broad range of biological activity, whereas hexahydropyrrolo[2,3-*b*]indole ring system is present in many biologically important alkaloids and in several marketed drugs and drug candidates.[65-66] It should be noted that these fused pyrroles are less stable than the corresponding indole derivatives and they cannot be synthesized by usual classical methods employed for indole synthesis.[60] We have therefore extended the above general indole methodology for the synthesis of hetero fused pyrroles such as thieno[2,3-*b*]pyrroles, pyrrolo[2,3-*b*]indoles and pyrazolo[3,2-*c*]pyrroles. These results are summarized below.

4.3.2.1 Synthesis of thieno[2,3-*b*]pyrroles 94a-f

The desired 2-(2-bromo-3-thienyl)-3-(methylthio)-3-(4-methoxyphenyl)-acrylonitrile precursors **92a-e** were prepared by following the earlier reported method[52] through base induced condensation of the corresponding 3-(2-bromothienyl)acetonitrile with (het)aryl dithioesters followed by in situ methylation of the resulting thioate with methyl iodide (Scheme 25).

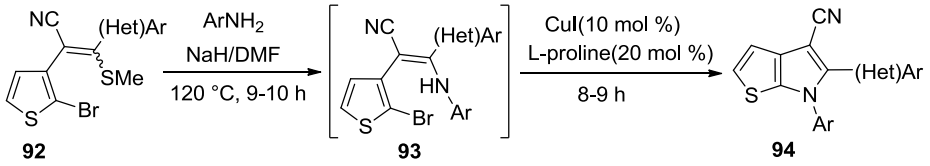


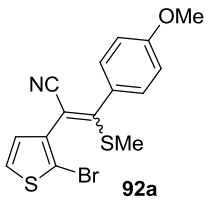
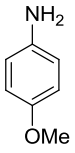
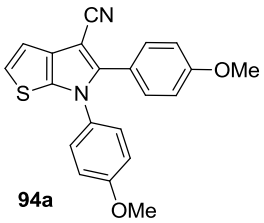
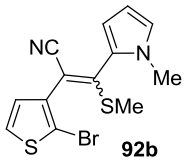
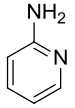
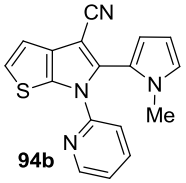
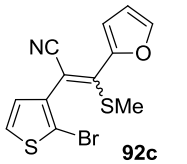
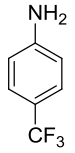
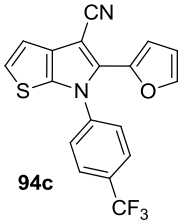
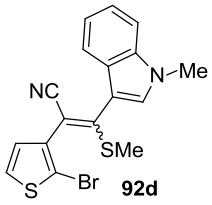
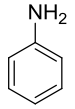
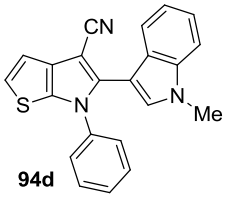
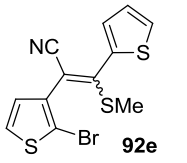
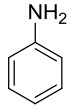
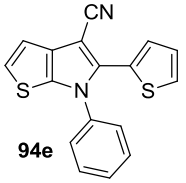
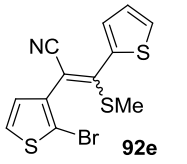
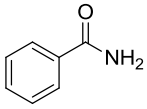
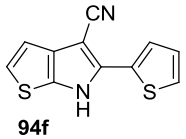
Scheme 25

We began this segment of our studies by examining the reaction of 2-(2-bromo-3-thienyl)-3-(methylthio)-3-(4-methoxyphenyl) acrylonitrile **92a** with 4-methoxyaniline under the previously described, two step one-pot, double C-N amination reaction conditions (Table 6), which furnished the desired 4-cyano-5,6-bis(4-methoxyphenyl)thieno[2,3-*b*]pyrrole **94a** in 69% yield (Table 6). Similarly, the other substituted thieno[2,3-*b*]pyrroles **94b-e** bearing diverse range of 5-(het)aryl groups and

N-aryl or N-(2-pyridyl) substituents, could also be prepared in 65-73% overall yields from the respective acrylonitrile precursors **92b-e** and approppriate anilines/pyridylamine (Table 6, entries 2-5). By subjecting one of the (2-bromothienyl)acrylonitriles (**92e**) to one-pot inter- and intramolecular amination with benzamide under previously described conditions (Scheme 4, Table 5), it was also possible to synthesize 6-unsubstituted NH thieno[2,3-*b*]pyrrole **94f** in 72% yield (Table 6, entry 6).

Table 6. Synthesis of substituted thieno[2,3-*b*]pyrroles 94a-f

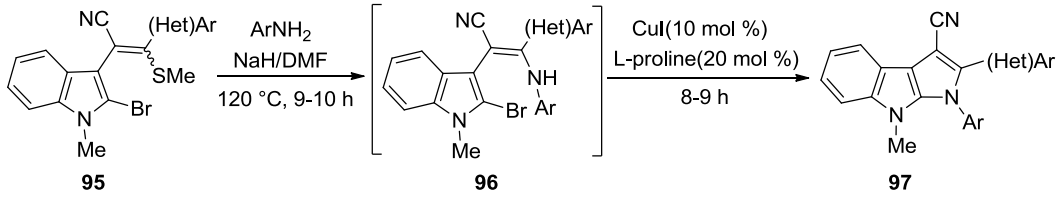


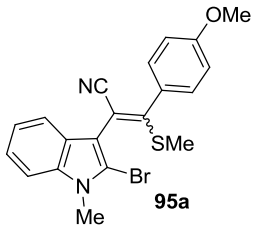
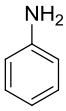
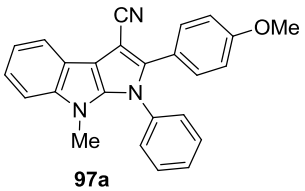
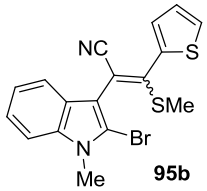
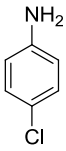
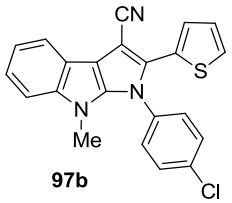
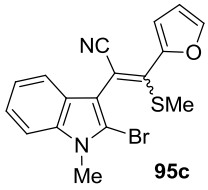
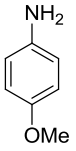
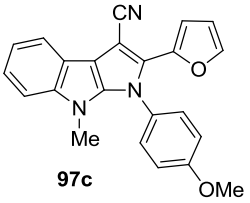
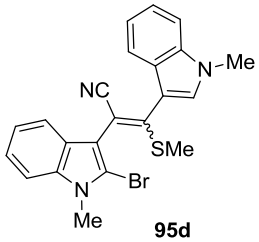
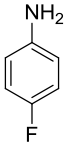
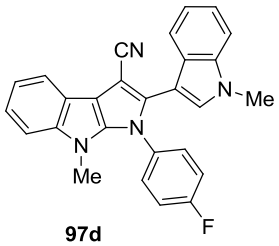
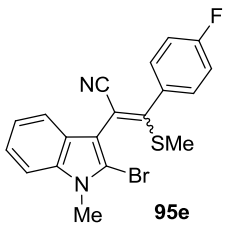
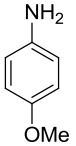
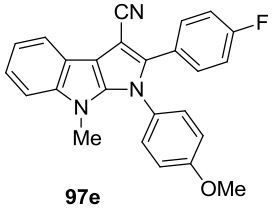
entry	substrate	amine/amide	product[a]	yield (%)
1	 **92a**		 **94a**	69
2	 **92b**		 **94b**	67
3	 **92c**		 **94c**	67
4	 **92d**		 **94d**	73
5	 **92e**		 **94e**	65
6	 **92e**		 **94f**	72

4.3.2.2 Synthesis of substituted pyrrolo[2,3-*b*]indoles 97a-e

The scope and generality of this novel pyrrole annulation protocol was next extended for the synthesis of pyrrolo fused indoles **97** by employing the corresponding 2-**[**(2-bromo-1-N-methyl)-3-indolyl]acrylonitrile precursors **95a-e** (prepared from the corresponding 2-bromo-3-(cyanomethy)l-1-*N*-methylindole and het(aryl)dithioesters in presence of sodium hydride) and substituted anilines under the previously optimized

Table 7. Synthesis of Pyrrolo[2,3-*b*]indoles 97a-e



entry	substrate	amine	product	yield (%)
1	 **95a**		 **97a**	61
2	 **95b**		 **97b**	58
3	 **95c**		 **97c**	67
4	 **95d**		 **97d**	60
5	 **95e**		 **97e**	65

reaction conditions (Table 7). Thus, the corresponding 3-cyano-2-het(aryl) pyrrolo[2,3-*b*]indoles **97a-e** were obtained in moderate to good yields (58-67%) through intermediacy of enaminonitrile **96** and no further attempts were made to improve the yields of the products (Table 7).The structures of all these fused indoles **97a-e** were confirmed with the help of spectral and analytical data and also by x-ray crystallographic data of **97c** (Figure 3).

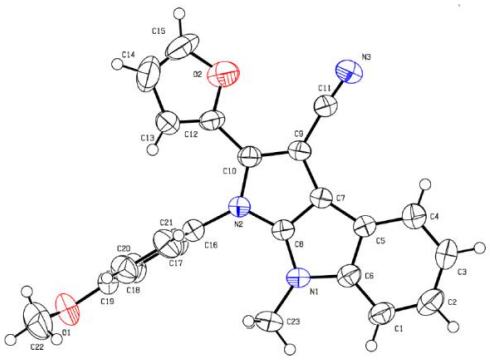
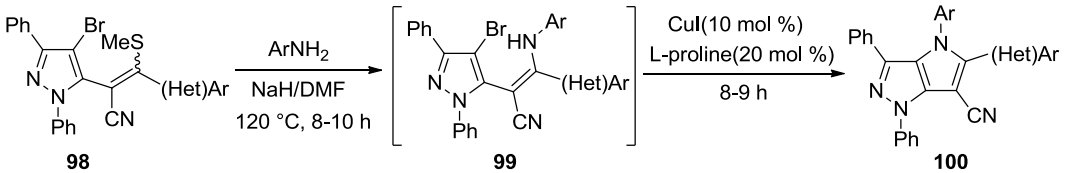


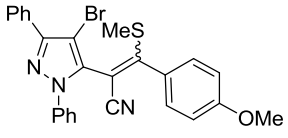
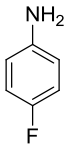
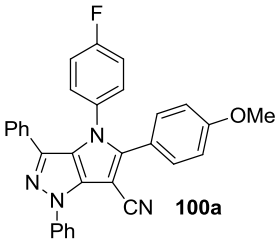
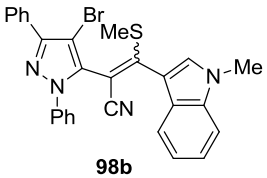
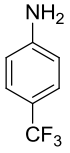
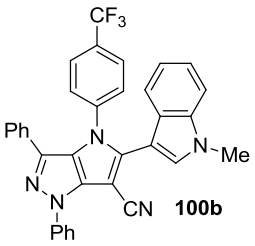
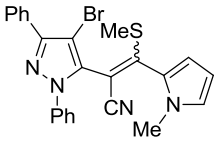
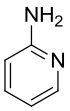
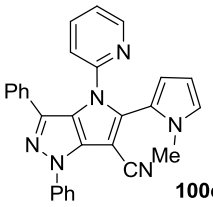
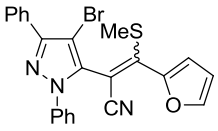
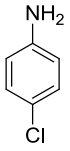
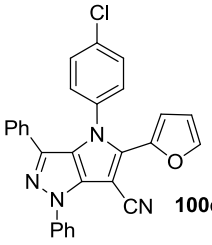
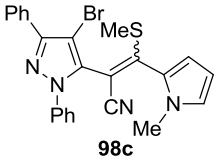
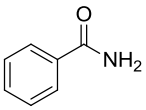
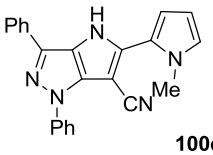
Figure 3. X-Ray crystal structure of **97c**

4.3.2.3 Synthesis of substituted pyrrolo[3,2-*c*]pyrazoles 100a-e

The present reaction conditions and catalytic system were found to be equally effective for the synthesis of annulated pyrrolopyrazoles such as **100**, which are shown to be useful subunits present in biologically relevant structures.[62a] Thus 6-cyano-1,3-bis(phenyl)-4,5-(het)arylpyrrolo[3,2-*c*]pyrazoles **100a-d** could be readily accessed in 62-80% overall yields by sequential inter- and intramolecular Cu catalyzed amination of the corresponding 2-(4-bromo-1,3-bisphenyl-5-pyrazolyl)acrylonitrile precursors **98a-d** with various primary amines (Table 8, entries 1-4) through intermediacy of enaminonitrile **99**. The corresponding 4-N-unsubstituted pyrrolo[3,2-*c*]pyrazole derivative **100e** could also be prepared in good yield by cycloannulation of acrylonitrile precursor **98c** with benzamide under earlier described conditions (Table 8, entry 5).

Table 8. Synthesis of Pyrrolo[3,2-*c*]pyrazoles 21a-e



entry	substrate	amine/amide	product[a]	yield (%)
1	 **98a**		 **100a**	80
2	 **98b**		 **100b**	70
3	 **98c**		 **100c**	65
4	 **98d**		 **100d**	62
5	 **98c**		 **100e**	62

4.4 Conclusion

In summary, we have developed an efficient protocol for assembly of N-functionalized/N*H* multisubstituted indoles from easily accessible acyclic 2-(2-bromoaryl)-3-[(methylthio)-(het)aryl]acrylonitrile precursors and primary amines, involving two key N(1)-C(2) and N(1)-C(7a) bond forming process, one base mediated intermolecular conjugate addition and other Cu catalyzed intramolecular arylamination, in a sequential two step one-pot procedure. The synthetic methodology is compatible with

a variety of electronically and structurally varied primary amines including primary alkylamines by tuning the reaction conditions, thus allowing installation of a broad range of functionalized N units. The cyclization precursors **80** are assembled by condensation of 2-bromo(het)arylacetonitriles and (het)aryl dithioesters with variation of both components well tolerated, thus allowing efficient synthesis of diversely functionalized indoles. Of particular importance is the synthesis of indoles bearing a wide range of 2-(het)aryl moieties such as (2-thienyl), (2-furyl), (2-pyrrollyl), (3-pyridyl) and (3-indolyl) groups, since most of the established palladium (or copper) catalyzed methods from either 2-amino(or 2-halo)arylacetylenes, usually lead to only 2-aryl (or 2-alkyl)indoles, with only few exceptions.[37b,50] Similary, there are only a few reports of the synthesis of indoles bearing reactive functionalities either at 2- or 3- positions, prepared by earlier reported cross-coupling reactions. The 3-nitrile moiety in these newly synthesized indoles provides a useful functionality, which can undergo a rich array of chemical transformations to form other functional groups. 1,2- and 1,2,3-Trisubstituted indoles generally display a broad range of biological activities (COX-II inhibitors, estrogen agonists and antagonists) and also find range of applications in material science (electroluminescence) industries.[44a] N-Substituted, especially N-aryl indoles skeleton represent an important subclass, due to their presence in many synthetically challenging pharmaceutically active compounds, however strategic approaches to N-aryl pattern of indole compounds are limited.[67a-b]

The broad scope of the methodology was further illustrated with the synthesis of biologically relevant N-H indoles by employing primary amides as coupling partners in this sequential one-pot C-N bond forming reaction. We are still not in a position to give a rational explanation for our failure to isolate the corresponding *N*-acylindoles **90**, which may probably, be due to steric hindrance by 2-(het)aryl group, thus facilitating the hydrolysis of **90** to the corresponding N*H*-indoles **91** during work-up under these conditions.[68]

The protocol also enables the facile and efficient synthesis of hetero fused pyrroles such as thieno[2,3-*b*]pyrrole, pyrrolo[2,3-*b*]indole and pyrrolopyrazole structural motifs by subjecting the corresponding 2-[2-bromo(het)aryl)]acrylonitrles to sequential two step one-pot cycloamination with various primary amines under identical conditions.

4.5 Experimental section

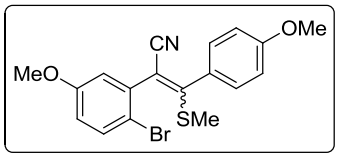
4.5.1 General information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using TLC Silica gel plates and visualized with UV light. Column chromatography was performed with Merck 100-200 mesh silica gel. Nuclear magnetic resonance spectra were recorded on (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$, DMSO-d_6, or acetone-d_6 as solvent. Chemical shifts were reported in δ ppm (parts per million) using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$, δ 2.50 for DMSO-d_6, and δ 2.05 for acetone-d_6 in ^{1}H-NMR, δ 77.16 for $CDCl_3$, δ 39.5 for DMSO-d_6 and δ 29.84 for acetone-d_6 in ^{13}C-NMR). Coupling constant (J) values are given in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), ddd, (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra were recorded using FTIR instrument and HRMS on Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. X-ray single crystal data of **87a**, **85d** and **97c** was collected on a Diffractometer using MoKα radiation (λ = 7107 Å), at room temperature. The structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares against F^2 using SHELXL-97 software.

The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem*. **2014**, *79*, 7961.

The desired acrylonitrile precursors **80a-m**, **92a-e**, **95a-e** and **98a-d** were prepared according to our earlier reported procedure[52] by reaction of the corresponding 2-bromo(het)arylacetonitrile (5.0 mmol) with the appropriate (het)aryl dithioester (5.0 mmol) using NaH (0.44 g, 11.0 mmol, 60%) in THF (15 mL), and subsequent alkylation with MeI (0.46 mL, 7.5 mmol). The known acrylonitrile precursors **80c**, **80e**, **80f**, **80h**, **92b-e**, **95b-d**, **98a-b** and **98d** were characterized by comparison of their spectral and analytical data with reported data,[52] whereas the spectral and analytical data for the unknown **80a-b**, **80d**, **80g**, **80i-m**, **92a**, **95a, 95e** and **98c** is given below. The enaminonitrile **87m-o** were prepared according to reported procedure[58a] by refluxing corresponding ketonitriles **88m** or **88o** and the appropriate anilines in glacial acetic acid for 6-7 h. The spectral and analytical data for the unknown enaminonitriles **87m-n** is given below, whereas the enamionitrile **87o** (obtained from ketonitrile **88o** and aniline)

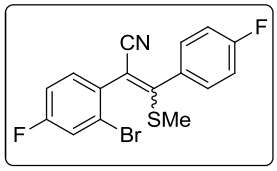
was found to be unstable and used as such without purification for further transformation.The corresponding thioketonitriles **88p-q** were obtained by condensation of the respective 2-bromoarylacetonitrile and dithioesters in the presence of sodium hydride in DMF[51e] and used as such without further purification.

2-(2-Bromo-5-methoxyphenyl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile



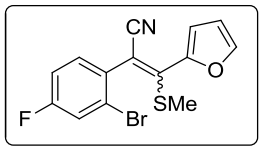
(80a). Obtained as a 4:1 inseparable mixture of geometrical isomers, off-white solid (1.65 g, 85%): mp 66-68 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2207, 1608, 1249, 1028, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 0.2H), 7.48 (d, J = 8.8 Hz, 0.4H), 7.35 (d, J = 8.8 Hz, 0.8H), 7.11 (d, J = 8.8 Hz, 1.6H), 7.02 (d, J = 8.8 Hz, 0.4H), 6.94 (d, J = 3.2 Hz, 0.2H), 6.83 (dd, J = 8.8 Hz, 3.2 Hz, 0.2H), 6.74 (d, J = 8.8 Hz, 1.6H), 6.62 (dd, J = 8.8 Hz, 3.2 Hz, 0.8H), 6.49 (d, J = 3.2 Hz, 0.8H), 3.87 (s, 0.6H), 3.83 (s, 0.6H), 3.75 (s, 2.4H), 3.60 (s, 2.4H), 2.11 (s, 2.4 H), 1.91 (s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 161.4, 161.1, 160.5, 159.2, 158.7, 136.1, 135.3, 133.9, 133.6, 130.9, 130.5, 127.1, 126.4, 117.63, 117.58, 117.1, 116.8, 116.7, 116.3, 114.7, 114.4, 114.1, 113.9, 107.9, 106.9, 55.7, 55.5, 55.4, 55.2, 16.51, 16.45; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}BrNO_2S$ $[M + H]^+$ 390.0163 and 392.0143, found 390.0160 and 392.0145.

2-(2-Bromo-4-fluorophenyl)-3-(4-fluorophenyl)-3-(methylthio)acrylonitrile (80b).



Obtained as a single geometrical isomer, white solid (1.46 g, 80%); mp 91-92 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2207, 1602, 1482, 1230, 845; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.259 (dd, J = 8.0 Hz, 2.8 Hz, 1H), 7.138 (dd, J = 8.8 Hz, 5.2 Hz, 2H), 6.97-6.91 (m, 3H), 6.82 (td, J = 8.8 Hz, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.4, 161.9, 161.2, 160.9, 133.7, 133.6, 131.24, 131.19, 131.1, 130.2, 130.1, 124.8, 124.7, 120.6, 120.4, 116.6, 116.2, 116.0, 115.3, 115.0, 108.0, 16.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{10}BrF_2NS$ $[M + H]^+$ 365.9764 and 367.9743, found 365.9760 and 367.9739

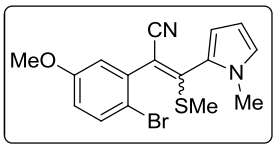
2-(2-Bromo-4-fluorophenyl)-3-(furan-2-yl)-3-(methylthio)acrylonitrile (80d).



Obtained as a 2:1 inseparable mixture of geometrical isomers, brown semisolid (1.26 g, 75%): R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2918, 2199, 1480, 1206, 876, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.65 (m, 0.33H), 7.43 (dd, J = 8.0 Hz, 2.4 Hz 0.33H), 7.38-7.32 (m, 1.67H), 7.19 (dd, J = 8.8 Hz, 5.6 Hz, 0.67H), 7.14-7.10 (m, 0.67H), 7.00 (td, J = 8.4 Hz, 2.4 Hz, 0.67H), 6.59 (dd, J = 2.8 Hz, 1.6 Hz, 0.33H), 6.47 (d, J = 3.6 Hz, 0.67H), 6.36

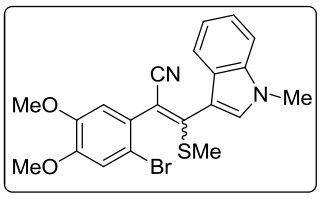
(dd, *J* = 2.8 Hz, 1.2 Hz, 0.67H), 2.47 (s, 2H), 2.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.7, 161.4, 161.2, 149.9, 148.4, 147.8, 147.1, 145.7, 145.4, 132.9, 132.8, 132.6, 132.5, 131.9, 131.8, 131.13, 131.10, 124.6, 124.5, 124.4, 124.3, 121.0, 120.73, 120.72, 120.5, 117.5, 117.3, 116.3, 115.6, 115.40, 115.35, 115.2, 112.4, 112.3, 108.3, 105.8, 17.9, 17.0; HRMS (ESI) *m/z* calcd for $C_{14}H_9BrFNOS$ $[M + H]^+$ 337.9651 and 339.9630, found 337.9645 and 339.9624.

2-(2-Bromo-5-methoxyphenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-



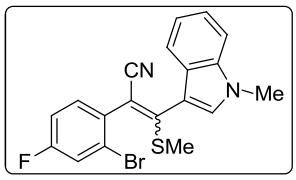
(methylthio)acrylonitrile (80g). Obtained as a single geometrical isomer, off-white solid (1.45 g, 80%): mp 105-106 °C; R_f 0.45 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2200, 1577, 1469, 1293, 1022, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0 Hz, 2.8 Hz, 1H), 6.59 (dd, *J* = 2.4 Hz, 2.0 Hz, 1H), 6.47 (d, *J* = 2.8 Hz, 1H), 6.13 (dd, *J* = 3.6 Hz, 2.0 Hz, 1H), 6.04 (dd, *J* = 3.6 Hz, 2.4 Hz, 1H), 3.60 (s, 3H), 3.43 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 153.0, 136.0, 134.1, 133.8, 126.4, 125.3, 117.1, 116.7, 114.8, 114.1, 109.1, 108.4, 55.6, 34.7, 16.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}BrN_2OS$ $[M + H]^+$ 363.0167 and 365.0146, found 363.0168 and 365.0151

2-(2-Bromo-4,5-dimethoxyphenyl)-3-(1-methyl-1H-indol-3-yl)-3-



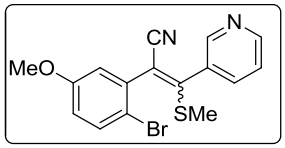
(methylthio)acrylonitrile (80i). Obtained as 3:1 inseparable mixture of geometrical isomers, pale yellow solid (1.66 g, 75%): mp 80-82 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2194, 1507, 1211, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 0.77H), 7.82 (d, *J* = 8.0 Hz, 0.23H), 7.57 (s, 0.77H), 7.39 (d, *J* = 8.0 Hz, 0.77H), 7.32 (td, *J* = 6.8 Hz, 2.8 Hz, 0.77H), 7.28-7.23 (m, 1.54H), 7.18-7.14 (m, 1H), 6.94 (s, 0.77H), 6.93 (s, 0.23H), 6.78 (s, 0.23H), 6.45 (m, 0.23H), 3.921 (s, 2.31H), 3.919 (s, 2.31H), 3.88 (s, 2.31H), 3.80 (s, 0.69H), 3.65 (s, 0.69H), 3.41 (s, 0.69H), 2.15 (s, 0.69H), 2.00 (s, 2.31); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 155.4, 150.0, 149.4, 148.8, 148.2, 137.4, 137.1, 131.1, 130.7, 128.4, 127.2, 126.5, 126.3, 122.9, 122.8, 121.2, 120.6, 120.2, 119.1, 118.1, 115.7, 115.3, 114.8, 114.7, 114.3, 114.1, 110.1, 109.9, 109.8, 109.6, 106.0, 104.5, 56.4, 56.3, 56.2, 55.9, 33.4, 33.3, 16.8, 16.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}BrN_2O_2S$ $[M + H]^+$ 443.0429 and 445.0408, found 443.0425 and 445.0407.

2-(2-Bromo-4-fluorophenyl)-3-(1-methyl-1*H*-indol-2-yl)-3-(methylthio)acrylonitrile (80j). Obtained as a 3:1 inseparable mixture of geometrical isomers, off-white solid (1.56 g, 78%): mp 95-97 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2919, 2200, 1589,



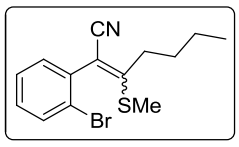
1467, 1200, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 0.75H), 7.74 (dt, J = 8.0 Hz, 0.8 Hz, 0.25H), 7.53 (s, 0.75H), 7.42-7.39 (m, 1.5H), 7.36-7.34 (m, 0.75H), 7.28 (td, J = 6.8 Hz, 0.8 Hz, 0.75 H), 7.24-7.20 (m, 1.75H), 7.14-7.06 (m, 1H), 6.95 (dd, J = 8.8 Hz, 6.0 Hz, 0.25H), 6.74 (s, 0.25H), 6.72-6.67 (m, 0.25H), 3.84 (s, 2.25H), 3.61 (s, 0.75H), 2.12 (s, 2.25H), 1.95 (s, 0.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 163.1, 161.2, 160.6, 157.8, 156.1, 137.5, 137.2, 133.4, 133.3, 133.2, 132.78, 132.75, 131.61, 131.57, 131.3, 131.2, 126.23, 126.19, 124.96, 124.86, 124.8, 124.7, 123.0, 121.4, 120.9, 120.6, 120.5, 120.4, 120.2, 118.0, 118.8, 115.4, 115.2, 115.0, 110.2, 109.9, 109.7, 109.3, 104.6, 103.5, 33.5, 33.3, 16.93, 16.86; HRMS (ESI) m/z calcd for $C_{19}H_{14}BrFN_2S$ $[M + H]^+$ 401.0123 and 403.0103, found 401.0128 and 403.0110.

2-(2-Bromo-5-methoxyphenyl)-3-(methylthio)-3-(pyridin-3-yl)acrylonitrile (80k).



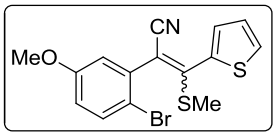
Obtained as a single geometrical isomer, pale yellow solid (1.08 g, 60%): mp 105-106 $^{\circ}$C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2200, 1589, 1463, 1236, 1016, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.0 Hz, 1H), 8.41 (s, 1H), 7.54 (dt, J = 7.6 Hz, 2.4 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.21 (dd, J = 7.6 Hz, 5.2 Hz, 1H), 6.64 (dd, J = 9.0 Hz, 3.2 Hz, 1H), 6.54 (d, J = 3.2 Hz, 1H), 3.63 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.5, 150.6, 149.7, 136.7, 135.0, 134.0, 130.8, 123.3, 117.7, 116.9, 116.4, 114.5, 110.4, 55.7, 16.6; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}BrN_2OS$ $[M + H]^+$ 361.001 and 362.9990, found 361.0005 and 362.9990.

2-(2-Bromophenyl)-3-(methylthio)hept-2-enenitrile (80l). Obtained as a single



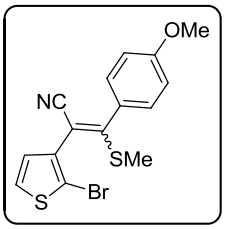
geometrical isomer, pale yellow liquid (1.01 g, 65%): R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2963, 2207, 1558, 1469, 1028, 757; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56-7.73 (m, 1H), 7.49-7.45 (m, 1H), 7.38-7.34 (m, 2H), 2.81-2.79 (m, 2H), 2.33 (s, 3H), 1.63 (quin, J = 7.2 Hz, 2H), 1.48 (sex, J = 7.2 Hz, 2H), 0.975 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 133.6, 133.0, 131.9, 131.1, 128.5, 123.2, 116.8, 104.0, 33.1, 30.8, 21.6, 13.7, 13.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BrNS$ $[M + H]^+$ 310.0265 and 312.0245, found 310.0256 and 312.0236.

2-(2-Bromo-5-methoxyphenyl)-3-(methylthio)-3-(thiophen-2-yl)acrylonitrile (80m).



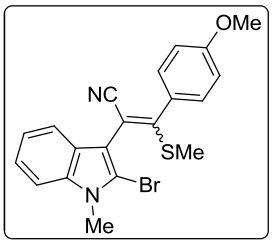
Obtained as a 9:1 inseparable mixture of geometrical isomers, pale yellow solid (1.50 g, 82%): mp 62-64 °C; R_f 0.6 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2200, 1564, 1463, 1236, 1016, 713; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (m, 0.3H), 7.43 (d, J = 8.4 Hz, 0.9H), 7.39 (dd, J = 5.2 Hz, 1.2 Hz, 0.9H), 7.17 (dd, J = 4.8 Hz, 3.2 Hz, 0.1H), 7.03 (dd, J = 3.6 Hz, 1.2 Hz, 0.9H), 6.94 (d, J = 2.8 Hz, 1H), 6.91 (dd, J = 5.2 Hz, 3.6 Hz, 0.9H), 6.84 (dd, J = 8.8 Hz, 3.2 Hz, 0.1H), 6.76-6.71 (m, 1.8H), 3.83 (s, 0.1H), 3.70 (s, 0.9H), 2.43 (s, 0.9H), 2.08 (s, 0.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 151.8, 137.4, 135.7, 133.9, 131.6, 130.9, 130.6, 130.0, 127.9, 127.6, 117.3, 117.0, 116.9, 116.8, 116.6, 114.7, 110.1, 55.7, 55.6, 18.1, 17.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}BrNOS_2$ $[M + H]^+$ 365.9622 and 367.9601, found 365.9620 and 367.9602.

2-(2-Bromothiophen-3-yl)-3-(4-methoxyphenyl)-3-(methylthio)acrylonitrile (92a).



Obtained as a single geometrical isomer, off-white solid (1.42 g, 78%): mp 101-102 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2200, 1602, 1255, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 9.2 Hz, 2H), 7.03 (d, J = 5.8 Hz, 1H), 6.79 (d, J = 9.2 Hz, 2H), 6.45 (d, J = 5.8 Hz, 1H), 3.79 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 160.9, 134.6, 131.3, 129.3, 126.6, 126.3, 117.0, 114.2, 113.2, 102.0, 55.4, 16.8; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}BrNOS_2$ $[M + H]^+$ 365.9622 and 367.9601, found 365.9618 and 367.9599.

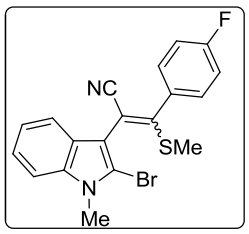
2-(2-Bromo-1-methyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-3-(methylthio)acrylo



nitrile (95a). Obtained as a 2:1 inseparable mixture of geometrical isomers, pale yellow solid (1.34 g, 65%): mp 86-88 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2200, 1608, 1457, 1249, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 0.33H), 7.53 (d, J = 8.8 Hz, 0.67H), 7.44 (d, J = 8.0 Hz, 0.67H), 7.34 (d, J = 8.0 Hz, 0.33H), 7.30-7.27 (m, 0.33H), 7.22-7.15 (m, 3H), 7.09-7.02 (m, 1.32H), 6.66 (d, J = 8.8 Hz, 1.32H), 3.88 (s, 0.99H), 3.83 (s, 0.99H), 3.71 (s, 2.01H), 3.66 (s, 2.01H), 2.16 (s, 2.01H), 1.89 (s, 0.99H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 161.0, 160.4, 160.1, 136.9, 136.7, 131.2, 128.0, 127.4, 126.4, 125.8, 122.8, 122.6, 120.8, 119.3, 118.9, 118.2, 118.1, 115.8, 115.6, 114.5, 113.9, 110.0, 109.8, 109.6, 109.0, 100.6, 99.6, 55.5,

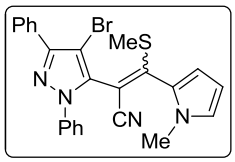
55.3, 31.9, 31.8, 17.0, 16.7; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}BrN_2OS$ $[M + H]^+$ 413.0323 and 415.0303, found 413.0326 and 415.0305.

2-(2-Bromo-1-methyl-1*H*-indol-3-yl)-3-(4-fluorophenyl)-3-(methylthio)acrylonitrile



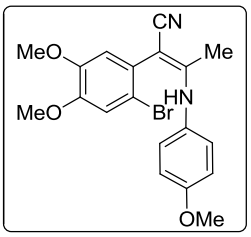
(95e). Obtained as a 3:2 inseparable mixture of geometrical isomers, off-white solid (1.45 g, 73%): mp 134-136 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2168, 1467, 1223, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.55 (m, 1.2H), 7.42 (d, *J* = 8.0 Hz, 0.6H), 7.37 (d, *J* = 8.0 Hz, 0.4H), 7.29 (dd, *J* = 7.2 Hz, 1.2H, 0.4H), 7.24-7.16 (m, 3.6H), 7.08 (ddd, *J* = 8.0 Hz, 6.8 Hz, 1.6 Hz, 0.6H), 6.85 (t, *J* = 8.8 Hz, 1.2H), 3.84 (s, 1.2H), 3.66 (s, 1.8H), 2.14 (s, 1.8H), 1.88 (s, 1.2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 163.4, 163.0, 161.5, 160.9, 159.9, 136.4, 136.2, 131.64, 131.60, 131.33, 131.29, 131.24, 131.20, 130.63, 130.60, 125.2, 124.7, 122.5, 122.4, 120.58, 120.56, 118.6, 117.8, 117.4, 117.1, 116.2, 116.0, 115.8, 115.74, 115.66, 115.4, 110.7, 110.5, 108.2, 107.4, 100.1, 99.1, 31.8, 31.7, 16.0, 15.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}BrFN_2S$ $[M + H]^+$ 401.0123 and 403.0103, found 401.0110 and 403.0091.

2-(4-Bromo-1,3-diphenyl-1*H*-pyrazol-5-yl)-3-(1-methyl-1*H*-pyrrol-2-yl)-3-



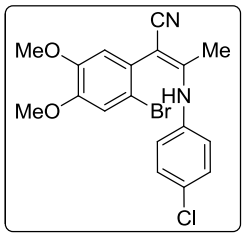
(methylthio)acrylonitrile (98c). Obtained as a 1:1 inseparable mixture of geometrical isomers, brown solid (1.54 g, 65%): mp 72-74 °C; R_f 0.35 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2207, 1495, 1306, 959, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 1H), 7.96-7.94 (m, 1H), 7.63-7.61 (m, 1H), 7.52-7.36 (m, 6H), 7.20-7.19 (m, 1H), 6.80 (t, *J* = 2.0 Hz, 0.5 H), 6.80 (t, *J* = 2.0 Hz, 0.5H), 6.55 (t, *J* = 2.0 Hz, 0.5H), 6.41 (dd, *J* = 4.0 Hz, 1.6 Hz, 0.5H), 6.21 (dd, *J* = 3.6 Hz, 2.8 Hz, 0.5H), 5.93 (dd, *J* = 3.6 Hz, 2.8 Hz, 0.5H), 5.77 (dd, *J* = 3.6 Hz, 2.0 Hz, 0.5H), 3.62 (s, 1.5H), 2.94 (s, 1.5H), 2.03 (s, 1.5H), 1.83 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 157.8, 149.9, 149.4, 139.6, 139.1, 135.6, 135.1, 131.62, 131.55, 129.4, 129.2, 128.83, 128.78, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.90, 127.8, 127.4, 125.4, 124.8, 124.45, 124.47, 116.5, 116.4, 115.5, 114.8, 109.7, 109.3, 97.6, 97.1, 96.4, 95.1, 34.7, 34.1, 16.4, 16.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{19}BrN_4S$ $[M + H]^+$ 475.0592 and 477.0572, found 475.0586 and 477.0566.

(*E*)-2-(2-Bromo-4,5-dimethoxyphenyl)-3-(4-methoxyphenylamino)but-2-enenitrile



(87m). Obtained from ketonitrile **9m** and 4-methoxyaniline, off-white solid (261 mg, 65%): mp 119-120 °C R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3329, 2939, 2179, 1600, 1508, 1245, 1023, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.89 (s, 3H), 6.83 (d, J = 8.8 Hz, 2H), 6.01 (br s, 1H), 3.88 (s, 6H), 3.79 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.6, 150.0, 149.4, 131.4, 127.7, 124.8, 121.4, 116.3, 116.2, 115.0, 114.5, 81.4, 56.37, 56.35, 55.6, 17.9; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}BrN_2O_3$ $[M + H]^+$ 403.0657 and 405.0637, found 403.0656 and 405.0638.

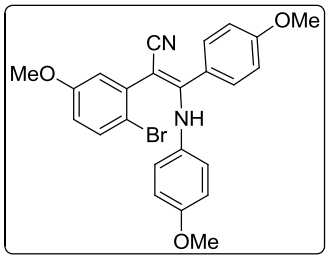
(*E*)-2-(2-Bromo-4,5-dimethoxyphenyl)-3-(4-chlorophenylamino)but-2-enenitrile



(87n). Obtained from ketonitrile **9m** and 4-chloroaniline, off-white solid (284 mg, 70%): R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3327, 2926, 2190, 1608, 1497, 1206, 1026, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 7.10 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 6.07 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.2, 149.4, 137.3, 131.6, 129.5, 126.4, 124.4, 120.8, 116.2, 116.1, 114.7, 83.9, 56.40, 56.36, 18.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}BrClN_2O_2$ $[M + H]^+$ 407.0162 and 409.0141, found 407.0153 and 409.0131.

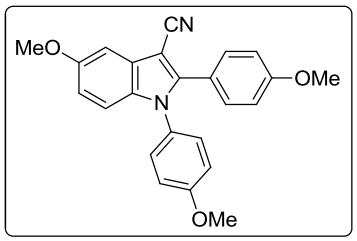
4.5.2 General procedure for the synthesis of enaminonitrile 87p-q. A solution of thioketonitriles **88p** or **88q** (1.0 mmol) and aliphatic amine (1.0 mmol) in CH_3CN (10 mL), was stirred at room temperature for 5-6 h (was monitored by TLC). The reaction mixture was concentrated under reduced pressure and the residue diluted with ice-cold water (20 mL), extracted with EtOAc (2 × 20 mL) and dried over Na_2SO_4, followed by removal of the solvent to give crude **87p-q**, which were found to be unstable and utilized for the next step without purification.

4.5.3 Procedure for the synthesis of (*E*)-2-(2-bromo-5-methoxyphenyl)-3-(4-methoxyphenyl)-3-(4-methoxyphenylamino) acrylonitrile (87a). A solution of **80a** (390 mg, 1.0 mmol) in dry DMF (5 mL) was added to a stirred suspension of 4-methoxyaniline (135 mg, 1.1 mmol) and NaH (44 mg, 1.1 mmol, 100%) in DMF (10 mL) at room temperature, followed by heating at 120 °C for 8 h (monitored by TLC).The reaction mixture after cooling was poured into ice-cold water (50 mL), extracted with EtOAc (2 × 50 mL) , the organic layer washed with water (2 × 50 mL), brine (1 × 50 mL)



and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude prduct, which was purified by column chromatography over silica gel using 30% EtOAc/hexane to give pure **87a**: off-white solid (0.348 g, 75%): mp 118-120 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3296, 2932, 2193, 1582, 1514, 1252, 1030, 835; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 3H), 7.03 (d, J = 3.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.76 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 6.64-6.58 (m, 4H), 6.10 (br s, 1H), 3.82 (s, 3H), 3.81 (S, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 159.8, 157.3, 156.4, 134.7, 133.0, 131.7, 125.0, 124.6, 121.6, 117.7, 116.1, 114.2, 114.1, 84.7, 55.8, 55.5, 55.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{21}BrN_2O_3$ $[M + Na]^+$ 487.0633 and 489.0613, found 487.0638 and 489.0702.

4.5.4 Procedure for copper catalyzed cyclization of enaminonitrile 8a to 5-methoxy-1,2-bis(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (85a). To a stirred solution of

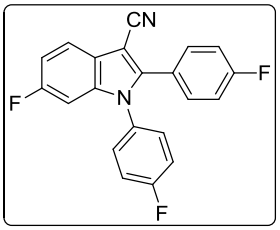


enaminonitrile **87a** (232 mg, 0.5 mmol) in DMF (5 mL) were added CuI (9 mg, 0.05 mmol), L-proline (12 mg, 1.0 mmol) and NaH (20 mg, 0.5 mmol, 100%) and the reaction mixture was heated at 120 °C with constant stirring for 8 h (monitored by TLC). It was then poured into ice-cold water (20 mL), extracted with EtOAc (3 × 10 mL), washed with brine (1 × 10 mL), dried over Na_2SO_4 followed by removal of the solvent to give crude product, which was purified by column chromatography over silica gel, using 12% EtOAc/hexane as eluent to give pure **85a**: white solid (0.172 mg, 90%): mp 141-142 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2930, 2205, 1607, 1470, 1246, 1021, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 9.2 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.5, 156.5, 147.4, 132.9, 131.3, 129.7, 129.2, 128.5, 121.4, 117.3, 115.0, 114.6, 114.3, 112.6, 100.6, 85.9, 56.0, 55.7, 55.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}N_2O_3$ $[M + H]^+$ 385.1552, found 385.1533.

4.5.5 General procedure for two step one-pot synthesis of indoles 85a-k, thieno[2,3-*b*]pyrroles 94a-e, pyrrolo[2,3-*b*]indoles 97a-e and pyrrolo[3,2-*c*]pyrazoles 100a-d. A solution of respective 2-[2-bromo(het)aryl]-3-(het)aryl/(methylthio)acrylonitriles **80**, **92**,

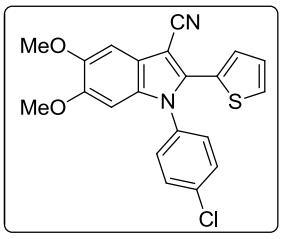
95, **98** (1.0 mmol) in dry DMF (5 mL) was added to a stirred suspension of the corresponding aniline (1.1 mmol) and NaH (80 mg, 2.0 mmol, 100%) in DMF (10 mL) at room temperature, followed by further heating at 120 °C for 8-10 h (monitored by TLC). After consumption of starting materials, CuI (19 mg, 0.1 mmol) and L-proline (23 mg, 0.2 mmol) were added to the reaction mixture and it was further heated at same temperature for 8-9 h (monitored by TLC). It was then cooled to room temperature, poured into ice-cold water (50 mL), extracted with EtOAc (2 × 50 mL), the combined extracts were washed with water (2 × 50 mL), brine (1 × 50 mL), dried over Na_2SO_4 and evaporated under reduced pressure, give crude products, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

6-Fluoro-1,2-bis(4-fluorophenyl)-1*H*-indole-3-carbonitrile (85b). Obtained from



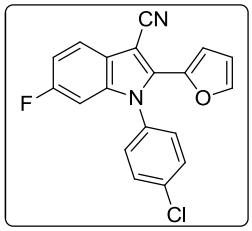
acrylonitrile **80b** and 4-fluoroaniline, white solid (295 mg, 85%): mp 167-168 °C; R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3070, 2220, 1608, 1507, 1230, 1155, 845, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.8 Hz, 5.2 Hz, 1H), 7.33 (dd, J = 8,8 Hz, 5.2 Hz, 2H), 7.20-7.09 (m, 5H), 7.08-7.03 (m, 2H), 6.90 (dd, J = 9.2 Hz, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 163.7, 162.4, 162.2, 161.2, 160.0, 146.88, 146.85, 138.0, 137.9, 132.23, 132.20, 131.9, 131.8, 129.8, 129.7, 124.6, 124.5, 123.7, 121.0, 120.9, 117.4, 117.1, 116.4, 116.2, 115.9, 112.3, 112.3, 112.1, 98.4, 98.1, 87.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{11}F_3N_2$ $[M + H]^+$ 349.0953, found 349.0948.

1-(4-Chlorophenyl)-5,6-dimethoxy-2-(thiophen-2-yl)-1*H*-indole-3-carbonitrile (85c).

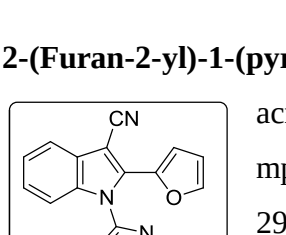


Obtained from acrylonitrile **80c** and 4-chloroaniline, white solid (291 mg, 74%): mp 195-196 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2936, 2207, 1486, 1275, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.34 (dd, J = 2.8 Hz, 1.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.03 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 6.50 (s, 1H), 3.98 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 147.9, 138.9, 135.7, 135.2, 132.4, 130.4, 130.2, 129.9, 129.6, 128.6, 127.6, 120.8, 116.8, 100.6, 94.2, 86.9, 56.6, 56.5; HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClN_2O_2S$ $[M + H]^+$ 395.0621 and 397.0592, found 395.0597 and 397.0560.

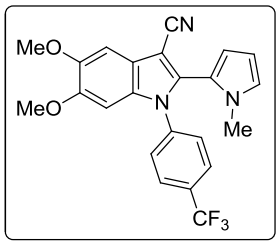
1-(4-Chlorophenyl)-6-fluoro-2-(furan-2-yl)-1*H*-indole-3-carbonitrile (85d). Obtained from acrylonitrile **80d** and 4-chloroaniline, white solid (252 mg, 75%): mp 180-182 °C; R_f 0.4 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2938, 2220, 1621, 1489, 1192, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.8 Hz, 4.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.08 (td, J = 8.8 Hz, 2.0 Hz, 1H), 6.73 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 6.41 (dd, J = 3.6 Hz, 2.0 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.1, 144.4, 143.3, 138.4, 138.3, 137.39, 137.36, 135.9, 135.2, 130.4, 129.5, 123.9, 120.9, 120.8, 115.7, 112.7, 112.3, 112.1, 111.9, 98.1, 97.9, 85.5; HRMS (ESI) *m/z* calcd for $C_{19}H_{10}ClFN_2O$ $[M + H]^+$ 337.0544 and 339.0514, found 337.0532 and 339.0508.



2-(Furan-2-yl)-1-(pyridin-2-yl)-1*H*-indole-3-carbonitrile (85e). Obtained from acrylonitrile **80e** and 2-aminopyridine, white solid (213 mg, 75%): mp 120-121 °C; R_f 0.4 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3052, 2919, 2220, 1476, 1445, 1244, 1022, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 8.68 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.74 (dq, J = 8.0 Hz, 1.6 Hz, 1H), 7.54 (ddd, J = 8.0 Hz, 4.8 Hz, 0.4 Hz, 1H), 7.40 (dd, J = 1.6 Hz, J = 0.4 Hz, 1H), 7.36 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.30 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.58 (dd, J = 3.2 Hz, 0.4 Hz, 1H), 6.44 (dd, J = 3.2 Hz, 1. Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.4, 144.4, 143.3, 138.1, 136.8, 135.9, 134.1, 127.7, 125.2, 124.3, 123.6, 119.9, 115.9, 113.3, 112.0, 111.0, 86.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{11}N_3O$ $[M + H]^+$ 286.0980, found 286.0979.

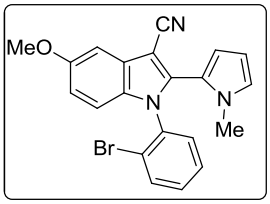


5,6-Dimethoxy-2-(1-methyl-1*H*-pyrrol-2-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-indole-3-carbonitrile (85f). Obtained from acrylonitrile **80f** and 4-(trifluoromethyl)aniline, white solid (290 mg, 68%): mp 184-185 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2944, 2215, 1494, 1329, 1164, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (s, 1H), 6.75 (s, 1H), 6.69 (t, J = 2.4 Hz, 1H), 6.13-6.12 (m, 2H), 4.0 (s, 3H), 3.85 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 147.9, 140.3, 137.4, 131.0, 130.6, 130.2, 127.5, 127.0, 126.93, 126.89, 125.3, 125.1, 120.7, 120.4, 116.2, 114.5, 109.1, 100.8, 94.3, 90.0, 56.57,



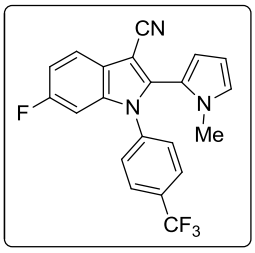
56.55, 34.8; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}F_3N_3O_2$ $[M + H]^+$ 426.1429, found 426.1423.

1-(2-Bromophenyl)-5-methoxy-2-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-indole-3-carbonitrile



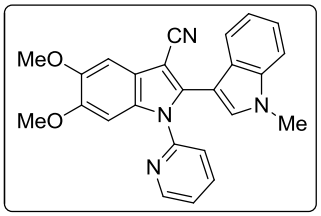
(85g). Obtained from acrylonitrile **80g** and 2-bromoaniline, white solid (315 mg, 78%): mp 188-190 °C; R_f 0.4 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2950, 2207, 1489, 1205, 1028, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.43 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.35-7.31 (m, 2H), 7.24 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.86 (d, J = 9.2 Hz, 1H) , 6.73 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 6.03 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 5.95 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 140.0, 136.3, 134.0, 132.0, 131.2, 130.9, 128.6, 128.3, 125.8, 123.2, 120.8, 116.6, 115.1, 114.0, 112.7, 108.7, 100.7, 88.0, 56.0, 35.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}BrN_3O$ $[M + H]^+$ 406.0555 and 408.0535, found 406.0556 and 408.0538.

6-Fluoro-2-(1-methyl-1*H*-pyrrol-2-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-indole-3-carbonitrile (85h).



Obtained from acrylonitrile **80h** and 4-(trifluoromethyl)aniline, white solid (272 mg, 71%): mp 131-132 °C; R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2220, 1615, 1489, 1325, 1161, 1060, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.8 Hz, 5.2 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.14 (td, J = 8.8 Hz, 2.4 Hz, 1H), 7.00 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.72 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 6.17 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.14 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.1, 140.1,140.0, 139.7, 137.1, 137.0, 131.0, 130.7, 127.5, 127.11, 127.07, 127.03, 127.0, 125.9, 123.9, 121.1, 121.0, 119.9, 115.5, 115.0, 112.5, 112.2, 109.4, 98.4, 98.1, 90.3, 35.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{13}F_4N_3$ $[M + H]^+$ 384.1124, found 384.1112.

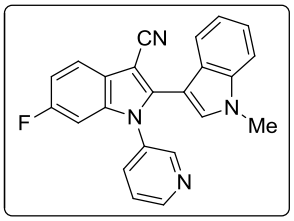
5,6-Dimethoxy-2-(1-methyl-1*H*-indol-3-yl)-1-(pyridin-2-yl)-1*H*-indole-3-carbonitrile



(85i). Obtained from acrylonitrile **80i** and 2-aminopyridine, off-white solid (306 mg, 75%): mp 213-215 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2207, 1589, 1469, 1236, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 4.8. Hz, 1.2 Hz, 1H), 7.47 (td, J = 8.0 Hz, 2.0 Hz, 1H), 7.45 (s, 1H), 7.30-7.28 (m, 2H), 7.22-7.14 (m, 3H), 7.04 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 4.0 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.2, 148.4, 147.5,

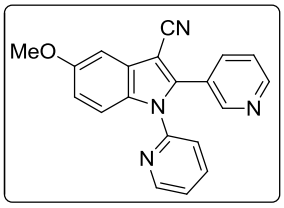
140.5, 138.5, 137.1, 131.1, 130.3, 125.9, 122.7, 122.6, 121.6, 121.2, 120.7, 120.0, 117.5, 109.7, 104.4, 100.4, 96.0, 87.7, 56.5, 56.4, 33.4; HRMS (ESI) *m/z* calcd for $C_{25}H_{20}N_4O_2$ $[M + H]^+$ 409.1665, found 409.1655.

6-Fluoro-2-(1-methyl-1*H*-indol-3-yl)-1-(pyridin-3-yl)-1*H*-indole-3-carbonitrile (85j).



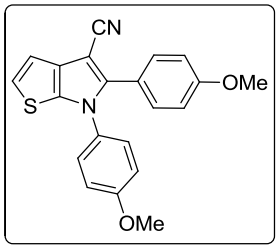
Obtained from acrylonitrile **80j** and 3-aminopyridine, pale yellow solid (285 mg, 78%): mp 190-192 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2220, 1583, 1489, 1243, 1028, 745; ^{1}H NMR (400 MHz, DMSO) δ 8.60 (d, *J* = 2.4 Hz, 1H), 8.56 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 7.99 (ddd, *J* = 8.4 Hz, 2.4 Hz, 1.6 Hz, 1H), 7.78 (dd, *J* = 8.8 Hz, 5.2 Hz, 1H), 7.62 (s, 1H), 7.51-7.47 (m, 2H), 7.29-7.24 (m, 2H), 7.18 (td, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.14 (dd, *J* = 9.6 Hz, 2.0 Hz, 1H), 6.99 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.8, 149.5, 148.4, 137.5, 137.4, 137.1, 134.6, 134.0, 130.8, 125.6, 124.4, 124.2, 122.9, 121.0, 120.6, 120.5, 119.9, 116.3, 112.0, 111.8, 110.0, 102.9, 98.0, 97.8, 88.0, 33.4; HRMS (ESI) *m/z* calcd for $C_{23}H_{15}FN_4$ $[M + Na]^+$ 389.1178, found 389.1177.

5-Methoxy-1-(pyridin-2-yl)-2-(pyridin-3-yl)-1*H*-indole-3-carbonitrile (85k). Obtained



from acrylonitrile **80k** and 2-aminopyridine, pale yellow solid (215 mg, 66%): mp 190-192 °C; R_f 0.4 (4:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3064, 2938, 2220, 1589, 1465, 1211, 1022, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.617 (ddd, J = 8.8 Hz, 2.0 Hz, 0.8 Hz, 1H), 8.61 (br s, 1H), 8.49 (s, 1H), 7.85 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.77 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.44 (dd, *J* = 8.8 Hz, 0.4 Hz, 1H), 7.37 (dd, *J* = 4.8 Hz, 0.8 Hz, 1H), 7.35 (dd, *J* = 4.8 Hz, 0.8 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.05 (dt, *J* = 8.0 Hz, 0.8 Hz, 1H), 6.99 (dd, *J* = 9.2 Hz, 3.6 Hz, 1H), 3.92 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 150.2, 150.1, 150.0, 149.98, 142.8, 138.9, 136.9, 132.2, 128.6, 125.8, 123.7, 122.1, 116.2, 115.9, 113.3, 100.8, 89.5, 56.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{14}N_4O$ $[M + H]^+$ 327.1246, found 327.1233.

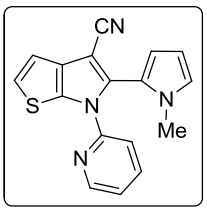
5,6-Bis(4-methoxyphenyl)-6*H*-thieno[2,3-*b*]pyrrole-4-carbonitrile (94a). obtained



from acrylonitrile **92a** and 4-methoxyaniline, white solid (248 mg, 69%): mp 89-90 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 2215, 1619, 1517, 1243,1031,835; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33-7.24 (m, 6H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.97 (d,

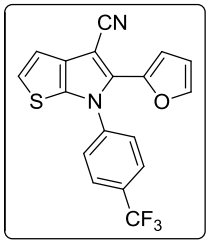
J = 9.2 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.2, 131.2, 130.9, 130.0, 126.6, 121.8, 120.1, 117.0, 116.9, 115.0, 114.9, 114.22, 114.16, 85.9, 55.5, 55.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}N_2O_2S$ $[M+H]^+$ 361.1011, found 361.1025.

5-(1-Methyl-1*H*-pyrrol-2-yl)-6-(pyridin-2-yl)-6*H*-thieno[2,3-b]pyrrole-4-carbonitrile



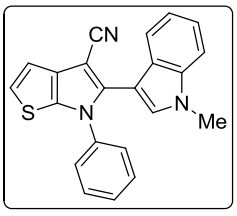
(94b). Obtained from acrylonitrile **92b** and 2-aminopyridine, white solid (203 mg, 67%); mp 104-105 °C; R_f 0.4 (1:4 EtOAc:hexane): IR (KBr, cm^{-1}) 2928, 2230, 1588, 1462, 1439, 1360, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 3.6 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.23-7.14 (m, 3H), 6.83 (br s, 1H), 6.48 (brs, 1H), 6.30 (d, *J* = 8.0 Hz, 2H), 3.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 148.4, 138.8, 134.9, 129.6, 125.2, 123.7, 121.5, 121.2, 115.8,115.7, 113.7, 113.2, 112.5, 109.4, 92.8, 34.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}N_4S$ $[M+H]^+$ 305.0861, found 305.0855.

5-(Furan-2-yl)-6-(4-(trifluoromethyl)phenyl)-6H-thieno[2,3-b]pyrrole-4-carbonitrile



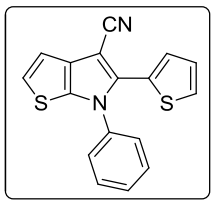
(94c). Obtained from **92c** and 4-(trifluoromethyl)aniline, white solid (240 mg, 67%); mp 158-160 °C; R_f 0.6 (1:9 EtOAc:hexane): IR (KBr, cm^{-1}) 2215, 1314, 1125, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 2.0 Hz, 0.4 Hz, 1H), 7.17 (d, *J* = 5.2 Hz, 1H), 7.04 (d, *J* = 5.2 Hz, 1H), 6.62 (dd, *J* = 3.6 Hz, 0.4 Hz, 1H), 6.46 (dd, *J* = 3.6 Hz, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 142.9, 141.6, 138.4, 135.5, 131.0, 130.8, 127.1, 127.09, 127.05, 127.02, 126.98, 125.6, 121.4, 117.1, 115.6, 111.8, 111.7, 87.1; HRMS(ESI) *m/z* calcd for $C_{18}H_9F_3N_2OS$ $[M+H]^+$ 359.0466, found 359.0445.

5-(1-Methyl-1*H*-indol-3-yl)-6-phenyl-6*H*-thieno[2,3-b]pyrrole-4-carbonitrile (94d).



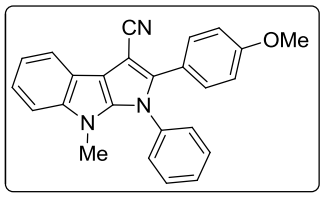
Obtained from acrylonitrile **92d** and aniline, brown solid (257 mg, 73%); mp 191-192 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 2215, 1596, 1510, 1235, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 6H), 7.25 (s, 1H), 7.19-7.14 (m, 3H), 7.01 (d, *J* = 5.2 Hz, 1H), 6.95 (dd, *J* = 7.6 Hz, 5.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 139.0, 137.1, 136.8, 130.4, 129.9, 129.6, 127.9, 126.0, 124.5, 122.3, 120.3, 120.2, 119.8, 117.14, 117.06, 109.5, 104.4, 86.9, 33.29; HRMS(ESI) *m/z* calcd for $C_{22}H_{15}N_3S$ $[M+H]^+$ 354.1065, found 354.1055.

6-Phenyl-5-(thiophen-2-yl)-6H-thieno[2,3-b]pyrrole-4-carbonitrile (94e). Obtained



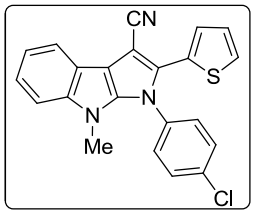
from acrylonitrile **92e** and aniline, pale yellow solid (198 mg, 65%): mp 206-207 °C; R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 3125, 2922, 2218, 1495, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 3H), 7.36-7.32 (m, 3H), 7.22 (dd, J = 3.6 Hz, 0.8Hz, 1H), 7.16 (d, J = 5.2 Hz, 1H), 7.02-7.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.9, 138.0, 130.5, 130.2, 130.1, 129.32, 129.31, 128.3, 127.5, 126.4, 121.0, 117.1, 116.5, 87.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{10}N_2S_2$ $[M + H]^+$ 307.0364, found 307.0354.

2-(4-Methoxyphenyl)-8-methyl-1-phenyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-

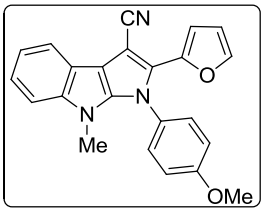


carbonitrile (97a). Obtained from acrylonitrile **95a** and aniline, off-white solid (230 mg, 61%): mp 180-181 °C; R_f 0.5 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2220, 1495, 1255, 751; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.47-7.46 (m, 3H), 7.36-7.33 (m, 2H), 7.28-7.24 (m, 3H), 7.21 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 9.2 Hz, 2H), 3.78 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 141.2, 140.7, 139.8, 136.5, 131.2, 129.7, 129.5, 129.0, 122.1, 122.0, 120.3, 119.6, 119.3, 117.9, 114.1, 109.5, 107.2, 84.2, 55.4, 30.6; HRMS (ESI) *m/z* calcd for $C_{25}H_{19}N_3O$ $[M +H]^+$ 378.1606, found 378.1599

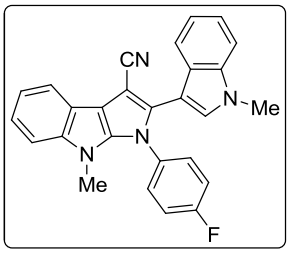
1-(4-Chlorophenyl)-8-methyl-2-(thiophen-2-yl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-



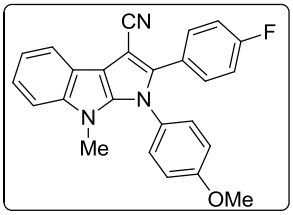
carbonitrile (97b). Obtained from acrylonitrile **95b** and 4-chloroanilne, off-white solid (224 mg, 61%): mp 255-256 °C; R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2213, 1558, 1482, 1085, 739; ^{1}HNMR (400 MHz, acetone-d_6) δ 7.84 (br d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.55 (dd, J = 5.2 Hz, 0.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.33 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.28-7.25 (m, 2H), 7.11 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 141.8, 141.1, 136.6, 135.5, 134.5, 132.3, 131.2, 130.7, 129.6, 128.7, 128.0, 123.0, 120.9, 119.8, 119.1, 117.3, 110.8, 107.6, 85.5, 30.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{14}ClN_3S$ $[M + H]^+$ 388.0675 and 390.0646, found 388.0667 and 390.0630.

2-(Furan-2-yl)-1-(4-methoxyphenyl)-8-methyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (97c). 

Obtained from acrylonitrile **95c** and 4-methoxyaniline, pale yellow solid (245 mg, 67%): mp 225-226 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2963, 2213, 1526, 1249, 745; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.93 (dt, J = 4.0 Hz, 1.6 Hz, 1H), 7.39-7.37 (m, 3H), 7.27-7.20 (m, 3H), 7.05 (d, J = 8.8 Hz, 2H), 6.30 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 5.90 (d, J = 3.6 Hz, 0.4 Hz, 1H), 3.92 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3, 144.1, 143.2, 140.5, 140.2, 130.3, 130.2, 127.8, 122.0, 120.0, 118.3, 117.9, 116.7, 114.9, 111.7, 110.3, 108.5, 106.1, 81.1, 55.6, 29.8; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{17}N_3O_2$ $[M + H]^+$ 368.1399, found 368.1398.

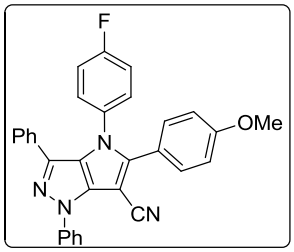
1-(4-Fluorophenyl)-8-methyl-2-(1-methyl-1*H*-indol-3-yl)-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (97d). 

Obtained from acrylonitrile **95d** and 4-fluoroaniline, brown solid (250 mg, 60%): mp 250-251 °C; R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2924, 2211, 1505, 1214, 735; ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 7.2 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 4.8 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.8 Hz, 2H), 7.38 (s, 1H), 7.30-7.24 (m, 3H), 7.19 (q, J = 7.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 1H), 3.77 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 160.7, 139.9, 139.4, 136.2, 136.0, 131.99, 131.96, 131.1, 131.0, 126.5, 121.8, 121.4, 119.80, 119.75, 119.4, 118.5, 117.6, 117.3, 116.2, 116.0, 110.23, 110.19, 105.4, 102.6, 83.6, 32.7, 30.2; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{19}FN_4$ $[M + H]^+$ 419.1672, found 419.1684.

2-(4-Fluorophenyl)-1-(4-methoxyphenyl)-8-methyl-1,8-dihydropyrrolo[2,3-*b*]indole-3-carbonitrile (97e). 

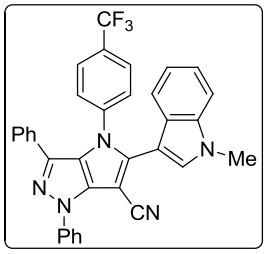
Obtained from acrylonitrile **95e** and 4-fluoroaniline, off-white solid (256 mg, 65%): mp 220-221 °C; R_f 0.4 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 2215, 1519, 1219, 744; ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 6.8 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 4.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.8 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.25-7.23 (m, 1H), 7.19 (td, J = 7.2 Hz, 0.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3, 160.8, 159.3, 141.1, 140.1, 139.6, 131.9, 131.8, 131.5, 131.4, 121.6, 121.2, 119.8, 118.4, 117.7, 117.2, 116.5, 116.3, 114.0, 110.3, 105.4, 82.6, 55.2, 30.1; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{18}FN_3O$ $[M + H]^+$ 396.1512, found 396.1505.

4-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1,3-diphenyl-1,4-dihydropyrrolo[3,2-*c*]



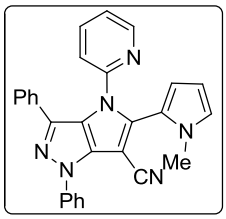
pyrazole-6-carbonitrile (100a). Obtained from acrylonitrile **98a** and 4-fluoroaniline, white solid (387 mg, 80%); mp 225-226 °C; R_f 0.7 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 2223, 1604, 1517, 1251, 1181, 789; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, J = 8.8 Hz, 1.2 Hz, 2H), 7.62 (br t, *J* = 7.6 Hz, 2H), 7.43-7.39 (m, 3H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.30-7.25 (m, 1H), 7.24-7.16 (m, 4), 7.10 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.0, 160.7, 150.0, 139.8, 136.2, 134.9, 133.4, 133.3, 131.7, 131.0, 129.8, 129.7, 129.6, 128.7, 128.2, 128.1, 128.0, 126.6, 120.89, 120.85, 116.4, 116.2, 116.1, 114.4, 78.0, 55.5; HRMS (ESI) *m/z* calcd for $C_{31}H_{21}FN_4O$ $[M + H]^+$ 485.1778, found 485.1771.

5-(1-Methyl-1*H*-indol-3-yl)-1,3-diphenyl-4-(4-(trifluoromethyl)phenyl)-1,4



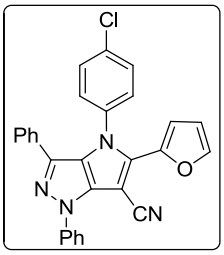
dihydropyrrolo[3,2-*c*]pyrazole-6-carbonitrile (100b). Obtained from acrylonitrile **98b** and 4-(trifluoromethyl)aniline, white solid (373 mg, 67%); mp 261-263 °C; R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2920, 2223, 1486, 1321, 1133, 1062, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.56 (dd, *J* = 8.8 Hz, 7.6 Hz, 2H), 7.40 (brd, *J* = 8.4 Hz, 2H), 7.37-7.32 (m, 2H), 7.248-7.245 (m, 1H), 7.23-7.10 (m, 9H), 7.01 (dd, *J* = 7.6 Hz, 7.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 140.5, 139.8, 137.0, 136.1, 135.2, 131.0, 130.9, 130.5, 130.1, 129.6, 128.9, 128.4, 128.1, 127.8, 127.4, 126.6, 126.23, 126.19, 126.16, 126.13, 122.9, 121.0, 120.9, 120.0, 116.2, 110.0, 103.3, 79.4, 33.5; HRMS (ESI) *m/z* calcd for $C_{34}H_{22}F_3N_5$ $[M + H]^+$ 558.1906, found 558.1902.

5-(1-Methyl-1*H*-pyrrol-2-yl)-1,3-diphenyl-4-(pyridin-2-yl)-1,4-dihydropyrrolo[3,2-*c*]



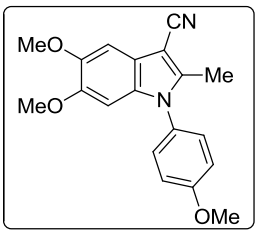
pyrazole-6-carbonitrile (100c). Obtained from acrylonitrile **98c** and 2-aminopyridine, White solid (286 mg, 65%); mp 202-204 °C; R_f 0.5 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3053, 2223, 1580, 1502, 1470, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (ddd, *J* = 4.8 Hz, 2.0 Hz, 0.8 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.63 (td, *J* = 7.8 Hz, 2.0 Hz, 1H), 7.56 (dd, *J* = 8.4 Hz, 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25-7.22 (m, 2H), 7.20-7.15 (m, 4H), 6.88 (dt, *J* = 8.0 Hz, 0.8 Hz,1H), 6.68 (dd, *J* = 2.8 Hz, 1.4 Hz, 1H), 6.30 (dd, *J* = 3.6 Hz, 1.4 Hz, 1H), 6.14 (dd, *J* = 3.6 Hz, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 149.2, 141.3, 139.8, 138.3, 136.7, 134.6, 131.7, 129.6, 128.7, 128.1, 127.9, 127.4, 126.6, 125.3, 123.4,

120.94, 120.92, 120.3, 115.3, 114.8, 108.9, 81.4, 34.8; HRMS (ESI) *m/z* calcd for $C_{28}H_{20}N_6$ $[M + Na]^+$ 463.1647, found 463.1643.

4-(4-Chlorophenyl)-5-(furan-2-yl)-1,3-diphenyl-1,4-dihydropyrrolo[3,2-*c*]pyrazole-6-carbonitrile (100d). 

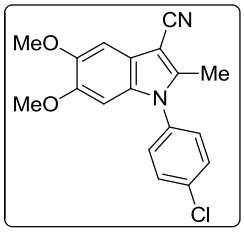
Obtained from acrylonitrile **98d** and 4-chloroaniline, off-white solid (285 mg, 62%); mp 128-130 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3058, 2226, 1489, 1085, 1016, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (td, *J* = 7.6 Hz, 1.2 Hz, 2H), 7.56 (dd, *J* = 8.4 Hz, 7.6 Hz, 2H), 7.43 (dd, *J* = 1.4 Hz, 0.6 Hz, 1H), 7.39-7.33 (m, 3H), 7.24-7.20 (m, 3H), 7.18-7.11 (m, 4H), 6.51 (dd, *J* = 3.4 Hz, 0.6 Hz, 1H), 6.44 (dd, *J* = 3.4 Hz, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.0, 139.6, 139.2, 136.3, 136.2, 135.5, 135.0, 130.7, 129.65, 129.59, 129.4, 128.8, 128.4, 128.3, 128.2, 126.8, 121.0, 115.4, 113.3, 111.8, 77.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{17}ClN_4O$ $[M + H]^+$ 461.1169 and 463.1140, found 461.1163 and 463.1128.

4.5.6 General procedure for the synthesis of 3-cyano-2-alkyl-*N*-arylindoles 85m-o and 3-cyano-2-(het)aryl-*N*-alkylindoles 85p-q from enaminonitriles 87m-q. To a stirred solution of either pure (**87m-n)** or the crude (**87o-q**) enaminonitriles (0.5 mmol) in DMF (5 mL) were added CuI (9 mg, 0.05 mmol), L-proline (12 mg, 0.1 mmol), Cs_2CO_3 (163 mg, 0.5 mmol, 1 eq) and the reaction mixture was heated at 90 °C with constant stirring for 9-10 h (monitored by TLC). It was then poured into ice-cold water (20 mL), extracted with EtOAc (3 × 10 mL),the combined extracts were washed with water (2x 10 mL), brine (1 × 10 mL), dried over Na_2SO_4 followed by removal of the solvent to give crude products, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

5,6-Dimethoxy-1-(4-methoxyphenyl)-2-methyl-1*H*-indole-3-carbonitrile (85m). 

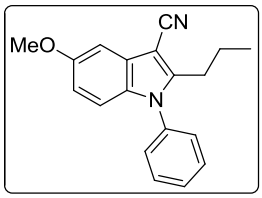
Obtained from enaminonitrile **87m**, white solid (128 mg, 80%); mp 131-132 °C; R_f 0.6 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 2919, 2220, 1608, 1482, 1224, 1022, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 7.11 (s, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.49 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.77 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 147.9, 147.1, 144.4 131.8, 128.98, 128.92, 119.76, 116.9, 115.3, 100.5, 94.5, 85.7, 56.5, 56.4, 55.8, 12.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2O_3$ $[M + H]^+$ 323.1396, found 323.1383.

1-(4-Chlorophenyl)-5,6-dimethoxy-2-methyl-1*H*-indole-3-carbonitrile (85n).



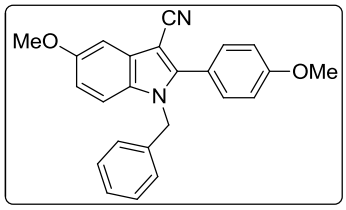
Obtained from enaminonitrile **87n**, white solid (127 mg, 78%): mp 185-186 °C; R_f 0.65 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2935, 2218, 1489, 1281, 1163, 831; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.12 (s, 1H) 6.49 (s, 1H), 3.95 (s, 3H), 3.78 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.3, 143.7, 135.3, 134.9, 131.6, 130.5, 129.1, 119.9, 116.6, 100.6, 94.2, 86.7, 56.5, 56.4, 12.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{15}ClN_2O_2$ $[M + H]^+$ 327.0900 and 329.0871, found 327.0880 and 329.0855.

5-Methoxy-1-phenyl-2-propyl-1*H*-indole-3-carbonitrile (85o). Obtained from



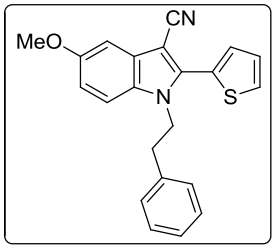
enaminonitrile **87o**, colorless liquid (87 mg, 60%); R_f 0.65 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2967, 2211, 1480, 1248, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57- 7.53 (m, 3H), 7.32-7.30 (m, 2H), 7.15 (d, J = 2.4 Hz 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.82 (dd, J = 8.6 Hz, 2.4 Hz, 1H), 3.87 (s, 3H), 2.78 (t, J = 7.6 Hz, 2H), 1.57 (sex, J = 7.2 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 150.1, 136.3, 132.5, 130.0, 129.3, 128.1, 127.9, 116.7, 113.8, 112.1, 100.5, 85.8, 56.0, 28.4, 22.5, 13.8; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2O$ $[M + H]^+$ 291.1497, found 291.1485.

1-Benzyl-5-methoxy-2-(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (85p). Obtained



from enaminonitrile **87p**, white solid (101 mg, 55%): mp 108-109 °C; R_f 0.6 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2932, 2207, 1608, 1489, 1255, 1028, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 2H), 7.32-7.28 (m, 3H), 7.215 (d, J = 2.4 Hz 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.99-6.97 (m, 4H), 6.88 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 5.32 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 156.2, 148.4, 136.5, 131.3, 131.0, 129.03, 128.7, 127.76, 125.8, 121.0, 117.0, 114.6, 114.4, 112.3, 100.8, 85.6, 55.8, 55.4, 48.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}N_2O_2$ $[M + H]^+$ 369.1603, found 369.1603.

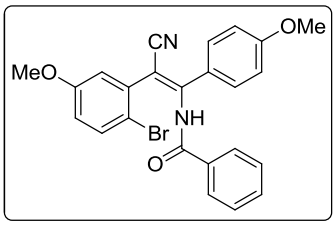
5-Methoxy-1-phenethyl-2-(thiophen-2-yl)-1*H*-indole-3-carbonitrile (85q). Obtained from enaminonitrile **87q**, yellow semisolid (103 mg, 58%): R_f 0.55 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2926, 2207, 1451, 1243, 1028, 707; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.226-7.19 (m, 4H), 7.17-7.14 (m, 2H), 6.99-6.94 (m, 3H), 4.44 (t, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.03 (t, J = 7.6 Hz, 2H);



^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 140.3, 137.3, 131.1, 130.5, 128.93, 128.9, 128.73, 128.7, 128.0, 127.2, 116.7, 115.1, 111.8,100.8, 87.09, 55.9, 46.5, 36.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_2OS$ $[M + H]^+$ 359.1218, found 359.1218.

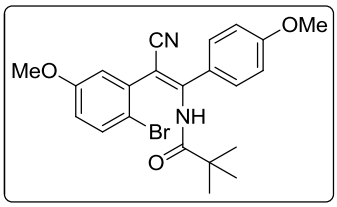
4.5.7 General procedure for the synthesis of *N*-acylenaminonitriles 89a-c from 80a. To a stirred suspension of NaH (40 mg, 1.0 mmol, 100%) in dry DMF (10 mL), a solution of the appropriate amide (1.1 mmol) in DMF (5 mL) was added drop-wise followed by addition of **80a** (0.39 g, 1.0 mmol) in DMF (5 mL) at room temperature and the reaction mixture was heated at 120 °C with stirring for 9-11 h (monitored by TLC). It was then poured into ice-cold water (50 mL), extracted with EtOAc (2 × 50 mL), washed with water (2 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to give crude N-acylenaminonitriles, which were purified by column chromatography over silica gel using EtOAc-hexane as eluent.

(*E*)-N-(2-(2-Bromo-5-methoxyphenyl)-2-cyano-1-(4-methoxyphenyl)vinyl)benzamide



(89a). Obtained as a 70:30 mixture of geometrical isomers, white solid (324 mg, 76%): mp 140-144 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3293, 2941, 2212, 1691, 1606, 1469, 1261, 1026, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 2.8 Hz, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.6, 161.9, 161.2, 159.9, 159.1, 152.1, 134.7, 134.01, 133.96, 133.7, 133.2, 133.1, 132.9, 130.7, 130.4, 129.2, 129.1, 127.8, 127.5, 125.4, 125.1, 118.7, 118.0, 117.8, 117.2, 116.8, 116.6, 115.4, 114.3, 114.2, 114.0, 99.3, 98.3, 55.9, 55.7, 55.5, 55.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{19}BrN_2O_3$ $[M + H]^+$ 463.0657 and 465.0637 found 463.0659 and 465.0639

(*E*)-N-(2-(2-Bromo-5-methoxyphenyl)-2-cyano-1-(4-methoxyphenyl)vinyl)pivalamide

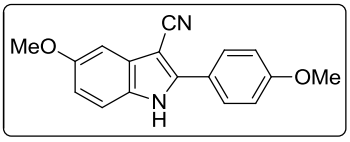


(89b). Obtained as a single geometrical isomer, white solid (345 mg, 78%): mp 184-186 °C; R_f 0.4 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3237, 2969, 2208, 1677, 1598, 1507, 1467, 1255, 1178, 1024, 834; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.69 (m, 1H), 6.57 (d, *J* = 2.8 Hz, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 161.1, 159.0, 152.0, 134.0, 130.4, 125.4, 117.9, 117.1, 116.8,

115.3, 113.9, 99.4, 55.6, 55.3, 40.2, 27.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}BrN_2O_3$ [M + H]$^+$ 443.0970 and 445.0950 found 443.0954 and 445.0937.

(*E*)-N-(2-(2-Bromo-5-methoxyphenyl)-2-cyano-1-(4-methoxyphenyl)vinyl)propionamide (89c). Obtained as 2:1 inseparable mixture of geometrical isomers, off-white solid (290 mg, 70%): mp 104-107 °C; R_f 0.3 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3234, 2929, 2203, 1687, 1595, 1251, 1023, 828; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 0.33H), 9.67 (s, 0.67H), 7.59-7.53 (m, 2.34H), 7.06 (dd, *J* = 8.8 Hz, 2.01H), 6.94-6.91(m, 1.32H), 6.86 (dd, *J* = 8.8 Hz, 2.4 Hz, 0.33H), 6.81 (d, *J* = 8.8 Hz, 0.67H), 6.66 (d, *J* = 2.4 Hz, 0.33H), 3.83 (s, 2.01H), 3.76 (s, 2.01H), 3.71 (s, 0.99H), 3.62 (s, 0.99H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 171.6, 161.1, 160.6, 158.7, 158.6, 152.0, 150.4, 135.1, 134.9, 133.9, 133.8, 130.9, 130.6, 126.8, 126.2, 119.1, 118.1, 117.0, 116.3, 115.4, 114.2, 113.7, 113.62, 113.59, 100.9, 98.4, 55.5, 55.45, 55.35, 55.22, 29.1, 28.9, 9.3, 9.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}BrN_2O_3$ [M + H]$^+$ 415.0657 and 417.0637 found 415.0677 and 417.0642

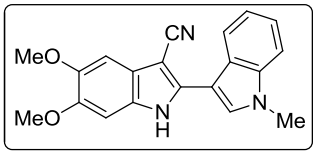
4.5.8 General procedure for the copper catalyzed cyclization of *N*-acylenaminonitriles 89a-c. *N*-Acylenaminonitriles **89a-c** (0.5 mmol) were subjected to coper catalyzed cyclization under identical conditions as described for enaminonitrile **87a** in the presence of CuI (9 mg, 0.05 mmol), L-proline (12 mg, 0.1 mmol) and NaH (20 mg, 0.5 mmol, 100%) in DMF. Work-up of the reaction mixture as described for **87a**, afforded in all three reactions 5-Methoxy-2-(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (**91a**): Off-white solid (73-75%, Scheme 4): mp 224-225 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}); 3201, 2960, 2225, 1469, 1248, 1026, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.92 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.2, 145.2, 130.0, 129.8, 128.3, 122.2, 117.5, 115.0, 114.8, 112.5, 100.8, 83.1, 56.0, 55.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N_2O_2$ [M + H]$^+$ 279.1134, found 279.1122.



4.5.9 General procedure for two step one-pot synthesis of 3-cyano-2-(het)aryl-1-N*H* indoles 91, 94f, 100e. To a stirred suspension of NaH (80 mg, 2.0 mmol, 100%) in dry DMF (5 mL), appropriate amide (1.1 mmol) in DMF (5 mL) was added dropwise at room temperature, followed by addition of acrylonitriles **80**, **92e** or **98c** (1.0 mmol) in DMF(10

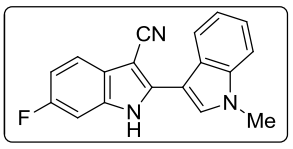
mL). The reaction mixture was heated at 120 °C with stirring for 10 hr, and after consumption of starting materials (monitored by TLC), CuI (19 mg, 0.1 mmol) and L-proline (23 mg, 0.2 mmol) were added and the reaction mixture was further heated (120 °C) for 9-10 hr (monitored by TLC). Work-up of the reaction mixture as described for preparation of N-arylindoles **85** afforded crude NH-indoles **91**, **94f** and **100e**, which were further purified by column chromatography over silica gel using EtOAc-hexane as eluent.

5,6-Dimethoxy-2-(1-methyl-1*H*-indol-3-yl)-1*H*-indole-3-carbonitrile (91b). Obtained



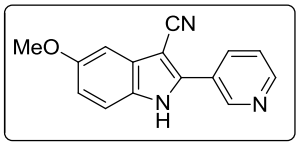
from **80i** and trimethylacetamide; white solid (244 mg, 74%): mp 138-140 °C; R_f 0.3 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3335, 2931, 2203, 1639, 1452, 1205, 1017, 742; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 7.94 (d, J= 8.0 Hz, 1H), 7.92 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.06 (s, 2H), 3.93 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.2, 139.8, 136.7, 129.62, 129.58, 127.4, 124.6, 122.3, 120.9, 120.3, 119.9, 117.8, 110.5, 104.6, 99.8, 95.9, 55.8, 55.7, 32.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_3O_2$ $[M + H]^+$ 332.1399, found 332.1391.

6-Fluoro-2-(1-methyl-1*H*-indol-3-yl)-1*H*-indole-3-carbonitrile (91c). Obtained from



80j and benzamide; off-white solid (187 mg, 65%): mp 255-256 °C; R_f 0.35 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3293, 2205, 1424, 1130, 740; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.0 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.58 (dd, J = 8.8 Hz, 5.2 Hz, 1H), 7.36-7.25 (m, 3H), 7.09 (td, J = 8.8 Hz, 2.4 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 158.1, 142.7, 136.8, 135.6, 135.5, 130.5, 124.7, 124.5, 122.5, 120.6, 119.9, 118.9, 117.1, 110.7, 110.0, 109.8, 104.0, 98.8, 98.6, 80.0, 33.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{12}FN_3$ $[M + H]^+$ 290.1094, found 290.1077

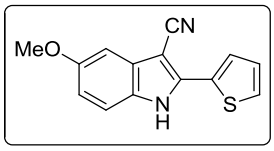
5-Methoxy-2-(pyridin-3-yl)-1*H*-indole-3-carbonitrile (91d). Obtained from **80k** and



trimethylacetamide; white solid (174 mg, 70%); mp 160-162 °C; R_f 0.3 (4:6 EtOAc:hexane); IR (KBr, cm^{-1}) 3458, 2925, 2212, 1598, 1474, 1212, 801; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, J = 2.0 Hz, 1H), 8.75 (dd, J = 4.6 Hz, 5.2 Hz, 1H), 8.25 (ddd, J = 8.6 Hz, 2.4 Hz, 1.6 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.65 (ddd, J = 8.6 Hz, 4.6 Hz, 0.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 9.0 Hz, 2.4 Hz, 0.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 152.0, 151.3, 148.2, 139.4, 135.6, 129.7, 127.4, 124.4, 124.3,

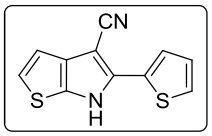
117.1, 114.5, 103.7, 102.3, 55.6; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}N_3O$ $[M + H]^+$ 250.0980, found 250.0978.

5-Methoxy-2-(thiophen-2-yl)-1*H*-indole-3-carbonitrile (91e). Obtained from **80m** and



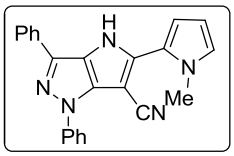
benzamide; off-white solid (178 mg, 70%); mp 190-192 °C; R_f 0.4 (2:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3234, 2941, 2205, 1463, 1222, 1033, 811, 707; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (br s, 1H), 7.74 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.47 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.19 (dd, J = 4.8 Hz, 3.6 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 139.2, 131.5, 129.8, 129.6, 128.7, 127.4, 127.3, 116.8, 115.4, 112.6, 100.8, 83.7, 55.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{10}N_2OS$ $[M + H]^+$ 255.0592, found 255.0588.

5-(Thiophen-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-4-carbonitrile (94f). Obtained from



acrylonitrile **92e** and benzamide, grey solid (150 mg, 65%): mp 155-156 °C; R_f 0.35 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3224, 2213, 1450, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (br s, 1H), 7.57 (dd, J = 3.6 Hz, 1.0 Hz, 1H), 7.38 (dd, J = 5.2 Hz, 1.0 Hz, 1H), 7.14 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 7.08 (d, J = 5.2 Hz, 1H), 7.0 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 134.2, 132.4, 131.9, 128.4, 126.3, 125.9, 121..4, 116.9, 116.7, 83.2; HRMS (ESI) *m/z* calcd for $C_{11}H_6N_2S_2$ $[M + H]^+$ 231.0051, found 231.0045.

5-(1-Methyl-1*H*-pyrrol-2-yl)-1,3-diphenyl-1,4-dihydropyrrolo[3,2-*c*]pyrazole-6-



carbonitrile (100e). Obtained from acrylonitrile **98c** and benzamide, brown solid (225 mg, 60%); mp 120-122 °C; R_f 0.35 (2:3 EtOAc:hexane): IR (KBr, cm^{-1}) 3404, 3064, 2953, 2211, 1601, 1497, 1275, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 2H), 7.55-7.52 (m, 2H), 7.50-7.46 (m, 2H), 7.38 (tt, J = 8.0 Hz, 1.2 Hz, 1H), 7.31 (tt, J = 8.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 2.4 Hz, 1.6 Hz, 1H), 6.56 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 6.27 (dd, J = 3.6 Hz, 2.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.9, 135.9, 134.9, 131.8, 129.6, 129.1, 128.5, 126.5, 126.4, 126.2, 125.7, 122.7, 120.6, 116.1, 113.1, 109.2, 77.8, 35.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{17}N_5$ $[M + H]^+$ 364.1562, found 364.1549.

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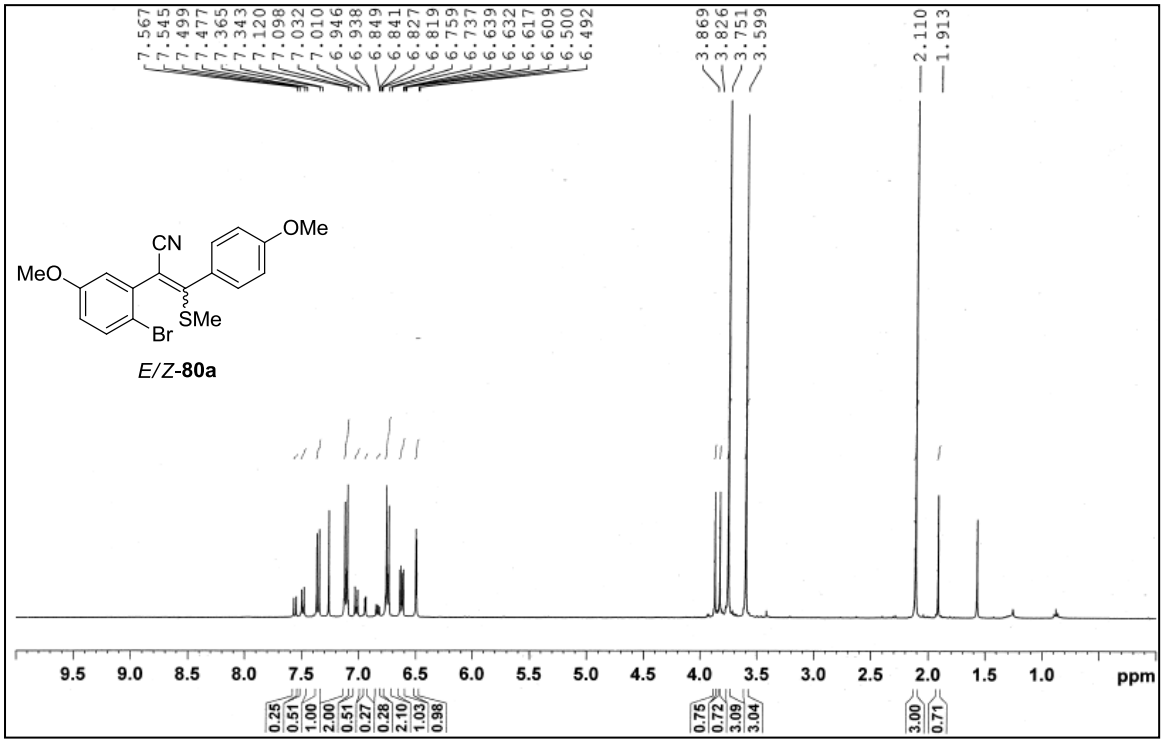
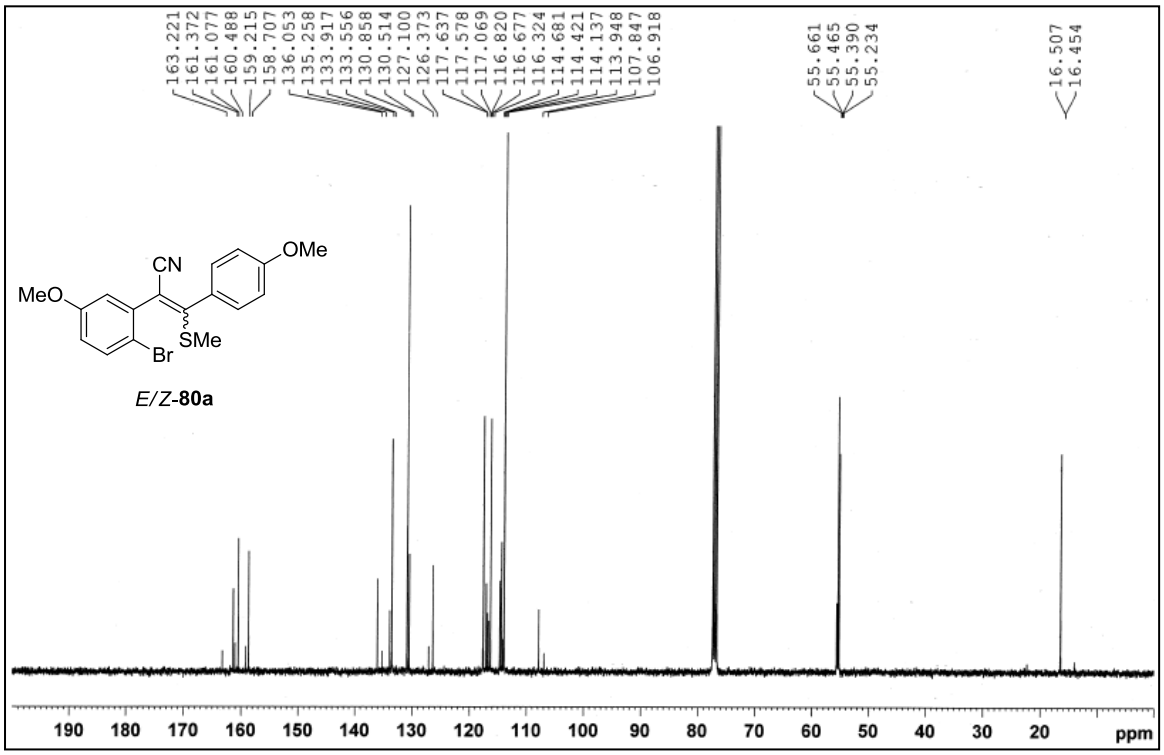
67. Recently, Zao and coworkers have reported synthesis of N-aryl/alkyl-2-alkyl-3-cyanoindoles by PIFA mediated intramolecular oxidative cyclization of the corresponding N-aryl/alkylenaminonitriles. However substituent diversity at 2-position of product indoles is limited only to 2-methyl group with only one exception, besides these 2-aryl-3-aryl/alkylamino-2-alkenenitriles are unstable and their isolation in pure form is experimentally difficult; (a) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett*. **2006**, *8*, 5919. For NBS induced similar transformation, see (b) Yan, Q.; Luo, J.; Zhang-Negrerie, D.; Li, H.; Qi, X.; Zhao, K. *J. Org. Chem*. **2011**, *76*, 8690.

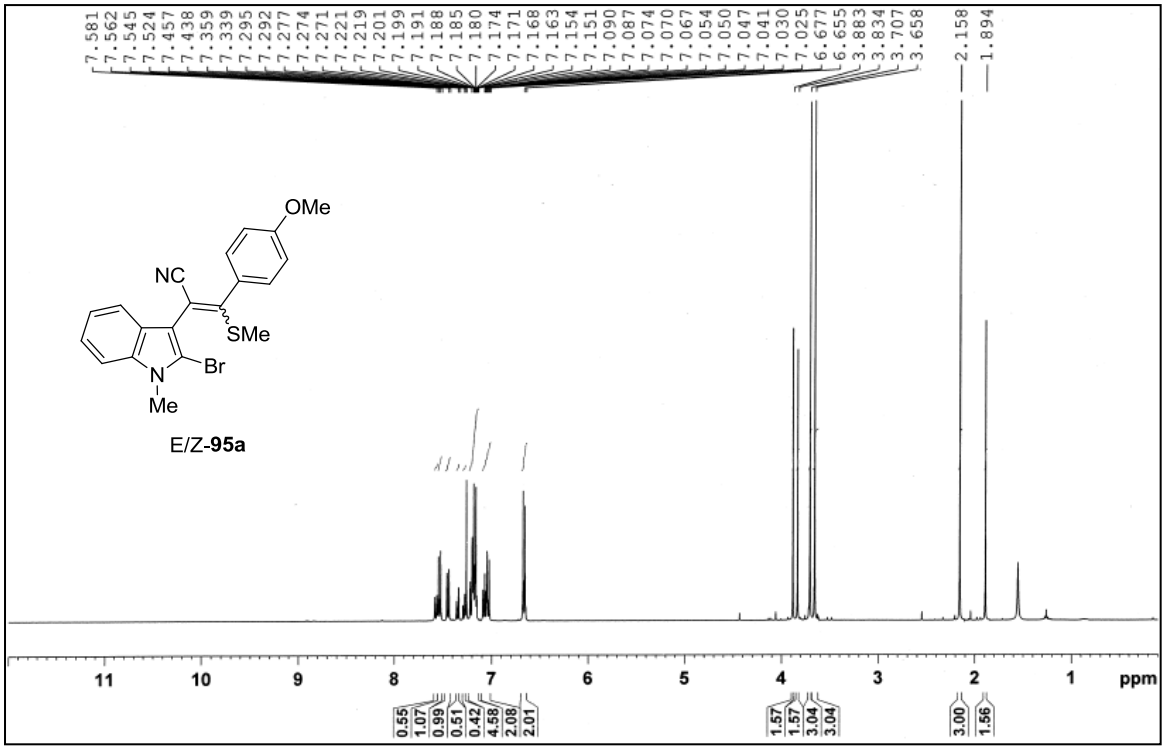
68. Attempted isolation of *N*-acylindole **90a** by directly evaporating the reaction mixture [either with NaH as base (Scheme 22) or with K_2CO_3 (Table 4, entry 3)] under reduced pressure, showed a new spot on TLC plate, however, work-up of this residue by pouring over water or by direct column chromatography of the residue furnished only NH-indole **91a**.

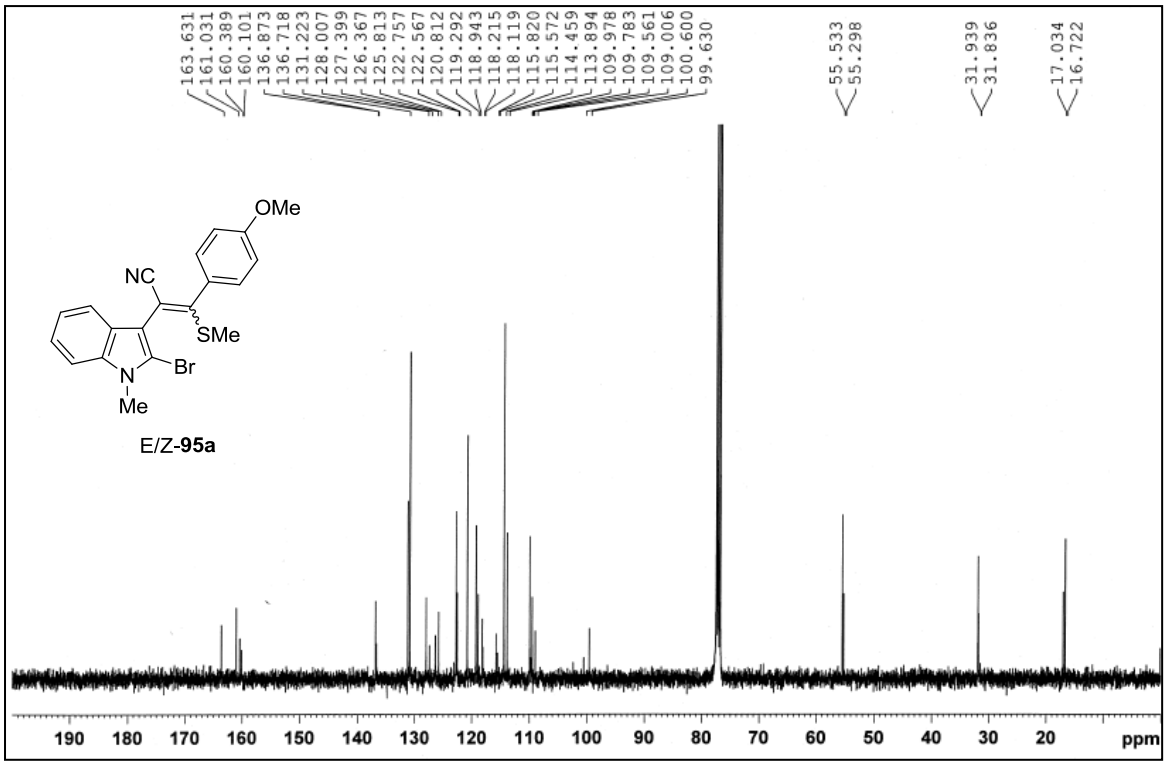
4.7 Representative spectra



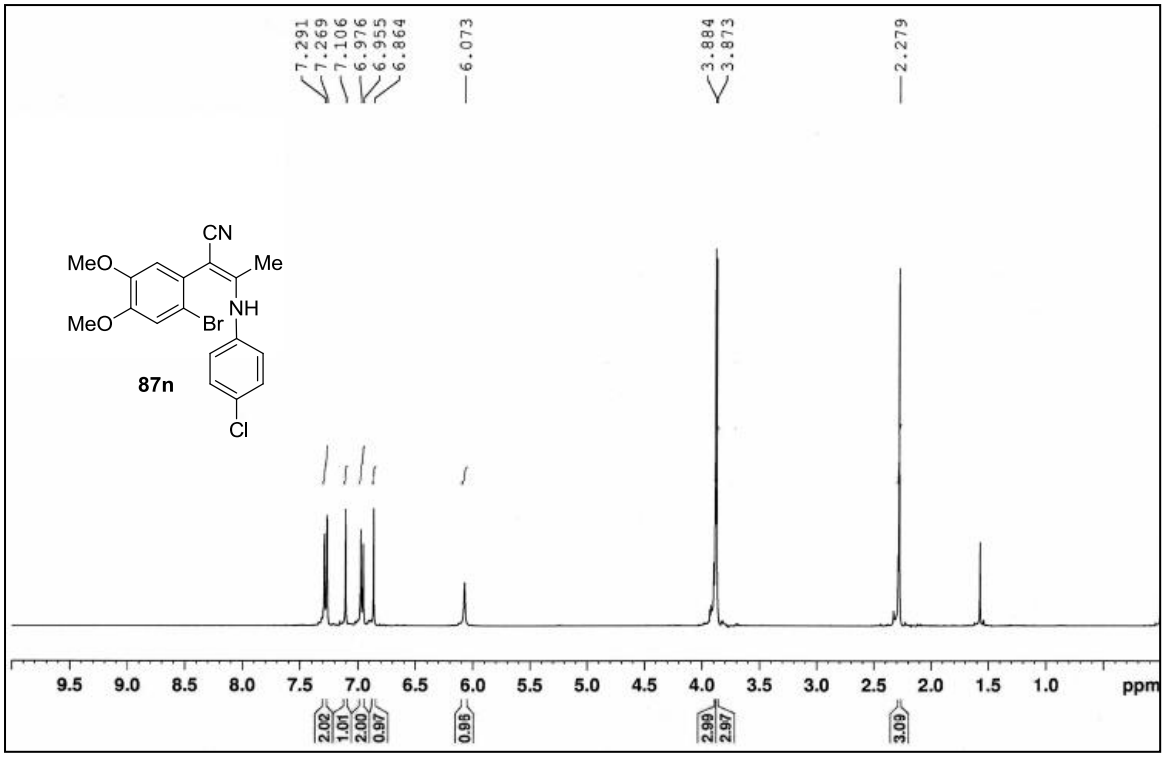


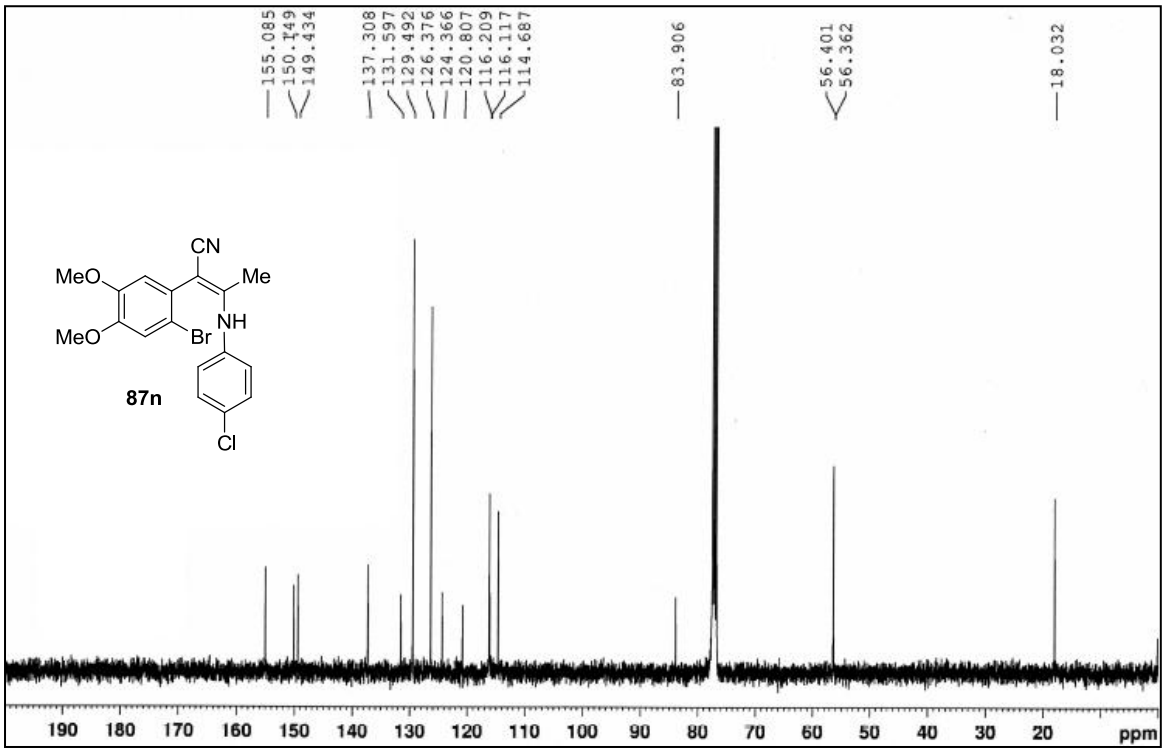
^{1}H NMR and ^{13}C NMR spectra for compound *E/Z*-**80a** in $CDCl_3$



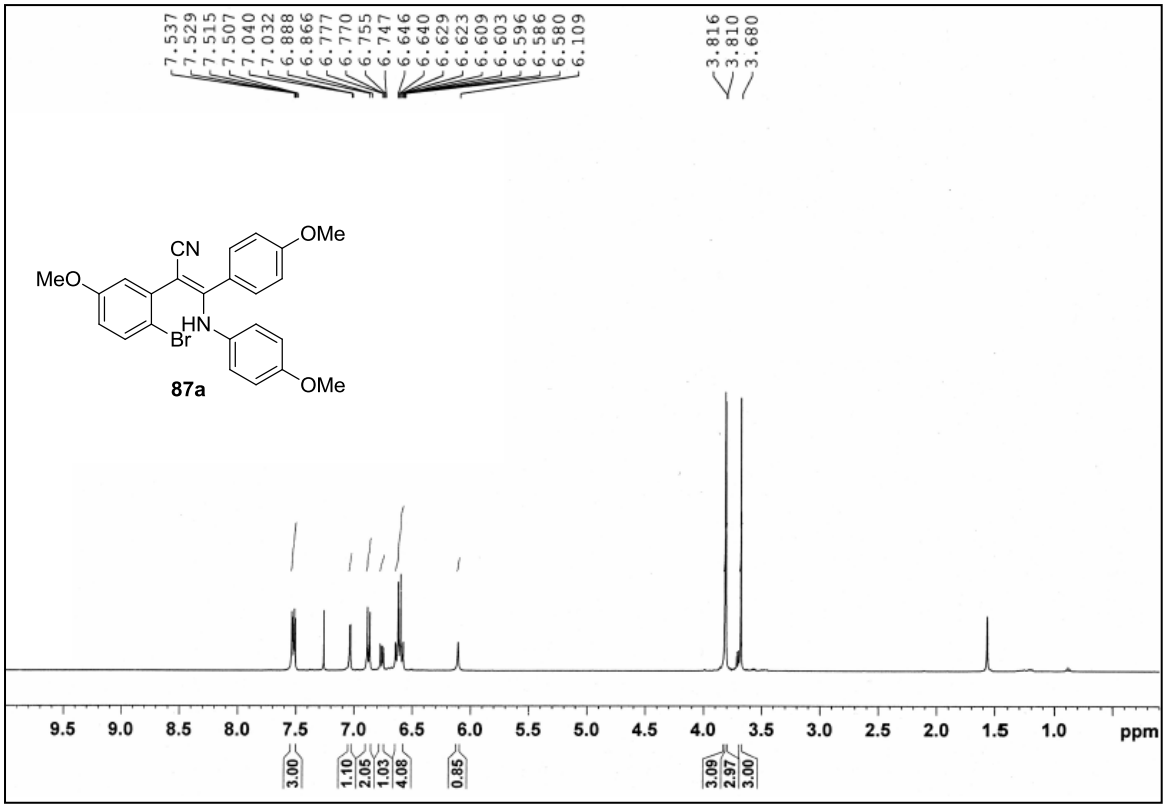


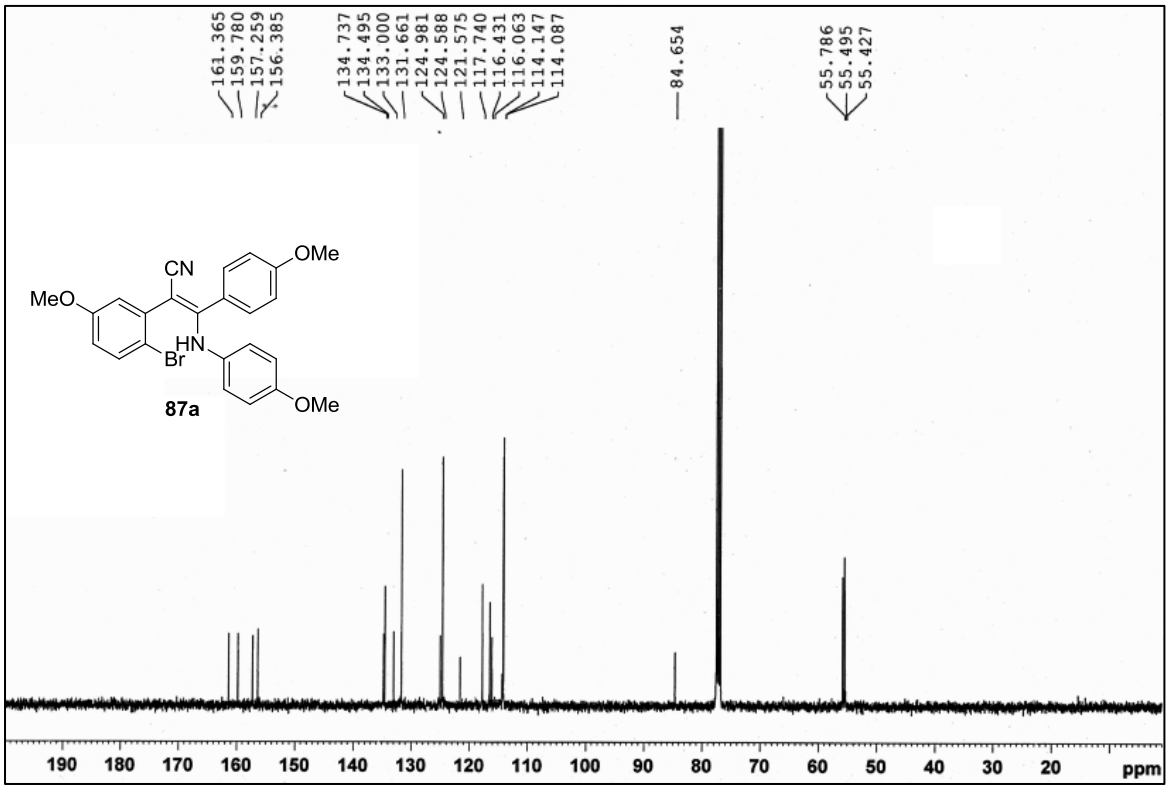
^{1}H NMR and ^{13}C NMR Spectra for compound *E/Z*-**95a** in $CDCl_3$



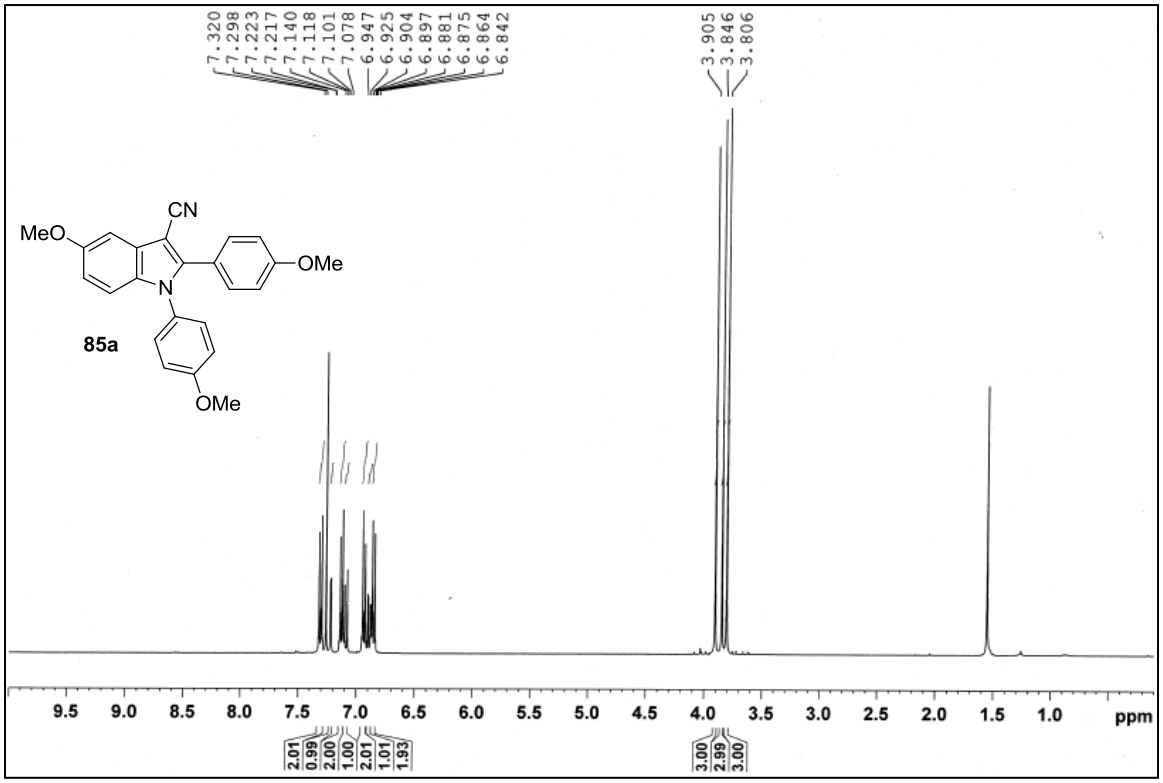


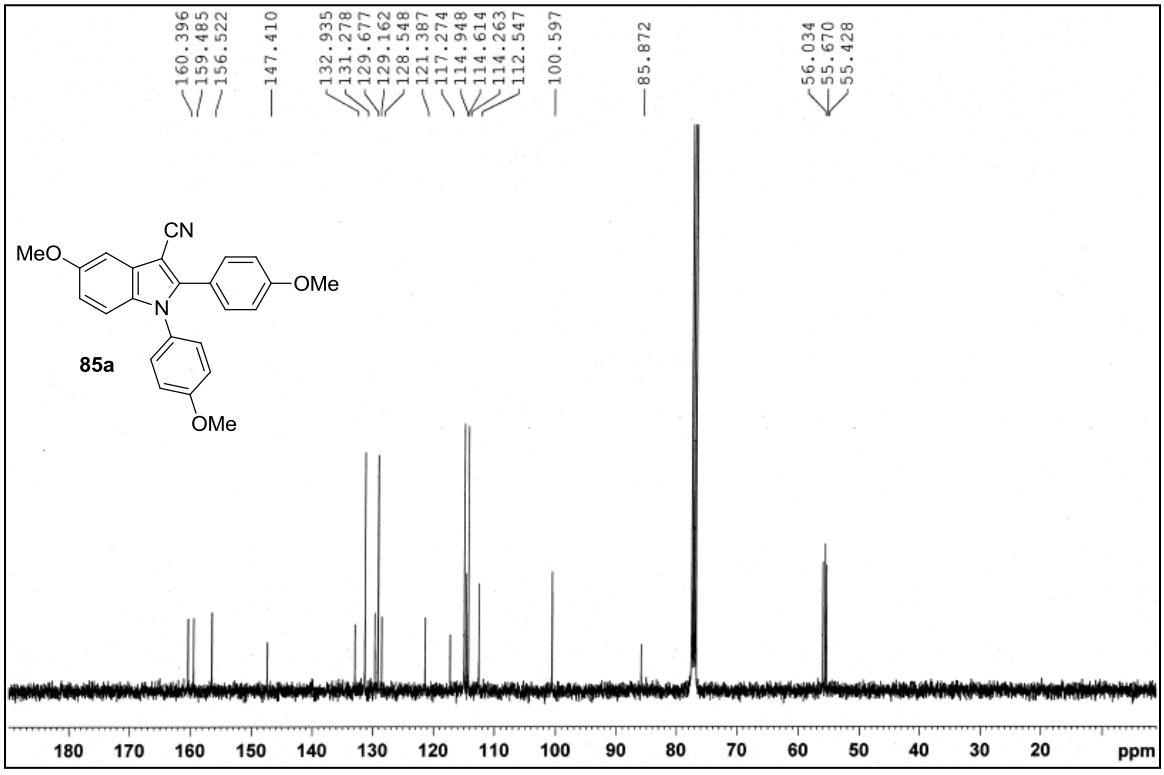
^{1}H NMR and ^{13}C NMR Spectra for compound **87n** in $CDCl_3$



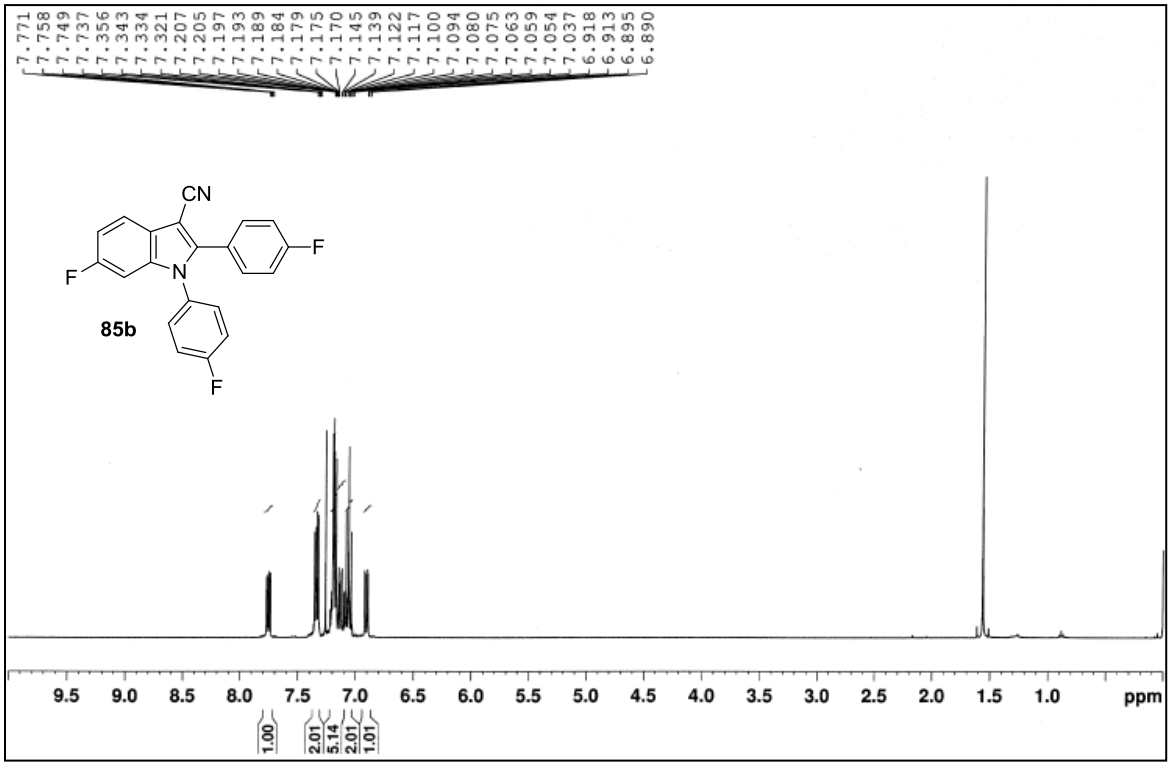


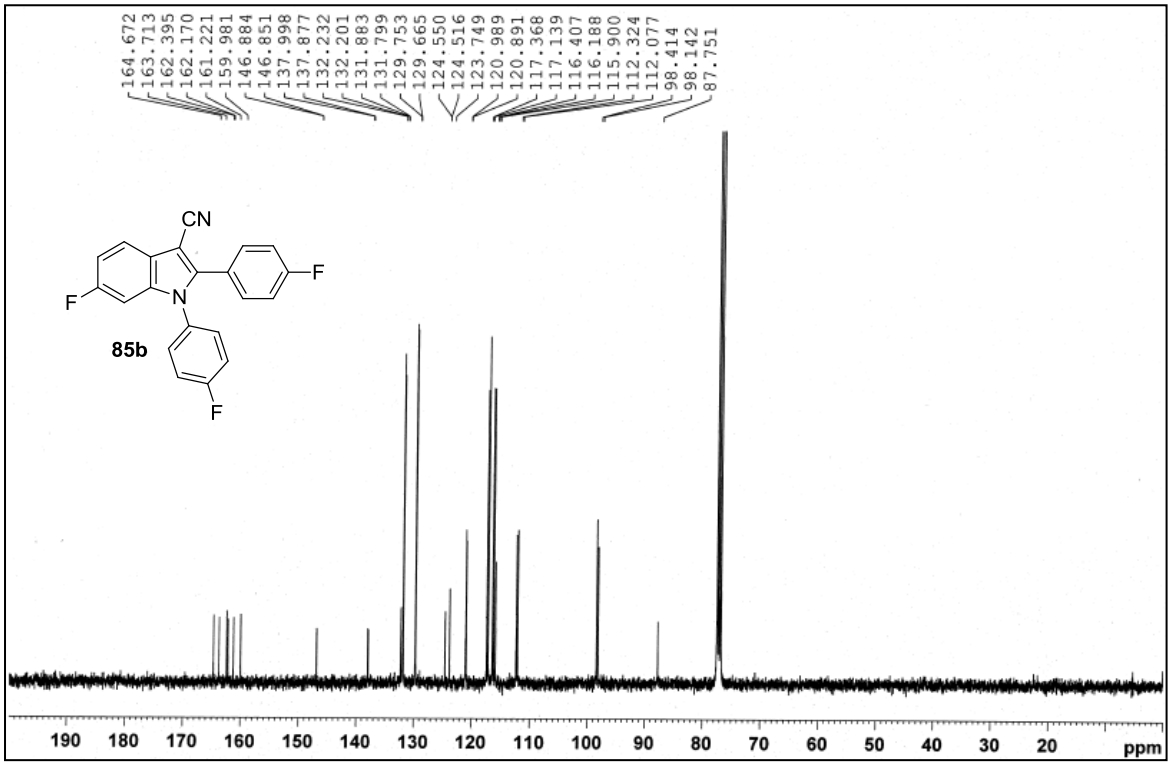
^{1}H NMR and ^{13}C NMR Spectra for compound **87a** in $CDCl_3$



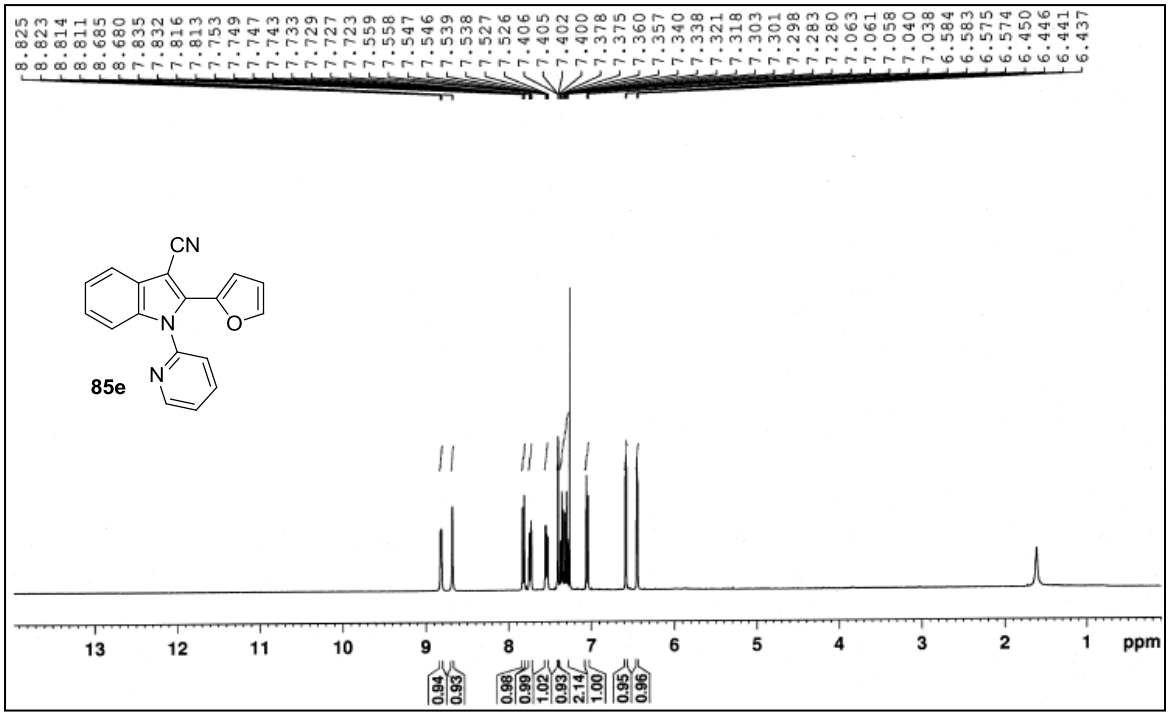


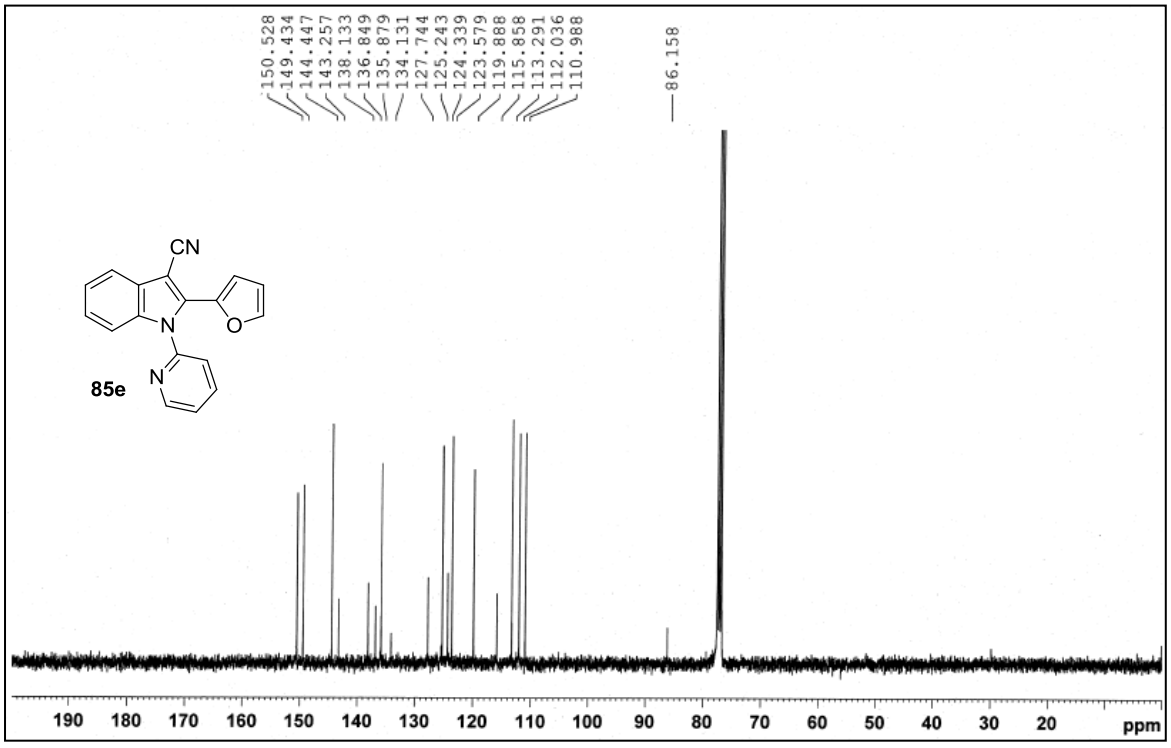
^{1}H NMR and ^{13}C NMR Spectra for compound **85a** in $CDCl_3$



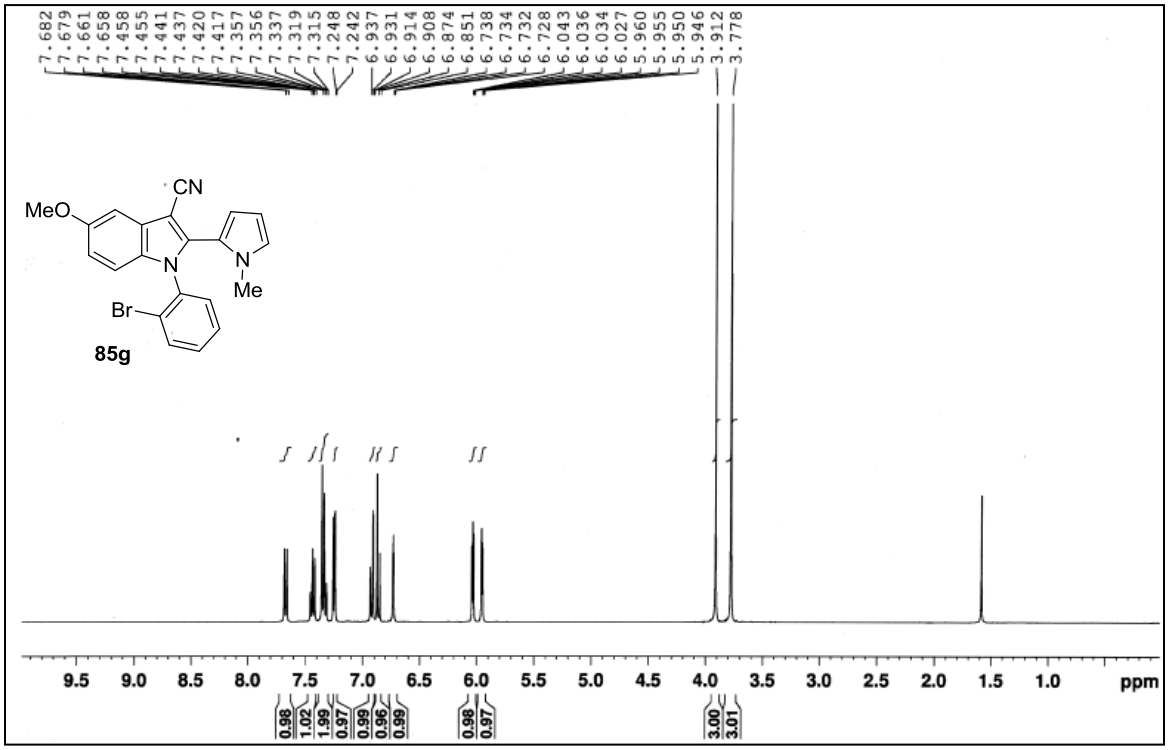


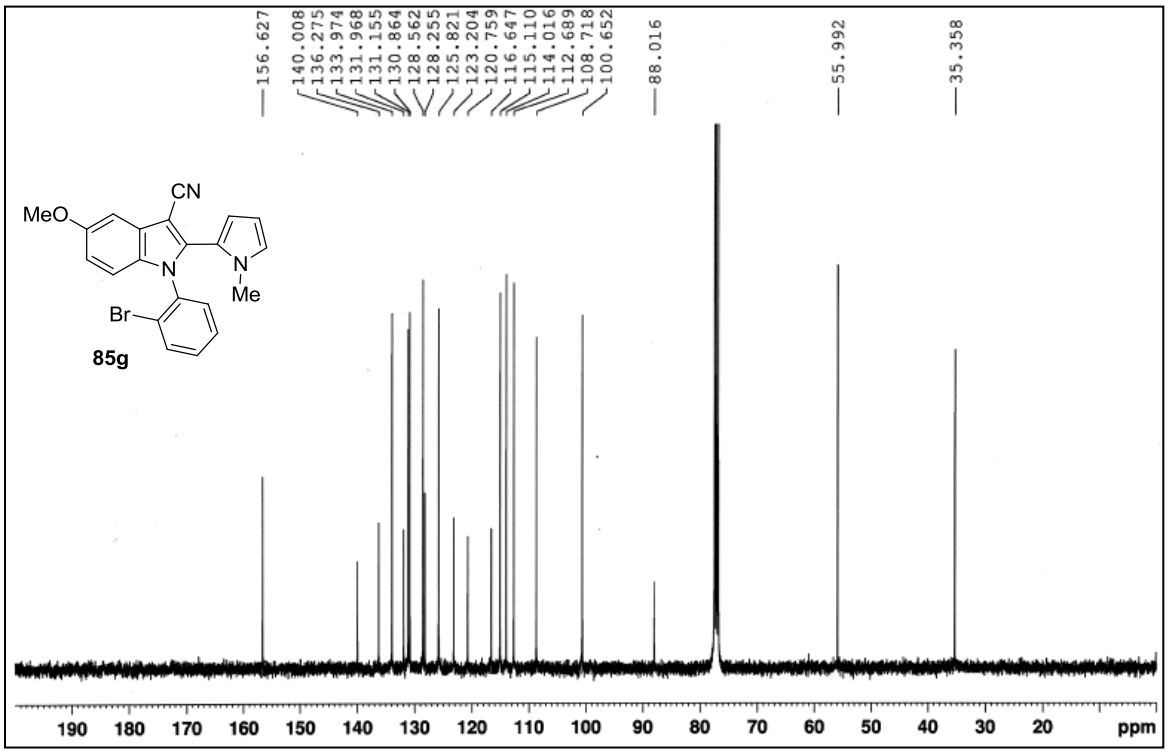
^{1}H NMR and ^{13}C NMR Spectra for compound **85b** in $CDCl_3$



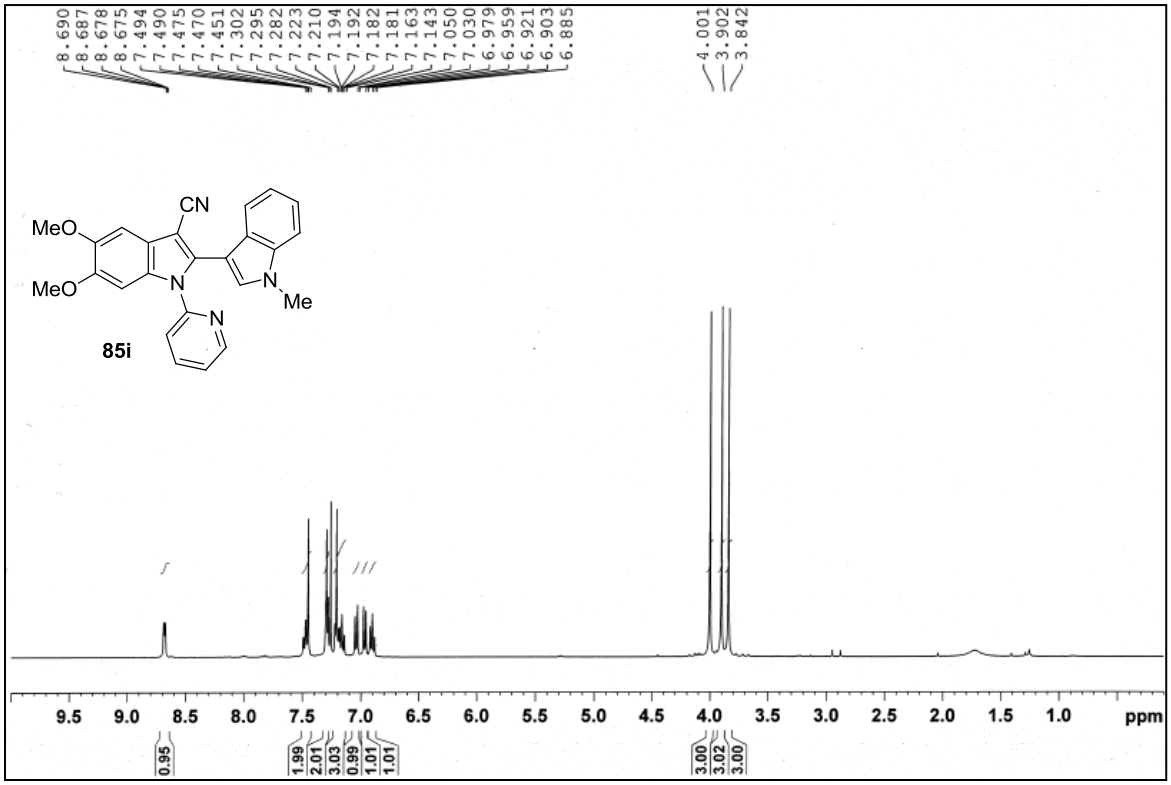


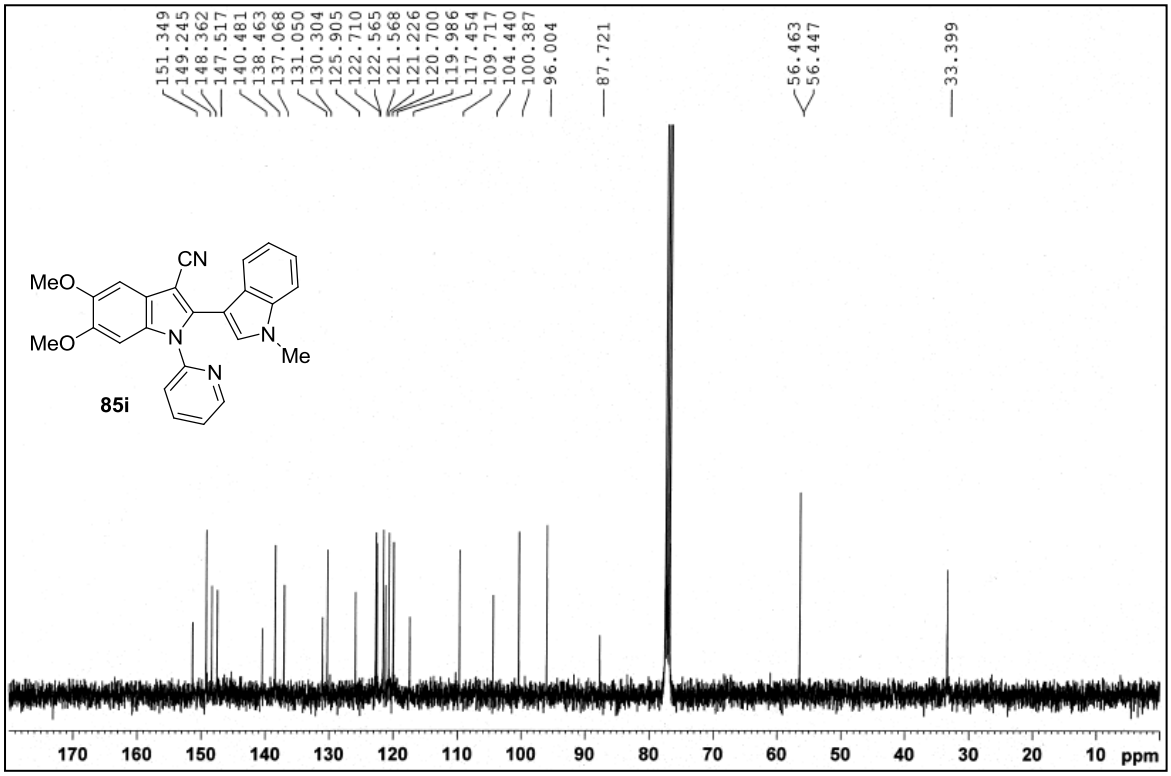
^{1}H NMR and ^{13}C NMR Spectra for compound **85e** in $CDCl_3$



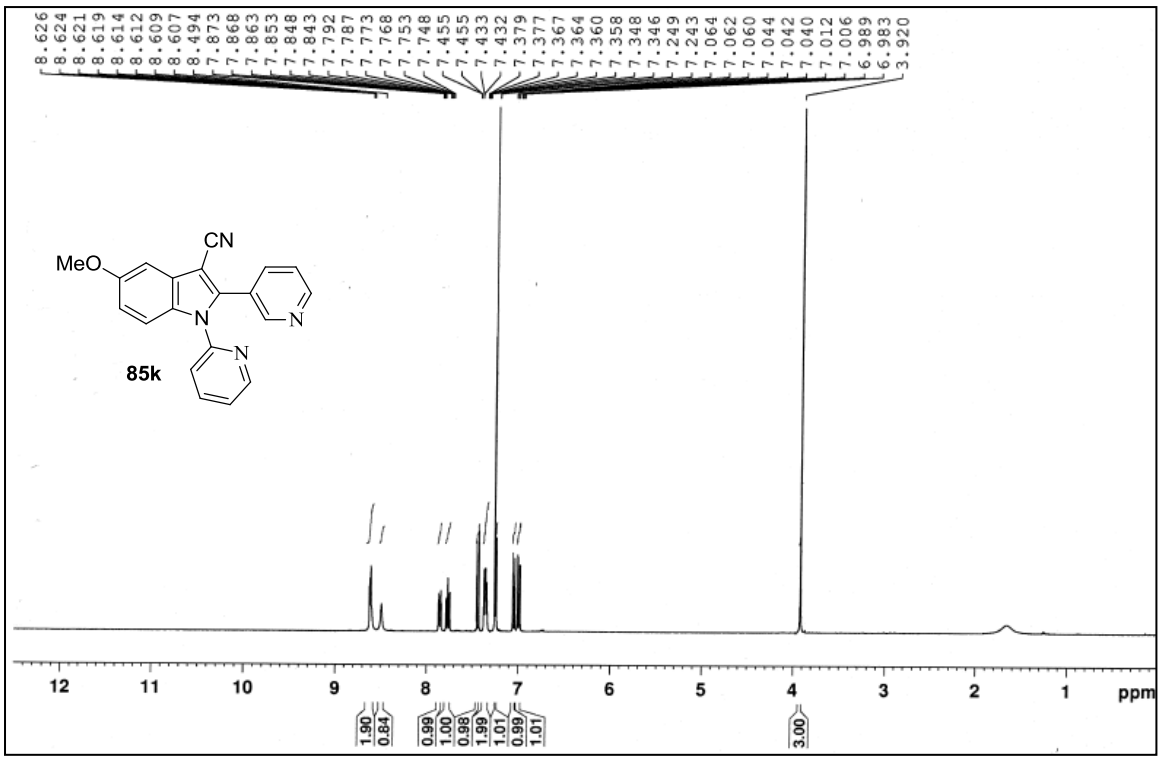


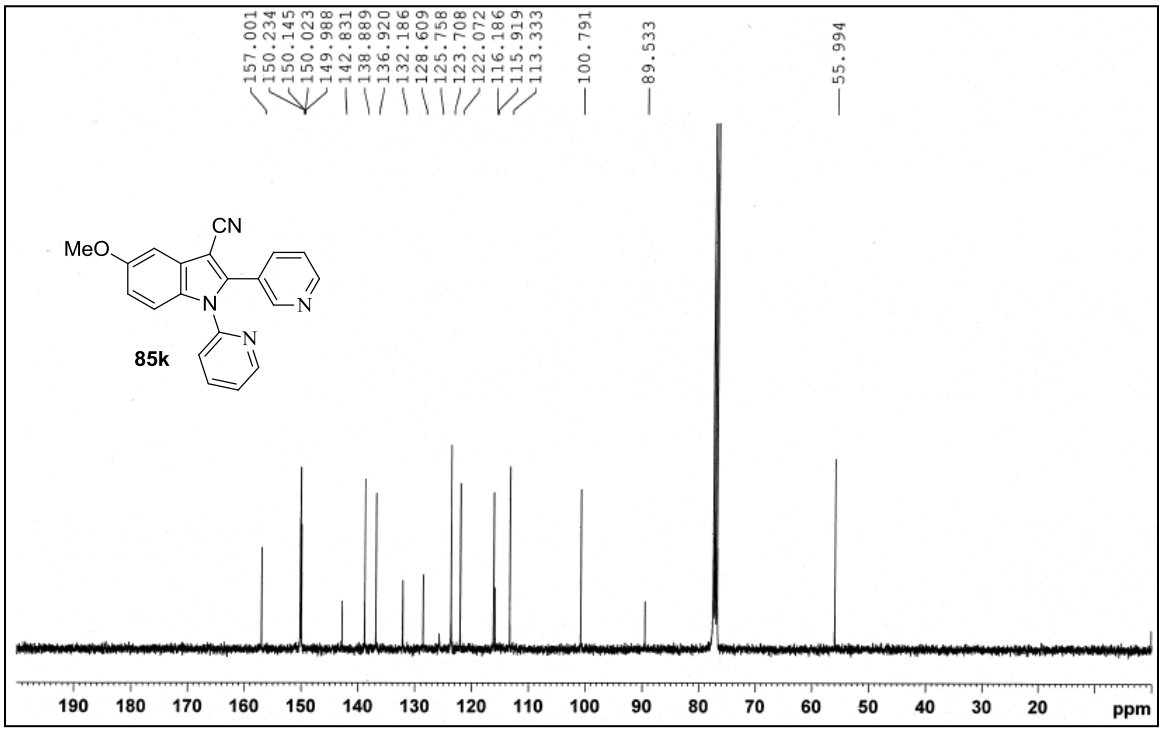
^{1}H NMR and ^{13}C NMR Spectra for compound **85g** in $CDCl_3$



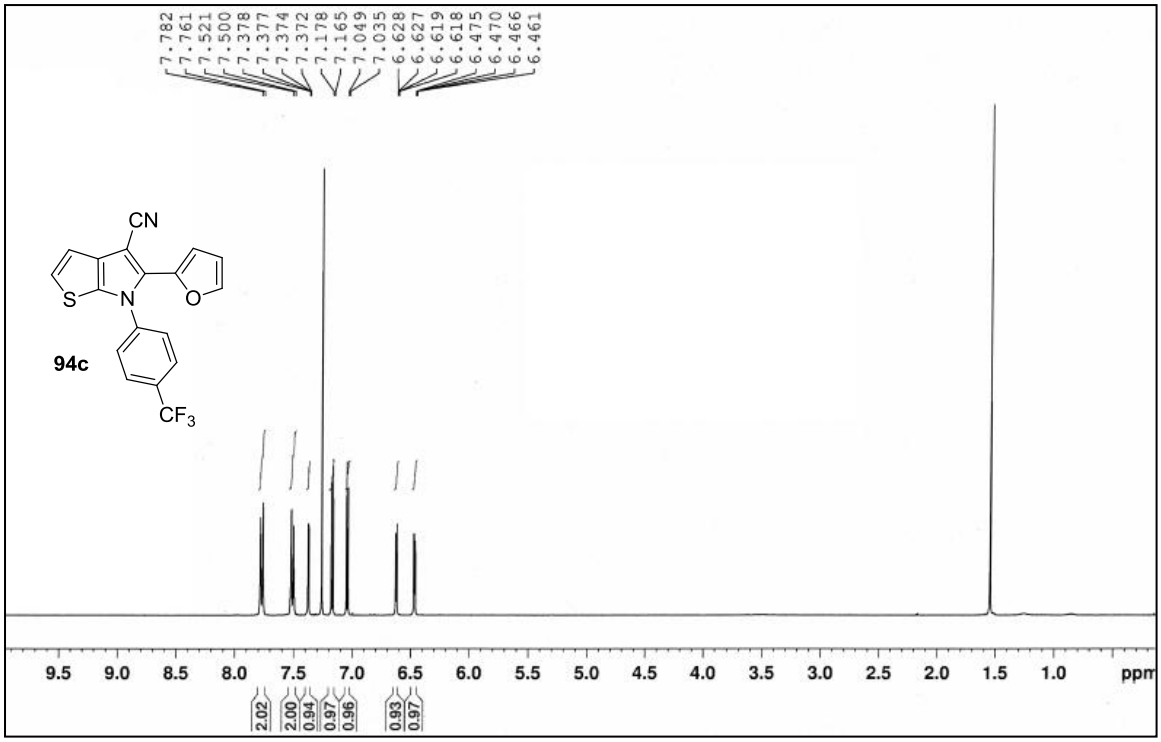


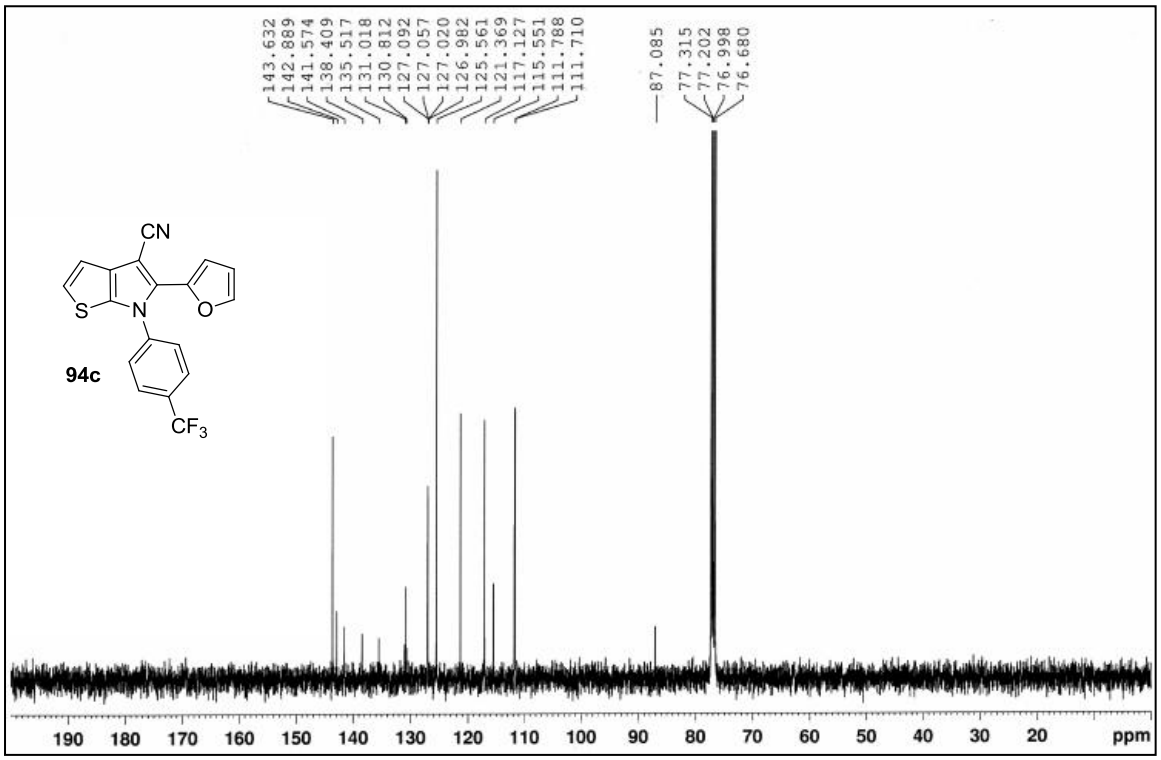
^{1}H NMR and ^{13}C NMR Spectra for compound **85i** in $CDCl_3$



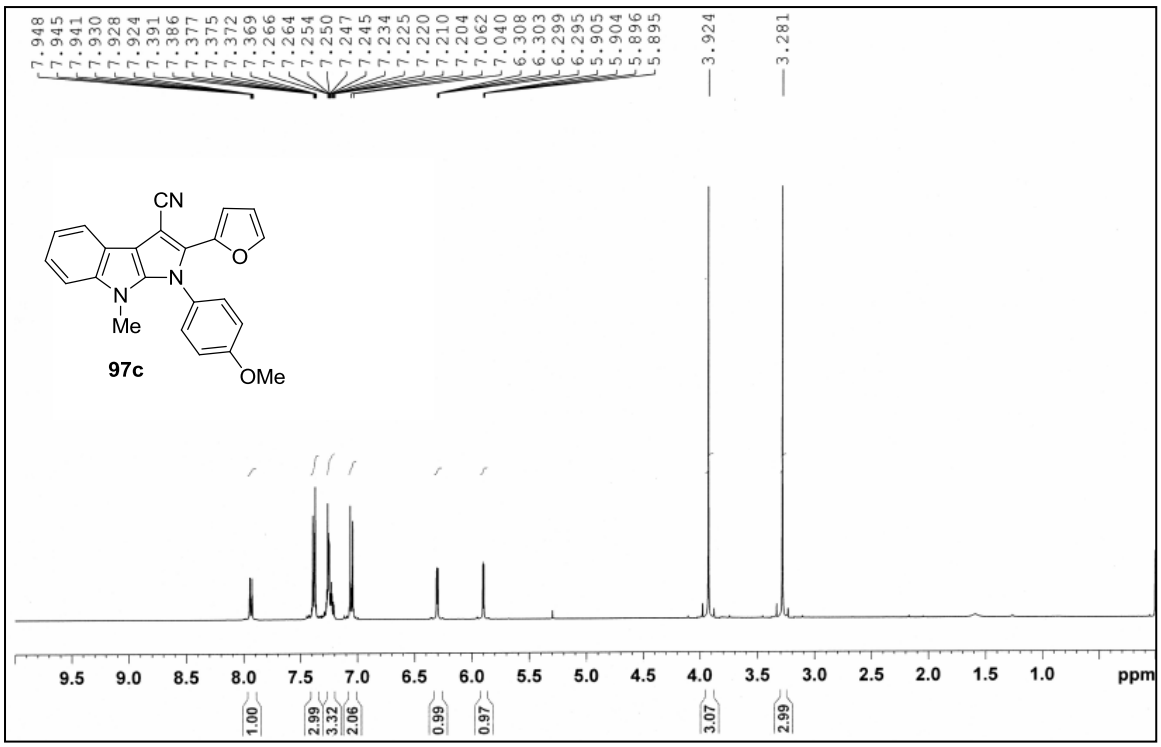


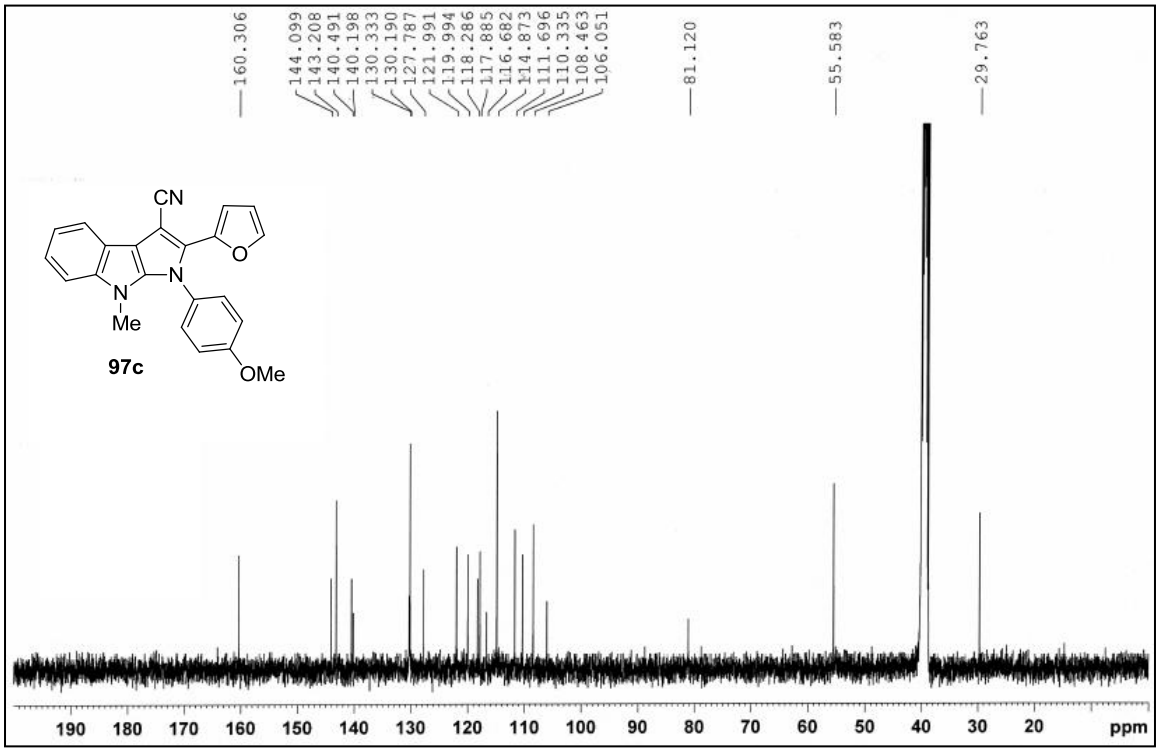
^{1}H NMR and ^{13}C NMR Spectra for compound **85k** in $CDCl_3$



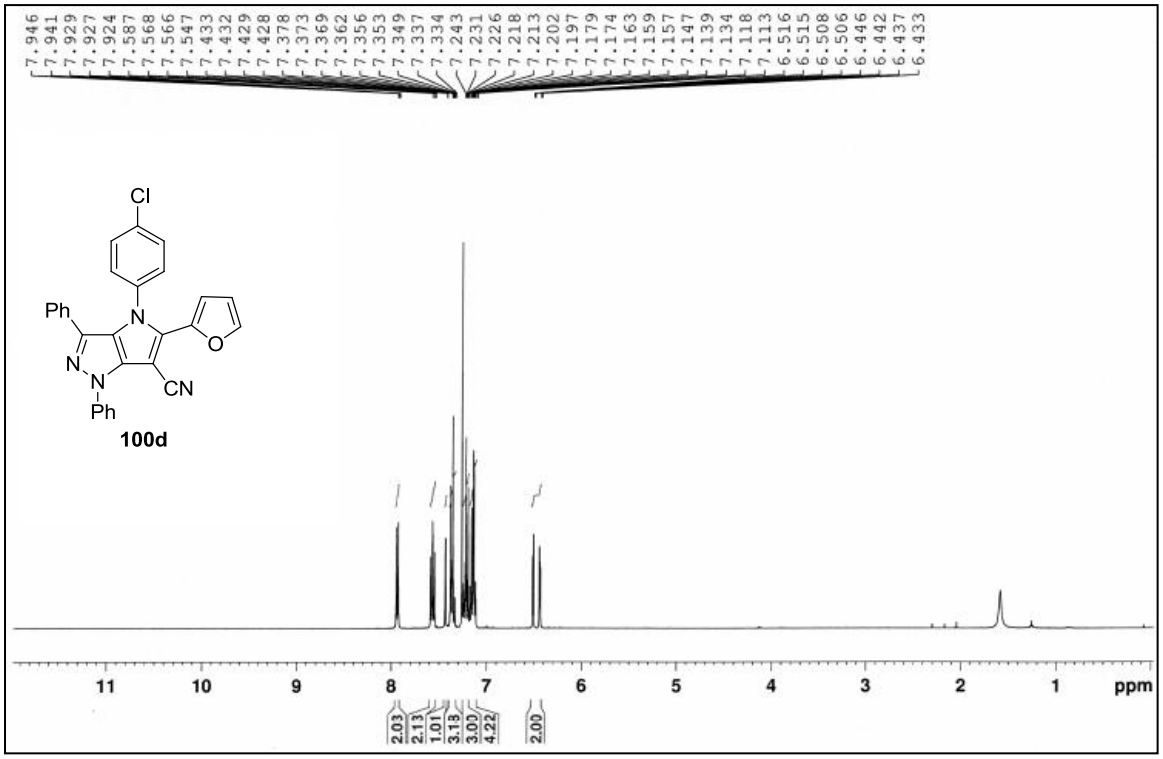


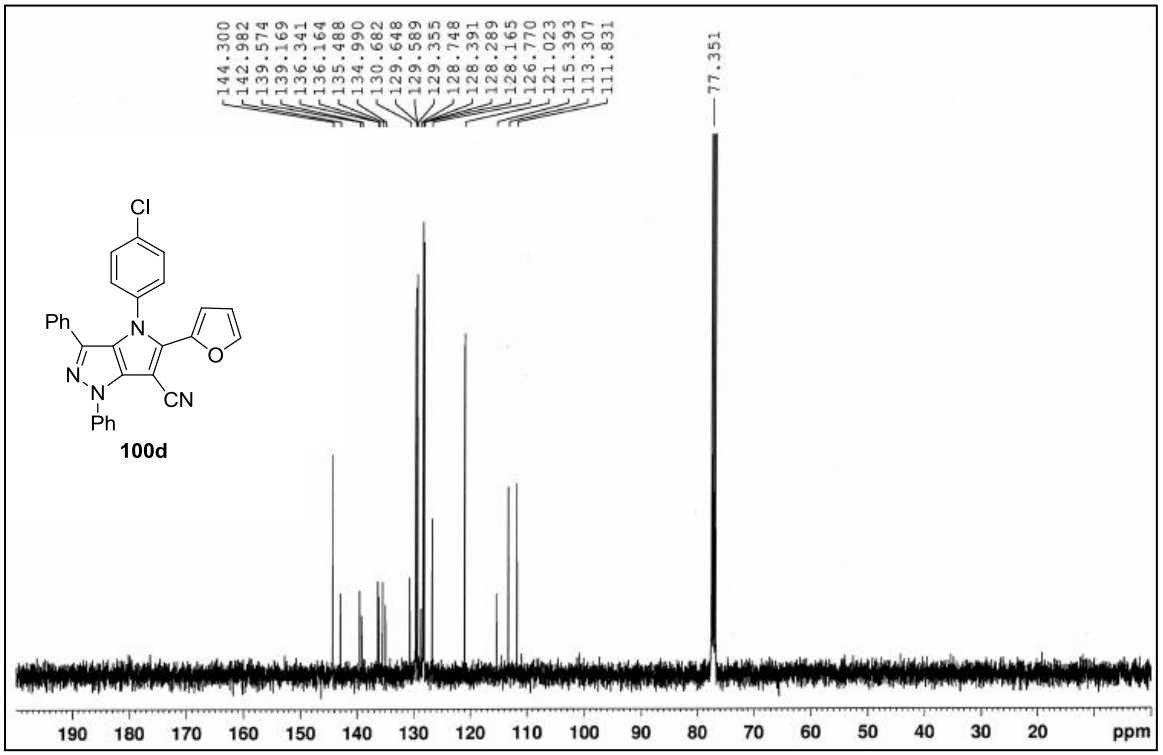
^{1}H NMR and ^{13}C NMR Spectra for compound **94c** in $CDCl_3$



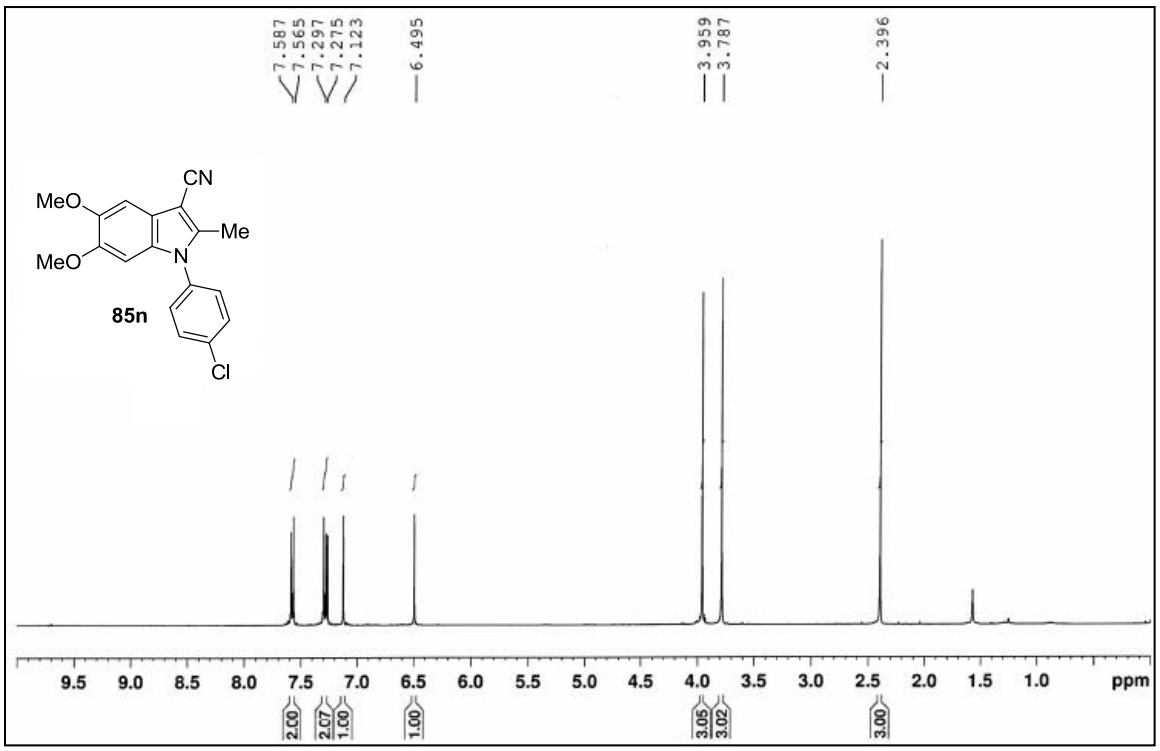


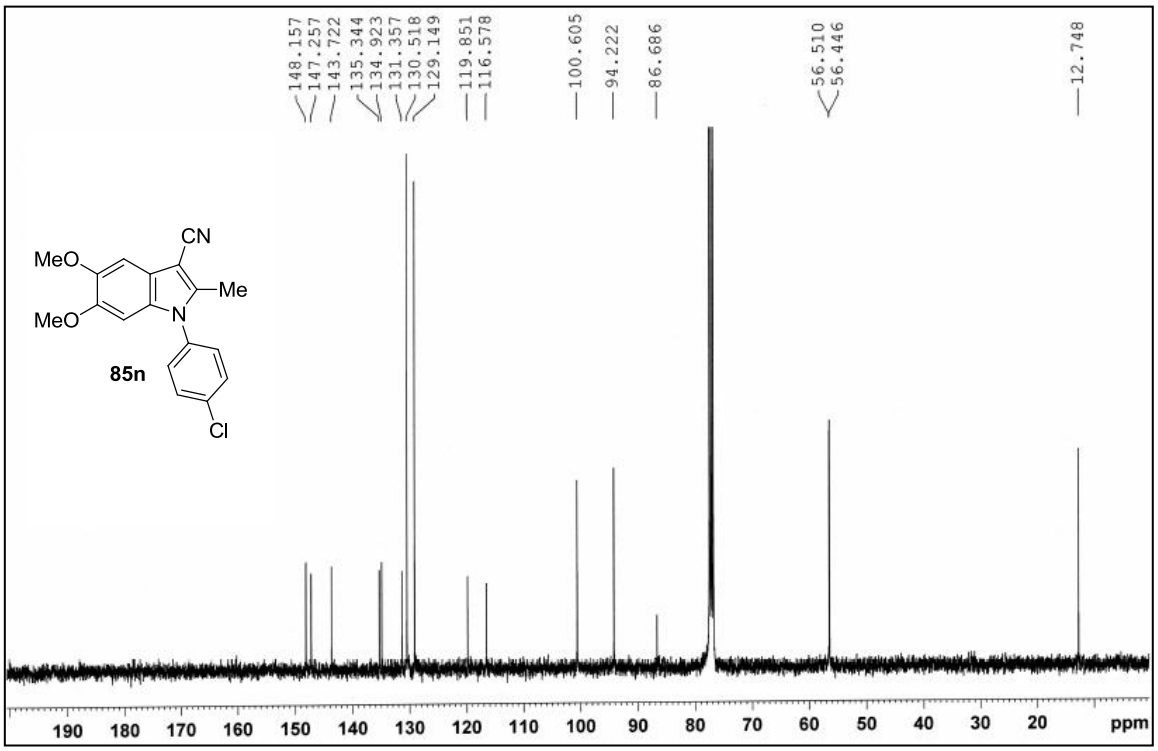
^{1}H NMR and ^{13}C NMR Spectra for compound **97c** in $CDCl_3$ and DMSO-d_6



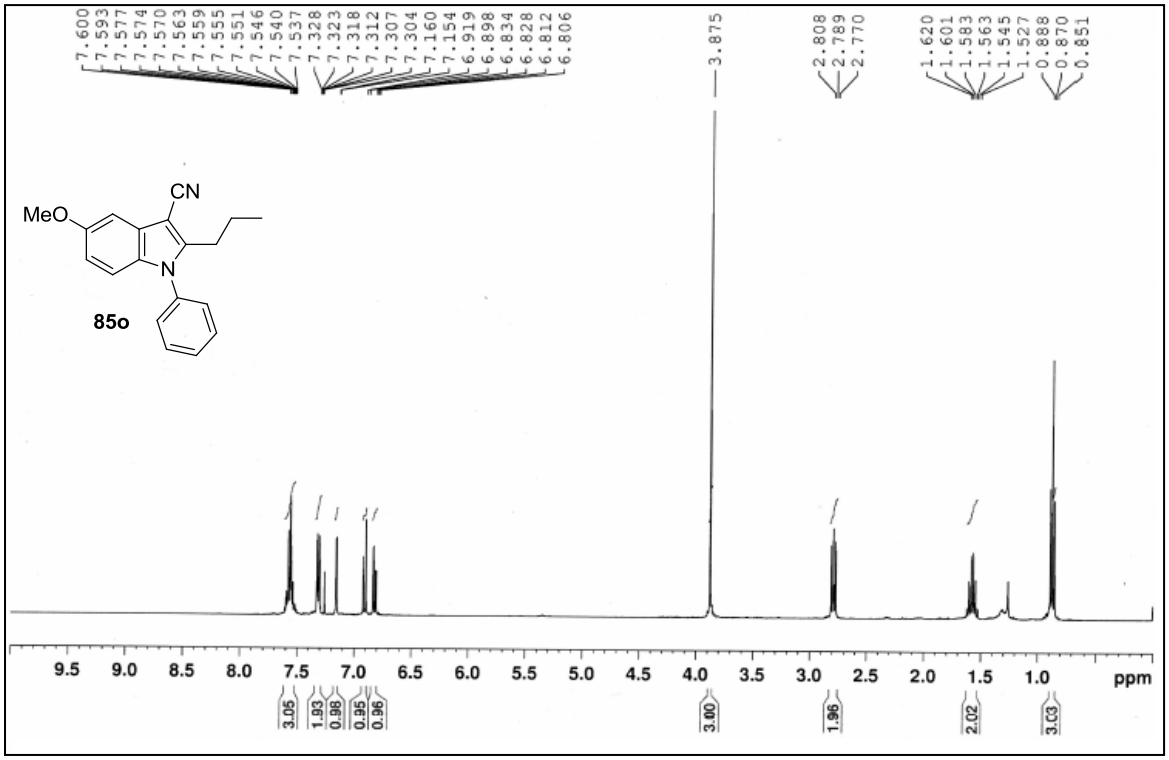


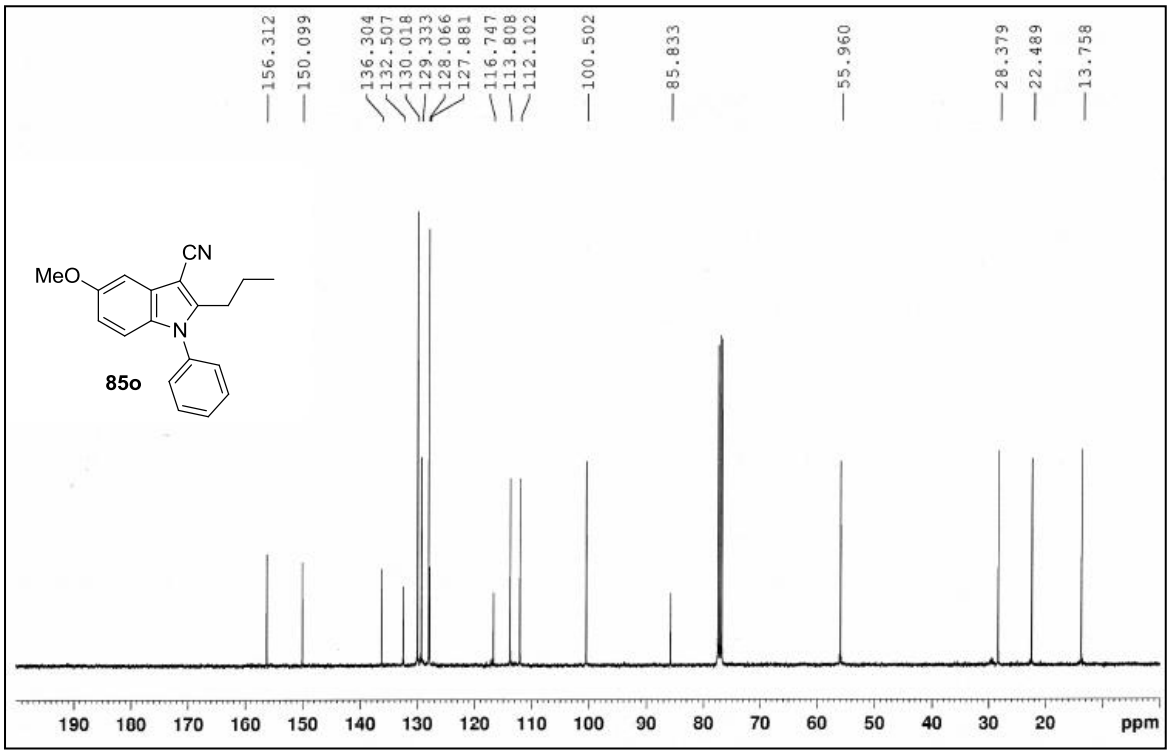
^{1}H NMR and ^{13}C NMR Spectra for compound **100d** in $CDCl_3$



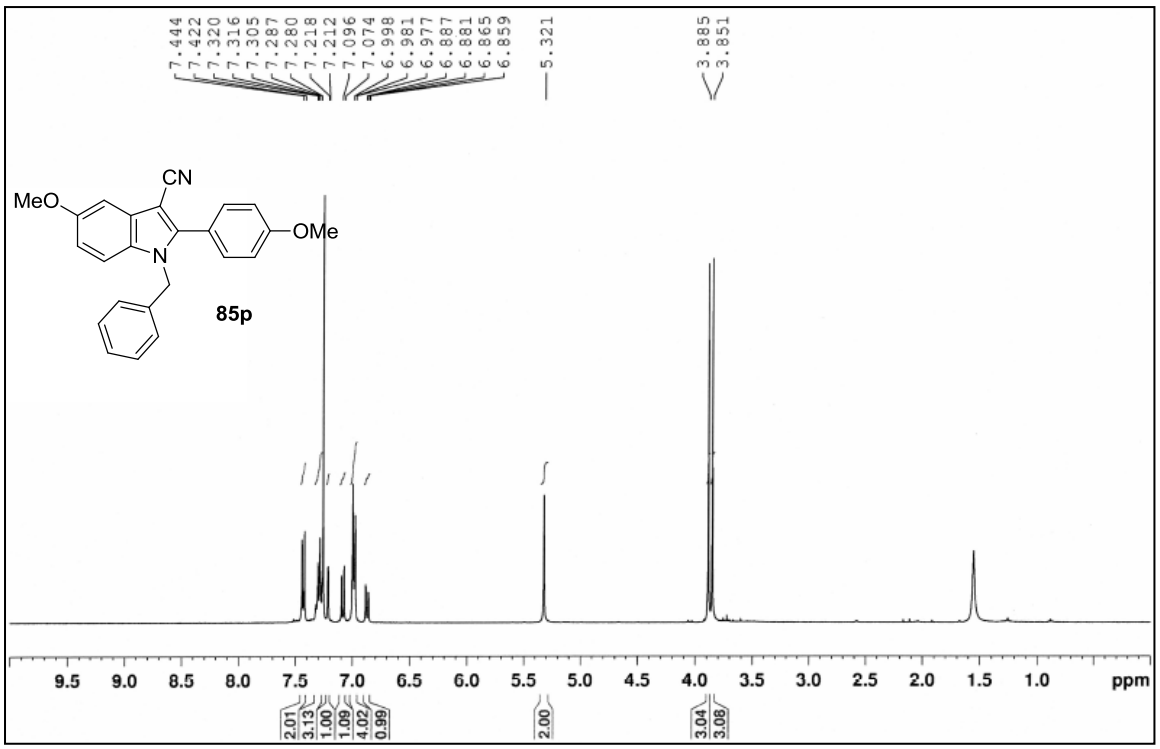


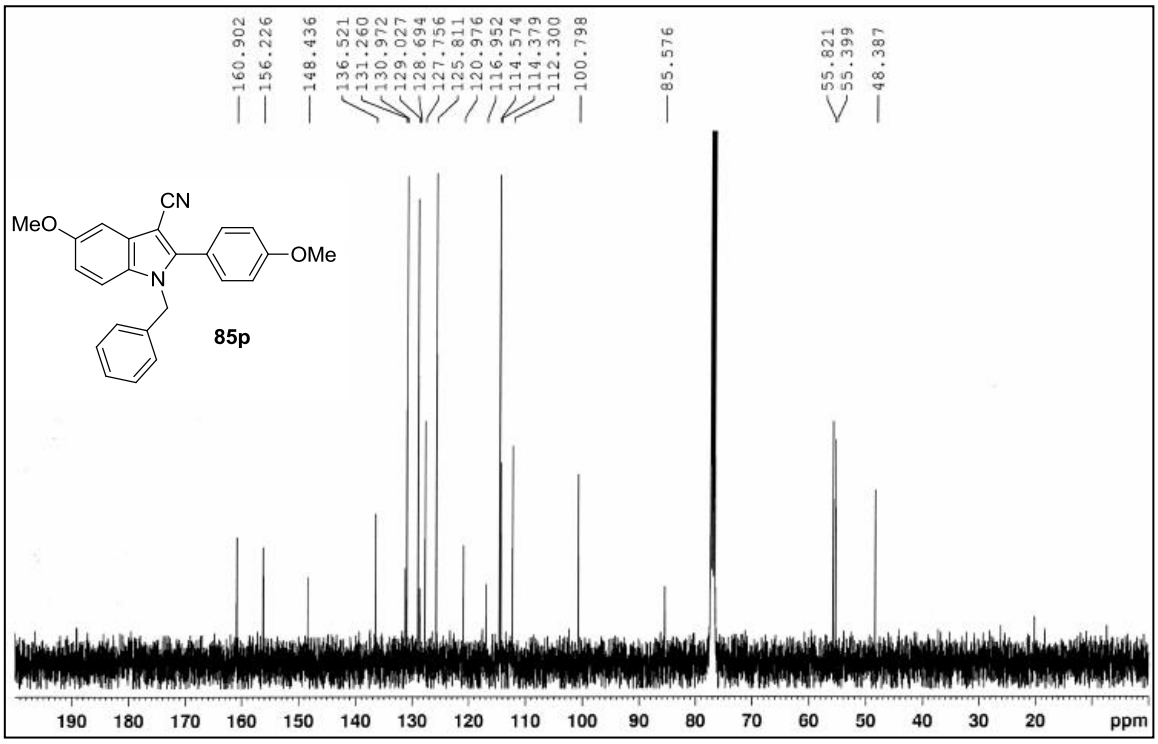
^{1}H NMR and ^{13}C NMR Spectra for compound **85n** in $CDCl_3$



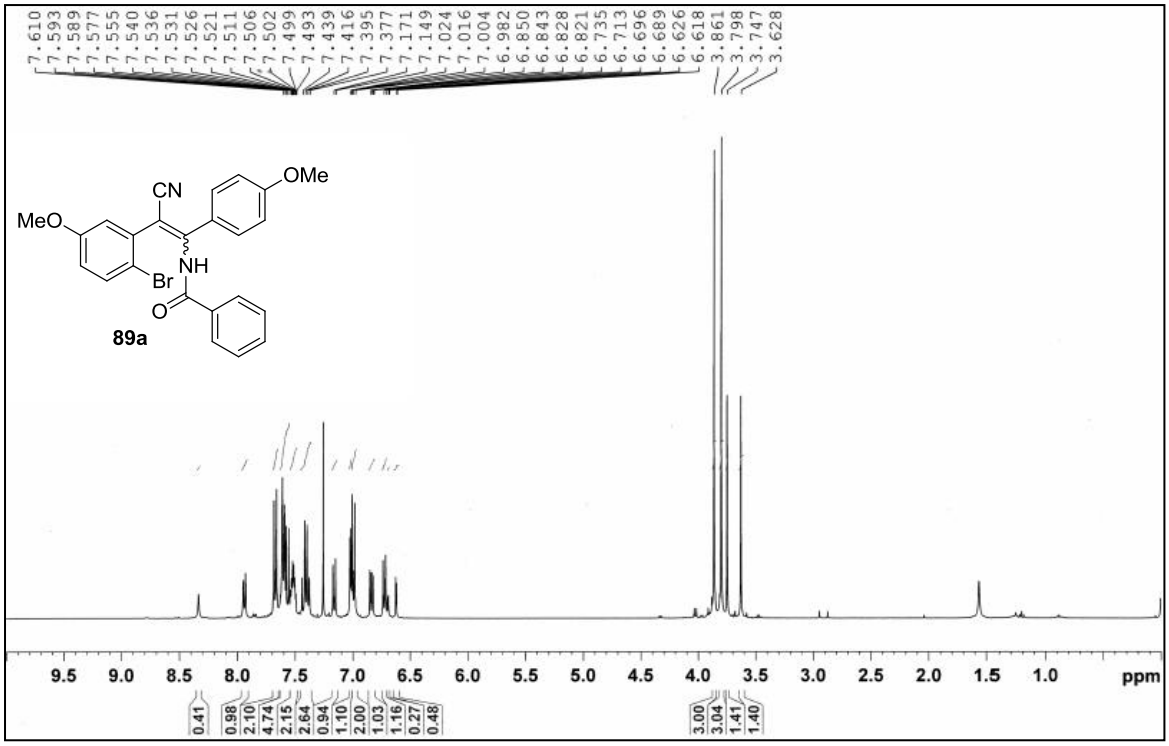


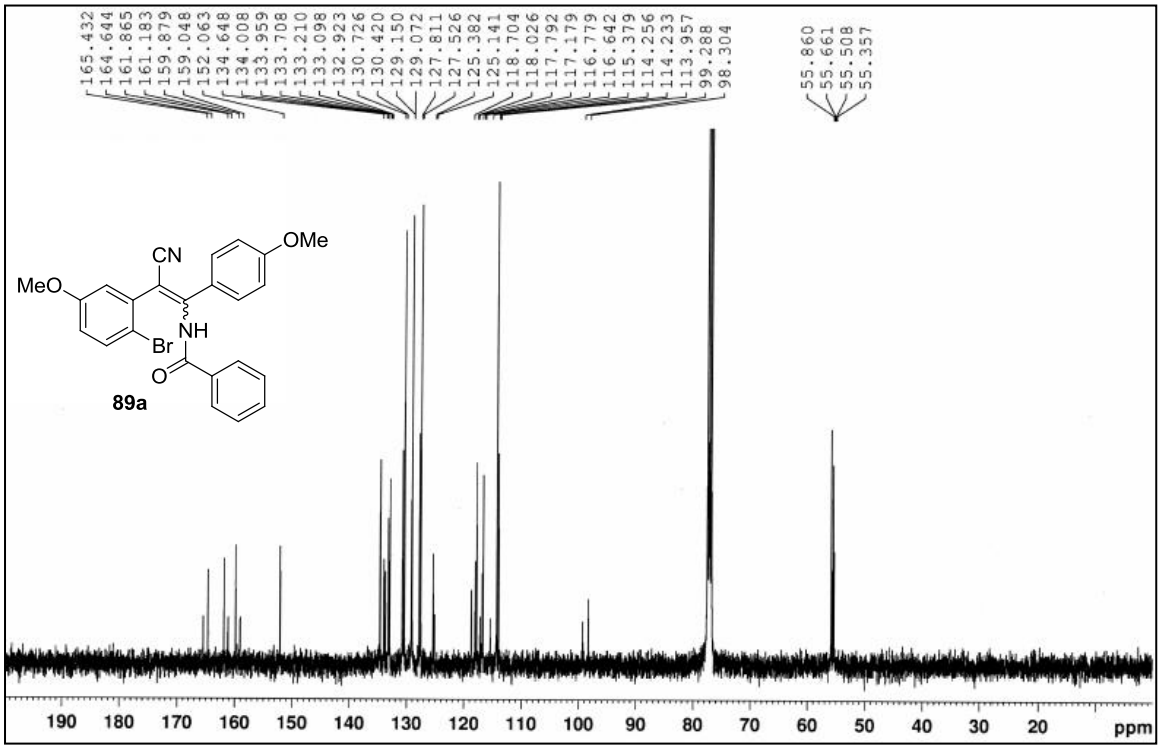
^{1}H NMR and ^{13}C NMR Spectra for compound **85o** in $CDCl_3$



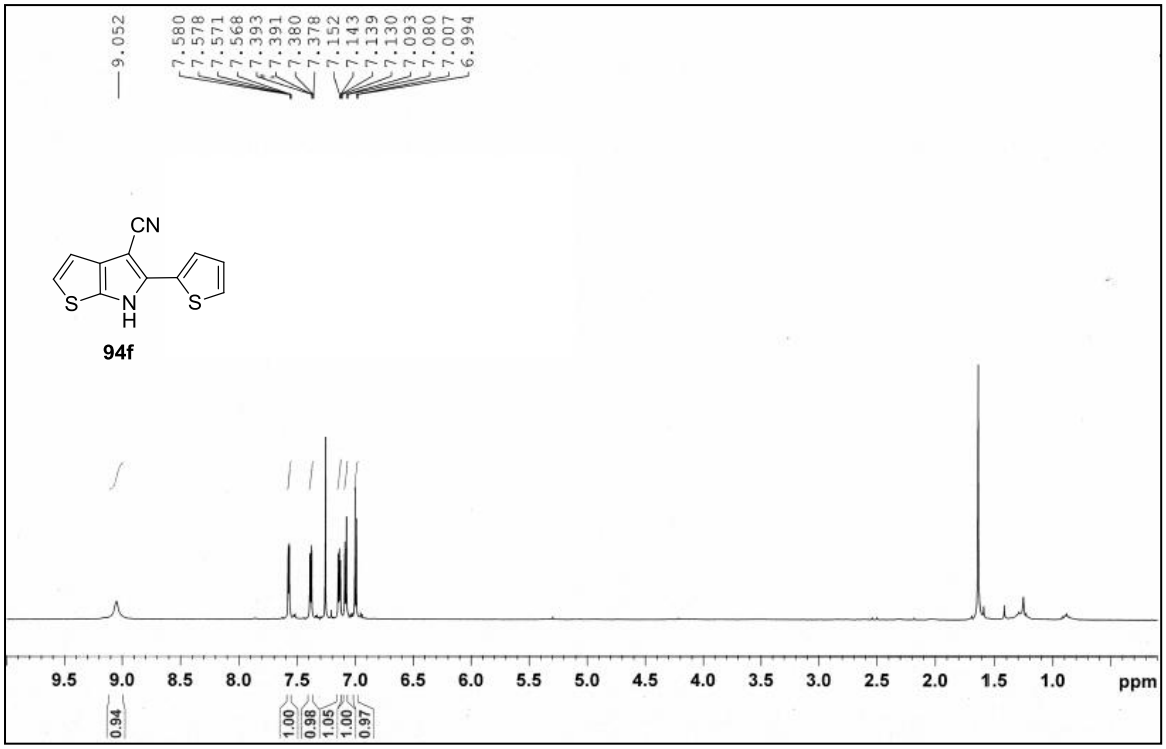


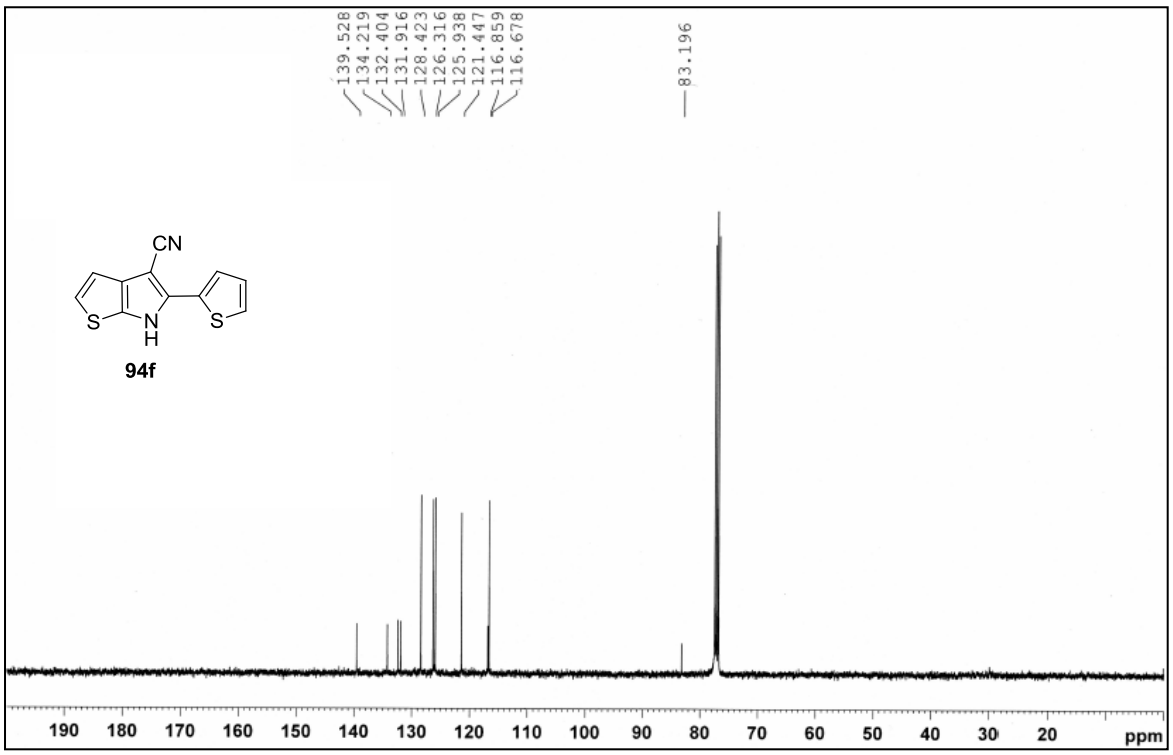
^{1}H NMR and ^{13}C NMR Spectra for compound **85p** in $CDCl_3$



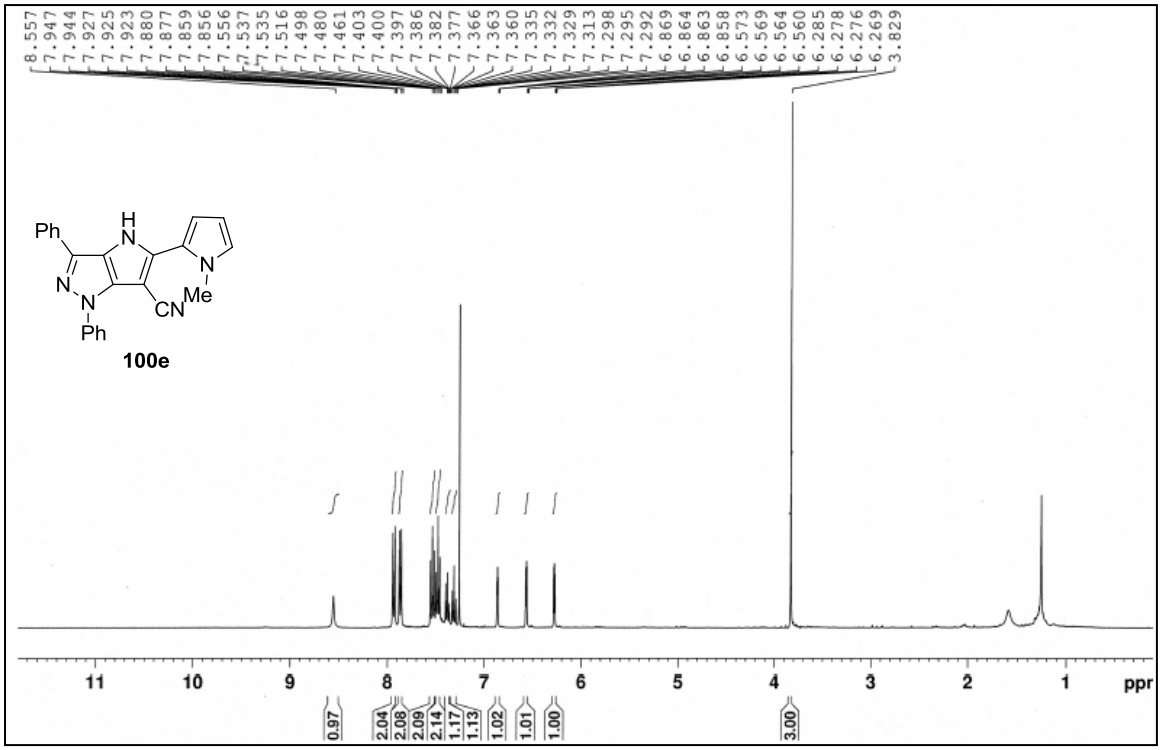


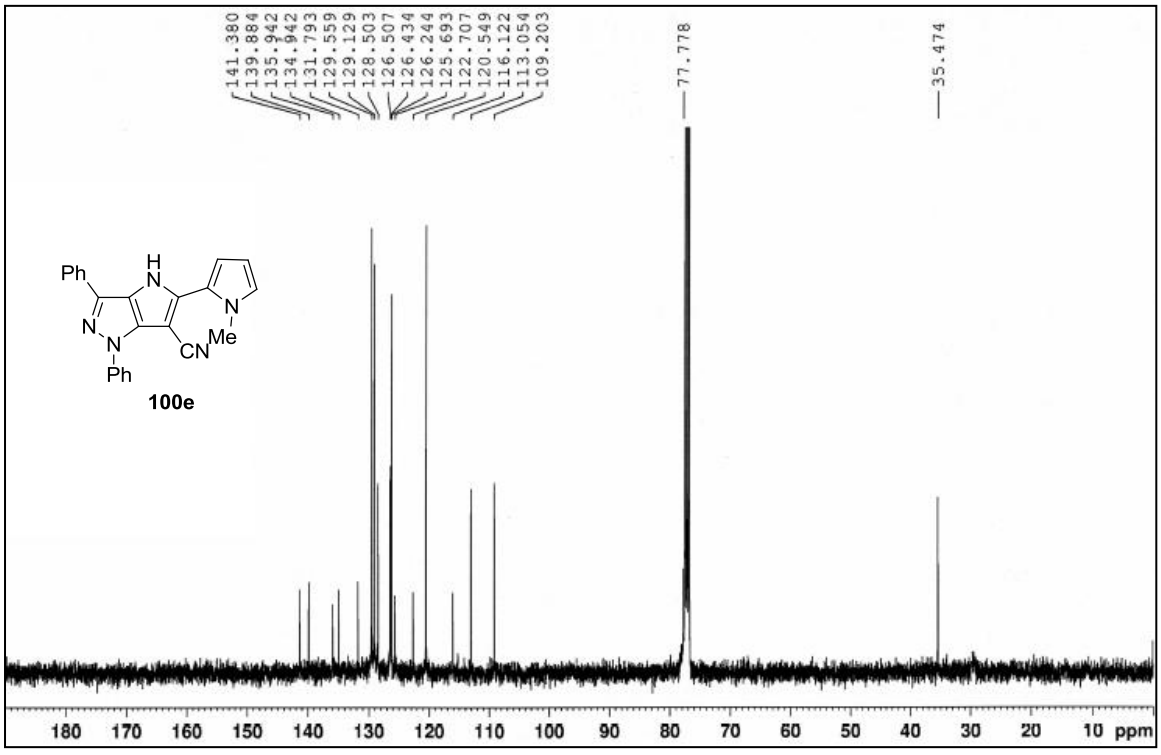
^{1}H NMR and ^{13}C NMR Spectra for compound **89a** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **94f** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **100e** in $CDCl_3$

Chapter 5

*Cyclocondensation of Arylhydrazines with 1,3-Bis(het) arylmonothio-1,3-diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 1-Aryl-3,5-bis(het) aryl pyrazoles with Complementary Regioselectivity**

5.1 Introduction

Substituted pyrazoles, although rarely found in nature, serve as important synthetic targets in medicinal chemistry and pharmaceutical industry.[1] Both 1,3,5-tri- and 1,3,4,5- tetrasubstituted pyrazoles constitute the core structure of several commercial drugs such as celebrex,[2] viagra,[3a] acomplia[3b] and 1-*N*-arylpyrazoles framework is present in many drug candidates as enzyme inhibitors such as COX-2 inhibitors (Searle Co.), IL-1-synthase inhibitors (Smith Kline Beecham Co.) and protein kinase inhibitors (Hoffmann LaRoche Co.). Some of these pyrazole derivatives are found to be potent and selective γ-aminobutyric acid (GABA)-gated chloride channel antagonists, as well as displaying anti-inflammatory, analgesic, sedative and hypnotic properties (Chart 1).[4] A few of the 1,5-diarylpyrazole derivatives have been shown to exhibit non-nucleoside

*The overall results of study described in this chapter have been published in *J. Org. Chem*. **2013**, *78*, 4960.

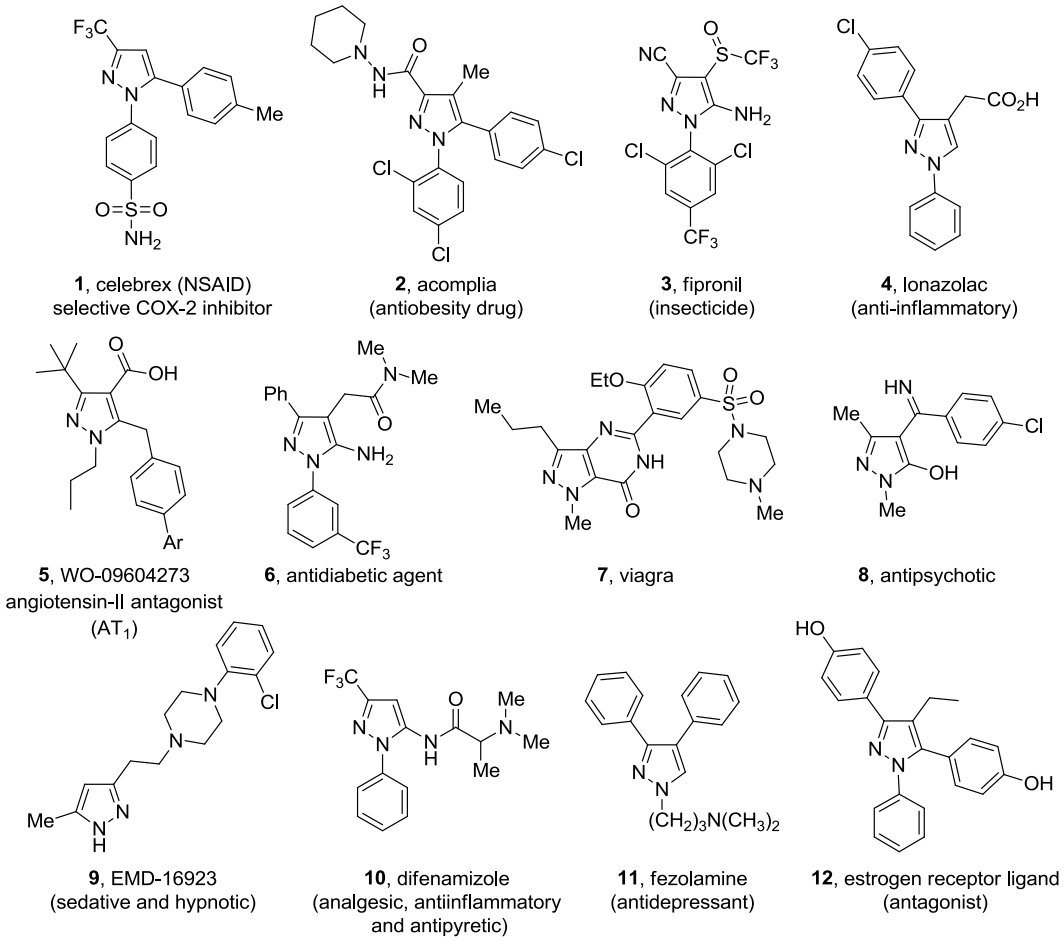
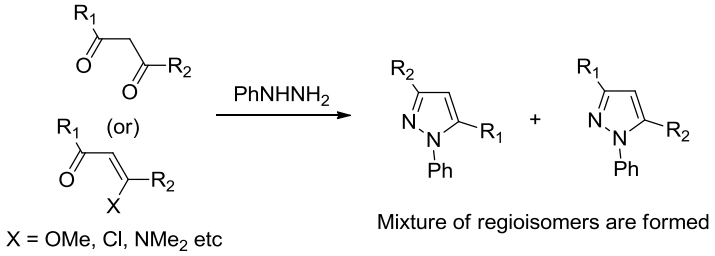


Chart 1

HIV-1 reverse transcriptase inhibitory activity and have also been identified as efficient ligands for estrogen receptor, displaying high binding affinities and selective transcriptional efficiency for ERα subtype.[5,6] Many of the substituted pyrazoles are useful in crop protection[7] as herbicides[8] and pesticides such as the insecticide fipronil (Chart 1).[9] Furthermore, substituted pyrazoles are also used as ligands in coordination chemistry,[10] as well as optical brightners,[11] UV stabilizers,[12] as photoelectron-induced electron transfer systems,[13] and supramolecular entity units.[14] As a result, continuous efforts have been devoted for the development of more general, efficient, versatile and regioselective methods to access substituted pyrazoles with a good level of molecular diversity.[1,15]

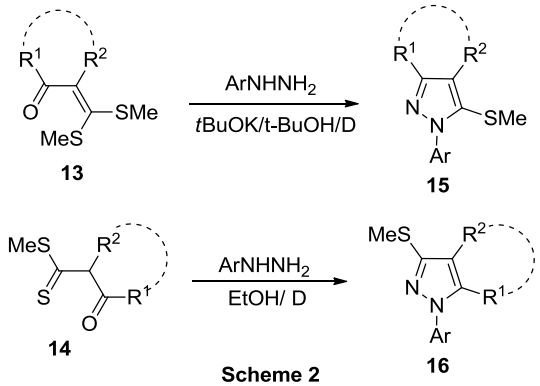
One of the most popular, oldest and frequently used methods for the synthesis of 1,3,5-trisubstituted pyrazoles is classical cyclocondensation of monosubstituted hydrazines with 1,3-dicarbonyl compounds (Knorr synthesis) or surrogates thereof.[16] However, the appealing generality of this method is somewhat vitiated due to the frequent formation of a regioisomeric mixture of unsymmetrical pyrazoles in these reactions

(Scheme 1).[4c-d,17] Modification of this method by employing *α,β*-acetylenic or olefinic ketones instead of 1,3-diketones usually allow better control of regioselectivity.[17e,18] However in the synthesis of 1-substituted 3,5-diarylpyrazoles, in which 3- and 5- aryl groups are similarly substituted, with only minor differences in electronic and steric nature of substituents, the complete control of regioselectivity becomes a daunting task. The other important methods for the synthesis of substituted pyrazoles, involving 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins and alkynes[15b,19] has found only limited applications, because these 1,3-dipoles are often difficult to prepare and potentially explosive.[19] Although recent efforts have greatly expanded the generality of these *de novo* approaches, each method has its scope, efficiency and limitations.[15-17,20] Since subtle variation and combination of arylation pattern on the pyrazole motif has profound effect on the biological activity,[2c,4e] development of efficient and general protocols for regiocontrolled synthesis of polysubstituted pyrazoles is highly desirable.



Scheme 1

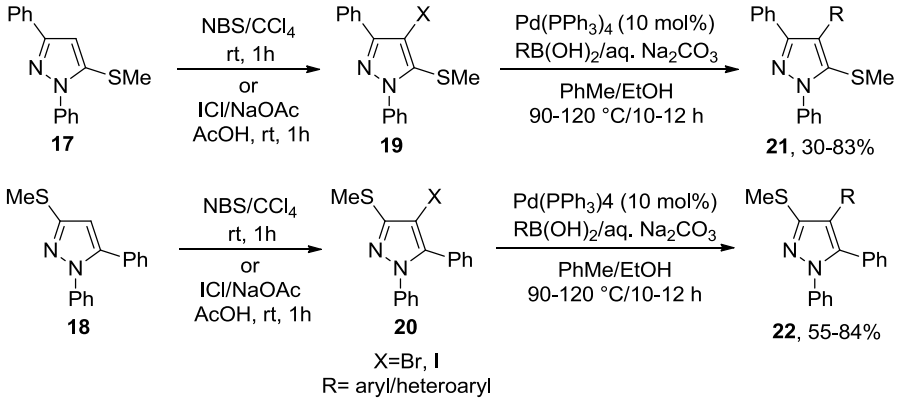
Our research group has earlier reported a regioselective synthesis of 1-aryl-3,4-(or 4,5-) substituted 5-(or 3-)(methylthio)-pyrazoles **15** and **16** by cyclocondensation of arylhydrazines with either *α*-oxoketene dithioacetals **13** or *β*-oxodithioesters **14**, respectively (Scheme 2).[21a]



Scheme 2

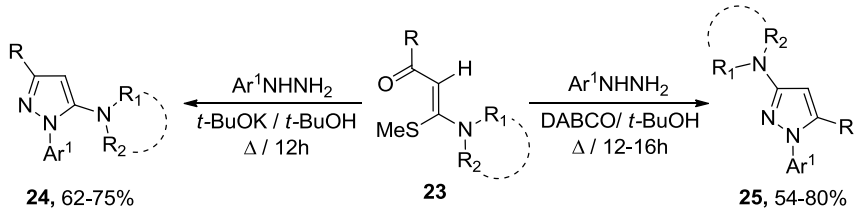
Further, our research group has recently described the synthesis of 1,3-(or 1,5-)diphenyl-4-aryl/heteroaryl-5-(or 3-)(methylthio)pyrazoles *via* Suzuki cross-coupling

reaction (Scheme 3). [21b] The pyrazoles unsubstituted at 4-position were treated with NBS or iodine monochloride to furnish the isomeric 4-bromo(or 4-iodo) 1,3-(or 1,5-)diphenyl-5-(or 3-) (methylthio)pyrazoles **19** and **20** in excellent yields. The pyrazole **19** and **20** were subsequently reacted with various (het)aryl boronic acids in the presence of $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base in toluene/ethanol/water solvent under reflux, affording 1,3,4,5-tetrasubstituted pyrazoles **21** and **22** in good yields as shown in Scheme 3.



Scheme 3

Similarly, our group has demonstrated that by proper manipulation of the reaction conditions and choice of base, it was possible to synthesize either 3-(or 5)-(cycloamino)-1,3 (or 1,5)-diaryl/alkyl substituted pyrazoles **24** or **25** respectively in highly regioselective fashion from the common α-oxoketene-N,S-acetal precursors **23** by their reaction with various arylhydrazines (Scheme 4). [21c]

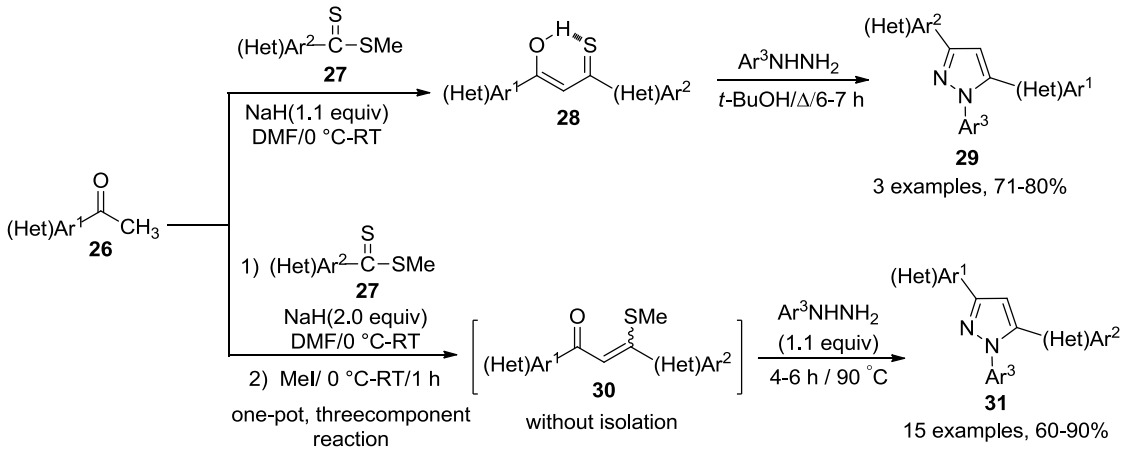


Scheme 4

In continuation of these studies, we became interested in monothio-1,3-diketones of general structure **26** potentially useful 3-carbon 1,3-bielectrophilic synthons for regiospecific construction of five and six membered heterocycles. Since, in Knorr pyrazole synthesis, the regioselectivity of the reaction relies on differential reactivity of two carbonyl groups of 1,3-diketones, it was speculated that cyclocondensation of monothio-1,3-diketones with various unsymmetrical heterobinucleophiles (i.e., monosubstituted hydrazines and hydroxylamine etc.) would be intrinsically more

regioselective, because of the significant difference in reactivity and electronic properties of carbonyl and thiocarbonyl groups. Our literature survey at this stage revealed that monothio-1,3-diketones and the corresponding β-thioxoesters have been known for a long time[22] and these intermediates have attracted considerable attention in the past as chelating agents, with promising applications, especially in analytical chemistry.[22-23] However synthetic potential of these compounds as useful precursors for regiospecific synthesis of five and six membered heterocycles is virtually unexplored.[24]

In the present chapter, we have developed a highly regioselective route for the synthesis of few 1-aryl-3,5-bis(het)arylpyrazoles **29** *via* cyclocondensation of arylhydrazines with monothio 1,3-diketones **28**. Further, we have also developed an efficient one-pot, three-component reaction for the synthesis of 1-aryl-3,5-bis(het)aryl pyrazoles **31** with complimentary regioselectivity directly from active methylene ketones **26** and arylhydrazines *via* formation of 1,3-bis(het)aryl-3-(methylthio)-2-propenones **30** (Scheme 5).



Scheme 5

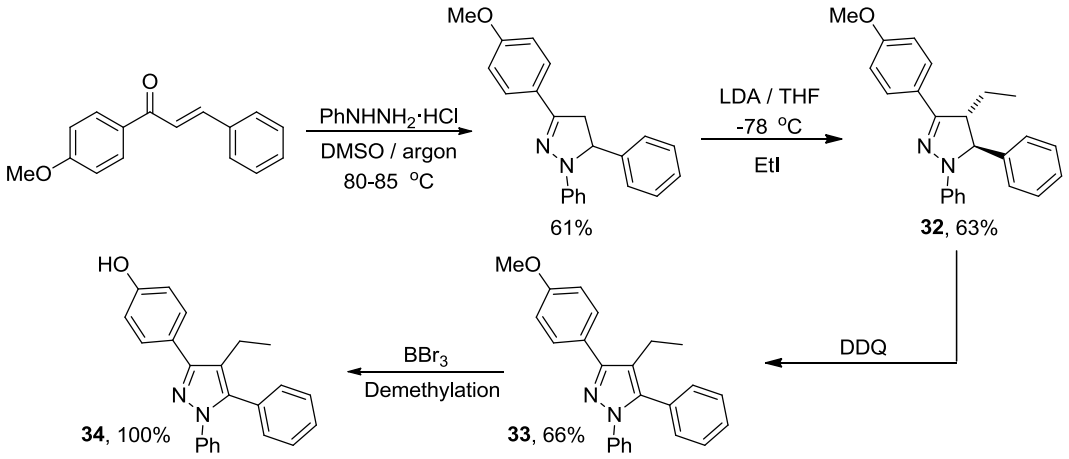
Before presenting these results of our investigation, a brief literature survey on some of the recent regioselective syntheses has been described in the following section.

5.2 Synthesis of substituted pyrazoles: A brief literature survey

5.2.1 Regioselective synthesis of 1-substituted-3,5-alkyl/aryl pyrazoles

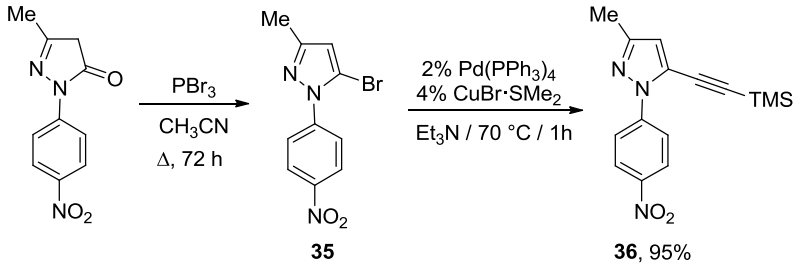
Katzenellenbogen and co-workers[17e] have developed a regioselective synthesis of 1,3,5-triaryl-4-alkylpyrazoles **34** as ligands for the estrogen receptors (Scheme 6). Thus, the reaction of α,β-unsaturated ketone with phenyhydrazine hydrochloride in DMSO at 80-85 °C yielded pyrazoline, which was alkylated with ethyl iodide in the presence of

LDA to give ethyl substituted pyrazoline **32** in good yield. The pyrazolines **32** was subsequently dehydrogenated with either MnO_2 or DDQ to afford 4-alkyl-1,3,5-triarylpyrazoles **33** which on demethylation with BBr_3 yielded the desired pyrazole **34** in quantitative yield (Scheme 6).



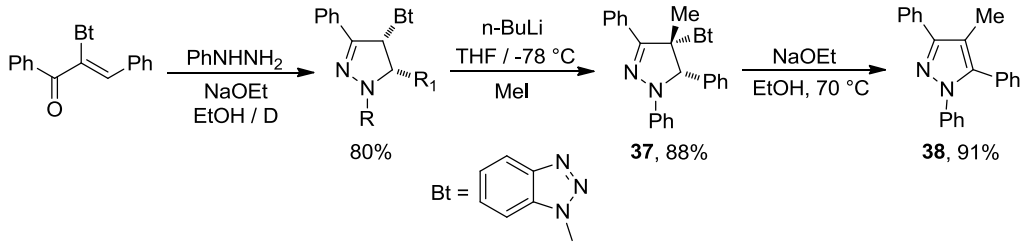
Scheme 6

Wang and coworkers[25] have described a regioselective synthesis of 3,5-disubstituted-1-arylpyrazoles *via* palladium catalyzed cross-coupling of 1-aryl-5-bromopyrazoles **35** with alkynes to afford unsymmetrical 3,5-disubstituted-1-arylpyrazoles such as **36** in excellent yields (Scheme 7). 1-Aryl-5-bromopyrazoles **35** were prepared from the corresponding 1-aryl-pyrazolones by reaction with PBr_3,as shown in Scheme 7.



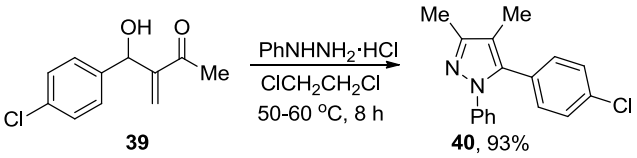
Scheme 7

Katritzky and coworkers[18a] have reported the regioselective synthesis of unsymmetrical 1,3,5-triaryl-4-alkylpyrazoles such as **38** by reaction of α-benzotriazolyl-α,β-unsaturated ketones with monosubstituted hydrazines and alkylation of the resulting pyrazolines **37** at 4-position followed by base induced elimination of benzotriazole (Scheme 8).



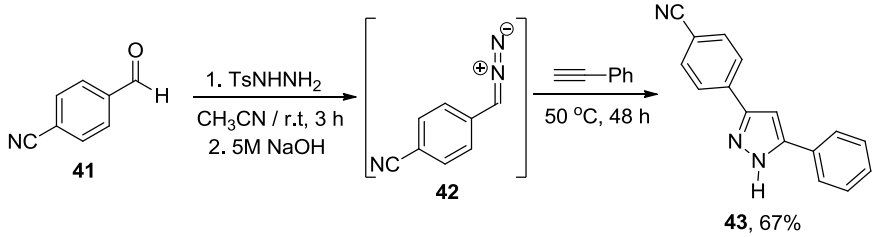
Scheme 8

Kim and coworkers have developed[4a] a regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles such as **40** involving the reaction of Baylis-Hillman adducts **39** with various alkyl and aryl hydrazine hydrochlorides in dichloroethane at 50-70 °C (Scheme 9).



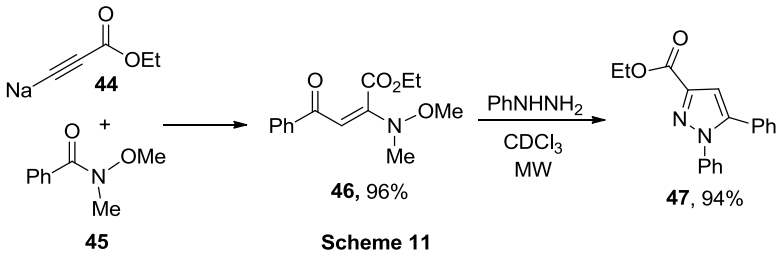
Scheme 9

Aggarwal and coworkers[19b] have demonstrated a novel one-pot protocol for the preparation of pyrazoles such as **43** by 1,3-dipolar cycloadditions of the corresponding diazo compounds **42** (generated *in situ* from aldehydes) with terminal alkynes (Scheme 10).



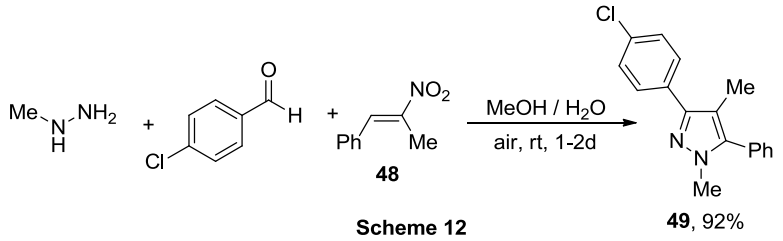
Scheme 10

Persson and Nielsen have described[26] a regioselective synthesis of 1,5-disubstituted pyrazole-3-carboxylates such as **47** by reaction of *N*-methoxy-*N*-methyl-β-enaminoketoesters such as **46** (obtained by the reaction of Weinreb amides **45** with Li or Na acetylide of ethyl propynoate **44**) with methyl or phenyl hydrazines in $CDCl_3$ under microwave irradiation as shown in Scheme 11.



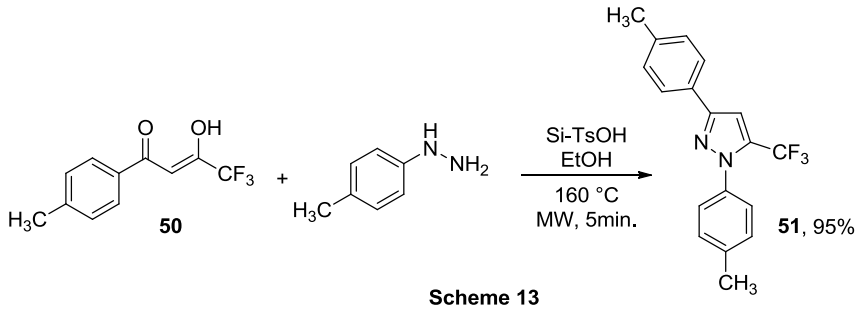
Scheme 11

Deng's research group[27] has reported a novel regioselective multicomponent synthesis of substituted pyrazoles such as **49** in one-pot protocol from *N*-monosubstituted hydrazines, aldehydes and nitroolefins **48** in MeOH at room temperature with concurrent elimination of nitro group (Scheme 12).



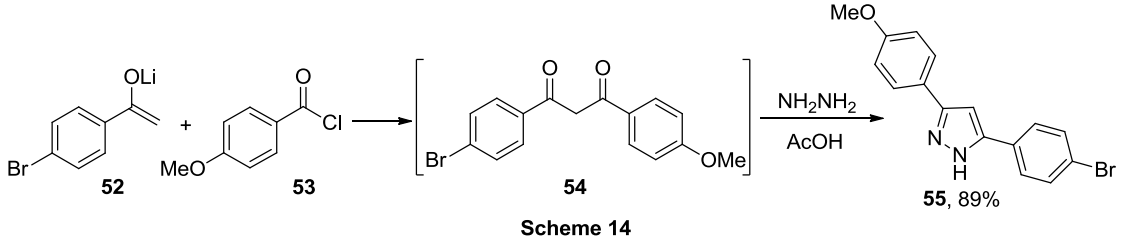
Scheme 12

Recently, Humphires and Finefield[28] have described a regioselective synthesis of 1,3-diaryl-5-trifluromethylpyrazoles such as **51** by cyclocondensation of 4-tolylhydrazine with trifluoromethyl substituted-β-diketone **50** in the presence of silica-supported *p*-toluenesulfonic acid under microwave conditions (Scheme 13).



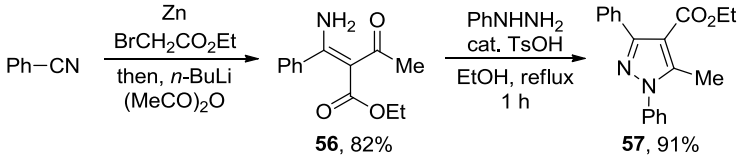
Scheme 13

Heller's group[17b] has also reported a rapid and general one-pot synthesis of NH-pyrazoles such as **55** by the reaction of *in situ* generated 1,3-diketones **54** (from enolates **52** and acid chloride **53**) with hydrazine (Scheme 14).



Scheme 14

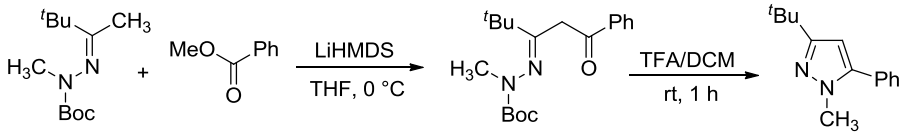
Young and coworkers[29] have developed a general route for the synthesis of 1-phenyl 2,3,4-substituted pyrazoles such as **57** from *β*-enaminoketoesters **56** (prepared by tandem Blaise-acylation). This method is applicable to a very broad range of substrates generating a diverse set of 3-aryl-5-alkyl, 3-alkyl-5-aryl, 3,5-diaryl and 3,5-dialkyl substituted pyrazoles in highly regioselective fashion (Scheme 15).



56, 82% **57**, 91%

Scheme 15

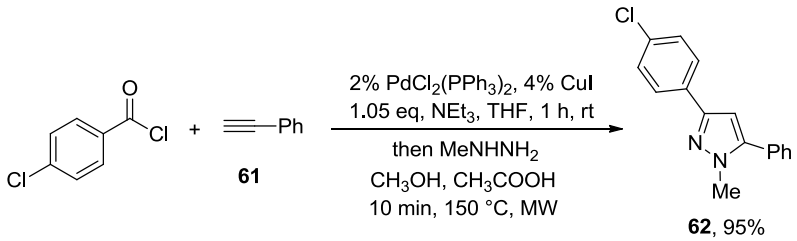
Tinarelli and coworkers[30] have shown that *β*-keto-(*N*-Boc-*N*-methy)hydrazones such as **59** undergo facile intramolecular cyclization in the presence of TFA to afford 1,3,5-trisubstituted pyrazole **60** in good yields (Scheme 16). These *β*-ketohydrazones **59** were obtained by LiHMDS mediated acylation of the corresponding *N*-Boc-*N*-methylhydrazones such as **58**.



58 **59** **60**, 69%

Scheme 16

Benjamin and Thomas[31] have developed an efficient synthesis of fluorescent 1,3,5-trisubstituted pyrazoles such as **62** from terminal alkynes such as **61**, acylchlorides and methyl hydrazines in a domino one-pot three component Sonogashira coupling/Michael addition/ cyclocondensation sequence as shown in Scheme 17.

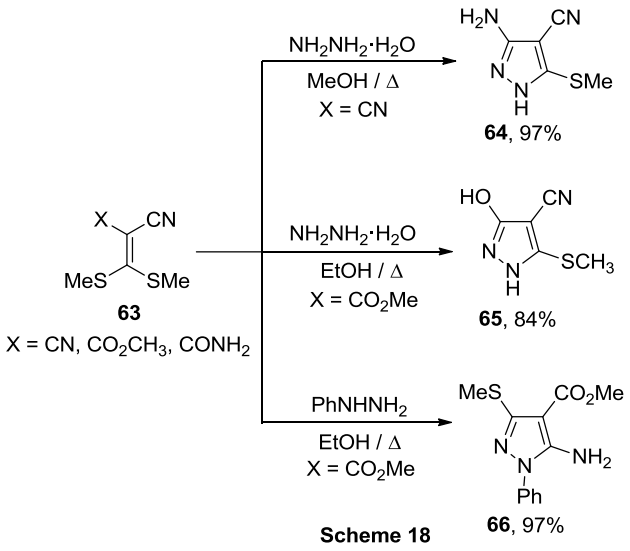


62, 95%

Scheme 17

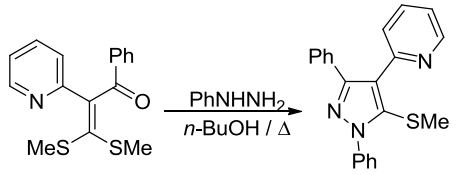
5.2.2 Pyrazoles from ketene dithioacetals and their variants

Gompper and Toepfl have first reported the synthesis of substituted (methylthio)pyrazoles of type **64-66** from the ketene dithioacetals **63** by reacting them with hydrazine, methylhydrazine or phenylhydrazine respectively (Scheme 18).[32]



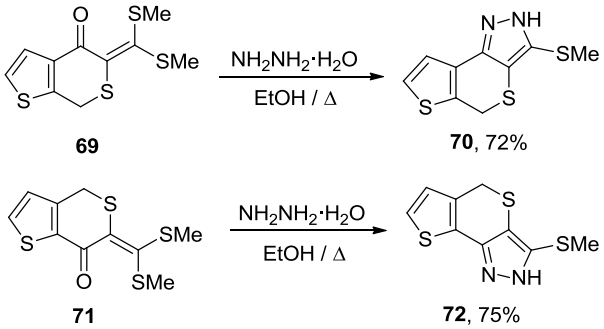
Scheme 18

Augustin and Doelling[33] have reported the synthesis of 1,3,4-triaryl-5-methylthio pyrazoles such as **68** involving the reaction of α-oxoketene dithioacetal **67** with various arylhydrazines in refluxing *n*-BuOH (Scheme 19).



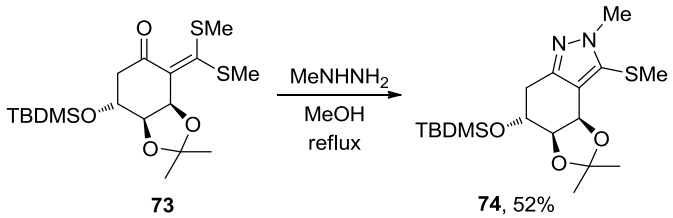
Scheme 19

De and coworkers[34] have described the synthesis of 2,5-dihydrothieno[3′,2′:4,5]- and 2,5-dihydrothieno[2′,3′:4,5]thiopyrano[3,2-*c*]pyrazoles **70** and **72** from the respective ketene dithioacetals **69** and **71** as shown in Scheme 20.



Scheme 20

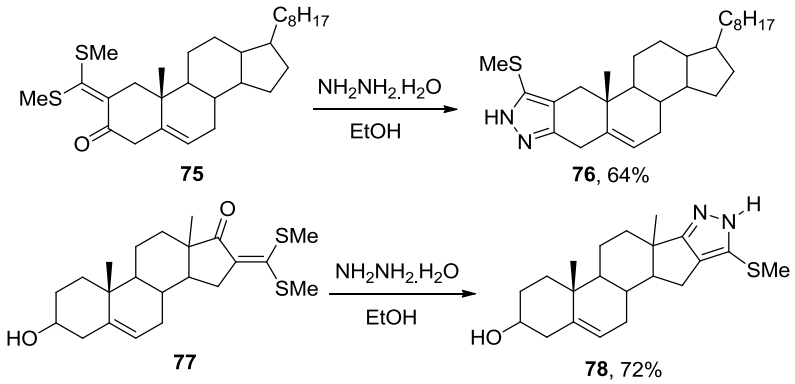
Peseke and coworkers[35] have developed the synthesis of pyrazoloannulated carbosugars **74** involving the reaction of (3*R*, 4*R*, 5*R*)-5-[(*t*-butyldimethylsilyl)oxy]-3,4-(isopropylidenedioxy)-2-[bis(methylthio)methylene]-1-cyclohexanone **73** with methyl hydrazine in refluxing methanol as shown in Scheme 21.



73 **74**, 52%

Scheme 21

Warjeet and coworkers[36] have prepared A- and D-ring fused steroidal pyrazoles **76** and **78** by the reaction of ketene dithioacetals **75** and **77** with hydrazine hydrate in refluxing ethanol (Scheme 22).



75 **76**, 64%

77 **78**, 72%

Scheme 22

From the foregoing discussion, it is evident that although a number of methods have been developed for regioselective synthesis of 1-aryl-3,5-substituted pyrazoles, each method has its scope and limitations. In continuation of our ongoing research programme on synthetic applications of polarized α-oxoketene dithioacetals and its variants, we have developed a highly regioselective route for the synthesis of 1-aryl-3,5-bis(het)arylpyrazoles **29** *via* cyclocondensation of arylhydrazines with monothio-1,3-diketones **28** (Scheme.5). Further, we have also developed an efficient one-pot, three-component reaction for synthesis of 1-aryl-3,5-bis(het)aryl pyrazoles **31** with complimentary regioselectivity directly from active methylene ketones *via* formation of 1,3-bis(het)aryl-3-(methylthio)-2-propenones **30** followed by addition of arylhydrazines (Scheme 5). These results have been highlighted in the following section.

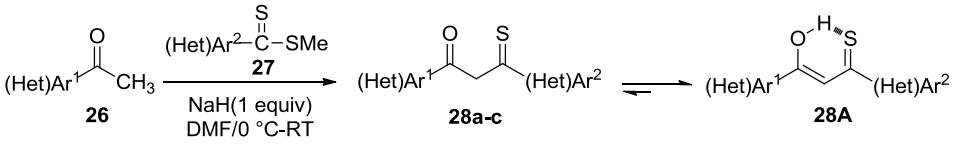
5.3 Results and discussion

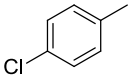
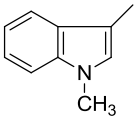
5.3.1 Synthesis of 1,3-bis(het)aryl monothio-1,3-diketones 28a-c

The desired 1,3-substituted monothio-1,3-diketones **28a-c** were prepared in excellent yields *via* modification of the reported procedure[22] by base induced thioacylation of various (het)arylmethyl ketones **26** with dithioesters **27** in the presence of

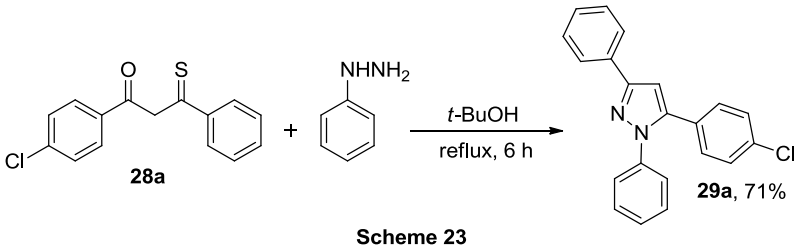
sodium hydride in DMF (Table 1). The structures of all these newly synthesized monothio 1,3-diketones **28a-c** were established with the help of spectral and analytical data. The ^{1}H NMR spectra of these monothio ketones showed that they exist in thioenol tautomeric form **28A** as evident from the presence of a low field signal at δ 16.2-12.02 due to intramolecular hydrogen bonded enolic OH group as reported earlier.[24c,39]

Table 1. Synthesis of monothio-1,3-diketones 28a-c



Entry	28	(Het)Ar^1	(Het)Ar^2	% Yield
1	**28a**			84
2	**28b**			86
3	**28c**			90

5.3.2 Regioselective synthesis of 1-aryl-3,5-bis(het)aryl/annulated pyrazoles from1,3-monothio-*β*-diketones



Scheme 23

The reaction of unsymmetrically substituted 1,3-monothio-*β*-diketone **28a** with phenylhydrazine was first examined under varying conditions with a view to optimize the reaction conditions for regioselective synthesis of 1,3,5-triarylpyrazole **29a** (Scheme 23). Our studies revealed that the reaction of **28a** and phenylhydrazine was very clean under neutral conditions in the presence of protic solvent like *t*-BuOH yielding only one product, whereas under mild acidic or basic conditions, intractable mixture of several products were formed. Best results were obtained when equimolar quantities of **28a** and phenylhydrazine were refluxed in *t*-BuOH for 6 h, furnishing only one product, which was characterized as 1,3-diphenyl-5-(4-chlorophenyl) pyrazole **29a** (71%) on the basis of

its spectral and analytical data (Scheme 23) and by comparison with the reported data.[18b,24c] The regiochemistry of triarylpyrazole **29a** was further confirmed by its X-ray crystal structure analysis (Figure 1).

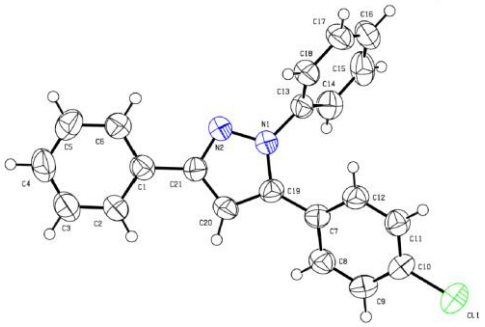
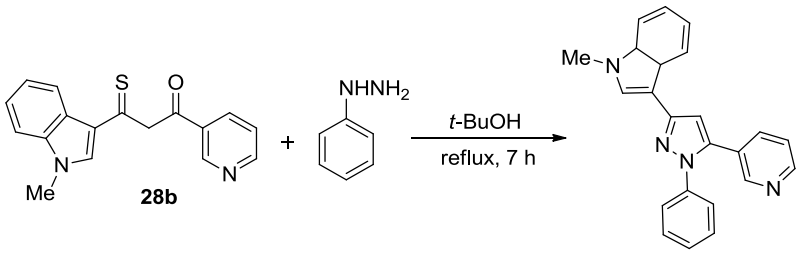


Figure 1. X-ray crystal structure of compound **29a**

The substrate scope of the reaction was further elaborated by installation of two heteroaryl groups in the product pyrazoles **29** in highly regiocontrolled fashion (Scheme 24). Thus, 1-*N*-phenylpyrazole **29b** bearing biologically important 3-(3-indolyl) and 5-(3-pyridyl) groups was obtained as exclusive product in 75% yield from the corresponding monothio-*β*-diketone **28b** and phenylhydrazine under identical reaction conditions.



Scheme 24 **29b**, 75%

The structure of the pyrazole **29b** was established with the help of spectral and analytical data. The assigned regiochemistry of the pyrazole **29b** was also confirmed from its X-ray crystallographic data (Figure 2).

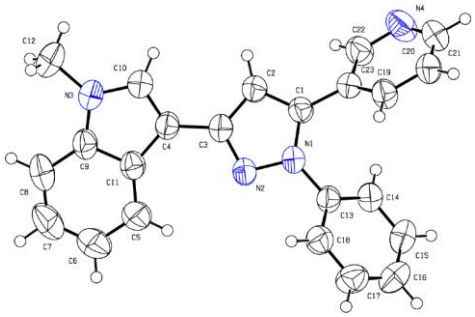
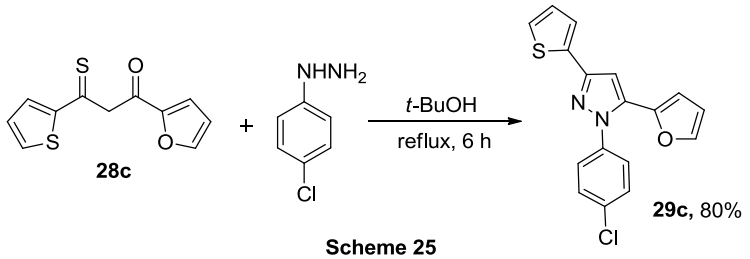


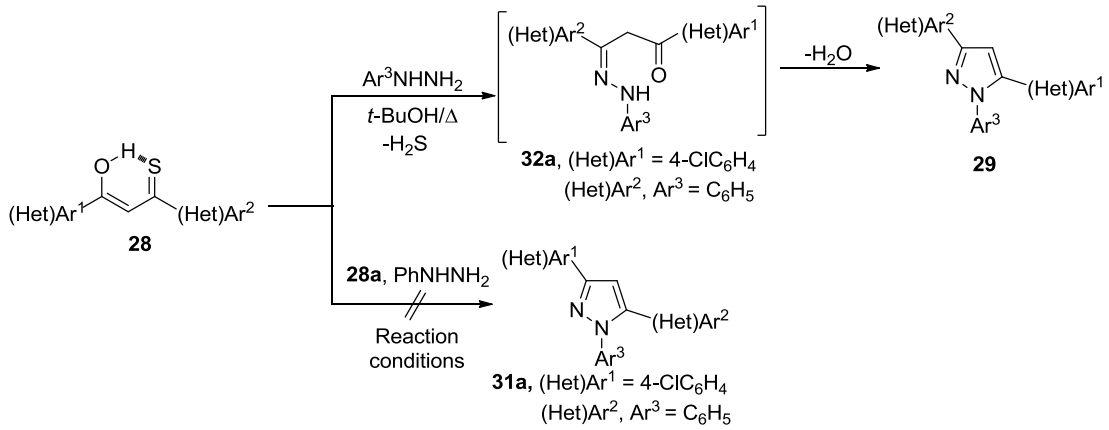
Figure 2. X-ray crystal structure of compound **29b**

In one example, substituted phenylhydrazine like 4-chlorophenylhydrazine was also used as coupling partner with the monothio 1,3-diketone **28c** providing the corresponding 1-(4-chlorophenyl)-5-(2-furyl)-3-(thiophen-2-yl)-1*H*-pyrazole **29c** in 80% yield (Scheme 25).



Scheme 25

Although no attempts were made to study detailed mechanism of this novel highly regioselective synthesis of unsymmetrically substituted 1,3,5-tri(het)arylpyrazoles **29** from 1,3-di(het)arylmonothio-*β*-diketones **28**, it is apparent from the structures of product pyrazoles **29**, that the reaction proceeds by nucleophilic addition of NH_2 group of phenylhydrazine on thiocarbonyl group of **28** with concommitant elimination of H_2S to give intermediate ketohydrazone **32**, which on subsequent dehydrative cyclization gives the pyrazoles **29** as the exclusive products (Scheme 26). However, our attempts to isolate the phenylhydrazone **32a** under various reaction conditions were not successful.

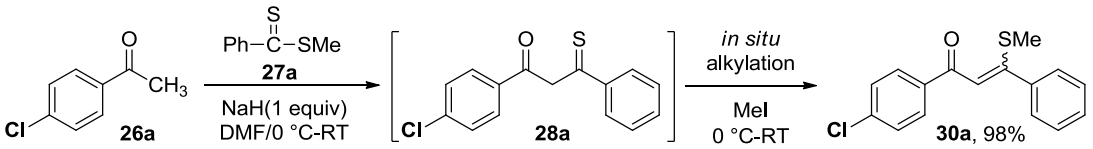


Scheme 26

5.3.3 Synthesis of regioisomeric 1-aryl-3,5-bis(het)arylpyrazole from *β*-(methylthio)-*β*-(het)arylenone

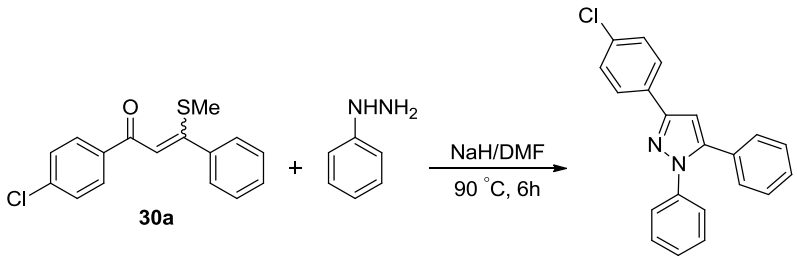
After successfully accomplishing the regiospecific synthesis of 1,3,5-triarylpyrazoles **29** from monothio-*β*-diketones **28**, in which the (het)aryl substituent attached to thiocarbonyl group of monothioketone **28** is installed at 3-position of the product pyrazoles **29**, we were further intrigued with the idea of reversing the reactivity

of monothioketone **28** towards arylhydrazines by varying the reaction conditions, so as to develop a general synthesis of regioisomeric pyrazoles **31** in which the (het)aryl substituent attached to carbonyl group of **28** occupies the 3-position of product pyrazoles (Scheme 26). However our various attempts to obtain the pyrazole **31a** by reacting **28a** with phenylhydrazine under neutral, mild acidic or basic conditions led only to intractable mixture. On the other hand, in a parallel study, we focused our attention towards *β*-(methylthio)-*β*-(het)arylenone **30a**, which was readily available in one-pot reaction by direct *in situ S*-methylation of the product 1,3-monothioketones **28a** prepared by base induced condensation of aryl methyl ketone **26a** with phenyl dithioester **27a** (Scheme 27).[24b,40-41]



Scheme 27

As a model experiment, we therefore investigated the reaction of unsymmetrical 1,3-bis(aryl)-3-(methylthio)-2-propenone **30a** with phenylhydrazine under a variety of reaction conditions (neutral, acidic, basic) with a view to obtain regioisomeric 1,3,5-tris(aryl)pyrazole **31a** (Scheme 28). To our delight, when **30a** was reacted with phenylhydrazine in the presence of NaH in DMF at 90 °C for 6 h, work-up and analysis of the reaction mixture revealed formation of only one product, which was characterized as the desired regioisomeric 1,5-diphenyl-3-(4-chlorophenyl) pyrazole **31a** from its spectral and analytical data and by comparision with the reported data (Scheme 28).[18b,42]



Scheme 28

The structure and regiochemistry of **31a** was further confirmed independently by its X-ray crystallographic data (Figure 3).

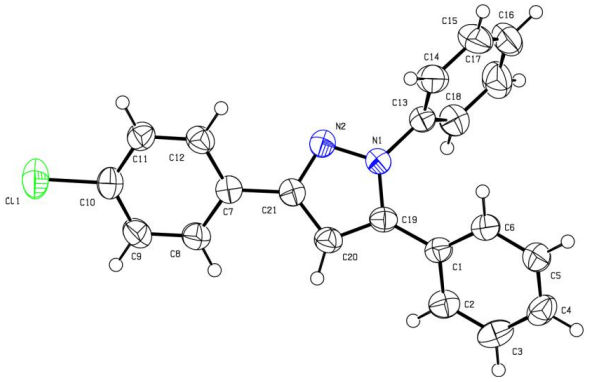
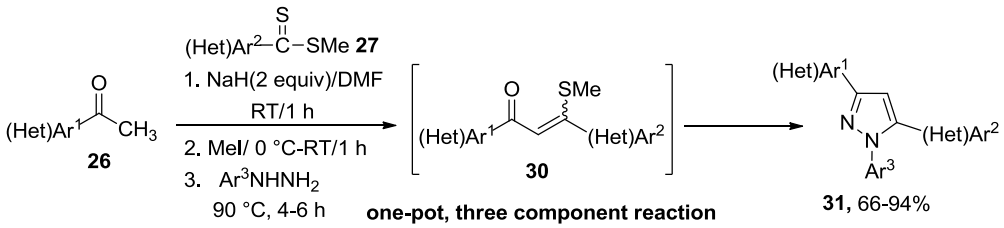


Figure 3. X-ray crystal structure of compound **31a**

5.3.4 Synthesis of regioisomeric 1-aryl-3,5-bis(het)arylpyrazole via a one-pot, three-component reaction

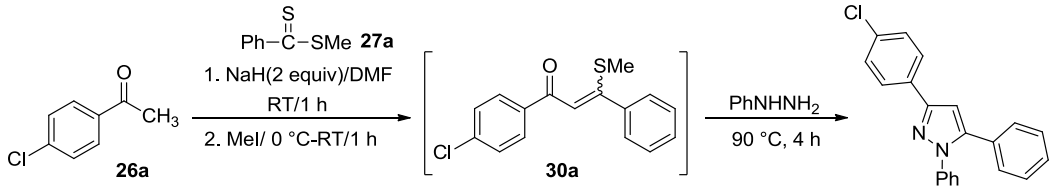
Having established the synthesis of both regioisomeric 1,3,5-trisubstituted pyrazoles **29a** and **31a** from 1,3-monothiodiketone and 1,3-bis(het)aryl-3-(methylthio)-2-propenone precursors **28a** and **30a** respectively, we became interested in developing a one-pot, three-component synthesis of the trisubstituted pyrazoles **31** directly from active methylene ketones **26** and dithioesters **27** without isolation of *β*-(methylthio)enone intermediates **30** (Scheme 29).



Scheme 29

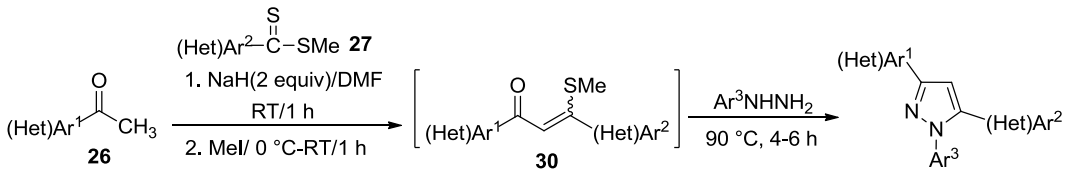
Thus in a model experiment, when 4-chloroacetophenone was reacted with dithioester **27a** ($Ar^2 = C_6H_5$) in the presence of NaH (2 equiv) in DMF at RT followed by sequential addition of methyl iodide and phenylhydrazine (monitored by TLC) and subsequent heating at 90 °C (4 h), work-up of the reaction mixture yielded only 1,5-diphenyl-3-(4-chlorophenyl)pyrazole **31a** exclusively in comparable yield of 85% (Scheme 28) and no trace of the isomeric pyrazole **29a** was detected in the reaction mixture (Scheme 30).

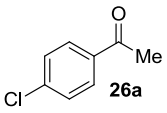
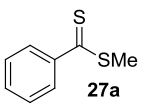
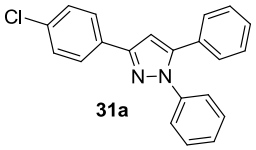
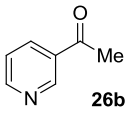
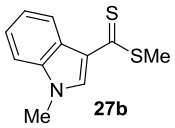
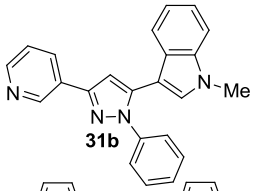
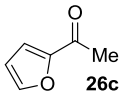
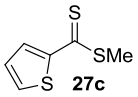
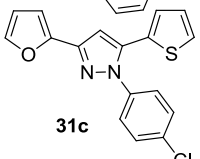
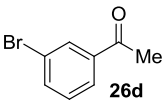
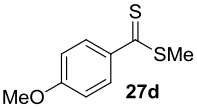
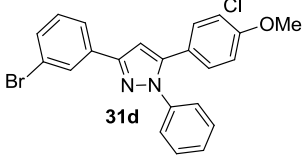
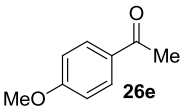
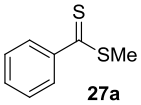
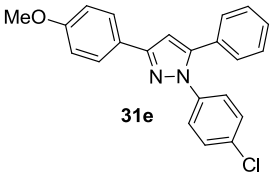
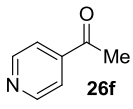
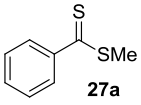
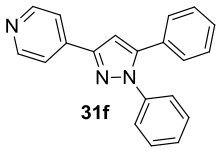
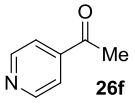
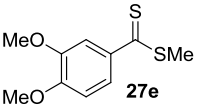
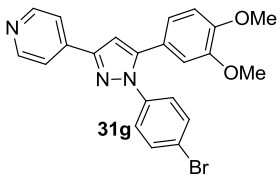
The generality and substrate scope of this novel, efficient one-pot reaction was further established by synthesis of other 1-aryl-3,5-bis(het)arylpyrazoles **31b-l** with complete regioselectivity by employing number of substituted active methelene ketones

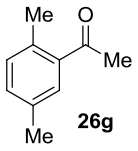
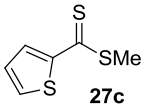
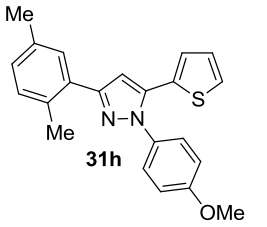
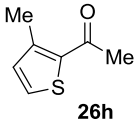
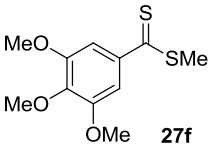
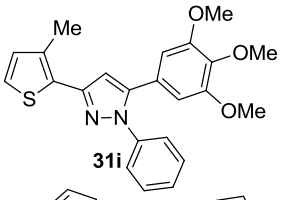
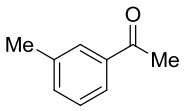
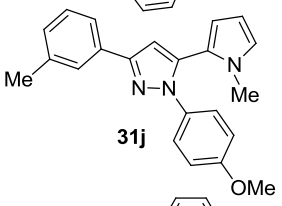
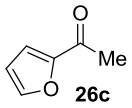
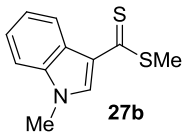
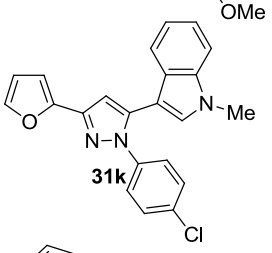
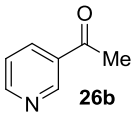
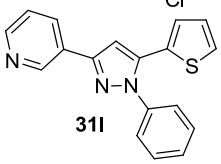
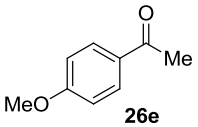
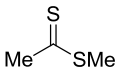
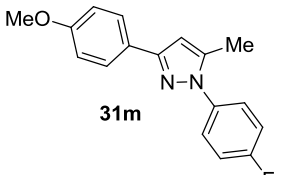
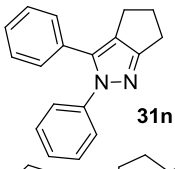
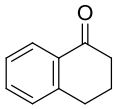
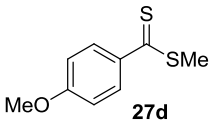
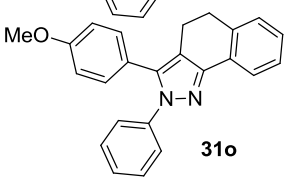


Scheme 30

Table 2. Synthesis of 1-aryl-3,5-bis(het)aryl/annulated pyrazoles 31a-m and 31n-o from active methelene ketones 26 *via* one-pot, three-component reaction



Entry	26	27	Ar^3	31	%Yield 31
1	 **26a**	 **27a**	C_6H_5	 **31a**	85%
2	 **26b**	 **27b**	C_6H_5	 **31b**	85%
3	 **26c**	 **27c**	4-ClC_6H_4	 **31c**	90%
4	 **26d**	 **27d**	C_6H_5	 **31d**	70%
5	 **26e**	 **27a**	4-ClC_6H_4	 **31e**	80%
6	 **26f**	 **27a**	C_6H_5	 **31f**	80%
7	 **26f**	 **27e**	4-BrC_6H_4	 **31g**	78%

Entry	26	27	Ar^3	31	%Yield 31
8	 **26g**	 **27c**	4-$OMeC_6H_4$	 **31h**	90%
9	 **26h**	 **27f**	C_6H_5	 **31i**	80%
10	 **26i**	 **27g**	4-$MeOC_6H_4$	 **31j**	90%
11	 **26c**	 **27b**	4-ClC_6H_4	 **31k**	85%
12	 **26b**	 **27c**	C_6H_5	 **31l**	80%
13	 **26e**	 **27h**	4-FC_6H_4	 **31m**	78%
14	 **26i**	 **27a**	C_6H_5	 **31n**	60%
15	 **26j**	 **27d**	C_6H_5	 **31o**	78%

26, with het(aryl)dithioesters **27** and various arylhydrazines under identical conditions (Table 2, entries 2-12). The corresponding 5-methyl-3-(4-methoxyphenyl)pyrazole **31m** was also obtained in good yield from the respective ketone **26e** and methyl dithioester **27h** (Table 2, entry 13). Similarly the cyclic ketones **26i** and **26j** were smoothly transformed into the corresponding annulated condensed pyrazoles **31n-o** when reacted

with phenyl dithioester and phenylhydrazine under similar reaction conditions (Table 2, entries 14-15).

The structures of all these newly synthesized regioisomeric pyrazoles **31a-o** were established with the help of spectral and analytical data. The regiochemistry of one of the pyrazole **31b** was further confirmed by its X-ray crystal structure data (Figures 4).

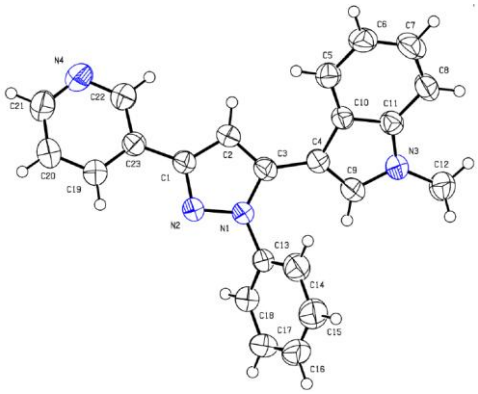
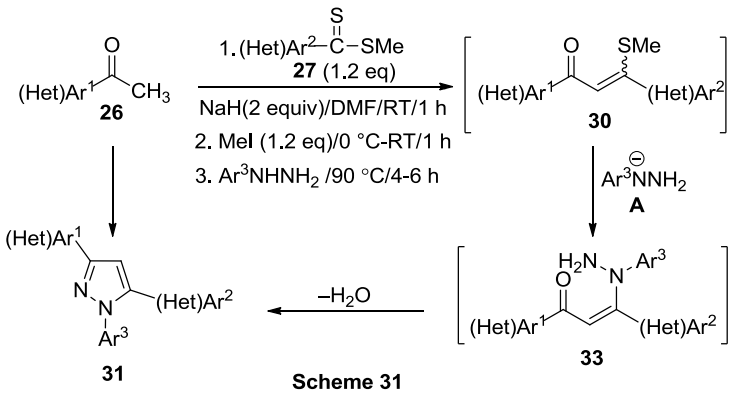


Figure 4. X-ray crystal structure of compound **31b**

5.3.5 Probable mechanism for the formation of 1-aryl-3,5-bis(het)arylpyrazoles 31 from active methylene ketones 26

The probable mechanism for the regioselective formation of the pyrazoles **31** from the reaction of arylhydrazines with 1,3-bis(het)arylpropen-2-ones **30** in the presences NaH appears to be similar to that suggested by us for the base mediated formation of 1,3-diaryl-5-(cycloamino)pyrazoles from the corresponding N,S-acetals in our previous study.[21c] Thus the anion **A** generated by abstraction of more acidic proton of arylhydrazine with base, undergoes conjugate addition-elimination with 3-(methylthio)propenones **30** followed by intramolecular cyclization of the resulting intermediate **33** yielding pyrazoles **31** as the exclusive products (Scheme 31).



Scheme 31

5.4 Conclusion

In summary, we have developed an efficient general synthesis of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles *via* two highly regioselective processes namely the cyclocondensation of arylhydrazines with either 1,3-bis(het)aryl monothio-*β*-diketones **28** or *in situ* generated 1,3-bis(het)aryl-3-(methylthio)-2-propenones **30** directly from active methylene ketones **26** in one-pot, three-component reaction. These two protocols are complimentary to each other in terms of regioselectivity of substituents at 3- and 5-positions of pyrazoles **29** and **31**. The flexibility and generality of this newly developed protocol has been demonstrated by efficient and regiocontrolled preparation of a range of 1-aryl-3,5-bis(het)aryl pyrazoles with minor difference in electronic/steric character of 3- and 5-(het)aryl substituents. The ready availability of starting materials along with mild and simple reaction conditions allowing rapid assembly of diversely substituted pyrazole core in highly regiocontrolled manner should make these reactions suitable for combinatorial synthesis in drug discovery research. We anticipate that our approach along with other reported *de novo* synthesis of pyrazoles will find application in both academia and in particular industry. Further it should be noted that the synthetic applications of 1,3-monothiodiketones, unlike their 1,3-diketone counterparts is virtually unexplored especially for regioselective synthesis of five and six membered heterocycles.

5.5 Experimental section

5.5.1 General information. All the chemicals were commercially purchased and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using Merck TLC Silica gel plates and visualized with UV light. Column chromatography was performed using Merck silica gel (100-200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) Fourier transform NMR spectrometer with $CDCl_3$ as solvent. Chemical shifts were reported in δ ppm (parts per million) using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ in ^{1}H-NMR, δ 77.16 for $CDCl_3$ in ^{13}C-NMR). Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (doublet of triplet), ddd, (doublet of doublet of doublet), quin (quintet), m (multiplet) and br (broad). Infrared spectra were recorded using FTIR instrument and HRMS on Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. X-ray single crystal data of all six crystals was collected on a

diffractometer using MoK_α radiation (λ = 0.71073 Å), at room temperature. The structure was solved by direct methods SHELXS-97 and refined by full-matrix least-squares against F^2 using SHELXL-97 software.

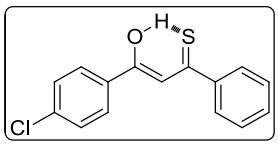
The scanned copies of ^{1}H-NMR and ^{13}C-NMR spectra of all the compounds are available in supporting information of *J. Org. Chem*. **2013**, *78*, 4960.

All the active methylene ketones **26a-k** were commercially purchased and the corresponding dithioesters **27a-e**,[37] **27h**,[37] **27f-g**,[38] were prepared according to the reported methods in literature.

5.5.2 General procedure for the preparation of 1,3-monothio-*β*-diketones [1-(het)aryl-3-thioxo-3-alkyl/(het)aryl propan-1-one] 28a-c.

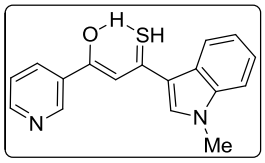
To a stirred suspension of NaH (1.1 mmol, 100%) in DMF (20 mL) under N_2 atmosphere, a solution of (het)aryl methyl ketone **26** (1.0 mmol) and (het)aryl dithioester **27** (1.2 mmol) in DMF (10 mL) was added dropwise at 0°C. The reaction mixture was further stirred at room temperature for 1 h (monitored by TLC) and was poured into ice cold water (100 mL) and acidified with acetic acid. The aqueous layer was extracted with EtOAc (3 x 50 mL), washed with H_2O (2 x 50 mL), brine (1x 50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude monothiodiketones **28**, which were purified by column chromatography using hexane:EtOAc as eluent.

(*Z*) 3-(4-Chlorophenyl)-3-hydroxy-1-phenylprop-2-ene-1-thione (28a): Obtained from



4- chloroacetophenone (**26a**) and dithioester **27a** (Ar = C_6H_5), red solid (0.24 g, 84%): mp 112-113 °C; R_f 0.7 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2923, 1583, 1549, 1482, 1246, 1087, 840; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.91 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.81-7.78 (m, 2H), 7.52-7.42 (m, 5H), 7.4 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7, 178.5, 145.2, 138.8, 134.2, 131.2, 129.2, 128.6, 128.5, 126.8, 110.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}ClOS$ $[M + H]^+$ 275.0297, found 275.0283.

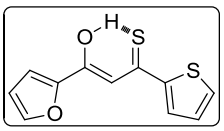
(*Z*) 3-Hydroxy-1-(1-methyl-1*H*-indol-3-yl)-3-(pyridin-3-yl)prop-2-ene-1-thione (28b):



Obtained from 3-acetylpyridine (**26b**) and dithioester **27b** [(Het)Ar = (N-methylindole-3-yl)], brown solid (0.25 g, 86%): mp 105-106 °C; R_f 0.4 (3:2 EtOAc:hexane); IR (KBr, cm^{-1}) 2924, 1590, 1517, 1457, 1349, 822; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.2 (s, 1H), 9.16 (d, J = 1.6

Hz, 1H), 8.71 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.56-8.53 (m, 1H), 8.22 (dt, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.96 (s, 1H), 7.42 (dd, *J* = 8.0 Hz, 3.2 Hz, 1H), 7.37-7.34 (m, 4H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 170.9, 151.9, 151.8, 147.8, 138.5, 134.3, 134.2, 134.0, 125.8, 125.6, 123.8, 123.7, 122.5, 122.4, 110.7, 33.8; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{14}N_2OS$ $[M + H]^+$ 295.0905, found 295.0897.

(*Z*) 3-(Furan-2-yl)-3-hydroxy-1-(thiophen-2-yl)prop-2-ene-1-thione (28c): Obtained

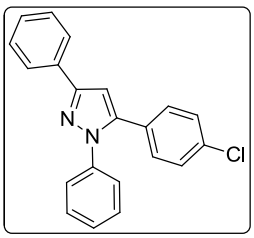


from 2- acetylfuran (**26c**) and dithioester **27c**, red solid (0.21 g, 90%): mp 94-95 °C; R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 3074, 1613, 1536, 1432, 1249, 703; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.53 (s, 1H), 7.77 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 7.65 (dd, *J* = 1.6 Hz, 0.4 Hz, 1H), 7.62 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.39 (s, 1H), 7.25 (dd, *J* = 3.2 Hz, 0.4 Hz, 1H), 7.14 (dd, *J* = 4.8 Hz, 4.0 Hz, 1H), 6.61 (dd, *J* = 3.2 Hz, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 166.2, 152.3, 149.8, 146.5, 134.2, 128.8, 127.7, 116.4, 113.3, 105.7; HRMS (ESI) *m*/*z* calcd for $C_{11}H_8O_2S_2$ $[M + H]^+$ 237.0044, found 237.0033.

5.5.3 General procedure for the preparation of 1-aryl-3,5-bis(het)arylpyrazoles 29 a-c from monothiodiketones 28a-c.

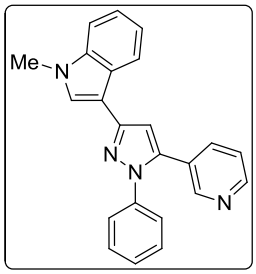
A solution of respective 1,3-monothiodiketone **28** (5.0 mmol) and arylhydrazine (5.5 mmol) in 25 mL *t*-BuOH was refluxed for 6-7 h with constant stirring (monitored by TLC). The reaction mixture was concentrated under reduced pressure and poured into water, extracted with DCM (3 × 50 mL), washed with H_2O (2 × 50 mL), brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give crude pyrazoles **29** which were purified by column chromatography over silica gel using EtOAc-hexane as eluent (Table 1).

5-(4-Chlorophenyl)-1,3-diphenyl-1*H*-pyrazole (29a). Obtained from monothio-1,3-



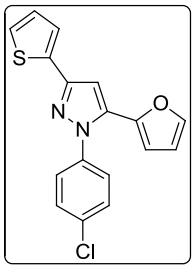
diketone **28a** and phenylhydrazine, white solid (1.52 g, 71%): mp 104-105 °C (lit. 104-105 °C);[18b] R_f 0.6 (1:9 EtOAc;hexane); IR (KBr, cm^{-1}) 2924, 1593, 1483, 1184, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.37-7.25 (m, 8H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 143.2, 139.7, 134.4, 132.6, 129.9, 129.0, 128.7, 128.2, 127.7, 125.8, 125.3, 105.2; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{15}ClN_2$ $[M + H]^+$ 331.1002, found 331.0997.

1-Phenyl-3-(1-Methyl-1*H*-indol-3-yl)-5-(pyridin-3-yl)-1*H*-pyrazole (29b). Obtained



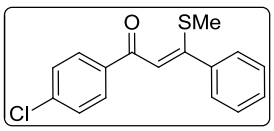
from monothio-1,3-diketone **28b** and phenylhydrazine, white solid (1.61 g, 75%): mp 151-152 °C; R_f 0.5 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 3046, 2928, 1613, 1308, 1246, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.57 (br d, J = 3.8 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.57 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 7.54 (s, 1H), 7.39-7.21 (m, 9H), 6.87 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.4, 148.2, 139.8, 139.7, 137.3, 136.6, 129.2, 127.6, 127.5, 127.2, 126.0, 125.3, 123.5, 122.1, 121.2, 120.2, 109.4, 108.4, 106.1, 33.0; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{18}N_4$ $[M + H]^+$ 351.1610, found 351.1603.

1-(4-Chlorophenyl)-5-(furan-2-yl)-3-(thiophen-2-yl)-1*H*-pyrazole (29c). Obtained



from monothio-1,3-diketone **28c** and 4-chlorophenylhydrazine, colorless liquid (1.56 g, 80%): R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 3114, 1494, 1088, 1038, 832, 703; ^{1}H NMR (400M Hz, $CDCl_3$) δ 7.39-7.37 (m, 6H), 7.25-7.21 (m, 1H), 7.05-7.02 (m, 1H), 6.82 (s, 1H), 6.34-6.32 (m, 1H), 6.06 (br d, J = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 143.6, 142.8, 138.3, 135.6, 135.4, 134.2, 129.2, 127.5, 127.0, 125.1, 124.4, 111.3, 109.4, 103.7; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{11}ClN_2OS$ $[M + H]^+$ 327.0359, found 327.0350.

5.5.4 Synthesis of (*Z*)-1-(4-Chlorophenyl)-3-(methylthio)-3-phenylprop-2-en-1-one



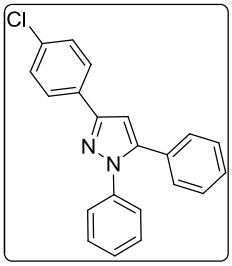
(30a). To a stirred suspension of NaH (1.1 mmol, 100%) in DMF (20 mL) under N_2 atmosphere, a solution of 4-chloroacetophenone **26a** (1 mmol) and phenyl dithioester **27a** (1.2 mmol) in DMF (10 mL) was added drop wise at 0 °C and the reaction mixture was further stirred at room temperature for 1 h. After complete formation of monothiodiketone **28a** (monitored by TLC), the reaction mixture was cooled to 0 °C, followed by drop wise addition of methyl iodide (1.2 mmol) and further stirring at room temperature for 2 h (monitored by TLC). It was then poured into water (50 mL), and extracted with EtOAc (3 x 50 ml). The combined organic extract was washed with H_2O (3 x 50 ml) followed by brine (1 x 50 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude products **30a** which were purified by column chromatography using EtOAc:hexane as eluent. Yellow solid (0.28 g, 98%); mp 78-79 °C; R_f (1:9 EtOAc:hexanes); IR (KBr, cm^{-1}) 2920, 1626, 1526, 1249, 695; ^{1}H NMR (400

MHz, $CDCl_3$): δ 7.82 (d, J = 7.4 Hz, 2H), 7.36-7.30 (m, 5H), 7.23 (d, J = 7.4 Hz, 2H), 6.95 (s, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.0, 165.9, 138.5, 138.4, 136.9, 129.4, 128.9, 128.8, 128.6, 127.9, 118.5, 16.6; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{13}ClOS$ $[M + H]^+$ 289.0454, found 289.0439.

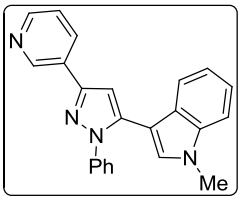
5.5.5 General procedure for the one-pot preparation of 1-aryl-3,5-bis(het)arylpyrazoles 31a-m and 1,5-bis(aryl)-3,4-annulated pyrazoles 31n-o from (het)aryl methyl ketones 26 and (het)aryl dithioesters 27.

To a stirred suspension of NaH (2 mmol, 100%) in DMF (20 mL) under N_2 atmosphere, was added a solution of appropriate (het)aryl methyl ketone **26** (1 mmol) in DMF, followed by drop wise addition of the corresponding (het)aryl dithioester **27** (1.2 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was further stirred at room temperature for 1 h (monitored by TLC), followed by addition of methyl iodide (1.2 mmol) at 0 °C and stirring was further continued for 1 h at room temperature (monitored by TLC). The appropriate arylhydrazine (1.1 mmol) was then added to the reaction mixture followed by heating at 90 °C for 4-6 h along with stirring (monitored by TLC). It was then poured into ice- cold water (1 x 50 mL), extracted with EtOAc (3 × 25 mL), the combined organic layer was washed with H_2O (2 × 50 mL), brine (1 × 50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude adduct, which was purified by column chromatography using Hexane:EtOAc as eluent (Table 2).

3-(4-Chlorophenyl)-1,5-diphenyl-1*H*-pyrazole (31a). Obtained from ketone **26a**, dithioester **27a** and phenylhydrazine, brown solid (1.44 g, 85%): R_f 0.5 (1:12 EtOAc:hexane); mp 145-146 °C (lit. 146-147 °C);[18b] IR (KBr, cm^{-1}) 2924, 1593, 1493, 1087, 765; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.35-7.25 (m, 10H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 144.8, 140.2, 133.9, 131.8, 130.6, 129.1, 129.0, 128.9, 128.7, 128.6, 127.7, 127.2, 125.4, 105.2; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{15}ClN_2$ $[M + H]^+$ 331.1002, found 331.0986.

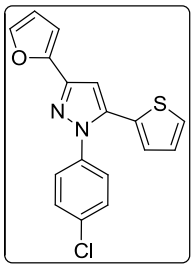


1-Phenyl-3-(pyridin-3-yl)-5-(1-Methyl-1*H*-indol-3-yl)-1*H*-pyrazole (31b). Obtained from ketone **26b**, dithioester **27b** and phenylhydrazine, off-white solid (1.58 g, 85%); mp 145-146 °C; R_f 0.6 (1:1 EtOAc:hexane); IR (KBr, cm^{-1}) 2924, 1644, 1238, 1499, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (dd, J = 2.0 Hz, 0.8 Hz, 1H), 8.58 (dd, J = 4.8 Hz, 1.6



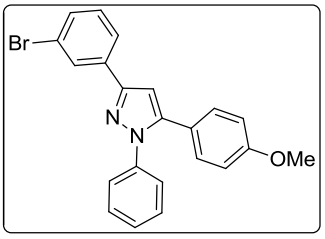
Hz, 1H), 8.27 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50-7.47 (m, 2H), 7.38-7.28 (m, 6H), 7.16-7.17 (m, 1H), 6.95 (s, 1H), 6.76 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 149.0, 147.5, 140.6, 139.1, 136.8, 133.1, 129.4, 129.1, 128.5, 127.8, 126.6, 125.4, 123.7, 122.5, 120.5, 120.1, 109.7, 104.9, 104.6, 33.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_4$ $[M + H]^+$ 351.1610, found 351.1595.

1-(4-Chlorophenyl)-3-(furan-2-yl)-5-(thiophen-2-yl)-1*H*-pyrazole (31c). Obtained



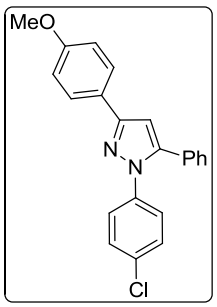
from ketone **26c**, dithioester **27c** and 4-chlorophenylhydrazine, viscous liquid (1.53 g, 90%): R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2925, 1495, 1152, 1089,701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz, 0.8 Hz, 1H), 7.38 (br s, 4H), 7.32 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 6.87 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 6.79 (s, 1H), 6.76 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 6.49 (dd, *J* = 3.6 Hz, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 144.9, 142.4, 138.3, 138.1, 134.3, 130.7, 129.3, 127.8, 127.6, 127.5, 127.1, 111.5, 106.8, 105.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{11}ClN_2OS$ $[M + H]^+$ 327.0359, found 327.0357

3-(3-Bromophenyl)-5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (31d). Obtained from



ketone **26d**, dithioester **27d** and phenylhydrazine, dark yellow solid (1.44 g, 70%): R_f 0.62 (1:4 EtOAc:hexane); mp 75-76 $^{\circ}$C; IR (KBr, cm^{-1}) 2923, 1458, 1375, 673; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.46-7.44 (m, 1H), 7.37-7.28 (m, 6H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 150.4, 144.5, 140.1, 135.3, 134.9, 130.8, 130.3, 130.1, 130.0, 129.4, 128.9, 127.5, 125.3, 124.3, 114.0, 104.7, 55.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}BrN_2O$ $[M + Na]^+$ 427.0422, found 427.0424 .

1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole (31e). Obtained from



ketone **26e**, dithioester **27a** and 4-chlorophenylhydrazine, white solid (1.48 g, 80%): mp 124-125 $^{\circ}$C, R_f 0.6 (1:9 EtOAc:hexane); IR (KBr, cm^{-1}) 2924, 1612, 1495, 1251, 1031, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.36-7.33 (m, 3H), 7.30-7.26 (m, 6H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 152.1, 144.3, 138.6, 132.9, 132.7, 130.0, 129.0, 128.6, 128.1, 126.3, 125.8, 122.5, 114.0, 105.0, 55.3; HRMS (ESI) *m/z* calcd for $C_{22}H_{17}ClN_2O$ $[M + H]^+$ 361.1108, found 361.1103.

1,5-Diphenyl-3-(pyridin-4-yl)-1*H*-pyrazol (31f). Obtained from ketone **26f**, dithioester **27a** and phenylhydrazine, yellow solid (1.23 g, 80%): mp 106-107 °C; R_f 0.35 (3:7 EtOAc:hexane); IR (KBr, cm^{-1}) 3028, 1603, 1494, 1211, 799; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 4 Hz, 2H), 7.79 (d, J = 4 Hz, 2H), 7.36-7.33 (m, 8H), 7.28-7.27 (m, 2H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.4, 145.0, 140.4, 139.9, 130.1, 129.0, 128.7, 128.6, 127.9, 125.3, 122.9, 120.1, 105.6; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{15}N_3$ $[M + H]^+$ 298.1344, found 298.1350.

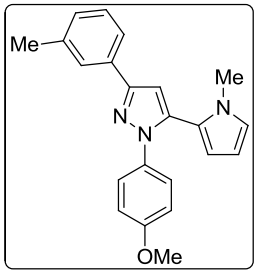
1-(4-Bromophenyl)-5-(3,4-dimethoxyphenyl)-3-(pyridin-4-yl)-1*H*-pyrazole (31g). Obtained from ketone **26f**, dithioester **27e** and 4-bromophenylhydrazine, yellow solid (1.74 g, 78%): mp 94-95 °C; R_f 0.37 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 3063, 2923, 1594, 1181, 806; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 6.0 Hz, 2H), 7.77 (d, J = 6.0 Hz, 2H), 7.50 (d, J =8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 6.85-6.84 (m, 3H), 6.72 (s, 1 H), 3.90 (s, 3 H), 3.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 149.7, 149.1, 145.1, 140.4, 139.1, 132.2, 126.9, 122.4, 121.8, 121.6, 120.2, 112.0, 111.4, 105.6, 56.1, 55.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{18}BrN_3O_2$ $[M + H]^+$ 436.0661, found 436.0661.

3-(2,5-Dimethylphenyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1*H*-pyrazole (31h). Obtained from ketone **26g**, dithioester **27c** and 4-methoxyphenylhydrazine, pale yellow solid (1.60 g, 90%): mp 152-153 °C; R_f 0.68 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2959, 1609, 1518, 1247, 712; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.2 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.94-6.87 (m, 4H), 6.87 (s, 1H), 6.70 (s, 1H), 3.85 (s, 3H), 2.52 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 152.1, 137.3, 135.2, 133.0, 132.9, 132.4, 131.7, 130.7, 129.9, 128.6, 127.7, 127.3, 127.0, 126.2, 114.1, 107.3, 55.5, 20.9, 20.8; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{20}N_2OS$ $[M + Na]^+$ 383.1194, found 383.1195.

3-(3-Methylthiophen-2-yl)-1-phenyl-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (31i). Obtained from ketone **26h**, dithioester **27f** and phenylhydrazine, white solid (1.66 g, 80%): mp 124-126 °C; R_f 0.45 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}); 3051, 2946, 1571, 1449, 765; ^1H

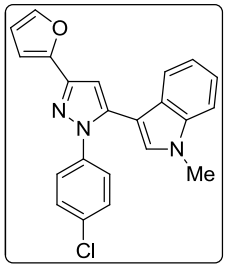
NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 7.18 (d, J = 5.2 Hz, 1H), 6.92 (d, J = 5.2 Hz, 1H), 6.67 (s, 1H), 6.45 (s, 2H), 3.86 (s, 3H), 3.67 (s, 6H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.3, 143.9, 140.1, 138.3, 134.9, 131.3, 129.9, 128.9, 127.6, 125.7, 125.6, 123.6, 106.3, 106.2, 61.1, 56.1, 15.6; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{22}N_2O_3S$ $[M + H]^+$ 407.1429, found 407.1431.

1-(4-Methoxyphenyl)-5-(1-methyl-1*H*-pyrrol-2-yl)-3-*m*-tolyl-1*H*-pyrazole (31j).



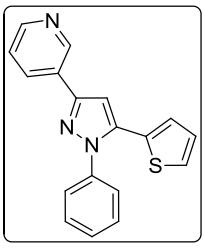
Obtained from ketone **26i**, dithioester **27g** and 4-methoxyphenylhydrazine, viscous liquid (1.54 g, 90%): R_f 0.71 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}); 2924, 1462, 1376, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 6.8 Hz, 1.6 Hz, 1 H), 8.03 (s, 1 H), 7.80-7.95 (m, 3 H), 7.48-7.56 (m, 2 H), 7.41-7.34 (m, 2 H), 7.30-7.27 (m, 2 H), 6.95 (t, J = 7.2 Hz, 1 H), 3.80 (s, 3 H), 3.53 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 145.8, 141.5, 139.6, 138.0, 132.5, 129.3, 129.1, 129.0, 128.8, 128.2, 125.8, 125.3, 122.7, 120.7, 115.6, 106.0, 58.1, 33.3, 20.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}N_3O$ $[M + H]^+$ 344.1763, found 344.1765.

5-(1-Methyl-1*H*-indol-3-yl)-3-(Furan-2-yl)-1-(4-chlorophenyl)-1*H*-pyrazole (31k).



Obtained from ketone **26c**, dithioester **27b** and 4-chlorophenylhydrazine, viscous liquid (1.61 g, 85%): R_f 0.5 (1:4 EtOAc:hexane); IR (KBr, cm^{-1}) 2923, 1594, 1494, 1329, 890, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.30-7.26 (m, 3H), 7.16-7.12 (m, 1H), 6.82 (s, 1H), 6.80-6.79 (m, 2H), 6.49 (dd, J = 3.2 Hz, 2.0 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 145.1, 142.2, 139.1, 138.5, 136.9, 133.2, 129.1, 128.5, 126.5, 122.7, 120.6, 120.0, 111.5, 109.7, 106.5, 104.9, 104.6, 33.2; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{16}ClN_3O$ 374.1060, found 374.1054.

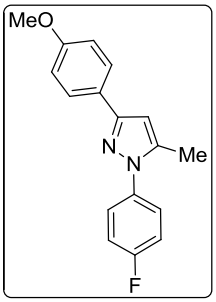
1-Phenyl-3-(pyridin-3-yl)-5-(thiophen-2-yl)-1*H*-pyrazole (31l). Obtained from ketone



26b, dithioester **27c** and phenylhydrazine, white solid (1.19 g, 80%); mp 107-108 °C; R_f 0.5 (1:3 EtOAc:hexane); IR (KBr, cm^{-1}) 3057, 1594, 1498, 957, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.58 (dd, J = 4.8 Hz, 1.4 Hz, 1H), 8.20 (dd, J = 8.0 Hz, 1.7 Hz, 1H), 7.45-7.26 (m, 7H), 6.98-6.86 (m, 2H), 6.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

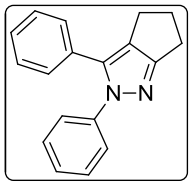
149.1, 149.0, 147.3, 139.6, 138.6, 133.0, 130.8, 129.1, 128.8, 128.6, 127.5, 127.4, 126.8, 126.2, 123.6, 104.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{13}N_3S$ $[M + H]^+$ 304.0908, found 304.0899.

1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-5-methyl-1*H*-pyrazole (31m). Obtained



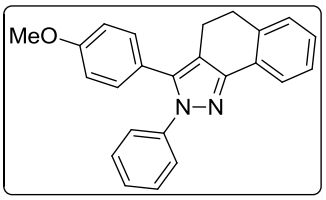
from ketone **26e**, dithioester **27h** and 4-fluorophenylhydrazine, white solid (1.18 g, 78%): mp 88-90 °C; IR (KBr, cm^{-1}) 2922, 1580, 1403, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.4 Hz, 2H), 7.48 (dd, J = 8.4 Hz, 4.8 Hz, 2H), 7.16 (t, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.44 (s, 1H), 3.84 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 160.5, 159.5, 151.4, 140.1, 136.2, 136.1, 127.0, 126.9, 126.8, 126.0, 116.0, 115.8, 114.0, 103.9, 55.3, 12.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}FN_2O$ $[M +H]^+$ 283.1247, found 283.1243.

2,3-Diphenyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole (31n). Obtained from ketone



26i, dithioester **27a** and phenylhydrazine, viscous liquid (0.86 g, 60%): R_f 0.7 (1:16); IR (KBr, cm^{-1}) 3059, 2952, 1596, 1506, 1362, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (m, 10H), 2.85 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.50 (quin, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.0, 140.8, 136.2, 130.9, 128.8, 128.5, 128.4, 127.6, 126.7, 125.0, 29.9, 24.8, 23.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N_2$ $[M + H]^+$ 261.1392, found 261.1390.

3-(4-Methoxyphenyl)-2-phenyl-4,5-dihydro-2*H*-benzo[*g*]indazole (31o). Obtained



from ketone **26j**, dithioester **27d** and phenylhydrazine, white solid (1.44 g, 78%): mp 118-119 °C; R_f 0.5 (1:16 EtOAc:hexane); IR (KBr, cm^{-1}) 2929, 1599, 1465, 1248, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.2 Hz, 1H), 7.35-7.21 (m, 8H), 7.12 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.98 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 149.0, 140.6, 138.6, 137.1, 130.8, 129.8, 128.9, 128.5, 127.9, 127.0, 125.2, 122.9, 122.8, 116.9, 114.1, 55.4, 29.9, 19.7; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}N_2O$ $[M + H]^+$ 353.1654, found 353.1640.

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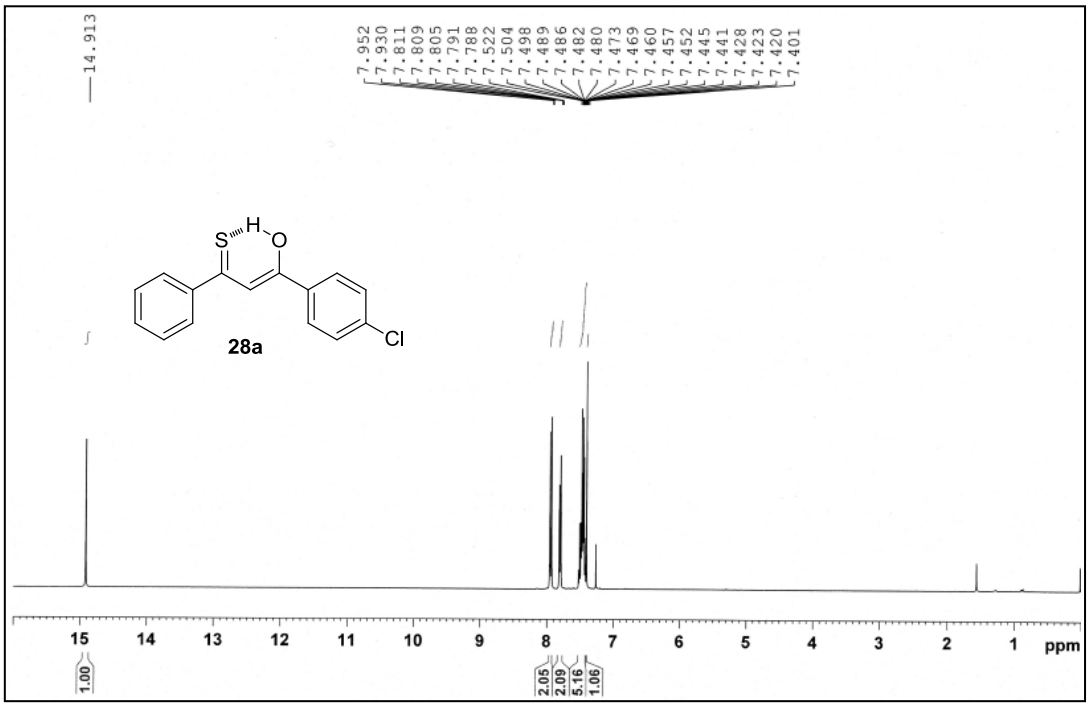
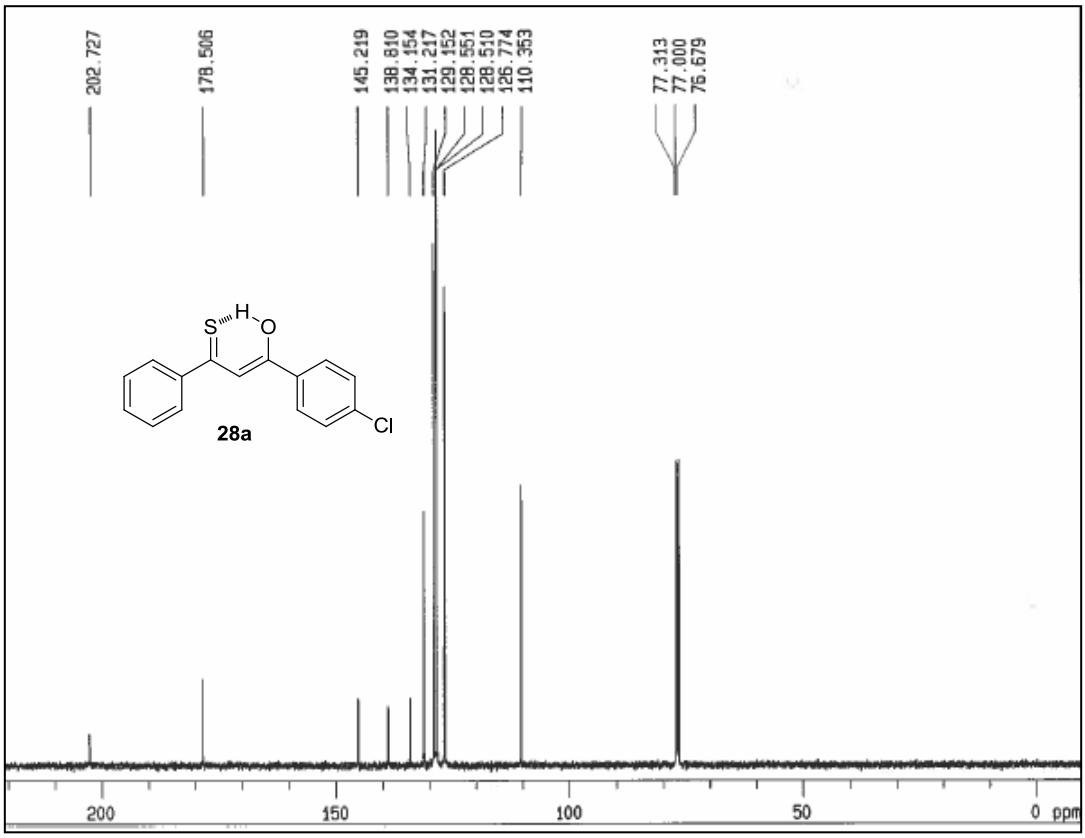
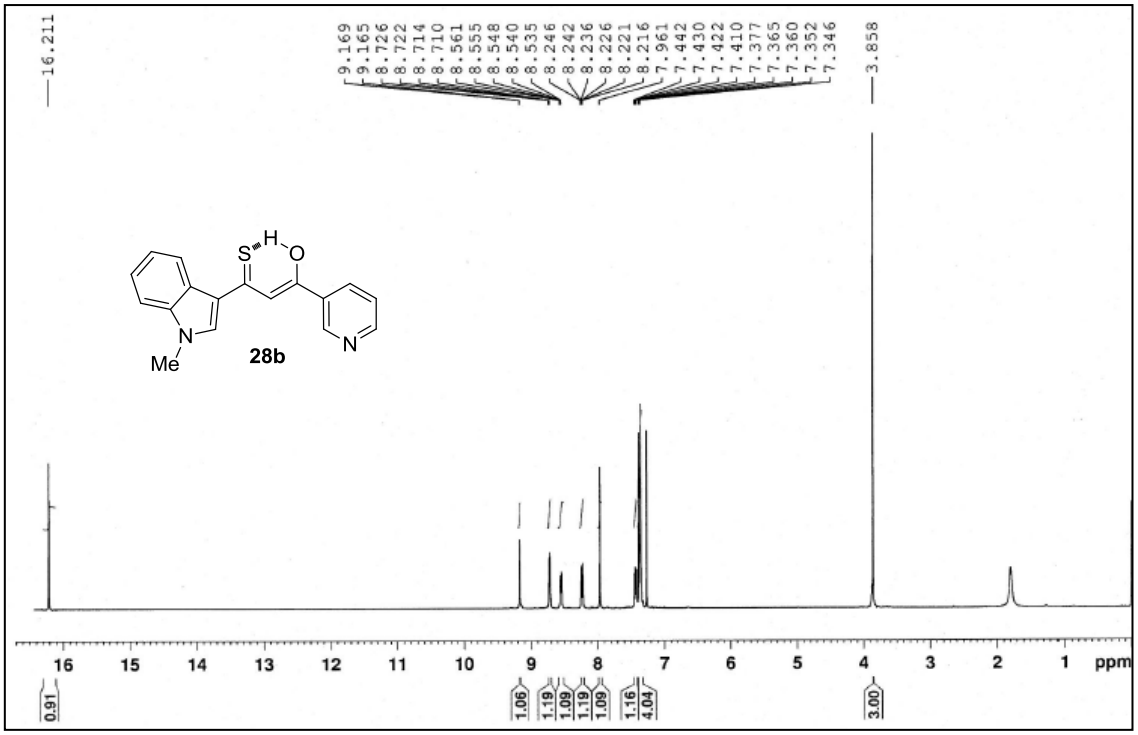
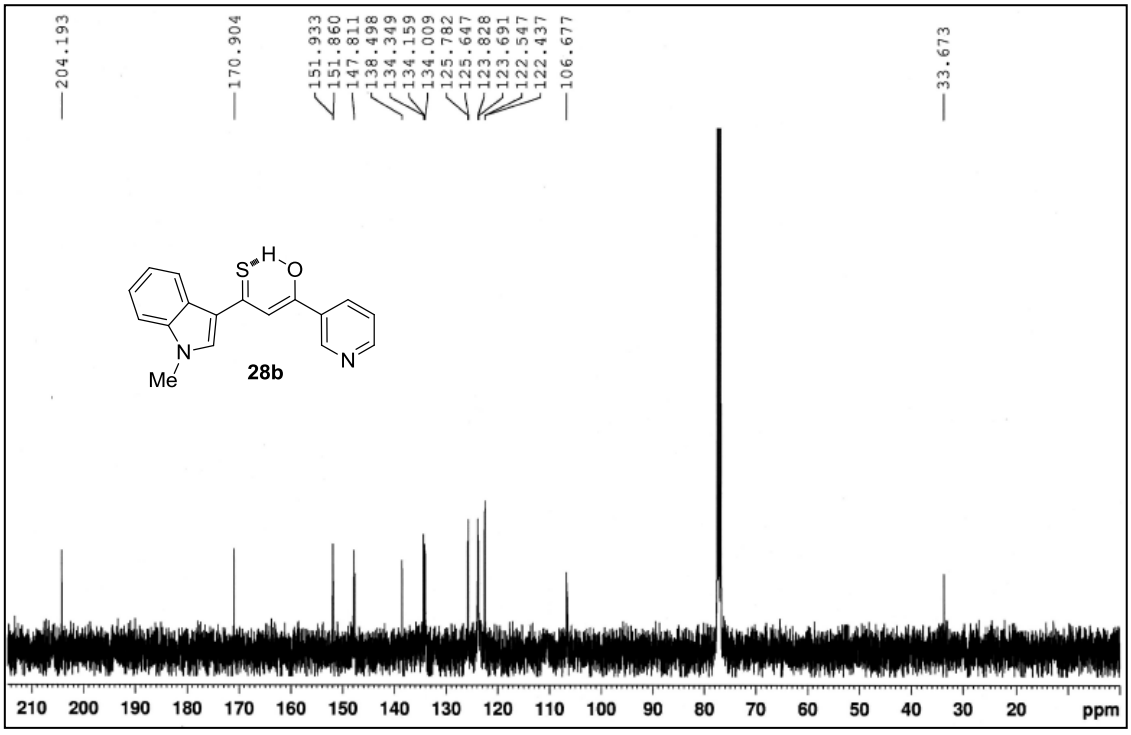
5.7 Representative spectra





^{1}H NMR and ^{13}C NMR Spectra for compound **28a** in $CDCl_3$





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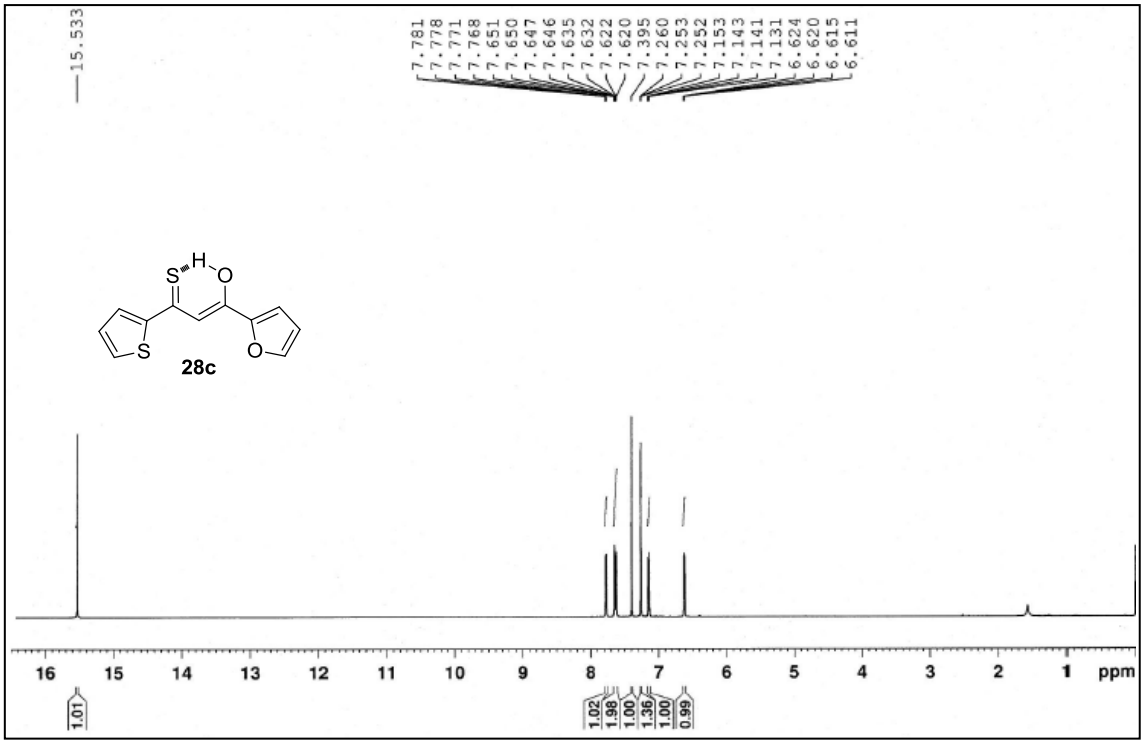

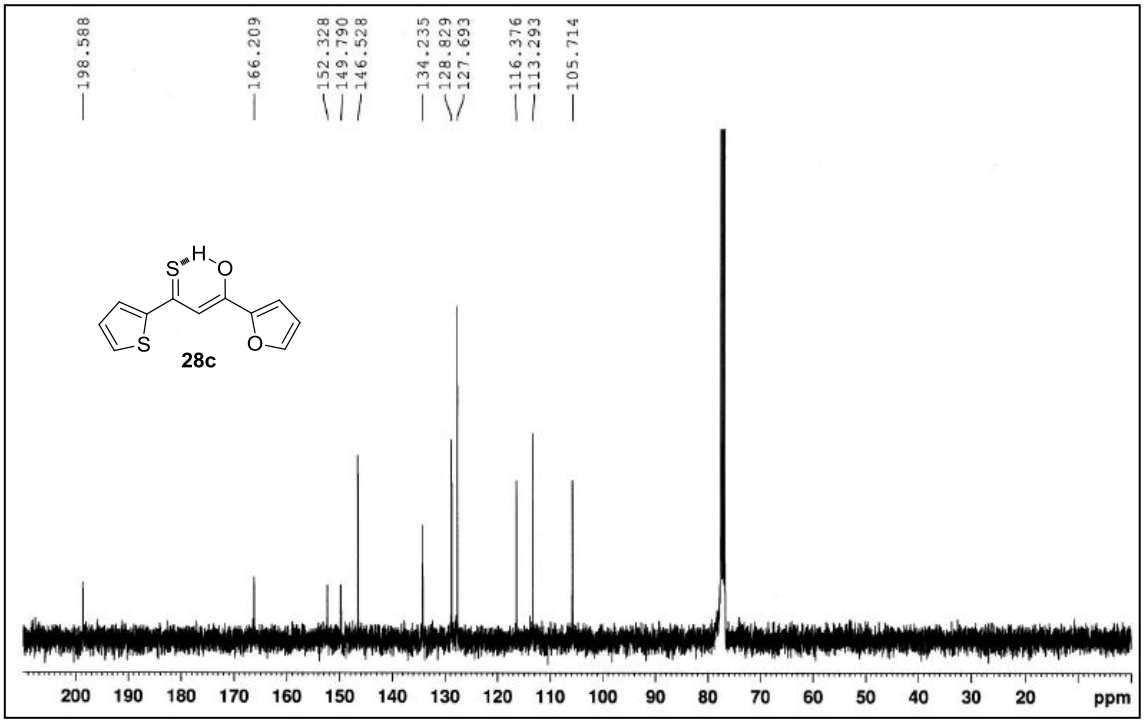

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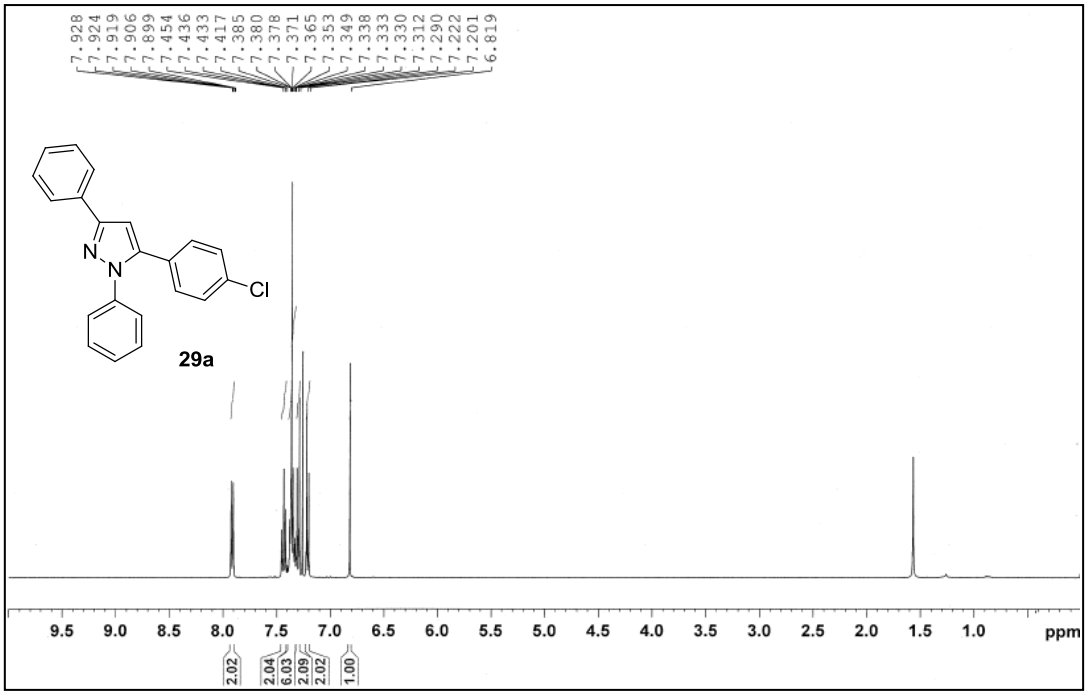

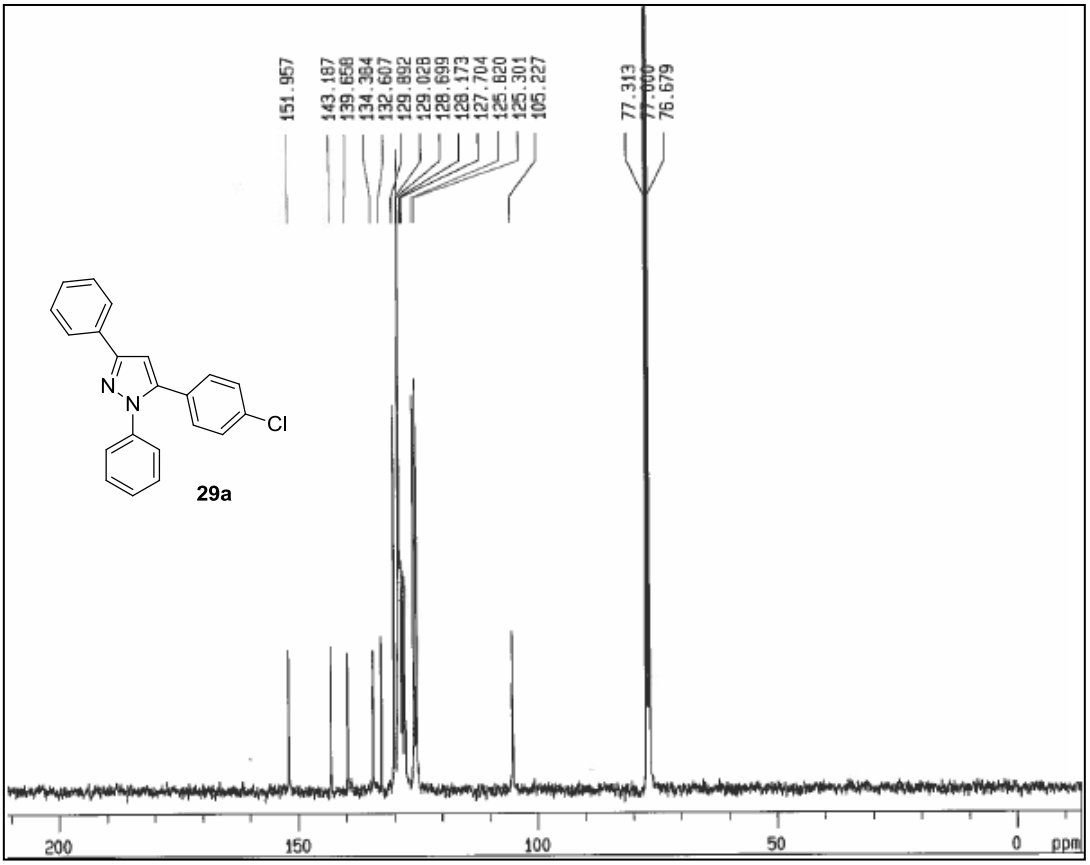

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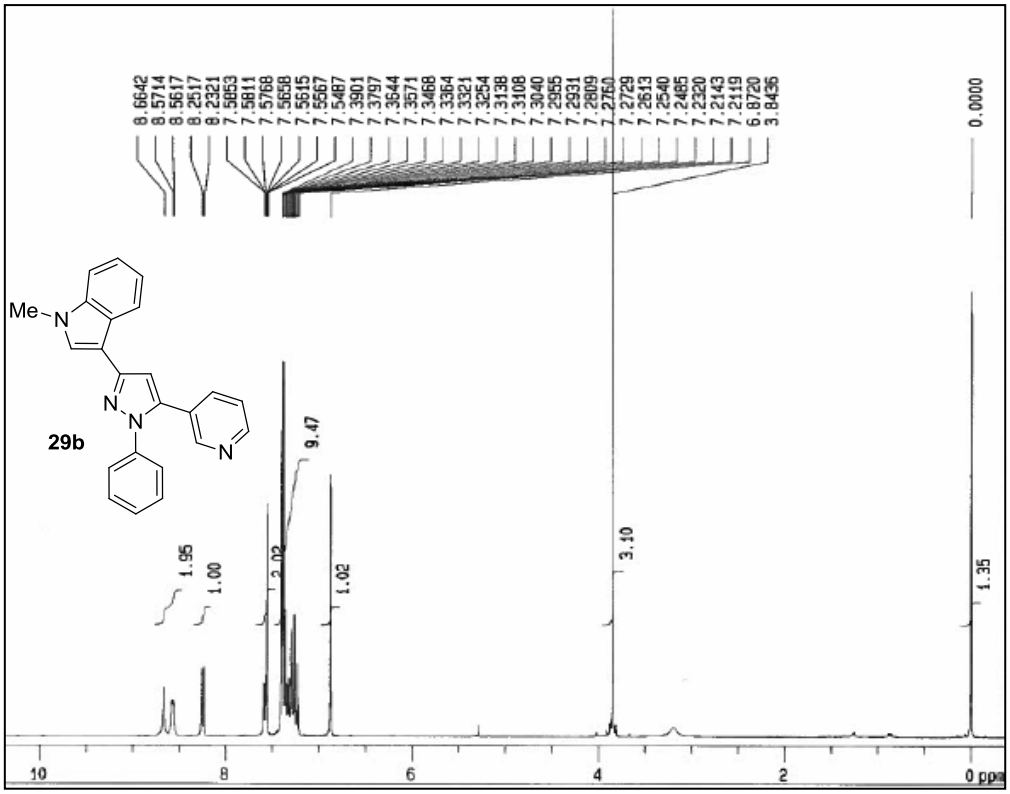

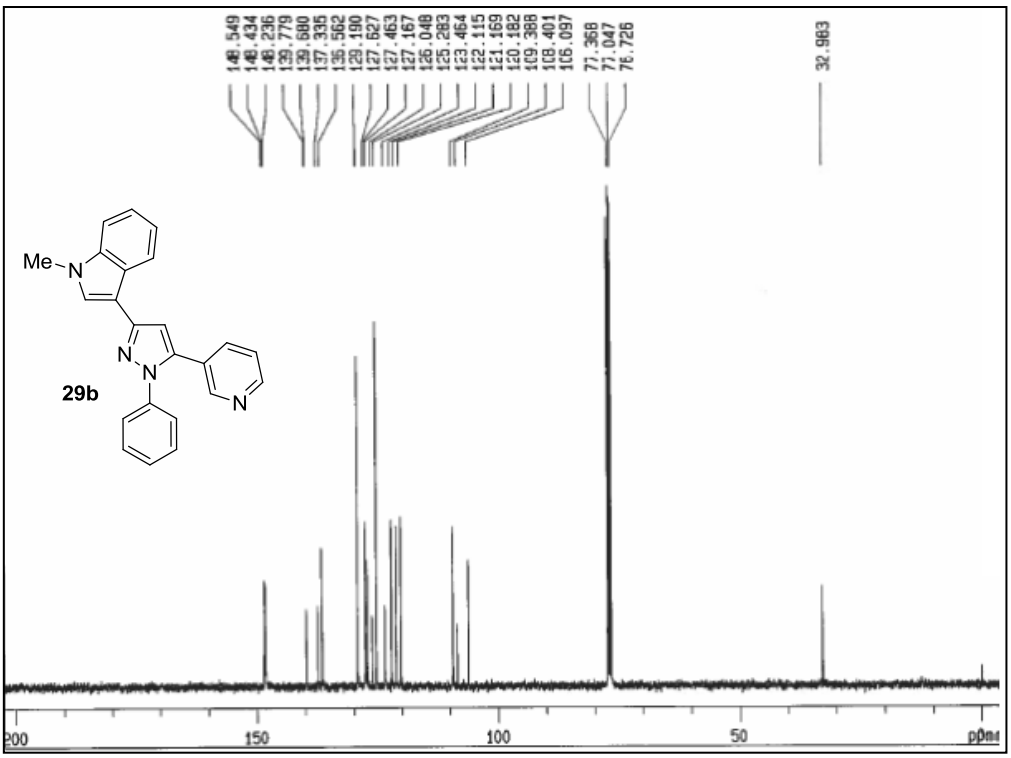

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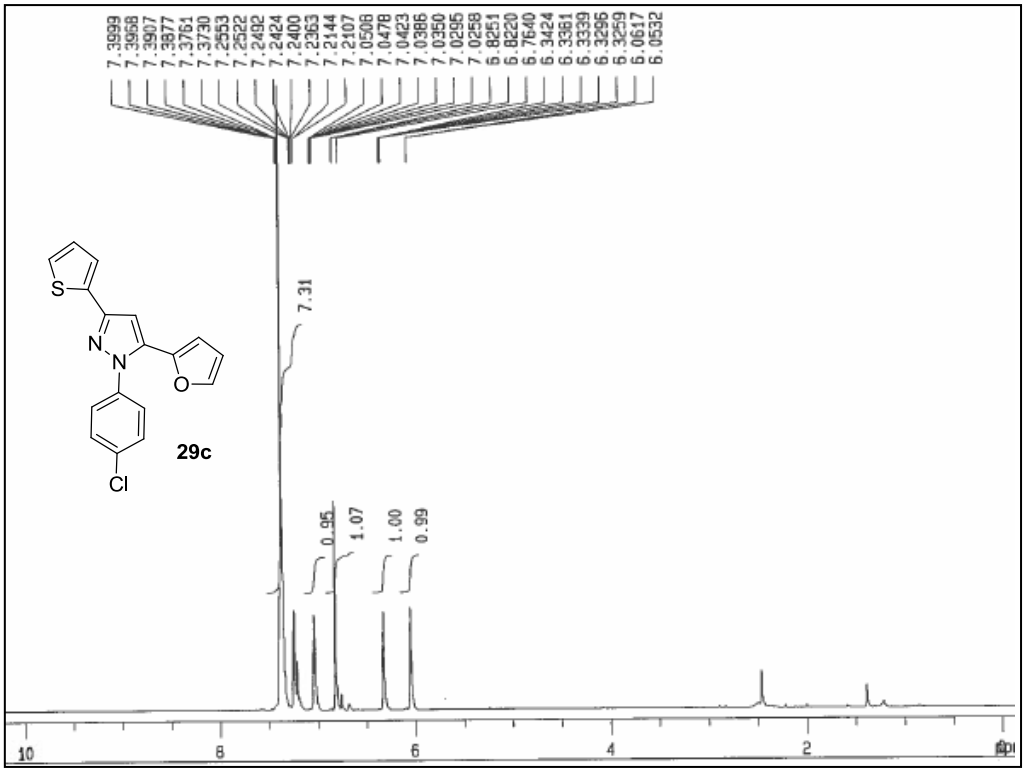

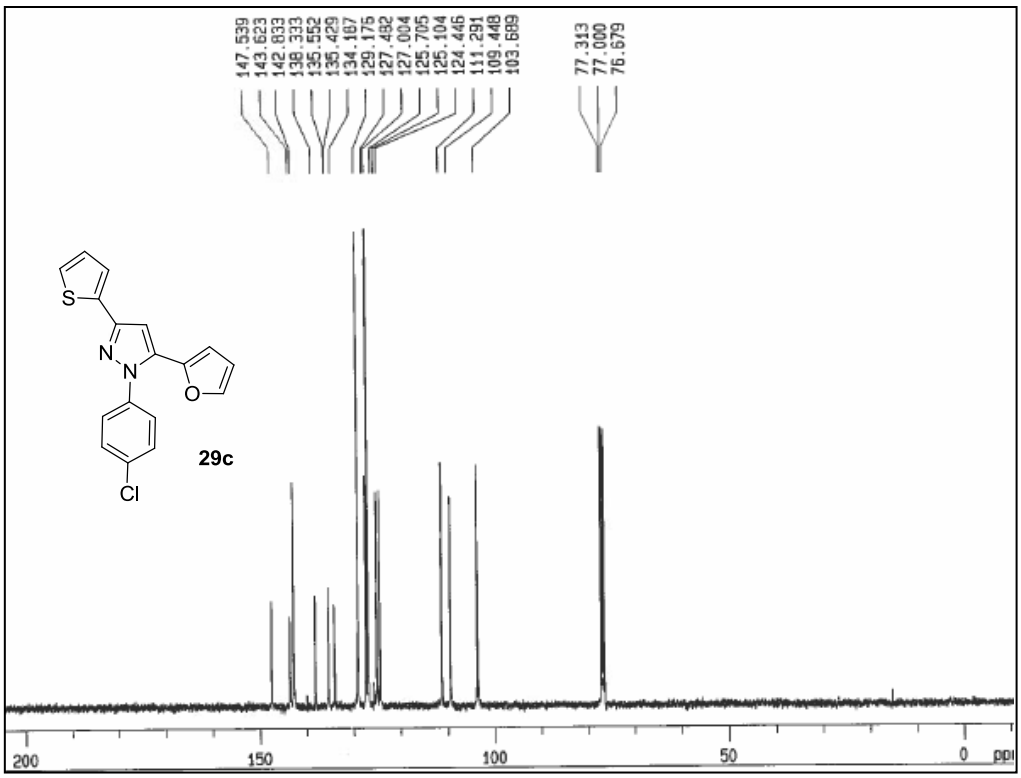

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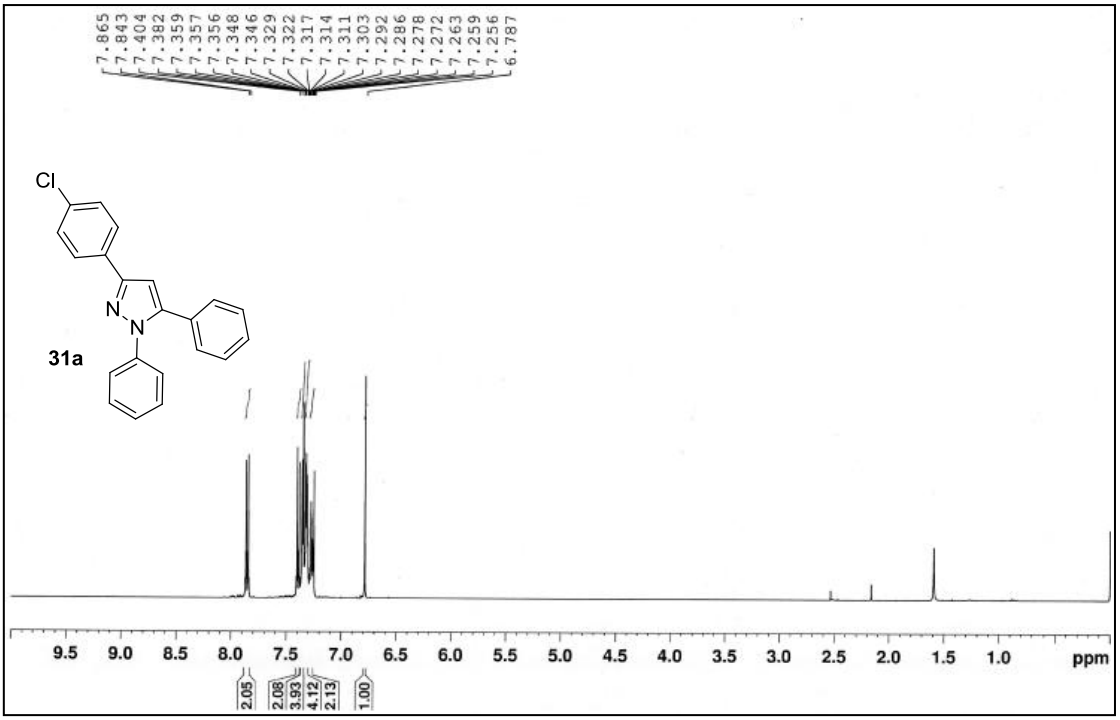

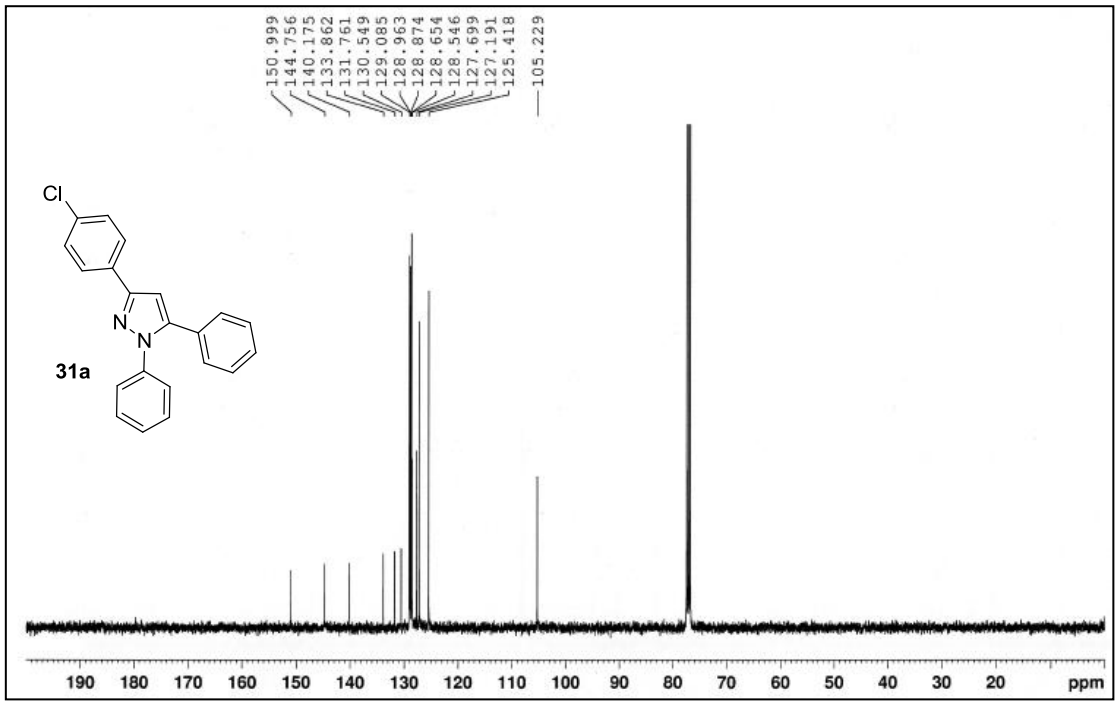

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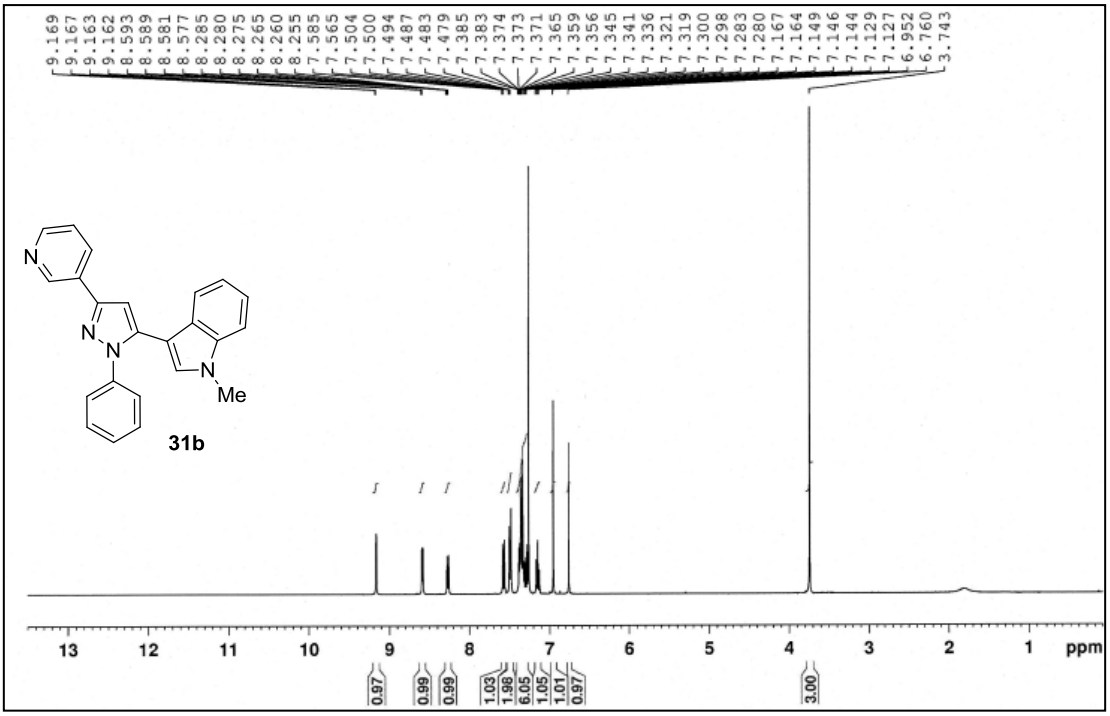

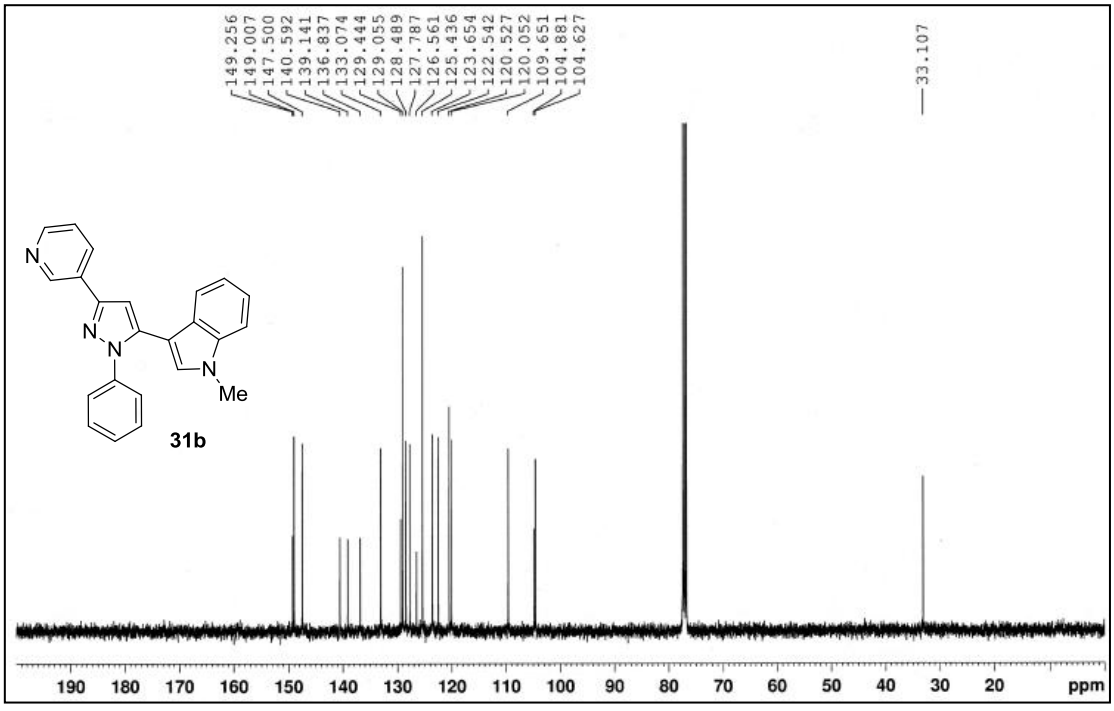

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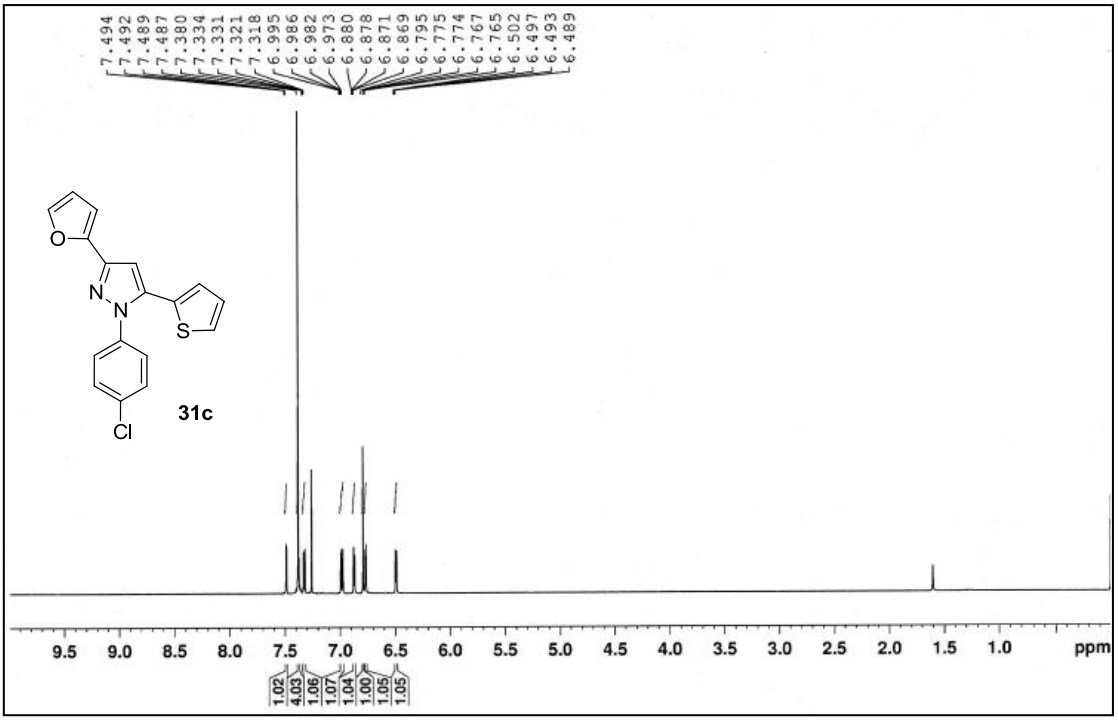

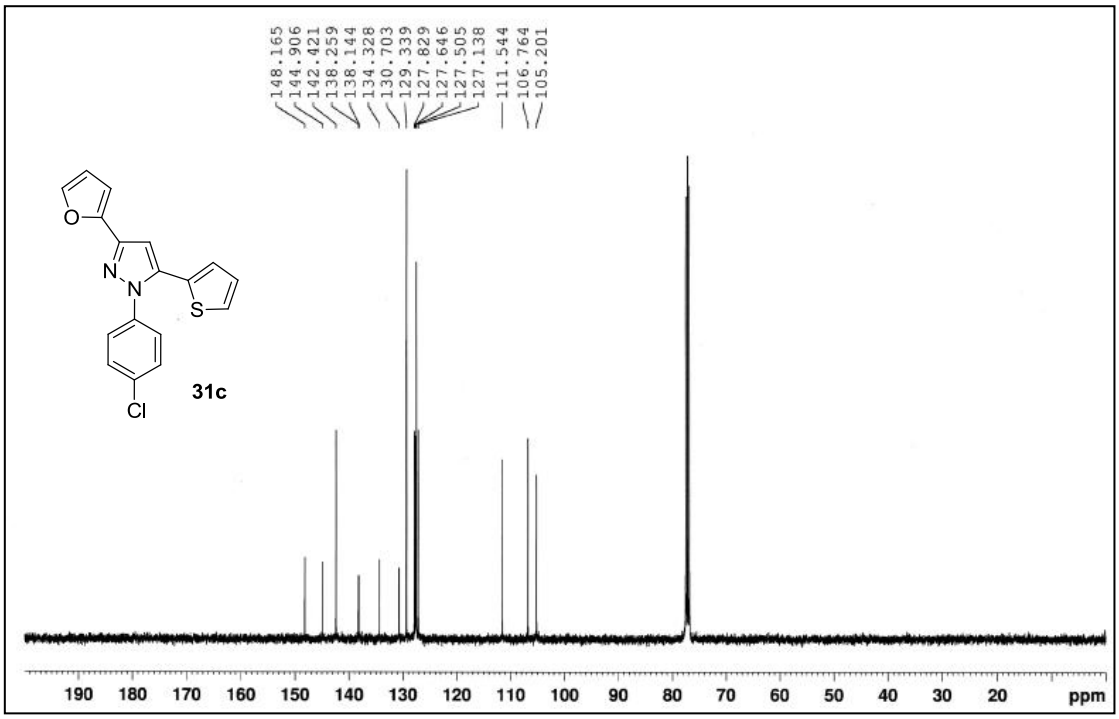

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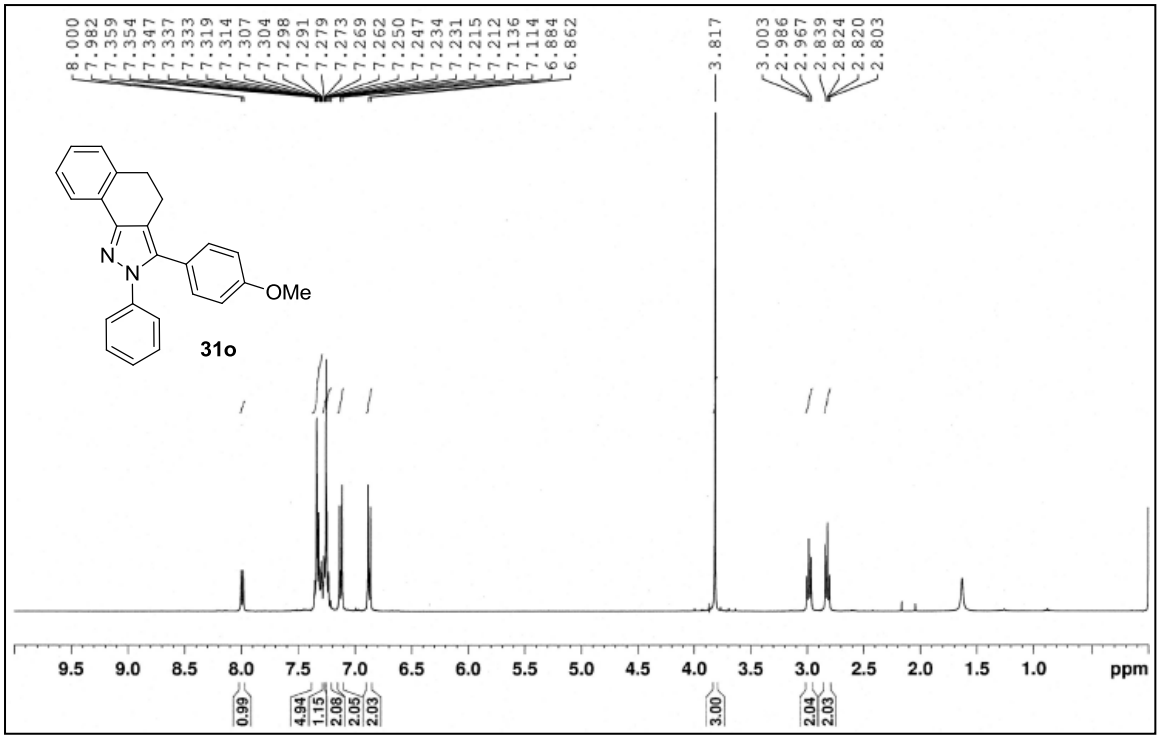
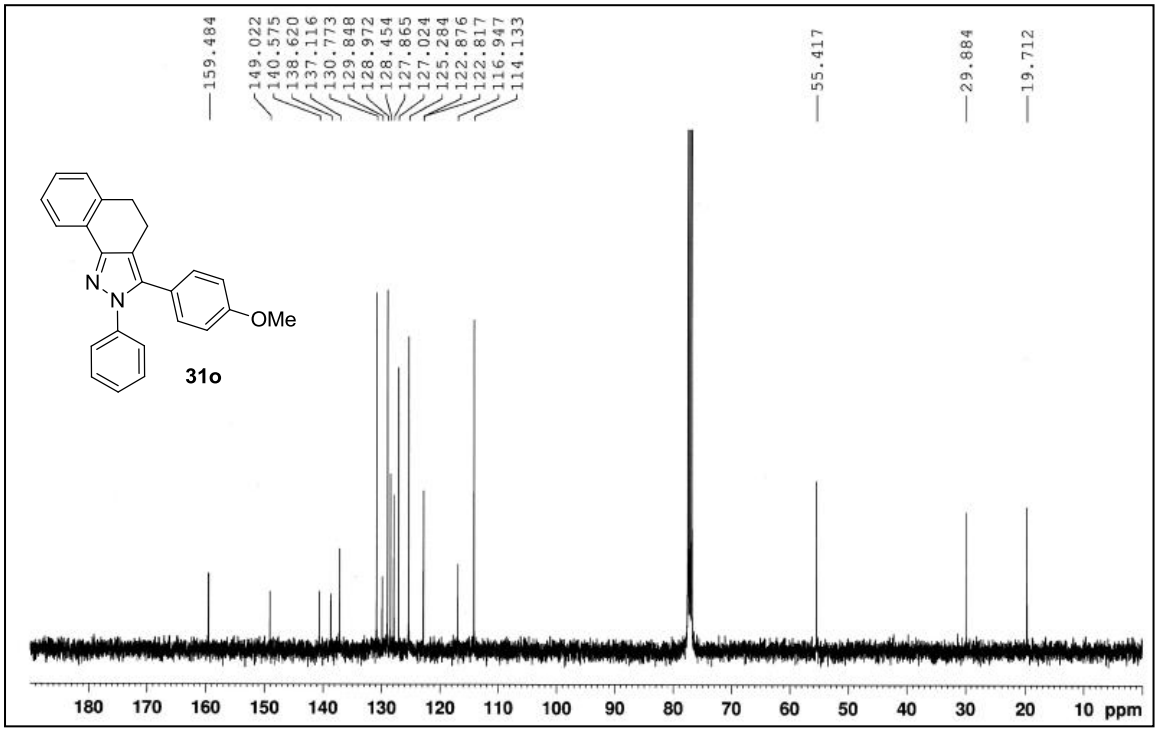




^{1}H NMR and ^{13}C NMR Spectra for compound **31o** in $CDCl_3$

Chapter 6

*Synthesis of 2,4,5-Trisubstituted Oxazoles with Complementary Regioselectivity from α-Oxoketene Dithioacetals and β-(methylthio)-β-(Het/Aryl)-2-propenones**

6.1 Introduction

Oxazole heterocycle represents an important structural motif, which constitutes key substructure of several potent therapeutics and biologically active naturally occurring compounds,[1] isolated from marine invertebrates and microorganisms.[2] Many of the oxazole derivatives display antibacterial, antifungal, anti-inflammatory and antitumor activities and act as enzyme inhibitors and peptidomimetics, hence represent valuable synthetic targets in medicinal chemistry and pharmaceuticals.[3] Oxazole derivatives have also found applications as functional materials,[4] as efficient luminophores for liquids and plastic scintillators, fluorescent probes for biological systems, corrosion inhibitor, as components of laser dyes, sensors, receptors, polymers and ligands for catalysis.[5] This has generated considerable interest in the synthesis of this class of heterocycles in recent years with development of several efficient synthetic methods.[6-21]

*Manuscript under preparation

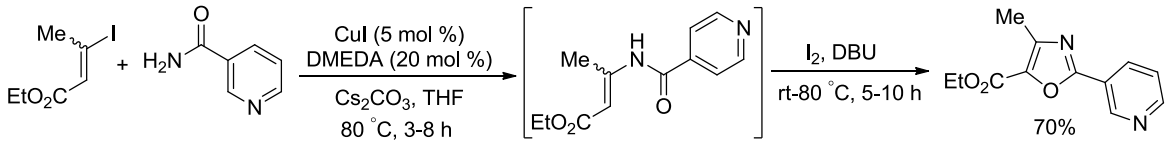
The classical methods for oxazole synthesis, include cyclization of acyclic precursors, coupling of prefunctionalized oxazoles with organometallic reagents[6] and oxidation of oxazolines.[7] Cyclization approach is much more effective due to diversity of substrates.[8-21] Among various cyclization strategies, Robinson-Gabriel condensation using α-acylaminoketones,[8] has been frequently utilized earlier to prepare a range of highly substituted oxazoles. However this method requires the use of Bronstead or Lewis acid catalysts/reagents which limits overall functional group tolerance of the transformation. The other previously reported syntheses include the Cornforth protocol,[9] catalytic decomposition of diazocarbonyl compounds in presence of nitriles or amides,[10] photolysis and pyrolysis of N-acylisoxazolones,[11a] and modified Robinson-Gabriel reactions.[11b-c] Among recently reported methods, oxidative [3+2] annulations of a prefunctionalized ketones or aldehydes with nitrile, benzyl amine or amides, have been well studied as straightforward procedures.[12] Other recent examples include addition of isocyanates to imines,[13] cycloaddition of acyl azide with alkynes,[14] gold catalyzed three component annulations of benzylamines,[15] acyl chloride and terminal alkynes,[16] TM catalyzed or organocatalytic [3+2] cycloadditions,[17] methods based on cyclization isomerization of propargylamides,[18] Pd catalyzed imidoylative cyclization of α-isocyanoacetamides,[19] oxidative annulations of enaminoesters/ketones in presence of hypervalent iodine reagents,[20] reactions of α-aminoketones and aldehydes.[21a] All these methods have been discussed earlier in the Chapter 2.

However, very few of these reports are general and do not deal with the synthesis of 2,4,5-trisubstituted oxazoles with flexible substitution pattern at all positions, besides direct introduction of functional groups at 2,4,5 positions is quite rare. Most of them suffer from low functional group compatibility, requiring multiple steps and tedious synthetic procedure. Therefore, developing a milder and more general procedure to access polysubstituted oxazole derivatives is still highly desirable.

Among various methods for oxazole synthesis, intramolecular cyclization of enamides derivatives carrying a leaving group at β-position provides a convenient access to oxazoles through intramolecular carbon-oxygen bond formation. For example, enamides bearing the β-vinylic C-heteroatom bonds (C-Br, C-I, C-OMe) serve as stable, easily accessible starting materials which can also be generated in situ and are shown to undergo facile intramolecular vinylation of amide oxygen in the presence of various

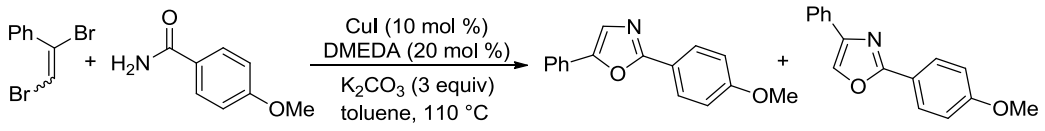
organic or inorganic bases or acids to provide a broad range of oxazoles under milder conditions.[21b-c] These enamide precursors are generated in several ways. Thus Ferreira and coworkers[22] have reported synthesis of *β*-haloenamides via sequential dehydration of *N*-acyl-*β*-hydroxy amino acids and subsequent halogenations with NBS or iodine, followed by treatment with DBU in a stepwise or one pot process to afford 2,5-disubstituted oxazole-4-carboxylates (Chapter 2, Scheme 19). On the other hand, Reissig[23] has developed an interesting mechanistically intriguing serendipitous synthesis of *β*-alkoxy-*β*-ketoenamides involving three component reaction using lithiated alkoxyallenes, nitrile and carboxylic acids. These functionalized enamides undergo facile intramolecular cyclization in presence of trifluoroacetic acid to furnish 2,4-disubstituted 5-acetyloxazoles (Chapter 2, Scheme 20).

Enamides have also been generated by copper catalyzed amidation of vinyl halides. Thus, Buchwald and co-workers[24] have previously reported a sequential (two step one-pot) synthesis of 2,4,5-trisubstituted oxazoles via copper catalyzed amidation of vinyl halides to form enamides followed by intramolecular cyclization promoted by iodine (Scheme 1).



Scheme 1

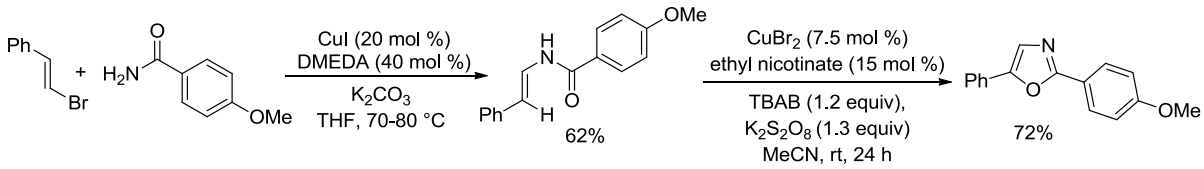
Glorious and co-workers have developed synthesis of disubstituted oxazoles via copper catalyzed annulations of 1,2-dihaloolefins with primary amides via intermediacy of halogen substituted enamides (Scheme 2).[25] However the reaction affords mixture of 2,4- and 2,5-substituted oxazoles as shown in the Scheme 2.



Scheme 2

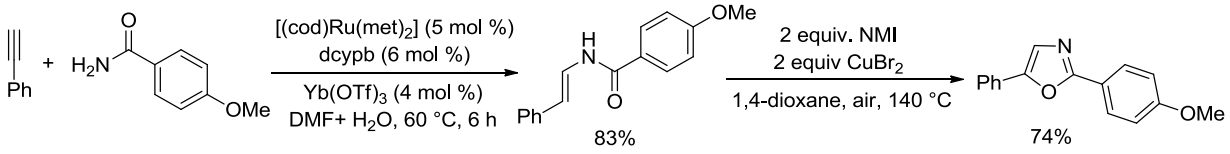
Recently, several examples of transition metal catalyzed methods for the direct intramolecular vinylic C-H functionalization of enamides have been described,[26] which provide a more direct approach to substituted oxazoles by avoiding the substrate functionalization. Thus, Buchwald has reported a copper(II) catalyzed oxidative

cyclization of enamides to 2,5-disubstituted oxazoles via vinylic C-H bond functionalization as complement to previous work (Scheme 3).[26a]



Scheme 3

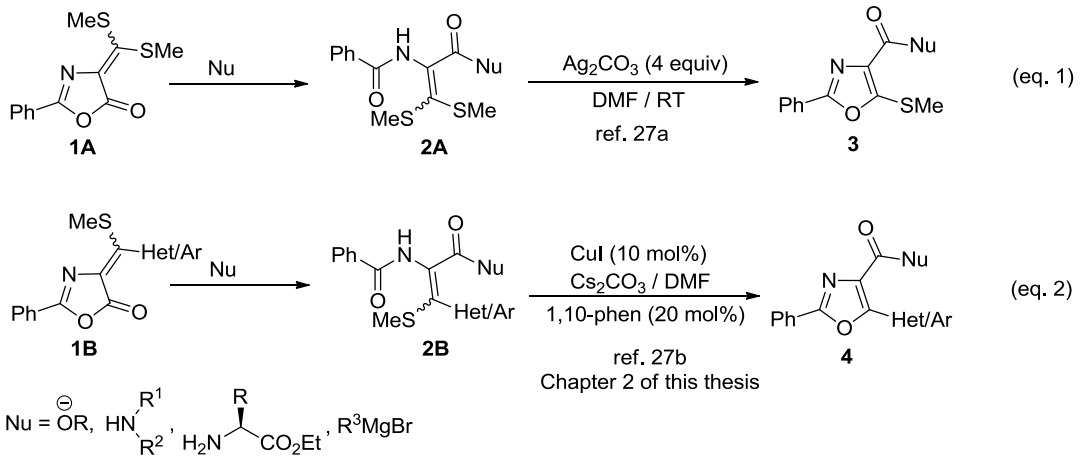
Stahl and coworkers[26b] have recently reported the synthesis of a series of enamide intermediates prepared via Ru-catalyzed anti-Markonikov hydroamination of alkynes with amide (Scheme 4). These enamides were subsequently converted to 2,5-disubstituted oxzaoles via Cu(II) mediated oxidative cyclization in presence of air (Scheme 4).



Scheme 4

Also, several oxidative cyclization approaches have been developed from enamides using I_2,[26c] hypervalent iodine,[26d] NBS[26e] as oxidants. Recently Jiang and coworkers have reported an efficient one step synthesis of trisubstituted oxazoles from amides and enolizable *β*-diketones via palladium or copper catalyzed oxidative C-H functionalization- cyclization ($K_2S_2O_8$ as oxidant) of in situ generated enamides.[26f]

In this context, as part of our programme to develop new synthetic methods for the construction of a wide range of small molecule heterocyclic libraries with potential biological activity, our research group has recently reported a substrate controlled diversity oriented efficient protocol for the synthesis of 2-phenyl-5-(methylthio)-4-functionalized oxazoles **3** via nucleophilic ring opening of 4-(arylidene)-5-oxazolones **1A** by silver carbonate mediated intramolecular 5-endocyclization of the resulting functionalized enamides **2A** (Scheme 5, eq. 1).[27a] We have further elaborated and expanded the synthetic scope of this strategy by developing an efficient synthesis of 2-phenyl-5-(het)aryl-4-functionalized oxazoles **4** and related natural products via nucleophilic ring opening of oxazolones **1B** and subsequent copper catalyzed intramolecular cyclization of enamide precursors **2B** (Scheme 5, eq. 2).[27b] These results have been described in detail in the Chapter 2.

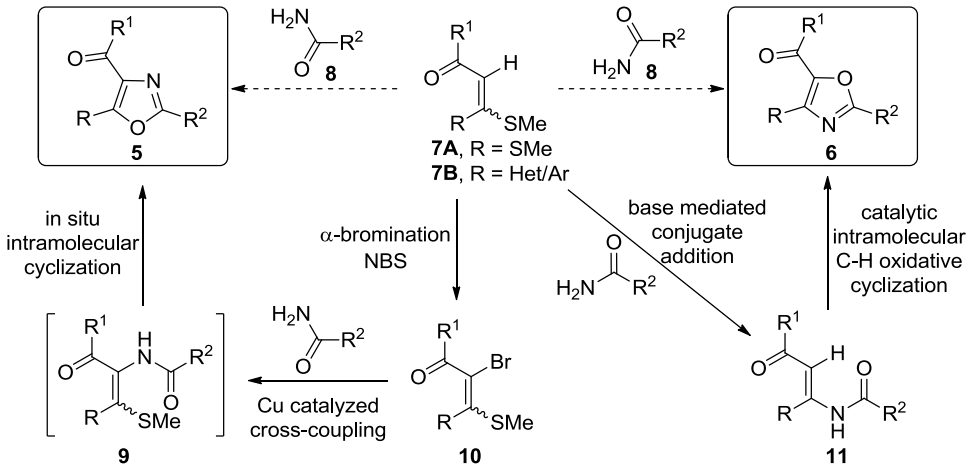


Scheme 5

During the course of these studies, we became interested in developing a [3+2] annulation approach for the synthesis of 2,4,5-trisubstituted oxazoles **5** and **6** with complementary regioselectivity from common two carbon precursors such as *α*-oxoketene dithioacetals or the corresponding *β*-(methylthio)-*β*-(het)aryl-enones **7A** and **7B** and a primary amides **8** via intermediacy of enamides **9** and **11** respectively (Scheme 6). We have demonstrated in our previous studies, synthetic applications of these readily accessible intermediates as versatile two and three carbon building blocks for the synthesis of a broad range of five and six membered heterocyclic compounds.[28]

Our proposed strategy for the synthesis of oxazoles **5** and **6** from **7A** and **7B** is shown in the Scheme 6. Thus, it was planned to synthesize 4-acyloxazoles **5** via copper catalyzed cross coupling of various primary amides with *α*-bromoalkenes such as **10** (generated by *α*-bromination of **7** with N-bromosuccinimide) followed by subsequent in situ intramolecular cyclization of the resulting enamides **9** (Scheme 6). In further continuation of these studies, we also considered of interest to develop synthesis of regioismeric 5-acyloxazole **6** from the same *β*-(methylthio)enone precursors **7A and 7B** as shown in Scheme 6. We speculated a two step approach (or one-pot) *via* base mediated conjugate addition-elimination of a primary amides to *β*-(methylthio)enones **7** to furnish the corresponding enamide precursors **11**. Subsequent catalytic oxidative cyclization of **11** through intramolecular vinylic C-H functonalization-C-O bond formation as demonstrated in earlier reports,[26] would provide the desired 5-acyloxazoles **6** (Scheme 6). We have successively achieved these goals and describe in the following section, an efficient synthesis of a 2,4,5-trisubstituted oxazoles **5** and **6** with complementary

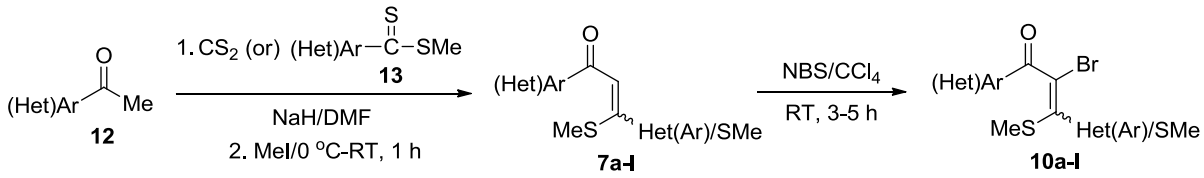
regioselectivity with a broad range of substituent pattern, from easily accessible common *β*-(methylthio)enone precursors **7A and 7B** and primary amides.



Scheme 6

6.2 Results and discussion

The desired *α*-oxoketene dithioacetal/*β*-(methylthio)-*β*-(het)arylenone precursors **7a-l** were prepared according to our earlier reported procedures[29] in excellent yields by reacting various (het)arylmethylene ketones **12** with either CS_2 (for **7a-e**) or dithioesters **13** (for **7f-l**) in the presence of sodium hydride in DMF followed by alkylation with methyl iodide. The corresponding *α*-bromoketene dithioacetals(**10a-e**) and *α*-bromo-*β*-(methylthio)-*β*-(het)arylenones (**10f-l**) were prepared in good yields by bromination of **7a-l** precursors with NBS in CCl_4 at room temperature as reported earlier (Scheme 7 and Table 1).[30]

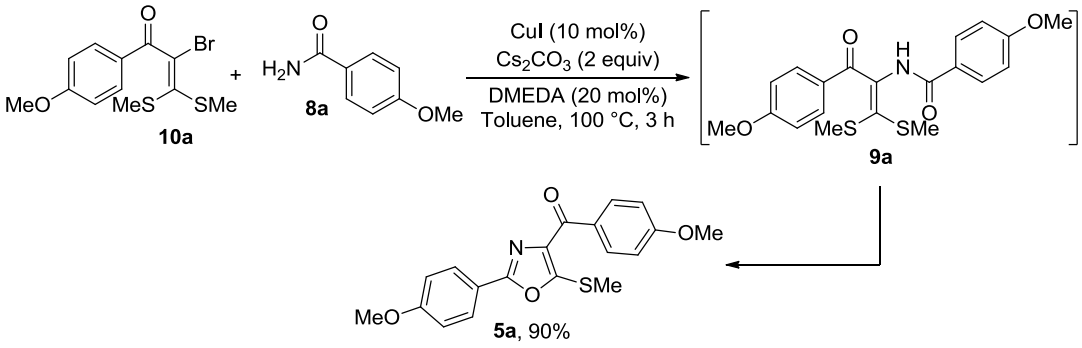


Scheme 7

6.2.1. Synthesis of 2-(het)aryl/alkyl-5-(methylthio)/(het)aryl-4-acyloxazoles 5a-l

In the preliminary experiments, *α*-bromoketene dithioacetal **10a** and the amide **8a** were selected as model substrates for optimization of reaction conditions for the formation of oxazole **5a**. Screening of various copper catalysts (CuCl, CuBr, CuI, Cu_2O, Cu powder), ligands (L-proline, 1,10-phenanthroline, *N*, *N'*-dimethylethylenediamine) and bases (Cs_2CO_3, K_2CO_3, K_3PO_4) in the presence of various solvents revealed that the

best results were obtained using 10 mol % of CuI as catalyst and 20 mol % of DMEDA as ligand in the presence of 2 equiv. of Cs_2CO_3 as a base in refluxing toluene furnishing the desired 2-(4-methoxyphenyl)-4-(4-methoxybenzoyl)-5-(methylthio)oxazole **5a** in 90% yield (Scheme 8). As is evident from these results, the intramolecular cross-coupling of *α*-bromoenone **10a** and amide **8a** to give intermediate enamide **9a** and its subsequent base mediated intramolecular cyclization proceeds efficiently in a one-pot process (Scheme 8). However, our attempts to isolate enamide **9a** under varying reaction conditions were not successful.

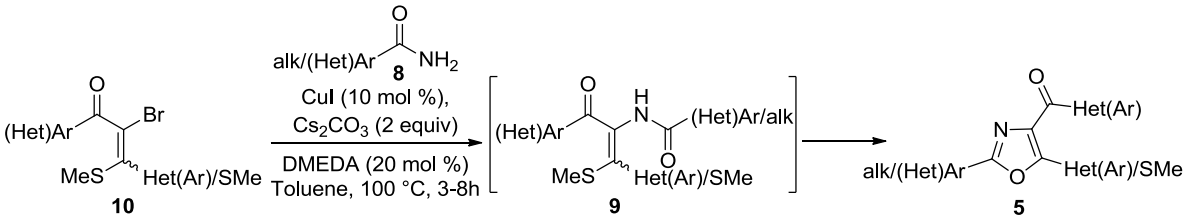


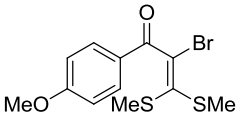
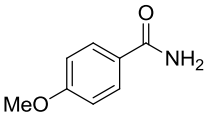
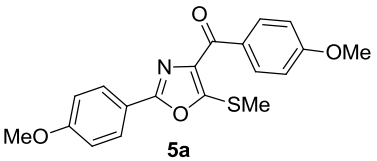
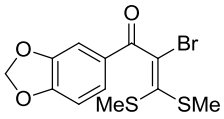
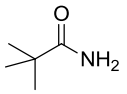
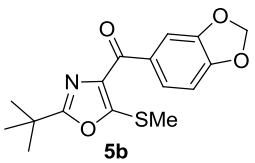
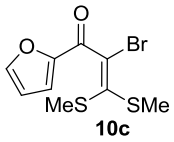
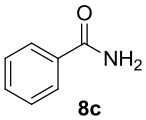
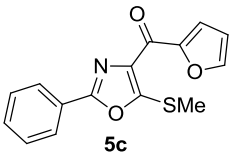
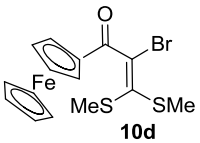
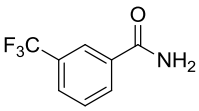
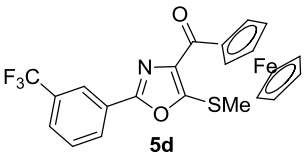
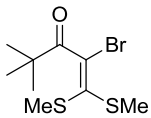
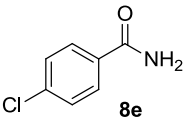
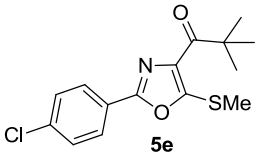
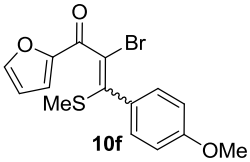
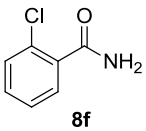
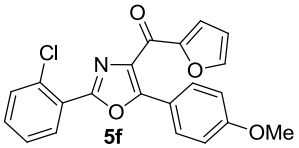
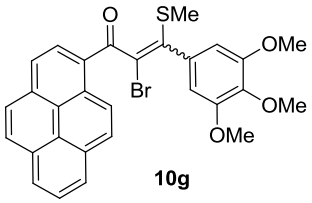
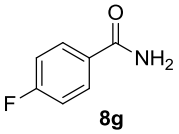
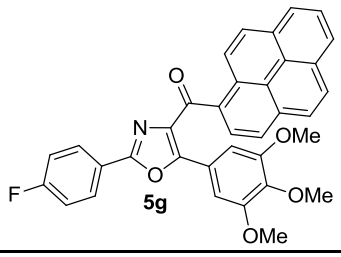
Scheme 8

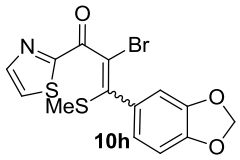
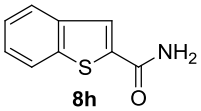
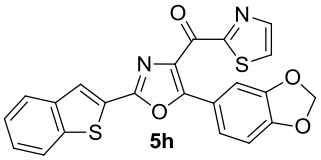
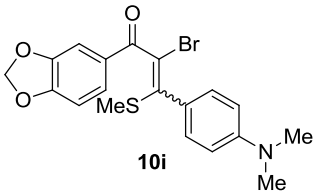
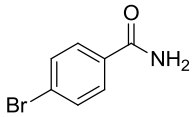
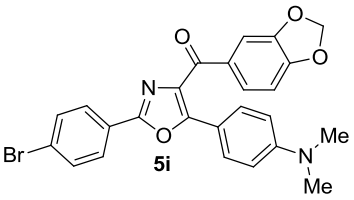
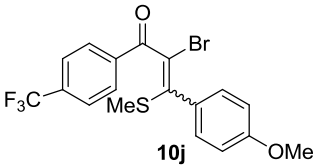
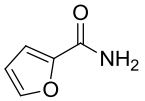
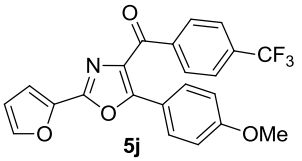
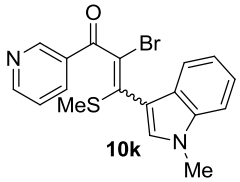
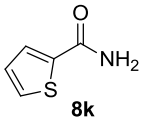
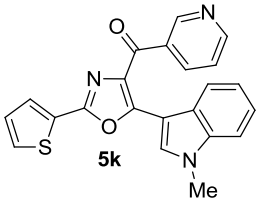
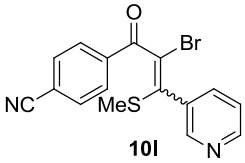
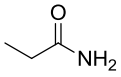
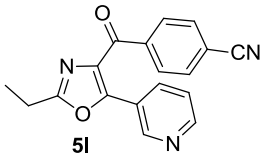
With the established optimized reaction conditions in hand, we next evaluated the generality and scope of this reaction with respect to a range of substituents at various positions in the substrates **10** and amide **8,** these results are presented in Table 1. Thus, the reaction was found to be equally efficient with other *α*-aroyl (**10b**), (het)aroyl (**10c**), ferrocenoyl (**10d**) and *α*-pivoloyl (**10e**) ketene dithioacetals, which afforded the respective 2,4-subtituted-5-(methylthio)oxazoles **5b-e** in excellent yields on copper catalyzed annulations with various substituted aromatic and aliphatic amides (entries 1-5, Table 1). Similarly, this copper catalyzed annulations process was found to be equally effective with various 2-bromo-3-(methylthio)-3-(het)arylenones **10f-k** affording the corresponding 2,5-bis(het)aryl-4- (het)aroyloxazoles **5f-k** in excellent yields on cyclization with various primary amides under identical conditions (entries 6-11, Table 1). Thus, it was possible to install a range of aryl and (het)aryl groups bearing electron donating as well as electron withdrawing and sterically incumbent (entry 6, Table 1) substituents at 2,5-position of oxazoles by utilizing various *β*-(het)arylenones **10f-k** and substituted aromatic amides **8f-k**. Similarly, a broad variety of (het)aroyl substituents could also be introduced at 4-position of these oxazoles **5f-k**. The entry 12 in Table 1 shows preparation of a 2-

alkyloxazole **5l** in high yield using an aliphatic amide like propionamide **8l** and enone **10l.**

Table 1. Synthesis of oxazoles 5a-l from 10a-l



S.No	Substrate **10**	Amide **8**	Oxazole **5**	Yield of **5** (%)
1	 **10a**	 **8a**	 **5a**	90
2	 **10b**	 **8b**	 **5b**	90
3	 **10c**	 **8c**	 **5c**	83
4	 **10d**	 **8d**	 **5d**	81
5	 **10e**	 **8e**	 **5e**	80
6	 **10f**	 **8f**	 **5f**	88
7	 **10g**	 **8g**	 **5g**	83

S.No	Substrate **10**	Amide **8**	Oxazole **5**	Yield of **7** (%)
8	 **10h**	 **8h**	 **5h**	85
9	 **10i**	 **8i**	 **5i**	70
10	 **10j**	 **8j**	 **5j**	85
11	 **10k**	 **8k**	 **5k**	90
12	 **10l**	 **8l**	 **5l**	82

The structures of these newly synthesized oxazoles **5a-l** were confirmed with the help of spectral (^{1}H and ^{13}C NMR) and analytical data, besides regiochemistry was further confirmed by X-ray crystallographic data of one of the oxazoles **5e** (Figure 1).

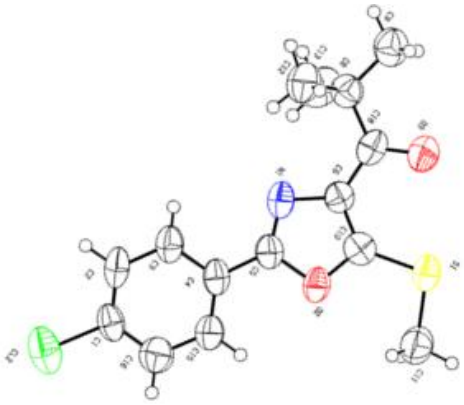
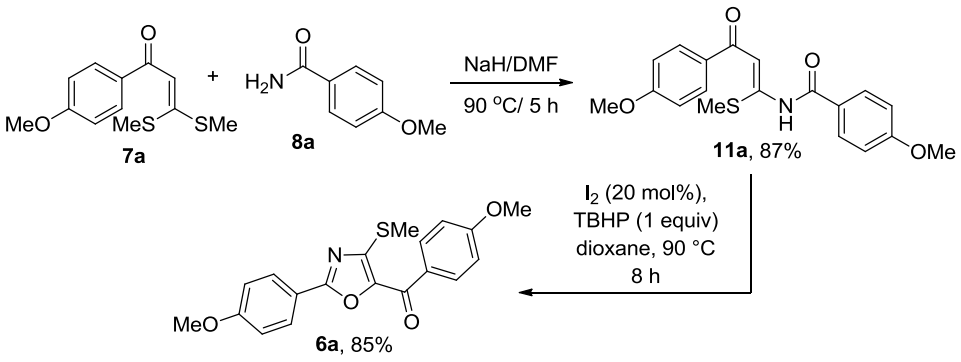


Figure 1. X-ray crystal structure of **5e**

6.2.2 Synthesis of regioisomeric 2-(het)aryl/alkyl-4-(methylthio)/(het)aryl-5-acyloxazoles 6a-l

Having successfully accomplished the synthesis of regioisomeric 2-(het)aryl/alkyl-5-(methylthio)/(het)aryl-4-(het)aroyloxazoles **5a-l** (Table 1), we further conceived of synthesizing the substituted 5-acyloxazoles **6** with complementary regiochemistry at 4,5-position. As proposed in Scheme 6, as a model experiment we first examined the synthesis of *β*-(methylthio)-*α*-aroylenamide **11a** via base mediated conjugate addition-elimination on ketene dithioacetal **7a** with primary amide **8a** (Scheme 9). Thus, treatment of **7a** with amide **8a** in the presence of NaH as base in DMF at 90 °C afforded the corresponding stable enamide **11a** in 87% yield (Scheme 9). Subsequent intramolecular oxidative C-H functionalization-C-O bond formation of enamide **11a** was attempted in presence of various iodine based reagents (I_2, PIDA, PIFA, DMP) or copper catalysis. The best results were obtained, when enamide **11a** was reacted with 20 mole% of iodine in presence of *t*-butylhydroperoxide (TBHP) (1 equiv) as reoxidant in dioxane at 90 °C furnishing the regioisomeric 2-(4-methoxyphenyl)-4-(methylthio)-5-(4-methoxybenzoyl) oxazole **6a** in 87% yield (Scheme 9).

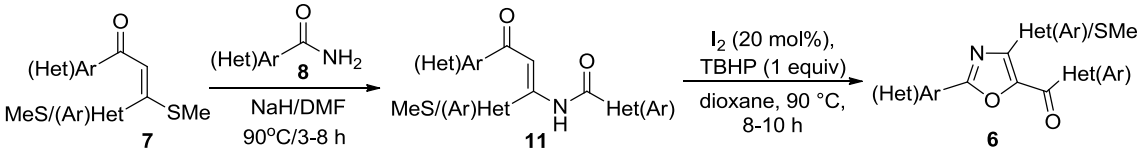


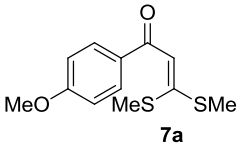
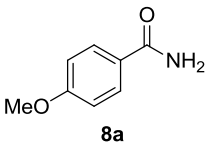
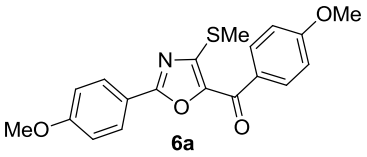
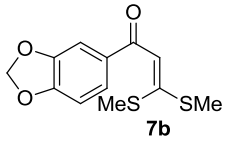
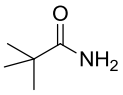
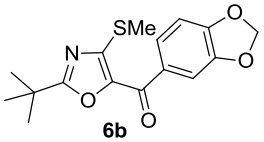
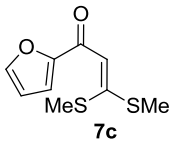
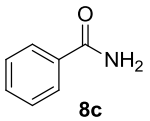
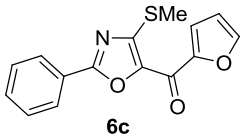
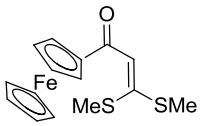
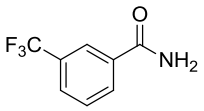
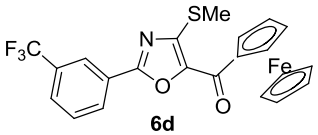
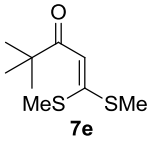
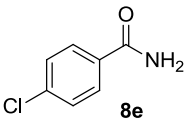
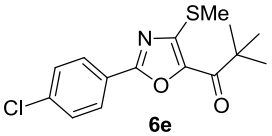
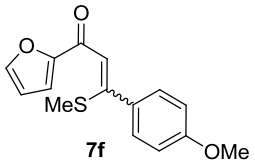
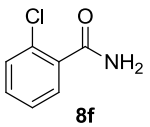
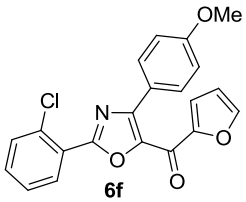
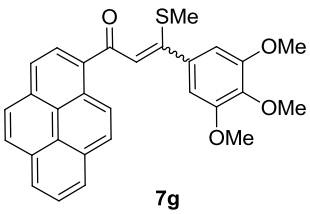
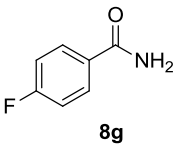
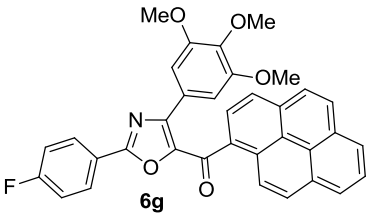
Scheme 9

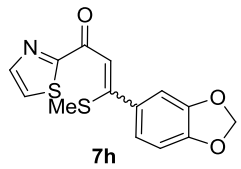
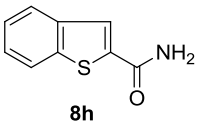
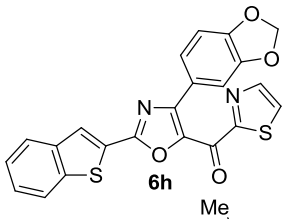
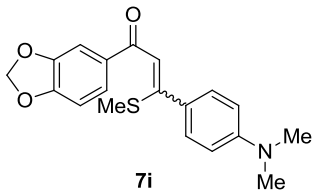
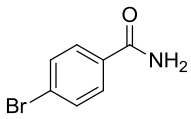
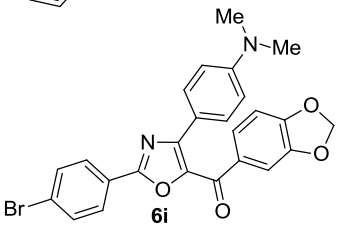
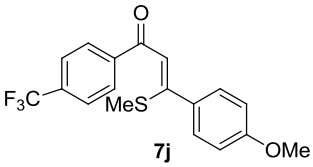
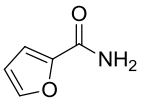
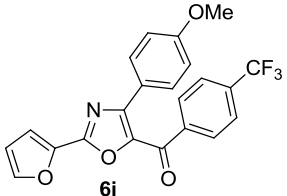
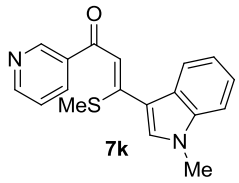
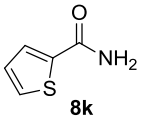
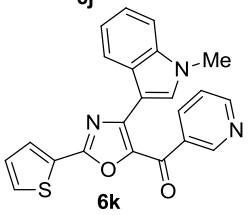
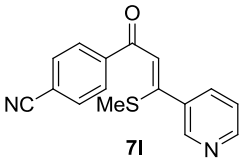
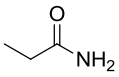
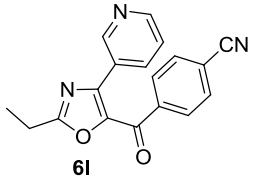
The versatility of this novel protocol was established by synthesizing the other regioisomeric 4-(methylthio)-5-(hetaroyl)oxazoles **6b-e** (entries 2-5, Table 2) in excellent yields by employing appropriate oxoketene dithioacetals **7b-e** and amides **8b-e**. The oxidative C-H functionalization/C-O bond formation reaction proceeded efficiently even when the crude enamides **11b-e** were used without further purification. Similarly, the corresponding 2,4,5-trisubstituted oxazoles **6f-k** with complementary regioselectivity were also obtained in excellent yields by intramolecular C-H functionalization/C-O bond formation of crude enamides **11f-k** (obtained from *β*-methylthio-*β*-(het)arylenones **7f-k** and amides **8f-k**) in presence of iodine/TBHP catalytic system (entries 6-11, Table 2).

However we failed to obtain the corresponding 2-ethyl oxazole **6l** from enamide **11l** under similar conditions yielding only intractable reaction mixture (entry 12, Table 2).

Table 2. Synthesis of regioisomeric oxazoles 6a-k from 7a-k



S.No	Substrate **7**	Amide **8**	Oxazole **6**	Yield of **6** (%)
1	 **7a**	 **8a**	 **6a**	85
2	 **7b**	 **8b**	 **6b**	89
3	 **7c**	 **8c**	 **6c**	81
4	 **7d**	 **8d**	 **6d**	77
5	 **7e**	 **8e**	 **6e**	85
6	 **7f**	 **8f**	 **6f**	80
7	 **7g**	 **8g**	 **6g**	55

S.No	Substrate **7**	Amide **8**	Oxazole **6**	Yield of **6** (%)
8	 **7h**	 **8h**	 **6h**	90
9	 **7i**	 **8i**	 **6i**	85
10	 **7j**	 **8j**	 **6j**	88
11	 **7k**	 **8k**	 **6k**	92
12	 **7l**	 **8l**	 **6l**	0

The structure and regiochemistry of these newly synthesized 2,4,5-trisubstituted oxazoles were confirmed with the help of the spectral and analytical data and also by X-ray crystallographic data of one of the oxazoles **6e** (Figure 2).

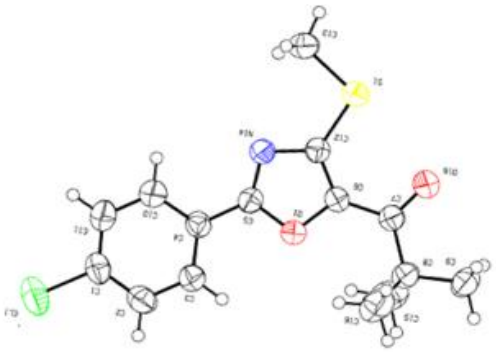
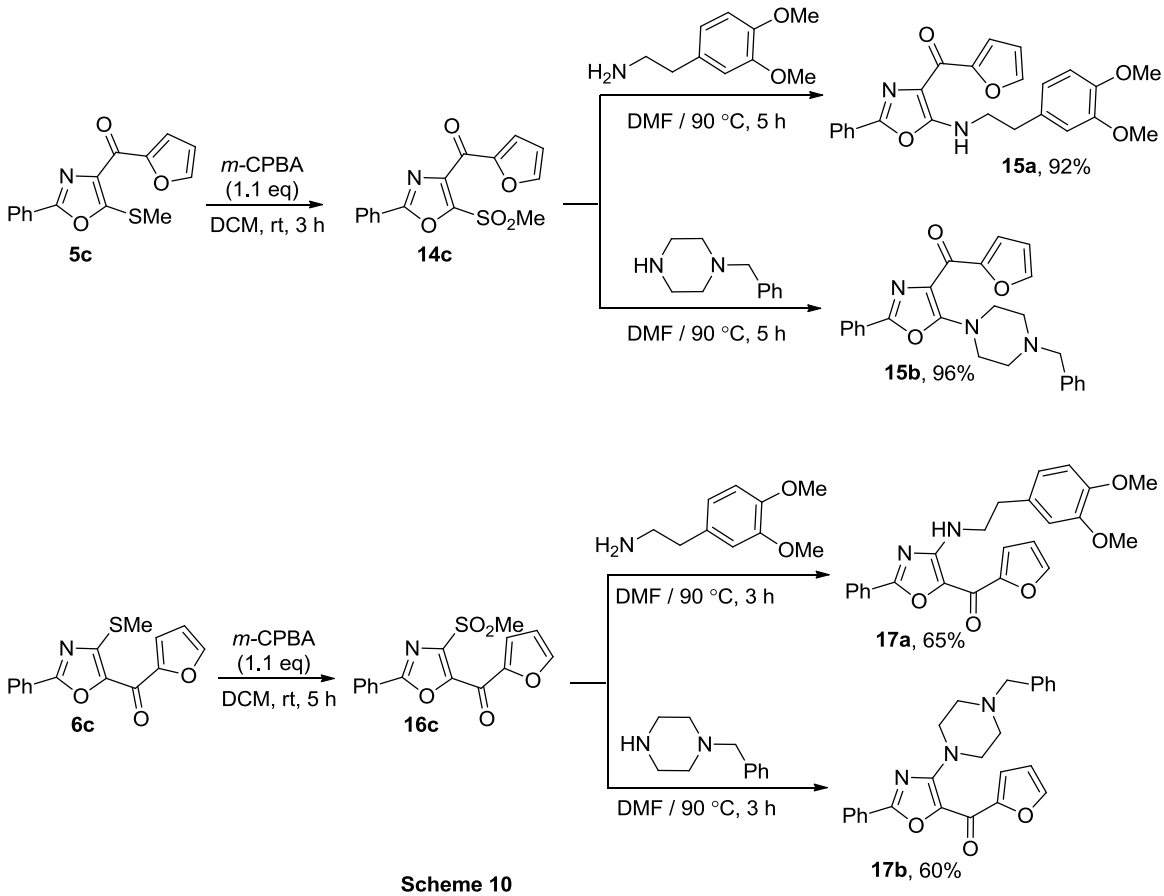


Figure 2. X-ray crystal structure of **6e**

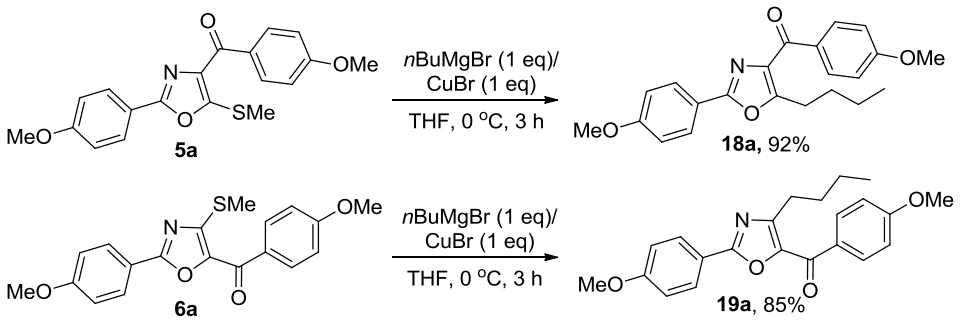
6.2.3 Synthesis of regioisomeric 4/5-amino substituted oxazoles 15a-b and 17a-b

To further examine the generality and scope of this novel regioselective synthesis of oxazoles, we proposed to synthesize regioisomeric 5-(or 4-) amino substituted oxazole **15** and **17** by nucleophilic substitution on 5-(or 4-)methylsulfonyloxazole **14c** and **16c** respectively by few amines as shown in the Scheme 10. These 5 (or 4-)-(methylsulfonyl)oxazoles **14c** and **16c** were obtained by *m*-CPBA oxidation of the respective 5/4-(methylthio)oxazoles **5c** and **6c** (Scheme 10). Thus, displacement reaction on 5 (or 4-)methylsulfonyl oxazoles **14c** and **16c** by either primary alkyl amine such as (3,4-dimethoxyphenyl)ethyl amine or secondary amine like *N*-benzylpiperazine proceeded smoothly at room temperature providing the corresponding 5 (or 4-) primary or secondary amino substituted oxazoles **15a-b** and **17a-b** in excellent yields (Scheme 10).



Scheme 10

The versatility of the reaction was further elaborated by copper mediated displacement of methylthio group in the oxazoles **5a** or **6a** by *n*-butylmagnesium bromide to give 4 (or 5)-(*n*-butyl) substituted regioisomeric oxazoles **18a** and **19a** in excellent yields (Scheme 11).



Scheme 11

6.3. Conclusion

We have developed an efficient protocol for the synthsis of 2-(het)aryl/alkyl-4-(het)aroyl-5-(methylthio)/(het)aryloxazoles **5** (Table 1) and the corresponding 2-(het)aryl /alkyl-4-(methylthio)/(het)aryl-5-(het)aroyloxazoles **6** (Table 2) with complementary regioselectivity from the corresponding α-oxoketenedithioacetals or β-(het)aryl/ (methylthio) enone precursors by employing two strategies. In the first approach, the α-oxoketene dithioacetals or β-(methylthio)enones were converted to the corresponding α-bromo substituted intermediates by bromination with *N*-bromosuccinamide. Subsequent copper catalyzed intramolecular annulations of these α-bromoenones with various primary amides afforded 2-(het)aryl/alkyl-4-(het)aroyl-5-(methylthio)/(het)aryloxazoles **5** in excellent yields via concomitant formation of C4-N and C5-O bond, without isolation of intermediate enamides (Table 1). In the second approach, the starting α-oxoketene dithioacetals or β-(methylthio)-β-(het)arylenones were subjected to base induced conjugate addition-elimination with various primary amides to furnish β-aroyl enamides, which, on subsequent iodine catalyzed oxidative intramolecular cyclization (through C-H functionalization-C-O bond formation) afforded the corresponding regioisomeric 2-(het)aryl/alkyl-4-(methylthio)/(het)aryl-5-(het)aroyl oxazoles **6** in excellent yields (Table 2). Further studies to examine synthetic application of these strategies to some biologically important oxazoles are in progress.

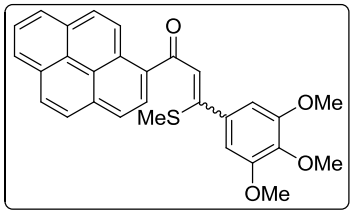
6.4 Experimental Section

6.4.1 General Information. All reagents were purchased from commercial suppliers and used without further purification. Solvents were dried according to the standard procedures. All the reactions were monitored by thin layer chromatography using standard TLC Silica gel plates and visualized with UV light. Column chromatography was performed using silica gel (100-200 mesh). Nuclear magnetic resonance spectra were recorded on (400 MHz) FT-NMR spectrometer with $CDCl_3$ (or) DMSO-d_6 as solvent.

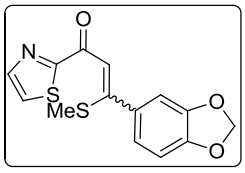
Chemical shifts were reported in δ ppm using residual solvent protons as internal standard (δ 7.26 for $CDCl_3$ and δ 2.50 for DMSO-d_6 in ^{1}H-NMR, δ 77.16 for $CDCl_3$ and δ 39.52 for DMSO-d_6 in ^{13}C-NMR). Coupling constants were reported as J values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), dd (double doublet), dt (doublet of triplet), td (triplet of doublet), ddd (doublet of doublet of doublet), m (multiplet) and br (broad). Infrared spectra of neat samples were recorded in ATR (attenuated total reflectance) mode using FT-IR instrument and HRMS on Q-TOF spectrometer. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. Electronic absorption spectra were recorded on a UV-Vis-NIR spectrometer. Emission spectra were recorded on a luminescence spectrometer. All the (het)aryl dithioesters were prepared according to the literature procedure.[30]

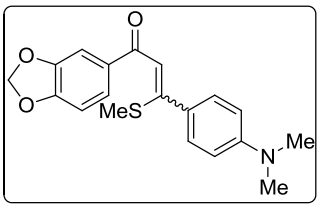
The desired α-oxoketene dithioacetal/β-(methylthio)-β-(het)arylenone precursors **7a-l** and the corresponding α-bromo derivatives **10a-l** were prepared according to our earlier reported procedures[28b,29]. The spectral and analytical data of the new α-oxoketene dithioacetal/β-(methylthio)-β-(het)arylenone precursors **7a-l** and the corresponding α-bromo derivatives **10a-l** is given below. Since **10h** and **10i** were unstable, they were used as such for the next step without further purification.

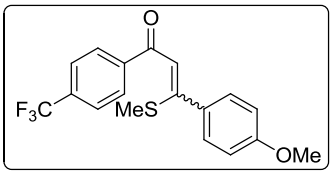
(*E*/*Z*)-3-(3,4,5-Trimethoxyphenyl)-3-(methylthio)-1-(pyren-1-yl)prop-2-en-1-one (7g).



Yellow solid (398 mg, 85%): mp 135-137 °C; R_f 0.5 (3:2 EtOAc/hexane); IR (neat, cm^{-1}) 1579, 1411, 1243, 1118, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 9.2 Hz, 0.55H), 8.54 (d, J = 9.2 Hz, 0.45H), 8. 30 (d, J = 8.0 Hz, 0.55H), 8.24-8.21 (m, 1.1H), 8.20-8.09 (m, 3.0H), 8.07-8.03 (m, 1.35H), 8.01-7.97 (m, 1.1H), 7.90 (t, J = 8.0 Hz, 0.9H), 7.16 (s, 0.55H), 6.61 (s, 1.1H), 6.55 (s, 0.45H), 6.22 (s, 0.9H), 3.89 (s, 3.3H), 3.89 (s, 1.65H), 3.43 (s, 2.7H), 2.96 (s, 1.35H), 2.49 (s, 1.35H), 2.11 (s, 1.65H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 192.6, 164.1, 161.4, 153.5, 152.1, 138.6, 138.3, 135.0, 134.74, 134.2, 133.4, 132.7, 132.4, 131.3, 131.2, 130.9, 130.7, 129.5, 129.3, 129.1, 128.9, 128.7, 127.3, 127.1, 126.8, 126.5, 126.4, 126.3, 126.2, 126.1, 126.0, 125.8, 125.2, 125.1, 124.8, 124.6, 124.5, 124.4, 124.3, 123.7, 122.0, 106.3, 105.6, 61.1, 60.2, 56.5, 55.7 ,16.9, 16.7; HRMS (ESI) m/z calcd for $C_{29}H_{25}O_4S$ $[M+H]^+$ 469.1474, found 469.1467.

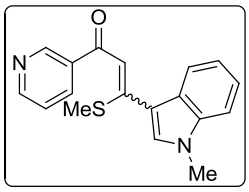
(*E/Z*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-2-bromo-3-(methylthio)-1-(thiazol-2-yl)prop-2-en-1-one (7h).  Yellow solid (244 mg, 80%): mp 110-112 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1627, 1536, 1481, 1231, 1016, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 3.2 Hz, 0.35H), 7.95 (d, J = 3.2 Hz, 0.65H), 7.62 (d, J = 3.2 Hz, 0.65H), 7.60 (d, J = 3.2 Hz, 0.35H), 7.50 (s, 0.65H), 7.22 (s, 0.35H), 6.92-6.81 (m, 3H), 6.02 (s, 1.3H), 5.99 (s, 0.7H), 2.53 (s, 1.05H), 2.09 (s, 1.95H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 177.1, 170.6, 169.7, 167.2, 166.1, 148.8, 148.6, 147.9, 147.5, 144.5, 144.4, 132.3, 131.3, 126.0, 125.9, 122.4, 122.2, 118.1, 111.9, 109.2, 108.9, 108.5, 108.2, 101.7, 101.5, 17.1, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{11}NO_3S_2Na$ $[M+Na]^+$ 328.0078, found 328.0062.

(*E/Z*)-1-(Benzo[*d*][1,3]dioxol-6-yl)-3-(4-(dimethylamino)phenyl)-3-(methylthio)prop-2-en-1-one (7i).  Yellow solid (255 mg, 75%): mp 126-128 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1602, 1506, 1248, 806; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 1.6 Hz, 0.8H), 7.49 (d, J = 1.6 Hz, 0.8H), 7.47 (d, J = 1.6 Hz, 0.2H), 7.34 (d, J = 1.6 Hz, 0.2H), 7.25 (d, J = 8.8 Hz, 1.8H), 6.99 (s, 0.8H), 6.82 (d, J = 8.0 Hz, 0.8H), 6.76 (d, J = 8.0 Hz, 0.4H), 6.73 (d, J = 8.8 Hz, 1.6H), 6.59 (d, J = 8.8 Hz, 0.4H), 6.41 (s, 0.2H), 6.01 (s, 1.6H), 5.98 (s, 0.4H), 3.01 (s, 4.8H), 2.95 (1.2H), 2.41 (s, 0.6H), 2.04 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 186.8, 164.6, 161.1, 151.3, 151.0, 150.9, 148.2, 147.9, 134.3, 134.1, 130.1, 129.5, 126.6, 124.8, 124.5, 123.8, 118.6, 114.6, 111.8, 111.4, 108.6, 108.3, 107.9, 107.7, 101.8, 101.3, 40.4, 40.3, 17.2, 16.6; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}NO_3S$ $[M+H]^+$ 342.1164, found 342.1158.

(*E/Z*)-1-(4-(Trifluoromethyl)phenyl)-3-(4-methoxyphenyl)-3-(methylthio)prop-2-en-1-one (7j).  Yellow solid (288 mg, 82%): mp 73-75 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat cm^{-1}) 1603, 1495, 1319, 1248, 1065, 809; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1.32H), 7.78 (d, J = 8.0 Hz, 0.68H), 7.61 (d, J = 8.4 Hz, 1.32H), 7.50 (d, J = 8.0 Hz, 0.68H), 7.20 (d, J = 8.8 Hz, 1.32H), 7.16 (d, J = 8.8 Hz, 0.68H), 6.97 (s, 0.66H), 6.89 (d, J = 8.8 Hz, 1.32H), 6.70 (d, J = 8.8 Hz, 0.68H), 6.41 (s, 0.34H), 3.77 (s, 1.98H), 3.67 (s, 1.02H), 2.37 (s, 1.02H), 1.93 (s, 1.98H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 187.1, 166.9, 163.2, 160.9, 160.5, 142.3, 141.8, 134.0, 133.6, 133.3, 133.0, 131.0, 130.3, 129.5, 128.8, 128.4, 125.7, 125.,65 125.61, 125.60, 125.34, 125.31, 125.27, 125.24, 122.5,

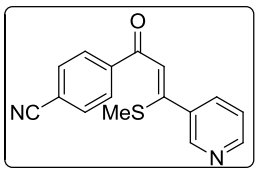
118.5, 115.3, 114.2, 113.8, 55.5, 55.3, 17.0, 16.6; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}F_3O_2S$ $[M+H]^+$ 353.0823, found 353.0819.

(*E*/*Z*)-3-(1-Methyl-1*H*-indol-3-yl)-3-(methylthio)-1-(pyridin-3-yl)prop-2-en-1-one



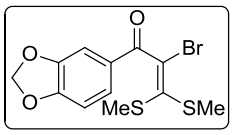
(7k). Brown semi solid (246 mg, 80%): R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2920, 1507, 1233, 1017, 741; ^1H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 1.6 Hz, 0.7H), 8.97 (d, *J* = 1.6 Hz, 0.3H), 8.72 (dd, *J* = 4.8 Hz, 1.6 Hz, 0.7H), 8.52 (dd, *J* = 4.8 Hz, 1.6H), 8.28 (dt, *J* = 8.0 Hz, 1.6 Hz, 0.7H), 7.96 (dt, *J* = 8.0 Hz, 1.6 Hz, 0.3H), 7.80 (d, *J* = 8.0 Hz, 0.7H), 7.45 (dt, *J* = 8.0 Hz, 0.8H), 7.41-7.37 (m, 1.7H), 7.33-7.29 (m, 1.4H), 7.24-7.16 (m, 2.0H), 7.14-7.07 (m, 0.6H), 6.54 (s, 0.3H), 3.86 (s, 2.1H), 3.72 (s, 0.9H), 2.52 (s, 0.9H), 2.19 (s, 2.1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9, 186.5, 160.3, 156.3, 152.2, 151.6, 149.3, 149.2, 137.3, 137.2, 135.5, 135.1, 134.6, 131.6, 129.1, 126.3, 125.9, 123.6, 122.9, 122.8, 122.7, 121.2, 120.82, 120.84, 120.2, 117.4, 114.3, 113.9, 113.1, 110.0, 109.7, 33.2, 33.1, 17.4, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{17}N_2OS$ $[M+H]^+$ 309.1062, found 309.1055.

4-((*Z*)-3-(Methylthio)-3-(pyridin-3-yl)acryloyl)benzonitrile (7l). Yellow solid (196 mg,



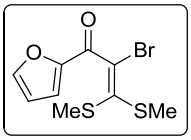
70%): mp 116-118 °C; R_f 0.3 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2924, 2231, 1623, 1521, 1254, 814; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.61 (dd, *J* = 2.4 Hz, 0.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.67 (dt, *J* = 7.6 Hz, 2.0 Hz, 1H), 7.41 (ddd, *J* = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 7.03 (s, 1H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 163.5, 150.5, 148.4, 141.6, 135.6, 134.5, 132.6, 128.5, 123.5, 119.3, 118.2, 115.8, 16.9; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{13}N_2OS$ $[M+H]^+$ 281.0749, found 281.0744.

1-(Benzo[*d*][1,3]dioxol-6-yl)-2-bromo-3,3-bis(methylthio)prop-2-en-1-one (10b).



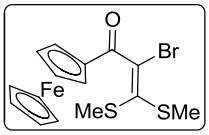
Obtained from **7b**, semi solid (328 mg, 95%): R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2920, 1644, 1562, 1457, 1274, 745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.40 (d, *J* = 1.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 2H), 2.46 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 152.7, 148.5, 137.7, 129.2, 126.9, 118.0, 108.9, 108.1, 102.1, 18.9, 16.3; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{12}BrO_3S_2$ $[M+H]^+$ 346.9411 and 348.9391, found 346.9415 and 348.9394.

2-Bromo-1-(furan-2-yl)-3,3-bis(methylthio)prop-2-en-1-one (10c). Obtained from **7c**,



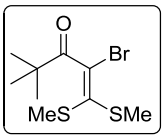
off-white solid (283 mg, 97%): mp 259-261 °C; R_f 0.6 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 1640, 1436, 1258, 1031, 784; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.19 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 6.57 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 2.46 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 150.7, 148.0, 140.3, 120.5, 116.3, 112.8, 19.3, 16.5; HRMS (ESI) *m*/*z* calcd for $C_9H_{10}BrO_2S_2$ $[M+H]^+$ 292.9306 and 294.9285, found 292.9311, 294.9290.

2-Bromo-(ferrocen-1-yl)-3,3-bis(methylthio)prop-2-en-1-one (10d). Obtained from **7d**,



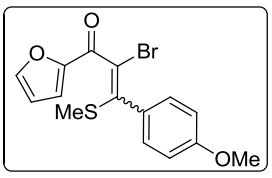
brown solid (336 mg, 82%): mp 259-261 °C; R_f 0.5 (1:4 EtOAc /hexane); IR (KBr, cm^{-1}) 1590, 1500, 1353, 1120, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (t, J = 2.0 Hz, 2H), 4.58 (t, J = 2.0 Hz, 2H), 4.29 (s, 5H), 2.43 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 138.1, 118.8, 72.9, 71.0, 70.2, 18.9, 16.5; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{16}BrFeOS_2$ $[M+H]^+$ 410.9175 and 412.9155, found 410.9150 and 412.9148

2-Bromo-4,4-dimethyl-1,1-bis(methylthio)pent-1-en-3-one (10e). Obtained from **7e**,

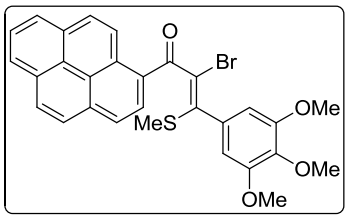


colorless liquid (253 mg, 90%): R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2968, 1689, 1477, 1100, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.23 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 134.0, 118.7, 43.9, 28.5, 18.9, 16.2; HRMS (ESI) *m*/*z* calcd for $C_9H_{16}BrOS_2$ $[M+H]^+$ 282.9826 and 284.9805, found 282.9832, 284.9811.

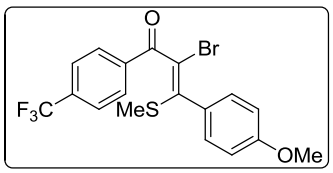
***(E/Z)*-2-Bromo-1-(furan-2-yl)-3-(4-methoxyphenyl)-3-(methylthio)prop-2-en-1-one**



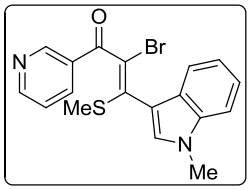
(10f). Obtained from **7f**, off-white solid (316 mg, 90%): mp 93-95 °C; R_f 0.7 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 1646, 1458, 1249, 1016, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 0.3H), 7.47 (d, J = 8.8 Hz, 0.7H), 7.43 (s, 0.7H), 7.32 (d, J = 8.8 Hz, 0.3H), 7.11 (d, J = 8.8 Hz, 1.4 H), 7.00 (d, J = 3.6 Hz, 0.6H), 6.96 (d, J = 8.8 Hz, 0.6H), 6.74 (d, J = 8.8 Hz, 1.4H), 6.59 (dd, J = 2.8 Hz, 1.2 Hz, 0.3H), 6.36 (dd, J = 2.8 Hz, 1.2 Hz, 0.7H), 3.85 (s, 0.9H), 3.72 (s, 2.1H), 1.94 (s, 2.1H), 1.85 (s, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 178.0, 160.3, 160.1, 150.8, 148.8, 147.8, 147.3, 143.0, 131.9, 130.9, 130.8, 128.3, 127.5, 120.6, 120.3, 114.1, 114.0, 112.8, 112.4, 110.9, 110.2, 55.4, 55.3, 17.3, 16.3; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}BrO_3S$ $[M+H]^+$ 352.9847 and 354.9827, found 352.9843, 354.9829.

(*E*)-2-Bromo-3-(3,4,5-trimethoxyphenyl)-3-(methylthio)-1-(pyren-1-yl)prop-2-en-1-one (10g). 

Obtained from **7g**, yellow solid (464 mg, 85%): mp 122-124 °C; R_f 0.5 (1:1 EtOAc/hexane); IR (neat, cm^{-1}) 1647, 1582, 1230, 1132, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 13.6 Hz, 1H), 8.18 (t, J = 7.2 Hz, 2H), 8.11 (d, J = 3.2 Hz, 1H), 8.08 (d, J = 3.2 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.98 (m, 3H), 5.87 (s, 2H), 3.34 (s, 6H), 2.51 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 164.6, 156.6, 153.2, 140.0, 134.8, 133.8, 131.7, 131.3, 131.0, 130.9, 130.8, 129.9, 129.6, 129.5, 129.3, 127.4, 126.6, 126.5, 126.3, 126.0, 125.1, 124.7, 124.6, 124.5, 116.4, 116.2, 110.3, 105.1, 61.1, 56.4; HRMS (ESI) m/z calcd for $C_{29}H_{24}BrO_4S$ $[M+H]^+$ 547.0579 and 549.0558, found 547.0567 and 549.0547.

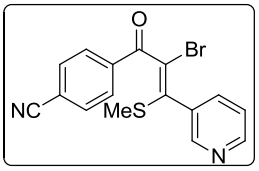
(*E*/*Z*)-2-Bromo-1-(4-(trifluoromethyl)phenyl)-3-(4-methoxyphenyl)-3-(methylthio) prop-2-en-1-one (10j). 

Obtained from **7j**, off-white solid (377 mg, 88%): mp 115-117 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1669, 1604, 1321, 1248, 1125, 858; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 0.4H), 7.77 (d, J = 8.0 Hz, 0.4H), 7.70 (d, J = 8.8 Hz, 1.6H), 7.53-7.49 (m, 2H), 7.01-6.98 (m, 2H), 6.66 (d, J = 8.8Hz, 1.6H), 3.86 (s, 0.6 H), 3.68 (s, 2.4H), 1.95 (s, 2.4H), 1.80 (s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 189.0, 160.5, 160.4, 151.6, 143.1, 139.7, 138.2, 134.3, 133.9, 133.6, 133.3, 130.95, 130.93, 129.8, 129.6, 127.8, 127.3, 126.0, 125.93, 125.90, 125.86, 125.22, 125.19, 125.15, 125.11, 125.0, 122.3, 114.2, 111.6, 55.5, 55.3, 17.1, 16.4; HRMS (ESI) m/z calcd for $C_{17}H_{15}BrF_3O_2S$ $[M+H]^+$ 430.9928 and 432.9908, found 430.9924 and 432.9906.

(*E*)-2-Bromo-3-(1-methyl-1*H*-indol-3-yl)-3-(methylthio)-1-(pyridin-3-yl)prop-2-en-1-one (10k). 

Obtained from **7k**, yellow solid (347 mg, 90%): mp 120-122 °C; R_f 0.5 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1630, 1504, 1257, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 1.6 Hz, 1H), 8.13 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 7.66-7.64 (m, 1H), 7.47 (dt, J = 8.0 Hz, 2.0 Hz, 1H), 7.18-7.15 (m, 2H), 7.02-7.00 (m, 1H), 6.82 (s, 1H), 6.66 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 3.53 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 150.9, 149.2, 149.1, 136.9, 134.6, 133.1, 132.1, 125.9, 123.4, 121.7, 121.5, 120.2, 112.2, 111.6, 109.6, 32.9, 16.7; HRMS (ESI) m/z calcd for $C_{18}H_{16}BrN_2OS$ $[M+H]^+$ 387.0167 and 389.0146, found 387.0163 and 389.0144.

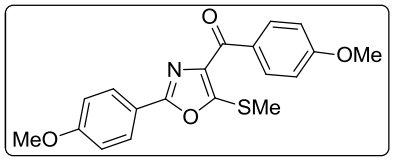
4-((*E*)-2-Bromo-3-(methylthio)-3-(pyridin-3-yl)acryloyl)benzonitrile (10l). Obtained



from **7l**, off-white solid (303 mg, 85%): mp 130-132 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2926, 2230, 1658, 1256, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 0.33H), 8.68 (d, J = 4.0 Hz, 0.33H), 8.46 (d, J = 4.0 Hz, 0.67H), 8.36 (s, 0.67H), 8.08 (d, J = 8.4 Hz, 0.66H), 7.87 (dt, J = 12.0 Hz, 2.0 Hz, 0.33H), 7.82 (d, J = 8.4 Hz, 0.66H), 7.76 (d, J = 8.4 Hz, 1.34H), 7.62 (d, J = 8.4 Hz, 1.34H), 7.48 (dt, J = 12.0 Hz, 2.0 Hz, 0.67H), 7.44 (dd, J = 7.6 Hz, 4.8 Hz, 0.33H), 7.18 (dd, J = 7.6 Hz, 4.8 Hz, 0.67H), 1.96 (s, 2.01H), 1.85 (s, 0.99H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 188.2, 150.5, 150.1, 149.3, 148.2, 140.5, 139.5, 138.2, 136.8, 136.6, 132.8, 132.3, 131.5, 129.9, 129.8, 123.7, 123.4, 117.9, 117.8, 117.1, 116.5, 114.3, 113.117.3, 16.4; HRMS (ESI) m/z calcd for $C_{16}H_{12}BrN_2OS$ $[M+H]^+$ 358.9854 and 360.9833, found 358.9842 and 360.9823.

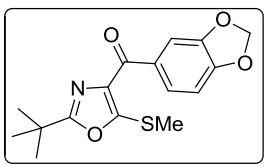
6.4.2 General procedure for the synthesis of 2,4,5-trisubstituted oxazoles 5a-l. To a stirring solution of α-bromo derivatives **10a-l** (1.0 mmol) and corresponding amides **8a-l** (1.0 mmol) in 5 mL Toluene, CuI (0.1 mmol, 19 mg), DMEDA (0.2 mmol, 17 mg) and Cs_2CO_3 (2.0 mmol, 650 mg) were added under N_2 atmosphere and heated at 90 °C (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25 mL) and the combined organic layer was washed with water (3 × 25 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent.

(4-Methoxyphenyl)(2-(4-methoxyphenyl)-5-(methylthio)oxazol-4-yl)methanone (5a).



Obtained from **10a** and amide **8a**, off-white solid (320 mg, 90%): mp 104-105 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2963, 1598, 1467, 1250, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 7.00-6.97 (m, 4H), 3.88 (s, 3H), 3.87 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 181.2, 163.4, 161.7, 159.8, 156.7, 136.0, 132.8, 130.2, 128.1, 119.6, 114.4, 113.6, 55.53, 55.51, 14.4; HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_4S$ $[M+H]^+$ 356.0957, found 356.0949.

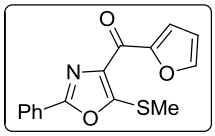
(2-*tert*-Butyl-5-(methylthio)oxazol-4-yl)(benzo[*d*][1,3]dioxol-5-yl)methanone (5b).



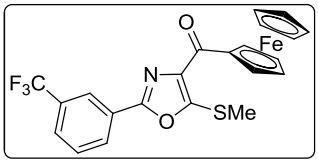
Obtained from **10b** and amide **8b**, pale yellow solid (287 mg, 90%): mp 106-108 °C; R_f 0.4 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2965, 1581, 1480, 1249, 850; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.95 (d, J = 1.6 Hz, 1H), 6.87 (d, J =8.0 Hz, 1H), 6.03 (s,

2H), 2.60 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 169.3, 156.9, 151.5, 147.7, 134.3, 131.7, 127.1, 110.3, 107.9, 101.7, 34.2, 28.5, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{17}NO_4S$ $[M+H]^+$ 320.0957, found 320.0953.

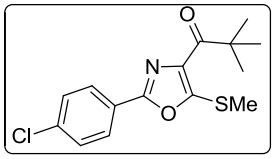
(Furan-2-yl)(5-(methylthio)-2-phenyloxazol-4-yl)methanone (5c). Obtained from **10c** and amide **8c**, off-white solid (236 mg, 83%): mp 130-132 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 1608, 1498, 856, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H), 8.05-8.02 (m, 2H), 7.71 (dd, *J* = 1.6 Hz, 0.8 Hz, 1H), 7.50-7.48 (m, 3H), 6.61 (dd, *J* = 3.6 Hz, 1.6 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 160.0, 157.3, 151.3, 147.3, 134.4, 130.9, 129.1, 126.7, 126.4, 121.9, 112.3, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{11}NO_3S$ $[M+H]^+$ 286.0538., found 286.0526.



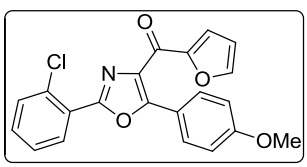
(2-(3-(Trifluoromethyl)phenyl)-5-(methylthio)oxazol-4-yl)(ferrocen-1-yl)methanone (5d). Obtained from **10d** and amide **8d**, maroon solid (381 mg, 81%): mp 190-192 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 1606, 1495, 1119, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.25 (m, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 5.47 (t, *J* = 2.0 Hz, 2H), 4.62 (t, *J* = 2.0 Hz, 2H), 4.19 (s, 5H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 158.1, 156.0, 136.4, 131.9, 129.7, 129.3, 127.9, 127.1, 127.09, 123.0, 122.9, 78.4, 72.8, 71.5, 70.2, 14.3; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{17}F_3FeNO_2S$ $[M+H]^+$ 472.0282, found 472.0291.



1-(2-(4-Chlorophenyl)-5-(methylthio)oxazol-4-yl)-2,2-dimethylpropan-1-one (5e). Obtained from **10e** and amide **8e**, off-white solid (247 mg, 80%): mp 97-99 °C; R_f 0.7 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2926, 1645, 1482, 1087, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 2.67 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 157.8, 157.1, 136.7, 134.6, 129.3, 127.5, 125.5, 43.8, 26.5, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{17}ClNO_2S$ $[M+H]^+$ 310.0669, found 310.0668.

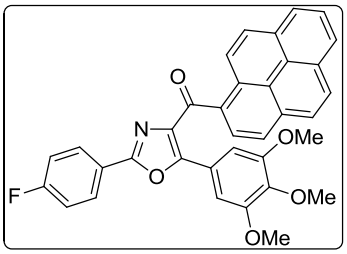


(2-(2-Chlorophenyl)-5-(4-methoxyphenyl)oxazol-4-yl)(furan-2-yl)methanone (5f). Obtained from **10f** and amide **8f**, yellow solid (333 mg, 88%): mp 153-155 °C; R_f 0.4 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 1634, 1493, 1179, 855, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.2 Hz, 2H), 8.19 (dd, *J* = 3.2 Hz, 0.4 Hz, 1H), 8.14-8.11 (m, 1H), 7.72 (dd, *J* =



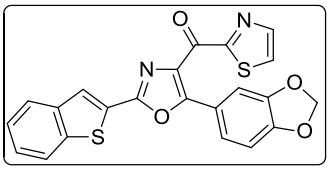
1.2 Hz, 0.4 Hz, 1H), 7.58-7.56 (m, 1H), 7.43-7.42 (m, 2H), 7.01 (d, *J* = 9.2 Hz, 2H), 6.62 (dd, *J* = 3.2 Hz, 1.2 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 161.7, 156.2, 156.1, 152.3, 147.4, 132.9, 132.8, 131.7, 131.6, 130.9, 130.4, 127.2 ,125.5, 122.9, 119.8, 114.1, 112.5, 55.6; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{14}ClNO_4$ $[M+H]^+$ 380.0690, found 380.0674.

(2-(4-Fluorophenyl)-5-(3,4,5-trimethoxyphenyl)oxazol-4-yl)(pyren-1-yl)methanone



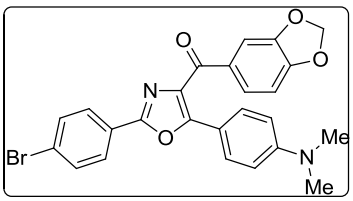
(5g). Obtained from **10g** and amide **8g**, yellow solid (462 mg, 83%): mp 192-194 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1498, 1128, 929, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 9.6 Hz, 1H), 8.28-8.26 (m, 2H), 8.23 (d, *J* = 3.2 Hz, 1H), 8.18 (s, 1H), 8.17 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.09-8.04 (m, 4H), 7.40 (s, 2H), 7.16-7.11 (m, 2H), 3.82 (s, 3H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 165.8, 163.3, 158.2, 155.3, 153.3, 140.3, 136.4, 133.8, 133.0, 131.2, 130.7, 130.3, 129.6, 129.4, 129.2, 129.1, 128.3, 127.3, 126.5, 126.4, 126.1, 125.0, 124.9, 124.6, 123.8, 123.0, 122.6, 116.4, 116.1, 105.8, 61.1, 56.3; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{25}FNO_5$ $[M+H]^+$ 558.1717, found 558.1699.

(2-(Benzo[*b*]thiophen-2-yl)-5-(benzo[*d*][1,3]dioxol-5-yl)oxazol-4-yl)(thiazol-2-



yl)methanone (5h). Obtained from **10h** and amide **8h**, pale yellow solid (367 mg, 85%): mp 179-180 °C; R_f 0.5 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2212, 1609, 1467, 1202, 813; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.0 Hz, 1H), 8.04 (s, 1H), 7.94 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.89-7.86 (m, 2H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.45 - 7.40 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 156.6, 154.8, 150.3, 148.1, 144.9, 141.0, 139.5, 133.0, 128.4, 126.9, 126.5, 125.8, 125.3, 125.0, 124.0, 122.7, 120.6, 108.7, 108.5, 101.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{13}N_2O_4S_2$ $[M+H]^+$ 433.0317, found 433.0310.

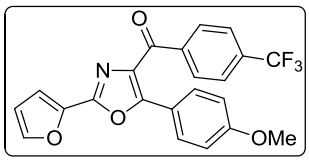
(Benzo[*d*][1,3]dioxol-5-yl)(2-(4-bromophenyl)-5-(4-(dimethylamino)phenyl)oxazol-4-



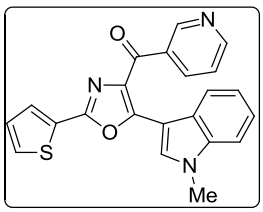
yl)methanone (5i). Obtained from **10i** and amide **8i**, yellow solid (343 mg, 70%): R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2920, 1609, 1482, 1249, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.96 (m, 4H), 7.87 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.05 (s, 2H), 3.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 156.7,

156.5, 151.7, 151.6, 147.8, 132.9, 132.6, 132.2, 129.4, 128.1, 127.4, 126.1, 125.0, 114.8, 11.6, 110.5, 107.9, 101.8, 40.2; HRMS (ESI) *m/z* calcd for $C_{25}H_{20}BrN_2O_4$ $[M+H]^+$ 491.0606 and 493.0586, found 491.0609 and 493.0579.

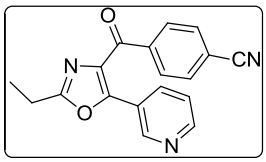
(4-(Trifluoromethyl)phenyl)(2-(furan-2-yl)-5-(4-methoxyphenyl)oxazol-4-yl) methanone (5j). Obtained from **10j** and amide **8j**, off-white solid (351 mg, 85%): mp 140-142 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2932, 1605, 1358, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.61 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.14 (dd, J = 3.2 Hz, 0.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.58 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 161.8, 155.8, 151.3, 145.2, 142.1, 140.9, 134.2, 133.8, 133.2, 130.8, 130.1, 125.33, 125.30, 125.26, 125.22, 119.5, 114.2, 112.9, 112.2, 55.6; HRMS (ESI) *m/z* calcd for $C_{22}H_{15}F_3NO_4$ $[M+H]^+$ 414.0953, found 414.0947.



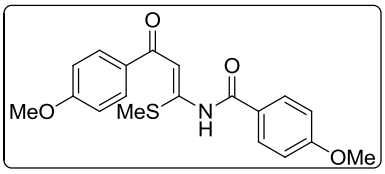
(5-(1-Methyl-1*H*-indol-3-yl)-2-(thiophen-2-yl)oxazol-4-yl)(pyridin-3-yl)methanone (5k). Obtained from **10k** and amide **8k**, yellow solid (346 mg, 90%): mp 133-135 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 1643, 1603, 1386, 880, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 9.16 (s, 1H), 8.78 (s, 1H), 8.58 (d, J = 7.6 Hz, 1H), 8.34 (t, J = 4.8 Hz, 1H), 7.84 (d, J = 3.2 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.47-7.36 (m, 4H), 7.19 (t, J = 4.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 155.9, 153.3, 152.4, 151.8, 137.8, 137.4, 135.1, 134.4, 131.8, 129.4, 128.8, 128.3, 128.26, 126.1, 123.43, 123.13, 122.1, 121.8, 110.3, 33.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{16}N_3O_2S$ $[M+H]^+$ 386.09632, found 386.0960.



4-(2-Ethyl-5-(pyridin-3-yl)oxazole-4-carbonyl)benzonitrile (5l). Obtained from **10l** and amide **8l**, off-white solid (248 mg, 82%): mp 82-83 °C; R_f 0.4 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2231, 1660, 1345, 902, 775; ^1H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.68 (d, J = 4.0 Hz, 1H), 8.50 (dt, J = 8.4 Hz, 1.6 Hz, 1H), 8.26(d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.42 (dd, J = 8.0 Hz, 4.8 Hz, 1H), 2.93 (q, J = 7.6 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 164.,5 153.5, 151.2, 148.9, 140.9, 135.4, 134.7, 132.1, 131.0, 123.88, 123.4, 118.3, 116.2, 21.8, 11.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ 304.1086, found 304.1076.

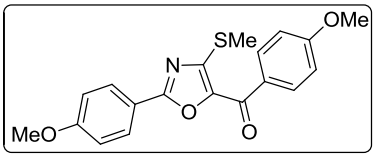


6.4.3 Synthesis of 4-methoxy-*N*-((*Z*)-3-(4-methoxyphenyl)-1-(methylthio)-3-oxoprop-1-enyl)benzamide (11a) from ketene dithioacetal 7a and amide 8a. To a stirring solution of oxoketene dithioacetal **7a** (1.0 mmol, 254 mg) and amide **8a** (1.0 mmol, 151 mg) in 5 mL DMF, NaH (60% emulsion in paraffin) (2.0 mmol, 80 mg) was added and heated at 90 °C (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent to get pure **11a**. Off-white solid (310 mg, 87%): mp 91-93 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1677, 1558, 1227, 1020, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.94 (s, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.11 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 165.8, 164.3, 163.4, 163.1, 132.0, 130.3, 129.8, 125.1, 114.3, 114.0, 94.7, 55.59, 55.57, 15.8; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}NO_4S$ $[M+H]^+$ 358.1113 found 358.1096.

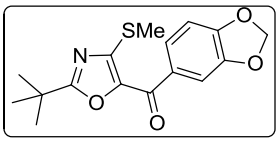


6.4.4 General procedure for the synthesis of oxazoles 6a-l. To a stirring solution of crude enamide **11a-l** in 5 mL 1,4-dioxane, iodine (0.2 mmol, 56 mg) and TBHP (70% aq. Solution, 1.0 mmol) were added and heated at 80 °C (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent.

(4-Methoxyphenyl)(2-(4-methoxyphenyl)-4-(methylthio)oxazol-5-yl)methanone (6a). Obtained from **7a** and amide **8a**, off-white solid (301 mg, 85%): mp 112-114 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (KBr, cm^{-1}) 2925, 1583, 1476, 1253, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H), 7.03-7.00 (m, 4H), 3.90 (s, 3H), 3.88 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 178.5, 163.3, 162.7, 162.4, 152.6, 131.6, 130.0, 129.7, 129.4, 119.0, 114.6, 113.9, 55.6, 55.59, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}NO_4S$ $[M+H]^+$ 356.0957, found 356.0956.

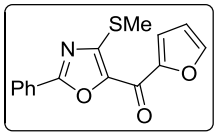


(2-*tert*-Butyl-4-(methylthio)oxazol-5-yl)(benzo[*d*][1,3]dioxol-6-yl)methanone (6b).



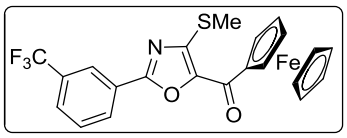
Obtained from **7b** and amide **8b**, off-white solid (284 mg, 89%): mp 140-142 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2965, 1480, 1245, 836, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.59 (d, J = 1.2 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H), 2.61 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 172.8, 151.5, 151.3, 148.1, 143.3, 131.2, 125.5, 109.3, 108.2, 101.9, 34.5, 28.6, 14.1; HRMS (ESI) m/z calcd for $C_{16}H_{17}NO_4S$ $[M+H]^+$ 320.0957, found 320.0952.

(Furan-2-yl)(4-(methylthio)-2-phenyloxazol-5-yl)methanone (6c). Obtained from **7c**



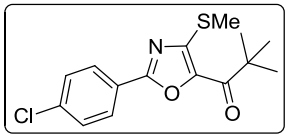
and amide **8c**, pale yellow solid (230 mg, 81%): mp 151-153 °C; R_f 0.4 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 1619, 1511, 1461, 1236, 858,; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.15 (m, 2H), 7.74 (dd, J = 1.6 Hz, 0.4 Hz, 1H), 7.61 (dd, J = 3.6 Hz, 0.4 Hz, 1H), 7.57-7.51 (m, 3H), 6.65 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.5, 152.6, 150.8, 147.3, 142.1, 132.2, 129.2, 127.6, 126.3, 119.3, 112.4, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{11}NO_3S$ $[M+H]^+$ 286.0538, found 286.0528.

(Ferrocen-1-yl)(4-(methylthio)-2-(3-(trifluoromethyl)phenyl)oxazol-5-yl)methanone



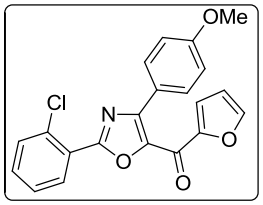
(6d). Obtained from **7d** and amide **8d**, red solid (362 mg, 77%): mp 172-174 °C; R_f 0.65 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 1592, 1504, 1335, 1130, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.35 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 5.20 (t, J = 2.0 Hz, 2H), 4.66 (t, J = 2.0 Hz, 2H), 4.20 (s, 5H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 159.9, 149.9, 144.0, 132.2, 131.9, 131.6, 130.2, 130.0, 128.3, 128.2, 127.5, 125.1, 124.2, 124.19, 122.4, 77.8, 72.9, 70.4, 70.3, 14.1; HRMS (ESI) m/z calcd for $C_{22}H_{17}F_3FeNO_2S$ $[M+H]^+$ 472.0282, found 472.0292.

1-(2-(4-Chlorophenyl)-4-(methylthio)oxazol-5-yl)-2,2-dimethylpropan-1-one (6e).



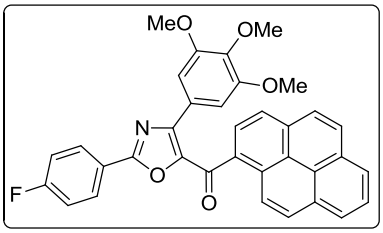
Obtained from **7e** and amide **8e**, white solid (262 mg, 85%): mp 118-120 °C; R_f 0.7 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 2925, 1636, 1471, 1086, 836, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 2.64 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 160.4, 151.8, 142.7, 138.2, 129.5, 128.6, 124.9, 42.9, 26.4, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{17}ClNO_2S$ $[M+H]^+$ 310.0669, found 310.0664.

(2-(2-Chlorophenyl)-4-(4-methoxyphenyl)oxazol-5-yl)(furan-2-yl)methanone (6f).



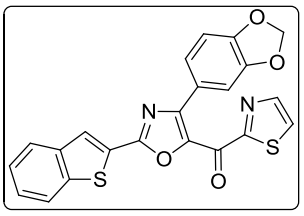
Obtained from **7f** and amide **8f**, off-white solid (303 mg, 80%): mp 120-122 °C; R_f 0.5 (1:9 EtOAc/hexane); IR (neat, cm^{-1}) 1630, 1456, 1247, 858, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 2H), 8.21 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.83 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.73 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.57 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.50-7.41 (m, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.63 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 161.4, 159.8, 151.4, 148.8, 147.7, 142.5, 133.0, 132.4, 132.3, 131.5, 131.4, 127.3, 125.3, 122.9, 120.7, 113.8, 112.6, 55.5 HRMS (ESI) m/z calcd for $C_{21}H_{14}ClNO_4$ $[M+H]^+$ 380.0690, found 380.0684.

(2-(4-Fluorophenyl)-4-(3,4,5-trimethoxyphenyl)oxazol-5-yl)(pyren-1-yl)methanone



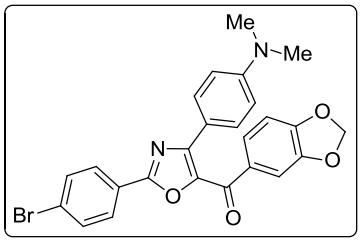
(6g). Obtained from **7g** and amide **8g**, pale yellow solid (306 mg, 55%): mp 203-205 °C; R_f 0.45 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 2942, 1583, 1498, 1228, 1124, 845; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 9.6 Hz, 1H), 8.26 (t, J = 8.0 Hz 2H), 8.20-8.17 (m, 2H), 8.15-8.03 (m, 6H), 7.44 (s, 2H), 7.11 (t, J = 4.8 Hz, 2H), 3.76 (s, 3H), 3.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3, 163.9, 161.7, 152.9, 149.5, 144.8, 139.7, 133.7 132.7, 131.3, 130.7, 130.1, 130.0, 129.8, 129.7, 129.5, 127.5, 127.3, 126.9, 126.7, 126.5, 126.3, 125.9, 124.9, 124.5, 124.3, 124.0, 122.6, 116.5, 116.3, 107.5, 106.8, 60.9, 56.1; HRMS (ESI) m/z calcd for $C_{35}H_{25}FNO_5$ $[M+H]^+$ 558.1717, found 558.1712.

(2-(Benzo[*b*]thiophen-2-yl)-4-(benzo[*d*][1,3]dioxol-6-yl)oxazol-5-yl)(thiazol-2-yl) methanone (6h).

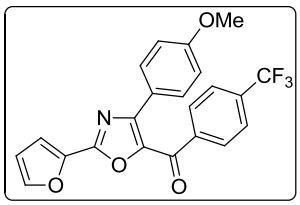


Obtained from **7h** and amide **8h**, yellow solid (388 mg, 90%): mp 208-210 °C; R_f 0.6 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 2923, 1584, 1447, 1248, 1040, 834, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.17 (d, J = 2.8 Hz, 1H), 7.94 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.92-7.89 (m, 2H), 7.85 (d, J = 1.6 Hz, 1H), 7.77 (d, J = 2.8 Hz, 1H), 7.45 -7.41 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 166.5, 159.1, 151.6, 149.8, 147.8, 145.4, 141.8, 141.7, 139.5 ,128.4, 127.9, 126.9, 126.2 125.4, 125.3, 125.0, 124.2, 122.8, 110.0, 108.3, 101.6; HRMS (ESI) m/z calcd for $C_{22}H_{13}N_2O_4S_2$ $[M+H]^+$ 433.0317, found 433.0293.

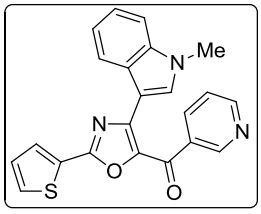
(Benzo[*d*][1,3]dioxol-6-yl)(2-(4-bromophenyl)-4-(4-(dimethylamino)phenyl)oxazol-5-yl)methanone (6i). Obtained from **7i** and amide **8i**, yellow solid (416 mg, 85%): mp 187-189 °C; R_f 0.7 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 1600, 1472, 1257, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 4.4 Hz, 1H), 7.48 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 2H), 6.06 (s, 2H), 3.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 160.6, 151.7, 151.6, 149.5, 148.1, 142.5, 132.6, 132.4, 130.7, 128.9, 126.3, 126.1, 125.8, 118.1, 111.6, 109.6, 108.0, 101.9, 40.3; HRMS (ESI) m/z calcd for $C_{25}H_{20}BrN_2O_4$ $[M+H]^+$ 491.0606 and 493.0586, found 491.0600 and 493.0583.



(4-(Trifluoromethyl)phenyl)(2-(furan-2-yl)-4-(4-methoxyphenyl)oxazol-5-yl) methanone (6j). Obtained from **7j** and amide **8j**, pale yellow solid (363 mg, 88%): mp 172-174 °C; R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 1622, 1495, 1315, 852, 765; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.66 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.25 (dd, J = 3.6 Hz, 0.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 6.61 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 161.6, 154.6, 150.1, 146.2, 142.1, 141.0, 131.3, 129.9, 125.5, 125.47, 125.43, 125.40, 122.6, 115.1, 113.8, 112.6, 55.5; HRMS (ESI) m/z calcd for $C_{22}H_{15}F_3NO_4$ $[M+H]^+$ 414.0953, found 414.0957.

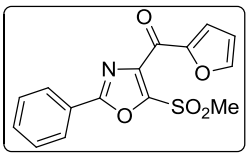


(4-(1-Methyl-1*H*-indol-3-yl)-2-(thiophen-2-yl)oxazol-5-yl)(pyridin-3-yl)methanone (6k). Obtained from **7k** and amide **8k**, brown solid (354 mg, 92%): mp 180-182 °C; R_f 0.45 (3:7 EtOAc/hexane); IR (neat, cm^{-1}) 1629, 1575, 1514, 1326, 1082, 879, 744; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (dd, J = 2.4 Hz, 0.8 Hz, 1H), 9.06 (s, 1H), 8.80-8.76 (m, 2H), 8.31 (dt, J = 8.0 Hz, 2.0 Hz, 1H), 7.86 (dd, J = 3.6 Hz, 1.2 Hz, 1H), 7.58 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 7.46 (ddd, J = 8.0 Hz, 4.8 Hz, 0.8 Hz, 1H), 7.38-7.31 (m, 3H), 7.18 (dd, J = 5.2 Hz, 3.6 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 158.8, 152.4, 150.4,5, 148.6, 141.4, 137.5, 136.7, 135.1, 134.5, 130.9, 130.5, 129.1, 128.5, 127.6, 123.4, 123.2, 122.9, 121.5, 109.7, 105.9, 33.6; HRMS (ESI) m/z calcd for $C_{22}H_{16}N_3O_2S$ $[M+H]^+$ 386.0963, found 386.0962.



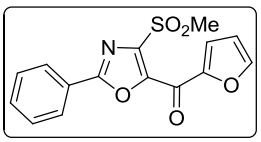
6.4.5 General procedure for synthesis of 5 (or 4)-(methylsulphonyl)oxazoles 14c and 16c. *m*-CPBA (1.1 mmol, 190 mg) was added to a stirring solution of oxazole (**5c** or **6c**) (1,0 mmol) in 5 mL DCM and the reaction mixture was stirred at ambient temperature (monitored by TLC). It was then diluted with water (25 mL) and extracted with DCM (3 × 25mL) and the combined organic layer was washed with sat. $NaHCO_3$ (3 ×25 mL), water (3 × 25 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/hexane as eluent.

(Furan-2-yl)(5-(methylsulfonyl)-2-phenyloxazol-4-yl)methanone (14c). Obtained



from oxazole **5c**, off-white solid (301 mg, 95%): mp 179-181 °C; R_f 0.45 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1645, 1460, 1331, 1147, 861, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 2H), 8.04 (d, J = 3.6 Hz, 1H), 7.79 (t, J = 0.8 Hz, 1H), 7.62-7.52 (m, 3H), 6.67 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 162.2, 151.0, 149.9, 149.1, 140.9, 132.8, 129.7, 127.7, 125.2, 124.6, 113.0, 44.2; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}NO_5S$ $[M+H]^+$ 318.0436, found 318.0436.

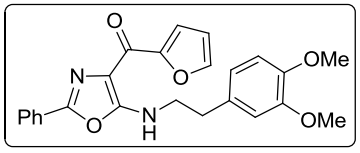
(Furan-2-yl)(4-(methylsulfonyl)-2-phenyloxazol-5-yl)methanone (16c). Obtained from



oxazole **6c**, white solid (285 mg, 90%): mp 171-173 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1637, 1461, 1315, 1148, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.17 (m, 2H), 7.83 (dd, J = 1.6 Hz, 0.4 Hz, 1H), 7.64 (dd, J = 3.6 Hz, 0.4 Hz, 1H), 7.61-7.53 (m, 3H), 6.72 (dd, J = 4.0 Hz, 1.6 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.8, 150.8, 149.2, 146.2, 146.0, 132.9, 129.4, 127.8, 125.1, 122.5, 113.3, 43.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}NO_5S$ $[M+H]^+$ 318.0436, found 318.0432.

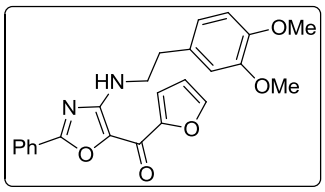
6.4.6 General procedure for the synthesis of 4/5-amino substituted oxazoles 15a-b and 17a-b. A solution of 5 (or 4)-(methylsuphonyl)oxazole **14c** (or **16c**) (1.0 mmol) and corresponding amine (1.1 mmol) in 3 mL DMF is heated at 90 °C (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent.

(5-(3,4-Dimethoxyphenethylamino)-2-phenyloxazol-4-yl)(furan-2-yl)methanone



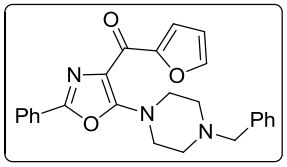
(15a). Obtained from oxazole **14c**, yellow solid (0.384 mg, 92%): mp 120-122 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3308, 1634, 1480, 1233, 1021, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 3.6 Hz, 0.4 Hz, 1H), 7.91 (dd, J = 8.4 Hz, 2.0 Hz, 2H), 7.86 (t, J = 6.0 Hz, 1H), 7.64 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.46-7.40 (m, 3H), 6.80 (s, 2H), 6.74 (s, 1H), 6.58 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.80 (q, J = 6.8 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 161.9, 151.3, 149.6, 149.3, 148.1, 145.9, 130.7, 129.9, 128.8, 126.9, 125.8, 120.9, 119.6, 113.5, 112.2, 112.0, 111.8, 56.0, 44.9, 36.4; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_5$ $[M+H]^+$ 419.1607, found 419.1601.

(4-(3,4-Dimethoxyphenethylamino)-2-phenyloxazol-5-yl)(furan-2-yl)methanone



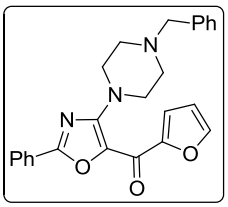
(17a). Obtained from oxazole **16c**, yellow semi-solid (271 mg, 65%): R_f 0.45 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 3340, 2920, 1634, 1511, 1231, 1143, 1027, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.14 (m, 2H), 7.68 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.56-7.51 (m, 3H), 7.45 (dd, J = 3.6 Hz, 0.4 Hz, 1H), 7.11 (t, J = 6.0 Hz, 1H), 6.84-6.77 (m, 3H), 6.61 (dd, J = 3.6 Hz, 2.0 Hz, 1H), 3.86 (q, J = 4.0 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.93 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 162.7, 158.4, 150.9, 149.1, 147.8, 145.9, 132.2, 131.5, 129.0, 128.7, 127.8, 126.5, 120.9, 116.9, 112.2, 112.0, 111.6, 56.0, 55.9, 44.5, 36.5; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_5$ $[M+H]^+$ 419.1607, found 419.1602.

(5-(4-Benzylpiperazin-1-yl)-2-phenyloxazol-4-yl)(furan-2-yl)methanone (15b).



Obtained from oxazole **14c**, yellow solid (396 mg, 96%): mp 143-145 °C; R_f 0.4 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1615, 1541, 1466, 1267, 849, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.93 (dd, J = 8.0 Hz, 1.6 Hz, 2H), 7.64 (dd, J = 1.6 Hz, 0.8 Hz, 1H), 7.46-7.40 (m, 3H), 7.34-7.31 (m, 4H), 7.29-7.27 (m, 1H), 6.57 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 3.83 (t, J = 4.8 Hz, 4H), 3.58 (s, 2H), 2.65 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 159.8, 152.7, 149.8, 145.9, 137.7, 129.9, 129.3, 128.9, 128.4, 127.4, 127.0, 125.7, 120.2, 115.7, 111.9, 63.1, 52.7, 48.4; HRMS (ESI) m/z calcd for $C_{25}H_{23}N_3O_3$ $[M+H]^+$ 414.1818, found 414.1812.

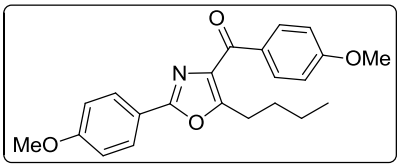
(4-(4-Benzylpiperazin-1-yl)-2-phenyloxazol-5-yl)(furan-2-yl)methanone (17b).



Obtained from oxazole **16c**, yellow semi-solid (247 mg, 60%): R_f 0.45 (2:3 EtOAc/hexane); IR (neat, cm^{-1}) 1615, 1541, 1466, 1267, 953, 849, 752; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.67 (dd, J = 1.6 Hz, 0.4 Hz, 1H), 7.54-7.51 (m, 3H), 7.45 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 7.36-7.27 (m, 5H), 6.61 (dd, J = 3.6 Hz, 1.6 Hz, 1H), 3.92 (t, J = 4.8 Hz, 4H), 3.60 (s, 2H), 2.64 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 161.,2 157.0, 152.2, 146.0, 132.1, 130.1, 129.5, 129.1, 129.0, 128.4, 127.7, 127.4, 126.5, 117.4, 112.0, 63.1, 53.0, 48.6; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{23}N_3O_3$ $[M+H]^+$ 414.1818, found 414.1815.

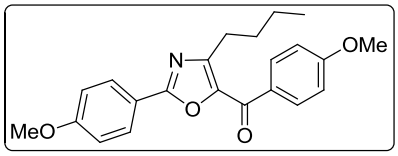
6.4.7 General procedure for synthesis of 5 (or 4)-alkyloxazoles 18a-19a from 5 (or 4)-(methylthio)oxazoles 5a-6a. To a solution of 5 (or 4)-(methylthio)oxazoles **5a-6a** (1.0 mmol, 355 mg) in 3 mL THF, CuBr (1.0 mmol, 142 mg) was added and cooled to 0 °C. A solution of freshly prepared *n*-butylmagnesium bromide (1.0 mmol, 160 mg) in 2 mL THF was added drop wise to the reaction mixture at 0 °C and stirred at the same temperature (monitored by TLC). It was then diluted with sat. NH_4Cl solution (25 mL), extracted with EtOAc (3 × 25mL) and the combined organic layer was washed with water (3 × 25 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/hexane as eluent.

(5-Butyl-2-(4-methoxyphenyl)oxazol-4-yl)(4-methoxyphenyl)methanone (18a).



Obtained from oxazole **5a**, off-white solid (0.335 mg, 92%): mp 83-85 °C; R_f 0.5 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2930, 1595, 1501, 1250, 1168, 1027, 909; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 4H), 3.88 (s, 3H), 3.86 (s, 3H), 3.13 (t, J = 7.6 Hz, 2H), 1.77 (quin, J = 7.6 Hz, 2H), 1.45 (q, J = 7.6 Hz, 2H), 0.96 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 163.3, 161.5, 160.2, 158.4, 135.2, 132.8, 130.6, 128.1, 119.8, 114.2, 113.4, 55.4, 55.36, 29.9, 26.3, 22.4, 13.8; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}NO_4$ $[M+H]^+$ 366.1705, found 366.1695.

(4-Butyl-2-(4-methoxyphenyl)oxazol-5-yl)(4-methoxyphenyl)methanone (19a).



Obtained from oxazole **6a**, colorless liquid (310 mg, 85%): R_f 0.6 (1:4 EtOAc/hexane); IR (neat, cm^{-1}) 2929, 1591, 1251, 1162, 1023, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 7.03-6.96 (m, 4H), 3.90 (s, 3H), 3.87 (s, 3H), 2.99 (t, J = 8.0 Hz, 2H), 1.76 (quin, J = 8.0 Hz, 2H), 1.46 (q, J = 8.0 Hz, 2H), 0.95 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 163.3, 162.2, 161.7, 153.2, 144.3, 131.7, 130.3, 130.1, 129.9, 129.0, 119.3, 114.4, 114.1, 113.8, 113.7, 55.5, 55.4, 30.6, 27.7, 22.6, 13.9; HRMS (ESI) m/z calcd for $C_{22}H_{24}NO_4$ $[M+H]^+$ 366.1705, found 366.1701.

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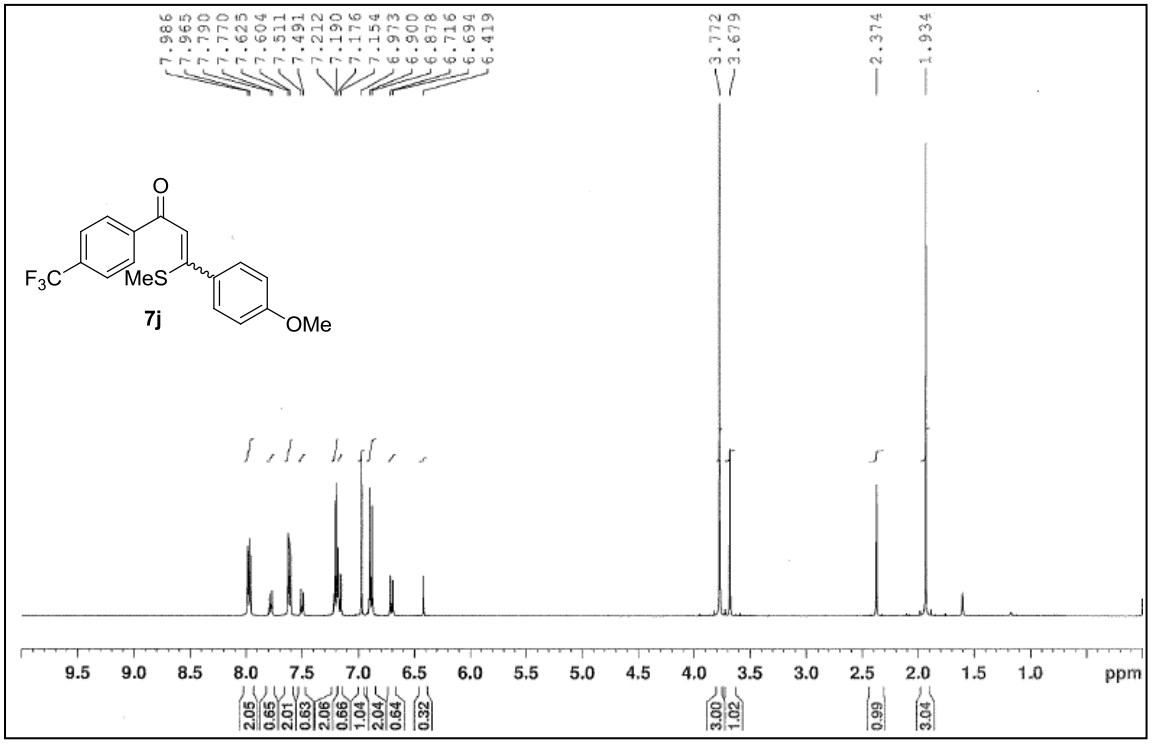
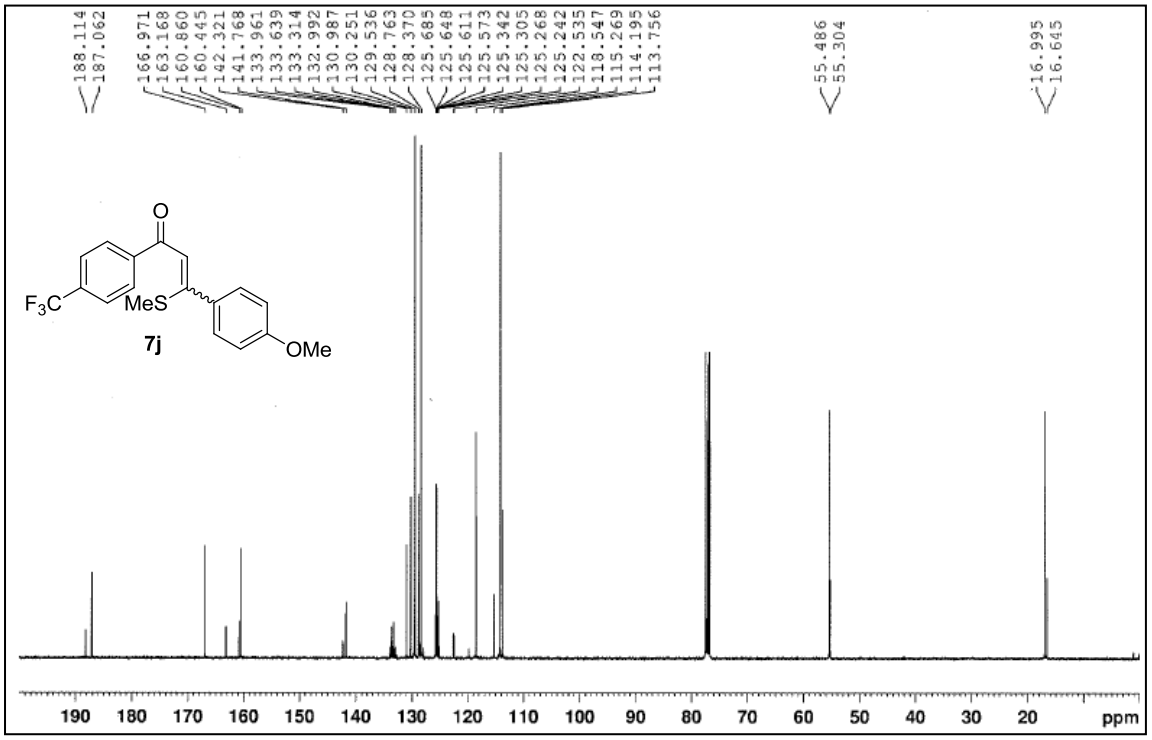
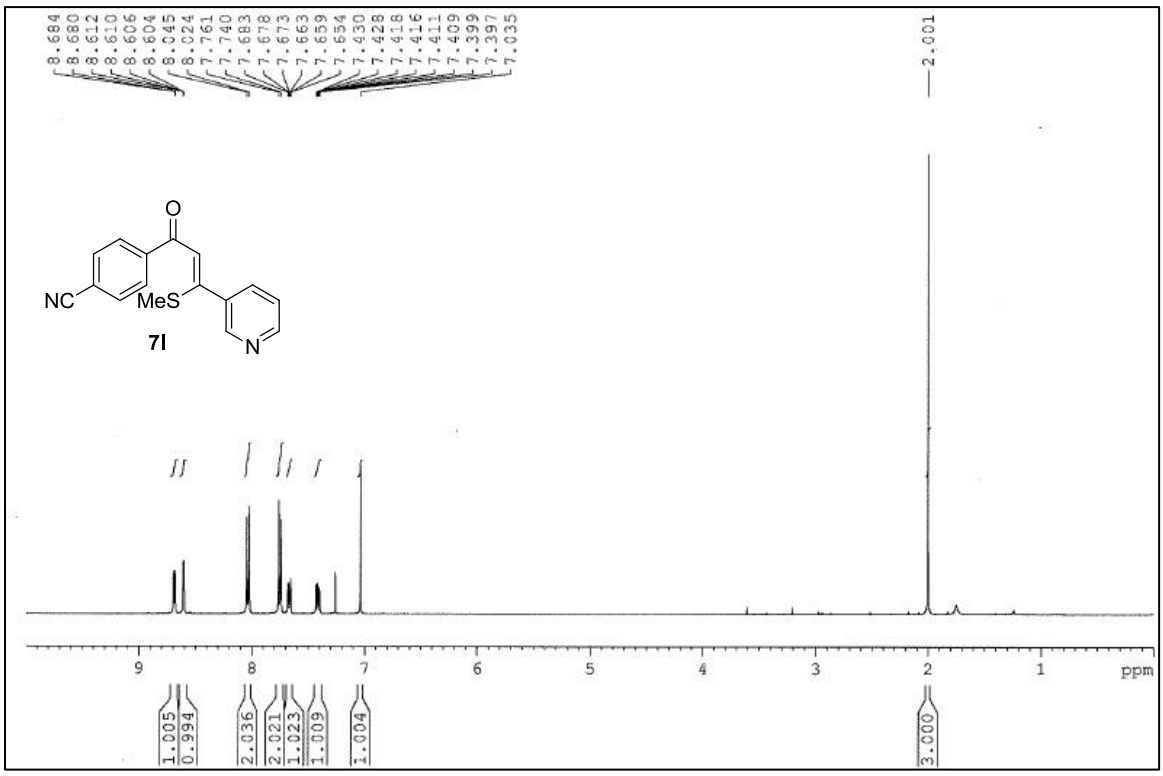
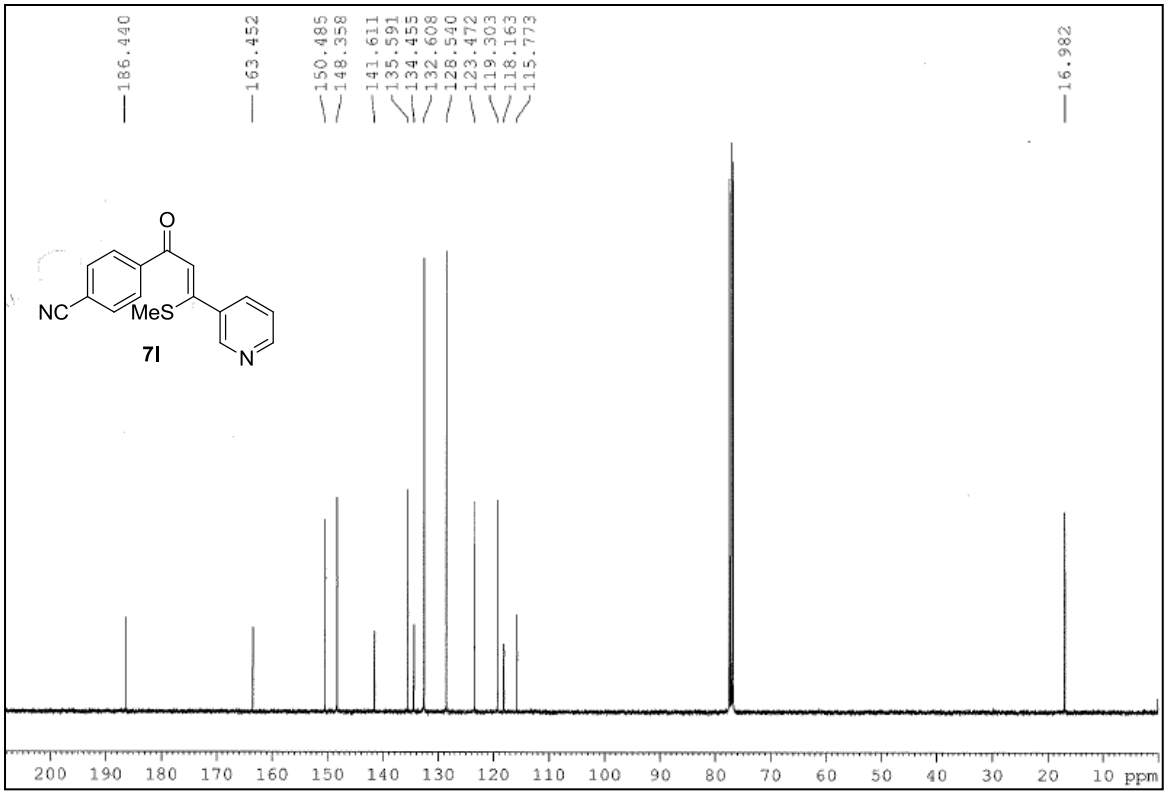
6.6 Representative spectra





^{1}H NMR and ^{13}C NMR Spectra for compound **7j** in $CDCl_3$





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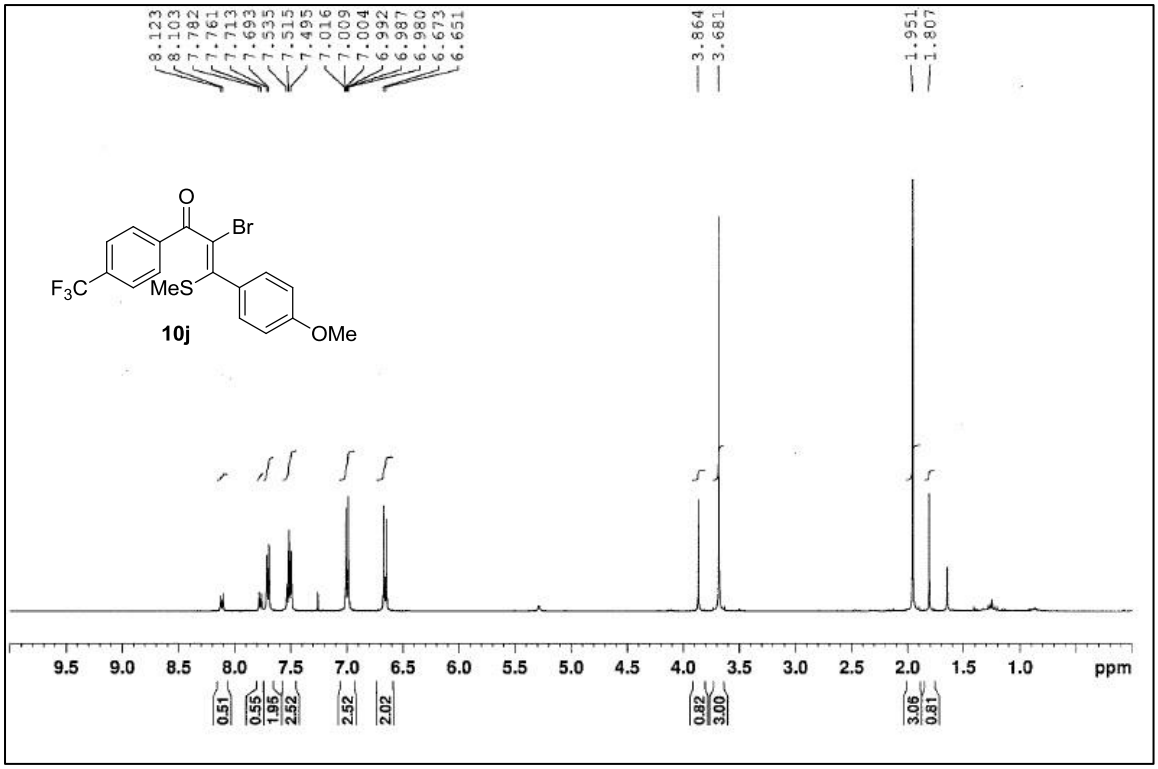

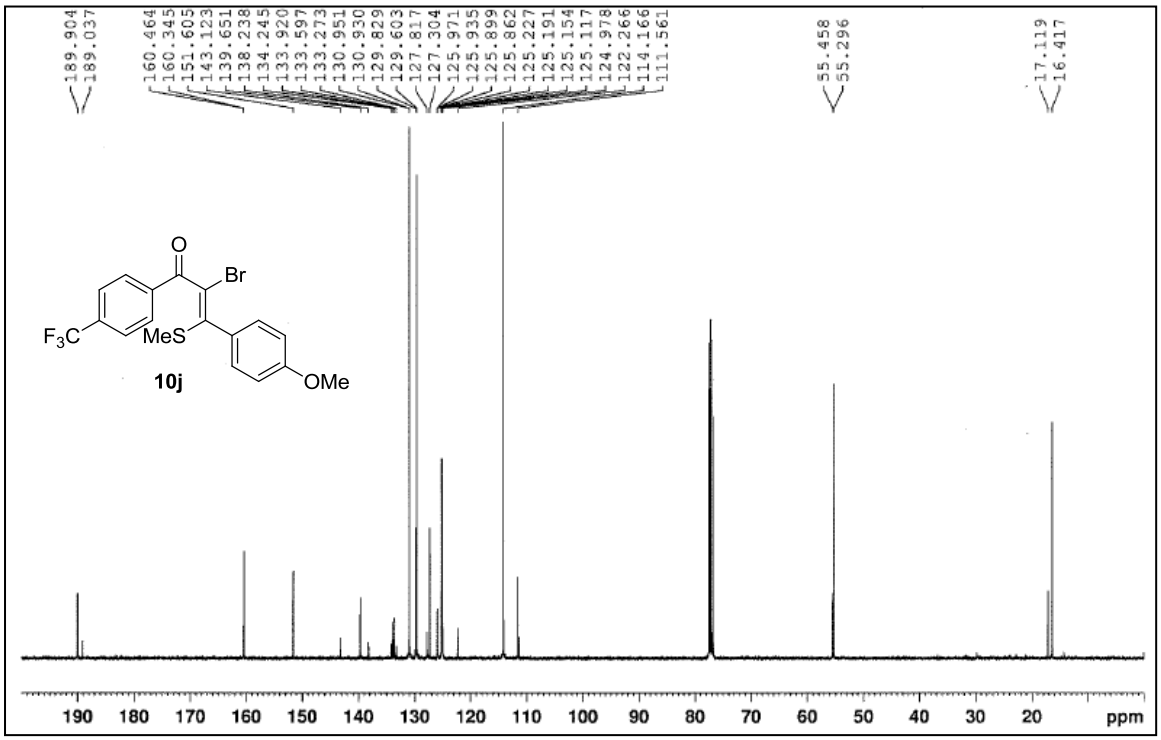

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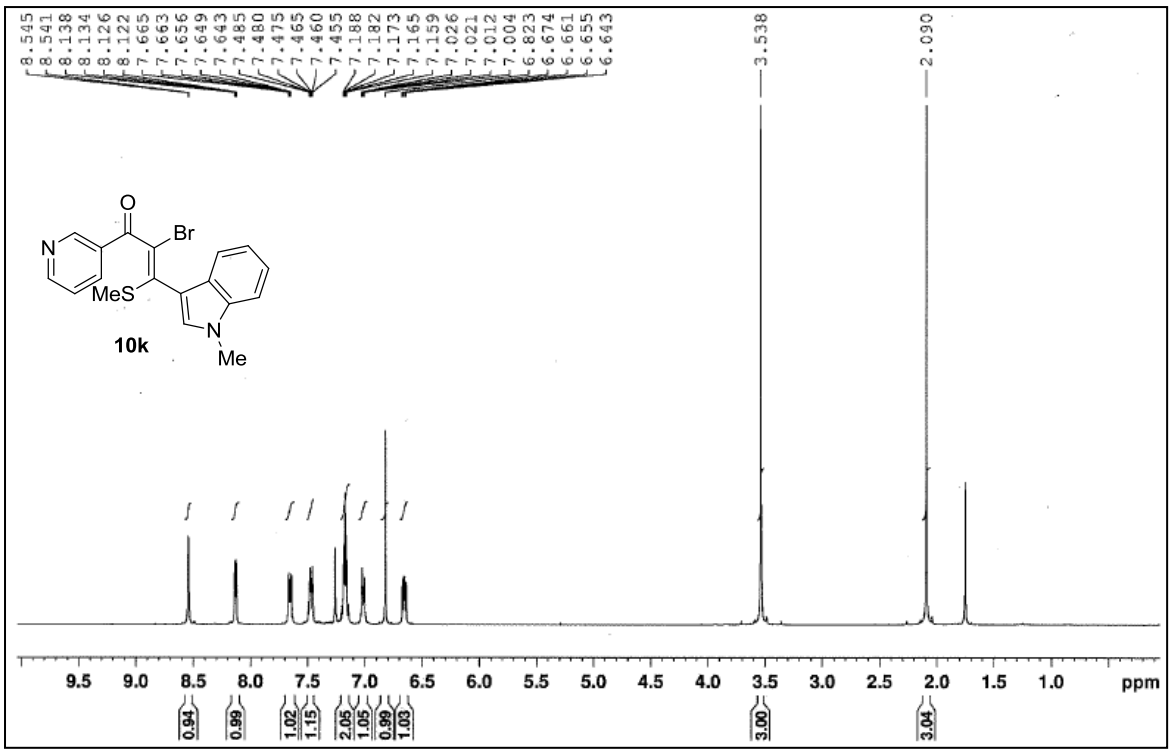
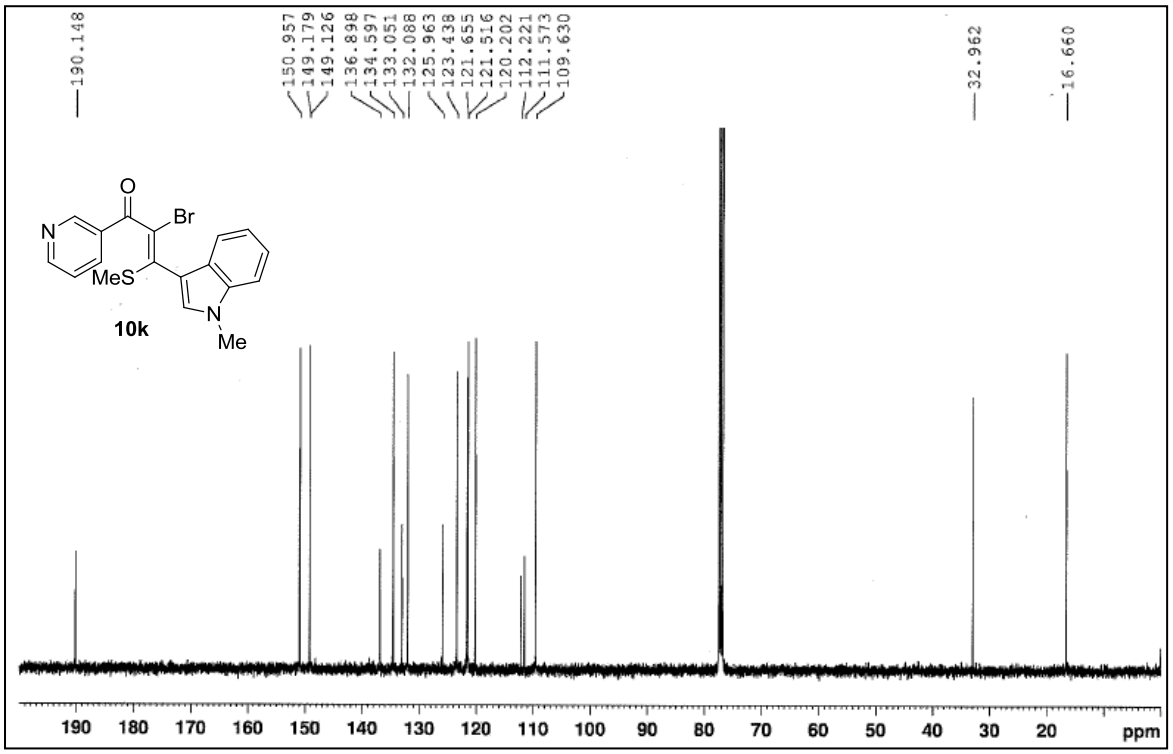
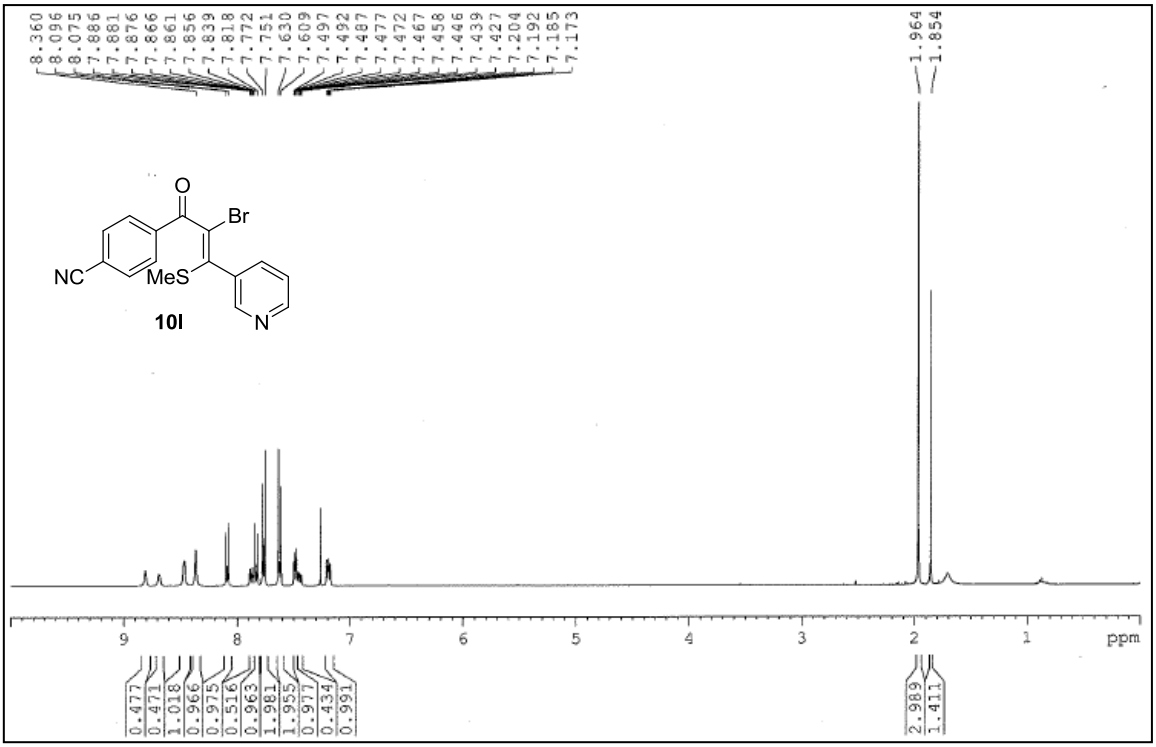
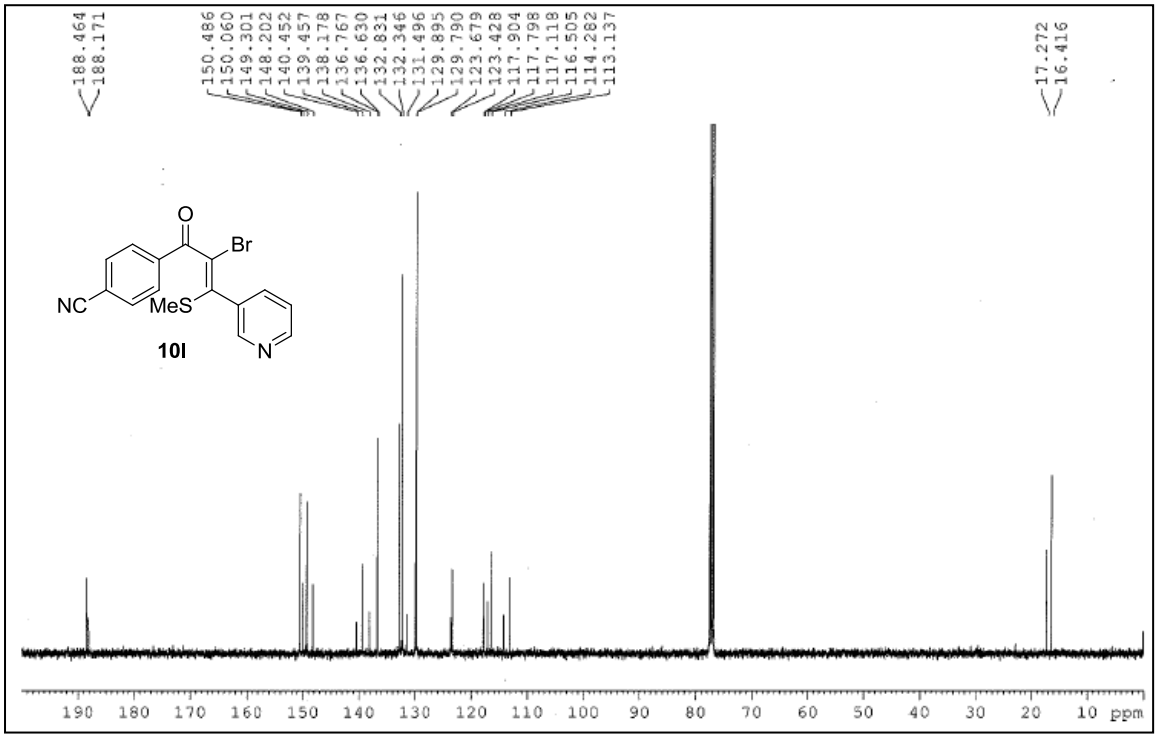


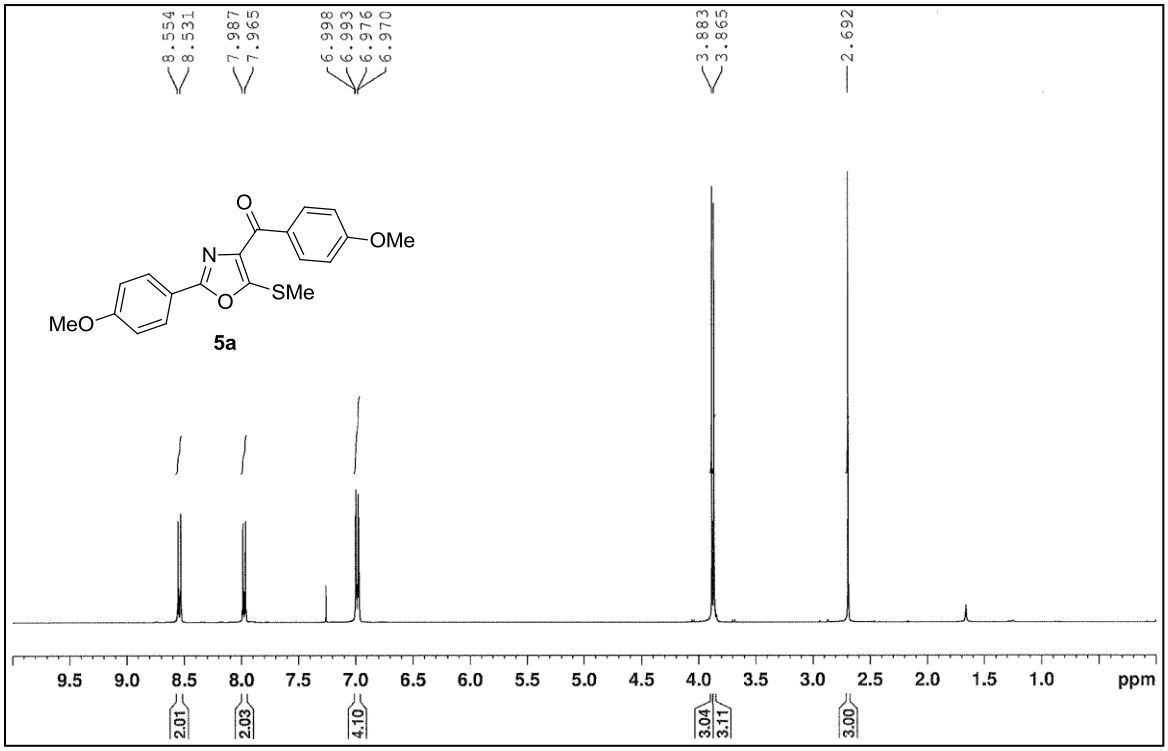


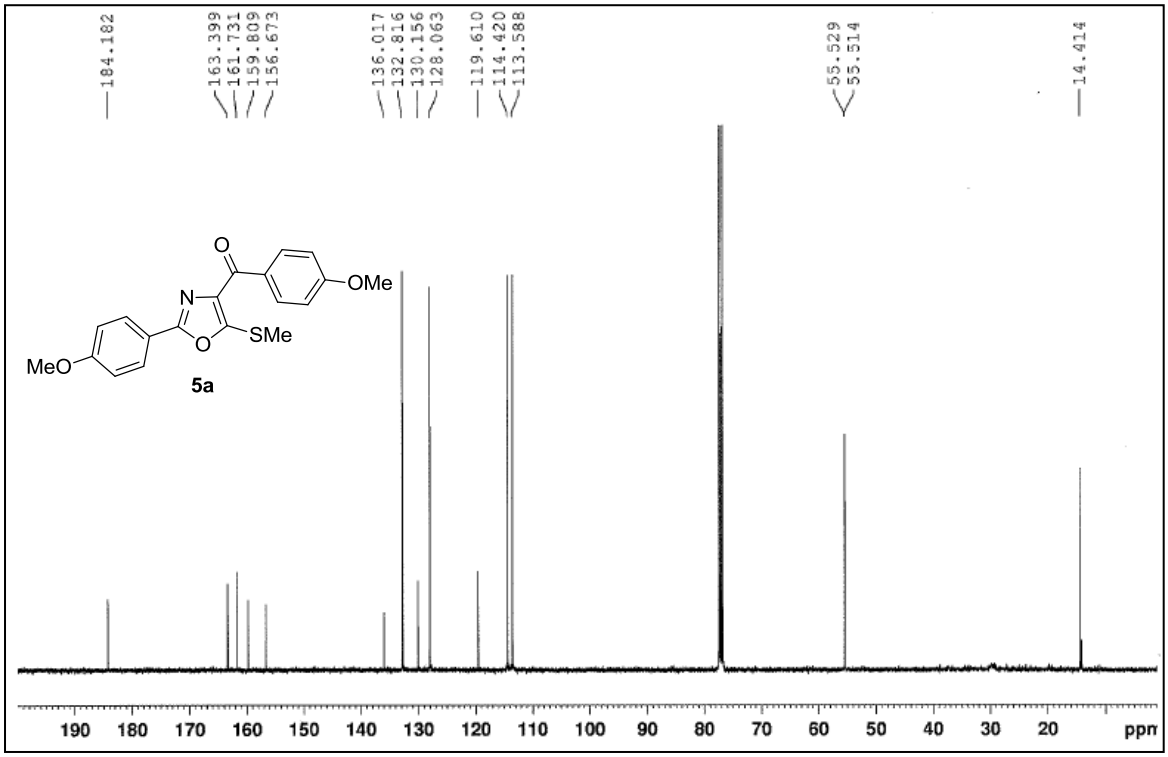
^{1}H NMR and ^{13}C NMR Spectra for compound **10k** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **10l** in $CDCl_3$





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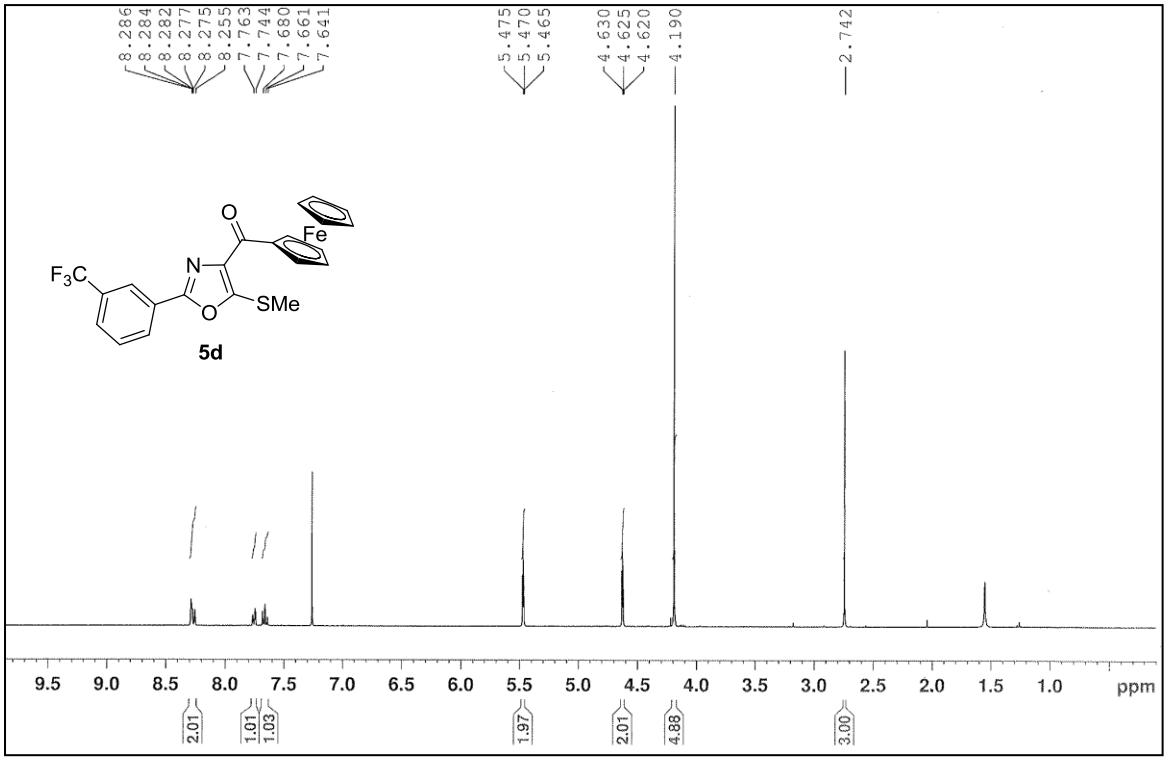
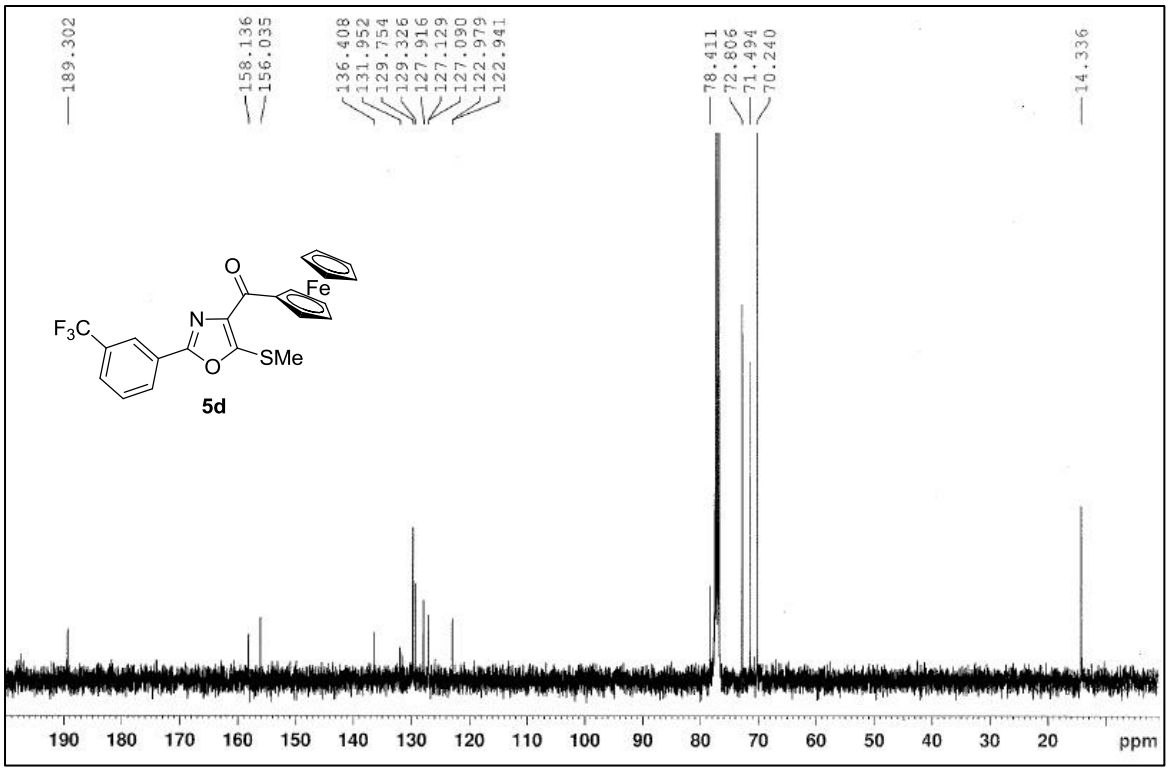
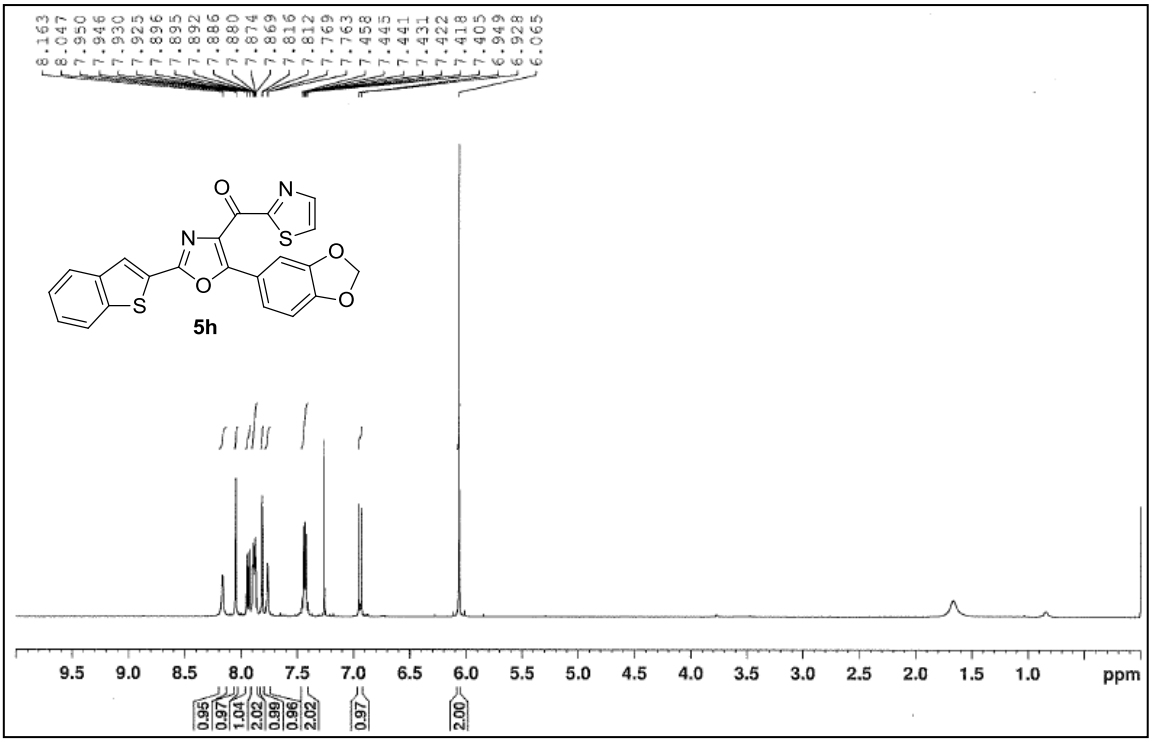
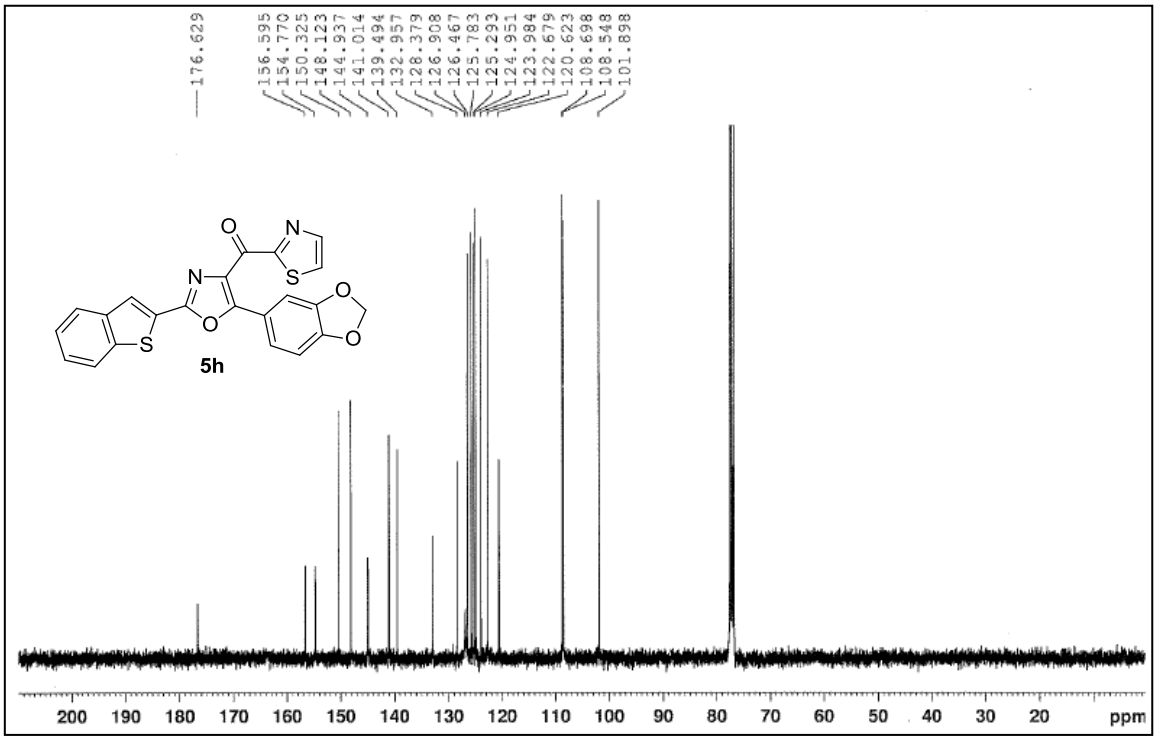




^{1}H NMR and ^{13}C NMR Spectra for compound **5d** in $CDCl_3$





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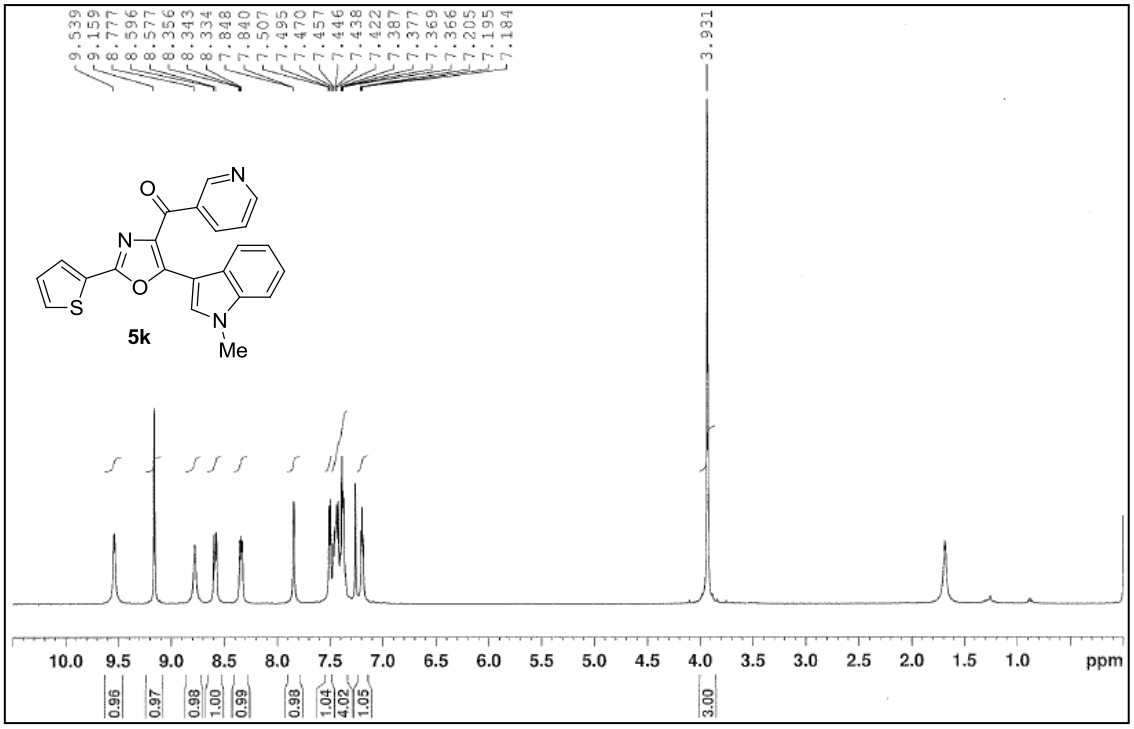
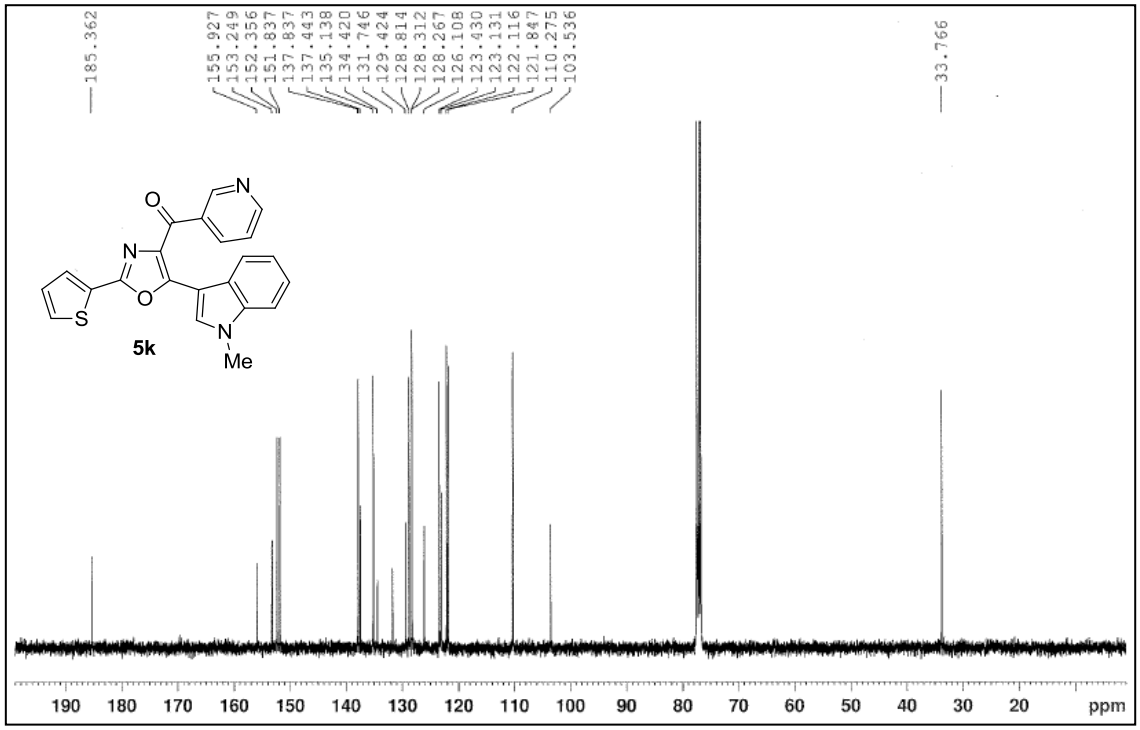
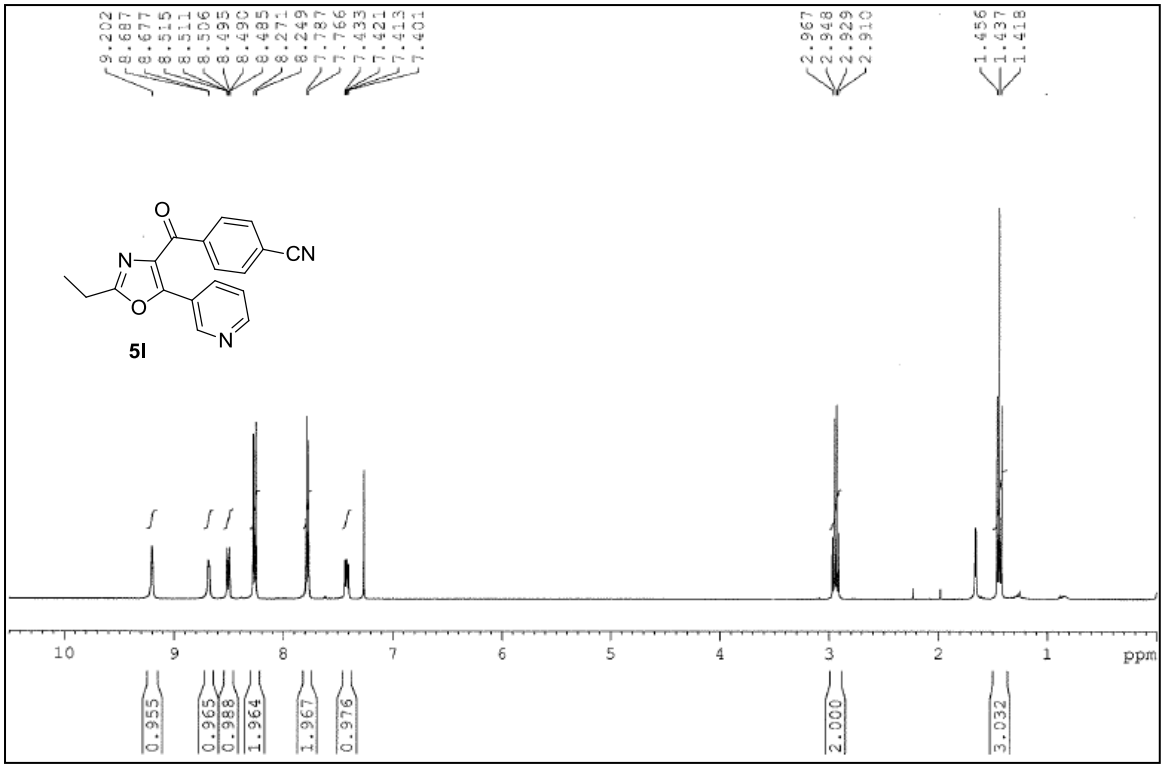
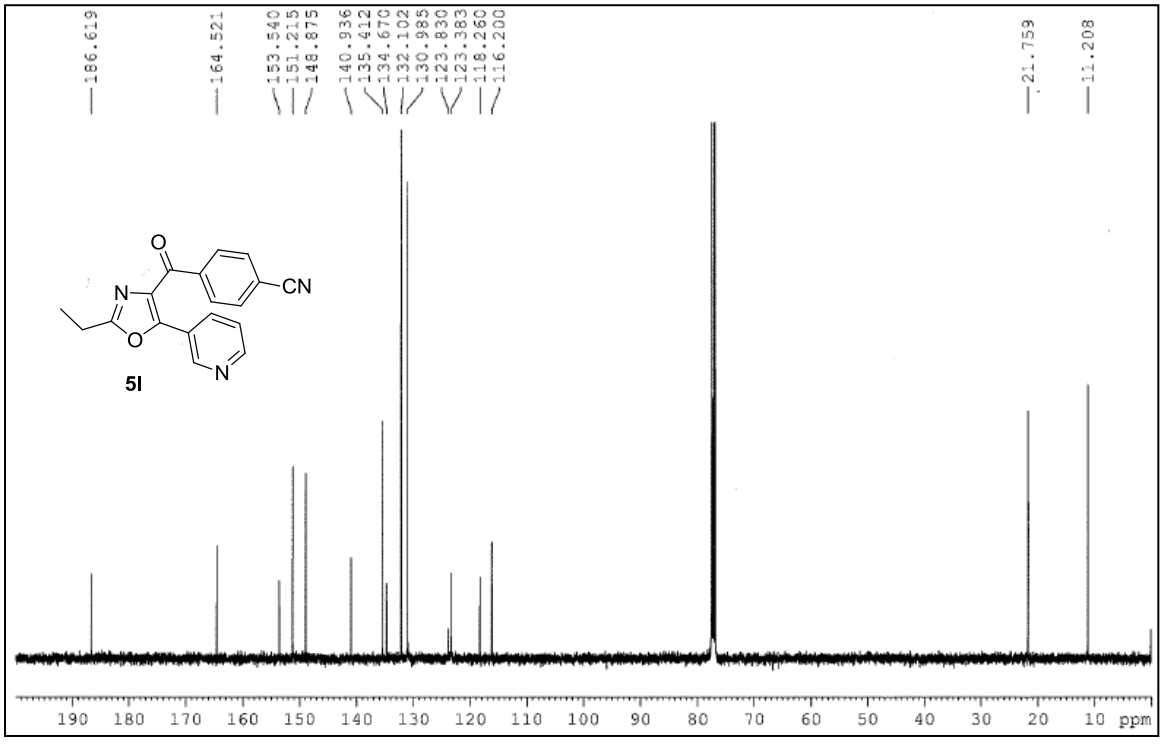




^{1}H NMR and ^{13}C NMR Spectra for compound **5k** in $CDCl_3$





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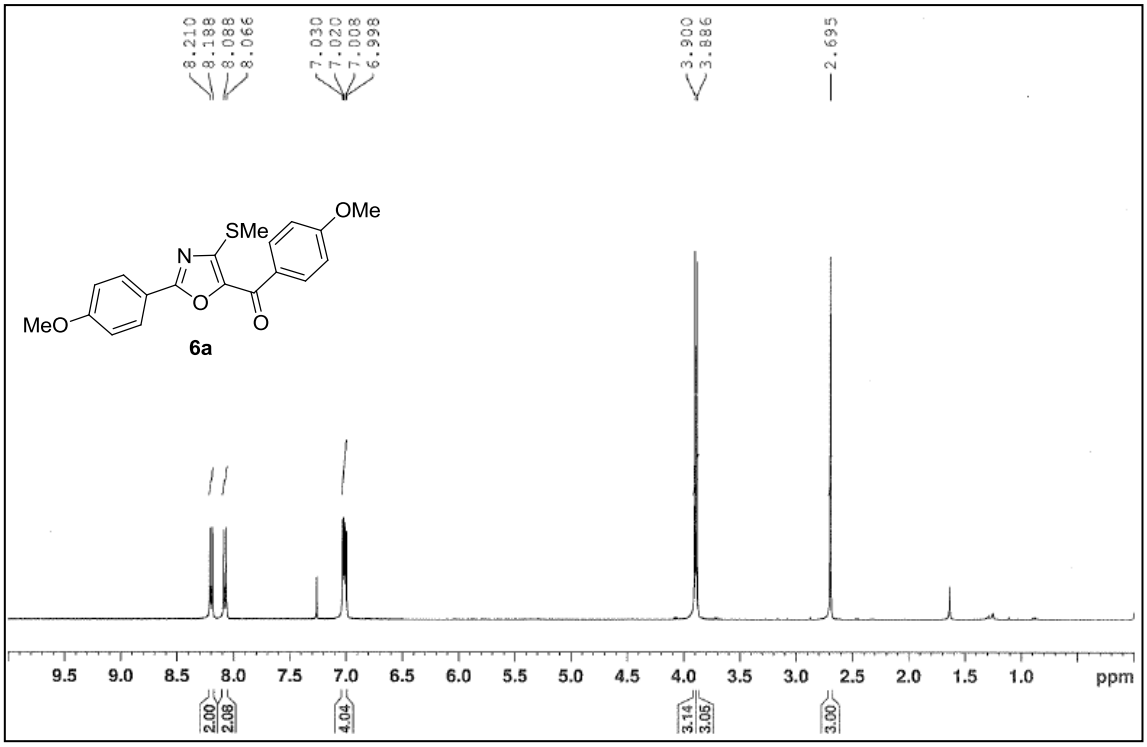
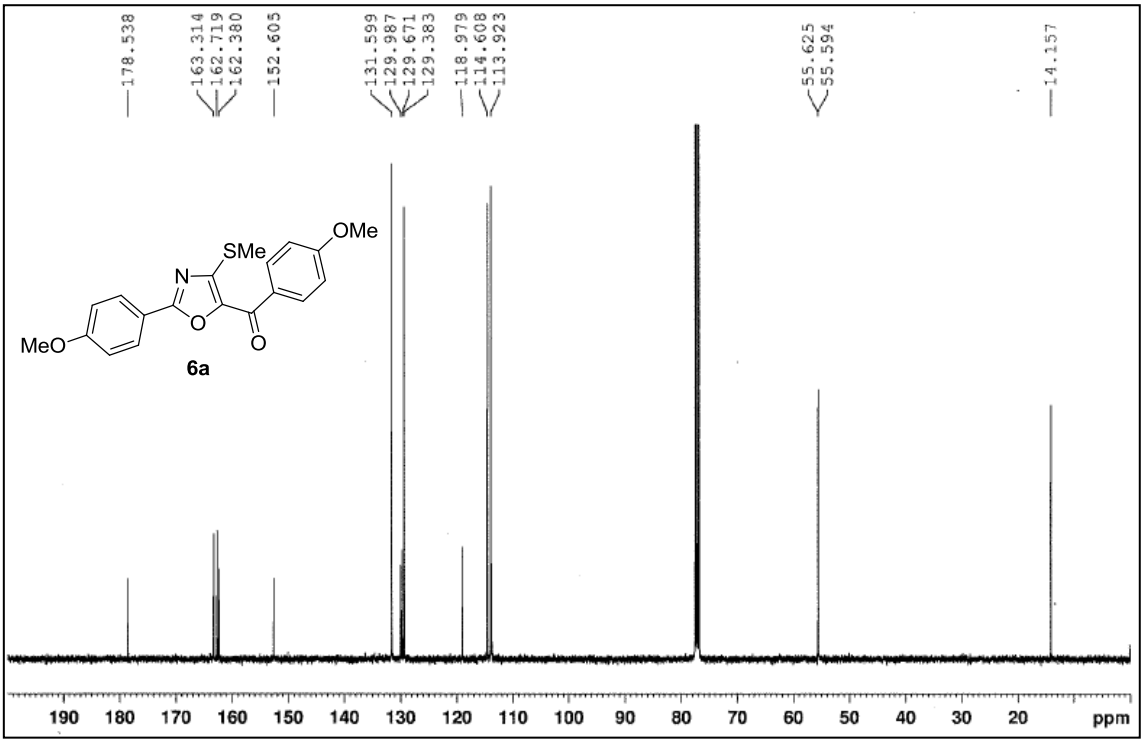
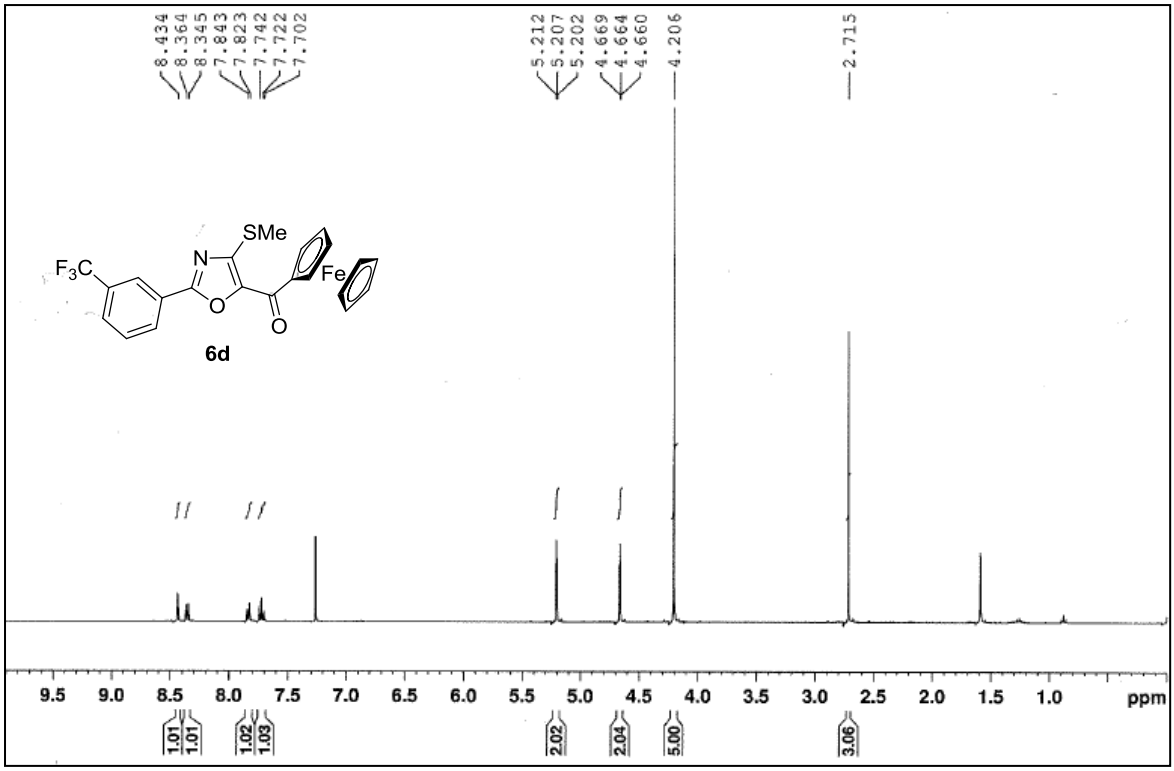
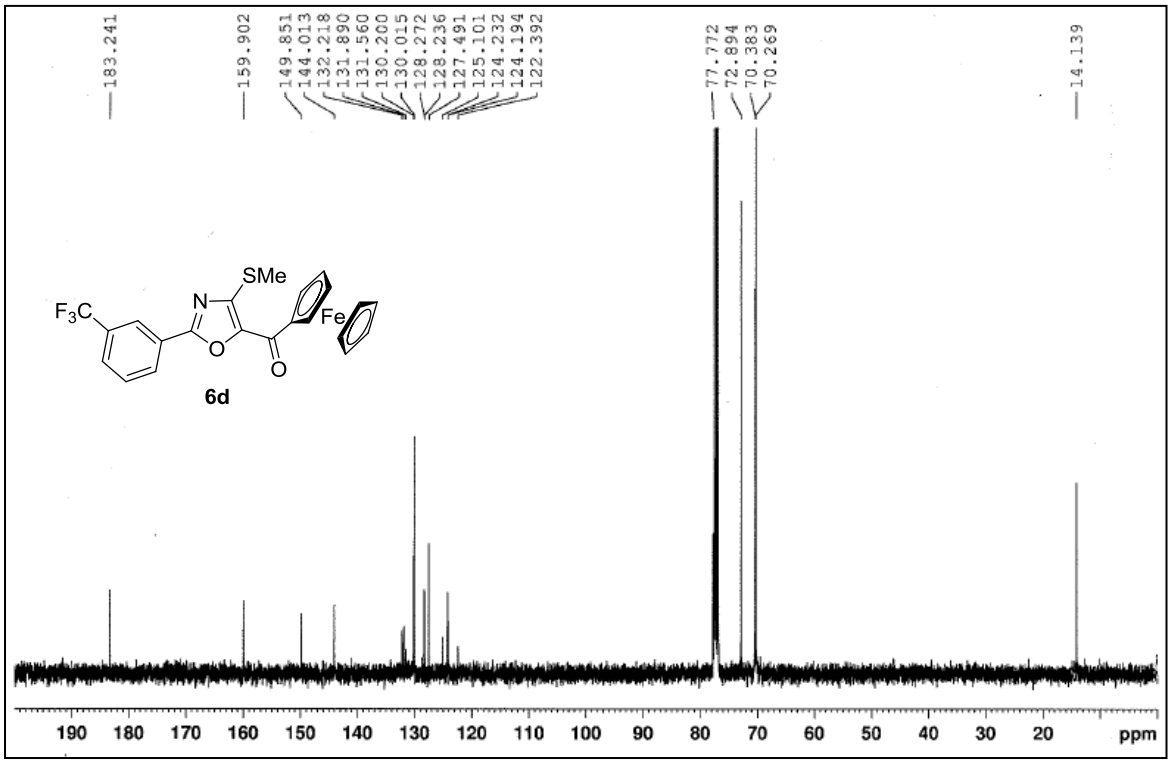




^{1}H NMR and ^{13}C NMR Spectra for compound **6a** in $CDCl_3$





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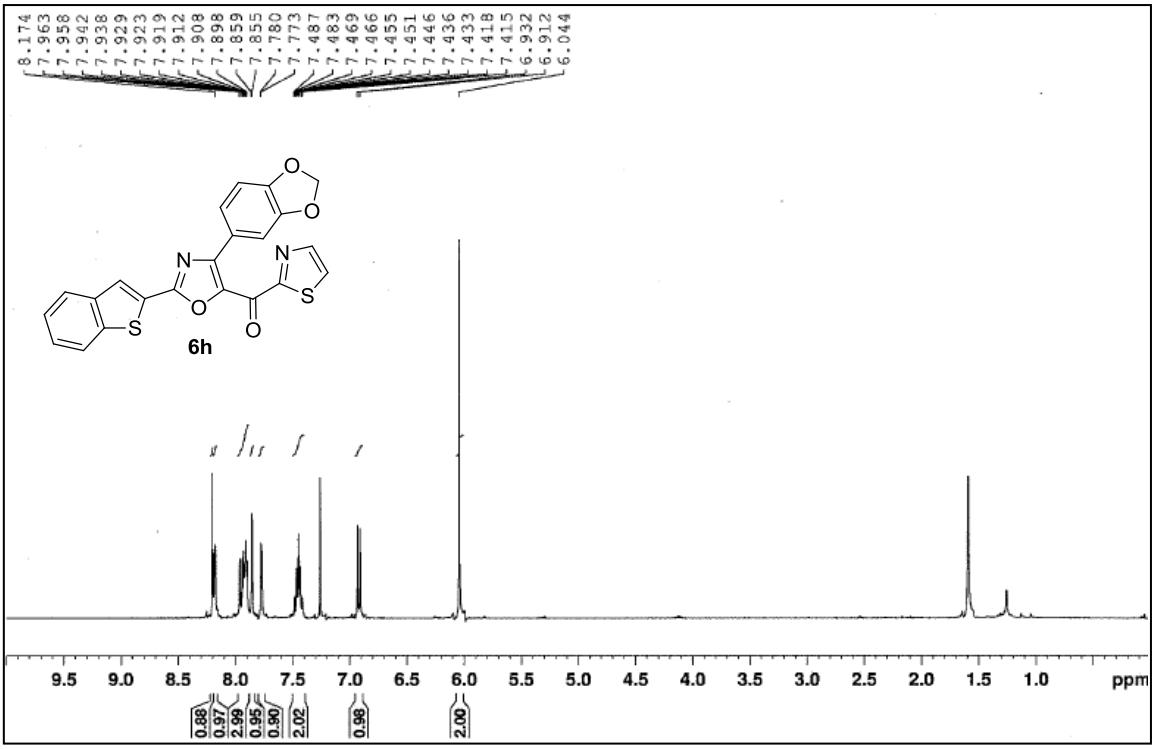
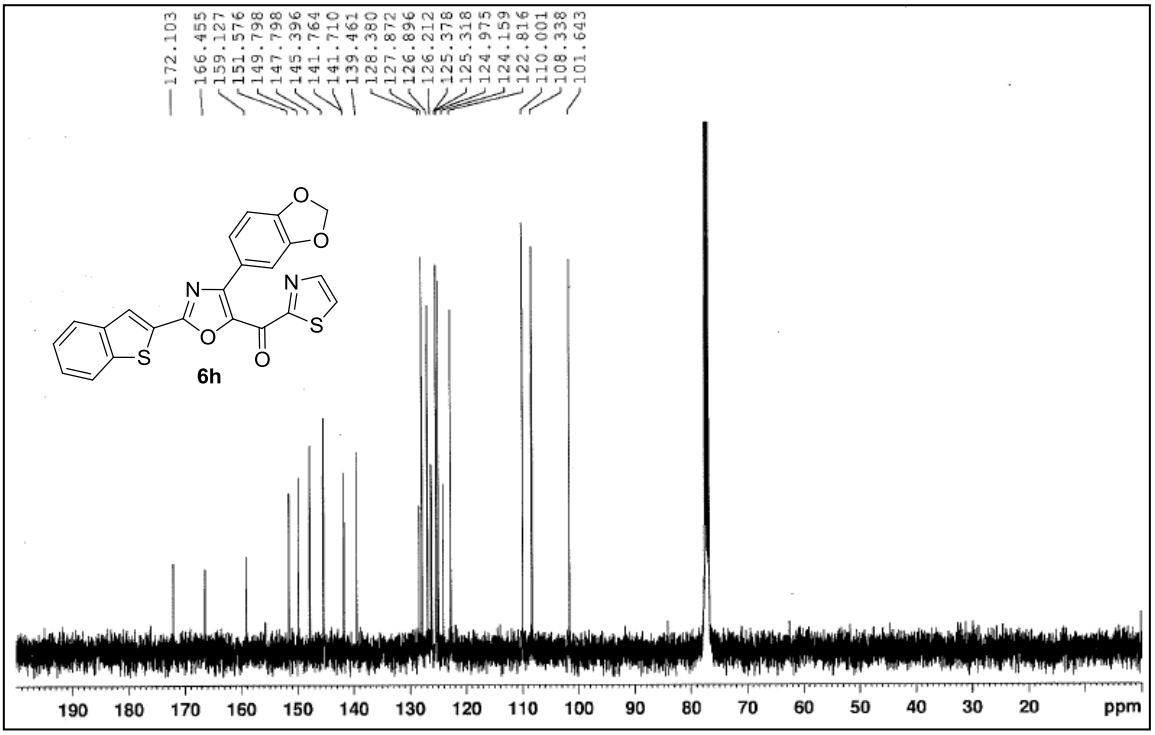
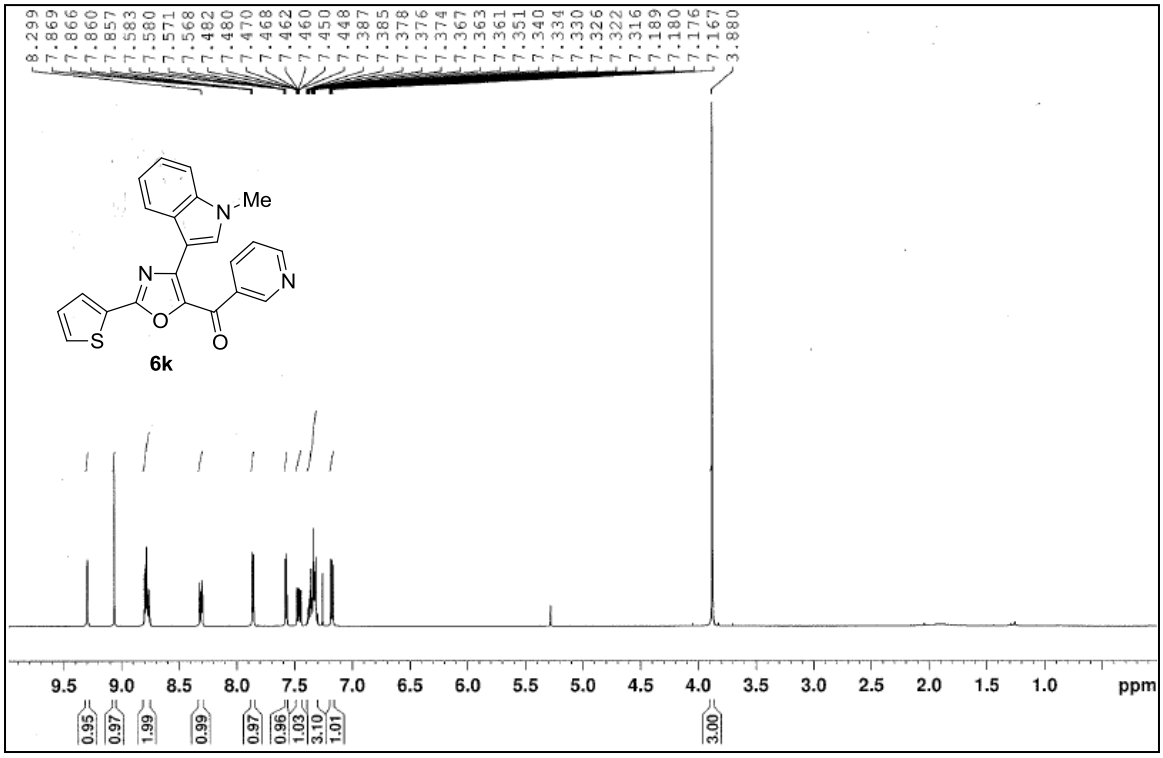
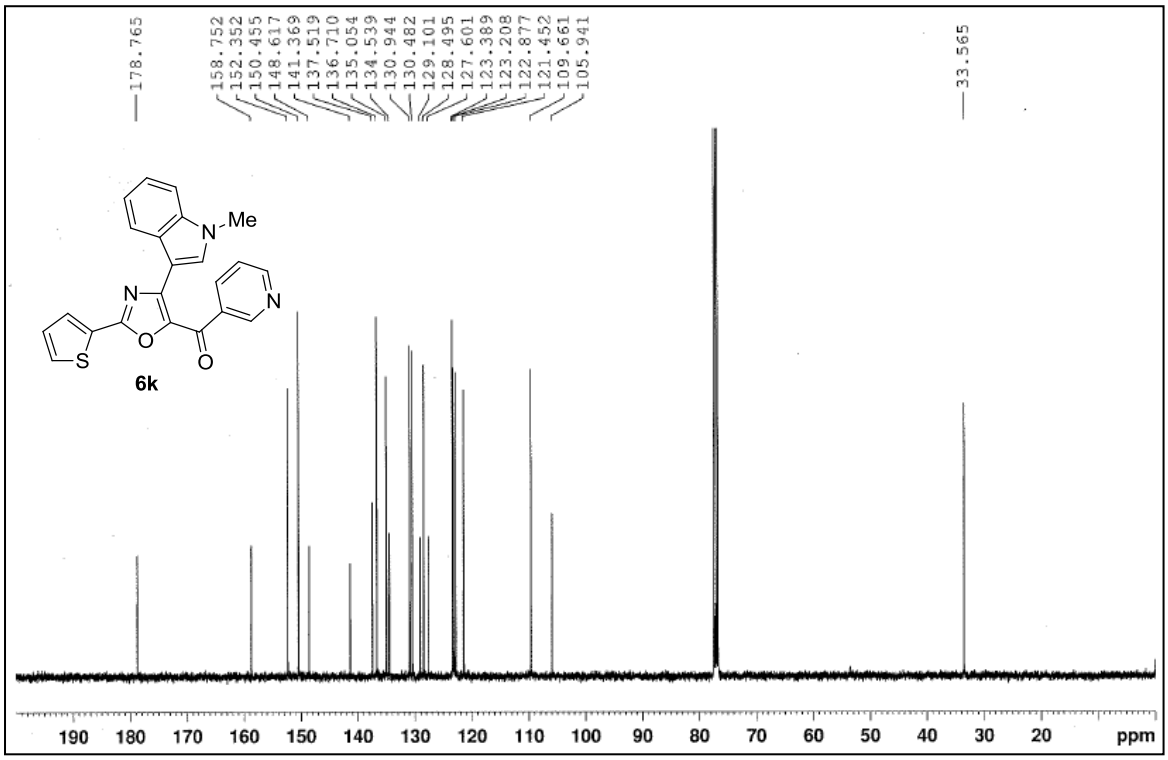


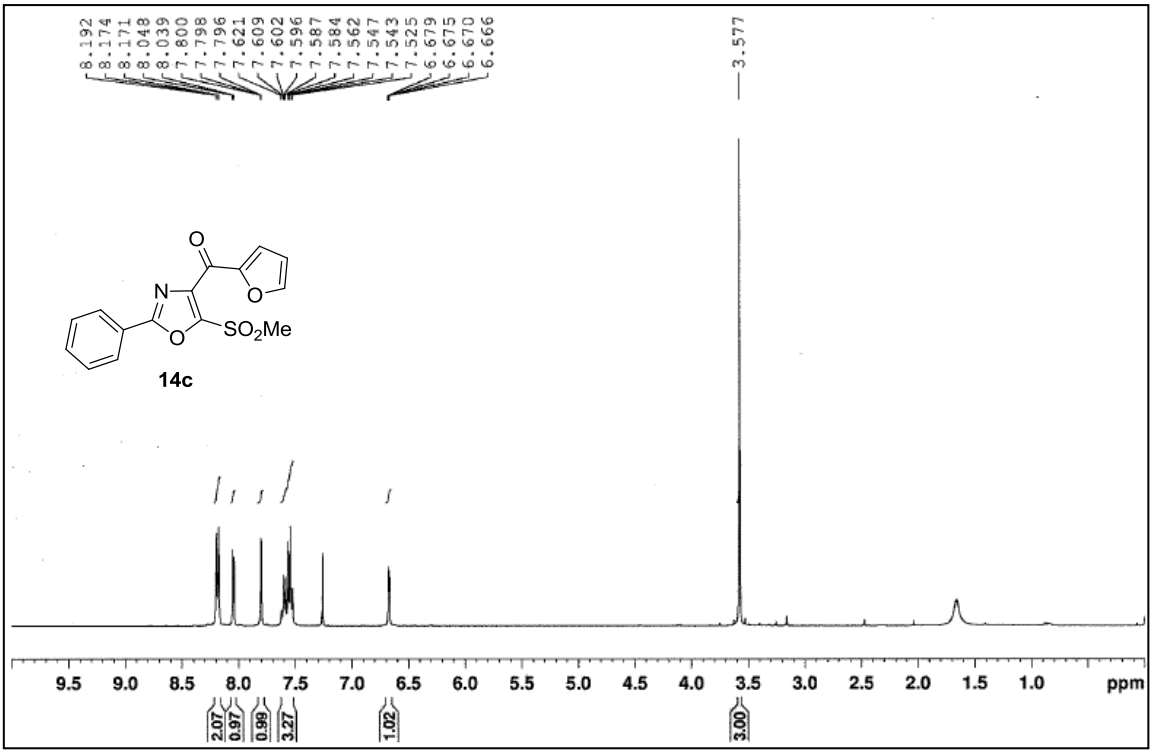


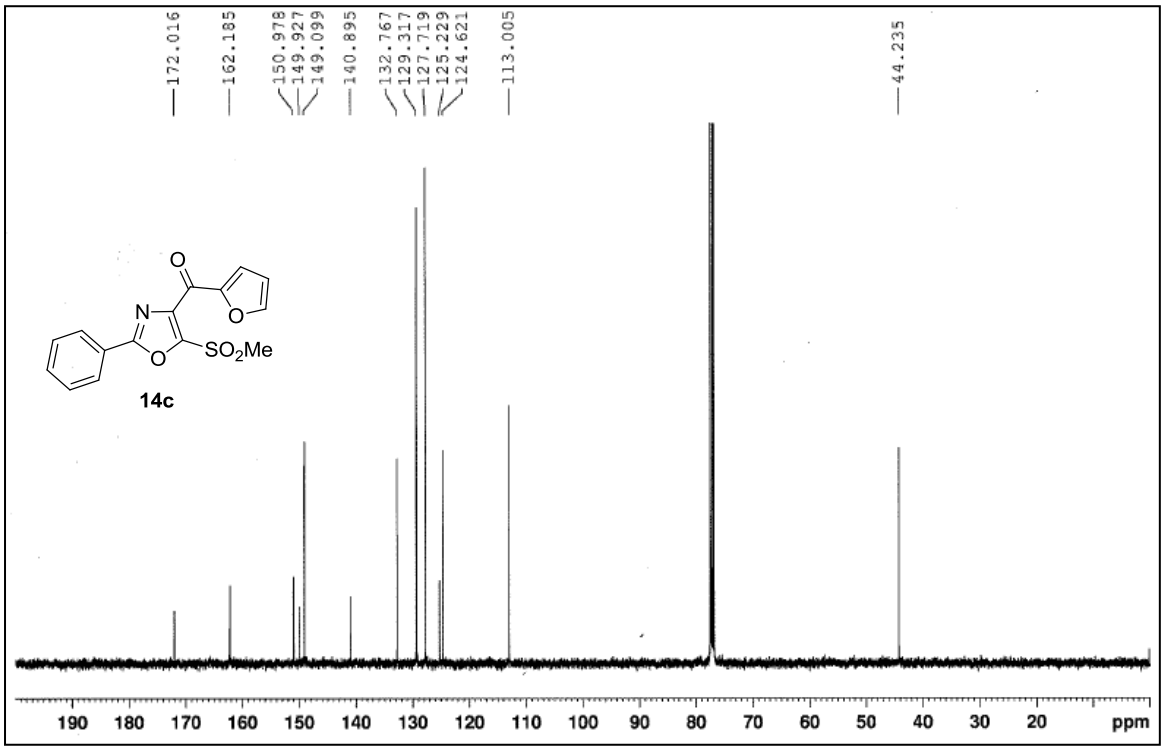
^{1}H NMR and ^{13}C NMR Spectra for compound **6h** in $CDCl_3$



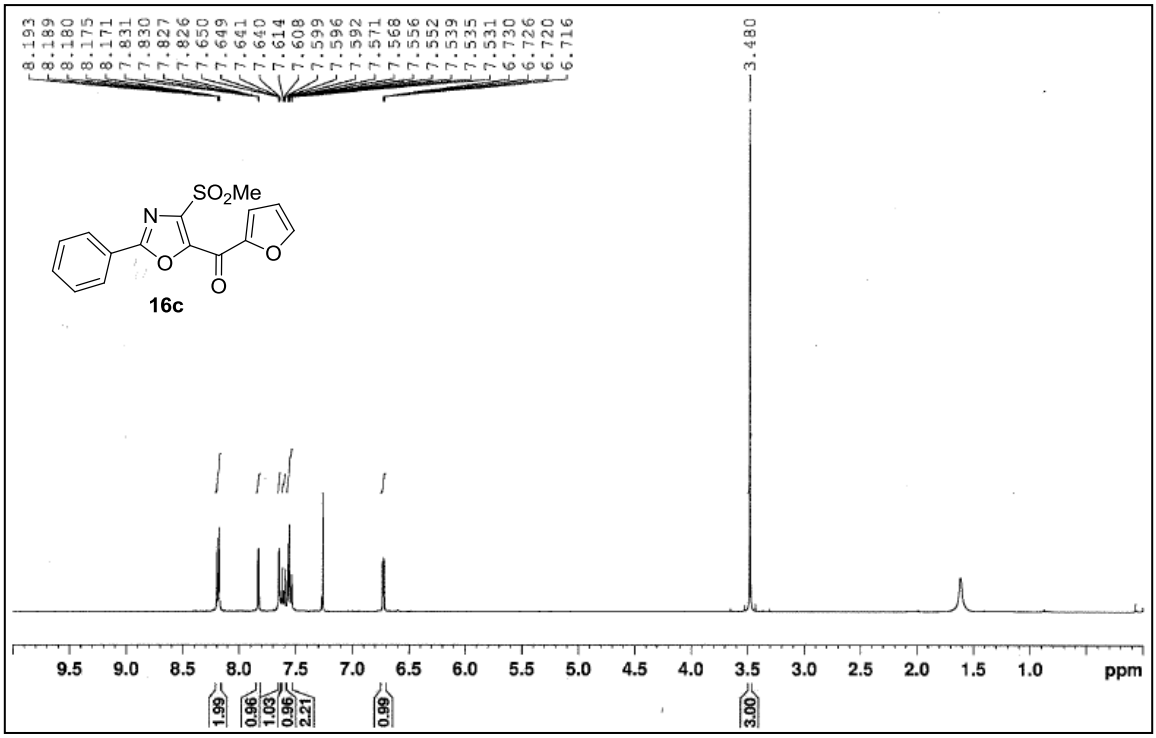


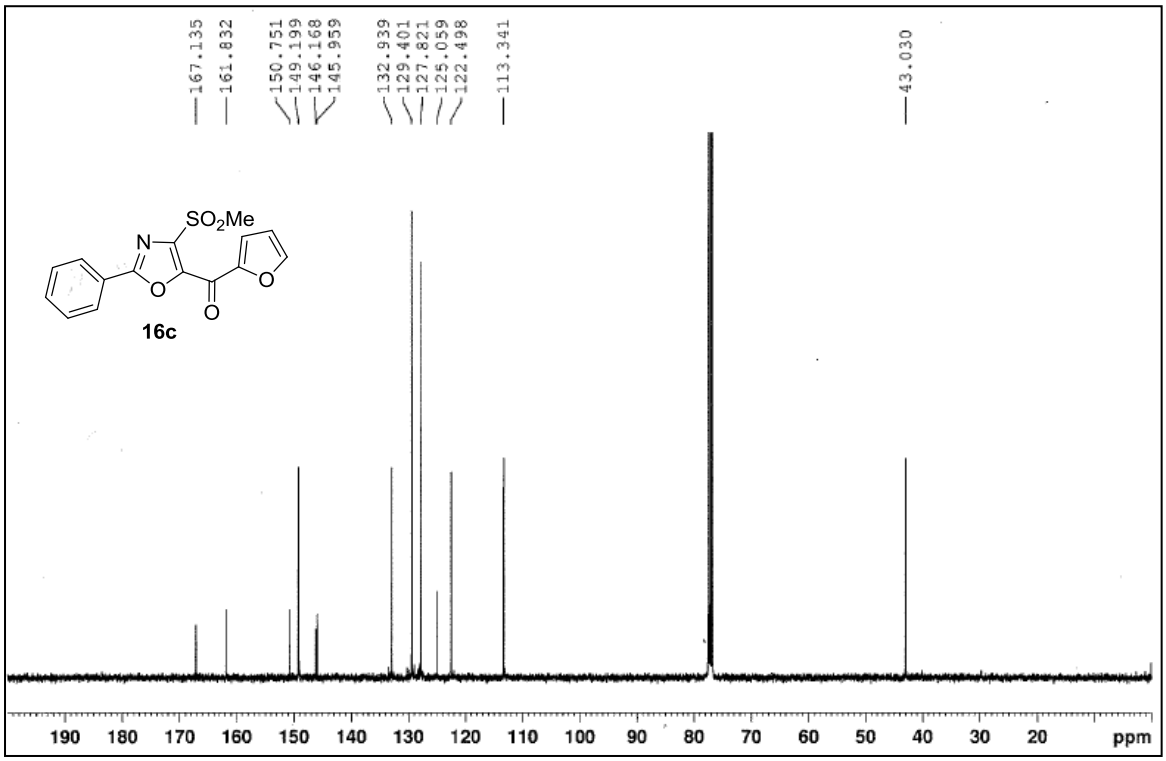
^{1}H NMR and ^{13}C NMR Spectra for compound **6k** in $CDCl_3$





^{1}H NMR and ^{13}C NMR Spectra for compound **14c** in $CDCl_3$





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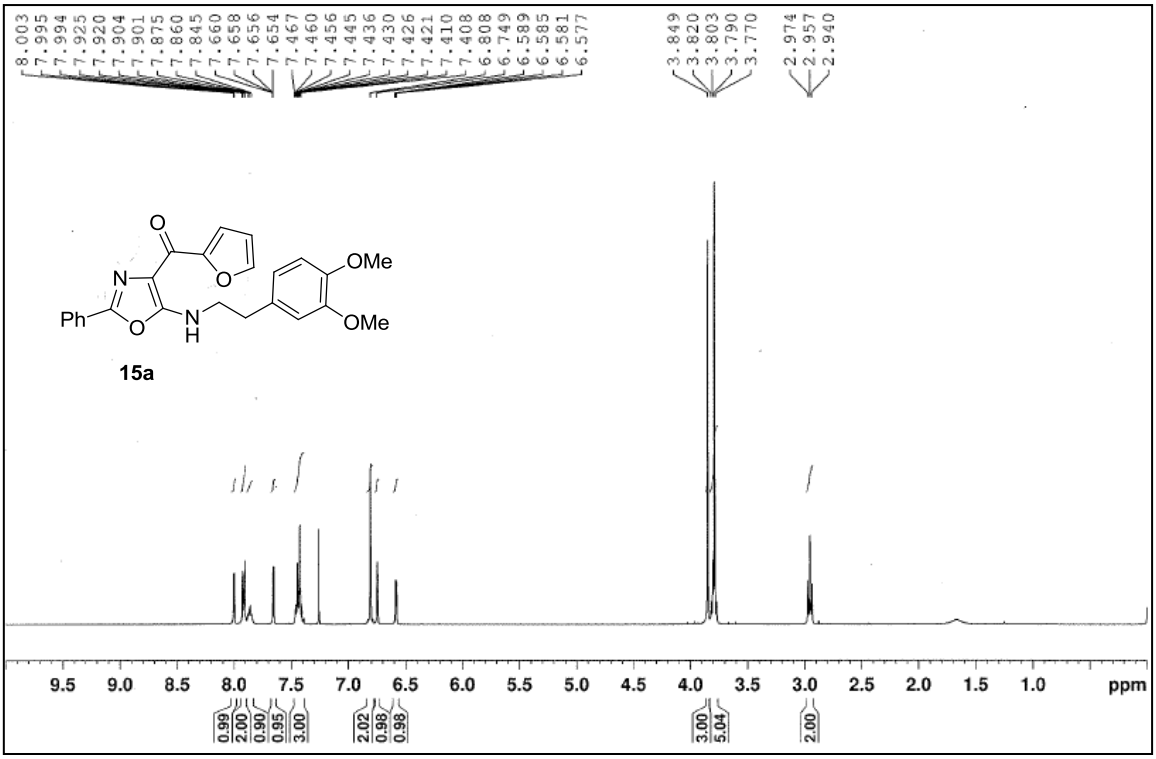
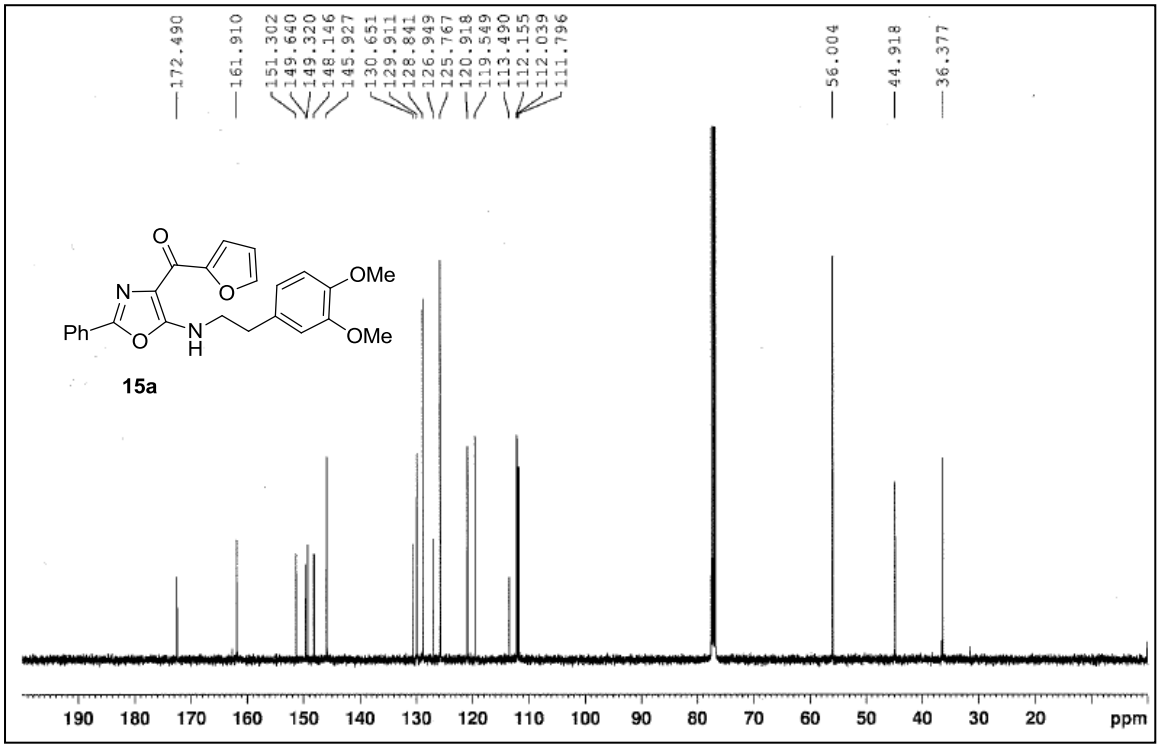
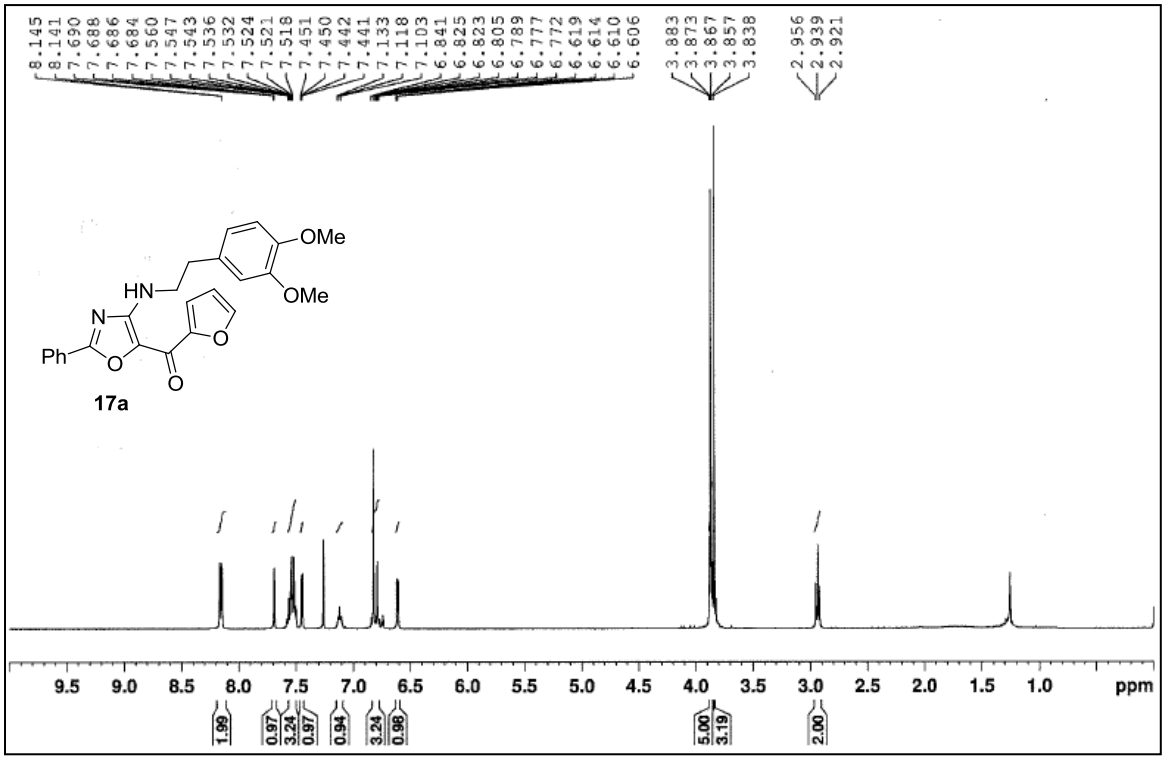
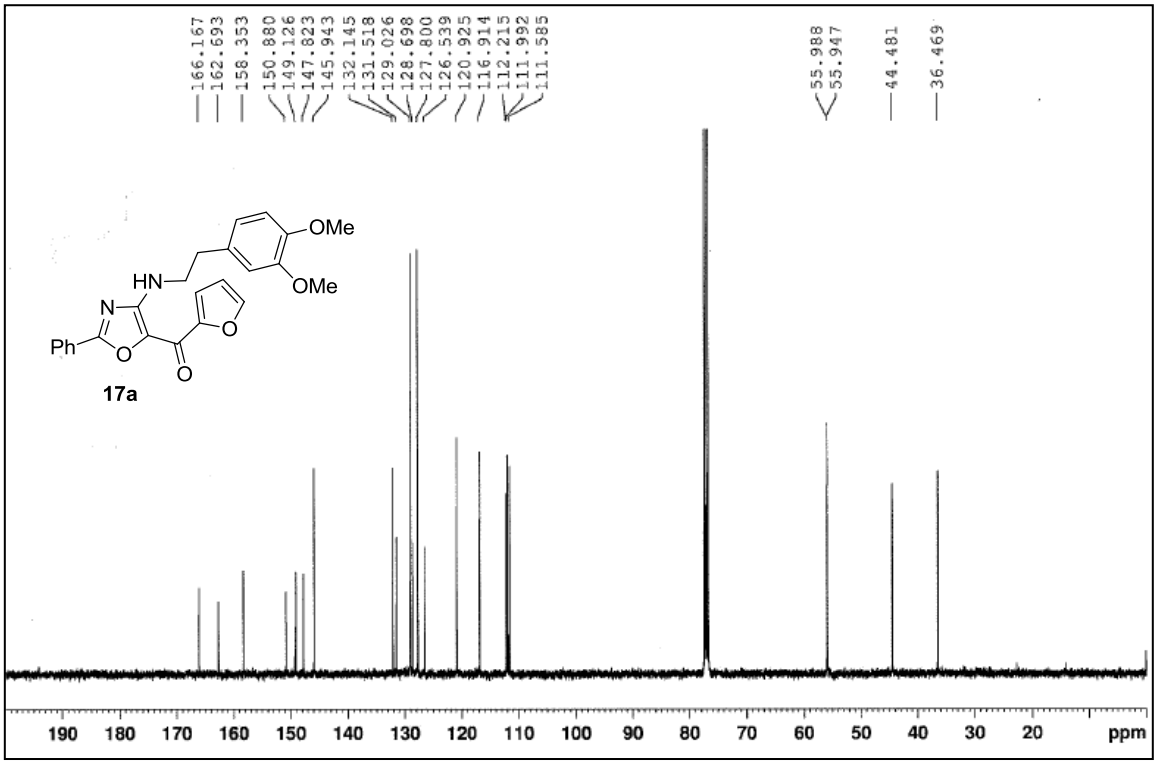




^{1}H NMR and ^{13}C NMR Spectra for compound **15a** in $CDCl_3$





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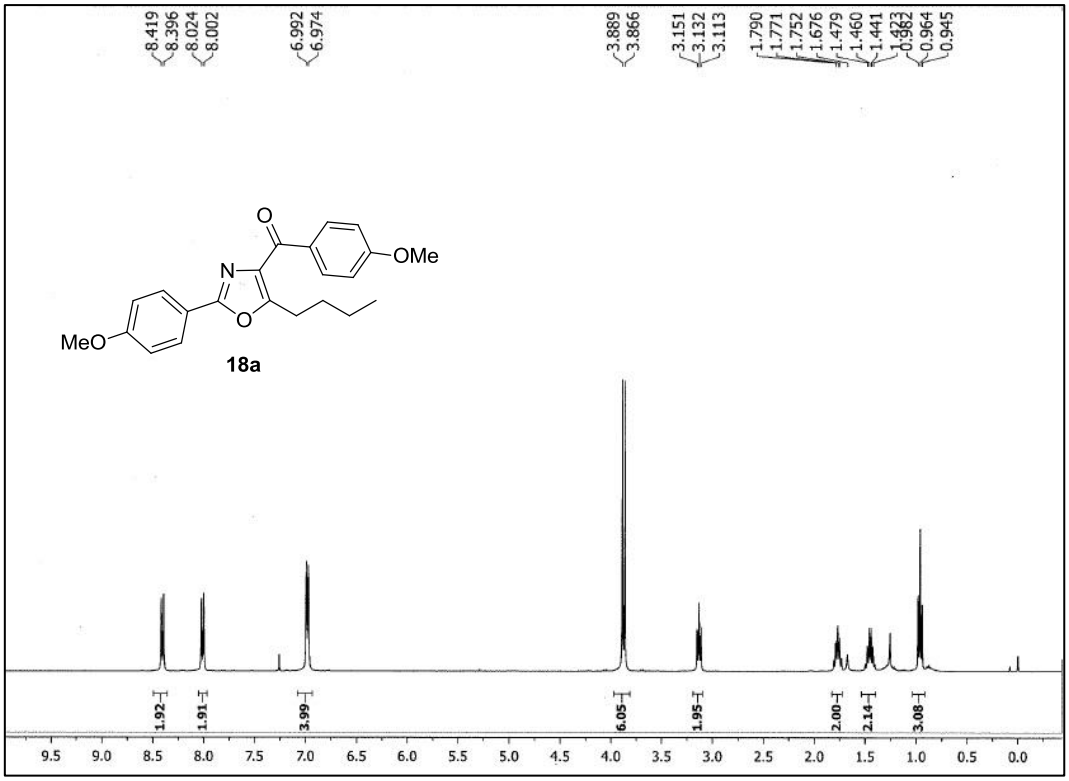

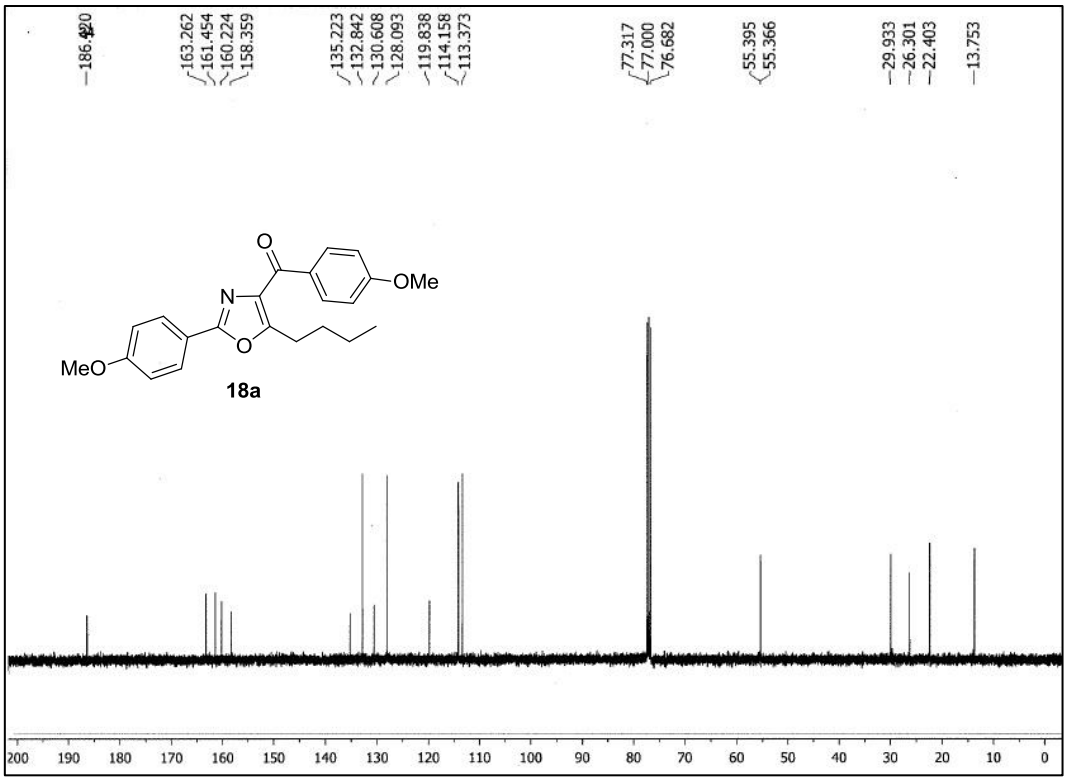

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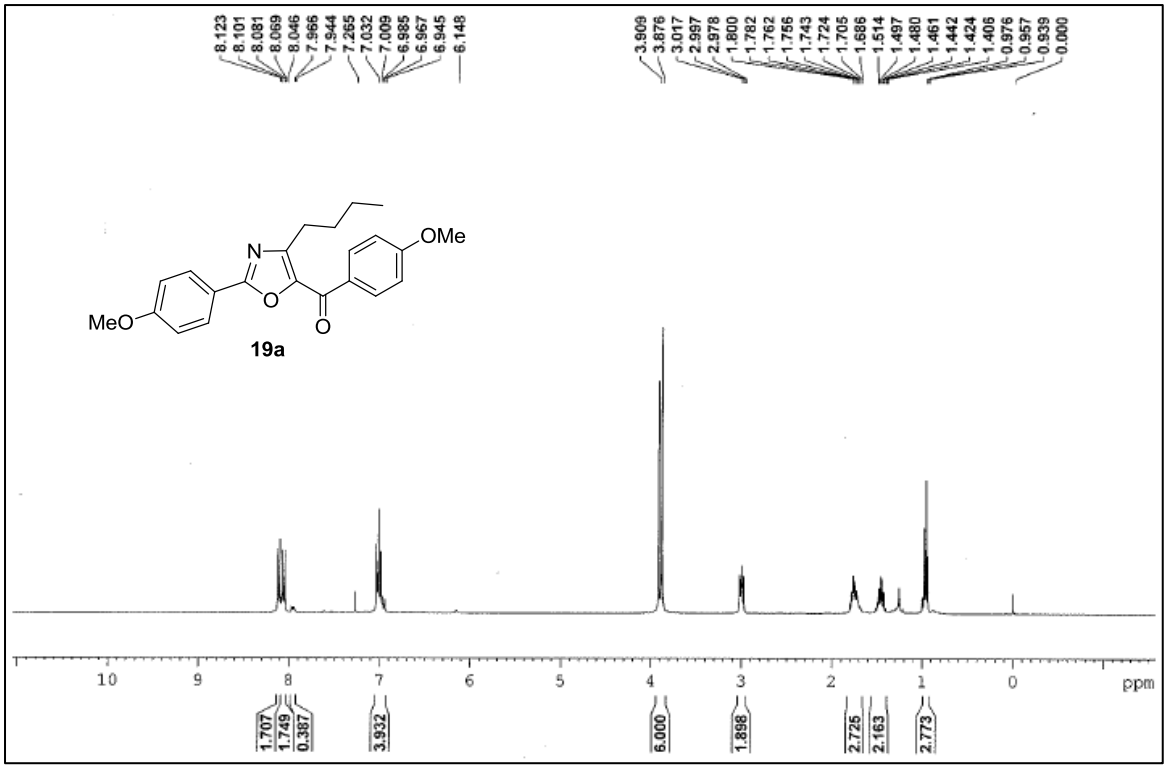

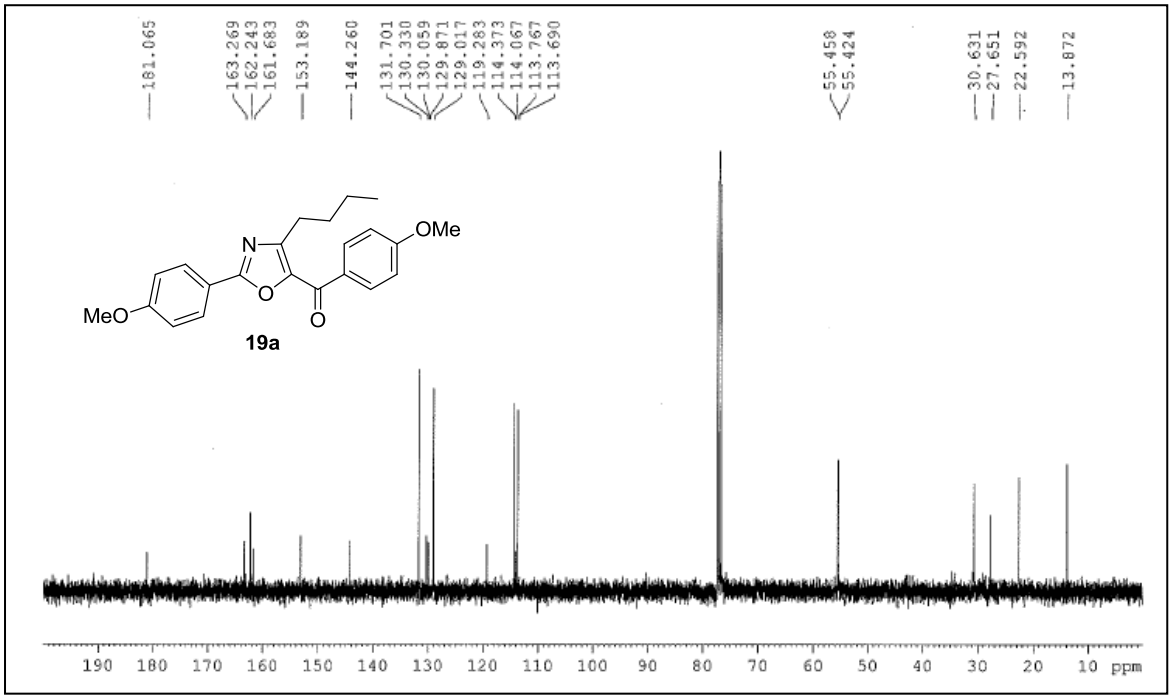

^{1}H NMR and ^{13}C NMR Spectra for compound **19a** in $CDCl_3$

List of publications

From thesis:

1) "Synthesis of 2-Phenyl-4,5-Substituted Oxazoles by Copper-Catalyzed Intramolecular Cyclization of Functionalized Enamides"
S. Vijay Kumar, B. Saraiah, N. C. Misra, and H. Ila. ***J. Org. Chem*. 2012*, 77,* 10752.**

2) "Cyclocondensation of Arylhydrazines with 1,3-Bis(het)arylmonothio-1,3-diketones and 1,3-Bis(het)aryl-3-(methylthio)-2-propenones: Synthesis of 1-Aryl-3,5-bis(het)aryl pyrazoles with Complementary Regioselectivity"
S. Vijay Kumar, Santosh K. Yadav, B. Raghava, B. Saraiah, H. Ila, K. S. Rangappa, and Arpan Hazra. ***J. Org. Chem*. 2013*, 78,* 4960.**

3) "Synthesis of 2,4,5-Trisubstituted Thiazoles via Lawesson's Reagent-Mediated Chemoselective Thionation-Cyclization of Functionalized Enamides"
S. Vijay Kumar, G. Parameshwarappa, and H. Ila. ***J. Org. Chem*. 2013*, 78,* 7362.**

4) "Synthesis of N-Functionalized/NH Multisubstituted Indoles, Thienopyrroles, Pyrroloindoles and Pyrazolopyrroles via Sequential One-Pot Base Mediated and Copper Catalyzed Inter- and Intramolecular Amination of 2-[2-Bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitriles"
S. Vijay Kumar, B. Saraiah, G. Parameshwarappa, H. Ila and Girijesh Kumar Verma. ***J.Org. Chem*. 2014, *79*. 7961.**

5) "Regioselective Synthesis of 2,4,5-Trisubstituted Oxazoles from Amides via Reversal of Reactivity of 1,3-Bis(het)aryl-3-(methylthio)-2-propenones"
S. Vijay Kumar, Anand Acharya, and H. Ila (**Manuscript under preparation).**

Other publications:

6) "One-Pot Synthesis of Functionalized Benzo[*b*]thiophenes and Their Hetero-Fused Analogues via Intramolecular Copper-Catalyzed S-Arylation of In Situ Generated Enethiolates"
Anand Acharya, **S. Vijay Kumar**, B. Saraiah and H. Ila. ***J. Org. Chem*. 2015*, 80,* 2884.**

7) "Diversity Oriented Synthesis of Substituted Benzo[*b*]thiophenes and Their Hetero-Fused Analogues via Palladium Catalyzed Oxidative C-H Functionalization-Intramolecular Arylthiolation"
Anand Acharya, **S. Vijay Kumar**, and H. Ila. ***Chem. Eur. J*. 2015*, 21,* 17116.**