STUDIES ON SYNTHESIS OF BIOLOGICALLY ACTIVE *N*-HETEROCYCLES: DEVELOPMENT OF ENVIRONMENT FRIENDLY SYNTHETIC METHODOLOGIES

THESIS

Submitted to the

UNIVERSITY OF PUNE

For the degree of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

By

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April 2008

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Studies on synthesis of biologically active *N*-heterocycles: Development of environment friendly synthetic methodologies"** which is being submitted to **University of Pune** for the award of **Doctor of Philosophy** in **Chemistry** by **Mr. T. M. Potewar** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled **"*Studies on synthesis of biologically active N-heterocycles: Development of environment friendly synthetic methodologies*"** submitted for the award of **Doctor of Philosophy** in **Chemistry** to the **University of Pune**, has not been submitted by me for a degree or diploma to any other university or institute. This work was carried out at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India.

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Acknowledgement

It gives me great pleasure to express my heartfelt gratitude to my research supervisor Dr. K. V. Srinivasan for his astute guidance, invaluable suggestions and keen criticism while carrying out the present work. His enduring passion, moral support and help out of the way led me to overcome all the difficulties I encountered during this endeavor. I am certain that the guidance and training provided by him has laid a foundation for future success.

I would like to thank Dr. R. J. Lahoti, Dr. U. R. Kalkote, Mr. V. K. Sharma, Dr. A. Sudalai and Dr. Thomas Daniel for their helpful suggestions and constant support during my Ph. D. programme. I also would like to thank Prof. R. S. Kusurkar for her fruitful suggestions during my work assessment.

I would like to thank my friends Sharad Panchgalle, Rashid Nadaf, Dr. Shafi Siddiqui, Dr. Dilip Jarikote and Sachin Ingale for their constant support and helpful suggestions during research. I am thankful to More, Jogdand, umesh and kiran for their help.

It's a pleasure to thank all my friends at NCL and around for their cheerful company, which made my stay at NCL memorable one. I would like to thank Shriram, Nagendra, Giri, Namdev, Umesh, Amol, Pandurang, kulbhushan, Nilesh, kale, Nagesh, Rohidas, Suleman, Deepak, Purude, Songire, Narayan, Pushpesh, Satyendra, Shiva, Pratap, Gaurav, Amit, Bapu, Mahendra, Rupali, Ganesh, Malwadkar, Kesari, Gaikwad, Mehraj, Haval for their friendly attitude. I also would like to thank my labmates Suresh, Palimkar, Harish, Atul and Venkateshan for cooperative atmosphere.

I would like to acknowledge all my teachers who guided me towards the right path to reach the present stage.

I thank NMR, elemental analysis, IR, HPLC and CMC groups for their help in obtaining the analytical data. I thank all the staff of NCL for their co-operation. I wish to thank great scientific community whose achievements are constant source of inspiration for me.

I am thankful to Dr. Ganesh Pandey (Head, Organic Chemistry Division), Dr. M. K. Gurjar, (Former Head, Organic Chemistry: Technology Division) and Dr. Shivram, Director, NCL for giving me this opportunity and providing all necessary infrastructure and facilities.

I simply do not have words to thank to my parents and family members whose everlasting encouragement, support and patience during my seemingly unending education have helped me to reach this juncture. I owe much towards my wife Meena for her patience and endless support during my Ph. D.

I thank CSIR, New Delhi for the financial assistance in the form of research fellowship.

I thank whole heartedly, the supreme God, the supreme Guide.

T. M. Potewar

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GENERAL REMARKS

- ^{1}H NMR spectra were recorded on Bruker AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on Bruker AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometers.
- Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer.
- Elemental analyses were obtained using a flash EA 1112 thermofinnigan instrument.
- Melting points were recorded in open capillary on Buchi melting Point B-540 apparatus and are uncorrected.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light and iodine.
- Organic layers were dried over anhydrous sodium sulfate otherwise stated.
- All solvents and reagents were purified and dried by known procedures in the literature.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned (silica gel, 60-120 mesh/100-200 mesh/230-400 mesh).
- Starting materials were obtained from commercial sources or prepared using known procedures. Petroleum ether used in the experiments was of 60-80 °C boiling range.
- The compound numbers, Scheme numbers, Figure numbers and Table numbers given in each Chapter refers to that particular chapter only. Independent compound numbering has been employed for abstract and chapter.
- All the compounds previously known in the literature were characterized by the comparison of melting point, IR and NMR spectra with authentic samples.

ABBREVIATIONS

AcOH	Acetic acid
AIBN	2,2'-Azodiisobutyronitrile
Aq.	Aqueous
Ar	Aryl
bbim	1,3-di-*n*-butyl imidazolium
BF_4	Tetrafluoroborate
Br	Bromide
brs	Broad singlet
Bu	Butyl
Bu_3P	Tributylphosphine
$CaCl_2$	Calcium chloride
Calcd.	Calculated
Cat.	Catalytic/catalyst
CAN	Cerric ammunium nitrate
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated chloroform
CF_3COOH	Trifluoorboric acid
$CHCl_3$	Chloroform
ClO_4	Chlorate
Conc.	Concentrated
CrO_3	Chromic acid
CuI	Copper iodide
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublet
DEAD	Diethyl azadicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DMF	Dimethyl formamide

DMSO	Dimethyl sulfoxide
e.g.	For example
equiv	Equivalent
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
EtOH	Ethanol
Et_2O	Diethyl ether
Fig.	Figure
g	Gram
h	hour
Hbim	1-*n*-butyl imidazolium
HBF_4	Tetrafluoboric acid
HCHO	Formaldehyde
$HC(OEt)_3$	Triethyl orthoformate
HCl	Hydrochloric acid
$HClO_4$	Perchloric acid
HPF_6	Hexafluorophosphoric acid
H_2SO_4	Sulfuric acid
HN_3	Hydrazoic acid
Hz	Hertz
I_2	Iodine
IL	Ionic liquid
Im	Imidazole
IR	Infrared
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
LDA	lithium diisopropylamide
LiOH	Lithium hydroxide
Lit.	Literature
m	Multiplate
Me	Methyl

MeCN	Acetonitrile
MeI	Methyl iodide
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
mL	Mililiter
mmol	Milimole
min	Minutes
M.P.	Melting point
MW	Microwave
MHz	Megahertz
N_2	Nitrogen
NaH	Sodium hydride
$NaBH_4$	Sodium borohydride
NBS	N-bromosuccinimide
NH_3	Ammonia
NH_4OAc	Ammonium acetate
NaI	Sodium iodide
NaOH	Sodium hydroxide
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
NaN_3	Sodium azide
NaOEt	Sodium ethoxide
O_3	Ozone
PF_6	Hexafluorophosphate
Ph	Phenyl
Ph_3P	Triphenyl phosphine
$POCl_3$	Phosphorus oxychloride
$POBr_3$	Phosphorus oxybromide
ppm	Parts per million
rt	Room temperature
RTIL	Room temperature ionic liquids

s	Singlet
t	Triplet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Crromatography

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Title of thesis	Studies on synthesis of biologically active *N*-heterocycles: Development of environment friendly synthetic methodologies
Registration number	EI/122/Ph.D/2005
Date of registration	28.06.2004
Place of work	Division of Organic Chemistry, National Chemical Laboratory, Pune- 411 008

Abstract

The thesis entitled "***studies on synthesis of biologically active N-heterocycles: Development of environment friendly synthetic methodologies***" has been divided into three chapters.

The first chapter is divided into three sections, section A provides a brief introduction to ionic liquids, section B describes the synthesis of ionic liquids and section C describes the application of ionic liquids as solvent as well as a promoter for the synthesis of biologically active *N*-heterocycles. This section is further divided into three parts which describes the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles, 3,5,6-trisubstituted-1,2,4-triazines and quinoxalines in ILs as solvent cum promoter.

The second chapter describes the environment-friendly synthetic methodologies for the synthesis of bio-active *N*-heterocycles and is divided into three sections. The section A describes the efficient synthesis of 2-aminothiazoles in water at ambient temperature, section B describes the efficient and rapid synthesis of 2-amino-1,3-selenazoles in an ionic liquid/water system at ambient temperature and section C describes the synthesis of 4-aryl-1,4-dihydropyridines unsubstituted at 2-and 6-positions from alkyl propiolate under catalyst- and solvent-free conditions.

The third chapter describes the synthesis of bio-active *N*-heterocycles based on (3*H*)-quinazolin-4-one skeleton and is divided into three sections. Section A deals with the synthesis of tryptanthrin, section B describes the synthesis of deoxyvasicinone and section C describes the synthesis of luotonin A.

Chapter 1: Synthesis of ionic liquids (ILs) and its application as solvent as well as a promoter for the synthesis of biologically active *N*-heterocycles

The first chapter is divided into three sections, section A provides a brief introduction to ionic liquids, section B describes the synthesis of ionic liquids and section C describes the application of ionic liquids as solvent as well as a promoter for the synthesis of bioactive *N*-heterocycles.

Section A: Intorduction to ionic liquids (ILs)

Ionic liquids (ILs) are often defined as salts that melt at or below 100 °C. In some cases, the ionic liquids are free-flowing liquids at room temperature, in which case they are termed as room temperature ionic liquids (RTILs). The dramatic growth of ionic liquid as potential 'Green designer solvent' has resulted in the development of a huge number of novel ionic liquids and its associated applications. Ionic liquids have the potential to increase chemical reactivity and thus lead to more efficient processes. They are non-flammable and due to their low vapor pressure less toxic than conventional solvents. A brief history of ionic liquids, structural features of ILs, relationship between the structural features of ILs and physical and chemical properties have been discussed in this section.

Section B: Synthesis of ionic liquids (ILs)

Among the various ionic liquids, imidazolium based ILs have attracted great deal of attention as a novel reaction media in organic synthesis due to their negligible vapor pressure, low melting point with high thermal and chemical stability.

This section describes in details about the synthesis of a series of 1,3-di-*n*-butylimidazolium and 1-*n*-butylimidazolium based ILs (**Fig. 1**).

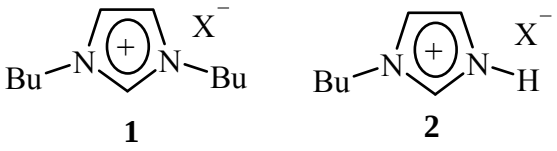


Figure 1. 1,3-di-*n*-butylimidazolium and 1-*n*-butylimidazolium ILs

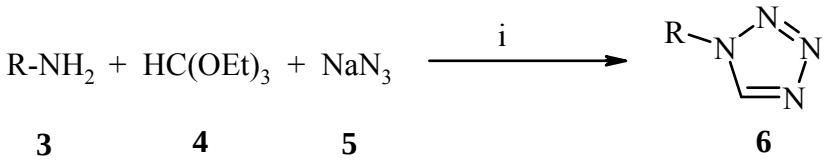
Section C: Applications of ionic liquids (ILs) as solvent as well as a promoter for the synthesis of biologically active *N*-heterocycles

Heterocyclic compounds, particularly *N*-heterocycles are of interest in medicinal science. This has accelerated the quest for new methods in heterocyclic chemistry. Most of the routes leading to the synthesis of heterocycles involve the use of conventional volatile organic solvents. However, these mainly organic solvents, belonging to the group of volatile organic compounds (VOC's) account for a great proportion of environmental pollution and waste material; their use is often problematic owing to their toxicity, volatility etc. Therefore, there is a need to replace these VOC's by alternative solvents. Among the alternative solvent studied as substitutes for classical organic solvents are ionic liquids. With respect to reaction carried out in conventional solvents, reactions in ILs have different thermodynamic and kinetic behaviors, which often lead to improved process performance. Furthermore, because of their low nucleophilicity, ionic liquids provide unique environment in stabilizing electron deficient intermediates. The aim of our work is to evaluate the potential of the ionic liquids with respect to their application not only as solvent, but also promoter in the synthesis of biologically active *N*-heterocycles. This section is further divided into three parts.

Part I: Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles

Tetrazole functionality plays important roles in coordination chemistry as a ligand, in medicinal and various materials sciences. Tetrazole moieties are important synthons in synthetic organic chemistry.

This section describes an efficient and rapid synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles **6** by one-pot condensation reaction of substituted amines **3**, sodium azide **5** and triethyl orthoformate **4** in the IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) at 100 °C (**Scheme 1**).



3 **4** **5** **6**

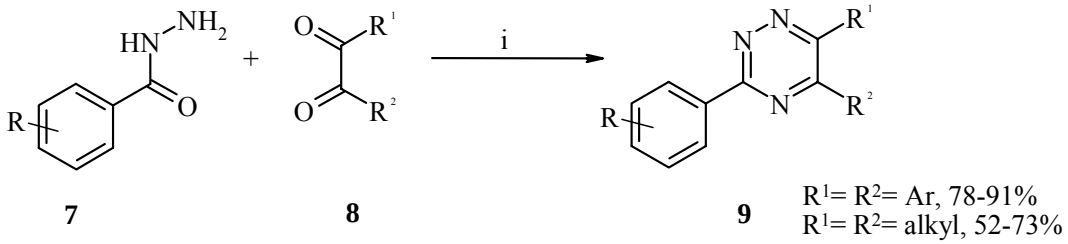
Scheme 1. Reaction Conditions**:** (i) $[Hbim]BF_4$, 100 °C, 15-35 min, 85-93%.

This wok is published in *Tetrahedron Letters*, **2007**, *48*, 1721.

<u>Part II</u>: Synthesis of 3,5,6-trisubstituted-1,2,4-triazines

1,2,4-triazines are a well known class among the heterocyclic compounds. These have been associated with diverse pharmacological activities.

This section describes an efficient synthesis of 3,5,6-trisubstituted-1,2,4-triazines **9** by a one-pot, three-componnt condensation reaction between aromatic acid hydrazides **7**, 1,2-diketones **8** and ammonium acetate in the IL, 1-*n*-butylimidazolium tetrafluoroborate ($[Hbim]BF_4$) (**Scheme 2**).



7 **8** **9**

$R^1 = R^2$= Ar, 78-91%
$R^1 = R^2$= alkyl, 52-73%

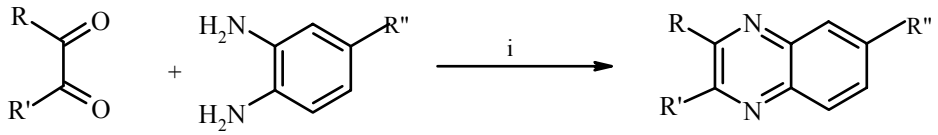
Scheme 2. Reaction conditions: (i) $[Hbim]BF_4$, NH_4OAc, 100 °C, 10-60 min.

This wok is published in *Synthetic Communications*, **2007**, *37*, 261.

<u>Part III</u>: Synthesis of quinoxalines

Quinoxalines are important components of several pharmacologically active compounds. Besides this, they are well known for their application in dyes, efficient electroluminescent materials, and organic semiconductors, building blocks for the synthesis of anion receptors, cavitands, dehydroannulenes and DNA cleaving agents.

This section describes the synthesis of quinoxalines **12** which has been achieved from 1,2-diketones **10** and aromatic 1,2-diamines **11** in excellent isolated yields using IL, 1-*n*-butylimidazolium tetraflouroborate ($[Hbim]BF_4$) as a reaction medium as well as a promoter (**Scheme 3**).



R=R'=alkyl, aryl
R"=H, CH_3, NO_2

R=aryl; 89-96%
R=alkyl; 69-78%

Scheme 3. Reaction conditions: (i) $[Hbim]BF_4$, rt, 10-40 min.

This wok is published in *Synthetic Communications*, **2008** (article in press).

Chapter 2. Environment-friendly synthesis of 2-aminothiazoles, 2-amino-1,3-selenazoles and 1,4-dihydropyridines

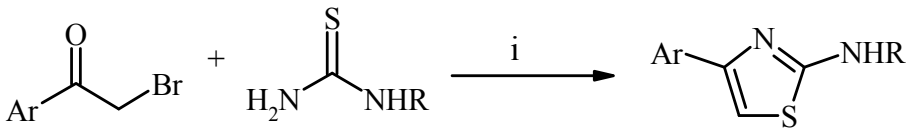
Organic solvents are conventionally used in chemical synthesis on a large scale for heat transfer and controlling chemical reactivity. However, these organic solvents, belonging to the group of volatile organic compounds (VOC's), account for a great proportion of environmental pollution and environmental hazards. A consequence of the necessity to minimize the amount of toxic waste and by-products from chemical processes is a need for the development of new, more environmentally- friendly synthetic methods in which fewer toxic substances are used. This trend towards what has become known as 'Green Chemistry' or 'Sustainable Technology' necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.

This chapter is divided into three sections and describes the environment-friendly synthesis of bioactive *N*-heterocycles such as 2-aminothiazoles, 2-amino-1,3-selenazoles and 1,4-dihydropyridines.

Section A: Synthesis of 2-aminothiazoles in water at ambient temperature

The thiazole ring system is a useful structural motif found in numerous biologically active molecules. The 2-aminothiazoles ring system is a useful structural element in medicinal chemistry having applications in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, and HIV infections.

This section describes an efficient and environment-friendly method for the synthesis of substituted 2-aminothiazoles **15** in water by reacting aromatic α-bromoketones **13** with thiourea derivatives **14** without any additional catalyst or co-organic solvent at ambient temperature and the products were obtained in excellent isolated yields (**Scheme 4**).



13 **14** **15**

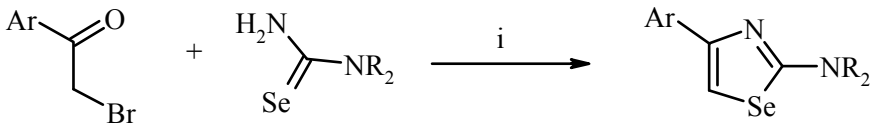
Scheme 4. Reaction conditions**:** (i) H_2O, rt, 1-2 h, 89-97%.

This wok is published in *Tetrahedron*, **2008** (article in press, doi:10.1016/j.tet.2008.03.082*48*, 1721)

<u>Section B</u>: Synthesis of 2-amino-1,3-selenazoles in an ionic liquid/water system at ambient temperature

1,3-Selenazoles are of pharmacological relevance, due to their antibiotic and cancerostatic activity. 2-Amino-1,3-selenazole are also good superoxide anion-scavengers. Moreover, 2-dialkylamino-1,3-selenazole has become of interest as a starting material for preparing dyes.

This section describes the efficient and rapid synthesis of 2-amino-1,3-selenazoles **18** in an ionic liquid/water solvent system by condensing aromatic α-bromoketones **16** with selenourea derivatives **17** at ambient temperature (**Scheme 5**).



16 **17** **18**

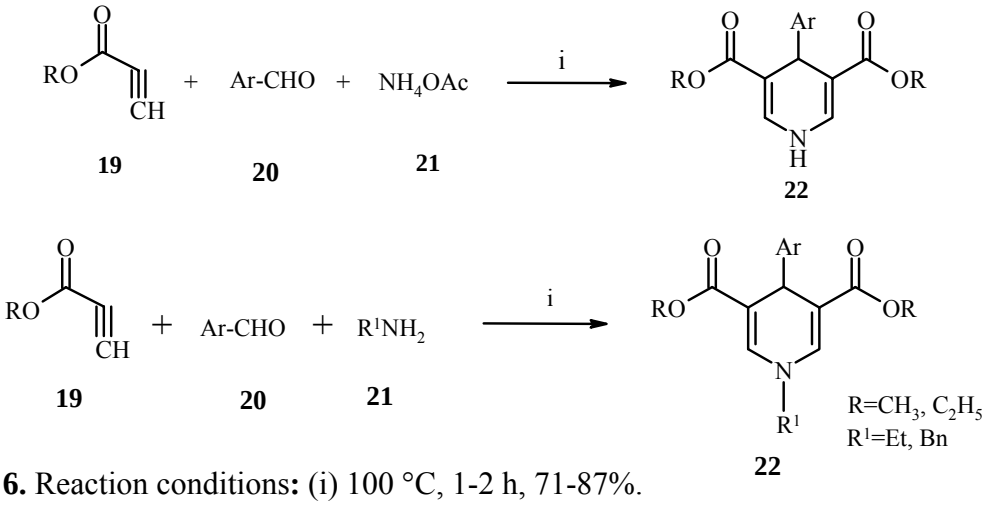
Scheme 5. Reaction conditions: (i) $[Hbim]BF_4/H_2O$ (1:1), rt, 10-20 min, 91-94%.

This wok is published in *arkivoc*, **2008** (article in press).

<u>Section C</u>: Synthesis of 4-aryl-1,4-dihydropyridines unsubstituted at 2- and 6-positions form alkyl propiolate under catalyst- and solvent-free conditions

4-Aryl-1,4-dihydropyridines of the nifedipine type are of interest because of their Ca^{+2} antagonistic and agonistic activities. 1,4-dihydropyridines without substituents in positions 2 and 6 exhibit many pharmaceutical activities and are highly light-sensitive in the solid state. It has been shown that these compounds could be dimerized; the dimers are of interest as novel potential inhibitors of HIV-1 protease and have anticancer activity.

This section describes the synthesis of 4-aryl-1,4-dihydropyridines **22** unsubstituted at 2- and 6-positions from the condensation of aromatic aldehydes **20** with alkyl propiolates **19** and NH_4OAc or alkyl amines **21** under catalyst- and solvent-free conditions (**Scheme 6**).



Scheme 6. Reaction conditions**:** (i) 100 °C, 1-2 h, 71-87%.

This wok is communicated to *Australian Journal of Chemistry.*

<u>Chapter 3</u>: Synthesis of bioactive molecules based on (3*H*)-quinazolin-4-one

The (3*H*)-quinazolin-4-one have interesting biological activity and have therefore been extensively investigated for useful pharmaceutical activities including anti-convulsant, anti-bacterial and antidiabetic activity. The (3*H*)-quinazolin-4-one ring is regarded as a 'privileged structure' in combinatorial synthesis. Synthesis of quinazolinone ring system, which provides the backbone for compounds having numerous biological activities, is an interesting challenge.

Chapter third describes the synthesis of bioactive molecules based on (3*H*)-quinazolin-4-one skeleton and is divided into three sections. Section A describes the

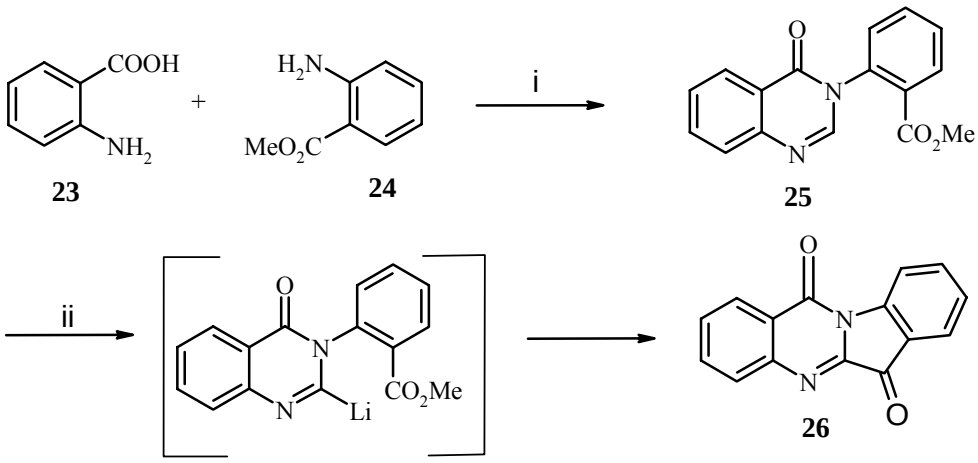
synthesis of tryptanthrin, section B describes the synthesis of deoxyvasicinone and section C describes the synthesis of luotonin A.

Section A: Synthesis of tryptanthrin

Tryptanthrin, a bioactive ingredient of *Polygonum tinctoriu* as a member of the Indigo plant family, is a quinazoline derivative and has been reported to have various biological activities, such as anti-microbial, antitumor and anti-inflammatory activities. In addition to being a source of a natural indigo dye, this plant has a folkloric reputation for the topical treatment of athlete's foot.

On reviewing the literature, it was found that among the reported method, none has reported its synthesis by applying the strategy of regioselective lithiation at C-2 of quinazolinone followed by subsequent reaction of lithiated intermediate with electrophile in an intramolecular fashion forming C-C bond to generate the cyclized product. We sought to apply this strategy for the synthesis of tryptanthrin.

Initially, synthesis of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **25** was obtained by condensing anthranilic acid **23** with methyl anthranilate **24** and triethyl orthoformate in the ionic liquid (IL), 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) in 67% yield. Regioselective lithiation of **25** was achieved by using lithium diisopropylamide (LDA) in anhydrous THF at -78 °C to form lithiated intermediate which on subsequent reaction with the electrophile viz. methyl carboxylate in an intramolecular fashion by forming C-C bond to afford tryptanthrin **26** in 81% yield (**Scheme 7**).



Scheme 7. Reaction conditions**:** (i) $(EtO)_3CH$, [Hbim]BF_4, 100 °C, 1.5 h, 67%;
(ii) LDA, dry THF, -78 °C, 2h, then rt, 2h, 81%.

We have achieved the synthesis of tryptanthrin in just two-steps in 54% overall yield from commercially available anthranilic acid and methyl anthranilate.

Section B: Synthesis of deoxyvasicinone

Deoxyvasicinone has been isolated from aerial parts of an evergreen subherbaceous bush *peganum harmala.* It possesses anti-microbial, anti-inflammatory and anti-depressant activities. Furthermore, deoxyvasicinone is key intermediate in natural product synthesis.

This section describes the synthesis of deoxyvasicinone **29** from quinazolinone **27**. First, 3-(3-bromopropyl)-quinazolin-4-one **28** was obtained from the reaction of (3*H*)quinazolin-4-one **27** with 1,3-dibromopropane using base, potassium carbonate in dry DMF at room temperature in 87% yield. This compound **28** on reaction with LDA in anhydrous THF at -78 °C forms lithiated intermediate which on subsequent reaction with electrophile in an intramolecular fashion afforded deoxyvasicinone **29** in 53% overall yield (**Scheme 8**).

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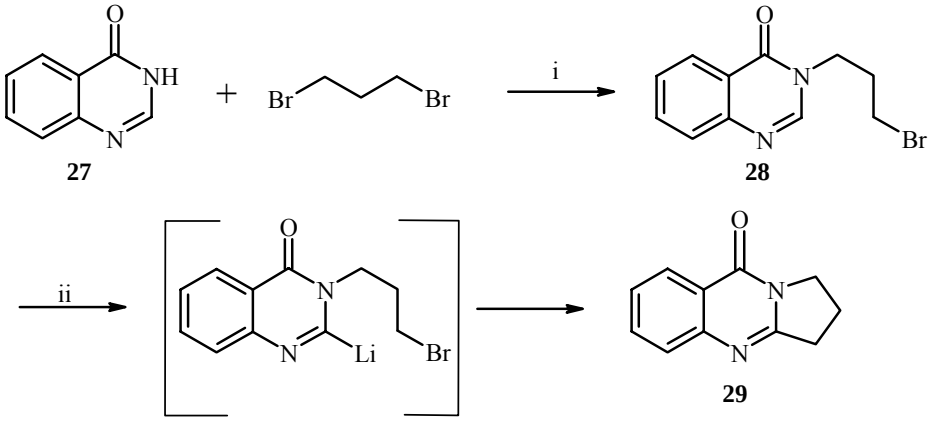


Scheme 8. Reaction conditions**:** (i) K_2CO_3, DMF, rt, 4 h, 87%; (ii) LDA, dry THF, -78 °C, 2 h, then rt, 2 h, 61%.

The key step for the reaction is regioselective lithiation at 2-position of quinazolinone followed by subsequent reaction of lithiated intermediate with electrophile in an intramolecular fashion to afford the cyclized product.

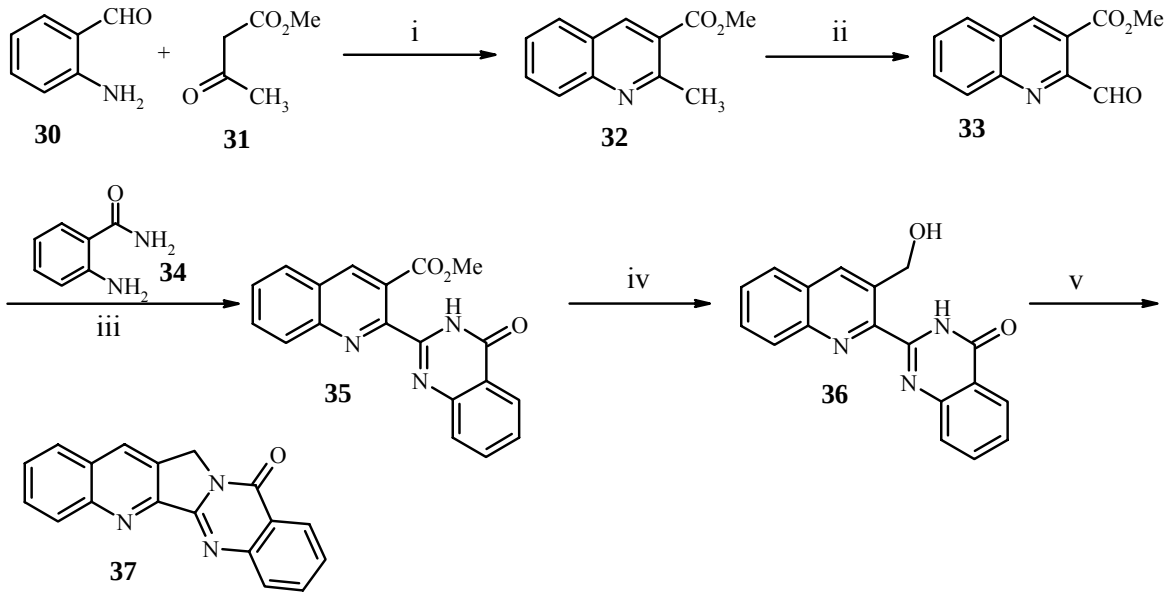
This wok is communicated to *Tetrahedron Letter.*

Section C: Synthesis of luotonin A

Luotonin A is a pyrroloquinazolinoquinoline alkaloid isolated from *peganum nigellastrum,* a Chinese herbal medicinal plant. Luotonin A shows cytotoxic activity against the murine

leukemia P-233 cell line by stabilizing the tropoisomerase I/DNA complex. Luotonin's structural and biological features make it an attractive synthetic target, and a number of total syntheses have been completed. Although these alkaloids have been the subject of numerous synthetic investigations, new approaches are always welcome.

This section describes the synthesis of luotonin A starting from 2-aminobenzaldehyde. 2-Aminobenazaldehyde **30** on treatment with methylacetoacetate **31** in the IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) at 100 °C afforded methyl 2-methylquinoline-3-carboxylate **32** in 73% yield. Next, **32** on oxidation using selenium dioxide in xylene furnished methyl 2-formylquinoline-3-carboxylate **33** in 69% yield. When **33** was condensed with 2-aminobenzamide **34** using $FeCl_3.6H_2O$ in water at reflux temperature, it afforded methyl 2-(3,4-dihydro-4-oxoquinazolin-2-yl)quinoline-3-carboxylate **35** in 76% yield. Then, **35** was reduced using sodium borohydride, calcium chloride in ethanol to afford 2-(3-(hydroxymethyl)quinolin-2-yl)quinazolin-4(3*H*)-one **36** in excellent yield. Because this compound **36** could be converted to luotonin A **37** in one additional step by using standard Mitsunobu reaction condition such as use of triphenyl phosphine, diethyl azodicarboxylate in THF, a formal synthesis of luotonin A was thus completed in an oveall yield of 31% (**Scheme 9**).



Scheme 9. Reaction conditions: (i) [Hbim]BF_4, 100 °C, 1.5 h, 73%; (ii) SeO_2 (1.05 equiv), xylene, reflux, 8 h, 69%; (iii) $FeCl_3.6H_2O$ (2.1 equiv), H_2O, reflux, 4 h, 76%; (iv) $NaBH_4$-$CaCl_2$ (5 equiv), EtOH, rt, 2 h, 87%; (v) Ph_3P, DEAD, THF, rt, 1 h, 95%.

Chapter 1

Synthesis of ionic liquids (ILs) and its application as solvent as well as a promoter for the synthesis of biologically active *N*-heterocycles

Chapter 1-Section A

Introduction to ionic liquids (ILs)

1.1.1 Introduction

Most chemical reactions carried out in the laboratory or in the industry takes place in solution. The most widely used solvents for chemical reactions and materials synthesis are organics that belong to the group of volatile organic compounds (VOCs), accounting for a great proportion of environmental pollution and waster material. Therefore, their use is often problematic owing to their toxicity, volatility, flammability and environmental hazardous effect. Because the constraints of environment are becoming more and more stringent, organic reactions, catalytic processes and separation technologies require the development of alternative solvents and technologies. This shift in the manufacturing paradigm is the basis of 'green chemistry', rather than pollutes and remediates.[1] Green chemistry also proposes optimized synthetic methodologies for high product yields and the generation of substances that offer little harm to the environment. In view of the heavy reliance on organic solvents in current manufacturing processes, the development of new technologies for pollution prevention can assist in the reduction of VOCs usage and associated volatility, environmental and human health concern that accompany exposure to organic solvents.

Among the alternative reaction media studied as substitutes for conventional organic solvents are plain water, fluorous media (e.g. highly fluorinated alkanes, ethers, tertiary amines), supercritical fluids and ionic liquids.

1.1.2 Alternative solvents in organic synthesis

1.1.2.1 Water

Water is perhaps one of the greener solvents, one can imagine in terms of costs, availability, safety and environmental impact. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of Breslow[2-4] and Grieco[5,6] in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results.[7,8]

1.1.2.2 Perfluorinated (fluorous) solvent

Fluorous compounds were defined as those compounds that are highly fluorinated and based upon sp^3 hybridized carbons. Fluorous solvents such as perfluoroalkenes, perfluoroalkyl ethers and perfluoroalkylamines are chemically benign and environment-friendly for being non-toxic, non-flammable, thermally stable and recyclable. More recently, they have proven their utility as solvents for many organic and catalytic reactions.[9,10] But their use is limited due to its decomposition at higher temperature with generation of toxic materials. Moreover, fluorous derivatives are often detected in the organic phase.

1.1.2.3 Supercritical fluids (SCF)

A supercritical fluid (SCF) is defined as a substance above its critical temperature (Tc) and critical pressure (Pc). The properties of an SCF lie between those of its liquid and gas phases. The most popular SCF is carbon dioxide ($scCO_2$). Supercritical fluids were also described as new solvents for organic and catalytic reactions.[11] Their physical and chemical stability make them as alternative green solvents.[12]

The use of $scCO_2$ as solvent is associated with some disadvantages such as, its reactivity towards powerful nucleophiles, need of specialized and expensive equipment to achieve critical conditions, low dielectric constant which can imply poor solvent power. Another drawback is that CO_2 behaves like a hydrocarbon solvent and for this reason reactants and/or catalysts are often not very soluble in it.

1.1.2.4 Ionic Liquids

Ionic liquids (ILs) are an unique class of novel solvents with very interesting properties, which are attracting the attention of a growing number scientists and engineers as shown by the increasing number of papers published in recent years. As a consequence of some of their peculiar properties such as negligible vapor pressure, ability to dissolve organic, inorganic and polymeric materials and high thermal stability, ILs have gained immense popularity as ‘green’ alternatives to volatile organic compounds (VOCs) for their application in electrochemical, synthetic and separation processes.

1.1.3 Introduction to ionic liquids (ILs)

Ionic liquids are generally defined as salts consisting of ions which melt at or below 100 °C. In some cases, the ionic liquids are free-flowing liquids at room temperature, in which case they can be called 'room temperature ionic liquids (RTILs).' There are many synonyms used for ionic liquids that complicate a literature search. "Molten salts" is the most common and most broadly applied term for ionic compounds in the liquid state. Now days, ionic liquids are clearly distinguished it from the classical definition of a molten salt. A molten salt is generally refers to a high-melting, highly viscous and very corrosive medium, while ionic liquids are non-corrosive, easy to handle, liquid at low temperatures (<100 °C) and have relatively low viscosity.

1.1.3.1 A brief history of ionic liquids

The early history of ionic liquids began in 1914 when the first report of a room temperature molten salt was reported by Walden.[13] He reported the synthesis of ethylammonium nitrate, $[C_2H_5NH_3]NO_3$, which has a melting point of 12 °C. This material was simply prepared by the reaction of ethylamine with concentrated nitric acid, but its discovery did not prompt any great amount of interest at that time.

Then, Hurley and Wier in 1948 prepared the first room temperature ionic liquid by mixing and warming 1-ethylpyridinium chloride with aluminum chloride at the Rice Institute in Texas as bath solutions for electroplating aluminum.[14,15] However, these systems were not investigated further until the late 1970s when the groups of Osteryoung and Wilkes rediscovered them and studied them for their electrochemical applications.[16-18] In the early 1980s, the groups of Seddon and Hussey began to use chloroaluminate melts as non-aqueous, polar solvents for the investigation of transition metal complexes. The investigations generally started with the electrochemical aspects of the relevant transition metal complexes,[19-22] spectroscopic and complex chemistry experiments followed.[23,24] The first report on the use of this type of low melting ionic liquids as reaction media for organic synthesis was in 1986, as a combined solvent and catalyst for Friedel-Crafts reaction.[25] Chauvin showed that nickel complexes dissolved in acidic chloroaluminate ionic liquids represent an excellent system for the dimerisation of alkenes[26] while Osteryoung used

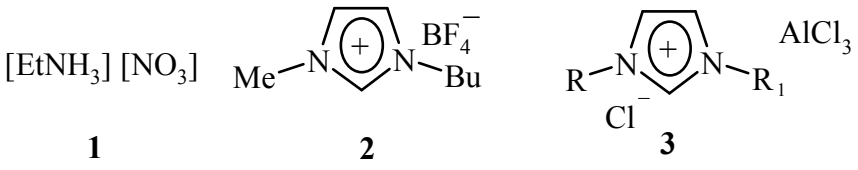
Ziegler-Natta catalysts in acidic chloroaluminates to polymerise ethylene.[27] The ionic liquids based on $AlCl_3$ can be regarded as the first generation of ionic liquids.

The hygroscopic nature of chloaluminate based ionic liquids limited their use in their application since they must be prepared and handled under inert atmosphere. In addition, these liquids are incompatible with many organic compounds such as alcohol and acetone. Thus, the synthesis of air and moisture stable ionic liquids, which are considered as the second generation of ionic liquids, attracted further interest. In 1992, Wilkes and Zaworotko[28] reported the first air and moisture stable ionic liquids based on 1-ethyl-3-methylimidazolium cation with either tetrafluoroborate or hexafluorophosphate as anions. Unlike the chloroaluminate ionic liquids, these ionic liquids could be easily prepared and safely stored outside of an inert atmosphere. Since then, various 1,3-dialkylimidazoium salts containing a wide variety of anions such as PF_6^-, CH_3COO^-, CF_3COO^-, $CF_3SO_3^-$, bis-(trifluoromethanesulfonyl)imide $[(CF_3SO_2)_2N]^-$, tris-(trifluoromethanesulfonyl)methide $[(CF_3SO_2)_3C]^-$ etc have been synthesized and many of them are currently receiving great deal of attraction as novel media in the various fields.[29-31]

1.1.3.2 Classification of ILs

Ionic liquids come in two main categories, namely simple salts (made up of single anion and cation) and binary ionic liquids (salts where equilibrium is involved). For example, $[EtNH_3][NO_3]$ is a simple salts whereas mixture of aluminum (III) chloride and 1,3-dialkylimidazolum chloride (a binary ionic liquid system) contain several different ionic species and their melting point and properties depends upon the mole fractions of the aluminum (III) chloride and 1,3-dialkylimidazolium chloride present. When the mole fraction of the [cation]Cl:$AlCl_3$ is 0.5 the $AlCl_4^-$ anion is essentially the only species present. If the mole fraction of $AlCl_3$ employed is greater than 0.5, then multinuclear species such as $Al_2Cl_7^-$and $Al_3Cl_{10}^-$ are formed and the ionic liquid is referred to as (Lewis) acidic. When the mole fraction of $AlCl_3$ employed is less than 0.5, the ionic liquid is basic. For this reason, chloroaluminate ionic liquids are often written as [cation]Cl-$AlCl_3$, rather than [cation]$AlCl_4$. Examples of ionic liquids of a simple salt and binary ionic liquid are given in **Fig. 1** respectively. The ionic liquids of simple salt show simple melting

behavior while for the binary ionic liquids, the melting point depends upon its composition.



1 **2** **3**

Examples of simple salts binary ionic liquid

Figure 1. Types of ionic liquids (ILs)

1.1.4 Structural feature of ILs

The simplest definition of an IL is a liquid composed exclusively of ions, with the forces overwhelmingly columbic. Ionic liquids typically consist of organic nitrogen-containing heterocyclic cations and organic or inorganic anions.

1.1.4.1 Cation

The cations are generally bulky organic moieties with low symmetry, weak intermolecular interactions and low charge densities. Those described until now are based on ammonium **4**,[32] sulfonium **5**,[33] phosphonium **6**,[34] lithium **7**,[35] imidazolium **8**,[29] pyridinium **9**,[36] pyrrolidinium **10**,[31] thiazolium **11**,[37] triazolium **12**,[38] oxazolium **13**[39] and pyrazolium **14**[40] differently substituted.

The most commonly used alkyl chains are methyl, ethyl, butyl, hexyl, octyl and decyl. Among these, of particular interest were the salts based on the *N,N'*-dialkylimidazolium cation because of their wide spectrum of physico-chemical properties. It is generally assumed that non-symmetrical *N,N'*-dialkylimidazolium cation give salts having lower melting point, even though 1,3-dialkylimidazolium hexafluorophosphate with dibutyl, dipentyl, dioctyl, dinonyl and didecyl substituents are found to be liquid at room temperature.[41] 1-Butyl-3-methylimidazolium [BMIm] and 1-ethyl-3-methylimidazolium [EMIm] cations are probably the most investigated structures of this class.

Recently it was reported that ionic liquids with planar trialkylsulfonium cation and NTf_2^- anion gave lower melting point salts with very high conductivity and low viscosity.[42]

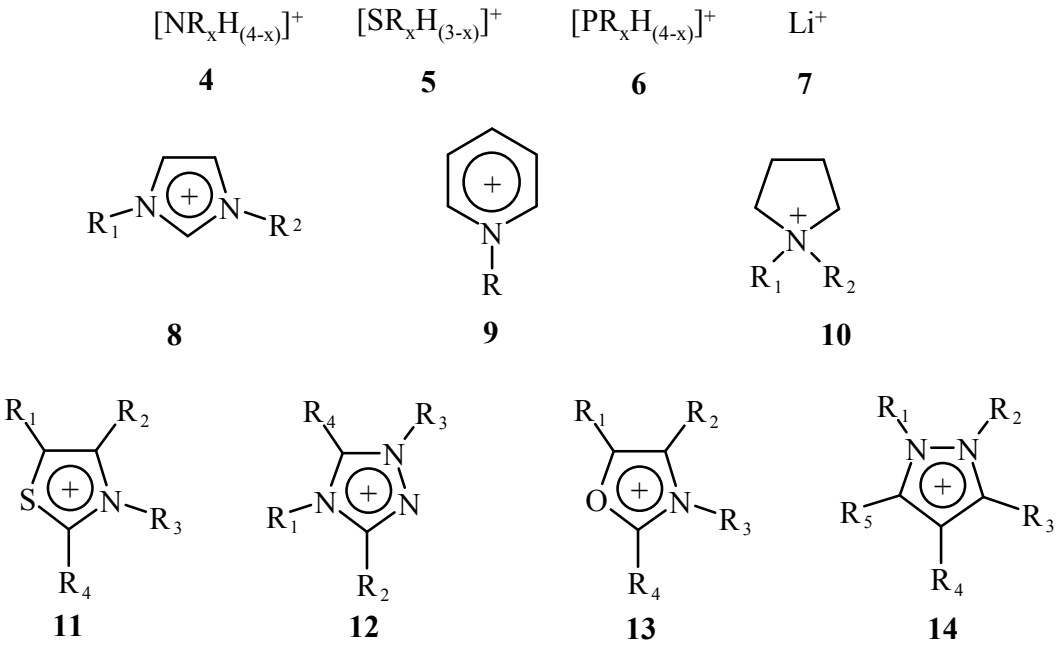


Figure 2. Different types of cations

1.1.4.2 Anion

Concerning the anion, it can be classified into two groups.

(1) Polynuclear anion such as $Al_2Cl_7^-$, $Al_3Cl_{10}^-$, $Au_2Cl_7^-$, $Fe_2Cl_7^-$, $Sb_2F_{11}^-$and $Cu_2Cl_3^-$ etc; these anions leads to water and air sensitive ILs;

(2) Mononuclear anions which lead to neutral ionic liquids e. g. Cl^-, Br^-, ClO_4^-, BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $[(CF_3SO_2)_2N]^-$, $[(C_2F_5SO_2)_2N]^-$, $[(FSO_2)_2N]^-$, $[(CF_3SO_2)_3C]^-$, $CF_3CO_2^-$, $CF_3SO_3^-$, $CH_3SO_3^-$, CH_3COO^-, NO_3^-, OTs^- etc. The most interesting is the bis-trifluoromethylsulfonylamide anion $[NTf_2]^-$ [43,44] which leads to salts with thermally stable up to 400 °C.

The physical and chemical properties of the ionic liquid, including their melting points are dependent on both the nature of the cation and the anion. The low melting nature of ILs can be engineered by combining cationic and anionic species to produce salts that, largely due to asymmetric cations, have low lattice energies. The anion is currently used to control

the water miscibility, but cation can also influence the hydrophobicity or hydrogen bonding ability.

As they are made up of at least two components (the anion and cation) which can be varied, the ILs can be designed with a particular end use in mind, or to possess a particular set of properties. Hence, they are termed as "designer solvents".[45] Properties such as melting point, viscosity, density and hydrophobicity can be varied by simple changes to the structure of the ions. The hydrophilicity/lipophilicity of an ionic liquid can be modified by a suitable choice of anion, *e.g.* $[BMIm]BF_4$ is completely miscible with water while the $[BMIm]PF_6$ salt is largely immiscible with water. The lipophilicity of dialkylimidazolium salts, or other ionic liquids, can also be increased by increasing the chain length of the alkyl groups.[41,46] This behavior can be of substantial benefit when carrying out solvent extractions or product separations, as the relative solubilities of the ionic and extraction phase can be adjusted to make the separation as easy as possible.

1.1.5 Physicochemical properties of ILs

The physical and chemical properties of ionic liquids can be specifically varied over a wide range by the selection of suitable cations and anions. An attempt is made to illustrate the relationship between the structural features of ILs and its important physical and chemical properties.

1.1.5.1 Melting point

Ionic liquids are defined as salts that have melting points below 100 °C and most of them are liquid at room temperature. Both cations and anions contribute to the low meting points of ionic liquids. The increase in anion size leads to a decrease in melting point.[47] For example, the melting points of 1-ethyl-3-methylimidazolium type ionic liquids with different anions such as $[BF_4]^-$ and $[Tf_2N]^-$ are 15 °C[48] and -3 °C[29] respectively. Cations size and symmetry make an important impact on the melting points of ionic liquids. Large cations and increased asymmetric substitution results in a melting point reduction.[49]

1.1.5.2 Vapor pressure and thermal stability

Ionic liquids have no measurable vapor pressure. This is a great advantage from a process engineering viewpoint, since product could be easily separated out by distilling a reaction mixture. The well-known problem of azeotrope formation between the solvent and the products does not arise.

Ionic liquids synthesized by direct protonation of an amine or phosphane show, for example, significantly restricted thermal stability. Many melts with trialkylammonium ions already decompose at a temperature below 80 °C in vacuo (depending on the boiling point of the related amine or acid). For the ionic liquids those obtained by alkylation of an amine or phosphane, the tendency to undergo thermally induced transalkylation or dealkylation reactions (retro-quaternization reaction) is strongly related to the nature of their anion. While 150 °C has to be considered as maximum working temperature for most of the quaternary ammonium chloride salts, 1-ethyl-3-methylimidazolium (EMIm) tetrafluoroborate, for example, has been reported to be stable to about 300 °C[50] and [EMIm][$(CF_3SO_2)_2N$] (m.p. -3 °C) is stable up to even more than 400 °C.[29] Consequently, some ionic liquids have, in contrast to water and most organic solvents, a liquid range of up to more than 400 °C.

1.1.5.3 Viscosity

Generally, ionic liquids are more viscous than common molecular solvents, having viscosity similar to oils. The viscosity of ionic liquids is determined by van der Waals forces, hydrogen bonding and electrostatic forces. Alkyl chain lengthening in the cation leads to an increase in viscosity.[29] This is due to stronger van der Waals forces between cations, leading to increase in the energy required for molecular motion. Also, the ability of anions to form hydrogen bonding has a pronounced effect on viscosity. The fluorinated anions such as BF_4^- and PF_6^- form viscous ionic liquids due to the formation of hydrogen bonding.[51] In general; all ionic liquids show a significant decrease in viscosity as the temperature increases.[52]

1.1.5.4 Density

Ionic liquids are generally more dense than water with values ranging from 1 to 1.6 g cm^{-3} and their densities decrease with increase in the length of the alkyl chain in the cation.[53]

For example, in ionic liquids composed of substituted imidazolium cations and $CF_3SO_3^-$ anion, the density decreases from 1.39 g cm^{-3} for $[EMIm]^+$ to 1.33 g cm^{-3} for $[EEIm]^+$, to 1.29 g cm^{-3} for $[BMIm]^+$ and to 1.27 g cm^{-3} for $[BEIm]^+$.[54]

The densities of ionic liquids are also affected by anions. For example, the densities of 1-butyl-3-methylimidazolium type ionic liquids with different anions, such as BF_4^-, PF_6^-, CF_3COO^- and Tf_2N^- are 1.12 g cm^{-3},[46] 1.21 g cm^{-3},[29] 1.36 g cm^{-3} [46] and 1.43 g cm^{-3},[29] respectively. The order of increasing density for ionic liquids composed of a single cation is: $[CH_3SO_3]^- \approx [BF_4]^- < [CF_3CO_2]^- < [CF_3SO_3]^- < [C_3F_7CO_2]^- < [(CF_3SO_2)_2N]^-$.[54]

1.1.5.5 Conductivity

Ionic liquids have reasonably good ionic conductivities compared with those of organic solvents/electrolyte systems (up to ~10 mS cm^{-1}).[55] At elevated temperatures of 200 °C a conductivity of 0.1 Ω^{-1} cm^{-1} can be achieved for some systems. However, at room temperature their conductivities are usually lower than those of concentrated aqueous electrolytes. Based on the fact that ionic liquids are composed solely of ions, it would be expected that ionic liquids have high conductivities. This is not the case since the conductivity of any solution depends not only on the number of charge carriers but also on their mobility. The large constituent ions of ionic liquids reduce the ion mobility which, in turn, leads to lower conductivities. Furthermore, ion pair formation and/or ion aggregation lead to reduced conductivity. The conductivity of ionic liquids is inversely linked to their viscosity. Hence, ionic liquids of higher viscosity exhibit lower conductivity. Increasing the temperature increases conductivity and lowers viscosity.

1.1.5.6 Polarity

A simplistic view might be that ionic liquids are composed entirely of ions, and are therefore very polar. As will be explained below, this is at best a great oversimplification and in some cases incorrect. One of the major differences between ionic liquids and a typical organic solvent is that the former is a binary mixture of two different species, and thus is likely to engage in a much wider range of solvent–solute interactions. Recently, therefore, a number of research groups have carried out investigations using solvatochromic probes to try to gain more insight into this important area. Studies using

Nile Red[56] and Reichardt's dye[57] have suggested that ionic liquids based on 1-alkyl-3-methylimidazolium cations act as H-bond donors to the same degree as short chain alcohols, and can thus be regarded as being relatively polar. Previous studies on alkylammonium salts using Reichardt's dye have shown that tetraalkyl derivatives are relatively non-polar, while those containing cations of the type $[NHxR(4-x)] + (x \geq 1)$ are considerably more polar. The fluorescent probes 4-aminophthalimide and 4-(*N*,*N*-dimethylamino)phthalimide have also been applied for investigations of the polarity of ionic liquids.[58] This study supported the measurements with Reichardt's dye[57] indicating that the polarity of 1-alkyl-3-methylimidazolium based ILs was similar to that of short chain alcohols, and that the polarity decreased somewhat as the alkyl chain length increased. In these studies, changing the anion appeared to have little effect on the polarity of the ionic liquid. Polarity of 1-butylpyridinium tetrafluoroborate was also measured using these probes, and shown polarity lower than the imidazolium salts. One feature highlighted in this study was the influence of water on position of λmax of 4-(*N*,*N*-dimethylamino)phthalimide which shifted from 526 nm in water-saturated [BMIm][PF_6] (water content ~0.324 M) to 512 nm (i.e. less polar) in [BMIm][PF_6] that had been dried by heating in vacuo for 24 h (water content ~0.015 M). Another example of this is shown by work from the author's own research group, where the λmax of Reichardt's dye displayed a shift from 526 nm in water-saturated [BMIm][PF_6] to 546.5 nm in dry solvent. This clearly shows that for any physical measurements carried out in ionic liquids, the water content should be established.

1.1.5.7 Electrochemical window

The electrochemical window is an important property and plays a key role in using ionic liquids in electrodeposition of metals and semiconductors. By definition, the electrochemical window is the electrochemical potential range over which the electrolyte is neither reduced nor oxidized at an electrode. This value determines the electrochemical stability of solvents. As known, the electrodeposition of elements and compounds in water is limited by its low electrochemical window of only about 1.2 V. On the contrary, ionic liquids have significantly larger electrochemical windows, e.g., 4.15 V for [BMIm]PF_6 at a platinum electrode,[59] 4.10 V for [BMIm]BF_4[59] and 5.5 V for [BMp]Tf_2N, [1-*n*-Butyl-1-

methylpyrrolidinium Bis(trifluoromethane sulfonyl)imide] at a glassy carbon electrode.[31] In general, the wide electrochemical windows of ionic liquids have opened the door to electrodeposit metals and semiconductors at room temperature which were formerly obtained only from high temperature molten salts. For example, Al, Mg, Si, Ge, and rare earth elements can be obtained from room temperature ionic liquids. The thermal stability of ionic liquids allows to electrodeposit Ta, Nb, V, Se and presumably many other ones at elevated temperature.

1.1.6 Task-specific ionic liquids (TSILs)

Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the ILs. These ILs can then act as reagents or catalysts in organic reactions.

Recently, many attempts have been made to explore functional ionic liquids through incorporation of additional functional groups as a part of the cation and/or anion. The incorporation of functional groups can impart a particular capability to the ionic liquids, enhancing their capacity for catalyst reusability as exemplified with imidazolium salt-functionalized phosphine-metal complexes, which showed dramatically increased reusability and stability in ionic liquids compared with the unfunctionalized ones. Moreover, specific functional groups can also be incorporated for task-specific purposes. For example, a primary amine functionalized imidazolium salt can separate CO_2 from gas streams,[60] while ionic liquids bearing appended sulfonic acid groups were used as solvent-catalyst for esterifications.[61] During the last five years, various types of functionalized ionic liquids expressly categorized as being ‘‘task-specific’’ ionic liquids (TSILs) have been designed and synthesized for specific purposes such as catalysis, organic synthesis, separation of specific materials as well as for the construction of nanostructure materials and ion conductive materials etc.[62] Many of them were focused on the incorporation of functionality into a branch appended to the cation, especially imidazolium cation.

The imidazolium salts are defined as TSILs when they have the following features: (i) ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the imidazolium salts, which behave not only as a reaction medium but also as a reagent or catalyst;. (ii) A conventional ionic liquid solution of a functionalized

imidazolium salt, which is not a liquid form at ambient temperature, could also be defined as a TSIL since the functionalized imidazolium salt become integral elements of the overall ionic liquid solution and can introduce a functional group into the liquid.

1.1.7 Chiral ionic liquids

Recently, few examples of chiral ionic liquids (CILs) have been reported in the literature.[63] Some representative examples are shown in **Fig 3**.

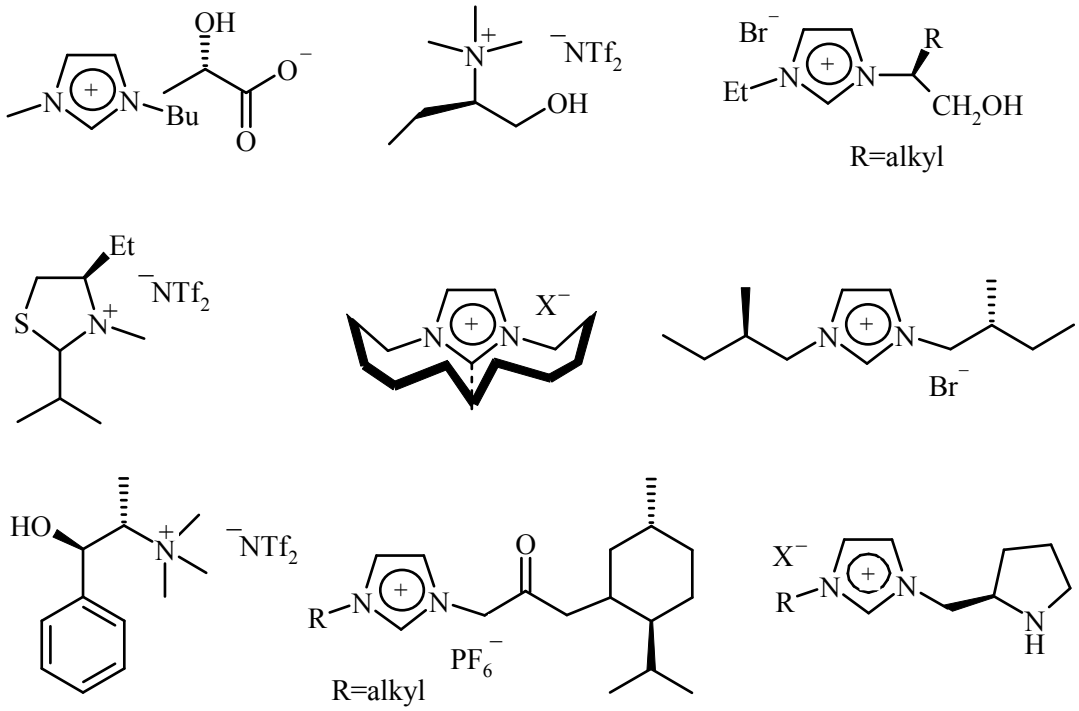


Figure. 3 Examples of chiral ILs

Due to their ease of synthesis and their peculiar properties, these new chiral solvents should play a central role in enantioselective organic synthesis and hopefully expand the scope of chiral solvents. Chiral ILs can be particularly attractive if one considers their potential applications to chiral discrimination, including asymmetric syntheses and optical resolution of racemates. For example, one can expect a significant transfer of chirality in these solvents due to their high degree of organization. Most reports deal with the synthesis and properties of the new chiral ILs and only a few deals with their application in organic reactions. The first reported chiral ionic liquid was 1-butyl-3-

methylimidazolium ([BMIm])lactate by Seddon *et al*. in 1999. The [bmim][lactate] was prepared by anion exchange between [bmim][Cl] and commercially available sodium (*S*)-2-hydroxypropionate. This ionic liquid was used in asymmetric Diels–Alder reactions between ethyl acrylate and cyclopentadiene. The Diels–Alder adducts were simply isolated by decanting off the upper organic layer. A good *endo*:*exo* selectivity of 4.4/1 was obtained but no enantioselectivity was observed.

1.1.8 How do ionic liquids compare with conventional solvents?

At the present time, there is still only an empirical knowledge of these media mainly developed on the basis of their solvent effect on organic reactions compared to that of well-known conventional solvents. The challenge would be to be able to predict their properties in order to optimize the choice for a given application.[64] Solvent polarity has often a strong influence on the outcome of reactions. However, the exact meaning of polarity is already complex, but even more complicated in the case of ionic solvents, as many interactions can be involved. Different investigations of solvent–solute interactions in ionic liquids using solvatochromic dyes have been reported.[56,58] The data indicate that polarities of 1,3-dialkylimidazolium salts based on the PF_6^-, BF_4^-, $CF_3SO_3^-$ and NTf_2^- anions can be compared to that of short chain primary alcohol. This is in agreement with the ionic liquid solvent effect described in the Diels–Alder reactions of cyclopentadiene with methyl acrylate.[65] The endo/exo selectivity, which may be viewed as being dependent on the polarity of the solvent, is high (6.1:1) when using $[BMIm]BF_4$ and compares quite well to that obtained with methanol (6.7:1). These selectivities are characteristic of hydrogen-bonded polar organic solvents. The ionic liquid nucleophilicity[57] is only anion dependant and much lower than that of polar solvents which makes ionic liquids unique. Surprisingly, NTf_2^- based salt appears more coordinating than the PF_6^- analog relative to the [Cu(acac)tmen][BPh_4] solvatochromic system (acac: acetylacetonate, tmen: *N*,*N*,*N'*,*N'*-tetramethylethylenediamine). This degree of coordination has been correlated to solvent effect observed in Ni catalyzed oligomerization of ethene.[66]

1.1.9 Features of ILs which make them as attractive potential solvents

ILs possesses a variety of special physical and chemical properties which make them as attractive potential solvents in many organic reactions.

(1) Negligible vapour pressure and non-flammable, therefore product can be easily isolated by vacuum distillation.

(2) High thermal stability and operate over large temperature range.

(3) Its a very good solvent to dissolve a wide range of organic, inorganic, organometallic compounds and polymeric material.

(4) ILs are often composed of poorly co-ordinating ions, so they have the potential to be highly polar yet non-coordinating solvents.

(5) ILs are immiscible with a number of organic solvents and thus provide a non-aqueous, polar alternative for two-phase systems.

(6) It serves as a good medium to solubilize gases such as H_2, CO, O_2 and CO_2 and many reactions are now being performed using ionic liquids and supercritical CO_2.

(7) Ionic liquids have polarities comparable to alcohols, but in contrast to alcohols, however, many ionic liquids are non-nucleophilic, which can have a pronounced effect on a catalyzed reaction.

(8) ILs possesses excellent and variable Lewis/Brønsted acidity.

(9) Most of the ionic liquids can be stored without decomposition for a long period of time.

1.1.10 Applications of ILs

The renewed interest in these solvents stems from the recent development of air and moisture stable room temperature ionic liquids. In addition, these salts have physical properties and synthetic applications that make them interesting for organic synthesis. Ionic liquids have been successfully applied as solvents for a wide range of organic reactions. It includes homogeneous catalysis,[67] transition metal catalyzed reaction,[47] hydrogenation,[68] oxidation,[68] reduction,[68] biotransformation,[68] transesterification,[68] nucleophilic reaction,[69] electrophilic reaction,[69] oligomerization,[70] polymerization,[70] carbonylation,[70] olefin metathesis[70] etc.

There is an increasing use of ILs as engineering liquids for industrial processing. For example, due to their adjustable hydrophobicity and dissolution ability, ILs have been

explored as effective solvents in traditional extraction processes and gas separations. These applications included IL extractions of metal ions, organic and bio-molecules, IL desulfurization of fuels, IL/$scCO_2$ extractions, and IL gas separations.
Moreover, ILs have also shown applications in the field of electrochemistry[71] and analytical chemistry.[72,73]

1.1.11 Toxicity and biodegradability of ILs

Room-temperature ionic liquids (ILs) are non-volatile organic solvents being designed to replace traditional volatile organic solvents (VOS). Although, the low vapor pressure of ILs may reduce the air pollution with respect to the typical volatile organic solvents, it must be considered that a release of ILs from industrial processes into aquatic environments may lead to water pollution, because of their high solubilities in water. Moreover, because of the high stability of ionic liquids in water these compounds could become as persistent pollutants in waste waters. For this reason it is prioritary to determine the further consequences and the environmental risk of the presence of ILs in waste waters.

Recent studies have shown that the toxicity of many ionic liquids can be similar to those of the industrial solvents they may replace.[74-77] While ILs pose little threat of airborne toxicity, a growing body of evidence suggests that they can be toxic to aquatic organisms, including bacteria, plants, invertebrates, and fish.[76,78,79-81] However, varying the anion and length of the side chains of ionic liquids can modify their toxicity to organisms[82,83] and thus provide one way to design ionic liquids in which function is balanced by low toxicity ILs ever be released into the environment. To avoid the potential contamination of the aqueous phase with ILs, several strategies should be planned. Firstly, it is important to improve the processes, minimizing the IL leaches to the aquatic media. Furthermore, downstream separation step must be required at the end of these processes to remove the ILs from waste water streams.

Because of the relative stability features of ionic liquids, their accumulation in the environment becomes feasible, if they are applied in operational use.[84] Thus, the fundamentals of ionic liquid biodegradability turn out to be an important issue for the reduction of ignition and landfill-waste risks. Wells and co-worker used measurements of Biochemical Oxygen Demand in five days (BOD5) to evaluate the biodegradation of ionic

liquids.[85] They found that none of the selected ILs, which are based on imidazolium, pyridinium, phosphonium, and ammonium, showed any sign of biodegradation by the BOD5 method. Gathergood and co-workers also tested the biodegradation of [bmim][PF_6] using a Closed Bottle Test (OECD 301D), in which no biodegradation was observed.[86] They also used modified Sturm tests (OECD 301B) where 60% mineralization of carbon dioxide was identified.[87] All the above facts demonstrate that the commonly used ionic liquids are not readily biodegradable. However, the properties of ionic liquids can be tuned through structural adjustment. Therefore, various efforts to produce biodegradable and bio-renewable ionic liquids (ionic liquids that can be obtained through modification of natural sources[88]) have been undertaken. Scammells and co-workers used the concept of biodegradable surfactants to develop a series of biodegradable-improved imidazolium-based ionic liquids incorporating ester or amide groups.[89] The Closed Bottle Test showed that ionic liquids with ester functionality have enhanced biodegradation compared to the non-functionalized equivalents, [BMim][BF_4] and [BMim][PF_6]. The susceptibility of the ester group to enzyme hydrolysis was thought to be the explanation of the observed improvement. Unfortunately, the improved biodegradability still cannot allow them be categorized as readily biodegradable.[90] To further improve the biodegradability, the authors continued to add a methyl group to the 2-position of the imidazolium cation and used octyl sulfate as counter anions.[91] The Closed Bottle Test combined with CO_2 Headspace test proved that the incorporation of these two groups contributes to significant improvement in biodegradability.

Davis Jr. and co-workers used saccharin and acesulfame, of which alkali-metal salts are extensively used foodstuffs as non-nutritive sweeteners, to form ionic liquids.[92] Their work should be considered as the first that employs a nontoxic precursor to create new environmentally and toxicologically benign ionic liquids. Kou and co-workers employed a new generation of ionic liquids, where the cations were derived directly from natural α-amino acids and α -amino acid ester salts.[93] The synthesis of these ionic liquids is simple and straightforward with many benefits including improved bio-renewable and biodegradable properties, maintainance of the chiral centre of the cation, and the possibility of additional functionalization being preserved. Consequently, the greenness level of this new generation of ionic liquids has been enhanced to full-greenness using nontoxic

inorganic or organic anions.[94] The nontoxic, pharmaceutically tolerable inorganic anion, NO_3^- and the saccharide anion were used to take the place of traditional anions that compose ionic liquids. Consequently, these ionic liquids are composed entirely of nontoxic and bio-renewable compositions and can be considered to be fully green. In addition, these liquids show Brønsted acidity, and can be used effectively to catalyze Diels-Alder reactions with comparable results as for traditional ionic liquids.[95] It is suggested that chemists working on developing green ionic liquids should cooperate with toxicologists with the purpose of perfecting the greenness of the new ionic liquids.

1.1.12 Conclusion

Interest in the properties of ILs is rapidly expanding. Although there have been numerous studies concerning their preparation, use as reaction media and their physical properties, little is known about how, and to what extent, the unusual physico-chemical properties of these media can affect reactivity. One important feature of these liquids is the possibility of tuning their physical and chemical properties by varying the nature of the anion and cation. If one consider all the possible combinations of the anions and cations, including the possibility of using mixtures of ILs, it is evident that the number of these 'new solvents' is extremely high and at least in principle it should always be possible to tailor the best ionic liquid for any application.

Understanding how chemical reactivity is influenced by different classes of ionic liquids is probably the key to obtaining the technological improvements for a safer, more secure society and to substantially benefit the environment and the economy.

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Chapter 1-Section B

Synthesis of ionic liquids (ILs)

1.2.1 Introduction

As the demands for more ideal synthetic practices continue to increase, greater and greater attention is focused on the development of new and improved synthetic methods. One of major topic of interest is to develop alternatives to conventional volatile organic solvents, since the latter materials are widely used and exhibit a number of hazardous properties. In this category, ionic liquids (ILs) have gained the greatest attention in recent years. Since the first report on water-stable imidazolium cation based ionic liquids, 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm]BF_4), by Wikes and Zaworotko, various 1,3-dialkylimidazolium salts containing a variety of anions have been synthesized, that are currently receiving a great deal of attention as novel media in various fields. A proper choice of cations and anions is required to achieve ionic salts that are liquids at room temperature and are appropriately termed room temperature ionic liquids (RTILs). Common RTILs consist of 1,3-dialkylimidazolium, alkylammonium, alkylphosphonium and *N*-alkylimidazolium as cations.[1]

1.2.2 Present work

1.2.2.1 Objectives

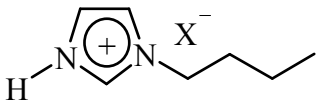
The ionic liquids based on 1,3-dialkylimidazolium are becoming more important for several synthetic applications. Most of the research was focused on the synthesis and application of ionic liquids involving non-symmetric *N,N'*-dialkylimidazolium cation. However, very little attention was focused on the synthesis of ionic liquids based on symmetric *N,N'*-dialkylimidazolium cation even though symmetric *N,N'*-dialkylimidazolium hexafluorophosphate with dibutyl, dipentyl, dioctyl, dinonyl and didecyl substituent are found to be ionic liquids.[2] Furthermore, Brønsted acidic ionic liquids (BAILs) are one kind of task-specific ionic liquids (TSILs), which contain a Brønsted acid functionalized component in the cation or anion. Some inorganic or organic acids such as HCl, HBF_4 and CF_3COOH, could react directly with *N*-alkylimidazoles to form a new class of protic ionic liquids, which bear an acidic proton on nitrogen 3 of the imidazolium ring. Thus, in view of keeping these facts, we became interested in the synthesis of symmetric Brønsted acidic *N,N'*-dialkylimidazolium salts and *N*-alkylimidazolium salts.

1.2.2.2 Results and discussion

Our research interest in this area has focused mainly on the development of new ionic liquids based on symmetric 1,3-di-*n*-butylimidazolium [bbim] cation **15** and Brønsted acidic 1-*n*-butylimidazolium [Hbim] salts **16** (**Fig. 4**) respectively and exploring their use as efficient reaction media.

[bbim]X

15

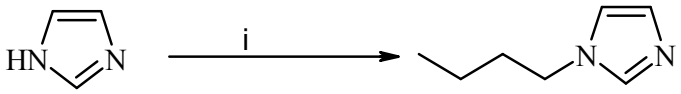


[Hbim]X

16 X= Br, Cl, BF_4, PF_6, ClO_4

Figure 4. Ionic liquids based on 1,3-di-*n*-butyl imidazolium and 1-*n*-butyl imidazolium cations

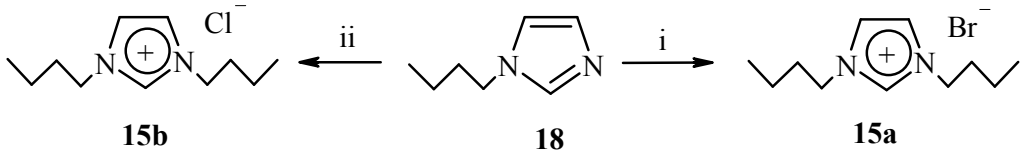
In this section we focused mainly on the synthesis of these ILs. For the synthesis of both the types of ILs, the required starting material, 1-*n*-butylimidazole was prepared initially.[3] Imidazole **17** on treatment with 1-butyl bromide using potassium hydroxide furnished 1-*n*-butylimidazole **18** (**Scheme 1**).



17 **18**

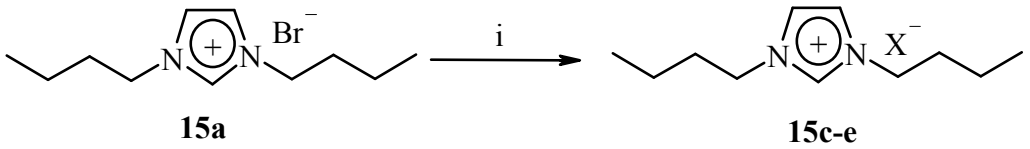
Scheme 1. Reaction conditions : (i) 1-butyl bromide, KOH, acetonitrile, 0 °C, 92%.

The desired IL, 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) **15a** was generated by direct alkylation on nitrogen atom by reacting 1-*n*-butylimidazole **18** with 1-butyl bromide at 70 °C for 4 h without any solvent. The synthesis of 1,3-di-*n*-butylimidazolium chloride ([bbim]Cl) **15b** was obtained by direct alkylation of 1-*n*-butylimidazole with 1-butyl chloride in toluene at 110°C (**Scheme 2**). Since butyl chloride is less reactive than butyl bromide, this reaction was only completed at higher temperature with longer reaction time. The reactions were typically carried out in an inert atmosphere (N_2, argon). ILs should be heated carefully, since excess heat during the preparation reaction generates a colored product indicating impurities might have been formed in the solvent.



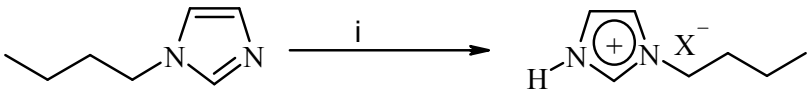
Scheme 2. Reaction conditions: (i) 1-butyl bromide, 70 °C, 4h, 96%; (ii) 1-butyl chloride, toluene, 110 °C, 8h, 95%.

The rest of ILs based on [bbim] cation with different anion which could not easily accessible by direct alkylation was prepared by direct anion-anion exchange from the desired acid or salt in the second step. This process is referred to as metathesis. Thus, other ILs such as 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4), 1,3-di-*n*-butylimidazolium hexafluorophosphate ([bbim]PF_6) and 1,3-di-*n*-butylimidazolium perchlorate ([bbim]ClO_4) were prepared from [bbim]Br **15a** by metathesis using sodium tetrafluoroborate, hexafluorophosphoric acid and perchloric acid respectively (**Scheme 3**).



Scheme 3.Reaction conditions**:** (i) RX, H_2O, rt, 86-97%.

The synthesis of ILs based on 1-*n*-butylimidazolium salts ([Hbim]X) **16** were very easy to achieve. In this case, 1-*n*-butylimidazole **18** was directly quaternized with protic acid to afford 1-*n*-butylimidazolium ([Hbim]X) salts. The desired anion was obtained from the choice of the parent protic acid used for the reaction. Thus, synthesis of 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) was achieved by reaction of 1-*n*-butylimidazole and tetrafluoroboric acid. In this way, other ILs were prepared by using 1-*n*-butylimidazole and protic acids such as hydrobromic acid, hydrochloric acid, hexafluorophosphoric acid and perchloric acid to afford [Hbim] salts with anion such as bromide, chloride, hexafluorophosphate and perchlorate respectively (**Scheme 4**). It was observed that ILs based on 1-*n*-butylimidazolium salts ([Hbim]X) are less viscous than ILs of 1,3-di-*n*-butylimidazolium salts [bbim]X. All the ILs synthesized were fully characterized.



18 **16a-e**

X= Br, Cl, BF_4, PF_6, ClO_4

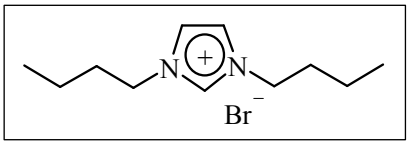
Scheme 4. Reaction conditions **: (**i) HX, 0 °C, 95-98%.

1.2.3 Conclusion

In conclusion, several ILs based on 1,3-di-*n*-butylimidazolium [bbim] cation and 1-*n*-butylimidazolium [Hbim] cation were prepared commencing from 1-*n*-butylimidazole in excellent yields and are fully characterized. The prepared salts are found to be room temperature ionic liquids (RTILs) and have shown excellent stability towards air and moisture. It was observed that ILs based on 1-*n*-butylimidazolium salts ([Hbim]X) are less viscous than ILs of 1,3-di-*n*-butylimidazolium salts [bbim]X.

1.2.4 Experimental

1.2.4.1 Synthesis of 1,3-di-*n*-butylimidazolium bromide [bbim]Br (15a)



A mixture of 1-*n*-butylimidazole **18** (12.4g, 0.1 mol) and 1-butyl bromide (15g, 0.11mol) was heated with stirring at 70 °C for 4 h. The excess 1-butyl bromide was distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [bbim]Br as colourless viscous liquid (24.9g, 96%).

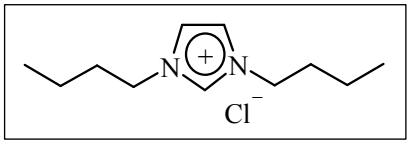
IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 3401, 3067, 2874, 1635, 1563, 1465, 1167, 753.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.85-0.93 (t, *J* = 7.1 Hz, 6H), 1.26-1.33 (m, 4H), 1.82-1.89 (m, 4H), 4.28-4.35 (t, *J* = 7.2 Hz, 4H), 7.54 (s, 2H), 10.41 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** δ 12.8, 18.8, 31.6, 49.1, 121.9, 135.9.

Elemental Analysis **: $C_{11}H_{21}N_2Br$** (261) Calcd: C, 50.57; H, 8.05; N, 10.73.
Found: C, 50.24; H, 7.91; N, 10.50.

1.2.4.2 Synthesis of 1,3-di-*n*-butylimidazolium chloride [bbim]Cl (15b)



A mixture of 1-*n*-butylimidazole (12.4g, 0.1 mol) and 1-butyl chloride (10.17g, 0.11 mol) was refluxed in toluene for 8 h. Toluene and excess 1-butyl chloride were distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the IL, [bbim]Cl as a viscous oil (20.61g, yield 95%).

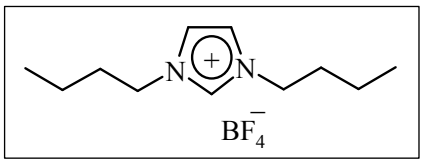
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3401, 3067, 2874, 1635, 1563, 1465, 1167, 753.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.85-0.92 (t, *J* = 7.2 Hz, 6H), 1.20-1.40 (m, 4H), 1.66-1.92 (m, 4H), 4.22 (t, *J* = 7.0 Hz, 4H), 7.48 (s, 2H), 10.76 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.1, 19.1, 31.9, 49.3, 122.2, 136.9.

Elemental Analysis : **$C_{11}H_{21}N_2Cl$** (217) Calcd: C, 60.82; H, 9.67; N, 12.90.
Found: C, 60.54; H, 9.51; N, 12.71.

1.2.4.3 Synthesis of 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim]BF_4 (15c)



To a solution of 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) **15a** (13.0g, 0.05 mol) in water (40 mL) was added a solution of sodium tetrafluoroborate (6.58g, 0.06 mol) in water (20 mL).

The reaction mixture was stirred at room temperature for 5 h. The IL, [bbim]BF_4 separated out as an immiscible layer. The mixture was extracted with dichloromethane (3x 30 mL). The combined organic layer was separated, washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure leaving behind the pure IL, [bbim]BF_4 as viscous oil (11.47g, yield 86%).

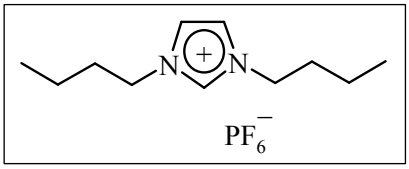
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3401, 3067, 2874, 1635, 1563, 1465, 1167, 753.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.12-1.20 (t, *J* = 7.2 Hz, 6H), 1.49-1.63 (m, 4H), 2.03-2.18 (m, 4H), 4.43-4.50 (t, *J* = 7.6 Hz, 4H), 7.74 (s, 2H), 9.20 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.1, 19.1, 31.8, 49.5, 122.3, 135.4.

Elemental Analysis : **$C_{11}H_{21}N_2BF_4$** (268) Calcd: C, 49.25; H, 7.83; N, 10.44.
Found: C, 49.05; H, 7.61; N, 10.28.

1.2.4.4 Synthesis of 1,3-di-*n*-butylimidazolium hexafluorphosphate [bbim]PF_6 (15d)



The procedure is followed as per above except hexafluorophosphoric acid (65% water solution) was used instead of sodium tetrafluoroborate to afford IL [bbim]PF_6 as viscous oil (14.93 g, yield 92%).

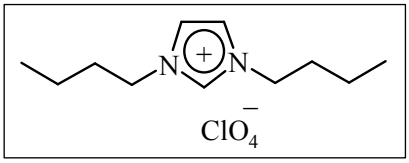
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.92-1.0 (t, *J* = 7.0 Hz, 6H), 1.27-1.44 (m, 4H), 1.79-1.94 (m, 4H), 4.15-4.23 (t, *J* = 7.5 Hz, 4H), 7.33 (s, 2H), 8.79 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.2, 19.3, 31.8, 49.8, 122.3, 135.2.

Elemental Analysis : **$C_{11}H_{21}N_2PF_6$** (326) Calcd: C, 40.61; H, 6.46; N, 8.61.
Found: C, 40.46; H, 6.29; N, 8.48.

1.2.4.5 Synthesis of 1,3-di-*n*-butylimidazolium perchlorate [bbim]ClO_4 (15e)



The procedure is followed as per above applied for [bbim]BF_4 **15c** except solution of perchloric acid was used instead to afford IL [bbim]ClO_4 as viscous oil (13.97 g, yield 97%).

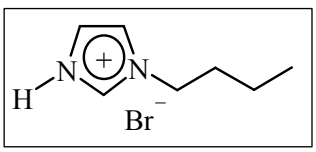
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.89-0.97 (t, *J* = 7.4 Hz, 6H), 1.25-1.40 (m, 4H), 1.79-1.94 (m, 4H), 4.19-4.26 (t, *J*= 7.3 Hz, 4H), 7.42 (s, 2H), 9.03 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.2, 19.2, 31.8, 49.8, 122.4, 135.5.

Elemental Analysis : **$C_{11}H_{21}N_2ClO_4$** (281) Calcd: C, 46.97; H, 7.47; N, 9.96.
Found: C, 46.74; H, 7.21; N, 9.87.

1.2.4.6 Synthesis of 1-*n*-butylimidazolium bromide [Hbim]Br (16a)



Hydrobromic acid (8.9g, 0.1 mol) (40% aqueous solution) was slowly added to 1-*n*-butylimidazole

(12.4 g, 0.1 mol) at 0 °C over a period of 30 min under stirring. The reaction mixture was stirred for an additional period of 2 h at the 0 °C. Water was removed from the reaction mixture by subjecting it to evaporation for 4 h at 80 °C under reduced pressure (10mm Hg) to afford the IL, [Hbim]Br as viscous oil (19.7 g, yield 96%).

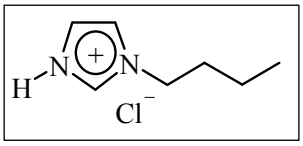
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3607, 3153, 2876, 1580, 1466, 894, 762.

^{1}H NMR ($CDCl_3$ as external lock) : δ 0.21 (brs, 3H), 0.64 (brs, 2H), 1.31 (brs, 2H), 4.03 (brs, 2H), 7.39 (s, 1H), 7.64 (s, 1H), 9.18 (s, 1H), 12.22 (brs, 1H, NH).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.1, 19.1, 32.4, 47.3, 120.0, 124.7, 136.1.

Elemental Analysis : **$C_7H_{13}N_2Br$** (206) Calcd: C, 40.97; H, 6.34; N, 13.65.
Found: C, 40.54; H, 6.11; N, 13.18.

1.2.4.7 Synthesis of 1-*n*-butylimidazolium chloride [Hbim]Cl (16b)



Hydrochloric acid (3.6g, 0.1 mol) (35% aqueous solution) was slowly added to 1-*n*-butylimidazole (12.4 g, 0.1 mol) at 0 °C over a period of 30 min under stirring. The reaction mixture was stirred for an additional period of 2 h at the 0 °C. Water was removed from the reaction mixture by subjecting it to evaporation for 4 h at 80 °C under reduced pressure (10mm Hg) to afford the IL, [Hbim]Cl as viscous oil (15.7 g, yield 98%).

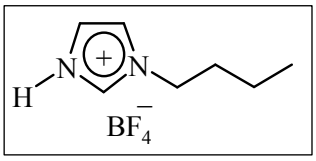
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3607, 3153, 2876, 1580, 1466, 894, 762.

^{1}H NMR ($CDCl_3$ as external lock) : δ 0.48 (brs, 3H), 0.88 (brs, 2H), 1.42 (brs, 2H), 4.00 (brs, 2H), 7.11 (s, 1H), 7.47 (s, 1H), 8.69 (s, 1H), 12.17 (brs, 1H, NH).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 11.7, 17.7, 30.9, 45.7, 118.3, 123.7, 134.7.

Elemental Analysis : **$C_7H_{13}N_2Cl$** (161) Calcd: C, 52.17; H, 8.07; N, 17.39.
Found: C, 52.02; H, 7.92; N, 17.18.

1.2.4.8 Synthesis of 1-*n*-butylimidazolium Tetrafluoroborate [Hbim]BF_4 (16c)



The procedure is followed as per above applied for [Hbim]Cl **16b** except tetrafluoroboric acid (8.7g, 0.1 mol) (40% aqueous solution) was used instead of hydrochloric acid to afford IL, [Hbim]BF_4 as viscous oil (20.1 g, yield 95%).

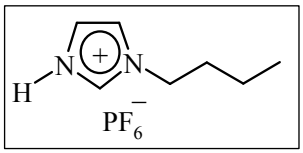
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3607, 3153, 2876, 1580, 1466, 894, 762.

^{1}H NMR ($CDCl_3$ as external lock) : δ 0.56 (brs, 3H), 0.95 (brs, 2H), 1.47 (brs, 2H,), 3.87 (s, 2H), 7.12 (s, 2H), 8.16 (s, 1H), 14.59 (brs, 1H, NH).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.1, 19.2, 32.1, 48.5, 120.9, 122.2, 135.2.

Elemental Analysis : **$C_7H_{13}N_2BF_4$** (212) Calcd: C, 39.81; H, 6.16; N, 13.27.
Found: C, 39.61; H, 6.01; N, 13.05

1.2.4.9 Synthesis of 1-*n*-butylimidazolium hexaflouorphosphate [Hbim]PF_6 (16d)



The procedure is followed as per above applied for [Hbim]Cl **16b** except hexafluorophosphoric acid (14.6g, 0.1 mol) (65% aqueous solution) was used instead of hydrochloric acid to afford IL, [Hbim]PF_6 as viscous oil (26.4 g, yield 98%).

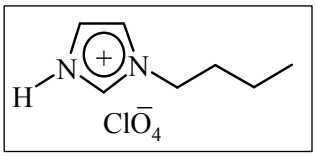
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3607, 3153, 2876, 1580, 1466, 894, 762,

^{1}H NMR ($CDCl_3$ as an external lock) : δ 0.42 (brs, 3H), 0.84 (brs, 2H), 1.43 (brs, 2H), 3.96 (brs, 2H), 7.18 (s, 2H), 8.56 (s, 1H), 12.91 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7.

Elemental Analysis : **$C_7H_{13}N_2PF_6$** (270) Calcd: C, 31.26; H, 4.83; N, 10.40.
Found: C, 31.10; H, 4.71; N, 10.18

1.2.4.10 Synthesis of 1-*n*-butylimidazolium perchlorate [Hbim]ClO_4 (16e)



The procedure is followed as per above applied for [Hbim]Cl **16b** except perchloric acid (10.0g, 0.1 mol) was used instead of hydrochloric acid to afford IL, [Hbim]ClO_4 as viscous oil (21.6 g, yield 96%).

IR ($CHCl_3$, cm^{-1}) : υ_{max} 3607, 3153, 2876, 1580, 1466, 894, 762.

^{1}H NMR ($CDCl_3$ as external lock) : δ 0.71 (brs, 3H), 1.17 (brs, 2H), 1.73 (brs, 2H), 4.16 (brs, 2H), 7.15 (s, 1H), 7.42 (s, 1H), 8.57 (s, 1H), 11.83 (brs, 1H).

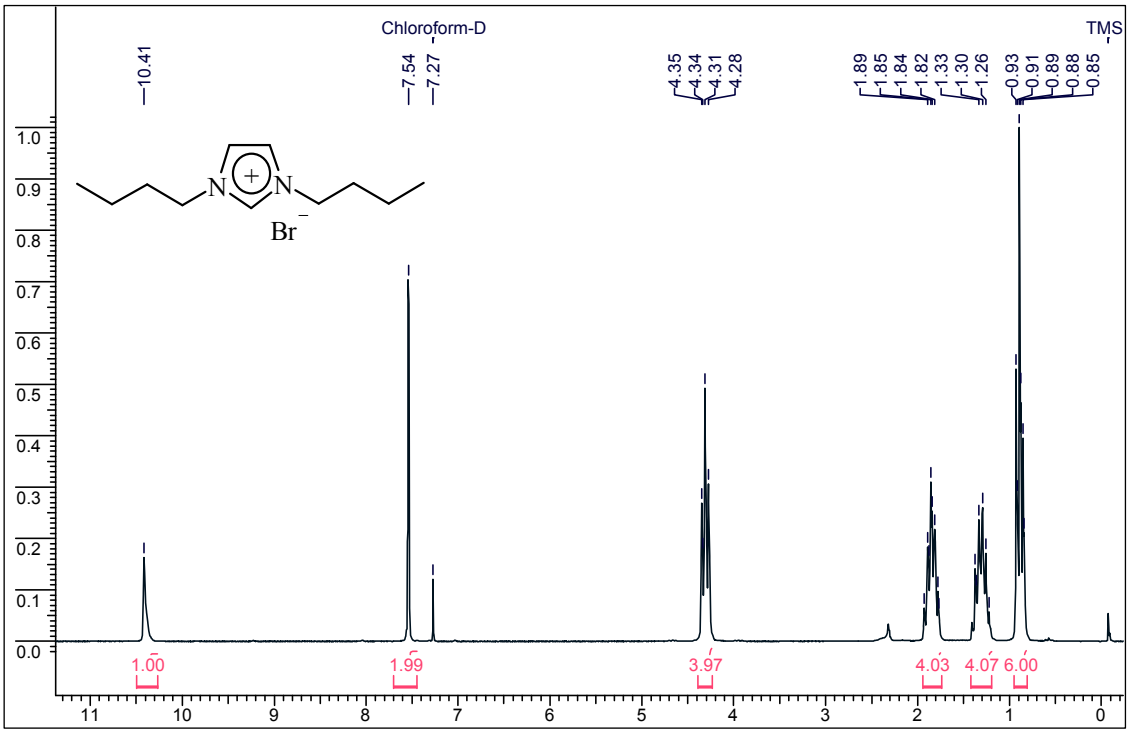
^{13}C NMR (50 MHz, $CDCl_3$) : δ 12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7.

Elemental Analysis : **$C_7H_{13}N_2ClO_4$** (225) Calcd: C, 37.33; H, 5.77; N, 12.44.
Found: C, 37.10; H, 5.61; N, 12.18.

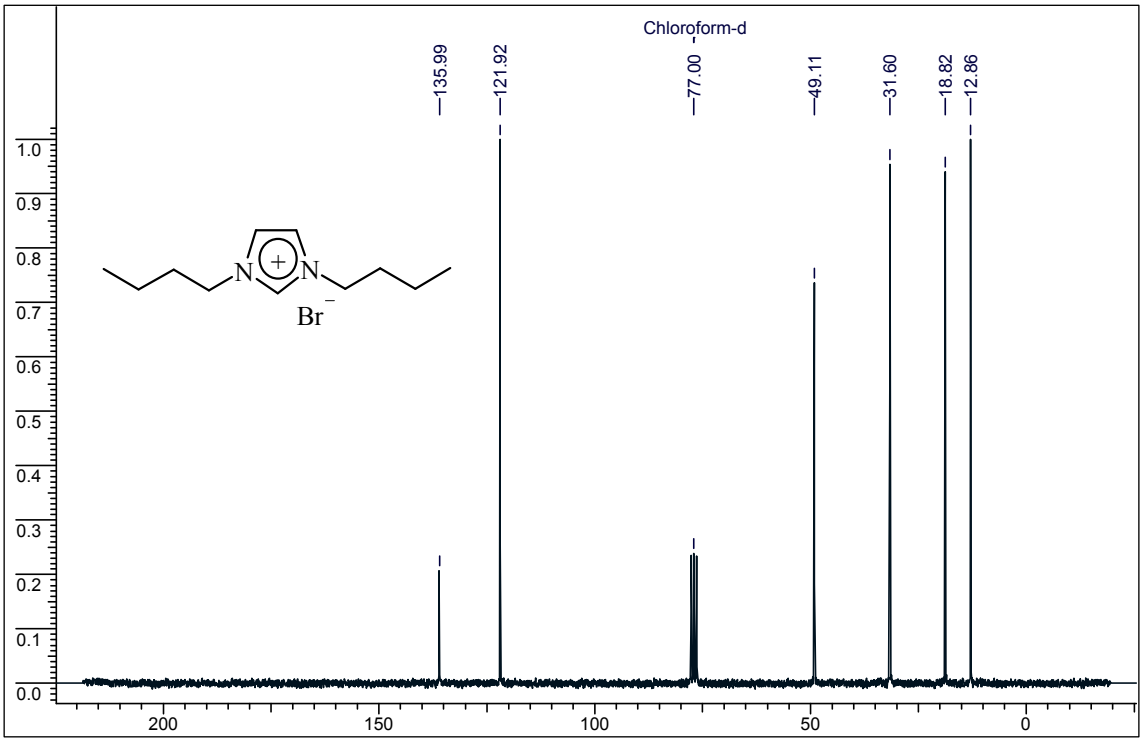
1.2.5 Spectra of representative compounds

Sr. No.	NMR Spectra
1	^{1}H and ^{13}C NMR spectra **15a**
2	^{1}H and ^{13}C NMR spectra **15c**
3	^{1}H and ^{13}C NMR spectra **16a**
4	^{1}H and ^{13}C NMR spectra **16c**

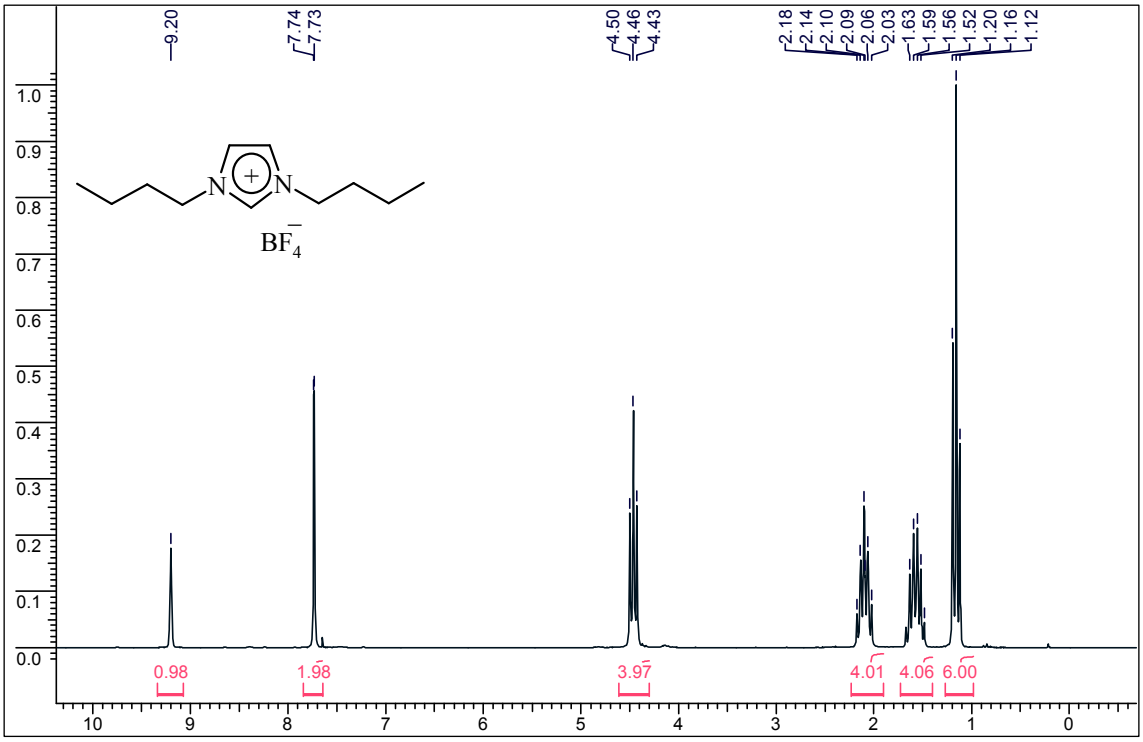
^{1}H NMR Spectra of 15a



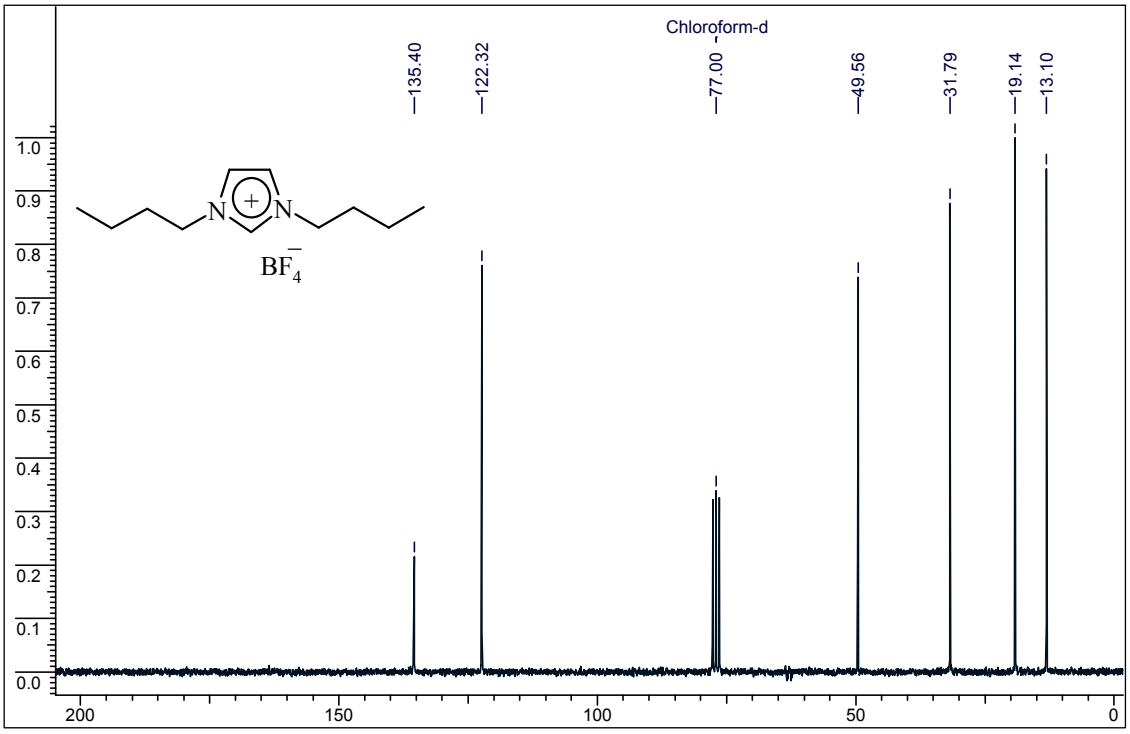
^{13}C NMR spectra of 15a



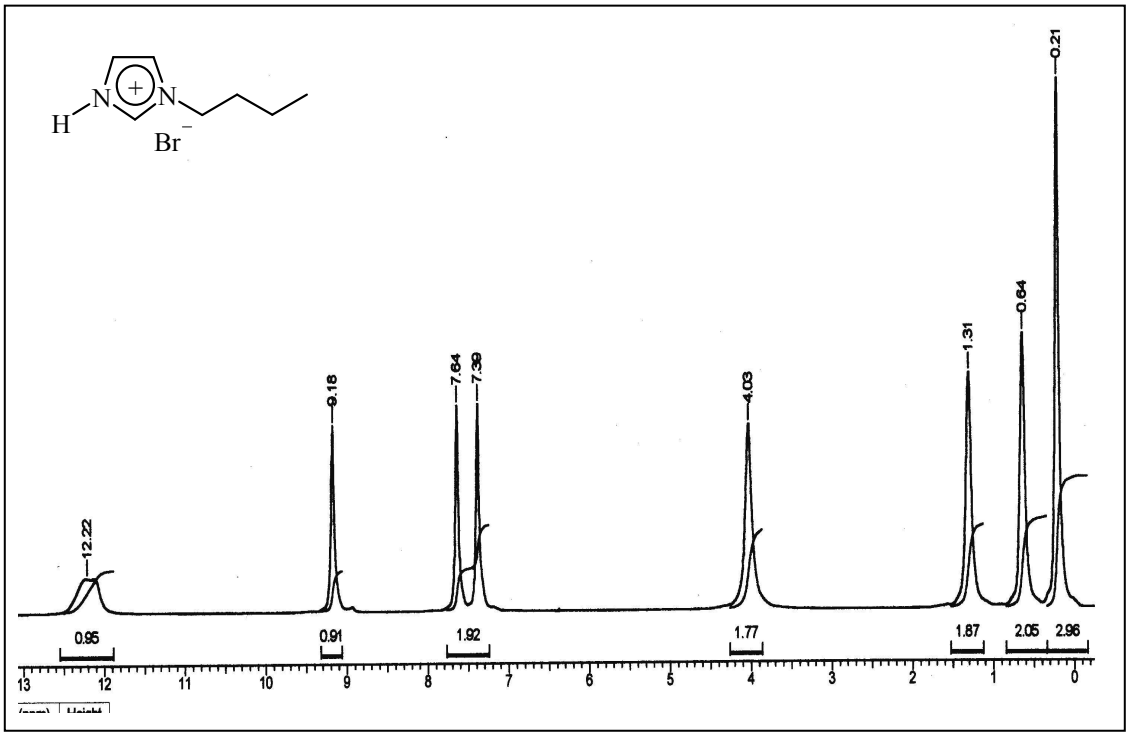
^{1}H NMR spectra of 15c



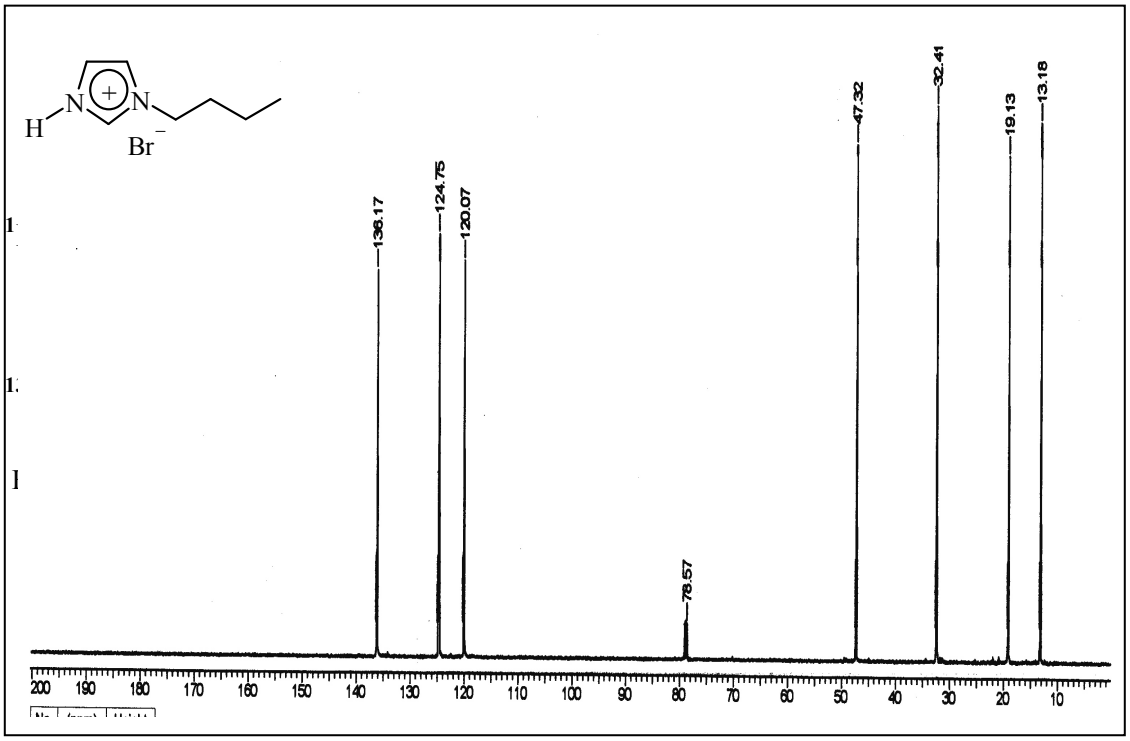
^{13}C NMR spectra of 15c



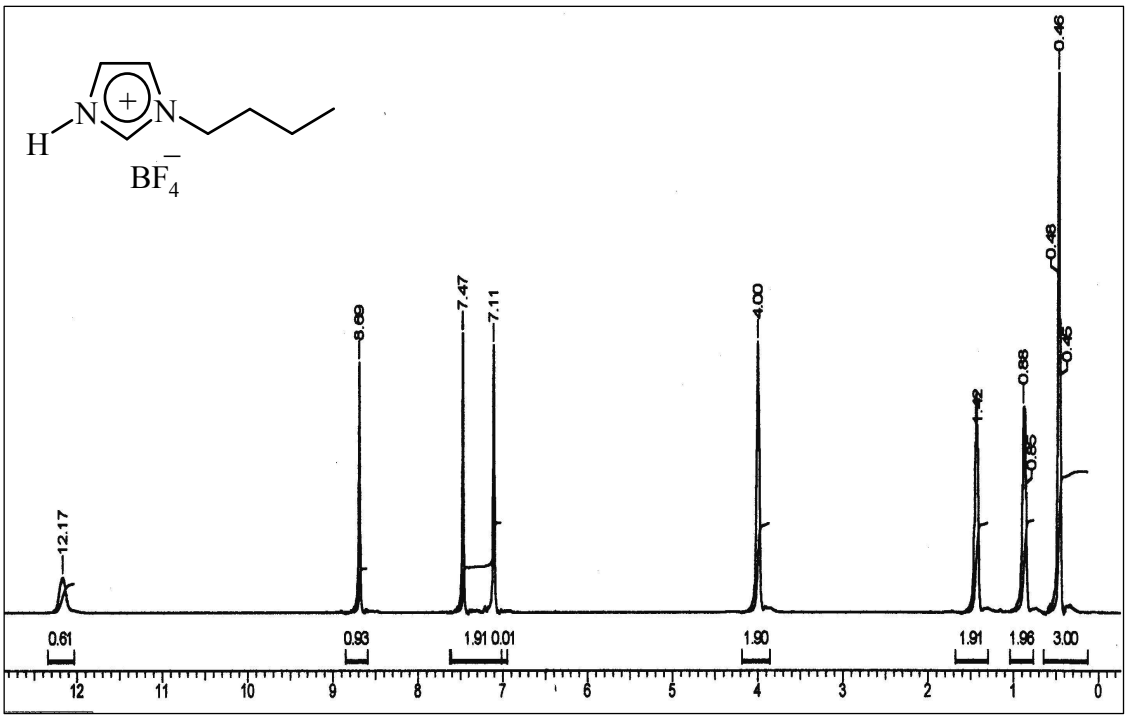
^{1}H NMR spectra of 16a



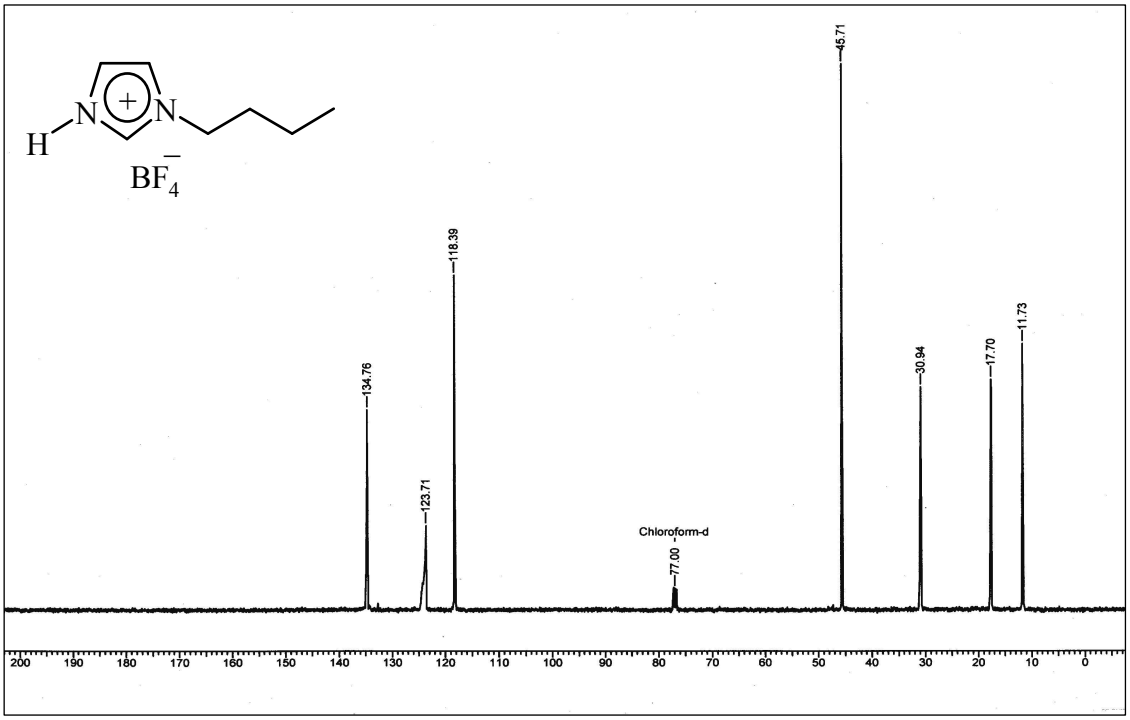
^{13}C NMR spectra of 16a



^{1}H NMR spectra of 16c



^{13}C NMR spectra of 16c



1.2.6 References

[1] Welton, T. *Chem. Rev.* **1999,** *99*, 2701.

[2] Dyzuba, S.V.; Bartsch, R. A. *Chem. Commun*. **2001**, *16*, 1466.

[3] Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371.

Chapter 1- Section C

Applications of ionic liquids (ILs) as solvent as well as a promoter for the synthesis of biologically active *N*-heterocycles

1.3.0 Introduction

Heterocyclic compounds, particularly *N*-heterocycles are of particular interest in medicinal science. This has accelerated the quest for new methods in heterocyclic chemistry. Most of the routes leading to the synthesis of heterocycles involve the use of conventional volatile organic solvents including higher polar and acidic solvent with or without catalyst. However, these mainly organic solvents, belonging to the group of volatile organic compounds (VOC's) account for a great proportion of environmental pollution and waste material; their use is often problematic owing to their toxicity, volatility. Therefore, there is a need to replace these VOC's by alternative solvents. Among the alternative reaction media studied as substitutes for classical organic solvents are ionic liquids. With respect to reaction carried out in conventional solvents, reactions in ILs have different thermodynamic and kinetic behaviors, which often lead to improved process performance. Furthermore, because of their low nucleophilicity, ionic liquids provide unique environment in stabilizing electron deficient intermediates. Another practical advantage of ionic liquids is that they could avoid problems associated with the neutralization of large quantities of acids generally needed in the classical routes. The aim of our work is to evaluate the potential of the ionic liquids with respect to their application not only as solvent, but also promoter in the synthesis of biologically active *N*-heterocycles.

This section is further divided into three parts. Part I describes the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles, part II describes the synthesis of 3,5,6-trisubstituted-1,2,4-triazines and part III describes the synthesis of quinoxalines in ILs as solvent cum promoter.

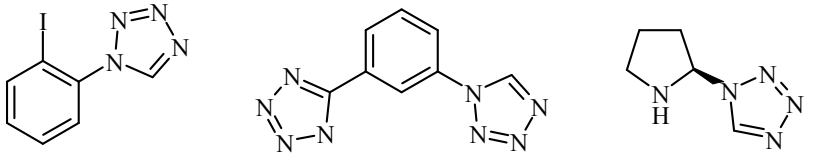
Chapter 1- Section C- Part I

Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles

1.3.1.1 Introduction

Tetrazoles are an increasingly popular functionality with wide ranging applications.[1] This functional group has roles in coordination chemistry as a ligand, in medicinal chemistry as a metabolically stable surrogate for a carboxylic acid group,[2] and in various materials science applications including propellants[3] and explosives.[4] Furthermore, tetrazole moieties are important synthons in the synthetic organic chemistry.[5] Tetrazoles have been studied extensively since the time they were first described in 1885.[6]

Several tetrazolyl ligands have found useful applications in several types of reaction. 1-(2-Iodophenyl)-1*H*-1,2,3,4-tetrazole **19** has been successfully employed as ligands for the Pd-catalyzed Heck reaction. 1,3-Phenylene-bis-(1*H*)-tetrazole pincer ligand **20** has been used successfully for Pd-catalyzed Suzuki reaction. 5-Pyrrolidin-2-yl tetrazole **21** has been found to be a new, catalytic, and more soluble alternative to proline in an organocatalytic asymmetric reaction (**Fig. 5**).



19 **20** **21**

Figure 5. Structures of tetrazolyl ligands

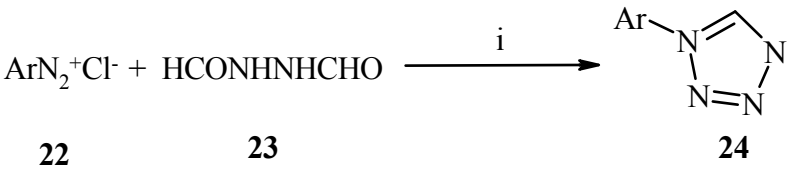
1.3.1.2 Review of literature

In 1947, Benson reported a review on tetrazole chemistry listing only seven examples of 1-substituted-1*H*-1,2,3,4-tetrazoles. After that time, several methods for the preparation of 1-substituted-1*H*-1,2,3,4-tetrazoles were reported, because of their wide utility. In this section, some of the more significant and recent methods of synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles are described.

Dimroth et al. approach (1910)[7]

Dimroth et al. reported the synthesis of 1-substituted tetrazoles **24** by the interaction of diazonium salts **22** with sym-diformylhydrazine **23** using dilute sodium hydroxide followed by cyclizing the resulting diazohydrazide with warm aqueous alkali. The reaction

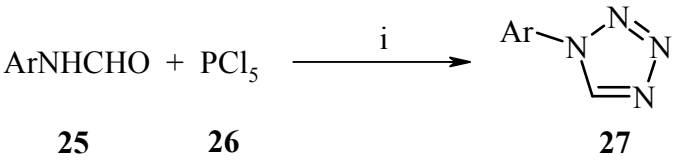
involved the loss of a formyl group and water molecule to afford 1-substituted tetrazoles (**Scheme 5**).



Scheme 5. Reaction conditions**:** (i) warm dilute NaOH, 60-73%.

Frances G. Fallon et al. approach (1957)[8]

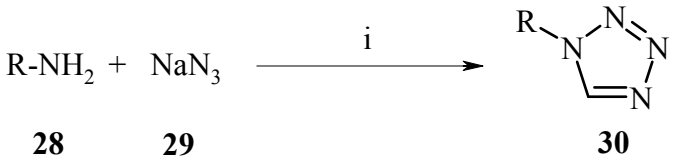
Frances G. Fallon et al. reported the synthesis of 1-aryltetrazoles **27** from the reaction of formanilides **25** with phosphorus pentachloride **26** and hydrazoic acid carried out in toluene (**Scheme 6**). However, the reported method suffers from longer reaction times (24 h) and very low yield (16-43%).



Scheme 6. Reaction conditions **:** (i) HN_3, Toluene, rt, 24 h, 16-43%.

Yoshitaka Satoh et al. approach (1995)[9]

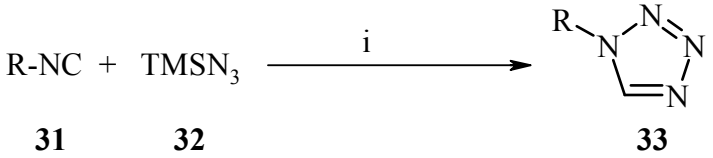
Yoshitaka Satoh et al. reported the synthesis of 1-substituted tetrazoles **30** from the reaction of amine **28** with triethyl orthoformate and sodium azide **29**. The reaction mixture containing amine **28**, triethyl orthoformate, and sodium azide **29** was heated at 80°C for a period of 6 h in acetic acid to afford 1-substituted tetrazoles **30** (**Scheme 7**).



Scheme 7. Reaction conditions **:** (i) $HC(OEt)_3$, Acetic Acid, 80 °C, 6 h, 66-78%.

Yoshinori Yamamoto et al approach (2004)[10]

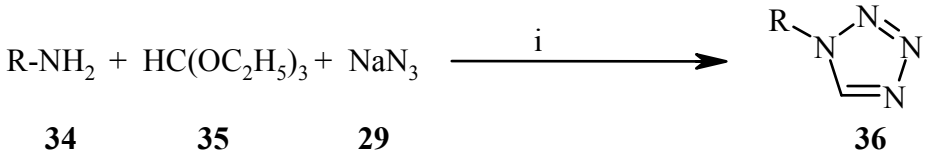
Yamamoto et al. in 2004 reported the synthesis of 1-substituted tetrazoles **33** via the [3+2] cycloaddition between isocyanides **31** and trimethylsilyl azide **32** in the presence of an acid as catalyst in methanol at 60 °C for a period of 4-6 h. The reaction probably proceeds through *in situ* formation of hydrazoic acid, followed by a successive [3+2] cycloaddition with the isocyanide activated by an acid (**Scheme 8**).



Scheme 8. Reaction conditions **:** i) cat. HCl, MeOH, 60 °C, 4-6 h, 58-92%.

Wei-Ke Su et al. approach (2006)[11]

Wei-Ke Su et al. reported the synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles **36** from amine **34**, triethyl orthoformate **35** and sodium azide **29** through $Yb(OTf)_3$ catalyzed reaction in methoxyethanol at 100 °C (**Scheme 9**). However, this method suffers from drawbacks such as use of highly polar solvent and longer reaction time (6-10 h) at 100 °C.



Scheme 9. Reaction conditions **:** i) $Yb(OTf)_3$ (20 mol%), $CH_3OC_2H_4OH$, 100 °C, 6-10 h, 82-97%

1.3.1.3 Present work

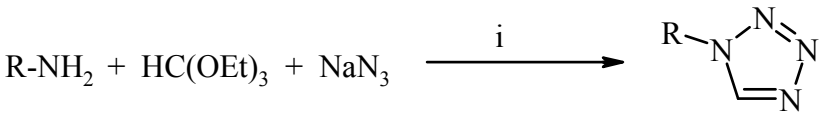
1.3.1.3.1 Objectives

Although many 5-substituted tetrazoles are known and their methods of synthesis were reported, there is still a dearth of efficient processes for the synthesis of 1-substituted tetrazoles. Development of improved synthetic methods for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles remains an active research area.

The methods reported so far for the synthesis of 1-substituted tetrazole, either in acidic condition using acids such as hydrochloric acid, acetic acid, trifluoroacetic acid, and sulfuric acid or in highly polar solvents such as 2-methoxyethanol, DMF, and methanol, required very harsh reaction condition such as refluxing for 6-24 h followed by very tedious work-up procedures such as distillation of high boiling solvent or neutralization followed by distillation under reduced pressure. These processes also generate waste-containing solvent and catalyst, which have to be recovered, treated and disposed off. Therefore we sought to develop a more efficient and convenient method that avoided these drawbacks and could be used both on a laboratory and industrial scale.

In view of the significance of 1-substituted tetrazoles due to wide ranging applications and as a part of our studies on the development of an environment-friendly synthetic methodology for the synthesis of biologically active *N*-heterocycles from common intermediates, we became interested in the synthesis of 1-substituted tetrazoles using room temperature ionic liquids (RTILs) as a reaction medium as well as promoter.

Herein, we report a one-pot condensation of sodium azide **29**, substituted amines **37** and triethyl orthoformate **35** in the IL to afford 1-substituted-1*H*-1,2,3,4-tetrazoles **38** **(Scheme 10)**.



Scheme 10. Reaction Conditions **:** (i) $[Hbim]BF_4$, 100 °C, 15-35 min, 85-93%.

1.3.1.3.2 Results and Discussion

Initially we chose the IL, 1-*n*-butylimidazolium tetrafluoroborate ($[Hbim]BF_4$) as reaction medium for this reaction. We carried out the reaction of 4-isopropyl aniline **37e** with triethyl orthoformate **35** and sodium azide **29** as a model reaction at lower temperatures such as 40 °C and 60 °C respectively where no formation of the expected product was observed as indicated by TLC. When, the model reaction was carried out at higher temperature (80 °C), some marginal reaction was observed, but the reaction did not go to completion even after long reaction period (8 h). Bearing in mind the effect of

temperature, we proceeded to carry out the reaction at 100 °C. The reaction went to completion in 25 min to afford 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole **38e** in excellent yield (90%) without any added catalyst. The progress of the reaction was monitored by TLC. The disappearance of spot on TLC corresponding to starting material 4-isopropyl aniline and appearance of an entirely new spot on TLC suggested the possible formation of product, 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole **38e** as the only product. The structure of the compound after isolation was further confirmed by ^{1}H and ^{13}C NMR spectral analysis and by comparison with authentic sample obtained by literature procedure. The ^{1}H NMR of the compound **38e** shows characteristic signal as singlet at δ 8.97 ppm corresponding to the hydrogen of tetrazole ring. Furthermore, a ^{13}C NMR spectrum shows a characteristic peak at δ 140.5 ppm corresponding to the carbon of tetrazole ring.

Once the reaction condition i.e. temperature, was optimized, we next screened several ionic liquids for this transformation. For this, ionic liquids (ILs) based on 1,3-di-*n*-butylimidazolium salts [bbim]X and 1-*n*-butylimidazolium salts [Hbim]X with varying basicity of anions were tested as solvents and promoters for the typical reaction of 4-isopropyl aniline **37e** with triethyl orthoformate **35** and sodium azide **29** at 100 °C without any added catalyst to afford 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole **38e**. No product formation could be observed in [bbim]X series ILs even after 12 h whereas in [Hbim]X series of the ILs, a facile reaction was observed to take place and the results are summarized in **Table 1**. The efficacy of the ILs to promote this transformation reaction was correlated to the basicity of the anions of the ILs as well as Brønsted acidity of the ILs. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing p*K*a of the corresponding acid), there is a progressive increase in yield (**Table 1**). This correlation was also evident when the yield of 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole (**38e**) was compared with -NH proton chemical shifts of the ILs indicative of the Brønsted acidities of the [Hbim]X ILs (Table 1). The yield of **38e** increases progressively with increasing Brønsted acidity of the ILs, as indicated by the increasing downfield shift of the -NH proton.

Table 1. Synthesis of 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole (**38e)** in [Hbim]X

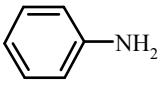
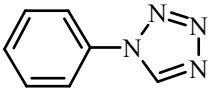
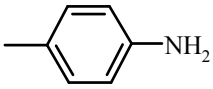
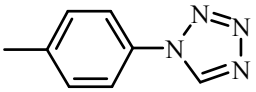
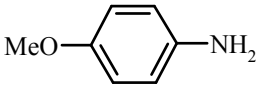
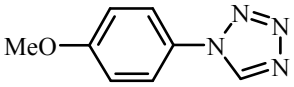
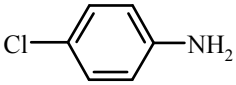
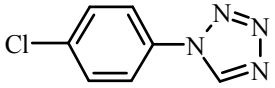
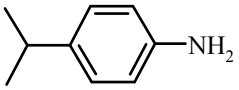
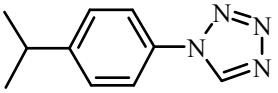
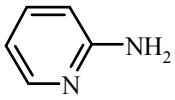
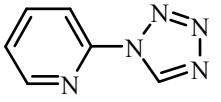
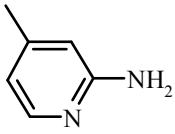
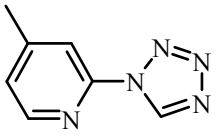
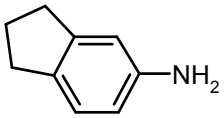
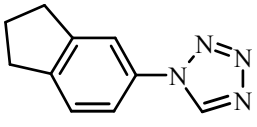
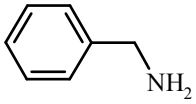
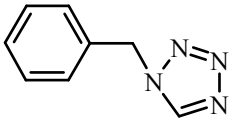
Entry	ILs	pKa[a]	–NH proton δ ppm	Time (min)	Yield (%)[b]
1	[Hbim]ClO_4	-11	11.83	210	75
2	[Hbim]Br	-9	12.17	120	78
3	[Hbim]Cl	-7	12.22	80	83
4	[Hbim]BF_4	0.5	14.59	25	89[c]

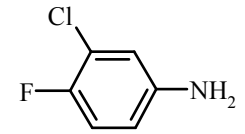
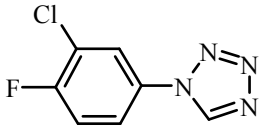
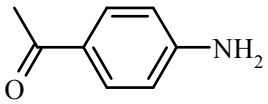
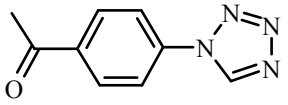
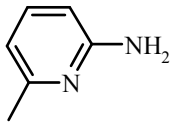
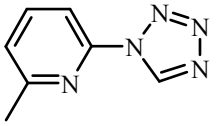
[a]:The pK_a values of the parent acid of the anions
[b:] Isolated yield after column chromatography

It becomes evident from these results (**Table 1**), the IL [Hbim]BF_4 by virtue of its inherent Brønsted acidity conferred by the most acidic -NH hydrogen (δ = 14.6 ppm) afforded the best results in terms of yield as well as time. It was postulated that the inherent Brønsted acidity of the ionic liquid plays an important role for the breakdown of triethyl orthoformate.

In order to investigate the scope and generality of this methodology, a variety of amines such as substituted anilines, heteroaromatic amines and an aliphatic amine (**Table 2, entry 9**) were employed. It was observed that under similar reaction conditions, a wide range of anilines having electron-withdrawing as well as electron-donating groups such as chloro, fluoro, acetyl, methoxy, isopropyl and methyl group smoothly reacted with triethyl orthoformate and sodium azide to afford a series of 1-substituted aryl-1*H*-1,2,3,4-tetrazole in excellent yields. Similarly, an aliphatic amine such as benzylamine (**37i)** also easily undergoes condensation reaction with triethyl orthoformate and sodium azide to give 1-benzyl-1*H*-1,2,3,4-tetrazole (**38i)** in short reaction times with excellent isolated yields. This methodology is further successfully extended to heteroaromatic amines such as substituted amino pyridines to afford 1-substituted-1*H*-1,2,3,4-tetrazoles. Almost all reactions were completed in just 15-35 min affording excellent yields of products (85-93%). The results are summarized in **Table 2**.

Table 2. Synthesis of 1-substituted-1H-1,2,3,4-tetrazoles in [Hbim]BF_4

Entry	Amine	Product	Time (min)	Yield[a] (%)
1	 **37a**	 **38a**	25	89
2	 **37b**	 **38b**	20	88
3	 **37c**	 **38c**	20	91
4	 **37d**	 **38d**	25	85
5	 **37e**	 **38e**	25	90
6	 **37f**	 **38f**	20	86
7	 **37g**	 **38g**	15	85
8	 **37h**	 **38h**	35	93
9	 **37i**	 **38i**	30	85

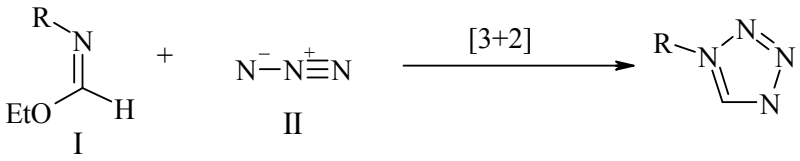
10	 **37j**	 **38j**	35	86
11	 **37k**	 **38k**	35	87
12	 **37l**	 **38l**	15	89

[a]: Isolated yield after column chromatography

The methods reported so far for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles used the reaction conditions such as use of protic acids, highly polar organic solvents, harsh reaction condition such as refluxing for 6-24 h followed by very tedious work-up procedures such as distillation of high boiling solvent or neutralization followed by distillation under reduced pressure. As compared to reported methods, the developed method is convenient, fast, safe, and having very easy work-up procedure, elements contributing to green chemistry.

1.3.1.3.3 Plausible Mechanism

As far as a plausible reaction mechanism is concerned, it is believed that the Brønsted acidity of ionic liquid plays an important role in the promotion of this heterocyclization reaction. In can be postulated that breakdown of triethyl orthoformate in the presence of the amine in acidic medium viz. [Hbim]BF_4 allows the formation of an imine I from the amine as already reported.[12] The imine I undergoes a [3+2] cycloaddition reaction with the azide II to form 1-substituted-1*H*-1,2,3,4-tetrazole (**Scheme 11**).



Scheme 11. Plausible mechanism

1.3.1.4 Conclusion

In conclusion, we have developed an efficient and environment-friendly protocol for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles via the condensation of amines, triethyl orthoformate and sodium azide using a RTIL as a recyclable medium as well as a promoter. The process gave rise to excellent isolated yields of 1-substituted-1*H*-1,2,3,4-tetrazoles in short reaction times (15-35 min). The reaction times achieved are shorter than those hitherto reported. The experimental procedure combining the features of simple isolation procedure, efficient recovery and recycling of IL and the absence of a catalyst makes this an environmentally benign methodology amenable for scale up.

1.3.1.5 Experimental

1.3.1.5.1 General Procedure for synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles

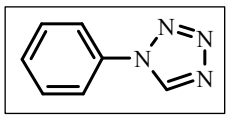
A mixture of amine **37** (1 mmol), triethyl orthoformate **35** (1.2 mmol) and sodium azide **29** (1 mmol) was taken in IL, [Hbim]BF_4 (2 mL) and heated at 100 °C with stirring. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with a mixture of ethyl acetate: petroleum ether (4:6) (3 x 20 mL). The product tetrazole extracts into the organic layer leaving behind the ionic liquid as an immiscible phase. The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to get crude product tetrazole. The crude product so isolated was pure (single spot on TLC). It was subjected to further purification by column chromatography (silica gel; ethylacetate:petroleum ether, 1:3) to yield the pure 1-substituted-1*H*-1,2,3,4-tetrazole in excellent yields.

The left behind immiscible IL layer was further extracted with ether to remove any leftover organic residue. The IL was successfully recycled and reused three times without any loss in yield for the typical reaction of 4-isopropyl aniline **37e** with triethyl orthoformate **35** and sodium azide **29** to afford 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole **38e.**

1.3.1.5.2 Characterization data for compounds 38a-l

1-Phenyl-1*H*-1,2,3,4-tetrazole (38a)

Pale yellow solid



M. P. (°C) : 64-65 (Lit.[11] 64-65)

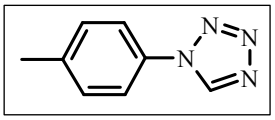
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1598, 1506, 1465, 1401, 1215, 1091, 1075, 1042, 998.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.51-7.75 (m, 5H, ArH), 9.02 (s, 1H, tetrazole H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 121.1, 129.9, 130.1, 133.7, 140.5.

Elemental Analysis : **$C_7H_6N_4$** (146) Calcd: C, 57.53; H, 4.14; N, 38.34.
Found: C, 57.23; H, 3.98; N, 38.12.

1-(4-Methylphenyl)-1*H*-1,2,3,4-tetrazole (38b)



White solid

M. P. (°C) : 92-93 (Lit.[11] 93-94)

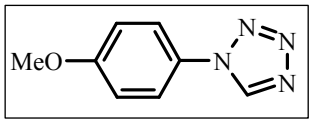
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2978, 2851, 1653, 1518, 1468, 1215, 1092, 1042, 998.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2. 46 (s, 3H, CH_3), 7.36-7.40 (d, *J* = 8.48 Hz, 2H, ArH), 7.57-7.61(d, *J* = 8.48 Hz, 2H, ArH), 8.97 (s, 1H, tetrazole H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 21.0, 121.0, 130.5, 131.3, 140.3, 140.5.

Elemental Analysis : **$C_8H_8N_4$** (160) Calcd: C, 59.99; H, 5.03; N, 34.98.
Found: C, 59.78; H, 4.92; N, 34.79.

1-(4-Methoxyphenyl)-1*H*-1,2,3,4-tetrazole (38c)



White needles

M. P. (°C) : 117-118 (Lit.[8] 116-117)

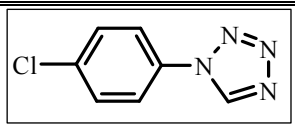
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2954, 1611, 1594, 1521, 1465, 1215, 1182, 1092, 1043, 996.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.89 (s, 3 H, OCH_3), 7.05-7.10 (dd, *J* = 7.06 & 2.10 Hz, 2 H, ArH), 7.58- 7.63 (dd, *J* = 7.06 & 2.10 Hz, 2H, ArH), 8.93 (s, 1H, tetrazole H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 55.6, 115.0, 122.8, 126.7, 140.6, 160.5.

Elemental Analysis : **$C_8H_8N_4O$** (176) Calcd: C, 54.54; H, 4.58; N, 31.80.
Found: C, 54.19; H, 4.37; N, 31.65.

1-(4-Chlorophenyl)-1*H*-1,2,3,4-tetrazole (38d)



White solid

M. P. (°C) : 154-156 (Lit.[11] 155-156)

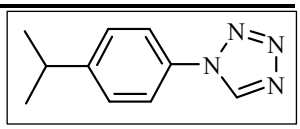
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1653, 1505, 1460, 1425, 1215, 1088, 1034, 996.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.55-7.62 (m, 2H, ArH), 7.66-7.73 (m, 2H, ArH), 9.02 (s, 1H, tetrazole H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 122.4, 130.4, 136.0, 140.4.

Elemental Analysis : **$C_7H_5N_4Cl$** (180) Calcd: C, 46.55; H, 2.79; N, 31.02.
Found: C, 46.28; H, 2.59; N, 30.91.

1-(4-Isopropylphenyl)-1*H*-1,2,3,4-tetrazole (38e)



Light brown solid

M. P. (°C) : 68-69

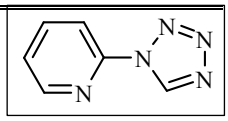
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2930, 2872, 1653, 1520, 1464, 1215, 1092, 1038, 998.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.29-1.33 (d, *J* = 6.95 Hz, 6 H, CH_3), 2.95-3.09 (m, 1H, CH), 7.42-7.46 (d, *J* = 8.69 Hz, 2H, ArH), 7.60-7.64 (d, *J*= 8.70 Hz, 2H, ArH), 8.97 (s, 1 H, tetrazole H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 23.6, 33.7, 121.1, 128.0, 131.5, 140.5, 151.1.

Elemental Analysis : **$C_{10}H_{12}N_4$** (188) Calcd: C, 63.81; H, 6.43; N, 29.77.
Found: C, 63.97; H, 6.29; N, 29.68.

1-(2-Pyridine)- 1*H*-1,2,3,4-tetrazole (38f)



White solid

M. P. (°C) : 127-128 (Lit.[11] 129-130)

IR ($CHCl_3$, cm^{-1}) : υ_{max} 1640, 1591, 1576, 1475, 1212, 1182, 1090, 1006.

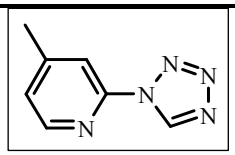
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.43-7.50 (m, 1H, ArH), 7.96-8.14 (m, 2H, ArH), 8.54-8.58 (m, 1H, ArH), 9.56 (s, 1H, tetrazole H).

^{13}C NMR : δ 114.2, 124.7, 139.7, 140.0, 148.9.

(50 MHz, $CDCl_3$)

Elemental Analysis : **$C_6H_5N_5$** (147) Calcd: C, 48.98; H, 3.43; N, 47.60.
Found: C, 48.70; H, 3.57; N, 47.71.

4-Methyl-2-(1*H*-1,2,3,4-tetrazol-1-yl)pyridine (38g)



White solid

M. P. (°C) : 130-131 (Lit.[11] 130)

IR ($CHCl_3$, cm^{-1}) : υ_{max} 2965, 2873, 1616, 1565, 1473, 1446, 1215, 1086, 1041, 996.

^{1}H NMR : δ 2.53 (s, 3H, CH_3), 7.25 (s, 1H, ArH), 7.93 (s, 1H, ArH),

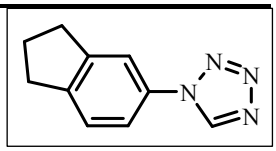
(200 MHz, $CDCl_3$) 8.38-8.40 (d, *J* = 5.02 Hz, 1H, ArH), 9.53 (s, 1H, tetrazole H).

^{13}C NMR : δ 21.2, 114.8, 125.7, 140.0, 146.8, 148.5, 151.7.

(50 MHz, $CDCl_3$)

Elemental Analysis : **$C_7H_7N_4$** (161) Calcd: C, 52.17; H, 4.38; N, 43.35.
Found: C, 51.98; H, 4.27; N, 43.13.

1-(2,3-Dihydro-1H-inden-6-yl)-1*H*-1,2,3,4-tetrazole (38h)



Light brownish solid

M. P. (°C) : 71-72

IR ($CHCl_3$, cm^{-1}) : υ_{max} 3019, 2940, 1653, 1497, 1481, 1457, 1215, 1101, 1029, 966.

^{1}H NMR : δ 2.10-2.25 (m, 2 H, CH_2), 2.96-3.06 (m, 4H, CH_2), 7.36-7.46 (m,

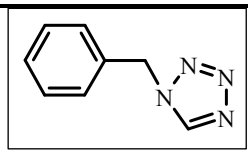
(200 MHz, $CDCl_3$) 2 H, ArH), 7.54 (s, 1H, ArH), 8.95 (s, 1H, tetrazole H).

^{13}C NMR : δ 25.4, 32.4, 32.7, 117.4, 119.2, 125.5, 131.9, 140.5, 146.5.

(50 MHz, $CDCl_3$)

Elemental Analysis : **$C_{10}H_{10}N_4$** (186) Calcd: C, 64.50; H, 5.41; N, 30.09.
Found: C, 64.15; H, 5.60; N, 30.23.

1-(Benzyl)-1*H*-1,2,3,4-tetrazole (38i)



White solid

M. P. (°C) : 59-60 (Lit.[11] 58-59)

IR ($CHCl_3$, cm^{-1}) : υ_{max} 2950, 2845, 1530, 1476, 1436, 1244, 1163, 1104.

^{1}H NMR : δ 5.60 (s, 2H, CH_2), 7.28-7.44 (m, 5H, ArH), 8.52 (s, 1H, tetrazole

(200 MHz, $CDCl_3$) H).

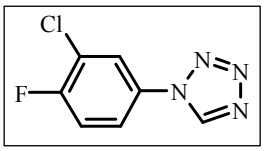
^{13}C NMR **:** δ 52.0, 128.2, 129.2, 129.3, 132.8, 142.4.

(50 MHz, $CDCl_3$)

Elemental Analysis **: $C_8H_8N_4$** (160) Calcd: C, 59.99; H, 5.03; N, 34.98.

Found: C, 59.67; H, 4.89; N, 34.67.

1-(3-Chloro-4-fluorophenyl)-1*H*-1,2,3,4-tetrazole (38j)



White solid

M. P. (°C) **:** 96-97

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 1654, 1505, 1460, 1525, 1215, 1088, 998.

^{1}H NMR **:** δ 7.35-7.40 (t, *J* = 8.58 Hz, 1H, ArH), 7.60-7.68 (m, 1H, ArH),

(200 MHz, $CDCl_3$) 7.83-7.87 (m, 1H, ArH), 8.99 (s, 1H, tetrazole H).

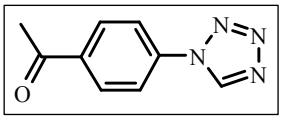
^{13}C NMR **:** δ 118.0, 118.2, 121.1, 121.2, 123.1, 123.3, 123.9, 130.2.

(50 MHz, $CDCl_3$) 140.5, 157.4, 159.9.

Elemental Analysis **: $C_7H_4ClFN_4$** (198) Calcd: C, 42.34; H, 2.03; N, 28.21.

Found: C, 42.18; H, 2.31; N, 28.32.

1-(4-Acetylphenyl)-1*H*-1,2,3,4-tetrazole (38k)



Faint yellow solid

M. P. (°C) **:** 175-176

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 3020, 1705, 1683, 1662, 1618, 1598, 1541, 1508, 1215, 1091, 956.

^{1}H NMR **:** δ 2.69 (s, 3H, CH_3), 7.86-7.91 (d, *J* = 8.86 & 2.03 Hz, 2H, ArH),

(200 MHz, $CDCl_3$) 8.18-8.22 (d, *J* = 8.86 & 2.03 Hz, 2H, ArH), 9.12 (s, 1H, tetrazole H).

^{13}C NMR **:** δ 26.4, 120.5, 130.0, 136.7, 137.5, 140.6, 196.1.

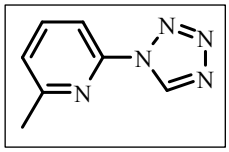
(CDCl3/DMSo-D_6,

50 MHz)

Elemental Analysis **: $C_9H_8N_4O$** (188) Calcd: C, 57.44; H, 4.28; N, 29.77.

Found: C, 57.13; H, 4.52; N, 29.52.

6-Methyl-2-(1*H*-1,2,3,4-tetrazol-1-yl)pyridine (38l)



White crystalline solid

M. P. (°C) : 106-107

IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 1612, 1573, 1541, 1506, 1479, 1217, 1087, 997.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.62 (s, 3H, CH_3), 7.28-7.31 (m, 1H, ArH), 7.81-7.91 (m, 2H, ArH), 9.55 (s, 1H, tetrazole H).

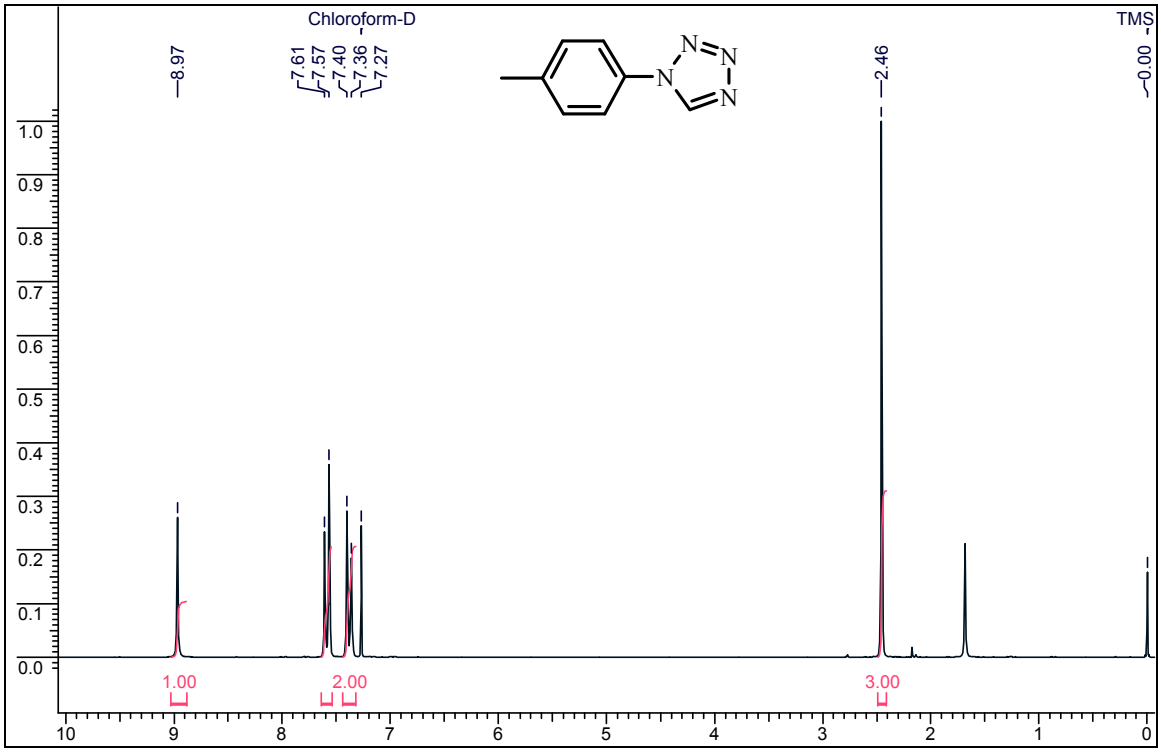
^{13}C NMR (50 MHz, $CDCl_3$) : δ 23.8, 110.9, 124.1, 139.6, 139.8, 145.9, 158.8.

Elemental Analysis : **$C_7H_7N_5$** (161) Calcd: C, 52.17; H, 4.38; N, 43.45.
Found: C, 52.33; H, 4.11; N, 43.72.

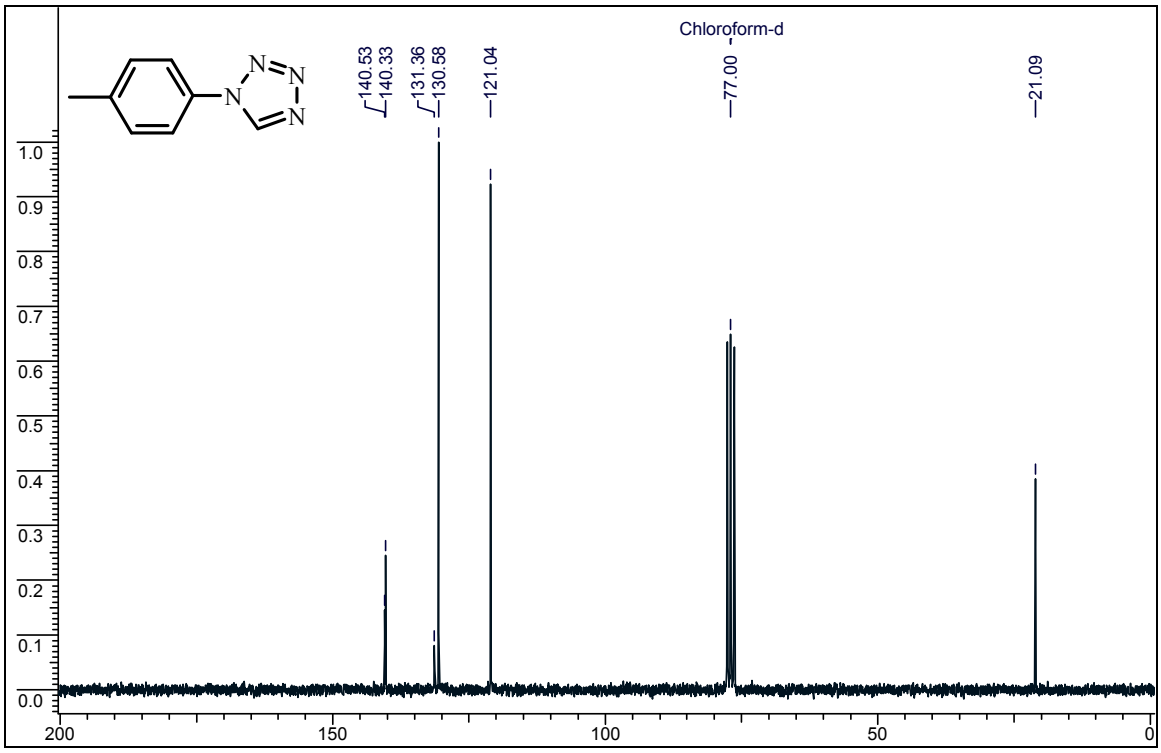
1.3.1.6 Spectra of some representative tetrazoles

Sr. No.	NMR spectra of **38**
1	^{1}H NMR and ^{13}C NMR spectra of **38b**
2	^{1}H NMR and ^{13}C NMR spectra of **38e**
3	^{1}H NMR and ^{13}C NMR spectra of **38g**
4	^{1}H NMR and ^{13}C NMR spectra of **38h**
5	^{1}H NMR and ^{13}C NMR spectra of **38i**
6	^{1}H NMR and ^{13}C NMR spectra of **38k**

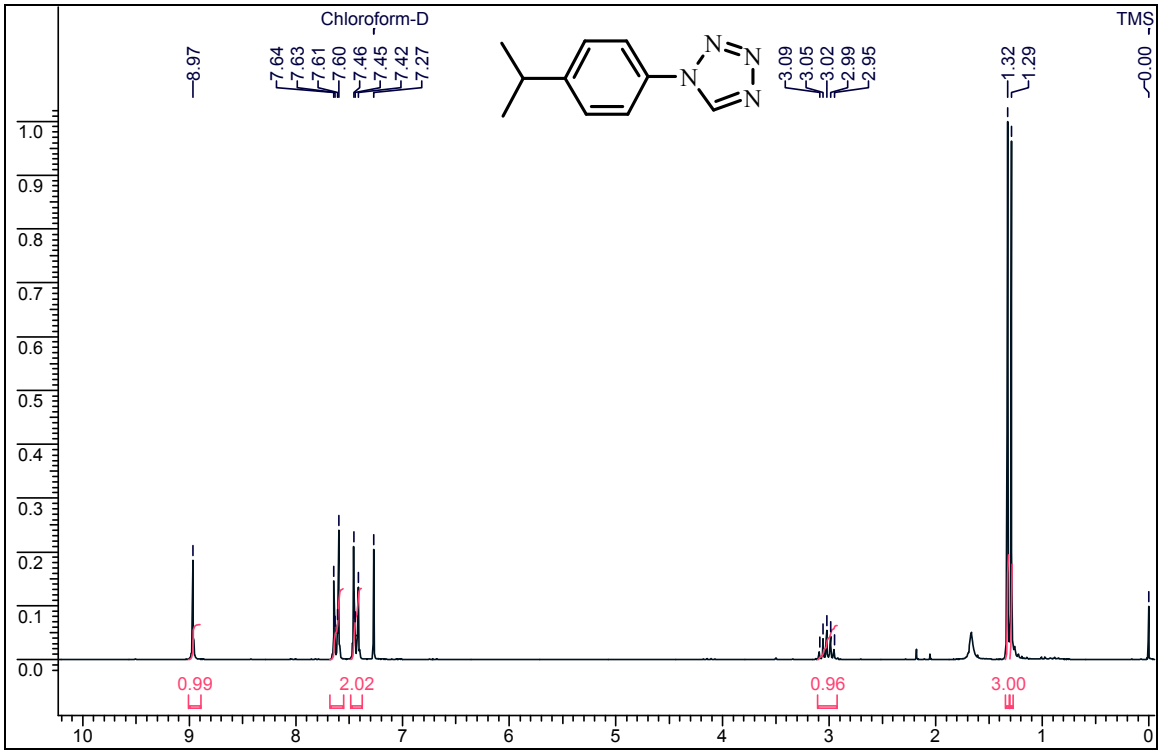
^{1}H NMR spectra of **38b**



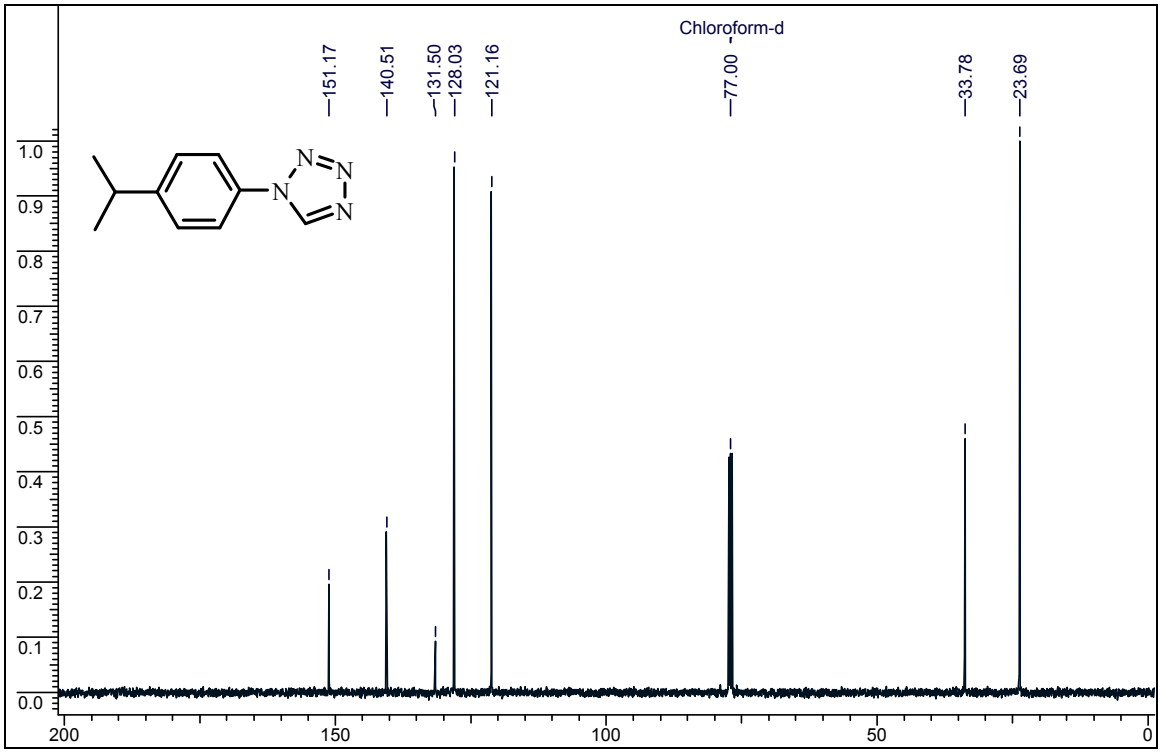
^{13}C NMR spectra of **38b**



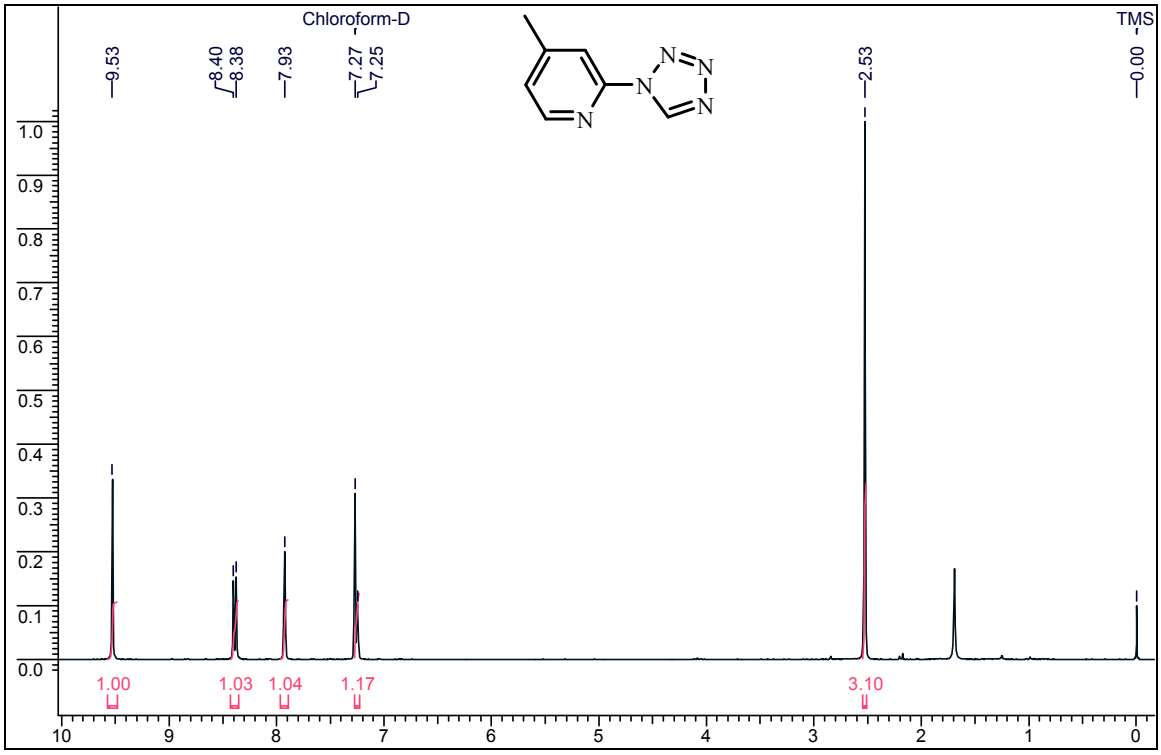
^{1}H NMR spectra of **38e**



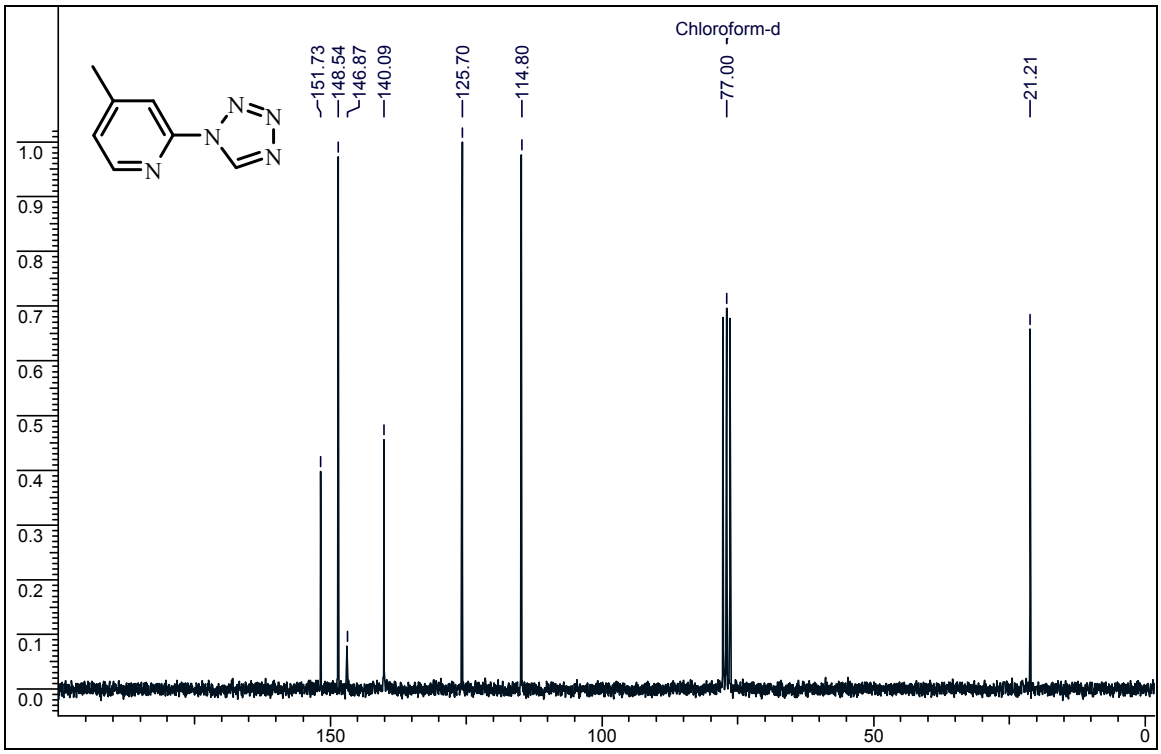
^{13}C NMR spectra of **38e**



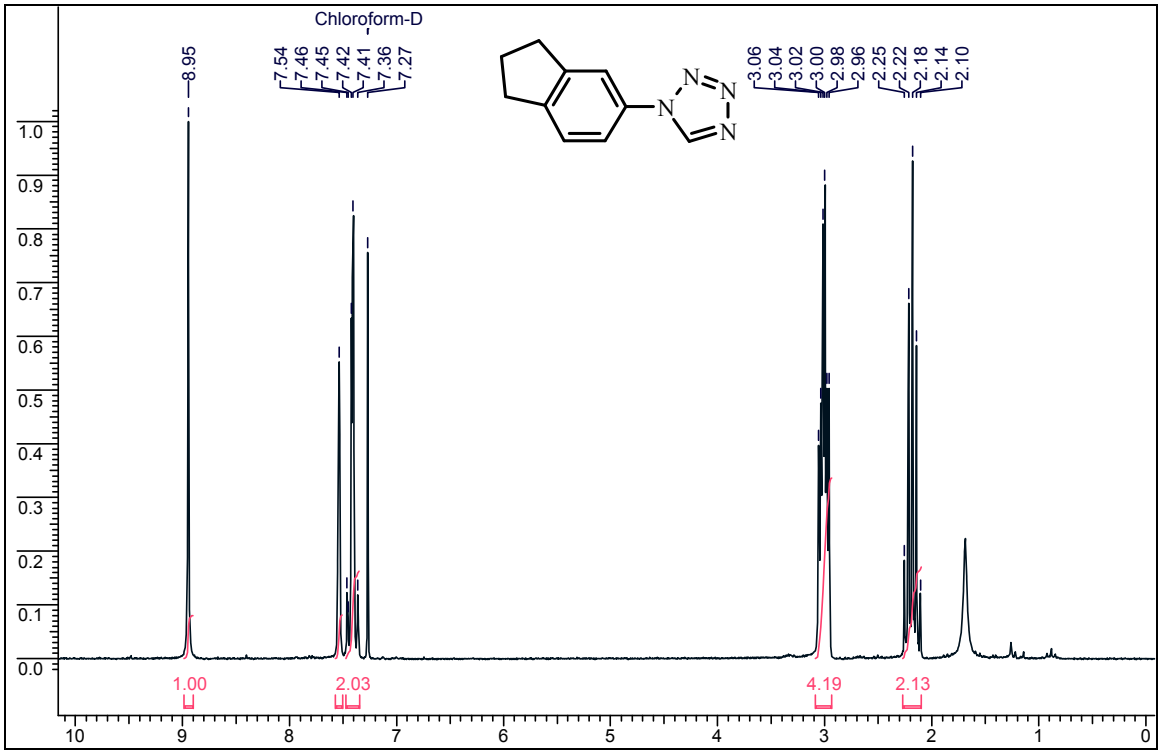
^{1}H NMR spectra of **38g**



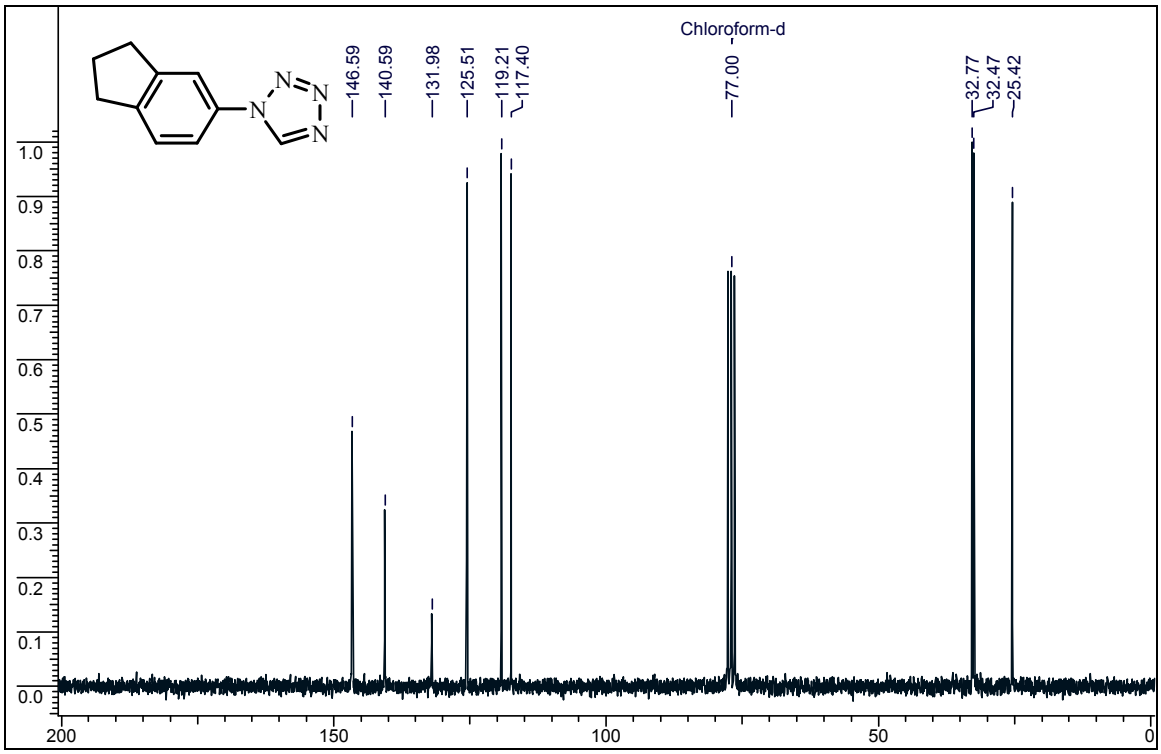
^{13}C NMR spectra of **38g**



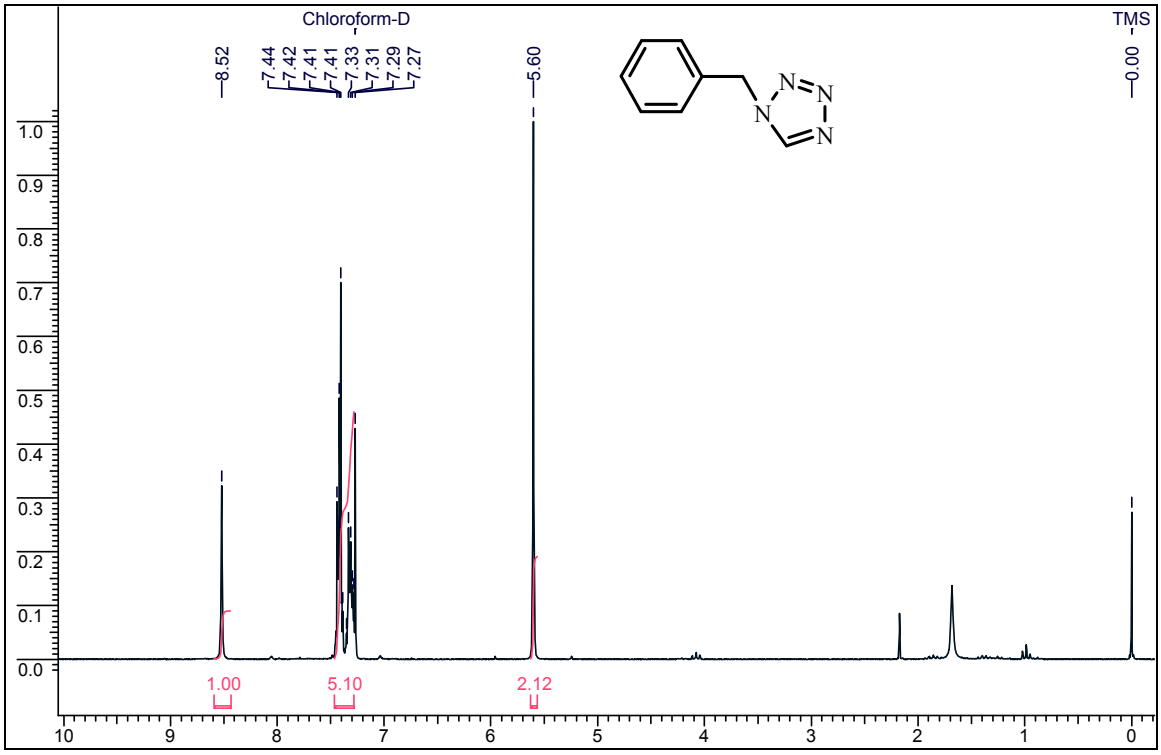
^{1}H NMR spectra of **38h**



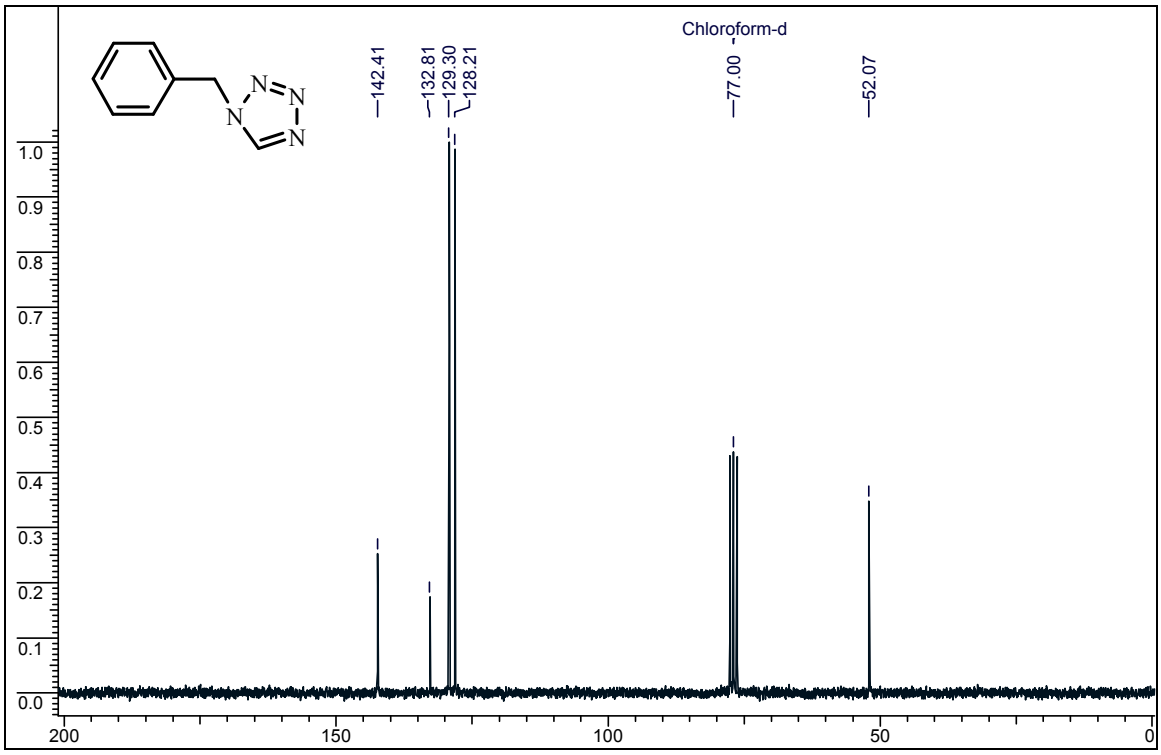
^{13}C NMR spectra of **38h**



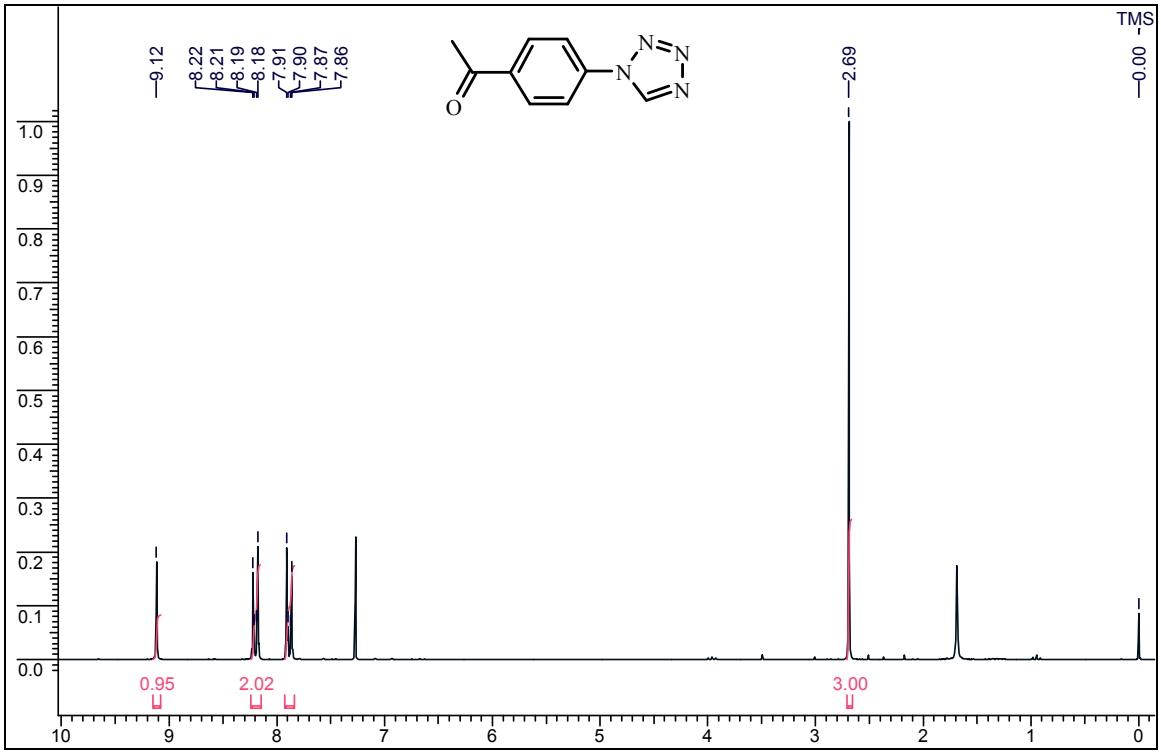
^{1}H NMR spectra of **38i**



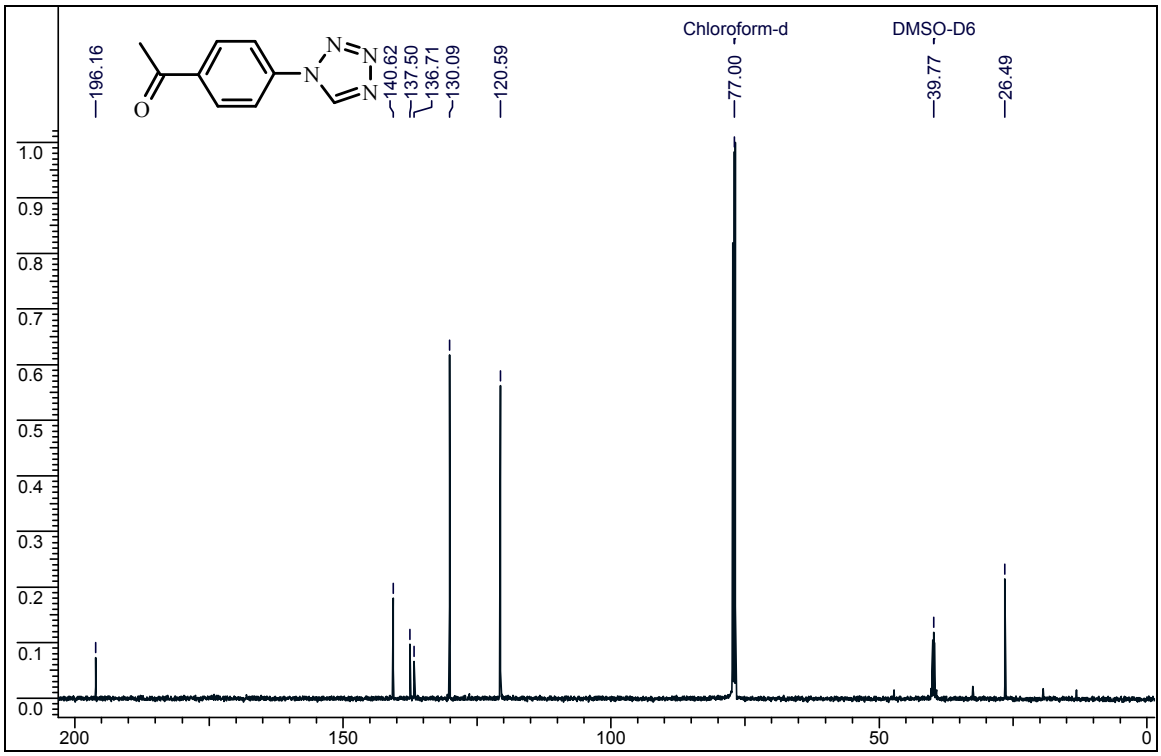
^{13}C NMR spectra of **38i**



^{1}H NMR spectra of **38k**



^{13}C NMR spectra of **38k**



1.3.1.7 References

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Chapter 1- Section C- Part II

Synthesis of 3,5,6-trisubstituted-1,2,4-triazines

1.3.2.1 Introduction

1,2,4-triazines are well known class among the heterocyclic compounds.[1] It has been associated with diverse pharmacological activities such as hypertension and inhibition of platelets,[2] antileukemic,[3] antiinflammatory[4] and potent neuroprotective agents.[5] The 1,2,4-triazine moiety is a structural element in antimalarial,[6] anticancer,[7] antifungal,[8] anticonvulsant,[9] antibacterial,[10] and antiviral[11] compounds. Certain compounds containing a 1,2,4-triazine nucleus have been reported to possess pesticidal,[12] neuropharmacological,[13] analgesic and antidepressant[14] properties. Some 1,2,4-triazine derivatives are used for the determination of metal ions and as dyes.[2] *N*-Methyl derivatives of 1,2,4-triazines are the naturally occurring antibiotics e.g. fervenulin (planomycin), toxoflavin (xanthothricin) and reumycin.

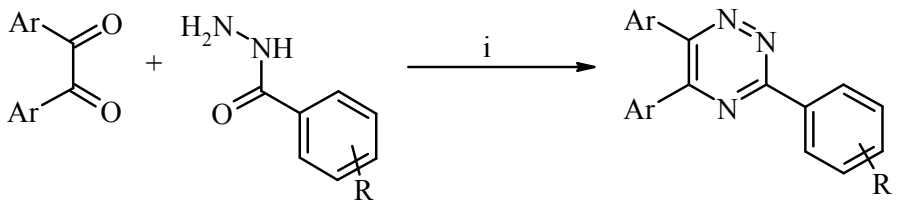
Many have been tested for the use in agrochemistry as well as ligands for metal ion complexation.[15] Furthermore 1,2,4-triazines have received considerable attention as heterocyclic azadienes in inverse electron demand Diels-Alder reaction with electron-rich dienophile.[16] Certain 3,5,6-trisubstituted 1,2,4-triazines have been used as analytical reagents.[17]

1.3.2.2 Review of literature

In view of the importance of triazines due to its pharmacological activities, its use in the field of agrochemistry and analytical chemistry, several methods for their preparation have been reported in the literature. On reviewing the literature, it was found that the most common methods involved the use of acid hydrazide and 1,2-diketone as a starting material using different approaches. In this section, we discuss some of the more significant work done previously.

P. V. Laakso et al approach (1957)[18]

P. V. Laakso et al. in 1957 reported the synthesis of 3,5,6-trisubstituted-1,2,4-triazines **41** from the reaction between benzil **39,** acid hydrazides **40** and ammonium acetate in acetic acid. The reaction mixture containing benzil, acid hydrazide and ammonium acetate was refluxed in acetic acid over a period of 0.5-6 h to afford triazine derivatives (**Scheme 12**).



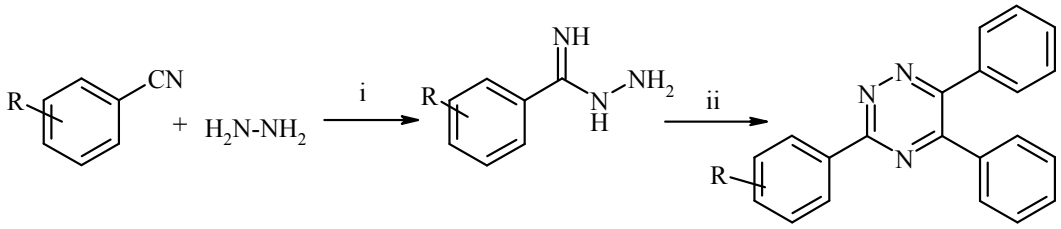
39 **40** **41**

Scheme 12. Reaction conditions **:** (i) NH_4OAc, AcOH, reflux, 0.5-6 h, 67-91%.

This method is limited to synthesis of 3,5,6-triaryl-1,2,4-triazines and did not report the synthesis of 1,2,4-triazines from aliphatic 1,2-diketone.

Francis H. Case et al. approach (1965)[19]

Francis H. Case et al. reported the synthesis of 3,5,6-trisubstituted-1,2,4-triazines **45** starting from nitrile **42**. Initially, hydrazidines **44** were prepared from nitrile **42** and hydrazine **43** in ethanol in 66-90% yield. Later on hydrazidine was condensed with benzil in ethanol over a period of 12 h to afford 1,2,4-triazine derivatives (**Scheme 13**).



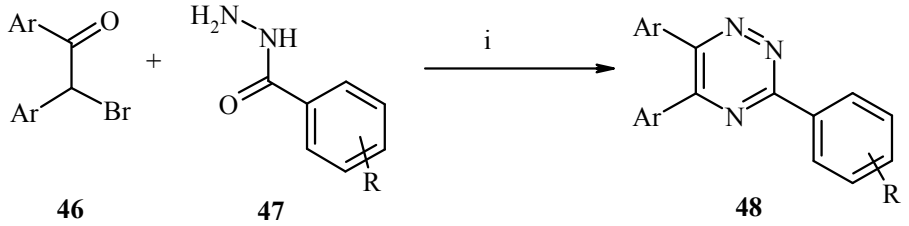
42 **43** **44** **45**

Scheme 13. Reaction conditions: (i) EtOH, rt, 2h, 66-90%; (ii) benzil, EtOH, rt,12 h, 45-84%.

However, this method is limited for synthesis of triaryl-1,2,4-triazine only and involves two step strategy.

V. R. Srinivasan et al. approach (1977)[20]

V. R. Srinivasan et al. reported the synthesis of 3,5,6-trisubstituted-1,2,4-triazines **48** by the reaction of α-bromo ketones **46** (1 mol) with acid hydrazides **47** (3 mol) in the presence of metal acetates such as sodium acetate (2 mol). The cyclization was carried out in acetic acid at reflux temperature over a period of 2 h (**Scheme 14**).



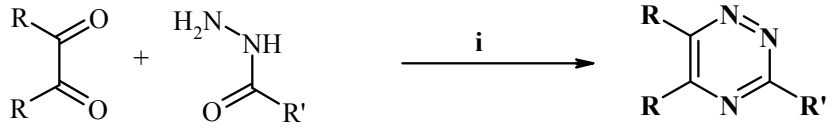
46 **47** **48**

Scheme 14. Reaction conditions : (i) NaOAc (2 mol), AcOH, reflux 2 h, 50-56%.

This process is suffering from disadvantages such as use of metal catalyst, lower yield of products and limited to the synthesis of triaryl-1,2,4-triazines only.

Shahnaz Rostamizadeh et al. approach (2002)[21]

Shahnaz Rostamizadeh et al. have reported the synthesis of 3,5,6-trisubstituted-1,2,4-triazines **51** by the condensation reaction of 1,2-diketones **49** with acid hydrazide **50** and ammonium acetate on the surface of silica gel in the presence of triethylamine under microwave irradiation (**Scheme 15**).

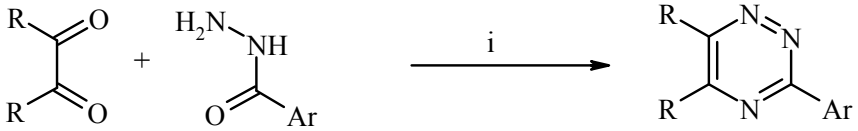


49 **50** **51**

Scheme 15. Reaction conditions : (i) NH_4OAc, SiO_2, MW, 61-93%.

Zhijian Zhao et al. approach (2003)[22]

Zhijian Zhao et al. reported the synthesis of 3,5,6-trisubstituted 1,2,4-triazines **54** from the reaction of aromatic 1,2-diketone **52** with heterocyclic acid hydrazide **53** and ammonium acetate in acetic acid under microwave irradiation at 180 °C (**Scheme 16**).



52 **53** **54**

Scheme 16. Reaction conditions **:** (i) NH_4OAc, AcOH, MW, 180 °C, 69-92%.

1.3.2.3 Present work

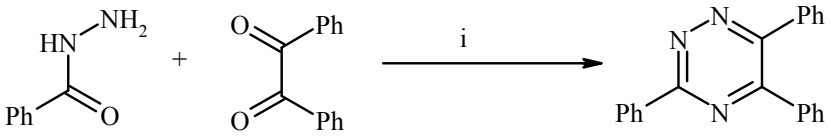
1.3.2.3.1 Objectives

In view of the importance of 1,2,4-triazines due to its pharmacological properties and its interesting reactivity, several methods were reported for its synthesis. Most of the method leading to synthesis of 1,2,4-triazines involves the use of solvent such as acetic acid, ethanol, dimethylformamide and dimethyl sulfoxide etc along with an acid catalyst and metal acetate. Most of the methods were carried out at reflux temperature in organic solvents for a longer period. Furthermore, some methods were carried out in microwave at much higher temperature.

The use of organic solvents gives rise to one of the most abundant sources of chemical waste in the fine chemicals and pharmaceutical industry and causes detrimental effects on the environment as well as human health. These processes also generate waste containing both catalyst and solvent, which have to be recovered, treated, and disposed of. Consequently, the methods that successfully minimize their use are the focus of much attention. So in continuation to use room temperature ionic liquids (RTILs) as useful reaction media for the synthesis of biologically active nitrogen containing heterocycles, we became interested for the synthesis of 3,5,6-trisubstituted-1,2,4-triazines from 1,2-diketone and aromatic acid hydrazide using IL as useful reaction media.

1.3.2.3.2 Results and discussion

When a mixture of benzoic hydrazide **55a**, benzil **56a** and ammonium acetate in IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) was heated at 100 °C, it afforded 3,5,6-triphenyl-1,2,4-triazine **57a** in 84% in 30 min (**Scheme 17**).



55a **56a** **57a**

Scheme 17. Reaction conditions : (i) [Hbim]BF_4, NH_4OAc, 100 °C, 30 min, 84%.

Initially, a set of experiment was done to establish optimum reaction conditions. For this, we chose the reaction of benzoic hydrazide **55a**, benzil **56a** and ammonium acetate in the IL, [Hbim]BF_4 as model reaction. We initially chose IL [Hbim]BF_4 for

optimizing the reaction temperature. When we carried out the reaction at room temperature even for a period of 12 h, reaction did not proceed to afford the expected product. Then, we carried out the reaction at higher temperatures such as 50 and 80 °C. There was a progress for the reaction at 50 °C, but it did not proceed beyond 53 % even after longer period (12 h), while at 80 °C reaction proceeded to completion but with a longer reaction time (12 h). Keeping in mind the effect of temperature, we carried out the model reaction at 100 °C, where it afforded 3,5,6-triphenyl-1,2,4-triazine in 84% yield in just 30 min. The reaction at further higher temperature such as 110 °C did not shown any further improvement. Thus, optimum results were obtained at 100 °C which was chosen for conducting further reactions. The progress of the reaction was monitored by TLC. The product was fully characterized by mp, IR, ^{1}H and ^{13}C NMR and elemental analysis. The ^{13}C NMR spectra of 3,5,6-triphenyl-1,2,4-triazine show peak at δ 155.2, 155.3 and 161.4 ppm corresponding to carbon of triazine ring confirming the structure.

Ionic liquids based on 1,3-di-*n*-butylimidazoliun salts [bbim]X and 1-*n*-butyl imidazolium salts [Hbim]X with anions such as BF_4, Br, Cl and ClO_4 were screened for the model reaction. The reaction in different ILs was carried out at 100 °C. When the reactions were carried out in different ILs of 1,3-di-*n*-butylimidazoliun series, it afforded the product in poor yields. Then, we carried out the reaction in different ILs of 1-*n*-butyl imidazolium series where it produced the compounds in enhanced yields, and the reports summarized in **Table 3**.

Table 3. Synthesis of 3,5,6-triphenyl-1,2,4-triazine **57a** in [Hbim]X

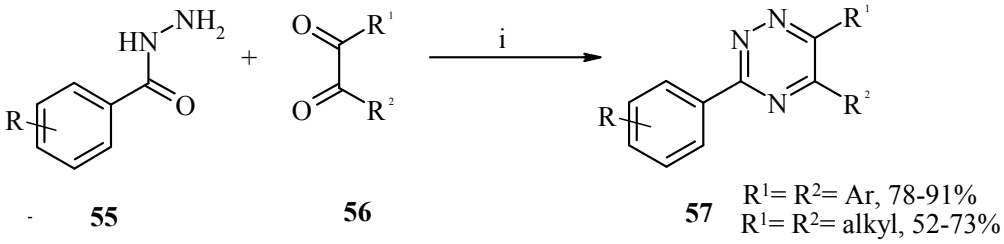
ILs	pK_a [a]	-NH proton δ ppm	Time (min) [b]	Yield (%) [c]
[Hbim]ClO_4	-11	11.83	360	67
[Hbim]Br	-9	12.17	100	77
[Hbim]Cl	-7	12.22	70	78
[Hbim]BF_4	0.5	14.59	30	84

[a] The pK_a values of the parent acid of the anions
[b] Time required for complete conversion of the starting material
[c] Isolated yield after column chromatography

It is evident from **Table 3**, the best results were obtained using $[Hbim]BF_4$ as reaction media in terms of time for complete conversion and yields. The reaction in the IL, $[Hbim]BF_4$ was completed successfully in just 30 min and afforded the 3,5,6-triphenyl-1,2,4-triazine **57a** in excellent yield of 84%.

The efficacy of the ILs to promote this reaction was correlated with basicity of the anions and chemical shifts of the –NH proton of the ILs. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (**Table 3**). This correlation was also evident when the yield of **57a** was compared with –NH proton chemical shifts of the ILs indicative of the Brønsted acidities of the [Hbim] ILs (**Table 3**). The yield of **57a** increases progressively with increasing Brønsted acicity of the ILs as indicated by increasing downfield shift of the –NH protons. The IL, $[Hbim]BF_4$ has promoted this heterocyclization reaction by virtue of its maximum inherent Brønsted acidity conferred by the most acidic –NH hydrogen [chemical shift δ ppm = 14.6].

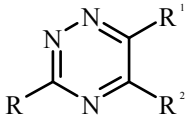
In order to investigate the scope and generality of this method, several benzoic hydrazides having different substituents were condensed with various aromatic 1,2-diketones and ammonium acetate using IL, $[Hbim]BF_4$ as a reaction medium as well as promoter at room temperature to afford a series of triazine derivatives (**Scheme 18**).



Scheme 18. Reaction conditions**:** (i) $[Hbim]BF_4$, NH_4OAc, 100 °C, 10-60 min.

It was found that the process tolerates both electron donating and electron withdrawing substituents on benzoic hydrazides to afford a series of 3,5,6-triaryl-1,2,4-triazines in excellent yields (82-91%) in short reaction times (15-60 min). The results are summarized in **Table 4**.

Table 4. Synthesis of 3,5,6-triaryl-1, 2,4-triazine **57a-m**

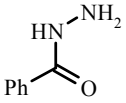
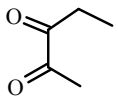
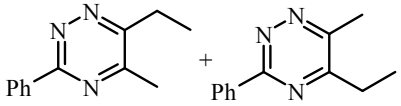
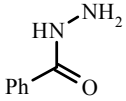
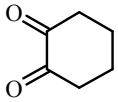
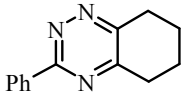
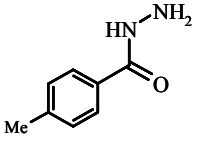
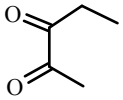
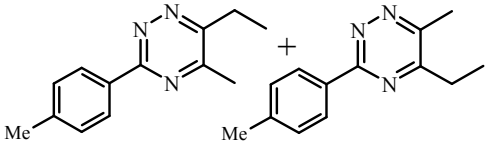
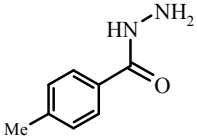
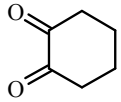
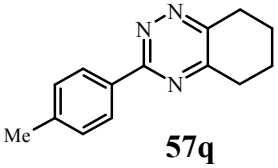
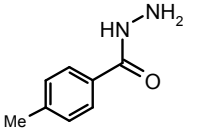
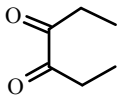
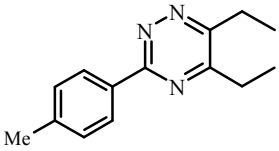


Entry	Acid hydrazide **55** R	1,2-Diketone **56** R^1	R^2	Triazine **57**	Time (min)	Yield[a] (%)
1	C_6H_5	C_6H_5	C_6H_5	**57a**	30	84
2	(4-Me)C_6H_4	C_6H_5	C_6H_5	**57b**	35	82
3	(3-OMe)C_6H_4	C_6H_5	C_6H_5	**57c**	20	77
4	(2-Cl)C_6H_4	C_6H_5	C_6H_5	**57d**	50	83
5	(4-Cl)C_6H_4	C_6H_5	C_6H_5	**57e**	45	90
6	C_6H_5	(4-Me)C_6H_4	(4-Me)C_6H_4	**57f**	20	88
7	(4-Me)C_6H_4	(4-Me)C_6H_4	(4-Me)C_6H_4	**57g**	15	85
8	(3-OMe)C_6H_4	(4-Me)C_6H_4	(4-Me)C_6H_4	**57h**	45	80
9	(4-NH_2)C_6H_4	(4-Me)C_6H_4	(4-Me)C_6H_4	**57i**	20	90
10	(2-Cl)C_6H_4	(4-Me)C_6H_4	(4-Me)C_6H_4	**57j**	60	81
11	(4-Cl)C_6H_4	(4-Me)C_6H_4	(4-Me)C_6H_4	**57k**	55	91
12	C_6H_5	(4-OMe)C_6H_4	(4-OMe)C_6H_4	**57l**	25	86
13	(4-Me)C_6H_4	(4-OMe)C_6H_4	(4-OMe)C_6H_4	**57m**	20	78

[a] : Isolated yields after column chromatography

The methodology is successfully extended for the synthesis of 3-aryl-5,6-dialkyl-1,2,4-triazines from aliphatic 1,2-diektone. Symmetrical as well unsymmetrical aliphatic 1,2-diketones were condensed with benzoic hydrazide and ammonium acetate in [Hbim]BF_4 to afford 3-aryl-5,6-dialkyl-1,2,4-triazines in 52-73% in short reaction times (10-40 min) and results are summarized in **Table 5**.

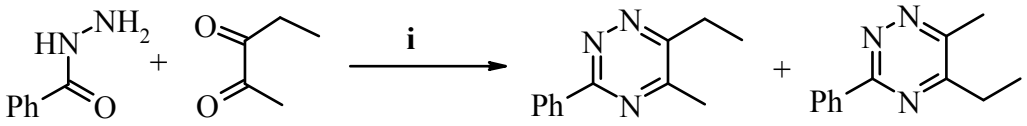
Table 5. Synthesis of 3-aryl-5,6-dialkyl-1,2,4-triazines **57n-r**

Entry	Acid hydrazide **55**	Aliphatic 1,2-diketone **56**	Triazine (**57**)	Time (min)	Yield[a] (%)
1			 **57n** **57n'**	35	73 (40:60)
2			 **57o**	25	61
3			 **57p** **57p'**	40	56 (58:42)[b]
4			 **57q**	10	52
5			 **57r**	15	68

[a]: Isolated yield after column chromatography

[b]: Regioisomers separated by column chromatography

However, during our studies on the synthesis of 3-aryl-5,6-dialkyl-1,2,4-triazine from unsymmetrical aliphatic 1,2-diketone, we obtained the mixture of two regioisomers which were separated by column chromatography and characterized by ^{1}H NMR. For example, a reaction between benzoic hydrazide **55a** and 2,3-pentanedione **56d** resulted in two regioisomers **57n** and **57n'**. In the case of regioisomers **57n** the methyl group of 1,2,4-triazine ring at 5 position appeared as a singlet at δ 2.61 ppm while for the regioisomers **57n'** the methyl group of 1,2,4-triazine ring at 6 position appeared as singlet at downfield δ 2.71 ppm due to deshielding effect of two adjacent nitrogen atoms. Furthermore in the case of regioisomers **57n** the quartet of 2H of ethyl group at 6-position appeared downfield at δ 2.97-3.08 ppm as compared to that of the regioisomers **57n'** which appeared at δ 2.48-2.91 ppm (**Scheme 19**).



55a **56a** **57n** **57n'**

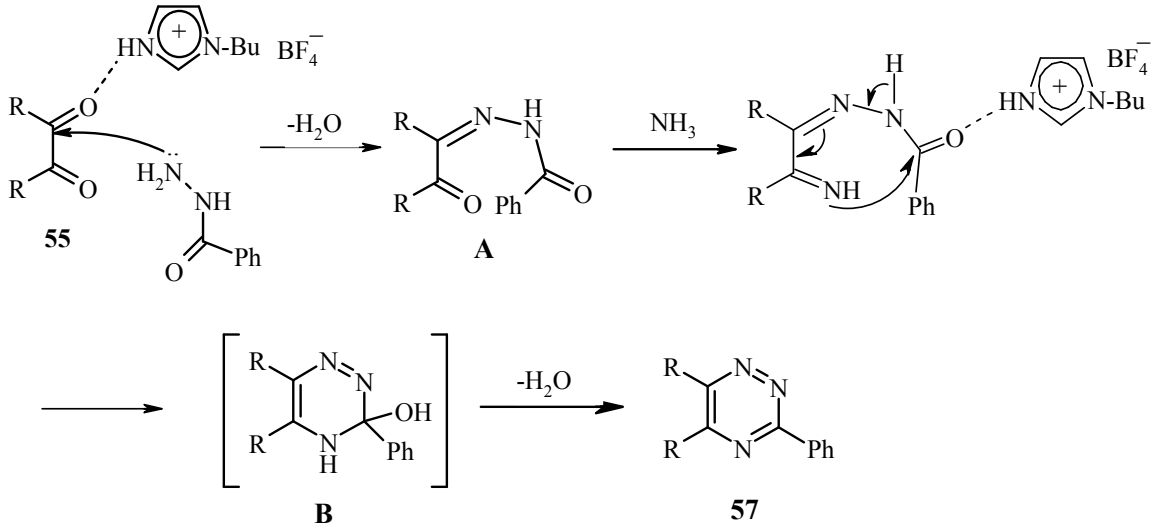
Scheme 19. Reaction conditions**:** (i) [Hbim]BF_4, NH_4OAc, 100 °C, 35 min, 73% (4:6).

All the compounds were well characterized by melting point, IR, ^{1}H and ^{13}C NMR spectral and elemental analyses. For the known compounds, the values were in agreement with those reported in literature.

It is important to note that in all cases, 1,2,4-triazines precipitated out easily on addition of water to the reaction mixture. The precipitated product was filtered and dried. This crude product, thus isolated, was pure enough (single spot on TLC) for all practical purposes. The aqueous layer containing IL was subjected to distillation at 80 ^{O}C under reduced pressure (10 mm Hg) for 4 h to remove water leaving behind the IL in almost complete recovery. The IL, thus recovered was further reused three times for the typical reaction of benzoic hydrazide, benzil and ammonium acetate to afford triazine **57a** without any significant loss in yield and purity.

1.3.2.3.3 Plausible Mechanism

The role of IL for promoting this reaction may be postulated in terms of its most acidic -NH proton of the imidazolium cation, capable of hydrogen bonding with the carbonyl oxygen atom thereby increasing the electrophilicity of carbon center which reacts with the nucleophilic nitrogen of the aryl hydrazide to form α-ketoaroylhydrazone **A** in first step followed by cyclized intermediate **B** in second step after the reaction with ammonium acetate which may be transformed to the stable product **57** by eliminating a water molecule (**Scheme 20**).



Scheme 20. Plausible mechanism

1.3.2.4 Conclusion

In conclusion, we have developed a one-pot three component method for the synthesis of a diverse array of 3,5,6-trisubstituted-1,2,4-triazines from aromatic acid hydrazide, 1,2-diketone and ammonium acetate in excellent isolated yields in short reaction times using the Brønsted acidic ionic liquid, [Hbim]BF_4 as a reaction medium as well as promoter. The methodology was general for the synthesis of 3,5,6-triaryl-1,2,4-triazines as well as 3-aryl-5,6-dialkyl-1,2,4-triazines. The easy work up procedures, the absence of any volatile solvent, either for reaction or during work up, the absence of any catalyst and recyclability of the IL used for the reaction as medium makes the method environment friendly and amenable for scale up.

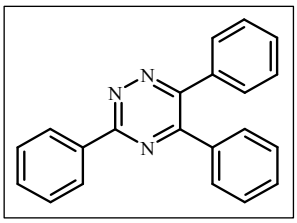
1.3.2.5 Experimental

1.3.2.5.1 General procedure for the synthesis of 3,5,6-trisubstituted-1, 2,4-triazines

A mixture of acid hydrazide **55** (1 mmol), 1,2-diketone **56** (1 mmol) and ammonium acetate (5 equiv) in 1-*n*-butylimidazolium tetrafluoroborate, [Hbim]BF_4 (2 mL) was heated with stirring at 100 °C for the appropriate time as mentioned in Tables 4 and 5. The completion of reaction was monitored by TLC. On completion of reaction, the reaction mixture was diluted with water (15 mL). The solid 3,5,6-trisubstituted-1,2,4-triazines, which separated out, was filtered, washed with water and dried. The crude products, thus isolated, were pure (single spot on TLC). They were subjected to further purification by chromatography through a column of silica gel using ethyl acetate: petroleum ether as eluent mixture to yield the desired 3,5,6-trisubstituted-1,2,4-triazines **57** and all the compounds were fully characterized. The aqueous layer consisting of the IL was subjected to distillation (80 °C at 10 mmHg) for 4 h to remove water, leaving behind the IL (recovery 98%), which was recycled.

1.3.2.5.2 Characterization data for triazines (57a-q)

3,5,6-Triphenyl-1,2,4-triazine (57a)



Yellow solid

M. P. (°C) : 146-147 (Lit.[20] 148)

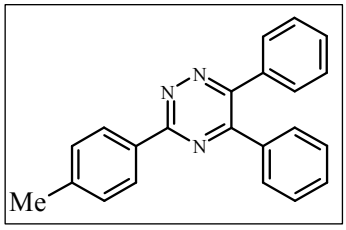
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 2928, 1602, 1504, 1445, 866, 755.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.32-7.46 (m, 6H, ArH), 7.54-7.69 (m, 7H, ArH), 8.65-8.69 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 128.2, 128.3, 128.4, 128.6, 129.3, 129.7, 130.5, 131.3, 134.7, 135.5, 135.8, 155.2, 155.3, 161.1.

Elemental Analysis : **$C_{21}H_{15}N_3$** (309) Calcd: C, 81.53, H, 4.89, N, 13.58.
Found: C, 81.67, H, 4.78, N, 13.48.

5,6-Diphenyl-3-(*p*-tolyl)-1,2,4-triazine (57b)



Yellow crystalline solid

M. P. (°C) : 138-139 (Lit.[20] 138)

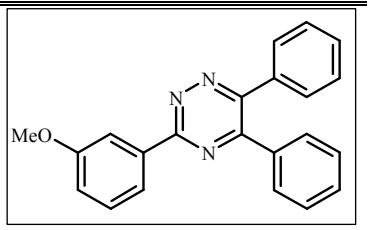
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3017, 2925, 2855, 1608, 1579, 1504, 1446, 816, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.46 (s, 3H, CH_3), 7.32-7.45 (m, 8H, ArH), 7.59-7.69 (m, 4H, ArH), 8.54-8.58 (d, *J* = 8.24 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.3, 128.0, 128.1, 128.2, 129.1, 129.3, 129.5, 130.3, 131.7, 135.3, 135.7, 141.7, 154.9, 155.1, 161.0.

Elemental Analysis : **$C_{22}H_{17}N_3$** (323) Calcd: C, 81.71, H, 5.30, N, 12.99.
Found: C, 81.63, H, 5.42, N, 13.08.

3-(3-Methoxyphenyl)-5,6-diphenyl-1,2,4-triazine (57c)



Yellow crystalline solid

M. P. (°C) : 130-131 (Lit.[18] 129-130)

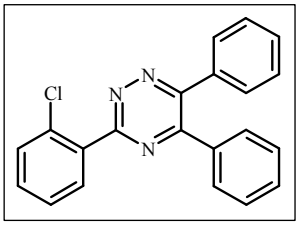
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3019, 2945, 1600, 1585, 1494, 1215, 822, 763.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.93 (s, 3H, OCH_3), 7.11-7.14 (t, *J* = 7.85 Hz, 2H, ArH), 7.33-7.51 (m, 7H, ArH), 7.61-7.70 (m, 3H, ArH), 8.25-8.29 (d, *J* = 7.48 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.3, 112.8, 117.9, 120.8, 128.3, 128.4, 129.3, 129.4, 129.7, 130.5, 135.4, 135.8, 136.0, 155.4, 160.0, 160.9.

Elemental Analysis : **$C_{22}H_{17}N_3O$** (339) Calcd: C, 77.86, H, 5.05, N, 12.38.
Found: C, 77.72, H, 5.18, N, 12.47.

3-(2-Chlorophenyl)-5,6-diphenyl-1,2,4-triazine (57d):



Yellow amorphous solid

M. P. (°C) : 169-170

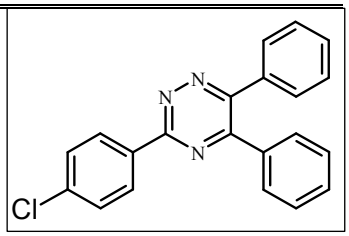
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3019, 2935, 2852, 1596, 1596, 1446, 759.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.29-7.47 (m, 8H, ArH), 7.53-7.69 (m, 5H, ArH), 8.04-8.08 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 126.8, 128.4, 128.5, 129.4, 129.6, 129.8, 130.7, 130.8, 131.1, 132.0, 133.3, 134.5, 135.1, 135.3, 154.9, 155.1, 162.3.

Elemental Analysis : **$C_{21}H_{14}ClN_3$** (343) Calcd: C, 73.36, H, 4.10, N, 12.22.
Found: C, 73.10, H, 4.25, N, 12.29.

3-(4-Chlorophenyl)-5,6-diphenyl-1,2,4-triazine (57e):



Yellow solid

M. P. (°C) : 135-136 (Lit.[18]134-135)

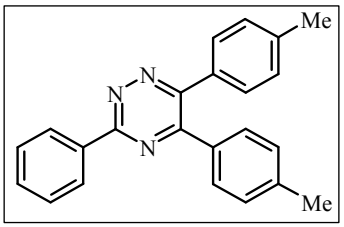
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3012, 2927, 1597, 1580, 1491, 1445.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.32-7.46 (m, 6H, ArH), 7.49-7.53 (d, *J* = 8.60 Hz, 2H, ArH), 7.59-7.68 (m, 4H, ArH), 8.58-8.62 (d, *J* = 8.60 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 128.4, 128.5, 129.0, 129.3, 129.5, 129.7, 130.7, 133.2, 135.3, 135.6, 137.7, 155.4, 155.5, 160.2.

Elemental Analysis : **$C_{21}H_{14}ClN_3$** (343) Calcd: C, 73.36, H, 4.10, N, 12.22.
Found: C, 73.23, H, 4.21, N, 12.34.

3-Phenyl-5,6-di-(*p*-tolyl)-1,2,4-triazine (57f):



Yellow amorphous solid

M. P. (°C) : 167-168

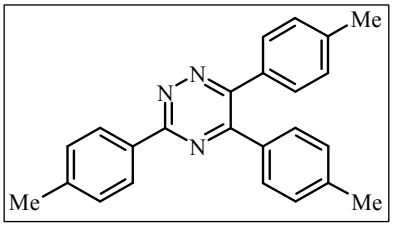
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 2924, 1609, 1596, 1493, 1443, 822, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.39 (s, 6H, CH_3), 7.16-7.21 (t, *J* = 6.70 Hz, 4H, ArH)), 7.52-7.61 (m, 7H, ArH), 8.64-8.67 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.2, 21.3, 128.1, 128.6, 129.0, 129.1, 129.6, 131.2, 132.7, 133.0, 134.8, 139.4, 140.9, 155.1, 155.2, 160.7.

Elemental Analysis : **$C_{23}H_{19}N_3$** (337) Calcd: C, 81.87, H, 5.68, N, 12.45.
Found: C, 81.75, H, 5.78, N, 12.39.

3,5,6-tri-(*p*-tolyl)-1,2,4-triazine (57g)



Yellow amorphous solid

M. P. (°C) : 165-166

IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 2923, 1611, 1495, 821, 758.

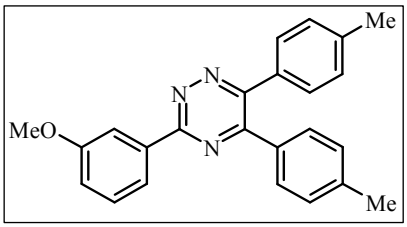
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.38 (s, 6H, CH_3), 2.45 (s, 3H, CH_3), 7.15-7.19 (t, *J* = 6.44 Hz, 4H, ArH), 7.33-7.36 (d, *J* = 8.10 Hz, 2H, ArH), 7.60-7.51 (dd, *J* =

8.07 Hz, 4H, ArH), 8.53-8.56 (d, *J* = 8.10 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 21.2, 21.4, 128.0, 129.0, 129.1, 129.3, 129.6, 132.0, 132.7, 133.0, 139.3, 140.8, 141.5, 154.9, 155.0, 160.8.

Elemental Analysis : **$C_{24}H_{21}N_3$** (351) Calcd: C, 82.02; H, 6.02; N, 11.96.
Found: C, 82.22, H, 5.87, N, 12.02.

3-(3-Methoxyphenyl)-5,6-di-(*p*-tolyl)-1,2,4-triazine(57h)



Yellow solid;

M. P. (°C) : 98-100

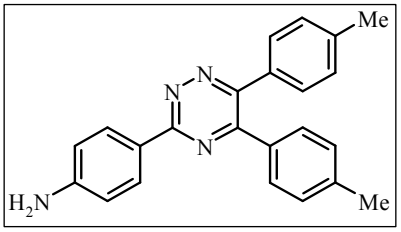
IR (CHCl$_3$, cm^{-1}) : υ_{max} 3015, 2923, 2837, 1609, 1585, 1496, 1453, 1215, 821, 758.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.38 (s, 6H, CH_3), 3.92 (s, 3H, OCH_3), 7.08-7.12 (m, 1H, ArH), 7.16-7.20 (m, 4H, ArH), 7.43-7.48 (t, *J* = 7.85 Hz, 1H), 7.52-7.61 (m, 4H, ArH), 8.22-8.26 (d, *J* = 8.43 Hz, 2H).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 21.3, 21.3, 55.3, 112.6, 117.7, 120.7, 129.1, 129.2, 129.7, 132.7, 133.0, 136.2, 139.5, 141.0, 155.1, 155.2, 159.9, 160.6.

Elemental Analysis : **$C_{24}H_{21}N_3O$** (367) Calcd: C, 78.45, H, 5.76, N, 11.44.
Found: C, 78.59, H, 5.43, N, 11.69.

3-(4-Aminophenyl)-5,6-di-(*p*-tolyl)-1,2,4-triazine (57i)



Dark yellow solid

M. P. (°C) : 201-202

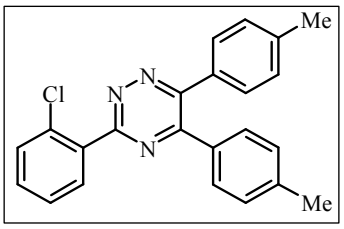
IR (CHCl$_3$, cm^{-1}) : υ_{max} 3487, 3400, 3017, 2923, 2862, 1606, 1577, 1519, 1497, 821, 756.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.35-2.36 (d, 6H, CH_3), 3.92 (bs, 2H, NH_2), 6.73-6.77 (d, *J* = 8.72 Hz, 2H, ArH), 7.11-7.18 9m, 4H, ArH), 7.47-7.57 (m, 4H, ArH), 8.43-8.47 (d, *J* = 8.72 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 21.2, 21.3, 114.6, 124.5, 129.0, 129.0, 129.6, 129.8, 133.01, 139.1, 140.6, 149.7, 154.1, 154.9, 160.9.

Elemental Analysis : **$C_{23}H_{20}N_4$** (352) Calcd: C, 78.38, H, 5.72, N, 15.90.
Found: C, 78.50, H, 5.51, N, 16.01.

3-(2-Chlorophenyl)-5,6-di-(*p*-tolyl)-1,2,4-triazine (57j)



Yellow solid

M. P. (°C) **:**150-151

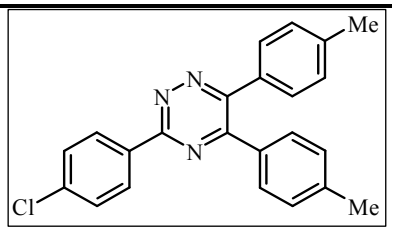
IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 3019, 2925, 2862, 1610, 1496, 1434, 822, 763.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 2.37-2.41 (d, 6H, CH_3), 7.14-7.24 (m, 4 H, ArH), 7.42-7.47 (m, 2H, ArH), 7.56-7.61 (m, 5H, ArH), 8.02-8.07 (m, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 21.2, 21.3, 126.7, 129.1, 129.2, 129.3, 129.8, 130.7, 130.9, 132.0, 132.5, 132.7, 133.4, 134.8, 139.7, 141.1, 154.7, 154.9, 162.1.

Elemental Analysis **: $C_{23}H_{18}ClN_3$** (371) Calcd: C, 74.29, H, 4.88, N, 11.30.
Found: C, 74.35, H, 4.81, N, 11.19.

3-(4-Chlorophenyl)-5,6-di-(*p*-tolyl)-1,2,4-triazine (57k)



Yellow solid;

M. P. (°C) :169-171

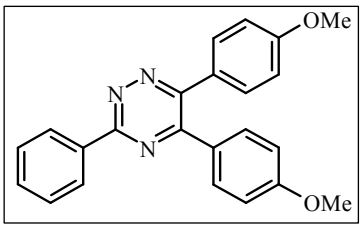
IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 3018, 2922, 2857, 1609, 1596, 1575, 1487, 820, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 2.40 (s, 6H, CH_3), 7.16-7.22 (m, 4H, ArH), 7.49-7.61 (m, 6H, ArH), 8.58-8.62 (d, *J* = 8.60 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 21.2, 21.3, 128.9, 129.1, 129.2, 129.4, 129.6, 132.7, 132.9, 133.4, 137.5, 139.6, 141.1, 155.2, 155.4, 160.0.

Elemental Analysis **: $C_{23}H_{18}ClN_3$** (371) Calcd: C, 74.29, H, 4.88, N, 11.30.
Found: C, 74.11, H, 4.98, N, 11.09.

5,6-bis-(4-Methoxyphenyl)-3-phenyl-1,2,4-triazine (57l)



Yellow amorphous solid;

M. P. (°C) **:**165-166

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 3018, 2967, 2840, 1607, 1518, 1489, 1465, 1216, 835, 758.

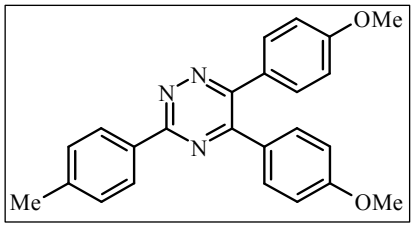
^{1}H NMR **:** δ 3.84-3.85 (d, 6H, ArH), 6.85-6.95 (m, 4H, ArH), 7.52-7.73 (m,

($CDCl_3$, 200 MHz) 7H, ArH), 8.62-8.67 (m, 2H, ArH);

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.1, 55.2, 113.8, 113.9, 128.0, 128.6, 130.6, 131.1, 131.3, 134.9, 154.4, 154.6, 160.4, 160.5, 161.6.

Elemental Analysis : **$C_{23}H_{19}N_3O_2$** (369) Calcd: C, 74.78; H, 5.18; N, 11.37.
Found: C, 74.52, H, 5.37, N, 11.51.

5,6-bis-(4-methoxyphenyl)-3-(*p*-tolyl)-1,2,4-triazine (57m)



Yellow crystalline solid

M. P. (°C) : 149-150

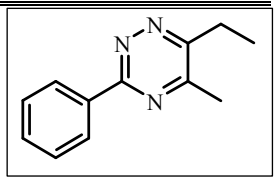
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3006, 2935, 2838, 1607, 1577, 1518, 1488, 1460, 1215, 833, 755.

^{1}H NMR ($CDCl_3$, 50 MHz) : δ 2.44 (s, 3H, CH_3), 3.82-3.83 (d, 6H, OCH_3), 6.85-6.93 (m, 4H, ArH), 7.32-7.36 (d, *J* =8.19 Hz, 2H, ArH), 7.56-7.70 (m, 4H, ArH), 8.50-8.54 (d, *J* = 8.19 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 200 MHz) : δ 21.4, 55.0, 55.1, 113.7, 113.8, 127.9, 128.0, 129.3, 130.5 131.3, 132.1, 141.4, 154.2, 160.4, 161.4.

Elemental Analysis : **$C_{24}H_{21}N_3O_2$** (383) Calcd: C, 75.18, H, 5.52, N, 10.96.
Found: C, 74.98, H, 5.67, N, 11.09.

6-Ethyl-5-methyl-3-phenyl-1,2,4-triazine (57n)



White needle crystals

M. P. (°C) : 102-103

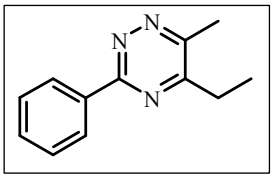
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2928, 2845, 1611, 1542, 1487, 742.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.39-1.47 (t, *J* = 7.48 Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.97-3.08 (q, *J* = 7.48 Hz, 2H, CH_2), 7.49-7.53 (m, 3H, ArH), 8.49-8.54 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.6, 21.2, 25.9, 127.8, 128.6, 131.0, 134.9, 158.0, 159.2, 161.5.

Elemental Analysis : **$C_{12}H_{13}N_3$** (199) Calcd: C, 72.33, H, 6.58, N, 21.09.
Found: C, 72.66, H, 6.47, N, 20.91.

5-Ethyl-6-methyl-3-phenyl-1,2,4-triazine (57n')



Faint Orange crystalline solid;

M. P. (°C) : 122-123 (Lit.[23] 122)

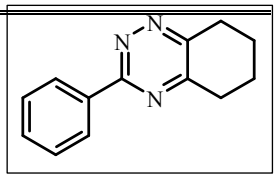
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2947, 2855, 1610, 1598, 1478, 748.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.37-1.44 (t, *J* =7.40 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.80-2.91 (q, *J* = 7.40 Hz, 2H, CH_2), 7.49-7.54 (m, 3H, ArH), 8.51-8.56 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 10.1, 18.8, 27.3, 127.7, 128.4, 130.8, 135.1, 155.1, 161.7, 161.9.

Elemental Analysis : **$C_{12}H_{13}N_3$** (199) Calcd: C, 72.33, H, 6.58, N, 21.09.
Found: C, 72.57, H, 6.33, N, 21.10.

5,6,7,8-tetrahydro-3-phenylbenzo[1,2,4]triazine (57o)



Orange solid

M. P. (°C) : 84-85

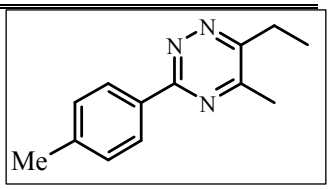
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3016, 2950, 2870, 1600, 1519, 1452, 1419, 1215, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.94-2.01 (m, 4H, CH_2), 2.99-3.02 (d, *J* = 6.45 Hz, 2H, CH_2), 3.14-3.18 (d, *J* = 6.45 Hz, 2H, CH_2), 7.49-7.54 (m, 3H, ArH), 8.44-8.51 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.6, 21.9, 29.1, 31.4, 127.7, 128.4, 130.8, 135.1, 156.4, 158.8, 161.5.

Elemental Analysis : **$C_{13}H_{13}N_3$ (**211) Calcd: C, 73.91, H, 6.20, N, 19.89.
Found: C, 74.05, H, 6.04, N, 19.96.

6-Ethyl-5-methyl-3-(*p*-tolyl)-1,2,4-triazine (57p)



Faint yellow crystalline solid

M. P. (°C) : 102-103

IR ($CHCl_3$, cm^{-1}) : υ_{max} 2953, 2848, 1608, 1541, 1459, 748.

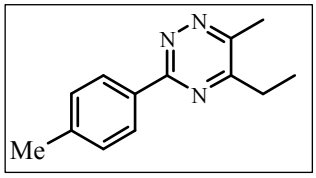
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.26-1.29 (t, *J* = 7.47 Hz, 3H, CH_3), 2.33 (s, 3H, Ph-CH_3), 2.48 (s, 3H, CH_3), 2.84-2.96 (q, *J* = 7.47 Hz, 2H, CH_2), 7.19-7.36 (dd, *J* = 7.92 Hz, 2H, ArH), 8.29-8.46 (dd, *J* = 7.92 Hz, 2H, ArH).

^{13}C NMR : δ 11.7, 21.3, 21.4, 25.9, 127.7, 129.3, 132.3, 141.3, 158.0, 158.9,

($CDCl_3$, 50 MHz) 161.6.

Elemental Analysis : **$C_{13}H_{15}N_3$** (213) Calcd: C, 73.21, H, 7.09, N, 19.70.
Found: C, 73.09, H, 7.16, N, 19.77.

5-Ethyl-6-methyl-3-(*p*-tolyl)-1,2,4-triazine (57p')



Orange crystalline solid;

M. P. (°C) : 77-78

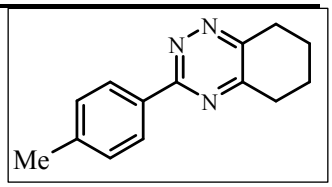
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2943, 2839, 1609, 1541, 1478, 740.

^{1}H NMR : δ 1.26-1.34 (t, *J* = 7.38 Hz, 3H, CH_3), 2.34 (s, 3H, Ph-CH_3), 2.60 (s, 3H, CH_3), 2.69-2.80 (q, *J* = 7.38 Hz, 2H, CH_2), 7.20-7.24 (d, *J* = 7.70 Hz, 2H, ArH), 8.31-8.35 (d, *J* = 7.70 Hz, 2H, ArH).
($CDCl_3$, 200 MHz)

^{13}C NMR : δ 10.2, 18.8, 21.3, 27.4, 127.8, 129.3 132.6, 141.2, 154.8, 161.8, 161.9.
($CDCl_3$, 50 MHz)

Elemental Analysis : **$C_{13}H_{15}N_3$** (213) Calcd: C, 73.21, H, 7.09, N, 19.70.
Found: C, 73.33, H, 6.98, N, 19.76.

5,6,7,8-tetrahydro-3-(*p*-tolyl)benzo[1,2,4]triazine (57q)



Faint yellow solid

M. P. (°C) : 100-101

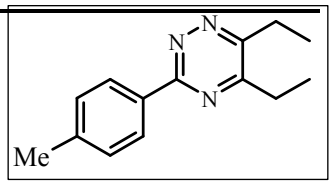
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 2949, 2888, 1613, 1532, 1517, 1453, 1215, 757.

^{1}H NMR : δ 1.90-1.91 (d, *J* = 2.92 Hz, 4H, CH_2), 2.35 (s, 3H, CH_3), 2.91-3.09 (dd, *J* = 5.80 Hz, 4H, CH_2), 7.21-7.25 (d, *J*= 7.70 Hz, 2H), 8.28-8.32 (d, *J* = 7.70 Hz, 2H, ArH).
($CDCl_3$, 200 MHz)

^{13}C NMR : δ 21.4, 21.7, 22.0, 29.1, 31.5, 127.7, 129.3, 132.4, 141.1, 156.2, 158.8, 161.6.
($CDCl_3$, 50 MHz)

Elemental Analysis : **$C_{14}H_{15}N_3$** (225) Calcd: C, 74.64, H, 6.71, N, 18.65.
Found: C, 74.55, H, 6.81, N, 18.59.

5,6-diethyl-3-(*p*-tolyl)-1,2,4-triazine (57r)



Faint Orange crystalline solid

M. P. (°C) : 88-89

IR ($CHCl_3$, cm^{-1}) : υ_{max} 2978, 2938, 2878, 1612, 1534, 1515, 1460, 1216, 757.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 1.36-1.46 (m, 6H, CH_3), 2.42 (s, 3H, CH_3), 2.80-3.05 (m, 4H, CH_2), 7.28-7.32 (d, *J* = 8.21 Hz, 2H, ArH), 8.41-8.45 (d, *J* =8.21 Hz, 2H, ArH)

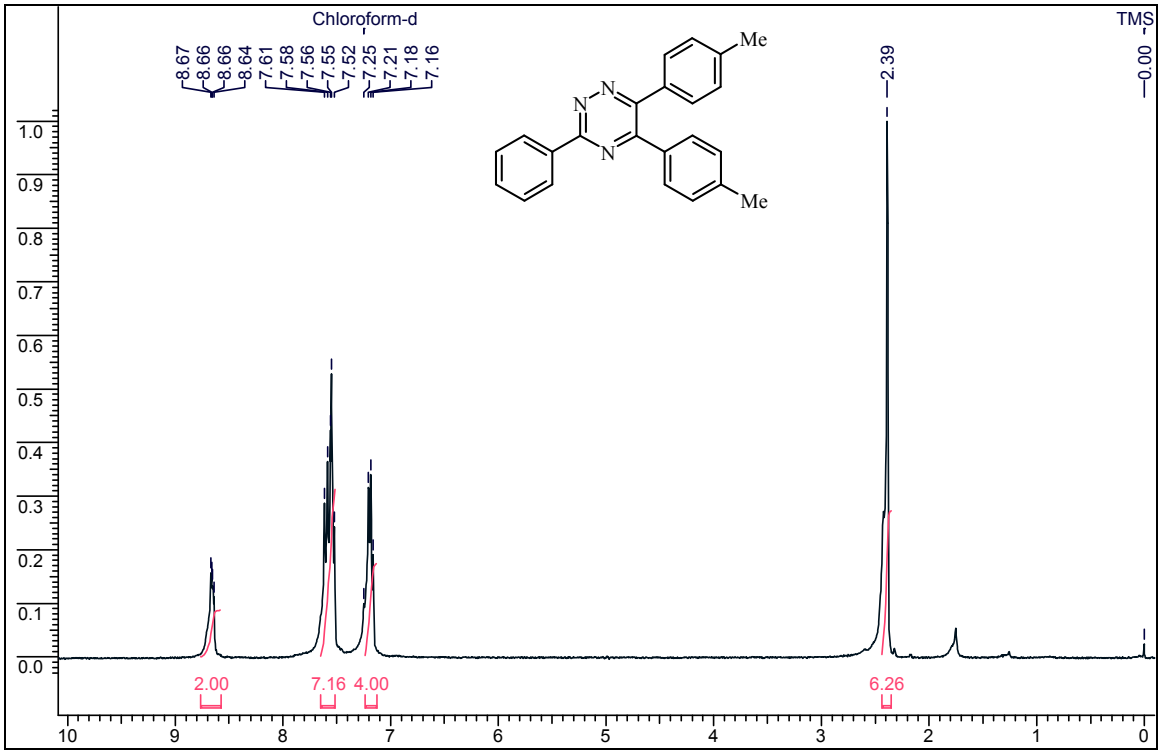
^{13}C NMR (CDCl$_3$, 50 MHz) : δ 10.4, 11.7, 21.2, 25.1, 26.5, 127.5, 129.0, 132.3, 140.9, 158.3, 161.2.

Elemental Analysis : **$C_{14}H_{17}N_3$** (227) Calcd: C, 73.98, H, 7.54, N, 18.49.
Found: C, 74.11, H, 7.43, N, 18.54.

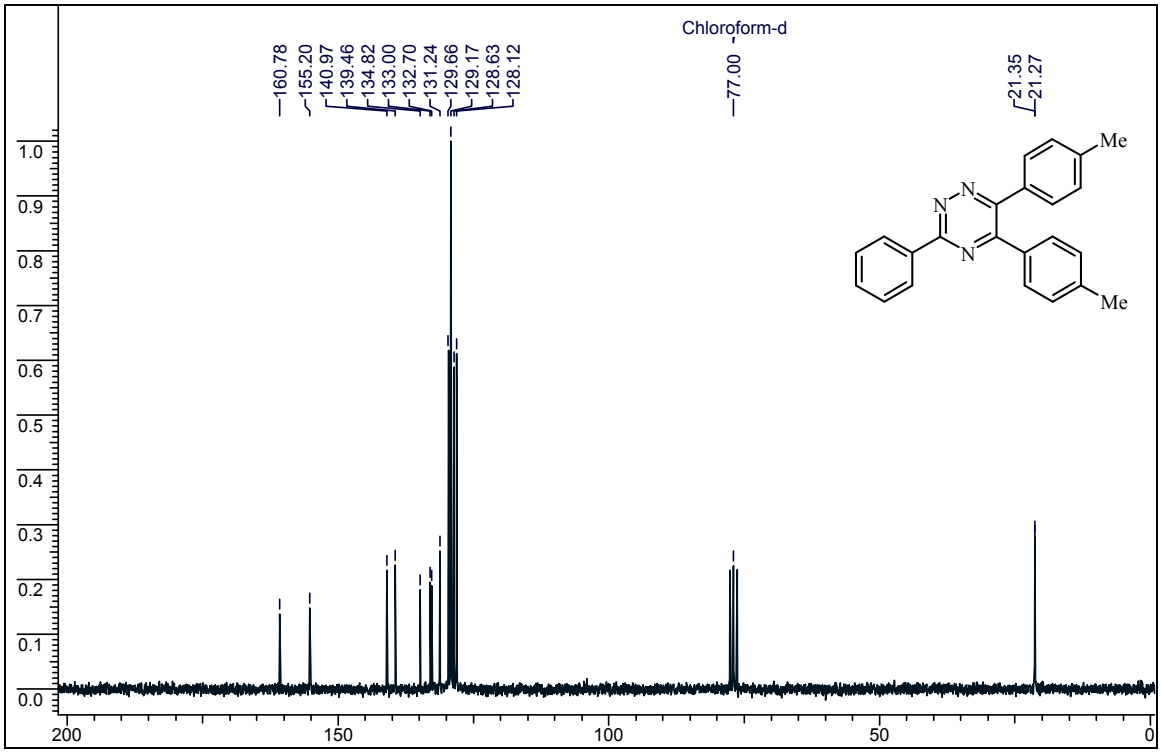
1.3.2.6 Spectra of representative triazines

Sr. No.	NMR spectra of **57**
1	^{1}H NMR and ^{13}C NMR spectra of **57f**
2	^{1}H NMR and ^{13}C NMR spectra of **57g**
3	^{1}H NMR and ^{13}C NMR spectra of **57h**
4	^{1}H NMR and ^{13}C NMR spectra of **57i**
5	^{1}H NMR and ^{13}C NMR spectra of **57k**
6	^{1}H NMR and ^{13}C NMR spectra of **57m**
7	^{1}H NMR and ^{13}C NMR spectra of **57n**
8	^{1}H NMR and ^{13}C NMR spectra of **57n'**
9	^{1}H NMR and ^{13}C NMR spectra of **57q**

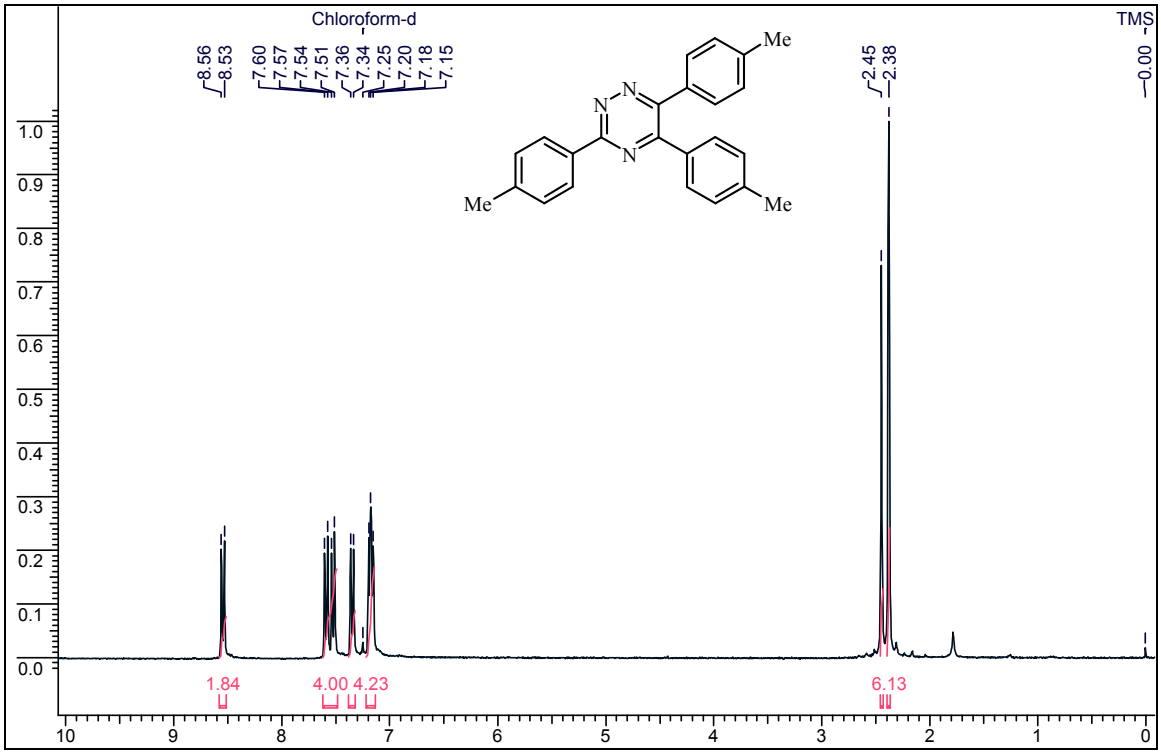
^{1}H NMR spectra of **57f**



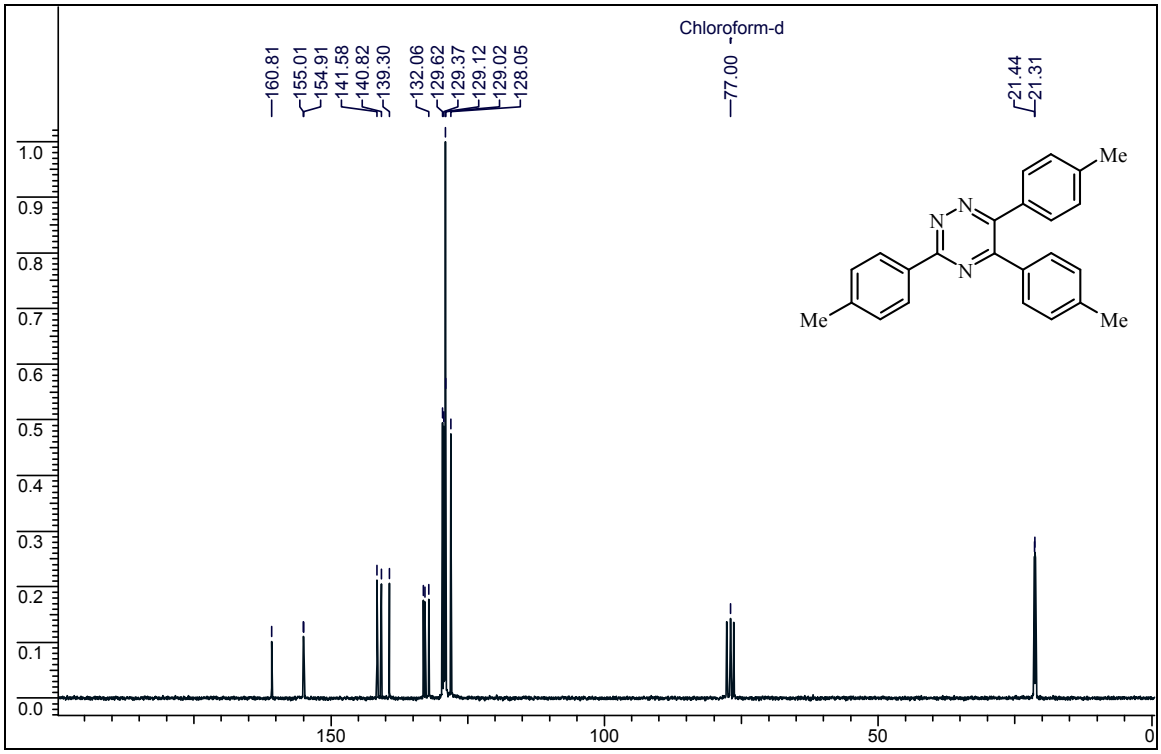
^{13}C NMR spectra of **57f**



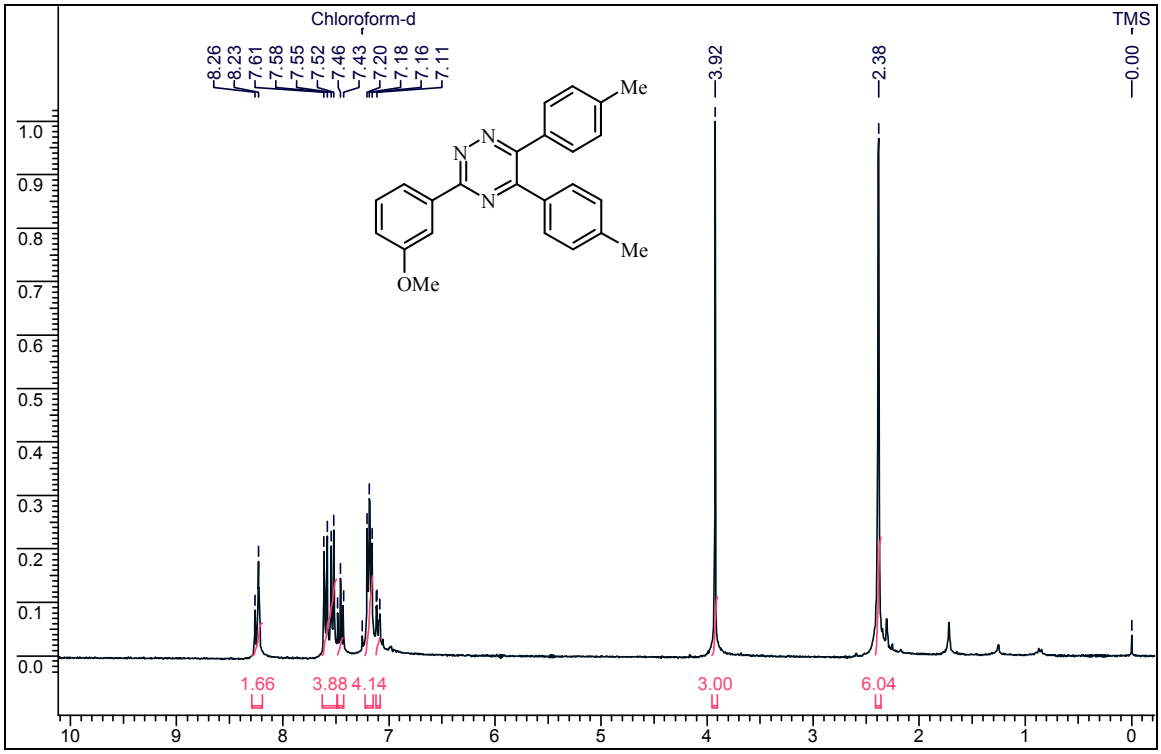
^{1}H NMR spectra of **57g**



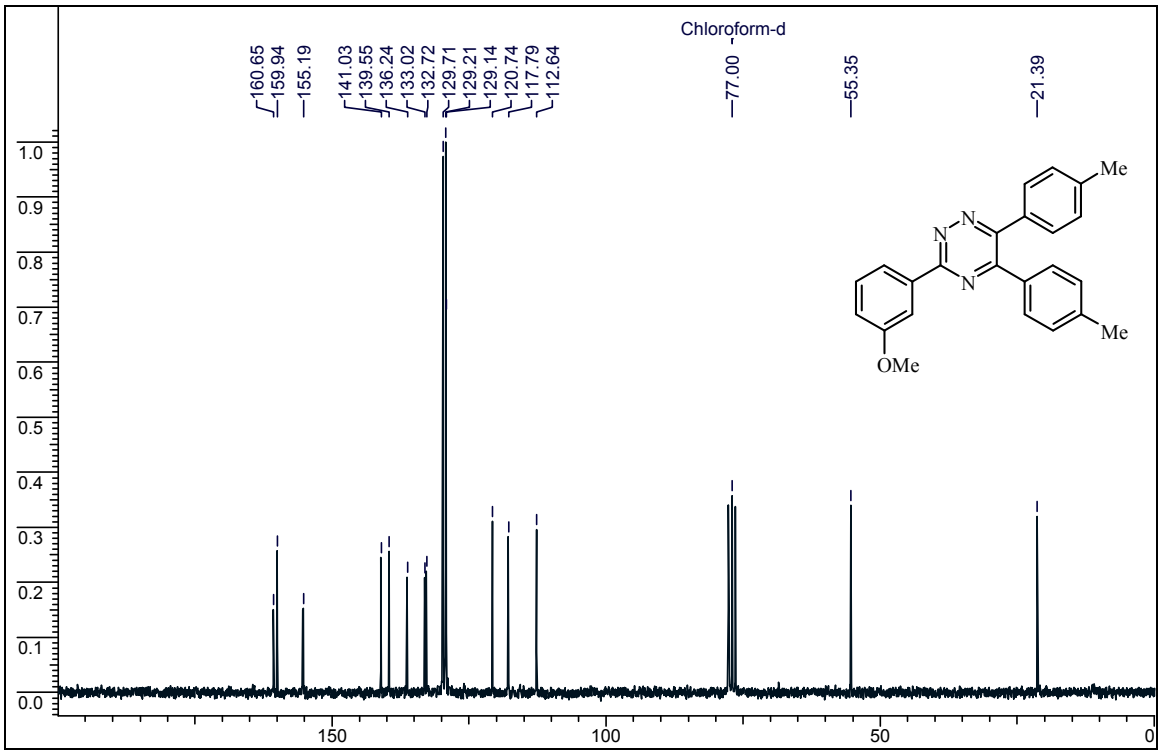
^{13}C NMR spectra of **57g**



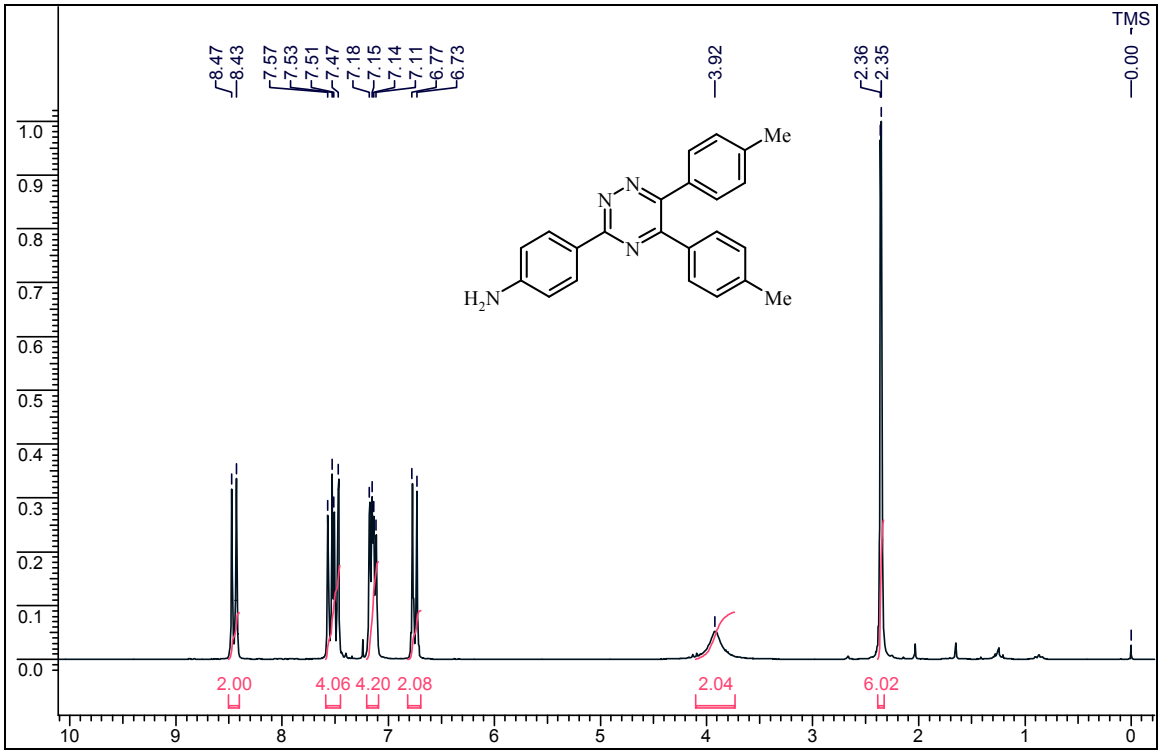
^{1}H NMR spectra of **57h**



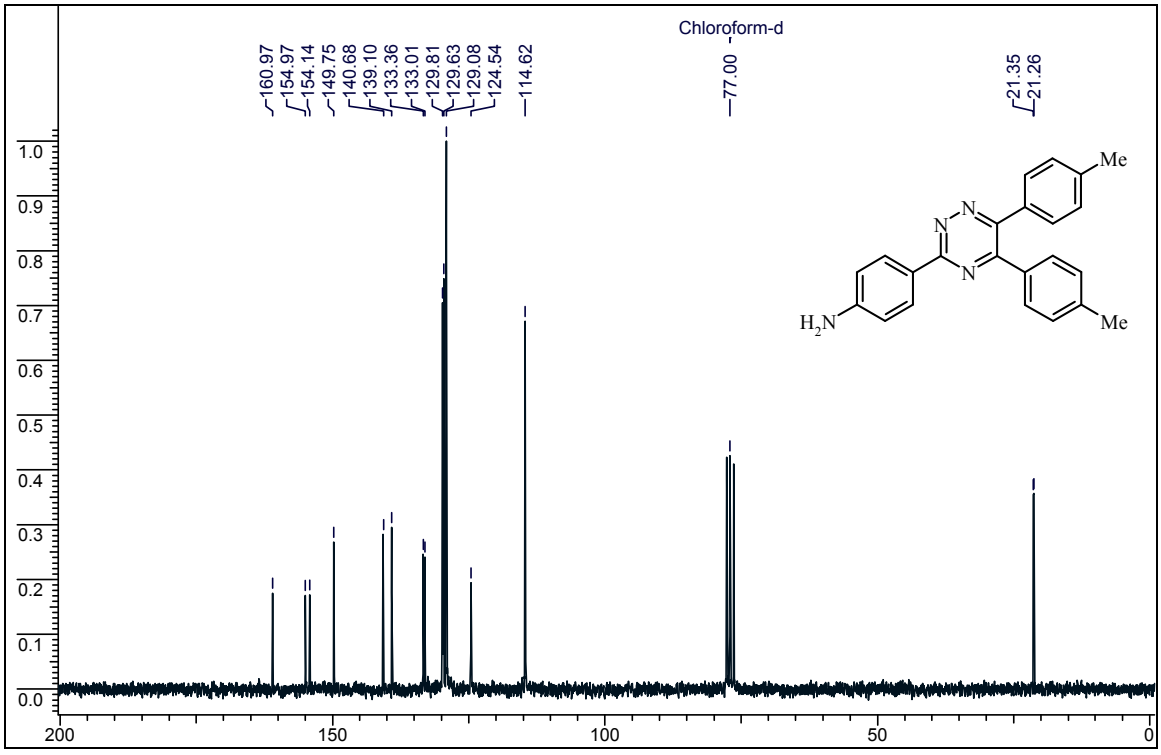
^{13}C NMR spectra of **57h**



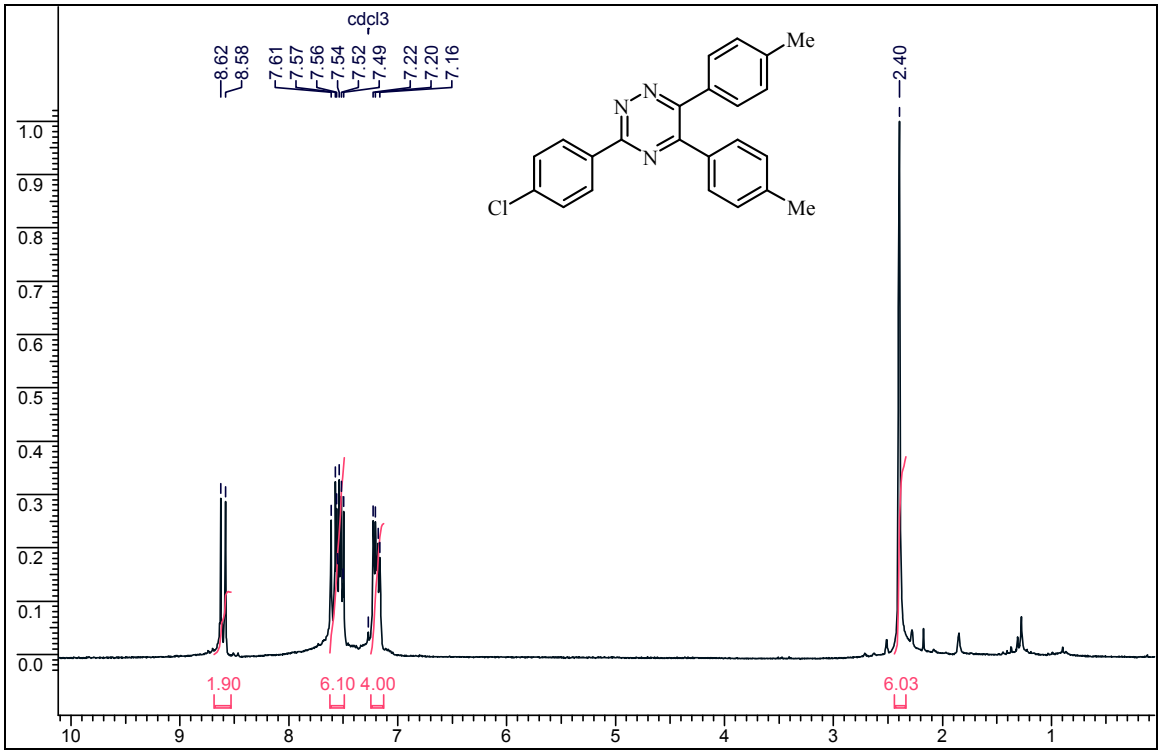
^{1}H NMR spectra of **57i**



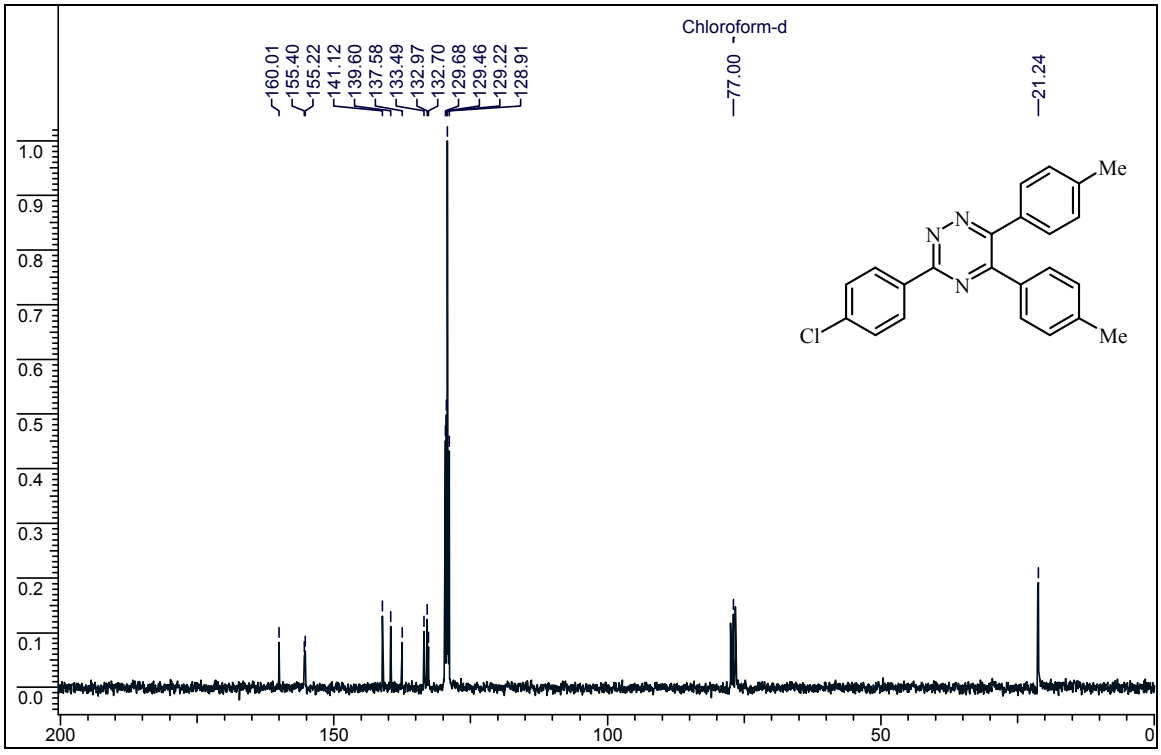
^{13}C NMR spectra of **57i**



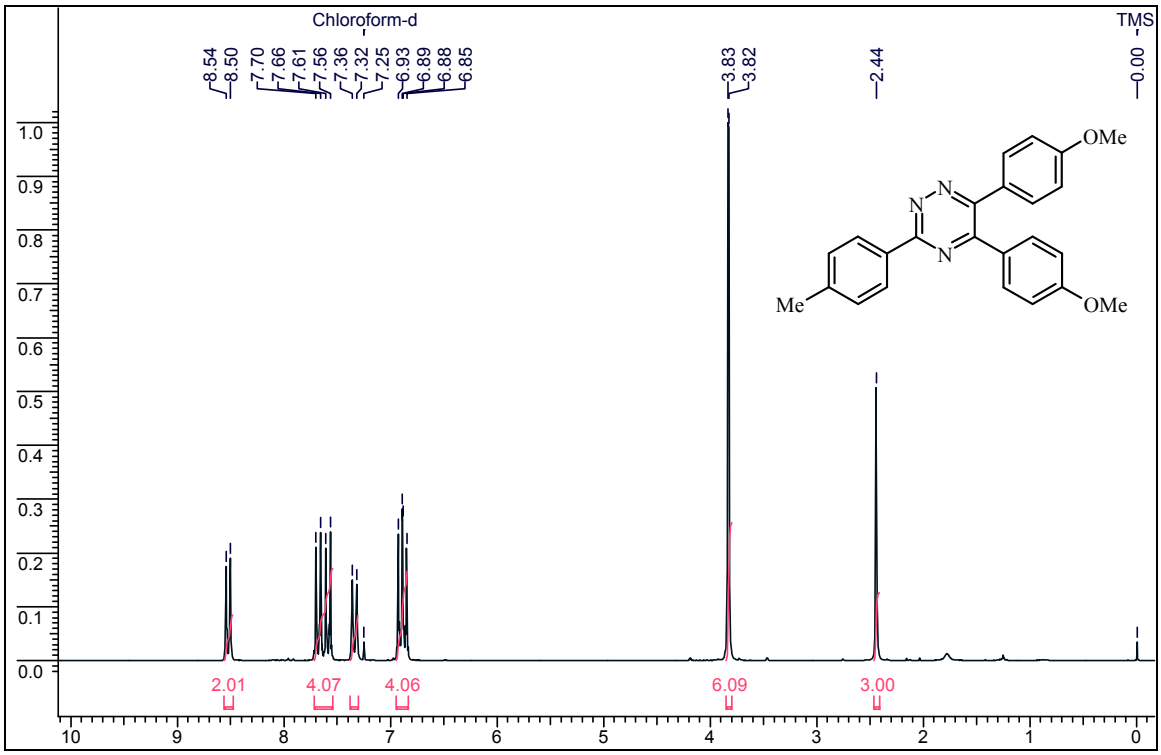
^{1}H NMR spectra of **57k**



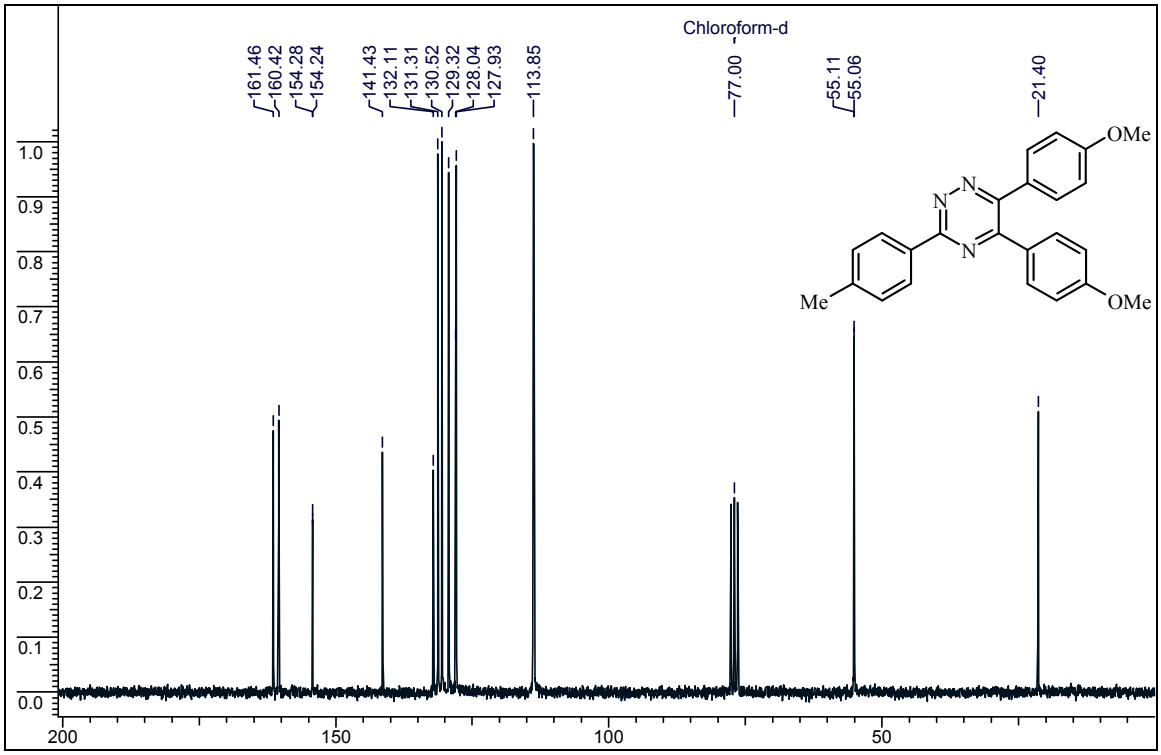
^{13}C NMR spectra of **57k**



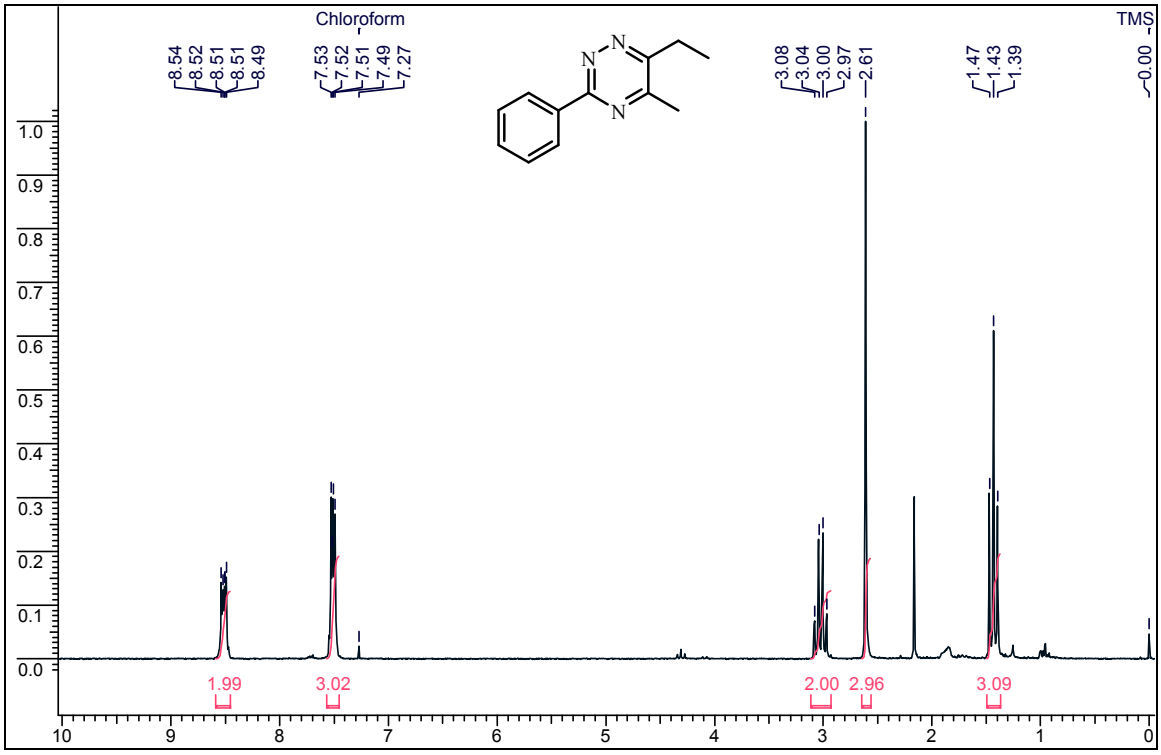
^{1}H NMR spectra of **57m**



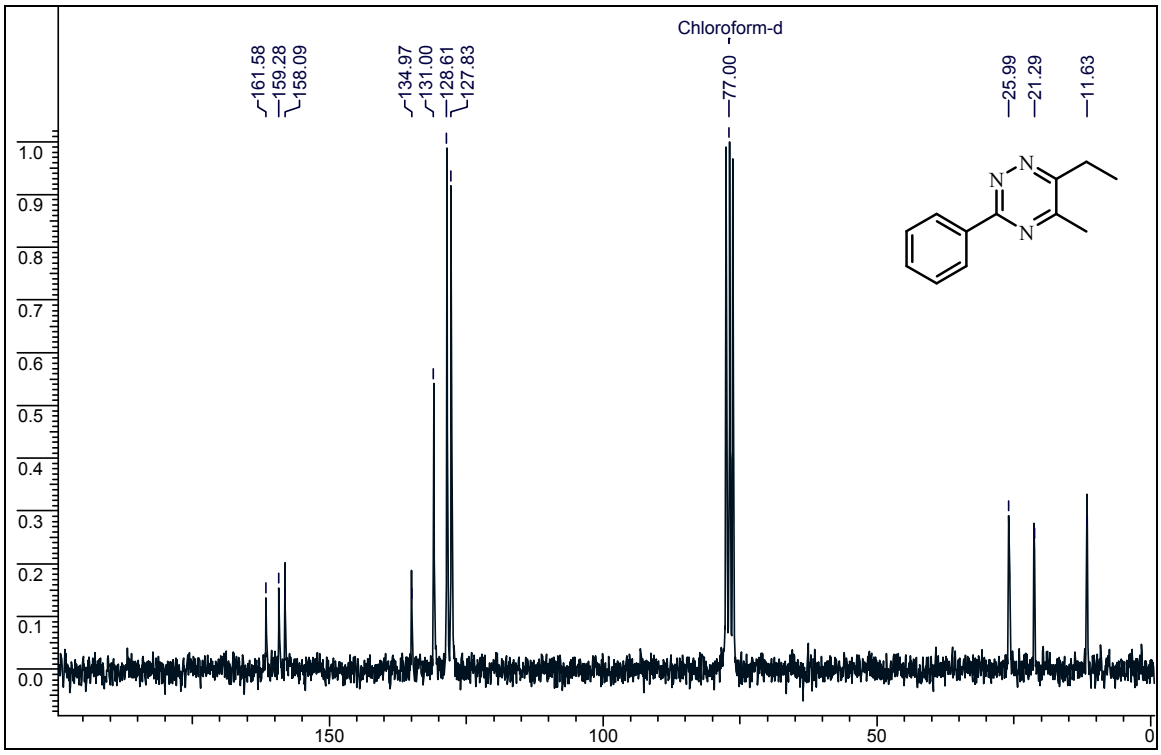
^{13}C NMR spectra of **57m**



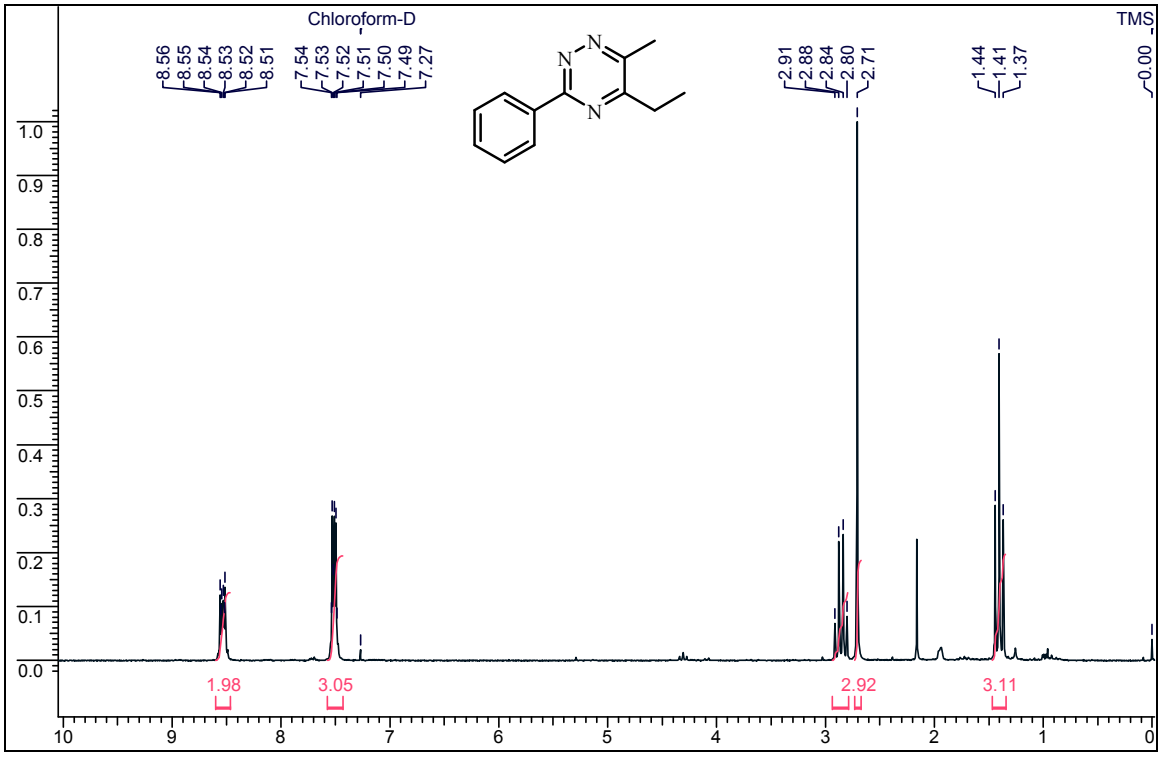
^{1}H NMR spectra of **57n**



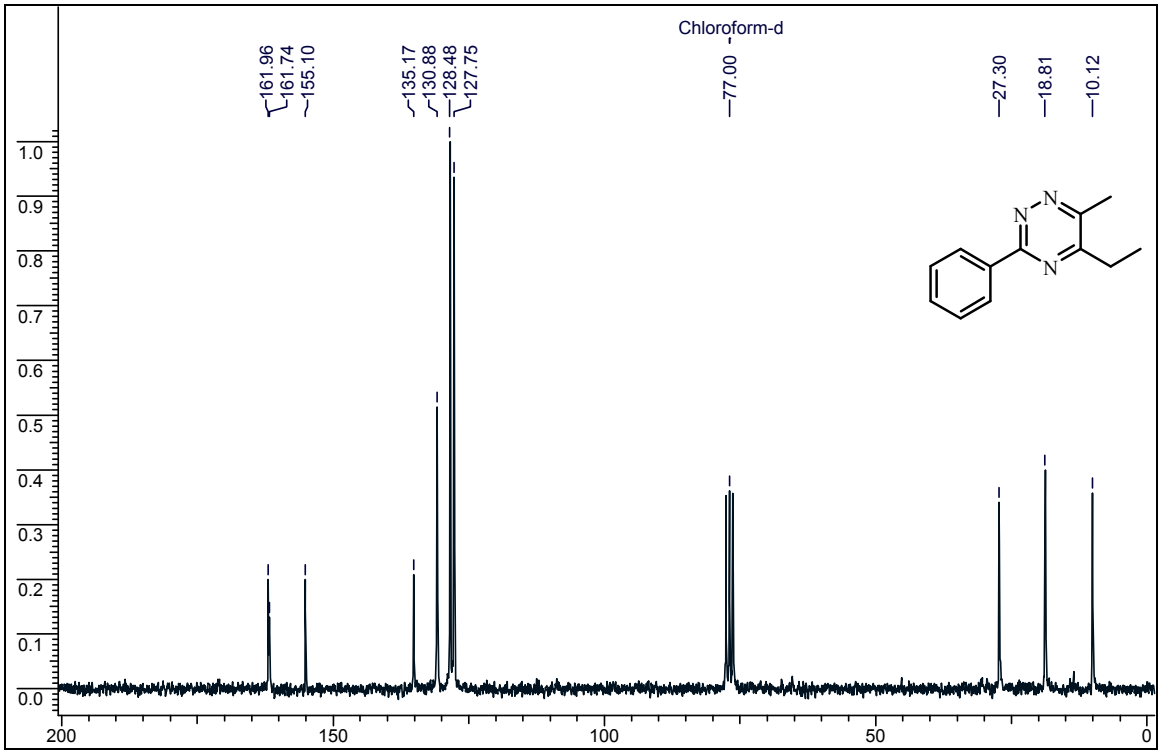
^{13}C NMR spectra of **57n**



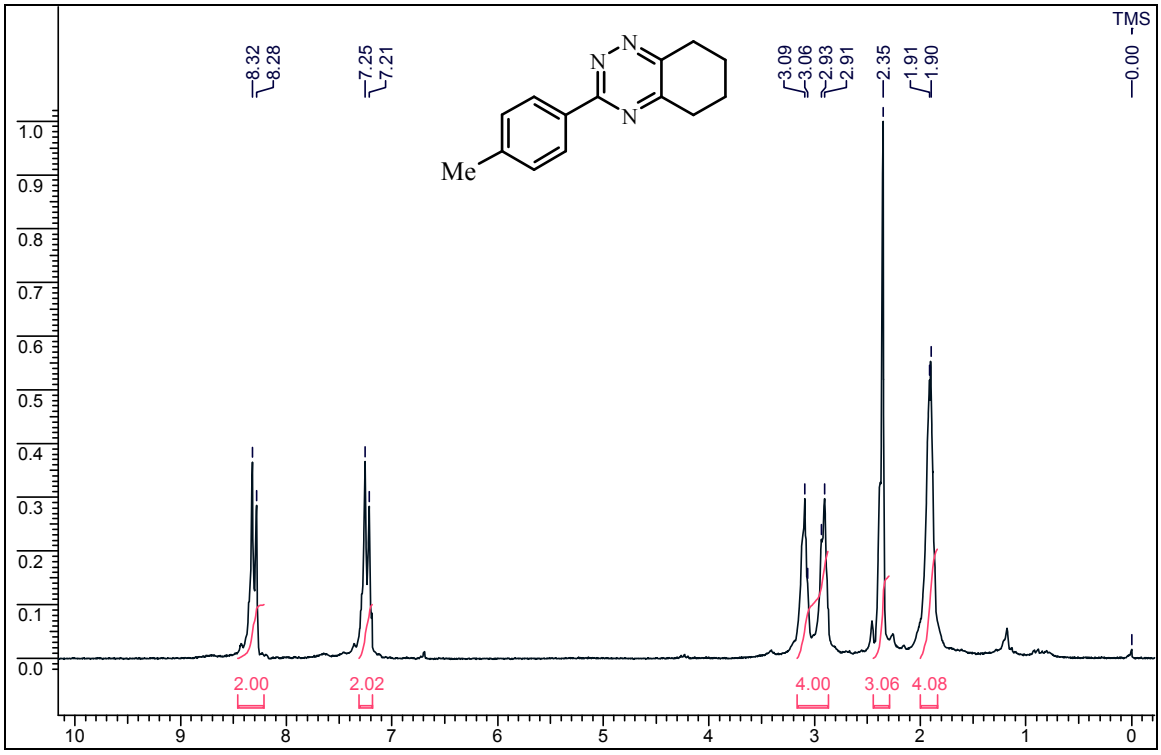
^{1}H NMR spectra of **57n'**



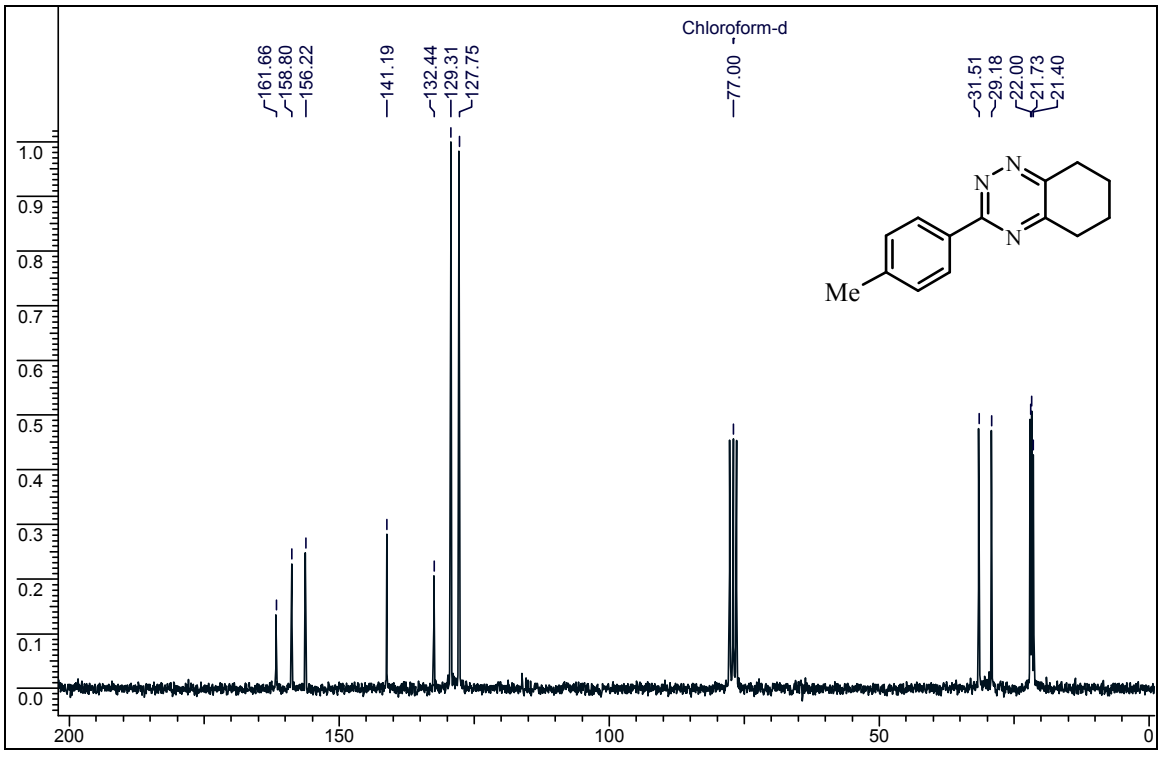
^{13}C NMR spectra of **57n'**



^{1}H NMR spectra of **57q**



^{13}C NMR spectra of **57q**



1.3.2.7 References

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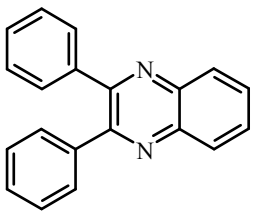
Chapter 1- Section C- Part III

Synthesis of quinoxalines

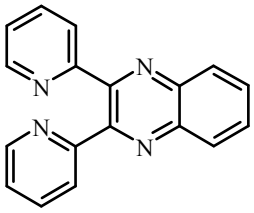
1.3.3.1 Introduction

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles and have shown a broad spectrum of biological activities. A review of the biological activity of quinoxaline derivatives up to 1987 has been published.[1] Apart from those described in the review, they were reported to have a variety of activities such as tranquilizing,[2] antimycobacterial,[3] cardiotonic,[4] antidepressant,[5] and antitumor[6] activities depending on the substitution pattern on the scaffold. Quinoxaline ring moiety constitute part of the various antibiotics such as Echinomycin, Levomycin, and Actinoleutin[7,8] that are known to inhibit growth of Gram positive bacteria, and are active against various transplantable tumors.[9] They have been reported for their applications in dyes,[10] pharmaceuticals,[11-12] and have also been used as building blocks for the synthesis of organic semiconductors.[13-14] Besides this, they are well known for their applications in efficient electroluminescent materials,[15] building blocks for the synthesis of anion receptors,[16] cavitands,[17] dehydroannulenes[18]and DNA cleaving agents.[19]

2,3-Diphenylquinoxaline has shown a high antimicrobial activity towards *Staphylococcus aureus*[20] and it had some inhibiting action on platelet-derived growth factor receptor (PDGFR) kinase.[21] 2,3-bis(2-pyridyl)quinoxaline (DPQ) complexed with transition metals are of current interest in view of its binding to DNA.



2,3-diphenylquinoxaline



2,3-bis(2-pyridyl)quinoxaline

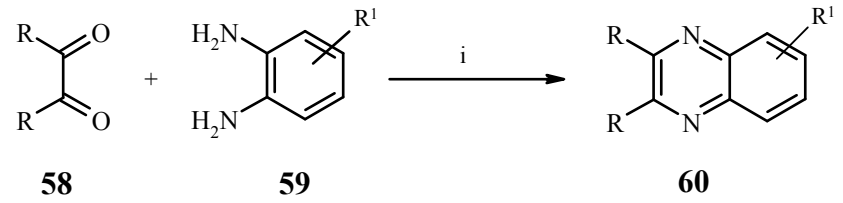
Figure 6. Structures of Quinoxalines

1.3.3.2 Review of literature

In view of the importance of the quinoxaline derivatives due to its biological activities, numerous methods were reported in the literature. By far, the most common method relies on the condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl compound. In this section, we described some of more significant and recent methods.

Brown D. J. et al. approach (2004) [22]

The most common method relies on the condensation of 1,2-dicarbonyl compound **58** with aryl-1,2-diamine **59** in refluxing ethanol or acetic acid for 2-12 h affording the product quinoxalines in 34-85% yields (**Scheme 21**).

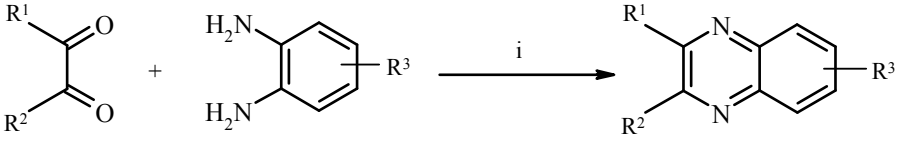


58 **59** **60**

Scheme 21. Reaction conditions**:** (i) AcOH, reflux, 2-12 h, 35-84%.

Craig W. Lindsley et al. approach (2004)[23]

Craig W. Lindsley et al. in 2004 reported the synthesis of quinoxaline derivatives **63** from 1,2-diketones **61** and aromatic-1,2-diamine **62** in microwave using methanol and acetic acid in 9:1 ratio at 160 °C. Aromatic 1,2-diketone as well as aliphatic 1,2-diketones were condensed with aromatic 1,2-diamines using these conditions (**Scheme 22**).

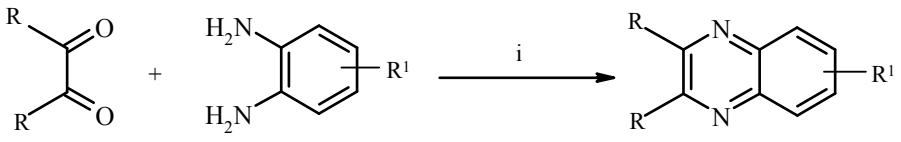


61 **62** **63**

Scheme 22. Reaction conditions**:** (i) MeOH:AcOH (9:1), MW, 160 °C, 5 min, 83-99%.

Rajendra P. Pawar et al. aproach (2005)[24]

Rajendra P. Pawar et al. described the synthesis of substituted quinoxaline derivatives **66** by condensing aromatic-1,2-diketone **64** with substituted aromatic-1,2-diamine **65** using iodine in DMSO, but author did not described the synthesis of quinoxalines by using aliphatic-1,2-diketone (**Scheme 23**).

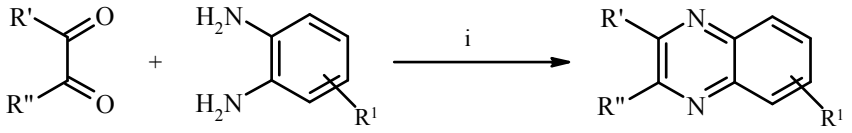


64 **65** **66**

Scheme 23. Reaction conditions: (i) I_2 (10 mol%), DMSO, 35-75 min, 85-95%.

Ching-Fa Yao et al. approach (2006)[25]

Yao et al. reported the synthesis of quinoxaline derivatives **69** using cerium (IV) ammonium nitrate (CAN) as catalyst in water by the condensation of 1,2-diketones **67** with 1,2-diamines **68** (**Scheme 24**).

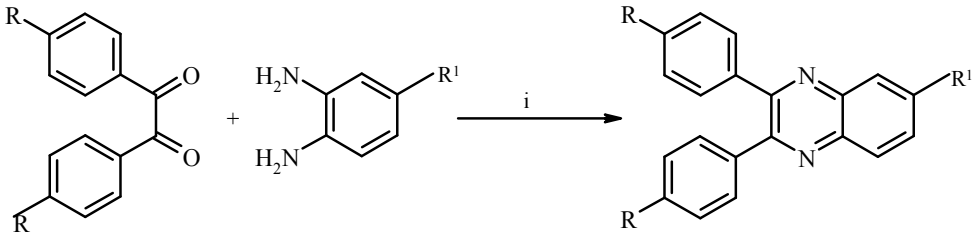


67 **68** **69**

Scheme 24. Reaction conditions: (i) CAN, H_2O,15-50 min, rt, 82-98%.

Majid M. Heravi et al. approach (2007)[26]

Majid M. Heravi et al. reported the synthesis of 2,3-disubstituted quinoxaline derivatives **72** by condensation of aromatic1,2-dicarbonyl compounds **70** with *o*-phenylenediamines **71** by using Zn[(L)proline] catalyst in acetic acid. However the method has some drawbacks such as tedious preparation of the catalyst which can be used in acetic acid only. Other solvents afforded poor results. Furthermore, this method is limited only to aromatic 1,2-dicarbonyl compounds (**Scheme 25**).

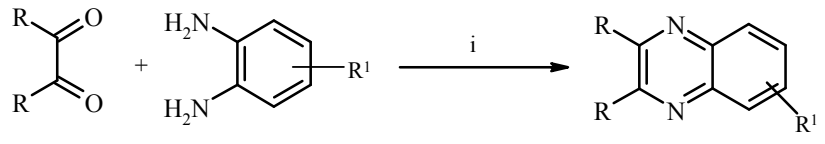


70 **71** **72**

Scheme 25. Reaction conditions: (i) Zn[(L)]proline (10 mol%), AcOH, rt, 92-96%.

S. Palaniappan et al. approach (2007)[27]

S. Palaniappan et al. reported the synthesis of quinoxaline derivatives **75** by condensing aromatic-1,2-dicarbonyls **73** with aromatic 1,2-diamines **74** using polyaniline catalyst or a mixture of polyaniline and sodium laurylsulfate as the catalyst in aqueous medium. No reactions were reported using aliphatic-1,2-diketone (**Scheme 26**).

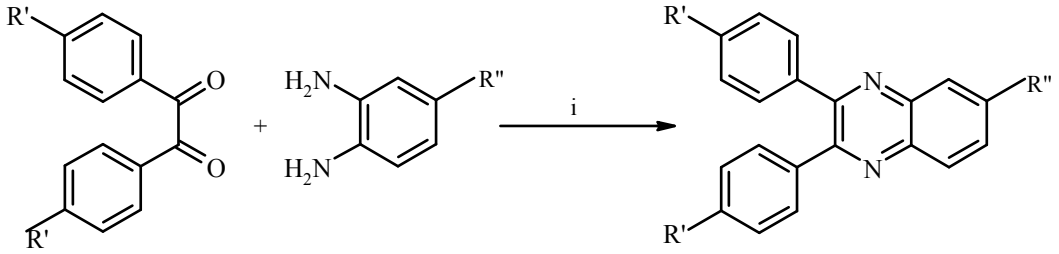


73 **74** **75**

Scheme 26. Reaction conditions**:** (i) polyaniline-sulfate salt, sodium lauryl sulfate, H_2O, 15 min - 2 h, rt, 82-95%.

Majid M. Heravi et al. approach (2007)[28]

Majid M. Heravi et al. reported the synthesis of quinoxalines **78** by the condensation reaction of aromatic-1,2-diketone **76** with aromatic-1,2-diamine **77** using Wells-Dawson heteropolyacid ($H_6P_2W_{18}O_{62}.24H_2O$) catalyst in acetic acid. Reactions were not reported for the synthesis of quinoxalines using aliphatic 1,2-diketone (**Scheme 27**).

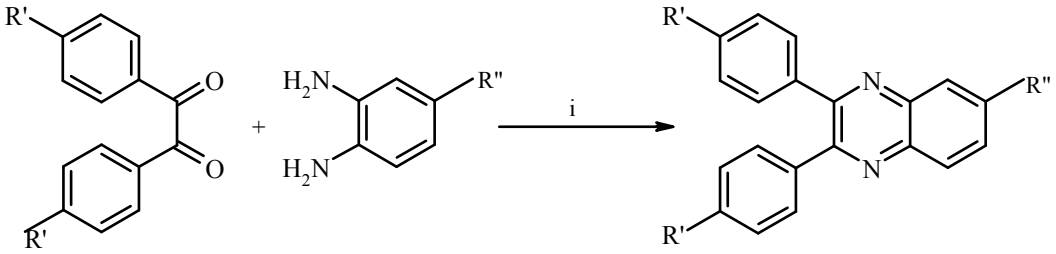


76 **77** **78**

Scheme 27. Reaction conditions**:** (i) Well-Dawson heteropolyacid, AcOH, 5- 20 min, rt, 96-99%.

Majid M. Heravi et al. approach (2007)[29]

Majid M. Heravi et al. reported the synthesis of quinoxaline derivatives **81** by reacting aromatic-1,2-diketones **79** with aromatic-1,2-diamine **80** using cupric sulfate pentahydrate ($CuSO_4.5H_2O$) catalyst in aqueous medium. However, there was no report for the synthesis of quinoxalines starting from aliphatic 1,2-diketone by using this method (**Scheme 28**).

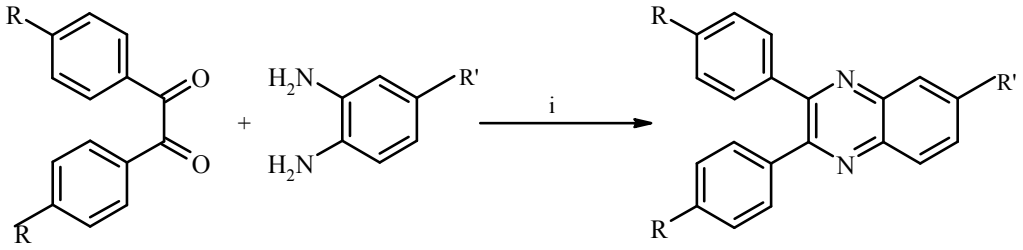


79 **80** **81**

Scheme 28. Reaction conditions**:** (i) cupric sulfate pentahydrate, H_2O, 10-30 min, rt, 94-98%.

Majid M. Heravi et al. approach (2007)[30]

Majid M. Heravi et al. reported the synthesis of quinoxalines **84** from the reaction of aromatic-1,2-diketones **82** with aromatic-1,2-diamine **83** using *o*-Iodoxybenzoic acid (IBX) in acetic acid. However, there was no report for the synthesis of quinoxalines starting from aliphatic-1,2-diketone by using this method (**Scheme 29**).

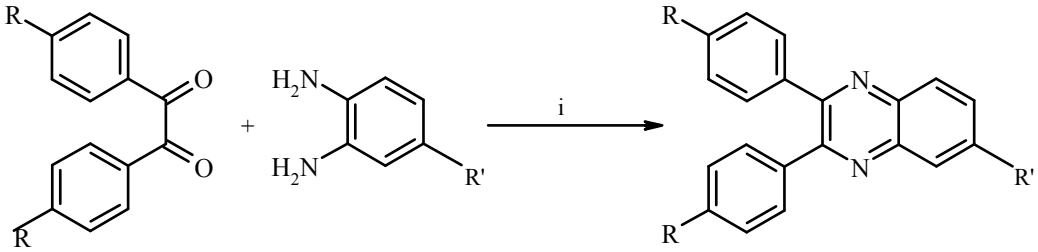


82 **83** **84**

Scheme 29. Reaction conditions: (i) 2-iodoxybenzoic acid (IBX), AcOH, 5-15 min, rt, 98-99%

Hossein A. Oskooie et al. approach (2007)[31]

Hossein A. Oskooie et al. reported the synthesis of substituted quinoxalines **87** from aromatic-1,2-diketone **85** and aromatic-1,2-diamine **86** catalyzed by potassium bisulfate ($KHSO_4$) in ethanol. The process did not mentioned synthesis of quinoxalines commencing from aliphatic 1,2-diketone (**Scheme 30**).



85 **86** **87**

Scheme 30. Reaction conditions: (i) $KHSO_4$ (10 mol%), EtOH, 10-30 min, rt, 93-99%.

1.3.3.3 Present work

1.3.3.3.1 Objectives

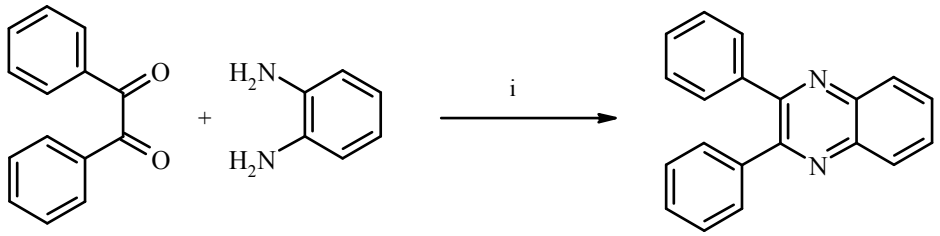
Quinoxaline and its derivatives are an important class of nitrogen containing heterocycles, displaying a broad spectrum of biological activities which have made them privileged structures in pharmacologically active compounds.

The synthesis of quinoxaline derivatives has been of considerable interest to chemists because of their wide range of biological and pharmaceutical properties. In the past ten years, the average number of publications including the keywords 'synthesis' and 'quinoxaline' has doubled. A large part of these papers concerns highly functionalized molecules with a quinoxaline skeleton designed for biological activities. Thus, the synthesis of quinoxalines currently is of great interest. Various methods have been developed for the preparation of substituted quinoxalines.

However, most of the existing methodologies suffer from disadvantages such as use of volatile organic solvents, critical and tedious product isolation procedures; expensive and detrimental metal precursors which limit their use under the aspect of environmentally benign processes. A new synthetic process for the preparation of quinoxaline derivatives which circumvents all the limitations mentioned above would be highly desirable. As a part of our ongoing program to develop more efficient methods for the synthesis of biologically active heterocycles using environment friendly green solvent such as ionic liquids (ILs), we herein report the synthesis of quinoxalines using IL as useful reaction media cum promoter without the need for any additional catalyst.

1.3.3.3.2 Results and discussion

In the beginning, a model reaction was carried out by condensing benzil **88a** with 1,2-diaminobenzene **89a** in IL, 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4. When a mixture of benzil **88a** and 1,2-diaminobenzene **89a** was stirred in [Hbim]BF_4 at room temperature, it afforded the desired product 2,3-diphenyl-quinoxaline **90a** in 96% yield in just 20 min (**Scheme 31**).



88a **89a** **90a**

Scheme 31. Reaction conditions: (i) [Hbim]BF_4, 20 min, rt, 96%.

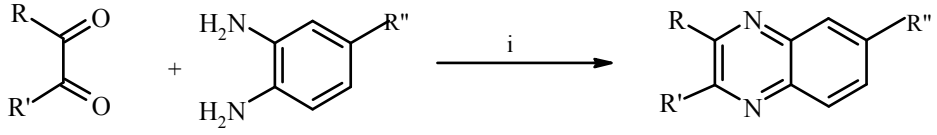
Further to optimize the reaction conditions, ILs based on 1-*n*-butylimidazolium [Hbim] cations with varying anions were screened for this model reaction at room temperature for 2 h to afford 2,3-diphenyl-quinoxaline **90a** and the results are summarized in **Table 6.** It is evident from the result that among the screened ILs, [Hbim]BF_4 was found to be best ILs by virtue of its maximum inherent Brønsted acidity conferred by the most acidic –NH hydrogen [chemical shift δ ppm = 14.6].

Table 6. Synthesis of 2,3-diphenyl-quinoxaline **90a** in different ILs

Entry	ILs	pKa[a]	-NH proton δ ppm	Yield (%)[b]
1	[Hbim]ClO_4	-11	11.83	62
2	[Hbim]Br	-9	12.17	79
3	[Hbim]Cl	-7	12.22	88
4	[Hbim]BF_4	0.5	14.59	96

[a]: The pKa values of the parent acid of the anions
[b]: Isolated yield after column chromatography

Consequently, all further studies were carried out using [Hbim]BF_4 as a reaction medium as well as promoter for the synthesis of quinoxaline derivatives. In order to investigate the scope and generality of this process, a series of aromatic-1,2-diketone **88** and substituted 1,2-diaminobenzene **89** were subjected to condensation using the IL, [Hbim]BF_4 as the reaction medium at room temperature (**Scheme 32**).



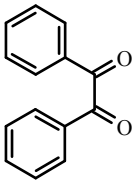
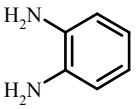
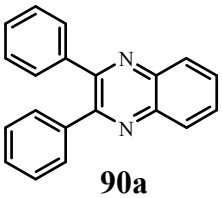
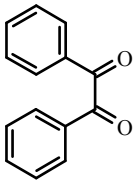
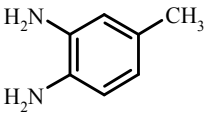
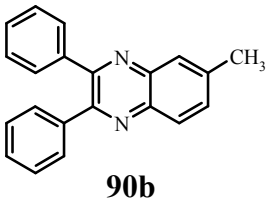
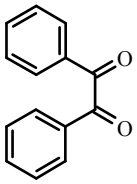
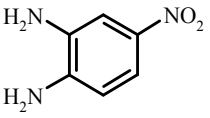
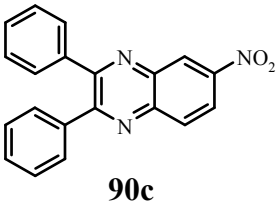
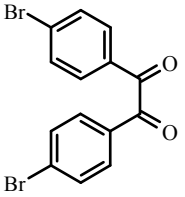
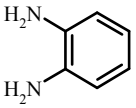
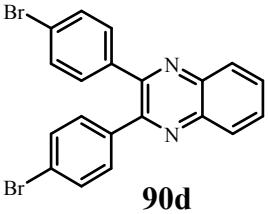
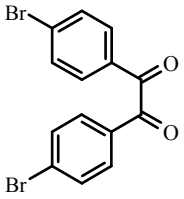
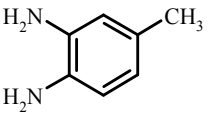
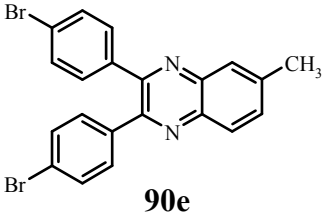
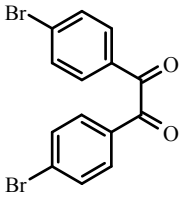
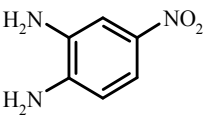
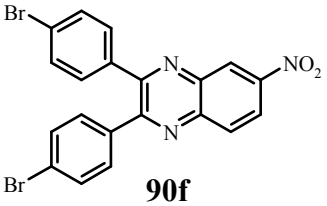
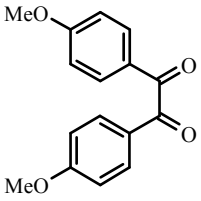
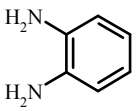
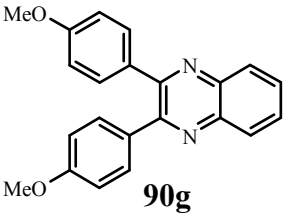
88 **89** **90**

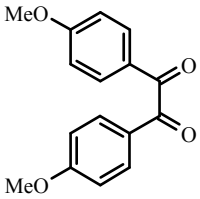
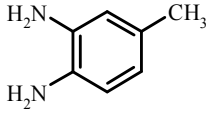
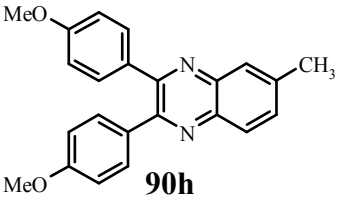
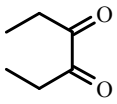
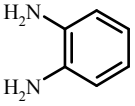
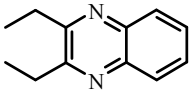
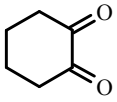
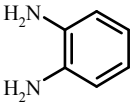
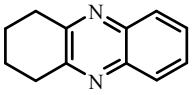
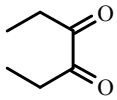
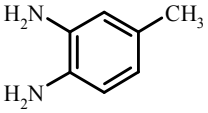
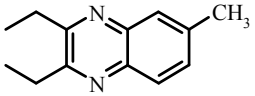
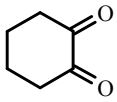
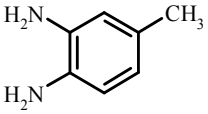
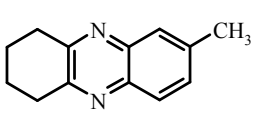
R=R'=alkyl, aryl
R"=H, CH_3, NO_2

R=aryl; 89-96%
R=alkyl; 69-78%

Scheme 32. Reaction conditions**:** (i) [Hbim]BF_4, rt, 10-40 min.

Table 7. Synthesis of quinoxalines **90**

Entry	Diketone **88**	1,2-diamine **89**	Quinoxaline **90**	Time (min)	Yield[a] (%)
1			 **90a**	20	96
2			 **90b**	15	95
3			 **90c**	15	96
4			 **90d**	20	94
5			 **90e**	25	92
6			 **90f**	25	89
7			 **90g**	20	91

8			 **90h**	40	96
9			 **90i**	10	78
10			 **90j**	15	69
11			 **90k**	15	75
12			 **90l**	10	71

[a]:Isolated yield after column chromatography

The process tolerates well both electron donating as well as electron withdrawing substituents on the 1,2-diaminobenzene and afforded the quinoxaline derivatives in excellent isolated yields. The applicability of the present methodology is further successfully extended for the synthesis of substituted quinoxalines by performing the reaction with aliphatic-1,2-diketones and 1,2-diaminobenzene. When, aliphatic-1,2-diketone such as 1,2-cyclohexandione and 3,4-hexanedione were subjected to condensation with 1,2-diaminobenzene, reactions were smoothly completed in shorter reaction times and afforded the corresponding 2,3-dialkyl-quinoxaline in very good isolated yields. However, the yields are relatively lower as compared to 2,3-diaryl-quinoxaline. On reviewing the literature on quinoxalines synthesis, it was observed that very few methods have been reported for the synthesis of 2,3-dialkyl-quinoxaline. Thus, it becomes noteworthy that our

process is equally applicable for both aromatic-1,2-diketones as well as for aliphatic-1,2-diketones (**Table 7, Entry 9-12**).

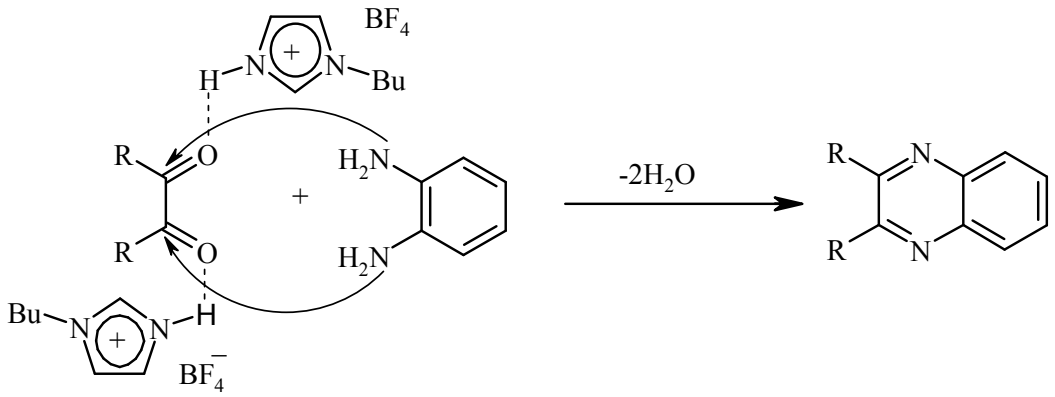
The efficacy of the ILs to promote these heterocyclization reactions was correlated with the basicity of the anions as well as -NH proton chemical shifts of the ILs. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (Table 6). This correlation was also evident when the yield of **90a** was compared with -NH proton chemical shifts of the ILs indicative of the Brønsted acidities of the [Hbim] ILs (Table 6). It is found that the IL, [Hbim]BF_4 has efficiently promoted this heterocyclization reaction by virtue of its inherent Brønsted acidity conferred by the most acidic –NH hydrogen [chemical shift δ ppm = 14.6].

The reaction procedure is very simple and easy to carry out. A mixture of 1,2-diketone and 1,2-diaminobenzenes in IL was stirred at ambient temperature till completion of reaction. On completion, the reaction mixture was diluted with water and product was extracted using ethyl acetate. Organic layer was separated from aqueous phase and evaporated under reduced pressure to afford crude quinoxalines which were further purified by column chromatography.

The aqueous layer containing IL was subjected to distillation at 80 °C under reduced pressure (10 mm Hg) for 4 h to remove water leaving behind the IL in almost complete recovery. The IL, thus recovered was further used three times for the typical reaction of benzil and 1,2-diaminobenzene without any loss in yield and purity.

1.3.3.3.3 Plausible mechanism

Based on the above observations, the following probable mechanism may be postulated for this reaction as shown in **Scheme 33**. The role of the IL may be postulated in terms of the Brønsted acidity of the -NH proton of the imidazolium cation, leading to its interaction through hydrogen bonding with the carbonyl oxygen atom of 1,2-diketone. This increases the electrophilicity of carbonyl carbon, thereby fascilating the attack of the nucleophilic nitrogen followed by the elimination of two molecules of water.



Scheme 33. Plausible mechanism

1.3.3.4 Conclusion

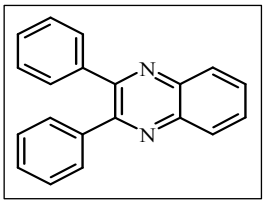
In conclusion, we have developed a simple, convenient, and efficient method for the synthesis of quinoxalines from various-1,2-diketones and 1,2-diaminobenzene using ionic liquid, 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF_4 as a reaction medium as well as a promoter under mild reaction conditions at room temperature. The process is general for the synthesis of quinoxaline derivatives from aromatic as well as aliphatic-1,2-diketones. The advantages of the present procedure viz. simplicity of operation, high yields of products, recyclability of the ILs and eco-friendly nature of the reaction medium make this method a valuable contribution to the existing methodologies.

1.3.3.5 Experimental

1.3.3.5.1 General procedure for the synthesis of 2,3-disubstituted quinoxalines

A mixture containing 1,2-diketone **88** (1 mmol), aryl 1,2-diamine **89** (1.1 mmol) in the IL, [Hbim]BF_4 (2 mL) was stirred at room temperature for the appropriate time as mentioned in **Table 7**. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted using ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the solvent evaporated under vacuum to obtain the crude product, which was further purified by column chromatography using petroleum ether: ethyl acetate (5:95) to obtain pure product viz 2,3-disubstituted-quinoxaline **90**. The pure products were further further fully characterized

1.3.3.5.2 Characterization data for quinoxaline



2,3-Diphenylquinoxaline (90a)

White Solid

M. P. (°C) : 128-129 (Lit.[29] 126-127)

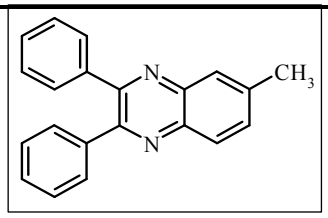
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3061, 1559, 1600, 1541, 1478, 1345, 1217, 1057, 816, 757, 698.

^{1}H NMR ($CDCl_3$,200 MHz) : δ 7.28-7.40 (m, 6H, ArH), 7.46-7.54 (m, 4H, ArH), 7.73-7.81 (m, 2H, ArH), 8.14-8.22 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 128.22, 128.75, 129.17, 129.81, 129.90, 139.06, 141.20, 153.43.

Elemental Analysis : $C_{20}H_{14}N_2$ (282) Calcd: C, 85.08; H, 5.00; N, 9.92.
Found: C, 85.21; H, 4.88; N, 9.85.

6-Methyl-2,3-diphenylquinoxaline (90b)



White solid

M. P. (°C) : 117-118 (Lit.[29] 116-117)

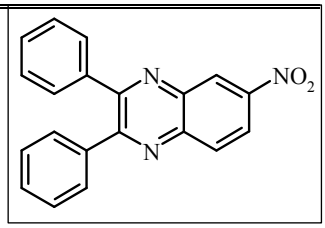
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 2981, 2924, 1621, 1536, 1346, 1215, 882, 757, 699.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.61 (s, 3H, CH_3), 7.29-7.38 (m, 6H, ArH), 7.45-7.52 (m, 4H, ArH), 7.57-7.62 (dd, *J* = 8.55 & 1.96 Hz, 1H, ArH), 7.94 (s, 1H, ArH), 8.04-8.08 (d, *J* = 8.55 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.8, 127.9, 128.1, 128.5, 128.6, 129.7, 132.2, 139.1, 139.6, 140.4, 141.2, 152.5, 153.2.

Elemental Analysis : $C_{21}H_{16}N_2$ (296) Calcd: C, 85.11; H, 5.44; N, 9.45.
Found: C, 85.23; H, 5.33; N, 9.57.

6-Nitro-2,3-diphenylquinoxaline (90c)



Yellow solid

M. P. (°C) : 193-194 (Lit.[29] 193-194)

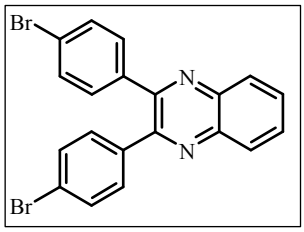
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3020, 1618, 1574, 1527, 1475, 1435, 1342, 1215, 1055, 928, 836, 669.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 7.31-7.43 (m, 6H, ArH), 7.53-7.58 (m, 4H, ArH), 8.27-8.31 (d, *J* = 9.18 Hz, 1H, ArH), 8.50-8.55 (dd, *J* = 9.18 & 2.50 Hz, 1H, ArH), 9.07-9.08 (d, *J* = 2.50 Hz, 1H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 123.2, 125.5, 128.4, 129.6, 129.7, 129.7, 129.8, 130.7, 137.9, 138.0, 139.9, 143.5, 147.7, 155.6, 156.2.

Elemental Analysis : **$C_{20}H_{13}N_3O_2$** (327) Calcd: C, 73.38; H, 4.00; N, 12.84.
Found: C, 73.23; H, 4.13; N, 12.93.

2,3-bis(4-bromophenyl)quinoxaline (90d)



White solid

M. P. (°C) : 194-195

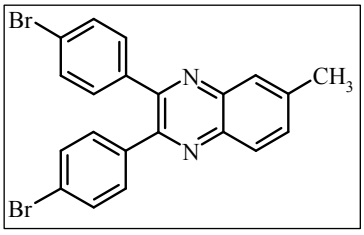
IR (CHCl$_3$, cm^{-1}) : υ_{max} 3019, 1589, 1343, 1216, 757.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 7.36-7.42 (m, 4H, ArH), 7.47-7.53 (m, 4H, ArH), 7.76-7.81 (q, *J* = 6.40 & 3.45 Hz, 2H, ArH), 8.12-8.17 (q, *J* = 6.40 & 3.45 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 123.6, 129.1, 130.3, 131.3, 131.6, 137.5, 141.1, 151.8.

Elemental Analysis : **$C_{20}H_{12}Br_2N_2$** (440) Calcd: C, 54.58; H, 2.75; N, 6.36.
Found: C, 54.67; H, 2.84; N, 6.48.

2,3-bis(4-bromophenyl)-6-methylquinoxaline (90e)



White solid

M. P. (°C) : 185-186

IR (CHCl$_3$, cm^{-1}) : υ_{max} 3019, 2974, 1619, 1589, 1484, 1342, 1215, 1073, 979, 833, 757, 669.

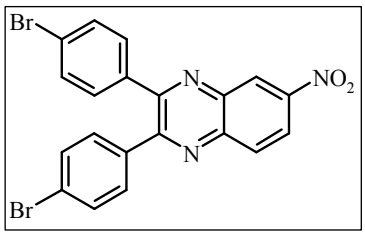
^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.61 (s, 3H, CH_3), 7.34-7.40 (m, 4H, ArH), 7.46-7.51 (m, 4H, ArH), 7.59-7.64 (dd, *J* = 8.58 & 1.88 Hz, 1H, ArH), 7.91 (s, 1H, ArH), 8.01-8.05 (d, *J* = 8.58 Hz, 1H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 21.9, 123.4, 123.5, 127.9, 128.6, 131.3, 131.5, 132.7, 137.7, 139.6, 141.0, 141.2, 150.9, 151.6.

Elemental Analysis : **$C_{21}H_{14}Br_2N_2$** (454) Calcd: C, 55.54; H, 3.11; N, 6.17.

Found: C, 55.41; H, 3.21; N, 6.32.

2,3-bis(4-bromophenyl)-6-nitroquinoxaline (90f)



Faint yellow solid

M. P. (°C) : 188-190

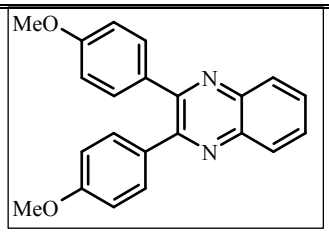
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3019, 1618, 1588, 1528, 1344, 1216, 1129, 1072, 758, 669.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.39-7.45 (m, 4H, ArH), 7.49-7.54 (m, 4H, ArH), 8.22-8.27 (d, *J* = 9.14 Hz, 1H, ArH), 8.47-8.53 (dd, *J* = 9.14 & 2.48 Hz, 1H, ArH), 8.99-9.00 (d, *J* = 2.48 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 200 MHz) : δ 123.6, 124.6, 124.7, 125.4, 130.7, 131.3, 131.8, 136.4, 136.5, 139.8, 143.3, 147.9, 154.0, 154.6.

Elemental Analysis : **$C_{20}H_{11}Br_2N_3O_2$** (485) Calcd: C, 49.52; H, 2.29; N, 8.66.
Found: C, 49.41; H, 2.17; N, 8.81.

2,3-bis(4-methoxyphenyl)quinoxaline (90g)



White solid

M. P. (°C) : 151-152 (Lit.[29] 151-152)

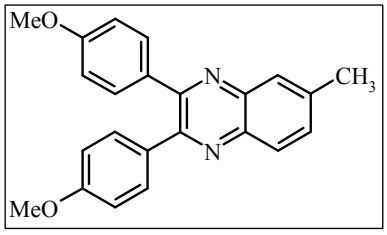
IR ($CHCl_3$, cm^{-1}) : υ_{max} 3019, 2922, 2852, 1608, 1514, 1346, 1031, 834, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.82 (s, 6H, OCH_3), 6.83-6.90 (m, 4H, ArH), 7.45-7.52 (m, 4H, ArH), 7.69-7.74 (q, *J* = 6.37 & 3.45 Hz, 2H, ArH), 8.09-8.14 (q, *J* = 6.37 & 3.45 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.2, 113.7, 128.9, 129.4, 131.1, 131.6, 140.9, 152.9, 160.0.

Elemental Analysis : **$C_{22}H_{18}N_2O_2$** (342) Calcd: C, 77.17; H, 5.30; N, 8.18.
Found: C, 77.09; H, 5.42; N, 8.26.

2,3-bis(4-methoxyphenyl)-6-methylquinoxaline (90h)



White solid

M. P. (°C) : 126-127 (Lit.[29] 125-127)

IR ($CHCl_3$, cm^{-1}) : υ_{max} 3016, 2961, 2837, 1608, 1556,

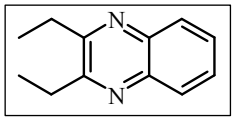
1488, 1441, 1216, 1031, 979, 836, 757, 666.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.59 (s, 3H, CH_3), 3.82 (s, 6H, OCH_3), 6.82-6.89 (m, 4H, ArH), 7.43-7.48 (m, 4H, ArH), 7.52-7.75 (dd, *J* = 8.55 & 1.86 Hz, 1H, ArH), 7.89 (s, 1H, ArH), 7.98-8.02 (d, *J* = 8.55 Hz, 1H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 21.7, 55.2, 113.6, 127.7, 128.4, 131.1, 131.7, 139.4, 139.9, 141.0, 152.0, 152.7, 159.9.

Elemental Analysis : **$C_{23}H_{20}N_2O_2$** (356) Calcd: C, 77.51; H, 5.66; N, 7.86.
Found: C, 77.39; H, 5.78; N, 7.78.

2,3-Diethylquinoxaline (90i)



White solid

M. P. (°C) : 51-52

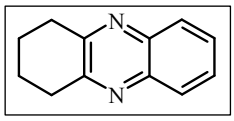
IR (CHCl$_3$, cm^{-1}) : υ_{max} 3064, 2974, 2875, 1607, 1487, 1459, 1397, 1283, 1046, 757, 666.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 1.37-1.44 (t, *J* = 7.51 Hz, 6H, CH_3), 2.99-3.10 (q, *J* = 7.51 Hz, 4H, CH_2), 7.62-7.67 (q, *J* = 6.30 & 3.50 Hz, 2H, ArH), 7.97-8.02 (q, *J* = 6.30 & 3.50 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 12.4, 28.2, 128.3, 128.5, 140.9, 157.1.

Elemental Analysis : **$C_{12}H_{14}N_2$** (186) Calcd: C, 77.38; H, 7.58; N, 15.04.
Found: C, 77.53; H, 7.67; N, 14.89.

1,2,3,4-tetrahydrophenazine (90j)



Faint yellow solid

M. P. (°C) : 94-95

IR (CHCl$_3$, cm^{-1}) : υ_{max} 3019, 2948, 2868, 1592, 1565, 1487, 1340, 1215, 1213, 928, 826, 756, 669.

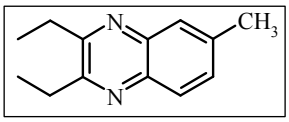
^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.03 (s, 4H, CH_2), 3.15 (s, 4H, CH_2), 7.62-7.67 (q, *J* = 6.40 & 3.45 Hz, 2H, ArH), 7.93-7.98 (q, *J* = 6.40 & 3.45 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 22.6, 33.0, 128.1, 128.8, 141.0, 153.9.

Elemental Analysis : **$C_{12}H_{12}N_2$ (184)** Calcd: C, 78.23; H, 6.57; N, 15.21.

Found: C, 78.11; H, 6.70; N, 15.29.

2,3-Diethyl-6-methylquinoxaline (90k)



White solid

M. P. (°C) : 41-42

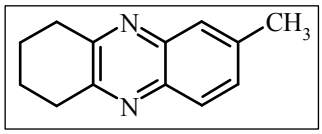
IR ($CHCl_3$, cm^{-1}) : υ_{max} 2974, 2876, 1623, 1563, 1459, 1377, 1240, 1046, 964, 829, 755, 665.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35-1.43 (t, *J* = 7.48 Hz, 6H, CH_3), 2.54 (s, 3H, CH_3), 2.96-3.07 (q, *J* = 7.48 Hz, 4H, CH_2), 7.45-7.50 (dd, *J* = 8.60 & 1.92 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.85-7.89 (d, *J* = 8.52 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.4, 12.5, 21.5, 28.1, 28.2, 127.3, 127.8, 130.7, 138.7, 139.3, 140.9, 156.1, 156.9.

Elemental Analysis : **$C_{13}H_{16}N_2$** (200) Calcd: C, 77.96; H, 8.05; N, 13.99.
Found: C, 77.83; H, 7.93; N, 14.15.

1,2,3,4-tetrahydro-7-methylphenazine (90l)



Brown solid

M. P. (°C) : 84-85

IR ($CHCl_3$, cm^{-1}) : υ_{max} 3018, 2947, 2867, 1622, 1495, 1454, 1215, 934, 817, 756, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.98- 2.05 (m, 4H, CH_2), 2.54 (s, 3H, CH_3), 3.09- 3.16 (m, 4H, CH_2), 7.45-7.50 (dd, *J* = 8.60 & 1.88 Hz, 1H, ArH), 7.72 (s, 1H, ArH), 7.81-7.86 (d, *J* = 8.60 Hz, 1H, ArH).

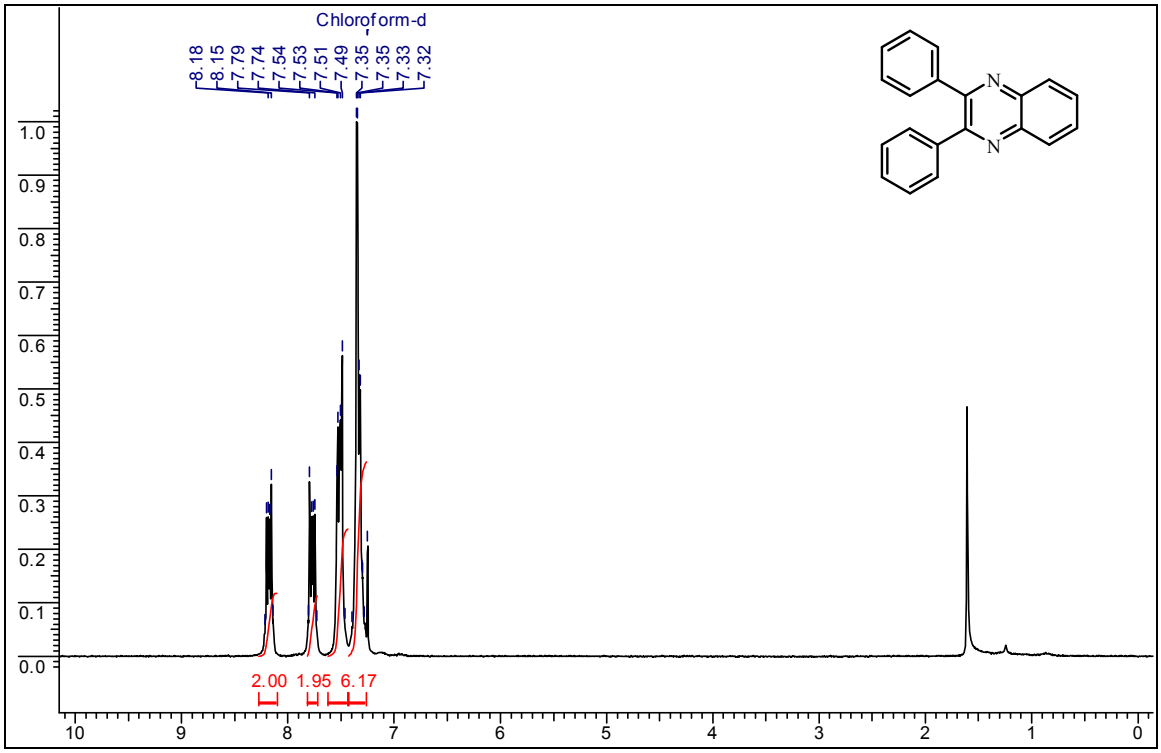
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.6, 22.7, 32.9, 33.0, 127.0, 127.6, 131.0, 139.0, 139.4, 141.1, 152.9, 153.7.

Elemental Analysis : **$C_{13}H_{14}N_2$** (198) Calcd: C, 78.75; H, 7.12; N, 14.13.
Found: C, 78.63; H, 7.33; N, 14.04.

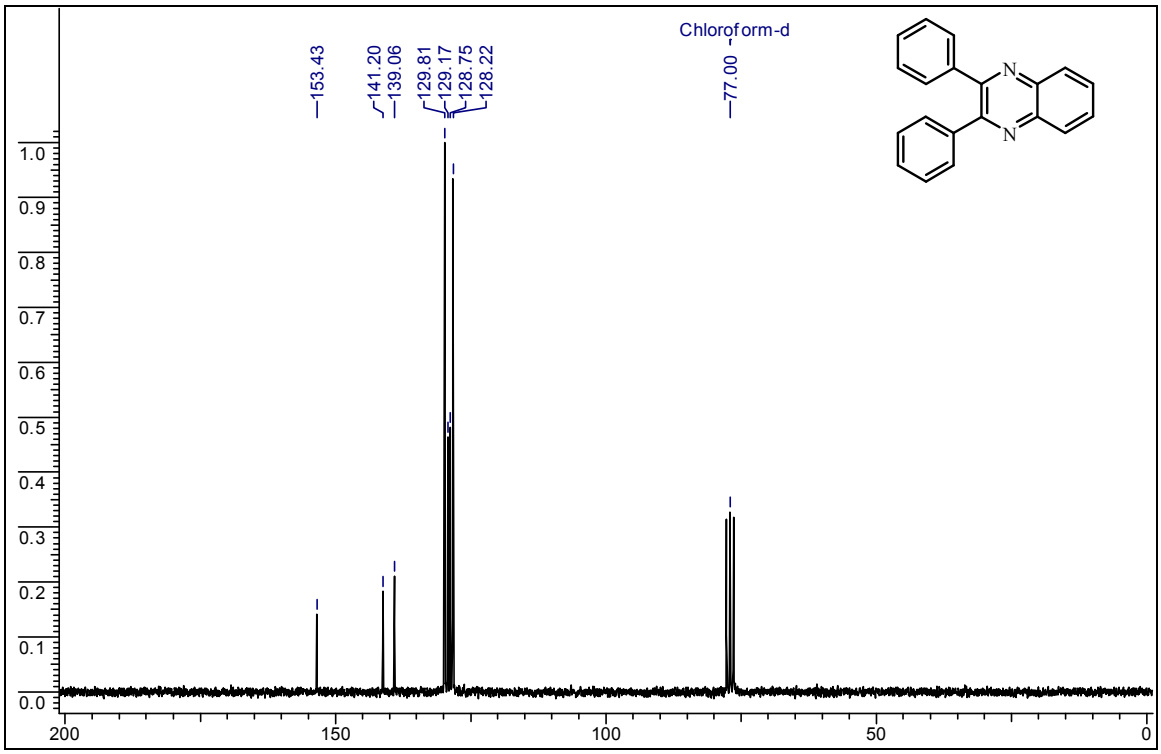
1.3.3.6 Spectra of representative quinoxalines

Sr. No.	NMR spectra of **90**
1	^{1}H NMR and ^{13}C NMR spectra of **90a**
2	^{1}H NMR and ^{13}C NMR spectra of **90d**
3	^{1}H NMR and ^{13}C NMR spectra of **90f**
4	^{1}H NMR and ^{13}C NMR spectra of **90g**
5	^{1}H NMR and ^{13}C NMR spectra of **90h**
6	^{1}H NMR and ^{13}C NMR spectra of **90i**
7	^{1}H NMR and ^{13}C NMR spectra of **90j**
8	^{1}H NMR and ^{13}C NMR spectra of **90k**
9	^{1}H NMR and ^{13}C NMR spectra of **90l**

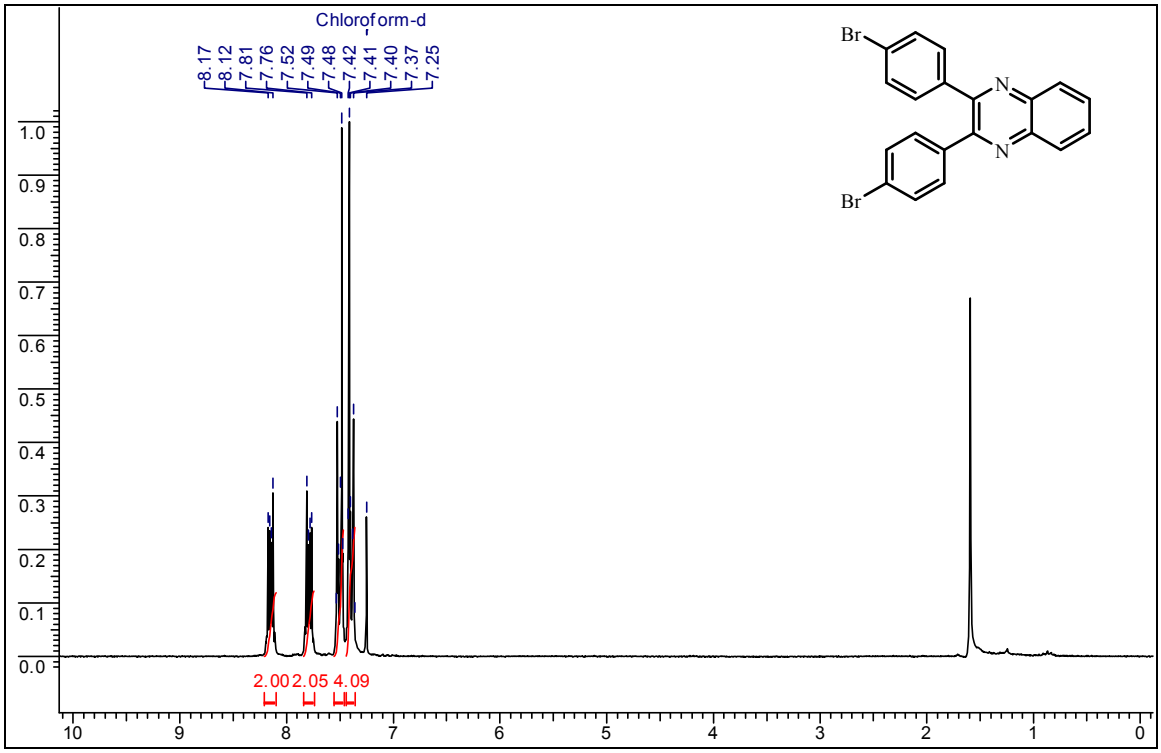
^{1}H NMR spectra of **90a**



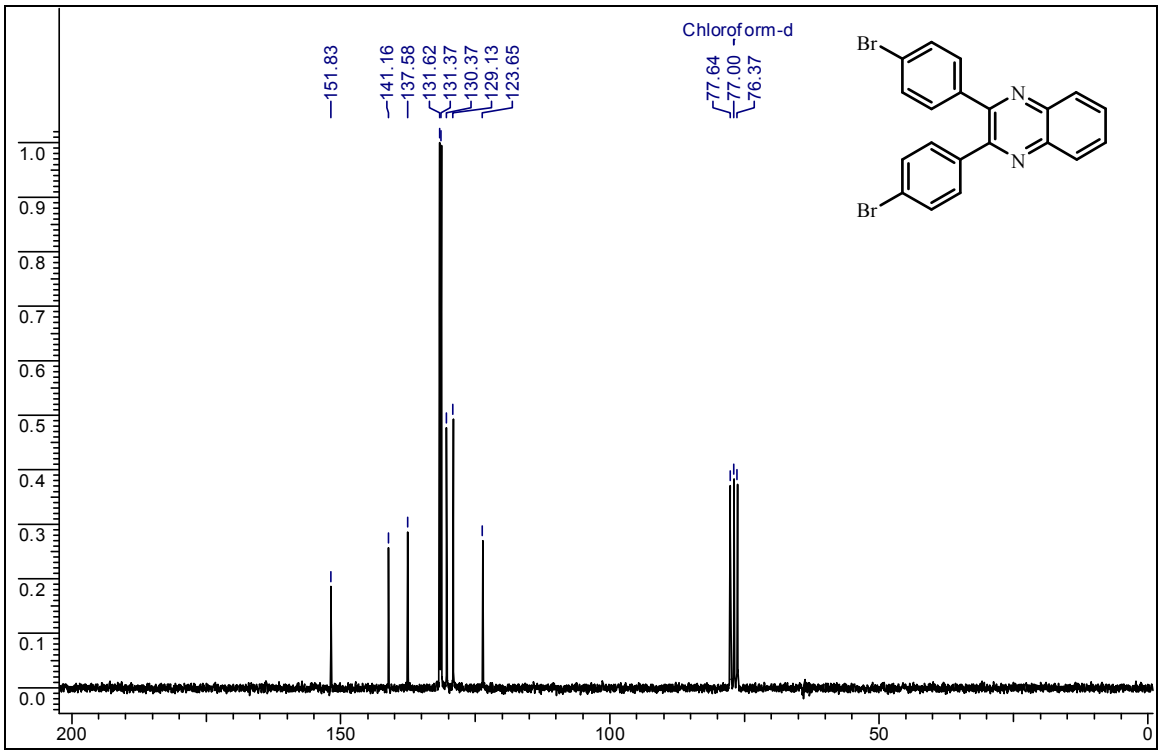
^{13}C NMR spectra of **90a**



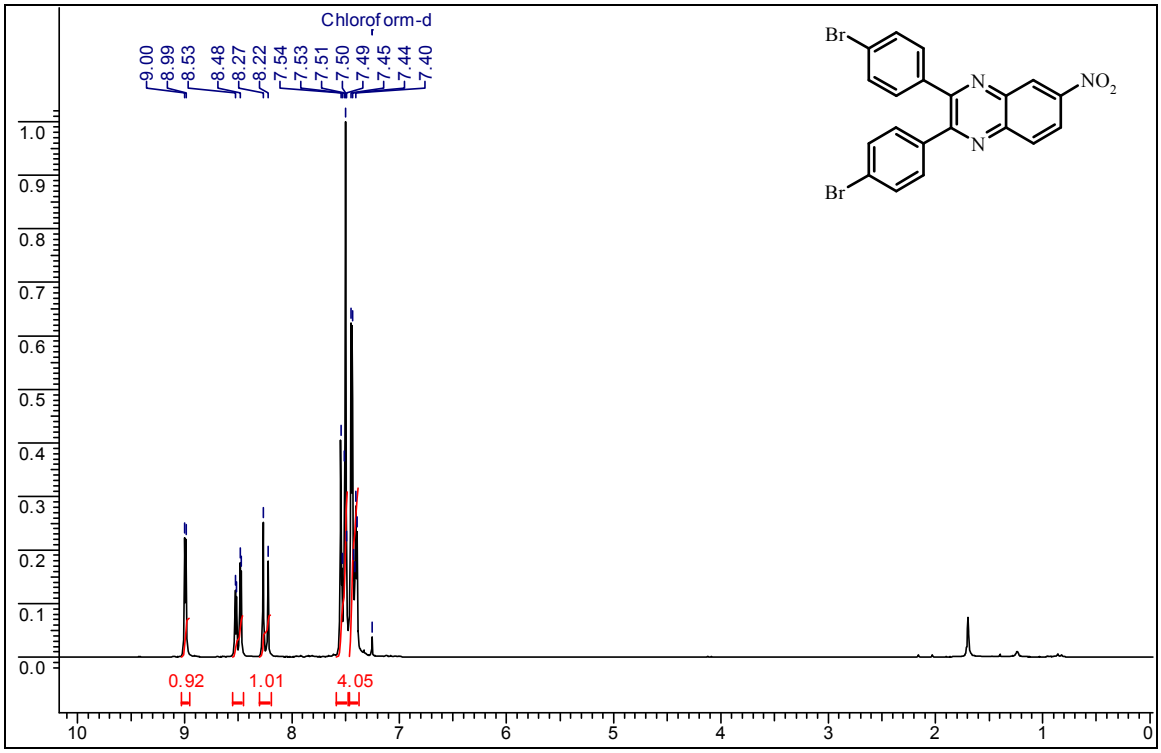
^{1}H NMR spectra of **90d**



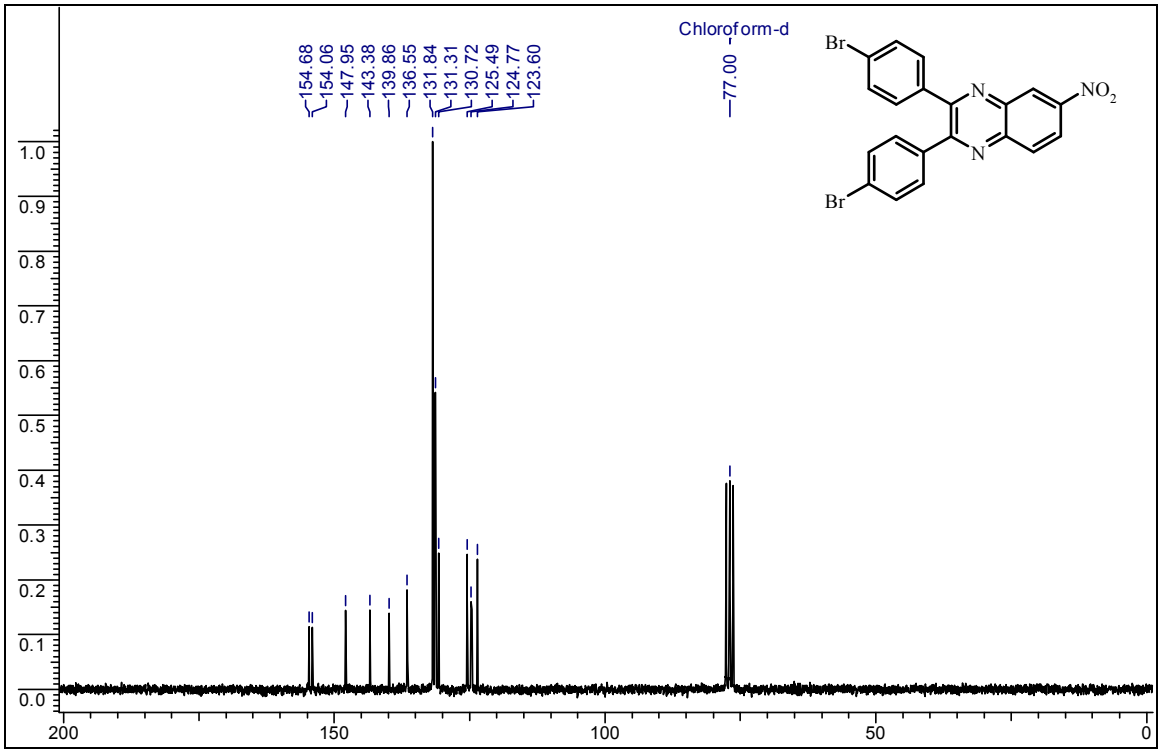
^{13}C NMR spectra of **90d**



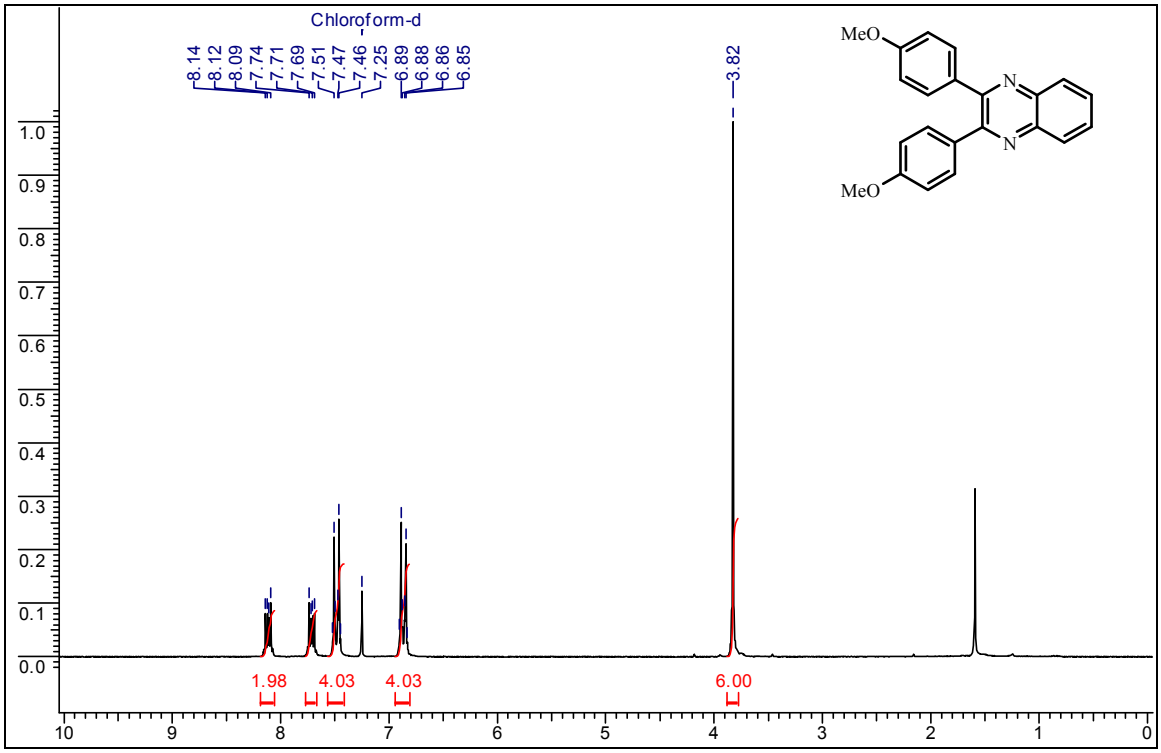
^{1}H NMR spectra of **90f**



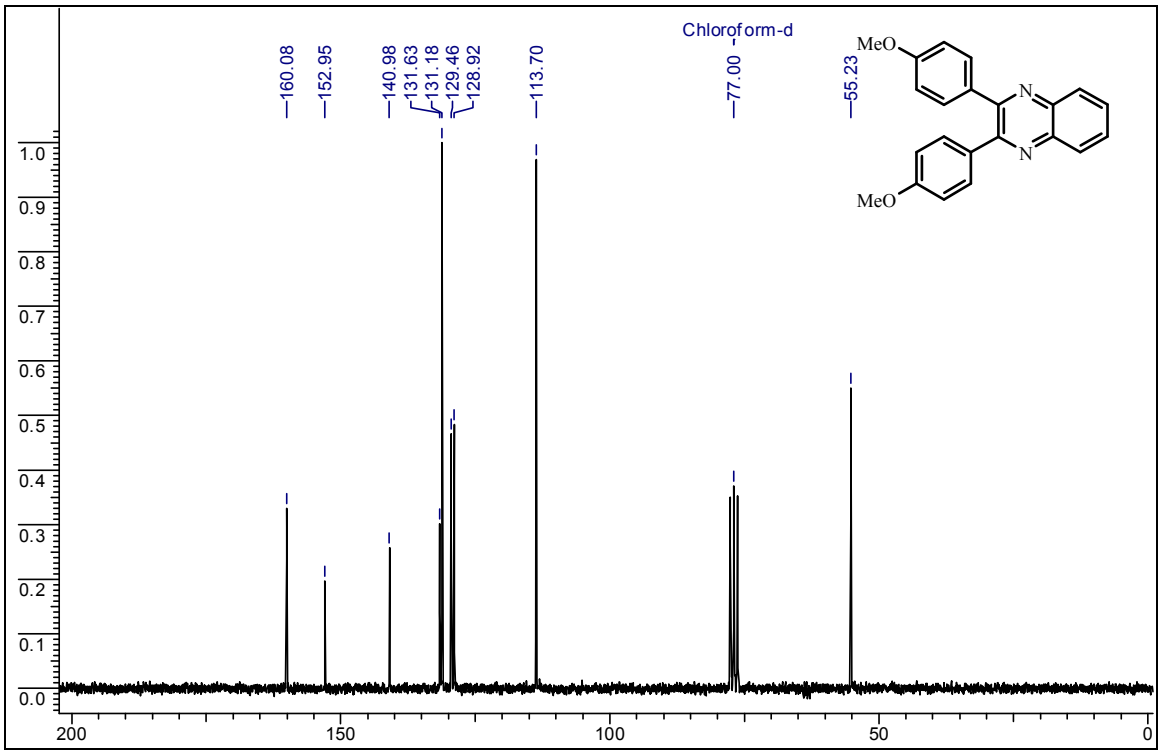
^{13}C NMR spectra of **90f**



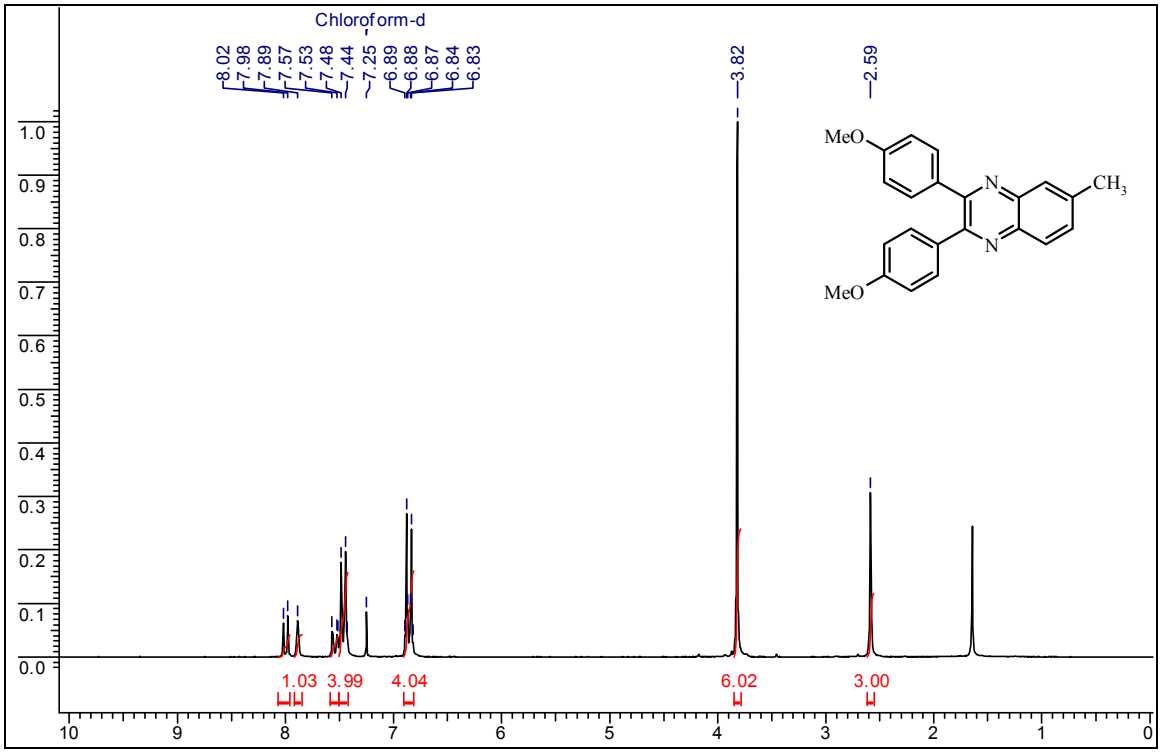
^{1}H NMR spectra of **90g**



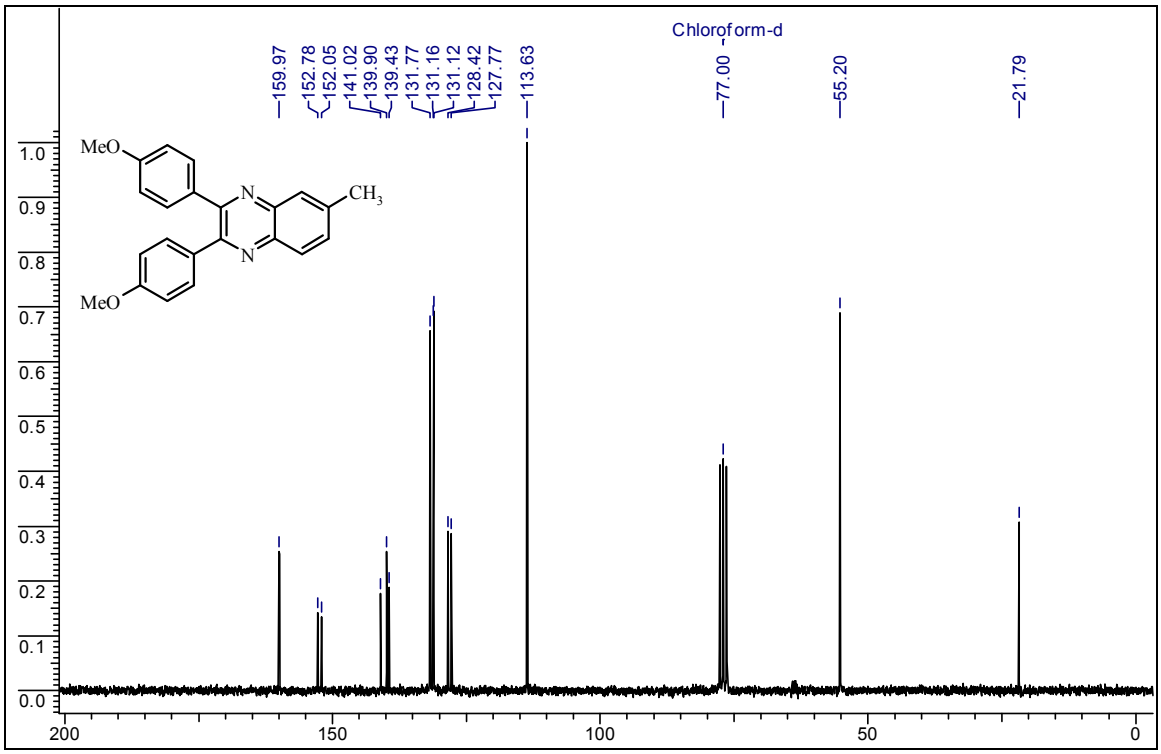
^{13}C NMR spectra of **90g**



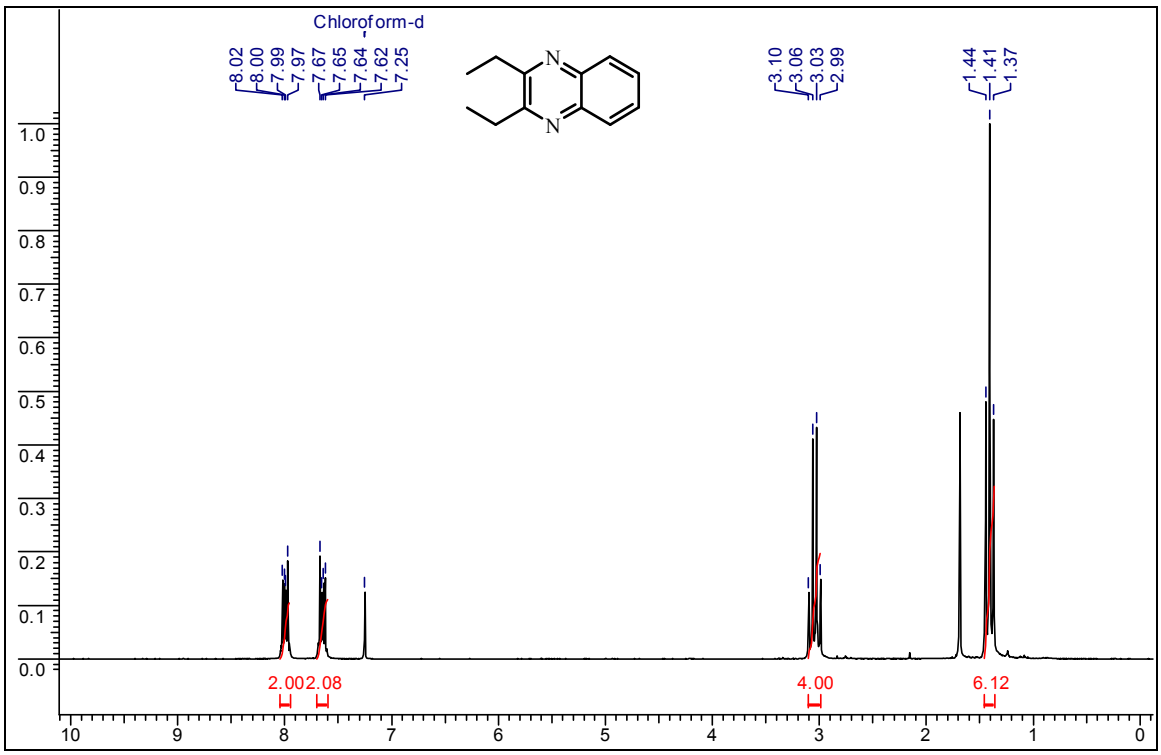
^{1}H NMR spectra of **90h**



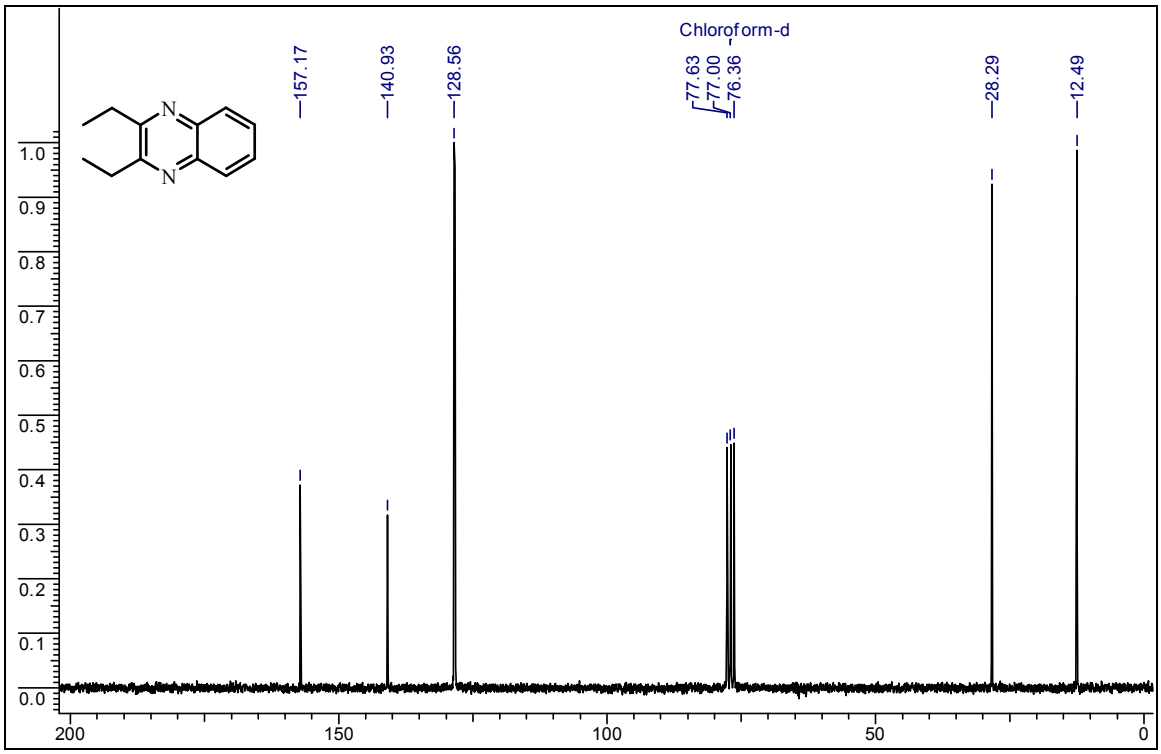
^{13}C NMR spectra of **90h**



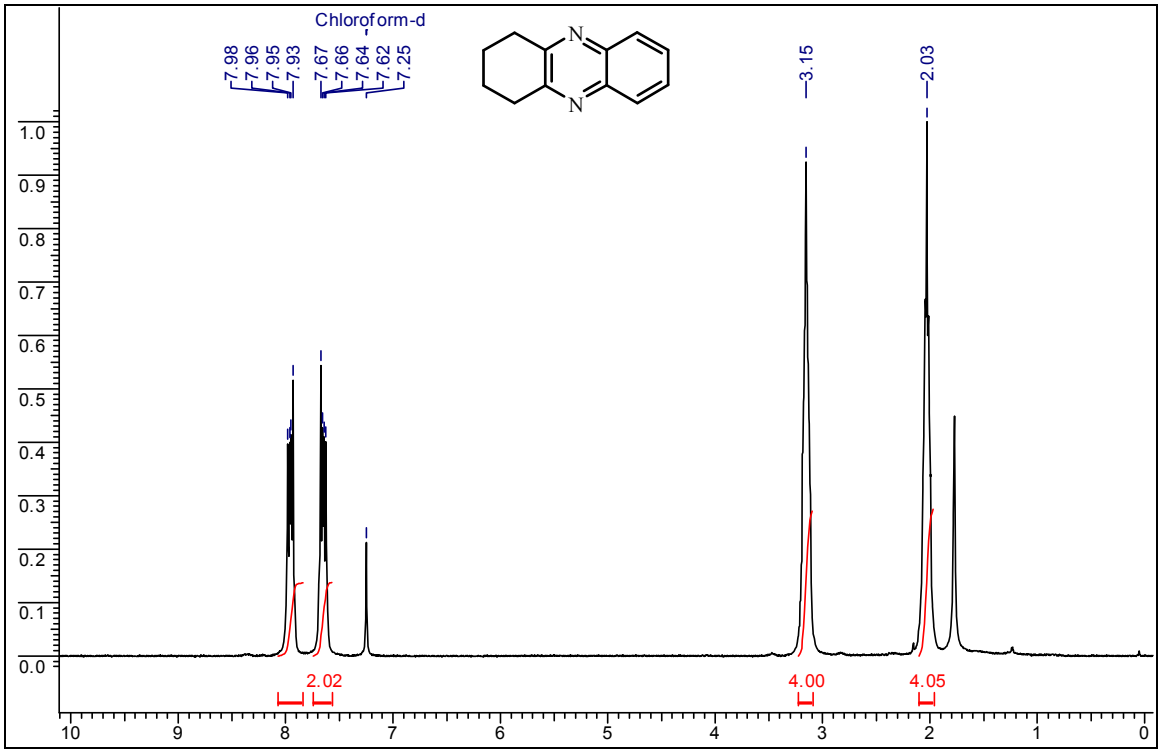
^{1}H NMR spectra of **90i**



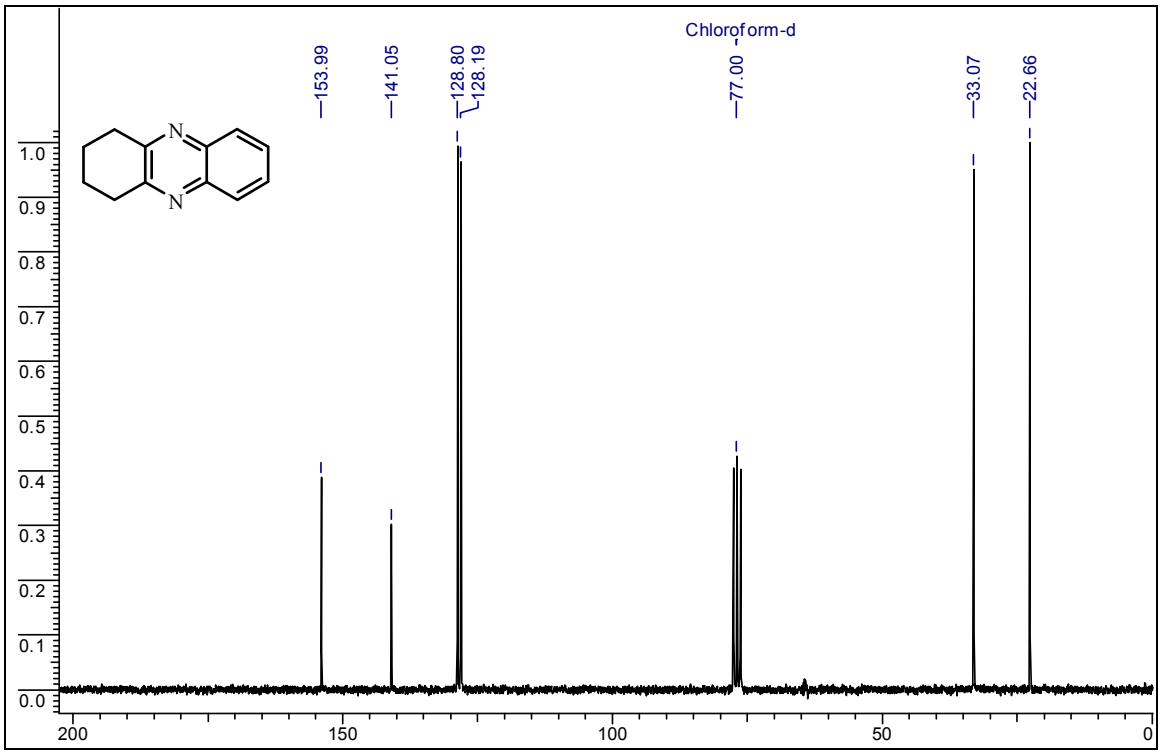
^{13}C NMR spectra of **90i**



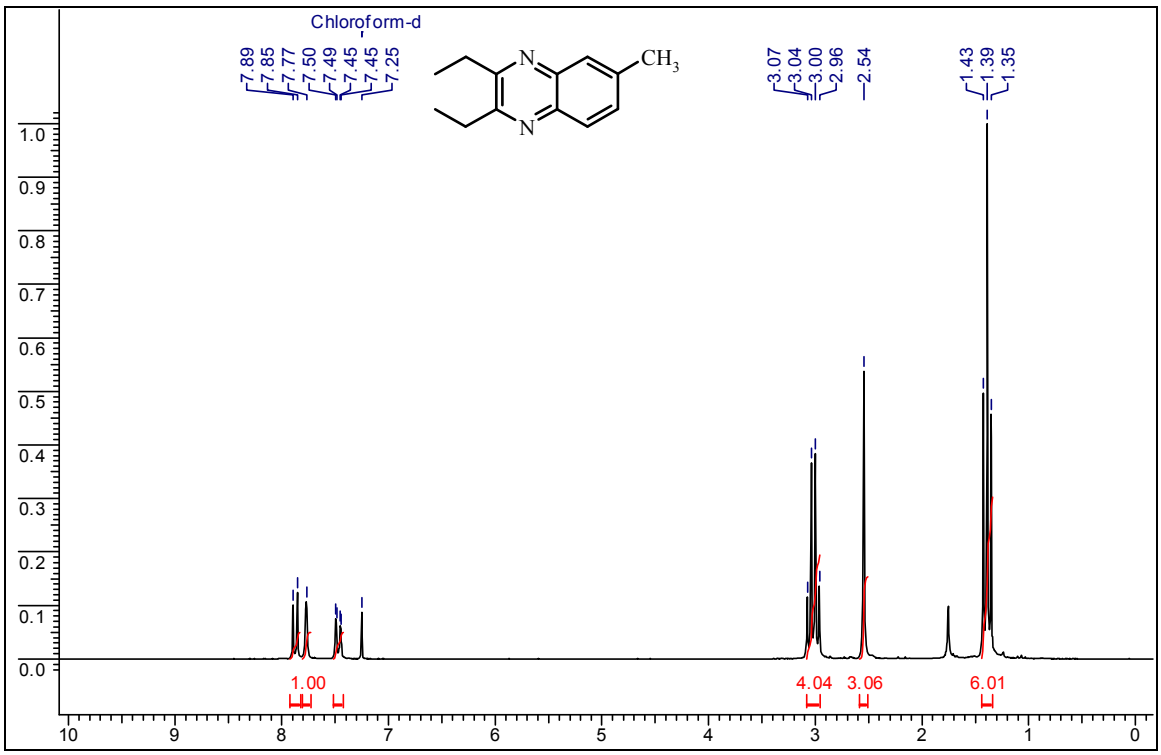
^{1}H NMR spectra of **90j**



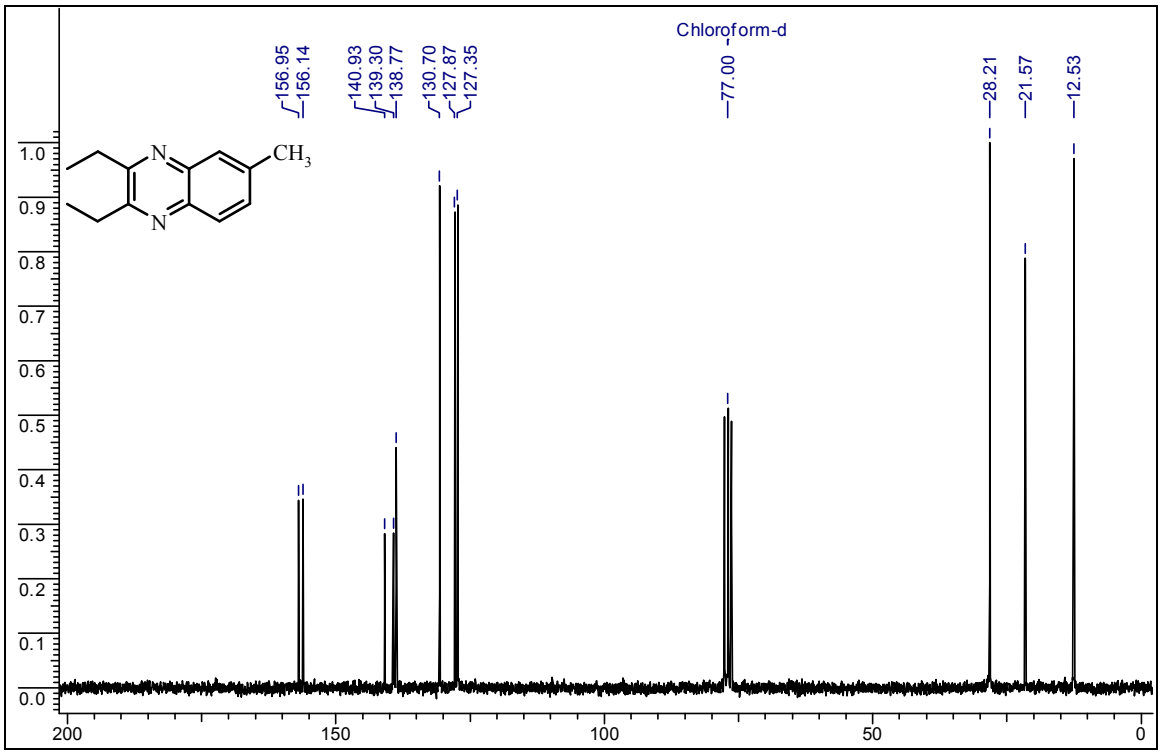
^{13}C NMR spectra of **90j**



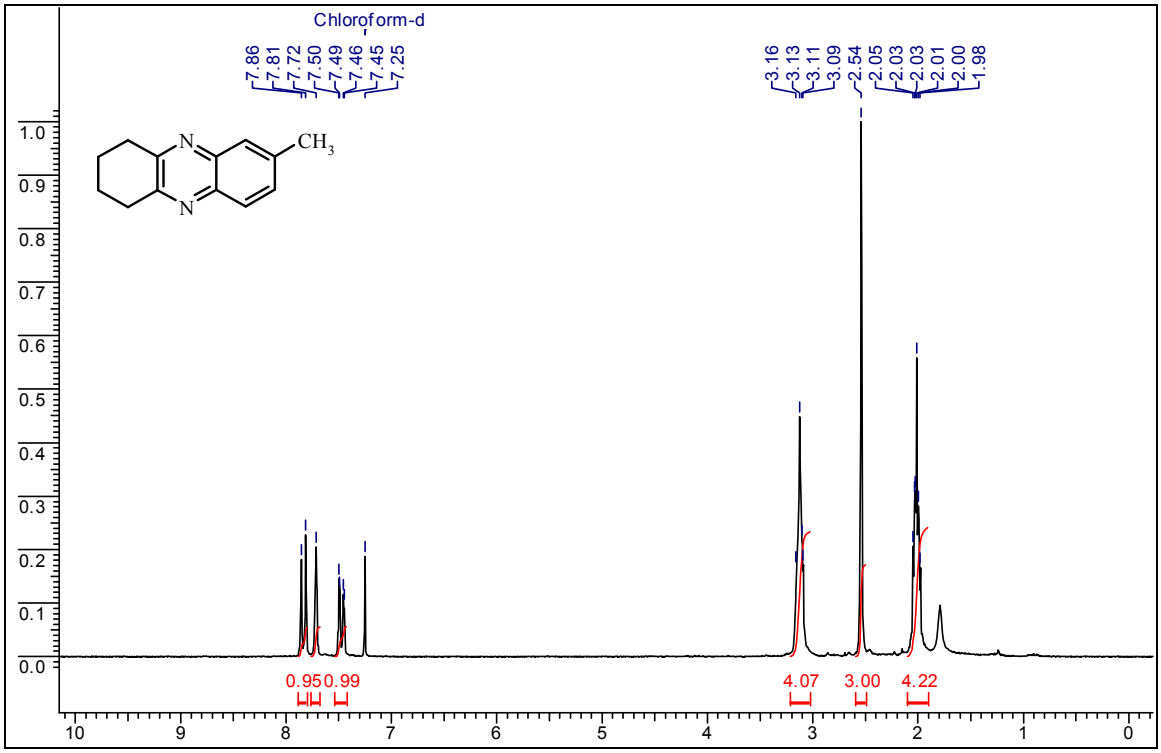
^{1}H NMR spectra of **90k**



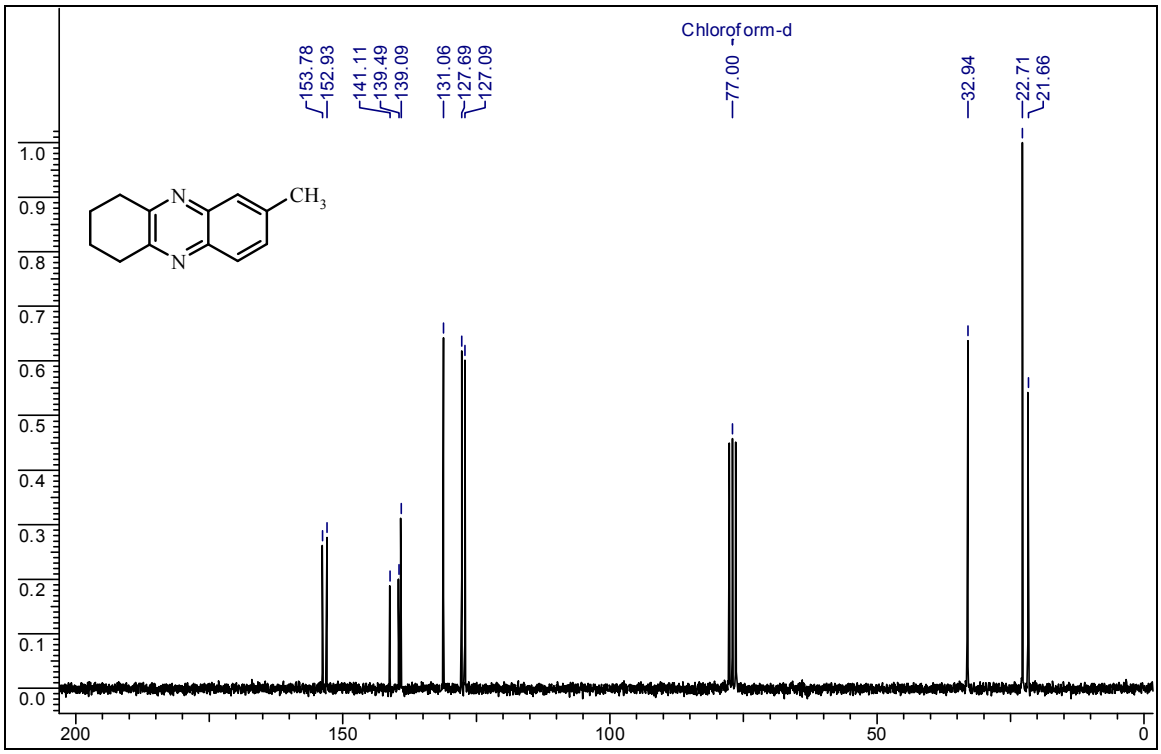
^{13}C NMR spectra of **90k**



^{1}H NMR spectra of **90l**



^{13}C NMR spectra of **90l**



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Chapter 2

Environment-friendly synthesis of 2-aminothiazoles, 2-amino-1,3-selenazoles and 1,4-dihydropyridines

2.0.1 Introduction

The synthesis of new heterocyclic small molecules is a challenging topic in organic chemistry. These compounds play a pivotal role in the search for new therapeutic and drug candidates,[1] in the elucidation of the chemistry of living processes,[2] and are important substrates for the preparation of new materials necessary to improve the quality of life at a sustainable environmental cost.

Organic solvents are conventionally used in chemical synthesis on a large scale for heat transfer and controlling chemical reactivity. However, these organic solvents, belonging to the group of volatile organic compounds (VOC's), account for a great proportion of environmental pollution and waste material; their use is often problematic owing to their toxicity, volatility, flammability, and environmental hazards.[3] In industry they are of course recycled wherever possible. However, in practice this is only rarely accomplished with complete efficiency, which means that some organic solvent from chemical production will inevitably escape and severely pollute the environment. A consequence of the necessity to minimize the amount of toxic waste and by-products from chemical processes is a need for the development of new, more environmentally- friendly synthetic methods in which fewer toxic substances are used. Nowadays in the development of new syntheses, ecological points of view must also be taken into consideration and apportioned due importance in the assessment of viability.[4] This trend towards what has become known as 'Green Chemistry' or 'Sustainable Technology' necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances. Green Chemistry also proposes optimized synthetic methodologies for high product yields and the generation of substances that offer little harm to the environment.

The "ideal synthesis'' should be high yielding (historically the most important measure of the success of a reaction), simple to perform and exhibit high atom efficiency, hence a reduced number of steps and no waste, are safe, and are environmentally acceptable (**Fig.1**)

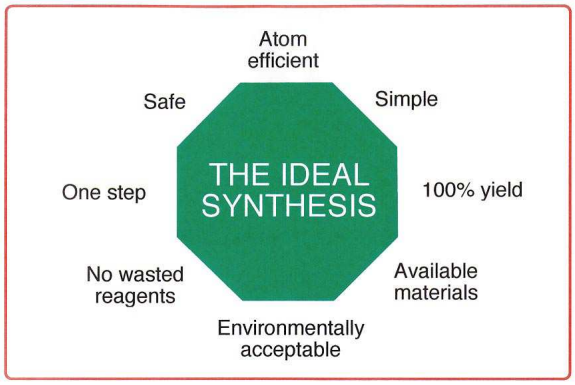

Fig. 1 The ideal synthesis

Since the beginning of "Green chemistry", chemists and scientists have focused on finding out an alternative to volatile organic compounds (VOCs). Among the alternative reaction media studied as substitutes for classical organic solvents are water, fluorous media (e.g. highly fluorinated alkanes, ethers, and tertiary amines), supercritical fluids (e.g. scf-CO2), and more particularly ionic liquids. Another alternative is not to use a reaction medium at all, the so called solvent-free reactions.

Among these alternatives, here we have mainly focused on alternative solvents such as water and solvent-free conditions.

2.0.2 Water as solvent

Among the alternative reaction media, water is one of the most intriguing due to its peculiar properties. Water is the most abundant and available molecule on the planet and many biochemical processes occur in aqueous medium. The recent surge of interest as well as progress in the use of water as a solvent for synthetic chemistry holds great promise for the future. Until, 1980s the use of water as solvent for organic reactions was mainly restricted to simple hydrolysis reactions. The discoveries made in the laboratories of Breslow[5] and Grieco[6] in the early 1980s on the positive effect on rates and selectivities of Diels-Alder reactions are often recognized as the "Big Bang" in aqueous synthesis that triggered a more widespread interest in aqueous media and new additions are continuously being made to the list of organic transformations.[7,8] Many excellent reviews dealing with different aspects on this field have appeared, witnessing the large number of scientists

nowadays involved in the study of water as reaction medium and its implications in different research areas.[9]

Water has unique physical and chemical properties such as a high dielectric constant, large heat capacity, and high cohesive energy density compared to organic solvents. It has also special effects on reactions arising from inter and intramolecular non-covalent interactions leading to novel solvation and assembly processes.

The use of water as the reaction medium offers several advantages as: (i) it is cheap, non-flammable, non-toxic and safe for use, providing opportunities for clean processing and pollution prevention; (ii) it eliminates the additional efforts required to make the substrates/reagents dry before use and thus reduces/eliminates the consumption of drying agents, energy and time; (iii) the unique physical and chemical properties of water often increase the reactivity or selectivity unattainable in organic solvents;[10] and (iv) the product may be easily isolated by filtration, decantation or extraction.

2.0.3 Solvent free-conditions

The best solvent from an ecological point of view is without a doubt no solvent. Solvent-free reactions promise to be an essential facet of 'Green Chemistry.' There are of course a great number of reactions that can already be carried out in the absence of solvent. Examples that spring to mind are the numerous industrially important gas-phase reactions and many polymerizations. Diels-Alder and other pericyclic reactions are also often carried out without solvent. Reports on solvent-free reactions have, however, become increasingly frequent and specialized over the past few years. Areas of growth include reactions between solids,[11] between gases and solids,[12] and on supported inorganic reagents,[13] which in many cases are accelerated or even made possible through microwave irradiation.[14] There are also reactions in which at least one reactant is liquid under the conditions employed, which means that the solvent that would normally be used can simply be left out.

Advantages in using solvent-free reactions, relative to using organic or other reaction media include: (i) there is no reaction medium to collect, purify and recycle; (ii) the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography, and indeed in some cases the need for recrystallization; (iii)

sequential solvent-free reactions are possible in high yielding systems; (iv) the reactions can be rapid, often reaching substantial completion in several minutes compared to hours in organic solvents, (v) there is often no need for specialized equipment; (vi) energy usage can be much lower; (vii) the need for pre-formed salts and metal–metalloid complexes may often be dispensed with; (viii) functional group protection–deprotection can be avoided; (ix) lower capital outlay for equipment in setting up industrial processes; and (x) considerable batch size reduction and processing cost savings are achievable such that such solvent-free protocols are not only more environmentally benign but are also more economically feasible.

2.0.4 References

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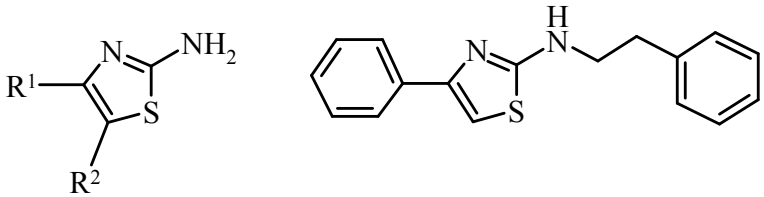
Chapter 2 - Section A

Synthesis of 2-aminothiazoles in water at ambient temperature

2.1.1 Introduction

Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids.[1] This heterocyclic system has found broad application in drug development for the treatment of inflammation,[2] hypertension,[3] bacterial,[4] and HIV infections.[5] Aminothiazoles are known to be ligands of estrogen receptors[6] as well as a novel class of adenosine receptor antagonists.[7] Other analogues are used as fungicides, inhibiting *in vivo* growth of *Xanthomonas*, as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[8] Fanetizole, a derivative of 2-aminothiazole is an anti-inflammatory agent. In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.



2-aminothiazole Fanetizole

Figure 2. Structures of 2-aminothiazoles

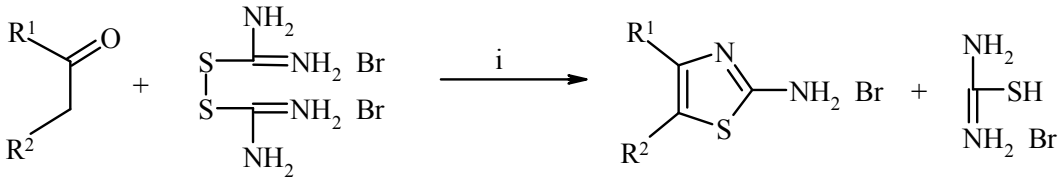
2-Aminothiazole is a commonly occurring structural unit in drug molecules. Indeed, more than 100 papers reporting structures containing 2-aminothiazoles have been published in the *Journal of Medicinal Chemistry* in the last ten years, and furthermore, these papers report activity for a diverse range of biological targets. Therefore, there is good precedent to suggest that libraries of 2-aminothiazoles might afford biologically active molecules. The Hantzsch synthesis of 2-aminothiazoles from α-haloketones and thioureas, first reported in 1887,[9] is a robust and well established procedure affording 2-aminothiazoles in high yield from readily accessible substrates.

2.1.2 Review of literature

In view of importance of 2-aminothiazoles due to its pharmocological properties, various methods were reported for its synthesis in the literature. In this section, we have covered some of the more significant methods.

L. C. King et al. approach (1947)[10]

L. C. King et al. reported the synthesis of 2-aminothiazoles **3** by reacting ketone **1** with formamidine disulfide dihydrobromide **2**. The reaction mixture containing ketone **1** and formamidine disulfide dihydrobromide **2** was heated on steam bath overnight to afford 2-aminothiazole **3**. Formamidine disulfide dihydrobromide initially was prepared from thiourea and bromine (**Scheme 1**).

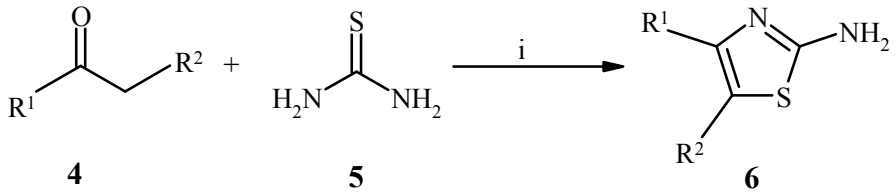


1 **2** **3**

Scheme 1. Reaction conditions: (i) heated on steam, overnight, 19-48%.

L. Carroll King et al. approach (1950)[11]

L. Carroll King et al. reported the synthesis of 2-aminothiazoles **6** from the reaction of ketone **4** (1 equiv), thiourea **5** (2 equiv) and iodine (1 equiv). The reaction mixture containing participating material was heated overnight on steam bath followed by extracting with ether to remove starting material, then the residue was dissolved in hot water, filtered and made basic to afford 2-aminothiazole derivatives (**Scheme 2**).



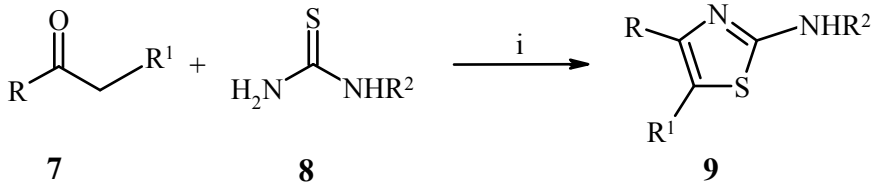
4 **5** **6**

Scheme 2. Reacion conditions: (i) Iodine, 100 °C (steambath), overnight, 18-97%.

H. K. Pujari et al. approach (1986)[12]

H. K. Pujari et al. reported the synthesis of 2-aminothiazoles **9** by reacting ketone **7** with thiourea **8** using *N*-bromosuccinimide (NBS) and catalytic amount of benzoyl peroxide in

anhydrous benzene under reflux conditions over a period of 6 h on steam bath. The initially formed hydrobromide salt was neutralised using potassium carbonate to afford 2-aminothiazole **9** (**Scheme 3**).

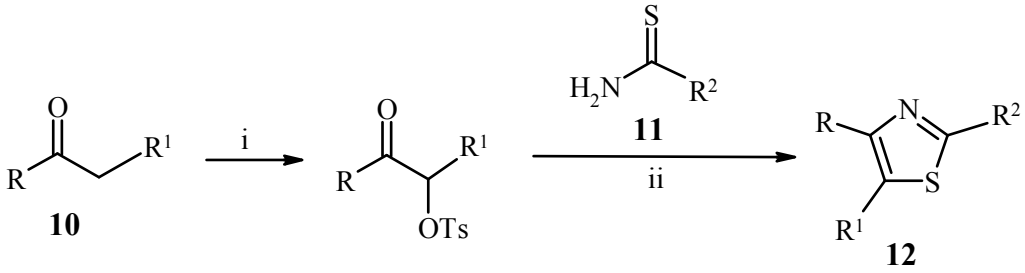


7 **8** **9**

Scheme 3. Reaction conditions: (i) *N*-bromosuccinimide, benzoyl peroxide, anhydrous benzene, reflux, 6 h, 56-90%.

Ram P. Kapoor et al. appraoch (1993)[13]

Ram P. Kapoor et al. reported the synthesis of 2-substituted thiazoles **12** by treating enolizable ketone **10** with thallium (III) *p*-tolylsulfonate as an oxidant in refluxing acetonitrile followed by addition of thiourea or thioamide **11**. An initially formed salt was made basic to afford 2-substituted thiazoles **12** (**Scheme 4**).

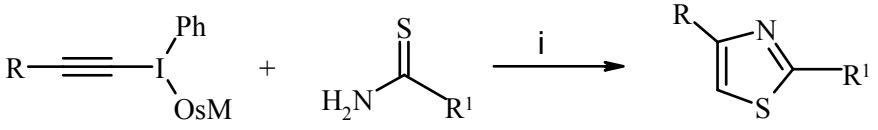


10 **11** **12**

Scheme 4. Reaction conditions: (i) thallanium (III) *p*-tolylsulfonate (TTS), MeCN, reflux 20-30 min;(ii) MeCN, reflux, 1-2 h, K_2CO_3, 70-86%.

Peter Wipf et al. approach (1996)[14]

Peter Wipf et al. reported the synthesis of 2-substituted thiazoles **15** from the reaction of alkynyl(phenyl)iodonium mesylate **13** with thioamide **14** using base such as carbonate or triethylamine in solvent such as Et_2O, EtOAc, MeOH at O°C over a period of 3 h (**Scheme 5**).

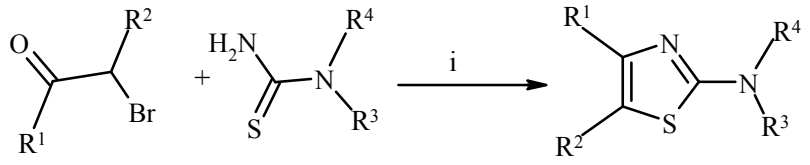


13 **14** **15**

Scheme 5. Reaction conditions : (i) MeOH or Et_2O, carbonate or Et_3N, 3 h, 0 °C, 32-64%.

Stephen P. Watson et al. approach (1996)[15]

Stephen P. Watson et al. in 1996 reported the synthesis of 2-aminothiazoles **18** by using solution phase preparation in which α-bromo ketones **16** were reacted with thiourea **17** in DMF at 75 °C for 5 h. In this way, a series of 2-aminothiazoles were prepared (**Scheme 6**).

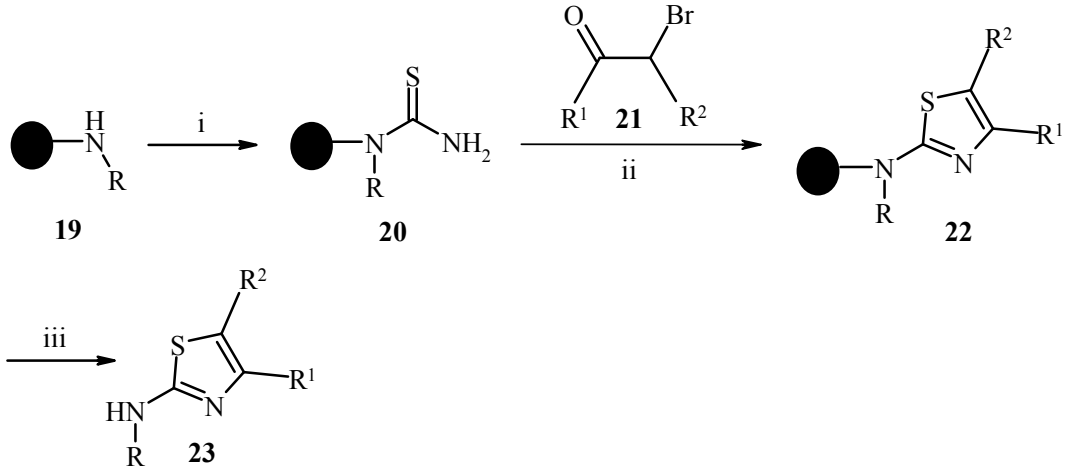


16 **17** **18**

Scheme 6. Reaction conditions **:** (i) DMF, 75 °C, 5 h, purity 44-98%.

John A. Flygare et al. approach (1998)[16]

John A. Flygare et al. reported the synthesis of 2-aminothiazole **23** starting from resin-bound primary or secondary amine **19**. Initially, **19** reacted with fluorenylmethyloxycarbonyl isothiocyanate (Fmoc-NCS) to afford Fmoc-protected thiourea which on further Fmoc-group deprotection under basic conditions, afforded free thiourea **20**. Thiazoles **23** were formed by treatment of the resins bonded thiourea **20** with a dioxane solution of α-bromo ketone **21 (Scheme 7)**.

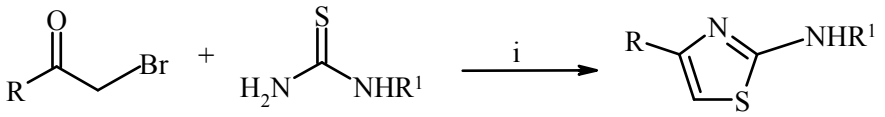


19 **20** **22** **23**

Scheme 7. Reaction conditions**:** (i) fluorenylmethyloxycarbonyl isothiocyanate (Fmoc-NCS), DCM, rt, 30 min; 20% piperidine in methanol, overnight; (ii) dioxane, rt ; (iii) 95% TFA, 5% H_2O, 65-77%.

Simon S. W. Leung et al. approach (2000)[17]

Simon S. W. Leung et al. reported the synthesis of 2-aminothiazoles **26** by heating the reaction mixture containing α-bromo ketone **24** and thiourea **25** in dry acetone at 57 °C for a period of 4 h (**Scheme 8**).

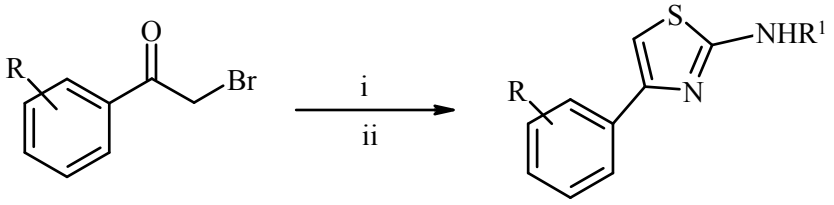


24 **25** **26**

Scheme 8. Reaction conditions **:** (i) dry acetone, 57 °C, 4 h, 32-97%.

Joachim Rudolph approach (2000)[18]

Joachim Rudolph reported the synthesis of 2-aminothiazoles **30** from the reaction of α-bromo ketones **27** with sodium thiocyanate **28** and amines **29** in ethanol at 50 °C over a period of 7-15 h (**Scheme 9**).

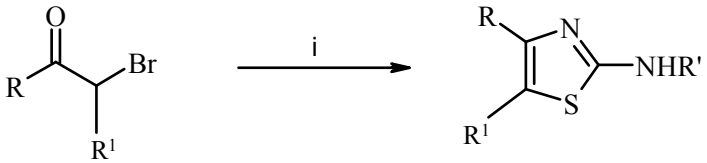


27 **30**

Scheme 9. Reaction conditions **:** (i) NaSCN (**28**), EtOH, 50 °C, 3h; (ii) R^1NH_2 (**29**), EtOH, 50 °C, 4-12 h; 18-99%.

Mitsuo Kodomari et al. approach (2002)[19]

Mitsuo Kodomari et al. reported the synthesis 2-aminothiazoles **32** from α-bromo ketones **31** using a supported reagents system, $KSCN/SiO_2–RNH_3OAc/Al_2O_3$, in which initially α-bromo ketone **31** reacted with $KSCN/SiO_2$ to form α-thiocyano ketone which further reacted with $R'NH_3OAc/Al_2O_3$ to afford 2-aminothiazole **32** (**Scheme 10**).

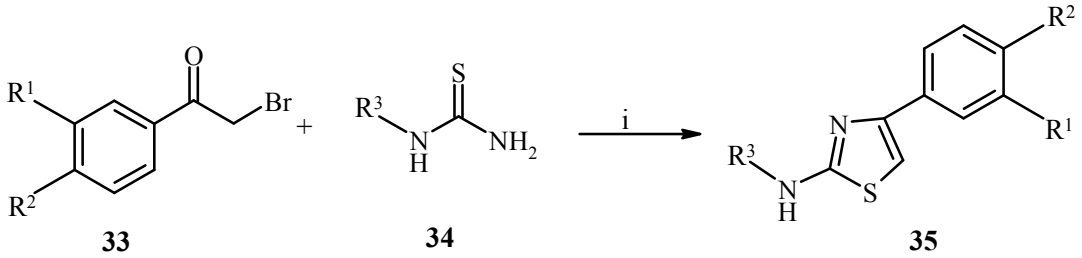


31 **32**

Scheme 10. Reaction conditions**:** (i) $KSCN/SiO_2$-$R'NH_3OAc/Al_2O_3$, benzene, 80 °C, 6 h, 46-96%.

Eduardo Garcia-Egido et al. approach (2002)[20]

Eduardo Garcia-Egido et al. reported the synthesis of 2-aminothiazoles **35** by reacting 1-methyl-2-pyrrolidinone (NMP) solution of α-bromoacetophenone **33** with NMP solution of 1-substituted-thiourea **34** in microreactor (500 V) at 70 °C for 30 min (**Scheme 11**).

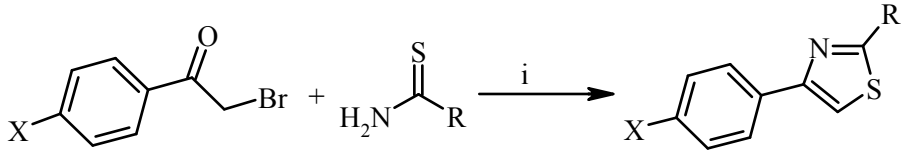


33 **34** **35**

Scheme 11. Reaction conditions : (i) NMP, 70 °C, 30 min, 44-99%

K. Rama Rao et al. approach (2005)[21]

K. Rama Rao et al. reported the synthesis of thiazoles and aminothiazoles **38** from the reaction of phenacyl bromides **36** with thioamide/thiourea **37** in the presence of β-cyclodextrine in water at 60 °C to afford thiazoles and aminothiazoles **38** (**Scheme 12**).

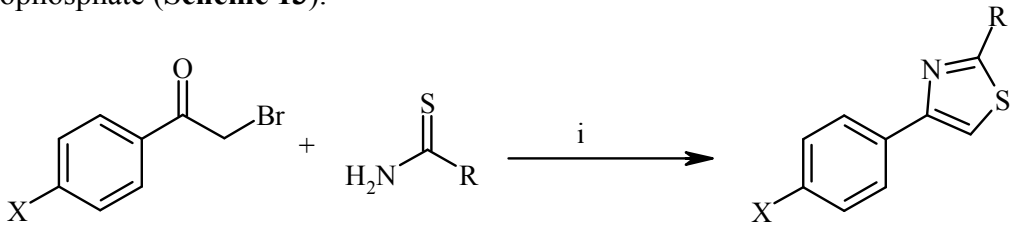


36 **37** **38**

Scheme 12. Reaction conditions: (i) β-cyclodextrin, H_2O, acetone, 50 °C, 1-2.5 h, 80-92%.

Biswanath Das et al. approach (2006)[22]

The authors descibed the synthesis of thiazoles **41** from the condensation of phenacyl bromide **39** with thioamide **40** in methanol by using the catalyst, ammonium 12-molybdophosphate (**Scheme 13**).

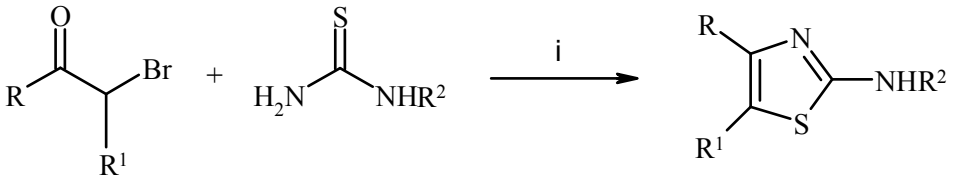


39 **40** **41**

Scheme 13. Reaction conditions **:**(i) ammonium 12-molybdophosphate (AMP), MeOH, rt, 92-98%.

George W. Kabalka et al. approach (2006)[23]

George W. Kabalka et al. reported the synthesis of 2-aminothiazoles **44** by condensing α-bromo ketone **42** with thiourea **43** using microwave in ethanol. The mixture containing α-bromo ketone and thiourea was microwave irradiated at 50 °C (100 W) for 5 min (**Scheme 14**).

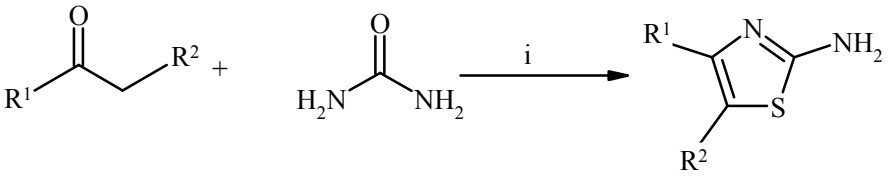


42 **43** **44**

Scheme 14. Reaction conditions**:** (i) MW (50 °C, 100 W), EtOH, 5 min, 87-98%.

M. P. Kaushik et al. appraoch (2007)[24]

M. P. Kaushik et al. reported the synthesis of 2-aminothiazoles **47** by reacting ketone **45** (1 equiv) with thiourea **46** (2 equiv) in acetonitrile using silica chloride catalyst (0.2 equiv) at 0 °C followed by refluxing for 1 h (**Scheme 15**).



45 **46** **47**

Scheme 15. Reaction conditions**:** (i) Silica chloride, MeCN, 80 °C, 1 h, 78-97%.

2.1.3 Present work

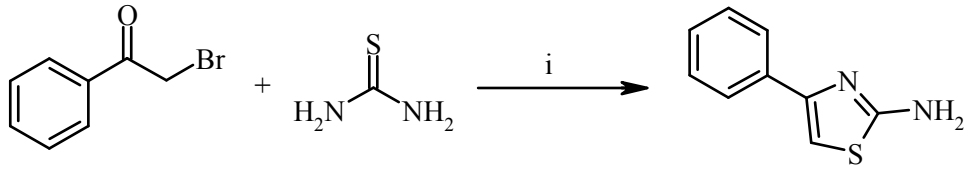
2.1.3.1 Objectives

On reviewing the literature, it can be seen that the various methods were reported for the synthesis of thiazole. However, in spite of their potential utility, many of these reported methods suffer from one or more drawbacks such as harsh reaction conditions, unsatisfactory yields, cumbersome product isolation procedures, polar/ volatile/ hazardous organic solvents and often expensive catalysts. Now days, there has been considerable interest in the development of alternative approaches avoiding the use of volatile polar organic solvents and expensive catalysts.

An alternative to this is the use of water as reaction medium since water has emerging as a 'Green solvent' in organic synthesis in recent years. The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvent but also because water exhibits unique reactivity and selectivity, which is different from those obtained in conventional organic solvents. Thus, elements of novel reactivity as well as selectivity that can not be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry.[25] In continuation to the synthesis of biologically active *N*-heterocycles by using environmentally friendly methods, we became interested in the synthesis of these types of compounds.

2.1.3.2 Results and discussion

When phenacyl bromide **48a** was treated with thiourea **49a** in water at room temperature, to our surprise, the reaction occurred readily affording 4-phenylthiazol-2-amine **50a** in 97% yield in just 1.5 h (**Scheme 16**).



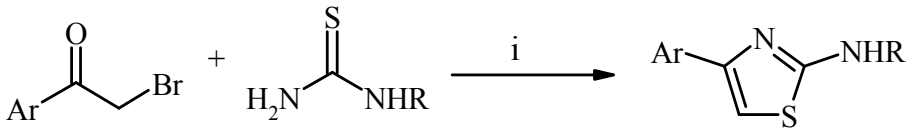
48a **49a** **50a**

Scheme 16. Reaction conditions**:** (i) H_2O, rt, 1.5 h, 97%.

To investigate the advantageous role of water as a solvent for this method, comparative reactions were carried out in other solvents. The reaction of phenacyl bromide **48a** with thiourea **49a** was carried out in DCM and toluene under similar reaction conditions, where it furnished the desired 4-phenylthiazol-2-amine **50a** in yields of only 48% and 12% respectively. When the similar reaction was carried out in more polar solvents such as THF, MeCN and MeOH under identical conditions, 4-phenylthiazol-2-amine **50a** was obtained in yield of 68, 73 and 72% respectively. It is remarkable that the reaction carrid out in water afforded 4-phenylthiazol-2-amine **50a** in excellent yield (97%) which is significantly higher than those obtained for the

volatile/ toxic/ polar organic solvents. The structure of **50a** was assigned on the basis of ^{1}H and ^{13}C spectral data and by comparison with authentic samples prepared by literature procedure. The ^{1}H NMR spectra of **50a** shows a characterstic peak at δ 6.48 ppm corresponding to the hydrogen of thiazole ring, whereas in the ^{13}C NMR spectrum, the peaks appearing at δ 101.4 and 167.8 ppm correspond to C-5 and C-2 respectively of the thiazole ring.

After optimizing the reaction conditions, we next examined the scope and generality of this process using different substituted phenacyl bromides and substituted thioureas (**Scheme 17**).



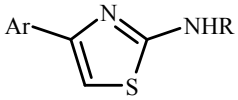
48 **49** **50**

Scheme 17. Reaction conditions**:** (i) H_2O, rt, 1-2 h, 89-97%.

The phenacyl bromide with electron-rich functionality (Table 1, entry 5-8) as well as electron-poor functionality (Table 1, entry 14-17) undergoes condensation reaction with thiourea/substituted thiourea to afford the corresponding thiazol-2-amine in excellent isolated yields. Furthermore, α-bromo-2-acetonaphthone smoothly reacted with thiourea and substituted thiourea affording the corresponding products **50r-v** in excellent yields (Table 1, entry 18-22). The results are summarized in **Table 1**.

N-phenethyl-4-phenylthiazol-2-amine, commonly known as Fanetizole is an anti-inflammatory agent that was reported to have reached phase II clinical trials for the treatment of rheumatoid arthritis.[26] Generally, Fanetizole has been synthesized by using stringent reaction conditions such as microreactors and heating in solvents such as DMF and NMP. Encouraged by our present results, we applied this protocol for the synthesis of an anti-inflammatory drug fanetizole **50d**. For this, we treated phenacyl bromide with 2-phenylethyl thiourea in water as reaction medium under similar conditions to afford Fanetizole in 92% yield in 1.5 h at ambient temperature (**Table 1, Entry 4**).

Table 1 Synthesis of 2-aminothiazoles **50a-v** in water



Entry	Ar	R	Product **50**	Time (h)	Yield (%)[a]
1	C_6H_5	H	**50a**	1.5	97
2	C_6H_5	CH_3	**50b**	2	94
3	C_6H_5	C_6H_5	**50c**	1	96
4	C_6H_5	$C_6H_4CH_2CH_2$	**50d**	1.5	92
5	4-CH_3-O-C_6H_4	H	**50e**	1	89
6	4-CH_3-O-C_6H_4	CH_3	**50f**	1	93
7	4-CH_3-O-C_6H_4	C_6H_5	**50g**	1	96
8	4-CH_3-O-C_6H_4	$C_6H_4CH_2CH_2$	**50h**	1.5	97
9	4-F-C_6H_4	H	**50i**	2	93
10	4-F-C_6H_4	CH_3	**50j**	2	93
11	4-F-C_6H_4	C_6H_5	**50k**	1	96
12	4-F-C_6H_4	$C_6H_4CH_2$	**50l**	1	96
13	4-F-C_6H_4	$C_6H_4CH_2CH_2$	**50m**	1	95
14	3-O_2N-C_6H_4	H	**50n**	2	97
15	3-O_2N-C_6H_4	CH_3	**50o**	2	92
16	3-O_2N-C_6H_4	C_6H_5	**50p**	1.5	90
17	3-O_2N-C_6H_4	$C_6H_4CH_2$	**50q**	2	91
18	β-$C_{10}H_7$	H	**50r**	1	94
19	β-$C_{10}H_7$	CH_3	**50s**	2	89
20	β-$C_{10}H_7$	C_6H_5	**50t**	2	90
21	β-$C_{10}H_7$	$C_6H_4CH_2$	**50u**	2	93
22	β-$C_{10}H_7$	$C_6H_4CH_2CH_2$	**50v**	2	92

[a]: Isolated yield after column chromatography

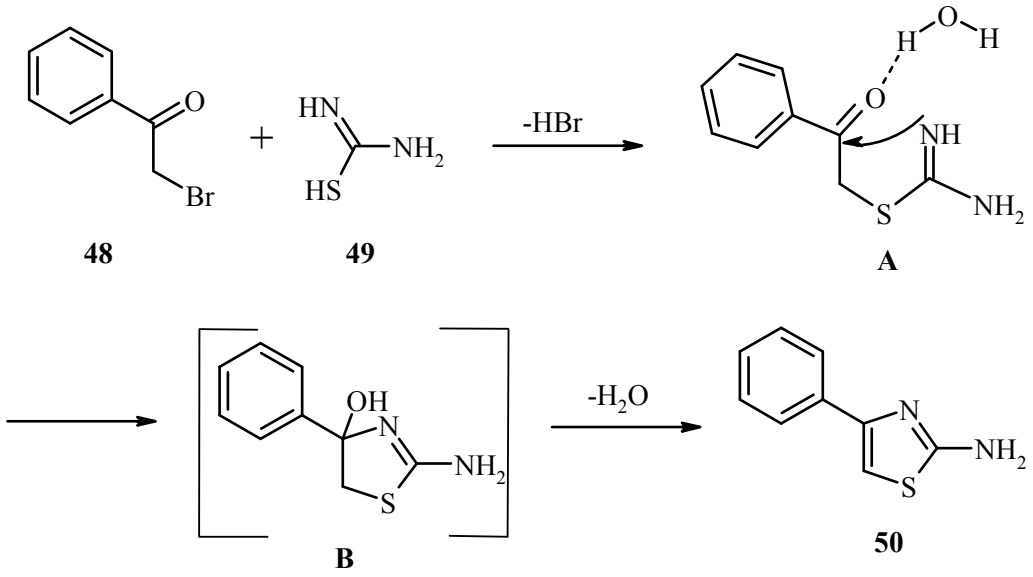
The experimental procedure is very simple and easy to carry out. A mixture of phenacyl bromide and thiourea was vigorously stirred in water at room temperature

until the completion of reaction. Progress of reaction was monitored by Thin-Layer Chromatography (TLC). On completion of the reaction, extraction of reaction mixture with ethyl acetate followed by evaporation of solvent gave products which were purified by column chromatography to yield pure products in excellent yields. All the products were characterized by IR, melting point, ^{1}H NMR, ^{13}C NMR spectral and elemental analyses. The structure of all the known compounds were further confirmed by comparing their melting points with those reported in literature.

Despite the various methods reported for the synthesis of the 2-aminothiazoles by using various organic solvents such as ethanol, methanol, DMF, acetone etc with or without catalyst, there has been considerable interest in the development of alternative approaches avoiding the use of volatile polar organic solvents and expensive catalyst. An alternative to this is the use of water as reaction medium since water has been emerging as a 'Green solvent' in organic synthesis. To the best of our knowledge, this is the first approach for the synthesis of 2-aminothiazoles carried out in water at ambient temperature. It can be observed that almost all reactions were complete in 1-2 h in water without any added catalyst or co-organic solvent at ambient temperature. Water itself promotes the reactions. The use of water as a clean, inexpensive and universal solvent combines features of both economic and environmental advantages. The amount of water used in the reaction did not have any significant influence on the overall rate of the reaction and yields of products. This was confirmed by scaling up the concentration from the present 2% solids (w/v) to 20% solids (w/v) in the case of 4-phenylthiazol-2-amine **50a**. The reaction went to completion in identical time and with the same isolated yields as for the diluted reaction mixture. This observation assumes great significance for optimizing reactor volumes during scale-up operations. A highly efficient stirring is required for the success of this reaction. The role of water as the reaction medium and its mechanism are still not clear. Water, probably due to its unique properties such as hydrogen bonding ability, high dielectric constant and high polarity appears to be more efficient medium for this reaction. The good results obtained following our simple procedure are a pleasant surprise in view of the numerous catalysts employed in organic solvents to synthesize this class of compounds.

2.1.3.3 Plausuble mechanism

The mechanism may be postulated as below. It may be possible that water promotes the reaction through hydrogen bond formation with carbonyl oxygen atom of intermediate **A** thereby increasing the electrophilicity of carbon center which may be attacked by nucleophilic nitrogen to from cyclized intermediate **B**. Intermediate **B** then thansformed to more stable product **50** (**Scheme 18**).



48 **49** **A** **B** **50**

Scheme 18. Plausible mechanism

2.1.4 Conclusion

In conclusion, we have described a simple, highly efficient and environment-friendly protocol for the synthesis of 2-aminothiazole derivatives in water as reaction medium at ambient temperature. This process avoids the use of highly polar and toxic volatile organic solvents such as DMF, dioxane, methanol and also a catalyst, with the water itself playing the dual role of a solvent and promoter. Furthermore, the procedure offers several advantages including improved yields, simple experimental procedure, cleaner reactions, and low cost which makes it a useful and attractive strategy in view of economic and environmental advantages. The successful application of this protocol for the preparation of the anti-inflammatory drug fanetizole is a significant contribution for the development of a green commercial process for the same.

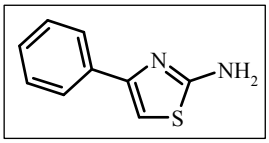
2.1.5 Experimental

2.1.5.1 General procedure for the synthesis of 2-aminothiazoles

A mixture of aromatic α-bromoketone **48** (1 mmol) and thiourea **49** (1.1 mmol) was stirred in water (5 mL) at room temperature under vigorous magnetic stirring for the specified time as mentioned in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (2 x 15 mL). The organic layer was separated from aqueous layer. The combined organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to obtain the crude solid product. The crude product was further purified by column chromatography using ethyl acetate/ petroleum ether as eluent to afford the pure product **50**.

2.1.5.2. Characterization data for 2-aminothiazoles 50a-v

4-Phenylthiazol-2-amine (50a)



Yellow solid

M. P. (°C) **:** 150-151 (Lit.[27] 150-151).

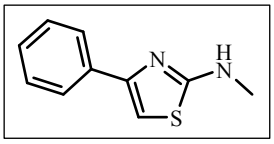
IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3433, 3019, 1602, 1531, 1519, 1482, 1339, 757.

^{1}H NMR ($CDCl_3$+DMSO-D_6, 200 MHz) **:** δ 5.87 (bs, 2H, NH_2), 6.48 (s, 1H, thiazole H), 7.02-7.20 (m, 3H, ArH), 7.54-7.59 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$+DMSO-D_6, 50 MHz) **:** δ 101.4, 125.3, 126.9, 128.0, 134.3, 150.2, 167.8.

Elemental Analysis : **$C_9H_8N_2S$** (176) Calcd: C, 61.34; H, 4.58; N, 15.90.
Found: C, 61.43; H, 4.46; N, 15.81.

***N*-methyl-4-phenylthiazol-2-amine (50b)**



Yellow solid

M. P. (°C) **:** 136-137 (Lit.[27] 135-136).

IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3428, 3018, 2957, 1668, 1560, 1526, 1482, 1328, 757.

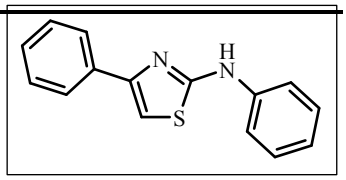
^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 2.90.2-92 (d, J = 4.8 Hz, 3H, CH_3), 5.62 (bs, 1H, NH), 6.64 (s, H, thiazole H), 7.19-7.35 (m, 3H, ArH), 7.70-7.75 (m, 2H, ArH).

^{13}C NMR **:** δ 32.2, 100.5, 126.0, 127.5, 128.4, 135.0, 151.6, 171.3.

($CDCl_3$, 50 MHz)

Elemental Analysis : **$C_{10}H_{10}N_2S$** (190) Calcd: C, 63.13; H, 5.30; N, 14.72.
Found: C, 63.21; H, 5.24; N, 14.81.

***N*,4-diphenylthiazol-2-amine (50c)**



Faint yellow solid

M. P. (°C) : 135-136 (Lit.[27] 136-137).

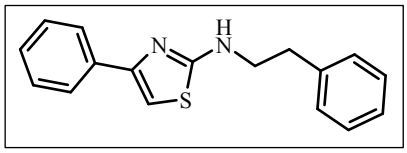
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3404, 3019, 1601, 1599, 1541, 1498, 1311, 758.

^1H NMR : δ 6.83 (s, 1H, thiazole H), 7.02-7.11 (m, 1H, ArH), 7.30-7.44 (m,
($CDCl_3$, 200 MHz) 7H, ArH), 7.49 (bs, 1H, NH), 7.83-7.87 (m, 2H, ArH).

^{13}C NMR : 101.6, 118.2, 122.8, 126.1, 127.8, 128.5, 129.3, 134.5, 140.3,
($CDCl_3$, 50 MHz) 151.2, 164.8.

Elemental Analysis : **$C_{15}H_{12}N_2S$** (252) Calcd: C, 71.40; H, 4.79; N, 11.10
Found: C, 71.54; H, 4.68; N, 11.22.

***N*-phenethyl-4-phenylthiazol-2-amine (Fanetizole) (50d)**



White crystalline solid

M. P. (°C) : 116-117.

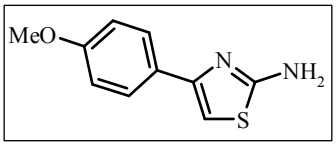
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3404, 3196, 3016, 2975, 1602, 1584, 1552, 1495, 1463, 1335, 754.

^1H NMR : δ 2.94-3.01 (t, *J* = 7.0 Hz, 2H, CH_2), 3.52-3.62 (q, *J* = 7.0 Hz, 2H,
($CDCl_3$, 200 MHz) CH_2), 5.24 (brs, 1H, NH), 6.70 (s, 1H, thiazole H), 7.24-7.37 (m, 8H, ArH), 7.76-7.80 (dd, *J* = 8.3 & 1.6 Hz, 2H, ArH).

^{13}C NMR : δ 35.4, 47.1, 100.7, 126.0, 126.5, 127.6, 128.5, 128.6, 128.7, 134.9,
($CDCl_3$, 50 MHz 138.4, 151.5, 169.4.

Elemental Analysis : **$C_{17}H_{16}N_2S$** (280) Calcd: C, 72.82; H, 5.75; N, 9.99.
Found: C, 72.68; H, 5.81; N, 10.04.

4-(4-Methoxyphenyl)thiazol-2-amine (50e)



White solid

M. P. (°C) : 206-207 (Lit.[11] 204-205).

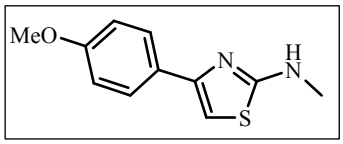
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3435, 3019, 1603, 1535, 1517, 1449, 1325, 758.

^{1}H NMR (CDCl$_3$+DMSO-D$_6$, 200 MHz) : δ 3.24 (s, 3H. OCH_3), 5.89 (bs, 2H. NH_2), 5.99 (s, 1H, thiazole H), 6.28-6.32 (d, *J* = 8.7 Hz, 2H, ArH), 7.10.7.15 (d, *J* = 8.7 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$+DMSO-D$_6$, 50 MHz) : δ 53.4, 97.6, 112.1, 125.3, 126.3, 148.4, 157.1, 166.7.

Elemental Analysis : **$C_{10}H_{10}N_2OS$** (206) Calcd: C, 58.23; H, 4.89; N, 13.58.
Found: C, 58.37; H, 4.72; N, 13.49.

4-(4-Methoxyphenyl)-*N*-methylthiazol-2-amine (50f)



Yellow solid

M. P. (°C) : 138-139 (Lit.[27] 138-139)

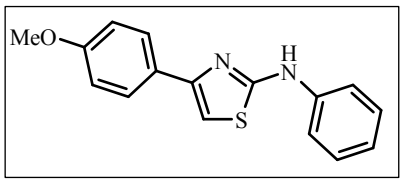
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3459, 3019, 2957, 2838, 1668, 1574, 1532, 1498, 1330, 758.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.93 (s, 3H, CH_3), 3,82 (s, 3H, OCH_3), 6.09 (bs, 1H, NH), 6.56 (s, 1H, thiazole H), 6.88-6.92 (d, *J* = 8.8 Hz, 2H, ArH), 7.69-7.74 (d, *J* = 8.8 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 32.2, 55.2, 98.7, 113.8, 127.3, 128.0, 151.4, 159.1, 171.2.

Elemental Analysis : **$C_{11}H_{12}N_2OS$** (220) Calcd: C, 59.97; H, 5.49; N, 12.72.
Found: C, 59.88; H, 5.57; N, 12.79.

4-(4-Methoxyphenyl)-*N*-phenylthiazol-2-amine (50g)



Yellow solid

M. P. (°C) : 138-139 (Lit.[27] 139-140)

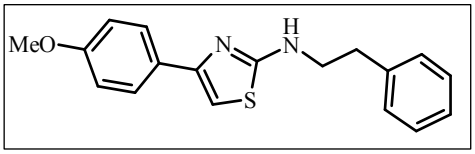
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3346, 3019, 2958, 2933, 1668, 1596, 1544, 1487, 1345, 757.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 3.84 (s, 3H, OCH_3), 6.69 (s, 1H, thiazole H), 6.90-6.95 (d, *J* = 8.8 Hz, 2H, ArH), 7.02-7.10 (m, 1H), 7.31-7.41 (m, 5H, ArH), 7.76-7.80 (d, *J* = 8.8 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 55.2, 99.9, 113.9, 118.11 122.8, 127.3, 129.3, 140.3,150.9, 164.5.

Elemental Analysis : **$C_{16}H_{14}N_2OS$** (282) Calcd: C, 68.06; H, 5.00; N, 9.92.
Found: C, 68.19; H, 4.89; N, 10.02.

4-(4-Methoxyphenyl)-*N*-phenethylthiazol-2-amine (50h)



White solid

M. P. (°C) : 121-122

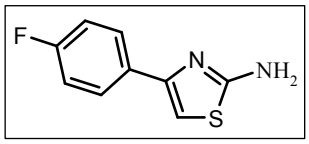
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3228, 3019, 2958, 1549, 1492, 1333, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.93-3.0 (t, *J* = 6.9 Hz, 2H, CH_2), 3.51-3.60 (q, *J* = 6.9 Hz, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 5.32 (bs, 1H, NH), 6.56 (s, 1H, thiazole H), 6.87-6.92 (d, *J* = 8.9 Hz, 2H, ArH), 7.21-7.37 (m, 5H, ArH), 7.69-7.74 (d, *J* = 8.9 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 35.3, 47.1, 55.2, 98.8, 113.8, 126.5, 127.2, 127.8, 128.6, 128.7, 138.4, 151.1, 159.1, 169.5.

Elemental Analysis : **$C_{18}H_{18}N_2OS$** (310) Calcd: C, 69.65; H, 5.84; N, 9.02.
Found: C, 69.52; H, 5.95; N, 9.11.

4-(4-Fluorophenyl)thiazol-2-amine (50i)



Yellow solid

M. P. (°C) : 102-103

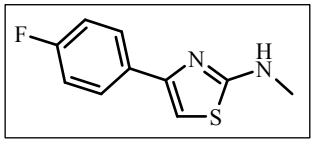
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3489, 3019, 1601, 1537, 1490, 1333, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 5.04 (bs, 2H, NH_2), 6.64 (s, 1H, thiazole H), 7.01-7.09 (m, 2H, ArH), 7.70-7.77 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 102.1, 115.3, 115.5, 127.6, 130.9, 150.1, 161.3, 163.3, 167.6.

Elemental Analysis : **$C_9H_7FN_2S$** (194) Calcd: C, 55.65; H, 3.63; N, 14.42.
Found: C, 55.73; H, 3.56; N, 14.53.

4-(4-Fluorophenyl)-*N*-methylthiazol-2-amine (50j)



White solid

M. P. (°C) : 136-137 (Lit.[28] 137-130)

IR ($CHCl_3$, cm^{-1}) : ν_{max} 3360, 3019, 1667, 1588, 1559, 1532, 14928, 1325, 758.

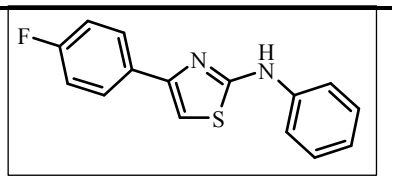
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.97-2.99 (d, *J* = 4.4 Hz, 3H, CH_3), 5.67 (bs, 1H, NH), 6.63 (s, 1H, thiazole H), 7.02-7.10 (m, 2H, ArH), 7.73-7.80 (m, 2H,

ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 32.1, 100.0, 115.1, 115.5, 127.6, 127.7, 131.2, 131.3, 150.6, 159.8, 164.7, 171.4.

Elemental Analysis : **$C_{10}H_9FN_2S$** (208) Calcd: C, 57.67; H, 4.36; N, 13.45. Found: C, 57.55; H, 4.51; N, 13.59.

4-(4-Fluorophenyl)-*N*-phenylthiazol-2-amine (50k)



Yellow solid

M. P. (°C) : 110-111 (Lit.[28] 111-112)

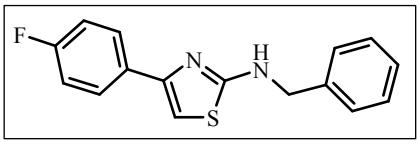
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3403, 3019, 1602, 1542, 1519, 1489, 1460, 1365, 758.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 6.74 (s, 1H, thiazole H), 7.03-7.11 (m, 3H), 7.34-7.36 (m, 4H, ArH), 7.60 (bs, 1H, NH), 7.78-7.85 (m, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 101.1, 115.2, 115.6, 118.3, 123.0, 127.73 127.8, 129.3, 130.7, 130.8, 140.2, 150.2, 160.0, 164.9, 165.1.

Elemental Analysis : **$C_{15}H_{11}FN_2S$** (270) Calcd: C, 66.65; H, 4.10; N, 10.36. Found: C, 66.73; H, 4.03; N, 10.47.

***N*-benzyl-4-(4-fluorophenyl)thiazol-2-amine (50l)**



White solid

M. P. (°C) : 109-110

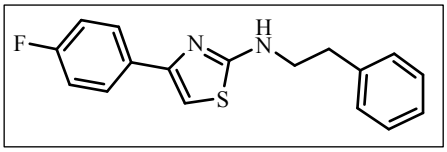
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3213, 3019, 2977, 1578, 1546, 1490, 1336, 757.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 4.49-4.51 (d, *J* = 5.0 Hz, 2H, CH_2), 5.69 (bs, 1H, NH), 6.62 (s, 1H, thiazole H), 6.98-7.09 (m, 2H, ArH), 7.29-7.40 (m, 5H, ArH), 7.71-7.81 (m, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 49.7, 100.4, 115.1, 115.5, 127.4, 127.5, 127.6, 127.7, 128.6, 131.08, 131.1, 137.5, 150.3, 159.8, 164.7, 169.7.

Elemental Analysis : **$C_{16}H_{13}FN_2S$** (284) Calcd: C, 67.58; H, 4.61; N, 9.85. Found: C, 67.72; H, 4.49; N, 9.72.

4-(4-Fluorophenyl)-*N*-phenethylthiazol-2-amine (50m)



White solid

M. P. (°C) : 108-109

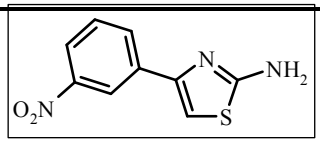
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3209, 3019, 2959, 1578, 1551, 1491, 1327, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.94-3.01 (t, *J* = 6.9 Hz, 2H, CH_2), 3.52-3.62 (q, *J* = 6.9 Hz, 2H, NCH_2), 5.21 (bs, 1H, NH), 6.62 (s, 1H, thiazole H), 6.99-7.10 (m, 2H, ArH), 7.21-7.37 (m, 5H, ArH), 7.70-7.80 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 35.3, 47.0, 100.2, 100.2, 115.1, 115.5, 126.6, 127.5, 127.7, 128.6, 128.7, 131.1, 131.2, 138.3, 150.5, 159.8, 164.7, 169.4.

Elemental Analysis : **$C_{17}H_{15}FN_2S$** (298) Calcd: C, 68.43; H, 5.07; N, 9.39.
Found: C, 68.32; H, 5.18; N, 9.51.

4-(3-Nitrophenyl)thiazol-2-amine (50n)



Yellow solid

M. P. (°C) : 189-190 (Lit.[11] 188-190)

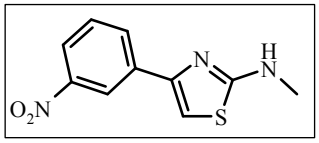
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3446, 3020, 1636, 1578, 1537, 1513, 1473, 1341, 758.

^{1}H NMR ($CDCl_3$+DMSO-D_6, 200 MHz) : δ 6.26 (bs, 2H, NH_2), 6.89 (s, 1H, thiazole H). 7.50-7-69 (t, *J* = 8.0 Hz, 1H, ArH), 8.07-8.13 (m, 2H, ArH), 8.64-8.66 (t, *J* = 1.8 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$+DMSO-D_6, 50 MHz) : δ 102.2, 118.6, 119.8, 128.0, 129.8, 134.9, 146.0, 146.6, 167.2.

Elemental Analysis : **$C_9H_7N_3O_2S$** (221) Calcd: C, 48.86; H, 3.19; N, 18.99.
Found: C, 48.77; H, 3.26; N, 19.05.

***N*-methyl-4-(3-nitrophenyl)thiazol-2-amine (50o)**



Orange needles

M. P. (°C) : 156-157

IR ($CHCl_3$, cm^{-1}) : ν_{max} 3431, 3019, 2923, 1591, 1565, 1534, 1517, 1353, 761.

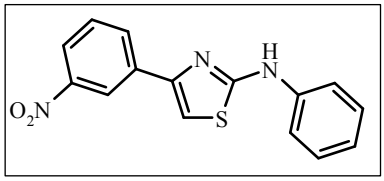
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.02-3.04 (d, *J* = 5.12 Hz, 3H, CH_3), 5.39 (bs, 1H, NH), 6.86 (s, 1H, thiazole H), 7.48-7.56 (t, *J* = 7.9 Hz, 1H, ArH), 8.09-8.13 (dd, *J* = 7.9 &1.9 Hz, 2H, ArH), 8.63-8.65 (t, *J* = 1.9 Hz, 1H, ArH).

^{13}C NMR : δ 32.1, 103.0, 120.8, 122.1, 129.4, 131.7, 136.5, 148.5, 149.2,

($CDCl_3$, 50 MHz) 170.8.

Elemental Analysis : **$C_{10}H_9N_3O_2S$** (235) Calcd: C, 51.05; H, 3.86; N, 17.86.
Found: C, 51.13; H, 3.77; N, 17.92.

4-(3-Nitrophenyl)-*N*-phenylthiazol-2-amine (50p)



Yellow solid

M. P. (°C) : 122-124

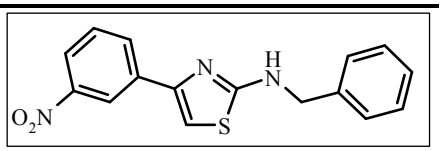
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3403, 3019, 1602, 1543, 1519, 1498, 1352, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 6.96 (s, 1H, thiazole H), 7.08-7.17 (m, 1H), 7.37-7.42 (m, 4H, ArH), 7.52-7.60 (t, *J* = 7.8 Hz, 1H, ArH), 7.94 (bs, 1H, NH), 8.12-8.20 (m, 2H, ArH), 8.66-8.88 (t, *J* = 1.8 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 103.7, 118.6, 120.8, 122.3, 123.5, 129.4, 129.5, 131.8, 135.7, 139.8, 148.3, 148.5, 165.3.

Elemental Analysis : **$C_{15}H_{11}N_3O_2S$** (297) Calcd: C, 60.59; H, 3.73; N, 14.13.
Found: C, 60.48; H, 3.81; N, 14.21.

***N*-benzyl-4-(3-nitrophenyl)thiazol-2-amine (50q)**



Yellow solid

M. P. (°C) : 102-103

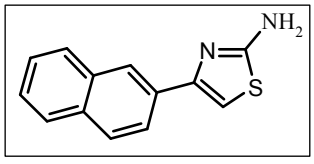
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3227, 3020, 2977, 1548, 1518, 1495, 1351, 755.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.53-4.55 (d, *J* = 5.5 Hz, 2H, CH_2), 5.67 (bs, 1H, NH), 6.85 (s, 1H, thiazole H), 7.29-7.41 (m, 5H, ArH), 7.47-7.55 (t, *J* = 8.0 Hz, 1H, ArH), 8.08-8.13 (m, 2H, ArH), 8.63-8.64 (t, *J* = 1.9 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 49.7, 103.2, 120.8, 122.0, 127.6, 127.7, 128.7, 129.3, 131.6, 136.4, 137.3, 148.5, 148.9, 169.5.

Elemental Analysis : **$C_{16}H_{13}N_3O_2S$** (312) Calcd: C, 61.72; H, 4.21; N, 13.50.
Found: C, 61.83; H, 4.13; N, 13.39.

4-(Naphthalen-2-yl)thiazol-2-amine (50r)



Yellow needle

M. P. (°C) : 153-154 (Lit.[27] 152-153)

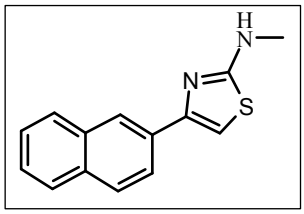
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3440, 3019, 1636, 1599, 1534, 1507, 1323, 755.

^{1}H NMR ($CDCl_3$+DMSO-D_6, 200 MHz) : δ 6.11 (bs, 2H, NH_2), 6.75 (s, 1H, thiazole H), 7.35-7.42 (m, 2H, ArH), 7.70-7.81 (m, 4H, ArH), 8.22 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$+DMSO-D_6, 50 MHz) : δ 102.0, 123.4, 124.1, 125.2, 125.6, 127.0, 127.4, 127.6, 131.6, 132.1, 132.9, 150.0, 167.7.

Elemental Analysis : **$C_{13}H_{10}N_2S$** (226) Calcd: C, 69.00; H, 4.45; N, 12.38.
Found: C, 69.11; H, 4.33; N, 12.47.

***N*-Methyl-4-(naphthalen-2-yl)thiazol-2-amine (50s)**



Yellow solid

M. P. (°C) : 123-124 (Lit.[27] 121-122)

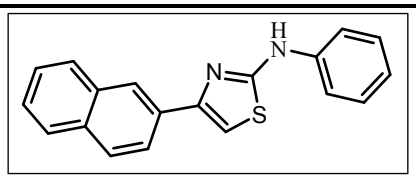
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3426, 3019, 2958, 1590, 1560, 1410, 1315, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.02-3.04 (d, *J* = 5.04 Hz, 3H, CH_3), 5.52 (bs, 1H, NH), 6.84 (s, 1H, thiazole H), 7.42-7.50 (m, 2H, ArH), 7.77-7.90 (m, 4H, ArH), 8.32 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 32.2, 101.2, 124.1, 124.9, 125.8, 126.2, 127.6, 128.1, 128.2, 132.3, 132.9, 135.6, 151.64 171.2.

Elemental Analysis : **$C_{14}H_{12}N_2S$** (240) Calcd: C, 69.97; H, 5.03; N, 11.66.
Found: C, 69.85; H, 5.11; N, 11.71.

4-(Naphthalen-2-yl)-*N*-phenylthiazol-2-amine (50t)



Faint yellow solid

M. P. (°C) : 149-150 (Lit.[27] 147-148)

IR ($CHCl_3$, cm^{-1}) : ν_{max} 3356, 3019, 1599, 1539, 1496, 1455, 1341, 755.

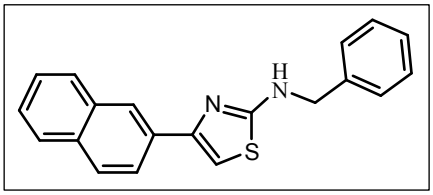
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 6.95 (s, 1H, thiazole H), 7.04-7.12 (m, 1H, ArH), 7.32-7.52 (m, 7H, ArH), 7.80-7.94 (m, 4H, ArH), 8.37 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 102.3, 118.3, 123.0, 124.0, 125.0, 125.9, 126.2, 127.6, 128.2, 128.3, 129.4, 131.7, 133.0, 133.5, 140.2, 151.2, 164.7.

Elemental Analysis : **$C_{19}H_{14}N_2S$** (302) Calcd: C, 75.47; H, 4.67; N, 9.26.

Found: C, 75.52; H, 4.59; N, 9.33.

***N*-benzyl-4-(naphthalen-2-yl)thiazol-2-amine (50u)**



Yellow solid

M. P. (°C) : 131-132

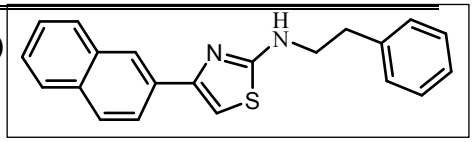
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3205, 3019, 2976, 1601, 1549, 1515, 1490, 135 , 757

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.54-4.56 (d, *J* = 4.7 Hz, 2H, CH_2Ar), 5.73 (s, 1H, NH), 6.83 (s, 1H, thiazole H), 7.29-7.50 (m, 7H, ArH), 7.78-7.90 (m, 4H, ArH), 8.33 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 49.8, 101.6, 124.0, 124.9, 125.8, 126.1, 127.5, 127.6, 128.0, 128.3, 128.6, 132.1, 132.9, 133.6, 137.5, 151.3, 169.5.

Elemental Analysis : **$C_{20}H_{16}N_2S$** (316) Calcd: C, 75.92; H, 5.10; N, 8.85.
Found: C, 75.81; H, 5.23; N, 8.72.

4-(Naphthalen-2-yl)-*N*-phenethylthiazol-2-amine (50v)



Yellow solid

M. P. (°C) : 125-126

IR ($CHCl_3$, cm^{-1}) : ν_{max} 3201, 3019, 2965, 1583, 1556, 1496, 1357, 757.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.96-3.03 (t, *J* = 6.9 Hz, 2H, CH_2), 3.56-3.66 (q, *J* = 6.9 Hz, 2H, NCH_2), 5.32 (bs, 1H, NH), 6.83 (s, 1H, thiazole H), 7.20-7.50 (m, 7H, ArH), 7.77-7.89 (m, 4H, ArH), 8.32 (s, 1H, ArH).

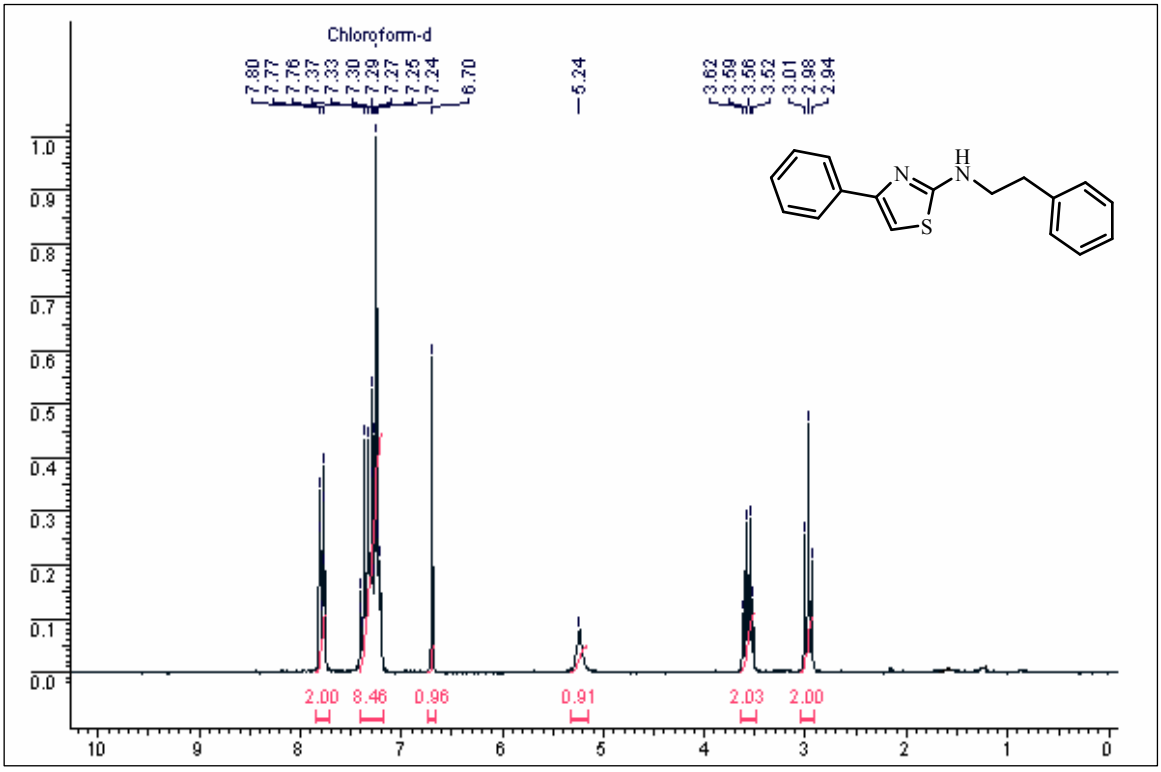
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 35.4, 47.2, 101.3, 124.0, 124.9, 125.8, 126.1, 126.6, 127.6, 128.0, 128.3, 128.6, 128.7, 132.1, 132.9, 133.6, 138.3, 151.4, 169.5.

Elemental Analysis : **$C_{21}H_{18}N_2S$** (330) Calcd: C, 76.33; H, 5.49; N, 8.48..
Found: C, 76.43; H, 5.35; N, 8.57.

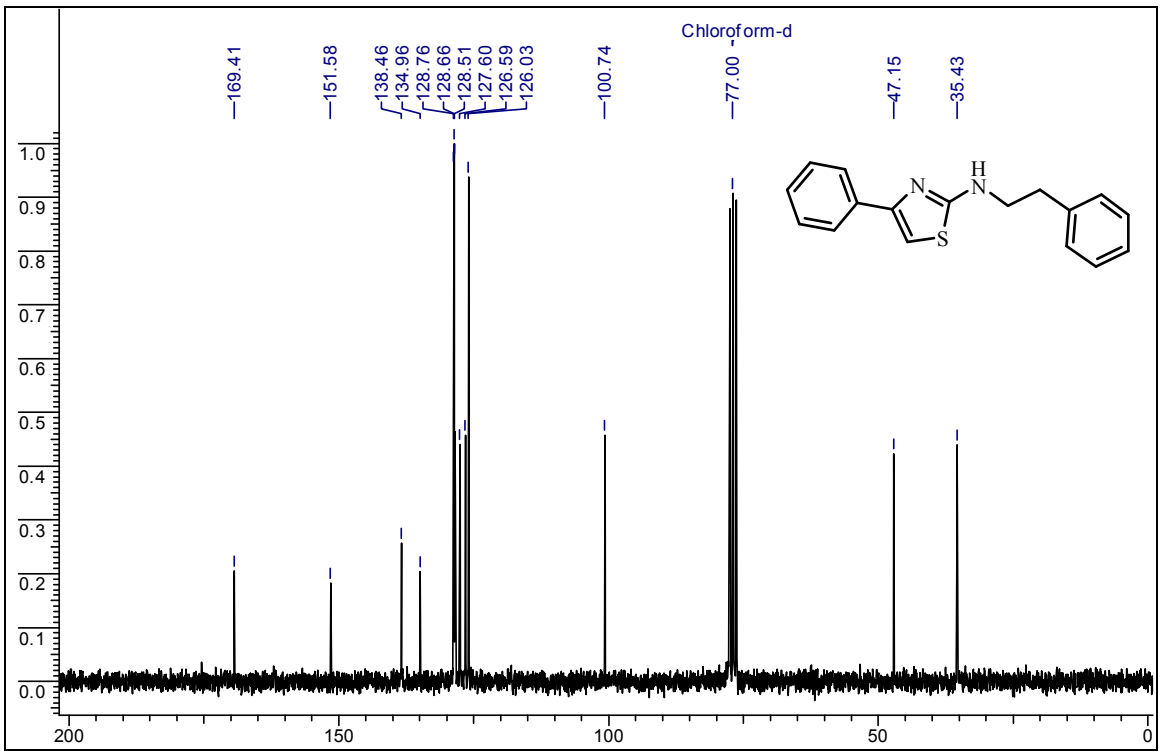
2.1.6 Spectra of representative 2-aminothiazoles

Sr. No.	NMR spectra of **50**
1	^{1}H NMR and ^{13}C NMR spectra of **50d**
2	^{1}H NMR and ^{13}C NMR spectra of **50e**
3	^{1}H NMR and ^{13}C NMR spectra of **50f**
4	^{1}H NMR and ^{13}C NMR spectra of **50h**
5	^{1}H NMR and ^{13}C NMR spectra of **50i**
6	^{1}H NMR and ^{13}C NMR spectra of **50n**
7	^{1}H NMR and ^{13}C NMR spectra of **50p**
8	^{1}H NMR and ^{13}C NMR spectra of **50q**
9	^{1}H NMR and ^{13}C NMR spectra of **50u**

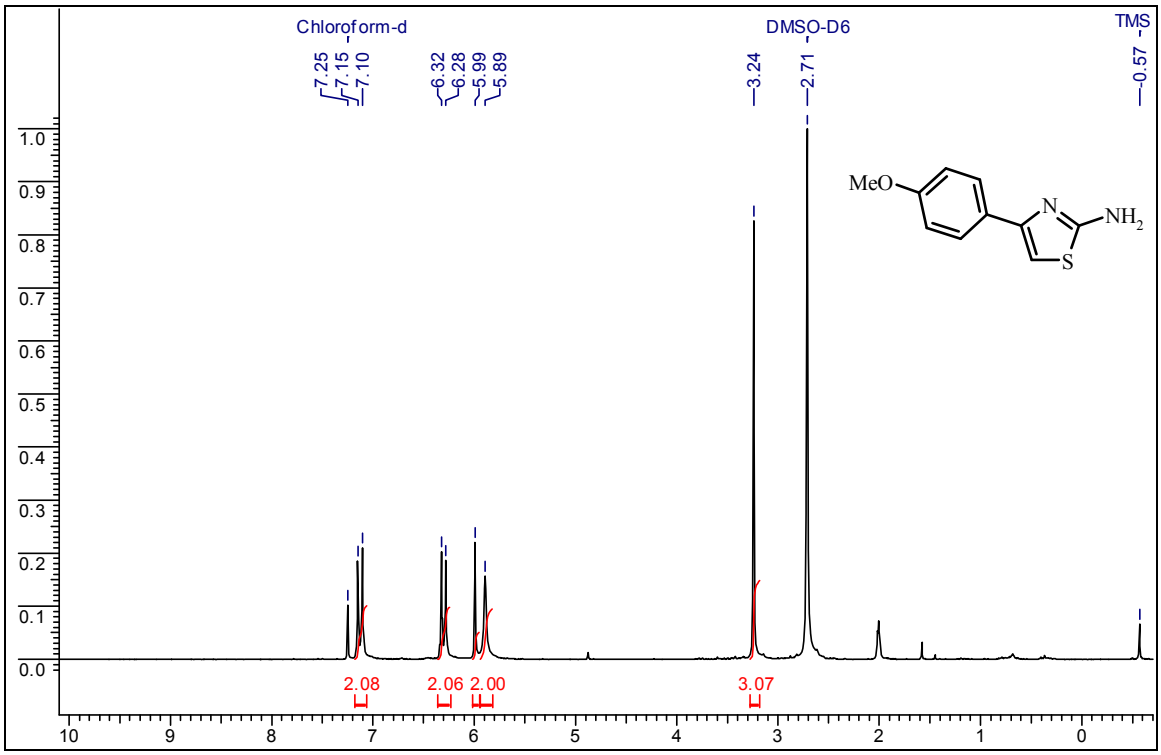
^{1}H NMR spectra of **50d**



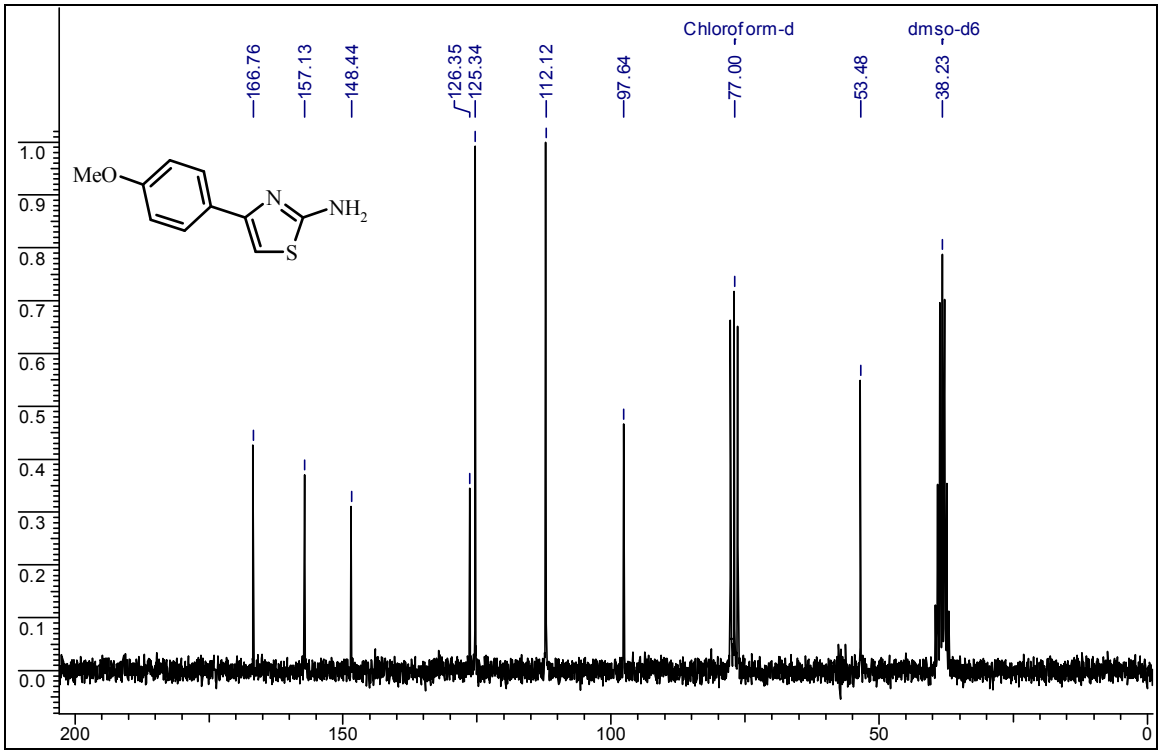
^{13}C NMR spectra of **50d**



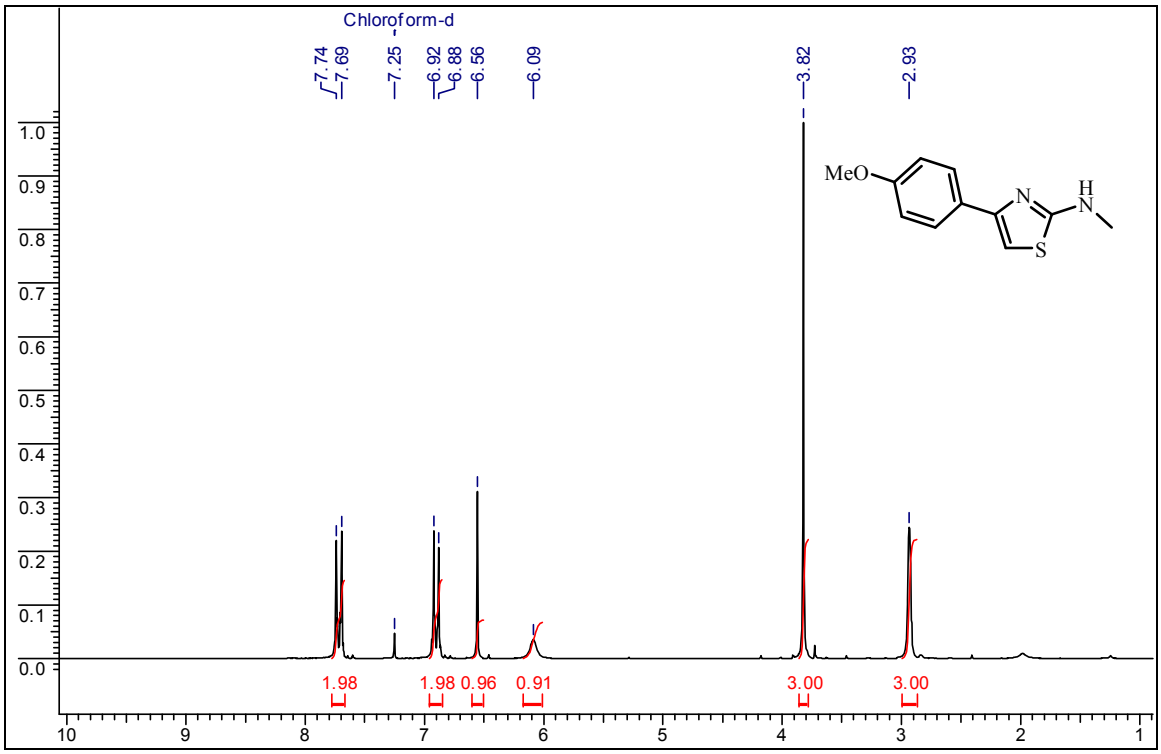
^{1}H NMR spectra of **50e**



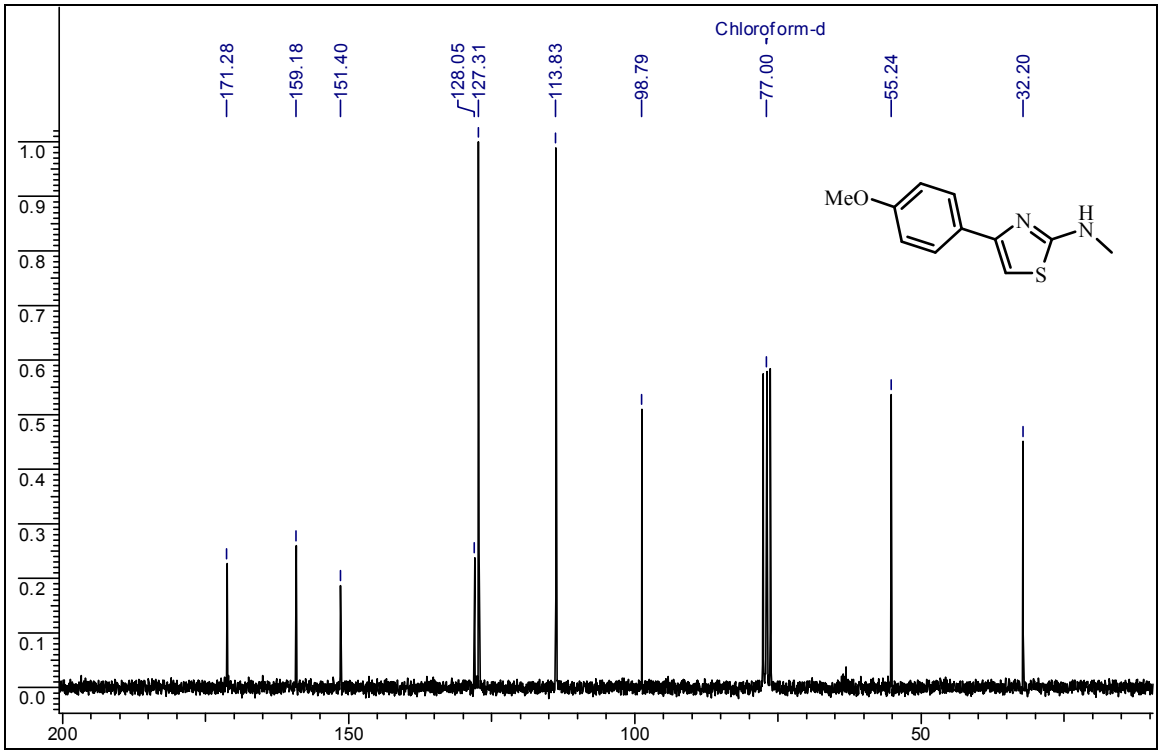
^{13}C NMR spectra of **50e**



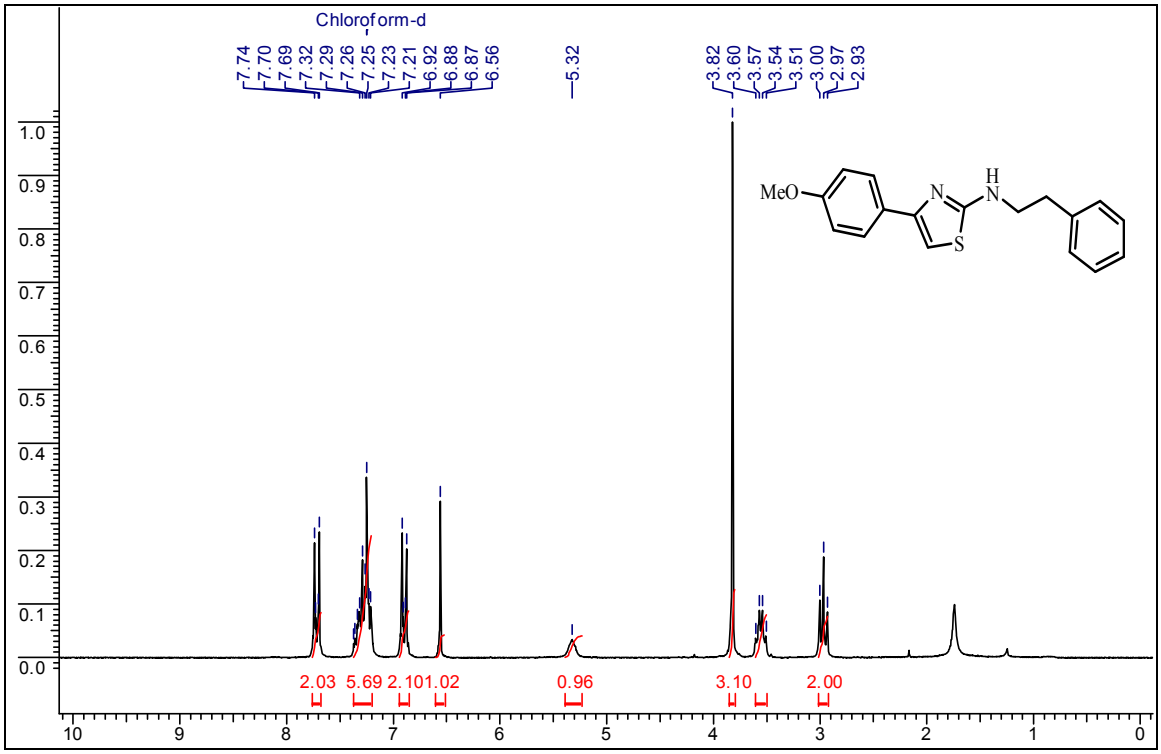
^{1}H NMR spectra of **50f**



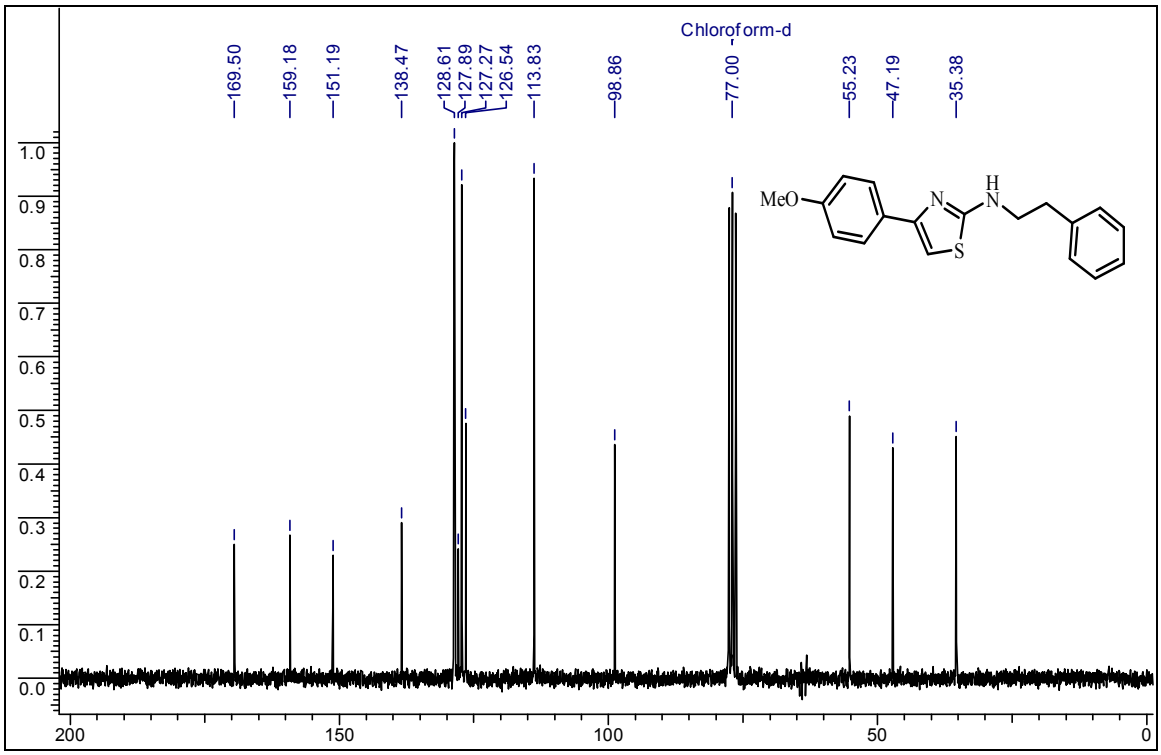
^{13}C NMR spectra of **50f**



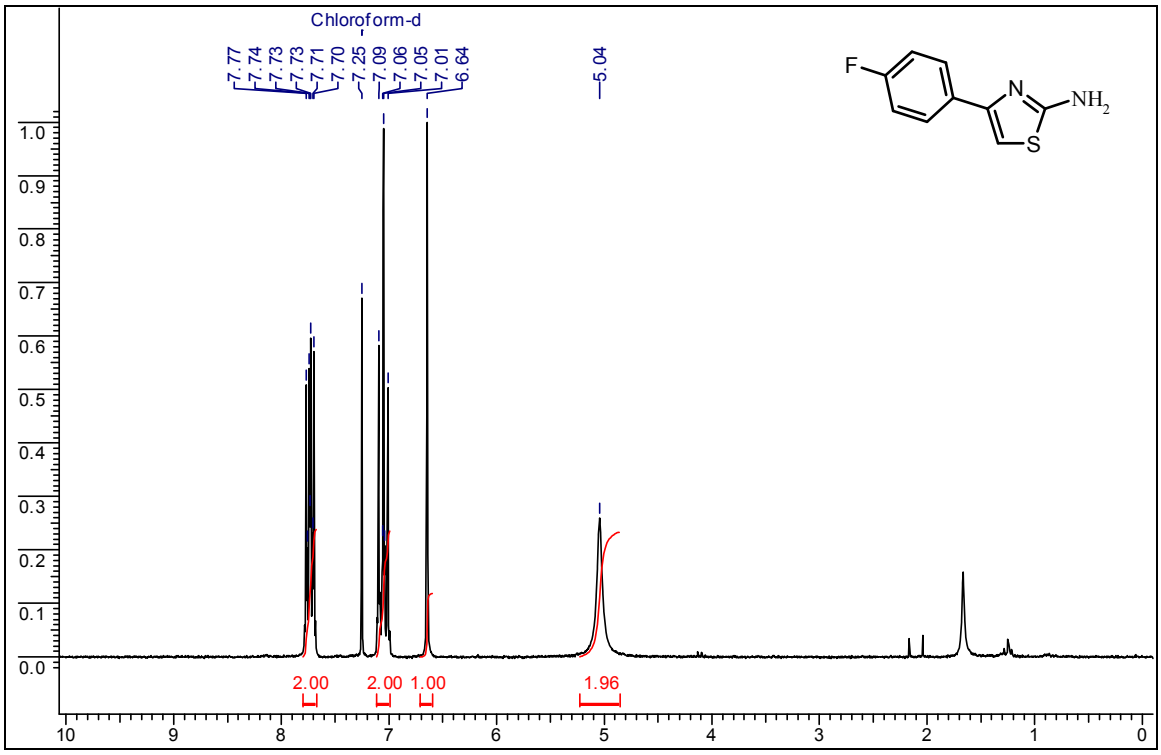
^{1}H NMR spectra of **50h**



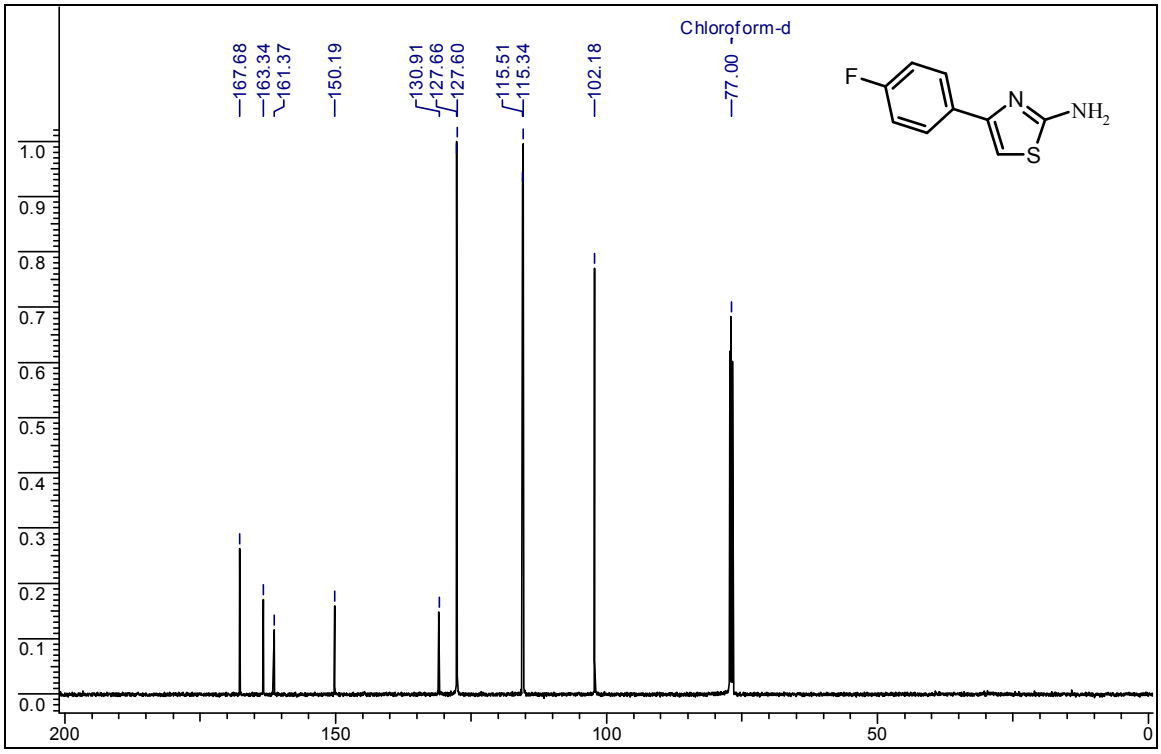
^{13}C NMR spectra of **50h**



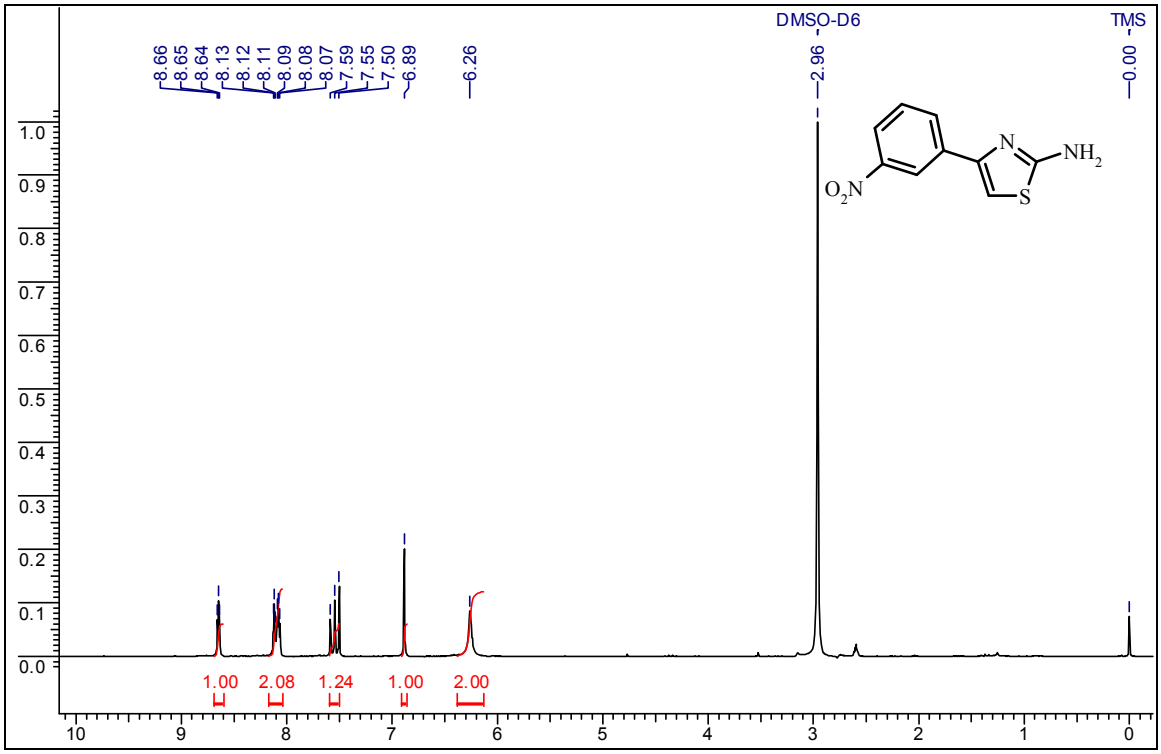
^{1}H NMR spectra of **50i**



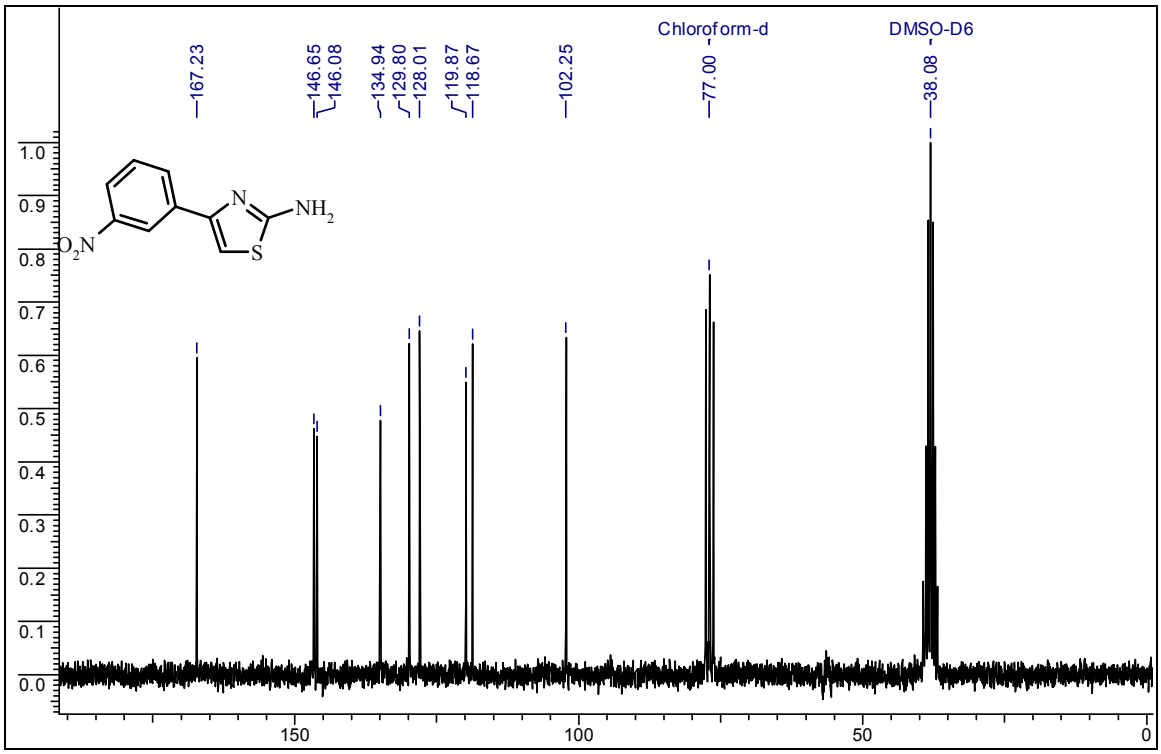
^{13}C NMR spectra of **50i**



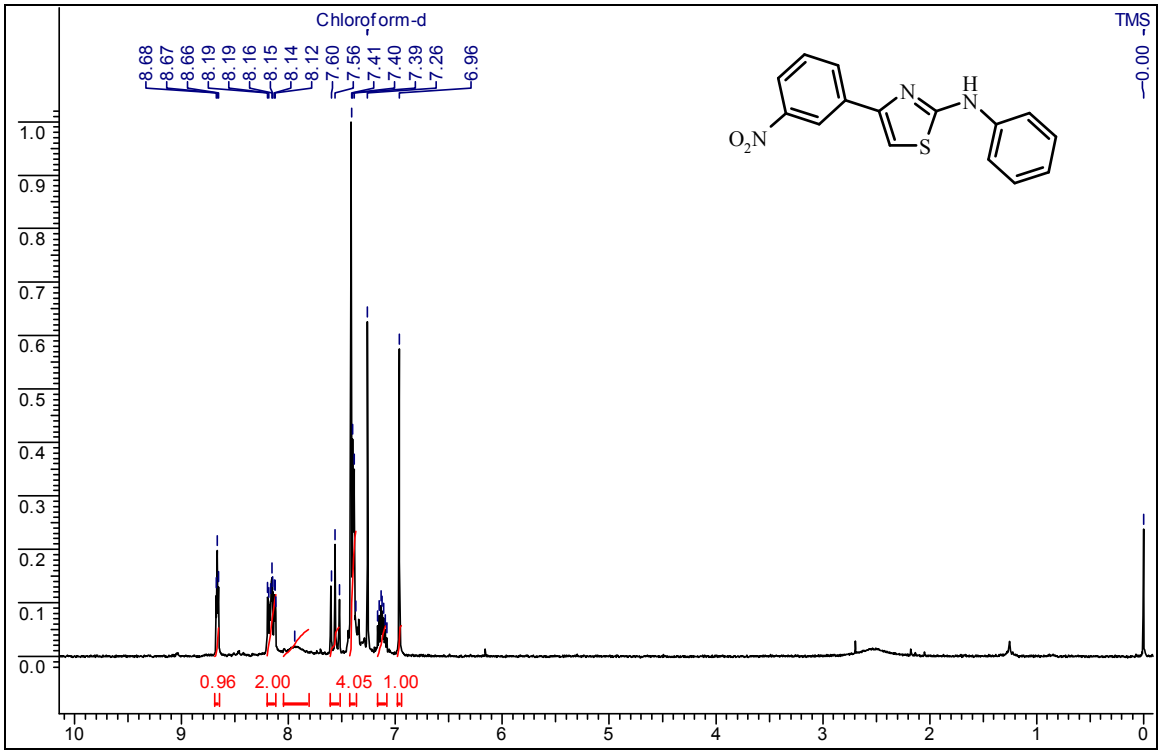
^{1}H NMR spectra of **50n**



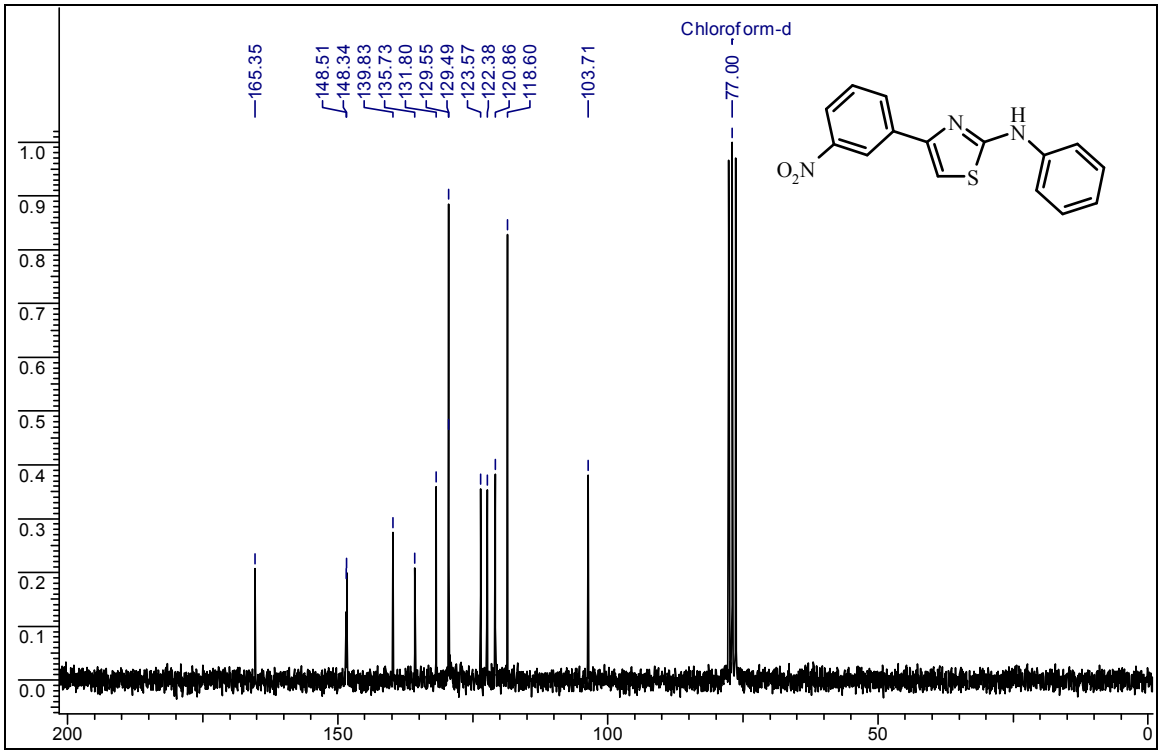
^{13}C NMR spectra of **50n**



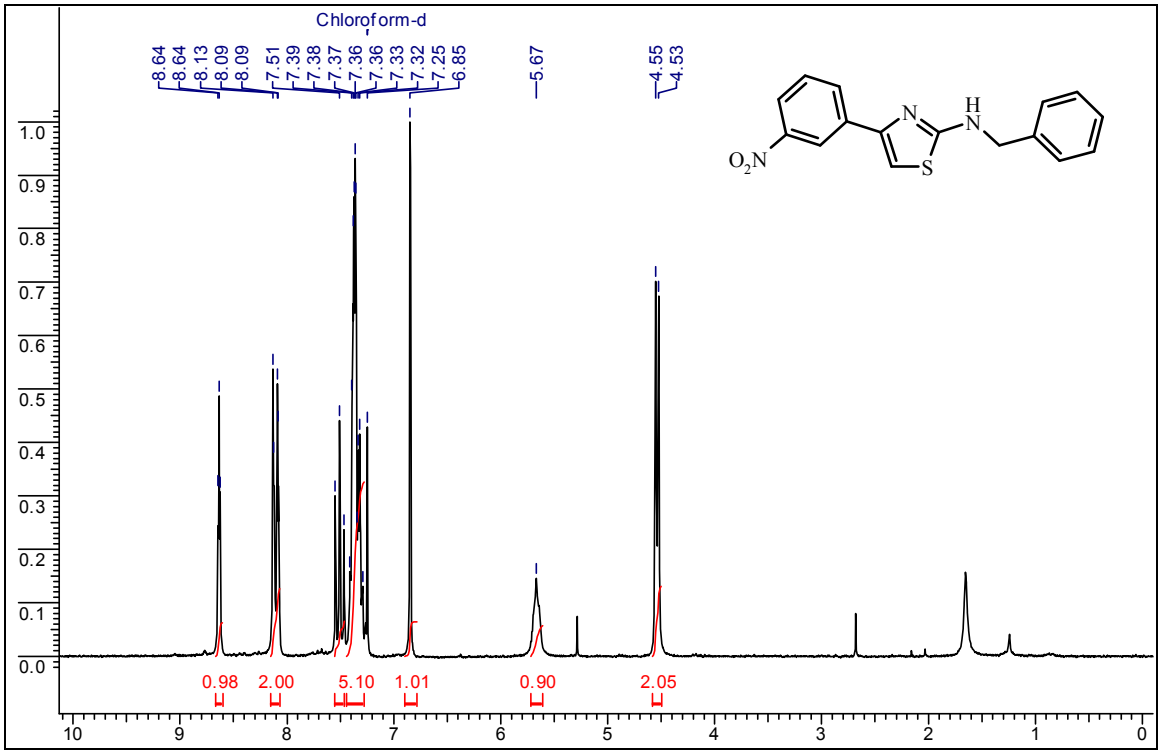
^{1}H NMR spectra of **50p**



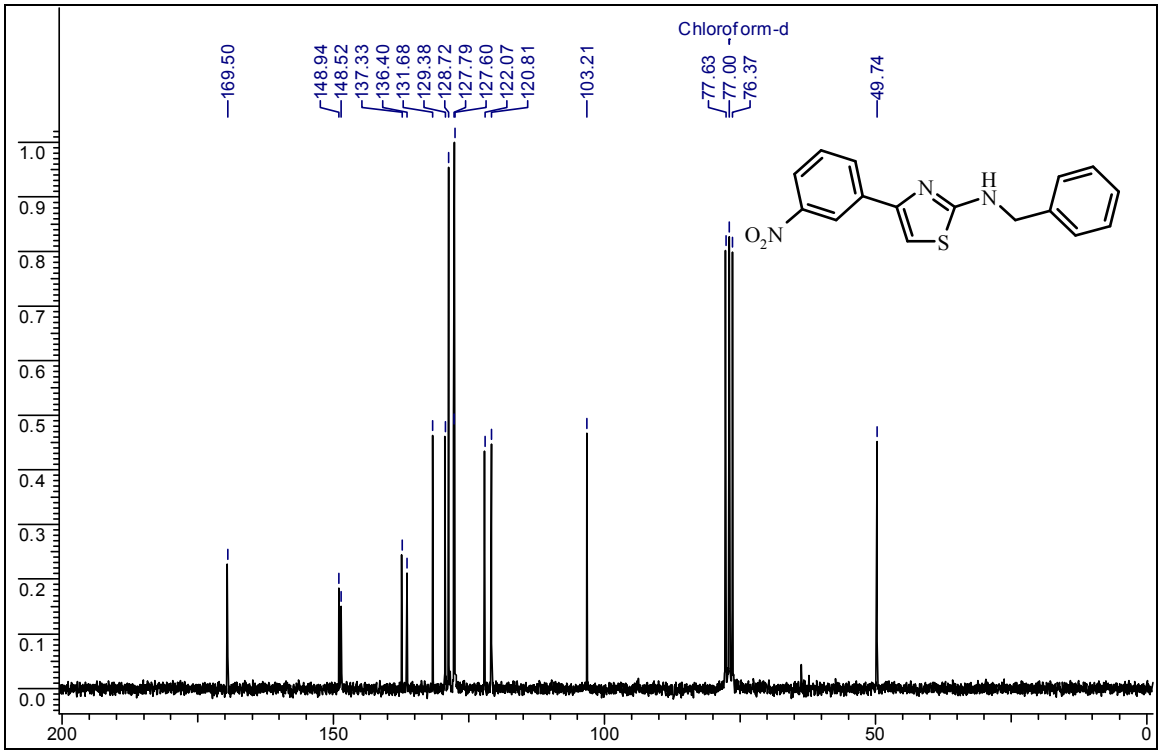
^{13}C NMR spectra of **50p**



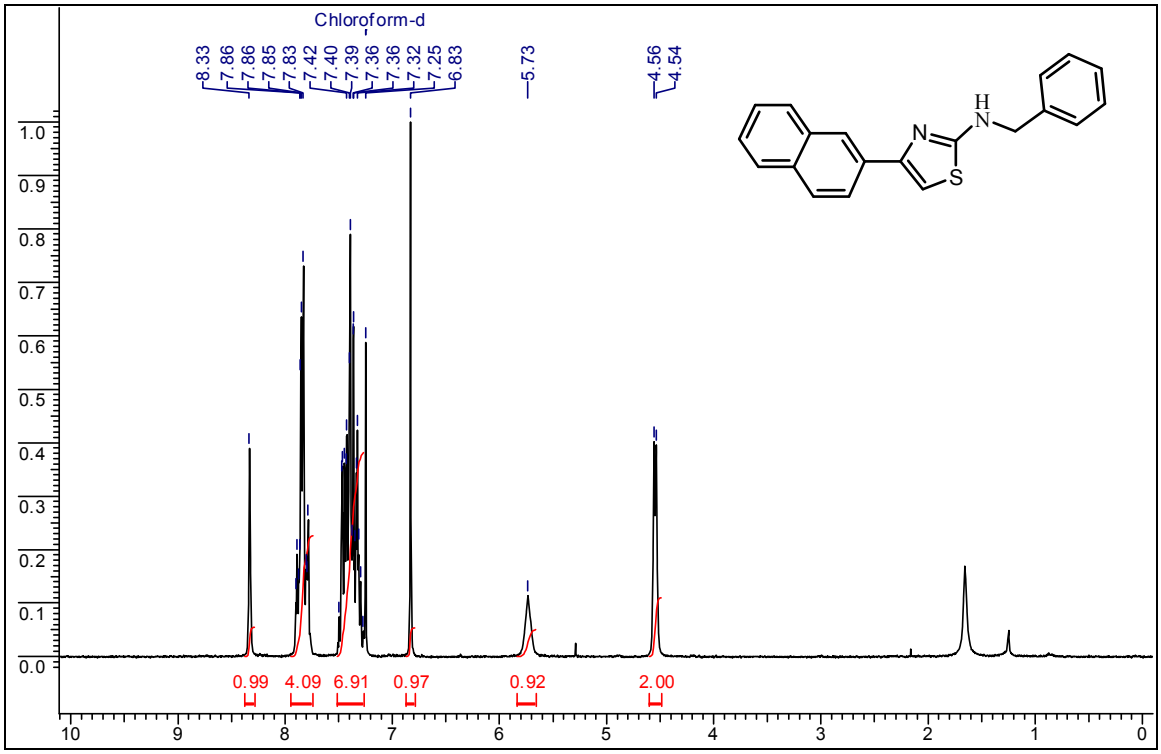
^{1}H NMR spectra of **50q**



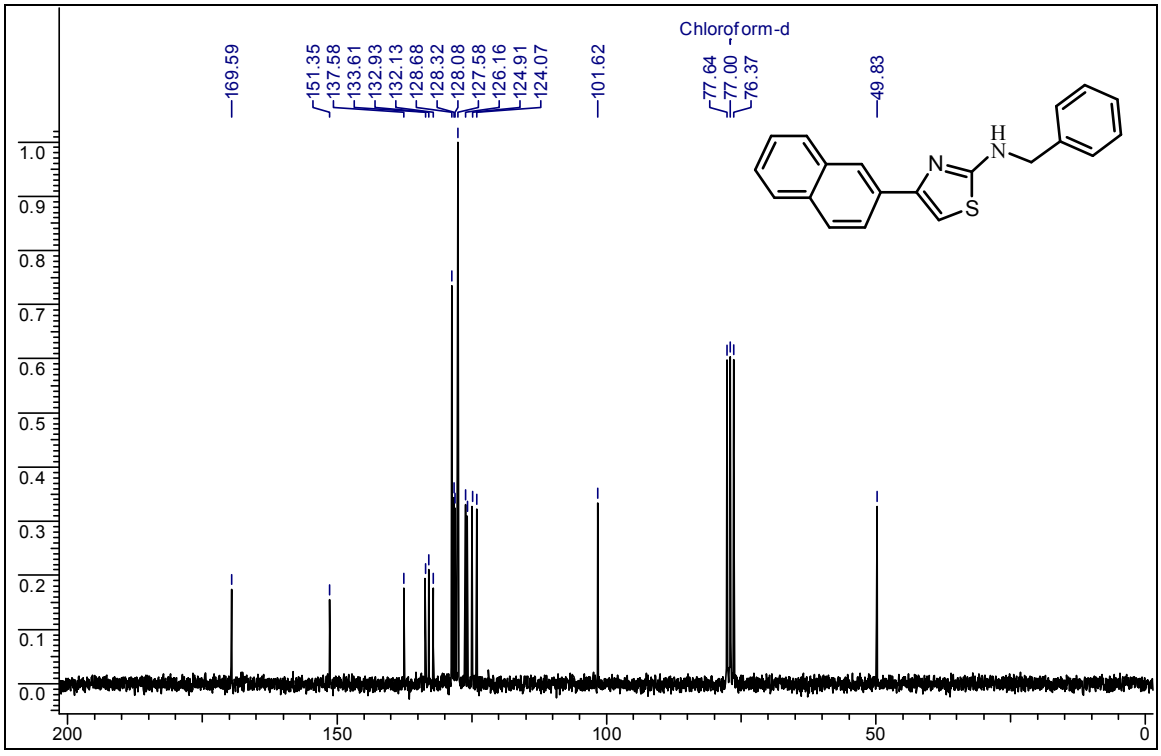
^{13}C NMR spectra of **50q**



^{1}H NMR spectra of **50u**



^{13}C NMR spectra of **50u**



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Chapter 2 - Section B

Synthesis of 2-amino-1,3-selenazoles in an ionic liquid/water system at ambient temperature

2.2.1 Introduction

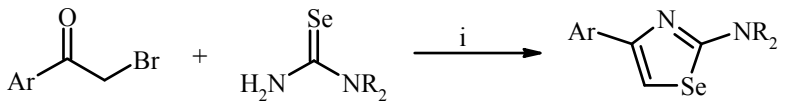
The synthesis of selenium containing heterocycles has been extensively studied, not only because of strong interest in these compounds as synthetic tools,[1] but also as a result of their biological activities.[2] 1,3-Selenazoles are of pharmacological relevance, due to their antibiotic and cancerostatic activity.[3] A prominent example is the antibiotically active *C*-glycosyl selenazole, *selenafurin*.[3a] Recently, it was reported that 1,3-selenazole possess strong inhibitory activity against inducible nitric oxide synthase.[4] 2-amino-1,3-selenazoles are also good superoxide anion-scavengers.[5] The synthesis of selenium heterocycles has been extensively studied using the carbon–selenium double bond as 2π dienophile intermediate for [4+2] cycloadditions.[6] Moreover, *N*,*N*-dialkyl-1,3-selenazol-2-amine has become of interest as a starting material for preparing dyes.[7]

2.2.2 Review of literature

In view of the importance of selenazole and its derivatives, several methods for the synthesis of selenazoles have been reported. The most widely used method is by the application of Hantzsch procedure. In this section, we have focused on some more significant methods for the synthesis of 2-amino-1,3-selenazoles.

Dietmer Keil et al. approach (1999)[8]

Dietmer Keil et al. reported the synthesis of 2-amino-1,3-selenazoles **53** from the reaction of α-bromoketone **51** with *N,N*-disubstituted selenourea **52** in ethanol at reflux temperature followed by treating with triethylamine (**Scheme 19**).



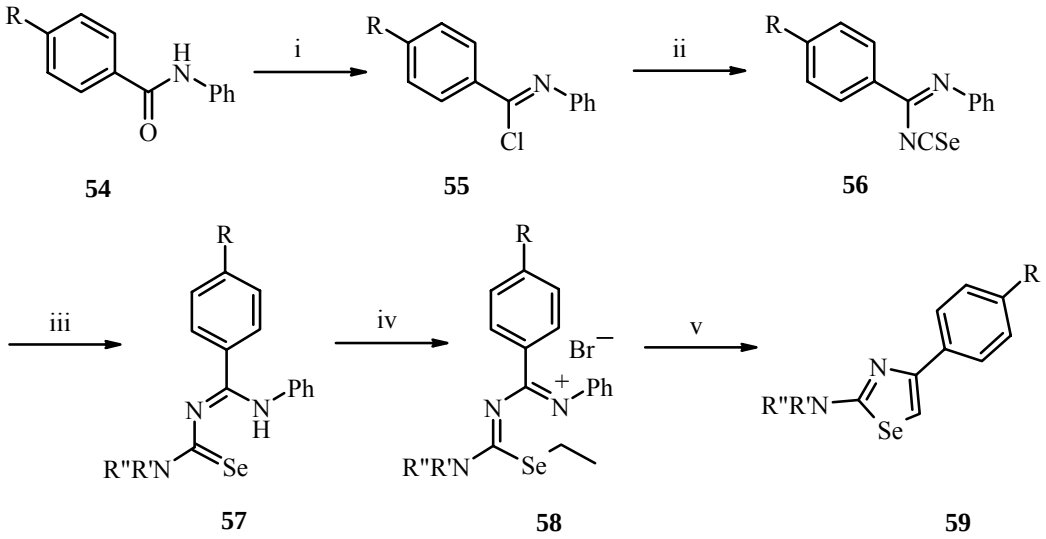
51 **52** **53**

Scheme 19. Reaction conditions: (i) EtOH, reflux, 50 min, Et_3N, 35-65%.

Heimgartner et al. approach (2000)[9]

Heimgartner et al. in 2000 synthesized 2-amino-1,3-selenazoles **59** from *N*-phenylbenzamide. A reaction mixture containing *N*-phenylbenzamide **54** and thionyl

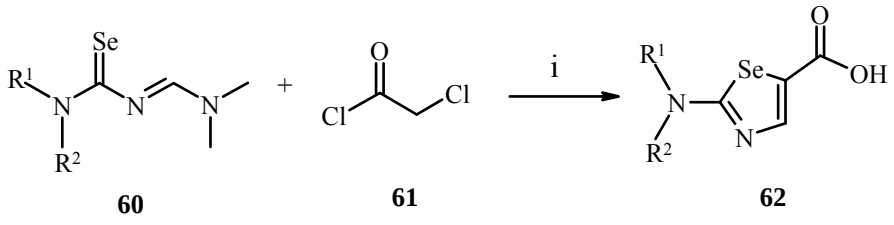
chloride was refluxed for 2 to 3 h to afford *N*-phenylbenzimidioyl chloride **55** which on further addition of KSeCN in acetone afforded *N*-phenylbenzimidioyl isoselenocyanate **56**. *N*-phenylbenzimidioyl isoselenocyanate **56** reacted with amine to afford selenourea derivatives **57** which on further reaction with α-bromoketone in acetone followed by the addition of a base afforded 1,3-selenazol-2-amines **59** (**Scheme 20**).



Scheme 20. Reaction conditions**:** (i) $SOCl_2$, reflux, 2-3 h; (ii) KSeCN, acetone, 98-99%; (iii) amine, acetone, 30 min- 1 h, 65-95%; (iv) bromoketone, acetone; (v) Et_3N or NaH, 20 min-1 h, 88-98%.

Mamoru Koketsu et al. approach (2004)[10]

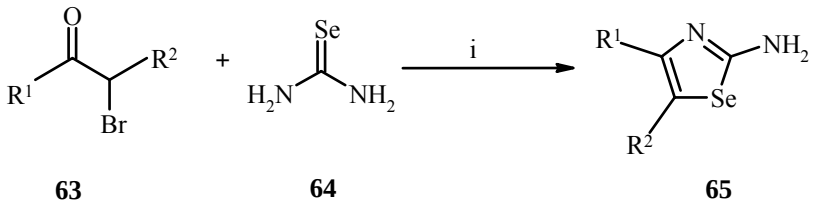
Mamoru Koketsu et al. in 2004 reported the synthesis of 2-amino-1,3-selenazoles **62** by reacting chloroacetyl chloride **61** (2 equiv) with *N*,*N*-dimethyl-*N*'-(dimethylaminoselenocarbonyl)formamidine **60** in anhydrous THF for 48 h under reflux conditions (**Scheme 21**).



Scheme 21. Reaction conditions**:** (i) anhydrous THF, reflux, H_2O, 48 h, 46-80%.

Peter Langer et al. approach (2004)[11]

Peter Langer et al. reported the synthesis of 2-amino-1,3-selenazoles **65** by refluxing α-bromoketones **63** with selenourea **64** in ethanol followed by treatment with base (**Scheme 22**).

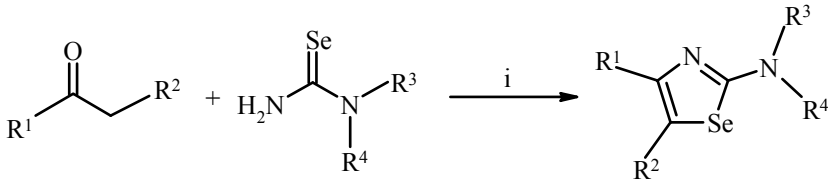


63 **64** **65**

Scheme 22. Reaction conditions**:** (i) EtOH, reflux, 10-30 min, aq. NH_3, 68-94%.

Mamoru Koketsu et al. approach (2006)[12]

Mamoru Koketsu et al. reported the synthesis of 2-amino-1,3-selenazoles **68** from the reaction of ketone **66** with selenourea **67** using ferric chloride in refluxing ethanol for 2 h (**Scheme 23**).

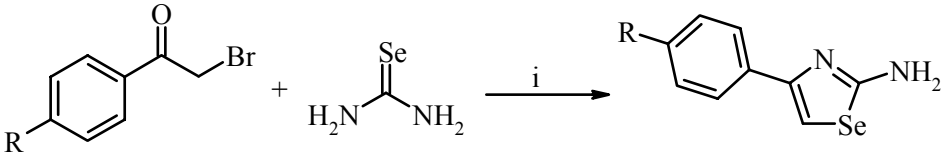


66 **67** **68**

Scheme 23. Reaction conditions**:** (i) $FeCl_3$, EtOH, reflux, 2 h, 19-97%.

K. Rama Rao et al. approach (2006)[13]

K. Rama Rao et al. reported the synthesis of 2-amino-1,3-selenazoles **71** from the reaction of α-bromo ketones **69** with selenourea **70** in the presence of β-cyclodextrin in water at 50 °C (**Scheme 24**).

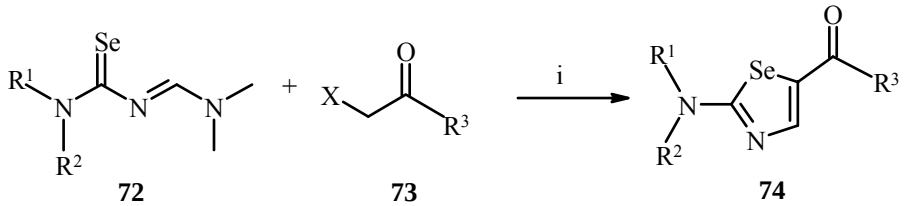


69 **70** **71**

Scheme 24. Reaction conditions**:** (i) β-cyclodextrin, H_2O, 50 °C, acetone, 35-60 min, 86-95%.

Mamoru Koketsu et al. approach (2006)[14]

Mamoru Koketsu et al. in 2006 reported the synthesis of 5-acyl-2-amino-1,3-selenazole derivatives **74** from the reaction of α-haloketone **73** with *N*,*N*-dimethyl-*N*'-(dimethylaminoselenocarbonyl)formamidine **72** in anhydrous methanol for 2 h under reflux condition (**Scheme 25**).



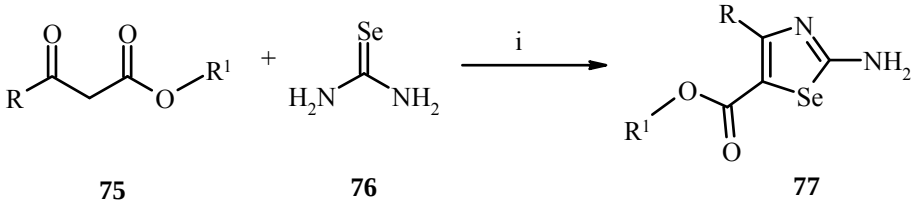
72 **73** **74**

X=Cl, Br

Scheme 25. Reaction conditions**:** (i) anhydrous MeOH, reflux, 2 h, 64-98%.

K. Rama Rao et al. approach (2007)[15]

K. Rama Rao et al. reported the synthesis of 2-amino-1,3-selenazole derivatives **77** from β-keto esters **75**. Initially β-keto esters **75** were halogenated using *N*-bromosuccinimide (NBS) to afford halogenated derivatives which further reacted with selenourea **76** using the catalyst β-cyclodextrin in water at 50 °C to afford 1,3-selenazol-2-amine derivatives **77** (**Scheme 26**).



75 **76** **77**

Scheme 26. Reaction conditions**:** (i) β-cyclodextrin, H_2O, 50 °C, NBS, acetone, 1.3 to 2 h, 89-93%.

2.2.3 Present work

2.2.3.1 Objectives

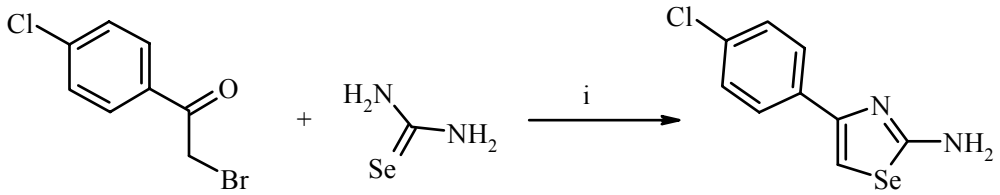
Most of the methods available for the synthesis of selenazole had drawbacks such as heating in highly polar and anhydrous organic solvents at elevated temperature (50-80 °C), basic reaction conditions such as the use of triethylamine/ammonia, use of catalyst such as

β-cyclodextrin, longer reaction times and low yields in the presence of water. Furthermore, selenoureas are air and light sensitive, so there is a need to develop a process under mild conditions such as ambient temperature at enhanced rate of reaction to prevent the unstable selenoureas triggering unwanted side reaction thereby reducing their air and light sensitivity thereby improving the selectivity to the required 2-aminoselenazoles.

Thus the development of a simple, convenient and environmentally friendly approach for the synthesis of 1,3-selenazole is still needed. Organic reactions in aqueous media have attracted much attention recently not only because water is the most abundant, environmentally benign, and cheapest solvent but also because unique selectivity and reactivity can be expected from this solvent.[16] Among a variety of possible green solvent alternatives for catalytic reactions, room-temperature ionic liquids (RTILs) as reaction media continue to be an area of increasing research activity. Moreover, they have shown great promise as attractive alternative to conventional solvents. These advantages become even more attractive if such reactions can be conducted using ionic liquids in aqueous media.[17] In continuation to our ongoing interest in the development of environment-friendly synthetic methodologies for the synthesis of biologically active heterocycles, we herein report for the first time a simple, efficient and eco-friendly process for the synthesis of substituted 2-amino-1,3-selenazoles in an ionic liquid/water mixture as an efficient solvent system at ambient temperature in significantly enhanced reaction rates.

2.2.3.2 Results and discussion

When 4-chlorophenacyl bromide **78d** was treated with selenourea **79a** in 1-*n*-butylimidazolium tetrafluoroborate/water ([Hbim]BF_4/H_2O) mixture (1:1) at ambient temperature, it afforded 4-(4-chlorophenyl)-1,3-selenazol-2-amine **80d** in 94% yield in just 10 min (**Scheme 27**).



78d **79a** **80d**

Scheme 27. Reaction conditions**:** (i) [Hbim]BF_4/H_2O (1:1), rt, 10 min, 94%.

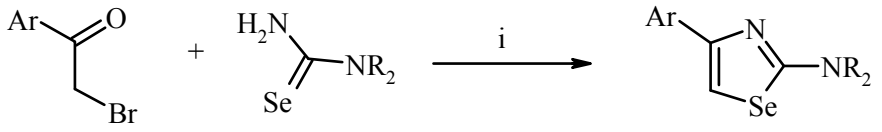
For the optimization of the reaction conditions, we chose the cyclocondensation reaction between 4-chlorophenacyl bromide **78d** and selenourea **79a** as a model reaction. Initially, we carried out the reaction between 4-chlorophenacyl bromide and selenourea in water at room temperature, where it furnished the desired product in low yield (58%) even after long reaction period (6 h) (Table 2, entry 8). Next, when we carried out the reaction in the IL, 1,3-di-*n*-butylimidazolium bromide ([Bbim]Br), it furnished the product in 91% in 35 min (Table 2, entry 1). However, a similar reaction in more Brønsted acidic IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) furnished the product in 94% yield in 15 min (Table 2, entry 2). Interestingly, it was observed that addition of water to ionic liquid, [Hbim]BF_4 in 1:1 ratio enhanced the rate of cyclocondensation reaction further as reaction time was reduced from 15 min to 10 min while in the case of [Bbim]Br, the reaction time was reduced from 35 min to 25 min on addition of water to [Bbim]Br in 1:1 ratio. It may be pointed out that the ionic liquid [Hbim]BF_4 and [Bbim]Br were selected for this transformation because of their excellent miscibility with water. The role of IL may be postulated in terms of Lewis/Brønsted acidity promoting the reaction. The addition of water to IL may have presumably played an important role in the process due to the good water solubility of the selenoureas.

Table 2. Optimization of solvent system for the synthesis of **80d**

Entry	Solvent	Time (min)	Yield(%)[a]
1	[Bbim]Br	35	91
2	[Hbim]BF_4	15	94
3	[Hbim]BF_4 + H_2O (1:1)	10	94
4	[Hbim]BF_4 + H_2O(2:1)	10	94
5	[Hbim]BF_4 + H_2O (1:2)	30	89
6	[Bbim]Br+ H_2O (1:1)	25	90
7	H_2O + [Hbim]BF_4[b]	60	87
8	H_2O	120[c]	58

[a]: Isolated yield after column chromatography
[b]: IL, [Hbim]BF_4 in catalytic amount
[c]: No further progress upto 6 h

For optimization of solvent system, different ratios of water and IL were investigated and the optimum results were obtained by using IL/water in 1:1 ratio (Table 2, entry 3). All further reactions were done using [Hbim]BF_4/H_2O system (1:1) as the reaction medium. Using these optimal reaction conditions, we next examined the scope and generality of this process by reacting different substituted aromatic α-bromoketone with selenourea and *N,N*-dimethylselenourea to afford various 1,3-selenazol-2-amine derivatives (**Scheme 28**).

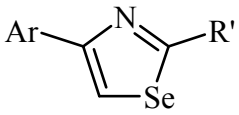


78 **79** **80**

Scheme 28. Reaction conditions: (i) [Hbim]BF_4/H_2O (1:1), rt, 10-20 min, 91-94%.

It was observed that under these conditions, a wide range of phenacyl bromides having electron-withdrawing as well as electron-donating groups such as nitro, chloro, fluoro, methyl and phenyl easily underwent cyclocondensation with selenourea **79a** as well as with *N,N*-dimethylselenourea **79b** to afford various 4-aryl-1,3-selenazol-2-amine in short reaction times in excellent isolated yields. The results are summarized in **Table 3**. Similarly, α-bromo-2-acetonaphthone smoothly reacted with selenourea and *N,N*-dimethylselenourea to afford the corresponding products in excellent yields (Table 3, Entry 7,14). It can be observed that almost all reactions were complete in just 10-20 min at ambient temperature. Selenoureas are air and light sensitive, so it becomes most necessary to develop a process which would be faster at mild conditions to avoid the unstable selenoureas triggering unwanted side reactions thereby reducing their air and light sensitivity thereby improving the selectivity to the required 2-aminoselenazoles. To the best of our knowledge, this is the first synthesis of 2-amino-1,3-selenazole which was carried out at ambient temperature at enhanced rate without any volatile, polar organic solvent and any added catalyst affording the products in excellent yields (91-97%).

Table 3. Synthesis of 1,3-selenazol-2-amine **80a-n**



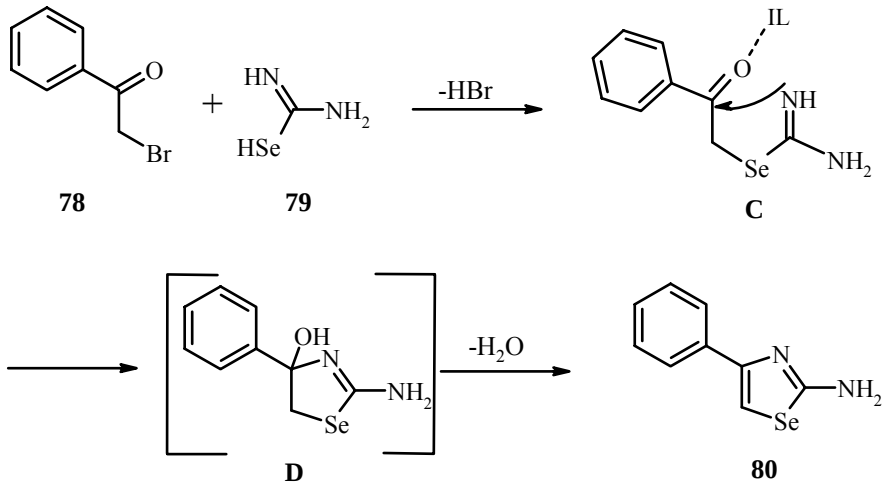
Entry	Ar	R'	Product **80**	Time (min)	Yield (%)[a]
1	C_6H_5	NH_2	**80a**	10	91
2	4-MeC_6H_4	NH_2	**80b**	10	93
3	4-FC_6H_4	NH_2	**80c**	15	94
4	4-ClC_6H_4	NH_2	**80d**	10	94
5	3-$(NO_2)C_6H_4$	NH_2	**80e**	15	97
6	4-$C_6H_5C_6H_4$	NH_2	**80f**	20	96
7	β-$C_{10}H_7$	NH_2	**80g**	10	95
8	C_6H_5	$N(CH_3)_2$	**80h**[b]	10	94
9	4-MeC_6H_4	$N(CH_3)_2$	**80i**	10	95
10	4-FC_6H_4	$N(CH_3)_2$	**80j**[b]	10	96
11	4-ClC_6H_4	$N(CH_3)_2$	**80k**	15	95
12	3-$(O_2N)C_6H_4$	$N(CH_3)_2$	**80l**	15	97
13	4-$C_6H_5C_6H_4$	$N(CH_3)_2$	**80m**	10	96
14	β-$C_{10}H_7$	$N(CH_3)_2$	**80n**	10	97

[a]: Isolated yield after column chromatography
[b]: viscous liquid

The experimental procedure is very simple. A mixture of aromatic α-bromo ketone **78** and selenourea **79** was stirred in [Hbim]BF_4/H_2O (1:1) system for 10-20 min at ambient temperature. The vigorous stirring is necessary for the success of the reaction. After completion of the reaction, as indicated by the disappearance of the spot corresponding to phenacyl bromide on TLC, the reaction mixture was poured into water and product was extracted using ethyl acetate. The aqueous layer consisting of the IL was dried in vacuo (80 °C at 10 mmHg) for 2 h to remove water, leaving behind the IL [Hbim]BF_4 which was reused and recycled three times for a typical reaction of 4-chlorophenacyl bromide and selenourea without any loss in yield. For this, recovered IL was mixed with water in 1:1 ratio and used as the solvent system.

2.2.3.3 Plausible mechanism

It is postulated that IL coordinates with carbonyl oxygen atom of intermediate **C** through hydrogen bond formation thereby increasing the electrophilicity of carbon center which may be attacked by nucleophilic nitrogen to from cyclized intermediate **D**. Intermediate **D** readilly transformed to the more stable product, 2-amino-1,3-selenazole **80** (**Scheme 29**).



78 **79** **C** **D** **80**

Scheme 29. Plausible mechanism

2.2.4 Conclusion

In conclusion, we have demonstrated that a highly efficient and eco-friendly synthesis of 4-aryl-2-amino-1,3-selenazoles has been achieved using [Hbim]BF_4/H_2O solvent system.

The current method presents a practicable synthetic process for 2-amino-1,3-selenazole because of the following advantages: (i) use of water and ionic liquid as environmentally benign reaction media; (ii) very high yield (91-97%) and short reaction time (10-20 min); (iii) ambient temperature; (iv) absence of any added catalyst and organic solvent as reaction medium; and (v) recyclability of the ionic liquid.

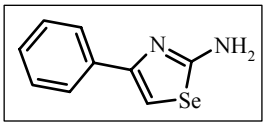
2.2.5 Experimental

2.2.5.1 General Procedures for the synthesis of 2-amino-1,3-selenazoles (80a-n).

A mixture of aromatic α-bromo ketone **78** (1 mmol) and selenourea **79** (1.1 mmol) in ([Hbim]BF_4/water (1:1, 3 mL) system was vigorously stirred at ambient temperature for an appropriate time (**Table 3**). After completion of the reaction as indicated by TLC, the reaction mixture was poured into water (10 mL) and the product was extracted using ethyl acetate (3x10 mL). The combined ethyl acetate extracts were concentrated in vacuo. The resulting crude product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate/petroleum ether to afford pure 2-aminoselenazole **80**.

2.2.5.2 Characterization data for 2-amino-1,3-selenazole derivatives 80a-n

4-Phenyl-1,3-selenazol-2-amine (80a)



Brown solid

M. P. (°C) **:** 131-132 (Lit.[13] 132).

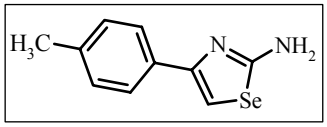
IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3412, 1590, 1455, 1377, 1299, 769, 722.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 5.36 (bs, 2H, NH_2), 7.27-7.40 (m, 4H, 3H of ArH & 1H selenazole ring), 7.74-7.79 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 107.2, 126.2, 127.5, 128.5, 135.4, 151.9, 169.1.

Elemental Analysis **:** **$C_9H_8N_2Se$** (223) Calcd: C, 48.45; H, 3.61; N, 12.55.
Found: C, 48.57; H, 3.49; N, 12.64.

4-*p*-tolyl-1,3-selenazol-2-amine (80b)



Brown solid

M. P. (°C) **:** 167-168 (Lit.[13] 167).

IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3449, 3350, 2924, 3854, 1598, 1518, 1459, 1376, 1215,

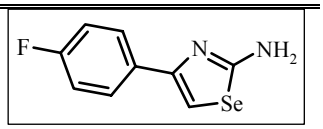
761, 724.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 2.34 (s, 3H, CH_3), 5.48 (bs, 2H, NH_2), 7.14-7.18 (d, *J* = 8.15 Hz, 2H, ArH), 7.21 (s, 1H, selenazole H), 7.63, 7.67 (d, *J* = 8.15 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 21.1, 106.3, 126.1, 129.2, 132.7, 137.2, 151.9, 169.1.

Elemental Analysis : **$C_{10}H_{10}N_2Se$** (237) Calcd: C, 50.64; H, 4.25; N, 11.81.
Found: C, 50.49; H, 4.18; N, 11.93.

4-(4-Fluorophenyl)-1,3-selenazol-2-amine (80c)



Brown solid

M. P. (°C) : 119-120

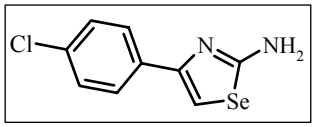
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3454, 3279, 1696, 1459, 1377, 1321, 1208, 771, 728.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 5.36 (bs, 2H, NH_2), 6.99-7.08 (m, 2H, ArH), 7.20 (s, 1H, selenazole H), 7.70-7.77 (m, 2H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 106.7, 115.1, 115.5, 127.8, 128.0, 131.7, 150.8, 159.7, 164.6, 169.3.

Elemental Analysis : **$C_9H_7FN_2Se$** (241) Calcd: C, 44.83; H, 2.93; N, 11.62.
Found: C, 44.69; H, 2.84; N, 11.77.

4-(4-Chlorophenyl)-1,3-selenazol-2-amine (80d)



Brown solid

M. P. (°C) : 155-156 (Lit.[13] 157)

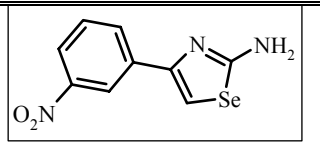
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3454, 3291, 1538, 1461, 1377, 1187, 770, 726.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 5.35 (bs, 2H, NH_2), 7.27 (s, 1H, selenazole H), 7.29-7.33 (d, *J* = 8.63 Hz, 2H, ArH), 7.68-7.72 (d, *J* = 8.63 Hz, 2H, ArH).

^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$, 50 MHz) : δ 126.0, 127.0, 130.6, 133.1, 148.5, 168.5.

Elemental Analysis : **$C_9H_7ClN_2Se$** (257) Calcd: C, 41.97; H, 2.74; N, 10.88.
Found: C, 42.09; H, 2.62; N, 10.77.

4-(3-Nitrophenyl)-1,3-selenazol-2-amine (80e)



Yellow solid

M. P. (°C) **:** 196-197

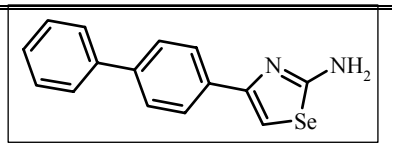
IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3443, 1633, 1463, 1455, 1155, 771, 722.

^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz) **:** δ 6.49 (bs, 2H, NH_2), 7.0 (s, 1H, selenazole H), 7.04-7.12 (t, *J* = 7.98 Hz, 1H, ArH), 7.59-7.69 (m, 2H, ArH), 8.21-8.23 (t, *J* = 1.98 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz) **:** δ 107.0, 119.7, 120.1, 128.2, 130.5, 136.2, 147.2, 147.6, 169.0.

Elemental Analysis **:** **$C_9H_7N_3O_2Se$** (268) Calcd: C, 40.32; H, 2.63; N, 15.67.
Found: C, 40.51; H, 2.74; N, 15.53.

4-(biphenyl-4-yl)-1,3-selenazol-2-amine (80f)



Brown solid

M. P. (°C) **:** 138-139

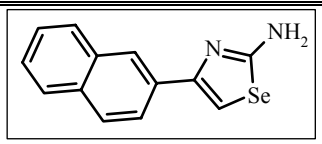
IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3412, 1538, 1462, 1376, 769, 733.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 5.30 (bs, 2H, NH_2) 7.34 (s, 1H, selenazole H), 7.36-7.48 (m, 3H, ArH), 7.58-7.65 (m, 4H, ArH), 7.82-7.87 (m, 2H).

^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz) **:** δ 104.0, 124.5, 124.7, 125.3, 126.9, 132.9, 136.7, 138.0, 148.5, 167.5.

Elemental Analysis **:** **$C_{15}H_{12}N_2Se$** (299) Calcd: C, 60.21; H, 4.04; N, 9.36.
Found: C, 60.37; H, 4.12; N, 9.23.

4-(Naphthalen-2-yl)-1,3-selenazol-2-amine (80g)



Brown solid

M. P. (°C) **:** 145-146

IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 3415, 1595, 1519, 1462, 1377, 770, 749.

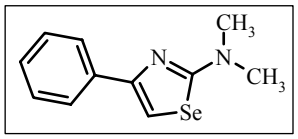
^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 5.47 (bs, 2H, NH_2), 7.41 (s, 1H, selenazole H), 7.43-7.53 (m, 2H, ArH), 7.48-7.89 (m, 4H, ArH), 8.30 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$+DMSO-d_6, **:** δ 105.5, 123.2, 123.8, 124.6, 125.1, 126.4, 126.8, 127.0, 131.4, 132.0, 132.4, 149.9, 168.8.

50 MHz)

Elemental Analysis : **$C_{13}H_{10}N_2Se$** (273) Calcd: C, 57.15; H, 3.69; N, 10.25.
Found: C, 57.04; H, 3.82; N, 10.37.

***N,N*-dimethyl-4-phenyl-1,3-selenazol-2-amine (80h)**



Viscous liquid

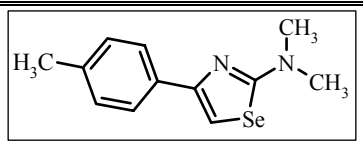
IR ($CHCl_3$, cm^{-1}) : ν_{max} 2921, 2871, 1566, 1479, 773.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.26 (s, 6H, CH_3), 7.38 (s, 1H, selenzole H), 7.40-7.52 (m, 3H, ArH), 7.96-8.01 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 40.9, 105.0, 126.3, 127.2, 128.3, 136.0, 153.0, 172.1.

Elemental Analysis : **$C_{11}H_{12}N_2Se$** (251) Calcd: C, 52.60; H, 4.82; N, 11.15.
Found: C, 52.47; H, 4.94; N, 11.03.

***N,N*-dimethyl-4-*p*-tolyl-1,3-selenazol-2-amine (80i)**



Dark brown solid

M. P. (°C) : 49-50

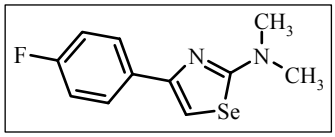
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3018, 2922, 2872, 1563, 1490, 1554, 1425, 1322, 1215, 758.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.35 (s, 3H, CH_3), 3.15 (s, 6H, CH_3), 7.15-7.19 (d, J = 7.96 Hz, 2H, ArH), 7.21 (s, 1H, selenazole H), 7.74-7.78 (d, J = 7.96 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.2, 40.9, 104.1, 126.2, 129.0, 133.3, 136.9, 153.1, 172.1.

Elemental Analysis : **$C_{12}H_{14}N_2Se$** (265) Calcd: C, 54.35; H, 5.32; N, 10.56.
Found: C, 54.53; H, 5.21; N, 10.68.

4-(4-Fluorophenyl)-*N,N*-dimethyl-1,3-selenazol-2-amine (80j)



Viscous liquid

IR ($CHCl_3$, cm^{-1}) : ν_{max} 2921, 2872, 1572, 1489, 843, 756, 728.

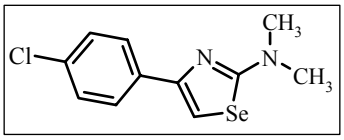
^{1}H NMR : δ 3.14 (s, 6H, CH_3), 6.99-7.08 (m, 2H, ArH), 7.17 (s, 1H,

($CDCl_3$, 200 MHz) selenazole H), 7.79-7.86 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 41.0, 104.4, 114.9, 115.3, 127.9, 128.0, 132.3, 152.0, 159.6, 164.5, 172.2.

Elemental Analysis : **$C_{11}H_{11}FN_2Se$** (269) Calcd: C, 49.08; H, 4.12; N, 10.41.
Found: C, 49.17; H, 4.23; N, 10.58.

4-(4-Chlorophenyl)-*N,N*-dimethyl-1,3-selenazol-2-amine (80k)



Brown solid

M. P. (°C) : 56-57

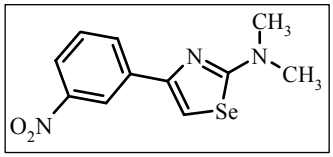
IR ($CHCl_3$, cm^{-1}) : ν_{max} 2924, 2871, 1558, 1475, 836, 724.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.03 (s, 6H, CH_3), 7.12-7.21 (t, *J* = 8.70 Hz, 2H of ArH & 1H of selenazole), 7.65-7.69 (d, *J* = 8.70 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 41.0, 105.3, 127.6, 128.4, 132.7, 134.5, 151.8, 172.2.

Elemental Analysis : **$C_{11}H_{11}ClN_2Se$** (285) Calcd: C, 46.26; H, 3.88; N, 9.81.
Found: C, 46.11; H, 3.72; N, 9.95.

***N,N*-dimethyl-4-(3-nitrophenyl)-1,3-selenazol-2-amine (80l)**



Yellow solid

M. P. (°C) : 104-105

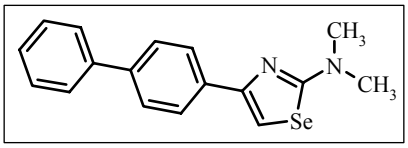
IR ($CHCl_3$, cm^{-1}) : ν_{max} 2924, 1566, 1529, 1348, 1048, 770, 697.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.17 (s, 6H, CH_3), 7.41 (s, 1H, selenazole H), 7.46-7.54 (t, *J* = 7.89 Hz, 1H, ArH), 8.07-8.19 (m, 2H, ArH), 8.68-8.70 (t, *J* = 1.96 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 41.0, 107.2, 121.2, 121.7, 129.2, 132.0, 137.5, 148.5, 150.6, 172.4.

Elemental Analysis : **$C_{11}H_{11}N_3O_2Se$** (296) Calcd: C, 44.61; H, 3.74; N, 14.19.
Found: C, 44.48; H, 3.91; N, 14.33.

4-(biphenyl-4-yl)-*N,N*-dimethyl-1,3-selenazol-2-amine (80m)



Brown solid

M. P. (°C) : 127-126

IR ($CHCl_3$, cm^{-1}) : ν_{max} 2921, 2872, 1574, 1477, 848, 730.

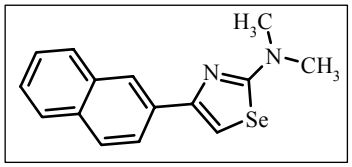
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.17 (s, 6H, CH_3), 7.31 (s, 1H, selenazole H), 7.33-7.48 (m, 3H, ArH), 7.58 -7.66 (m, 4H, ArH), 7.92-7.96 (dd, *J* = 8.41 & 1.76 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 41.0, 105.1, 126.7, 126.8, 127.0, 128.6, 135.1, 139.8, 140.8, 152.7, 172.1.

Elemental Analysis : **$C_{17}H_{16}N_2Se$** (327) Calcd: C, 62.39; H, 4.93; N, 8.56.
Found: C, 62.28; H, 4.81; N, 8.67.

***N,N*-dimethyl-4-(naphthalen-2-yl)-1,3-selenazol-2-amine (80n)**

Brown solid



M. P. (°C) : 123-124

IR ($CHCl_3$, cm^{-1}) : ν_{max} 3018, 2924, 1560, 770.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.20 (s, 6H, CH_3), 7.40 (s, 1H, selenazole H), 7.42-7.49 (m, 2H, ArH), 7.78-7.96 (m, 4H, ArH), 8.40 (s, 1H, ArH).

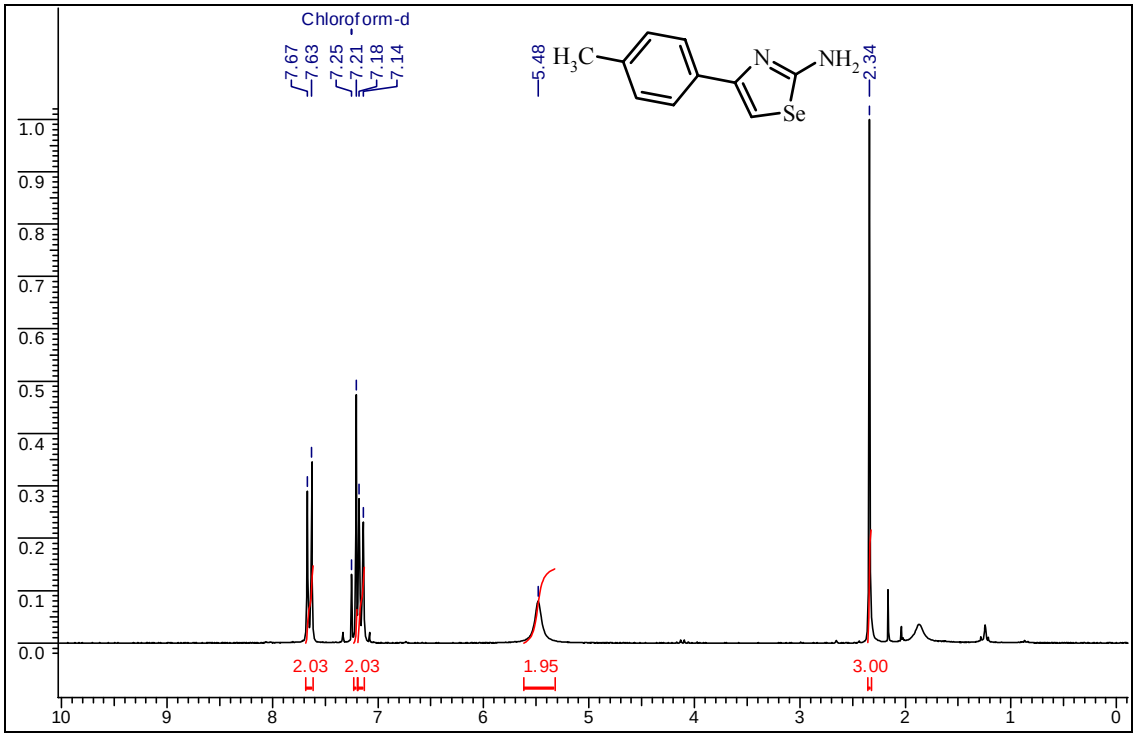
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 41.0, 105.7, 114.9, 124.4, 125.3, 125.5, 125.9, 127.5, 127.8, 128.2, 132.7, 133.3, 133.6, 152.9, 172.1.

Elemental Analysis : **$C_{15}H_{14}N_2Se$** (301) Calcd: C, 59.81; H, 4.68; N, 9.30.
Found: C, 59.89; H, 4.77; N, 9.37.

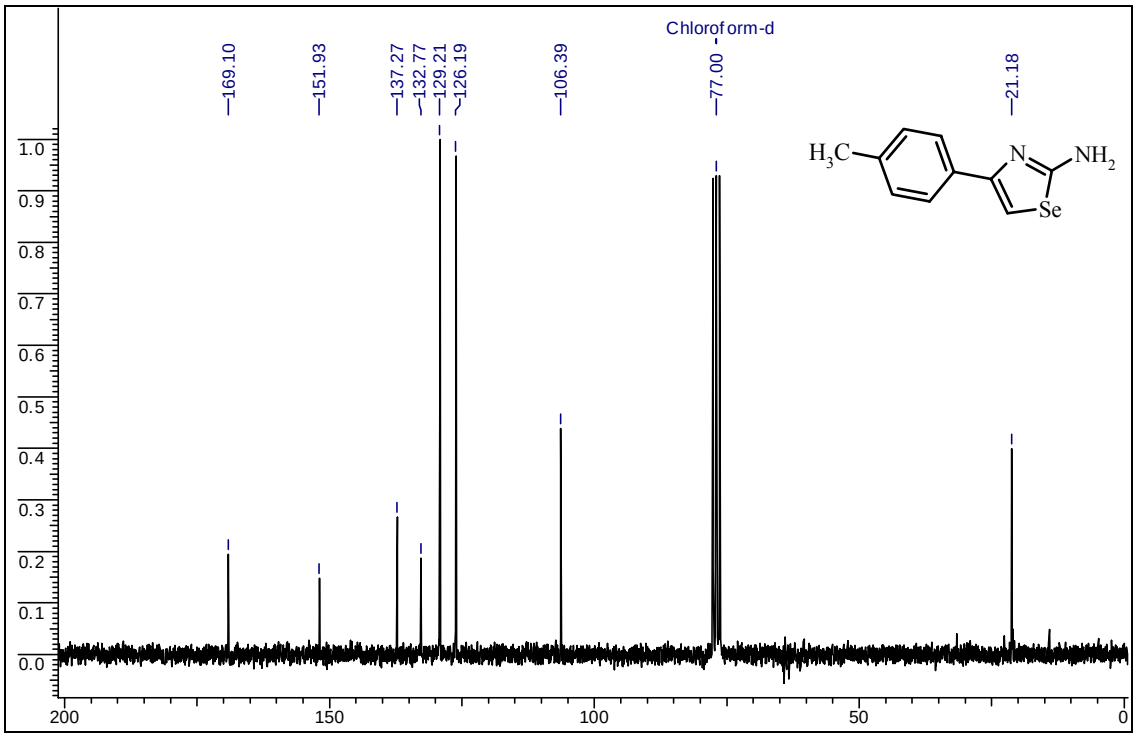
2.2.6 Spectra of representative 2-amino-1,3-selenazoles

Sr. No.	NMR spectra of **80**
1	^{1}H NMR and ^{13}C NMR spectra of **80b**
2	^{1}H NMR and ^{13}C NMR spectra of **80c**
3	^{1}H NMR and ^{13}C NMR spectra of **80e**
4	^{1}H NMR and ^{13}C NMR spectra of **80g**
5	^{1}H NMR and ^{13}C NMR spectra of **80h**
6	^{1}H NMR and ^{13}C NMR spectra of **80i**
7	^{1}H NMR and ^{13}C NMR spectra of **80j**

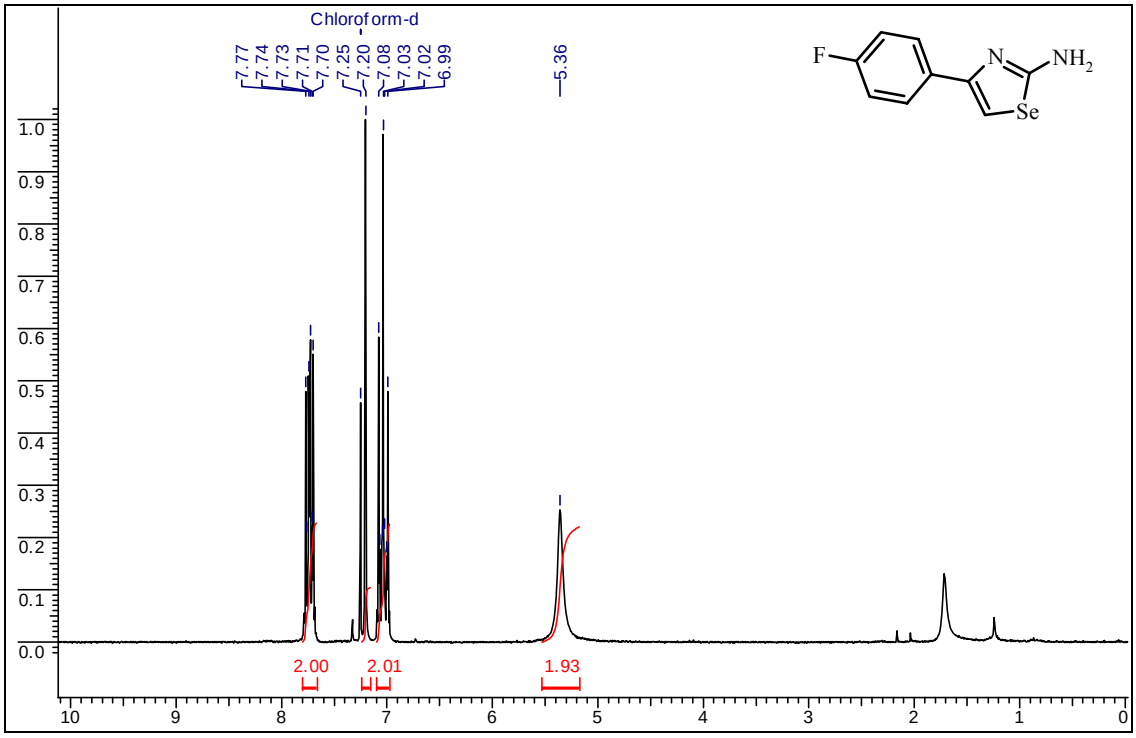
^{1}H NMR spectra of **80b**



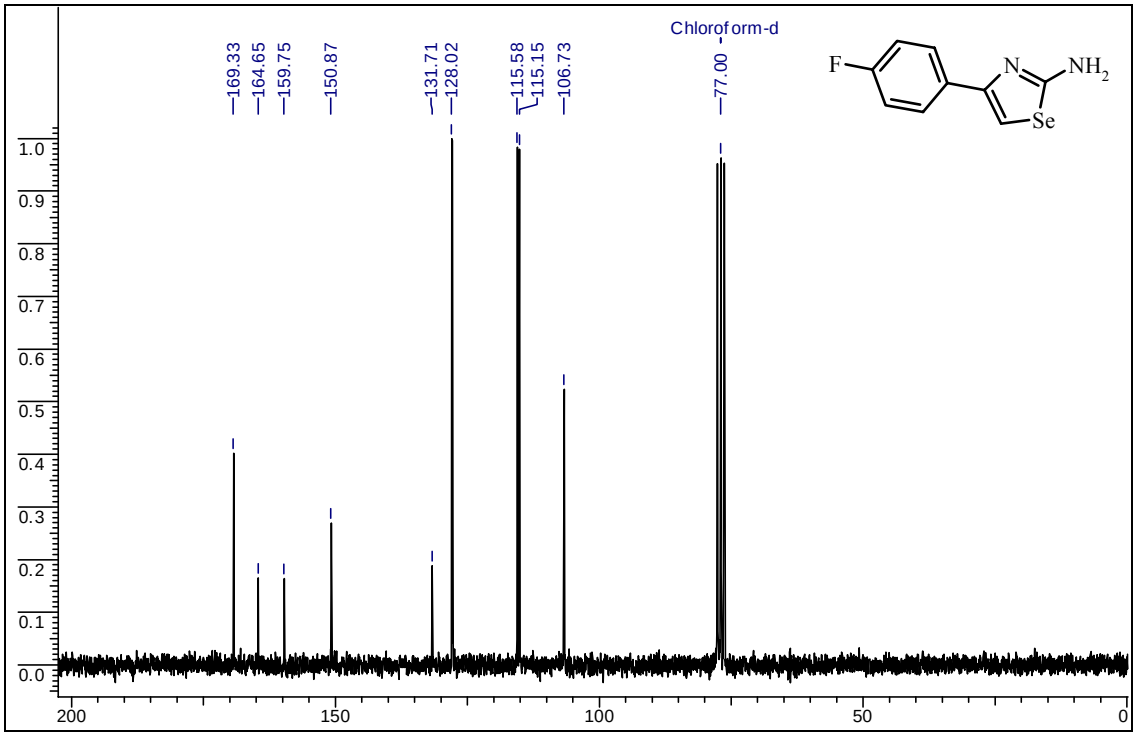
^{13}C NMR spectra of **80b**



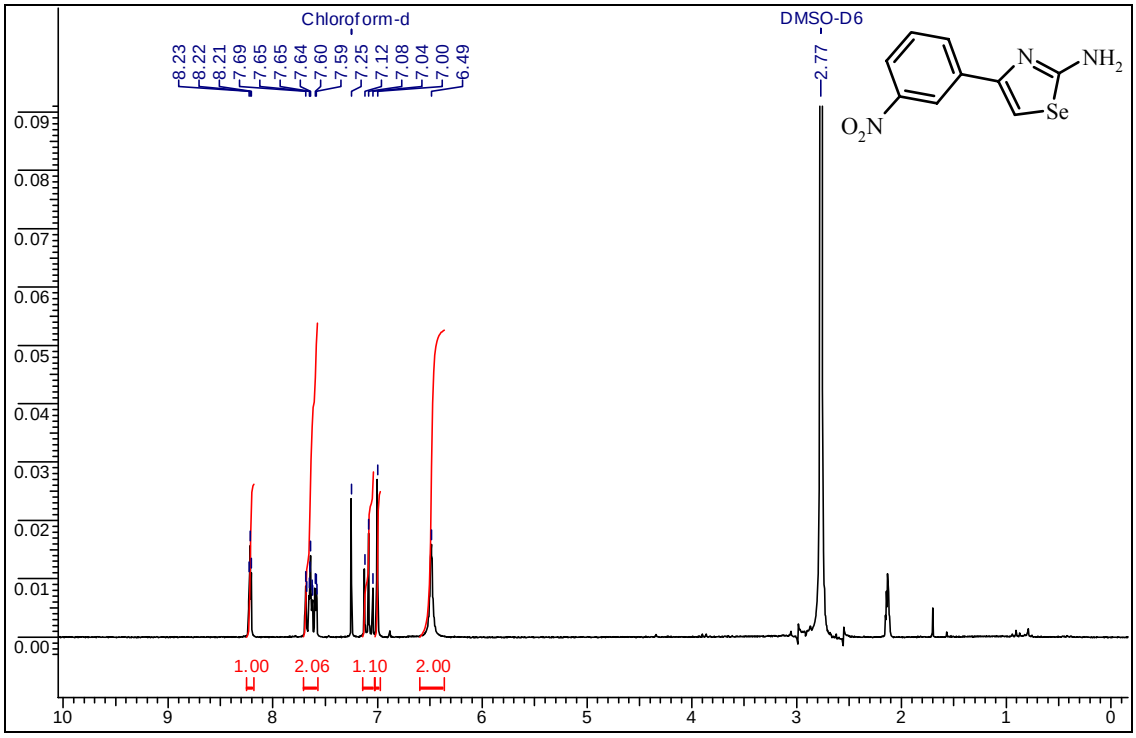
^{1}H NMR spectra of **80c**



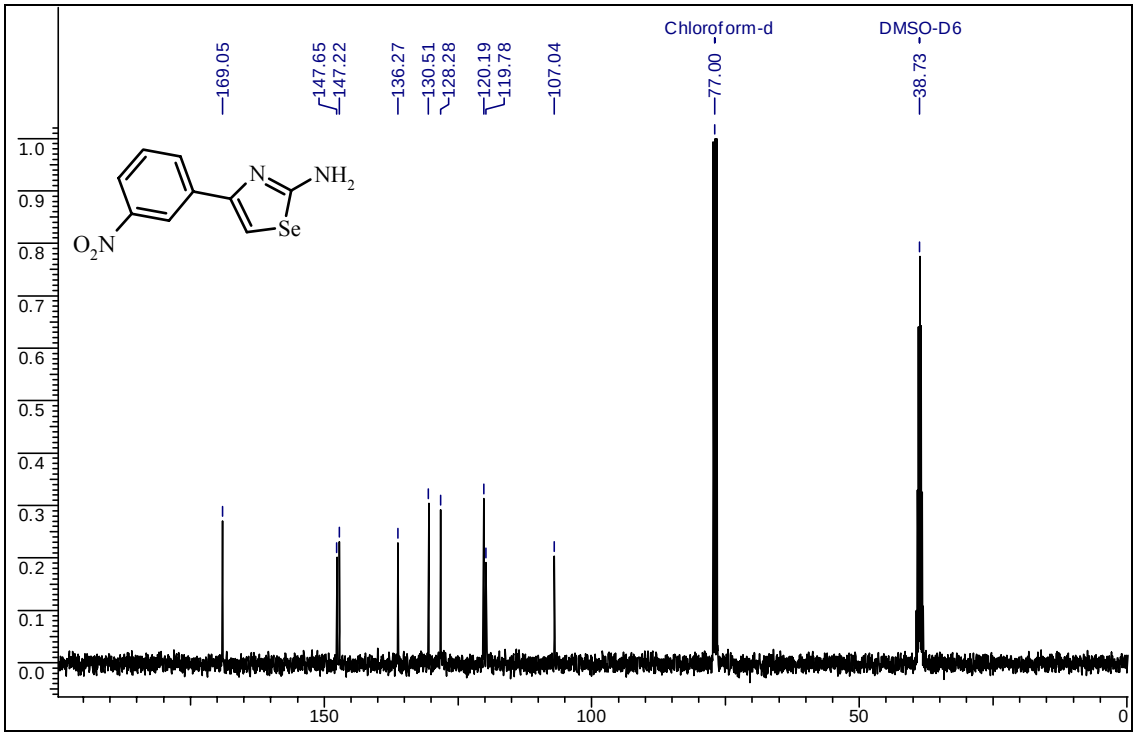
^{13}C NMR spectra of **80c**



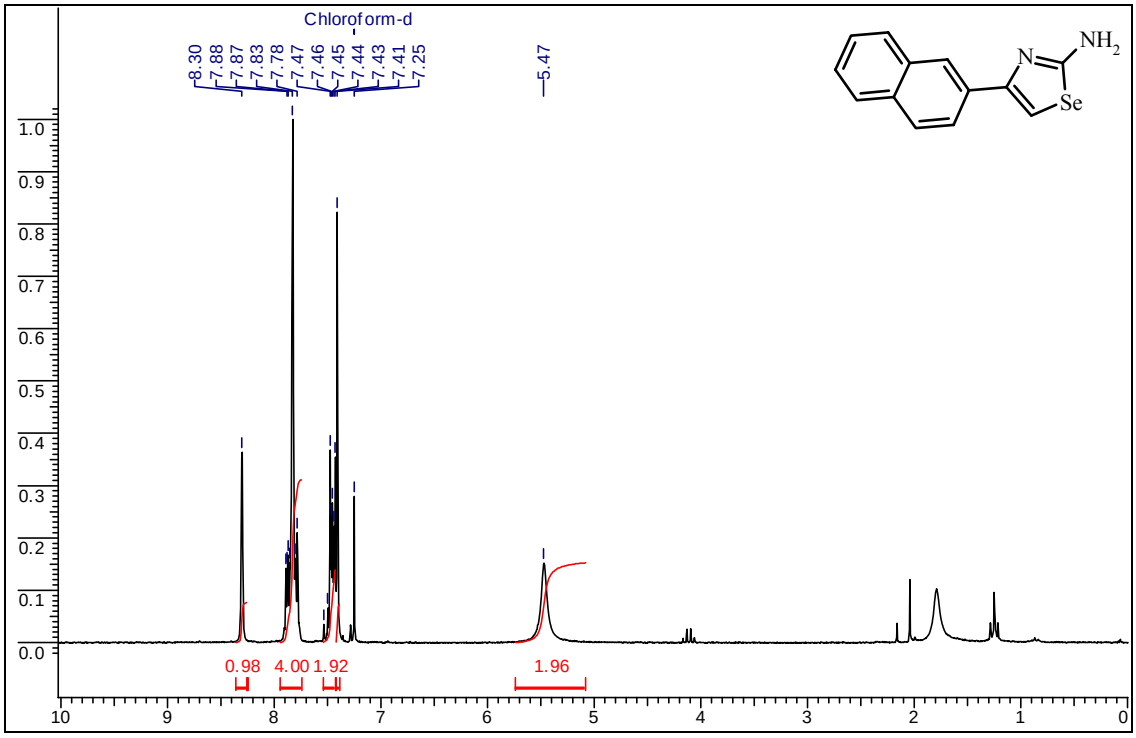
^{1}H NMR spectra of **80e**



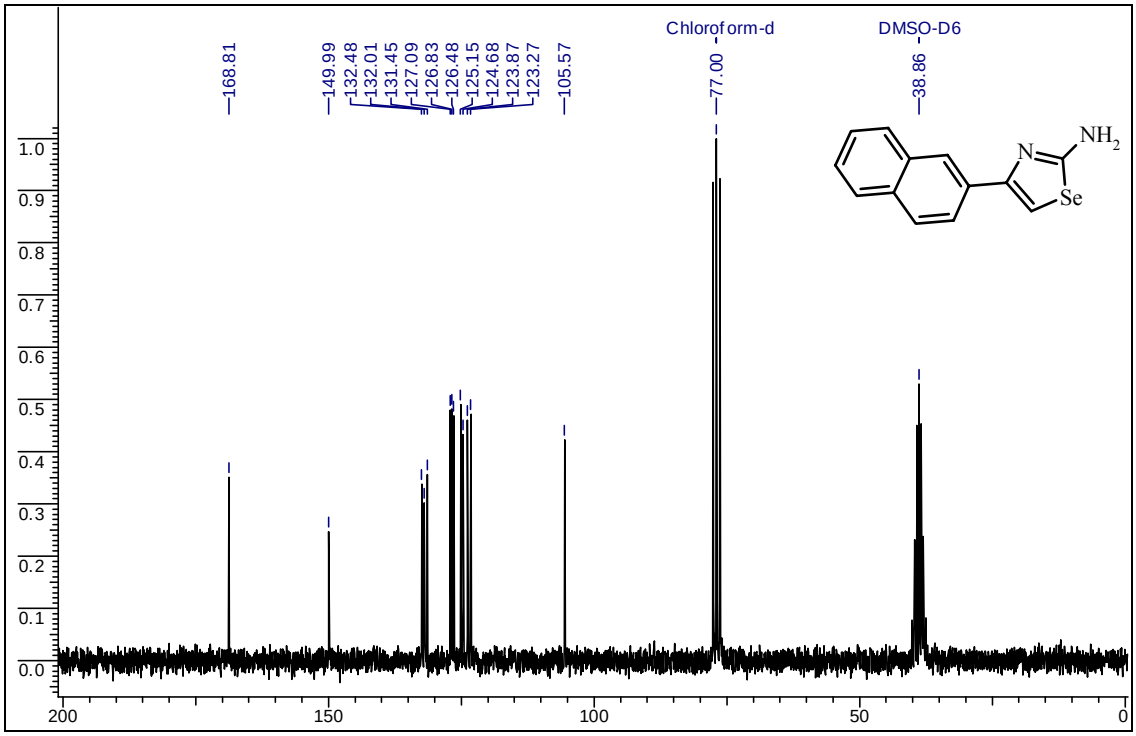
^{13}C NMR spectra of **80e**



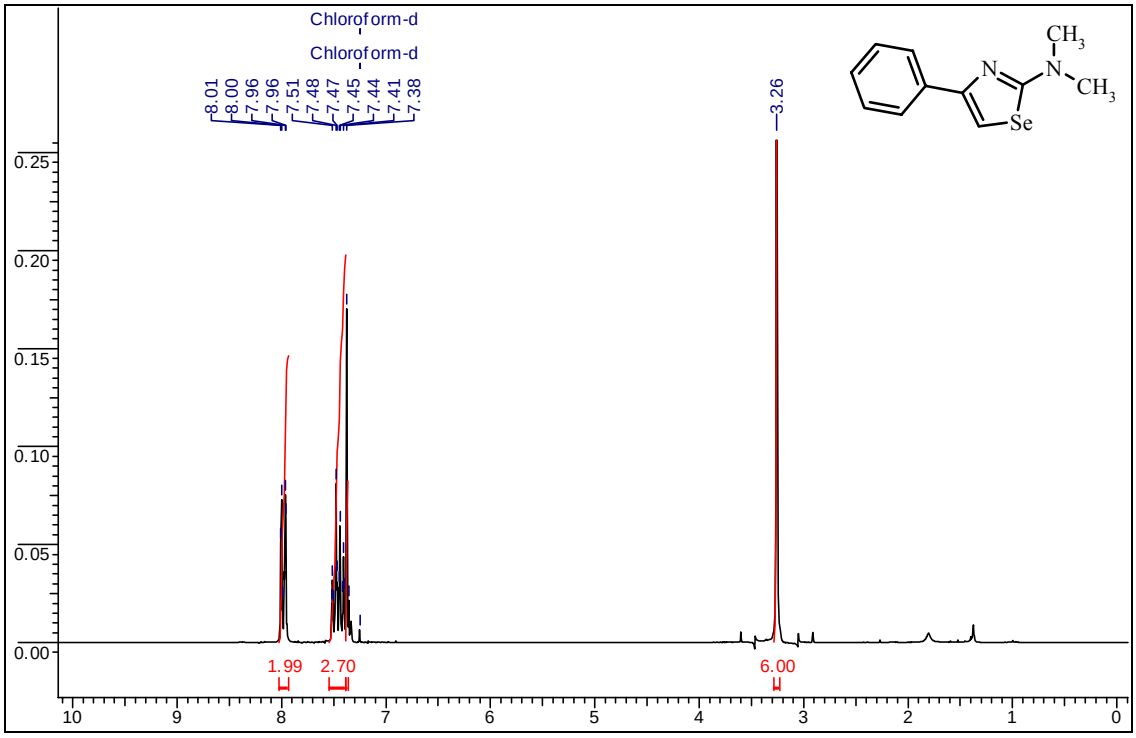
^{1}H NMR spectra of **80g**



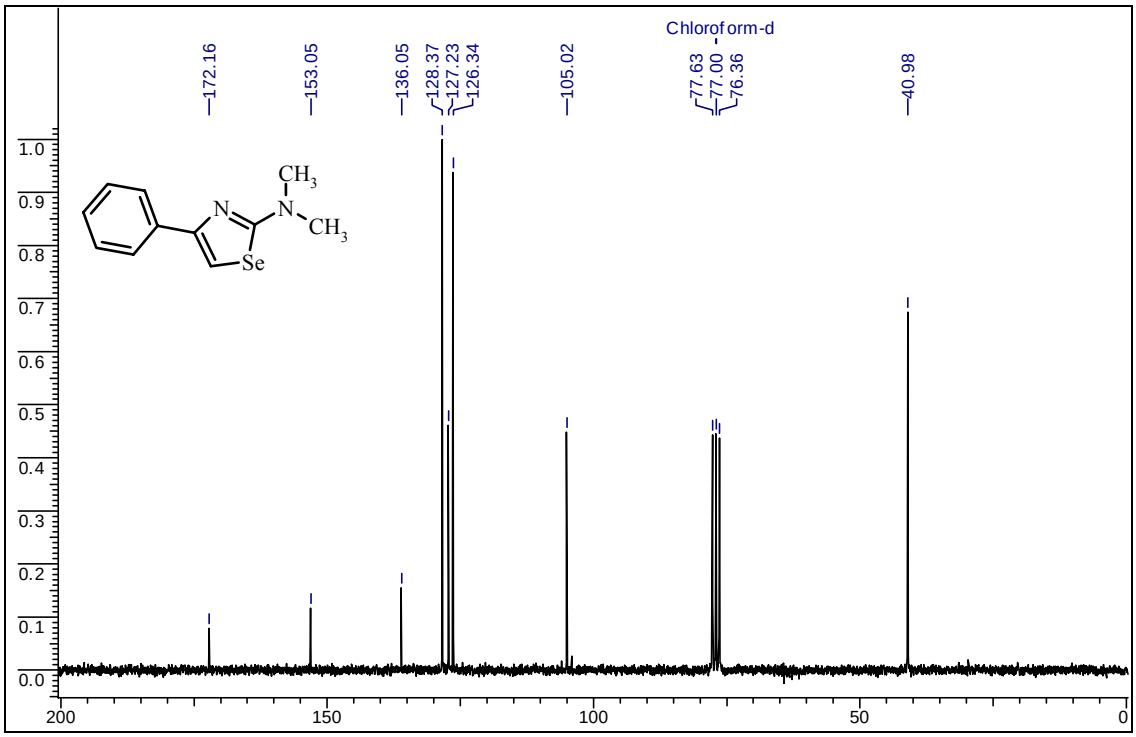
^{13}C NMR spectra of **80g**



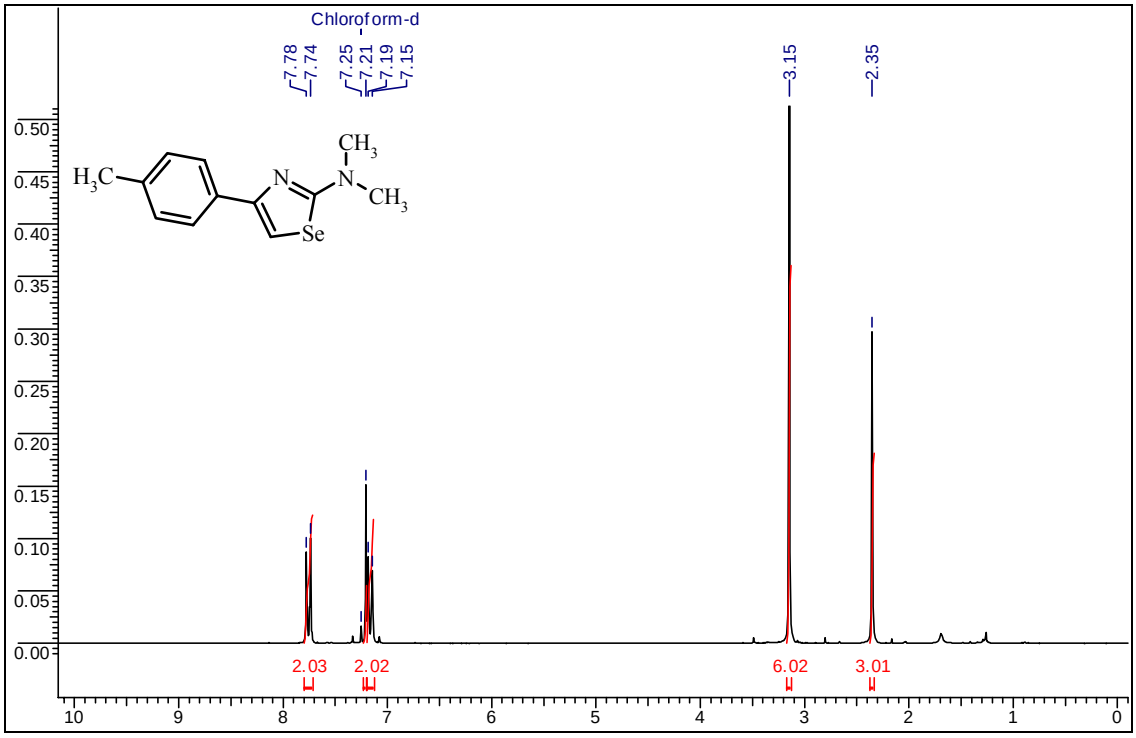
^{1}H NMR spectra of **80h**



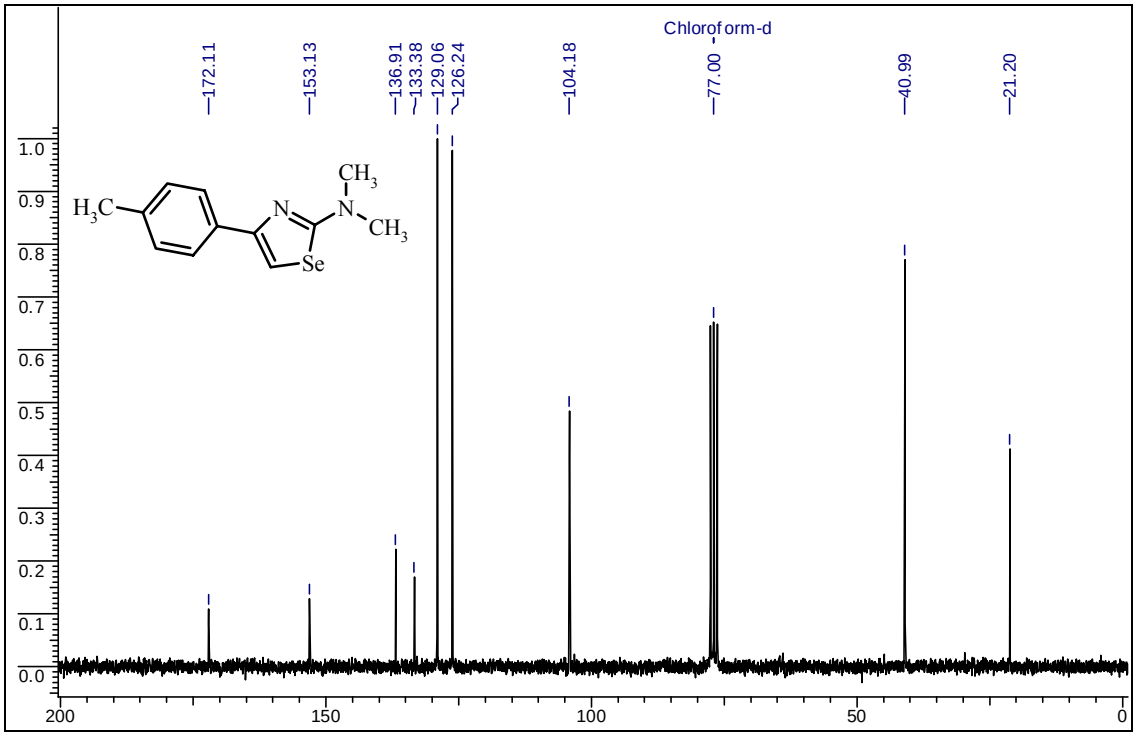
^{13}C NMR spectra of **80h**



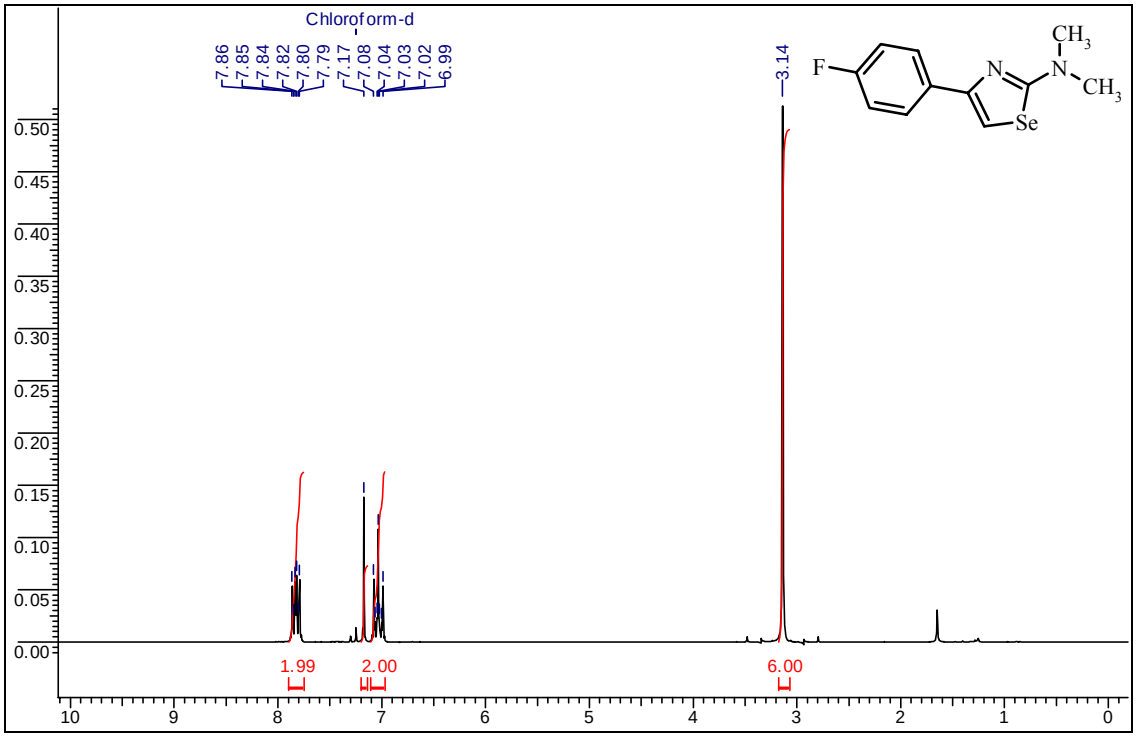
^{1}H NMR spectra of **80i**



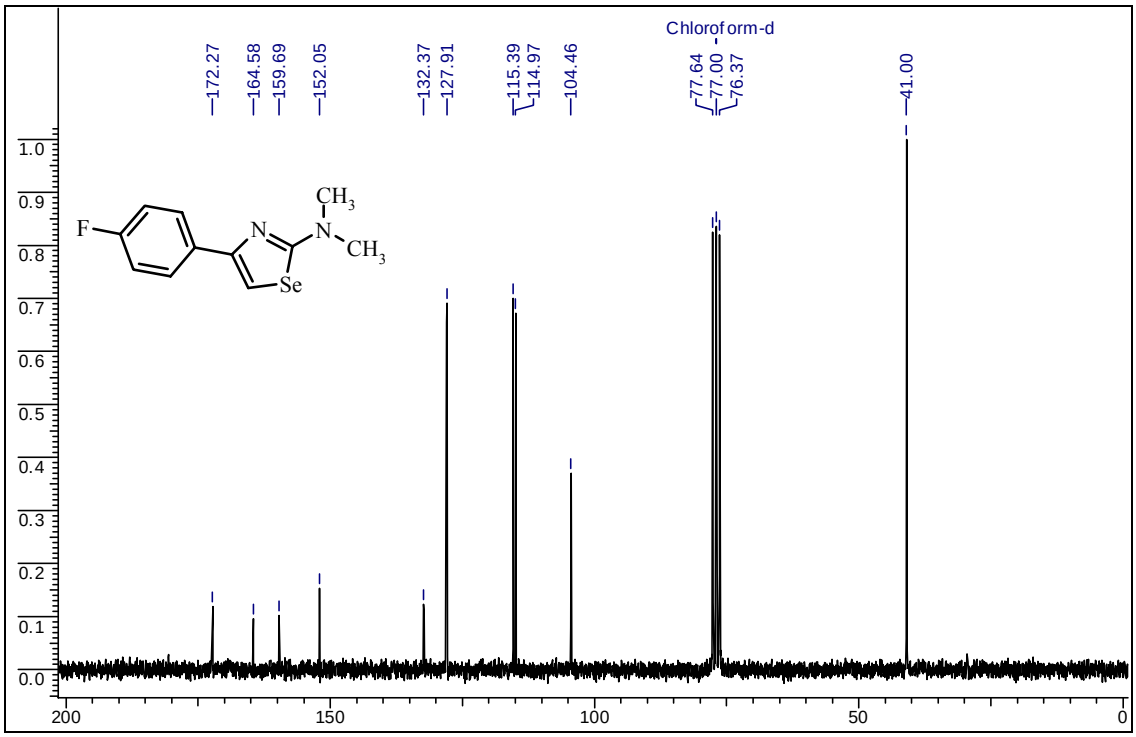
^{13}C NMR spectra of **80i**



^{1}H NMR spectra of **80j**



^{13}C NMR spectra of **80j**



2.2.7 References

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Chapter 2 - Section C

Synthesis of 4-aryl-1,4-dihydropyridines unsubstituted at 2- and 6-positions from alkyl propiolate under catalyst- and solvent-free conditions

2.3.1 Introduction

1,4-Dihydropyridines (DHP) occupies an important position in chemistry and biology. The prominent biological activities associated with 1,4-dihydropyridines are as Ca^{2+} channel blockers and as drugs for the treatment of cardiovascular diseases and hypertension.[1] The dihydropyridine skeleton is common in many vasodilator, bronchiodilator, anti-atherosclerotic, anti-tumour, hepatoprotective and anti-diabetic agents.[2,3] They are also known as neuroprotectants, as anti-platelet treatment of aggregators and are important in Alzheimer's disease as anti-ischaemic agents.[4] The recent interest in 1,4-dihydropyridines also relates to nicotinamide dinucleotide (NADH), a co-enzyme, and its unique ability to reduce many functional groups in biological systems. It has been postulated that dihydropyridines are involved in the cross-linking of elastin[5] and in the biosynthesis of indole alkaloids.[6,7] In addition to their role in biological phenomena, 1,4-dihydropyridines have the attracting ability to induce asymmetry[8,9] in organic molecules and have wide applicability as starting materials or intermediates in natural product synthesis,[10-13] particularly the alkaloids of pyridine as well as pyridobenzcquinolizine systems.

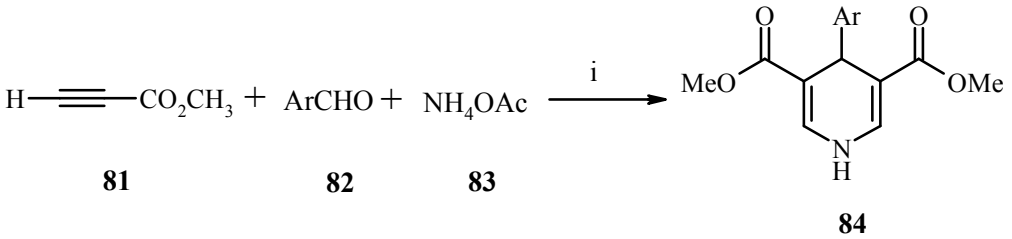
One of the most versatile[14] syntheses of 1,4-dihydropyridines is that due to Hantzsch[15] which uses a dicarbonyl compound or enamine, an aldehyde, and ammonia. However, owing to the lack of availability of suitable reagents, the Hantzsch synthesis generally leads to 1,4-dihydropyridines with substituents at 2- and 6-positions. Such substituents affect the properties of the dihydropyridines by their steric effect[16-18] and render them less suitable as model compounds for the coenzyme NADH. *N*-Substituted 1,4-dihydropyridines without substituents at 2- and 6-positions exhibit many pharmaceutical activities and are highly light-sensitive in the solid state. It has been shown that these compounds could be dimerized; the dimers are of interest as novel potential inhibitors of HIV-1 protease and have anticancer activity.[19]

2.3.2 Review of literature

In view of the importance of 1,4-dihydropyridines due to their biological activities, various methods have been reported for the synthesis of 1,4-dihydropyridines unsubstituted at 2- and 6-position. In this section we have focused on some more significant methods for the synthesis of 1,4-dihydropyridines without substituent at 2- and 6-positions.

Ulli Eisner et al. approach (1975)[20]

Ulli Eisner et al. reported the synthesis of 4-aryl-1,4-dihydropyridines **84** unsubstituted in the 1-, 2-, and 6-positions from the reaction of methyl propiolate **81** with aromatic aldehydes **82** and ammonium acetate **83** in acetic acid (**Scheme 30**).

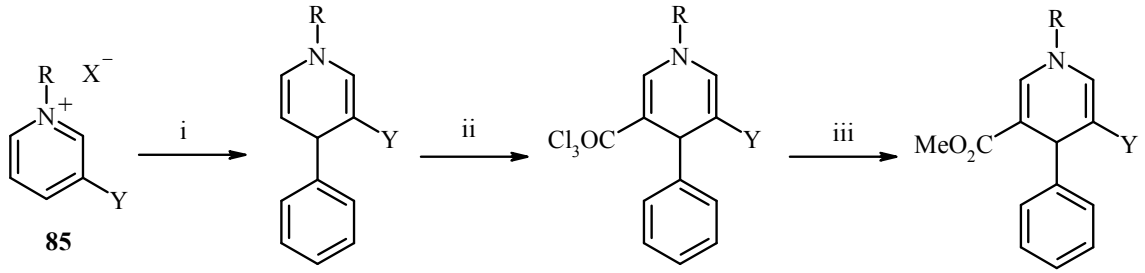


81 **82** **83** **84**

Scheme 30. Reaction conditions**:** (i) AcOH, reflux, 10-15 min, 56-79%.

M.-L. Bennasar et al. approach (1998)[21]

M.-L. Bennasar et al. reported the synthesis of *N*-substituted-3,5-diacyl-4-phenyl-l,4-dihydropyridines **89** from β-substituted-*N*-alkylpyridinium salts **85**. The addition of cyanocuprates such as $Ph_2Cu(CN)Li_2$ **86** to β-substituted-*N*-alkylpyridinium salts **85** at -40 °C resulted in 1,4-dihydropyridines **87** which was then further treated with trichloroacetic anhydride (TCAA) at 0 °C to afford the (trichloroacetyl)-1,4-dihydropyridines **88**. Finally 3,5-diacyl-4-phenyl-l,4-dihydropyridines **89** were obtained in 80-93% from the reaction of **88** with sodium methoxide in methanol (**Scheme 31**).



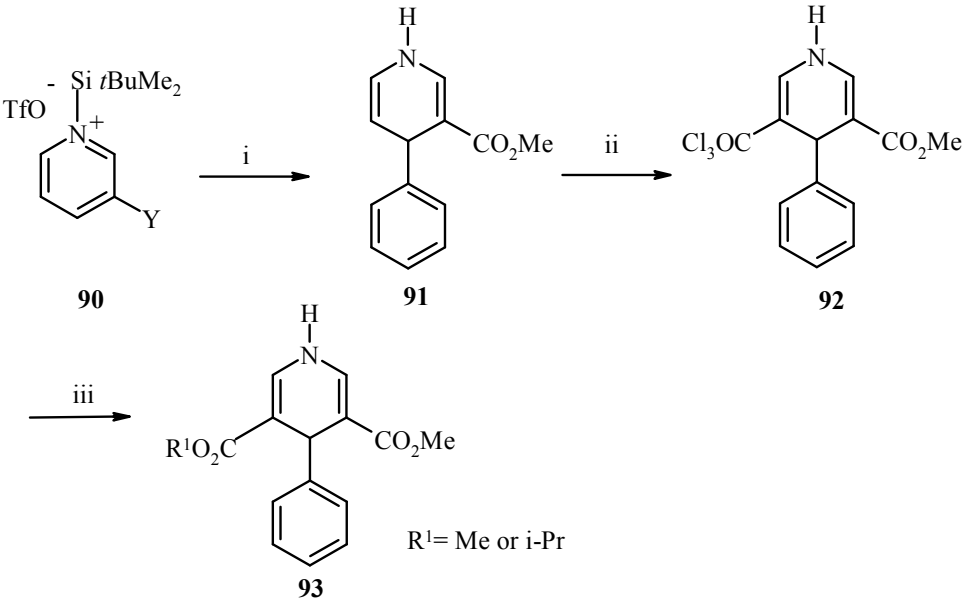
85 **87** **88** **89**

R=CH_3, CH_2Ph
Y= CO_2Me, COMe, NO_2, CHO, CN,

Scheme 31. Reaction conditions: (i) $Ph_2Cu(CN)Li_2$ (**86**), THF, -40 °C, 1.5 h, 42-75%; (ii) trichloroacetic anhydride(TCAA), THF, 0 °C, 2 h, 35-90%; (iii) MeONa, MeOH, 80-93%.

Furthermore, author described the synthesis of *N*-unsubstituted-3,5-diacyl-4-phenyl-l,4-dihydropyridines **93** from *N-(tert*-butyldimethylsilyl)pyridinium salts **90.** Organomagnesium compounds such as phenylmagnesium chloride and tetrabutyl ammonium fluoride (TBAF) was added to *N-(tert*-butyldimethylsilyl)pyridinium salts **90** at

-40 °C to afford 1,4-dihydropyridine **91** which on further reaction with TCAA at 0 °C afforded the (trichloroacetyl)-1,4-dihydropyridines **92.** Finally, the corresponding *N*-unsubstituted-3,5-diacyl-4-phenyl-l,4-dihydropyridines **93** were obtained from **92** by treating them with sodium methoxide or sodium isopropoxide (**Scheme 32**).

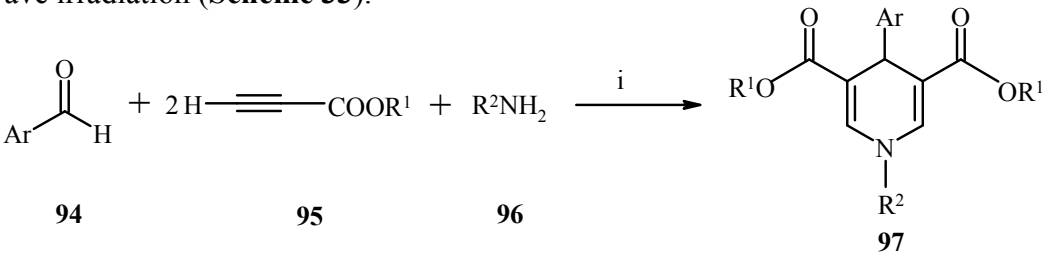


90 **91** **92** **93**

Scheme 32. Reaction conditions**:** (i) Phenylmagnesium chloride, TBAF, THF, - 40 °C; (ii) TCAA, 0 °C, 40%; (iii) R^1ONa, R^1OH, 75-80%.

Saeed Balalaie et al. approach (2001)[22]

Saeed Balalaie et al. reported the synthesis of *N*-substituted 4-aryl-1,4-dihydropyridines **97** by three-component condensation of benzaldehyde derivatives **94** (1 equiv), alkyl propiolates **95** (2 equiv) and primary amines **96** (1 equiv) catalyzed by silica gel under microwave irradiation (**Scheme 33**).



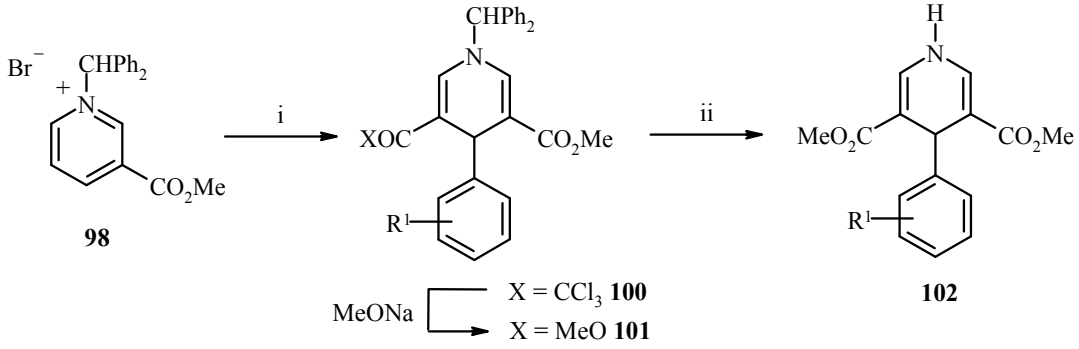
94 **95** **96** **97**

Scheme 33. Reaction conditions**:** (i) silica gel, MW,4 min, 60-94%.

M.-L. Bennasar et al. approach (2002)[23]

M.-L. Bennasar et al. reported the synthesis of 4-aryl-3,5-diacyl-1,4-dihydropyridines **102** by the copper-mediated addition of functionalized aryl magnesium halide **99** (prepared from aryl iodide and isopropyl magnesium bromide) to 1-benzhydryl-3-

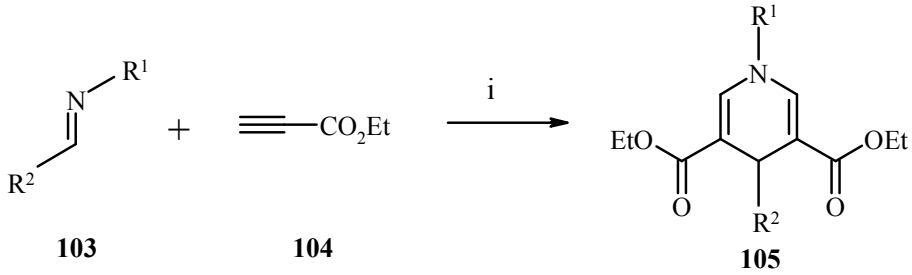
(methoxycarbonyl)pyridinium bromide **98** (prepared from methyl nicotinate and benzhydryl bromide) at -40 °C followed by acylation using trichloroacetic anhydride and subsequent haloform reaction and *N*-deprotection using TFA and phenol (**Scheme 34**).



Scheme 34. Reaction conditions**:** (i) arylmagnesium halides **(99)**, CuI, -40 °C, trichloroacetic anhydride (TCAA), 35-60 %; (ii) phenol, TFA, rt, overnight, 70-98%.

Shin-ichi Fukuzawa et al. appraoch (2008)[24]

Shin-ichi Fukuzawa et al. reported the synthesis of *N*-substituted-1,4-dihydropyridines **105** from the reaction of imines **103** (1 mmol) with ethyl propiolate **104** (2.1 mmol) using scandium (III) triflate [$Sc(OTf)_3$] in toluene at reflux temperature (**Scheme 35**).



Scheme 35. Reaction conditions**:** (i) $Sc(OTf)_3$ (10 mol%), toluene, reflux, 24 h, 18-77%.

2.3.3 Present work

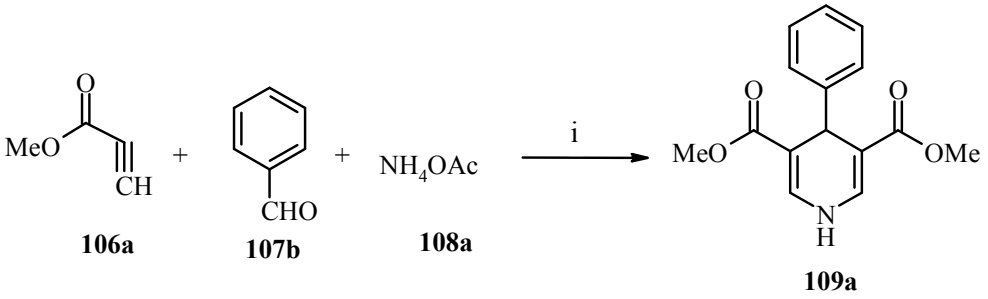
2.3.3.1 Objectives

On reviewing literature, it was observed that very few methods were reported for the synthesis of 4-aryl-1,4-dihydropyridine unsubstituted at 2- and 6-position. These reported methods suffer from drawbacks such as multi-step synthetic protocol, harsh reaction conditions such as refluxing in solvent, cumbersome product isolation procedures, use of polar/volatile/ hazardous organic solvents and often expensive catalysts.

The development of efficient and environment-friendly chemical processes for the preparation of biologically active molecules constitute a major challenge for chemists in organic synthesis. Nowadays in the development of new synthetic processes, ecological points of view must also be taken into consideration and apportioned due importance in the assessment of viability.[25] In this process the solvents are especially important, as they are generally used in large quantities. Many organic solvents are ecologically harmful, and their use should therefore be minimized as far as possible or even avoided altogether. The best solvent from an ecological point of view is without a doubt no solvent. In the recent years, there has been increasing interest in solvent free organic reactions. The solvent-free synthetic method is valuable for ecological and economical reasons. Furthermore, the reported examples have demonstrated that solvent-free reactions are generally faster, give higher selectivity and yields and usually require easier workup-procedures and simpler equipment. Thus, development of solvent-free organic reactions is gaining prominence.[26] In continuation to our ongoing interest in development of environment-friendly synthetic methologies for biologically active heterocycles, here we report an efficient, one pot- and three-component method for the synthesis of 4-aryl-1,4-dihydropyridine derivatives unsubstituted at 2- and 6-position by the condensation of alkyl propiolate, aromatic aldehyde and ammonium acetate (or alkyl amine) under solvent- and catalyst-free conditions.

2.3.3.2 Results and discssion

When a mixture containing methyl propiolate **106a,** benzaldehyde **107a** and ammonium acetate **108a** was heated with stirring at 100 °C without any solvent or catalyst, it afforded the corresponding dimethyl 1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate **109a** in 87% yield in 1 h (**Scheme 36**).

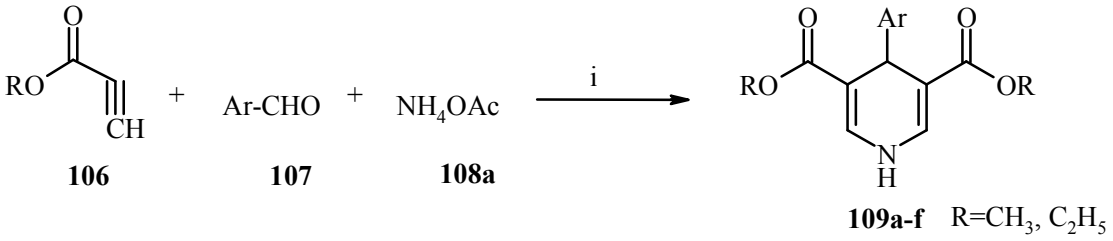


106a **107b** **108a** **109a**

Scheme 36. Reaction conditions**:** (i) 100 °C, 1 h, 87%.

To optimize the reaction conditions, initially we carried out a reaction by treating methyl propiolate with benzaldehyde and ammonium acetate as a model reaction at room temperature, where in no reaction was observed to afford the desired product. Later on, we tried this model reaction at 60 °C, where it gave the desired product in 23% yield only after 2 h. Then the reaction was conducted at 80 °C, where it afforded the product in 42% yield only after 2 h. Keeping in mind the effect of temperature as a factor for favoring reaction, we carried out the model reaction at 100 °C where it smoothly proceeded in 1 h and gave the desired product, dimethyl 1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate **109a** in 87% yield. The progress of the reaction was monitored by TLC. Moreover, there was no further improvement in reaction rate as well as in the yield when the reaction was carried out at temperature higher than 100 °C. Hence we chose this temperature as an optimized temperature for the further reactions. No additional catalyst is required for the reaction and it proceeded under solvent-free conditions.

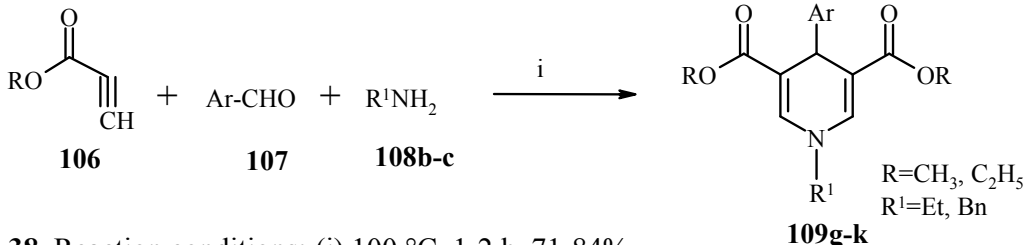
To investigate the scope and generality of this process, alkyl propiolate **106** were reacted with a range of aryl aldehyde **107** and ammonium acetate **108a** to generate the derivatives of 4-aryl-1,4-dihydropyridine unsubstituted at 2- and 6-position (**109a-f)** using these optimized reaction condition (**Scheme 37**).



106 **107** **108a** **109a-f** R=CH_3, C_2H_5

Scheme 37. Reaction conditions**:** (i) 100 °C, 1-1.5 h, 78-87%.

Replacing the ammonium acetate with alkyl amine such as benzyl amine or ethyl amine, furnished the corresponding *N*-substituted-dialkyl-1,4-dihydro-4-arylpyridine-3,5-dicarboxylate (**109g-k**) in good yields (**Scheme 38**).

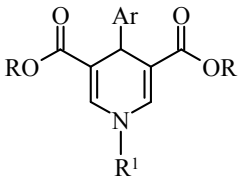


106 **107** **108b-c** **109g-k**

Scheme 38. Reaction conditions**:** (i) 100 °C, 1-2 h, 71-84%.

The process tolerates both electron-rich as well as electron-poor functionality on aromatic aldehyde and reacted well with alkyl propiolate such as methyl propiolate and ethyl propiolate using ammonium acetate as well as alkyl amines. The results are summarized in **Table 4**.

Table 4. Synthesis of 4-aryl-1,4-dihydropyridines **(109a-k)**



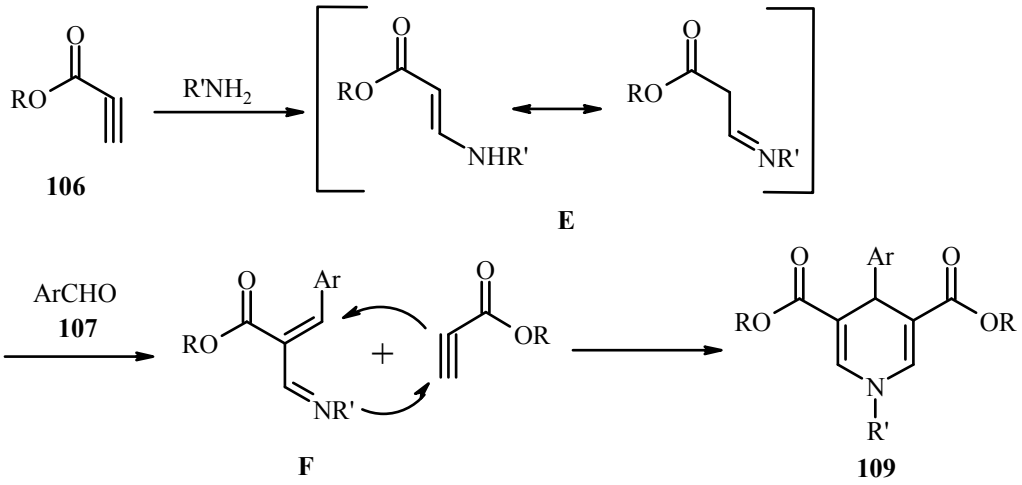
Entry	Ar	R	R^1	Product **109a-k**	Time (h)	Yield[a] (%)
1	C_6H_5	CH_3	H	**109a**	1.0	87
2	4-CH_3-C_6H_4	CH_3	H	**109b**	1.0	78
3	4-CH_3O-C_6H_4	CH_3	H	**109c**	1.5	79
4	3-Cl-C_6H_4	CH_3	H	**109d**	1.5	78
5	4-Cl-C_6H_4	CH_3	H	**109e**	1.0	81
6	C_6H_5	C_2H_5	H	**109f**	1.5	83
7	C_6H_5	CH_3	C_2H_5	**109g**	2	73
8	C_6H_5	CH_3	$C_6H_4CH_2$	**109h**	1.0	75
9	4-CH_3-C_6H_4	CH_3	$C_6H_4CH_2$	**109i**	1.0	84
10	C_6H_5	C_2H_5	C_2H_5	**109j**	1.0	76
11	C_6H_5	C_2H_5	$C_6H_4CH_2$	**109k**	1.5	71

[a]: Isolated yield after column chromatography

A variety of combination can do to produce a series of dihydropyridines. All the reactions were completed within the period of 1 - 2 h at 100 °C and afforded the product in good yields. The products were isolated by adding water to reaction mixture and extracting them with ethyl acetate which on evoporation afforded crude solid products. The crude product was purified by column chromatography to afford pure products. All the compounds were characterized by using IR, melting points, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. The ^{1}H NMR spectra of dialkyl 1,4-dihydro-4-arylpyridine-3,5-dicarboxylate shows a characteristic peak in the region δ 4.8-4.9 ppm corresponding to hydrogen at fourth carbon of DHP ring. Similarly, ^{13}C NMR spectra show characteristic peak in the region δ 36-38 ppm corresponding to fourth carbon of DHP ring.

2.3.3.3 Plausible mechanism

The mechanism is postulated as follows. The addition of ammonia (or amine) may take place at the triple bond of propiolate **106** to form enaminone intermediate **E** which may convert to **F** on reaction with the aldehyde **107**. The intermediate **F** may undergo cyclization in a [4+2] manner with another molecule of propiolate to give the final product 1**09** (**Scheme 39**).



Scheme 39. Palausible mechanism

2.3.4 Conclusion

In conclusion, we have achieved an efficient method for the one-pot synthesis of 4-aryl-1,4-dihydropyridines and *N*-alkyl-4-aryl-1,4-dihydropyridines without having any substituent at 2- and 6-position under catalyst- and solvent-free conditions by one-pot, three component condensation of alkyl propiolate, aromatic aldehyde and ammonium acetate or alkyl amine.

2.3.5 Experimental

2.3.5.1 General procedure for the synthesis of 4-aryl-1,4-dihydropyridines (109a-f).

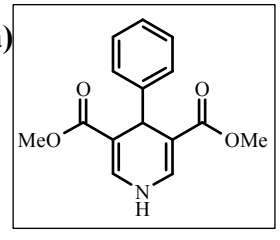
A mixture of alkyl propiolate **106** (2 mmol), aromatic aldehyde **107** (1 mmol) and ammonium acetate **108a** (1.2 mmol) was heated with stirring at 100 °C for the specified time (**Table 4**). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and product was extracted using ethyl acetate (3x10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get crude product which was further purified by column chromatography using petroleum ether:ethyl acetate (7.5:2.5) to obtain pure 4-aryl-1,4-dihydropyridines (**109a-f)**.

2.3.5.2 General procedure for synthesis of *N*-substituted-4-aryl-1,4-dihydropyridines (109g-k).

A mixture of alkyl propiolate **106** (2 mmol), aromatic aldehyde **107** (1 mmol) and alkyl amine **108b-c** (1 mmol) was heated with stirring at 100 °C for the specified time (**Table 4**). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with water (10 mL) and product was extracted using ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get crude product which was further purified by column chromatography using petroleum ether:ethyl acetate (9:1) to obtain pure *N*-alkyl-4-aryl-1,4-dihydropyridines **109g-k**.

2.3.5.3 Characterization data for 1,4-dihydropyridines

Dimethyl 1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (109a)



Yellow solid

M. P. (°C) : 209-211 (Lit.[20] 211-212)

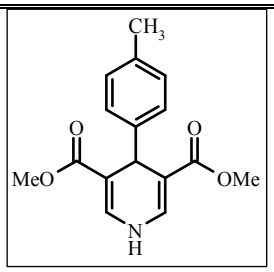
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3336, 3027, 2949, 1705, 1631, 1491, 1435, 1188, 1083, 754.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.63 (s, 6H, OCH_3), 4.91 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.38 (bs, 1H, NH), 7.15-7.37 (m, 7H, ArH).

^{13}C NMR ($CDCl_3$+ DMSO-D_6, 50 MHz) : δ 36.9, 50.5, 106.5, 125.7, 127.4, 127.5, 134.1, 146.7, 167.0.

Elemental Analysis : **$C_{15}H_{15}NO_4$** (273) Calcd: C, 65.93; H, 5.53; N, 5.13.
Found: C, 65.87; H, 5.41; N, 5.21.

Dimethyl 1,4-dihydro-4-*p*-tolylpyridine-3,5-dicarboxylate (109b)



Yellow solid

M. P. (°C) : 211-212 (Lit.[20] 213-215)

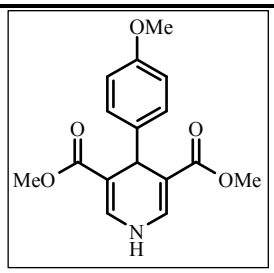
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3318, 2950, 2889, 1710, 1661, 1629, 1510, 1436, 1187, 1082, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.28 (s, 3H, CH_3), 3.63 (s, 6H, OCH_3), 4.86 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.46 (bs, 1H, NH), 7.04-7.08 (d, *J* = 7.98 Hz, 2H, ArH), 7.21-7.25 (d, *J* = 7.98 Hz, 2H, ArH), 7.29-7.31 (d, *J* = 5.28 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, DMSO-D_6, 50 MHz) : δ 20.3, 36.2, 50.3, 106.3, 127.2, 128.0, 133.9, 134.9, 143.8, 166.9.

Elemental Analysis : **$C_{16}H_{17}NO_4$** (287) Calcd: C, 66.89; H, 5.96; N, 4.87.
Found: C, 66.81; H, 5.88; N, 4.76.

Dimethyl 1,4-dihydro-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (109c)



Yellow solid

M. P. (°C) : 198-199 (Lit.[20] 197-198)

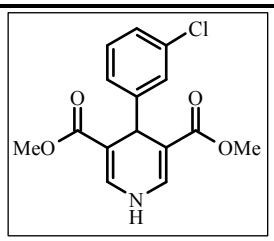
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3327, 2950, 2846, 1703, 1660, 1626, 1508, 1435, 1239, 1187, 1083, 770.

^1H NMR ($CDCl_3$, 200 MHz) : δ 3.63 (s, 6H, OCH_3), 3.75 (s, 3H, OCH_3), 4.85 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.45 (bs, 1H, NH), 6.77-6.81 (d, *J* = 8.74 Hz, 2H, ArH), 7.24-7.32 (m, 4H, ArH).

^{13}C NMR ($CDCl_3$, DMSO-D*6*, 50 MHz) : δ 35.2, 49.7, 53.8, 105.6, 112.1, 127.7, 133.4, 138.7, 156.7, 166.2.

Elemental Analysis : **$C_{16}H_{17}NO_5$** (303) Calcd: C, 63.36; H, 5.65; N, 4.62.
Found: C, 63.45; H, 5.57; N, 4.57.

Dimethyl 4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (109d)



Yellow solid

M. P. (°C) : 205-207

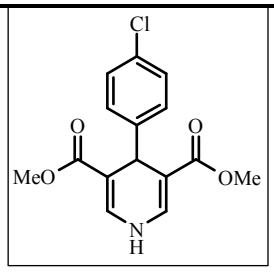
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3375, 2923, 2853, 1703, 1676, 1609, 1463, 1376, 1286, 1196, 1079, 942, 722.

^1H NMR ($CDCl_3$, 200 MHz) : δ 3.64 (s, 6H, OCH_3), 4.90 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.59 (bs, 1H, NH), 7.11-7.18 (m, 2H, ArH), 7.21-7.24 (m, 1H. ArH), 7.26-7.28 (d, *J* = 1.72 Hz, 1H, ArH) 7.33-7.36 (d, *J* = 5.30 Hz, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 37.3, 51.3, 107.8, 126.4, 126.7, 128.2, 129.1, 133.9, 148.5, 167.1.

Elemental Analysis : **$C_{15}H_{14}ClNO_4$** (307) Calcd: C, 58.55; H, 4.59; N, 4.55.
Found: C, 58.59; H, 4.64 N, 4.48.

Dimethyl 4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (109e)



Faint yellow solid

M. P. (°C) : 218-219 (Lit.[20] 219-221)

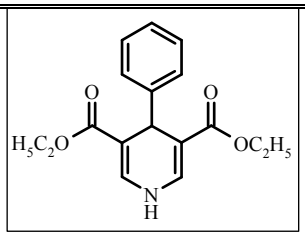
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3340, 2927, 2850, 1707, 1626, 1575, 1472, 1245, 758.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 3.56 (s, 6H, OCH_3), 4.81 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.40 (bs, 1H, NH), 7.12-7.24 (m, 6H, ArH).

^{13}C NMR (CDCl$_3$+DMSO-d_6, 50 MHz) : δ 35.9, 50.0, 105.2, 126.8, 128.5, 130.4, 133.9, 145.0, 166.2.

Elemental Analysis : **$C_{15}H_{14}ClNO_4$** (307) Calcd: C, 58.55; H, 4.59; N, 4.55.
Found: C, 58.67; H, 4.48 N, 4.63.

Diethyl 1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (109f)



Faint yellow solid

M. P. (°C) : 121-122

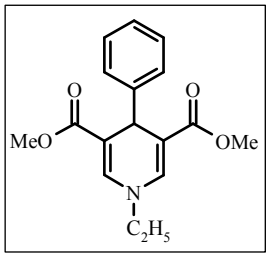
IR (CHCl$_3$, cm^{-1}) : ν_{max} 3330, 2982, 1691, 1604, 1491, 1373, 1190, 1077, 754.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 1.10-1.18 (t, J = 7.10 Hz, 6H, $\underline{CH_3}CH_2$), 3.90-4.14 (m, 4H, $O\underline{CH_2}CH_3$), 4.84 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.56 (bs, 1H, NH), 7.09-7.32 (m, 7H, ArH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 14.1, 37.5, 59.9, 108.1, 126.3, 127.8, 128.23, 133.8, 146.9, 167.2.

Elemental Analysis : **$C_{17}H_{19}NO_4$** (301) Calcd: C, 67.76; H, 6.36; N, 4.65.
Found: C, 67.65; H, 6.47; N, 4.58.

Dimethyl 1-ethyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (109g)



Yellow solid

M. P. (°C) : 129-130

IR (CHCl$_3$, cm^{-1}) : ν_{max} 3024, 2950, 1704, 1665, 1578, 1409, 1208, 1175, 1075, 752.

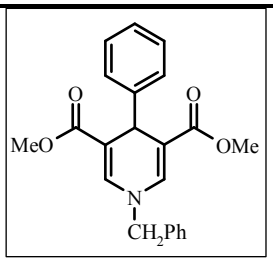
^{1}H NMR (CDCl$_3$, 200 MHz : δ 1.34-1.41 (t, J = 7.25 Hz, 3H, $\underline{CH_3}CH_2$), 3.44-3.55 (q, J = 7.25 Hz, 2H, $N\underline{CH_2}CH_3$), 3.66 (s, 6H, OCH_3), 4.92 (s, 1H, $C_4\underline{H}$ of DHP ring), 7.18-7.36 (m, 7H, ArH).

^{13}C NMR : δ 15.5, 37.1, 49.6, 51.1, 108.4, 126.3, 127.9, 128.0, 137.2, 146.5,

($CDCl_3$, 50 MHz) 167.2.

Elemental Analysis : **$C_{17}H_{19}NO_4$** (301) Calcd: C, 67.76; H, 6.36; N, 4.65.
Found: C, 67.69; H, 6.27; N, 4.73.

Dimethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (109h)



Yellow solid

M. P. (°C) : 162-163 (Lit.[22] 160-162)

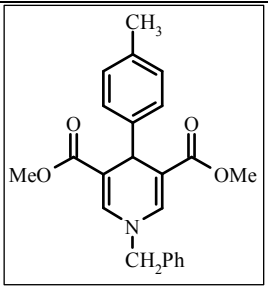
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3016, 2972, 2856, 1707, 1656, 1545, 1465, 1215, 1078, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.60 (s, 6H, OCH_3), 4.57 (s, 2H, NCH_2), 4.90 (s. 1H, $C_4\underline{H}$ of DHP ring), 7.12-7.15 (t, *J* = 7.27 Hz, 1H, ArH), 7.20-7.23 (t, *J* = 7.01 Hz, 2H, ArH), 7.25-7.27 (m, 6H, ArH), 7.35-7.42 (m, 3H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 37.16, 51.28, 58.33, 108.77, 126.46, 127.22, 128.05, 128.41, 129.15, 136.05, 137.72, 146.26, 167.20.

Elemental Analysis : **$C_{22}H_{21}NO_4$** (363) Calcd: C, 72.71; H, 5.82; N, 3.85.
Found: C, 72.57; H, 5.94; N, 3.77.

Dimethyl 1-benzyl-1,4-dihydro-4-*p*-tolylpyridine-3,5-dicarboxylate (109i)



Pale yellow solid

M. P. (°C) : 172-174

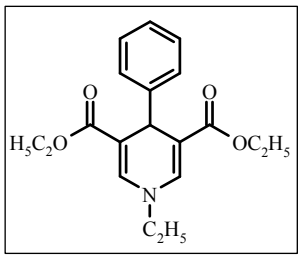
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3024, 2948, 1712, 1682, 1511, 1428, 1220, 1096, 749.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.26 (s, 3H, $C\underline{H_3}Ph$), 3.59 (s, 6H, OCH_3), 4.56 (s, 2H, $N\underline{CH_2}Ph$), 4.86 (s, 1H, $C_4\underline{H}$ of DHP ring), 6.99-7.03 (d, *J* = 7.82 Hz, 2H, ArH), 7.13-7.17 (d, *J* = 8.10 Hz, 2H, ArH), 7.24-7.28 (m, 4H, ArH), 7.34-7.40 (m, 3H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.0, 36.6, 51.2, 58.2, 108.8, 127.1, 127.8, 128.3, 128.7, 129.1, 135.9, 136.0, 137.6, 143.4, 167.2.

Elemental Analysis : **$C_{23}H_{23}NO_4$** (377) Calcd: C, 73.19; H, 6.14; N, 3.71.
Found: C, 73.31; H, 6.21; N, 3.88.

Diethyl 1-ethyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (109j)



faint yellow solid

M. P. (°C) : 123-124

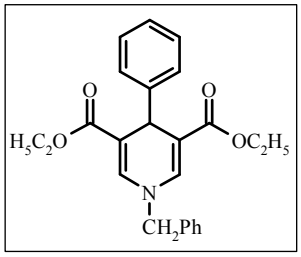
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3016, 2980, 2934, 1700, 1578, 1456, 1415, 1208, 1180, 1073, 769.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.19-1.26 (t, *J* = 7.10 Hz, 6H, $OCH_2\underline{CH_3}$), 1.35-1.42 (t, *J* = 7.15 Hz, 3H, $NCH_2\underline{CH_3}$), 3.45-3.56 (q, *J* = 7.15 Hz, 2H, $N\underline{CH_2}CH_3$), 4.03-4.17 (m, 4H, $O\underline{CH_2}CH_3$), 4.92 (s, 1H, $C_4\underline{H}$ DHP of ring), 7.17- 7.36 (m, 7H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.1, 15.5, 37.3, 49.5, 59.9, 108.6, 126.2, 127.8, 128.1, 137.0, 146.8, 166.9.

Elemental Analysis : **$C_{19}H_{23}NO_4$** (329) Calcd: C, 69.28; H, 7.04; N, 4.25.
Found: C, 69.15; H, 7.17; N, 4.33.

Diethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (109k)



Yellow solid

M. P. (°C) : 135-136 (Lit.[22] 133-135)

IR ($CHCl_3$, cm^{-1}) : ν_{max} 2980, 2928, 1699, 1579, 1454, 1229, 1187, 1075, 754.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.17-1.24 (t, *J* = 7.10 Hz, 6H, $\underline{CH_3}CH_2$), 4.03-4.16 (m, 4H, OCH_2), 4.62 (s, 2H, $\underline{CH_2}Ph$), 4.94 (s, 1H, C_4H of DHP ring), 7.16- 7.24 (m, 2H), 7.27-7.35 (m, 7H, ArH), 7.39-7.46 (m, 3H, ArH).

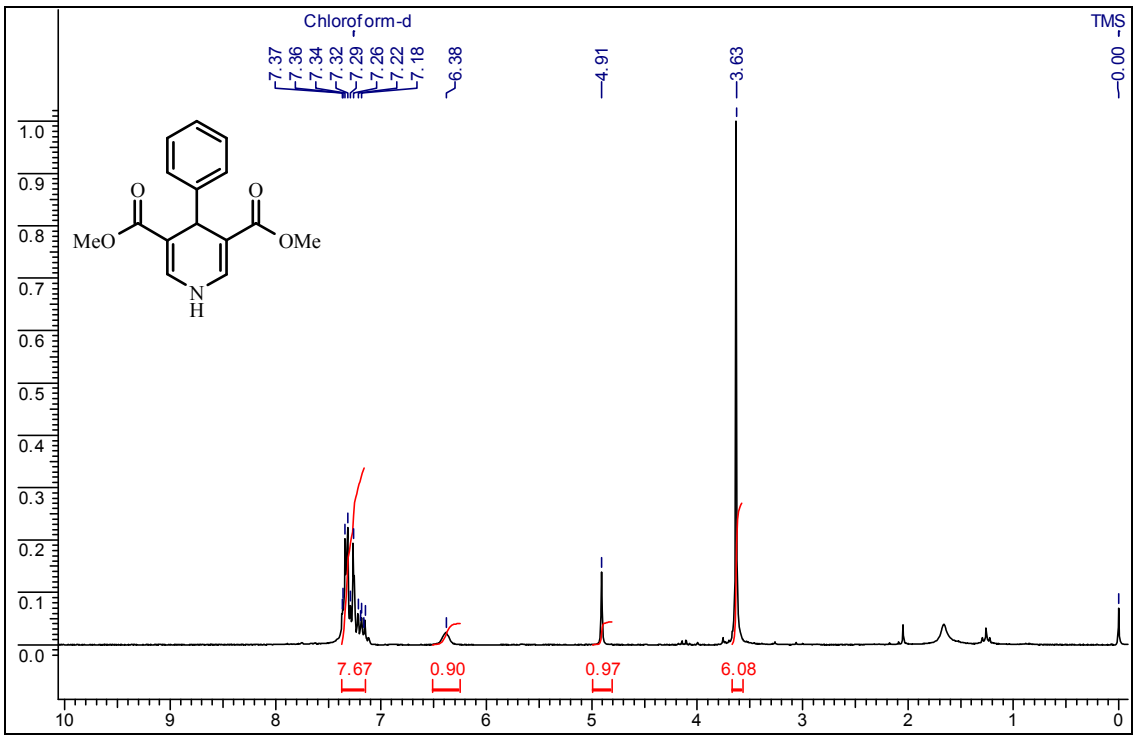
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.1, 37.3, 58.2, 59.9, 109.0, 126.2, 127.1, 127.8, 128.2, 128.2, 129.0, 136.1, 137.5, 146.5, 166.8.

Elemental Analysis : **$C_{24}H_{25}NO_4$** (391) Calcd: C, 73.64; H, 6.44; N, 3.58.
Found: C, 73.81; H, 6.32; N, 3.67.

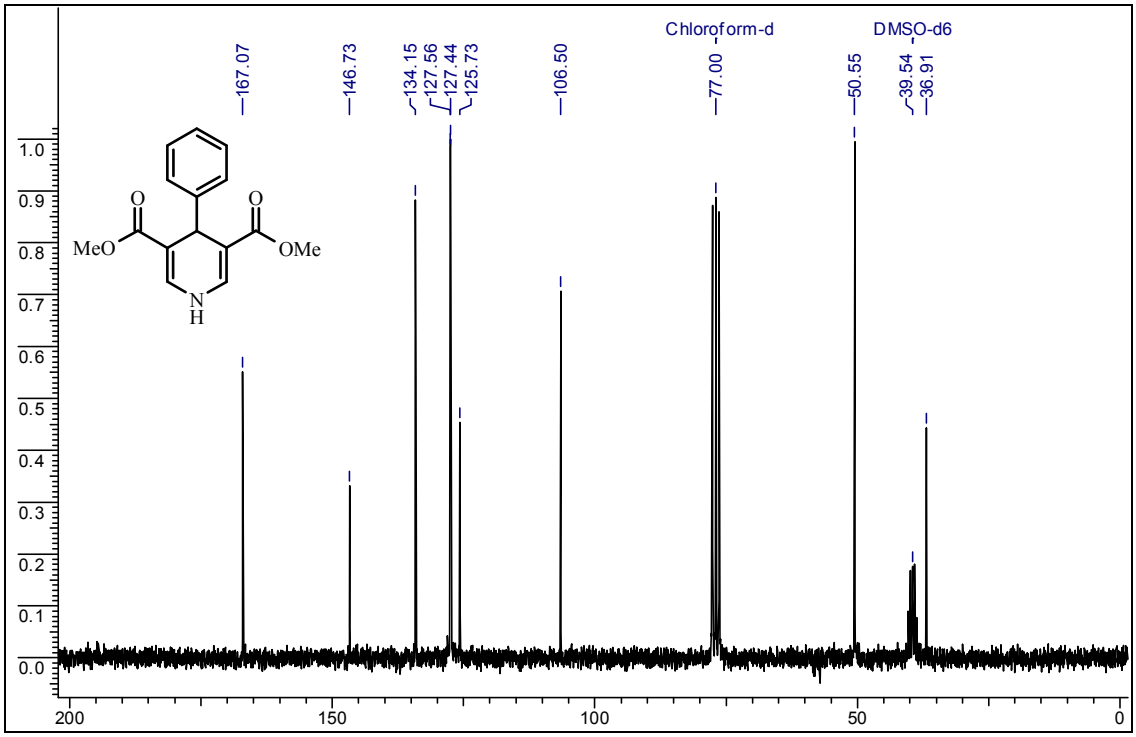
2.3.6 Spectra of representative 4-aryl-1.4-dihydropyridines

Sr. No.	NMR spectra of **109**
1	^{1}H NMR and ^{13}C NMR spectra of **109a**
2	^{1}H NMR and ^{13}C NMR spectra of **109c**
3	^{1}H NMR and ^{13}C NMR spectra of **109f**
4	^{1}H NMR and ^{13}C NMR spectra of **90g**
5	^{1}H NMR and ^{13}C NMR spectra of **109i**
6	^{1}H NMR and ^{13}C NMR spectra of **109j**

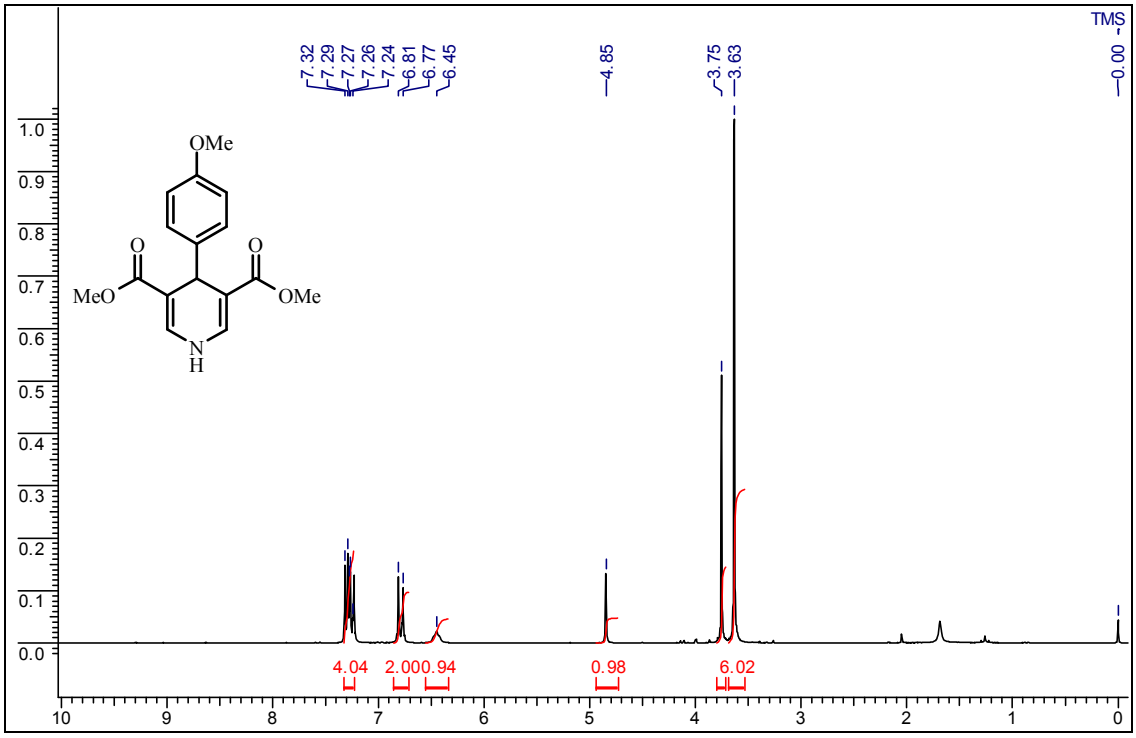
^{1}H NMR spectra of **109a**



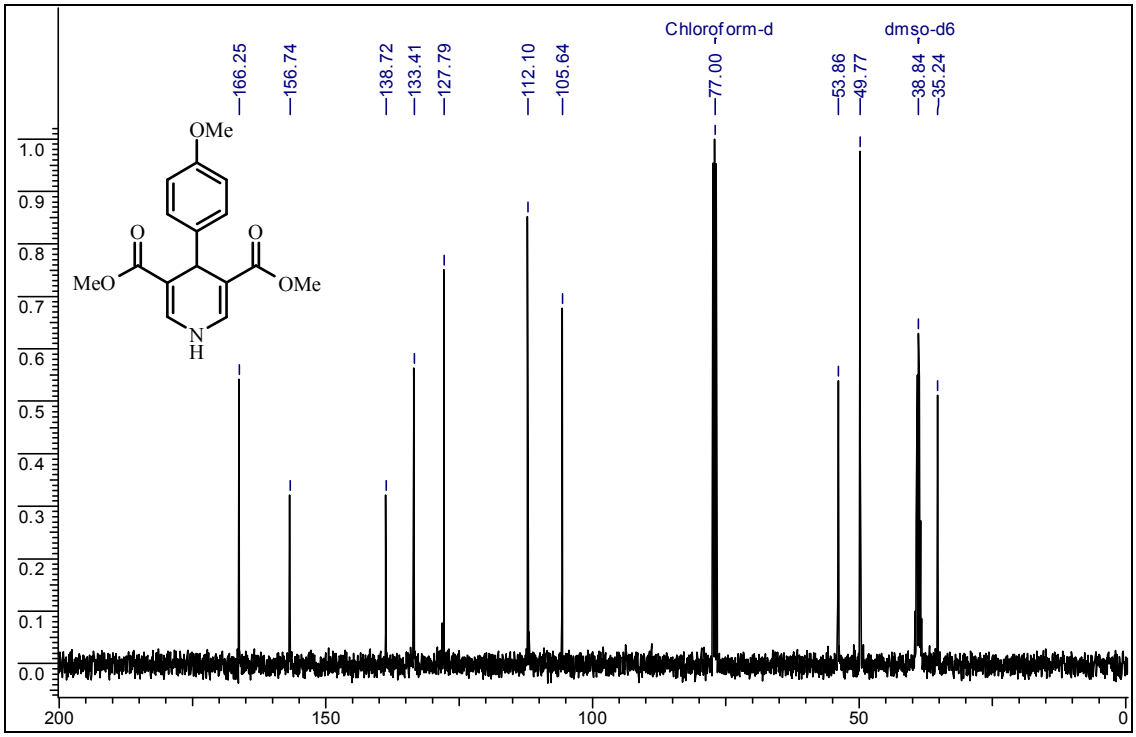
^{13}C NMR spectra of **109a**



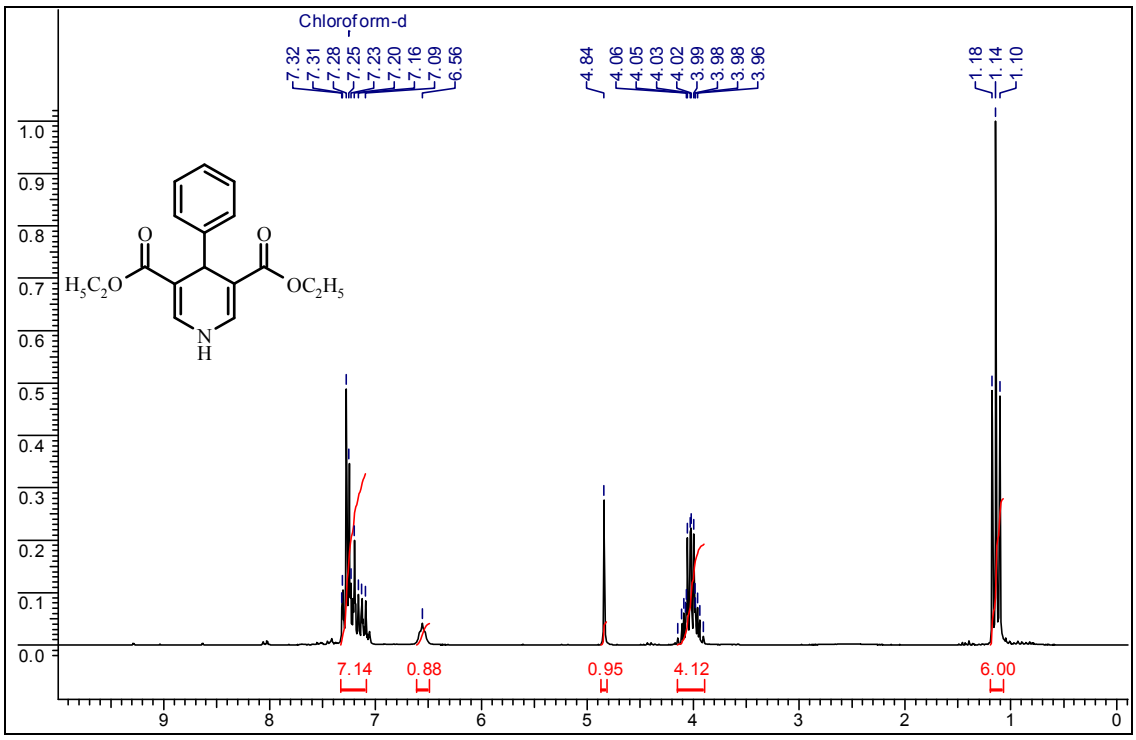
^{1}H NMR spectra of **109c**



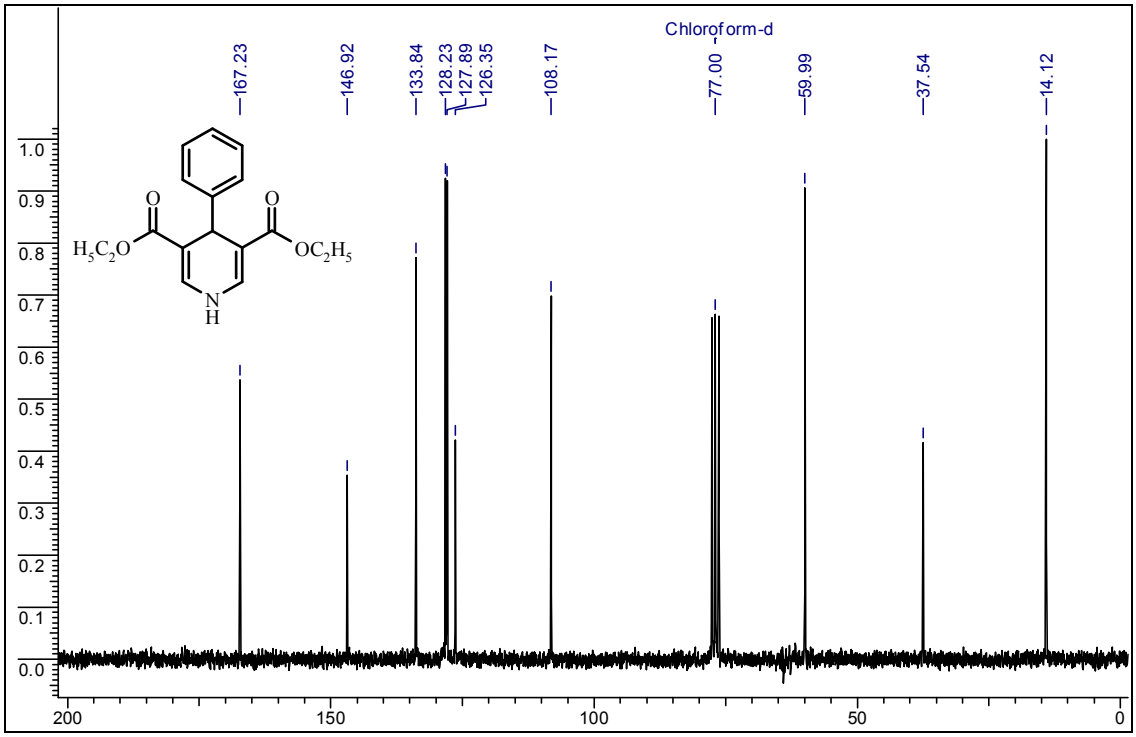
^{13}C NMR spectra of **109c**



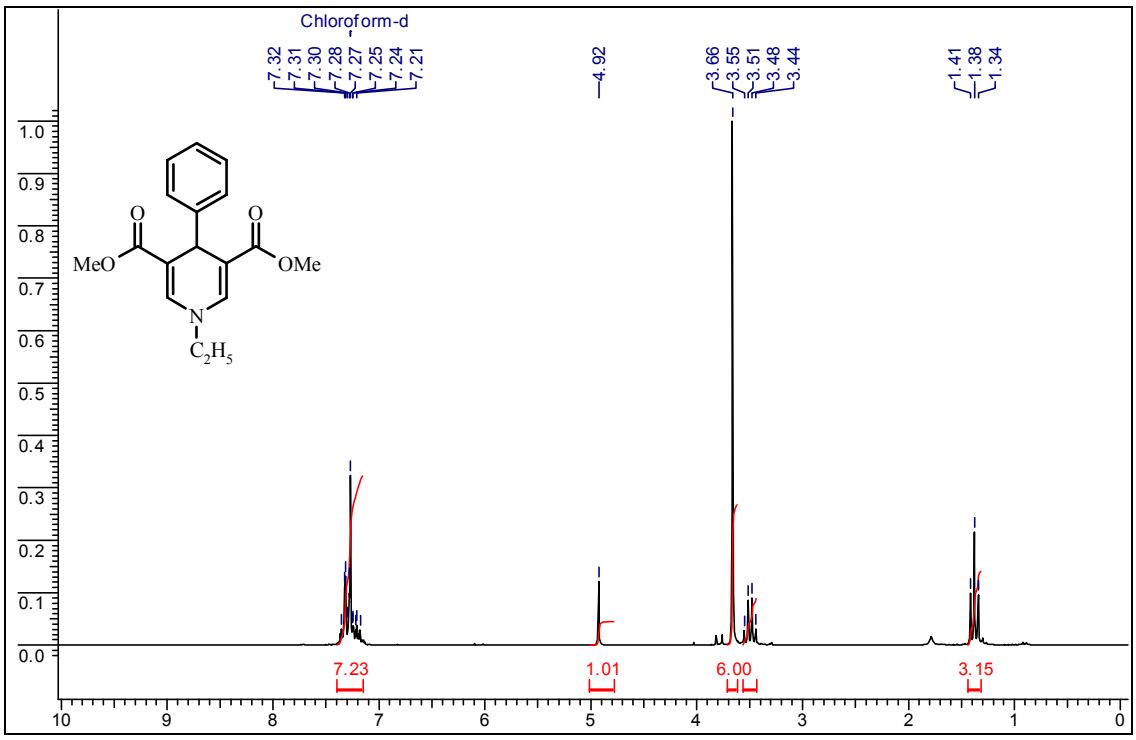
^{1}H NMR spectra of **109f**



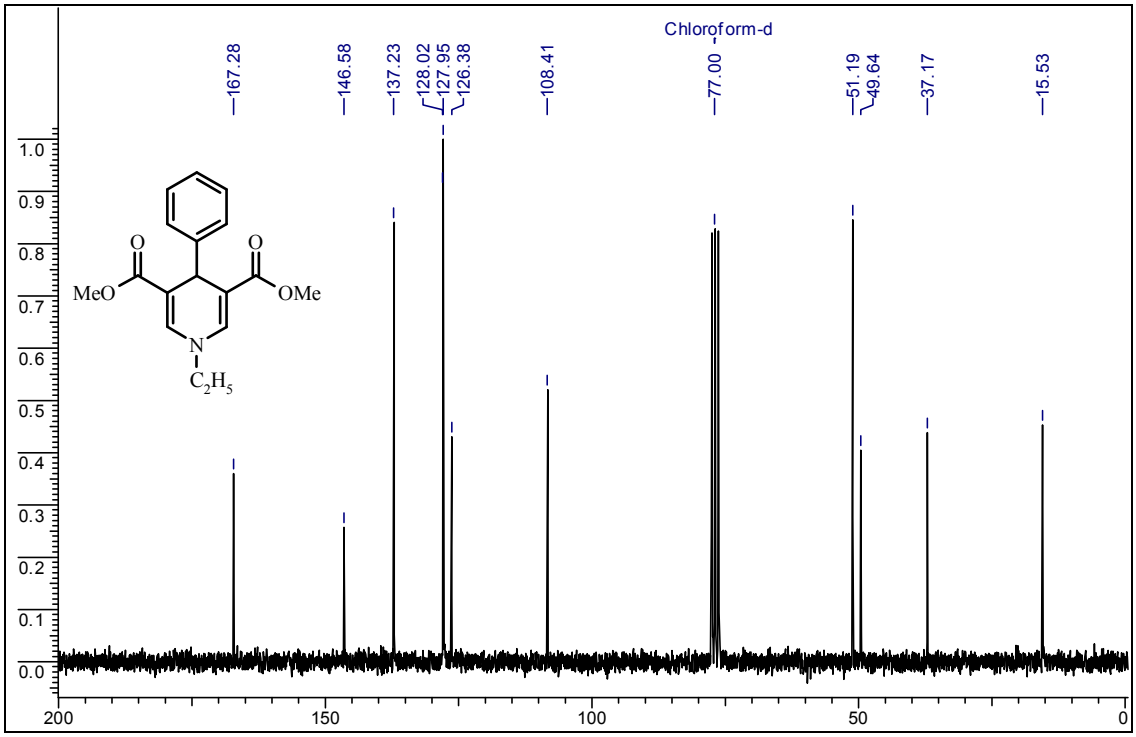
^{13}C NMR spectra of **109f**



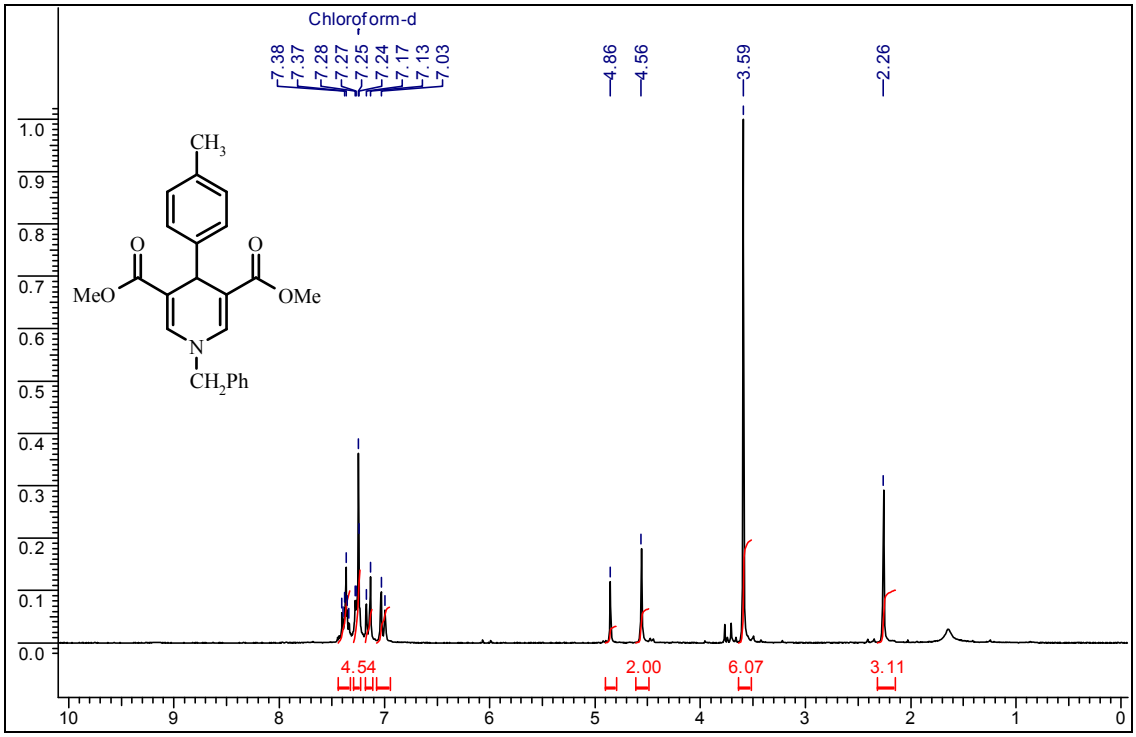
^{1}H NMR spectra of **109g**



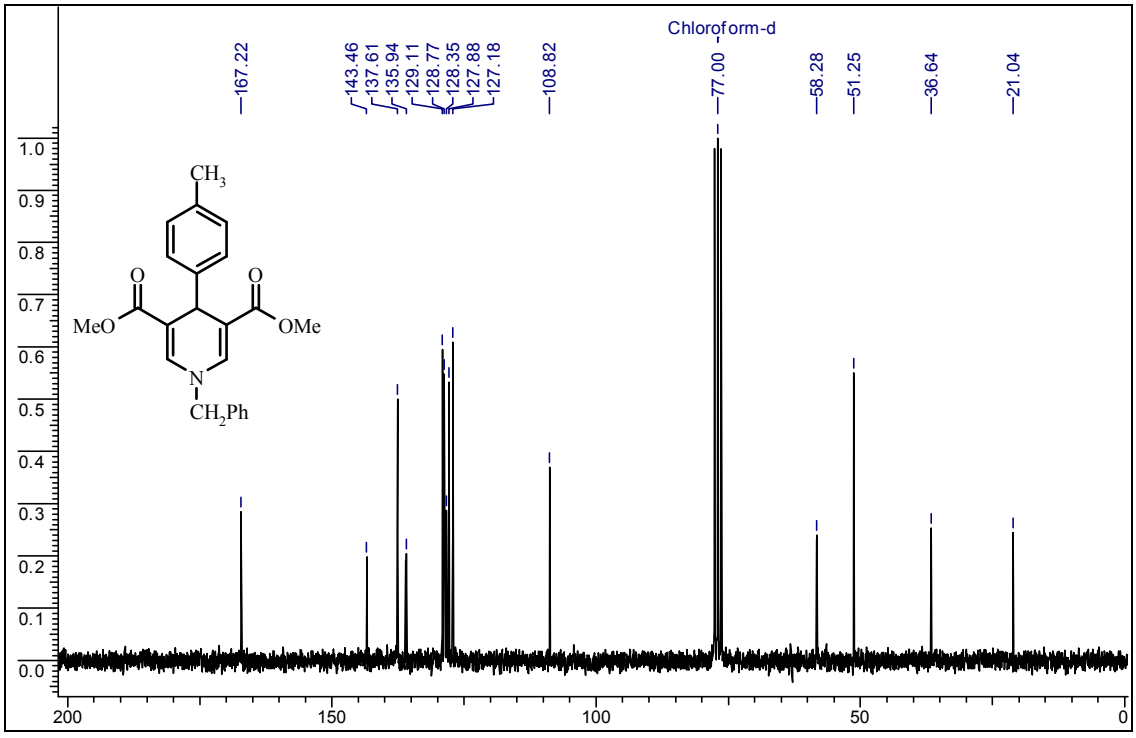
^{13}C NMR spectra of **109g**



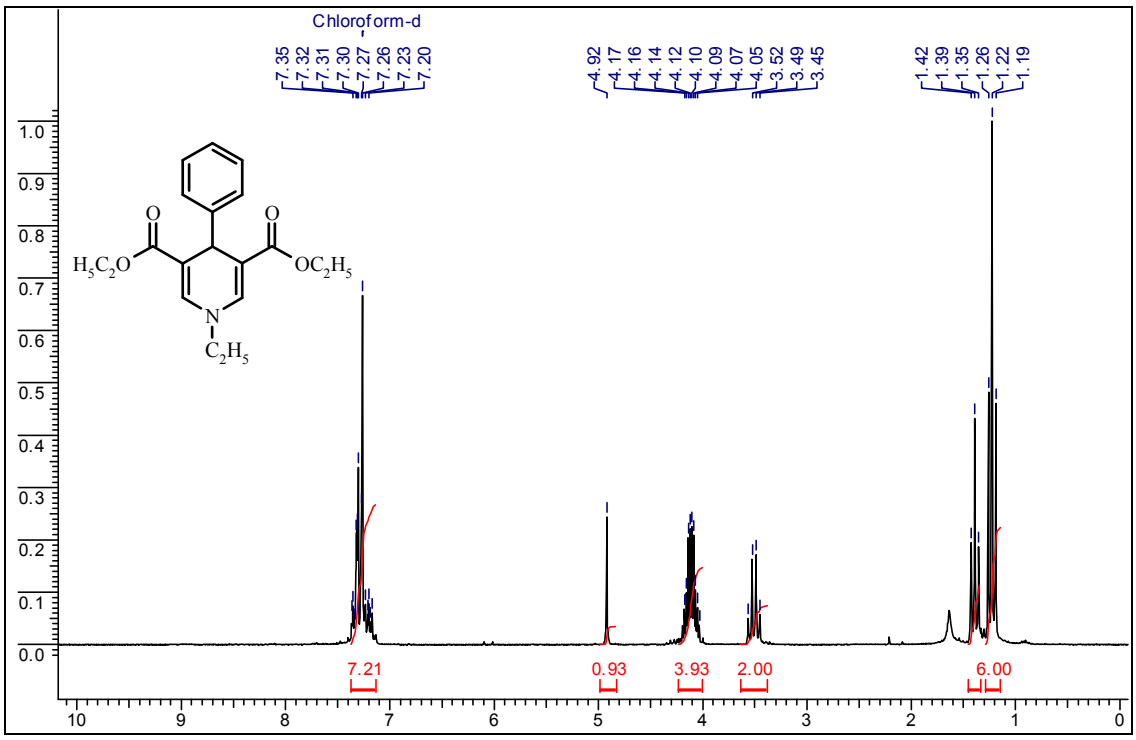
^{1}H NMR spectra of **109i**



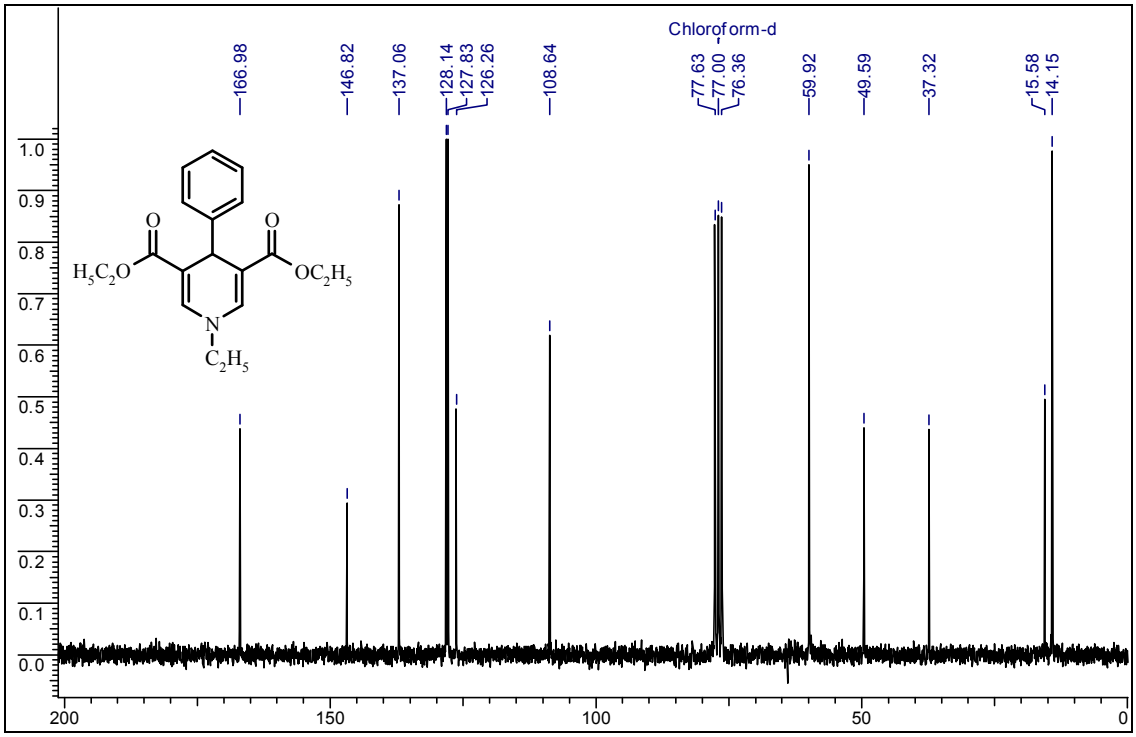
^{13}C NMR spectra of **109i**



^{1}H NMR spectra of **109j**



^{13}C NMR spectra of **109j**



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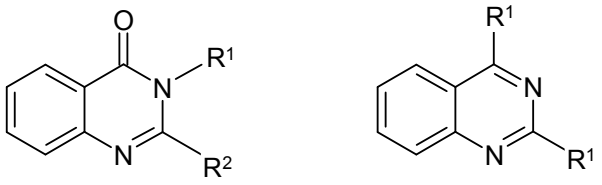
Chapter 3

Synthesis of bioactive molecules based on (3*H*)-quinazolin-4-one

3.0.1 Introduction

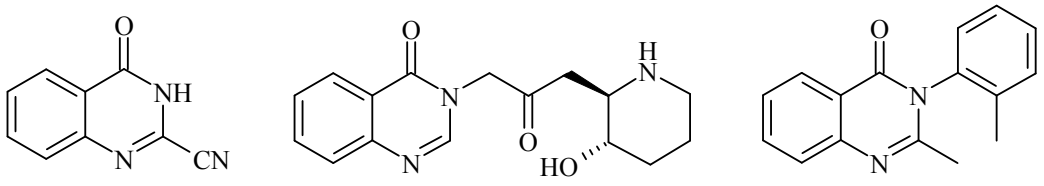
Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. 4(3*H*)-Quinazolinones **1** and related quinazolines **2 (Fig. 1)** are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties.



1 **2**

Figure 1. Quinazolinone and quinazoline

Quinazolinone **1** (**Fig. 1**) is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. The first quinazolinone was synthesized[1] in the late 1860s from anthranilic acid and cyanogen to give 2-cyanoquinazolinone **3** (**Fig. 2**). Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of the structure of a quinazolinone alkaloid, 3-[*β*-keto-*γ*-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone (febrifugine)[2] **4** (**Fig. 2**) from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria.



3 **4** **5**

Figure 2. Synthetic and natural quinazolinone

In the quest to find additional potential quinazolinone based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of its derivative, 2-methyl-3-*o*-tolyl-4-(3*H*)-quinazolinone (methaqualone) **5** (**Fig. 2**).

Methaqualone (**5**) was synthesized[3] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects.[4] The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the isolation, synthesis, and studies on the pharmacological properties of the quinazolinones and related compounds. The chemistry of the quinazolinone alkaloids is well documented[5,6] in a number of comprehensive reviews and monographs and is continuously updated in *Natural Product Reports*.[7]

Quinazolinones are a class of natural and synthetic compounds possessing a variety of biological activities such as anticancer activity (including inhibitory activity of topoisomerase I and II,[8] kinesin spindle proteins (KSP or Eg5),[9] thymidylate synthase,[10] and tubulin polymerization[11] etc), anti-inflammatory activity (including inhibition of cyclooxygenase activity and leukocyte function),[12] and cardiovascular activity (including antihypertensive, antiarrhythmic, vasodilatory, and lipid-lowering effects).[13,14] These compounds also act as cardiotonic, antihistamine, antifungal, antiviral, antimicrobacterial, and antimalarial agents,[15] and they have demonstrated psychotropic, hypnotic and a range of other central nervous system (CNS) effects (including analgesic, antiparkinsonian, CNS depressant, and CNS stimulant activities, as well as tranquilizing, antidepressant, and anticonvulsant effects).[16]

The third chapter is divided into three sections which deal with the total synthesis of natural products based on (3*H*)-quinazolin-4-one such as tryptanthrin, deoxyvasicionone and luotonin A.

3.0.2 References

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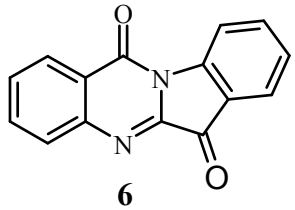
Chapter 3, Section A

Synthesis of tryptanthrin

3.1.1 Introduction

All the (3*H*)-quinazolin-4-one natural products have interesting biological activity and have therefore been extensively investigated for useful pharmaceutical activity. The (3*H*)-quinazolin-4-one ring is regarded as a 'privileged structure' in combinatorial synthesis.[1] These are structures which represent molecules that are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds.[1]

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) **6** (**Fig. 3**) is a weak basic alkaloid found in a number of plant species.[2] Tryptanthrin is the active principal of a traditional Japanese herbal remedy for fungal infections.[3] Tryptanthrin is a compound with a long history.[4] This alkaloid is unusual as its synthesis was described a half century before it was discovered as a natural product.[5] This compound possesses antibacterial activity against a variety of pathogenic bacteria, particularly the causative agent of tuberculosis[6] and has displayed remarkable *in vitro* antileishmanial activity against *Leishmania donovani*,[7] and against *Trypanosoma brucei*, an extracellular protozoan parasite, that is, transmitted by tsetse flies.[8] Indolo[2,1-*b*]-quinazoline-6,12-dione can be produced by *Candida lipolytica* when grown in media containing an excess of tryptophan,[9] hence the name tryptanthrin. In recent years, tryptanthrin has attracted much attention as an aryl hydrocarbon receptor agonist,[10] anti-inflammatory agent,[11] inducer of caspase-3/Fas mediated apoptosis,[12] and anticancer agent.[13]



6

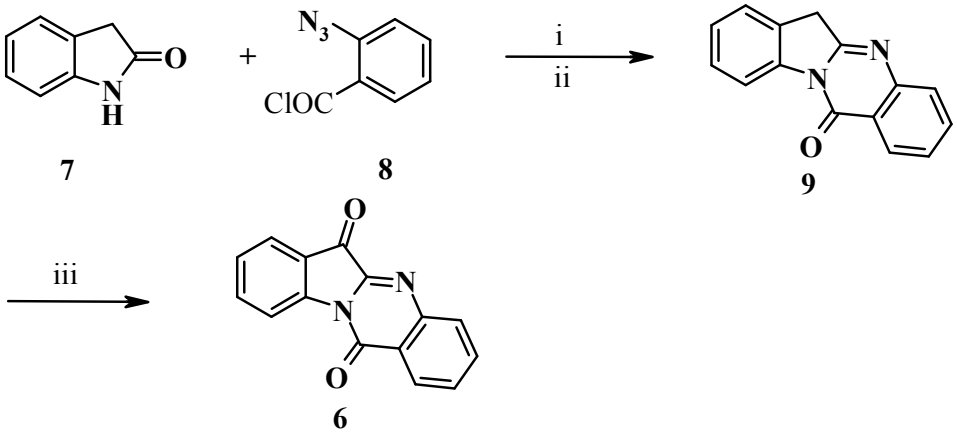
Figure 3. Structure of tryptanthrin

3.1.2 Review of literature

In view of the importance of tryptanthrin and its attractive *in vitro* properties, synthesis of tryptanthrin was pursued intensively. In this section, we have described in brief some of the more significant literature methods reported already.

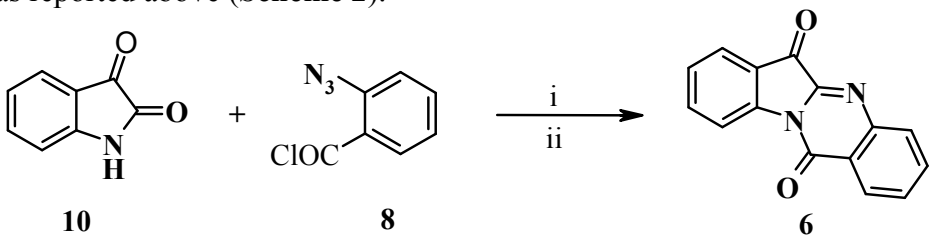
S. Eguchi et al. approach (1992)[14]

S. Eguchi et al. reported the synthesis of tryptanthrin **6** by annulation of quinazolinone. The treatment of 2-indolinone **7** with 2-azidobenzoyl chloride **8** by using triethylamine and 4-dimethylaminopyridine (DMAP) followed by reaction with tributylphosphine afforded indolo[2,1-*b*]quinazolin-12-(6*H*)-one **9** in 26% yield which on further oxidation by air in benzene afforded tryptanthrin **6** in 14% yields (**Scheme 1**).



Scheme 1. Reaction conditions**:** (i) Et_3N, DMAP, rt , 3h; (ii) *n*-Bu_3P, dioxane, rt, 2 h, 26% (**9**); (iii) benzene**,** air oxidation, 14 %.

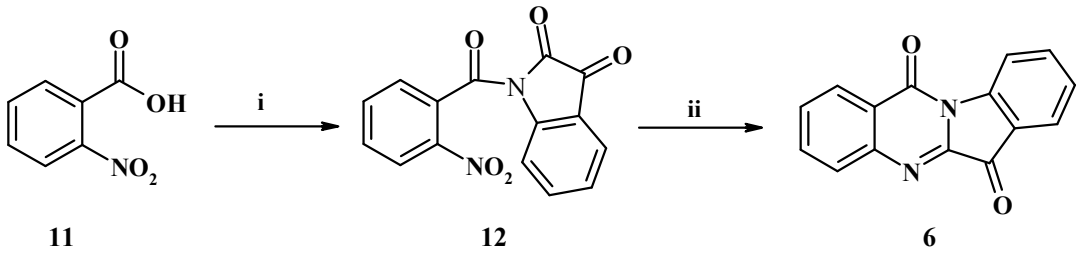
S. Eguchi et al. reported the synthesis of tryptanthrin **6** in 43% yield from isatin **10** and 2-azidobenzoyl chloride **8** by quinazolinone annulation using the same reaction condition as reported above (**Scheme 2**).



Scheme 2. Reaction conditions**:** (i) Et_3N, DMAP, rt , 3h; (ii) *n*-Bu_3P, dioxane rt, 2 h, 43%.

Y. Watanabe et al. approach (1993)[15]

Y. Watanabe et al. reported the synthesis of tryptanthrin **6** by the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides 1**2** under carbon monoxide pressure using catalyst $Ru_3(CO)_{12}$. Initially, amide **12** was prepared from *o*-nitrobenzoic acid **11** and isatin **10 (Scheme 3)**.

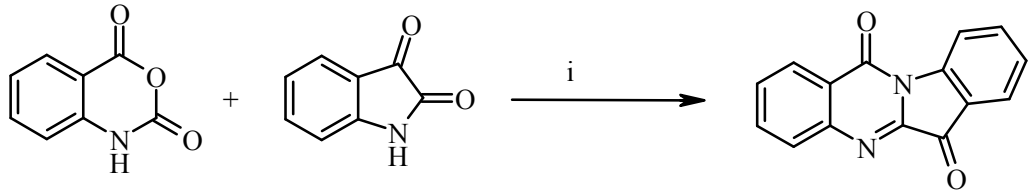


11 **12** **6**

Scheme 3. Reaction conditions: (i) $SOCl_2$, benzene, reflux, 3 h, then isatin (**10**), Et_3N, rt, 56%; (ii) $Ru_3(CO)_{12}$ (3.3 mol%), CO 40 $kgcm^{-2}$, 140 °C, 16 h, 48%.

A. K. Bhattacharjee et al. approach (2002)[7]

A. K. Bhattacharjee et al. reported the synthesis of tryptanthrin **6** from the reaction of isatoic anhydride **13** with isatin **10** using *N*-methylpiperidine and diisopropyl carbodiimide in dry pyridine at 60–100 °C (**Scheme 4**).

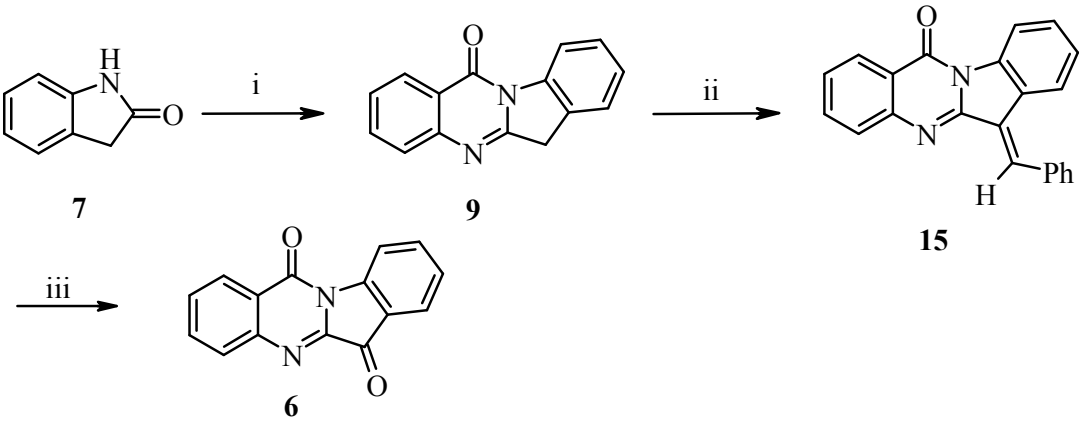


13 **10** **6**

Scheme 4. Reaction conditions**:** (i) *N*-methylpiperidine, Diisopropyl carodiimide, dry pyridine, 60-100 °C, quantitative.

Y. Jahng et al. approach (2003)[16]

Y. Jahng et al. reported the synthesis of tryptanthrin **6** from 2-indolinone **7** (**Scheme 5**).



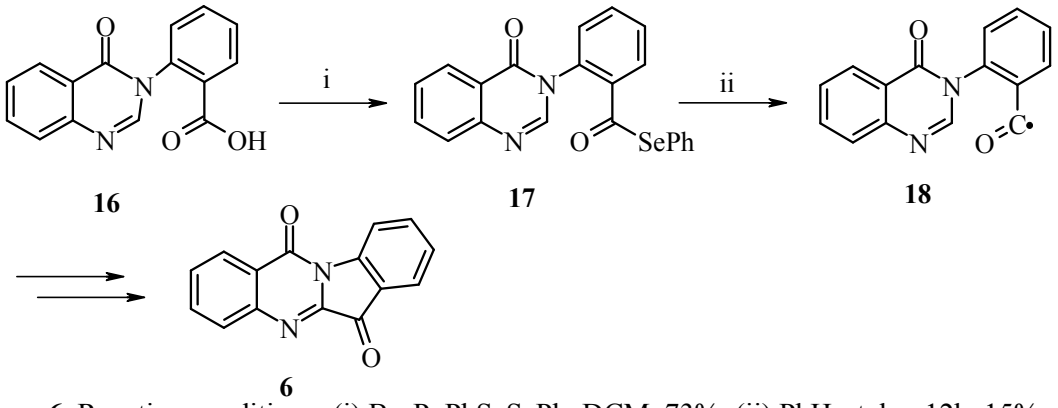
7 **9** **15** **6**

Scheme 5. Reaction conditions: (i) HCl, $POCl_3$, methyl anthranilate (**14**), 82%; (ii) PhCHO, acetic anhydride; (iii) O_3, dimethyl sulfide, 76%.

Initially the hydrochloric salt of 2-indolinone **7** was condensed with methyl anthranilate **14** by using $POCl_3$ to afford quinazolinone **9** which was further converted into **15** using benzaldehyde and acetic anhydride. Finally, ozonolysis of **15** afforded tryptanthrin **6**

W. S. Bowman et al. approach (2007)[17]

W. S. Bowman et al. reported the synthesis of tryptanthrin **6** by acyl radical cyclization onto (3*H*)-quinazolin-4-one moiety. Acid **16** (prepared by literature method)[18] was converted into acyl radical precursor viz. acyl selenide **17** using tributyl phosphine (Bu_3P) and diphenyl diselenide which further cyclized onto (3*H*)-quinazolin-4-one *via* formation of intermediate acyl radical **18** to afford tryptanthrin **6** (**Scheme 6**). Several conditions were used for cyclization step and highest (15%) yield was obtained by photolysis, which is very poor.



16 **17** **18** **6**

Scheme 6. Reaction conditions**:** (i) Bu_3P, PhSeSePh, DCM, 73%; (ii) PhH, rt, hv, 12h, 15%.

3.1.3 Present work

3.1.3.1 Objectives

In view of the importance of tryptanthrin, several methods were reported in the literature for the synthesis of tryptanthrin. As a part of our interest on the synthesis of quinazolinone related molecules, our interest was kindled towards the synthesis of tryptanthrin. On reviewing the literature, it was found that among the reported method, none has reported its synthesis by applying the strategy of regioselective lithiation at C-2 of quinazolinone followed by subsequent reaction of lithiated intermediate with electrophile in an

intramolecular fashion forming C-C bond to generate the cyclized product. We sought to apply this strategy for the synthesis of tryptanthrin.

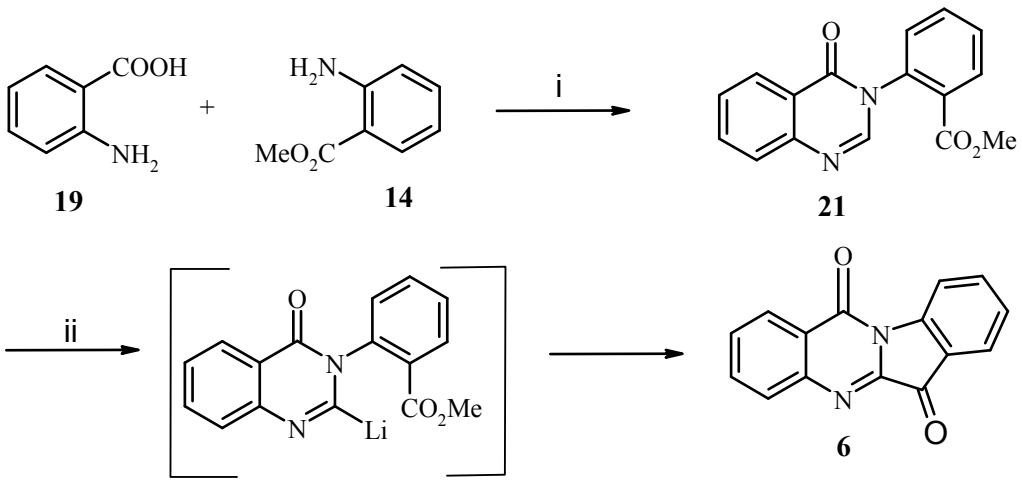
3.1.3.2 Result and discussion

X. Dai et al. reported the synthesis of 2-substituted-4(3*H*)-quinazolinone by direct lithiation of the 2-unsubstituted quinazolinone using LDA followed by reaction of intermediate with electrophile.[19] However, to the best of our knowledge, there is no report on direct lithiation of a 2-unsubstituted quinazolinone at C-2 followed by subsequent reaction of intermediate with electrophiles in an intramolecular fashion to afford cyclized product. We anticipated that the lithiation of 2-unsubstituted quinazolinone at 2-position would be facilitated by the acidity of the proton at this position. If the regioselective lithiation could be realized, its subsequent reaction with electrophile in an intramolecular fashion would probably afford the cyclized product in a straightforward fashion.

The synthesis of tryptanthrin **6** was initiated with a formation of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **21**. The synthesis of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **21** was obtained by condensing anthranilic acid **19** with methyl anthranilate **14** and triethyl orthoformate **20** in the ionic liquid (IL), 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) in 67% yield. This condensation reaction is promoted by the Brønsted acidity of the IL and in this case the IL plays a dual role as reaction medium as well as a promoter. The structure of **21** was confirmed by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectrum of **21** shows singlet at δ 3.69 ppm corresponding to methyl carboxylate group. Furthermore, compound **21** shows singlet of single hydrogen at δ 8.00 ppm corresponding to hydrogen at C-2 of quinazolinone, which is characteristic peak for quinazolinone, confirming its structure. Furthermore, ^{13}C NMR spectrum also supported the structure of **21**.

Once compound **21** was prepared, regioselective lithiation of **21** was achieved by using lithium diisopropylamide (LDA) which proceeded readily at -78 °C in dry THF under inert atmosphere to give a reddish solution. The reaction mixture was stirred at -78 °C for additional 2 h and brought to room temperature and stirred further at this temperature for 2 h. It was expected that the carbanion formed at 2-position of quinazolinone **21** would react with the electrophile viz. methyl carboxylate in an

intramolecular fashion by forming C-C bond to afford the cyclized product. The reaction was quenched with aqueous ammonium chloride and product was extracted using ethyl acetate. Further purification by column chromatography afforded tryptanthrin **6** in 81% yield (**Scheme 7**).



Scheme 7. Reaction conditions**:** (i) $(EtO)_3CH$ (**20**), $[Hbim]BF_4$, 100 °C, 1.5 h, 67%; **(**ii) LDA, dry THF, -78 °C, 2h, then rt, 2h, 81%.

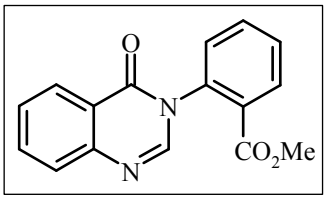
The structure of tryptanthrin **6** was confirmed by mp, IR, ^1H NMR, ^{13}C NMR and elemental analysis. The ^1H NMR spectra of **6** shows the absence of peak as singlet at δ 3.69 ppm and δ 8.00 ppm support its formation. Furthermore, the ^{13}C NMR spectra of **6** shows peak at δ 182.5 ppm corresponding to carbonyl carbon of the ketone. Furthermore, the disappearance of peak at δ 52.4 ppm corresponding to methyl of carboxylic acid ester supports its structure.

3.1.4 Conclusion

In conclusion, we have achieved the synthesis of tryptanthrin in just two-steps in 54% overall yield from commercially available anthranilic acid and methyl anthranilate. The key step for the reaction is regioselective lithiation at 2-position of quinazolinone followed by subsequent reaction of lithiated intermediate with electrophile in an intramolecular fashion to afford the cyclized product. The advantage of this method is the access of tryptanthrin from readily available and cheap starting materials.

3.1.5 Experimental

3.1.5.1 Synthesis of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate (21)



A mixture of anthranilic acid **19** (0.685 g, 5 mmol), methyl anthranilate **14** (0.830 g, 5.5 mmol) and triethyl orthoformate **20** (0.815 g, 5.5 mmol) in the IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) (10 mL) was heated with stirring at 100 °C for 1.5 h.

The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into water (25 mL) and the product was extracted using ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column chromatography with petroleum ether:ethyl acetate (6.5:3.5) to afford 0.938 g (67%) of pure methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **21** as white needles.

M. P. (°C) : 181-182

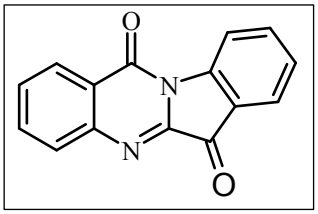
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3019, 2954, 1725, 1683, 1612, 1473, 1274, 1215, 917, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.69 (s, 3H, OCH_3), 7.36-7.40 (dd, *J* = 7.73, 1.38 Hz, 1H, ArH), 7.47-7.5 (m, 1H, ArH), 7.58-7.63 (dd, *J* = 7.70, 1.44 Hz, 1H, ArH), 7.67-7.72 (dd, *J* = 7.70, 1.75 Hz, 1H, ArH), 7.74-7.79 (m, 2H, ArH), 8.00 (s, 1H, ArH), 8.14-8.19 (dd, *J* = 7.70, 1.70 Hz, 1H, ArH), 8.29-8.34 (m, 1H, ArH);

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 52.4, 122.1, 127.0, 127.4, 127.5, 128.1, 129.3, 129.7, 131.8, 133.6, 134.5, 137.3, 145.8, 147.9, 161.0, 164.8.

Elemental Analysis : **$C_{16}H_{12}N_2O_3$** (280) Calcd: C, 68.56; H, 4.32; N, 9.99.
Found: C, 68.39; H, 4.48; N, 10.13.

3.1.5.2 Synthesis of tryptanthrin (6)



To a freshly prepared LDA (0.160 g, 1.5 mmol) in dry THF (10 mL) at -78 °C under inert atmosphere, was added dropwise a solution of **21** (0.280 g, 1 mmol) in dry THF (5 mL) under nitogen and the reaction mixture was stirred at -78 °C for additional 2 h.

As soon as addition of **21** started, the colour of the solution changed to red. The reaction mixture was then slowly warmed at room temperature and further stirred at this temperature for 2 h. The reaction mixture was quenched with aqueous ammonium chloride and product was extracted by using ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column chromatography with petroleum ether:ethyl acetate (8.5:1.5) to afford 0.200 g (81%) of pure tryptanthrin **6** as yellow needles.

M. P. (°C) **:** 266-267 (Lit.[16] 267-268)

IR ($CHCl_3$, cm^{-1}) **:** ν_{max} 1725, 1680, 1645, 1555, 1428.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 7.37-7.45 (ddd, *J* = 7.59, 0.84 Hz, 1H, ArH), 7.62-7.92 (m, 4H, ArH), 8.00-8.04 (dd, *J* = 8.07, 0.91 Hz, 1H, ArH), 8.40-8.45 (dd, *J* = 7.89, 1.56 Hz, 1H, ArH), 8.59-8.63 (d, *J* = 8.12 Hz, 1H, ArH).

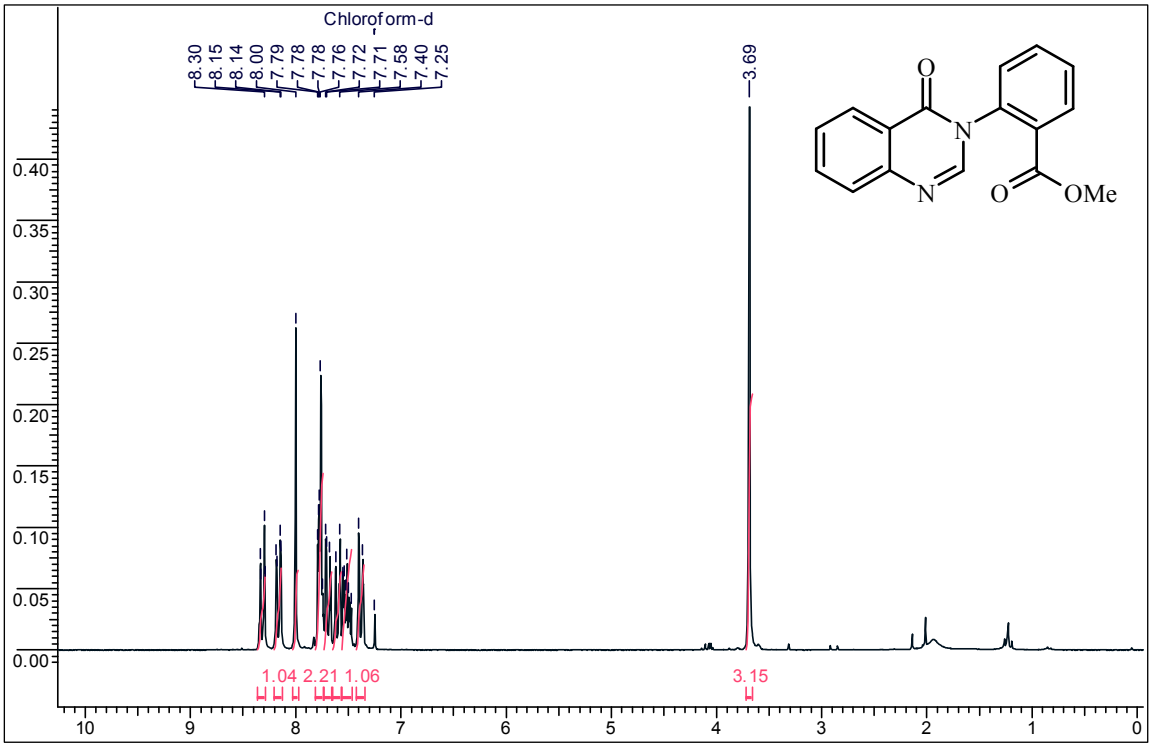
^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 117.9, 121.9, 123.7, 125.3, 127.1, 127.5, 130.2, 130.6, 135.1, 138.2, 144.3, 146.3, 146.6, 158.0, 182.5.

Elemental Analysis **:** **$C_{15}H_8N_2O_2$** (248) Calcd: C, 72.58; H, 3.25; N, 11.28.
Found: C, 72.71; H, 3.12; N, 11.17.

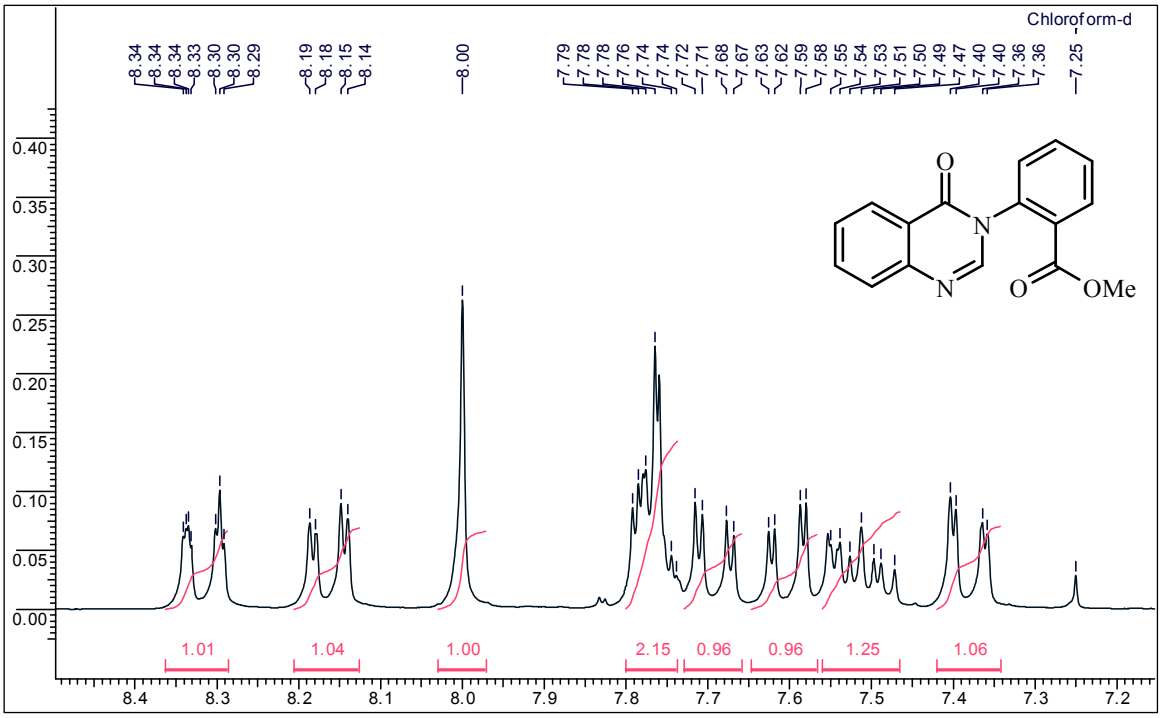
2.3.6 Spectra of compounds

Sr No.	NMR spectra
1	^{1}H NMR, ^{13}C NMR and DEPT of **21**
2	^{1}H NMR, ^{13}C NMR and DEPT of **6**

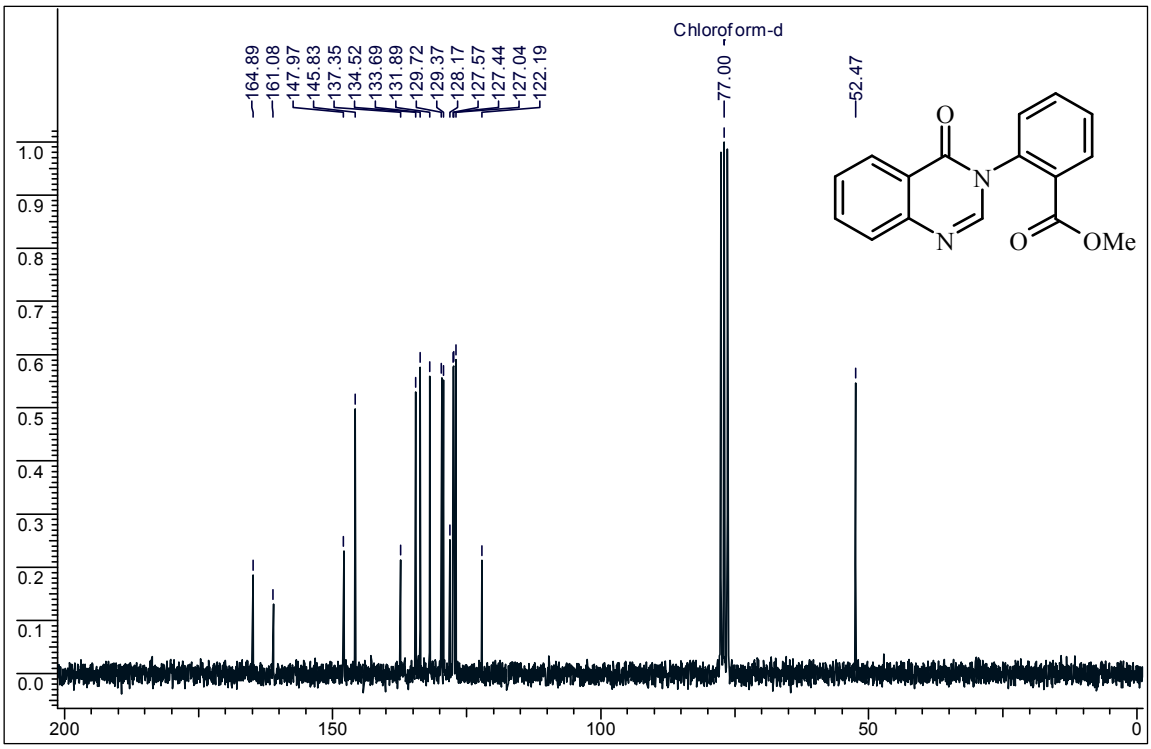
^{1}H NMR spectra of **21**



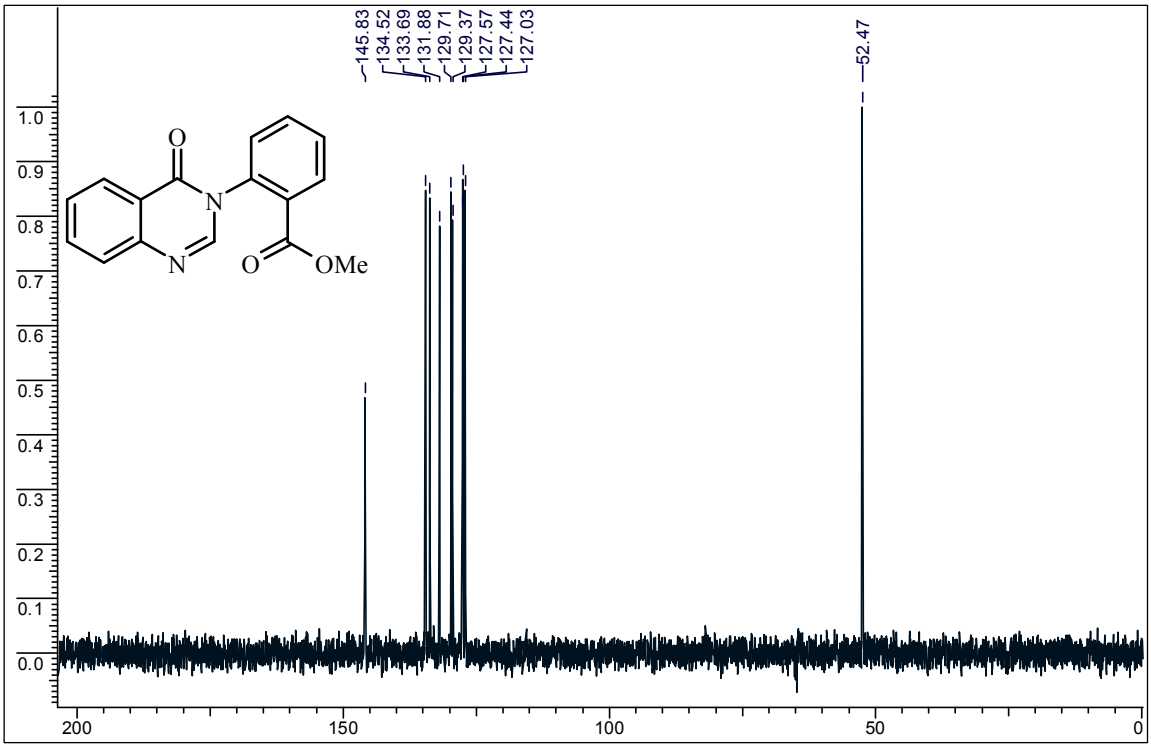
^{1}H NMR spectra (extended view)of **21**



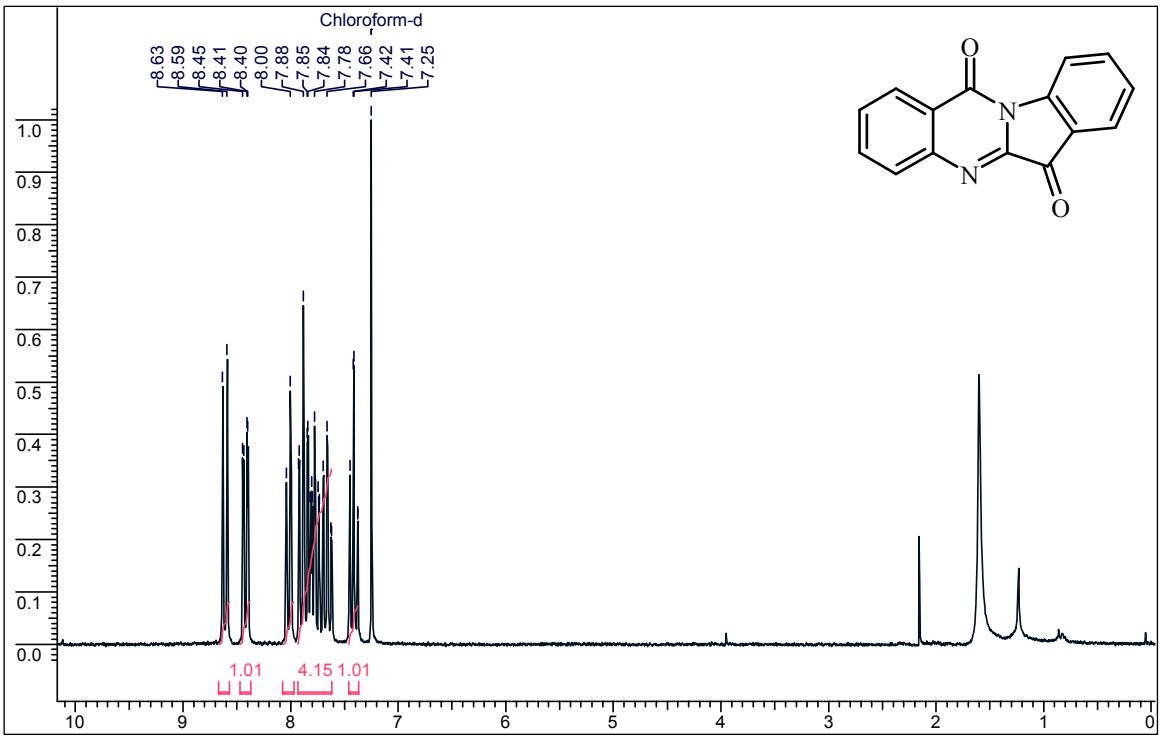
^{13}C NMR spectra of **21**



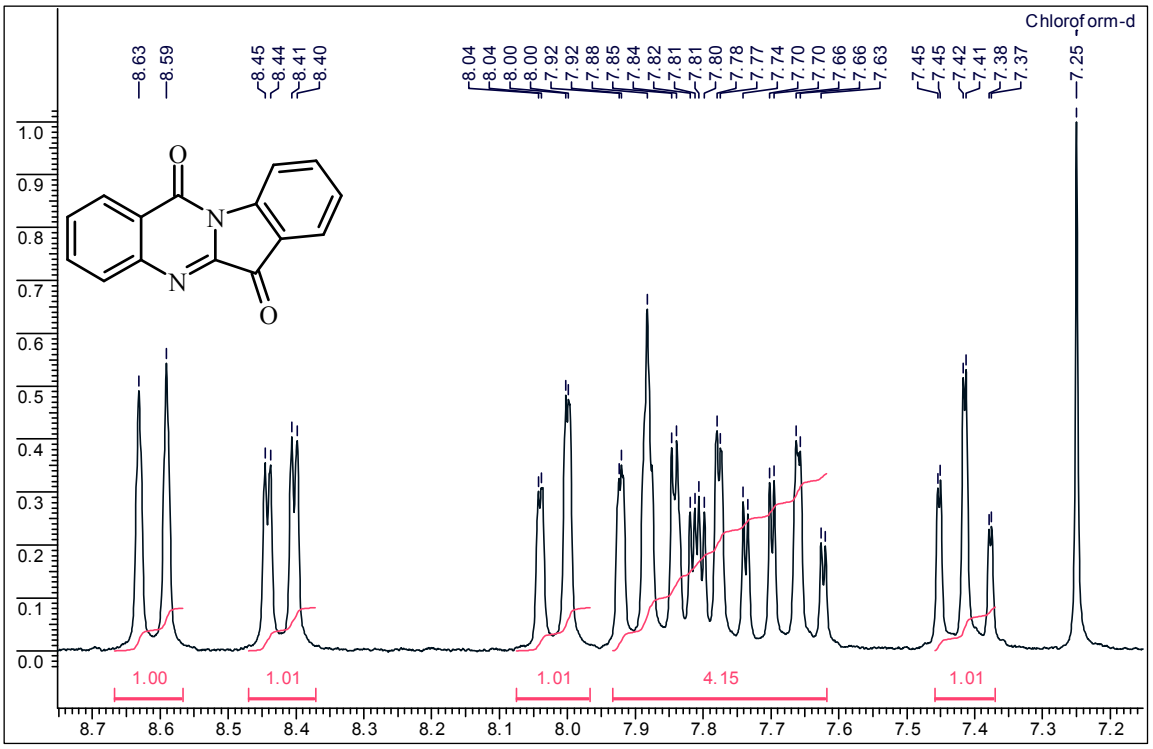
^{13}C DEPT spectra of **21**



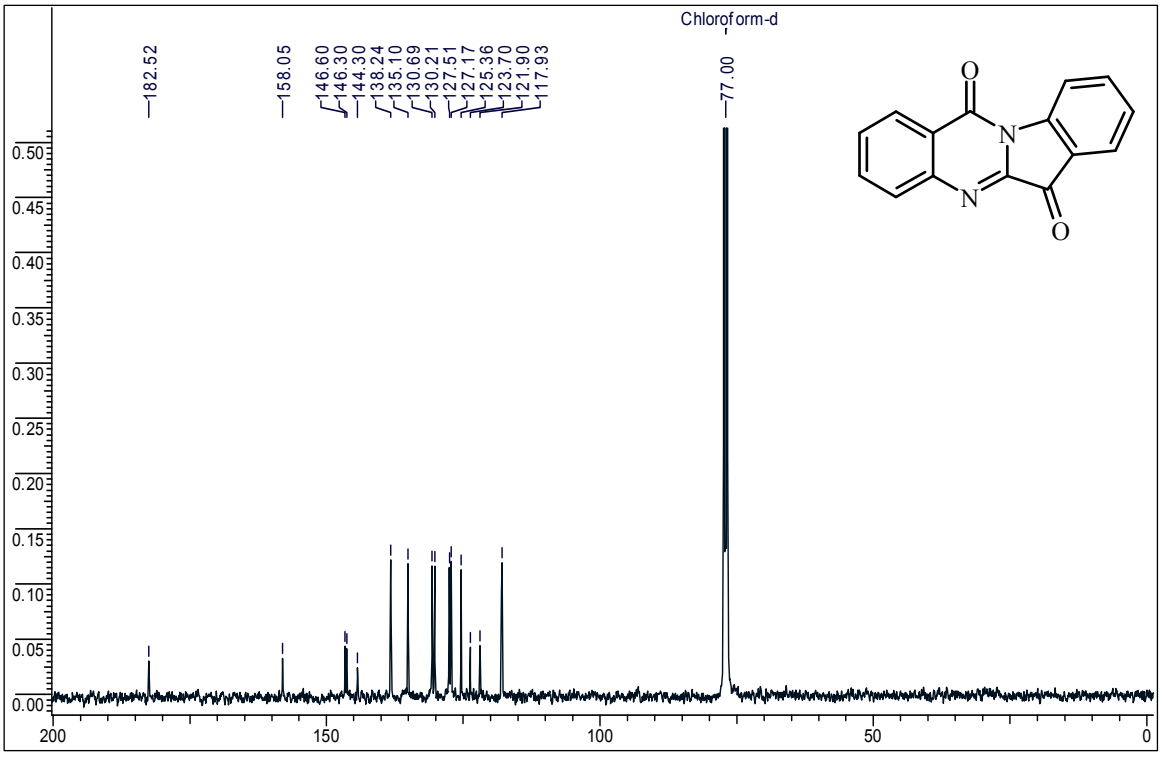
^{1}H NMR spectra of **6**



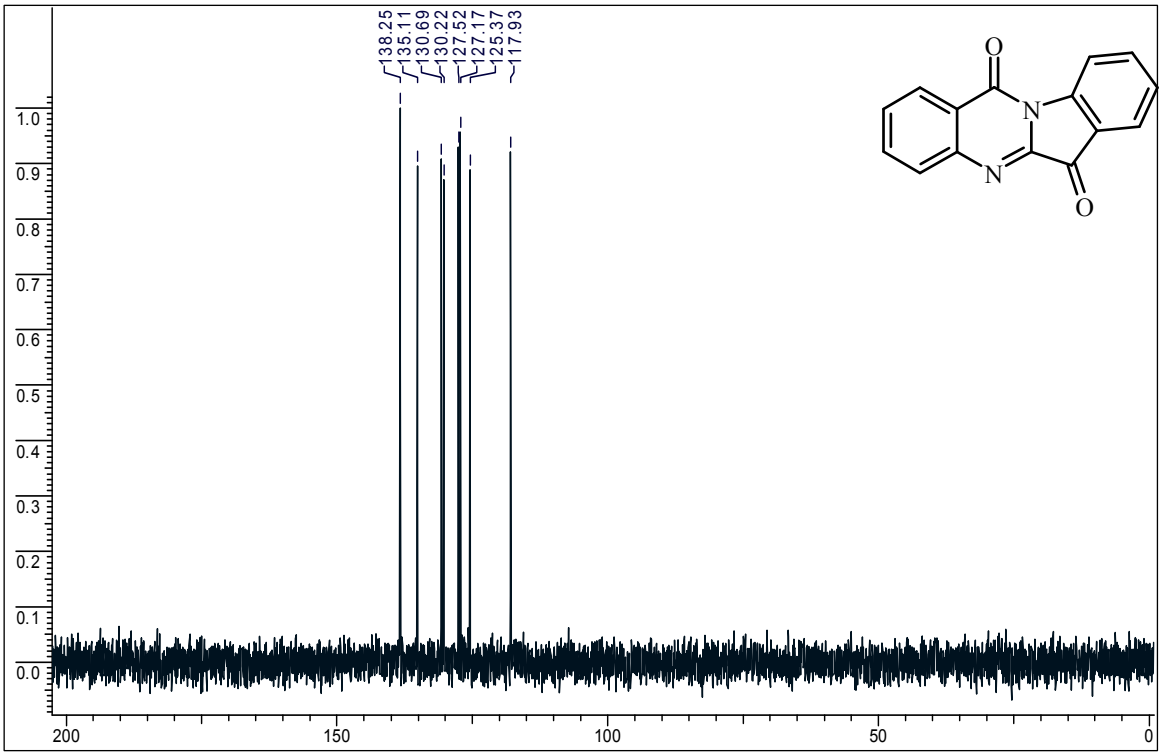
^{1}H NMR spectra (extended view) of **6**



^{13}C NMR spectra of **6**



^{13}C DEPT spectra of **6**



3.1.7 References

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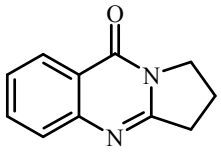
Chapter 3, Section B

Synthesis of deoxyvasicinone

3.2.1 Introduction

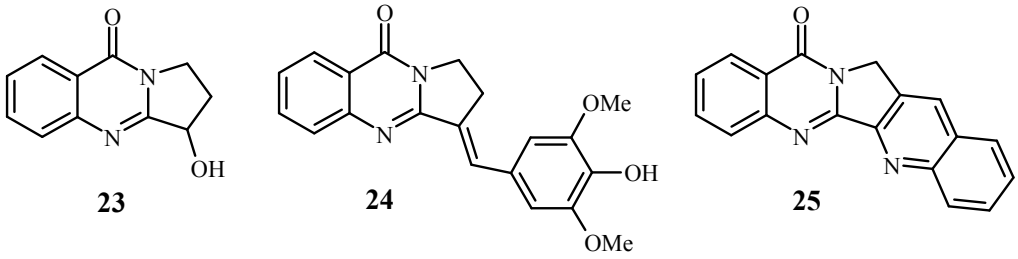
(3*H*)-Quinazolin-4-one alkaloids are a class of natural products that display a variety of biological activities.[1] Among them, deoxyvasicinone (**22**) (**Fig. 4**) is a pyrrolo[2,1-*b*]quinazolinone alkaloids isolated from the aerial parts of *Adhatoda vasica* (from the family Acanthacea, Sankrit-Vasaka), an evergreen subherbaceous bush, used extensively in indigenous medicine for cold, cough, bronchitis, and asthma.[2] Deoxyvasicinone possesses antimicrobial, anti-inflammatory and antidepressant activities.[3]



22

Figure 4. Structure of deoxyvasicinone

In addition, deoxyvasicinone is a very important key intermediate for the synthesis of various natural products such as vasicinone[4] (**23**), isaindigotone[5] (**24**), and luotonin A[5] (**25**) (**Fig. 5**).



23 **24** **25**

Figure 5. Structures of quinazolinone

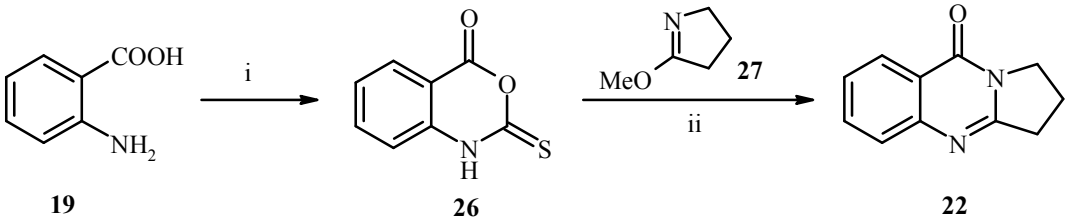
3.2.2 Review of Literature

In view of the importance of deoxyvasicinone in medicinal chemistry as well as a synthon in organic chemistry, various methods were reported in the literature. In this section, we have discussed in brief some of the more significant methods.

Tetsuji Kametani et al. approach (1976)[6]

Tetsuji Kametani et al. reported the synthesis of deoxyvasicionone **22** by reacting anthranilic acid **19** with thionyl chloride in dry benzene at reflux temperature to afford

sulfinamide anhydride **26** which subsequently reacted with 2-methylpyrrolidinone **27** in dry benzene (**Scheme 8**).

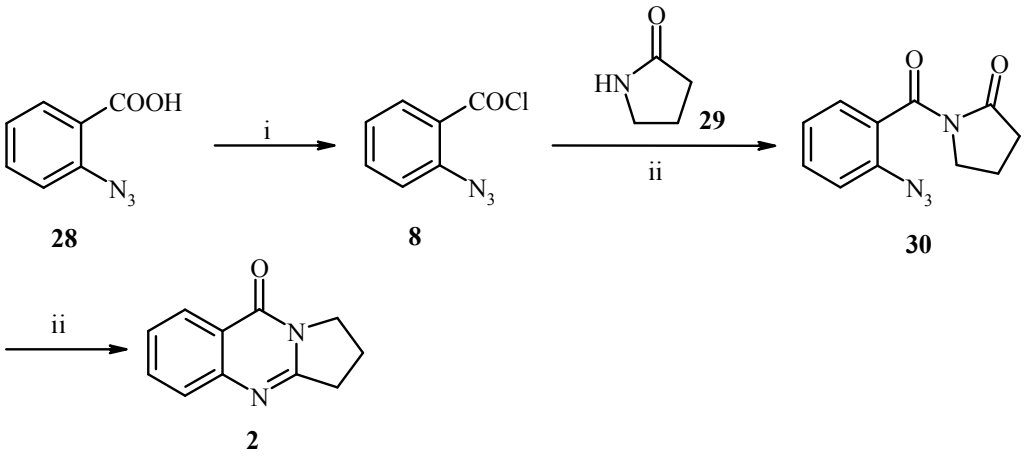


19 **26** **22**

Scheme 8. Reaction conditions**: (**i) $SOCl_2$, dry benzene, reflux, 2 h; (ii) 2-methylpyrrolidinone (**27**), dry benzene, rt, 2 h, 64%.

Shoji Eguchi et al. approach (1989)[7]

Shoji Eguchi et al. reported the synthesis of deoxyvasicinone **22** by intramolecular aza-wittig reaction. For this, *o*-azidobenzoic acid **28** was converted to the corresponding acid chloride **8** by refluxing it in thionyl chloride ($SOCl_2$), which further reacted with 2-pyrrolidinone **29** using sodium hydride (NaH) in dry THF to afford 1-(2-azidobenzoyl)azacyclopent-2-one **30.** Finally deoxyvasicinone **22** was obtained from **30** by treatment with tributylphosphine (**Scheme 9**).



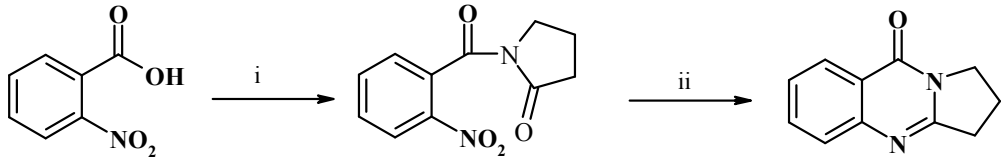
28 **8** **30** **2**

Scheme 9. Reaction conditions**:** (i) $SOCl_2$, reflux, 2 h ; (ii) NaH, dry THF, 0 °C, then rt, 2 h, 75 %; (iii) Bu_3P, xylene, rt, 1 h, then 50 °C, 3 h, 99%.

Y. Watanabe et al. approach (1993)[8]

Y. Watanabe et al. reported the synthesis of deoxyvasicinone **22** by the reductive *N*-heterocyclization strategy. Initially *N*-(2-nitrobenzoyl)amide **31** was obtained form *o*-nitrobenzoic acid **11** and 2-pyrrolidinone **29**. Finally deoxyvasicinone **22** was obtained

from **31** by *N*-heterocyclization using catalyst $Ru_3(CO)_{12}$ under carbon monoxide pressure **(Scheme 10)**.

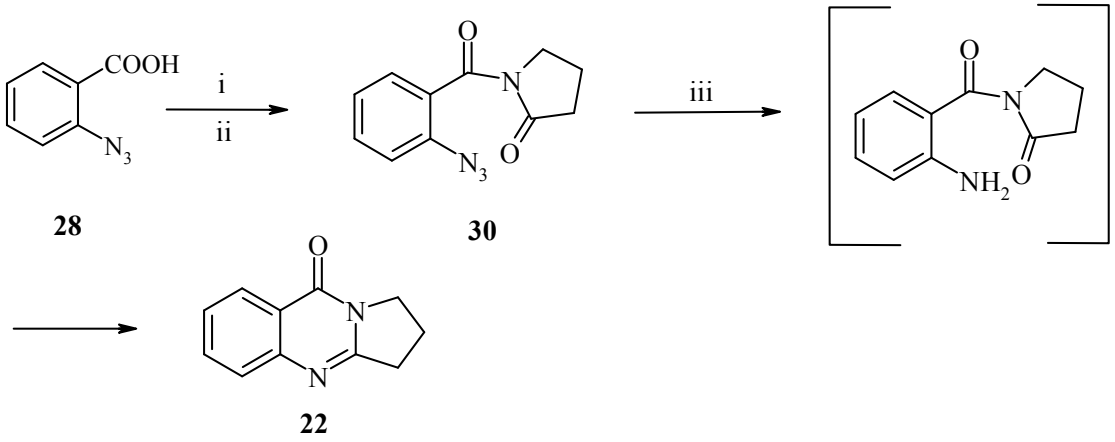


11 **31** **22**

Scheme 10. Reaction conditions**:** (i) $SOCl_2$, benzene, reflux, 3 h, then 2-pyrrolidinone (**29**), Et_3N, rt, 56%; (ii) $Ru_3(CO)_{12}$ (3.3 mol%), CO 40 $kgcm^{-2}$, 140 °C, 16 h, 68%.

Ahmed kamal et al. appraoch (2001)[4]

Ahmed kamal et al. reported the synthesis of deoxyvasicionone **22** by azidoreductive cyclization strategy. 2-Azidobenzoic acid **28** was converted to corresponding acid chloride using thionyl chloride which was reacted *in situ* with 2-pyrrolidinone **29** to afford *N*-(2-azidobenzoyl)lactams **30**. Finally, deoxyvasicinone **22** was obtained from **30** by reductive cyclization with trimethyl silyl chloride-sodium iodide (**Scheme 11**).

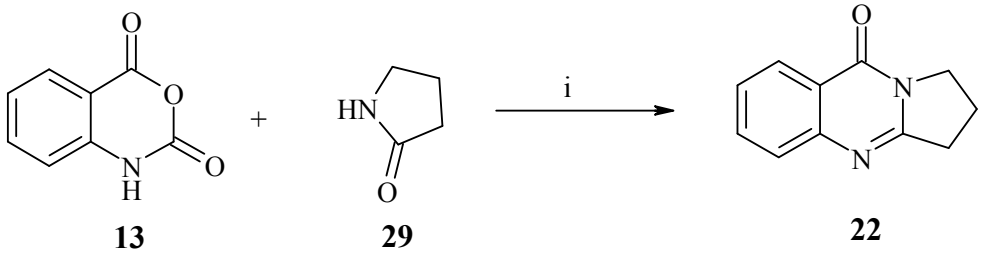


28 **30** **22**

Scheme 11. Reaction conditions**:** (i) $SOCl_2$,benzene, DMF, rt, 5 h; (ii) dry THF, 2-pyrrolidinone (**29**), Et_3N, rt, 2 h, 75%; (iii) NaI, TMSCl, MeCN, rt, 25 min, quantitative.

J. S. Yadav et al. approach (2002)[9]

J. S. Yadav et al. reported the synthesis of deoxyvasicinone **22** from the reaction of isatoic anhydride **13** with 2-pyrrolidinone **29** using microwave irradiation (**Scheme 12**).

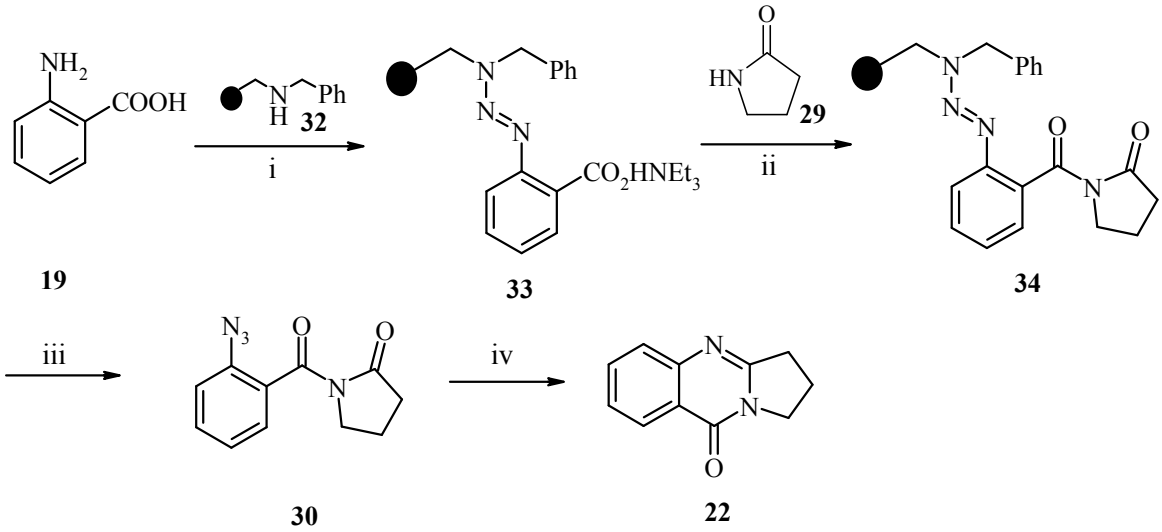


13 **29** **22**

Scheme 12. Reaction conditions**:** (i) MW (450 watts), 6 min, 92%.

Stefan Bräse et al. appraoch (2005)[10]

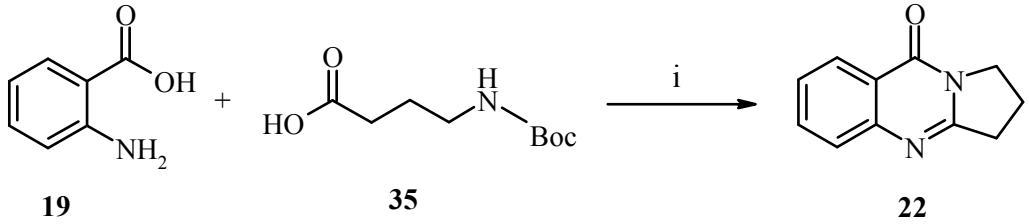
Stefan Bräse et al. reported the synthesis of deoxyvasicinone **22** using solid phase synthesis by intramolecular Aza-Wittig reaction. Initially, triazene carboxylate resin **33** was prepared by diazotization of the anthranilic acid **19** with isoamyl nitrite followed by subsequent coupling to the benzylamine resin **32**. The treatment of the triazene carboxylate resin **33** with triphenyl phosphine and tetrachloromethane generated the acyl chlorides, which reacted *in situ* with the 2-pyrrolidinone **29** to afford amide **34**. The azide **30** was then obtained in moderate yields (20%) by cleavage of the corresponding triazene resin **34** with trifluroacetic acid (TFA). Finally, deoxyvasicinone **22** was obtained from **30** by treatment with triphenyl phosphine polystyrene at 100 °C for 132 h (**Scheme 13**).



Scheme 13. Reaction conditions**:** (i) (a) $BF_3.OEt_2$, *i*AmONO, THF, -10 °C, 1 h; (b) pyridine/ DMF (1:1), rt, 1 h; (c) Et_3N; (ii) PPh_3, CCl_4, THF, *i*Pr_2NEt, 60 °C, 5h ; (iii) TFA, Me_3Si-N_3, 20%; (iv) triphenylphosphine polystyrene, 1 h, rt, then 100 °C, 132 h, 99%.

J.-F. Liu et al. approach (2005)[11]

J.-F. Liu et al. reported the synthesis of deoxyvasicinone **22** via novel microwave-assisted domino reactions. Anthranilic acid **19** was reacted with 4-(*tert*-butoxycarbonylamino)butyric acid **35** in the presence of triphenyl phosphite [$P(OPh)_3$] (1.2 equiv) in pyridine under microwave irradiation at 200 °C for 20 min to afford deoxyvasicinone **22** (**Scheme 14**).

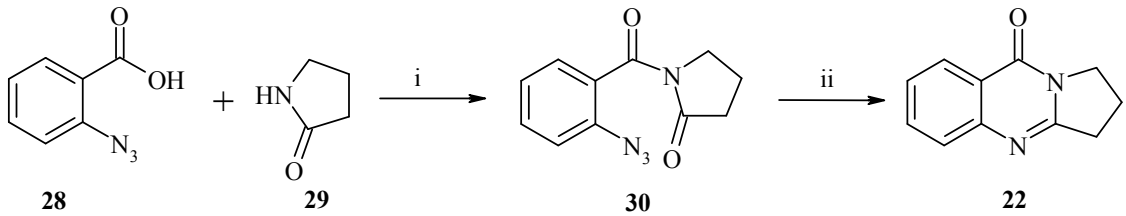


19 **35** **22**

Scheme 14. Reaction conditions**:** (i) $P(OPh)_3$, Pyridine, MW, 20 min, 200 °C, 89%.

Ahmed Kamal et al. approach (2006)[12]

Ahmed Kamal et al. reported the synthesis of deoxyvasicionone **22** using polymer-supported reagents. In the first step 2-azidobenzoic acid **28** was coupled with 2-pyrrolidinone **29** employing *N*-cyclohexylcarbodiimide *N*′-methyl polystyrene (**A)** to afford *N*-(2-azidobenzoyl) lactams **30**. Finally deoxyvasicionone **22** was obtained by intramolecular azidoreductive cyclization of the azido-lactams **30** using triphenyl phosphine-impregnated polystyrene (**B)** (**Scheme 15**).



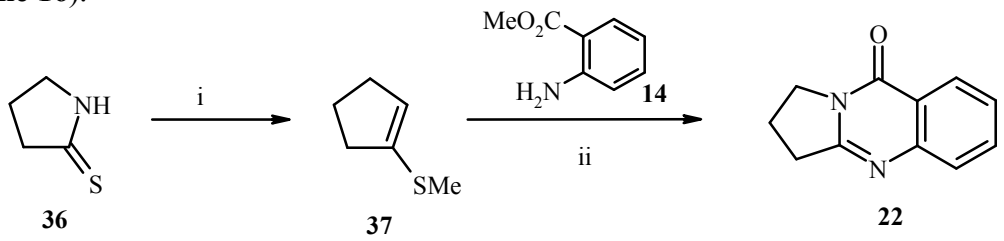
28 **29** **30** **22**

Scheme 15. Reaction conditions**:** (i) *N*-Cyclohexylcarbodiimide *N*-methyl polystyrene *(***A**), dry resin, dry DCM, 10h, 97%; ii) triphenylphosphine-impregnated polystyrene (**B**), dry DCM, 5 h, 98%.

A. Hamid et al. approach (2006)[13]

A. Hamid et al. reported the synthesis of deoxyvasicione **22** by intramolecular aza-displacement of a methylthio group followed by spontaneous cyclodehydration strategy. Initially, *S*-methyl derivatives of pyrrolidinone **37** was prepared from thiopyrrolidinone **36**

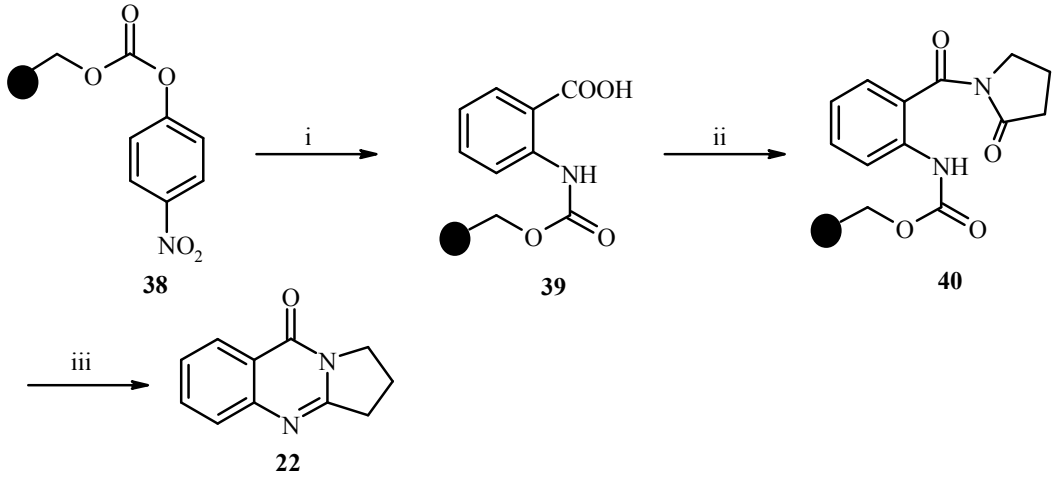
using methyl iodide and sodium hydroxide in ethanol which was further reacted with methyl anthranilate **14** in acetic acid at reflux temperature to afford deoxyvasicinone **22** (**Scheme 16**).



Scheme 16. Reaction conditions**:** (i) MeI, 2% NaOH, EtOH, 24 h; (ii) AcOH, reflux, 24 h, 86%.

Ahmed kamal et al. appraoch (2006)[14]

Ahmed kamal et al. reported the synthesis of deoxyvasicinone **22** by applying the strategy of solid-phase synthesis. Polymer supported-*p*-nitrophenyl carbonate **38** was coupled with anthranilc acid **19** using 1-hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIPEA) in DCM-DMF (2:1) to afford **39** which was further coupled to 2-pyrrolidinone **29** utilizing dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in DCM to afford **40**. Finally, **40** was treated with 50% TFA–DCM (1:1) to effect cleavage from the resin followed by cyclization to produce deoxyvasicinone **22 (Scheme 17)**.

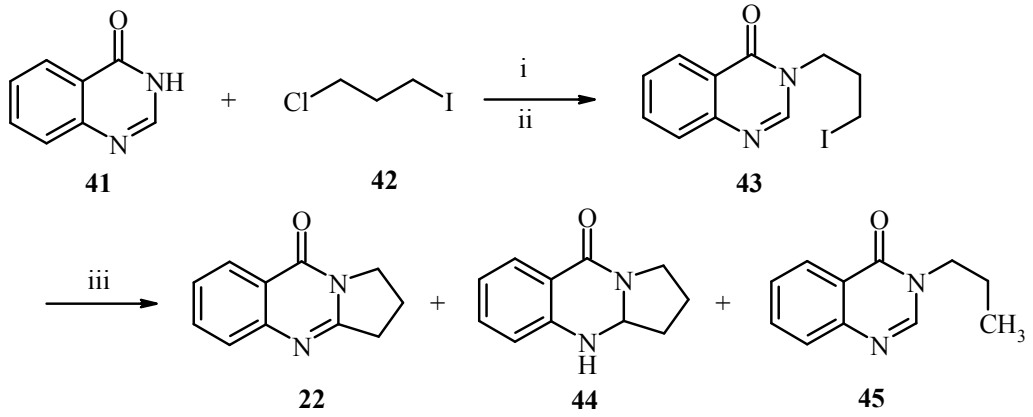


Scheme 17. Reaction conditions**:** (i) Anthranilic acid (**19**), HOBt, DIPEA, DCM-DMF, 6 h, rt; (ii) 2-pyrrolidinone (**29**), DCC, DMAP, DCM, 0 °C, 12 h, rt; (iii) TFA-DCM, 2 h, 88%.

W. R. Bowman et al. approach (2007)[15]

W. R. Bowman et al. reported the synthesis of deoxyvasicinone **22** using radical cyclization. (3*H*)-Quinazolin-4-one **41** was treated with 1-chloro-3-iodopropane **42** using

base sodium hydride in DMF followed by treating with sodium iodide in acetone to afford radical precursors, 3-(3-iodopropyl)quinazolin-4(3*H*)-one **43** which on further treatment with hexamethylditin [$(Me_3Sn)_2$] in *tert*-butyl benzene under reflux conditions in presence of 300 W sunlamp afforded deoxyvasicinone **22** in 20% along with other side product **44** and **45** (**Scheme 18**).



41 **42** **43** **22** **44** **45**

Scheme 18. Reaction conditions**:** (i) NaH, DMF, 51%; (ii) NaI, acetone, reflux, 53%; (iii) $(Me_3Sn)_2$, *tert*-BuPh, reflux, hv, 150 °C, 10h, 20% (**22**), 13% (**44**), 6% (**45**).

3.2.3 Present work

3.2.3.1 Objectives

In view of the importance of deoxyvasicinone due to its biological activities as well as its role as a important intermediate[4,5] for the preparation of natural products, several methods were reported in the literature for the synthesis of deoxyvasicinone. Although some methods were efficient, but most of the methods are based upon slight modification of previously reported methods. Similarly, among these none has employed the strategy of regioselective lithiation at C-2 of quinazolinone followed by subsequent reaction of lithiated intermediate with electrophile in an intramolecular fashion forming C-C bond to generate the cyclized product. As a part of our interest on the synthesis of quinazolinone related molecules, we became interested towards synthesis of deoxyvasicinone.

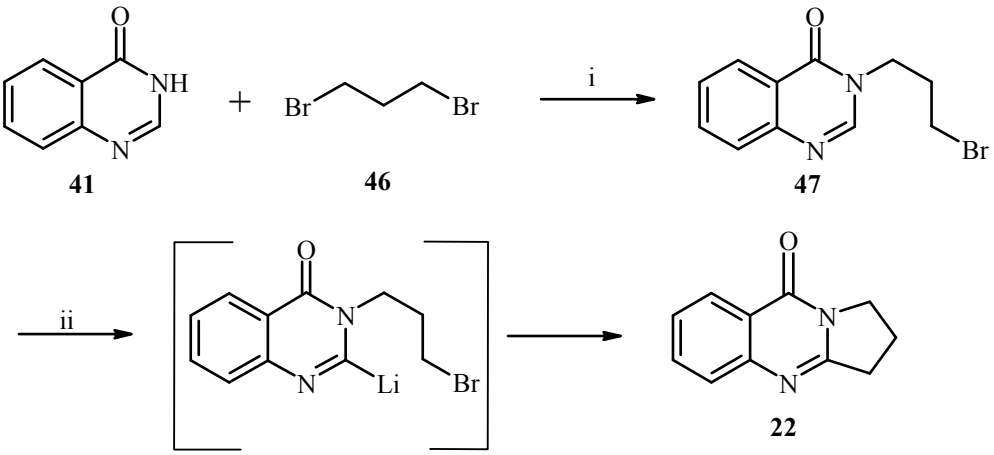
3.2.3.2 Present work

From our previous experience during the synthesis of tryptanthrin, it was found that quinazolinone unsubstituted at 2-position was regioselectively lithiated at C-2 using LDA at -78 °C which was subsequently reacted with electrophile in an intramolecular fashion to

afford the cyclized product. We anticipated that synthesis of deoxyvasicinone could be achieved using a similar strategy.

The synthesis of deoxyvasicinone was initiated with the formation of 3-(3-bromopropyl)-quinazolin-4(3*H*)-one **47**. Initially, (3*H*)-quinazolin-4-one **41** was alkylated employing 1,3-dibromopropane **46**, potassium carbonate in dry DMF at room temperature to afford 3-(3-bromopropyl)-quinazolin-4(3*H*)-one **47** in 81% yields. The compound **47** was fully characterized using mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The absence of band in IR spectra in the region 3300-3400 cm^{-1} corresponding to -NH and presence of band in the region 2800-3000 cm^{-1} corresponding to methyl group suggest the formation of *N*-alkyl derivative. The ^{1}H NMR of **47** shows peaks at δ ppm 2.33-2.45 (m, 2H), 3.42-3.48 (t, 2H), 4.16-4.22 (t, 2H) corresponding to group (–$CH_2CH_2CH_2$-) suggest presence of propyl group. Furthermore, the ^{13}C NMR spectrum of **47** showing peaks at δ 29.7, 31.0, 45.4 ppm respectively for the carbon of propyl group confirmed the structure.

Once 3-(3-bromopropyl)quinazolin-4(3*H*)-one **47** was prepared, its regioselective lithiation was achieved by using LDA in dry THF at -78 °C under inert atmosphere to give a reddish colour. The reaction mixture was stirred at -78 °C for additional 2 h and brought to room temperature and stirred further at this temperature for 2 h. It was expected that carbanion formed at 2-position of quinazolinone **47** would react with electrophile viz alkyl bromide in an intramolecular fashion forming C-C bond to afford the cyclized product, deoxyvasicinone (**Scheme 19**).



Scheme 19. Reaction conditions**:** (i) K_2CO_3, DMF, rt, 4 h, 87%; (ii) LDA, dry THF, -78 °C, 2 h, then rt, 2 h, 61%.

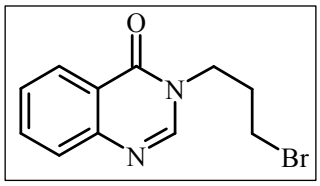
The reaction was quenched with aqueous ammonium chloride and product was extracted using ethyl acetate. Further purification by column chromatography afforded deoxyvasicinone **22** in 61 % yield. The structure of deoxyvasicinone **22** was confirmed by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectrum of **22** with the absence of peak as singlet at δ 8.12 ppm corresponding to hydrogen at C-2 of quinazolinone supports its formation. Furthermore, ^{13}C NMR spectra of **22** shows a peak at δ 159.0 ppm indicating that C-alkylation has taken place at the 2-position of (3*H*)-quinazolin-4-one.

3.2.4 Conclusion

In conclusion, we have achieved the synthesis of deoxyvasicinone in two-steps in 53% overall yield from (3*H*)-quinazolin-4-one and 1,3-dibromopropane. The key step for the reaction is regioselective lithiation at 2-position of quinazolinone followed by subsequent reaction of lithiated intermediate with electrophile in an intramolecular fashion to afford the cyclized product. The advantage of this method is the access of deoxyvasicinone from readily available and cheap starting materials.

3.2.5 Experimental

3.2.5.1 Synthesis of 3-(3-bromopropyl) quinazolin-4(3*H*)-one 47.



To a well stirred solution of (3*H*)-quinazolin-4-one **41** (0.500 g, 3.42 mmol) and potassium carbonate (0.519 g, 3.76 mmol) in dry DMF (15 mL) at room temperature was added 1,3-dibromopropane **46** (0.83 gm, 3.76 mmol) dropwise over 20 min and reaction mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under vacuum to obtain solid to which water (30mL) was added and product was extracted using ethyl acetate (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column chromatography with petroleum ether:ethyl acetate (6:4) to afford 0.798 g (87%) of pure 3-(3-bromopropyl)quinazolin-4(3*H*)-one **47** as white solid.

M. P. (°C) : 178-180

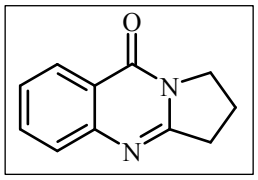
IR ($CHCl_3$, cm^{-1}) : ν_{max} 2931, 2854, 1681, 1561, 1450.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.33-2.45 (m, *J* = 6.66 & 6.15 Hz, 2H, $NCH_2\underline{CH_2}CH_2$), 3.42-3.48 (t, *J* = 6.15 Hz, 2H, $NCH_2CH_2\underline{CH_2}Br$), 4.16-4.22 (t, *J* = 6.66 Hz, 2H, $N\underline{CH_2}CH_2CH_2$), 7.48-7.56 (m, 1H, ArH), 7.70-7.82 (m, 2H, ArH), 8.12 (s, 1H, $C_2\underline{H}$ quinazolinone), 8.28-8.33 (dd, *J* = 7.96 & 1.02 Hz, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 29.7, 31.0, 45.4, 121.8, 126.5, 127.3, 134.3, 146.5, 147.8, 160.9.

Elemental Analysis : **$C_{11}H_{11}BrN_2O$** (267) Calcd: C, 49.46; H, 4.15; N, 10.49.
Found: C, 49.53; H, 4.09; N, 10.57.

3.2.5.2 Synthesis of deoxyvasicinone (22)



To a freshly prepared LDA (0.180 g, 1.68 mmol) in dry THF (5 mL) at -78 °C under inert atmosphere was added dropwise a solution of **47** (0.300 g, 1.12 mmol) in dry THF (5 mL) under nitrogen atmosphere. The reaction mixture was stirred at -78 °C for additional 2 h. As soon as addition of **47** started, the solution changed to a reddish color. The reaction mixture was slowly allowed to warm to room temperature and further stirred at this temperature for 2 h. The reaction mixture was quenched with aqueous ammonium chloride and product was extracted using ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column chromatography with petroleum ether:ethyl acetate (2:8) to afford 0.128 g (61%) of pure deoxyvasicinone **22** as solid.

M. P. (°C) : 196-197 (Lit.[6] 196-198)

IR ($CHCl_3$, cm^{-1}) : ν_{max} 2931, 2855, 1679, 1600, 1556, 1455.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.21-2.36 (m, *J* = 7.94 & 7.21 Hz, 2H, $NCH_2\underline{CH_2}CH_2$), 3.14-3.22 (t, *J* = 7.94 Hz, 2H, $NCH_2CH_2\underline{CH_2}$), 4.17-4.24 (t, *J* = 7.21 Hz, 2H, $N\underline{CH_2}CH_2CH_2$), 7.40-7.48 (m, 1H, ArH), 7.62-7.77 (m, 2H, ArH), 8.22-8.30 (dd, *J* = 8.00 &1.14 Hz, 1H, ArH).

^{13}C NMR : δ 19.4, 32.4, 46.4, 120.4, 126.2, 126.3, 126.7, 134.1, 149.0, 159.4,

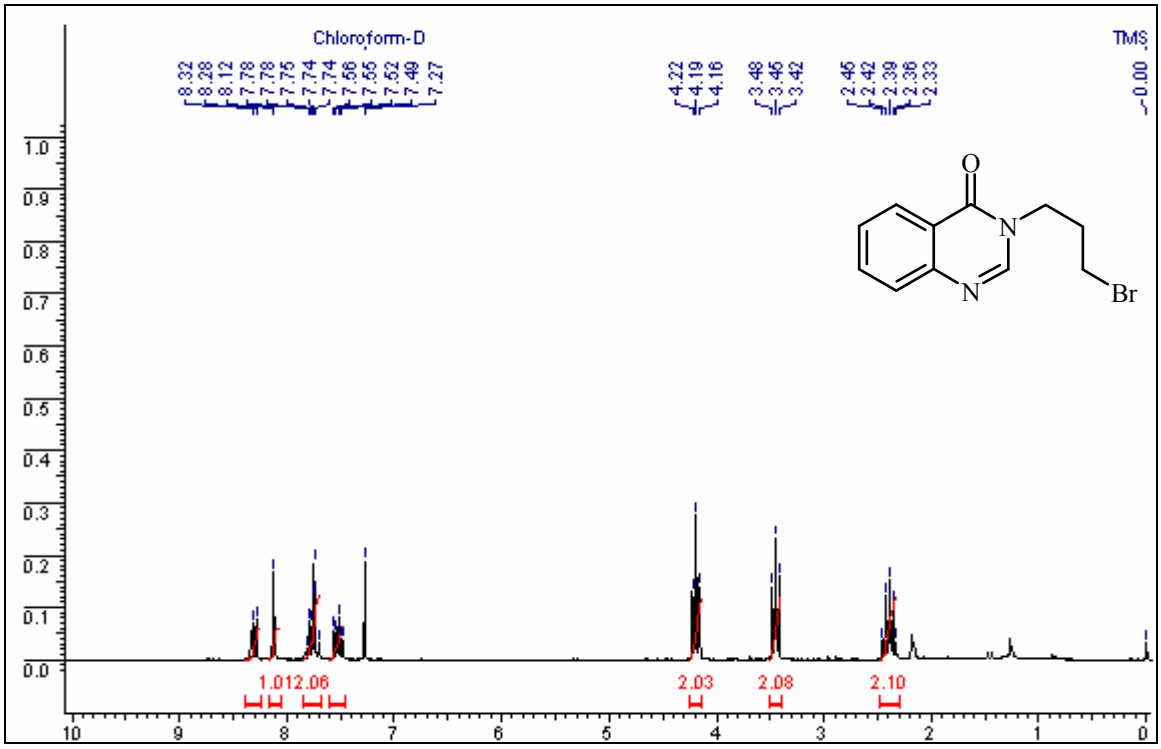
($CDCl_3$, 50 MHz) 160.9.

Elemental Analysis : $C_{11}H_{10}N_2O$ (186) Calcd: C, 70.95; H, 5.41; N, 15.04.
Found: C, 71.02; H, 5.38; N, 15.17.

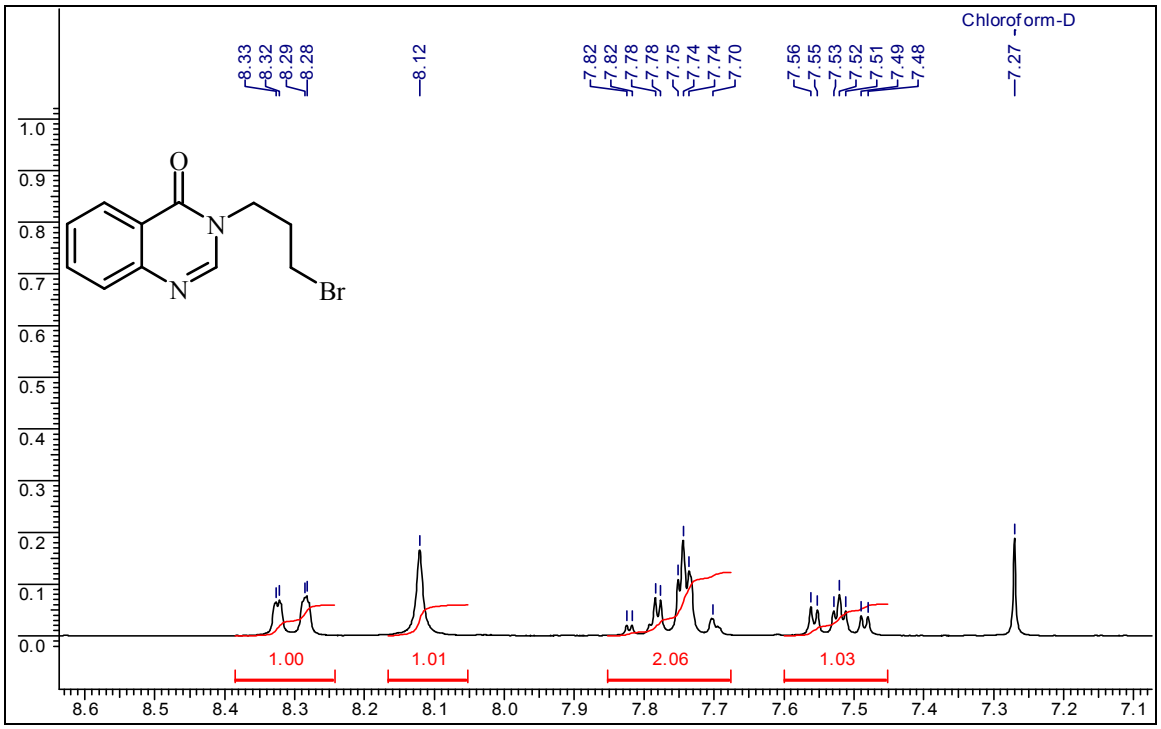
3.2.6 Spectra of compounds

Sr No.	NMR spectra
1	^{1}H NMR, ^{13}C NMR and DEPT of **47**
2	^{1}H NMR, ^{13}C NMR and DEPT of **22**

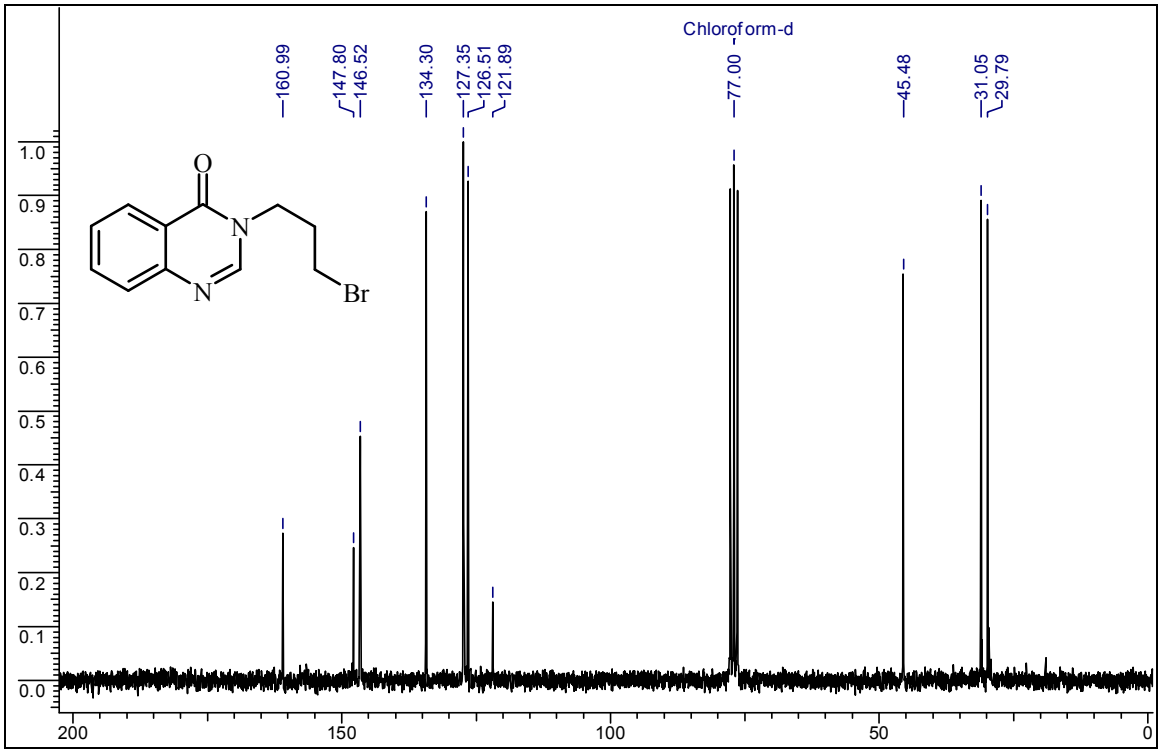
^{1}H NMR spectra of **47**



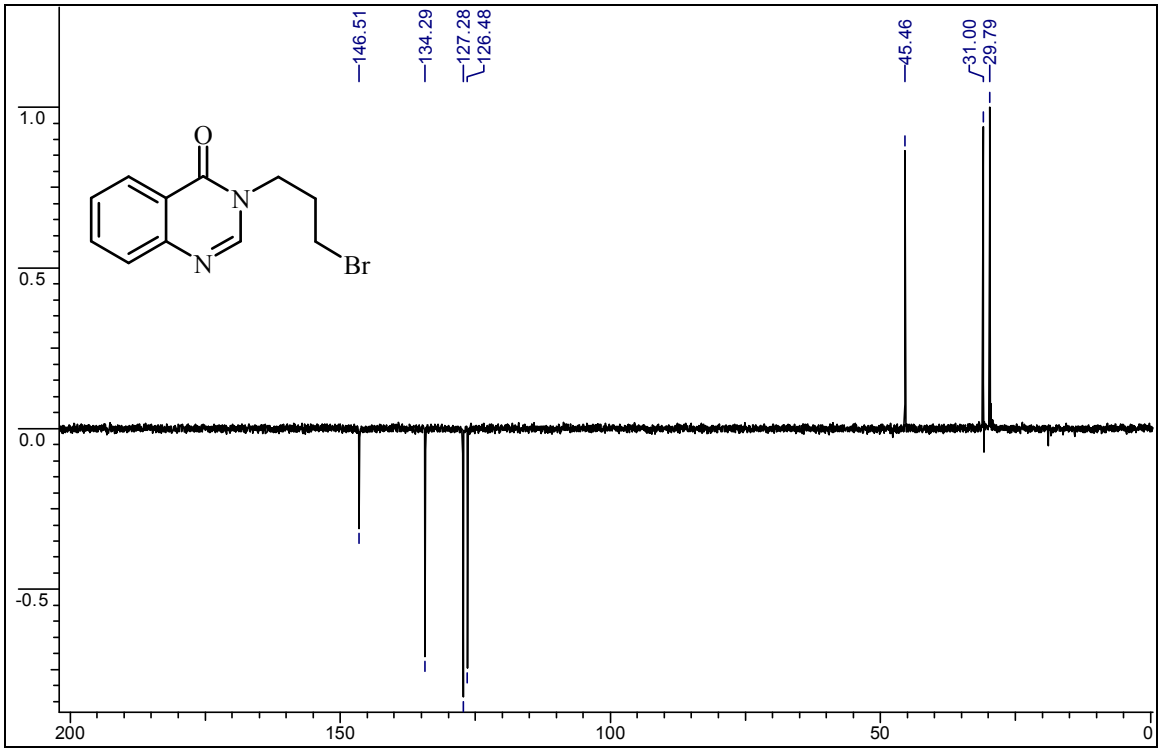
^{1}H NMR spectra of **47** (extended view)



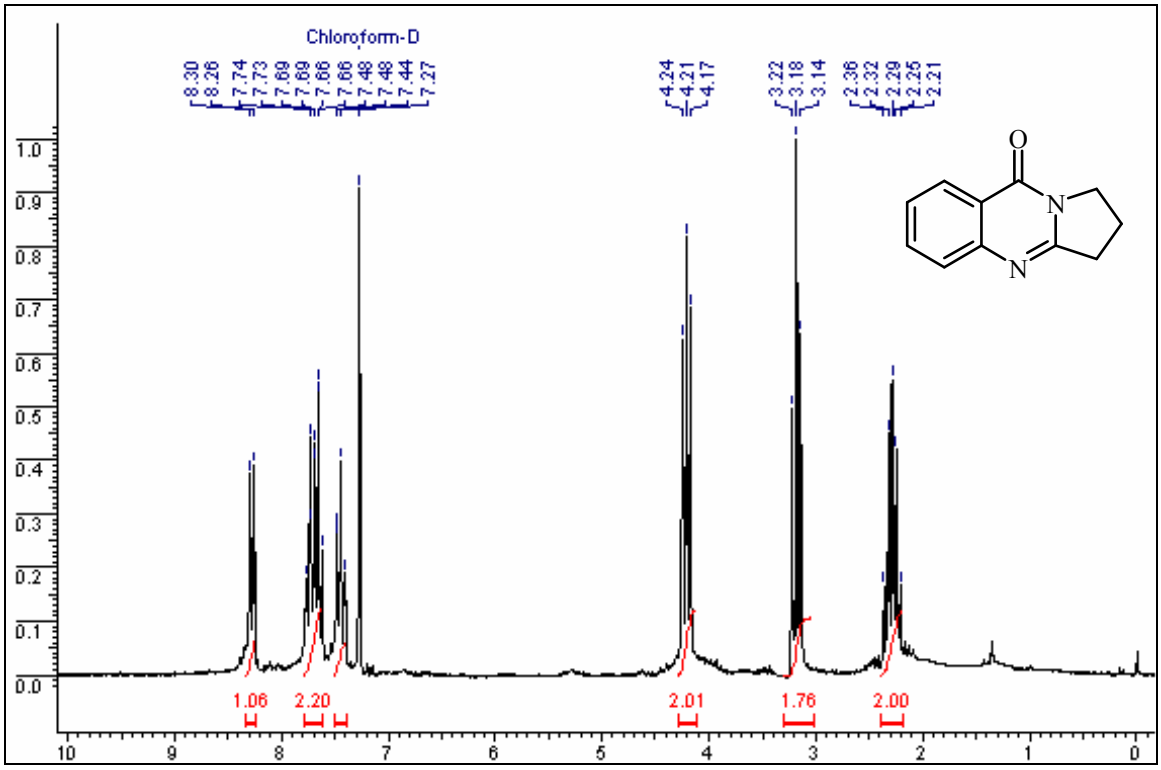
^{13}C NMR spectra of **47**



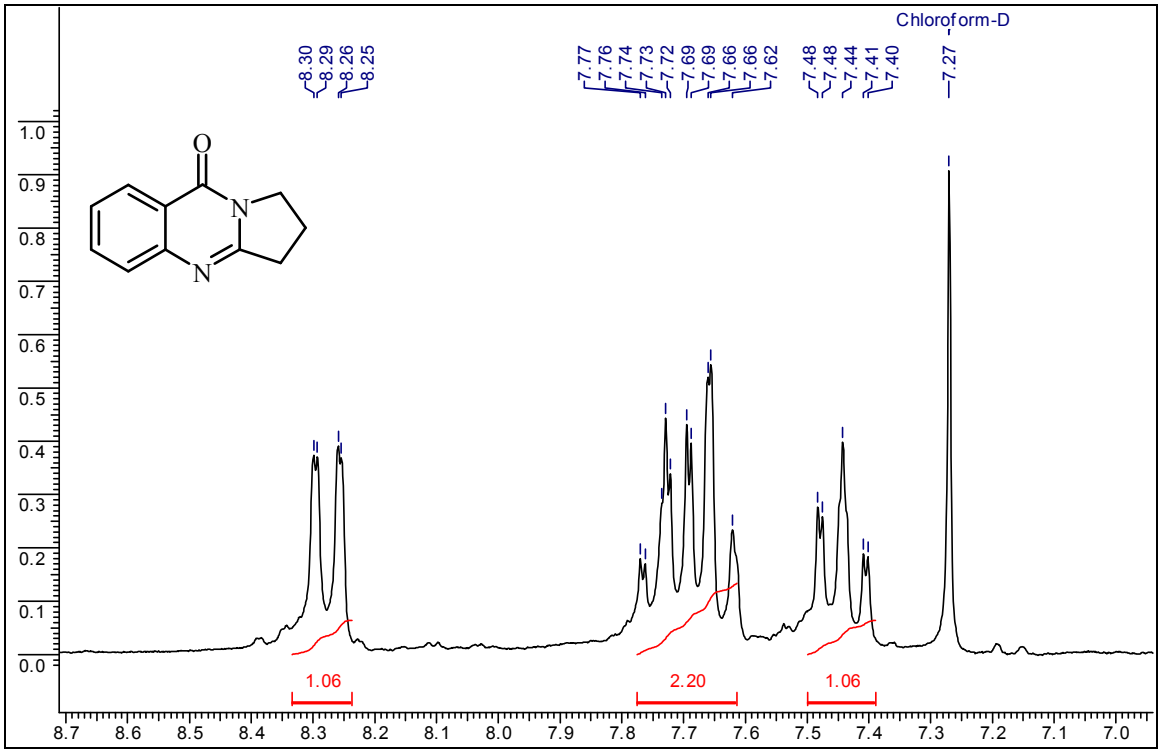
^{13}C DEPT of **47**



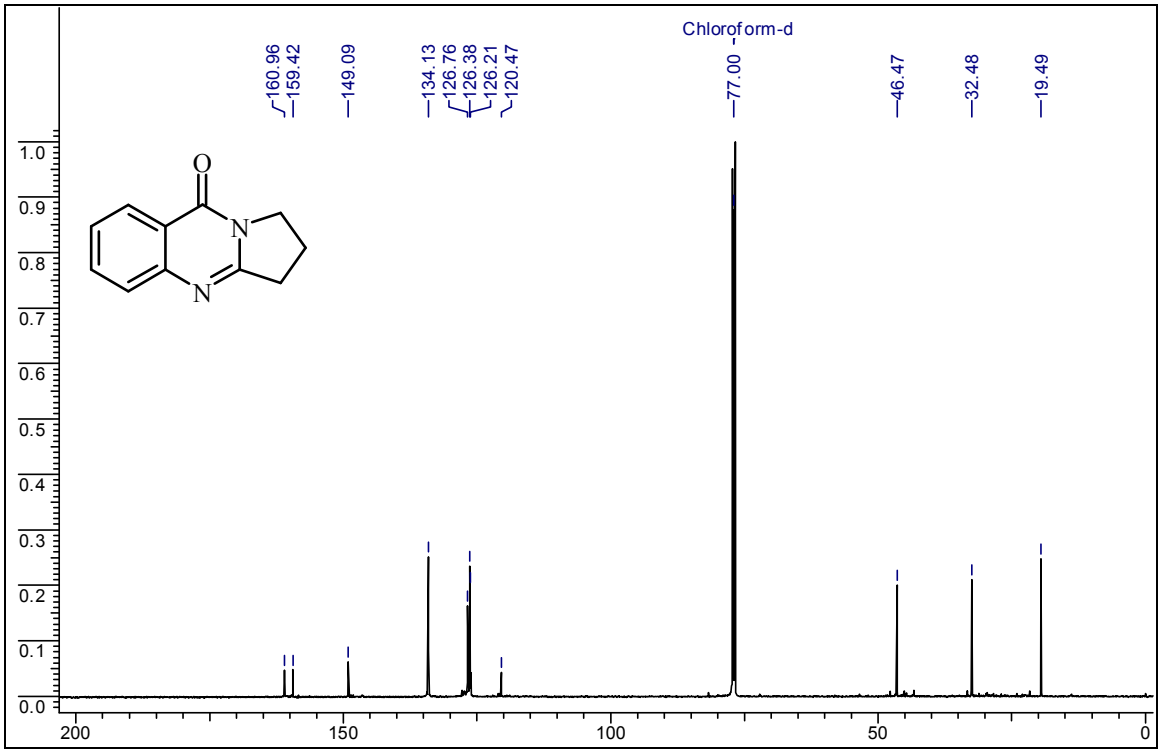
^{1}H NMR spectra of **22**



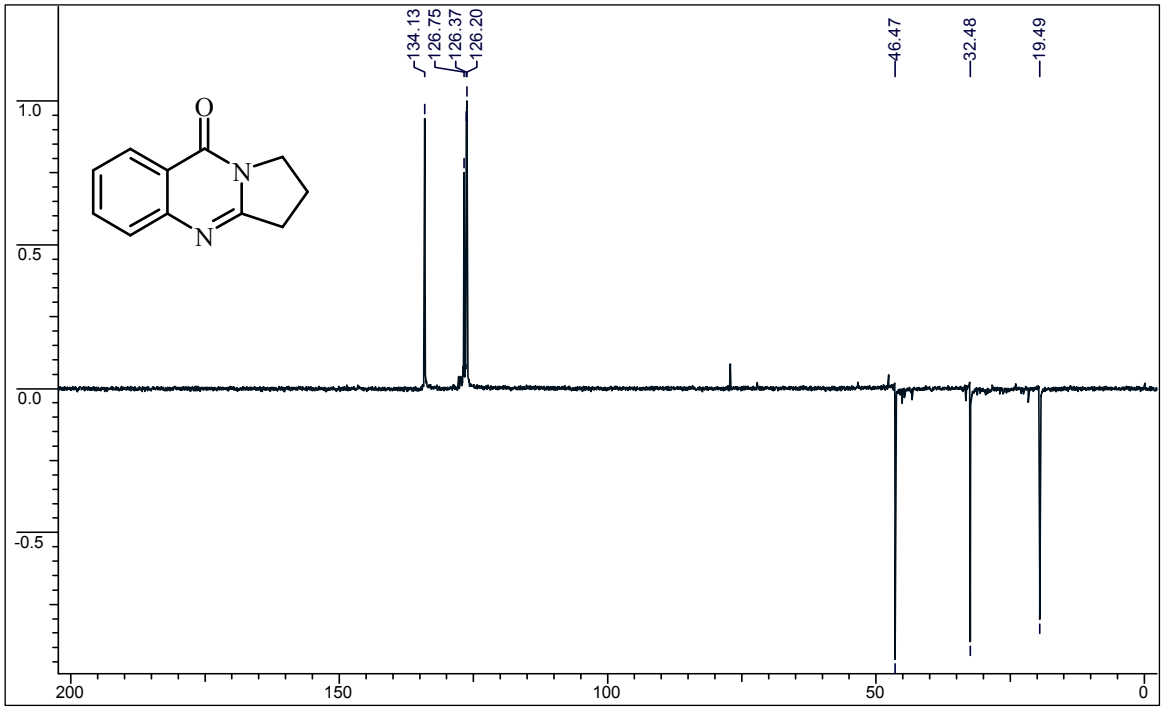
^{1}H NMR spectra of **22** (extended view)



^{13}C NMR spectra of **22**



^{13}C DEPT of **22**



3.2.7 References

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Chapter 3, Section C

Synthesis of luotonin A

3.3.1 Introduction

Heterocyclic compounds are of particular interest in medicinal science. Among these, alkaloids that incorporate the pyrroloquinazoline chromophore have been isolated from natural sources[1] and display a wide range of biological activities.[2]

Luotonin A **25** (**Fig. 6**), the first known natural product to possess the heteroaromatic pyrroloquinazolinoquinoline ring system, was isolated by Nomura and coworkers in 1997 from the aerial parts of the *Peganum nigellastrum* (Chinese Bunge), commonly known as "*luo-tuo-hao*". This plant has a history of use in Chinese traditional medicine for the treatment of various conditions, including rheumatism and inflammation. Luotonin A showed potent cytotoxic activity against *mouse leukemia* P-388 cells[3] and has been the subject of several syntheses.

There are obvious structural similarities between potent anti-cancer agent, 20-(*S*)-campothecin[4] **48** (**Fig. 6**) and luotonin A, notably in identical rings A-C. The greatest differences are in ring E, which is known to be critical for campothecin function as a topoisomerase I inhibitor and antineoplastic agent.[5]

Interest in luotonin A has increased considerably following the report by Hecht and coworkers that it mediates topoisomerase-dependent cytotoxicity.[6] Like camptothecin, luotonin A is a 'topoisomerase I poison' that stabilizes the topoisomerase I-DNA complex by forming a ternary complex. These observations are important because it has been thought until very recently that the E-ring hydroxylactone of campothecin was indispensable for anti-cancer activity.[7]

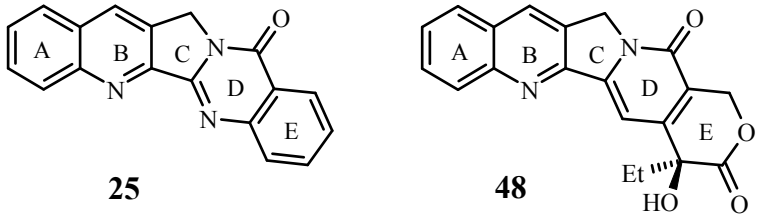


Figure 6. Structures of luotonin A and 20-(*S*)-campothecin

But, luotonin A is not nearly as potent as campothecin, and it is not likely to be a drug candidate for cancer chemotherapy. However, it is a good lead compound, and

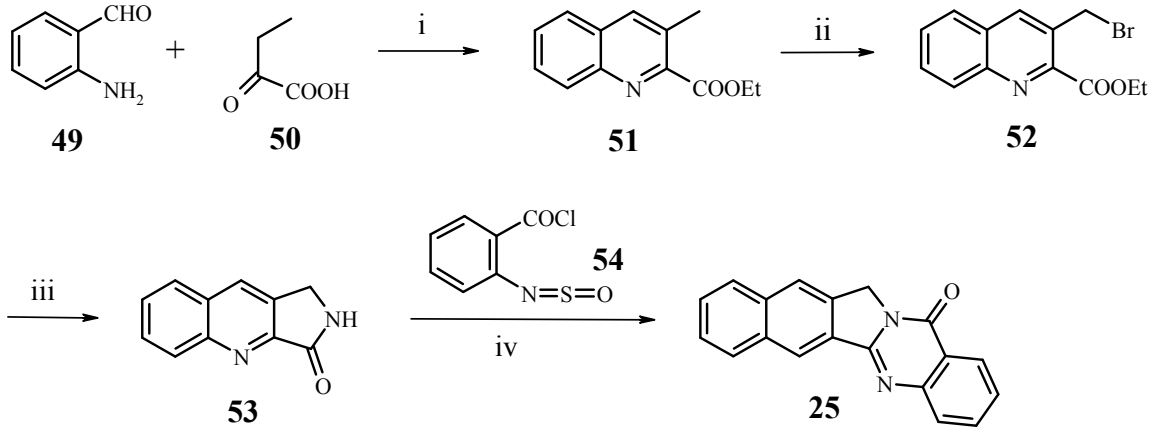
Hecht,[8] Dallavalle[9] and their coworkers recently reported the synthesis of an assortment of substituted E-ring analogues[8,9] along with a few A-ring analogues.[9]

3.3.2 Review of literature

In view of the importance of luotonin A in medicinal chemistry, a number of total syntheses have been reported in literature. In this section, we have discussed in brief some of the important methods.

A. Ganesan et al. approach (1998)[10]

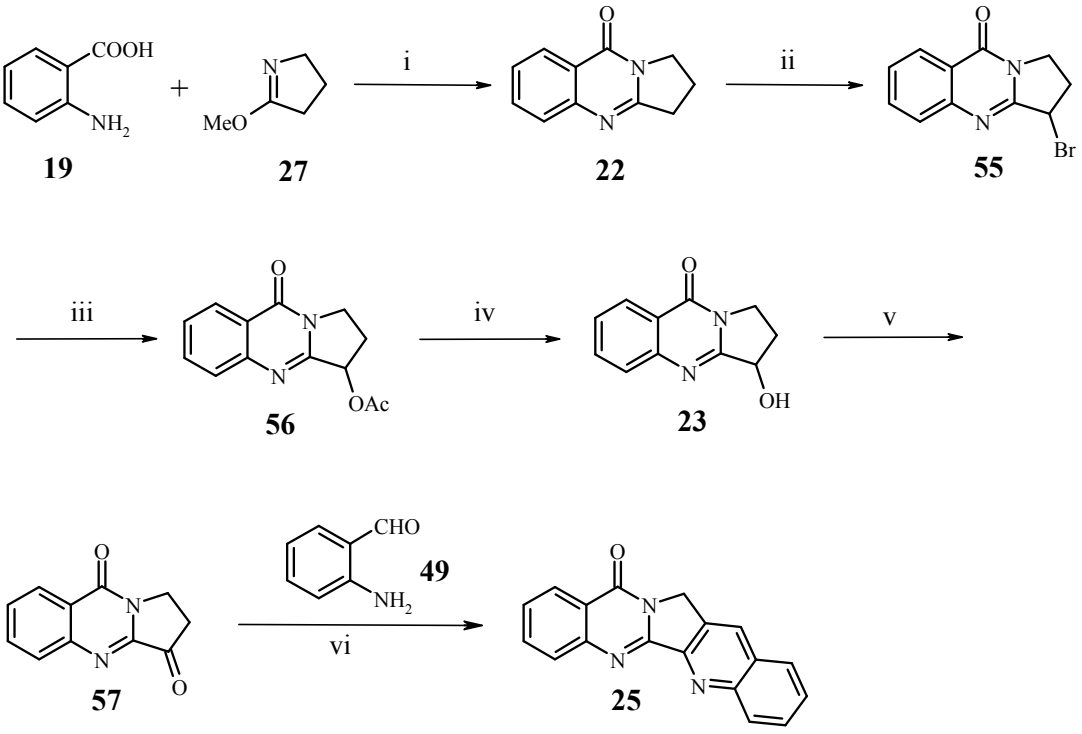
A. Ganesan et al. reported the synthesis of luotonin A from 2-aminobenzaldehyde **49**. Initially ethyl 3-methylquinoline-2-carboxylate **51** was prepared from the reaction of 2-aminobanzeldehyde **49** and 2-ketobutyric acid **50** in 60% yield. Ethyl 3-methylquinoline-2-carboxylate **51** was reacted with *N*-bromosuccinimide using catalytic amount of AIBN in refluxing carbon tetrachloride for 7 h to affird ethyl 3-(bromomethyl)quinoline-2-carboxylate **52** in 33% yield which on further reaction with ammonia in methanol afforded 3-oxo-l*H*-pyrrolo[3,4-*b*]quinoline **53**. Finally, luotonin A **25** was obtained by treating **53** with 2-sulfinylaminobenzoyl chloride **54** using lithium bis(trimethylsilyl)amide in THF for 11 h (**Scheme 20**).



Scheme 20. Reaction conditions: (i) NaOEt, MeOH, reflux, 16.5 h; H_2SO_4, MeOH, reflux, 24.5 h, 60%; (ii) NBS, AIBN, CCl_4, reflux, 7 h, 33%; (iii) NH_3, MeOH, 74%; (iv) $LiN(TMS)_2$, THF, 11 h, rt, 84%.

T. Ross Kelly et al. approach (1999)[11]

T. Ross Kelly et al. reported the synthesis of Luotonin A starting from anthranilic acid **19**. Deoxyvasicinone **22** was obtained from anthranilic acid **19** and O-methylbutyrolactim **27** in refluxing benzene. Then, deoxyvasicinone **22** was brominated using NBS and catalytic amount of benzoyl peroxide in refluxing carbon tetrachloride to afford bromo compound **55** which was further reacted with sodium acetate-acetic acid to afford acetylvasicinone **56.** Vasicinone **23** was then obtained from acetylvasicinone **56** by hydrolysis. Thus, oxidation of vasicinone **23** using Jones reagent gave dione **57** which on further reaction with 2-aminobanzaldehyde **49** afforded Luotonin A **25 (Scheme 21).**

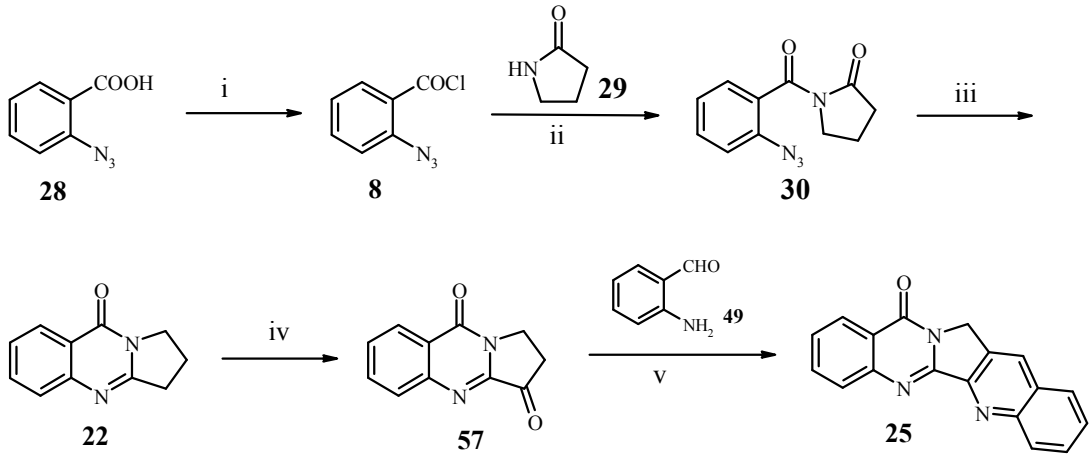


Scheme 21. Reaction conditions: (i) benzene, reflux, 82%: (ii) NBS, benzoyl peroxide, CCl_4, reflux, 57%; (iii) NaOAC-AcOH, 33%; (iv) hydrolysis; (v) CrO_3, Aq. H_2SO_4 (Jones reagent), acetone, 56%; (vi) triton B, EtOH, reflux, 2 h, 36%.

Pedro Molina et al. approach (2000)[12]

Pedro Molina et al. reported the synthesis of luotonin A starting from 2-azidobenzoic acid **28.** Initially, 2-azidobenzoic acid **28** was converted to the corresponding acid chloride **8** by refluxing it in thionyl chloride which was further reacted with 2-pyrrolidinone **29** using sodium hydride (NaH) in dry THF to afford 1-(2-azidobenzoyl)azacyclopent-2-one **30.**

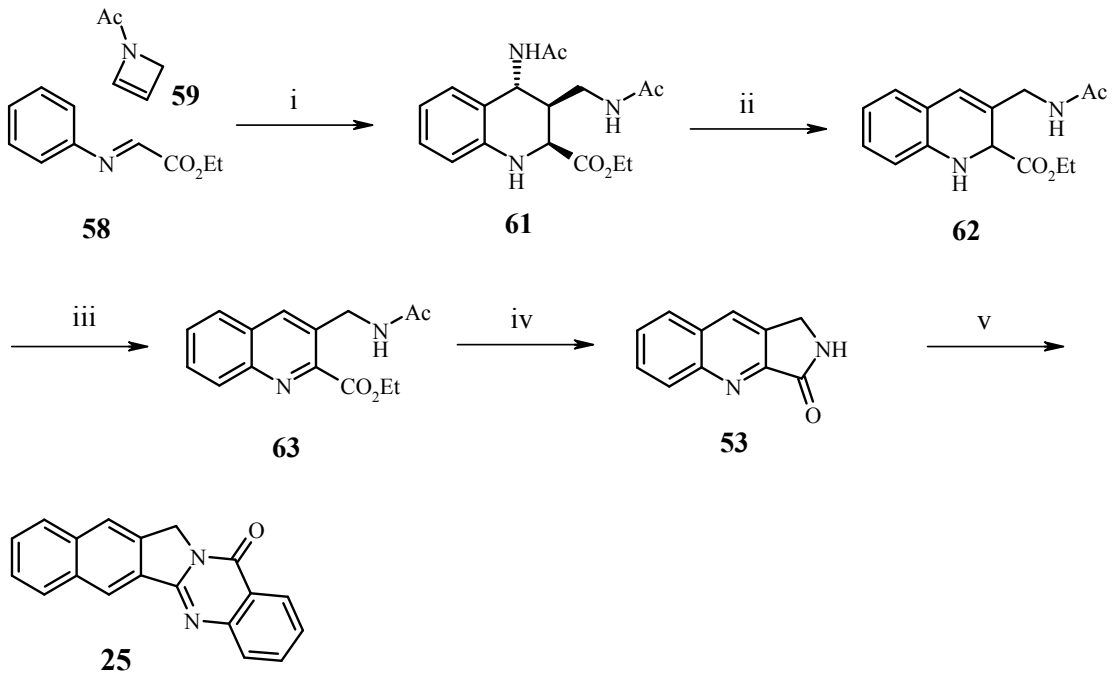
Intermediate deoxyvasicinone **22** was obtained from **30** by treatment with tributylphosphine in xylene. Later on, deoxyvasicinone **22** was oxidized to pyrrolo[2,1-*b*]quinazoline-3,9-dione **57** in 42% yield using selenium dioxide in dioxane at reflux temperature. Finally Luotonin A **25** was obtained from the reaction of **57** with 2-aminobenzaldehyde **49** using triton B in ethanol (**Scheme 22**).



Scheme 22. Reaction conditins: (i) $SOCl_2$, reflux, 2 h; (ii) NaH, dry THF, 0 °C, then rt 2 h, 75%; (iii) Bu_3P, xylene, rt, 1 h, then, 50 °C, 3 h, 99%; (iv) SeO_2, xylene, reflux, 12 h, 42%; (v) triton B, EtOH, reflux, 2 h, 36%.

Paul J. Stevenson et al. approach (2002)[13]

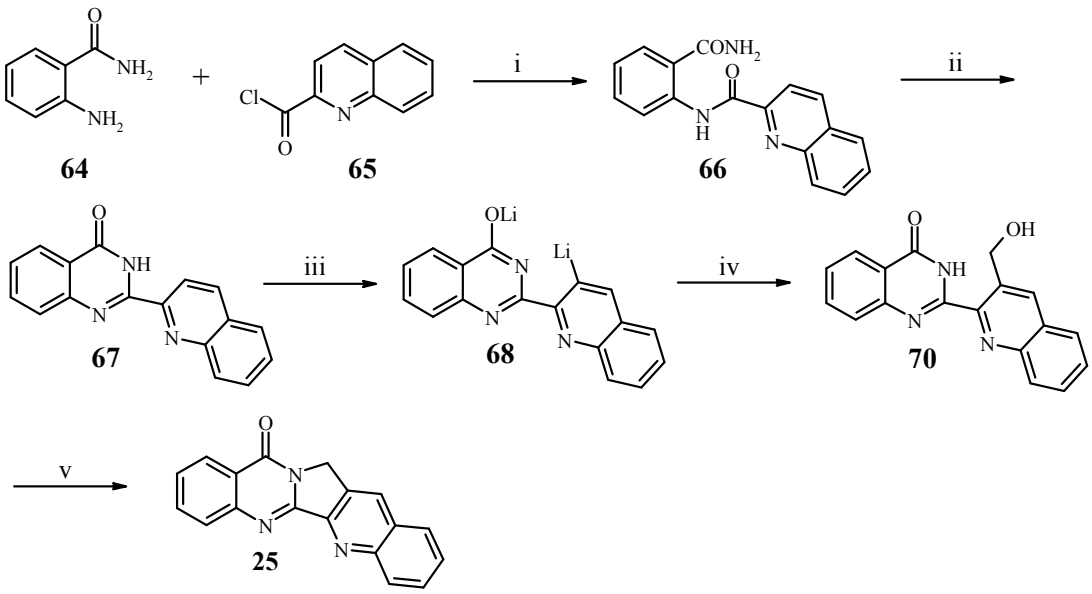
Paul J. Stevenson et al. reported the synthesis of luotonin A **25** by Lewis acid catalyzed [4+2] cycloaddition between *N*-Acetyl-2-azetine and imines derived from aniline. Reaction of ethylglyoxylate aniline imine **58** with *N*-acetyl-2-azetine **59**, aniline **60** and a catalytic quantity of yttrium triflate at room temperature for 12 h gave a tetrahydroquinoline **61** in 97% isolated yield. 2,3-Disubstituted quinoline **63** was isolated in 78% overall yield by adding few drops of concentrated hydrochloric acid to the acetonitrile solution of **62**. Finally, treatment of **63** with sodium ethoxide in ethanol resulted in cyclization followed by cleavage of the resulting imide gave lactam **53** in 99% yield. Because this lactam was converted to luotonin A **25** in one additional step by reaction with 2-sulfinylaminobenzoyl chloride or isatoic anhydride, this represents a formal synthesis luotonin A (**Scheme 23**).



Scheme 23. Reaction conditions: (i) $Y(OTf)_3$ (3 mol%), aniline (**60**), MeCN, 12 h, 97%; (ii) 5 h at 80 °C; (iii) HCl, MeCN, 1 h, reflux, 78%; (iv) NaOEt, EtOH, 78 °C, 99%; (v) $NaN(SiMe_3)_2$, 2-sulfinylaminobenzoyl chloride, 2 h, 85%.

N. P. Argade et al. approach (2004)[14]

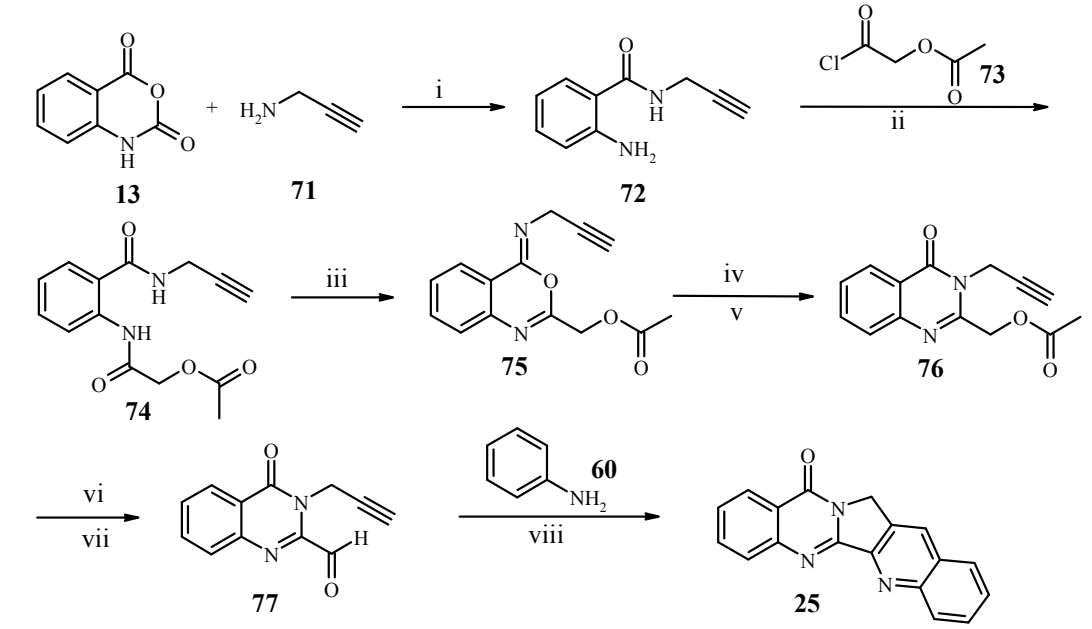
N. P. Argade et al. reported the synthesis of luotonin A **25** by using regioselective quinazolinone-directed ortho lithiation on an adjacent quinoline moiety as a key step. Initially anthranilamide **64** was treated with quinaldic acid chloride **65** using triethyl amine to furnish diamide **66** which was further cyclized using aqueous potassium hydroxide in ethanol to afford 2-quinolinoquinazolinone **67.** The reaction of 2-quinolinoquinazolinone **67** with 2.2 equiv of *in situ* generated mesityllithium at -20 °C furnished the dilithiated species **68** via lithiation of the quinazolinone nitrogen at the 3-position as a first step followed by directed ortho lithiation at the 3'-position. The reaction of dilithiated intermediate **68** with formaldehyde **69** exclusively yielded 2-hydroxymethylquinolinoquinazolinone **70** which on Mitsunobu cyclization using triphenyl phosphine and diethyl azadicarboxylate (DEAD) afforded product luotonin A **25** (**Scheme 24**).



Scheme 24. Reaction conditions: (i) Et_3N (2 equiv), THF, rt, 3 h, 96%; (ii) aq. KOH, EtOH, reflux, 98%; (iii) mesityllithium, (2.2. equiv), -78 °C, 30 min to -20 °C, 30 min; (iv) HCHO (**69**) (5 equiv), THF, - 30 °C, 20 min, sat. NH_4Cl; (v) PPh_3, DEAD, THF, rt, 1 h, 95%.

Robert A. Batey et al. approach (2004)[15]

Robert A. Batey et al. reported the synthesis of Luotonin A from isatoic anhydride **13**.

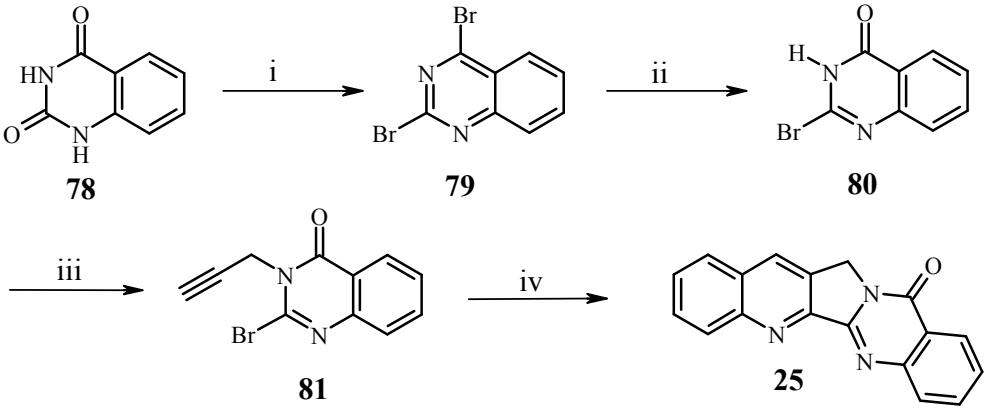


Scheme 25. Reaction conditions: (i) DMF, 40-50 °C, 3h, 65%; (ii) Et_3N, benzene, 40 °C to rt, 16 h, 68%; (iii) Ph_3P (5 equiv), I_2, EtN-^{i}Pr$_2$ (10 equiv), DCM, 5 h, rt, 89%; (iv) Piperidine in EtOAc, 1 h, (v) silica gel, EtOAc, 16 h, rt 85% (two-step); (vi) NaOH, TFA/H_2O, 2 h, rt, 83% (vii) Dess-martin periodinane, pyridine, MeCN, 1 h, rt, 73%; (viii) $Dy(OTf)_3$ (10 mol%), MeCN, 24 h, 51%.

The reaction of isatoic anhydride **13** with propargyl amine **71** gave 2-aminobenzamide **72** which on treatment with acetoxyacetyl chloride **73** using triethyl amine afforded **74.** Reaction of **74** with triphenyl phosphine and iodine in the presence of Hünig's base (ethyl diisopropyl amine) afforded **75**. A two-sep, one-pot arrangement of **75** using piperidine followed by silica gel gave quinazolinone **76**. The final steps in the synthesis of luotonin A **25** involve removal of the acetate group from **76** using 1 M sodium hydroxide in THF/H_2O and subsequent oxidation using Dess-Martin periodinane afforded aldehyde precursor **77** over the two steps. Intramolecular Povarov reaction between **77** and aniline **60** occurred in the presence of 10 mol % $Dy(OTf)_3$ in acetonitrile for 24 h to afford luotonin A **25** (**Scheme 25**).

D. P. Curran et al. approach (2005)[16]

D. P. Curran et al. reported the synthesis of luotonin A by applying the strategy of cascade radical annulation of phenyl isonitrile. Conversion of benzoyleneurea **78** to the dibromide **79** followed by monohydrolysis with 1 N sodium hydroxide provided bromoquinazolone **80** as a single regioisomer in 52% yield. Propargylation of **80** afforded **81** in 66% yield. The photoirradiation of **81** and phenyl isonitrile **82** with a sunlamp in the presence of hexamethylditin provided luotonin A **25** in 47% yield (**Scheme 26**).

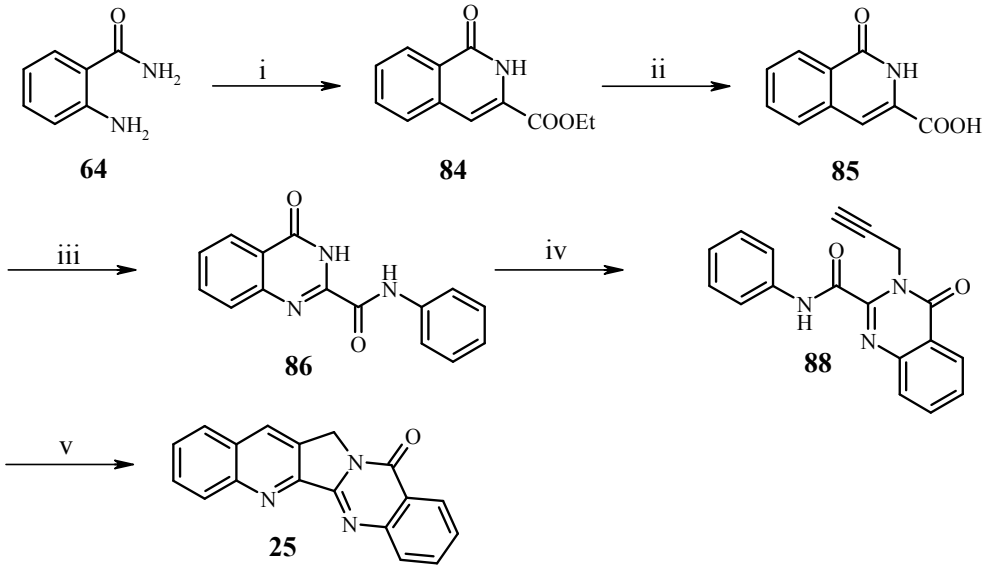


Scheme 26. Reaction conditions: (i) $POBr_3$, *N,N*-dimethylaniline, 105 °C, 4 h, 52%; (ii) NaOH, DMF, rt, 2 h, 100%; (iii) NaH, DMF, 0 °C, then propargyl bromide (**87**), rt, 6.5 h, 66%; (iv) benzene, phenyl isonitrile (**82**), $(Me_3Sn)_2$, hv, 8 h, 47%.

Z.-J. Yao et al. approach (2007)[17]

Z.-J. Yao et al. reported the synthesis of Luotonin A by using cascade strategy. Reaction of the commercially available anthranilamide **64** with diethyl oxalate **83** yielded a

quinazolinone derivative **84** in 81% yield. Quinazolinone ethyl ester **84** was then hydrolyzed with lithium hydroxide to afford corresponding acid **85**. Conversion of **85** to its corresponding acid chloride, followed by coupling with aniline **60** afforded the amide **86** in 67% yield (from **85**). *N*-Alkylation of amide **86** with propargyl bromide **87** afforded the precursor amide **88** in 87% yield. Finally, the cascade annulation was carried out by treating **88** with triphenylphosphone oxide and trifluoromethanesulfonic anhydride 0 °C followed by rt for 1 h to afford luotonin A **25** in 99% yield. This five-step synthesis of luotonin A represents an overall yield of 47% from the commercially available **64** **(Scheme 27)**.

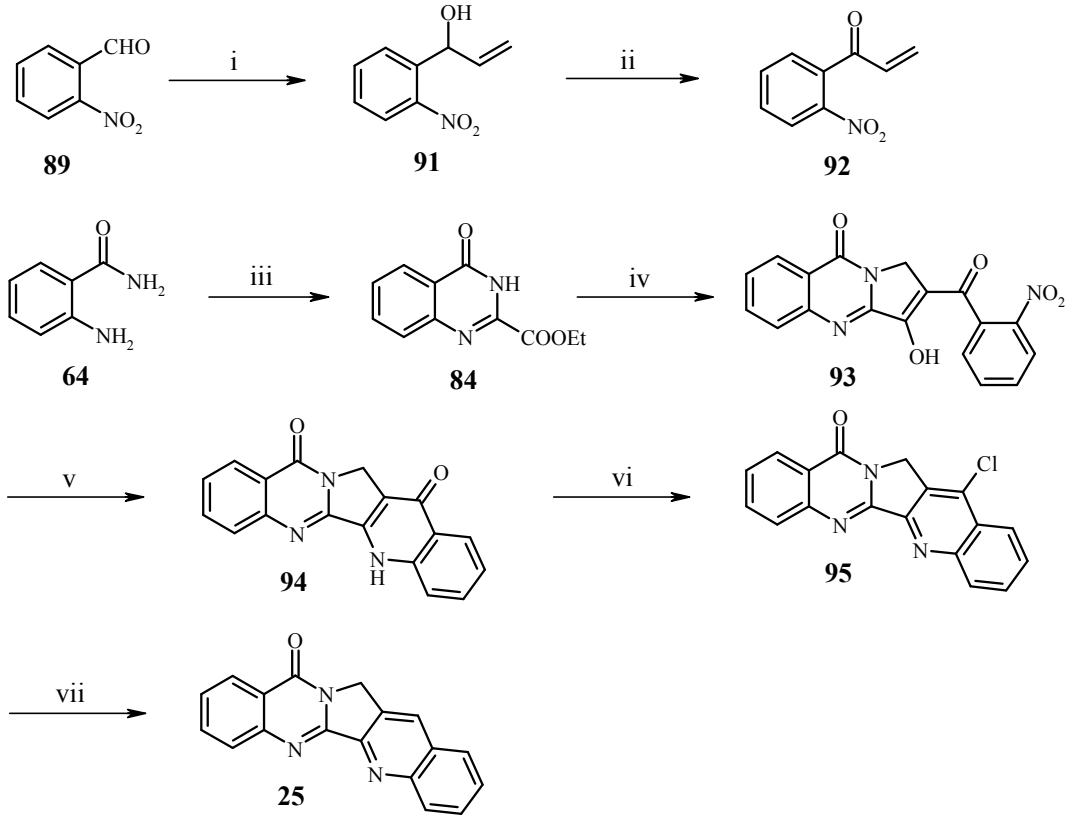


Scheme 27. Reaction conditions**:** (i) diethyl oxalate (**83**), 185-186 °C , 5 h, 87%; (ii) LiOH, THF/H_2O (3:1); 20 min, rt; (iii) $(COCl)_2$, DCM, then aniline (**62**), DCM, rt, 67% (from 85); (iv) propargyl bromide **(87)**, K_2CO_3, LiBr, Bu_4NBr, toluene with cat. H_2O, 87%; (v) Ph_3PO (3 equiv), Tf_2O (1.5 equiv), 0 °C to rt, 99%.

Jan Bergman et al. approach (2007)[18]

Jan Bergman et al. reported the synthesis luotonin A starting from 1-(2-nitrophenyl)propenone **92.** Formation of 1-(2-nitrophenyl)propenone **92** was achieved in two-step from 2-nitrobenzaldehyde **89** and vinyl magnesium bromide **90** followed by oxidation in 86% yield. Meanwhile ethyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate **84** was prepared from anthranilamide **64** and diethyl oxalate **83** in 90% yield. The Michael addition of **84** with the propenone compound **92** was done and an intramolecular Claisen

condensation followed to produce compound **93.** Catalytic hydrogenation of **93** with Pd/C in DMF produced compound **94** in quantitative yield. Chlorination of **94** using phosphorus oxychloride gave 14-chloroluotonin A **95**. Reduction of **95** to the target molecule **25** (84% yield) was obtained using freshly activated Raney nickel catalyst at room temperature (**Scheme 28**).

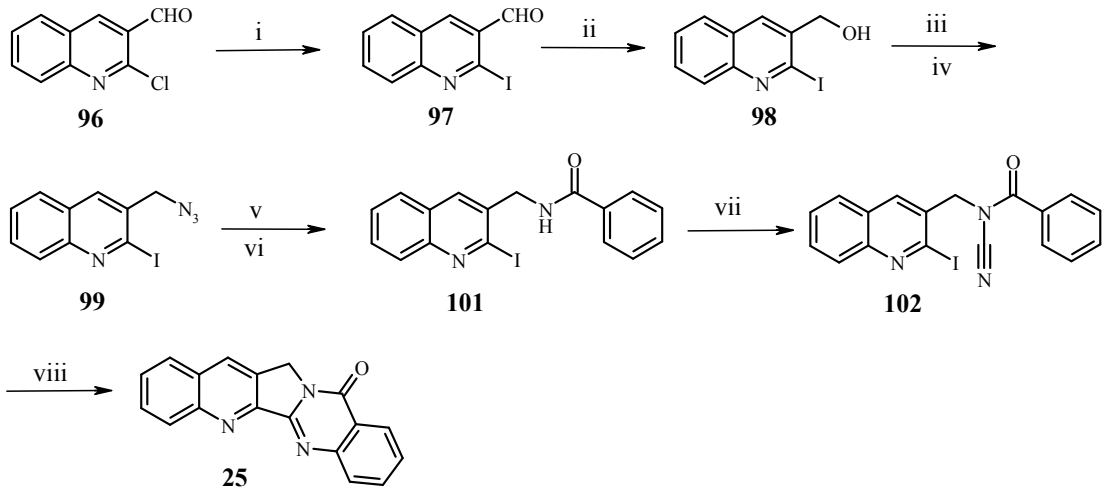


Scheme 28. Reaction conditions: (i) THF, - 70 °C, vinylmagnesium bromide (**90**); (ii) Jones reagent, 86%, over two-step; (iii) diethyl oxalate (**83**), 185-186 °C, 5 h, 90%; (iv) DMF, *t*-BuOK, 60 °C, 30 min, then **92,** 60 °C, 2 h then rt, 2 h, 83%; (v) Pd/C, H_2, DMF, 1 h, 96%; (vi) $POCl_3$, reflux, 1 h, 99%; (vii) Raney nickel, dioxane, 1 h, 84%.

Max Malacria et al. approach (2007)[19]

Max Malacria et al. reported the synthesis of Luotonin A by using radical cyclization cascades strategy. Initially, 2-iodo-quinoline-3-carbaldehyde **97** was prepared from 2-chloro-quinoline-3-carbaldehyde **96** using sodium iodide following Meth-Cohn's procedure in 70% yield which was further reduced to (2-iodoquinolin-3-yl)methanol **98** using sodium borohydride in 84% yield. Compound (2-iodoquinolin-3-yl)methanol **98** was converted to (2-iodoquinolin-3-yl)methyl methanesulfonate using mesyl chloride in

quantitative yield which on further reaction with sodium iodide afforded azide **99** (two-steps). Staudinger reduction of the azide **99** using triphenyl phosphine delivered an amine, which was benzoylated using benzoyl chloride **100** to furnish amide **101** in 47% yield (two-steps). Cyanation of amide **101** using cyanogen bromide and sodium hydride yielded *N*-acylcyanamide **102** in 41% yield. Finally Luotonin A **25** was achieved from **102** using hexabutylditin in refluxing toluene under irradiation for 6 h (**Scheme 29**).



Scheme 29. Reaction conditions: (i) NaI, HCl (55% aq. Solution), MeCN, Reflux, 4.5 h, 70%; (ii) $NaBH_4$, MeOH, 0 °C, 30 min, 84%; (iii) Mesyl chloride, Et_3N, DCM, 0 °C to rt, quantitative; (iv) NaN_3, DMF, 1 h, 95%; (v) Ph_3P, THF, water, 3 h; (vi) benzoyl chloride (**100**), Et_3N, DCM, 19 h, 47 % (two-step); (vii) NaH, BrCN, THF, 20 h, 41%; (viii) $(Bu_3Sn)_2$, toluene, reflux, sunlamp, 43%.

3.3.3 Present work

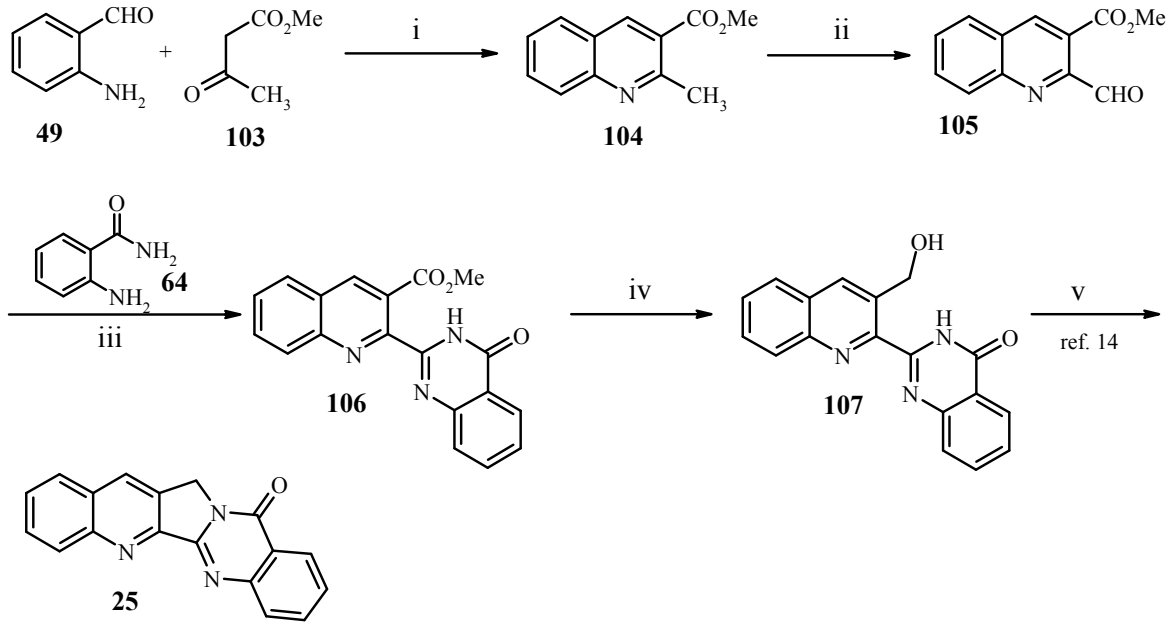
3.3.3.1 Objectives

Luotonin's structural and biological features make it an attractive synthetic target, and a number of total syntheses have been completed. Although these alkaloids have been the subject of numerous synthetic investigations, new approaches are always welcome. We planned the synthesis of Luotonin A starting from 2-aminobenzaldehyde.

3.3.3.2 Results and discussion

The synthesis of Luotonin A was initiated from 2-aminobenzaldehyde **49**. Initially, 2-aminobenzaldehyde **49** was condensed with methyl acetoacetate **103** by Friedlander quinoline synthesis using the IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) as

reaction medium as well as promoter to afford 2-methylquinoline-3-carboxylic acid methyl ester **104** in 73% yield. This condensation reaction is promoted by the Brønsted acidity of the IL. The ^{1}H NMR spectra of **104** shows peak at δ 8.76 ppm as singlet corresponding to the hydrogen at C-4 of quinoline ring. Furthermore, peak at δ 3.01 ppm as singlet corresponding to the methyl at C-2 and peak at δ 3.99 ppm as singlet corresponding to methyl of methyl carboxylate supports the formation of **104**. The ^{13}C NMR of compound **104** shows peak at δ 25.5 (carbon of methyl at C-2), 52.2 (carbon of methyl ester), 139.9 (C-4 of quinoline ring), 158.3 (C-2 of quinoline ring) and 166.7 ppm (carbonyl carbon) confirmed the structure.



Scheme 30. Reaction conditions: (i) $[Hbim]BF_4$, 100 °C, 1.5 h, 73%; (ii) SeO_2 (1.05 equiv), xylene, reflux, 8 h, 69%; (iii) $FeCl_3.6H_2O$ (2.1 equiv), H_2O, reflux, 4 h, 76%; (iv) $NaBH_4$-$CaCl_2$ (5 equiv), EtOH, rt, 2 h, 87%; (v) Ph_3P, DEAD, THF, rt, 1 h, 95% (ref. 14).

Later on, 2-methylquinoline-3-carboxylic acid methyl ester **104** was oxidized using selenium dioxide in xylene where it afforded oxidized product, 2-formylquinoline-3-carboxylic acid methyl ester **105** in 69% yield. The formation of compound **105** was observed by NMR spectroscopy. The appearance of peak at δ 10.4 ppm in ^{1}H NMR spectrum corresponding to hydrogen of aldehyde and disappearance of peak at δ 3.01 ppm

corresponding to the methyl at C-2 supports the formation of **105**. The ^{13}C NMR spectra of compound **105** shows peak at 191.5 corresponding to carbonyl carbon of aldehyde confirmed the structure of **105**.

2-formylquinoline-3-carboxylic acid methyl ester **105** was then condensed with anthranilamide **64** using ferric chloride ($FeCl_3.6H_2O$) in water to afford 2-(quinoline-3'-carboxylic acid methyl ester)-4(3*H*)-quinazolinone **106** in 76%. The appearance of peak in ^1H NMR spectrum at δ 4.02 ppm corresponding to methyl ester (singlet) and 11.01 ppm corresponding to –NH (broad singlet) supports for the formation of **106**. The ^{13}C NMR of compound **106** shows peak at δ 52.8 (carbon of methyl ester), δ 161.2 (carbonyl carbon of amide), δ 168.8 (carbonyl carbon of ester) and δ 148.3 ppm (C-2 of quinazolinone) confirmed its structure.

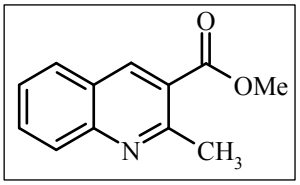
Once the compound 2-(quinoline-3'-carboxylic acid methyl ester)-4(3*H*)quinazolinone **106** was synthesized, then it was reduced by using sodium borohydride-calcium chloride in ethanol to furnish 2-(quinoline-3'-hydroxymethyl)-4(3*H*)quinazolinone **107**. When the reduction of **106** was carried out using sodium borohydride alone without calcium chloride in ethanol, it afforded the product **107** in lower yield. The appearance of peak in ^1H NMR spectra at δ 5.09 (singlet, 2H) and δ 6.37 ppm (broad singlet, 1H) corresponding to group CH_2OH and disappearance of peak at δ 4.04 ppm corresponding to the methyl ester supports the formation of **107**. The ^{13}C NMR spectra of compound **107** shows peak at δ 63.9 ppm ($\underline{C}H_2OH$) confirmed the structure of **107**. Because this compound **107** could be converted to luotonin A **25** in one additional step, by using standard Mitsunobu reaction condition[14] such as use of triphenyl phosphine, diethyl azodicarboxylate in THF by a simple procedure, a formal synthesis of luotonin A was thus completed.

3.3.4 Conclusion

In conclusion, we have achieved a formal synthesis of luotonin A starting from 2-aminobenzaldehyde in five steps in an overall yield of 31%.

3.3.5 Experimental

3.3.5.1 Synthesis of methyl 2-methylquinoline-3-carboxylate (104)



A mixture of 2-aminobenzaldehyde **49** (1 gm, 8.25 mmol) and methyl acetoacetate **103** (1.15 gm, 9.9 mmol) in the IL, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) (10 mL) was heated at 100 °C with stirring for 1.5 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted water (10 mL) and product was extracted using ethyl acetate (3x30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a crude product which was purified by column chromatography using petroleum ether: ethyl acetate (9:1) to obtain 1.21 gm (73%) of the pure methyl 2-methylquinoline-3-carboxylate **104** as white solid.

M. P. (°C) : 67-69

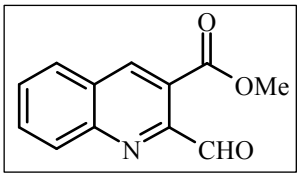
IR ($CHCl_3$, cm^{-1}) : ν_{max} 2951, 1726, 1621, 1565, 1489, 1438, 1278, 1200, 1127, 1064, 788.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.01 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.51-7.59 (m, 1H, ArH), 7.76-7.89 (m, 2H, ArH), 8.04-8.08 (d, J = 8.49 Hz, 1H, ArH), 8.76 (s, 1H, ArH).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 25.5, 52.2, 123.3, 125.6, 126.2, 128.3, 131.6, 139.9, 148.48, 158.39, 166.77.

Elemental Analysis : **$C_{12}H_{11}NO_2$** (201) Calcd: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.67; N, 7.08.

3.3.5.2 Synthesis of methyl 2-formylquinoline-3-carboxylate (105)



A mixture of methyl 2-methylquinoline-3-carboxylate **104** (0.800 gm, 4 mmol) and selenium dioxide (0.460 gm, 4.2 mmol) in xylene (25 mL) was refluxed for 8 h. The progress of the reaction was monitored by TLC. After completion of reaction, solvent was evaporated under reduced pressure to get a blackish residue. Water (30 mL) was added to residue and the product was extracted using ethyl acetate (3x30 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude product which was purified by column

chromatography using petroleum ether:ethyl acetate (8.5:1.5) to afford 0.590 gm (69%) of the pure methyl 2-formylquinoline-3-carboxylate **105** as dark brown viscous liquid.

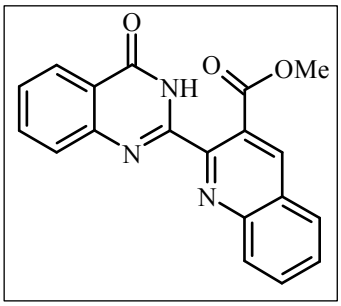
IR ($CHCl_3$, cm^{-1}) : ν_{max} 3020, 2954, 2853, 1770, 1727, 1567, 1439, 1216, 1051, 945, 756, 667.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.02 (s, 3H, OCH_3), 7.71-7.79 (m, 1H, ArH), 7.87-7.99 (m, 2H, ArH), 8.28-8.32 (d, *J* = 8.49 Hz, 1H, ArH), 8.61 (s, 1H, ArH), 10.41 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 53.0, 124.4, 127.8, 128.3, 129.7, 130.4, 132.1, 138.5, 147.9, 151.2, 166.9, 191.5.

Elemental Analysis : **$C_{12}H_9NO_3$** (215) Calcd: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.87; H, 4.35; N, 6.67.

3.3.5.3 Synthesis of methyl 2-(4-oxo-3,4-dihydroquinazolin-2-yl)quinoline-3-carboxylate (106)



A mixture of methyl 2-formylquinoline-3-carboxylate **105** (0.400 g, 1.86 mmol), anthranilamide **64** (0.265 gm, 1.95 mmol) and ferric chloride hexahydrate (1.05 gm, 3.9 mmol) in water (20 mL) was refluxed for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted using ethyl acetate (3 x 30 mL).

The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude solid product which was purified by column chromatography using petroleum ether:ethyl acetate (8:2) to afford 0.470 gm (76%) of the pure methyl 2-(4-oxo-3,4-dihydroquinazolin-2-yl)quinoline-3-carboxylate **106** as a white solid.

M. P. (°C) : 226-227

IR ($CHCl_3$, cm^{-1}) : ν_{max} 3331, 3019, 2926, 2854, 1731, 1681, 1608, 1469, 1406, 1215, 1051, 902, 757, 668.

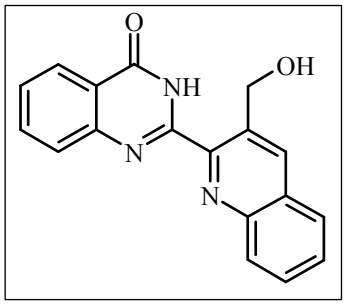
^{1}H NMR ($CDCl_3$, 200 MHz) : 4.04 (s, 3H, OCH_3), 7.50-7.58 (m, 1H, ArH), 7.65-7.81 (m, 3H, ArH), 7.83-7.94 (m, 2H, ArH), 8.16-8.20 (d, *J* = 8.42 Hz, 1H,

ArH), 8.35-8.38 (d, *J* = 6.58 Hz, 2H, ArH), 11.01 (bs, 1H, NH).

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 52.8, 122.4, 126.5, 126.7, 127.5, 127.8, 127.9, 128.0, 129.1, 129.5, 131.6, 134.5, 136.9, 144.6, 146.4, 147.6, 148.3, 161.2.

Elemental Analysis : **$C_{19}H_{13}N_3O_3$** (331) Calcd: C, 68.88; H, 3.95; N, 12.68.
Found: C, 68.76; H, 3.81; N, 12.81.

3.3.5.4 Synthesis of 2-(3-(hydroxymethyl)quinolin-2-yl)quinazolin-4(3*H*)-one (107)



To a well stirred solution of methyl 2-(4-oxo-3,4-dihydroquinazolin-2-yl)quinoline-3-carboxylate **106** (0.165 gm, 0.5 mmol) in ethanol (5 mL) was added $CaCl_2$ (0.273 gm, 2.5 mmol) and the resulting solution was stirred for 15 min. Finely powdered sodium borohydride (0.094 gm, 2.5 mmol) was then added slowly in three portions and the reaction mixture was further stirred at room temperature for 2 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with aqueous ammonium chloride. The solvent was evaporated under vacuo to get residue. Water (10 mL) was added to the residue and the product was extracted using ethyl acetate (2 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give crude solid product which was purified by column chromatography with petroleum ether:ethyl acetate (6.5:3.5) to afford 0.130 gm (87%) of the pure 2-(3-(hydroxymethyl)quinolin-2-yl)quinazolin-4(3*H*)-one **107** as white solid.

M. P. (°C) : 209-211

IR (CHCl$_3$, cm^{-1}) : ν_{max} 3423, 3308, 3018, 2926, 2855, 1682, 1606, 1565, 1470, 1236, 1215, 1021, 951, 758, 668.

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 5.09 (s, 2H, CH_2), 6.37 (bs, 1H, OH), 7.59-7.71 (m, 2H, ArH), 7.81-7.92 (m, 4H, ArH), 8.18-8.20 (d, *J* = 8.36 Hz, 1H, ArH), 8.31 (s, 1H, ArH), 8.40-8.42 (d, *J* = 8.02 Hz, 1H, ArH), 11.49 (bs, 1H, NH).

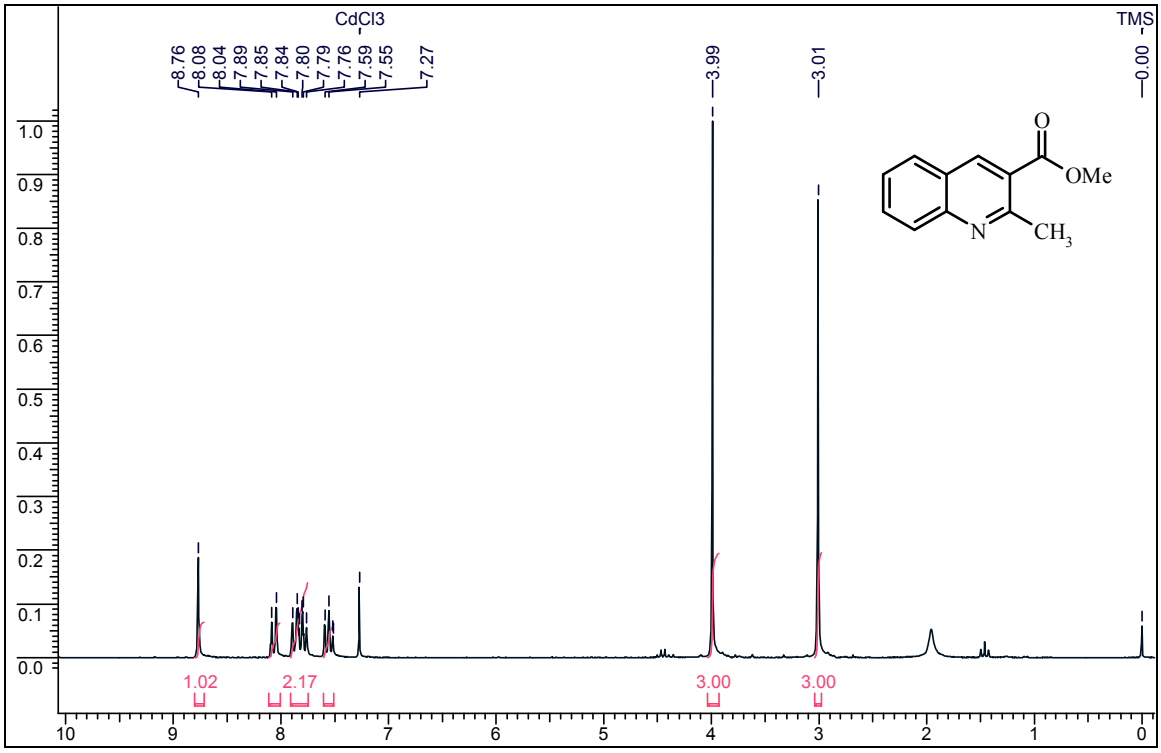
^{13}C NMR (CDCl$_3$, 50 MHz) : δ 63.9, 122.4, 126.9, 127.5, 127.6, 128.2, 128.9, 129.0, 129.3, 130.8, 133.9, 134.9, 139.2, 145.8, 146.5, 147.8, 150.1, 161.0.

Elemental Analysis : $C_{18}H_{13}N_3O_2$ (303) Calcd: C, 71.28; H, 4.32; N, 13.85.
Found: C, 71.43; H, 4.28; N, 13.68.

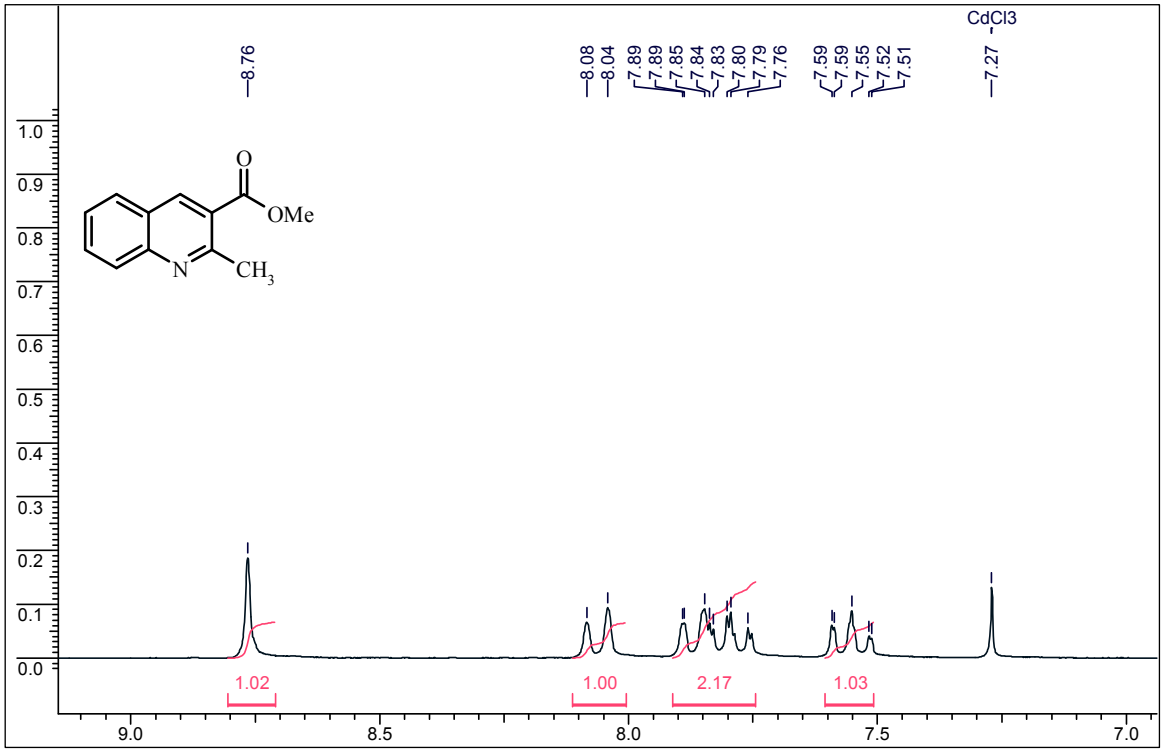
3.3.6 Spectra of compounds

Sr No.	NMR spectra
1	^{1}H NMR, ^{13}C NMR and DEPT of **104**
2	^{1}H NMR, ^{13}C NMR and DEPT of **105**
3	^{1}H NMR, ^{13}C NMR and DEPT of **106**
4	^{1}H NMR and ^{13}C NMR **107**

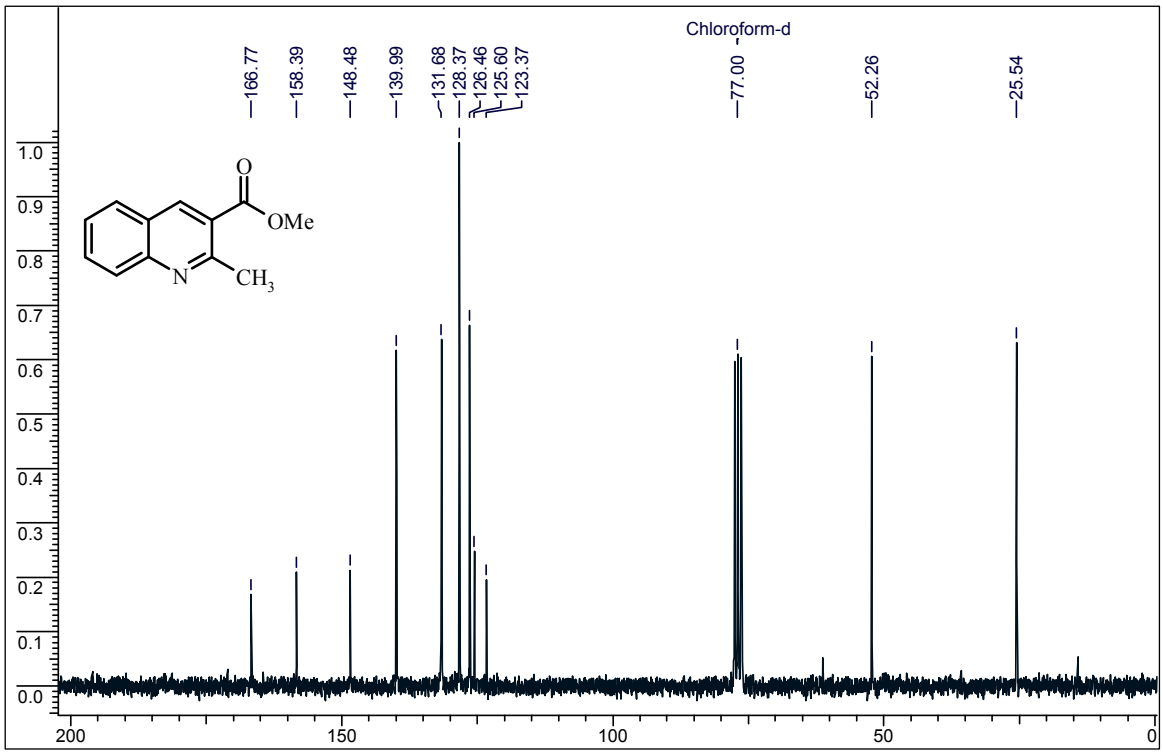
^{1}H NMR spectra of **104**



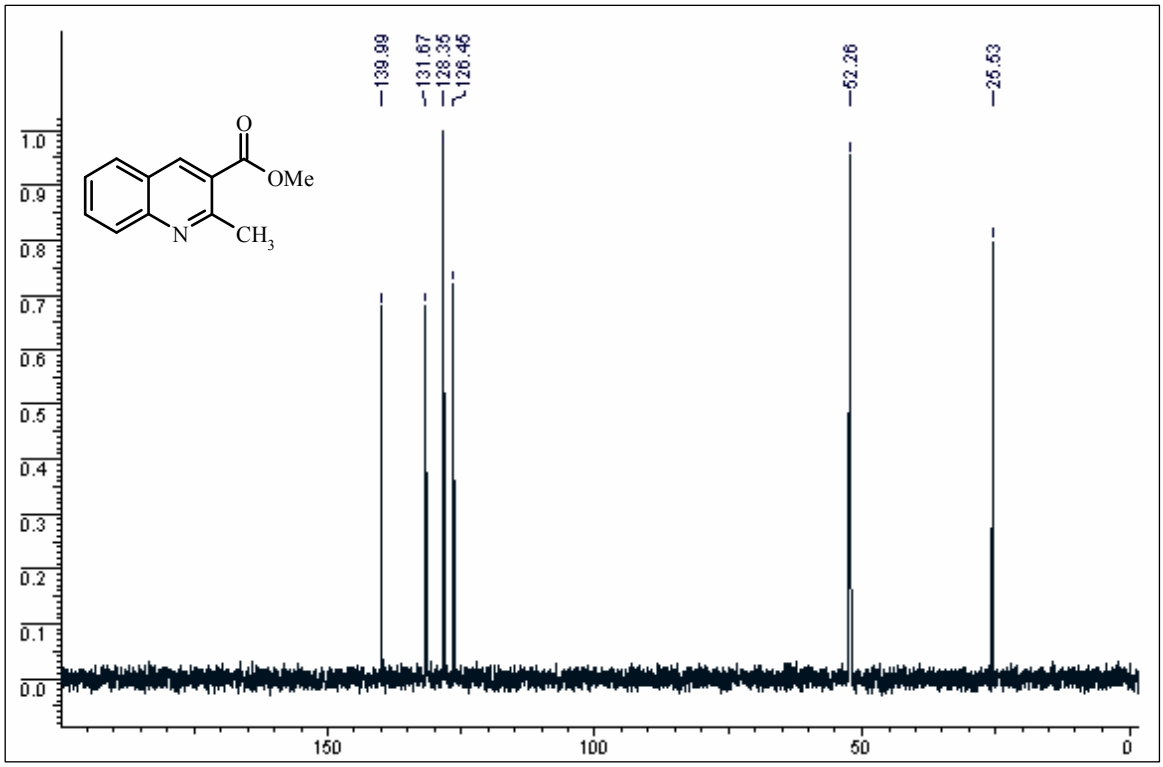
^{1}H NMR spectra of **104** (extended view)



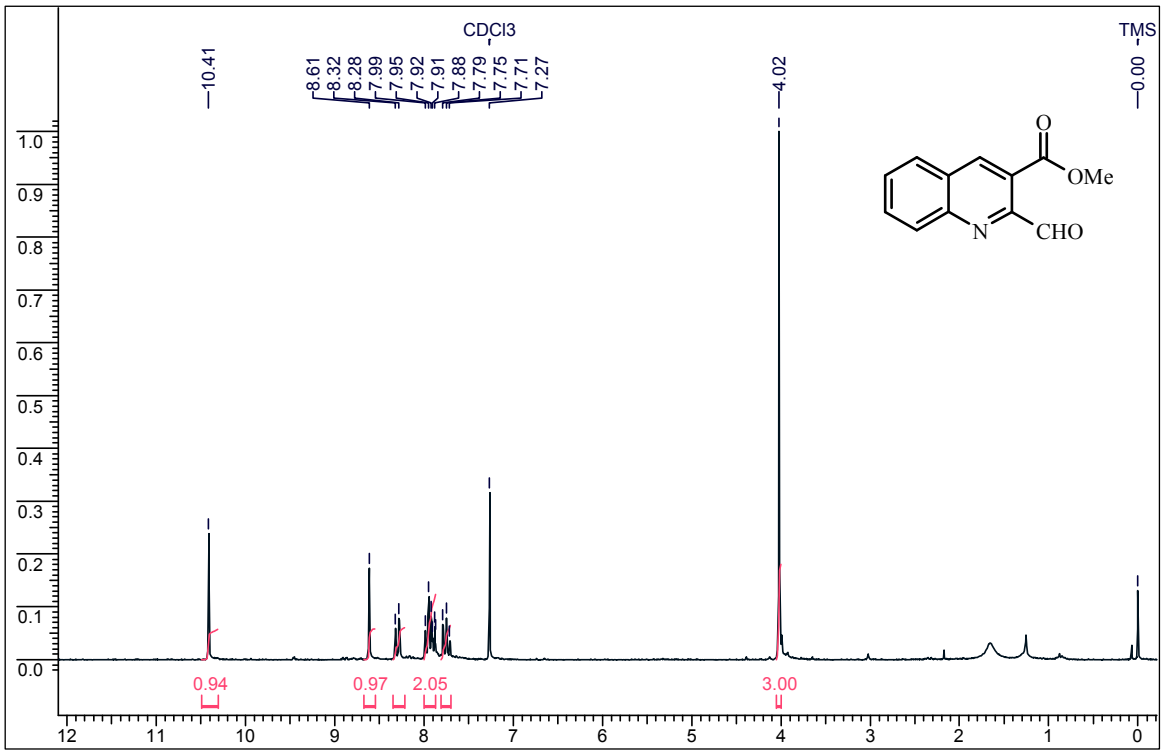
^{13}C NMR spectra of **104**



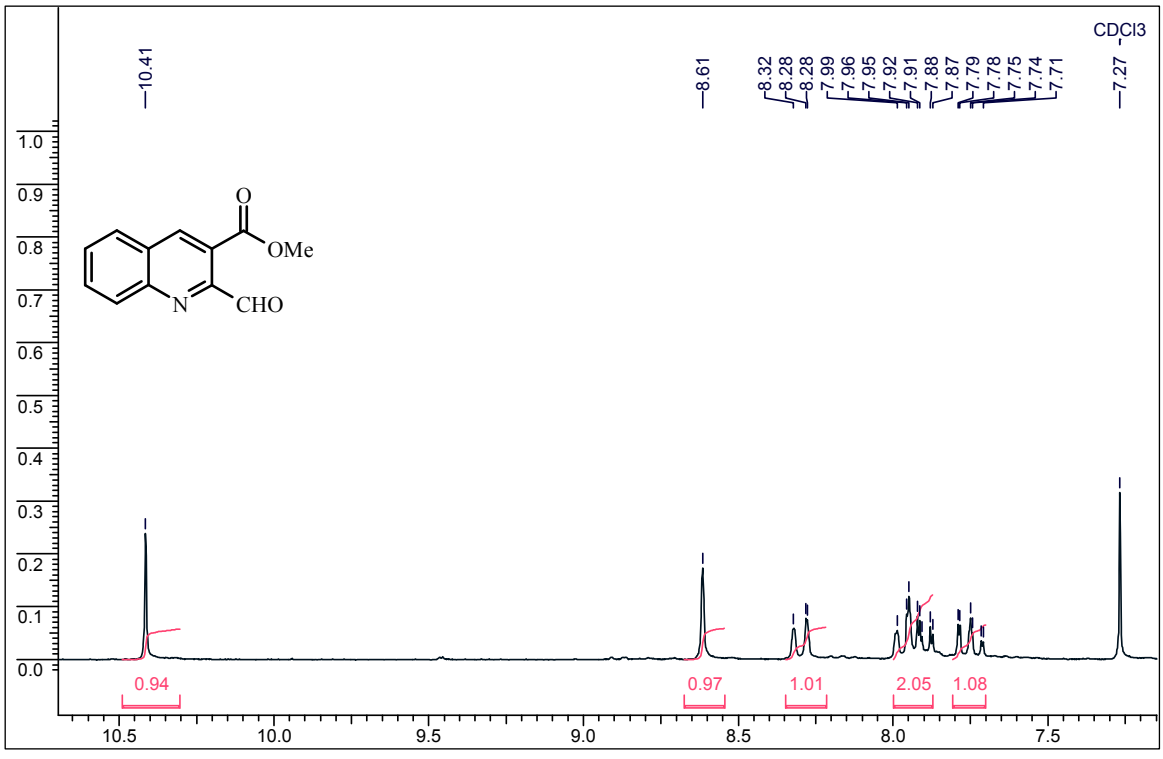
DEPT of **104**



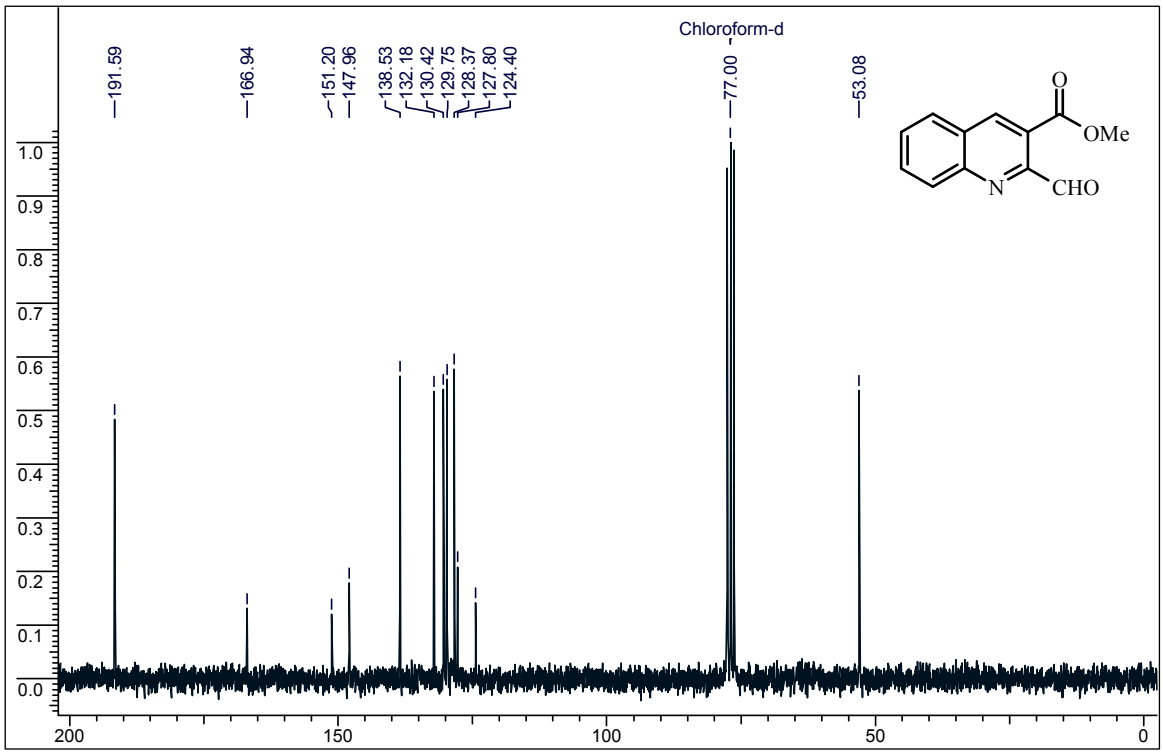
^{1}H NMR spectra of **105**



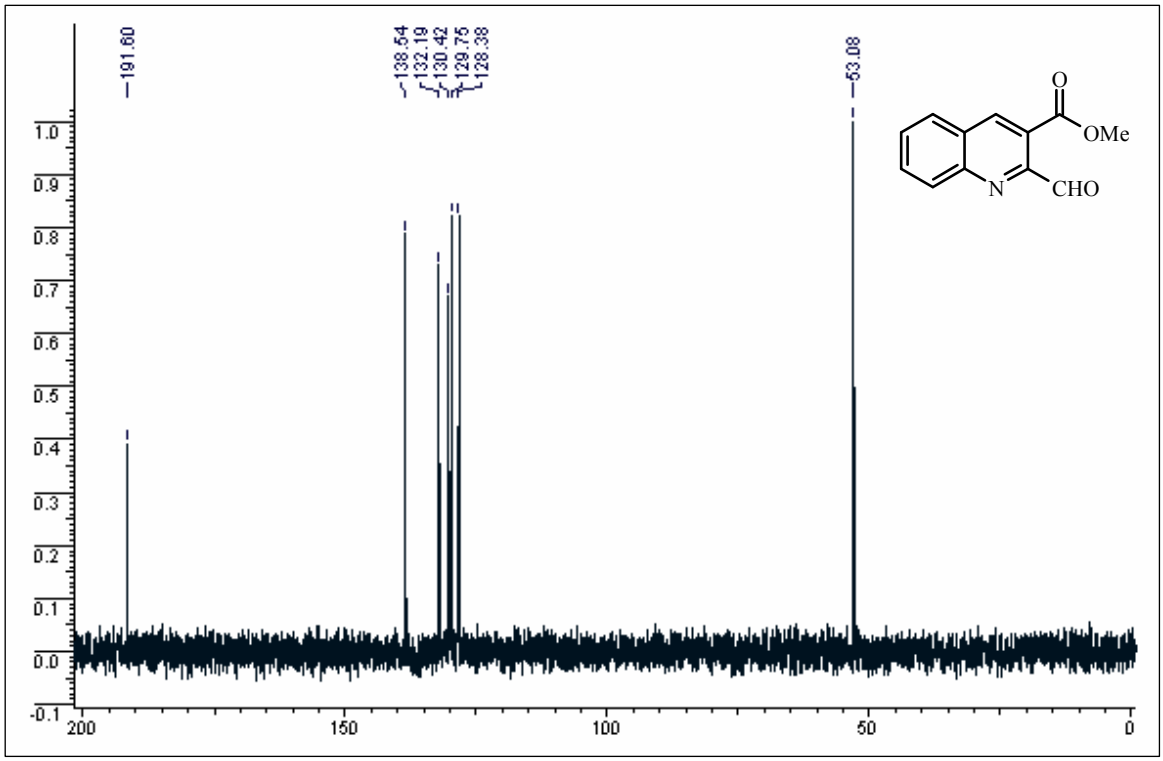
^{1}H NMR spectra of **105** (extended view)



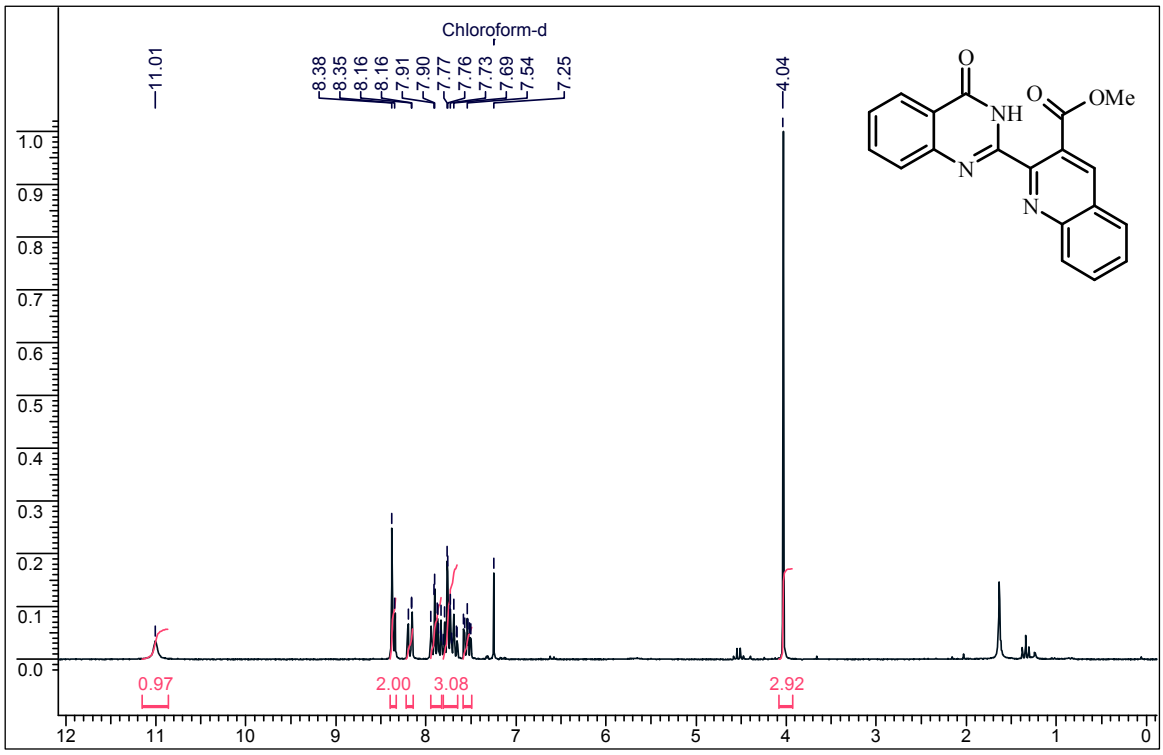
^{13}C NMR spectra of **105**



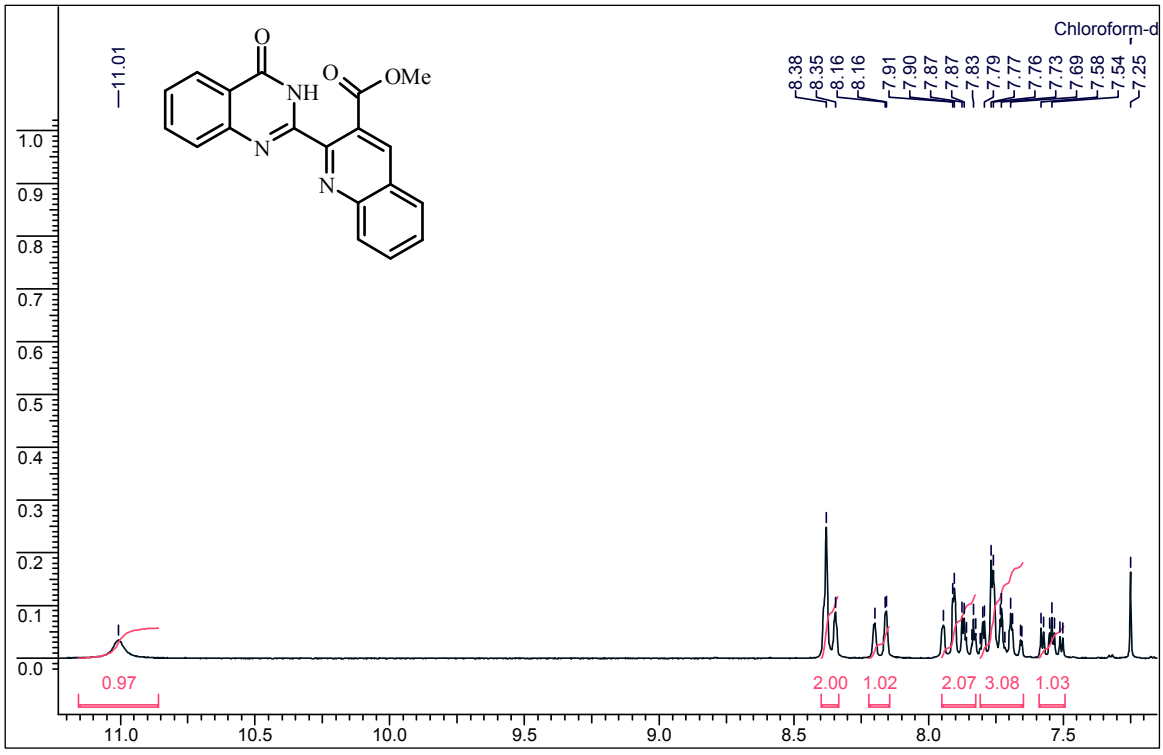
DEPT of **105**



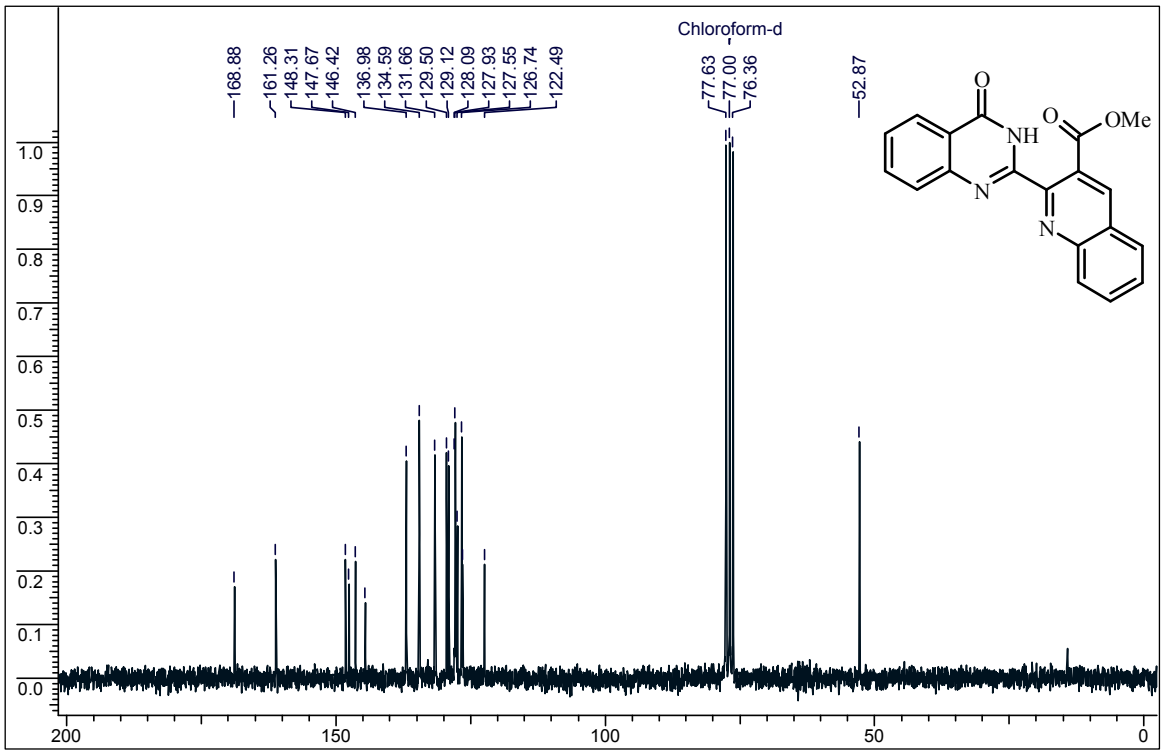
^{1}H NMR spectra of **106**



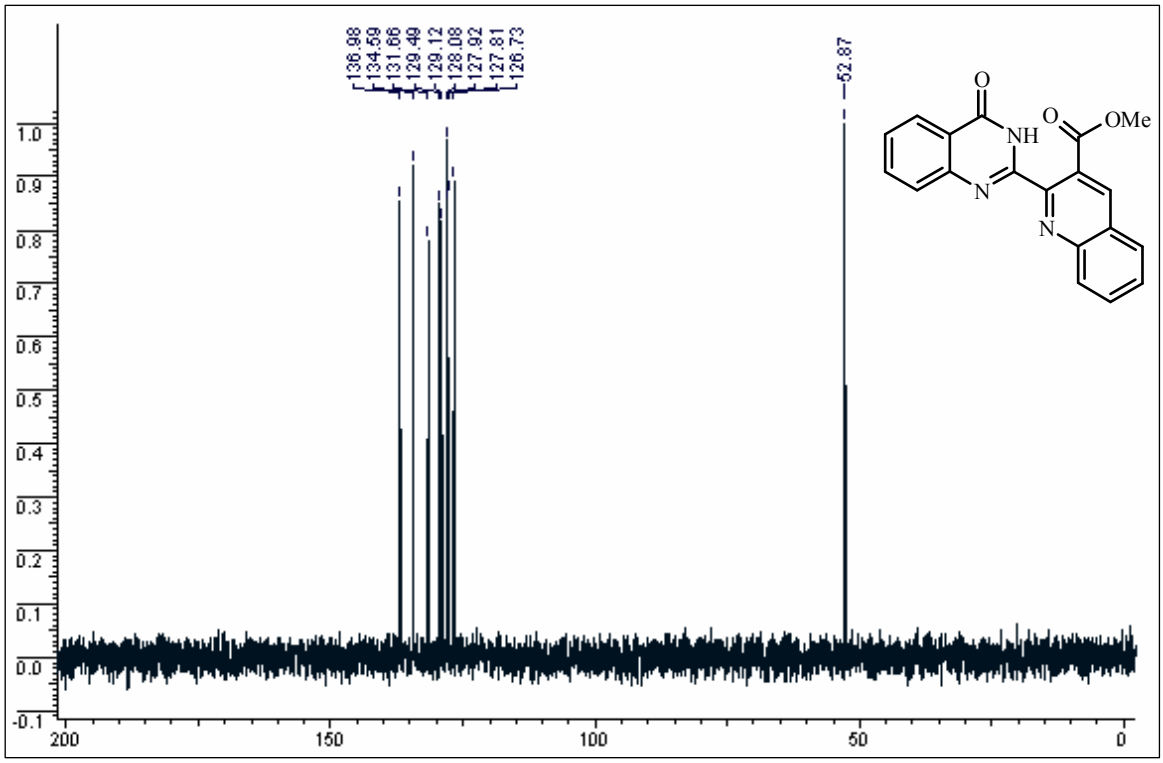
^{1}H NMR spectra of **106** (extended view)



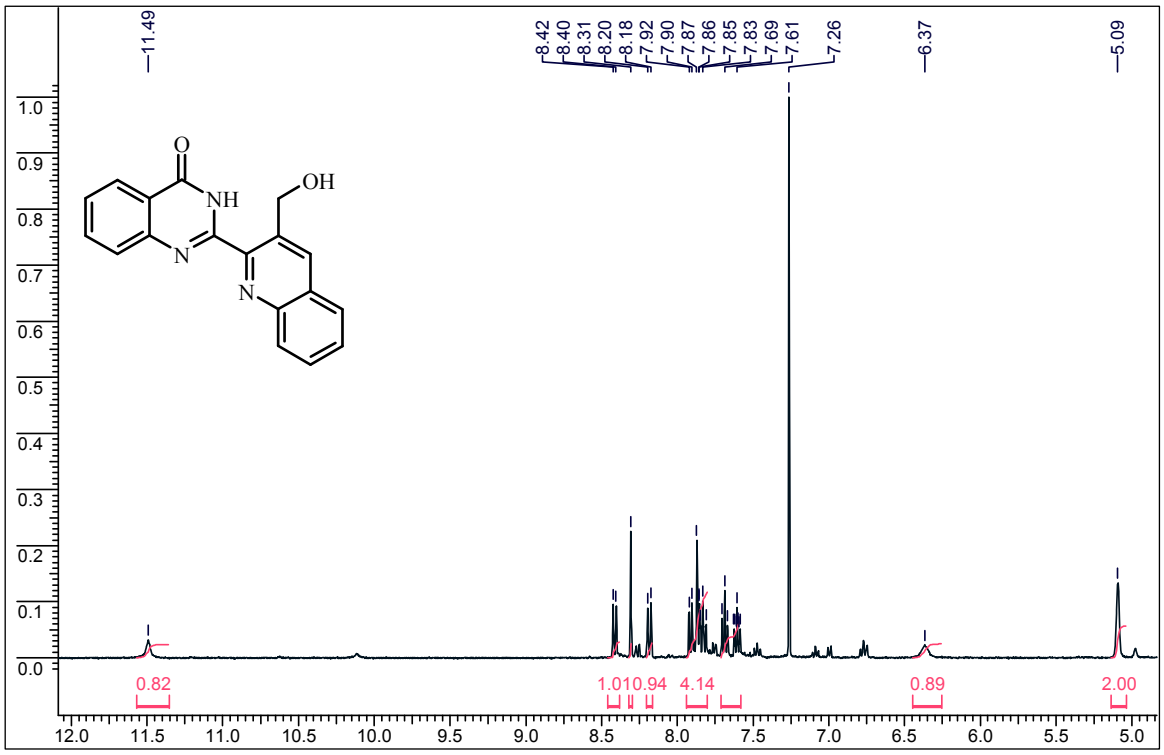
^{13}C NMR spectra of **106**



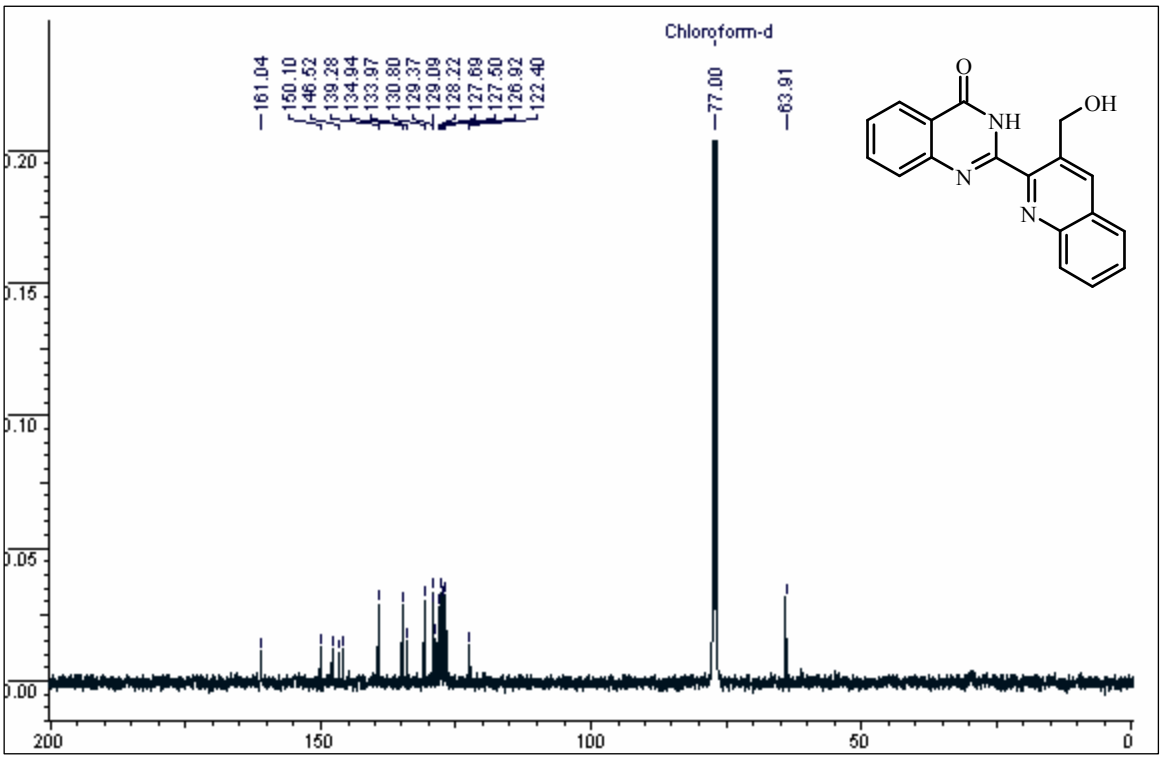
DEPT of **106**



^{1}H NMR spectra of **107** (extended view)



^{13}C NMR spectra of **107**



3.3.7 References

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LIST OF PUBLICATIONS

[1] Formal synthesis of luotonin A

T. M. Potewar and K. V. Srinivasan* (Manuscript under preparation)

[2] Synthesis of tryptanthrin and deoxyvasicinone by regioselective lithiation-intramolecular electrophilic reaction approach

T. M. Potewar, S. A. Ingale and K. V. Srinivasan*

(Manuscript communicated to ***Tetrahedron Lett.)***

[3] An efficient synthesis of 4-aryl-1,4-dihydropyridines from alkyl propiolate under catalyst- and solvent-free conditions

T. M. Potewar, S. A. Ingale and K. V. Srinivasan*

(Manuscript communicated to ***Australian J. Chem.*)**

[4] Catalyst-free efficient synthesis of 2-aminothiazoles in water at ambient temperature

T. M. Potewar, S. A. Ingale and K. V. Srinivasan*

***Tetrahedron,* 2008** (article in press doi:10.1016/j.tet.2008.03.082)

[5] An efficient and eco-friendly synthesis of 2-amino-1,3-selenazoles in an ionic liquid/water system under ambient conditions

T. M. Potewar, S. A. Ingale and K. V. Srinivasan*

***Arkivoc,* 2008** (article in press)

[6] Efficient synthesis of quinoxalines in the ionic liquid, 1-*n*-butylimidazolium tetrafluoroborate, ([Hbim]BF_4) at ambient temperature

T. M. Potewar, S. A. Ingale and K. V. Srinivasan*

***Synthetic Communications,* 2008** (article in press)

[7] Efficient synthesis of 2,4-disubstituted thiazoles using ionic liquid under ambient conditions: a practical approach towards the synthesis of Fanetizole

T. M. Potewar, S. A. Ingale and K. V. Srinivasan*

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T. M. Potewar, Shafi A. Siddiqui, R. J. Lahoti and K. V. Srinivasan*
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