APPLICATION OF IONIC LIQUIDS/ULTRASOUND TOWARDS THE STUDY OF CROSS-COUPLING REACTIONS, MULTI-COMPONENT REACTIONS; SYNTHESIS OF ENAMINONES/Pd ENAMINONE COMPLEXES AND THEIR APPLICATIONS; STUDIES TOWARDS THE SYNTHESIS OF NOVEL BIOLOGICALLY ACTIVE NITROGEN HETEROCYCLES

A Thesis

Submitted to the

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For the degree of

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IN

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BY

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Dedicated to
my beloved parents

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Application of Ionic liquids/ultrasound towards the study of cross-coupling reactions, multi-component reactions; Synthesis of enaminones/Pd enaminone complexes and their applications; Studies towards the synthesis of novel biologically active nitrogen heterocycles**" which is being submitted to the University of Pune for the award of **Doctor of Philosophy in Chemistry** by **Mr. Atul R. Gholap** 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.

Dr. K. V. Srinivasan

(Research Supervisor)

Candidate's Declaration

I hereby declare that the thesis entitled "**Application of Ionic liquids/ultrasound towards the study of cross-coupling reactions, multi-component reactions; Synthesis of enaminones/Pd enaminone complexes and their applications; Studies towards the synthesis of novel biologically active nitrogen heterocycles**" submitted for the award of degree of **Doctor of Philosophy** in **Chemistry** to the University of Pune has not been submitted by me to any other university or institution. This work was carried out by me at the **National Chemical Laboratory**, Pune, India.

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Atul R. Gholap

CONTENTS

Chapter 3: Synthesis of novel biologically active nitrogen heterocycles

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
Aq.	Aqueous
BBIm	1,3-di-*n*-butyl imidazolium
brs	Broad singlet
Bu	Butyl
t-Bu	*tert*-Butyl
Calcd.	Calculated
cat.	Catalytic/catalyst
$CDCl_3$	Deuterated chloroform
conc.	Concentrated
CILs	Chiral ionic liquids
d	Doublet
dd	Doublet of doublet
DCM	Dichloromethane
DHPMs	3,4-dihydropyrimidin-2-(1*H*)-one
DMA	*N,N*-Dimethylacetamide
DMF	*N,N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
equiv.	Equivalents
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
g	Gram
GC	Gas chromatography
h	hours
HBIm	*n*-Butylimidazolium
Hz	Hertz
i-Pr	Isopropyl
Im	Imidazole

ILs	Ionic liquids
IR	Infrared
KHz	Kilohertz
Me	Methyl
MCR	Multicomponent reaction
mg	Miligram
MH	Mizoroki-Heck
min	Minutes
mmol	Milimole
MP	Melting point
NMR	Nuclear magnetic resonance
NMP	*N*-methylpyrrolidine
NR	No reaction
ORTEP	Orthogonal thermal ellipsoid plots
Ph	Phenyl
ppm	Parts per million
p-TSA	*p*-Toluene sulfonic acid
rt	Room temperature
RTILs	Room temperature ionic liquids
RDX	Research Department composition X
s	Singlet
satd.	Saturated
SAED	Selected area electron diffraction
TBAA (Bu_4NOAc)	Tetra-*n*-butyl ammonium acetate
TBAB (Bu_4NBr)	Tetra-*n*-butyl ammonium bromide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane
TEM	Transmission electron microscope

General Remarks

- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}
- ^{1}H Nuclear Magnetic Resonance spectra were recorded on Varian FT-200 MHz (Gemini), AC-200 MHz, MSL-300 MHz, AV-400 MHz and Bruker-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C Nuclear Magnetic Resonance spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz and Bruker-125 MHz spectrometer.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 and anisaldehyde reagent in ethanol as development reagents.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.
- All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

ABSTRACT

Application of Ionic liquids/ultrasound towards the study of cross-coupling reactions, multi-component reactions; Synthesis of enaminones/Pd enaminone complexes and their applications; Studies towards the synthesis of novel biologically active nitrogen heterocycles

The title of the thesis clearly indicates the objective that is to interface synthetic organic chemistry for the development of new methodologies and synthesize biologically active nitrogen heterocycles. The thesis is divided into three chapters. The first chapter is divided into six sections. Section A and Section B deals with the brief introduction of ionic liquids, synthesis and their characterization. Section C deals with the introduction to sonochemistry. Section D, Section E and Section F describes the study of sonochemical transformation such as multi-component Biginelli reaction, Sonogashira reaction and Mizoroki-Heck reaction. The second chapter is divided into four sections. Section A describes the synthesis of enaminones. Section B describes the current therapeutic treatment of mycoses. Section C describes the synthesis and evaluation of antifungal properties of a new series of novel 2-amino-5,6,7,8-tetrahydro-5-oxo-4-phenylquinoline-3-carbonitrile and its analogues. Section D deals with synthesis of Pd enaminone complexes and their application for C–C coupling reaction such as Sonogashira, Heck and Suzuki reaction. Third chapter is divided into two sections; Section A describes a novel process for the synthesis of Cibenzoline and its analogue and Section B describes the efficient synthesis of antifungal pyrimidines from easily accessible Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones.

CHAPTER 1: Application of ionic liquids/ultrasound towards the cross-coupling reactions, multicomponent reactions.

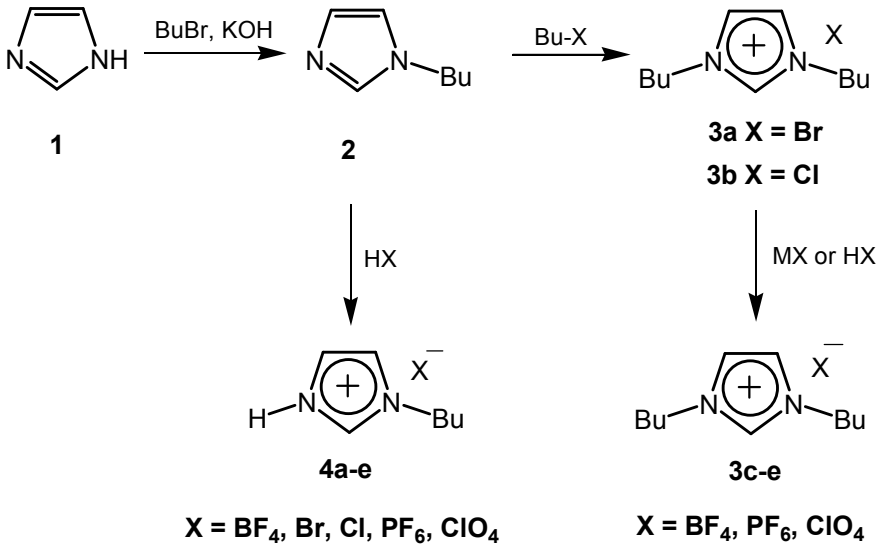
This chapter is divided into six sections. Section A and Section B deals with the brief introduction of ionic liquids, synthesis and their characterization. Section C deals with the introduction to sonochemistry. Section D, Section E and Section F describes the study of

sonochemical transformation such as multi-component Biginelli reaction, Sonogashira reaction and Mizoroki-Heck reaction.

Section A: ***Ionic Liquid-A brief introduction***

The term "ionic liquid" is commonly used for salts whose melting point is relatively low (below 100 °C). In particular, the salts that are liquid at room temperature are called room-temperature ionic liquids, or RTILs. The dramatic growth in ionic liquid research over the past decade has resulted in the development of a huge number of novel ionic liquids, as well as many 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, general method for their synthesis, list of cations and anions reported in the literature, their physico-chemical properties and dependence of it on their structure is described in this Section in details. Also applications of ILs in organic synthesis, new emerging concepts in ILs such as task specific ILs (TSILs), chiral ionic liquids (CILs) is discussed in this section.

Section B: ***Synthesis and Characterization of 1,3-di-n-butyl and 1-n-butyl imidazolium based Ionic Liquids***



Scheme 1.

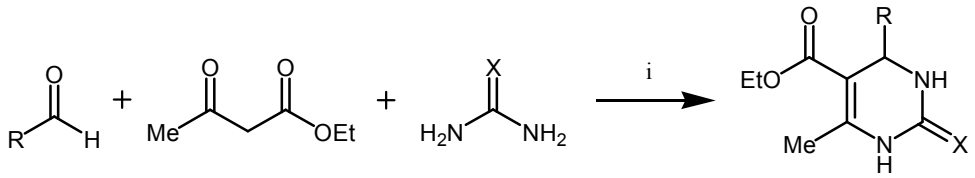
In this section synthesis and characterization of several ionic liquids based upon the imidazolium cations has been described. Two sets of ILs based on 1,3-di-*n*-butylimidazolium [BBIM] and 1-*n*-butylimidazolium [HBIm] salts with varying basicity of the anions were synthesized as shown in **Scheme 1.**

Section C: ***Introduction to Sonochemistry***

Section C covers the introduction to sonochemistry, factors influencing sonochemical process, laboratory equipment, sonochemistry in ionic liquids and the phenomenon of cavitation. The ultrasound mediated reactions in ionic liquids are reviewed.

Section D: ***Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones***

This section starts with an introduction to Biginelli reaction. In the present work, 3,4-Dihydropyrimidin-2-(1*H*)-ones have been synthesized in excellent yields in short reaction time at ambient temperature in the absence of any added catalyst by the reaction of aromatic or aliphatic aldehydes with ethyl acetoacetate (EAA) and urea (or thiourea) in room temperature ionic liquid [HBIm] BF_4 under ultrasound irradiation (**Scheme 2**). The evidence for the role of IL in promoting this multicomponent reaction has been given. Based on this evidence, a plausible mechanistic pathway has been postulated.



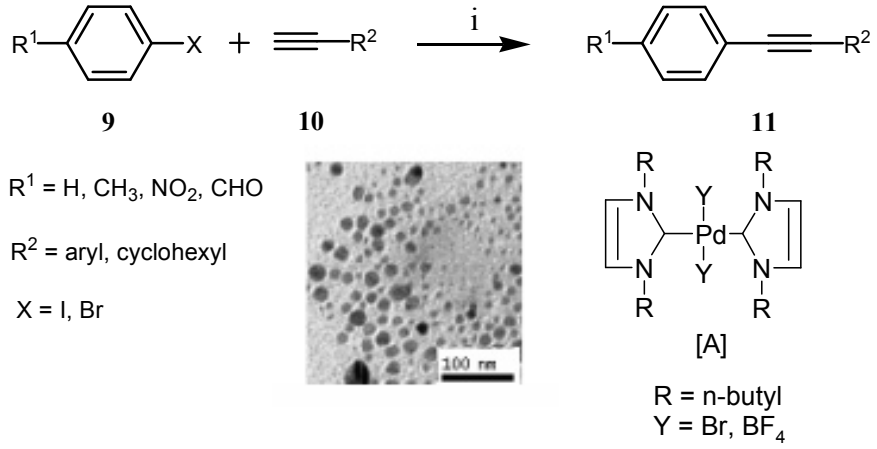
5 **6** **7** **8**

Scheme 2. Reaction conditions: (i) [HBIm] BF_4,)))), 28 ºC, 45-70 min, 82-97%.

Section E: ***The Sonogashira reaction***

The present study deals with the ultrasound promoted palladium catalyzed C-C bond formation Sonogashira reactions in room temperature ionic liquids as well as in molecular solvents at ambient temperature. This section starts with an introduction to Sonogashira reaction. Methods, types of ligands, conditions and mechanism are discussed. In the present work, palladium catalyzed Sonogashira reaction of aryl halide with terminal acetylenes was carried out in ILs 1,3-di-*n*-butylimidazolium

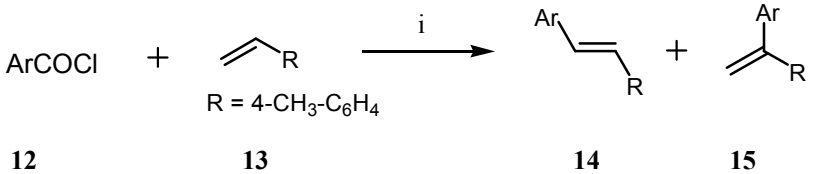
tetrafluoroborate [BBIm]BF_4 as well as in molecular solvent like acetone under ultrasound irradiation at ambient conditions (**Scheme 3**). The formation of Palladium bis carbene complex [A] in ionic liquid medium and the generation of palladium nanoparticles under the ultrasound irradiation have been shown and investigated by transmission electron microscope (TEM) studies.



Scheme 3. Reaction conditions: (i) $PdCl_2$, TEA, acetone**,**))))), (50 KHz), 30 ºC, 15-90 min, 66-85% or [BBIm]BF_4,))))), (50 KHz), 30 ºC, 2-3 h, 68-93%.

Section F: ***The Mizoroki-Heck reaction***

This section describes the sonochemical decarbonylation of acid chlorides catalyzed by palladium (0) nanoparticles at ambient conditions. The decarbonylative Heck coupling was carried out in short reaction times with good isolated yields at ambient temperature under ultrasonic irradiation in acetonitrile in the presence of $Pd(OAc)_2$ and 1,3-di-*n*-benzylimidazolium bromide as a additive in the absence of any base. The Mizoroki-Heck reaction proceeds at ambient temperature (30 °C) with considerably enhanced reaction rate through the formation of stabilized clusters of zero-valent Pd nanoparticles in acetonitrile medium under sonolytic conditions (**Scheme 4**).



Scheme 4. Reaction conditions: (i) $Pd(OAc)_2$, 1,3 di-*n*-benzylimidazolium bromide, MeCN,))))), slow stream of N_2, 3 h, 66-76%.

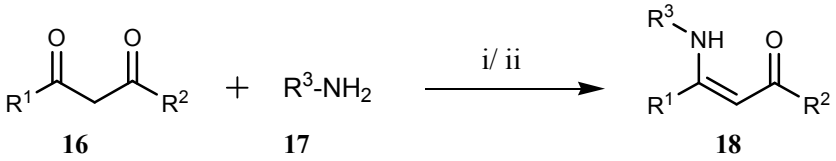
Sonochemical reactions proceed via acoustic cavitation generating transient cavitation bubbles, the implosive collapse of which under adiabatic conditions gives rise to high temperature and pressure. As a result of this cavitation phenomenon, "micro bombs" with high temperature and pressure are generated for a very short period of time facilitating the oxidative addition of an aroyl chloride toward Pd(0) nano particles generated *in situ* and the subsequent decarbonylation of the resulting aroylpalladium species affords an arylpalladium intermediate. Insertion of an alkene to the intermediate and β-hydrogen elimination give the corresponding stilbene.

CHAPTER 2: Synthesis of enaminones/Pd enaminone complexes and their applications.

Enaminones are polyfunctionalized compounds possessing both electrophilic and nucleophilic properties. Due to this type of the reactivity they are well-established, three-carbon building blocks in heterocyclic chemistry. This chapter is divided into four sections. Section A describes the synthesis of enaminones using silica chloride in a heterogeneous as well as an ionic liquid in a homogenous medium at room temperature. Section B describes the current therapeutic treatment of mycoses. Section C describes the synthesis and evaluation of antifungal properties of a new series of novel 2-amino-5, 6, 7, 8-tetrahydro-5-oxo-4-phenylquinoline-3-carbonitrile and its analogues. Section D deals with synthesis of Pd enaminone complexes and their application for C–C coupling reaction such as Sonogashira, Heck and Suzuki reaction.

Section A: *Synthesis of enaminones*

Enaminones have attracted much attention due to the fact that they are important synthons for the synthesis of many biologically active compounds. This section describes the use of silica chloride as a heterogeneous catalyst for the regioselective synthesis of β-amino-α, β-unsaturated esters and ketones. Similar regioselective synthesis was also performed using an ionic liquid 1-*n*-butyl imidazolium tetrafluoroborate [HBIm] BF_4 as a recyclable homogeneous medium as well as a promoter without the need for any added catalyst. Both the methods were found to be remarkably rapid and afforded the β-enaminones in excellent isolated yields (**Scheme 5**).



16 **17** **18**

$R^1 = CH_3$, Ph; $R^2 = CH_3$, OEt; $-(CH_2)_3-$; R^3 = H, Bu, aryl

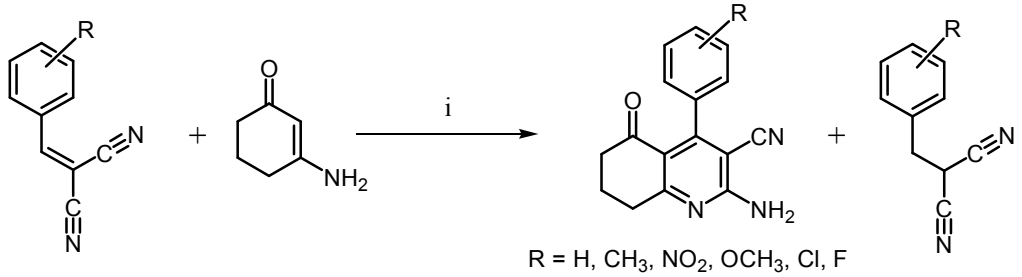
Scheme 5. Reaction conditions: (i) Silica chloride, solvent-free, rt, 5-15 min, 90-96%.
(ii) $[HBIm]BF_4$, rt, 5-30 min, 89-93%.

Section B: ***The current therapeutic treatment of mycoses***

This section describes the current available antifungal agents currently utilized for the treatment of mycoses and their targets in fungal pathogens.

Section C: ***Synthesis of novel antifungal agents***

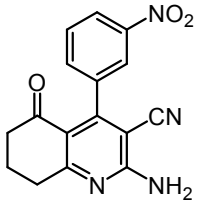
This section describes the synthesis of new series of the novel 2-amino-5-oxo-4-phenyl-5, 6, 7, 8-tetrahydroquinoline-3-carbonitrile and its various analogues in excellent isolated yields by refluxing a mixture of various arylidenemalononitrile **19** and 3-amino-2-cyclohexen-1-one in 1-propanol **20** in the absence of any added catalyst (**Scheme 6**). All the synthesized compounds were evaluated for their antifungal activity by disc-diffusion method. The relationships between functional group variation and biological activity of the evaluated compounds are discussed.



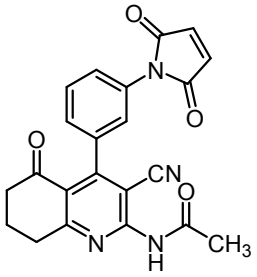
19 **20** **21** **22**

Scheme 6. Reaction conditions: (i) *n*-propanol, reflux, 4-7 h, 81-94%.

To study the significance of each group on core structure vis-á-vis the antifungal activity, the respective modifications of amino and cyano functional groups were carried out and their antifungal activity have been discussed. Antiproliferative activity of most active antifungal compound among the synthesized compounds have been checked.



23



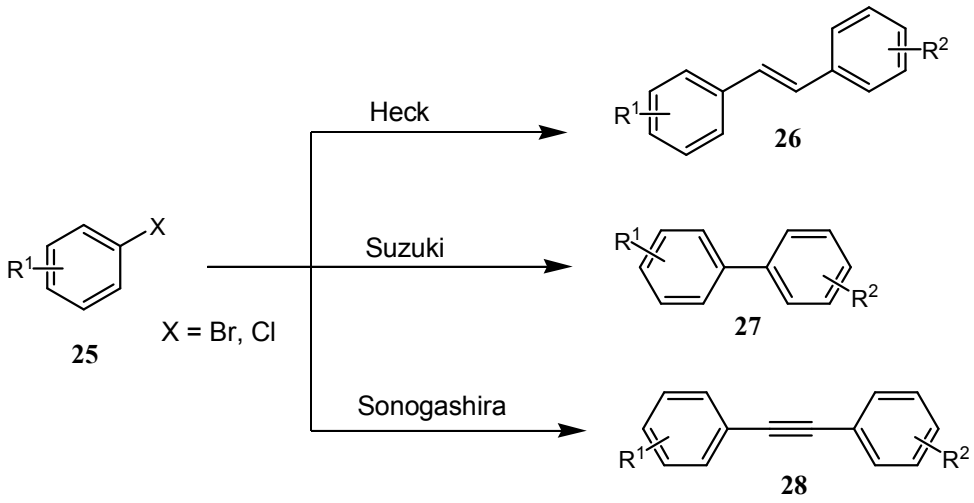
24

Figure 1.

Compound **23** and **24** (**Fig. 1**) are most active compounds among the synthesized compounds against the *C. albicans* 1 and 2, *F. Oxysporum* and *Mucor*. The antiproliferative activities of compounds **23** and **24** were similar to that of amphotericin B though only slight differences in the levels of toxicities to the two cell lines (MCF-7, Hep-3B) were observed.

Section D: ***Synthesis of Pd-enaminone complexes and their applications in C-C coupling reactions.***

The present section deals with the synthesize of novel Pd enaminone complex as a monoanionic bidentate complex starting from easily available enaminone. The anions $[R'C(O)CHC(NAr)R]^-$ generated from the above enaminones offer potential isoelectronic alternatives to the cyclopentadienyl-based anions and can be used as good chelating ligands for palladium complexes.



Scheme 7.

In the present work synthesis of two enaminones [$C_6H_5C(O)CH=C$-(NH-C_6H_2-2,4,6 $(CH_3)_3)CH_3$] and [$C_6H_5C(O)CH=C$-(NH-C_6H_2-3,4,5$(OCH_3)_3)CH_3$] are carried out and their Palladium complexes are prepared and characterized by spectral, elemental and X-ray crystallography. The catalytic activity of these Pd (II) enaminone complexes toward the Suzuki, Heck and Sonogashira reaction were investigated (**Scheme 7**).

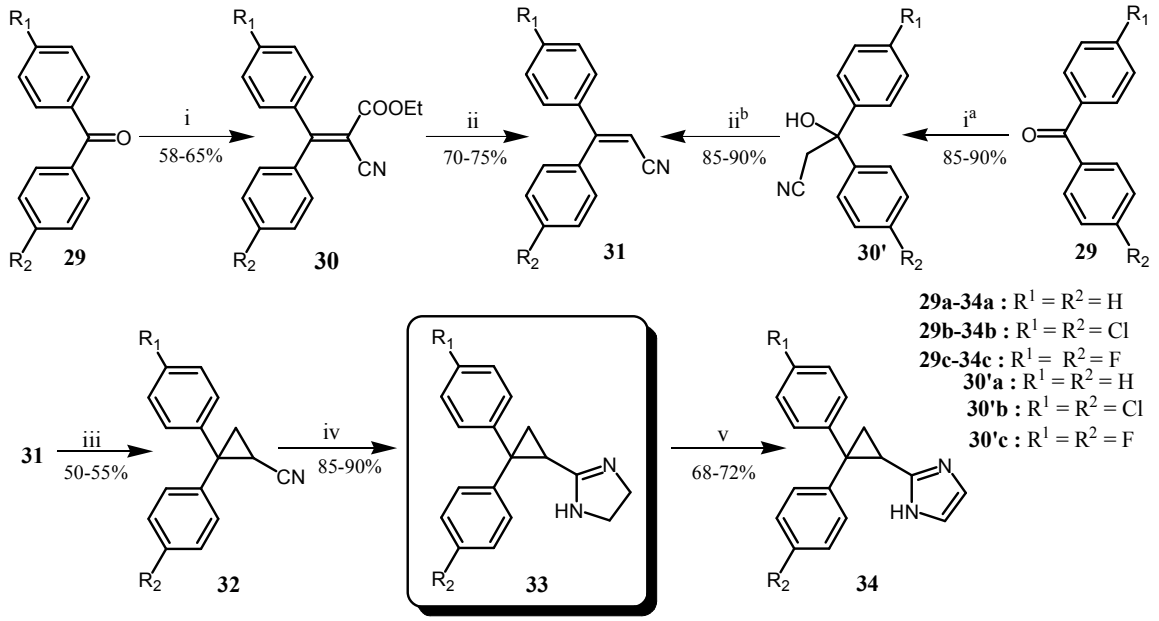
CHAPTER 3: Synthesis of novel biologically active nitrogen heterocycles

There are a large number of synthetic heterocyclic compounds with important applications and many are valuable intermediates in organic synthesis. Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. Therefore, organic chemists have been making extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. This chapter divided into two sections.

Section A: ***Synthesis of class I antiarrhythmic agent (±) cibenzoline and its analogues***

Atrial fibrillation represents an important medical problem, not only because of increased incidence in elderly population, but also a major cause of embolic stroke. (±)-2-(2, 2-diphenylcyclopropyl)-2-imidazoline succinate has been clinically used as one of the Class I antiarrhythmic agents. Cibenzoline is marketed under the trade names Cipralan (USPA) and Exacor (Monsanto). In this section we have described an improved strategy for the synthesis of Cibenzoline and its analogs from commercially available benzophenones as starting material avoiding toxic reagents like mercuric oxide and avoiding high temperature for the final condensation process.

The synthesis of imidazoles **34a-34c** is outlined in **Scheme 8.** Thus benzophenone **29** was converted to the tetrasubstituted olefin **30** with ethylcyanoacetate by Knoevenagel condensation. The cyanoester **30** was isolated by column chromatography. The deethoxycarbonylation of 2-cyano-2-alkenoates **30** to the unsaturated nitrile **31** was carried out by Krapcho's protocol using wet DMSO containing sodium chloride in good yields. The synthesis of unsaturated nitrile **31** by sequence of Knoevenagel condensation followed by deethoxycarbonylation was inconvenient due to longer reaction time (90 h) and lower yields (58-65%). So as to achieve the higher yields and short reaction time, synthesis of intermediate **31** was also carried out by an alternative route.



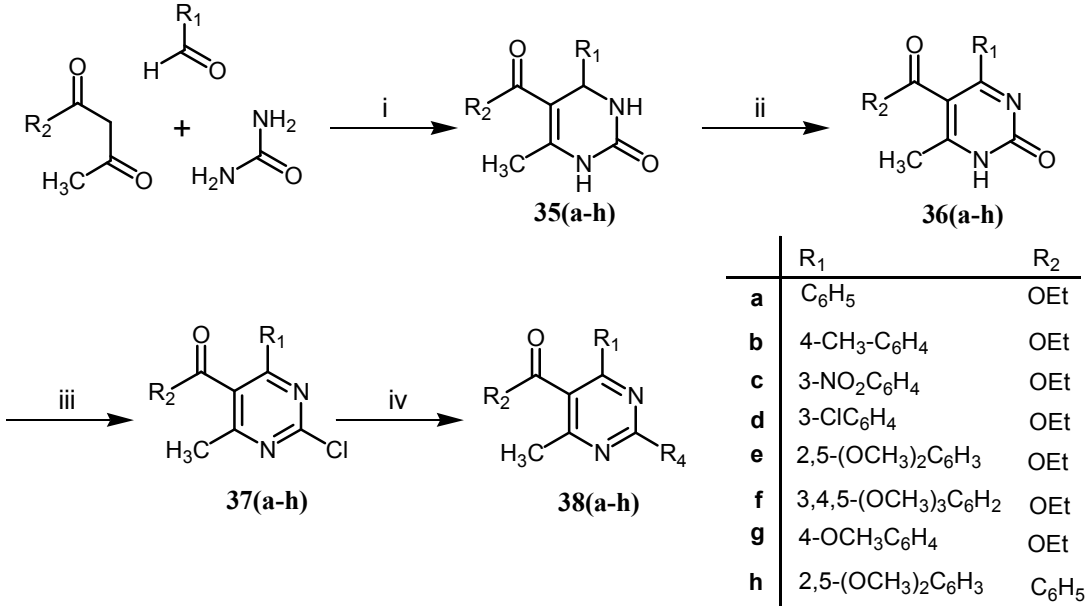
Scheme 8. Reaction conditions: (i) $CNCH_2COOEt$, $HOAc/C_6H_6$, β-alanine at reflux, 90 h; (i^a) CH_3CN, *n*-BuLi, dry THF, -80°C, 2 h; (ii) NaCl, H_2O, DMSO, 160-170 °C, 4 h; (ii^b) $SOCl_2$, dry pyridine, dry DCM, 0°C to rt, 3 h; (iii) $Me_3S(O)I$, NaH, DMSO, rt, 24 h; (iv) sulfur, ethylenediamine, reflux, 4 h; (v) (diacetoxyiodo) benzene, K_2CO_3, DMSO, rt, 48 h.

The intermediate **31** can be prepared starting from substituted benzophenone. The ionization of acetonitrile and its condensation with substituted benzophenone were both carried out at –80 °C to get the β-hydroxynitrile followed by the elimination of hydroxyl group using thionyl chloride/pyridine gave exclusively compound **31**. Unsaturated nitrile was cyclopropanated by addition of trimethyl sulfoxonium iodide and sodium hydride in dry DMSO at room temperature to afford the nitriles as a mixture of diastereomers **32**. The conversion of nitrile group to 2-imidazoline was achieved by refluxing **33** with ethylenediamine in the presence of a catalytic amount of sulfur. The oxidation of imidazoline to imidazole **34** derivatives was carried out smoothly in good yields using (diacetoxyiodo) benzene in presence of K_2CO_3 in DMSO at room temperature.

Section B: ***Synthesis of novel antifungal pyrimidines***

Pyrimidines represent an important class of heterocycles and their structural framework is a key constituent for numerous pharmacophores with antibacterial, antimicrobial, antifungal, antimycotic, antiviral and antitumar activity. Besides this pyrimidine

derivative MKC-442 is already in clinical trials and similar compounds are expected to inhibit the HIV virus. The Biginelli DHPMs are chemical precursors of multifunctionalized pyrimidines. However there is no methodology reported for the direct arylation of the oxidized products of DHPMs, the corresponding 2-halopyrimidines **37**. In this section we have described a short and efficient conversion of Biginelli DHPMs to multifunctionalized pyrimidines via oxidation, halogenation followed by Suzuki/Sonogashira cross coupling reactions (**Scheme 9**). All the synthesized compounds were evaluated *in vitro* for their antifungal activities against *C. albicans*, *C. neoformans*, *B. poitrasii*, *Y. lipolytica* and *F. oxysporum* and antibacterial activities against Gram-negative *E. coli* and Gram- positive *S. aureus.*



	R_1	R_2
a	C_6H_5	OEt
b	4-CH_3-C_6H_4	OEt
c	3-$NO_2C_6H_4$	OEt
d	3-ClC_6H_4	OEt
e	2,5-$(OCH_3)_2C_6H_3$	OEt
f	3,4,5-$(OCH_3)_3C_6H_2$	OEt
g	4-$OCH_3C_6H_4$	OEt
h	2,5-$(OCH_3)_2C_6H_3$	C_6H_5

Scheme 9. Reaction conditions: (i) $[HBIm]BF_4$,)))), 70 min, 80-92%; (ii) ceric ammonium nitrate (CAN), acetone, $NaHCO_3$, -5 °C to rt, 12 h, 70-92%; (iii) *N,N*-dimethylaniline, $POCl_3$, reflux, 12 h, 68-82%; (iv) 4-(*N,N*-dimethylamino)phenylboronic acid, $Pd(OAc)_2$, PPh_3, sat. solution of Na_2CO_3,: Dioxane (4:6), 110 °C, 3-5 h., 78-95%.

CHAPTER-1

Application of Ionic liquids/ultrasound towards the study of cross-coupling reactions, multi-component reactions

Section-A

Ionic Liquids-

A Brief Introduction

Introduction to Ionic Liquids

1.1.1 Introduction

It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry. 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.

A reasonable working definition of green chemistry can be formulated as follows: *green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.*

Chemistry is undeniably a very prominent part of our daily lives. Food and drink has been made safe to consume, the development of cosmetics has enabled us to beautify and admire our appearances and the whole area of pharmaceuticals has allowed the development and synthesis of new cures for illnesses and diseases, all as a result of chemistry. However, in the chemical industry, solvents are used in large quantities. In particular, in fine-chemical and pharmaceutical production, large amounts are used per mass of final products. Therefore, solvents define a major part of the environmental performance of a process and also impact on cost, safety and health issues as well as the continuously increasing air pollution has brought about changes in the global climate. The idea of "green" solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production. Recently, four directions towards green solvents have been developed:

(i) substitution of hazardous solvents with ones that show better EHS (environmental, health and safety) properties, such as increased biodegradability or reduced ozone depletion potential[1-3] (ii) use of "bio-solvents," i.e. solvents produced with renewable resources such as ethanol produced by fermentation of sugar-containing feeds, starchy feed materials or lignocelluloses materials[4] (this substitution of petrochemically fabricated solvents leads to an avoidance of fossil resource use and fossil fuel CO_2 emissions to the environment); (iii) substitution of organic solvents either with

supercritical fluids that are environmentally harmless (e.g. the use of supercritical CO_2 in polymer processing[5-8] avoids the use of chlorofluorocarbons, and thus reduces ozone depletion); (iv) Use of non-volatile and thermally stable ionic liquids as solvents in the place of traditional industrial solvents, most of which are volatile organic compounds (VOCs). Replacement of conventional solvents by ionic liquids would prevent the emission of VOCs, a major source of environmental pollution. Ionic liquids can be designed to be environmentally benign, with large potential benefits for sustainable chemistry.

A green solvent must ideally have negligible vapour pressure, high boiling point, be non-toxic, have capacity to dissolve wide range of organic, inorganic and organometallic compounds, it should be chemically and physically stable, recyclable, reusable, inexpensive and eventually easy to handle. In addition to these, solvents that allow more selective and rapid transformations will have a significant impact. Therefore, many attempts have been made to substitute conventional organic solvents with novel alternative reaction media which include: supercritical fluids, per fluorinated solvents, low melting polymers, water and more particularly ionic liquids.

1.1.2 Alternative solvents in organic synthesis

1.1.2.1 Supercritical fluids

A supercritical fluid (SCF) is defined as a substance above its critical temperature (T_c) and critical pressure (P_c). Supercritical carbon dioxide has been receiving increasing attention as an alternative reaction medium in recent years. Several features of $scCO_2$ make it an interesting solvent in the context of green chemistry and catalysis. The critical pressure and temperature for carbon dioxide are moderate (74 atm and 31.1 ºC) and these conditions are easily achieved in laboratory. Thus the amount of energy required to generate supercritical carbon dioxide is relatively small. In addition, carbon dioxide is nontoxic, chemically inert towards many substances, nonflammable and simple depressurization results in its removal. It is miscible with, e.g. hydrogen, making it an interesting solvent for hydrogenation and hydroformylation. Furthermore, the physical properties of $scCO_2$, e.g. polarity, can be tuned by manipulation of the temperature and pressure. Although it is a greenhouse gas its use involves no net addition to the atmosphere; it is borrowed as it were. Its main uses are as a replacement for VOCs in

extraction processes. For example it is widely used for the decaffeination of coffee where it replaced the use of a chlorinated hydrocarbon.

1.1.2.2 Poly(ethylene glycol) – PEG

Poly (ethylene glycol) is the linear polymer formed from the polymerization of ethylene oxide. PEG usually indicates the polyether of molecular weight less than 20,000 and is known to be inexpensive, thermally stable, recoverable, biologically compatible and non-toxic.[9] Furthermore, PEG and its monomethylethers have a low vapor pressure, are nonflammable, present simple workup procedures and can be recycled. For these reasons PEG is considered to be an environmentally benign alternative to chemical volatile solvents and a highly practical medium for organic reactions.

PEG is most commonly employed as support for various transformations (PEG 2,000-20,000)[10] and as a biologically acceptable polymer used extensively in drug delivery and bioconjugates as tools for diagnostics but it can also be employed as an efficient medium for phase transfer catalysts. Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter its properties can not be easily tuned. One of the major drawbacks in its use in organic reactions that also applies to ionic liquids is the inconvenience of using organic solvents to extract the products, even though $scCO_2$ can also be used in both cases. Probably due to the higher popularity of other alternative solvents, especially ionic liquids, there are only a few examples in the literature that uses PEG as solvent in organic reactions.

1.1.2.3 Perfluorinated (fluorous) solvents

The fluorous compounds were defined as being compounds that are highly fluorinated and based upon sp^3-hybridized carbons. Fluorous (perfluorinated) solvents as perfuoroalkenes, perfluorolkyl ethers and perfluoroalkylamines are generally chemically benign and environmentally-friendly for being non-toxic (unlike the freons), nonflammable, thermally stable, recyclable, and for their high ability to dissolve oxygen gas, which is an advantage used in medical technology.

Fluorous fluids have very unusual properties, such as high density and high stability (mainly due to the stability of the C-F bond), low solvent strength, and extremely low solubility in water and organic solvent,[11] although they are miscible at higher temperature. The poor solubility of fluorinated solvents can be explained based on their low surface tensions, low intermolecular interactions, high densities and low dielectric

constants. The manufacture of these fluorous solvents is not so simple generally requiring the use of huge amounts of high volatile organic solvents and toxic reagents such as fluorine gas and HF.

1.1.2.4 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[12] and Grieco[13] 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. For instance, the rates and stereoselectivities of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. The use of organic cosolvents or surfactants helps to increase the solubility of nonpolar reactants in water by disrupting the strong hydrogen-bond network of pure water.[14] The discovery that Lewis acids, especially some metal triflates, can efficiently catalyze reactions in water also contributed to popularize it as solvent in organic reactions.[15]

1.1.2.5 Ionic liquid

In the past two decades, ionic liquids have been widely used as "green solvents" replacing traditional organic solvents for organic synthesis and catalysis. The great interest for such compounds relies on the fact that they posses several attractive properties such as negligible vapor pressure, chemical and thermal stability, nonflammability, high ionic conductivity, wide electrochemical potential window and moreover the ability to act as catalysts. In contrast to conventional solvents that are constituted of molecules, ionic liquids consist of ions and are liquid at room temperature (RTILs) or have a low melting point (generally below 100ºC). This ionic character allows them to potentially behave in a very different manner when used as solvents as compared to conventional molecular liquids.

By changing the anion or alkyl chain of the cation, one can vary physical properties such as the hydrophobicity, viscosity, density, and solvation of the ionic liquid system. For this reason they have been referred to as "designer solvents"[16] ILs can be easily separated from the organic products of a reaction but this process usually requires extraction with a

non polar organic solvent. Their high viscosities make stirring and homogenization of the reaction medium difficult, which causes slow dissolution of solids. Other drawbacks are their higher costs as compared to most organic solvents and also little is known about their toxicity.

1.1.3 Brief history of ionic liquid

The early history of ionic liquids began in 1914 when the first report of a room temperature molten salt was reported by Walden.[17] He reported the physical properties of ethylammonium nitrate, $[C_2H_5NH_3]\ NO_3$, which has a melting point of 12 ºC, formed by the reaction of ethylamine with concentrated nitric acid. This salt is liquid at room temperature but usually contains a small amount of water (200-600ppm).

The first ionic liquid with chloroaluminate ions were developed in 1948 for applications in aluminium electroplating by Hurley and Weir[18] by mixing and warming 1-ethylpyridinium chloride with aluminum chloride. As early as 1967, a publication by Swain *et al.* described the use of tetra-*n*-hexylammonium benzoate as a solvent for kinetic and electrochemical investigation.[19] Room temperature ionic liquids only really reached a more general audience with the reopening of development in this area by the groups of Osteryoung *et al.*[20] and Hussey *et al.*[21] in 1970s and 1980s, they carried out extensive research on organic chloride-aluminium chloride ambient temperature ionic liquids and the first major review of room temperature ionic liquids was written by Hussey.[22] The ionic liquids based on $AlCl_3$ can be regarded as the first generation of ionic liquids.

The first publications in which ionic liquids were described as new reaction media and catalyst for organic synthesis appeared in 1986s. Acidic ionic liquids with chloroaluminate ions proved to be effective Friedal-Crafts catalysts.[23] Phosphonium halide melts were used successfully in nucleophilic aromatic substitution reactions.[24]

The use of ionic liquids as solvents for homogeneous transition metal catalysts was described for the first time in 1990 by Chauvin *et al.* and by Wilkes *et al*. Chauvin's group dissolved nickel catalyst in weakly acidic chloroaluminate melts and investigated the resulting ionic catalysed solutions for the dimerization of propene.[25]Also Wilkes *et al.* used weekly acidic chloroaluminate melts and studied therein in the ethylene polymerization with Ziegler-Natta catalyst.[26]

The hygroscopic nature of $AlCl_3$ based ionic liquids has delayed the progress in their use in many applications since they must be prepared and handled under inert gas atmosphere. Thus, the synthesis of air and water stable ionic liquids, which are considered as the second generation of ionic liquids, attracted further interest in the use of ionic liquids in various fields. In 1992, Wilkes and Zaworotko[26] 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 prepared and safely stored outside of an inert atmosphere. Generally, these ionic liquids are water insensitive, however, the exposure to moisture for a long time can cause some changes in their physical and chemical properties. It was found that using in situ scanning tunneling microscopy that the undried ionic liquid $[BMIm]PF_6$ attacks the gold substrate and its aggressiveness increases with the increase in water content. This is due to the formation of HF as a result of decomposition of the ionic liquid in presence of water. Therefore, ionic liquids based on more hydrophobic anions such as tri-fluoromethanesulfonate ($CF_3SO_3^-$), bis-(trifluoromethanesulfonyl)imide [$(CF_3SO_2)_2N^-$] and tris-(trifluoromethanesulfonyl) methide [$(CF_3SO_2)_3C^-$] have been developed.[27–29] These ionic liquids have received extensive attention not only because of their low reactivity with water but also because of their large electrochemical windows. Usually these ionic liquids can be well dried the water contents below 1 ppm under vacuum at temperatures between 100-150 ºC.

MacFarlane works on the synthesis of new air and water stable ionic liquids with the purpose of employing such ionic liquids as indicators for sensing and displaying an environmental parameter such as humidity. This process is controlled by the color change of the ionic liquids where they are synthesized with either a colored cation or anion, so that the ionic liquids themselves are sensors. Also, he has published many papers on the use of ionic liquids in electropolymerization and in batteries.

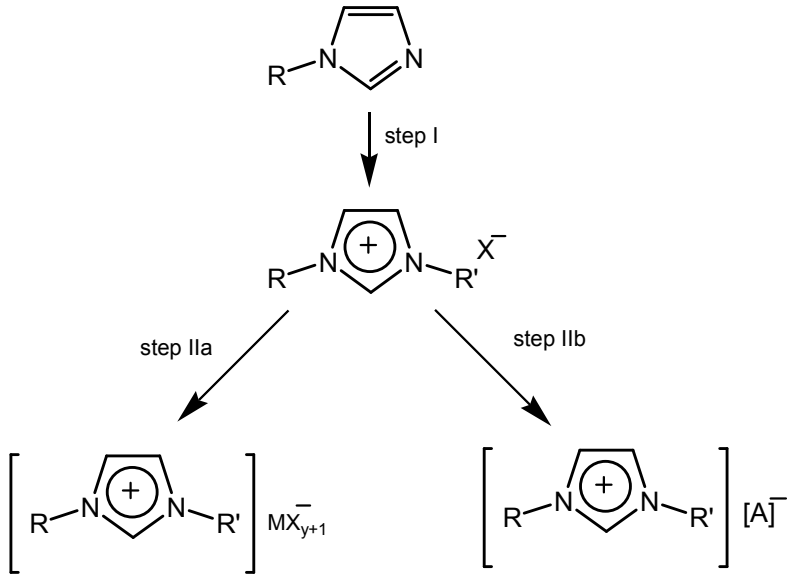
Ohno concentrates his work on the synthesis of a series of polymerizable ionic liquids and their polymerization to prepare a new class of ion conductive polymers. For example, he prepared polymer electrolytes with high ionic conductivity and good elasticity by mixing nitrite rubber (poly(acrylonitrile-cobutadiene) rubber) with the ionic liquid N-ethylimidazoliumbis(trifluoromethanesulfonyl)imide. He also edited a book entitled

"Electrochemical aspects of ionic liquids," which introduces some basic and advanced studies on ionic liquids in the field of electrochemistry.[30]

Davis, Jr introduced the concept of "task-specific ionic liquids" (TSILs) in the field of ionic liquids. TSILs are ionic liquids in which a functional group is incorporated enabling the liquid to behave not only as a reaction medium but also as a reagent or catalyst in some reactions or processes.[31] Abbott has recently developed a range of ionic compounds, which are fluid at room temperature. These ionic liquids are based on simple precursors such as choline chloride (vitamin B_4) which is cheap and produced on a multi-tone scale and hence these ionic liquids/deep eutectic solvents can be applied to large scale processes for the first time. Using these liquids, a number of applications are now under development such as electrodeposition of metals, electropolishing and ore processing.

1.1.4 Synthesis of Ionic liquids

The synthesis of ILs normally consists of two major steps. In the first step, the desired cations has to be generated, usually by direct alkylation/quaternisation of a nitrogen or phosphorus atom. In the second step, the anion resulting from the alkylation reaction can be exchanged for a different one.



Step I: R'-X heat; **Step IIa** : Lewis acid MX_y; **Step IIIb**: 1) Metal salt $M^+[A]^-$; 2) strong acid $H^+[A]^-$; 3) ion exchange resin

Figure 1. General synthetic paths for imidazolium based ionic liquids

Since the imidazolium based ILs have reached some kind of "standard" status in the IL community due to good thermal stability, high ionic conductivity and large electrochemical window as well as the possibility to tune their physical and chemical properties, the general and detailed synthesis of imidazolium-based ionic liquids is represented in (**Fig. 1**) and discussed further.

Imidazolium salts with different anions are obtained by the Quaternization reaction depending upon the alkylating reagent (step I). In case where it is not possible to obtain imidazolium salt with required anion then there further steps IIa and Iib (**Fig. 1**) are required. Two different paths are possible to replace anion formed resulting from initial quarerinazation step. First is the imidazolium salts directly treated with Lewis acids, this leads to the formation of first generation ionic liquids of the type $[RR'im][MX_{y+1}]$ (step IIa, **Fig. 1**). Alternatively it is possible to exchange anion with desired anion by addition of metal salt $M+[A]^-$ (with precipitation of M^+X^-), by displacement of anion by a strong acid $H^+[A]^-$ (with evaporation of HX) or by passing over ion-exchange resin (step IIb, **Fig. 1**).

1.1.5 Cations

Developments in the field of ILs are being reported constantly in the form of novel cations and anions combination. The cations are generally bulk organic with low symmetry. Those described until now are based on tetraalkylammonium[32](**1**), trialkylsulphonium[33] (**2**), tetralkylphosphonium[34] (**3**), 1,3-dialkylimidazolium[27] (**4**), N-alkylpyridinium[35] (**5**), N,N-dialkylpyrrolidinium[29] (**6**), N-alkylthiazolium[36] (**7**), N,N-dialkyltriazolium[37](**8**), N,N-dialkyloxazonium[38] (**9**), N,N-dialkylpyrazolium[39] (**10**) isoquinolinium[40] (**11**), Organic polycations such as (**12**)[41] and (**13**),[42] have also been envisioned. Associated with bromide anions, the dication **13** (n = 4, $R^1 = R^2$ = methyl) gives a salt melting at 67-69 ºC. Cyclic hexaalkylguanidinium[43] (**14**) and Wasserscheid's chiral cations[44] (**15**, **16** and **17**) was reported in literature (**Fig. 2**).

Besides organic cations based ionic liquids, lithium salts are increasingly being developed particularly for secondary batteries and storage of energy. They have often have lower lattice energy and therefore, lower melting points than their neighboring elements in the periodic table. As an example the mixture of LiCl and $EtCl_2$ gives a liquid, on a large range of composition, at temperatures lower than 0 ºC.[45]

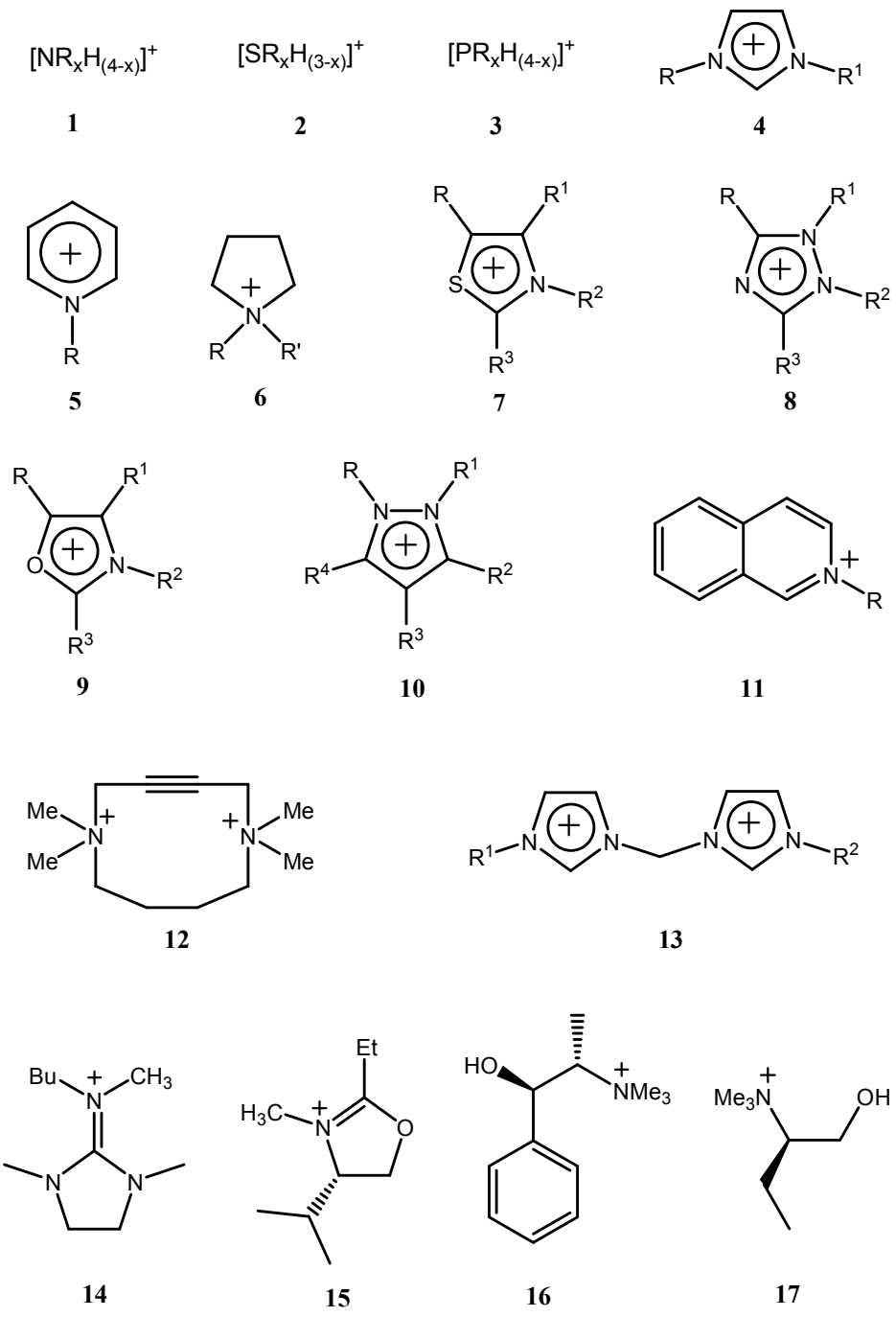


Figure 2. Different types of organic cations in ionic liquids

1.1.6 Anions

The anion chemistry has a large influence on the properties of IL. The most commonly employed IL anions are polyatomic inorganic species. The introduction of different anions has become more popular as an increasing number of alternatives are being

discovered. In the future, list of cations and anions will be extended to a nearly limitless number. Some authors speak about 10^{18} possible cation/anion combinations.[46] Various combinations of cations and anions provide finely designed ionic liquids for different applications.

Table 1. A list of some anions in ionic liquids.

Sr. NO.	Anions	Ref.	Sr. No	Anions	Ref.
1	BF_4	26	16	$ZnCl_3$	58
2	PF_6	47	17	$CuCl_2$	58
3	SbF_6	48	18	$SnCl_3$	58
4	CH_3CO_2	26	19	$N(EtSO)_2$	58
5	HSO_4	49	20	$N(FSO_2)$	55
6	NO_3	26	21	$C(CF_3SO_2)_3$	55
7	NO_2	26	22	CH_3SO_3	58
8	CF_3SO_3	27	23	$N(CN)_2$	56
9	$(CF_3SO_2)_2N$	27	24	Halides	57
10	CF_3CO_2	27	25	Al_2Cl_7	58
11	$B(Et_3Hex)$	50	26	Al_3Cl_{10}	58
12	OTs	51	27	Au_2Cl_7	58
13	$AuCl_4$	52	28	Fe_2C_{17}	58
14	$AlCl_4$	53	29	Sb_2F_{11}	58
15	Carborane anions(as1-R-$CB_{11}H_6Cl_6$)	54			

1.1.7 Purity of ionic liquids.

The physical and chemical properties of ionic liquids can be altered by the presence of impurities arising from their preparation.[59] Purity is a major issue one has to deal with when using ILs as reaction media, especially for transition metal catalysis. Although few reports on "distillable ionic liquid" were reported in literature,[60] but most of these neither be distilled nor be recrystallized. Also the purification of ILs via column chromatography is tricky. As a consequence once the ILs has formed in the course of the synthesis, purification can become a nuisance. For transition metal catalysis, one major problem is halide impurities stemming from incomplete anion exchange. For imidazolium-based

systems with medium side chains (C_4-C_8), these can be removed by extraction with water.[61] [EMIm]-based ILs are too soluble in water for this method of purification, while the ones with longer alkyl chains are amphiphilic, resulting in quite a robust foam when extracted with water and thus present difficulties with phase separation. For these cases, it may sometimes be necessary to remove any residual halides by titration with $AgBF_4$, which can also be, of course, quite expensive and may lead to silver impurities in the IL. Gallo *et al.*[62] have systematically studied the influence of halide impurities on catalytic Michael addition reactions. They have found that the system is strongly sensitive to the amount of halides present in the IL, inhibiting the activity of the transition metal catalyst. Furthermore, the total amount of halide impurities in different IL batches is variable even if the same synthetic protocol is followed. For a palladium-catalyzed copolymerization of styrene and carbon monoxide, Klingshirn *et al.*[63] came to the same conclusions. Daguenet and Dyson[64] explained this fact as a consequence of the extremely weak interactions between the halide anion and the imidazolium cation, through which the dissociation of the halide from a transition metal complex can become thermodynamically disfavored in ILs.

The second major purity problem is "color." Most ILs are colorless in pure form, but in reality, they are more likely to be pale yellow to dark orange. The origin of this is still somewhat unclear, since these (often trace) impurities are not detectable via NMR or IR spectroscopy. Most likely, the color is due to degradation of the starting material N-methylimidazole. A colorimetric method has been developed to determine the level of unreacted alkylimidazole (<0.2 mol%) in the ionic liquid.[65] By taking some precautions, colourless ILs can be obtained by (1) using freshly distilled N-methylimidazole for the synthesis, (2) performing the alkylation step at the most modest temperatures possible (i.e., avoiding overheating) under a protective atmosphere, and (3) by cleaning the final IL product through stirring with activated charcoal.[66]

The third issue concerning purity is the amount of water present in the ILs. This is not only a problem for running reactions with water-sensitive compounds, but the amount of water can change the physical properties of an IL dramatically.[61] Therefore, it is always advisable to dry ILs at elevated temperature in high vacuum with vigorous stirring overnight before using them. Stirring is crucial here because of high viscosities and because the water desorption takes place only via the surface of the liquid phase. In

critical cases, the amount of water present can additionally be checked by IR spectroscopy[61] or, of course, by standard Karl Fischer titration. In some cases, e.g. PF_6 based salts, traces of water can generate the decomposition of the anion and the formation of HF.

1.1.8 Physicochemical properties of ILs

A fundamental understanding must be established for the chemical and physical properties of new solvents before its incorporation in to an industrial application. Optimal physical properties would include low viscosity to facilitate mixing and a large density differences in comparison to other process fluids to hasten phase separation. Chemically, the solvent would have a high capacity for the solute. To encourage widespread use of the solvent, it would be inexpensive to produce, recyclable, and robust to endure various processing environments. Physical properties such as melting point, boiling point, density, and viscosity, are related to the mechanics and engineering components associated with a process. For example, densities, viscosities, and surface tensions will determine important parameters including rates of liquid–liquid phase separation, mass transfer, power requirements of mixing and pumping. Other physical properties, such as refractive index, are related to certain chemical properties despite providing a bulk property description. Chemical properties such as the structuredness, polarity, and relative hydrogen bonding donating and accepting ability are more obviously related to the molecular chemistry of their application.[67] Due to the obvious intermolecular interactions that these parameters measure, these chemical properties are belived to play a major role in determining solubilities, partition constants, and reaction rates.

The physical and chemical properties of ionic liquids can be specifically varied over a wide range by the selection of suitable cations and anions. The possibility arises to optimize the ionic reaction medium for specific applications by stepwise tuning the relevant solvent properties. For this reason ionic liquid have been referred to as "designer solvents."

1.1.8.1 Melting points

The most interesting and most debated property of the IL is the melting point. The melting point of IL lies below 100 °C. With a given cation the choice of anion has a strong effect on the melting point.[68] Coordinating and hydrophilic anions like the halides lead to high melting points, whereas weakly coordinating and hydrophobic anions result

in low melting points. Also increase in size of the anion with same charge leads to a decrease in melting points (**Table 2**).

Table 2. Influence of different anions on the melting point of imidazolium salts.

Entry	Imidazolium salts	MP (°C)	Ref.
1	[EMIm]Cl	87	21a
2	[EMIm]NO_2	55	26
3	[EMIm]NO_3	38	26
4	[EMIm]$AlCl_4$	7	53
5	[EMIm]BF_4	15	21c
6	[EMIm]PF_6	62	21c
7	[EMIm]CF_3SO_3	-9	27
8	[EMIm]CF_3CO_2	-14	27
9	[EMIm]$(CF_3SO_2)_2N$	-3	21c

By variation of the alkyl chain length in the cation, fine-tuning of the melting point can be achieved.[58] Symmetrically substituted cations can crystallize easily and therefore often lead to "ionic solids" (i.e. high melting points). Low symmetry in substitution can prevent easy crystallization, resulting in low melting points (**Table 3**).

Table 3. Melting points of various salts.

Entry	**salts**	**Melting point (°C)**
1	NaCl	803
2	KCl	772
3	[MMIm]Cl	125
4	[EMIm]Cl	87
5	[BMIm]Cl	65
6	[NMe_4][Br]	>300
7	[NEt_4][Br]	284
8	[NBu_4][Br]	124-128
9	[$NHex_4$][Br]	99-100
10	[$NOct_4$][Br]	95-98

The longer alkyl chain, the lower is the melting point, but only up to certain extent. Beyond that, prolongation of the alkyl chain raises the melting points. Additionally, a good distribution of the positive charge over a number of atoms seems to favor low melting points. Comparison of the melting points of different salts clearly illustrate that, cation size, symmetry, charge distribution and alkyl chain length affects the melting points of ILs.

1.1.8.2 Viscosity

One of the largest barriers to the application of ILs arises from their high viscosity. A high viscosity may produce a reduction in the rate of many organic reactions and a reduction in the diffusion rate of the redox species. Current research for new and more versatile ILs is driven, in part, by the need for materials with low viscosity. Generally, ionic liquids are more viscous than common molecular solvents and their viscosities are ranging from 10 mPa·s to about 500 mPa·s at room temperature. The viscosity of ionic liquids is determined by van der Waals forces and hydrogen bonding. For e.g. an increase in viscosity was observed for butylmethylimidazolium IL when triflate anion was displaced with $(n\text{-}C_4F_9SO_3)^-$ ion and from the trifluoroacetate ion to $(n\text{-}C_3H_7COO)^-$ ions. Comparison of the viscosities of $[BMIm]CF_3SO_3^-$ with $[BMIm](CF_3SO_2)_2N$, reveals a lower viscosity despite stronger van der waals interactions for ILs with $(CF_3SO_2)_2N^-$ ion. In this case, the almost complete suppression of hydrogen bonding overcompensates for the expected increase in viscosity. Electrostatic forces may also play an important role. Alkyl chain lengthening in the cation and fluorination in the cation/anion leads to an increase in viscosity.[69] 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. In general, all ionic liquids show a significant decrease in viscosity as the temperature increases.[70]

As an evident from **Table 4**, viscosity increases with increasing alkyl chain length, also fluorination in anions causes increases in viscosity. Strength of hydrogen bonding decreases in the order $[PF_6]^- > [BF_4]^- > [NTf_2]^-$ which results in decrease in viscosity.

Table 4. Influence of alkyl chain length, fluorination in anion and strength of hydrogen bonding on viscosity of different imidazolium based ILs at 25 ^{o}C unless indicated otherwise

Entry	Ionic Liquid	Viscosity (mPa·s)
1	[EMIm][BF_4]	43
2	[BMIm][BF_4]	233
3	[HMIm][BF_4] (20 ^{o}C)	314
4	[BMIm][CF_3SO_3]	90
5	[BMIm][n-$C_4F_9SO_3$]	373
6	[BMIm][CF_3CO_2]	73
7	[BMIm][n-$C_3F_7CO_2$]	182
8	[BMIm][PF_6]	450
9	[BMIm][Tf_2N]	52

1.1.8.3 Density

Density is one of the most often measured properties of ILs, probably because nearly every application requires knowledge of the density. ILs in general are denser than water with values ranging from 1 to 1.6 g cm.$^{-3}$

Table 5. Densities of different ILs at 25 ^{o}C

Entry	Ionic liquid	Density (g/ml)
1	[BMIm][Cl]	1.08
2	[HMIm][Cl]	1.03
3	[OMIm][Cl]	1.00
4	[BMIm][I]	1.44
5	[BMIm][BF_4]	1.12
6	[BMIm][PF_6]	1.36
7	[BMIm][Tf_2N]	1.43
8	[BMIm][CF_3CO_2]	1.209
9	[BMIm][CF_3SO_3]	1.29

The density of an ionic liquid depends on the length and type of substituents in the cation, and also on the kind of the anion. The molar mass of the anion,[69] alkyl chain length and bulkiness in the cation significantly affects the overall density of ILs. The density of ionic liquids is also temperature dependent. As temperature changes from 293 to 313 K, the density of [EMIm][BF_4] decreases linearly as the temperature increases.[67]

1.1.8.4 Vapour pressure and thermal stability

Ionic liquids have no vapour pressure. This is a great advantage from a process engineering viewpoint, since separation by distillation of a reaction mixture becomes more effective as a method of product isolation. The well-known problem of azeotrope formation between the solvent and the products does not arise.

The thermal stability of ionic liquids is limited by the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds, respectively. Ionic liquids synthesized by direct protonation of an amine or phosphane show, for example, significantly restricted thermal stability. In general, most of ILs have high thermal stability, the decomposition temperature reported in the literature are generally > 400 ^oC, with minimal vapor pressure below their decomposition temperature.

Recent reports have described the TGA of imidazolium salts and noted that the thermal decomposition is heavily dependent on the salt structure and, for certain samples, the type of sample pan (i.e., aluminium or alumina) used in the analysis.[71] Literature reports indicate that experiments performed under N_2 or air produce the same results.[71] The onset of thermal decomposition is furthermore similar for the different cations but appears to decrease as the anion hydrophilicity increases. It has been suggested that the stability dependence on the anion is $[PF_6]^-$>$[Tf_2N]^-$~$[BF_4]^-$>halides.[71] Halide anions dramatically reduce the thermal stability with the onset of decomposition occurring at least 100 °C below the corresponding ILs with non-halide anions. An increase in cation size, at least from 1-ethyl to 1-octyl, [EMIM] to [OMIM], does not appear to have a large effect (**Table 6**).

Table 6. Thermal decomposition temperature for different ILs

Entry	Ionic Liquid	Decomposition temperature (ºC)
1	[EMIm][Cl]	285
2	[PMIm][Cl]	282

3	[BMIm][Cl]	254
4	[HMIm][Cl]	253
5	[OMIm][Cl]	243
6	[BMIm][I]	265
7	[BMIm][BF_4]	403
8	[BMIm][PF_6]	349
9	[BMIm][Tf_2N]	439

1.1.8.5 Polarity

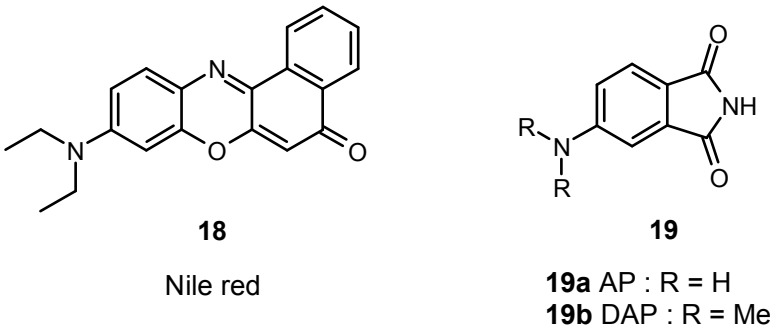
The key features of a liquid that is to be used as solvent are those which determine how it will interact with potential solutes. For molecular solvents, this is commonly recorded as the 'polarity' of the pure liquid, and is generally expressed by its dielectric constant. ILs can be classified, as all the other solvents, on the basis of their bulk physical constants, reported above. At variance with molecular solvents, however, dielectric constants cannot be used in the quantitative characterization of solvent polarity. Actually, this scale is unable to provide adequate correlations with many experimental data also in the case of molecular solvents, and the quantitative characterization of the 'solvent polarity' is a problem not completely solved even for molecular solvents. The exact meaning of 'solvent polarity' is complex, since this term takes into account all the possible microscopic properties responsible for all the interactions between solvent and solute molecules such as coulumbic, directional, inductive, dispersion, hydrogen bonding, electron pair donor and electron pair acceptor forces.

Empirical polarity parameter scales were described by observing the effect of the solvent on solvent-dependent processes, such as the rate of chemical reactions, the absorption of light by solvatochromic dyes and partition methods.[72] These approaches have been applied also to ILs and both solvatochromic and fluorescent dyes, and also partition coefficients, have been utilized to determine the polarity of these new solvents.

ILs-solvatochromic probe interactions. Studies of solute-solvent interactions by means of solvatochromic probes are generally easy to perform, and they may be convenient if the interpretation is carefully considered. Generally, each probe is sensitive to a particular kind of interaction (hydrogen bonding, dipolarity/polarizability, etc.) but solvent polarity

arises from the sum of all possible intermolecular interactions, and therefore different probes can give different polarity scales.

Neutral probes: Nile red and aminophthalimides. The first experiment using a solvatochromic dye, in particular Nile red (**Fig. 3**), was carried out[73] by Carmichael and Seddon on a series of 1-alkyl-3-methylimidazolium ILs. The visible absorption band for Nile red displays one of the largest solvatochromic shifts known. This probe is most likely sensitive to changes in solvent dipolarity/polarizability, although exactly which factors dominate the shift in its absorption maximum is unclear. The values found for a number of 1-alkyl-3-methylimidazolium ILs shows[73,74,75] that the polarity of these salts is comparable to that of short-chain alcohols. The range of values is narrow and the small variations in polarity seems to be determined by the anion in the case of ILs containing short 1-alkyl groups, and by the cation for those containing long 1-alkyl groups. For the $[bmim]^+$ ILs, the polarity decreases through the series $[NO_2]^-$>$[NO_3]^-$> $[BF_4]^-$>$[NTf_2]^-$>$[PF_6]^-$. The decrease in polarity correlates with anion size, i.e. with the effective charge density. The anomalous behaviour of $[NTf_2]^-$ has been attributed to the partial charge delocalization within this anion. The presence of some functional groups (OH or OR) on the alkyl chain of the imidazolium cation[75] is able to vary the polarity of the corresponding salts over a wide range.



18 Nile red

19 **19a** AP : R = H **19b** DAP : R = Me

Figure 3. Solvatochromoc dyes

It is noteworthy, however, that the data on polarity obtained using other neutral solvatochromic dyes show some variability. For example, a different polarity trend has been found when two fluorescent neutral probes, 4-aminophthalimide (AP) **19a** and *N,N'*-dimethyl-4-aminophthalimide (DAP) **19b** (**Fig. 3**), have been used with a series of ILs.[76]

According to these latter probes, [BMIm][PF_6] is more polar than acetonitrile and less polar than methanol. The imidazolium salts are more polar than pyridinium and the polarity of N-butylpyridinium tetrafluoroborate is near that of acetonitrile; furthermore, with these probes the replacement of the counter anion, $[PF_6]^-$ by $[NO_3]^-$ does not change the apparent polarity of the medium, in contrast to results with Nile red.

***$E_{T(30)}$* values:** Probably the most widely used empirical scale of polarity is the $E_{T(30)}$ scale, where $E_{T(30)}$ (in kcal mol^{-1}; 1 kcal = 4.184 kJ) = 28 592/λ_{max} (in nm) and λ_{max} is the wavelength maximum of the lowest energy π-π* absorption band of the zwitterionic Reichardt's dye. Often a normalized scale of $E_{T(30)}$ polarity, E_N^T, obtained by assigning water the value of 1.0 and tetramethylsilane zero, is used.

Because of its structure (**Fig. 4**), the solvatochromic shift of this probe is strongly affected by the hydrogen- bond donor ability of the solvent, which stabilizes the ground more than the excited state.

The $E_{T(30)}$ scale is therefore largely, but not exclusively, a measure of hydrogen-bonding acidity of the solvent system. The E_N^T values of several ILs are reported in **Table 7**.

Table 7. E_N^T values of several ILs

Entry	Imidazolium salts	E_N^T	Ref.
1	[BMIm][$BF]_4$	0.67	77
2	[BMIm][$PF]_6$	0.669	77
3	[BMIm][TfO]	0.656	77
4	[BMIm][Tf_2N]	0.644	77
5	[BMIm][$BF]_4$	0.576	77
6	[BMIm][Tf_2N]	0.544	77
7	[BMIm][Tf_2N]	0.541	77
8	[BMIm][$PF]_6$	0.633	78
9	[BMIm][Tf_2N]	0.629	78
10	[BMIm][Tf_2N]	0.525	78
11	[BMIm][$BF]_4$	0.543	78

The alkyl chain length for the 1-alkyl-3-methylimidazolium ILs hardly affects the E_N^T values, which are similar to that for ethanol (E_N^T = 0:65), but the introduction of a methyl

at C-2 reduces the solvent polarity.[78] These data are in agreement with the often proposed ability of the proton at C-2 to give hydrogen bonding and with the presumption that changes in E_N^T values are dominated by the hydrogen-bonding acidity of the solvent. The values for 1,2,3-trialkylimidazolium ILs are similar to those characterizing the pyrrolidinium salts and not very far from the value reported for acetonitrile (E_N^T = 0:47). Alteration of the anion ($[PF_6]^-$ $[BF_4]^-$ $[TfO]^-$) has very little effect on the E_N^T values, with the exception of [BMIm][Tf_2N], which seems to be less polar than[BMIm][PF_6].

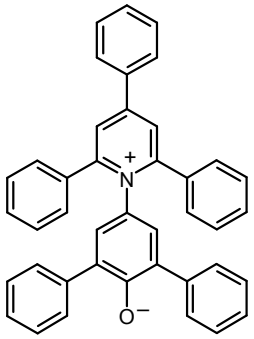


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Figure 4. Reichardt's dye

1.1.8.6 Solubility in water

The hydrophilic/hydrophobic behaviour is important for the solvation properties of ILs as it is necessary to dissolve reactants, but it is also relevant for the recovery of products by solvent extraction. Furthermore, the water content of ILs can affect the rates and selectivity of reactions. The solubility of ILs in water is, moreover, an important factor for the industrial application of these solvents. One potential problem with ILs is the possible pathway into the environment through waste water. Extensive data are available on the miscibility of alkylimidazolium ILs with water. The solubility of these ILs in water depends on the nature of the anion, temperature and the length of the alkyl chain on the imidazolium cation. For the $[BMIm]^+$ cation the $[BF_4]^-$ $[CF_3CO_2]^-$ $[NO_3]^-$ $[NMs_2]^-$and halide salts display complete miscibility with water at 25 ^oC. However, upon cooling the $[BMIm][BF_4]^-$ water solution to 4 ºC, a water rich-phase separates. In a similar way, 1-hexyl-3-methylimidazolium hexafluorophosphate, [HMIm][PF_6], shows a low solubility in water even at 25^oC. $[PF_6]^-$ $[SbF_6]^-$ $[NTf_2]^-$ and $[BR_4]^-$ salts are characterized by very low solubilities in water, but 1,3-dimethylimidazolium

hexafluorophosphate is water soluble.[72] Also, the ILs which are not water soluble tends to adsorb water from the atmosphere. On the basis of IR studies it has been established[66] that water molecules absorbed from the air are mostly present in the 'free' state, bonded via H-bonding with $[PF_6]^-$, $[BF_4]^-$, $[SbF_6]^-$, $[ClO_4]^-$, $[CF_3SO_3]^-$ and $[Tf_2N]^-$ with a concentration of the dissolved water in the range 0.2-1.0 mol dm.$^{-3}$ Most of the water molecules should exist in symmetrical 1:2 type H-bonded complexes: anion…HOH…anion. The strength of H-bonding between anion and water increases in the order $[PF_6]^- < [SbF_6]^- < [BF_4]^- < [Tf_2N]^- < [ClO_4]^- < [NO_3]^- < [CF_3CO_2]^-$.

1.1.8.7 Surface tension

Surface tension may be an important property in multiphase processes. ILs are widely used in transition metal catalyzed reactions, carried out under multiphase conditions, reactions that are believed to occur at the interface between the IL and the overlying organic phase. These reactions should therefore be dependent on the access of the catalyst to the surface and on the transfer of the material across the interface, i.e. the rates of these processes depend on surface tension.

In general, liquid/air surface tension values for ILs are somewhat higher than those for conventional solvents [(3.3-5.7) $\times 10^{-4}$ Ncm^{-1}], although not as high as for water, and span an unusually wide range. Surface tension values vary with temperature and are affected by the alkyl chain length, decreasing with increasing length. For a fixed cation, in general, the compound with the larger anion has the higher surface tension[69] (**Table 8**).

Table 8. Surface tension of different imidazolium based ILs

Entry	Ionic Liquid	Surface tension (dyne cm^{-1})
1	[BMIm][PF_6]	48.8
2	[HBIm] [PF_6]	43.4
3	[OMIm] [PF_6]	36.5
4	[HMIm][Cl]	42.5
5	[OMIm][Cl]	33.8
6	[BMIm][I]	54.7
7	[BMIm][BF_4]	46.6
8	[BMIm][Tf_2N]	37.5

1.1.8.8 Refractive index

This parameter is related to polarizability/dipolarity of the medium and the excess molar refraction is used in the least-squares energy relationship of Abraham as a predictor of solute distribution. The values found for [BMIm][X] salts are comparable to those for organic solvents.[69]

Table 9. Refractive index of different ILs

Entry	Ionic Liquid	Refractive index
1	[BMIm][PF_6]	1.409
2	[OMIm] [PF_6]	1.423
3	[HMIm][Cl]	1.515
4	[OMIm][Cl]	1.505
5	[BMIm][I]	1.572
6	[BMIm][Tf_2N]	1.4271

1.1.8.9 Conductivity

Ionic liquids have reasonably good ionic conductivities compared with those of organic solvents/electrolyte systems (up to ~10 mS cm^{-1}).[58] At elevated temperatures of e.g. 200 ^oC 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.

1.1.8.10 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,[79] 4.10 V for [BMIm]BF_4[79] and 5.5 V for [BMP]Tf_2N at a glassy carbon electrode.[29] In general, the wide electrochemical window 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.

1.1.9 What features makes ILs so attractive?

Development of alternatives for innovative chemical technologies, in order to reduce the use or generation of hazardous substances, eliminates corrosion problems, and lower energy consumption has always been of particular interest. Some of the features of ionic liquids such as their application as environmentally safe, non-corrosive media for absorption of acidic gases in the process of natural gas refining, where they replace amines and thereby increase production capacities of gas refineries. Furthermore, obtaining expensive and higher purity grade chemical and petrochemical products using ILs can be of great importance. ILs are classified as "Green Solvents" and some of their physical properties, which make them attractive as potential solvents include:

- They have essentially no vapour pressure and thus serve as potential replacements for volatile organic compounds in the chemical industry.
- They possess good thermal stability and do not decompose over a large temperature range, thereby making it feasible to carry out reactions requiring high temperature conveniently in ionic liquids.
- They are able to dissolve a wide range of organic, inorganic and organometallic compounds.
- They serve 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.
- The solubility of ionic liquids depends upon the nature of the cations and counter anions.

- They generally do not co-ordinate to metal complexes, enzymes and different organic substrates.
- Their ionic character enhances the reaction rates to a great extent in many reactions including microwave assisted organic synthesis.
- Most of the ionic liquids can be stored without decomposition for a long period of time.
- They show a high degree of potential for enantioselective reactions as a significant impact on the reactivities and selectivities due to their polar and non-coordinating properties can be achieved. In addition, chiral ionic liquids have been used to control the stereoselectivity.
- The viscosity of 1-alkyl-3-methyl imidazolium salts can be decreased for more facile reaction by using highly branched and compact alkyl chain, as well as by changing the nature of anion.

1.1.10 Applications of ILs in organic synthesis

Ionic liquid is a booming concept in modern synthetic organic chemistry. Recently, ILs have been generating enormous interest in organic synthesis due to their unique properties, in combination with their tunability. Their high polarity, in combination with variable miscibility with organic solvents, and their non-volatile nature gives rise to easy product isolation, catalyst heterogenisation and recycling techniques. Current applications of ionic liquids in catalysis as alternatives to conventional media are concentrated in two directions. One is to take the place of organic solvents due to their unique solvent properties and the other is to take the place of liquid acids due to their variable acidities. The former applications include dimerization reactions, Heck reactions and hydroformylation, while the latter includes alkylation reactions and Friedel–Crafts reactions. Many of these studies have significant commercial applications but fundamental studies of the relationship between the properties of ionic liquids and the improved performance compared with conventional solvents are still rare. The ILs are widely used in organic synthesis especially in transition metal catalyzed reaction as reaction media, reagent and catalyst. In most of the cases ILs enhance rate of reactions, yields, selectivities in comparison to conventional organic solvents. **Table 10** contain some of the synthetic applications of ILs as a solvent for organic reactions (nucleophilic

and electrophilic reactions including acidic catalyzed reactions) and solvent for reactions catalyzed by transition complexes.

Table 10. Examples of applications of ionic liquids as solvents for chemistry

Reaction	Nature of the ionic liquid	catalyst	Ref.
Diels-Alder reaction	[BMIm][BF_4], [BMIm][PF_6], [BMIm][lactate], [BMIm][OTf]	_	80
	[$EtNH_3$][NO_3]	_	81
Aza Diels-Alder reaction	[EtDBU][Otf]	$Sc(OTf)_3$	82
N or O alkylation	[BMIm][PF_6], [BMIm][BF_4]	KOH	83
Biginelli reaction	[BMIm][PF_6], [HBIm]BF_4	–	84
Witting reaction	[BMIm]BF_4	–	85
Allylation of alcohols	[BMIm][PF_6], [BMIm][BF_4]	R_4Sn	86
Reduction of aldehydes	[EMIm][PF_6], [EMIm][BF_4]	BR_3	87
Synthesis of cyclopropanes	[NBu_4][Br]	NaOAc	88
Benzoin condensation	[Thiazolium][BF_4]	NEt_3	36
Preparation of α-fluoro-α, β-unsaturated esters	[EtDBU][Otf]	Base	89
Reformatsky reaction	[EtDBU][Otf], [EtDBU][BF_4], [EtDBU][PF_6], [BMI][PF_6], [BMIm][BF_4]	Zn	90
1,3-Dipolar cycloaddition	[EMIm][PF_6], [EMIm][BF_4], [EMIm][NFO]	AcOH	91
Cycloaddition of CO_2 to propylene oxide	[BMIm][BF_4], [EMIm][BF_4], [1-BuPy][Cl]	–	92
Nucleophilic displacement: Cl → CN	[BMIm][PF_6]		93
Electrophilic reactions			
Nitration of aromatics	[EMIm][CF_3CO_2], [EMIm][OTf]	TfOH	94

Reaction	Nature of the ionic liquid	catalyst	Ref.
Beckmann rearrangement	[BMIm][BF_4], [BMIm][CF_3CO_2], [1-BuPy][BF_4]	$POCl_3$	95
Aromatic benzoylation	[1-BuPy][Cl]/$AlCl_3$	–	96
Fisher Indole synthesis	[n-BuPy][Cl]/$AlCl_3$		97
Friedel-crafts alkylation	[BMIm][PF_6], [PMIm[PF_6], [HMIm[PF_6], [BMIm][SbF_6], [EMIm][BF_4], [EMIm][SbF_6], [EMIm][OTf], [BMIm][OTf]	$Sc(OTf)_3$	98
	[BMIm[Cl]/$AlCl_3$ supported on silica	–	
	[BMIm][PF_6], [EMIm][Cl]/$AlCl_3$	–	99
	[EMIm[Cl]/$AlCl_3$	–	23
Friedel-Crafts acylation	Acidic chloroaluminates	–	100
	Silica supported [BMIm][Cl]/$FeCl_3$	–	101
	[EMIm][I]/$AlCl_3$	–	102
	[EMIm][Cl]/$AlCl_3$	–	23
Organometallic synthesis of iron complexes	[BMIm][Cl]/$AlCl_3$	[BMI][HCl_2] as H^+ source	103
Synthesis of transition metal-cyclophane complexes	[BMIm][Cl]/$AlCl_3$		104
Condensation of alcohol	[NR_4][NTf_2]	H_3PO_4, TsOH	105
Claisen rearrangement	[EtDBU][OTf], [MeDBU][OTf], [BMIm][BF_4], [BMIm][PF_6]	$Sc(OTf)_3$	106
Heterocyclization	[HBIm][BF_4], [BBIm][BF_4]		107
	[EMIm][OTf], [HBIm][BF_4]		108

Transition metal catalyzed reactions

Reaction	Nature of the ionic liquid	Catalyst	Ref.
Olefin hydroformylation	[BMIm][BF_4], [EMIm][BF_4], [BMIm][PF_6], [BMIm][SbF_6]	$Rh(CO)_2$(acac) with PPh_3	109
	[BMIm][PF_6]	$Rh(CO)_2$(acac)/ cobaltocenium salt	110
Olefin hydrocyanation	[BMIm][$CuCl_2$]	[BMI][$CuCl_2$]	111
	[Et_3NH][$CuCl_2$], [BMIm][$CuCl_2$], [Li][$CuCl_2$]	Cu	112
Carbonylation	[BMIm][BF_4], [BMImI][PF_6]	$Pd(OAc)_2/NEt_3$	113
Allylic alkylation	[BMIm][BF_4]	$Pd(OAc)_2$/phosphine	114
	[BMIm][BF_4]	$Pd(OAc)_2/PPh_3$	115
Negishi cross-coupling	[BDMIm][BF_4]	$Pd(dba)_2$	116
Trost-Tsuji C-C coupling	[BMIm][Cl]		117
Suzuki cross-coupling	[BMIm][BF_4]	$Pd(PPh_3)_4$ with Na_2CO_3	118
	[BBIm][BF_4]	$Pd(OAC)_2$, base	119
Heck reaction	[BMIm][BF_4], [BMIm][Br]	$Pd(OAc)_2$/NaOAc	120
	[n-Bu_4N][Br]/base	"Pd-benzothiazole carbene"	121
	[n-Bu_4N][Br]/base	Phosphapalladacycle $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$	122
	[BMIm][X], [1-hexylPy][X]	$Pd(OAc)_2$, base, phosphane	123
Sonogashira reaction	[BMIm][PF_6],	$PdCl_2(PPh_3)_2$, base	124

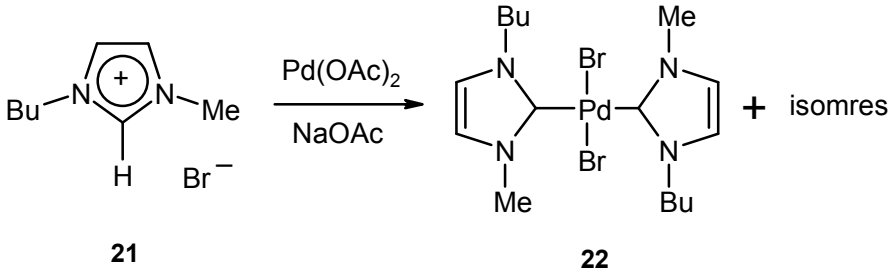
	[BBIm][BF_4]	$Pd(OAc)_2$, base,	125
Hydrogenation of olefins	[BMIm][BF_4], [BMIm][PF_6]	$Pd(acac)_2$	126
	[BMIm][BF_4], [BMIm][PF_6]	$RhCl(PPh_3)_3$,	127
Arene hydrogenation	[BMIm[BF_4]	$[H_4Ru_4(\eta^6C_6H_6)_4][BF_4]_2$	128
Asymmetric hydrogenation	[BMIm][PF_6]/$ScCO_2$	$Ru(O_2CMe)_2$(BINAP)	129
Esterification	[BMIm][BF_4]	$PdCl_2(PhCN)_2$, (+)-NMDPP/TsOH	130
Olefin dimerization	[BMIm][PF_6], [HMIm][PF_6],	[(allyl)(NiL_2)][SbF_6]	131
1,3-Butadiene dimerization	[BMIm][BF_4], [BMIm][PF_6], [BMIm][OTf]	$PdCl_2$, $Pd(OAc)_2$, $Pd(acac)_2$, $PdCl_2$(PhCN)	132
Olefin metathesis	[EMIm][Cl]/$AlCl_3$, [EMIm][PF_6]	Ruthenium carbene	133
Oxidation	[BMIm][PF_6]	Mn(salen) complex	134
	[BMIm][PF_6], [BMIm[SbF_6], [BMIm][BF_4], [BMIm][OTf]	Cr(salen)	135
	[BMIm][BF_4], [BMIm][OTf], [EMIm][BF_4]	$MeReO_3$	136
Transesterification	[BMIm][BF_4], [HMIm][BF_4], [OMI][BF_4], [BMIm][PF_6], [BMIm][OTf], [BMIm][NTf_2]	Lipase	137

1.1.10.1 Solvents for transition metal catalysis

One of the major problem with transition metal catalyzed reactions is the recycle of expensive catalysts and ligands. In **Table 10**, we can find different examples of immobilization and recycling of the catalyst. When the active catalytic species is ionic, it can be retained in the ionic liquid without the need of specially designed ligand. This is the case of olefin hydrogenation reactions catalyzed by the cationic $[HRh(PPh_3)_2(L_2)][PF_6]$ complexes. The cationic $[H_4Ru_4(C_6H_6)_4][BF_4]$ cluster is also soluble and stable in $[BMIm][BF_4]$ ionic liquid.[128] In the presence of hydrogen, it probably forms the $[H_6Ru_4(C_6H_6)_4][BF_4]_2$ complex which is arene hydrogenation effective catalyst. Another example is given by the olefin dimerization catalyzed by the active cationic [HNi(olefin)][A] complexes. This active species can be formed by in situ alkylation of a nickel(II) salt using an acidic alkylchloroaluminate ionic liquids as both the solvent and the co-catalyst.[138] The cationic $[(methallyl)NiPh_2\text{-}PCH_2PPh_2(O)][SbF_6]$ complex proved to be stable and active for ethene oligomerization in PF_6^- based ionic liquids without the addition of Lewis acid. The high electrophilicity of the Ni center, which is responsible for the activity of the catalyst, is probably not altered by the ionic solvent.[131] In the Suzuki reaction, the active species in $[BMIm][BF_4]$ is supposed to be the tricoordinated $[Pd(PPh_3)_2(Ar)][X]$ complex which forms after oxidative addition of the aryl halide to the $[Pd^0(PPh_3)_4]$.[118] Therefore, thanks to their low nucleophilicity, ionic liquids do not compete with the unsaturated organic substrate for the coordination to the electrophilic active metal center. The anionic active $[HPt(SnCl_3)_4]^{3-}$ species have been isolated from the $[NEt_4][SnCl_3]$ solvent after hydrogenation of ethylene.[139] The $PtCl_2$ precursor used in this reaction is stabilized by the ionic salt (liquid at the reaction temperature) since no metal deposition occurs at 160 ºC and 100 bar. The catalytic solution can be used repeatedly without apparent loss of catalytic activity.

In the case of Pd-mediated reactions, the loss of Pd by the formation of Pd black is often a main difficulty to recover the catalyst. The imidazolium cation is presumed to be a simple inert component of the solvent system. However, the C(2) proton of the imidazolium is acidic and can be deprotonated, by basic ligands of the metal complex, to form carbenes. The ease of formation of the carbene depends on the nucleophilicity of the anions associated with the imidazolium. For example when $Pd(OAc)_2$ is heated in the

presence of [BMIm][Br] the formation of a mixture of Pd imidazolylidene complexes occurs. The Pd-bis-carbene complex **22** has been shown to be active and stable catalysts for Heck and C–C coupling reactions.[120] The highest activity and stability of Pd is observed in [BMIm][Br] ionic liquid.



21 **22**

Figure 5. Formation of carbene Pd-complex by deprotonation of the imidazolium cation.

1.1.11 Task Specific Ionic Liquids [TSILs]

The covalent tethering of a functional group to one or both of the ions of an otherwise ordinary ionic liquid can inculcate the resulting salt with a capacity to interact with dissolved substrates in specific ways generates what are called as ‘‘task-specific’’ ionic liquids (TSIL). These low melting salts are finding an increasing number of applications in synthesis, separations, catalysis, and electrochemistry.

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 phosphane-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,[140] while ionic liquids bearing appended sulfonic acid groups were used as solvent-catalyst for esterifications.[141] 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.[142] Many of them were focused on the incorporation of functionality into a branch appended to the cation, especially to the imidazolium cation. The imidazolium salts are defined as TSILs when they have the following features:

- 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.
- 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.

1.1.12 Chiral Ionic Liquids

Even though a limited number of chiral RTILs have been designed and synthesized in an attempt to influence the outcome of asymmetric organic reactions,[143] there are only a few chiral ionic liquids that can effectively influence the outcome of asymmetric reactions.[144] 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.

A thorough literature review reveals that the design of existing chiral RTILs is based on modifications of the ammonium,[145] pyridinium,[146] oxazolinium,[146a] or thiazolium cations.[147] There are several chiral RTILs in which the chiral moiety is contained in the anion **23, 24**[148] (**Fig. 6**), but the modification of imidazolium cation-derived RTILs offers extreme promise in the design of chiral RTILs due to their facile preparation, low melting points, and relatively favorable viscosity. Shown in **Figure 6** are some imidazole-derived chiral RTILs that have been used as solvents, they contain chiral moieties bonded to one or both of the nitrogen atoms on positions 1st and 3rd of the imidazolium cation **25-29**[149] Imidazolium ionic liquids with chirality bonded to the 4th position **30**[150] and bonded to the 2nd position with a spiro skeleton **31**[151] have also been prepared.

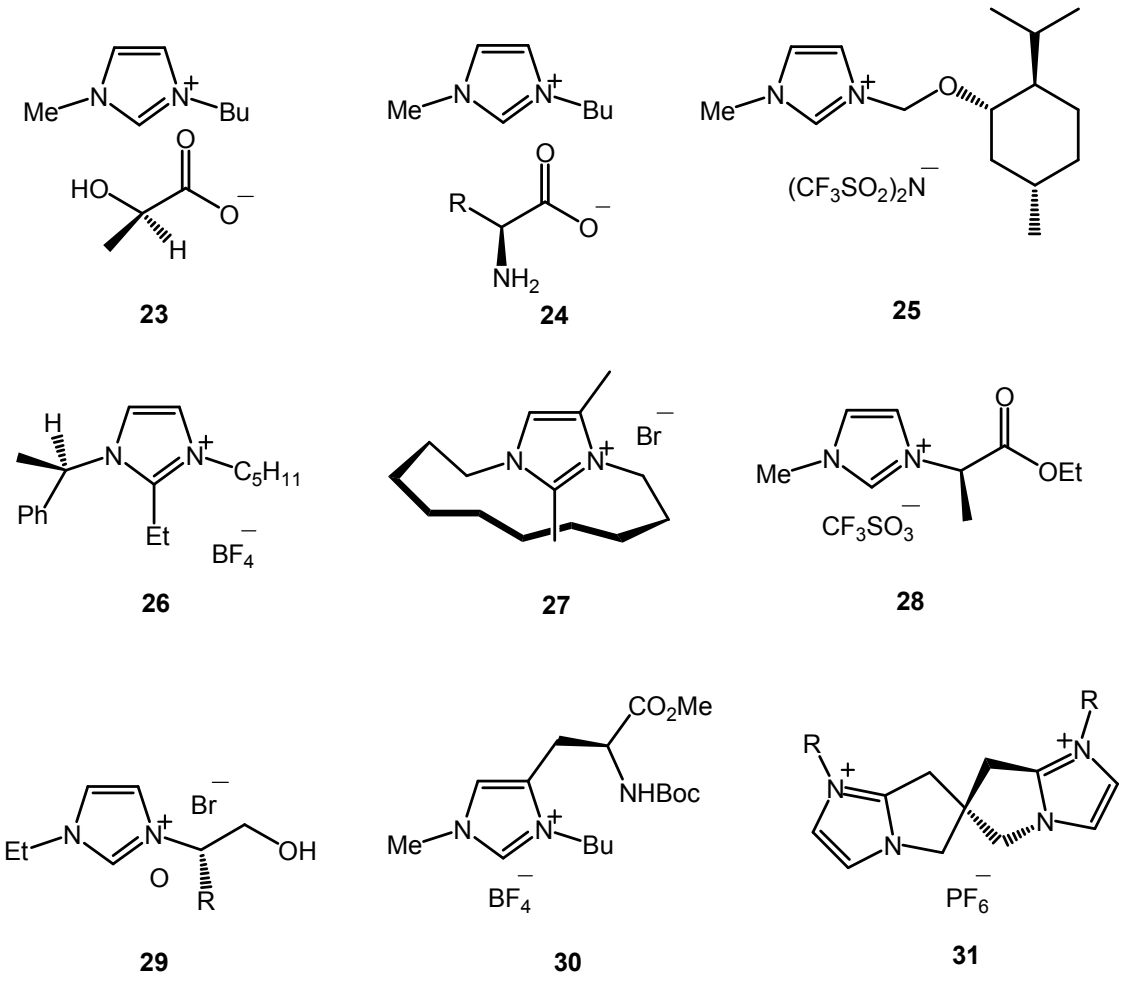


Figure 6. Chiral ILs

1.1.13 Biotransformations in ionic liquids

Ionic liquids are used in three different methods in the enzyme systems, namely 1) as a co-solvent in aqueous phase, 2) as a pure solvent and 3) as a two-phase system together with other solvents. The use of ionic liquids in biocatalytic transformations has solved some of the problems encountered in their applications in aqueous and organic solvents. Their use in lipase-catalyzed reactions has increased the solubility of the substrate by 3-fold, and in the *N*-acetyl-lactosamine synthesis using b-galactosidase, the yield has been doubled by minimising the side reactions.[152] Enhanced enantioselectivity in dynamic, kinetic and distillative work-up is possible for lipases in ionic liquids and, additionally, the physical properties of the ionic liquids can be varied very widely by using different

cation and anion combinations.[153] This makes it possible to dissolve enzymes directly in certain ionic liquids and to dissolve substrates (e.g., carbohydrates) that would not normally dissolve adequately in organic solvents.[154] Different enzymes such as hydrolases(proteases and lipases) and oxidoreductases (peroxidases and dehydrogenases) retain their activity when suspended in ionic liquids, which present a very promising 'green' alternative to organic solvents for enzyme-catalysed reactions. Cull *et al.* have published first results on the use of an ionic liquid as a reaction medium for whole-cell biotransformations.[155] They reported the use of a [BMIm][PF_6] ionic liquid in a two-phase system for the hydration of 1,3-cyanobenzene catalysed by nitrile hydratase from *Rhodococcus* 312 to give 3-cyanobenzamide and 3-cyanobenzoic acid.

1.1.14 Volatility of ionic liquids

It is widely believed that a defining characteristic of ionic liquids (or low-temperature molten salts) is that they exert no measurable vapour pressure, and hence cannot be distilled.[156] But recently Widegren *et al.*[157] demonstrate that some selected families of commonly used aprotic ionic liquids can be distilled at 200–300 ºC and at low pressure, with concomitant recovery of significant amounts of pure substance. In there study they uncovered two general features of IL volatility. First, a peak in volatility is observed when the alkyl side chains on the ions are of intermediate length. Second, certain classes of salts e.g., $[(C_2F_5SO_2)_2N]^-$ are more volatile than others $[PF_6]^-$regardless of the counter ions present. However, near ambient temperature the vapour pressure of ionic liquids remains negligible.

1.1.15 Summary and Conclusion

The unique physico-chemical properties of ILs should increase the clean technology development in organic synthesis, pharmaceuticals, radiopharmaceuticals, biocatalysis, and biotransformation and especially in industrial catalytic processes. The possibility to adjust the properties of ILs such as the hydrophobicity, viscosity, density, thermal stability, polarity and solubility to suit to the particular process is one of their key advantages and thus they can be truly described as designer solvents. Their non-volatile nature enables significant engineering advantages for distilative product separation and prevents uncontrolled evaporation and azeotrope formation between the products and

solvents. ILs represents a unique class of new reaction media for transition metal catalysis. In majority of cases, ILs containing the catalyst could be readily recycled. They provide the medium for performing clean reaction with minimum waste generation and high yields and selectivities can be obtained. Thus the use of ILs as solvents for transition metal catalysis opens up a wide field for future investigation. ILs are not only restricted to as simple substitutes to organic solvents as reaction media for organic reactions, but also in some cases they can act as reagent or catalyst (task-specific ILs) and as media for immobilizing catalyst or inducing chirality. It must be emphasized that reaction in ILs are not difficult to perform and usually require no special apparatus or methodologies. The reactions are often quicker and easier to carry out than in conventional solvents.

In addition to the above mentioned advantages of ILs, they have some limitations such as in most of the cases separation of the products from the ILs usually requires extraction with non-polar volatile organic solvents. Their high viscosity as compared to conventional solvents make stirring and homogenization of reaction medium difficult, which causes slow dissolution of solids reactant which results reduction in the rate of reactions. Other drawbacks are their higher cost as compared to most commonly used organic solvents and the ionic liquids commonly used to date are toxic in nature, which has been proven by various toxicological data collections aimed at a wide range of organisms. So there is a need to plan to synthesis non-toxic and environmentally friendly ionic liquids.

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Section-B

Synthesis and Characterization of 1,3-di-n-butyl and 1-n-butyl imidazolium based Ionic Liquids

Synthesis and Characterization of Ionic Liquids

1.2.1 Introduction

The previous section provided a brief introduction to ILs including a definition, brief history of ILs, their characteristic physico-chemical properties, application of ILs in organic synthesis, new concepts in ILs such as task specific ionic liquids (TSILs) and chiral ionic liquids (CILs). Ionic liquids are organic salts, invariably possessing a high degree of asymmetry that frustrates packing and thus inhibits crystallization. The permutation and combination of anions and cations can result in numerous ILs with varied chemical and physical properties. This section deals with the synthesis and characterization of ionic liquids based upon imidazolium cation with different anions of varying basicity.

1.2.2 Present work

The ionic liquids based upon the imidazolium cations have been described in this section. Two sets of ILs based on 1,3-di-*n*-butylimidazolium [BBIm] and 1-butylimidazolium [HBIm] salts with varying basicity of the anions were synthesized.

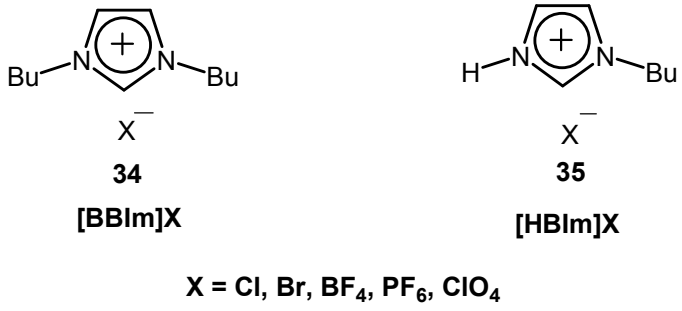
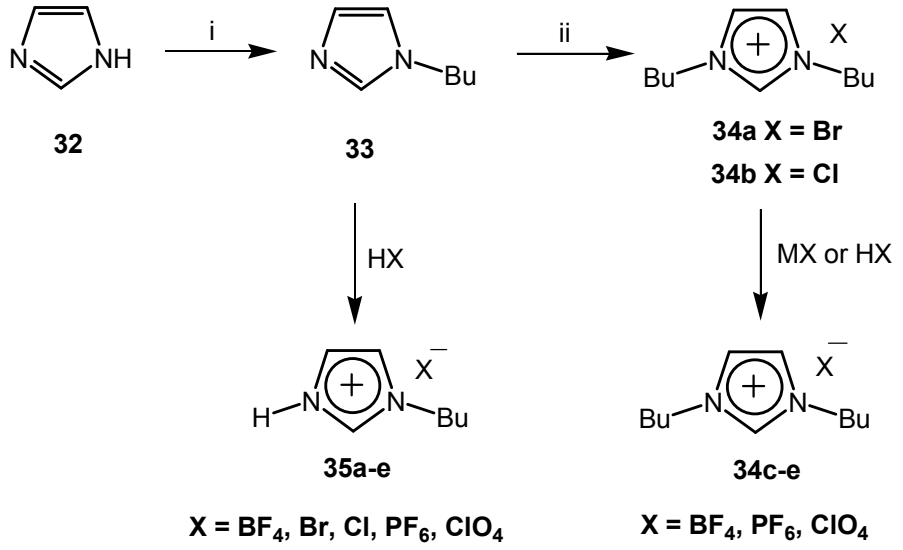


Figure. 7. Imidazolium based ionic liquids

1.2.3 Results and Discussion

The different 1,3-di-*n*-butylimidazolium ILs **34**, **35** were prepared starting from imidazole **32**. Imidazole was stirred with potassium hydroxide in acetonitrile for 2 h at room temperature to form the potassium salt of imidazole, and reacted with butyl bromide at 0 ºC to obtain the 1-*n*-butyl imidazole **33** in good yield. The imidazolium bromide salt **34a** was obtained quantitaly in a neat reaction of butyl bromide with 1-*n*-

butylimidazole at 70 ºC under inert atmosphere. A very viscous liquid was obtained with a yellowish color. The color can be removed to a certain extent by charcoal treatment. The methasis reaction was carried out in water. To the aqueous solution of the IL, sodium tetrafluoroborate/hexafluorophosphate/perchloric acid solution in water was added with stirring. The solution turns milky immediately due to the precipitation of respective salt. After 12 h of stirring, the layer containing the ILs with the BF_4, PF_6, and ClO_4 anion separates out and extracted with ethyl acetate. The organic layer was washed with water and brine. Evaporation of solvent furnished the respective ILs containing the anion BF_4 (**34c)**, PF_6 (**34d)**, and ClO_4 (**34e)** with high purity.



Scheme 1. Synthesis of ionic liquids

A series of 1-butylimidazolium [HBIm] salts **35a-e** were synthesized by direct quaternization of 1-*n*-butyl imidazole **33** to give series of [HBIm] salts with corresponding anion of the acids as shown in **Scheme 1**.

They were fully characterized by spectral and elemental analyses. For the [HBIm] ILs the chemical shifts for the NH protons were not observable in the ^1H NMR spectra when recorded in $CDCl_3$. However, the NH proton chemical shifts were observed as broad singlet with accompanying changes in the chemical shifts of the imidazolium protons of the ILs when the ^1H NMR spectra were recorded neat using $CDCl_3$ as external lock. In mass spectra, all the ILs showed [M-X] as the base peak and peaks corresponding to the

respective molecular ion were not observed. The elemental analyses of the ILs were in conformity with their structures. The list of ionic liquids prepared given in **Table 11**.

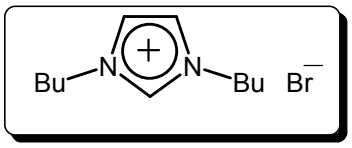
Table 11. List of the ILs prepared

Sr. No	Ionic Liquid		Sr. No	Ionic Liquid	
1	[BBIm]Br	**34a**	**6**	[HBIm]BF_4	**35a**
2	[BBIm]Cl	**34b**	**7**	[HBIm]Br	**35b**
3	[BBIm]BF_4	**34c**	**8**	[HBIm]Cl	**35c**
4	[BBIm]PF_6	**34d**	**9**	[HBIm]PF_6	**35d**
5	[BBIm]ClO_4	**34e**	**10**	[HBIm]ClO_4	**35e**

1.2.4 Experimental Section

1.2.4.1 Preparation and characterization of different ionic liquids (ILs):

[1] 1, 3-Di-*n*-butylimidazolium Bromide [BBIm]Br (34a):



A mixture of 1-*n*-butylimidazole (15 g, 1 mmol) and *n*-butyl bromide (14.24 ml, 1.1 mmol) was heated with stirring at 80 °C for 4 h. Excess *n*-butyl bromide was distilled off at 90 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [BBIm]Br as a yellow viscous liquid (30.01 g, yield 96%).

Nature : Yellow viscous oil.

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

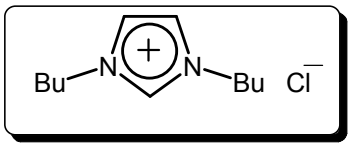
^{1}H NMR 200 MHz ($CDCl_3$) : δ 0.85-0.93 (t, *J* = 7.1 Hz), 6H), 1.21-1.41 (m, 4H), 1.78-1.93 (m, 4H), 4.28-4.35 (t, *J* = 7.1 Hz, 4H), 7.54 (s, 2H), 10.41 (S, 1H).

^{13}C NMR 50 MHz : δ 12.8, 18.8, 31.6, 49.1, 121.9, 135.9.

MS 181(M-X), 165, 138, 124, 97,81,68,57.

Elemental analysis : Calcd. : C, 50.57; H, 8.05; N, 10.73.
$C_{11}H_{21}N_2Br$ (261) Found : C, 50.37; H, 8.15; N, 10.82.

[2] 1, 3-Di-*n*-butylimidazolium Chloride [BBIm]Cl (34b):



A mixture of 1-*n*-butylimidazole (15 g, 1 mmol) and *n*-butyl chloride (13.91ml, 1.1 mmol) was refluxed in toluene for 8 h. Toluene and excess *n*-butyl chloride were distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [BBIm]Cl.

Yield : 24.6 g; yield 94%

Nature : Viscous oil.

IR ($CHCl_3$) cm^{-1} : 3607, 3253, 2876, 1645, 1580, 1466, 894, 762.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 0.87-0.92 (t, *J* = 7.2 Hz), 6H), 1.20-1.40 (m, 4H), 1.66-1.92 (m, 4H), 4.22 (t, *J* = 7.2 Hz, 4H), 7.48 (s, 2H), 10.60 (S, 1H).

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

MS 181(M-X), 165, 151, 138, 124, 109, 97, 81, 68, 57.

Elemental analysis : Calcd. **:** C, 60.82; H, 9.67; N, 12.90.

$C_{11}H_{21}N_2Cl$ (217) Found **:** C, 60.70; H, 9.52; N, 12.82.

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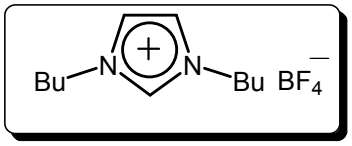
[3] 1, 3-Di-*n*-butylimidazolium Tetrafluoroborate [BBIm]BF_4 (34c):



To a solution of 1,3-di-*n*-butylimidazolium bromide [BBIm]Br (10 g, 1 mmol) in water (50 ml) was added a solution of sodium tetrafluoroborate (5.04 g, 1.2 mol) in water (25 ml), and the mixture was stirred at 30 °C for 5 h. The ionic liquid [BBIm]BF_4 separated out as an immiscible layer. The mixture was extracted with $CHCl_3$ (3×30 mL). The combined organic layer, which was separated, was washed with water and brine and dried over anhydrous sodium sulfate. The solvent $CHCl_3$ was distilled off under reduced pressure leaving behind the pure IL viscous [BBIm]BF_4.

Yield : 8.82 g; yield 86%

Nature : Viscous oil.

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

^{1}H NMR 200 MHz : δ 0.83 (t, *J* = 7.0Hz), 6H), 1.19-1.30 (m, 4H), 1.70-1.85 (m,

($CDCl_3$)		4H), 4.13 (t, *J* = 7.0 Hz, 4H), 7.41(s, 2H), 8.87 (S, 1H).
^{13}C NMR 50 MHz	**:**	δ 13.1, 19.1, 31.8, 49.5, 122.3, 135.4.
MS		181(M-X), 165, 151, 138, 124, 107, 97, 81, 68, 57.
Elemental analysis	**:**	Calcd. **:** C, 49.25; H, 7.83; N, 10.44.
$C_{11}H_{21}N_2BF_4$ (268)		Found **:** C, 49.46; H, 7.65; N, 10.32.

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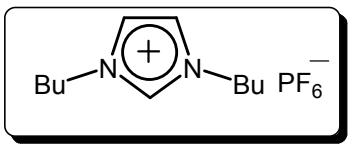
[4] 1, 3-Di-*n*-butylimidazolium Tetrafluoroborate [BBIm]PF_6 (34d):



To a solution of 1,3-di-*n*-butylimidazolium bromide [BBIm]Br (10 g, 1 mmol) in water (50 ml) was added a solution of hexafluorophosphoric acid (65% water solution) (20.43 g, 1.4 mmol) in water (25 ml), and the mixture was stirred at 30 °C for 5 h. The ionic liquid [BBIm]PF_6 separated out as an immiscible layer. The mixture was extracted with $CHCl_3$ (3×30 mL). The combined organic layer, which was separated, was washed with water and brine and dried over anhydrous sodium sulfate. The solvent $CHCl_3$ was distilled off under reduced pressure leaving behind the pure IL viscous [BBIm]PF_6.

Yield	**:**	11.5 g, 92%
Nature	**:**	Viscous oil.
IR ($CHCl_3$) cm^{-1}	**:**	3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623.
^{1}H NMR 200 MHz	**:**	δ 0.96 (t, *J* = 7.2 Hz), 6H), 1.27-1.46 (m, 4H), 1.79-1.94 (m,
($CDCl_3$)		4H), 4.19 (t, *J* = 7.2 Hz, 4H), 7.33 (s, 2H), 8.79 (S, 1H).
^{13}C NMR 50 MHz	**:**	δ 13.2, 19.3, 31.8, 49.8, 122.3, 135.2.
MS		181(M-X), 165, 151, 138, 124, 109, 97, 81, 68, 57.
Elemental analysis	**:**	Calcd **:** C, 40.61; H, 6.46; N, 8.61.
$C_{11}H_{21}N_2PF_6$ (326)		Found **:** C, 40.78; H, 6.52; N, 8.50.

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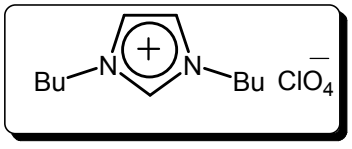
[5] 1, 3-Di-*n*-butylimidazolium perchlorate [BBIm]ClO_4 (34e):



To a solution of 1,3-di-*n*-butylimidazolium bromide [BBIm]Br (10 g, 1 mmol) in water (50 ml) was added a solution of perchloric acid (5.11 g, 1.2 mmol) in water (25 ml), and the mixture was stirred at 30 °C for 5 h. The ionic liquid [BBIm]ClO_4 separated

out as an immiscible layer. The mixture was extracted with $CHCl_3$ (3×30 ml). The combined organic layer, which was separated, was washed with water and brine and dried over anhydrous sodium sulfate. The solvent $CHCl_3$ was distilled off under reduced pressure leaving behind the pure IL viscous [BBIm]ClO_4.

Yield	**:**	9.84 g, 92%
Nature	**:**	Viscous oil.
IR ($CHCl_3$) cm^{-1}	**:**	3615, 3126, 2986, 1555, 1476, 1152, 1086, 758.
^{1}H NMR 200 MHz ($CDCl_3$)	**:**	δ 0.93 (t, *J* = 7.4 Hz), 6H), 1.25-1.40 (m, 4H), 1.79-1.94 (m, 4H), 4.22 (t, *J* = 7.4 Hz, 4H), 7.42 (s, 2H), 9.03 (S, 1H).
^{13}C NMR 50 MHz	**:**	δ 13.2, 19.2, 31.8, 49.8, 122.4, 135.5.
MS		181(M-X), 165, 151, 138, 124, 109, 97, 81, 68, 57.
Elemental analysis	**:**	Calcd **:** C, 46.97; H, 7.47; N, 9.96
$C_{11}H_{21}N_2ClO_4$ (281)		Found **:** C, 46.74; H, 7.21; N, 9.87.

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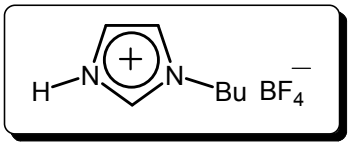
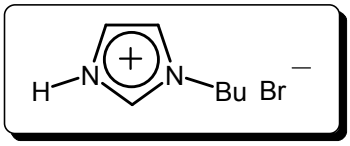
[6] 1-*n*-Butylimidazolium Tetrafluoroborate [HBIm]BF_4 (35a):



Tetrafluoroboric acid (10.5 g, 1mmol) as 40% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (15 g, 1mmol) at 0 ºC under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water from the reaction mixture was removed by subjecting it to evaporation for 4 h at 80 ºC under reduced pressure (10 mm Hg) to give the product [HBIm] BF_4 as a viscous oil.

Yield	**:**	24.4, 96%
Nature	**:**	Viscous oil.
IR ($CHCl_3$) cm^{-1}	**:**	3607, 3153, 2876, 1580, 1466, 894, 762.
^{1}H NMR 200 MHz ($CDCl_3$ as external lock)	**:**	δ 0.56 (s, 3H), 0.95 (s, 2H), 1.47 (s, 2H), 3.87 (s, 2H), 7.12 (s, 2H), 8.16 (s, 1H), 14.59 (brs, 1H).
^{13}C NMR 50 MHz	**:**	δ 13.2, 19.3, 32.3, 48.1, 120.3, 123.4, 135.6
MS		124 (M-X), 109, 97, 81, 68, 55.
Elemental analysis	**:**	Calcd **:** C, 39.81; H, 6.16; N, 13.27.
$C_7H_{13}N_2BF_4$ (211)		Found **:** C, 39.92; H, 6.32; N, 13.45.

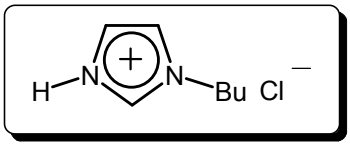
[7] 1-*n*-Butylimidazolium bromide [HBIm]Br (35b):



Hydrobromic acid (9.8 g) as 40% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (15 g, 1mmol) at 0 ºC under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water from the reaction mixture was removed by subjecting it to evaporation for 4 h at 80 ºC under reduced pressure (10 mm Hg) to give the product [HBIm] Br as a viscous oil.

Yield	**:**	23.6 g, 95%
Nature	**:**	Viscous oil.
IR ($CHCl_3$) cm^{-1}	**:**	3612, 3140, 2865, 1575, 1450, 844, 780.
^1H NMR 200 MHz ($CDCl_3$ as external lock)	**:**	δ 0.21 (s, 3H), 0.64 (s, 2H), 1.31 (s, 2H), 4.03 (s, 2H), 7.39 (s, 1H), 7.64 (s, 1H), 9.18 (s, 1H), 12.22 (brs, 1H).
^{13}C NMR 50 MHz	**:**	δ 13.1, 19.2, 32.3, 47.8, 120.3, 119.8, 123.8, 135.7.
MS		124 (M-X), 109, 97, 81, 68, 55.
Elemental analysis	**:**	Calcd **:** C, 40.97; H, 6.34; N, 13.65.
$C_7H_{13}N_2Br$ (206)		Found **:** C, 40.88; H, 6.22; N, 13.76.

[8] 1-*n*-Butylimidazolium chloride [HBIm]Cl (35c):



Hydrochloric acid (4.35 g, 1 mmol) as 35% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (15 g, 1mmol) at 0 ºC under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water from the reaction mixture was removed by subjecting it to evaporation for 4 h at 80 ºC under reduced pressure (10mm Hg) to give the product [HBIm] Cl as a viscous oil.

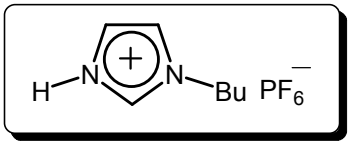
Yield	**:**	18.23 g, 94%
Nature	**:**	Viscous oil.
IR ($CHCl_3$) cm^{-1}	**:**	3612, 3140, 2865, 1575, 1450, 844, 780.
^1H NMR 200 MHz	**:**	δ 0.48 (s, 3H), 0.88 (s, 2H), 1.42 (s, 2H), 4.00 (s, 2H), 7.11

($CDCl_3$ as external lock)		(s, 1H), 7.47 (s, 1H), 8.69 (s, 1H), 12.17(brs, 1H).
^{13}C NMR 50 MHz	**:**	δ 13.0, 18.9, 31.8, 49.0, 119.5, 120.7, 134.6.
MS		124 (M-X), 109, 97, 81, 68, 55.
Elemental analysis	**:**	Calcd **:** C, 52.17; H, 8.07; N, 17.39.
$C_7H_{13}N_2Cl$ (161)		Found **:** C, 52.25; H, 8.28; N, 17.50.

---

[9] 1-Butylimidazolium hexaflouorphosphate [HBIm]PF_6 (35d):

Hexafluorophosphoric acid (17.64 g, 1 mmol) as 65% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (15 g, 1mmol) at 0 ºC under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water from the reaction mixture was removed by subjecting it to evaporation for 4 h at 80 ºC under reduced pressure (10mm Hg) to give the product [HBIm] PF_6 as a viscous oil.



Yield	**:**	30.9 g, 95%
Nature	**:**	Viscous oil.
IR ($CHCl_3$) cm^{-1}	**:**	3605, 3146, 2872, 1565, 1454, 840, 750.
^{1}H NMR 200 MHz ($CDCl_3$ as external lock)	**:**	δ 0.42 (s, 3H), 0.84 (s, 2H), 1.43 (s, 2H), 3.96 (brs, 2H), 7.18 (s, 1H), 8.56 (s, 1H), 12.61 (brs, 1H).
^{13}C NMR 50 MHz	**:**	δ 12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7.
MS		124 (M-X), 109, 97, 81, 68, 55.
Elemental analysis	**:**	Calcd **:** C, 31.26; H, 4.83; N, 10.40.
$C_7H_{13}N_2PF_6$ (269)		Found **:** C, 31.35; H, 4.98; N, 10.55.

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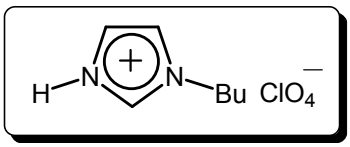
[10] 1-Butylimidazolium bromide [HBIm]ClO_4 (35e):

Similarly, the IL [HBIm]ClO_4, were prepared as above using the corresponding acid of the anion.



Yield	**:**	17.7 g, 98%
Nature	**:**	Viscous oil

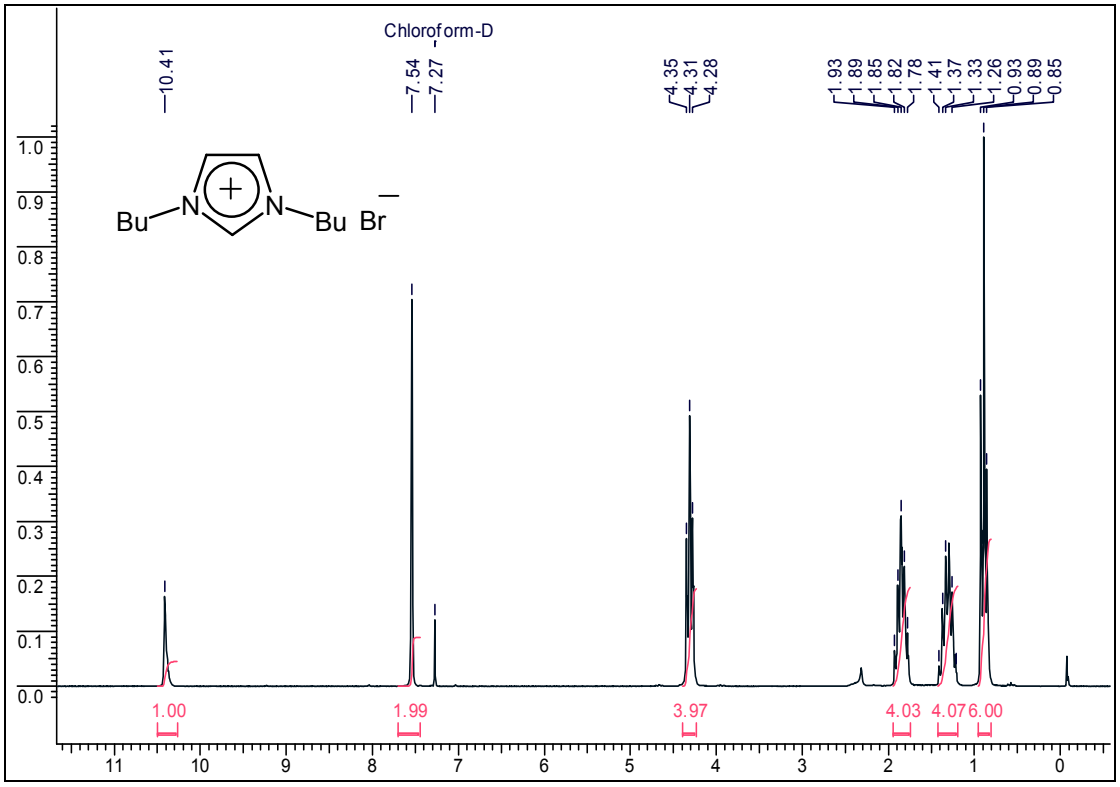
IR ($CHCl_3$) cm^{-1}	**:**	3610, 3150, 2880, 1581, 1455, 880, 765.
^1H NMR 200 MHz ($CDCl_3$ as external lock)	**:**	δ 0.71 (brs 3H), 1.17 (brs, 2H), 1.73 (brs, 2H), 4.16 (brs, 2H), 7.15 (s, 1H), 7.42 (s, 1H), 8.57 (s, 1H), 11.83 (brs, 1H)
^{13}C NMR 50 MHz	**:**	δ 12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7.
MS		124 (M-X), 109, 97, 81, 68, 55.
Elemental analysis	**:**	Calcd **:** C, 37.33; H, 5.77; N, 12.44.
$C_7H_{13}N_2ClO_4$ (225)		Found **:** C, 37.45; H, 5.85; N, 12.20.

1.2.5 Spectra

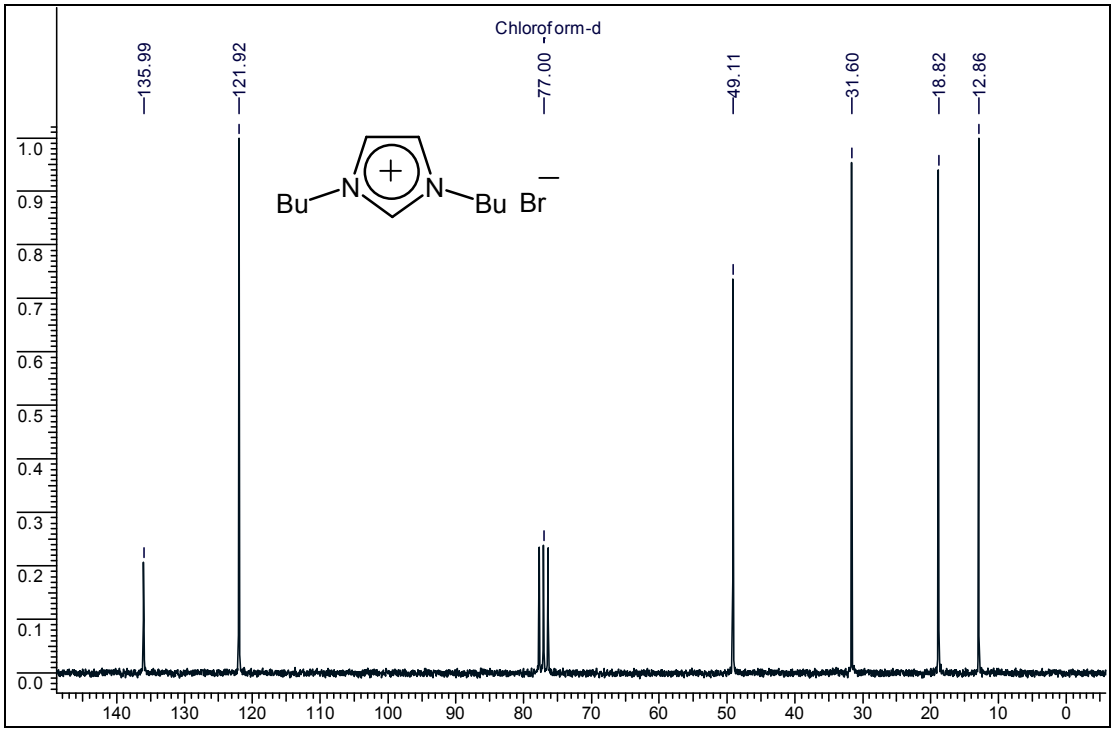
Table 12. ^1H and ^{13}C spectra of some selected ILs are given below:

Sr. No.	Spectra
1	^1H NMR and ^{13}C NMR Spectra of **[BBIm]Br (34a)**
2	^1H NMR and ^{13}C NMR Spectra of **[BBIm]BF_4 (34c)**
3	^1H NMR and ^{13}C NMR Spectra of **[BBIm]PF_6 (34d)**
4	^1H NMR and ^{13}C NMR Spectra of **[BBIm]ClO_4 (34e)**
5	^1H NMR and ^{13}C NMR Spectra of **[HBIm] BF_4 (35a)**
6	^1H NMR and ^{13}C NMR Spectra of **[HBIm]Br (35b)**
7	^1H NMR and ^{13}C NMR Spectra of **[HBIm]Cl (35c)**
8	^1H NMR and ^{13}C NMR Spectra of **[HBIm]ClO_4 (35e)**

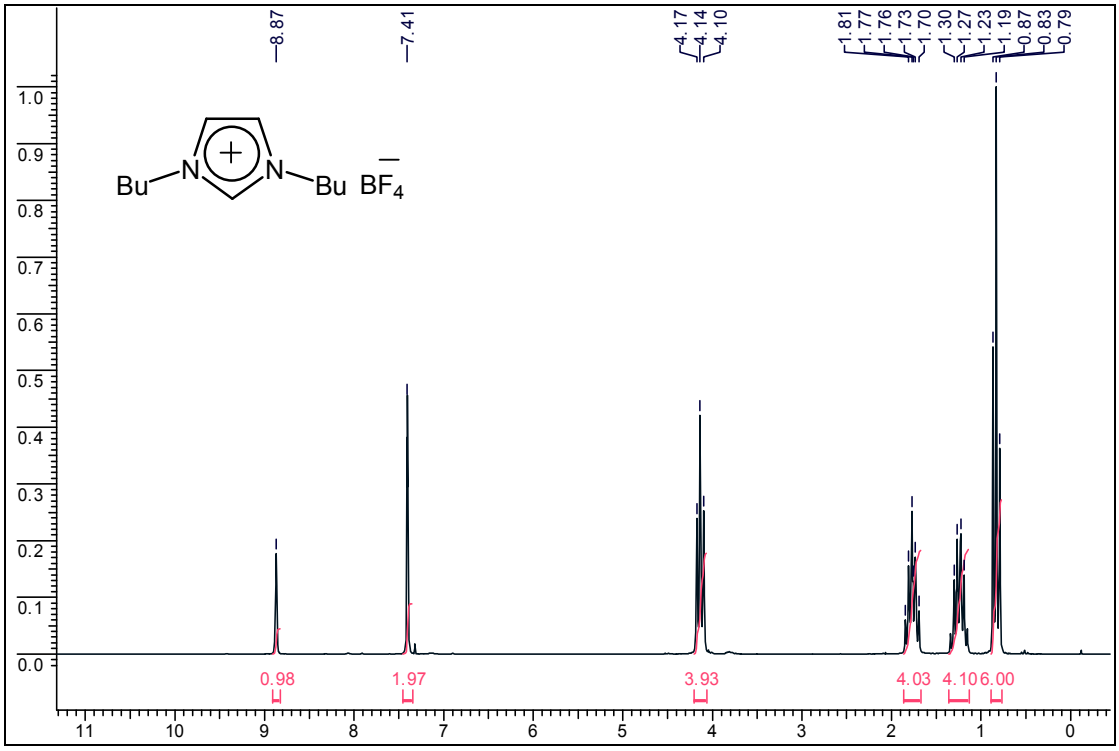
[1] ^{1}H NMR spectra of [BBIm]Br (34a)



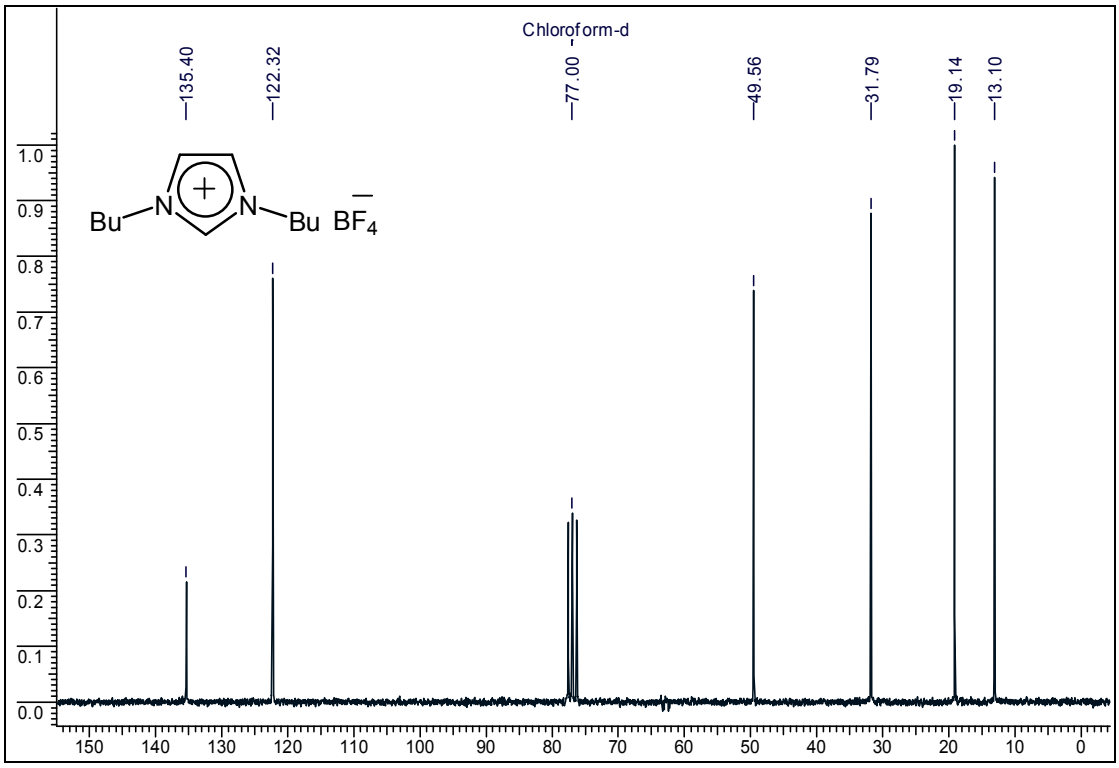
[1] ^{13}C NMR spectra of [BBIm]Br (34a)



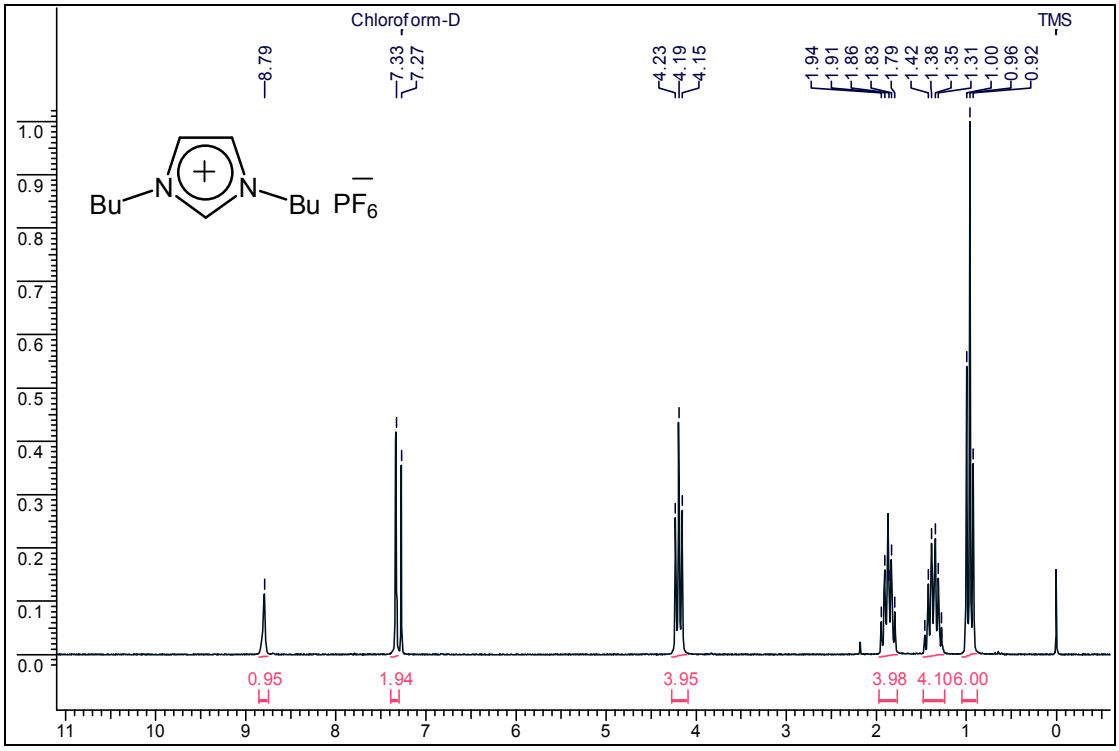
[3] ^{1}H NMR spectra of [BBIm]BF_4 (34c)



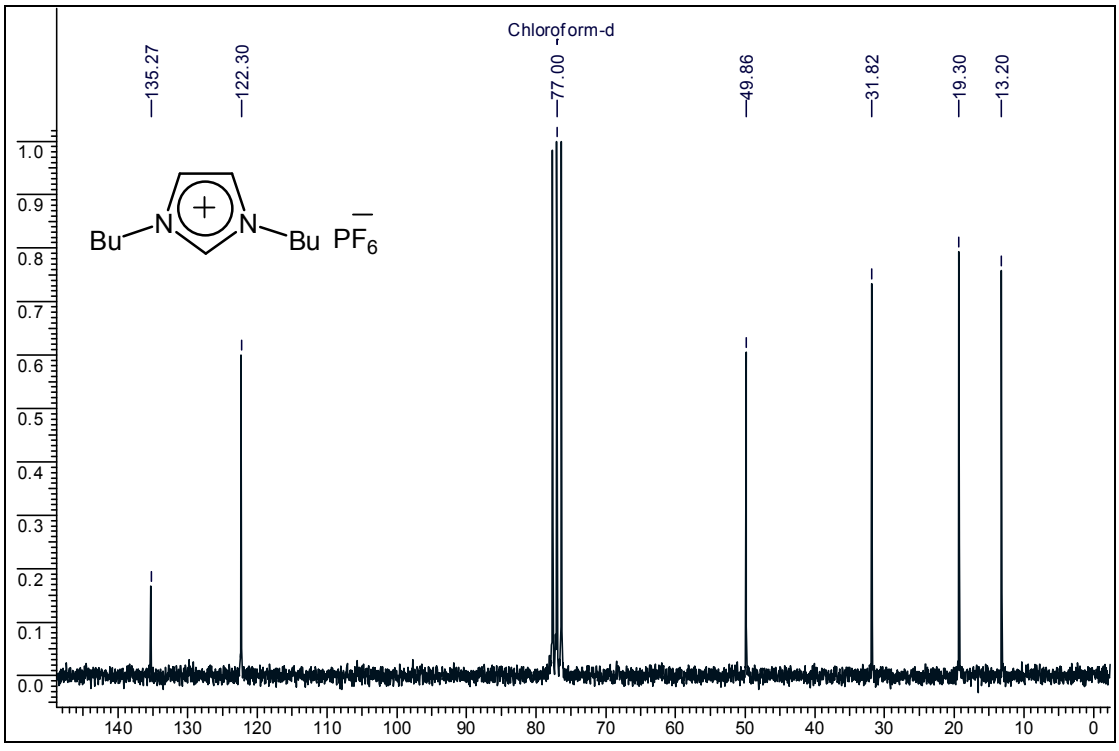
[3] ^{13}C NMR spectra of [BBIm]BF_4 (34c)



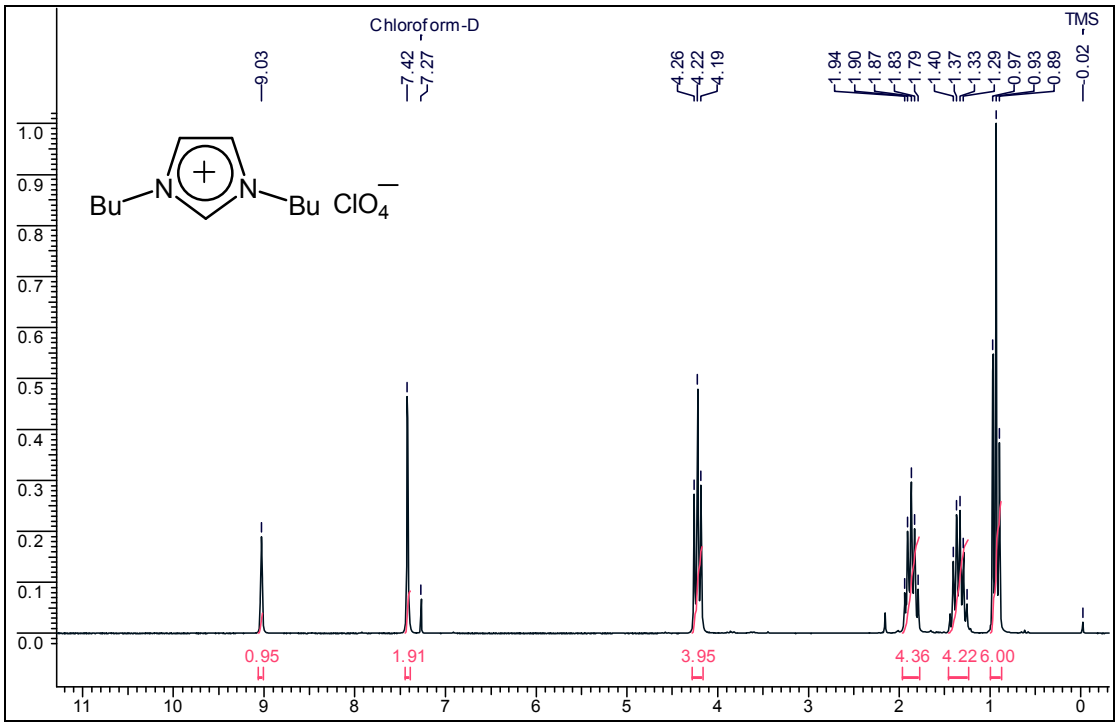
[4] ^{1}H NMR spectra of [BBIm]PF_6 (34d)



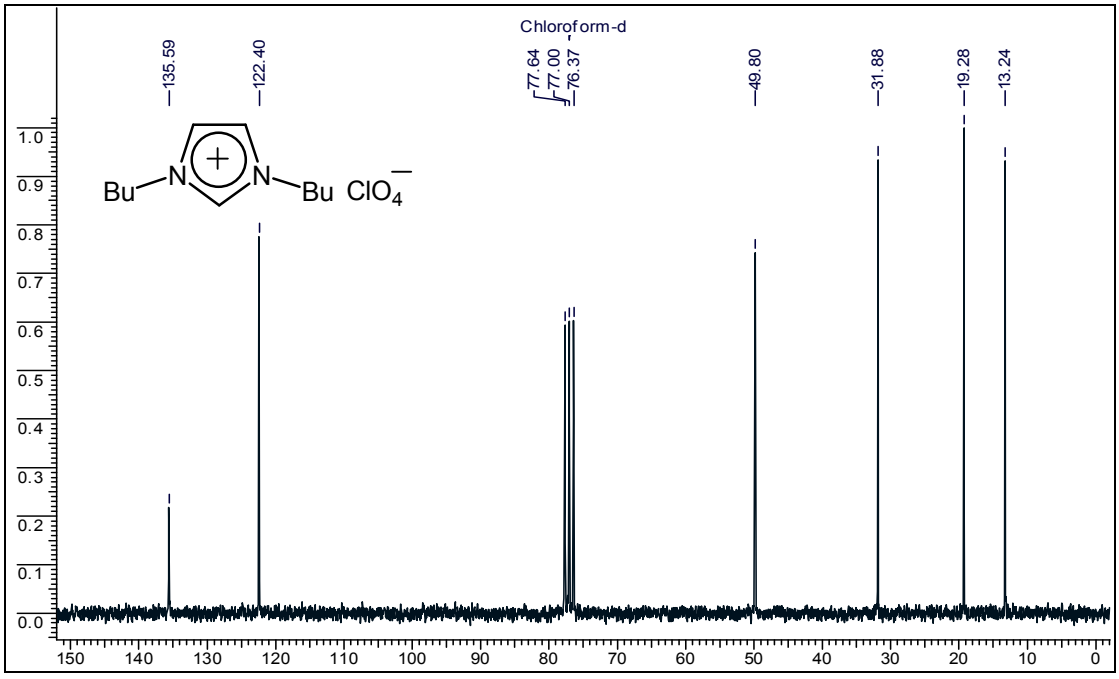
[4] ^{13}C NMR spectra of [BBIm]PF_6 (34d)



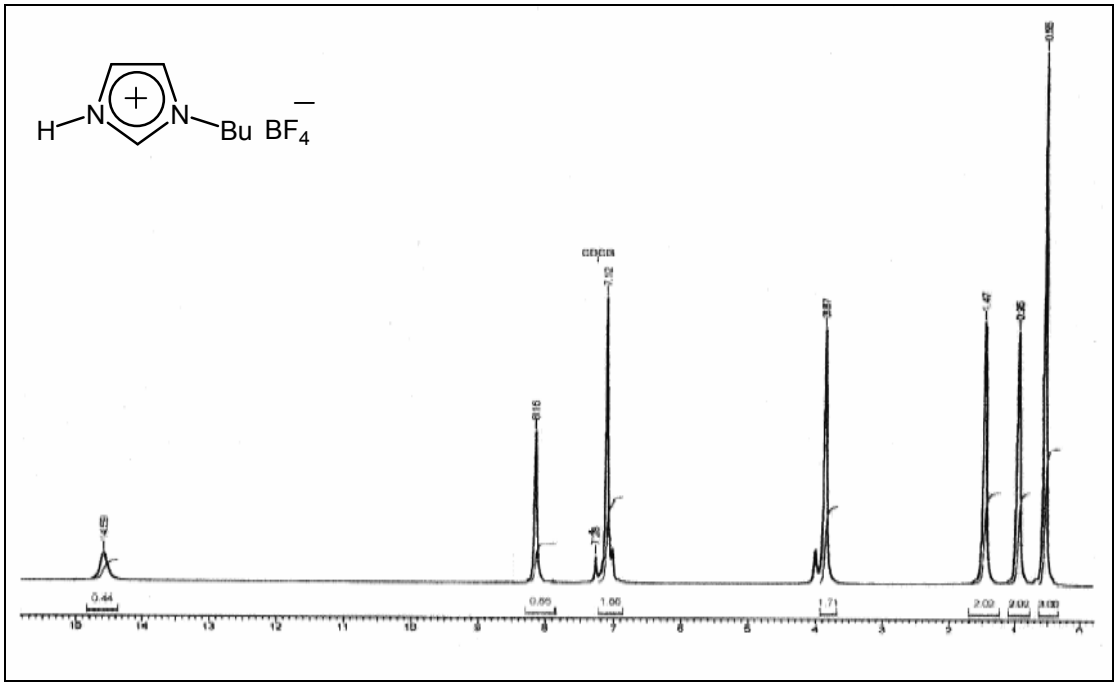
[5] ^{1}H NMR spectra of [BBIm]ClO_4 (34e)



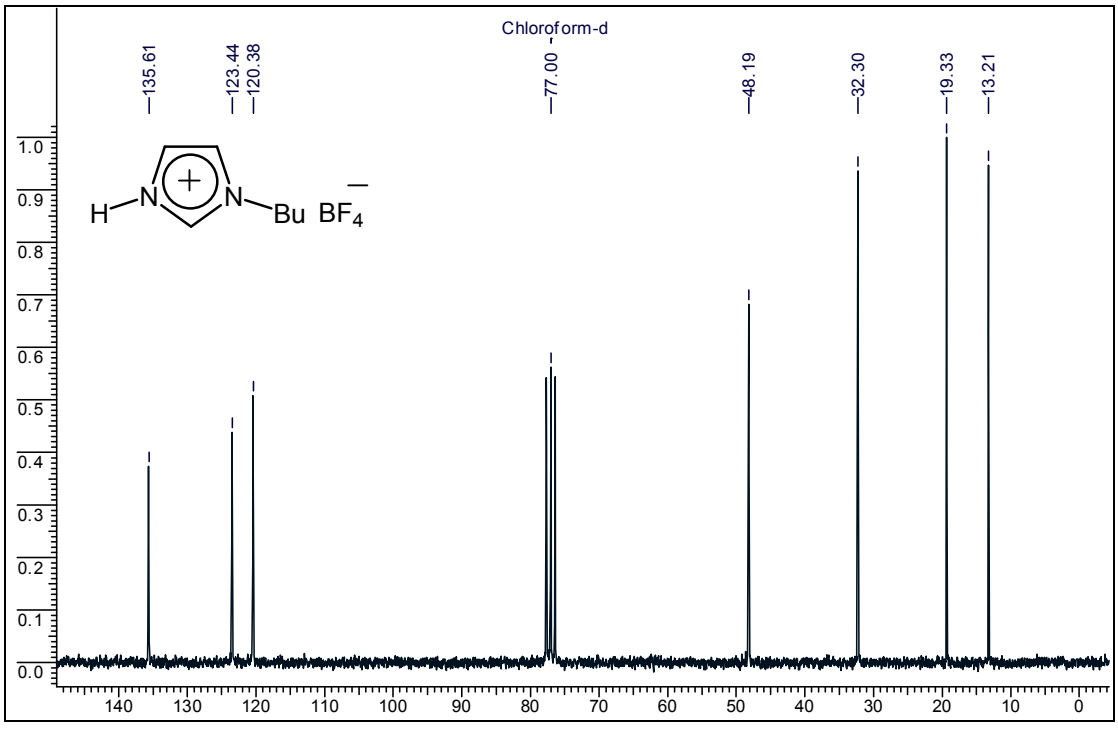
[5] ^{13}C NMR spectra of [BBIm]ClO_4 (34e)



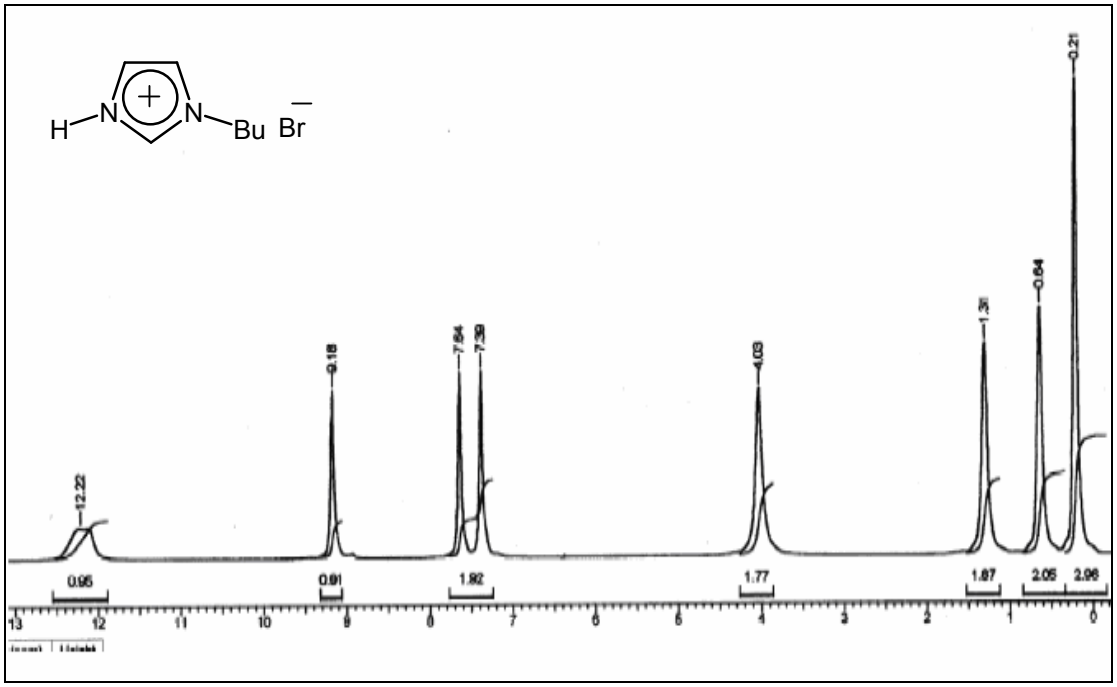
[6] ^{1}H NMR spectra of [HBIm]BF_4 (35a)



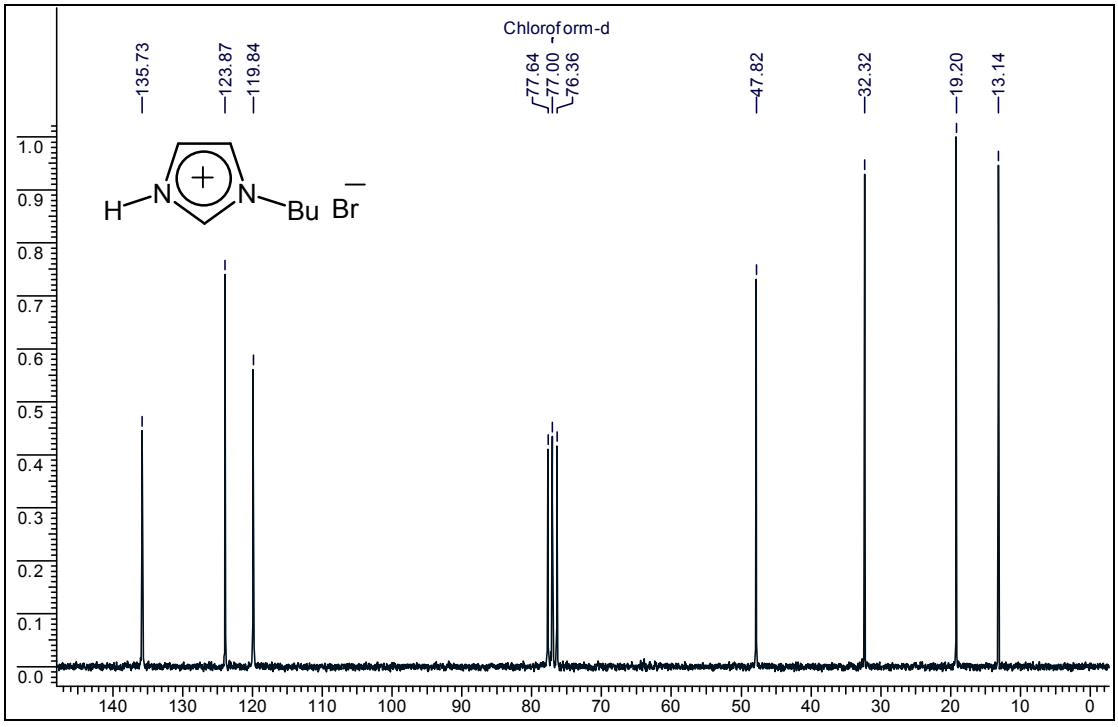
[6] ^{13}C NMR spectra of [HBIm]BF_4 (35a)



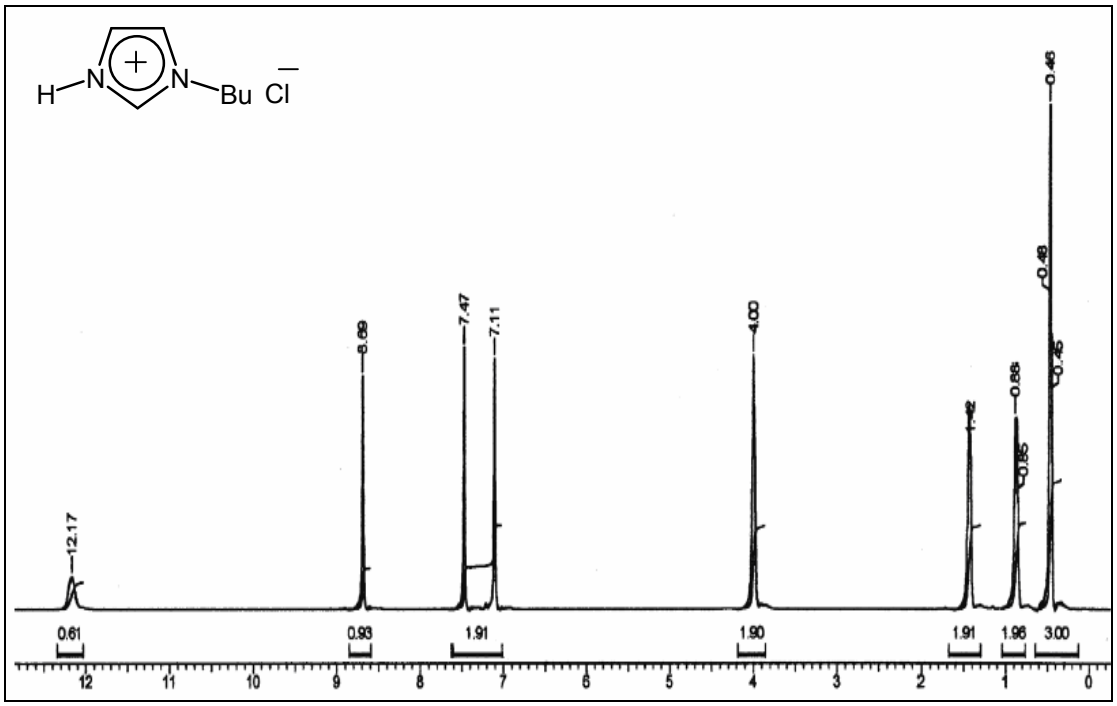
[7] ^{1}H NMR spectra of [HBIm]Br (35b)



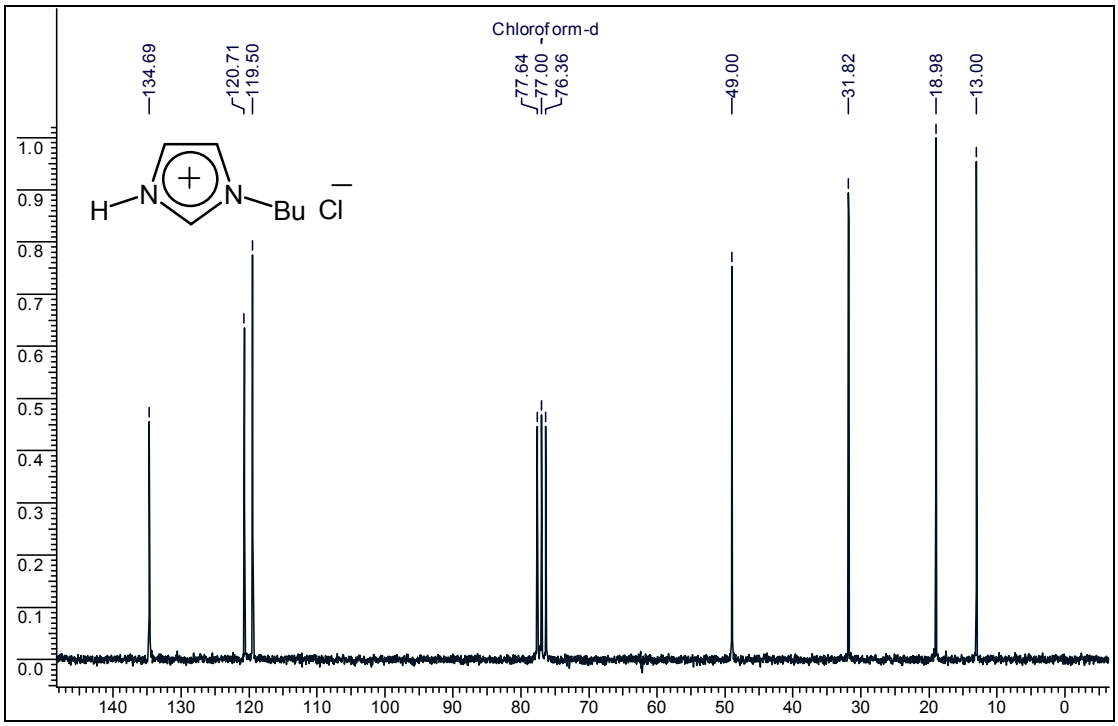
[7] ^{13}C NMR spectra of [HBIm]Br (35b)



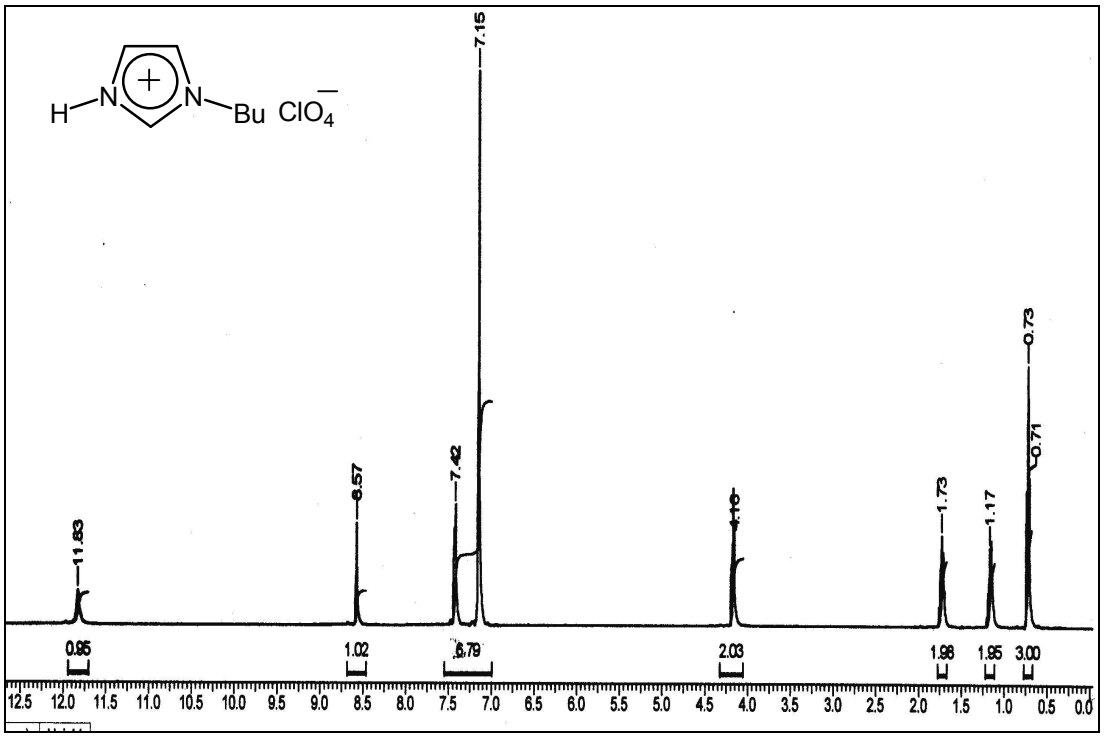
[8] ^{1}H NMR spectra of [HBIm]Cl (35c)



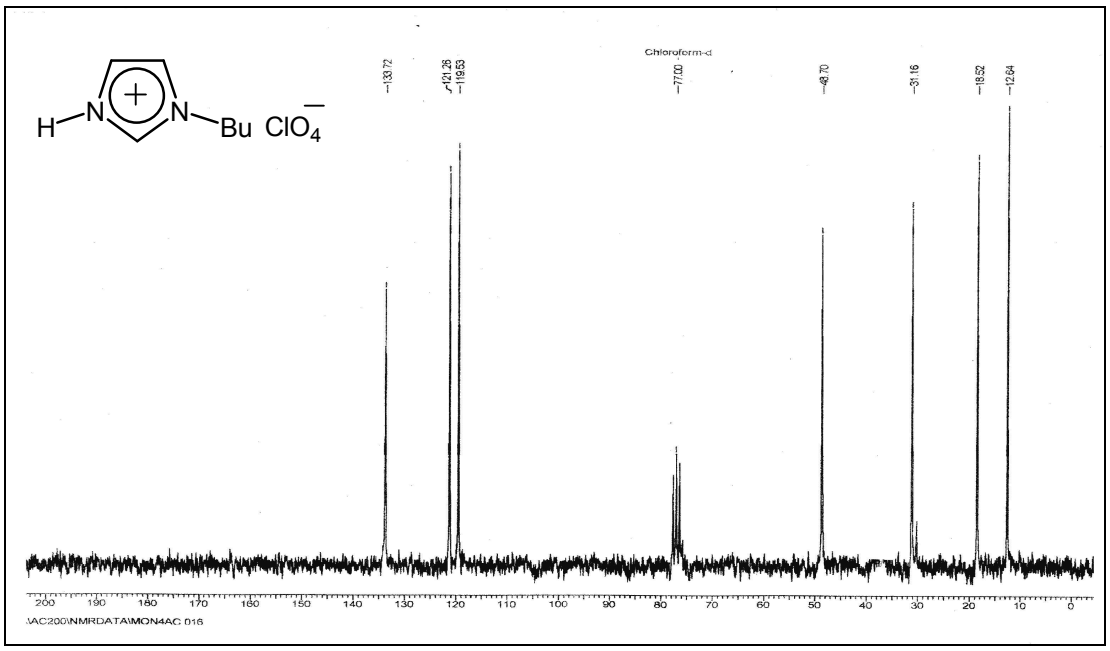
[8] ^{13}C NMR spectra of [HBIm]Cl (35c)



[10] ^{1}H NMR spectra of [HBIm]ClO_4 (35e)



[10] ^{13}H NMR spectra of [HBIm]ClO_4 (35e)



Section-C

Introduction to Sonochemistry

Introduction to Sonochemistry

1.3.1 Introduction

Ultrasound is defined as sound of a frequency beyond that to which the human ear can respond. The normal range of hearing is between 10 Hz and about 18 kHz and ultrasound is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and 40 kHz because this is the range employed in common laboratory equipment. However since acoustic cavitation can be generated well above these frequencies, recent researches into sonochemistry use a much broader range (**Fig. 8**). High frequency ultrasound from around 5 MHz and above does not produce cavitation and this is the frequency range used in medical imaging.

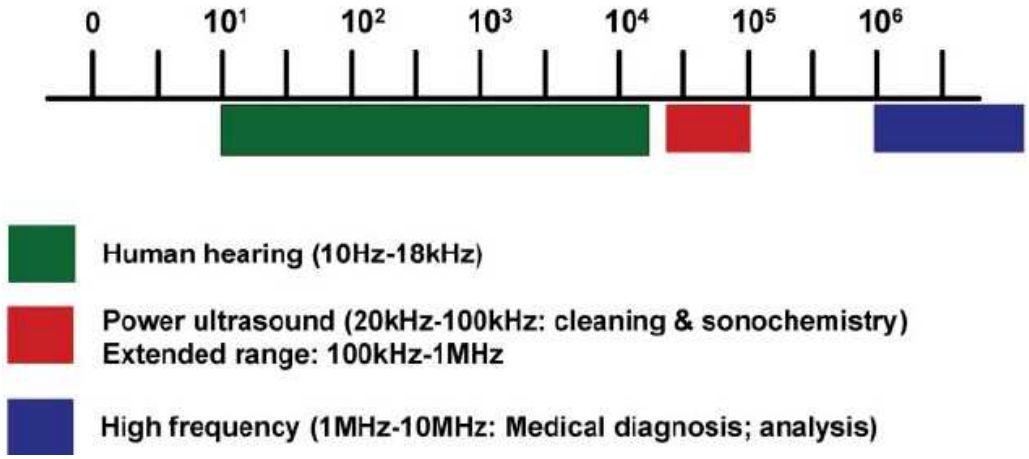


Figure 8. Sound frequencies (in Hz).

When ultrasonic energy at high power is applied to a liquid, a phenomenon called 'cavitation' occurs. Cavitation is the formation, growth and collapse of bubbles in the liquid.[1,2] This results in the 'cold boiling' of liquid. Ultrasonic vibration reduces the thickness of liquid films, enhances gas transfer and reduces bubble coalescence, which increases the interfacial area of gas transfer.[3-6] This can be used to separate gases as lighter molecules in an ultrasonic field will travel further than heavier ones. Ultrasonic energy can also be used to remove contaminants from air and to break down toxic components in soil and water. The role of ultrasound in homogeneous and heterogeneous chemistry has been well documented in the literature. Ultrasounds are waves at

frequencies above those within the hearing range of the average person, i.e., at frequencies above 16 kHz.

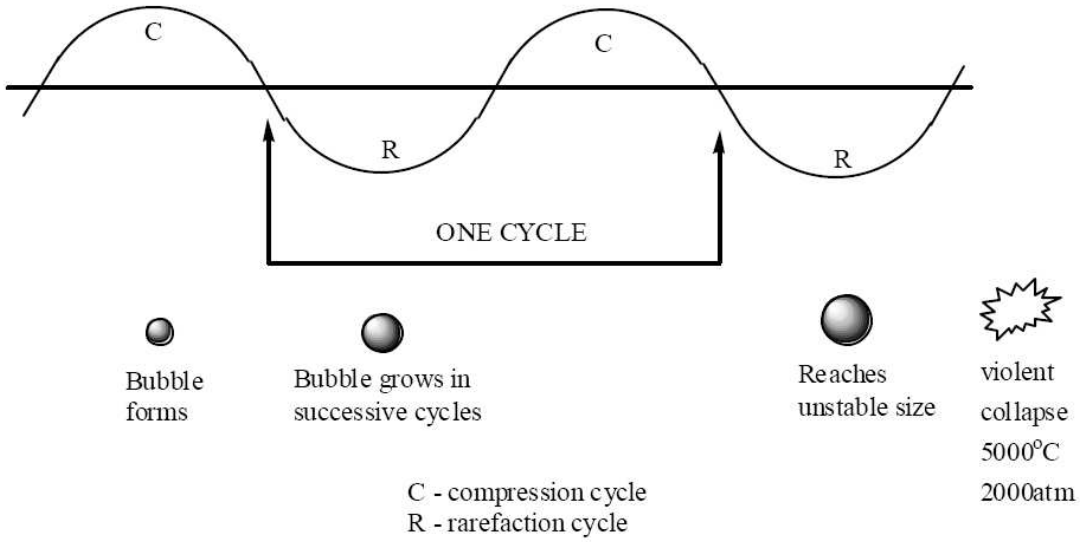


Figure 9. Sound propagation in a liquid showing cavitation bubble formation and collapse

Ultrasonic energy (high frequency sound waves) produces an alternating adiabatic compression and rarefaction of the liquid media being irradiated (**Fig. 9**). In the rarefaction part of the ultrasonic wave (when the liquid is unduly stretched or "torn apart"), microbubbles form because of reduced pressure (i.e. sufficiently large negative pressures). These microbubbles contain vaporized liquid or gas that was previously dissolved in the liquid. The microbubble can be either stable about their average size for many cycles (stable cavitation) or transient when they grow to certain size and violently collapse or implode during the compression part of the wave (transition cavitation). The critical size depends on the liquid and the frequency of the sound; at 20 kHz, for example, it is roughly 100-170 mm. The energy put into the liquid to create microvoids is released during implosion creating high local pressures upto 1000 atm and high transitory temperatures up to 5000K.[7-11] This energy releasing phenomena of the bubble formation and collapse is termed as acoustic cavitation.[12-14]

Cavitation can also be achieved by throttling a valve downstream from a pump. When the pressure at an orifice or any other mechanical constriction falls below the vapour pressure of the liquid, cavitations are generated which then collapse downstream with a recovery

of pressure, giving rise to high temperature and pressure pulses. This cavitation is termed as hydrodynamic cavitation.[15]

1.3.2 Factors influencing Sonochemical processes

Application of ultrasound to chemical transformations may be termed as Sonochemistry. Sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse.[14]

1.3.2.1 Effect of solvent

Cavities are readily formed when using solvents with high vapour pressure, low viscosity and low surface tension. The intermolecular forces in the liquid must be overcome in order to form the bubbles. Thus, solvents with high densities, surface tensions and viscosities generally have higher threshold for cavitation but more harsh condition are required when cavitation begins.[12]

1.3.2.2 Effect of ambient gas

There are several properties of gases that can affect sonochemical activities.[5] The heat capacity ratio Cp/Cv or polytropic ratio of the gas in the bubble affects the amount of heat released and, hence the final temperature produced in an adiabatic compression and the cause of the reaction. Higher temperatures and pressures are generated with monoatomic gases with higher polytropic ratio than those with polyatomic gases with lower polytropic ratio.[5] Another parameter that affects cavitational collapse is the thermal conductivity of gases. A gas with low thermal conductivity reduces heat dissipation from cavitation site following adiabatic collapse and should favour higher collapse temperature compared with high thermal conductivity gas.[1]

1.3.2.3 Effect of temperture

Unlike most of the reaction systems, lowering of reaction temperature increases the rate of reaction. This is attributed to the lowering of the solvent vapor pressure, which increases the intensity of cavitation. At low vapor pressure, less vapor has an opportunity to diffuse into the bubble and making the implosion more violent. Also, as liquid temperature decreases, the amount of gas dissolved increases and the vapor pressure of the liquid decreases. Very volatile solvents lead to relatively high pressures in the bubble and also 'cushion' the collapse.[16] The solubility of gas is also an important aspect. The more soluble the gas, the more likely it is to diffuse in to the cavitation bubble. Soluble

gases should result in the formation of larger number of cavitation nuclei and extensive bubble collapse since these gases are readily forced back to the bulk phase.[1]

1.3.2.4 Effect of pressure

Effect of pressure in reaction can cause some increase in the rate of sonochemical reaction due to the magnified effect of cavitation implosions. Too much pressure reduces the rate of reaction by decreasing the frequency or efficiency of bubble formations.[14]

1.3.2.5 Effect of acoustic intensity

An increase in ultrasound intensity implies an increase in the acoustic amplitude. The collapse time, the temperature and the pressure of collapse are all dependent on the acoustic amplitude. The cavitation bubble collapse will be more violent at higher acoustic amplitudes. So an increase in intensity will result in greater sonochemical effects in the collapsing bubble.[5,17]

1.3.2.6 Effect of acoustic power

Power delivered to the system can increase the sonochemical activity to an optimum level after which it falls.[18,19] When acoustic power increases and simultaneously increases amplitude of vibration, the maximum radius of the cavity bubble also increases as well as its time of collapse and this bubble is not able to collapse within time equal half of the period i.e. before the sound field reverses itself, the rarefaction phase begins acting on the collapsing bubble.[20,21]

1.3.2.7 Frequency of ultrasonic irradiation

Frequency has significant effect on the cavitation process because it alters the critical size of the cavitational bubble.[22-27] At high frequencies, the cavitational effect is reduced because either (i) the rarefaction cycle of the sound wave produces a negative pressure which is insufficient in its duration and/or intensity to initiate cavitation or (ii) the compression cycle occurs faster than the time for the microbubble to collapse. Lower frequency ultrasound produces more violent cavitation, leading to higher localized temperature and pressure.

1.3.3 Fundamentals of sonochemical reactions

The influence of ultrasonic energy on chemical activity may involve any of the following:[2,3,28,29]

- production of heat

- promotion of mixing (stirring) or mass transfer
- promotion of intimate contact between materials
- production of free radicals

The physical effects of ultrasound can enhance the reactivity of a catalyst by enlarging its surface area or accelerate a reaction by proper mixing of reagents. The chemical effects of ultrasound enhance reaction rates because of the formation of highly reactive radical species formed during cavitation.[4,11] Homogeneous sonochemistry examines, mainly in the liquid phase, the activity of radicals or excited species formed in the bubble gas phase during the violent implosion and their possible release into the liquid.[17] The cavitation event also gives rise to acoustic microstreaming or formation of miniature eddie current that enhances the mass and heat transfer in the liquid, and also causes velocity gradients that results in shear forces. In heterogeneous sonochemistry, the mechanical effects of cavitation resulting from the erosion action of microjets formed during the asymmetric collapse of bubbles at the vicinity of interfaces are also important.[17]

The following theories have been proposed to explain the sonochemical events.

1. hot-spot theory
2. electrical theory
3. plasma discharge theory
4. super-critical theory

The hot-spot theory suggests that a pressure of the order of 1000 atm is generated and a temperature of about 5000K results during violent collapse of the bubble.[7-9] The electrical theory suggested by Margulis[30] says that during bubble formation and collapse, enormous electrical field gradients are generated and these are sufficiently high to cause bond breakage and chemical activity. The plasma theory by Lepoint and Mullie[31] also suggests that the extreme conditions associated with the fragmentative collapse is due to intense electrical fields and seems to involve a true implosion which is related to corona-like discharges caused by fragmentation process and the formation of microplasmas inside the bubbles. Hoffmann[32] proposed super-critical theory, in which the existence of a layer in the bubble-solution interface where temperature and pressure may be beyond the critical conditions of water and which may have physical properties intermediate between those of a gas and a liquid. They also proved that supercritical water is obtained during the collapse of cavitation bubbles generated sonolytically. In general, most studies have

adopted 'hot spot' concept for experimental result interpretation. Hot spot theory suggests a sonochemical reaction as a highly heterogeneous reaction in which reactive species and heat are produced from a well defined microreactor i.e. 'cavitation bubble'.[11,33]

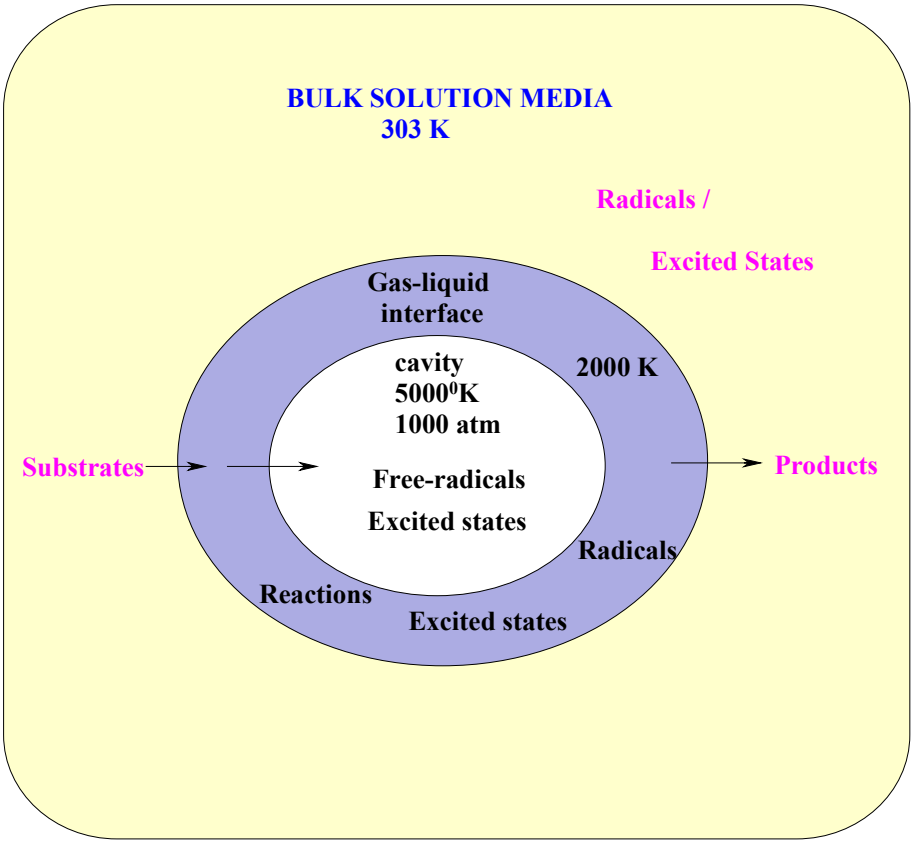


Figure 10. Schematic diagram of Cavitation Bubble

In the figure, three regions for occurrence of reactions are postulated

i) A hot gaseous nucleus

ii) An interfacial region and radial gradient in temperature and local radical density.

iii) The bulk solution at ambient temperature.

Reactions involving free radicals can occur within the collapsing bubble, at the interface of the bubble and in the surrounding liquid. Within the center of the bubble, harsh conditions generated on bubble collapse cause bond breakage and/or dissociation of the water and other vapors and gases, leading to the formation of free radicals to the formation of excited states. Solvent and/or substrates suffer homolytic bond breakage to produce reactive species. High temperatures and pressures created during cavitation

provide the activation energy required for the bond cleavage. The radicals generated either react with each other to form new molecules and radicals or diffuse into the bulk liquid to serve as oxidants. The second reaction site is the liquid shell immediately surrounding the imploding cavity, which has been estimated to heat up to approximately 2000K during cavitation implosion (**Fig. 10**). In this solvent layer surrounding the hot bubble, both combustion and free-radical reactions (involving $^{\cdot}OH$ derived from decomposition of water) occur. Pyrolysis in the interfacial region is predominant at high solute concentrations, while at low solute concentrations, free-radical reactions are likely to predominate. At the interface between bubble and bulk liquid, surface-active reagents also accumulate and species produced in the bubble first react with chemicals in the bulk liquid. It has been shown that the majority of degradation takes place in the bubble-bulk interface region.[34,35]

1.3.4 Laboratory equipment

The first requirement for sonochemistry is a source of ultrasound and whatever type of commercial instrument is used the energy will be generated via an ultrasonic transducer a device by which mechanical or electrical energy can be converted to sound energy. There are three main types of ultrasonic transducer used in sonochemistry: liquid-driven (effectively liquid whistles), magnetostrictive (based on the reduction in size of certain metals, e.g. nickel, when placed in a magnetic field) and piezoelectric. Most of the current equipment used for sonochemistry utilises transducers constructed of piezoelectric ceramics. These are brittle and so it is normal

practise to clamp them between metal blocks for protection. The overall structure is known as a piezoelectric 'sandwich'. Usually two ceramic elements are combined so that their overall mechanical motion is additive Piezoelectric transducers are very efficient and, depending on their dimensions, can be made to operate over the whole ultrasonic range. The two most common sources of ultrasound for laboratory sonochemistry are the ultrasonic cleaning bath and the ultrasonic horn or probe system.[36] These generally operate at frequencies of around 40 and 20 kHz, respectively.

1.3.4.1 The ultrasonic cleaning bath

The simple ultrasonic cleaning bath is by far the most widely available and cheapest source of ultrasonic irradiation for the chemical laboratory. It usually consist of a tank

fitted with transducers at the bottom. The reaction flask can be immersed into the tank filled with some liquid mostly water. The amount of energy, which reaches the reaction through the vessel walls is low, normally between 1 and 5 W cm.$^{-2}$ Temperature control in the commercial cleaning bath is very poor and may require additional thermostatic control (**Fig. 11**).

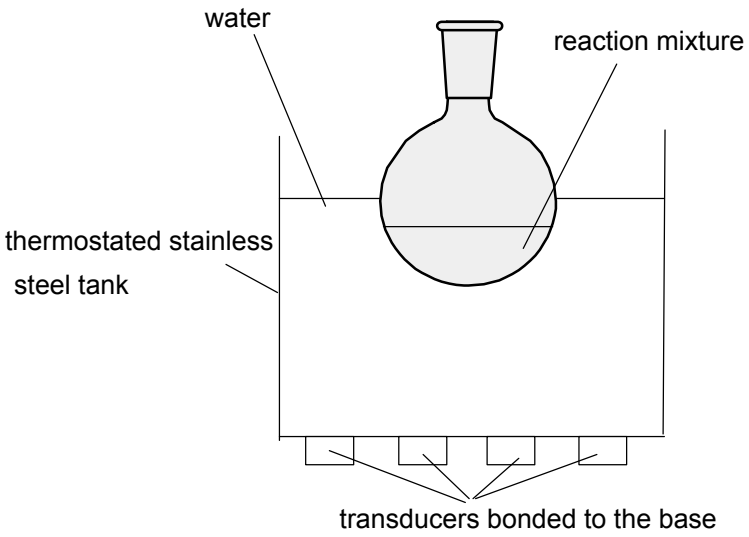


Figure 11. The ultrasonic cleaning bath in sonochemistry

1.3.4.2 The ultrasonic probe

This apparatus allows acoustic energy to be introduced directly into the system rather than rely on its transfer through the water of a tank and the reaction vessel walls (**Fig. 12**). The power of such systems is controllable and the maximum can be several hundred W cm.$^{-2}$ The probe system is more expensive than the bath and it is slightly less convenient because of the requirement of special seals for the closed reaction vessels which carry inert atmospheres or pressures above ambient or reflux temperatures. The maximum power out put can be as high as several hundreds W cm^{-2} and is tunable (**Fig. 12**).

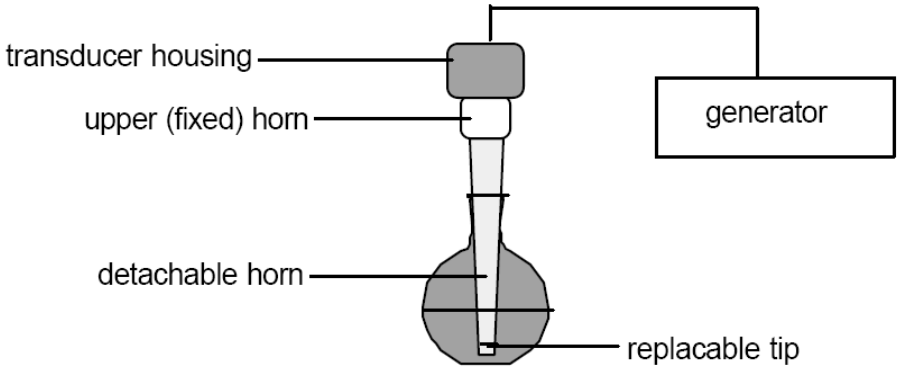


Figure 12. The ultrasonic probe system in sonochemistry

1.3.5 Rules of sonochemistry

One of the earliest tenets of sonochemistry was that it is particularly good at assisting reactions involving solid reagents. This is generally but not exclusively correct. A number of groups are attempting to gain an understanding of the underlying principles of sonochemistry in order to be able to predict which type of reaction would be most susceptible to sonication. As a result of these efforts some guidelines have been identified. An empirical classification of sonochemical reactions into three types was proposed by J.-L. Luche and was based upon the purely chemical effects induced by cavitation.[37]

a. Homogeneous systems which proceed via radical or radical-ion intermediates- This implies that sonication is able to effect reactions proceeding through radicals and further it is unlikely to effect ionic reactions.

b. Heterogeneous systems proceeding via ionic intermediates- The reaction is influenced primarily through mechanical effects of cavitation such as surface cleaning, particle size reduction and improved mass transfer.

c. Heterogeneous reactions, which include a radical pathway or a mixed mechanism i.e. radical and ionic- radical reactions will be chemically enhanced by sonication but the general mechanical effect referred to above in b may still apply. If the radical and ionic mechanisms lead to different products ultrasound should favour the radical pathway and this could lead to a switch in the nature of the reaction products.

1.3.6 Sonochemistry in ionic liquid.

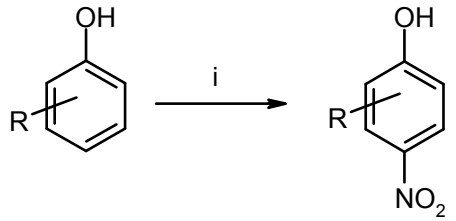
The driving energy for sonochemical organic reaction is provided by phenomenon of acoustic cavitation which is initiation, propagation and implosive collapse of the bubbles under adiabic conditions generating intercavity temperatures >5000 K and pressure up to 1200 bars. Since these micro-bubbles are unstable and collapse over a very short period of time, ca. 10^{-5} to 10^{-7} seconds, there is no bulk heating of the medium. The atmosphere of the bubbles, which contains gases, vapours of the solvent and of the volatile solutes, is compressed and heated leading to pyrolytic reactions. The resulting species, generally free radicals and other reactive intermediated are injected into the bulk medium, which remain at ambient temperature. A thermal quenching of the species occurs, followed by diverse reactions with other molecules. Thus, only volatile molecules which can penetrate the bubbles will undergo the extreme conditions produced during the collapse. In most cases, the low volatility of the substrates/solutes used and relatively higher volatility of the molecular solvents used which exerts a cushioning effect, limit the efficiency of cavitation. To overcome this, high boiling solvents such as dodecane have been used to maximize temperature within the cavity but this resulted in carbon contamination of the products due to sonochemical degradation of the solvent. Complementarily, ILs are thermally stable non-volatile media, with a polar character favoring reaction which develop charges at some stage of the pathway. A logical conclusion is that cavitation bubbles in ILs should contain essentially molecules of the solutes, leading to their preferential activation without participation of the solvent. This activation should result in increased rates of the thermolytic processes, if the whole reaction occurs inside the cavity. Moreover, this increased intensity of cavitation leads to high intensity micro-streaming enhancing mass and heat transfer in the IL which in turn can generate reactive intermediates, nano-particles etc. On the other hand it is also possible that the strong polarity of the ILs should stabilize charges in reaction intermediates, broadening thus the domain of sonochemistry to polar pathways, of low sensitivity to sonication up to now. It is worth noting here that so far Sonochemistry is a method whose privileged domain is that of reactions proceeding via radicals or radical ions.

From the above presentation of both the physical aspects of sonochemistry and the properties of ILs, it can be deduced that sonochemistry in ILs should offer a number of

advantages which was indeed found to be the case as can be seen in the following examples.

1.3.6.1 Nitration of Phenols[38]

The nitration of phenols consisting of electron donating as well as electron withdrawing substituents using ferric nitrate as nitrating agent in the IL, ethyl ammonium nitrate was carried out under ultrasound irradiation to afford the p-nitrophenols in excellent isolated yields and in very high selectivity (para to ortho ratio, 16:1). Interestingly, the corresponding reactions in a molecular solvent such as dioxane afforded the same isolated yield of the mixture of nitrophenol, the para-selectivity was poor (3:1). Considerable reaction rate enhancement was observed in the sonochemical reaction as compared to the silent stirred reaction. The products could be isolated by distillation or selective extraction from the non-volatile IL, which could be recycled giving rise to a process with minimal waste (**Scheme 2**).

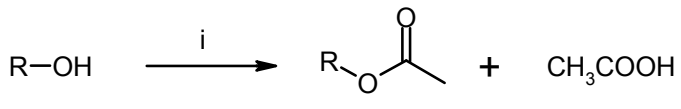


36 **37**

Scheme 2. Reaction conditions: i) ethyl ammonium nitrate, $Fe(NO_3)_3$,)))), 30ºC, 1-3 h.

1.3.6.2 The *O*-acetylation of alcohols[39]

The *O*-acetylation of a variety of alcohols with acetic anhydride to the corresponding esters has been acheived by Srinivasan *et al.* in short reaction times with excellent isolated yields under ambient conditions without the need for any additional catalyst by the combined use of ultrasonic irradiation and a 'green' room temperature ionic liquid as a reaction medium and promoter (**Scheme 3**).



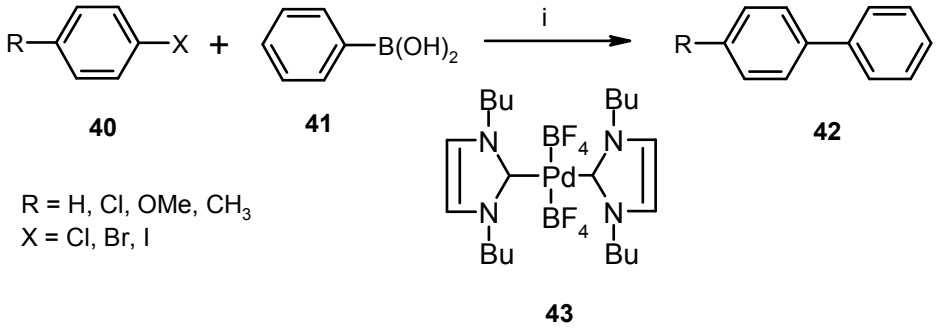
38 **39**

Scheme 3. Reaction conditions: i) [BBIm]Br, acetic anhydride,)))), 30ºC, 5-60 min.

The role of ultrasound in promoting the *O*-acetylation is evident from the fact that the corresponding reactions under stirred conditions without ultrasound (silent reactions) needed much longer time for complete conversion, with lowered yields. Likewise, the unique role of ionic liquids in promoting the sonochemical reaction was evident from the fact that the *O*-acetylation of benzyl alcohol with acetic anhydride in molecular solvents such as dichloromethane,acetonitrile, chloroform, toluene and hexane under ultrasonic irradiation did not show any conversion even after several hours of sonication.

1.3.6.3 Suzuki coupling[40]

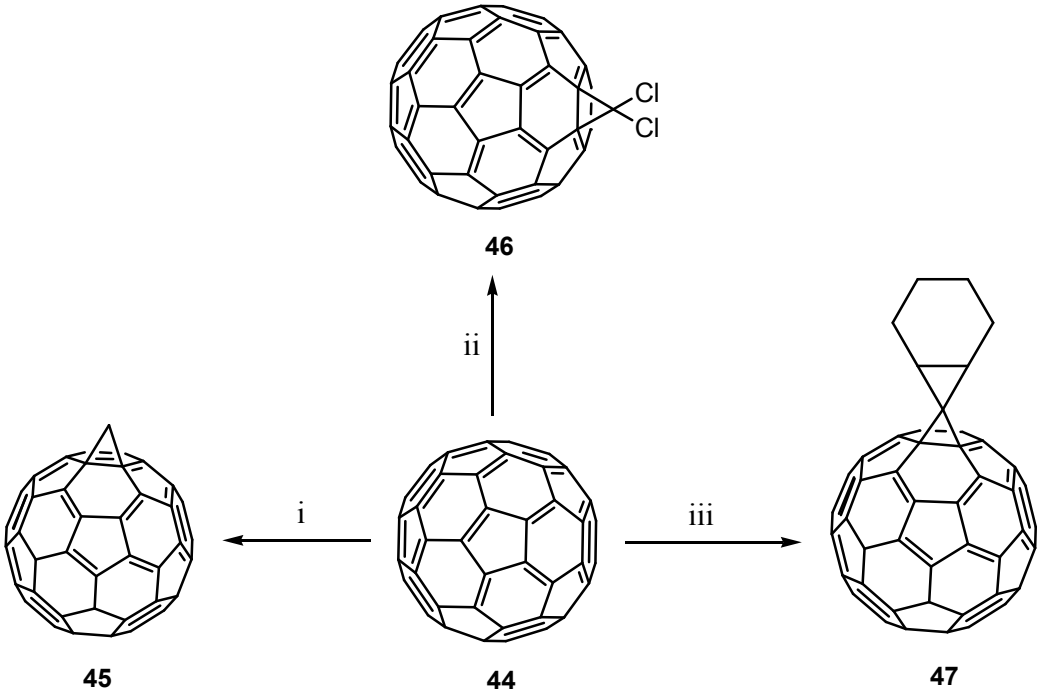
The sonochemical Suzuki coupling reaction of iodobenzene with phenylboronic acid was carried out in the IL [BBIm][BF_4] as solvent. It was observed that phenylboronic acid was insoluble in the IL under the reaction conditions. Subsequently, the sonochemical reaction was performed in the IL with methanol as co-solvent, which resulted in a homogeneous solution and complete conversion. The reactants and products could be easily separated from the IL by selective extractions. The IL recovered in its pure form could be recycled several times. The reaction carried out in this manner also led to the formation of inactive Pd black preventing the recycling of the expensive palladium catalyst. This approach, which required inert conditions, always led to the formation of inactive Pd black, thus preventing recycling of the catalyst. A modified process was sought in which the Pd–biscarbene complex **43** was synthesized and used as the catalyst for the Suzuki coupling using only methanol under sonochemical conditions. These conditions allowed the reaction to be carried out in the presence of air and no Pd nanoparticles were detected under the conditions employed for Suzuki coupling (**Scheme 4**).



Scheme 4. Reaction conditions: i) [BBIm]BF_4/MeOH, $Pd(OAc)_2$, NaOAc,)))), 30ºC, 20-90 min.

1.3.6.4 Dehalogenation of polyhalides[41]

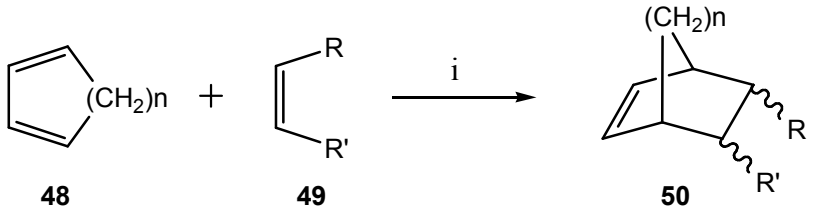
Dehalogenation of the polyhalides, $CHCl_3$, CH_2I_2, and 7,7-dibromobicyclo (4,1,0) heptane, by treatment with zinc, magnesium or NaOH powder, followed by the in situ reaction with fullerene in the presence of ultrasonic irradiation and in the ionic liquid solvents, [BMIm][PF_4] or [OMIm][BF_4], provided [6,6]-junction cycloaddition products in 53–79% yields. The good yields and the exclusive [6,6]-cycloaddition, suggests that combined effect of ionic liquid and ultrasonic irradiation play a special role in the formation of specific intermediates that lead to single products (**Scheme 5**).



Scheme 5. Reaction conditions: i) [BMIm]PF_6, Zn, CH_2I_2,))))), 30ºC, 2.5 days; ii) [BMIm]PF_6, $CHCl_3$, NaOH,))))), 3 days; iii) [BMIm]PF_6, 7,7-dibromobicyclo[4.1.0]heptane, Mg,))))), 3 days.

1.3.6.5 Cycloaddition[42]

Bravo *et al.* described a series of sonochemical cycloadditions involving cyclopentadiene or 1,3-cyclohexadiene with carbonyl dienophiles in an imdazolium-based [HMIm]BF_4 ionic liquid as reaction medium (**Scheme 6**).



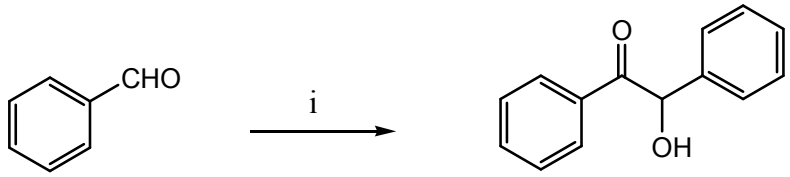
48 **49** **50**

Scheme 6. Reaction conditions: i) [HMIm]BF_4,)))), 30ºC, 60-120 min.

It was observed that ultrasound does effectively improve the cycloaddition in terms of higher yields and/or shorter reaction times when compared with the corresponding silent reactions. Stereoselectivites, however, remain practically unaffected by sonication.

1.3.6.6 Benzoin Condensation[43]

Lévêque *et al.* were carried out benzoin condensaiton in the IL [OMIm]Br at low frequency ultrasound irridation without addition of any added catalyst such as thiamin, triazolium, or thiazolium salts. No product formation was observed at silent condition. It was observed that the yield of benzoin **52** decresesed drastically when only 2% of ionic liquid was used for reaction (**Scheme 7**).



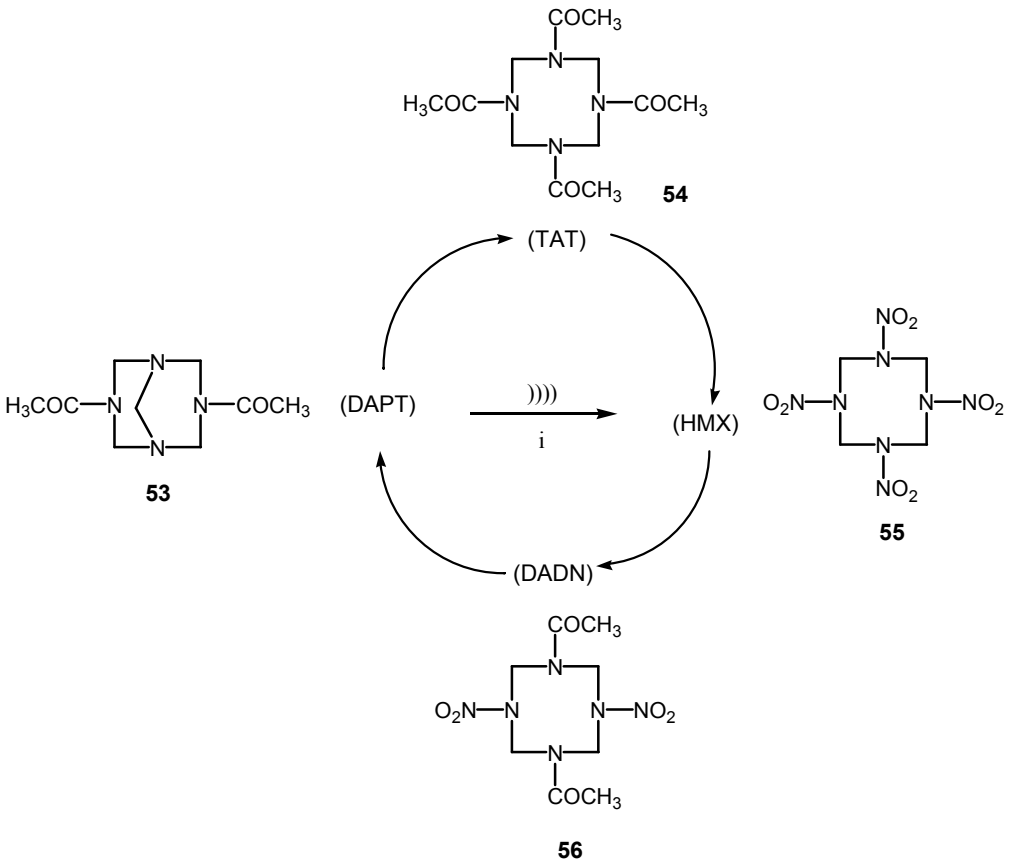
51 **52**

Scheme 7. Reaction conditions: i) [OMIm]Br, MeONa,)))), 30-50ºC, 30 min.

1.3.6.7 Nitrolysis[44]

Recently Zhiwen *et al.* developed a new process to synthesize HMX **55** (1,3,5,6-tetranitro-1,3,5,7-tetea-azacyclooctane is one of the most powerful military explosives, just as RDX (cyclotrimelhylene-trinitramine) from DAPT **53** (3,7-diacetyl-1,3,5,7-tetra-azacyclo-[3.3.1]-octane) using ultrasound in IL [BMIm]PF_6. Effect of presence and absence of ultrasound has been investigated. In the absence of ultrasound at silent condition the isolated yield of HMX was found to be 9.6%. However ultrasonically

promoted Nitrolysis of DAPT to HMX in IL has exhibited significant enhancement in yield (67%) at ambient condition (**Scheme 8**).



Scheme 8. Reaction conditions: i) [BMIm]PF_6, DAPT, N_2O_5 in HNO_3,)))), 30-50ºC, 30 min.

1.3.7 References

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Section-D

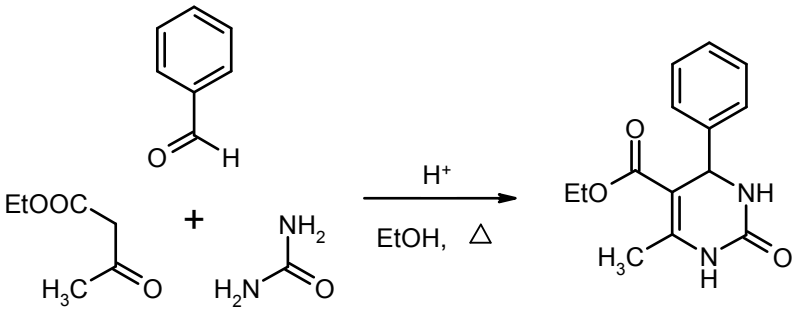
Synthesis of

3,4-Dihydropyrimidin-2-(1H)-ones

Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

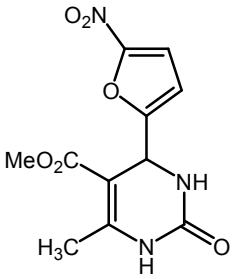
1.4.1 Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[1-5] MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components.[1-5] In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations. One prominent MCR that produces an interesting class of nitrogen heterocycles is the Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported the acid catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde, and urea.[6] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Pietro Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one (DHPMs).



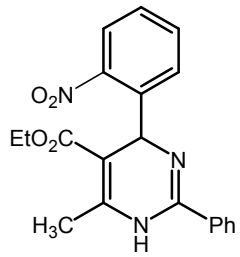
Scheme 9. Biginelli Dihydropyrimidine Synthesis

Apart from a series of publications by Karl Folkers[7] in the mid 1930s, the "Biginelli reaction" was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction shown in **Scheme 9** was gradually extended by variation of all three building blocks such as aldehydes, 1,3 diketone and urea, allowing access to a large number of multifunctionalized dihydropyrimidines.[8]



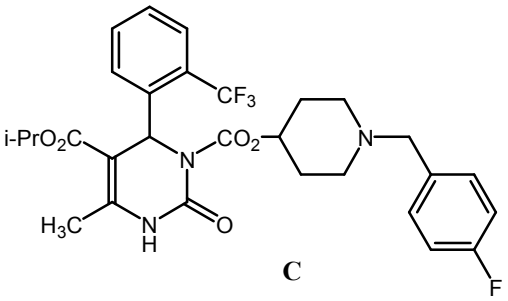
A

Nitractin
antiviral



B

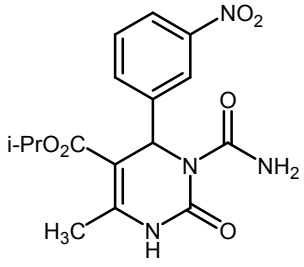
Calcium channel blocker



C

SQ32547

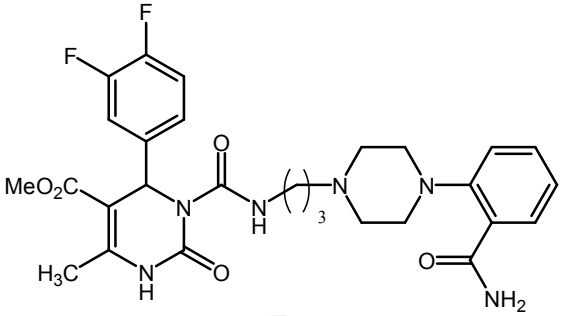
antihypertensive activity



D

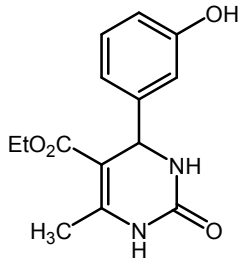
SQ32926

antihypertensive agent



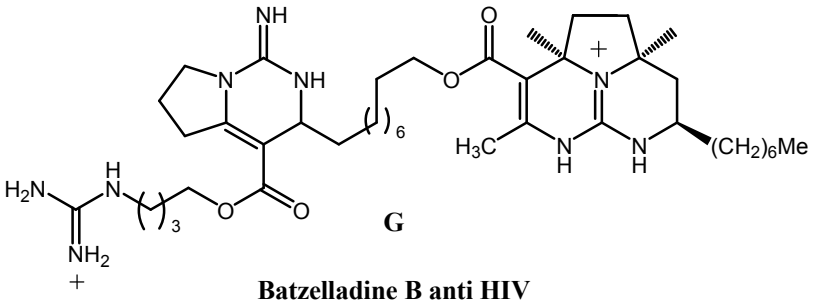
E

adrenocepor-selective anatogonists



F

Monastrol
anticancer



G

Batzelladine B anti HIV

Figure 13. Examples of biologically active DHPMs

During the last 20 years extensive studies on the pharmacology of this ring system have been reported, such as the nitrofuryl-substituted analog nitractin (**A**) (**Fig. 13**) was

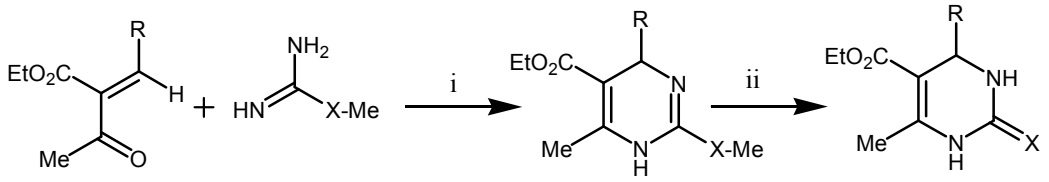
developed, which displayed good activity against the viruses of the trachoma group[9-10] in addition to showing modest antibacterial activity.[11] The partly reduced pyrimidine derivative (**B**) which closely mimics the dihydropyridine (DHP) scaffold are potent calcium channel blockers.[12] More recently, appropriately functionalized DHPMs have emerged as, orally active antihypertensive agents (**C**, **D**)[13-15] or α_{1a} adrenoceptor-selective antagonists (**E**).[16] A new highlight in this context has been the identification of the structurally rather simple DHPM Monastrol (**F**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest.[17] Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs.[17] Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have been isolated.[18] Most notable among these are the batzelladine alkaloids A and B (**G**), which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.[19]

1.4.2 Review of Literature

In recent years, interest in this multicomponent reaction has increased rapidly and several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis have been reported. However, some of these procedures involve difficulties such as the use of stoichiometric amounts of catalysts, high temperatures, the use of metal halides as catalysts, the separation of the product from the catalyst, etc. Moreover, the recovery and reuse of catalysts in any such process offers advantages in terms of a clean and environmentally benign process.

Atwal *et al.* [20]

Atwal and co-workers reported a more reliable approach to Biginelli compounds called 'Atwal modification' of the Biginelli reaction. In the first step an unsaturated ketoester **57** is condensed with a suitable protected urea or thiourea derivative **58** in the presence of sodium bicarbonate. The reaction presumably proceeds through a Michael addition product and affords dihydropyrimidines **59.** Deprotection with HCl or trifluoroacetic acid/ ethanethiol leads to the desired Biginelli compounds **60** in good overall yield (**Scheme 10).**

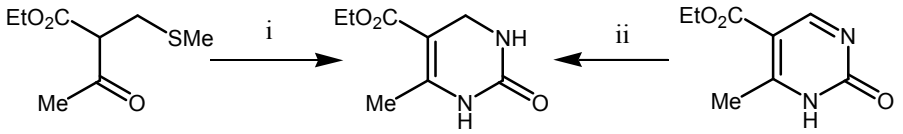


57 **58** **59** **60**

R = aryl or alkyl X = O, S

Scheme 10. Reaction conditions: (i) $NaHCO_3$, DMF, 100 ºC, 55-70%; (ii) aq. 10% HCl, MeOH, 60 ºC, or trifluoroacetic acid, ethanethiol, 60 ºC, 40-87%.

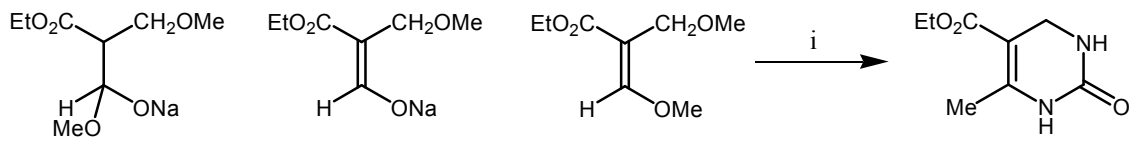
Apart from the procedure described in **Scheme 10** there are few other methods that leads to Biginelli compounds. Most of them however, are limited in their scope and are hardly ever used for synthetic purposes. When substituted acetoacetate **61** was allowed to react with urea, elimination of MeSH was takes place to furnish DHPM compound **62**.[21] The same compound **62** is obtained upon hydrogenation of pyrimidine **63** with H_2/Pt **(Scheme 11).**



61 **62** **63**

Scheme 11. Reaction conditions: (i) urea, DMF, 100 ºC, 60%; (ii) 10% Pt/C, H_2, (1 atm), MeOH, 60 ºC, 80%.

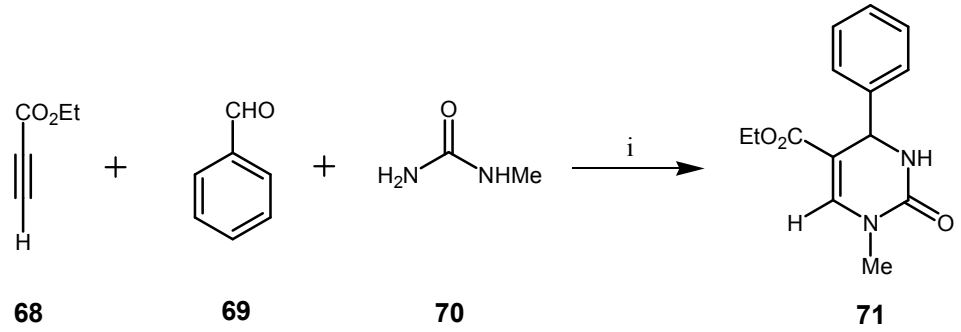
A route leading to DHPM **67** having a hydrogen atom in position 6 is the acid catalyzed condensation of urea with precursors such as sodium salt of ethyl-3-methoxy-2-(methoxymethyl)propionate **64**, sodium enolate of methyl 2-formyl-3-methoxy-propionate **65** or ethyl 3-hydroxy-2-(methoxymethyl)acrylate **66 (Scheme 12).**[22]



64 **65** **66** **67**

Scheme 12. Reaction conditions: (i) urea, aq. 10% HCl, MeOH, 60 ºC, 30-75%.

Another route leading to Biginelli compounds with a hydrogen atom at 6 position of DHPM **71** is the condensation of ethyl propiolate with *N*-methylurea and benzaldehyde **(Scheme 13)**[23].



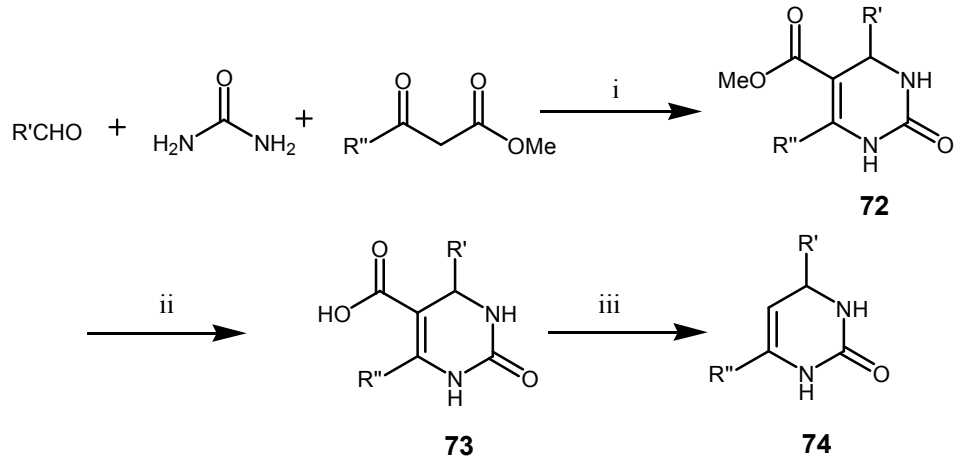
68 **69** **70** **71**

Scheme 13. Reaction conditions: (i) aq. 10% HCl, EtOH, 60 ºC, 55%.

Literature search also revealed that several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis are known in the literature. Many of these methods make use of transition metal based Lewis acid catalysts for Biginelli dihydropyrimidine synthesis such as $InCl_3$,[24a] $LaCl_3$,[24b] $Yb(OTf)_3$,[25] $CeCl_3$,[26] $BiCl_3$,[27a] $Mn(OAc)_3$,[28] $FeCl_3$,[29] $NiCl_3$,[30] $In(OTf)_3$,[31] $ZnCl_2$,[32] $MgBr_2$,[33] $Sr(OTf)_2$,[34] and $Ni(NTf_2)_2$, $Cu(NTf_2)_2$ and $Yb(NTf_2)_3$[35] etc. In this section we have covered some of more significant and useful synthetic methods for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones.

Patane *et al.*[36]

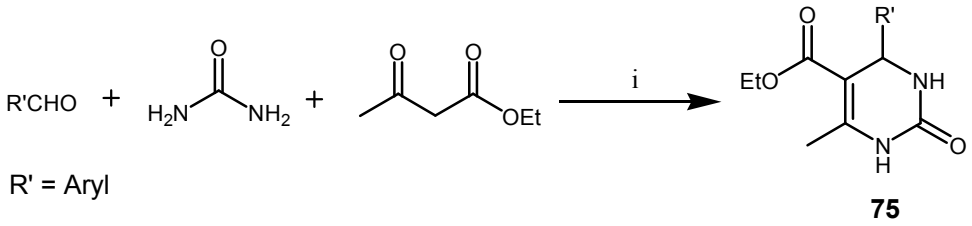
Patane and co-worker developed a new procedure for the synthesis of 5-unsubstituted 3, 4-dihydropyrimidin-2-(1*H*)-ones which represent a significant improvement over existing methods. In this method classical Biginelli products **72** was further hydrolyzed with 1 N NaOH yielding corresponding acids **73** which are decarboxylated with sodium hydride to produce 5-unsubstituted DHPMs **74**. This method provides a variety of new DHPMs **74** ring systems accessible for inclusion into pharmacologically important agents **(Scheme 14).**



Scheme 14. Reaction conditions: (i) $BF_3{\cdot}OEt_2$, THF, cat. AcOH, cat. CuO, reflux, 45-80%; (ii) 1N NaOH, MeOH, 70 ºC, 1h, 25 ºC, 12h, 60-70%; (iii) NaH, dry MeOH, reflux, 10 min 70-80%.

Sartori *at al.*[37]

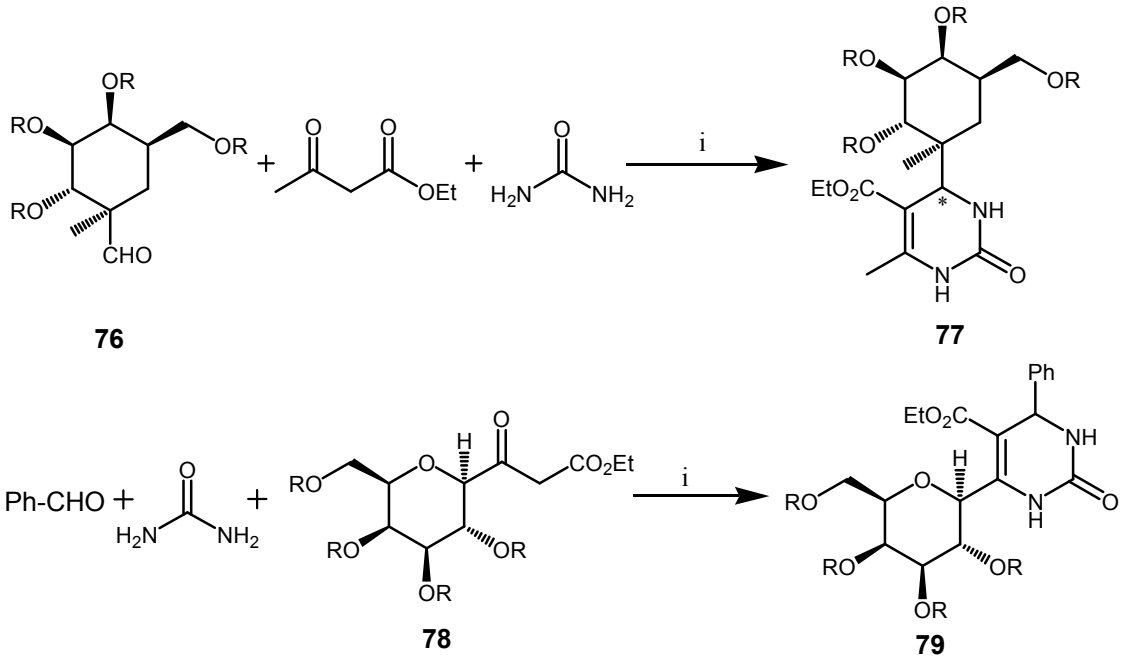
Sartori *et al.* were efficiently carried out the Biginelli reaction under solvent free conditions or in water in presence of clay catalyst (KSF), and it gives good yields of dihydropyrimidinone **75** up to 88 % at 100 ºC **(Scheme 15).**



Scheme 15. Reaction conditions: (i) KSF, 100 ºC, 74-88%.

Dondoni *et al.*[38]

Dondoni *et al*. demonstrated that the three-component Biginelli reaction can be applied to the synthesis of different mono- and bis-*C*-glycosylated DHPMs using $CuCl/AcOH/BF_3{\cdot}Et_2O$ as a promoter. Given the availability of various sugar aldehydes **76** and keto esters **78**, the access to a combinatorial library of glycosylated Biginelli products **77**, **79** with a wide range of structural and stereochemical library of dihydropyrimidinone glycoconjugates is obtained. This new concept was applied to the synthesis of two C4 epimer monastrol analogues bearing the ribofuranosyl moiety at C6 position (**Scheme 16**).



Scheme 16. Reaction conditions: (i) CuCl/AcOH/BF_3·Et_2O, 4ºA MS, THF, 65 ºC, 12-24h.

Deng *et al.*[39]

Deng *et al.* reported an improved method for the synthesis of Biginelli DHPMs by using room temperature ionic liquids (1-*n*-butyl-3-methylimidazolium tetrafluoroborate (0.4 mol% of [BMIm]BF_4) as catalyst under solvent-free and at 100 ºC. The main advantages of this methodology are: (1) relatively simple catalyst system; (2) shorter reaction times; (3) higher yields; (4) free of organic solvent, and (5) easy to handle synthetic procedure.

Kappe *et al.*[40]

Kappe *et al*. introduced automated sequential microwave-assisted library synthesis. For this purpose a dedicated single-mode microwave reactor with a robotics interface including a liquid handler and gripper was employed. The liquid handler allows dispensing of reagents into the Teflon sealed reaction vials, while the gripper moves each sealed vial in and out of the microwave cavity after irradiation. This technology was employed for the Biginelli three-component cyclocondensation reaction. For most building block combinations 10 min of microwave flash heating at 120 °C using AcOH/EtOH (3:1) and 10 mol% $Yb(OTf)_3$ as solvent/catalyst system proved to be

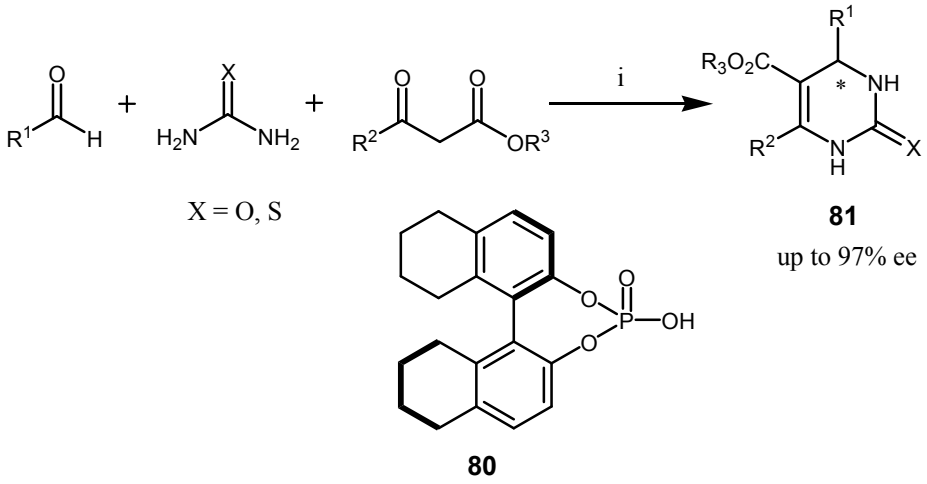
successful, leading to an isolated yield of 40-70% of DHPMs. This flexibility is a distinct advantage of sequential over parallel microwave-assisted processes where all reactions are exposed to the same irradiation conditions.

Debache *et al.*[41]

Debache *et al*. employed phenylboronic acid as catalysts to promote the Biginelli three-component condensation of a diversity of aromatic aldehydes, ethyl acetoacetate and urea or thiourea.

Gong *et al.*[42]

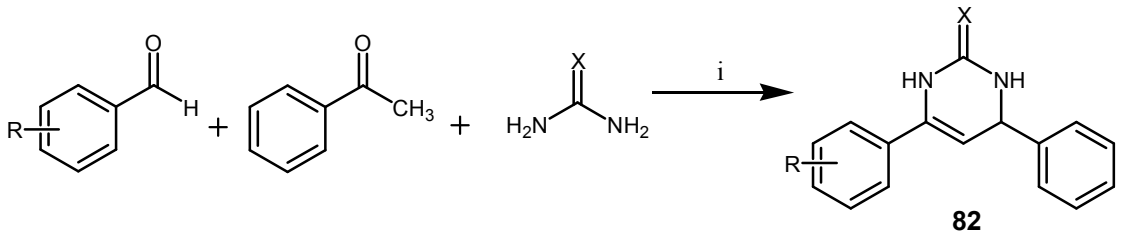
Gong *et al.* discovered the first organocatalytic asymmetric Biginelli reaction. The optimal chiral phosphoric acid **80**, derived from H_8-binol, afforded the reaction in high yields with excellent enantioselectivities of up to 97% ee **(Scheme 17).**



Scheme 17. Reaction conditions: (i) 10 mol% **80**, CH_2Cl_2, 25 ºC, 4 days, 40-86%.

Wang *et al.*[43]

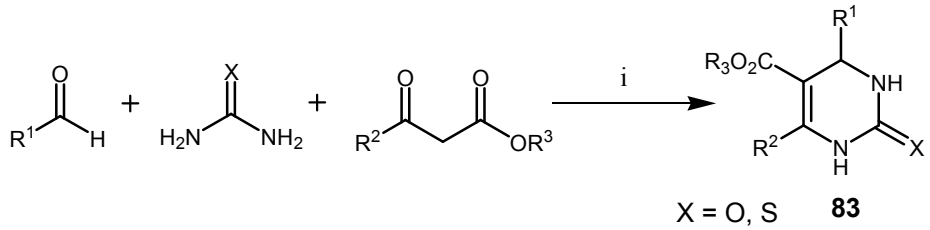
Wang *et al.* reported the microwave-assisted three-component Biginelli reactions in the presence of ZnI_2 as a catalyst expanding the synthetic scope of the multicomponent Biginelli reaction with ketones instead of activated β-dicarbonyl compounds (acetoacetate) for the synthesis of interesting 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones **82** in 75-96 % yield **(Scheme 18).**



Scheme 18. Reaction conditions: (i) ZnI_2, MW, 5 min, 75-96%.

Kumar *et al.*[44]

Very recently Kumar *et al.* successfully developed an efficient and versatile chemo-enzymatic method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones from the reaction of aldehydes, β-keto esters and urea/thiourea catalyzed by bakers' yeast *(Saccharomyces cerevisiae)* at room temperature. The process does not require the use of any volatile organic solvent and harmful metal catalyst **(Scheme 19).**



Scheme 19. Reaction conditions: (i) Bakers' yeast, D-glucose, phosphate buffer (pH 7.0), rt, 24 h., 62-84%.

1.4.3 Present work

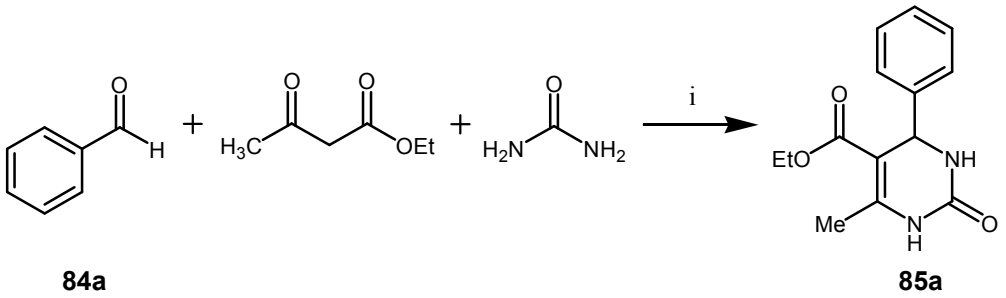
1.4.3.1 Objective

It is seen from the foregoing discussion that there are many catalytic methods available in the literature for the synthesis of dihydropyrimidinones (DHPMs). However most of the methods reported above use expensive catalysts, strong acidic conditions, higher temperatures and require longer reaction times. Some of the methods resulted in unsatisfactory yields and involved cumbersome product isolation procedures. Consequently, we thought, there is scope for further innovation towards milder reaction conditions, absence of a catalyst, short reaction times and better yields which can possibly be achieved by a combination of 'green' room temperature ionic liquids (ILs) as solvents and ultrasound as energy source for this multicomponent reaction (MCR).

The use of ultrasound in these ILs, which have no vapour pressure, should change considerably the characteristics of cavitation in the bulk and force even less volatile substrates to undergo the cavitational activation. Continuing our investigations in this area, we have evaluated a novel synthesis of DHPMs promoted by the combined use of ultrasound and the IL, 1-*n* butylimidazolium tetrafluoroborate, [HBIm]BF_4 under ambient conditions in excellent isolated yields in short reaction times.

1.4.3.2 Results and discussion

In a model study a mixture of benzaldehyde, ethylacetoacetate and urea was sonicated in ionic liquid [BBIm]Br up to 80 min at ambient condition. The products 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one **85a** was easily isolated by dilution with water and filtration of the precipitated DHPM. The compound **85a** was recrystallized from EtOH and characterized **(Scheme 20).**



84a **85a**

Scheme 20. Reaction conditions: (i) [BBIm]Br,)))), 28 ºC, 80 min, 92%.

The formation of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one **85a** was confirmed by ^{1}H, ^{13}C-NMR, IR, and MS spectroscopy. The IR spectrum of the compound **85a** showed typical absorption band in the region 1637 and 1721 cm^{-1} for amide and ester C=O stretching frequencies respectively. The ^{1}H-NMR spectrum exhibits benzylic proton signal at δ 5.14 and typical broad signals at δ 7.73 and δ 9.19 suggesting cyclic amide NH protons present in the molecule. The ^{13}C-NMR spectra showed typical amide and ester carbonyl carbon signals at δ 152.2 and 165.4 respectively confirming the formation of **85a.**

As we had synthesized several ionic liquids (ILs) based on 1,3-di-*n*-butylimidazolium salts [BBIm]X and 1-*n*-butyl imidazolium salts [HBIm]X. Obviously, our next target was to find out the best ionic liquid among them. Several ILs belonging to the [BBIm] and

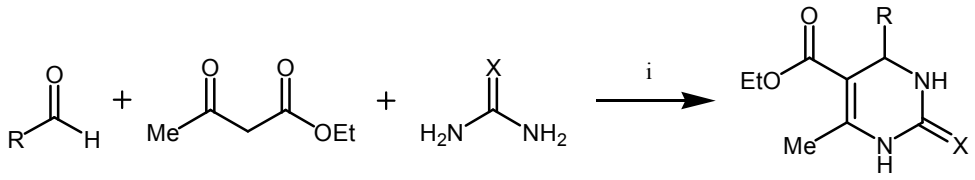
[HBIm] series were screened for the typical sonochemical MCR of benzaldehyde, ethyl acetoacetate and urea to afford 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one **85a** The results are recorded in **Table 13**.

Table 13. The Biginelli reaction of **84a** with EAA and urea in various ILs

Entry	Ionic liquid	Time	*Yield (%)
1	[BBIm]Br	80	92
2	[BBIm]Cl	75	88
3	[BBIm]ClO_4	95	87
4	[BBIm]BF_4	110	86
5	[BBIm]PF_6	125	83
6	[HBIm]Br	60	66
7	[HBIm]Cl	60	64
8	[HBIm]ClO_4	90	75
9	[HBIm]BF_4	45	97

*Isolated yields of **85a.**

Evidently, the IL [HBIm]BF_4 afforded the best results. Consequently, a variety of aldehydes including aliphatic, aromatic, cyclic and cinnamyl aldehydes were chosen to be condensed with ethyl acetoacetate and urea (or thiourea) using IL [HBIm]BF_4 as the reaction medium as shown in the **Scheme 21**.



84a-v **85a-v**

Scheme 21. Reaction conditions: (i) [HBIm]BF_4,)))), 28 ºC, 45-70 min, 82-97%.

All the reactions were monitored by TLC and taken to completion. The results are recorded in **Table 14**. All the known and new compounds were well characterized by melting point, IR, ^{1}HNMR, ^{13}C-NMR and mass spectral data. For the known compounds,

the values were in agreement with those reported in literature. It can be observed that all the aldehydes have reacted in short reaction times under ambient conditions to afford the DHPMs in very good to excellent isolated yields.

Table 14. Condensation of aldehydes **85a-v** with EAA and urea/thiourea in $[HBIm]BF_4$

Entry	R-	Atom 'X'	Product **85**	Time/min	Yield* (%)	Mp (ºC)
1	C_6H_5	O	**85a**	45	97	200-202
2	2-Cl-C_6H_4	O	**85b**	30	90	221-223
3	3-Cl-C_6H_4	O	**85c**	45	92	190-193
4	4-Cl-C_6H_4	O	**85d**	60	85	212-214
5	2,5-$(Cl)_2$-C_6H_3	O	**85e**	45	92	>290
6	3-NO_2-C_6H_4	O	**85f**	45	90	226-228
7	4-NO_2-C_6H_4	O	**85g**	60	85	206-208
8	3-OMe-4-OH–C_6H_3	O	**85h**	50	88	228-230
9	4-OMe-C_6H_4	O	**85i**	60	85	201-203
10	2,5-$(OMe)_2$-C_6H_3	O	**85j**	55	82	210-212
11	3,4,5-$(OMe)_3$-C_6H_2	O	**85k**	45	90	180-182
12	4-Br-C_6H_4	O	**85l**	60	88	203-205
13	2-Br-C_6H_4	O	**85m**	60	85	206-208
14	3-Pyridyl	O	**85n**	60	82	218-220
15	2-Furyl	O	**85o**	45	90	206-208
16	c-C_6H_{11}	O	**85p**	50	88	236-238
17	1-Naphthyl	O	**85q**	50	90	246-248
18	C_6H_5-CH=CH-	O	**85r**	45	85	228-230
19	*m,di-tert*-Bu, *p*-OH-C_6H_2	O	**85s**	60	92	238-240
20	C_6H_5	S	**85t**	50	88	205-207
21	3,4,5-$(OMe)_3$-C_6H_2	S	**85u**	55	82	202-204
22	4-OMe-C_6H_4	S	**85v**	70	84	151-153

*Isolated yields

The process tolerates aromatic aldehydes containing both electron donating and electron withdrawing substituents. The substituted aromatic, heterocyclic as well as aliphatic

aldehydes all produced significantly improved yields as compared to the classical Biginelli protocol.

The products were easily isolated by dilution with water and filtration of the precipitated DHPMs. The DHPMs, thus isolated were homogeneous on TLC and were pure enough for all practical purposes. However, they were subjected to further purification by recrystallization for characterization and the yields reported are after this procedure. The combined aqueous filtrate was then subjected to distillation at 80 °C/10 mmHg for 4 h to remove water leaving behind [HBIm]BF_4 in near quantitative yield. The IL, thus recovered could be used at least three times for the sonochemical synthesis of **85a** without loss in yield. Furthermore, the stability of the IL under the sonochemical reaction conditions and recycle batches was investigated by recording the ^{19}F NMR spectra of the IL recovered after the reaction (**Fig. 14**) as such before the reaction (**Fig. 15**),

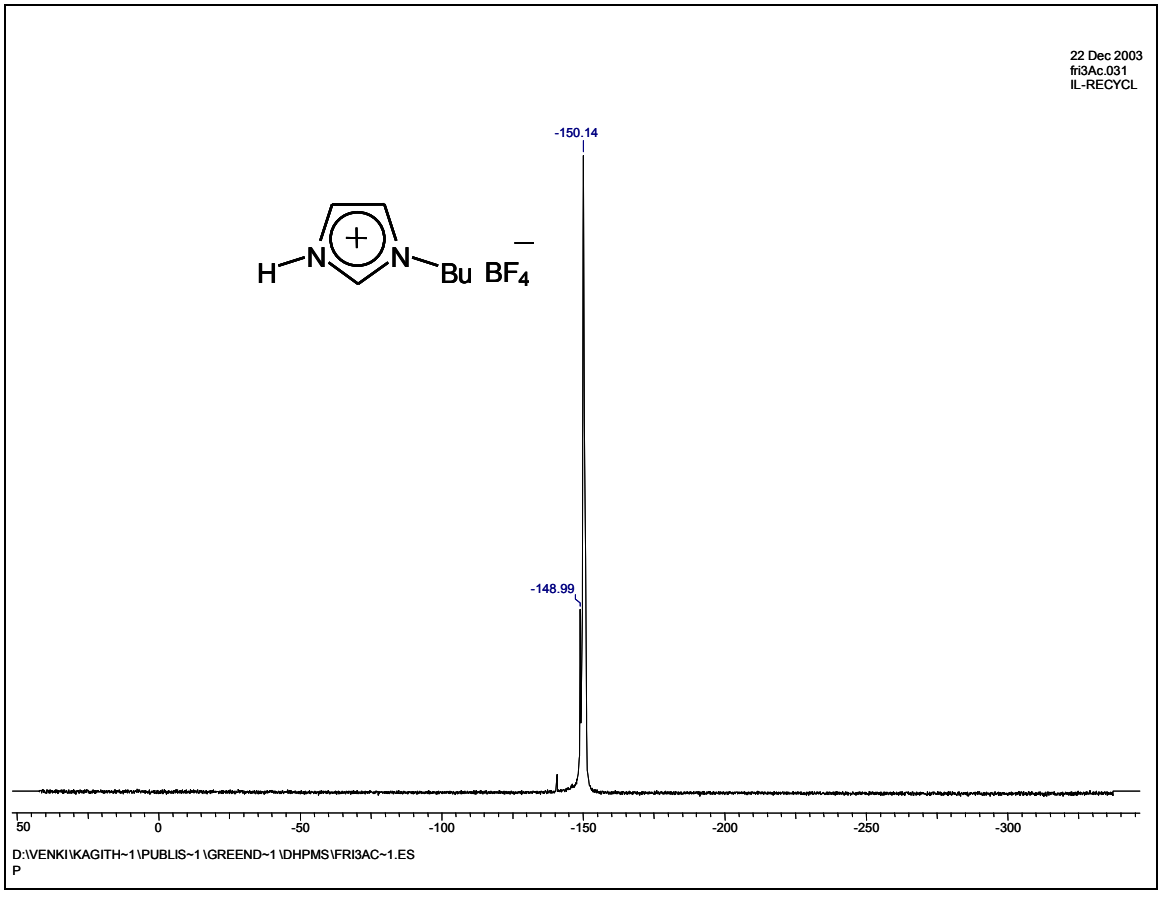


Figure 14. ^{19}F NMR spectrum of [HBIm]BF_4 recovered after reaction

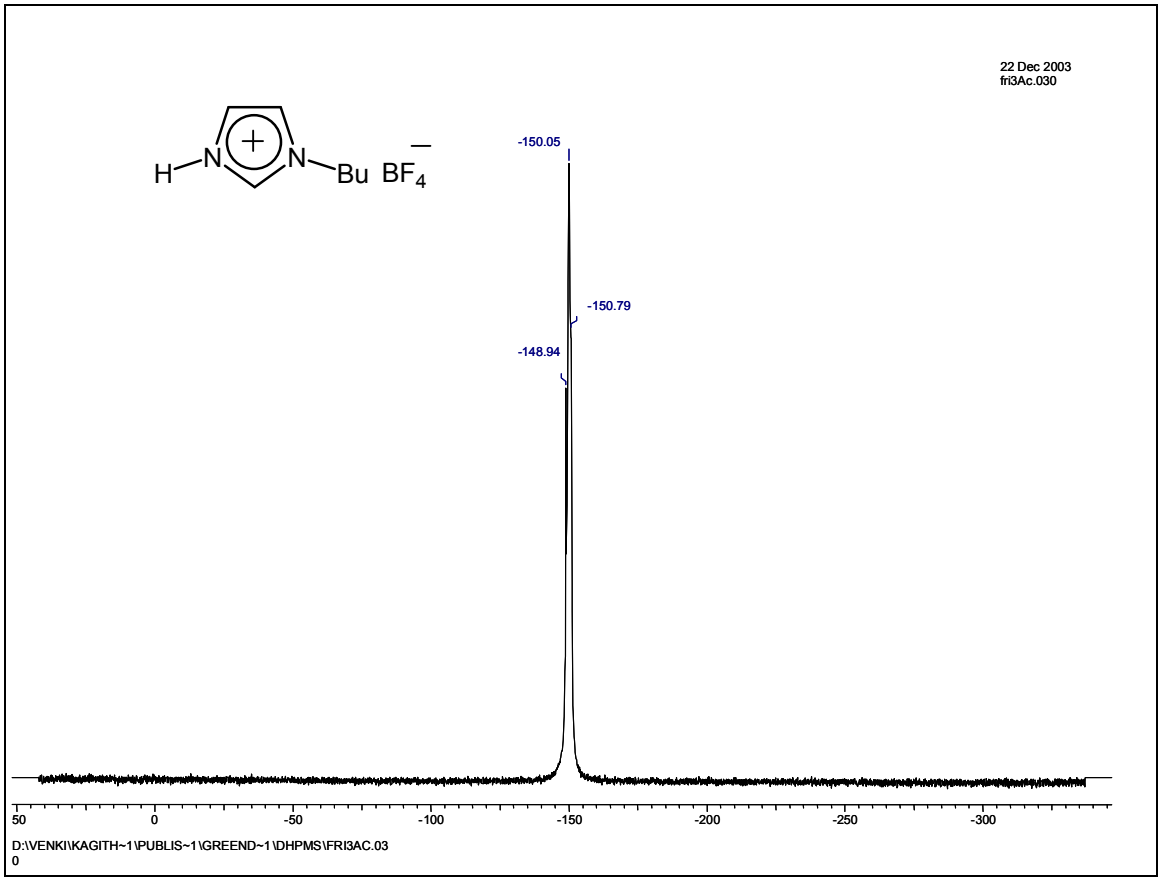


Figure 15. ^{19}F NMR spectrum of [HBIm]BF_4 as such before the reaction

after recovery for recycle and after subjecting the IL to ultrasound irradiation for 60 min in the absence of any substrate respectively.

The ^{19}F NMR spectra of the IL were recorded neat with an external lock of D_2O and using trifluoroacetic acid as an internal standard. The ^{19}F NMR spectra were identical and no changes were observed indicating the stability of the IL under these conditions (**Fig. 14**)

It was observed that the reactions did not proceed even after several hours of sonication in molecular solvents such as acetonitrile, ethanol, THF and dichloromethane instead of the IL under otherwise similar conditions. Similarly, no formation of DHPMs was observed when the reactions were conducted in the IL under silent conditions (stirring at 30 °C without ultrasound irradiation). Thus it becomes evident that it is the synergic effect of the combined use of ultrasound and the IL as the reaction medium that has promoted this MCR at ambient conditions in the absence of any added catalyst. Previous reports[45] on the ultrasound promoted synthesis of DHPMs make use of catalysts such as

sulfamic acid (0.8 equivalents) and ceric ammonium nitrate, and require higher reaction temperature (50–60 °C) and long reaction times (7 h).

The IL [HBIm]BF_4 has not only acted as a favorable medium with improved energetics of cavitation for the sonochemical MCR, but also promoted the reaction with its inherent Brønsted acidity thus obviating the necessity of using additional acid catalyst. The Brønsted acidity is conferred by the –NH proton of [HBIm]BF_4 (chemical shift of 14.59 ppm) capable of bonding with the carbonyl oxygen of the aldehydes as well as that of the β-keto ester EAA as shown in **Fig 16**. Evidence for this was obtained by recording the ^{13}C-NMR spectra of *p*-tolualdehyde and EAA (neat) with an external lock of D_2O and with one equivalent of the IL under similar conditions.

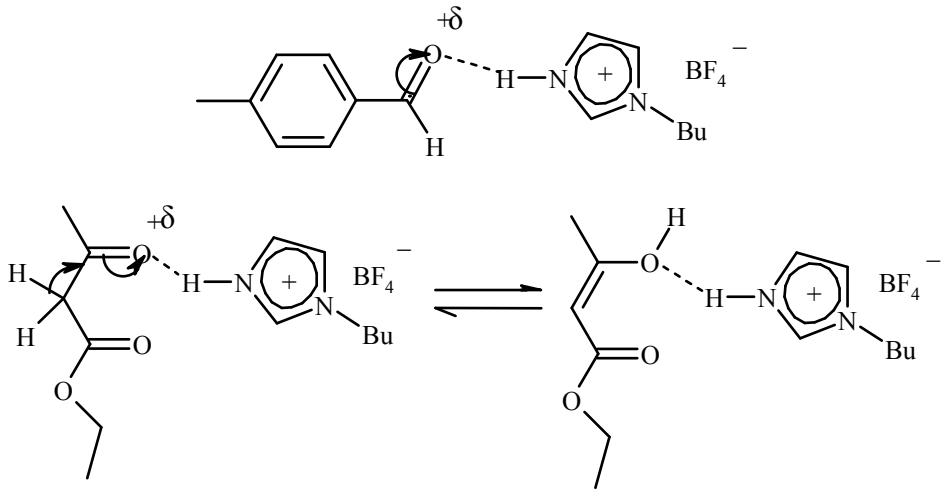
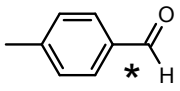
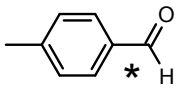
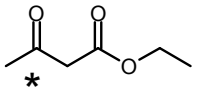
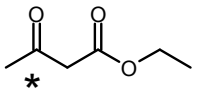


Figure 16

The results are recorded in **Table 15**. A significant shift of ~3 ppm for the carbonyl carbons of both the aldehyde and EAA by their interaction with the IL were observed.

Table 15. The ^{13}C-NMR chemical shifts and IR data for the carbonyl group

Entry	Substrate	Chemical shift,[a] ppm	IR values,[b] ν, cm^{-1}
1		204.3	1703.2

2	 + [HBIm]BF_4	207.4	1685.1
3		214.1	1742.1
4	 + [HBIm]BF_4	217.1	1735.5

[a] Recorded neat with D_2O as external lock. [b] Recorded with neat sample.

Additional evidence was obtained by recording their IR spectra neat wherein also a significant shift to a lower wave number by 7-18 cm^{-1} was observed (**Table 15**). Based on this plausible mechanism may be postulated for the reaction as outlined in **Fig. 17**.

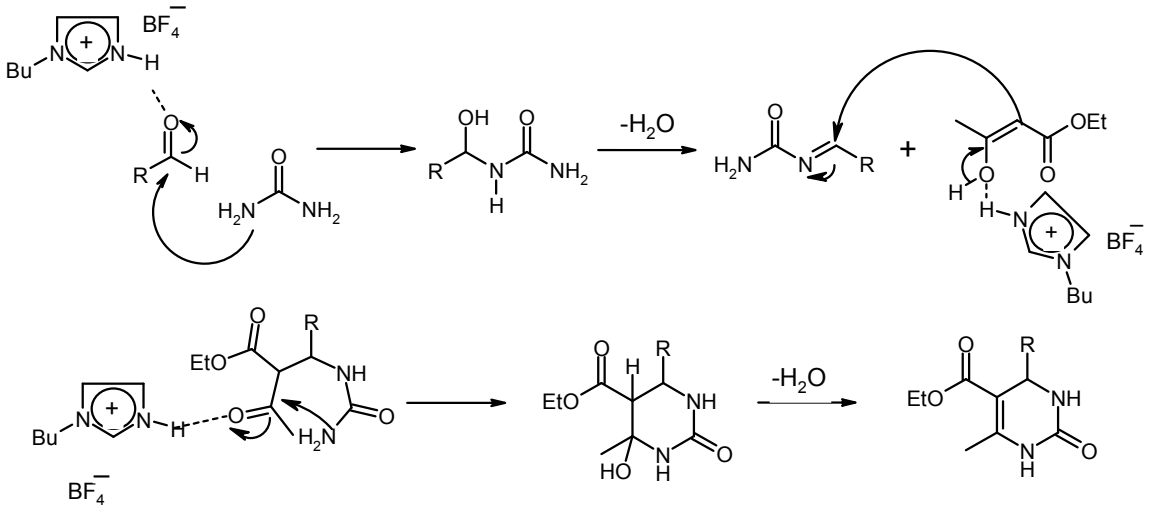


Figure 17. Plausible mechanism

1.4.4 Conclusion

Thus, this one pot MCR promoted by the synergy of combined use of IL and ultrasound offers an easy access to substituted DHPMs in excellent yields. The products can be easily isolated by simple work up procedures such as dilution and filtration of the precipitated product (DHPMs) leaving behind an aqueous filtrate from which the IL can

be completely recovered and recycled. The role of IL in promoting this MCR has been established in terms of ^{1}H-NMR and IR spectral evidence. Based on this evidence, a plausible mechanistic pathway has been postulated. The ambient conditions, absence of a catalyst, high reaction rates, excellent isolated yields and easy work up procedures makes this methodology an improved practical alternative to the conventional acid/base catalyzed thermal processes and is environment friendly with minimal or no waste.

1.4.5 Experimental section

General procedure for the synthesis of DHPMs

A mixture containing aldehyde **84a-v** 1 (10 mmol), ethyl acetoacetate (EAA, 10 mmol) and urea or thiourea (11 mmol) in [HBIm]BF_4 (2.0 g) was sonicated in an atmosphere of argon at ambient conditions in a thermostated (30 ± 1 °C) ultrasonic cleaning bath. After completion of the reaction (indicated by TLC), the reaction mixture was poured into crushed ice (20 g) and stirred for 10-15 min. The solid separated was filtered through a sintered funnel under suction, washed with ice-cold water (20 ml) and then recrystallized from hot ethanol or *i*PrOH to afford pure DHPMs, **85a-v**. The combined aqueous filtrate was subjected to distillation at 80 °C under reduced pressure (10 mmHg) over 4 h to leave behind the IL in near complete recovery, pure enough for recycle. The recovered ionic liquid was found to be effective for at least 3 recycles in the synthesis of **85a**.

1.4.5.1 Characterization data for compounds 85a-v

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one (85a):

Nature	**:**	Colorless solid
MP	**:**	200-202 ^{o}C (crystallized from EtOH), (Lit.[46] 202-204 ^{o}C).
IR (Nujol) cm^{-1}	**:**	3242, 3120, 2950, 1721, 1702, 1637, 1590.
^{1}H NMR 200 MHz ($CDCl_3$+DMSO-d_6)	**:**	δ 1.09 (t, *J* = 6.9 Hz, 3H), 2.24 (s, 3H), 3.40 (q, *J* = 6.9 Hz, 2H), 5.14 (s, 1H). 7.20-7.28 (m, 5H), 7.73 (s, 1H), 9.19 (s, 1H).
^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6)	**:**	δ 14.1, 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4.

Elemental analysis : Calcd: C, 64.60; H,6.20; N, 10.76.
$C_{14}H_{16}N_2O_3$ (260) Found: C, 64.51; H, 6.28; N,10.62.

5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85b):

Nature : Colorless solid
MP : 221-223 ^oC (crystallized from *i*PrOH), (Lit.[47] 222-224 ^oC)
IR (Nujol) cm^{-1} : 3416, 3224, 3098, 2980, 2926, 1704, 1651, 1593.
^1H NMR 200 MHz ($CDCl_3$+DMSO-d_6) : δ 1.17 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 4.08 (q, *J* = 7.2 Hz, 2H), 5.40 (d, *J* = 3.2 Hz, 1H). 6.96 (s, 1H), 7.29-7.40 (m, 4H), 8.35 (s, 1H).
^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6) : δ 14.1, 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4.
Elemental analysis : Calcd: C, 57.05; H, 5.13; N, 9.50.
$C_{14}H_{15}ClN_2O_3$ (294) Found: C, 57.11; H, 5.28; N, 9.29.

5-Ethoxycarbonyl-4-(3-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85c):

Nature : Colorless solid
MP : 190-193 ^oC (crystallized from EtOH), (Lit.[47] 193-195 ^oC)
IR (Nujol) cm^{-1} : 3228, 3100, 2995, 2925, 1708, 1652, 1590.
^1H NMR 200 MHz ($CDCl_3$+DMSO-d_6) : δ 1.15 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 4.05 (q, *J* = 7.2 Hz, 2H), 5.37 (d, *J* = 3.2 Hz, 1H). 6.93 (s, 1H), 7.26-7.37 (m, 4H), 8.31 (s, 1H).
^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6) : δ 14.5, 18.4, 55.6, 60.2, 100.8, 125.9, 127.5, 128.2, 131.1, 134.5, 148.3, 149.1, 152.6, 166.1.
Elemental analysis : Calcd: C, 57.05; H, 5.13; N, 9.50.
$C_{14}H_{15}ClN_2O_3$ (294) Found: C, 57.31; H, 5.37; N, 9.14.

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (85d):

Nature : Colorless solid

MP : 212-214 ^{o}C (crystallized from *i*PrOH), (Lit.[46] 213-215 ^{o}C).

IR (Nujol) cm^{-1} : 3241, 3109, 2975, 1702, 1645, 1469, 1400, 1321, 1228.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.09 (t, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 5.14 (s, 1H). 7.26 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 9.25 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 14.1, 17.8, 53.4, 59.3, 98.8, 128.2, 128.4, 131.8, 143.8, 148.7, 151.9, 165.2.

Elemental analysis : Calcd: C, 57.05; H, 5.13; N, 9.50.

$C_{14}H_{15}ClN_2O_3$ (294) Found: C, 56.88; H, 5.42; N, 9.29.

5-Ethoxycarbonyl-4-(2,6-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85e):

Nature : White solid

MP : >290 ^{o}C (crystallized from *i*PrOH).

IR (Nujol) cm^{-1} : 3340, 2854, 1689, 1633, 1560, 1457, 1376, 1231, 1100.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 0.92 (t, *J* = 7.0 Hz, 3H), 2.18 (s, 3H), 3.82 (q, *J* = 7.0 Hz, 2H), 6.22 (s, 1H). 7.09 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.69 (s, 1H), 8.89 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 13.7, 17.8, 52.2, 58.7, 94.0, 129.3, 135.1, 137.6, 149.8, 150.5, 164.2.

Elemental analysis : Calcd: C, 51.08; H, 4.29; N, 8.51.

$C_{14}H_{14}Cl_2N_2O_3$ (329) Found: C, 50.92; H, 4.45; N, 8.35.

5-Ethoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85f):

Nature : Yellow solid

MP : 226-228 ^{o}C (crystallized from EtOH), (Lit.[47] 229-231 ^{o}C)

IR (Nujol) cm^{-1} : 3235, 3109, 2981, 1724, 1702, 1645, 1594, 762.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.09 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 5.30 (s, 1H). 7.71 (m, 2H), 7.91 (s, 1H), 8.15 (m, 2H), 9.38 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 14.1, 18.1, 54.2, 59.8, 99.1, 123.0, 128.1, 147.0, 149.6, 152.4, 152.7, 165.9.

Elemental analysis : Calcd: C, 55.08; H, 4.95; N, 13.76.

$C_{14}H_{15}N_3O_5$ (305) Found: C, 55.25; H, 4.78; N, 13.55.

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85g):

Nature : Yellow solid

MP : 206-208 °C (crystallized from *i*PrOH), (Lit.[47] 207-209 °C)

IR (Nujol) cm^{-1} : 3235, 3109, 2981, 1724, 1702, 1645, 1594, 762.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.12 (t, *J* = 6.9 Hz, 3H), 2.26 (s, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.27 (s, 1H). 7.52 (d, *J* = 8.7 Hz, 2H), 7.90 (s, 1H), 8.23 (d, *J* = 8.7 Hz, 2H), 9.36 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 14.2, 18.0, 53.9, 59.7, 98.5, 124.0, 127.9, 146.9, 149.6, 152.1, 152.2, 165.3.

Elemental analysis : Calcd: C, 55.08; H, 4.95; N, 13.76.

$C_{14}H_{15}N_3O_5$ (305) Found: C, 55.22; H, 5.12; N, 13.65.

5-Ethoxycarbonyl-4-(3-methoxy-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85h):

Nature : White solid

MP : 228-230 °C (crystallized from MeOH), (Lit.[30] 231-232 °C)

IR (Nujol) cm^{-1} : 3348, 3247, 3118, 2977, 1728, 1696, 1681, 1515.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.11 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 3.72 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 5.05 (s, 1H). 6.60 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 7.66 (s, 1H), 8.95 (s, 1H), 9.15 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 17,8 50.8, 53.6, 55.8, 99.5, 111.1, 115.4, 118.3, 135.8, 146.0, 147.5, 148.2, 152.3, 166.1.

Elemental analysis : Calcd: C, 58.82; H, 5.92; N, 9.15.

$C_{15}H_{18}N_2O_5$ (306) Found: C, 58.68; H, 6.12; N, 9.38.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85i):

Nature : Cream color solid

MP : 201-203 °C (crystallized from EtOH), (Lit.[30] 201-202 °C)

IR (Nujol) cm^{-1} : 3415, 3241, 3114, 2954, 1708, 1646, 1512 841.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.09 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.72 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 5.08 (s, 1H). 6.86 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 9.14 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 14.1, 17.7, 53.3, 55.0, 59.1, 99.6, 113.7, 127.4, 137.1, 148.0, 152.2, 158.4, 165.4.

Elemental analysis : Calcd: C, 62.06; H, 6.25; N, 9.65.

$C_{15}H_{18}N_2O_4$ (290) Found: C, 61.88; H, 6.18; N, 9.52.

5-Ethoxycarbonyl-4-(2, 5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85j):

Nature : Light yellow solid

MP : 210-212 °C (crystallized from EtOH).

IR (Nujol) cm^{-1} : 3252, 3114, 3114, 2854, 1704, 1646, 1495, 1230.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.10 (t, *J* = 7.2 Hz, 3H), 2.35 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 4.00 (q, *J* = 7.1 Hz, 2H), 5.55 (s, 1H). 6.62 (d, *J* = 3 Hz, 1H), 6.74 (dd, *J* = 3 & *J* = 8.8 Hz, 1H), 6.84 (s, *J* = 8.8 Hz, 1H), 7.95 (s, 1H), 9.10 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 14.0, 17.6, 49.1, 55.2, 55.9, 59.0, 97.5, 111.9, 112.1, 114.0, 132.8, 148.8, 150.7, 152.1, 152, 165.3.

Elemental analysis : Calcd: C, 59.99; H, 6.29; N, 8.74.

$C_{16}H_{20}N_2O_5$ (320) Found: C, 60.18; H, 6.14; N, 8.62.

5-Ethoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85k)

Nature : White solid

MP : 180-182 °C (crystallized from EtOH) (Lit.[27a]179-180 °C)

IR (Nujol) cm^{-1} : 3210, 3069, 2910, 1713, 1651, 1587, 1281, 1125, 1092.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.21 (t, *J* = 7.2 Hz, 3H), 2.37 (s, 3H), 3.83 (s, 3H), 3.84 (s, 6H), 4.12 (q, *J* = 7.2 Hz, 2H), 5.37 (d, *J* = 2.7 Hz, 1H), 5.52 (s, 1H), 6.54 (s, 2H), 7.42 (s, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 14.2, 18.5, 55.7, 56.0, 60.0, 60.7, 101.1, 103.5, 137.6, 139.3, 146.2, 153.3, 165.6.

Elemental analysis : Calcd: C, 58.28; H, 6.33; N, 8.00.

$C_{17}H_{22}N_2O_6$ (350) Found: C, 58.41; H, 6.24; N, 8.18.

5-Ethoxycarbonyl-4-(4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85l):

Nature : Colorless solid

MP : 203-205 °C (crystallized from *i*PrOH).

IR (Nujol) cm^{-1} : 3250, 3112, 2985, 1705, 1648, 1470, 1405, 1325, 1230.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.19 (t, *J* = 7.2 Hz, 3H), 2.35 (s, 3H), 4.09 (q, *J* = 7.2 Hz, 2H), 5.37 (d, *J* = 2.8 Hz, 1H), 5.64 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.65 (s, 1H).

^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6) : δ 13.1, 17.1, 53.1, 58.4, 98.5, 119.8, 127.4, 130.1, 142.9, 147.1, 151.9, 164.5.

Elemental analysis : Calcd: C, 49.58; H, 4.46; N, 8.26.

$C_{14}H_{15}BrN_2O_3$ (339) Found: C, 49.70; H, 4.28; N, 8.42.

5-Ethoxycarbonyl-4-(2-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85m):

Nature : Colorless solid

MP : 206-208 °C (crystallized from *i*PrOH) (Lit.[27b] 206-208 °C)

IR (Nujol) cm^{-1} : 3340, 1686, 1635, 1450, 1415, 1310, 1240.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.02 (t, *J* = 7.2 Hz, 3H), 2.30 (s, 3H), 3.92 (q, *J* = 7.2 Hz, 2H), 5.30 (d, *J* = 2.7 Hz, 1H), 7.19 (m, 1H), 7.34 (m, 2H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.71 (s, 1H), 9.28 (s, 1H).

^{13}C NMR 50 MHz : δ 14.4, 18.0, 54.0, 59.5, 98.9, 125.1, 126.5, 127.4, 130.6,

($CDCl_3$+DMSO-d_6) 133.1, 147.4, 149.1, 152.1, 165.3.

Elemental analysis : Calcd: C, 49.58; H, 4.46; N, 8.26.

$C_{14}H_{15}BrN_2O_3$ (339) Found: C, 49.71; H, 4.50; N, 8.24.

5-Ethoxycarbonyl-6-methyl-4-(3-pyridyl)-3,4-dihydropyrimidin-2-(1*H*)-one (85n)

Nature : Light yellow

MP : 218-220 ^oC (crystallized from EtOH)

IR (Nujol) cm^{-1} : 3347, 3069, 2910, 1682, 1644, 1462, 1377, 1292, 1215.

^1H NMR 200 MHz ($CDCl_3$+DMSO-d_6) : δ 1.11 (t, *J* = 7.0 Hz, 3H), 2.29 (s, 3H), 4.01 (q, *J* = 7.0 Hz, 2H), 5.35 (d, *J* = 3 Hz, 1H), 6.40 (s, 1H), 7.17-7.23 (m, 1H), 7.59-7.64 (s, 1H), 8.37 (s, 1H), 8.43-8.46 (m, 1H), 8.53 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6) : δ 12.3, 16.2, 50.6, 57.5, 96.9, 121.7, 132.2, 138.4, 146.4, 146.6, 147.2, 150.5, 163.4.

Elemental analysis : Calcd: C, 59.76; H, 5.79; N, 16.08.

$C_{13}H_{15}N_3O_3$ (261) Found: C, 59.85; H, 5.70; N, 16.22.

5-Ethoxycarbonyl-4-furyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85o):

Nature : Brown solid

MP : 206-208 ^oC (crystallized from MeOH) (Lit.[47] 209-211 ^oC).

IR (Nujol) cm^{-1} : 3413, 3239, 3119, 2984, 1712, 1644, 1457.

^1H NMR 200 MHz ($CDCl_3$+DMSO-d_6) : δ 1.12 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 5.20 (d, *J* = 3.6 Hz, 1H), 6.07 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 2.8 Hz, 1H), 7.53 (s, 1H), 7.74 (s, 1H), 9.22 (s, 1H).

^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6) : δ 14.2, 17.9, 47.8, 59.3, 96.9, 105.5, 110.6, 142.3, 149.5, 152.4, 155.9, 165.0.

Elemental analysis : Calcd: C, 57.59; H, 5.64; N, 11.19.

$C_{12}H_{14}N_2O_4$ (250) Found: C, 57.45; H, 5.55; N, 11.25.

5-Ethoxycarbonyl-4-cyclohexyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85p):

Nature : Brown solid

MP : 236-238 ^{o}C (crystallized from *i*PrOH) (Lit.[48] 237-238 ^{o}C).

IR (Nujol) cm^{-1} : 3240, 3115, 2918, 2855, 1720, 1700, 1655, 1450, 1235, 1095.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 1.15 (m, 4H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.50 (m, 3H), 1.80 (m, 3H), 2.35 (s, 3H), 4.20 (m, 3H), 6.20 (s, 1H), 8.50 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 13.7, 17.2, 25.0, 26.4, 27.4, 32.8, 48.4, 59.9, 112.7, 138.8, 156.8, 165.1.

Elemental analysis : Calcd: C, 63.14; H, 8.33; N, 10.52.

$C_{14}H_{22}N_2O_3$ (266) Found: C, 63.20; H, 8.28; N, 10.22.

5-Ethoxycarbonyl-4-naphthyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one (85q):

Nature : Colorless solid

MP : 246-248 ^{o}C (crystallized from EtOH) (Lit.[49] 246 ^{o}C).

IR (Nujol) cm^{-1} : 3245, 3118, 2977, 1698, 1647, 1431, 1231, 1088, 790.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : 0.90 (t, *J* = 7.0 Hz, 3H), 2.40 (s, 3H), 3.90 (q, *J* = 7.0 Hz, 2H), 6.10 (s, 1H), 7.40-7.55 (m, 4H), 7.80 (t, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 9.10 (s, 1H).

^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$) : δ 14.1, 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4.

Elemental analysis : Calcd: C, 69.66; H, 5.85; N, 9.03.

$C_{18}H_{18}N_2O_3$ (310) Found: C, 69.85; H, 5.80; N, 9.18.

5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2-(1*H*)-one (85r):

Nature : Colorless solid

MP : 230-232 ^{o}C (crystallized from EtOH) (Lit.[24a] 232 ^{o}C).

IR (Nujol) cm^{-1} : 3245, 3114, 1724, 1655, 1463, 1377, 1232, 1088, 761.

^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$) : 1.18 (t, *J* = 7.3 Hz, 3H), 2.20 (s, 3H), 4.08 (q, *J* = 7.3 Hz, 2H), 4.86 (s, 1H), 6.0 (s, 1H), 6.11 (dd, *J* = 6.5 Hz, *J* = 16 Hz 1H), 6.38 (d, *J* = 16 Hz, 1H), 7.10-7.26 (m, 5H), 8.13 (s, 1H).

^{13}C NMR 50 MHz : δ 12.3, 15.8, 49.9, 57.2, 95.9, 124.3, 125.5, 126.1, 128.0,

($CDCl_3$+DMSO-d_6) 134.3, 146.5, 150.8, 163.2.

Elemental analysis : Calcd: C, 67.12; H, 6.34; N, 9.78.

$C_{16}H_{18}N_2O_3$ (286) Found: C, 67.25; H, 6.21; N, 9.69.

5-Ethoxycarbonyl-6-methyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,4 dihydropyrimidin-2-(1*H*)-one (85s):

Nature : Colorless solid

MP : 235-237 °C (crystallized from EtOH).

IR (Nujol) cm^{-1} : 3600, 3190, 2977, 1713, 1694, 1651, 1463, 1455, 1377, 1230.

^{1}H NMR 200 MHz ($CDCl_3$) : 1.19 (t, *J* = 7.0 Hz, 3H), 1.42 (s, 18H), 2.35 (s, 3H), 4.10 (q, *J* = 7.0 Hz, 2H), 5.19 (s, 1H), 5.33 (br s, 2H), 6.97 (br s, 1H), 7.11 (s, 2H).

^{13}C NMR 50 MHz ($CDCl_3$+DMSO-d_6) : δ 13.7, 17.7, 29.6, 33.7, 54.5, 58.9, 100.6, 122.4, 134.8, 135.7, 146.3, 152.5, 152.9, 165.4.

Elemental analysis : Calcd: C, 68.01; H, 8.30; N, 7.21.

$C_{22}H_{32}N_2O_4$ (388) Found: C, 68.18; H, 8.14; N, 7.34.

5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-thione (85t):

Nature : Colorless solid

MP : 205-207 °C (crystallized from EtOH) (Lit.[47] 208-210 °C).

IR (Nujol) cm^{-1} : 3259, 3195, 3100, 1710, 1690 1435, 1230.

^{1}H NMR 200 MHz ($CDCl_3$+DMSO-d_6) : 1.09 (t, *J* = 7.0 Hz, 3H), 2.28 (s, 3H), 4.00 (q, *J* = 7.0 Hz, 2H), 5.16 (t, *J* = 3.5 Hz, 1H), 7.20-7.38 (m, 5H), 9.64 (s, 1H), 10.33 (s, 1H).

Elemental analysis : Calcd: C, 60.85; H, 5.84; N, 10.14.

$C_{14}H_{16}N_2O_2S$ (276) Found: C, 60.78; H, 5.65; N, 10.28.

5-Ethoxycarbonyl-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2-(1*H*)-thione (85u):

Nature : Colorless solid

MP : 202-204 °C (crystallized from *i*PrOH)

IR (Nujol) cm^{-1}	**:**	3297, 3169, 2925, 2854, 1661, 1589, 1571, 1509, 1419, 1340.
^{1}H NMR 200 MHz (CDCl$_3$+DMSO-*d*$_6$)	**:**	1.04 (t, *J* = 7.0 Hz, 3H), 2.12 (s, 3H), 3.53-3.62 (m, 9H), 3.94 (q, *J* = 7.0 Hz, 2H), 5.04 (s, 1H), 7.29 (s, 2H), 9.49 (s, 1H), 10.22 (s, 1H).
^{13}C NMR 50 MHz (CDCl$_3$+DMSO-*d*$_6$)	**:**	14.5, 17.6, 54.3, 56.2, 60.1, 60.4, 101.1, 103.9, 137.5, 139.5, 145.5, 153.3, 165.6, 174.9.
Elemental analysis	**:**	Calcd: C, 55.72 H, 6.05; N, 7.64.
C$_{17}$H$_{22}$N$_2$O$_5$S 366)		Found: C, 55.55; H, 5.98; N, 7.59.

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-(1*H*)-thione (85v):

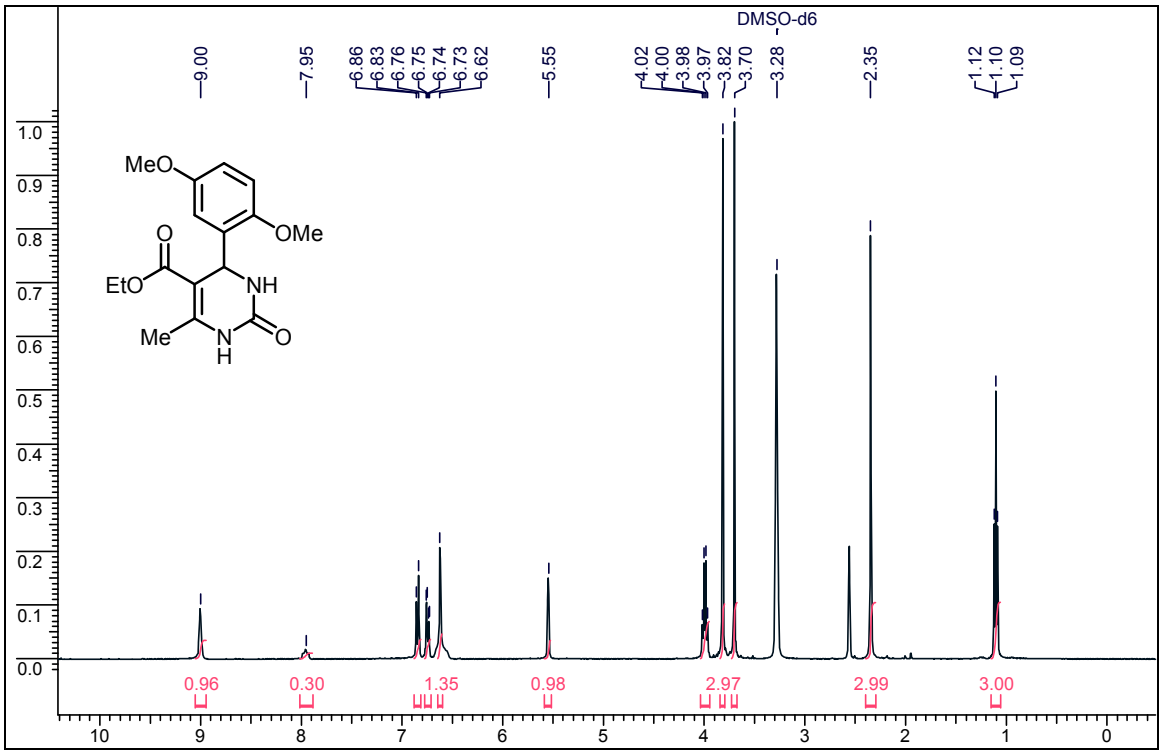
Nature	**:**	Colorless solid
MP	**:**	151-153 °C (crystallized from *i*PrOH) (Lit.[47] 150-152 °C)
IR (Nujol) cm^{-1}	**:**	3250, 1651, 1598, 1561, 1510, 1425, 1345.
^{1}H NMR 200 MHz (CDCl$_3$)	**:**	1.09 (t, *J* = 7.2 Hz, 3H), 2.25 (s, 3H), 3.70 (s, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 1H), 6.80-7.15 (m, 4H), 9.50 (s, 1H), 10.25 (s, 1H).
^{13}C NMR 50 MHz (CDCl$_3$)	**:**	14.1, 17.2, 53.5, 55.1, 59.6, 101.1, 113.9, 127.7, 135.8, 144.7, 158.8, 165.2, 174.0.
Elemental analysis	**:**	Calcd: C, 58.80 H, 5.92; N, 9.14.
C$_{15}$H$_{18}$N$_2$O$_3$S (306)		Found: C, 58.78; H, 5.79; N, 9.05.

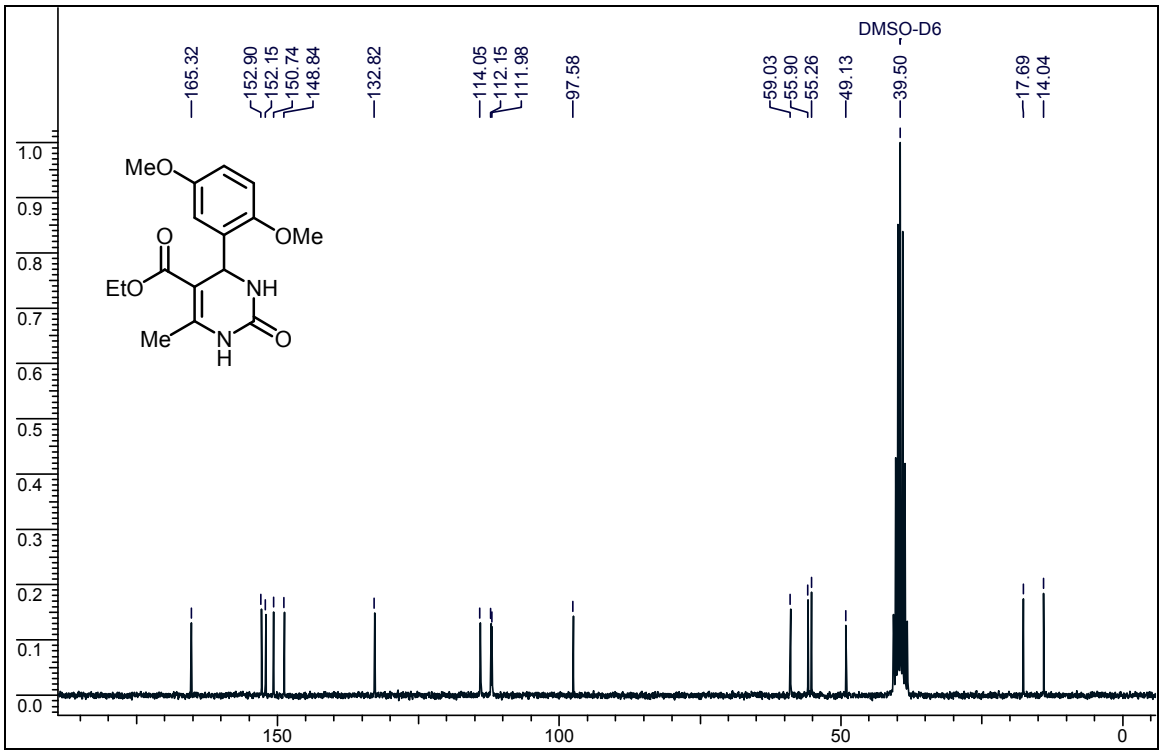
1.4.6 Spectra

Table 16. ^{1}H and ^{13}C spectra of some selected DHPMs are given below:

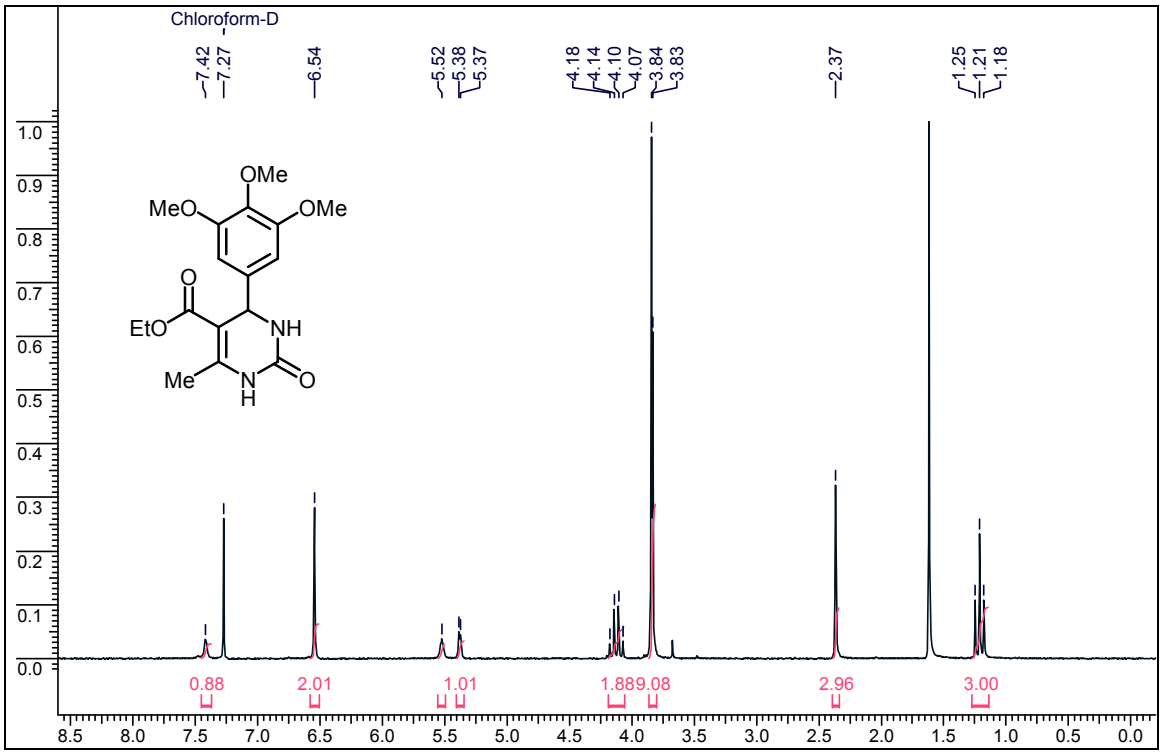
Sr. No.	Spectra	
[1]	^{1}H NMR and ^{13}C NMR Spectra of	**85j**
[2]	^{1}H NMR and ^{13}C NMR Spectra of	**85k**
[3]	^{1}H NMR and ^{13}C NMR Spectra of	**85l**
[4]	^{1}H NMR and ^{13}C NMR Spectra of	**85n**
[5]	^{1}H NMR and ^{13}C NMR Spectra of	**85r**
[6]	^{1}H NMR and ^{13}C NMR Spectra of	**85s**

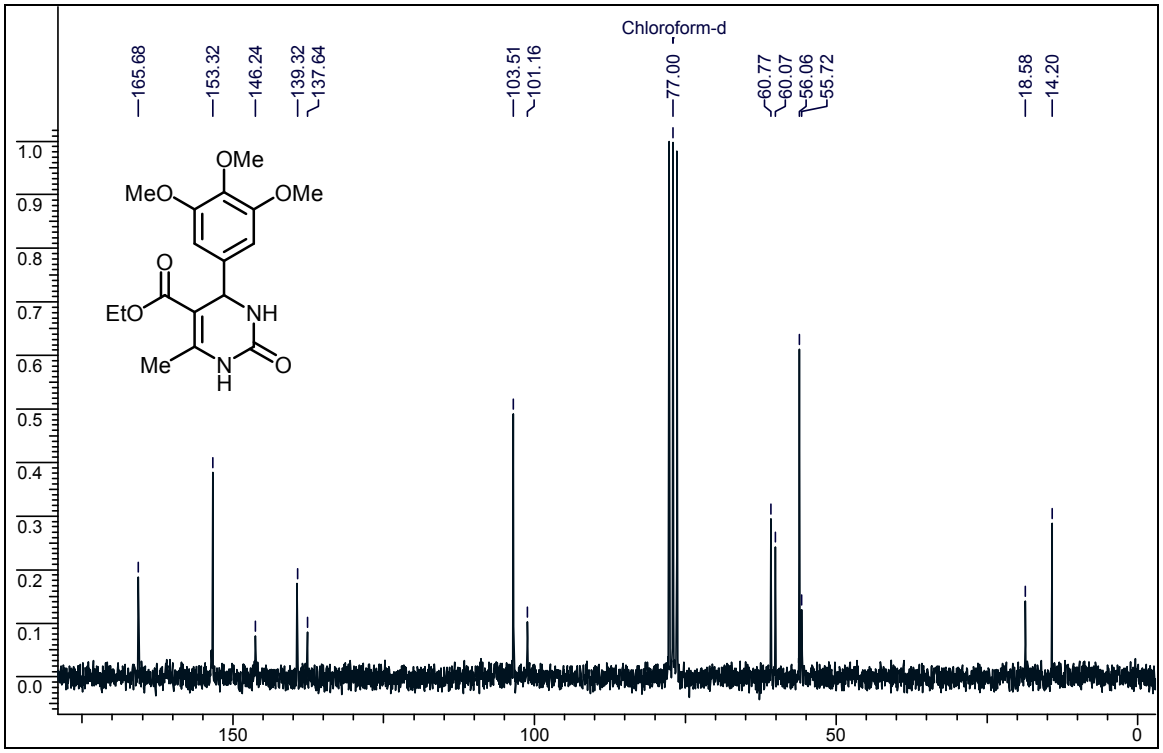
[1] ^{1}H NMR and ^{13}C NMR Spectra of 85j



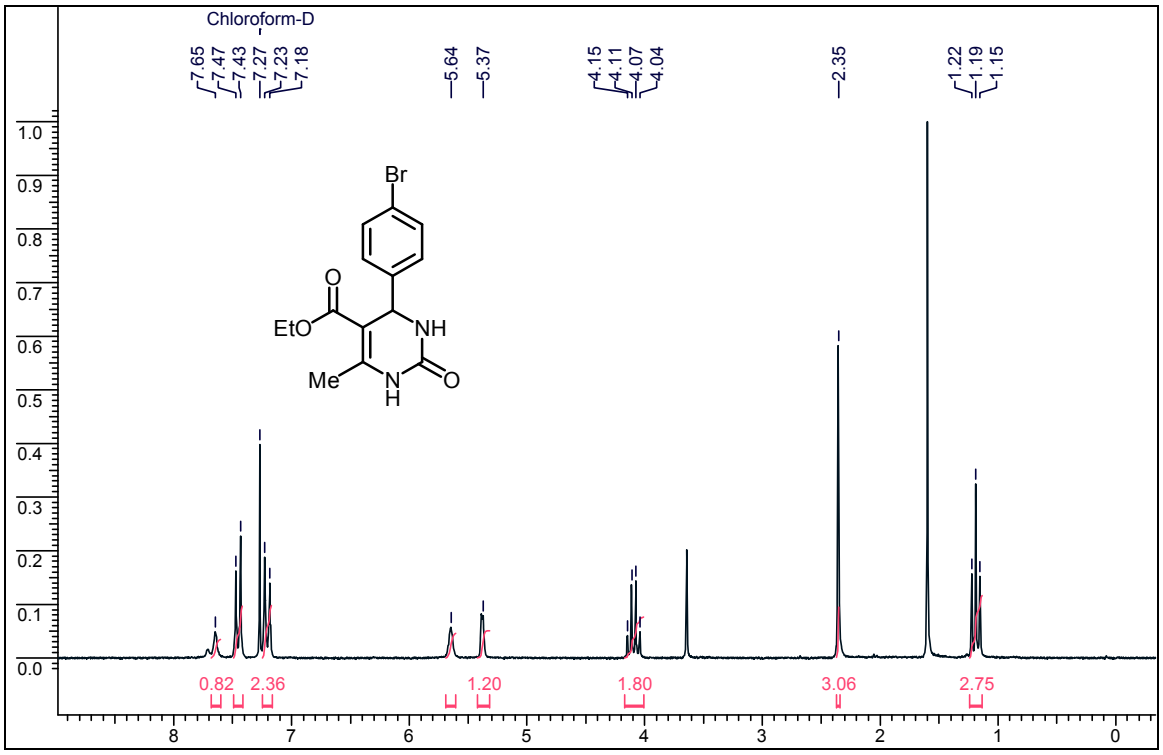


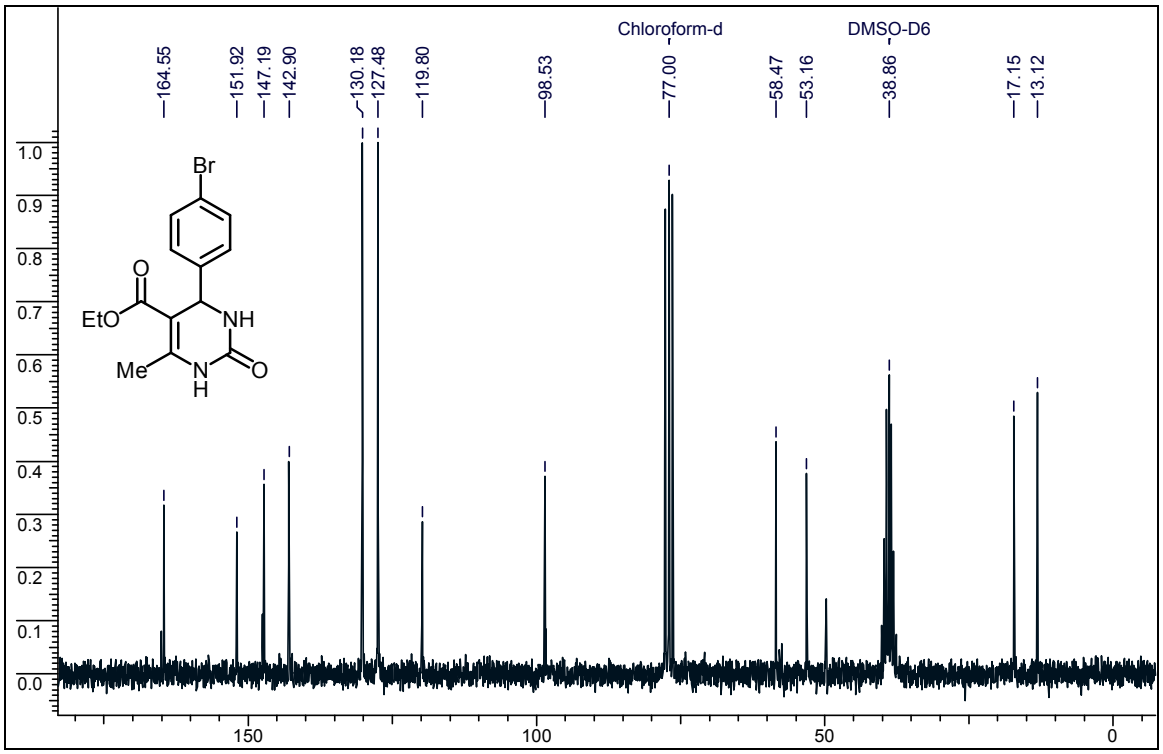
[2] ^{1}H NMR and ^{13}C NMR Spectra of 85k



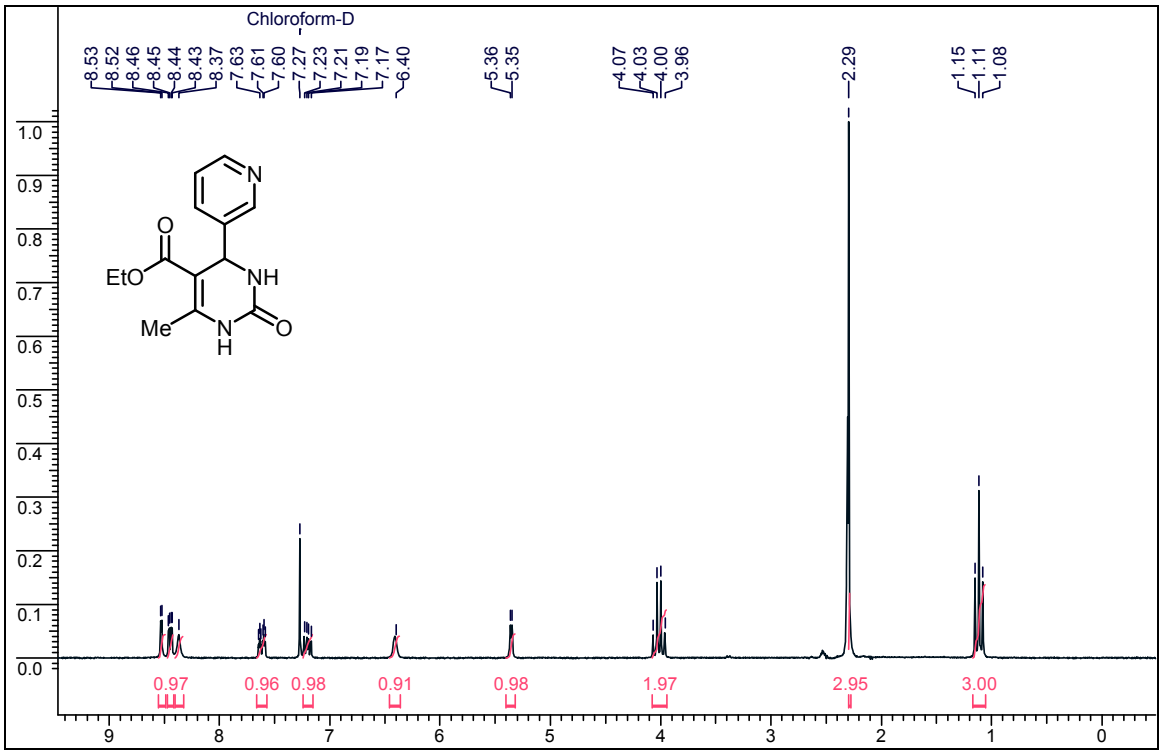


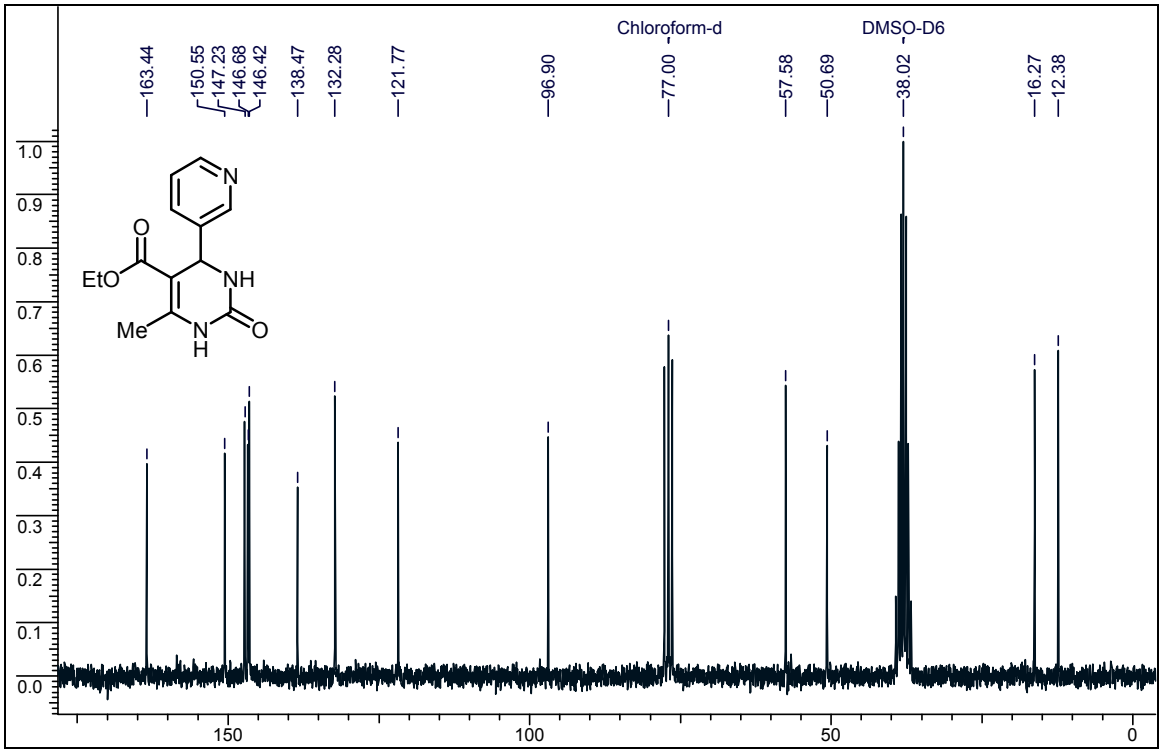
[3] ^{1}H NMR and ^{13}C NMR Spectra of 85l



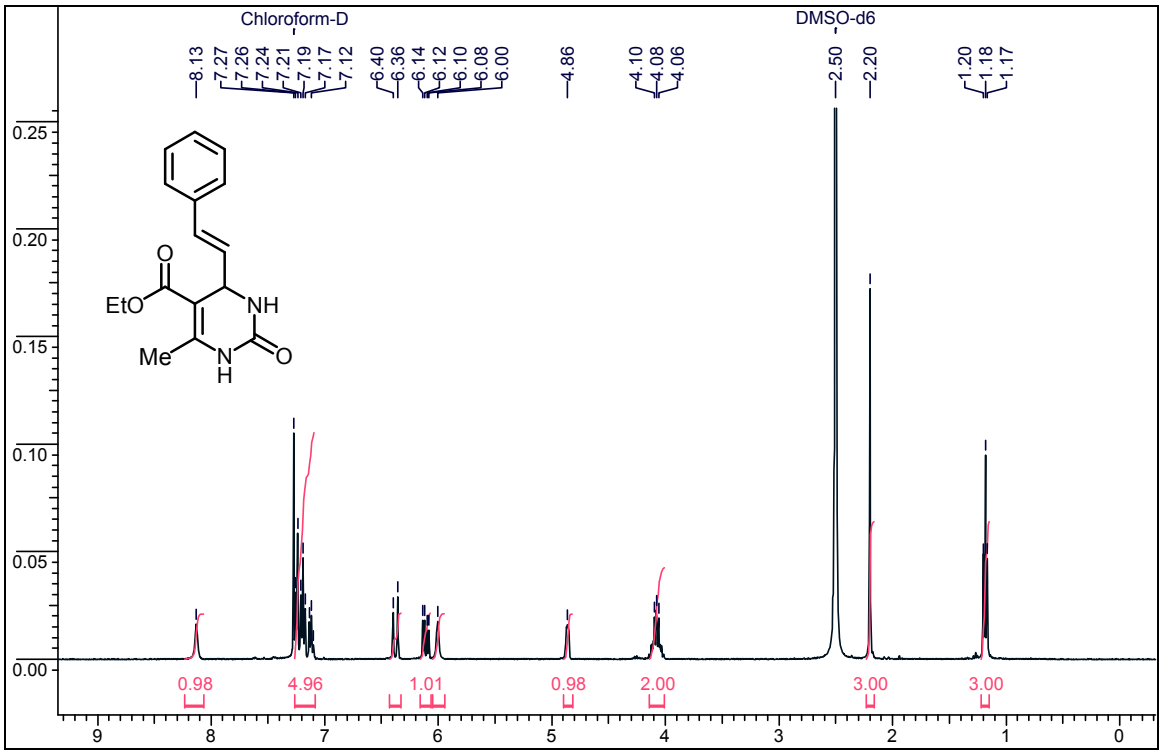


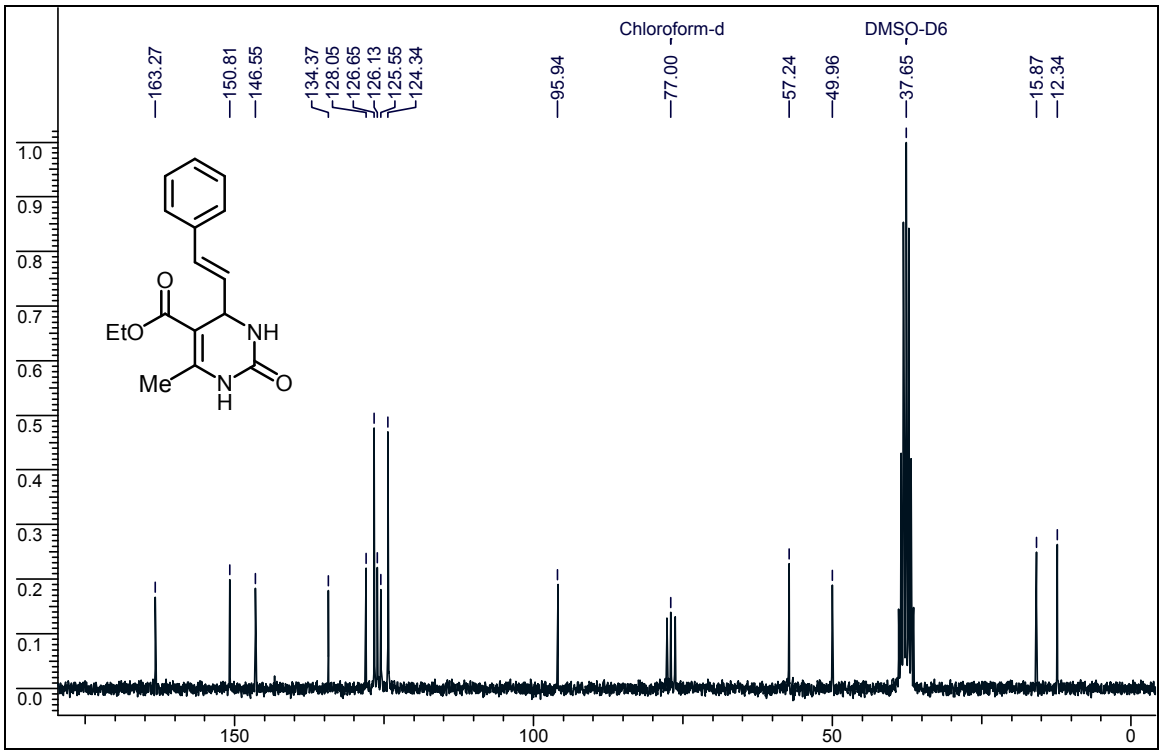
[4] ^{1}H NMR and ^{13}C NMR Spectra of 85n



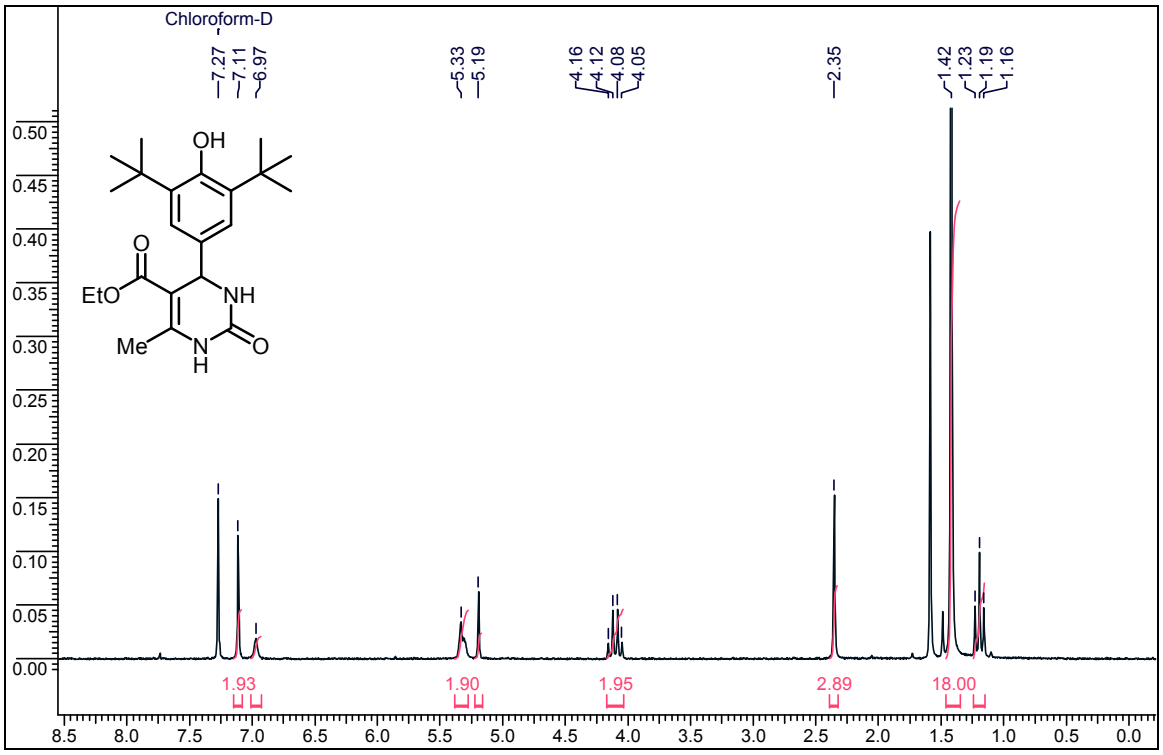


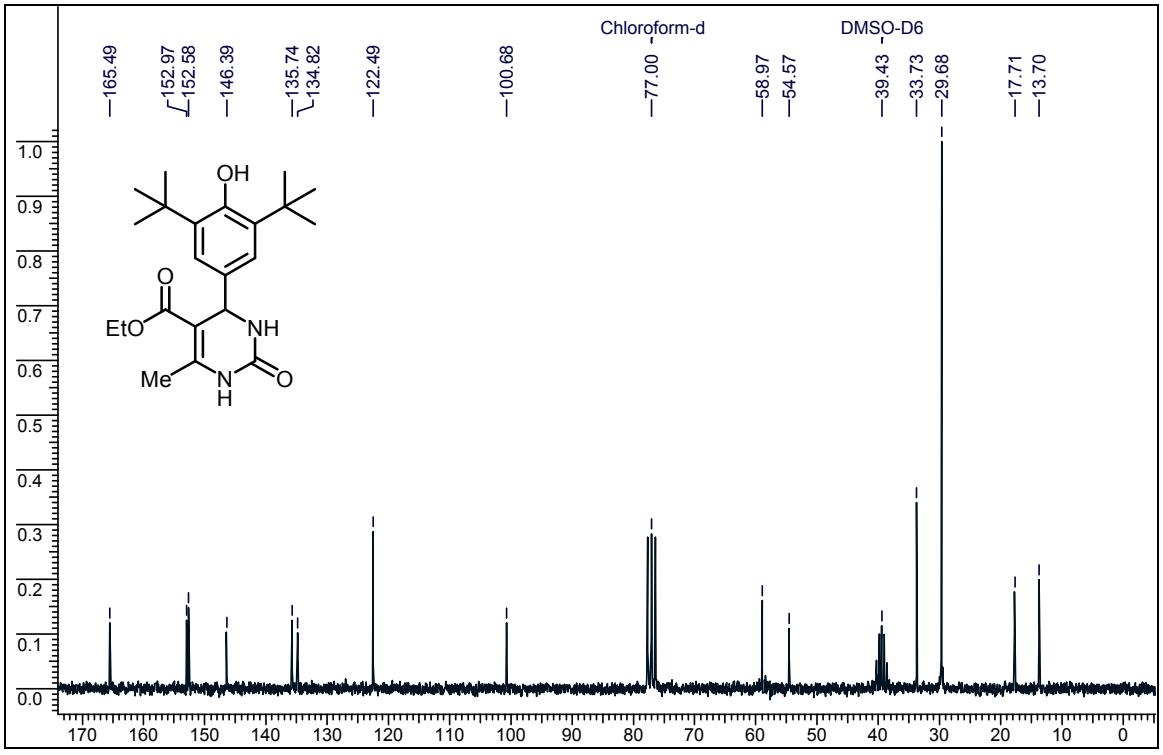
[5] ^{1}H NMR and ^{13}C NMR Spectra of 85r





[6] ^{1}H NMR and ^{13}C NMR Spectra of 85s





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Section-E

The

Sonogashira reaction

The Sonogashira Reaction

1.5.1 Introduction

The palladium-catalyzed sp^2-sp coupling reaction between aryl halides or triflates and terminal alkynes, with or without the presence of a copper(I) cocatalyst, has become the most important method to prepare arylalkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials.[1]

In 1975 Sonogashira and Hagihara reported that addition of a catalytic amount of copper(I) iodide greatly accelerates the reaction, thus allowing performance of the alkynylation at room temperature,[2] an observation related to the already known coupling between copper acetylides and phenyl or vinyl halides (the so-called Stephens-Castro reaction).[3] Therefore, the Sonogashira-Hagihara protocol (more often simply known as Sonogashira coupling) became the most popular procedure for the alkynylation of aryl or alkenyl halides.

The addition of copper salts as co-catalysts in the typical Sonogashira cross-coupling reactions also has drawbacks, apart from including in the reacting mixture another environmentally unfriendly and difficult to recover reagent. Thus, the *in situ* generation of copper acetylides under the reaction conditions often generates homo-coupling products of the terminal alkyne (the so-called Glaser coupling),[4] along with the main reaction product, upon exposure to oxidative agents or air. This side reaction is especially problematic when the terminal acetylene is difficult to obtain or expensive, and although it has been shown that the presence of a reductive atmosphere formed by hydrogen can diminish homocoupling,[5] as well as the slow addition of the acetylene,[6] significant efforts have being dedicated to develop coupling procedures working in the absence of copper salts. These procedures generally aim to increase the reactivity of the catalytic system, thus making the presence of copper unnecessary. All these copper-free methodologies are usually called copper-free Sonogashira couplings.

1.5.2 Mechanistic Considerations

The exact mechanism of the homogeneous copper-co-catalyzed Sonogashira reaction is unknown, with some obscure points and not unequivocally proven assertions still remaining. Although physical measures suggest plausible mechanistic paths based on the

identification of some of the transient species formed in the homogeneous catalytic reactions, it is a very difficult task to isolate and characterize the organometallic intermediates from a homogeneous mixture to validate a mechanism beyond any doubt.

1.5.2.1 The copper-co-catalyzed Sonogashira reaction:

The copper-co-catalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles as shown in **Fig. 18,** where a tertiary amine is represented as base. The generally accepted catalytic cycle for the palladium catalysis (the Pd-cycle) is based on a usually fast oxidative addition of R^1-X (R^1 = aryl, heteroaryl, vinyl; X = I, Br, Cl, OTf) to the real catalyst generated from the initial palladium complex.

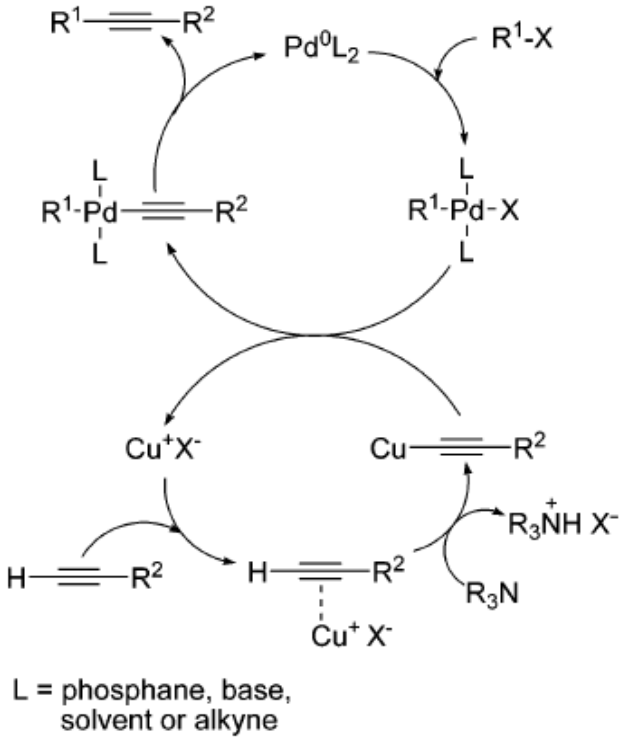


Figure 18. Mechanism of copper catalyzed Sonogashira reaction

In the oxidative addition step, the characteristics of the R^1-X substrate are crucial, with this step being facilitated if X = I or OTf and if the electronic density is reduced on the C-X bond by the presence of electron-withdrawing groups. The next step in the Pd-cycle would connect with the cycle of the copper co-catalyst (the Cu-cycle). Thus, a usually rate-determining transmetalation from the copper acetylide formed in the Cu cycle would

generate a $R^1Pd(-C{\equiv}CR^2)L_2$ species, which gives the final coupled alkyne after trans/cis isomerization and reductive elimination with regeneration of the catalyst.

The second Cu-cycle is still poorly understood. The base (generally an amine) is supposed to abstract the acetylenic proton of the terminal alkyne, thus forming a copper acetylide in the presence of the copper(I) salt. It should be pointed out that the generally employed amines are usually not basic enough to deprotonate the alkyne in order to generate the anionic nucleophile that should form the copper acetylide. Therefore, a π-alkyne- Cu complex as shown in **Fig. 18** could be involved in the cycle,[7] thus making the alkyne proton more acidic for easier abstraction. Recently, NMR studies have shown that π-alkyne-Ag complexes are formed after generation of silver acetylides in silver-co-catalyzed Sonogashira couplings,[8] something that could be extended to the typical copper co-catalyzed reaction. In fact, the always assumed *in situ* formation of a copper acetylide as intermediate has never been proven, although recent indirect evidence has been found.[7] These copper acetylides could also be involved in the formation of the initial Pd^0L_2 catalytic species by reaction with the starting palladium(II) complexes, thus forming $Pd(-C{\equiv}CR^2)_2L_2$, which after reductive elimination would afford active Pd^0L_2 and some amounts of a diacetylene byproduct.

1.5.2.2 The Copper-free Sonogashira reaction:

The mechanism of the copper-free Sonogashira reaction is also not well-known. The first step would be the oxidative addition of R^1-X to the palladium(0) complex (**Fig. 19**).

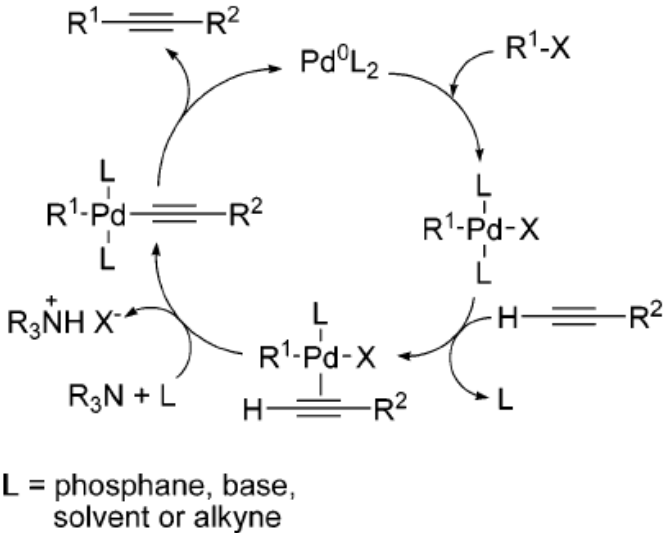


Figure 19. Mechanism of copper free Sonogashira reaction

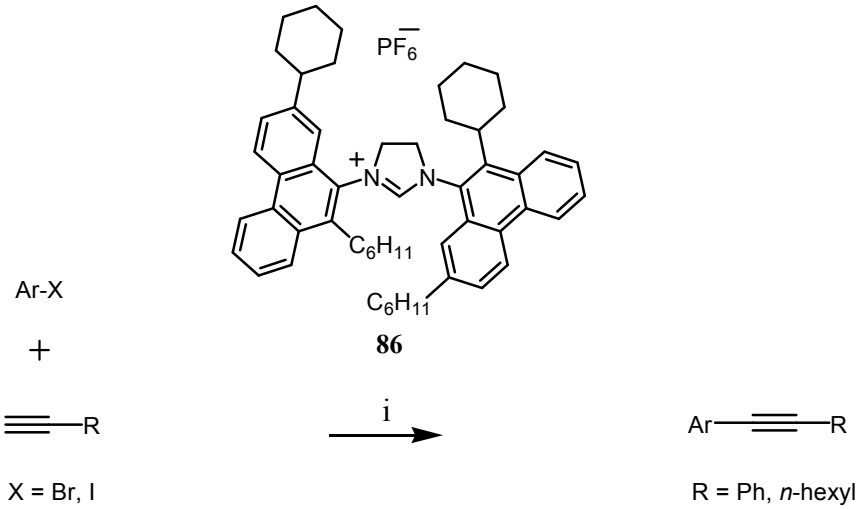
As previously mentioned, the amines generally employed are usually not able to deprotonate the alkyne for the reaction with the trans- R^1PdXL_2; therefore, complexation of the alkyne to the complex is supposed to proceed first with displacement of one ligand to give intermediate complex (η^2-RC≡CH)-$PdXL_2$.[9] The ligated alkyne would be more easily deprotonated by the amine, forming the new complex R^1Pd-(-C≡CR^2)L_2, which gives the coupling product R^1-C≡C-R^2 by reductive elimination.

1.5.3 Review of Literature

There are several synthetic procedure for Sonogashira coupling reported in the literature. In this section we have covered some copper free Sonogashira reactions.

Andrus *et al.*[10]

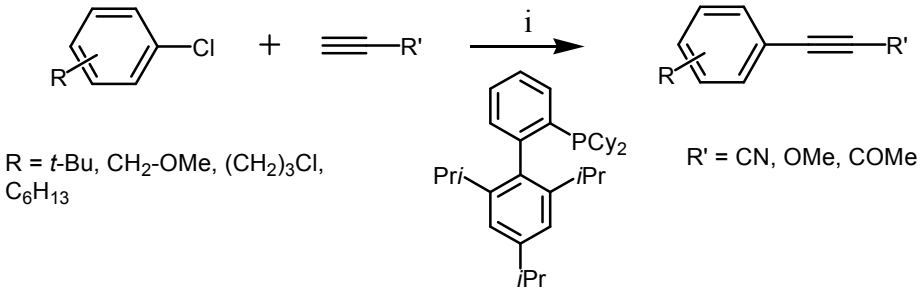
Bulky phenanthracenyl imidazolium-derived carbene ligands were investigated by Andrus *et al.* for copper-free Sonogashira coupling with terminal acetylenes. Aryl bromides and iodides gave coupled products in excellent yields from the $Pd(PPh_3)_2Cl_2$ complex with potassium *t*-butoxide and 18-crown-6 in THF. A remarkable dependence on the size of the ligand was found. The highest yields were obtained with the bulky 2,9-dicyclohexyl-10-phenanthryl ligand **86** (**Scheme 22**).



Scheme 22. Reaction conditions: (i) $Pd(PPh_3)_2Cl_2$, ligand **86** 3 mol%, KOt-Bu, 18-crown-6, THF, 65 ºC, 2-2.5 h., 56-96%.

Buchwald *et al.*[11]

Buchwald *et al.* developed a general protocol for the palladium-catalyzed coupling of aryl chlorides and alkynes, by using 1 mol% of $[PdCl_2(CH_3CN)_2]$, 3 mol% of **87**, 1.3 equivalents of the terminal alkyne, and 2.6 equivalents of Cs_2CO_3 in acetonitrile at 70-90ºC. The choice of the solvent as well as the base was important for the success of the reaction. Only moderately polar aprotic solvents (acetonitrile, dioxane), in combination with inorganic bases such as Cs_2CO_3, K_3PO_4 showed better results. This new protocol requires less catalyst, lower temperature, and has greater generality than those previously reported **(Scheme 23).**



87

Scheme 23. Reaction conditions: (i) $[PdCl_2(CH_3CN)_2]$, ligand **87** 3 mol%, Cs_2CO_3, CH_3CN, 70-95 ºC, 1.5-9 h., 77-95%.

Leadbeater *et al.*[12]

Leadbeater *et al*. employed $PdCl_2(PPh_3)_2$ as catalysts to promote the Sonogashira reaction in presence of piperidine as a base without addition of any copper co-catalyst. This methodology works well for a range of aryl iodides and activated aryl bromides.

Soheili *et al.*[9]

Soheili *et al*. has developed a mild and general protocol for the copper-free Sonogashira coupling of aryl bromides with acetylenes. The use of $(AllylPdCl)_2$ and $P(t\text{-}Bu)_3$ provides the active Pd(0) catalyst that allows subsequent coupling of various alkynes at room temperature. The reaction proceeds in excellent yield with activated and electron-rich aryl bromides with aromatic and aliphatic acetylenes.

Alper *et al.*[13]

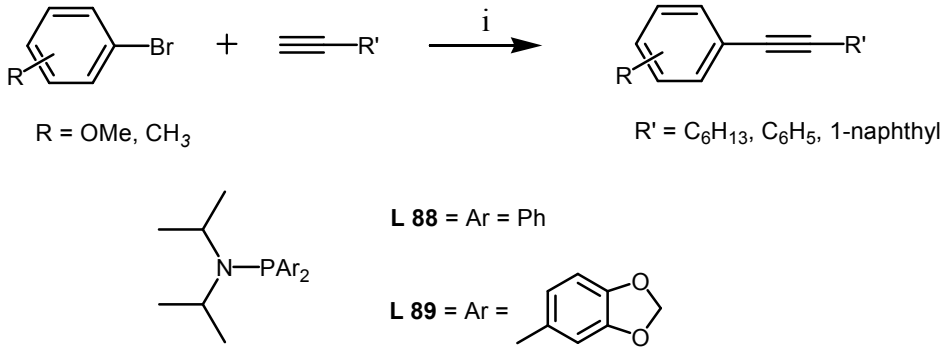
An efficient and recyclable Sonogashira coupling reaction without copper salts or bulky phosphine ligands, using (Bisimidazole)Pd(Me)Cl as a catalyst in an ionic liquid. This copper free Sonogashira coupling of various iodoarenes with aryl or alkyl acetylenes was carried out in IL[BMIm] PF_6 at 120 ºC to obtain the cross coupled product.

Verkade *et al.*[14]

Verkade *et al.* have established the first ligand-, copper-, and amine-free method for the cross-coupling of aryl iodides and bromides with terminal alkynes. The Sonogashira reaction proceeds in presence of $Pd(OAc)_2$ or $Pd_2(dba)_3$ and in absence of ligand, amine, and Cu(I) to obtain the cross coupled product. The use of tetrabutylammonium acetate as the base is important for obtaining high yields of arylalkynes.

Zhang *et al.*[15]

Zhang *et al.* developed an efficient, copper and amine-free Sonogashira reaction in presence of $Pd(OAc)_2$ and air-stable aminophosphines as the ligands **88** and **89**. The mild reaction conditions, the obviation of copper salt as co-catalyst and amine as solvent, and the utilization of inorganic base are the most attractive features of the reaction. Both **88** and **89** are highly effective ligands in this reaction The reaction proceeded well in THF as a solvent at 65 ºC (**Scheme 24**).



Scheme 24. Reaction conditions: (i) $Pd(OAc)_2$, ligand **88 or 89** 2 mol%, K_2CO_3, THF, 65 ºC, 8h., 78-96%.

Yang *et al.*[16]

A mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal acetylenes in water under aerobic conditions has been developed by Yang *et al.* The use

of 1 mol % $PdCl_2$ in the presence of pyrrolidine allows the coupling reaction to proceed at room temperature or 50 °C to obtain the cross coupled product with good to excellent yields.

Li *et al.*[17]

Li *et al.* reported the Sonogashira reaction under copper-, amine-, and solvent-free conditions. A number of Ar-X species (X = I, Br, Cl) were coupled with alkynes in presence of $PdCl_2(PPh_3)_2$ combined with TBAF under solvent-free conditions to afford the corresponding cross-coupled products in moderate to excellent yields.

Hua *et al.*[18]

Hua *et al.* carried out the Sonogashira reaction under copper-free conditions using Cs_2CO_3 as base and $PdCl_2(PCy_3)_2$. The electron-rich, electron-neutral, and electron deficient aryl chlorides was reacted with a variety of terminal alkynes in DMSO at 100-120 °C affording internal arylated alkynes in good to excellent yields. The advantages of this catalytic procedure include (1) omission of a copper co-catalyst, (2) ready availability and easily handling of catalyst, and (3) the high catalytic activity for not only electron-poor aryl chlorides but also electron-rich aryl chlorides under mild and convenient conditions.

Arylalkynes are interesting intermediates for the preparation of a variety of target compounds with applications ranging from natural products[19] and pharmaceuticals[20] to optoelectronic applications.[21] Due to that a variety of modifications have so far been developed for this reaction including the phase transfer,[22] aqueous,[23] solventless,[24] the use of a variety of promoters[25] and solvents.[26] Beside these, new catalytic systems without palladium, such as nickel system,[27] CuI system,[28] and transition-metal free/microwave irradiation system[29] were also reported in literature.

1.5.4 Present work

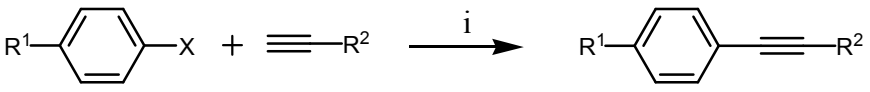
1.5.4.1 Objective

Since its introduction in 1975, the reaction has been well studied, making use of a variety of ligands and copper salts as co-catalysts. However, the copper salts used as co-catalysts can also induce Glaser-type homocoupling of the alkynes to the corresponding

symmetrical diyne via., the copper acetylide formed. To avoid this, copper- and phosphine-free Sonogashira reactions have been developed in recent times resulting in excellent chemoselectivity. Extensive research continues to push the limits of this methodology to more and more facile procedures wherein attempts may be made to practice this reaction at ambient temperature without the use of a copper cocatalyst and a ligand. In the present work, we have evaluated copper- and ligand-free Sonogashira reaction at ambient temperature effected by ultrasound irradiation in a molecular solvent such as acetone as well as a room-temperature ionic liquid (IL), 1,3-di-*n*-butylimidazolium tetrafluoroborate [BBIm]BF_4, in excellent chemoselectivity with considerably enhanced reaction rates through the formation of stable and crystalline clusters of zerovalent Pd nanoparticles.

1.5.4.2 Results and discussion

The sonochemical reactions were carried out in a thermostated (30 ±1 °C) ultrasonic cleaning bath at 50 kHz in an inert atmosphere of argon. A variety of aryl halides consisting of substituted iodo- and bromobenzenes were reacted with terminal acetylenic compounds in the absence of any added copper co-catalyst and phosphine ligands in acetone or the IL [BBIm]BF_4 as solvent using $PdCl_2$ as catalyst and triethylamine as base under ultrasonic irradiation (**Scheme 25**).



90 (a-g) **91 (a-d)** **92 (a-t)**

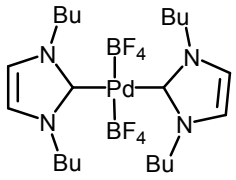
R^1 = H; X = I = **90a**
R^1 = CH_3; X = I = **90b**
R^1 = NO_2; X = I = **90c**
R^1 = Cl; X = I = **90d**
R^1 = $COCH_3$; X = I = **90e**
R^1 = $COCH_3$; X = Br = **90f**
R^1 = NO_2; X = Br = **90g**

R^2 = C_6H_5 = **91a**
R^2 = C_6H_4F = **91b**
R^2 = CH_3-C_6H_4 = **91c**
R^2 = cyclohexanol = **91d**

Scheme 25. Reaction conditions: (i) $PdCl_2$, TEA, acetone**,**)))), (50 KHz), 30 ºC, 15-90 min, 66-85% or [BBIm]BF_4,)))), (50 KHz), 30 ºC, 2-3 h, 68-93%.

In the case of acetone, the products were isolated by evaporation of the solvent followed by extraction with 10% ethyl acetate in petroleum ether (bp 60-80 °C) and filtration through a celite bed to separate the Pd catalyst. The Pd catalyst in the form of Pd(0)

nanoparticles was difficult to recover and recycle. However, from the point of view of ease of recovery and recycle of the expensive Pd catalyst, the reactions were performed in the IL [BBIm]BF_4. In this case, the products were selectively extracted with 10% ethyl acetate in petroleum ether leaving behind the Pd catalyst in the form of Pd(0) nanoparticles as a solution in IL. As reported previously,[30] the complete formation of a Pd-biscarbene complex (A) takes place during the reaction in [BBIm]BF_4 as solvent. This complex (A) formed "*in situ*" was selectively extracted into chloroform separating it from the ionic liquid medium, purified by column chromatography, and completely characterized. The complex (A) under the sonochemical conditions gives rise to the stable, crystalline, and polydispersed Pd(0) nanoparticles as the catalyst for the reaction.

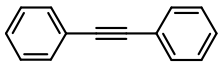
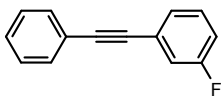
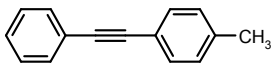


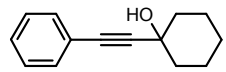
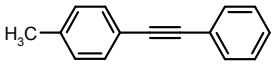
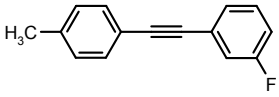
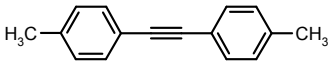
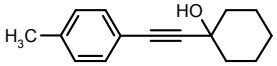
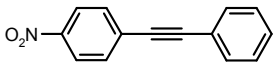
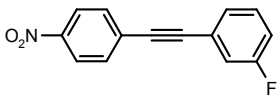
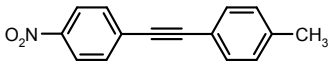
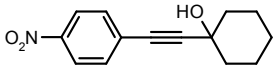
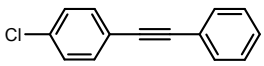
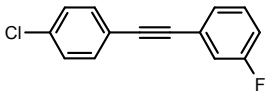
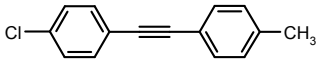
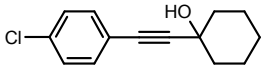
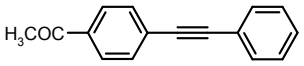
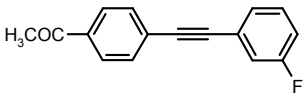
93

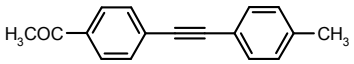
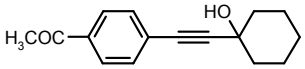
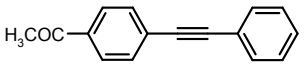
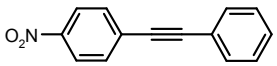
Figure 20. ***Pd -biscarbene complex [A]***

In all cases, pure products were isolated by subjecting the organic layer to column chromatography and characterized by mp, spectral, and elemental analyses. The results are recorded in **Table 17**.

Table 17. Synthesis of Diacetylene Derivatives 92(a-t)

Entry	Aryl halide	Acetylene	Product **(92a-92t)**	Acetone		[BBIm]BF_4	
				Time (min)	Yield *(%)	Time (h)	Yield* (%)
1	**90a**	**91a**	 **92a**	15	85	2	93
2	**90a**	**91b**	 **92b**	15	78	2	89
3	**90a**	**91c**	 **92c**	20	75	2	84

4	**90a**	**91d**	 **92d**	30	65	2.5	78
5	**90b**	**91a**	 **92e**	20	75	2	85
6	**90b**	**91b**	 **92f**	20	72	2	84
7	**90b**	**91c**	 **92g**	35	70	2	80
8	**90b**	**91d**	 **92h**	35	68	2.5	74
9	**90c**	**91a**	 **92i**	15	80	2	89
10	**90c**	**91b**	 **92j**	15	78	2	85
11	**90c**	**91c**	 **92k**	25	74	2	80
12	**90c**	**91d**	 **92l**	35	68	2.5	72
13	**90d**	**91a**	 **92m**	15	77	2	88
14	**90d**	**91b**	 **92n**	15	72	2	82
15	**90d**	**91c**	 **92o**	20	70	2	80
16	**90d**	**91d**	 **92p**	35	66	2.5	72
17	**90e**	**91a**	 **92q**	15	84	2	90
18	**90e**	**91b**		15	80	2	86

19	**90e**	**91c**	**92r** 	15	85	2	95
20	**90e**	**91d**	**92s** 	15	78	2	89
21	**90f**	**91a**	**92t** 	90	65	3	68
22	**90g**	**91a**	**92q**  **92i**	90	70	3	72

*Isolated yields after column chromatography; 1-ethynylbenzene (**91a);** 3-fluoroethynylbenzene (**91b);** 4-tolylylbenzene (**91c);** 1-ethynylcyclohexanol (**91d).**

As is evident, the ultrasound-assisted Sonogashira reaction proceeds smoothly at ambient temperature even in the absence of copper co-catalyst and phosphine ligands to afford the products in excellent isolated yields. The reactions were significantly faster in acetone as the reaction medium (15-90 min) as compared to those in the IL (2-3 h). However, the reactions in the IL afforded the products in relatively higher yields with the added advantage of the recyclability of both catalyst and the reaction medium. The IL consisting of the Pd catalyst was recycled five times for the reaction of iodobenzene with ethynylbenzene. The results are recorded in **Table 18**. It was observed that the catalyst exhibits only a marginal loss in activity spread over five recycle batches

Table 18. Reuse of Catalyst System for Synthesis of diphenylacetylene (entry 1)

entry	1	2	3	4	5
*yield (%)	93	91	89	88	85

*Isolated yield after column chromatography

It was important to note that no Glaser coupling product even in traces could be observed for all the reactions involving iodobenzene. However, in the case of less reactive bromobenzenes, the homocoupled product arising out of the terminal acetylene was formed to an extent of 6-7%. The extent of formation of Glaser coupling product was determined by GC analysis. It can be observed that the process tolerates both electron-

donating and electron-withdrawing substituents in the aryl halides as well as terminal acetylenes

A Pd(0) species stabilized by ligands is proposed to be involved in the catalytic cycle comprising of oxidative insertion, trans-metalation, and reductive elimination of the Sonogashira reaction. Consequently, the formation of such Pd(0) nanoparticles was investigated in the present work by subjecting the reaction mixture after a successful Sonogashira reaction of iodobenzene with 1-ethynylbenzene in acetone and the IL respectively under the sonochemical conditions for "*in situ*" TEM analysis. TEM analysis was carried out in a Transmission Electron Microscope operated at 100 kV with the magnification varying from 100 to 300 k. The sample after appropriate dilution with isopropyl alcohol was directly deposited on carbon coated 400 mesh Cu TEM grids.

TEM Measurements in acetone medium

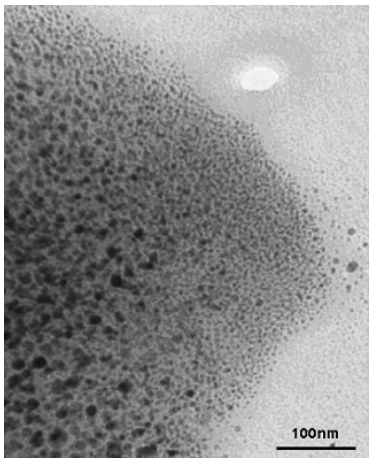


Figure 21

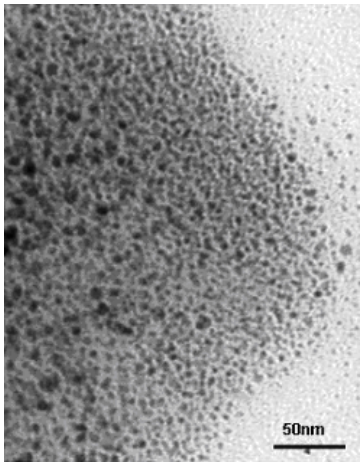
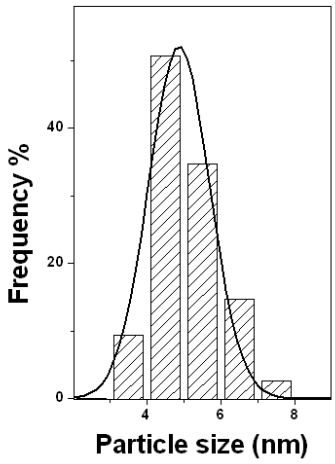


Figure 22

TEM images of Pd(0) nanoparticles in acetone medium at different magnifications

The micrograph shows the presence of polydispersed Pd(0) nanoparticles varying in size from 3-8 nm and of irregular morphology and spherical in shape (**Fig**. **21** and **22**). The average size of the grains obtained from the TEM picture from acetone medium is about 4.18 nm (**Fig. 23**).



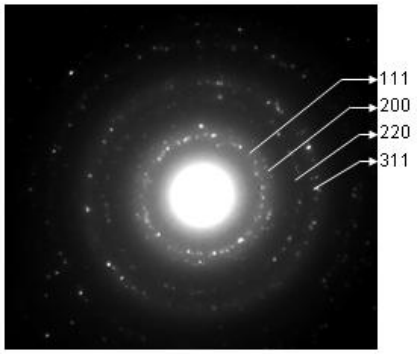
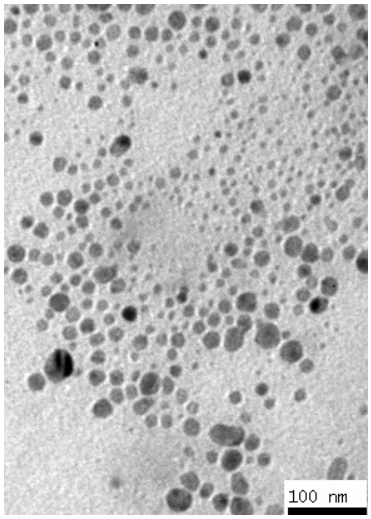


Figure 23 **Figure 24**

Histogram and SAED pattern of Pd(0) nanoparticles in acetone medium

The inset picture of **Fig. 24** show the SAED (Selected Area Electron Diffraction) pattern of the palladium nanoparticles in the acetone medium. It is clear from SAED pattern that the Pd particles are polycrystalline in nature and it can be indexed as the (111), (200), (220), (311) allowed reflections from face-centered cubic (fcc) palladium.

TEM Measurements in ionic liquid medium



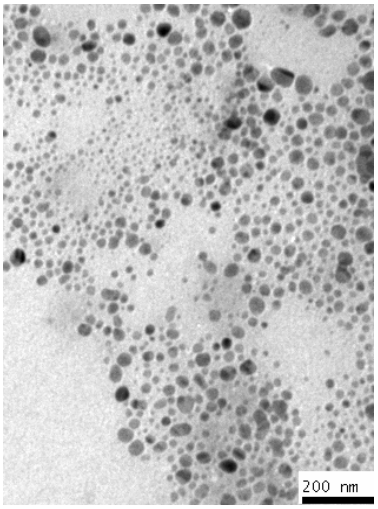


Figure 25 **Figure 26**

TEM images of Pd(0) nanoparticles in ionic liquid medium at different magnifications

In the TEM images (**Fig. 25** and **26**) obtained from the ionic liquid medium, after the reaction of 1-ethynylbenzene with iodobenzene, it is observed that the palladium nanoparticles are almost spherical in nature and the boundaries are clear. They are well dispersed and the histogram (**Fig. 27**) shows the size to be in the range of 10-13 nm. The SAED pattern (**Fig. 28**) indicates the polycrystalline nature of the nanoparticles and can be indexed as the (111), (200), (220), (222), (331) allowed reflections from the fcc palladium.

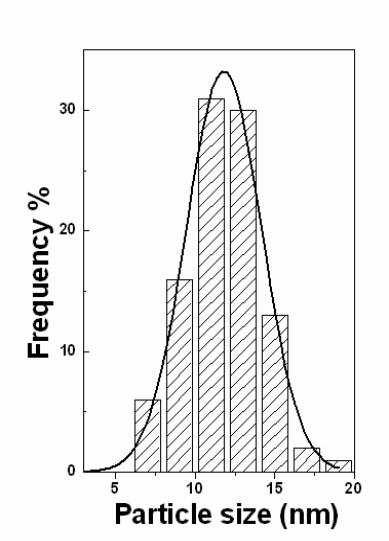


Figure 27

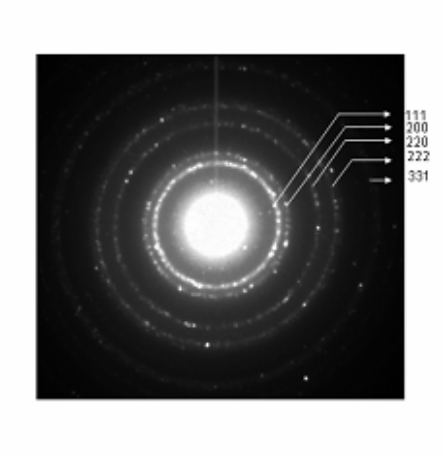
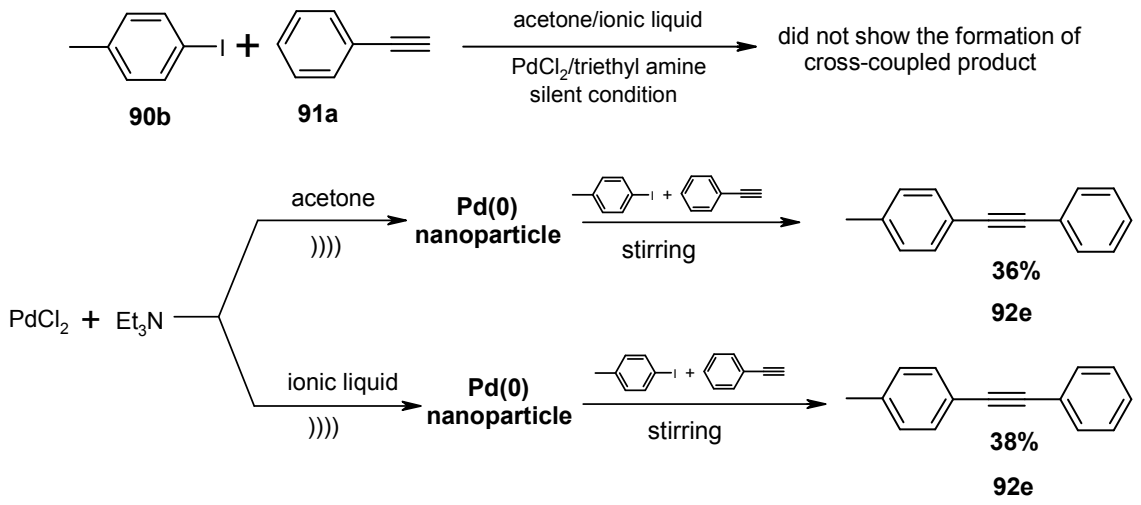


Figure 28

Histogram and SAED pattern of Pd(0) nanoparticles in IL medium

It is important to note that the reaction of 4-iodotoluene with 1-ethynylbenzene in acetone or IL at room temperature under similar conditions but in the absence of ultrasound (silent condition) did not show the formation of any cross-coupled product even after several hours (6 h) of stirring.

Moreover, in a blank experiment, Pd(0) nanoparticles were formed by sonicating a mixture of $PdCl_2$ and triethylamine in either acetone or IL, respectively. To this were added the reactants, viz. 4-iodotoluene and 1-ethynylbenzene, and the mixture was stirred for 6 h at ambient temperature under silent conditions. The cross-coupled product 4-(phenylethynyl)toluene was obtained to an extent of 36% and 38% (isolated yields) in acetone and the IL, respectively, as against the 75% and 85% yields obtained in the total sonochemical reaction (**Scheme 26**).



Scheme 26. Blank experiment

This implies that ultrasound not only brings about the formation of highly crystalline, active Pd(0) nanoparticles required for the Sonogashira reaction but also promotes the activity of the catalytic species in the oxidative insertion, trans-metalation, and reductive elimination catalytic cycle of the Sonogashira reaction. This is made possible by the phenomenon of acoustic cavitation generating transient cavitation bubbles of very short lifetimes (~10^{-9} s), the implosive collapse of which under adiabatic conditions gives rise to high temperatures and pressures.[31]

It was interesting to ascertain whether this reaction is effective with similar room-temperature ILs belonging to the imidazolium class. Thus, a variety of ILs as shown in **Table 19** were screened as solvents for the synthesis of diphenylacetylene under identical sonochemical reaction conditions. It was also observed that all the ionic liquids with varying cations and anions were found to give more or less similar results as shown in **Table 19**.

Table 19. Synthesis of Diphenylacetylene in Various

Entry	Ionic liquid	Time (h)	*Yield (%)
1	[BMIm]Br	2	89
2	[BEIm]BF_4	2	90
3	[BPIm]Br	2	92

4	$[EMIm]BF_4$	2	89
5	[BBIm]Cl	2	88
6	[BBIm]Br	2	92
7	$[BBIm]BF_4$	2	93
8	$[BBIm]PF_6$	2	90
9	$[BBIm]ClO_4$	2	85

*Isolated yields after column chromatography

1.5.5 Conclusion

In conclusion, the Sonogashira reaction has been achieved in short reaction times, excellent chemoselectivity, and high isolated yields at ambient temperature under ultrasonic irradiation in a molecular solvent as well as a room-temperature ionic liquid even in the absence of a phosphine ligand and copper co-catalysts. For iodobenzenes, no traces of Glaser coupling product were detected, whereas in the case of bromobenzenes the homocoupled product was formed to the extent of 6-7% only. The formation of stable and crystalline Pd(0) nanoparticles under the sonochemical conditions has been shown by TEM measurements. It was ascertained that ultrasound not only generated the Pd(0) nanoparticles as the active catalyst for the reaction but also promoted and enhanced the catalytic activity of this species in the catalytic cycle of the Sonogashira cross coupling reaction. The short reaction times, excellent chemoselectivity, high isolated yields, and easy workup procedure make this sonochemical methodology an efficient protocol for the rapid synthesis of disubstituted acetylene libraries.

1.5.6 Experimental

1.5.6.1 General consideration

All sonochemical reactions were carried out in an argon atmosphere. All chemicals were of research grade and used without further purification. The reactions were carried out in a thermostated (30 ± 1 °C) ultrasonic cleaning bath at 50 kHz. The ultrasonic cleaner had an output power of 120 W and a power supply of 450 W. The tank dimensions were 290 × 240 × 150 mm with a liquid holding capacity of 9.5 L. The reactions were carried out in a RB flask of 10 ml capacity suspended at the centre of the cleaning bath, 5 cm below the surface of the liquid. The melting points of the products were uncorrected and compared with the reported literature values. The TEM analysis was carried out in a

Transmission Electron Microscope operating at 100 kV at different magnifications varying from 100 to 300 k.

1.5.6.2 Sample Preparation and TEM analysis

After completion of the reaction a sample is removed from the reaction mixture and after appropriate dilution with isopropyl alcohol was directly deposited on carbon coated 400 mesh Cu TEM grids. TEM pictures of each sample were taken at 100 kV operating voltage at multiple random locations in the sample and at two different magnifications. The size distribution histogram was obtained on the basis of about 100 particles.

1.5.6.3 Preparation of Acetylene Derivatives

General Procedure for the Sonogashira Reaction in Acetone medium

A mixture of aryl halide (1 mmol), terminal acetylenes (1 mmol), $PdCl_2$ (0.02 mmol) and triethylamine (1.5 mmol) in 5mL of acetone was sonicated for the appropriate time under argon at 30 ^oC. The reaction was monitored by TLC, and after completion of reaction, acetone was removed from reaction mixture under reduced pressure. The residue was dissolved in 10% ethyl acetate in petroleum ether (bp 60-80 ^oC), clarified by filtration through Celite filter bed, and washed with water. The organic layer was separated and dried over anhyd Na_2SO_4 and concentrated in a vacuum. The crude product obtained was further purified by column chromatography through a column of silica gel using petroleum ether (bp 60-80 ^oC) or an appropriate mixture of petroleum ether and ethyl acetate as eluent to afford the pure product.

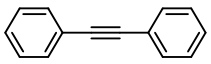
General Procedure for the Sonogashira Reaction in $[BBIm]BF_4$

A mixture of aryl halide (1 mmol), terminal acetylenes (1 mmol), $PdCl_2$ (0.02 mmol), and triethylamine (1.5 mmol) in 2 ml of dry ionic liquid was sonicated for the appropriate time under argon at 30 ^oC. The reaction was monitored by TLC, and after completion of reaction, the product was selectively extracted with 10% ethyl acetate in petroleum ether (bp 60-80 ^oC) from the reaction mixture leaving behind the ionic liquid consisting of the Pd catalyst as an immiscible layer. The hydrophobic ionic liquid layer was washed with

water to remove the amine hydrochloride salt, and the ionic liquid was dried under reduced pressure at 60 ^{o}C for 30 min and used as such for further reaction. The separated organic layer was dried over anhyd Na_2SO_4 and concentrated in a vacuum. The crude product obtained was further purified by column chromatography through a column of silica gel using petroleum ether (bp 60-80 ^{o}C) or an appropriate mixture of petroleum ether and ethyl acetate as eluent to afford the pure product.

1.5.6.4 Characterization data for compounds 92a-t

Diphenylacetylene (92a)



Nature : White solid

MP : 60 ^{o}C, (Lit.[10] 58-60 ^{o}C).

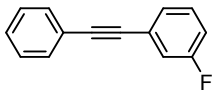
^{1}H NMR 200 MHz (CDCl$_3$) : δ 7.27-7.24 (m, 6H), 7.48-7.43 (m, 4H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 131.6, 128.3, 128.2, 123.3, 89.4.

Elemental analysis : Calcd: C, 94.34; H,5.66.

$C_{14}H_{10}$ (178) Found: C, 94.23; H, 5.70.

1-Fluoro-3-(phenylethynyl)benzene (92b)



Nature : White solid

MP : 36 ^{o}C, (Lit.[32] 36 ^{o}C).

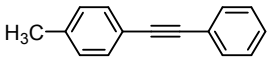
^{1}H NMR 200 MHz (CDCl$_3$) : δ 7.58-7.54 (m, 2H), 7.39-7.31 (m, 5H), 7.27-7.23 (m, 1H), 7.11-7.01 (m, 1H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 162.3 (d, J = 246.27), 131.62, 129.8 (d, J = 8.42 Hz), 128.4, 128.3, 127.4 (d, J = 2.56Hz), 125.08 (d, J = 9.52 Hz), 122.7, 118.3 (d, J = 23.05 Hz), 115.5 (d, J = 21.22 Hz), 90.2, 88.0 (d, J = 2.93 Hz).

Elemental analysis : Calcd: C, 85.70; H, 4.62, F, 9.68.

$C_{14}H_9F$ (196) Found: C, 85.78; H, 4.54; F, 9.75.

4-(phenylethynyl)toluene (92c)



Nature : White solid

MP : 70 °C, (Lit.[10] 71 °C)

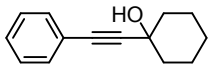
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.45-7.40 (m, 2H), 7.33 (d, *J* = 8.22 Hz, 2H), 7.27-7.21 (m, 3H), 7.05 (d, *J* = 8.22 Hz, 2H), 2.28 (s, 3H)

^{13}C NMR 50 MHz ($CDCl_3$) : δ 138.3, 131.5, 131.4, 129.0, 128.8, 128.0, 123.4, 120.1, 89.5, 88.7, 21.6.

Elemental analysis : Calcd: C, 93.71; H,6.29

$C_{15}H_{12}$ (192) Found: C, 93.62; H, 6.17

1-phenylethynylcyclohexanol (92d)



Nature : White solid

MP : 64 °C, (Lit.[33] 65 °C).

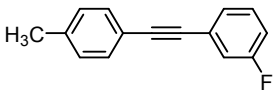
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.44-7.30 (m, 5H), 2.00 (s, 1H), 1.74-1.43 (m, 10 H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ δ 131.5, 128.0, 127.9, 122.9, 92.9, 84.2, 68.8, 39.9, 25.1, 23.2.

Elemental analysis : Calcd: C, 83.96; H,8.05

$C_{14}H_{16}O$ (200) Found: C, 83.92; H, 8.15

1-Fluoro-3-(phenylethynyl)toluene (92e)



Nature : White solid

MP : 61°C

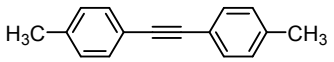
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.25-7.16 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.02-6.90 (m, 1H), 2.30 (s, 3H)

^{13}C NMR 50 MHz ($CDCl_3$) : δ 162.4 (d, *J* = 246.47 Hz), 138.7, 131.5, 130.1 (d, *J* = 9.22 Hz), 129.8 (d, *J* = 9.22 Hz), 129.1, 128.4, 127.3, 125.4 (d, *J* = 11.52 Hz), 119.7, 119.2 (d, *J* = 23.03 Hz), 118.2 (d, *J* = 20.73 Hz), 116.8 (d, *J* = 20.73 Hz), 115.3 (d, *J* = 20.73 Hz), 90.5, 87.5, 21.4.

Elemental analysis : Calcd: C, 85.69; H, 5.27; F, 9.04

$C_{15}H_{11}F$ (210) Found: C, 85.73; H, 5.32; F, 9.19

Di-*p*-tolylacetylene (92g)



Nature : White solid

MP : 139 °C, (Lit.[34] 138°C).

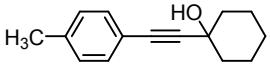
^{1}H NMR 200 MHz ($CDCl_3$) : δ δ 7.44 (d, *J* = 8Hz, 4H), 7.17 (d, *J* = 8Hz, 4H), 2.38 (s, 6H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 138.1, 131.3, 129.0, 120.3, 88.8, 21.4. 21.4.

Elemental analysis : Calcd: C, 93.16; H, 6.84.

$C_{16}H_{14}$ (206) Found: C, 93.23; H, 6.70.

1-*p*-Tolylethynylcyclohexanol (92h)



Nature : White solid

MP : 139 °C.

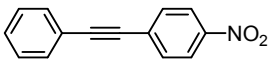
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 2.34 (s, 3H), 1.98 (s, 1H), 1.73-1.57 (m, 10 H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 138.0, 131.5, 128.9, 119.8, 92.1, 84.4, 68.9, 40.0, 25.2, 23.4, 21.4.

Elemental analysis : Calcd: C, 84.07; H, 8.47.

$C_{15}H_{18}O$ (214) Found: C, 84.16; H, 8.52.

1-Nitro-(4-phenylethynyl)benzene (92i)



Nature : White solid

MP : 118-120 °C, (Lit.[35] 118-120°C).

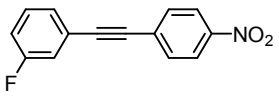
^{1}H NMR 200 MHz ($CDCl_3$) : δ 8.22 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.57-7.55 (m, 2H), 7.40-7.37 (m, 3H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 146.9, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 122.0, 94.6, 87.6.

Elemental analysis : Calcd: C, 75.33; H, 4.06; N, 6.27.

$C_{14}H_9NO_2$ (223) Found: C, 75.27; H, 4.13; N, 6.15.

1-Fluoro-3-(phenylethynyl)nitrobenzene (92j)



Nature : White solid

MP : 139 °C.

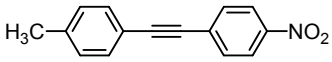
^{1}H NMR 200 MHz ($CDCl_3$) : δ 8.24 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.41-7.08 (m, 4H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 162.3 (d, *J* = 247.61 Hz), 147.1, 132.3, 130.1 (d, *J* = 9.60 Hz), 129.5, 127.6 (d, *J* = 3.83 Hz), 123.8 (d, *J* = 9.60 Hz), 123.6, 118.5 (d, *J* = 23.03 Hz), 116.5, (d, *J* = 21.22 Hz), 96.09, 88.19.

Elemental analysis : Calcd: C, 69.71; H, 3.34; N, 5.81.

$C_{14}H_8FNO_2$ (241) Found: C, 69.83; H, 3.40; N, 5.74.

1-Methyl-4-(phenylethynyl)nitrobenzene (92k)



Nature : Yellow solid

MP : 157 °C.

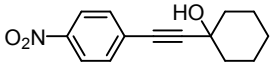
^{1}H NMR 200 MHz ($CDCl_3$) : δ 8.23 (d, *J* = 8.61 Hz, 2H), 7.66 (d, *J* = 7.43 Hz, 2H), 7.42 (d, *J* = 7.44 Hz, 2H) 7.21 (d, *J* = 7.82 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 146.7, 139.6, 132.0, 131.6, 130.4, 129.2, 123.5, 118.9, 95.0, 87.0, 21.5.

Elemental analysis : Calcd: C, 75.94; H, 4.67; N, 5.90.

$C_{15}H_{11}NO_2$ (237) Found: C, 75.80; H, 4.59; N, 5.82.

1-(4-Nitro-phenylethynyl)cyclohexanol (92l)



Nature : White solid

MP : 101 °C.

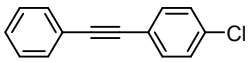
^{1}H NMR 200 MHz ($CDCl_3$) : δ 8.15 (d, *J* = 8.25 Hz, 2H), 7.54 (d, *J* = 8.25 Hz, 2H), 2.01 (s, 1H), 1.76-1.55 (m, 10H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 146.9, 132.3, 129.8, 123.4, 98.3, 82.4, 69.0, 39.7, 25.0, 23.2.

Elemental analysis : Calcd: C, 68.56; H, 6.16; N, 5.71.

$C_{14}H_{15}NO_3$ (245) Found: C, 68.48; H, 6.22; N, 5.68.

1-Chloro-4-(phenylethynyl)benzene (92m)



Nature : White solid

MP : 83 °C, (Lit.[35] 79.5-81.5 °C)

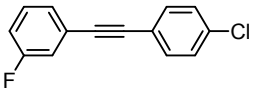
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.29-7.23 (m, 5H), 7.48-7.37 (m, 4H)

^{13}C NMR 50 MHz ($CDCl_3$) : δ 134.2, 132.7, 131.6, 128.6, 128.4, 128.3, 122.9, 121.8, 90.3, 88.2.

Elemental analysis : Calcd: C, 79.07; H, 4.27.

$C_{14}H_9Cl$ (212) Found: C, 79.01; H, 4.23.

1-Fluoro-3-(phenylethynyl)chlorobenzene (92n)



Nature : White solid

MP : 86 °C.

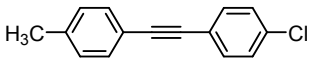
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.39 (d, *J* = 8.33 Hz), 7.31-7.11 (m, 5H), 7.03-6.93 (m, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 162.4 (d, *J* = 246.48 Hz), 134.6, 132.8, 131.5, 129.9 (d, *J* = 6.91 Hz), 128.7, 128.3, 127.4, 124.8 (d, *J* = 9.21 Hz), 121.31, 118.3 (d, *J* = 23.03 Hz), 115.7 (d, *J* = 20.73 Hz), 89.0 (d, *J* = 9.22 Hz).

Elemental analysis : Calcd: C, 72.90; H, 3.50.

$C_{14}H_8ClF$ (230) Found: C, 72.83; H, 3.45.

1-Chloro-4-(phenylethynyl)toluene (92o)



Nature : White solid

MP : 149 °C, (Lit.[36] 150-151 °C).

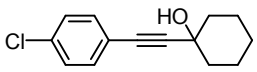
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.39-7.32 (m, 4H), 7.26-7.17 (m, 2H), 7.08 (d, *J* = 7.83, 2H Hz), 2.29 (s, 3H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ δ 138.6, 134.0, 132.7, 131.5, 129.1, 128.6, 122.1, 119.9, 90.5, 87.6, 21.4.

Elemental analysis : Calcd: C, 79.47; H, 4.89.

$C_{15}H_{11}Cl$ (226) Found: C, 79.42; H, 4.91.

1-(4-Chloro-phenylethynyl)cyclohexanol (92p)



Nature : White solid

MP : 78 °C.

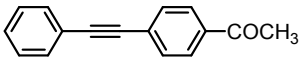
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.31-7.18 (m, 4H), 1.92 (s, 1H), 1.68-1.49 (m, 10 H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 134.2, 132.6, 128.5, 121.3, 93.8, 83.8, 69.0, 39.9, 25.1, 23.3.

Elemental analysis : Calcd: C, 71.64; H, 6.44; Cl, 15.10.

$C_{15}H_{11}ClO$ (234) Found: C, 71.58; H, 6.38; Cl, 15.12.

1-(4-Phenylethynyl-phenyl)ethanone (92q)



Nature : White solid

MP : 95-96 °C, (Lit.[10] 95-97 °C).

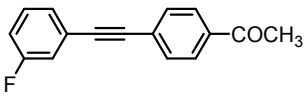
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.87 (d, *J* = 8.72 Hz, 2H), 7.54 (d, *J* = 8.59 Hz, 2H), 7.50 - 7.46 (m, 2H), 7.31-7.28 (m, 3H), 2.54 (s, 3H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 197.1, 136.0, 131.6, 131.5, 128.7, 128.3, 128.1, 128.0, 122.5, 92.6, 88.5, 26.4.

Elemental analysis : Calcd: C, 87.25; H, 5.49.

$C_{16}H_{12}O$ (220) Found: C, 87.31; H, 5.42.

1-[4-(3'-Fluoro-phenylethynyl)-phenyl]ethanone (92r)



Nature : White solid

MP : 90-91 °C.

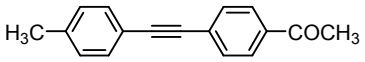
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.87 (d, *J* = 8.79 Hz, 2H), 7.53 (d, *J* = 8.06 Hz, 2H), 7.27-6.99 (m, 4H), 2.54 (s, 3H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 197.1, 162.2 (d, *J* = 247.0 Hz), 136.3, 131.6, 129.9 (d, *J* = 8.78 Hz), 128.1, 127.56, 127.50, 124.3 (d, *J* = 9.52 Hz), 118.3 (d, *J* = 23.05 Hz), 116.05 (d, *J* = 21.22 Hz), 91.1, 89.3, 26.4.

Elemental analysis : Calcd: C, 80.66; H, 4.65; F, 7.97.

$C_{16}H_{11}FO$ (238) Found: C, 80.64; H, 4.66; F, 7.90.

1-(4-*p*-Tolylethynyl-phenyl)ethanone (92s)



Nature : White solid

MP : 126-127 °C, (Lit.[37] 126-128 °C).

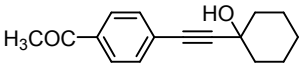
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.86 (d, *J* = 8.59 Hz, 2H), 7.52 (d, *J* = 8.59 Hz, 2H), 7.37 (d, *J* = 8.08 Hz, 2H), 7.10 (d, *J* = 7.83 Hz, 2H), 2.54 (s, 3H), 2.31 (s, 3H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 197.2, 139.0, 135.9, 131.57, 131.53, 129.1, 128.3, 128.1, 119.4, 92.9, 88.0, 26.5, 21.5.

Elemental analysis : Calcd: C, 87.15; H, 6.02.

$C_{17}H_{14}O$ (234) Found: C, 87.16; H, 5.98.

1-[4-(1'-Hydroxy-cyclohexylethynyl)-phenyl]ethanone (92t)



Nature : White solid

MP : 82-83 °C.

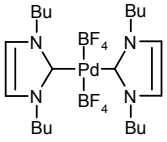
^{1}H NMR 200 MHz ($CDCl_3$) : δ 7.88 (d, *J* = 8.79 Hz, 2H), 7.48 (d, *J* = 8.79 Hz, 2H), 2.58 (s, 3H), 1.99 (s, 1H), 1.7-1.54 (m, 10 H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 197.4, 136.0, 131.7, 128.1, 127.8, 96.3, 83.4, 69.0, 39.8, 26.5, 25.0, 23.2.

Elemental analysis : Calcd: C, 79.31; H, 7.49.

$C_{16}H_{18}O_2$ (242) Found: C, 79.35; H, 7.44.

Pd-biscarbene Complex [A] (93)



Nature : White solid

MP : 105-106 °C, (Lit.[30] 105-106 °C).

^{1}H NMR 200 MHz ($CDCl_3$) : δ 6.81 (s, 4H), 4.52 (t, 8H), 2.08 (m, 8H), 1.47 (m, 8H,), 1.01 (t, 12H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 169.2, 119. 8, 50.1, 32.6, 19.6, 13.3.

Elemental analysis : Calcd: C, 41.25; H, 6.25; N, 8.75.

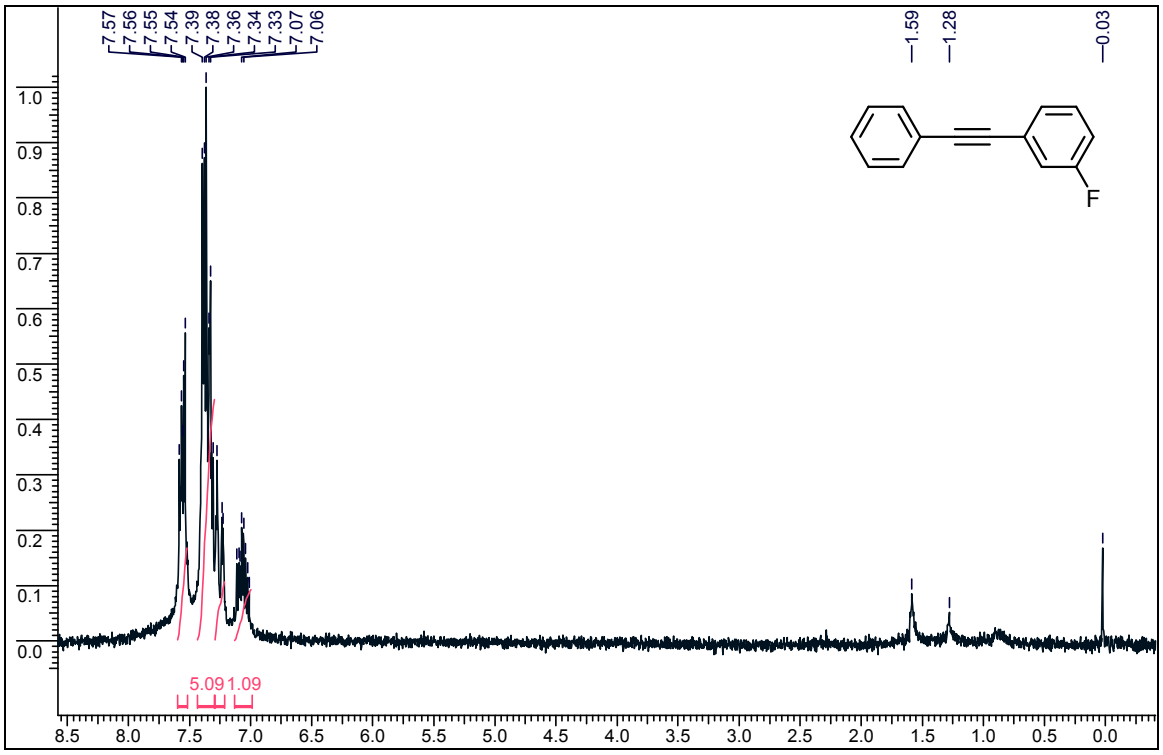
$C_{22}H_{40}N_4B_2F_8Pd$ (640) Found: C, 41.52; H, 6.27; N, 8.97.

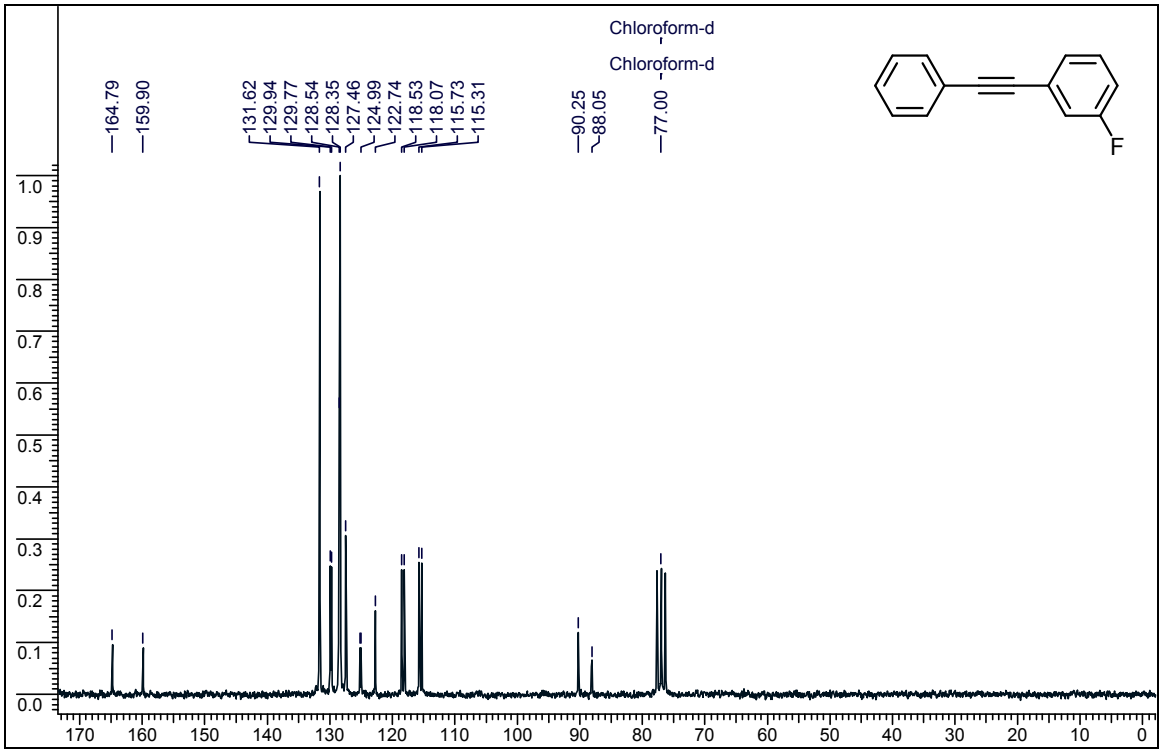
1.5.7 Spectra

Table 20. ^{1}H and ^{13}C spectra of some selected compounds are given below:

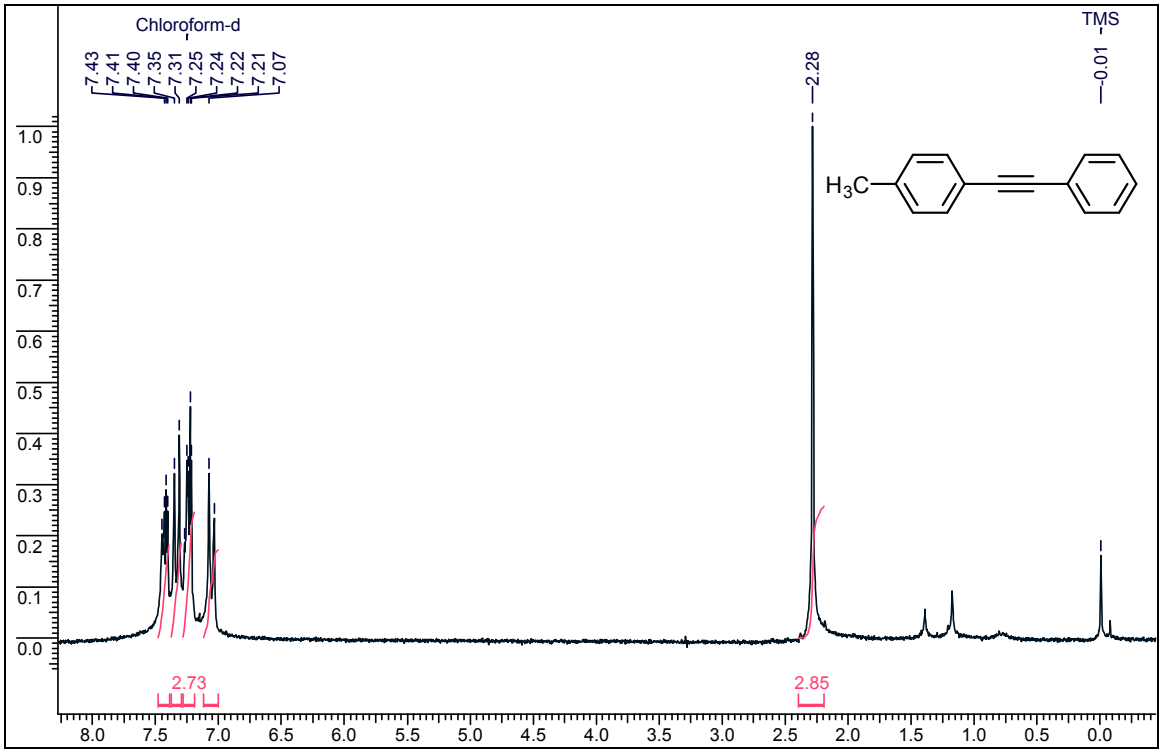
Sr. No.	Spectra	
[1]	^{1}H NMR and ^{13}C NMR Spectra of	**92b**
[2]	^{1}H NMR and ^{13}C NMR Spectra of	**92c**
[3]	^{1}H NMR and ^{13}C NMR Spectra of	**92d**
[4]	^{1}H NMR and ^{13}C NMR Spectra of	**92g**
[5]	^{1}H NMR and ^{13}C NMR Spectra of	**92h**
[6]	^{1}H NMR and ^{13}C NMR Spectra of	**92k**
[7]	^{1}H NMR and ^{13}C NMR Spectra of	**92m**
[8]	^{1}H NMR and ^{13}C NMR Spectra of	**92r**
[9]	^{1}H NMR and ^{13}C NMR Spectra of	**92s**
[10]	^{1}H NMR and ^{13}C NMR Spectra of	**93**

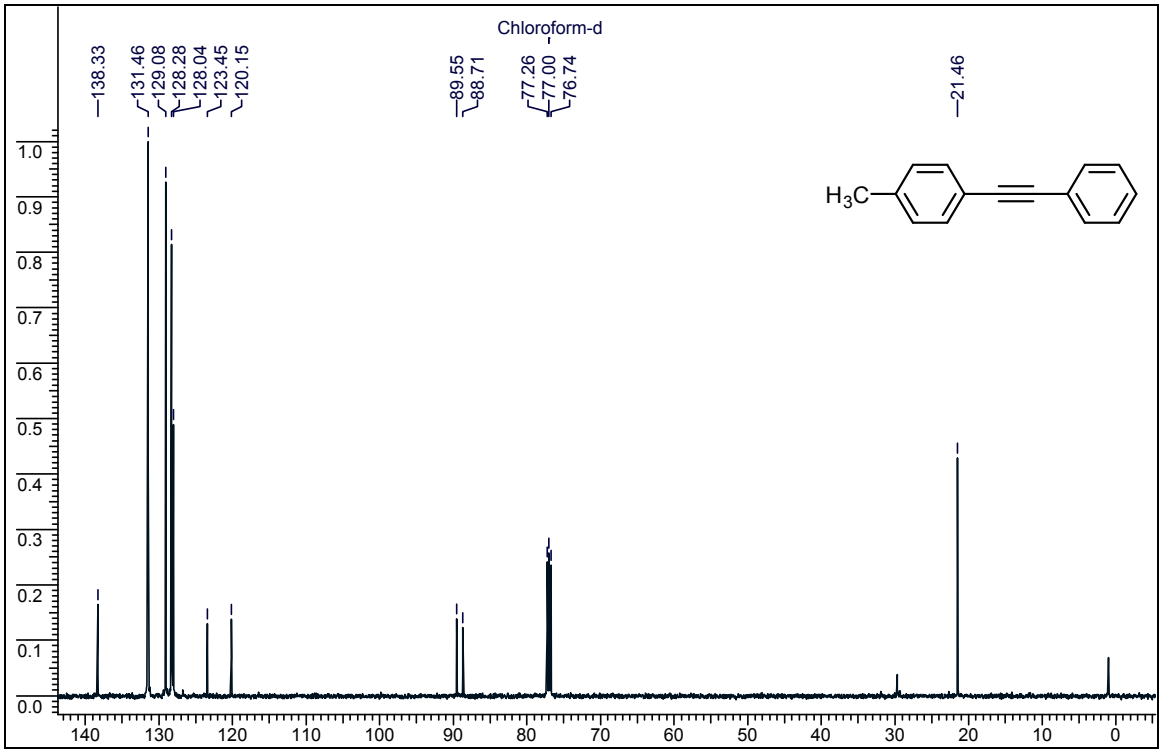
[1] ^{1}H NMR and ^{13}C NMR Spectra of 92b



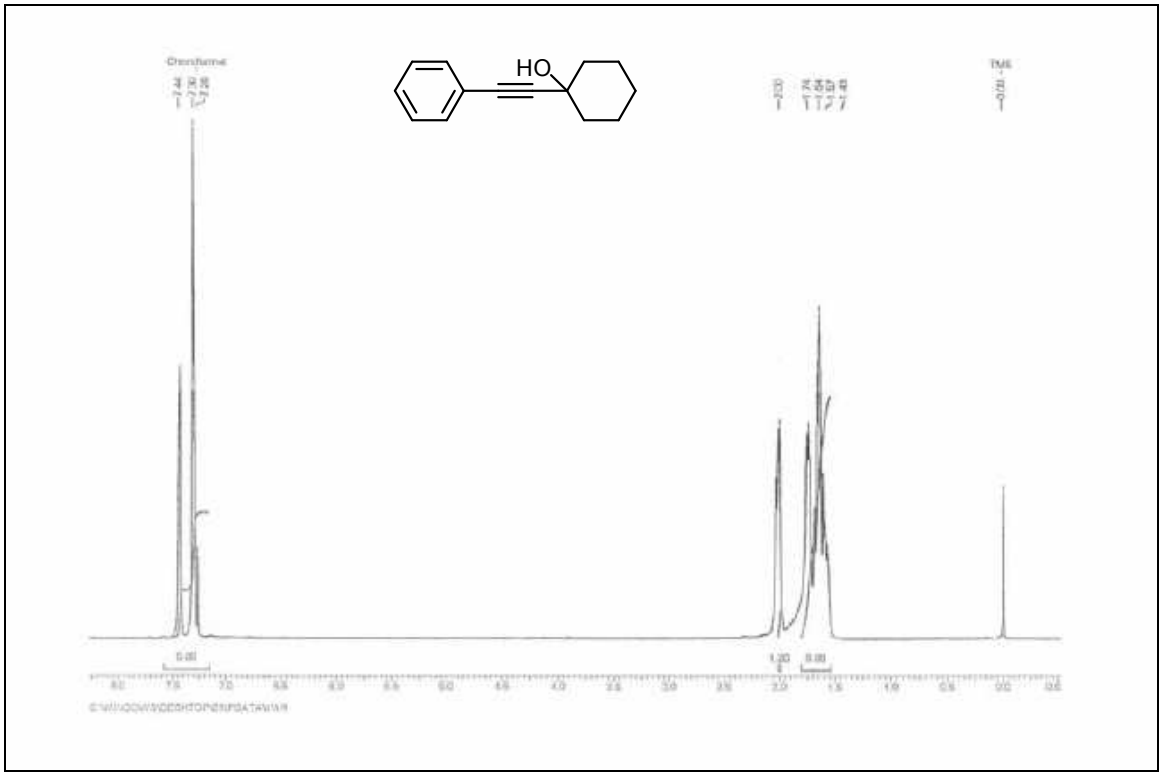


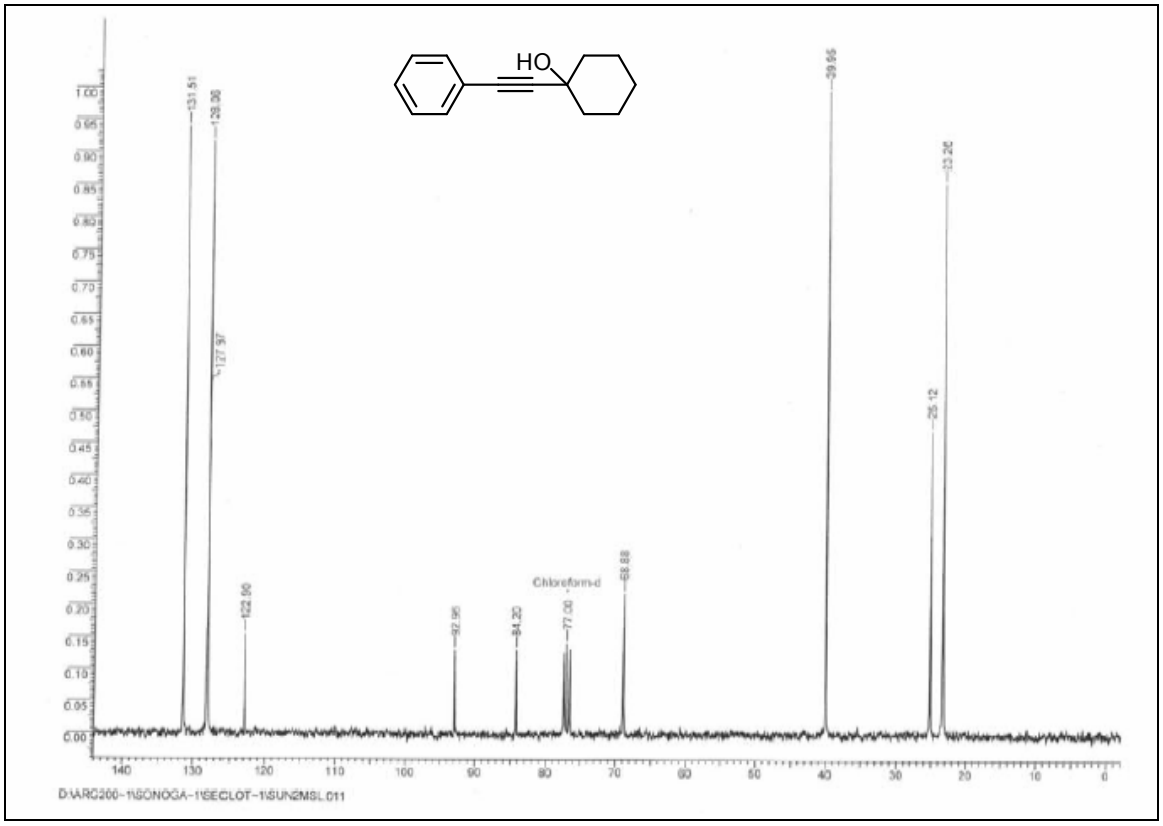
[2] ^{1}H NMR and ^{13}C NMR Spectra of 92c



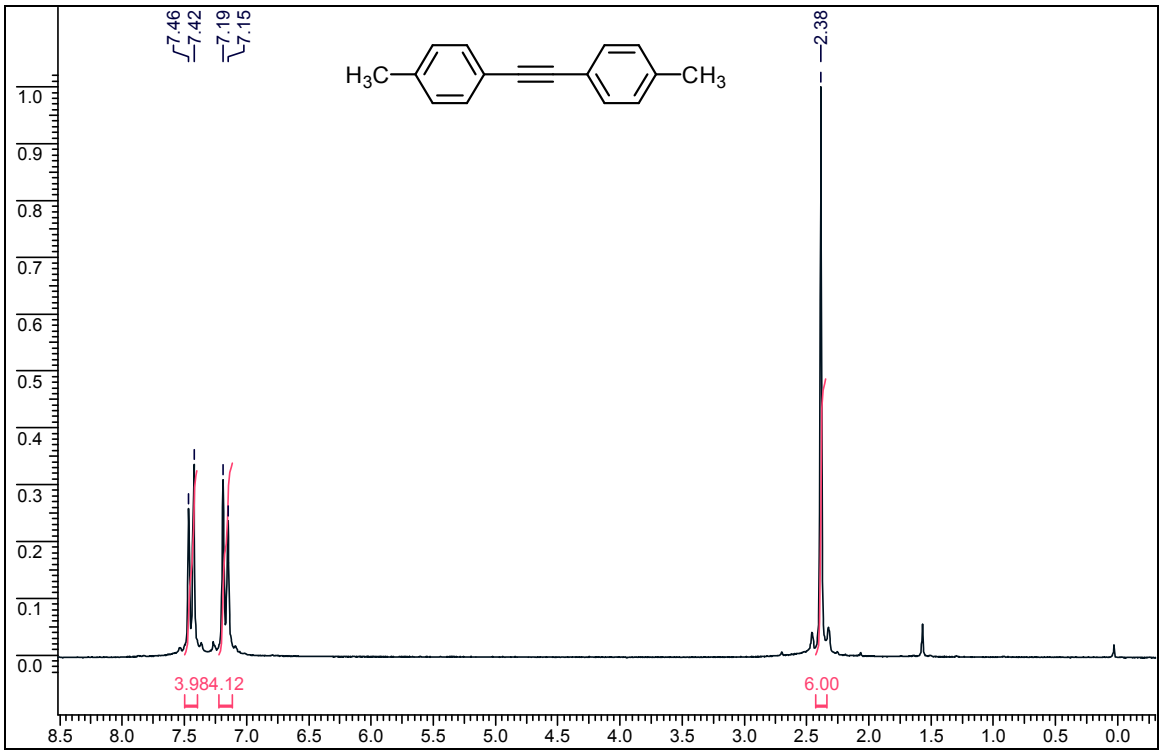


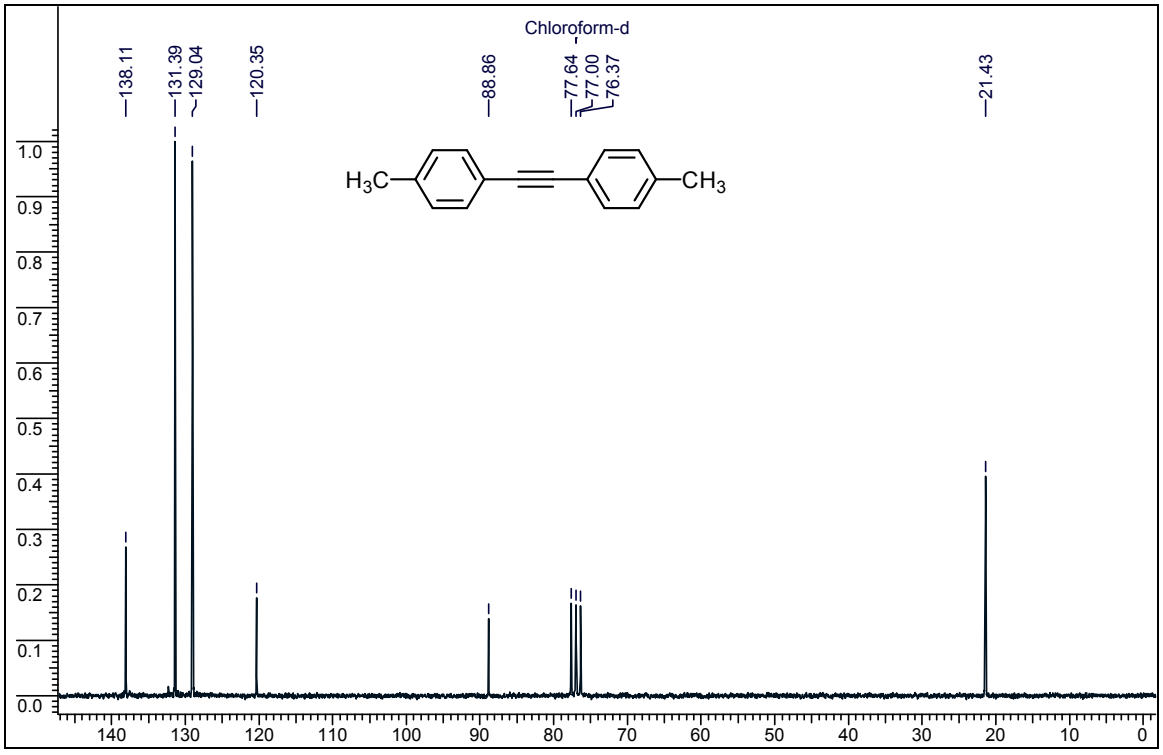
[3] ^{1}H NMR and ^{13}C NMR Spectra of 92d



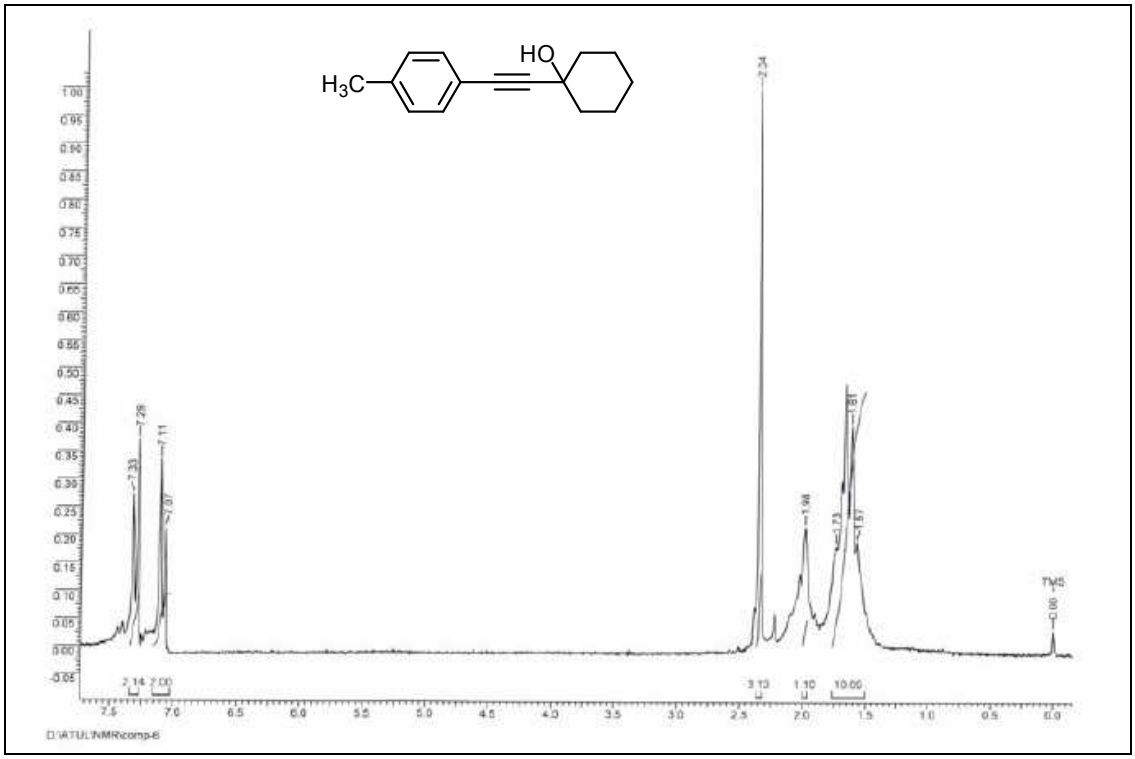


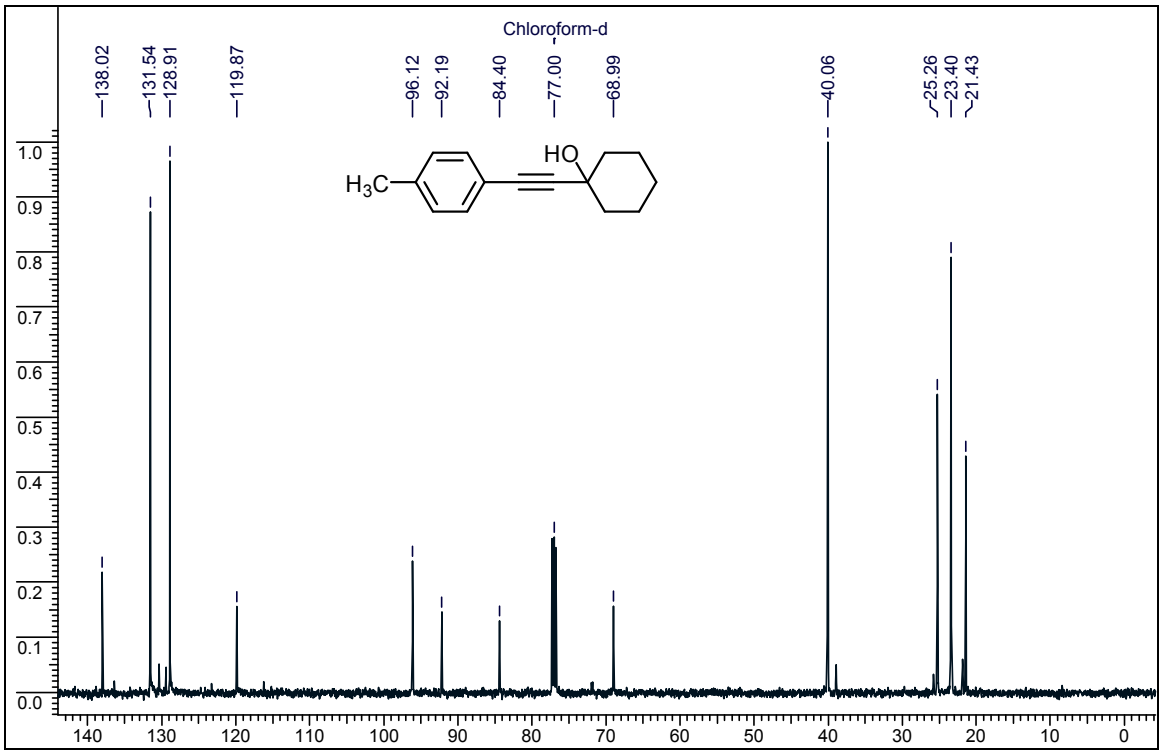
[4] ^{1}H NMR and ^{13}C NMR Spectra of 92g



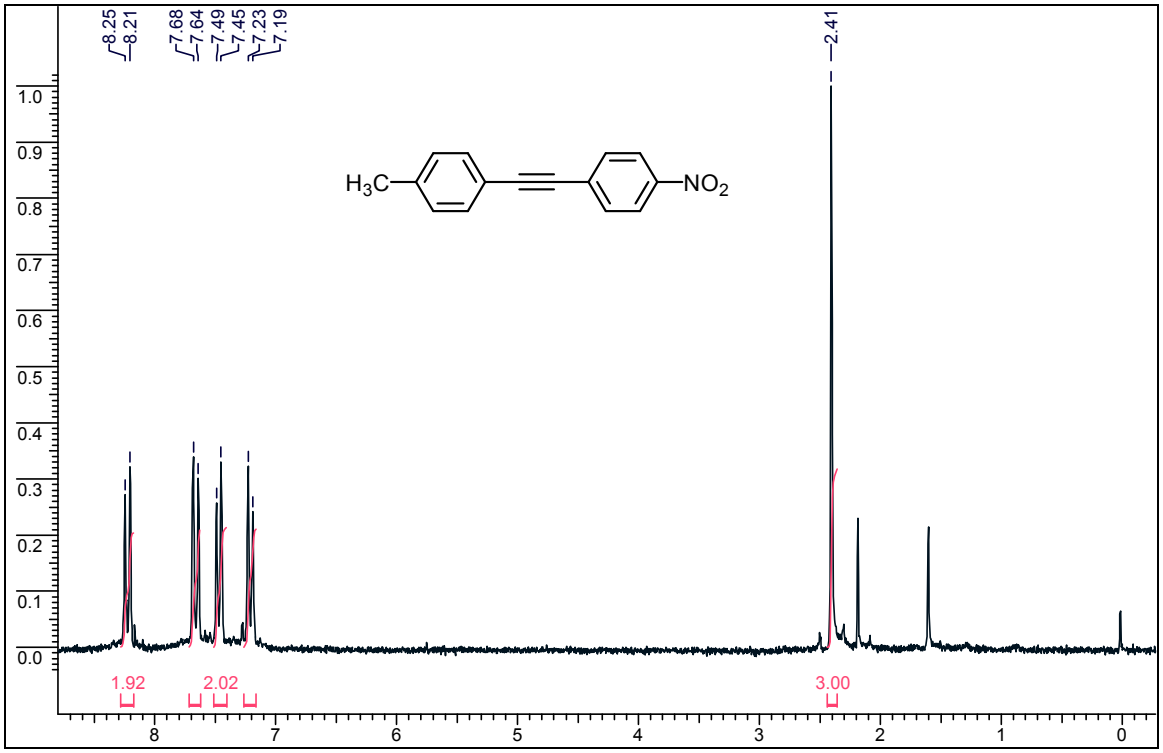


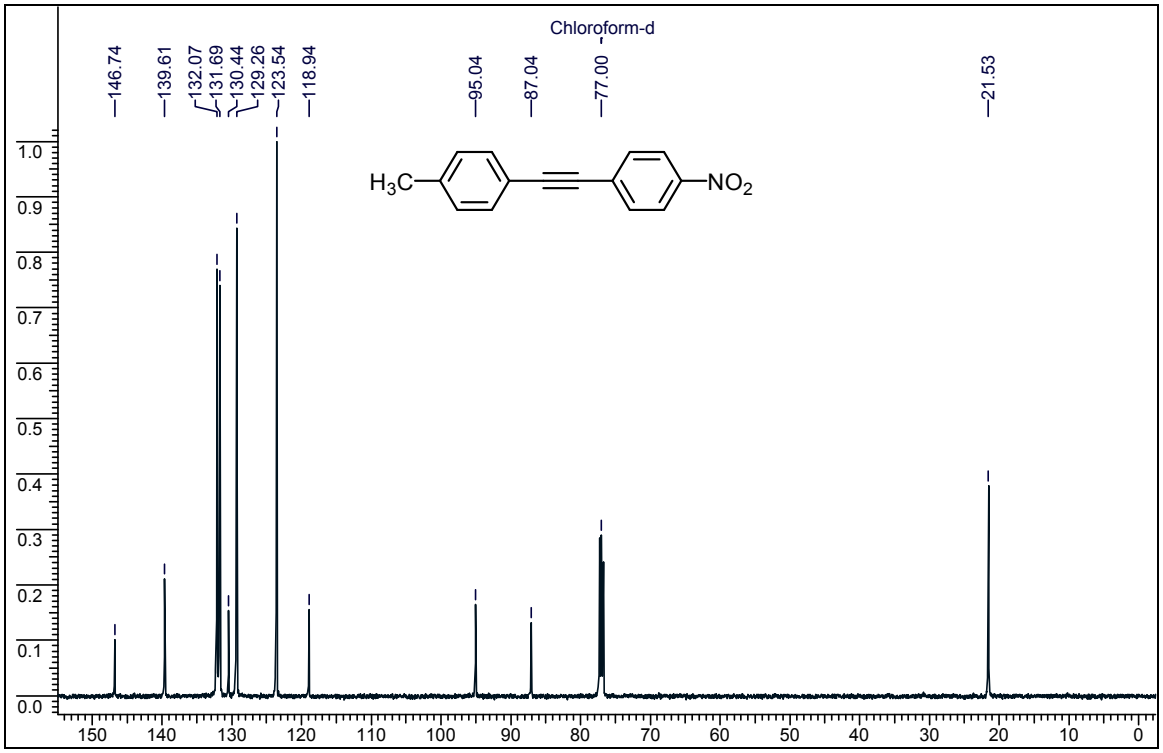
[5] ^{1}H NMR and ^{13}C NMR Spectra of 92h



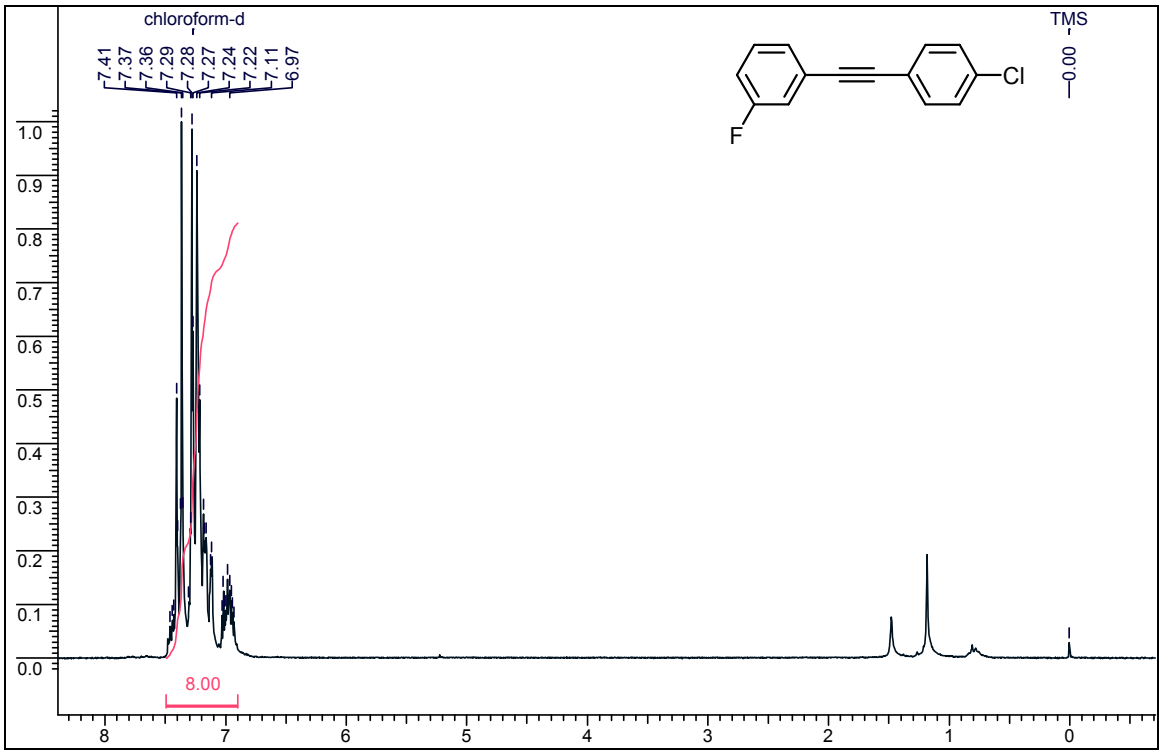


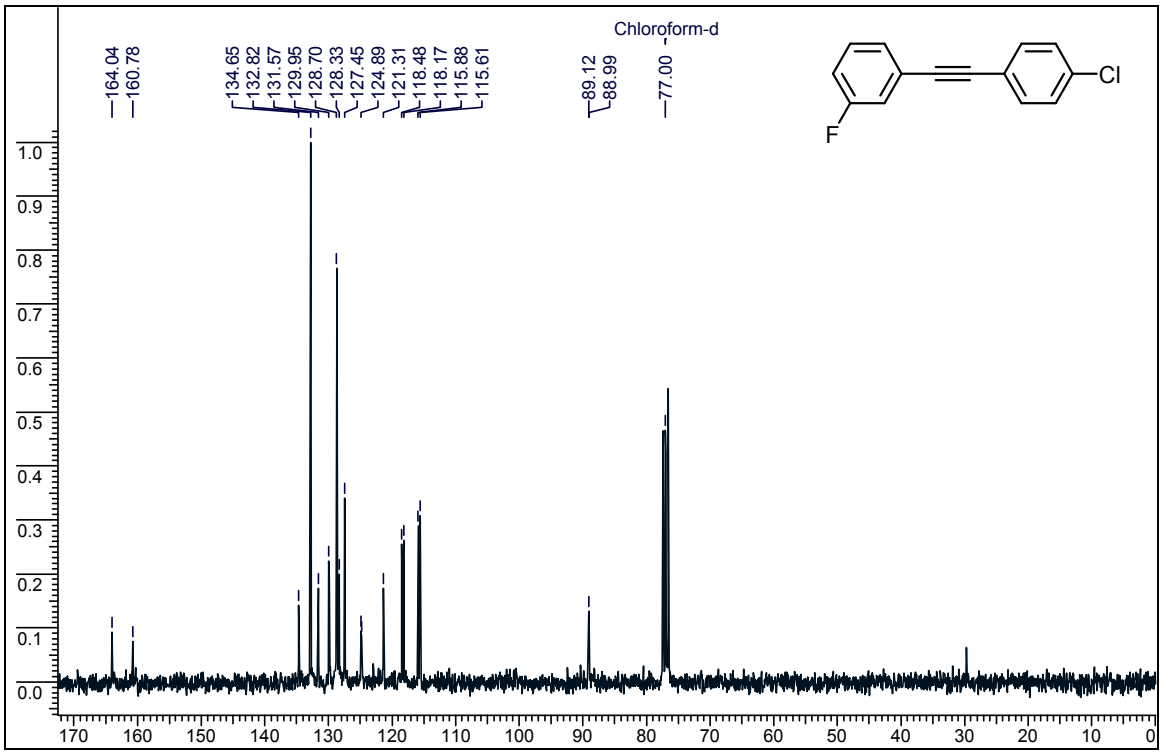
[6] ^{1}H NMR and ^{13}C NMR Spectra of 92k



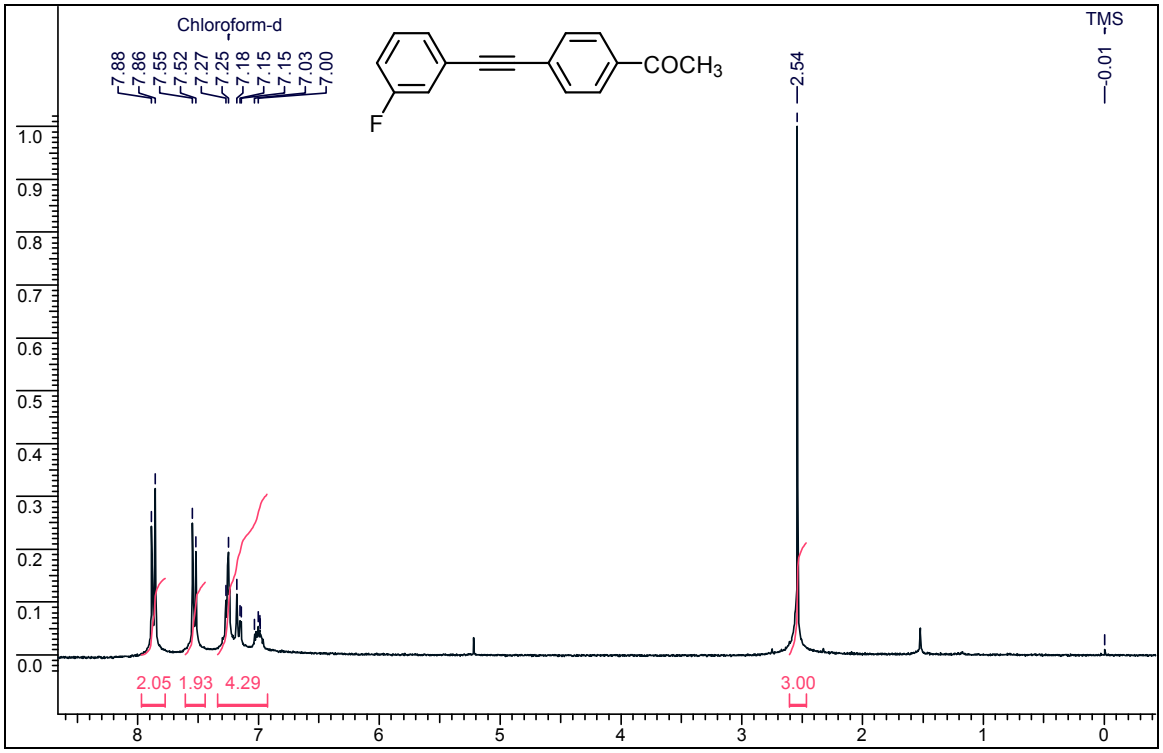


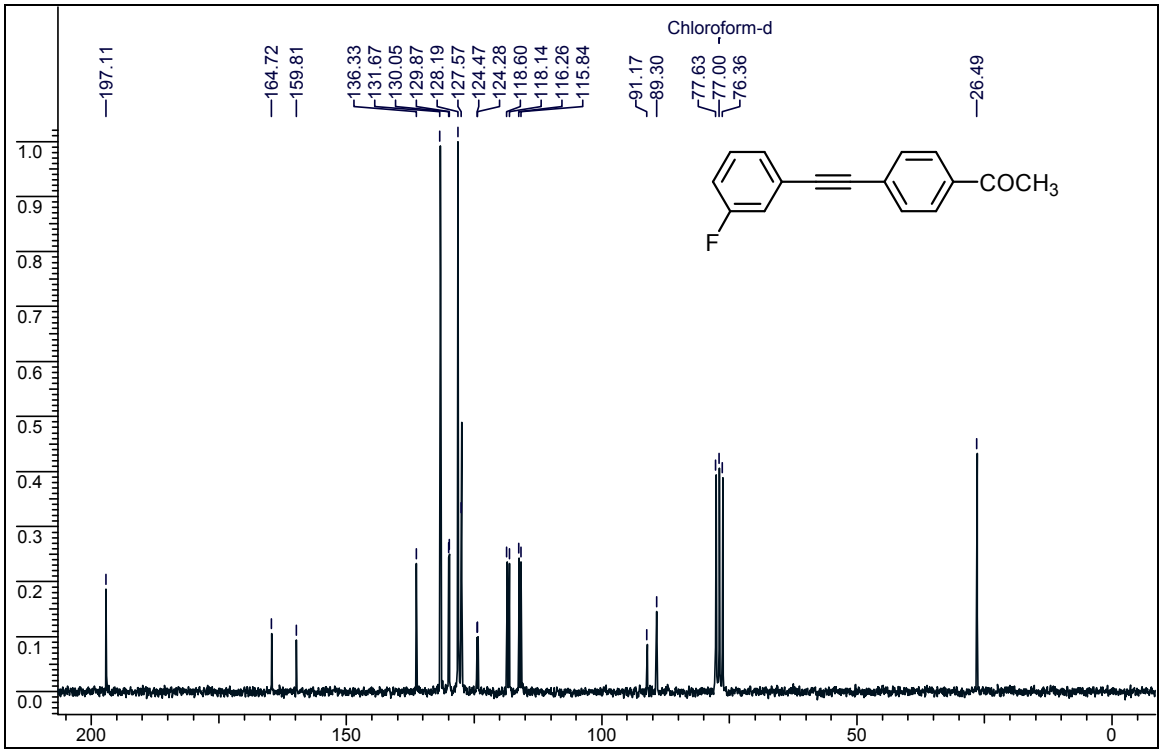
[7] ^{1}H NMR and ^{13}C NMR Spectra of 92m



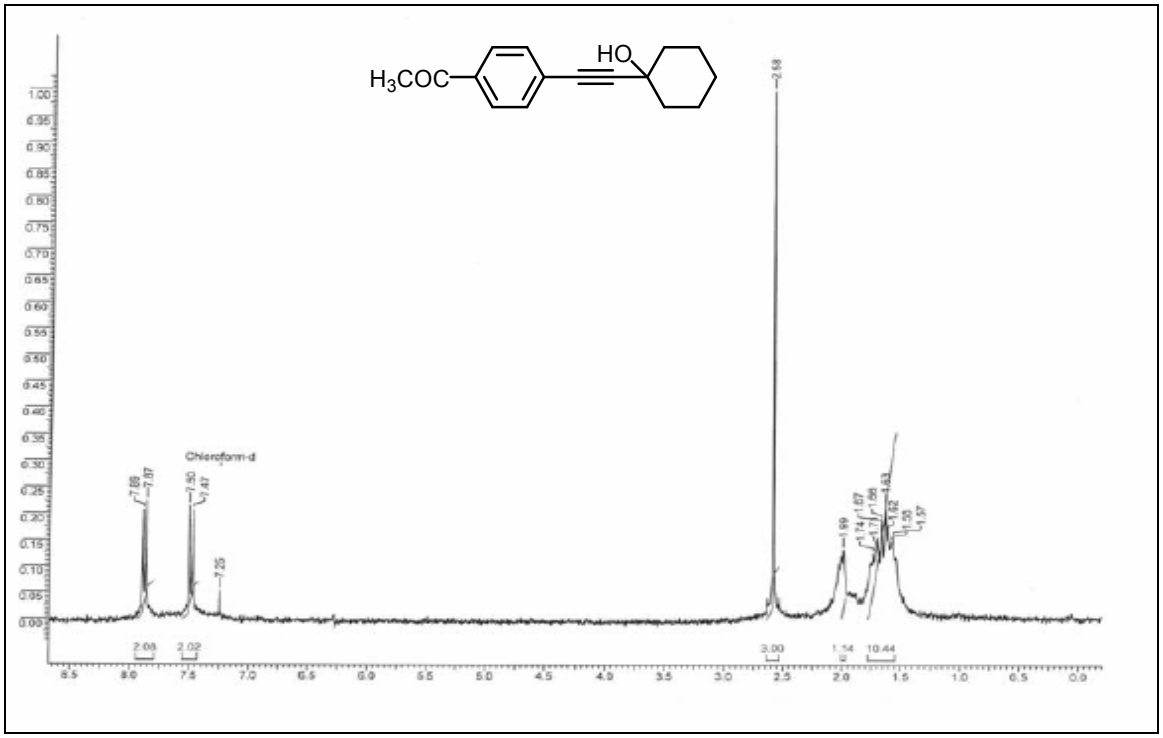


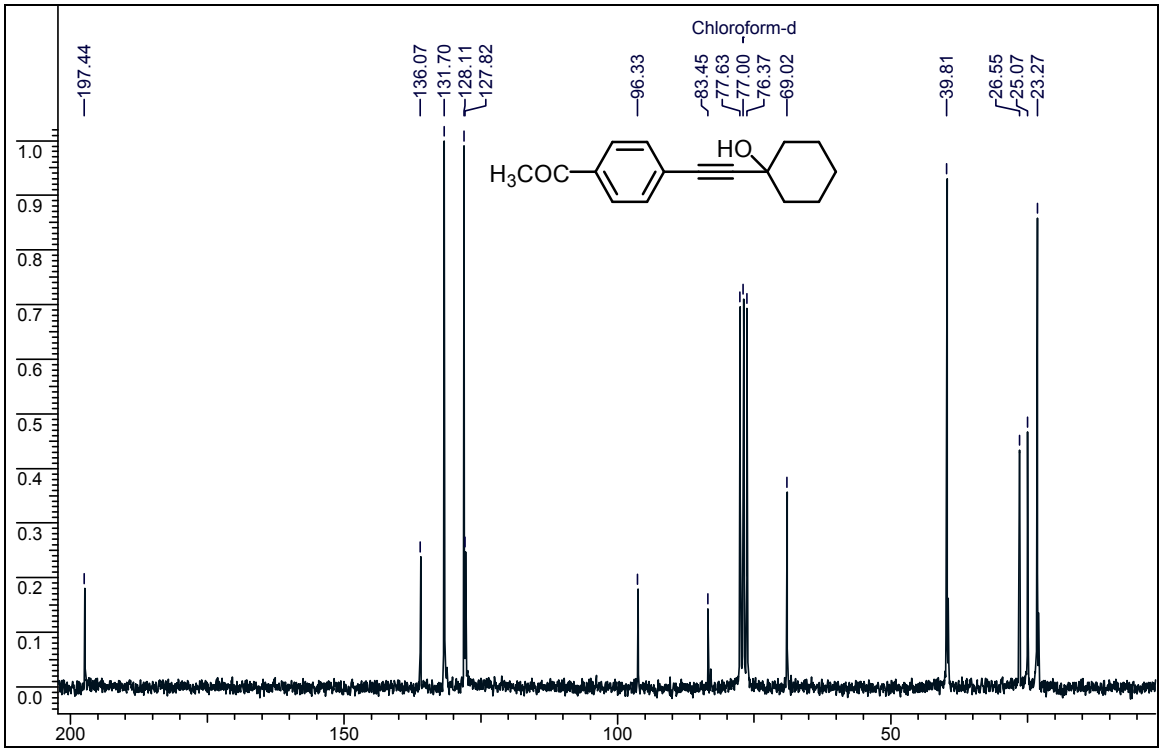
[8] ^{1}H NMR and ^{13}C NMR Spectra of 92r



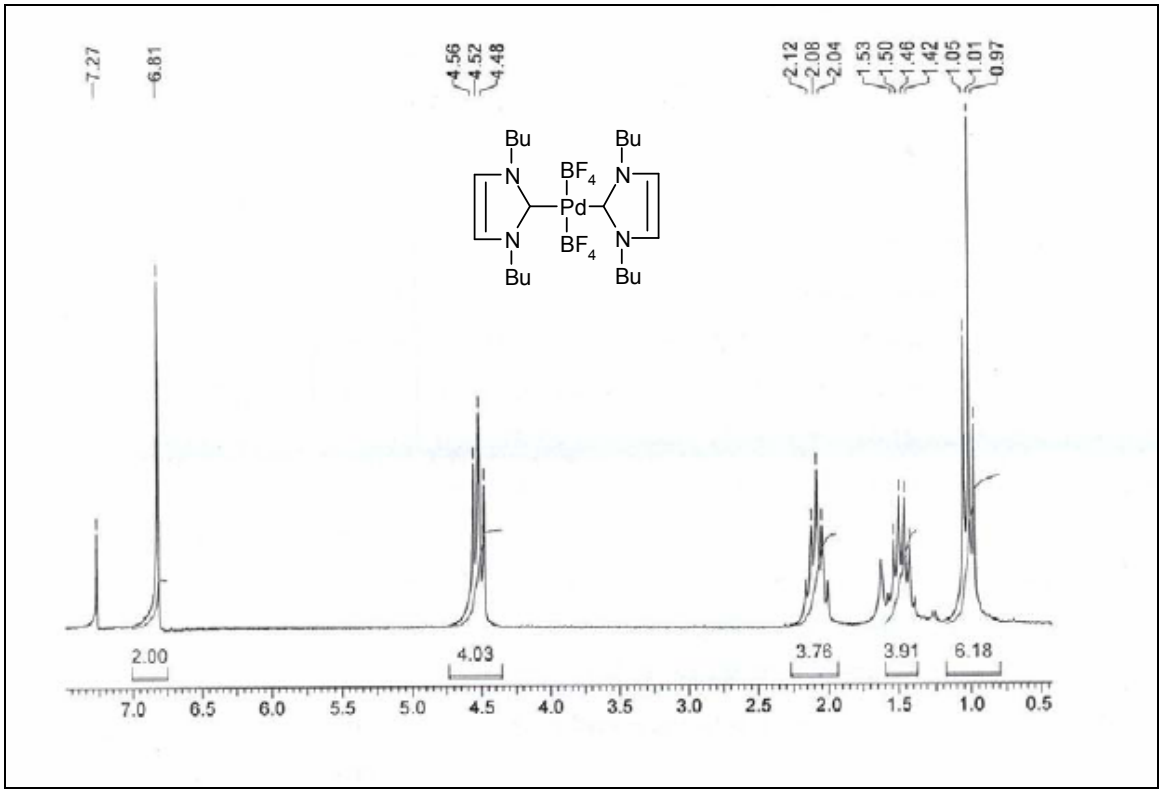


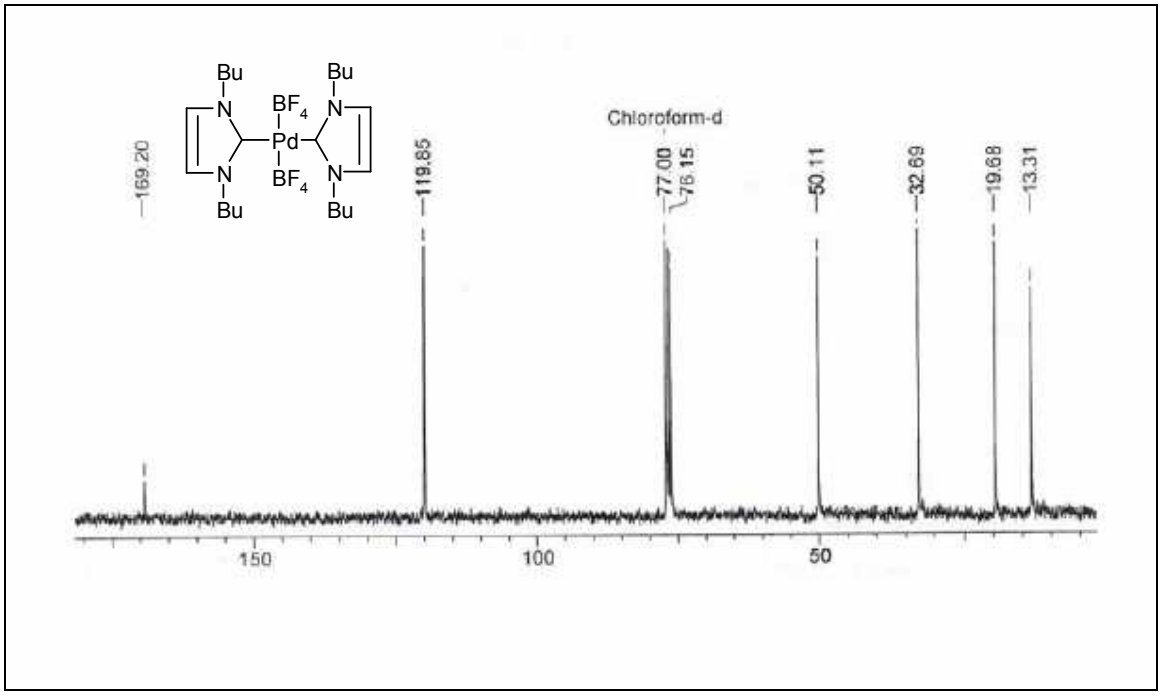
[9] ^{1}H NMR and ^{13}C NMR Spectra of 92s





[10] ^{1}H NMR and ^{13}C NMR Spectra of 93





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Section-F

The

Mizoroki-Heck reaction

The Mizoroki-Heck Reaction

1.6.1 Introduction

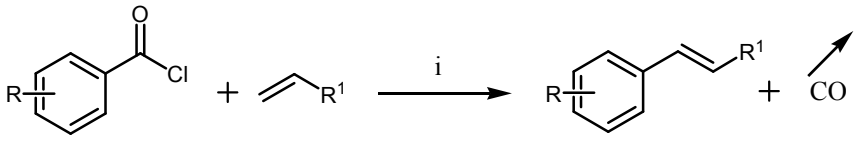
The palladium-catalyzed arylation of alkenes with aryl halides (Ar-X) is well known as the Mizoroki–Heck (MH) reaction and is now recognized to be of genuine synthetic utility for preparing aromatic fine chemicals.[1] Besides the halides, various synthetic equivalents including aryl triflates,[2] diazonium salts,[3] sulfonyl halides,[4] aromatic carboxylic anhydrides[5] and carboxylic acids via their nitrophenol esters[6] can also be employed as the arylating reagents. Aroyl chlorides are among the practically useful aryl sources, as they are relatively reactive and a wide range of aromatic carboxylic acids are available as their precursors.

1.6.2 Review of Literature

The decarbonylative Heck reaction is known since the beginning of the eighties. Spencer has described the palladium-catalyzed arylation of alkenes with aroyl chlorides in the presence of a tertiary amine as a base. After that some base free methodologies have been developed by using various Pd or rhodium metal complexes. Some important Heck olefinations are discussed below.

Spencer *et al.*[7]

In 1982 Spencer *et al.* first time reported the Mizoroki-Heck coupling between aroyl chlorides and activated alkenes in the presence of a tertiary amine and a catalytic amount of palladium acetate to give arylated alkenes, specifically cinnamic acid derivatives and stilbenes (**Scheme 27**).



94 **95**

R = Cl, Me, MeO, NO_2, CO_2Me

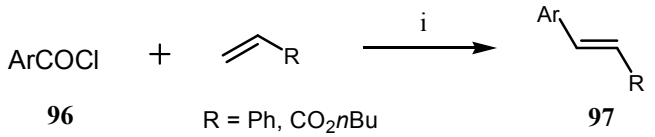
R^1 = Ar

Scheme 27. Reaction conditions: (i) $Pd(OAc)_2$, *N*-benzyldimethylamine, *p*-xylene, 130 ºC, 1.5-3 h, 55-93%.

The reaction involves a highly efficient decarbonylation of the aroyl chloride. High yields can be obtained at low catalyst concentration by choice of an appropriate base. The reaction is not particularly sensitive to substituents in the aroyl chloride, although strongly electron-donating groups are advantageous (yields up to 93%). With monosubstituted alkenes *E*-isomers are formed with almost complete specificity.

Miura *et al.*[8]

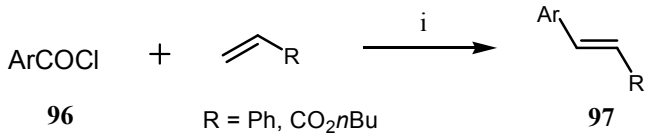
Miura *et al*. reported the new findings that styrene and acrylate ester can also be arylated by using an appropriate phosphane-free rhodium catalyst [{RhCl(C_2H_4)$_2$}$_2$]. Thus, the alkenes efficiently undergo Mizoroki-Heck type coupling with aroyl chlorides in the absence of any base and phosphane ligand to form the trans alkenes. The by-products (CO and HCl) are readily removed under a slow stream of N_2 gas (**Scheme 28**).



Scheme 28. Reaction conditions: (i) [{RhCl(C_2H_4)$_2$}$_2$], *o*-xylene, LiCl, reflux, slow stream of N_2, 3-48 h, 51-98%.

Miura *et al.*[9]

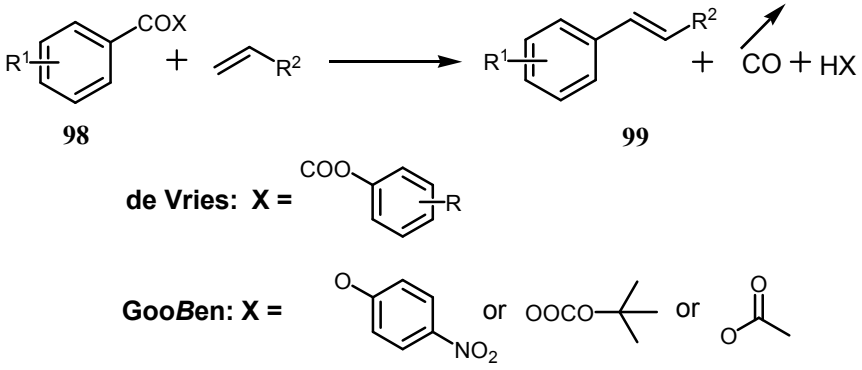
Recently Miura *et al*. established that the MH type arylation of alkenes such as styrene and acrylate ester using aroyl chlorides can be effectively performed in the presence of the palladium catalyst system, $PdCl_2(PhCN)_2/(PhCH_2)Bu_3NCl$, without adding any base. The simple conditions make the product isolation procedure significantly simple (**Scheme 29**).



Scheme 29. Reaction conditions: (i) $PdCl_2(PhCN)_2/(PhCH_2)Bu_3NCl$, *o*-xylene, reflux, slow stream of N_2, 3 h, 73-95%.

Use of aromatic anhydrides and activated esters as a substrate for Mizoroki-Heck reaction

In the late 1990s, de Vries[10] and Gooβen[6a] developed the idea further and found that also anhydrides and activated phenolic esters served as substrates for the Pd catalyzed arylation of olefins in moderate to very good yields (**Scheme 30**).



Scheme 30.

Major advantage claimed for this variant is the fact that no extra base is needed and no inorganic salt is produced, thereby eliminating a waste disposal problem. On the other hand, the remaining carboxylic acid or phenol has to be recycled in order to make the process acceptable. de Vries and coworkers have applied high temperatures (160 ºC in NMP) with 0.1 mol% catalyst and 0.4% of a bromide salt to get good yields. Gooβen obtained trans alkenes in the presence of chloride ions and isoquinoline was used as a necessary additive. Further, Gooβen has reported two methods which do not need substrate recycling. In the first variant,[6b] mixed anhydrides were prepared *in situ* by treating ArCOOH with di-*tert*-butyl dicarbonate and coupled directly with the olefin under conditions similar to those of de Vries. In the second it was shown that enol esters can also be used as substrates, which were reacted with alkenes in the presence of 3 mol% Pd catalyst at 160 ºC.[6c] As by-products only CO and CO_2/t-BuOH or acetone, respectively, are formed, making work-up very easy. How ever, compared to other coupling methods, the atom economy of the reaction is diminished.

1.6.3 Present work

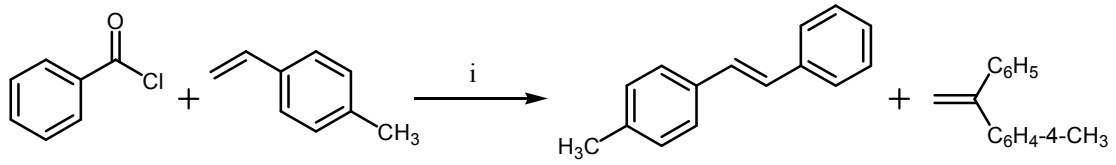
1.6.3.1 Objective

One of the early significant examples of the decarbonylative MH type reaction using aroyl chlorides as described earlier was reported by Blaser and Spencer, in which an amine base, typically *N,N*-dimethyl benzylamine, for trapping the HCl evolved was employed in a less polar solvent such as *p*-xylene. Under the conditions, however, the undesirable direct reaction of the chlorides, especially electron- deficient ones, with the amine competitively takes place to a considerable extent, which diminishes the product yield.

The use of ultrasound in organic transformation is now well known to enhance reaction rates, yield/selectivity and facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure. In the present work we have evaluated the decarbonylative Heck arylation by reaction of aroyl chlorides with alkenes under sonochemical conditions at ambient temperature under base free condition.

1.6.3.2 Results and discussion

Initially, benzoyl chloride (**100a)** (1 mmol) was treated with 4-methylstyrene (**101a**) (1.2 mmol) in the presence of $Pd(OAc)_2$ (0.035 mmol) in acetonitrile for 2 h under ultrasound irradiation (**Scheme 31**). The reaction was carried out in a thermostated (30 ±1 °C) ultrasonic cleaning bath off frequency 50 kHz in an inert atmosphere of argon. The reaction was followed by GC. After 2 h GC indicates the formation of the (*E*)-stilbene to an extent of only 25%.



100a **101a** **102a** **103a**

Scheme 31. Reaction of benzoyl chloride (**100a**) with 4-methylstyrene (**101a**)

This indicates that the presence of additive is crucial for the activity of the Pd catalyst. This is probably due to the fact that an additive like $R_4N^+X^-$ facilitates the stabilization of palladium clusters. In this respect, utility of various additive was checked for the reaction

benzoyl chloride and methyl styrene with out addition of any base. The results are recorded in **Table 21**. It was observed that the stabilizing ligands such as phosphines inhibit the reaction giving greatly lowered yields.

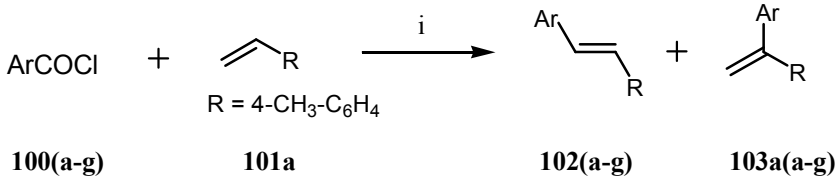
The use of LiBr (0.07 mmol) as an additive did not affect the reaction at all, But the same amount of quaternary ammonium salts significantly enhanced the reaction and yields. Among these quaternary ammonium salts examined, the 1,3 di-*n*-benzylimidazolium bromide was found to be most effective.

Table 21: Optimization of reaction conditions

Entry	Additive	Time	Yield (%)*	
		(h)	**102a**	**103a**
1	none	4	25	–
2	LiBr	4	28	–
3	Bu_4NOAc	3	54	2
4	Bu_4NCl	3	52	2
5	Bu_4NBr	3	60	3
6	1,3 di-*n*-benzylimidazolium bromide	3	80 (72%)	5

Reaction conditions: **100a** (1 mmol), **101a** (1.2 mmol), $Pd(OAc)_2$ (0.035 mmol), **additive** (0.07 mmol) in acetonitrile (10 ml) under a stream of N_2,)))), 3-4 h *GC yield. Value in parenthesis indicates isolated yield.

Thus, using the ammonium salt without adding any base, **102a** was obtained in 80% yield along with a minor amount of 1,1-diphenylethylene (**103a**) (entry 6). Consequently, a variety of aroyl chlorides were chosen for decarbonylative heck coupling under sonochemical conditions as shown in **Scheme 32.** The results are recorded in **Table 22.**



Scheme 32. Reaction conditions: (i) $Pd(OAc)_2$, 1,3 di-*n*-benzylimidazolium bromide, MeCN,)))), slow stream of N_2, 3 h, 66-76%.

The reactions were carried out under a slow stream of N_2 to effectively remove HCl and CO evolved. In the presence of $Pd(OAc)_2$/1,3 di-*n*-benzylimidazolium bromide various aroyl chlorides reacted to give the corresponding stilbene derivatives in good to moderate yield along with minor amounts of 1,1-diarylethylenes. The crude products were isolated by filtration of reaction mixture, purified by column chromatography and characterized by spectral and elemental analyses.

Table 22: Reaction of aroyl chlorides with 4-methylstyrene.

Entry	**100**	Ar	Product		[a]Yield%		
1	**100a**	C_6H_5	**102a**	(72)	80	**103a**	5
2	**100b**	4-CN-C_6H_4	**102b**	(75)	86	**103b**	3
3	**100c**	4-H_3COC-C_6H_4	**102c**	(76)	85	**103c**	4
4	**100d**	4-F-C_6H_4	**102d**	(70)	78	**103d**	4
5	**100e**	4-MeO-C_6H_4	**102e**	(68)	78	**103e**	3
6	**100f**	4-Me-C_6H_4	**102f**	(72)	82	**103f**	4
7	**100g**	2-naphthyl	**102g**	(66)	72	**103g**	5

Reaction conditions: **100** (1 mmol), **101a** (1.2 mmol), $Pd(OAc)_2$ (0.035 mmol), 1,3 di-*n*-benzylimidazolium bromide (0.07 mmol) in acetonitrile (10 ml) under stream of N_2,)))), 3h, [a]GC yield. Value in parenthesis indicates isolated yield.

The present reaction may proceed by the mechanism similar to that proposed previously.[7] Due to cavitation phenomenon high temperature and pressure generated for a very short period of time facilitating the oxidative addition of Pd(0) species on C-Cl bond of aryol chloride. Aryl migration takes place followed by release of carbon monoxide. Insertion of an alkene to the intermediate and β-hydrogen elimination gave the product stilbene with H-Pd-Cl complex. Sonochemical conditions was considered to facilitate the elimination of HCl from H-Pd-Cl to regenerate Pd(0) species. A Pd(0) species stabilized by ligands is proposed to be involved in the catalytic cycle comprising of oxidative insertion, trans-metalation, and reductive elimination step (**Fig 29**).

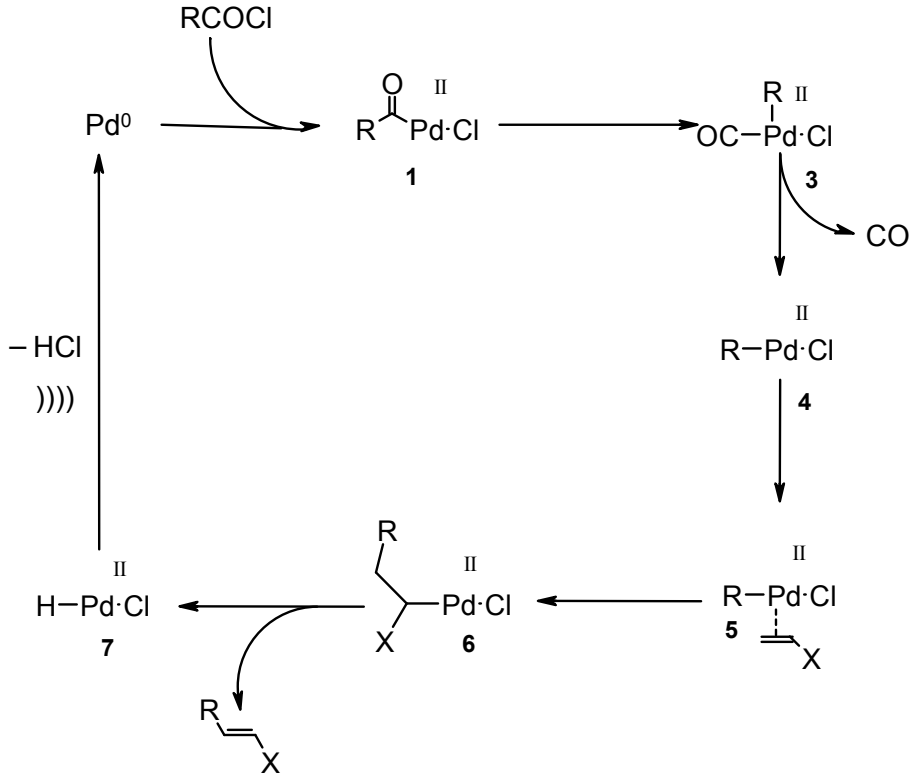


Figure 29. Mechanism: decarbonylative heck coupling

Consequently, the formation of such Pd(0) nanoparticles was investigated in the present work by subjecting an aliquots of the reaction mixture after a successful Mizoroki-Heck reaction of benzoyl chloride and 4-methylstyrene in acetonitrile under ultrasonic irradiation for "*in situ*" TEM analysis.

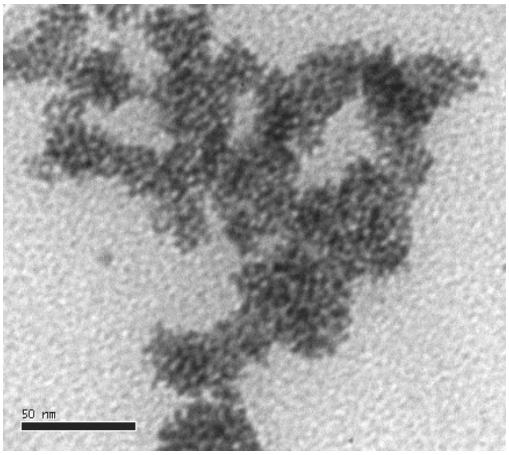


Figure 30. TEM image of Pd(0) nanoparticles in acetonitrile

TEM analysis was carried out in Transmission Electron Microscope Model JEOL-1200 EX operated at 100 kV with a magnification of 200 K. The sample after appropriate dilution with isopropyl alcohol was directly deposited on carbon film coated TEM grids forming a thin film of colloidon. The TEM image (**Fig. 30**) shows the presence of monodispersed grains nearly spherical in shape. The average size of the grains obtained from the TEM picture was about 15-20 nm.

It is important to note that the reaction of benzoyl chloride with 4-methylstyrene in acetonitrile under similar conditions but in the absence of ultrasound (silent condition) did not show the formation of any cross-coupled product even after several hours (24 h) of stirring. Moreover, in a blank experiment, Pd(0) nanoparticles were formed by sonicating a mixture of $Pd(OAc)_2$ and 1,3 di-*n*-benzylimidazolium bromide acetonitrile. To this were added the reactants, viz. benzoyl chloride and 4-methylstyrene, and the mixture was stirred at ambient temperature under silent conditions. But under this condition also no any formation of even trace amount of (*E*) stilbene was observed. This implies that ultrasound not only brings about the formation of highly crystalline, active Pd(0) nanoparticles required for the Mizoroki-Heck reaction but also promotes the activity of the catalytic species in the oxidative insertion, trans-metalation, and reductive elimination catalytic cycle of the Mizoroki-Heck reaction. This is made possible by the phenomenon of acoustic cavitation generating transient cavitation bubbles of very short lifetimes ($\sim 10^{-9}$ s), the implosive collapse of which under adiabatic conditions gives rise to high temperatures and pressures.

1.6.4 Conclusion

The decarbonylative Heck coupling was carried out in short reaction times with good isolated yields at ambient temperature under ultrasonic irradiation in acetonitrile in the presence of $Pd(OAc)_2$ and 1,3-di-*n*-benzylimidazolium bromide as a additive in the absence of any base. Along with mild reaction conditions since the product isolation procedure is significantly simple, this protocol appears to provide a practical, convenient route to synthesis trans stilbenes.

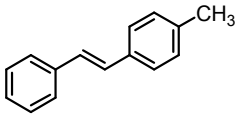
1.6.5 Experimental

General Procedure for the sonochemical Mizoroki-Heck reaction in acetonitrile medium

Typical procedure: A mixture of benzoyl chloride **100a** (0.140 g, 1 mmol), 4-methylstyrene **101a** (0.141 g, 1.2 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), and 1, 3 di-*n*-benzylimidazolium bromide (0.023 g, 0.07 mmol) in acetonitrile (10 ml) was sonicated under the slow stream of N_2. After 3 h, the mixture was diluted with ethyl acetate and filtered through a celite bed to obtain the crude product. The crude product obtained was further purified by column chromatography through a column of silica gel using petroleum ether (bp 60-80 ^oC) or an appropriate mixture of petroleum ether and ethyl acetate as eluent to afford the pure product.

1.6.5.1 Characterization data for compounds 102a-g

(*E*) 4-Methyl-stilbene (102a)



Nature : Colorless solid

MP : 119-120 ^oC.

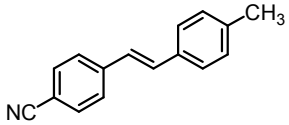
^{1}H NMR 200 MHz (CDCl$_3$) : 2.37 (s, 3H), 7.08 (s, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.25-7.45 (m, 5H), 7.49-7.54 (m, 2H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.2, 126.3, 126.4, 127.3, 127.6, 128.6, 129.3, 134.5, 137.47, 137.49.

Elemental analysis : Calcd: C, 92.74; H, 7.26.

$C_{15}H_{14}$ (194) Found: C, 92.68; H, 7.38.

(*E*) 4-Cyano-4'methyl-stilbene (102b)



Nature : Colorless solid

MP : 184-185 ^oC.

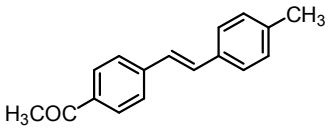
^{1}H NMR 200 MHz (CDCl$_3$) : 2.38 (s, 3H), 7.03 (d, *J* = 16.4 Hz, 1H), 7.16-7.24 (m, 3H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.54-7.65 (m, 4H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.2, 110.2, 119.0, 125.6, 126.6, 126.8, 129.5, 132.2, 132.3, 133.4, 138.6, 141.9.

Elemental analysis : Calcd: C, 87.64; H, 5.98; N, 6.39.

$C_{16}H_{13}N$ (219) Found: C, 87.72; H, 5.85; N, 6.52.

(*E*) 4-Acetyl-4'methyl-stilbene (102c)



Nature : Colorless solid

MP : 176-177 ^{o}C.

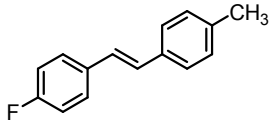
^{1}H NMR 200 MHz (CDCl$_3$) : 2.37 (s, 3H), 2.61 (s, 3H), 7.02 (d, *J* = 16.4 Hz, 1H), 7.18-7.21 (m, 3H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.2, 26.4, 126.2, 126.3, 126.6, 128.7, 129.4, 131.3, 133.8, 135.6, 138.2, 142.1, 197.3.

Elemental analysis : Calcd: C, 86.41; H, 6.82.

$C_{17}H_{16}O$ (236) Found: C, 86.62; H, 6.72.

(*E*) 4-Fluoro-4'methyl-stilbene (102d)



Nature : Colorless solid

MP : 158-160 ^{o}C.

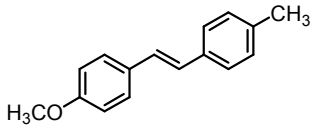
^{1}H NMR 200 MHz (CDCl$_3$) : 2.37 (s, 3H), 7.00-7.09 (m, 4H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.38-7.50 (m, 4H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.2, 115.5 (d, *J* = 21.6 Hz), 126.3, 126.4, 127.8 (d, *J* = 8.0 Hz, 2H), 128.4 (d, *J* = 2.5 Hz, 2H), 129.4, 133.6 (d, *J* = 3.3 Hz, 2H), 134.3, 135.5, 162.1 (d, *J* = 247.4 Hz, 2H).

Elemental analysis : Calcd: C, 84.88; H, 6.17.

$C_{15}H_{13}F$ (212) Found: C, 84.92; H, 6.10.

(*E*) 4-Methoxy-4'methyl-stilbene (102e)



Nature : Colorless solid

MP : 164-167 ^{o}C.

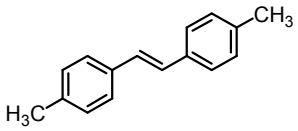
^{1}H NMR 200 MHz (CDCl$_3$) : 2.36 (s, 3H), 3.83 (s, 3H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.98-7.08 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.37-7.47 (m, 4H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.1, 55.2, 114.0, 126.1, 126.5, 127.2, 127.5, 129.3, 130.3, 134.8, 137.0.

Elemental analysis : Calcd: C, 85.68; H, 7.19.

$C_{16}H_{10}O$ (224) Found: C, 85.84; H, 7.04.

(*E*) 4-4'-dimethyl-stilbene (102f)



Nature : Colorless solid

MP : 178-180 °C.

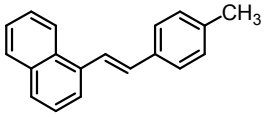
^{1}H NMR 200 MHz (CDCl$_3$) : 2.36 (s, 6H), 7.04 (s, 2H), 7.16 (d, *J* = 8.0 Hz, 4H), 7.41 (d, *J* = 8.0 Hz, 4H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.2, 126.2, 127.6, 129.3, 134.7, 137.2.

Elemental analysis : Calcd: C, 92.26; H, 7.74.

$C_{16}H_{10}$ (208) Found: C, 92.42; H, 7.65.

(*E*) 1-(4-methylstyryl)naphthalene (100g)



Nature : Colorless solid

MP : 84-86 °C.

^{1}H NMR 200 MHz (CDCl$_3$) : 2.40 (s, 3H), 7.14 (d, *J* = 16.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.46-7.56 (m, 5H), 7.74-7.79 (m, 4H), 8.21-8.26 (m, 1H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 21.2, 123.4, 123.7, 124.7, 125.6, 125.7, 125.9, 126.5, 127.8, 128.5, 129.4, 131.3, 131.6, 133.7, 134.8, 135.1, 137.6.

Elemental analysis : Calcd: C, 93.40; H, 6.60.

$C_{19}H_{16}$ (244) Found: C, 93.32; H, 6.72.

1,3-di-*n*-benzylimidazolium bromide

Nature : Solid

MP : 282-284 °C.

^{1}H NMR 200 MHz (DMSO-d_6) : 5.52 (s, 4H), 7.47 (brs, 10H), 7.93 (s, 2H), 9.60 (s, 1H).

^{13}C NMR 50 MHz (DMSO-d_6) : δ 52.2, 122.5, 123.2, 128.6, 129.0, 134.2, 137.7

Elemental analysis : Calcd: C, 62.00; H, 5.16; N, 8.51

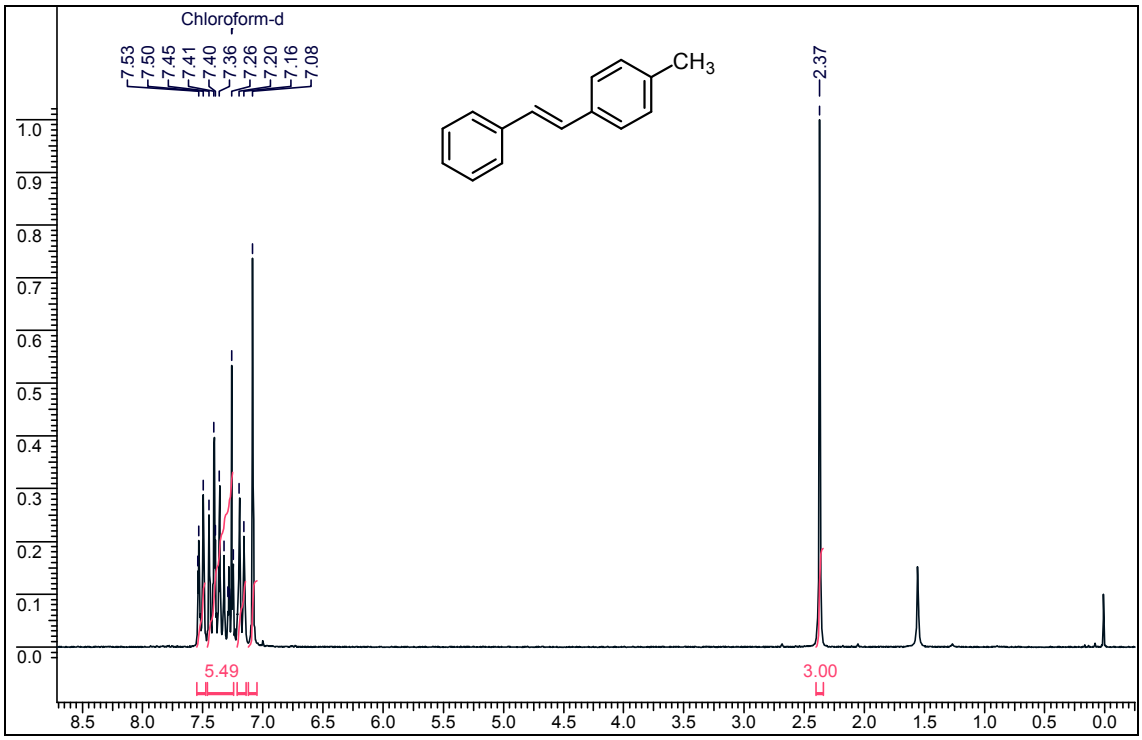
$C_{17}H_{17}N_2Br$ (329) Found: C, 62.13; H, 5.10; N; 8.40

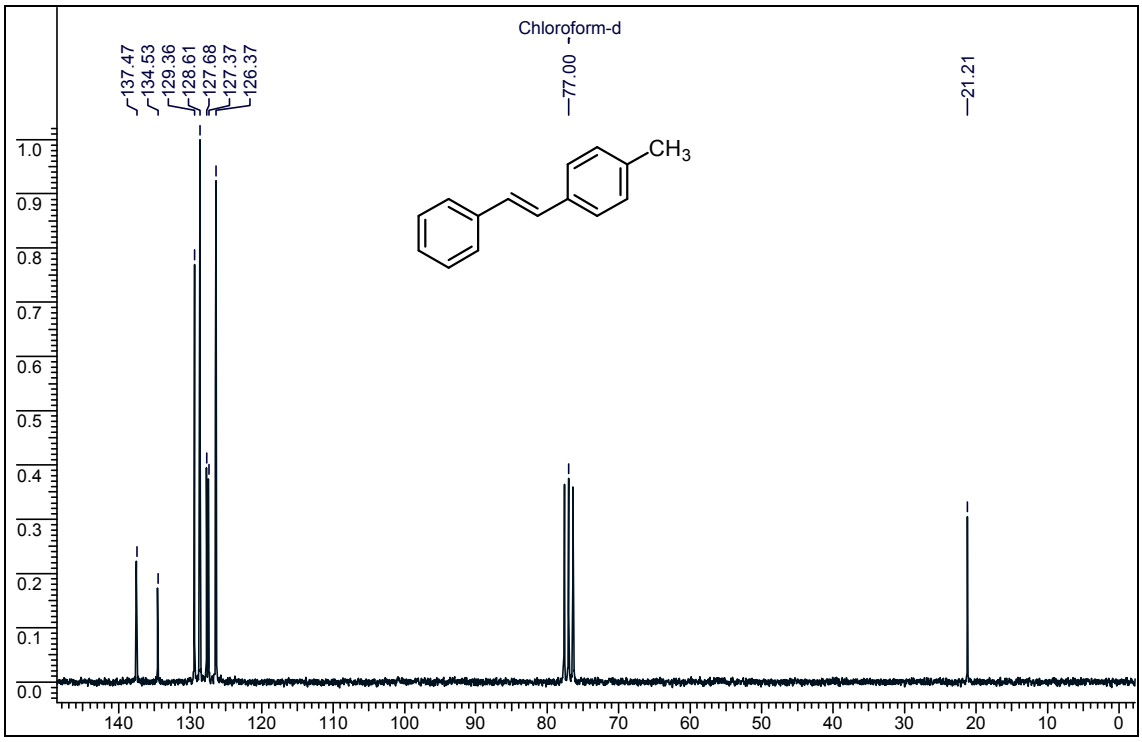
1.6.6 Spectra

Table 23. ^{1}H and ^{13}C spectra of some synthesized compounds are given below:

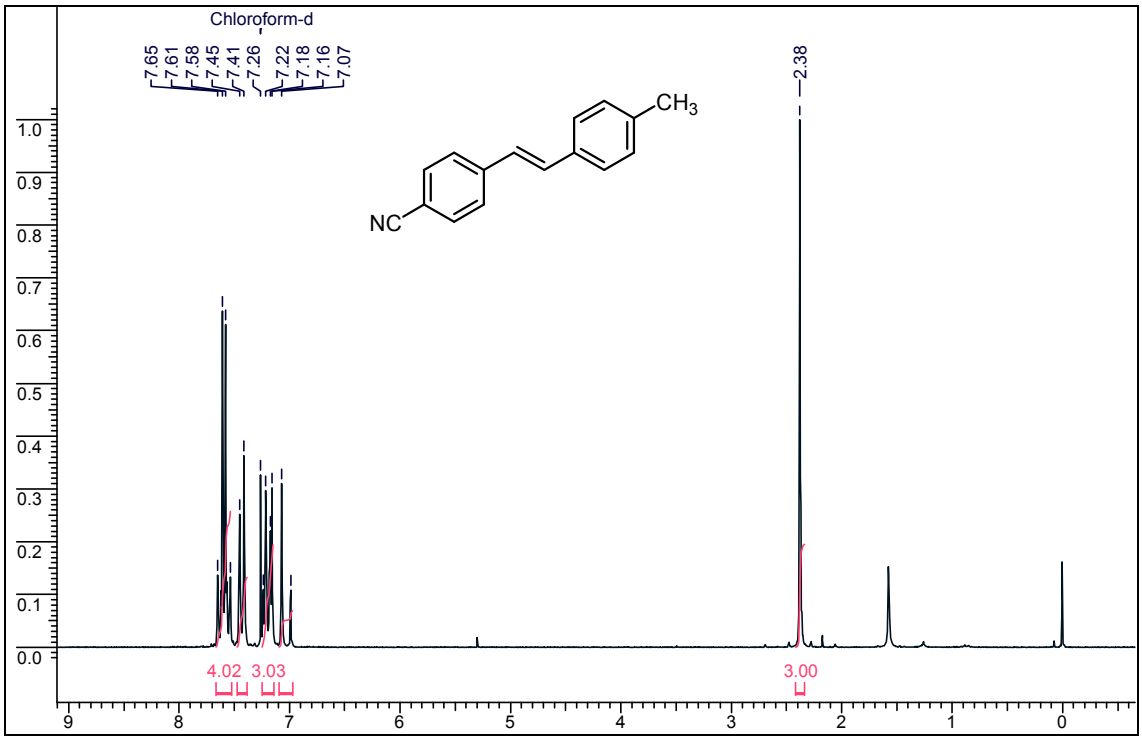
Sr. No.	Spectra	
[1]	^{1}H NMR and ^{13}C NMR Spectra of	**102a**
[2]	^{1}H NMR and ^{13}C NMR Spectra of	**102b**
[3]	^{1}H NMR and ^{13}C NMR Spectra of	**102c**
[4]	^{1}H NMR and ^{13}C NMR Spectra of	**102d**
[5]	^{1}H NMR and ^{13}C NMR Spectra of	**102e**
[6]	^{1}H NMR and ^{13}C NMR Spectra of	**102f**
[7]	^{1}H NMR and ^{13}C NMR Spectra of	**102g**

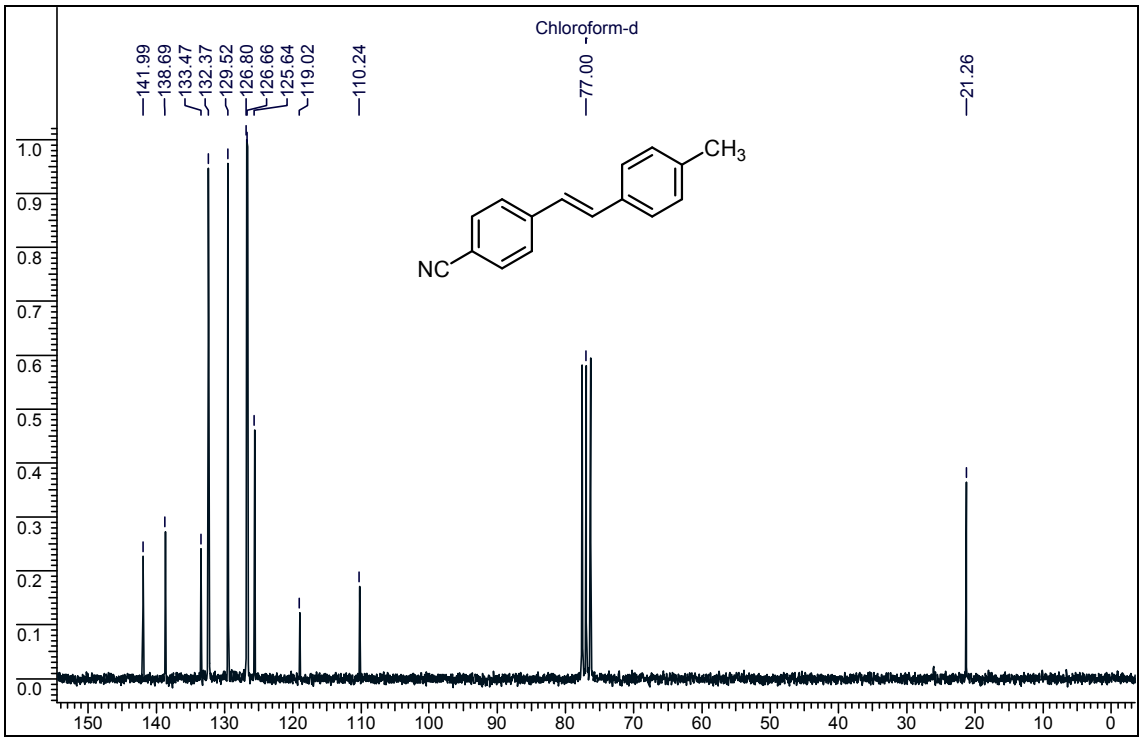
[1] ^{1}H NMR and ^{13}C NMR Spectra of 102a



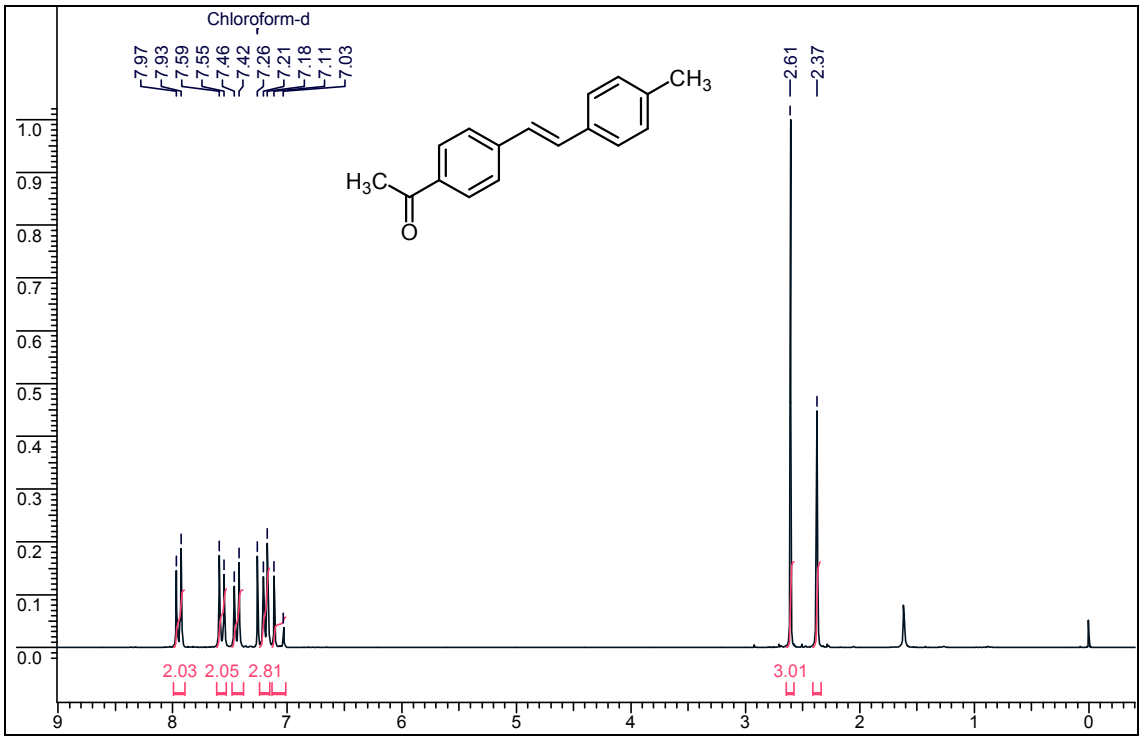


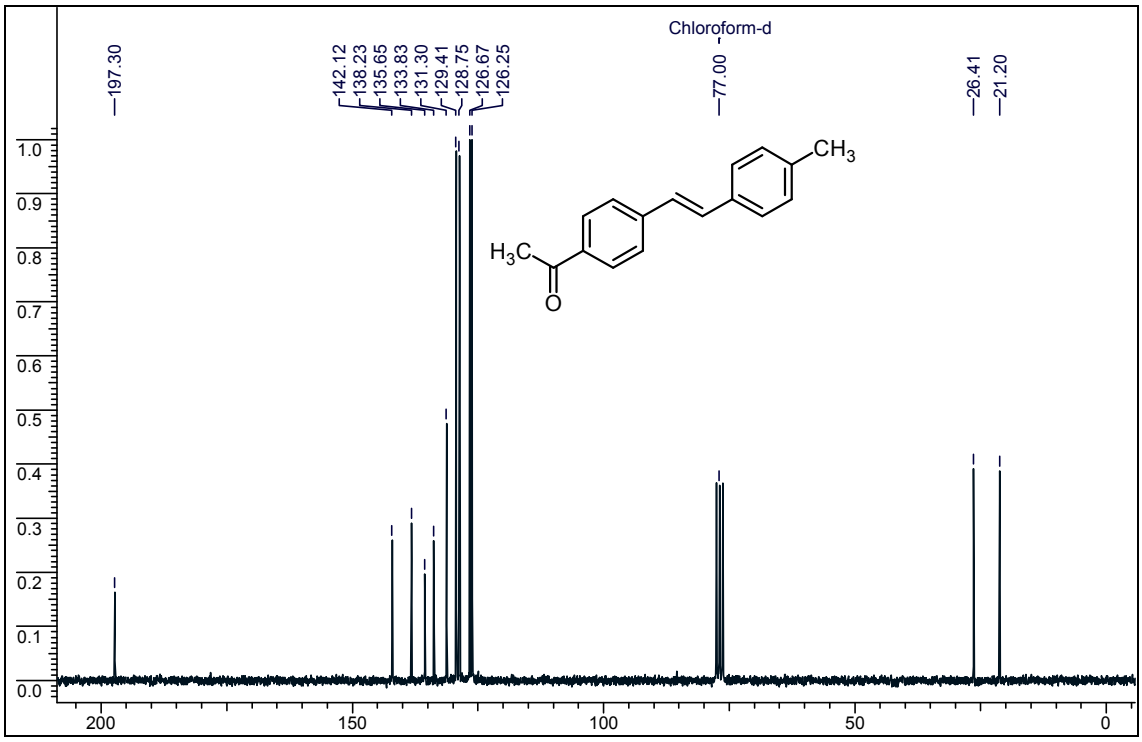
[2] ^{1}H NMR and ^{13}C NMR Spectra of 102b



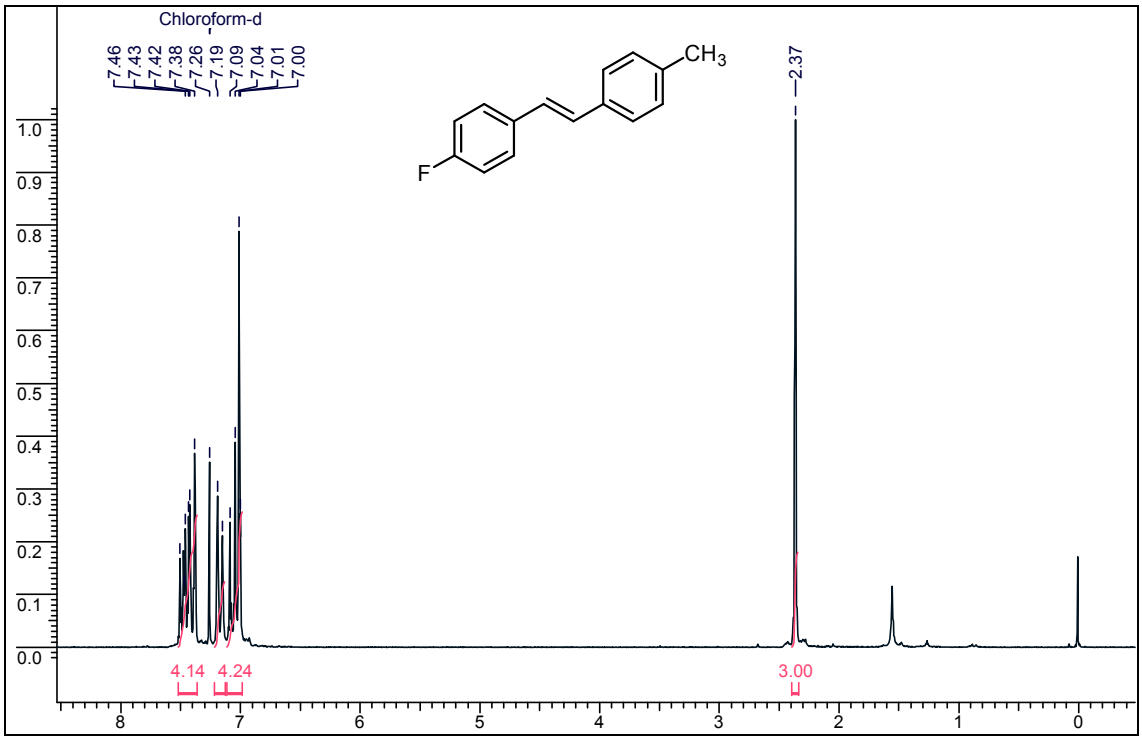


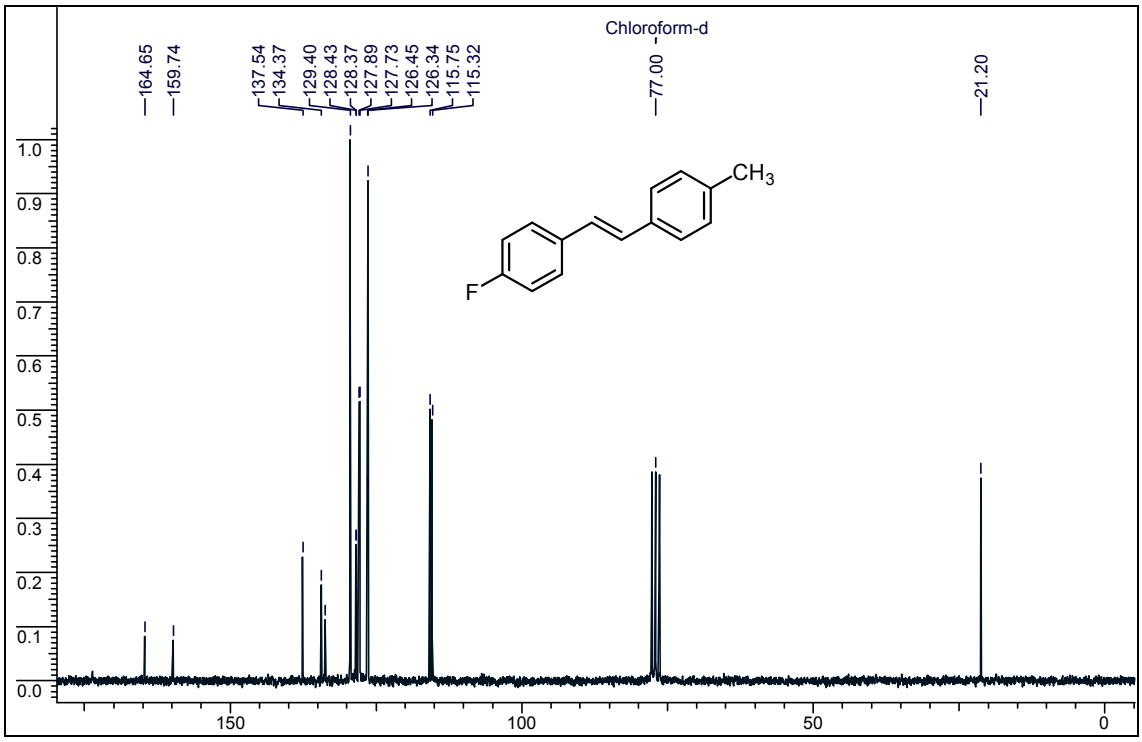
[3] ^{1}H NMR and ^{13}C NMR Spectra of 102c



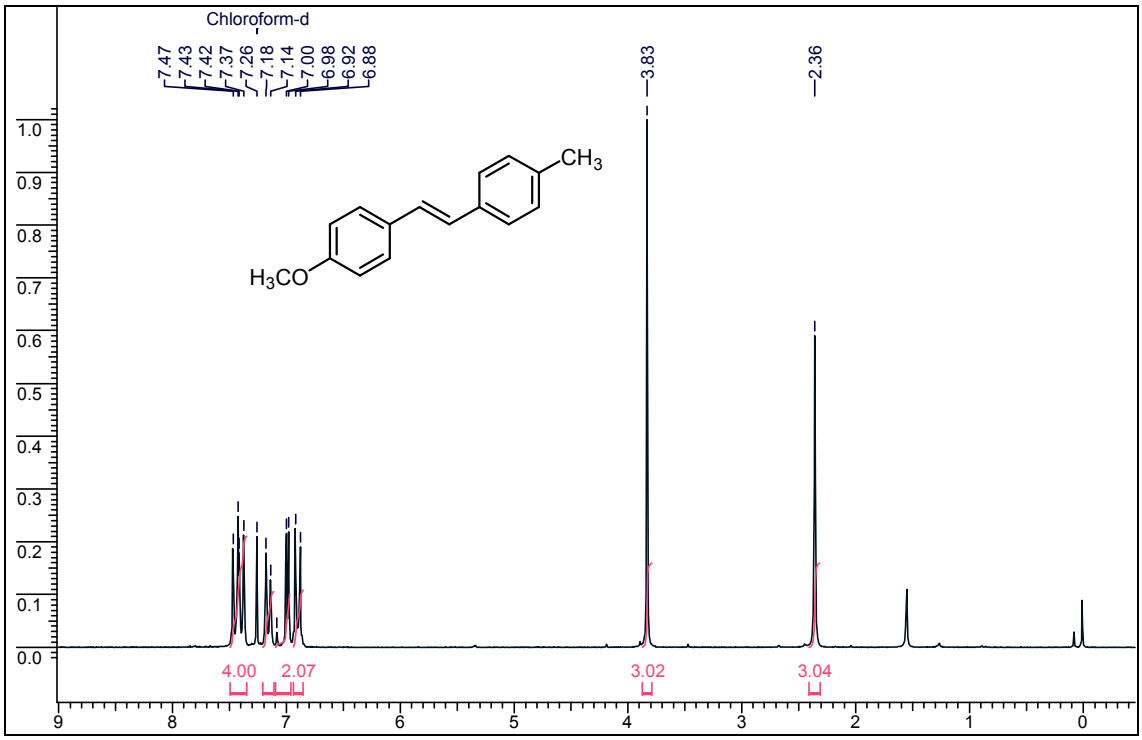


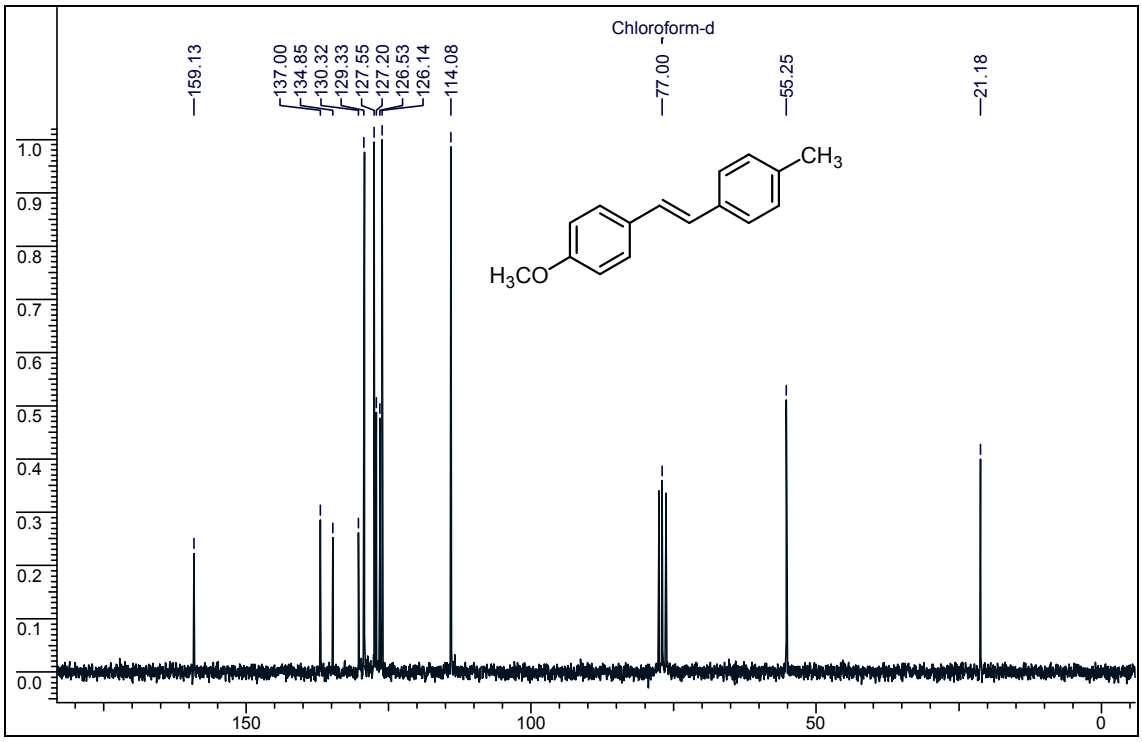
[4] ^{1}H NMR and ^{13}C NMR Spectra of 102d



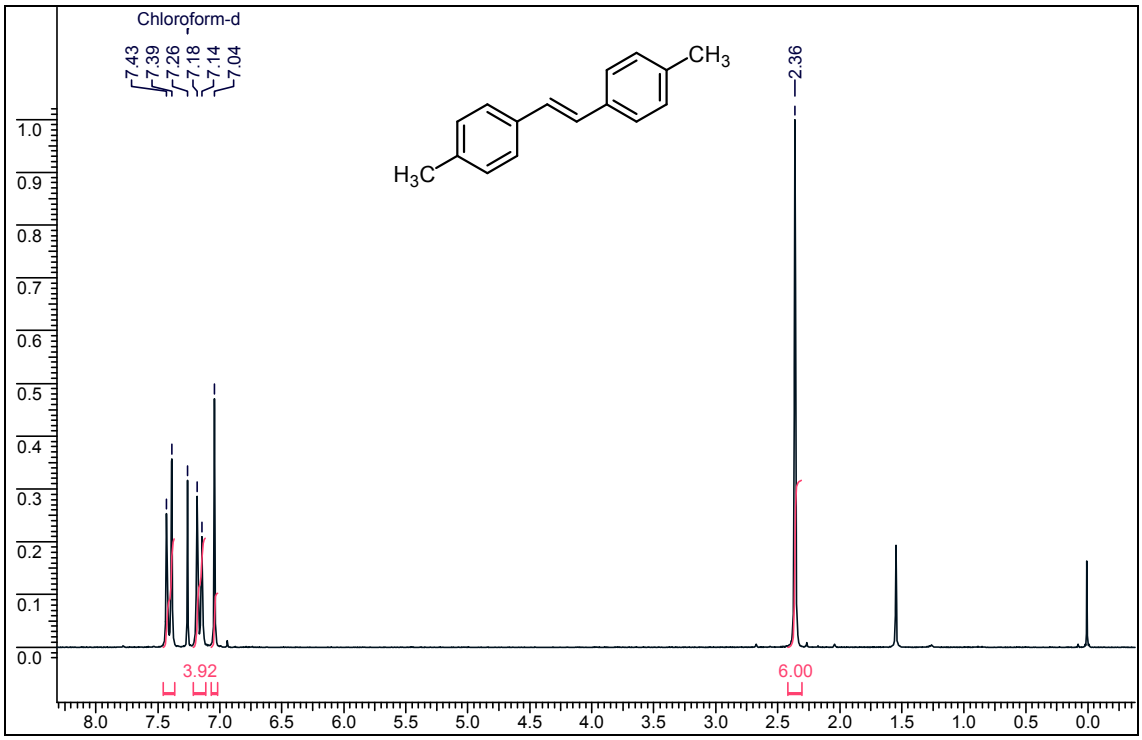


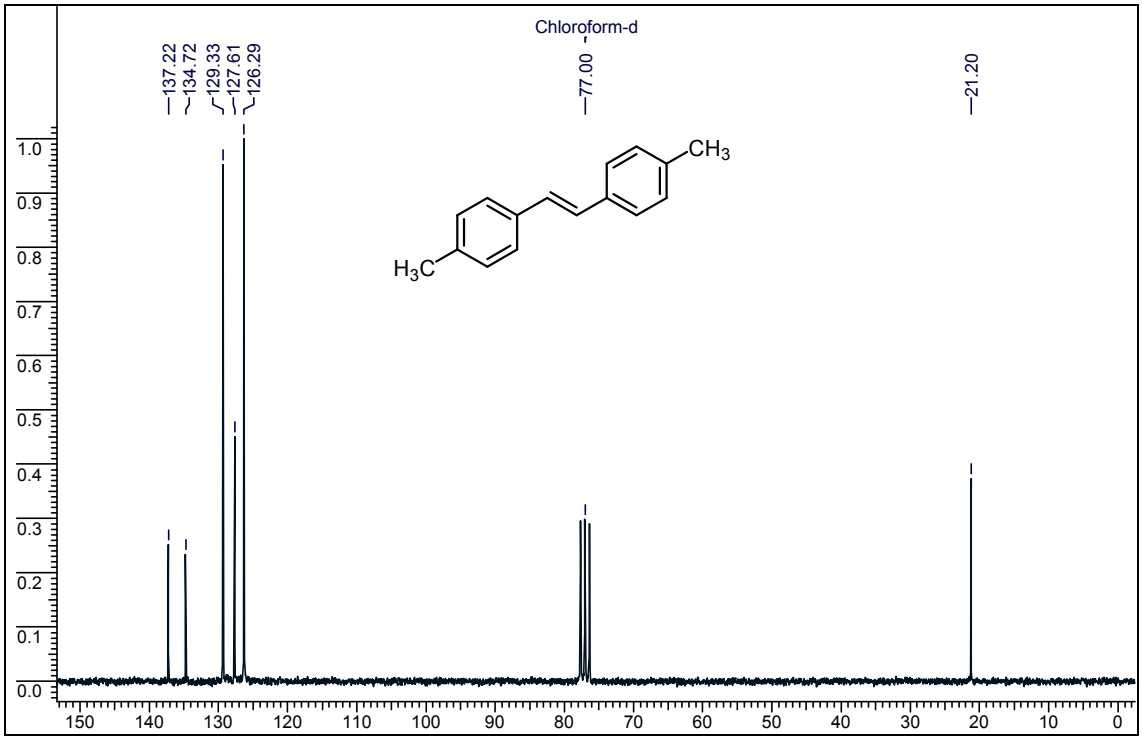
[5] ^{1}H NMR and ^{13}C NMR Spectra of 102e



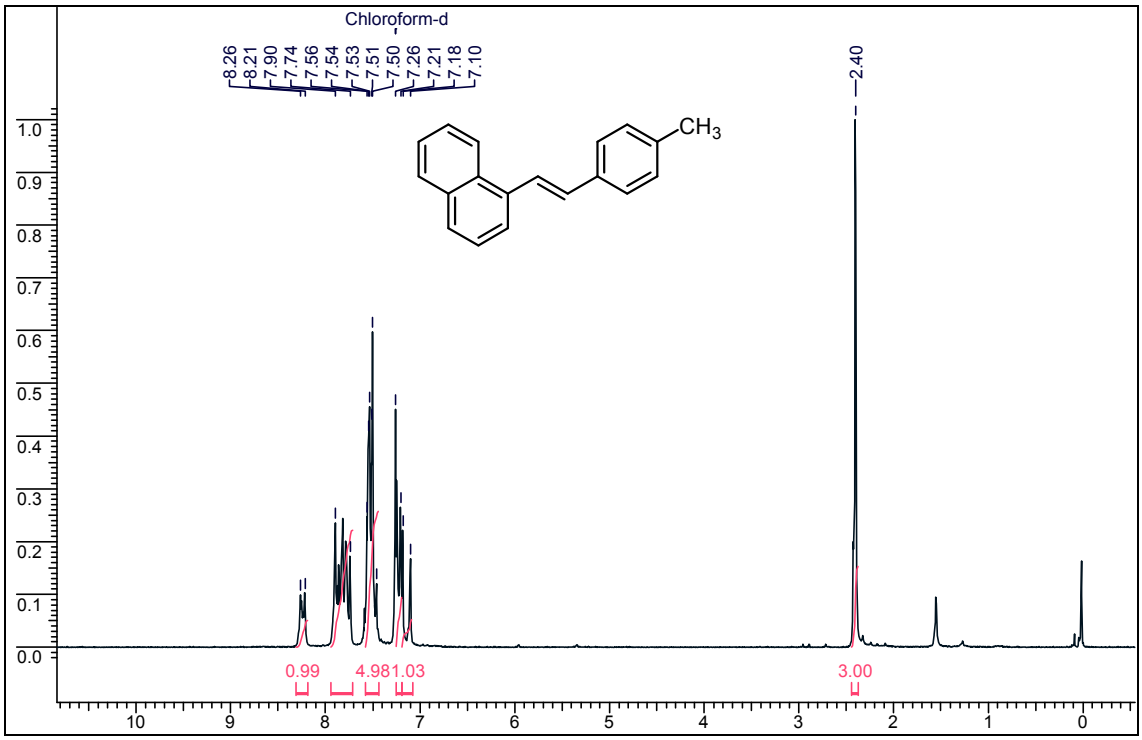


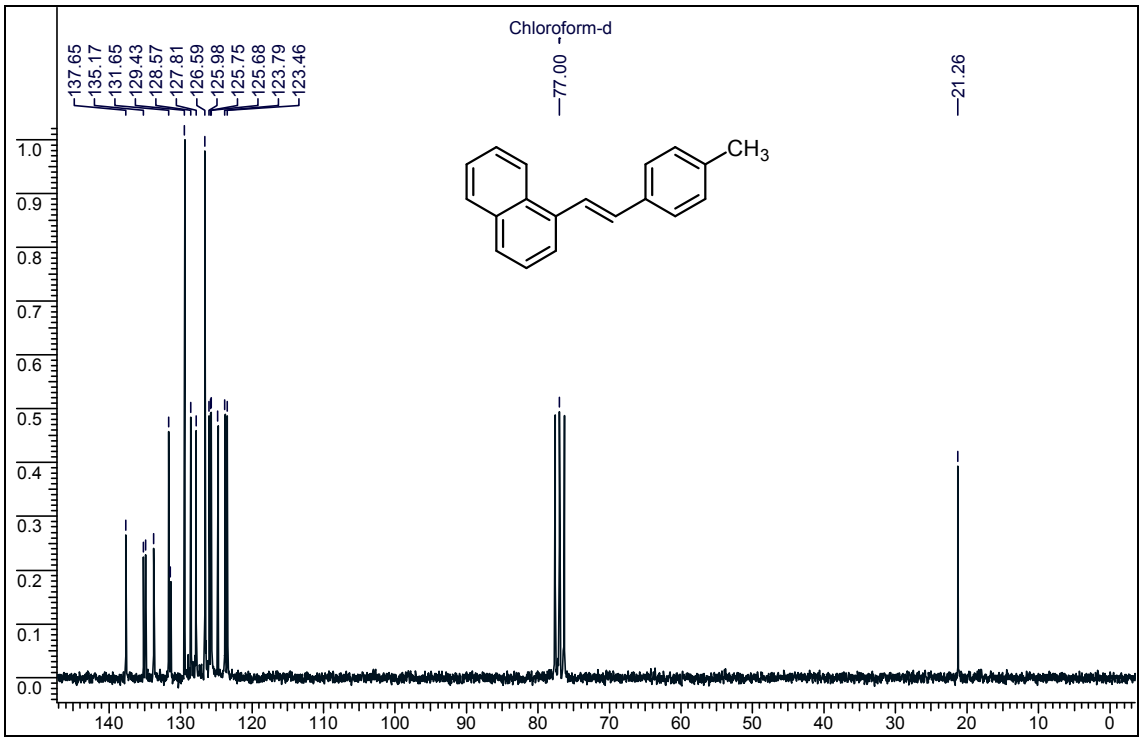
[6] ^{1}H NMR and ^{13}C NMR Spectra of 102f





[7] ^{1}H NMR and ^{13}C NMR Spectra of 102g





1.6.7 References

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CHAPTER-2

Synthesis of enaminones/Pd enaminone complexes and their applications

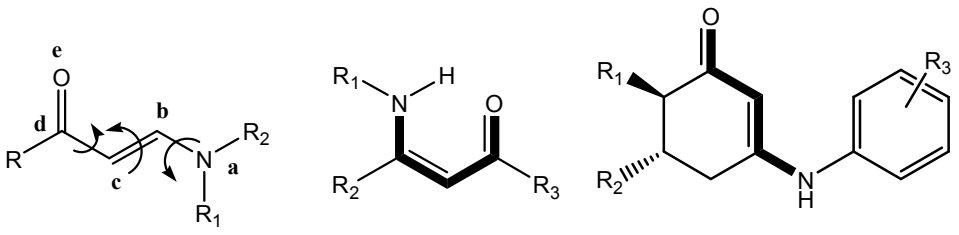
Section-A

Synthesis of Enaminones

Synthesis of enaminones

2.1.1 Introduction

Enaminones a group of organic compounds containing the conjugated system N–C=C–C=O, combine the ambident nucleophility of enamines (sites a, c and e) with the ambident electrophility of enones (sites b and c) (**Fig. 1**). Such enaminones, can be synthesized, isolated and stored at ambient conditions since the carbonyl group, conjugated to the enamine moiety gives this system enough stability. A number of reviews has been published about the chemistry of enaminones[1-3] their physicochemical properties and biological uses, particularly as anti-convulsant agents.[4,5]



enaminone (**A**) *open-chain enaminone* (**B**) *cyclic enaminone* (**C**)

Figure 1.

Biologically active enaminones can be classified into two types:

- *Open-chain enaminones* (**B**)

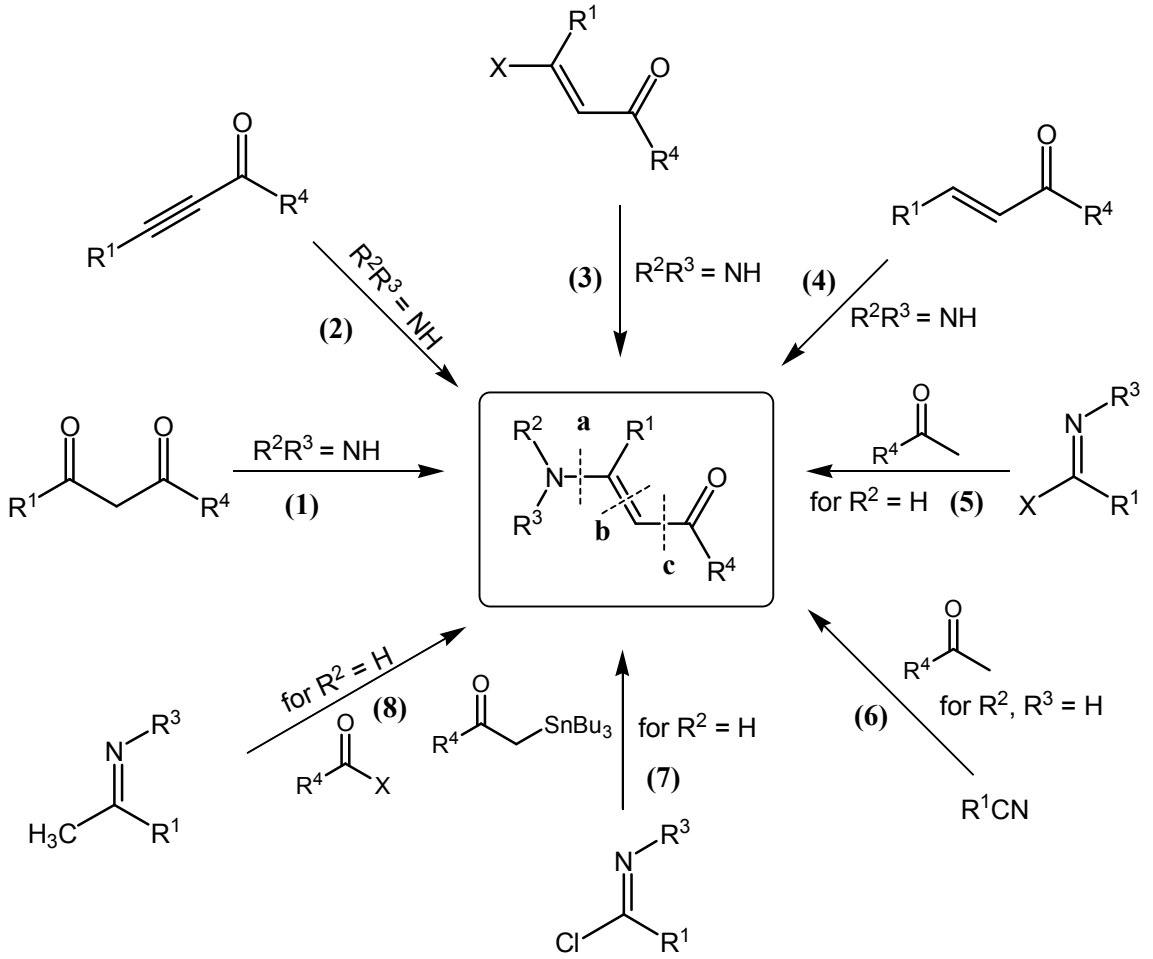
when the characteristic group is part of a chain. These compounds may be potential pro-drugs since they could release biologically active primary amines

- *Cyclic enaminones* (**C**)

when the characteristic group is part of a ring, showing structural similarities with known anti-epileptic or anti-convulsant drugs.

Enaminones have attracted much attention due to the fact that they are important synthons for the synthesis of many biologically active compounds such as dopamine auto-receptor agonists,[6] acetylcholinestersase inhibitors[7] and anticonvulsants.[8] They are also useful intermediates for the preparation of several aminoacids,[9] aminols,[10] peptides and alkaloids.[11] Thus it is very important to search for a convenient and efficient method for the synthesis of this type of compounds.[12] Several methods have been developed for

the synthesis of enaminones. The literature methods for the synthesis of enaminones can be classified according to the bond which was formed (**Scheme 1**).



Scheme 1. Synthesis of β-Enaminones.

Four approaches were used to form bond a:

(1) Condensation of 1,3-diketones with amines in the presence of catalysts

(2) Addition of amines to ynones[13]

(3) Substitution of β-functional groups, such as alkylthio,[14] imidazolyl[15] or methoxy[16]

(4) Pd-catalyzed amination of α,β-unsaturated ketones[17]

Three approaches were used to form bond b:

(5) The reaction of imidoyl chlorides[18] or imidoylbenzotriazoles[19] with enolates

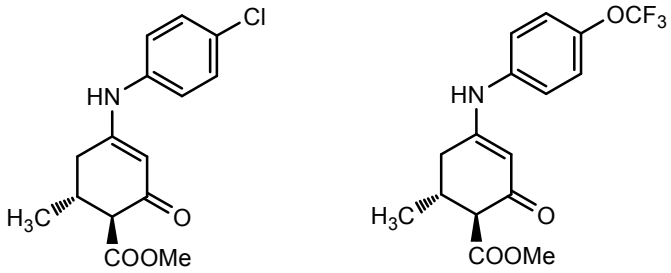
(6) The reaction of nitriles with ketones.[20]

(7) The reaction of imidoyl chlorides with acetonyltributyltin.[21]

(8) The only route to the formation of β-enaminones via bond c: the reaction between imine anions and esters[22] or acylbenzotriazoles[23]

Various modified synthetic pathways have been reported in literature as shown above (**Scheme 1**). However, most of the methods suffer from certain drawbacks including long reaction times, unsatisfactory yields, application of costly reagents, uses of hazardous solvents and tedious experimental procedures. Thus there is a still need to develop a suitable method for the convenient synthesis of enaminones and enamino esters.

Apart from their enormous synthetic potential, β-enaminones in their own right are highly pharmacologically active and reveal a pronounced anticonvulsant activity.[24] It was shown that these compounds cause their anticonvulsant properties by binding to the voltage-dependent sodium channel. Among 103 tested β-enaminones, two showed the biological activity in the μM range (**Fig. 2**).



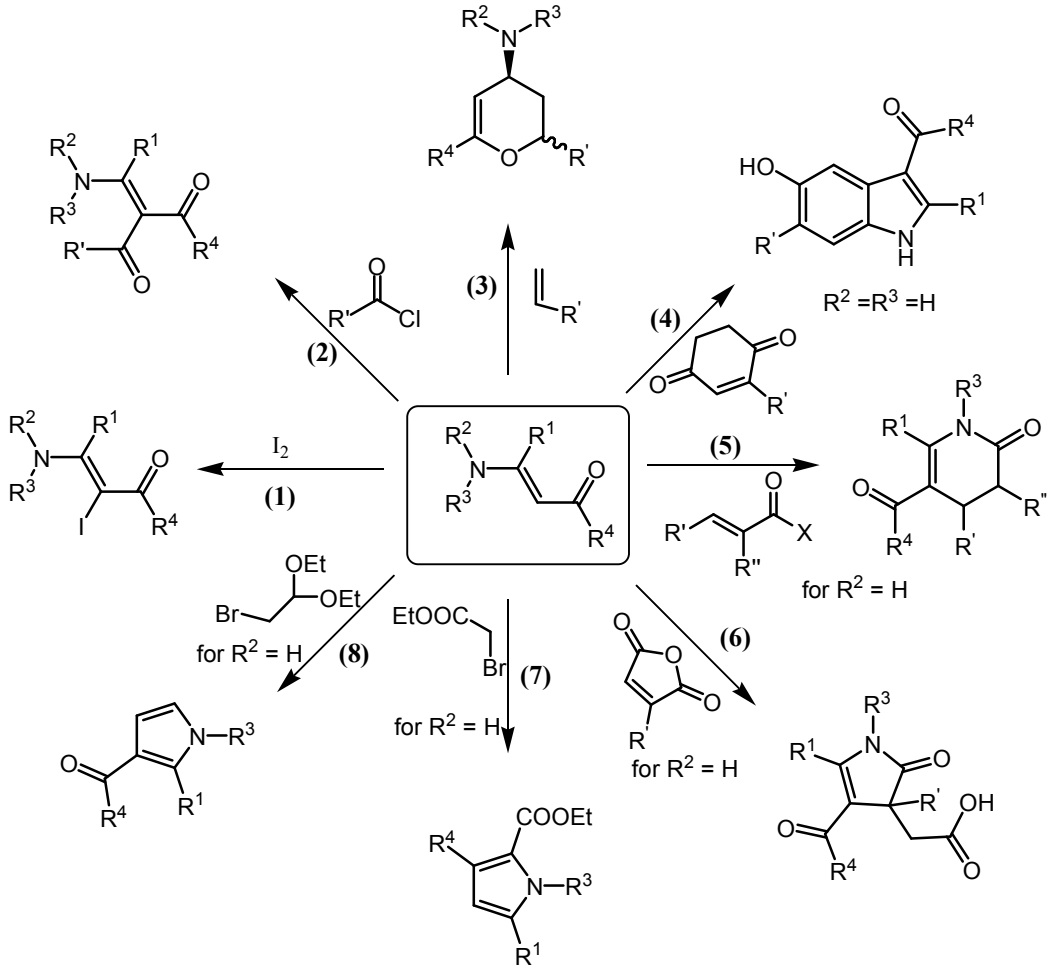
IC_{50} = 489 μM IC_{50} = 170 μM

Figure 2. Selected Potential Anticonvulsant compound

Synthetic transformation of β-enaminones

The most of the applications of β-enaminones were developed for the β-enaminones derived from the primary amines (R^2 = H). Except for iodination **(1)**,[25] reactions with acid chlorides **(2)**[26] and hetero Diels-Alder reactions **(3)**[27] in all cases the monosubstituted nitrogen is required for the successful consecutive transformations (**Scheme 2**). The reaction **(4)** between β-enaminones and *p*-benzoquinones is known in the literature as the Nenitzescu synthesis of 5-hydroxyindoles.[28] It has generally been thought that this reaction proceeds via Michael addition of enaminones, followed by several steps including an internal oxidation-reduction protocol.[29] The treatment of β-enaminones with α,β-unsaturated acid derivatives provides access to a lactam system **(5)**. This type of transformation, which is believed to proceed via initial Michael addition of the enamine to an α,β-unsaturated acid derivative followed by an intramolecular N-acylation is known

as the aza-annulation reaction.[30] In a similar way, the reaction of β-enaminones proceeds with maleic or citraconic anhydride **(6)**. The [3+2] cyclocondensation with 1,2-electrophilic species, such as ethyl bromoacetate **(7)** or bromoacetaldehyde diethylacetal **(8)** leads to pyrrol derivatives.[31]



Scheme 2. Transformations of β-enaminones

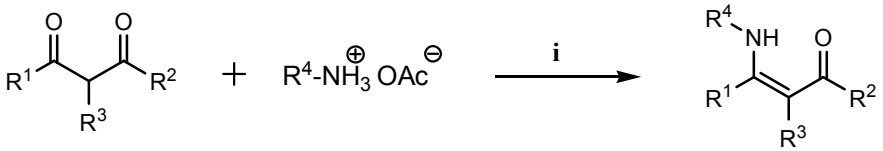
2.1.2 Review of literature

The enaminones are an important class of organic synthetic intermediate. They have a very high impact as synthons for the synthesis of various heterocyclic and biologically active analogues as shown above (**Scheme 2**). Due to their wide range of activity and importance there are several synthetic methods reported in the literature for the synthesis of enaminones. Here in this section we have covered some recent and useful synthetic

methods for the preparation of enaminones from a 1,3-diketone and an amine in the presence of a lewis acid catalyst.

Baraldi *et al.* (1983)[32]

Baraldi and co-workers carried out the preparation of enaminones **3** starting from1,3-diketones **1** and ammonium acetate **2** as an active form of ammonia or by the corresponding easily manipulable acetates in place of low boiling amines. The reaction is simply carried out by refluxing the component in the presence of acetic acid in benzene solution with azeotropic removal of water. In the absence of acetic acid, the reaction is slower and does not go to completion (**Scheme 3**).



1 **2** **3**

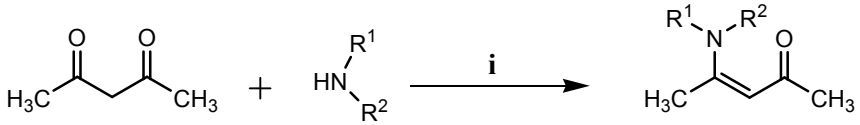
$R^1 = CH_3, C_6H_5, -(CH_2)_3-$ $R^3 = H, -CH_2-CH=CH_2$

$R^2 = CH_3$ $R^4 = H, C_2H_5$

Scheme 3. Reaction conditions: i) acetic acid, benzene, reflux,

Hamelin *et al.* (1993)[33]

Hamelin *et al.* carried out the synthesis of β-enaminones **6** by reaction of β-diketone **4** with variety of amines **5** over clay K10 or silica under microwave irradiation with in few minutes (**Scheme 4**).



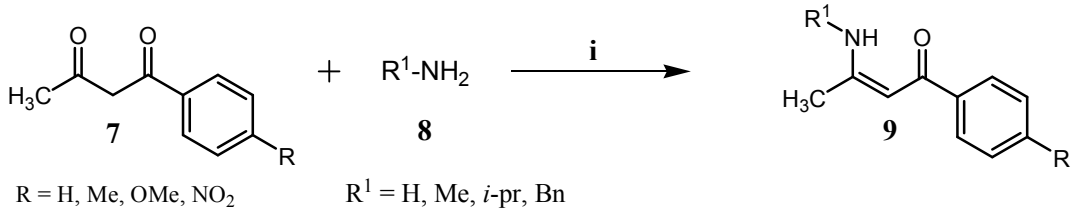
4 **5** **6**

$R^1 = R^2 =$ Me, Bu, Bz.

Scheme 4. Reaction conditions: i) MW, support or catalyst, 1-10 min, 53-99%

Braibante *et al.* (1998)[34]

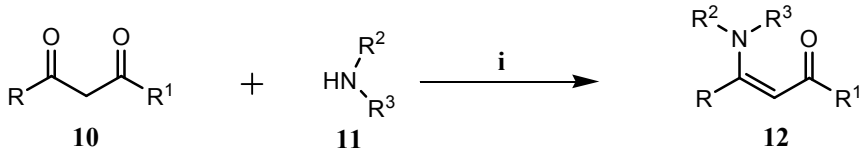
Braibante and co-workers synthesized *p*-phenyl substituted β-enamino ketones **9** by dispersing 1,3-diketones **7** and amines **8** on montmorillonite K-10 under sonication (**Scheme 5**).



Scheme 5. Reaction conditions: i) K-10,)))), 35 ºC, 5-20 h, 45-95%

Arcadi *et al.* (2003)[35]

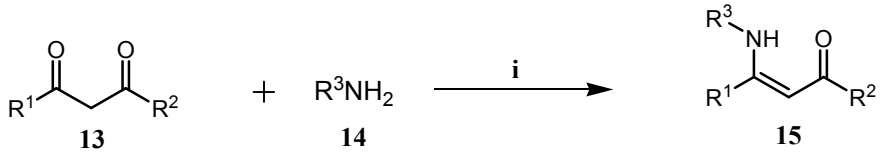
Arcadi *et al.* reported an efficient gold(III) catalyzed synthesis of enaminones **12** from 1,3-dicarbonyl compounds **10** and ammonia/amines **11** providing an attractive and environmental friendly alternative to the more vigorous reagents and drastic conditions. The catalysis of gold(III) is also extended to reaction of cyclic 1,3-dicarbonyls with O-, P- and S-nucleophiles (**Scheme 6**).



Scheme 6. Reaction conditions: i) EtOH, $NaAuCl_4$, rt, 7 h, 60-96%

Khosropour *et al.* (2004)[36]

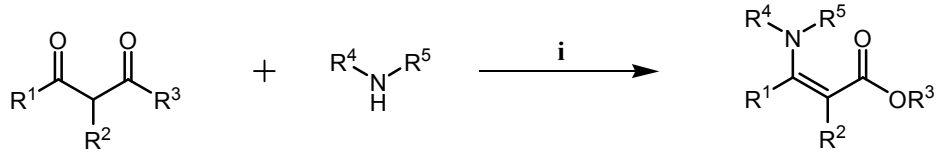
Khosropour *et al.* carried out the synthesis of β-enaminones **15** in water by the reaction of β-diketone **13** with different amines **14** in the presence of catalytic amount of Bismuth(III) trifluoroacetate (**Scheme 7**).



Scheme 7. Reaction conditions: i) $Bi(TFA)_3$, H_2O, rt, 5-180 min, 64-98%

Bartoli *et al.* (2004)[37]

Bartoli *et al.* reported the synthesis of β-enaminones **18** by the reaction of various β-diketone **16** with different amines **17** such as primary, secondary, benzylic and aromatic amine with various substrates in the presence of catalytic amount of $Zn(ClO_4)_2 \cdot 6H_2O$ at room temperature in DCM. Moreover, the catalyst is cheap and easily available, it is stable to air moisture and can be recycled (**Scheme 8**).



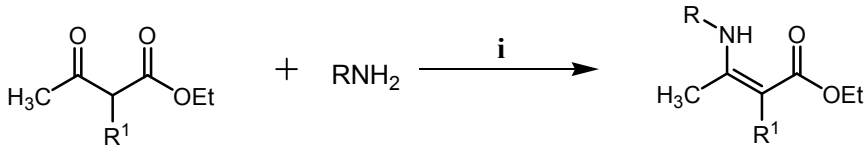
16 **17** **18**

R^1 = Me, Et, Ph R^3 = Et, t-Bu R^5 = H
R^2 = H, Me, Cl R^4 = Ph, CH_2Ph, nBu

Scheme 8. Reaction conditions: i) $Zn(ClO_4)_2 \cdot 6H_2O$, DCM, rt, 5-30 h, 64-98%

Brandt *et al.* (2004)[38]

Brandt *et al.* carried out the synthesis of β-enaminones **21** by the reaction of β-diketone **19** with various amines **20** in presence of catalytic amount of acetic acid under ultrasound irradiation at room temperature with good yields (**Scheme 9**).



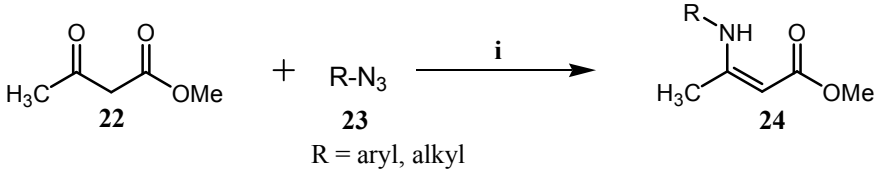
19 **20** **21**

$R^1 = CH_2\text{-}CH{=}CH_2$ R = aryl, alkyl

Scheme 9. Reaction conditions: i) AcOH,)))), rt, 0.2-3 h, 60-98%.

Reddy *et al.* (2005)[39]

Reddy *et al.* reported a mild and efficient one-pot method for the synthesis of β-enaminones **24** starting from alkyl azides **23** and β-diketone **22** under a hydrogen atmosphere using 10% Pd/C at room temperature. Alkyl azides undergo reduction to form alkyl amines under hydrogen atmosphere in presence of 10% Pd/C. Further the alkyl amines react with β-diketones to form the β-enaminones **24** (**Scheme 10**).



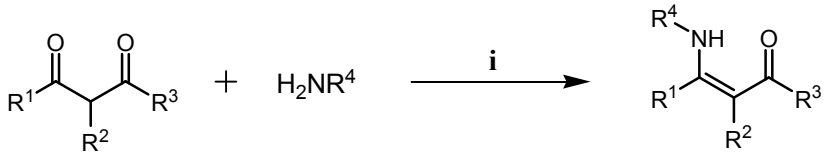
22 **23** **24**

R = aryl, alkyl

Scheme 10. Reaction conditions: i) 10%, Pd/C, H_2, EtOAc, rt, 0.5-2 h, 48-100%

Wang *et al.* (2006)[40]

Wang *et al.* synthesized β-enaminones **27** starting from a variety of β-diketone **25** and amines **26** in excellent yields by using catalytic amount of indium tribromide. The reaction proceeds smoothly at room temperature in a short reaction time under solvent-free conditions (**Scheme 11**).



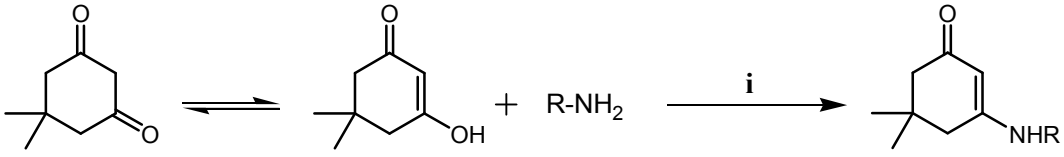
25 **26** **27**

R^1 = Me, Ph; R^2 = H R^3 = OMe, OEt; R^4 = alkyl, aryl

Scheme 11. Reaction conditions: i) $InBr_3$, solvent-free, rt, 1-24 h, 76-95 %

Pawar *et al.* (2006)[41]

Pawar *et al.* carried out an efficient synthesis of β-enaminones **31** starting from dimedone **28** and amine **30** in ionic liquid ethyl ammonium nitrate $[EtNH_3]NO_3$ at room temperature in the absence of any added catalyst. Excellent yields were obtained and the ionic liquid can be recycled and reused **(Scheme 12)**.



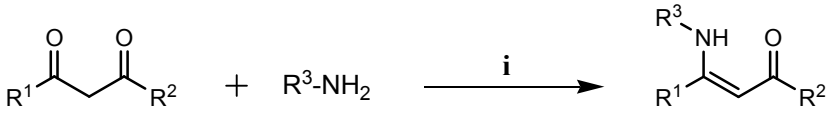
28 **29** **30** **31**

R = aryl

Scheme 12. Reaction conditions: i) $[EtNH_3]NO_3$, rt, 3-4.2 h, 80-90%

Das *et al.* (2006)[42]

Das *et al.* utilized silica supported perchloric acid ($HClO_4 \cdot SiO_2$) as a heterogeneous recyclable catalyst for a highly efficient and chemo- and stereoselective conversion of β-diketones **32** to β-enaminones and β-enamino esters **34** by treatment with amines **33** under solvent-free conditions at room temperature **(Scheme 13)**.



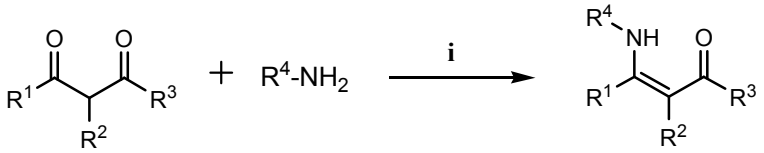
32 **33** **34**

R^1 = CH_3; R^2 = CH_3; R^3 = aryl

Scheme 13. Reaction conditions: i) ($HClO_4 \cdot SiO_2$), solvent-free, rt, 5-14 h, 91-99%

Zhang *et al.* (2006)[43]

Zhang *et al.* carried out the synthesis of variety of β-enaminones and β-enamino esters **37** by the reaction of 1,3 dicarbonyl compounds **35** with amines **36** in the presence of a catalytic amount of cobalt (II) chloride at room temperature under solvent free-condition **(Scheme 14)**.



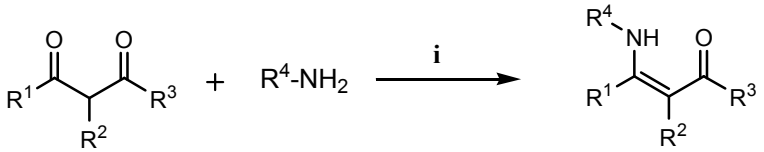
35 **36** **37**

R^1 = Me R^2 = H R^3 = Me, OMe, OEt, Ph

Scheme 14. Reaction conditions: i) $COCl_2 \cdot 6H_2O$, solvent-free, rt, 15-100 min, 80-95%

Yadav *et al.* (2006)[44]

Yadav *et al.* synthesized library of β-enamino compounds **40** by the reaction of β-dicarbonyl compounds **38** with various aliphatic and aromatic amines **39** in the presence of scandium triflate $Sc(OTf)_3$ under solvent free conditions in excellent isolated yields. The catalyst can be recovered after completion of reaction by simple filtration and can be recycled in subsequent reactions **(Scheme 15)**.



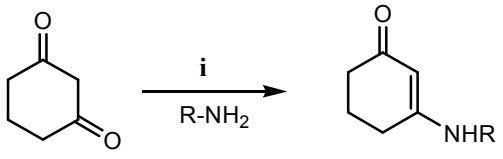
38 **39** **40**

R^1, R^2, R^4 = alkyl, aryl R^3 = alkyl, aryl, O-alkyl, O-aryl

Scheme 15. Reaction conditions: i) $Sc(OTf)_3$, solvent-free, rt, 1-3 h, 83-95%

Epifano *et al.* (2007)[45]

Recently Epifano and co-workers synthesized β-enaminones **42** in very good yield under solvent-free conditions from various amines and β-diketones **41** in the presence of $Yb(OTf)_3$ as catalyst. The catalyst can be recovered by filtration and this recycled catalyst could be reused several times without any loss of activity **(Scheme 16)**.



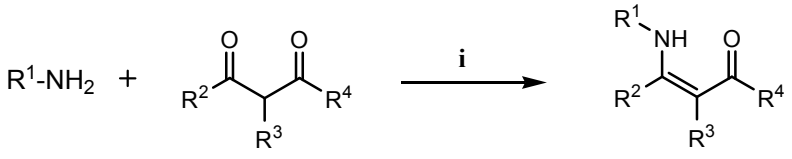
41 **42**

R = alkyl, aryl

Scheme 16. Reaction conditions: i) $Yb(OTf)_3$, solvent-free, rt, 12 h, 93-99%

Lin *et al.* (2007)[46]

Recently Lin *et al.* carried out a facile synthesis of β-enaminones and enamino esters **45** by condensation of β-dicarbonyl **44** compounds with differently substituted amines **43** in the presence of $ZrCl_4$ under solvent-free conditions **(Scheme 17)**.



43 **44** **45**

Scheme 17. Reaction conditions: i) $ZrCl_4$, solvent-free, rt, 18-240 min, 81-95%

2.1.3 Present work

2.1.3.1 Objective

Due to their wide range of activity and importance, a simple and high yielding one-pot approach for the synthesis of β-enaminones is highly desirable. The conventional method for the synthesis of enaminones is the azeotropic removal of water by refluxing an amine with 1,3-diketone in an aromatic solvent. Many of the methods reported so far suffer from one or more drawbacks such as long reaction time, unsatisfactory yields and hazardous and expensive catalysts. Taking into consideration all these limitations, we investigated the progress of the reaction of various amines with 1,3-diketones in a novel heterogeneous as well as a homogeneous medium. For the first time, silica chloride was used as a solid catalyst for the enamination under heterogeneous conditions. For the homogeneous conditions, a recyclable ionic liquid (IL) viz. 1-*n*-butylimidazolium tetrafluoroborate [HBIm] BF_4 was used as a reaction medium as well as a promoter for the first time in the absence of any added catalyst. For both the methodologies which

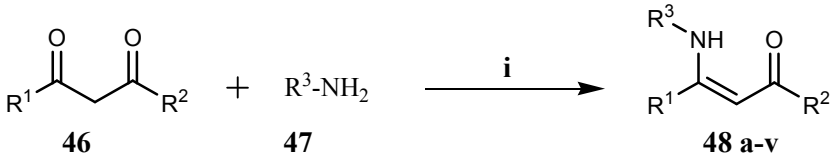
were performed under ambient temperature, the reaction rates were significantly higher than those reported so far for the synthesis of β-enaminones at room temperature

2.1.3.2 Results and discussion

Enamination in heterogeneous medium using silica chloride

Recently heterogeneous catalysts like silica chloride, a modified silica, have proven to be useful for various organic transformations.[47] These transformations are effected by the reagents immobilized on the porous solid supports of the modified silica and have advantages such as enhanced reaction rates, higher yields, greater selectivity and ease of manipulation over the conventional solution phase reaction. Consequently, in the case of enamination reaction, we thought there is scope for further innovation towards milder reaction conditions, short reaction time and better yields. This work deals with the regio- and chemo- selective enamination of β-dicarbonyl compounds under mainly solvent free conditions using silica chloride at room temperature in excellent yields and purity.

In a model study a mixture of ammonium acetate and acetylacetone was stirred at room temperature in the presence of silica chloride as a catalyst (**Scheme 18**). The rate of the reaction was rapid and the reaction goes to completion within 10 min. The pure product was isolated by column chromatography and fully characterized. The IR spectra of **48a** showed absorption at 1535, 1710, 3366 cm^{-1} corresponding to C=C, C=O and $–NH_2$ groups respectively. The ^1H NMR spectra of **48a** showed broad singlet of $–NH_2$ at δ 9.81 and sharp singlet of olefinic proton at δ 5.01. The ^{13}C NMR spectrum showed peaks at δ 95.2, 161.7 and 196.1 corresponding to C=C and C=O of enaminone moiety. Analytical data conforms to the structure of **48a** and melting point is matching with an authentic sample as well as with that reported in literature. Thus by using the above procedure a variety of amines including ammonium acetate, aliphatic and aromatic amines were condensed with various 1,3-diketones like ethyl acetoacetate, acetyl acetone and 1,3-cyclohexanedione using silica chloride as a heterogeneous catalyst at 28 ^oC. The results are recorded in **Table 1**.



46 **47** **48 a-v**

$R^1 = CH_3$, Ph; $R^2 = CH_3$, OEt; $-(CH_2)_3-$; R^3 = H, Bu, aryl

Scheme 18. Reaction conditions: i) Silica chloride, solvent-free, rt, 5-15 min, 90-96%

In majority of the cases, where even one of the reactants is a liquid, the reaction was carried out under solvent free condition. In others which constitute a minority where both the reactants are solids (entries 3, 6, 12, 15), chloroform was used as the solvent as indicated in Table **1**. All the isolated products were well characterized by their IR, ^{1}H and ^{13}C-NMR spectral analysis and their elemental analysis was in conformity with their structures. It is clear from our results that the silica chloride catalyzed condensation reaction of 1,3-dicarbonyls with the amines provides a remarkably rapid and viable alternative route for the synthesis of β-enaminones. All the reactions were complete in just 5-15 min affording the products **48a-v** in excellent isolated yields. It is observed that both the highly reactive aliphatic and the less reactive aromatic amines undergo the reaction in an equally facile manner. It is noteworthy that by this methodology the reaction of acetyl acetone with ammonium acetate gave the enaminone **48a** in 93% yield in just 10 min (entry 1) instead of long reaction time (24 h) in the previously reported method[48] using silica gel as a catalyst. This highlights the significantly higher Lewis acid character of silica chloride as against silica gel for the enamination reaction. This method has been successfully applied for the enamination of cyclic 1,3-diketones affording potential pharmaceutically important anticonvulsant compounds and appears to be more convenient and superior to the preparative methods reported so far for such compounds. The reported methods take much longer time, make use of hazardous solvents and involve complex isolation procedures. For instance, the enamination of 1,3-cyclohexanedione with aniline showed only 30% conversion to **48i** even after 24 h in the presence of silica gel as catalyst as against 100% conversion with an isolated yield of 92 % for **48i** in just 10 min using silica chloride.

The recycle data for the typical reaction of aniline with acetyl acetone using silica chloride as catalyst under the conditions of our methodology are recorded in **Table 2**.

There is a progressive decrease in the isolated yields as well as the chlorine content of the recovered catalyst and a corresponding increase in the reaction time.

Table 2. Recycle study of recovered silica chloride

Batch	Chlorine content (%)	Reaction time (min)	[a]Yield (%)
First batch	4.26	5	91
Recycle 1	1.62	30	88
Recycle 2	1.05	120	80

[a]Isolated yields after column chromatography.

Based on the above observations a plausible mechanism for the reaction is postulated as shown in **Fig. 3**. The Si-Cl bond is labile and can give rise to Lewis acid centers on silica. The Cl is easily displaced selectively by the acetyl oxygen of 1,3-dicarbonyl compounds by a nucleophilic substitution reaction generating a cationic center on the carbonyl carbon, which is easily attacked by the nucleophilic primary amines to form the imine which after tautomerisation forms the enaminone. It is important to note that the original activity of the recovered silica chloride from recycle batch 2 could be restored by treatment with thionyl chloride under reflux.

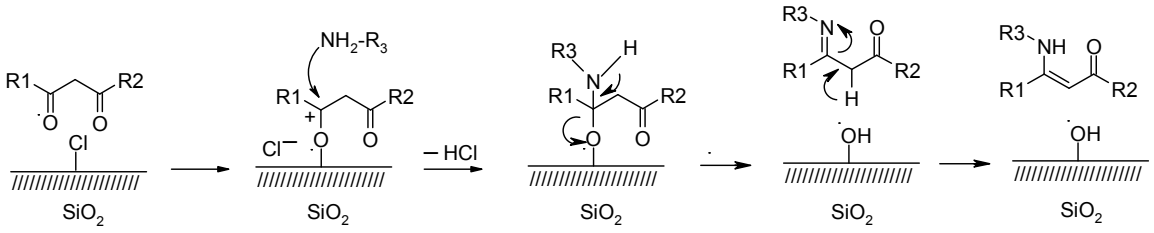


Figure 3. Plausible mechanisms for the synthesis of enaminones

The reactivity of silica chloride was also checked by taking low catalyst loading for the reaction of aniline with acetyl acetone. It was observed that as wt % of catalyst based on acetyl acetone decreases the reaction time increases, but the low % of catalyst does not affect the yields. This proportion of the catalyst was the optimum since any loading beyond 10% w/w did not bring about any further decrease in reaction time and increase in yield. The results are summarized in **Table 3**.

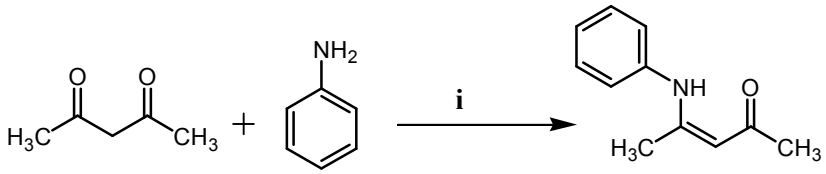
Table 3. Effect of wt % of silica chloride on reaction rate of aniline with acetyl acetone

Entry	Silica chloride (wt%)	Time (min)	[a]Yield%
1	2	20	89
2	4	16	90
3	5	12	88
4	6	8	90
5	10	5	91

[a]Isolated yields after column chromatography

Enamination in a homogeneous medium using ionic liquid

In recent times ionic liquids continue to receive much attention as green solvents, with many excellent reviews available summarizing their preparation, use, and advantages compared to traditional solvents[49] Thus the non-volatile, non-flammable, and thermally stable ionic liquids can be used as replacements for the selected organic solvents for various transformations, since the latter are very often volatile, hazardous and pose problems of recovery. The IL's belonging to the 1-*n*-butylimidazolium [HBIm] series were screened for the reaction of aniline with acetyl acetone to afford 4-phenylamino-pent-3-en-2-one **48g** (**Scheme 19**). The compound **48g** was purified by column chromatography and completely characterized.



49 **50** **48 g**

Scheme 19. Reaction conditions: i) HBIm series ionic liquid, rt, 20-55 min, 91-93%

All the ILs were subjected to a thorough drying protocol of 80 ^{o}C at 10 mm Hg for 4h and their moisture content estimated. The reaction in different ILs was followed by subjecting aliquots of reaction mixture to TLC at five minute intervals using 10% ethyl acetate in petroleum ether (bp 60-80 ^{o}C) as eluent. The time for complete conversion of acetyl acetone was noted at which point the reaction was stopped and the product was isolated. The results are recorded in **Table 4**.

Table 4. Screening of various ILs for reaction of aniline with acetyl acetone

Entry	Ionic liquid	Moisture content wt%	Chemical shift δ (ppm) -NH proton	Time for complete conversion (min)	[a]Yield (%)
1	[HBIm] ClO_4	0.014	11.83	55	93
2	[HBIm] Cl	0.013	12.17	35	91
3	[HBIm] Br	0.013	12.22	35	90
4	[HBIm] BF_4	0.012	14.59	20	92

[a]Isolated yields after column chromatography.

It was observed that the nature of the anion governs the electrophilicity of the imidazolium cation, which in turn influences the acidity of the –NH proton. This is indicated by increasing downfield shift of the –NH proton. This –NH proton is capable of hydrogen bonding with acetyl oxygen generating the cationic center as shown in **Fig. 4** which is easily attacked by the nucleophilic amines.

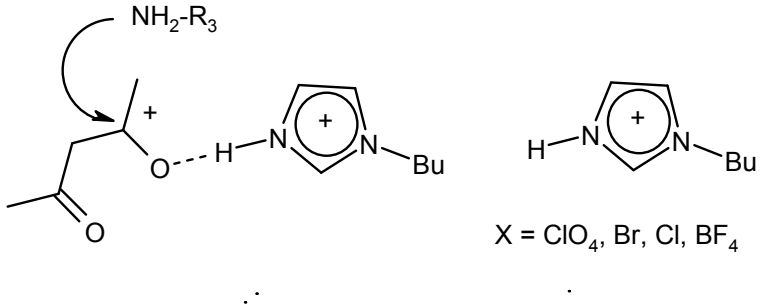


Figure 4. The hydrogen bond interaction of the imidazolium cation

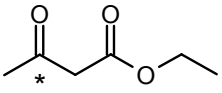
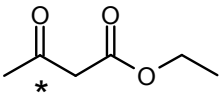
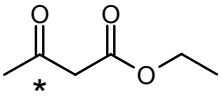
Consequently, it can be observed from **Table 4**, the IL [HBIm]BF_4 with most deshielded –NH proton afforded the best results in terms of time of complete conversion although all the ILs afforded more or less similar isolated yields. Therefore, all further reactions were carried out in this IL.

The IL [HBIm] BF_4 acts as a solvent medium and has also promoted the reaction with its inherent Brønsted acidity. The Brønsted acidity is conferred by the –NH proton of [HBIm]BF_4 (chemical shift of 14.59 ppm) capable of bonding with carbonyl oxygen of 1,3-dicarbonyl compound as shown in **Fig. 4**. Evidence for this was obtained by

recording the ^{13}C-NMR spectra of ethyl acetoacetate with an external lock of D_2O and with one equivalent of the IL. The results are recorded in **Table 5**.

A significance shift of ~ 3 ppm for the carbonyl carbon of EAA by its interaction with IL was observed. Additional evidence was obtained by recording their IR spectra neat wherein also a significant shift to lower wave number by 7cm^{-1} was observed.

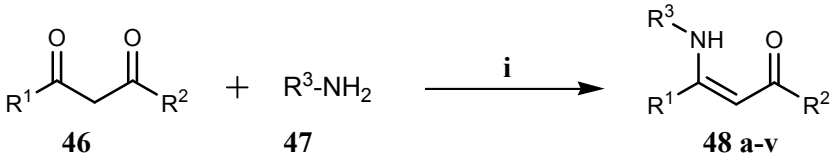
Table 5. The ^{13}C-NMR chemical shifts and IR data for the carbonyl

Entry	Substrate	Chemical shift[a] (ppm)	IR values[b] ν, cm^{-1}
1		214.1	1742.1
2	 + [HBIm]BF_4	217.1	1735.5
3	 + [BBIm]BF_4	214.1	1741.2

[a] Recorded neat with D_2O as external lock; [b] Recorded with neat sample

For comparison and to substantiate the above observations, the reaction of aniline with acetylacetone was carried out in the non-acidic IL [BBIm]BF_4 under similar conditions. The time for complete conversion was considerably longer (5 h) to afford the product in 89% yield. Moreover, no shift in the ^{13}C-NMR and IR spectra for the carbonyl carbon and C=O stretching frequency respectively for the ethylacetoacetate with one equivalent of [BBIm]BF_4 was observed thereby confirming the poor catalytic activity of the relatively non-acidic [BBIm]BF_4.

Consequently all the amines and 1,3-diketones used in the silica chloride catalyzed reaction were subjected to the enamination using ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [HBIm]BF_4 as the solvent as well as promoter at 28 ^{o}C (**Scheme 20**) in the absence of any added catalyst. The results are recorded in **Table 1**.

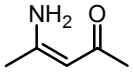
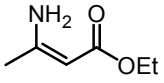
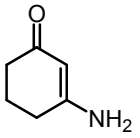
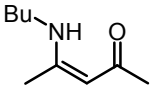
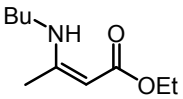
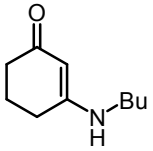


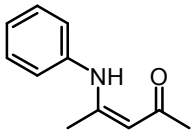
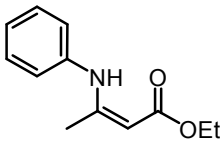
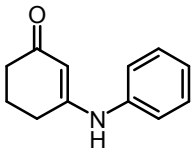
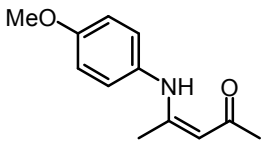
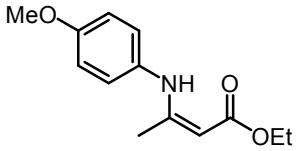
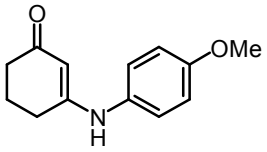
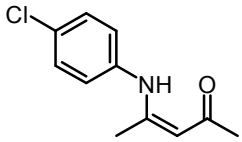
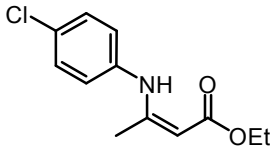
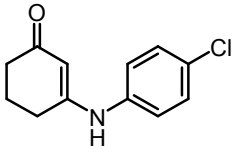
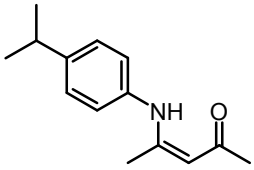
R^1 = CH_3, Ph; R^2 = CH_3, OEt; -$(CH_2)_3$-; R^3 = H, Bu, aryl

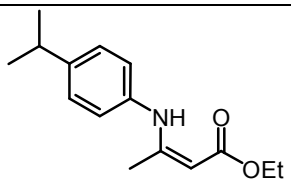
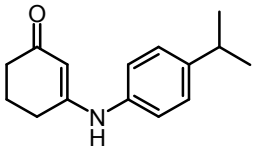
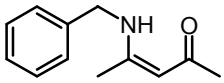
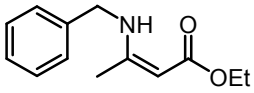
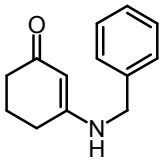
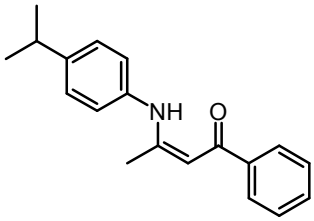
Scheme 20. Reaction conditions: i) [HBIm]BF_4, rt, 5-30 min, 89-93%

Both acyclic and cyclic 1,3-dicarbonyl compounds undergo enamination with amines in excellent isolated yields. In majority of the cases, the products were selectively extracted from the ionic liquid medium using 10% ethyl acetate in petroleum ether (bp 60-80 ^oC) leaving behind the ionic liquid, which was recovered and recycled. In the case of the reaction between 1,3-cyclohexanedione and amines the products were isolated by dilution with water and filtration of the precipitated cyclic enaminones. The aqueous layer

Table 1. Synthesis of enaminones (**48 a-v**) using silica chloride or [HBIm]BF_4

Entry	**48 a-v**	Product	Silica chloride		[HBIm]BF_4	
			Reaction time (min)	Yield[a] (%)	Reaction time (min)	Yield[a] (%)
1	**48a**		10	93	30	92
2	**48b**		15	90	30	90
3	**48c**[b]		15	90	5	93
4	**48d**		5	96	5	92
5	**48e**		5	94	5	92
6	**48f**[b]		5	93	20	92

7	**48g**		5	91	25	91
8	**48h**		8	90	25	93
9	**48i**		10	92	20	93
10	**48j**		5	94	25	92
11	**48k**		5	92	25	92
12	**48l**[b]		5	90	20	93
13	**48m**		5	91	30	93
14	**48n**		8	90	30	92
15	**48o**[b]		10	90	30	91
16	**48p**[c]		5	93	20	92

17	**48q**[c]		8	92	30	90
18	**48r**[c]		10	90	30	92
19	**48s**		5	96	5	90
20	**48t**		5	93	10	89
21	**48u**		5	91	10	90
22	**48v**[c]		15	93	30	91

[a]Isolated yields after column chromatography.
[b]Chloroform used as a solvent.
[c] New compound.

containing the IL was subjected to distillation at 80 ^{o}C at a reduced pressure of 10 mm Hg for 4 h to remove all traces of water. The recovered IL from both the above mentioned procedures could be recycled five times with almost no loss of activity. The IL [HBIm]BF_4 was recycled five times for the reaction of acetyl acetone with aniline. The results are recorded in **Table 5**. It was observed that the IL exhibits only a marginal loss in activity spread over five recycle batches.

Table 6. Reusability of ionic liquid for synthesis of enaminones (entry 7)

Entry	1	2	3	4	5
Yield[a] (%)	91	91	90	88	90

[a] Isolated yields after column chromatography.

The enaminones resulting from the cyclic diketone are reported to be pharmaceutically important potential anticonvulsant compounds.[8]

The regioselectivity of the methodology was confirmed by performing the reaction of benzoyl acetone with 4-Isopropylamine using silica chloride and [HBIm]BF_4 respectively at room temperature to obtain the enaminone **48v** as the only product. This was confirmed by comparing the ^{13}C-NMR values of the acetyl carbonyl carbon and the benzoyl carbonyl carbon in both the substrate and the product **48v** respectively. The ^{13}C-NMR shift of the acetyl carbonyl carbon (193.5 δ) changes to 162.3 δ retaining the value of the benzoyl carbonyl carbon at 188.2 δ without any change. The ^{13}C-NMR spectra **48v** is given in experimental section. This clearly indicates that the enamination has taken place regioselectively at the acetyl carbonyl carbon and not at the benzoyl carbonyl carbon. Evidently, this regio-selectivity at acetyl carbonyl carbon has been maintained for the β-keto-esters as well wherein no formation of the amide from the ester was observed. The structure of the new cyclic enaminone **48r** was confirmed by X-ray crystallography.[50] The ORTEP diagram is shown in **Fig. 5**.

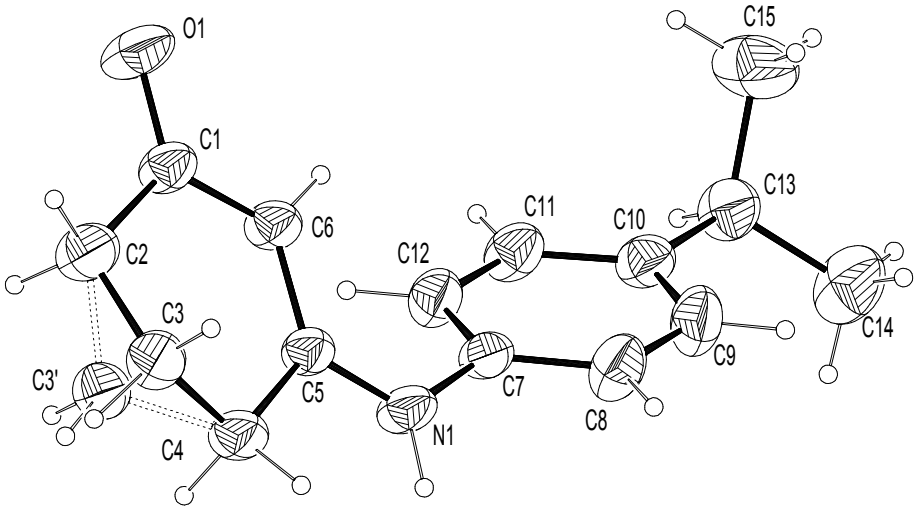


Figure 5. ORTEP diagram of the X-ray crystal structure of compound **48r** with thermal ellipsoids at 50% probability.

Table 7. Data collection and refinement parameters for compound **48r**

Crystal data	
Chemical formula	$C_{15}H_{19}NO$
M_r	229.31
Cell setting, space group	MONOCLINIC, *P*2(1)/*c*
a, *b*, *c* (Å)	8.476 (3), 13.527 (5), 12.092 (5)
β (°)	108.500 (7)
V (Å^3)	1314.8 (9)
Z	4
D_x (Mg m^{-3})	1.158
Radiation type	Mo *K*α
No. of reflections for cell parameters	2764
θ range (°)	2.3–22.9
μ (mm^{-1})	0.07
Temperature (K)	293 (2)
Crystal form, colour	PRISM, colorless
Crystal size (mm)	0.55 × 0.32 × 0.24

Data collection	
Diffractometer	CCD Area Detector
Data collection method	ω and phi Scan
Absorption correction	MULTI-SCAN
T_{min}	0.962
T_{max}	0.983
No. of measured, independent and observed parameters	9272, 2310, 1765
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.023
θ_{max} (°)	25.0
Range of h, k, l	$-10 \rightarrow h \rightarrow 10$
	$-16 \rightarrow k \rightarrow 16$
	$-14 \rightarrow l \rightarrow 14$
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.060, 0.181, 1.09
No. of relections	2310 reflections
No. of parameters	169
H-atom treatment	Mixture of independent and constrained refinement
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0905P)^2 + 0.3904P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	3.333
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.41, –0.19
Extinction method	SHELXL
Extinction coefficient	0.003 (3)

2.1.4 Conclusion

A remarkably rapid, efficient and regioselective synthesis of β-amino-α, β unsaturated esters and ketones has been achieved at ambient temperature using for the first time silica chloride as solid catalyst and an ionic liquid viz. 1-*n*-butylimidazolium tetrafluoroborate respectively. The reactions proceeded to completion in just 5-30 min giving rise to the β-enaminones in excellent isolated yields. For the reactions involving the IL, the IL acted

both as a recyclable reaction medium as well as promoter and did not require any additional catalyst. The enamination in both the cases takes place regioselectively at the acetyl carbonyl carbon in the case of β-keto esters and benzoyl acetone respectively. The methodologies described have been proven to be a superior alternative to existing methods of enamination of cyclic 1,3-diketones, which give rise to pharmaceutically important anticonvulsant compounds. The short reaction times, recyclability of solid catalyst as well as the IL and easy work up procedures make these methodologies generally environment friendly and amenable for scale up.

2.1.5 Experimental

Procedure for the synthesis of silica chloride:

Flame dried silica gel (20 g) and freshly distilled thionyl chloride (100 ml) was refluxed for 50 h under argon atmosphere. The excess unreacted thionyl chloride was distilled out and the resulting greyish silica chloride was flame dried, stored in airtight container and used as it is for the reactions.

Typical procedure for synthesis of β-amino- α, β- unsaturated ketones and esters using silica chloride as a heterogeneous catalyst:

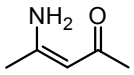
A mixture of 1,3-dicarbonyl compound (2 mmol), amine (2.2 mmol) and silica chloride (10 % w/w) was stirred at room temperature (28 ^{o}C). The completion of reaction was followed by TLC using 10% EtOAc in petroleum ether (bp 60-80 ^{o}C) as eluent. After completion of reaction, the crude reaction product which is a paste was subjected to column chromatography using 1% EtOAc in petroleum ether (bp 60-80 ^{o}C) as eluent to isolate pure products and were fully characterized

Typical procedure for synthesis of β-amino- α, β- unsaturated ketones and esters in ionic liquid [HBIm] BF_4 as a homogeneous medium.

A mixture of 1,3-dicarbonyl compound (2 mmol) and amine (2.2 mmol) in [HBIm]BF_4 (2 ml) was stirred at room temperature (28 ^{o}C). The completion of reaction was followed by TLC using 10% EtOAc in petroleum ether (bp 60-80 ^{o}C) as eluent. After completion of reaction the product was selectively extracted using 10% EtOAc in petroleum ether (2 ×

10ml) leaving behind the ionic liquid. The immiscible organic layer was separated, dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to afford the crude product. The crude product was purified by column chromatography using 1% EtOAc in petroleum ether (bp 60-80 ^{o}C) as eluent. The recovered [Hbim]BF_4 was used as such for the recycle studies.

2.1.5.1 Characterization data for compounds 48a-v



4-Amino-pent-3-en-2-one (48a): The above general procedure, starting from acetyl acetone (0.3g, 3 mmol) and ammonium acetate (0.27g, 3.6 mmol) gave compound **48a**.

Nature : White solid

MP : 32 ^{o}C (Lit.[48] 30-32 ^{o}C).

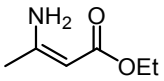
IR ($CHCl_3$) cm^{-1} : 3366, 3013, 1710, 1621, 1535, 1431, 1288, 1216, 754.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.90 (s, 3H), 2.03 (s, 3H), 5.01 (s, 1H), 9.81 (brs, 2H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 21.7, 28.6, 95.2, 161.7, 196.1.

Elemental analysis : Calcd: C, 60.58; H, 9.15; N, 14.13

C_5H_9NO (99) Found: C, 60.72; H, 8.95; N, 14.24



3-Amino-but-2-enoic acid ethyl ester (48b)[48]: The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and ammonium acetate (0.21 g, 2.76 mmol) gave compound **48b**.

Nature : Yellow oil

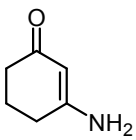
IR ($CHCl_3$) cm^{-1} : 3450, 3336, 2981, 1716, 1621, 1567, 1446, 1288, 1163, 1045, 788, 565.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.25 (t, 3H, *J* = 7.2 Hz), 1.90 (s, 3H), 4.12 (q, 2H, *J* = 7.2 Hz), 4.50 (s, 1H), 7.95 (brs, 2H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 14.0, 21.5, 57.9, 83.0, 159.9, 169.8.

Elemental analysis : Calcd: C, 55.80; H, 8.58; N, 10.84.

$C_6H_{11}NO_2$ (129) Found: C, 55.72; H, 8.41; N, 10.68.



3-Amino-cyclohex-2-enone (48c): The above general procedure, starting from 1,3-cyclohexanedione (0.3 g, 2.67 mmol) and ammonium acetate (0.24 g, 3.21 mmol) gave compound **48c**.

Nature : Yellow solid

MP : 126 ^oC (Lit.[32] 130-131).

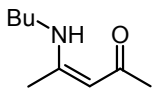
IR ($CHCl_3$) cm^{-1} : 3262, 2925, 1591, 1569, 1243.

^1H NMR 200 MHz ($CDCl_3$) : δ 1.92-1.98 (m, 2H), 2.24-2.27 (m, 2H), 2.31-2.34 (m, 2H), 4.88 (brs, 2H), 5.22 (s, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 20.7, 27.3, 34.8, 97.3, 166.8, 195.5.

Elemental analysis : Calcd: C, 64.84; H, 8.16; N, 12.60.

C_6H_9NO (111) Found: C, 64.68; H, 8.25; N, 12.78.



4-Butylamino-pent-3-en-2-one (48d): The above general procedure, starting from acetyl acetone (0.3 g, 3 mmol) and butylamine (0.26 g, 3.6 mmol) gave compound **48d**.

Nature : Yellow oil

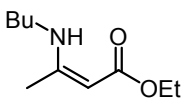
IR ($CHCl_3$) cm^{-1} : 3450, 2959, 2932, 1611, 1578, 1299, 1020, 736.

^1H NMR 200 MHz ($CDCl_3$) : δ 0.96 (t, 3H, *J* = 7.3 Hz), 1.36-1.40 (m, 2H), 1.45-1.60 (m, 2H), 1.94 (s, 3H), 2.01 (s, 3H), 3.12 (q, 2H, *J* = 7.3 Hz), 5.35 (s, 1H), 10.90 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 13.7, 20.5, 27.4, 27.8, 34.7, 49.4 96.7, 156.6, 194.7.

Elemental analysis : Calcd: C, 69.63; H, 11.04; N, 9.02

$C_9H_{17}NO$ (155) Found: C, 69.50; H, 11.21; N, 8.80



3-Butylamino-but-2-enoic acid ethyl ester (48e): The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and butylamine (0.2 g, 2.76 mmol) gave compound **48e**.

Nature : Yellow oil

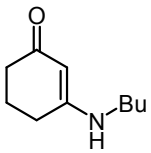
IR ($CHCl_3$) cm^{-1} : 3141, 3016, 2962, 1644, 1605, 1403, 1275, 1176, 1059, 757, 666.

^1H NMR 200 MHz ($CDCl_3$) : δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.24 (t, 3H, *J* = 7.2 Hz), 1.33-1.38 (m, 2H), 1.42-1.58 (m, 2H), 1.90 (s, 3H), 3.14 (q, 2H, *J* = 7.2 Hz), 4.10 (q, 2H, *J* = 7.2 Hz), 4.42 (s, 1H), 8.55 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 12.7, 13.6, 18.0, 19.0, 31.6, 41.6, 56.9, 81.0, 160.6, 169.4.

Elemental analysis : Calcd: C, 64.83; H, 10.34; N, 7.56.

$C_{10}H_{19}NO_2$ (185) Found: C, 64.72; H, 10.41; N, 7.42.



3-Butylamino-cyclohex-2-enone (48f): A mixture of 1,3 cyclohexanedione (0.3 g, 2.67 mmol) and butylamine (0.23 g, 3.21 mmol) gave compound **48f**.

Nature : Yellow solid

MP : 94-96 °C.

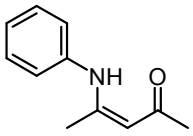
IR ($CHCl_3$) cm^{-1} : 3262, 2925, 1591, 1569, 1243.

^1H NMR 200 MHz ($CDCl_3$) : δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.32-1.38 (m, 2H), 1.55.1.59 (m, 2H), 1.88-1.94 (m, 2H), 2.32-2.42 (m, 4H), 3.05 (q, 2H, *J* = 7.2 Hz), 5.14 (s, 1H), 5.38 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 12.7, 19.3, 21.0, 28.4, 29.4, 35.0, 41.8, 94.2, 166.3, 196.1.

Elemental analysis : Calcd: C, 71.81; H, 10.25; N, 8.37.

$C_{10}H_{17}NO$ (167) Found: C, 71.65; H, 10.38; N, 8.44.



4-Phenylamino-pent-3-en-2-one (48g): The above general procedure, starting from acetyl acetone (0.3 g, 3 mmol) and aniline (0.33 g, 3.6 mmol) gave compound **48g**.

Nature : white solid

MP : 50 °C (Lit.[48] 48-49 °C).

IR ($CHCl_3$) cm^{-1} : 3450, 3032, 3020, 1620, 1571, 1509, 1278, 1188, 1024, 921,

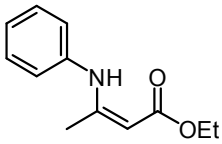
751, 697, 505.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.97 (s, 3H), 2.09 (s, 3H), 5.18 (s, 1H), 7.07-7.36 (m, 5H). 12.48 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 19.3, 28.6, 97.2, 124.1, 125.0, 128.6, 138.2, 159.7, 195.5.

Elemental analysis : Calcd: C, 75.40; H, 7.48; N, 7.99.

$C_{11}H_{13}NO$ (175) Found: C, 75.21; H, 7.56; N, 7.81.



3-Phenylamino-but-2-enoic acid ethyl ester (48h): The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and aniline (0.25 g, 2.76 mmol) gave compound **48h.**

Nature : Yellow oil

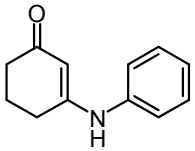
IR ($CHCl_3$) cm^{-1} : 3563, 3018, 2928, 1649, 1615, 1596, 1272, 1166, 1059, 757, 698.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.28 (t, 3H, *J* = 7.2 Hz), 1.99 (s, 3H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.69 (s, 1H), 7.05-7.34 (m, 5H). 10.38 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 14.2, 19.8, 58.3, 86.0, 124.0, 124.5, 128.7, 139.2, 158.4, 170.0.

Elemental analysis : Calcd: C, 70.22; H, 7.37; N, 6.82.

$C_{12}H_{15}NO_2$ (205) Found: C, 70.09; H, 7.15; N, 6.74.



3-Phenylamino-cyclohex-2-enone (48i): The above general procedure, starting from 1,3-cyclohexanedione (0.3 g, 2.67 mmol) and aniline (0.3 g, 2.67 mmol) gave compound **48i**.

Nature : Yellow solid

MP : 178-180 ^oC.

IR ($CHCl_3$) cm^{-1} : 3262, 2925, 2855, 1591, 1569, 1526, 1451, 1243, 1182, 670

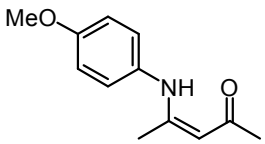
^{1}H NMR 200 MHz ($CDCl_3$) : δ 2.02 (quin, *J* = 6.5 Hz, 2H), 2.35 (t, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.5 Hz, 2H), 5.58 (s, 1H). 6.67 (brs, 1H), 7.12-7.19 (m, 3H), 7.29-7.37 (m, 2H).

^{13}C NMR 50 MHz : δ 21.6, 29.2, 36.2, 98.6, 123.8, 125.1, 128.9, 138.2, 163.7,

($CDCl_3$) 198.2.

Elemental analysis : Calcd: C, 76.98; H, 7.00; N, 7.48.

$C_{12}H_{13}NO$ (187) Found: C, 77.11; H, 7.18; N, 7.29.



4-(4-Methoxy-phenylamino)-Pent-3-en-2-one (48j): The above general procedure, starting from acetyl acetone (0.3 g, 3 mmol) and 4-methoxy aniline (0.3 g, 2.67 mmol) gave compound **48j**.

Nature : Yellow oil

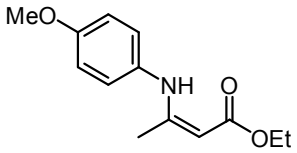
IR ($CHCl_3$) cm^{-1} : 3438, 3000, 2960, 2836, 1607, 1568, 1515, 1440, 1278, 1187, 1033, 843, 750.

^1H NMR 200 MHz ($CDCl_3$) : δ 1.90 (s, 3H,), 2.08(s, 3H,), 3.80 (s, 3H,), 5.15 (s, 1H), 6.8 (d, 2H, *J* = 8Hz), 7.03 (d, 2H, *J* = 8Hz), 12.28 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 19.5, 28.9, 55.3, 96.7, 114.1, 126.5, 131.3, 157.6, 161.1, 195.7.

Elemental analysis : Calcd: C, 70.22; H, 7.37; N, 6.82.

$C_{12}H_{15}NO_2$ (205) Found: C, 70.40; H, 7.48; N, 6.70.



3-(4-Methoxy-phenylamino)-but-2-enoic acid ethyl ester (48k): The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and 4-methoxy aniline (0.34 g, 2. 76 mmol) gave compound **48k**.

Nature : Yellow oil

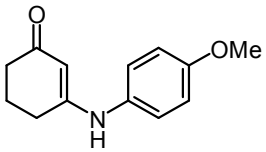
IR ($CHCl_3$) cm^{-1} : 3265, 2949, 2836, 1655, 1613, 1514, 1247, 1164, 1035, 786.

^1H NMR 200 MHz ($CDCl_3$) : δ 1.27 (t, 3H, *J* = 7.2 Hz), 1.87 (s, 3H,), 3.78 (s, 3H,), 4.15 (q, 2H, *J* = 7.2 Hz), 4.64 (s, 1H), 6.84 (d, 2H, *J* = 8.2 Hz), 7.01 (d, 2H, *J* = 8.2 Hz), 10.20 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 14.2, 19.7, 55.0, 58.2, 84.4, 113.8, 126.4, 131.8, 157.1, 159.6, 170.1.

Elemental analysis : Calcd: C, 66.36; H, 7.28; N, 5.95.

$C_{13}H_{17}NO_3$ (235) Found: C, 66.52; H, 7.39; N, 5.72.



3-(4-Methoxy-phenylamino)-cyclohex-2-enone (48l): The above general procedure, starting from 1,3-cyclohexanedione (0.3 g, 2.67 mmol) and 4-methoxy aniline (0.39 g, 3.2 mmol) gave compound **48l**.

Nature : Yellow solid

MP : 166-168 ^{o}C.

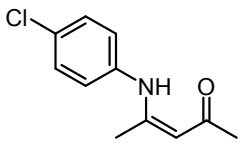
IR ($CHCl_3$) cm^{-1} : 3417, 3255, 3019, 1579, 1509, 1242, 1215, 1185, 1035, 758, 668.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.94-1.98 (m, 2H), 2.27-2.29 (m, 2H), 2.44-2.48 (m, 2H), 3.77 (s, 3H), 5.33 (s, 1H), 6.81 (d, 2H, *J* = 8 Hz), 7.02 (d, 2H, *J* = 8 Hz).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 21.7, 29.1, 36.2, 55.3, 98.0, 114.2, 125.9, 130.9, 157.3, 164.4, 197.8.

Elemental analysis : Calcd: C, 71.87; H, 6.96; N, 6.45.

$C_{13}H_{15}NO_2$ (217) Found: C, 71.96; H, 7.18; N, 6.58.



4-(4-Chloro-phenylamino)-pent-3-en-2-one (48m): The above general procedure, starting from acetyl acetone (0.3 g, 3 mmol) and 4-chloro aniline (0.45 g, 3.6 mmol) gave compound **48m**.

Nature : white solid

MP : . 61-63 ^{o}C.

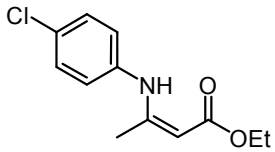
IR ($CHCl_3$) cm^{-1} : 3335, 3017, 1615, 1570, 1508, 1282, 1215, 1024, 758, 668.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 2.01 (s, 3H), 2.13 (s, 3H), 5.24 (s, 1H,), 7.08 (d, 2H, *J* = 8Hz), 7.33 (d, 2H, *J* = 8Hz), 12.46 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 19.4, 29.0, 98.1, 116.5, 124.6, 126.9, 135.5, 159.3, 196.6.

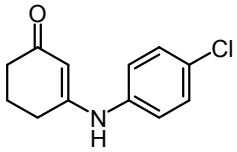
Elemental analysis : Calcd: C, 63.01; H, 5.77; N, 6.68.

$C_{11}H_{12}ClNO$ (209) Found: C, 63.27; H, 5.64; N, 6.52.



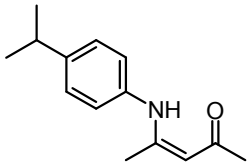
3-(4-Chloro-phenylamino)-but-2-enoic acid ethyl ester (48n): The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and 4-chloro aniline (0.35 g, 2.76 mmol) gave compound **48n**.

Nature	**:**	yellow oil
IR ($CHCl_3$) cm^{-1}	**:**	3374, 3262, 3019, 2983, 1651, 1621, 1504, 1277, 1249, 1170, 1058, 754, 667.
^1H NMR 200 MHz ($CDCl_3$)	**:**	δ 1.28 (t, 3H, *J* = 7.2 Hz), 1.95 (s, 3H), 4.16 (q, 2H, *J* = 7.2 Hz), 4.72 (s, 1H), 7.10-7.34 (m, 4H), 10.28 (brs.1H).
^{13}C NMR 50 MHz ($CDCl_3$)	**:**	δ 14.4, 19.9, 58.8, 87.2, 116.5, 124.3, 126.7, 136.1, 158.1, 170.2.
Elemental analysis $C_{12}H_{14}ClNO_2$ (239)	**:**	Calcd: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.20; H, 5.77; N, 5.72.



3-(4-Chloro-phenylamino)-cyclohex-2-enone (48o): The above general procedure, starting from 1,3-cyclohexanedione (0.3 g, 2.67 mmol) and 4-chloro aniline (0.41 g, 3.21 mmol) gave compound **48o**.

Nature	**:**	grayish solid
MP	**:**	188-190 °C (Lit.[51] 186-190 °C).
IR ($CHCl_3$) cm^{-1}	**:**	3416, 3253, 1603, 1575, 1522, 1251, 1215, 1014, 758, 668.
^1H NMR 200 MHz ($CDCl_3$)	**:**	δ 1.92-1.96 (m, 2H), 2.25-2.27 (m, 2H), 2.43-2.49 (m, 2H), 5.39 (s, 1H), 6.99 (d, 2H, *J* = 8.2 Hz), 7.19 (d, 2H, *J* = 8.2 Hz).
^{13}C NMR 50 MHz ($CDCl_3$)	**:**	δ 21.5, 29.0, 36.1, 98.6, 125.0, 129.0, 130.4, 136.8, 164.1, 198.3.
Elemental analysis $C_{12}H_{12}ClNO$ (221)	**:**	Calcd: C, 65.02; H, 5.46; N, 6.32. Found: C, 65.24; H, 5.22; N, 6.48.



4-(4-Isopropyl-phenylamino)-pent-3-en-2-one (48p): The above general procedure, starting from acetyl acetone (0.3 g, 3 mmol) and 4-isopropyl aniline (0.48 g, 3.6 mmol) gave compound **48p**.

Nature : yellow oil

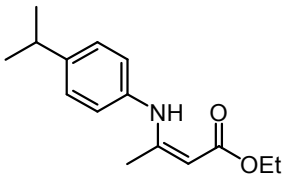
IR ($CHCl_3$) cm^{-1} : 3338, 2960, 2928, 1617, 1568, 1518, 1355, 1277, 1186, 1017, 750.

^1H NMR 200 MHz ($CDCl_3$) : δ 1.30 (d, 6H, *J* = 7.2 Hz), 1.97 (s, 3H,), 2.09 (s, 3H,), 2.90 (sept, 1H, *J* = 6.9 Hz), 5.17 (s, 1H), 7.03 (d, 2H, *J* = 8 Hz), 7.19 (d, 2H, *J* = 8 Hz), 12.45 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 19.7, 23.8, 28.9, 33.5, 97.1, 124.7, 126.9, 136.2, 146.3, 160.3, 195.7.

Elemental analysis : Calcd: C, 77.38; H, 8.81; N, 6.45.

$C_{14}H_{19}NO$ (217) Found: C, 77.45; H, 8.68; N, 6.64.



3-(4-Isopropyl-phenyl amino)-but-2-enoic acid ethyl ester (48q): The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and 4-isopropyl aniline (0.37 g, 2.76 mmol) gave compound **48q.**

Nature : yellow oil

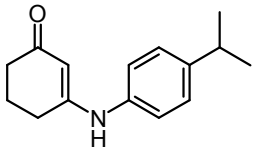
IR ($CHCl_3$) cm^{-1} : 3260, 2961, 2931, 1654, 1619, 1518, 1360, 1331, 1272, 1162, 1058, 758, 668, 544.

^1H NMR 200 MHz ($CDCl_3$) : δ 1.28 (t, 3H, *J* = 7.2 Hz), 1.39 (d, 6H, *J* = 7.2 Hz), 1.97 (s, 3H), 2.92 (sept, 1H, *J* = 6.9 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 5.10 (s, 1H,), 7.01(d, 2H, *J* = 8 Hz), 7.17 (d, 2H, *J* = 8 Hz), 10.28 (brs, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 14.4, 19.9, 23.7, 33.3, 58.3, 85.4, 124.4, 126.7, 136.9, 145.5, 158.9, 170.1.

Elemental analysis : **Calcd:** C, 72.84; H, 8.56; N, 5.66.

$C_{15}H_{21}NO_2$ (247) **Found:** C, 72.91; H, 8.68; N, 5.48.



3-(4-Isopropyl-phenyl amino)-cyclohex-2-enone (48r): The above general procedure, starting from 1,3 cyclohexanedione (0.3 g, 2.67 mmol) and 4-isopropyl aniline (0.43 g, 3.21 mmol) gave compound **48r**.

Nature : yellow solid

MP : 153-155 ^{o}C

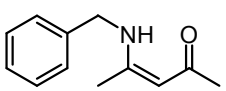
IR ($CHCl_3$) cm^{-1} : 3241, 3178, 3098, 2958, 1602, 1537, 1417, 1361, 1249, 1185, 817, 754

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.38 (d, 6H, *J* = 7.2 Hz), 1.97-2.03 (m, 2H), 2.30-2.36 (m, 2H), 2.47-2.53 (m, 2H), 2.90 (sept, 1H, *J* = 6.9 Hz), 5.50 (s, 1H), 7.06 (d, 2H, *J* = 8 Hz), 7.18 (d, 2H, *J* = 8 Hz)

^{13}C NMR 50 MHz ($CDCl_3$) : δ 21.7, 23.8, 29.2, 33.4, 36.3, 98.5, 124.0, 126.9, 135.7, 146.1, 163.7, 198.1.

Elemental analysis : Calcd: C, 78.56; H, 8.35; N, 6.11.

$C_{15}H_{19}NO$ (229) Found: C, 78.71; H, 8.19; N, 6.25.



4-Benzylamino-pent-3-en-2-one (48s)[48]: The above general procedure, starting from acetyl acetone (0.3 g, 3 mmol) and benzylamine (0.34 g, 3.20 mmol) gave compound **48s**.

Nature : yellow viscous oil

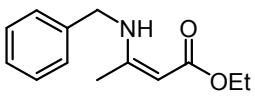
IR ($CHCl_3$) cm^{-1} : 3417, 3030, 1607, 1573, 1356, 1295, 1027, 736, 697.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.90 (s, 3H), 2.03 (s, 3H), 4.45 (d, 2H, *J* = 5.5 Hz), 5.04 (s, 1H), 7.23-7.37 (m, 5H), 11.17 (brs. 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 19.0, 27.4, 46.0, 96.3, 125.7, 127.0, 129.2, 137.4, 162.4, 194.5.

Elemental analysis : Calcd: C, 76.16; H, 7.99; N, 7.40.

$C_{12}H_{15}NO$ (189) Found: C, 76.37; H, 7.80; N, 7.22.



3-Benylamino-but-2-enoic acid ethyl ester (48t)[48]: The above general procedure, starting from ethyl acetoacetate (0.3 g, 2.30 mmol) and benzylamine (0.29 g, 2.76 mmol) gave compound **48t.**

Nature : colorless liquid

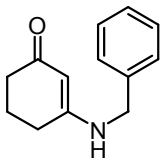
IR ($CHCl_3$) cm^{-1} : 3291, 3030, 2978, 1651, 1607, 1453, 1272, 1235, 1171, 1059, 784, 697

^1H NMR 200 MHz ($CDCl_3$) : δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.92 (s, 3H), 4.13 (q, 2H, *J* = 7.2 Hz), 4.41 (d, 2H, *J* = 5.5 Hz), 4.51 (s, 1H), 7.32-7.45 (m, 5H), 8.97 (brs, 1H)

^{13}C NMR 50 MHz ($CDCl_3$) : δ 14.3, 19.0, 46.5, 58.1, 82.9, 126.4, 127.0, 128.5, 138.5, 161.5, 170.3

Elemental analysis : Calcd: C, 71.21; H, 7.81; N, 6.39.

$C_{13}H_{17}NO_2$ (219) Found: C, 71.37; H, 7.65; N, 6.18.



3-Benzylamino-cyclohex-2-enone (48u)[51]: The above general procedure, starting from 1,3-cyclohexanedione (0.3 g, 2.67 mmol) and benzylamine (0.30 g, 3.21 mmol) gave compound **48u.**

Nature : Yellow solid

MP : 123-125 °C (Lit.[51] 122-124 °C).

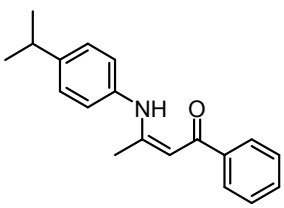
IR ($CHCl_3$) cm^{-1} : 3426, 3261, 3018, 2952, 1577, 1525, 1260, 1216, 757, 667.

^1H NMR 200 MHz ($CDCl_3$) : δ 1.91-2.01 (m, 2H), 2.24-2.30 (m, 2H), 2.36-2.42 (m, 2H), 4.21 (d, 2H, *J* = 5.5 Hz), 5.13 (s, 1H), 5.59 (brs, 1H), 7.27-7.32 (m, 5H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 21.5, 28.7, 35.9, 46.3, 96.0, 126.9, 128.1, 136.7, 165.4, 196.7.

Elemental analysis : Calcd: C, 77.58; H, 7.51; N, 6.96.

$C_{13}H_{15}NO$ (201) Found: C, 77.40; H, 7.80; N, 7.12.



3-(4-Isopropyl-phenylamino)-1-phenyl-but-2-en-1-one (48v): The above general procedure, starting from benzoylacetone (0.3 g, 1.85 mmol) and 4-isopropyl aniline (0.3 g, 2.21 mmol) gave compound **48v**.

Nature : Yellow solid

MP : 76-78 °C.

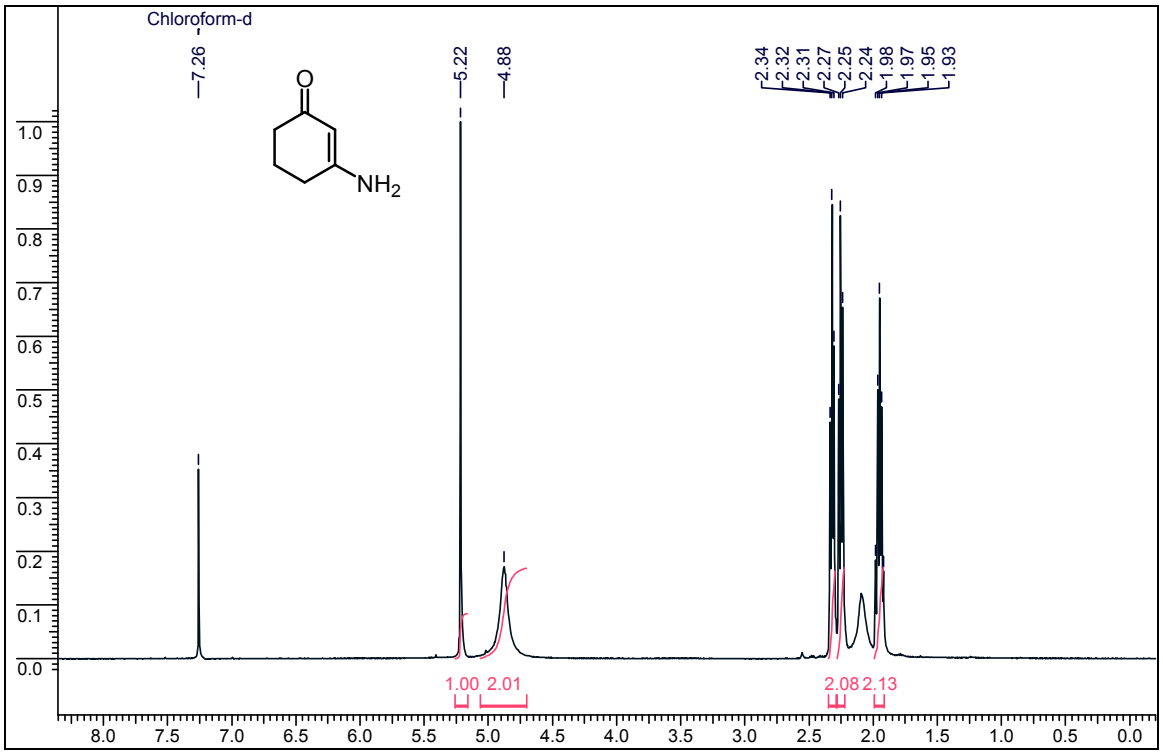
IR ($CHCl_3$) cm^{-1}	**:**	3410, 3054, 2958, 1588, 1545, 1319, 852, 744, 686.
^1H NMR 200 MHz ($CDCl_3$)	**:**	δ 1.39 (d, 6H, *J* = 7.2 Hz), 2.27 (S, 3H), 3.05 (sept, 1H, *J* = 6.9 Hz), 6.01 (s, 1H), 7.24 (d, 2H, *J* = 8.2 Hz), 7.35 (d, 2H, *J* = 8.2 Hz), 7.55-7.58 (m, 3H), 8.05 (dd, 2H, *J* = 2.2 Hz, 8.2 Hz), 13.18 (brs, 1H).
^{13}C NMR 50 MHz ($CDCl_3$)	**:**	δ 20.1, 23.7, 33.4, 93.8, 124.6, 126.9, 128.0, 130.5, 136.2, 140.0, 146.4, 162.3, 188.3.
Elemental analysis $C_{19}H_{21}NO$	**:**	Calcd: C, 81.68; H, 7.58; N, 5.01 Found: C, 81.79; H, 7.74; N, 4.86.

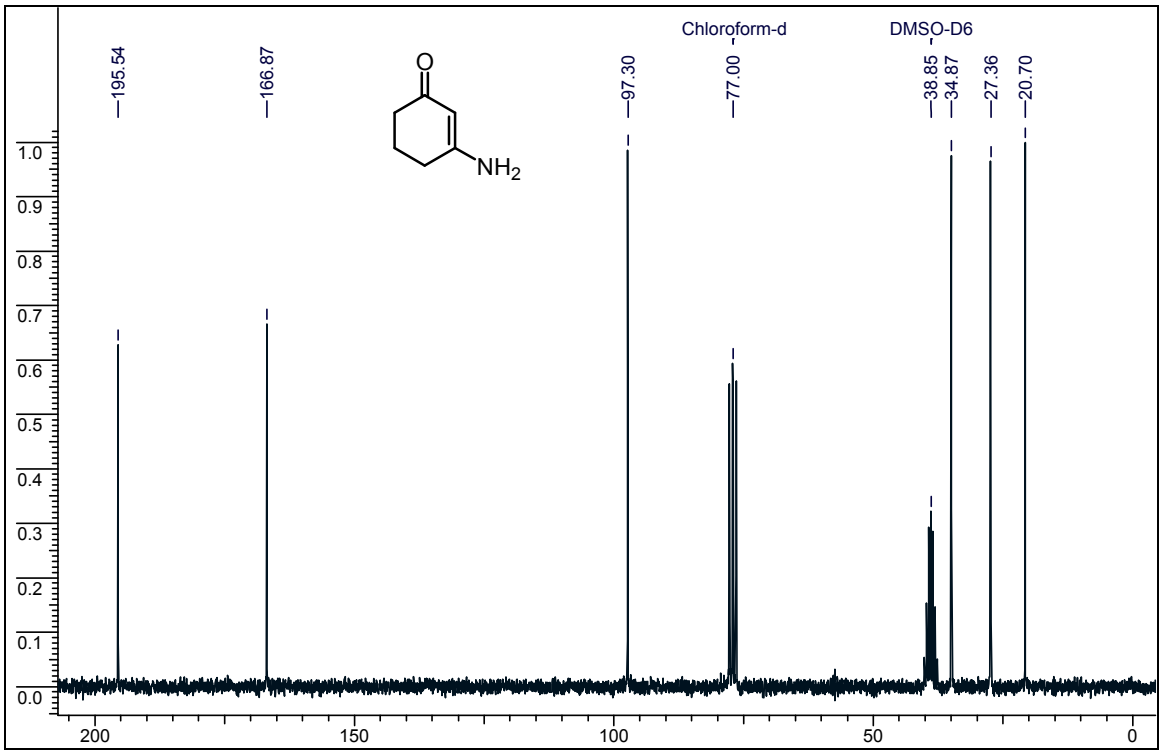
2.1.6 Spectra

Table 8. ^1H and ^{13}C spectra of some representative enaminones

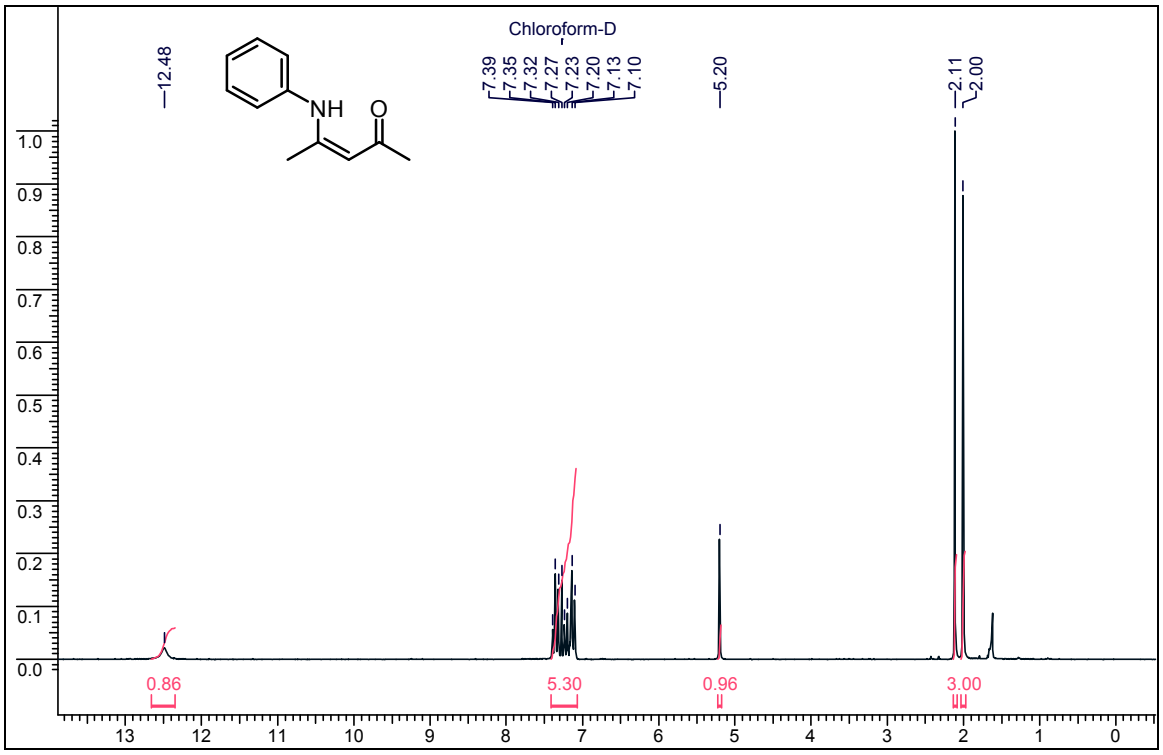
Sr. No.	Spectra
1	^1H and ^{13}C spectra of **48c**
2	^1H and ^{13}C spectra of **48g**
3	^1H and ^{13}C spectra of **48i**
4	^1H and ^{13}C spectra of **48l**
5	^1H and ^{13}C spectra of **48r**
6	^1H and ^{13}C spectra of **48v**

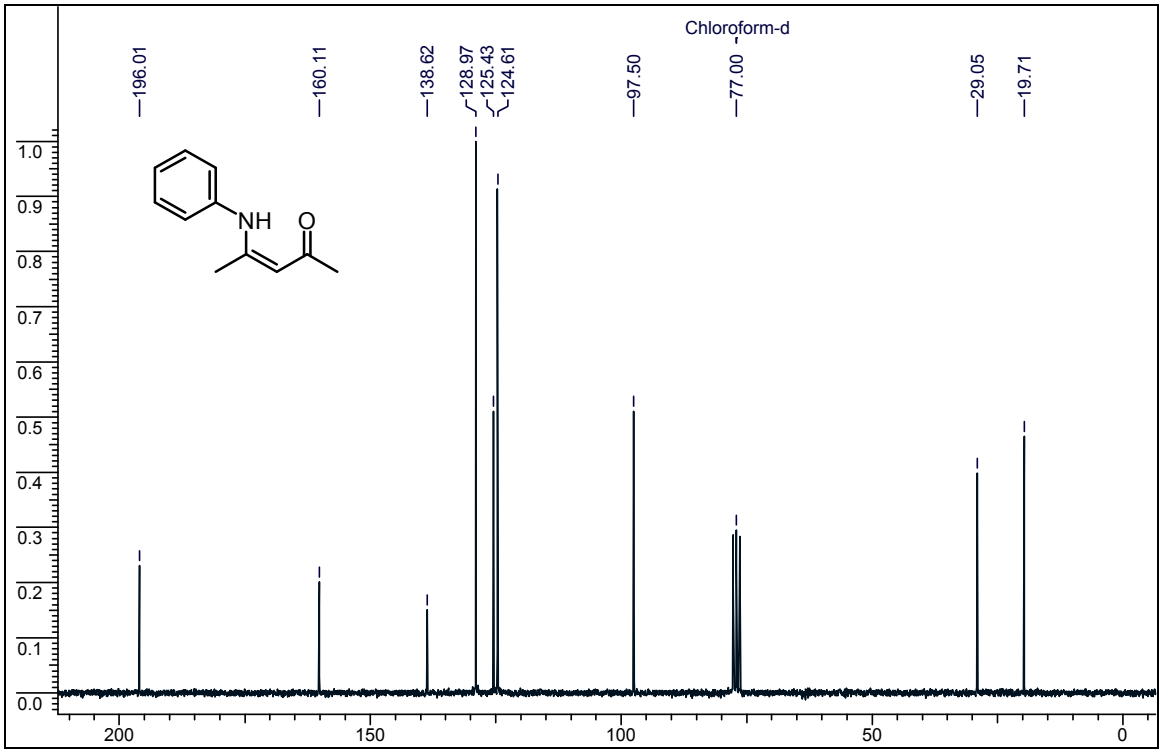
[1] ^{1}H NMR and ^{13}C NMR spectra of compound 48c



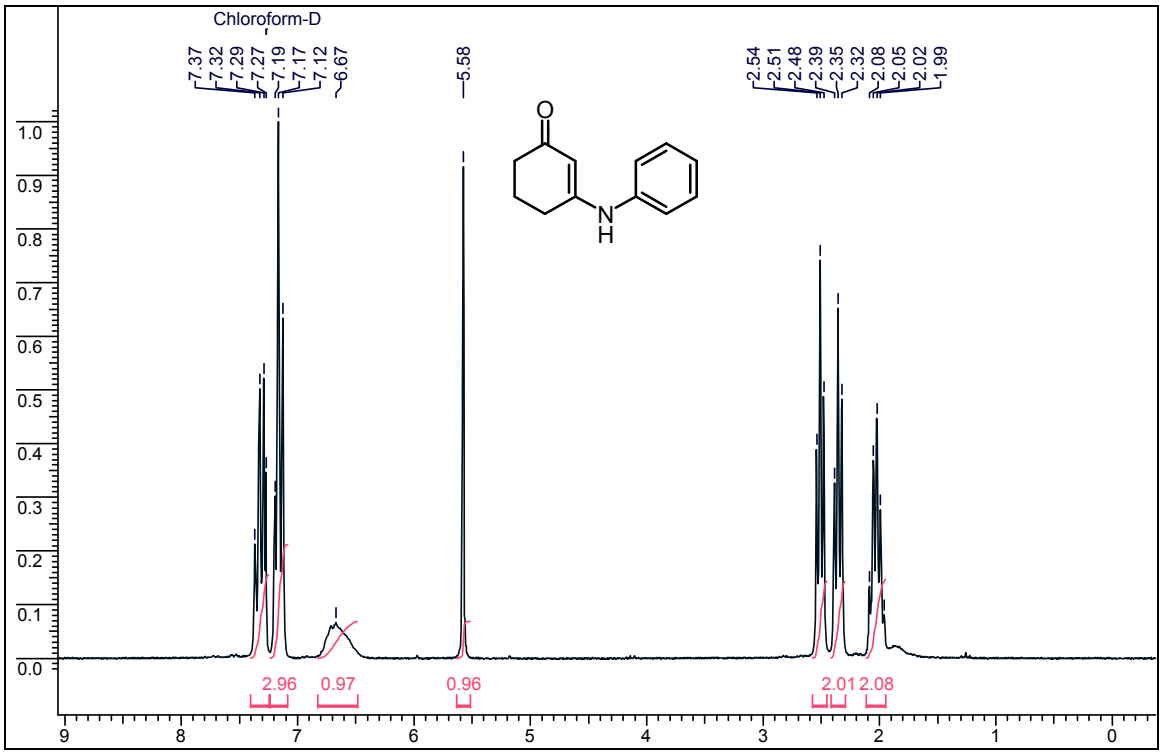


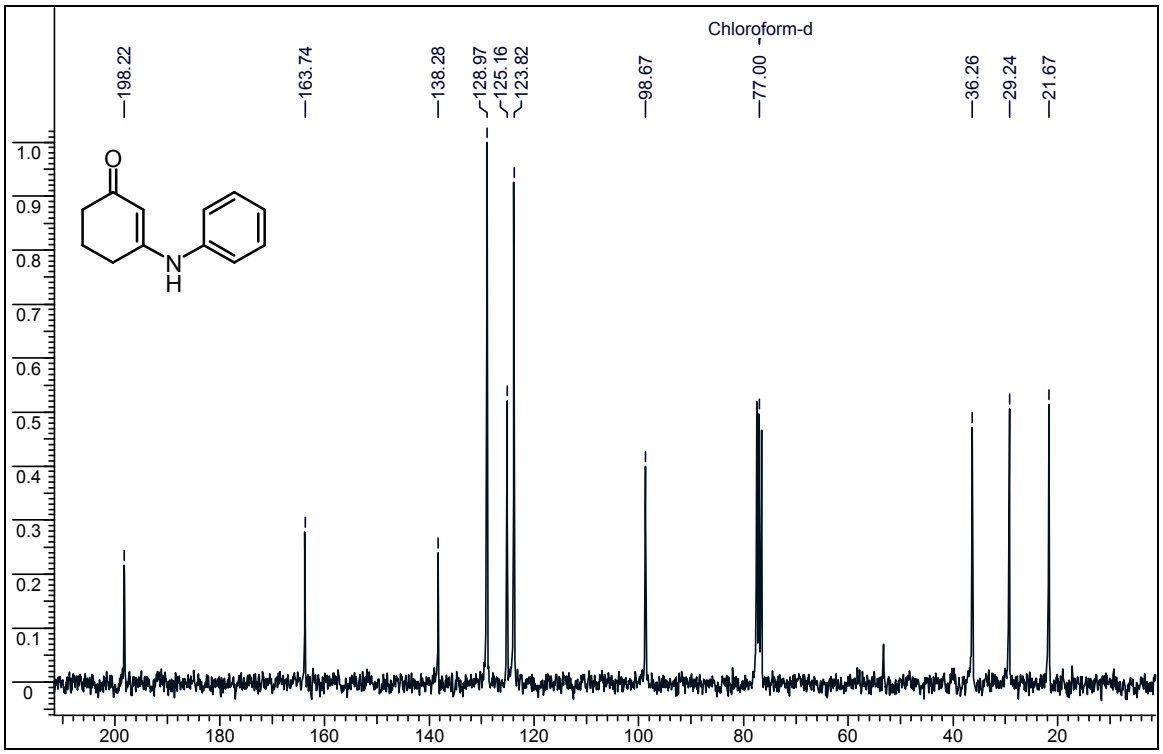
[2] ^{1}H NMR and ^{13}C NMR spectra of compound 48g



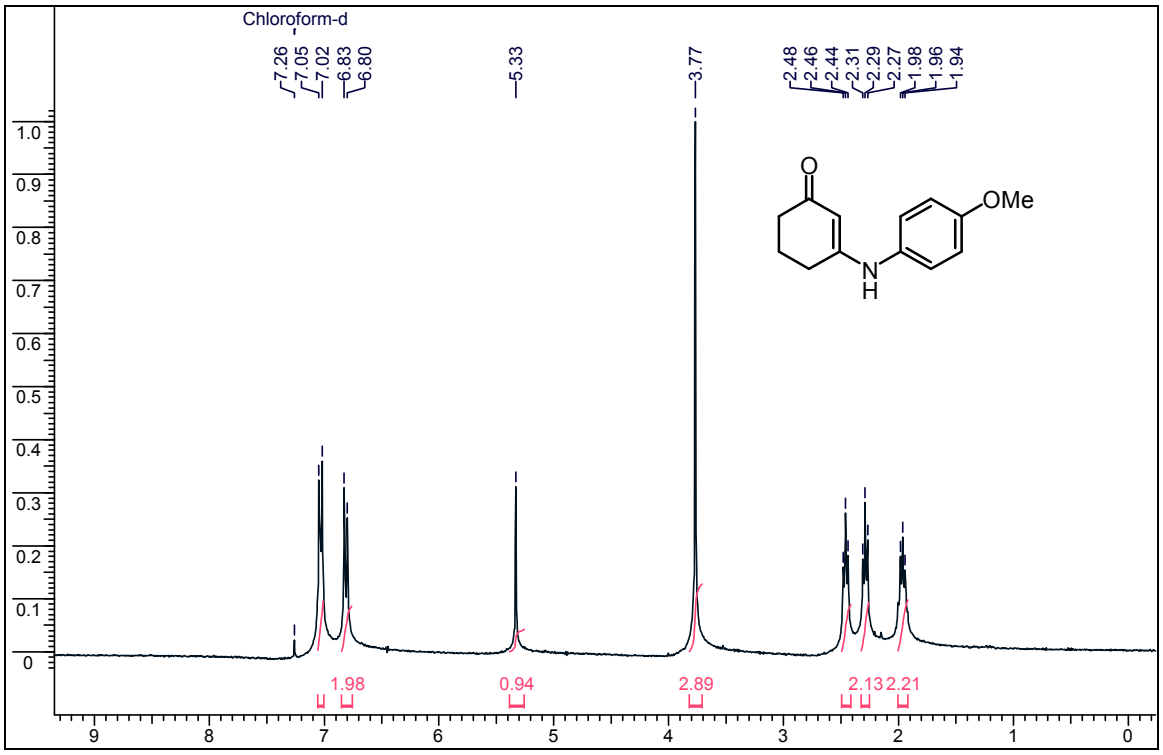


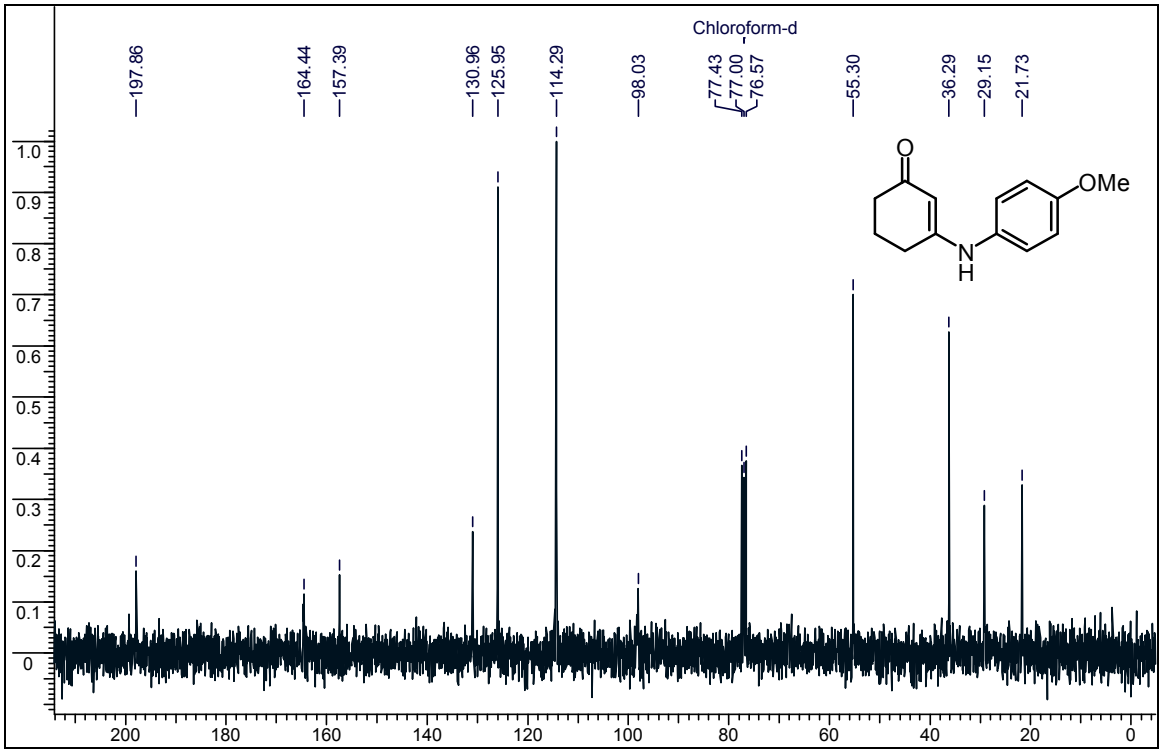
[3] ^{1}H NMR and ^{13}C NMR spectra of compound 48i



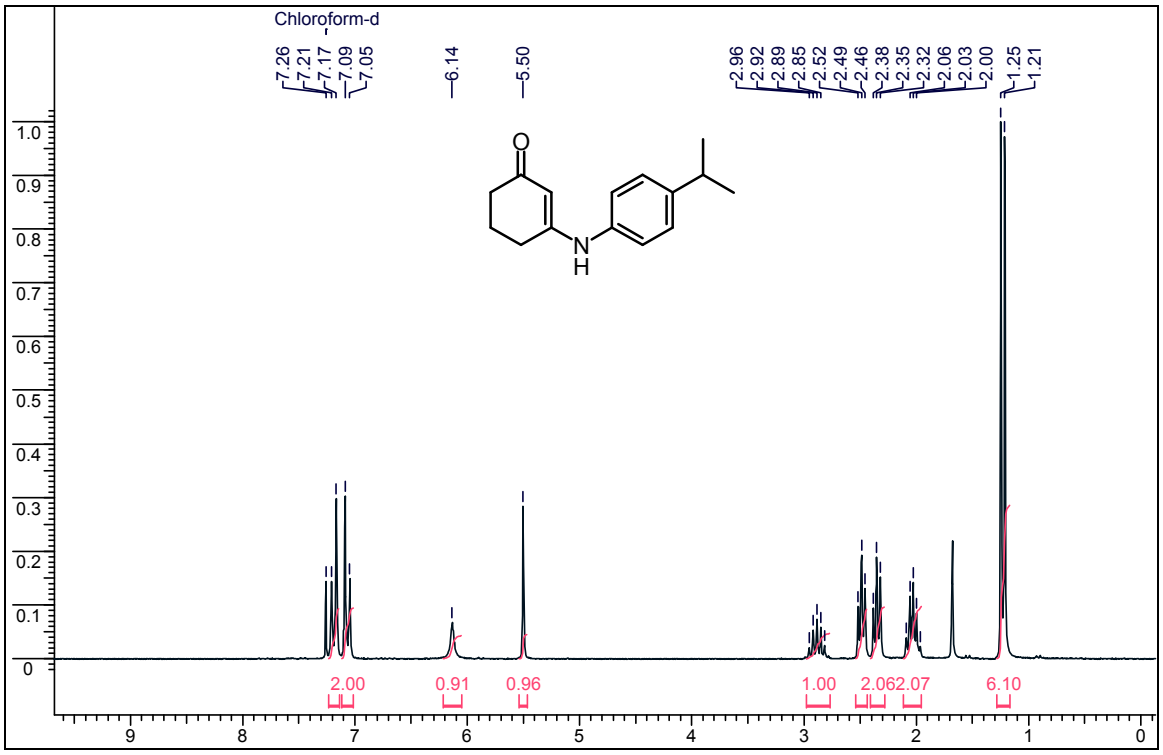


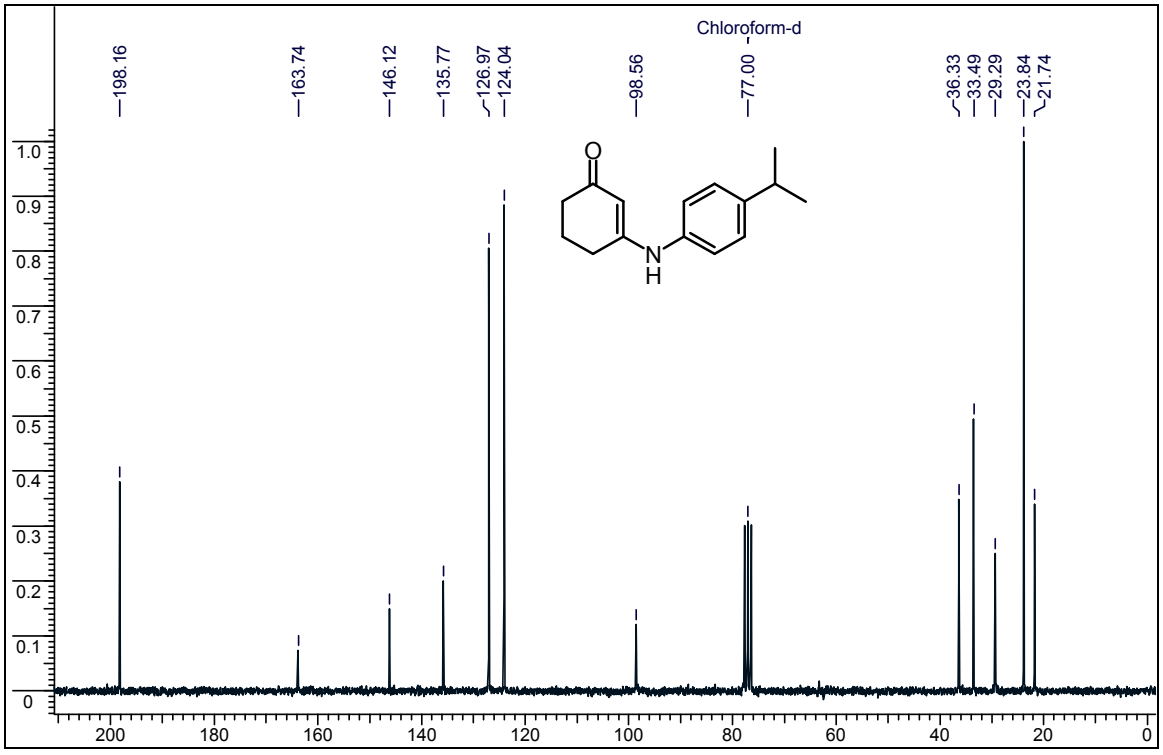
[4] ^{1}H NMR and ^{13}C NMR spectra of compound 48l



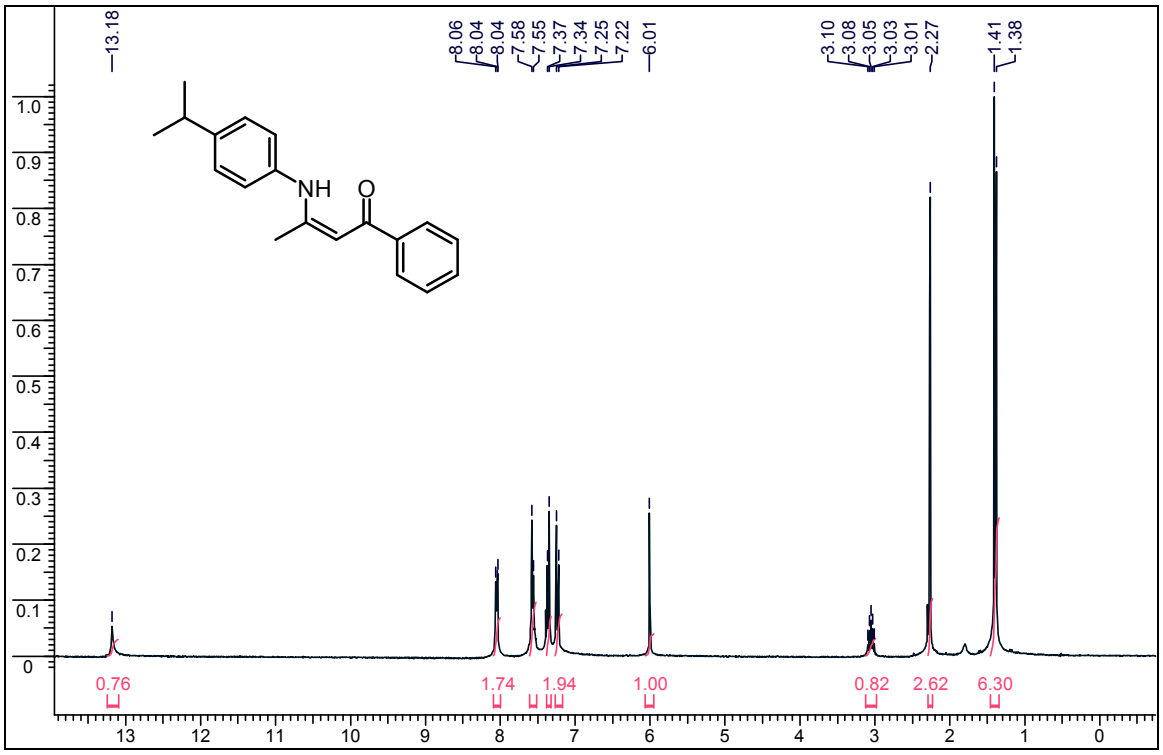


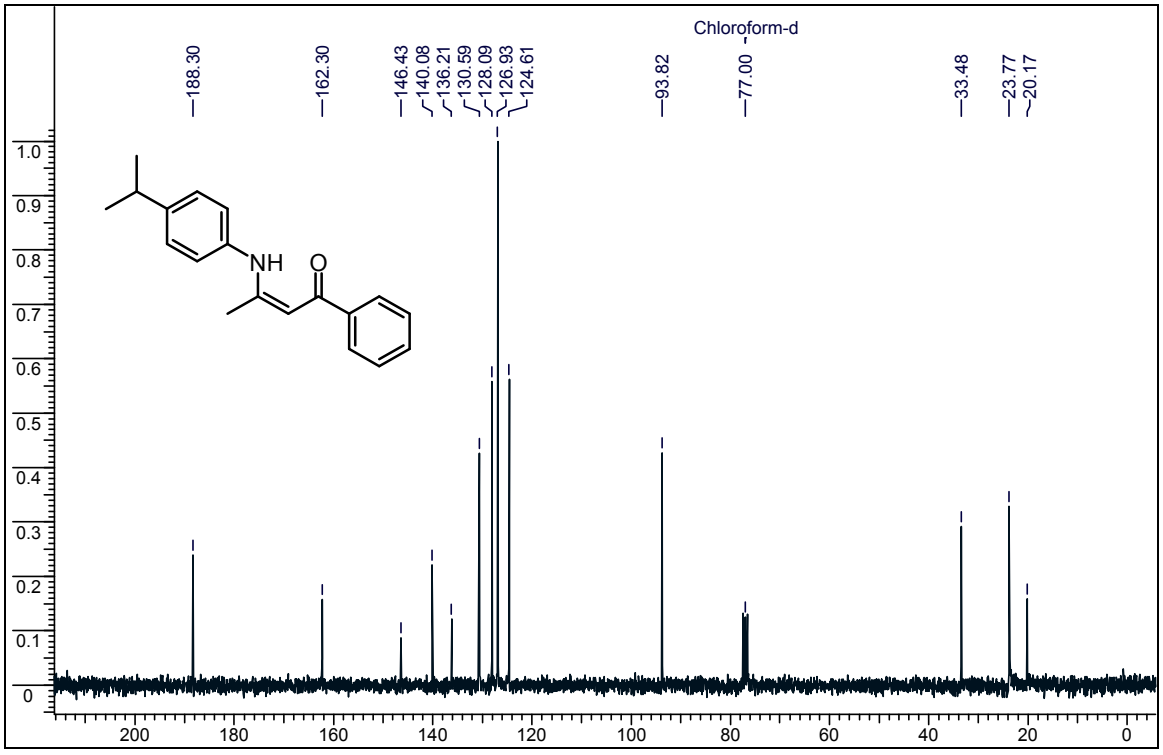
[5] ^{1}H NMR and ^{13}C NMR spectra of compound 48r





[6] ^{1}H NMR and ^{13}C NMR spectra of compound 48v





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Section-B

The current therapeutic treatment of mycoses

The Current Therapeutic Treatment of Mycoses

2.2.1 Introduction

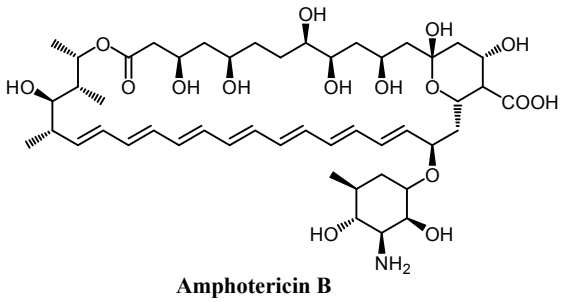
Fungi are plant-like organisms that lack chlorophyll and are classified into one of the five kingdoms of life. Among over 1,500,000 estimated species of fungi, approximately 72,000 species have been identified.[1] Fungal infections have emerged as a significant clinical problem in recent years due to number of fungal infections and increasing number of the fungal species. Consequently the exponential number of immunosuppressed and immunocompromised patients are increasing.[2] Due to the increasing frequency of fungal infections and development of resistance to the current treatment,[3] mycology is today undergoing a true regeneration. Fungi cause a range of illnesses (mycoses) ranging from the chronic to the serious infections in humans. Invasive fungal infections are nowadays a major cause of morbidity and mortality in patients such as with neutropenic, AIDS, organ transplantation, etc.[4]

2.2.2 Available antifungal drugs in Clinical Use

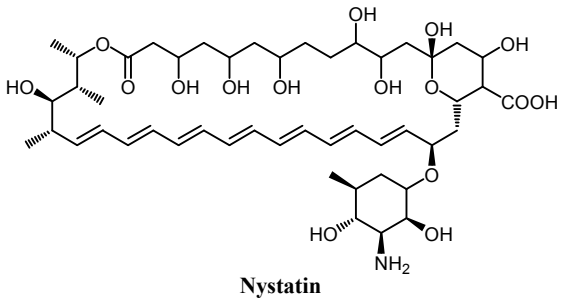
Antifungal agents currently utilized for the treatment of mycoses and their targets in fungal pathogens are as follows.

2.2.2.1 Polyene Antifungals: Amphotericin B and Nystatin

Amphotericin B is produced by *Streptomyces nodusus*, was discovered in 1955 by Gold and coworkers. The polyenes act by binding to ergosterol in the fungal cell membrane. The binding results in depolarization of the membrane and formation of pores that increases permeability to proteins and monovalent and divalent cations, eventually leading to cell death.



Amphotericin B



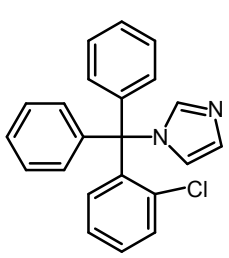
Nystatin

Figure 6.

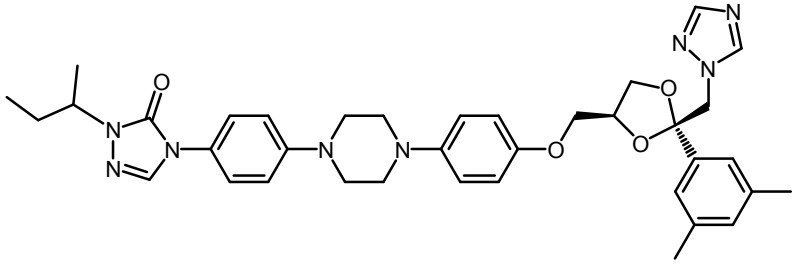
Although amphotericin B binds approximately 10 times more strongly to fungal cell membrane components than mammalian cell membrane cholesterol, it definitely disrupts mammalian cell giving rise to adverse side effects. Therefore ployenes have greater toxicities for mammalian cells and causes nephrotoxicity that limits the clinical use of polyenes. Resistant strains have also been isolated under laboratory conditions with alteration in the nature and amount of sterols present in the membrane.

2.2.2.2 Azole Antifungals:

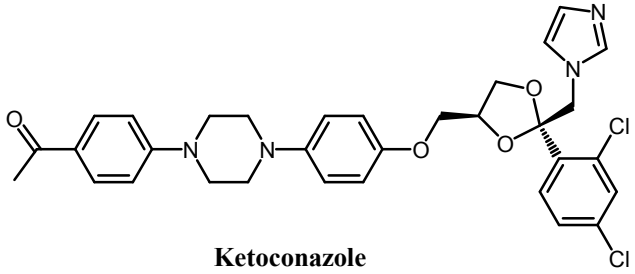
Azole antifungals are the major class of drugs which are widely used against fungal infection. Miconazole, Clortrimazole and Econazole are the topical agents and Ketoconazole, Itraconazole and Fluconazole are useful in the treatment of systemic mycoses (**Fig. 7**). The mode of action of azole antifungals is inhibition of ergosterol biosynthesis by inhibiting the fungal cytochrome P-450 3-A dependent enzyme, lanosterol 14-α-demethylase, thereby interrupting the synthesis of ergosterol. Inhibition of the enzyme leads to the depletion of ergosterol in the cell membrane and accumulation of toxic intermediate sterols, causing increased membrane permeability and inhibition of fungal growth.



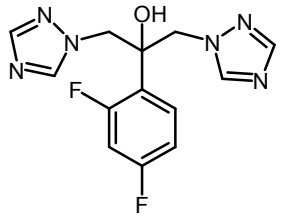
Clotrimazole



Itraconazole



Ketoconazole



Fluconazole

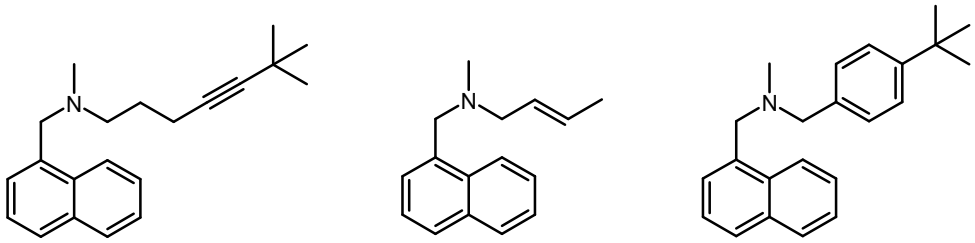
Figure 7.

Azole antifungals can also inhibit mammalian cytochrome P450-dependent enzymes involved in hormone synthesis or drug metabolism. Therefore, azole antifungals cause

hepatoxicity. Due to the increased administration of Azole antifungals for the treatment of systemic fungal infections, pathogenic yeasts are developing resistance to these drugs. Target modification is a common factor contributing to clinical resistance to azole therapy. However, azole moiety itself has been proved to be effective pharmacophores.

2.2.2.3 Allylamines as Antifungals:

Allylamines are the other class of antifungals which also work in a similar fashion like azoles by inhibiting the synthesis of ergosterol. However, allylamines act at an earlier step in the ergosterol synthesis pathway by inhibiting the enzyme squalene epoxidase leading to the accumulation of intracellular squalene that causes fungicidal effect upon exposer to the drug. Like the azoles, terbinafine causes hepatic toxicity and has the potential for drug interaction with other medications metabolized through the mammalian cytochrome P-450 pathway (**Fig. 8**).

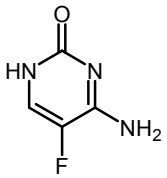


Terbinafine **Naftifine** **Butenafine**

Figure 8.

2.2.2.4 Antimetabolites: Flucytosine

Flucytosine or 5-fluorocytosine (5-FC) (**Fig. 9**) was originally developed in the 1957 as a potential antineoplastic agent. It was found to have antifungal activity in 1968 to treat candida and cryptococal infections in human. Flucytosine inhibits DNA synthesis by blocking the functions of a key enzyme thymidylate synthetase in the DNA replication.



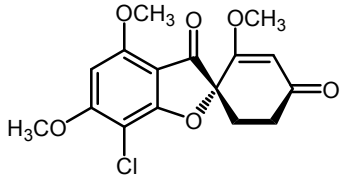
Flucytosine

Figure 9.

Flucytosine is also incorporated in fungal RNA, thereby disrupting transcription and translation. Selectivity is achieved because mammalian cells are unable to convert flucytosine to fluorouracil. But flucytosine can be converted to 5- fluorouracil (5-FU) by bacteria residing in the gastrointestinal tract. The most common adverse effects seen with flucytosine are similar to 5-FU chemotherapy (diarrhea, nausea and vomiting, bone marrow suppression) however with reduced intensity. The serious side effects associated with flucytosine are hematological, manifested as leucopenia and thrombocytopenia.

2.2.2.5 Griseofulvin:

Griseofulvin is a natural product first isolated in 1939 from *Penicillium griseofulvum*. It inhibits fungal cell mitosis by disrupting mitotic spindle formation a critical step in cellular division. Griseofulvin served as first line drug for treatment of dermatophytosis for many years. Because of its limited efficacy and untoward side effects, it is recently being replaced by itraconazole and terbinafine (**Fig 10**).



Griseofulvin

Figure 10.

Other Class of Medicinal Interest:

Besides above class of antifungals there are few other classes of antifungals such as N-Myristoyl Transferase Inhibitors, Fungal Efflux inhibitors, etc.

2.2.3 Need for Further Research in Antifungal Agents

There are mainly three challenging problems for antifungal researchers in development of an effective drug in combating severely invasive mycosis.

2.2.3.1 Toxicity of currently used antifungal agents:

The currently administered drugs are only fungistatic and causes sever side effects such as Nephrotoxicity[5] (polyenes) and hepatotoxicity[6] (azole), as the fungi shares similar cellular components and mechanism, as that of mammalian cell.

2.2.3.2 Resistance of yeasts to clinically useful antifungal agents:

The molecular basis of resistance to azole antifungals, there are three different resistance mechanisms are known in pathogenic yeasts.[7]

- First, the reduced access of the agents to the target cytochrome P450 enzyme because of increased efflux of antifungals, caused by the action of resistance gene products.
- Second, the over production of cytochrome P450 enzyme, possibly by gene amplification.
- Third resistance mechanism a structural alteration in cytochrome P450 enzyme which results in lower susceptibility to azole antifungals.

2.2.3.3 Emergence of newer strains by mutation:

The treatment of immunosuppressed and immunocompromised patients such as in Cancer and AIDS patient needs long term administration of antifungal drugs to treat the invasive infection caused by opportunistic pathogenic fungi. The consequence leads to the development of resistance of fungi to these drugs by mutation in the genes leading to the birth of newer resistant strains.

2.2.4 References

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Section-C

Synthesis of novel antifungal agents

Synthesis of novel antifungal agent

2.3.1 Introduction

Many naturally occurring as well as synthetic compounds containing the pyridine scaffold exhibit interesting pharmacological properties.[1] As a consequence many efficient procedures have been reported in the literature for the synthesis of functionalized pyridines.[2] Pyridine is one of the most popular *N*-heteroaromatics incorporated into the structure of many pharmaceuticals (**Fig. 11**). Among these, cyanopyridines with different alkyl and aryl groups were found to have antimicrobial,[3] antihypertensive,[4] cardiovascular[5] anti-inflammatory, analgesic, antipyretic properties[6] as well as 1KK-β inhibitor properties.[7]

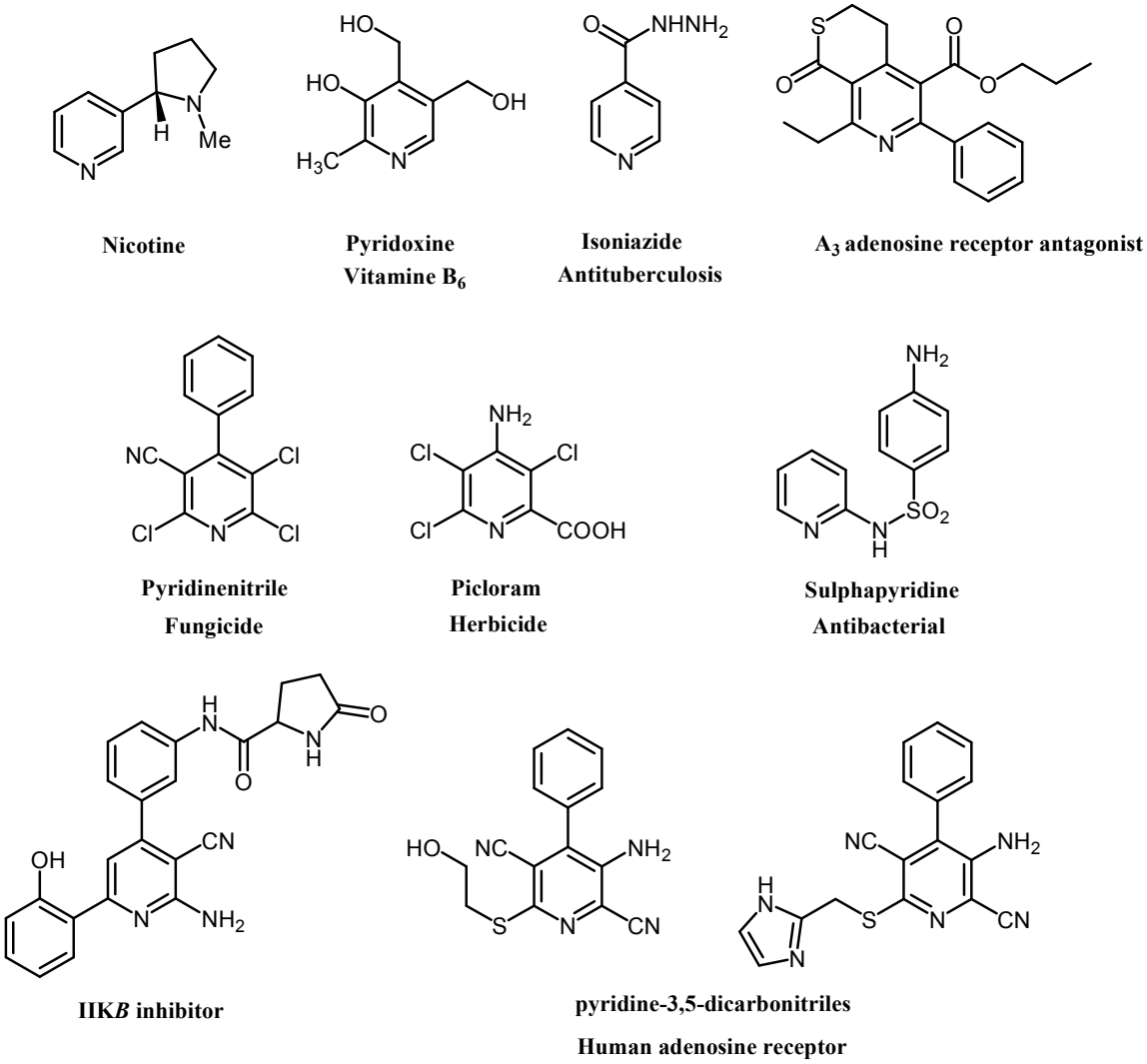


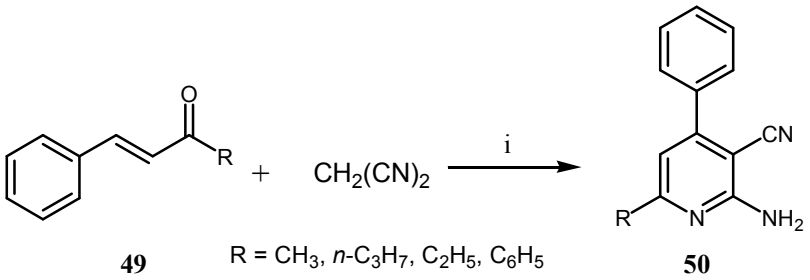
Figure 11. Biologically active pyridine derivative.

2.3.2 Review of Literature

After reviewing the literature it was observed that the 2-amino-3-carbonitrile derivative synthesized by us is not reported in literature. But few methods are available in literature for the preparation of the cyanopyridines with presence of different alkyl and aryl groups. The reported methods are discussed below.

Sakuri *et al.*[8a]

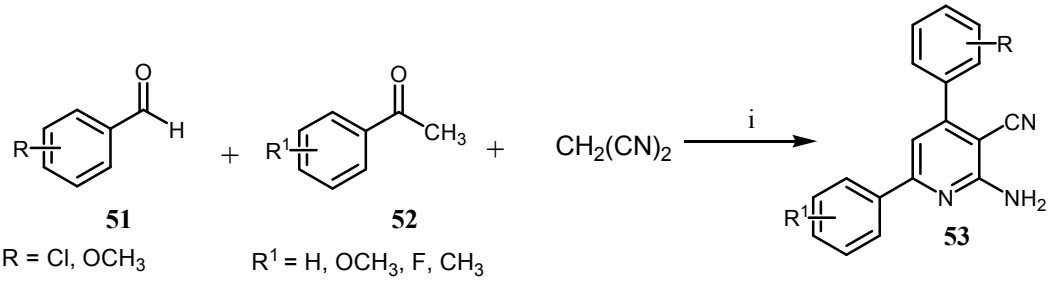
Sakuri *et al.* carried out the synthesis of 2-amino-3-cyano-4,6-dialkylpyridines **50** by refluxing a 1:1 molar proportion of α, β-unsaturated ketones **49** and malononitrile for 3-7 h in ethanol through Michael reaction, with the elimination of 1 mol of each of water and hydrogen (**Scheme 21**). For the similar examples see the references.[8b,8c]



Scheme 21. Reaction conditions: (i) ammonium acetate**,** ethanol, reflux, 3-7 h. 15-34%

Tu *et al.*[9a]

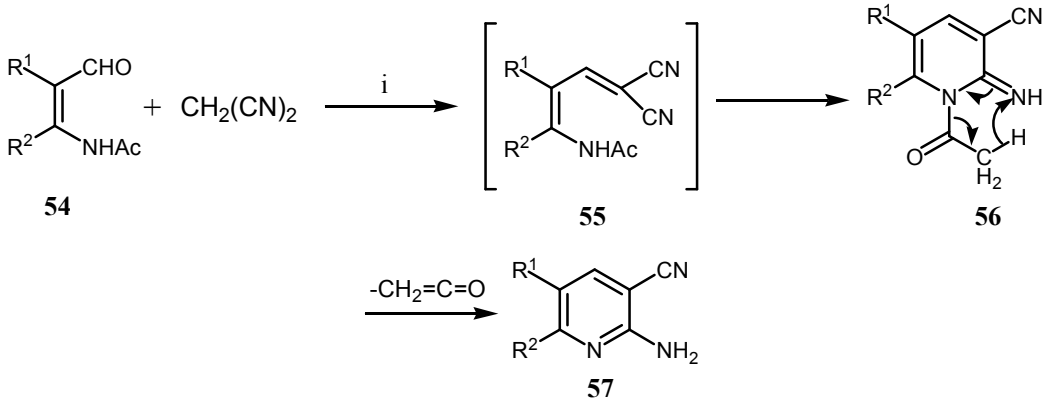
Tu *et al.* prepared a series of 2-amino-3-cyanopyridine **53** derivatives by one-pot condensation from malononitrile, aromatic aldehyde, ketone and ammonium acetate under microwave irradiation without solvent. This method has the advantage of short routine, high yields and being environmentally-friendly (**Scheme 22**). Same transformation was also carried out by Kambe *et al.* by using conventional heating mode.[9b]



Scheme 22. Reaction conditions: (i) neat, ammonium acetate, MW, 7-8 min, 72-86%

Boruah *et al.*[10]

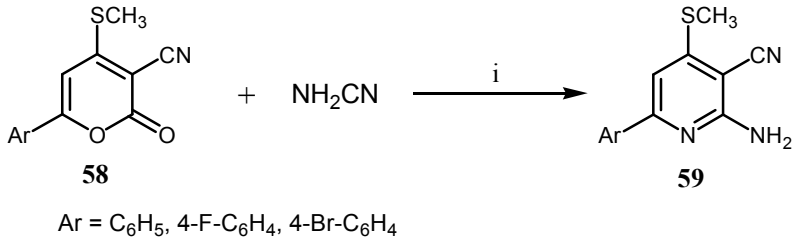
Boruah *et al.* have described a simple, facile method for the high yield synthesis of pyridine hybrids via a one-pot reaction. The formation of product **57** was envisaged to occur via Knoevenagel condensation to form the intermediate **55** followed by basic alumina catalysed intramolecular cyclization into **56**. The formation of product from intermediate **56** may be accounted by an intramolecular hydride shift from the *N*-acetyl group to the imino group followed by loss of ketene involving a six membered transition state (**Scheme 23**).



Scheme 23. Reaction conditions: (i) neat, Al_2O_3 MW, 8.5-10 min, 81-88%.

Goel *et al.*[11]

Goel *et al.* has developed a methodology for the synthesis of 2-Amino-6-aryl-4-methylsulfanylnicotinonitrile **59** through base catalyzed ring transformation by the reaction of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones **58** and cyanamide in DMF (**Scheme 24**).



Scheme 24. Reaction and conditions: (i) powdered KOH, DMF, rt, 30-50 h, 38-42%.

2.3.3 Present work

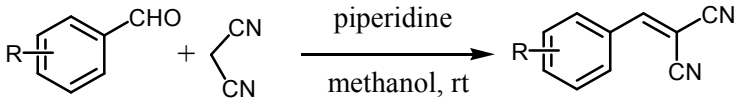
2.3.3.1 Objective

The commercially available antifungal drug amphotericin-B remains the standard therapy for life-threatening mycoses. However this drug is associated with significant toxicity including fever, headache, nausea and vomiting, and dose-limiting nephrotoxicity.[12,13] Moreover, recent studies have documented resistance of *Candida* species to fluconazole[14] and other azole and triazole drugs,[15,16] which have been used widely. A potential approach to overcome this resistance problem is to design new and innovative agents with a completely different mode of action so that no cross-resistance with the present therapeuticals can occur. In the present work we carried out short and efficient synthesis of the novel 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile and further they were evaluated for their antifungal activity.

2.3.3.2 Results and discussion

The starting arylidenemalononitriles **61(a-i)** were synthesized by reacting the corresponding aromatic aldehyde and malononitrile in methanol in the presence of a catalytic amount of piperidine at room temperature. The solid separated was filtered through a sintered funnel under suction, washed with water and dried. The results are recorded in **Table 9**.

Table 9. Syntheses of arylidenemalononitriles



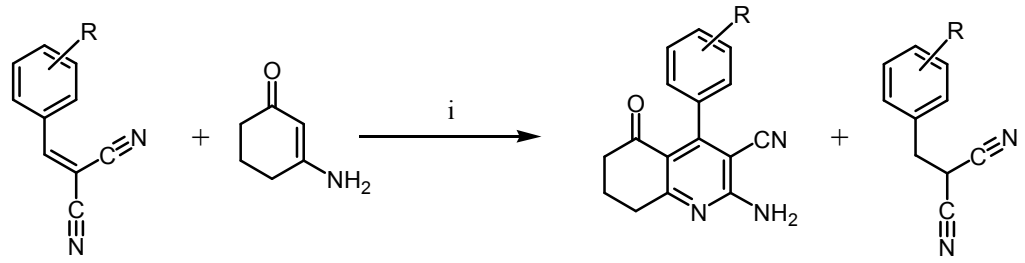
60(a-i) **61(a-i)**

Entry	**R**	**61(a-i)**	Time (h)	Yield[a] (%)
1	4-Cl	**61a**	4	85
2	4-F	**61b**	4	88
3	3-NO_2	**61c**	3	92
4	4-CH_3	**61d**	5	87
5	2-Cl	**61e**	4	84
6	3,4,5-OMe	**61f**	5	82

7	4-OMe	**61g**	5	84
8	H	**61h**	4	85
9	4-NO_2	**61i**	3	94

[a]Isolated yields

The product arylidenemalononitriles **61a-i** formed were used as such for the reaction with 3-amino-2-cyclohexen-1-one **62** in refluxing *n*-propanol for an appropriate time to afford the arylquinoline carbonitrile **63a–i** in excellent isolated yields (**Scheme 25**). The results are recorded in **Table 10**.



61(a-i) **62** **63(a-i)** **64(a-i)**

Scheme 25. Reaction conditions: (i) *n*-propanol, reflux, 4-7 h, 81-94%.

Table 10. Syntheses of compounds **63(a-i).**

Entry	**R**	**63(a-i)**	Time (h)	Yield[a] (%)
1	4-Cl	**63a**	4	92
2	4-F	**63b**	4	94
3	3-NO_2	**63c**	4	95
4	4-CH_3	**63d**	5	87
5	2-Cl	**63e**	7	82
6	3,4,5-OMe	**63f**	5	89
7	4-OMe	**63g**	6	90
8	H	**63h**	7	81
9	4-NO_2	**63i**	4	90

[a]Isolated yields after column chromatography

The products thus obtained **63a–i** were well characterized by their IR and ^{1}H NMR spectral analysis, additionally the elemental analyses were in conformity with the respective structures.

The IR spectra of **63a** showed sharp bands at 3422 and 3306 cm^{-1} (NH_2), 2215 cm^{-1} (CN), and 1685 cm^{-1} (C=O). The ^1H NMR spectrum showed triplet at δ 2.63, δ 2.13 and quintet at δ 1.72 for methylene protons of cyclohexanone ring. The by-product 2-(4-nitrobenzyl) malononitrile **64i** was isolated after the reaction of **62** with 2-(4-nitrobenzyledine) malononitrile **61i** and was completely characterized by spectral analysis. The formation of the reduced by-product **64i** indicates the dual role of arylidenemalononitrile as reactant as well as an oxidizing agent. The formation of hexahydroquinoline intermediate **65** was observed as a major product in the reaction mixture when equimolar amounts of **61i** and **62** were allowed to reflux in *n*-propanol.

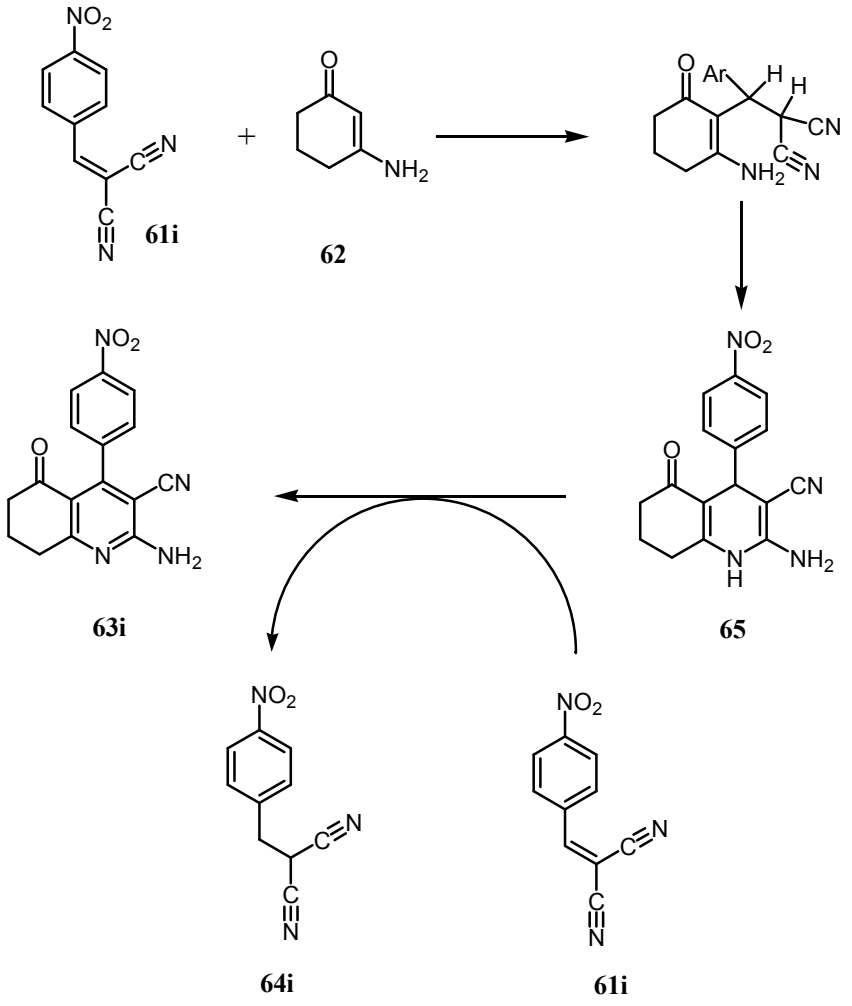


Figure 12: Mechanism

A reasonable mechanism for the formation of **63i** could be explained via initial Michael addition of **62** to **61i** followed by cyclization to hexahydroquinoline intermediate **65**

which subsequently underwent oxidation in the presence of two molar excess of the cynoolefine **61i** to the fully aromatized product **63i.** The formation of nearly equimolar proportion of compound **64i** as compared to **63i** confirms the participation of **61i** in the hydrogen transfer process (**Fig. 12**). Additional evidence for the formation of fully aromatized product **63** was obtained by the X-ray crystallographic studies on **63f**.[17] The ORTEP diagram of **63f** shows the formation of a fully aromatized product (**Fig. 13**).

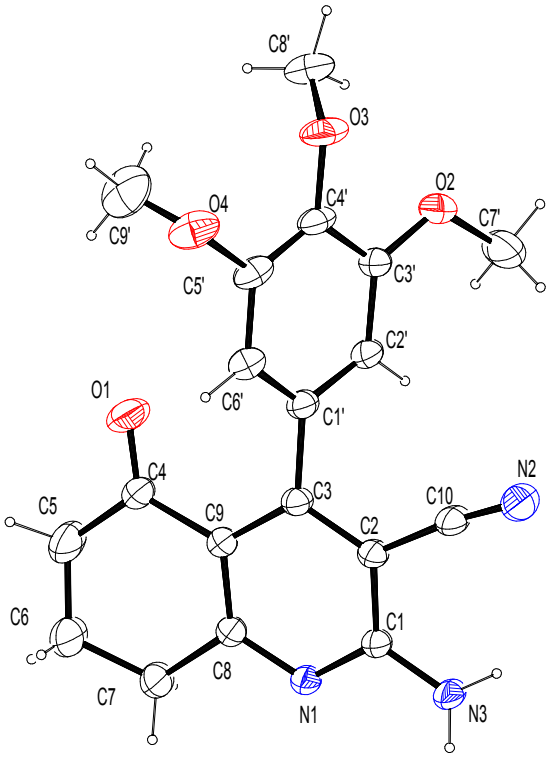


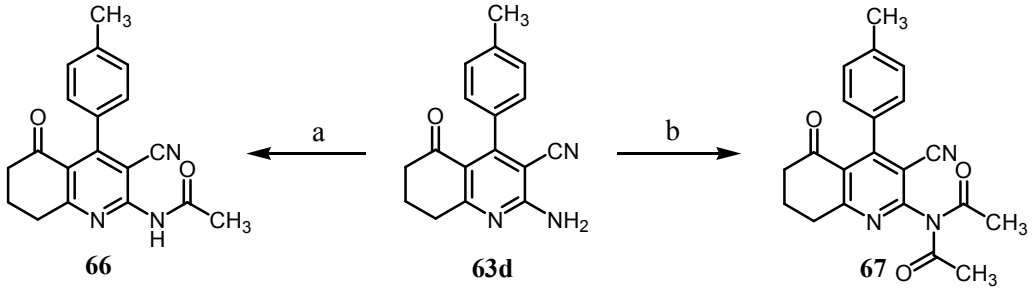
Figure 13. X-ray crystal structure of compound **63f.**

Table 11. Data collection and refinement parameters for compound **63f.**

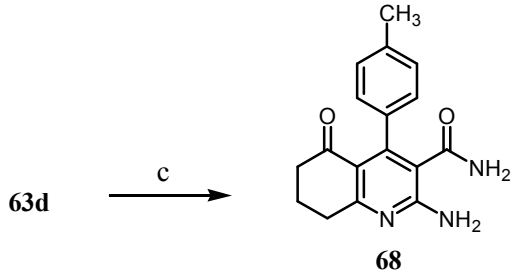
Parameter	
Emperical formula	$C_{19}H_{19}N_3O_4$
Formula weight	353.37
Temperature	293 (2)K
a, *b*, *c* (Å)	7.382 (2), 8.791 (3), 14.750 (4)
α, β, γ (°)	79.676 (5), 79.999 (5), 70.828 (4)
Crystal system space group	Triclinic, *P*-1

V (Å^3)	882.7 (4)
D_x (Mg m^{-3})	1.329
Z	2
Crystal form, colour	PLATE, pale yellow
Absorption coefficient	MULTI-SCAN
Crystal size	0.59 × 0.37 × 0.25mm
Diffractometer	CCD Area Detector
Data collection method	ω and phi Scan
Range of h, k, l	$-8 \rightarrow h \rightarrow 8$
	$-10 \rightarrow k \rightarrow 10$
	$-17 \rightarrow l \rightarrow 17$
T_{min}	0.946
T_{max}	0.977
No. of observed parameters	8429, 3093, 2635
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.41, –0.31

To study the significance of each group on core structure vis-à-vis the antifungal activity, the respective modifications of amino and cyano functional groups were carried out. Compound **63d** was selectively monoacetylated to **66** by using acetyl chloride in dry pyridine at reflux temperature for 3 h. The preparation of the diacylated derivative **67** was achieved by refluxing **63d** in acetic anhydride for 12 h. The conversion of the nitrile group in **63d** to the amide **68** was carried out by hydrolysis using 60% H_2SO_4 at 80 ºC for 24 h (**Scheme 26**).

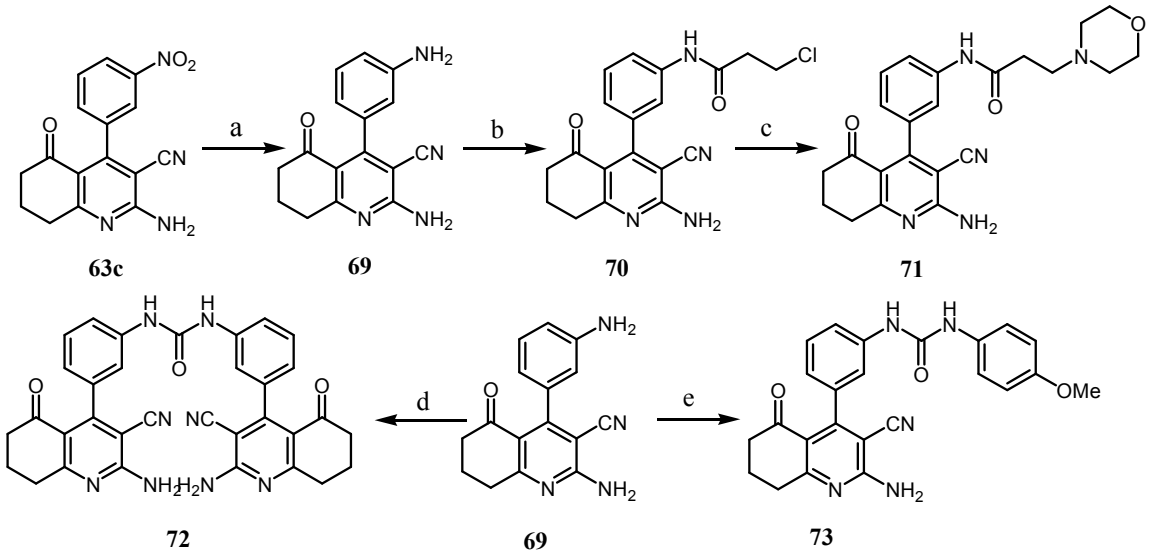


66 **63d** **67**



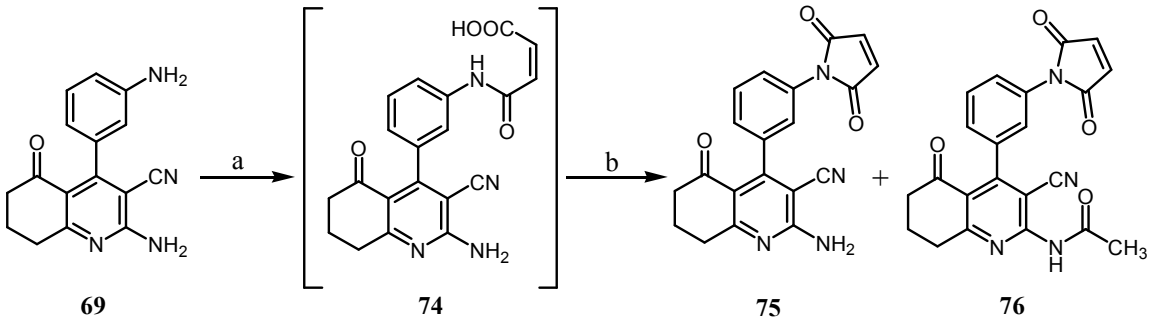
Scheme 26. Reaction conditions: (a) pyridine, acetyl chloride, rt to reflux 3 h, 85%; (b) acetic anhydride, reflux 12 h, 90%; (c) 60% H_2SO_4, 80 ºC 24 h, 88%.

To modify the functionality in the aryl ring so as to incorporate groups which can enhance biological activity, the nitro derivative **63c** (**Table 9**) was reduced to 2-amino-5-oxo-4-(3-aminophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile **69** using $SnCl_2 \cdot H_2O$ in absolute ethanol. N-Acylation of **69** with 3-chloropropionyl chloride in THF and in the presence of $NaHCO_3$ gave chloropropionyl derivative **70**. Amination of **70** was carried out by refluxing it in morpholine for 4 h to afford **71**. Compound **72** was obtained by refluxing compound **69** and carbonyldiimidazole in dry THF for 16 h. The urea derivative **73** was obtained by the reaction of compound **69** with 4-methoxyphenylisocyanate in dry THF for 12 h at reflux temperature as shown in **Scheme 27**.



Scheme 27. Reaction conditions**:** (a) $SnCl_2 \cdot 2H_2O$, ethanol, reflux 3 h, 97%; (b) 3-chloropropionyl chloride, THF, 0 ºC - rt, 2 h, 92%; (c) morpholine reflux 4 h, 87%; (d) carbonyldiimidazole, THF, reflux 16 h, 80%; (e) 4-methoxyphenyl isocyanate, THF, reflux 12 h, 86%.

Likewise, reaction of **69** with maleic anhydride gave maleanilic acid derivative **74** which was used as such for the next step, without any further purification and characterization, to obtain a mixture of the desired maleimide derivative **75** and N-acylated product **76** (in 60% and 32% yield, respectively) by heating it with a mixture of fused NaOAc and acetic anhydride at 60 ºC for 1 h as shown in **Scheme 28.** The products **75** and **76** were separated by column chromatography and completely characterized by spectral and elemental analyses.



69 **74** **75** **76**

Scheme 28. Reaction conditions: (a) maleic anhydride, THF, rt, 12 h, 95%; (b) acetic anhydride, NaOAc, 60 ºC, 1 h, (**75**: 60%, **76**: 32%).

2.3.4 Antifungal activity

All the synthesized compounds were screened for their *in vitro* antifungal activities. For preliminary screening the antifungal tests were carried out by disc-diffusion method as described earlier.[18]

Table 12. *In vitro* antifungal activity detection by using disc-diffusion method.

Sr. No	Comp. (µg/disc)	Zone of inhibition (mm)														
		C.albicans 1			*C.albicans* 2			*F. oxysporum* 1			*F. oxysporum* 2			*Mucor*		
		40	60	100	40	60	100	40	60	100	40	60	100	40	60	100
1	**63a**	2	3	5	2	3	5	–[a]	4	7	–	4	7	–	7	10
2	**63b**	2	4	6	2	4	6	–	3	7	–	3	7	–	9	12
3	**63c**	3	4	7	3	4	7	3	4	7	3	4	7	–	9	15
4	**63d**	3	4	7	3	4	7	2	3	7	2	3	7	–	10	14
5	**63e**	–	2	4	–	2	4	2	3	6	2	3	6	–	7	10
6	**63f**	–	–	7	–	–	7	2	2	4	2	2	4	–	–	–

7	**63g**	–	3	4	–	3	4	–	–	6	3	–	6	–	–	–
8	**63h**	–	2	6	–	2	6	–	3	6	3	3	6	–	–	–
9	**63i**	–	3	5	–	3	5	–	2	3	–	2	3	–	–	–
10	**66**	–	3	7	–	3	7	–	3	5	–	3	5	–	–	–
11	**67**	–	4	6	–	4	6	–	2	4	–	2	4	3	7	10
12	**68**	–	2	4	–	2	4	–	–	4	–	2	4	–	–	–
13	**69**	–	3	6	–	3	6	2	3	5	2	3	5	5	7	10
14	**71**	2	2	7	2	2	7	2	3	5	2	3	5	–	–	–
15	**72**	3	3	7	3	3	7	–	2	6	–	2	6	–	–	–
16	**73**	2	3	6	2	3	6	–	–	2	–	–	2	–	–	–
17	**75**	3	5	7	3	5	7	3	3	7	3	3	7	–	–	–
18	**76**	2	2	7	2	2	7	2	2	6	2	2	6	8	9	11
19	**A**	2	4	7	2	4	7	3	5	7	3	5	7	–	–	–
20	**B**	4	7	12	4	7	12	2	6	9	3	6	9	5	7	10

Positive control, **A** = Cycloheximide and **B** = Amphotericin B.

Negative control, DMSO (50% v/v).

[a] No inhibition.

Amphotericin B (ergosterol synthesis inhibitor) and cycloheximide (protein synthesis inhibitor) were used as a positive control in the disc diffusion method. The yeast cell suspension for *Candida albicans* strains 1 and 2 (human pathogen), mycelial suspension for *Fusarium oxysporum* strains 1 and 2 (plant pathogen), and *Mucor sp.* (saprophyte) (100 µl) were spread on sterile YPG (yeast extract, 0.3%, peptone, 0.5%, and glucose, 1%) and PDA (potato, 20% dextrose, 2%) agar plates separately. Sterile Whatman filter paper No. 1 discs were placed on each plate. Different concentrations of the compounds were added on the filter paper discs. DMSO (50% v/v) without inhibitor was used as a control. The plates were then incubated at 28 ºC for 24 h and antifungal activity was evaluated by measuring the diameter of zone of inhibition against that of the test organisms (**Table 12**).

Before discussing the structure–activity relationship it must be pointed out that the ratio between the highest and the lowest concentrations of compounds is only 2:3. The effective concentrations sometimes alter deceptively in the biological experiments because of conditions of living things. Moreover, since the antifungal assays are done

using paper discs the structure–activity relationship is described purely on a qualitative basis with respect to substituents incorporated in the molecular skeleton.

It was observed that activity of the synthesized compounds was dependent on the substituent present at 3 or 4 position of the phenyl ring in 2-amino-3-cyano-4-arylpyridine moiety. In terms of structure–activity relationship, 2-amino-5-oxo-4-(3-nitro-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile, **63c** with a nitro group substituent in the meta position showed, in general, a more potent antifungal activity than other compounds synthesized (**Table 9**). Thus the compound with meta substituted $–NO_2$ group **63c** had prominent activity against all the species studied than the compound with para substituted $–NO_2$ group **63i**. The compound **63i** did not have any activity against *Mucor* but compound **63c** showed good activity against *Mucor*. Compound **63h** without any substitution on phenyl ring showed poor activity against *C. albicans* 1 and 2, *F. oxysporum* 1 and no activity against *Mucor*, but showed comparable activity with those of the standards against *F. oxysporum* 2. The compound with halogen substituents showed good to moderate activity. Among the halogen substituted compounds **63e** showed the better activity than **63a** and **63b** against *F. oxysporum* species emphasizing the importance of the positioning of the functional group on the aryl ring. It was observed that compounds **63a**, **63b**, **63c**, and **63d** were effective against *C. albicans* 1 and 2 whereas compounds **63c**, **63d**, **63e**, and **63f** were more effective against *F. oxysporum* 1 and 2 and compounds **63a–e** were effective against *Mucor sp.* at higher concentration, the results are comparable with those of the standards. The studied compounds could be divided into two groups. One group includes compounds **63a** to **63i** which are generic and the second group includes compounds **66–76** with modification of functional groups present in parent compounds. N-Diacetylation of compound **63d** gave compound **67**, which showed poor activity as compared to **63d** in the case of *C. albicans* 1, 2 and *F. oxysporum* 1, 2. But in the case of *Mucor* compound **67** showed good activity, while compounds **66** and **67** which were acylated derivatives of compound **63d** had less activity than parent compound having free NH_2 group.

All the synthesized compounds **71–76** from **Schemes 27** and **28** were effective against both the species of *C. albicans* and *F. oxysporum*, but compounds **71–75** did not show activity against *Mucor*. Compound **69** and its monoacylated maleimide derivative showed good activity against *Mucor*. Compounds **63c**, **63d**, and **72** showed activity

comparable to that of cycloheximide. It was compound **76**, the N-acetylated maleimide derivative, which showed the best activity against all the fungal species studied and greater activity than amphotericin B against *Mucor*.

2.3.4.1 Yeast-hypha transition experiment

Most of the pathogenic fungi change their morphology viz. unicellular yeast or filamentous hypha for survival and proliferation in the host. The yeast-hypha transition experiment was carried out in a model non-pathogenic fungus *Benjaminiella poitrasii* to check the effect of compounds as described earlier.[19,20]

Yeast inoculum was grown in YPG medium for 24 h at 37 ºC and the transition was studied in YP medium at 28 ºC. The yeast cells were inoculated in YP broth (with and without compounds) at 28 ºC for 4 h and the percentage of cells forming germ tubes was assessed as described earlier.[21]

Nikkomycin Z (chitin synthase inhibitor) was used as a positive control in the yeast-hypha transition experiment (**Table 13**). It was seen that compounds **63a**, **63b**, **63e-63g**, **63i**, **68**, **69**, **71-73**, **75**, and **76** exhibited 95-99% of inhibition while **63c**, **63d**, **63h**, **66**, and **67** showed 85-95% of inhibition at 20µg/ml. Minimum inhibitory concentration

Table 13. Effect of compounds on yeast-hypha transition.

Group	Compounds (20 µg/ml)	Inhibition (%)
1	**63a, 63b, 63e, 63f, 63g, 63i, 68, 69, 71, 72, 73, 75, 76**	95-99
2	**63d, 63h, 66, 67**	90-95
3	**63c**	85-90
4	Nikkomycin Z (4µg/ml)	>90

Standard used was Nikkomycin Z (4 µg/ml)

(MIC) of the compounds was estimated by disc-diffusion method. Cycloheximide showed 2-7 mm inhibition in case of *C. albicans* and 3-7 mm inhibition for *F. oxysporum* at 40 µg/ml. While amphotericin B showed 4-12 mm inhibition in *C. albicans*, 2-9 mm inhibition in *F. oxysporum*, and 5-10 mm inhibition in *Mucor* at 40 µg/ml. Therefore for other compounds the zone of inhibition 2 mm at 28 ºC for 24 h was considered as minimum inhibitory concentration (MIC) (**Table 14**).

Table 14. Minimum inhibitory concentration values of the compounds against the fungal species using disc diffusion method.

Sr. No.	Comp.	Concentration of compounds (µg/ml)				
		C. albicans	*C. albicans*	*F. oxysporum*	*F. oxysporum*	*Mucor*
1	**63a**	40	40	60	60	60
2	**63b**	40	40	40	40	60
3	**63c**	40	40	20	20	60
4	**63d**	40	40	40	40	60
5	**63e**	60	60	40	40	60
6	**63f**	100	100	20	20	–[a]
7	**63g**	60	60	100	100	–
8	**63h**	60	60	60	60	–
9	**63i**	60	60	60	60	–
10	**66**	60	60	60	60	–
11	**67**	60	60	60	60	40
12	**68**	60	60	100	100	–
13	**69**	60	60	40	40	40
14	**71**	40	40	40	40	–
15	**72**	40	40	60	60	–
16	**73**	40	40	100	100	–
17	**75**	40	40	40	40	–
18	**76**	40	40	40	40	40
19	**A**	40	40	20	20	–
20	**B**	40	40	40	40	40

Standard used were cycloheximide and amphotericin B.

[a] Not detected.

2.3.4.2 Non-radioactive chitin synthase assay

Chitin synthase activity from *B. poitrasii* was estimated with and without compounds (4 µg/ml) using a non-radioactive chitin synthase assay according to Lucero *et al.*[22]

It was seen that compounds **63d**, **72**, **75**, and **76** inhibited 91–95% chitin synthase activity, **63a-63c**, **63e-63g** exhibited 80-90% of inhibition. The rest of the compounds exhibited substantial percentage of inhibition in the range of 60-80% (**Table 15**).

Table 15. *In vitro* antifungal activity of selected compounds for the inhibition of chitin synthase enzyme from *B. poitrasii.*

Group	Compounds	Inhibition (%)
1	**63d**, **72**, **75**, **76**	91-95
2	**63e**	86-90
3	**63a**, **63b**, **63c**, **63f**, **63g**	81-85
4	**69**	76-80
5	**73**	71-75
6	**63h**, **66**, **68**	66-70
7	**63i**, **67**, **71**	61-65
8	Nikkomycin Z	>90

2.3.5 Antiproliferative activity: materials and methods

Human hepatocellular carcinoma Hep3B and human mammary adenocarcinoma (MCF-7) cell lines were obtained from American Type Culture Collection (Manassas, VA, USA), and maintained in our in-house National Cell Repository. Cells were maintained as a monolayer in culture medium consisting of nutrient media MEM supplemented with heat-inactivated fetal bovine serum (10%), penicillin (100 μg/ml), and streptomycin (100 μg/ml) (Invitrogen Life Technologies, MD, USA). The cells were grown at 37 ºC in 5% CO_2 and humidified air atmosphere. Stock solutions of all compounds were prepared in DMSO (concentration of 4 mg/ml) and afterwards diluted to the required concentration in cell culture media. The 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) was dissolved (1 mg/ml) in MEM (without phenol red) and filtered through a Millipore filter, 0.22 μm, before use. The generic compound **63c** and the functionalized derivative **76** prepared from **63**c which showed the highest antifungal activity were taken up for the determination of their antiproliferative activity.

2.3.5.1 Antiproliferative activity-MTT cell proliferation assay

Hep3B and MCF-7 cells were plated at a density of 10,000 cells per well in 96-well tissue culture plates. Cells were allowed to adhere for 24 h at 37 ºC and then treated with various concentrations (0, 1, 10, 100, 1000, and 2000 µg/ml) of compounds diluted in culture medium, for additional 48 h. In the cells in control wells a culture medium consisting of corresponding concentration of DMSO only was added. After 48 h of drug treatment growth medium was removed from each well containing cells and fresh culture medium was added to each well. Cells were allowed to grow for another 24 h

Thereafter, cell proliferation was assessed by replacing culture medium with 50 µl MEM containing 1 mg/ml MTT and subsequently incubated for additional 4 h at 37 ºC. The medium was then aspirated off and formazan crystals were solubilized in 50 µl of 2-propanol. The optical density was read on a microplate reader at 570 nm using 630 nm as a reference filter against a blank prepared from cell-free wells. Absorbance given by cells treated with the carrier DMSO alone was taken as 100% cell growth. All assays were performed in triplicate.

2.3.5.2 Antiproliferative activity

The antiproliferative activity of all the three compounds, **63c** and **76** and amphotericin B, was tested against human cancer cells MCF-7 and Hep3B, which were grown *in vitro.*

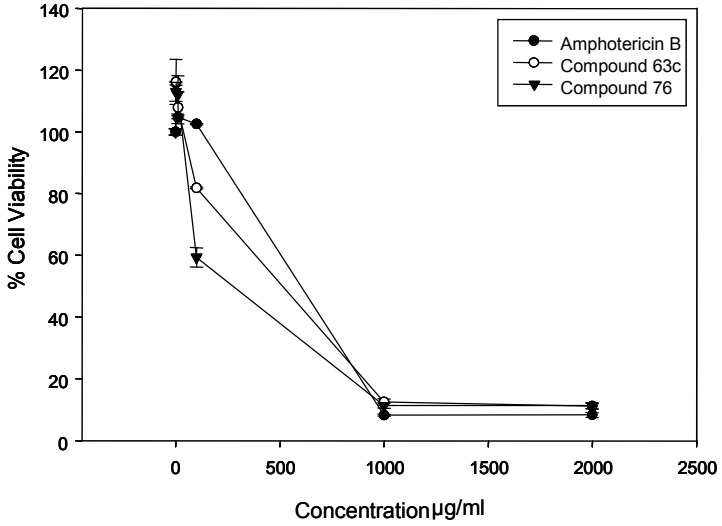


Figure 14. Antiproliferative activities of compounds in MCF-7 cells.

Compounds **63c** and **76** as well as amphotericin B at high doses were toxic to both MCF-7 (**Fig. 14**) and Hep3B cells (**Fig. 15**).

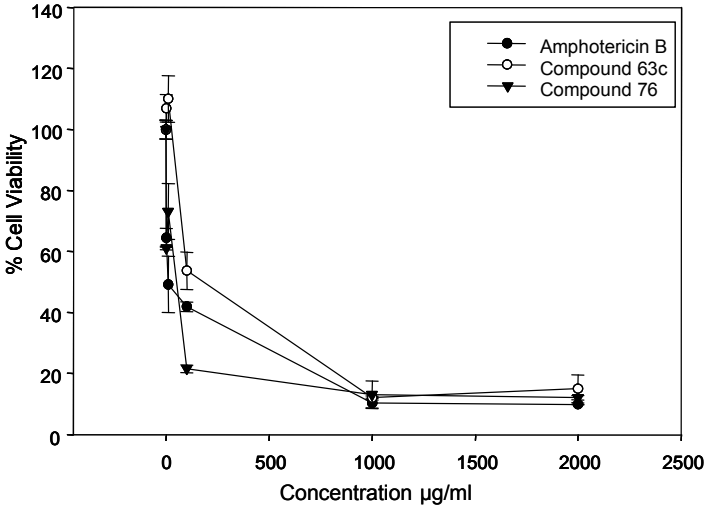


Figure 15. Antiproliferative activities of compounds in Hep3B cells.

However, at lower doses MCF-7 cells were resistant to compound **63c** and the IC_{50} value was found to be 293.4 µg/ml. Both compound **76** and amphotericin were similar in their toxicity to MCF-7 cells and their IC_{50} values were between 50 and 60 µg/ml. All the three compounds were identical in their effect on the survival of Hep3B cells. In fact none of the three compounds were toxic to the Hep3B cells up to a concentration of 400 µg/ml. At a concentration of 1 mg/ml or more all the three compounds were toxic to both the cells and inhibited growth.

2.3.6 Conclusion

A series of 2-amino-5,6,7,8-tetrahydro-5-oxo-4-phenylquinoline-3-carbonitrile and its various analogues have been synthesized in excellent isolated yields in the absence of any added catalyst by the reaction of 3-amino- cyclohexen-1one **62** with various arylidenemalononitriles **61(a-i)** and their biological activities were evaluated. The dual role of **61** as a reactant in the Michael addition step and as an oxidizing agent in the aromatization contributing to the mechanism has been established with experimental evidence. The antifungal activity of compounds **63c**, **63d**, and **72** (40-100 µg/ml) showed activity comparable to that of cycloheximide (40-100 µg/ml) under similar experimental conditions. Compound **76** exhibited (2-11 mm) activity against all the test fungal strains.

However a greater zone of inhibition with compound **76** was observed against *Mucor*. All the compounds have profound suppressive effect on yeast hypha transition, exhibiting greater than 85% inhibition at concentration 20 µg/ml. Compounds **63d**, **73**, **75**, **76** exhibited more than 90% inhibition of chitin synthase activity comparable to that of Nikkomycin. All other compounds exhibited 61-90% inhibition of chitin synthase activity at concentration 4 µg/ml. The generic compound **63c** and the functionalized derivative **76** prepared from **63c** showed the most potent antifungal activity. The presence of halogen and nitrogen containing substituents on aryl ring seems to generate compounds with good antifungal activities. The antiproliferative activities of compounds **63c** and **76** were similar to that of amphotericin B though only slight differences in the levels of toxicities to the two cell lines were observed. It was observed that at low doses the mammary adenocarcinoma cells MCF-7 were less sensitive to all the three compounds whereas hepatocellular carcinoma cells Hep-3B were more resistant to all the compounds. These results indicate that compounds **63c** and **76** do not have any profound effect on proliferation of human cancer cell lines at lower concentrations and their activity is comparable to that of amphotericin B.

2.3.7 Experimental section

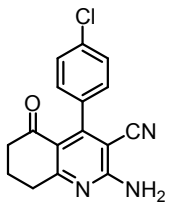
General procedure for the preparation of compounds 63(a-i):

A solution of 3-amino-2-cyclohexen-1-one **62** (2 g, 10 mmol) and arylidenemalononitrile **61(a-i)** (30 mmol) was refluxed in 40 ml of *n*-propanol for the requisite time as shown in **Table 10.** After completion of reaction *n*-propanol was removed under reduced pressure and the product was isolated by column chromatography using 60% ethyl acetate in pet ether as eluent.

2.3.7.1 Characterization data for compounds 63(a-i)

2-Amino-5-oxo-4-(4-chloro-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63a):

The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61a** (1.01 g, 5.40 mmol) gave compound **63a**.



Nature : White solid

MP : 289 ºC.

Yield : 0.492 g, 92%.

^{1}HNMR (200MHz) (CDCl$_3$+DMSO-d_6) : δ: 7.03 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.63 (br s, 2H), 2.63 (t, *J* = 6.3 Hz, 2H), 2.13 (t, *J* = 6.3 Hz, 2H), 1.72 (quin, *J* = 6.3 Hz, 2H).

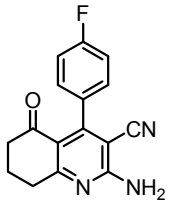
IR (CHCl$_3$, cm^{-1}) : 3422, 3306, 2215, 1685, 1648, 1537, 1461, 1243.

Elemental Analysis : Calcd: C, 64.54; H, 4.06; N, 14.11.

$C_{16}H_{12}ClN_3O$ (297) Found: C, 64.32; H, 4.15; N, 14.24.

2-Amino-5-oxo-4-(3-nitro-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63b):

The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61b** (0.935 g, 5.40 mmol) gave compound **63b**.



Nature : White solid

MP : 286 ºC.

Yield : 0.475 g, 94%.

^{1}HNMR (200MHz) (CDCl$_3$+DMSO-d_6) : δ 6.89-6.73 (m, 4H), 6.51 (br s, 2H), 2.66 (t, *J* = 6.5 Hz, 2H), 2.17 (t, *J* = 6.5 Hz, 2H), 1.75 (quin, *J* = 6.5 Hz, 2H).

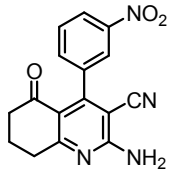
IR (CHCl$_3$, cm^{-1}) : 3397, 3309, 2215, 1684, 1649, 1511, 1460, 1217.

Elemental Analysis : Calcd: C, 68.32; H, 4.30; N, 14.94.

$C_{16}H_{12}FN_3O$ (281) Found: C, 68.45; H, 4.54; N, 14.82.

2-Amino-5-oxo-4-(3-nitro-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63c):

The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61c** (1.07 g, 5.40 mmol) gave compound **63c**.



Nature : White solid

MP : 243 ºC.

Yield : 0.526 g, 95%.

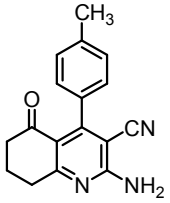
^{1}HNMR (200MHz) (CDCl$_3$+DMSO-d_6) : δ 8.34-8.28 (m, 1H), 8.05 (t, *J* = 1.9 Hz,1H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.55-7.50 (m, 1H) 5.74 (br s, 2H), 3.04 (t, *J* = 6.2 Hz, 2H), 2.58-2.51 (m, 2H), 2.13 (quin, *J* = 6.2 Hz, 2H).

^{13}C NMR (CDCl$_3$+DMSO-d_6) : δ 192.8, 168.2, 158.6, 153.1, 146.1, 138.3, 132.2, 127.9, 121.3, 120.8, 115.2, 113.5, 90.2, 37.6, 32.2, 19.1.

IR (CHCl$_3$, cm^{-1}) : 3483, 3323, 2211, 1674, 1622, 1552, 1346, 755.

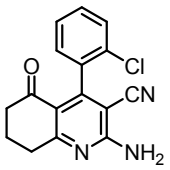
Elemental Analysis	**:**	**Calcd:**	C, 62.34; H, 3.92; N, 18.17.
$C_{16}H_{12}N_4O_3$ (308)		**Found:**	C, 62.40; H, 3.80; N, 18.02.

2-Amino-5-oxo-4-(4-methyl-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63d): The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61d** (0.908 g, 5.40 mmol) gave compound **63d**.



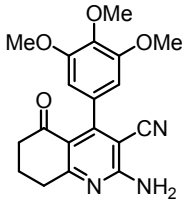
Nature	**:**	White solid
MP	**:**	258 ºC.
Yield	**:**	0.434 g, 87%.
^{1}HNMR (200MHz) (CDCl$_3$+DMSO-d_6)	**:**	δ: 7.24 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.74 (br s, 2H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.53 (t, *J* = 6.2 Hz, 2H), 2.40 (s, 3H), 2.09 (quin, *J* = 6.2 Hz, 2H).
^{13}C NMR (CDCl$_3$+DMSO-d_6)	**:**	192.1, 167.3, 158.3, 155.6, 135.4, 133.3, 126.6, 125.4, 115.3, 113.7, 89.9, 37.5, 31.9, 19.3, 18.9.
IR (CHCl$_3$, cm^{-1})	**:**	3423, 3296, 2208, 1682, 1642, 1555, 1535, 1459.
Elemental Analysis	**:**	Calcd: C, 73.63; H, 5.45; N, 15.15.
$C_{17}H_{15}N_3O$ (277)		Found: C, 73.77; H, 5.62; N, 15.32.

2-Amino-5-oxo-4-(2-chloro-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63e). The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61e** (1.01 g, 5.40 mmol) gave compound **63e**.



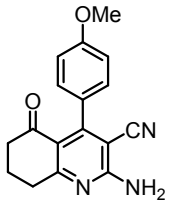
Nature	**:**	White solid
MP	**:**	286 ºC.
Yield	**:**	0.438 g, 82%.
^{1}HNMR (200MHz) (CDCl$_3$+DMSO-d_6)	**:**	δ 7.11-6.93 (m, 3H), 6.77-6.73 (m, 1H), 6.33 (br s, 2H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.17-2.09 (m, 2H), 1.72 (quin, *J* = 6.0 Hz, 2H).
IR (CHCl$_3$, cm^{-1})	**:**	3392, 3308, 2218, 1680, 1647, 1543, 1462, 1377.
Elemental Analysis	**:**	Calcd: C, 64.54; H, 4.06; N, 14.11.
$C_{16}H_{12}ClN_3O$ (297)		Found: C, 64.41; H, 4.16; N, 14.30.

2-Amino-5-oxo-4-(3,4,5-trimethoxy-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63f): The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61f** (1.31 g, 5.40 mmol) gave compound **63f**.



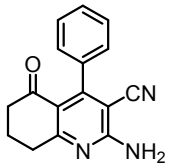
Nature	**:**	White solid
MP	**:**	219 ºC.
Yield	**:**	0.566 g, 89%.
^{1}HNMR (200MHz) ($CDCl_3$+DMSO-d_6)	**:**	δ 6.38 (s, 2H), 5.73 (br s, 2H), 3.89 (s, 3H), 3.82 (s, 6H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.55 (t, *J* = 6.2 Hz, 2H), 2.11 (quin, *J* = 6.2 Hz, 2H).
^{13}C NMR ($CDCl_3$+DMSO-d_6)	**:**	δ 194.4, 169.1, 159.4, 157.6, 152.9, 138.0, 132.5, 118.3, 115.2, 104.4, 93.1, 60.8, 55.9, 39.4, 33.7, 20.7.
IR ($CHCl_3$, cm^{-1})	**:**	3417, 3308, 2213, 1681, 1651, 1555, 1459, 1093.
Elemental Analysis	**:**	Calcd: C, 64.58; H, 5.42; N, 11.89.
$C_{19}H_{19}N_3O_4$ (353)		Found: C, 64.73; H, 5.60; N, 11.70.

2-Amino-5-oxo-4-(4-methoxy-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63g): The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61g** (0.994 g, 5.40 mmol) gave compound **63g**.



Nature	**:**	White solid
MP	**:**	278 ºC.
Yield	**:**	0.474 g, 90%.
^{1}HNMR (200MHz) ($CDCl_3$+DMSO-d_6)	**:**	δ 6.72 (d, *J* = 8.7 Hz, 2H), 6.53 (d, *J* = 8.7 Hz, 2H), 6.44 (br s, 2H), 3.44 (s, 3H), 2.57 (t, *J* = 6.2 Hz, 2H), 2.09 (t, *J* = 6.2 Hz, 2H), 1.67 (quin, *J* = 6.2 Hz, 2H).
IR ($CHCl_3$, cm^{-1})	**:**	3393, 3307, 2217, 1680, 1651, 1512, 1459, 1243.
Elemental Analysis	**:**	Calcd: C, 69.61; H, 5.15; N, 14.33.
$C_{17}H_{15}N_3O_2$ (293)		Found: C, 69.76; H, 5.04; N, 14.45.

2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63h): The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61h** (0.832 g, 5.40 mmol) gave compound **63h**.



Nature : White solid

MP : 257 ºC.

Yield : 0.383 g, 81%.

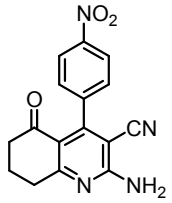
^{1}HNMR (200MHz) (CDCl$_3$+DMSO-*d*$_6$) : δ 6.90-6.87 (m, 3H), 6.69-6.61 (m, 2H), 2.45 (t, *J* = 6.2 Hz, 2H), 1.91 (t, *J* = 6.2 Hz, 2H), 1.56 (quin, *J* = 6.2 Hz, 2H).

IR (CHCl$_3$, cm^{-1}) : 3391, 3299, 2208, 1692, 1651, 1585, 1478, 1404, 1215, 1082, 930, 758, 669.

Elemental Analysis : Calcd: C, 72.99; H, 4.98; N, 15.96.

$C_{16}H_{13}N_3O$ (263) Found: C, 72.80; H, 5.05; N, 15.80.

2-Amino-5-oxo-4-(4-nitro-phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (63i): The above general procedure, starting from 3-amino-2-cyclohexen-1-one **62** (0.2 g, 1.80 mmol) and cyano olefin **61i** (1.07 g, 5.40 mmol) gave compound **63i**.



Nature : White solid

MP : 260 ºC.

Yield : 0.498 g, 90%.

^{1}HNMR (200MHz) (CDCl$_3$+DMSO-*d*$_6$) : δ 8.31 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5, Hz, 2H), 5.76 (brs, 2H), 3.03 (t, *J* = 6.5 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 2.12 (quin, *J* = 6.2 Hz, 2H).

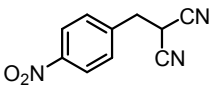
IR (CHCl$_3$, cm^{-1}) : 3407, 3323, 2216, 1680, 1612, 1555, 1523, 1430, 1349, 1215, 929, 777, 669.

Elemental Analysis : Calcd: C, 62.34; H, 3.92; N, 18.17.

$C_{16}H_{12}N_4O_3$ (308) Found: C, 62.48; H, 3.79; N, 18.26.

Isolation of 2-(4-nitrobenzyl) malononitrile (64i).

Compound **64i** was isolated after the reaction of **62** (1.80 mmol) with 2-(4-nitrobenzyledine) malononitrile **61i** (5.40 mmol) by column chromatography using 5% ethyl acetate in pet ether as eluent.



Nature : White solid

MP : 156 ºC.

Yield : 2.54 g, 80%.

^{1}HNMR (200MHz) (CDCl$_3$+DMSO-*d*$_6$) : δ 8.29 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 4.02 (t, *J* = 6.5 Hz, 1H), 3.40 (d, *J* = 6.5 Hz, 2H).

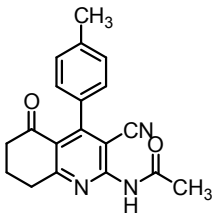
^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$) : 147.0, 140.2, 129.9, 123.2, 111.9, 34.7, 23.3.

IR (CHCl$_3$, cm^{-1}) : 2256, 1526, 1444, 1421, 1350, 1215, 758, 669.

Elemental Analysis : **Calcd:** C, 59.70; H, 3.51; N, 20.89.

$C_{10}H_7N_3O_2$ (201) **Found:** C, 59.74; H, 3.55; N, 20.95.

***N*-(3-Cyano-5,6,7,8-tetrahydro-5-oxo-4-*p*-tolylquinolin-2-yl) acetamide (66):** To a solution of compound **63d** (0.5 g, 1.80 mmol) in dry pyridine (3 ml), acetyl chloride (0.16 ml, 2.16 mmol) was added dropwise at 0 ºC in an inert atmosphere. The temperature was allowed to rise to reflux for 3 h. After completion of reaction pyridine was removed under reduced pressure to obtain a white solid. The solid obtained was washed with water, dried, and purified by column chromatography by using 30% ethyl acetate in pet ether as eluent to obtain pure product **66**.



Nature : White solid

MP : 208-210 ºC.

Yield : 0.489 g, 85%.

^{1}HNMR (200MHz) (CDCl$_3$+DMSO-*d*$_6$) : δ 8.08 (br s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.16 (t, *J* = 6.2 Hz, 2H), 2.62 (t, *J* = 6.2 Hz, 2H), 2.52 (s, 3H), 2.41 (s, 3H), 2.17 (quin, *J* = 6.2 Hz, 2H).

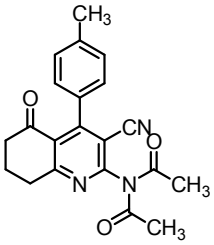
^{13}C NMR (CDCl$_3$+DMSO-*d*$_6$) : δ 194.9, 169.8, 167.7, 158.0, 152.9, 139.0, 133.1, 129.0, 127.1, 122.8, 114.0, 100.5, 39.5, 33.7, 25.0, 21.3, 20.7.

IR (CHCl$_3$, cm^{-1}) : 3270, 2224, 1694, 1546, 1516, 1262, 1215, 766, 668.

Elemental Analysis : Calcd: C, 71.46; H, 5.37; N, 13.16.

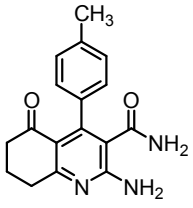
$C_{19}H_{17}N_3O_2$ (319) Found: C, 71.62; H, 5.49; N, 13.10.

***N*-Acetyl-N-3-cyano-5,6,7,8-tetrahydro-4-(4-methylphenyl-5-oxo-4-p-tolylquinolin-2-yl) acetamide (67):** A mixture of compound **63d** (0.277 g, 1 mmol) and acetic anhydride (5 ml) was refluxed for 12 h. After completion of reaction excess acetic anhydride was removed under reduced pressure. The residue obtained was added in water (15 ml) and extracted with ethyl acetate (3×15 ml). The organic layer was separated, dried over anhydrous sodium sulfate, and evaporated to obtain the crude product. The pure product **67** was obtained by column chromatography using 15% ethyl acetate in pet ether as eluent.



Nature	**:**	White solid
MP	**:**	183-185 ºC.
Yield	**:**	0.325 g, 90%.
^{1}HNMR (200MHz) ($CDCl_3$)	**:**	δ 7.28 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 3.26 (t, *J* = 6.3 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 2H), 2.42 (s, 3H), 2.37 (s, 6H) 2.24 (quin, *J* = 6.3 Hz, 2H).
^{13}C NMR ($CDCl_3$)	**:**	δ 195.0, 171.2, 167.9, 157.8, 155.6, 139.3, 132.0, 129.0, 127.2, 126.6, 113.2, 110.9, 39.4, 33.3, 26.0, 21.2, 20.5.
IR ($CHCl_3$, cm^{-1})	**:**	2229, 1721, 1707, 1557, 1509, 1459, 1416, 1367, 1263, 1228, 1208, 1037, 979, 931, 823.
Elemental Analysis	**:**	Calcd: C, 69.79; H, 5.30; N, 11.63.
$C_{21}H_{19}N_3O_3$ (361)		Found: C, 69.68; H, 5.11; N, 11.44.

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-*p*-tolylquinoline-3-carboxamide (68).



A solution of 60% aqueous H_2SO_4 (10 ml) and compound **63d** (1.2 g, 4.33 mmol) was heated at 80 ºC for 24 h with stirring. The reaction mixture was cooled to room temperature, diluted with water, and neutralized by 10% aqueous sodium hydroxide solution. The resulting precipitate was filtered, dried, and purified by column chromatography by using 70% ethyl acetate in pet ether to obtain pure product **68**.

Nature	**:**	White solid
MP	**:**	250 ºC.
Yield	**:**	1.124 g, 88%.

^{1}HNMR (200MHz) (CDCl$_3$) : δ 7.22 (d, *J* = 8.2, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.43 (br s, 2H), 5.39 (s, 1H), 4.95 (s, 1H), 2.95 (t, *J* = 6.2 Hz, 2H), 2.49 (t, *J* = 6.2 Hz, 2H), 2.39 (s, 3H), 2.07 (quin, *J* = 6.2 Hz, 2H).

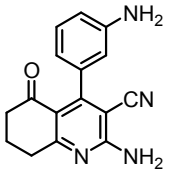
^{13}C NMR (CDCl$_3$) : 193.0, 166.5, 163.4, 155.2, 146.8, 134.1, 134.0, 126.0, 115.2, 115.1, 37.8, 31.5, 19.5, 19.2.

IR (CHCl$_3$, cm^{-1}) : 3400, 3300, 3250, 3150, 1678, 1655, 1605, 1551, 1215.

Elemental Analysis : Calcd: C, 69.14; H, 5.80; N, 14.23.

$C_{17}H_{17}N_3O_2$ (295) Found: C, 69.25; H, 5.69; N, 14.15.

2-Amino-4-(3-aminophenyl)-5,6,7,8-tetrahydro-5-oxoquinoline-3-carbonitrile (69):



A mixture of nitro derivative **63c** (0.695 g, 1 mmol) and $SnCl_2 \cdot 2H_2O$ (2.54 g, 5 mmol) was heated up to reflux in absolute ethanol (30 ml) for 3 h. After completion of reaction, ethanol was removed under reduced pressure. Water (30 ml) was added to the oily residue and the mixture was neutralized to pH 7-8 by adding aqueous saturated $NaHCO_3$ solution followed by extraction with ethyl acetate (3×20 ml). The combined ethyl acetate extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the pure product **69**.

Nature : Yellow solid

MP : 276-278 ºC.

Yield : 1.124 g, 88%.

^{1}HNMR (200MHz) (CDCl$_3$+DMSO-*d$_6$*) : δ 6.95 (t, *J* = 8.0 Hz, 1H), 6.57-6.52 (m, 1H), 6.33-6.30 (m, 2H), 3.06 (br s, 2H), 2.73 (t, *J* = 6.2 Hz, 2H), 2.25 (t, *J* = 6.2 Hz, 2H), 1.83 (quin, *J* = 6.2 Hz, 2H).

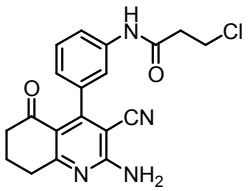
^{13}C NMR (100MHz) (CDCl$_3$+DMSO-*d$_6$*) : δ 192.5, 167.6, 158.5, 156.4, 145.3, 137.4, 127.1, 115.9, 114.6, 114.1, 113.1, 112.0, 90.5, 37.9, 32.3, 19.3.

IR (nujol, cm^{-1}) : 3397, 3363, 3313, 2219, 1655, 1457, 1285.

Elemental Analysis : Calcd: C, 69.05; H, 5.07; N, 20.13.

$C_{16}H_{14}N_4O$ (278) Found: C, 69.27; H, 5.24; N, 20.11.

***N*-(3-(2-Amino-3-cyano-5,6,7,8-tetrahydro-5-oxoquinolin-4-yl)phenyl)-3-**



chloropropanamide (70): To a solution of compound **69** (0.504 g, 1.8 mmol) and $NaHCO_3$ (0.152 g, 1.8 mmol) in THF, chloropropionyl chloride (0.18 ml, 1.8 mmol) was added at 0 ºC over a period of 10 min and then stirred for 2 h at room temperature. After completion of reaction, THF was removed under reduced pressure to obtain a yellow solid. The solid was washed with excess water, dried and finally washed with pet ether to obtain a pure product.

Nature : Yellow solid

MP : 284 ºC (dec).

Yield : 0.614 g, 92%.

^{1}HNMR (200MHz) (CDCl$_3$) : δ 10.31 (s, 1H), 7.86 (br s, 2H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.57 (t, *J* = 6.0 Hz, 2H), 2.14 (quin, *J* = 6.0 Hz, 2H).

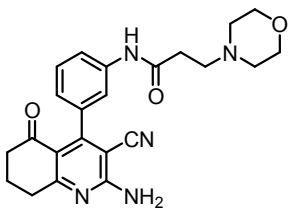
^{13}C NMR (125 MHz) (DMSO-*d*$_6$) : δ 193.8, 169.4, 167.9, 159.9, 156.9, 138.6, 128.3, 122.0, 118.3, 117.3, 116.7, 115.2, 91.0, 40.7, 40.0, 39.0, 33.4, 20.4.

IR (CHCl$_3$, cm^{-1}) : 3440, 3315, 3219, 2216, 1666, 1626, 1586, 1553, 1447, 1421, 1320, 1284, 886, 774.

Elemental Analysis : Calcd: C, 61.88; H, 4.65; N, 15.19.

$C_{19}H_{17}ClN_4O_2$ (368) Found: C, 61.98; H, 4.60; N, 15.08.

***N*-(3-(2-Amino-3-cyano-5,6,7,8-tetrahydro-5-oxoquinolin-4-yl)phenyl)-3-**



morpholinopropanamide (71): A solution of compound **70** (0.150 g, 0.4 mmol) and excess morpholine (15 ml) was heated to reflux for 4 h. After completion of reaction, morpholine was removed under reduced pressure to obtain a residue. Water (20 ml) was added to the residue and neutralized by diluted HCl to obtain a yellow solid which was further filtered and washed with 1:1 ethyl acetate and pet ether mixture to get the pure product.

Nature : Yellow solid

MP : 162-164 ºC.

Yield : 0.148 g, 87%.

^{1}HNMR (200MHz) (CDCl$_3$) : δ 10.94 (s, 1H), 7.68 (s, 1H), 7.40-7.37 (m, 2H), 6.95-6.89 (m, 1H), 5.64 (s, 2H), 3.83 (t, *J* = 4.8 Hz, 4H), 3.01 (t, *J* = 6.2 Hz, 2H), 2.74 (t, *J* = 6.2 Hz, 2H), 2.63 (t, *J* = 4.8 Hz, 4H), 2.57-2.51(m, 4H), 2.11 (quin, *J* = 6.2 Hz, 2H).

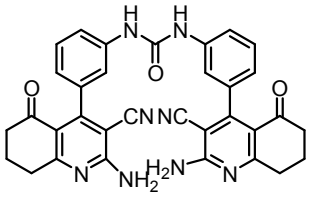
^{13}C NMR (100 MHz) (CDCl$_3$) : δ 193.1, 169.2, 168.2, 159.0, 156.2, 137.8, 137.5, 127.3, 121.0, 117.8, 116.9, 116.4, 114.4, 91.2, 65.7, 53.1, 51.9, 38.3, 32.8, 32.3, 19.8.

IR (CHCl$_3$, cm^{-1}) : 3440, 3315, 3219, 2216, 1666, 1626, 1586, 1553, 1447, 1421, 1320, 1284, 886, 774.

Elemental Analysis : **Calcd:** C, 65.86; H, 6.01; N, 16.70.

$C_{23}H_{25}N_5O_3$ (419) **Found:** C, 65.78; H, 6.10; N, 16.58.

1,3-Bis(3-(2-amino-3-cyano-5,6,7,8-tetrahydro-5-oxoquinolin-4-yl)phenyl) urea (72):



A solution of compound **69** (0.200 g, 0.71 mmol) and carbonyldiimidazole (0.058 g, 0.35 mmol) in dry THF (30 ml) was heated to reflux and maintained at reflux for 16 h. After completion of reaction, THF was removed under reduced pressure to obtain a pale yellow solid. The solid was washed with water, dried, and then washed with cold ethyl acetate to obtain the pure product **72**.

Nature : Pale yellow solid

MP : 285-287 ºC.

Yield : 0.335 g, 80%.

^{1}HNMR (200MHz) (DMSO-*d*$_6$) : δ 8.80 (s, 2H), 7.70 (s, 4H), 7.38-7.25 (m, 6H), 6.78 (d, *J* = 7.5 Hz, 2H), 2.97-2.91 (m, 4H), 2.57-2.41 (m, 4H), 2.03-1.97 (m, 4H).

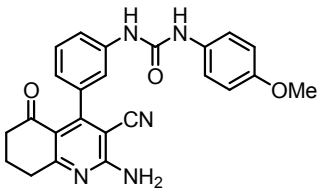
^{13}C NMR (100 MHz) (CDCl$_3$) : δ 193.7, 169.2, 159.8, 157.1, 152.3, 139.1, 138.6, 128.3, 120.7, 117.5, 116.7, 116.5, 115.2, 91.0, 39.0, 33.3, 20.4.

IR (CHCl$_3$, cm^{-1}) : 3377, 2219, 1646, 1589, 1542, 1460, 1377.

Elemental Analysis : **Calcd:** C, 68.03; H, 4.50; N, 19.23.

$C_{33}H_{26}N_8O_3$ (582) **Found:** C, 68.25; H, 4.32; N, 19.42.

1-(3-(2-Amino-3-cyano-5,6,7,8-tetrahydro-5-oxoquinolin-4-yl)phenyl)-3-(4-methoxyphenyl) urea (73): A solution of compound **69** (0.250 g, 0.89 mmol) and 4- methoxyphenyl isocyanate (0.11 ml, 0.89 mmol) was refluxed in dry THF (60 ml) for 12 h. After completion of reaction THF was removed under reduced pressure and the solid obtained was washed with water, dried, and recrystallized from acetone to obtain a pure solid **73**.

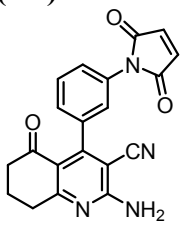


Nature	**:**	Pale yellow solid
MP	**:**	225-227 ºC.
Yield	**:**	0.330 g, 86%.
^{1}HNMR (400MHz) ($CDCl_3$+DMSO-d_6)	**:**	δ 8.08 (s, 1H), 7.85 (s, 1H), 7.40 (s, 1H), 7.21-7.19 (m, 4H), 6.93 (br s, 2H), 6.69-6.67 (m, 3H), 3.64 (s, 3H), 2.94 (t, *J* = 6.2 Hz, 2H), 2.38 (t, *J* = 6.2 Hz, 2H), 1.98 (m, 2H).
^{13}C NMR (100 MHz DMSO-d_6)	**:**	δ 193.8, 169.3, 159.9, 157.2, 154.5, 152.6, 139.4, 138.6, 132.6, 128.3, 120.4, 120.0, 117.3, 116.7, 116.4, 115.3, 113.9, 91.1, 55.0, 39.0, 33.4, 20.4
IR ($CHCl_3$, cm^{-1})	**:**	3405, 3320, 3168, 2215, 1712, 1675, 1650,1598, 1560, 1541, 1461, 1377, 1294, 1244.
Elemental Analysis	**:**	**Calcd:** C, 67.44; H, 4.95; N, 16.38.
$C_{24}H_{21}N_5O_3$ (427)		**Found:** C, 67.19; H, 4.89; N, 16.45.

Synthesis of compounds 75 and 76: To a stirred solution of maleic anhydride (0.177 g, 1.8 mmol) in dry THF (15 ml) was added a solution of amine compound **69** (0.500 g, 1.8 mmol) in dry THF (60 ml) dropwise at room temperature over a period of 20 min and the reaction mixture was further stirred for 12 h. After completion of reaction, THF was removed under reduced pressure to obtain maleanilic acid derivative **74** in quantitive yield, which was used for the next step without any further purification and characterization. A mixture of maleanilic acid derivative **74**, acetic anhydride (10 ml), and fused sodium acetate (75 mg) was heated in an oil bath at 60 ºC for 1h. When complete consumption of starting material was observed along with the formation of two new spots on TLC, the reaction mixture was cooled to room temperature and acetic anhydride was removed under reduced pressure to obtain mixture of products, which

were separated by flash column chromatography using 15% ethyl acetate in pet ether as eluent to get **75** (0.386 g, 60% yield) and **76** (0.230 g, 32% yield).

2-Amino-5,6,7,8-tetrahydro-5-oxo-4-(3-(2,5-dioxo-*2H*-pyrrol-1-(*5H*)-yl)phenyl)quinoline-3-carbonitrile (75):



Nature : Gray solid

MP : 262-264 ºC.

Yield : 0.386 g, 60%.

^{1}HNMR (200MHz) ($CDCl_3$+DMSO-d_6) : δ 7.20-7.11 (m, 2H), 6.90-6.87 (m,1H), 6.85-6.80 (m, 1H), 6.55 (s, 2H), 6.47 (br s, 2H), 2.64-2.56 (m, 2H), 2.14 (t, *J* = 6.2 Hz, 2H), 1.80-1.67 (m, 2H).

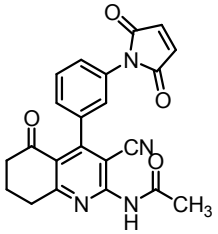
^{13}C NMR (100 MHz DMSO-d_6) : δ 194.1, 169.8, 169.6, 160.0, 156.1, 138.8, 134.7, 131.3, 128.5, 126.5, 125.8, 124.9, 116.8, 115.2, 91.3, 39.0, 33.5, 20.5.

IR ($CHCl_3$, cm^{-1}) : 3465, 3357, 2222, 1702, 1683, 1461, 1377, 833.

Elemental Analysis : **Calcd:** C, 67.03; H, 3.94; N, 15.63.

$C_{20}H_{14}N_4O_3$ (358) **Found:** C, 67.15; H, 3.80; N, 15.52.

***N*-3-Cyano-5,6,7,8-tetrahydro-5-oxo-4-(3-(2,5-dioxo-2,4-pyrrol-(*5H*)phenyl)quinolin-2-yl) acetamide (76):**



Nature : White solid

MP : 242-245 ºC.

Yield : 0.230 g, 32%.

^{1}HNMR (200MHz) ($CDCl_3$+DMSO-d_6) : δ 8.11 (brs, 1H), 7.59-7.51 (m, 2H), 7.33-7.31 (m, 1H), 7.22-7.17 (m, 1H), 6.83 (s, 2H), 3.17 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.52 (s, 3H), 2.17 (quin, *J* = 6.4 Hz, 2H).

^{13}C NMR (125 MHz DMSO-d_6) : δ 192.9, 167.5, 167.1, 165.8, 153.5, 152.0, 135.7, 132.7, 129.7, 126.7, 124.9, 124.0, 123.1, 121.5, 112.2, 37.4, 31.4, 21.5, 18.7.

IR ($CHCl_3$, cm^{-1}) : 3359, 2229, 1717, 1693, 1557, 1537, 1492, 1462, 1378, 1245, 992, 827, 701.

Elemental Analysis : Calcd: C, 66.00; H, 4.03; N, 13.99.

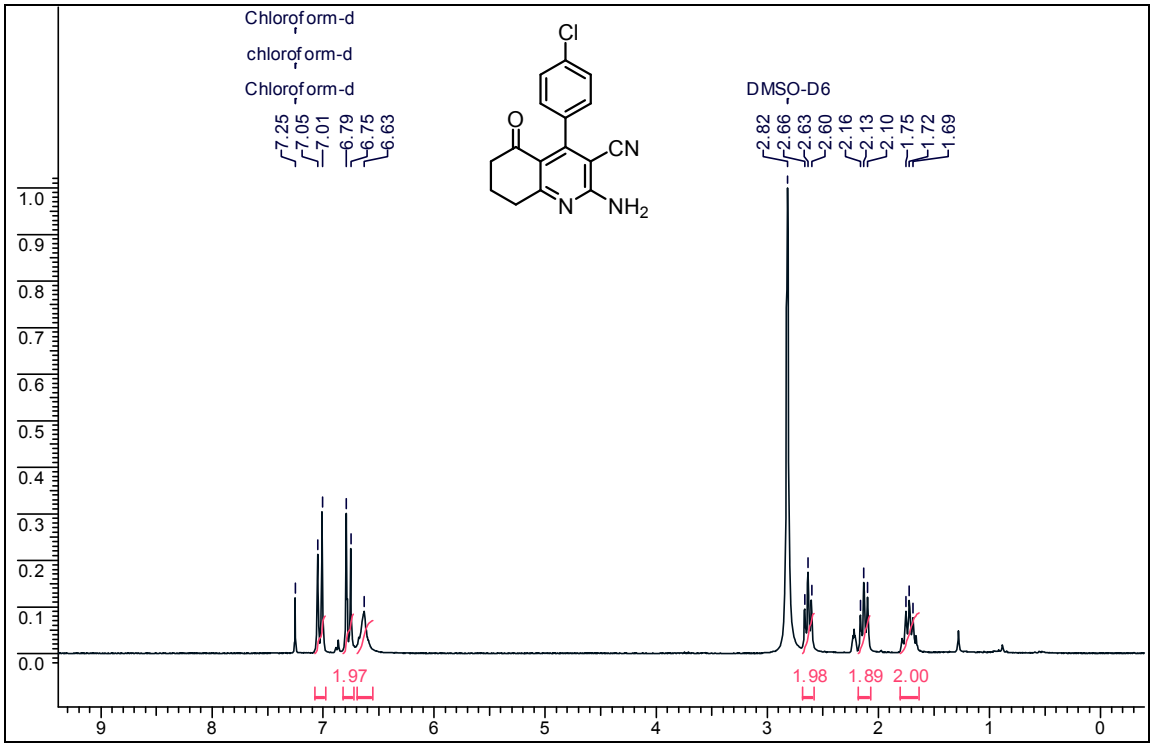
$C_{22}H_{16}N_4O_4$ (400) Found: C, 66.20; H, 4.19; N, 13.81.

2.3.8 Spectra

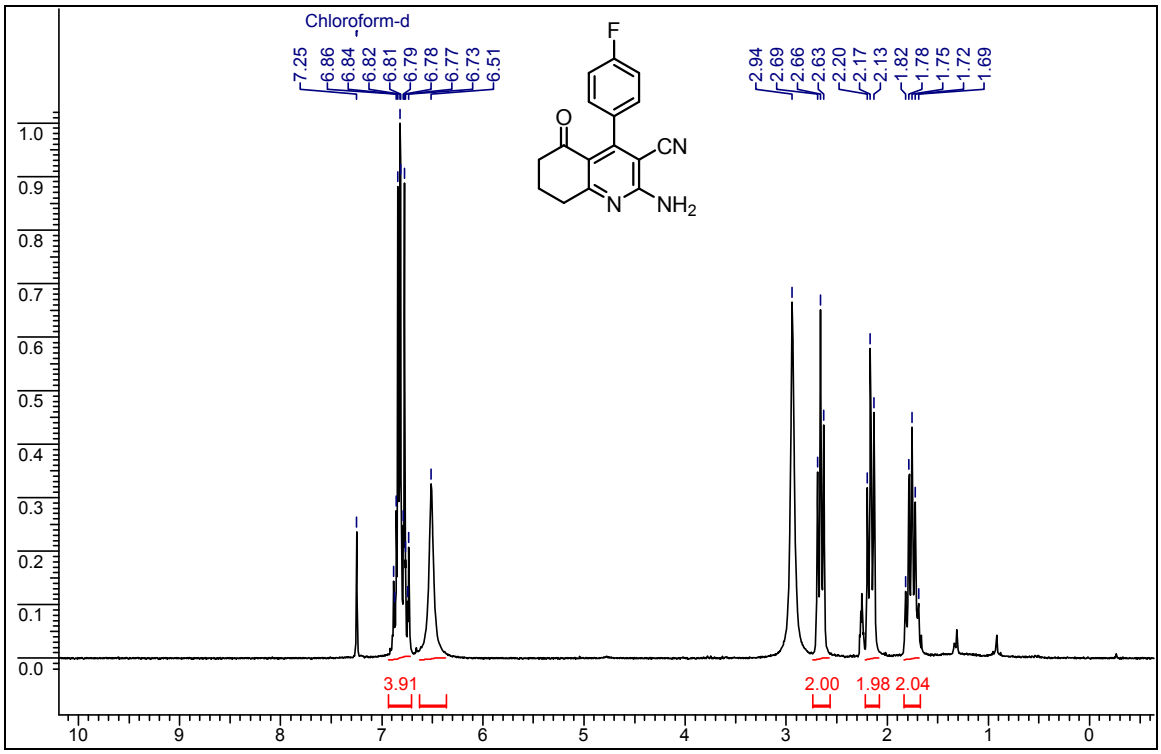
Table 16. ^{1}H and ^{13}C spectra of some selected compounds

Sr. No.	Specra	
1	^{1}H NMR spectra of compound	**63a**
2	^{1}H NMR spectra of compound	**63b**
3	^{1}H and ^{13}C NMR spectra of compound	**63c**
4	^{1}H and ^{13}C NMR spectra of compound	**63f**
5	^{1}H and ^{13}C NMR spectra of compound	**67**
6	^{1}H and ^{13}C NMR spectra of compound	**71**
7	^{1}H and ^{13}C NMR spectra of compound	**76**

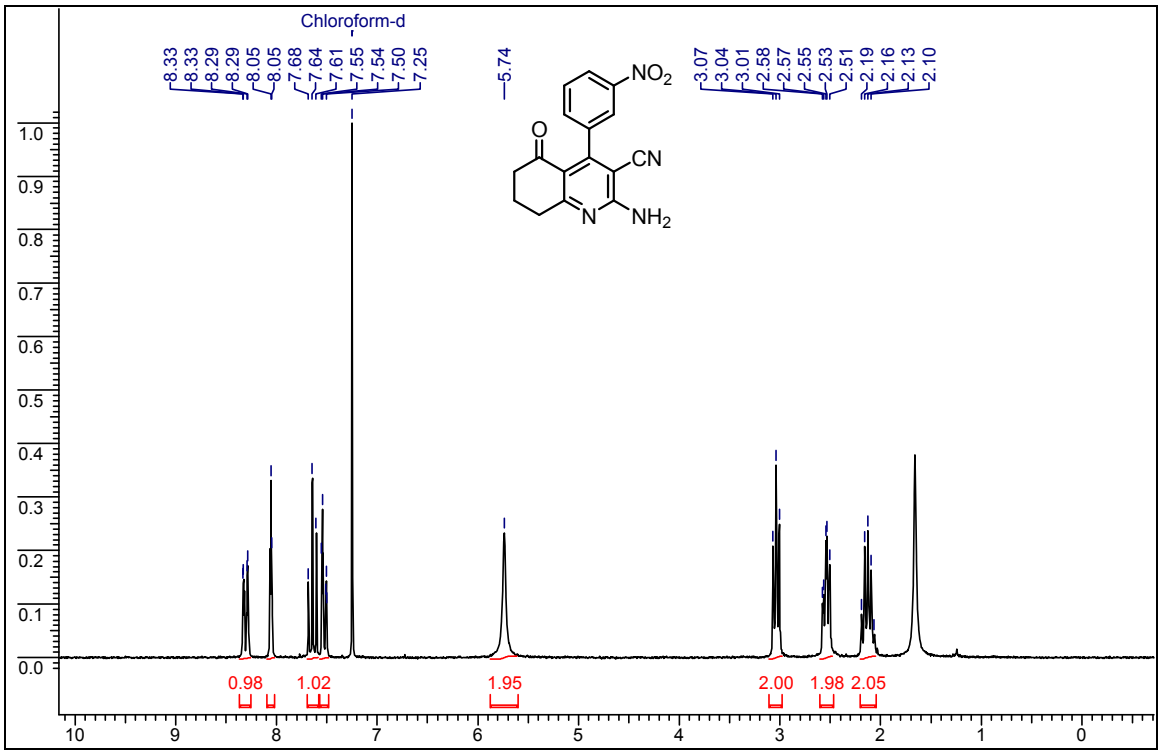
[1] ^{1}H-NMR Spectra of Compound 63a

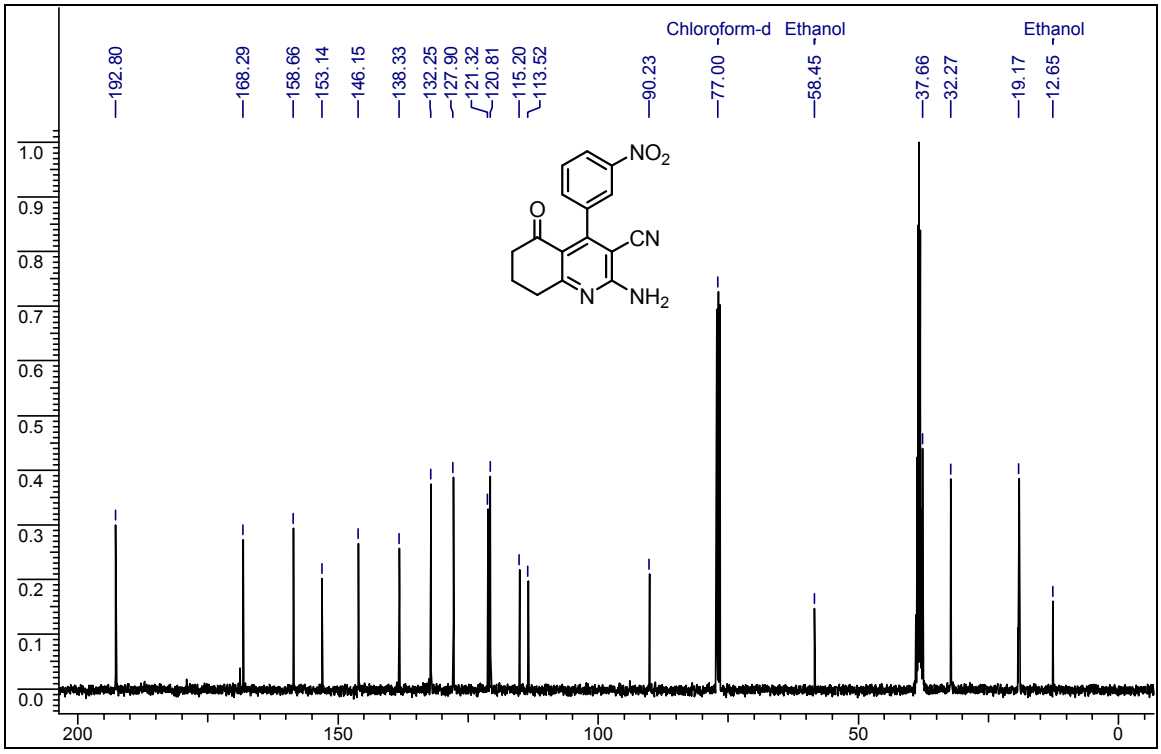


[2] ^{1}H-NMR Spectra of Compound 63b

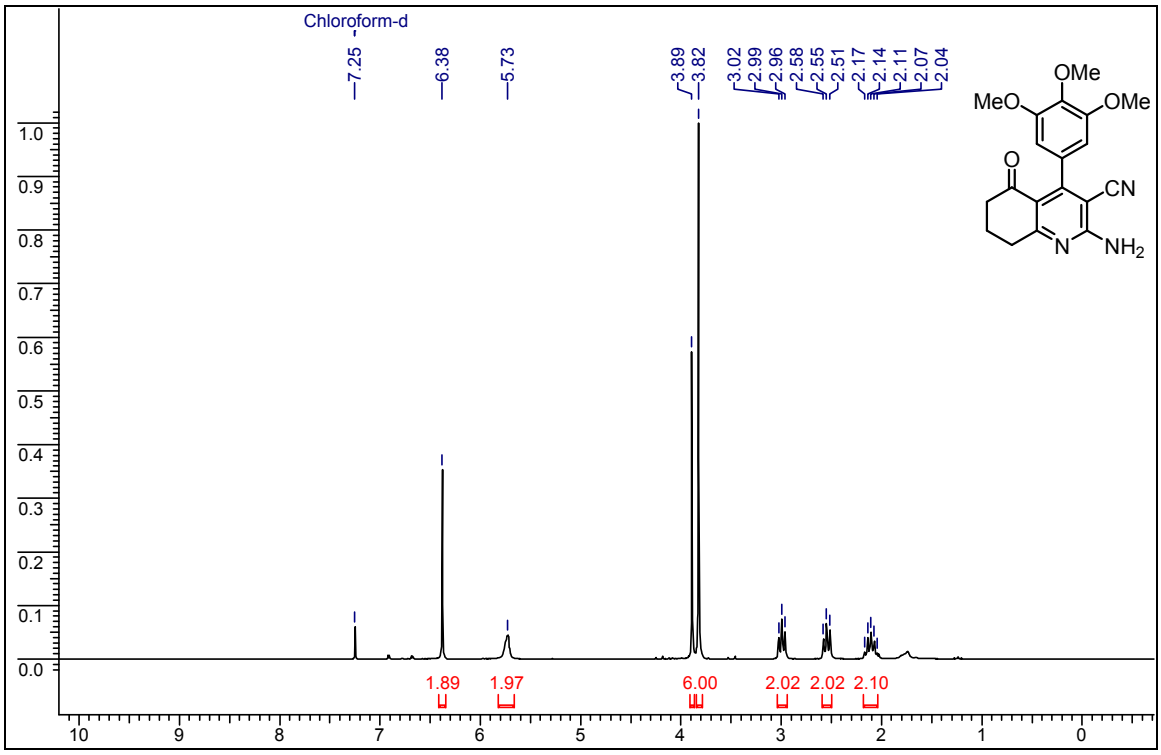


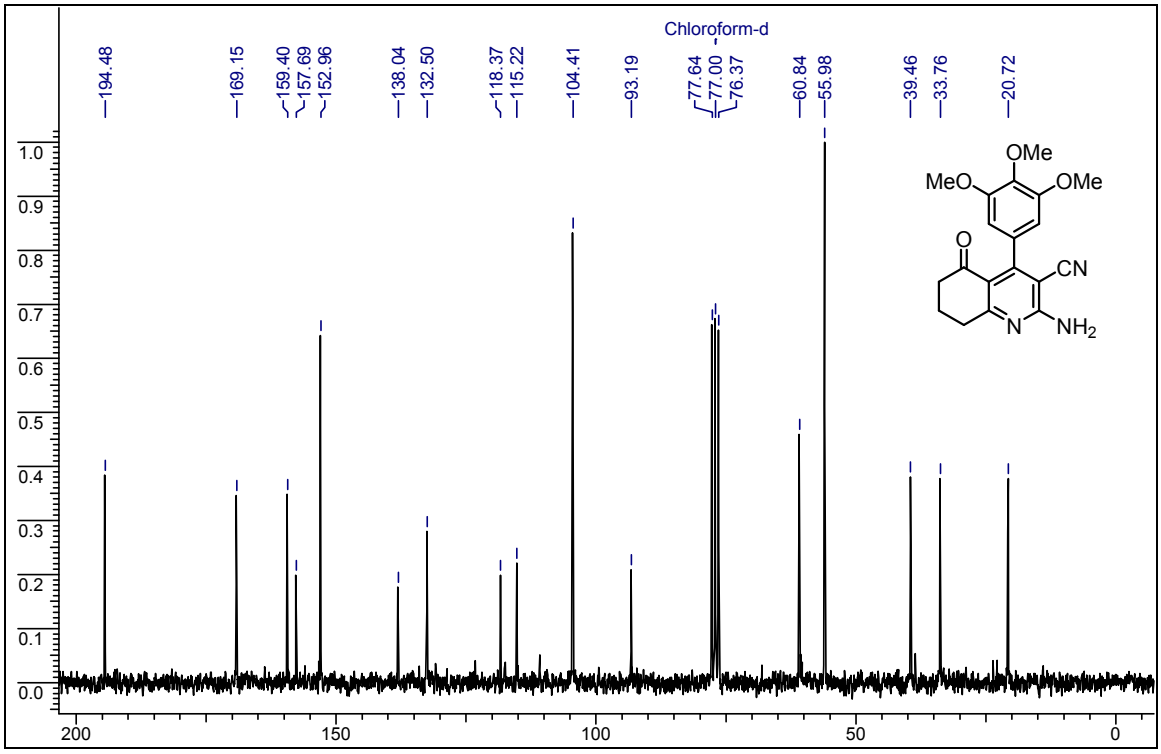
[3] ^{1}H and ^{13}C-NMR Spectra of Compound 63c



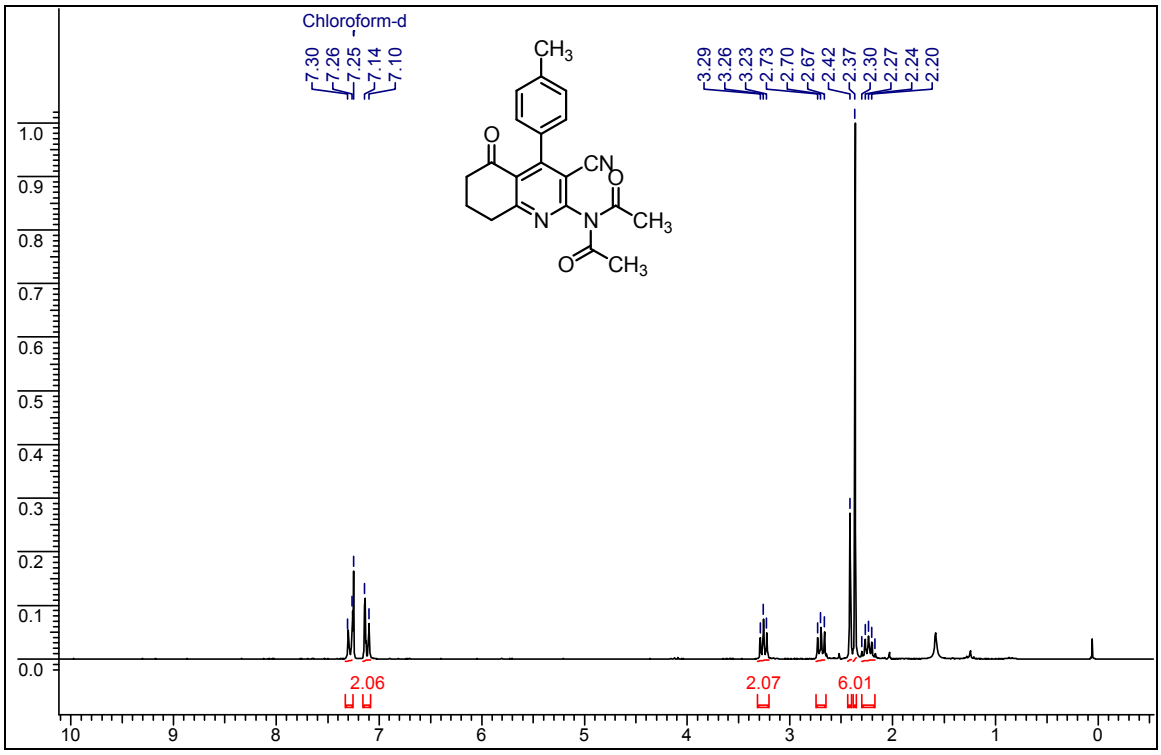


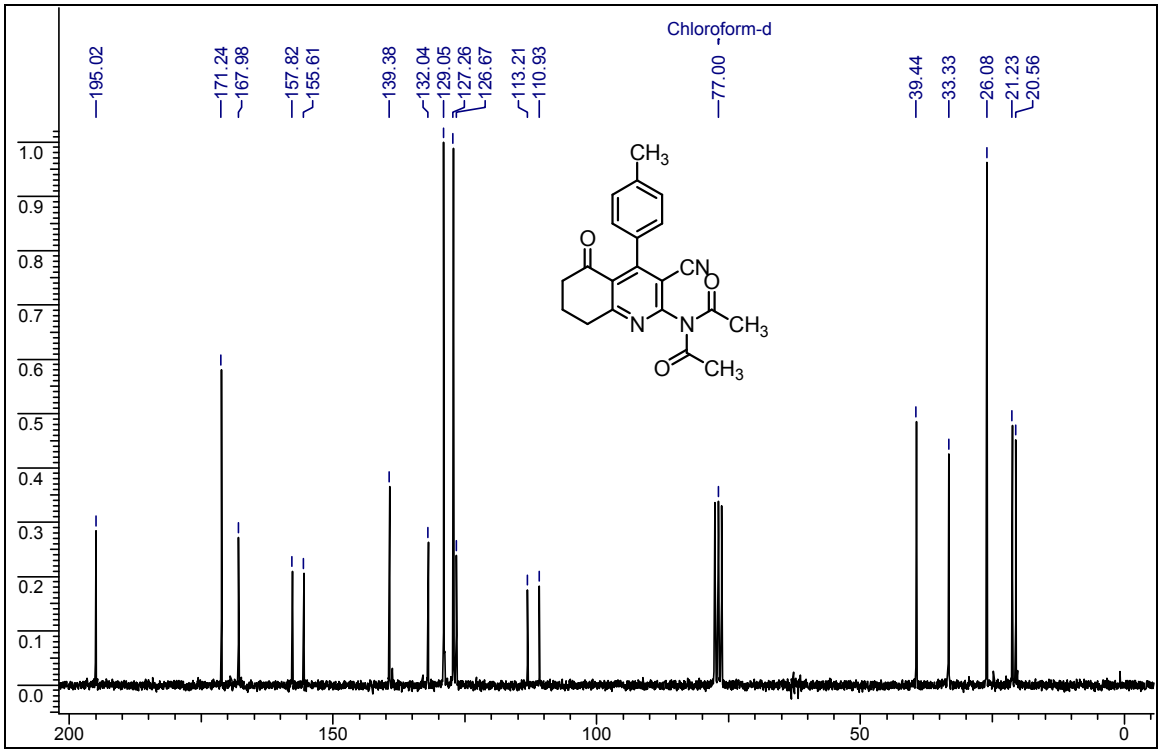
[4] ^{1}H and ^{13}C-NMR Spectra of Compound 63f



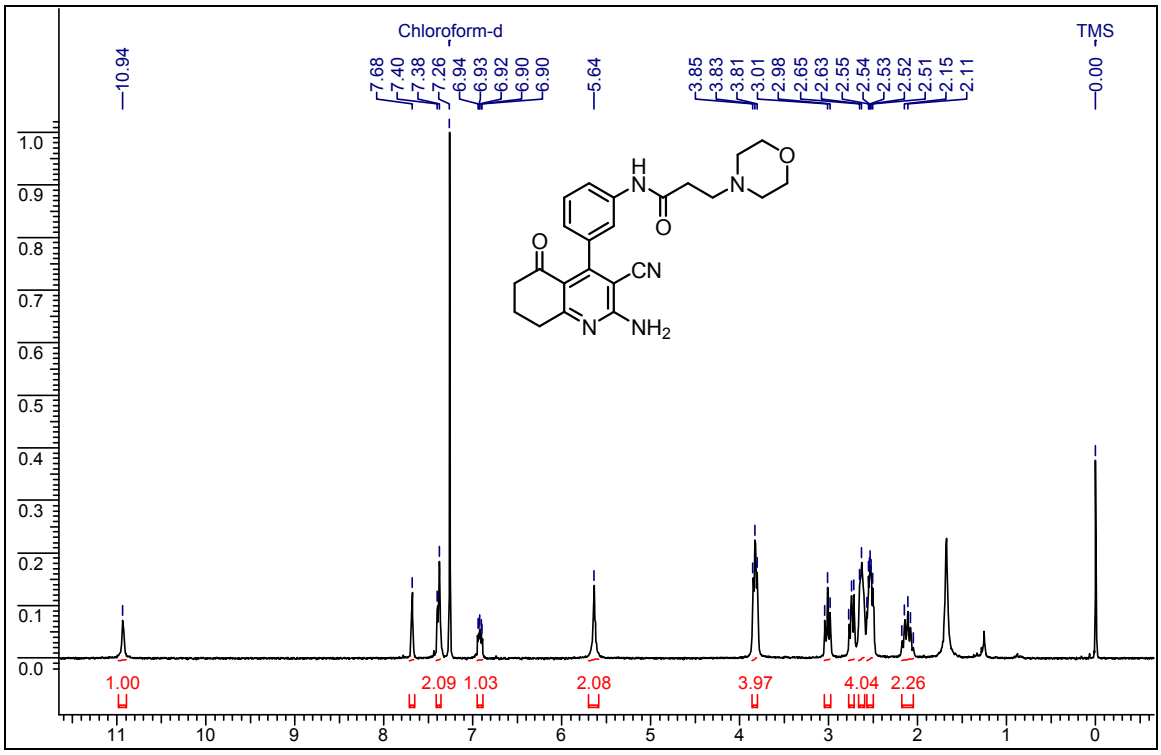


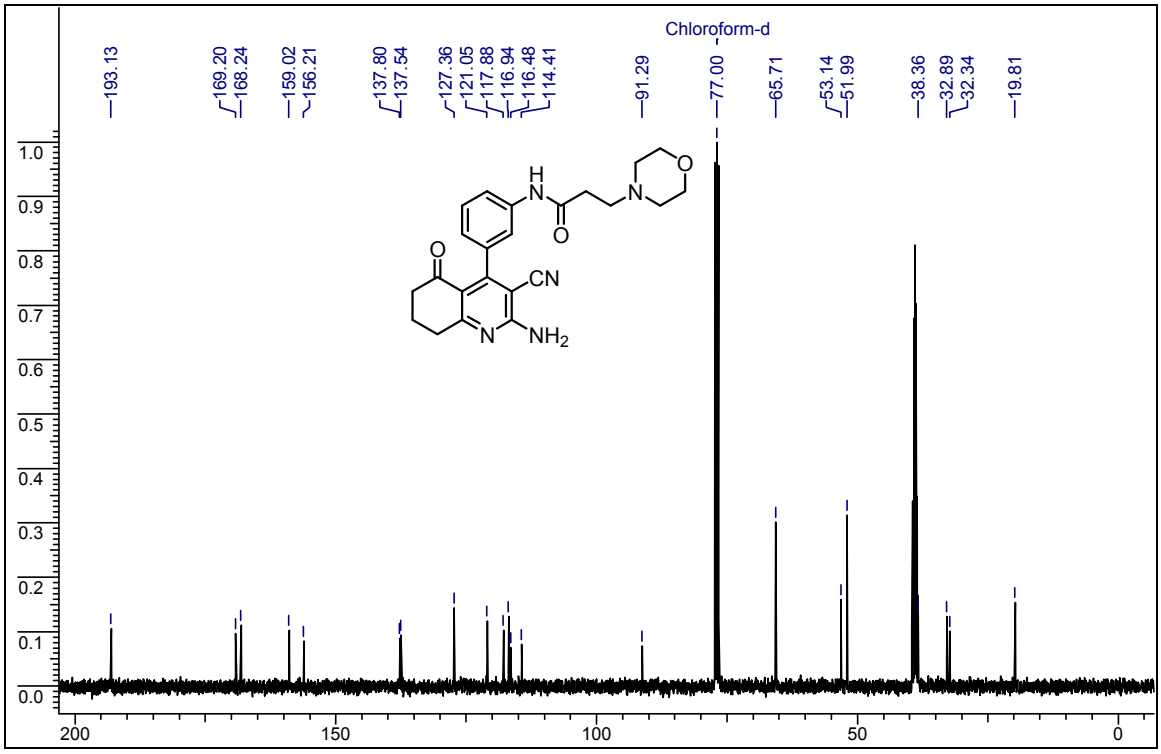
[5] ^{1}H and ^{13}C-NMR Spectra of compound 67



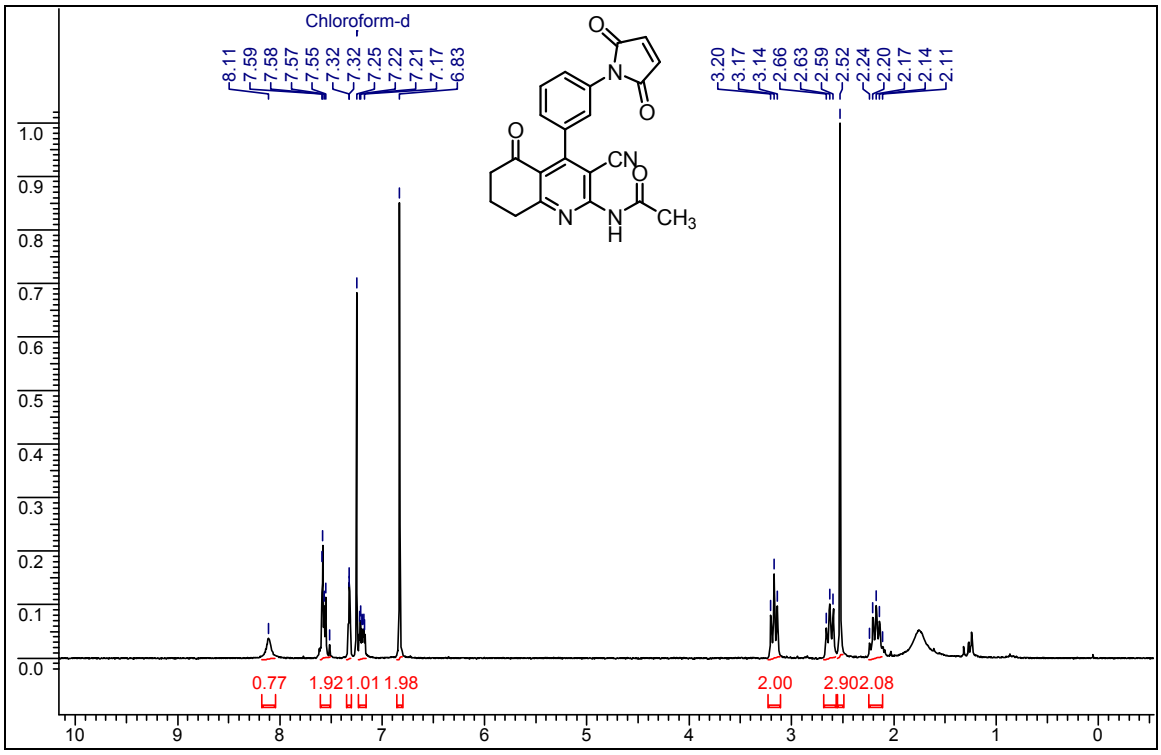


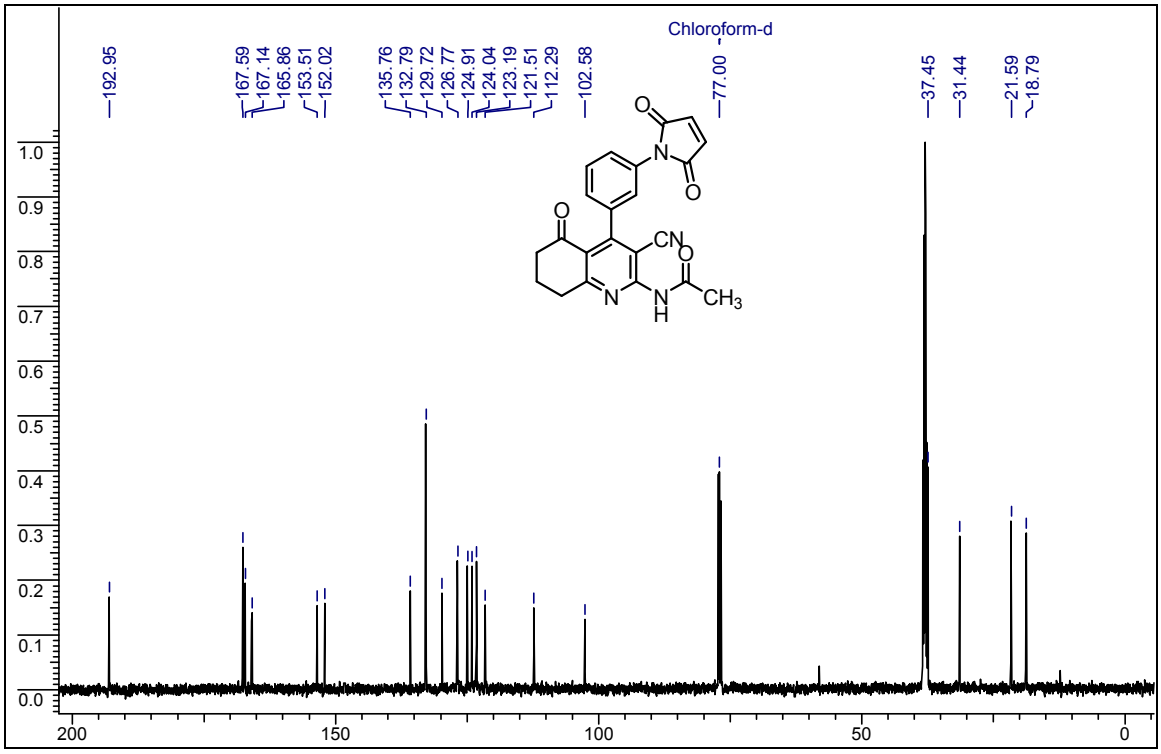
[6] ^{1}H and ^{13}C-NMR Spectra of compound 71





[7] ^{1}H and ^{13}C-NMR Spectra of compound 76





2.3.9 References

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17. Single-crystal data and CIF file of compound **63f** (**CCDC # 282502**) have been deposited at the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1123-336-033; or email: deposit@ccdc.ac.uk).
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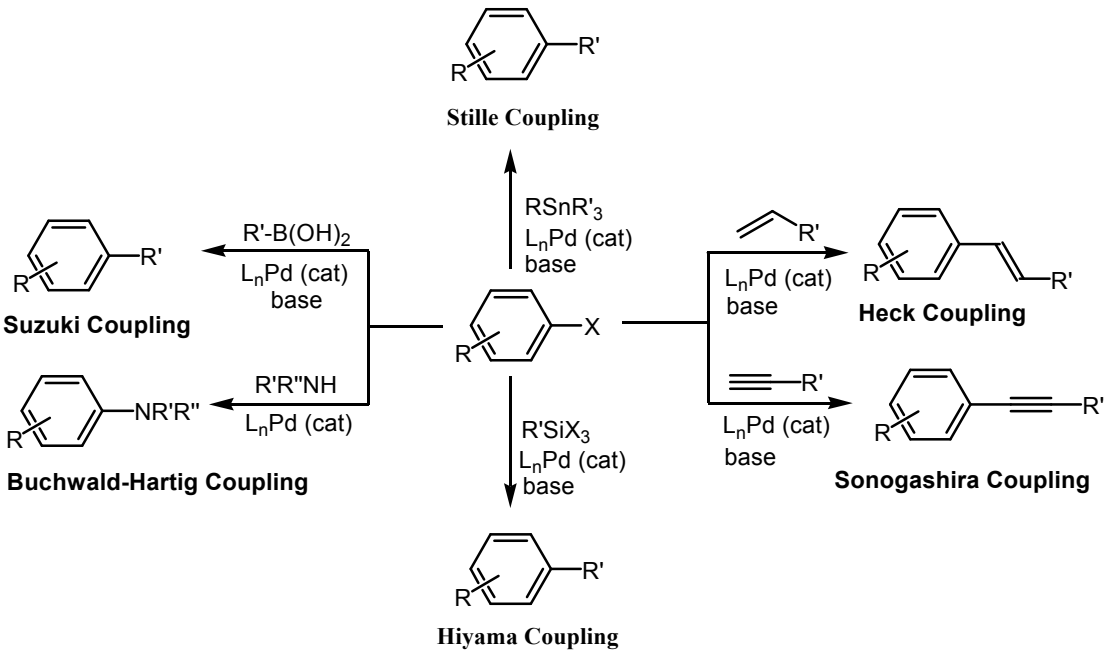
Section-D

Synthesis of Pd-enaminone complexes and their application in C-C coupling reactions

Synthesis of Pd-enaminone complexes and their application in C-C coupling reactions.

2.4.1 Introduction

Palladium-catalyzed cross-coupling reactions, such as the Heck,[1] Suzuki,[2,3] Stille,[4] Sonogashira,[5] and Hartwig-Buchwald [6,7] couplings (**Scheme 29**), have become powerful tools for carbon–carbon and carbon–heteroatom bond formation in the synthetic chemist's arsenal.[8] These coupling reactions are highly versatile in the types of substrates that can be coupled, as well as being highly functional group tolerant. In the thirty years since the initial report of these reactions, there has been an extensive amount of effort devoted to developing ever more active, general, and long-lived catalysts. These coupling reactions are increasingly being applied in the manufacture of fine chemicals and pharmaceuticals, although the catalyst activity and separation continue to be hurdles to implementation.[9-11]



Scheme 29. Palladium-catalyzed cross-coupling reactions.

Research focusing on palladium complexes and their use in C-C bond formation reaction has exponentially increased during the last 10 years. It is well understood that the ancillary ligation to the metal center plays a crucial role in dictating the efficiency of a

catalytic system.[12] As a result many efforts have been developed to the finding of air and moisture stable, more efficient and reactive Pd complexes for C-C coupling reaction. Moreover, the process of the complexation of ligand with palladium is straightforward and their palladium complexes are found to be quite suitable for cross-coupling reactions.

2.4.2 Review of Literature

In recent years, interest in cross coupling reactions has increased rapidly and several modified, stable, palladium-based catalysts have been reported in the literature for Heck, Suzuki and Sonogashira reaction. In this section we have covered some recent notable advances which have emerged as effective catalyst for cross-coupling reaction.

2.4.2.1 Palladium-Nitrogen complexes

Pyridines and pyrimidines have shown good complexation properties for palladium and have been employed in the formation of catalysts suitable for cross-coupling reactions such as Heck, Suzuki and Sonogashira couplings. Thus, the dipyrimidyl-palladium complex **77**[13] and **78**[14] (**Fig. 16**) were prepared by mixing the corresponding ligand with H_2PdCl_4 and employed for cross-coupling reactions.

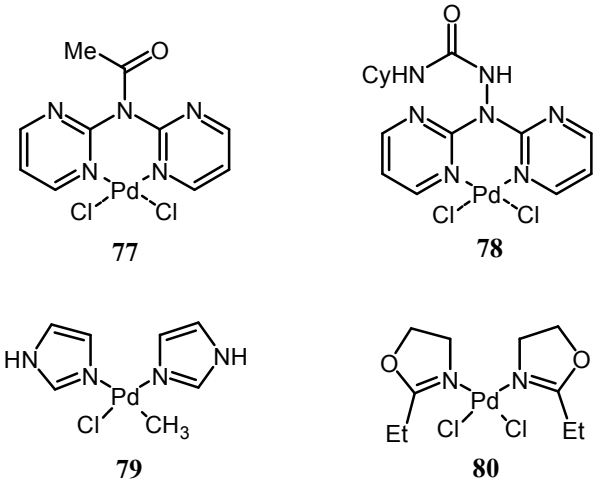
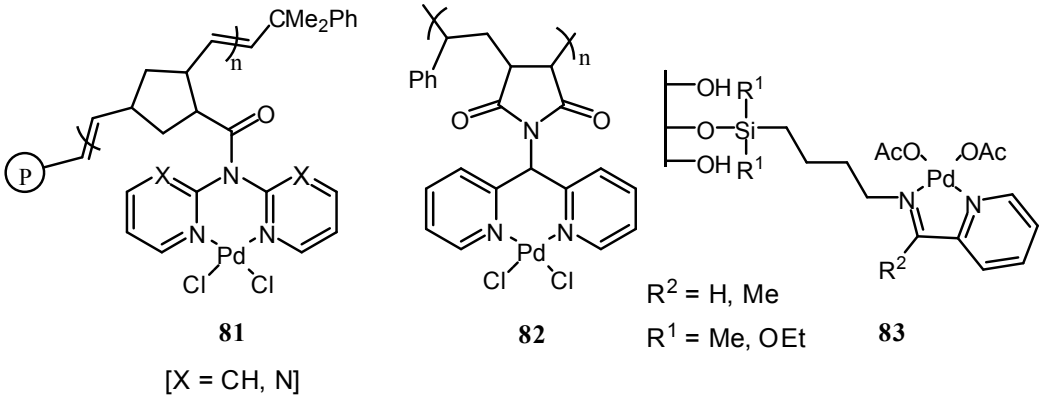


Figure 16.

The moisture and air stable bis-imidazolyl-derived palladium[15] **79** and bis-oxazoline palladium complex[16] **80** have been used in cross-coupling reactions (**Fig. 16**). Dipyridyl-based, ROMP-polymer-anchored palladium complex[17] **81** (X = CH) and Dipyridyl-based

poly-(styrene-alt-maleimide)-anchored palladium complex[18] **82** are excellent catalysts for C-C bond-forming processes such as the Heck, Suzuki, and Sonogashira reactions.



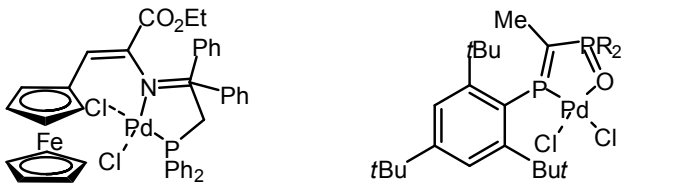
81 [X = CH, N] **82** **83**

Figure 17.

This polymeric catalyst showed a higher efficiency than its monomeric counterpart **78**, and also higher recyclability than that when using a polyurea-encapsulated palladium (II) catalyst such as Pd EnCat 40. The above mentioned catalyst was reused upto five times without appreciable losts of catalytic activity. Supported dinitrogenated ligands useful in cross-coupling reactions have been recently obtained by reaction of amino-containing silanes with silica gel. Thus, recyclable pyridine-oxime-containing palladium catalysts[19] **83** (R^1=OEt; R^2=H, Me) supported on silica gel have promoted the cross coupling reaction. The catalyst **83** could be filtered and reused, and showed some partial loss in activity after Suzuki, Heck and Sonogashira coupling (**Fig. 17**).

2.4.2.2 Palladium-P,N- and Palladium-P,O complexes

P,N-Donor bidentate ligands exhibit hemilabile behavior when coordinated to palladium, with the soft phosphorus atom coordinating strongly whereas the hard nitrogen donor is weakly bound.



84 **85**

R = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *n*Bu

Figure 18.

To this category belongs the palladium (II) complex **84**, containing a ferrocene-based phosphiniminephosphane ligand,[20] which has been used in the amine- and copper-free Sonogashira coupling. In addition, complexes **85** containing P,O-bidentate 3-oxo-1,3-diphosphapropene ligands[21] have been examined in Suzuki and Sonogashira cross-coupling reactions (**Fig. 18**).

2.4.2.3 *N*-Heterocyclic Carbene (NHC) Palladium complexes

Nucleophilic *N*-heterocyclic carbenes (NHCs) behave like typical σ-donor ligands that can substitute classical 2-electron ligands such as amines and phosphanes in metal coordination chemistry. The combination of the imidazolium salt with a palladium source under basic conditions generates the NHC-palladium complex. Batey *et al.* carried out Sonogashira reaction by using complex **86** as a catalyst.[22] Tridentate bis-carbene-pincer complex **87** has been also used in C-C cross coupling reaction.[23] Few more (NHC) palladium complexes are also reported in literature such as **88**[24], **89**[25] and **90**[26] as a catalyst for C-C cross coupling reaction (**Fig. 19**).

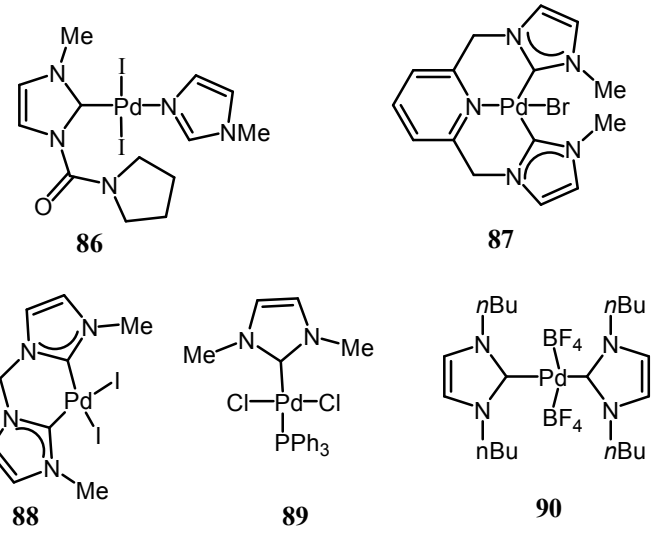


Figure 19.

2.4.2.4 Palladacycle catalysts

Palladacycles have emerged as a very promising family of organometallic catalyst precursors in C-C bond-forming processes, often showing interesting mixed characteristics such as high catalytic activity and, at the same time, high stability. It has been proven that palladacycles are not the "true" active catalyst, but rather the precatalyst

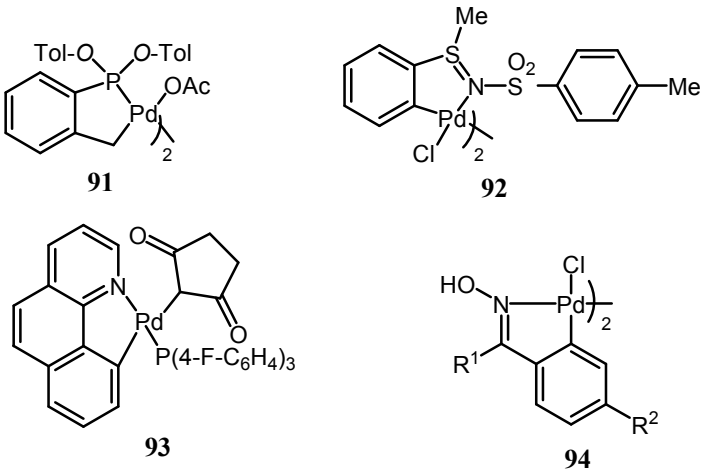


Figure 20.

that undergoes an activation process acting as a source for the formation of low-coordinate palladium(0) such as palladium nanoparticles.[27] Some of these palladacycles such as phosphapalladacycle[28] **91**, Sulfinimine palladacycle[29] **92**, cyclopaladated palladacycles[30] **93** and oxime-derived palladacycles[31] **94**, have been employed in C-C cross-coupling reactions (**Fig. 20**).

2.4.3 Present work

2.4.3.1 Objective

The basic purpose of synthetic organic chemistry is the construction of organic molecules and one of the key elements in this field is the formation of carbon-carbon bonds and is often accomplished using transition metal catalyst. Thus, these carbon-carbon bond formations have become key steps in numerous organic processes. Therefore development of a new class of active and efficient catalytic system by modifying traditional ligands is an ongoing challenge. In recent years great advances has been achieved in the synthesis of bulky phosphanes and phosphates ligands. But uses of phosphane-based ligands are moisture sensitive and create difficulties with separation of ligands and their degradation product like phosphine oxides etc.

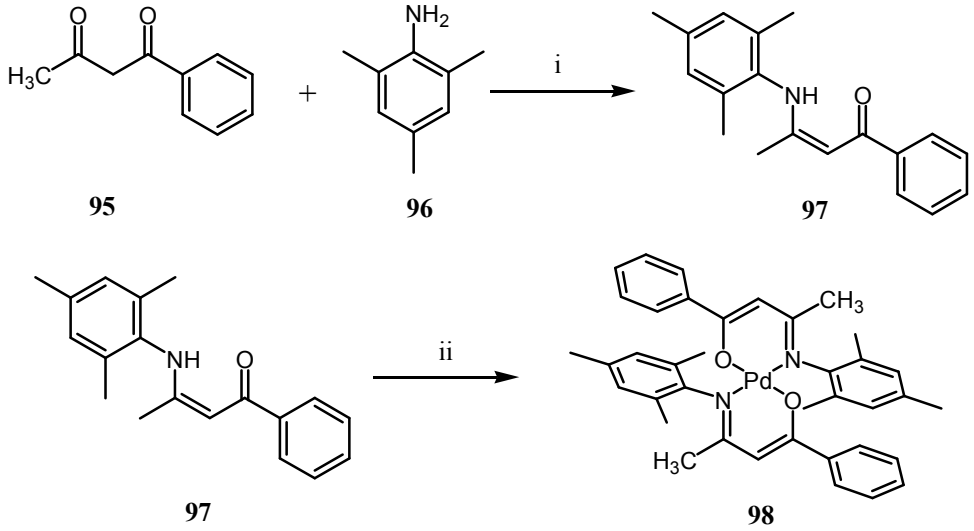
Recent developments in this area suggest that an electron rich metal center facilitates oxidative addition and steric congestion around the metal accelerates the reductive elimination step.[32] Accordingly, we designed novel Pd enaminone complex as a monoanionic bidentate complex starting from easily available enaminone. The anions $[R'C(O)CHC(NAr)R]^-$ generated from the above enaminones offer potential isoelectronic

alternatives to the cyclopentadienyl-based anions[33] and can be used as good chelating ligands for palladium complexes. In the present work we carried out the synthesis of novel Pd(II) enaminone complexes. The catalytic activity of these Pd(II) enaminone complexes toward the Suzuki, Heck and Sonogashira reaction were investigated.

2.4.3.2 Results and discussion

2.4.3.2.1 Synthesis of Pd-enaminone complex (98)

It was planned to synthesize different Pd enaminone complexes with electronic and steric variations. Both electronic and steric effects can be addressed effectively by incorporating electron donating/electron withdrawing groups on the aromatic rings present on enaminone moiety. As shown in **Scheme 30**, the Pd enaminone complex was **98** prepared starting from benzoylacetone **95** and 2,4,6 trimethyl aniline **96** in the presence of catalytic amount of *p*-toulenesulfonic acid in refluxing toluene via the removal of water using a Dean-Stark apparatus affording the corresponding enaminone **97** in good yield. The enaminone **97** stirred with $Pd(OAc)_2$ in absolute ethanol at 24 h generating the Pd-enaminone complex **98** as yellow solid in 80% yield.



Scheme 30. Reaction conditions: (i) PTSA, toluene, reflux 3 h, 90%; (ii) $Pd(OAc)_2$, ethanol, rt, 24 h, 80%.

The Pd(II) enaminone complex **98** was completely characterized by ^1H NMR, ^{13}C NMR and elemental analysis. The single crystal of this complex suitable for X-ray crystal structure analysis was grown from dichloromethane/petroleum ether (6:4) solution.

According to ORTEP diagram[34] the Pd metal center is surrounded by four heteroatom having planar or tetrahedral co-ordination geometry. The two phenyl rings containing 2,4,6 trimethyl group are anti or syn in arrangement (**Fig. 21**).

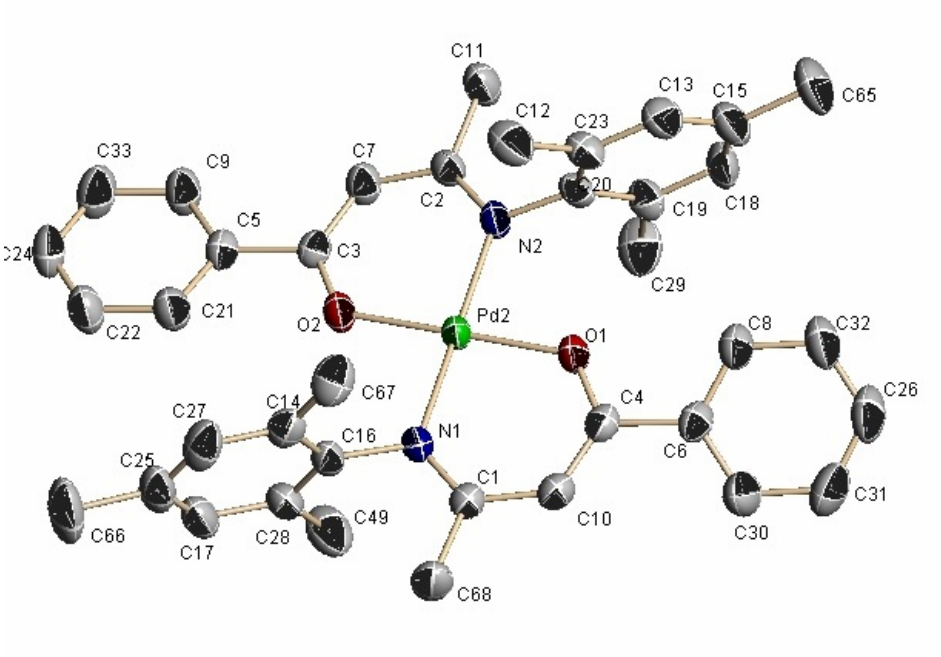


Figure 21. ORTEP diagram of Pd(II) enaminone complex **98.**

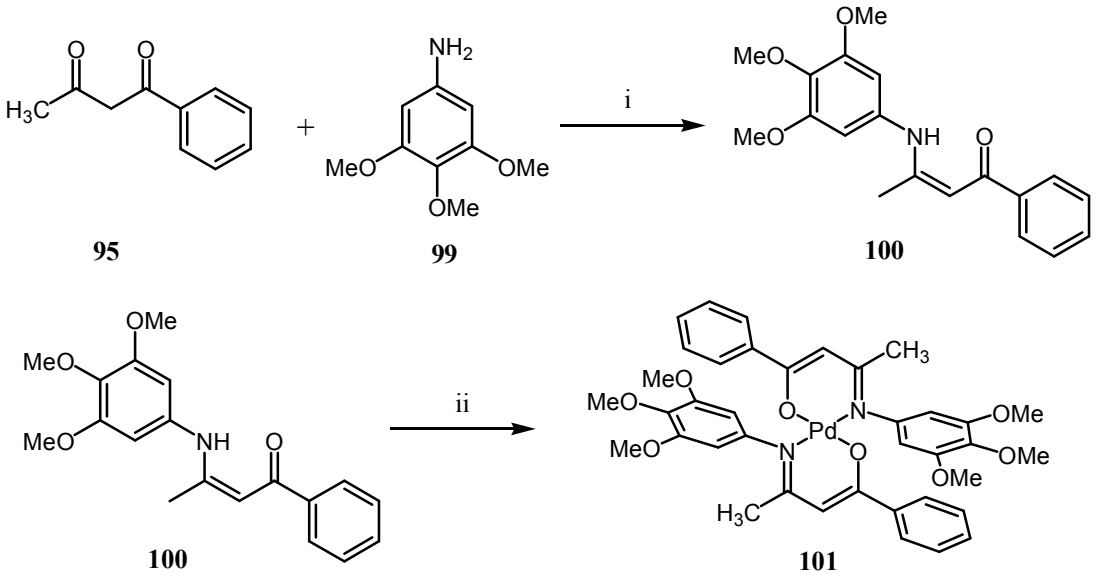
Table 17. Data collection and refinement parameters for compound **98**

Crystal data	
Chemical formula	$C_{38}H_{40}N_2O_2Pd$
M_r	663.12
Cell setting, space group	Monoclinic, *C*2
Temperature (K)	298 (2)
a, *b*, *c* (Å)	23.435 (4), 13.391 (2), 16.047 (3)
β (°)	101.497 (3)
V (Å^3)	4935.0 (14)
Z	6
D_x (Mg m^{-3})	1.339
Radiation type	Mo *K*α
μ (mm^{-1})	0.60
Crystal form, colour	Flat, orenge

Crystal size (mm)	0.59 × 0.17 × 0.14
Data collection	
Diffractometer	CCD Area Detector
Data collection method	ω and phi Scan
Absorption correction	Multi-scan
T_{min}	0.719
T_{max}	0.921
No. of measured, independent and observed reflections	12421, 8084, 7604
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.023
θ_{max} (°)	25.0
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.035, 0.091, 1.11
No. of relections	8084 reflections
No. of parameters	594
H-atom treatment	Riding
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0448P)^2 + 0.3411P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.090
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.65, –0.38

2.4.3.2.2 Synthesis of Pd-enaminone complex (101)

Reaction of benzoylacetone **95** and 3,4,5 trimethoxy aniline **99** in the presence of catalytic amount of *p*-toulenesulfonic acid in refluxing toluene via the removal of water using a Dean-Stark apparatus affords the corresponding enaminones **100** in good yield (**Scheme 31**).



Scheme 31. Reaction conditions: (i) PTSA, toluene, reflux 4 h, 88 %; (ii) $Pd(OAc)_2$, ethanol, rt, 24 h, 82%.

The palladium enaminone complex **101** was obtained as a yellow solid by the reaction of enaminone **100** by stirring with palladium acetate in absolute ethanol for 24 h. It was thought that Pd enaminone complex **101** will become more electron rich around the Pd center than the complex **98** due to the presence of six electron donating methoxy groups present on *N*-substituted phenyl ring. The complex is completely characterized by spectral and elemental analysis.

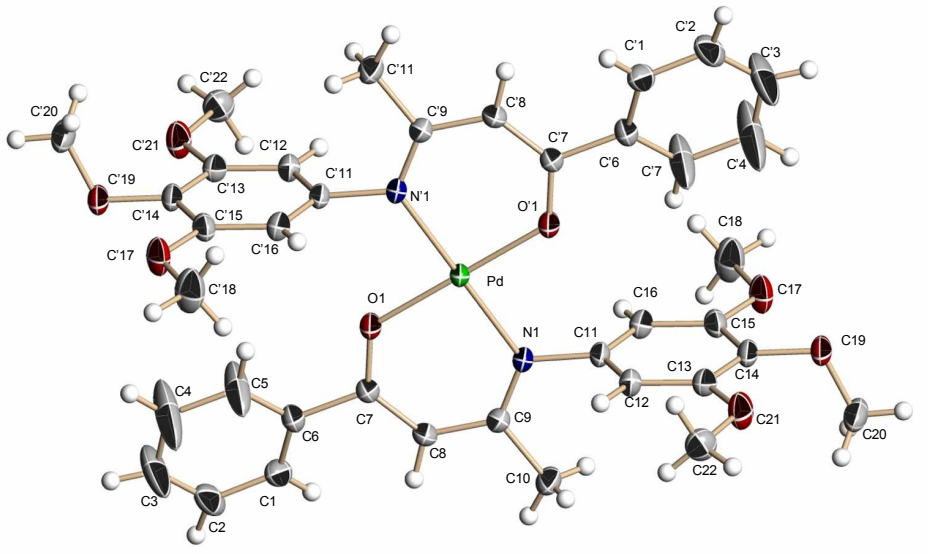


Figure 22. ORTEP diagram of Pd(II) enaminone complex **101.**

Single crystal for X-Ray diffraction study[34] was grown from dichloromethane/petroleum ether (8:2) solution. The ORTEP diagram of complex **101** shows the planar and tetrahedral geometry of molecule with metal center surrounded with four hetero atoms. Two *N*-substituted 3,4,5 trimethoxy phenyl rings are in syn or anti position to each other (**Fig. 22**).

Table 18. Data collection and refinement parameters for compound **101**

Crystal data	
Chemical formula	$C_{38}H_{40}N_2O_8Pd$
M_r	759.12
Cell setting, space group	Monoclinic, *P*2(1)/*n*
Temperature (K)	298 (2)
a, *b*, *c* (Å)	11.571 (3), 12.933 (3), 12.251 (3)
β (°)	106.915 (4)
V (Å^3)	1754.0 (7)
Z	2
D_x (Mg m^{-3})	1.437
Radiation type	Mo *K*α
μ (mm^{-1})	0.58
Crystal form, colour	Plate, yellow
Crystal size (mm)	0.37 × 0.21 × 0.04
Data collection	
Diffractometer	CCD Area Detector
Data collection method	ω and phi Scan
Absorption correction	Multi-scan
T_{min}	0.813
T_{max}	0.977
No. of measured, independent and observed reflections	8687, 3079, 2521
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.022
θ_{max} (°)	25.0
Refinement	

No. of measured, independent and observed reflections	8687, 3079, 2521
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.032, 0.088, 1.03
No. of relections	3079 reflections
No. of parameters	280
H-atom treatment	Riding
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0517P)^2 + 0.6846P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.43, –0.33

The anilines, with strongly electron withdrawing groups such as 4-nitroaniline did not yield any product with reaction of benzoylacetone. As a result all our attempts were failed to synthesis Pd enaminone complex having electron withdrawing NO_2 group.

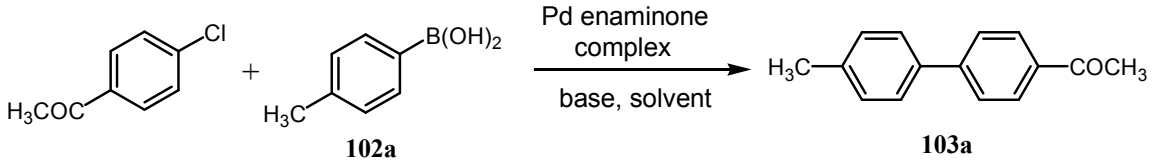
As is well known now the performance of a palladium catalyst for carbon-carbon cross-coupling reaction is governed by a number of factors such as: palladium source, ligand, base, solvent, temperature, etc. There is not a set rule that each catalyst needs a specific solvent and a certain base to attain the highest efficiency. Here, Suzuki coupling reactions were carried out by employing the newly synthesized Pd(II) enaminone complex **(98)** and **(101)** as a catalyst respectively.

2.4.3.3 Suzuki-Miyaura reaction using Pd-enaminone complexes (98 and 101).

The Suzuki-Miyaura reaction has become the method of choice for biaryl and heterobiaryl synthesis. These moieties are widely present in numerous classes of organic compounds, such as natural products, pharmaceuticals, agrochemicals. Some of the challenges related to the industrial applications of this cross-coupling reaction are focused on the use of aryl chlorides and bromides as substrates. In the present work the coupling of aryl chlorides and bromides with arylboronic acid was carried out by using Pd(II) enaminone complexes without the addition of any additive.

Optimization of reaction conditions for Suzuki-Miyura reaction:

To begin with study, we performed the Suzuki reaction between 4-chloroacetophenone and *p*-tolylboronic acid with 2 mol% of Pd(II) enaminone complex **(98)** using various solvent and base combinations at thermal condition to find the optimum reaction condition (**Scheme 32**).



102a **103a**

Scheme 32.

The results are recorded in **Table 19.** We found that poor yields were obtained when etheral solvents such as dioxane and THF or nonploar solvent toluene were used in combination with bases such as K_3PO_4, K_2CO_3 and CS_2CO_3 (**entries 1-5**).

Table 19. Suzuki reaction: reaction conditions study

Entry	Solvent	Base	Temp. °C	Time (h)	[c]Yield (%)
[a]1	1,4-dioxane	K_3PO_4	100	12h	55
[a]2	1,4-dioxane	K_2CO_3	100	12h	45
[a]3	1,4-dioxane	Cs_2CO_3	100	12h	48
[a]4	THF	K_3PO_4	80	12h	30
[a]5	Toluene	K_3PO_4	110	12h	50
[a]6	Water	K_2CO_3	100	12h	NR
[a]7	Ethanol:water (80:20)	K_3PO_4	100	12h	NR
[a]8	DMF	K_3PO_4	120	5h	85
[a]9	DMF:H_2O (95:5)	K_2CO_3	120	2h	90
[a]10	DMF:H_2O (95:5)	K_3PO_4	120	2h	95
[a]11	DMF:H_2O (95:5)	Cs_2CO_3	120	2h	92
[b]12	DMF:H_2O (95:5)	K_3PO_4	120	1h	98

[a]Reaction catalyzed by Pd enaminone complex **(98)**
[b]Reaction catalyzed by Pd enaminone complex **(101)**
[c]Isolated yields.

The polar solvents such as water and aqueous ethanol failed to generate any cross-coupled product (**entries 6, 7**). It was found that the reaction proceeded smoothly at 120

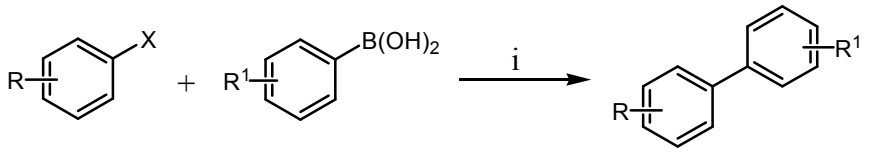
ºC in DMF as a solvent and K_3PO_4 as base (**entry 8**). The cross-coupled product was obtained with good yield without any inert gas protection. We then discovered that mixture of DMF and water (95:5) as solvent gave the best results (**entries 9-11**). The cross coupled product was isolated in 90-92% yields. However, the best optimized conditions were obtained by making the use of K_3PO_4 as the base in DMF-H_2O, and Pd enaminone complex **(98)** 2 mol% as the catalyst wherein the cross-coupled product could be isolated in 95% yield in a reaction time of 2 h (**entry 10**).

The optimized reaction conditions (K_3PO_4, DMF:H_2O 95:5, 120 ºC) as mentioned above (**entry 10**) was applied for the reaction of 4-chloroacetophenone with *p*-tolylboronic acid using 2 mol% of Pd(II) enaminone complex **(101)**. The reaction was followed by subjecting aliquots of reaction mixture to GC at 10 min intervals. It was observed that all the starting material consumed completely after 60 min. The cross coupled product was isolated in 98% yield after column chromatography (**entry 12**). Thus from this result it was observed that Pd(II) enaminone complex **101** is significantly more reactive as compared to Pd(II) enaminone complex **(98).**

This trend in reactivity is in agreement with the stronger electron donating ability of methoxy groups present on the phenyl ring making the palladium metal center more electron rich. The established mechanism for the Suzuki reaction is believed to proceed through three discrete steps: oxidative addition, transmetalation, and finally, reductive elimination concomitant with regeneration of the Pd(0) species. Oxidative addition is believed to be enhanced by an electron-rich palladium centre. Thus the presence of methoxy substituents present on two phenyl ring of Pd enaminone complex **(101)** makes the palladium metal center electron rich and the electron rich metal centre has facilitated the oxidative addition by virtue of the enhanced activity of the catalyst for the oxidative addition more than that for Pd(II) enaminone complex **98** with miniature electron donating nature of the methyl group.

The Pd-enaminone complex **98** and **101** appear to be useful in the C-C coupling reaction, but to achieve the higher yields in short reaction time and to evaluate the scope and limitation of this procedure, we performed a number of coupling reactions of a variety of aryl bromides and aryl chlorides with phenylboronic acid using Pd-enaminone complex (**101**) as Pd source without any additive under aerobic conditions in consideration of its beneficial air- and moisture stable properties.

Aryl bromides and chlorides are cheaper and more readily available substrates than the corresponding iodides but are more reluctant to undergo the catalytic Suzuki reaction. The coupling reaction between a range of substrates and several arylboronic acids was then conducted to explore the general effectiveness of the Pd(II) enaminone complex **(101)** 2 mol% /K_3PO_4/DMF: H_2O (95:5) system (**Scheme 33**).



102(a-f) **103(a-r)**

X = Br, Cl

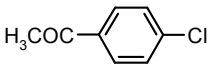
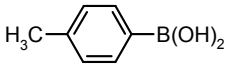
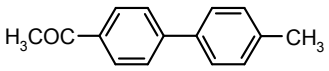
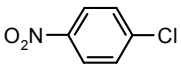
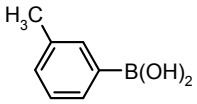
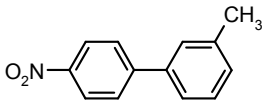
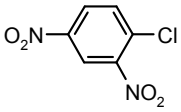
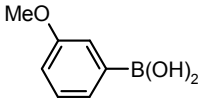
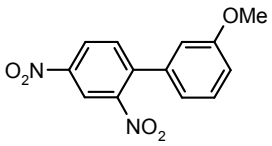
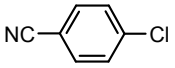
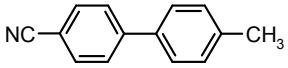
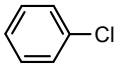
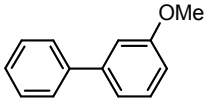
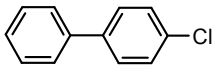
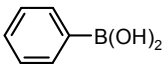
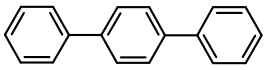
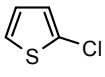
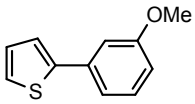
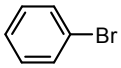
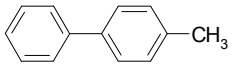
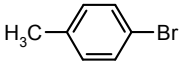
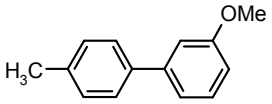
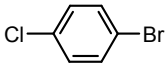
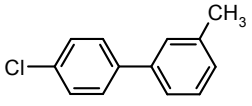
R = H, CH_3, OH, F, Cl, $COCH_3$, NO_2, CN R^1 = H, CH_3, OMe, F, $COCH_3$

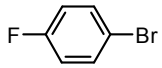
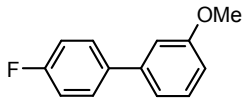
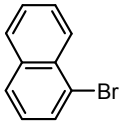
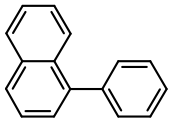
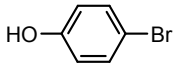
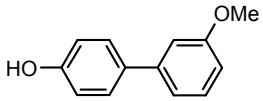
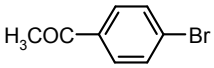
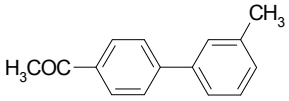
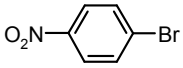
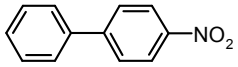
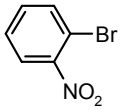
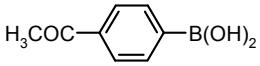
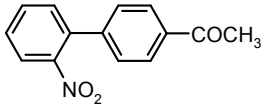
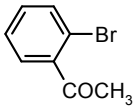
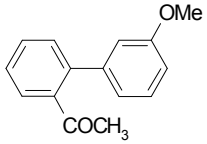
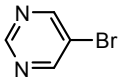
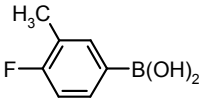
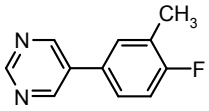
Scheme 33. Reaction conditions: (i) Pd(II) enaminone complex **(101)** 2 mol%, K_3PO_4, DMF:H_2O 95:5, 120 ºC, 1-12 h, 65-99%.

The results are recorded in **Table 20**. Under the above optimized reaction conditions, a wide range of electron-deficient aryl chlorides **(entry 1-5),** undergoes cross-coupling reaction efficiently with arylboronic acids. Moreover, electron-neutral aryl chlorides gave moderate yields by coupling arylboronic acid (**entry 5** and **6**).

With the excellent reaction conditions in hand, we then decided to explore the couplings of aryl bromides with various arylboronic acids as shown in **Table 20**. The reactions between aryl bromides and arylboronic acids were go to completion in short reaction times to afford the corresponding biaryls in excellent yields (**Table 20, entry 8-18**).

Table 20. Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acids in presence of Pd-enaminone complex (**101**).

Entry	Aryl halide	Boronic acid 102(a-f)	Time (h)	[a]Yield (%)	Product 103(a-r)
1		 **102a**	1	98	 **103a**
2		 **102b**	1	95	 **103b**
3		 **102c**	1	96	 **103c**
4		**102a**	1	97	 **103d**
5		**102c**	12	65	 **103e**
6		 **102d**	12	68	 **103f**
7		**102c**	1	92	 **103g**
8		**102a**	1	95	 **103h**
9		**102c**	1	96	 **103i**
10		**102b**	1	94	

					103j
11		**102c**	1	97	 **103k**
12		**102d**	1	98	 **103l**
13		**102c**	1	95	 **103m**
14		**102b**	0.5	97	 **103n**
15		**102d**	0.5	99	 **103o**
16		 **102e**	0.5	98	 **103p**
17		**102c**	0.5	96	 **103q**
18		 **102e**	0.5	95	 **103r**

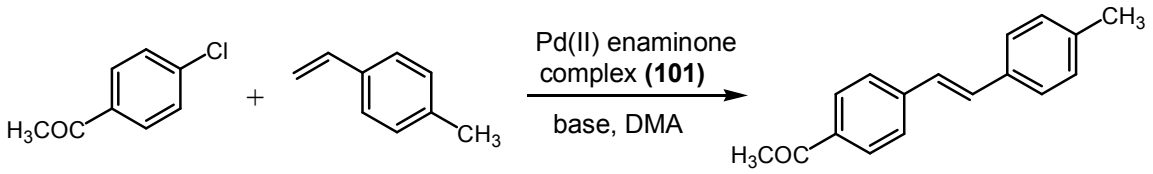
[a]Isolated yields after column chromatography

2.4.3.4 Heck reaction using Pd-enaminone complex (101)

The Pd-catalyzed cross-coupling of olefins with aryl halides is known as the Heck reaction.[35] This reaction normally performed with phosphine ligands and has become a widely used C-C bond forming process in academic institutions. However, industrial applications of the Heck reaction are still rare due to use of phosphine ligands.[36] Many phosphine ligands are more expensive, and they are not pleasant to work as they are

poisonous, air sensitive and subject to P-C bond degradation at elevated temperature. Accordingly, one of the current focuses in the field is the development of air, moisture stable and inexpensive non-phosphine Pd complexes. In the present work we have investigated the efficacy of Pd(II) enaminone complex **(101)** as a catalyst for Heck reaction without the need for a phosphine ligand.

We examined the catalytic activity of **101** in the Heck reaction using the coupling of 4-chloroacetophenone with 4-methylstyrene in DMA at 140 ºC in the presence of various bases (**Scheme 34**). The results are recorded in **Table 21**.



104a **105a**

Scheme 34. Reaction conditions: (i) Pd(II) enaminone complex (1 mol%), base, TBAB (20 mol%), DMA, 140 ºC, 5 h.

We found that NaOAc afforded the best results for this reaction and offered the coupling product in **105a** in 95% isolated yield under aerobic condition in the presence of Pd(II)-enaminone complex **(101)** (1 mol%) and TBAB (20 mol%) as additive (**entry 6**, **Table 21**).

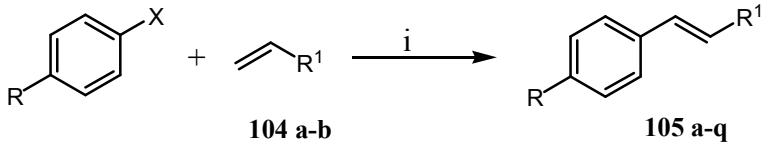
Table 21. Pd(II)-enaminone complex **(101)** catalyzed Heck coupling in various bases

[a]**Entry**	**Base**	**Time (h)**	[b]**Yield (%) 105a**
1	K_2CO_3	5	75
2	Na_2CO_3	5	70
3	CS_2CO_3	5	80
4	KF	5	85
5	K_3PO_4	5	84
6	NaOAc	5	95

[a]TBAB (20 mol%) was used in all cases
[b]Isolated yields

The presence of TBAB in Pd-catalyzed cross-coupling reactions, especially in Heck reactions, increase the conversion rate by formation and stabilization of Pd colloids.[37]

Using these optimized reaction conditions, we next examined the Heck coupling of a number of activated aryl chlorides and bromides with olefins in the presence of Pd(II) enaminone complex (1 mol%) (**101**), NaOAc and TBAB as additive in DMA at 140 ºC. The products are obtained with good yields and >99% *trans*-selectivity. The chloroarenes where the chlorine is activated by electron withdrawing group undergo olefination smoothly giving good to excellent isolated yields of cross-coupled product. In the case of electron-neutral chlorobenzene the reaction required longer duration (12 h) to obtained cross coupled product in 65% isolated yield. In case of activated as well as deactivated aryl bromides the palladium enaminone



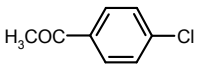
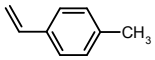
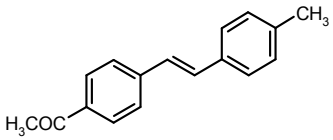
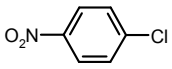
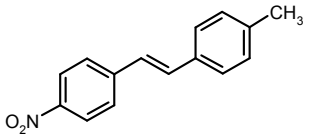
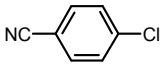
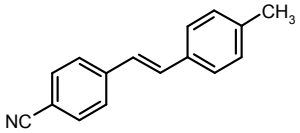
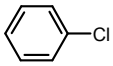
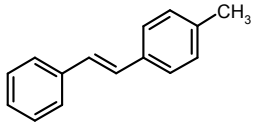
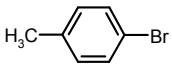
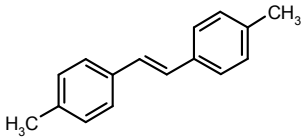
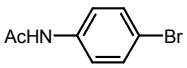
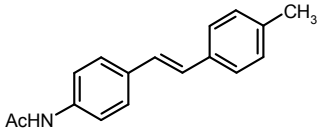
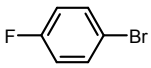
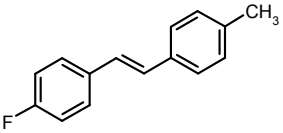
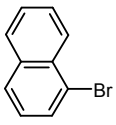
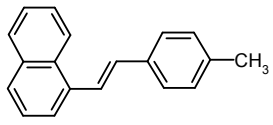
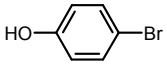
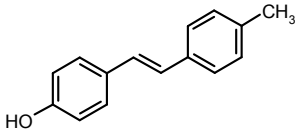
104 a-b **105 a-q**

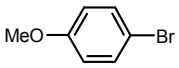
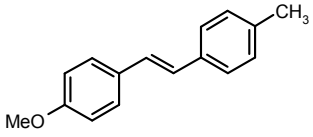
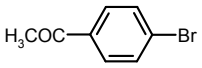
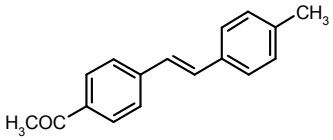
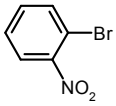
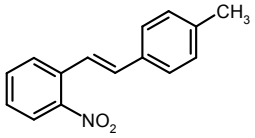
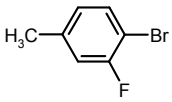
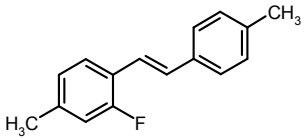
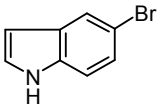
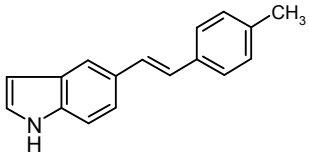
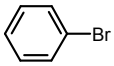
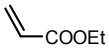
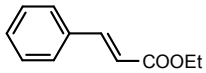
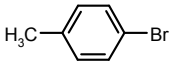
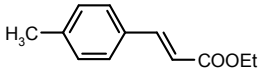
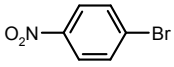
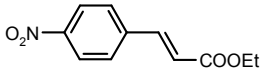
X =Cl, Br R^1 = CH_3-C_6H_4 **104a** = COOEt **104b** R = H, $COCH_3$, NO_2, CN, CH_3, Cl, F, OH, OMe,

Scheme 35 Reaction conditions: (i) Pd(II) enaminone complex **(101)** (1 mol%), NaOAc, TBAB (20 mol%), DMA, 140 ºC, 3-12 h.

complex **(101)** was found to be active and resulted in full conversion to obtain the cross-coupled product in excellent isolated yields in presence of 1 mol% of the catalyst **101.** Under these optimized reaction conditions structurally diverse aryl halides could be cross-coupled efficiently with ethyl acrylate. The results are listed in **Table 22.** The data from **Table 22** suggest that styrene with aryl halides required the longer reaction time than ethyl acrylate with aryl halides.

Table 22. Heck cross-coupling reaction of aryl halides.

Entry[a]	Aryl halide	Olefin 104a-b	Time (h)	Yield[b] (%)	Product 105 a-q
1		 **104a**	5	95	 **105a**
2		**104a**	5	94	 **105b**
3		**104a**	5	92	 **105c**
4		**104a**	12	65	 **105d**
5		**104a**	4	92	 **105e**
6		**104a**	4	94	 **105f**
7		**104a**	4	91	 **105g**
8		**104a**	4	94	 **105h**
9		**104a**	4	92	 **105i**

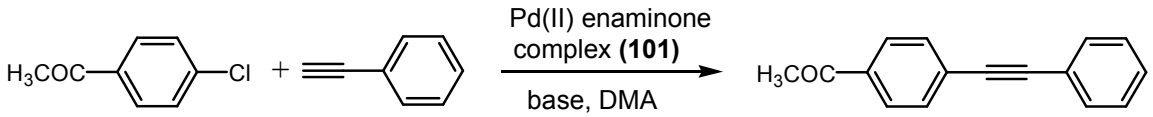
10		**104a**	4	90	 **105j**
11		**104a**	3	95	 **105k**
12		**104a**	3	96	 **105l**
13		**104a**	4	93	 **105m**
14		**104a**	4	90	 **105n**
15		 **104b**	2	92	 **105o**
16		**104b**	2	94	 **105p**
17		**104b**	2	97	 **105q**

[a]TBAB (20 mol%) was used in all cases
[b]Isolated yields

2.4.3.5 A copper-free Sonogashira reaction using Pd enaminone complex (101).

Cross-coupling reactions of acetylenes with aryl or alkenyl halides or triflates in the presence of a palladium salt or complex, copper iodide and an amine known as Sonogashira reaction are extensively used in organic chemistry and materials science for the preparation of internal alkynes and enynes.[38]

In order to simplify the Sonogashira reaction protocol, several important aspects have to be improved. First, to eliminate the use of copper(I) iodide as co-catalyst, because it induces homocoupling reactions (Glaser-type reactions) of terminal alkynes to diynes in the presence of oxygen.[39] Second to avoid, expensive and air-sensitive phosphine ligands, which places significant limits on their synthetic applications.[40] Another facet is to improve the ability to perform this reaction in air using reagent-grade chemicals and solvents. In present work, we performed the coupling of phenylacetylene and aryl halides by using Pd(II) enaminone complex **(101)** (1mol %), pyrrolidine as a base in DMA as a solvent under aerobic condition in the absence of any copper co-catalyst (**Scheme 36**).



106 **107a**

Scheme 36. Reaction conditions: (i) Pd(II) enaminone complex (1 mol%), base, TBAB (20 mol%), DMA, 110 ºC, 4h.

We have found that this alkynylation process can be performed under very convenient copper- and phosphine-free conditions in air using reagent-grade chemicals.

The alkynylation reaction of aryl halides was evaluated with Pd(II) enaminone complex **101**. In order to determine the optimum reaction conditions, we chose the coupling between 4-chloroacetophenone and phenyl acetylene in the presence of catalyst Pd(II) enaminone complex **101** (0.5-1 mol%) as a model reaction.

The coupling reaction between 4-chloroacetophenone and phenyl acetylene provided a good yield when Et_3N was used as solvent and base in the presence of CuI as co-catalyst (2.5 mol%) at 100 ºC under air using **(101)** 0.5 mol% (**Table 23**, **Entry 1**) under aerobic conditions in 10 h.

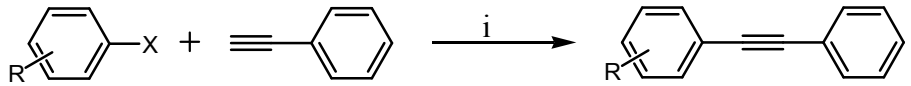
Table 23. Sonogashira coupling: reaction conditions study

Entry	Solvent	Base	Additive	(101) mol%	Time (h)	[a]Yield (%)
1	Et_3N	–	CuI	0.5	10	80
2	NMP	Pyrrolidine	TBAB	0.5	8	85
3	DMA	Pyrrolidine	TBAB	0.5	6	92
4	DMA	Pyrrolidine	TBAB	1	3	90

[a]Isolated yield after column chromatography.

When using *N*-methylpyrrolidine (NMP) as solvent and 2 equiv of pyrrolidine as base in the presence of TBAB (20 mol%) at 110 ºC (**Table 22**, **entry 2**) good yield of diphenylacetylene was obtained after 8 h of heating. When DMA was used as solvent cross-coupled product was obtained with 92% isolated yield after 6h of heating. The results showed that DMA is a better solvent than NMP and Et_3N under these conditions. Reaction time was reduced to 3h when Pd(II) enaminone complex **(101)** was taken to 1 mol% (**entry 4**, **Table 23**).

Using these optimized reaction conditions (**101** (1 mol%)**,** TBAB (20 mol%), pyrrolidine, DMA, 110 ºC) as shown in **entry 4**, we next examined the Sonogashira coupling of a number of activated aryl chlorides and bromides with phenyl acetylene (**Scheme 37**). It was found that activated aryl chlorides and aryl bromides undergoes Sonogashira reaction effectively and higher yields were obtained (**Table 24**).



106 **107a-n**

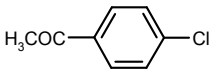
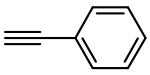
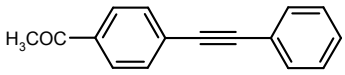
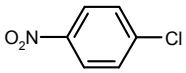
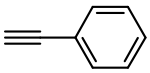
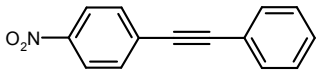
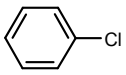
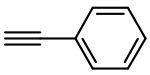
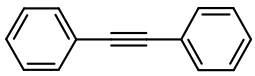
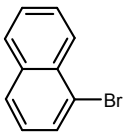
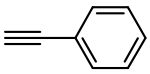
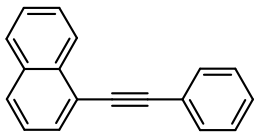
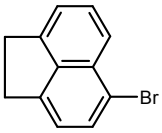
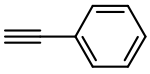
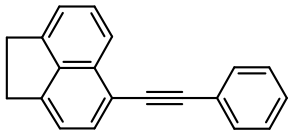
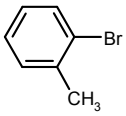
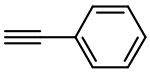
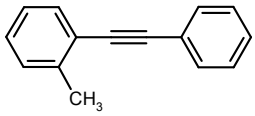
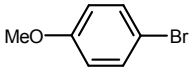
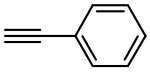
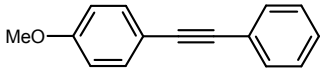
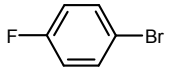
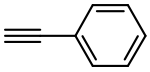
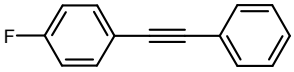
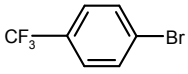
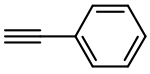
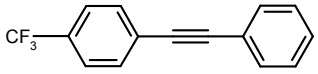
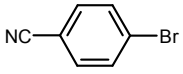
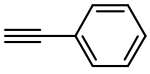
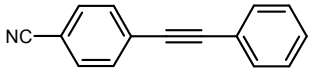
X = Cl, Br R = H, $COCH_3$, NO_2, CH_3, OMe, F, CF_3, COOEt

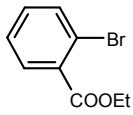
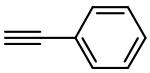
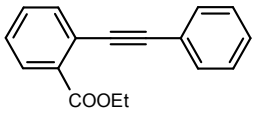
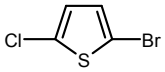
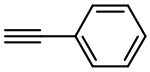
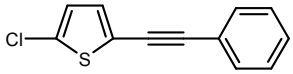
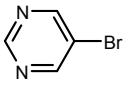
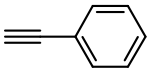
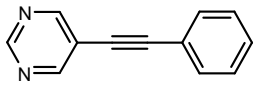
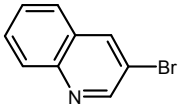
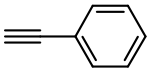
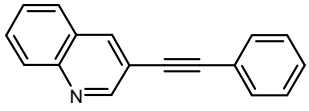
Scheme 37. Reaction conditions: (i) Pd(II) enaminone complex **(101)**, (1 mol%), pyrrolidine, TBAB (20 mol%), DMA, 110 ºC, 3-12 h.

It was observed, in the case of the less reactive aryl chlorides, the homo-coupled product arising out of the terminal acetylene was formed to an extent of 8-10%. The extent of formation of Glaser coupling product was determined by GC analysis. However, in the case of aryl bromides no Glaser coupling product was observed. In all cases, pure products were isolated by subjecting the organic layer to column

chromatography and characterized by mp, spectral, and elemental analyses. The results are recorded in **Table 24**.

Table 24. Sonogashira cross-coupling reaction of aryl halides.

[a]Entry	Aryl halide	Acetylene 106	Time (h)	Yield[b] (%)	Product 107(a-n)
1			4	90	 **107a**
2			4	91	 **107b**
3			12	50	 **107c**
4			3	91	 **107d**
5			3	90	 **107e**
6			3	89	 **107f**
7			3	85	 **107g**
8			3	92	 **107h**
9			3	90	 **107i**
10			3	92	 **107j**

11			3	91	 **107k**
12			3	85	 **107l**
13			3	88	 **107m**
14			3	86	 **107n**

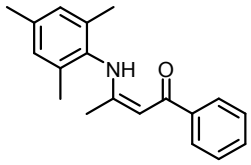
[a]TBAB (20 mol%) was used in all cases
[b] Isolated yields

2.4.4 Conclusion

In conclusion, we have described the reaction of enaminones and palladium acetate affords planar complexes **98** and **101** with electronic variations in which the enaminone coordinates to the palladium ion as a monoanionic bidentate ligand via carbonyl oxygen and enamine nitrogen atoms after deprotonation. Both complexes are air and moisture stable and can be prepared on multigram scale in high yields. The Pd enaminone complex **101** displays high activity for Suzuki, Heck and Sonogashira coupling reactions. We have also shown that the Pd enaminone complex **101** is an efficient and versatile catalyst for copper- and phosphine free Sonogashira reaction. The ease of preparation of the complex, its high solubility in organic solvents, stability towards air and moisture make it an ideal catalyst for the above transformations.

2.4.5 Experimental section

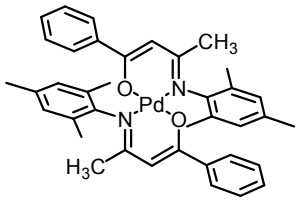
(*Z*)-3-(mesitylamino)-1-phenylbut-2-en-1-one (97):



A solution of benzoylacetone (3 g, 18.51 mmol), 2,4,6 trimethylaniline (3.24 g, 24.07 mmol) and a catalytic amount of *p*-TsOH (~10 mg) in 25 ml of toluene was refluxed with a Dean-Stark apparatus to remove water for 3 h. The solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using petroleum ether and ethyl acetate (9:1) to afford the pure product.

Nature	**:**	White solid
Yield	**:**	4.64 g, 90%
MP	**:**	78-80 ºC.
^{1}HNMR (200MHz) ($CDCl_3$)	**:**	1.78 (s, 3H), 2.20 (s, 6H), 2.30 (s, 3H), 5.92 (s, 1H), 6.93 (s, 2H), 7.40-7.46 (m, 3H), 7.92-7.97 (m, 2H), 12.44 (s, 1H).
^{13}C NMR (50MHz) ($CDCl_3$)	**:**	18.1, 19.4, 20.9, 92.1, 126.9, 128.1, 128.9, 130.6, 133.8, 135.5, 137.1, 140.0, 165.0, 188.3.
Elemental Analysis	**:**	Calcd: C, 81.68; H, 7.58; N, 5.01.
$C_{19}H_{21}NO$ (279)		Found: C, 81.75; H, 7.42; N, 4.88.

Pd enaminone complex (98):



A solution of enaminone ligand (**97**) (0.5 g, 1.79 mmol) in absolute ethanol (10 ml) was added dropwise to a stirred solution of $Pd(OAc)_2$ (0.201 g, 0.89 mmol) in the same solvent (10 ml). The mixture was stirred for 24 h at room temperature and then filtered to afford the crude product. The resultant product was purified by repeatedly washing the crude product with ethanol.

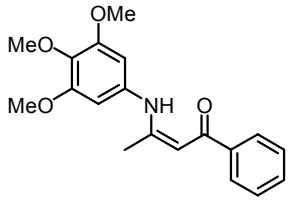
Nature	**:**	Yellow solid
Yield	**:**	0.64 g, 80%.
MP	**:**	238-242 ºC.
^{1}HNMR (200MHz) ($CDCl_3$)	**:**	1.62 (s, 6H), 2.24 (s, 12H), 2.36 (s, 6H), 5.65 (s, 2H), 6.81-6.89 (m, 8H), 7.07-7.14 (m, 4H), 7.21-7.25 (m, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : 18.6, 21.1, 23.5, 95.9, 126.9, 127.2, 128.9, 129.0, 132.3, 134.1, 137.4, 144.2, 163.5, 170.6.

Elemental Analysis : Calcd: C, 68.82; H, 6.08; N, 4.22.

$C_{38}H_{40}N_2O_2Pd$ (663) Found: C, 68.90; H, 6.16; N, 4.20.

(*Z*)-3-(3,4,5-trimethoxyphenylamino)-1-phenylbut-2-en-1-one (100):



A solution of benzoylacetone (3 g, 18.51 mmol), 3,4,5 trimethoxyaniline (4.40 g, 24.07 mmol) and a trace amount of *p*-TsOH (~10 mg) in 25 ml of toluene was refluxed for 3 h with a Dean-Stark apparatus to remove water. The solvent was evaporated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography using petroleum ether and ethyl acetate (8:2) to afford pure product.

Nature : Yellow solid

Yield : 5.32 g, 88%.

MP : 92-94 ºC.

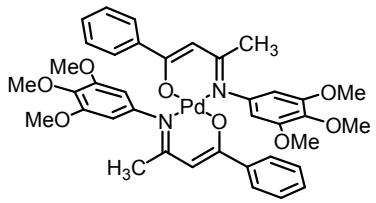
^{1}HNMR (200MHz) (CDCl$_3$) : 2.15 (s, 3H), 3.85 (s, 6H), 3.86 (s, 3H), 5.89 (s, 1H), 6.41 (s, 2H), 7.42-7.47 (m, 3H), 7.89-7.94 (m, 2H), 13.02 (br s, 1H).

^{13}C NMR (50MHz) (CDCl$_3$) : 20.2, 56.0, 60.8, 93.9, 102.5, 126.9, 128.1, 130.8, 134.2, 136.0, 139.8, 153.2, 162.3, 188.5.

Elemental Analysis : Calcd: C, 69.71; H, 6.47; N, 4.28.

$C_{19}H_{21}NO_4$ (327) Found: C, 69.58; H, 6.45; N, 4.34.

Pd enaminone complex (101)



A solution of enaminone ligand (**100**) (0.5 g, 1.52 mmol) in absolute ethanol (10 ml) was added dropwise to a stirred solution of $Pd(OAc)_2$ (0.171 g, 0.76 mmol) in the same solvent (10 ml). The mixture was stirred for 24 h at room temperature and then filtered to afford the crude product. The resultant product was purified by repeatedly washing the crude product with ethanol.

Nature : Yellow solid

Yield : 0.68 g, 82%.

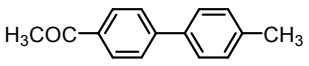
MP	**:**	258-260 ºC.
^{1}HNMR (200MHz) (CDCl$_3$)	**:**	1.90 (s, 6H), 3.73 (s, 12H), 3.94 (s, 6H), 5.67 (s, 2H), 6.41 (s, 4H), 7.06-7.09 (m, 4H), 7.23-7.35 (m, 6H).
^{13}C NMR (50MHz) (CDCl$_3$)	**:**	24.3, 55.9, 60.9, 96.7, 103.4, 126.5, 127.6, 129.5, 135.5, 137.6, 144.4, 153.1, 164.5, 171.7.
Elemental Analysis	**:**	Calcd: C, 60.12; H, 5.31; N, 3.69.
$C_{38}H_{40}N_2O_8Pd$ (759)		Found: C, 60.20; H, 5.22; N, 3.74.

General experimental procedure for Suzuki cross coupling reaction

A mixture of aryl halide (1 mmol), arylboronic acid (1.2 mmol), Pd(II) enaminone complex **(101)** (2 mol%), K_3PO_4 (2 mmol) and DMF:H_2O (95:5) (10ml) was heated at 120 ºC for appropriate time as shown in **Table 20**. The reaction mixture was then cooled to room temperature, diluted with water and ethyl acetate. The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to obtain a crude product, which was purified by column chromatography (silica gel, 60-120 mesh) pet ether/EtOAc as eluent to afford the desired coupled product, which was confirmed by spectral and elemental analysis.

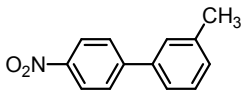
2.4.5.1 Characterization data for synthesized biaryls 103(a-r).

4-Acetyl-4'-methyl-biphenyl (103a):



Nature	**:**	White Solid
MP	**:**	116-118 ºC.
^{1}HNMR (200MHz) (CDCl$_3$)	**:**	δ 2.41 (s, 3H), 2.64 (s, 3H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.5 Hz, 2H).
^{13}C NMR (50MHz) (CDCl$_3$)	**:**	δ 14.5, 115.8, 116.2, 125.8, 126.0, 129.8, 130.0, 130.1, 130.6, 154.6, 157.1.
Elemental Analysis	**:**	Calcd: C, 85.68; H, 6.71.
$C_{15}H_{14}O$ (210)		Found: C, 85.72; H, 6.65.

3-Methyl-4'-nitro-biphenyl (103b):



Nature : White Solid

MP : 116-118 ºC.

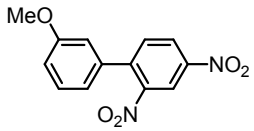
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.45 (s, 3H), 7.24-7.29 (m, 1H), 7.39-7.44 (m, 3H), 7.73 (d, *J* = 9.0 Hz, 2H), 8.29 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.1, 26.6, 126.8, 127.0, 128.8, 129.6, 135.5, 136.8, 138.1, 145.6, 197.7.

Elemental Analysis : Calcd: C, 73.23; H, 5.20; N, 6.57.

$C_{13}H_{11}NO_2$ (214) Found: C, 73.31; H, 5.04; N, 6.65.

3-Methoxy-2'-4'-dinitro-biphenyl (103c):



Nature : Yellow solid

MP : 97-99 ºC.

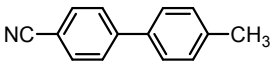
^{1}HNMR (200MHz) (CDCl$_3$) : δ 3.84 (s, 3H), 6.87-7.04 (m, 3H), 7.27-7.44 (m, 1H), 7.66-7.72 (m, 1H), 8.45-8.49 (m, 1H), 8.70 (s, 1H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 55.3, 113.4, 114.8, 119.5, 119.8, 126.3, 130.1, 133.0, 136.3, 142.0, 146.8, 149.0, 159.8.

Elemental Analysis : Calcd: C, 56.94; H, 3.68; N, 10.22.

$C_{13}H_{10}N_2O_5$ (274) Found: C, 57.10; H, 3.84; N, 10.17.

4-Cyano-4'-methyl-biphenyl (103d):



Nature : White solid

MP : 106-108 ºC.

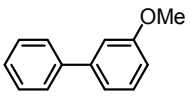
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.42 (s, 3H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H) 7.64-7.74 (m, 4H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.1, 110.5, 118.9, 127.0, 127.4, 129.8, 132.5, 136.2, 138.7, 145.5.

Elemental Analysis : Calcd: C, 87.01; H, 5.74; N, 7.25.

$C_{14}H_{11}N_9$ (193) Found: C, 87.42; H, 5.82; N, 7.10.

3-Methoxy-biphenyl[40] (103e):



Nature : Liquid

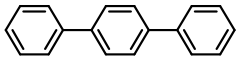
^{1}HNMR (200MHz) (CDCl$_3$) : δ 3.76 (s, 3H), 6.17-6.82 (dd, *J* = 2.5 Hz, *J* = 8.0 Hz, 1H), 7.02-7.51 (m, 8H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.1, 110.5, 118.9, 127.0, 127.4, 129.8, 132.5, 136.2, 138.7, 145.5.

Elemental Analysis : Calcd: C, 84.75; H, 6.57.

$C_{13}H_{12}O$ (184) Found: C, 84.68; H, 6.45.

***p*-Terphenyl (103f):**



Nature : White solid

MP : 210-212 ºC (Lit.[41] 212-213 °C).

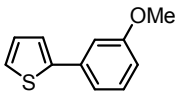
^{1}HNMR (200MHz) (CDCl$_3$) : δ 7.22-7.41 (m, 6H), 7.53-7.58 (m, 8H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 127.0, 127.3, 127.4, 128.8, 140.0, 140.6 142.6.

Elemental Analysis : Calcd: C, 93.87; H, 6.13.

$C_{18}H_{14}$ (230) Found: C, 93.78; H, 6.25.

2-(3-Methoxyphenyl)thiophene (103g):



Nature : Liquid

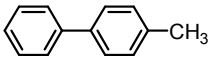
^{1}HNMR (200MHz) (CDCl$_3$) : δ 3.92 (s, 3H), 6.88-6.93 (m, 1H), 7.12-7.39 (m, 6H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 55.2, 111.5, 112.8, 118.5, 123.2, 124.8 127.9, 129.8, 135.5, 144.1, 159.8.

Elemental Analysis : Calcd: C, 69.44; H, 5.30; S, 16.85.

$C_{11}H_{10}OS$ (190) Found: C,69.65; H, 5.25; S, 16.67.

4-Methyl-biphenyl (103h):



Nature : White solid

MP : 45-47ºC(Lit.[41] 46 °C).

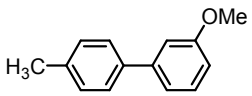
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.38 (s, 3 H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.32 (m, 1 H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.1, 127.0, 127.2, 127.3, 128.7, 129.5 137.0, 138.3, 141.1.

Elemental Analysis : Calcd: C, 92.81; H, 7.19.

$C_{13}H_{12}$ (168) Found: C,92.72; H, 7.31.

4-Methyl-3'-methoxy-biphenyl (103i):



Nature : White solid

MP : 50-52 ºC.

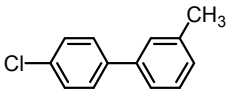
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.40 (s, 3H), 3.86 (s, 3H), 6.85-6.91 (m, 1H), 7.10-7.23 (m, 4H), 7.31-7.39 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.0, 55.2, 112.3, 112.6, 119.4, 126.9 129.4, 129.6, 137.1 138.1, 142.6, 159.8.

Elemental Analysis : Calcd: C, 84.81; H, 7.12.

$C_{14}H_{14}O$ (198) Found: C, 84.74; H, 7.20.

4-Chloro-3'-methyl-biphenyl (103j):



Nature : White solid

MP : 33-35 ºC.

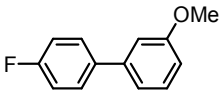
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.35 (s, 3 H), 7.09-7.14 (m, 1H), 7.29-7.38 (m, 5H), 7.42-7.47 (dd, *J* = 2.5 Hz, *J* = 8.5 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.4, 124.0, 127.7, 128.3, 128.7, 133.1 138.4, 139.7, 139.8.

Elemental Analysis : Calcd: C, 77.04; H, 5.47.

$C_{13}H_{11}Cl$ (202) Found: C, 76.82; H, 5.38.

4-Fluoro-3'-methoxy-biphenyl (103k):



Nature : Liquid

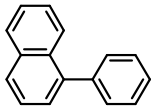
^{1}HNMR (200MHz) (CDCl$_3$) : δ 3.77 (s, 3 H), 6.77-6.83 (m, 1H), 6.97-7.07 (m, 4H), 7.22-7.32 (m, 1H), 7.41-7.48 (m, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 55.1, 112.4, 112.7, 115.5, (d, *J* = 21.5 Hz), 119.4, 128.6 (d, *J* = 8.0 Hz), 129.7, 139.4 (d, *J* = 230 Hz), 162.4 (d, *J* = 252 Hz).

Elemental Analysis : Calcd: C, 77.21; H, 5.48.

$C_{13}H_{11}FO$ (202) Found: C, 77.39; H, 5.40.

1-phenylnaphthalene[40](103l):



Nature : Liquid

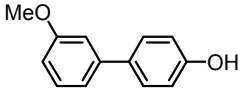
^{1}HNMR (200MHz) (CDCl$_3$) : δ 7.39-7.58 (m, 9H), 7.85-7.94 (m, 3H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 25.3, 125.7, 125.9, 126.8, 127.1, 127.6, 128.2, 130.0, 131.6, 133.7, 140.2, 140.7.

Elemental Analysis : Calcd: C, 94.08; H, 5.92.

$C_{16}H_{12}$ (204) Found: C, 94.16; H, 5.80.

3-Methoxy -4'-hydroxy-biphenyl (103m):



Nature : White solid

MP : 78-80 ºC

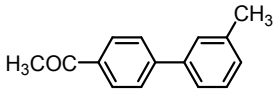
^{1}HNMR (200MHz) (CDCl$_3$) : δ 3.75 (s, 3H), 6.72-6.81 (m, 3H), 6.96-7.04 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H)

^{13}C NMR (50MHz) (CDCl$_3$) : δ 55.2, 112.0, 112.4, 115.6, 119.3, 128.3, 129.7, 133.5, 142.2, 155.0, 159.6

Elemental Analysis : Calcd: C, 77.98; H, 6.04

$C_{13}H_{12}O_2$ (200) Found: C, 78.14; H, 6.12

4-Acetyl-3'-methyl-biphenyl (103n):



Nature : White solid

MP : 90-92 ºC.

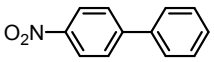
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.34 (s, 3H), 2.54 (s, 3H), 7.10-7.16 (m, 1H), 7.22-7.34 (m, 3H), 7.57 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz, 2H), 7.92 (dd, *J* = 2.0 Hz, *J* = 8.5 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 21.4, 26.5, 124.2, 127.0, 127.8, 128.7, 128.8, 135.6, 138.4, 139.6, 145.7, 197.6.

Elemental Analysis : Calcd: C, 85.68; H, 6.71.

$C_{15}H_{14}O$ (210) Found: C, 85.74; H, 6.50.

4-Nitro-biphenyl (103o):



Nature : Gray solid

MP : 113-115 ºC (Lit.[42] 114-116 ºC).

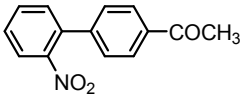
^{1}HNMR (200MHz) (CDCl$_3$) : δ 7.41-7.55 (s, 3H), 7.61-7.66 (m, 2H), 7.74 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 8.9 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 124.0, 127.3, 127.7, 128.8, 129.0, 138.6, 146.9, 147.5.

Elemental Analysis : Calcd: C, 72.35; H, 4.55; N, 7.03.

$C_{12}H_9NO_2$ (199) Found: C, 72.40; H, 4.61; N, 7.12.

4-Acetyl-2'-nitro-biphenyl (103p):



Nature : Yellow solid

MP : 106-108 ºC.

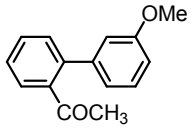
^{1}HNMR (200MHz) (CDCl$_3$) : δ 2.64 (s, 3H), 7.40-7.46 (m, 3H), 7.50-7.71 (m, 2H), 7.91-7.96 (dd, *J* = 1.5 Hz, *J* = 8.0 Hz, 1H), 8.00-8.04 (dd, *J* = 2.0 Hz, *J* = 2.0 Hz, 2H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 26.6, 124.3, 128.1, 128.5, 128.8, 131.6, 132.6, 135.3, 136.4, 142.2, 148.7, 197.4.

Elemental Analysis : Calcd: C, 69.70; H, 4.60; N, 5.81.

$C_{14}H_{11}NO_3$ (241) Found: C, 69.62; H, 4.65; N, 5.88.

2-Acetyl-3'-methoxy-biphenyl (103q):



Nature : Yellow liquid

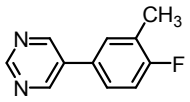
^{1}HNMR (200MHz) (CDCl$_3$) : δ 1.95 (s, 3H), 3.75 (s, 3H), 6.82-6.89 (m, 3H), 7.18-7.49 (m, 5H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 30.2, 55.1, 113.3, 114.1, 121.2, 127.4, 127.6, 129.6, 129.9, 130.5, 140.1, 140.7, 141.9, 159.5, 204.8.

Elemental Analysis : Calcd: C, 79.62; H, 6.24.

$C_{15}H_{14}O_2$ (226) Found: C, 79.71; H, 6.35.

2-(4-fluoro-3-methylphenyl)pyrimidine (103 r):



Nature : White solid

MP : 73-75 ºC.

^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.29 (s, 3H), 7.03-7.12 (m, 1H), 7.19-7.33 (m, 2H), 8.84 (s, 2H), 9.12 (s, 1H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 14.5, 116.0 (d, *J* = 22.9 Hz), 125.9 (d, *J* = 8.5 Hz), 126.3, 130.09 (d, *J* = 5.5 Hz), 133.6, 154.6, 157.1, 161.9 (d, *J* = 248.0 Hz).

Elemental Analysis : Calcd: C, 70.20; H, 4.82; N, 14.88.

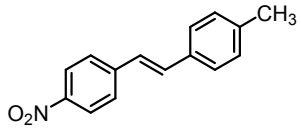
$C_{11}H_9FN_2$ (188) Found: C, 70.14; H, 4.85; N, 14.96.

General experimental procedure for Heck reaction

A mixture of aryl halide (1 mmol), alkene (1.2 mmol), Pd(II) enaminone complex (**101**) (1 mol%), NaOAc (2 mmol), TBAB (20 mol%) and DMA (5 ml) was stirred at 140 ºC appropriate time as shown in **Table 22**. The reaction mixture was then cooled to room temperature, diluted with water and chloroform. The phases were separated and the aqueous layer was extracted with chloroform. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to obtain a crude product, which was purified by column chromatography (silica gel, 60-120 mesh) pet ether/EtOAc as eluent to afford the desired coupled product, which was confirmed by spectral and elemental analysis.

2.4.5.2 Characterization data for compounds 105(a-q)

(*E*) 4-Methyl-4'nitro-stilbene (105b):



Nature : White solid

MP : 147-149 ºC.

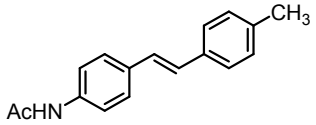
^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.38 (s, 3H), 7.09 (d, *J* = 16.2 Hz, 1H), 7.19-7.23 (m, 3H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.59-7.61 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 2H), 8.19-8.23 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 2H)..

^{13}C NMR (50MHz) ($CDCl_3$) : δ 21.2, 124.0, 125.1, 126.6, 126.9, 129.5, 133.2, 133.3, 138.9, 144.0, 146.4.

Elemental analysis : Calcd: C, 75.30; H, 5.48; N, 5.85.

$C_{15}H_{13}NO_2$ (239) Found: C, 75.35; H, 5.56; N, 5.72.

(*E*)-*N*-(4-(4-methylstyryl)phenyl)acetamide (105f):



Nature : White solid

MP : 248-249 ºC.

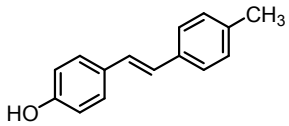
^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.14 (s, 3H), 2.35 (s, 3H), 7.00 (s, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.37-7.44 (m, 4H), 7.60 (d, *J* = 8.5 Hz, 2H), 9.64 (br s 1H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 20.7, 24.0, 119.0, 126.1, 126.72, 126.78, 127.0, 129.2, 131.9, 134.4, 136.6, 138.7, 168.2.

Elemental analysis : Calcd: C, 81.24; H, 6.82; N, 5.57.

$C_{17}H_{17}NO$ (251) Found: C, 81.31; H, 6.69; N, 5.42.

(*E*) 4-Methyl-4'hydroxy-stilbene (105i):



Nature : White solid.

MP : 204-206 ºC.

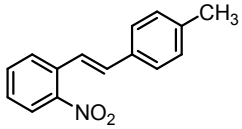
^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.35 (s, 3H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.93-7.05 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.34-7.40 (m, 4H), 8.60 (br s 1H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 20.7, 115.3, 125.0, 125.5, 127.12, 127.18, 128.3, 128.9, 134.4, 136.3, 156.6.

Elemental analysis : Calcd: C, 85.68; H, 6.71.

$C_{15}H_{14}O$ (210) Found: C, 85.53; H, 6.64.

(*E*) 4-Methyl-2'nitro-stilbene (105l):



Nature : Yellow Liquid

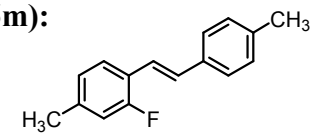
^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.38 (s, 3H), 7.07 (d, *J* = 16.3 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.34-7.63 (m, 5H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.93-7.97 (m, 1H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 21.2, 122.2, 124.6, 126.9, 127.6, 127.9, 129.4, 132.9, 133.0, 133.6, 133.7, 138.6, 147.8.

Elemental analysis : Calcd: C, 75.30; H, 5.48; N, 5.85.

$C_{15}H_{13}NO_2$ (239) Found: C, 75.21; H, 5.56; N, 5.82.

(*E*)-2-fluoro-4-methyl-1-(4-methylstyryl)benzene (105m):



Nature : White solid

MP : 166-168 ºC.

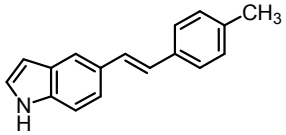
^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.29 (s, 3H), 2.37 (s, 3H), 7.01-7.02 (m, 2H), 7.14-7.19 (m, 5H), 7.40 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 14.3, 21.2, 112.2 (d, *J* = 22.7 Hz), 122 (d, *J* = 3.0 Hz), 123.8 (d, *J* = 17.3 Hz), 126.4, 126.5 (d, *J* = 2.8 Hz), 128.8, 129.4, 131.4 (d, *J* = 5.8 Hz), 134.2, 137.3 (d, *J* = 8.0 Hz), 137.6, 161.5 (d, *J* = 243.8 Hz).

Elemental analysis : Calcd: C, 84.92; H, 6.68.

$C_{16}H_{15}F$ (226) Found: C, 85.05; H, 6.72.

(*E*)-5-(4-methylstyryl)-1*H*-indole (105n):



Nature : Gray solid

MP : 178-180 ºC.

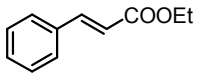
^{1}HNMR (200MHz) ($CDCl_3$) : δ 2.37 (s, 3H), 6.55-6.58 (m, 1H), 7.06 (d, J = 15.5 Hz, 1H), 7.15-7.22 (m, 4H), 7.35-7.48 (m, 4H), 7.75 (s, 1H), 8.15 (br s, 1H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 20.7, 100.9, 110.8, 118.1, 118.8, 124.3, 124.4, 125.0, 127.3, 127.7, 128.3, 128.4, 134.2, 135.0, 135.6.

Elemental analysis : Calcd: C, 87.52; H, 6.48; N, 6.00.

$C_{17}H_{15}N$ (233) Found: C, 87.48; H, 6.62; N, 6.10.

Ethyl (*E*)-3-phenyl-2-propenoate[43] (105o):



Nature : Light yellow Liquid

^{1}HNMR (200MHz) ($CDCl_3$) : 1.32 (t, *J* = 7.2 Hz, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 6.40 (d, *J* = 16.2 Hz, 1H), 7.32-7.35, (m, 3H), 7.46-7.48 (m, 2H), 7.66 (d, *J* = 16.2 Hz, 1H).

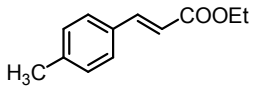
^{13}C NMR (50MHz) : δ 14.2, 60.3, 118.4, 127.8, 128.6, 130.2, 134.2, 144.5, 166.8.

($CDCl_3$)

Elemental analysis : Calcd: C, 74.98; H, 6.86.

$C_{11}H_{12}O_2$ (176) Found: C, 75.19; H, 6.72.

Ethyl (*E*)-3-(4-methylphenyl)-2-propenoate[43] (105p):



Nature : Light yellow Liquid

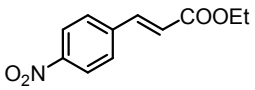
^{1}HNMR (200MHz) ($CDCl_3$) : 1.33 (t, *J* = 7.1 Hz, 3H), 2.30 (s, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.35 (d, *J* = 16.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 16.0 Hz, 1H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 14.4, 21.4, 60.2, 117.2, 128.0, 129.6, 131.5, 140.2, 144.8, 167.0.

Elemental analysis : Calcd: C, 75.76; H, 7.42.

$C_{12}H_{14}O_2$ (190) Found: C, 75.48; H, 7.56.

Ethyl (*E*)-3-(4-nitrolphenyl)-2-propenoate (105q):



Nature : Light yellow solid

MP : 132-135 ^{o}C (Lit.[44] 134-136 ^{o}C).

^{1}HNMR (200MHz) ($CDCl_3$) : 1.35 (t, *J* = 7.2 Hz, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 6.58 (d, *J* = 16.2 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 16.2 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 14.2, 60.9, 122.7, 124.2, 128.6, 140.2, 141.6, 148.2, 166.0.

Elemental analysis : Calcd: C, 59.73; H, 5.01; N, 6.33.

$C_{11}H_{11}NO_4$ (221) Found: C, 59.69; H, 4.80; N, 6.18.

Note: Compound **105a, 105c, 105d, 105e, 105g, 105h, 105j, 105k,** were synthesized previously. For characterization data of above compound please see the experimental section in Section **F**-Chapter **1**.

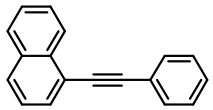
General experimental procedure for Sonogashira cross coupling reaction:

A mixture of aryl halide (1 mmol), alkyne (1.2 mmol), Pd(II) enaminone complex (**101**) (1 mol%), TBAB (20 mol%), pyrrolidine, DMA was stirred at 110 ºC appropriate time as

shown in **Table 24**. The reaction mixture was then cooled to room temperature, diluted with water and ethyl acetate. The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to obtain a crude product, which was purified by column chromatography (silica gel, 60-120 mesh) pet ether/EtOAc as eluent to afford the desired coupled product, which was confirmed by spectral and elemental analysis.

2.4.5.3 Characterization data for compounds 107(d-n).

(1-Phenylethynyl)naphthalene[45] (107d):



Nature : Yellow liquid

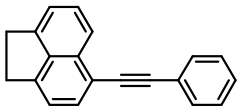
^{1}HNMR (200MHz) (CDCl$_3$) : δ 7.39 (m, 8H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.84-7.90 (m, 2H), 8.46 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 87.5, 94.3, 120.8, 123.3, 125.2, 126.1, 126.4, 126.7, 128.2, 128.3, 128.4, 128.7, 130.3, 131.6, 133.1, 133.2.

Elemental analysis : Calcd: C, 94.70; H: 5.30.

$C_{18}H_{12}$ (228) Found: C, 94.85; H: 5.28.

1,2-dihydro-5-(2-phenylethynyl)acenaphthylene (107e):



Nature : White solid

MP : 72-75 ºC.

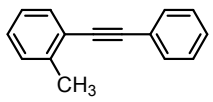
^{1}HNMR (200MHz) (CDCl$_3$) : δ 3.42 (s, 4H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.36-7.45 (m, 4H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.60-7.67 (m, 2H), 7.71 (d, *J* = 7.2 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 30.4, 87.6, 93.1, 115.9, 118.9, 119.9, 121.1, 123.7, 128.0, 128.3, 128.5, 131.5, 131.7, 132.0, 138.9, 146.2, 147.4.

Elemental analysis : Calcd: C, 94.45; H: 5.55.

$C_{20}H_{14}$ (254) Found: C, 94.50; H: 5.42.

1-(2-*o*-tolylethynyl)benzene[46] (107f):



Nature : Colorless liquid

^{1}HNMR (200MHz) : δ 2.53 (s, 3H), 7.13-7.25 (m, 3H), 7.34-7.39 (m, 3H), 7.49-

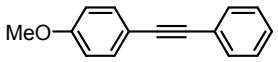
($CDCl_3$) 7.57 (m, 3H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 20.7, 88.3, 93.3, 123.0, 123.5, 125.5, 128.1, 128.2, 128.3, 129.4, 131.4, 131.8, 140.1.

Elemental analysis : Calcd: C, 93.71; H: 6.29.

$C_{15}H_{12}$ (192) Found: C, 93.58; H: 6.40.

(4-Methoxyphenyl)phenylacetylene (107g):



Nature : White solid

MP : 59-61 ºC (Lit.[46] 58–60 ºC).

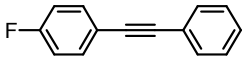
^{1}HNMR (200MHz) ($CDCl_3$) : δ 3.83 (s, 3H), 6.88 (dd, *J* = 2.1 Hz, *J* = 8.8 Hz 2H), 7.32-7.37 (m, 3H), 7.46-7.55 (m, 4H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 55.2, 88.0, 89.3, 113.9, 115.3, 123.5, 127.8, 128.2, 131.4, 133.0, 159.5.

Elemental analysis : Calcd: C, 86.51; H: 5.81.

$C_{15}H_{12}O$ (208) Found: C, 86.38; H: 5.75.

(4-Fluorophenyl)phenylacetylene (107h):



Nature : White solid

MP : 108-110 ºC (Lit.[47]108–110 ºC).

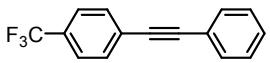
^{1}HNMR (200MHz) ($CDCl_3$) : δ 7.00-7.06 (m, 2H), 7.31-7.35 (m, 3H), 7.47-7.53 (m, 4H).

^{13}C NMR (50MHz) ($CDCl_3$) : δ 88.3, 89.0, 115.6 (d, *J* = 22.4 Hz), 119.3 (d, *J* = 5.6 Hz), 123.1, 128.3, 131.5 (d, *J* = 8.9 Hz),133.5, 162.5 (d, *J* = 248.1 Hz).

Elemental analysis : Calcd: C, 85.69; H: 4.62.

$C_{14}H_{19}F$ (196) Found: C, 85.53; H: 4.75.

(4-Trifluoromethylphenyl)phenylacetylene (107i):



Nature : White solid

MP : 104-106 ºC (Lit.[47]103–105 ºC).

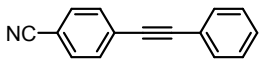
^{1}HNMR (200MHz) ($CDCl_3$) : δ 7.36-7.39 (m, 3H), 7.53-7.58 (m, 2H), 7.62-7.67 (m, 4H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 87.9, 91.7, 122.5, 123.9 (*J* = 270.1 Hz), 125.2 (*J* = 3.7 Hz), 127.1 (*J* = 1.5 Hz), 128.4, 128.8, 129.8 (*J* = 32.6 Hz), 131.73, 131.78.

Elemental analysis : Calcd: C, 73.17; H: 3.68.

$C_{15}H_9F$ (246) Found: C, 73.28; H: 3.74.

(4-Cyanophenyl)phenylacetylene (107j):



Nature : White solid

MP : 108-110 ºC (Lit.[47] 109–110 ºC).

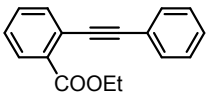
^{1}HNMR (200MHz) (CDCl$_3$) : δ 7.37-7.40 (m, 3H), 7.52-7.57 (m, 2H), 7.62-7.67 (m, 4H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 87.6, 93.7, 111.3, 118.4, 122.1, 128.1, 128.4, 129.0, 131.7, 131.97, 131.99.

Elemental analysis : Calcd: C, 88.64; H: 4.46; N, 6.89.

$C_{15}H_9N$ (203) Found: C, 88.70; H: 4.54; N, 6.84.

Ethyl 2-(2-phenylethynyl)benzoate (107k):



Nature : Liquid

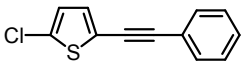
^{1}HNMR (200MHz) (CDCl$_3$) : δ 1.41 (t, J = 7.2 Hz, 3H), 4.42 (q, *J* = 7.2 2H), 7.34-7.50 (m, 5H), 7.53-7.67 (m, 3H), 7.95-8.00 (dd, *J* = 1.5 Hz, *J* = 7.5 1H).

^{13}C NMR (50MHz) (CDCl$_3$) : δ 14.2, 61.1, 88.2, 94.1, 123.2, 123.4, 127.8, 128.2, 128.4, 130.3, 131.4, 131.5, 132.1, 133.9, 166.2.

Elemental analysis : Calcd: C, 81.58; H: 5.64.

$C_{17}H_{14}O_2$ (250) Found: C, 81.44; H: 5.70.

2-chloro-5-(2-phenylethynyl)thiophene (107l):



Nature : White solid

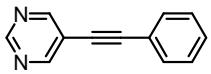
MP : 52-54 ºC

^{1}HNMR (200MHz) (CDCl$_3$) : δ 6.81 (d, *J* = 3.9 Hz, 1H), 7.02 (d, *J* = 3.9 Hz, 1H), 7.33-7.38 (m, 3H), 7.48-7.53 (m, 2H).

^{13}C NMR (50MHz) : δ 81.7, 93.4, 122.2, 122.4, 126.3, 128.3, 128.6, 130.6, 131.3,

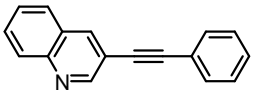
($CDCl_3$)	131.4.		
Elemental analysis	**:**	Calcd:	C, 65.90; H: 3.23; S, 14.66.
$C_{12}H_7ClS$ (218)		Found:	C, 65.85; H: 3.30; S, 14.48.

5-(2-phenylethynyl)pyrimidine (107m):



Nature	**:**	Thick yellow liquid
^{1}HNMR (200MHz) ($CDCl_3$)	**:**	δ 7.36-7.41 (m, 3H), 7.54-7.59 (m, 2H), 8.86 (s, 2H), 9.15 (s, 1H).
^{13}C NMR (50MHz) ($CDCl_3$)	**:**	δ 82.1, 96.2, 119.8, 121.6, 128.4, 129.2, 131.6, 156.5, 158.5.
Elemental analysis	**:**	Calcd: C, 79.98; H: 4.47; N, 15.54.
$C_{12}H_8N_2$ (180)		Found: C, 80.10; H: 4.39; N, 15.50.

3-(Phenylethynyl)quinoline (107n):



Nature	**:**	Gray solid
MP	**:**	50-52 ºC (Lit.[48] 50–51 ºC).
^{1}HNMR (200MHz) ($CDCl_3$)	**:**	δ 7.36-7.43 (m, 3H), 7.56-7.64 (m, 3H), 7.71-7.76 (m, 1H), 7.79-7.85 (m, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 2.0 Hz 1H), 9.02 (d, *J* = 2.0 Hz, 1H).
^{13}C NMR (50MHz) ($CDCl_3$)	**:**	δ 86.4, 92.6, 117.4, 122.5, 127.2, 127.2, 127.5, 128.4, 128.7, 129.1, 130.0, 131.6, 138.2, 146.5, 151.8.
Elemental analysis	**:**	Calcd: C, 89.06; H: 4.84; N, 6.11.
$C_{17}H_{11}N$ (229)		Found: C, 88.90; H: 4.70; N, 6.15.

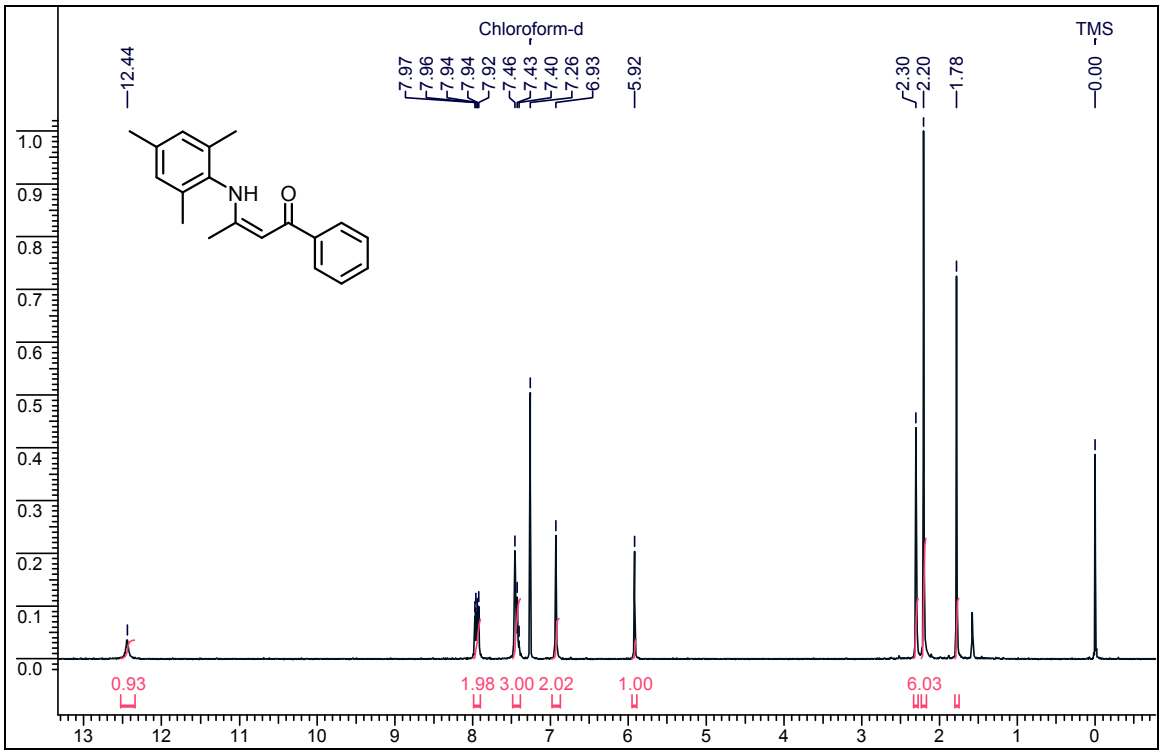
Note: Compound **108a, 108b, 108c,** were synthesized previously. For characterization data of above compound please see the experimental section in Section **E**-Chapter **1**.

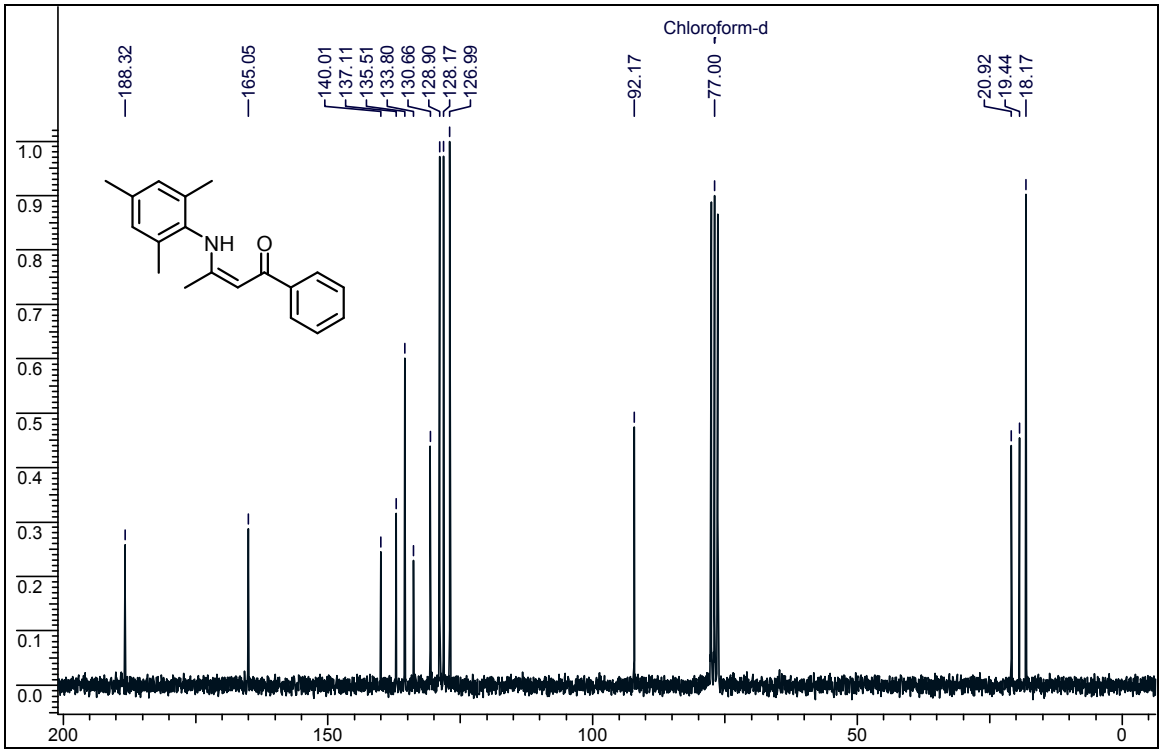
2.4.6 Spectra

Table 25. ^{1}H and ^{13}C spectra of selected compounds are given below:

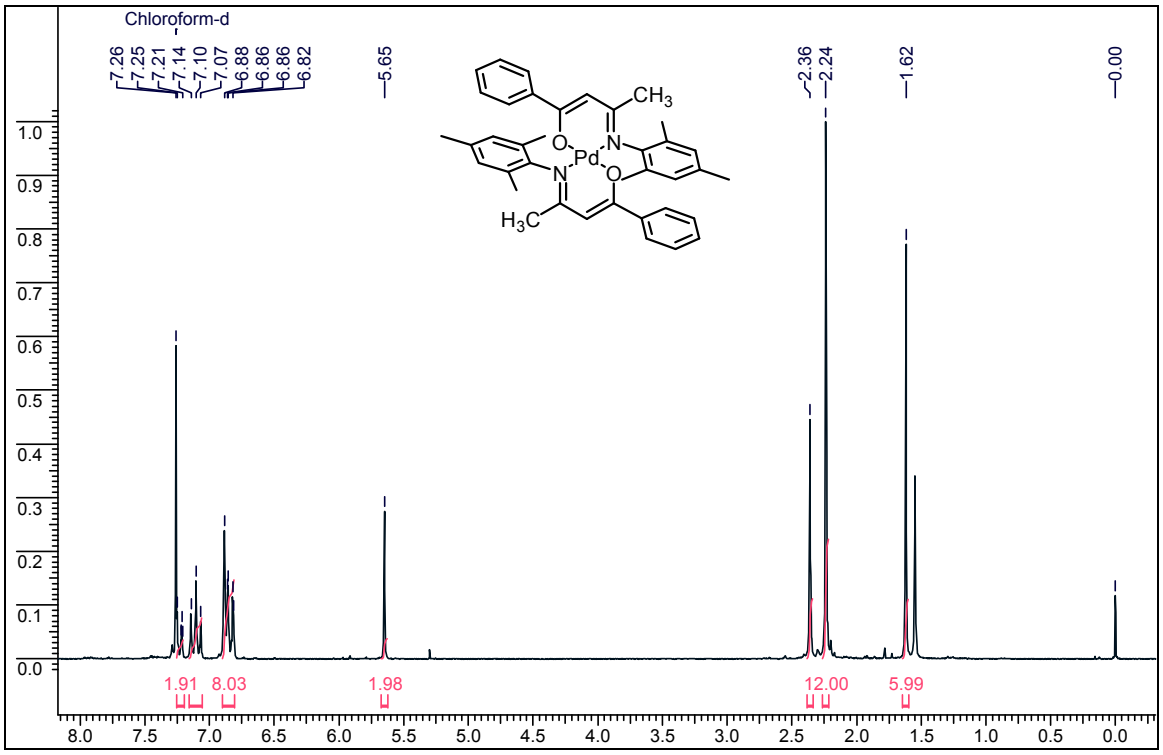
Sr. No	Spectra	
[1]	^{1}H NMR and ^{13}C NMR spectra of	**97**
[2]	^{1}H NMR and ^{13}C NMR spectra of	**98**
[3]	^{1}H NMR and ^{13}C NMR spectra of	**100**
[4]	^{1}H NMR and ^{13}C NMR spectra of	**101**

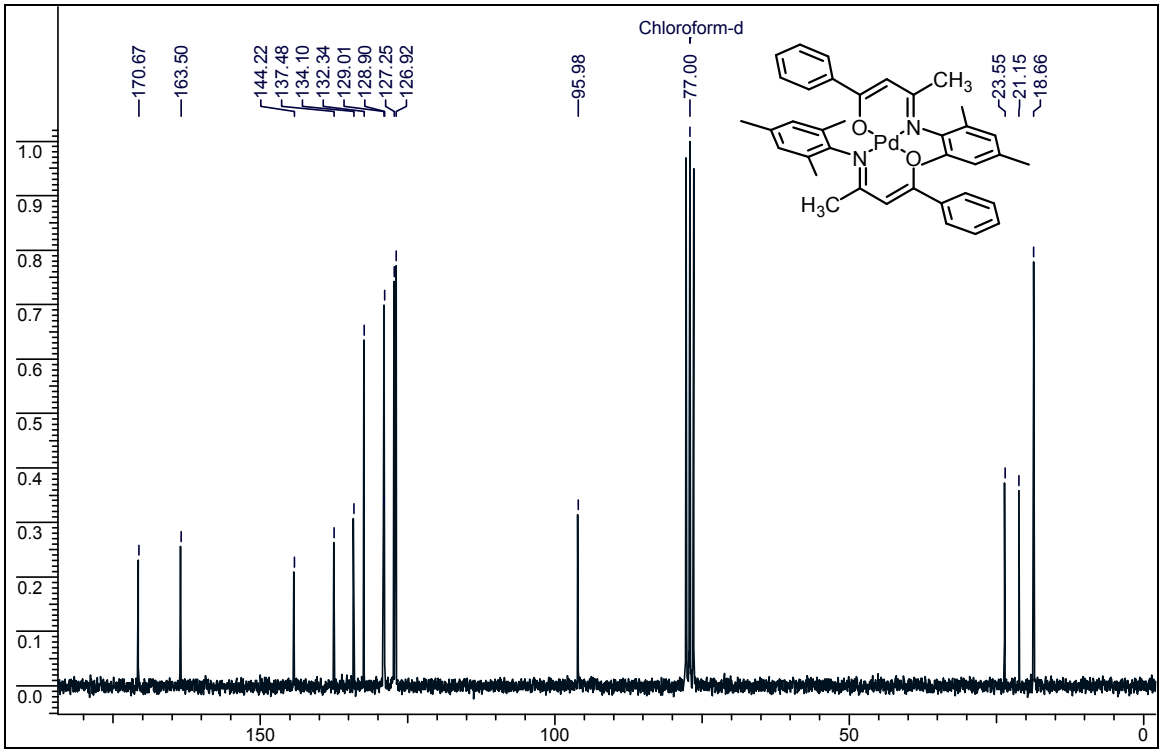
[1] ^{1}H NMR and ^{13}C NMR spectra of 97



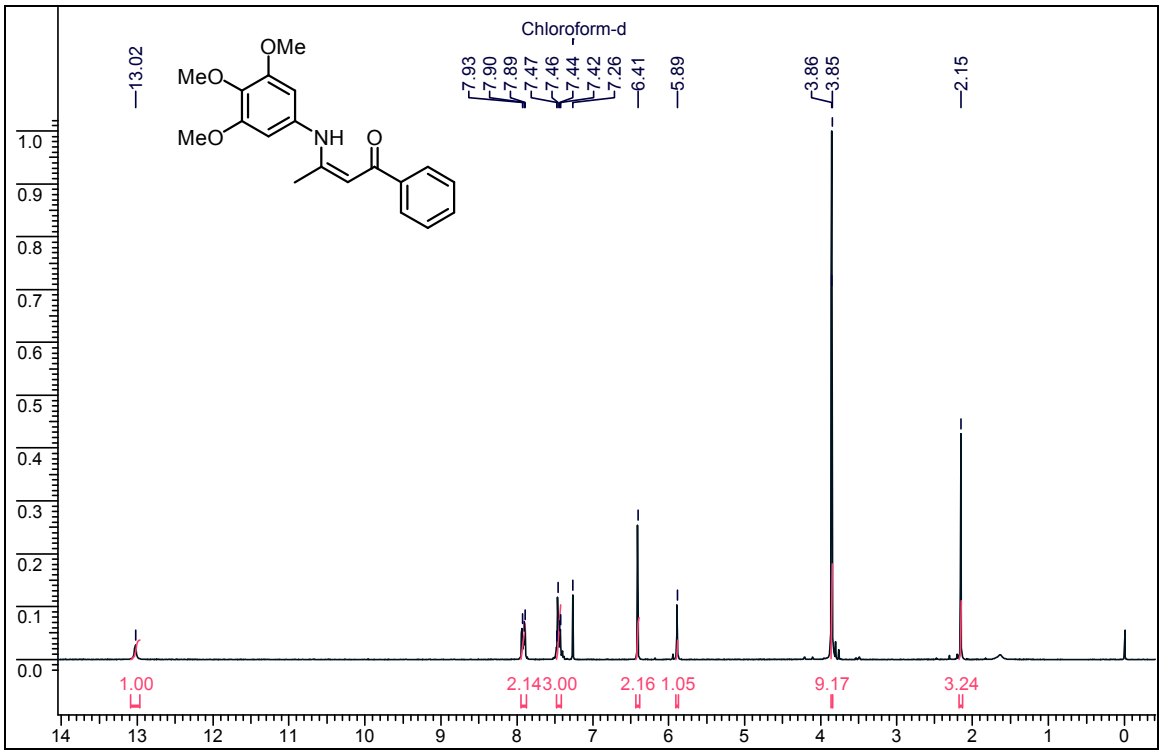


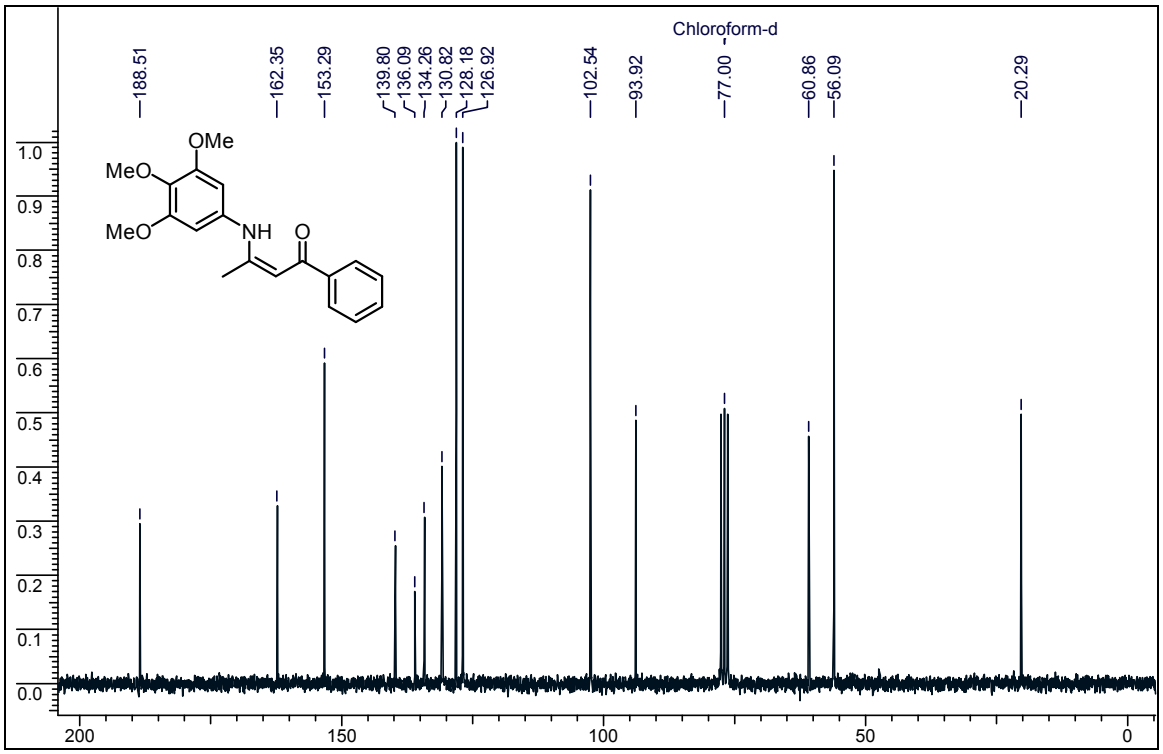
[2] ^{1}H NMR and ^{13}C NMR spectra of 98



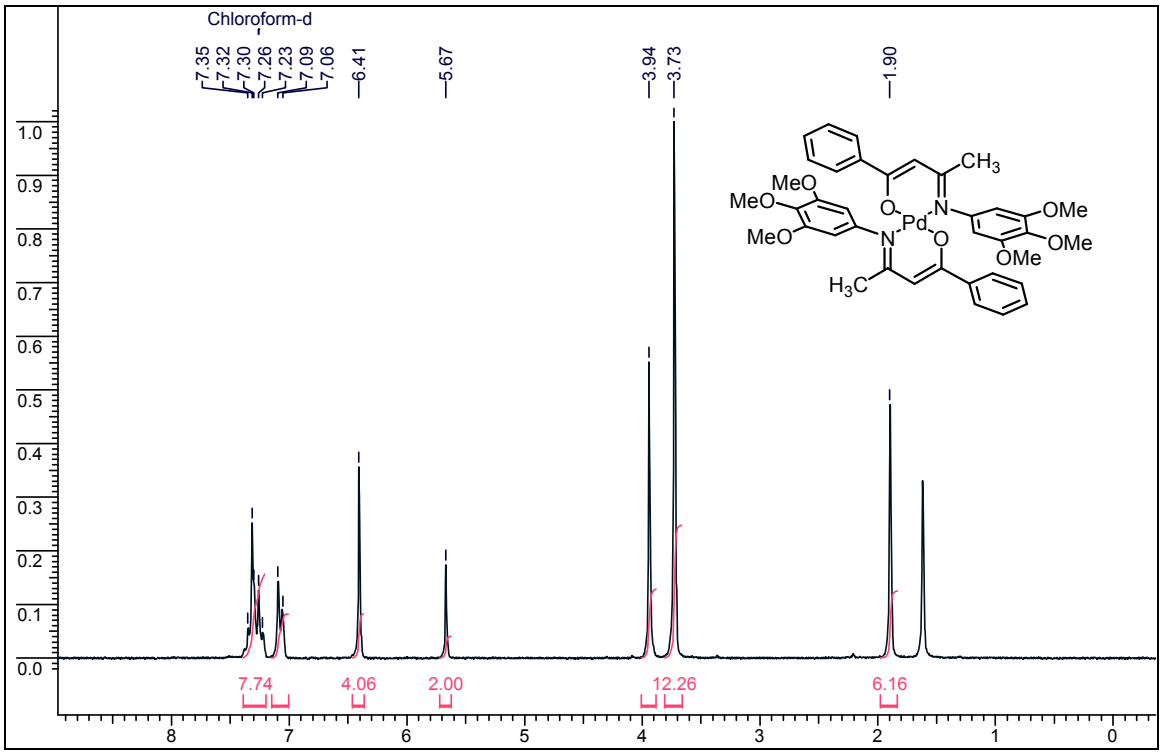


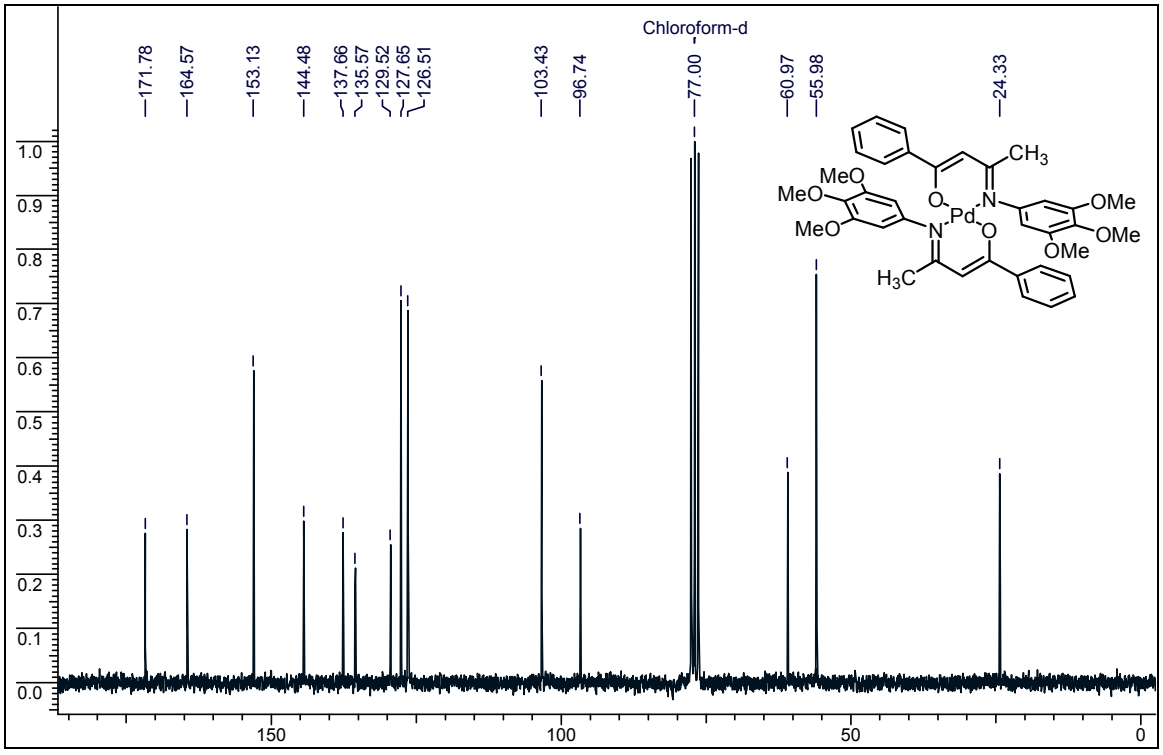
[3] ^{1}H NMR and ^{13}C NMR spectra of 100





[4] ^{1}H NMR and ^{13}C NMR spectra of 101





2.4.7 References

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CHAPTER-3

Synthesis of novel biologically active nitrogen heterocycles

Section-A

Synthesis of class (I) antiarrhythmic agent (±) Cibenzoline and its analogues

Synthesis of antiarrhythmic agent: (±) Cibenzoline

3.1.1 Introduction

Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress fast rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation. While the use of antiarrhythmic agents to suppress atrial arrhythmias (atrial fibrillation and atrial flutter) is still in practice, it is unclear whether suppression of atrial arrhythmias will prolong life.[1, 2]

In the past, it was believed that following myocardial infarction (heart attack), suppression of ventricular arrhythmias would prolong life. However large clinical trials found that suppression of these arrhythmias would paradoxically increase mortality, which may happen due to the proarrhythmic effect these drugs may have. In individuals with atrial fibrillation, antiarrhythmic are still used to suppress arrhythmias. This is often done to relieve the symptoms that may be associated with the loss of the atrial component to ventricular filling (*atrial kick*) that is due to atrial fibrillation or flutter. In individuals with ventricular arrhythmias, antiarrhythmic agents are often still in use to suppress arrhythmias. In this case, the patient may have frequent arrhythmic events or be at high risk for ventricular arrhythmias. Antiarrhythmic agents may be considered the first-line therapy in the prevention of sudden death in certain forms of structural heart disease, and failure of these agents to suppress arrhythmias may lead to implantation of an implantable cardioverter-defibrillator (ICD). The use of antiarrhythmic agents in this population may be in conjunction with an ICD. In this case, the ICD is used to prevent sudden death due to ventricular fibrillation, while the antiarrhythmic agent(s) are used to suppress ventricular tachyarrhythmia so that the ICD doesn't shock the patient frequently.

Many attempts have been made to classify antiarrhythmic agents. The problem arises from the fact that many of the antiarrhythmic agents have multiple modes of action, making any classification imprecise.

Vaughan Williams antiarrhythmic classification

The Vaughan Williams classification is one of the most widely used classification schemes for antiarrhythmic agents. This scheme classifies a drug based on the primary mechanism of its antiarrhythmic effect. However, its dependence on primary

mechanism is one of the limitations of the VW classification, since many antiarrhythmic agents have multiple action mechanisms. Amiodarone, for example, has effects consistent with all of the first four classes. Another limitation is the lack of consideration within the VW classification system for the effects of drug metabolites. Procainamide a class Ia agent whose metabolite N-acetyl procainamide (NAPA) has a class III action is one such example. A historical limitation was that drugs such as digoxin and adenosine which are the important antiarrhythmic agents had no place at all in the VW classification system. This has since been rectified by the inclusion of class V.

There are five main classes in the Vaughan Williams classification of antiarrhythmic agents

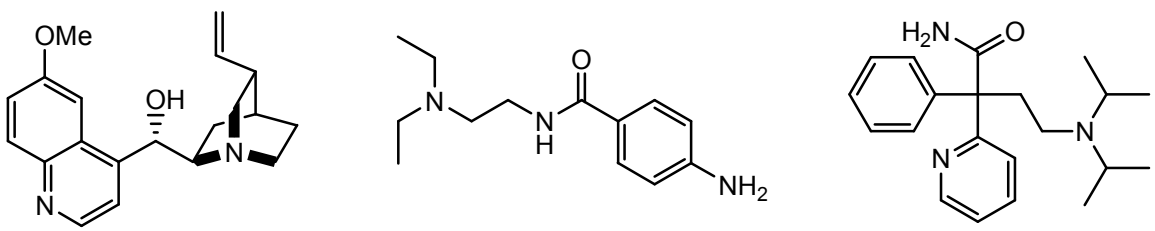
- Class I agents interfere with the sodium (Na^+) channel
- Class II agents are anti-sympathetic nervous system abents. All agents in this class are beta blockers.
- Class III agents affect potassium (K^+) efflux.
- Class IV agents affect AV node.
- Class V agents work by other or unknown mechanisms.

Class I agents:

The class I antiarrhythmic agents interfere with the sodium (Na^+) channel. Class **I** agents are grouped by what effect they have on the Na^+ channel, and what effect they have on cardiac action potentials.

Class Ia agents:

Class Ia agents include quinidine, procainamide, and disopyramide, which block the fast sodium channel. Blocking this channel depresses the phase 0 depolarization (reduces V_{max}). This prolongs the action potential duration by slowing conduction. Agents in this class also cause decreased conductivity and increased refractoriness (**Fig. 1**).

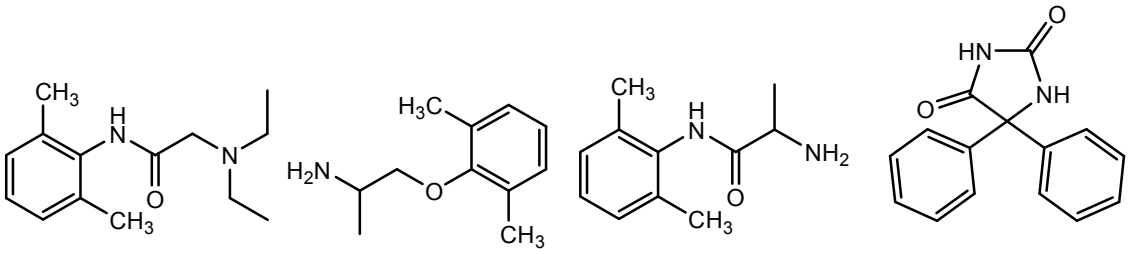


Quinidine **Procainamide** **Disopyramide**

Figure 1.

Class Ib agents:

Class Ib antiarrhythmic agents are sodium channel blockers. Class Ib agents include lidocaine, mexiletine, tocainide and phenytoin, which have fast onset and offset kinetics, meaning that have little or no effect at slower heart rates, and more effects at faster heart rates. Class Ib agents shorten the action potential duration and reduce refractoriness. These agents will decrease V_{max} in partially depolarized cells with fast response action potentials. They either do not change the action potential duration, or they may decrease the action potential duration (**Fig. 2**).

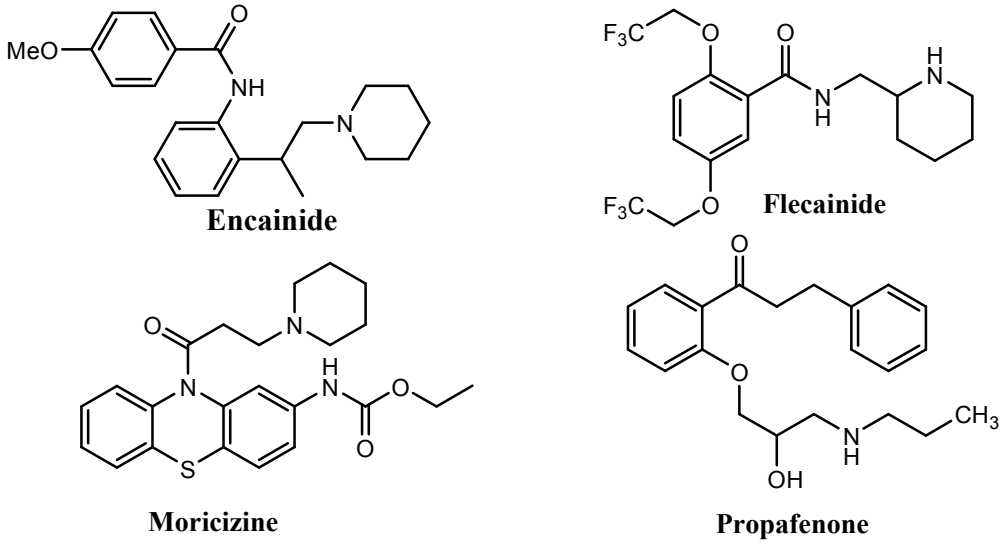


Lidocaine **Mexiletine** **Tocainide** **Phenytoin**

Figure 2.

Class Ic agents:

Class Ic antiarrhythmic agents markedly depress the phase 0 depolarization (decreasing V_{max}). Class Ic agents include encainide, flecainide, moricizine, and propafenone.



Encainide **Flecainide**

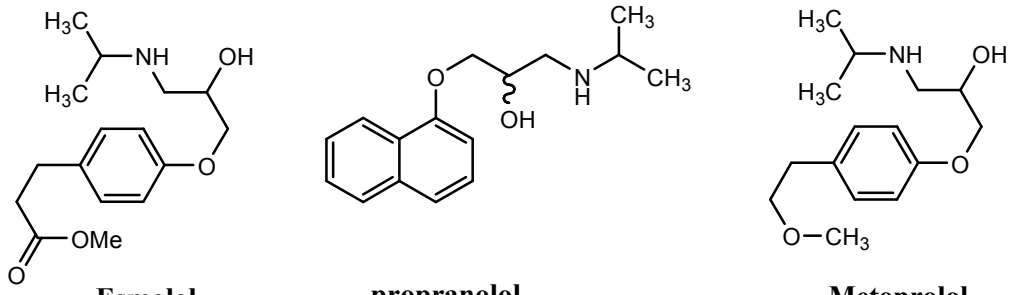
Moricizine **Propafenone**

Figure 3.

They decrease conductivity, but have a minimal effect on the action potential duration of the sodium channel blocking antiarrhythmic agents (the class I antiarrhythmic agents), the class Ic agents have the most potent sodium channel blocking effects (**Fig. 3**).

Class II agents:

Class **II** agents are conventional beta blockers. Class **II** agents include esmolol, propranolol and metoprolol.



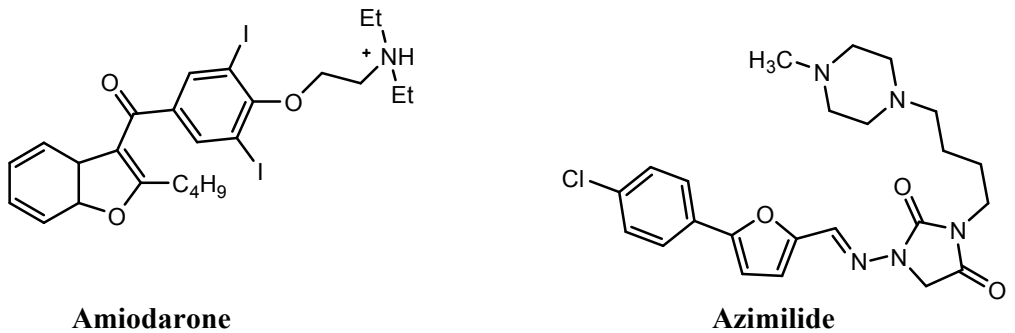
Esmolol **propranolol** **Metoprolol**

Figure 4.

They act by selectively blocking the effects of catecholamines at the β_1-adrenergic receptors, thereby decreasing sympathetic activity on the heart. These agents are particularly useful in the treatment of supraventricular tachycardias. They decrease conduction through the AV node (**Fig. 4**).

Class III agents:

Class **III** agents predominantly block the potassium channels, thereby prolonging repolarization.[3] Since these agents do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. (The re-entrant rhythm is less likely to interact with tissue that has become refractory). Class **III** agents include amiodarone, azimilide, bretylium, dofetilide, ibutilide, sematilide and sotalol. Sotalol is indicated for the treatment of atrial or ventricular tachyarrhythmias, and AV re-entrant arrhythmias. Ibutilide is the only antiarrhythmic agent currently approved by the Food and Drug Administration for acute conversion of atrial fibrillation to sinus rhythm (**Fig**. **5**).



Amiodarone **Azimilide**

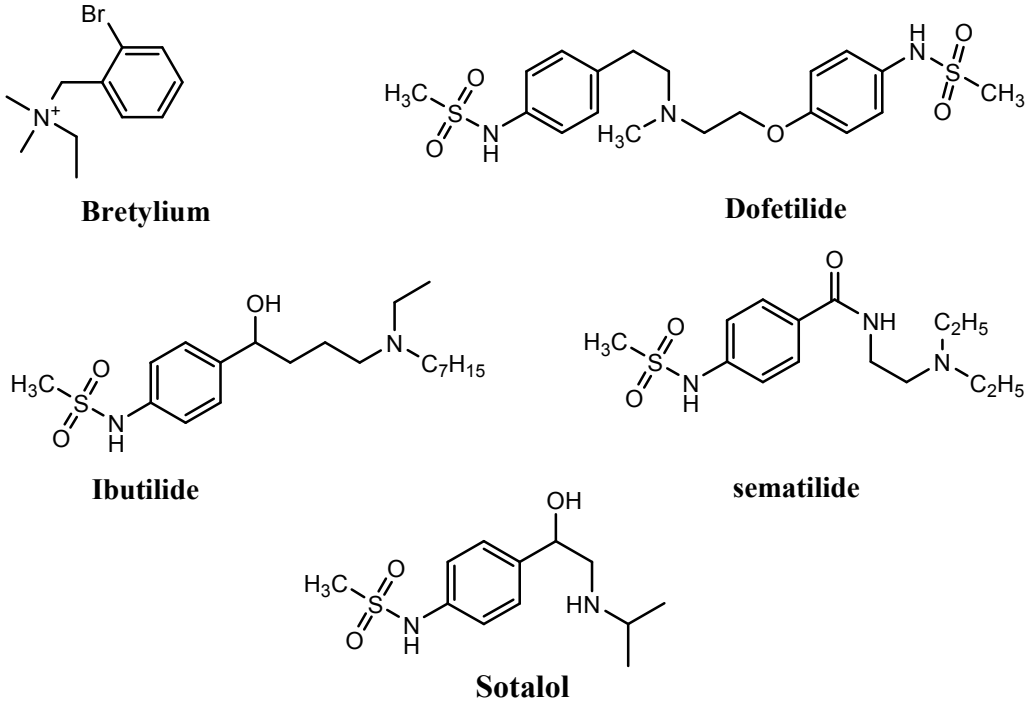


Figure 5.

Class IV agents:

Class **IV** agents are slow calcium channel blockers. They decrease conduction through the AV node, and shorten phase two (the plateau) of the cardiac action potential.

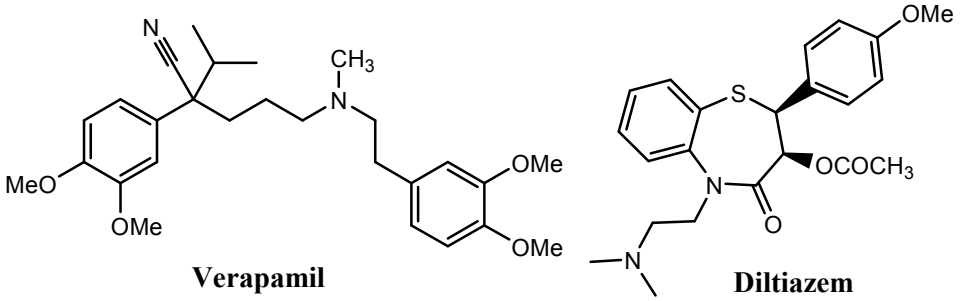
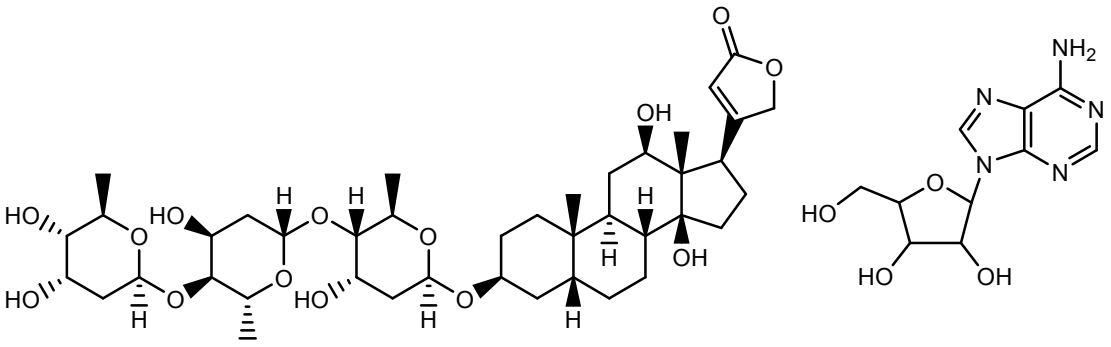


Figure 6.

They thus reduce the contractility of the heart, so may be inappropriate in heart failure. However, in contrast to beta blockers, they allow the body to retain adrenergic control of heart rate and contractility. Class **IV** agents include verapamil and diltiazem (**Fig. 6**).

Class V agents:

Class V agents include digoxin and adenosine. Digoxin increases vagal activity via its central action on the central nervous system, thus decreasing the conduction of electrical impulses through the AV node (**Fig. 7**).



Digoxin **Adenosine**

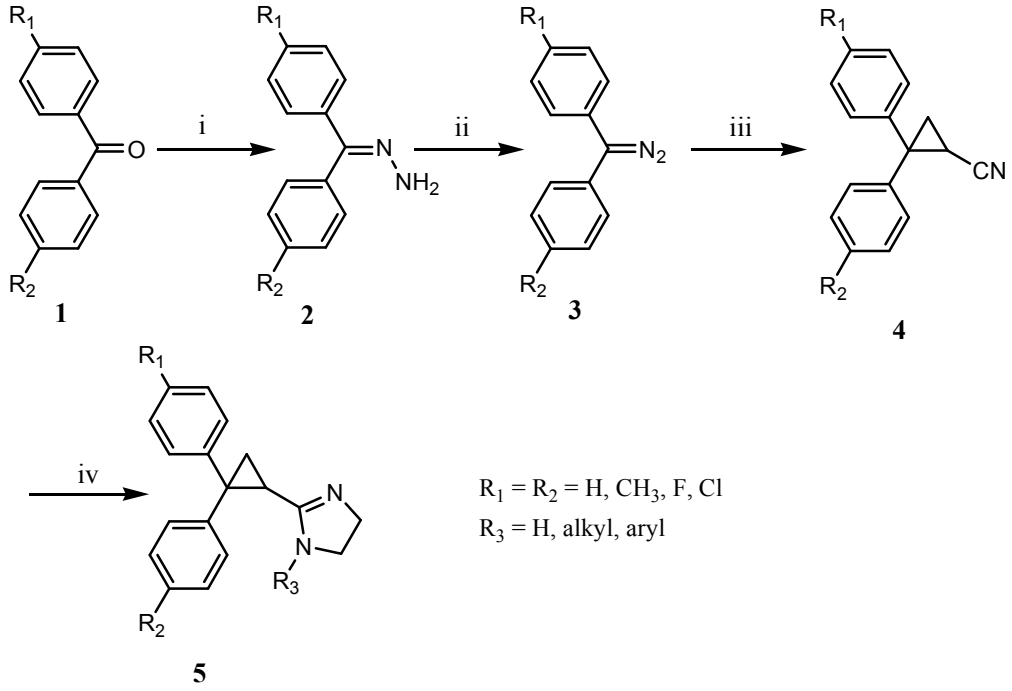
Figure 7.

3.1.2 Review of Literature

As per our knowledge, literature cites only six reports so far, including four patents for the synthesis of cibenzoline from diphenyldiazomethane,[4-8] and chiral cibenzoline from chiral 2,2-disubstituted cyclopropylmethanols.[9] In the patented method, the synthesis of diphenyldiazomethane has been carried out by the oxidation of benzophenone hydrazone with toxic reagents like mercuric oxide or manganese dioxide and high temperature of about 200 ^{o}C was needed for the final condensation process with ethylenediamine monotosylate. It is observed that all the reported methods are cumbersome and expensive for a process scale preparation. They entail certain inconvenient reagents to handle, such as an unstable diphenyldiazomethane and HgO. This prompted us to initiate studies designed towards developing a novel and less hazardous synthetic route amenable for scale-up operations. The procedure reported so far are as follows.

Hexachimie *et al.* (1974)[4-6]

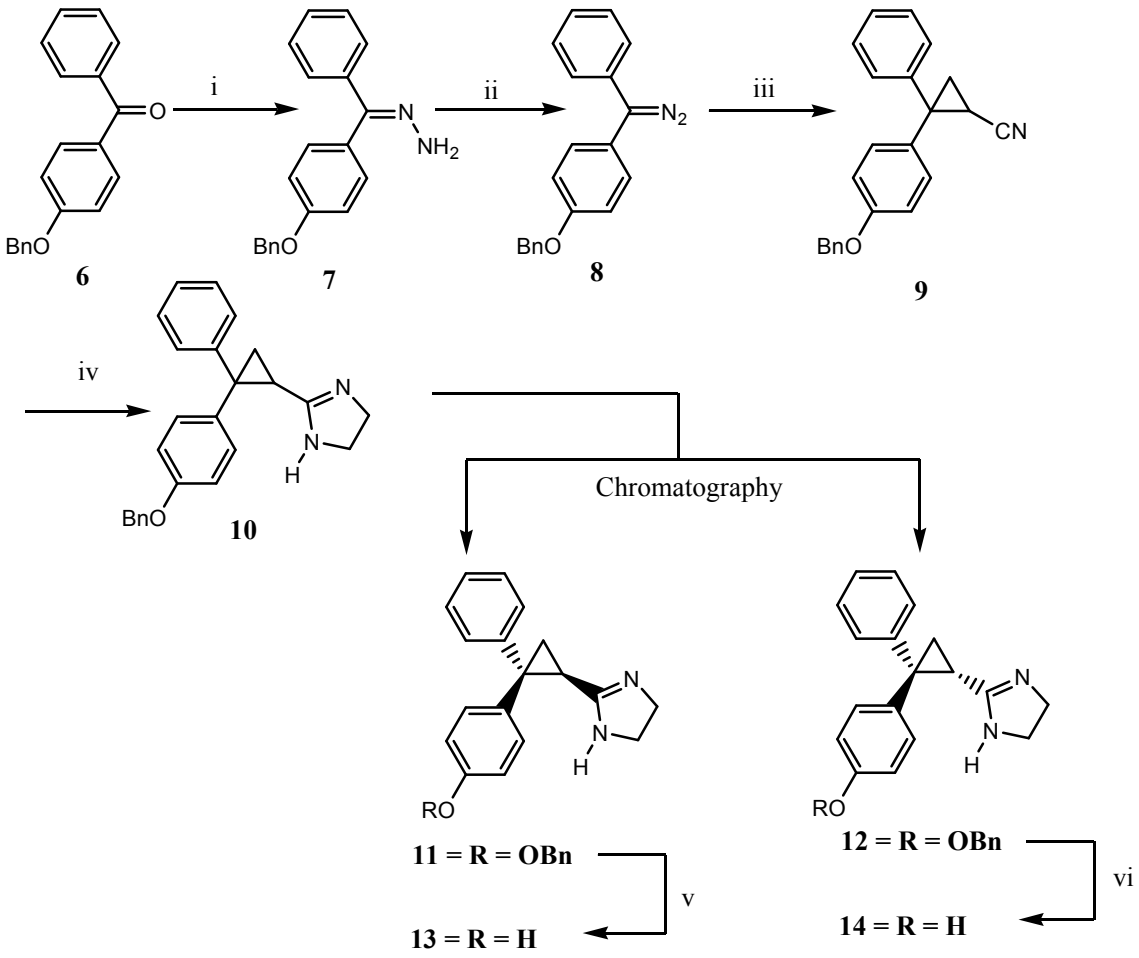
Hexachimie synthesized the cibenzoline and its analouge starting from benzophenone **1**. Benzophenone was converted to benzophenone hydrazone **2** followed by oxidation with HgO to obtain diphenyldiazomethane **3**, which was after treatment with acrylonitrile form 2,2-diphenylcyclpropanecarbonitrile **4**. Further a mixture of ethylenediamine monotosylate and 2,2-diphenylcyclopropanecarbonitrile **4** was heated up to 200 ºC to form the cibenzoline and its analogues **5** (**Scheme 1**).



Scheme 1. Reaction conditions: (i) 80% NH_2-NH_2, ethanol, reflux, 87%, 10h; (ii) HgO, pet ether, rt, 6h, 89%; (iii) acrylonitrile, Chloroform, 40 ºC, 85%, 5 h; iv) ethylene diamine monotosylate, 200 ºC, 70%, 2 h.

Tilly *et al.* (1985)[7]

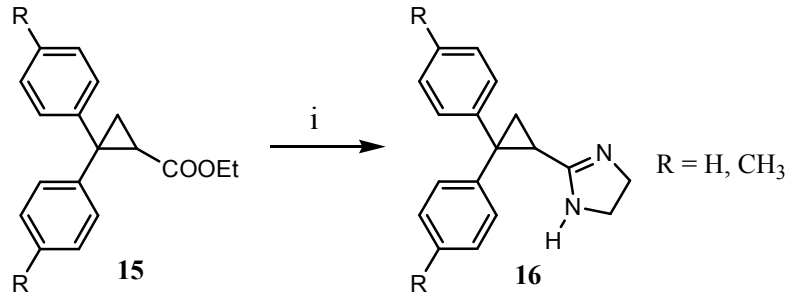
Tilly *et al.* synthesized hydroxylated 1,1-Diphenyl-2-imidazolylcyclopropane. The protected benzophenone **6** was converted to the hydrazone with excess hydrazine in ethanol. The crude hydrazone **7** was oxidized with manganese dioxide in dichloromethane to the corresponding purple diphenyldiazomethane **8** which was in turn reacted with acrylonitrile to give the nitriles **9** in good yield as a mixture of diastereomers. The reaction of nitrile **9** with ethylenediamine monotosylate at 200 ºC gave the target molecule **10**. Further the Z and E isomer was separated by preparative high-pressure liquid chromatography, performed on silica Prep-Pak 500 cartridges using a Waters Associates Prep LC 500A (**Scheme 2**).



Scheme 2. Reaction conditions: (i) NH_2-NH_2, absolute ethanol, reflux, 18h, 40%; (ii) MnO_2, DCM, rt, 3h; (iii) acrylonitrile, heptane, 80 ºC, 6 h, 78%; (iv) ethylene diamine monotosylate, 200 ºC, 8 h, 70%; (v) 10% Pd/C, ethanol, 3.9 M ethanolic HCl, cyclohexene, reflux, 5 h, 59%; (vi) 10% Pd/C, ethanol, 3.9 M ethanolic HCl, cyclohexene, reflux, 3 h, 94%.

Sebastian *et al.* (1988)[8]

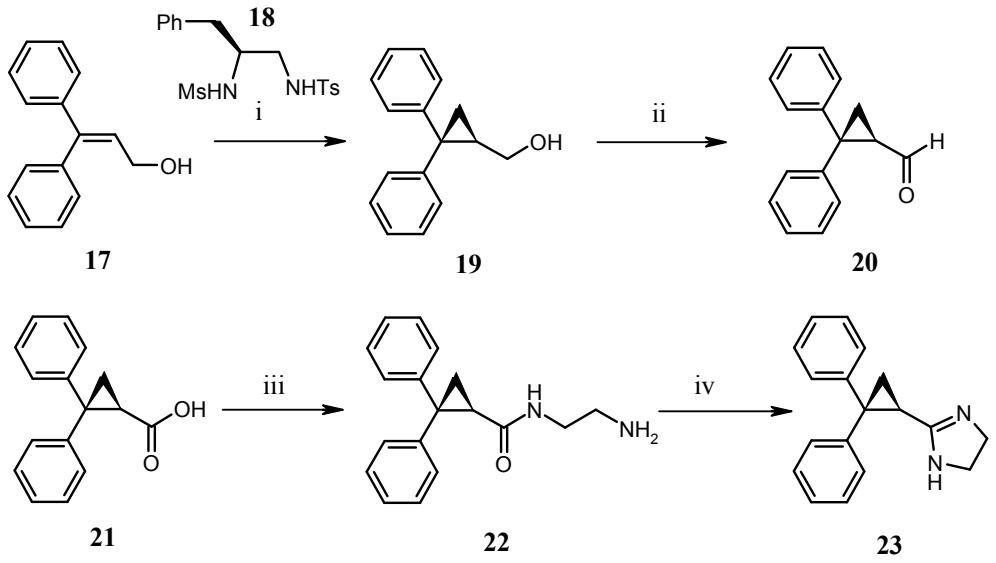
The target compound **16** was prepared by cyclocondensation of 2,2-diarylcyclopropanecarboxylates (R= H, CH_3) with $Me_2AlNHCH_2$-CH_2-NH_2 in toluene in 74% yield (R = H) (**Scheme 3**).



Scheme 3. Reaction conditions: (i) ethylene diamine, $AlMe_3$, Toluene, 5 ºC to rt, reflux, 4 h, 74%.

Imai *et al.* (2006)[9]

Recently Iami *et al*. carried out the synthesis of chiral cibenzoline **23.** The cyclopropanation of 3,3-diaryl-2-propen-1-ols **17** with Et_2Zn and CH_2I_2 proceeds in the presence of a catalytic amount of (S)-2-(methanesulfonyl) amino-1-(*p*-toluenesulfonyl) amino-3-phenylpropane **18** to afford the corresponding cyclopropylmethanols **19** with 20–76% ee (**Scheme 4**).



Scheme 4. Reaction conditions: (i) compound **18**, Et_2Zn, CH_2I_2, DCM, 0 ºC, 24 h; (ii) IBX, DMSO, rt, 3 h; (iii) $NaClO_2$, H_2O_2, NaH_2PO_4, $CH_3CN–H_2O$, rt. 30 min; (iv) ethylene diamine, PyBOP, Et_3N, DCM, rt, 5 h; 2 mmHg, 160 ºC, 37 h.

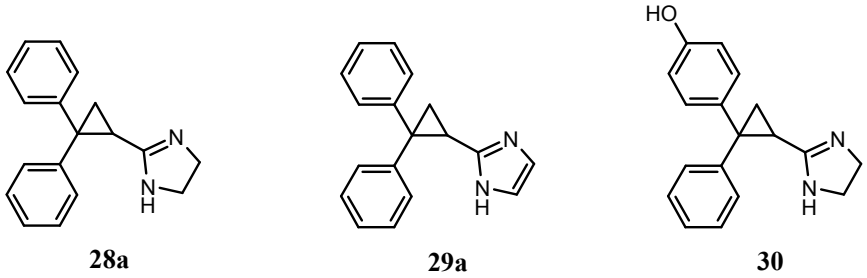
(+)-2,2-Diphenylcyclopropylmethanol **19** (76% ee) was oxidized with IBX in DMSO to corresponding aldehyde **20**, followed by $NaClO_2$, H_2O_2, and NaH_2PO_4 in $CH_3CN–H_2O$ to

give the corresponding acid **21**, which was treated with ethylenediamine, in the presence of PyBOP and Et_3N in CH_2Cl_2, to afford the amide **22** in quantitative overall yield. Amide **21** was cyclized at 160 ºC under reduced pressure (2 mmHg) to afford (R)-(+)-cibenzoline **23** in 55% yield.

3.1.3 Present work

3.1.3.1 Objective

Atrial fibrillation represents an important medical problem,[10] not only because of increased incidence in elderly population, but also a major cause of embolic stroke. Atrial fibrillation is the most commonly sustained cardiac arrhythmia and is a frequent reason for antiarrhythmic therapy.[11] Numerous antiarrhythmic drugs have been developed and used to treat arrhythmia, but clinical efficacy is often less than satisfactory. (±)-2-(2,2-diphenylcyclopropyl)-2-imidazoline **28a** (**Fig. 8**), has been clinically used as one of the Class I antiarrhythmic agents.[12-13] This drug relieves arrhythmia by restricting fast inward Na^+ current and blocking the slow inward Ca^{2+} channel in myocytes.[14] It was shown that micromolar concentrations of cibenzoline blocked ATP-sensitive K^+ (KATP) channel in excised membranes from rat heart and pancreatic β cells.[15-17] Cibenzoline is marketed under the trade names Cipralan (Glaxo) and Exacor (Monsanto). This drug is used as a racemic mixture of R (+) and S (-) cibenzoline. The S (-) enantiomer is approximately twice more potent than the R(+)-enantiomer.[18] Recently it is reported that cibenzoline is the first drug that inhibits gastric H^+, K^+-ATPase.[19]



28a **29a** **30**

Figure 8. Metabolites of Cibenzoline.

The metabolism of ^{14}C-cibenzoline has been investigated in rats and dogs; after oral dosing, these animals excrete unchanged cibenzoline **28a**, the imidazole **29a** and hydroxylated metabolites in their conjugated form **30** (**Fig. 8**).[20-21]

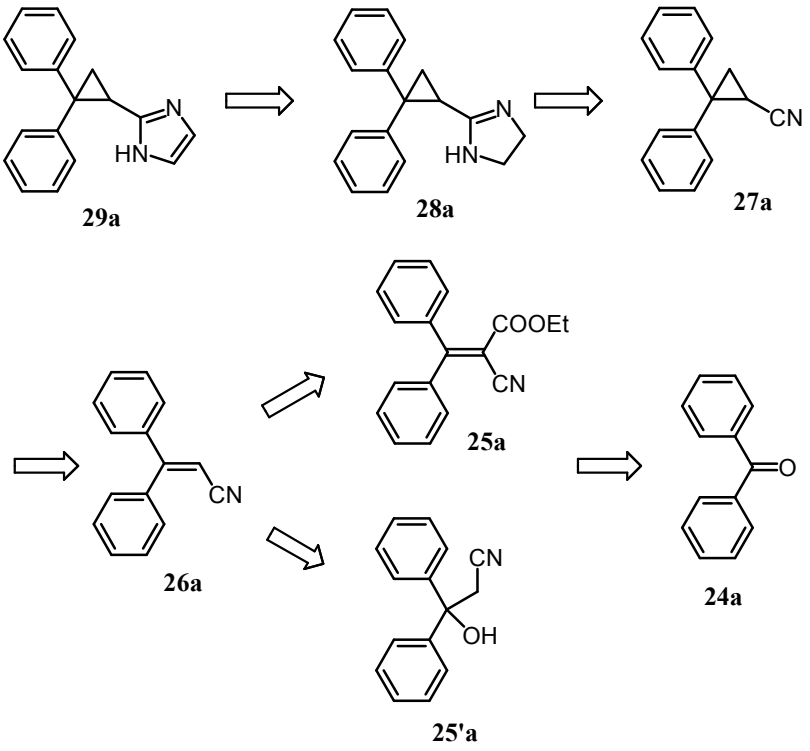


Figure 9. Retosynthetic analysis of cibenzoline

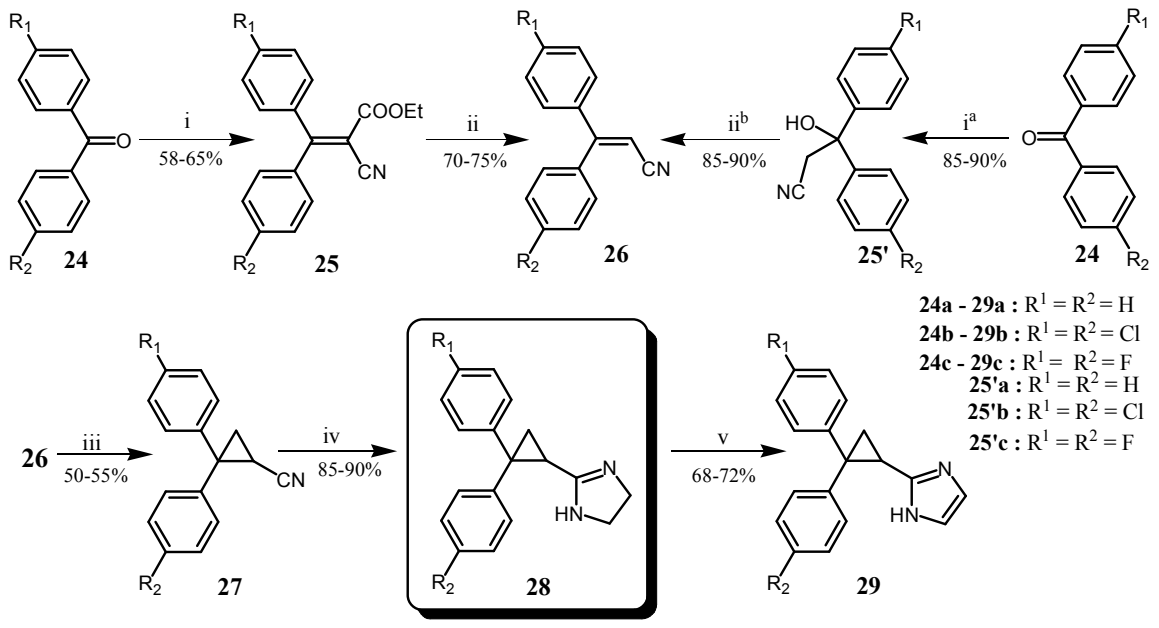
The retro synthesis strategy for cibenzoline is outlined in **Fig. 9**. Cibenzoline can be obtained starting from benzophenone **24a**. The unsaturated nitrile **26a** can be obtained either from tetrasubstituted olefin **25a** or from β-hydroxynitrile **25'a**. The 2,2-diphenylcyclopropanecarbonitrile **27a** can be obtained from **26a** and can be converted to target molecule **28a.**

We here in discuss an improved strategy for the synthesis of cibenzoline and its analogues avoiding toxic reagents like mercuric oxide and avoiding high temperature for the final condensation process from commercially available benzophenone as starting material. The synthesis of the analogues has been carried out in order to create a more potent and well tolerated therapeutic which will not induce spordic hypoglycemia[22-23] and stimulate insulin secretion in the potential treatment of cardiac arrhythmias.[24]

3.1.3.2 Results and discussions

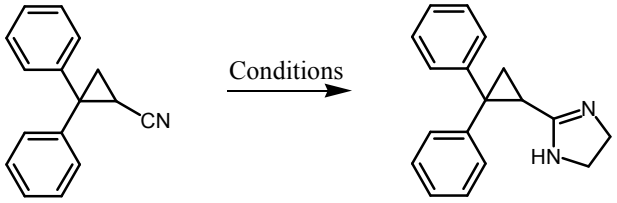
The synthesis of imidazoles **29a-29c** is outlined in **Scheme 5**. Thus benzophenone **24a** was converted to the tetra substituted olefin **25a** with ethylcyanoacetate by Knoevenagel condensation.[25-27] The reported procedure which makes use of ammonium acetate as a catalyst failed to initiate the condensation of benzophenone and ethylcyanoacetate. [28]

When a molar mixture of these components were heated to reflux in the presence of β-alanine in a mixture of glacial acetic acid and benzene for several hours, the formation of desired product **25a** was detected by GC. The condensation reaction reached equilibrium after 90 h with continuous removal of water (Dean-Stark water trap). It was observed that the rate of condensation was slow and was further retarded if higher boiling solvents such as toluene and xylene were used.



Scheme 5. Reaction conditions: (i) $CNCH_2COOEt$, $HOAc/C_6H_6$, β-alanine at reflux, 90 h; (i^a) CH_3CN, *n*-BuLi, dry THF, -80°C, 2 h; (ii) NaCl, H_2O, DMSO, 160-170 °C, 4 h; (ii^b) $SOCl_2$, dry pyridine, dry DCM, 0°C to rt, 3 h; (iii) $Me_3S(O)I$, NaH, DMSO, rt, 24 h; (iv) sulfur, ethylenediamine, reflux, 4 h; (v) (diacetoxyiodo) benzene, K_2CO_3, DMSO, rt, 48 h.

The cyanoester **25** was isolated by column chromatography. The deethoxycarbonylation of 2-cyano-2-alkenoates **25** to the unsaturated nitriles **26** was carried out in good yields by the Krapcho's protocol[29] using wet DMSO containing sodium chloride. The synthesis of unsaturated nitriles **26** by the sequence of Knoevenagel condensation followed by deethoxycarbonylation was inconvenient due to longer reaction time (90 h) and lower yields (58-65%). To achieve higher yields and short reaction time, synthesis of intermediate **26** was also carried out by an alternative route as shown in **Scheme 5**. The intermediate **26** can be prepared by starting from the substituted benzophenone. Acetonitrile was found to undergo mainly ionization of an α-hydrogen with n-butyl lithium in tetrahydrofuran, rather than an addition reaction involving the nitrile group. The ionization of acetonitrile with n-butyl lithium in tetrahydrofuran and its condensation with substituted benzophenone was carried out at -80 ^{o}C to get the β-hydroxynitrile in just 2 h, followed by the elimination of hydroxyl group using thionyl chloride and pyridine, which gave exclusively the compound **26**. The unsaturated nitrile **26** was cyclopropanated by addition of trimethylsulfoxonium iodide and sodium hydride in dry DMSO at room temperature to afford the 2,2-diphenylcyclopropanecarbonitriles **27** as a mixture of diastereomers.



27a **28a**

Table 1. Method for conversion of nitrile to 2-imidaoline

Entry	Conditions	Time (h)	Results
1	i) Dry HCl/EtOH, 0 ºC, ii) Et_3N, ethylenediamine, MeOH, reflux[30]	12	No expected product
2	CuCl/MeOH, ethylenediamine, reflux[31]	24	No reaction
3	Ethylenediamine monotosylate 200 °C[7]	10	No expected product
4	Ethylediamine, reflux	12	No reaction
5	Ethylediamine, sulfur, reflux[32]	4	88% isolated yield

Attempts were made towards the synthesis of 4,5-dihydro-2-(2,2-diphenylcyclopropyl)-1*H*-imidazole **28a** by the reaction of ethylenediamine with 2,2-diphenylcyclopropanecarbonitrile **27a** using reported methods in literature as shown above.(**Table 1**).[30-32]

Thus various methods (entry 1 to 4) as shown in **Table 1** were tried which failed to convert the nitrile to 2-imidazoline. But finally the conversion of the nitrile group to 2-imidazoline was achieved by refluxing **27a** with ethylenediamine in the presence of a catalytic amount of sulfur. The plausible explanation[33-35] is that sulfur reacts with nitrile to produce a thioamide **31** (**Fig. 10**).

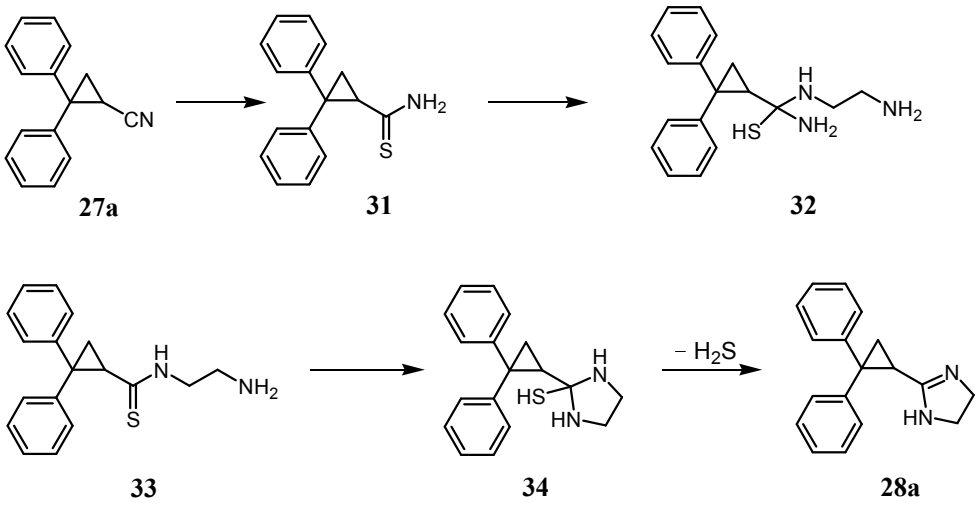


Figure 10. Plausible mechanism for conversion of nitrile to imidazoline in presence of sulfur.

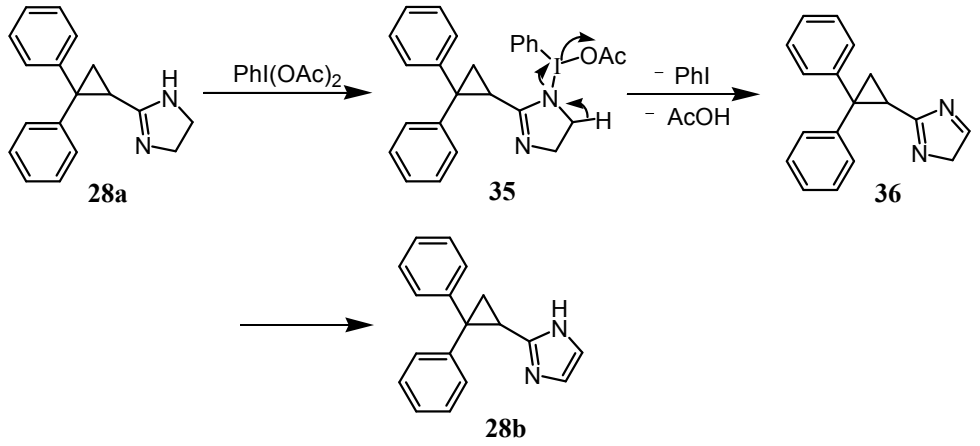
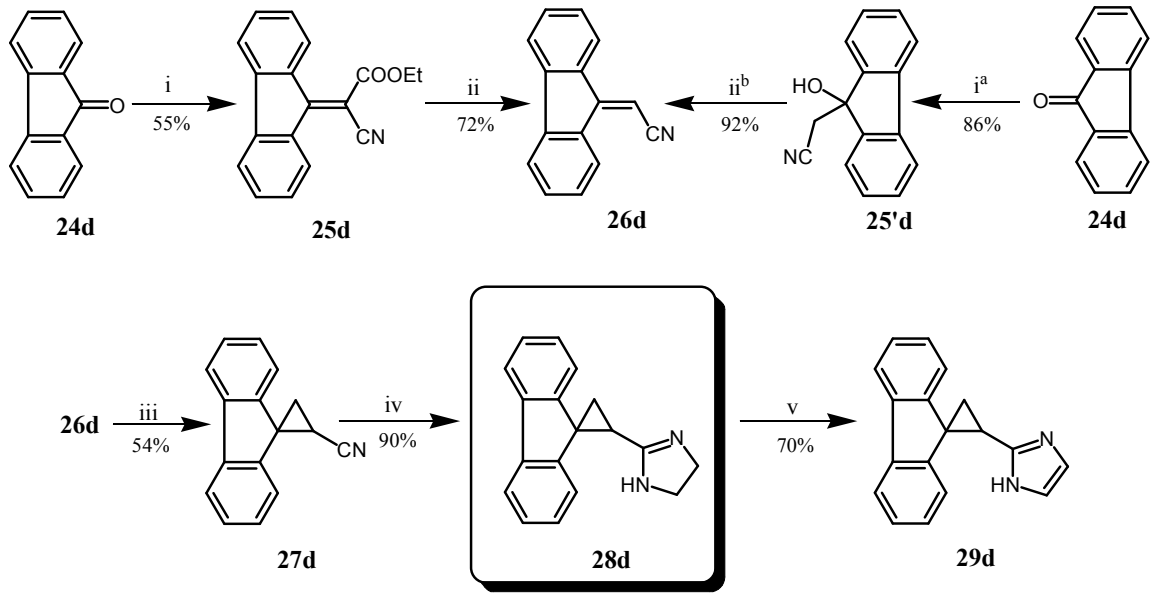


Figure 11. Plausible mechanism for imidazoline to imidazole.

The thioamide reacts with ethylenediamine, which upon elimination of hydrogen sulfide and ammonia produces the target molecule cibenzoline **28a**. The oxidation of imidazoline to imidazole **29a** derivative was carried out smoothly in good yields using (diacetoxyiodo) benzene in the presence of K_2CO_3 in DMSO at room temperature[36] (**Fig. 11**).

Recently Imai *et al.*[9] failed to synthesis cibenzoline analogue from 9-fluorenone. However using our methodology of our present study, we have successfully synthesized the racemic analogue of cibenzoline starting from 9-fluorenone as shown in **Scheme 6**. The sterically hindered two benzene rings of spiro (cyclopropane-1,9'-fluorene)-2-carbonitrile **27d** fixed in the same plane can stereochemically hinder the formation of the imidazoline ring. In our hands, however **27d** was easily converted to the target molecule **28d** by heating with ethylenediamine in the presence of sulfur. Further, **28d** was oxidized to **29d** (**Scheme 6**).



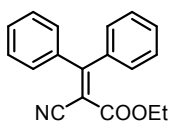
Scheme 6. Reaction conditions: (i) $CNCH_2COOEt$, $HOAc/C_6H_6$, β-alanine at reflux, 90 h; (i[a]) CH_3CN, *n*-BuLi, dry THF, -80°C, 2 h; (ii) NaCl, H_2O, DMSO, 160-170 °C, 4 h; (ii[b]) $SOCl_2$, dry pyridine, dry DCM, 0°C to rt, 3 h; (iii) $Me_3S(O)I$, NaH, DMSO, rt, 24 h; (iv) sulfur, ethylenediamine, reflux, 4 h; (v) (diacetoxyiodo) benzene, K_2CO_3, DMSO, rt, 48 h.

3.1.4 Conclusion

In summary, we have presented an efficient and simple four-step organic transformation for the synthesis of cibenzoline and its analogues. The synthesis of intermediate **26** via β-hydroxynitrile is more convenient with higher yields. The nitrile group of intermediate **27** was easily converted into the imidazoline ring in the presence of elemental sulfur as catalyst, which is relatively less toxic among the commercially available sulfur sources. We believe that this less hazardous and simple organic transformations makes the process amenable for scale-up operations.

3.1.5 Experimental

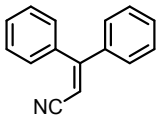
3.1.5.1 Procedure and Characterization data:



[A] Ethyl 2-cyano-3, 3-diphenyl acrylate 25a. A mixture of benzophenone **24a** (20.0 g, 110 mmol), ethyl cyanoacetate (13.65 g 121 mmol) and catalytic amount of β-alanine (0.9 g) was refluxed with separation of water with a Dean-Stark water trap in a mixed solvent of benzene (100 ml) and glacial acetic acid (20 ml). Separation of water was rapid during the first 2 h but became slower afterwards. Azeotropic distillation was continued for a period of 90 h. Benzene was removed under reduced pressure and the crude product was dissolved in ethyl acetate and washed with water. The ethyl acetate layer was separated, dried over Na_2SO_4 and concentrated in vacuo to afford the residue which was chromatographically purified on silica gel by using pet ether/EtOAc (9.8:0.2) as eluent to afford the compound **25a**.

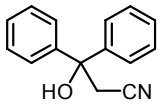
Nature	**:**	White solid
Yield	**:**	19.6 g, 64%.
MP	**:**	97-99 ^{o}C, (Lit.[37] 97.6-98.9 ^{o}C).
IR ($CHCl_3$, cm^{-1})	**:**	3020, 2220, 1958, 1731, 1558, 1445, 1368, 1246, 1111, 757
^{1}H NMR 200MHz, ($CDCl_3$)	**:**	δ 1.15 (t, *J* = 7.2 Hz, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 7.13-7.18 (m, 2H), 7.33-7.50 (m, 8H).
^{13}C NMR 50 MHz, ($CDCl_3$)	**:**	δ 13.4, 61.9, 103.8, 116.6, 127.9, 128.2, 129.0, 129.9, 130.1, 131.1, 138.0, 138.3, 162.4, 168.7.

Elemental Analysis	:	Calcd: C, 77.96; H, 5.45; N, 5.05.
$C_{18}H_{15}NO_2$ (277)		Found: C, 77.82; H, 5.62; N, 4.95.



[B] 3,3-diphenylacrylonitrile 26a. A mixture of ethyl 2-cyano-3,3-diphenyl acrylate **25a** (15 g, 54 mmol), sodium chloride (0.949 g, 16.2 mmol) and H_2O (0.584 g, 32.5 mmol) in 35 ml DMSO was heated up to 160-170 ^oC for 4 h. After completion of reaction, the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude residue which was chromatographically purified on silica gel by using pet ether/EtOAc, (9.9:0.1) to afford the pure product **26a**.

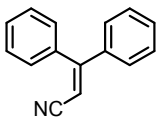
Nature	:	Colorless liquid
Yield	:	8 g, 72%.
IR	:	3018, 2239, 1951, 1599, 1496, 1216, 1025, 880
^{1}H NMR 200MHz, ($CDCl_3$)	:	δ 5.74 (s, 1H), 7.25-7.45 (m, 10H).
^{13}C NMR 50 MHz, ($CDCl_3$)	:	δ 94.8, 117.8, 128.40, 128.48, 128.5, 129.4, 129.9, 130.3, 136.9, 138.8, 163.0.
Elemental Analysis	:	Calcd: C, 87.77; H, 5.40; N, 6.82.
$C_{15}H_{11}N$ (205)		Found: C, 87.89; H, 5.48; N, 6.71.



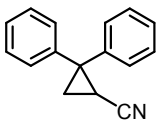
[C] 3-hydroxy-3,3-diphenylpropanenitrile 25'a. To a stirred solution of anhydrous THF (20 ml), n-butyl lithium in hexane 1.6 M (13.4 ml, 21.46 mmol) was added at -80 $^\circ C$ under argon atmosphere, followed by a solution of acetonitrile (1.02 ml, 19.51 mmol) in THF (15 ml). After stirring the reaction mixture for 1h at -80 $^\circ C$, benzophenone (3.55 g, 19.5 mmol) in anhydrous THF (20 ml) was added to the resulting white suspension over a period of 5 min and stirred further for 30 min at -80 $^\circ C$. The bath was removed after 30 min and the pale yellow solution was further stirred for 10 min after attaining room temperature, before it was poured into ice-water-hydrochloric acid mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate. Organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo to obtain the residual crude product which was purified by column

chromatography by using pet ether/EtOAc (9:1) as a eluent to obtain **25'a.** Compounds **25'b**, **25'c** and **25'd** were similarly synthesized by using the above procedure.

Nature	**:**	White solid.
MP	**:**	141-143 ^{o}C, (Lit.[38] 142-143 ^{o}C).
Yield	**:**	3.9 g, 90%.
IR ($CHCl_3$) CM^{-1}	**:**	3390, 2269, 1884, 1683, 1449, 1378, 1189, 1055.
^{1}H NMR 200MHz, ($CDCl_3$)	**:**	δ 2.80 (s, 1H), 3.28 (s, 2H), 7.31-7.43 (m, 10H).
^{13}C NMR 50 MHz, ($CDCl_3$)	**:**	δ 32.5, 76.4, 117.1, 125.7, 128.1, 128.6, 143.8.
Elemental Analysis	**:**	Calcd: C, 80.69; H, 5.87; N, 6.27.
$C_{15}H_{13}NO$ (223)		Found: C, 80.60; H, 5.79; N, 6.38.



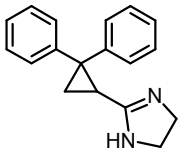
[D] 3,3-diphenylacrylonitrile (26a from 25'a). A solution of 3-hydroxy-3,3-diphenylpropanenitrile **25'a** (3.5 g, 15.69 mmol) in dry CH_2Cl_2 (30 ml) was stirred under an atmosphere of argon. Dry pyridine (1.50 ml, 18.52 mmol) was added and the reaction mixture was cooled to 0 °C using an ice-salt mixture. After 20 min $SOCl_2$ (1.27 ml, 17.42 mmol) was added drop wise at 0 °C over a period of 10 min and stirred at room temperature for 3 h. After completion of reaction, ice-cold water (10 ml), and CH_2Cl_2 (30 ml) was added to the reaction mixture. The CH_2Cl_2 layer was then washed with dilute HCl, water, and $NaHCO_3$ (5%, 15 ml). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to afford the residue, which was chromatographically purified on silica gel by using pet ether/EtOAc (9.9:0.1) as a eluent to afford the product **26a** as colorless liquid (2.79 g, 87%).



[E] 2,2-diphenylcyclopropanecarbonitrile 27a. Sodium hydride (2.48 g, as 60% dispersion in mineral oil, 62.43 mmol) was washed with dry hexane and suspended in anhydrous DMSO (40 ml) under a nitrogen atmosphere. Trimethylsulfoxonium iodide (13.73 g, 62.43 mmol) was added in portions to the heterogeneous reaction mixture, which was stirred until the foaming subsided. The reaction was cooled to 0 ^{o}C and 3,3-diphenylacrylonitrile **26a** (8 g, 39.02 mmol) dissolved in anhydrous DMSO (20 ml), was added to the reaction mixture over a period

of 20 min. The reaction mixture was allowed to warm to room temperature with stirring overnight. The crude reaction mixture was slowly poured into saturated aqueous ammonium chloride and the resulting mixture was further diluted with ethyl acetate. The phases were separated and the aqueous layer was extracted several times with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to obtain a crude product, which was chromatographically purified on silica gel by using pet ether/EtOAc (9.5:0.5) to afford **27a.** Compounds **27b**, **27c** and **27d** were synthesized similarly by using the above procedure.

Nature	**:**	White solid
MP	**:**	108-110 ^oC, (Lit.[39]107-108 ^oC).
Yield	**:**	4.68 g, 55%.
IR ($CHCl_3$) cm^{-1}	**:**	3058, 2213, 1662, 1592, 1494, 1445, 1355, 1251, 1078, 827.
^1H NMR 200MHz, ($CDCl_3$)	**:**	1.78 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 2.01 (t, *J* = 5.5 Hz,1H), 2.20 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 7.20-7.46 (m, 10H).
^{13}C NMR 50 MHz, ($CDCl_3$)	**:**	12.0, 20.8, 38.0, 119.3, 127.2, 127.6, 127.7, 128.60, 128.66, 129.2,138.3, 142.1.
Elemental Analysis	**:**	Calcd: C, 87.64; H, 5.98; N, 6.39.
$C_{16}H_{13}N$ (219)		Found: C, 87.48; H, 5.78; N, 6.45.



[F] 4,5-dihydro-2-(2,2-diphenylcyclopropyl)-1*H*-imidazole 28a. A mixture of 2,2-diphenylcyclopropanecarbonitrile **27a** (0.790 g, 3.60 mmol), sulfur (0.029 g, 0.90 mmol) in ethylenediamine (5 ml) was refluxed with stirring for 4 h under inert atmosphere. After completion of the reaction, ethylenediamine was removed under reduced pressure to obtain a yellow solid, which was dissolved in $CHCl_3$ and the organic layer was washed with water and dried over anhydrous Na_2SO_4. Thick oily residue was obtained after evaporation of solvent, which was chromatographically purified on silica gel by using CH_3OH/Et_3N (9.8:0.2) to afford a sticky product **28a** which was recrystallized from pet ether. Compounds **28b**, **28c** and **28d** were synthesized by similarly using the above procedure.

Nature	**:**	White solid
MP	**:**	100-102 ^oC, (Lit.[6] 103-104 ^oC).
Yield	**:**	0.830 g, 88%.

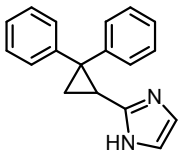
IR ($CHCl_3$) cm^{-1} : 3140, 2970, 2400, 2219, 1617, 1495, 1446, 930.

^{1}H NMR 200MHz, ($CDCl_3$) : 1.70 (dd, *J* = 5.8 Hz, *J* = 8.8 Hz, 1H), 2.10 (t, *J* = 5.8 Hz, 1H), 2.66 (dd, *J* = 5.8 Hz, *J* = 8.8 Hz, 1H), 3.17-3.28 (m, 2H), 3.40-3.51 (m, 2H), 4.09 (s, 1H), 7.20-7.48 (m, 10H).

^{13}C NMR 50 MHz, ($CDCl_3$) : 19.7, 25.5, 37.6, 49.5, 126.3, 127.0, 127.4, 128.3, 128.4, 129.6, 140.3, 144.9, 166.1.

Elemental Analysis : Calcd: C, 82.41; H, 6.92; N, 10.68.

$C_{18}H_{18}N_2$ (262) Found: C, 82.59; H, 6.74; N, 10.49.



[G] 2-(2,2-diphenylcyclopropyl)-1*H*-imidazole 29a. To a mixture of 4,5-dihydro-2-(2,2-diphenylcyclopropyl)-1*H*-imidazole **28a** (0.5 g, 1.90 mmol) and K_2CO_3 (0.290 g, 2.10 mmol) in DMSO (15 ml) was added DIB (0.614 g, 2.10 mmol). Then the mixture was stirred for 48 h at room temperature under an argon atmosphere. After completion of the reaction, the reaction mixture was diluted with sat. aq $NaHCO_3$ and EtOAc, and was stirred for 5 min. The mixture was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo to obtain the residual crude product, which was purified by column chromatography by using EtOAc/MeOH (9.9:0.1) as a eluent to afford (±) 2-(2,2-diphenylcyclopropyl)-1*H*-imidazole **29a** as a white solid. Compounds **29b**, **29c** and **29d** were synthesized similarly by using the above procedure.

Nature : white solid

MP : 218-220 °C.

Yield : 0.357 g, 72%.

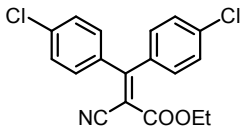
IR ($CHCl_3$) cm^{-1} : 3365, 3140, 1581, 1496, 1462, 1377, 1077, 862.

^{1}H NMR 200MHz, ($CDCl_3$/DMSOd_6) : δ 1.76 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 2.31 (t, *J* = 5.5 Hz, 1H), 2.85 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 6.71 (s, 2H), 7.05-7.36 (m, 10H), 7.75 (s, 1H).

^{13}C NMR 50 MHz, ($CDCl_3$/DMSOd_6) : δ 18.2, 25.1, 37.8, 125.9, 126.1, 127.5, 127.7, 128.2, 130.1, 140.9, 144.7, 146.1.

Elemental Analysis : Calcd: C, 83.04; H, 6.19; N, 10.76.

$C_{18}H_{16}N_2$ (260) Found: C, 82.87; H, 6.24; N, 10.59.



Ethyl 3,3-bis(4-chlorophenyl)-2-cyanoacrylate 25b: Compound **24b** (20 g, 80 mmol) was reacted as described in the procedure **[A]** to give compound **25b**.

Nature : White solid

MP : 90-92°C.

Yield : 18 g, 65%.

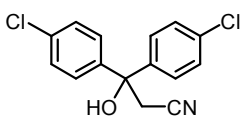
IR ($CHCl_3$) cm^{-1} : 3020, 2219, 1911, 1732, 1590, 1490, 1247, 1215, 1093, 833

^1H NMR 200MHz, ($CDCl_3$) : 1.21 (t, *J* = 7.1 Hz, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 7.05-7.12 (m, 2H), 7.31-7.44 (m, 6H).

^{13}C NMR 50 MHz, ($CDCl_3$) : 13.7, 62.4, 104.6, 116.3, 128.6, 129.0, 130.6, 131.5, 136.2, 136.3, 136.9, 138.0, 162.0, 166.4.

Elemental Analysis : Calcd: C, 62.45; H, 3.78; N, 4.05.

$C_{18}H_{13}Cl_2NO_2$ (346) Found: C, 62.52; H, 3.84; N, 4.22.



3,3-bis(4-chlorophenyl)-3-hydroxypropanenitrile 25'b: Compound **24b** (4 g, 16 mmol) was reacted as described in the procedure **[C]** to give compound **25'b.**

Nature : White solid

MP : 115-117 °C.

Yield : 3.95 g, 85%.

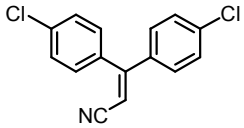
IR ($CHCl_3$) cm^{-1} : 3385, 2262, 1890, 1650, 1485, 1462, 1367, 1254, 1168, 1094

^1H NMR 200MHz, ($CDCl_3$) : 2.87 (s, 1H), 3.23 (s, 2H), 7.29-7.39 (m, 8H).

^{13}C NMR 50 MHz, ($CDCl_3$) : δ 32.3, 75.6, 116.7, 127.1, 128.7, 134.2, 141.9.

Elemental Analysis : Calcd: C, 61.67; H, 3.79; N, 4.79.

$C_{15}H_{11}Cl_2NO$ (292) Found: C, 61.80; H, 3.67; N, 4.90.



3,3-bis(4-chlorophenyl)acrylonitrile 26b: Compound **25b** (10 g, 28.90 mmol) was reacted as described in the procedure **[B]** to give **26b** as a white solid (5.65 g, 71%); **26b from 25'b:** Compound **25'b** (3 g, 10.27 mmol) was reacted as described in the procedure **[D]** to give product **26b.**

Nature : White solid

MP : 100-102 ^{o}C.

Yield : 2.54 g, 90%.

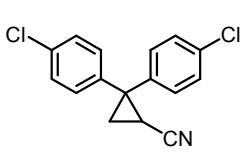
IR ($CHCl_3$) cm^{-1} : 3019, 2216, 1909, 1590, 1494, 1403, 1253, 1093, 834.

^{1}H NMR 200MHz ($CDCl_3$) : 5.73 (s, 1H), 7.19-7.25 (m, 2H), 7.34-7.47 (m, 6H).

^{13}C NMR 50 MHz, ($CDCl_3$) : 95.6, 117.3, 128.9, 129.0, 129.6, 130.8, 134.8, 136.3, 136.80, 136.87, 160.5.

Elemental Analysis : Calcd: C, 65.72; H, 3.31; N, 5.11.

$C_{15}H_9Cl_2N$ (274) Found: C, 65.80; H, 3.17; N, 5.24.



2,2-bis(4-chlorophenyl) cyclopropanecarbonitrile 27b: Compound **26b** (8.5 g, 31.02 mmol) was reacted as described in the procedure **[E]** to give product **27b.**

Nature : White solid

MP : 139-140 ^{o}C.

Yield : 4.65 g, 52%.

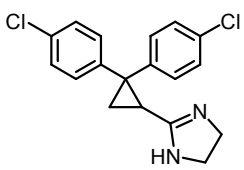
IR ($CHCl_3$) cm^{-1} : 3019, 2241, 1596, 1492, 1401, 1215, 758.

^{1}H NMR 200 MHz ($CDCl_3$) : 1.82 (dd, J = 5.5 Hz, J = 9.2 Hz, 1H), 2.05 (t, J = 5.5 Hz, 1H), 2.25 (dd, J = 5.5 Hz, J = 9.2 Hz, 1H), 7.18-7.39 (m, 8H)

^{13}C NMR 50 MHz ($CDCl_3$) : 12.3, 20.9, 36.9, 118.8, 128.9, 129.0, 129.1, 130.5, 133.4, 134.0,136.9, 140.1.

Elemental analysis : Calcd: C, 66.69; H, 3.85; N, 4.86.

$C_{16}H_{11}Cl_2N$ (288) Found: C, 66.80; H, 3.62; N, 4.98.



2-(2,2-bis(4-chlorophenyl)cyclopropyl)-4,5-dihydro-1*H*-imidazole 28b: Compound **27b** (0.7 g, 2.43 mmol) was reacted as described in the procedure **[F]** to give product **28b.**

Nature : White solid

MP : 155-158 ^{o}C.

Yield : 0.684 g, 85%.

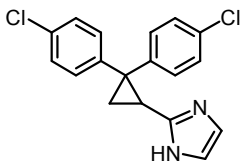
IR ($CHCl_3$) cm^{-1} : 3153, 2974, 2400, 1621, 1493, 1215, 846.

^1H NMR, 200 MHz, ($CDCl_3$) : δ 1.62 (dd, *J* = 5.5 Hz, *J* = 9.0 Hz, 1H), 2.00 (t, *J* = 5.5 Hz, 1H), 2.46 (dd, *J* = 5.5 Hz, *J* = 9.0 Hz, 1H), 2.71 (brs, 1H), 3.15-3.27 (m, 2H), 3.38-3.50 (m, 2H), 7.13-7.29 (m, 8H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 19.5, 25.6, 36.4, 49.6, 128.5, 128.7, 130.9, 132.3, 132.9, 138.5, 143.1, 164.8.

Elemental analysis : Calcd: C, 65.27; H, 4.87; N, 8.46.

$C_{18}H_{16}Cl_2N_2$ (331) Found: C, 65.42; H, 4.71; N, 8.54.



2-(2,2-bis(4-chlorophenyl)cyclopropyl)-1*H*-imidazole 29b: Compound **28b** (0.290 g, 0.87 mmol) was reacted as described in the procedure **[G]** to give product **29b.**

Nature : White solid

MP : 224-226 ^oC.

Yield : 0.196 g, 68%.

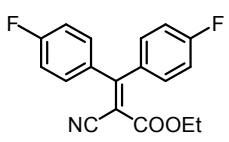
IR ($CHCl_3$) cm^{-1} : 3497, 3356, 1668, 1583, 1462, 1220, 1377, 861.

^1H NMR 200 MHz ($CDCl_3$/DMSO-d_6) : δ 1.75 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 2.31 (t, *J* = 5.5 Hz, 1H), 2.87 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 6.76 (s, 2H), 7.09 (s, 4H), 7.23 (s, 4H), 7.42 (s, 1H).

^{13}C NMR 50 MHz ($CDCl_3$/DMSO-d_6) : δ 18.4, 25.1, 36.5, 127.8, 128.2, 129.4, 130.8, 130.9, 131.8, 139.4, 144.2, 144.4.

Elemental analysis : Calcd: C, 65.67; H, 4.29; N, 8.51.

$C_{18}H_{14}Cl_2N_2$ (329) Found: C, 65.79; H, 4.42; N, 8.49.



Ethyl 2-cyano-3,3-bis(4-fluorophenyl)acrylate 25c. Compound **24c** (20 g, 91.74 mmol) was reacted as described in the procedure **[A]** to give product **25c.**

Nature : White solid

MP : 114-116 ^oC

Yield : 16.7 g, 58 %

IR ($CHCl_3$) cm^{-1} : 3010, 2225, 1931, 1605, 1513, 1250, 844.

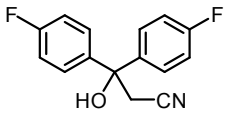
^1H NMR 200 MHz : δ 1.20 (t, *J* = 7.2 Hz, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 7.04-7.19

($CDCl_3$) (m, 6H), 7.38-7.45 (m, 2H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 13.7, 62.2, 103.8, 115.5 (d, *J* = 22.0 Hz), 115.8 (d, *J* = 22.0 Hz), 116.7, 131.5 (d, *J* = 9.00 Hz), 132.6 (d, *J* = 9.00 Hz), 134.1, 134.1, 134.2, 164.0 (d, *J* = 252.4 Hz), 164.5 (d, *J* = 252.4 Hz), 166.8.

Elemental analysis : Calcd: C, 69.01; H, 4.18; N, 4.47.

$C_{18}H_{13}F_2NO_2$ (313) Found: C, 68.90; H, 4.25; N, 4.62.



3,3-bis(4-fluorophenyl)-3-hydroxypropanenitrile 25'c. Compound **24c** (4 g, 18.34 mmol) was reacted as described in the procedure **[C]** to give product **25'c.**

Nature : White solid

MP : 98-100 ^{o}C.

Yield : 4.1 g, 86%.

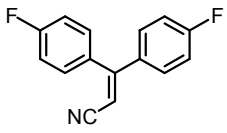
IR ($CHCl_3$) cm^{-1} : 3384, 2267, 1898, 1603, 1508, 1461, 1387, 1231, 1164, 1065.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 2.82 (s, 1H), 3.24 (s, 2H), 7.00-7.12 (m, 4H), 7.31-7.42 (m, 4H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 32.71, 75.68, 115.4 (d, *J* = 21.6 Hz), 116.9, 127.6 (d, *J* = 8.4 Hz), 139.5 (d, *J* = 3.3 Hz), 162.2 (d, *J* = 248.1 Hz).

Elemental analysis : Calcd: C, 69.49; H, 4.28; N, 5.40.

$C_{15}H_{11}F_2NO$ (259) Found: C, 69.58; H, 4.12; N, 5.26.



3,3-bis(4-fluorophenyl) acrylonitrile 26c. Compound **25c** (9 g, 28.75 mmol) was reacted as described in the procedure **[B]** to give product **26c** (5.2 g, 75%); (**26c** from **25'c**): Compound **25'c** (3.8 g, 14.67 mmol) was reacted as described in the procedure **[D]** to give product **26c.**

Nature : White solid

MP : 80-82 ^{o}C.

Yield : 3.0 g, 85%.

IR ($CHCl_3$) cm^{-1} : 3027, 2215, 1943, 1602, 1495, 1237, 1160, 843.

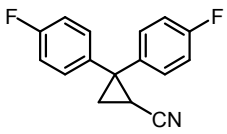
^{1}H NMR 200 MHz : 5.61 (s, 1H), 7.01-7.37 (m, 8H).

($CDCl_3$)

^{13}C NMR 50 MHz ($CDCl_3$) : δ 94.7, 115.7 (d, *J* = 21.8 Hz), 115.7 (d, *J* = 21.8 Hz), 117.5, 130.3 (d, *J* = 8.6 Hz), 131.5 (d, *J* = 8.6 Hz), 133.7 (d, *J* = 100.5 Hz), 133.7 (d, *J* = 100.5 Hz), 160.7, 163.5 (d, *J* = 252.3 Hz), 164.0 (d, *J* = 252.3 Hz).

Elemental analysis : Calcd: C, 74.68; H, 3.76; N, 5.81.

$C_{15}H_9F_2N$ (241) Found: C, 74.51; H, 3.89; N, 5.75.



2,2-bis(4-fluorophenyl)cyclopropanecarbonitrile 27c. Compound **26c** (8 g, 31.19 mmol) was reacted as described in the procedure **[E]** to give **27c** as a white solid.

Nature : White solid

MP : 97-99 °C, (Lit.[6] 95 °C).

Yield : 4.24 g, 50%.

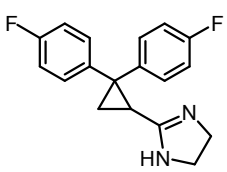
IR ($CHCl_3$) cm^{-1} : 3019, 2240, 1889, 1661, 1602, 1512, 1219, 1159, 837, 758.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.77 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 1.99 (t, *J* = 5.5 Hz, 1H), 2.19 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 6.94-7.10 (m, 4H), 7.18-7.25 (m, 2H), 7.36-7.43 (m, 2H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 12.3, 21.0, 36.8, 115.6 (d, *J* = 21.6 Hz), 115.9 (d, *J* = 21.6 Hz), 119.1, 129.3 (d, *J* = 8.3 Hz), 130.9 (d, *J* = 8.3 Hz), 136.2 (d, *J* = 158.9 Hz), 136.2 (d, *J* = 158.9 Hz), 161.8 (d, *J* = 247.3 Hz), 162.1 (d, *J* = 247.3 Hz).

Elemental analysis : Calcd: C, 75.28; H, 4.34; N, 5.49.

$C_{16}H_{11}F_2N$ (255) Found: C, 75.36; H, 4.20; N, 5.35.



2-(2,2-bis(4-fluorophenyl)cyclopropyl)-4,5-dihydro-1*H*-imidazole 5c. Compound **27c** (0.8 g, 3.12 mmol) was reacted as described in the procedure **[F]** to give compound **28c.**

Nature : White solid

MP : 112-115 °C.

Yield : 0.841 g, 90%.

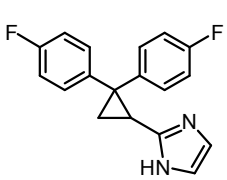
IR ($CHCl_3$) cm^{-1} : 3150, 2924, 1594, 1510, 1461, 1377, 1223, 1158, 830.

^{1}H NMR 200 MHz (CDCl$_3$) : δ 1.61 (dd, *J* = 5.8 Hz, *J* = 9.0 Hz, 1H), 1.96 (t, *J* = 5.8 Hz, 1H), 2.46 (dd, *J* = 5.8 Hz, *J* = 9.0 Hz, 1H), 3.14-3.24 (m, 2H), 3.37-3.49 (m, 2H), 6.89-7.03 (m, 4H), 7.18-7.38 (m, 4H).

^{13}C NMR 50 MHz (CDCl$_3$) : δ 19.6, 25.5, 36.2, 49.9, 115.1 (d, *J* = 21.4 Hz), 115.2 (d, *J* = 21.4 Hz), 128.9 (d, *J* = 8.0 Hz), 131.0 (d, *J* = 8.0 Hz), 138.3 (d, *J* = 227.7 Hz), 138.4 (d, *J* = 227.7 Hz), 161.2 (d, *J* = 246.3), 161.6 (d, *J* = 246.3Hz).

Elemental analysis : Calcd: C, 72.47; H, 5.41; N, 9.39.

$C_{18}H_{16}F_2N_2$ (298) Found: C, 72.52; H, 5.60; N, 9.22.



2-(2,2-bis(4-fluorophenyl)cyclopropyl)-1*H*-imidazole 29c. Compound **28c** (0.180 g, 0.60 mmol) was reacted as described in the procedure **[G]** to give product **29c.**

Nature : White solid

MP : 224-226 ^oC.

Yield : 0.126 g, 71%.

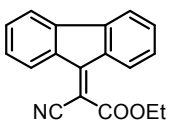
IR (CHCl$_3$) cm^{-1} : 3356, 3152, 1595, 1583, 1511, 1462, 1377, 1233, 1106, 832

^{1}H NMR 200 MHz (CDCl$_3$/DMSO-*d$_6$*) : δ 1.66 (dd, *J* = 5.8 Hz, *J* = 9.2 Hz, 1H), 2.15 (t, *J* = 5.8 Hz, 1H), 2.79 (dd, *J* = 5.8 Hz, *J* = 9.2 Hz, 1H), 6.67 (s, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.86 (t, *J* = 8.8 Hz, 2H), 7.01-7.08 (m, 2H), 7.17-7.24 (m, 2H).

^{13}C NMR 50 MHz (CDCl$_3$/DMSO-*d$_6$*) : δ 17.4, 24.0, 35.4, 113.6 (d, *J* = 24.1 Hz), 114.0 (d, *J* = 24.1 Hz), 128.5 (d, *J* = 8.0 Hz), 130.8 (d, *J* = 8.0 Hz), 138.60 (d, *J* = 253.5 Hz), 138.65 (d, *J* = 253.5 Hz), 143.5, 159.6 (d, *J* = 242.8).

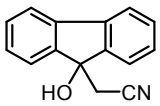
Elemental analysis : Calcd: C, 72.96; H, 4.76; N, 9.45.

$C_{18}H_{14}F_2N_2$ (296) Found: C, 73.12; H, 4.55; N, 9.28.



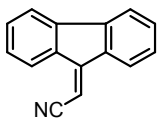
Ethyl 2-cyano-2-(9H-fluoren-9-ylidene)acetate 25d. Compound **24d** (20 g, 111.1 mmol) was reacted as described in the procedure **[A]** to give product **25d.**

Nature	:	Orange color solid
MP	:	97-99 ^{o}C.
Yield	:	17.7 g, 55%.
IR ($CHCl_3$) cm^{-1}	:	3020, 2211, 1960, 1732, 1584, 1450, 1248, 1155, 857.
^{1}H NMR 200 MHz ($CDCl_3$)	:	δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.17-7.58 (m, 6H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H).
^{13}C NMR 50 MHz ($CDCl_3$)	:	δ 13.9, 62.9, 99.6, 116.3, 119.9, 126.2, 127.8, 128.1, 128.5, 132.7, 134.3, 135.3, 141.9, 142.1, 154.7, 162.4.
Elemental analysis	:	Calcd: C, 78.53; H, 4.76; N, 5.09.
$C_{18}H_{13}NO_2$ (275)		Found: C, 78.45; H, 4.58; N, 4.95.



2-(9-hydroxy-9*H*-fluoren-9-yl) acetonitrile 25'd. Compound **24d** (4 g, 22.2 mmol) was reacted as described in the procedure **[C]** to give compound **25'd.**

Nature	:	White solid
MP	:	98-100 ^{o}C, (Lit.[40] 97.5-98.5 ^{o}C).
Yield	:	4.3 g, 86%.
IR ($CHCl_3$) cm^{-1}	:	3370, 2257, 1608, 1451, 1063, 942, 862.
^{1}H NMR 200 MHz ($CDCl_3$)	:	δ 2.37 (s, 1H), 2.96 (s, 2H), 7.32-7.48 (m, 4H), 7.65-7.74 (m, 4H).
^{13}C NMR 50 MHz ($CDCl_3$)	:	δ 29.2, 78.1, 116.7, 120.3, 123.5, 128.4, 130.0, 138.8, 145.7.
Elemental analysis	:	Calcd: C, 81.43; H, 5.01; N, 6.33.
$C_{15}H_{11}NO$ (221)		Found: C, 81.62; H, 5.14; N, 6.28.



2-(9*H*-fluoren-9-ylidene)acetonitrile 26d. Compound **25d** (9 g, 32.72 mmol) was reacted as described in the procedure **[B]** to give **26d** as a yellow solid (4.78 g, 72%); **26d from 25'd:** Compound **25'd** (4 g, 18.09 mmol) was reacted as described in the procedure **[D]** to give product **25d.**

Nature	:	Yellow solid
MP	:	110-112 ^{o}C, (Lit.[40] 109-111 ^{o}C).
Yield	:	3.38 g, 92%.

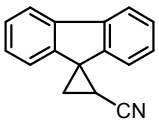
IR ($CHCl_3$) cm^{-1} : 3017, 2213, 1715, 1601, 1451, 1078, 820.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 6.07 (s, 1H), 7.23-7.64 (m, 7H), 8.39 (d, J = 7.5 Hz, 1H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 88.3, 117.3, 120.06, 120.12, 121.4, 125.1, 127.7, 128.2, 131.60, 131.67, 134.7, 136.2, 140.4, 141.7, 153.2.

Elemental analysis : Calcd: C, 88.64; H, 4.46; N, 6.89.

$C_{15}H_9N$ (203) Found: C, 88.60; H, 4.58; N, 6.95.



Spiro(cyclopropane-1,9'-fluorene)-2-carbonitrile 27d. Compound **26d** (9 g, 44.33 mmol) was reacted as described in the procedure **[E]** to give product **27d.**

Nature : White solid

MP : 107-109 °C.

Yield : 5.19 g, 54%.

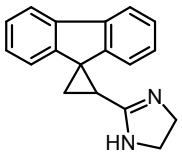
IR ($CHCl_3$) cm^{-1} : 3024, 2232, 1655, 1461, 1377, 759.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.79 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 2.02 (t, *J* = 5.5 Hz, 1H), 2.22 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 7.28-7.46 (m, 8H).

^{13}C NMR 50 MHz ($CDCl_3$) : δ 12.1, 20.9, 38.1, 119.3, 127.2, 127.6, 127.8, 129.2, 138.8, 142.2.

Elemental analysis : Calcd: C, 88.45; H, 5.10; N, 6.45.

$C_{16}H_{11}N$ (217) Found: C, 88.27; H, 5.38; N, 6.61.



2-(spiro(cyclopropane-1,9'-flurene)-2-yl)-4,5-dihydro-1*H*-imidazole 28d. Compound **27d** (1 g, 4.60 mmol) was reacted as described in the procedure **[F]** to give **28d** as a white solid.

Nature : White solid

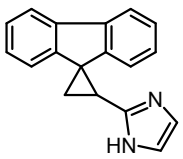
MP : 97-99 °C.

Yield : 1.07 g, 90%.

IR ($CHCl_3$) cm^{-1} : 3135, 2925, 1954, 1617, 1463, 1377, 1283, 899.

^{1}H NMR 200 MHz ($CDCl_3$) : δ 1.65 (dd, *J* = 5.4 Hz, *J* = 9.0 Hz, 1H), 1.98 (t, *J* = 5.4 Hz, 1H), 2.57 (dd, *J* = 5.4 Hz, *J* = 9.0 Hz, 1H), 3.09-3.25 (m, 2H), 3.34-3.46 (m, 2H), 7.15-7.43 (m, 8H).

^{13}C NMR 50 MHz (CDCl$_3$)	**:**	δ 19.6, 25.5, 37.5, 49.6, 126.2, 126.9, 127.4, 128.2, 128.3, 129.6, 140.4, 144.9, 166.0.
Elemental analysis $C_{18}H_{16}N_2$ (260)	**:**	Calcd: C, 83.04; H, 6.19; N, 10.76. Found: C, 83.21; H, 6.04; N, 10.62.



2-(spiro(cyclopropane-1,9'-flurene)-2-yl)-1*H*-imidazole **29d**. Compound **28d** (0.165 g, 0.63 mmol) was reacted as described in the procedure **[G]** to give compound **29d.**

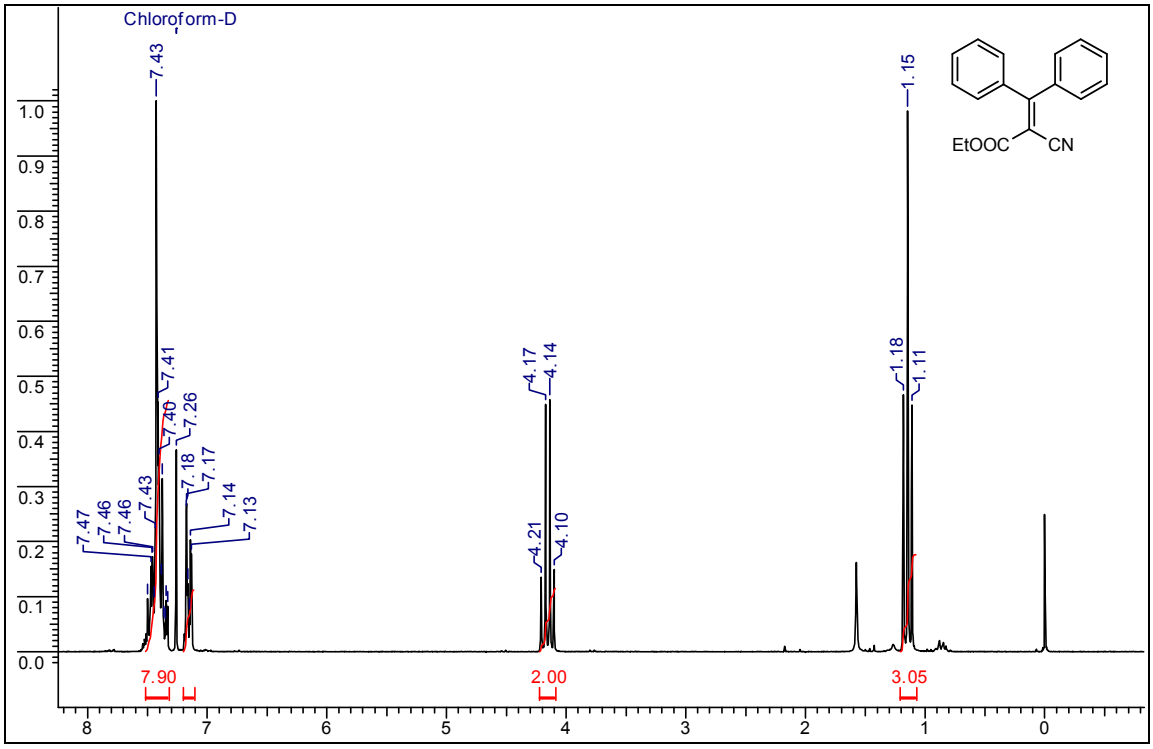
Nature	**:**	White solid
MP	**:**	219-221^{o}C.
Yield	**:**	0.114 g, 70%.
IR (CHCl$_3$) cm^{-1}	**:**	3460, 3356, 1668, 1582, 1496, 1461, 1377, 861.
^{1}H NMR 200 MHz (CDCl$_3$/DMSO-*d$_6$*)	**:**	δ 1.80 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 2.26 (t, *J* = 5.5 Hz, 1H), 2.92 (dd, *J* = 5.5 Hz, *J* = 9.2 Hz, 1H), 6.74 (s, 2H), 7.10-7.22 (m, 5H), 7.29-7.37 (m, 3H).
^{13}C NMR 50 MHz (CDCl$_3$/DMSO-*d$_6$*)	**:**	δ 18.1, 25.1, 37.7, 125.9, 126.1, 127.5, 127.7, 128.2, 130.0, 140.9, 144.7, 146.1.
Elemental analysis $C_{18}H_{14}N_2$ (258)	**:**	Calcd: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.54; H, 5.67; N, 10.76.

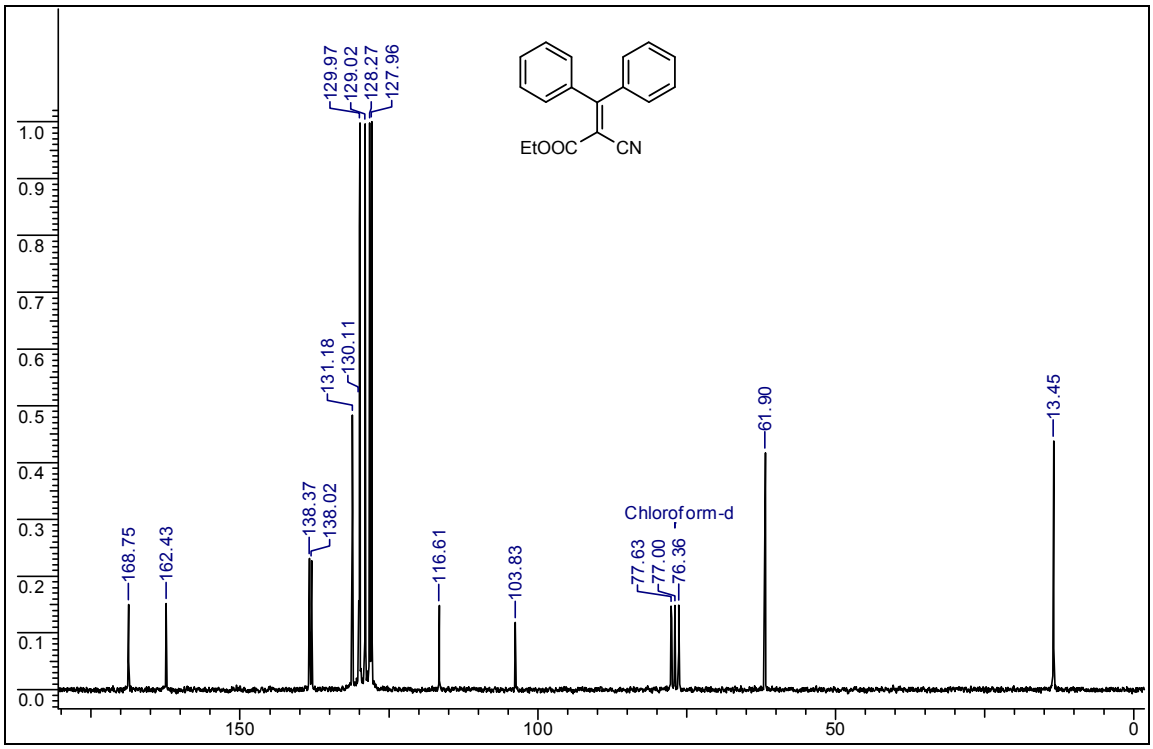
3.1.6 Spectra

Table 2. ^{1}H and ^{13}C spectra of some selected compounds are given below:

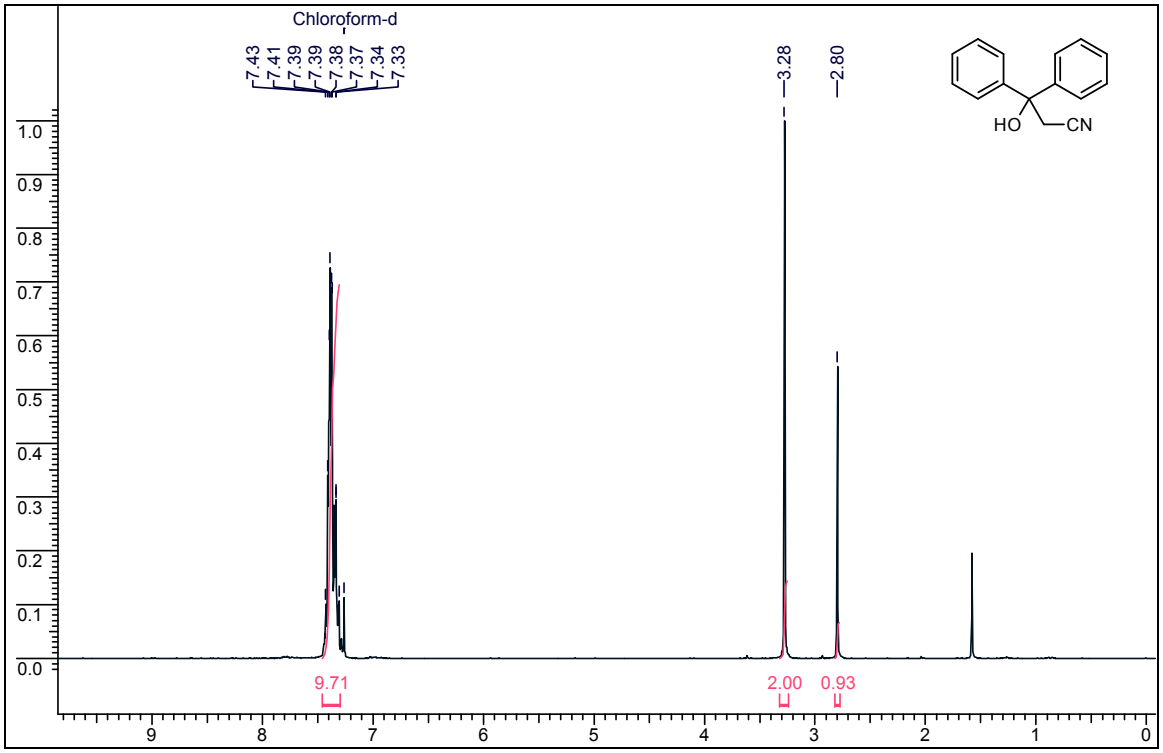
Sr. No.	Spectra	
1	^{1}H and ^{13}C NMR spectra of compound	**25a**
2	^{1}H and ^{13}C NMR spectra of compound	**25'a**
3	^{1}H and ^{13}C NMR spectra of compound	**26a**
4	^{1}H and ^{13}C NMR spectra of compound	**27a**
5	^{1}H and ^{13}C NMR spectra of compound	**28a**
6	^{1}H and ^{13}C NMR spectra of compound	**29a**
7	^{1}H and ^{13}C NMR spectra of compound	**28b**
8	^{1}H and ^{13}C NMR spectra of compound	**29b**
9	^{1}H and ^{13}C NMR spectra of compound	**28c**
10	^{1}H and ^{13}C NMR spectra of compound	**29c**
11	^{1}H and ^{13}C NMR spectra of compound	**27d**
12	^{1}H and ^{13}C NMR spectra of compound	**28d**
13	^{1}H and ^{13}C NMR spectra of compound	**29d**

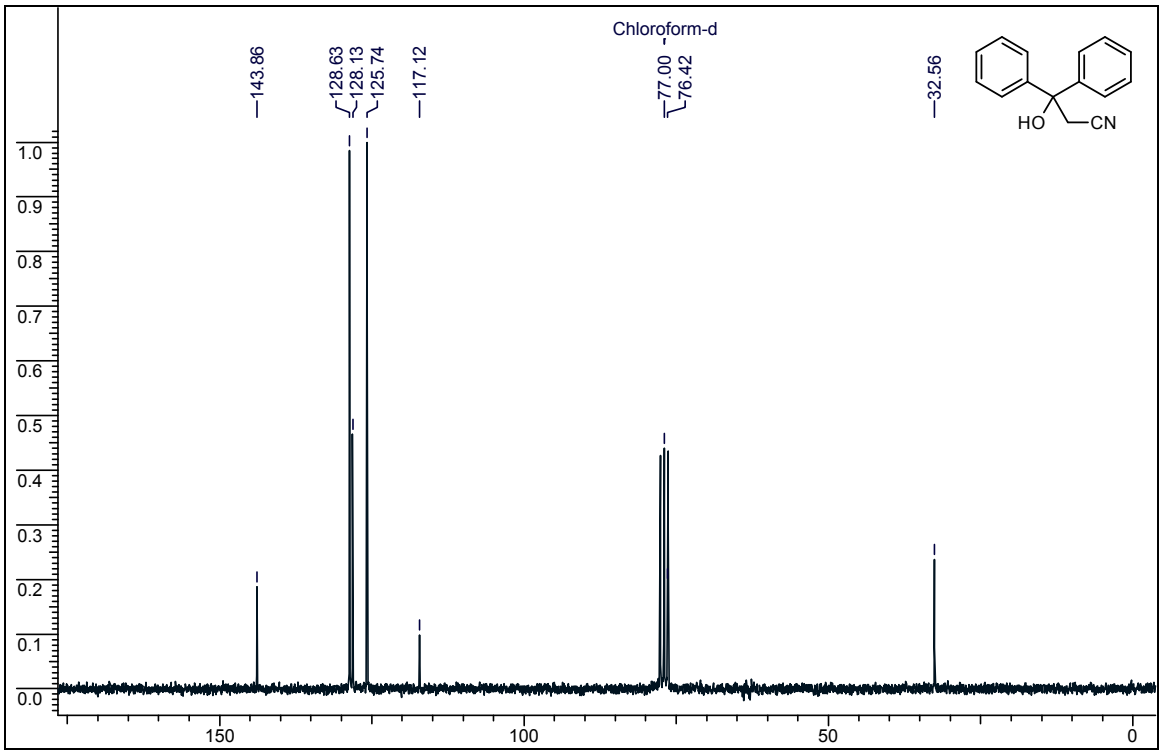
[1] ^{1}H and ^{13}C NMR spectra of compound 25a



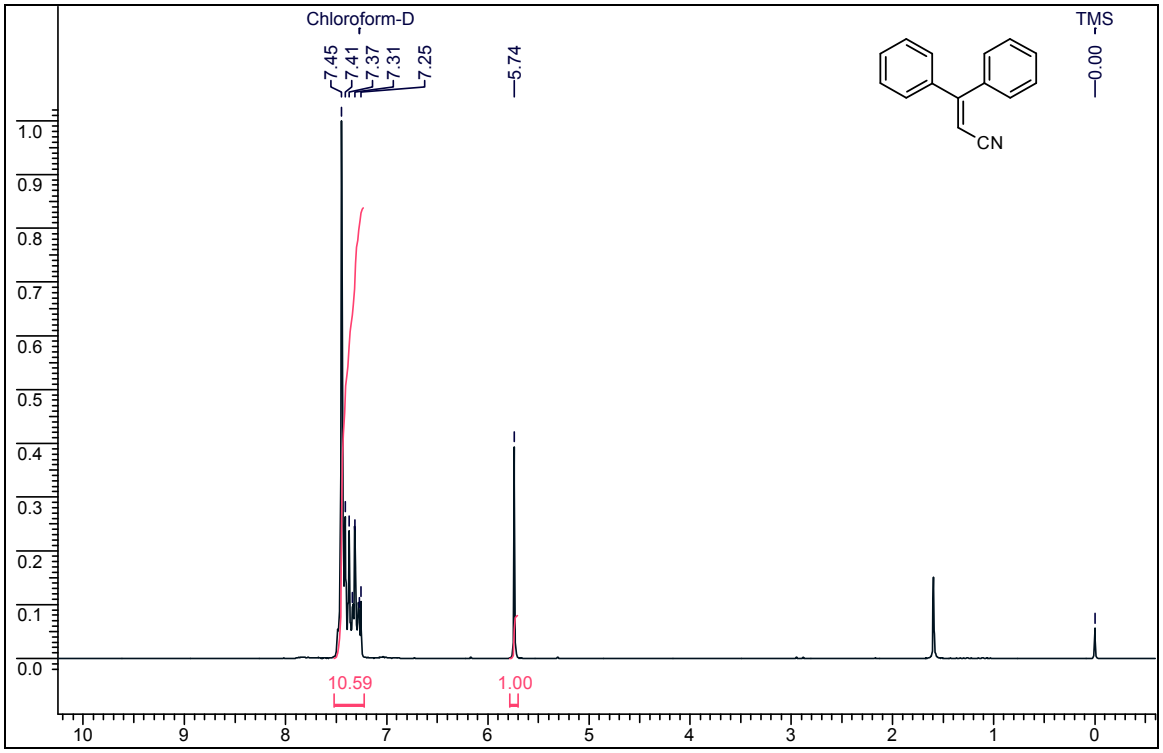


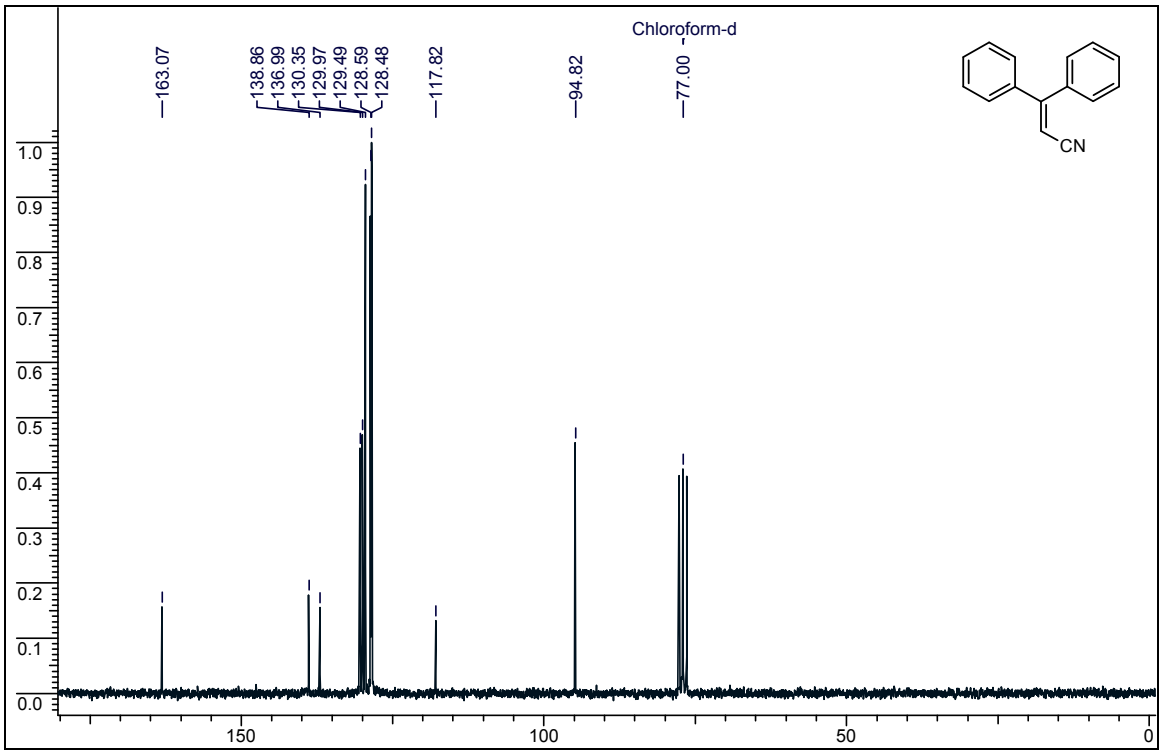
[2] ^{1}H and ^{13}C NMR spectra of compound 25'a



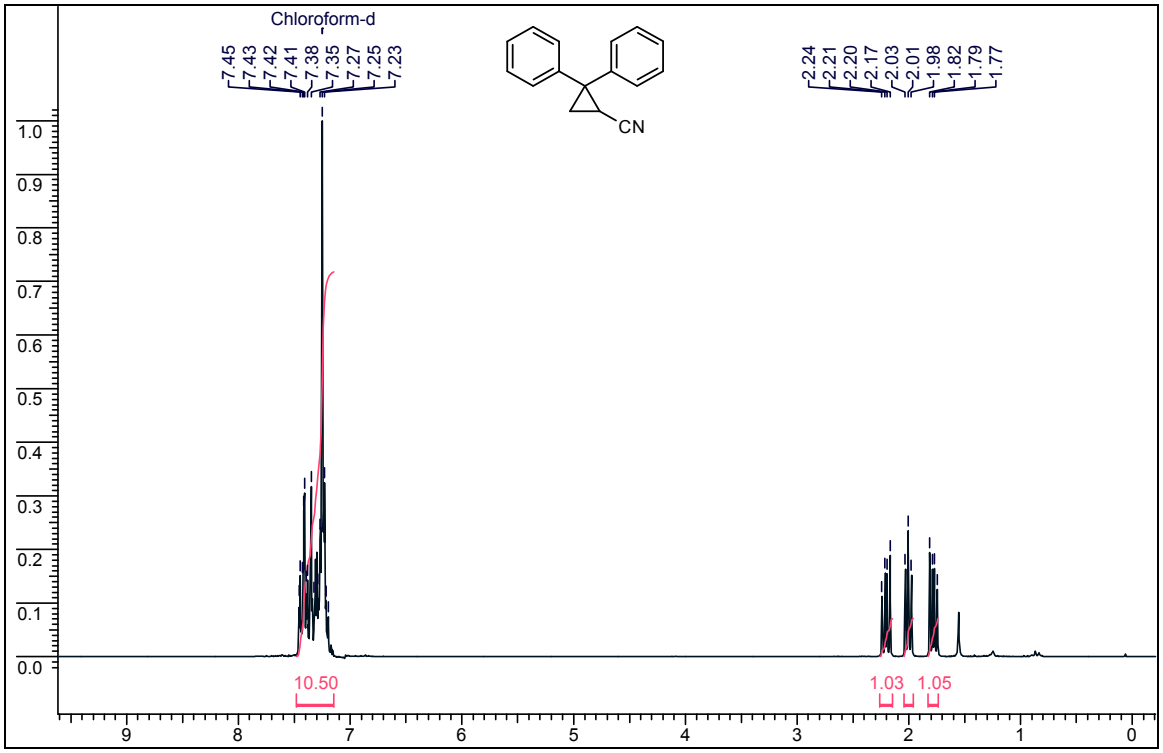


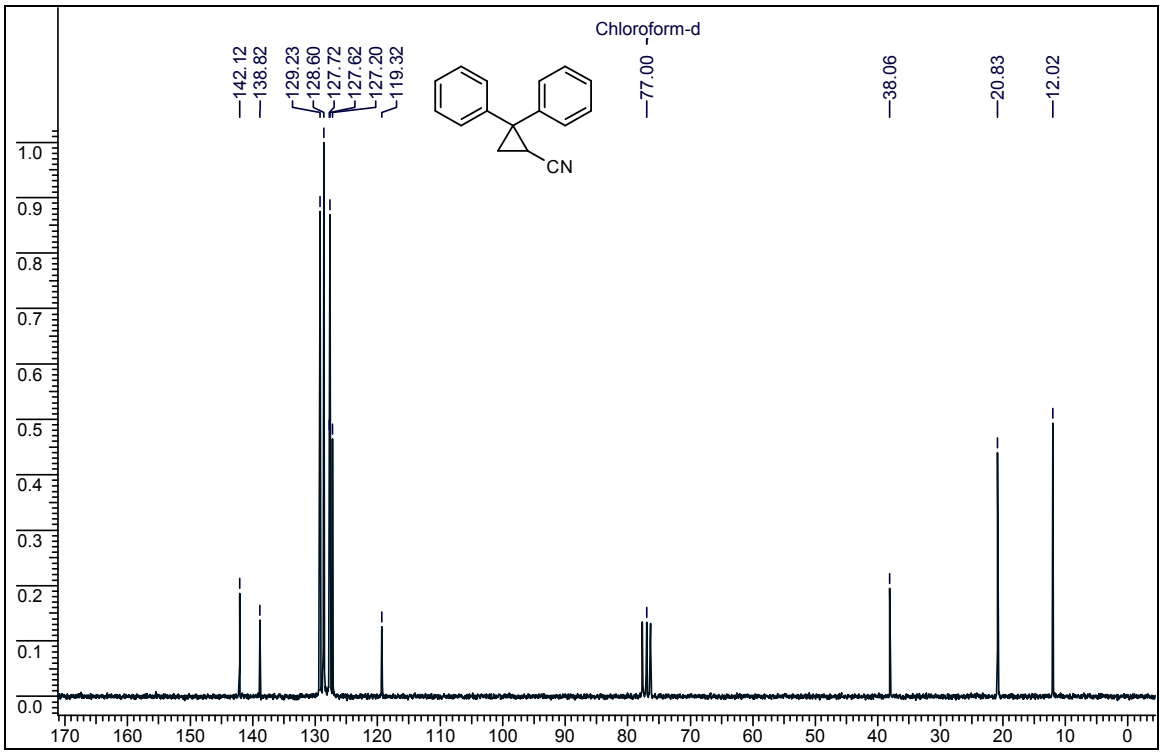
[3] ^{1}H and ^{13}C NMR spectra of compound 26a



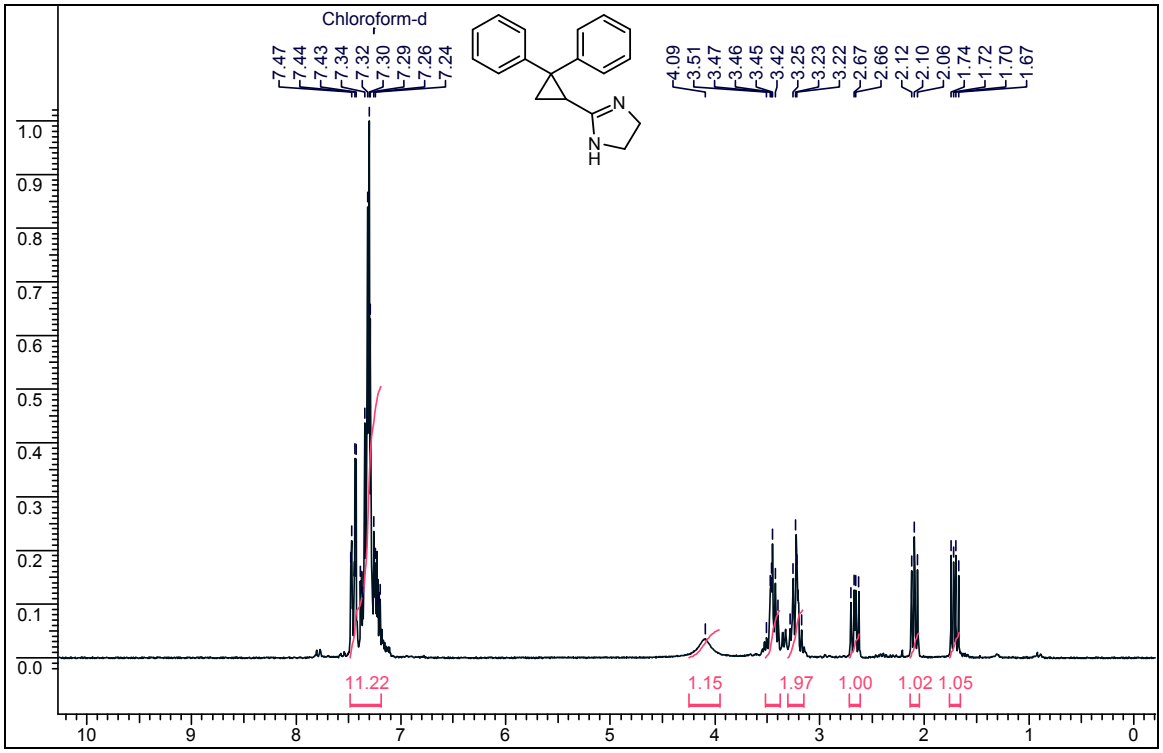


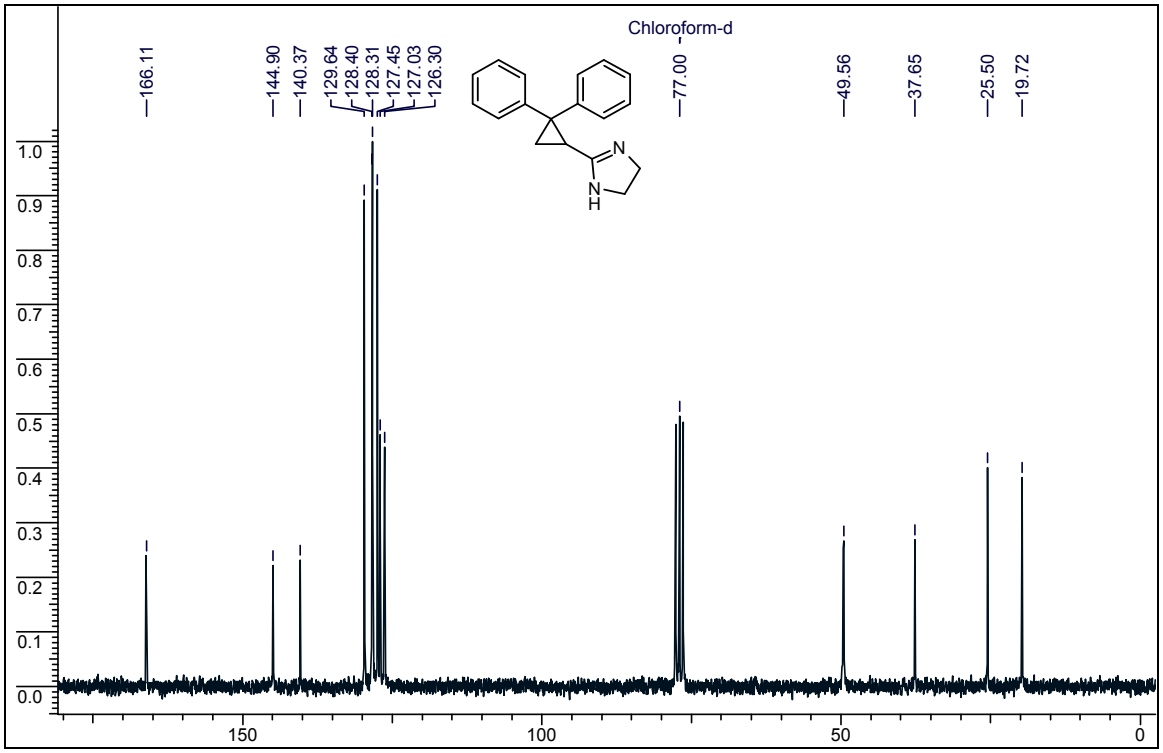
[4] ^{1}H and ^{13}C NMR spectra of compound 27a



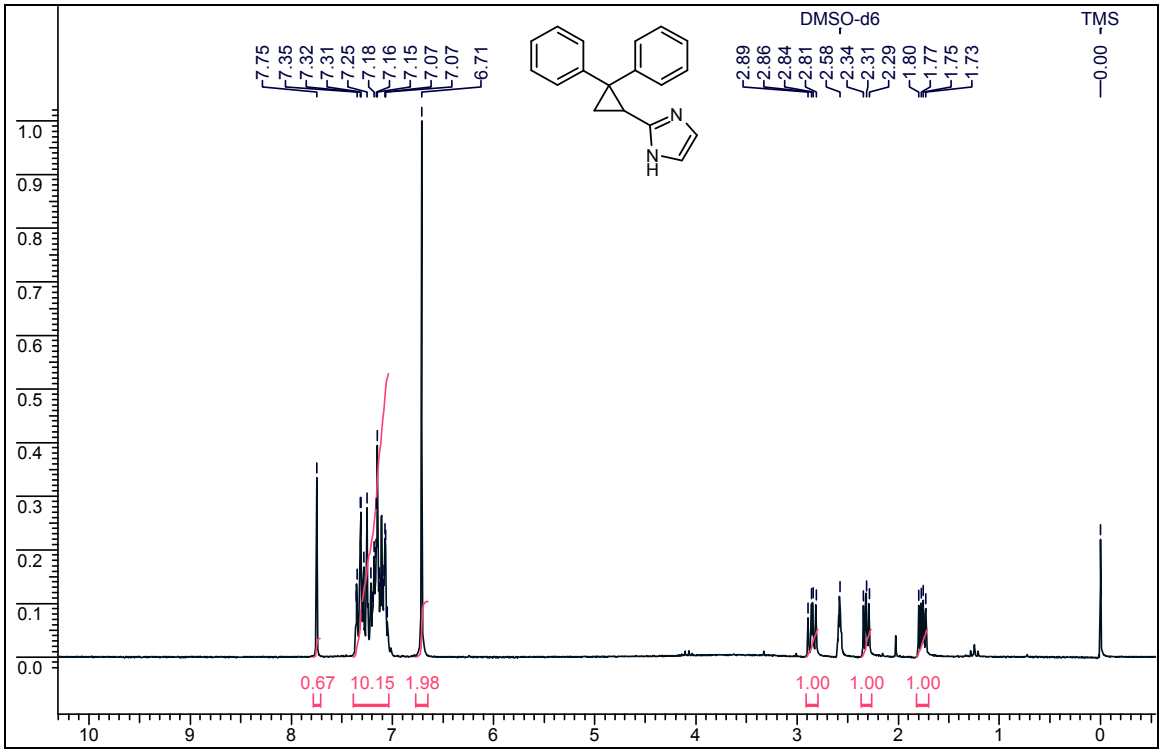


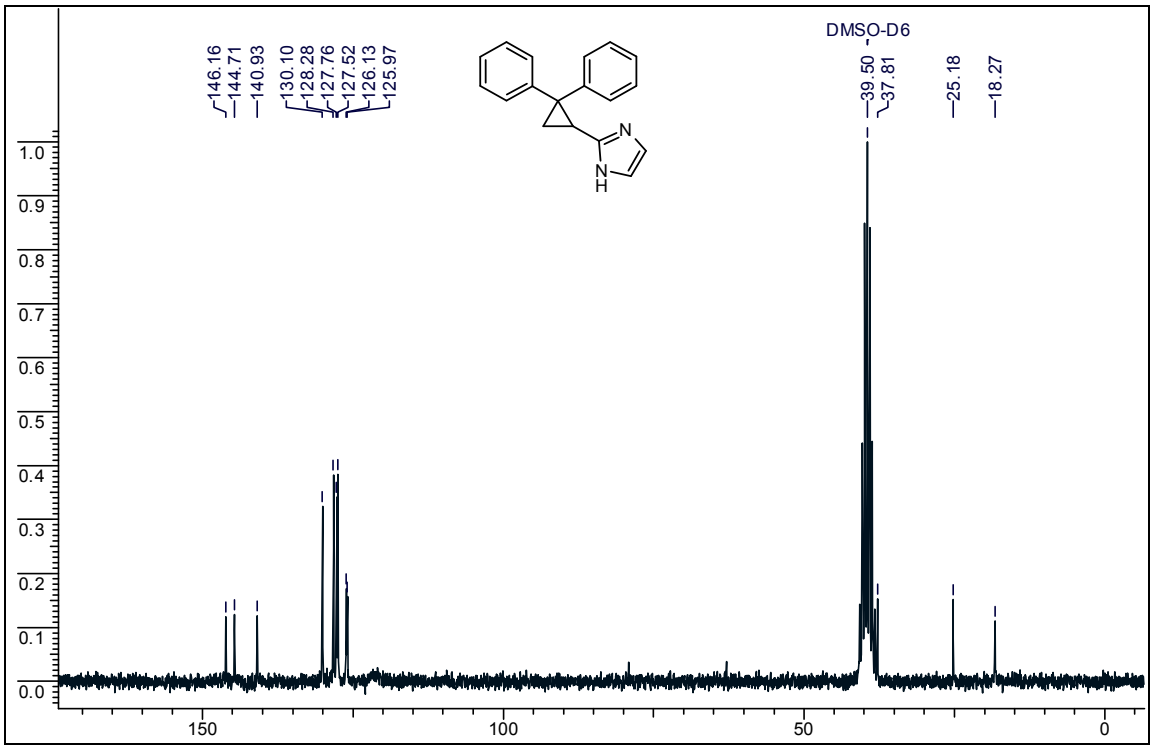
[5] ^{1}H and ^{13}C NMR spectra of compound 28a



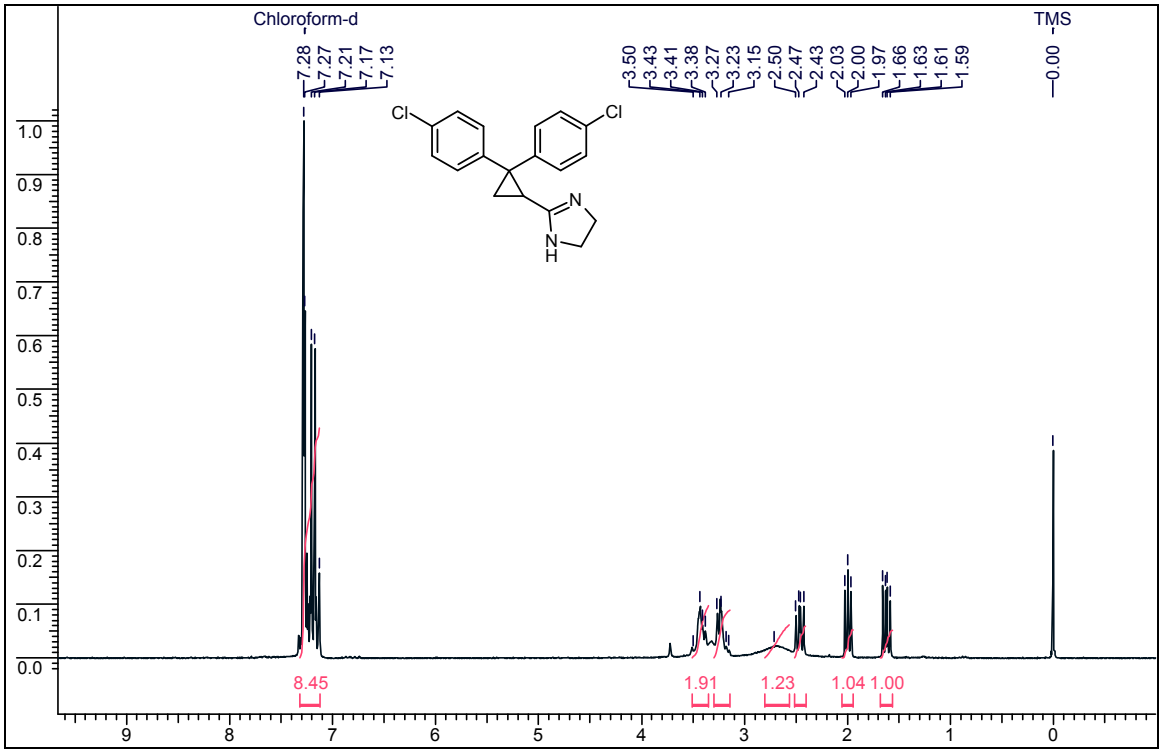


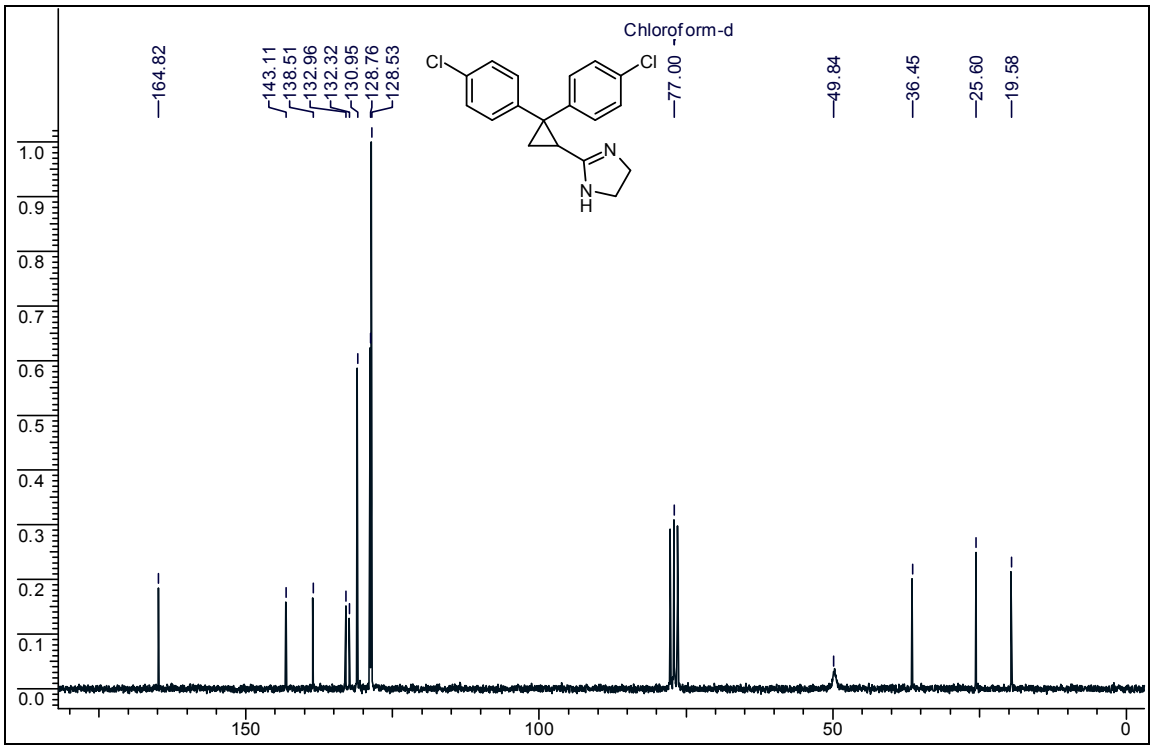
[6] ^{1}H and ^{13}C NMR spectra of compound 29a



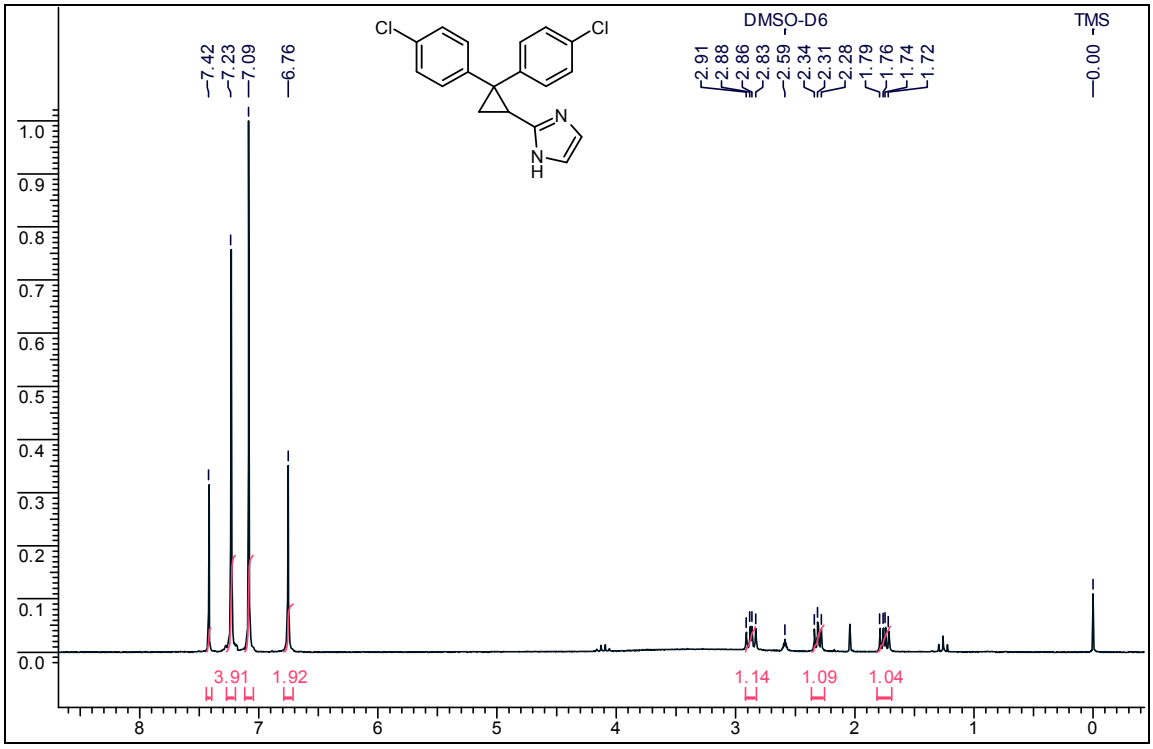


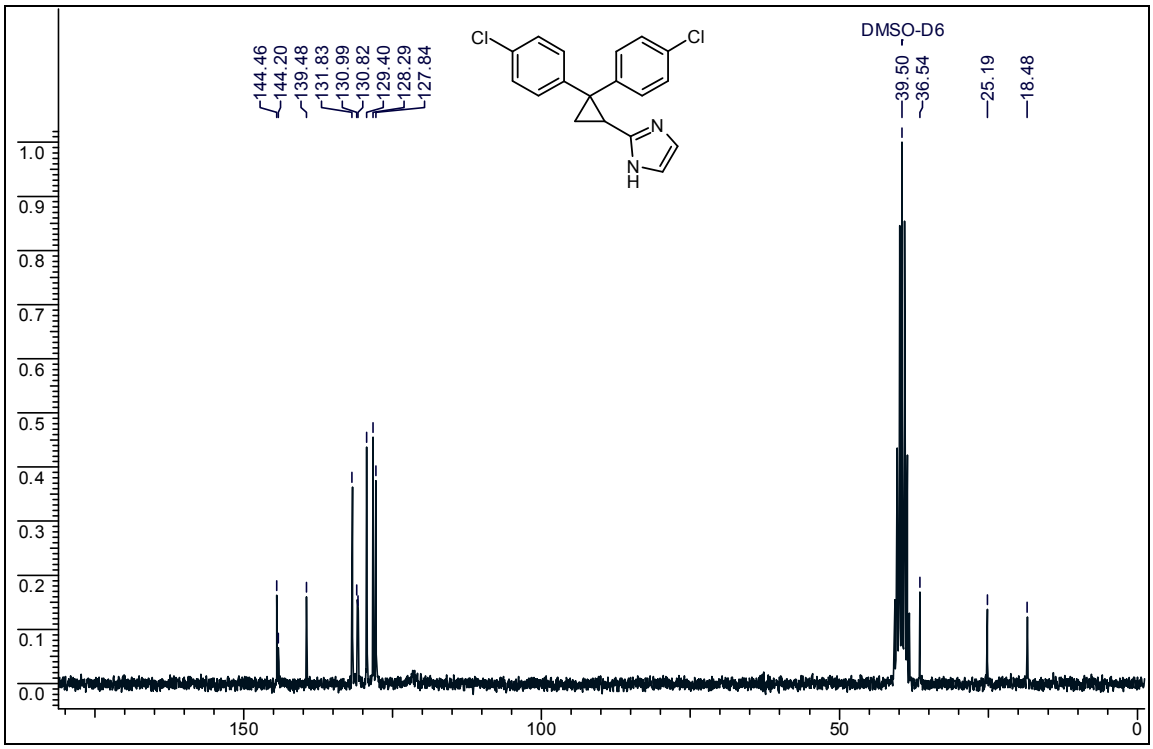
[7] ^{1}H and ^{13}C NMR spectra of compound 28b



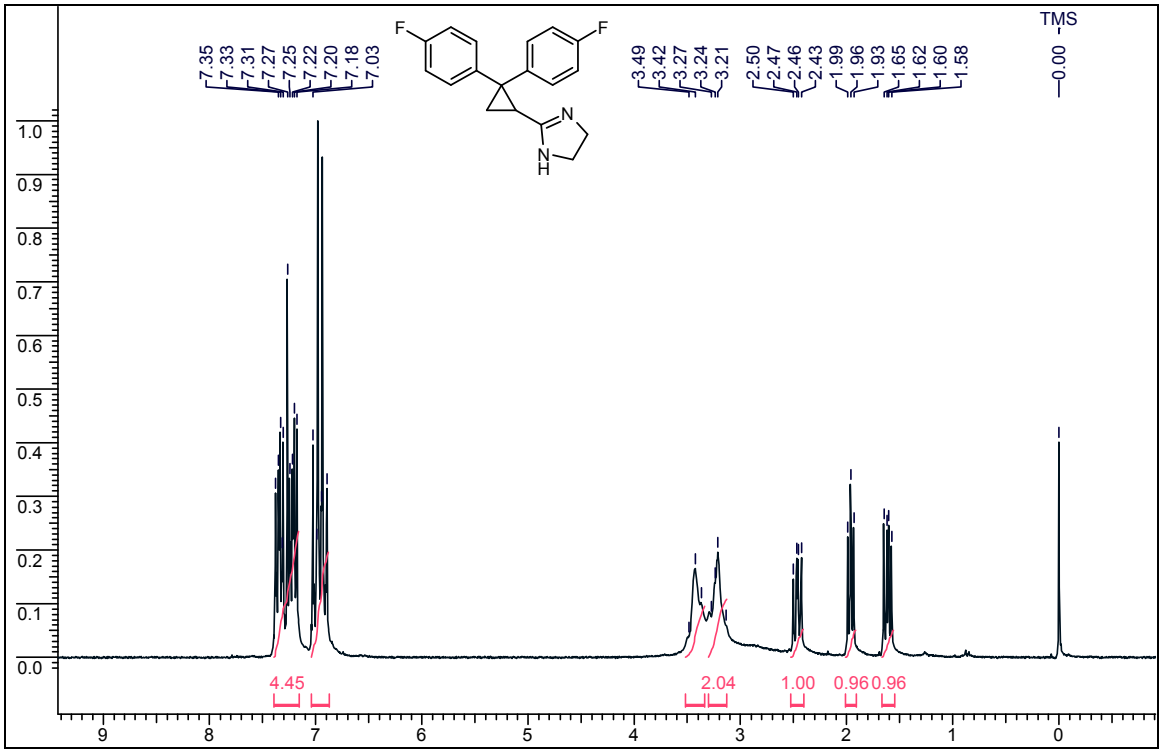


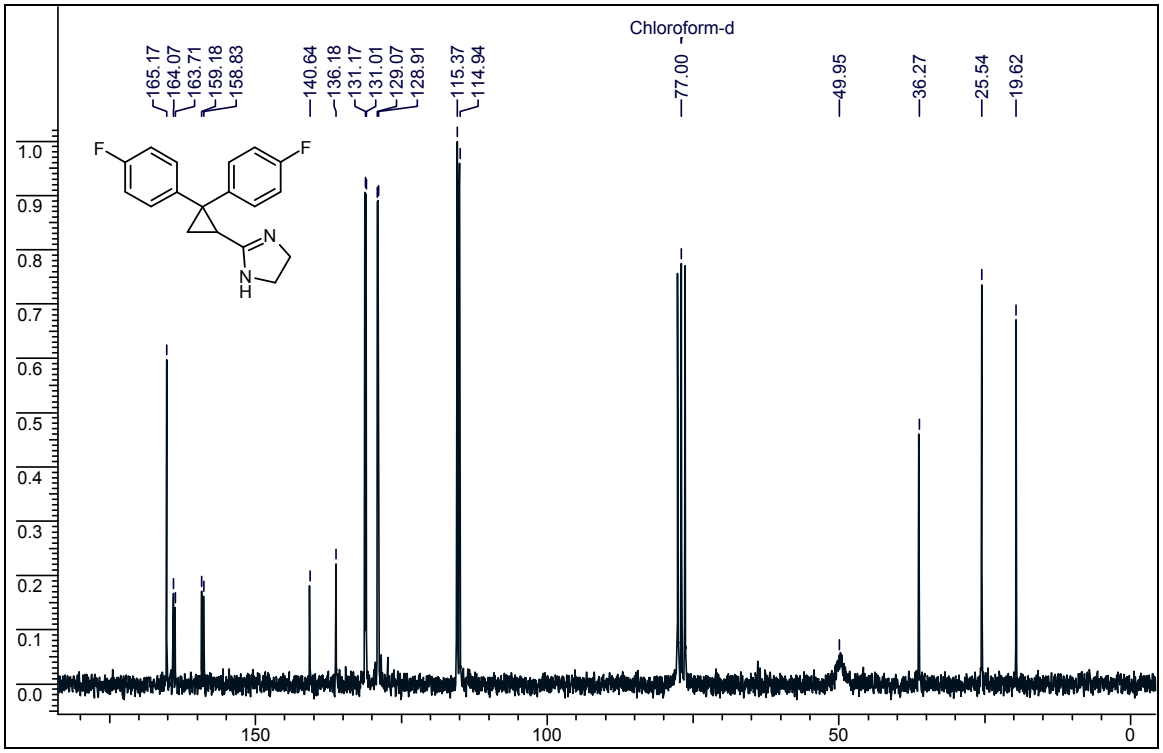
[8] ^{1}H and ^{13}C NMR spectra of compound 29b



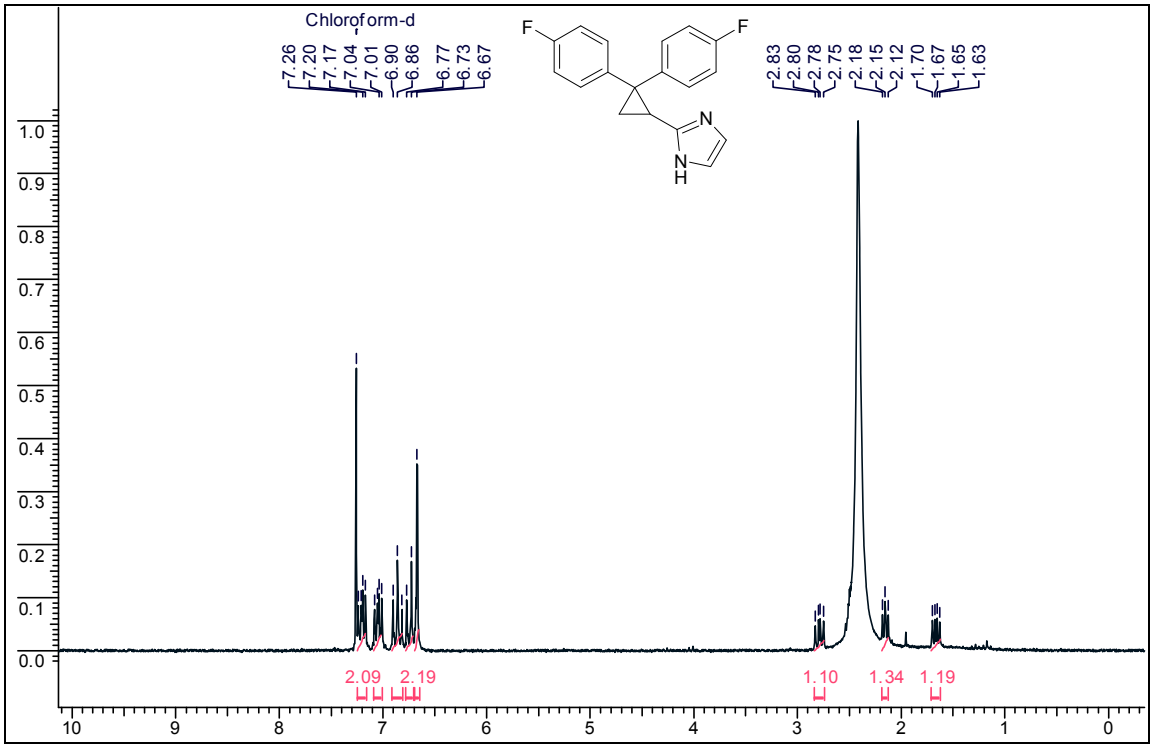


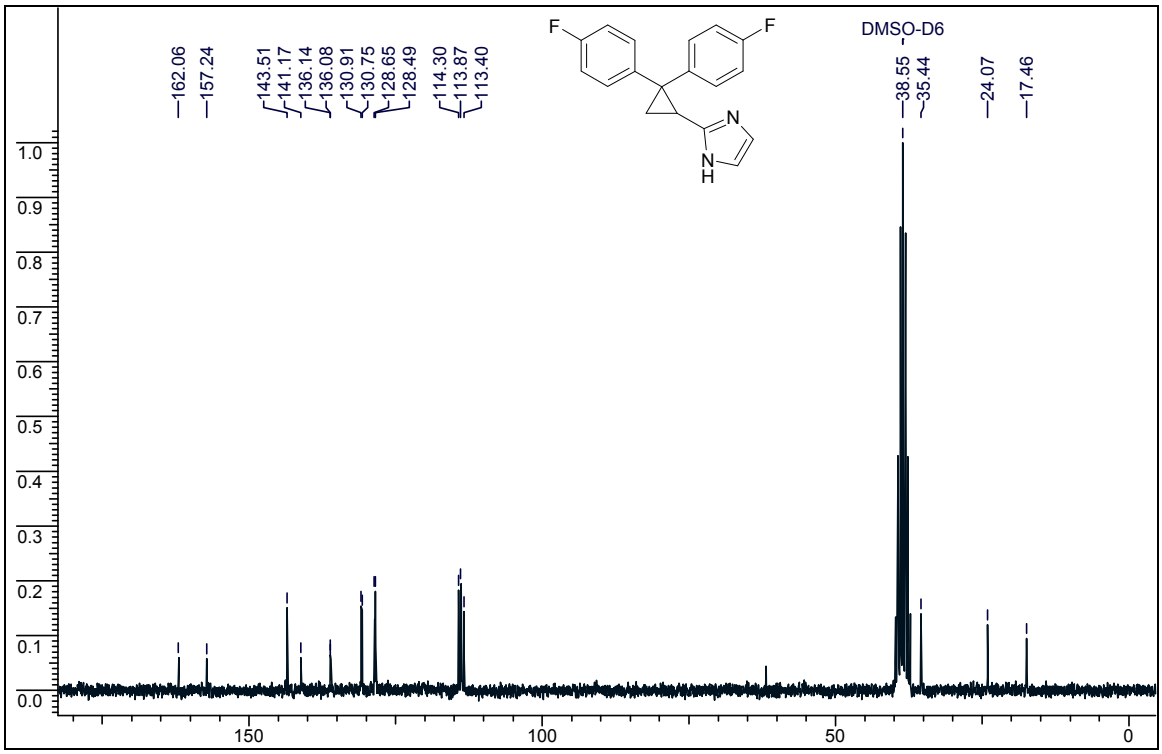
[9] ^{1}H and ^{13}C NMR spectra of compound 28c



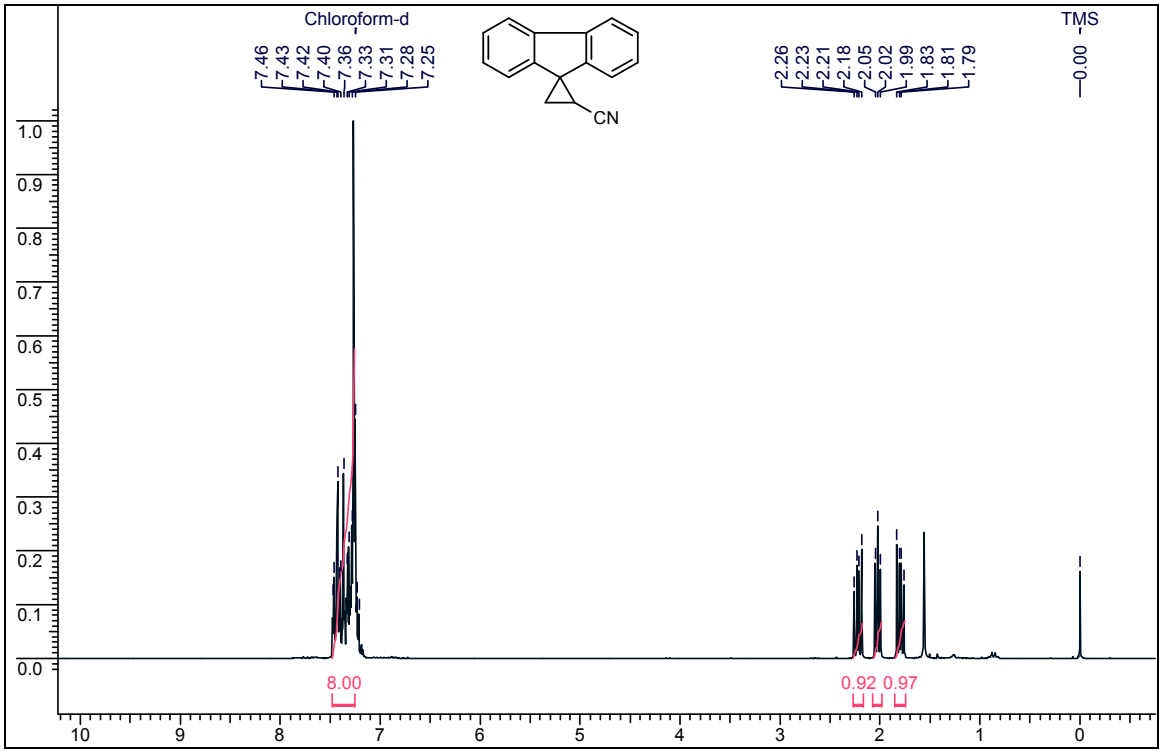


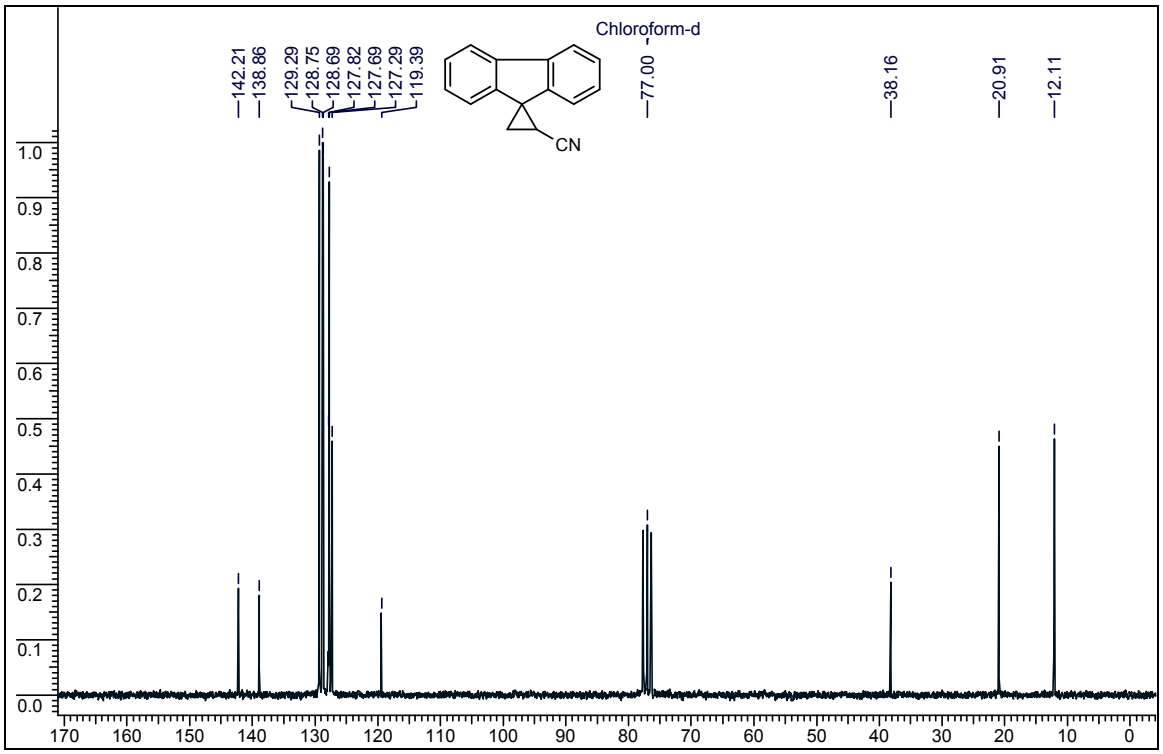
[10] ^{1}H and ^{13}C NMR spectra of compound 29c



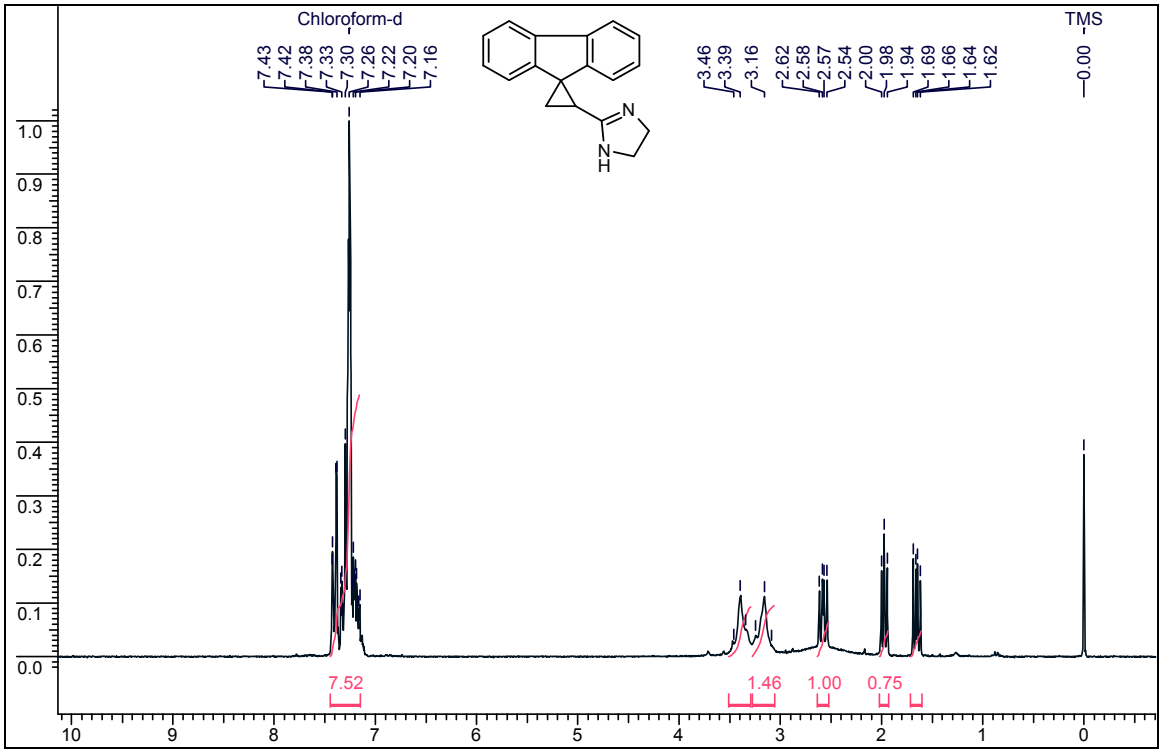


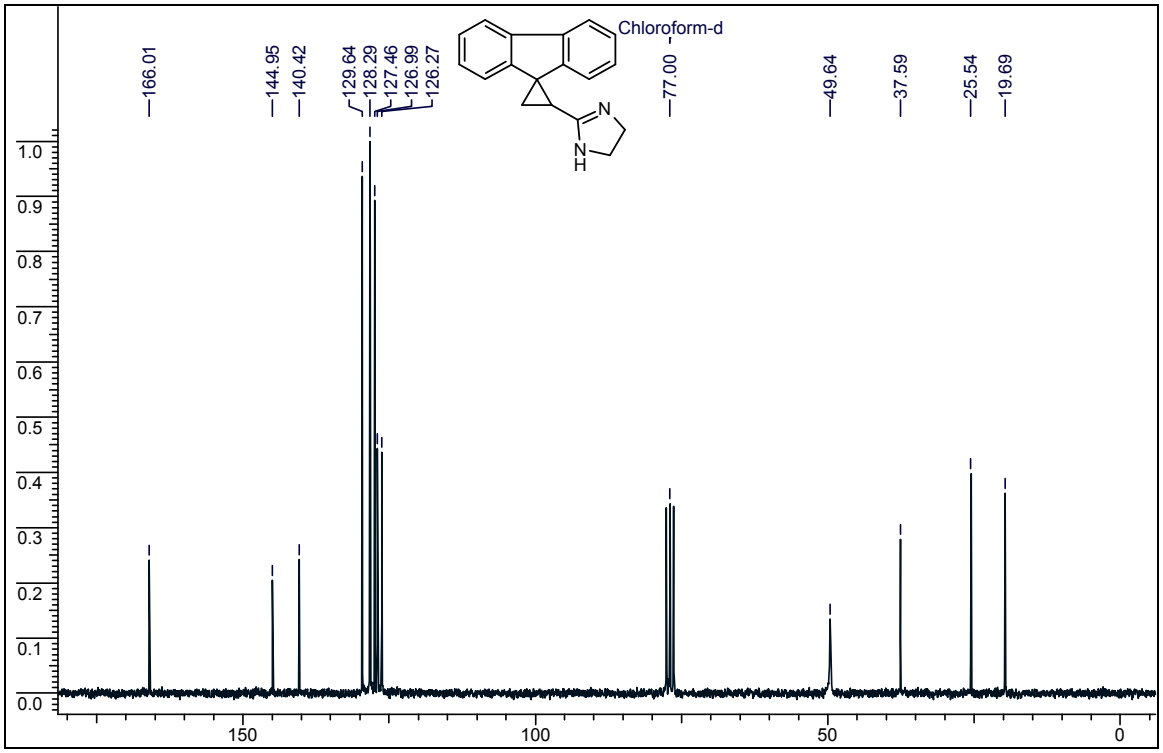
[11] ^{1}H and ^{13}C NMR spectra of compound 27d



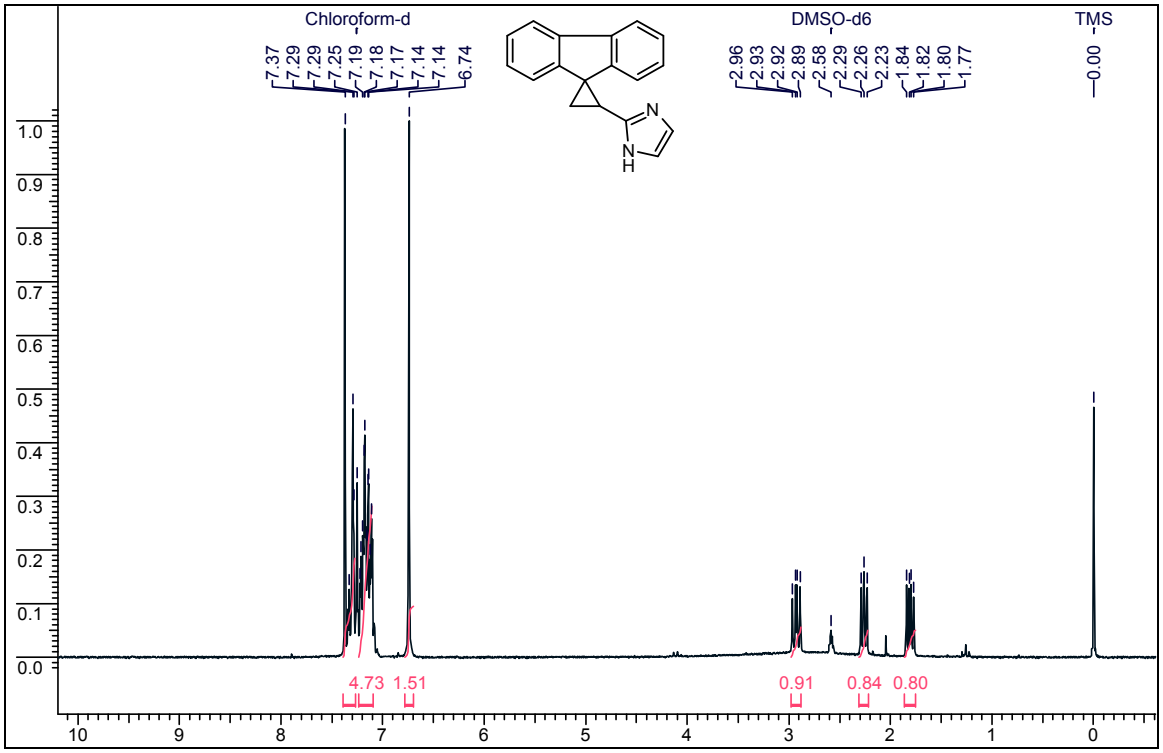


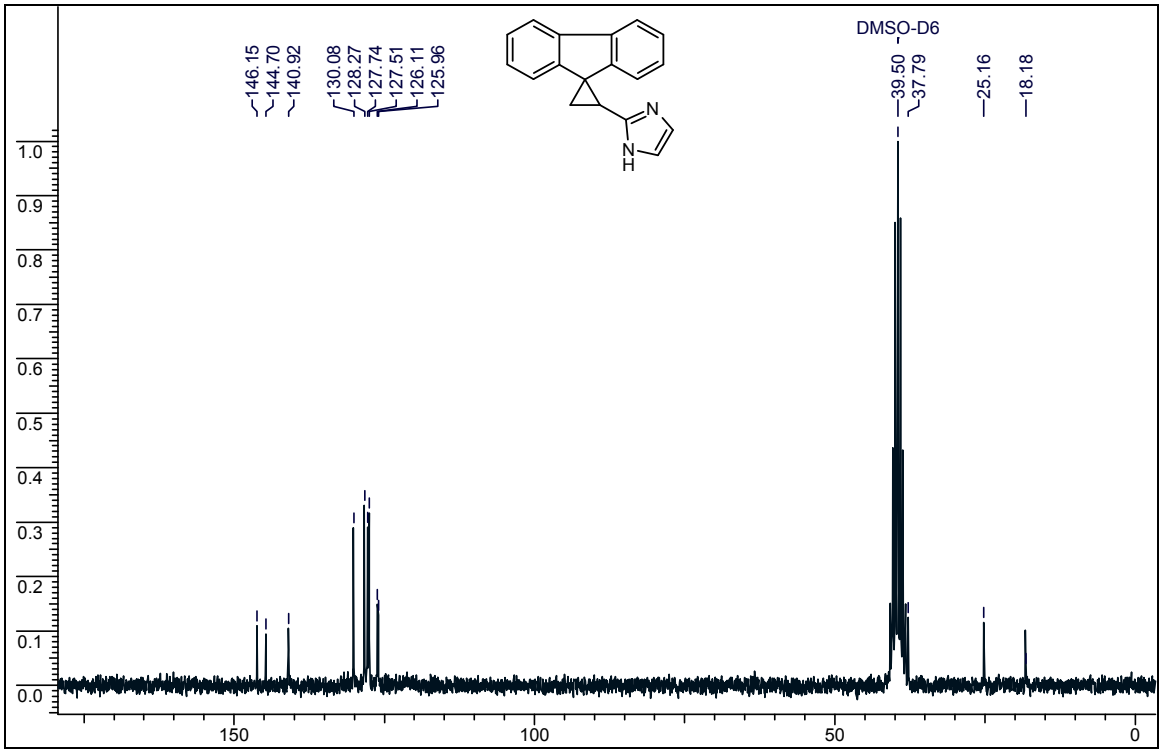
[12]^{1}H and ^{13}C NMR spectra of compound 28d





[13] ^{1}H and ^{13}C NMR spectra of compound 29d





3.1.7 References

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Section-B

Efficient synthesis of novel antifungal Pyrimidines

Efficient Synthesis of novel antifungal Pyrimidines

3.2.1 Introduction

Pyrimidine occupies a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A large array of pyrimidine drugs possesses a variety of medicinal properties. Pyrimidines have a long and distinguished history as important constituents of nucleic acids to their current use in the chemotherapy of AIDS extending from the days of their discovery. Alloxan is known for its diabetogenic action in a number of animals.[1] Uracil, thymine, and cytosine are the three important constituents of nucleic acids (**Fig. 12**).

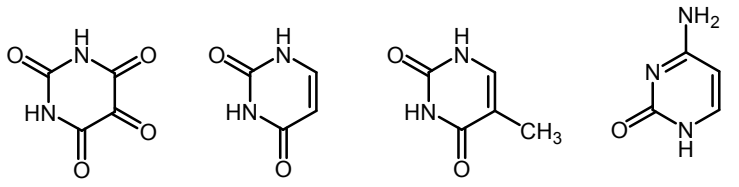


Figure 12

The pyrimidine ring is found in vitamins like thiamine, riboflavin, and folic acid.[2] Barbitone, the first barbiturate hypnotic sedative and anticonvulsant is a pyrimidine derivative[1] (**Fig. 13**).

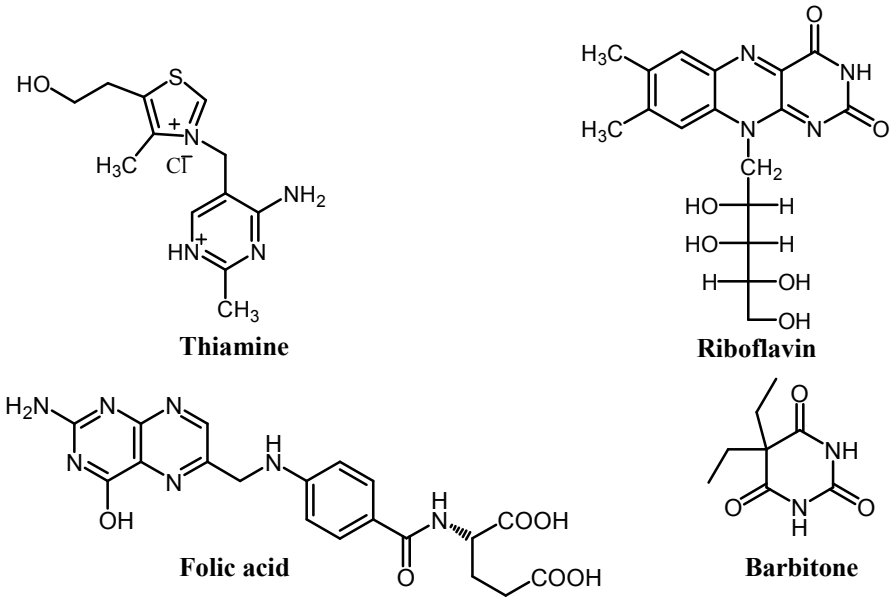


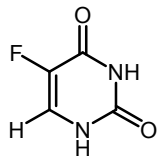
Figure 13

Medical Significance

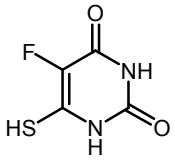
During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications.

Antineoplastics and anticancer agents.

There are a large number of pyrimidine-based antimetabolites. They are usually structurally related to the endogenous substrates that they antagonize. The structural modification may be on the pyrimidine ring or on the pendant sugar groups. One of the early metabolites prepared was 5-fluorouracil[3] (5-FU), a pyrimidine derivative. 5-Thiouracil also exhibits some useful antineoplastic activities[4] (**Fig. 14**).



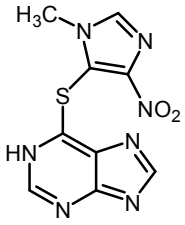
5-fluorouracil



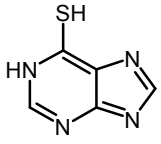
5-thiouracil

Figure 14

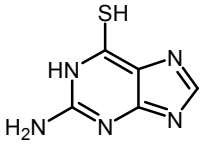
The antineoplastic compounds[5] possessing the guanine nucleus like azathioprine[6] mercaptopurine,[7] thioguanine,[8] tegafur,[9] etc. were discovered after formulation of the antimetabolite theory by Woods and Fildes in 1940. These drugs prevent the utilization of normal cellular metabolites[5] (**Fig. 15**).



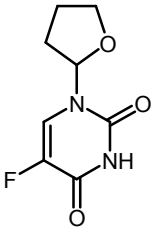
Azathioprine



Mercaptopurine



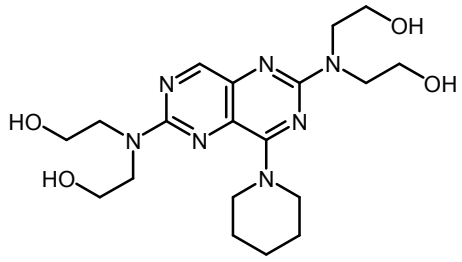
Thioguanine



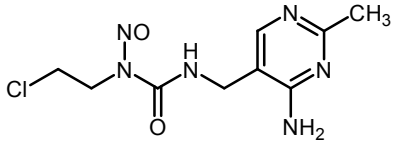
Tegafur

Figure 15

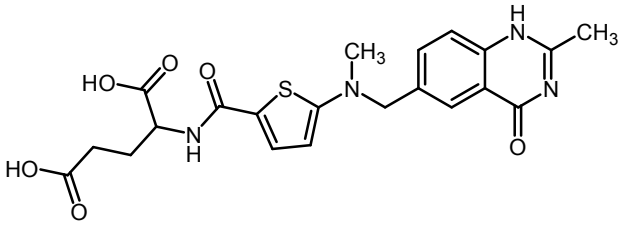
There are many more drugs reported in recent times, like mopidamol,[10] nimustine,[11] raltitrexed,[12] uramustine,[13] and trimetrixate[14](**Fig. 16**).



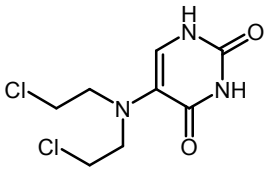
Mopidamol



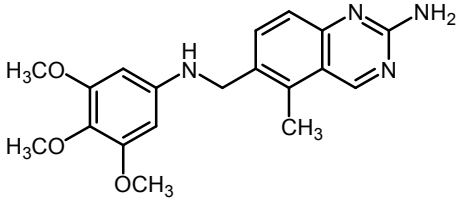
Nimustine



Raltitrexed



Uramustine

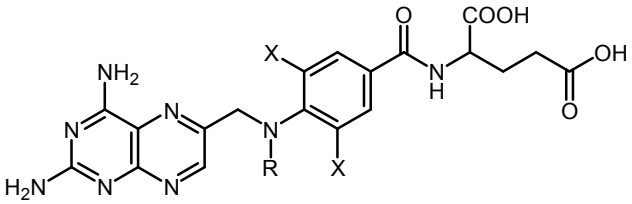


Trimetrexate glucuronate

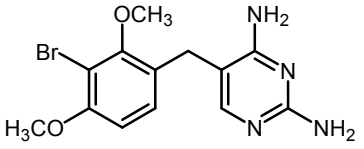
Figure 16

Antifolates, antibacterials and antiprotozoals

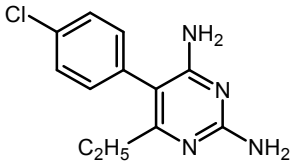
In 1948, Hitchings made an important observation that a large number of 2,4-diaminopyrimidines and some 2-amino-4-hydroxypyrimidines are antagonists of folic acid.[15] Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates. It was eventually proved that these pyrimidines are inhibitors of the enzyme dihydrofolate reductase (DHFR).[16] Notable amongst the 2,4-diaminopyrimidine drugs are pyrimethamine, a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim, an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate and aminopterin, both used in cancer chemotherapy.[17] 3',5-Dichloromethotrexate, which is less toxic and more readily metabolized than methotrexate, has recently been introduced for anticancer therapy.[18] Brodimoprim is also found to be an effective antibacterial compound[19] (**Fig. 17**).



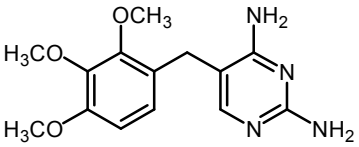
R = CH_3, X = H; **Methotrexate**
R = X = H; **Aminopterin**
R = CH_3, X = Cl; **3',5'-dichloromethotrexate**



Brodimoprim



Pyrimethamine

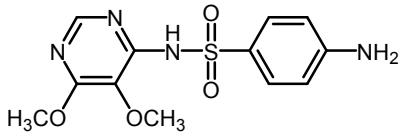


Trimethoprim

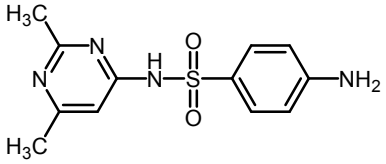
Figure 17

Sulfa drugs

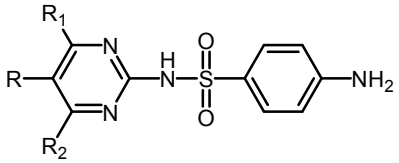
Pyrimidine derivatives of sulfa drugs, namely sulfadiazine, sulfamerazine and sulfadimidine are superior to many other sulfonamides and are used in some acute UT infections, cerebrospinal meningitis and for patients allergic to pencillins.[20] Sulfonamide-trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS.[21] Sulfadoxine,[22] a short and intermediate acting sulfonamide with a half-life of 7-9 days is used for malarial prophylaxis. Sulfisomidine with a half life of 7h is used as a combination sulfa therapy in veterinary medicine.[23] Sulfadiazine, sulfamerzine, and sulfadimidine possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal functions (**Fig. 18**).



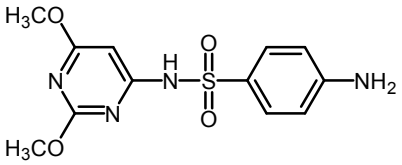
Sulfadoxine



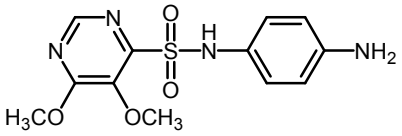
Sulfisomidine



Sulfadiazine R=H, R_1=H, R_2=H
Sulfamerazin R=H, R_1=CH_3, R_2=H
Sulfadimidine R=H, R_1=CH_3, R_2=CH_3
Sulfametoxydiazine R=OCH_3, R_1=H, R_2=H
Methyldiazine R=CH_3, R_1=H, R_2=H



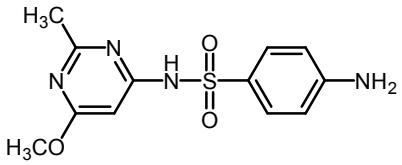
Sulfadimethoxine



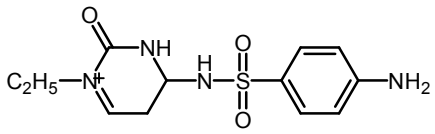
Sulfamethoxine

Figure 18

In 1959, sulfadimethoxine[24] was introduced with a half-life of approximately 40h. The related 4-sulfonamidopyrimidine, sulfamethoxine[24] having two methoxy groups in 5 and 6 positions, has by far the longest half-life of about 150h. Methyldiazine has a half-life of 65h. Also, sulfamethoxydiazine[24] possesses good half-life. A new broad-spectrum sulfonamide, sulfamethomidine[24] is relatively nontoxic and patients do not need extra fluid intake or alkalization. Sulfacytine[24] has been reported to be 3-10 times more potent than sulfaisoxazole and sulfisodimidine[24] (**Fig. 19**).



Sulfamethomidine

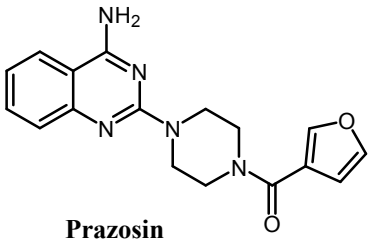


Sulfacytine

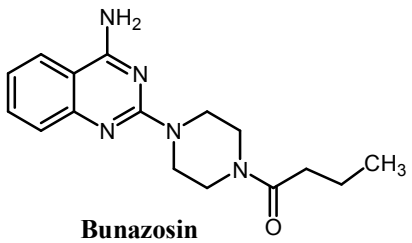
Figure 19

Cardiac agents

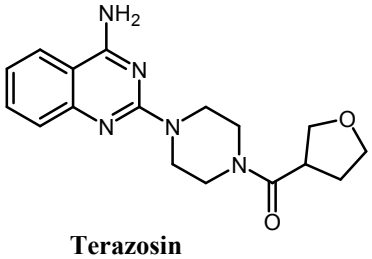
Several pyrimidine ring-containing drugs have exhibited antihypertensive activity. Prazosin, a quinozoline derivative, is a selective α_1-adrenergic antagonist.[25] Its related analogues bunazosin,[26] terazosin[27] and trimazosin[28] are potent antihypertensive agents (**Fig. 20**).



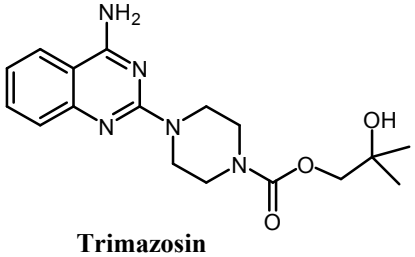
Prazosin



Bunazosin



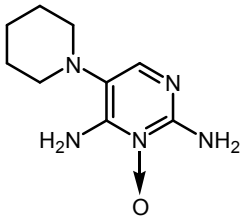
Terazosin



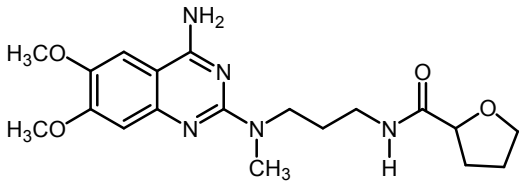
Trimazosin

Figure 20

A triaminopyrimidine derivative, minoxidil, whose mechanism of action and therapeutic action are similar to Prazosin, has been introduced in therapy for its side effects, in the treatment of alopecia, male baldness.[29] Besides these, a pyrimidine derivative Alfuzocin a Prazosin analogue is used especially in urinary obstruction caused by benign prostate hyperplasia[30] (**Fig. 21**).



Minoxidil

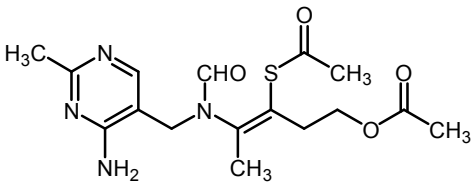


Alfuzocin

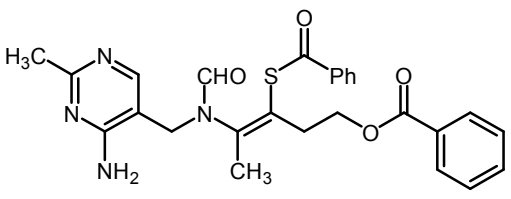
Figure 21

Analgesics and NSAID drugs

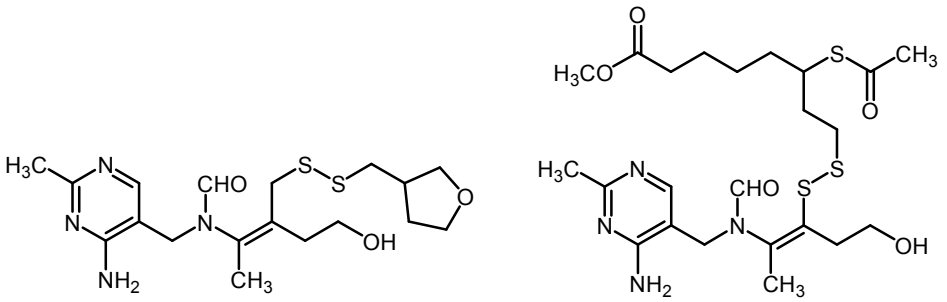
Acetiamine,[31] bentiamine,[31] and fursultiamine[32] are new lipid-soluble forms of thiamine having therapeutic use in beriberi, polyneuritis, encephalopathy, pain, malnutrition and alcoholism and especially in the treatment of long-standing insulin-dependent diabetes mellitus. Fursultamine has been reported to inhibit the arachadonic acid cascade-line activation and reverse the increase in CBF (Coronary Blood Flow). Octotiamine,[33] a vitamin B_1 derivative also exhibits anti-inflammatory activity (**Fig. 22**).



Acetiamine



Bentiamine



Fursultiamine **Octotiamine**

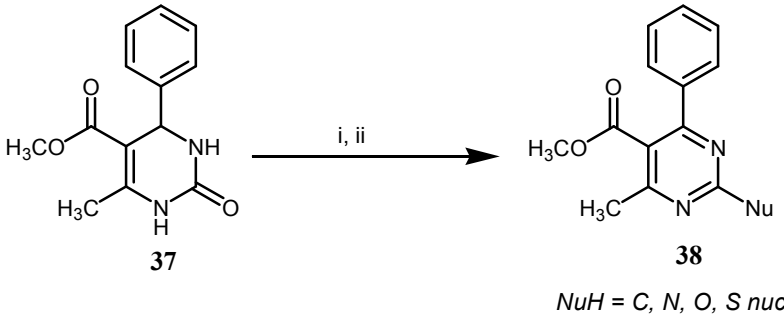
Figure 22

3.2.2 Review of Literature

Literature search revealed that over the past few decades, there are only a few methodologies that have been developed for the synthesis of tetra substituted pyrimidines starting from various starting material. Among them synthesis of pyrimidine from easily accessible Biginelli 3,4-Dihydropyrimidin-2(1*H*)-ones is scanty.

Kang *et al.*[34]

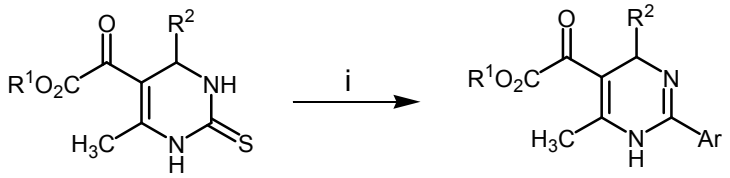
Kang *et al.* developed an efficient two-step procedure to convert the Biginelli 3,4-dihydropyrimidin-2(1*H*)-one to various multifunctionalized pyrimidines via the Kappe dehydrogenation and a new mild PyBroP-mediated coupling with C, N, O, and S nucleophiles, which provides a readily accessible multifunctionalized pyrimidine template for diversity oriented synthesis (**Scheme 7**).



Scheme 7. Reaction conditions: (i) 60% nitric acid, 0 ºC to rt, 30 min, 70%; (ii) PyBroP,Et_3N, dioxane, rt, NuH, 24-72 h, rt, 92-96%.

Kappe *et al.*[35]

Kappe *et al.* established the thioether-boronic acid cross-coupling chemistry (Liebeskind-Srogl couplings). The microwave-assisted Pd(0)-catalyzed/Cu(I)-mediated carbon-carbon cross-coupling of 3,4-dihydropyrimidine-2-thiones and boronic acids under Liebeskind-Srogl conditions leads to 2-aryl-1,4-dihydropyrimidines in moderate to high yield (**Scheme 8**).



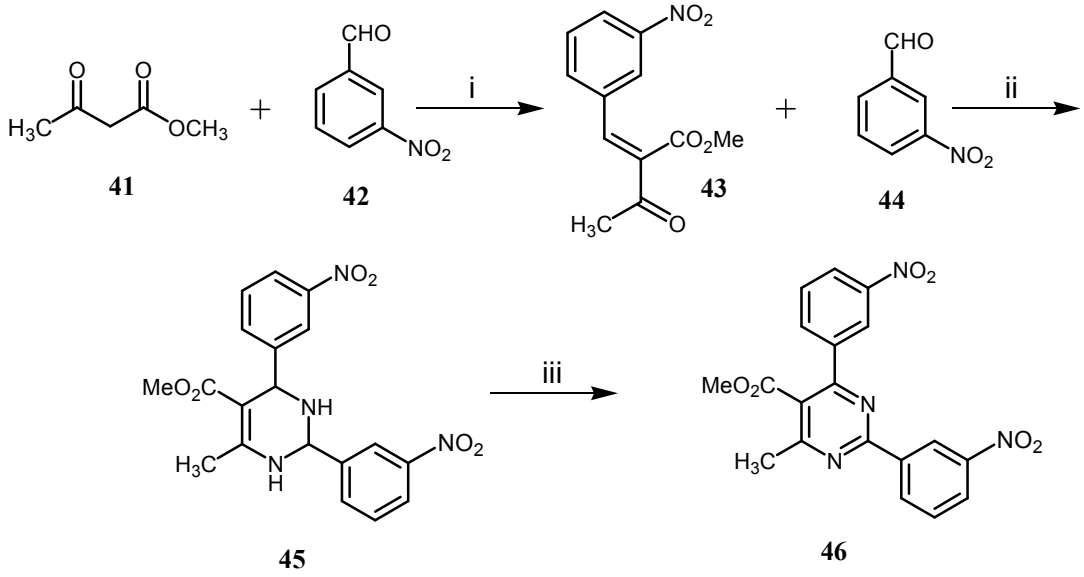
39 **40**

R^1 = OMe, R^2 = Phenyl, Ar = Ph, 4-ClPh, 3-MePh

Scheme 8. Reaction conditions: (i) $Pd(PPh_3)_4$, Cu-(I)-thiophene-2-carboxylate (CuTc), MW, 100ºC, 25-60 min, 14-82%.

Heinrici *et al.*[36]

Heinrici *et al.* reported the synthesis of tetrasubstituted pyrimidine by the reaction of the nitrobenzylidene acetoacetic esters with nitrobenzaldehyde and ammonium acetate to obtain the 1,2,3,4-tetrahydropyrimidines followed by dehydrogenation yielded the tetrasubstituted pyrimidines (**Scheme 9**).



41 **42** **43** **44** **45** **46**

Scheme 9. Reaction conditions: (i) Knoevenagel condensation; (ii) NH_4OAc, ethanol, stirring 24 h, 33%; (iii) MnO_2, toluene, rt, 8h, 78%.

3.2.3 Present Work

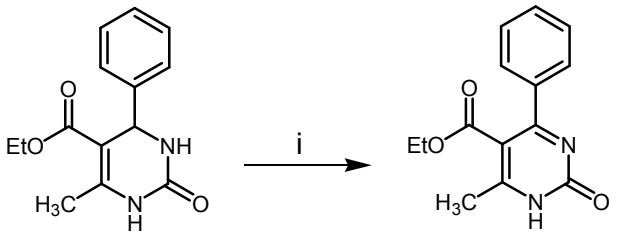
3.2.3.1 Objective

The Biginelli 3,4 dihydropyrimidin-2(1*H*)-ones (DHPMs) were known for more than a centuary.[37] These non planar heterocyclic compounds have interesting multifaceted pharmacological profiles such as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors and hepatitis B virus replication inhibitors.[38] The Biginelli DHPMs are chemical precursors of multifunctionalized pyrimidines. Recently, Kang *et al.*[34] developed a novel and efficient synthesis of multifunctionalized pyrimidines through Kappe dehydrogenation and PyBroP-mediated coupling with nucleophiles. However there is no methodology reported for the direct arylation of the oxidized products of DHPMs, the corresponding halopyrimidines. In the present work we carried out short and efficient conversion of Biginelli DHPMs to multifunctionalized pyrimidines via oxidation, halogenation followed by Suzuki/Sonogashira cross coupling reactions and the preliminary biological evaluation of all the synthesized compounds.

3.2.3.2 Results and Discussion

Biginelli Reaction and Oxidation of DHPM:

The easily available Biginelli 3,4-Dihydropyrimidin-2(1*H*)-one was used as starting material for preparation of new difunctionalized pyrimidines. A series of DHPM libraries were synthesized by the method reported by us.[39] For the second reaction step, we initially attempted to oxidize DHPMs using 60% nitric acid as reported in literature.[40] The method in general provides moderate to good yields of pyrimidones, However, factors such as steric hindrance, the presence of electron withdrawing substituents on phenyl ring and solubility of DHPMs affect the yield and rate of reaction, fine-tuning of conditions with respect to HNO_3 concentration and the reaction time was necessary in every case. In light of recent method reported by Perumal *et al.*[41] avoiding the said limitations, oxidation of DHPMs was carried out by the addition of CAN (Ceric Ammonium Nitrate) solution in water (3 equiv) to a mixture of **47(a-h)** and $NaHCO_3$ (5 equiv) suspended in acetone at ice-salt bath temperature, followed by stirring the reaction mixture at ambient temperature for 12 h as shown in **Scheme 10.**



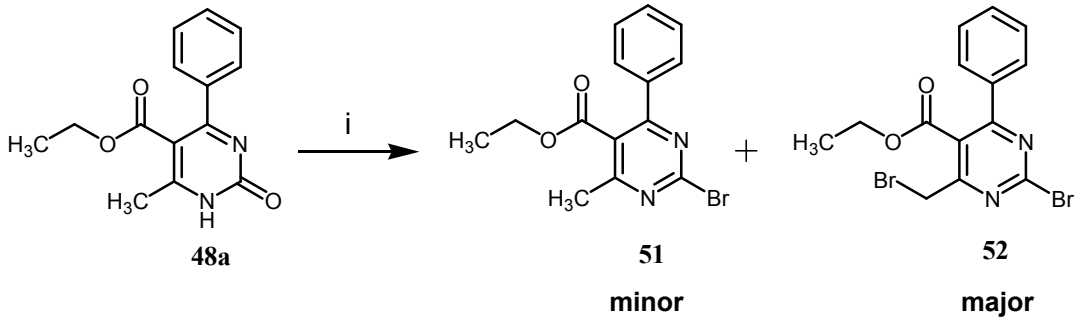
47a **48a**

Scheme 10. Reaction conditions: Oxidation of DHPM **47a**. (i) ceric ammonium nitrate (CAN), acetone, $NaHCO_3$, -5 °C to RT, 12 h, 80%.

Halogenation Reaction

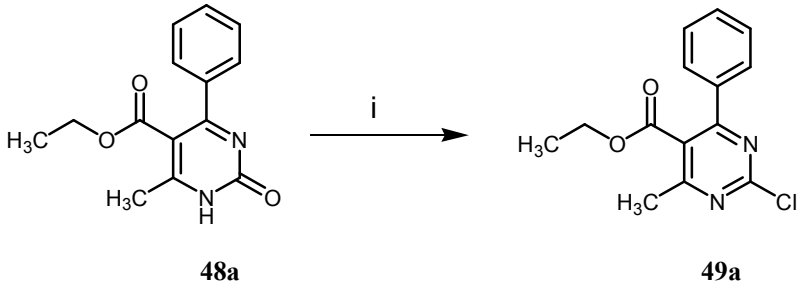
To achieve the better yields in Suzuki cross-coupling reaction and keeping in mind the low dissociation energy of carbon bromine bond, ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate **48a** was heated with $POBr_3$ at 175 ºC (Scheme **11**) according to literature procedure[42] to obtain 2-bromopyrimidine derivative **51**.

However, contrary to literature report, we obtained the dibrominated ethyl 2-bromo-4-(bromomethyl)-6-phenylpyrimidine-5-carboxylate **52** as major product and the expected monobrominated compound **51** was detected as a minor product (5%) by GC analysis. The formation of dibrominated product was unambiguously supported by spectroscopic and analytical data. In the ^{1}H-NMR spectra of compound **52** the methylene protons of the bromomethylene group attached to C_6 carbon can be readily assigned as a singlet at δ 4.63 ppm with an integration of two protons confirming the presence of the methylene group. Accordingly, in the ^{13}C NMR spectra of the compound **52** the methylene carbon attached to C_6 carbon can be unambiguously assigned at δ 28.2 ppm. In addition, the mass spectrum showed a peak for the molecular ion at *m*/*z* 397, 399, 402, confirming the dibrominated product **52**. Thus the compound **52** was well characterized by IR and NMR spectral analysis; additionally the mass spectrum and elemental analysis are in conformity with the structure **52** (**Scheme 11**).



Scheme 11. Reaction conditions: (i) $POBr_3$, 175 °C, 1 h, 85% (**52**).

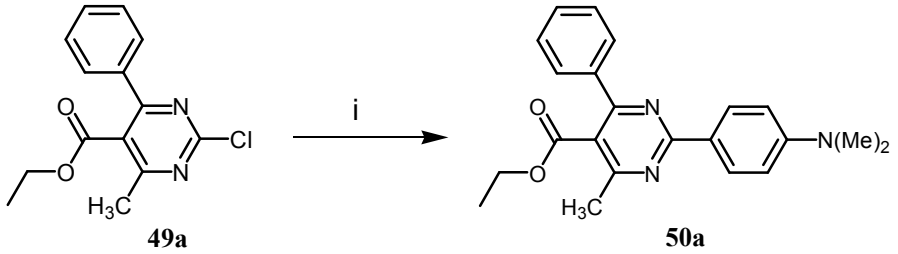
In order to avoid the above complication $POCl_3$ was used as chlorinating agent. A mixture of compound **48a** and *N,N*-dimethyl aniline was refluxed in $POCl_3$ for 12h to achieve ethyl 2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate **49a** in 82% isolated yield (**Scheme 12**).



Scheme 12. Reaction conditions: (i) *N,N*-dimethylaniline**,** $POCl_3$, reflux, 12 h.

Palladium catalyzed Suzuki-Miyaura C-C bond formation reaction:

The palladium catalyzed Suzuki-Miyaura cross-coupling reaction offers an attractive methodology for the introduction of aryl, alkenyl and alkyl substituents in to the electrophilic aromatic ring (Ar-X, where X= Cl, Br, I, OTf). From a survey of the literature it was found that Carbon-Carbon bond formation on 2-halopyrimidines via transition–metal catalyzed cross-coupling reaction is well documented.[43]



49a **50a**

Scheme 13. Reaction conditions: (A): **49a**, 4-(*N*,*N*-dimethylamino)phenyl boronic acid (1.2 equiv), $Pd(PPh_3)_4$ (4 mol%), Na_2CO_3 (3.0 equiv), DME-H_2O, (8:2) Reflux, 5h. (B): **49a**, 4-(*N*,*N*-dimethylamino)phenylboronic acid (1.2 equiv), $Pd(dppe)Cl_2$ (4 mol%), Na_2CO_3 (3.0 equiv), dioxane, Reflux, 5h. (C): **49a**, 4-(*N*,*N*-dimethylamino)phenylboronic acid (1.2 equiv), $Pd(OAc)_2$, (4 mol%), PPh_3 (0.2 equiv), sat. solution of Na_2CO_3 : dioxane, (4:6), Reflux, 3 h.

Table 3. Optimization of Suzuki-Miyaura reaction

Entry	Pd Catalyst	Method	Product	*Yield %
1	$Pd(PPh_3)_4$	A	**50a**	**65%**
2	$Pd(dppe)Cl_2$	B	**50a**	**60%**
3	$Pd(OAc)_2$	C	**50a**	**85%**

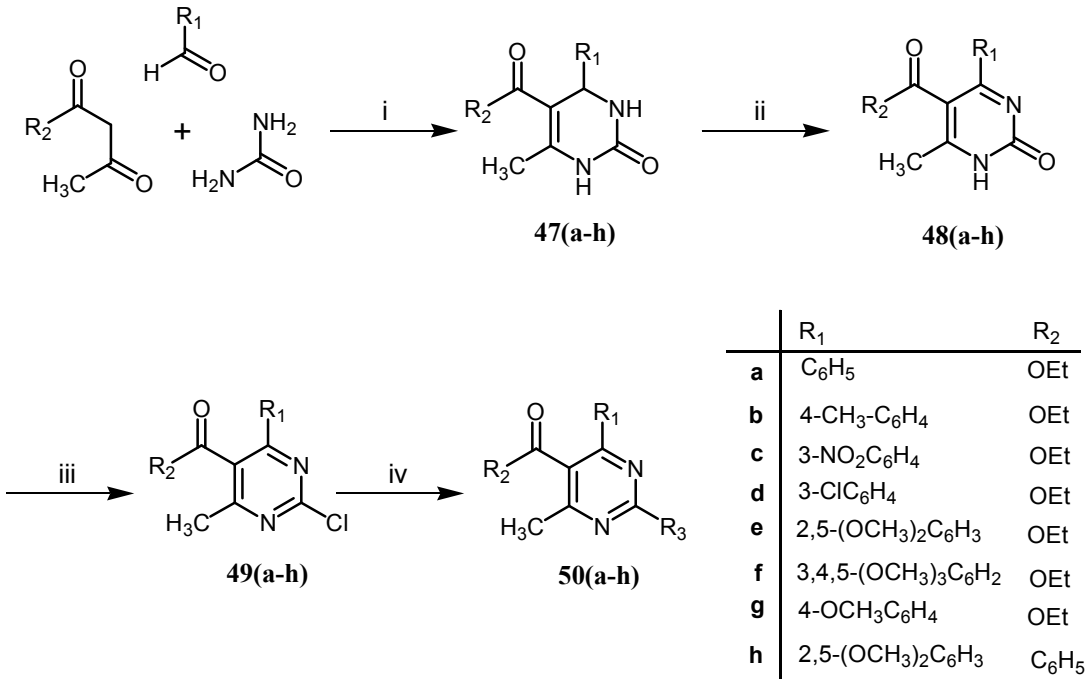
*Isolated yields after column chromatography.

A wide variety of solvents and bases are commonly used in the Suzuki-Miyaura coupling reaction. Depending upon the position of the chloro substituents in the pyrimidine ring, the choice of solvent, base and catalyst varies. Initially, we attempted to use reaction conditions reported for the 2-chloro-pyrimidine (**Scheme 13**). However, this resulted in affording the cross-coupled product in moderate yields. Then we proceeded to optimize conditions to improve yields. The results obtained are reported in **Table 3**.

In method A, the Suzuki coupling has been carried out using the classical terakis(triphenylphosphine) palladium (0) as a catalyst in DME-H_2O (8:2) and Na_2CO_3 as base to achieve the cross coupled product **50a** in 65% isolated yield. Likewise, in method B 1,2-bis(diphenylphosphinoethane) palladium (II) chloride in dioxane and Na_2CO_3 as base gave the product ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate **50a** in 60% yield. When we used saturated aqueous solution of Na_2CO_3 as base with dioxane as solvent in 4:6 proportion in presence of 0.2 equivalent of PPh_3 and 4

mol% of $Pd(OAc)_2$ cross coupled product **50a** was isolated in 85% yield after column chromatography.

Encouraged by the results obtained from CAN mediated oxidation of DHPMs, chlorination and Suzuki-Miyaura sequence, it was obvious to extend this concept to the synthesis of various 2,4,5,6-tertasubstitued pyrimidines (**Scheme 14**).

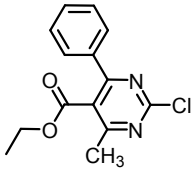
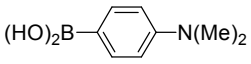
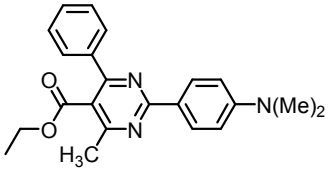
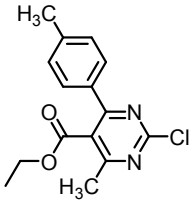
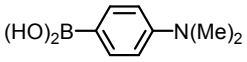
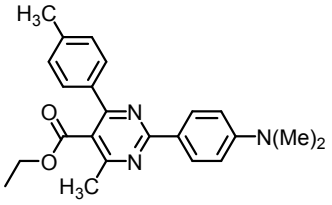
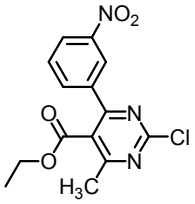
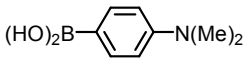
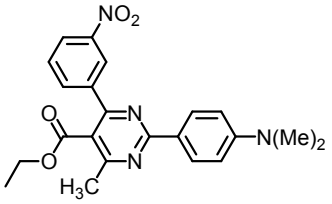
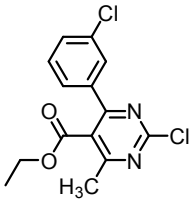
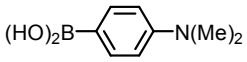
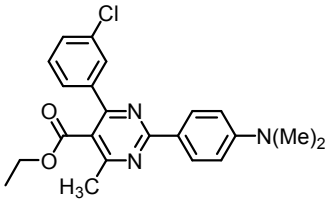
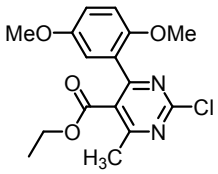
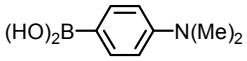
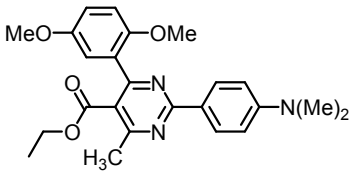
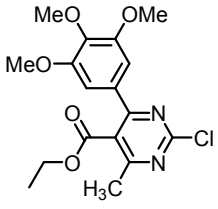
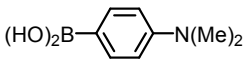
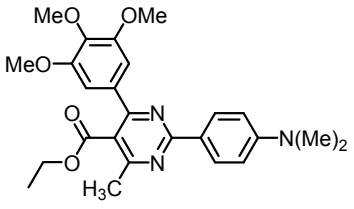


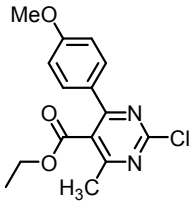
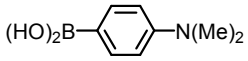
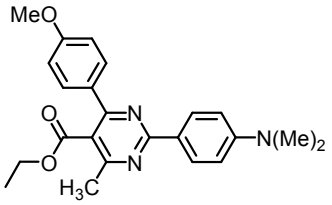
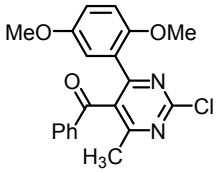
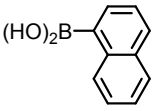
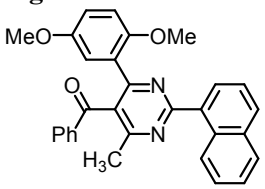
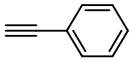
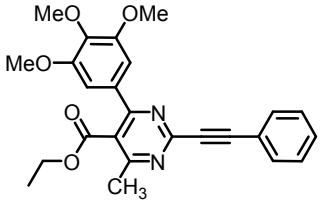
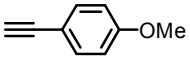
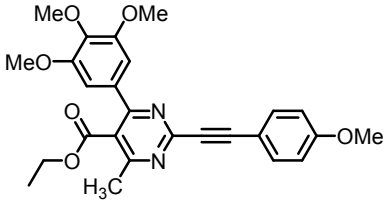
	R_1	R_2
a	C_6H_5	OEt
b	4-CH_3-C_6H_4	OEt
c	3-$NO_2C_6H_4$	OEt
d	3-ClC_6H_4	OEt
e	2,5-$(OCH_3)_2C_6H_3$	OEt
f	3,4,5-$(OCH_3)_3C_6H_2$	OEt
g	4-$OCH_3C_6H_4$	OEt
h	2,5-$(OCH_3)_2C_6H_3$	C_6H_5

Scheme 14. Reaction conditions: (i) ref. 39; 80-92%; (ii) ceric ammonium nitrate (CAN), acetone, $NaHCO_3$, -5 °C to rt, 12 h, 70-92%; (iii) *N,N*-dimethylaniline, $POCl_3$, reflux, 12 h, 68-82%; (iv) 4-(*N,N*-dimethylamino)phenylboronic acid, $Pd(OAc)_2$, PPh_3, sat. solution of Na_2CO_3,: dioxane (4:6), 110 °C, 3-5 h., 78-95%.

As a result various DHPMs were synthesized by using multicomponent approach from a variety of aromatic aldehydes, 1,3-diketones and urea and subjected to chlorination followed by Suzuki-Miyaura cross coupling to obtain the various tetrasubstituted pyrimidines as a crystalline solid (**50a**, **50b**, **50c**, **50d**, **50e** and **50h**) or as yellow oil (**50f**, **50g**, **50i** and **50j**) in excellent yields as shown in **Table 4**.

Table 4: Synthesis of tetra substituted pyrimidines

Entry	Chloropyrimidine **49(a-h)**	Boronic acid/ acetylenes	[a]Yield (%)	[b]Product **50(a-j)**
a			85	 **50a**
b			80	 **50b**
c			95	 **50c**
d			82	 **50d**
e			85	 **50e**
f			88	 **50f**

g			82	 **50g**
h			78	 **50h**
i	**49f**		85	 **50i**
j	**49f**		90	 **50j**

[a]Isolated yield of products after column chromatography. [b]All the synthesized compounds are novel. Compounds **50i** and **50j** were synthesized by the classical Sonogashira reaction (see experimental section).

The alkynyl group introduction into ethyl 2-chloro-4-(3,4,5-trimethoxyphenyl)-6-methyl pyrimidine-5-carboxylate **49f** was carried out by using standard Sonogashira reaction conditions. 2-Chloropyrimidine **49f** reacted with aryl acetylene (**Table 4**) at reflux temperature of acetonitrile in the presence of (20 mol%) $Pd(PPh_3)_4$ and CuI to form the corresponding 2-(arylethynyl) pyrimidine **50i** and **50j** in 85 and 90% isolated yield respectively. The products thus obtained **50i** and **50j** were well characterized by their IR and ^1H NMR spectral analyses, additionally the elemental analyses was in conformity with the respective structures. X-ray crystal structure of compound **50b** confirms is to be a tetra substituted pyrimidine derivative as shown by its ORTEP diagram[44] (**Fig. 23**).

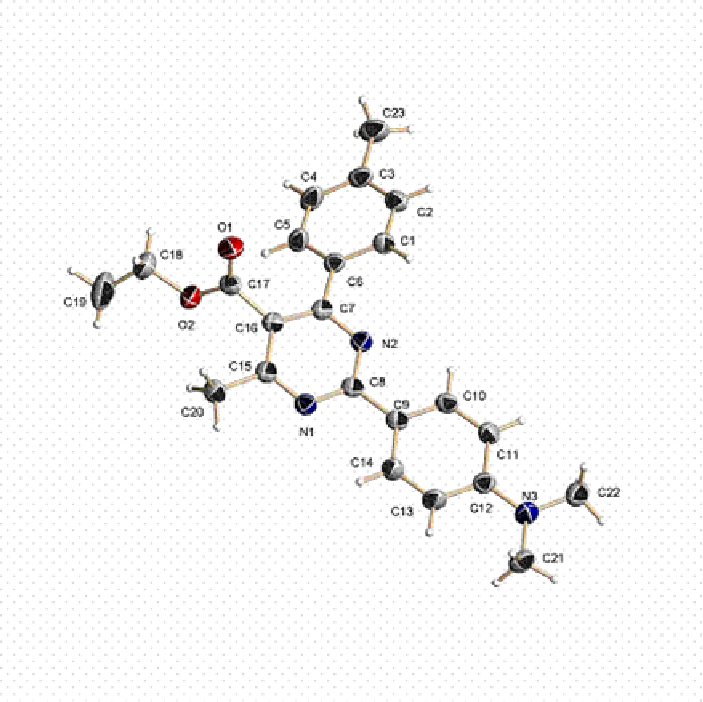


Figure 23. X-ray crystal structure of compound **50b**

Table 5. Data collection and refinement parameters for compound **50b**

Crystal data	
Chemical formula	$C_{23}H_{25}N_3O_2$
M_r	375.46
Cell setting, space group	Monoclinic, *P*2(1)/*c*
Temperature (K)	298 (2)
a, *b*, *c* (Å)	9.2990 (7), 17.7576 (14), 12.6159 (10)
β (°)	97.7180 (10)
V (Å^3)	2064.4 (3)
Z	4
D_x (Mg m^{-3})	1.208
Radiation type	Mo *K*α
μ (mm^{-1})	0.08
Crystal form, colour	Block, yellow
Crystal size (mm)	0.44 × 0.29 × 0.09
Data collection	
Diffractometer	CCD Area Detector
Data collection method	ω and phi Scan

Absorption correction	MULTI-SCAN
T_{min}	0.966
T_{max}	0.993
No. of measured, independent and observed reflections	24165, 3631, 3311
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.033
θ_{max} (°)	25.0
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.064, 0.163, 1.14
No. of relections	3631 reflections
No. of parameters	258
H-atom treatment	Constrained to parent site
Weighting scheme	Calculated $w = 1/[\sigma^2(F_o^2) + (0.0687P)^2 + 0.7073P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.22, –0.18

3.2.4 Antifungal activity

3.2.4.1 Materials and Methods.

NCL isolates *Candida albicans* strains 1 and 2, *Cryptococcus neoformans* (human pathogens), *Benjaminiella poitrasii* and *Yarrowia lipolytica* (saprophytes) were maintained on YPG (yeast extract, 0.3%, peptone, 0.5%, and glucose, 1%) agar slants. *Fusarium oxysporum* strains 1 and 2 (plant pathogens) were maintained on PDA (potato, 20% dextrose, 2%) agar slants at 28 °C. *Escherichia coli* (NCIM 2574) and *Staphylococcus aureus* (NCIM 2122) were maintained on NA (beef extract, 0.3%, peptone, 0.5%, sodium chloride, 0.5%) agar slants. Strains of *C. albicans, C. neoformans, Y. lipolytica* were inoculated in YPG broth at 28 °C and *B. poitrasii* at 37 °C for 24 h respectively, *F.oxysporum* in potato dextrose at 28 °C for 48 h whereas bacterial strains *E.coli* and *S.aureus* in NA broth for 24 h. Compounds were solubilized in DMSO, and stock solutions of 1.28 mg/ml were prepared. Amphotericin B (membrane sterols), fluconazole (ergosterol synthesis inhibitor), and tetracycline (protein synthesis inhibitor)

and erythromycin (cytochrome P450) were also dissolved in DMSO, and were used as a positive control.

In vitro antifungal activity of the newly synthesized compounds were evaluated against the fungal strains viz., *C. albicans* 1 and 2, *C. neoformans, B. poitrasii, Y. lipolytica, F. oxysporum* 1 and 2 strains and bacterial strains *E. coli* (NCIM 2574), and *S. aureus* (NCIM 2122) by microbroth dilution assay to determine the minimum inhibitory concentration (MIC) and IC_{50} values considering amphotericin-B, fluconazole, erythromycin and tetracycline as a standard drug in accordance with the guidelines in the NCCLS documents M27-A and M38-P.[45] MIC is defined as the lowest concentration of compounds that inhibited the visible growth.

All the newly synthesized compounds exhibited reasonable activity against the tested fungal strains compared to reference drugs within MIC range 8-128 µg/ml concentration (**Table 6/7**). Amongst all the screened compounds **50c**, **50d**, **50e** and **50j** displayed very good activity against *C. albicans* 1 and 2. Among these, compound **50e** having methoxy substituents present at 2 and 5 position on aryl ring was the most potent compound displaying significant activity at 8µg/ml concentration.

Table 6. *In vitro* antifungal activity for compounds **50(a-j)**

	Inhibitory concentration in µg/ml against						
Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
50a	>128	>128	128	>128	128	>128	>128
50b	128	128	128	64	64	128	>128
50c	16	16	>128	32	128	32	32
50d	32	32	64	32	64	32	32
50e	8	8	128	64	>128	>128	>128
50f	>128	>128	32	32	64	64	64
50g	64	64	64	16	64	32	32
50h	128	128	64	32	32	64	64
50i	128	128	64	16	>128	128	128
50j	32	32	64	64	>128	32	32
Amphotericin-B	4	4	64	8	32	16	16

Fluconazole	32	32	128	64	16	8	8

1. *Candida albicans 1* **2.** *Candida albicans 2* **3.** *Cryptococcus Neoformans* **4.** *Benjaminiella poitrasii* **5.** *Yarrowia lipolytica* **6.** *Fusarium oxysporum* 1 **7**. *Fusarium oxysporum* 2.

[a]MIC_{90} (Minimum inhibitory concentration) was determined as 90% inhibition of growth with respect to the growth control.

Table 7. IC_{50} values for the compounds **50(a-j)**

	Inhibitory concentration in µg/ml against						
Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
50a	128	128	64	128	64	64	64
50b	64	64	64	32	32	64	64
50c	8	8	64	16	64	16	16
50d	16	16	32	16	32	16	16
50e	4	4	32	32	64	64	64
50f	64	64	16	16	32	32	32
50g	32	32	32	8	16	16	16
50h	64	64	16	16	16	32	32
50i	64	64	32	8	128	64	64
50j	16	16	16	32	128	16	16
Amphotericin-B	0.5	0.5	8	2	8	8	8
Fluconazole	32	32	128	64	16	8	8

1. *Candida albicans 1* **2.** *Candida albicans 2* **3.** *Cryptococcus Neoformans* **4.** *Benjaminiella poitrasii* **5.** *Yarrowia lipolytica* **6.** *Fusarium oxysporum* 1 **7**. *Fusarium oxysporum* 2.

[b]IC_{50} was the concentration at which 50% growth inhibition was observed.

Negative control, DMSO, No inhibition.

However compounds **50d** and **50(f-j)** are highly active *against C. neoformans* and compound **50g** and **50i** having methoxy substituents present on aryl ring was found to be more potent against *B. poitrasii* at 16µg/ml concentration. While the compounds **50b**, **50d**, **50f** and **50g** showed moderate activity against *Y. lipolytica*, best result was obtained with compound **50h** having naphthalene ring at 2 position the activity of which was

comparable to that of amphotericin B. Compounds **50c**, **50d**, **50g** and **50j** showed good activity against *F. oxysporum* 1 and 2 (**Table 6**).

In vitro antibacterial activities of the newly synthesized compounds were also evaluated against the bacterial strains *E. coli* (NCIM 2574) and *S. aureus* (NCIM 2122) (**Table 8**).

Table 8. *In vitro* antibacterial activity for compounds **50(a-j)**

Compound	Inhibitory concentration in µg/ml			
	E. coli		S. aureus	
	[a]MIC	[b]IC_{50}	MIC	IC_{50}
50a	16	8	32	16
50b	32	16	32	16
50c	32	16	64	32
50d	64	32	128	32
50e	32	16	64	32
50f	32	16	16	8
50g	64	32	32	16
50h	32	16	64	32
50i	64	32	128	64
50j	32	16	64	32
Tetracycline	8	4	16	8
Erythromycin	64	32	32	16

[a]MIC_{90} (Minimum inhibitory concentration) was determined as 90% inhibition of growth with respect to the growth control.

[b]IC_{50} was the concentration at which 50% growth inhibition was observed.

Negative control, DMSO, No inhibition.

All the synthesized compounds **50(a-j)** showed comparable or better activity against the strain of *E. coli.* with reference to erythromycin. Compounds **50d**, **50g** and **45i** showed the comparable activity with standard drug erythromycin. Compounds **50a**, **50b**, **50c**, **50e**, **50f**, **50h**, and **50j** showed greater activity than erythromycin. It was compound **43a** with no substituents present at phenyl ring which showed the most potent activity

(MIC_{90} = 16μg/ml) as compared to the rest of the synthesized compound. Compounds **50a**, **50b**, **50g** were found to be more potent against the strains of *S. aureus* and activity of these compounds was comparable to that of the standard erythromycin. Among these series compound **50f** showed the highest activity (MIC_{90} = 16μg/ml) against *S. aureus.* The activity is comparable with the activity of the standard drug tetracycline (**Table 8**).

3.2.4.2 Antiproliferative activity: materials and methods

Human acute monocytic leukemia THP 1, Human epithelial carcinoma A431 and human mammary adenocarcinoma (MCF-7) cell lines were obtained from American Type Culture Collection (Manassas, VA, USA), and maintained in our in-house National Cell Repository. Cells were maintained as a monolayer in a culture medium consisting of nutrient media MEM supplemented with heat-inactivated fetal bovine serum (10%), penicillin (100 μg/ml), and streptomycin(100 μg/ml) (Invitrogen Life Technologies, MD, USA). The cells were grown at 37 ºC in 5% CO_2 and humidified air atmosphere. Stock solutions of all compounds were prepared in DMSO (concentration of 4 mg/ml) and afterwards diluted to the required concentration in cell culture media. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was dissolved (1 mg/ml) in MEM (without phenol red) and filtered through a Millipore filter, 0.22 μm, before use. The compound **50c**, **50d** and **50e** which showed the highest antifungal activity were taken up for the determination of their antiproliferative activity.

3.2.4.3 Antiproliferative activity: MTT cell proliferation assay

THP-1, A431 and MCF-7 cells were seeded with 10,000 cells per well in 96 well tissue culture plates. Cells were allowed to adhere for 24h at 37°C and then treated with various concentrations (2, 10, 20, 50, 100, 200, 500, 1000, 2000 ug/ml) of compounds diluted in culture medium and again incubated for additional 72h, 120h, and 192h respectively. In control wells, a culture medium consisting of corresponding concentration of DMSO only was added.

After incubation, proliferation of drug treated cells was assessed by adding 10 μl medium containing 5 mg/ml MTT to each well and subsequently incubated for another 1h at 37°C. The formazan crystals formed due to the reduction of the dye within the cells were solubilized by incubating for another 4h in the presence of 200 μl of isopropanol.

The optical density was read on SpectraMax 384 plate reader at 490 nm against a blank prepared from cell-free wells. Absorbance given by cells treated with the carrier DMSO alone was taken as 100% cell growth. All assays were performed in triplicate under similar experimental conditions.

3.2.4.4 Antiproliferative activity

The antiproliferative activity of all the four compounds, **50c**, **50d**, **50e** and amphotericin B, was tested against human cancer cells THP 1, A431 and MCF-7 which were grown in vitro. Compounds **50c**, **50d**, **50e** and amphotericin B at high doses were toxic to all three THP 1, A431 and MCF-7 cells. However, at lower doses all cell lines were resistant to tested compounds. At lower doses THP 1 cells were resistant to all four compounds and the IC_{50} values were between 90 and 95 µg/ml (**Fig. 24**). All the our compounds were almost identical in their effect on the survival of A431 cells. In fact none of the four compounds was toxic to A431 cells up to concentration of 500 µg/ml and IC_{50} values were between 85 to 95µg/ml. At concentration of 1 mg/ml or more all the four compounds were toxic to THP 1 and A431 cell lines (**Fig. 25**) and inhibted growth. It was observed that compounds **50c**, **50d** and **50e** were less toxic to MCF cells.

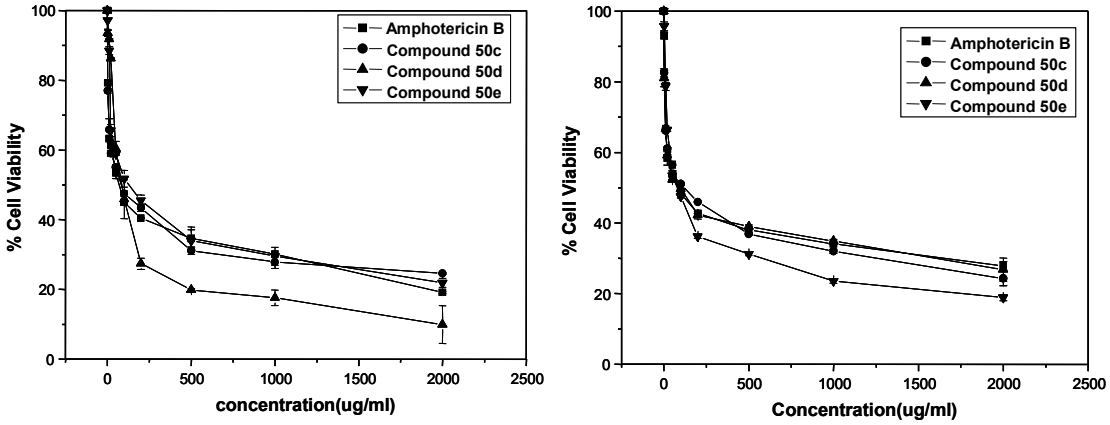


Figure 24. Antiproliferative activities of compounds in THP-1 cells.

Figure 25. Antiproliferative activities of compounds in A431 cells.

The IC_{50} values of compounds **50c**, **50d**, **50e**, and amphotericin B are 651 µg/ml, 2 mg/ml, 1.26 mg/ml, and 2 mg/ml respectively. At concentration of 2 mg/ml or more all the four compounds were toxic to MCF-7 cells (**Fig. 26**).

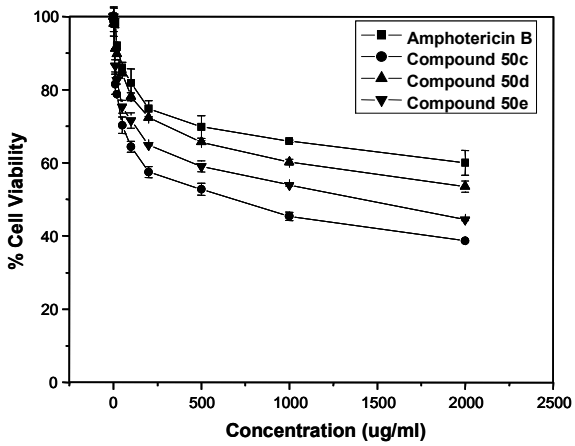


Figure 26. Antiproliferative activities of compounds in MCF-7 cells.

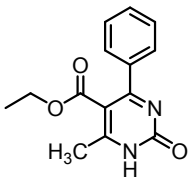
3.2.5 Conclusion

In conclusion, we have developed a four step protocol for the synthesis of diversely substituted novel pyrimidines. A series of halogenated pyrimidines was synthesized from easily available Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones and subjected to the conditions normally employed for Suzuki/Sonogashira coupling reactions and obtained *C*-phenyl pyrimidines. All the new molecules exhibited excellent *in vitro* antifungal and antibacterial profile. The potency of some of the active compounds was greater than or comparable to standard drug fluconazole. There seems to exist a structure activity relation between antifungal activity and the structure of pyrimidines. The presence of strongly electron donating methoxy or electron withdrawing nitro substituents in the aryl ring governs the antifungal activity of pyrimidine. Against fungus *C. albicans* these compounds showed significantly better activity than fluconazole. However, their MIC values were comparable with that of fluconazole for the other fungal strains viz *C. neoformans, B. poitrasii, Y. lipolytica* and *F. oxysporum*. These compounds also possess significant activity against bacterial strains comparable or better than that of erythromycin. Even **50a** with no substituents on phenyl ring showed better activity against bacterial strains than erythromycin. However, its antifungal activity was much inferior to amphotericin B. The antiproliferative activities of compound **50c**, **50d**, and **50e** were observed to be similar to that of amphotericin B with only small differences in the levels of their toxicities. The MCF-7 cell line was less sensitive to **50d**, **50e** and amphotericin B up to 1.25 mg/ml concentration of all the three compounds. Overall, the

results indicate that the tested compounds do not have any profound effect on proliferation of human cancer cell lines at lower concentrations. The cytotoxic MIC values of compound **50c**, **50d** and **50e** are significantly higher than that of antifungal ones. This shows that the tetra substituted pyrimidine derivatives are safe drug candidates. Furthermore, since chloro compounds tend to be more available commercially, as well as less costly, this pathway is quite desirable for the preparation of pyrimidines. A variety of commercially available 1,3 diketones, various substituted aldehydes and boronic acids can be used as building blocks to generate diversity on core pyrimidine ring to obtain more potent antifungal and antibacterial compounds.

3.2.6 Experimental Section

[A] Ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (48a):



A mixture of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-one **47a** (1.0 g, 3.84 mmol) and $NaHCO_3$ (1.61 g, 19.23 mmol) in 50 ml of acetone was cooled to -5 °C using ice-salt mixture. To this stirred suspension ceric ammonium nitrate CAN (6.32 g, 11.53 mmol) in water (25 ml) was added for 1h at -5 °C under argon atmosphere. The stirring was continued overnight at room temperature and the reaction mixture was diluted with $CHCl_3$ (50 ml) and decanted. The residue was washed with $CHCl_3$ (2 × 40ml). The combined $CHCl_3$ layer was neutralized, washed with brine solution, dried over anhydrous Na_2SO_4, and purified by column chromatography using ethyl acetate and petroleum ether (1:1) to afford pure product.

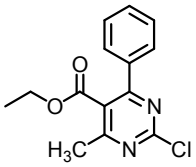
Nature	**:**	White solid
Yield	**:**	0.793 g, 80%.
MP	**:**	191-193 °C.
IR ($CHCl_3$, cm^{-1})	**:**	3150, 2600, 1723, 1654, 1603, 14656, 1424, 1280, 1105, 755.
^{1}H NMR (200MHz, $CDCl_3$)	**:**	δ 0.92 (t, *J* = 7.1 Hz, 3H), 2.61 (s, 3H), 4.04 (q, *J* = 7.1 Hz, 2H), 7.37-7.48 (m, 3H), 7.57-7.62 (m, 2H), 13.73 (brs, 1H).
^{13}C NMR	**:**	δ13.3, 61.5, 111.4, 127.9, 128.2, 130.7, 158.2, 166.0.

(50 MHz, $CDCl_3$)

Elemental Analysis : Calcd: C, 65.11; H, 5.46; N, 10.85.

$C_{14}H_{14}N_2O_3$ (258) Found: C, 64.97; H, 5.58; N, 10.62.

[B] Ethyl 2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate (49a):



N,N-Dimethylaniline (0.515 ml, 4.06 mmol) was added to a stirred solution of Ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate **48a** (0.750 g, 2.90 mmol) in $POCl_3$ (20 ml) and the reaction mixture was refluxed overnight. Excess of $POCl_3$ was removed under reduced pressure and the residue poured in to ice water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuuo. The crude product was purified by column chromatography using pet ether/EtOAc 9.5:0.5 to afford colorless thick liquid

Nature : Thick liquid

Yield : 0.670 g, 82%.

IR ($CHCl_3$, cm^{-1}) : 3062, 2983, 1728, 1538, 1446, 1380, 1306, 1207, 1185, 937, 863.

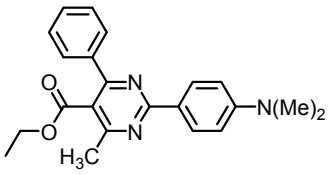
^{1}H NMR (200MHz, $CDCl_3$) : 1.07 (t, *J* = 7.2 Hz, 3H), 2.62 (s, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 7.40-7.50 (m, 3H), 7.63-7.67 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ: 13.5, 22.4, 62.1, 124.3, 128.3, 128.5, 130.6, 136.1, 160.4, 166.1, 166.9, 168.5.

Elemental Analysis : Calcd: C, 60.77; H, 4.74; N, 10.12.

$C_{14}H_{13}ClN_2O_2$ (276) Found: C, 60.92; H, 4.51; N, 9.95.

[C] Ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (50a):



A mixture of Ethyl 2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate **49a** (0.5 g, 1.81 mmol), 4-(*N,N*-dimethylamino)-phenylboronic acid (0.358 g, 2.17 mmol) was dissolved in dioxane (12 ml) and stirred for 5 minutes at room temperature, to this mixture saturated solution of Na_2CO_3 (8 ml) was added followed by palladium acetate (0.016 g, 0.072 mmol), and triphenylphosphine (0.094 g, 0.36 mmol). The reaction mixture was heated to

110 °C for 3 h. The cooled mixture was diluted with ethyl acetate, filtered over a plug of celite bed and the filtrated was evaporated in vacuo. The residue was purified by column chromatography using pet ether/EtOAc 9.5:0.5 to afford pale yellow solid.

Nature : Pale yellow solid

Yield : 0.560 g, 85%.

MP : 122–124 °C.

IR ($CHCl_3$, cm^{-1}) : 3017, 2984, 1718, 1608, 1535, 1402, 1364, 1265, 1188.

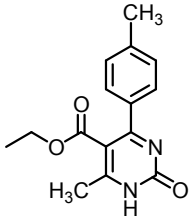
^{1}H NMR (200MHz, $CDCl_3$) : δ 1.05 (t, *J* = 7.2 Hz, 3H), 2.65 (s, 3H), 3.06 (s, 6H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.76 (d, *J* = 9.1 Hz, 2H), 7.45-7.48 (m, 3H), 7.71-7.76 (m, 2H), 8.45 (d, *J* = 9.1 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ13.5, 22.9, 40.1, 61.4, 111.3, 121.4, 124.6, 128.2, 128.3, 129.6, 130.0, 138.7, 152.3, 163.4, 163.9, 165.0, 168.8.

Elemental Analysis : Calcd: C, 73.11; H, 6.41; N, 11.63.

$C_{22}H_{23}N_3O_2$ (361) Found: C, 73.32; H, 6.54; N, 11.75.

Ethyl 1,2-dihydro-6-methyl-2-oxo-4-*p*-tolylpyrimidine-5-carboxylate (48b): Compound **47b** (1g, 3.64 mmol) was reacted as described in the procedure **[A]** to give **48b** as white solid.



Nature : White solid

Yield : 0.812 g, 82%.

MP : 167-169 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ: 0.99 (t, *J* = 7.0 Hz, 3H), 2.39 (s, 3H), 2.58 (s, 3H), 4.08 (q, *J* = 7.0, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 13.64 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ: 13.4, 21.3, 61.5, 111.3, 128.0, 129.0, 141.3, 158.3, 166.2

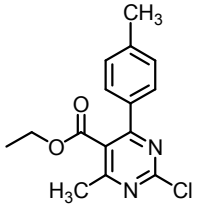
IR ($CHCl_3$, cm^{-1}) : 3150, 2600, 1730, 1545, 1645, 1600, 1524, 1424, 1250, 1180, 820, 756.

Elemental Analysis : Calcd: C, 66.16; H, 5.92; N, 10.29.

$C_{15}H_{16}N_2O_3$ (272) Found: C, 66.04; H, 5.75; N, 10.41.

Ethyl 2-chloro-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (49b):

Compound **48b** (0.8 g, 2.94 mmol) was reacted as described in the procedure **[B]** to give **49b** as colorless liquid.



Nature : Colorless liquid

Yield : 0.664 g, 78 %

^{1}H NMR (200MHz, $CDCl_3$) : δ: 1.13 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 2.60 (s, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H).

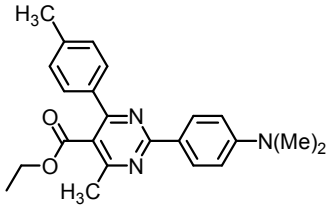
^{13}C NMR (50 MHz, $CDCl_3$) : δ: 13.6, 21.3, 22.4, 62.1, 124.1, 128.3, 129.3, 133.3, 141.3, 160.4, 166.0, 167.2, 168.3.

IR ($CHCl_3$, cm^{-1}) : 3058, 2982, 1728, 1612, 1540, 1445, 1378, 1306, 1207, 1185.

Elemental Analysis : Calcd: C, 61.97; H, 5.20; N, 9.64.

$C_{15}H_{15}ClN_2O_2$ (291) Found: C, 61.84; H, 5.25; N, 9.79.

Ethyl 2-(4-(dimethylamino) phenyl)-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (50b): Compound **49b** (0.4 g, 1.37 mmol) was reacted as described in the procedure **[C]** to give **50b.**



Nature : Pale yellow solid

Yield : 0.413 g, 80%.

MP : 117-119 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ: 1.11 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H), 2.64 (s, 3H), 3.05 (s, 6H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 8.44 (d, *J* = 9.2 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ: 13.6, 21.3, 22.8, 40.0, 61.4, 111.3, 121.3, 124.8, 128.3, 129.0, 129.9, 135.8, 139.7, 152.2, 163.1, 163.8, 164.7, 169.0.

IR ($CHCl_3$, cm^{-1}) : 3020, 1717, 1605, 1530, 1462, 1376, 1360, 1266, 1185, 1076.

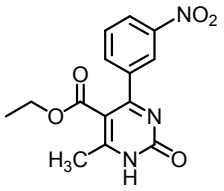
Elemental Analysis : Calcd: C, 73.57; H, 6.71; N, 11.19.

$C_{23}H_{25}N_3O_2$ (375) Found:

C, 73.64; H, 6.55; N, 11.28.

Ethyl 1,2-dihydro-6-methyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxylate (48c):

Compound **47c** (0.850 g, 2.78 mmol) was reacted as described in the procedure **[A]** to give **48c** as yellow solid.



Nature : Pale yellow solid

Yield : 0.607 g, 72%.

MP : 213-215 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 0.89 (t, *J* = 7.2 Hz, 3H), 2.76 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 7.33-7.38 (m, 1H), 7.56-7.76 (m, 2H), 8.21-8.26 (m, 1H), 13.70 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.3, 20.3, 61.2, 109.6, 124.1, 128.9, 129.6, 133.6, 146.2, 157.6, 163.5.

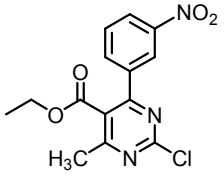
IR ($CHCl_3$, cm^{-1}) : 3362, 1715, 1659, 1592, 1532, 1460, 1376, 1353, 1287.

Elemental Analysis : Calcd: C, 55.45; H, 4.32; N, 13.86.

$C_{14}H_{13}N_3O_5$ (303) Found: C, 55.34; H, 4.15; N, 13.97.

Ethyl 2-chloro-4-methyl-6-(3-nitrophenyl)pyramidine-5-carboxylate (49c):

Compound **48c** (0.720 g, 2.37 mmol) was reacted as described in the procedure **[B]** to give **49c** as yellow solid.



Nature : Yellow solid

Yield : 0.533 g, 70%.

MP : 98-100 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ: 1.19 (t, *J* = 7.2 Hz, 3H), 2.66(s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 8.01-8.06 (m, 1H), 8.34-8.40 (m, 1H), 8.55 (t, *J* = 2.0 Hz, 1H).

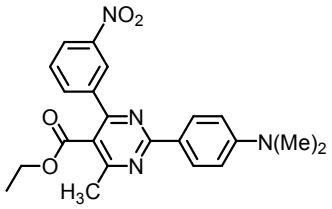
^{13}C NMR (50 MHz, $CDCl_3$) : δ: 13.6, 22.6, 62.6, 123.4, 124.5, 125.2, 129.8, 134.3, 137.6, 148.2, 160.7, 163.3, 166.3, 169.3.

IR ($CHCl_3$, cm^{-1}) : 3008, 2925, 1726, 1614, 1535, 1462, 1376, 1309, 1280, 1232, 1083, 1012, 907, 862.

Elemental Analysis : Calcd: C, 52.27; H, 3.76; N, 13.06.

$C_{14}H_{12}ClN_3O_4$ (322) Found: C, 52.34; H, 3.62; N, 13.22.

Ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate (50c): Compound **49c** (0.450 g, 1.40 mmol) was reacted as described in the procedure **[C]** to give **50c** as light yellow solid.



Nature : Yellow solid

Yield : 0.540 g, 95%.

MP : 138-140 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ: 1.15 (t, *J* = 7.1 Hz, 3H), 2.68 (s, 3H), 3.07 (s, 6H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 8.04-8.09 (m, 1H), 8.31-8.37 (m, 1H), 8.43 (d, *J* = 9.2 Hz, 2H), 8.63 (t, *J* = 2.0 Hz, 1H).

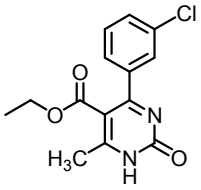
^{13}C NMR (50 MHz, $CDCl_3$) : δ: 13.7, 23.1, 40.1, 61.8, 111.4, 121.3, 123.5, 124.0, 124.2, 129.3, 130.1, 134.4, 140.3, 148.2, 152.5, 160.9, 164.2, 165.7, 168.1.

IR ($CHCl_3$, cm^{-1}) : 2940, 1701, 1608, 1533, 1462, 1377, 1271, 1192, 1117, 1082, 945, 862, 802, 746.

Elemental Analysis : Calcd: C, 65.01; H, 5.46; N, 13.78

$C_{22}H_{22}N_4O_4$ (406) Found: C, 65.20; H, 5.58; N, 13.62.

Ethyl 4-(3-chlorophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (48d): Compound **47d** (0.8 g, 2.72 mmol) was reacted as described in the procedure **[A]** to give **48d** as white solid.



Nature : White solid

Yield : 0.603 g, 76%.

MP : 153-155 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.01 (t, *J* = 7.2 Hz, 3H), 2.64 (s, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 7.33-7.65 (m, 4H), 13.82 (brs, 1H).

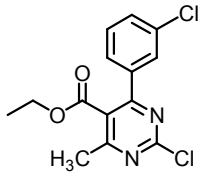
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.4, 18.8, 61.6, 111.2, 126.0, 128.1, 129.4, 130.5, 134.3, 139.1, 158.1, 165.4.

IR ($CHCl_3$, cm^{-1}) : 3325, 3090, 1719, 1655, 1603, 1571, 1474, 1445, 1369, 1280, 1266, 1215, 1108, 1015, 971.

Elemental Analysis : Calcd: C, 57.44; H, 4.48; N, 9.57.

$C_{14}H_{13}ClN_2O_3$ (293) Found: C, 57.58; H, 4.55; N, 9.74.

Ethyl 2-chloro-4-(3-chlorophenyl)pyrimidine-5-carboxylate (49d): Compound **48d** (0.550 g, 1.88 mmol) was reacted as described in the procedure **[B]** to give **49d** as colorless solid.



Nature : Colorless solid

Yield : 0.460 g, 79%.

MP : 62-64 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.14 (t, *J* = 7.2 Hz, 3H), 2.63 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H), 7.35-7.68 (m, 4H).

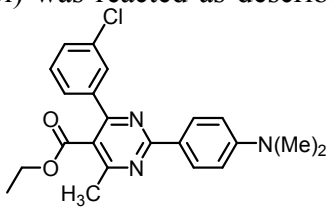
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.6, 22.5, 62.3, 124.4, 126.5, 128.4, 129.9, 130.7, 134.7, 137.8, 160.5, 164.5, 166.6, 168.9.

IR ($CHCl_3$, cm^{-1}) : 3070, 2984, 1731, 1537, 1478, 1431, 1374, 1308, 1268.

Elemental Analysis : Calcd: C, 54.04; H, 3.89; N, 9.00.

$C_{14}H_{12}Cl_2N_2O_2$ (311) Found: C, 54.20; H, 3.71; N, 9.14.

Ethyl 4-(3-chlorophenyl)-2-(4-(dimethylamino)phenyl)-6-methylpyrimidine-5-carboxylate (50d): Compound **49d** (0.4 g, 1.29 mmol) was reacted as described in the procedure **[C]** to give **50d** as yellow solid.



Nature : Yellow solid

Yield : 0.417 g, 82%.

MP : 124-126 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.12 (t, *J* = 7.2 Hz, 3H), 2.66 (s, 3H), 3.06 (s, 6H), 4.21 (q, *J* = 7.2 Hz, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 7.34-7.48 (m, 2H), 7.56-7.61 (m, 1H), 7.74-7.76 (m, 1H), 8.44 (d, *J* = 9.2 Hz, 2H).

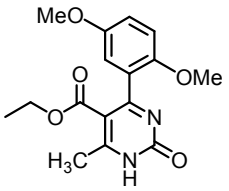
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.6, 22.9, 40.0, 61.6, 111.3, 121.3, 124.3, 126.5, 128.5, 129.5, 129.6, 130.0, 134.3, 140.4, 152.4, 161.9, 164.0, 165.3, 168.3.

IR ($CHCl_3$, cm^{-1}) : 2981, 2902, 1721, 1608, 1583, 1478, 1401, 1364, 1262.

Elemental Analysis : Calcd: C, 66.75; H, 5.60; N, 10.61.

$C_{22}H_{22}ClN_3O_2$ (396) Found: C, 66.70; H, 5.42; N, 10.49.

Ethyl 1,2-dihydro-4-(2,5-dimethoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (48e): Compound **47e** (0.7 g, 2.18 mmol) was reacted as described in the procedure **[A]** to give product **48e**.



Nature : Light brown solid

Yield : 0.612 g, 88%.

MP : 171-173 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 0.97 (t, *J* = 7.2 Hz, 3H), 2.66 (s, 3H), 3.71 (s, 3H), 3.81 (s, 3H), 4.03 (q, *J* = 7.2 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 1H), 6.96 (dd, *J* = 3.0 Hz, *J* = 8.9 Hz, 1H), 7.12 (d, *J* = 3.0 Hz, 1H).

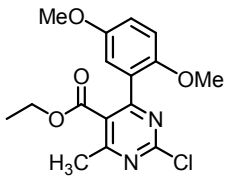
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.5, 55.6, 55.8, 60.8, 111.3, 112.3, 115.0, 117.5, 150.5, 153.6, 158.3, 165.1.

IR ($CHCl_3$, cm^{-1}) : 3311, 3073, 1717, 1657, 1594, 1494, 1456, 1436, 1365, 1322, 1284, 1267, 1223, 1130.

Elemental Analysis : Calcd: C, 60.37; H, 5.70; N, 8.80.

$C_{16}H_{18}N_2O_5$ (318) Found: C, 60.48; H, 5.92; N, 8.95.

Ethyl 2-chloro-4-(2,5-dimethoxyphenyl)-6-methyl pyrimidine-5-carboxylate (49e): Compound **48e** (0.5 g, 1.57 mmol) was reacted as described in the procedure **[B]** to give **49e.**



Nature : Light brown solid

Yield : 0.406 g, 77%.

MP : 90-92 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.03 (t, *J* = 7.2 Hz, 3H), 2.69 (s, 3H), 3.69 (s, 3H), 3.81 (s, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.97 (dd, *J* = 3.0 Hz, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 3.0 Hz, 1H).

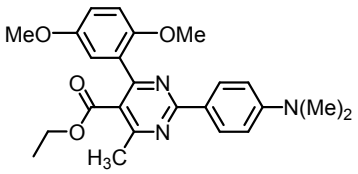
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.5, 23.2, 55.5, 55.8, 61.3, 111.5, 115.6, 117.2, 125.1, 126.6, 150.4, 153.7, 160.5, 165.5, 165.8, 168.9.

IR ($CHCl_3$, cm^{-1}) : 3017, 2907, 1728, 1587, 1538, 1502, 1464, 1424, 1310, 1273, 1215, 1183, 1086.

Elemental Analysis : Calcd: C, 57.06; H, 5.09; N, 8.32.

$C_{16}H_{17}ClN_2O_4$ (337) Found: C, 56.88; H, 5.25; N, 8.45.

Ethyl 2-(4-(dimethylamino)phenyl)-4-(2,5-dimethoxyphenyl)-6methylpyrimidine-5 carboxylate (50e): Compound **49e** (0.380 g, 1.13 mmol) was reacted as described in the procedure **[C]** to give **50e.**



Nature : Yellow solid

Yield : 0.404 g, 85%.

MP : 133-136 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 0.97 (t, *J* = 7.2 Hz, 3H), 2.65 (s, 3H), 2.97 (s, 6H), 3.63 (s, 3H), 3.76 (s, 3H), 4.03 (q, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.1 Hz, 1H), 6.89 (dd, *J* = 3.0 Hz, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 3.0 Hz, 1H), 8.36 (d, *J* = 9.0 Hz, 2H).

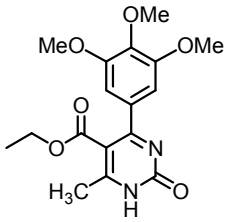
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.5, 23.7, 40.0, 55.6, 55.7, 60.6, 111.3, 111.4, 115.7, 116.2, 122.1, 124.7, 129.3, 130.0, 150.7, 152.2, 153.6, 162.4, 164.2, 165.3, 167.4.

IR ($CHCl_3$, cm^{-1}) : 2934, 1723, 1609, 1537, 1500, 1428,, 1402, 1363, 1260, 1224, 1189, 1077, 1047.

Elemental Analysis : Calcd: C, 68.39; H, 6.46; N, 9.97.

$C_{24}H_{27}N_3O_4$ (421) Found: C, 68.44; H, 6.55; N, 10.14.

Ethyl 1,2-dihydro-4-(3,4,5-trimethoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (48f): Compound **47f** (0.750 g, 2.14 mmol) was reacted as described in the procedure **[A]** to give product **48f**.



Nature : Yellow solid

Yield : 0.685 g, 92%.

MP : 137-139 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.03 (t, *J* = 7.2 Hz, 3H), 2.60 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.11 (q, *J* = 7.2, 2H), 6.88 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.5, 56.1, 60.8, 61.6, 105.3, 111.5, 140.3, 153.0, 158.2, 166.3.

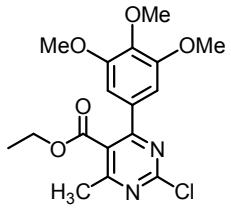
IR ($CHCl_3$, cm^{-1}) : 3052, 1720, 1699, 1604, 1506, 1463, 1433, 1385, 1321, 1265, 1241, 1128, 855.

Elemental Analysis : Calcd: C, 58.61; H, 5.79; N, 8.04.

$C_{17}H_{20}N_2O_6$ (348) Found: C, 58.74; H, 5.68; N, 7.95.

Ethyl 2-chloro-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate (49f):

Compound **48f** (0.6 g, 1.72 mmol) was reacted as described in the procedure **[B]** to give product **49f.**



Nature : Colorless solid

Yield : 0.473 g, 75%.

MP : 74-77 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.15 (t, *J* = 7.1 Hz, 3H), 2.61 (s, 3H), 3.90 (s, 9H), 4.25 (q, *J* = 7.1 Hz, 2H), 6.91 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.7, 22.3, 56.2, 60.9, 62.2, 105.7, 124.3, 131.4, 140.3, 153.3, 160.3, 165.6, 167.3, 168.3.

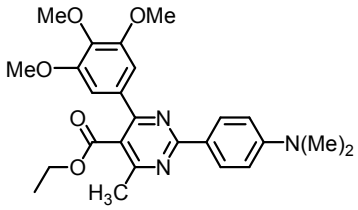
IR ($CHCl_3$, cm^{-1}) : 3002, 2907, 1736, 1586, 1544, 1506, 1464, 1417, 1380, 1279, 1226.

Elemental Analysis : Calcd: C, 55.67; H, 5.22; N, 7.64.

$C_{17}H_{19}ClN_2O_5$ (367) Found: C, 55.53; H, 5.32; N, 7.45.

Ethyl 2-(4-(dimethylamino)phenyl)-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate (50f):

Compound **49f** (0.450 g, 1.22 mmol) was reacted as described in the procedure **[C]** to give **50f.**



Nature : Thick yellow liquid

Yield : 0.487 g, 88%.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.12 (t, *J* = 7.0 Hz, 3H), 2.63 (s, 3H), 3.06 (s, 6H), 3.90 (s, 3H), 3.91 (s, 6H), 4.21 (q, *J* = 7.0 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.99 (s, 2H), 8.43 (d, *J* = 9.0 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.6, 22.6, 39.9, 56.0, 60.7, 61.4, 105.5, 111.2, 121.3, 124.4, 129.9, 134.0, 139.3, 152.2, 153.0, 162.7, 163.7, 164.7, 168.9.

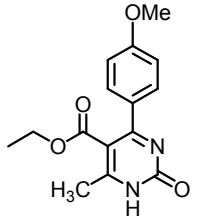
IR ($CHCl_3$, cm^{-1}) : 2937, 1717, 1609, 1588, 1538, 1504, 1400, 1363, 1301,

1259, 1188, 1135.

Elemental Analysis : **Calcd:** C, 66.50; H, 6.47; N, 9.31.

$C_{25}H_{29}N_3O_5$ (451) **Found:** C, 66.42; H, 6.59; N, 9.22.

Ethyl 1, 2-dihydro-4-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (48g): Compound **47g** (0.780 g, 2.68 mmol) was reacted as described in the procedure **[A]** to give **48g.**



Nature : White solid

Yield : 0.657 g, 85%.

MP : 163-165 °C.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.06 (t, *J* = 7.2 Hz, 3H), 2.59 (s, 3H), 3.86 (s, 3H), 4.12 (q, *J* = 7.2, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 13.64 (brs, 1H).

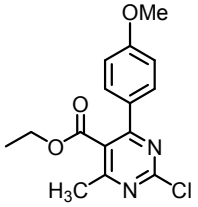
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.5, 52.2, 55.2, 61.5, 111.0, 113.7, 130.0, 158.3, 161.9, 166.4.

IR ($CHCl_3$, cm^{-1}) : 3357, 1713, 1667, 1592, 1449, 1377, 1881, 1262, 1213, 1168.

Elemental Analysis : **Calcd:** C, 62.49; H, 5.59; N, 9.72.

$C_{15}H_{16}N_2O_4$ (288) **Found:** C, 62.64; H, 5.48; N, 9.90.

Ethyl 2-chloro-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (49g): Compound **48g** (0.6 g, 2.08 mmol) was reacted as described in the procedure **[B]** to give compound **49g.**



Nature : Colorless liquid

Yield : 0.496 g, 78%.

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.18 (t, *J* = 7.2 Hz, 3H), 2.59 (s, 3H), 3.87 (s, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.7, 22.4, 55.3, 62.1, 114.1, 123.7, 128.4, 130.2, 160.3, 161.9, 165.3, 167.5, 168.1.

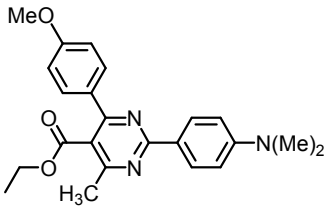
IR ($CHCl_3$, cm^{-1}) : 3003, 2937, 1727, 1608, 1530, 1514, 1380, 1301, 1258,

1207, 1181, 1138.

Elemental Analysis : Calcd: C, 58.73; H, 4.93; N, 9.13.

$C_{15}H_{15}ClN_2O_3$ (307) Found: C, 58.65; H, 4.65; N, 9.22.

Ethyl 2-(4-(dimethylamino)phenyl)-4-(4-methoxyphenyl)-6-methylpyrimidine-5 carboxylate (50g): Compound **49g** (0.4 g, 1.30 mmol) was reacted as described in the procedure **[C]** to give compound **50g.**



Nature : Yellow liquid

Yield : 0.419 g, 82%

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.15 (t, *J* = 7.1 Hz, 3H), 2.63 (s, 3H), 3.06 (s, 6H), 3.87 (s, 3H), 4.23 (q, *J* = 7.1 Hz, 2H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 8.44 (d, *J* = 9.1 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.7, 22.8, 40.1, 55.3, 61.4, 111.3, 113.7, 121.0, 124.8, 129.95, 129.98, 131.0, 152.3, 161.0, 162.5, 163.8, 164.7, 169.2

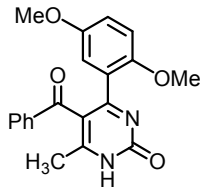
IR ($CHCl_3$, cm^{-1}) : 2981, 2934, 1717, 1608, 1533, 1509, 1432, 1418, 1399, 1363, 1293, 1263, 1187, 1076, 1032.

Elemental Analysis : Calcd: C, 70.57; H, 6.44; N, 10.73.

$C_{23}H_{25}N_3O_3$ (391) Found: C, 70.74; H, 6.52; N, 10.94.

5-Benzoyl-4-(2,5-dimethoxyphenyl)-6-methylpyrimidin-2(1*H*)-one (48h):

Compound **47h** (0.920 g, 2.61 mmol) was reacted as described in the procedure **[A]** to give compound **48h.**



Nature : Light brown solid

Yield : 0.639 g, 70%.

MP : 191-193 °C.

^{1}H NMR (400MHz, $CDCl_3$) : δ 2.40 (s, 3H), 3.41 (s, 3H), 3.71 (s, 3H), 6.55 (d, *J* = 9.0 Hz, 1H), 6.76-6.79 (dd, *J* = 3.2, Hz, *J* = 9.0 Hz, 1H), 6.97 (s, 1H), 7.32-7.36 (m, 2H), 7.44-7.49 (m, 1H), 7.69-7.71 (m, 2H).

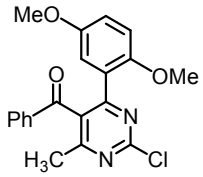
^{13}C NMR (50 MHz, $CDCl_3$) : δ54.6, 55.7, 111.5, 115.4, 117.8, 118.3, 128.2, 129.1, 133.1, 137.3, 149.9, 153.3, 158.6, 192.7.

IR ($CHCl_3$, cm^{-1}) : 3330, 1690, 1665, 1639, 1597, 1498, 1461, 1430, 1376, 1269, 1228, 1179, 1043, 814.

Elemental Analysis : Calcd: C, 68.56; H, 5.18; N, 8.00.

$C_{20}H_{18}N_2O_4$ (350) Found: C, 68.64; H, 5.02; N, 7.89.

(2-chloro-4-(2,5-dimethoxyphenyl)-6-methylpyrimidin-5-yl) (phenyl)methanone (49h): Compound **48h** (0.6 g, 1.71 mmol) was reacted as described in the procedure **[B]** to give compound **49h.**



Nature : Thick light blue liquid

Yield : 0.428 g, 68%.

MP : 191-193 °C.

^{1}H NMR (400MHz, $CDCl_3$) : δ 2.42 (s, 3H), 3.26 (s, 3H), 3.74 (s, 3H), 6.59 (d, *J* = 9.0 Hz, 1H), 6.79-6.85 (dd, *J* = 3.2 Hz, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 3.2 Hz, 1H), 7.36-7.44 (m, 2H), 7.50-7.57 (m, 1H), 7.70-7.75 (m, 2H).

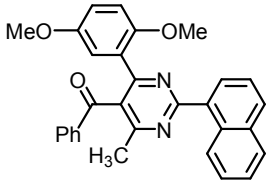
^{13}C NMR (50 MHz, $CDCl_3$) : δ 23.5, 54.4, 55.7, 111.5, 115.9, 117.6, 125.2, 126.2, 128.5, 129.1, 130.4, 133.6, 136.3, 149.9, 153.5, 160.4, 165.2, 167.6, 193.6.

IR ($CHCl_3$, cm^{-1}) : 3019, 2920, 1670, 1598, 1582, 1534, 1503, 1449, 1464, 1424, 1274, 1215, 1180, 1045, 950.

Elemental Analysis : Calcd: C, 65.13; H, 4.56; N, 7.60.

$C_{20}H_{17}ClN_2O_3$ (369) Found: C, 65.24; H, 4.41; N, 7.74.

(4-(2,5-dimethoxyphenyl)-6-methyl-2-(naphthalen-1-yl)pyrimidin-5-yl)(phenyl) methanone (50h): Compound **49h** (0.350 g, 0.95 mmol) was reacted as described in the procedure **[C]** to give product **50h.**



Nature : Gray solid

Yield : 0.340 g, 78%.

MP : 67-69 °C.

^{1}H NMR : δ 2.57 (s, 3H), 3.38 (s, 3H), 3.73 (s, 3H), 6.64 (d, *J* = 9.0

(400MHz, $CDCl_3$) Hz, 1H), 6.79-6.85 (dd, *J* = 3.0 Hz, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 3.0 Hz, 1H), 7.40-7.59 (m, 6H), 7.83-8.01 (m, 4H), 8.18-8.22 (dd, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 8.81-8.85 (m, 1H).

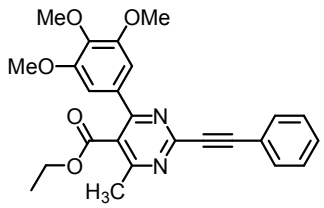
^{13}C NMR (50 MHz, $CDCl_3$) : δ 23.8, 54.5, 55.7, 111.5, 116.2, 116.7, 125.2, 125.8, 125.9, 126.7, 126.8, 128.4, 129.2, 129.4, 129.5, 130.6, 131.0, 133.4, 134.0, 135.5, 136.8, 150.1, 153.4, 162.3, 164.4, 166.3, 195.2.

IR ($CHCl_3$, cm^{-1}) : 2930, 1666, 1581, 1595, 1530, 1499, 1462, 1377, 1269, 1250, 1223, 1044, 1023, 926.

Elemental Analysis : Calcd: C, 78.24; H, 5.25; N, 6.08.

$C_{30}H_{24}N_2O_3$ (460) Found: C, 78.12; H, 5.34; N, 6.23.

Ethyl 4-(3,4,5-trimethoxyphenyl)-6-methyl-2-(2-phenylethynyl)pyrimidine-5-carboxylate (50i):



A mixture of ethyl 2-chloro-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate **49f** (0.356 g, 0.97 mmol) and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol) was dissolved in MeCN (10 ml). To this mixture, phenylacetylene (0.119 g, 1.16 mmol), trimethyl amine (0.4 ml, 2.91 mmol) and CuI (0.073 g, 0.038 mmol) was added and the mixture was refluxed under argon for 4h up to complete consumption of starting material as judged by TLC and GC analysis. After the completion of reaction, reaction mixture was filtered and evaporated and the residue was purified by column chromatography by using pet ether/EtOAc (8.5:1.5) as a eluent to obtain product **50i.**

Nature : Thick liquid

Yield : 0.357 g, 85%.

^{1}H NMR (400MHz, $CDCl_3$) : δ 1.14 (t, *J* = 7.2 Hz, 3H), 2.64 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 4.23 (q, *J* = 7.2 Hz, 2H), 6.92 (s, 2H), 7.37-7.42 (m, 3H), 7.67-7.72 (dd, *J* = 2 Hz, *J* = 7.5 Hz, 2H).

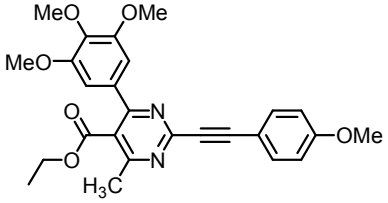
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.6, 22.4, 56.1, 60.8, 62.0, 87.9, 88.5, 105.5, 121.1, 124.0, 128.3, 129.7, 132.3, 132.6, 139.7, 152.1, 153.2, 163.5, 165.4, 167.7.

IR ($CHCl_3$, cm^{-1}) : 2981, 2223, 1728, 1588, 1538, 1505, 1463, 1384, 1305, 1244, 1211, 1085, 1023, 854.

Elemental Analysis : Calcd: C, 69.43; H, 5.59; N, 6.48.

$C_{25}H_{24}N_2O_4$ (432) Found: C, 69.51; H, 5.42; N, 6.39.

Ethyl 4-(3,4,5-trimethoxyphenyl)-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyrimidine-5-carboxylate (50j): Compound **49f** (0.210 g, 0.57 mmol) was reacted as described in the above procedure to give **50j.**



Nature : Thick liquid

Yield : 0.238 g, 90%.

^{1}H NMR (400MHz, $CDCl_3$) : δ 1.13 (t, *J* = 7.1 Hz, 3H), 2.63 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 4.25 (q, *J* = 7.1 Hz, 2H), 6.84-6.94 (m, 4H), 7.64 (d, *J* = 8.5 Hz, 2H).

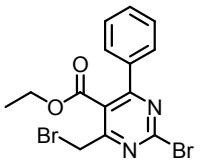
^{13}C NMR (50 MHz, $CDCl_3$) : δ 13.7, 22.4, 55.2, 56.1, 60.8, 62.0, 87.3, 89.3, 105.5, 113.0, 114.0, 123.7, 132.5, 134.4, 139.7, 152.4, 153.2, 160.7, 163.5, 165.3, 167.8.

IR ($CHCl_3$, cm^{-1}) : 3013, 2838, 2212, 1725, 1604, 1588, 1528, 1509, 1464, 1383, 1293, 1249, 1211, 1128.

Elemental Analysis : **Calcd:** C, 67.52; H, 5.67; N, 6.06.

$C_{26}H_{26}N_2O_6$ (462) **Found:** C, 67.45; H, 5.54; N, 6.22.

Ethyl 2-bromo-4-(bromomethyl)-6-phenylpyrimidine-5-carboxylate 52:



A mixture of ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate **48a** (0.212 g, 0.82 mmol) and $POBr_3$ (0.707 g, 2.46 mmol) was heated up to 175 ºC for 1h. After 1h reaction mixture was cooled room temperature and ice-water was added slowly. The reaction mixture was further neutralized with $NaHCO_3$ and extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and concentrated in vacuo to obtain the residual crude product which was purified by column chromatography by using pet ether/EtOAc (9:1) as a eluent to obtain **52** (0.278 g, 85%) as a thick liquid.

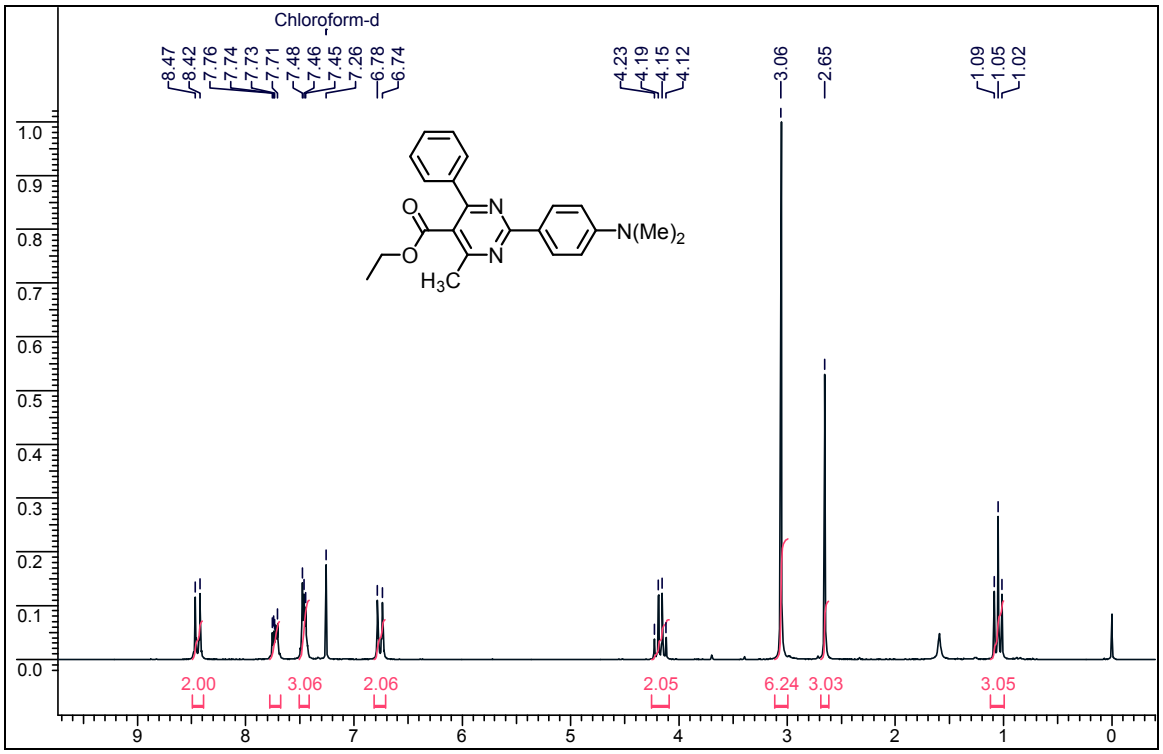
Nature	**:**	Thick liquid
Yield	**:**	0.278 g, 85%.
^{1}H NMR (400MHz, $CDCl_3$)	**:**	δ 1.06 (t, *J* = 7.2 Hz, 3H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.63 (s, 2H), 7.43-7.54 (m, 3H), 7.63-7.68 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	**:**	δ 13.4, 28.2, 62.5, 123.9, 128.5, 128.6, 131.0, 135.8, 152.5, 165.8, 166.1, 167.5.
IR ($CHCl_3$, cm^{-1})	**:**	3016, 2938, 1723, 1537, 1520, 1378, 1238, 1216, 757.
MS: *m/z*	**:**	402, 399, 397, 371, 292, 128, 77.
Elemental Analysis	**:**	**Calcd:** C, 42.03; H, 3.02; N, 7.00.
$C_{14}H_{12}Br_2N_2O_2$ (400)		**Found:** C, 42.14; H, 2.84; N, 6.82.

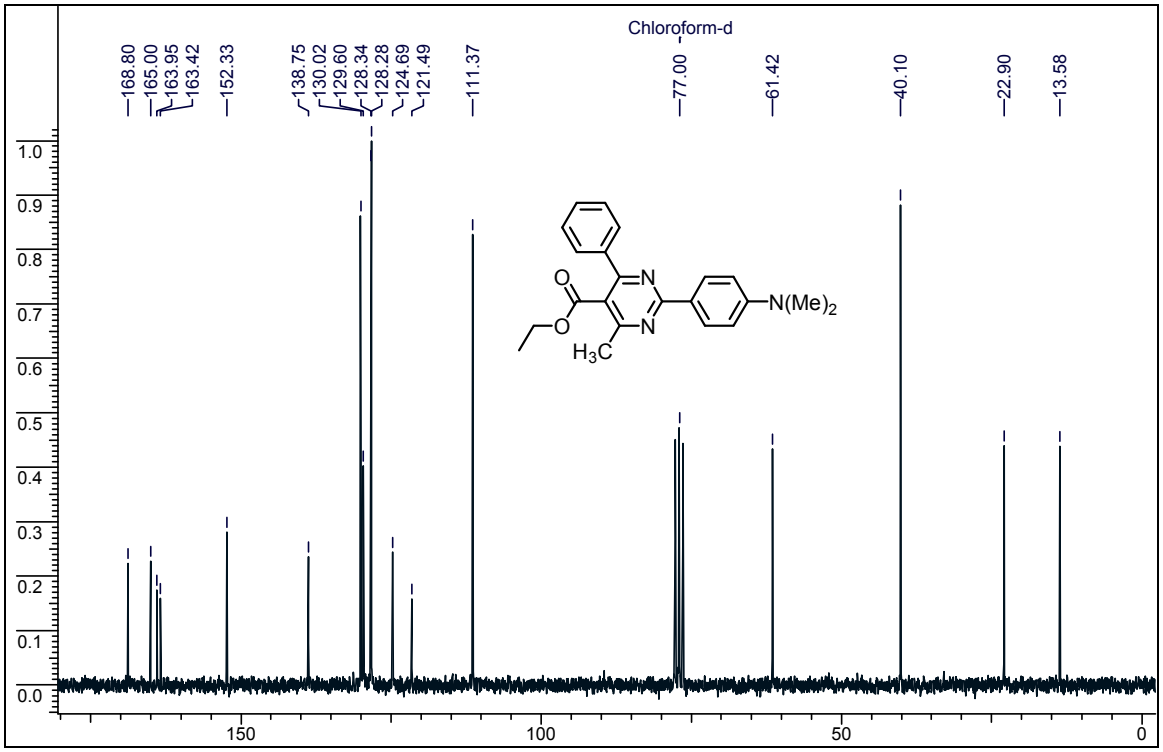
3.2.7 Spectra

Table 9. ^{1}H and ^{13}C spectra of some selected compounds are given below:

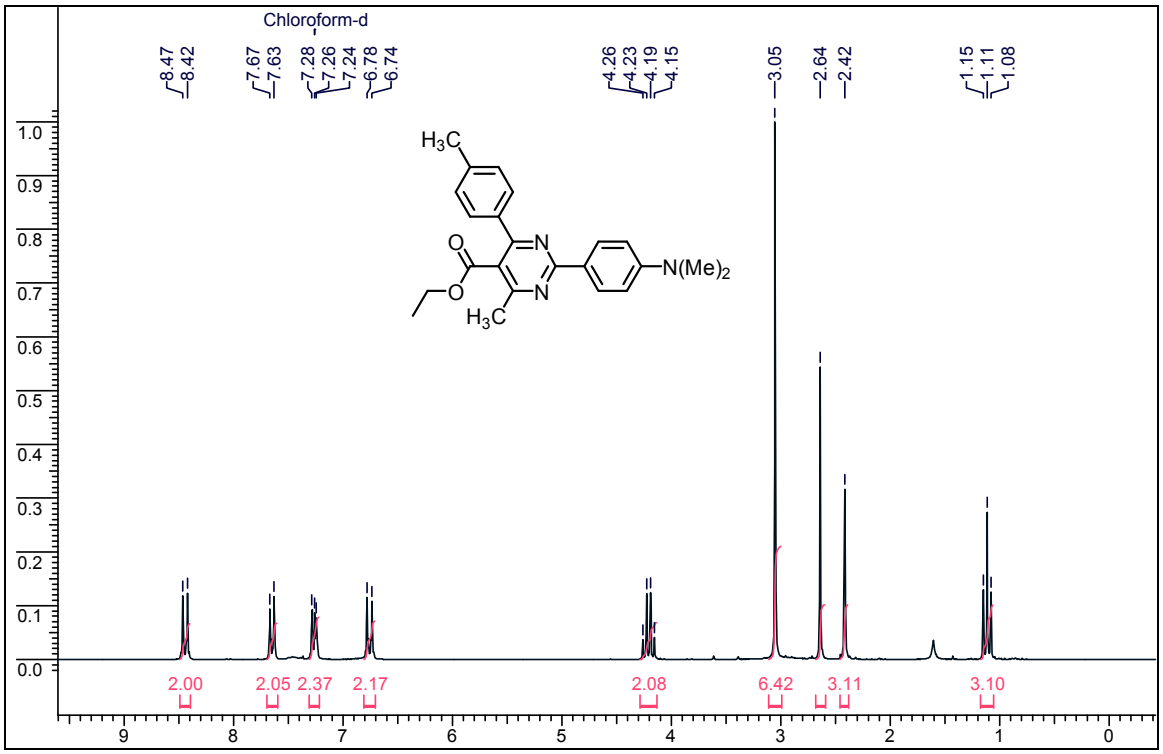
Sr. No.	Spectra	
[1]	^{1}H NMR and ^{13}C NMR Spectra of	**50a**
[2]	^{1}H NMR and ^{13}C NMR Spectra of	**50b**
[3]	^{1}H NMR and ^{13}C NMR Spectra of	**50c**
[4]	^{1}H NMR and ^{13}C NMR Spectra of	**50d**
[5]	^{1}H NMR and ^{13}C NMR Spectra of	**50e**
[6]	^{1}H NMR and ^{13}C NMR Spectra of	**50f**
[7]	^{1}H NMR and ^{13}C NMR Spectra of	**50g**
[8]	^{1}H NMR and ^{13}C NMR Spectra of	**50h**
[9]	^{1}H NMR and ^{13}C NMR Spectra of	**50i**
[10]	^{1}H NMR and ^{13}C NMR Spectra of	**50j**
[11]	^{1}H NMR and ^{13}C NMR Spctra of	**52**

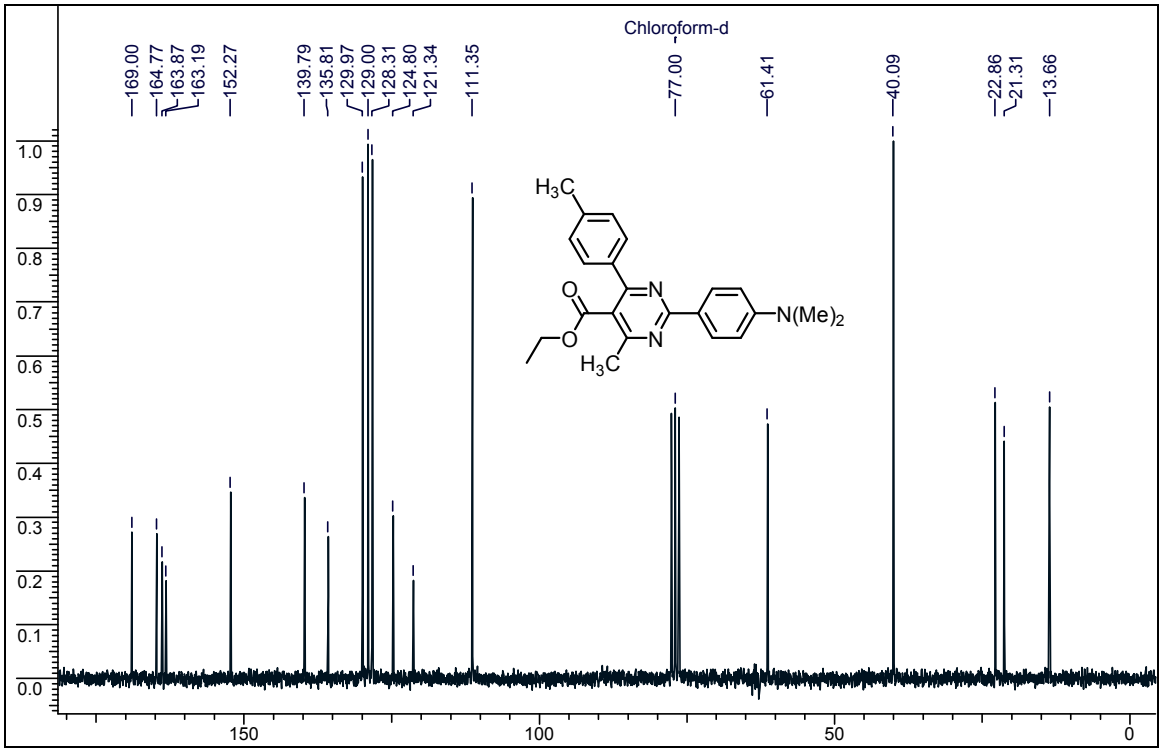
[1] ^{1}H NMR and ^{13}C NMR spectra of compound 50a



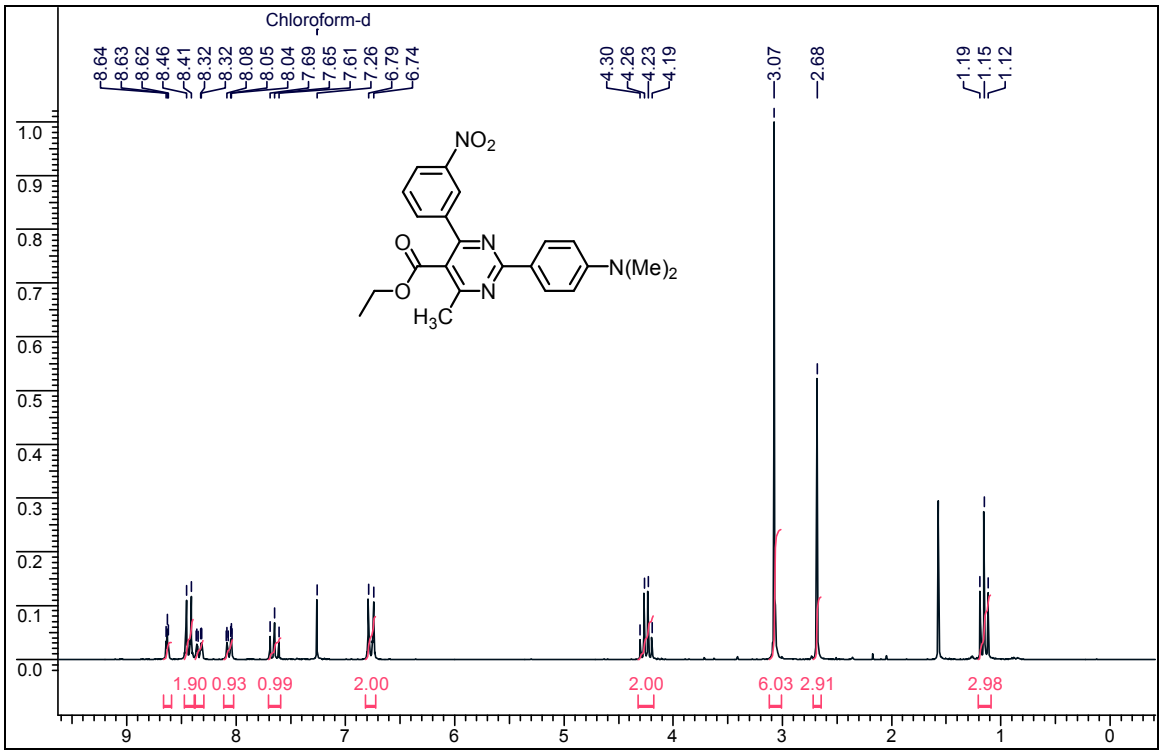


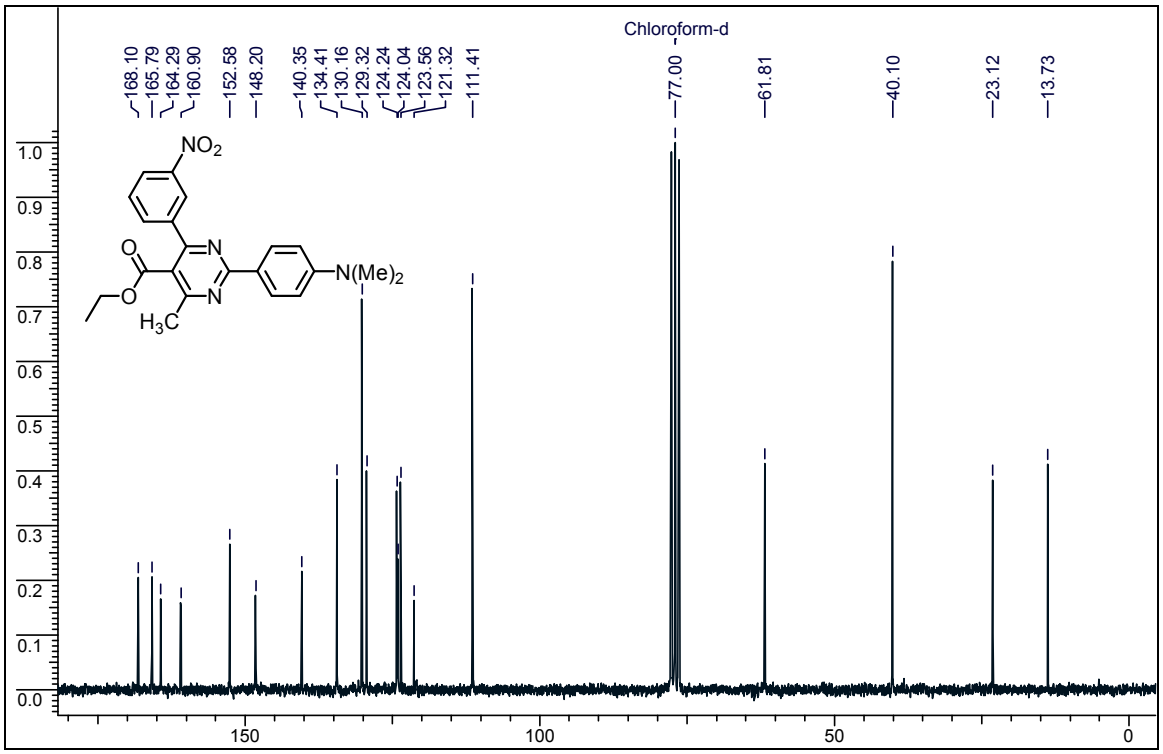
[2] ^{1}H NMR and ^{13}C NMR spectra of compound 50b



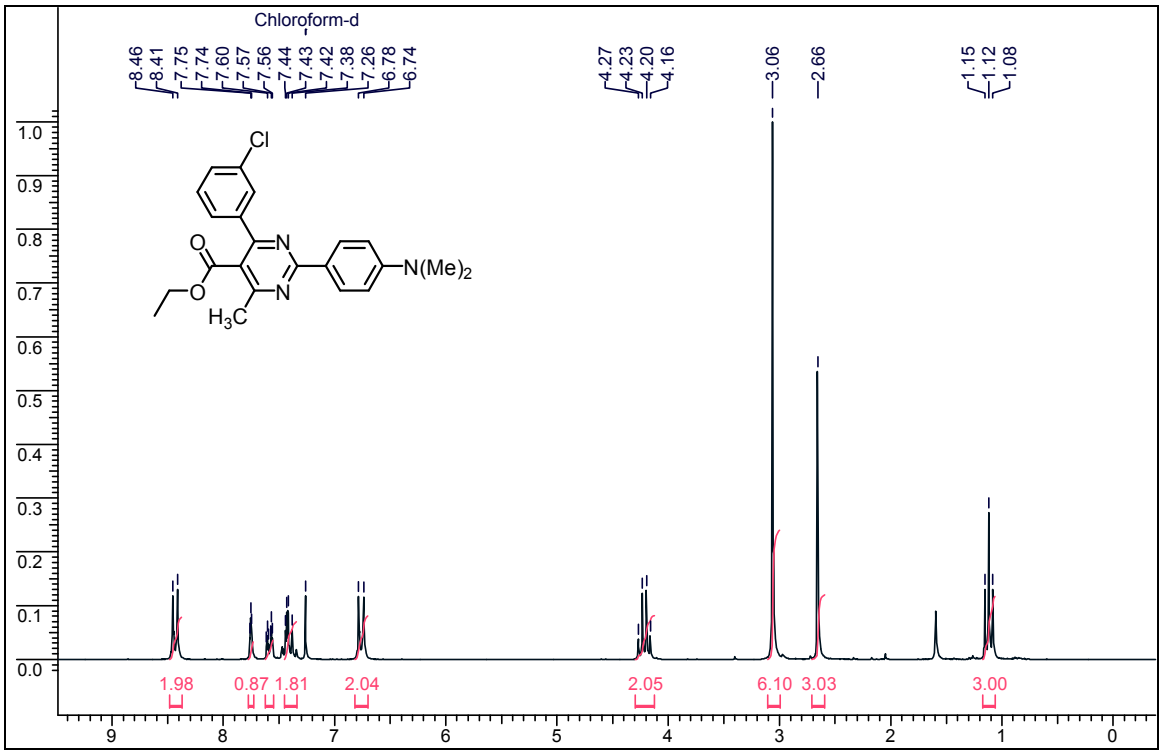


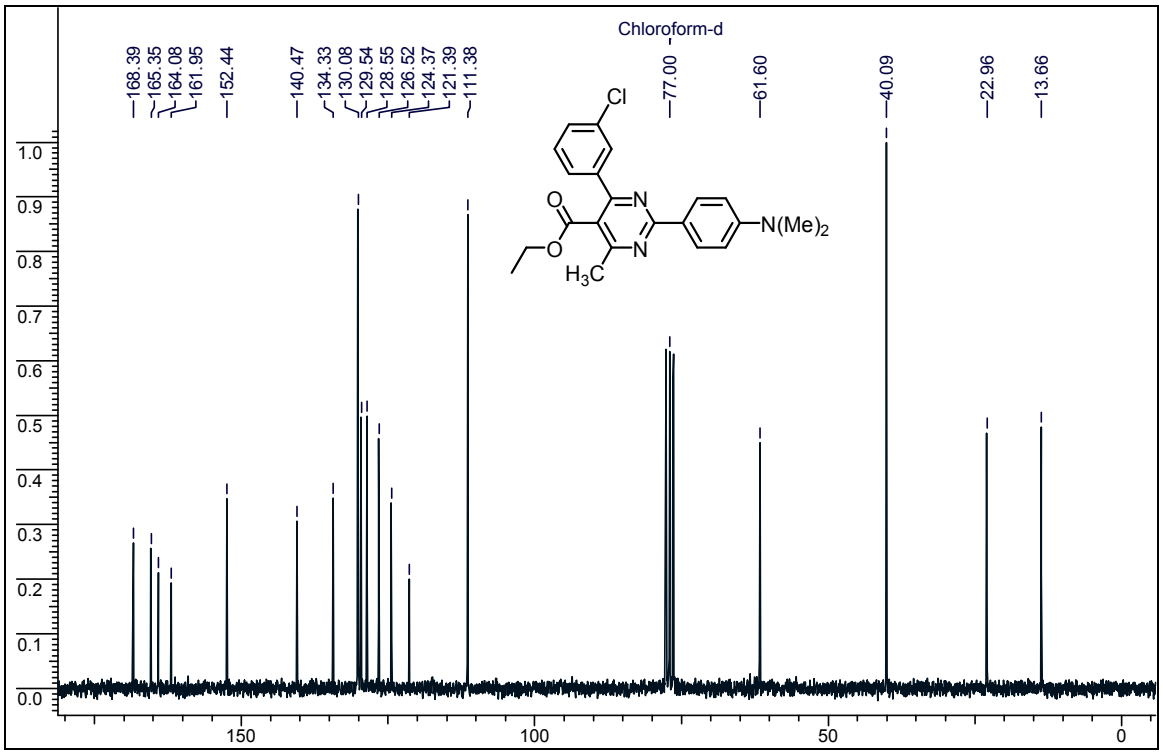
[3] ^{1}H NMR and ^{13}C NMR spectra of compound 50c



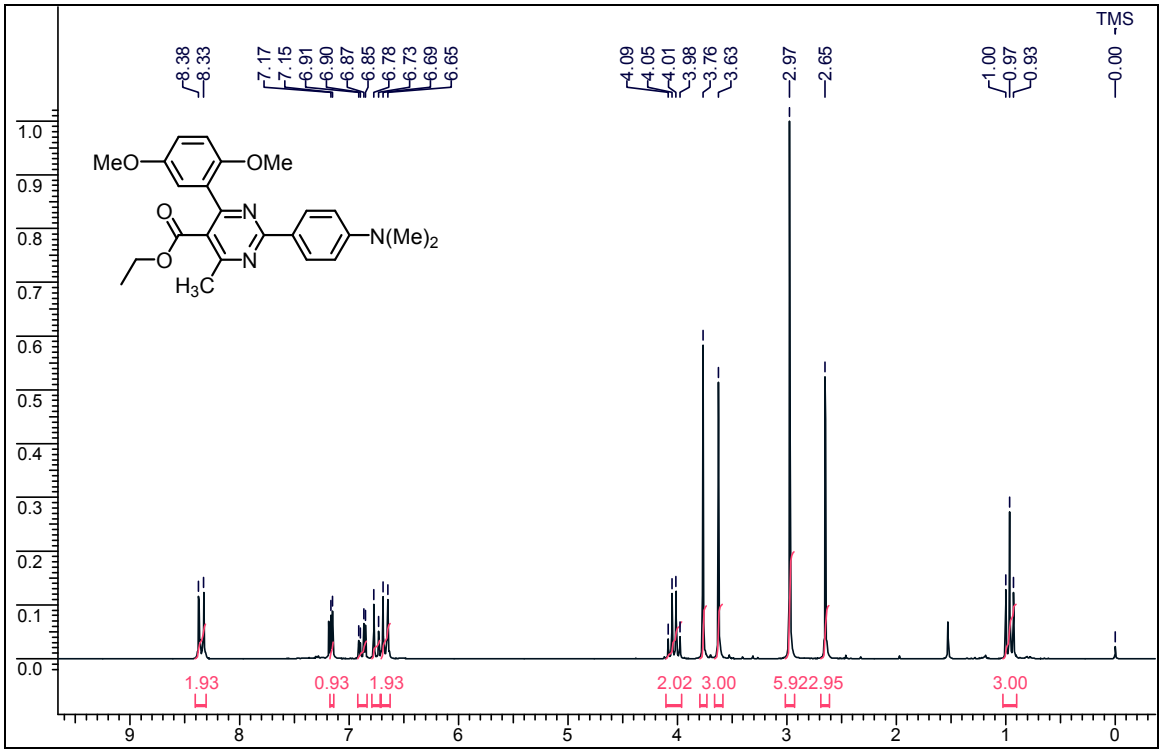


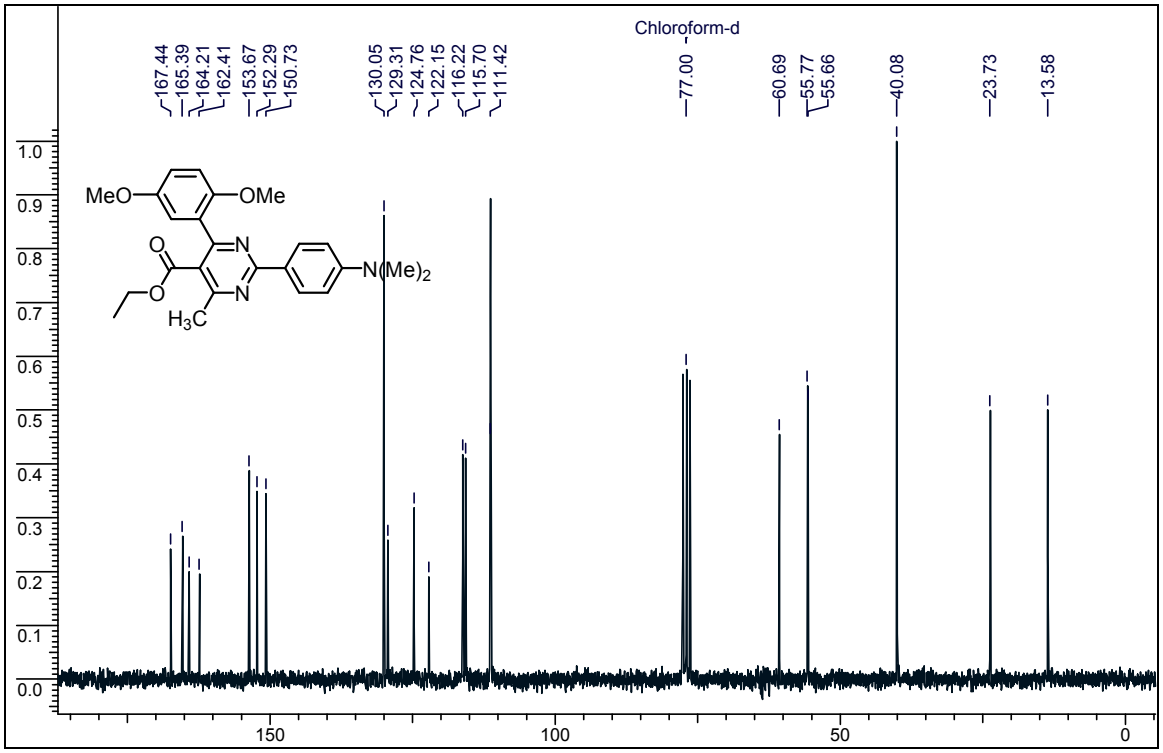
[4] ^{1}H NMR and ^{13}C NMR spectra of compound 50d



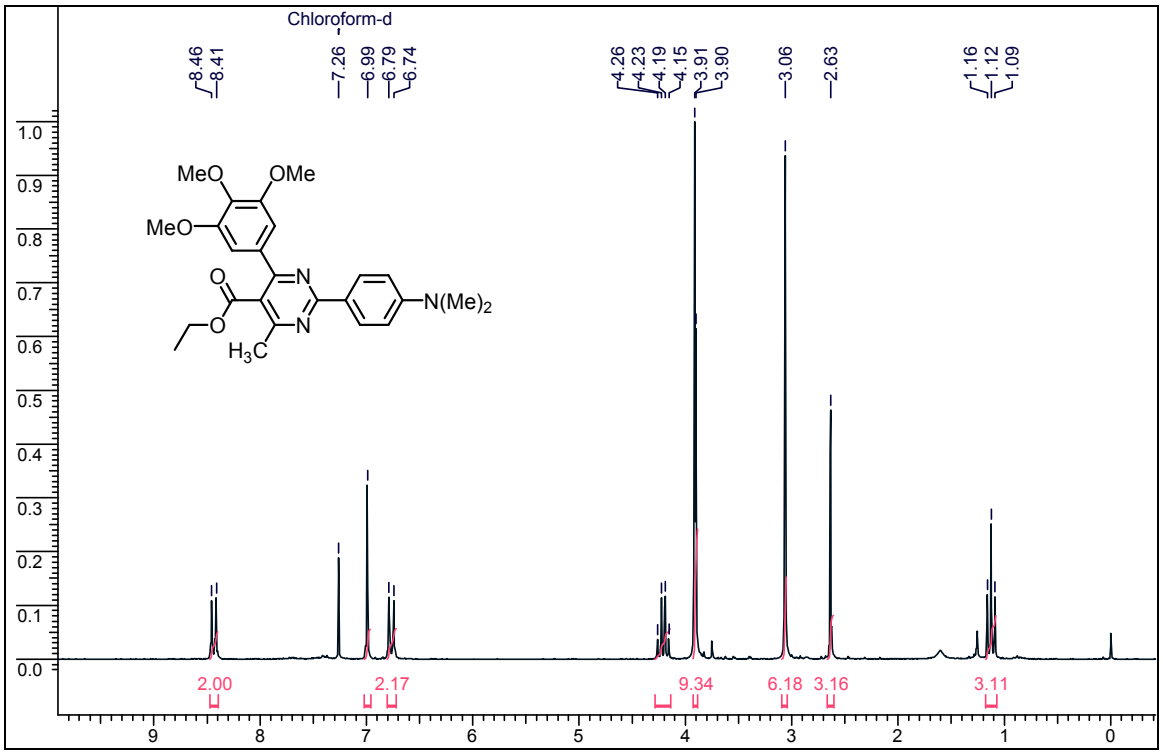


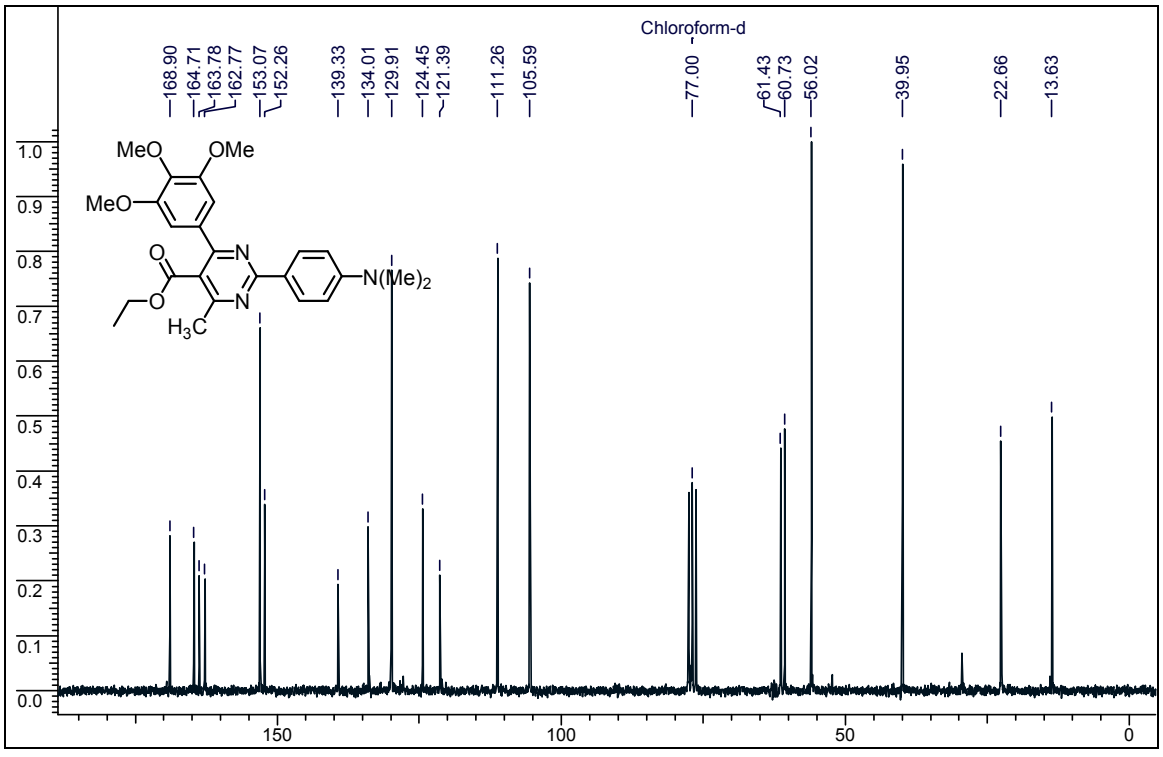
[5] ^{1}H NMR and ^{13}C NMR spectra of compound 50e



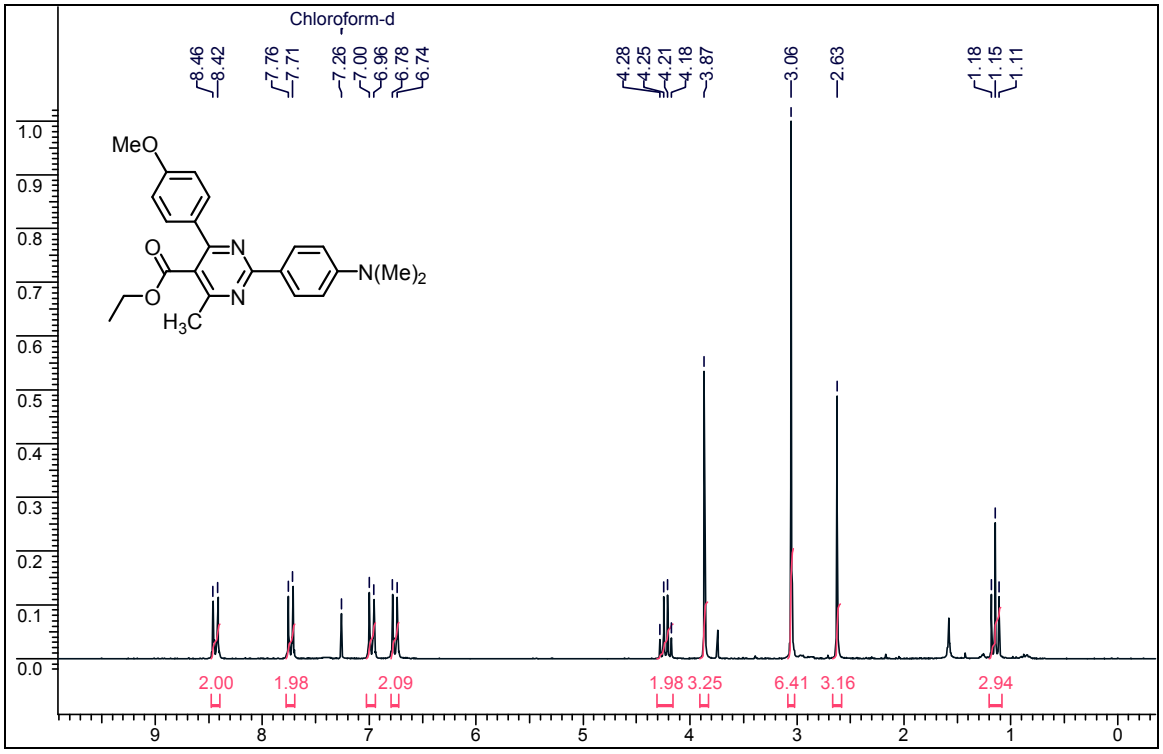


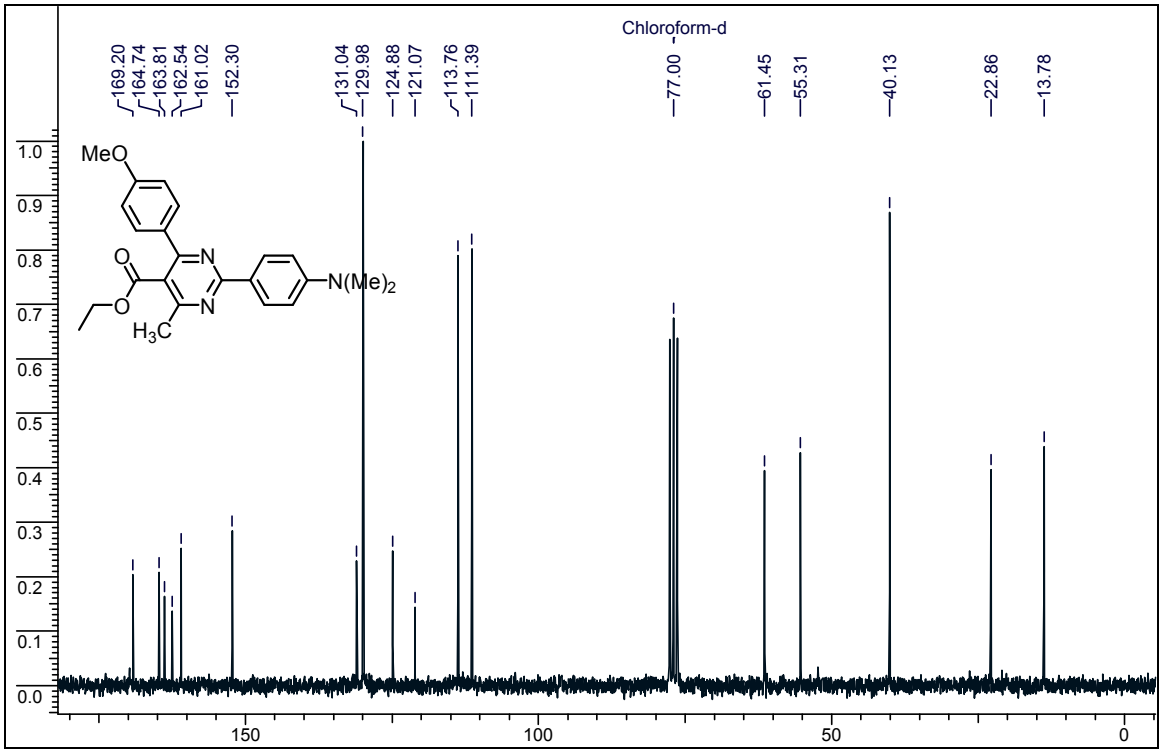
[6] ^{1}H NMR and ^{13}C NMR spectra of compound 50f



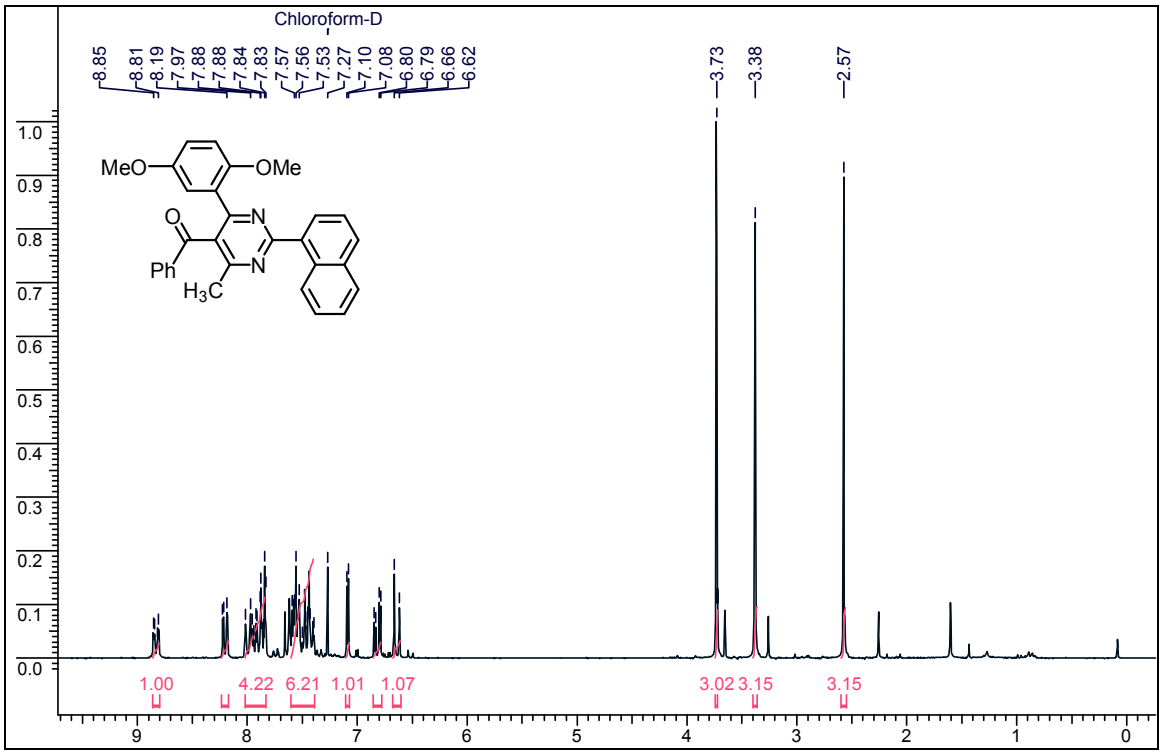


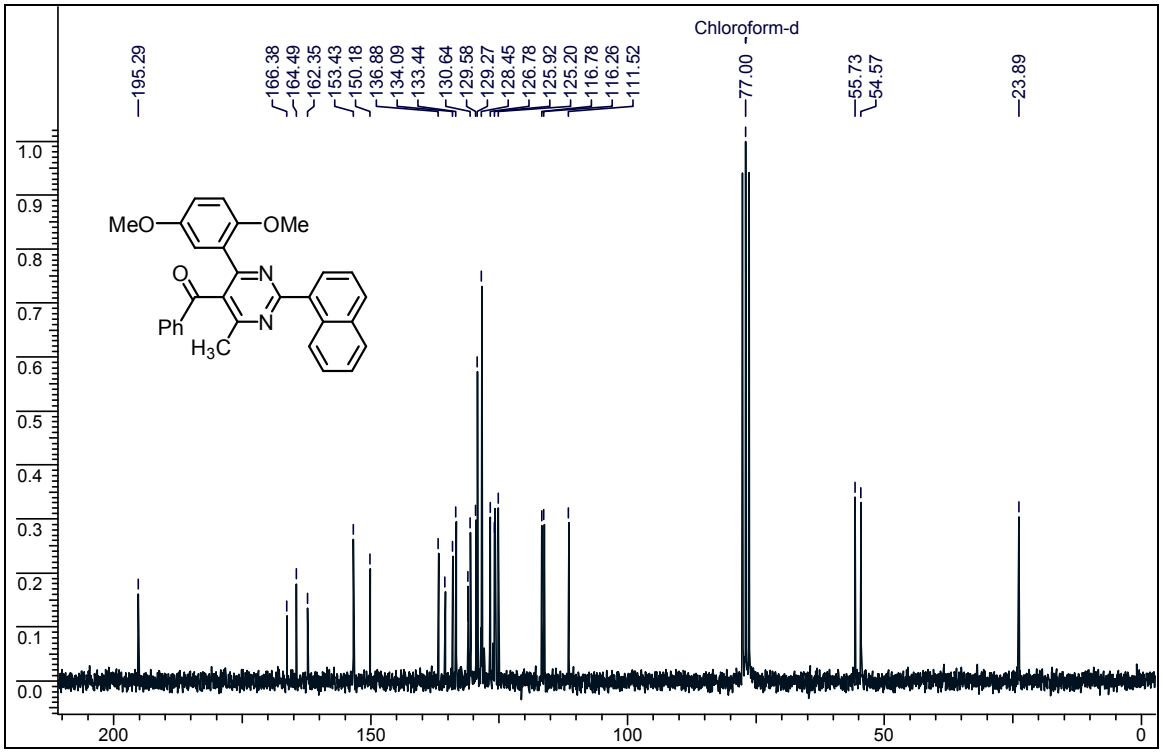
[7] ^{1}H NMR and ^{13}C NMR spectra of compound 50g



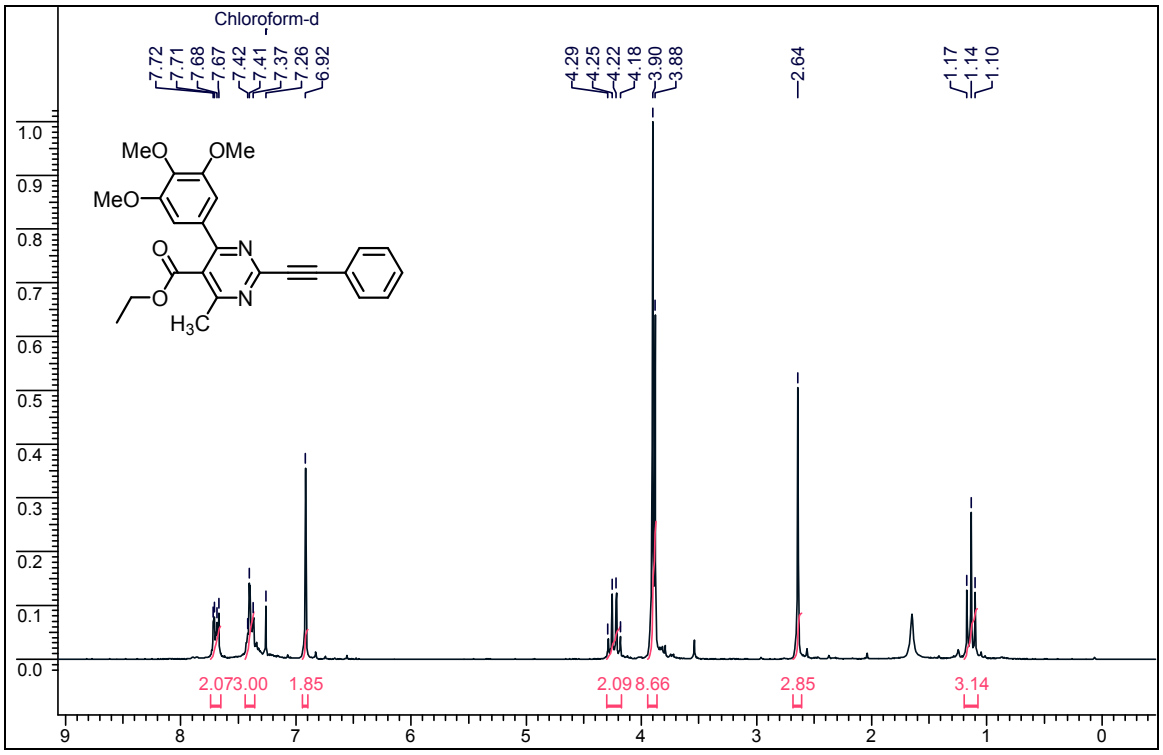


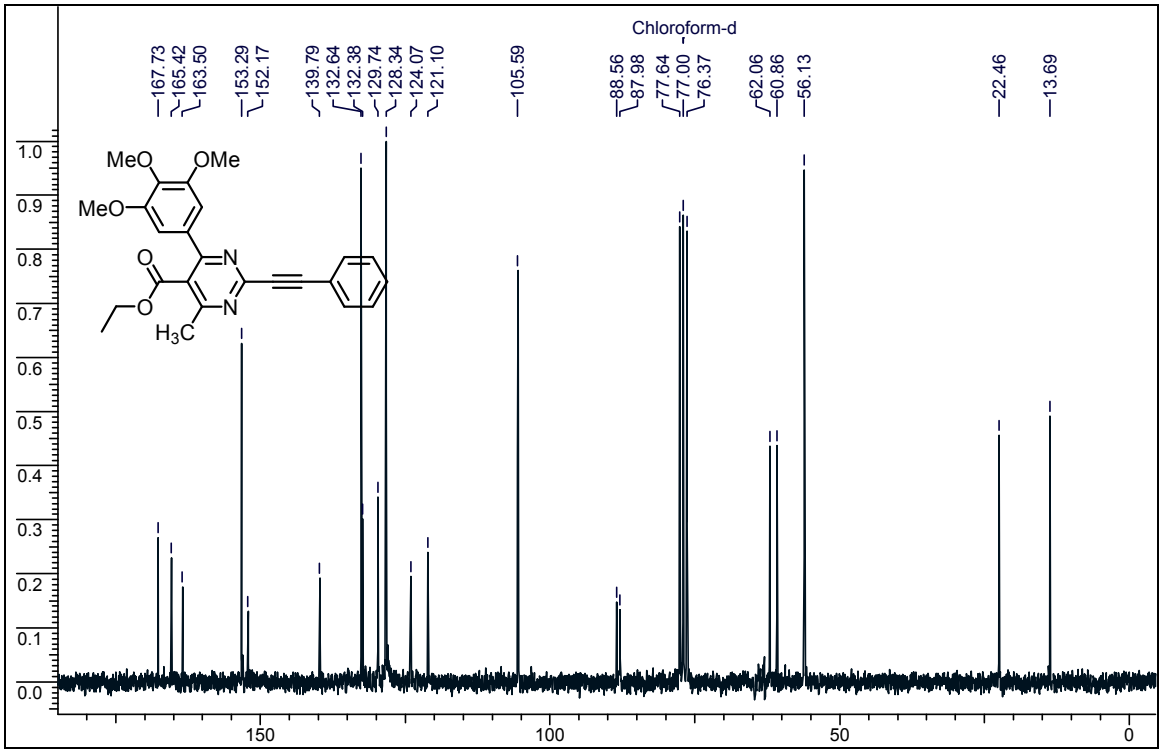
[8] ^{1}H NMR and ^{13}C NMR spectra of compound 50h



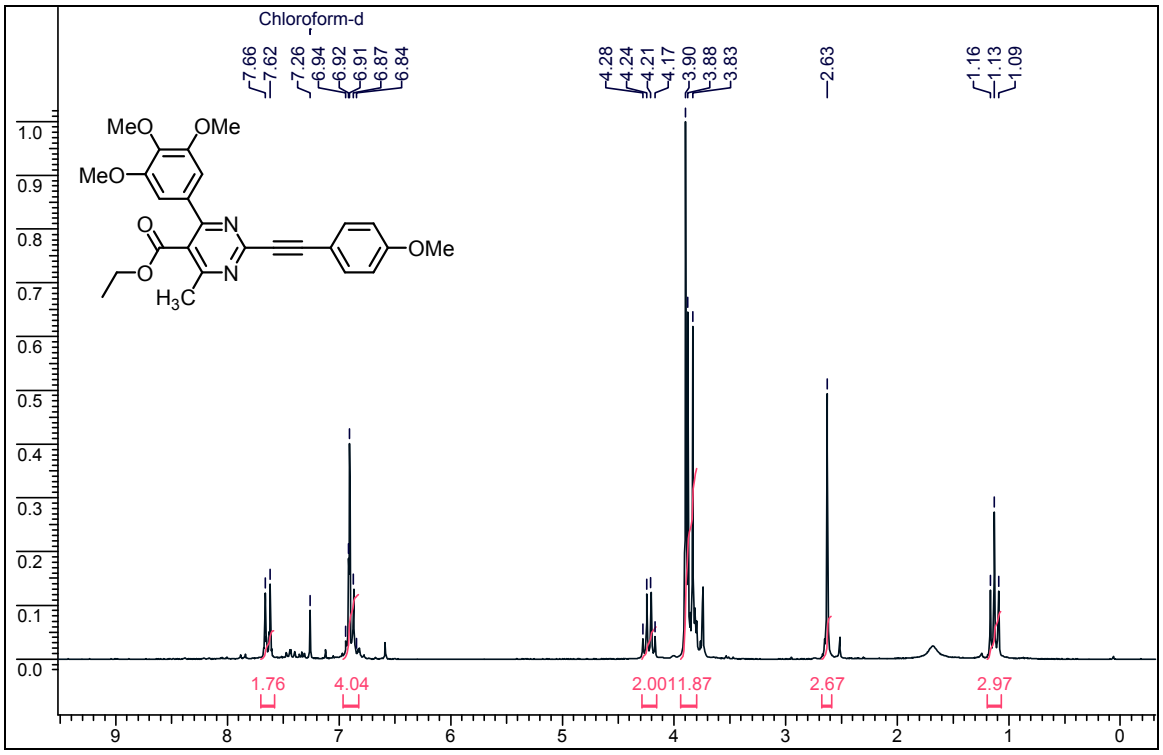


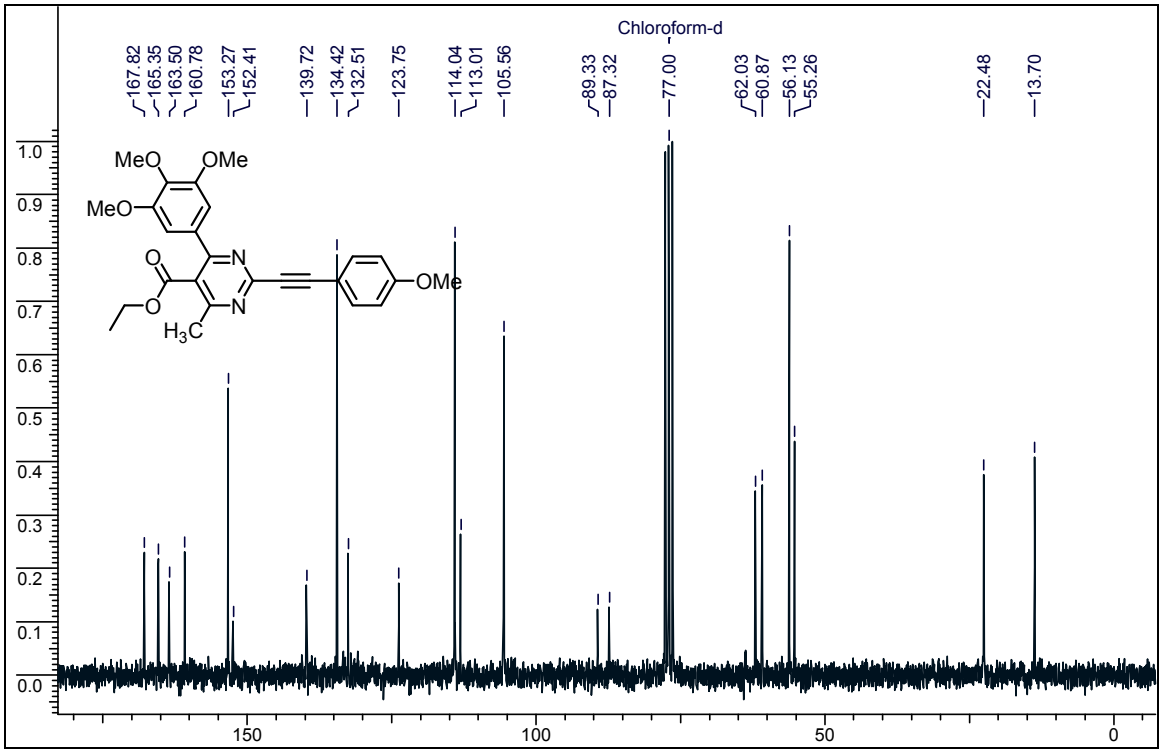
[9] ^{1}H NMR and ^{13}C NMR spectra of compound 50i



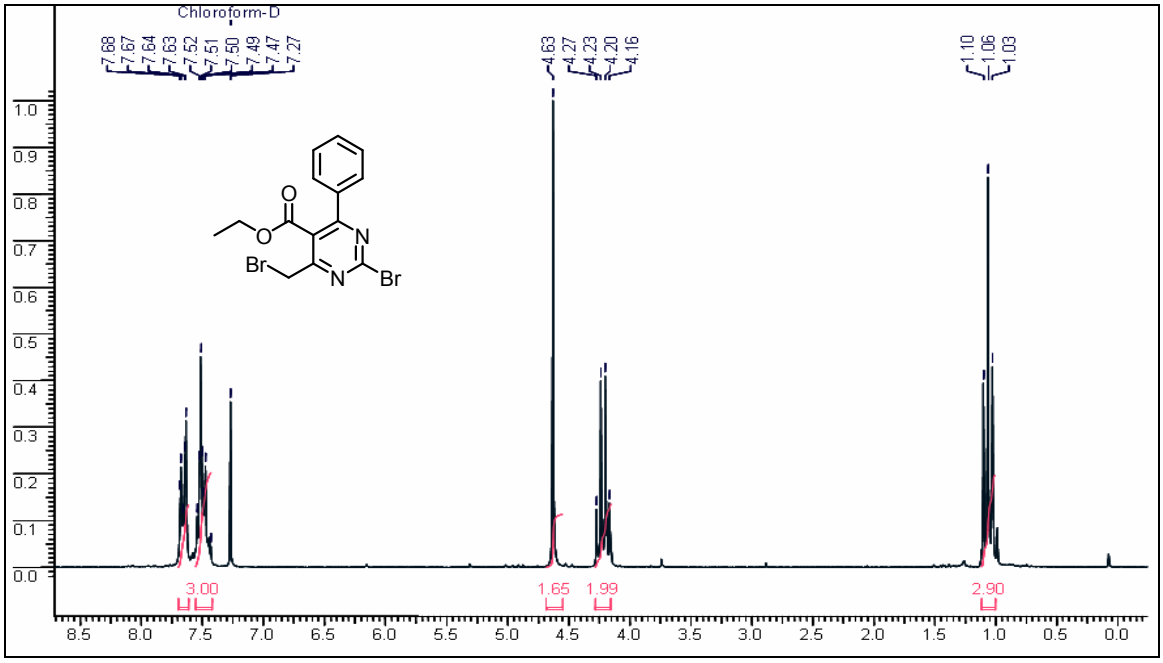


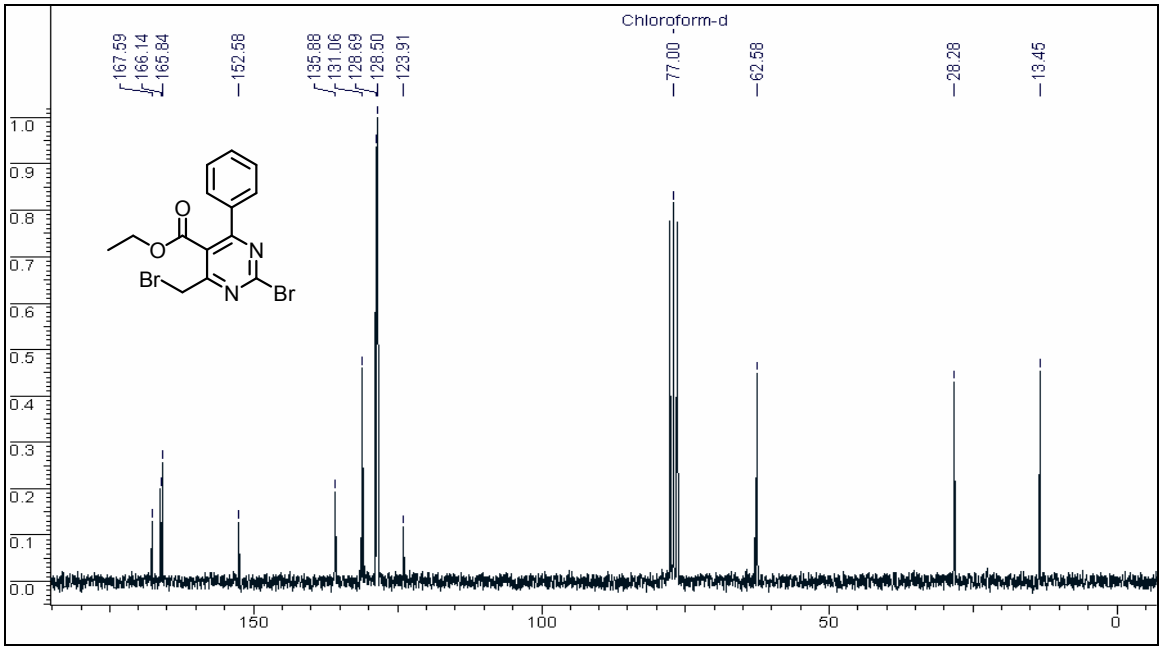
[10] ^{1}H NMR and ^{13}C NMR spectra of compound 50j





[11] ^{1}H NMR and ^{13}C NMR spectra of compound 52





3.2.8 References

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List of Publications

[1] Synthesis and evaluation of antifungal properties of a series of the novel 2-amino-5-oxo-4-phenyl-5, 6, 7, 8-tetrahydroquinoline-3-carbonitrile and its analogues. **Atul R. Gholap**, Kiran S. Toti, Fazal Shirazi, Ratna Kumari, Manoj Kumar Bhatt, Mukund V. Deshpande, K. V. Srinivasan,* ***Bioorg. Med. Chem.*** **2007**, *15,* 6705-6715.

[2] A novel process for the synthesis of class I antiarrhythmic agent (±) Cibenzoline and its analogues.

Atul R. Gholap, Vincent Paul and K. V. Srinivasan,* ***Synth. Commun.*** (Article is in press).

[3] A remarkably rapid regioselective synthesis of β-enaminones using silica chloride in a heterogeneous as well as an ionic liquid in a homogeneous medium at room temperature.

Atul R. Gholap, Narayan S. Chakor, Thomas Daniel, R. J. Lahoti and K. V. Srinivasan,* ***Journal of Molecular Catalysis A: Chemical*** **2006**, *245*, 37-46.

[4] Copper- and Ligand-Free Sonogashira Reaction Catalyzed by Pd (0) Nanoparticles at Ambient Conditions under Ultrasound Irradiation.

Atul R. Gholap, K. Venkatesan, Renu Pasricha, Thomas Daniel, R. J. Lahoti and K. V. Srinivasan,* ***J. Org. Chem.*** **2005,** *70*, 4869-4872.

[5] Ionic liquid promoted novel and efficient one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones at ambient temperature under ultrasound irradiation.

Atul R. Gholap, K. Venkatesan, Thomas Daniel, R. J. Lahoti, K. V. Srinivasan,* ***Green Chem.*** **2004**, 6, 147-150.

[6] Efficient Synthesis of novel antifungal Pyrimidines via Palladium catalyzed Suzuki/Sonogashira cross-coupling reaction from easily accessible Biginelli 3,4-Dihydropyrimidin-2(1*H*)-one.

Atul R. Gholap, Kiran S. Toti, Fazal Shirazi, Mukund V. Deshpande, K. V. Srinivasan,* ***Tetrahedron*** (Accepted).

[7] A Novel Palladium containing Enaminones as a Monoanionic bidentate complex for Suzuki, Heck and Sonogashira reaction.

Atul R. Gholap and K. V. Srinivasan* **Communicated to *Tetrahedron.***

[8] Sonochemical decarbonylation of acid chlorides catalyzed by palladium (0) nanoparticles at ambient conditions.

Atul R. Gholap and K. V. Srinivasan* **Communicated to *Ultrasonic Sonochemistry***

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