NOVEL SYNTHETIC METHODOLOGIES: IONIC LIQUID PROMOTED FRIEDLANDER HETEROANNULATION AND PALLADIUM-CATALYZED COPPER/LIGAND/SOLVENT FREE CARBON-CARBON COUPLING WITH HETEROCYCLIZATION REACTIONS

THESIS

Submitted to the

UNIVERSITY OF PUNE

For the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

BY

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Dedicated to my beloved

Parents

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October 15, 2007

CERTIFICATE

This is to certified that the work incorporated in the thesis entitled "**Novel Synthetic Methodologies: Ionic Liquid Promoted Friedlander Heteroannulation and Palladium-Catalyzed Copper/Ligand/Solvent Free Carbon-Carbon Coupling with Heterocyclization Reactions**" which is being submitted to the University of Pune for the award of **Doctor of Philosophy in Chemistry** by **Mr. Sanjay S. Palimkar** 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)

National Chemical Laboratory

Candidate's Declaration

I hereby declare that the thesis entitled "Novel Synthetic Methodologies: Ionic Liquid Promoted Friedlander Heteroannulation and Palladium-Catalyzed Copper/Ligand/Solvent Free Carbon-Carbon Coupling with Heterocyclization Reactions" 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.

(**Sanjay S. Palimkar**)
National Chemical Laboratory
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October 15, 2007

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Section B *Synthesis of an indole containing KDR kinase inhibitor by tandem Sonogashira coupling - 5 - endo - dig - cyclization as a key step*

Section C *Ultrasound-promoted copper-, ligand- and amine-free synthesis of benzo[b]furans/nitro benzo[b]furans via Sonogashira coupling-5-endo-dig-cyclization*

ACKNOWLEDGEMENT

I wish to express my sincere gratitude to my research supervisor ***Dr. Kumar V. Srinivasan****, for giving me the chance to work in this fascinating realm of chemistry. My interactions with him have improved my quality of research life. I sincerely thank him for his splendid guidance, constant support and excellent work ethics that he bestowed on me. I learnt from him be it chemistry or patience or perseverance.*

I would like to thank Dr. R. J. Lahoti, Dr. Thomas Daniel and Mr. Sharma Sir, for their affection, suggestions and support during my Ph. D program especially during the times of frustration.

A special thanks goes to Dr. U. R. Kalkote for their generosity and encouragement in pursuing carrier at NCL. Help rendered from all the senior scientists Dr. Pradeepkumar Tripathi, Dr. A. Sudalai, Dr. Vincent Pal, Dr. R. A. Joshi, and Dr. Muthukrishnan of NCL is gratefully acknowledged. I would also like to thank Dr. Dhavale for his fruitful suggestions during my work presentations.

I am thankful to Dr. M. K. Gurjar, (Former Head, Organic Chemistry: Technology Division), Dr. Ganesh Pandey (Head, Organic Chemistry Division) and Dr. Shivram, Director, NCL for giving me this opportunity and providing all necessary infrastructure and facilities. Financial assistance from CSIR, New Delhi is gratefully acknowledged.

I thank NMR, elemental analysis, IR, HPLC and CMC groups for their help in obtaining the analytical data. I am very thankful to Dr. Mohan M. Bhadbhade and Dr. Rajesh G. Gonade for fruitful discussions and valuable suggestions as well as for providing X-ray crystal structure analysis. I thank the library staff, chemical stores, purchase staff and glass blowing section NCL for their co-operation.

My sincere thanks for the help rendered by my labmates Harishkumar, Rashid, K. Venkatesan, Atul, Potewar, Jogdand, Kiran, Umesh, Narayan, Pujari, Sachin, Shapi, Udavant and Vijay more and also thanks to my seniors Dr. Rajagopal and Dr. Jarikote, who helped me through various phases of my tenure in the lab. It has been a great learning experience for me.

I would like to thanks all my friends in NCL Ajay Kale, Drugkar, Amol, Pushpesh, Kondekar, Kotkar, Ramesh, Victor, Pandu, Giri, Namdev, Bapu, Nilkant, Sailesh, Gaikwad, Dipak, Jogdand and Ramdas etc. who made my tenure at NCL cheerful.

I am thankful to my mentors at my Schools, College and University for their inspirational teaching, ethics and discipline. I acknowledge all my college friends Dr. Vartale, Dr. Shindalkar, Vikram Patil, Manoj Deshpande, Annapure etc. for their wonderful company during my college days.

No word would suffice to express my gratitude and love to my parents, sisters, brother Dr. Dilip Palimkar and all family members for their continuous showering of boundless affection on me and supporting me in whatever I chose or did. I owe much towards my wife Jyoti for her patience and encouragement throughout my career. I thank my son Master Aryan for making my life more beautiful than it was.

I wish to thank great scientific community whose achievements are constant source of inspiration for me.

The completion of this work could not have been accomplished without generous help and perseverance of number of people. I would like to thank every one of them for the help they rendered for the accomplishment of work presented in this dissertation.

Finally, my acknowledgement would not be complete without thanking the almighty, for giving me the strength and the determination to overcome the hardship faced in my life.

Sanjay S. Palimkar

General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned and (silica gel, 60-120 mesh/100-200 mesh/230-400 mesh).
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60 F_{254}) with UV light and I_2
- All melting points are uncorrected and the temperatures are in the centigrade scale. Melting points were recorded in open capillary using Buchi melting point B-540 apparatus.
- The compound numbers, Scheme numbers, Figure numbers and Tables numbers given in each Chapter refers to that particular Chapter only. However independent referencing is used for each Section and introduction of chapter II and III.
- Organic layers were dried over anhydrous magnesium sulfate.
- ^{1}H NMR spectra were recorded on Bruker Avance AC-200 MHz and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz and DRX-125 MHz spectrometers.
- Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR Spectrometer.
- Elemental analysis was performed on Flash EA 1112 Thermo Finnigan Instrument.
- Starting materials were obtained from commercial sources or prepared using known procedures.
- Mass spectra were recorded on Finnigan-Mat 102 ^{0}C mass spectrometer and were obtained at an ionization potential of 70 eV.

Abbreviations and Symbols

Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
$[bbim]^+$	Di-n-butylimidazolium
BF_4^-	Tetrafluoroborate
$[bmim]^+$	n-Butylmethylimidazolium
Boc	*t*-Butoxycarbonyl
^tBu	*t*-butyl
br s	Broad singlet
ClO_4^-	Chlorate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DMA	Dimethyl acetamide
DMF	N,N-Dimethyl form amide
eq	Equivalent(s)
Et	Ethyl
EtOAc	Ethyl acetate
$[emim]^+$	Ethylmethylimidazolium
g	Gram
GC	Gas Chromatography
h	Hours
$[Hbim]^+$	n-Butylimidazolium
$[hmim]^+$	n-Hexylmethylimidazolium
Hz	Hertz
ILs	Ionic liquids
Im	Imidazole
IR	Infra red

KDR	kinase insert domain receptor
LDA	Lithium diisopropylamide
M	Molar
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmol	Millimole(s)
M.P.	Melting point
Ms	Methanesulfonyl
MS	Mass spectrum
MsCl	Methanesulfonyl chloride
NMP	N-Methylpyrrolidinone
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect /enhancement
NOESY	Nuclear Overhauser enhancement spectroscopy
ORTEP	Orthogonal thermal ellipsoid plots
Pd/C	Palladized carbon
PF_6^-	Hexafluorophosphate
Ph	Phenyl
PPh_3	Tri phenyl phosphine
ppm	Parts per million
py	pyridine
rt	Room temperature
TBAA	*Tetra*-n-butyl ammonium acetate
TBABr	*Tetra*-n-butyl ammonium bromide
TBAF	*Tetra*-n-butyl ammonium fluoride
TBAOH	*Tetra*-n-butyl ammonium hydroxide
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMG	Tetra methyl guanidine
TMS	Trimethylsilane
Ts	Tosyl
TsCl	*p*-Toluenesulfonyl chloride

Abstract

The thesis entitled "**Novel synthetic methodologies: Ionic liquid-promoted Friedlander heteroannulation and palladium-catalyzed copper/ligand/solvent free carbon-carbon coupling with heterocyclization reactions''** has been divided into three chapters.

The title of the thesis clearly reflects the objective, development of novel and efficient synthetic methods for the construction of carbon-carbon bonds and synthesis of biologically active heterocycles. **Chapter I** is divided into three sections, Section A provides the brief introduction to ionic liquids and Section B describes the synthesis and characterization of novel ionic liquids. Section C of this chapter deals with the efficacy of synthesized ILs for the Friedlander heteroannualtion and synthesis of a variety of quinolines and fused polycyclic quinolines by using ionic liquid as a recyclable reaction medium as well as a promoter. **Chapter II** describes the eco-friendly methods for the synthesis of versatile synthetic intermediates ynones and β-enaminones and biologically active heterocycle *viz.* 1, 5- Benzodiazepines. It is divided into three sections, Section A of this chapter describes an efficient, rapid method for the synthesis of versatile synthetic intermediate ynones under copper-, ligand- and solvent-free conditions by using $Pd(OAc)_2$ as a catalyst and Section B describes the one-pot three-component synthesis of potentially valuable synthetic intermediate β-enaminones under solvent-free conditions. A novel one-pot three-component synthesis of 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines in water is described in Section C. **Chapter III** is divided into three sections, Section A deals with efficient synthesis of indoles, Section B describes novel synthetic route to the synthesis of novel, potent and selective KDR kinase inhibitor which has potential use in cancer therapy by using Sonogashira coupling-5-*endo*-*dig*-cyclization strategy. In Section C improved method for the synthesis of benzo[b]furan/nitro benzo[b]furans is discussed.

Chapter I: Ionic Liquid-Promoted Regiospecific Friedlander Annulation: Novel Synthesis of Quinolines and Fused Polycyclic Quinolines

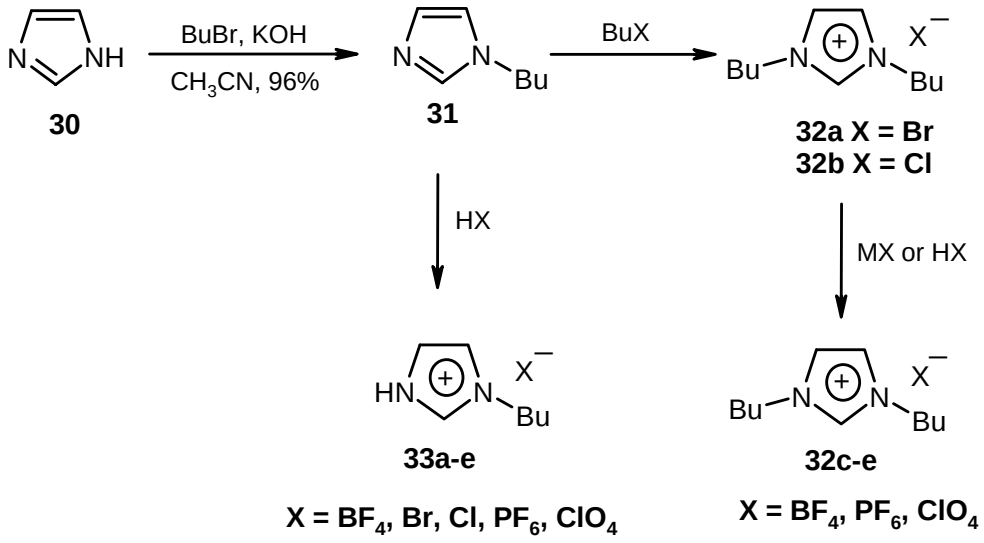
This chapter is divided into three Sections, Section A provides the brief introduction to ILs, Section B deals with the synthesis and characterization of novel ionic liquids and in Section C studied their efficacy for Friedlander heteroannulation.

Section A: Introduction to ionic liquids

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. What features makes ILs so attractive? Explained with reasons behind it.

Section B: Synthesis and characterization of novel ILs based on 1-n-butyl and 1, 3-di-n-butyl imidazolium salts

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



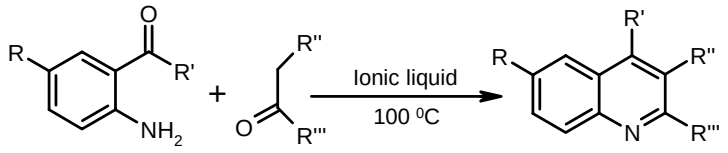
Scheme 1

They were fully characterized by ^{1}H and ^{13}C NMR Spectroscopy, mass and elemental analyses. 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.

Section C: Ionic Liquid-Promoted Synthesis of Quinolines by Friedlander Heteroannulation

The quinoline nucleus occurs in several natural compounds (cincona alkaloids) and pharmacologically active substances displaying a broad range of biological activity.

This section describes the evaluation of the effect of several room-temperature ionic liquids (ILs) based on 1-(n-butyl) imidazolium $[Hbim]^+$ and di- (n-butyl) imidazolium $[bbim]^+$ cations with various anions with varying basicity on the Friedlander heteroannulation reaction. On screening, 1-butylimidazolium tetrafluoroborate $[Hbim]BF_4$ was found to be the best ionic liquid for the heteroannulation reaction and the reasons to this effect are well explained. The reactions proceed very well under relatively mild conditions without any added catalyst. The IL acts as a promoter for this regiospecific synthesis and can be recycled. By this green approach, various biologically active substituted quinolines and fused polycyclic quinolines were prepared in excellent yields as shown in **Scheme 2.**



57 **58a-k** **59a-v**

57a R = H, R' = CH_3
57b R = Cl, R' = Ph

Scheme 2

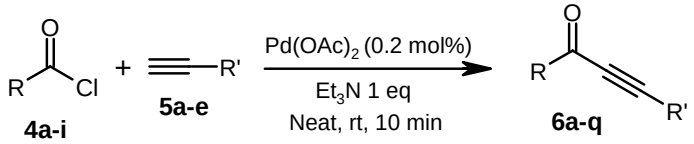
Chapter II: Eco-friendly synthesis of ynones, β-enaminones and 1, 5- benzodiazepines

Sustainability is increasingly an important issue in the wider context dealing with population, health, the environment, energy, technology, renewable resources, and, in the sciences, as an integral part of the rapidly emerging field called Green Chemistry. This chapter describes the green process for the synthesis of ynones**,** β-enaminones and 1, 5- benzodiazepines and it is divided into three Sections.

Section A: *Copper-, ligand-* and *solvent*-free synthesis of ynones by coupling acid chlorides with terminal alkynes

Ynones are of considerable synthetic interest because of their widespread occurrence among natural products and their physiological properties. They are extremely versatile intermediates for the synthesis of important biologically active heterocycles.

This Section describes a simple, efficient, rapid, *copper*-, *ligand*-, and *solvent*-free synthesis of ynones by coupling of a variety of acid chlorides with terminal alkynes as shown in **Scheme 3**.



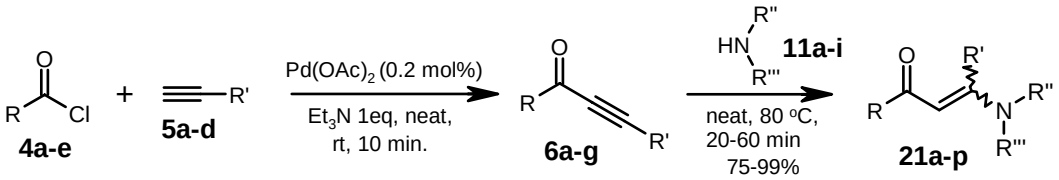
4a-i **5a-e** **6a-q**

Scheme 3

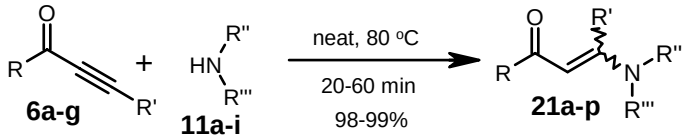
Section B: A simple and efficient one-pot three-component *solvent-Free* synthesis of β-enaminones *via* Sonogashira coupling-Michael addition sequences

β-enaminones are versatile synthetic intermediates, extensively employed in organic synthesis. In particular, such compounds are important precursors for the synthesis of a wide variety of heterocycles.

A simple, efficient and environment friendly, solvent-free, one-pot three-component synthesis of β-enaminones *via* coupling of acid chlorides with terminal alkynes followed by the *in situ* Michael addition of the resulting ynones with amines in good to excellent isolated yields has been developed and described in this section as shown **Scheme 4.**



and

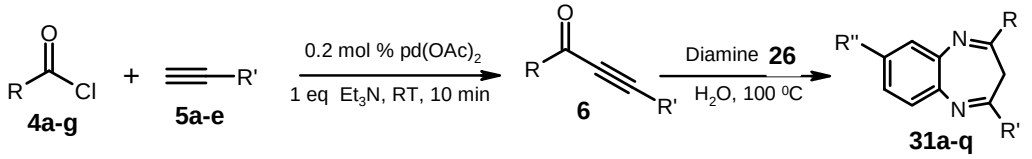


Scheme 4

Section C: A novel one-pot three-component synthesis of 2, 4-disubstituted- 3*H*-benzo[*b*][1,4]diazepines in water

Benzodiazepines and their polycyclic derivatives, target molecules of the present work are a very important class of bioactive compounds, widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative and anti-depressive agents.

A novel one-pot three-component synthesis of 2,4-disubstituted-3*H*-benzo[b][1,4]diazepines *via* the coupling of acid chlorides with terminal alkynes followed by the *in situ* Michael addition and cyclocondensation of the resulting ynones with *o*-phenylenediamines (OPDs) using water as a solvent as shown in **Scheme 5** is described in this section.



Scheme 5

Chapter III : Synthesis of an indole, KDR kinase inhibitor and benzofurans *via* Sonogashira coupling-5-*endo-dig*-cyclization

Heterocyclic compounds are worth our attention for many reasons; chief among them are their biological activities, and many drugs are heterocycles. Therefore, organic chemists have been making extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations.

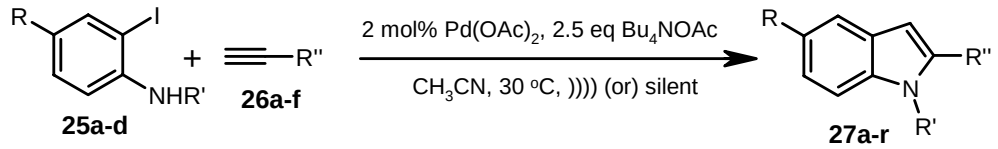
Palladium-catalyzed processes have proven to be a powerful and useful tool for the synthesis of heterocycles. The palladium-catalyzed Sonogashira coupling-5-*endo-dig*-cyclization of terminal alkynes has proven to be extremely useful for the one-pot synthesis of a wide variety of N-heterocycles, O-heterocycles and S-heterocycles etc.

In this chapter, improved methods for the synthesis of indoles and benzo[b]furans by tandem Sonogashira coupling-5-*endo-dig*-cyclization strategy is described. Synthesis of a novel potent and selective KDR kinase inhibitor 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2- yl]quinoline-2-(1*H*)-one (**28**) by using the same strategy is described in this Chapter.

Section A: Ligand-, copper-, and amine-free one-pot synthesis of 2-substituted indoles *via* Sonogashira coupling 5-*endo-dig*-cyclization

The substituted indole nucleus [indole is the acronym from *indigo* (the natural dye) and *ole*um (used for the isolation)] is a structural component of a vast number of biologically active natural and unnatural compounds. The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents.

The conditions were optimized for the one-pot synthesis of 2-substituted indoles **27** *via* palladium acetate catalyzed tandem Sonogashira coupling 5-*endo*-*dig*-cyclization at room temperature under ultrasonic irradiation and standard stirred conditions respectively. An efficient protocol for one-pot synthesis of 2-substituted indoles **27** *via* Sonogashira coupling 5-*endo*-*dig* cyclization under *ligand*-, *copper*-, and *amine*-free conditions at room temperature under ultrasonic irradiation and silent stirred conditions respectively has been developed which is described in this Section as shown in **Scheme 6.**



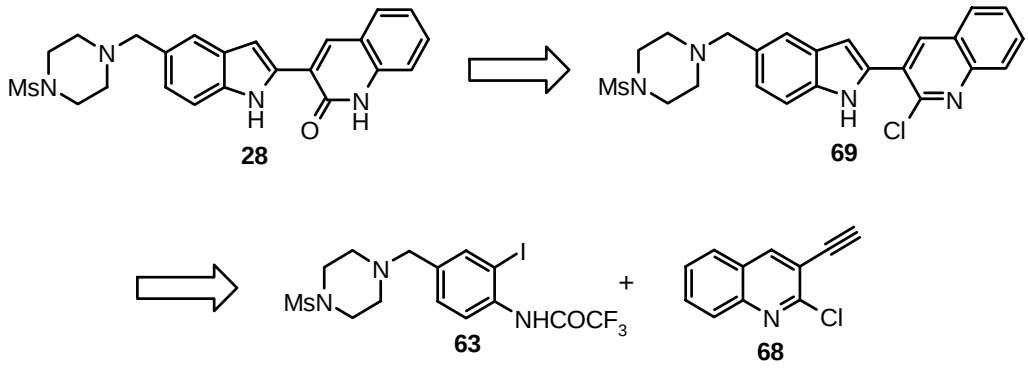
Scheme 6

Section B: Synthesis of an indole containing KDR kinase inhibitor by tandem Sonogashira coupling - 5 - *endo* - *dig* - cyclization as a key step

The kinase insert domain receptor (KDR) is a tyrosine kinase that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor induced angiogenesis. Compounds which inhibit, modulate or regulate the KDR receptor are useful for the prevention and treatment of tumor induced angiogenesis.

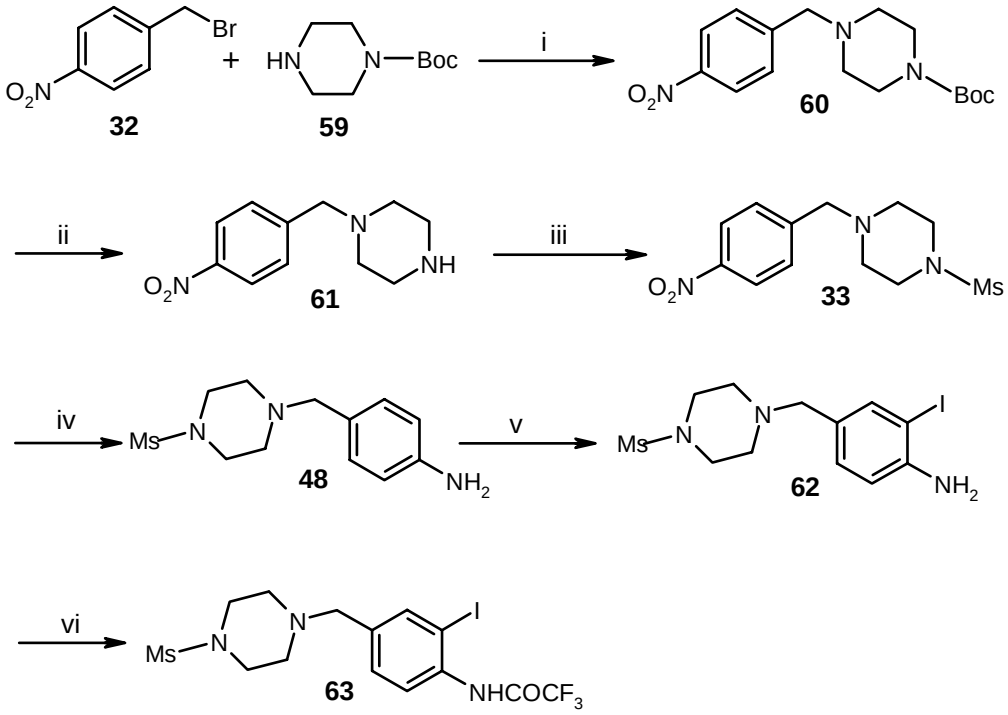
This Section describes a novel route to synthesis of KDR kinase inhibitor using Sonogashira coupling-5-*endo*-*dig*-cyclization as a key step.

A retro synthetic analysis of **28** revealed that the synthesis of **28** could be achieved by a Sonogashira coupling-5-*endo*-*dig*-cyclization **Scheme 7**. A tandem coupling-cyclization between substituted *o*-iodoanilide **63** and 2- chloro-3- ethynyl quinoline **68** would give the indole-chloroquinoline **69**. The indole-chloroquinoline **69**, which is known to readily hydrolyze upon treatment with a 1:1 mixture of acetic acid/water will give the indole-quinolone core.[4a]



Scheme 7. Retro synthetic Key Steps for the Synthesis of KDR Kinase Inhibitor 28.

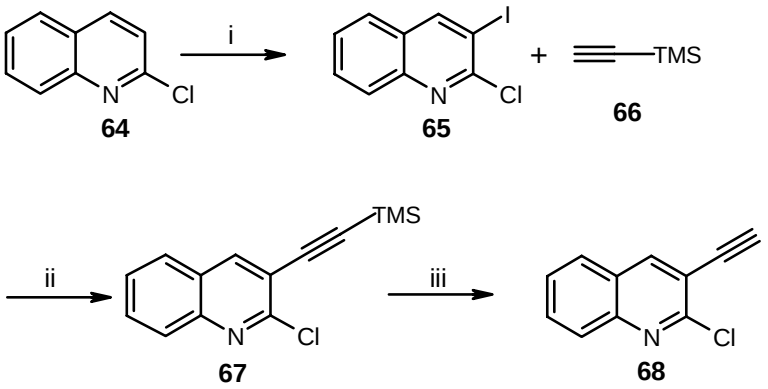
The *o*-iodoanilide fragment **63** was conveniently constructed from the commercially available 4-nitrobenzyl bromide **32** and N-boc piperazine **59** in six reaction steps as shown in **Scheme 8.**



Scheme 8

Reagents and conditions: (i) Na_2CO_3, DMF, 0 ^oC to rt, 6 h,96% (ii) TFA : DCM, 0 ^oC to rt, 3 h, 99% (iii) MsCl, Et_3N, DCM, 0 ^oC to rt, 6 h, 98%, (iv) Pd/C, EtOAc, H_2, rt, 24 h, 86% (v) Ipy_2BF_4, DCM, -30 ^oC to 0 ^oC, 18 h, 65%, (vi) $(CF_3CO)_2O$, Et_3N, THF, -15 ^oC to rt,13 h, 90%.

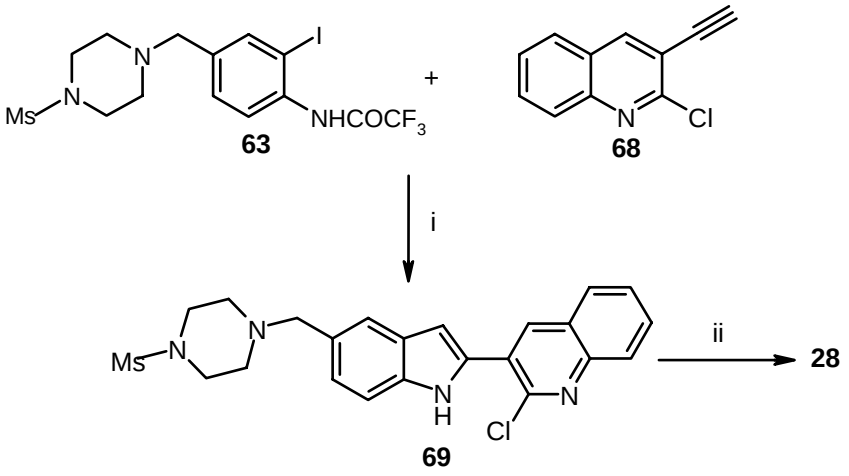
The synthesis of the other coupling partner 2-chloro-3-ethynyl quinoline **68** was successfully accomplished starting from the commercially available 2-chloroquinoline **64** as shown in **Scheme 9.**



Scheme 9

Reagents and conditions: (i) BuLi, DIPA, I_2, -78 ^oC to rt, THF, 8 h, 75% (ii) $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, 80 ^oC, 3 h, 98% (iii) K_2CO_3, MeOH, rt, 1 h, 96%.

Palladium-catalyzed tandem Sonogashira coupling-5-*endo*-*dig*-cyclization of *o*-iodoanilide derivative **63** with terminal alkyne **68** proceeded smoothly in acetonitrile by using $Pd(OAc)_2$ as the catalyst, Bu_4NOAc as the base under *ligand-, copper-* and *amine-* free conditions to give the indole-chloroquinoline **69** as a pale yellow foamy solid in good yield (80%) as shown in **Scheme 10.** The deprotection of the masked quinolin-2-one moiety of chloroquinoline **69** to get target compound **28** was accomplished in a straightforward manner under acidic conditions. Hydrolysis of chloroquinoline **69** in a 1:1 mixture of acetic acid/water as per the method reported in literature gave KDR inhibitor **28** in 93% yield.



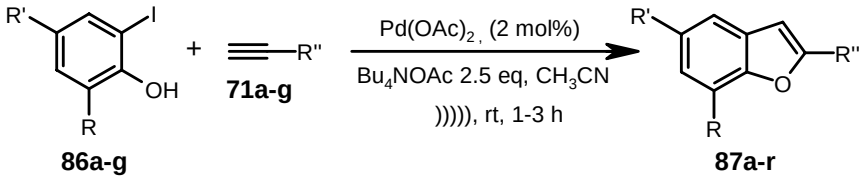
Scheme 10. Sonogashira coupling-5-*endo*-*dig*-cyclization

Reagents and conditions: (i) $Pd(OAc)_2$ (2 mol%), Bu_4NOAc (2.5 eq), CH_3CN, 85 ^oC, 12 h, 80% (ii) AcOH:H_2O, 110 ^oC, 16 h, 93%.

Section C: Ultrasound-promoted copper-, ligand- and amine-free synthesis of benzo[*b*]furans/nitro benzo[*b*]furans *via* Sonogashira coupling-5-*endo*-*dig*-cyclization

Benzo[*b*]furan derivatives are of considerable interest because of their occurrence in a wide range of natural substances and biologically active compounds.

In this section, the results obtained from the optimization of reaction conditions for the synthesis of benzo[*b*]furans are discussed. A simple and efficient ultrasound-promoted $Pd(OAc)_2$ catalyzed one-pot synthesis of 2-substituted benzo[*b*]furans/nitro benzo[*b*]furans **87** *via* a Sonogashira coupling-5-*endo*-*dig*-cyclization protocol under *copper-, ligand-* and *amine-free* conditions at room temperature is described in this Section as sown in **Scheme 11.**



Scheme 11

Note: Scheme numbers given in Abstract are different from those given in Chapters.

Chapter I

Ionic Liquid-Promoted Regiospecific Friedlander Annulation: Novel Synthesis of Quinolines and Fused Polycyclic Quinolines

Section A

Introduction to Ionic Liquids

1.1.0 Introduction

Most of the chemical reactions carried out in the laboratory as well as in industry take place in solution. Also solvents are used in the later stage of reaction, for example extraction and purification of the products. That means chemistry is dominated by the study of the species in solution. When planning an organic reaction, one of the major concerns to chemist is the choice of solvent and this is not without a reason. Solvent play an important role in chemical processes not only serving to put reactants into contact by dissolution but also affecting rates, chemo-, regio- and sterioselectivities of the reactions. However, most of the organic solvents are volatile, highly flammable, toxic and hazardous. Solvents are high on the list of most damaging chemicals because they are used in large quantities as reaction media, for extraction and formulation and they are difficult to contain. Solvent is an ubiquitous feature of modern industry and each year millions of tons of solvents are discharged into the atmosphere by industries worldwide. As a result deleterious effects of these materials are felt on human health, safety and on the environment. In recent times, the continuously increasing air pollution has brought about changes in the global climate. Thus one of the most important and challenging area of research in chemistry is the development of green and clean technologies replacing conventional volatile, hazardous and environmentally unfriendly organic solvents by alternative non-volatile, non-flammable, non-toxic, safe and environmentally friendly solvents. In this context, much attention has been devoted recently to develop more and more environmentally benign process by using so-called green solvents under the concept of green chemistry, which has emerged as an important area of chemistry and has achieved outstanding progress towards the development of green reaction processes.[1]

A green solvent must ideally have negligible vapour pressure, high boiling point, be non-toxic, have high 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,

perfluorinated solvents, low melting polymers, water and more particularly ionic liquids.

1.1.1 Alternative solvents in organic synthesis

1.1.1.0 Supercritical fluids

A supercritical fluid (SCF) is defined as a substance above its critical temperature (T_c) and critical pressure (P_c). The properties of an SCF lie between those of its liquid and gas phases. These properties can be specifically tuned by varying the pressure and the temperature. The most popular SCF is carbon dioxide ($scCO_2$). The critical point of CO_2 is at 73 atm and 31.1 ºC, which are conditions easily achieved in the laboratory.

The advantages related to the use of $scCO_2$ are numerous and were clearly addressed in a recent article[2]: CO_2 is non-flammable and less toxic than most organic solvents; it is relatively inert towards reactive compounds and is a natural, unregulated solvent, with high availability; it can be easily removed by depressurization, which renders it an easy separation from the products of a reaction. Other advantages include high gas solubility, weak solvation, high diffusion rates and good mass transfer. Furthermore, the selectivity of a reaction can be dramatically changed when conducted in a supercritical fluid as compared to traditional organic solvents.

1.1.1.1 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 20000 and is known to be inexpensive, thermally stable, recoverable, biologically compatible and non-toxic.[3] 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 volatile solvents and a highly practical medium for organic reactions.

Its use as solvent in organic reactions is relatively recent and it is usually used in low molecular weights (< 2000) because it is either liquid at room temperature or has a low melting point. 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.

1.1.1.2 Perfluorinated (fluorous) solvents

Fluorous (perfluorinated) solvents as perfuoroalkenes, perfluoroalkyl ethers and perfluoroalkylamines are generally chemically benign and environmentally-friendly for being non-toxic (unlike the freons), non-flammable, thermally stable, recyclable, and for their high ability to dissolve oxygen gas, which is an advantage used in medical technology.

Due to their extremely non-polar characteristics they are not suitable for most organic reactions and tend to be used in conjunction with a traditional organic solvent (or some sort of immiscible solvent) to form a biphasic system.[4]

1.1.1.3 Water

Why water as solvent? Not only is water non-toxic and readily available at low cost, it is also non-flammable and environmentally benign, providing opportunities for clean processing and pollution prevention. 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[5] and Grieco[6] in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results. 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 co-solvents or surfactants helps to increase the solubility of non-polar reactants in water by disrupting the strong hydrogen-bond network of pure water.[7]

1.1.1.4 Ionic Liquids (ILs)

In the past 15 years, ionic liquids used in the present study have become alternative reaction media for organic transformations, especially for transition metal catalysis.

An ionic liquid (IL) is a liquid containing only ions, but it is different from the classic definition of a molten salt.[8] More recently melting point criterion has been proposed to distinguish between molten salts and ionic liquids. Molten salts are usually defined as a highly-melting, highly viscous and highly corrosive liquid medium, while ionic

liquids are defined as pure compounds, consisting only of cations and anions (i. e. salts), which melts at or below 100 ^{o}C and has lower viscocity.[9] In some cases ionic liquids are free-flowing liquid at room temperature, in which case they can be called room temperature ionic liquids (RTILs). Most characteristics feature of ionic liquids which is not included in definition of ionic liquid is that, usually they are composed of a bulky organic cation with low degree of symmetry and bulky inorganic/organic anion.

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, non-flammability, high ionic conductivity, wide electrochemical potential window and moreover the ability to act as catalysts. In addition, many of their physicochemical properties are changed substantially by variation of the cation and the anion; thus, they are "tunable" to the desired reaction. For this reason ILs have been referred to as "designer solvents'' in many publications.

1.1.2 Brief history of Ionic Liquids

In the past decade, ionic liquids have been developed from curiosity to a new class of solvents with attractive properties. However, history of these salts goes back to the early twentieth century. In 1914, Walden reported the synthesis of ethyl ammonium nitrate salt.[10] He reported the physical properties of ethyl ammonium nitrate, $[EtNH_3]NO_3$, which has a melting point of 8 ^{o}C and formed by the reaction of ethylamine with concentrated nitric acid, which was a liquid at room temperature. This interesting property did not attract a lot of interest until it was observed that mixture of $AlCl_3$ and N-alkyl pyridium halide salt could be liquid at room temperature. The first research into chloroaluminate ionic liquid was oriented toward their use in electrochemistry, for example the first ionic liquid with chloroaluminate ion such as ethyl pyridinium bromide/$AlCl_3$ ionic liquid was developed in 1948 by Hurley and Wier at the Rice Institute as bath solution for electroplating aluminium.[11] The use of chloroaluminate ionic liquids as electrolyte attracted interest from both fundamental and applied research. However, these systems were not studied further until the late 1970s when groups of Osteryoung and Wilkes rediscovered them. They prepared and studied the all-chloride system butyl pyridinium chloride/$AlCl_3$, which

was not stable toward reduction, limiting its use an electrolyte.[12] Efforts were made to develop alternative low-melting chloroaluminate ionic liquids that would be less subject to reduction and this led to the discovery by Wilkes and Hussey in 1982 that mixture of dialkyl imidazolium chloride salts and $AlCl_3$ formed ionic liquids.[13]

Through the 1980s chloroaluminate ionic liquids were studied by, especially the groups of Hussey *et al*.[14] and Seddon *et al*.[15] as solvents for transition metal complexes, mainly through electrochemical and spectroscopic investigations. The first report on the use of this type of low melting ionic liquids as reaction media for organic synthesis was in 1986, as combined solvents and catalysts for Friedel–Crafts reactions.[16] Their first applications as solvents for biphasic catalysis came in 1990 by Chauvin *et al*., who reported the dimerisation of propene by nickel complexes dissolved in acidic chloroaluminate melts[17] and Osteryoung who reported the polymerisation of ethylene by Ziegler–Natta catalysts.[18] The ionic liquids based on $AlCl_3$ can be regarded as the first generation of ionic liquids.

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. The real breakthrough occurred in 1992; when Wilkes and Zaworotko[19] 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. This is due to the formation of HF as a result of decomposition of the ionic liquid in the 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 [$(CF_3SO_2)_3C^-$] were developed.[20-22] 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 to a water content below 1 ppm under vacuum at temperatures between 100 and 150 ^{o}C. In contrast to chloroaluminate ionic liquids, these system offer high tolerance versus functional groups which opens up a larger range of applications especially for transition metal catalysis.

Beside Osteryoung, Wilkes, Hussey and Seddon who are pioneers in the field of ionic liquids, there are several scientists, e.g. Rogers, Welton, Wasserscheid, MacFarlane, Ohno, Endres, Davis, Jr, Abbott, and others, who entered this field having a strong impact in introducing the ionic liquids in many applications.

Rogers is one of the highly cited authors in the field of ionic liquids. He focuses on the synthesis and characterization of environmentally friendly ionic liquids as green solvents. He measured and published physicochemical properties of many ionic liquids with the aim of providing data to start evaluating the use of ionic liquids in a variety of processes. Also, he worked on the development of new materials from cellulose utilizing ionic liquids.

Welton has published many papers dealing with the applications of ionic liquids as solvents for synthesis and catalysis. He focuses on how the ionic liquids interact with solute species to affect their reactivity and he works on replacing environmentally damaging solvents with more benign alternatives. He is also the author of one of the most cited papers[23] which was cited 1719 times up to November 2005.

Wasserscheid is an active member of the ionic liquid community and focuses on the preparation and characterization of ionic liquids for use in the biphasic catalysis. For example, he could show that the use of hexafluorophosphate ionic liquids allows selective, biphasic oligomerization of ethylene to 1-olefins. Together with Welton, he edited a very important book entitled “Ionic Liquids in Synthesis” which presents the synthesis and physicochemical properties of ionic liquids as well as their use in catalysis, polymerization, and organic and inorganic synthesis.[24]

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-ethylimidazolium bis(trifluoromethanesulfonyl)imide. Quite recently, he edited a book entitled "Electrochemical Aspects of Ionic Liquids" which introduces some basic and advanced studies on ionic liquids in the field of electrochemistry.[25]

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. 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 multitonne 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.

1.1.3 Synthesis of Ionic Liquids

The synthesis of ionic liquids normally consists of two major steps. In the first step, desired cation has to be generated, usually by direct alkylation/quaternization of a nitrogen or phosphorus atom. In the second step, the anion resulting from the alkylation reaction can be exchanged for a different one by metathesis reaction or by direct combination with Lewis acid. Since imidazolium based ILs have reached some kind of standard in the IL community, because of weak interaction between anion and cations and good thermal stability as compared to other ammonium salts, the general and detailed synthesis of imidazolium-based ionic liquids is represented in Fig.**1** and discussed further.

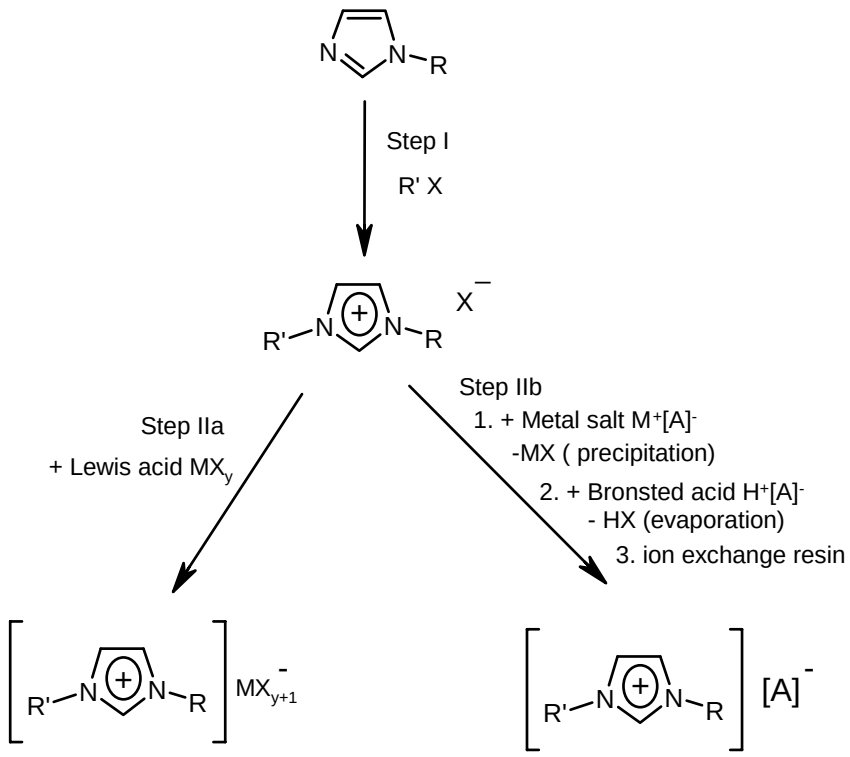


Fig. 1. General synthetic paths for imidazolium-based ionic liquids

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 quaternization 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**).

1.1.4 Cations

Although the list of the ionic liquids keeps on growing on a day to day basis, the cations are generally bulky, unsymmetrical ammonium or phosphonium salts, or heteroaromatics, with low symmetry, weak intermolecular interactions and low charge densities. Those described in literature include: tetraalkylammonium (**1**),[26]

trialkylsulphonium (**2**),[27] tetraalkylphoshonium(**3**),[28] 1,3-dialkylimidazolium(**4**),[20] N-alkylpyridinium (**5**),[29] N,N-dialkylpyrrolidinium (**6**),[22] N-alkylthiazolium (**7**),[30] N, N-dialkyltriazolium (**8**),[31] N,N-dialkyloxazolium (**9**),[32] N, N-dialkylpyrazolium, (**10**)[33] isoquinolinium (**11**),[50] guanidium (**12),**[51] morpholium (**13**), polycations (**14),**[52] and **(15**)[53] and dimethyl ammonium form amide (**16**)[54] (Fig. **2**).

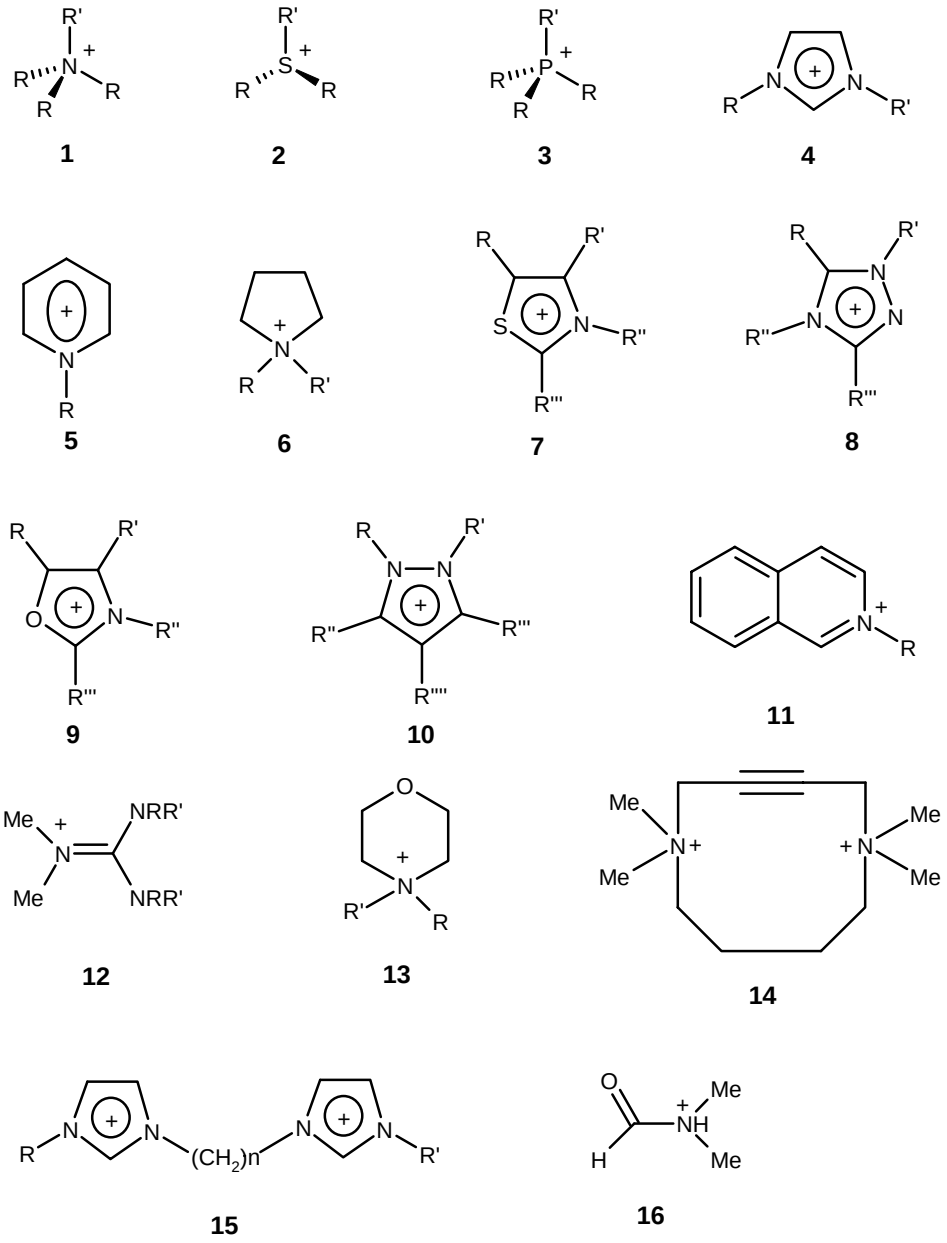


Fig. 2. Different types of organic cations in ionic liquids

1.1.5 Anions

Number of anions has been investigated in literature as listed in Table **1**.

Table 1 A list of some anions in ionic liquids and their references

Sr. No.	Anions	Ref.	Sr. No.	Anions	Ref.
1	BF_4	19	16	$ZnCl_3$	24
2	PF_6	34	17	$CuCl_2$	24
3	SbF_6	35	18	$SnCl_3$	24
4	CH_3CO_2	19	19	$N(EtSO_2)_2$	24
5	HSO_4	36	20	$N(FSO_2)$	42
6	NO_3	19	21	$C(CF_3SO_2)_3$	42
7	NO_2	19	22	CH_3SO_3	24
8	CF_3SO_3	20	23	$N(CN)_2$	44
9	$(CF_3SO_2)_2N$	20	24	halides	43
10	CF_3CO_2	20	25	Al_2Cl_7	24
11	$B(Et_3Hex)$	37	26	Al_3Cl_{10}	24
12	OTs	38	27	Au_2Cl_7	24
13	$AuCl_4$	39	28	Fe_2C_{l7}	24
14	$AlCl_4$	40	29	Sb_2F_{11}	24
15	Carborane anions (as1-R-$CB_{11}H_6Cl_6$)	41			

In the near future, list of cations and anions will be extended to a nearly limitless number. Various combinations of cations and anions provide finely designed ionic liquids for different applications.

1.1.6 Purity of ionic liquids

Purity of the system is essential for many solvent applications especially for transition metal catalyzed reaction and for the characterization of their physical and chemical properties. The chemical and physical properties of ionic liquids can be altered by presence of impurities arising from their preparation.[45] Also purity of IL is essential, when ILs are used as reaction media, especially for transition metal catalysis. The main contamination in ILs are halide anions, organic bases that are generally produced from unreacted starting material and water.[46] A colorimetric method has

been recently developed to determine the level of unreacted alkylimidazole (<0.2 mol%) in the ionic liquid.[46] Halide impurities can have a detrimental effect on transition metal catalyzed reactions. Halide impurities can be removed by washing of ILs with water and also by titration with $AgBF_4$ which can also be, of course quite expensive and may lead to silver impurities in ILs. Alternatively methods of preparations have been proposed to avoid the use of halide containing starting materials.

Gallo *et al*.[47] 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.

The second major purity problem is the "colors". Most of the 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 e. g. N-methylimidazole. Therefore, with a few precautions, colorless 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 decolorizing the final IL product through stirring with activated charcoal.[48] The third issue concerning the purity of ILs 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.[24,49] 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[48] or, of course, by standard Karl Fischer titration. Organic solvents are usually purified by distillation before use, this method is not suitable to clean up ionic liquids, due to their non-volatile nature. Due to these reasons, the highest purity possible must be attained during synthesis itself.

1.1.7 Physicochemical properties of ILs

Before considering a new solvent for incorporation into an industrial application, a fundamental understanding must be established for the chemical and physical properties of the solvent. Ideally, if a new solvent is to be introduced as a 'green' solvent, it would be an improvement over the solvents currently available. Optimal physical properties would include low viscosity to facilitate mixing and a large density difference 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 solvents 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.[57] Due to the obvious intermolecular interactions that these parameters measure, these chemical properties are believed 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. Thus their properties can be adjusted to suit the requirements of a particular process. Because of this reason the ILs have been referred to as "designer" solvents.

Thus it is necessary to understand how the physico-chemical properties of ionic liquids are able to affect organic reactivity as well as how they depend upon their structural features. This will be illustrated on the basis of a few selected examples which are as follows:

1.1.7.0 Melting point

By definition, ionic liquids are the salts whose melting points are below 100 ^{o}C. Thus the melting point is the key criteria for the evaluation of an ionic liquid. Low melting point is an important reason that ILs have become popular as a medium in organic reactions and other chemical processes. Both cations and anions contribute to the low melting points of the ILs. Cation size and symmetry make an important impact on the melting points of ILs. Symmetrically substituted cations can crystallize easily and therefore often lead to ionic solids with high melting point. Low symmetry in substitution can prevent easy crystallization, resulting in low melting points.

By variation of the alkyl chain length in the cation, fine-tuning of the melting point can be achieved.[9,24] Longer the alkyl chain, lower is the melting point, but only up to a certain extent (rule of thumb for imidazolium cations: C_8 gives the lowest melting points [24]). Beyond that, prolongation of the alkyl chain raises the melting point again. In addition to this, a good distribution of charge in cation and weak intermolecular interaction such as weak hydrogen bonding are also responsible for the lowering of melting points of ILs.[9] 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 (Table **2**).

Table 2. Melting points of various salts

Entry	Salt	M. P. (^{o}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

Besides the cation, the anion influences the melting point. With a given cation, the choice of anion has a strong effect on the melting point[9] (Table **3**). Coordinating and hydrophilic anions like the halides lead to high melting points, whereas weakly co-ordinating and hydrophobic anions result in low melting points. Also increase in size of the anion with same charge leads to a decrease in melting point.

Table 3 Influence of different anions on the melting point of imidazolium salts

Entry	Imidazolium salts	M. P. (^{o}C)	Ref.
1	[EMIM][Cl]	87	13
2	[EMIM][$NO_{2]}$	55	19
3	[EMIM][NO_3]	38	19
4	[EMIM][$AlCl_4$]	7	40
5	[EMIM][BF_4]	15	15
6	[EMIM][PF_6]	62	15
7	[EMIM][CF_3SO_3]	-9	20
8	[EMIM][CF_3CO_2]	-14	20
9	[EMIM] [$(CF_3SO_2)_2N$]	-3	15

1.1.7.1 Viscosity

Generally viscosity of ILs is higher than that of common molecular solvent or water and their viscosity ranges from 10 mpa. s to about 500 mpa. s at room temperature, similar to those of oil. A high viscosity may produce a reduction in the rate of reactions and reduction in the diffusion rate of the redox species. Thus the recent efforts have been made to develop low viscous ILs.[44] The viscosity of ionic liquids is determined by van der Waals forces and hydrogen bonding. Electrostatic forces may also play an important role. Comparing viscosity of different ILs based upon the imidazolium cation, shows that increase in length of the alkyl chain and fluorination in the cation/anion strongly influences the viscosity of ILs[56] Table **4**. 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.[56]

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	Vscosity (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

As an evident from Table **4**, that viscosity increases with increasing alkyl chain length (entry 1-3 Table **4**), also fluorination in anions causes increase in viscosity (entry 4-7 Table **4**). Strength of hydrogen bonding decreases in the order $[PF_6]^- > [BF_4]^- > [NTf_2]^-$ which results in decrease in viscosity (entry 2, 8, 9 Table **4**).

1.1.7.2 Density

Generally ILs are denser than water with values ranging from 1 to 1.6 g cm^{-3}. Density is one of the most often measured properties of ILs, probably because nearly every application requires knowledge of the density. The molar mass of the anion, alkyl chain length and bulkiness in the cation significantly affects the overall density of ILs. Density of ILs decreases with increase in length of the alkyl chain in cation and increases with increase in molar mass of anion[56] (Table **5**)

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 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.[57]

1.1.7.3 Vapour pressure and thermal stability

Clean technology requires the design of safe and environmentally benign chemical processes and thus reduces the waste from an industrial process to its minimum. Ionic liquids have no measurable vapor pressure, which makes them a part of the green chemistry. This attractive feature is one of the most important reasons that ionic liquids are emerging as novel alternatives for volatile organic compounds (VOCs) traditionally employed as industrial solvents. From an engineering point of view, this also has great advantages, since isolation of product by distillation of reaction mixture becomes a more effective method. The well-known problem in distillation process is the formation of azeotrope between the solvent and products and it does not occur in the case of ILs due to the non-volatile nature of ILs. The thermal stability of ionic liquid is limited by the strength of their heteroatom-carbon and their heteroatom-hydrogen bonds, respectively.[9] Since ILs have no measurable vapour pressure, as a result of heating, first event is the thermal decomposition. In general, most of ILs have high thermal stability, the decomposition temperature reported in the literature

are generally > 400 ^{o}C, 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.[56] Literature reports indicate that experiments performed under N_2 or air produce the same results.[56] 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.[56] 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 temperatures for different ILs

Entry	Ionic Liquid	Temperature on set for decomposition (^{o}C)
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

1.1.7.4 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. Since solvent polarity and polarizability are the critical indexes of solvent strength, they may have significant influence on the chemical reactions. Although different characteristic parameters (for example, dielectric constant, dipole moments, refractive index, and polarizabilities, etc.) reflect

the solvent strength from different aspects, solvent polarity can not be simply described by any one of those terms because the individual interactions between a solvent and a solute are not accounted for. 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 (e.g. Coulumbic, directional, inductive, dispersion, hydrogen bonding, electron pair donor and electron pair acceptor forces), excluding such interactions leading to definite chemical alterations on the solute.

For decades, in the case of molecular solvents, attempts have been made to develop empirical solvent polarity scales, which should help to explain differences in solvent-mediated reaction pathways, reaction yields, synthesis product ratios, chromatographic retention and extraction coefficients. 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.[58] 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 **17** (Fig. **3**), was carried out[59] 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

show[59,60,61] 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 $[bmim]^+$ cation ILs, the polarity decreases through the series $[NO_2]^- > [NO_3]^- > [BF_4]^- > [NTf_2]^- > [PF6]^-$. The decrease in polarity correlates with anion size, i.e. with the effective charge density. The anomalous behaviour of $[Tf_2N]^-$ 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[60] is able to vary the polarity of the corresponding salts over a wide range.

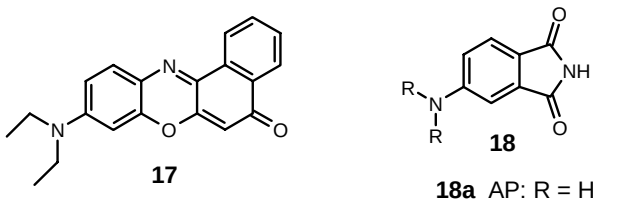


Fig. 3. Solvatochromic dyes

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 **18a** (AP) and N,N-dimethyl-4-aminophthalimide (DAP) **18b** (Fig. **3**), were used with a series of ILs.[61] 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.

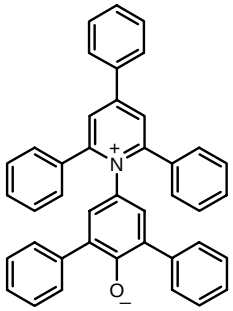
Because of its structure **19** (Fig. **4**), the solvatochromic shift of this probe is strongly affected by the hydrogen- bond donor ability of the solvent, which stabilizes the ground more than the excited state.

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	62
2	[BMIM][PF_6]	0.669	62
3	[BMIM][TfO]	0.656	62
4	[BMIM][Tf_2N]	0.644	62
5	[BM_2IM][BF_4]	0.576	62
6	[BMPyrr][Tf_2N]	0.544	62
7	[BM_2IM][Tf_2N]	0.541	62
8	[OMIM][PF_6]	0.633	63
9	[OMIM] [Tf_2N]	0.629	63
10	[OM_2IM][Tf_2N]	0.525	63
11	[OM_2IM][BF_4]	0.543	63

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.[63] These data are in agreement with the often proposed ability of the proton at C-2 to give hydrogen bonding interactions 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].



19

Fig. 4. Reichardt's dye

1.1.7.5 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.[58]

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[48] 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 $[PF_6]^-$ < $[SbF_6]^-$ < $[BF_4]^-$ < $[Tf_2N]^-$ < $[ClO_4]^-$<$[NO_3]^-$ < $[CF_3CO_2]^-$.

1.1.7.6 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 homogeneous 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 rate of these processes depends 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 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[56] (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

1.1.7.7 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.[56]

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

1.1.7.8 Conductivity

Ionic liquids have reasonably good ionic conductivities compared with those of organic solvents/electrolyte systems (up to ~10 mS cm^{-1}).[24] 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.

1.1.7.9 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,[64] 4.10 V for [BMIm]BF_4[64] and 5.5 V for [BMP]Tf_2N at a glassy carbon electrode.[22] In general, the wide electrochemical windows of ionic liquids have opened the door to electrodeposit metals and semiconductors at room temperature which were formerly obtained only from high temperature molten salts. For example, Al, Mg, Si, Ge, and rare earth elements can be obtained from room temperature ionic liquids. The thermal stability of ionic liquids allows to electrodeposit Ta, Nb, V, Se and presumably many other ones at elevated temperature.

1.1.8 What features makes ILs so attractive?

Following characteristics features of ILs makes them attractive:

1. Negligible vapour pressure and non-flammable.
2. High thermal stability.
3. They have outstanding capacity to dissolve a wide range of organic, inorganic, organometallic compounds and polymeric material.
4. They are often composed of poorly co-ordinating ions, so they have the potential to be highly polar yet non-coordinating solvents.
5. 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.
6. Their ionic character enhances the reaction rates to a great extent in many reactions including microwave assisted organic synthesis.
7. Most of the ionic liquids can be stored without decomposition for a long period of time.
8. They are immiscible with a number of organic solvents and provide a non aqueous, polar alternative for two-phase systems. Hydrophobic ionic liquids can also be used as immiscible polar phases with water.
9. Because of their non-volatile nature, product can be easily isolated by vacuum distillation.

10. They are recyclable and they make product isolation easy because of their water solubility and immiscibility with number of molecular organic solvents.
11. ILs may be termed as "designer" and 'neoteric" solvents since their properties can be adjusted to suit for the particular process by changing anion/cation or both.
12. They exhibit Brønsted, Lewis and Franklin acidity, as well as superacidity.
13. They are relatively cheap, and easy to prepare.

1.1.9 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. 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. Some of the synthetic applications of ILs are discussed in the following section:

1.1.9.0 Palladium-catalyzed C-C coupling reactions

Heck reaction

The vinylation of aryl halides catalyzed by palladium complexes, commonly called the Heck reaction, has received increasing attention because of its enormous synthetic potential for generating carbon–carbon bonds and its tolerance towards a wide range of functional groups.[65] However, the high consumption of the expensive palladium catalyst makes it a relatively impractical process on an industrial scale. Recycling the catalyst is therefore a key objective.

The first example of a Heck coupling in an ionic liquid was reported by Kaufmann *et al.* in 1996.[66] Butyl *trans*-cinnamate was produced in high yield by reaction of bromobenzene with butyl acrylate in molten tetraalkylammonium and tetraalkylphosphonium bromide salts. No formation of palladium metal was observed and the product was isolated by distillation from the ionic liquid.

Herrmann and Böhm[67] subsequently showed that molten Bu_4NBr (mp 103 °C) is a particularly suitable reaction medium for Heck reactions, affording superior results

compared with commonly used organic solvents such as DMF. For example, in the reaction of bromobenzene with styrene, using diiodobis(1,3-dimethylimidazolin-2-ylidine)palladium(II) as the catalyst, the yield of stilbene was increased from 20% in DMF to 99% in Bu_4NBr under otherwise identical conditions. The product was separated by distillation and the catalyst containing ionic liquid recycled up to 13 times without significant loss of activity.

Seddon and coworkers[68] performed Heck couplings in [bmim]PF_6 or [*n*-hexylpyridinium]PF_6 using $PdCl_2$ or $Pd(OAc)_2$–Ar_3P as the catalyst and Et_3N or $NaHCO_3$ as the base. For example, $Pd(OAc)_2$–Ph_3P-catalyzed coupling of 4-bromoanisole with ethyl acrylate in [bmim]PF_6 at 140 °C, afforded ethyl 4-methoxycinnamate in 98% yield. The high solubility of the catalyst in the ionic liquid allows for product isolation by extraction into a hydrocarbon solvent, *e.g.* hexane or toluene. Furthermore, if water is added, a triphasic system is obtained in which the salt formed in the reaction, $Et_3N.HBr$, is extracted into the aqueous phase. It was also noted that palladium complexes of imidazolylidene carbenes, formed by reaction of the base with the imidazolium cation, may be implicated in these reactions.[68]

This was later confirmed by Xiao and coworkers[69] who observed a significantly enhanced rate of the Heck coupling in [bmim]Br compared to the same reaction in [bmim]BF_4. This difference could be explained by the formation of the corresponding palladium–carbene complexes (which were isolated and characterized) in the former but not in the latter. The isolated carbene complexes were shown to be active catalysts when redissolved in [bmim]Br. Presumably, the formation of the carbene in [bmim]Br can be attributed to the stronger basicity of bromide compared to tetrafluoroborate.

Prompted by these results, Srinivasan *et al*. subjected the reaction mixture from the Heck reaction of iodobenzene with ethyl acrylate in [bbim][BF_4] carried out under ultrasound conditions to *in situ* transmission electron microscopy. These studies showed the presence of highly stabilized clusters of zero-valent Pd nanoparticles.[70]

The authors demonstrated the formation of a Pd–carbene complex by subjecting a mixture of $Pd(OAc)_2$ or $PdCl_2$ and NaOAc in the ionic liquids, [bbim][Br] and

[bbim]BF_4, to ultrasonication for an hour. The formation of the carbene complex was shown by ^1H NMR analysis.

The Heck arylation of electron-rich enol ethers generally leads to a mixture of regio isomers owing to competition between cationic and neutral pathways, leading to α- and β-arylation, respectively. The ionic pathway is favored with aryl triflates but these are less available and much more expensive than the corresponding chlorides and bromides. The ionic pathway would also be expected to be favored by conducting the reaction in an ionic liquid and this proved to be the case. Thus, Xiao and coworkers[71] achieved > 99% selectivity to the α-arylation product in the Heck coupling of 1-bromonaphthalene to butyl vinyl ether in [bmim]BF_4. In contrast, the same reaction in toluene, acetonitrile, DMF or DMSO afforded mixtures of the α- and β-regio isomers. A range of 4-substituted bromobenzenes were similarly shown to give α / β -regioselectivities of > 99%.

Suzuki reaction

Mathews *et al*. reported that Suzuki cross-coupling reactions using $Pd(PPh_3)_4$ as catalyst and [bmim]BF_4 as solvent gave excellent yields and TONs at room temperature.[72] The reactions of phenyl boronic acids with haloarenes have been conducted by $Pd(PPh_3)_4$ immobilized in [bmim]BF_4 ionic liquid with several advantages over reactions performed in classical organic solvents. The reactions show a significant increase in reactivity, the homocoupling aryl byproducts can be eliminated, the reaction can be performed in air, and the catalyst can be reused several times without loss of catalyst activity. In these cases the products were extracted with diethyl ether and the byproducts ($NaHCO_3$ and $Na[XB(OH)_2]$) washed out with water affording the clean ionic liquid catalytic solution. After this the ionic liquid/catalyst system was used for three further reaction cycles with no decrease in either yield or TON.

In this system, it was found that optimum catalytic activity was achieved by pre-heating the catalyst with the aryl halide in [bmim][BF_4] at 110 ^oC, after which the reaction was started by addition of the arylboronic acid and Na_2CO_3 at room temperature. An extremely large increase in reaction rate was observed compared with the conventional Suzuki conditions. The reaction of bromobenzene with

phenylboronic acid under conventional Suzuki conditions result gave an 88% yield in 6 h (TON, 5 h^{-1}), while the equivalent reaction in [bmim][BF_4] gave 93% in 10 min (TON, 455 h^{-1}).

Srinivasan *et al*. reported that Suzuki cross-coupling reaction of halobenzenes with phenylboronic acid has been carried out under mild conditions in an ionic liquid with methanol as a co-solvent using ultrasound.[73]

Stille coupling

The Stille coupling reaction has been one of the most widely used steps in the preparation of a wide variety of materials including polyarenes and diaryl and aromatic carbonyl compounds.[74] Like all transition metal-catalyzed cross-coupling reactions, there is the problem of the expense of the catalyst and the need for expensive and/or toxic ligands. The use of palladium complexes immobilized in ionic liquids offers great advantages over the classical organic solvents used for Stille coupling reactions. A series of Stille coupling reactions with Pd(0) or Pd(II) catalyst precursors associated with Ph_3As in the presence of CuI has been demonstrated in [bmim][BF_4].[75] This procedure permitted extensive recycling of the solvent and catalyst without a significant loss in activity. Furthermore, an interesting selectivity for aryl bromides and iodides was observed.

Trost-Tsuji reaction

The Trost–Tsuji coupling involving nucleophilic allylic substitution catalyzed by Pd(0) complexes is an attractive method to form C–C bonds in organic synthesis. This reaction has also been performed in ionic liquids, both in a mono- and biphasic system, using $Pd(OAc)_2$-PPh_3/K_2CO_3 in [bmim][BF_4][76] and $PdCl_2$-TPPTS, (TPPTSZ triphenylphosphine trisulphonate, sodium salt) in [bmim][Cl]/cyclohexene,[77] respectively An enhancement of the catalytic activity by 10-fold was observed in the ionic liquid biphasic condition, as compared to the aqueous reaction conditions. Furthermore, the reaction in biphasic ionic liquid conditions showed a significantly improved selectivity, since the formation of cinnamyl alcohol and of phosphonium salts was suppressed and very much decreased, respectively, in ionic liquids.

Negishi reaction

Palladium-catalyzed Negishi cross-couplings of organozinc reagents were achieved in 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bm_2im][BF_4]) using a novel ionic phosphine prepared by reaction of PPh_2Cl with [bmim][PF_6].[78] Yields of 70–92% were obtained using a variety of substrates, the fastest reactions being observed for aryl iodides. Recycling of the catalyst/IL system was attempted, but after the third cycle a decrease in yield and increase in reaction time was observed, suggesting that catalyst decomposition or leaching was occurring.

Sonogashira reaction

Ryu *et al*. reported a Sonogashira coupling reaction in an ionic liquid, namely, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6].[79] Using $PdCl_2$-$(PPh_3)_2$ as catalyst and diisopropylamine or piperidine as base, the Sonogashira coupling reaction proceeded efficiently without using a copper co-catalyst. In this case the products were extracted with hexane, the resulting ionic liquid layer was washed with water to remove ammonium salts. The resulting ionic liquid containing the Pd catalyst could be reused successfully several times with only a slight loss in its activity.

Srinivasan *et al*. have demonstrated that the *copper*- and *ligand*-free Sonogashira reaction catalyzed by Pd(0) nanoparticles proceeds under ultrasound irradiation in the ionic liquid [bbim][BF_4].[80] The formation of Pd(0) nanoparticles was investigated in this reaction by subjecting the reaction mixture (after a successful Sonogashira reaction between iodobenzene and 1-ethynylbenzene in [bbim][BF_4] under sonochemical conditions) to *in situ* TEM analysis.

1.1.9.1 Other transition metal catalyzed reactions:

Hydrogenation

The first example of catalytic hydrogenation in an ionic liquid was reported by Chauvin *et al.* in 1995.[81] A solution of the cationic [Rh(nbd)$(Ph_3P)_2$]PF_6 complex [nbd = norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)] in [bmim]PF_6 or [bmim]SbF_6 was shown to be an effective catalyst for the biphasic hydrogenation of pent-1-ene. Reaction rates were up to five times higher than in acetone as solvent which was attributed to the formation of an unsolvated cationic rhodium(III) dihydride complex

with two free coordination sites in the non-solvating ionic liquid. In contrast, poor results were obtained with [bmim]BF_4 which was ascribed to the presence of trace amounts of strongly coordinating chloride ions in their sample of this ionic liquid. The catalyst solution in the ionic liquid could be reused with rhodium losses below the detection limit of 0.02%.

Similarly, advantage was taken of the biphasic system to perform the selective hydrogenation of cyclohexadiene. The solubility of cyclohexadiene in [bmim]SbF_6 is about five times that of cyclohexene and, hence, the latter was obtained in 98% selectivity at 96% conversion.

Dupont and coworkers[82] performed the biphasic hydrogenation of cyclohexene with $Rh(cod)_2BF_4$ (cod = cycloocta-1,5-diene) in ionic liquids. They observed roughly equal rates (turnover frequencies of *ca*. 50 h^{-1}) in [bmim]BF_4 and [bmim]PF_6 (presumably their [bmim]BF_4 was chloride-free). The same group showed that $RuCl_2(Ph_3P)_3$ in [bmim]BF_4 is an effective catalyst for the biphasic hydrogenation of olefins, with turnover frequencies up to 540 h^{-1}.[83] Similarly, [$(bmim)_3$]-$Co(CN)_5$ dissolved in [bmim]BF_4 catalyzed the hydrogenation of butadiene to but-1-ene, in 100% selectivity at complete conversion.[83]

Hydroformylation

The hydroformylation of olefins has been employed industrially since the 1940s, and it is one of the most important catalytic industrial chemical processes. Hydroformylation of propene in an aqueous biphasic system, using a water-soluble rhodium complex of the sodium salt of trisulfonated triphenylphosphine (tppts) forms the basis of the Ruhr Chemie Rhone Poulenc process for the manufacture of butanal.[84] Unfortunately this process is limited to C_2 to C_5 olefins owing to the very low solubility of higher olefins in water. Hence, one can envisage that the use of an appropriate ionic liquid could provide the basis for biphasic hydroformylation of higher olefins.

As noted earlier, Parshall showed, in 1972, that platinum catalyzed hydroformylations could be performed in tetraethyl ammonium trichlorostannate melts.[85] More recently, Waffenschmidt and Wasserscheid[86] studied the platinum-catalyzed hydroformylation of oct-1-ene in [bmim]$SnCl_3$ which is liquid at room temperature. Despite the limited

solubility of oct-1-ene in the ionic liquid, high activities (TOF = 126 h^{-1}) were observed together with a remarkably high regioselectivity (n/iso = 19). The product was recovered by phase separation and no leaching of platinum was observed.

The ruthenium- and cobalt-catalyzed hydroformylation of internal and terminal olefins in molten tetra-*n*-butylphosphonium bromide was reported by Knifton in 1987.[87] More recently, the rhodium-catalyzed hydroformylation of hex-1-ene was conducted in molten phosphonium tosylates, *e.g.* $Bu_3PEt^+TsO^-$ and $Ph_3PEt^+TsO^-$ having melting points of 81–83 °C and 94–95 °C, respectively, at 120 °C and 40 bar.[88] Advantage was taken of the higher melting points of these 'ionic liquids' to decant the product from the solid catalyst medium at room temperature.

Chauvin and coworkers[81] investigated the rhodium-catalyzed biphasic hydroformylation of pen-1-tene in [bmim]PF_6. High activities (TOF = 333 h^{-1} compared with 297 h^{-1} in toluene) were observed with the neutral $Rh(CO)_2(acac)$–Ph_3P as the catalyst precursor but some leaching of the catalyst into the organic phase occurred. This could be avoided by using $Rh(CO)_2(acac)$ with tppts or tppms (monosulfonated triphenylphosphine) as the catalyst precursor, albeit at the expense of rate (TOF = 59 h^{-1} with tppms). Higher activities (TOF = 810 h^{-1}) and high regioselectivity (n/iso = 16) were observed in the biphasic hydroformylation of oct-1-ene in [bmim]PF_6 using cationic cobaltocenium diphosphine ligands but some catalyst leaching (< 0.5%) was observed.[89]

Oxidation

Low-melting imidazolium and pyridinium ionic liquids are stable towards strong chemical oxidizing agents and have a large electrochemical window and are therefore suitable media for oxidation reactions. Various transition metal-catalyzed oxidation reactions have been performed in these ionic liquids and the results obtained so far demonstrate the advantage of the ionic liquids over other immobilizing agents.

ILs are, of course, suitable solvents for oxidation reactions, such as the oxidation of aromatic aldehydes with molecular oxygen and a nickel(II)catalyst.[90] For a TEMPO-CuCl catalyzed aerobic oxidation of alcohols to aldehydes/ketones,[91] it has been shown that the reaction, run in [bmim]PF_6, yielded no overoxidised carboxylic acid products. The catalyst/IL solution could be reused for different types of substrates

without any contamination of the earlier product. Alkene epoxidation with hydrogen peroxide and iron(III) porphyrins also ran smoothly, even in the halide-containing and thus easily and cleanly available IL [bmim]Br.[92]

A speciality of ILs, namely the immobilization of OsO_4 and its utilization for olefin dihydroxylation, was published almost simultaneously by three groups.Yanada *et al.* have used [emim]BF_4 for the dihydroxylation of various olefins.[93] They reported that the volatility of OsO_4 and therefore its toxicity is greatly suppressed when dissolved in the IL, which is clearly an advantage over the use of classical organic solvents. Yao[94] has used [bmim]PF_6 in combination with 4-(dimethylamino)pyridine to immobilize OsO_4 in the IL. Branco and Afonso[95] have exploited biphasic and triphasic water/IL/*tert*-butanol systems for asymmetric olefin dihydroxylation with OsO_4. For a variety of simple olefins they report enantiomeric excesses up to 99% with full reusability of the catalyst.

1.1.9.2 Other organic reactions in ILs

Diels-Alder reaction

Ionic liquids such as [bmim][BF_4], [bmim][ClO_4], [emim][CF_3SO_3], [emim][NO_3] and [emim][PF_6] were demonstrated as effective solvents for Diels–Alder reactions between cyclopentadiene and methyl acrylate and showed significant rate enhancements, high yields and strong endo selectivities comparable with the best results obtained in conventional solvents.[96,97]

Baylis–Hillman reaction

Baylis–Hillman reaction is atom efficient and allows the generation of a highly functionalized molecule in a single step, but it suffers from slow reaction rates (often requiring days for completion), even under solvent-free conditions and in the presence of a large amount of base.

Afonso *et al.* reported the use of ionic liquids as solvents for this reaction.[98] They reported that the Baylis–Hillman reaction between benzaldehyde and methyl acrylate in the ionic liquid, [bmim][PF_6], was 33 times faster than the reaction in CH_3CN, although only moderate yields of the desired product were obtained. The relative reaction rates were measured by monitoring the disappearance of benzaldehyde by gas chromatography. The (incorrect) assumption that all of the benzaldehyde was

being converted to the desired product led to the erroneous conclusion that the observed rate enhancement was ionic liquid induced.

Although Aggarwal *et al.* were unable to achieve good yields in the Baylis–Hillman reaction using ionic liquids, prompted by the above report, they revisited their own previous work. In an elegant study, they discovered that under the basic reaction conditions, the aldehyde was actually being consumed in a side reaction with the imidazolium cation, thus demonstrating convincingly that ionic liquids are not always inert solvents.[99] They showed that the acidic nature of the C(2) hydrogen of the imidazolium cation was responsible for this side reaction.

Since the problems associated with the use of imidazolium-based ionic liquids, in the Baylis–Hillman reaction, arise from the acidity of C(2) imidazolium cation, Hsu *et al*. synthesized an ionic liquid substituted at the 2-position and studied its utility in the Baylis–Hillman reaction.[100] They found that the Baylis–Hillman reaction between a variety of aldehydes and methyl acrylate proceeded smoothly in the ionic liquid, $[bm_2im][PF_6]$, in contrast to results obtained with $[bmim][PF_6]$.

Wittig reaction

The Wittig reaction is amongst the most popular methods for C=C bond formation, giving in most cases good to excellent stereocontrol. The separation of the alkene from the by-product (TPPO) is a classical problem, which is usually done by crystallization and/or chromatography. It has been demonstrated that $[bmim]BF_4$ can be used as a medium to perform Wittig reactions using stabilized ylides allowing both easier separation of alkenes from Ph_3PO and also the recycling of the solvent.[101]

Michael addition reaction

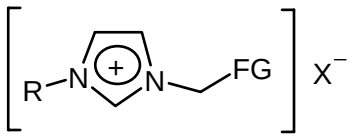
The Michael addition reaction is one of the most useful C–C bond-forming reactions and has wide synthetic applications in organic synthesis. The Lewis acids $Ni(acac)^2$, $Yb(OTf)_3$, and $FeCl_3.6H_2O$ have been used for the metal-catalyzed Michael addition in the ionic liquid $[bmim][BF_4]$, focusing mainly on the addition of acetylacetone (Hacac) to methyl vinyl ketone as a model reaction.[102] The results have been compared with those obtained using dioxane as a solvent or carrying out the reaction without solvents. Among the catalysts tested in $[bmim][BF_4]$, $Ni(acac)_2$ appeared to be outstanding in terms of activity, making up a recyclable catalytic system and

affording a very high selectivity. On the contrary, both catalytic systems based on ytterbium and iron were less active in the ionic liquid than in the solvent-free conditions.

1.1.10 Task Specific Ionic Liquids [TSILs]

Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the ILs.[24] These ILs can then act as reagents or catalysts in organic reactions.

Recently, many attempts have been made to explore functional ionic liquids through incorporation of additional functional groups as a part of the cation and/or anion. The incorporation of functional groups can impart a particular capability to the ionic liquids, enhancing their capacity for catalyst reusability as exemplified with imidazolium salt-functionalized phosphine-metal complexes, which showed dramatically increased reusability and stability in ionic liquids compared with the unfunctionalized ones. Moreover, specific functional groups can also be incorporated for task-specific purposes. For example, a primary amine functionalized imidazolium salt can separate CO_2 from gas streams,[103] while ionic liquids bearing appended sulfonic acid groups were used as solvent-catalyst for esterifications.[104] 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.[105] Many of them were focused on the incorporation of functionality into a branch appended to the cation, especially imidazolium cation (Fig. **5**).



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FG = NH_2, OH, OR, SH, PPh_2, $Si(OR)_3$, urea and thiurea, metal complex,

CN, COOH, SO_3H, SO_2Cl, SCN etc

Fig. 5. Task specific ILs

The imidazolium salts are defined as TSILs when they have the following features: (i) ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the imidazolium salts, which behave not only as a reaction medium but also as a reagent or catalyst. (ii) A conventional ionic liquid solution of a functionalized imidazolium salt, which is not a liquid form at ambient temperature, could also be defined as a TSIL since the functionalized imidazolium salt become integral elements of the overall ionic liquid solution and can introduce a functional group into the liquid.

1.1.11 Chiral Ionic Liquids

Recently, few examples of chiral ionic liquids (CILs) have been reported in the literature.[106] Some representative examples are shown in Fig **6**. Due to their ease of synthesis and their peculiar properties, these new chiral solvents should play a central role in enantioselective organic synthesis and hopefully expand the scope of chiral solvents. Chiral ILs can be particularly attractive if one considers their potential applications to chiral discrimination, including asymmetric syntheses and optical resolution of racemates. For example, one can expect a significant transfer of chirality in these solvents due to their high degree of organization. Most reports deal with the synthesis and properties of the new chiral ILs and only a few deals with their application in organic reactions. The first reported chiral ionic liquid was 1-butyl-3-methylimidazolium ([BMIM])lactate **21** by Seddon *et al*. in 1999.[97] The [bmim][lactate] was prepared by anion exchange between [bmim][Cl] and commercially available sodium (*S*)-2-hydroxypropionate. This ionic liquid was used in asymmetric Diels–Alder reactions between ethyl acrylate and cyclopentadiene. The Diels–Alder adducts were simply isolated by decanting off the upper organic layer. A good *endo*:*exo* selectivity of 4.4/1 was obtained but no enantioselectivity was observed.

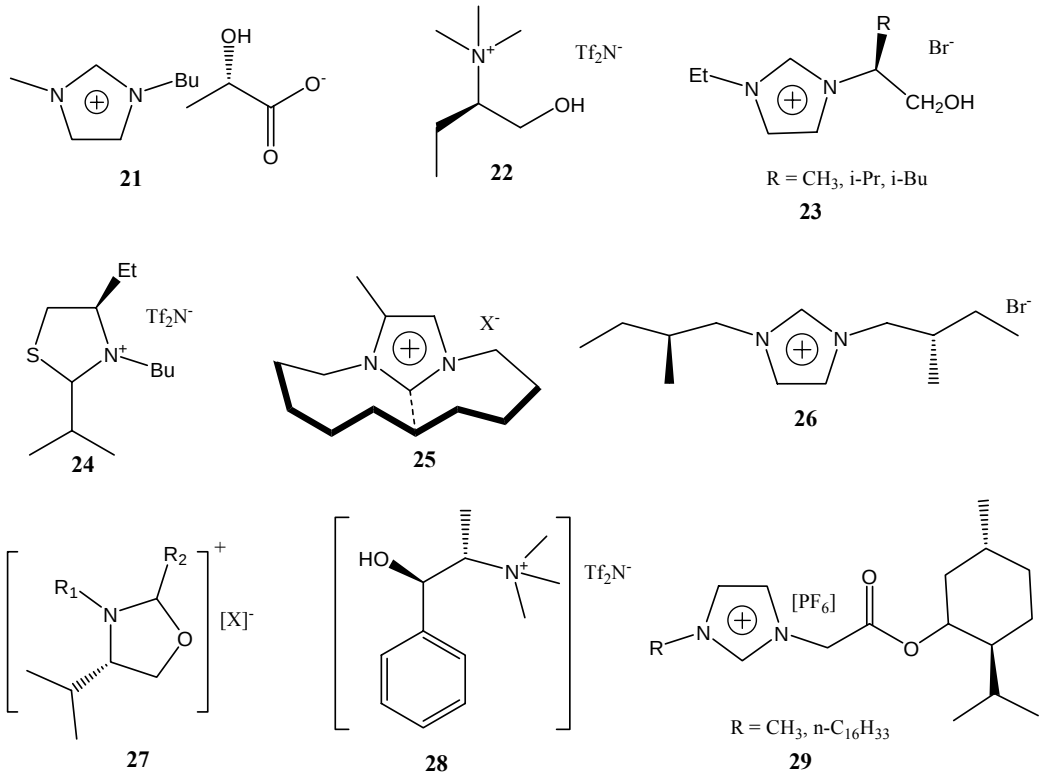

Fig. 6. Chiral ILs

1.1.12 Summary and Conclusion

The unique physico-chemical properties of ILs should boost clean technology development in organic synthesis, pharmaceuticals, radiopharmaceuticals, biocatalysis, and biotransformation and especially in industrial catalytic processes. For example, IFP (Rueil-Malmaison, France) has just launched a commercial process for the dimerization of butenes to isooctenes (Difasol process). This new process provides significant benefits over existing homogenous Dimersol X process. 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. The advent of the system that is easy to handle will allow those without special knowledge of the field to use them for the first time.

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 require 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 also little is known about their toxicity. Further, there is a lack of information regarding the role of ILs in many reactions.

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Section B

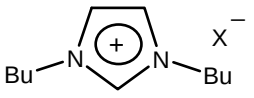
Synthesis and characterization of novel ILs based on 1-n-butyl and 1, 3-di-n-butyl imidazolium salts

1.2.0 Introduction

In the previous Section **A** 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) has been described. Considerable inherent Brønsted acidity of imidazolium ring protons and Lewis acidity of imidazolium nucleus due to positive charge delocalization prompted us to explore their use for Friedlander heteroannulation which is catalyzed by both Lewis and Brønsted acids and it is described in Section **C**. In addition to this, ILs based upon imidazolium cation have good thermal stability, large electrochemical window, most of them liquid at room temperature, have low viscosity and high polarity as compared to other ILs. Thus considering these important features of ILs based upon imidazolium cations, we synthesized several ILs based upon imidazolium cation with different anions of varying basicity and studied their efficacy for Brønsted and Lewis acid catalyzed Friedlander heteroannulation.

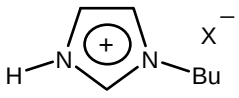
1.2.1 Present work

In this section synthesis and characterization of several ionic liquids based upon the imidazolium cations has been described. Two sets of ILs based on N, N-di-n-butylimidazolium $[bbim]^+$ and N-butylimidazolium $[Hbim]^+$ salts with varying basicity of the anions were synthesized (Figure **7**).



32

[bbim]X



33

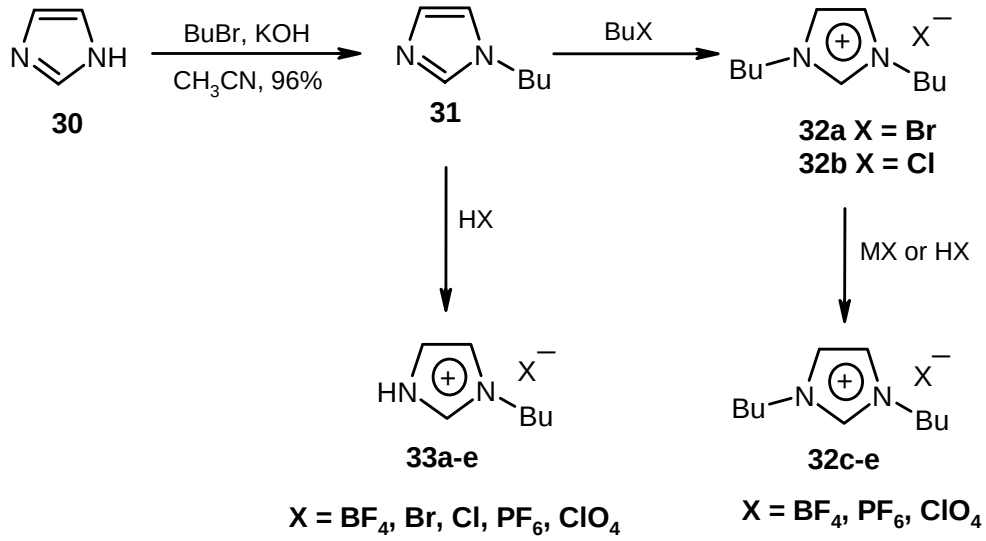
[Hbim]X

X = Cl, Br, BF_4, PF_6, ClO_4

Figure 7. Ionic liquids synthesized, characterized, and studied their efficacy for Friedlander annulation.

1.2.2 Results and Discussion

The ILs were synthesized from an inexpensive raw material such as imidazole **30**. N-Butylation of imidazole **30** by the reaction of imidazole with n-butyl bromide in the presence potassium hydroxide base in acetonitrile gave 1-n-butyl imidazole **31** with excellent yield (96%). Quaternization of 1-n-butyl imidazole **31** with butyl bromide or chloride to afford a 1,3-di-n-butyl imidazolium bromide **32a** or chloride **32b** respectively. Metathesis of 1,3-di-n-butyl imidazolium bromide **32a** with sodium tetrafluoroborate, potassium hexafluorophosphate and perchloric acid gave 1, 3-di-n-butyl imidazolium $[bbim]^+$ ILs **32c-e** with corresponding anions. 1-n-Butyl imidazolium $[Hbim]^+$ ILs **33a-e** were synthesized by direct quaternization of 1-n-butyl imidazole **31** with acids to give 1-n-butyl imidazolium salts $[Hbim]^+$ ILs **33a-e** with corresponding anion of the acids as shown in Scheme **1**.



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 **10**.

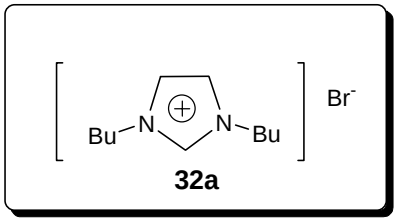
Table 10. List of the ILs prepared

Sr. No.	Ionic Liquid	Sr. No.	Ionic Liquid
1	[bbim]Br (**32a**)	6	[Hbim]BF_4 (**33a**)
2	[bbim]Cl (**32b**)	7	[Hbim]Br (**33b**)
3	[bbim]BF_4 (**32c**)	8	[Hbim]Cl (**33c**)
4	[bbim]PF_6 (**32d**)	9	[Hbim]PF_6 (**33d**)
5	[bbim]ClO_4 (**32e**)	10	[Hbim]ClO_4 (**33d**)

1.2.3 Experimental Section

Preparation and characterization of different ionic liquids (ILs):

(1) 1, 3-Di-*n*-butylimidazolium Bromide [bbim]Br (32a):



32a

A mixture of 1-*n*-butylimidazole (12.4 g, 0.1 mol) and *n*-butyl bromide (15.0 g, 0.11 mol) was heated with stirring at 70 °C for 4 h. Excess *n*-butyl bromide was distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [bbim]Br: colorless liquid (25.06 g; yield 96%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753
^{1}H NMR (CDCl$_3$, 500 MHz) δ	**:**	0.74 (t, *J* = 7.0 Hz, 6H, $\underline{CH_3}$), 1.13 (sept, *J* = 7.6 Hz, 4H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.69 (pent, *J* = 7.5 Hz, 4H, $NCH_2\underline{CH_2}$), 4.13 (t, *J* = 7.0 Hz, 4H, $N\underline{CH_2}$), 7.47 (s, 2H, N$\underline{CH}$C$\underline{H}$N), 10.08 (s, 1H, N$\underline{CH}$N).
^{13}C NMR (CDCl$_3$, 125 MHz) δ	**:**	12.4, 18.4, 31.1, 48.7, 121.6, 135.6.
Elemental analysis	**:**	Anal. Calcd for $C_{11}H_{21}N_2Br$ (261): C, 50.57; H, 8.05; N, 10.73. Found: C, 50.24; H, 7.91; N, 10.54.
GC-MS	**:**	181 (M - X, 31%), 165 (3%), 151 (6%), 138 (37%),

124 (53%), 109 (8%), 97 (100%), 81 (87%), 68 (21%), 57 (29%).

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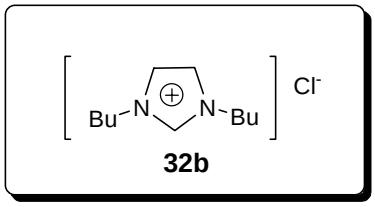
(2) 1, 3-Di-*n*-butylimidazolium Chloride [bbim]Cl (32b):



32b

A mixture of 1-*n*-butylimidazole (12.4 g, 0.1 mol) and *n*-butyl chloride (10.17 g, 0.11 mol) 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: viscous oil (20.61 g; yield 95%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753.
^{1}H NMR	**:**	0.80 (t, *J* = 7.0 Hz, 6H, $\underline{CH_3}$), 1.24 (sept, *J* = 7.6 Hz,
($CDCl_3$, 500 MHz) δ		4H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.72 (pent, *J* = 7.5 Hz, 4H, NCH2$\underline{CH_2}$), 4.22 (t, *J* = 7.0 Hz, 4H, N$\underline{CH_2}$), 7.48 (s, 2H, N$\underline{CH}$CH$\underline{CH}$N), 10.38 (s, 1H, N$\underline{CH}$N).
^{13}C NMR	**:**	13.1, 19.1, 31.9, 49.3, 122.2, 136.9.
($CDCl_3$, 125 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for $C_{11}H_{21}N_2Cl$ (217): C, 60.82; H, 9.67; N, 12.9. Found: C, 60.64; H, 9.71; N, 12.81.
GC-MS	**:**	181 (M - X, 31%), 165 (3%), 151 (6%), 138 (37%), 124 (53%), 109 (8%), 97 (100%), 81 (87%), 68 (21%), 57 (29%).

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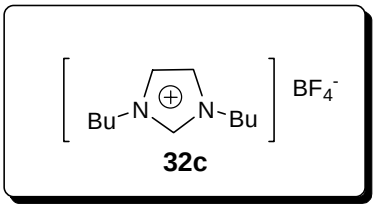
(3) 1, 3-Di-*n*-butylimidazolium Tetrafluoroborate [bbim]BF_4 (32c):



32c

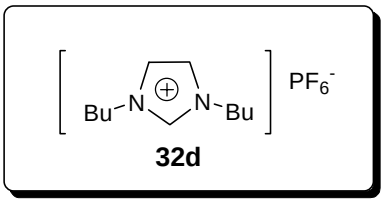
To a solution of 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) (10 g, 0.1 mol) in water (50 mL) was added to a solution of sodium tetrafluoroborate (5.11 g, 1.2 mol) in water (25 mL), and the mixture was stirred at 30 °C for 5 h. The ionic liquid [bbim]BF_4 separated out as an immiscible layer.

The mixture was extracted with dichloromethane (3 ×30 mL). The combined DCM (dichloromethane) layer, which was separated, was washed with water and brine and dried over anhydrous sodium sulfate. The solvent DCM was distilled off under reduced pressure leaving behind the pure IL [bbim]BF_4: viscous oil (8.72 g; yield 86%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753.
^{1}H NMR	**:**	0.96 (t, *J* = 7.0 Hz, 6H, $\underline{CH_3}$), 1.40 (sept, *J* = 7.6 Hz,
($CDCl_3$, 500 MHz) δ		4H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.97 (pent, *J* = 7.5 Hz, 4H, $NCH_2\underline{CH_2}$), 4.41 (t, *J* = 7.0 Hz, 4H, $N\underline{CH_2}$), 7.87 (s, 2H, N<u>CHCH</u>N), 9.20 (s, 1H, N<u>CH</u>N).
^{13}C NMR	**:**	12.9, 18.9, 31.6, 49.3, 122.2, 135.2.
($CDCl_3$, 125 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for $C_{11}H_{21}N_2BF_4$ (268): C, 49.25; H, 7.83; N, 10.44. Found: C, 49; H, 7.71; N, 10.21.
GC-MS	**:**	181 (M - X, 100%), 165 (15%), 151 (12%), 138 (61%), 124 (40%), 107 (33%), 97 (65%), 81 (62%), 68 (16%), 57 (42%).

Similarly, other ionic liquids such as [bbim]PF_6 and [bbim]ClO_4 were prepared as above using the corresponding acid of the anion.

(4) 1, 3-Di-*n*-butylimidazolium hexafluorphosphate [bbim]PF_6 (32d):



32d

Viscous oil (11.17 g; yield 92%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623.
^{1}H NMR	**:**	0.89-0.92 (t, *J* = 7.0 Hz, 6H, $\underline{CH_3}$), 1.29-1.34 (sept, *J* =
($CDCl_3$, 500 MHz) δ		7.6 Hz, 4H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.81-1.84 (pent, *J* = 7.5 Hz, 4H, $NCH_2\underline{CH_2}$), 4.15-4.18 (t, *J* = 7.0 Hz, 4H, $N\underline{CH_2}$), 7.35 (s, 2H, N<u>CHCH</u>N), 8.86 (s, 1H, N<u>CH</u>N).
^{13}C NMR	**:**	13.1, 19.2, 31.8, 49.8, 122.4, 135.2.

($CDCl_3$, 125 MHz) δ

Elemental analysis : Anal. Calcd for $C_{11}H_{21}N_2PF_6$ (325): C, 40.61; H, 6.46; N, 8.61. Found: C, 40.56; H, 6.31; N, 8.52.

GC-MS : 181 (M - X, 100%), 165 (15%), 151 (12%), 138 (61%), 124 (40%), 107 (33%), 97 (65%), 81 (62%), 68 (16%), 57 (42%).

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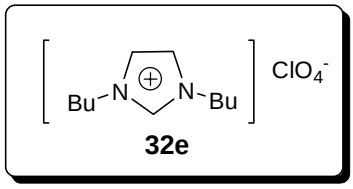
(5) 1, 3-Di-*n*-butylimidazolium perchlorate [bbim]ClO_4 (32e):



32e

Viscous oil (10.55 g; yield 98%).

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

^{1}H NMR : 0.88-0.91 (t, *J* = 7 Hz, 6H, $\underline{CH_3}$), 1.29-1.36 (sept, *J* = 7.6 Hz, 4H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.80-1.85 (pent, *J* = 7.5 Hz, 4H, $NCH_2\underline{CH_2}$), 4.16-4.21 (t, *J* = 7 Hz, 4H, $N\underline{CH_2}$), 7.4 (s, 2H, N$\underline{CH}\underline{CH}$N), 9.02 (s, 1H, N$\underline{CH}$N).

($CDCl_3$, 500 MHz) δ

^{13}C NMR : 13.1, 19.1, 31.8, 49.6, 122.5, 135.3.

($CDCl_3$, 125 MHz) δ

Elemental analysis : Anal. Calcd for $C_{11}H_{21}N_2ClO_4$ (281): C, 46.97; H, 7.47; N, 9.96. Found: C, 46.74; H, 7.21; N, 9.82.

GC-MS : 181 (M - X, 100%), 165 (15%), 151 (12%), 138 (61%), 124 (40%), 107 (33%), 97 (65%), 81 (62%), 68 (16%), 57 (42%).

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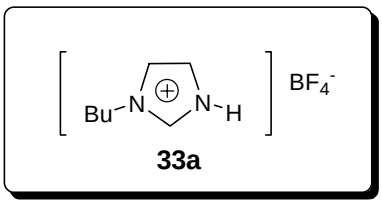
(6) 1-Butylimidazolium Tetrafluoroborate [Hbim]BF_4 (33a):



33a

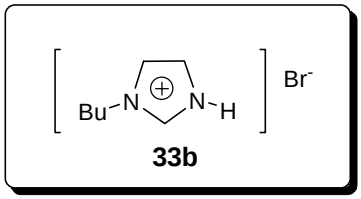
Tetrafluoroboric acid (8.7 g, 0.1 mol) as 40% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (12.4 g, 0.1 mol) at 0 °C under stirring. The reaction mixture was stirred for an additional period of 2 h at the same temperature.

Water was removed from the reaction mixture by subjecting it to evaporation for 4 h at 80 °C under reduced pressure (10 mm Hg) to give the product [Hbim]BF_4: viscous oil (19.97 g; yield 96%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3607, 3153, 2876, 1580, 1466, 894, 762.
^{1}H NMR	**:**	0.56 (s, 3H, $\underline{CH_3}$), 0.95 (s, 2H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.47
($CDCl_3$, 500 MHz) δ		(s, 2H, $NCH_2\underline{CH_2}$), 3.87 (s, 2H, $N\underline{CH_2}$), 7.12 (s, 2H, N$\underline{CH}$C$\underline{H}$N), 8.16 (s, 1H, N$\underline{CH}$N), 14.59 (br s, 1H, $\underline{NH}$);
^{13}C NMR	**:**	13.1, 19.2, 32.1, 48.5, 120.9, 122.8, 135.2.
($CDCl_3$, 125 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for $C_7H_{13}N_2BF_4$ (211): C, 39.81; H, 6.16; N, 13.27. Found: C, 39.81; H, 6.05; N, 13.18.
GC-MS	**:**	124 (M – X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

Similarly, the other ILs, *viz.* [Hbim]Br, [Hbim]Cl, [Hbim]PF_6, and [Hbim]ClO_4, were prepared as above using the corresponding acid of the anion.

(7) 1-Butylimidazolium bromide [Hbim]Br (33b):



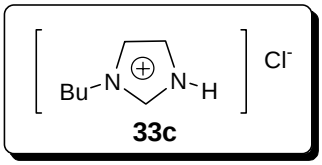
33b

Viscous oil (16.20 g; yield 98%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3607, 3153, 2876, 1580, 1466, 894, 762.
^{1}H NMR	**:**	0.21 (s, 3H, $\underline{CH_3}$), 0.64 (s, 2H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.31
($CDCl_3$, 500 MHz) δ		(s, 2H, $NCH_2\underline{CH_2}$), 4.03 (s, 2H, $N\underline{CH_2}$), 7.39 (s, 1H, N$\underline{CH}$CHN), 7.64 (s, 1H, NH$\underline{CH}$N), 9.18 (s, 1H, N$\underline{CH}$N), 12.22 (br s, 1H, $\underline{NH}$).
^{13}C NMR	**:**	13.1, 19.1, 32.4, 47.3, 120, 124.7, 136.1.
($CDCl_3$, 125 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for $C_7H_{13}N_2Br$ (206): C, 40.97; H, 6.34; N, 13.65. Found: C, 40.54; H, 6.11; N, 13.18.

GC-MS	**:**	124 (M - X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(8) 1-Butylimidazolium chloride [Hbim]Cl (33c):

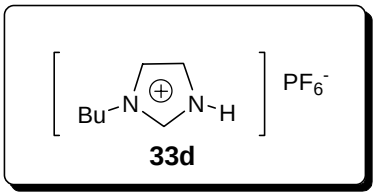


33c

Viscous oil (12.72 g; yield 98%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3607, 3153, 2876, 1580, 1466, 894, 762.
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	0.48 (s, 3H, $\underline{CH_3}$), 0.88 (s, 2H, $CH_3\underline{CH_2}$ $(CH_2)_2N$), 1.42 (s, 2H, $NCH_2\underline{CH_2}$), 4 (s, 2H, $N\underline{CH_2}$), 7.11 (s, 1H, N<u>CH</u>CHN), 7.47 (s, 1H, NH<u>CH</u>N), 8.69 (s, 1H, N<u>CH</u>N), 12.17 (br s, 1H, <u>NH</u>).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	11.7, 17.7, 30.9, 45.7, 118.3, 123.7, 134.7.
Elemental analysis	**:**	Anal. Calcd for $C_7H_{13}N_2Cl$ (161): C, 52.17; H, 8.07; N, 17.39. Found: C, 52.08; H, 8; N, 17.28.
GC-MS	**:**	124 (M - X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(9) 1-Butylimidazolium hexaflouorphosphate [Hbim]PF_6 (33d):



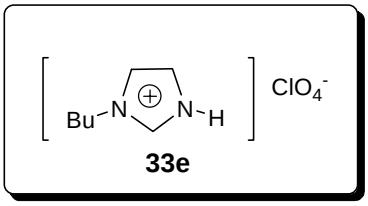
33d

Viscous oil (21.25 g; yield 98%).

IR: (KBr) υ_{max} (cm^{-1})	**:**	3607, 3153, 2876, 1580, 1466, 894, 762.
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	0.42 (s, 3H, $\underline{CH_3}$), 0.84 (s, 2H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.43 (s, 2H, $NCH_2\underline{CH_2}$), 3.96 (s, 2H, $N\underline{CH_2}$), 7.18 (s, 2H, N<u>CHCH</u>N), 8.56 (s, 1H, N<u>CH</u>N), 12.61 (br s, 1H, <u>NH</u>).
^{13}C NMR	**:**	12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7.

($CDCl_3$, 125 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for $C_7H_{13}N_2PF_6$ (269): C, 31.26; H, 4.83; N, 10.40. Found: C, 31.10; H, 4.71; N, 10.18.
GC-MS	**:**	124 (M - X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

(10) 1-Butylimidazolium perchlorate [Hbim]ClO_4 (33e):



33e

Viscous oil (17.78 g; yield 98%).

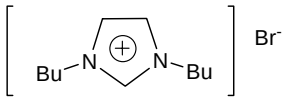
IR: (KBr) υ_{max} (cm^{-1})	**:**	3607, 3153, 2876, 1580, 1466, 894, 762.
^{1}H NMR	**:**	0.71 (t, *J* =7.0 Hz, 3H, CH_3); 1.17 (sept, *J* = 7.6 Hz, 2H, $CH_3\underline{CH_2}(CH_2)_2N$), 1.73 (pent, *J* = 7.5 Hz, 2H, $NCH_2\underline{CH_2}$), 4.16 (t, *J* = 7.0 Hz, 2H, $N\underline{CH_2}$), 7.15 (s, 1H, N<u>CH</u>CHN), 7.42 (s, 1H, NH<u>CH</u>N), 8.57 (s, 1H, N<u>CH</u>N), 11.83 (br s, 1H, <u>NH</u>).
^{13}C NMR	**:**	12.6, 18.5, 31.1, 48.7, 119.5, 121.2, 133.7.
($CDCl_3$, 125 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for $C_7H_{13}N_2ClO_4$ (225): C, 37.33; H, 5.77; N, 12.44. Found: C, 37.10; H, 5.61; N, 12.18.
GC-MS	**:**	124 (M - X, 26%), 109 (3%), 97 (92%), 81 (100%), 68 (26%), 55 (56%).

1.2.4 Spectra

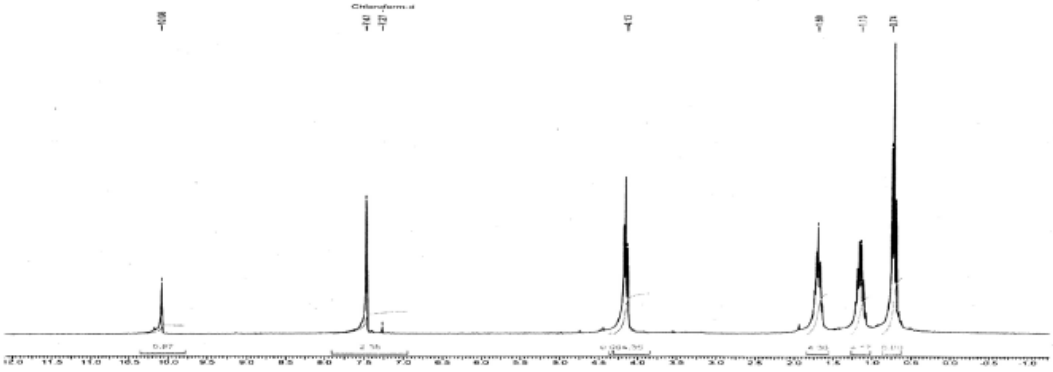
Table 11. ^{1}H & ^{13}C spectra of some selected ILs are given below:

Sr. No.	Spectra
1	^{1}H & ^{13}C spectra of **[bbim]Br (32a)**
2	^{1}H & ^{13}C spectra of **[bbim]BF_4 (32c)**
3	^{1}H & ^{13}C spectra of **[bbim]PF_6 (32d)**
4	^{1}H & ^{13}C spectra of **[Hbim]BF_4 (33a)**
5	^{1}H & ^{13}C spectra of **[Hbim]Br (33b)**
6	^{1}H & ^{13}C spectra of **[Hbim]Cl (33c)**
7	^{1}H & ^{13}C spectra of **[Hbim]ClO_4 (33e)**

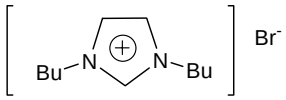
^{1}H NMR of [bbim]Br (**32a**)



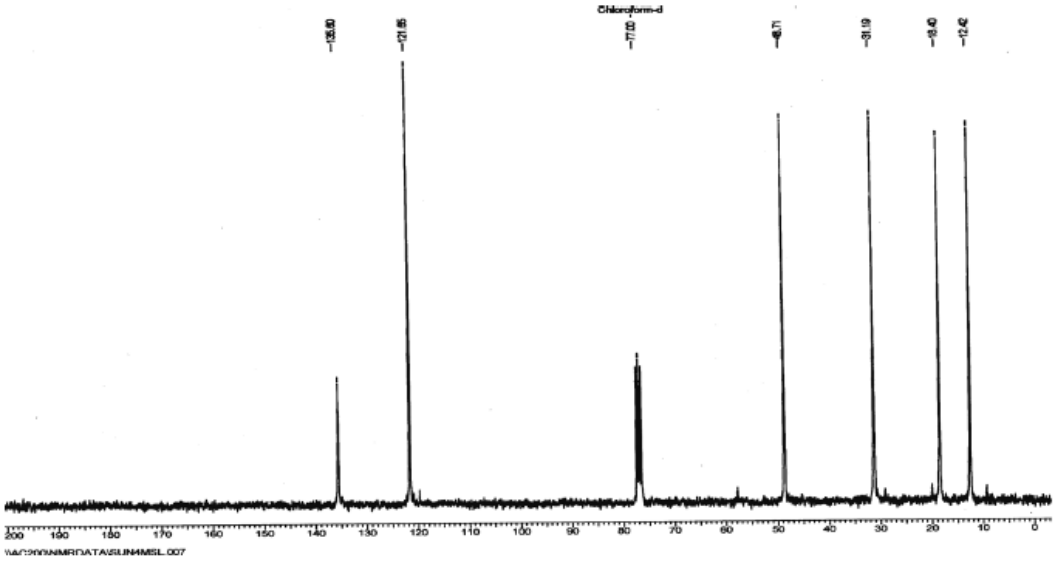
32a



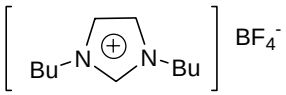
^{13}C NMR of [bbim]Br (**32a**)



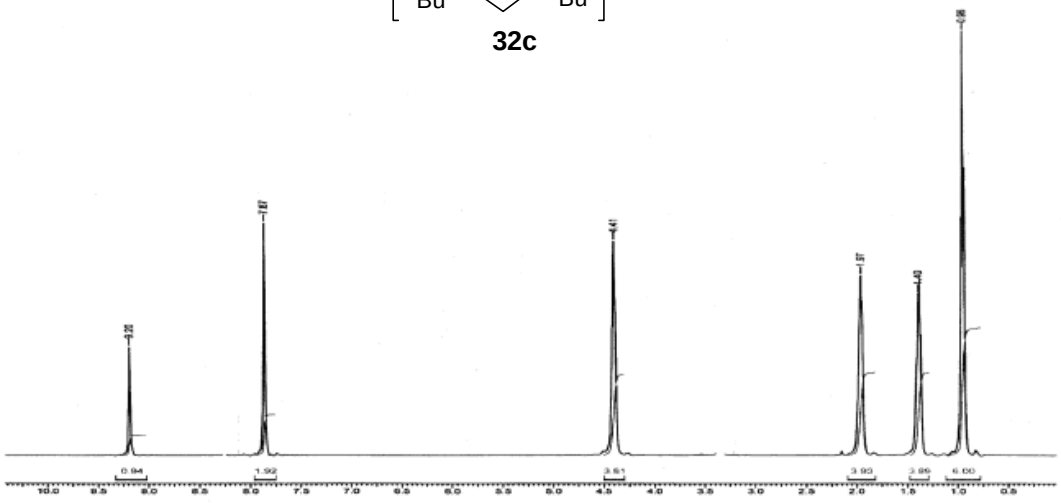
32a



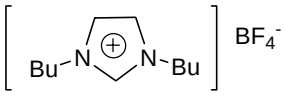
^{1}H NMR of [bbim]BF_4 (**32c**)



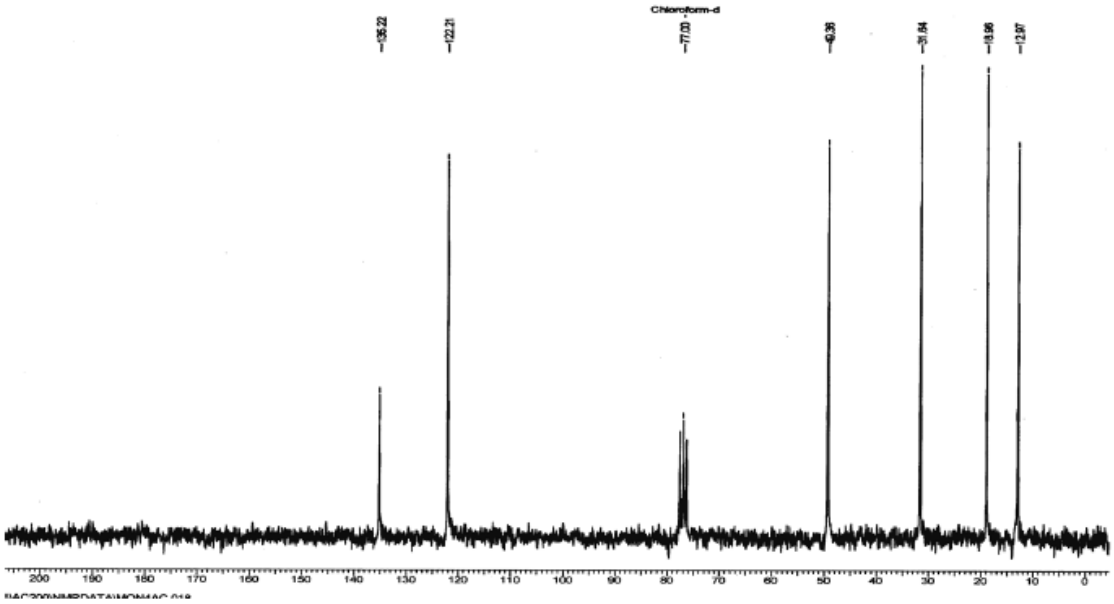
32c



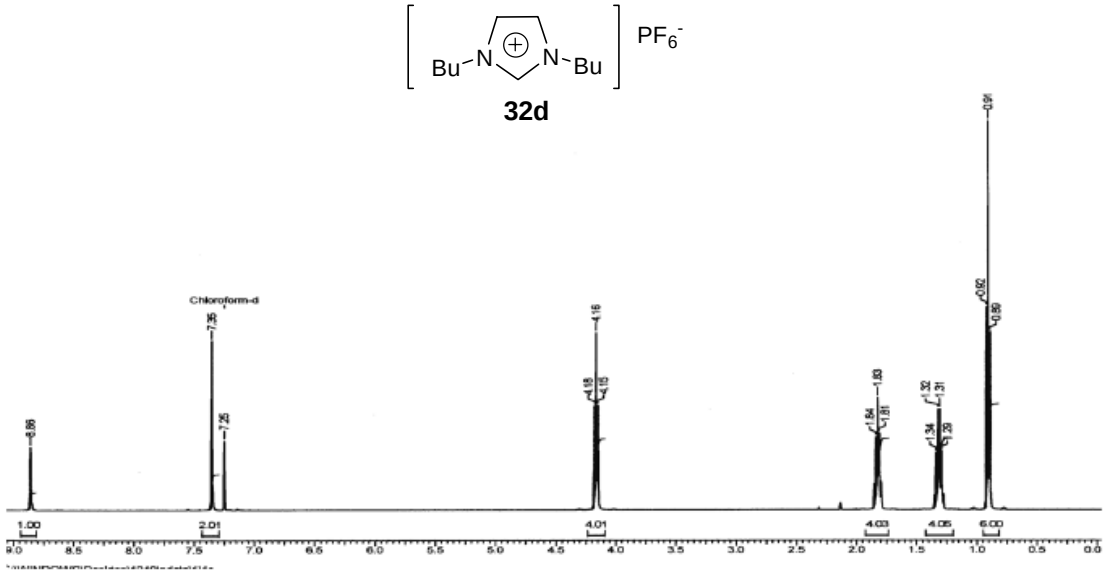
^{13}C NMR of [bbim]BF_4 (**32c**)



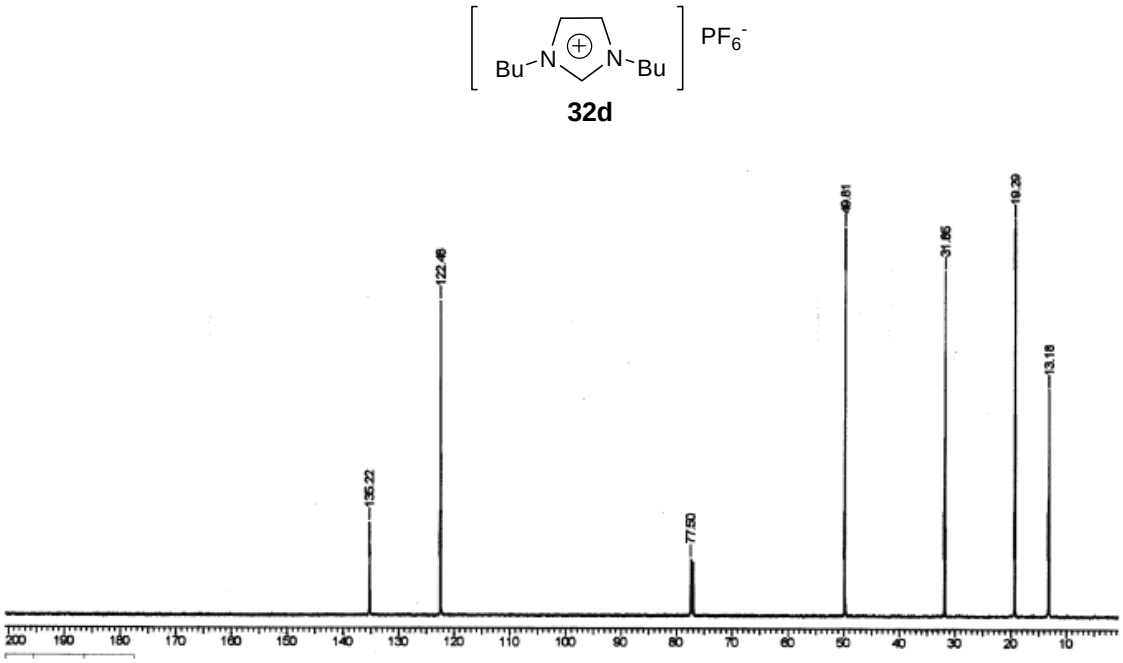
32c



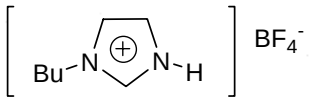
^{1}H NMR of [bbim]PF_6 (**32d**)



^{13}C NMR of [bbim]PF_6 (**32d**)

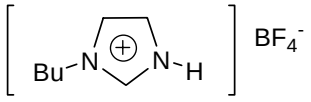


^{1}H NMR of [Hbim]BF_4 (**33a**)

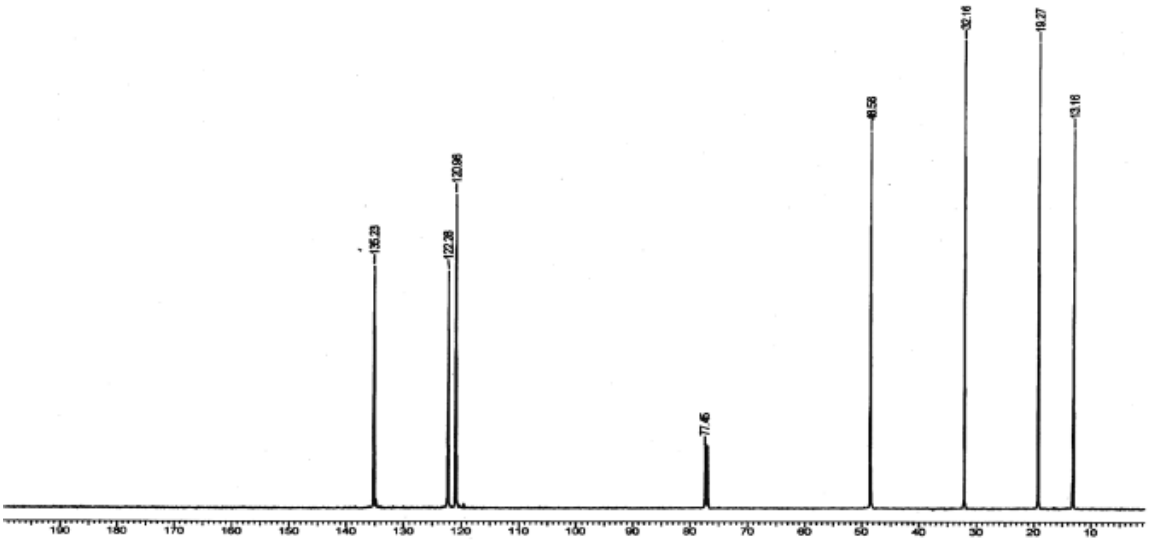


33a

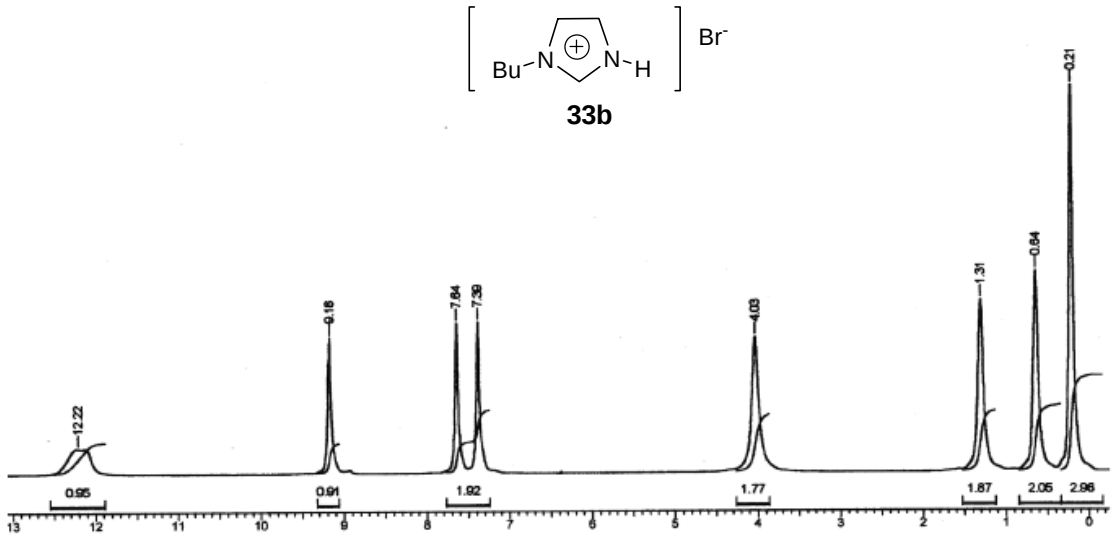
^{13}C NMR of [Hbim]BF_4 (**33a**)



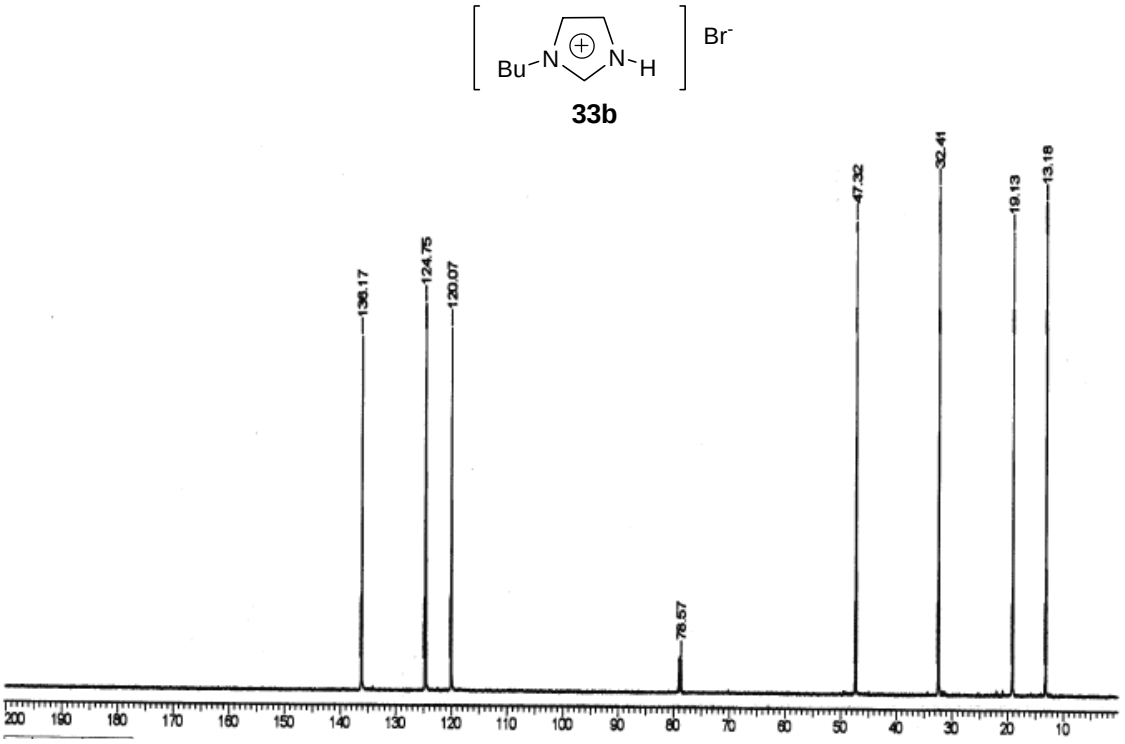
33a



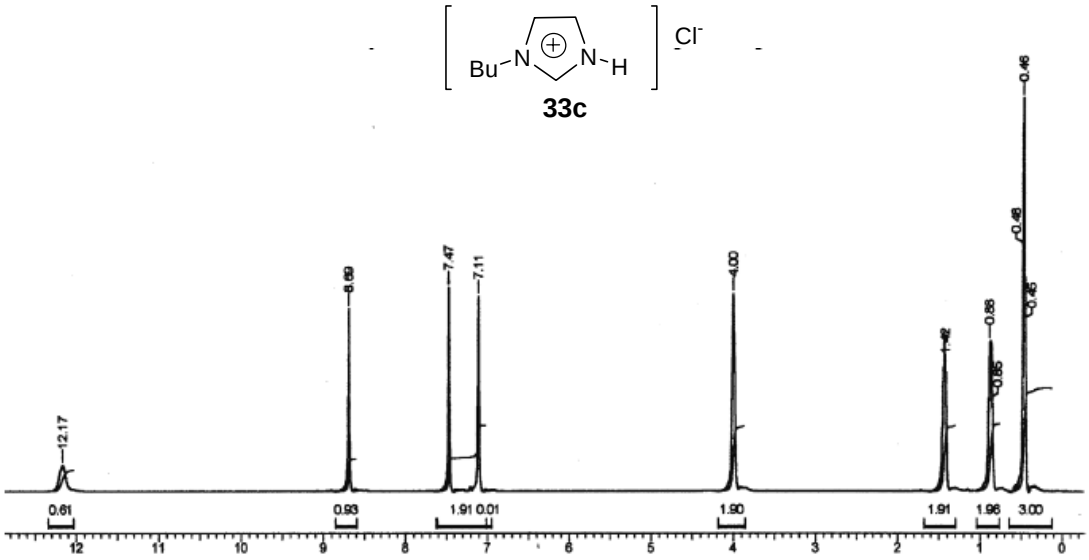
^{1}H NMR of [Hbim]Br (**33b**)



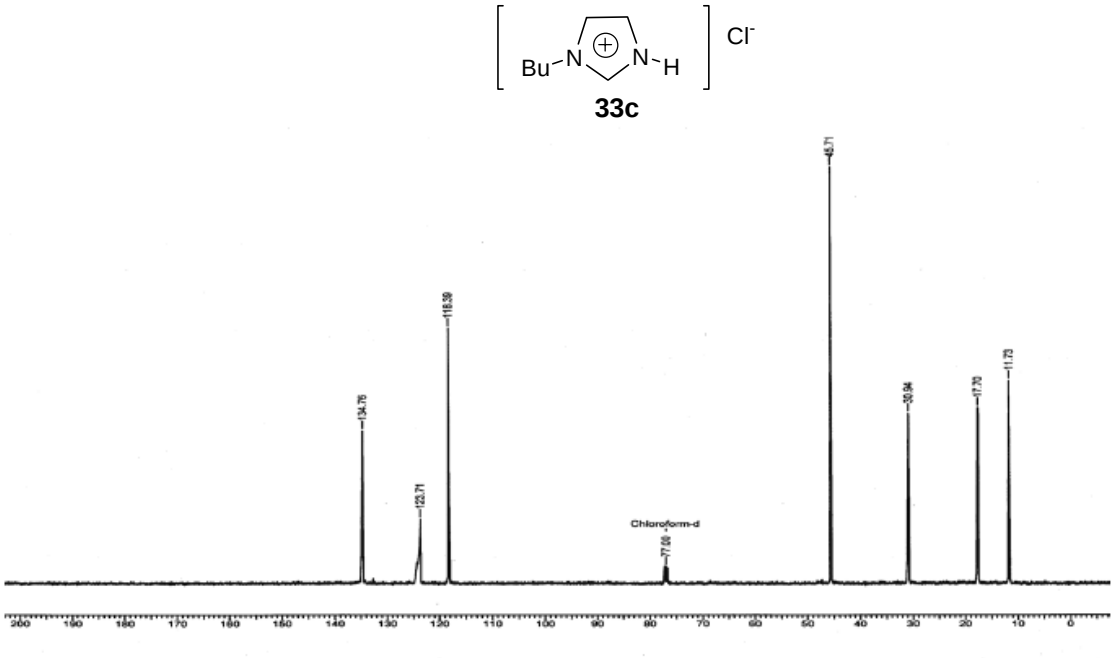
^{13}C NMR of [Hbim]Br (**33b**)



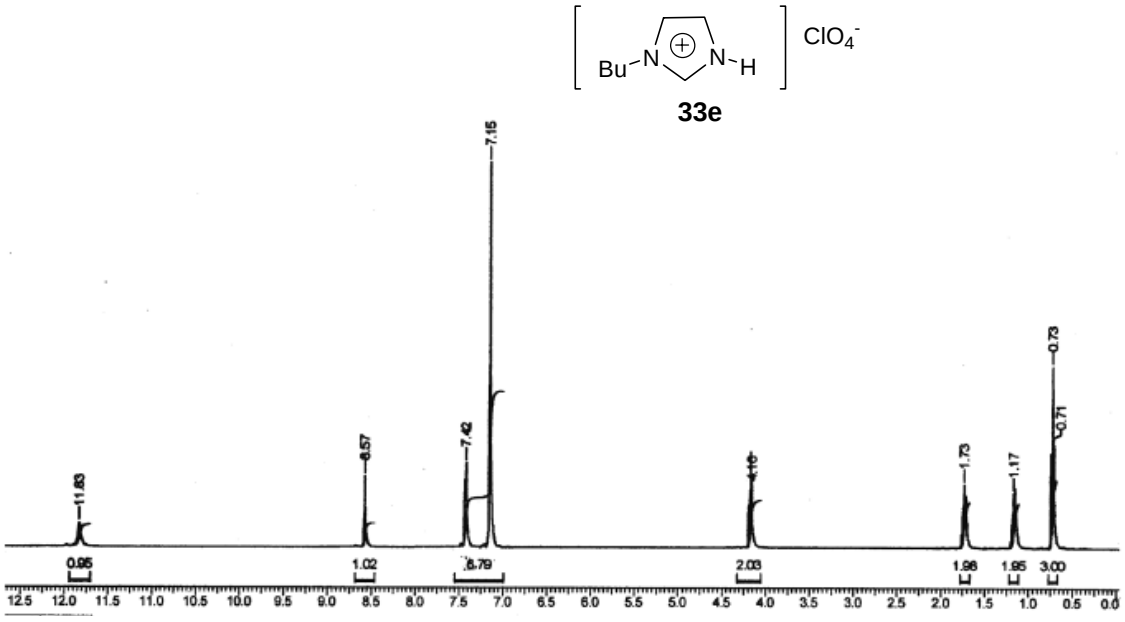
^{1}H NMR of [Hbim]Cl (**33c**)



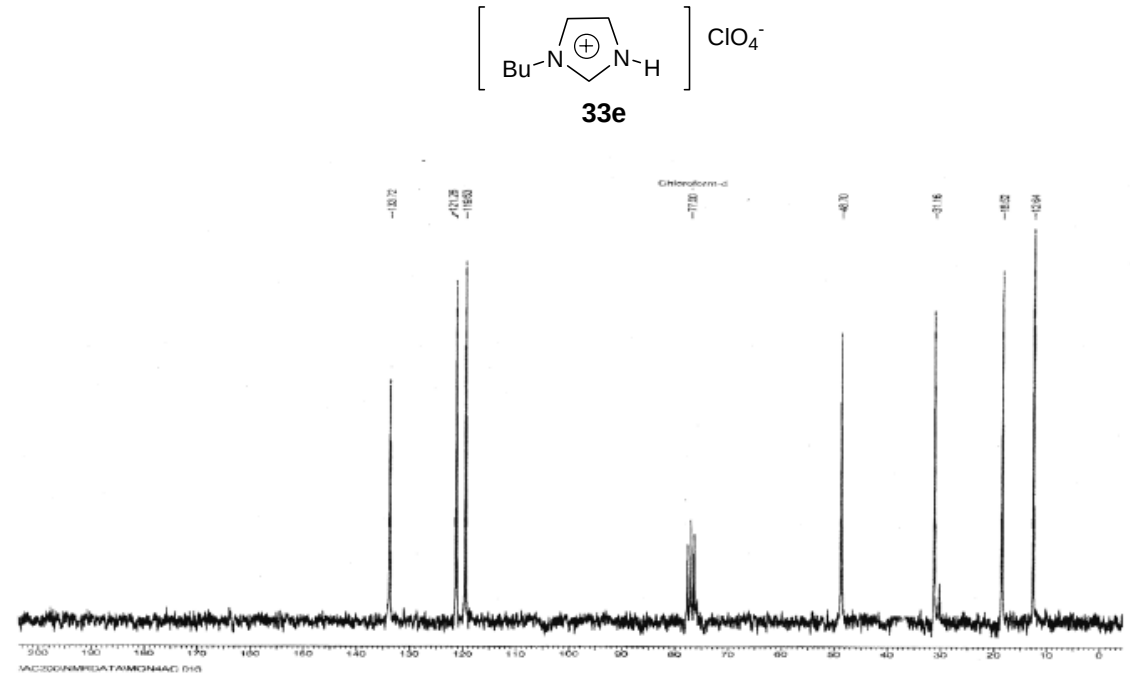
^{13}C NMR of [Hbim]Cl (**33c**)



^{1}H NMR of [Hbim]ClO_4 (**33e**)



^{13}C NMR of [Hbim]ClO_4 (**33e**)



Section C

Ionic Liquid-Promoted Synthesis of Quinoline by Friedlander Heteroannulation Reaction

1.3.0 Introduction

This section describes the evaluation of the effect of several room-temperature ionic liquids (ILs) based on 1-(n-butyl) imidazolium $[Hbim]^+$ and di- (n-butyl) imidazolium $[bbim]^+$ cations with varying anions on the Friedlander heteroannulation reaction. On screening, 1-butylimidazolium tetrafluoroborate $[Hbim]BF_4$ (**33a**)was found to be the best ionic liquid for the heteroannulation reaction and the reasons to this effect are well explained. The reactions proceed very well under relatively mild conditions without any added catalyst. The IL acts as a promoter for this regiospecific synthesis and can be recycled. By this green approach, various biologically active substituted quinolines and fused polycyclic quinolines were prepared in excellent yields and purity and well-characterized.

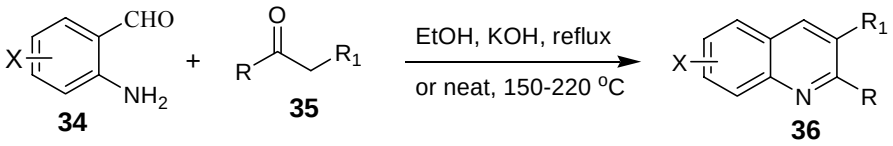
The quinoline nucleus occurs in several natural compounds (cincona alkaloids) and pharmacologically active substances displaying a broad range of biological activity.[1] The biological activity of quinoline compounds has been found in the form of antiasthmatic,[2] antibacterial,[3] antiinflammatory[4] and antihypertensive[5] properties. In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes.[6] They are also known for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties.[7]

1.3.1 Review of Literature

Considering the significant applications in the fields of medicinal, bioorganic, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinolines. Consequently, various procedures such as the Skraup, Doebner-Von Miller, Friedlander and Combes methods have been developed for the synthesis of quinoline derivatives.[8,9] Among the various methods that are available for the synthesis of quinoline, the Friedlander annulations is still one of the most simple and straightforward approaches for the synthesis of polysubstituted quinolines. Although it has been known for more than a century, it is still the most useful method for the preparation of such a class of compounds.

Friedlander annulation (1882) [9b]

In 1882, Pual Friedlander discovered the reaction of *o*-aminoarylaldehyde with active methylene compounds for the synthesis of quinoline. The Friedlander quinoline synthesis consists of the condensation followed by a cyclodehydration between *o*-amino aryl aldehydes/ketones and aldehyde/ketone/ketoesters having active α-methylene group. Generally Friedlander reactions are carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of a base or by heating a mixture of the reactants at high temperatures ranging from 150 to 220 ^{o}C in the absence of a catalyst[9b, 10](Scheme **2**).

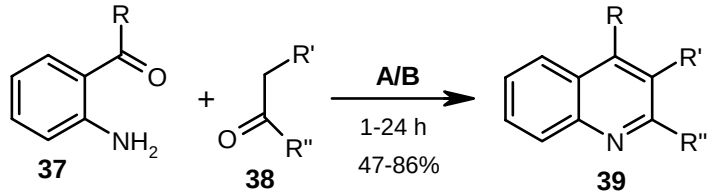


Scheme 2

Under thermal or basic catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone, deoxybenzoin and β-keto esters.[11a] This difficulty was overcome by Fehnels work; he reported acid catalysts are more effective than base catalysts for Friedlander reaction. Also in recent years various methods have been developed for an efficient synthesis of quinoline by Friedlander heteroannulation. Some of the important methods are described below.

Fehnel's approach (1966)[11]

Fehnel, E. D. have reported the Friedlander synthesis of quinolines **39** by using sulfuric acid as a catalyst refluxing in acetic acid and also under solvent-free condition in a temperature range between 100 -200 ^{o}C using hydrochloric acid as a catalyst (Scheme **3**).



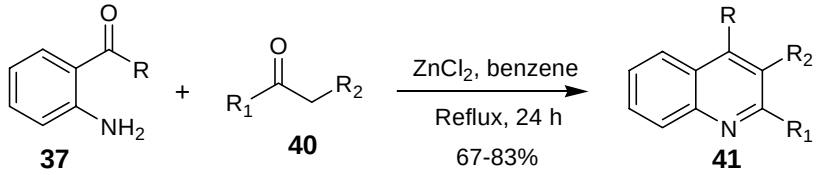
Method A : AcOH:H_2SO_4, reflux.

Method B : HCl, neat, 100-200 ^{o}C

Scheme 3

Walser's approach (1975)[12]

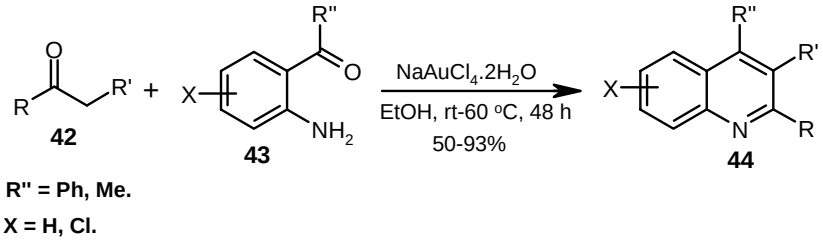
Walser, A. *et al.* reported the $ZnCl_2$ catalyzed synthesis of quinolines **41** by Friedlander annulations in benzene at reflux temperature (Scheme **4**).



Scheme 4

Arcadi's approach (2003)[13]

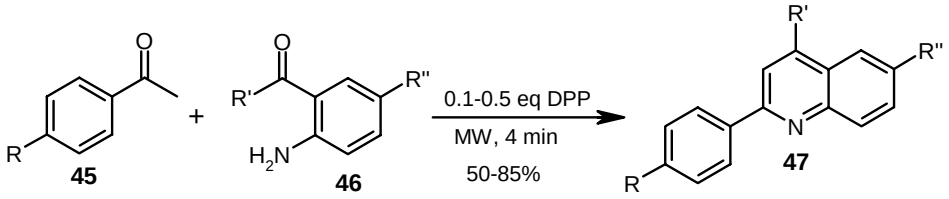
Arcadi, A *et al.* reported a new green approach for Friedlander synthesis of quinoline derivatives **44** using gold(III) as catalyst *via* a sequential condensation/annulation reaction in ethanol at room temperature to 60 ^oC (Scheme **5**).



Scheme 5

Kwon's approach (2003)[14]

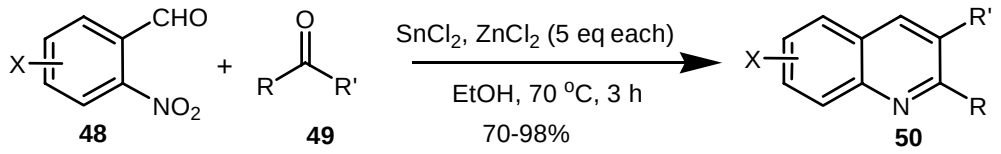
Kwon, T. W. *et al.* have reported microwave enhanced solvent-free synthesis of a library of quinolines derivatives **47** by using 0.1–0.5 equiv. of diphenylphosphate as a catalyst (Scheme **6**).



Scheme 6

Miller's approach (2003)[15]

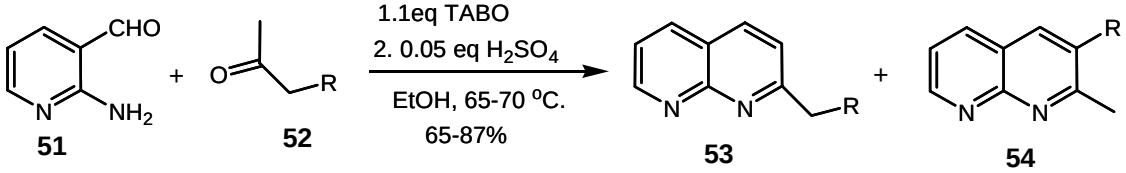
Miller, B. L. *et al.* reported a mild, efficient, high-yielding one-pot synthesis of quinolines **50** from direct *o*-nitro benzaldehyde *via* reduction-condensation sequences by using $ZnCl_2$: $SnCl_2$ catalytic system as shown in Scheme **7**.



Scheme 7

McWilliams's approach (2003)[16]

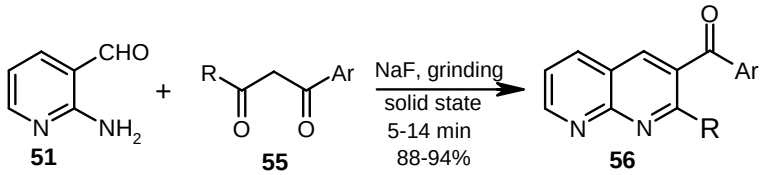
McWilliams, J. C. *et al.* reported the highly regioselective Friedlander annulations with unmodified ketones employing novel amine catalysts. They evaluated role of different catalyst such as hydroxide, alkoxide, various *primary*, *sec*- and *tert*- cyclic and acyclic amines. They found that oxide catalysts yielded the 2,3-dialkyl substituted products, and cyclic secondary amines provided the 2-alkylsubstutited products regioselectively. In particular, pyrrolidine derivatives provided the highest regioselectivity favoring the 2-substituted products. The most reactive and regioselective catalyst was the bicyclic pyrrolidine derivative, TABO (1, 3, 3-trimethyl-6-azabicyclo[3.2.1]octane) (Scheme **8**).



Scheme 8

Mogilaiah's approach (2003)[17]

Mogilaiah, K. *et al*. described a rapid synthesis of 1,8-naphthyridine derivatives **56** using sodium fluoride catalyzed Friedlander condensation of 2-aminonicotinaldehye **51** with various carbonyl compounds **55** containing α-methylene group by grinding at room temperature as shown in Scheme **9** below.



Scheme 9

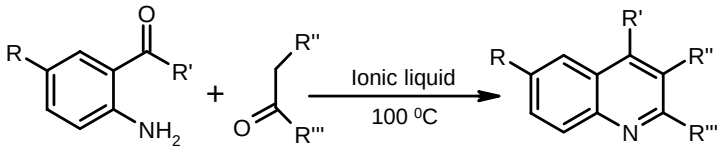
However, most of the synthetic protocols reported so far suffer from high temperatures, prolonged reaction times, harsh reaction conditions, low yields of the

products and the use of hazardous and often expensive acid and base catalysts. Moreover, this reaction is usually carried out in polar solvents such as acetonitrile, THF, DMF and DMSO leading to tedious work-up procedures. These processes also generate waste-containing solvent and catalyst, which have to be recovered, treated, and disposed off. The main disadvantage of most of the existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or re-used. Therefore, the development of simple, convenient and environmentally benign approaches for the synthesis of quinolines is still desirable.

1.3.2 Present Work

In recent years, studies of low waste routes and reusable reaction media for enhanced selectivity and energy minimization are the key interests of synthetic organic chemists world over.[18] In this context, in recent times, the use of room-temperature ionic liquids (ILs) as "green" solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapor pressure, and easy recyclability.[19] They have the potential to be highly polar yet non-coordinating.

Thus, we explored the use of ILs as green reaction media as well as promoters for synthesis of biologically active quinolines and related polyheterocycles by using Friedlander heteroannulation protocol in the absence of any added catalyst. For this purpose, 2-aminoacetophenone (**57a**) and 2-amino-5-chlorobenzophenone (**57b**) were reacted with a variety of ketones/ketoesters (**58**) in the ionic liquid as shown in Scheme **10**.



57 **58a-k** **59a-v**

57a R = H, R' = CH_3
57b R = Cl, R' = Ph

Scheme 10

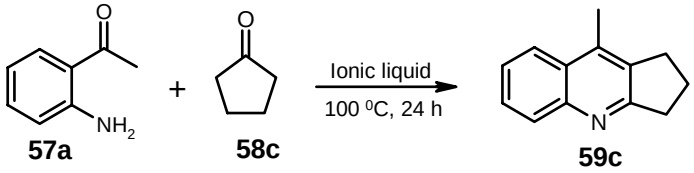
Herein we disclose the successful outcome of this endeavor in which *o*-amino substituted aromatic carbonyls and ketones/diketones/ketoesters (containing active

methylene groups) afforded excellent yields of the annulation products in the IL, 1-butylimidazolium tetrafluoroborate [Hbim]BF_4 among several ILs screened.

1.3.3 Results and Discussion

In view of the emerging importance of the imidazolium based ILs as novel reaction media, we synthesized several ILs based upon imidazolium cation and they were fully characterized, the details one described in the Section **B** of this chapter. In this Section **C** efficacy of ionic liquids as a solvents as well as promoter for the synthesis of the biologically active quinolines and related polyheterocycles using the Friedlander has been studied.

The synthesized novel ILs were then tested as solvents and promoters for the typical reaction of *o*-amino acetophenone **57a** with cyclopentanone **58c** in the absence of any added catalyst to afford 9-methyl-2, 3-dihydro-1*H*-cyclopenta[*b*]quinoline **59c** (Scheme **11**). The reactions in the various ILs were carried out at 100 °C for 24 h. The yield data are recorded in Tables **12** and **13**.



Scheme 11: Screening of ILs for Friedlander annulation

Table 12. Screening of [Bbim] ILs for the synthesis of **59c**

Entry	Ionic liquid	pK_a of acid of the anion	Yield (%)
1	[Bbim]ClO_4	-11	37
2	[Bbim]Br	-9	50
3	[Bbim]Cl	-7	50
4	[Bbim]PF_6		70
5	[Bbim]BF_4	0.5	75

Table 13. Screening of [Hbim] ILs for the synthesis of **59c**

Entry	Ionic liquid	pK_a of acid of the anion	Chemical shift NH-proton δ (ppm)	Yield (%)
1	[Hbim]ClO_4	-11	11.83	50
2	[Hbim]Br	-9	12.17	75
3	[Hbim]Cl	-7	12.22	73.8
4	[Hbim]PF_6		12.61	90
5	[Hbim]BF_4	0.5	14.59	96

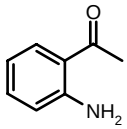
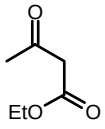
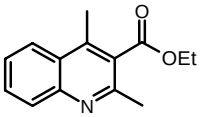
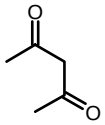
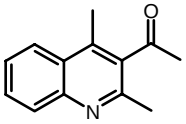
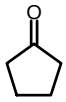
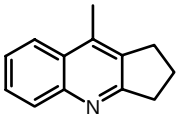
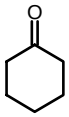
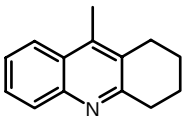
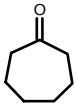
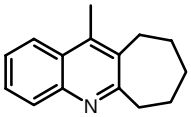
The efficacy of the ILs to promote these heterocyclization reactions was correlated to the basicity of the anions of the ILs. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. Thus, the yield of 9-methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (**59c**) for the reaction in different ILs was compared against the *p*Ka values of the corresponding acid of the anion (Tables **12** and **13**). The *p*Ka values were obtained from literature.[20] It was observed that with increasing basicity of the anion (increasing *p*Ka of the corresponding acid) there is a progressive increase in yield. This correlation was more evident in the case of [Hbim] ILs when the yield of **59c** was compared with -NH proton chemical shifts of the ILs indicative of the Brønsted acidities of the ILs (Table **13**). The yield of **59c** increases progressively with increasing Brønsted acidity of the ILs as indicated by the increasing downfield shift of the NH proton**.**

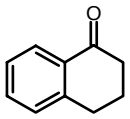
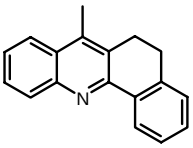
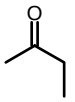
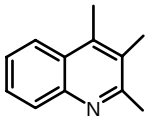
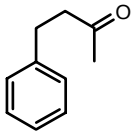
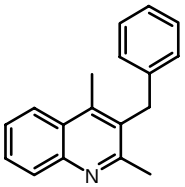
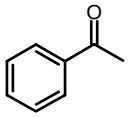
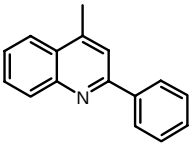
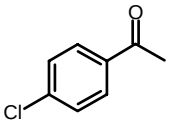
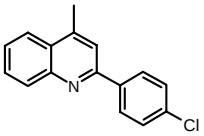
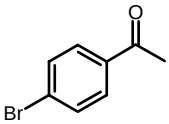
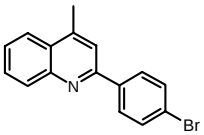
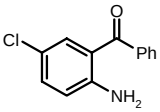
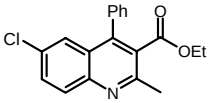
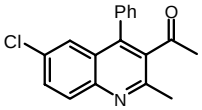
It becomes evident from the foregoing results, the IL [Hbim]BF_4 afforded the best results. Consequently, all further studies were conducted using this IL as the reaction medium. The reaction of *o*-aminoacetophenone (**57a**) with cyclopentanone (**58c**) in [Hbim]BF_4 was then carried out at temperatures below and above 100 °C, respectively. At 90 °C, the conversion does not go beyond 30% even after 24 h. At 130 °C, the reflux temperature of cyclopentanone, the IL decomposed to give a black charry material. This was further confirmed by running a thermal gravimetric analysis (TGA), differential thermal gravimetric (DTG) analysis and differential thermal analysis (DTA) of a pure sample of [Hbim]BF_4. The thermal decomposition started at 152.7 °C and at 335.3 °C complete weight loss was observed. An endotherm which

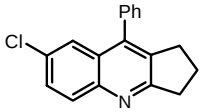
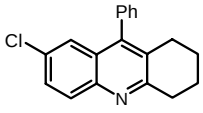
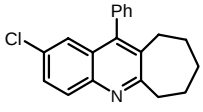
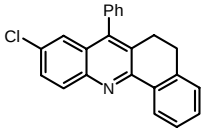
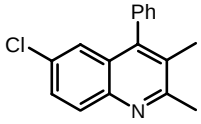
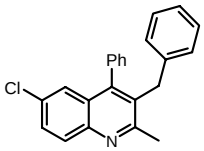
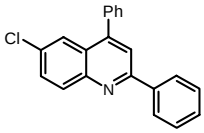
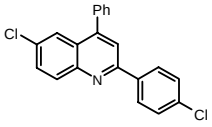
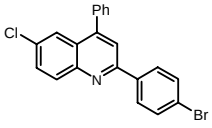
was observed at 324.5 °C in DTA may be the result of the decomposition of the BF_4^- species into the stable BF_3 and F^-. Hence, all subsequent reactions using this IL were carried out at 100 °C.

The IL [Hbim]BF_4 was used as a reaction medium and promoter to generate a variety of quinolines and fused polycyclic quinolines (**59a-v**) by the reaction of 2-aminoacetophenone (**57a**) and 2-amino-5-chloro-benzophenone (**57b**) with cyclic/acyclic ketones and keto esters (**58a-k**), respectively. The results are recorded in Table **14**.

Table 14. Synthesis of the Quinolines 59a-v in [Hbim]BF_4

Entry	Compound 57	Compound 58	Product 59a-v	Time (h)	Yield (%)		
					First	Recycle I	Recycle II
1	 **57a**	 **58a**	 **59a**	**3**	**94**	**93**	**93**
2	**57a**	 **58b**	 **59b**	**3.3**	**94**	**94**	**93**
3	**57a**	 **58c**	 **59c**	**3**	**96**	**95**	**94**
4	**57a**	 **58d**	 **59d**	**3**	**96**	**96**	**94**
5	**57a**	 **58e**	 **59e**	**3**	**97**	**96**	**95**

6	**57a**	 **58f**	 **59f**	**4**	**94**	**94**	**93**
7	**57a**	 **58g**	 **59g**	**6**	**93**	**92**	**90**
8	**57a**	 **58h**	 **59h**	**3.3**	**93**	**93**	**91**
9	**57a**	 **58i**	 **59i**	**6**	**93**	**92**	**91**
10	**57a**	 **58j**	 **59j**	**6**	**94**	**93**	**92**
11	**57a**	 **58k**	 **59k**	**6**	**94**	**94**	**93**
12	 **57b**	**58a**	 **59l**	**3**	**94**	**94**	**93**
13	**57b**	**58b**	 **59m**	**3.3**	**93**	**93**	**91**

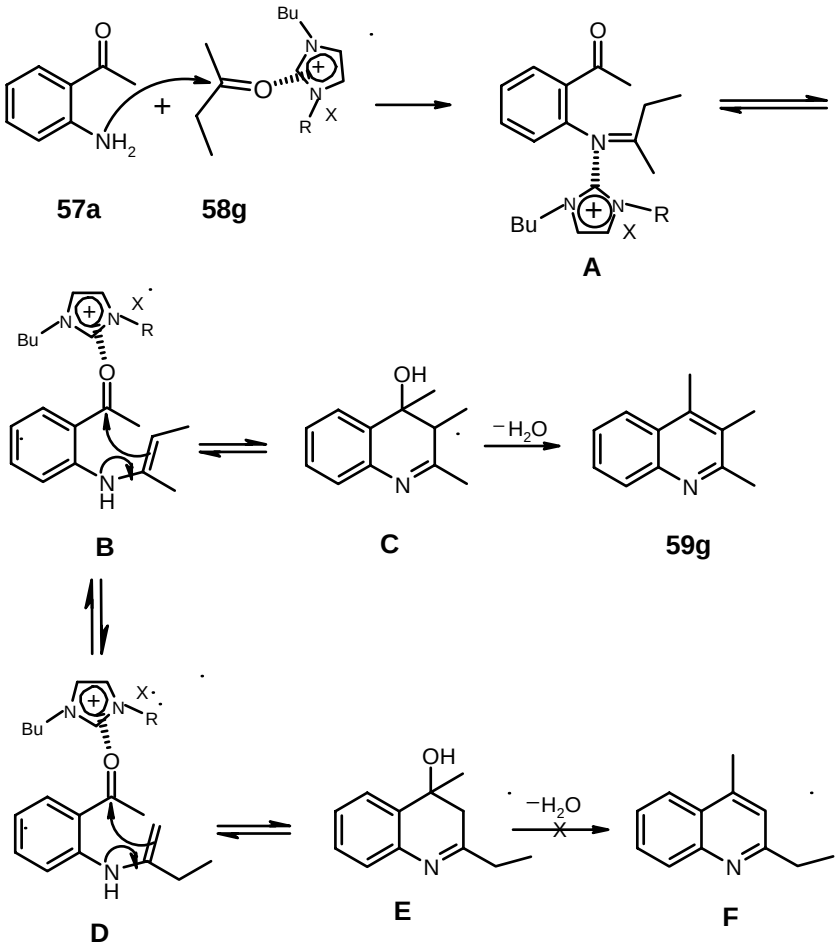
14	**57b**	**58c**	 **59n**	**3**	**97**	**96**	**95**
15	**57b**	**58d**	 **59o**	**3**	**98**	**96**	**96**
16	**57b**	**58e**	 **59p**	**3**	**97**	**95**	**95**
17	**57b**	**58f**	 **59q**	**4**	**93**	**92**	**91**
18	**57b**	**58g**	 **59r**	**6**	**91**	**90**	**90**
19	**57b**	**58h**	 **59s**	**3.3**	**93**	**93**	**92**
20	**67b**	**58i**	 **59t**	**6**	**92**	**92**	**90**
21	**57b**	**58j**	 **59u**	**6**	**90**	**90**	**88**
22	**57b**	**58k**	 **59v**	**6**	**92**	**92**	**90**

All the reactions proceed to completion at the time indicated in the Table **14** without any catalyst, and the yield data are for the isolated products. All the compounds were well characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analyses. In all the cases, the IL could be recovered almost completely (98%) and recycled twice with only a very marginal loss in yield (1-2%) in the second recycle.

Theoretically, the Friedlander reaction with unsymmetrical ketones such as ethyl methyl ketone **58g** can have two possible modes of cyclization giving rise to two regioisomers *viz*., 2,3-dimethylquinoline and 2-ethylquinoline, respectively. Depending upon the catalyst, the modes of cyclization can change. In the Brønsted acid catalyzed reaction, 2, 3-dimethylquinoline **59g** was reported to be the major product (80%) along with minor amounts (20%) of the 2-ethylquinoline **F**, whereas under basic conditions, the 2-ethylquinoline **F** was the major product and 2,3-dimethylquinoline **59g** was the minor product.[11a] To our surprise, however, the ionic liquid promoted Friedlander reaction with unsymmetrical ketones such as ethyl methyl ketone **58g**/benzyl acetone **58h** respectively afforded regiospecifically the 2,3-dialkylquinoline only in excellent isolated yields (entries 7, 8, 18, and 19, Table **14**). No trace of the isomeric 2-ethylquinoline **F** could be detected either on TLC or in ^{1}H NMR of the crude product mixture before purification by column chromatography. The relatively mild conditions of the reaction and the absence of Brønsted/Lewis acid catalyst, both factors promoted by the use of the IL as the reaction medium may have contributed to this phenomenon. Additionally, the polarity and the large electrochemical window of the IL may also have contributed to the observed regiospecificity.

1.3.4 Plausible Mechanism

A plausible mechanism involving ILs as catalyst for Friedlander heteroannulation reaction is shown in Scheme **12**:



Scheme 12. Plausible Mechanism

The Brønsted and Lewis acidic character of the ILs can activate the carbonyl group of ketone **58g,** it can facilitate a nucleophilic attack of amino group of the *o*- amino aryl ketone **57a** giving rise to imine **A,** which tautomerizes to the more stable enamine **B.** Ionic liquid further activates carbonyl group of **B** and promotes the intramoleculer nucelophilic attack of β-carbon atom of **B** on activated carbonyl group, giving rise to alcohol **C** which readily undergoes aromatization *via* dehydration to form the stable quinoline **59g**. The formation of an isomer **F** was not observed under these mild reaction conditions.

1.3.5 Summary

It is clear from our results that the ionic liquid catalyzed reaction of *o*-amino substituted aromatic carbonyls with cyclic and acyclic ketones provides an efficient new tool for the regiospecific synthesis of quinolines and fused polycyclic quinolines

under relatively mild conditions. In conclusion, we have developed a green approach to Friedlander synthesis of quinolines that requires neither harsh conditions nor the use of hazardous acids or bases. The solvent IL can be recovered and reused twice without any loss of activity. Several new ILs were synthesized, characterized and screened for this heterocyclization reaction. The efficacy of the ILs for the heterocyclization reaction has been correlated to the acidity of the ILs in terms of basicity of the anions and ^{1}H NMR chemical shifts. The moderate reaction conditions, absence of a catalyst and recyclability of the nonvolatile IL makes this an environment friendly methodology amenable for scale-up.

1.3.6 Experimental Section

Preparation of quinolines and polyheterocycles: General Procedure for 59a-v:

A mixture of *o*-amino-substituted ketones (**57a** or **57b,** 1 mmol), ketone (**58,** 1 mmol), and [Hbim]BF_4 (2 mL) was heated at 100 °C with good stirring for the appropriate time mentioned in Table **14**. The completion of reaction was monitored by TLC using eluent 20% ethyl acetate in petroleum ether. After completion of the reaction, the reaction mixture was diluted with water (25 mL). The solid quinoline product which separated out was filtered, washed with water, and dried. The quinolines which are liquids were extracted with ethyl acetate (2×10 mL) and dried over sodium sulfate, and the solvent was evaporated under reduced pressure to furnish crude product. The crude products, thus isolated, were pure (single spot on TLC). They were subjected to further purification by chromatography through a column of silica gel using 20% EtOAc in petroleum ether as eluent to yield the desired substituted quinolines **59** in an average 85-96% and were fully characterized. The aqueous layer consisting of the IL was subjected to distillation (80 °C at 10 mm Hg) for 2 h to remove water, leaving behind the IL [Hbim]BF_4 (recovery 98%), which was recycled.

Characterization data of quinoline 59a-v:

2,4-Dimethylquinoline-3-carboxylic acid ethyl ester (59a):

Nature of compound **:** Yellow oil.

IR: (KBr) υ_{max} (cm^{-1}) **:** 3070, 2930, 2873, 1725, 1614, 1589, 1214, 1082, 578.

^{1}H NMR **:** 1.8 (t, *J* = 7 Hz, 3H), 3 (s, 3H), 3.1 (s, 3H), 4.8 (q, *J* = 7

($CDCl_3$, 500 MHz) δ		Hz, 2H), 7.8-8.4 (m, 4H).
^{13}C NMR	**:**	14.1, 15.4, 23.6, 61.4, 123.8, 125.7, 126.1, 127.9, 129.2,
($CDCl_3$, 125 MHz) δ		129.8, 141.2, 147, 154.2, 168.9.
Elemental analysis	**:**	Anal. Calcd for $C_{14}H_{15}NO_2$ (230): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.12; H, 6.48; N, 6.05.
LC-MS	**:**	230 (M^+).

1-(2, 4-Dimethylquinolin-3-yl)ethanone (59b):

Nature of compound	**:**	Yellow oil.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3068, 2959, 1703, 1614, 1585, 1208, 758.
^{1}H NMR	**:**	2.57 (s, 3H), 2.58 (s, 3H), 2.62 (s, 3H), 7.53-8.01 (m,
($CDCl_3$, 500 MHz) δ		4H).
^{13}C NMR	**:**	15, 23.3, 32.4, 123.5, 126.2, 129, 129.6, 135.6, 138.4,
($CDCl_3$, 125 MHz) δ		146.7, 152.4, 206.3.
Elemental analysis	**:**	Anal. Calcd for $C_{13}H_{13}NO$ (200): C, 78.38; H, 6.58; N, 7.03. Found: C, 78.12; H, 6.48; N, 6.85.
LC-MS	**:**	200 (M^+).

9-Methyl-2, 3-dihydro-1*H*-cyclopenta[*b*]quinoline (59c):

Nature of compound; mp	**:**	Light yellow solid, 60 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3065, 2957, 1613, 908, 751.
^{1}H NMR	**:**	2.2 (m, 2H), 2.5 (s, 3H), 3 (t, *J* = 7.5 Hz, 2H), 3.3 (t, *J* =
($CDCl_3$, 500 MHz) δ		6.9 Hz, 2H), 7.46-8 (m, 4H).
^{13}C NMR	**:**	14.6, 22.7, 29.4, 34.8, 123.1, 125, 126.9, 127.8, 128.9,
($CDCl_3$, 125 MHz) δ		133.7, 137.8, 147.2, 166.7.
Elemental analysis	**:**	Anal. Calcd for $C_{13}H_{13}N$ (183): C, 85.21; H, 7.15; N, 7.64. Found: C, 85.12; H, 6.98; N, 7.55.
GC-MS	**:**	183 (M^+, 40%), 168 (100%), 154 (5%), 140 (5%), 127 (10%), 115 (13%), 102 (5%), 90 (18%), 77 (91%), 63 (9%), 57 (3%).

9-Methyl-1, 2, 3, 4-tetrahydroacridine (59d):

Nature of compound; mp	**:**	Light yellow solid, 78 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3068, 2935, 1614, 1581, 1350, 755.
^{1}H NMR	**:**	1.73 (m, 4H), 2.25 (s, 3H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.94
(CDCl$_3$, 500 MHz) δ		(t, *J* = 7.6 Hz, 2H), 7.24-7.83 (m, 4H).
^{13}C NMR	**:**	12.9, 22.3, 22.7, 26.5, 33.9, 122.8, 124.7, 126.4, 127.6,
(CDCl$_3$, 125 MHz) δ		128.4, 140.7, 145.4, 157.9
Elemental analysis	**:**	Anal. Calcd for $C_{14}H_{15}N$ (198): C, 85.24; H, 7.66; N, 7.10. Found: C, 85.12; H, 6.58; N, 7.05.
LC-MS	**:**	198 (M^+).

11-Methyl-7, 8, 9, 10-tetrahydro-6*H*-cyclohepta[*b*]quinoline (59e):

Nature of compound; mp	**:**	Light yellow solid, 108 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3073, 2928, 1645, 1215, 755.
^{1}H NMR	**:**	1.61-1.79 (m, 6H), 2.54 (s, 3H), 2.90 (t, *J* = 6.4 Hz, 2H),
(CDCl$_3$, 500 MHz) δ		3.12 (t, *J* = 6.9 Hz, 2H), 7.39-7.90 (m, 4H).
^{13}C NMR	**:**	14.3, 27.1, 28, 31.9, 40.1, 124, 125.7, 128.1, 129.3,
(CDCl$_3$, 125 MHz) δ		134.4, 139.3, 145.8, 164.5.
Elemental analysis	**:**	Anal. Calcd for $C_{15}H_{17}N$ (212): C, 85.26; H, 8.11; N, 6.63. Found: C, 85.12; H, 8.15; N, 6.55.
LC-MS	**:**	212 (M^+).

7-Methyl-5, 6-dihydrobenzo[*c*]acridine (59f):

Nature of compound; mp	**:**	Light yellow solid, 112 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3070, 3018, 2946, 2842, 1680, 1582, 1499, 1215, 758.
^{1}H NMR	**:**	2.56 (s, 3H), 2.90 (t, *J* = 7 Hz, 2H), 3.03 (t, *J* = 6.8 Hz,
(CDCl$_3$, 500 MHz) δ		2H), 7.17-8.49 (m, 8H).
^{13}C NMR	**:**	13.6, 25, 27.8, 123.3, 125.2, 126.1, 126.9, 127.4, 128,
(CDCl$_3$, 125 MHz) δ		128.9, 129.1, 129.9, 133.1, 134.9, 138.8, 139.4, 146.6, 152.3.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{15}N$ (246): C, 88.13; H, 6.16; N, 5.71. Found: C, 88.12; H, 6.09; N, 5.63.

LC-MS	**:**	246 (M^+).

2, 3, 4-Trimethylquinoline (59g):

Nature of compound; mp	**:**	Light yellow solid, 110 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3070, 2927, 1523, 1497, 1373, 1216, 753.
^1H NMR ($CDCl_3$, 500 MHz) δ	**:**	2.41 (s, 3H), 2.6 (s, 3H), 2.71 (s, 3H), 7.46-7.99 (m, 4H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	14.2, 15.6, 24.6, 123.3, 125.2, 127.7, 129.1, 140.3, 145.8, 158.2.
Elemental analysis	**:**	Anal. Calcd for $C_{12}H_{13}N$ (172): C, 84.17; H, 7.65; N, 8.18. Found: C, 84.12; H, 7.59; N, 8.13.
LC-MS	**:**	172 (M^+).

2, 4-Dimethyl-3-benzylquinoline (59h):

Nature of compound; mp	**:**	Light yellow solid, 143 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3064, 3017, 2932, 1604, 1586, 1494, 1216, 755.
^1H NMR ($CDCl_3$, 500 MHz) δ	**:**	2.53 (s, 3H), 2.57 (s, 3H), 4.2 (s, 2H), 6.93-7.95 (m, 9H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	14.3, 24.3, 35, 123.6, 125.4, 126, 127.1, 127.7, 128.4, 128.7, 129.1, 129.7, 138.7, 141.8, 146.2, 158.7;
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{17}N$ (262): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.12; H, 6.89; N, 5.63.
LC-MS	**:**	262 (M^+).

4-Methyl-2-phenylquinoline (59i):

Nature of compound	**:**	Pale yellow oil.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3061, 2958, 1684, 1265, 770.
^1H NMR ($CDCl_3$, 500 MHz) δ	**:**	2.51 (s, 3H), 7.35- 8.08 (m, 10H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	18.8, 119.6, 123.6, 126, 127.5, 128, 128.3, 128.5, 128.7, 129.2, 133, 137.2, 139.8, 144.7, 148.2, 156.9.
Elemental analysis	**:**	Anal. Calcd for $C_{16}H_{13}N$ (220): C, 87.64; H, 5.98; N,

		6.39. Found: C, 87.12; H, 5.89; N, 6.33.
LC-MS	**:**	220 (M^+).

2-(4-Chlorophenyl)-4-methylquinoline (59j):

Nature of compound; mp	**:**	Colorless solid; 75 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3019, 1685, 1597, 1215, 757.
^1H NMR	**:**	2.5 (s, 3H), 7.3-8.08 (m, 9H).
($CDCl_3$, 500 MHz) δ		
^{13}C NMR	**:**	18.7, 119, 123.4, 126, 127.1, 128.6, 129.5, 130.1, 135.2,
($CDCl_3$, 125 MHz) δ		138, 139.3, 146, 147.9, 155.4.
Elemental analysis	**:**	Anal. Calcd for $C_{16}H_{12}ClN$ (254): C, 75.74; H, 4.77; N, 5.52. Found: C, 75.68; H, 4.71; N, 5.48.
LC-MS	**:**	254 (M^+).

2-(4-Bromophenyl)-4-methylquinoline (59k):

Nature of compound	**:**	Pale yellow oil.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3019, 1685, 1597, 1215, 757.
^1H NMR	**:**	2.24 (s, 3H), 7.21-7.85 (m, 9H).
($CDCl_3$, 500 MHz) δ		
^{13}C NMR	**:**	18.7, 118.9, 123.6, 126, 126.3 127.1, 128.8, 129.6,
($CDCl_3$, 125 MHz) δ		130.1, 131.6, 135.7, 138.3, 144.8, 147.9, 155.3.
Elemental analysis	**:**	Anal. Calcd for $C_{16}H_{12}BrN$ (298): C, 64.45; H, 4.06; N, 4.70. Found: C, 64.39; H, 4.10; N, 4.66.
LC-MS	**:**	298 (M^+).

6-Chloro-2-methyl-4-phenyl-quinoline-3-carboxylic acid ethyl ester (59l):

Nature of compound; mp	**:**	Yellow solid; 108 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3064, 2983, 1725, 1605, 1224, 907, 732.
^1H NMR	**:**	0.92-0.95 (t, J = 7 Hz, 3H), 2.73 (s, 3H), 4.03-4.07 (q, J
($CDCl_3$, 500 MHz) δ		= 7 Hz, 2H), 7.32-8 (m, 8H).
^{13}C NMR	**:**	13.5, 23.6, 61.4, 125.1, 125.9, 128.4, 128.7, 129.2,
($CDCl_3$, 125 MHz) δ		130.5, 131, 132.3, 135, 145.3, 146, 154, 168.

Elemental analysis	**:**	Anal. Calcd for $C_{20}H_{19}ClNO_2$ (325): C, 70.05; H, 4.95; N, 4.30. Found: C, 70.09; H, 4.90; N, 4.36.
GC-MS	**:**	325 (M^+, 77%), 296 (10%), 280 (100%), 252 (35%), 217 (63%), 189 (22%), 176 (53%), 149 (53%), 123 (13%), 109 (19%), 88 (19%), 71 (19%), 57 (33%).

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (59m):

Nature of compound; mp	**:**	Yellow solid; 151 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3029, 2960, 1701, 1606, 1567, 1481, 909, 692.
^1H NMR ($CDCl_3$, 500 MHz) δ	**:**	1.98 (s, 3H), 2.66 (s, 3H), 7.32-7.98 (m, 8H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	23.6, 31.6, 124.7, 125.8, 128.8, 129.1, 129.8, 130.8, 132.3, 134.5, 135.4, 142.9, 145.8, 153.8, 204.9.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{14}ClNO$ (295): C, 73.10; H, 4.77; N, 4.74. Found: C, 73.03; H, 4.60; N, 4.66.
GC-MS	**:**	295 (M^+, 41%), 280 (100%), 252 (29%), 217 (48%), 189 (15%), 176 (47%), 149 (27%), 109 (11%), 94 (9%), 75 (7%).

7-Chloro-9-phenyl-2, 3-dihydro-1*H*-cyclopenta[*b*]quinoline (59n):

Nature of compound; mp	**:**	Yellow solid; 105 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3060, 2958, 1606, 1487, 828, 715.
^1H NMR ($CDCl_3$, 500 MHz) δ	**:**	2.12 (m, 2H), 2.87 (t, J = 7.2 Hz, 2H), 3.19 (t, J = 7 Hz, 2H), 7.3-7.98 (m, 8H).
^{13}C NMR ($CDCl_3$, 125 MHz) δ	**:**	23.3, 30.2, 35, 124.4, 126.9, 128.2, 128.6, 129, 130.3, 131.2, 134.3, 135.9, 141.8, 146.3, 167.7.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{14}ClN$ (279): C, 77.28; H, 5.04; N, 5.01. Found: C, 77.19; H, 4.94; N, 4.86.
GC-MS	**:**	279 (M^+, 80%), 244 (100%), 202 (16%), 167 (19%), 121 (52%), 114 (17%), 94 (10%), 87 (5%), 75 (6%), 63 (5%).

7-Chloro-9-phenyl-1, 2, 3, 4-tetrahydroacridine (59o):

Nature of compound; mp	**:**	Yellow solid; 163 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3060, 2944, 1604, 1572, 1481, 1215, 703.
^{1}H NMR (CDCl$_3$, 500 MHz) δ	**:**	1.55 (m, 2H), 1.59 (m, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 3.3 (t, *J* = 7 Hz, 2H), 7.2-8 (m, 8H).
^{13}C NMR (CDCl$_3$, 125 MHz) δ	**:**	23, 28.2, 34.3, 124.6, 127.5, 128.2, 128.9, 129.1, 129.3, 129.5, 130.2, 131.3, 136.5, 144.8, 145.8, 159.6.
Elemental analysis	**:**	Anal. Calcd for $C_{19}H_{16}ClN$ (293): C, 77.68; H, 5.49; N, 4.77. Found: C, 77.59; H, 5.34; N, 4.68.
GC-MS	**:**	293 (M^+, 100%), 278 (9%), 258 (83%), 242 (14%), 230 (20%), 201 (15%), 189 (11%), 176 (6%), 150 (8%), 89 (8%), 77 (48%).

2-Chloro-11-phenyl-7, 8, 9, 10-tetrahydro-6*H*-cyclohepta-[*b*]quinoline (59p):

Nature of compound; mp	**:**	Yellow solid; 175 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3063, 2955, 1603, 1560, 1482, 907, 707.
^{1}H NMR (CDCl$_3$, 500 MHz) δ	**:**	0.93 (m, 2H), 1.26 (m, 2H), 1.56 (m, 2H), 2.67 (t, *J* = 7 Hz, 2H), 3.27 (t, *J* = 7.3 Hz, 2H), 7.1-7.97 (m, 8H).
^{13}C NMR (CDCl$_3$, 125 MHz) δ	**:**	26.8, 28.3, 30.6, 31.8, 40, 125, 127.8, 127.9, 128.5, 128.9, 129.2, 130.1, 131.2, 132.4, 134.8, 136.8, 144.1, 144.6, 165.
Elemental analysis	**:**	Anal. Calcd for $C_{20}H_{18}ClN$ (307): C, 77.04; H, 5.89; N, 4.55. Found: C, 76.95; H, 5.74; N, 4.46.
GC-MS	**:**	307 (M^+, 100%), 292 (16%), 278 (36%), 253 (11%), 241 (41%), 216 (17%), 203 (10%), 189 (13%), 176 (8%), 167 (16%), 149 (54%), 126 (29%), 95 (31%), 82 (30%), 71 (35%), 57 (35%).

9-Chloro-7-phenyl-5, 6-dihydrobenzo[*c*]acridine (59q):

Nature of compound; mp	**:**	Yellow solid; 130 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	2960, 2860, 1600, 1488, 704.
^{1}H NMR	**:**	2.86 (m, 4H), 7.25-8.61 (m, 12H).

($CDCl_3$, 500 MHz) δ		
^{13}C NMR	**:**	26.4, 28, 124.8, 126.3, 127.2, 127.4, 127.9, 128.4,
($CDCl_3$, 125 MHz) δ		128.7, 129.1, 129.3, 129.8, 130.9, 131.1, 131.6, 132.4, 136.1, 139.2, 144.5, 145.5, 153.3, 167.7.
Elemental analysis	**:**	Anal. Calcd for $C_{23}H_{16}ClN$ (341): C, 80.81; H, 4.72; N, 4.10. Found: C, 80.65; H, 4.64; N, 4.
GC-MS	**:**	341 (M^+, 10%), 279 (11%), 167 (30%), 149 (100%), 104 (13%), 77 (37%).

6-Chloro-2, 3-dimethyl-4-phenylquinoline (59r):

Nature of compound; mp	**:**	Yellow solid; 127 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3063, 2954, 1605, 1484, 1215, 755.
^{1}H NMR	**:**	1.96 (s, 3H), 2.52 (s, 3H), 6.99-7.75 (m, 8H).
($CDCl_3$, 500 MHz) δ		
^{13}C NMR	**:**	16.9, 24.4, 124.8, 127.6, 128, 128.7, 128.9, 129.2,
($CDCl_3$, 125 MHz) δ		130.1, 131.2, 136.8, 144.4, 145.5, 159.2.
Elemental analysis	**:**	Anal. Calcd for $C_{17}H_{14}ClN$ (268): C, 76.26; H, 5.27; N, 5.23. Found: C, 76.15; H, 5.14; N, 5.1.
LC-MS	**:**	268 (M^+).

3-Benzyl-6-chloro-2-methyl-4-phenylquinoline (59s):

Nature of compound; mp	**:**	Yellow solid; 136 ^oC.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3063, 2957, 1603, 1482, 1215, 756.
^{1}H NMR	**:**	2.51 (s, 3H), 3.92 (s, 2H), 6.81-7.93 (m, 13H).
($CDCl_3$, 500 MHz) δ		
^{13}C NMR	**:**	24.3, 36, 125.1, 126, 127.8, 128.2, 128.4, 129, 129.5,
($CDCl_3$, 125 MHz) δ		130.1, 131.4, 136.2, 139.4, 144.9, 146.9, 159.7.
Elemental analysis	**:**	Anal. Calcd for $C_{23}H_{18}ClN$ (344): C, 80.34; H, 5.28; N, 4.07. Found: C, 80.25; H, 5.18; N, 4.
LC-MS	**:**	344 (M^+).

6-Chloro-2, 4-diphenylquinoline (59t):

Nature of compound; mp	**:**	Yellow solid; 102 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3056, 1684, 1483, 908, 730.
^{1}H NMR	**:**	7.4-8 (m, 14H).
(CDCl$_3$, 500 MHz) δ		
^{13}C NMR	**:**	120, 124.4, 126.4, 127.5, 128.7, 128.8, 129.4, 130.4,
(CDCl$_3$, 125 MHz) δ		131.6, 132.7, 137.7, 139.1, 147.2, 148.4, 157.
Elemental analysis	**:**	Anal. Calcd for $C_{21}H_{14}ClN$ (316): C, 79.87; H, 4.47; N, 4.44. Found: C, 79.79; H, 4.38; N, 4.38.
LC-MS	**:**	316 (M^+).

6-Chloro-2-(4-chlorophenyl)-4-phenylquinoline (59u):

Nature of compound; mp	**:**	Yellow solid; 161 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3019, 1588, 1215, 755.
^{1}H NMR	**:**	7.48-8.15 (m, 13H).
(CDCl$_3$, 500 MHz) δ		
^{13}C NMR	**:**	119.5, 124.5, 126.5, 128.7, 128.8, 129, 129.4, 130.6,
(CDCl$_3$, 125 MHz) δ		131.7, 132.4, 135.8, 137.5, 147.2, 148.7, 155.7.
Elemental analysis	**:**	Anal. Calcd for $C_{21}H_{13}Cl_2N$ (349): C, 72.01; H, 3.74; N, 4. Found: C, 71.95; H, 3.68; N, 3.92.
GC-MS	**:**	349 (M^+, 100%), 314 (40%), 278 (15%), 236 (16%), 201 (21%), 176 (19%), 157 (26%), 139 (52%), 125 (28%), 112 (8%), 87 (5%), 75 (14%), 63 (5%).

6-Chloro-2-(4-bromophenyl)-4-phenylquinoline (59v):

Nature of compound; mp	**:**	Yellow solid; 195 ^{o}C.
IR: (KBr) υ_{max} (cm^{-1})	**:**	3018, 2928, 1645, 1580, 1215, 755.
^{1}H NMR	**:**	7.48-8.15 (m, 13H).
(CDCl$_3$, 500 MHz) δ		
^{13}C NMR	**:**	119.4, 124.2, 124.5, 126.5, 128.2, 128.8, 129, 129.3,
(CDCl$_3$, 125 MHz) δ		129.8, 132, 132.5, 135.9, 137.5, 137.9, 147, 148.8, 155.6.

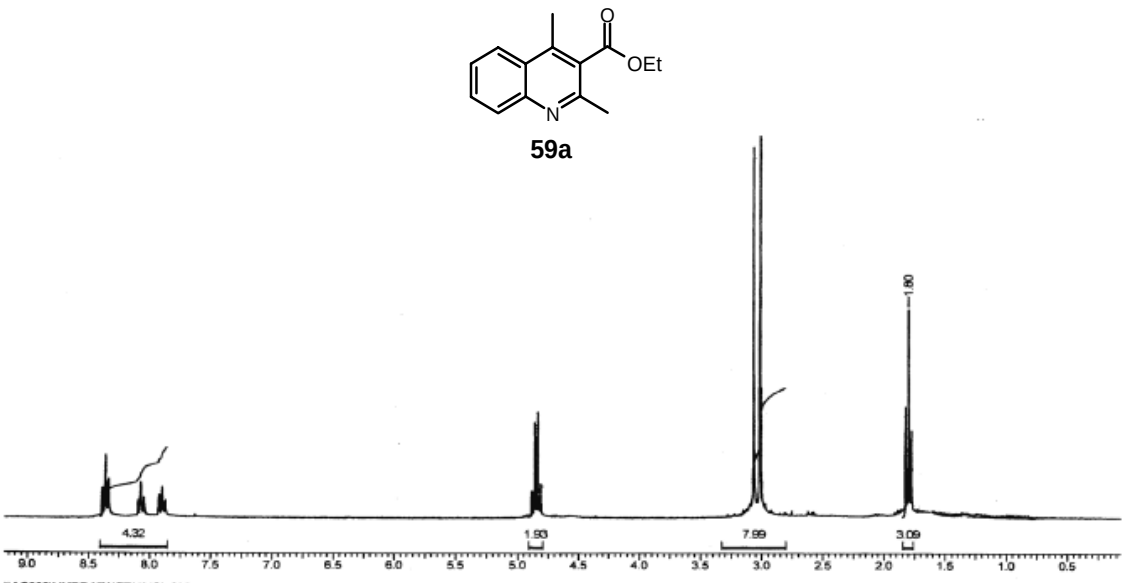
Elemental analysis	**:**	Anal. Calcd for $C_{21}H_{13}BrClN$ (394): C, 63.91; H, 3.32; N, 3.55. Found: C, 63.85; H, 3.28; N, 3.32.
LC-MS	**:**	394 (M^+).

1.3.7 Spectra

Table 15. ^{1}H & ^{13}C spectra of some selected quinoline derivatives and TGA of HbimBF$_4$ 33a are given below:

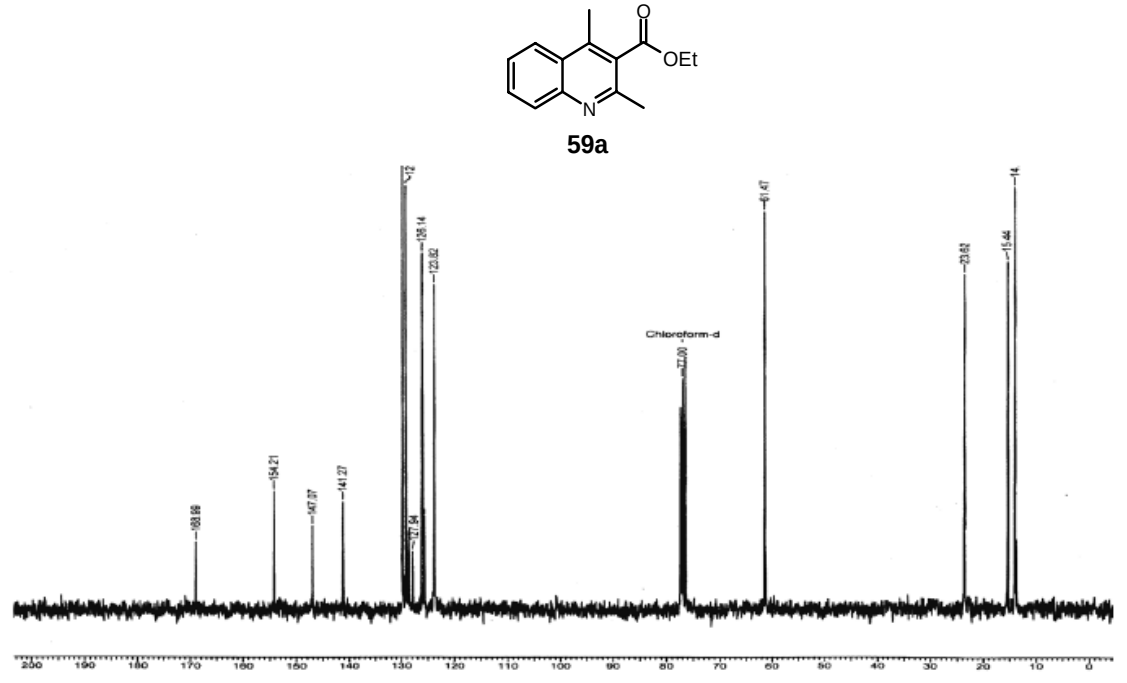
Sr. No.	Spectra
1	^{1}H & ^{13}C spectra of **59a**
2	^{1}H & ^{13}C spectra of **59b**
3	^{1}H & ^{13}C spectra of **59d**
4	^{1}H & ^{13}C spectra of **59f**
5	^{1}H & ^{13}C spectra of **59g**
6	^{1}H & ^{13}C spectra of **59h**
7	^{1}H & ^{13}C spectra of **59j**
8	^{1}H & ^{13}C spectra of **59l**
9	^{1}H & ^{13}C spectra of **59m**
10	^{1}H & ^{13}C spectra of **59n**
11	^{1}H & ^{13}C spectra of **59r**
12	^{1}H & ^{13}C spectra of **59s**
13	TGA, DTG and DTA curves for **[Hbim]BF$_4$ (33a)**

^{1}H NMR of **59a**



59a

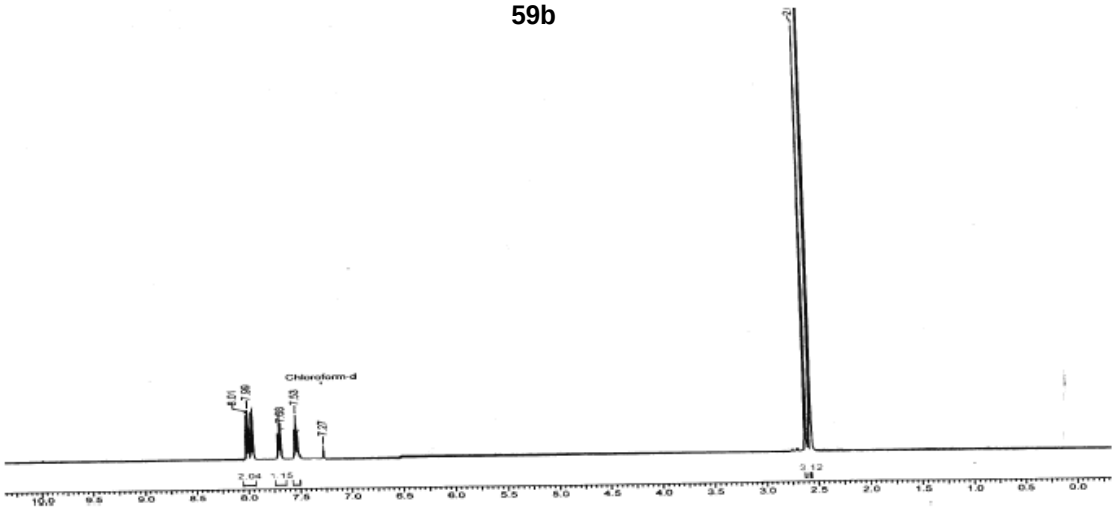
^{13}C NMR of **59a**



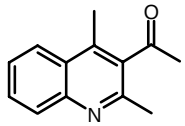
59a

^{1}H NMR of **59b**

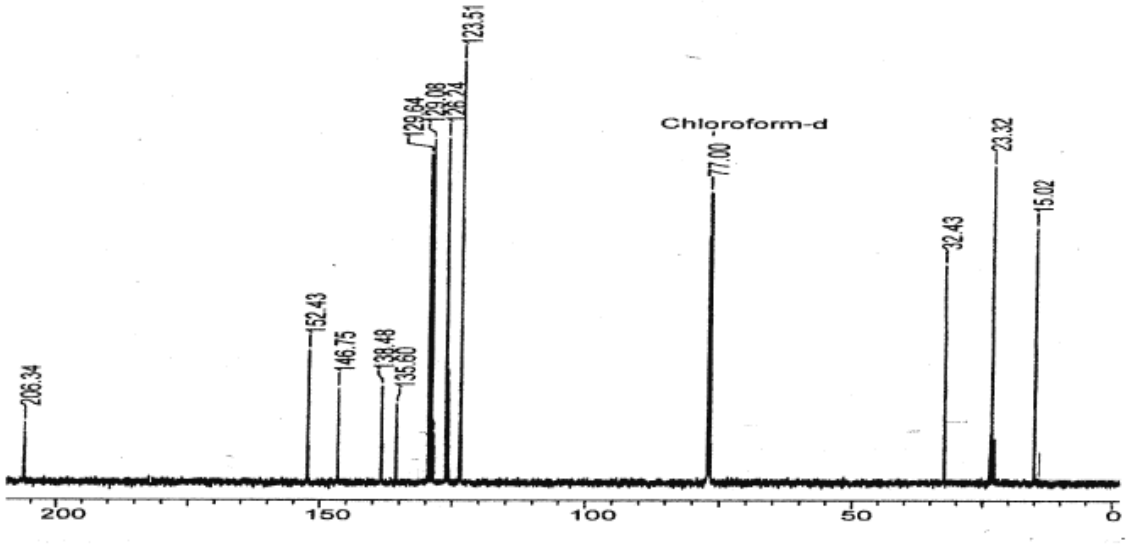
59b



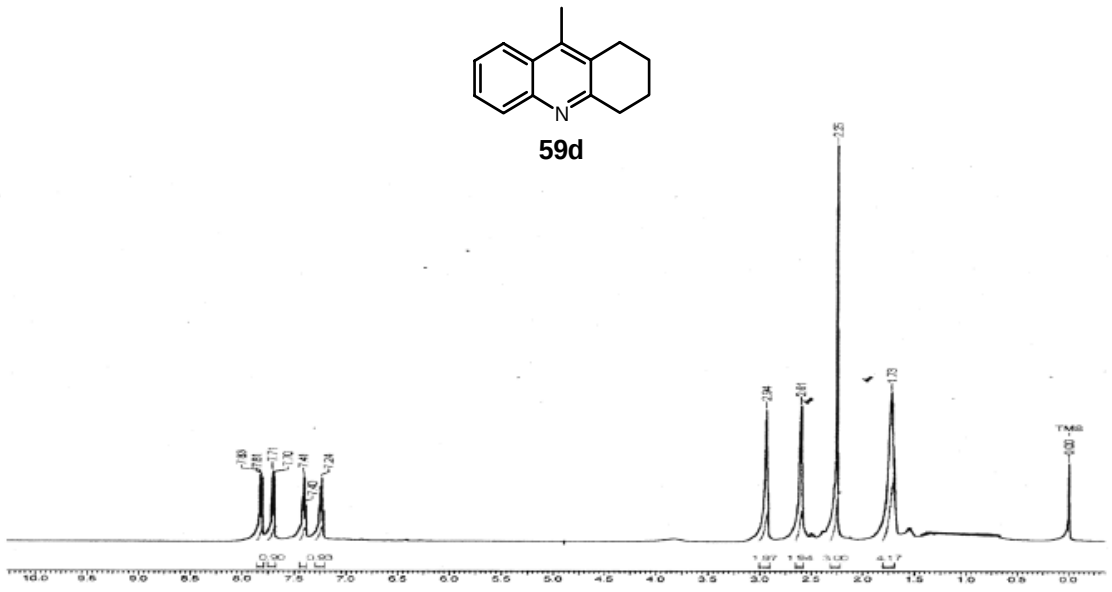
^{13}C NMR of **59b**



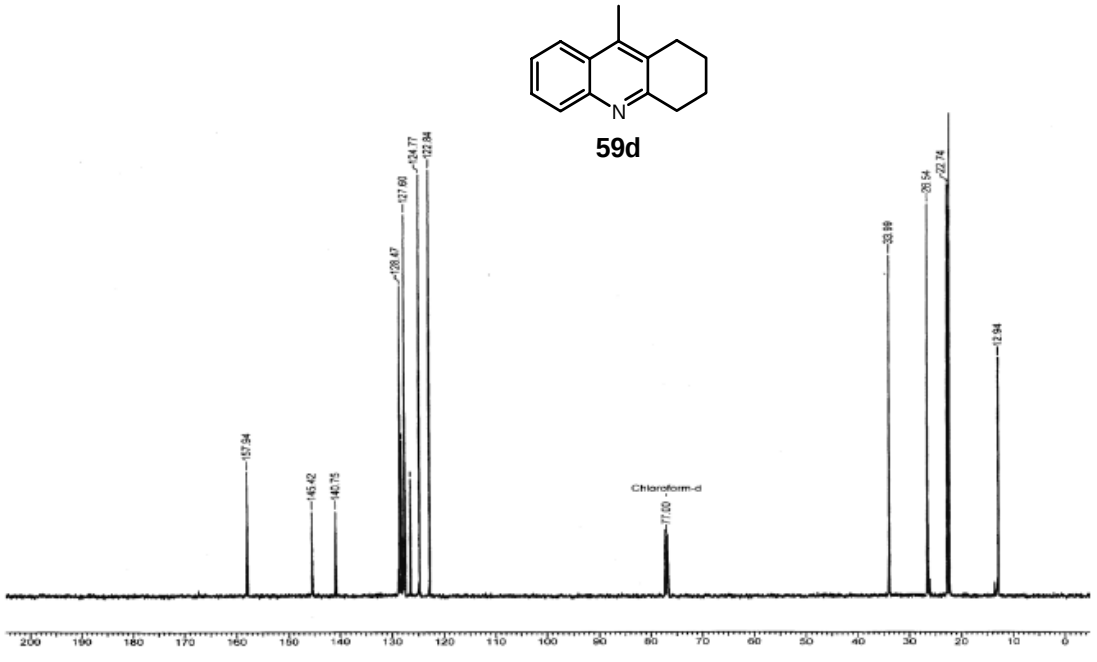
59b



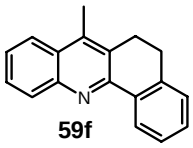
^{1}H NMR of **59d**



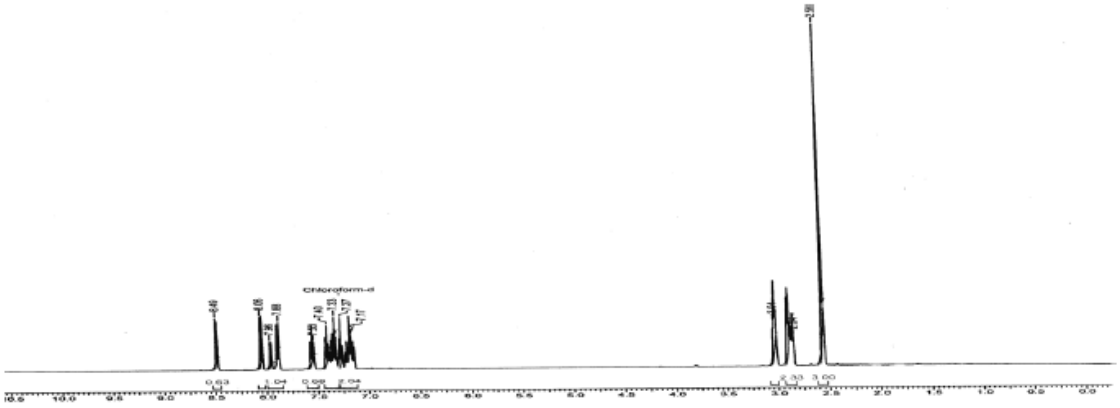
^{13}C NMR of **59d**



^{1}H NMR of **59f**



59f



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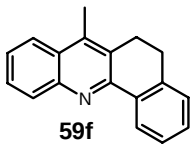

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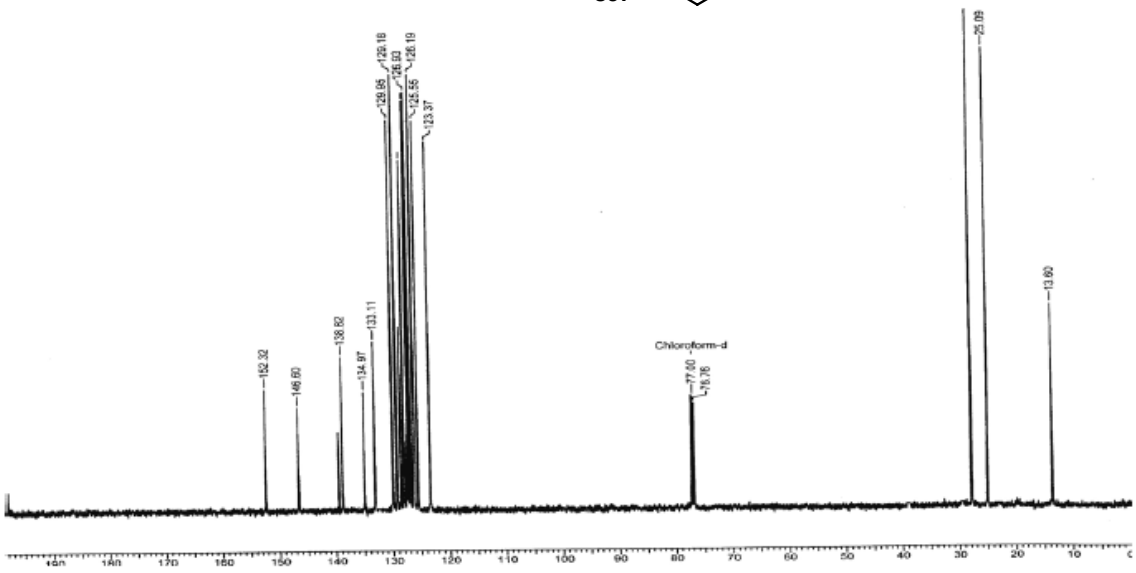

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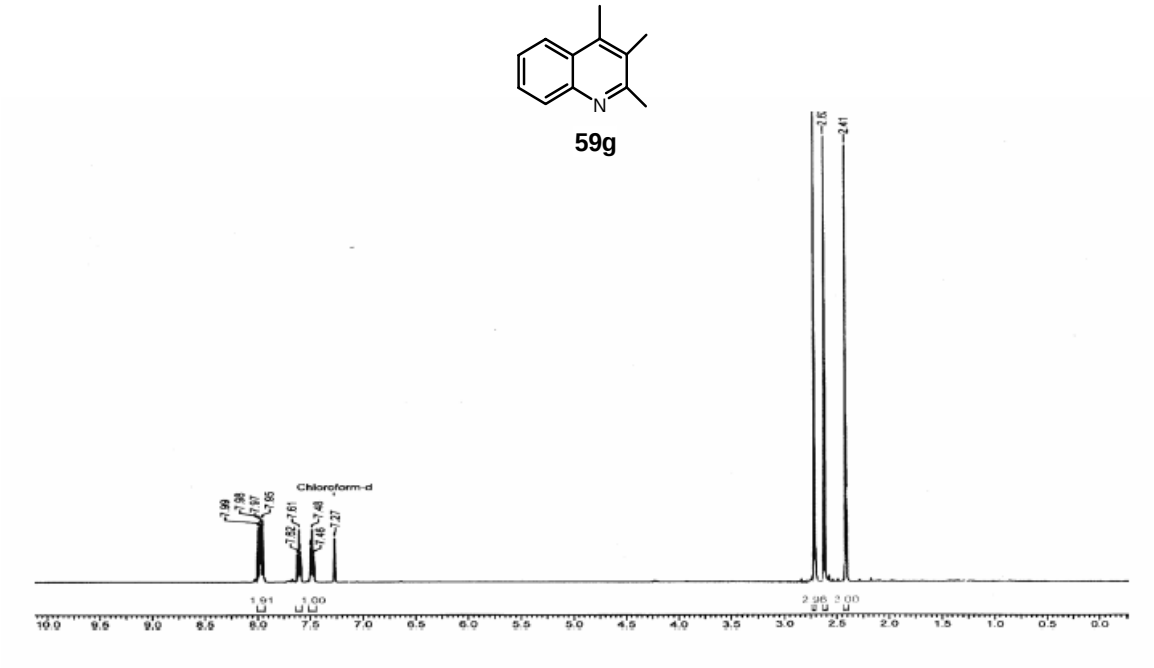

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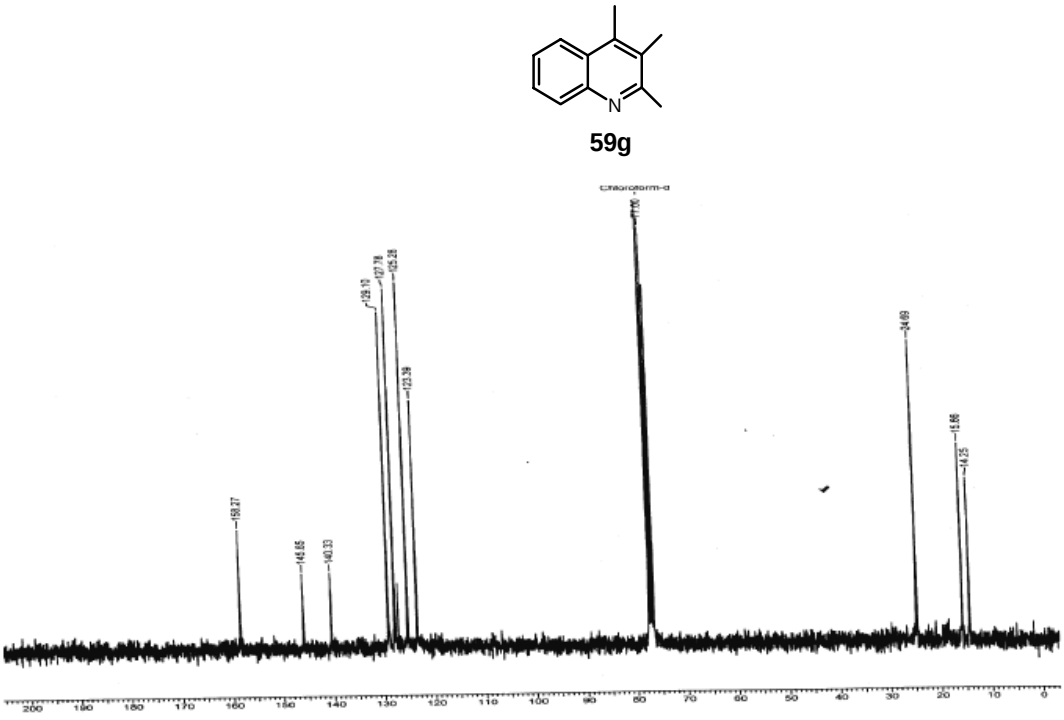

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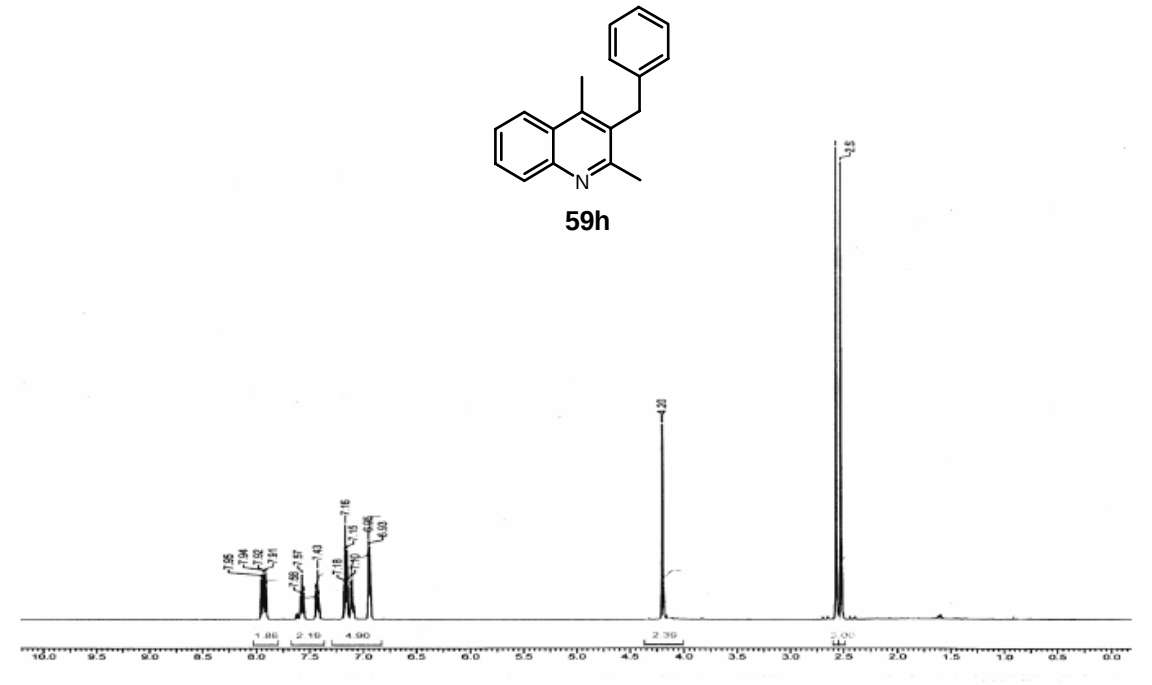

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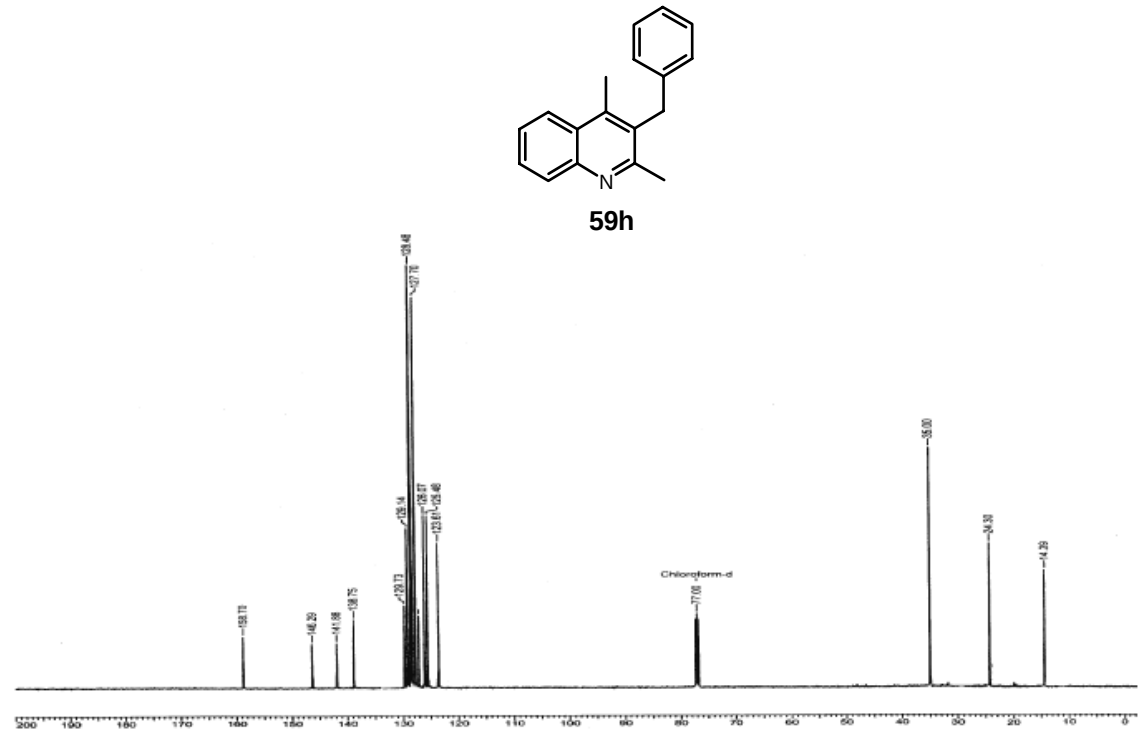

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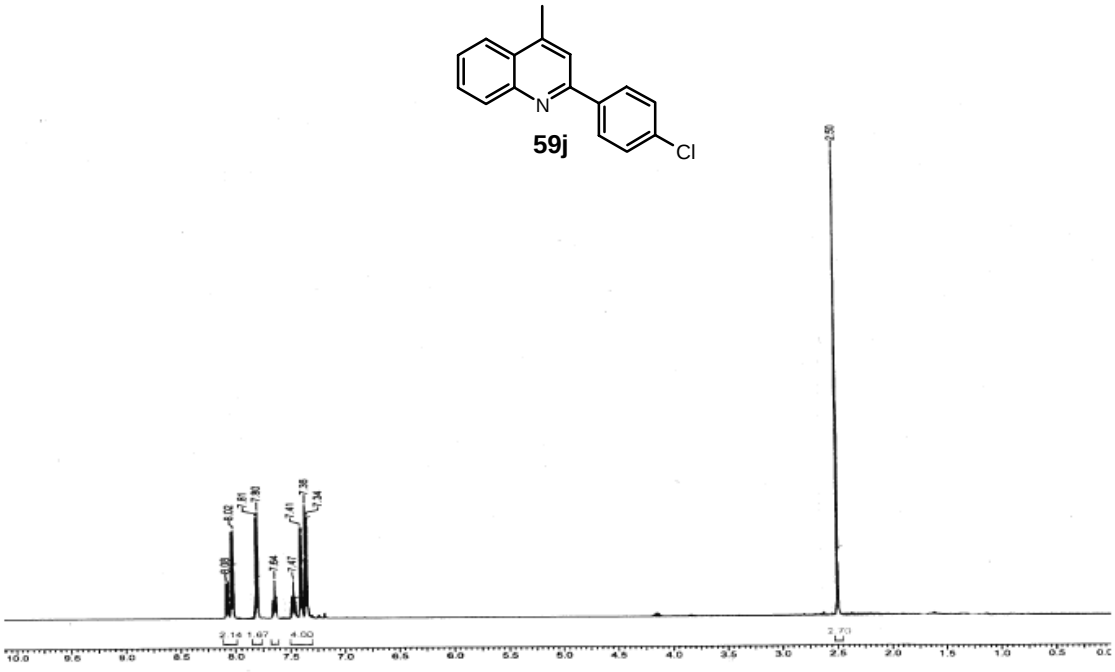

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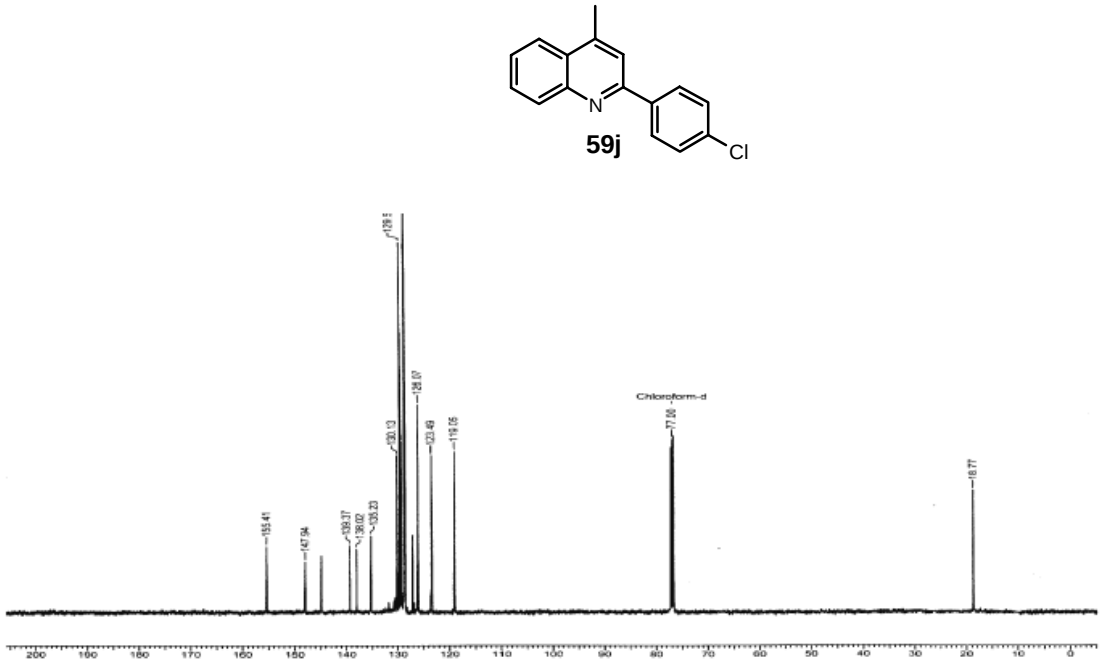

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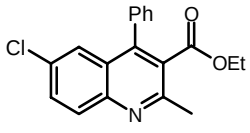

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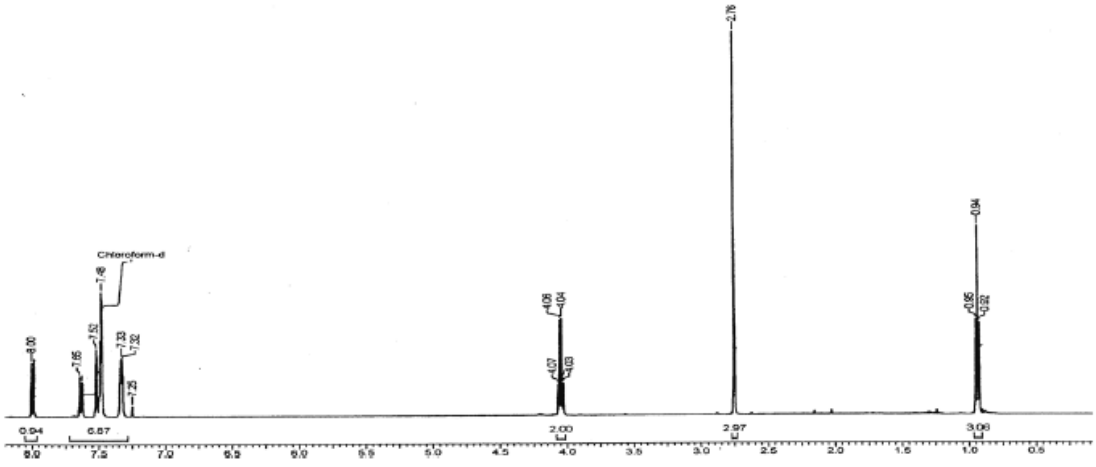

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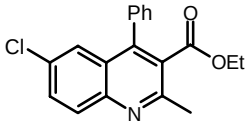

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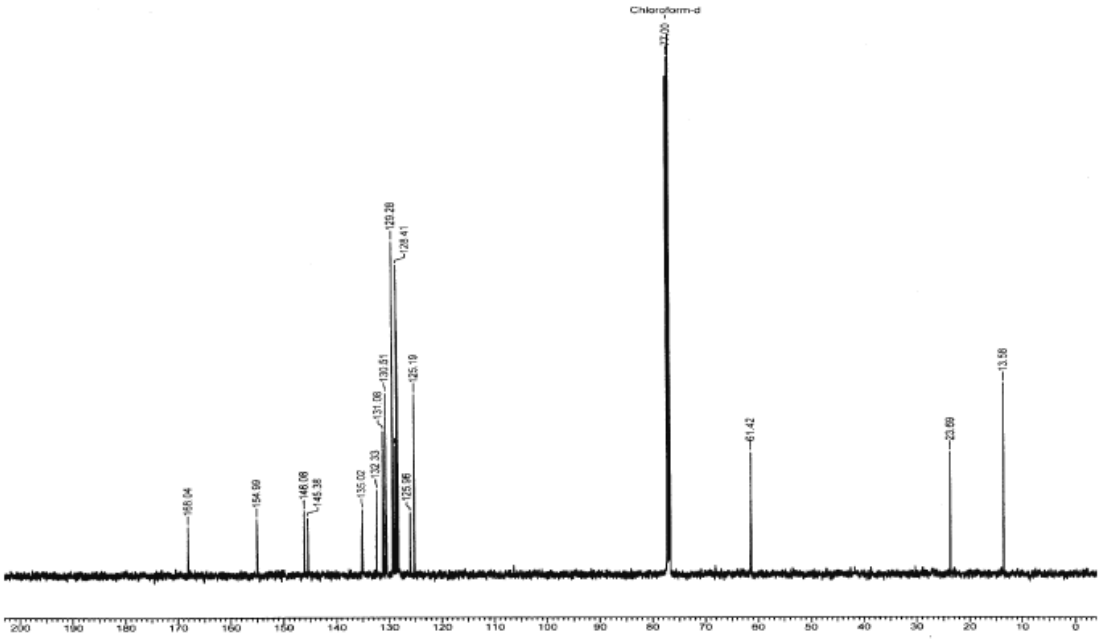

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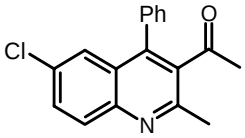

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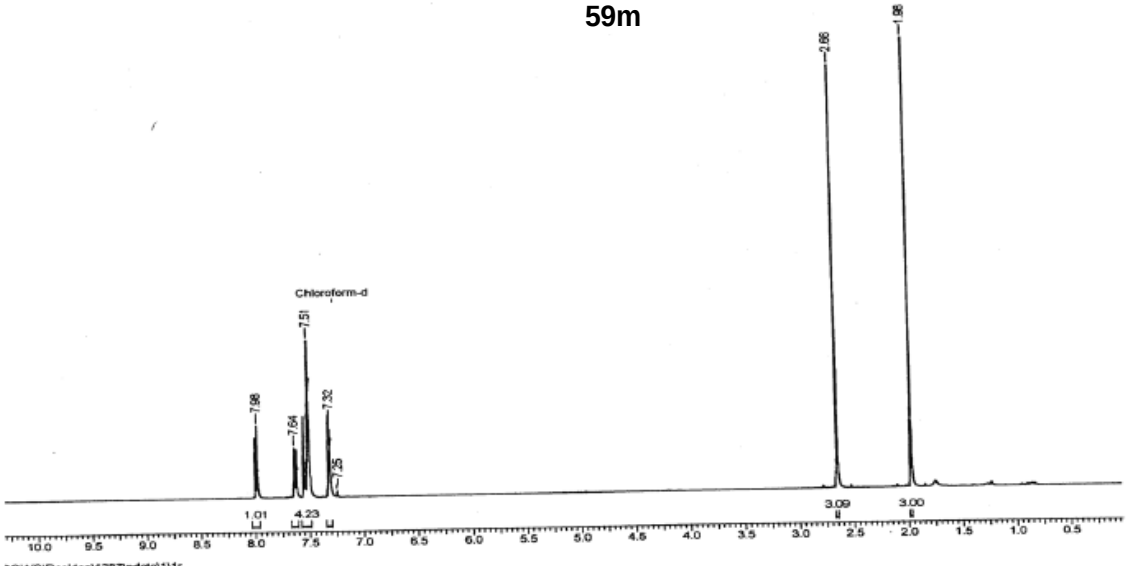

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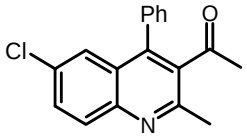

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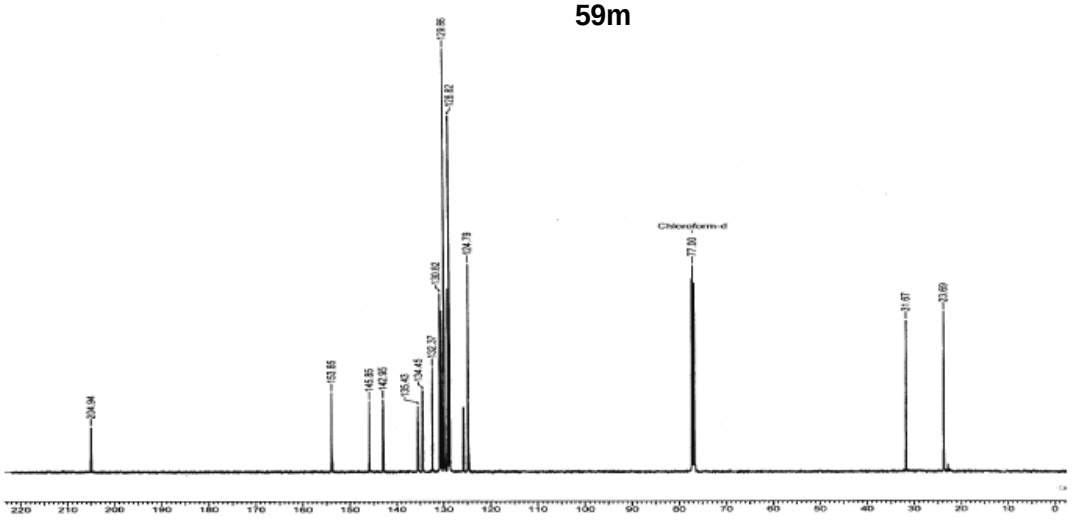

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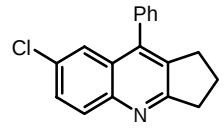

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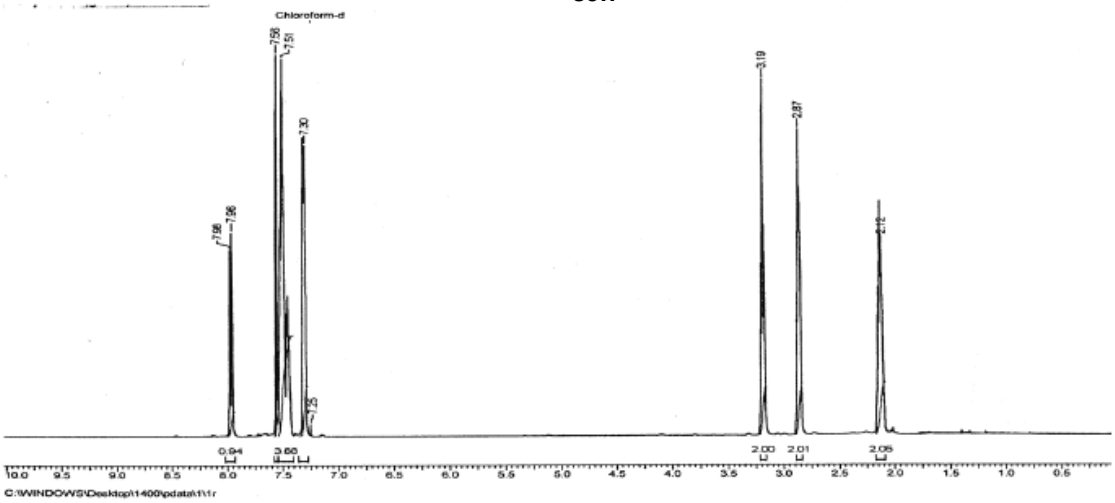

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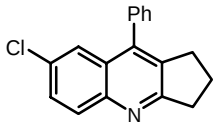

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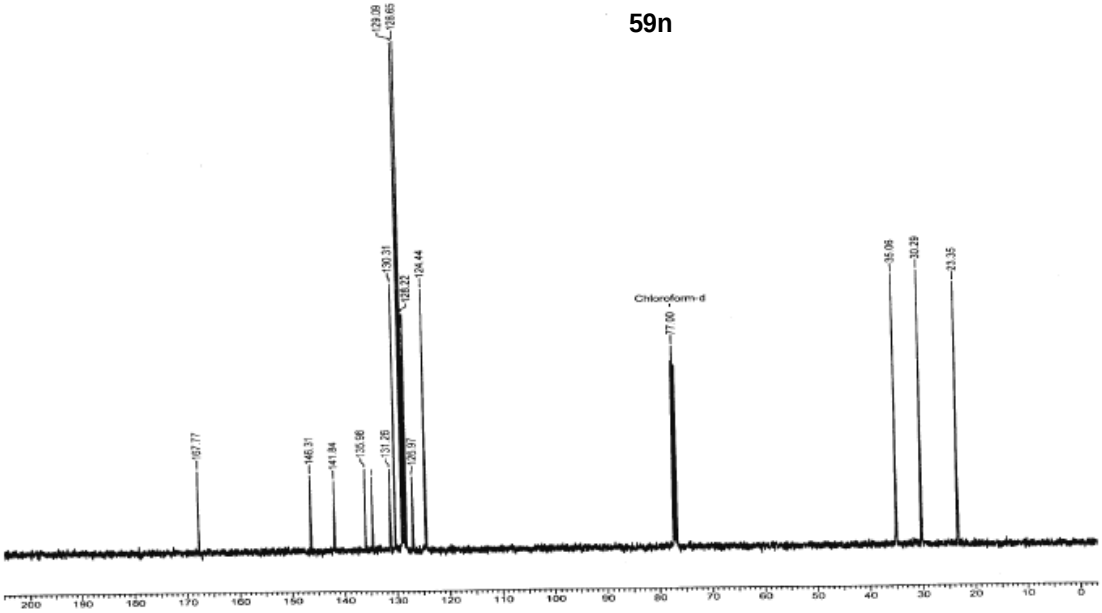

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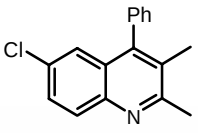

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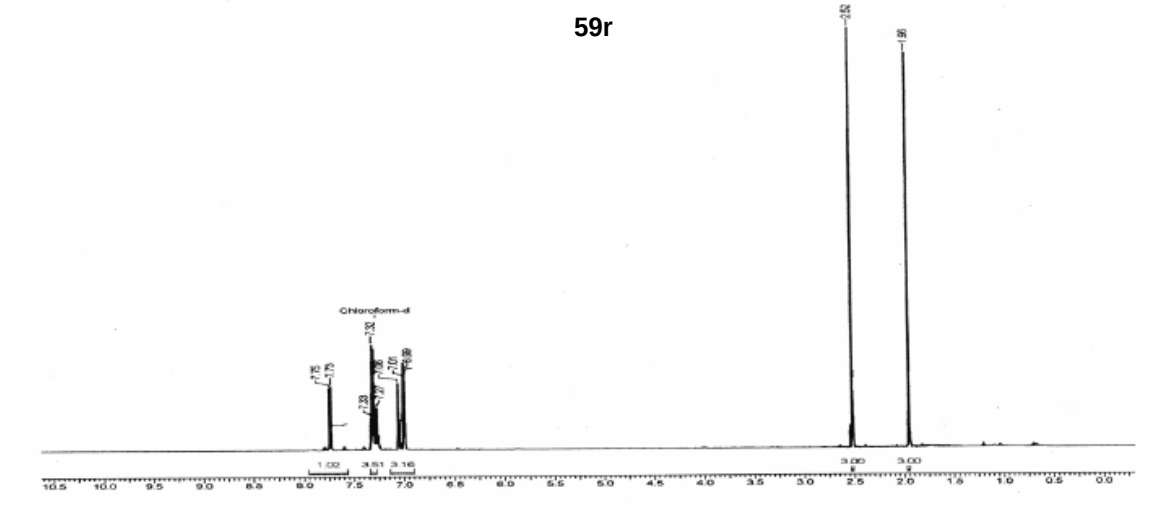

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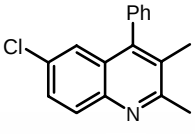

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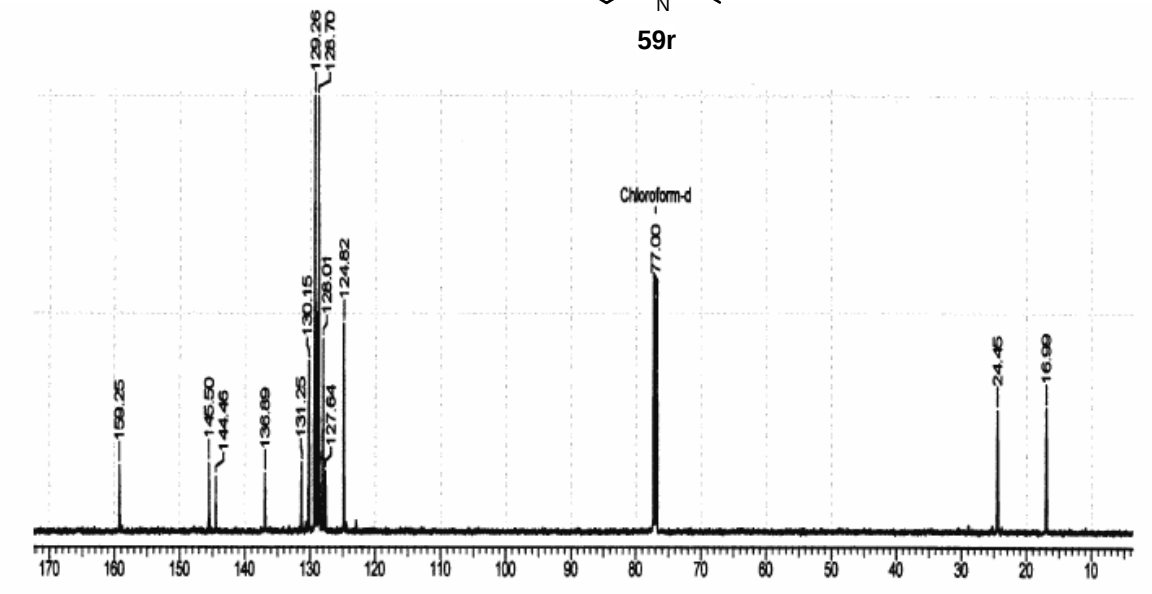

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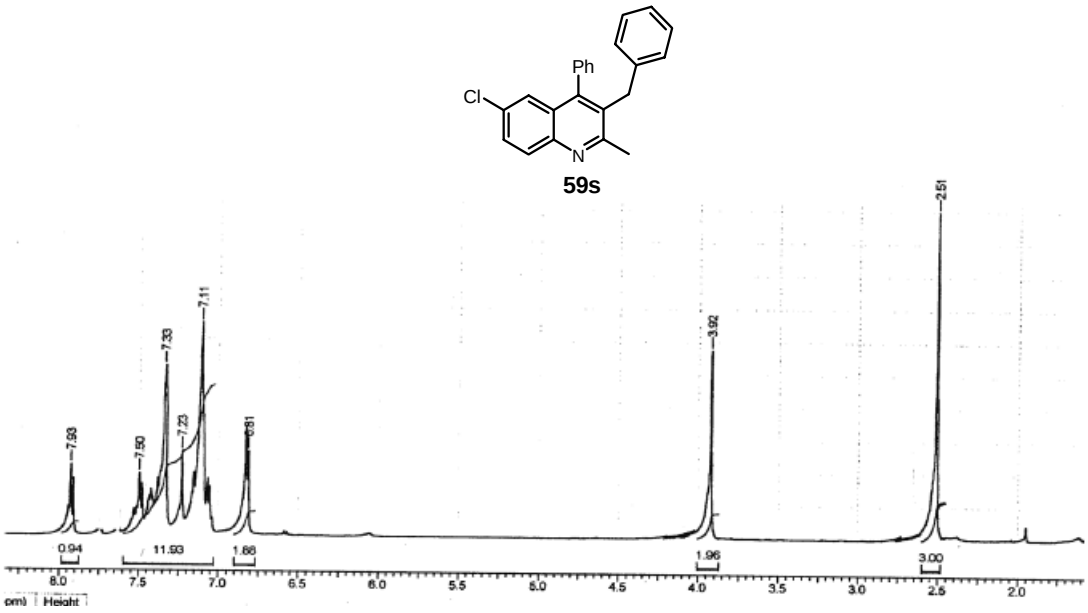

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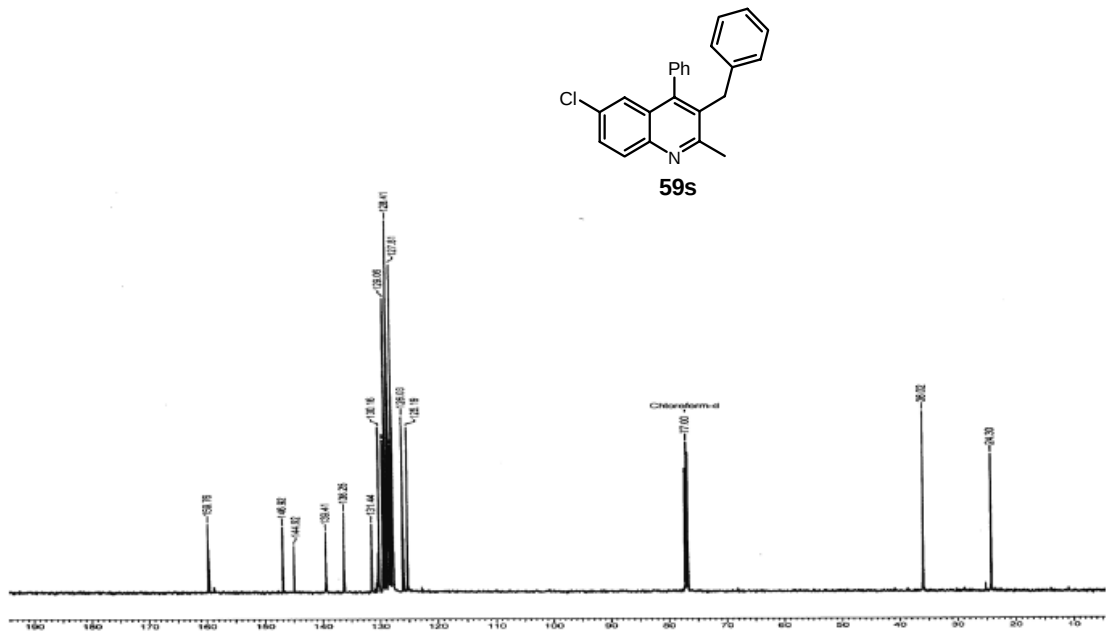

1.3.8 TGA, DTG and DTA curves for $[Hbim]BF_4$ (33a)

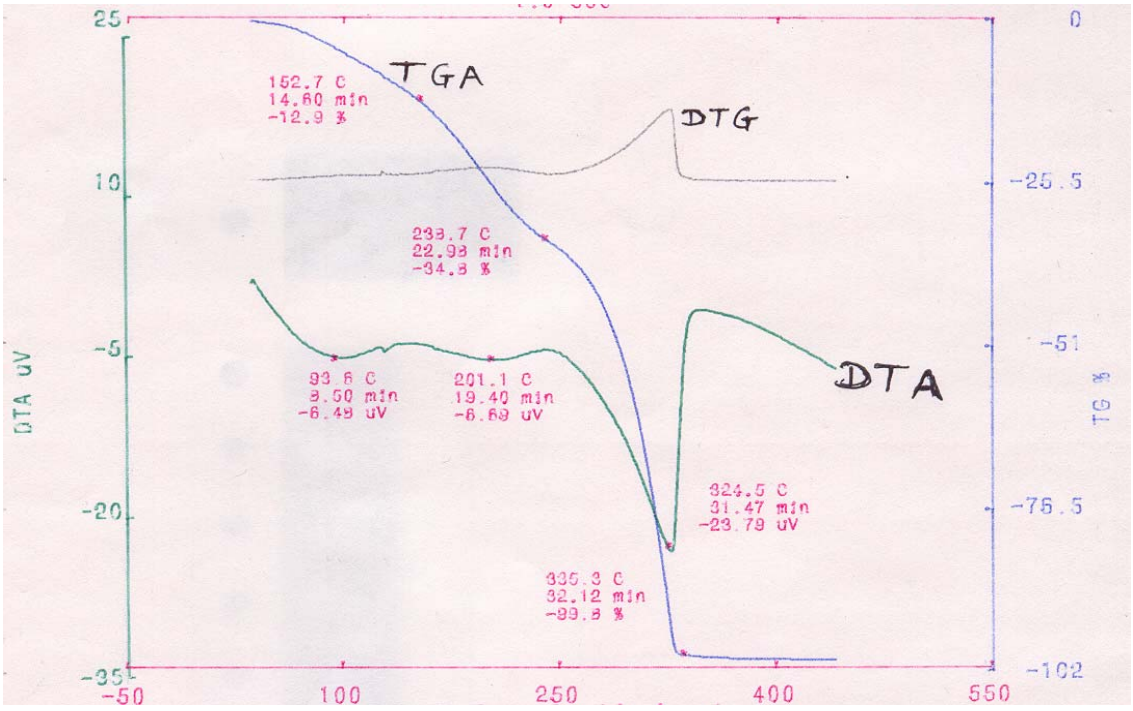

Fig. 8. TGA, DTG and DTA curves for $[Hbim]BF_4$ (33a)

1.3.9 References

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Chapter II

Eco-friendly synthesis of ynones, β-enaminones and 1, 5-benzodiazepines

2.0 Introduction

Sustainability is increasingly an important issue in the wider context dealing with population, health, the environment, energy, technology, renewable resources, and, in the sciences, as an integral part of the rapidly emerging field called Green Chemistry.[1, 2] This is a multidisciplinary field, requiring integrated study in the chemical, biological and physical sciences as well as many aspects of engineering. The twelve principles of "Green Chemistry", as defined by Anastas and Warner,[1] and generally accepted internationally, cover complex issues including waste minimization, reduction in energy usage, and the use of renewable resources rather than depleting natural resources such as oil, coal and gas.

As a consequence of the necessity to minimize the amount of toxic waste and by-products from chemical processes is a need for the development of new, more environmentally friendly synthetic methods in which fewer toxic substances are used. In this process the solvents are especially important, as they are generally used in large quantities. Organic solvents are high on the list of toxic or otherwise damaging compounds because of the large volumes used in industry, and difficulties in containing volatile compounds. Many organic solvents are ecologically harmful, and their use should therefore be minimized as far as possible or even avoided altogether. In industry they are of course recycled wherever possible.

The "ideal synthesis'' (Fig. **1**) should be high yielding (historically the most important measure of the success of a reaction), are simple to perform and exhibit high atom efficiency, hence a reduced number of steps and no waste, are safe, and are environmentally acceptable.[3]

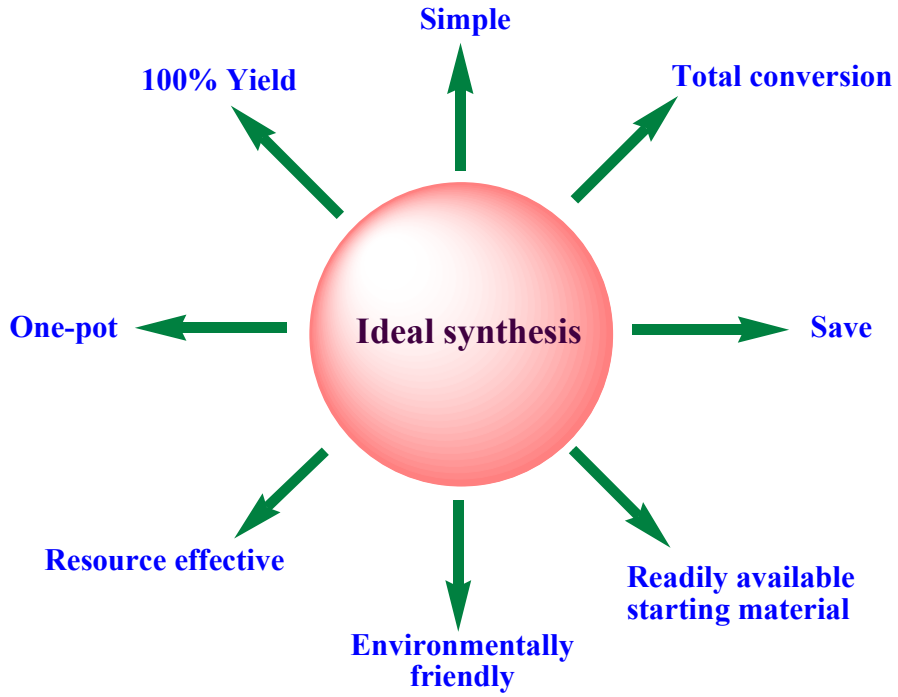

Fig 1. The ideal chemical synthesis adapted from Wender *et al.*[2]

With increasing awareness for the concept of green chemistry,[1] the chemical community focused their attention towards the development of environment friendly processes based upon the replacement of such volatile organic solvents by alternative non-toxic, non-flammable and non-volatile media such as ionic liquids, super critical fluids and water or alternatively the reactions have been carried out under *solvent-free* conditions.[4]

In this chapter eco-friendly methods are developed for synthesis of important synthetic intermediate such as ynones, β-enaminones under solvent-free conditions and a novel one-pot three-component synthesis of the biologically active benzodiazepines in water. Advantages of solvent-free reactions, water as a solvent and multi-component reactions are described below.

2.0.1 Solvent-free reactions

The best solvent from an ecological point of view is without a doubt no solvent. These are not only of interest from an ecological point of view, but in many cases they also offer considerable synthetic advantages in terms of yields, selectivity and simplicity of the reaction procedures. Other advantages of solvent-free reactions, relative to using organic or other reaction media includes: (i) there is no reaction

medium to collect, purify and recycle, (ii) the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography, and indeed in some cases the need for recrystallization, (iii) sequential solvent less reactions are possible in high yielding systems, (iv) the reactions can be rapid, often reaching substantial completion in several minutes compared to hours in organic solvents, (v) there is often no need for specialized equipment (vi) energy usage can be much lower and (vii) considerable batch size reduction and processing cost savings are achievable such that such solvent-free protocols are not only more environmentally benign but are also more economically feasible. This is one of the original considerations in bringing Green Chemistry to the fore.[1] These factors are especially important in industry.

2.0.2 Water as solvent

Approximately 70% of the earth's surface is comprised of water, making it the most abundantly existing liquid solvent. In fact, for many hundreds of years water was the only solvent available to chemists to carry out their reactions. It was not until organic solvents came into use that a whole new area of chemistry was born, and many types of reactions were conducted and compounds made that previously had not been thought possible. Nevertheless, in the most recent decades, chemists have begun to reinvestigate the possibility of using water as solvent for organic reactions.

Why Water?

Until recently, the use of water as solvent for organic reactions was mainly restricted to simple hydrolysis reactions. Accordingly, most reagents and catalysts in organic synthesis have been imperiously developed for use in anhydrous, organic reaction media. Why should we now spend time "rediscovering" reactions for use in water that already work well in familiar molecular organic solvents such as THF, toluene, DMF or methylene chloride? Because there are many potential advantages of replacing these and other unnatural solvents with water. The most obvious are the following. (1) **Cost:** It does not get any cheaper than water! (2) **Safet:** Most of the organic solvents used in the lab today are associated with risks: Flammables, explosives, carcinogenics, etc. (3) **Environmental concerns:** The chemical industry is a major contributor to environmental pollution. With increasing regulatory pressure focusing

on organic solvents, the development of non-hazardous alternatives is of great importance. In addition to these advanvatages, in many cases, due to hydrophobic effects, using water as a solvent not only accelerates reaction rates but also enhances reaction selectivities, even when the reactants are sparingly soluble or insoluble in this medium.[5,6]

Furthermore, the low solubility of oxygen gas in water, an important property in the early development of life in an anaerobic environment, can facilitate air-sensitive transition-metal catalysis in open air. The use of water as a solvent also implies the elimination of tedious protection–deprotection processes for certain acidic-hydrogen containing functional groups, which contributes to the overall synthetic efficiency. Water soluble compounds such as carbohydrates, can be used directly without the need for laborious derivatization and water-soluble catalysts can be reused after separation from water-insoluble organic products. Aqueous organic chemistry is also essential for the emerging field of chemical biology which uses chemical tools to study biological systems. Thus the aqueous organic chemistry has broad applications and has a bright future.

2.0.3 Multi-component reactions

Multi-component reactions[7] are a powerful tool for the generation of collections of molecules; they are extremely convergent and produce a remarkably high increase of molecular complexity in just one step. Sequential transformations and multi-component one-pot reactions are always resource effective and environmentally acceptable and thus greener as compared to multi-step reactions.[8] They offer significant advantages over conventional linear step syntheses, by reducing time, saving money, energy and raw-materials thus resulting in both economical and environmental benefits. At the same time, diversity can be achieved for building up libraries by simply varying each component.[9]

Taking into account of above mentioned advantages of solvent-free reactions, organic reactions in water and multi-component reaction, we developed novel methodologies for the preparation of versatile synthetic intermediates *viz.* ynones and β-enaminones under solvent-free conditions and a novel one-pot three-component synthesis of the

highly important class of biologically active compounds *viz.* benzodiazepines in water which are described in this chapter **II**.

2.0.4 References

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Section A

Copper-, ligand- and solvent-free synthesis of ynones by coupling acid chlorides with terminal alkynes

2.1.0 Introduction

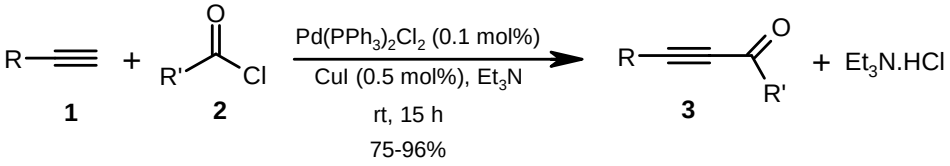
Ynones are of considerable synthetic interest because of their widespread occurrence among natural products and their physiological properties.[1] They are extremely versatile intermediates for the synthesis of important biologically active heterocycles.[2] Also ynones are useful synthetic precursors of compounds such as chiral propargyl alcohols,[3] α, β-unsaturated ketones, dienones,[4] allylic alcohols, as well as a variety of Michael addition products, and thus have served as crucial intermediates for the synthesis of several natural products.[5]

2.1.1 Review of Literature

After the survey of literature for the synthesis of ynones, we observed that several methods are reported for the synthesis of ynones among which the synthesis of ynones *via* the palladium-catalyzed coupling of acid chlorides and terminal alkynes has been widely employed due to the versatile nature of this protocol, increased functional group tolerance and improved yields. Some important methods based upon the palladium-catalyzed coupling of acid chlorides with terminal alkynes are discussed below.

Hagihara's approach (*Synthesis*, 1977)[6]

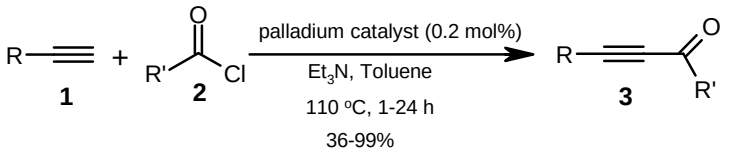
Hagihara and co-workers, reported for the first time, synthesis of 1-alkynyl ketones **3** by coupling terminal alkynes **1** with acid chlorides **2** catalyzed by $PdCl_2(PPh_3)_2$/CuI in Et_3N, but the reactions were limited by unwanted side reactions between the acid chlorides **2** and the Et_3N solvent, reducing the yields (Scheme **1**).

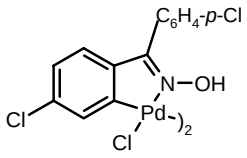


Scheme 1

Najera's approach (*J. Org. Chem.* 2004)[7]

Najera, C. *et al.* recently reported a similar reaction catalyzed by an oxime derived palladacycle under phosphine and copper free conditions at high temperature in toluene using 3 equiv of Et_3N as the base. (Scheme **2**).





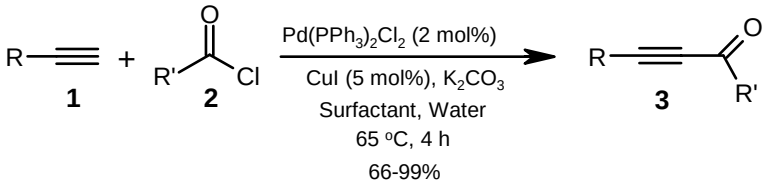
palladium catalyst

Scheme 2

In their study, they also reported the coupling of acid chlorides with terminal alkynes employing $Pd(OAc)_2$ as the catalyst requiring much longer reaction times (23 h) with lowered yields.

Li's approach (*org. Lett.* 2004)[8]

Li and Chen, reported the synthesis of ynones **3**, catalyzed by $PdCl_2(PPh_3)_2$/CuI with a catalytic amount of sodium lauryl sulfate as the surfactant and K_2CO_3 as the base in water (Scheme **3**).

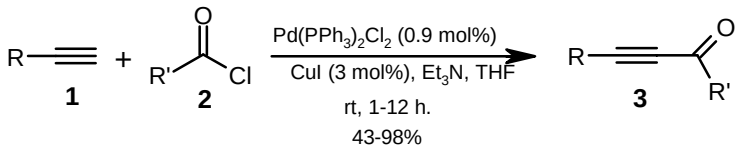


Scheme 3

However, their methodology involved the use of 5 mol % CuI and the reactions were carried out at 65 ^oC for 4 h.

Cox's approach (*Chem. Commun.* 2005)[9]

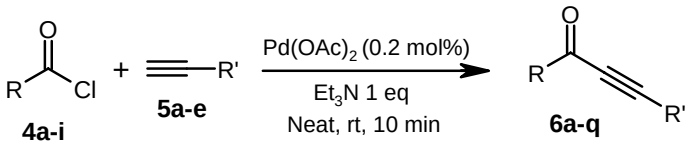
More recently, Cox *et al*. reported the room temperature palladium-catalyzed coupling of acyl chlorides **2** with terminal alkynes **1** as shown in Scheme **4**. Their protocol also involves the use of CuI and $PdCl_2(PPh_3)_2$ in THF.



Scheme 4

2.1.2 Present Work

The reported methods suffer from various drawbacks such as use of hazardous volatile organic solvents, require moisture sensitive phosphine based palladium catalyst, and also make use of CuI as co-catalyst. It should also be noted that almost all the methods reported so far make use of an excess of the acid chloride (1.5–2 mol per mole of phenyl acetylene) and Et_3N (2–3 equiv). Thus there is still scope for the development of more efficient, simple, green method for the synthesis of extensively employed synthetic intermediate ynones. The solvent-free as well as copper- and ligand-free synthesis of ynones *via* Sonogashira coupling of acid chlorides with terminal alkynes is not reported. We optimized the conditions for this coupling reaction, and developed a simple, efficient, rapid, *copper*-, *ligand*-, and *solvent*-free synthesis of ynones by coupling of a variety of acid chlorides with terminal alkynes (Scheme **5**) which is described in this Section **A**.

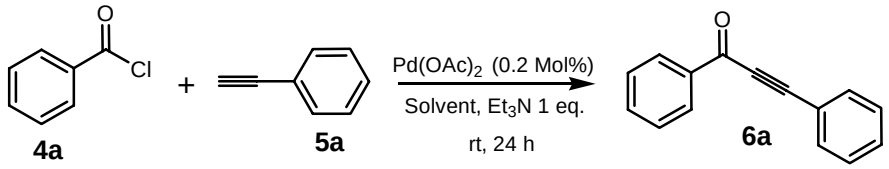


Scheme 5

2.1.3 Results and Discussion

In the present study, we first tested the role of solvent for the coupling of benzoyl chloride with phenyl acetylene. The results are reported in Table **1**.

Table 1. Effect of solvents on the coupling of benzoyl chloride with phenyl acetylene



Entry	Solvent	Yields (%)[a]
1	Et_3N	60
2	Toluene	87
3	DCM	85
4	THF	51
5	DMF	46
6	Acetonitrile	30
7	Neat	93[b]

[a] Isolated yields
[b]Reaction time 10 min.

It was noted that toluene and dichloromethane were good solvents for this coupling reaction. However, dipolar aprotic solvents, such as THF, DMF and acetonitrile gave inferior results with the formation of the corresponding anhydride as a side product. To our surprise, when the reaction was performed without a solvent the highest yield of the product was obtained. Consequently, benzoyl chloride and substituted benzoyl chlorides were reacted with a variety of phenyl acetylenes using the present methodology. The results are recorded in Table **3**.

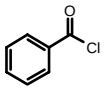
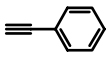
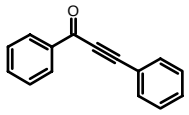
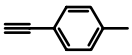
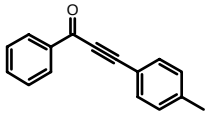
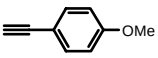
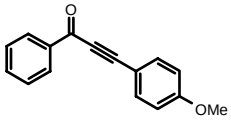
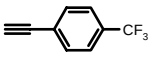
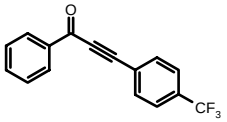
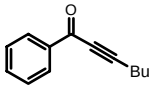
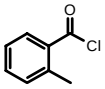
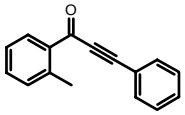
A comparative study of the reaction conditions and results for the palladium-catalyzed cross-coupling of benzoyl chloride with phenyl acetylene using the methods described above and that reported in the present work is recorded in Table **2** which clearly demonstrates the advantages of the present methodology.

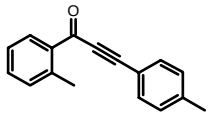
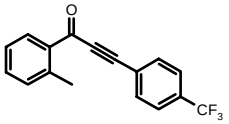
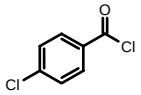
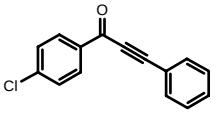
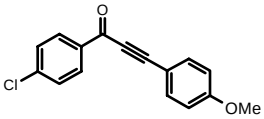
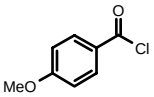
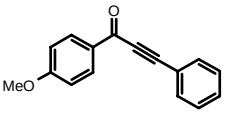
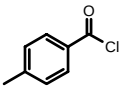
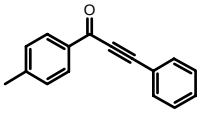
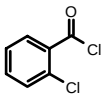
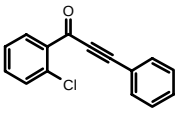
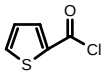
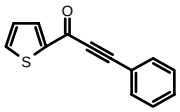
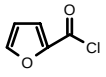
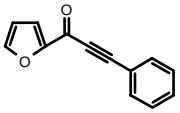
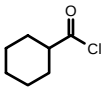
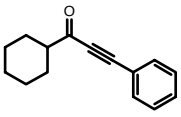
Table 2. Comparison of the reaction conditions and the results of coupling of benzoyl chloride with phenyl acetylene at room temperature

Entry	Pd catalyst (mol %)	CuI (mol %)	Solvent	Time	Yield	Ref.
1	$Pd(PPh_3)_2Cl_2$ (0.1)	0.5	Et_3N	15 h	96	6
2	$Pd(OAc)_2$ (0.5)	None	Toluene	23 h	99[a]	7
3	$Pd(PPh_3)_2Cl_2$ (2)	5	Water	4 h	98[b]	8
4	$Pd(PPh_3)_2Cl_2$ (0.9)	3	THF	10 min	96	9
5	$Pd(OAc)_2$ (0.2)	None	None	10 min	93	Present method

[a]GC yield.
[b] Reaction was carried at 65 °C.

Table 3. Synthesis of ynones by coupling of acid chlorides with terminal alkynes[a]

Entry	Alkyne 4	Acetylene 5	Product 6	Yield (%)[b]
1	 **4a**	 **5a**	 **6a**	**93**
2	**4a**	 **5b**	 **6b**	**84**
3	**4a**	 **5c**	 **6c**	**82**
4	**4a**	 **5d**	 **6d**	**65**
5	**4a**	 **5e**	 **6e**	**40[c]**
6	 **4b**	**5a**	 **6f**	**98**

7	**4b**	**5b**	 **6g**	**75**
8	**4b**	**5d**	 **6h**	**93**
9	 **1c**	**5a**	 **6i**	**86**
11	**4c**	**5c**	 **6k**	**84**
12	 **4d**	**5a**	 **6l**	**93**
13	 **4e**	**5a**	 **6m**	**95**
14	 **4f**	**5a**	 **6n**	**95**
15	 **4g**	**5a**	 **6o**	**91**
16	 **4h**	**5a**	 **6p**	**85**
17	 **4i**	**5a**	 **6q**	**89**

[a] Reaction conditions: acid chloride **4** (1 mmol), 1-alkyne **5** (1 mmol), $Pd(OAc)_2$ (0.2 mol%) and Et_3N (1 mmol). [b] Isolated yields. [c] Reaction time was 3 h.

Table **3** shows that the reaction is equally facile for both electron-donating and electron- withdrawing substituents present on the aryl ring of both the aroyl chloride **4** and the terminal alkynes **5** resulting in excellent isolated yields of ynones. Hetero-aryl acid chlorides, such as 2-thiophene carbonyl chloride **4g** (Table **3**, entry 15) and

furoyl chloride **4h** (Table **3**, entry 16), reacted smoothly with phenyl acetylene to give the isolated products in 91% and 85% yields, respectively. Cyclohexane acid chloride **4i** (Table **3**, entry 17) also afforded the desired product in 89% isolated yield. The reaction was sluggish in the case of the aliphatic alkyne, 1-hexyne **5e** (Table **3**, entry 5), giving a relatively lower yield after a much longer time (3 h).

2.1.4 Summary

In conclusion, we have developed a simple, efficient, improved and rapid *copper*-, *ligand*- and *solvent*-free synthesis of ynones at room temperature by the coupling of a variety of acid chlorides with terminal alkynes, catalyzed by $Pd(OAc)_2$ using Et_3N as the base. The rapid reaction rates, high selectivity and excellent isolated yields make the method well suited to generate a combinatorial library of a diverse array of ynones.

2.1.5 Experimental Section

General procedure for the synthesis of ynones:

A mixture of acid chloride **4** (1 mmol), terminal alkyne **5** (1 mmol), Et_3N (1 mmol) and $Pd(OAc)_2$ (0.2 mol%) was stirred at room temperature for 10 min under an atmosphere of argon. Completion of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water to dissolve the amine hydrochloride formed. The organic layer was then separated, dried over magnesium sulfate, filtered and concentrated under vacuum to obtain the crude product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as eluent to afford the desired product **6**.

Analytical data for the ynones (6a-q)

1, 3-Diphenylprop-2-yn-1-one (6a).

Nature of compound	**:**	Pale yellow liquid.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2200, 1640, 1215, 757.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.12-7.27 (m, 5H), 7.33-7.43 (m, 3H), 7.97 (d, *J* = 7.3 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	86.9, 92.9, 120.0, 128.5, 129.4, 132.8, 133.9, 136.9, 177.7.

Elemental analysis	**:**	Anal Calcd for $C_{15}H_{10}O$: C, 87.36; H, 4.89. Found: C, 87.67; H, 4.67.

1-Phenyl-3-*p*-tolylprop-2-yn-1-one (6b).

Nature of compound; mp	**:**	Colorless solid; mp 60–61 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2196, 1637, 1215, 700.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.41 (s, 3H), 7.23 (d, *J* = 8.08 Hz, 2H), 7.47–7.67 (m, 5H), 8.23 (dt, *J* = 6.96 Hz, 1.64 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.7, 86.7, 93.7, 116.9, 128.5, 129.4, 133.0, 133.9, 136.9, 141.5, 177.9.
Elemental analysis	**:**	Anal. Calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.15; H, 5.43.

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (6c).

Nature of compound; mp	**:**	Colorless solid; mp 82-83 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2193, 1635, 1602, 1215, 701.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.86 (s, 3H), 6.94 (d, *J* = 8.93 Hz, 2H), 7.48-7.68 (m, 5H), 8.23 (dt, *J* = 6.90 Hz, 1.60 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	55.3, 86.8, 94.2, 111.7, 114.3, 128.4, 129.3, 133.8, 135.0, 136.9, 161.6, 177.8.
Elemental analysis	**:**	Anal Calcd for $C_{16}H_{12}O$: C, 81.34; H, 5.12. Found: C, 80.94; H, 5.02.

3-(4-(Trifluoromethyl) phenyl)-1-phenylprop-2-yn-1-one (6d).

Nature of compound; mp	**:**	Colorless solid; mp 86-87 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2205, 1643, 1322, 699.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.42-7.56 (m, 3H), 7.61 (d, *J* = 8.55 Hz, 2H), 7.72 (d, *J* = 8.12 Hz, 2H), 8.12-8.17 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	88.1, 90.4, 120.8, 123.9, 125.6, 128.7, 129.6, 132.5, 133.1, 134.2, 136.6, 177.6.
Elemental analysis	**:**	Anal Calcd for $C_{16}H_9F_3O$: C, 70.07; H, 3.31. Found: C, 69.72; H, 3.08.

1-Phenylhept-2-yn-1-one (6e).

Nature of compound	**:**	Pale yellow oil.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3011, 2823, 2200, 1663, 1389, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	0.96 (t, *J* = 7.01 Hz, 3H), 1.61 (m, 4H), 2.49 (t, *J* = 7.21 Hz, 2H), 7.19-7.69 (m, 3H), 7.89-8.18 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	13.4, 18.7, 22.2, 29.8, 79.9, 96.7, 128.5, 129.4, 133.7, 137.0, 178.2.
Elemental analysis	**:**	Anal Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.72; H, 7.49.

3-Phenyl-1-*o*-tolylprop-2-yn-1-one (6f).

Nature of compound	**:**	Pale yellow oil.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3062, 2927, 2197, 1639, 1202, 731.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.66 (s, 3H), 7.22-7.43 (m, 5H), 7.62 (d, *J* = 7.56 Hz, 2H), 8.28 (d, *J* = 8.13 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.6, 88.1, 91.4, 119.9, 125.6, 128.3, 130.1, 131.8, 132.5, 132.6, 132.9, 135.3, 140.0, 179.2.
Elemental analysis	**:**	Anal Calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.52; H, 5.29.

1-*o*-Tolyl-3-*p*-tolylprop-2-yn-1-one (6g).

Nature of compound	**:**	Pale yellow oil.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	2925, 2194, 1638, 1202, 731.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.44 (s, 3H), 2.76 (s, 3H), 7.25-7.63 (m, 7H), 8.39 (d, *J* = 7.75 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.5, 21.7, 88.1, 92.3, 116.9, 125.7, 129.3, 131.9, 132.7, 132.9, 135.6, 140.1, 141.1, 179.5.
Elemental analysis	**:**	Anal Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.46; H, 5.31.

3-(4-(Trifluoromethyl) phenyl)-1-*o*-tolylprop-2-yn-1-one (6h).

Nature of compound; mp	**:**	Colorless solid; mp 72 ^{o}C
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	2926, 2160, 1650, 1303, 757.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.68 (s, 3H), 7.26–7.54 (m, 3H), 7.67 (d, *J* = 8.48 Hz, 2H), 7.77 (d, *J* = 8.21 Hz, 2H), 8.29 (d, *J* = 7.50 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.9, 89.2, 89.5, 120.7, 124.2, 125.6, 125.9, 131.7, 132.3, 132.9, 133.2, 135.3, 140.7, 179.2.
Elemental analysis	**:**	Anal Calcd for $C_{17}H_{11}F_3O$: C, 70.83; H, 3.85. Found: C, 70.81; H, 3.71.

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (6i).

Nature of compound; mp	**:**	Colorless solid; mp 105-106 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	2926, 2160, 1650, 1303, 757.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.43-7.70 (m, 7H), 8.16 (d, *J* = 7.92 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	86.6, 93.6, 119.8, 128.7, 128.9, 130.8, 133.1, 135.3, 140.7, 176.6.
Elemental analysis	**:**	Anal Calcd for $C_{15}H_9ClO$: C, 74.85; H, 3.77. Found: C, 74.58; H, 3.49.

1-(4-Chlorophenyl)-3-*p*-tolylprop-2-yn-1-one (6j).

Nature of compound; mp	**:**	Colorless solid; mp 117-119 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2196, 1636, 1215, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.40 (s, 3H), 7.23 (d, *J* = 8.09 Hz, 2H), 7.48 (d, *J* = 8.65 Hz, 2H), 7.57 (d, *J* = 8.07 Hz, 2H) 8.15 (d, *J* = 8.71 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.7, 86.4, 94.3, 116.7, 128.9, 129.5, 130.7, 133.1, 135.3, 140.5, 141.7, 176.6.
Elemental analysis	**:**	Anal Calcd for $C_{16}H_{11}ClO$: C, 75.45; H, 4.35. Found: C, 75.78; H, 4.31.

1-(4-Chlorophenyl)-3-(4-methoxyphenyl) prop-2-yn-1-one (6k).

Nature of compound; mp	**:**	Colorless solid; mp 116-117 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2192, 1635, 1215, 758.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.79 (s, 3H), 6.86 (dt, *J* = 9.07, 1.94 Hz, 2H), 7.41 (dt, *J* = 8.75, 1.89 Hz, 2H), 7.56 (dt, *J* = 8.91, 2.11 Hz, 2H), 8.07 (dt, *J* = 8.75, 2.05 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	55.3, 86.5, 94.8, 111.5, 114.4, 128.8, 130.7, 135.1, 135.3, 140.3, 161.8, 176.5.
Elemental analysis	**:**	Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10. Found: C, 70.84; H, 4.42.

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (6l).

Nature of compound; mp	**:**	Colorless solid; mp 99-100 ^{o}C
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	2929, 2200, 1631, 1597, 1163, 908, 733.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.89 (s, 3H), 6.99 (dt, *J* = 9.00 Hz, 2.05 Hz, 2H), 7.36-7.48 (m, 3H), 7.65-7.70 (m, 2H), 8.19 (dt, *J* = 8.95 Hz, 2.00 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	55.5, 86.8, 92.3, 113.8, 120.2, 128.5, 130.5, 131.8, 132.8, 164.4, 176.5.
Elemental analysis	**:**	Anal Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 80.90; H, 5.14.

3-Phenyl-1-*p*-tolylprop-2-yn-1-one (6m).

Nature of compound; mp	**:**	Colorless solid; mp 64-66 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3017, 2200, 1635, 1286, 688.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.44 (s, 3H), 7.31 (d, *J* = 8.04 Hz, 2H), 7.37-7.52 (m, 3H), 7.66-7.71 (m, 2H), 8.12 (d, *J* = 8.28 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.7, 87.1, 92.5, 120.4, 128.6, 129.3, 129.7, 132.9, 134.8, 145.1, 177.6.
Elemental analysis	**:**	Anal Calcd for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.38; H, 5.76.

1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-one (6n).

Nature of compound	**:**	Pale yellow oil.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3015, 2210, 1620, 1421, 755.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.34-7.51 (m, 6H), 7.61-7.66 (m, 2H), 8.08 (dt, *J* = 7.66, 1.48 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	88.2, 93.6, 119.8, 126.7, 128.6, 130.8, 131.4, 132.4, 132.9, 133.3, 133.4, 135.7, 176.6.
Elemental analysis	**:**	Anal Calcd for $C_{15}H_9ClO$: C, 74.85; H, 3.77. Found: C, 74.48; H, 3.56.

3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-one (6o).

Nature of compound; mp	**:**	Colorless solid; mp 53–54 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3016, 2200, 1618, 1411, 756.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.17–7.21 (m, 1H), 7.37–7.53 (m, 3H), 7.64–7.74 (m, 3H), 8.01 (dd, *J* = 2.96, 1.31 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	86.4, 91.6, 119.7, 128.3, 128.6, 130.7, 132.8, 135.2, 144.8, 169.6.
Elemental analysis	**:**	Anal. Calcd for $C_{13}H_8OS$: C, 73.56; H, 3.80. Found: C, 73.48; H, 4.16.

1-(Furan-2-yl)-3-phenylprop-2-yn-1-one (6p).

Nature of compound	**:**	Yellow oil.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2202, 1629, 1462, 1215, 1043, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	6.59 (dd, *J* = 3.51, 1.95 HZ, 1H), 7.43-7.46 (m, 4H), 7.60-7.68 (m, 3H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	86.0, 91.6, 112.4, 119.5, 120.6, 128.4, 130.5, 132.7, 147.7, 152.9, 164.3.
Elemental analysis	**:**	Anal Calcd for $C_{13}H_8O_2$: C, 79.58; H, 4.11. Found: C, 79.48; H, 4.13.

1-Cyclohexyl-3-phenylprop-2-yn-1-one (6q).

Nature of compound	**:**	Yellow oil.

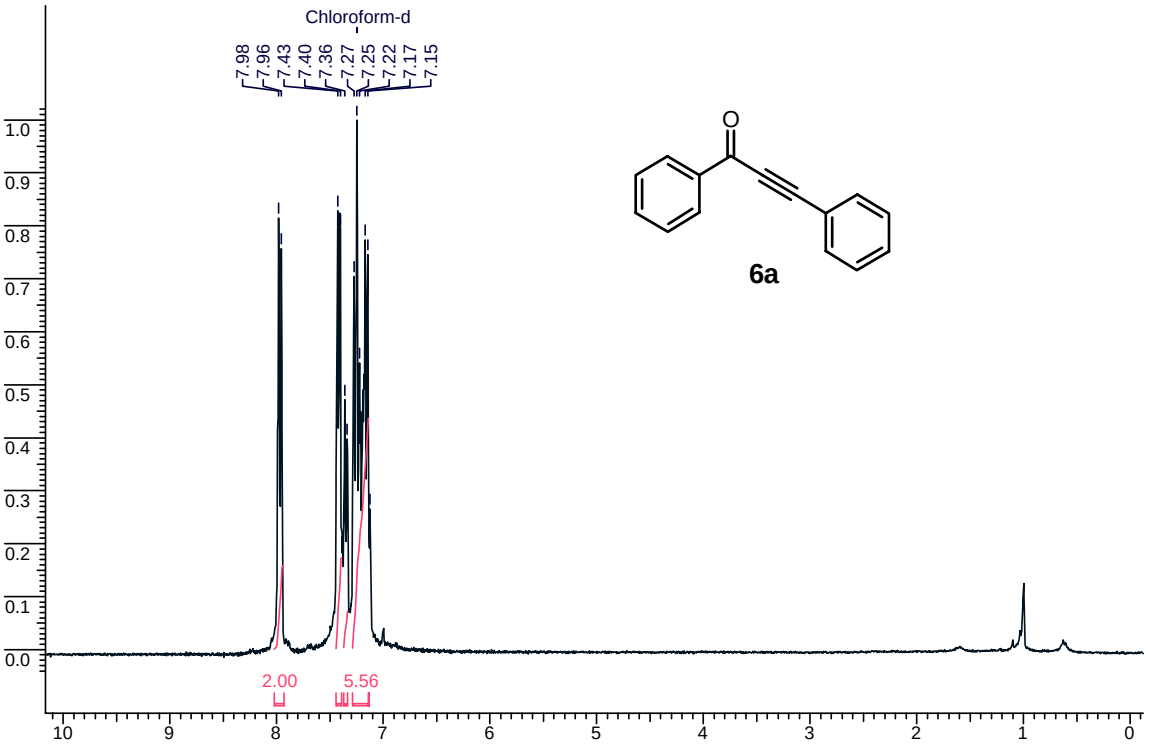
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2932, 2856, 2200, 1662, 1450, 1216, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.19-2.18 (m, 10H), 2.44-2.57 (m, 1H), 7.38-7.45 (m, 3H), 7.56-7.61 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	25.5, 25.8, 28.4, 52.4, 87.3, 91.5, 120.4, 128.6, 130.7, 132.8, 190.9.
Elemental analysis	**:**	Anal Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.77; H, 7.56.

2.1.6 Spectra

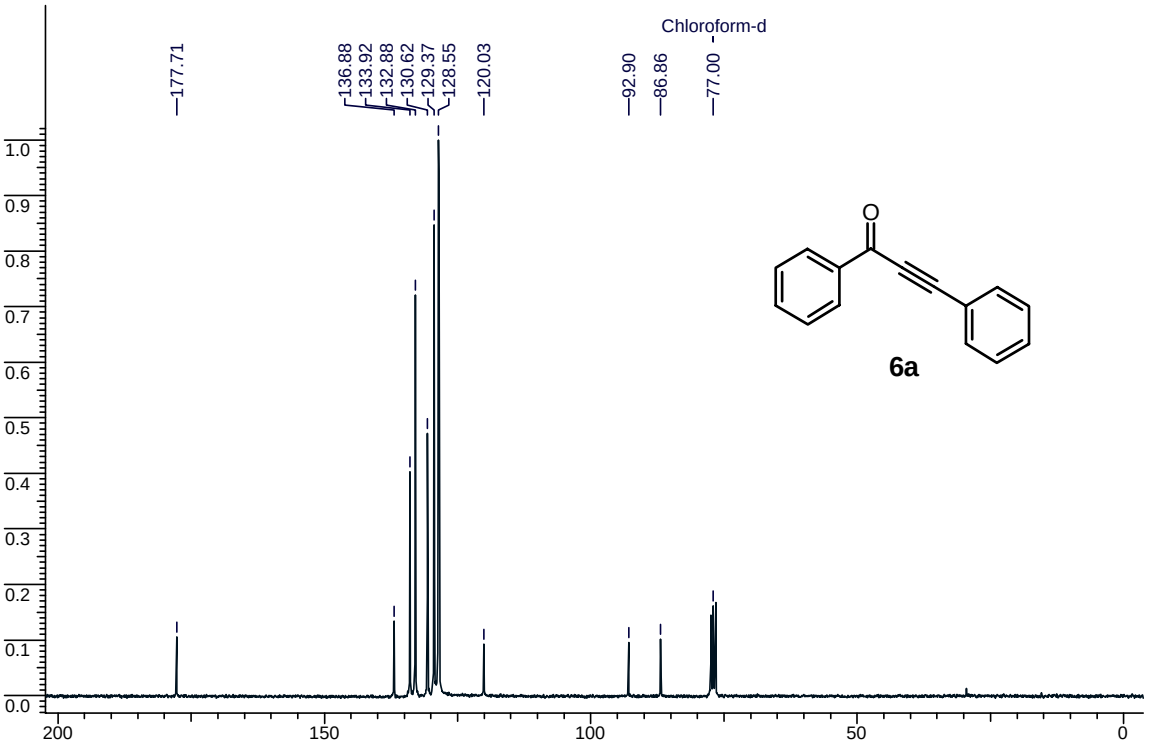
Table 4. ^{1}H and ^{13}C spectra of some representative Ynones.

Sr. No.	Spectra
1	^{1}H and ^{13}C spectra of **6a**
2	^{1}H and ^{13}C spectra of **6b**
3	^{1}H and ^{13}C spectra of **6c**
4	^{1}H and ^{13}C spectra of **6d**
5	^{1}H and ^{13}C spectra of **6h**
6	^{1}H and ^{13}C spectra of **6i**
7	^{1}H and ^{13}C spectra of **6k**
8	^{1}H and ^{13}C spectra of **6l**
9	^{1}H and ^{13}C spectra of **6m**
10	^{1}H and ^{13}C spectra of **6o**

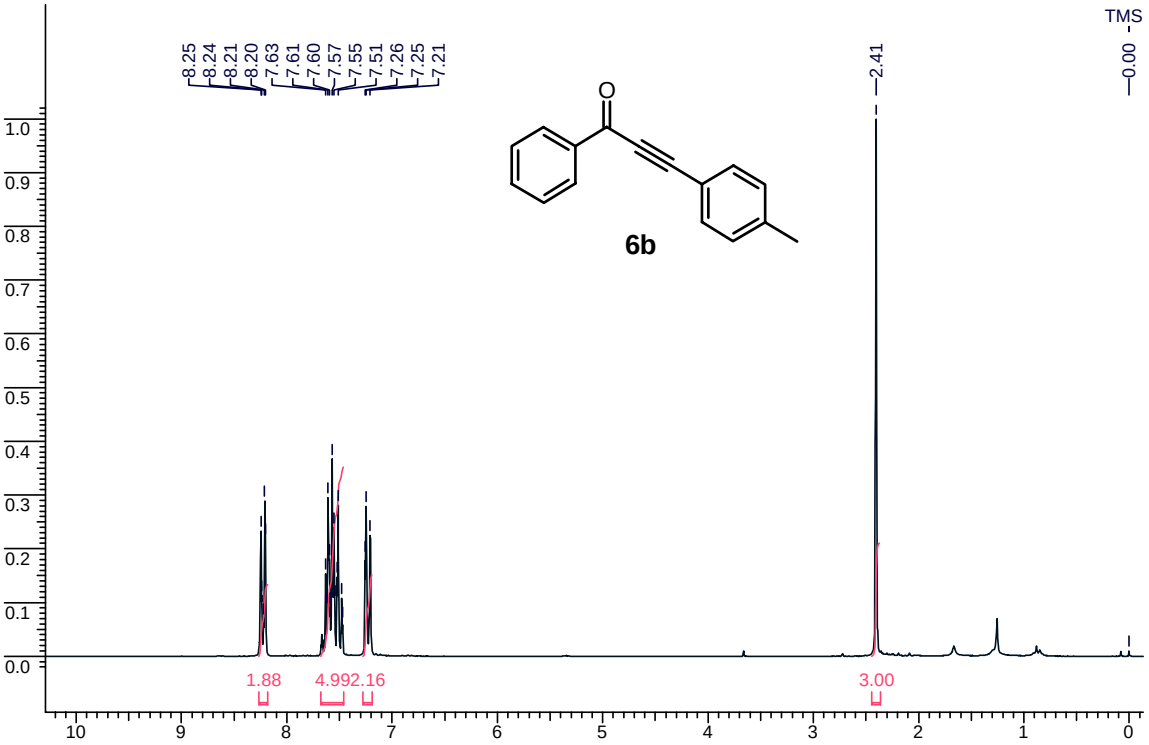
^{1}H NMR of **6a**



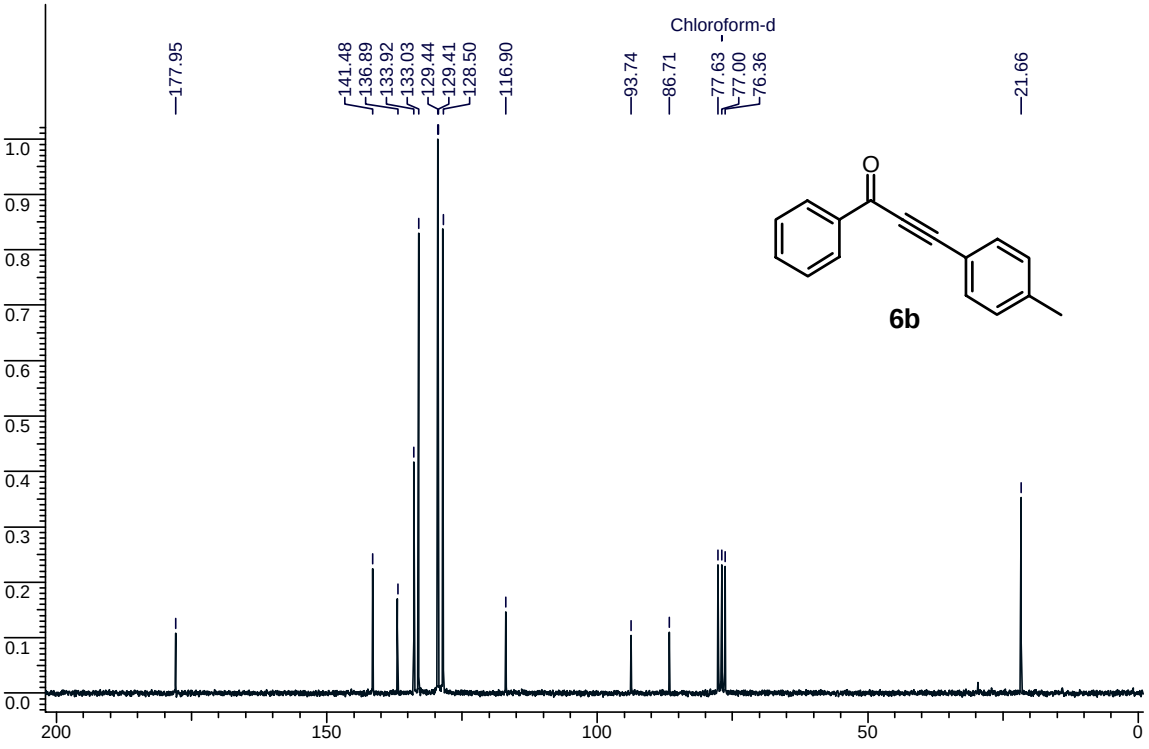
^{13}C NMR of **6a**



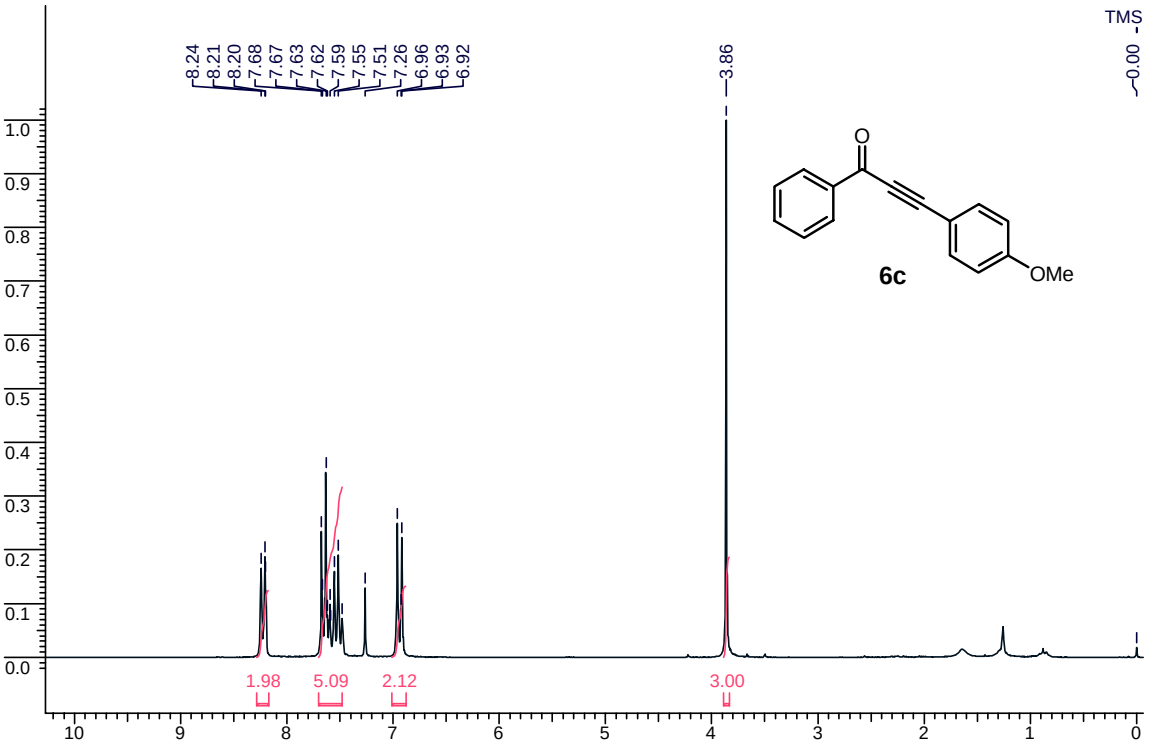
^{1}H NMR of **6b**



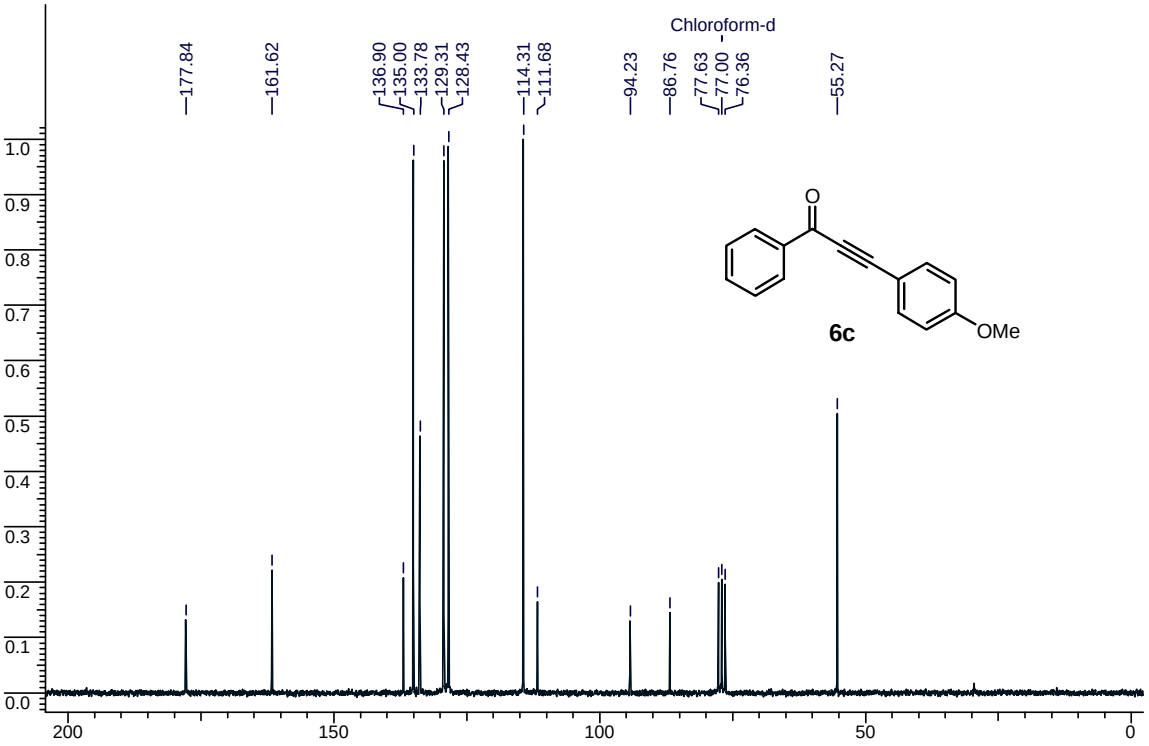
^{13}C NMR of **6b**



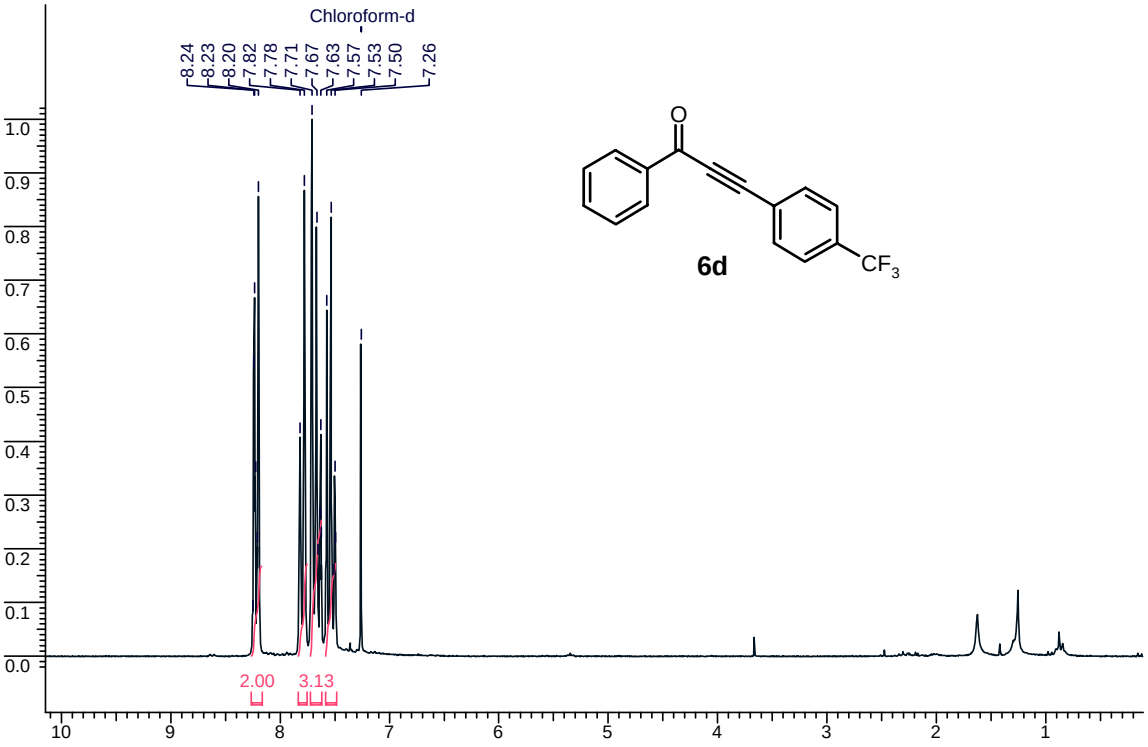
^{1}H NMR of **6c**



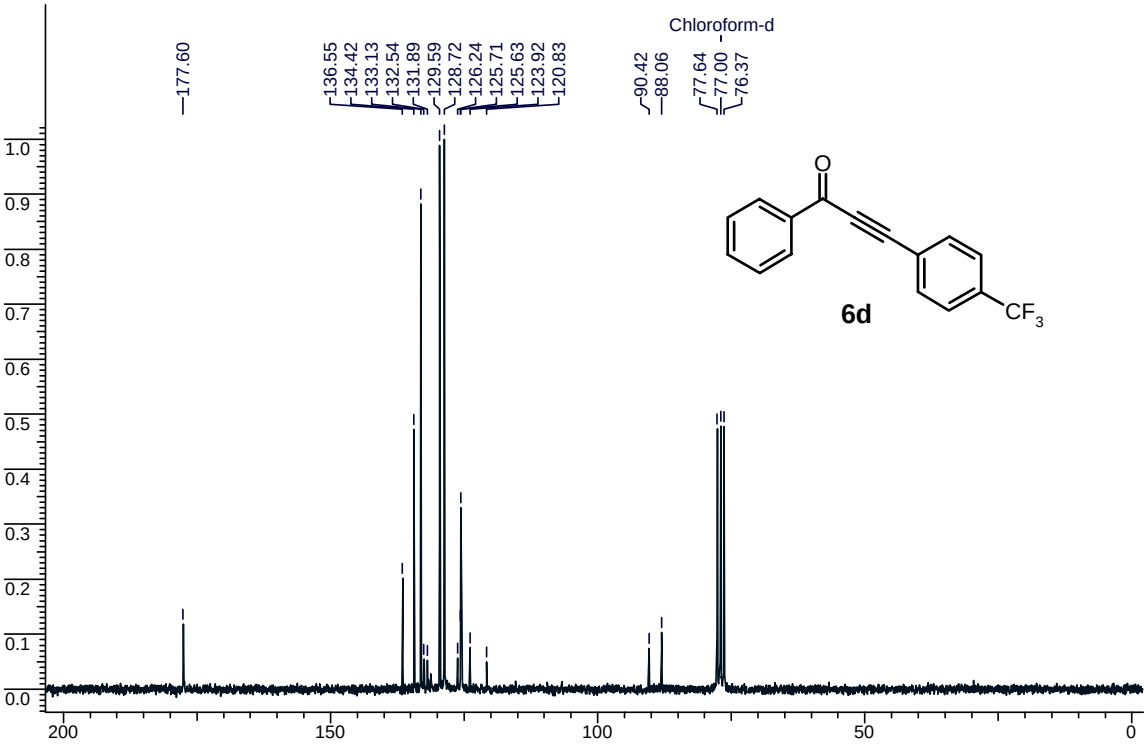
^{13}C NMR of **6c**



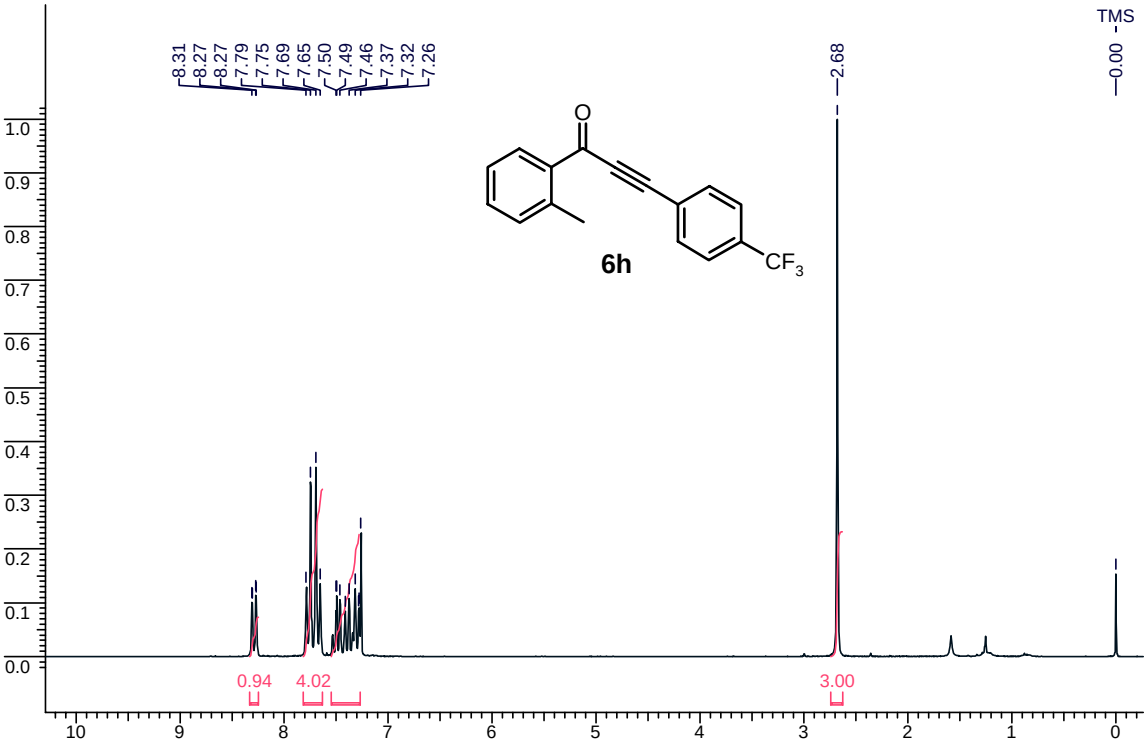
^{1}H NMR of **6d**



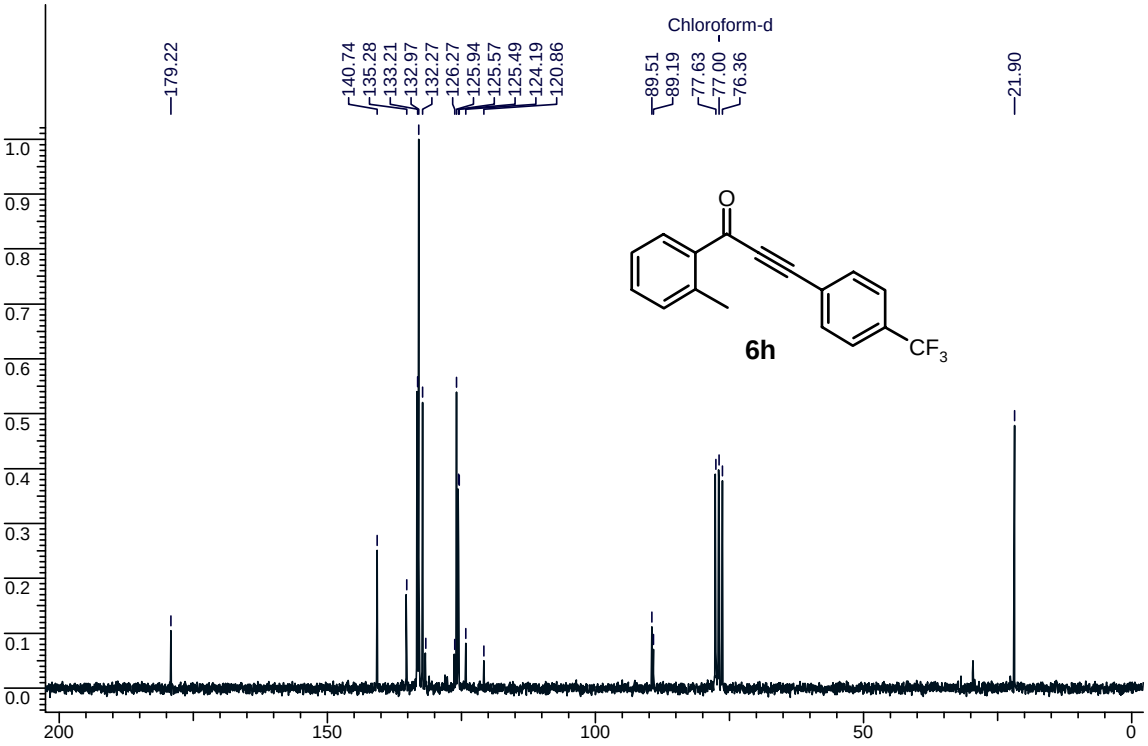
^{13}C NMR of **6d**



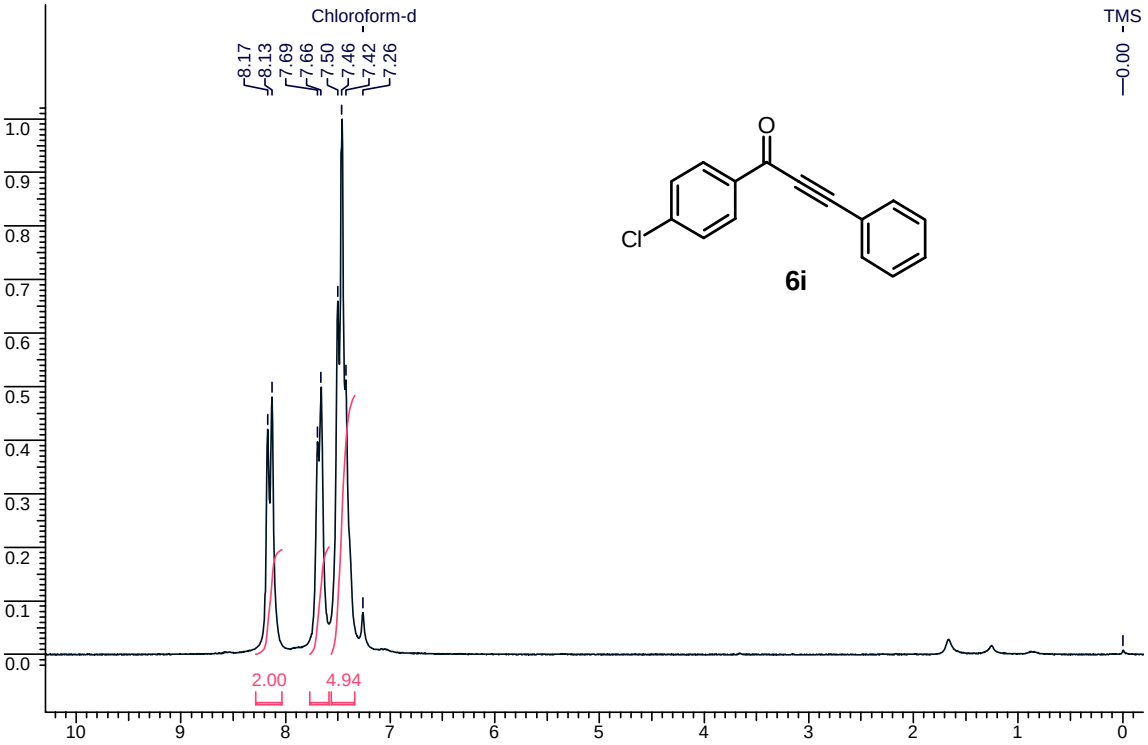
^{1}H NMR of **6h**



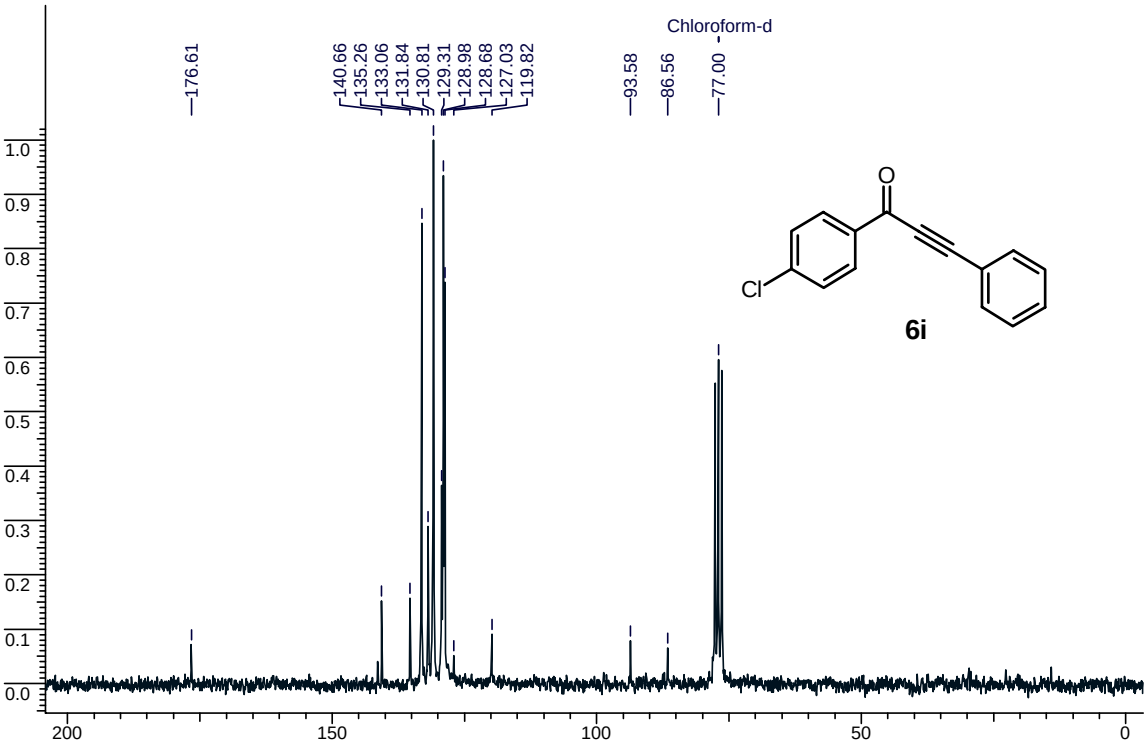
^{13}C NMR of **6h**



^{1}H NMR of **6i**



^{13}C NMR of **6i**



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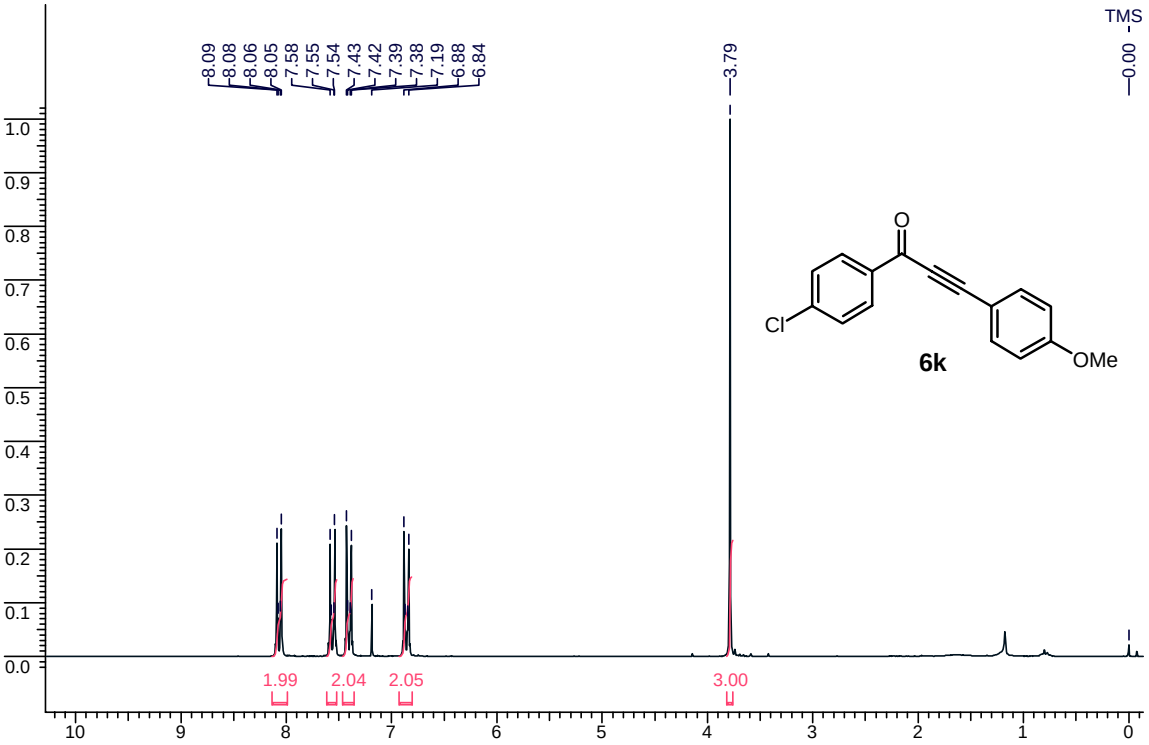

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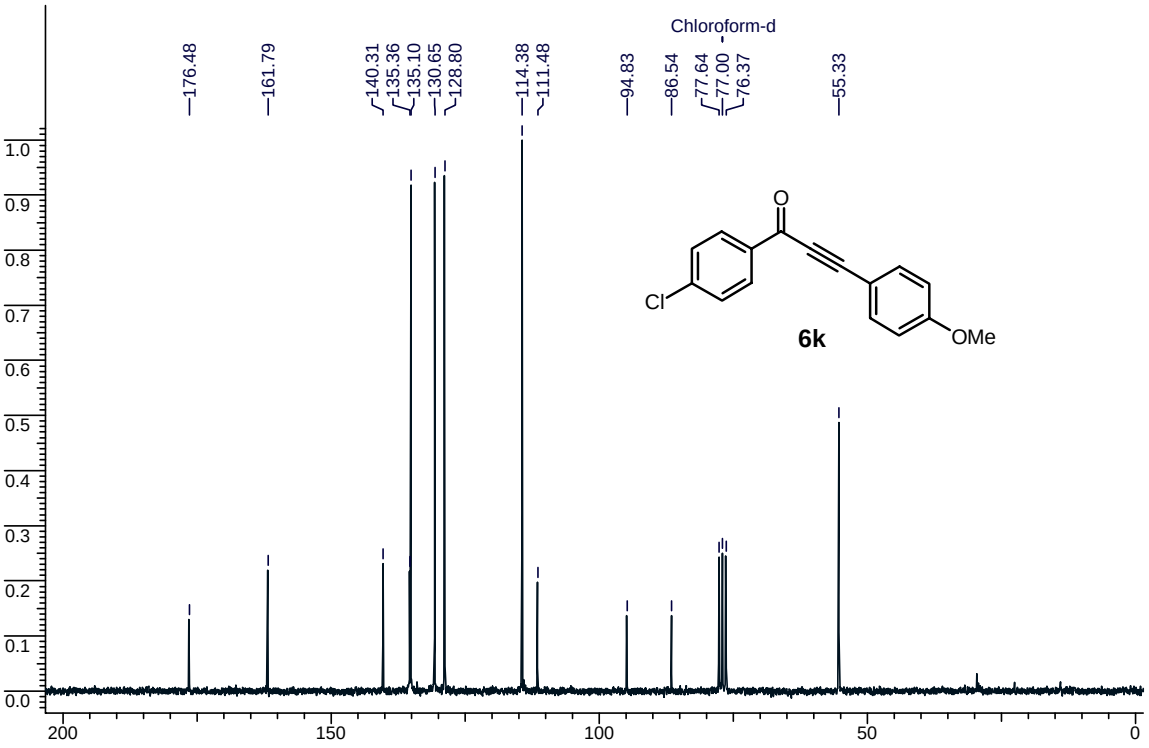

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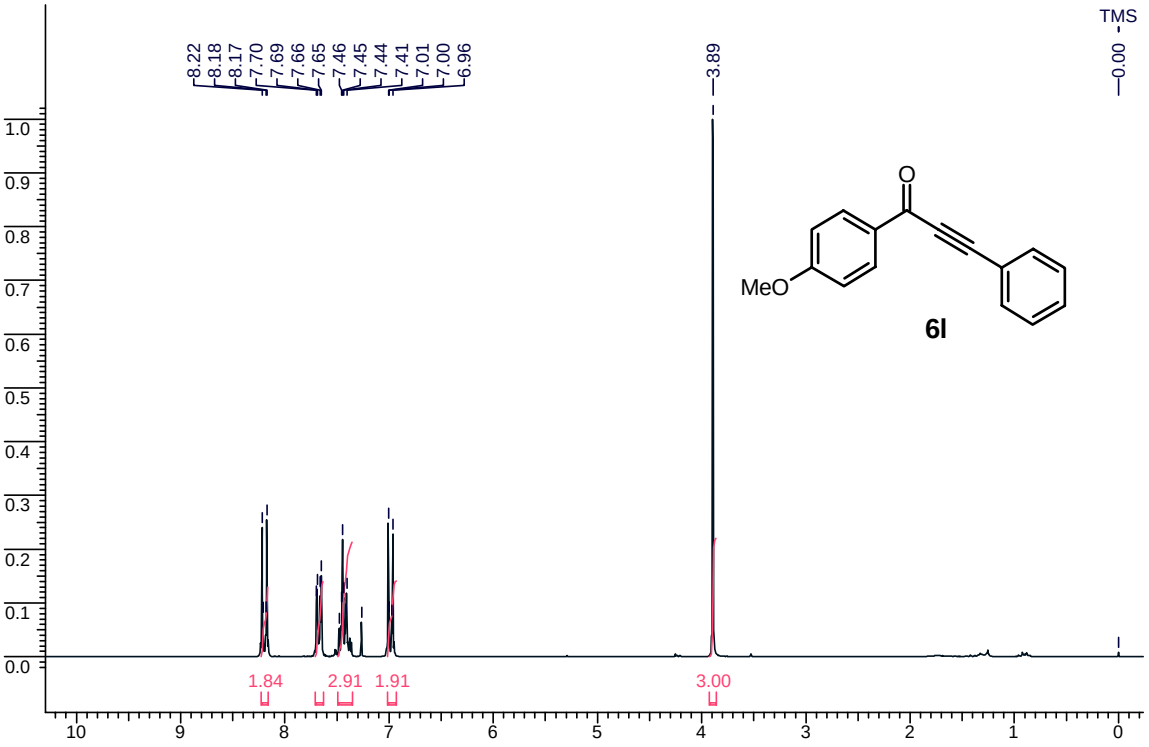
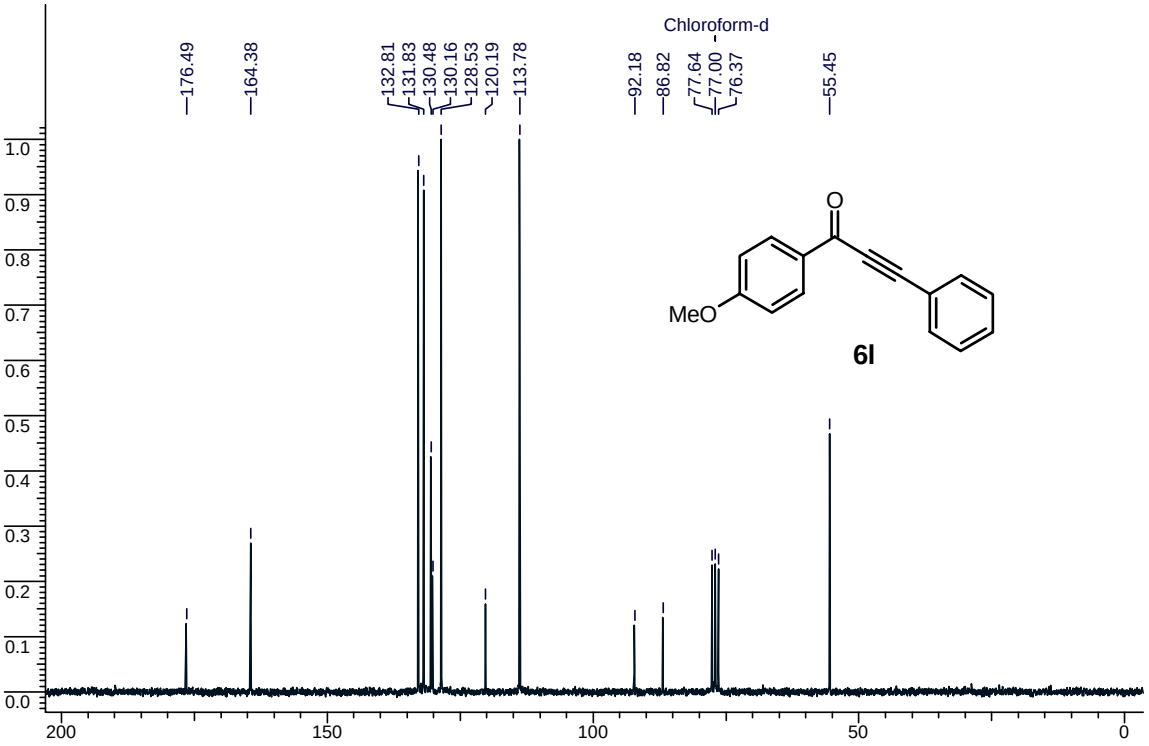
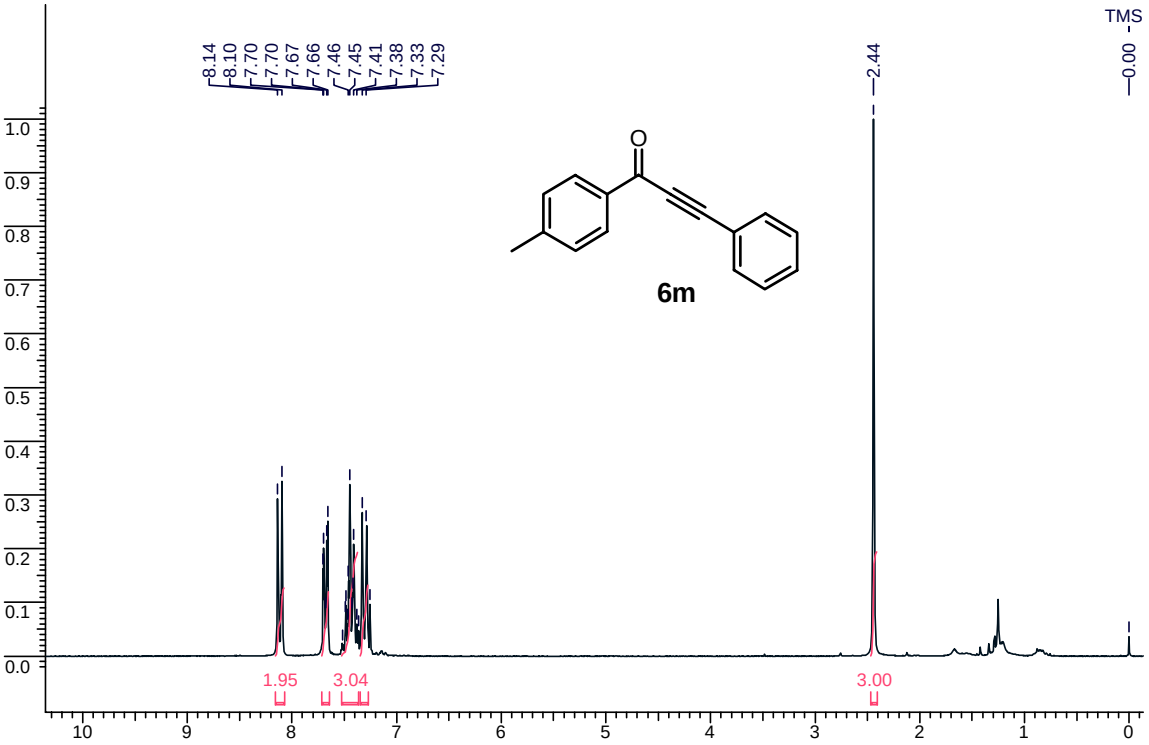


^{13}C NMR of **6l**



^{1}H NMR of **6m**



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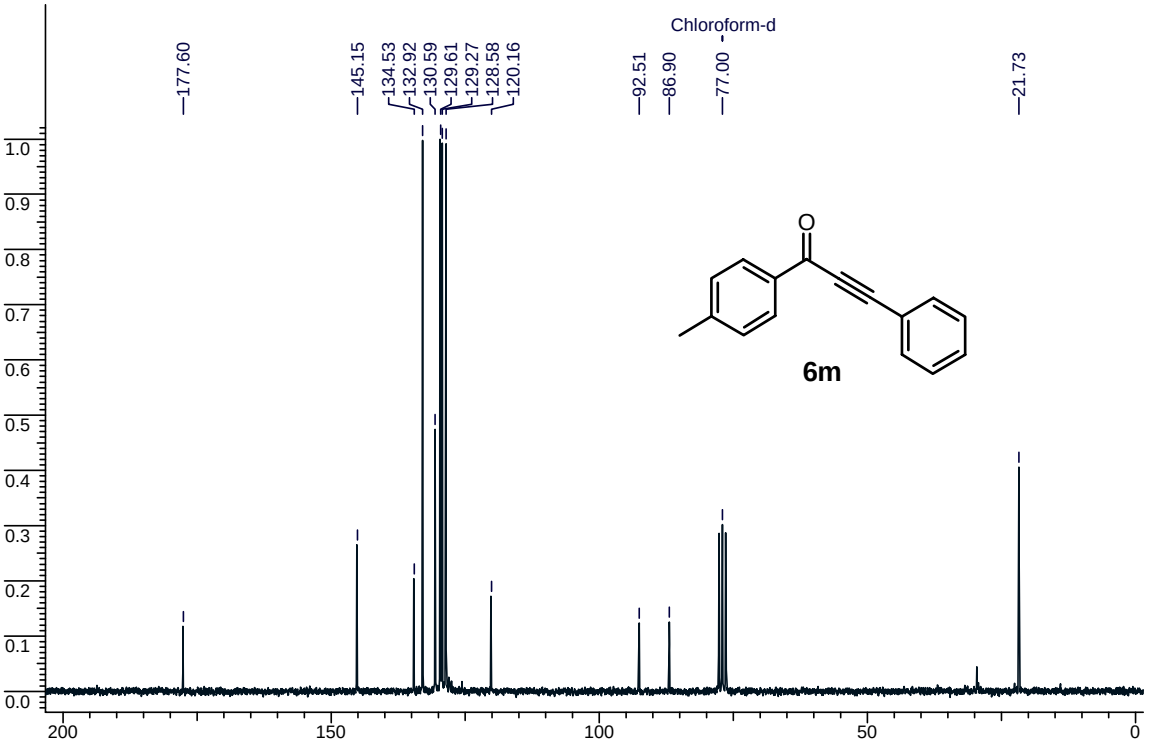
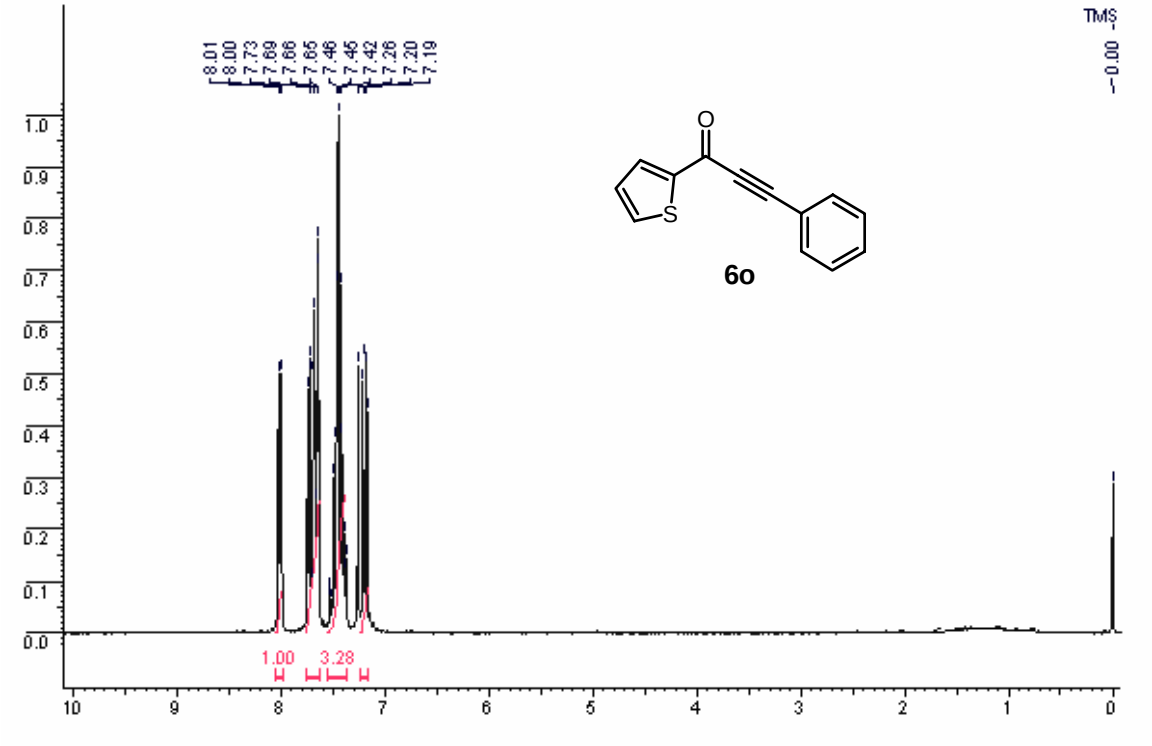


^{1}H NMR of **6o**



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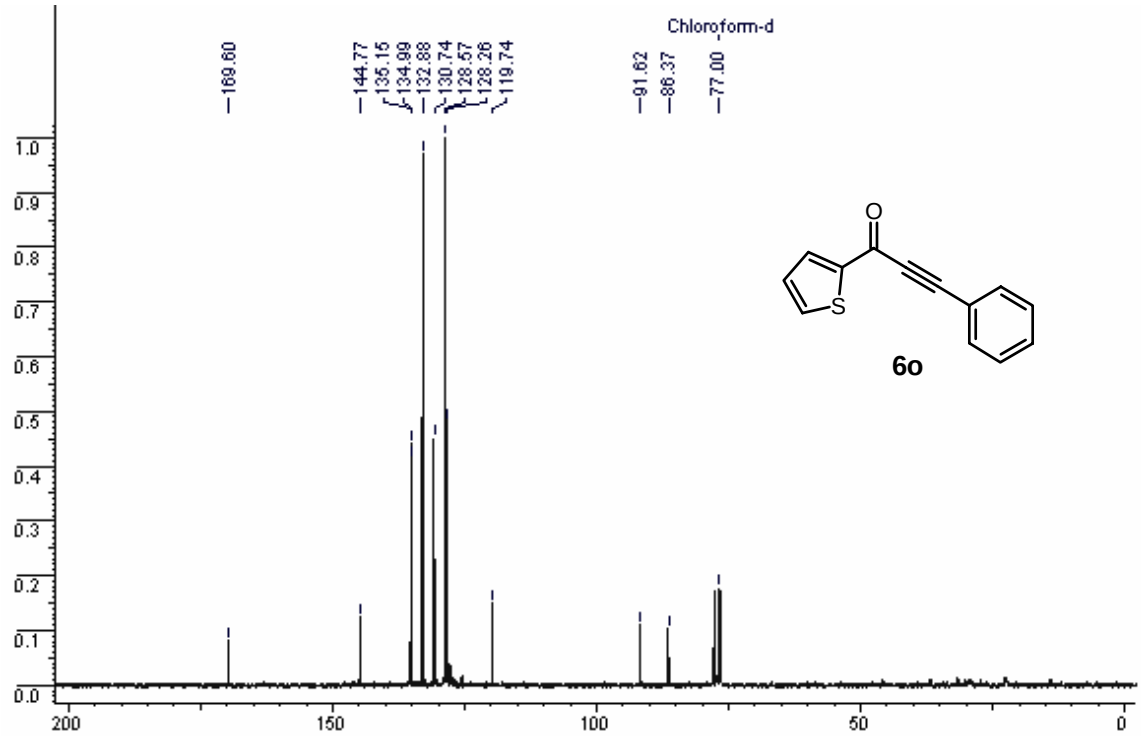

2.1.7 References

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Section B

A simple and efficient one-pot three-component solvent-Free synthesis of β-enaminones via Sonogashira coupling-Michael addition sequences

2.2.0 Introduction

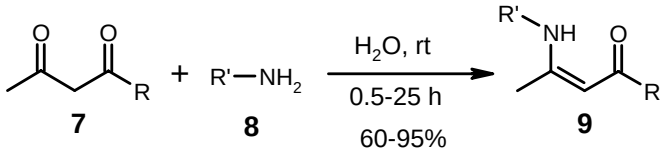
β-enaminones are versatile synthetic intermediates, extensively employed in organic synthesis.[1] In particular, such compounds are important precursors for the synthesis of a wide variety of heterocycles.[2] Also they have been employed as synthons of pharmaceutical compounds having anti-epileptic,[3] anti-molluscicidal and larvicidal activities[4] and as intermediates for the synthesis of naturally occurring alkaloids.[5]

2.2.1 Review of Literature

The most well known and explored route to β-enaminones involves the direct condensation of β-dicarbonyl compounds with amines in refluxing aromatic hydrocarbons with azeotropic removal of water.[6] In recent years, several important improved environmentally benign procedures have been reported, some of the representative methods are discussed below.

Stefani's approach (2000)[7]

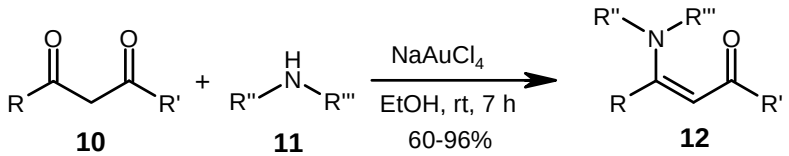
Stefani, H. A. *et al*. reported, a simple procedure for the synthesis of β-enamino esters and β-enaminoketones **9** starting from β-ketoesters /1, 3-diketones **7** and primary amines **8** using water as a solvent in the absence of catalyst as shown in Scheme **6**.



Scheme 6

Marinelli's approach (2003)[8]

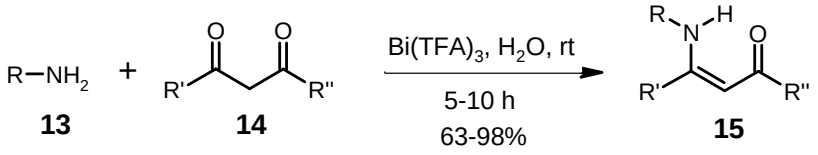
Marinelli, F. *et al.* reported an efficient gold (III) catalyzed environmental friendly method for the synthesis of β-enaminones **12** in ethanol at room temperature as shown in Scheme **7**.



Scheme 7

Khosropour's approach (2004)[9]

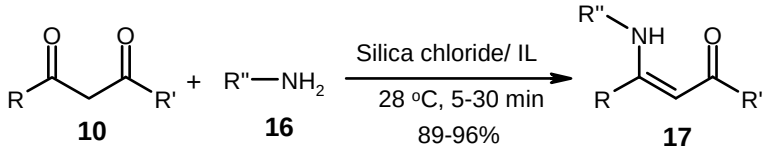
Khosropour, A. R. *et al.* reported bismuth(III)trifluoroacetate as an extremely efficient catalyst for the preparation of β-enaminones **15** in water at room temperature is presented in Scheme **8**.



Scheme 8

Srinivasan's approach (2006)[10]

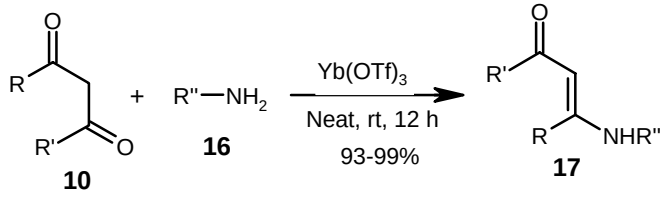
Srinivasan, K. V. *et al.* reported a remarkably rapid regioselective synthesis of β-enaminones using ionic liquid in homogeneous medium as well as silica chloride in a heterogeneous medium (Scheme **9**).



Scheme 9

Epifano's approach (2007)[11]

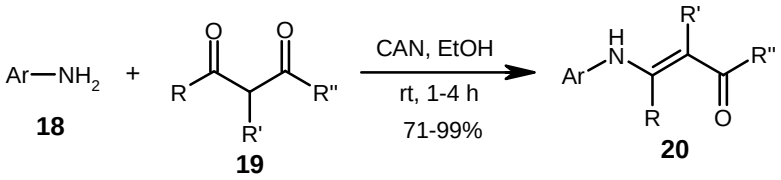
Epifano, F. *et al.* have reported the synthesis of β-enaminones **17** by using ytterbium triflate as a catalyst under solvent-free conditions (Scheme **10**).



Scheme 10

Menendez's approach (2007)[12]

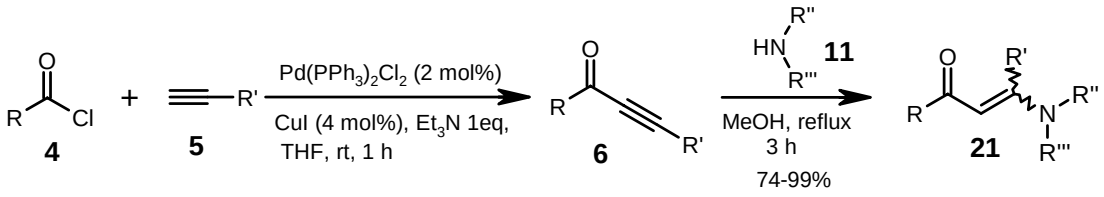
Menendez, J. C. *et al.* reported general, mild and efficient synthesis of β-enaminones **20** catalyzed by ceric ammonium nitrate in ethanol at room temperature (Scheme **11**).



Scheme 11

Müller's approach (2003)[13]

Müller, T. J. J. *et al.* reported a straightforward one-pot synthesis of β-enaminones **21** by coupling-addition sequences in THF and methanol solvent system under reflux condition as shown in Scheme **12**.

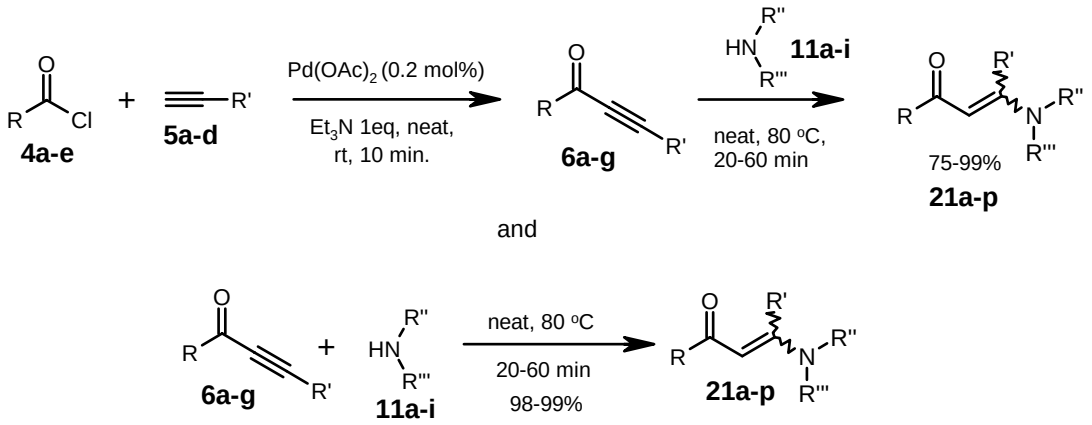


Scheme 12

2.2.2 Present Work

Many of these processes suffer from major or minor limitations such as drastic reaction conditions, tedious work-up procedures, low selectivity (co-occurrence of several side reactions). Although several methods are available for the synthesis of β-enaminones, the development of a clean, facile, high yielding and non-polluting protocols for the construction of this highly versatile synthetic intermediate β-enaminone is still a synthetic challenge to organic chemists. The synthesis of β-enaminones under solvent-free condition by the reaction of ynones with amines has not been reported so far.

A simple, efficient and environment friendly, solvent-free, one-pot three-component synthesis of β-enaminones *via* coupling of acid chlorides with terminal alkynes followed by the *in situ* Michael addition of the resulting ynones with amines in good to excellent isolated yields has been developed and described in this section. The synthesis of β-enaminones by the direct reaction of amines with corresponding ynones in very high isolated yields under *solvent-free* conditions is also discussed in this Section **B** as shown in Scheme **13**.

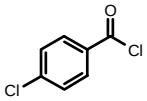
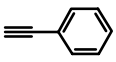
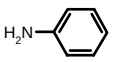
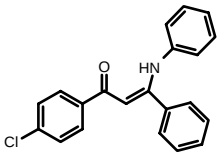
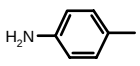
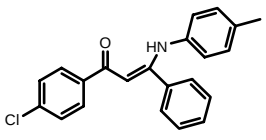
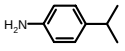
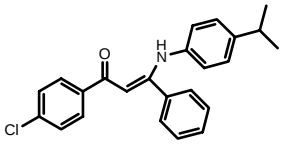


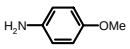
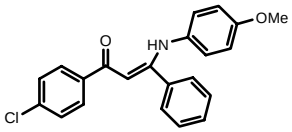
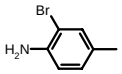
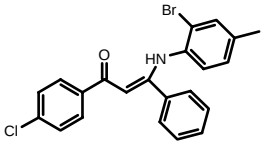
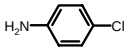
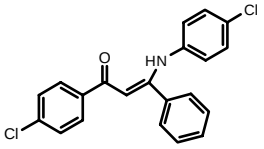
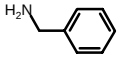
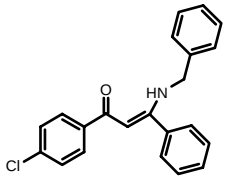
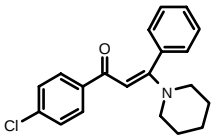
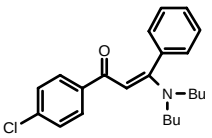
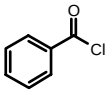
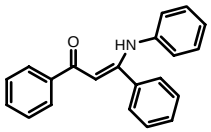
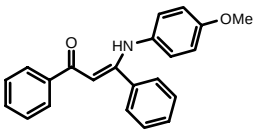
Scheme 13

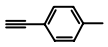
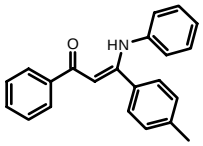
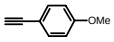
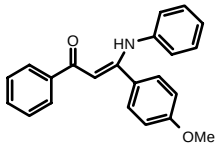
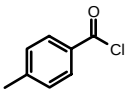
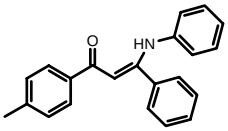
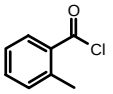
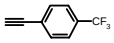
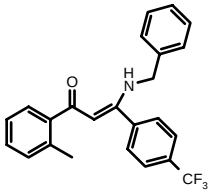
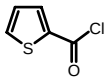
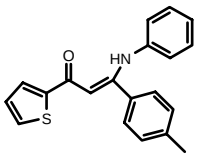
2.2.3 Results and Discussion

Initially, the Sonogashira coupling of acid chlorides **4** with 1-alkynes **5** was achieved under *copper-, ligand- and solvent-free* conditions using $Pd(OAc)_2$ (0.2 mol%) as catalyst and one equivalent of triethyl amine as the base followed by the *in situ* addition of respective amines **11** and the resulting reaction mixture was further subjected to heating at 80 °C for 20-60 min to afford β-enaminones **21** in very good to excellent isolated yields. The results are summarized in Table **5.**

Table 5. One-pot three-component s*olvent - free* synthesis of β-enaminones

Entry	Acid chloride 4	1-Alkyne 5	Amine 11	β-enaminones 21	Reaction time (min)	Yield (%)[a]
1	 **4a**	 **5a**	 **11a**	 **21a**	**60**	**85**
2	**4a**	**5a**	 **11b**	 **21b**	**60**	**80**
3	**4a**	**5a**	 **11c**	 **21c**	**60**	**79**

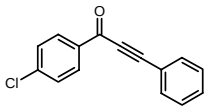
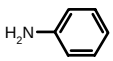
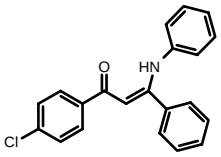
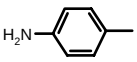
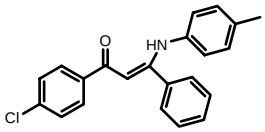
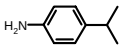
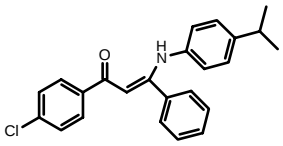
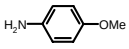
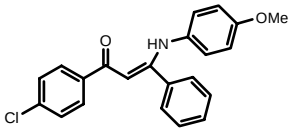
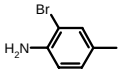
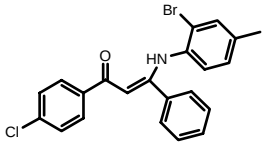
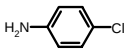
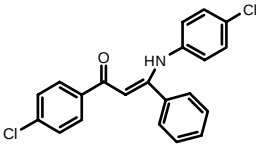
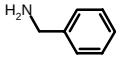
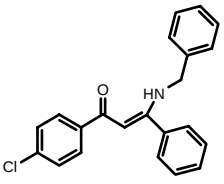
4	**4a**	**5a**	 **11d**	 **21d**	**50**	**82**
5	**4a**	**5a**	 **11e**	 **21e**	**60**	**76**
6	**4a**	**5a**	 **11f**	 **21f**	**60**	**95**
7	**4a**	**5a**	 **11g**	 **5g**	**30**	**99**
8	**4a**	**5a**	 **11h**	 **21h**	**20**	**90**
9	**4a**	**5a**	 **11i**	 **21i**	**20**	**85**
10	 **4b**	**5a**	**11a**	 **21j**	**60**	**75**
11	**4b**	**5a**	**11d**	 **21k**	**50**	**80**

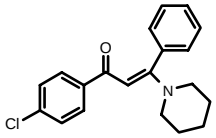
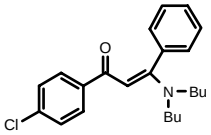
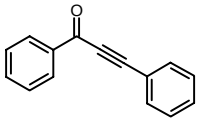
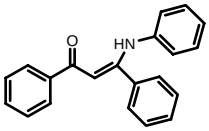
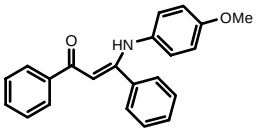
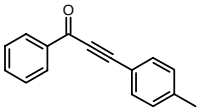
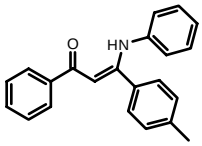
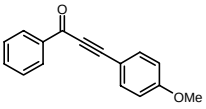
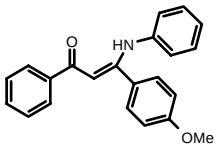
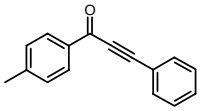
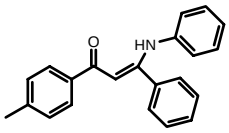
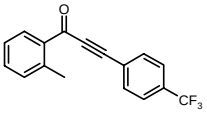
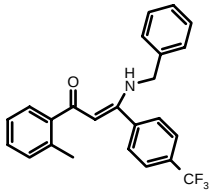
12	**4b**	 **5b**	**11a**	 **21l**	**60**	**91**
13	**4b**	 **5c**	**11a**	 **21m**	**60**	**89**
14	 **4c**	**5a**	**11a**	 **21n**	**60**	**77**
15	 **4d**	 **5d**	**11g**	 **21o**	**30**	**90**
16	 **4e**	**5b**	**11a**	 **21p**	**60**	**96**

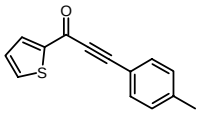
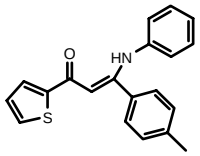
[a]Isolated yields by using method **A**

Also the direct reaction of amines with corresponding ynones have been carried out at 80 ^{o}C for 20-60 min under neat conditions to afford the β-enaminones in very high yields and purity and there was no need of column chromatography for the purification of the products in this case. The results are summarized in Table **6**.

Table 6. S*olvent-free* synthesis of β-enaminones by reaction of amines with corresponding ynones

Entry	Ynones 6	Amine 11	β-enaminones 21	Reaction time (min)	Yield (%)[a]
1	 **6a**	 **11a**	 **21a**	**60**	**99**
2	**6a**	 **11b**	 **21b**	**60**	**99**
3	**6a**	 **11c**	 **21c**	**60**	**98**
4	**6a**	 **11d**	 **21d**	**50**	**99**
5	**6a**	 **11e**	 **21e**	**60**	**98**
6	**6a**	 **11f**	 **21f**	**60**	**99**
7	**6a**	 **11g**	 **21g**	**30**	**99**

8	**6a**	 **11h**	 **21h**	**20**	**99**
9	**6a**	 **11i**	 **21i**	**20**	**98**
10	 **6b**	**11a**	 **21j**	**60**	**98**
11	**6b**	**11d**	 **21k**	**50**	**99**
12	 **6c**	**11a**	 **21l**	**60**	**99**
13	 **3d**	**11a**	 **21m**	**60**	**99**
14	 **6e**	**11a**	 **21n**	**60**	**98**
15	 **6f**	**11g**	 **21o**	**30**	**99**

16	 **6g**	**11a**	 **21p**	**60**	**98**

[a]Isolated yields by using method **B**

The scope and generality of this method could be validated by observing that a wide range of amines **11a-i** including aromatic amines having both electron-donating and electron-withdrawing groups, aliphatic primary and secondary amines were well tolerated giving excellent isolated yields of the β-enaminones **21**. Moreover, the various acid chlorides **4** and terminal alkynes **5** including different substituents such as methyl, methoxy, chloro and trifluoromethyl were equally facile for the reaction resulting in the formation of β-enaminones **21** in excellent isolated yields.

The structure of all the β-enaminones **21** synthesized were well characterized by ^{1}H, ^{13}C, NOESY NMR spectral analyses and their elemental analyses were in conformity with their structures. Most characteristically, in the ^{1}H spectra, the –NH proton signal appeared as a broad singlet in the range δ = 11-13 (ppm) for primary amines and olefinic protons appear as a distinct singlet in the range δ = 5.50-6.02 (ppm). The configuration of carbon-carbon double bond was determined by NOE experiment. It was found that the β-enaminones (**21h & 21i**) obtained from secondary amines have (*E*) configuration and β-enaminones (**21a-g, 21j-p**) obtained from the primary amines have the thermodynamically favored (*Z*) configuration, due to the hydrogen bonding between oxygen atom of the carbonyl group and NH-hydrogen.

2.2.4 Conclusion

In conclusion, we disclose here a simple, clean, atom-efficient, environment friendly and solvent-free one-pot three-component as well as two-pot procedure for the synthesis of β-enaminones *via* Sonogashira coupling- Michael addition sequences. A simple experimental procedure, relatively fast reaction rates, excellent yields, selectivity and purity are the key advantages of our protocol enabling it to be operated in combi-chem mode to generate libraries constituting a diverse array of the β-enaminones. Various substituents (Electron-donating and electron -withdrawing) deployed on acid chlorides, terminal alkynes and amines were well tolerated. Most

significantly, efficiency, cost-effectiveness and green methodology will make this procedure useful to academia as well as industry.

2.2.5 Experimental Section

General procedure for synthesis of β-enaminones:

Method-A:

To a stirred mixture of $Pd(OAc)_2$ (0.2 mol%), acid chloride **4** (1 mmol) and terminal alkyne **5** (1 mmol) was added drop wise dry triethyl amine (1 mmol) at room temperature under an atmosphere of argon. The reaction mixture was further stirred at room temperature for 10 min. After completion of reaction as monitored by TLC, amine **11** (1 mmol) was added to the same flask. The resulting reaction mixture was further subjected to heating at 80 ^oC in pre-heated oil bath for the time indicated in Table **5**. After the completion of reaction, reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was separated and dried over anhydrous $MgSO_4$, followed by the evaporation of solvent to obtain the crude product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as an eluent to afford the desired pure product **21**.

Method-B:

Ynones were used synthesized by using our improved procedure, a protocol which is free from the use of *copper, ligand* and *solvent.* A mixture of ynones **6** (1 mmol) and amines **11** (1 mmol) was stirred at 80 ^oC in pre-heated oil bath for 20-60 min (Table **6**). After the completion of reaction as indicated by TLC, the reaction mixture was cooled and the product was recrystallized from the mixture of hexane: ethyl acetate to afford analytically pure β-enaminones **21** in excellent yields.

Characterization data of β-enaminones 21a–p

(*Z*)-1-(4-Chlorophenyl)-3-phenyl-3-(phenylamino) prop-2-en-1-one (21a):

Nature of compound; mp	**:**	Yellow solid; mp 160-161 ^oC.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	5.94 (s, 1H), 6.71 (d, *J* = 7.42 Hz, 2H), 6.92 (dt, *J* = 7.22, 1.23 Hz, 1H), 7.05 (dt, *J* = 7.90, 1.63 Hz, 2H), 7.21-7.35 (m, 7H), 7.82 (dt, *J* = 8.58, 1.88 Hz, 2H), 12.82 (br s, 1H).
^{13}C NMR	**:**	96.5, 123.2, 124.3, 128.3, 128.5, 128.6, 128.7, 129.7,

($CDCl_3$, 50 MHz) δ		135.6, 137.4, 138.2, 139.2, 161.9, 188.0.
Elemental analysis	**:**	Anal Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20 Found: C, 75.40; H, 4.60; N, 4.01.

(*Z*)-3-(4-Tolylamino)-1-(4-chlorophenyl)-3-phenyl prop-2-en-1-one (21b):

Nature of compound; mp	**:**	Yellow solid; mp 158-159 ^oC.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.24 (s, 3H), 5.99 (s, 1H), 6.69 (d, *J* = 8.30 Hz, 2H), 6.93 (d, *J* = 8.29 Hz, 2H), 7.32-7.43 (m, 7H), 7.90 (dt, *J* = 8.60, 1.91 Hz, 2H), 12.90 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	20.7, 96.1, 123.2, 128.3, 128.5, 128.6, 129.3, 129.6, 134.1, 135.7, 136.5, 137.3, 138.3, 162.1, 187.8.
Elemental analysis	**:**	Anal Calcd for $C_{21}H_{16}ClNO$: C, 75.97; H, 5.22; N, 4.03 Found: C, 75.93; H, 5.60; N, 3.80.

(*Z*)-3-(4-Isopropylphenylamino)-1-(4-chlorophenyl-3-phenylprop-2-en-1-one (21c):

Nature of compound; mp	**:**	Yellow solid; mp 117-118 ^oC.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.17 (d, *J* = 6.82 Hz, 6H), 2.69-2.90 (m, 1H), 5.98 (s, 1H), 6.71 (d, *J* = 8.44 Hz, 2H), 6.98 (d, *J* = 8.44 Hz, 2H), 7.33-7.43 (m, 7H), 7.89 (dt, *J* = 8.69, 1.99 Hz, 2H), 12.93 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	23.8, 33.4, 96.1, 123.0, 126.6, 128.3, 128.5, 128.6, 129.6, 135.7, 136.7, 137.2, 138.3, 144.9, 162.0, 187.7.
Elemental analysis	**:**	Anal Calcd for $C_{24}H_{22}ClNO$: C, 76.69; H, 5.90; N, 3.73 Found: C, 76.50; H, 6.01; N, 3.81.

(*Z*)-3-(4-Methoxyphenylamino)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (21d):

Nature of compound; mp	**:**	Yellow solid; mp 126-127 ^oC.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.72 (s, 3H), 5.98 (s, 1H), 6.64-6.78 (m, 4H), 7.32-7.42 (m, 7H), 7.89 (dt, *J* = 8.60, 1.80 Hz, 2H), 12.91 (br s, 1H).

^{13}C NMR	**:**	55.3, 95.6, 113.9, 124.9, 128.3, 128.5, 129.6, 132.2,
($CDCl_3$, 50 MHz) δ		135.6, 137.2, 138.3, 156.6, 162.5, 187.6.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{18}ClNO_2$: C, 72.62; H, 4.99; N, 3.85 Found: C, 72.40; H, 5.07; N, 4.01.

(*Z*)-3-(2-Bromo-4-methylphenylamino)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (21e):

Nature of compound	**:**	Yellow viscous oil.
^{1}H NMR	**:**	2.14 (s, 3H), 6.01 (s, 1H), 6.29 (d, *J* = 8.23 Hz, 1H),
($CDCl_3$, 200 MHz) δ		6.63 (d, *J* = 9.61 Hz, 1H), 7.28-7.35 (m, 8H), 7.85 (dt, *J* = 8.59, 1.94 Hz, 2H), 12.64 (br s, 1H).
^{13}C NMR	**:**	20.4, 97.2, 117.4, 125.6, 127.9, 128.2, 128.5, 128.6,
($CDCl_3$, 50 MHz) δ		128.8, 129.8, 136.2, 135.5, 135.6, 135.7, 137.5, 138.0, 161.4, 188.3.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{17}BrClNO$: C, 61.92; H, 4.02; N, 3.28 Found: C, 62.20; H, 4.35; N, 3.01.

(*Z*)-3-(4-Chlorophenylamino)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (21f):

Nature of compound; mp	**:**	Yellow solid; mp 187-188 ^{o}C.
^{1}H NMR	**:**	5.96 (s, 1H), 6.62 (d, *J* = 8.71 Hz, 2H), 7.00 (d, *J* = 8.70
($CDCl_3$, 200 MHz) δ		Hz, 2H), 7.26-7.36 (m, 7H), 7.81 (dt, *J* = 8.71, 1.90 Hz, 2H), 12.77 (br s, 1H).
^{13}C NMR	**:**	96.9, 124.3, 128.2, 128.6, 128.7, 128.8, 128.9, 129.6,
($CDCl_3$, 50 MHz) δ		129.9, 135.2, 137.6, 137.9, 161.5, 188.3.
Elemental analysis	**:**	Anal Calcd for $C_{21}H_{15}Cl_2NO$: C, 68.49; H, 4.11; N, 3.80 Found: C, 68.20; H, 4.44; N, 3.66.

(*Z*)-3-(Benzylamino)-1-(4-chlorophenyl)-3-phenyl prop-2-en-1-one (21g):

Nature of compound	**:**	Pale yellow oil.
^{1}H NMR	**:**	4.42 (d, *J* = 6.57 Hz, 2H), 5.78 (s, 1H), 7.20-7.46 (m,
($CDCl_3$, 200 MHz) δ		12H), 7.84 (d, *J* = 8.60 Hz, 2H), 11.71 (br s, 1H).
^{13}C NMR	**:**	48.4, 93.5, 126.8, 127.4, 127.6, 128.3, 128.4, 128.5,

($CDCl_3$, 50 MHz) δ		128.7, 129.6, 135.1, 136.8, 138.1, 138.4, 167.0, 187.0.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{18}ClNO$: C, 75.97; H, 5.22; N, 4.03 Found: C, 75.60; H, 5.48; N, 4.40.

(*E*)-1-(4-Chlorophenyl)-3-phenyl-3-(piperidin-1-yl) prop-2-en-1-one (21h):

Nature of compound; mp	**:**	Pale yellow solid; mp 131-132 ^oC.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.57 (m, 6H), 3.18 (m, 4H), 5.68 (s, 1H), 7.14-7.24 (m, 3H), 7.28-7.42 (m, 4H), 7.64-7.78 (m, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	24.3, 25.7, 26.8, 49.2, 94.6, 128.0, 128.2, 128.3, 128.5, 128.7, 129.0, 129.2, 129.4, 136.4, 136.4, 136.7, 140.0, 164.9, 186.8.
Elemental analysis	**:**	Anal Calcd for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19; N, 4.30 Found: C, 73.78; H, 6.40; N, 4.21.

(*E*)-1-(4-Chlorophenyl)-3-(dibutylamino)-3-phenyl prop-2-en-1-one (21i):

Nature of compound; mp	**:**	Pale yellow solid; mp 88-90 ^oC.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	0.88 (m, 6H), 1.27 (m, 4H), 1.54 (m, 4H), 3.19 (m, 4H) 5.86 (s, 1H), 7.18-7.24 (m, 2H), 7.27-7.29 (m, 2H), 7.38-7.45 (m, 2H), 7.75 (d, J = 8.63 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	13.7, 20.1, 50.2, 92.9, 127.7, 127.9, 128.2, 128.4, 128.9, 136.3, 136.9, 140.4, 163.9, 185.4.
Elemental analysis	**:**	Anal Calcd for $C_{23}H_{28}ClNO$: C, 74.68; H, 7.63; N, 3.79 Found: C, 74.43; H, 7.93; N, 3.82.

(*Z*)-1, 3-Diphenyl-3-(phenylamino)prop-2-en-1-one (21j):

Nature of compound; mp	**:**	Yellow solid; mp 101-102 ^oC.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	6.09 (s, 1H), 6.79 (d, J = 7.45 Hz, 2H), 6.99 (tt, J = 7.18, 1.10 Hz, 1H), 7.13 (tt, J = 7.83, 1.49 Hz, 2H) 7.30-7.50 (m, 8H), 7.95-7.99 (m, 2H), 12.90 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	97.0, 123.2, 124.1, 127.2, 128.3, 128.5, 128.6, 128.7, 131.3, 135.8, 139.4, 139.8, 161.4, 189.6.
Elemental analysis	**:**	Anal Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68

Found: C, 84.18; H, 5.34; N, 4.71.

(*Z*)-3-(4-Methoxyphenylamino)-1, 3-diphenylprop-2-en-1-one (21k):

Nature of compound; mp	**:**	Yellow solid; mp 126-127 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.71 (s, 3H), 6.04 (s, 1H), 6.67 (d, *J* = 9.03 Hz, 2H), 6.75 (d, *J* = 8.77 Hz, 2H), 7.29-7.39 (m, 5H), 7.41-7.47 (m, 3H), 7.95-7.97 (m, 2H), 12.91 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	55.2, 96.0, 113.9, 124.8, 127.1, 128.3, 128.4, 128.5, 131.1, 132.4, 135.7, 139.9, 156.4, 162.0, 189.2.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25 Found: C, 80.32; H, 5.63; N, 4.26.

(*Z*)-1-Phenyl-3-(phenylamino)-3-*p*-tolylprop-2-en-1-one (21l):

Nature of compound; mp	**:**	Yellow solid; mp 94-96 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.36 (s, 3H), 6.08 (s, 1H), 6.82 (d, *J* = 7.43 Hz, 2H), 6.99 (tt, *J* = 7.32, 1.26 Hz, 1H), 7.10-7.18 (m, 4H), 7.25-7.32 (m, 2H), 7.41-7.50 (m, 3H), 7.94-7.99 (m, 2H), 12.90 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.3, 96.8, 123.2, 124.0, 127.2, 128.3, 128.6, 129.2, 131.2, 132.8, 139.5, 139.9, 161.6, 189.5.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47 Found: C, 84.30; H, 6.09; N, 4.26.

(*Z*)-3-(4-Methoxyphenyl)-1-phenyl-3-(phenylamino) prop-2-en-1-one (21m):

Nature of compound; mp	**:**	Yellow solid; mp 96-98 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.81 (s, 3H), 6.07 (s, 1H), 6.80-6.87(m, 4H), 6.99 (t, *J* = 7.36 Hz, 1H), 7.15 (t, *J* = 7.89 Hz, 2H), 7.31-7.49 (m, 5H), 7.94-7.99 (m, 2H), 12.89 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	55.2, 96.6, 113.8, 123.2, 123.9, 127.1, 127.8, 128.3, 128.7, 129.9, 131.1, 139.6, 139.9, 160.7, 161.3, 189.3.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25 Found: C, 80.30; H, 5.78; N, 4.54.

(*Z*)-3-Phenyl-3-(phenylamino)-1-*p*-tolylprop-2-en-1-one (21n):

Nature of compound; mp	**:**	Yellow solid; mp 137-139 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.33 (s, 3H), 6.00 (s, 1H), 6.69 (d, *J* = 7.58 Hz, 2H), 6.89 (t, *J* = 7.11 Hz, 1H), 7.04 (t, *J* = 7.82 Hz, 2H), 7.15-7.35(m, 7H), 7.79 (d, *J* = 8.32 Hz, 2H), 12.80 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.5, 96.9, 123.1, 123.9, 127.3, 128.3, 128.5, 128.6, 129.0, 129.6, 135.9, 137.1, 139.5, 141.7, 161.1, 189.5.
Elemental analysis	**:**	Anal Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47 Found: C, 84.53; H, 6.22; N, 4.52.

(*Z*)-3-(Benzylamino)-3-(4-(trifluoromethyl)phenyl)-1-*o*-tolylprop-2-en-1-one (21o):

Nature of compound	**:**	Pale yellow oil.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.44 (s, 3H), 4.30 (d, *J* = 6.57 Hz, 2H), 5.38 (s, 1H), 7.09-7.26 (m, 8H), 7.37-7.44 (m, 3H), 7.58 (d, *J* = 8.08 Hz, 2H), 11.39 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	20.4, 48.3, 98.1, 120.9, 125.4, 125.5, 125.6, 126.7, 127.5, 128.2, 128.7, 129.3, 131.1, 131.8, 135.9, 138.1, 138.7, 141.4, 164.2, 194.1.
Elemental analysis	**:**	Anal Calcd for $C_{24}H_{20}F_3NO$: C, 72.90; H, 5.10; N, 3.54 Found: C, 73.01; H, 5.20; N, 3.72.

(*Z*)-3-(Phenylamino)-1-(thiophen-2-yl)-3-*p*-tolyl prop-2-en-1-one (21p):

Nature of compound; mp	**:**	Yellow solid; mp 110-111 ^{o}C.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.36 (s, 3H), 5.95 (s, 1H), 6.78 (d, *J* = 7.66 Hz, 2H), 6.98 (tt, *J* = 7.26, 2.15 Hz, 1H), 7.08-7.16 (m, 5H), 7.27 (d, *J* = 8.32 Hz, 2H), 7.52 (dd, *J* = 3.93, 1.15 Hz, 1H), 7.65 (dd, *J* = 2.66, 1.01 Hz, 1H), 12.56 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.3, 96.6, 122.9, 123.9, 127.8, 128.2, 128.4, 128.6, 129.2, 130.9, 132.6, 139.5, 139.9, 146.8, 161.2, 182.3.

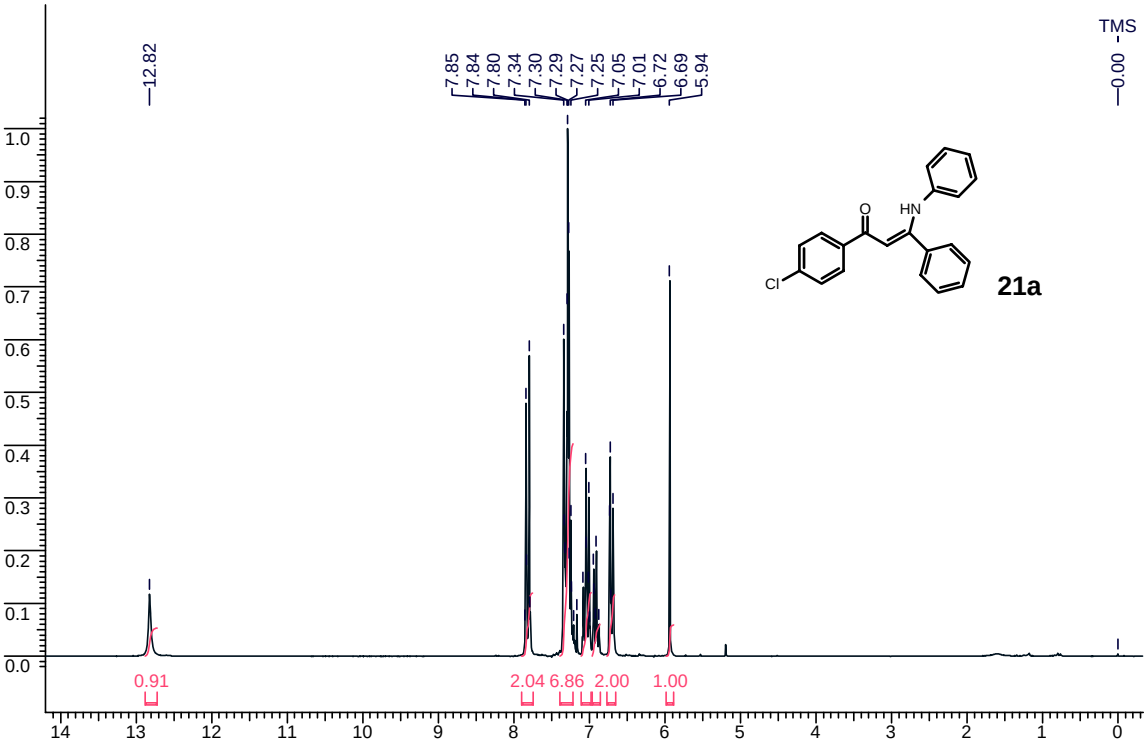
Elemental analysis	**:**	Anal Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39 Found: C, 75.02; H, 5.13; N, 4.40.

2.2.6 Spectra

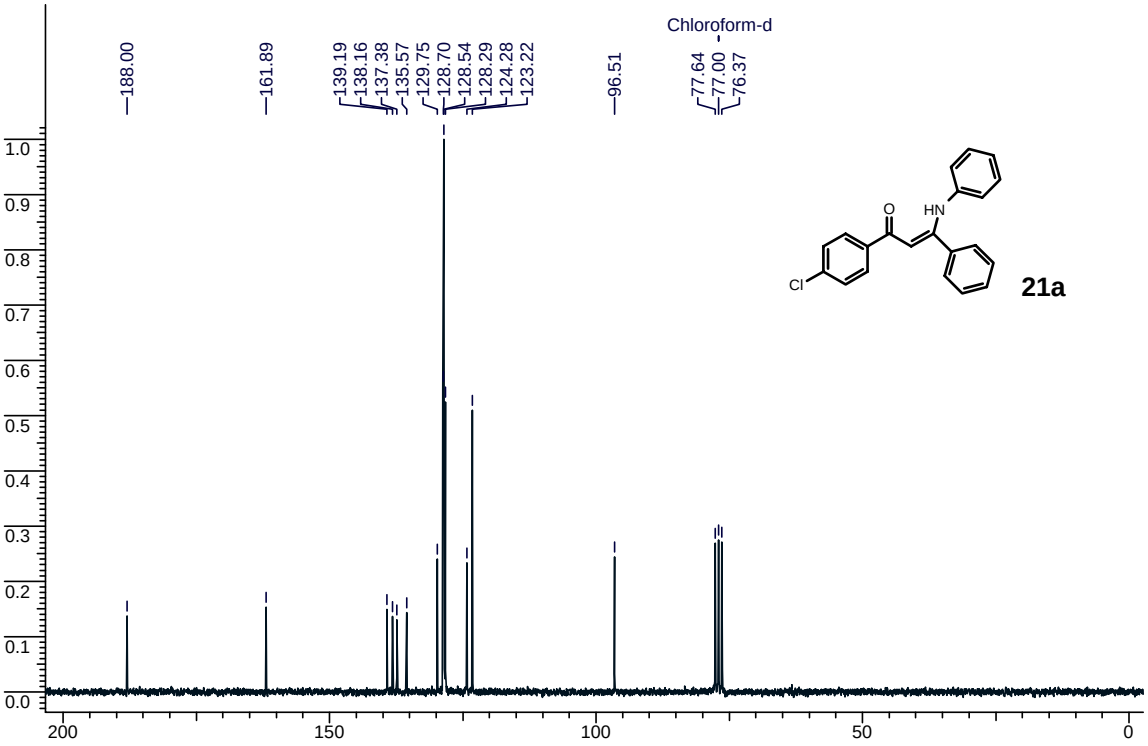
Table 7. ^{1}H and ^{13}C spectra of some representative β-enaminones

Sr. No.	Spectra
1	^{1}H and ^{13}C spectra of **21a**
2	^{1}H and ^{13}C spectra of **21c**
3	^{1}H and ^{13}C spectra of **21d**
4	^{1}H and ^{13}C spectra of **21e**
5	^{1}H and ^{13}C spectra of **21f**
6	^{1}H and ^{13}C spectra of **21g**
7	^{1}H and ^{13}C spectra of **21k**
9	^{1}H and ^{13}C spectra of **21m**
9	^{1}H and ^{13}C spectra of **21n**
10	^{1}H and ^{13}C spectra of **21o**
11	^{1}H and ^{13}C spectra of **21p**
12	NOE of **21k**

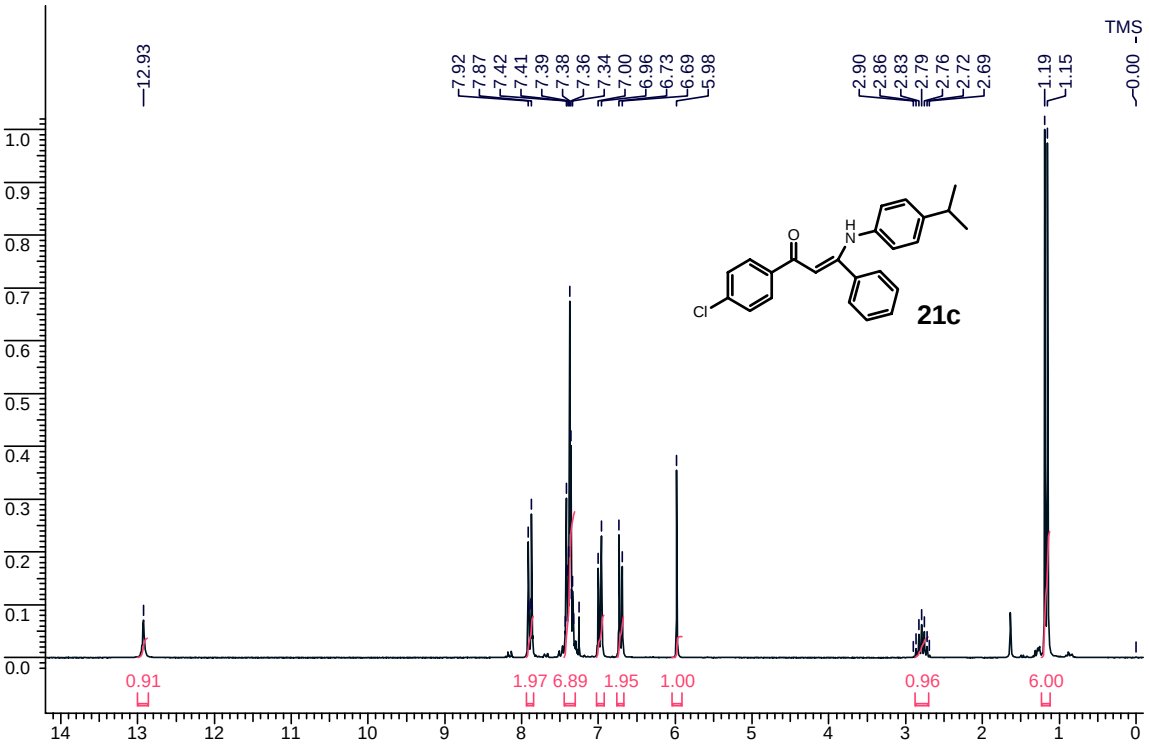
^{1}H NMR of **21a**



^{13}C NMR of **21a**



^{1}H NMR of **21c**



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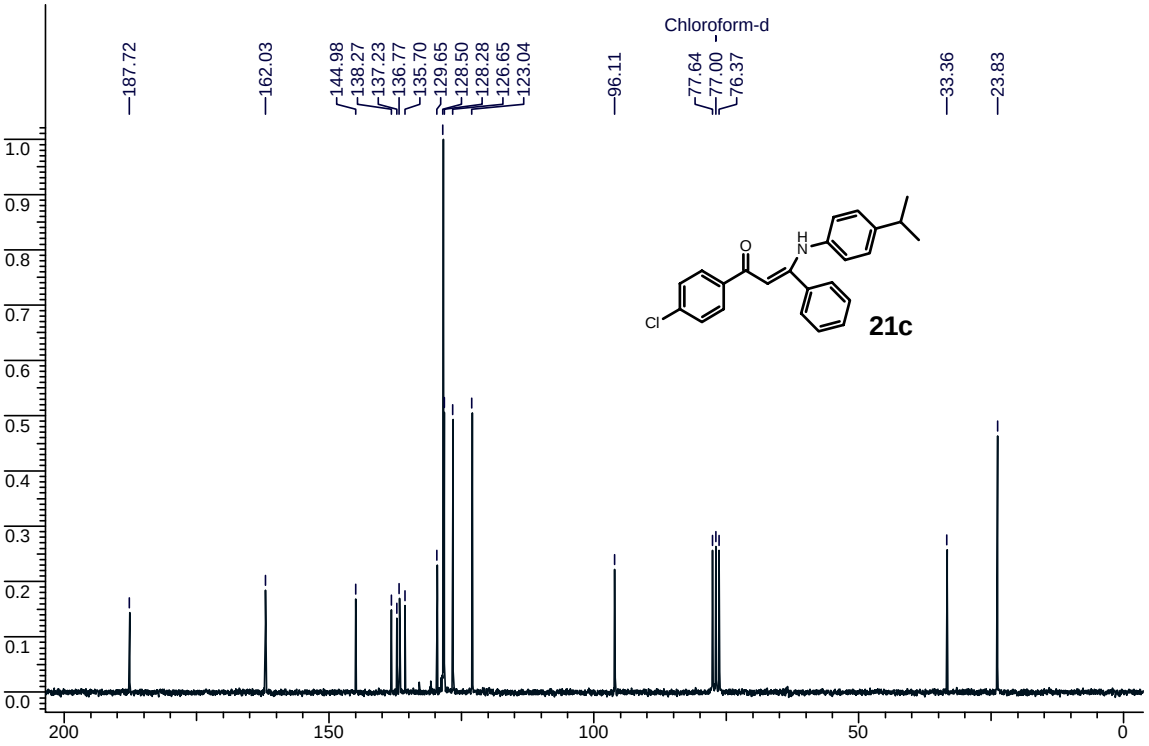

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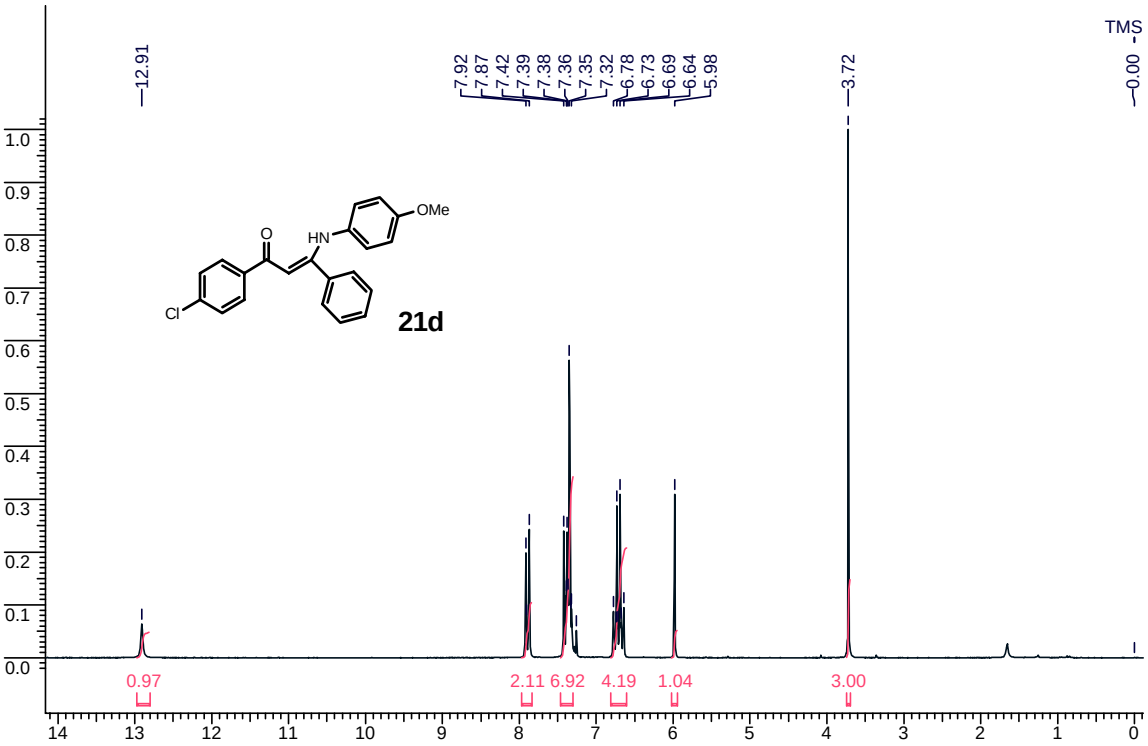

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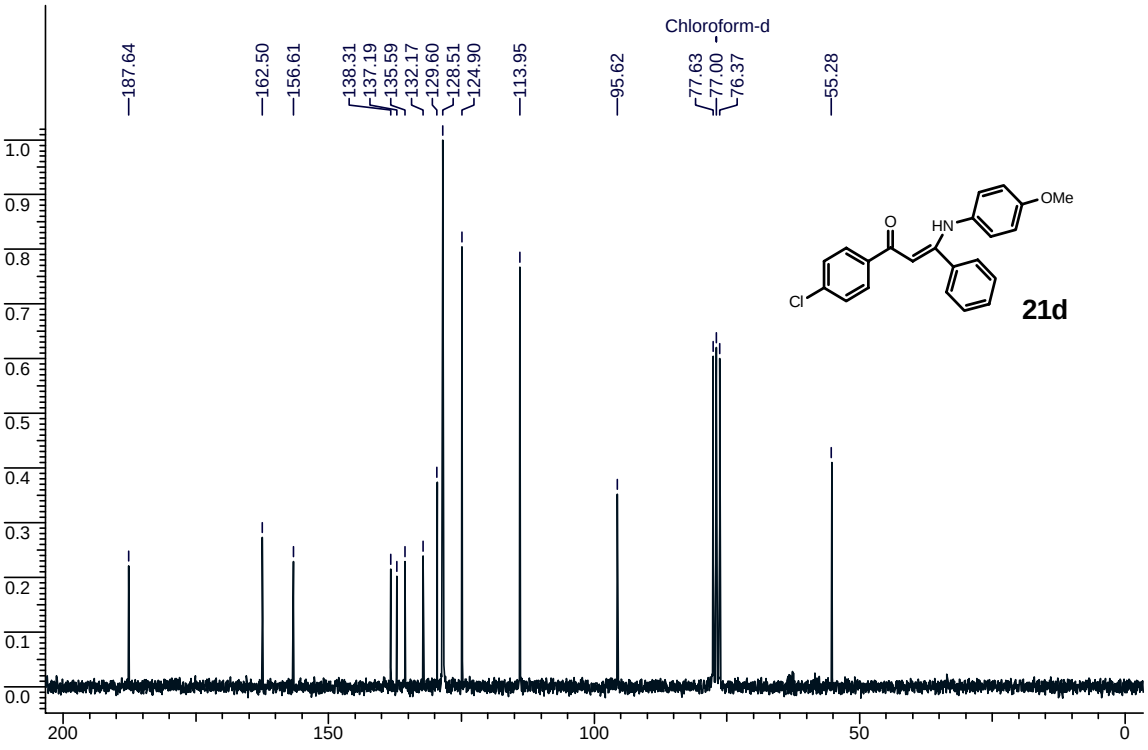

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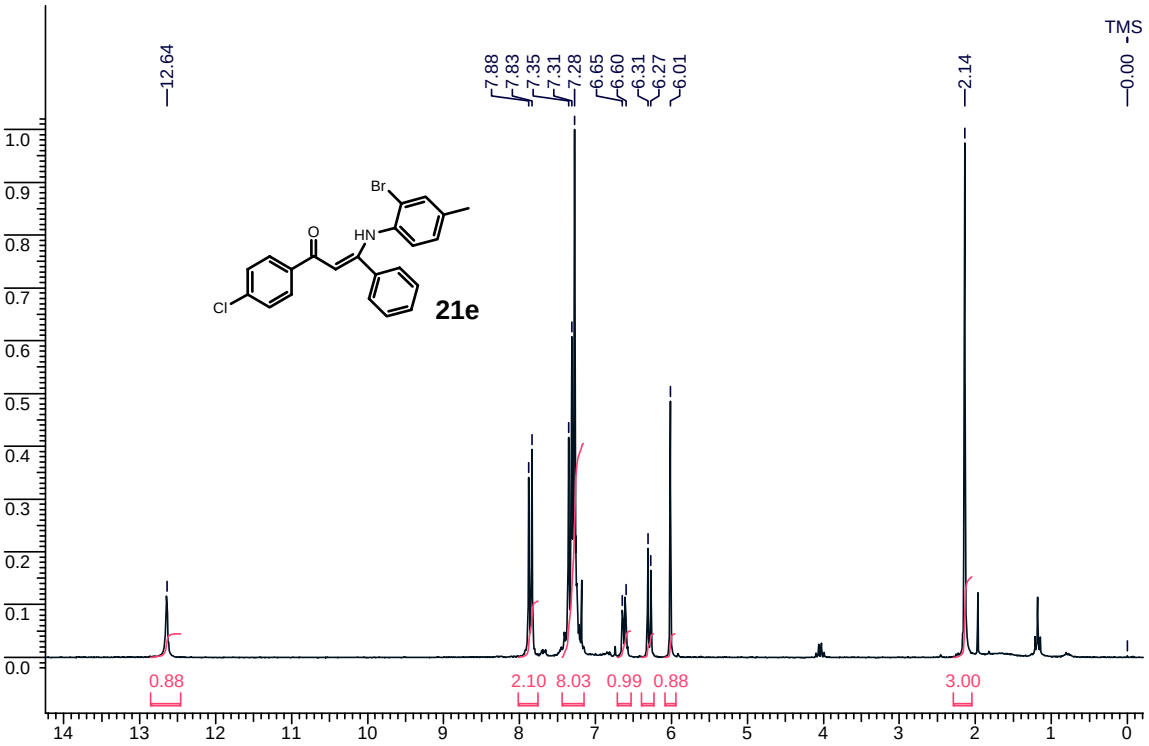

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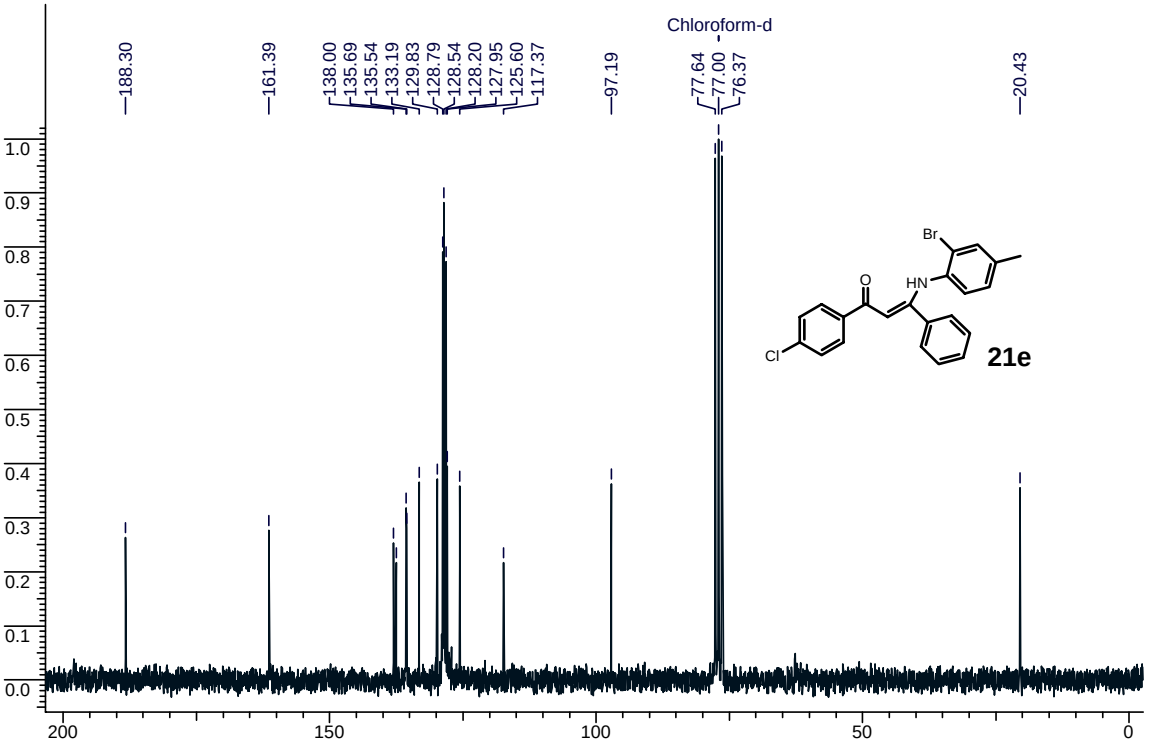

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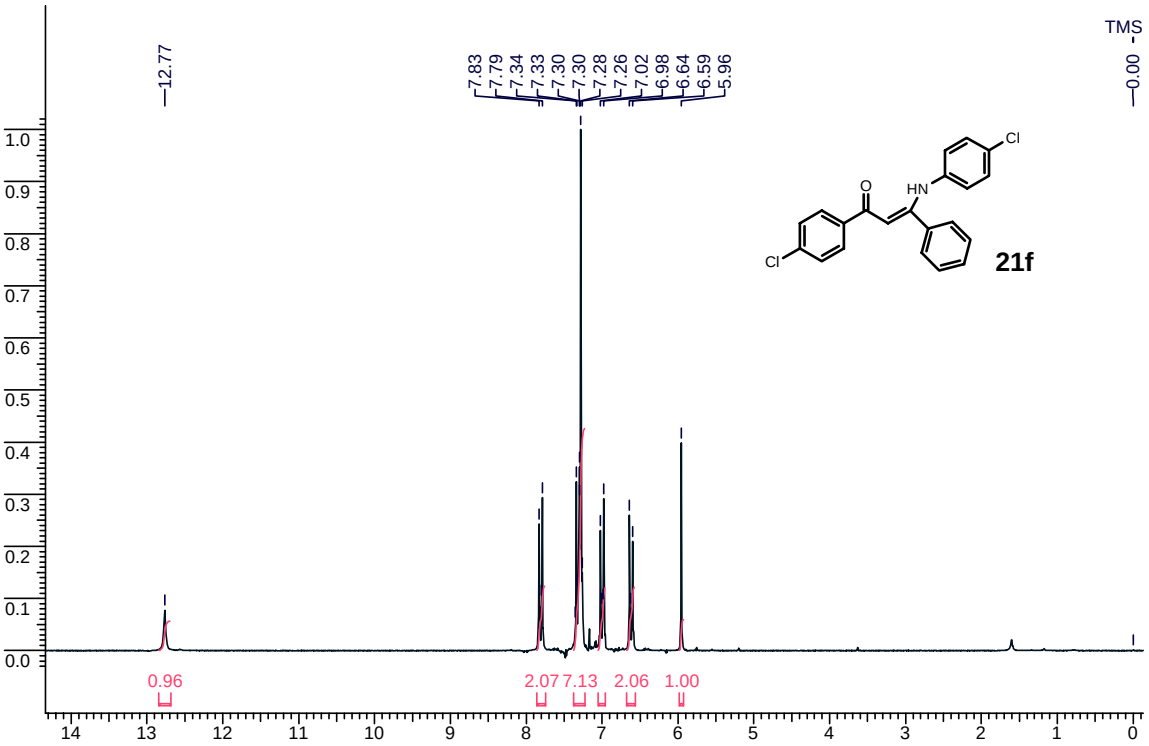

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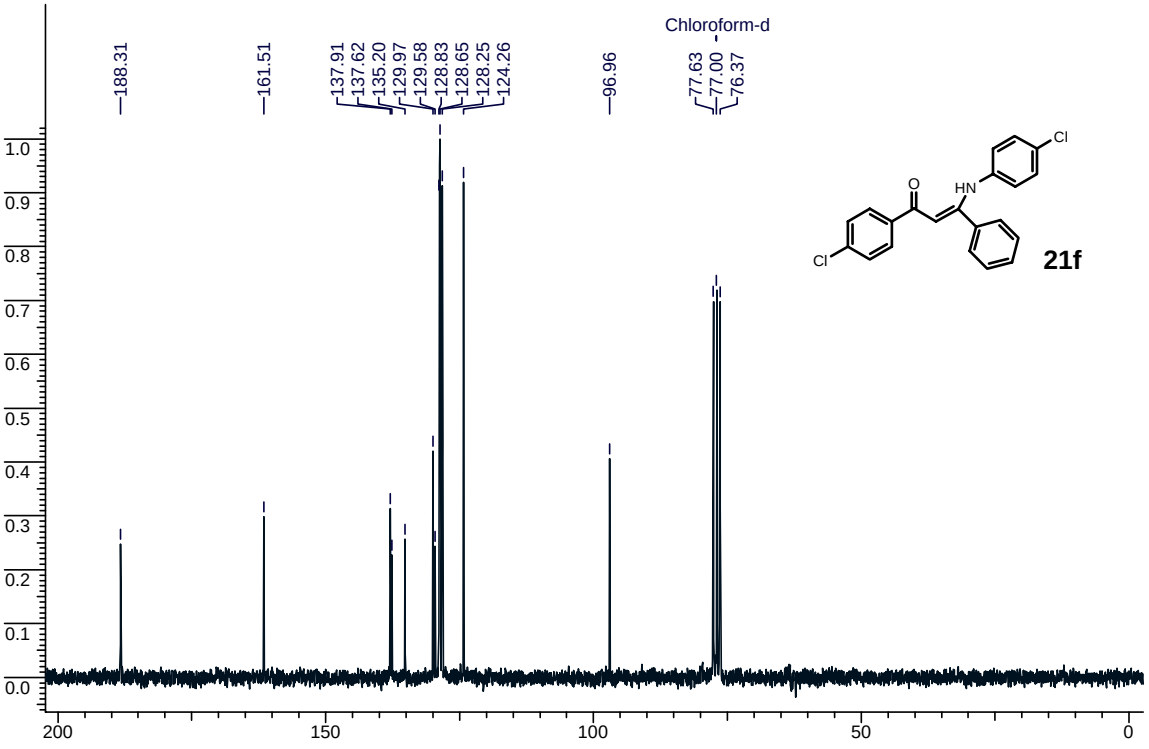

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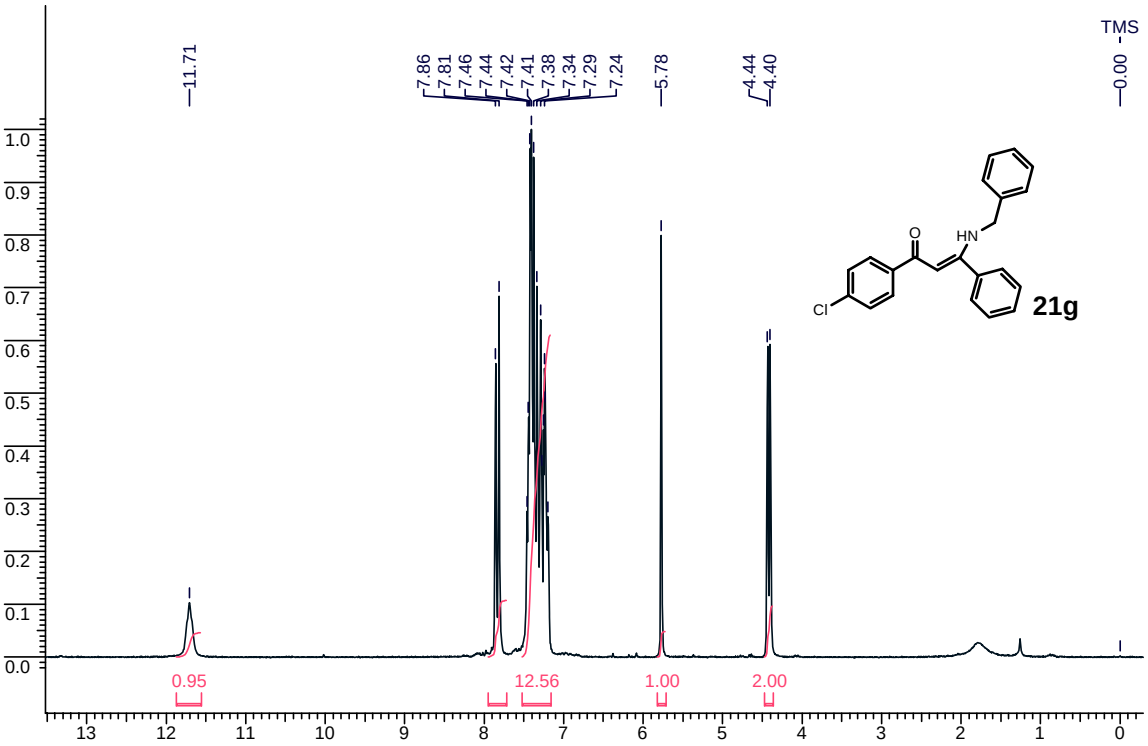

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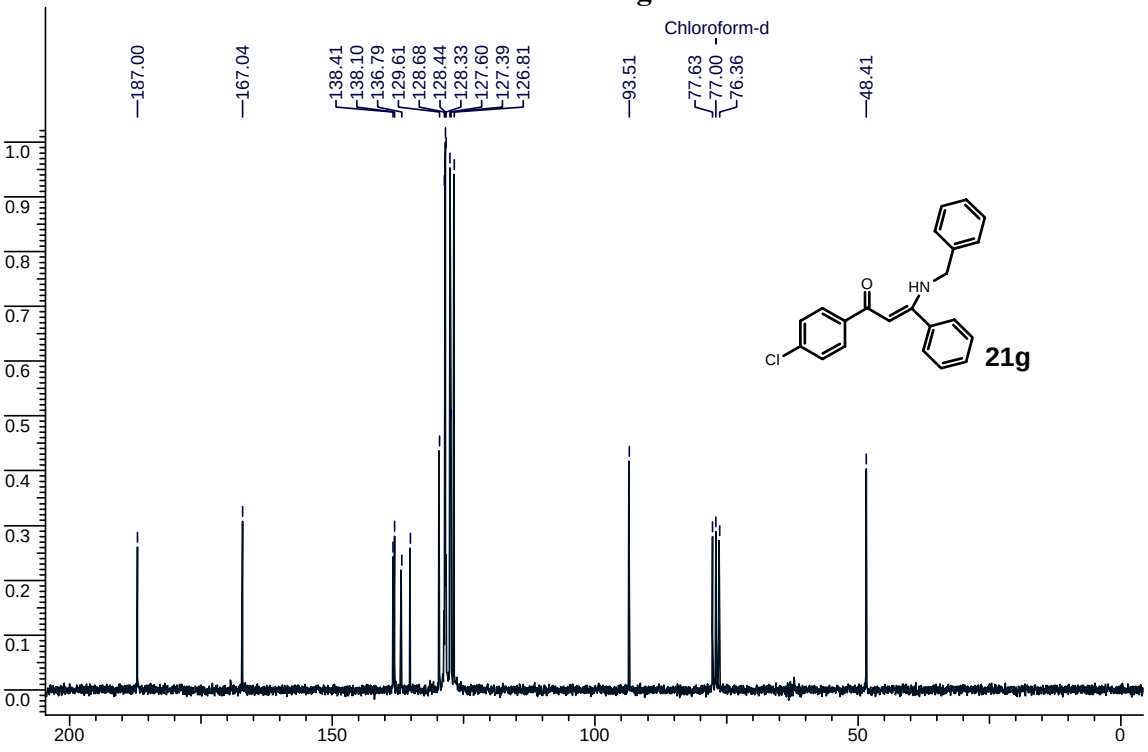

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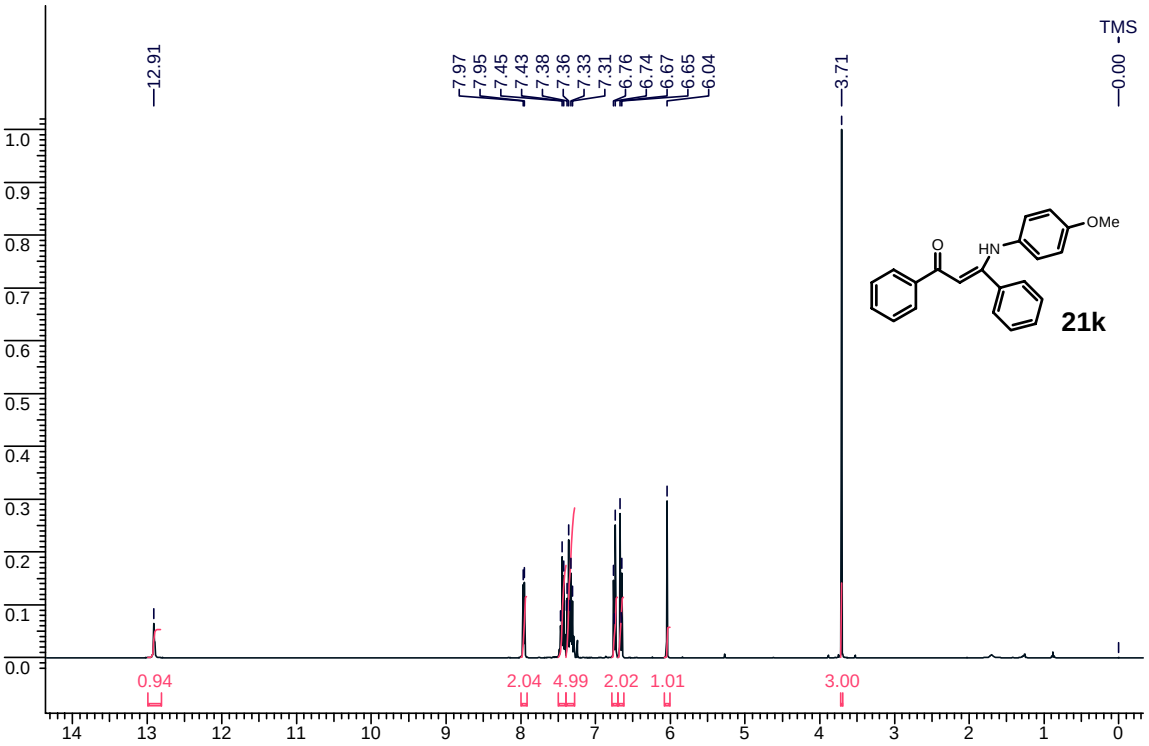

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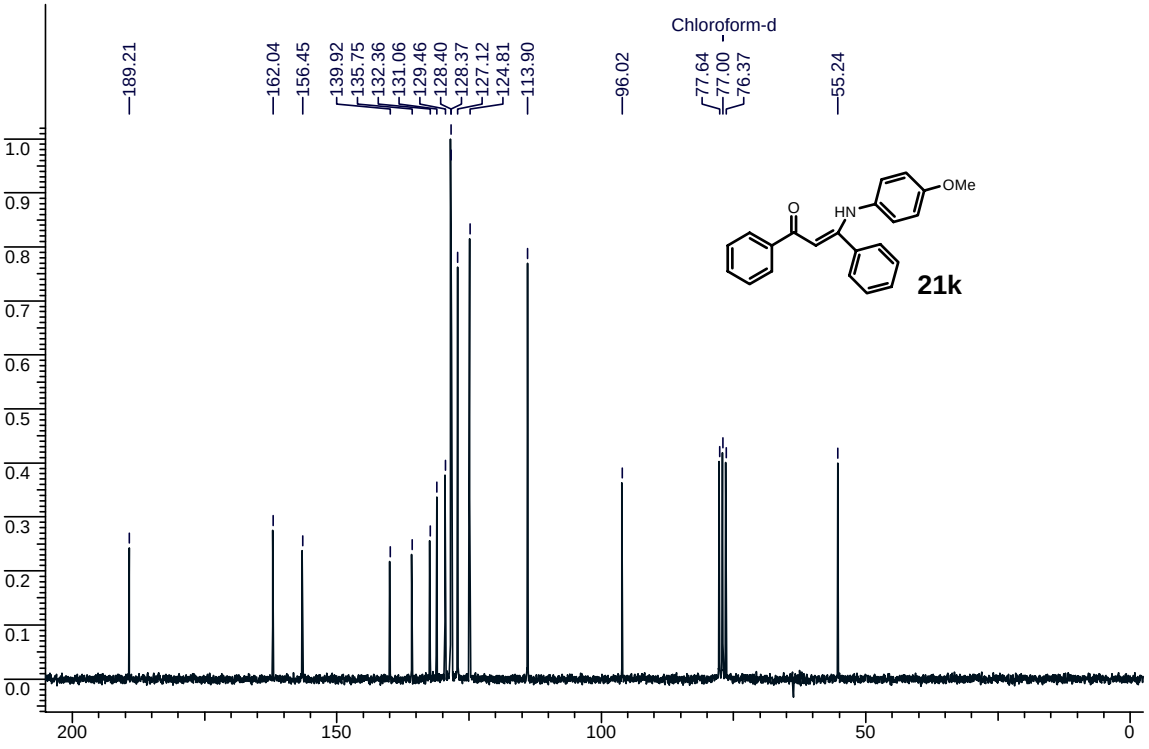

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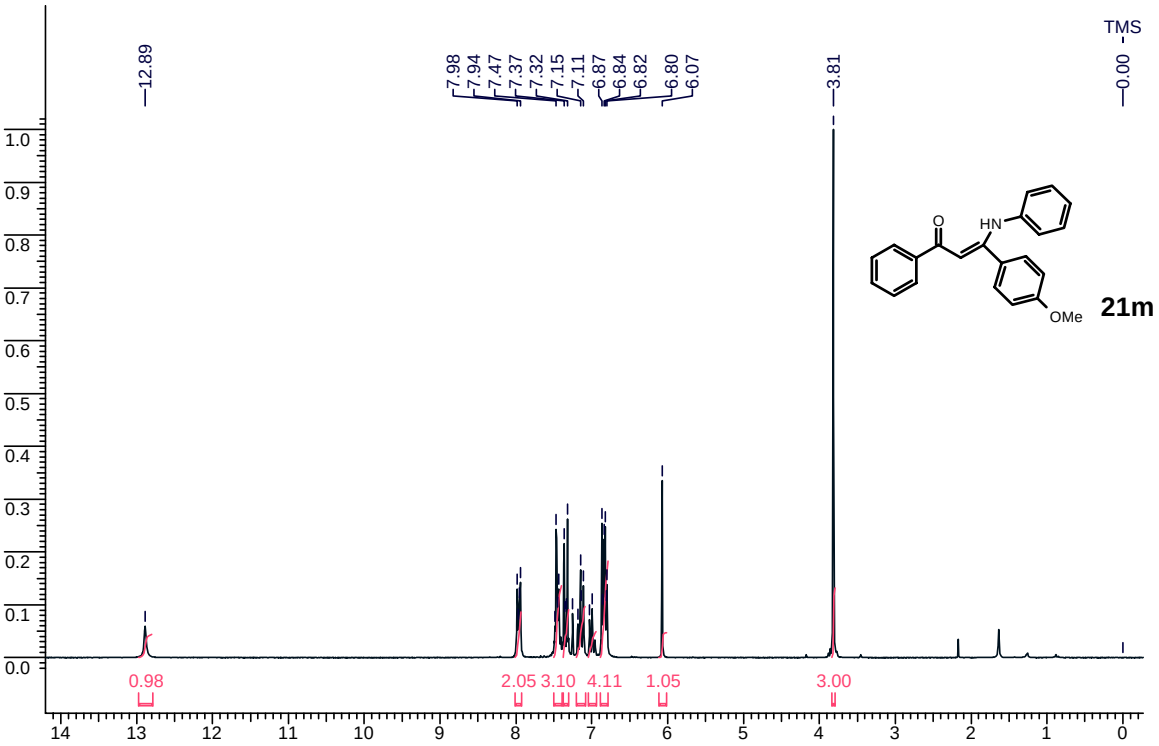

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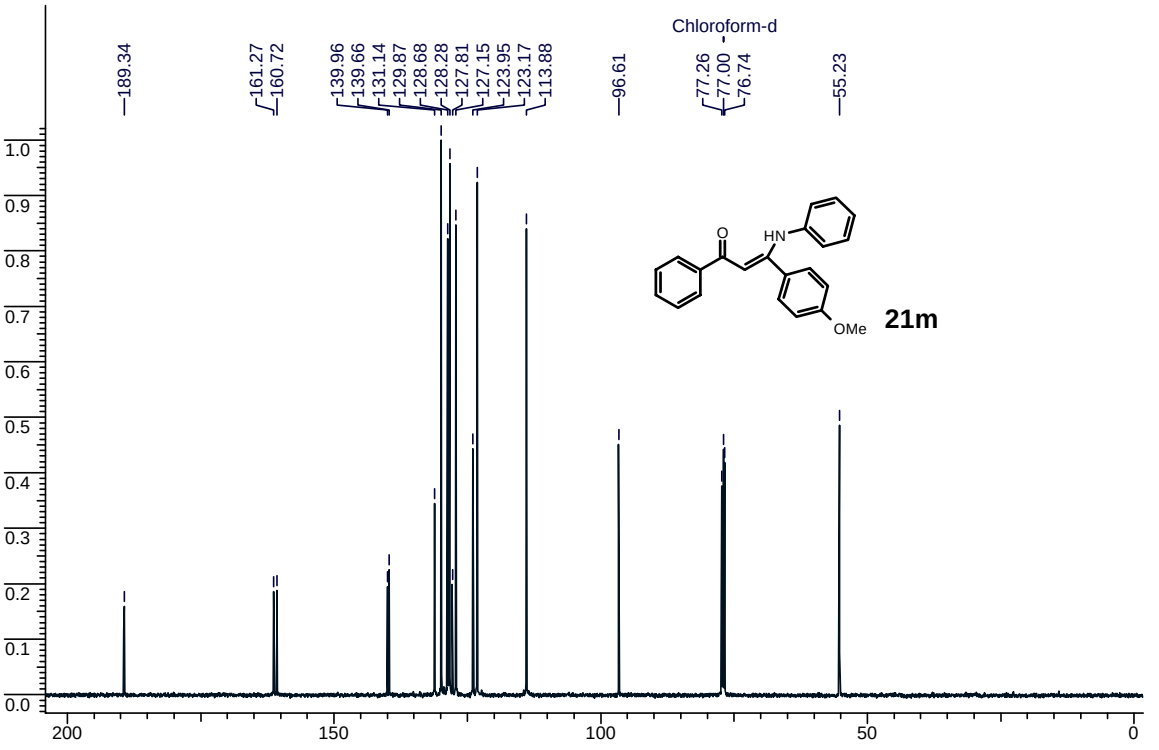

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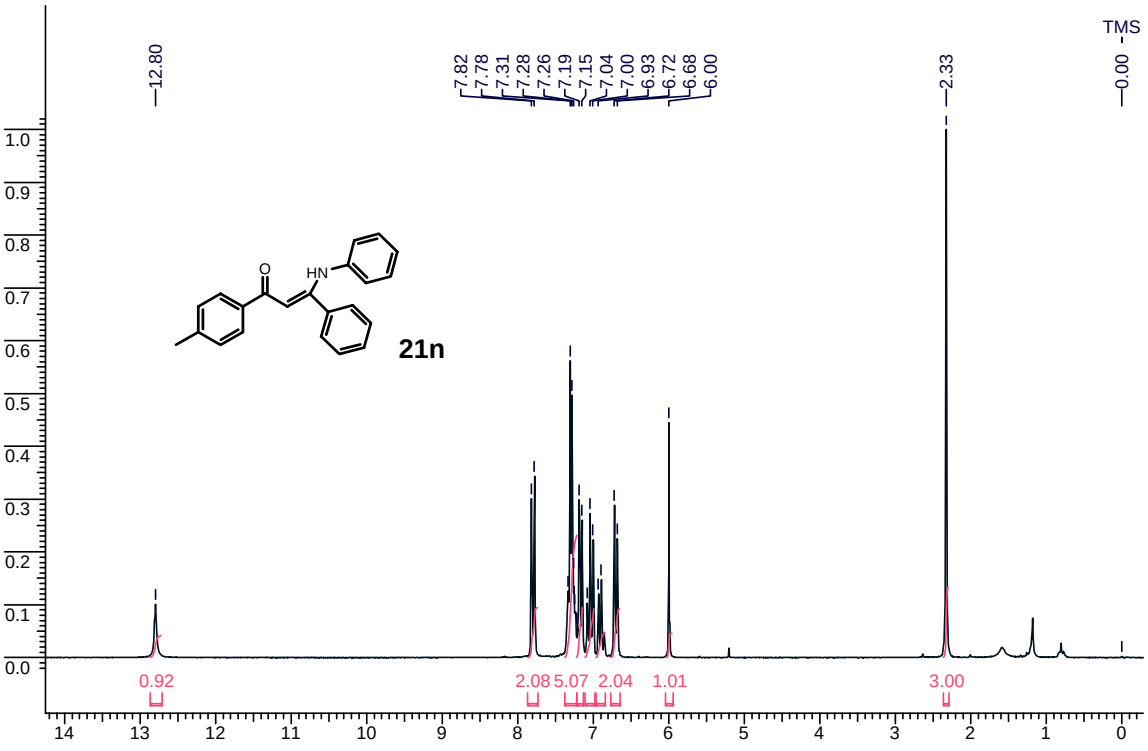

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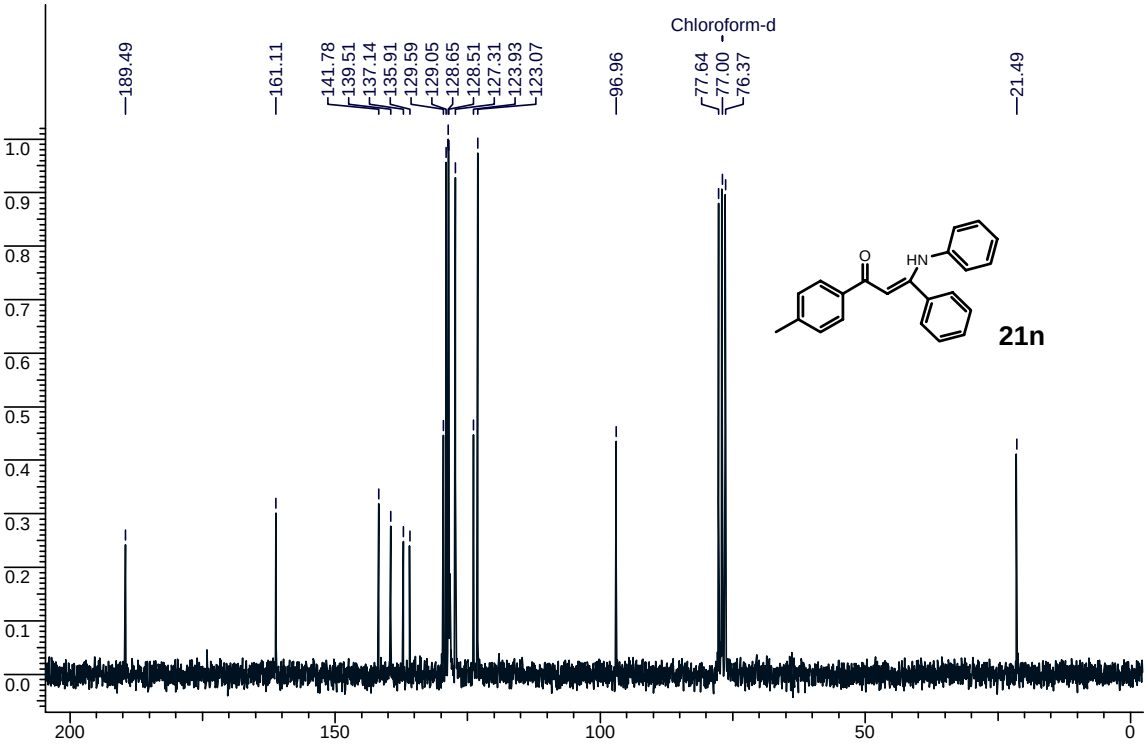

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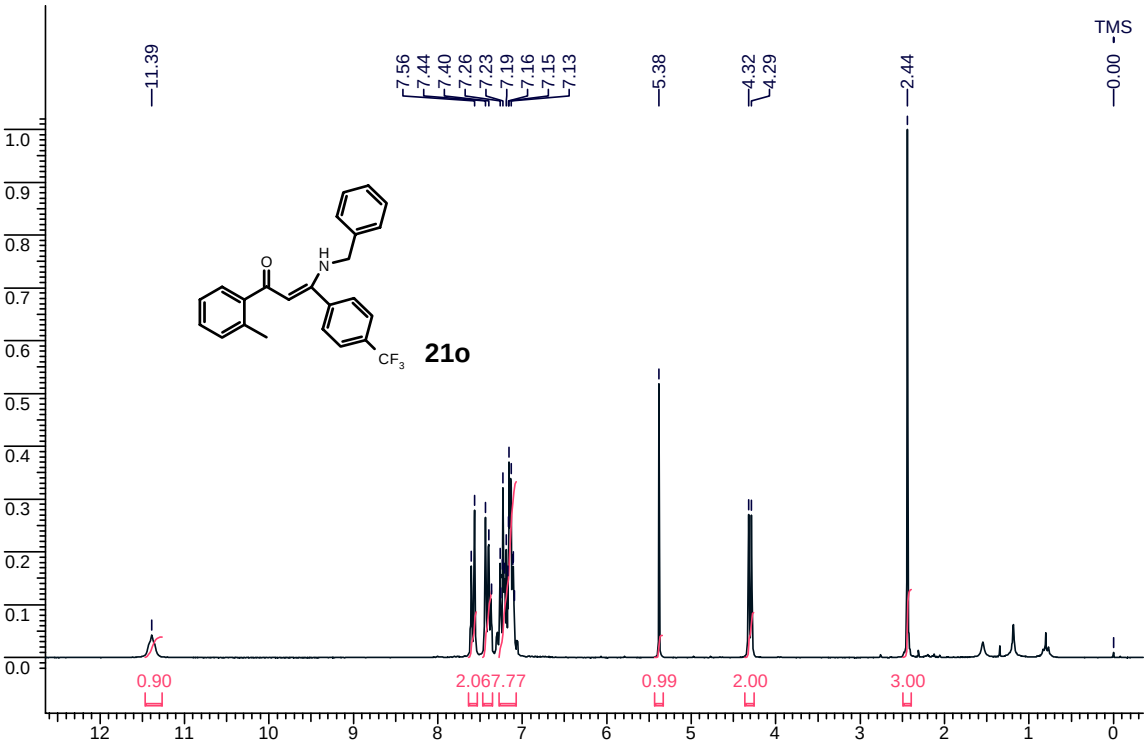

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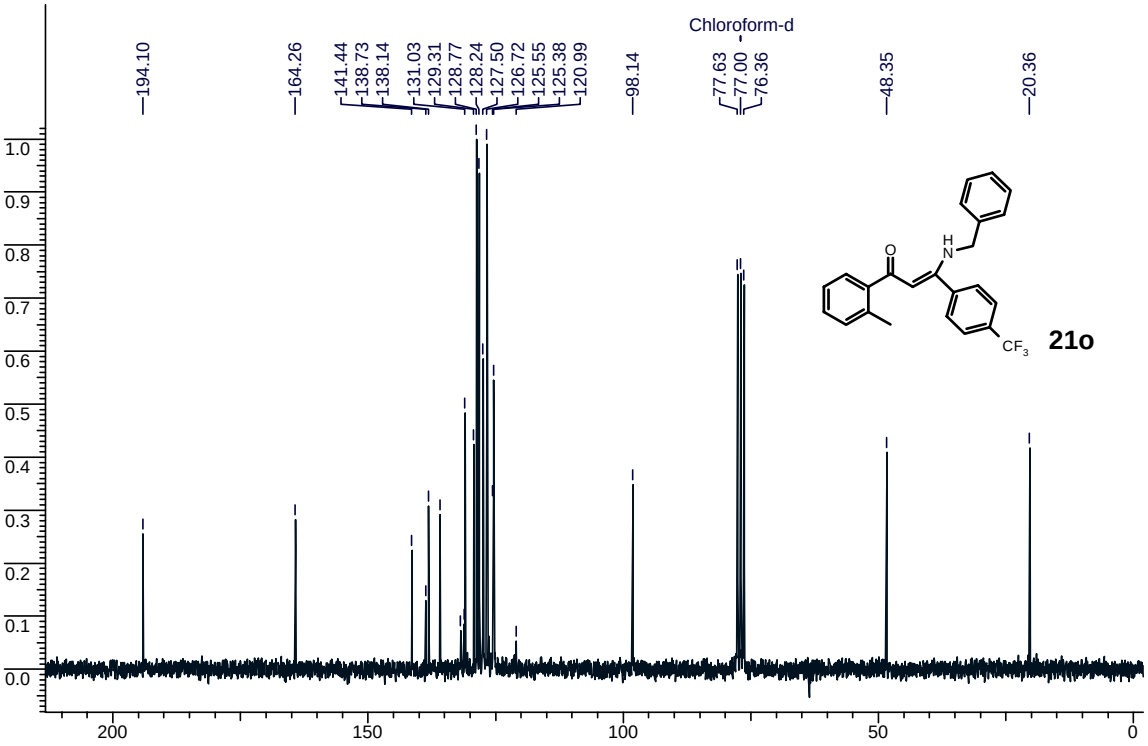

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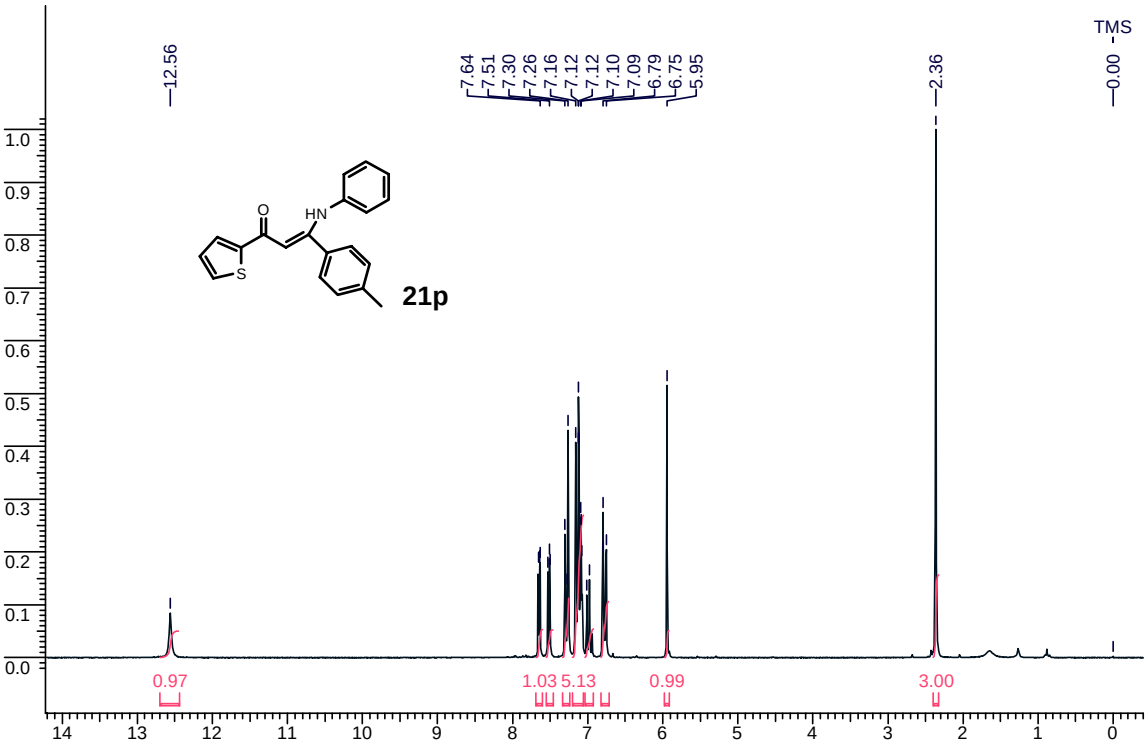

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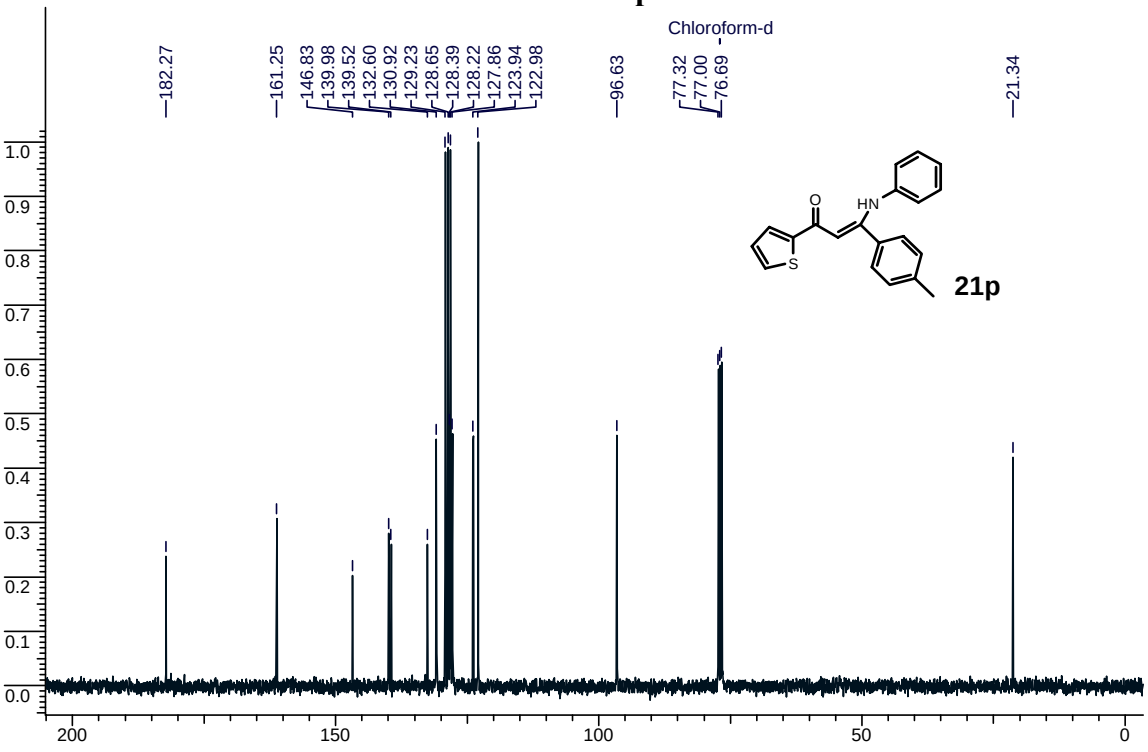
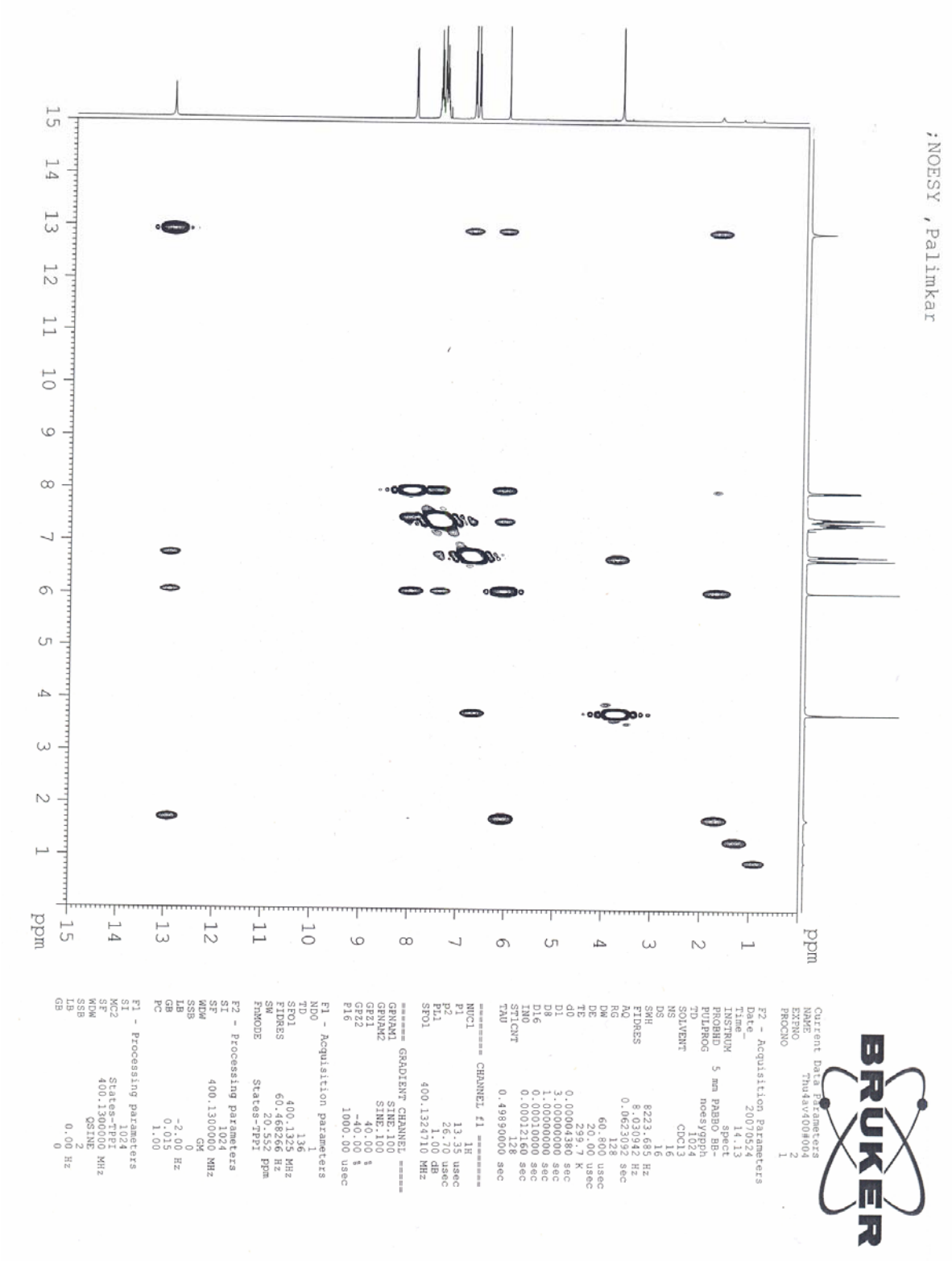


NOE of **21k**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ppm
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Time_
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SOLVENT
NS
DS
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FIDRES
AQ
RG
DW
DE
TE
d0
D1
D8
D16
IN0
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TAU
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NUC1
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PL1
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====== GRADIENT CHANNEL =====
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PC
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MC2
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Section C

A novel one-pot three-component synthesis of 2, 4-disubstituted-3H-benzo[b][1,4]diazepines in water

2.3.0 Introduction

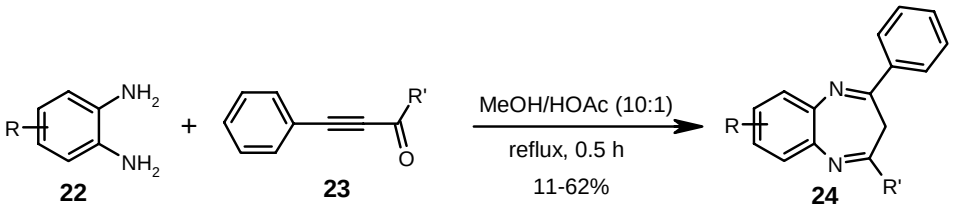
Benzodiazepines and their polycyclic derivatives, target molecules of the present work are a very important class of bioactive compounds, widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative and anti-depressive agents.[1] In addition to this, 2,4-disubstituted-3*H*-1,4-benzodizepines[2] are especially useful synthons for the rapid construction of polyheterocyclic systems due to the presence of two possible dipolarophile sites. This structural feature could allow the diversity-oriented synthesis[3] of small libraries of benzodiazepine-based compounds for pharmacological testing on a wide range of biological targets.[4]

2.3.1 Review of Literature

After reviewing the literature of the synthesis of biologically active benzodiazepines indicates that several methods are available for their synthesis. Among these methods, methods based upon the reaction of *o*-phenylene diamines with ynones are discussed below.

Reid's approach[5]

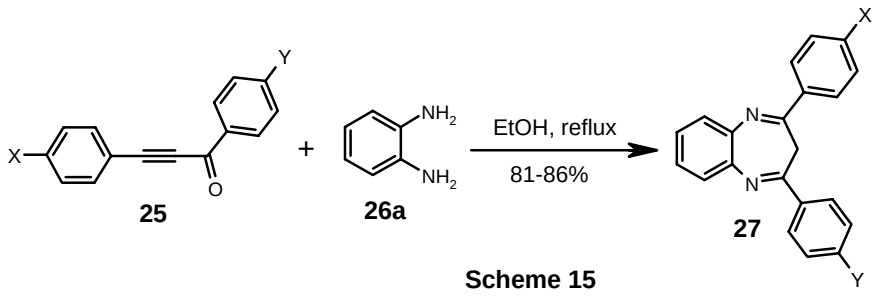
Reid, W. *et al.* have reported the reaction of *o*-phenylenediamines **22** with α, β-acetylenic ketones **23** in methanol catalyzed by acetic acid to give 3*H*-1,5-benzodiazepines **24** as shown in Scheme **14**.



Scheme 14

Korshunov's approach[6]

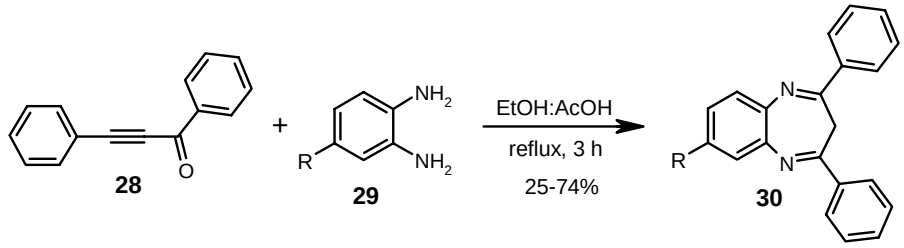
Korshunov, S. P. *et al.* have reported the synthesis of 2,4-diaryl-3*H*-benzo-1,5-diazepines **27** by refluxing alcoholic solution of *o*-penylenediamines **26a** and ynones **25** is presented in Scheme **15**.



Scheme 15

Amey's approach[7]

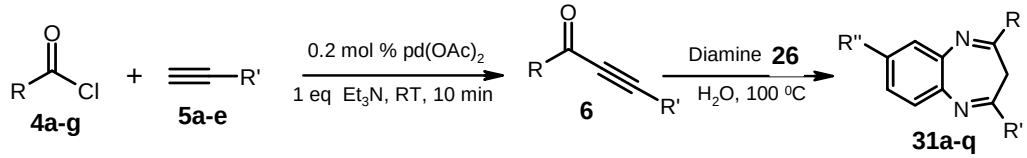
Amey, R. L. *et al.* have synthesized various 7-substituted-2,4-diphenyl-3*H*-1,5-benzodiazepines **30** by refluxing a mixture of 3-substituted *o*-phenylenediamines **29** with 1, 3-diphenyl-2-propyn-1-one **28** in ethanol-acetic acid medium as shown in Scheme **16**.



Scheme 16

2.3.2 Present Work

Reported methods makes use of volatile organic solvents which are at the top in the list of most damaging chemicals, hazardous acids and synthesis started from direct reaction of ynones with *o*-phenylene diamines. Thus the development of safe, simple, green, convenient and efficient one-pot method for the construction of pharmacologically interesting benzodiazepines is still desirable. A novel one-pot three-component synthesis of 2,4-disubstituted-3*H*-benzo[b][1,4]diazepines **31** *via* the coupling of acid chlorides **4** with terminal alkynes **5** followed by the *in situ* Michael addition and cyclocondensation of the resulting ynones with *o*-phenylenediamines **26** (OPDs) using water as a solvent (Scheme **17**) has been described in this section.

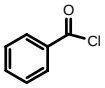
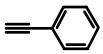
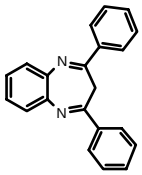
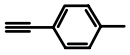
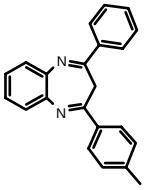
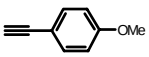
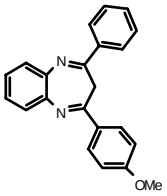
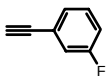
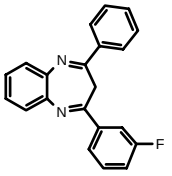


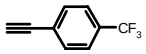
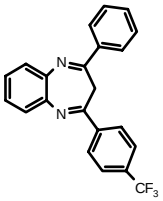
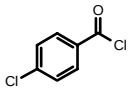
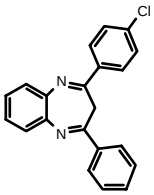
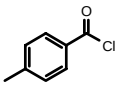
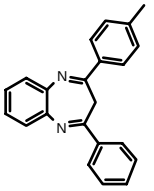
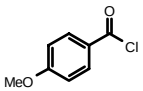
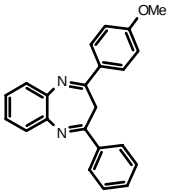
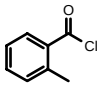
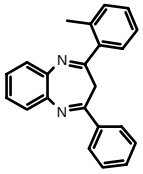
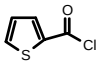
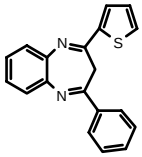
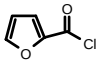
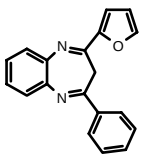
Scheme 17

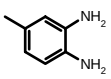
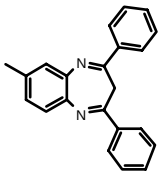
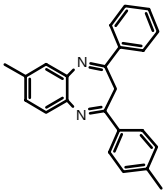
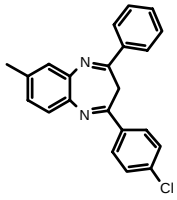
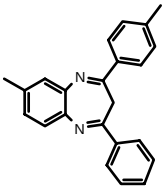
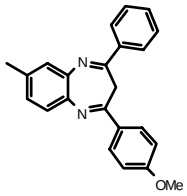
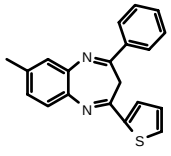
2.3.3 Results and Discussion

Initially, the coupling of benzoyl chloride **4a** with phenyl acetylene **5a** was achieved under *copper*-, *ligand*- and *solvent*-free condition using $Pd(OAc)_2$ (0.2 mol%) as a catalyst and one equivalent of triethylamine as the base. After complete formation of the product ynone **6a** as monitored by TLC (in all the cases the reaction time is just 10 min), OPD **26a** was added along with water as solvent and reaction was carried out at reflux temperature (100 ^oC) for 2 h to afford the 2,4-diphenyl-3*H*-benzo[*b*][1,4]diazepine **31a** in excellent isolated yield. To survey the generality and scope of this one-pot three-component protocol, the methodology was applied to the synthesis of a variety of benzodiazepine derivatives. The results are summarized in Table **8**.

Table 8 One-pot three-component synthesis of benzodiazepines in water[a]

Entry	Acid chloride 4	1-alkyne 5	Diamine 26	Product 31	Reaction time (h)[b]	Yield (%)[c]
1	 **4a**	 **5a**	 **26a**	 **31a**	**2**	**80**
2	**4a**	 **5b**	**26a**	 **31b**	**2**	**81**
3	**4a**	 **5c**	**26a**	 **31c**	**2**	**72**
4	**4a**	 **5d**	**26a**	 **31d**	**2**	**85**

5	**4a**	 **5e**	**26a**	 **31e**	**2**	**60**
6	 **4b**	**5a**	**26a**	 **31f**	**2**	**82**
7	 **4c**	**5a**	**26a**	 **31g**	**4**	**75**
8	 **4d**	**5a**	**26a**	 **31h**	**4**	**85**
9	 **4e**	**5a**	**26a**	 **31i**	**4**	**60**
10	 **4f**	**5a**	**26a**	 **31j**	**2**	**82**
11	 **4g**	**5a**	**26a**	 **31k**	**2**	**89**

12	**4a**	**5a**	 **26b**	 **31l**	**2**	**85**
13	**4a**	**5b**	**26b**	 **31m**	**2**	**76**
14	**4b**	**5a**	**26b**	 **31n**	**2**	**90**
15	**4c**	**5a**	**26b**	 **31o**	**4**	**89**
16	**4d**	**5a**	**26b**	 **31p**	**4**	**90**
17	**4f**	**5a**	**26b**	 **31q**	**2**	**83**

[a]1 mmol of acid chloride **4**, 1 mmol of 1-alkyne **5**, 1 mmo of Et_3N, 0.2 mol% of $pd(OAc)_2$, 1.2 mmol of diamine **26**, 5 ml water at 100 ^{0}C, [b]Time of reflux, [c]Isolated yields after column chromatography.

We investigated further, the electronic effect of different substituents present on each component of the coupling partners. We observed that a wide range of acid chlorides **4a-g** having both electron-donating and electron-withdrawing groups were equally

facile for the reaction resulting in the formation of benzodiazepine derivatives in excellent isolated yields. Even the hetro-aryl acid chlorides such as 2-thiophene carbonyl chloride **4f** (entries 10, 17, Table **8**) and 2-furoyl chloride **4g** (entry 11, Table **8**) reacted smoothly to give the heterodiazepine derivatives in excellent yields. For a comparative study, the various terminal alkynes **5a-e** including different substituents such as methyl, methoxy, fluoro and trifluoromethyl were used. Among these, it was found that a relatively low yield in the case of trifluoromethyl substituted terminal alkyne **5e** was obtained as compared to other substituted terminal alkynes (entry 5, Table **8**). Moreover, both the unsubstituted OPD **26a** and the substituted OPD **26b** having electron-donating group on the aromatic moiety gave benzodiazepienes in excellent yields. However in the case of OPD having an electron-withdrawing group such as $–NO_2$, no reaction was observed even after refluxing for a prolonged period (24 h).

All the benzodiazepine derivatives synthesized were well characterized by ^{1}H, ^{13}C NMR, IR, and elemental analyses. The benzodiazepine derivatives **31b**, **31g** and **31c**, **31h** obtained from the isomeric ynones intermediates respectively are identical. Furthermore, the structure of benzodiazepines **31** was confirmed by an X-ray crystallographic analysis of the compound **31b** (Fig. **2**).

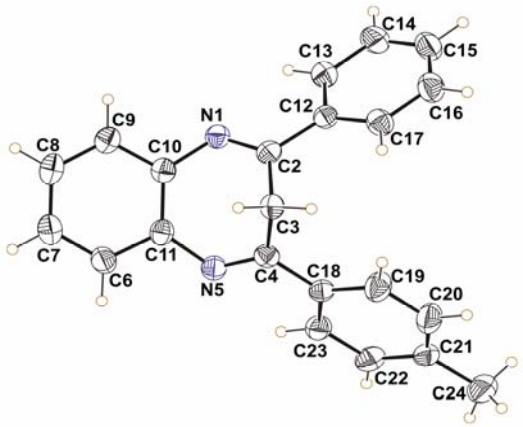


Figure 2. X-ray single crystal structure of compound 31b

X-ray crystallographic data confirm the structure of the benzodiazepine **31** to be in the diimine form as indicated rather than the enamine form, additional evidence for which is obtained by the presence of $-CH_2$ protons (chemical shift 3.65) as a broad

singlet in the ^{1}H-NMR spectra and the absence of –NH stretching frequency at 3300–3400 cm^{-1} in the IR spectra.

2.3.4 Conclusion

In summary, we have developed a novel, efficient and environment friendly one-pot three-component method for the synthesis of 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines in excellent isolated yields using water as a non-hazardous, inexpensive and readily available solvent. The methodology does not require the use of any organic solvent or a ligand, thus eminently meeting green chemistry objectives. Although the various substituents (electron-donating and electron-withdrawing) on each component of the coupling partner were well tolerated, the reaction became very sluggish when a strongly electron-withdrawing functionality such as a CF_3 or a NO_2 was present either in the terminal alkyne or OPD, respectively. The combination of the relatively fast reaction times, easy work-up procedures and the features stated above means that the methodology can be operated in a combi-chem mode to generate libraries constituting a diverse array of benzodiazepine derivatives.

2.3.5 Experimental Section

General procedure for the one-pot syntheses of 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines:

A mixture of acid chloride **4** (1 mmol), terminal alkyne **5** (1 mmol), triethyl amine (1 mmol) and $Pd(OAc)_2$ (0.2 mol%) was stirred at room temperature for 10 min under an atmosphere of argon. After the completion of reaction as monitored by TLC, diamine **26** (1.2 mmol) and water (5 ml) were added to the same reaction flask. The resulting reaction mixture was further subjected to heating at 100 ^oC for the time indicated in Table **8**. After the completion of reaction, the reaction mixture was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous magnesium sulfate, followed by the evaporation of solvent to obtain a crude product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as eluent to afford the desired product **31**.

Selected Crystallographic data and structure refinement of (31b)

(1*E*, 4*E*)-2-Phenyl-4-*p*-tolyl-3*H*-benzo[*b*][1,4]diazepine (31b): $C_{22}H_{18}N_2$. A single crystal suitable for structural analysis was grown from a mixture of petroleum ether-dichloromethane (9:1) as a colorless needle. Selected crystallographic data see in Table **9.**

Table 9. Selective X-Ray crystallographic data for compound 31b

Empirical formula	$C_{22}H_{18}N_2$
Formula weight	310.38
Temperature	297(2) K
Wavelength	0.71073 mm^{-1}
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a = 17.3650(17) Å α = 90º.
	b = 9.9287(10) Å β = 113.400(2)º.
	c = 20.981(2) Å γ = 90º.
Volume	3319.9(6) $Å^3$
Z, calculated density	8, 1.242 Mg m^{-3}
Absorption coefficient	0.073 mm^{-1}
F(000)	1312
Crystal size	0.49 × 0.10 × 0.03 mm
Theta range for data collection	2.12–25.00º
Limiting indices	$-20 \le h \le 20$, $-11 \le k \le 11$, $-24 \le l \le 24$
Reflections collected/unique	23493/5837 [R(int) = 0.0691]
Completeness to θ = 25.00	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9978 and 0.9651
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5837/0/436
Goodness-of-fit on F^2	1.042
Final R indices [I > 2σ(I)]	$R1$ = 0.0771, w$R2$ = 0.1717
R indices (all data)	$R1$ = 0.1434, w$R2$ = 0.2055
Extinction coefficient	0.0005(5)
Largest diff. peak and hole	0.577 and 20.257 e A^{-3}

Characterization data for the benzodiazepines 31a–q

(1*E*, 4*E*)-2, 4-Diphenyl-3*H*-benzo[*b*][1,4]diazepine (31a).

Nature of compound; mp : Colorless solid, mp 139 °C (lit.[5] 140–141 °C).

IR: ($CHCl_3$)υ_{max} (cm^{-1}) : 3018, 2400, 1602, 1447, 1216, 692, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 3.64 (br s, 2H, CH_2), 7.31–7.44 (m, 8H, H Ar), 7.57–7.63 (m, 2H, H Ar), 7.93–7.98 (m, 4H, H Ar).

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 34.9, 125.4, 128.1, 128.6, 128.7, 130.5, 137.2, 140.7, 154.1.

Elemental analysis (%) : Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45; Found: 84.75; H, 5.30; N, 9.46.

(1*E*, 4*E*)-2-Phenyl-4-*p*-tolyl-3*H*-benzo[*b*][1,4]diazepine (31b and 31g).

Nature of compound; mp : Colorless solid, mp 160–162 °C (lit.[6] 160–161 °C).

IR: ($CHCl_3$)υ_{max} (cm^{-1}) : 3018, 2400, 1595, 1215, 691, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.36 (s, 3H, CH_3), 3.65 (br s, 2H, CH_2), 7.19–7.25 (m, 2H, H Ar), 7.30–7.35 (m, 2H, H Ar), 7.39–7.44 (m, 3H, H Ar), 7.57–7.62 (m, 2H, H Ar), 7.87 (dt, J = 8.33, 1.93 Hz, 2H, H Ar), 7.94–7.99 (m, 2H, H Ar).

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 21.3, 34.8, 125.2, 125.3, 128.0, 128.1, 128.6, 128.7, 129.4, 130.5, 134.5, 137.3, 140.7, 140.8, 140.9, 154.0, 154.2.

Elemental analysis (%) : Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03; Found: C, 84.95; H, 5.68; N, 9.37.

(1*E*, 4*E*)-2-(4-Methoxyphenyl)-4-phenyl-3*H*-benzo [*b*][1,4]diazepine (31c and 31h).

Nature of compound; mp : Colorless solid, mp 148–150 °C.

IR: ($CHCl_3$)υ_{max} (cm^{-1}) : 3019, 2400, 1606, 1215, 692, 668.

^{1}H NMR ($CDCl_3$, 200 MHz) δ : 3.82 (s, 3H, OCH_3), 8.91 (dt, J = 8.97, 2.04 Hz, 2H, H Ar), 7.25–7.43 (m, 2H, H Ar), 7.39–7.43 (m, 3H, H Ar), 7.56–7.62 (m, 2H, H Ar), 7.92–7.99 (m, 4H, H Ar).

^{13}C NMR : 34.7, 55.3, 113.9, 125.4, 128.1, 128.6, 129.9, 130.5,

($CDCl_3$, 50 MHz) δ		137.4, 140.6, 140.9, 153.5, 154.2, 61.6.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58 Found: C, 81.23; H, 5.54; N, 8.34.

(1*E*, 4*E*)-2-(3-Fluorophenyl)-4-phenyl-3*H*-benzo[*b*][1,4]diazepine (31d).

Nature of compound; mp	**:**	Colorless solid, mp 138–140 °C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2400, 1587, 1446, 1215, 690, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.66 (br s, 2H, CH_2), 7.06–7.16 (m, 1H, H Ar), 7.31–7.46 (m, 6H, H Ar), 7.55–7.74 (m, 4H, H Ar), 7.93–8.00 (m, 2H, H Ar).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	34.9, 114.8, 115.3, 117.4, 117.8, 123.5, 123.6, 125.5, 125.7, 128.1, 128.7, 130.7, 137.1, 139.5, 140.3, 140.8, 152.6, 153.9, 160.5, 165.4.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{21}H_{15}FN_2$: C, 80.24; H, 4.81; N, 8.91 Found: C, 80.18; H, 4.52; N, 8.70.

(1*E*,4*E*)-2-(4-(Trifluoromethyl)phenyl)-4-phenyl-3*H*-benzo[*b*]-[1,4]diazepine (31e).

Nature of compound; mp	**:**	Colorless solid, mp 107–108 °C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1601, 1318, 1215, 759, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.79 (br s, 2H, CH_2), 7.32–7.49 (m, 5H, H Ar), 7.57–7.68 (m, 4H, H Ar), 7.94–7.99 (m, 2H, H Ar), 8.07 (d, *J* = 8.13 Hz, 2H, H Ar).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	34.9, 125.6, 126.0, 128.2, 128.3, 128.8, 130.9, 137.0, 140.2, 140.8, 152.4, 153.8.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{22}H_{15}F_3N_2$: C, 72.52; H, 4.15; F, 15.64, N, 7.69; Found: C, 72.32; H, 4.21; N, 7.64.

(1*E*, 4*E*)-2-(4-Chlorophenyl)-4-phenyl-3*H*-benzo [*b*][1,4] diazepine (31f).

Nature of compound; mp	**:**	Colorless solid, mp 172–174 °C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1593, 1215, 700, 668.
^{1}H NMR	**:**	3.66 (br s, 2H, CH_2), 7.30–7.46 (m, 7H, H Ar), 7.54–

($CDCl_3$, 200 MHz) δ		7.63 (m, 2H, H Ar), 7.87–7.99 (m, 4H, H Ar).
^{13}C NMR	**:**	34.8, 125.5, 128.1, 128.7, 129.4, 130.7, 135.6, 137.1,
($CDCl_3$, 50 MHz) δ		140.4, 140.7, 152.6 and 153.9.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47; Found: C, 76.12; H, 4.71; N, 8.50.

(1*E*, 4*E*)-2-Phenyl-4-*o*-tolyl-3*H*-benzo[*b*][1, 4]diazepine (31i).

Nature of compound; mp	**:**	Colorless solid, mp 117–118 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3016, 1602, 1215, 759, 692, 666.
^{1}H NMR	**:**	2.26 (s, 3H, CH_3), 3.55 (br s, 2H, CH_2), 7.20–7.27 (m,
($CDCl_3$, 200 MHz) δ		3H, H Ar), 7.29–7.39 (m, 6H, H Ar), 7.55–7.64 (m, 2H, H Ar) and 7.77–7.82 (m, 2H, H Ar).
^{13}C NMR	**:**	20.9, 35.1, 126.8, 126.9, 127.6, 127.9, 128.5, 128.7,
($CDCl_3$, 50 MHz) δ		130.4, 130.8, 131.0, 135.4, 137.1, 137.8, 138.7, 139.8, 140.7, 143.9, 147.7, 148.2, 153.1, 153.6.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03 Found: C, 84.95; H, 6.08; N, 9.20.

(1*E*, 4*E*)-2-Phenyl-4-(thiophen-2-yl)-3*H*-benzo[*b*][1,4]diazepine (31j).

Nature of compound; mp	**:**	Colorless solid, mp 130–131 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1596, 692.
^{1}H NMR	**:**	3.66 (br s, 2H, CH_2), 6.99–7.03 (m, 1H, H Ar), 7.26–
($CDCl_3$, 200 MHz) δ		7.35 (m, 2H, H Ar), 7.38–7.46 (m, 4H, H Ar), 7.52–7.60 (m, 3H, H Ar), 7.98–8.05 (m, 2H, H Ar).
^{13}C NMR	**:**	35.2, 125.4, 127.7, 128.1, 128.6, 128.8, 131.2, 137.0,
($CDCl_3$, 50 MHz) δ		140.1, 140.9, 143.9, 148.6, 154.1.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26; S, 10.60 Found: C, 75.58; H, 4.83; N, 9.46.

(1*E*, 4*E*)-2(Furan-2-yl)-4-phenyl-3*H*-benzo[*b*][1, 4]diazepine (31k).

Nature of compound	**:**	Dark liquid.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2399, 1596, 1261, 669.

^{1}H NMR	**:**	3.55 (br s, 2H, CH_2), 6.41–6.44 (m, 1H, H Ar), 7.02 (dd,
($CDCl_3$, 200 MHz) δ		*J* = 3.53 and 0.75 Hz, 1H, H Ar), 7.20–7.29 (m, 2H, H Ar), 7.33–7.41 (m, 3H, H Ar), 7.48–7.55 (m, 3H, H Ar), 7.99–8.08 (m, 2H, H Ar).
^{13}C NMR	**:**	33.9, 112.4, 113.8, 125.4, 128.1, 128.5, 128.7, 130.6,
($CDCl_3$, 50 MHz) δ		136.9, 140.2, 140.9, 144.9, 145.3, 152.0, 154.1.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78 Found: C, 79.68; H, 4.91; N, 9.74.

(1*E*, 4*E*)-7-Methyl-2, 4-diphenyl-3*H*-benzo[*b*][1, 4]diazepine (31l).

Nature of compound; mp	**:**	Colorless solid, mp 112–114 ^oC (lit.[8] 111 ^oC).
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1602, 1215, 758, 669.
^{1}H NMR	**:**	2.46 (s, 3H, CH_3), 3.70 (br s, 2H, CH_2), 7.17 (dd, *J* =
($CDCl_3$, 200 MHz) δ		8.20, 1.63 Hz, 1H, H Ar), 7.37–7.44 (m, 7H, H Ar), 7.50 (d, *J* = 8.21 Hz, 1H, H Ar), 7.93–7.97 (m, 4H, H Ar).
^{13}C NMR	**:**	21.1, 34.9, 126.8, 127.9, 128.6, 130.4, 135.3, 137.4,
($CDCl_3$, 50 MHz) δ		138.5, 140.5, 153.3, 153.7.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03 Found: C, 85.09; H, 5.77; N, 8.78.

(1*E*, 4*E*)-7-Methyl-4-phenyl-2-*p*-tolyl-3*H*-benzo[*b*][1,4]diazepine (31m).

Nature of compound; mp	**:**	Colorless solid, mp 124–126 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2400, 1655, 1215, 758, 691, 667.
^{1}H NMR	**:**	2.23 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.55 (br s, 2H,
($CDCl_3$, 200 MHz) δ		CH_2), 7.02–7.12 (m, 3H, H Ar), 7.25–7.29 (m, 4H, H Ar), 7.40 (d, *J* = 8.34 Hz, 1H, H Ar), 7.75 (d, *J* = 8.21 Hz, 2H, H Ar), 7.82–7.87 (m, 2H, H Ar).
^{13}C NMR	**:**	21.0, 21.2, 34.7, 126.7, 127.9, 128.5, 129.3, 130.4,
($CDCl_3$, 50 MHz) δ		134.6, 134.9, 135.2, 137.3, 138.6, 140.4, 140.7, 153.1, 153.6, 153.7.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63

Found: C, 84.87; H, 6.30; N, 8.86.

(1*E*,4*E*)-2-(4-Chlorophenyl)-7-methyl-4-phenyl-3*H*-benzo[*b*][1,4]diazepine (31n).

Nature of compound; mp	**:**	Colorless solid, mp 125–127 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1593, 1215, 758, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.46 (s, 3H, CH_3), 3.63 (br s, 2H, CH_2), 7.17 (dd, *J* = 8.22, 1.39 Hz, 1H, H Ar), 7.34–7.52 (m, 7H, H Ar), 7.87–7.95 (m, 4H, H Ar).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.1, 34.8, 127.1, 128.1, 128.5, 128.6, 128.7, 128.9, 129.4, 130.6, 135.5, 135.7, 136.8, 137.2, 138.5, 140.2, 152.2, 153.0.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{22}H_{17}ClN_2$: C, 76.63; H, 4.97; Cl, 10.28; N, 8.12 Found: C, 76.61; H, 4.89; N, 8.11.

(1*E*, 4*E*)-7-Methyl-2-phenyl-4-*p*-tolyl-3*H*-benzo [*b*][1, 4] diazepine (31o).

Nature of compound; mp	**:**	Colorless solid, mp 111–113 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1595, 1216, 757, 692, 668.
^{1}H NMR ($CDCl_3$, 500 MHz) δ	**:**	2.31 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.62 (br s, 2H, CH_2), 7.10–7.18 (m, 3H, H Ar), 7.34–7.39 (m, 4H, H Ar), 7.49 (d, *J* = 8.20 Hz, 1H, H Ar), 7.84 (d, *J* = 8.07 Hz, 2H, H Ar), 7.90–7.95 (m, 2H, H Ar).
^{13}C NMR ($CDCl_3$, 200 MHz) δ	**:**	21.0, 21.2, 34.7, 126.6, 127.9, 128.5, 129.3, 130.3, 134.4, 134.9, 135.1, 137.4, 138.4, 140.5, 140.8, 153.3, 153.5.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63 Found: C, 84.97; H, 6.32; N, 8.66.

(1*E*,4*E*)-2-(4-Methoxyphenyl)-7-methyl-4-phenyl-3*H*-benzo[*b*][1,4]diazepine (31p).

Nature of compound; mp	**:**	Colorless solid, mp 155–157 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2400, 1606, 1513, 1215, 692, 668.
^{1}H NMR	**:**	2.44 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.89 (d, *J* = 8.85

($CDCl_3$, 200 MHz) δ		Hz, 2H, H Ar), 7.13 (dt, *J* = 8.33, 1.51 Hz, 1H, H Ar), 7.37–7.40 (m, 4H, H Ar), 7.49 (dd, *J* = 8.21, 2.40 Hz, 1H, H Ar), 7.90–7.96 (m, 4H, H Ar).
^{13}C NMR	**:**	21.0, 34.6, 55.2, 113.9, 126.4, 126.7, 127.9, 128.5,
($CDCl_3$, 50 MHz) δ		129.8, 130.3, 134.8, 135.2, 137.4, 138.4, 140.7, 153.0, 153.3, 161.5.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23 Found: C, 81.10; H, 5.90; N, 8.20.

(1*E*, 4*E*)- 7-Methyl-4-phenyl-2-(thiophen-2-yl)-3*H*-benzo[*b*][1, 4]diazepine (31q).

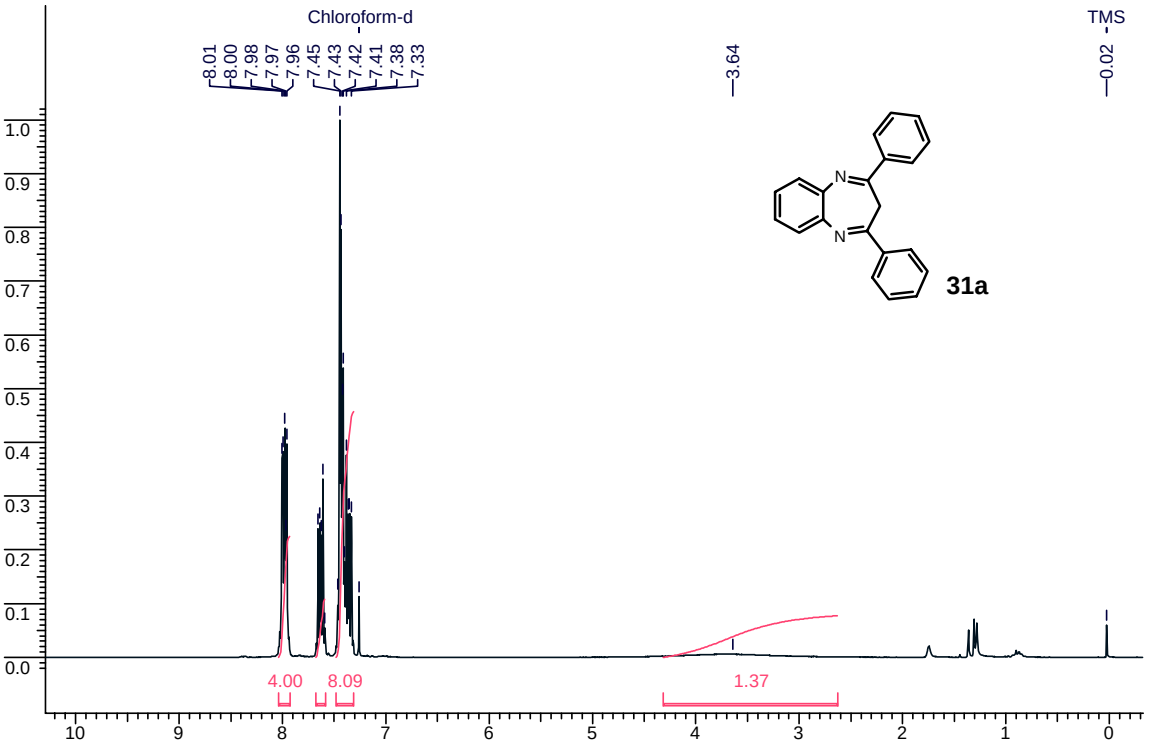
Nature of compound; mp	**:**	Colorless solid, mp 115–117 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 2400, 1576, 1432, 1215, 757, 668.
^{1}H NMR	**:**	2.45 (s, 3H, CH_3), 3.67 (br s, 2H, CH_2), 7.04 (m, 1H, H
($CDCl_3$, 200 MHz) δ		Ar), 7.15 (dd, *J* = 8.20, 1.49 Hz, 1H, H Ar), 7.38–7.50 (m, 6H, H Ar), 7.59–7.69 (m, 1H, H Ar), 8.01–8.06 (m, 2H, H Ar).
^{13}C NMR	**:**	20.2, 39.5, 125.2, 125.4, 125.9, 127.8, 128.2, 128.3,
($CDCl_3$, 50 MHz) δ		128.5, 129.3, 130.4, 131.0, 136.3, 137.4, 138.8, 140.3, 153.4, 156.9.
Elemental analysis (%)	**:**	Anal. Calcd for $C_{20}H_{16}N_2S$: C, 75.92; H, 5.10; N, 8.85 Found: C, 75.69; H, 5.12; N, 8.75.

2.3.6 Spectra

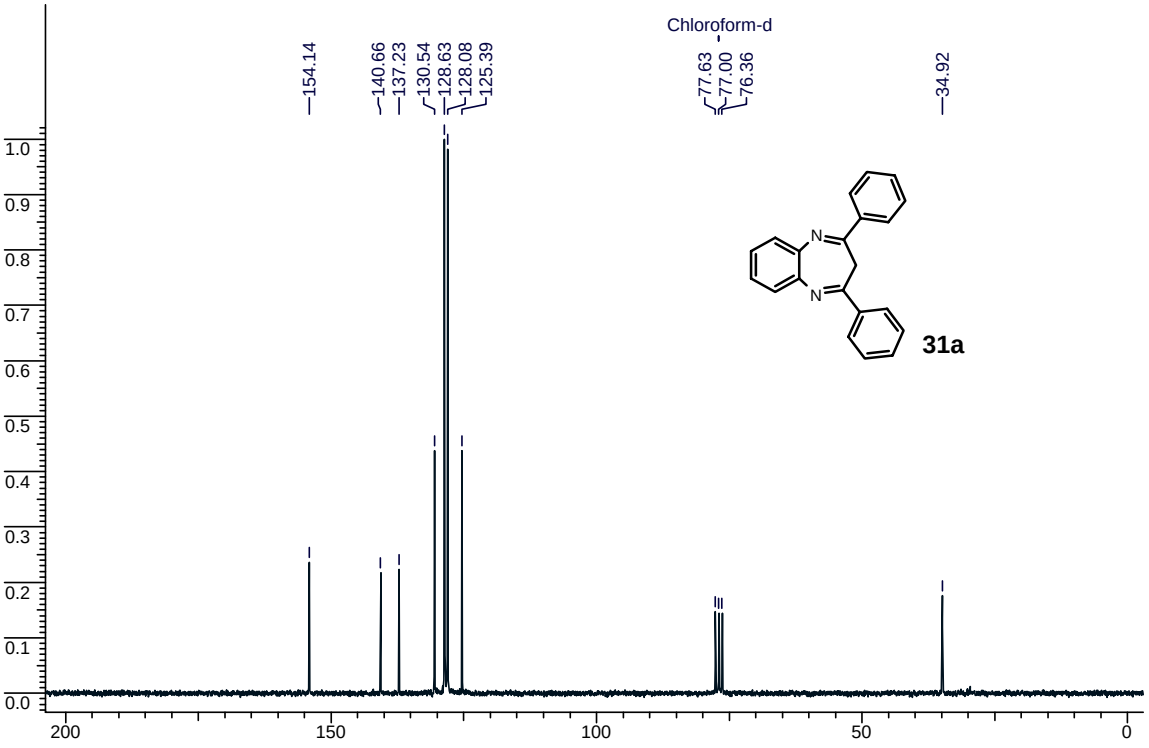
Table 10. ^{1}H and ^{13}C spectra of some representative benzodiazepines

Sr. No.	Spectra
1	^{1}H and ^{13}C spectra of **31a**
2	^{1}H and ^{13}C spectra of **31c**
3	^{1}H and ^{13}C spectra of **31d**
4	^{1}H and ^{13}C spectra of **31f**
5	^{1}H and ^{13}C spectra of **31i**
6	^{1}H and ^{13}C spectra of **31j**
7	^{1}H and ^{13}C spectra of **31l**
8	^{1}H and ^{13}C spectra of **31m**
9	^{1}H and ^{13}C spectra of **31n**
10	^{1}H and ^{13}C spectra of **31p**
11	^{1}H and ^{13}C spectra of **31q**

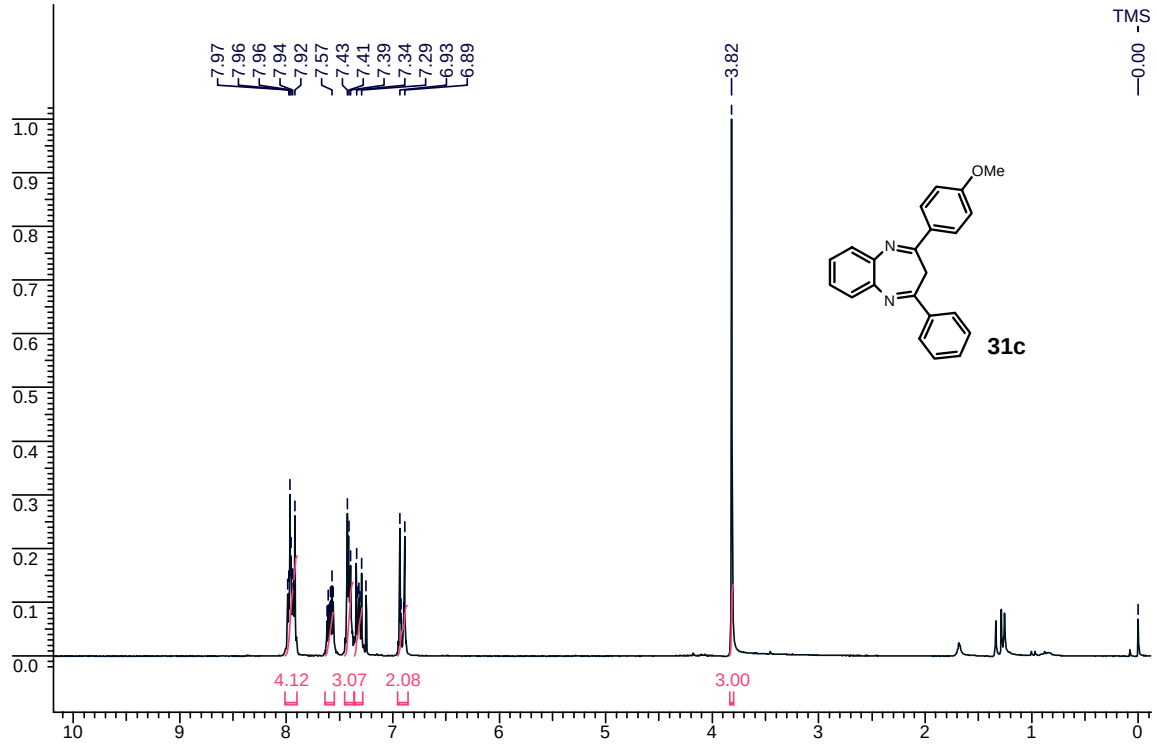
^{1}H NMR of **31a**



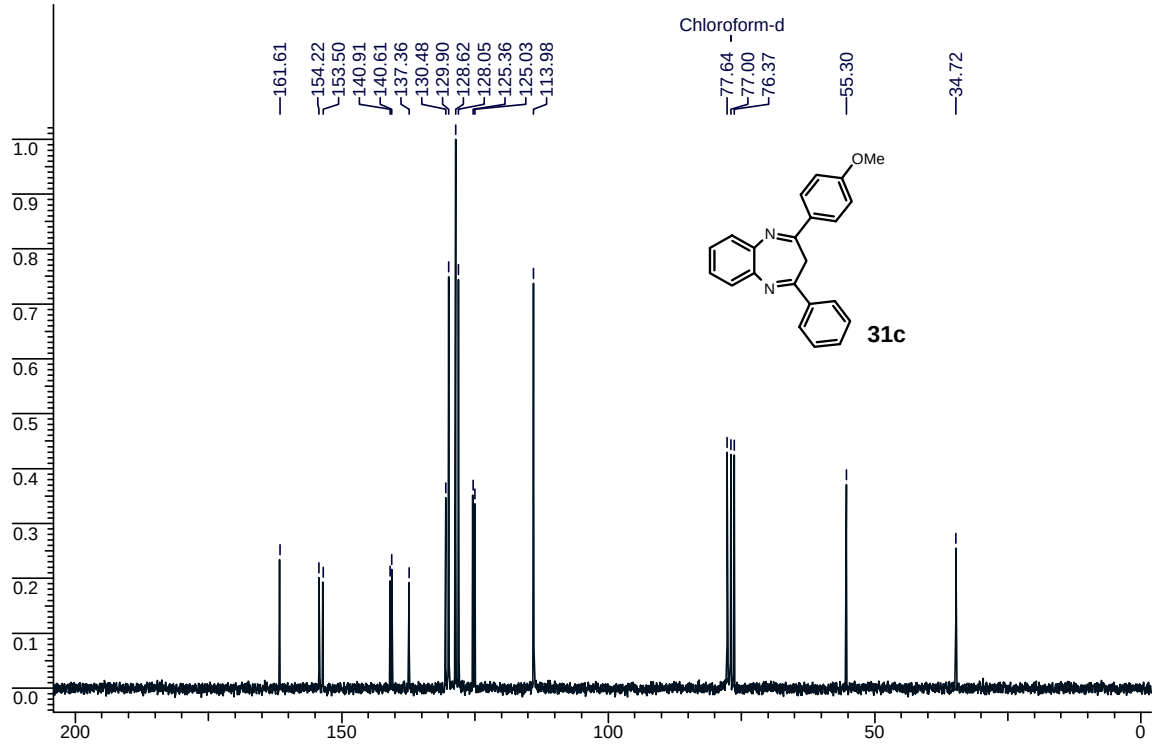
^{13}C NMR of **31a**



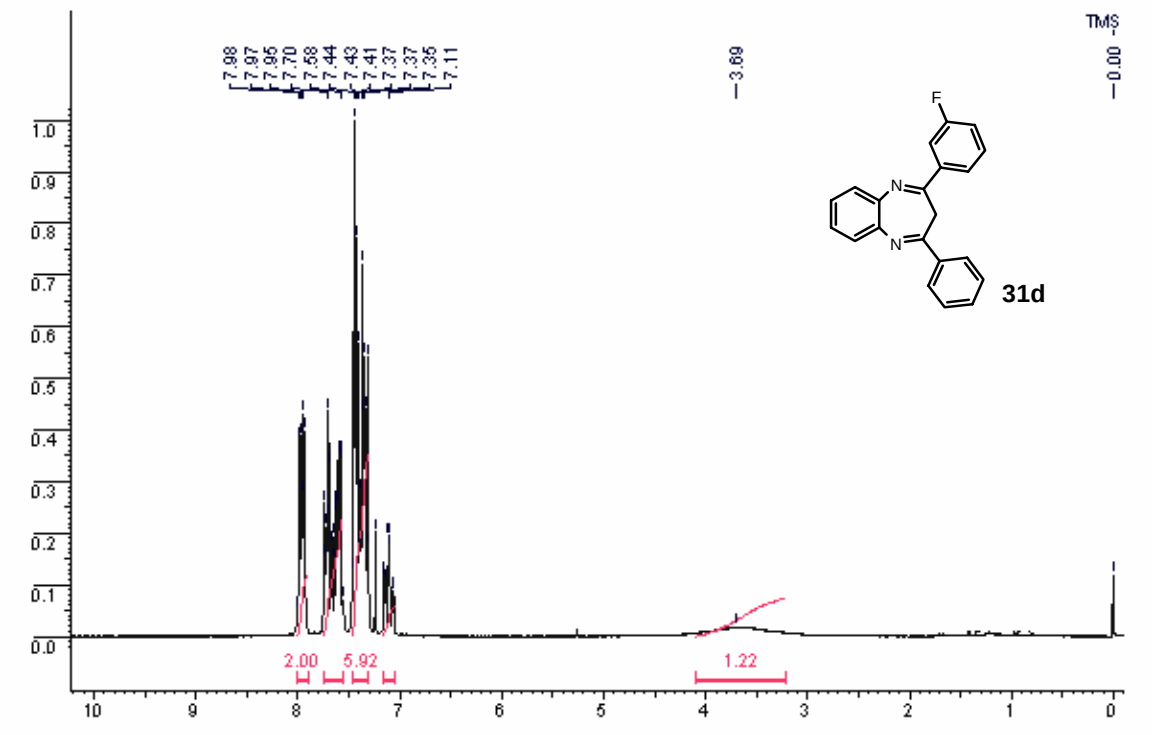
^{1}H NMR of **31c**



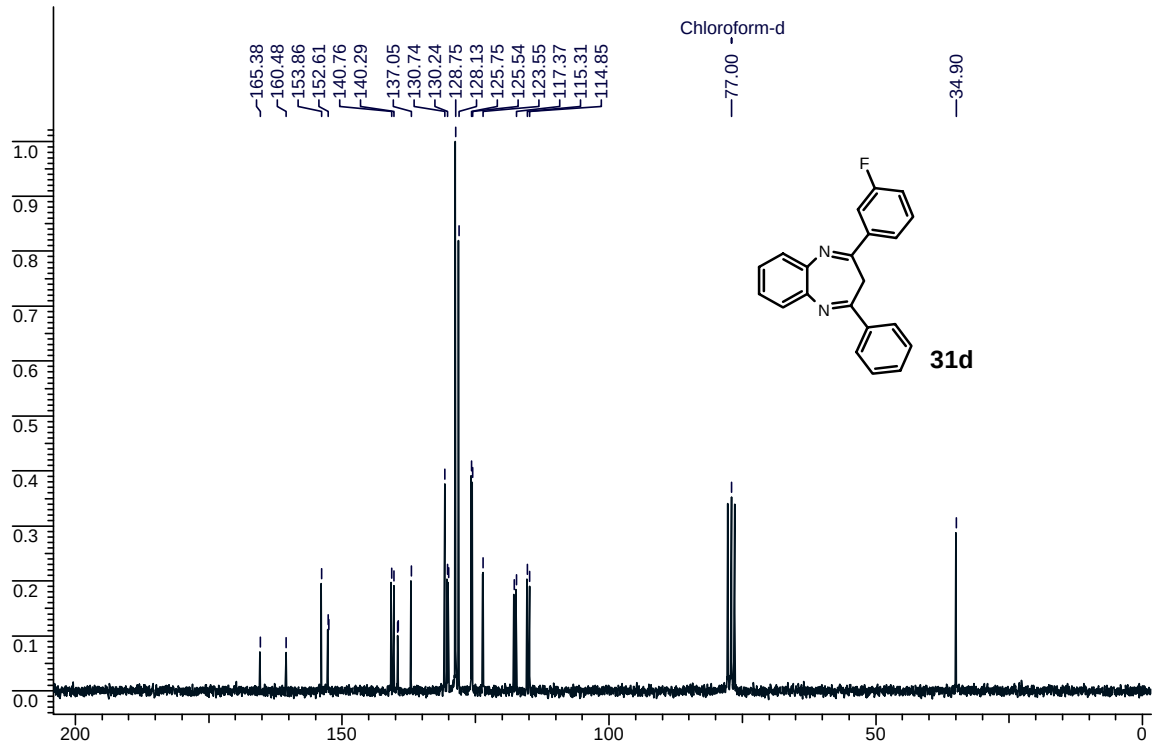
^{13}C NMR of **31c**



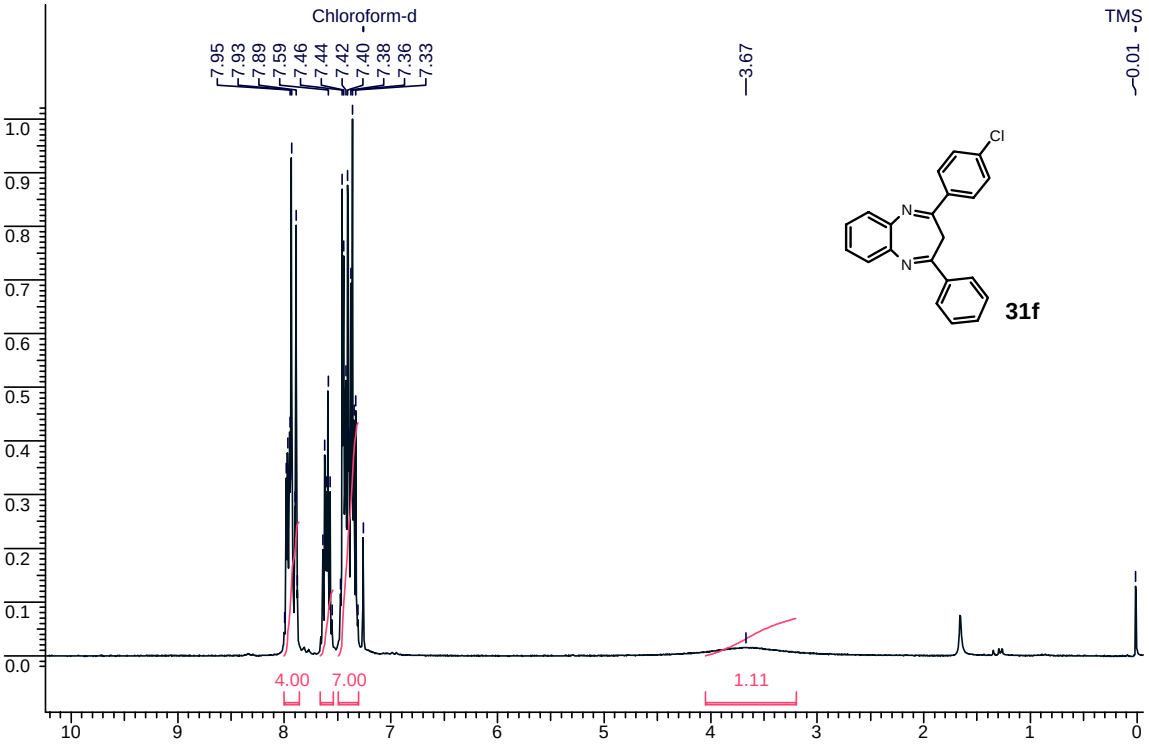
^{1}H NMR of **31d**



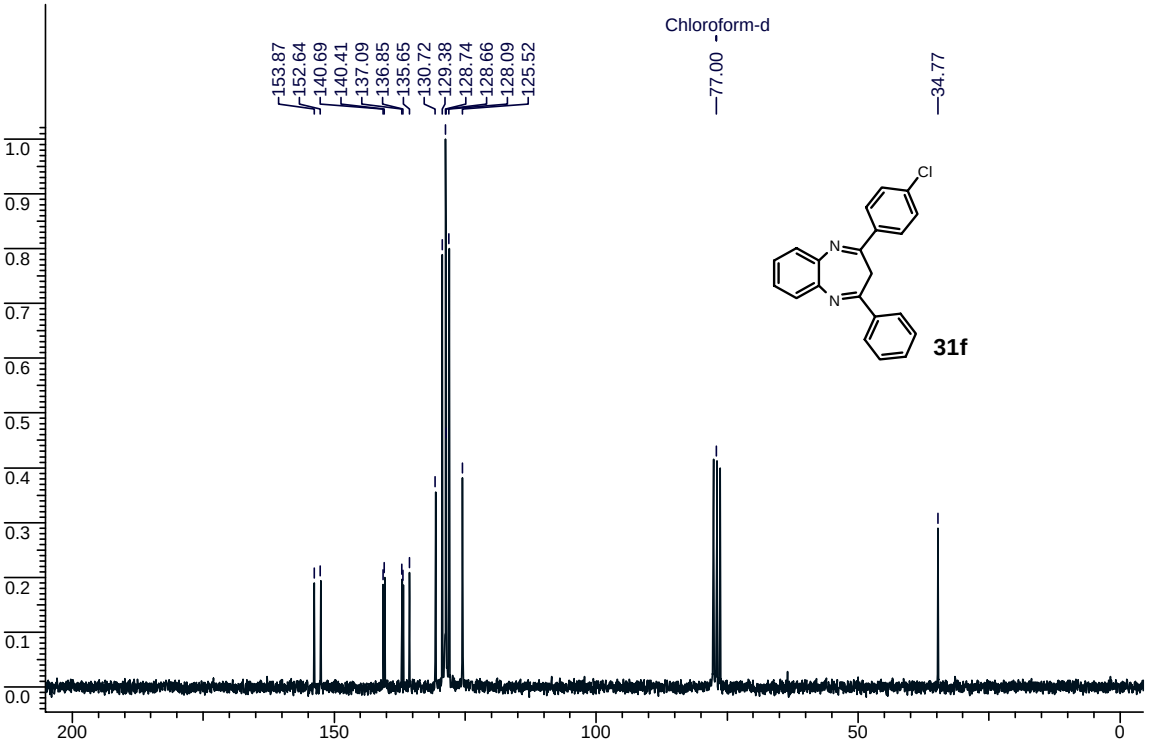
^{13}C NMR of **31d**



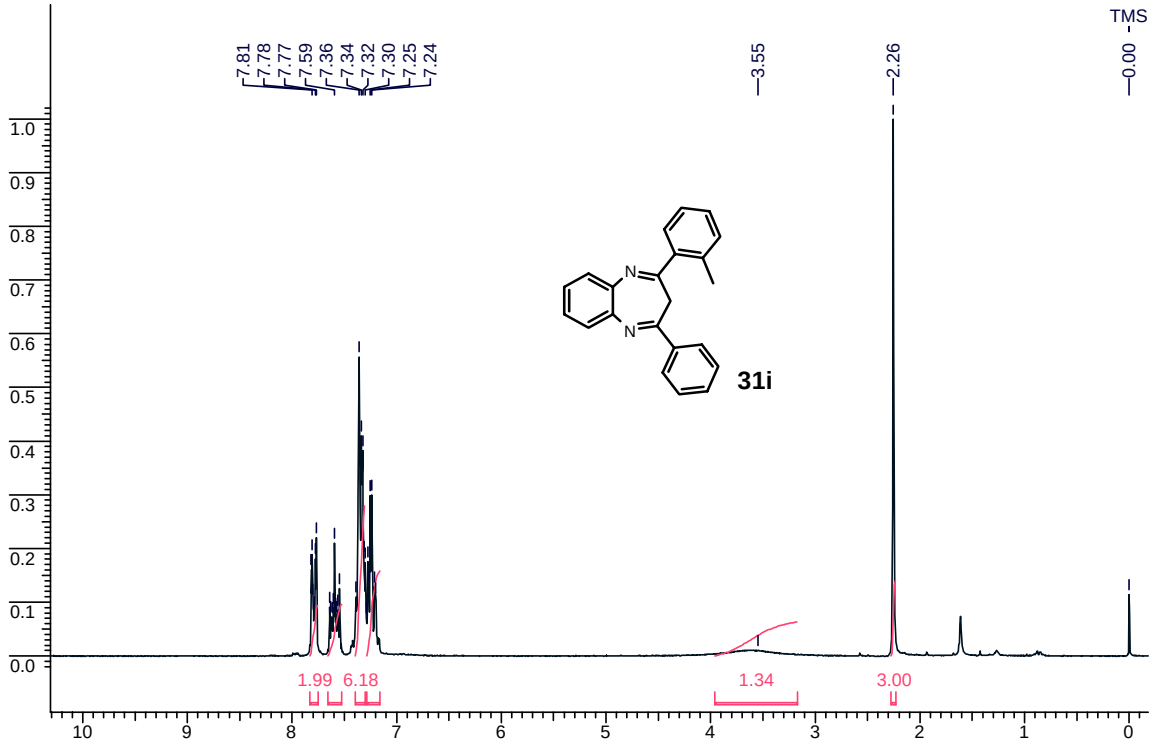
^{1}H NMR of **31f**



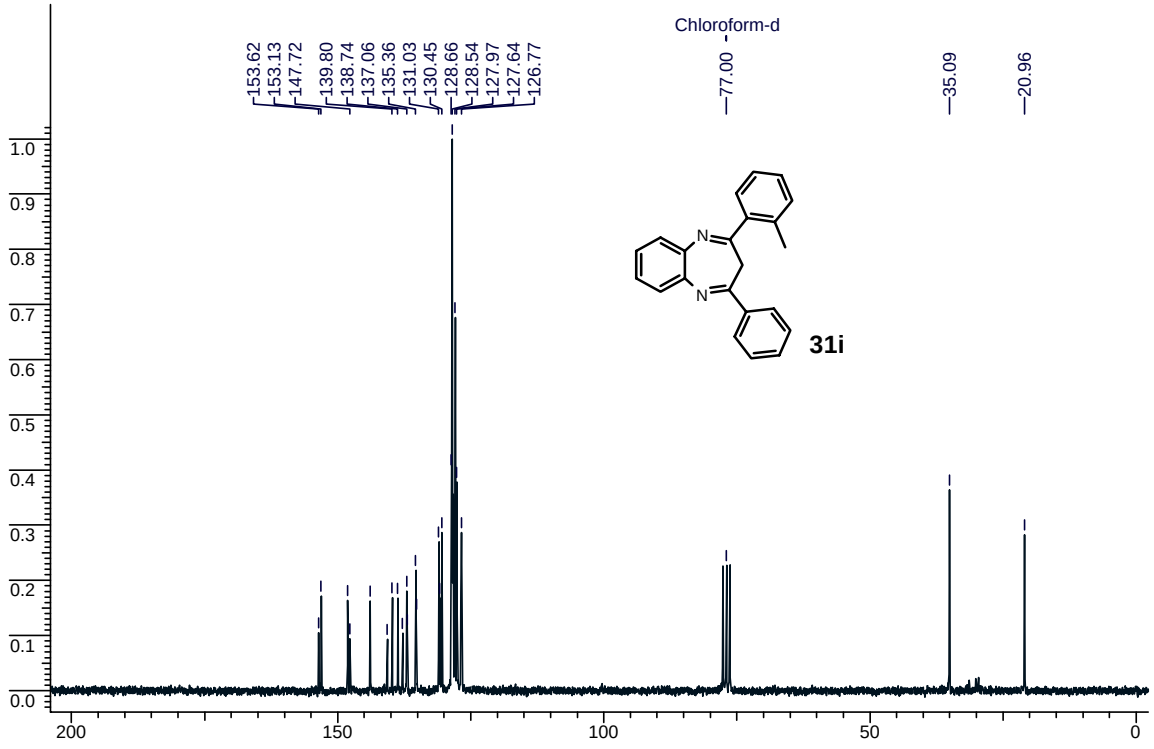
^{13}C NMR of **31f**



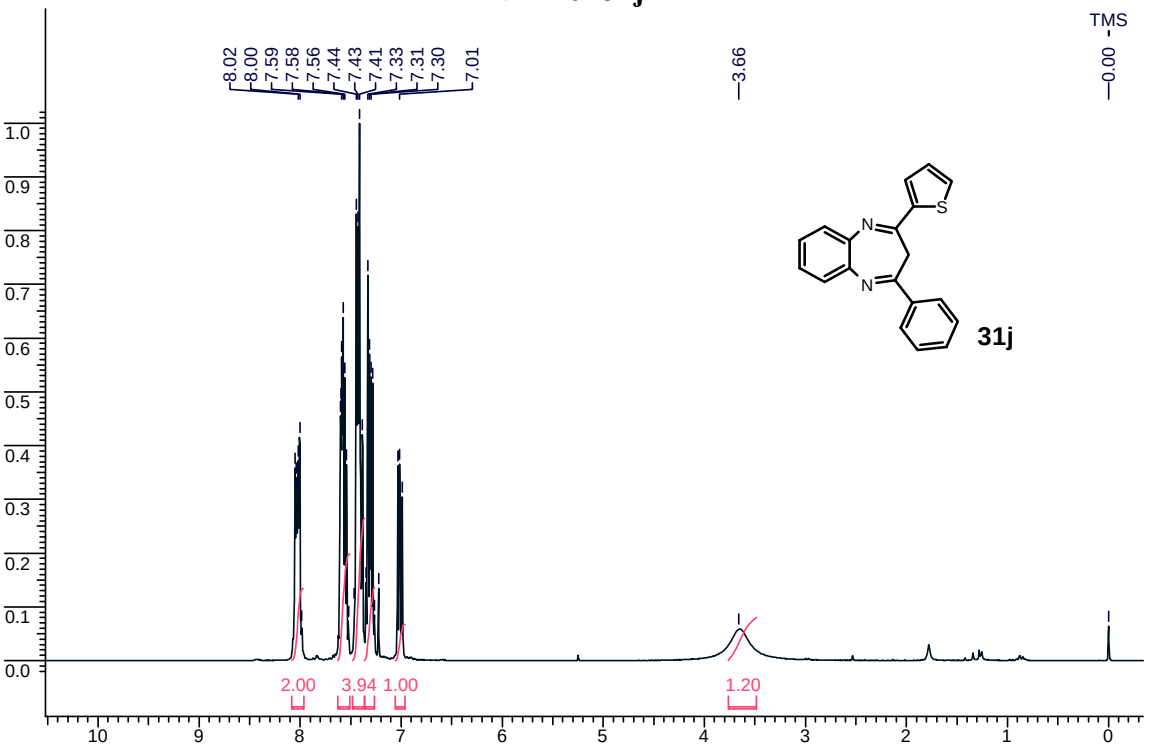
^{1}H NMR of **31i**



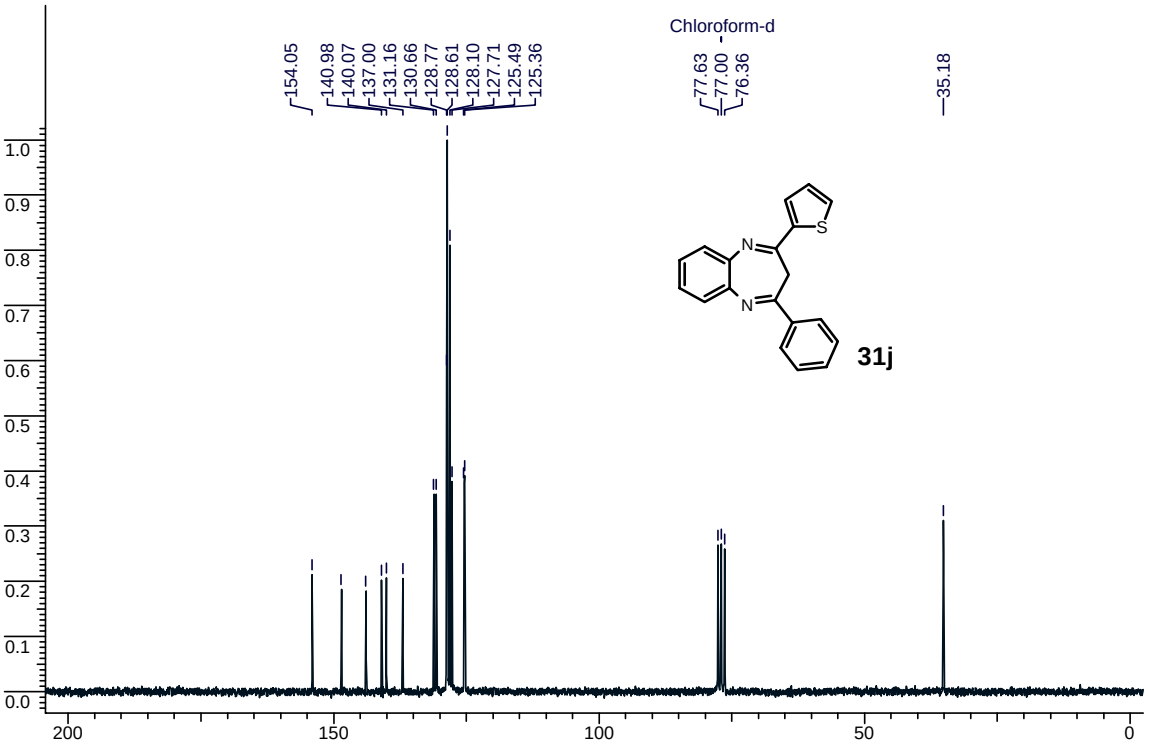
^{13}C NMR of **31i**



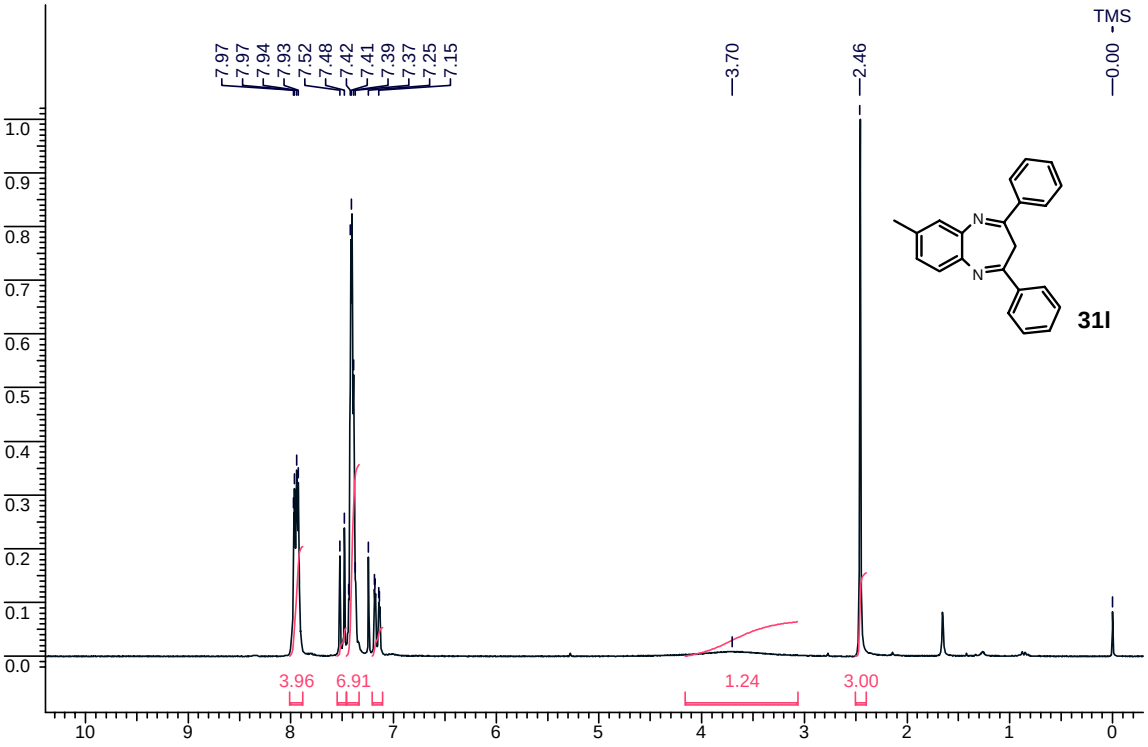
^{1}H NMR of **31j**



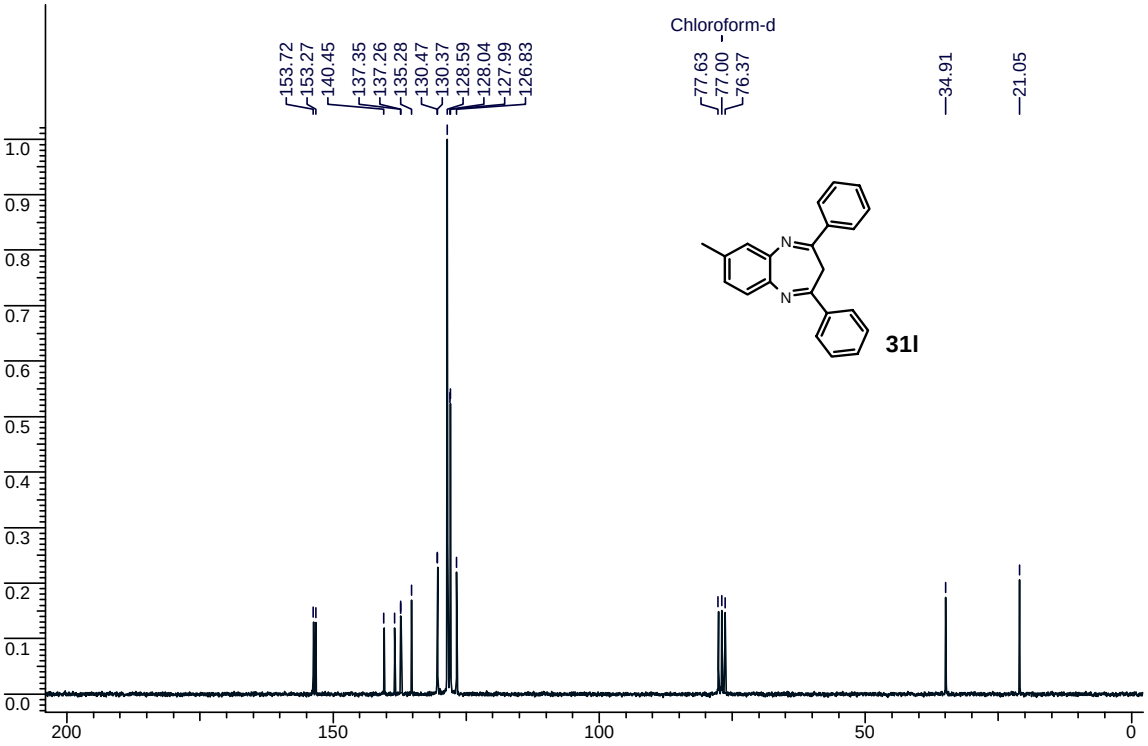
^{13}C NMR of **31j**



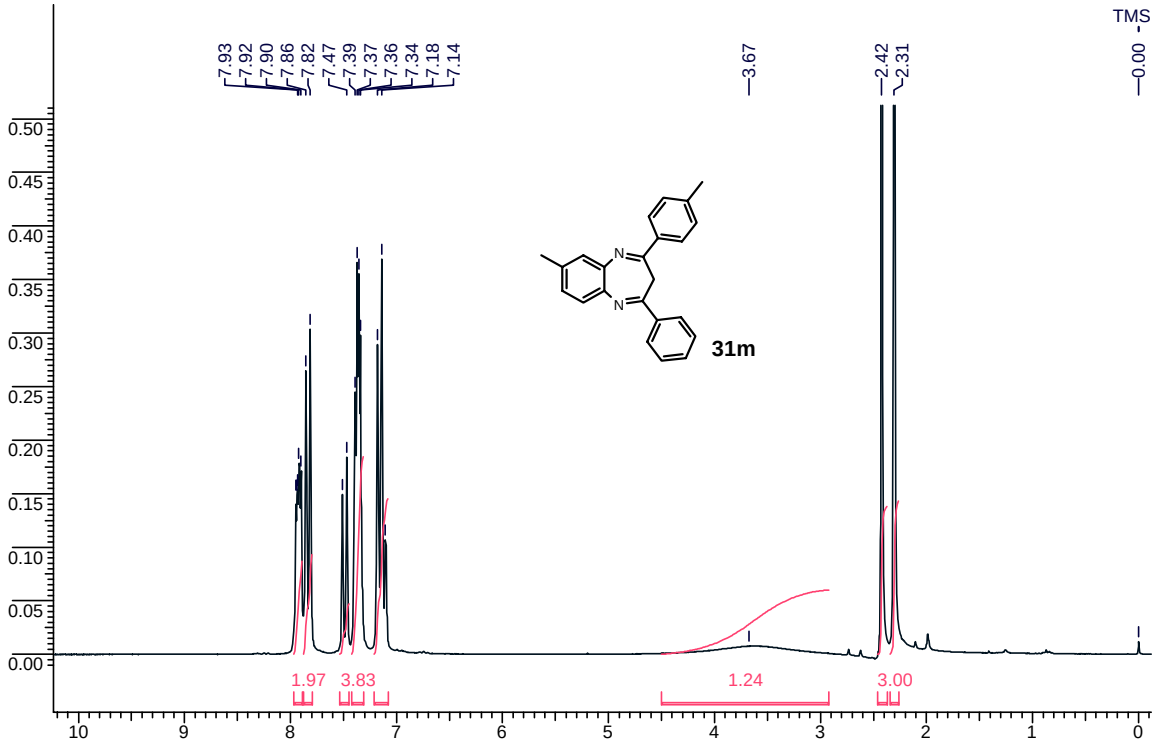
^{1}H NMR of **31l**



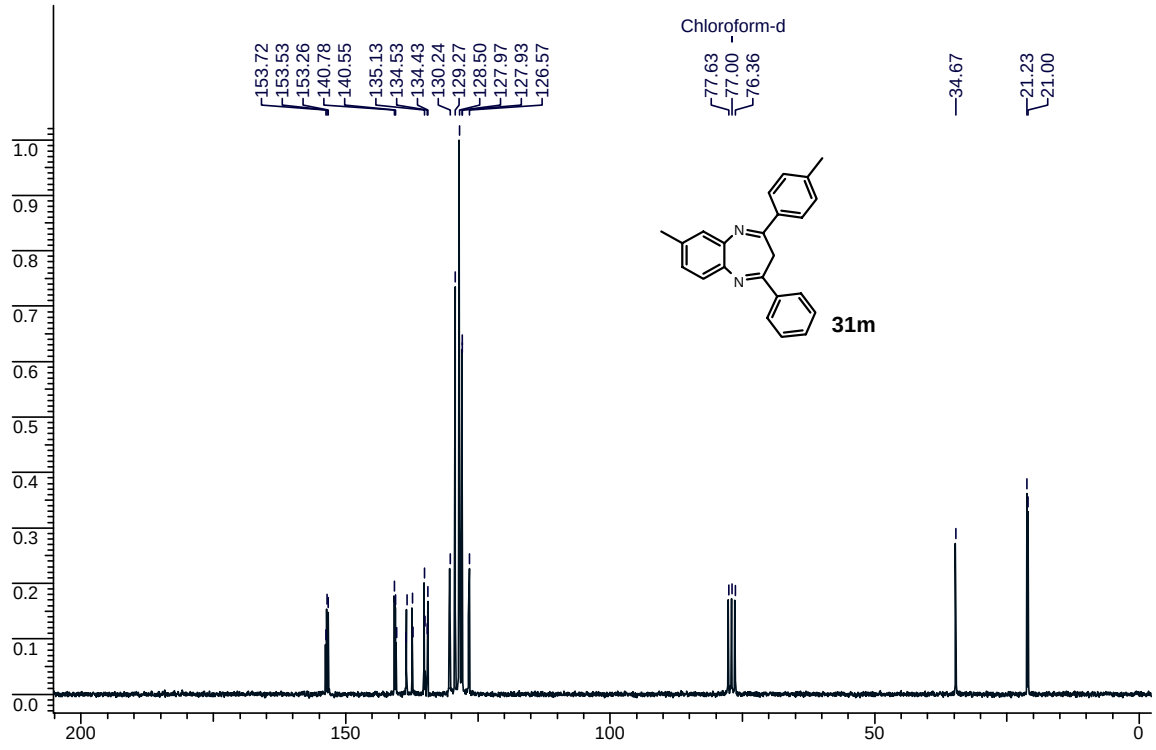
^{13}C NMR of **31l**



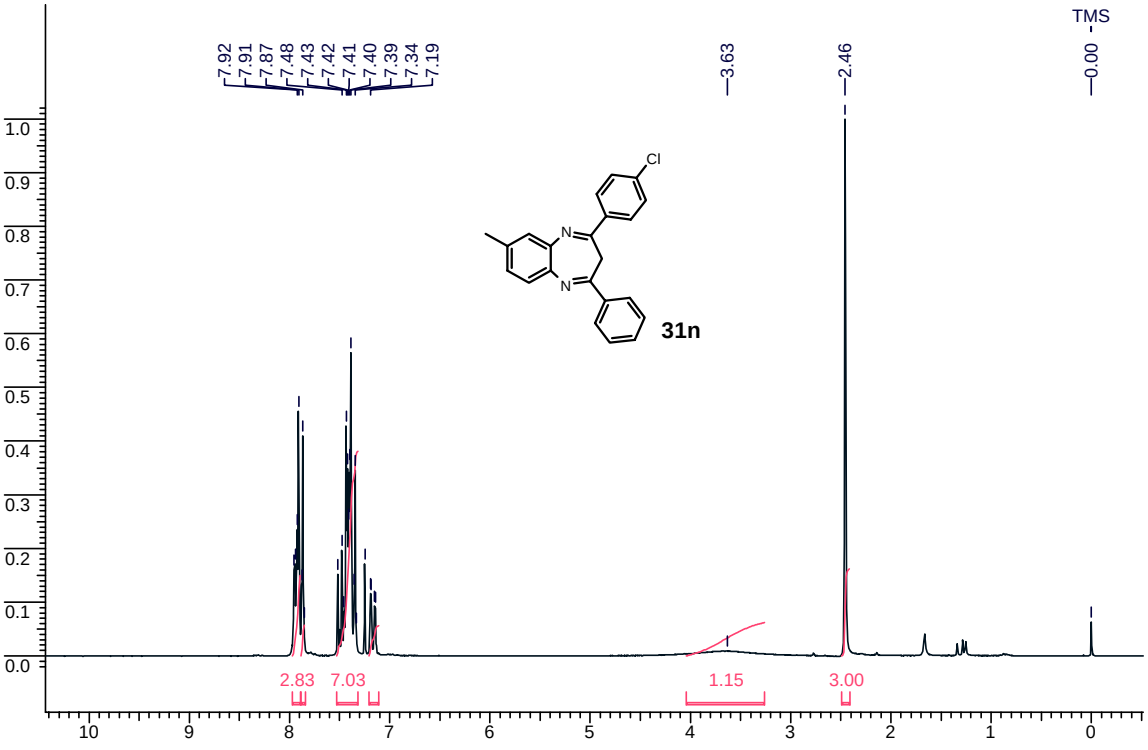
^{1}H NMR of **31m**



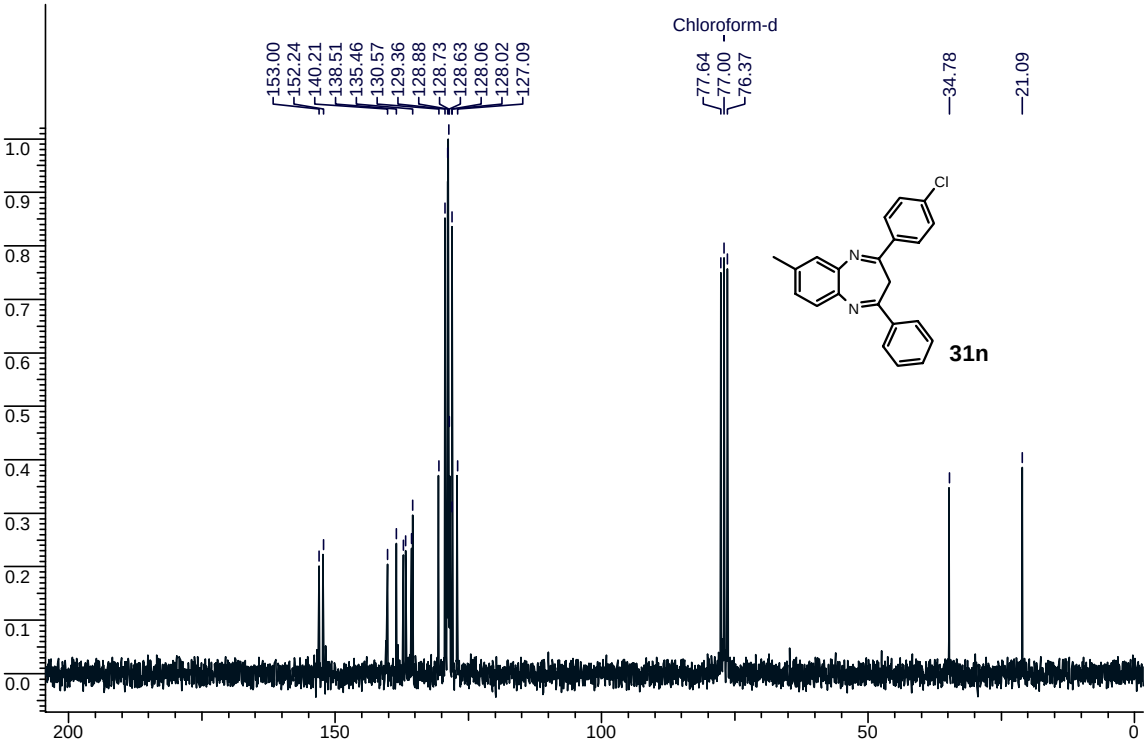
^{13}C NMR of **31m**



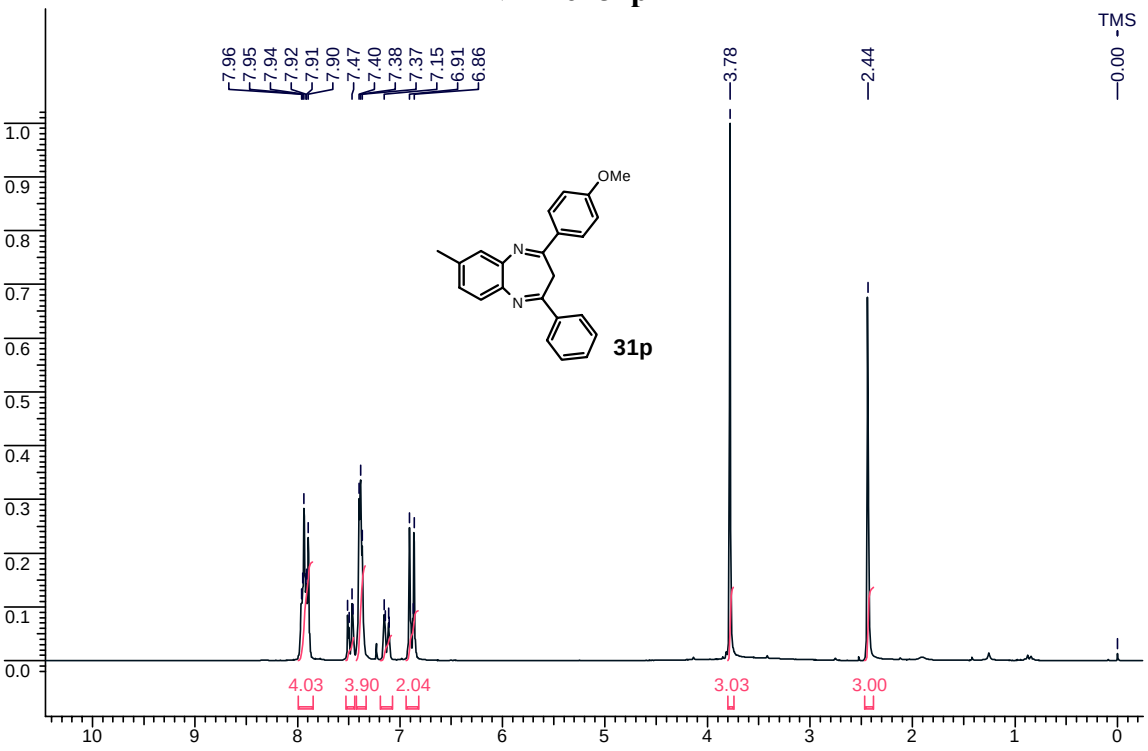
^{1}H NMR of **31n**



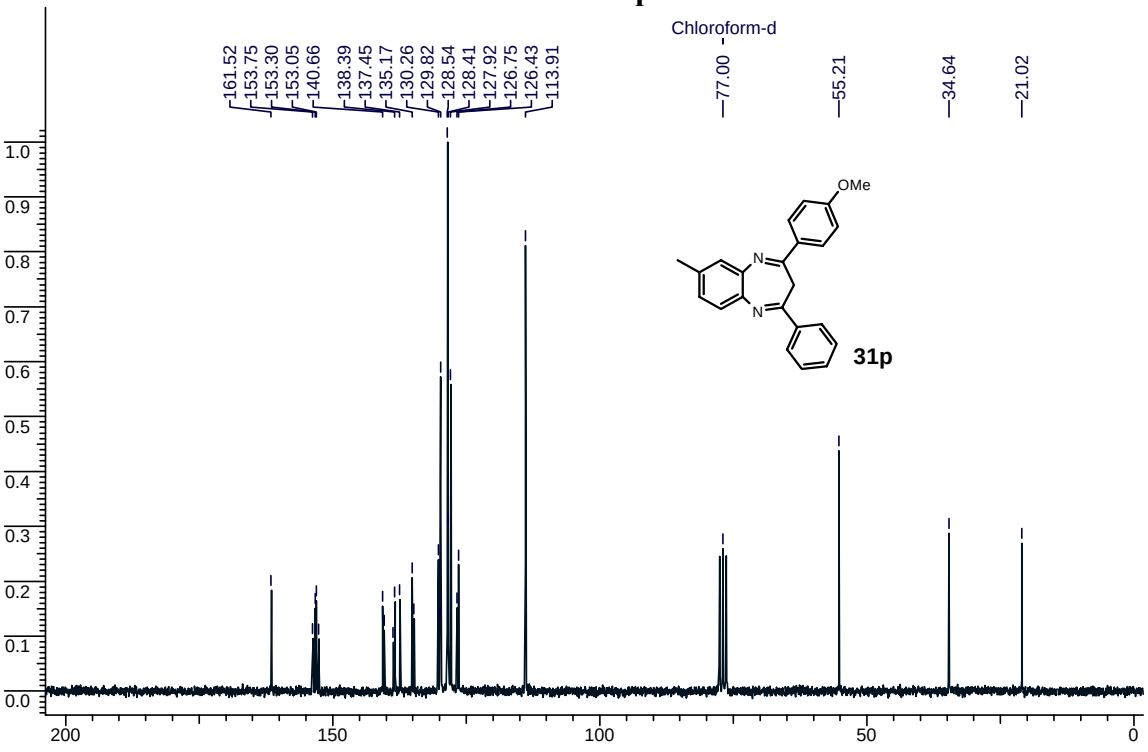
^{13}C NMR of **31n**



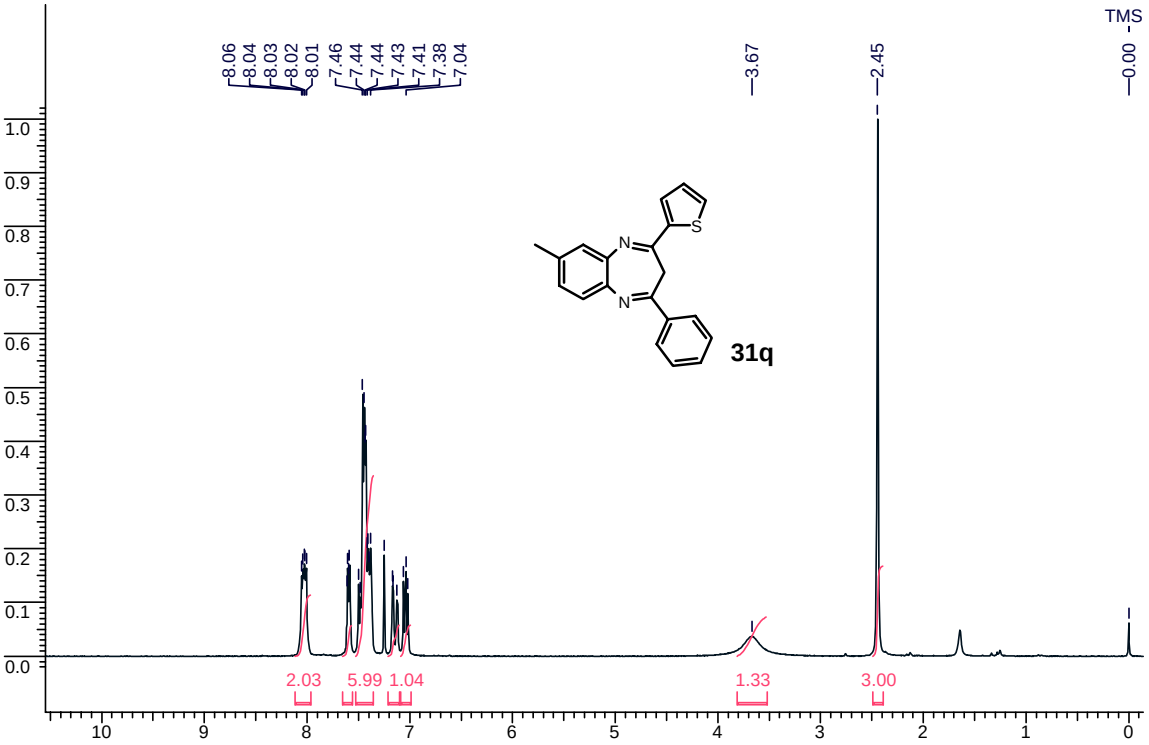
^{1}H NMR of **31p**



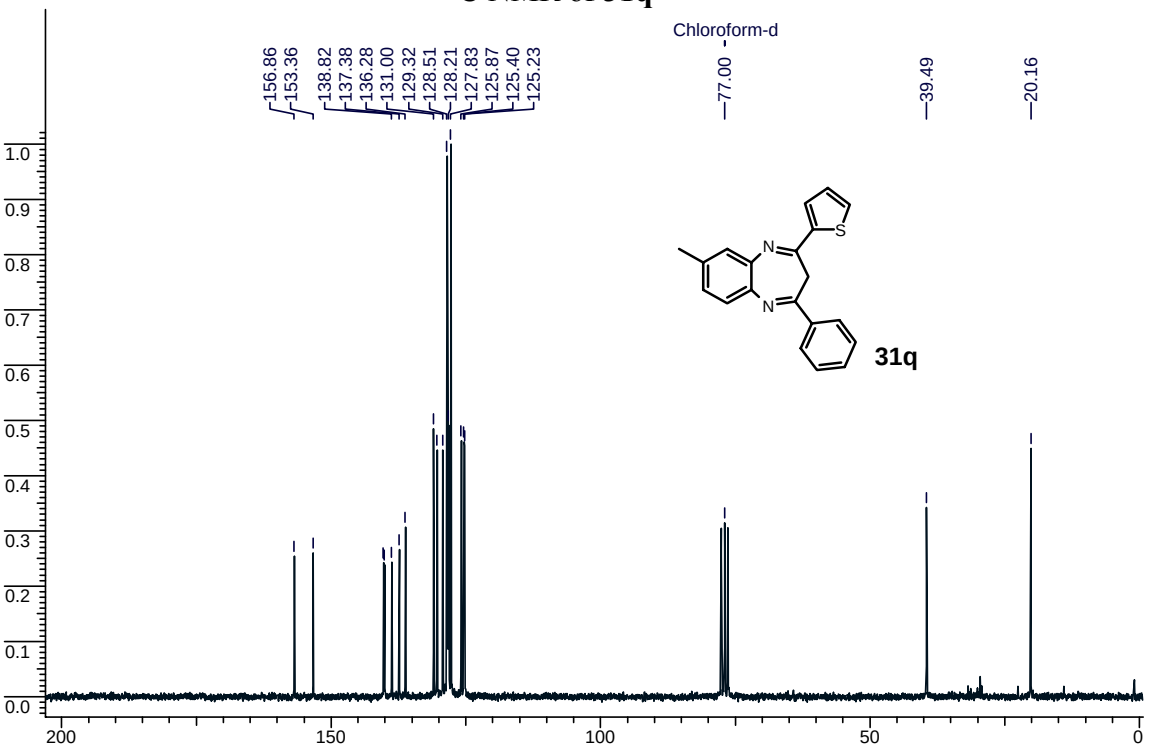
^{13}C NMR of **31p**



^{1}H NMR of **31q**



^{13}C NMR of **31q**



2.3.7 References

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Chapter III

Synthesis of an indole, KDR kinase inhibitor and benzofurans via Sonogashira coupling-5-endo-dig-cyclization

3.0 Introduction

Heterocyclic compounds are worth our attention for many reasons; chief among them are their biological activities, and many drugs are heterocycles. Therefore, organic chemists have been making extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among a variety of new synthetic transformations, transition-metal-catalyzed reactions, particularly palladium-catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds, since a transition-metal-catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions. Palladium is probably the most versatile and widely used metal for the synthesis of heterocycles today. Palladium-catalyzed processes have proven to be a powerful and useful tool for the synthesis of heterocycles. Palladium has found such wide utility because it affects an extraordinary number of very different reactions, including many carbon-carbon bond-forming reactions, under relatively mild reaction conditions.

Furthermore, palladium can usually be used in only catalytic amounts and tolerates a wide variety of functional groups, thus avoiding protection group chemistry. Most palladium-based methodology proceeds stereo- and regioselectively in excellent yields. Thus, a number of books[1] and major review papers[2] have been published on various aspects of organopalladium chemistry, including one book devoted exclusively to heterocycle synthesis.[1f]

3.0.1 Palladium Chemistry: General Comments

Palladium is a member of the nickel triad in the periodic table. Palladium complexes exist in three oxidation states: Pd(0), Pd(II), and Pd(IV). The facile interconversion between these oxidation states is responsible for the broad utility of palladium in organic chemistry, since each oxidation state exhibits different chemistry. Palladium(0) complexes are fairly nucleophilic, rather labile, and also easily oxidized, usually to the Pd(II) state. The most synthetically useful Pd(0) chemistry is based on the oxidative addition of aryl, vinylic, or allylic halides or triflates to Pd(0). This chemistry can be very useful for the synthesis of heterocycles.

Palladium(II) complexes are extremely important in organopalladium chemistry. They are typically electrophilic, soluble in most common organic solvents and stable to air. Thus, they are easily stored and handled. The most common organic substrates for Pd(II) are electron-rich species, such as olefins, alkynes, and arenes. Some of the most useful Pd(II) chemistry is based on the fast and reversible formation of Pd(II) complexes with olefins and alkynes, which undergo subsequent attack by nucleophiles. That chemistry has recently been reviewed elsewhere. Numerous Pd(II) complexes of the type L_2PdCl_2 are easily formed from $PdCl_2$ and the appropriate ligand L. The most useful Pd(II) complexes are $PdCl_2(PPh_3)_2$,[3] $Pd(OAc)_2$,[4] and $PdCl_2(RCN)_2$.[5] Pd(II) complexes are often added to reactions as precatalysts, since they are readily reduced by various species to Pd(0), which then catalyzes the desired process. Pd(IV) complexes are quite rare, although a few complexes are known.[6] These complexes have been little explored, but transient Pd(IV) species have been increasingly implicated as intermediates in palladium reactions. They appear to play little role in palladium-catalyzed oxidative addition chemistry directed toward heterocyclic synthesis. There are a large number of organic reactions, which palladium catalyzes, which generate heterocycles.

3.0.2 Heterocycles *via* Sonogashira coupling-5-*endo*-*dig*-cyclization

The palladium-catalyzed Sonogashira coupling-5-*endo*-*dig*-cyclization of terminal alkynes has proven to be extremely useful for the one-pot synthesis of a wide variety of N-heterocycles, O-heterocycles and S-heterocycles.[7]

In this chapter, improved methods for the synthesis of indoles and benzo[b]furans by tandem Sonogashira coupling-5-*endo*-*dig*-cyclization strategy have been described. Also synthesis of a novel potent and selective KDR kinase inhibitor 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2- yl]quinoline-2-(1*H*)-one (**28**) by using the same strategy has been described in this chapter.

3.0.2 Mechanism of Sonogashira coupling-5-*endo*-*dig*-cyclization

This process generally involves the addition of a covalent molecule to a Pd(0) complex, with cleavage of the covalent bond and oxidation of Pd(0) to Pd(II), to afford a σ-organopalladium(II) halide complex. The σ-bonded species, once formed, generally undergoes rapid insertion of an unsaturated species or other reactions as

outlined in Fig. **1**. Subsequent reductive elimination affords the *o*-substituted alkynyl derivative and Pd(0), which reenters the catalytic cycle directly. The *o*-substituted alkynyl derivative subsequently undergoes cyclization *via* nucleophilic addition of neighboring group on C-C triple bond to afford the desired heterocycles. The mechanistic details of these processes have been outlined in Fig. **1**.

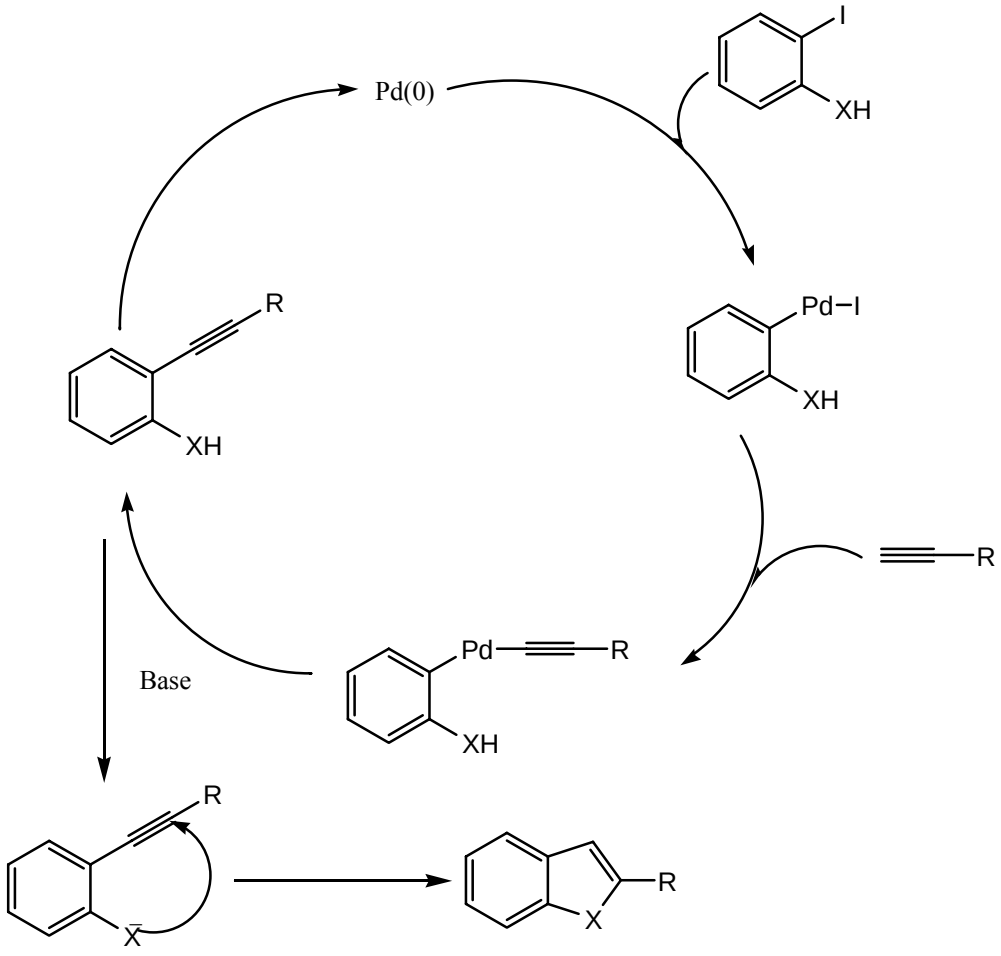

Fig. 1. Mechanism of Sonogashira coupling-5-*endo-dig*-cyclization

3.0.3 References

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Section A

Ligand-, copper-, and amine-free one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-endo-dig-cyclization

3.1.0 Introduction

The substituted indole nucleus [indole is the acronym from *indigo* (the natural dye) and *ole*um (used for the isolation)] is a structural component of a vast number of biologically active natural and unnatural compounds. The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents.[1] Substituted indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[2] Various 2-substituted indoles exhibit interesting pharmacological properties such as antithrombatic,[3] anti-cancer,[4] histamine H_3 receptor antagonism, [5] etc.

3.1.1 Review of Literature

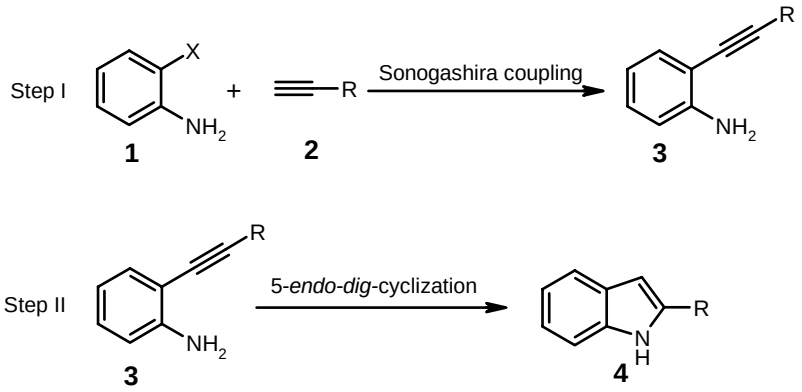
The synthesis and functionalization of indoles has been the object of research for over 100 years, and a variety of well-established classical methods are now available, to name a few of them, the Fisher indole synthesis, the Gassman synthesis of indoles from N-halo-anilines, the Madelung cyclizatoin of N-acyl-*o*-toluidines, the Bischler indole synthesis, the Batcho-Leimgruber synthesis of indoles from *o*-nitrotoluenes and dimethylformamide acetals and the reductive cyclization of *o*-nitrobenzyl ketones.[1b]

The process chemist is primarily interested in mild synthetic methods that provide rapid assembly of the indole ring, tolerate a wide range of functional groups, and are atom economical. The implementation of practical, safe, and scalable methods for the large-scale preparation of indoles is of critical interest to synthetic chemists who design industrial or manufacturing syntheses, as well as researchers in academia. In the last 40 years or so, however, palladium-catalyzed reactions, generally tolerant of a wide range of functionalities and milder as compared to classical methods and therefore applicable to complex molecules, have achieved an important place in the arsenal of the practicing organic chemist. The impact of palladium chemistry of indoles in academic and medicinal chemistry communities has been extraordinary, as outlined by the number of studies developed in this area. Thus the palladium-catalyzed synthesis and funtionalization of indoles has been employed widely due to

the versatile nature of these protocols, increased functional group tolerance, and improved yields.[6]

Among these palladium-catalyzed annulation of *o*-haloanilines and terminal alkynes *via* Sonogashira coupling-5-*endo-dig*-cyclization has proven to be a powerful and useful tool for the construction of the indole nucleus.

The synthesis of indoles *via* Sonogashira reaction is generally carried out in two steps *viz*. the palladium–copper-catalyzed Sonogashira cross-coupling between 2-aminoaryl halide **1** and alkyne **2** followed by cyclization of the resulting 2-alkynylanilines **3** (Scheme **1**)

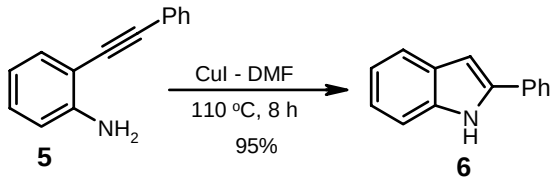


Scheme 1

The review of literature showed that various catalysts and promoters have been reported for the cyclization of 2-alkynylanilines **3**. Some representative methods are discussed below.

Castro's approach (1966)[7]

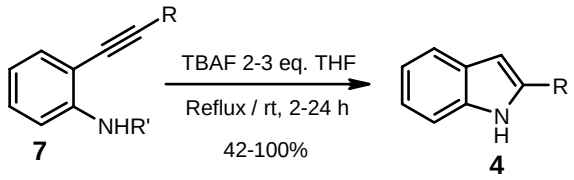
Castro *et al*. have reported the cyclization of 2-(2-phenylethynyl)benzenamine **5** by using catalyst CuI (50 mol %) in DMF at 110 ^{o}C to give corresponding 2-substituted indoles **6** in excellent yield **(Scheme 2)**.



Scheme 2

Sakamoto's approach (1999)[8]

Sakamoto, T. *et al*. studied the cyclization of different N-protected derivatives of 2-alkynylaniline **7** by using *tetra* butyl ammonium fluoride in THF at reflux temperature or at room temperature in which 2-substituted indoles **4** were obtained in moderate to excellent yields **(Scheme 3).**

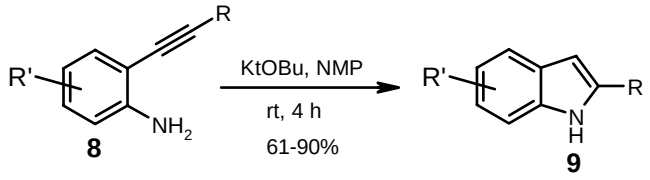


R' = Ms, COOEt, Boc, Ac, CHO, CO*t*-Bu

Scheme 3

Paul Knochel's approach (2000)[9]

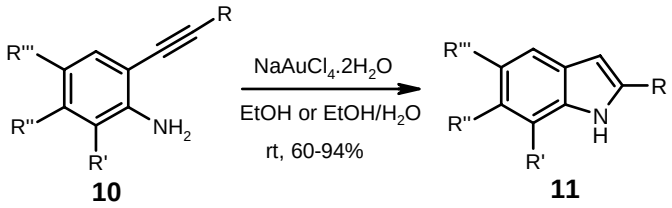
Knochel P. *et al*. reported the efficient method for the cyclization of substituted 2-alkynylanilines **8** by using pot- *tert*- butoxide as base at room temperature in polar aprotic solvent such as NMP, to afford the 2-substituted indoles **9** in quantitative yields **(Scheme 4).**



Scheme 4

Marinelli's approach (2004)[10]

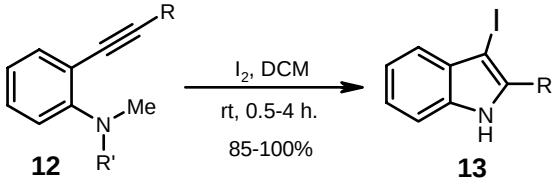
Marinelli F. *et al*. reported the Gold (III)-catalyzed annulation of substituted 2-alkynylanilines **10** in EtOH or EtOH–water mixtures at room temperature which gave indole derivatives **11** in good yields (**Scheme 5).**



Scheme 5

Larock's approach (2004)[11]

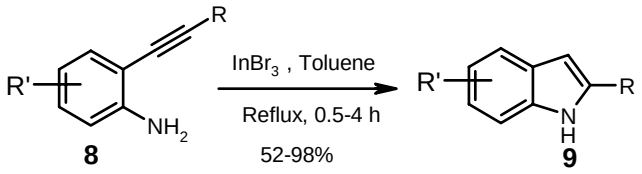
Larock, R. C. *et al*. reported efficient approach to 3-iodoindoles **13** by electrophilic cyclization of N-methylalkyl-2-ethynyl aniline **12** using iodine **(Scheme 6).**



Scheme 6

Konakahara's approach (2006)[12]

Konakahara, T. *et al*. described $InBr_3$-catalyzed cyclization of 2-alkynylaniline derivatives **8** having a variety of functional groups producing poly substituted indoles **9 (Scheme 7).**

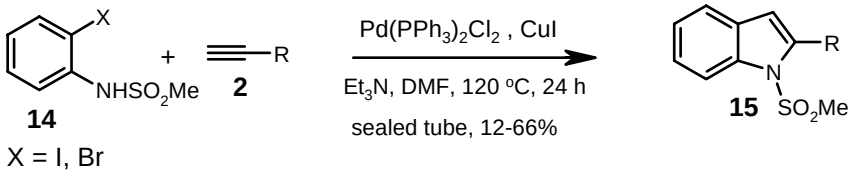


Scheme 7

Also, several methods are reported for one-pot synthesis of indole *via* tandem Sonogashira coupling 5-*endo*-*dig*-cyclization. Among them some representative methods are described below.

Yamanaka's approach (1988)[13]

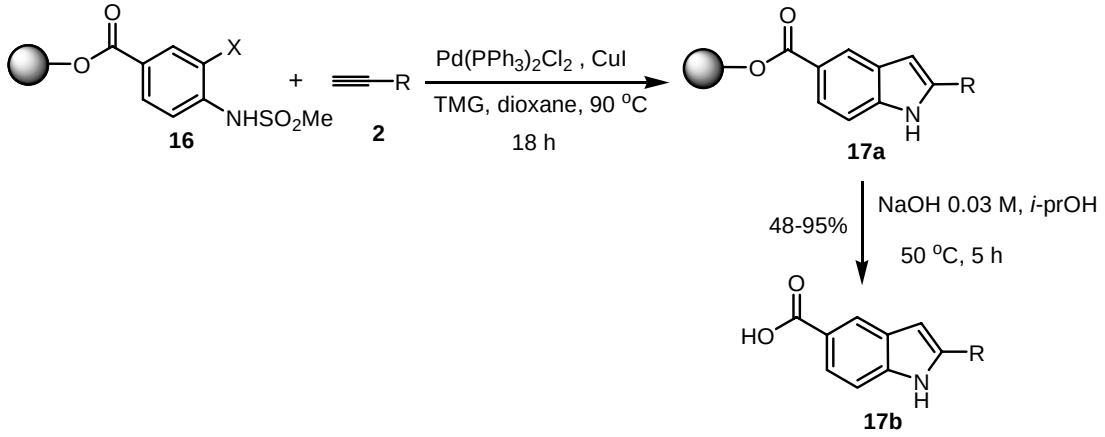
Yamanaka, H. *et al*. reported the one-pot synthesis of indole derivatives **15** *via* Sonogashira coupling-5-*endo*-*dig*-cyclization reaction of N-(2-bromophenyl)- and N-(2-iodophenyl) methanesulfonamide **14** with terminal acetylenes **2** in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (8 mol%) as the catalyst and Et_3N as the base in DMF. The reaction was carried out in the sealed tube at 120 ^oC for 24 h **(Scheme 8).**



Scheme 8

Bedeschi's approach (1997)[14]

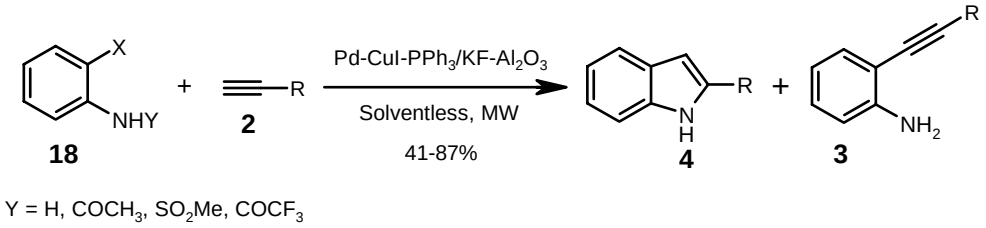
Bedeschi, A. *et al*. reported the solid-phase synthesis of indoles **17b** using $Pd(PPh_3)_2Cl_2$ and CuI catalytic system, TMG as the base and co-solvent in dioxane at 90 ^oC **(Scheme 9).**



Scheme 9

Kabalka's approach (2001)[15]

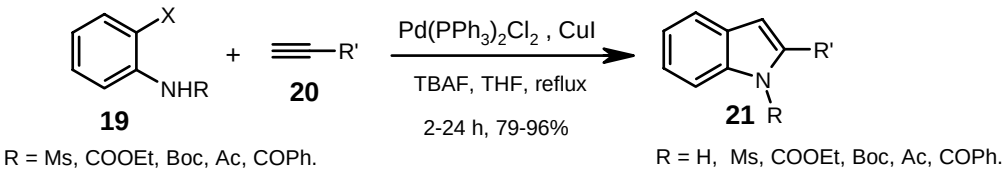
Kabalka, G. W. *et al*. reported the microwave promoted solventless one-pot synthesis of indoles **4** in the presence of potassium fluoride doped alumina, palladium powder, CuI, and triphenyl phosphine **(Scheme 10).**



Scheme 10

Sakamoto's approach (2003)[16]

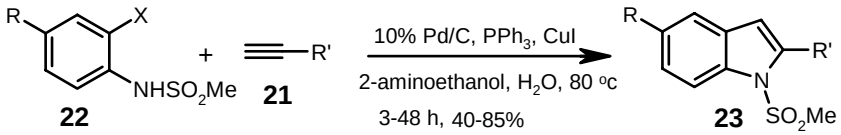
Sakamoto, T. *et al*. reported the tetrabutylammonium fluoride (TBAF) promoted one-pot synthesis of indoles **21** *via* Sonogashira coupling-5-*endo*-*dig*-cyclization by using $Pd(PPh_3)_2Cl_2$ (5 mol%) & CuI (10 mol%) as the catalyst in THF at reflux temperature in good yields **(Scheme 11).**



Scheme 11

Pal's approach (2004)[17]

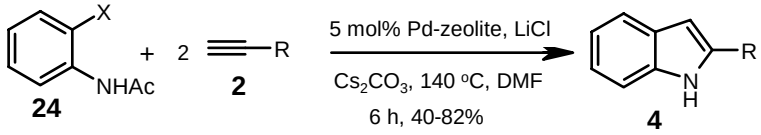
M. Pal *et al*. reported one-pot synthesis of 2-alkyl/aryl substituted indoles **23** *via* a tandem Pd/C mediated coupling/5-*endo*-*dig*-cyclization of terminal alkynes **21** with *o*-iodoanilides **22** in water **(Scheme 12)**.



Scheme 12

Yum's approach (2004)[18]

Yum E. K. *et al*. synthesized the various 2-substituted indoles **4** by heteroannulation of *o*-iodoacetanilide **24** with terminal alkynes **2** in one-pot by using Pd(II)-NaY zeolite catalyst **(Scheme 13)**.



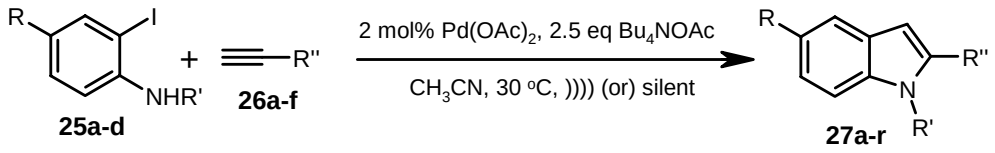
Scheme 13

Most of these reported methods suffer from some drawbacks such as harsh reaction conditions, prolonged reaction period, and cumbersome isolation procedure. Many of these methods employ moisture sensitive phosphine ligands and phosphine based palladium catalysts such as $PdCl_2(PPh_3)_2$ and also make use of copper iodide as co-catalyst. With the presence of copper(I) as a co-catalyst the Glaser type oxidative dimerization of alkynes[19] is encountered thus lowering chemoselectivity. In addition to this, the amines generally used in excess as the base have a characteristic foul smell and industrial waste containing them would require treatment for environmental purposes. Moreover, many of the phosphine ligands are sensitive to air, and they are also expensive, toxic and unrecoverable, which results in significant limitations in their use in organic synthesis.

This section describes the development of a more general, convenient and versatile *copper-, ligand-* and *amine-free* approach for the synthesis of indoles *via* palladium-catalyzed Sonogashira coupling-5-*endo-dig*-cyclization.

3.1.2 Present Work

The conditions were optimized for the one-pot synthesis of 2-substituted indoles **27** *via* palladium acetate catalyzed tandem Sonogashira coupling 5-*endo-dig*-cyclization at room temperature under ultrasonic irradiation and standard stirred conditions respectively. An efficient protocol for one-pot synthesis of 2-substituted indoles **27** *via* Sonogashira coupling 5-*endo-dig* cyclization under *ligand-*, *copper-*, and *amine-*free conditions at room temperature under ultrasonic irradiation and silent stirred conditions respectively has been developed **(Scheme 14).**



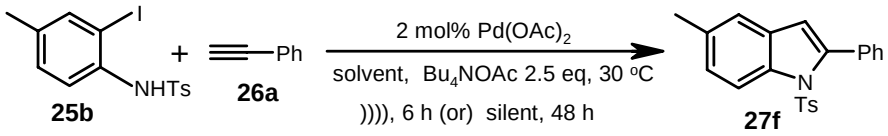
Scheme 14

The optimized reaction conditions has been applied to the synthesis of the various indole derivatives **27a-r**.

3.1.3 Results and Discussion

Palladium-catalyzed reactions are strongly dependent on a number of factors such as base, solvent, stabilizing ligand, other additives, temperature and the combined effect of these. For this purpose, we systematically evaluated the role of base and solvent for this synthetic protocol by subjecting 2-iodo-4-methyl-N-tosylbenzenamine **25b** to the tandem coupling–cyclization process. The results are summarized in Tables **1** and **2**, respectively.

Table 1. **Effect of base on Sonogashira coupling-5-*endo-dig*-cyclization reaction.**



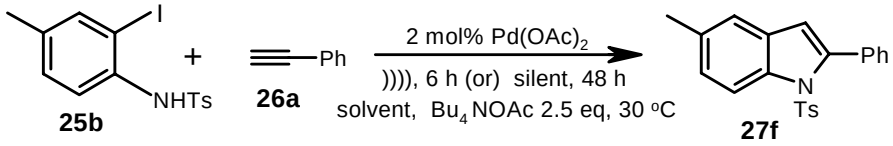
Entry	Base	Yield (%)[a]	
		Ultrasonic irradiation	Silent conditions
1	Diisopropyl amine	7	6
2	DABCO	44	25
3	Et_3N	23	26
4	NaOAc	4	5
5	Cs_2CO_3	10	9
6	K_2CO_3	13	12
7	K_3PO_4	11	9
8	Piperidine	0	0
9	Potassium-*tert*-butoxide	0	0
10	Bu_4NBr	0	0
11	Bu_4NOH (in Methanol 0.1 N)	0	0
12	Bu_4NF (in water 75% solution)	23	15
13	Bu_4NF (in THF 1M solution)	39	68
14	Bu_4NOAc	74	71

[a] isolated yields

Bu_4NOAc was found to be the most effective base (entry 14, Table **1**). Other bases (entries 1–7, Table **1**) were substantially less effective. Potassium-*tert*-butoxide and piperidine failed to promote the reaction. Tetrabutylammonium salts are known to facilitate the reduction of $Pd(OAc)_2$ to catalytically active Pd(0) species.[20] Recently Verkade and Urgaonkar reported the Bu_4NOAc promoted Sonogashira reaction.[21] We investigated the effect of counter anions (entries 10–14, Table **1**) of the tetrabutylammonium salts. It was found that acetate and fluoride (entry 13 and 14, Table **1**) promote this coupling–cyclization reaction whereas, bromide and hydroxide (entry 10 and 11, Table **1**) did not promote the reaction. Even though Bu_4NF (in THF 1 M solution) gave an appreciable yield nearly comparable to that with Bu_4NOAc under standard stirred conditions, surprisingly, the yield was low under ultrasonic irradiation.

Next, the above benchmark reaction using Bu_4NOAc as the base was examined in various solvents. As is evident, from Table **2** acetonitrile was found to be the most suitable solvent. These tests showed that the optimal reaction conditions for synthesizing 2-substituted indoles required 2 mol% of $Pd(OAc)_2$, 2.5 equiv of Bu_4NOAc and acetonitrile as the solvent.

Table 2. Effect of solvent on Sonogashira coupling-5-*endo-dig*-cyclization reaction.



Entry	Solvent	Yield (%)[a]	
		Ultrasonic irradiation	Silent conditions
1	DMF	50	32
2	NMP	0	0
3	DMA	5	14
4	THF	44	26
5	CH_3CN	74	71
6	CH_3CN	74[b]	71[c]
7	Acetone	50	49

[a] isolated yields. [b] yield after 5 h. [c] yield after 30 h.

The reaction time was optimized for the benchmark reaction under both ultrasonic irradiation and standard stirred conditions. The isolated yields at various time intervals are given in Table **3**. It can be observed for the reaction employing ultrasonic irradiation, the yield was found to increase up to 5 h after which there was no further conversion. Similarly, for the standard stirred conditions the isolated yield was optimized at 30 h.

Table 3. Optimization of reaction time for the benchmark reaction

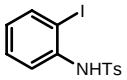
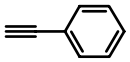
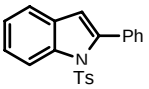
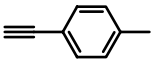
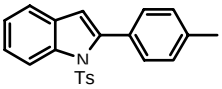
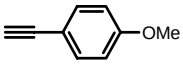
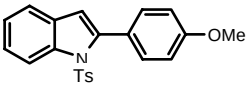
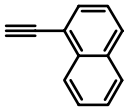
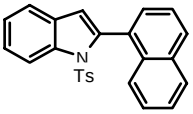
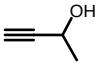
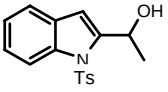
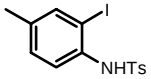
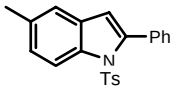
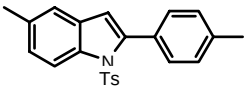
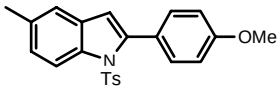
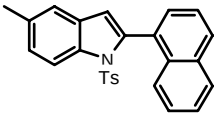
Standard stirred conditions	**Time (h)**	5	12	18	24	30	36
	Yield (%)[a]	39	48	58	64	71	71
Ultrasonic irradiation	**Time (h)**	3	4	5	6		
	Yield (%)[a]	58	65	74	74		

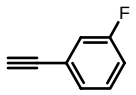
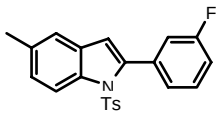
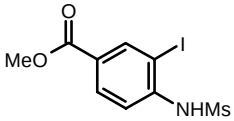
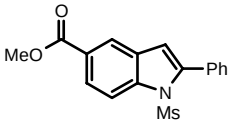
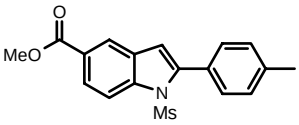
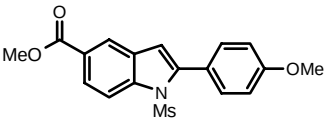
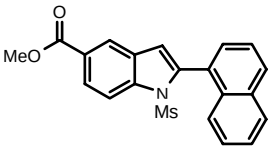
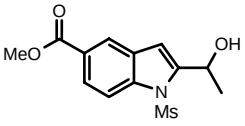
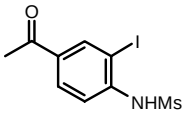
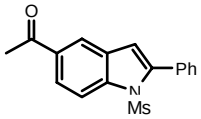
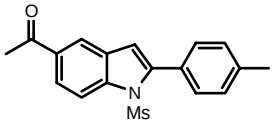
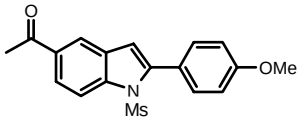
[a] Isolated yields.

For the identical time (5 h), yield for the reaction employing ultrasonic irradiation was 74% in comparison to that for the standard stirred condition, which gave only 39% yield. This clearly shows significant enhancement in the reaction rate for the reaction employing ultrasonic irradiation.

To survey the generality of this protocol the optimized reaction conditions were applied to the synthesis of various 2-substituted indole derivatives. The results are summarized in Table **4**. In all the cases, the reaction time was optimized as for the benchmark reaction. The time of reaction indicated in Table **4** is the optimized time after which no further conversion and improvement in the isolated yields were observed.

Table 4. **Synthesis of indole derivatives under silent conditions and ultrasonic irradiation[a]**

Entry	o-Iodoaniline 25	1-alkyne 26	Product 27	Ultrasonic irradiation		Silent conditions	
				Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
1	 **25a**	 **26a**	 **27a**	**4**	**82**	**24**	**80**
2	**25a**	 **26b**	 **27b**	**5**	**71**	**30**	**69**
3	**25a**	 **26c**	 **27c**	**6**	**72**	**30**	**76**
4	**25a**	 **26d**	 **27d**	**6**	**63**	**24**	**67**
5	**25a**	 **26e**	 **27e**	**6**	**44**	**24**	**41**
6	 **25b**	**26a**	 **27f**	**5**	**74**	**30**	**71**
7	**25b**	**26b**	 **27g**	**5**	**90**	**36**	**87**
8	**25b**	**26c**	 **27h**	**5**	**90**	**36**	**74**
9	**25b**	**26d**	 **27i**	**6**	**42**	**30**	**46**

10	**25b**	 **26f**	 **27j**	**6**	**65**	**36**	**56**
11	 **25c**	**26a**	 **27k**	**6**	**51**	**12**	**43**
12	**25c**	**26b**	 **27l**	**6**	**54**	**12**	**58**
13	**25c**	**26c**	 **27m**	**6**	**60**	**12**	**54**
14	**25c**	**26d**	 **27n**	**6**	**61**	**12**	**60**
15	**25c**	**26e**	 **27o**	**6**	**58**	**12**	**56**
16	 **25d**	**26a**	 **27p**	**6**	**52**	**12**	**45**
17	**25d**	**26b**	 **27q**	**6**	**65**	**12**	**71**
18	**25d**	**26c**	 **27r**	**6**	**66**	**12**	**67**

[a] Reaction conditions: 1.0 mmol 2-iodoanilide **25**, 1.1 mmol alkyne **26**, 0.02 mmol $Pd(OAc)_2$ and 2.5 mmol Bu_4NOAc with 5 ml of acetonitrile. [b] Isolated yields.

We studied the effect of different substituents on *o*-iodoanilides **25** and 1-alkynes **26**. Both the unsubstituted *o*-iodoanilides **25a** and the substituted *o*-iodoanilides **25b** having an electron-donating group on the aromatic ring moiety gave indoles in good yields. It is noteworthy that even if R (Table **4**) is an electron-withdrawing group (–COMe, $–CO_2Me$, entries 11–18, Table **4**) the reaction proceeded smoothly to afford the 2-substituted indoles **27k-r** in moderate yields. Another remarkable feature of this protocol is that the base sensitive ester group was not affected by our mild reaction conditions. Moreover, various substituted terminal alkynes reacted smoothly giving moderate to good yields.

During the course of the reaction under standard conditions as well as ultrasound conditions we did not observe any uncyclized product. However, the formation of the homocoupled product arising out of the terminal acetylene was observed to an extent of 2–8%. It should also be noted that we did not observe any reaction when 2-bromo-N-tosylbenzenamine and phenyl acetylene was subjected to this coupling–cyclization protocol under the optimized reaction conditions. Moreover, the reaction of *o*-iodoaniline with the free amino group and phenyl acetylene using the standard reaction conditions yielded only Sonogashira coupled product in 92 and 82% yield by employing the ultrasonic irradiation and standard stirred conditions, respectively. It is worth noting that the *p*-toluene sulfonyl/methane sulfonyl groups were found to be stable under the mild reaction conditions of this protocol. The corresponding N-*p*-toluene sulfonyl/methane sulfonyl indoles **27a–r** were isolated in moderate to good yields. These N-protected indole derivatives allow us the flexibility to further functionalize the indole nucleus.

Ultrasound as a non-thermal energy transfer source is well known to enhance reaction rates/yields/selectivity in organic synthesis and has found widespread application in synthetic organic chemistry.[22] Significant enhancement in rate of reaction (5–10 folds) and improved yields for the sonochemical reactions relative to the standard stirred reactions were observed (Table **4**).

3.1.4 Conclusion

In conclusion, we have developed a mild, efficient, and general one-pot synthesis of 2-substituted indoles at room temperature under ultrasonic irradiation and standard

stirred conditions in the absence of any *ligand*, *copper*, and *amine* by using $Pd(OAc)_2$ as the catalyst, Bu_4NOAc as the base in acetonitrile. Both electron-donating and electron withdrawing substituents on the aryl ring of *o*-iodoanilides were tolerated.

3.1.5 Experimental Section

General procedure for preparation of 2-substituted indoles:

To the mixture of *o*-iodoanilide **25** (1 mmol), $Pd(OAc)_2$ (2 mmol %), and Bu_4NOAc (2.5 mmol) in dry acetonitrile under argon atmosphere was added phenyl acetylene **26** (1.1 mmol). The reaction mixture was then stirred at room temperature or sonicated for the time as shown in Table **4**. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated under reduced pressure, diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue thus obtained was purified by column chromatography using ethyl acetate/petroleum benzine as eluent to afford the desired product **27**. To the best of our knowledge, N-tosyl derivative of indoles **27** have not been previously reported and hence the complete characterization data is given as follows.

Characterization data of indoles 27a-r

2-Phenyl-1-tosyl-1*H*-indole (27a).

Nature of compound; mp	**:**	Light brown solid; mp 145-147 ^oC.
IR: ($CHCl_3$) υ_{max} (cm^{-1})	**:**	3019, 2400, 1450, 1374, 1215, 669.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.20 (s, 3H), 6.47 (s, 1H), 6.96 (d, *J* = 8.13 Hz, 2H), 7.15-7.29 (m, 4H), 7.32-7.46 (m, 6H), 8.24 (d, *J* = 7.58 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.4, 113.2, 116.6, 120.5, 124.2, 124.5, 126.7, 129.1, 130.1, 130.6, 134.5, 138.1, 138.5, 142.2, 144.4.
Elemental analysis	**:**	Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.79; H, 5.15; N, 4.27.

2-*p*-Tolyl-1-tosyl-1*H*-indole (27b).

Nature of compound; mp	**:**	Light brown solid; mp 108-110 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3027, 2922, 1597, 1504, 1449, 1188, 812, 752, 571.

^{1}H NMR	**:**	2.20 (s, 3H), 2.36 (s, 3H), 6.43 (s, 1H), 6.96 (d, *J* = 8.08
($CDCl_3$, 200 MHz) δ		Hz, 2H), 7.14-7.37 (m, 9H), 8.22 (d, *J* = 8.58 Hz, 1H).
^{13}C NMR	**:**	21.4, 113.2, 116.6, 120.5, 124.2, 124.5, 126.7, 129.1,
($CDCl_3$, 50 MHz) δ		130.1, 130.6, 131.3, 134.6, 138.1, 138.5, 142.2, 144.4.
Elemental analysis	**:**	Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88.
		Found: C, 72.96; H, 5.28; N, 4.26.

2-(4-Methoxyphenyl)-1-tosyl-1*H*-indole (27c).

Nature of compound; mp	**:**	Light brown solid; mp 126-128 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1505, 1215, 668, 572.
^{1}H NMR	**:**	2.28 (s, 3H), 3.88 (s, 3H), 6.48 (s, 1H), 6.93-7.05 (m,
($CDCl_3$, 200 MHz) δ		4H), 7.24-7.34 (m, 4H), 7.40-7.44 (m, 3H), 8.30 (d, *J* =
		8.28 Hz, 1H).
^{13}C NMR	**:**	21.4, 55.2, 112.7, 112.9, 116.5, 120.4, 122.3, 124.1,
($CDCl_3$, 50 MHz) δ		126.6, 127.4, 129.1, 129.5, 131.6, 134.9, 135.9, 137.5,
		139.1, 144.1, 144.4, 160.0.
Elemental analysis	**:**	Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N, 3.71.
		Found: C, 69.54; H, 4.72; N, 3.81.

2-(Naphthalen-1-yl)-1-tosyl-1*H*-indole (27d).

Nature of compound; mp	**:**	Light brown solid; mp 132-134 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1598, 1449, 1373, 667, 569.
^{1}H NMR	**:**	2.24 (s, 3H), 6.65 (s, 1H), 6.94 (d, *J* = 8.06 Hz, 2H),
($CDCl_3$, 200 MHz) δ		7.24-7.34 (m, 5H), 7.39-7.54 (m, 4H), 7.64 (d, *J* = 8.79
		Hz, 1H), 7.91 (dd, *J* = 13.19, 8.06 Hz, 2H), 8.39 (d, *J* =
		8.79 Hz, 1H).
^{13}C NMR	**:**	21.4, 113.6, 115.7, 120.7, 123.9, 124.4, 124.7, 125.7,
($CDCl_3$, 50 MHz) δ		126.0, 126.2, 126.8, 127.9, 129.1, 129.4, 129.9, 132.9,
		133.3, 135.2, 137.5, 138.7, 144.5.
Elemental analysis	**:**	Anal. Calcd for $C_{25}H_{19}NO_2S$: C, 75.54; H, 4.82; N, 3.52.
		Found: C, 75.64; H, 4.52; N, 3.20.

1-(1-Tosyl-1*H*-indol-2-yl) ethanol (27e).

Nature of compound; mp	**:**	Light brown solid; mp 136-137 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3551, 3018, 2985, 2401, 1597, 1451, 1215, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.67 (d, *J* = 6.57 Hz, 3H), 2.33 (s, 3H), 3.48 (br s, 1H), 5.35 (q, *J* = 6.57 Hz, 1H), 6.68 (s, 1H), 7.16-7.33 (m, 4H), 7.45-7.50 (m, 1H), 7.66 (dt, *J* = 8.33, 1.76 Hz, 2H), 8.09 (d, *J* = 8.08 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.4, 21.5, 62.6, 108.8, 114.7, 121.1, 123.8, 124.9, 126.3, 127.4, 129.1, 129.9, 135.6, 137.2, 144.8, 145.0.
Elemental analysis	**:**	Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.62; H, 5.32; N, 4.34.

5-Methyl-2-phenyl-1-tosyl-1*H*-indole (27f).

Nature of compound; mp	**:**	Light brown solid; mp 113-114 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1598, 1372, 1215, 668, 588.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.19 (s, 3H), 2.33 (s, 3H), 6.39 (s, 1H), 6.94 (d, *J* = 8.31 Hz, 2H), 7.06-7.21 (m, 4H), 7.32-7.45 (m, 5H), 8.09 (d, *J* = 8.52 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.2, 21.5, 113.5, 116.4, 120.6, 126.1, 126.7, 127.4, 129.1, 130.2, 131.4, 133.9, 134.6, 136.5, 142.2, 144.4.
Elemental analysis	**:**	Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.97; H, 5.21; N, 4.27.

5-Methyl-2-*p*-tolyl-1-tosyl-1*H*-indole (27g).

Nature of compound; mp	**:**	Light brown solid; mp 145–147 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3025, 2921, 1597, 1371, 1174, 811, 573.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.20 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 6.36 (s, 1H), 6.96 (d, *J* = 8.00 Hz, 1H), 7.05-7.23 (m, 7H), 7.33 (dt, *J* = 8.21, 1.91 Hz, 2H), 8.08 (d, *J* = 8.45 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.2, 21.4, 21.5, 113.2, 116.4, 120.5, 125.9, 126.8, 128.2, 129.1, 129.6, 130.1, 130.9, 133.8, 134.6, 138.5, 144.3.

Elemental analysis	**:**	Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.85; H, 5.75; N, 3.92.

2-(4-Methoxyphenyl)-5-methyl-1-tosyl-1*H*-indole (27h).

Nature of compound; mp	**:**	Light brown solid; mp 138–139 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3028, 2924, 1611, 1506, 1371, 1175, 575.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.28 (s, 3H), 2.40 (s, 3H), 3.88 (s, 3H), 6.41 (s, 1H), 6.92-7.05 (m, 4H), 7.12-7.27 (m, 4H), 7.42 (dt, *J* = 8.83, 2.14 Hz, 2H), 8.16 (d, *J* = 8.44 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.2, 21.4, 55.2, 112.7, 112.9, 116.3, 120.4, 122.8, 124.8, 125.8, 126.7, 129.1, 131.5, 133.8, 134.6, 136.3, 139.2, 142.1, 144.3, 159.9.
Elemental analysis	**:**	Anal. Calcd for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.26; H, 5.35; N, 3.81.

5-Methyl-2-(naphthalen-1-yl)-1-tosyl-1*H*-indole (27i).

Nature of compound; mp	**:**	Light brown solid; mp 159–161 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 2924, 1597, 1365, 1172, 592.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.25 (s, 3H), 2.46 (s, 3H), 6.58 (s, 1H), 6.95 (d, *J* = 7.95 Hz, 2H), 7.21-7.36 (m, 5H), 7.41-7.55 (m, 3H), 7.66 (d, *J* = 8.34 Hz, 1H), 7.85–7.96 (m, 2H), 8.26 (d, *J* = 8.46 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.2, 21.3, 113.6, 115.5, 120.6, 124.4, 125.6, 126.1, 126.8, 127.4, 127.9, 129.1, 129.2, 129.4, 129.5, 129.9, 130.2, 130.3, 133.0, 133.3, 133.5, 135.2, 135.7, 138.8, 144.4.
Elemental analysis	**:**	Anal. Calcd for $C_{26}H_{21}NO_2S$: C, 75.89; H, 5.14; N, 3.40. Found: C, 75.59; H, 5.03; N, 3.39.

2-(3-Fluorophenyl)-5-methyl-1-tosyl-1*H*-indole (27j).

Nature of compound; mp	**:**	Yellow oil.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	2925, 2856, 1615, 1373, 757, 588.

^{1}H NMR (CDCl$_3$, 200 MHz) δ	**:**	2.21 (s, 3H), 2.33 (s, 3H), 6.42 (s, 1H), 6.95–7.33 (m, 10H), 8.09 (d, *J* = 8.33 Hz, 1H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	**:**	21.2, 21.4, 114.2, 116.3, 116.7, 120.8, 126.1, 126.5, 126.7, 129.1, 130.6, 134.1, 136.6, 140.7, 144.6, 159.4, 164.3.
Elemental analysis	**:**	Anal. Calcd for $C_{22}H_{18}FNO_2S$: C, 69.64; H, 4.78; F, 5.01; N, 3.69. Found: C, 69.54; H, 4.72; F, 4.98; N, 3.81.

1-Methanesulfonyl-2-phenyl-1*H*-indole-5-carboxylic acid methyl ester (27k).

Nature of compound; mp	**:**	Colorless solid; mp 131– 132 ^{o}C.
IR: (CHCl$_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1717, 1375, 1216, 669.
^{1}H NMR (CDCl$_3$, 200 MHz) δ	**:**	2.82 (s, 3H), 3.96 (s, 3H), 6.76 (s, 1H), 7.43-7.46 (m, 2H), 7.54-7.59 (m, 2H), 8.03-8.20 (m, 2H), 8.32 (d, *J* = 1.75 Hz, 1H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	**:**	40.4, 52.2, 112.6, 115.3, 123.1, 126.1, 127.8, 130.3, 131.4, 140.3, 142.9, 167.1.
Elemental analysis	**:**	Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 62.31; H, 4.65; N, 4.47.

1-Methanesulfonyl-2-*p*-tolyl-1*H*-indole-5-carboxylic acid methyl ester (27l).

Nature of compound; mp	**:**	Colorless solid; mp 146– 147 ^{o}C.
IR: (CHCl$_3$)υ_{max} (cm^{-1})	**:**	3011, 2400, 1716, 1215, 669.
^{1}H NMR (CDCl$_3$, 200 MHz) δ	**:**	2.48 (s, 3H), 2.86 (s, 3H), 4.01 (s, 3H), 6.77 (s, 1H), 7.30 (d, *J* = 7.92 Hz, 2H), 7.50 (d, *J* = 8.08 Hz, 2H), 8.10 (dd, *J* = 7.27, 1.61 Hz, 1H), 8.22 (d, *J* = 8.88 Hz, 1H), 8.36 (d, *J* = 1.29 Hz, 1H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	**:**	21.4, 40.4, 52.1, 112.4, 115.3, 122.9, 125.9, 128.5, 130.2, 139.3, 143.1, 167.1.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.64; H, 4.88; N, 4.36.

1-Methanesulfonyl-2-(4-methoxyphenyl)-1*H*-indole-5-carboxylic acid methyl ester (27m).

Nature of compound; mp	**:**	Colorless solid; mp 144–146 ^{0}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1716, 1290, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.74 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 6.64 (s, 1H), 6.91 (d, *J* = 8.73 Hz, 2H), 7.43 (d, *J* = 8.83 Hz, 2H), 7.98 (dd, *J* = 7.19, 1.64 Hz, 1H), 8.11 (d, *J* = 8.73 Hz, 1H), 8.24 (d, *J* = 1.19 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	40.4, 52.1, 55.3, 112.1, 113.3, 115.3, 118.9, 122.8, 123.4, 125.8, 129.8, 131.6, 140.2, 142.8, 160.3, 167.1.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{17}NO_5S$: C, 60.15; H, 4.77; N, 3.90. Found: C, 59.70; H, 4.59; N, 4.30.

1-Methanesulfonyl-2-(naphthalen-1-yl)-1*H*-indole- 5-carboxylic acid methyl ester (27n).

Nature of compound; mp	**:**	Colorless solid; mp 144–146 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 2400, 1715, 1375, 1215, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.91 (s, 3H), 3.98 (s, 3H), 6.86 (s, 1H), 7.45-7.61 (m, 4H), 7.71 (d, *J* = 8.97 Hz, 1H), 7.90-7.99 (m, 2H), 8.09-8.22 (m, 2H), 8.39 (d, *J* = 1.65 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	41.1, 52.2, 112.9, 114.5, 123.2, 124.7, 125.5, 126.1, 126.2, 126.7, 128.4, 128.8, 129.2, 129.5, 129.9, 133.1, 133.3, 139.5, 139.9, 167.1.
Elemental analysis	**:**	Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.87; H, 4.71; N, 3.94.

1-Methanesulfonyl-2-(1-hydroxyethyl)-1*H*-indole-5-carboxylic acid methyl ester (27o).

Nature of compound; mp	**:**	Colorless solid; mp 132– 133 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3326, 3019, 2930, 2400, 1716, 1215, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.72 (d, *J* = 6.57, 3H), 3.24 (s, 3H), 3.95 (s, 3H), 5.39 (q, *J* = 6.44 Hz, 1H), 6.78 (s, 1H), 8.03-8.05 (m, 2H),

		8.28 (d, *J* = 1.39 Hz, 1H).
^{13}C NMR	**:**	21.6, 41.3, 52.1, 62.1, 108.1, 113.7, 123.4, 126.2, 128.5,
($CDCl_3$, 50 MHz) δ		131.1, 139.5, 145.4, 167.0.
Elemental analysis	**:**	Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71.
		Found: C, 52.56; H, 4.64; N, 4.44.

1-(1-Methanesulfonyl-2-phenyl-1*H*-indol-5-yl)-ethanone (27p).

Nature of compound; mp	**:**	Colorless solid; mp 170–171 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2919, 2400, 1681, 1374, 1215, 668.
^{1}H NMR	**:**	2.69 (s, 3H), 2.83 (s, 3H), 6.77 (s, 1H), 7.44-7.47 (m,
($CDCl_3$, 200 MHz) δ		3H), 7.56 (dd, *J* = 7.57, 2.24 Hz, 2H), 8.00 (dd, *J* =
		7.41, 1.40 Hz, 1H), 8.19 (d, *J* = 8.87 Hz, 1H), 8.23 (s,
		1H).
^{13}C NMR	**:**	26.7, 40.6, 112.7, 115.4, 121.8, 125.1, 127.8, 129.2,
($CDCl_3$, 50 MHz) δ		130.3, 133.8, 140.3, 143.1, 197.5.
Elemental analysis	**:**	Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47.
		Found: C, 65.15; H, 4.42; N, 4.52.

1-(1-Methanesulfonyl-2-*p*-tolyl-1*H*-indol-5-yl)-ethanone (27q).

Nature of compound; mp	**:**	Colorless solid; mp 138–139 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2400, 1678, 1375, 1216, 668.
^{1}H NMR	**:**	2.35 (s, 3H), 2.61 (s, 3H), 2.75 (s, 3H), 6.67 (s, 1H),
($CDCl_3$, 200 MHz) δ		7.18 (d, *J* = 7.75 Hz, 2H), 7.38 (d, *J* = 8.17 Hz, 2H),
		7.91 (dd, *J* = 7.02, 1.70 Hz, 1H), 8.12 (d, *J* = 9.56 Hz,
		2H).
^{13}C NMR	**:**	21.3, 26.6, 40.4, 112.4, 115.3, 121.7, 124.8, 128.2,
($CDCl_3$, 50 MHz) δ		128.4, 130.1, 133.5, 139.2, 140.2, 143.1, 197.6.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28.
		Found: C, 65.89; H, 4.93; N, 4.52.

1-(1-Methanesulfonyl-2-(4-methoxyphenyl)-1*H*-indol-5-yl)-ethanone (27r).

Nature of compound; mp	**:**	Colorless solid; mp 187–189 ^oC.

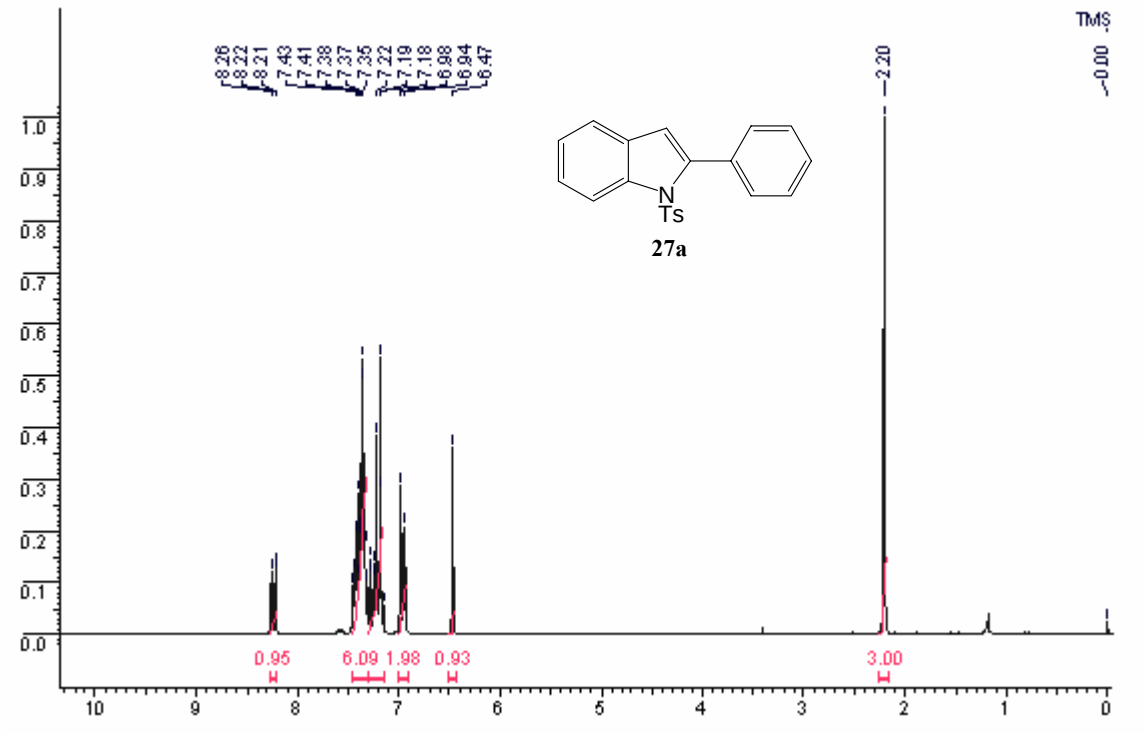
IR: ($CHCl_3$) υ_{max} (cm^{-1})	**:**	3019, 2400, 1677, 1216, 758, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.69 (s, 3H), 2.81 (s, 3H), 3.87 (s, 3H), 6.72 (s, 1H), 6.97 (dt, *J* = 8.87, 2.19 Hz, 2H), 7.49 (d, *J* = 8.87, 2.19 Hz, 2H), 7.98 (dd, *J* = 6.97, 1.74 Hz, 1H), 8.18 (d, *J* = 8.71 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	26.7, 40.4, 55.2, 112.2, 113.3, 115.5, 121.6, 123.4, 124.8, 129.9, 131.6, 140.3, 143.1, 160.4, 197.6.
Elemental analysis	**:**	Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.91; H, 4.91; N, 4.48.

3.1.6 Spectra

Table 5. ^{1}H and ^{13}C spectra of some representative indole derivatives

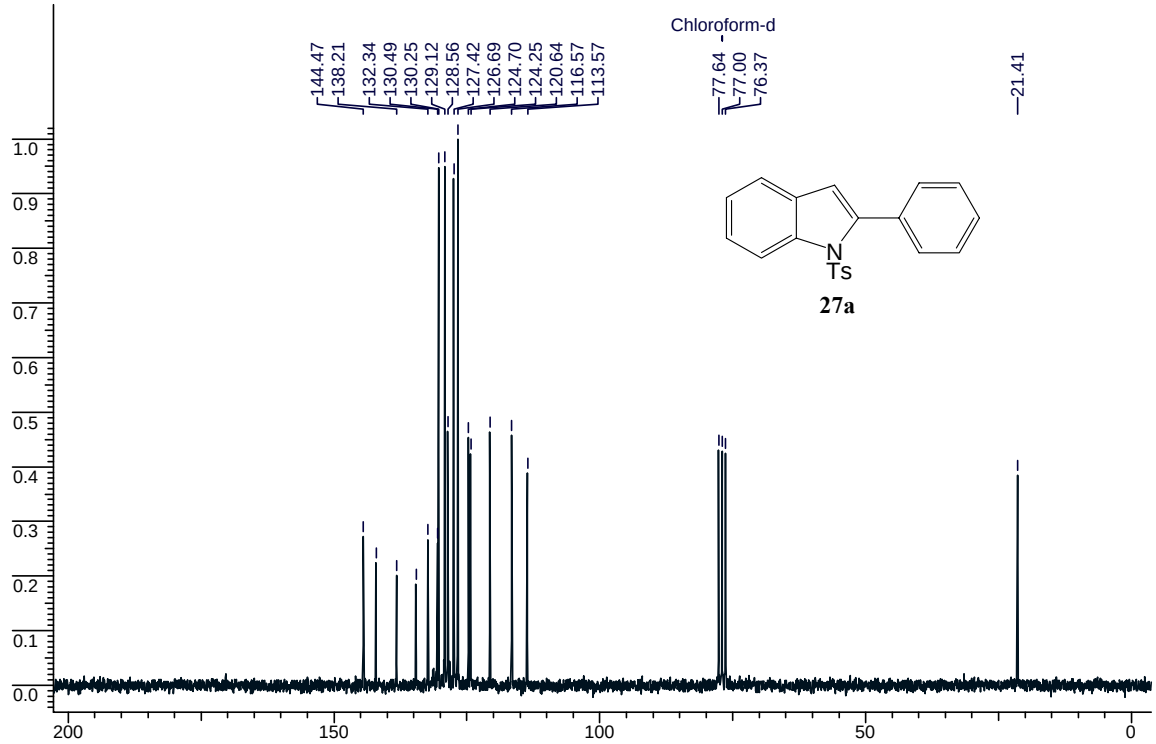
Sr. No.	Spectra
1	^{1}H and ^{13}C spectra of **27a**
2	^{1}H and ^{13}C spectra of **27c**
3	^{1}H and ^{13}C spectra of **27e**
4	^{1}H and ^{13}C spectra of **27f**
5	^{1}H and ^{13}C spectra of **27h**
6	^{1}H and ^{13}C spectra of **27i**
7	^{1}H and ^{13}C spectra of **27k**
8	^{1}H and ^{13}C spectra of **27l**
9	^{1}H and ^{13}C spectra of **27m**
10	^{1}H and ^{13}C spectra of **27n**
11	^{1}H and ^{13}C spectra of **27p**
12	^{1}H and ^{13}C spectra of **27r**

^{1}H NMR of **27a**



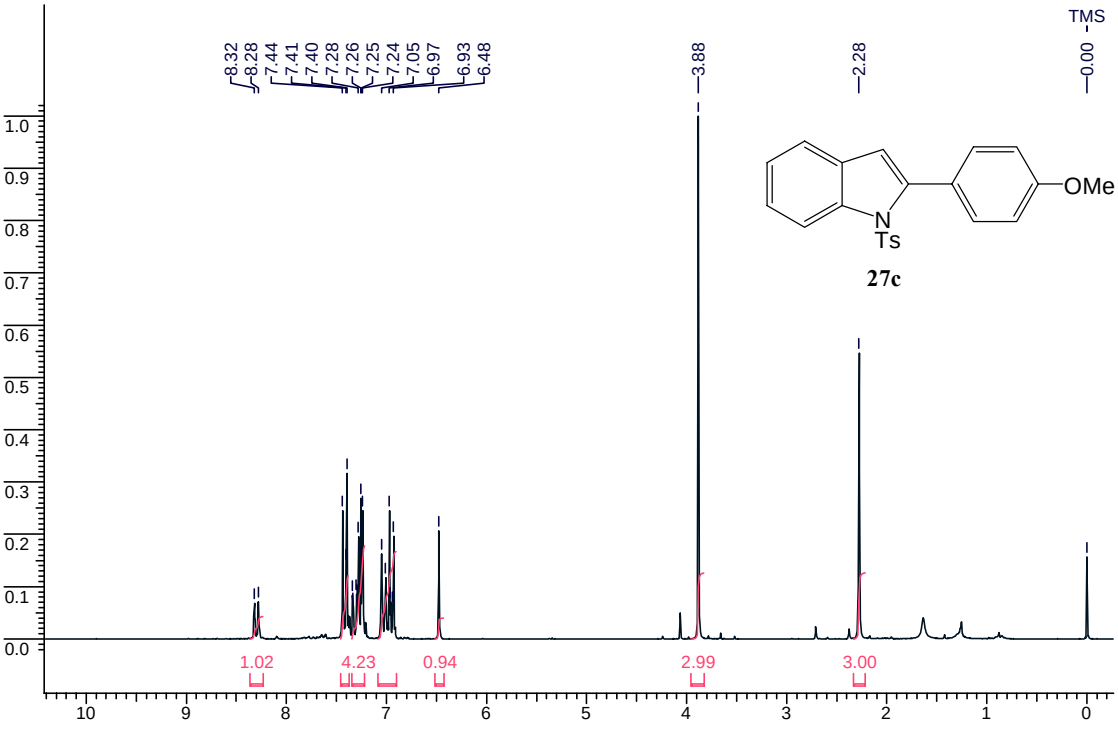
27a

^{13}C NMR of **27a**

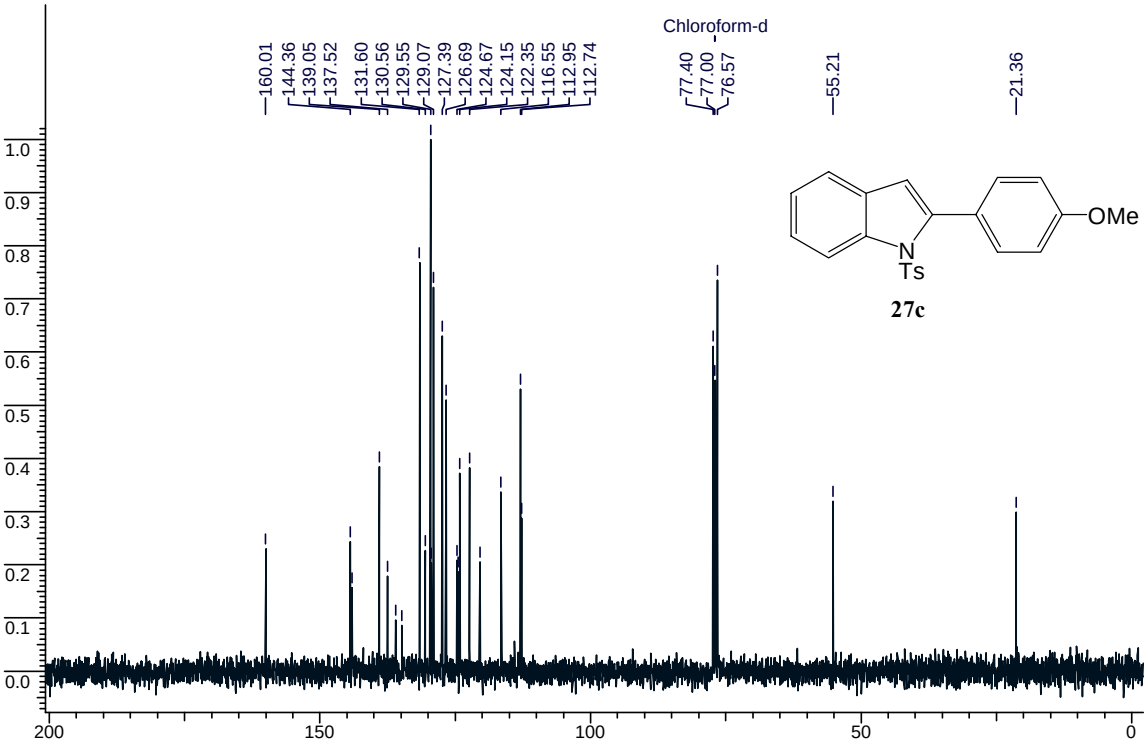


27a

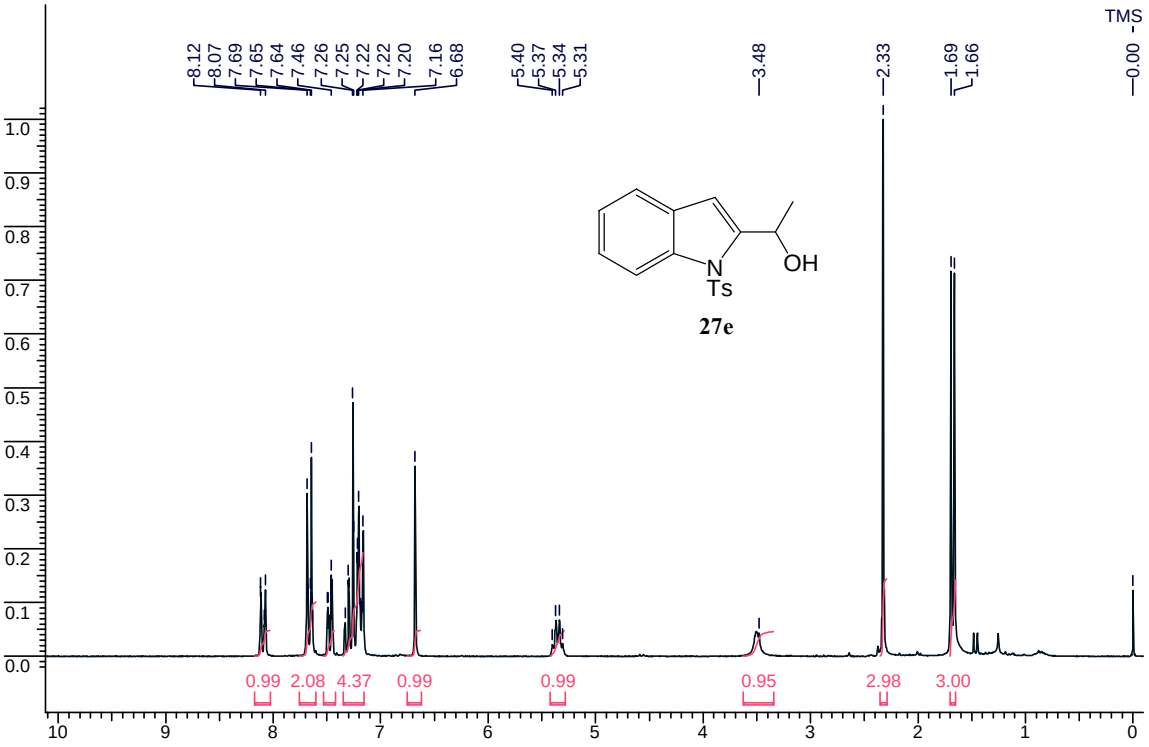
^{1}H NMR of **27c**



^{13}C NMR of **27c**

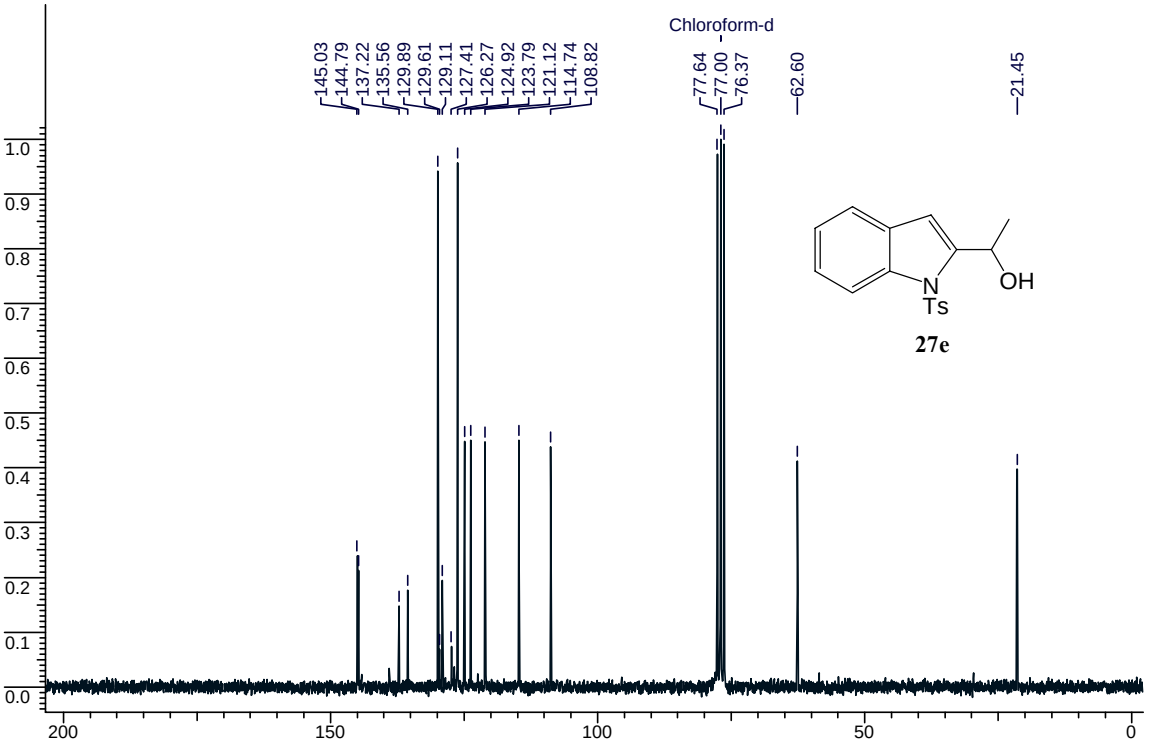


^{1}H NMR of **27e**



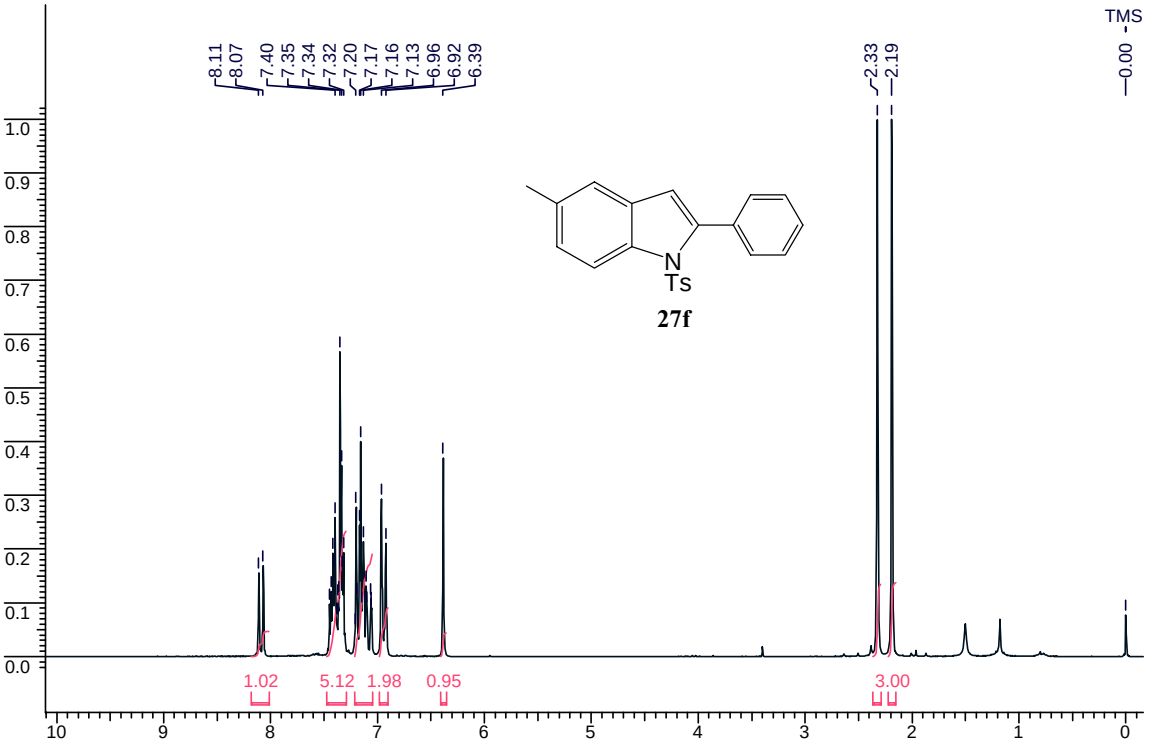
27e

^{13}C NMR of **27e**

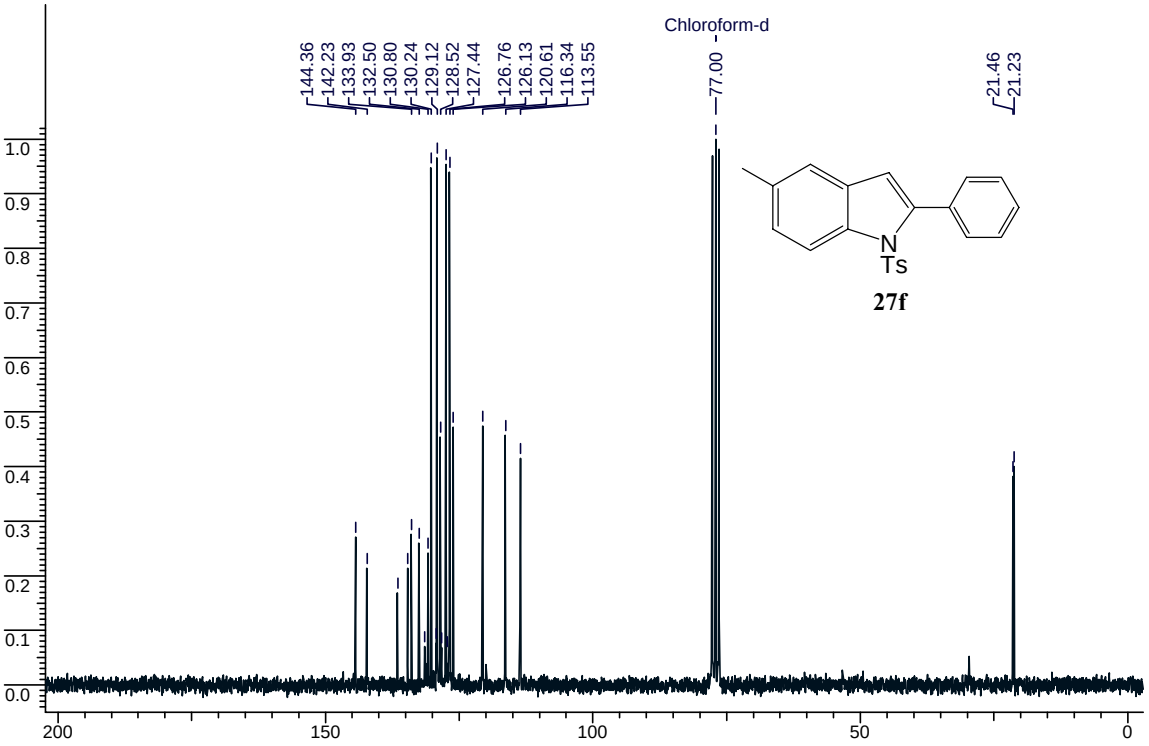


27e

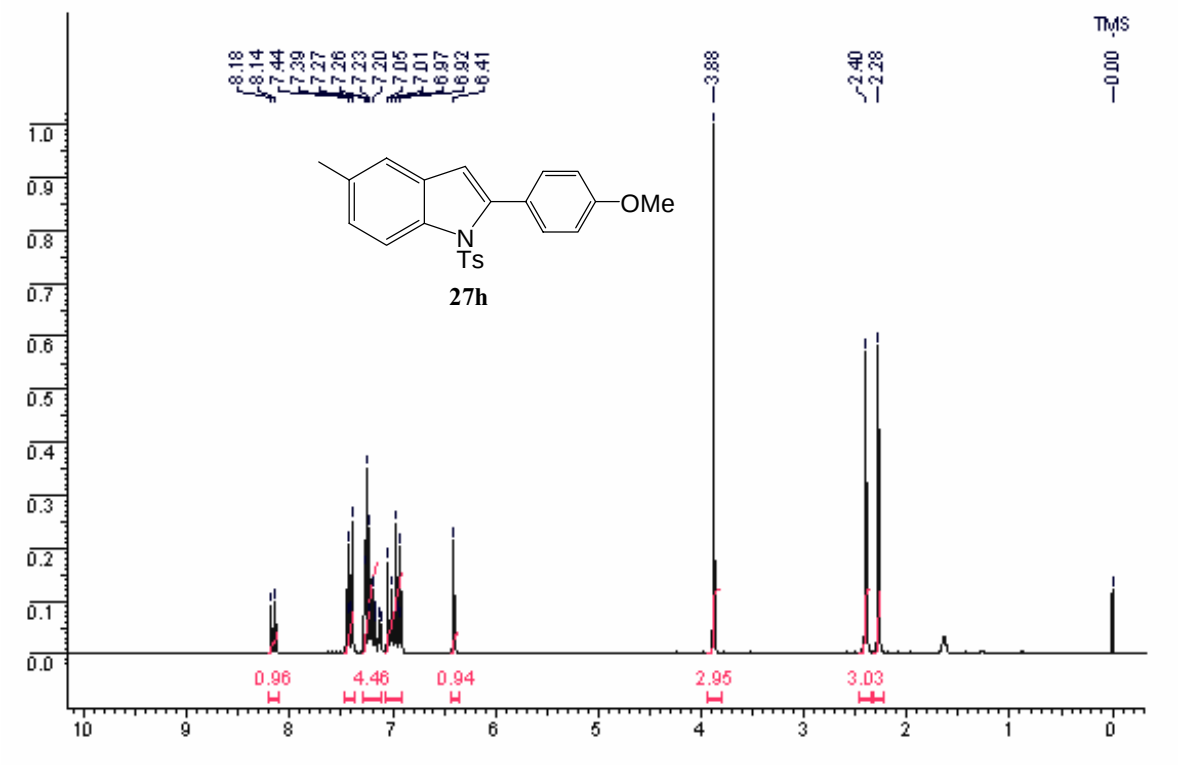
^{1}H NMR of **27f**



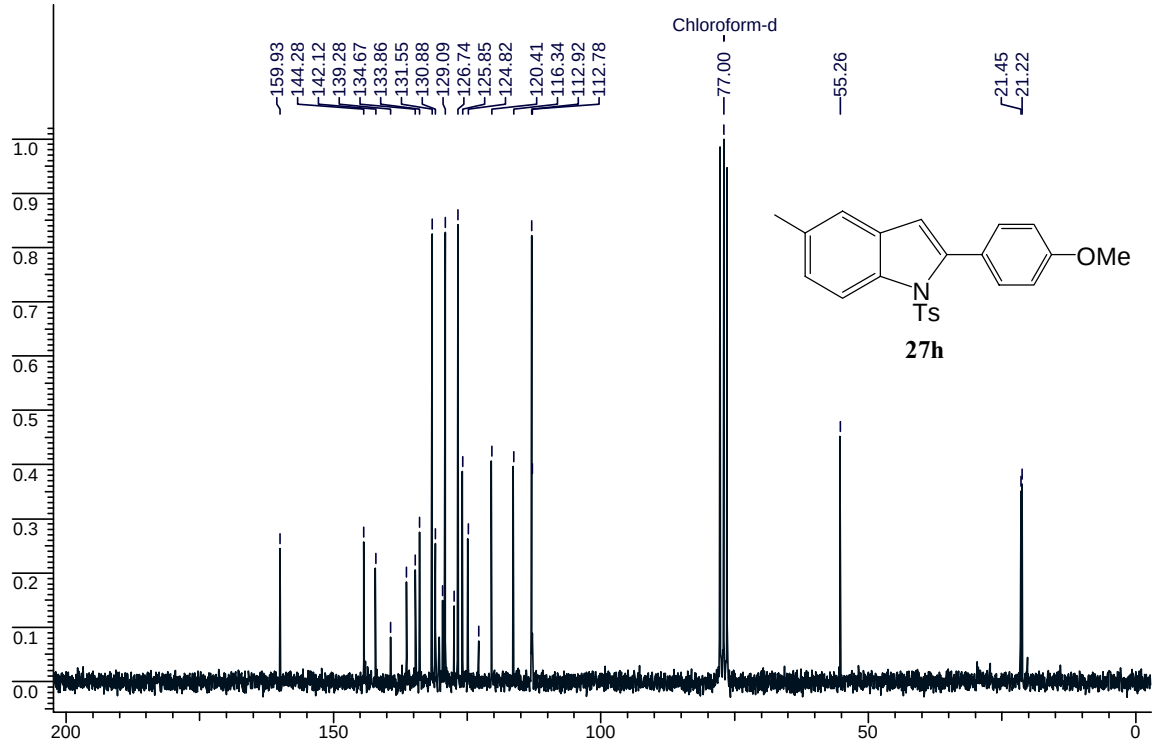
^{13}C NMR of **27f**



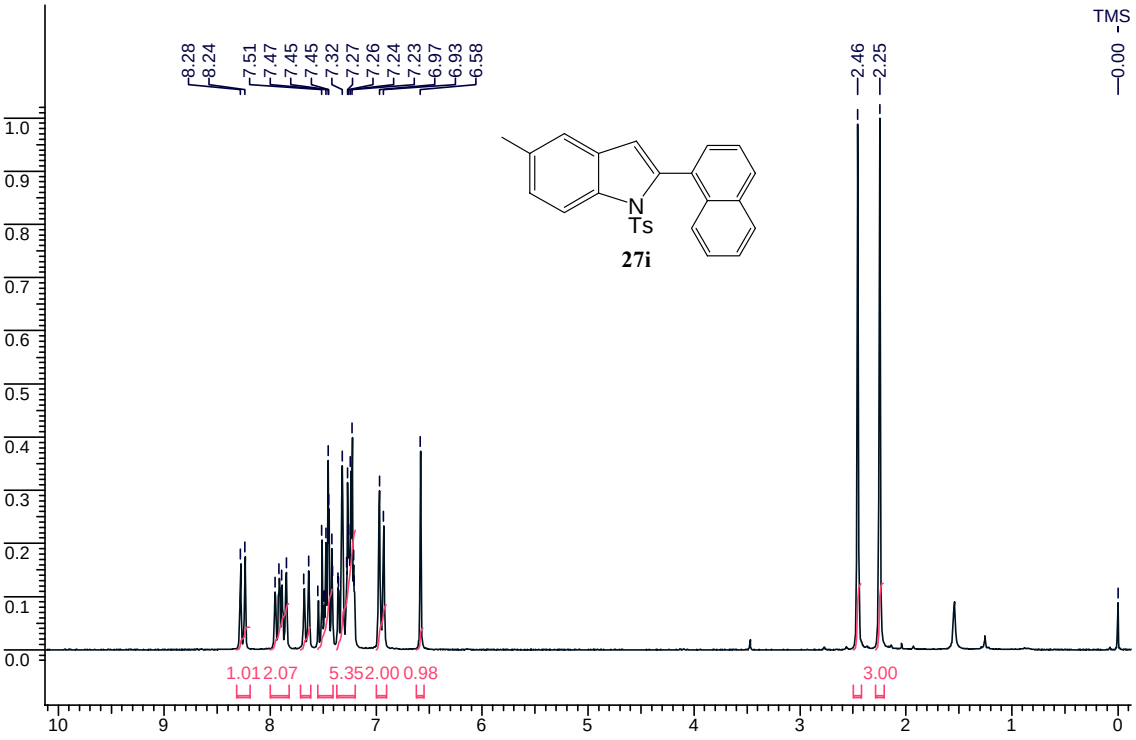
^{1}H NMR of **27h**



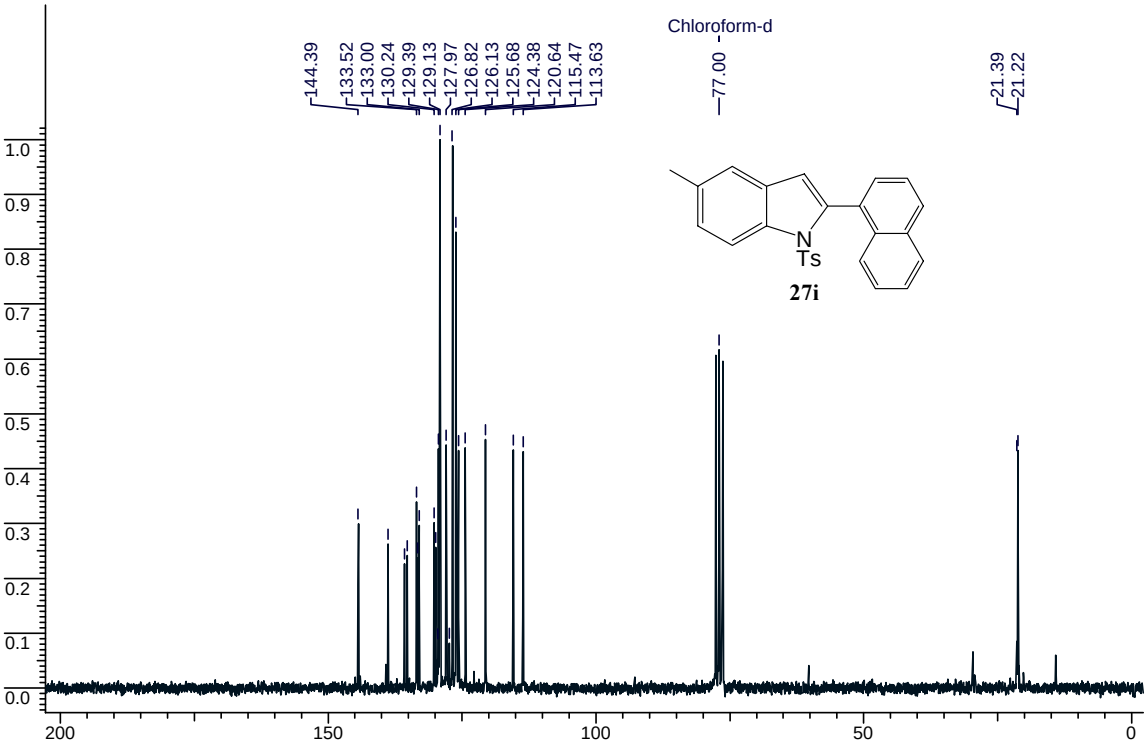
^{13}C NMR of **27h**



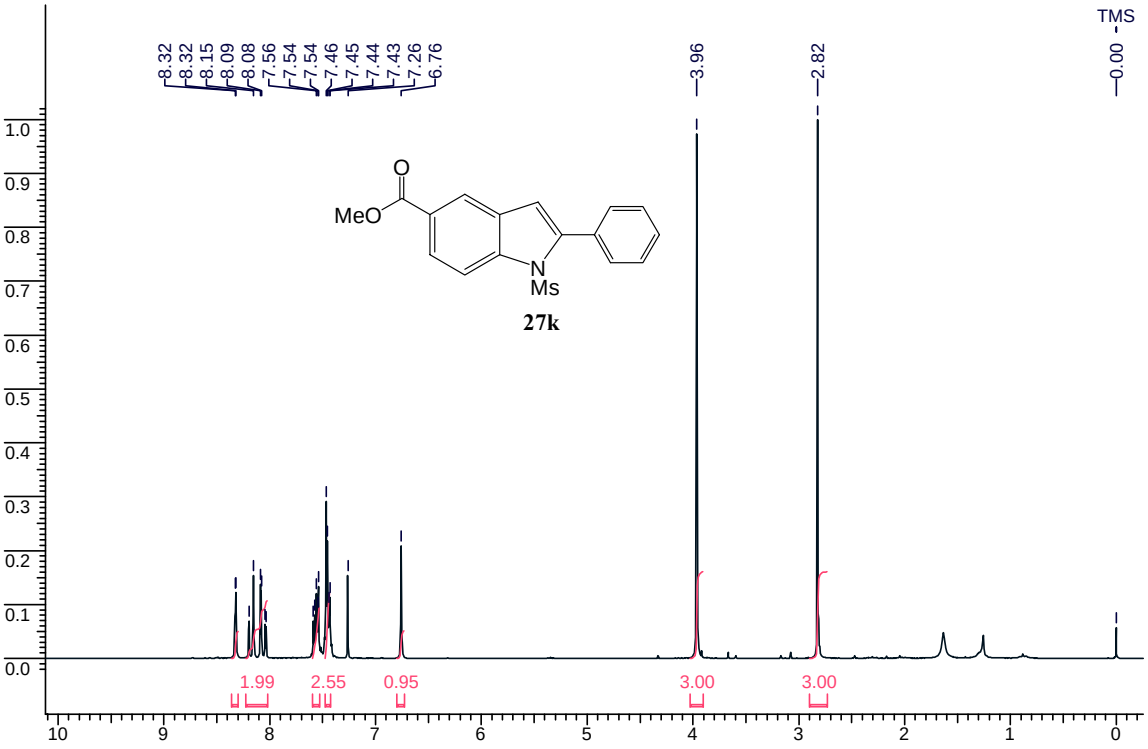
^{1}H NMR of **27i**



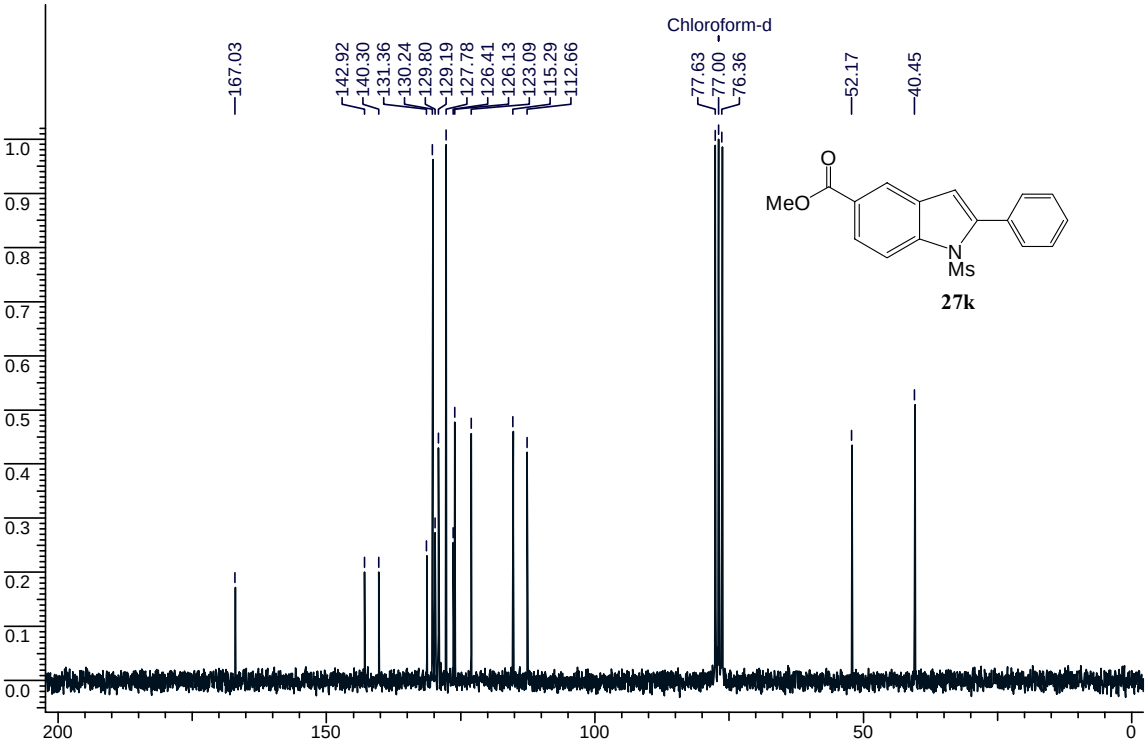
^{13}C NMR of **27i**



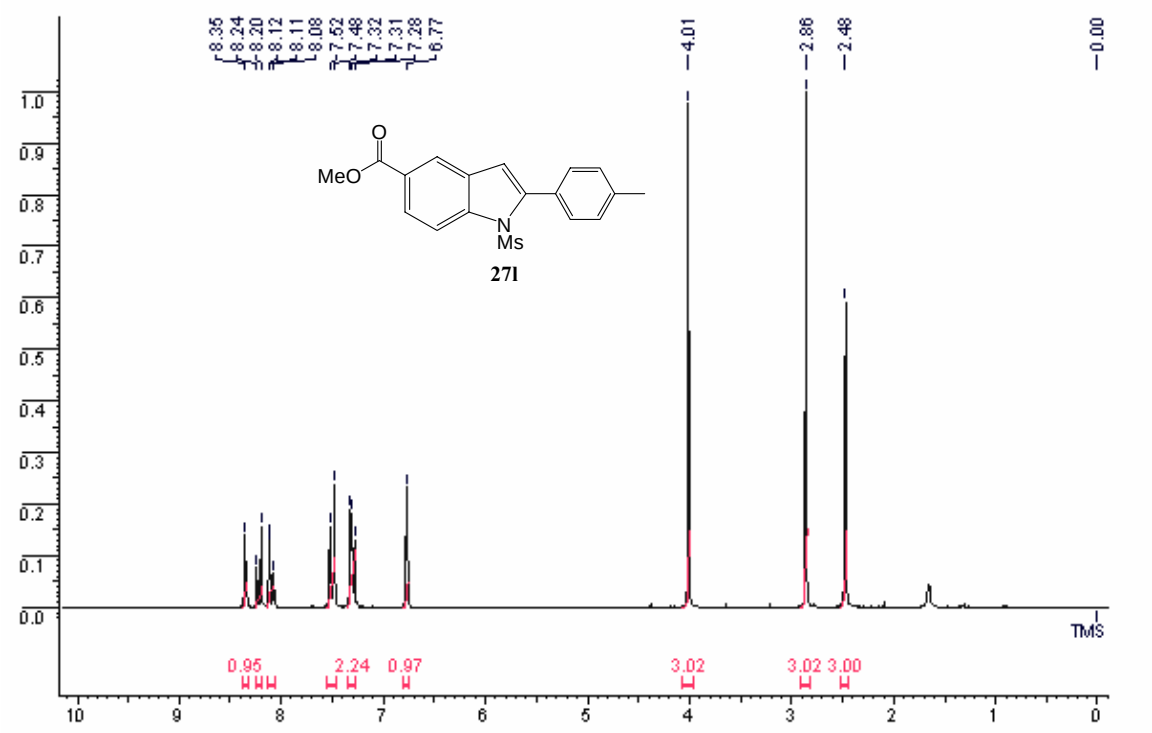
^{1}H NMR of **27k**



^{13}C NMR of **27k**

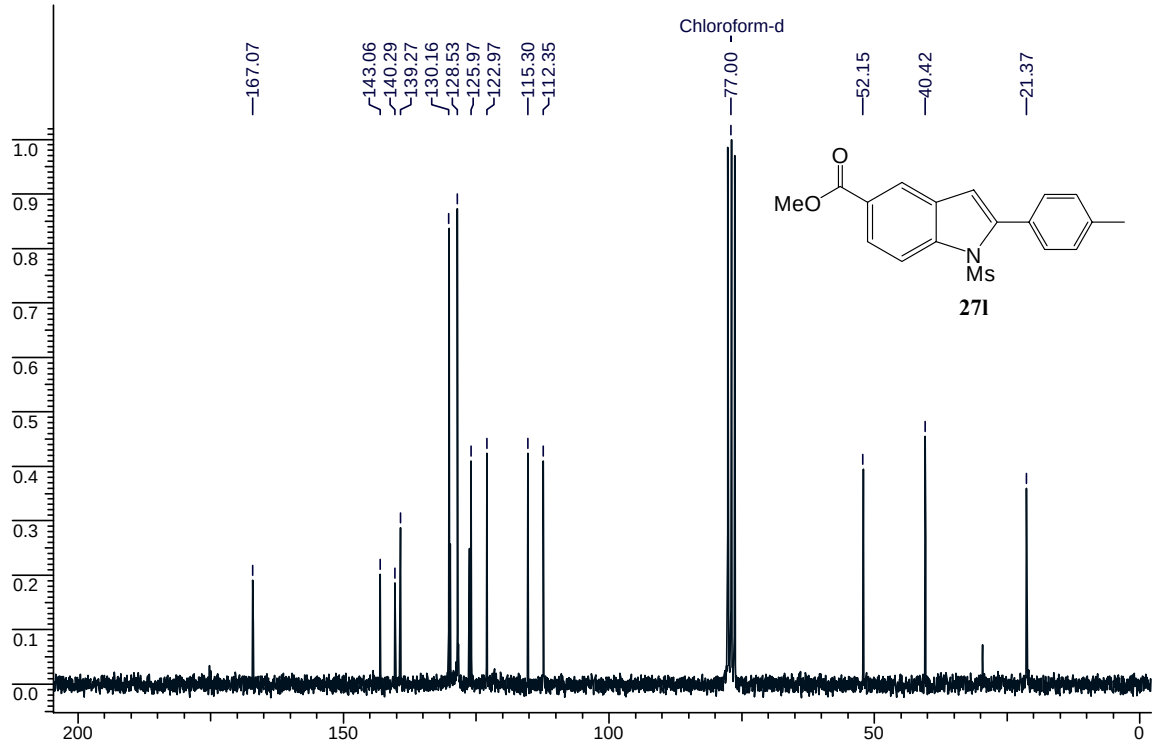


^{1}H NMR of **27l**



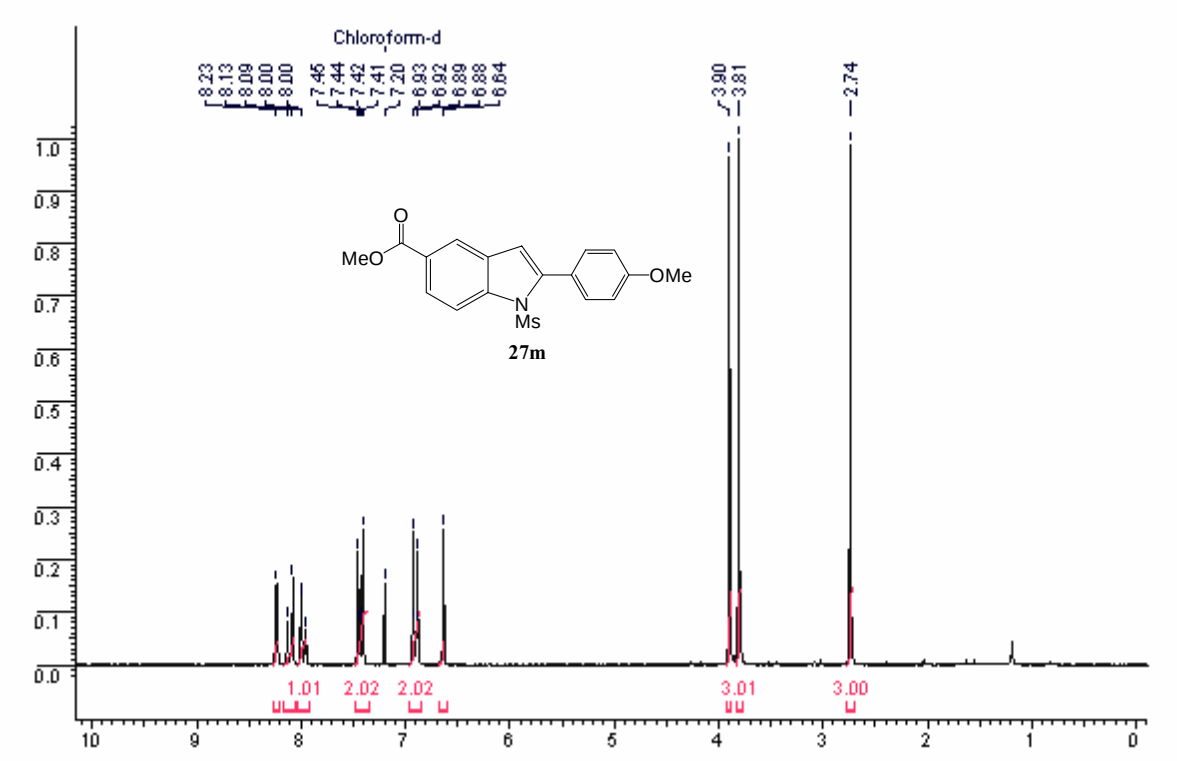
27l

^{13}C NMR of **27l**

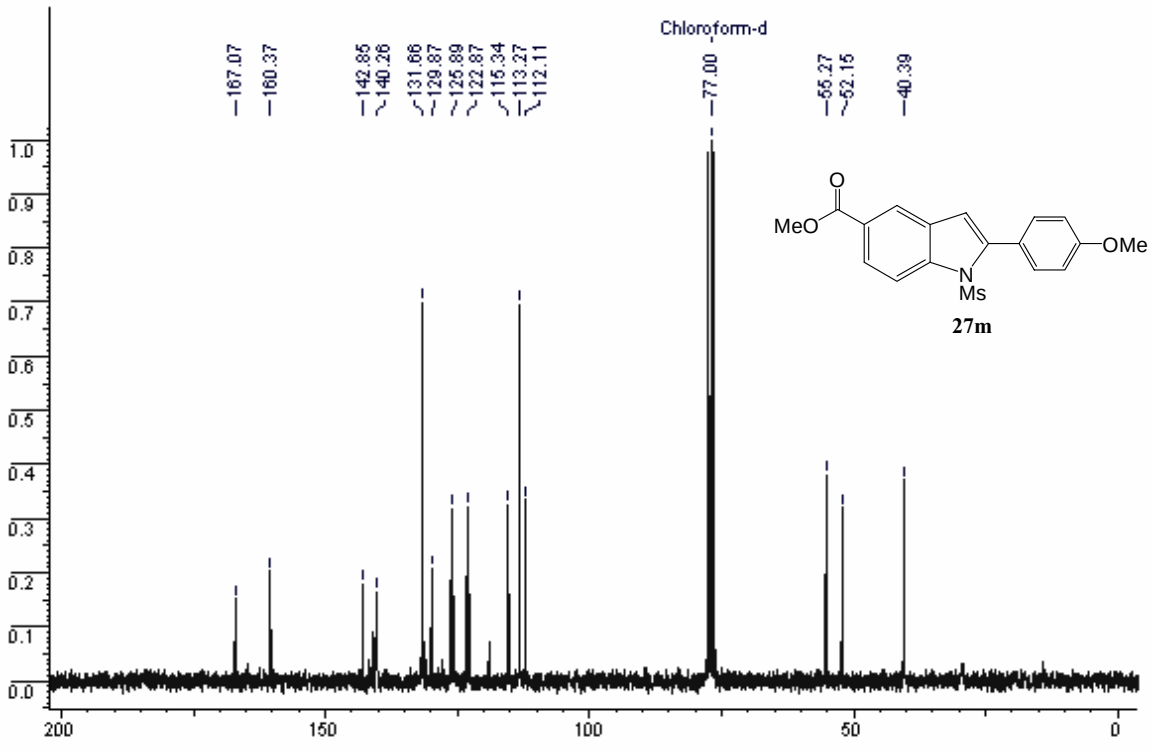


27l

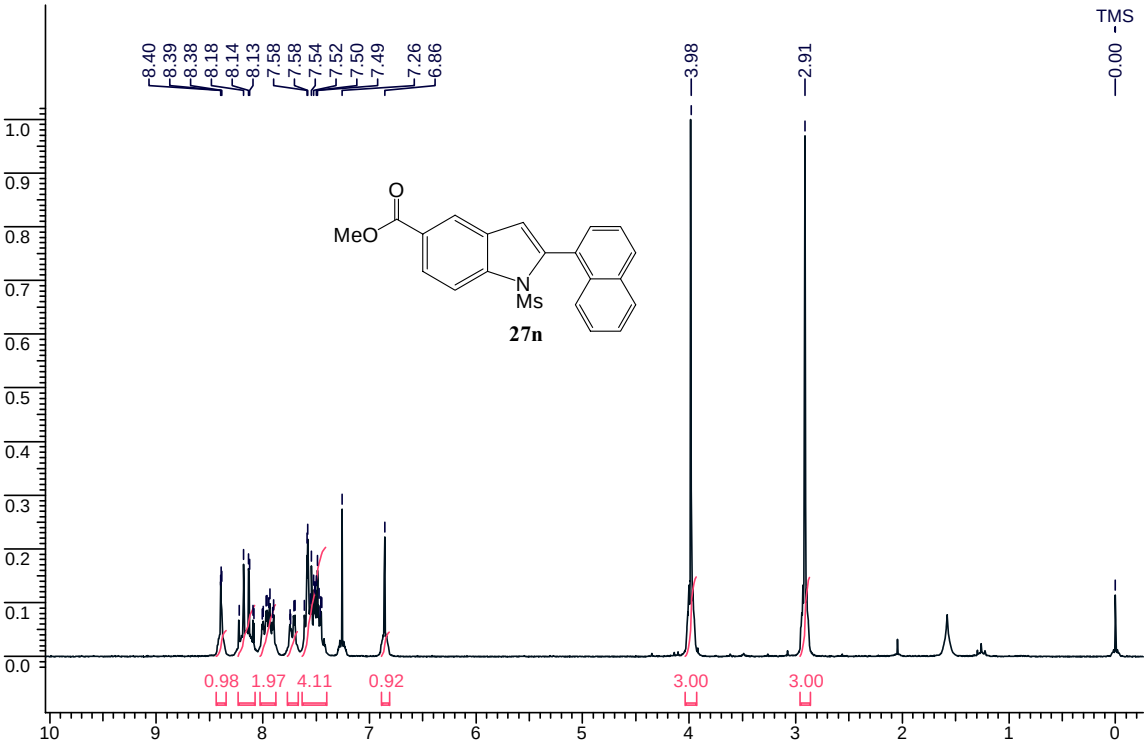
^{1}H NMR of **27m**



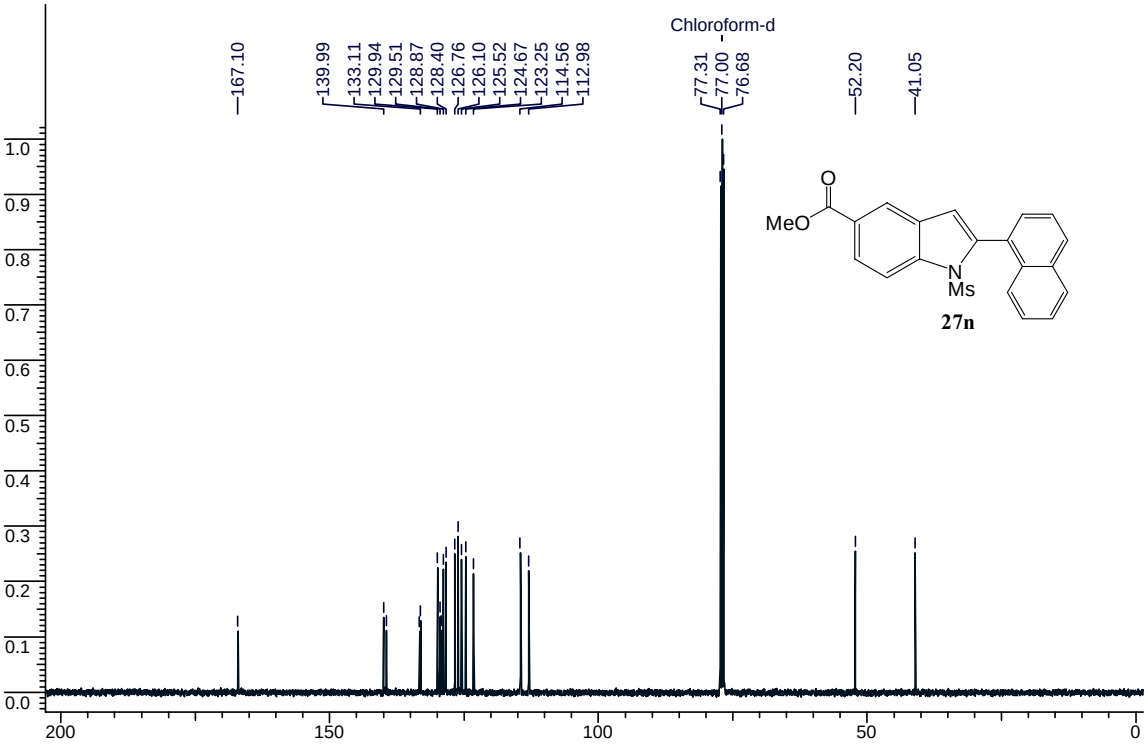
^{13}C NMR of **27m**



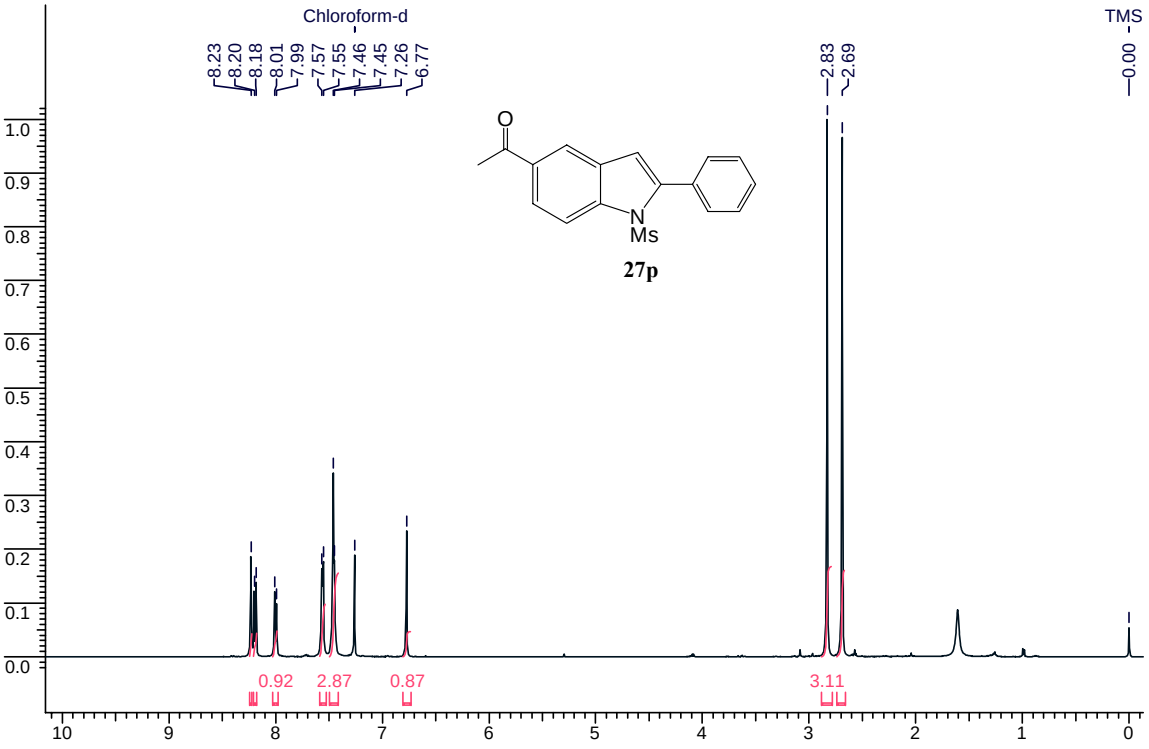
^{1}H NMR of **27n**



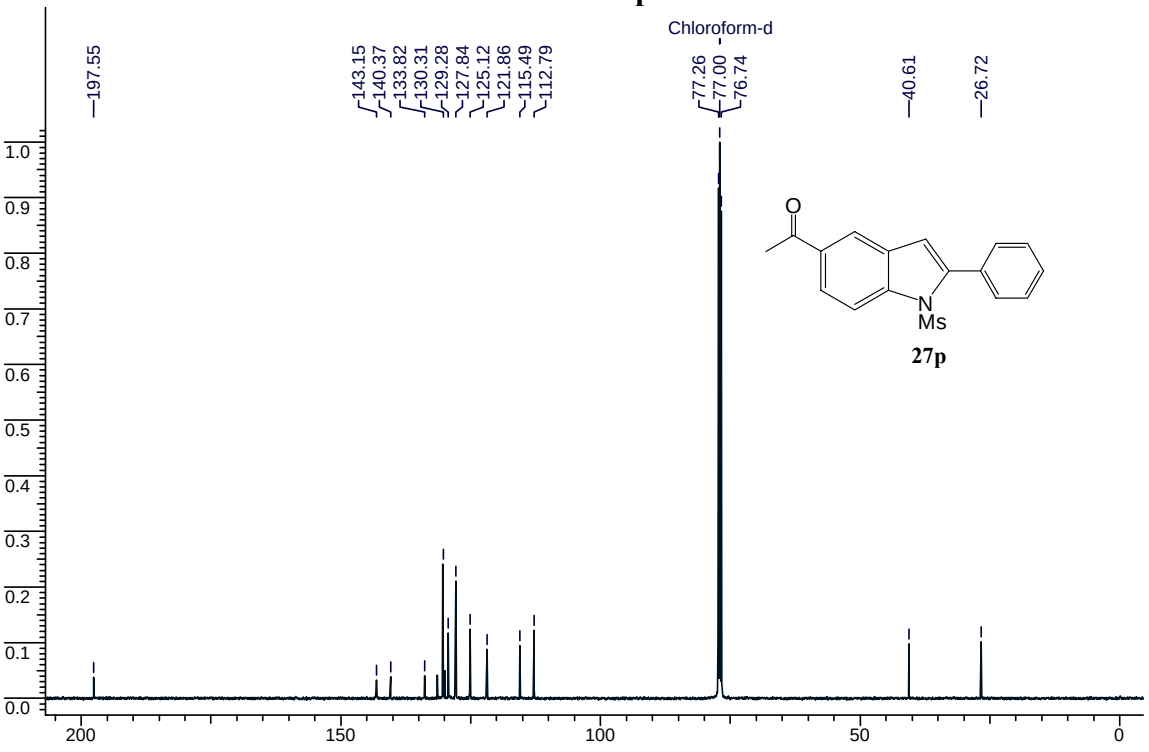
^{13}C NMR of **27n**



^{1}H NMR of **27p**



^{13}C NMR of **27p**



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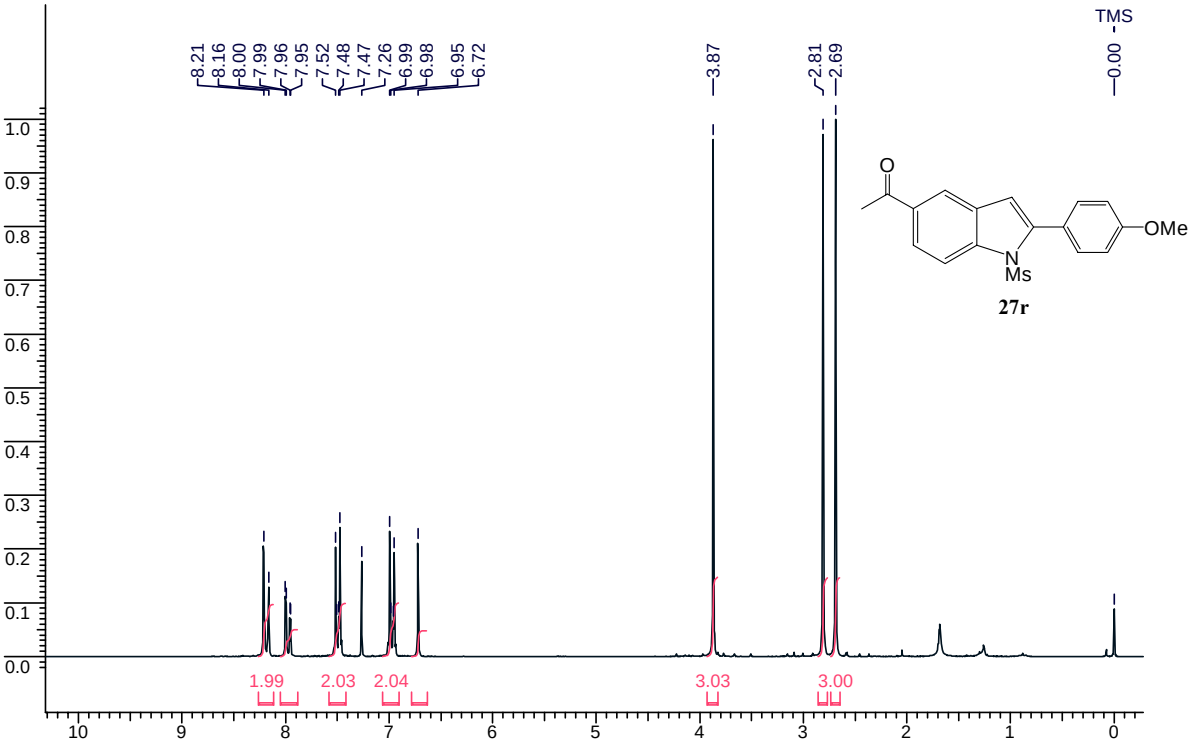
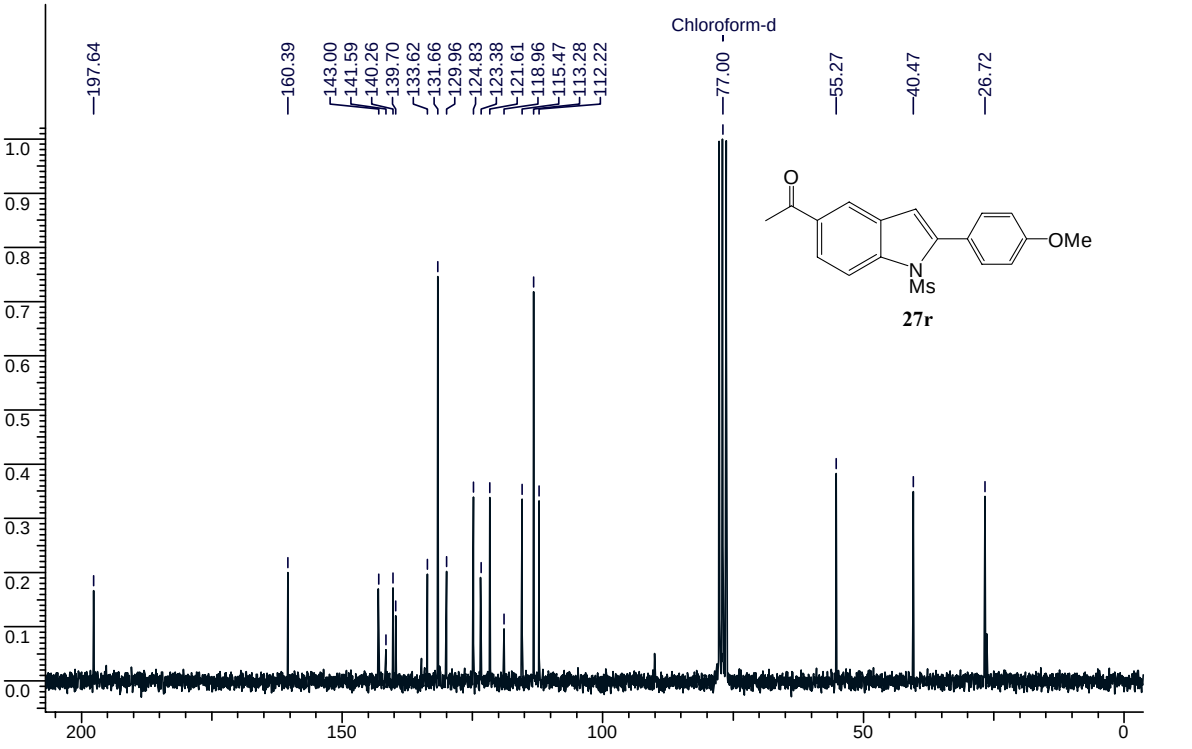


^{13}C NMR of **27r**



3.1.7 References

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Section B

Synthesis of an indole containing KDR kinase inhibitor by tandem Sonogashira coupling - 5 - endo - dig - cyclization as a key step

3.2.0 Introduction

The substituted indole nucleus is a structural component of a vast number of biologically active natural and unnatural compounds. Due to the existence of a an array of structurally diverse and biologically active indoles, it is not surprising that the indole nucleus is an important feature in many therapeutic agents.[1]

Tyrosine kinases are a class of enzymes which are believed to play a critical role in signal transduction in a number of cellular functions and have been implicated in a wide range of diseases and conditions including angiogenesis, cancer, tumor growth, atherosclerosis, diabetic retinopathy and inflammatory diseases to name a few.[2] The kinase insert domain receptor (KDR) is a tyrosine kinase that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor induced angiogenesis.[3] Compounds which inhibit, modulate or regulate the KDR receptor are useful for the prevention and treatment of tumor induced angiogenesis.

Recently Merck reported a class of potent KDR kinase inhibitors containing the *indol-2-yl quinoline-2-one* as the key pharmacophore[4] **(Fig. 2**). Compound **28** was found to be of use in the treatment of certain types of cancer.[5]

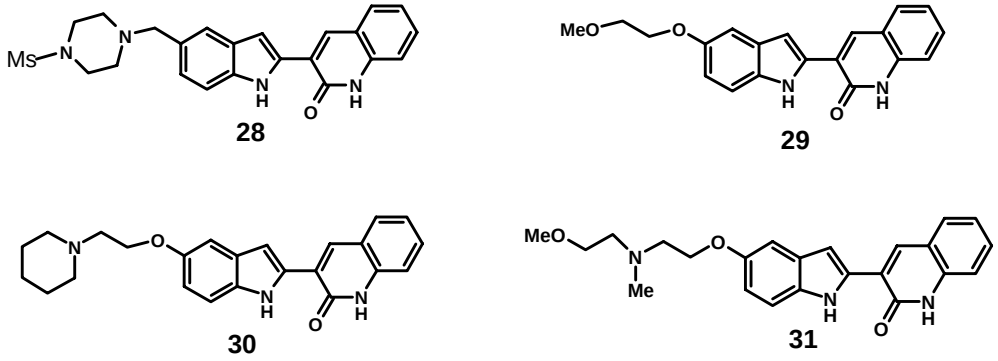


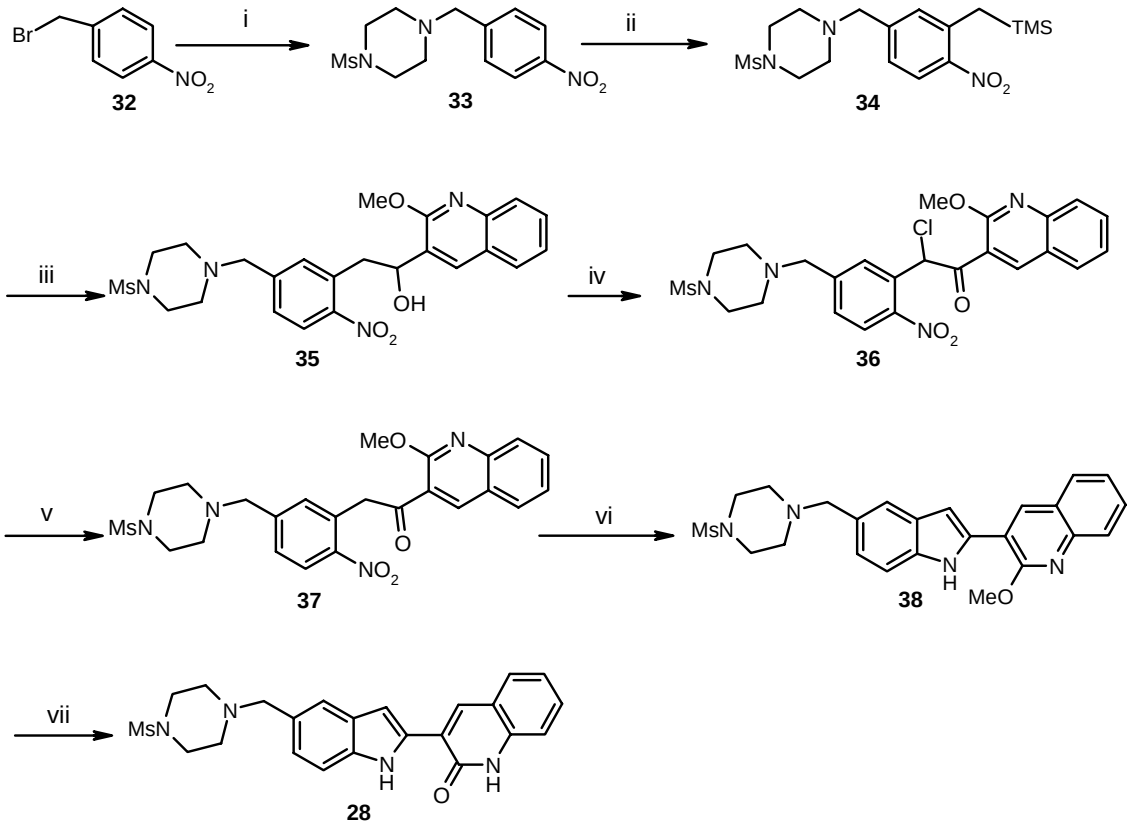
Fig. 2: KDR inhibitor developed by Merck

3.2.1 Review of Literature

Literature search revealed that there are only a few reports available for the synthesis of KDR kinase inhibitor 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline-2-(1*H*)-one (**28**) which are described below.

Wong's approach (*J. Org. Chem.* 2004)[4c]

Wong, A. *et al.* reported the synthesis of KDR kinase inhibitor **28** by reductive cyclization of *o*-nitro benzyl carbonyl compound **37** by using Raney nickel as a catalyst to give 1*H*-indol-2-yl-1*H*-quinoline **38** which on hydrolysis affords the KDR kinase inhibitor **28** (Scheme **15**). In their study, they have optimized the reaction conditions for the reductive cyclization.

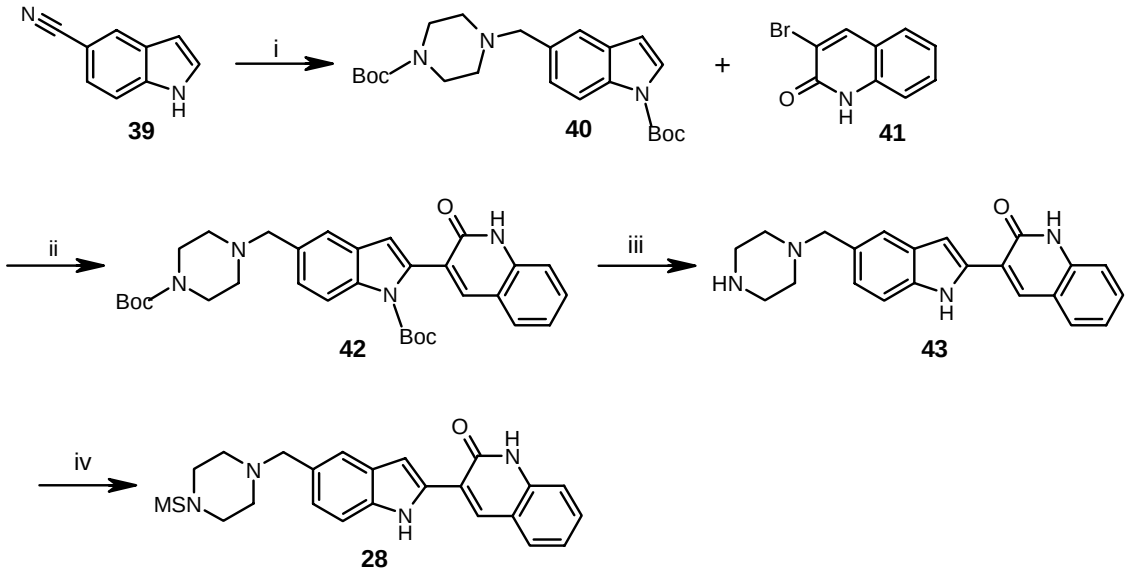


Scheme 15

Reagents and conditions: (i) 1-methanesulfonyl piperazine, Na_2CO_3, DMF, 0 ^oC- rt, 4h, 99% (ii)$TMSCH_2MgCl$, 1N I_2 solution, THF, -20 ^oC-rt, 3h, 85 % (iii) 3-formyl-2-methoxy-quinoline, TBAF, isopropyl acetate, rt, 30 min, 89% (iv) oxalyl chloride, DMSO, Et_3N, DCM, - 65 ^oC, 45 min, 47% (v) Ac_2O, DMSO, isopropyl acetate, 80 ^oC, 2h, 78%. (vi) Raney nickel, H_2, THF, 65 ^oC, 7.5 h, 90%. (vii) HCl, MeOH, 90 ^oC, 12 h, 95%.

Payack's approach (*J. Org. Chem.* 2005)[4b]

Payack, J. F. *et al.* reported the synthesis of KDR kinase inhibitor **28** by using Suzuki coupling strategy in multi-gram scale (Scheme **16**).



Scheme 16

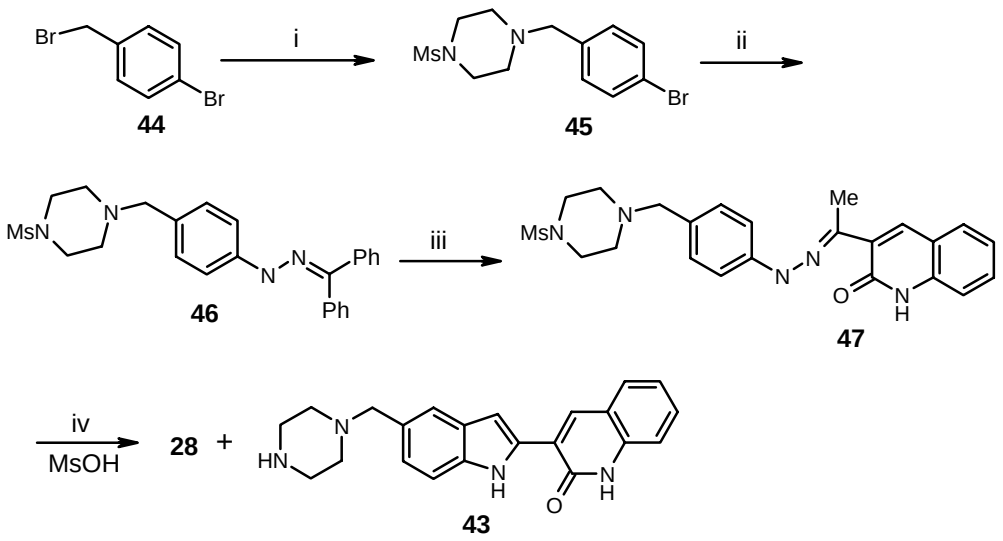
Reagents and conditons: (i) (a) Boc_2O, DMAP, toluene, 20-25 ^oC, 30 min. (b) DIBAL, 15-18 ^oC, 1h (c) $NaHSO_4$ (d) Boc-piperazine, $NaH(B(OAc)_3$, 23-27 ^oC, 1.5 h, 80% (ii) (a) LDA, $B(Oipr)_3$, THF, 5 ^oC, 1h (b) $Pd(OAc)_2$, PPh_3, dicyclohexyl amine, THF, 60 ^oC, 12 h, 88% (iii) aq. HCl, EtOH, 65 ^oC, 8h, 97% (iv) MsCl, DIPA, DMF, 40-45 ^oC, 91%.

Kuethe's approaches (*J. Org. Chem.* 2005)[4a]

Kuethe, J. T. *et al.* reported the various approaches for the synthesis of KDR kinase inhibitor **28** which are described below.

Fischer-indole approach

In this approach methanesulfonic acid catalyzed Fischer-cyclization of hydrazone **47** obtained from 4-bromobenzyl bromide **44** as a starting material has been described for the synthesis of KDR kinase inhibitor **28** (Scheme **17**).

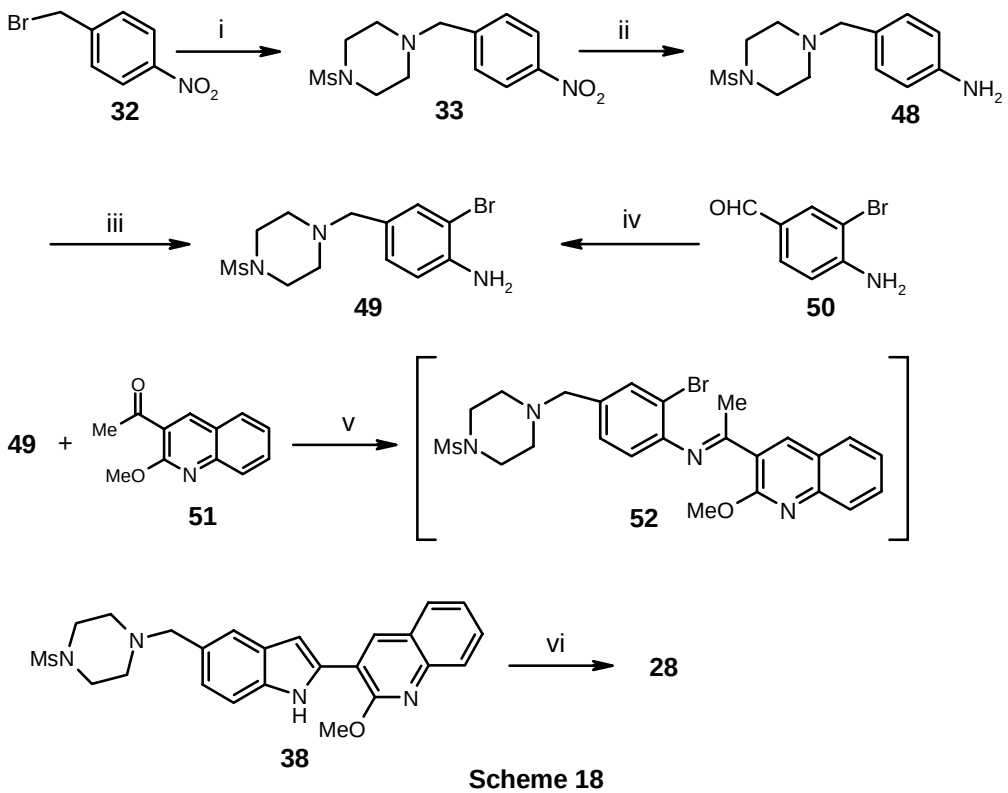


Scheme 17

Reagents and conditions: (i) 1-metthanesulfonylpiperzine, Et_3N, THF, rt, 3 h, 91% (ii) benzophenone hydrazone, $Pd(OAc)_2$, BINAP, KO^tBu, toluene, 105 ^oC, 4 h, 100% (iii) 3-acetyl-1*H*-quinlin-2-one, HCl, 1:1 EtOH:toluene, 100 ^oC, 12 h, 90% (iv) MsOH, 130 ^oC, 7 min. 45%.

Palladium-catalyzed annulation approach

In this approach KDR kinase inhibitor **28** has been synthesized by palladium-catalyzed cyclization of imine **52** which is obtained from either 4-nitrobenzyl bromide **32** or 4-amino-3-bromobenzaldehyde **50** as shown in Scheme **18**.

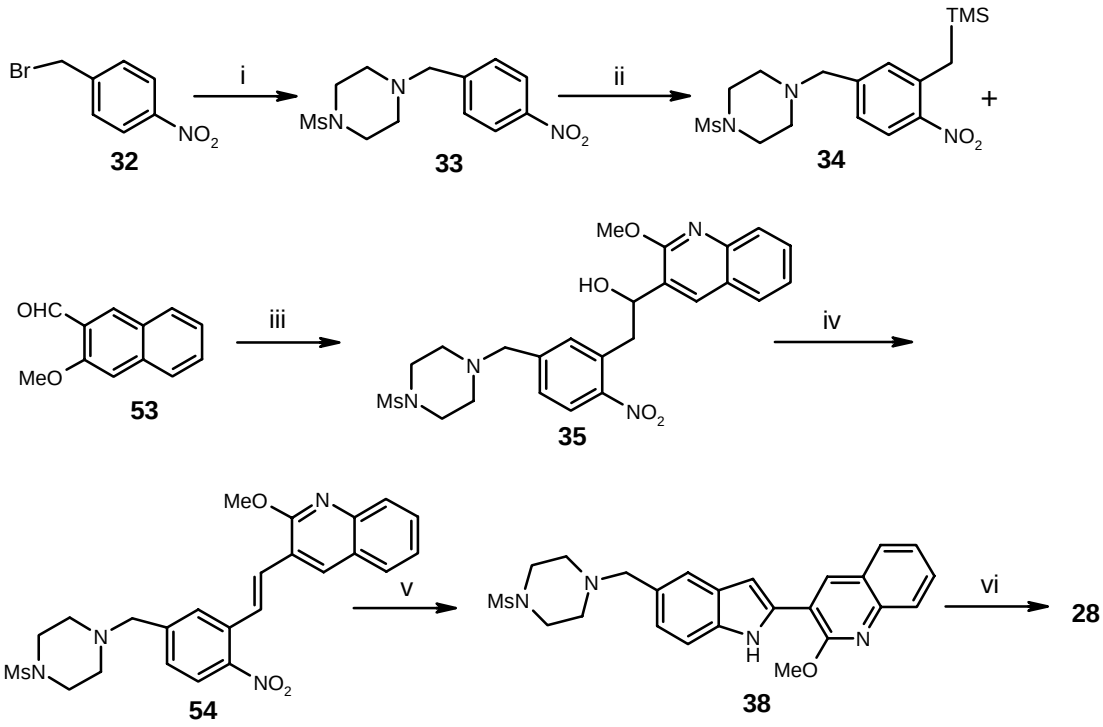


Scheme 18

Reagent and conditions: (i) 1-methanesulfonylpiperazine, Na_2CO_3, DMF, 0 ^oC-rt, 3 h, 99% (ii) Pd/C, H_2, EtOAc, rt, 4h, 85% (iii) KBr, $(NH_4)_6Mo_7O_{24}.4H_2O$, sodium perborate, AcOH, rt, 4 h, 78% (iv) 1-methanesulfonylpiperazine, $NaBH(OAc)_3$, DCM, rt, 70% (v) (a) $P(OEt)_3$, aq. H_3PO_4, DMF, reflux, 8 h (b) P(*o*-tol)$_3$, $Pd(OAc)_2$, Et_3N, DMF, reflux, 6 h, 37% (vi) HCl, DMF, 70 ^oC, 2 h, 100%.

Approach involving the reductive cyclization of nitro styrene

In this approach KDR kinase inhibitor **28** has been synthesized by reductive cyclization of nitro styrene **54** which is represented in Scheme **19**.

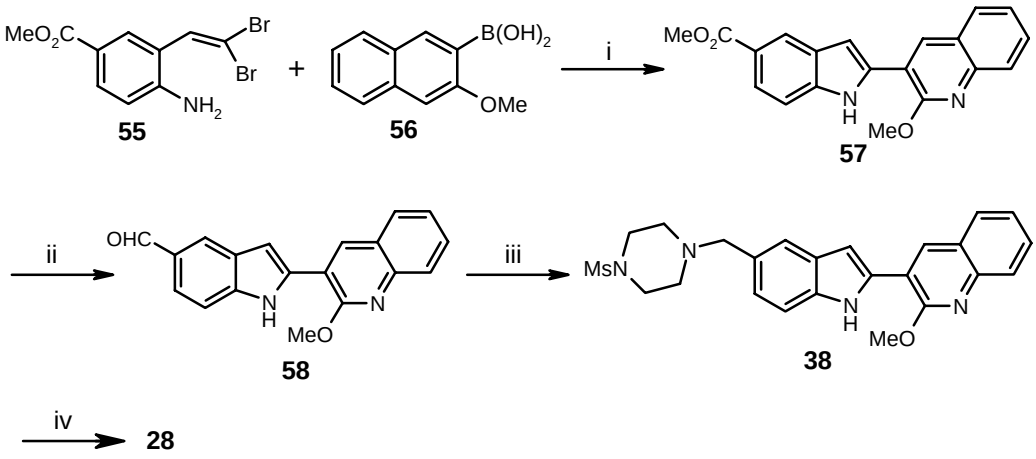


Scheme 19

Reagents and conditions: (i) 1-mesyl piperazine, Na_2CO_3, DMF, 0 ^oC- rt, 4h, 99% (ii)$TMSCH_2MgCl$, 1N I_2, solution, THF, -20 ^oC-rt, 3h, 85 % (iii) TBAF, isopropyl acetate, rt, 30 min, 89% (iv) TFAA, DBU, rt-60 ^oC, 1h, 80 % (v) $Pd(OAc)_2$, 1,10-phenanthroline, CO, DMF, 70 ^oC, 15 h, 95%. (vi) HCl, DMF, 70 ^oC, 2 h, 100%.

Lautens's approach (*J. Org. Chem.* 2007)[6]

Very recently Lautens, M. *et al.* reported the efficient synthesis of KDR kinase inhibitor **28** by using Pd-catalyzed tandem C-N/Suzuki coupling as the key step which is shown in Scheme **20**.



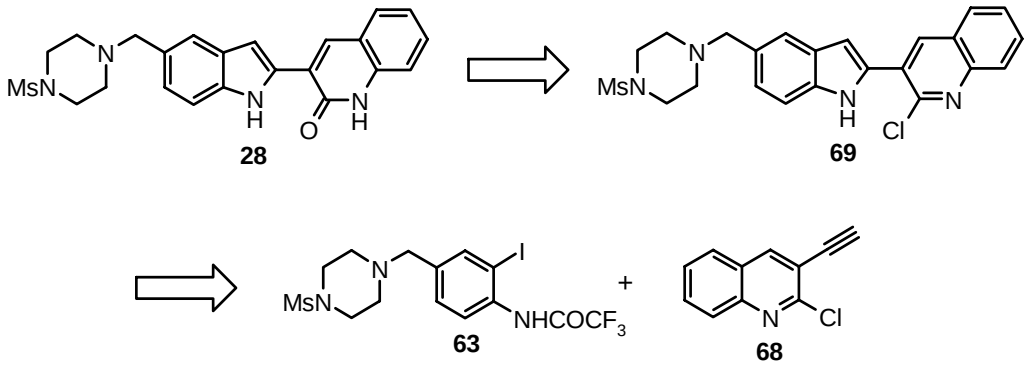
Scheme 20

Reagents and conditions: (i) $Pd(OAc)_2$, S-phos, $K_2PO_4.H_2O$, PhMe, 100 ^oC, 1.5 h, 86 % (ii) (a) $LiAlH_4$, Et_2O, -10-0 ^oC, 95% (b) TPAP, NMO, PhMe, 4 ^oA MS, 91% (iii) 1-methanesulfonylpiperazine, $NaHB(OAc)_3$, 4 ^oA MS, DCM, 92% (iv) HCl, MeOH, 90 ^oC, 12 h, 95%.

3.2.2 Present Work and Retro Synthetic Route to 28

Literature search revealed that the synthesis of this potent and selective KDR kinase inhibitor **28** by tandem Sonogashira coupling-5-*endo-dig*-cyclization as a key step has not been reported. Thus we planed to synthesize this molecule *via* palladium-catalyzed tandem Sonogashira coupling-5-*endo-dig*-cyclization strategy. The palladium-catalyzed annulation of *o*-haloanilines with terminal alkynes under Sonogashira reaction conditions has been employed widely due to the versatile nature of these protocols, increased functional group tolerance and improved yields.

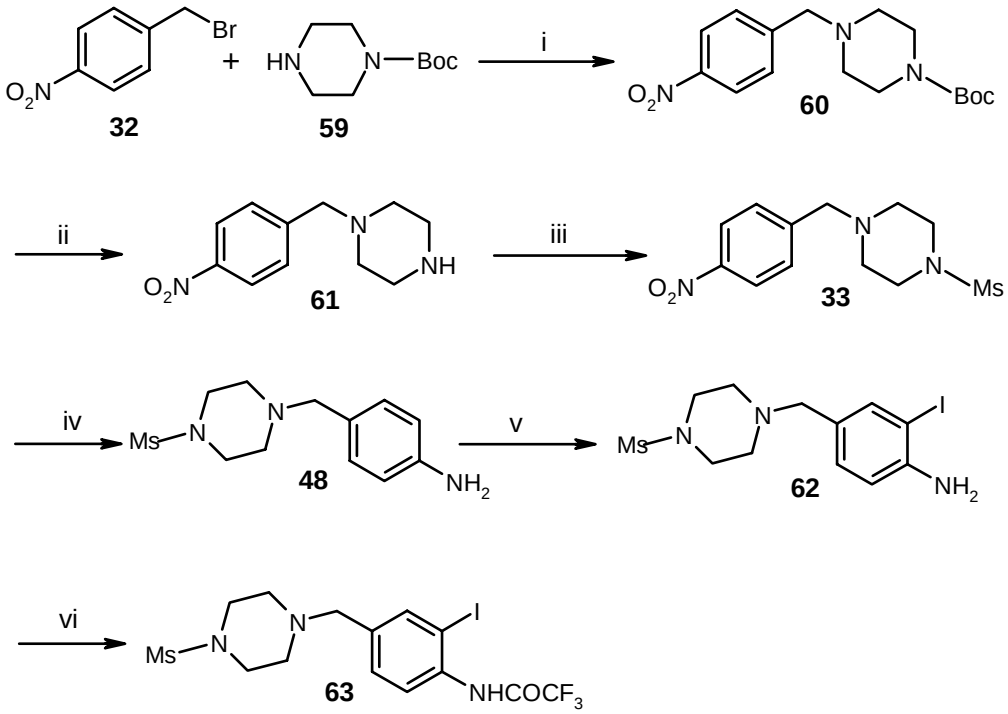
A retro synthetic analysis of **28** revealed that the synthesis of **28** could be achieved by a Sonogashira coupling-5-*endo-dig*-cyclization (Scheme **21**). A tandem coupling-cyclization between substituted *o*-iodoanilide **63** and 2- chloro-3- ethynyl quinoline **68** would give the indole-chloroquinoline **69**. The indole-chloroquinoline **69**, which is known to readily hydrolyze upon treatment with a 1:1 mixture of acetic acid/water will give the indole-quinolone core.[4a]



Scheme 21. Retro synthetic Key Steps for the Synthesis of KDR Kinase Inhibitor 28.

3.2.3 Results and Discussion

The *o*-iodoanilide fragment **63** was conveniently constructed from the commercially available 4-nitrobenzyl bromide **32** and N-boc piperazine **59** in six reaction steps (Scheme **22**).

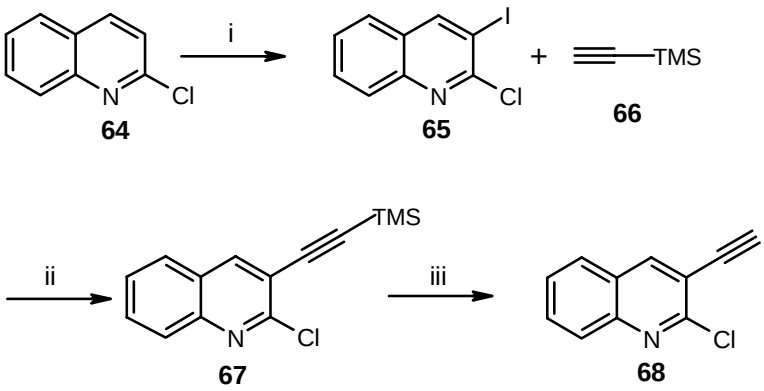


Scheme 22

Reagents and conditions: (i) Na_2CO_3, DMF, 0 ^oC to rt, 6 h,96% (ii) TFA : DCM, 0 ^oC to rt, 3 h, 99% (iii) MsCl, Et_3N, DCM, 0 ^oC to rt, 6 h, 98%, (iv) Pd/C, EtOAc, H_2, rt, 24 h, 86% (v) Ipy_2BF_4, DCM, -30 ^oC to 0 ^oC, 18 h, 65%, (vi) $(CF_3CO)_2O$, Et_3N, THF, -15 ^oC to rt,13 h, 90%.

The reaction of 4-nitrobenzyl bromide **32** with N-boc piperazine **59** for 6 h in DMF in the presence of Na_2CO_3 at room temperature afforded the nitro derivative **60** in 96% yield (isolated). Deprotection of N-boc group in DCM by using TFA and subsequent mesylation of –NH group afforded the mesyl derivative **33** in 98% yield. The catalytic hydrogenation of **33** by using 10 mol % Pd/C in ethyl acetate gave the aniline **48** in 86% yield (isolated). The aniline **48** was iodinated regioselectively at the ortho position by using Ipy_2BF_4.[7] When iodination was carried out at room temperature with dropwise addition of iodinating reagent in DCM, the procedure gave only 35% of the desired *o*-iodoaniline **62** along with 20% diiodo derivative. In order to avoid diiodination and achieve better regioselectivity and yield in the formation of **62**, the conditions for the iodination were optimized. After several experiments which were carried out at different temperatures under the slow addition of the iodinating reagent solution in DCM, it was found that the best condition for the iodination was the reaction carried out at -30 ^oC with dropwise addition of the iodinating reagent solution in DCM to afford regioselectively the *o*- iodoaniline derivative **62** in 65% isolated yield. In order to achieve coupling-cyclization and deprotection smoothly in one-pot, *o*-iodo aniline **62** was protected by trifluoroacetyl group. The trifluoroacetyl derivative **63** of the *o*-iodoaniline **62** was prepared in excellent yield (90%) according to the procedure given in literature.[8] The overall yield of **63** is 47% over six linear steps.

The synthesis of the other coupling partner 2-chloro-3-ethynyl quinoline **68** was successfully accomplished starting from the commercially available 2-chloroquinoline **64** (Scheme **23**).

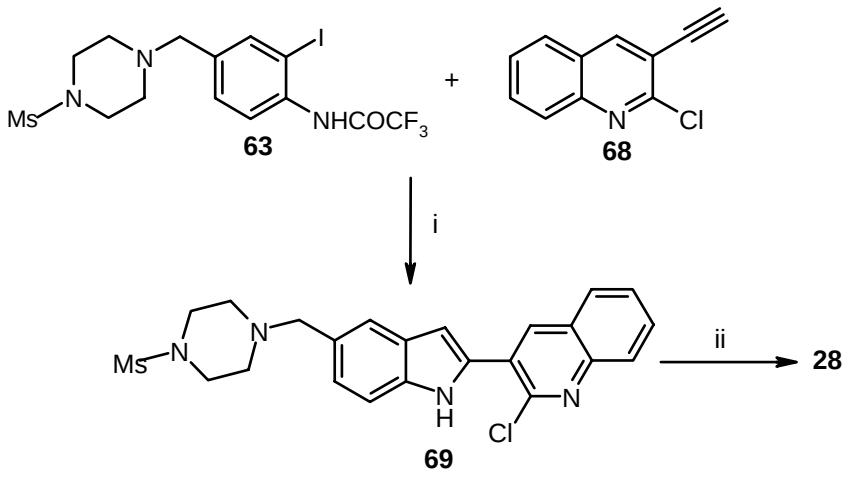


Scheme 23

Reagents and conditions: (i) BuLi, DIPA, I_2, -78 ^oC to rt, THF, 8 h, 75% (ii) $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, 80 ^oC, 3 h, 98% (iii) K_2CO_3, MeOH, rt, 1 h, 96%.

The regioselective iodination of 2-chloroquinoline **64** at the 3-position was carried out using a literature procedure[9] to give 2-chloro-3-iodoquinoline **65** as colorless solid in good yield (75%). Furthermore, the regioselective coupling of **65** with TMS-acetylene **66** was performed in the presence of catalytic amount of $Pd(OAc)_2$, using PPh_3 as ligand in acetonitrile employing Et_3N as the base to afford TMS protected alkyne **67** as colorless solid in excellent yield (98%). The deprotection of TMS group by using catalytic amount of K_2CO_3 in methanol afforded the terminal alkyne fragment **68** as colorless crystalline solid in excellent isolated yield (96%).

Palladium-catalyzed tandem Sonogashira coupling-5-*endo*-*dig*-cyclization of *o*-iodoanilide derivative **63** with terminal alkyne **68** proceeded smoothly in acetonitrile by using $Pd(OAc)_2$ as the catalyst, Bu_4NOAc as the base under *ligand-, copper*- and *amine*- free conditions[5] to give the indole-chloroquinoline **69** as a pale yellow foamy solid in good yield (80%) (Scheme **24**)



Scheme 24. Sonogashira coupling-5-*endo-dig*-cyclization

Reagents and conditions: (i) $Pd(OAc)_2$ (2 mol%), Bu_4NOAc (2.5 eq), CH_3CN, 85 ^oC, 12 h, 80% (ii) $AcOH:H_2O$, 110 ^oC, 16 h, 93%.

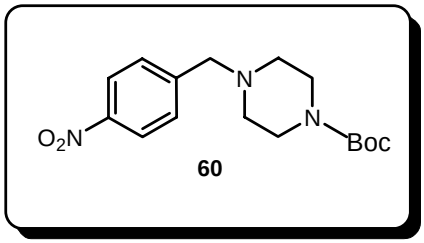
The deprotection of the masked quinolin-2-one moiety of chloroquinoline **69** to get target compound **28** was accomplished in a straightforward manner under acidic conditions. Hydrolysis of chloroquinoline **69** in a 1:1 mixture of acetic acid/water as per the method reported in literature[4a] gave KDR inhibitor **28** in 93% yield. All the compounds were well characterized by ^1H and ^{13}C NMR spectroscopy, elemental analysis, IR and LC-MS. The structure of the target molecule **28** was confirmed by comparing its characterization data with literature data which was found to be identical.

3.2.4 Conclusion

In conclusion, we have developed a new alternative route to the synthesis of the potent and selective KDR kinase inhibitor **28** which has potential use in cancer therapy by using Sonogashira coupling-5-*endo-dig*-cyclization strategy. The overall yield of compound **28** was 35% with respect to **32** in eight linear steps.

3.2.5 Experimental Section

1. Preparation of *tert*-Butyl-4-(4-nitrobenzyl) piperazine-1-carboxylate (60):



60

To a slurry of 1- boc-piperazine **59 (**5 g, 26.8 mmol) and Na_2CO_3 (2.85 g, 26.8 mmol) in DMF (20 mL) at 0 ^oC was added dropwise 4-nitrobenzyl bromide **32 (**5.81 g, 26.8 mmol) in DMF (10 mL). After stirring for 6 h at room temperature, the reaction mixture was cooled to 0 ^oC and 50 mL of water was slowly added dropwise. The resulting slurry of the product was stirred for 1 h at room temperature and filtered, and the product was washed with water. The product was dried under vacuum of 0 mbar at 40 ^oC to give 8.28 g of **60** (96%) as a white solid: mp 98-99 ^oC.

IR: (KBr) υ_{max} (cm^{-1})	**:**	3019, 2400, 1685, 1523, 1346, 1216, 668.
^{1}H NMR	**:**	1.46 (s, 9H), 2.39-2.44 (m, 4H), 3.43-3.48 (m,
($CDCl_3$, 200 MHz) δ		4H), 3.61 (s, 2H), 7.53 (d, 2H, *J* = 8.60 Hz), 8.19 (d, 2H, *J* = 8.74 Hz).
^{13}C NMR	**:**	28.4, 52.9, 62.1, 76.7, 123.5, 129.4, 145.9, 147.2,
($CDCl_3$, 50 MHz) δ		154.7.
Elemental analysis	**:**	Anal. Calcd for: $C_{16}H_{23}N_3O_4$: C, 59.80; H, 7.21; N, 13.08.
		Found: C, 59.46; H, 7.31; N, 13.17.
LC-MS	**:**	Mol. Wt. calcd for $C_{16}H_{23}N_3O_4$ ($[M+H]^+$) 322.17 found 322.14.

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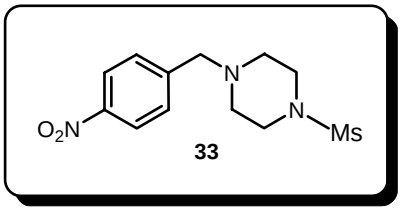
2. Preparation of 1- methanesulfonyl-4-(4-nitrobenzyl)-piperazine (33)



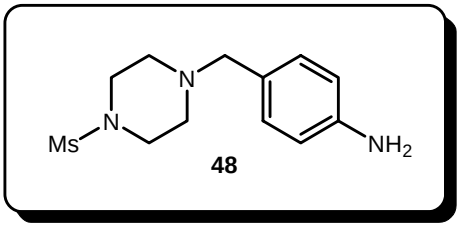
33

To a solution of **60** (8.28 g, 25.7 mmol) in DCM (10 mL) at 0 ^oC was added dropwise TFA (10 mL). After stirring for 3 h at room temperature, the reaction mixture was neutralized with 10 % aqueous NaOH to a pH of 8.0 and extracted with DCM. The extract was

dried over $MgSO_4$ and concentrated under reduced pressure, to afford the 5.62 g of crude **61** (99%) as colorless solid, which was used directly in the next step without further purification as follows: To a mixture of the above deprotected product **61** (5.62 g, 25.5 mmol) and Et_3N (2.83 g, 28.0 mmol) in dry DCM (20 mL) at 0 ^oC was added dropwise methanesulfonyl chloride (3.96 g, 28.0 mmol). The resulting reaction mixture was further stirred for 6 h at room temperature, neutralized with 10% aqueous NaOH and then extracted with DCM. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, by eluting with 70% ethyl acetate/petroleum ether to afford 7.48 g 0f **33** (98%) as a colorless solid: mp 133-135 ^oC (lit. 116-117 ^oC)[4a].

IR: (KBr) υ_{max} (cm^{-1})	**:**	3023, 1606, 1521, 1347, 962, 668.
^{1}H NMR	**:**	2.56-2.61 (m, 4H), 2.81 (s, 3H), 3.25-3.30 (m, 4H),
($CDCl_3$, 200 MHz) δ		3.66 (s, 2H), 7.53 (d, 2H, *J* = 8.84 Hz), 8.19 (d, 2H, *J* = 8.88 Hz).
^{13}C NMR	**:**	34.2, 45.7, 52.2, 61.5, 123.5, 129.4, 145.4, 147.2.
($CDCl_3$, 50 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for: $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.72; N, 14.04.
		Found: C, 48.36; H, 5.70; N, 13.66.
LC-MS	**:**	Mol. Wt. calcd for $C_{12}H_{17}N_3O_4S$ ($[M+H]^+$) 300.09 found 300.99.

3. Preparation of 4-(4-methanesulfonyl piperazine-1-yl-methyl)-aniline (48):



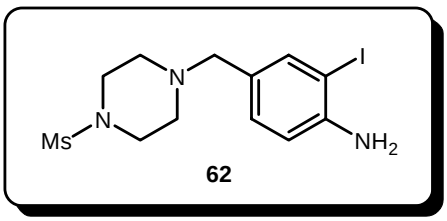
48

To a solution of **33** (5 g, 16.7mmol) in ethyl acetate (200 mL) was added 10 % Pd/C (1 g). The resulting reaction mixture was stirred at room temperature under an atmosphere of hydrogen balloon positive pressure for 24 h until all the starting material was consumed. After the completion of the reaction, the catalyst was

removed by filtration through a pad of celite. The solvent was removed under vacuum to afford 3.86 g of **48** (86%) as a colorless analytically pure sample without the need for further chromatographic purification: mp 168-169 °C (lit. 161-162 °C).[4a]

IR: (KBr) υ_{max} (cm^{-1})	**:**	3393, 3020, 2400, 1622, 1518, 1324, 1215, 961, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.50-2.55 (m, 4H), 2.76 (s, 3H), 3.20-3.25 (m, 4H), 3.43 (s, 2H), 6.64 (d, 2H, *J* = 8.37 Hz), 7.07 (d, 2H, *J* = 8.37 Hz).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	34.0, 45.8, 51.9, 62.1, 114.8, 126.9, 130.2, 145.7.
Elemental analysis	**:**	Anal. Calcd for $C_{12}H_{19}N_3O_2S$: C, 53.51; H, 7.11; N, 15.60. Found: C, 53.71; H, 6.81; N, 15.23.

4. Preparation of 2-iodo-4-(4-methanesulfonylpiperazine-1-yl methyl) aniline (62):



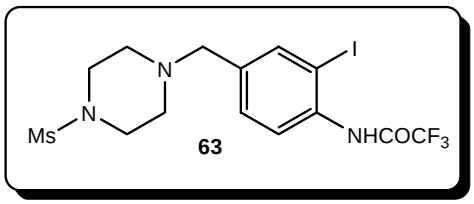
62

To a solution of **48** (2.0 g, 7.43 mmol) in DCM (50 mL) at -30 °C was added dropwise Ipy_2BF_4 (2.76 g, 7.43 mmol) solution in DCM (20 mL) over a period of 6 h. The reaction mixture was further stirred for 1 h at the same temperature. After stirring for 1h at -30 °C, the reaction mixture was allowed to warm up to 0 °C and stirred overnight. After the completion of reaction, solvent was removed under reduced pressure. The residue was purified by silica gel chromatography by eluting with 75% ethyl acetate/ petroleum ether to afford 1.90 g of **62** (65%) as a colorless solid: mp 185-187 °C.

IR: (KBr) υ_{max} (cm^{-1})	**:**	3480, 3387, 3133, 3019, 2400, 1617, 1500, 1318, 1215, 1071, 757, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.52-2.57 (m, 4H), 2.78 (s, 3H), 3.22-3.27 (m, 4H), 3.41 (s, 2H), 6.70 (d, 1H, *J* = 8.06 Hz), 7.06 (dd, 1H, *J* = 6.17, 1.94 Hz), 7.58 (d, 1H, *J* = 1.72 Hz).
^{13}C NMR	**:**	34.1, 45.7, 51.9, 61.2, 83.9, 114.3, 128.6, 130.4,

($CDCl_3$, 50 MHz) δ		139.4 146.1.
Elemental analysis	**:**	Anal. Calcd for $C_{12}H_{18}IN_3O_2S$: C, 36.54; H, 4.56; N, 10.65. Found: C, 36.40; H, 4.52; N, 10.62.
LC-MS	**:**	Mol. Wt. calcd for $C_{12}H_{18}IN_3O_2S$ $[M]^+$ 395.02 found 395.92.

5. Preparation of 2-iodo-4-(4-methanesulfonyl piperazine-1-yl-methyl) trifluoroacetanilide (63):

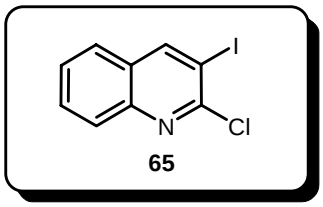


63

The literature procedure[7] for the preparation of trifluoro acetyl derivative **63** of *o*-iodoaniline derivative **62** was followed: To a stirred solution of **62** (0.8 g, 2.03 mmol) and Et_3N (0.3 mL, 2.15 mmol) in THF (5 mL) at -15 ^oC was added drop wise a solution of $(CF_3CO)_2O$ (0.426 g, 2.03 mmol) in THF (3 mL). After 1 h of stirring at -15 ^oC, the reaction mixture was allowed to warm up to room temperature, stirred overnight and then poured into a seperatory funnel containing water (50 mL). The product was extracted into ethyl acetate, the combined organic layer was then dried over $MgSO_4$, the solvent was evaporated and product chromatographed with 60% ethyl acetate in pet ether to afford 0.89 g of **63** (90%) as a colorless solid. mp 124-126 ^oC.

IR: (KBr) υ_{max} (cm^{-1})	**:**	3363, 3022, 2401, 1736, 1536, 1348, 1215, 962, 756, 667.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.50-2.54 (m, 4H), 2.73 (s, 3H), 3.19-3.23 (m, 4H), 3.46 (s, 2H), 7.30 (dd, *J* = 8.30, 1.66 Hz, 1H), 7.76 (d, *J* = 1.82 Hz, 1H), 7.09 (d, *J* = 8.45 Hz, 1H), 8.20 (br s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	34.3, 45.6, 52.2, 60.9, 90.4, 114.4, 116.7, 121.8, 130.2, 134.9, 139.4, 154.9.
Elemental analysis	**:**	Anal. Calcd for $C_{14}H_{17}F_3IN_3O_3S$: C, 34.23; H, 3.49; N, 8.55. Found: C, 34.26; H, 4.3.61; N, 8.72.
LC-MS	**:**	Mol. Wt. calcd for $C_{14}H_{17}F_3IN_3O_3S$ $[M+H]^+$ 492 found 491.99.

6. Preparation of 2- chloro-3-iodoquinoline (65)[8]:

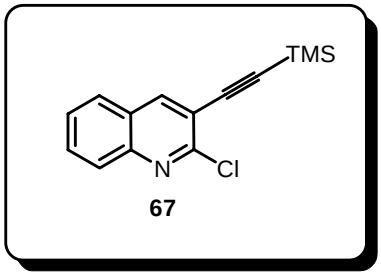


65

n-BuLi (1.6 M in hexane, 19 mL, 50 mmol) was slowly added to a magnetically stirred solution of diisopropylamine (3.07 g, 50 mmol) in dry THF (100 mL) under argon at -78 ^{o}C. The solution of LDA was stirred at -78 ^{o}C for 1 h. 2-chloroquinoline **64** (5 g, 30 mmol) in THF (25 mL) was added slowly to the reaction mixture at -78 ^{o}C and stirred for 4 h at the same temperature. A solution of iodine (9.25 g, 36.7 mmol) in THF (40 mL) was slowly added to a solution of lithiated 2-chloroquinoline. The resulting solution was stirred for 2 h at -78 ^{o}C and allowed to warm to room temperature over 5 h. After removing the solvent under reduced pressure, the residue was extracted using Et_2O and decolorized with saturated aqueous $NaHSO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography, by eluting with 1% ethyl acetate/petroleum ether to afford 6.49 g 0f **65** (75%) as a colorless solid: mp; 144-145 ^{o}C (lit. 145-146 ^{o}C).[8]

IR: (KBr) υ_{max} (cm^{-1})	**:**	3018, 2400, 1548, 1487, 1361, 1215, 952, 755, 668.
^{1}H NMR	**:**	7.49-7.57 (m, 1H), 7.65-7.75 (m, 2H), 7.95 (d, 1H, *J* =
($CDCl_3$, 200 MHz) δ		8.95), 8.60 (s, 1H).
^{13}C NMR	**:**	90.9, 126.3, 127.6, 128.4, 130.9, 146.7, 148.5, 152.2.
($CDCl_3$, 50 MHz) δ		
Elemental analysis	**:**	Anal. Calcd for C_9H_5ClIN: C, 37.34; H, 1.74; N, 4.84. Found: C, 37.68; H, 1.90; N, 4.95.

7. Preparation of 2-chloro-3-[2-(trimethylsilyl) ethynyl]quinoline (67):



67

A mixture of **65** (0.5 g, 1.76 mmol), trimethylsilylacetylene **66** (0.258 g, 2.64 mmol), $Pd(OAc)_2$ (3.9 mg, 1 mol %), PPh_3 (9.1 mg, 2 mol%) and Et_3N (0.889 g, 8.80 mmol) in acetonitrile (5 mL) was heated at 80 ^{o}C for 3 h under argon atmosphere. After the completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated,

dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography by eluting with 1% ethyl acetate in petroleum ether to afford 0.448 g of **67** (98%) as a colorless solid: mp; 96-97 ^oC.

IR: (KBr) υ_{max} (cm^{-1})	**:**	3018, 2400, 2160, 1618, 1487, 1336, 1215, 858, 760, 668.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	0.31 (s, 9H), 7.49-7.57 (m, 1H), 7.66-7.76 (m, 2H), 7.97 (d, 1H, *J* = 8.31), 8.27 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	– 0.32, 99.7, 102.4, 117.7, 126.2, 127.2, 127.4 128.5, 131.1, 141.7, 146.3, 150.6.
Elemental analysis	**:**	Anal. Calcd for $C_{14}H_{14}ClNSi$: C, 64.72; H, 5.43; N, 5.39. Found: C, 65.10; H, 5.40; N, 5.71.
LC-MS	**:**	Mol. Wt. calcd for $C_{14}H_{14}ClNSi$ ($[M+H]^+$) 259.06 found 260.03.

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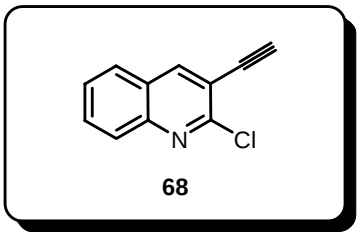
8. Preparation of 2-chloro-3-ethynyl quinoline (68):



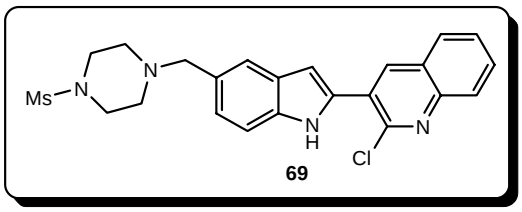
68

To a solution of **67** (0.4 g, 1.53 mmol) in methanol (5 mL) was added K_2CO_3 (5 mg, 2 mol%). The resulting reaction mixture was stirred at room temperature under an atmosphere of argon for 1 h. Then the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography by eluting with 3% ethyl acetate in petroleum ether to afford 0.277 g of **68** (96%) as a colorless solid: mp; 115-116 ^oC.

IR: (KBr) υ_{max} (cm^{-1})	**:**	3304, 3018, 2400, 1619, 1487, 1339, 1215, 1040, 756, 668.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	3.50 (s, 9H), 7.54-7.62 (m, 1H), 7.71-7.80 (m, 2H), 7.98-8.03 (m, 1H), 8.33 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	78.7, 83.9, 116.5, 125.8, 127.0, 127.4, 128.2, 131.2, 142.3, 146.3, 150.2.
Elemental analysis	**:**	Anal. Calcd for $C_{11}H_6ClN$: C, 70.42; H, 3.22; N, 7.47. Found: C, 70.32; H, 3.22; N, 7.47.

LC-MS : Mol. Wt. calcd for $C_{11}H_6ClN$ $[M+H]^+$ 188.02 found 187.97.

9. Preparation of 2-chloro-3-[5-[[4-(methysulfonyl)-1-piperazinyl] methyl]-1*H*-indol-2-yl]-quinoline (69):



69

A mixture of **63** (0.2 g, 0.40 mmol), **68** (0.085 g, 0.49 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol%) and Bu_4NOAc (0.307 g, 1.01 mmol) in acetonitrile (5 mL) was heated at 85 ^oC to reflux under an atmosphere of argon for 12 h. After the completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography by using 60% ethyl acetate in petroleum ether as the eluent system to afford 0.149 g of **69** (80%) as a pale yellow foamy solid. mp 108-110 ^oC.

IR: (KBr) υ_{max} (cm^{-1}) : 3467, 3019, 2400, 1670, 1346, 1328, 1215, 1159, 960, 756, 668.

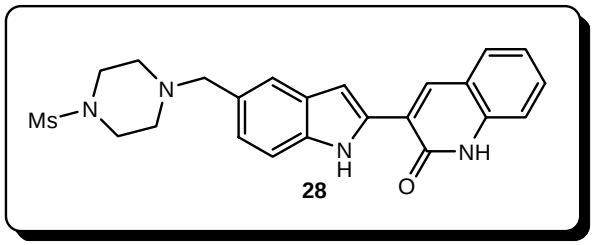
^{1}H NMR ($CDCl_3$, 200 MHz) δ : 2.61-2.66 (m, 4H), 2.78 (s, 3H), 3.26-3.30 (m, 4H), 3.70 (s, 2H), 6.96 (s, 1H), 7.25 (d, *J* = 9.79 Hz, 1H), 7.44 (d, *J* = 8.24 Hz, 1H), 7.56-7.64 (m, 2H), 7.76 (t, *J* = 8.58 Hz, 1H), 7.87 (d, *J* = 9.12 Hz, 1H), 8.05 (d, *J* = 7.88 Hz, 1H), 8.41 (s, 1H), 8.92 (br s, 1H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 34.1, 45.8, 52.1, 62.9, 104.7, 111.2, 121.5, 124.7, 125.8, 127.0, 127.5, 127.6, 128.1, 128.3, 130.8, 134.4, 136.3, 138.3, 146.6, 147.6.

Elemental analysis : Anal. Calcd for $C_{23}H_{23}ClN_4O_2S$: C, 60.72; H, 5.10; Cl, 7.79; N, 12.31, S, 7.05. Found: C, 60.32; H, 5.17; N, 11.93; S, 6.65.

LC-MS : Mol. Wt. calcd for $C_{23}H_{23}ClN_4O_2S$ ($[M+H]^+$) 455.12 found 455.14.

10. Preparation of 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline-2-(1*H*)-one (28):



28

Compound **69** (50 mg, 0.11 mmol) in a mixture of AcOH (1mL) and H_2O (1mL) was heated at 100 ^oC for 16 h. After the completion of the reaction, the solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash column chromatography by eluting with ethyl acetate to afford 44 mg of **28** (93%) as a yellow solid. mp 273-275 ^oC (lit. 275-277 ^oC).[4b]

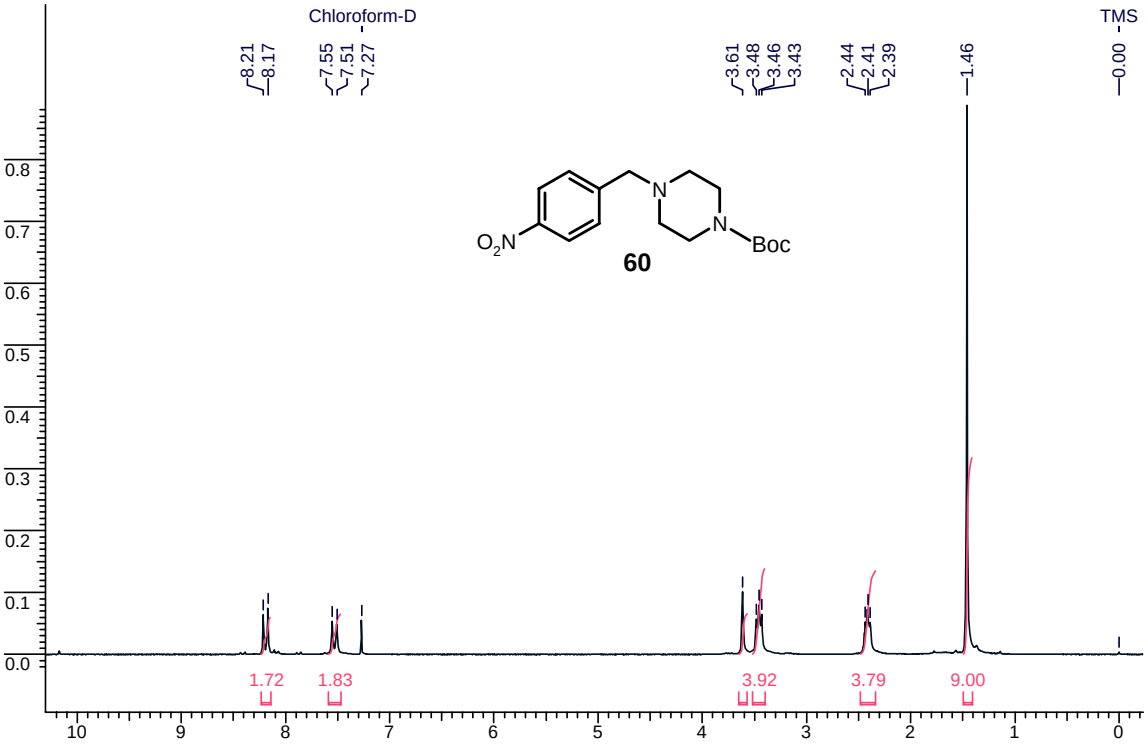
IR: (KBr) υ_{max} (cm^{-1})	**:**	3454, 2924, 2854, 1651, 1462, 1376, 1167, 961.
^{1}H NMR	**:**	2.43 (s, 4H), 2.79 (s, 3H), 3.02 (s, 4H), 3.51 (s, 2H),
($CDCl_3$, 200 MHz) δ		7.25 (t, *J* = 7.57, 7.01 Hz, 1H), 7.36 (d, *J* = 4.28 Hz, 2H), 7.39 (d, *J* = 8.26 Hz , 1H), 7.51 (s, 1H), 7.54 (d, *J* = 8.53 Hz, 1H), 7.73 (d, *J* = 7.74 Hz, 1H), 7.79 (s, 1H), 8.55 (s, 1H), 11.71 (s, 1H), 12.28 (br s, 1H).
^{13}C NMR	**:**	35.0, 45.8, 55.3, 61.7, 102.7, 111.7, 115.4, 119.8,
($CDCl_3$, 50 MHz) δ		120.7, 122.7, 122.8, 125.5, 127.1, 128.0, 128.3 128.6, 130.7, 132.8, 134.8, 134.9, 137.3, 138.1, 161.0.
Elemental analysis	**:**	Anal. Calcd for $C_{23}H_{24}N_4O_3S$: C, 63.28; H, 5.54; N, 12.83, S, 7.33. Found: C, 63.07; H, 5.50; N, 12.72.

3.2.6 Spectra

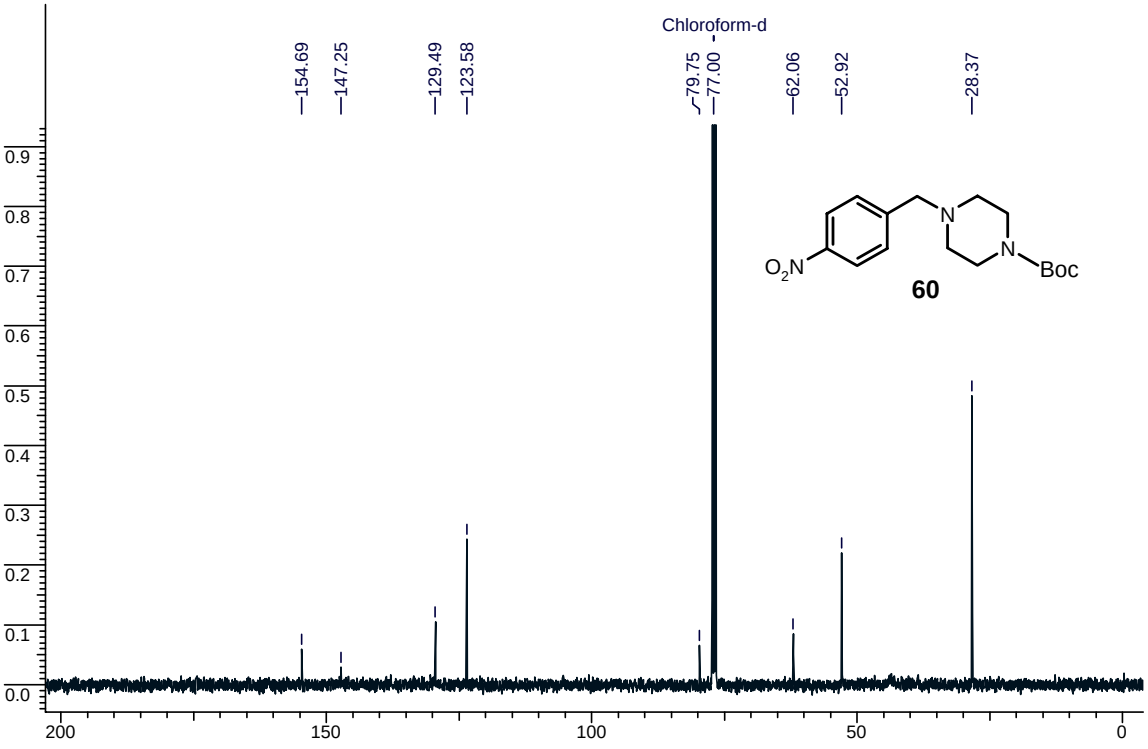
Table 6. ^{1}H and ^{13}C NMR spectra

Sr. No.	Spectra
1	^{1}H and ^{13}C spectra of **60**
2	^{1}H and ^{13}C spectra of **33**
3	^{1}H and ^{13}C spectra of **48**
4	^{1}H and ^{13}C spectra of **62**
5	^{1}H and ^{13}C spectra of **63**
6	^{1}H and ^{13}C spectra of **65**
7	^{1}H and ^{13}C spectra of **67**
8	^{1}H and ^{13}C spectra of **68**
9	^{1}H and ^{13}C spectra of **69**

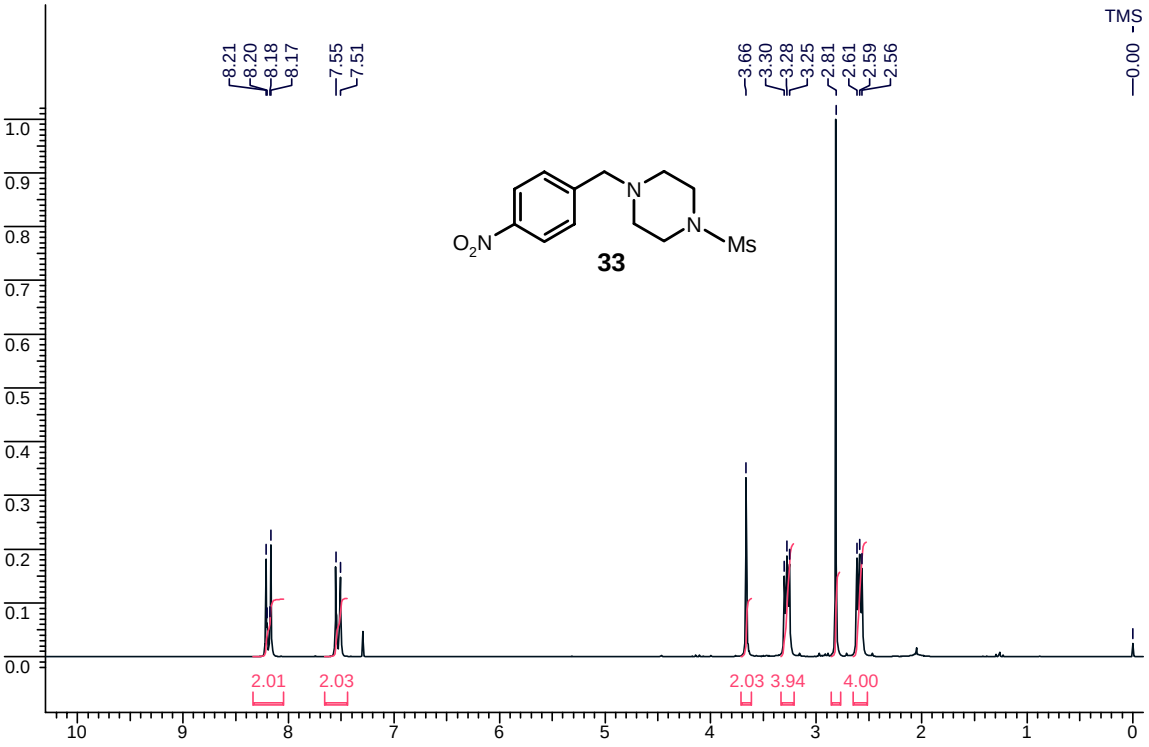
^{1}H NMR of **60**



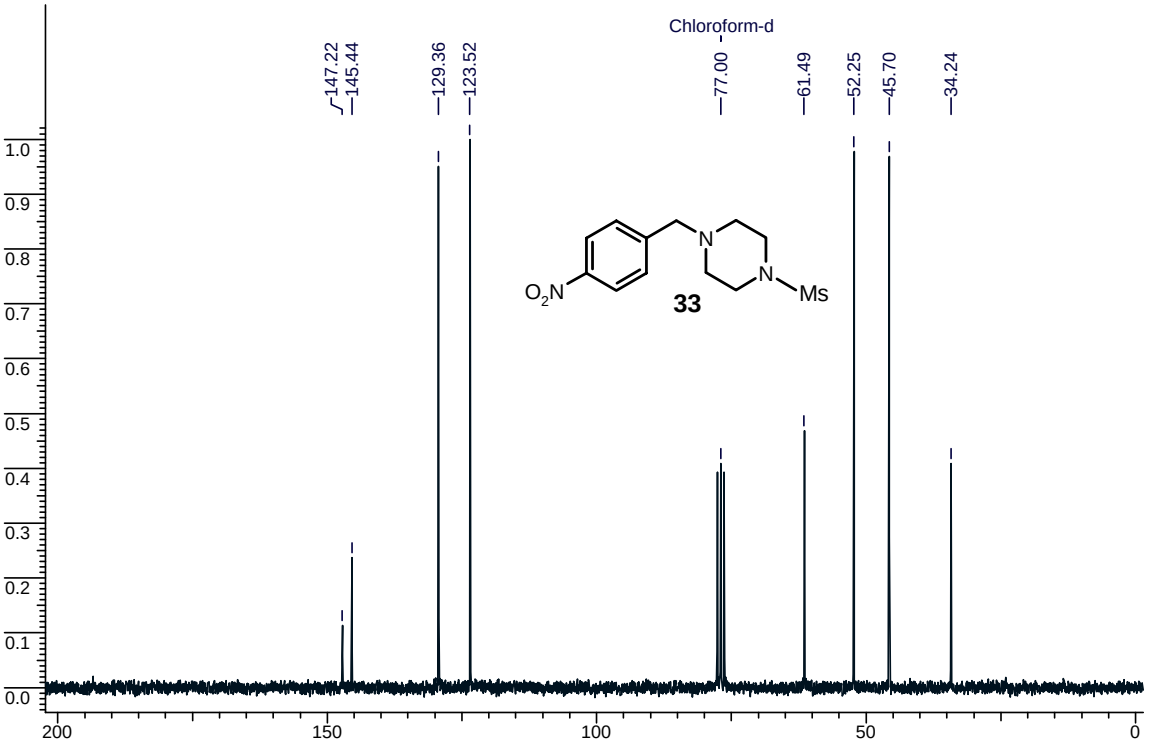
^{13}C NMR of **60**



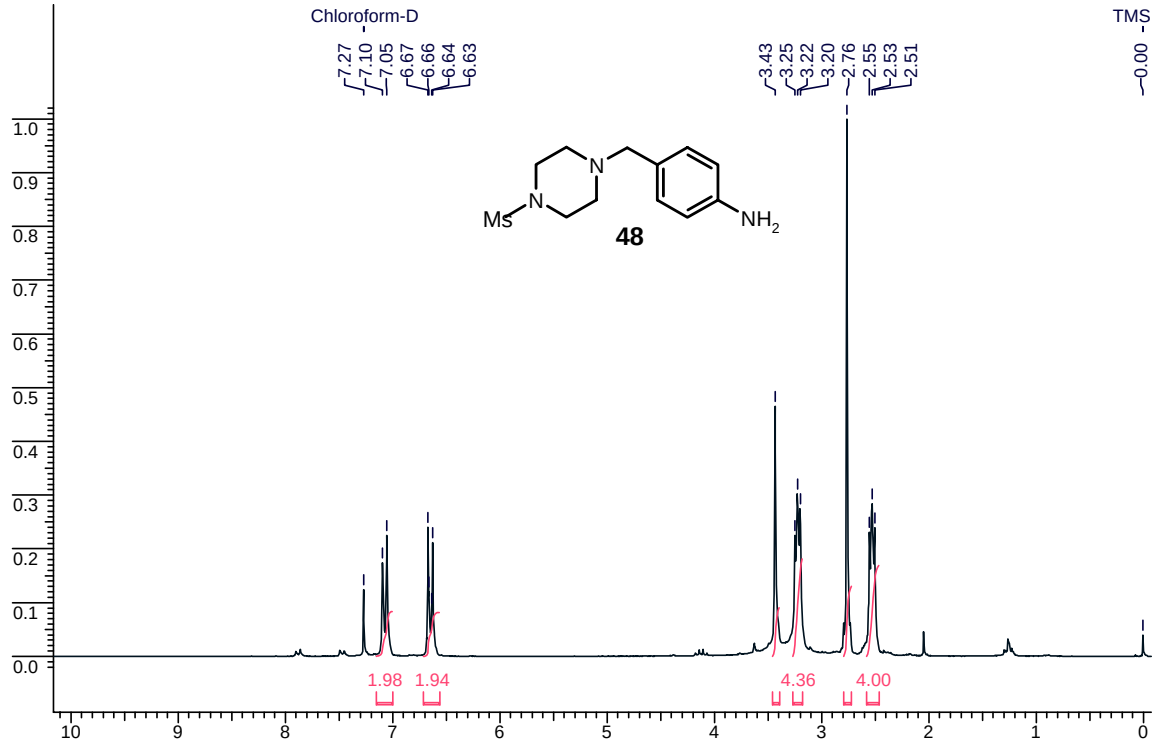
^{1}H NMR of **33**



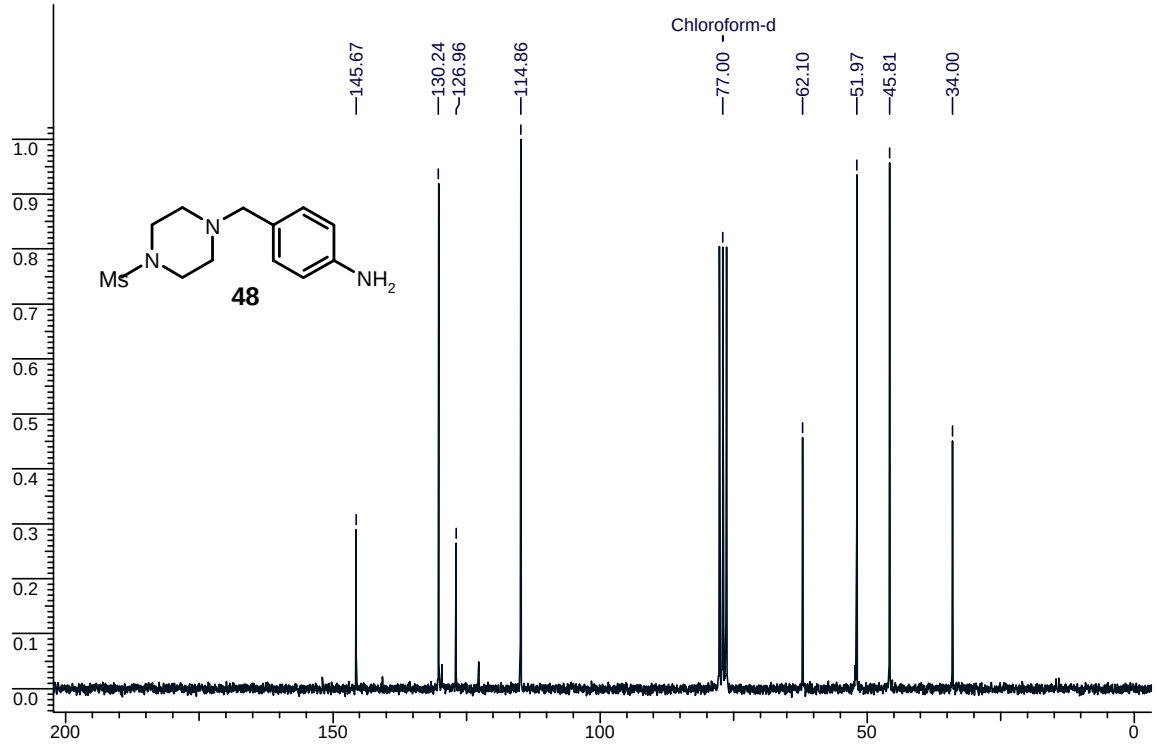
^{13}C NMR of **33**



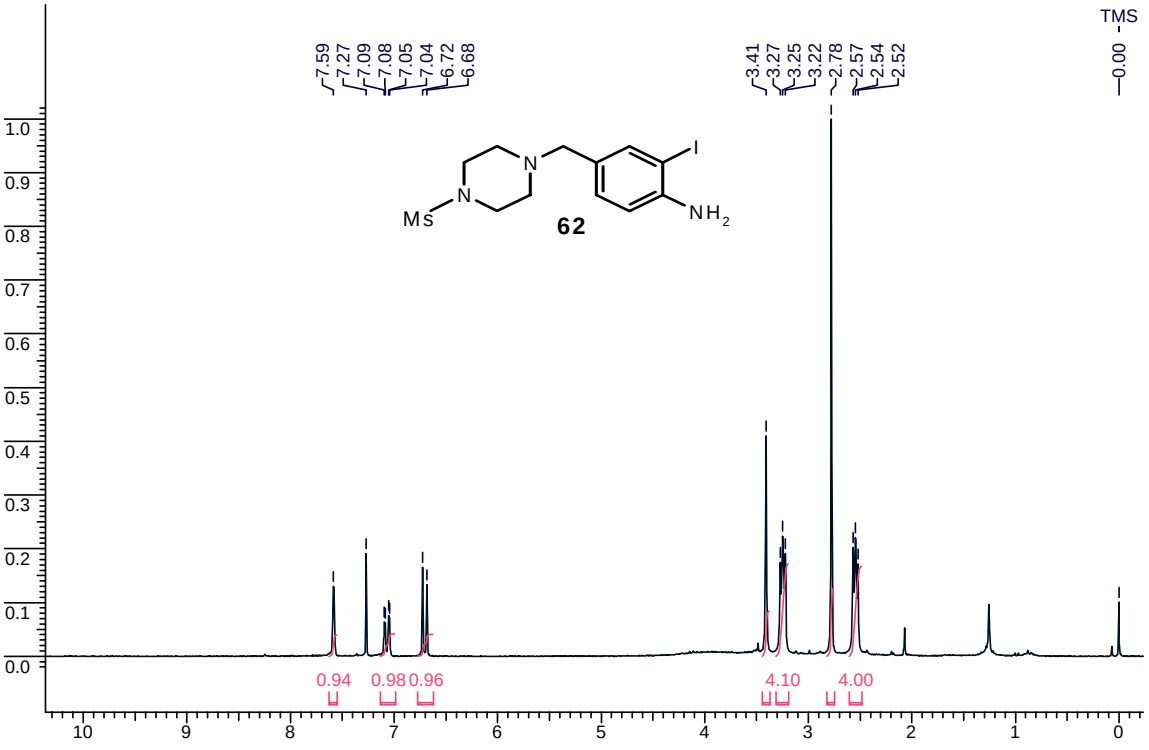
^{1}H NMR of **48**



^{13}C NMR of **48**



^{1}H NMR of **62**



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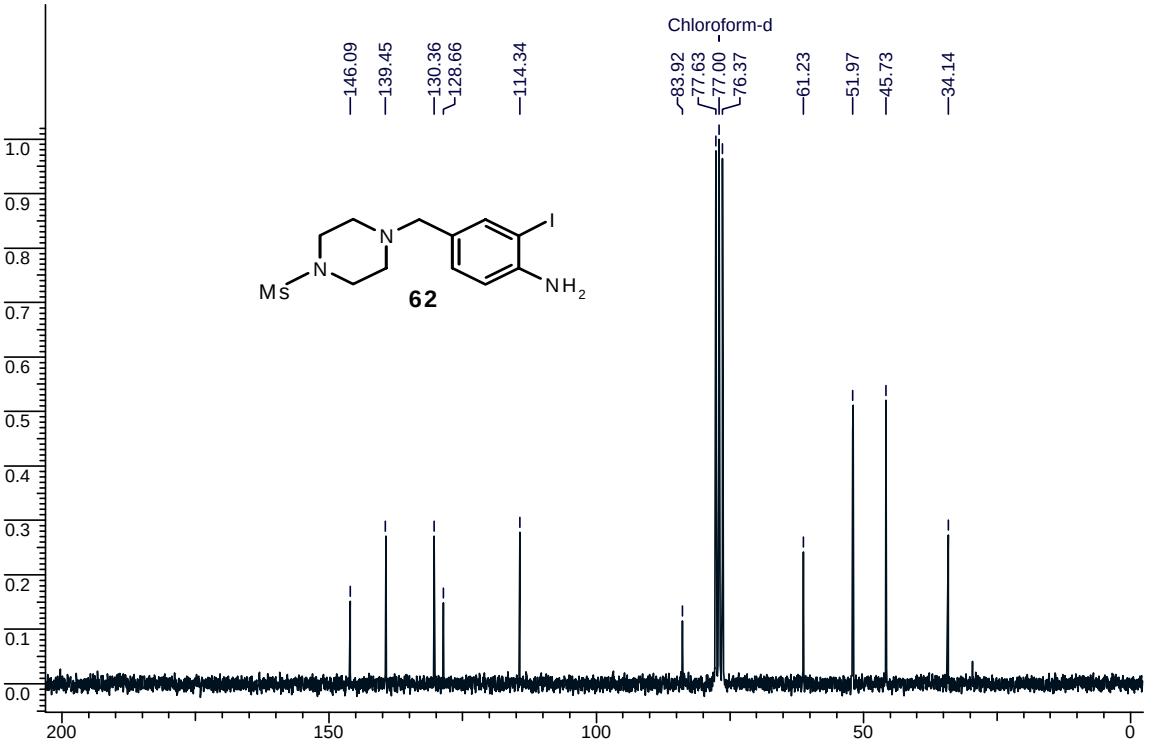
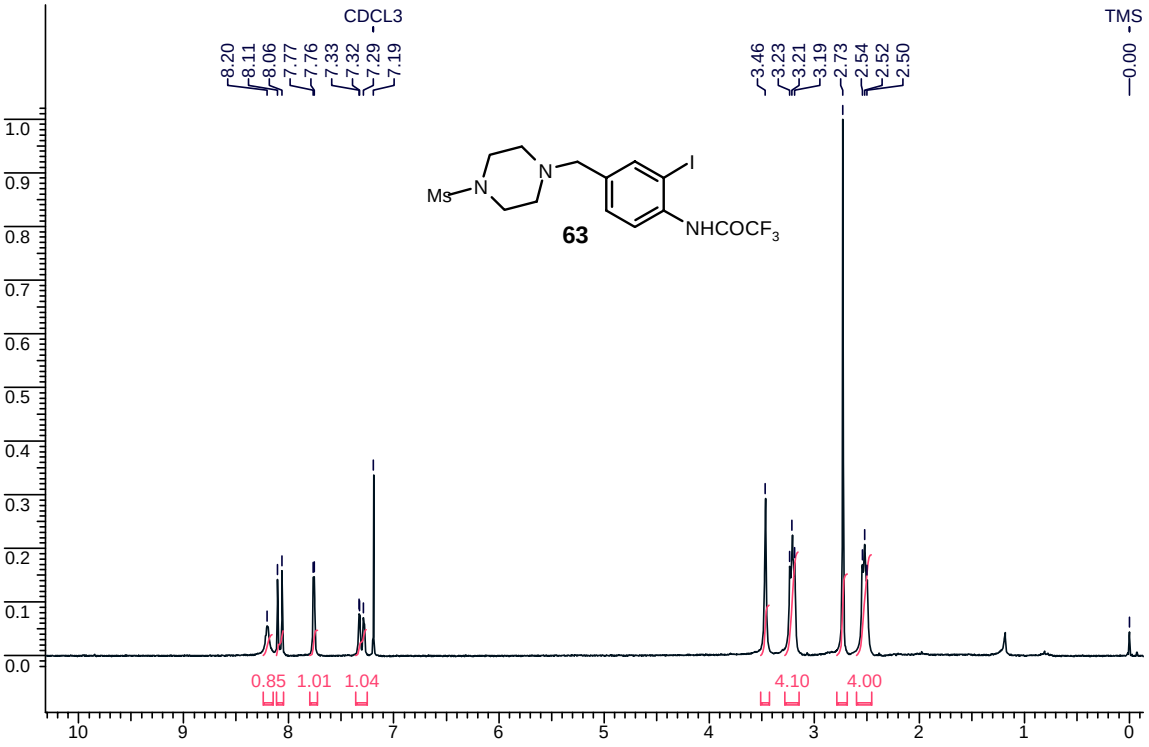


^{1}H NMR of **63**



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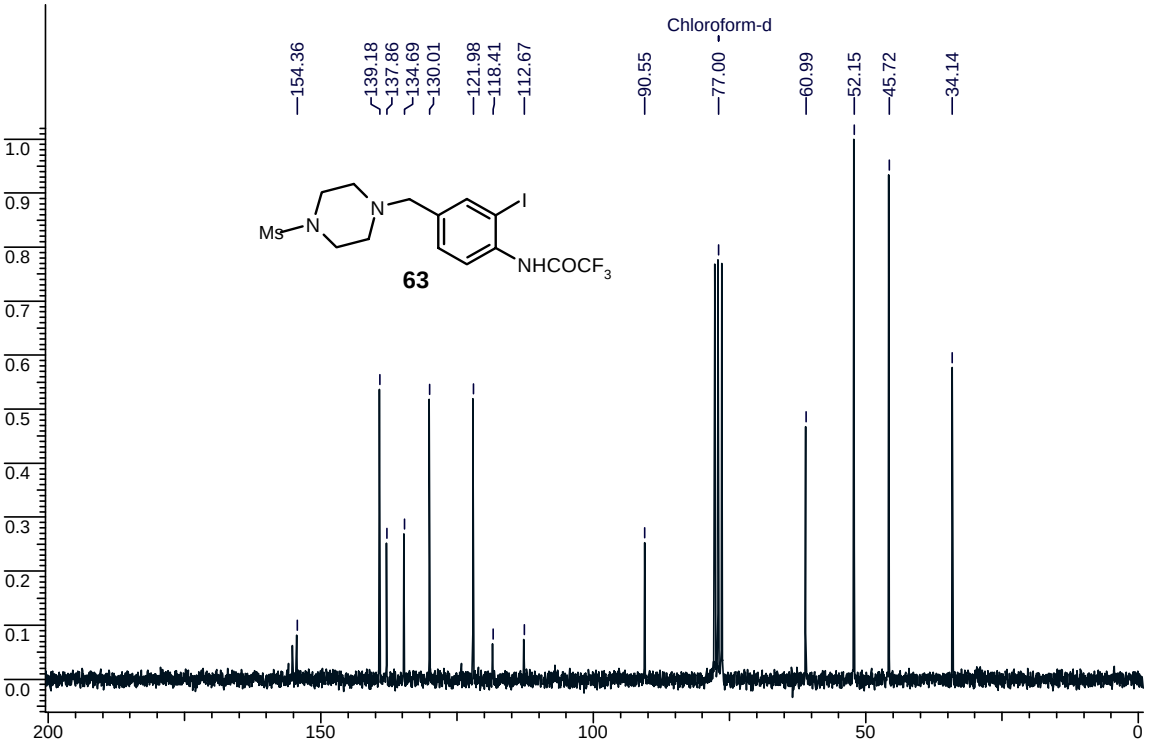

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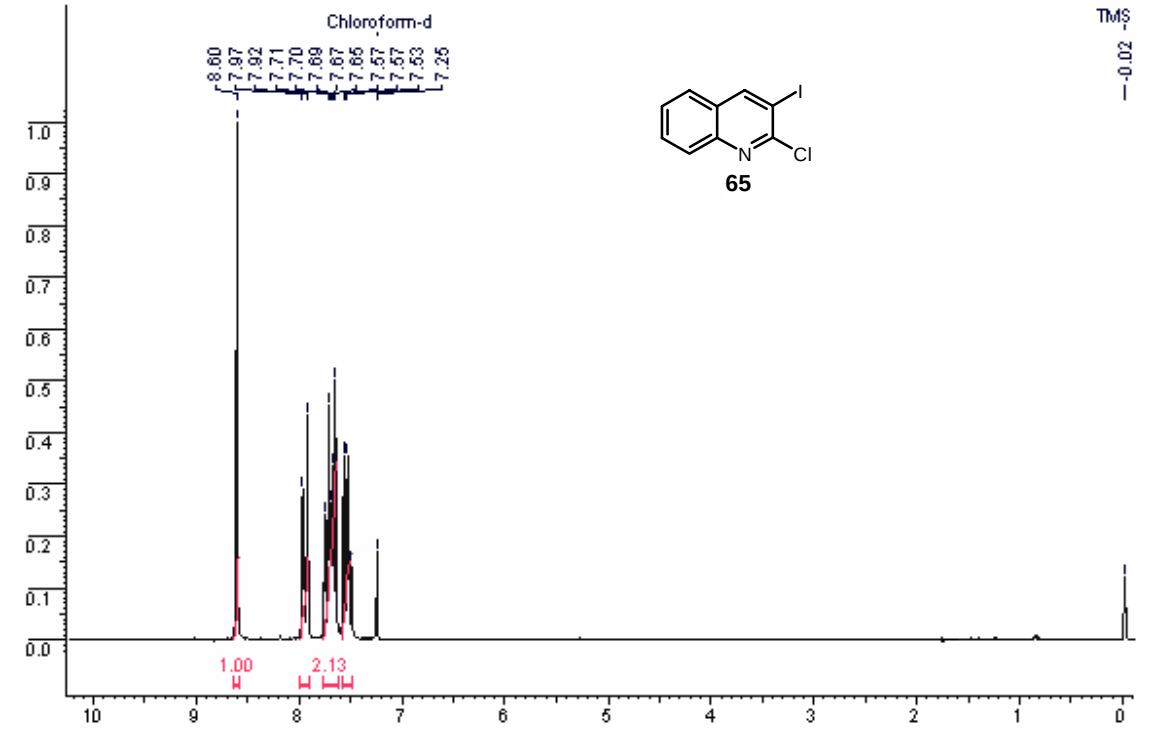

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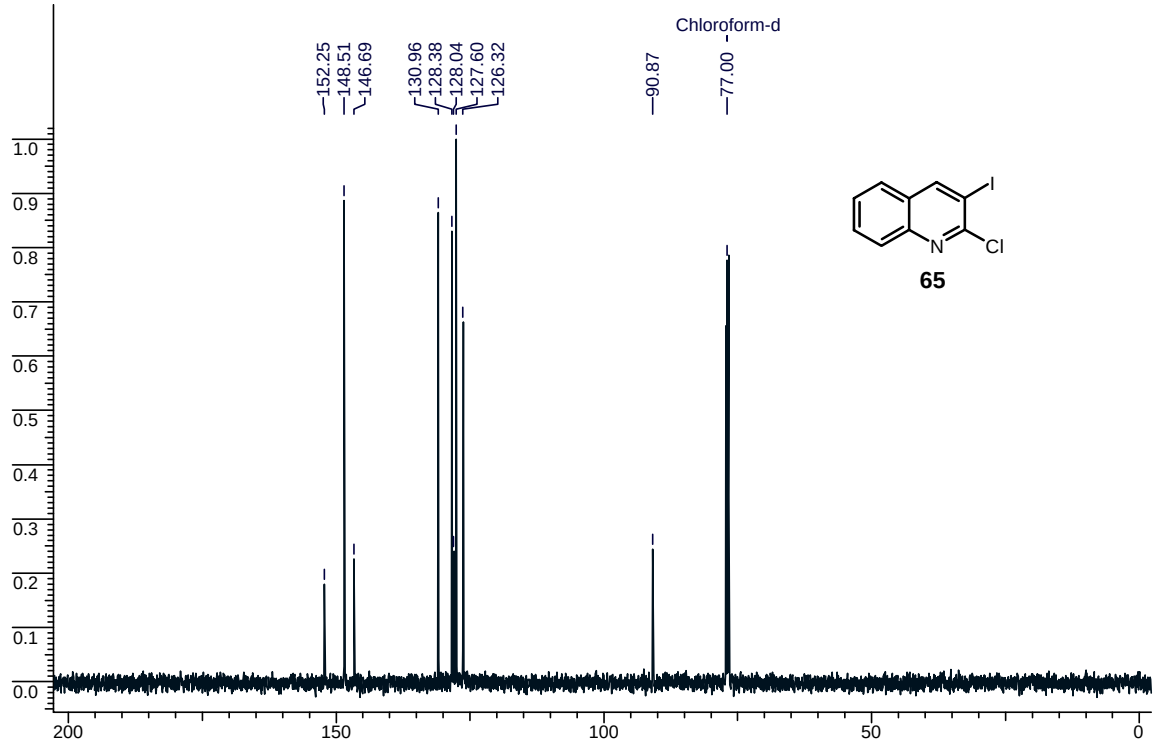

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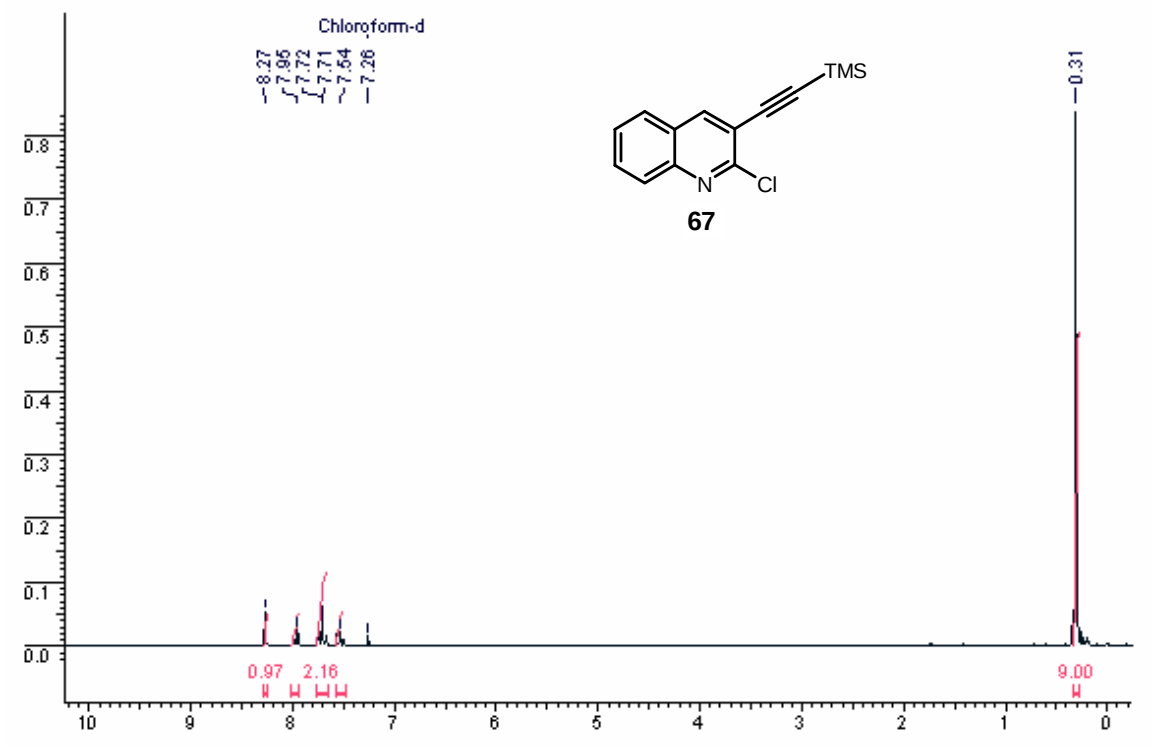
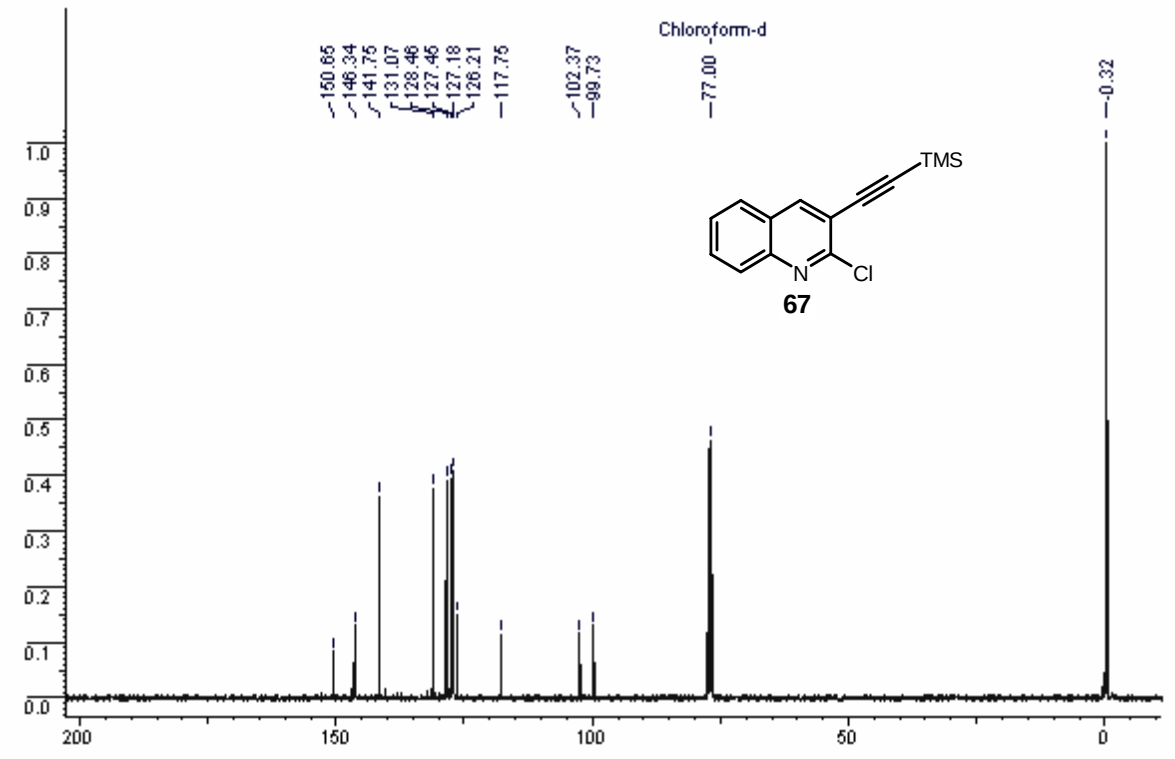
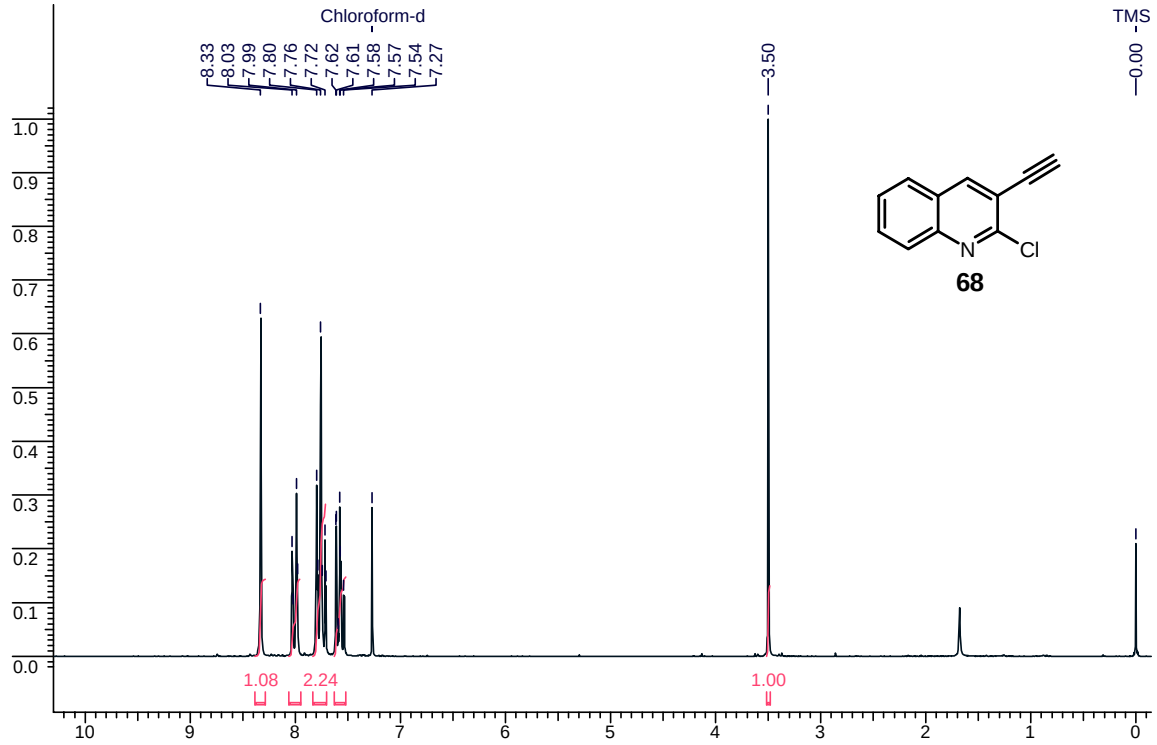


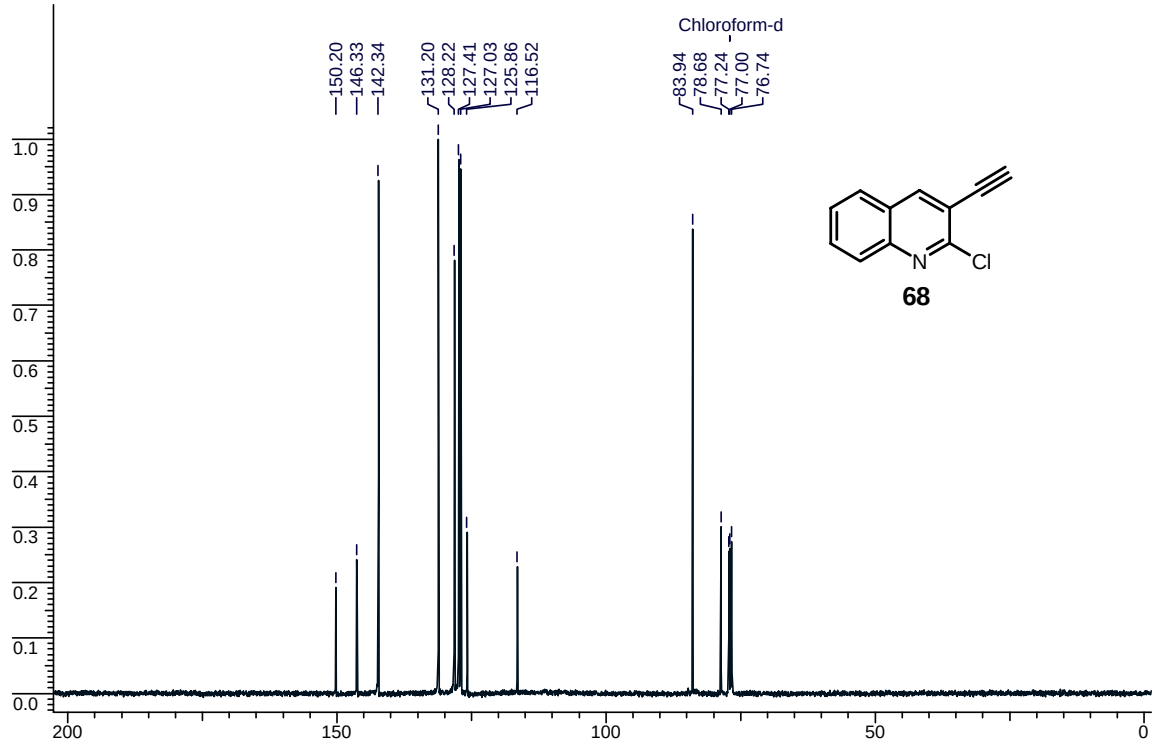
^{13}C NMR of **67**



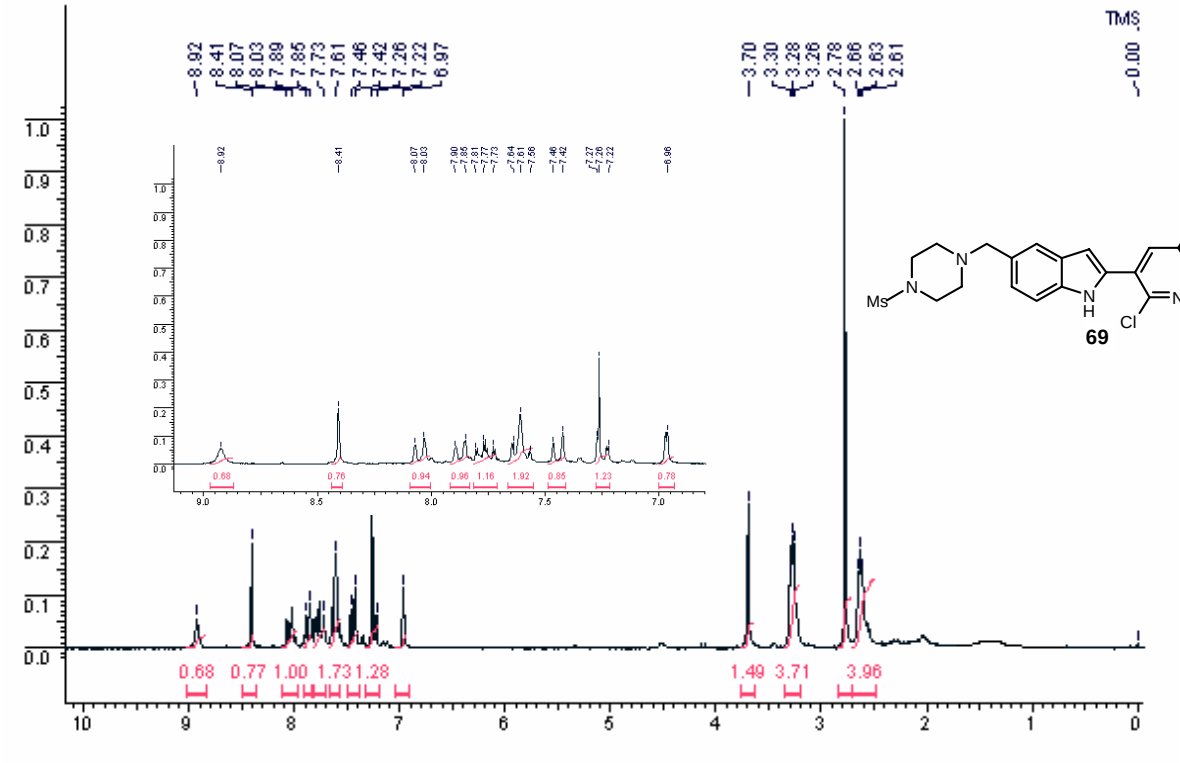
^{1}H NMR of **68**



^{13}C NMR of **68**



^{1}H NMR of **69**



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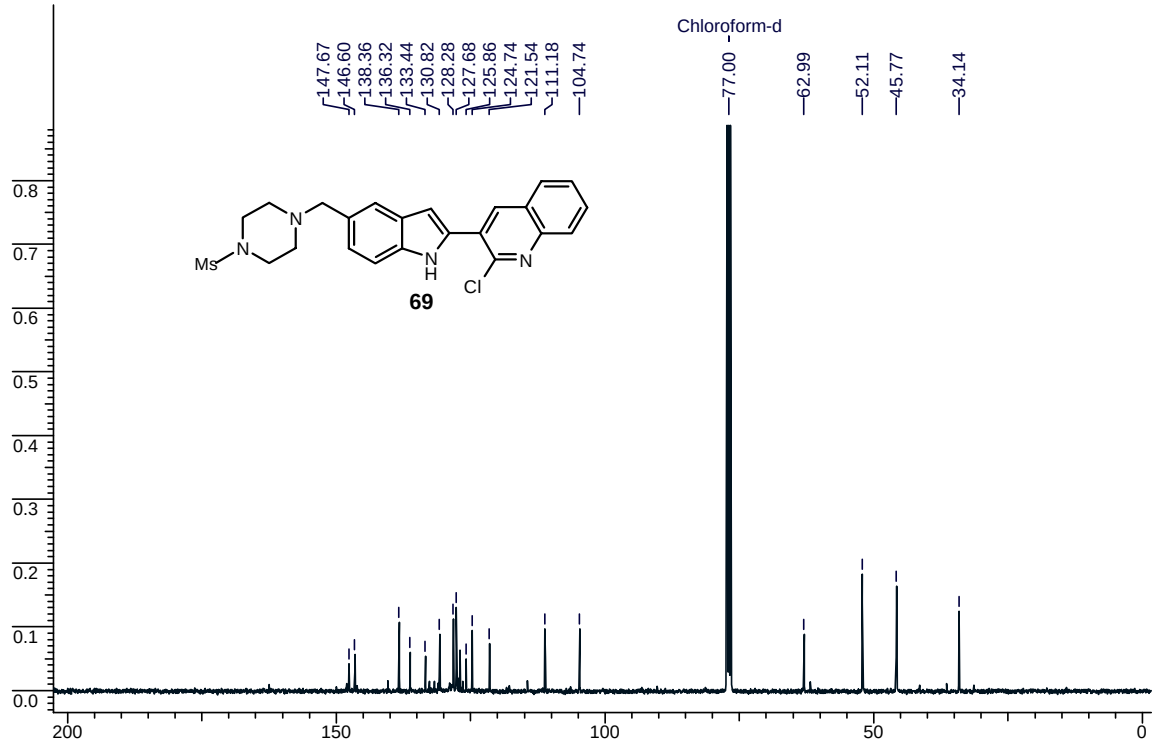

3.2.7 References

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Section C

Ultrasound-promoted copper-, ligand- and amine-free synthesis of benzo[b]furans/nitro benzo[b]furans via Sonogashira coupling-5-endo-dig-cyclization

3.3.0 Introduction

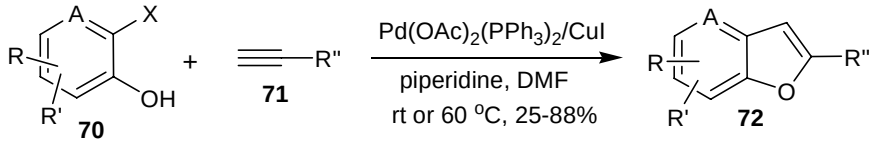
Benzo[*b*]furan derivatives are of considerable interest because of their occurrence in a wide range of natural substances and biologically active compounds.[1] For example, benzo[*b*]furans are active as inhibitor of 5-lipoxygenase,[2] as antitumor agents,[3] as calcium entry blockers,[4] as antagonists of the angiotensin II receptor,[5] as ligand of adenosine A_1 receptor[6] and as modulators of vitamin-D receptor.[7] Pharmaceutically, these potential properties of the benzo[*b*]furans are useful in the treatment of cancer, cardiovascular disease, type 2 diabetes, migraines, dementia and anxiety.[8] Nitro benzo[*b*]furans also have interesting pharmacological properties.[9]

3.3.1 Review of Literature

Various methods are known[10, 11] for the synthesis of benzo[*b*]furans and its derivatives.[12] Among these, in recent years palladium-catalyzed heteroannulation of *o*-halophenols and alkynes has been employed widely due to the versatile nature of these protocols, increased functional group tolerance and improved yields and among these some of the important methods are described below.

Cacchi's approach (1986)[13]

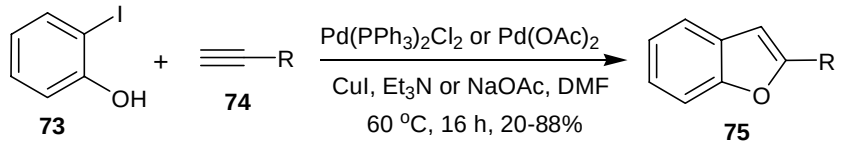
Cacchi, F. *et al*. have reported for the first time the palladium-catalyzed synthesis of benzo[*b*]furans and furo[3,2-*b*]pyridine **72** *via* the reaction of 2-hydroxyaryl and hydroxylheteroaryl halides **70** with a variety of alkynes **71** in the presence of $Pd(OAc)_2(PPh_3)_2$ as a catalyst and copper(I) iodide as co-catalyst as shown in Scheme **25**.



Scheme 25

Kundu's approach (1992)[14]

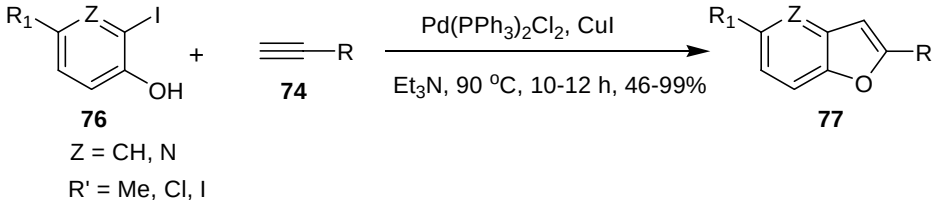
Kundu, N. G. *et al*. reported a facile method for the synthesis of benzofurans **75** *via* palladium-catalyzed heteroannulation of acetylenic compounds **74** as shown in Scheme **26**.



Scheme 26

Torii's approach (1992)[15]

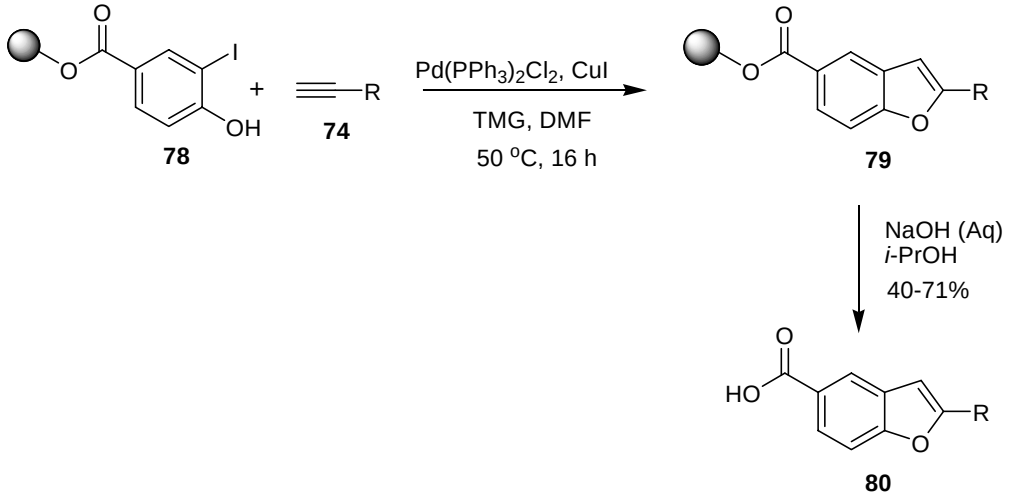
Torii, S. *et al*. reported a novel synthesis of functionalized benzo[*b*]furans and homologues **77** by using $Pd(PPh_3)_2Cl_2$-CuI as a catalytic system at 90 ^oC in triethylamine (Scheme **27**).



Scheme 27

Fancelli's approach (1997)[16]

Fancelli, D. *et al*. reported the solid phase synthesis of 2-substututed benzo[*b*]furans **80** *via* palladium-catalyzed heteroannulation of acetylenes **74** under mild conditions by using tetramethyl guanidine (TMG) as a base as shown in Scheme **28**.

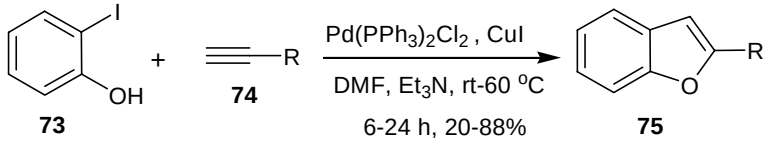


Scheme 28

Kundu's approach (1997)[17]

Kundu, N. G. *et al*. optimized the conditions for the heteroannulation of *o*-iodophenol **73** with acetylenic substrates **74** through palladium-copper catalysis leading to the synthesis of the 2-substitued benzofurans **75**. They also illustrated the

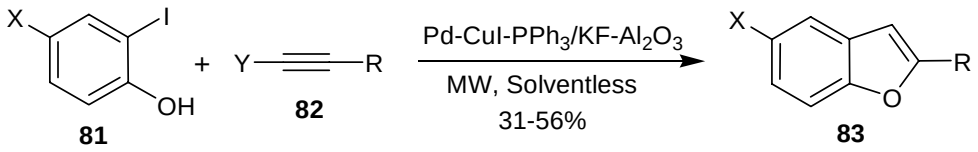
mechanism of this reaction giving experimental evidence for the formation of 2-alkynylphenol as an intermediate (Scheme **29**).



Scheme 29

Kabalka's approach (2001)[18]

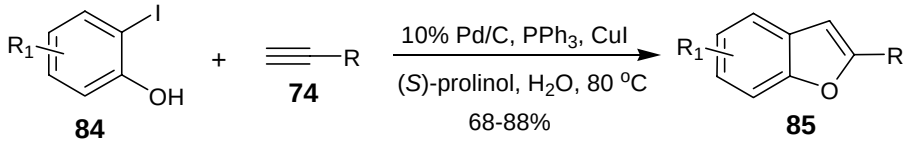
Kabalka, G. W. *et al*. reported solventless microwave-enhanced synthesis of benzofurans **83** on potassium fluoride doped alumina in the presence of palladium powder, cuprous iodide and triphenyl phosphine as shown in Scheme **30**.



Scheme 30

Pal's approach (2003)[19]

Pal, M. *et al*. reported an efficient synthesis of 2-aryl/alkyl substituted benzo[*b*]furans/nitrobenzo[*b*]furans **85** *via* Pd/C catalyzed reaction of *o*-iodophenols **84** with terminal alkynes **74** in the presence of PPh_3 as a ligand, CuI as a co-catalyst and (S)-prolinol as base in water (Scheme **31**).



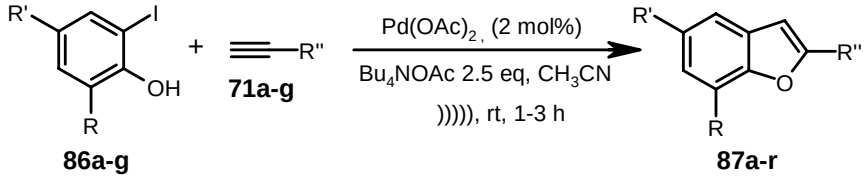
Scheme 31

However, most of these reported methods suffer from major or minor drawbacks such as harsh reaction conditions, generally reactions are carried out at elevated temperatures, requires phosphine ligand for the stabilization of the active catalytic species and also Cu(I) as co-catalyst. However, many of the phosphine ligands are sensitive to air and they are also expensive, toxic and unrecoverable, which results in significant limitations in their use in organic synthesis. With the presence of copper(I) as a co-catalyst the Glazer-type oxidative dimerization of terminal alkyne is

encountered, thus lowering the chemo selectivity and yields of the benzo[*b*]furans.[20] In addition to this, the amines generally used in excess as the base have a characteristic foul smell and industrial waste containing them would require treatment for environmental purposes. Thus, there is still scope for development of a more general, convenient and versatile *copper-, ligand-* and *amine-free* approach for the synthesis of benzo[*b*]furans *via* palladium-catalyzed Sonogashira coupling-5-*endo-dig*-cyclization.

3.3.2 Present Work

In this section, the results obtained from the optimization of reaction conditions for the synthesis of benzo[*b*]furans are discussed. A simple and efficient ultrasound-promoted $Pd(OAc)_2$ catalyzed one-pot synthesis of 2-substituted benzo[*b*]furans/nitro benzo[*b*]furans **87** *via* a Sonogashira coupling-5-*endo-dig*-cyclization protocol under *copper-, ligand-* and *amine-free* conditions at room temperature has been described (Scheme **32**).

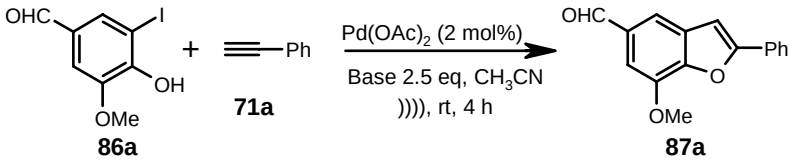


Scheme 32

3.3.3 Results and Discussion

Palladium-catalyzed reactions are known to be strongly dependent on a number of factors such as base, solvent, stabilizing ligand, other additives, temperature and combined effect of these. In the previous (Section **A**), we observed that, the base and solvent strongly influence the one-pot synthesis of indole *via* a Sonogashira coupling-5-*endo-dig*-cyclization. Thus, here we sought to initially optimize the reaction conditions for this protocol under ultrasonic irradiation at ambient temperature. For this purpose, we systematically evaluated the role of base and solvent for the typical Sonogashira coupling-5-*endo-dig*-cyclization reaction of 5-iodovanilin **86a** with phenyl acetylene **71a**. The results are summarized in Tables **7** and **8** respectively.

Table 7. Effect of base on Sonogashira coupling-5-*endo-dig*-cyclization reaction.

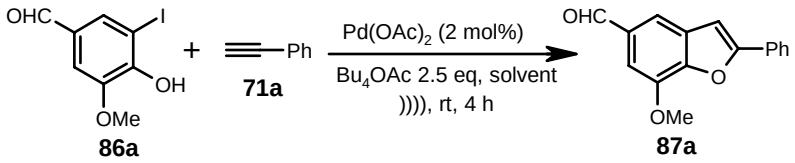


Entry	Base	Yield (%)[a]
1	Piperidine	28
2	NaOAc	10
3	K_2CO_3	06
4	Diisopropyl ethyl amine	31
5	pyrrolidine	20
6	Et_3N	39
7	Cs_2CO_3	60
8	DABCO	63
9	Bu_4NF (1 M soln in THF)	61
10	Bu_4NOAc	91
11	Bu_4NOH (0.1N soln in methanol)	00
12	Bu_4NBr	00
13	KO ^tBu	00

[a]isolated yields

Among the various bases screened, Bu_4NOAc was found to be the most effective base for this coupling-5-*endo-dig*-cyclization process (entry 10, Table **7**). Other bases such as TBAF (1M solution in THF), Cs_2CO_3 and DABCO (entry 7-9, Table **7**) gave moderate yields of the benzo[*b*]furan (**87a**). Moreover, the bases (entry 1-6 Table **7**) were substantially less effective, while potassium-*tert*-butoxide, *tetra*-butyl ammonium hydroxide/bromide failed to promote the reaction.

Table 8. Effect of solvent on Sonogashira coupling-5-*endo-dig*-cyclization reaction.



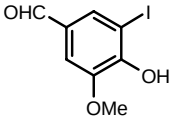
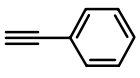
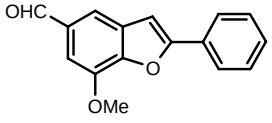
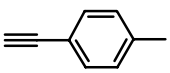
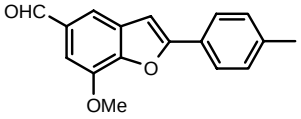
Entry	Solvent	Yield (%)[a]
1	DMF	54
2	DMA	53
3	THF	58
4	NMP	60
5	CH_3CN	91

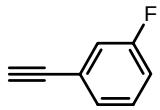
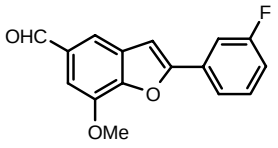
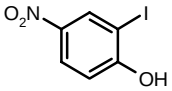
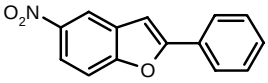
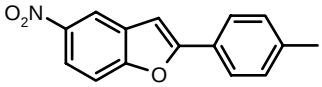
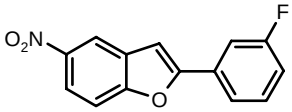
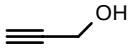
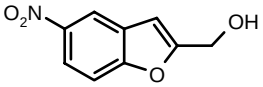
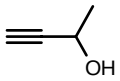
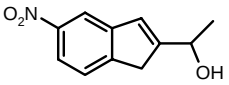
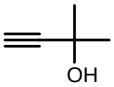
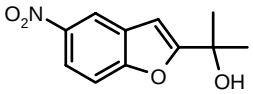
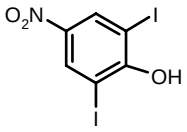
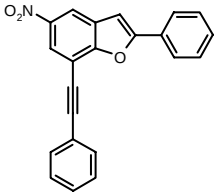
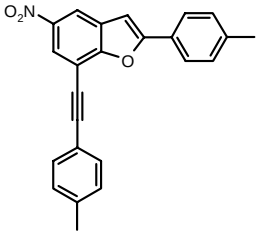
[a]isolated yields

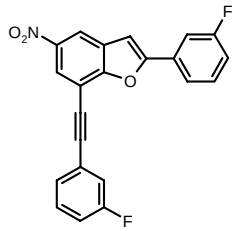
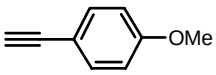
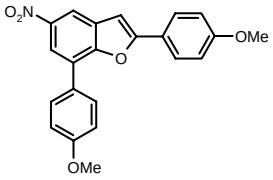
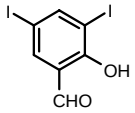
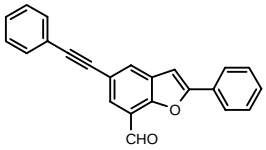
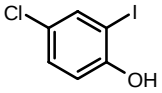
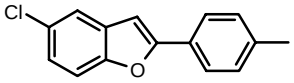
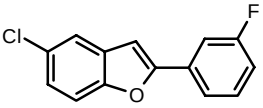
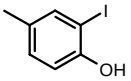
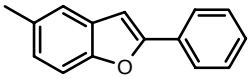
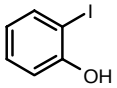
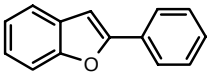
Next, the above benchmark reaction using Bu_4NOAc as base was examined in various solvents. As is evident, from Table **8**, acetonitrile was found to be the most suitable solvent. Other solvents such as DMF, DMA, THF and NMP (entry 1-4 Table **8**) gave only moderate yield of benzo[*b*]furan (**87a**).

These observations showed that the optimal reaction condition for the synthesis of 2-substituted benzo[*b*]furans **87** require 2 mol% $Pd(OAc)_2$ as catalyst, 2.5 eq Bu_4NOAc as base and acetonitrile as solvent. To survey the scope and generality of this protocol, the optimized reaction conditions were applied to the synthesis of a variety of benzo[*b*]furans/nitro benzo[*b*]furans. The results are summarized in Table **9**.

Table 9: Synthesis of 2-substituted benzo[*b*]furan/nitro benzo[*b*]furan under ultrasonic irradiation.

Entry	*o*-iodophenol 86	1-alkyne 71	Product 87	Reaction time(h)	Yield (%)[a]
1	 **86a**	 **71a**	 **87a**	**3**	**91**
2	**86a**	 **71b**	 **87b**	**3**	**79**

3	**86a**	 **71c**	 **87c**	**3**	**81**
4	 **86b**	**71a**	 **87d**	**1**	**95**
5	**86b**	**71b**	 **87e**	**1**	**94**
6	**86b**	**71c**	 **87f**	**1**	**91**
7	**86b**	 **71d**	 **87g**	**3**	**92**
8	**86b**	 **71e**	 **87h**	**1.5**	**98**
9	**86b**	 **71f**	 **87i**	**1.5**	**97**
10	 **86c**	**71a**	 **87j**	**1**	**76**
11	**86c**	**71b**	 **87k**	**1**	**78**

12	**86c**	**71c**	 **87l**	**1**	**72**
13	**86c**	 **71g**	 **87m**	**1**	**85**
14	 **86d**	**71a**	 **87n**	**2**	**76**
15	 **86e**	**71b**	 **87o**	**3**	**55**
16	**86e**	**71c**	 **87p**	**3**	**50**
17	 **86f**	**71a**	 **87q**	**3**	**40 (13)[b]**
18	 **86g**	**71a**	 **87r**	**3**	**42 (18)[b]**

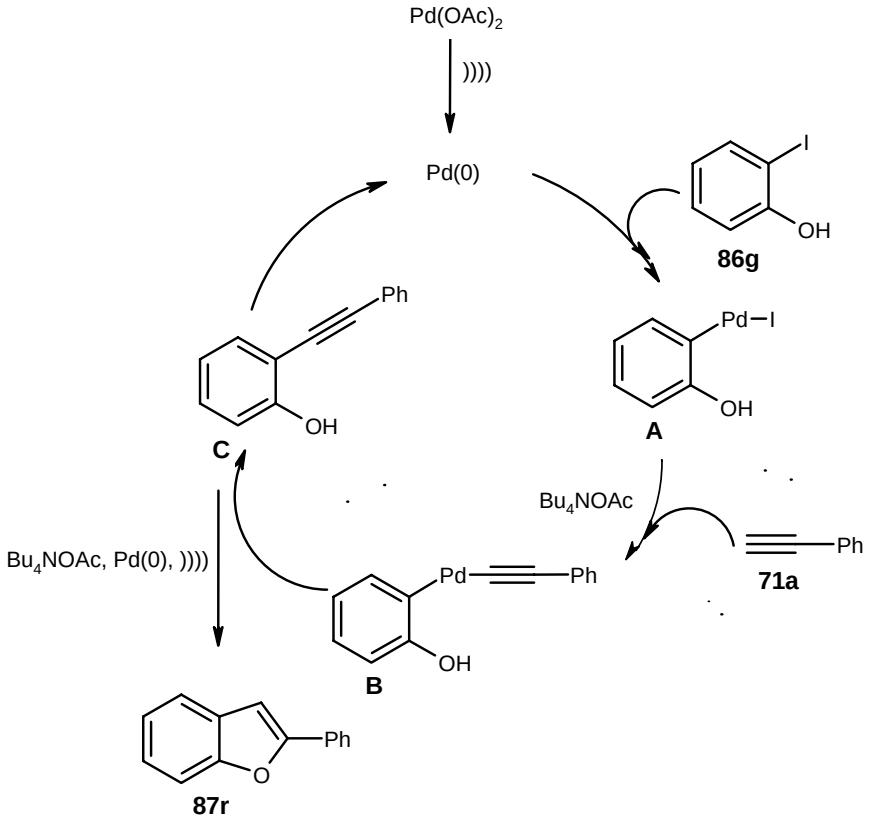
[a]Isolated yields
[b]Isolated yield of 1,3-diyne.

Different substituents including electron-withdrawing and electron-donating group present on both *o*-iodophenol **86** and terminal alkynes **71** were tolerated giving rise to moderate to very good yields of benzo[*b*]furans **87**. Most interesting characteristic feature of this protocol is that, the base labile nitro group present on *o*-iodophenol **86b,c** were well tolerated under these mild reaction conditions giving excellent yields of the nitro benzo[*b*]furans **87d-m** (entry 4-13, Table **9**). This is in contradiction to the earlier method reported by Dai *et al*. for the one-pot synthesis of nitro

benzo[*b*]furans *via* a Sonogashira coupling-5-*endo*-*dig*-cyclization using Pd[$(PPh_3)_2$]Cl_2-CuI as a catalytic system in toluene which afforded only low to moderate yields of desired nitro benzo[*b*]furans.[21] Also M. Pal *et al.*[19] recently reported the improved method for the one-pot synthesis of nitro benzo[*b*]furans *via* a Sonogashira coupling-5-*endo*-*dig*-cyclization in water. However, it makes use of PPh_3 as a ligand along with Pd/C catalyst, with CuI as a co-catalyst, expensive S-prolinol as a base and the reaction was carried out at 80 ^oC. Other *o*-iodophenols such as 5-iodovanilin **86a** underwent effective coupling-cyclization giving excellent yields of benzo[*b*]furans and also diiodophenols *viz.* 4-nitro-2,6-diiodophenol (**86c**) and 3,5-diiodo salicylaldehyde (**86d**) effectively coupled with terminal alkynes to give expected alkynyl substituted benzo[*b*]furans as the only product. These are synthons which can be exploited by elongation of conjugated system of benzo[*b*] furan ring for further functionalization. 5-Chloro-2-iodophenol (**86e**) gave moderate yields of the products. Unfortunately, unsubstituted *o*-iodophenol (**86g**) and iodophenol having electron donating group i. e. methyl (**86f**) gave lower yields of the benzo[*b*]furans under these mild reaction conditions along with the formation of 1,3-diyne as the side product arising from the Glazer-type homo coupling of terminal alkyne. Moreover, various substituted terminal alkynes underwent coupling-cyclization smoothly giving moderate to excellent yields of the benzo[*b*]furans.

3.3.4 Mechanism of the reaction

Mechanistically, the formation of 2-substituted benzofurans *via* palladium-catalyzed tandem Sonogashira coupling-5-*endo*-*dig*-cyclization reaction of *o*-iodophenol with terminal alkyne proceed[17] *via* oxidative insertion of *o*-iodophenol to a ligand stabilized Pd(0) complex gives a σ-arylpalladium(II) complex which on trans-metallation to generate the aryl alkynylpalladium(II) species. This on reductive elimination of Pd(0) then affords acyclic products, e. g. 2-alkynylphenol. The latter on cyclization in the presence of base resulted in the formation of the benzofuran. The mechanism of the Sonogashira coupling-5-*endo*-*dig*-cyclization reaction is represented in Scheme **33**.



Scheme 33. Mechanism of Sonogashira coupling-5-*endo*-*dig*-cyclization

This means that Pd(0) species stabilized by ligands is proposed to be involved in the catalytic cycle comprising of oxidative insertion, trans-metallation and reductive elimination. Consequently, the formation of Pd(0) nanoparticles was investigated in the present work by subjecting the reaction mixture after a successful Sonogashira coupling-5-*endo*-*dig*-cyclization reaction of 5-iodovanilin with phenyl acetylene in acetonitrile 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. The TEM measurements for the acetonitrile medium (**Figure 3**) show the presence of polydispersed Pd(0) nanoparticles of irregular morphology varying in diameter from 3 to 8 nm.

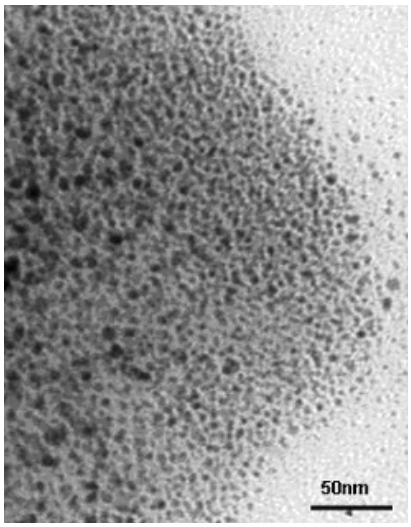


Figure 3

It is important to note that, the Sonogashira coupling-5-*endo-dig*-cyclization reaction of 5-iodovanilin with phenyl acetylene when performed using same conditions but in the absence of ultrasound (silent condition) showed only 60% yield of the benzo[*b*]furan (**87a**) even after 24 h, which clearly highlights the role played by ultrasound in enhancing the rate of reaction and yield of the desired product. Moreover, under a control experiment, Pd(0) nanoparticles were formed by sonicating a mixture of $Pd(OAc)_2$ and Bu_4NOAc in acetonitrile. To this the reactants, *viz.* 5-iodovanilin and phenyl acetylene were added and mixture was stirred for 3 h at ambient temperature under silent conditions. The benzofuran (**87a**) was obtained in 64% isolated yield against the 39% yield of total reaction under silent condition after same reaction time (3 h). In another control experiment, after the initial formation of Pd(0) nanoparticles by sonicating a mixture of $Pd(OAc)_2$ and Bu_4OAc, the reactants 5-iodovanilin and phenyl acetylene were added and the reaction mixture subjected to ultrasonication for 2.5 h. This afforded 94% yield of benzofuran (**87a**) as against 64% yield when the same reaction was carried out at under silent conditions. This indicates that although the pre-formed nanoparticles promote the coupling-cyclization reaction, however the yield was relatively lower under silent stirred conditions as compared to total sonochemical reaction. This implies that ultrasound not only brings about the formation of highly crystalline, active Pd(0) nanoparticles required for the coupling-cyclization process, but also has promoted the activity of the catalytic species in the

oxidative insertion, trans-metallation, reductive elimination and cyclization of the Sonogashira coupling-5-*endo*-*dig*-cyclization process. 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.[22]

Effect of ultrasound on the cyclization step were also studied. The *o*-(phenylethynyl) phenol (**C**, Scheme **33**) was prepared according to procedure given in the literature.[23] The cyclization of *o*-(phenylethynyl) phenol was carried out under ultrasonic irradiation using $Pd(OAc)_2$ as a catalyst and Bu_4NOAc as a base in acetonitrile. The 2-phenylbenzofuran (**87r**) was obtained 99 % isolated yield after 1 h, which was better as compared to the yield of 64% when cyclization was carried out under similar conditions but without ultrasound for the same reaction time (1 h). In another control experiment, after the initial formation of Pd(0) nanoparticles by sonicating a mixture of $Pd(OAc)_2$ and Bu_4OAc, the intermediate *o*-(phenylethynyl)phenol was added and the reaction mixture subjected to ultrasonication for 1 h. This afforded 100% yield of the cyclized 2-phenylbenzofuran (**87r**) as against 74% yield when the same reaction was carried out at under silent conditions. This implies that ultrasound by itself also enhances the rate of cyclization and yield of the product by the phenomemon of acoustic cavitation probably further enhancing the activities of the catalyst and base. We observed that cyclization does not proceed in the absence of either of Bu_4NOAc and $Pd(OAc)_2$, this indicates that both are required for the cyclization step.

3.3.5 Conclusion

In summary, we have developed a mild, efficient and general *copper*-, *ligand*- and *amine*-free one-pot synthesis of benzo[*b*]furans/nitro benzo[*b*]furans *via* a Sonogashira coupling-5-*endo*-*dig*-cyclization by using $Pd(OAc)_2$ (2 mol%) as the catalyst, Bu_4NOAc as the base in acetonitrile under ultrasonic irradiation at ambient temperature. Base labile nitro group present on *o*-iodophenol were well tolerated under these mild reaction conditions giving rise to good to excellent yields of the nitro benzo[*b*]furans which is a characteristic feature of this protocol. Various other substituents present on both the coupling component are also more or less effectively tolerated. Some of these substituents present in the benzo[*b*]furan ring are amenable

for further functionalization of the benzo[*b*]furan nucleus. The ultrasonication produced Pd(0) nanoparticles stabilized by Bu_4NOAc (TEM). Evidence, by way of control experiments clearly suggests that ultrasound has uniquely promoted by the phenomenon of acoustic cavitation both the Sonogashira coupling-5-*endo*-*dig*-cyclization in totality as well as the cyclization step in the presence of the catalyst and the base.

3.3.6 Experimental Section

General procedure for the synthesis of benzo[*b*]furans/nitro benzo[*b*]furans

To the mixture of *o*-iodophenol **86** (1 mmol), $Pd(OAc)_2$ (2 mol%) and Bu_4NOAc (2.5 mmol or 3.5 mmol for diiodophenol) in dry acetonitrile was added terminal alkyne **71** (1.1 mmol or 2.2 mmol for diiodophenol) under argon atmosphere. The resulting reaction mixture was then sonicated for the time indicated in Table **9**. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated under reduced pressure, the residue diluted with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the crude product. The crude product was further purified by column chromatography using ethyl acetate/petroleum ether as eluent to afford the pure product **87**.

Characterization data for the Benzo[*b*]furans 87a-r

7-Methoxy-2-phenylbenzofuran-5-carbaldehyde (87a):

Nature of compound; mp	**:**	Pale yellow solid, mp 148-149 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 1693, 1593, 1475, 1342, 1216, 757.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	4.04 (s, 3H), 7.01 (s, 1H), 7.30 (d, *J* = 1.37 Hz, 1H), 7.35-7.47 (m, 3H), 7.62 (d, *J* = 1.40 Hz, 1H), 7.82 (d, *J* = 1.41 Hz, 1H), 7.85 (d, *J* = 1.75 Hz, 1H), 9.94 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	56, 101.4, 119.2, 125, 128.7, 129.1, 129.4, 130.1, 133.3, 145.9, 147.5, 157.6, 191.6.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79; Found: C, 75.83; H, 4.54.

7-Methoxy-2-*p*-tolylbenzofuran-5-carbaldehyde (87b):

Nature of compound; mp	**:**	Pale yellow solid, mp 154-155 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 1692, 1595, 1215, 757.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.38 (s, 3H), 3.96 (s, 3H), 6.87 (s, 1H), 7.13 (d, *J* = 8.09 Hz, 2H), 7.22 (s, 1H), 7.53 (s, 1H), 7.64 (d, *J* = 8.06 Hz, 2H), 9.85 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.3, 56.2, 101.0, 104.7, 118.8, 125.1, 126.8, 129.5, 130.9, 133.5, 139.3, 145.9, 147.5, 158.1, 191.5.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30; Found: C, 76.53; H, 5.13.

2-(3-Fluorophenyl)-7-methoxybenzofuran-5-carbaldehyde (87c):

Nature of compound; mp	**:**	Yellow solid, mp 154-155 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 1693, 1595, 1342, 1216, 668.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	4.08 (s, 3H), 7.06 (dd, *J* = 8.04, 2.94 Hz, 1H), 7.10 (s, 1H), 7.36-7.45 (m, 2H), 7.57 (d, *J* = 9.55 Hz, 1H), 7.64 (d, *J* = 6.89 Hz, 1H), 7.70 (s, 1H), 9.99 (s, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	56.0, 102.7, 104.7, 111.6, 112.1, 115.6, 116.1, 119.2, 120.7, 130.3, 131.5, 133.4, 145.9, 147.5, 156.2, 160.5, 191.5.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{17}H_{14}O_3$: C, 71.11; H, 4.10; Found: C, 70.85; H, 3.70.

5-Nitro-2-phenylbenzofuran (87d):

Nature of compound; mp	**:**	Yellow solid, mp 145-146 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 1524, 1350, 1215, 756, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.08 (s, 1H), 7.40-7.58 (m, 4H), 7.83 (d, *J* = 1.38 Hz, 1H), 7.87 (d, *J* = 1.78 Hz, 1H), 7.79 (dd, *J* = 9.08, 2.38 Hz, 1H), 8.47 (d, *J* = 2.27 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	101.5, 11.3, 117.2, 120.0, 125.2, 128.9, 129.6, 144.2, 157.5, 159.1.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86

Found: C, 70.68; H, 4.05; N, 6.10.

5-Nitro-2-*p*-tolylbenzofuran (87e):

Nature of compound; mp	**:**	Yellow solid, mp 170 °C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 1620, 1590, 1522, 1347, 1215, 757, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.45 (s, 3H), 7.07 (s, 1H), 7.32 (d, *J* = 8.72 Hz, 2H), 7.59 (d, *J* = 8.88 Hz, 1H), 7.78 (d, *J* = 8.23, 2H), 8.21 (dd, *J* = 9.10, 2.39 Hz, 2H), 8.49 (d, *J* = 2.12 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.4, 100.7, 111.2, 116.9, 119.7, 125.2, 126.4, 129.6, 139.9, 144.2, 157.5, 159.5.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53 Found: C, 70.98; H, 4.63; N, 5.90.

2-(3-Fluorophenyl)-5-nitrobenzofuran (87f):

Nature of compound; mp	**:**	Yellow solid, mp 148 °C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 1620, 1595, 1525, 1350, 1215, 758, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.09 (dd, *J* = 8.32, 1.03 Hz, 1H), 7.14 (s, 1H), 7.39-7.67 (m, 4H), 8.23 (dd, *J* = 8.95, 2.38 Hz, 1H), 8.51 (d, *J* = 2.27 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	101.5, 11.3, 117.2, 120.0, 125.2, 128.9, 129.6, 131.1, 144.3, 157.5, 159.2.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{14}H_8FNO_3$: C, 65.37; H, 3.13; N, 5.45 Found: C, 65.23; H, 3, 21; N, 5.70.

(5-Nitrobenzofuran-2-yl)methanol (87g):

Nature of compound; mp	**:**	Brown solid, mp 116-118 °C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3418, 2922, 1590, 1455, 1344, 1266, 731, 685.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	4.76 (s, 2H), 6.74 (s, 1H), 7.47 (d, *J* = 9.01 Hz, 1H), 8.13 (dd, *J* = 9.00, 2.40 Hz, 1H), 8.40 (d, *J* = 2.26 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	157.8, 104.6, 11.5, 117.6, 120.2, 128.5, 143.2, 152.4, 159.9.

Elemental analysis (%)	**:**	Anal.Calcd.for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25 Found: C, 55.73; H, 3, 41; N, 7.50.

1-(5-Nitrobenzofuran-2-yl)ethanol (87h):

Nature of compound; mp	**:**	Yellow solid; mp 71-73 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3399, 3020, 1592, 1524, 1346, 1265, 754, 667.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.71 (d, *J* = 6.68 Hz, 3H), 5.10 (q, *J* = 6.61 Hz, 1H), 6.80 (s, 1H), 7.56 (d, *J* = 9.17 Hz, 1H), 8.49 (d, *J* = 2.29 Hz, 1H), 8.62 (d, *J* = 2.68 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.3, 64.0, 101.6, 111.5, 117.5, 120.0, 128.5, 143.9, 160.8, 163.5.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76 Found: C, 57.83; H, 4, 41; N, 6.53.

2-(5-Nitrobenzofuran-2-yl)propan-2-ol (87i):

Nature of compound; mp	**:**	Yellow solid, mp. 59-61 ^oC. (lit.[19] mp. 60-62 ^oC).
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3400, 2984, 1592, 1523, 1451, 1348, 1266, 1167, 754, 685.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	1.73 (s, 6H), 2.48 (br s, 1H), 6.76 (s, 1H), 7.54 (d, *J* = 9.11 Hz, 1H), 8.21 (dd, *J* = 8.98, 2.41 Hz, 1H), 8.46 (d, *J* = 2.40 Hz, 1H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	28.5, 69.3, 101.1, 111.4, 117.4, 119.8, 128.6, 143.8, 157.4, 166.5.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33 Found: C, 59.80; H, 5, 11; N, 6.52.

5-Nitro-2-phenyl-7-(2-phenylethynyl)benzofuran (87j):

Nature of compound; mp	**:**	Yellow solid, mp 152 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2219, 1618, 1590, 1535, 1350, 1215, 787, 669.
^1H NMR ($CDCl_3$, 200 MHz) δ	**:**	7.13 (s, 1H), 7.39-7.54 (m, 6H), 7.62-7.69 (m, 2H), 7.92 (dd, *J* = 8.22, 1.78 Hz, 2H), 8.34 (d, *J* = 2.25 Hz, 1H), 8.43 (d, *J* = 2.25 Hz, 1H).

^{13}C NMR	**:**	81.7, 95.8, 101.7, 108.2, 116.7, 122.2, 122.8, 125.3,
($CDCl_3$, 50 MHz) δ		128.5, 128.9, 129.8, 131.9, 144.0, 156.9, 159.4.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13
		Found: C, 77.48; H, 3.54; N, 3.90.

5-Nitro-2-*p*-tolyl-7-(2-*p*-tolylethynyl)benzofuran (87k):

Nature of compound; mp	**:**	Yellow solid, mp 162 -164 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 2218, 1617, 1591, 1534, 1348, 1215, 759, 668.
^{1}H NMR	**:**	2.38 (s, 3H), 2.40 (s, 3H), 6.95 (s, 1H), 7.19-7.24 (m,
($CDCl_3$, 200 MHz) δ		4H), 7.52 (d, *J* = 7.41 Hz, 2H), 7.70 (d, *J* = 8.15 Hz,
		2H), 8.24 (d, *J* = 19.05 Hz, 2H).
^{13}C NMR	**:**	21.4, 21.5, 81.2, 96.0, 100.8, 108.2, 116.2, 119.2, 122.4,
($CDCl_3$, 50 MHz) δ		125.1, 126.0, 129.1, 129.2, 129.6, 131.7, 139.4, 139.9,
		143.9, 159.5.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{24}H_{17}NO_3$: C, 78.46; H, 4.66; N, 3.81
		Found: C, 78.12; H, 4.59; N, 3.75.

2-(4-Methoxyphenyl)-7-(2-(4-methoxyphenyl)ethynyl)-5-nitrobenzofuran (87l):

Nature of compound; mp	**:**	Yellow solid, mp 165 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 2216, 1614, 1533, 1348, 1215, 759, 669.
^{1}H NMR	**:**	3.78 (s, 6H), 6.83-6.89 (m, 4H), 6.93 (s, 1H), 7.50 (d, *J*
($CDCl_3$, 200 MHz) δ		= 8.82 Hz, 2H), 7.72 (d, *J* = 8.98 Hz, 2H), 8.04 (dd, *J* =
		12.50, 2.26 Hz, 2H).
^{13}C NMR	**:**	55.9, 80.8, 96.0, 100.1, 108.5, 114.2, 114.5, 115.9,
($CDCl_3$, 50 MHz) δ		121.7, 122.2, 126.9, 129.8, 133.4, 144.2, 156.9, 159.6,
		160.4, 160.9.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{24}H_{17}NO_5$: C, 72.17; H, 4.29; N, 3.51
		Found: C, 71.92; H, 4.21; N, 3.17.

2-(3-Fluorophenyl)-7-(2-(3-fluorophenyl)ethynyl)-5-nitrobenzofuran (87m):

Nature of compound; mp	**:**	Yellow solid, mp 155 ^oC.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3020, 2216, 1610, 1581, 1537, 1343, 1215, 757, 669.

^{1}H NMR (CDCl$_3$, 200 MHz) δ	**:**	7.08-7.18 (m, 2H), 7.32-7.71 (m, 7H), 8.35 (d, *J* = 2.26 Hz, 1H), 8.45 (d, *J* = 2.15 Hz, 1H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	**:**	82.2, 94.5, 102.7, 107.8, 119.9, 112.4, 116.4, 116.5, 116.8, 116.9, 117.2, 118.4, 118.8, 120.9, 121.0, 123.3, 127.7, 127.8, 129.3, 130.1, 130.2, 130.6, 130.7, 144.1, 156.8, 157.9, 159.8, 160.5, 164.8, 165.4.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{22}H_{11}F_2NO_3$: C, 70.40; H, 2.95; N, 3.73 Found: C, 70.42; H, 2.73; N, 3.69.

2-Phenyl-5-(2-phenylethynyl)benzofuran-7-carbaldehyde (87n):

Nature of compound; mp	**:**	Yellow solid, mp 141-142 ^oC.
IR: (CHCl$_3$)υ_{max} (cm^{-1})	**:**	3019, 2925, 2853, 2219, 1696, 1595, 1350, 1215, 753, 668.
^{1}H NMR (CDCl$_3$, 200 MHz) δ	**:**	7.01 (s, 1H), 7.35-7.55 (m, 8H), 7.87 (d, *J* = 6.60 Hz, 2H), 7.91 (m, 2H), 10.50 (s, 1H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	**:**	88.3, 89.2, 100.5, 118.8, 120.8, 123.0, 125.2, 128.3, 128.9, 129.4, 131.2, 131.6, 153.6, 158.4, 187.4.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{32}H_{14}O_2$: C, 85.70; H, 4.38 Found: C, 85.56; H, 4.28.

5-Chloro-2-*p*-tolylbenzofuran (87o):

Nature of compound; mp	**:**	Colorless solid, mp 182-183 ^oC.
IR: (CHCl$_3$)υ_{max} (cm^{-1})	**:**	3020, 1613, 1444, 1215, 758, 669.
^{1}H NMR (CDCl$_3$, 200 MHz) δ	**:**	2.51 (s, 3H), 7.01 (s, 1H), 7.29-7.39 (m, 3H), 7.53 (d, *J* = 8.68 Hz, 1H), 7.63 (d, *J* = 1.95, 1H), 7.85 (d, *J* = 8.23 Hz, 2H).
^{13}C NMR (CDCl$_3$, 50 MHz) δ	**:**	21.4, 100.0, 111.9, 120.2, 124.0, 124.9, 127.2, 128.3, 129.5, 130.7, 139.1, 153.1, 157.6.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57 Found: C, 74.12; H, 4.26.

5-Chloro-2-(3-fluorophenyl)benzofuran (87p):

Nature of compound; mp	**:**	Colorless solid, mp 120-121 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 1614, 1585, 1488, 1445, 1215, 759, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	6.87 (s, 1H), 6.92-7.02 (m, 1H), 7.13-7.19 (m, 1H), 7.29-7.54 (m, 5H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	101.7, 111.7, 112.1, 115.6, 120.5, 124.8, 128.7, 130.4, 132.1, 153.2, 155.9, 161.4, 164.7.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{14}H_8ClFO$: C, 68.17; H, 3.27 Found: C, 67.86; H, 3.08.

5-Methyl-2-phenylbenzofuran (87q):

Nature of compound; mp	**:**	Colorless solid, mp 128 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3019, 1472, 1215, 759, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	2.36 (s, 3H), 6.86 (s, 1H), 7.01 (d, *J* = 8.35 Hz, 1H), 7.31-7.40 (m, 5H), 7.76 (d, *J* = 6.98 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	21.3, 101.0, 110.6, 120.7, 124.8, 125.5, 128.3, 128.7, 129.2, 130.5, 132.3, 153.3, 155.9.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{15}H_{12}O$: C, 85.51; H, 5.81 Found: C, 85.19; H, 5.94.

2-Phenylbenzofuran (87r):

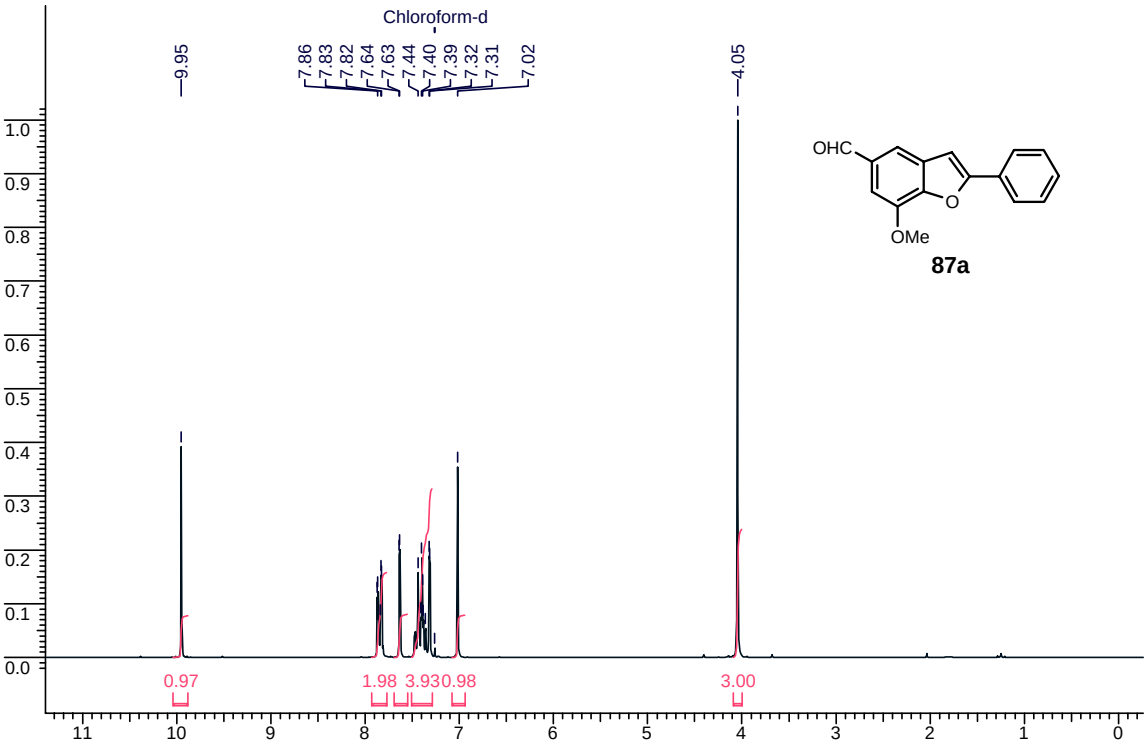
Nature of compound; mp	**:**	Colorless solid, mp 118 ^{o}C.
IR: ($CHCl_3$)υ_{max} (cm^{-1})	**:**	3018, 1611, 1491, 1215, 758, 669.
^{1}H NMR ($CDCl_3$, 200 MHz) δ	**:**	6.93 (s, 1H), 7.10-7.52 (m, 7H), 7.79 (d, *J* = 6.93 Hz, 2H).
^{13}C NMR ($CDCl_3$, 50 MHz) δ	**:**	101.2, 111.1, 120.8, 122.8, 124.2, 124.8, 128.5, 128.7, 129.2, 130.4, 154.8, 155.8.
Elemental analysis (%)	**:**	Anal.Calcd.for $C_{14}H_{10}O$: C, 86.57; H, 5.19 Found: C, 86.29; H, 5.57.

3.3.7 Spectra

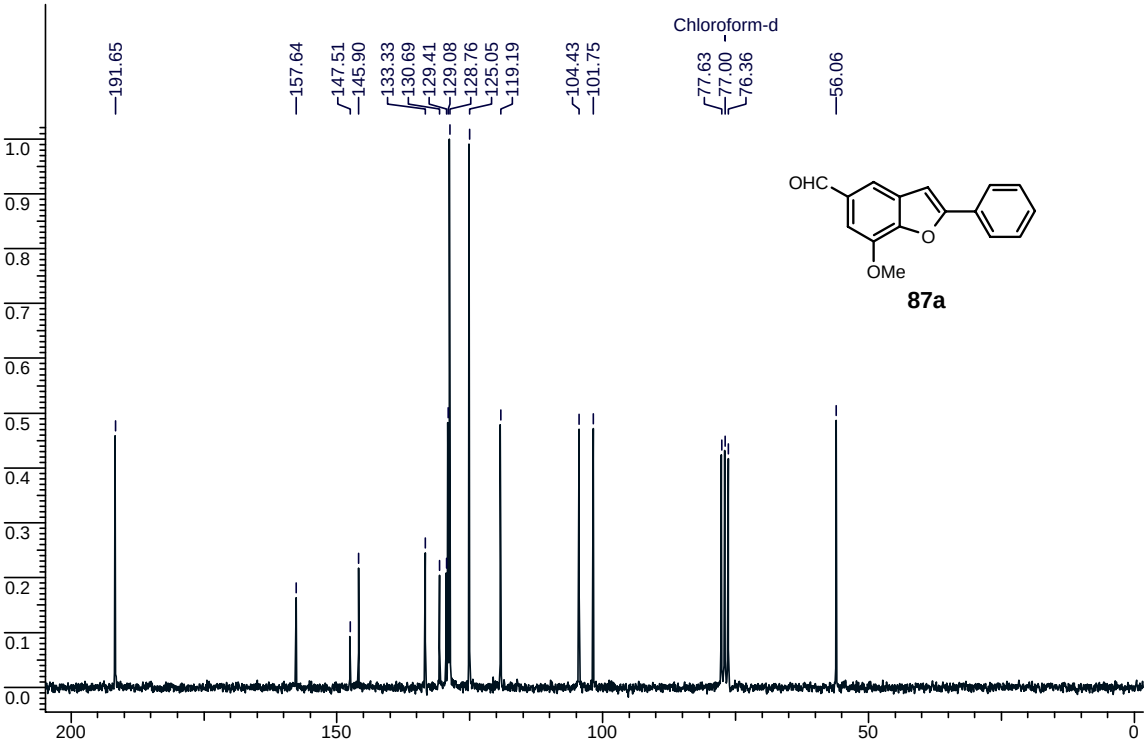
Table 10. ^{1}H and ^{13}C spectra of some representative Benzo[*b*]furans

Sr. No.	Spectra
1	^{1}H and ^{13}C spectra of **87a**
2	^{1}H and ^{13}C spectra of **87e**
3	^{1}H and ^{13}C spectra of **87i**
4	^{1}H and ^{13}C spectra of **87k**
5	^{1}H and ^{13}C spectra of **87n**
6	^{1}H and ^{13}C spectra of **87o**
7	^{1}H and ^{13}C spectra of **87q**
8	^{1}H and ^{13}C spectra of **87r**

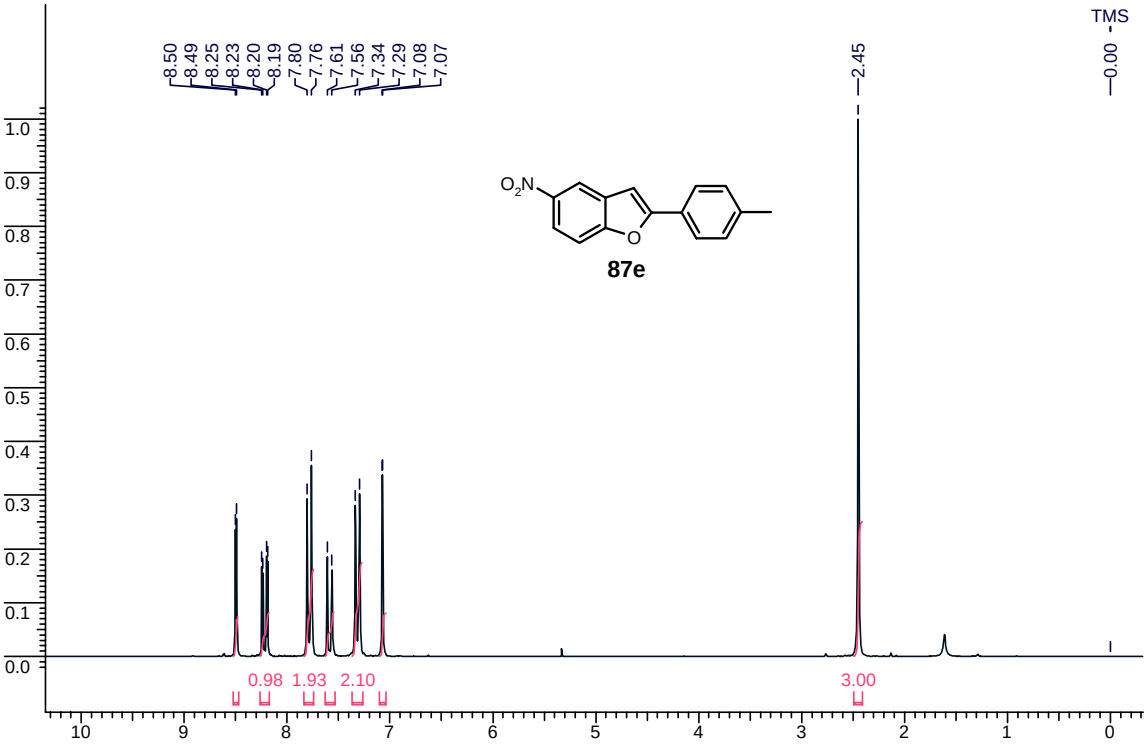
^{1}H NMR of **87a**



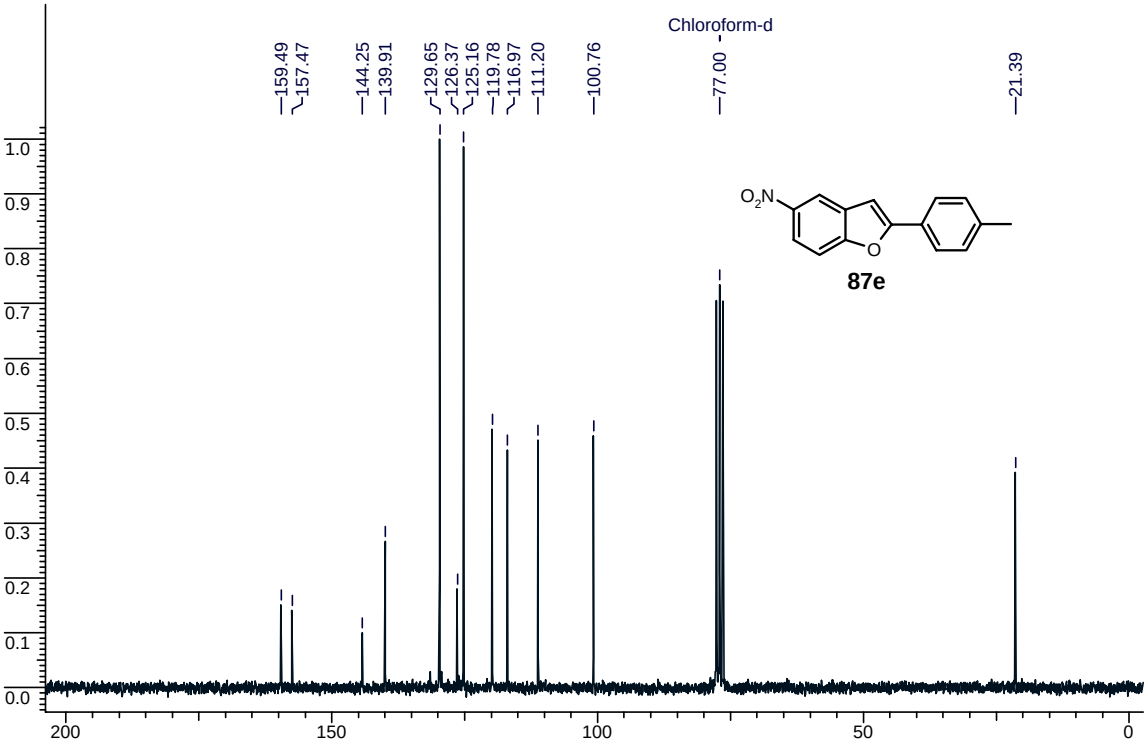
^{13}C NMR of **87a**



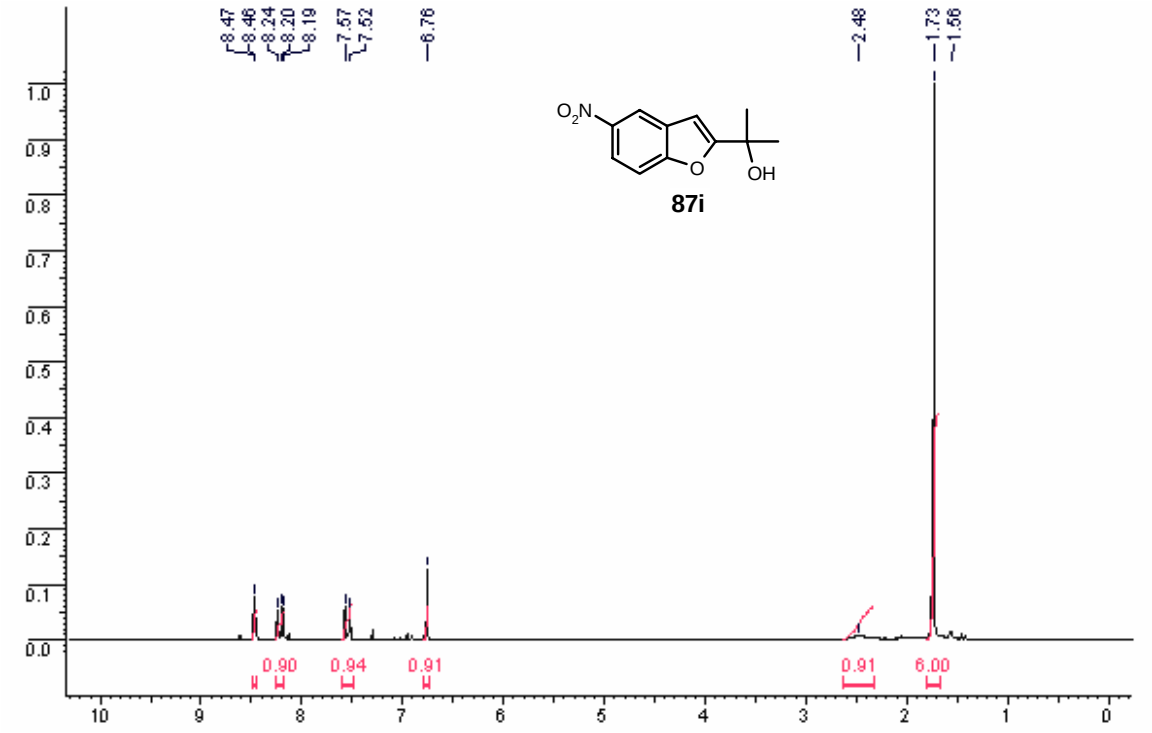
^{1}H NMR of **87e**



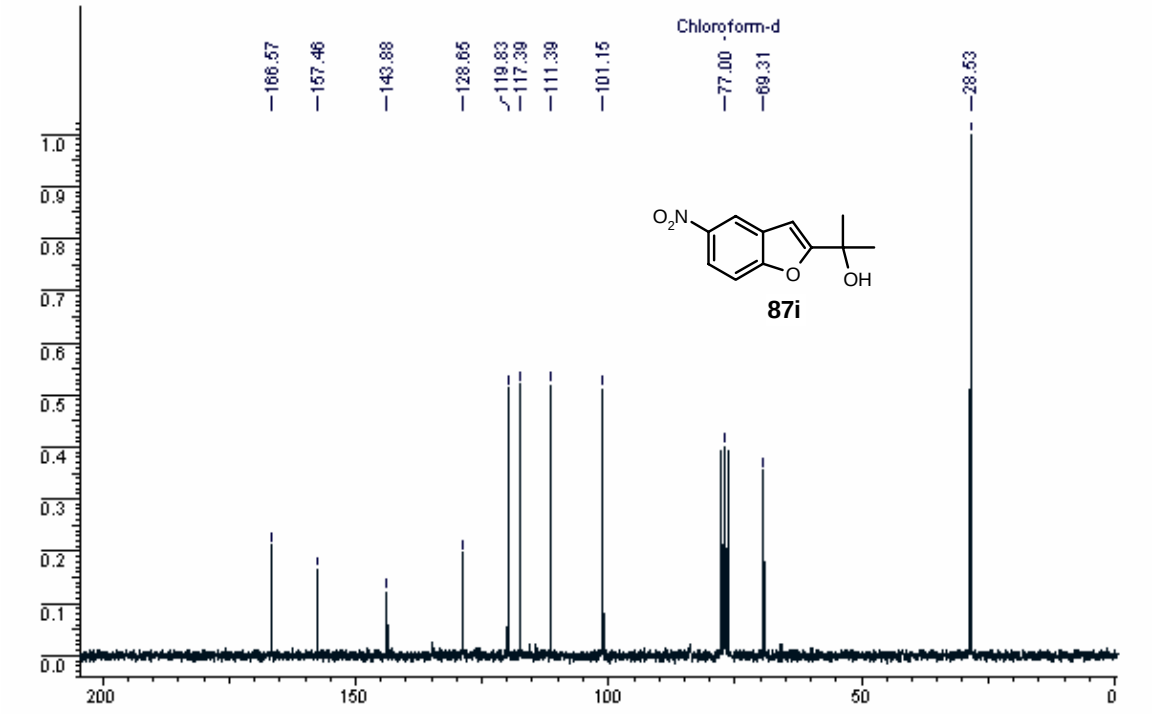
^{13}C NMR of **87e**



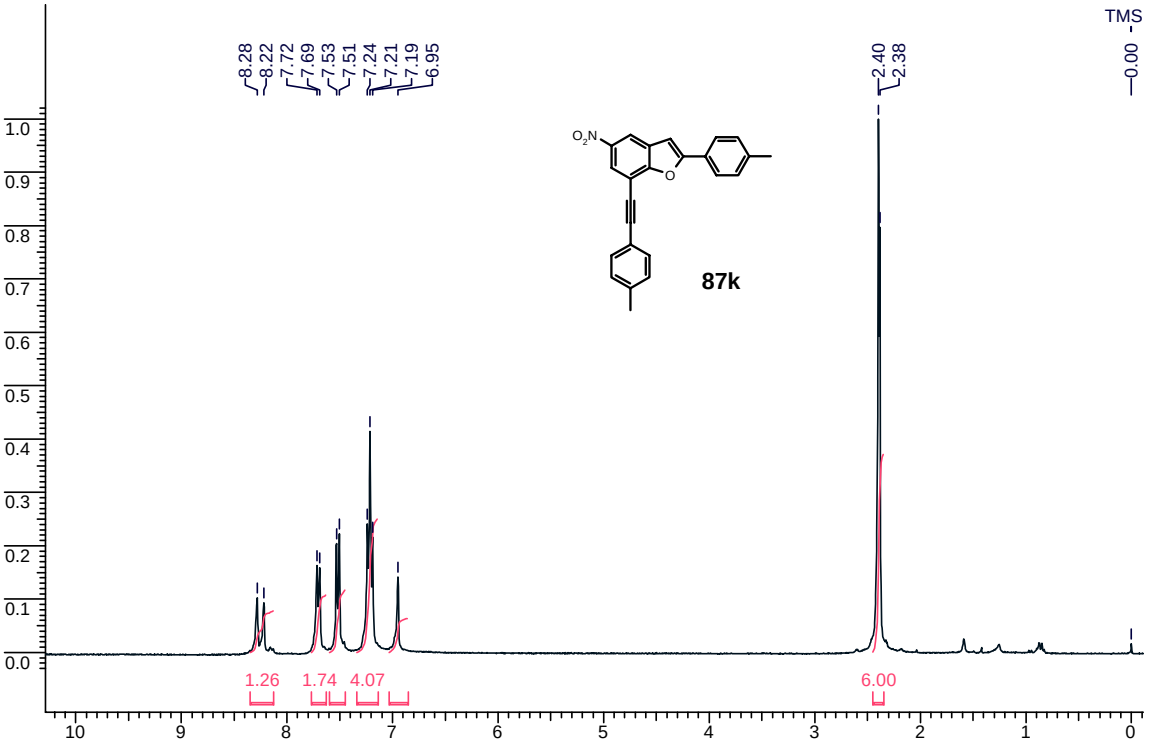
^{1}H NMR of **87i**



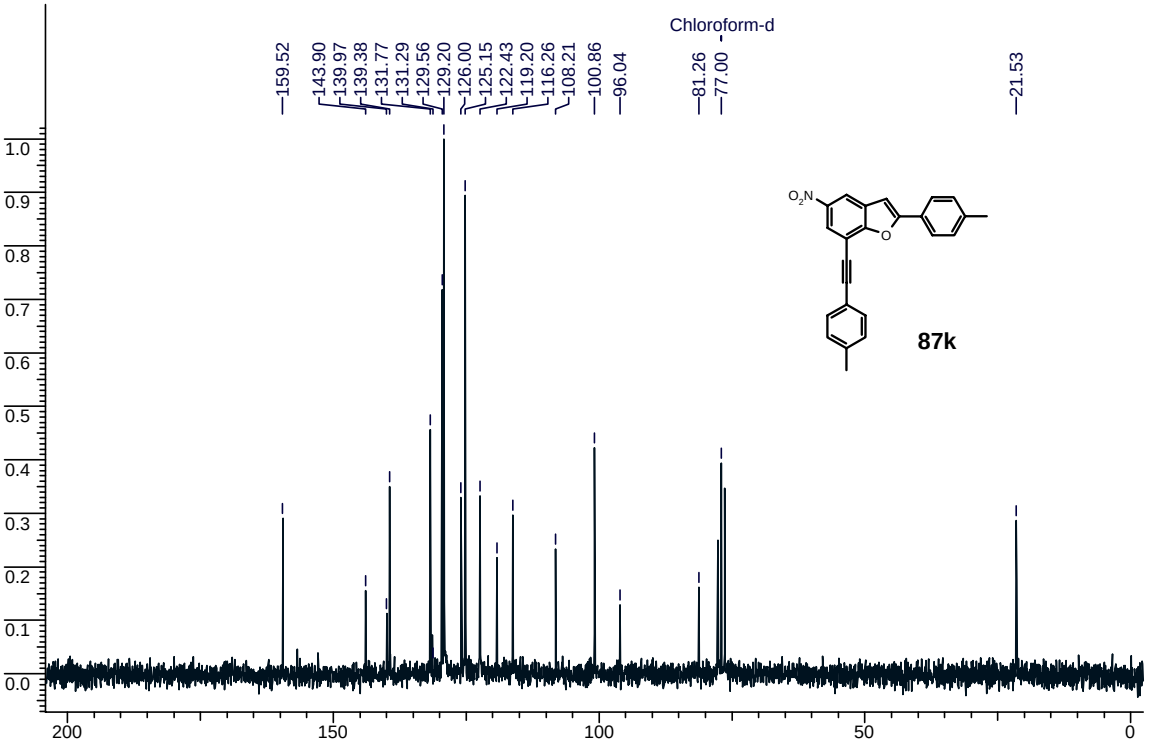
^{13}C NMR of **87i**



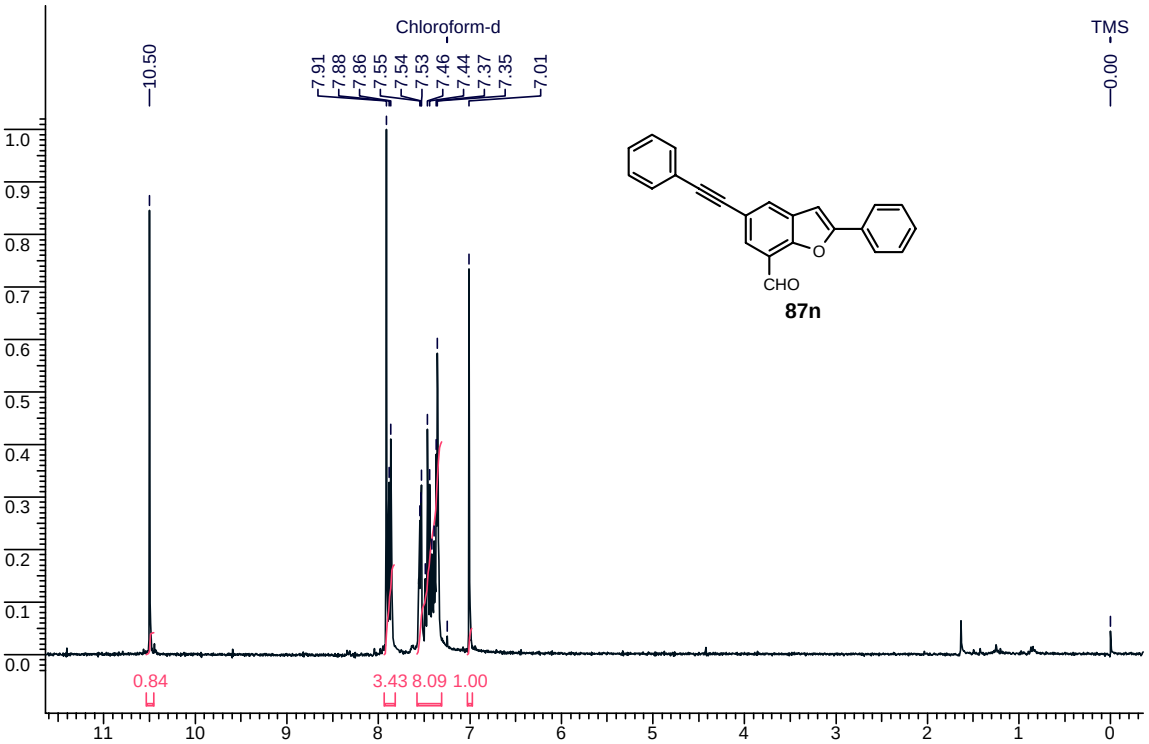
^{1}H NMR of **87k**



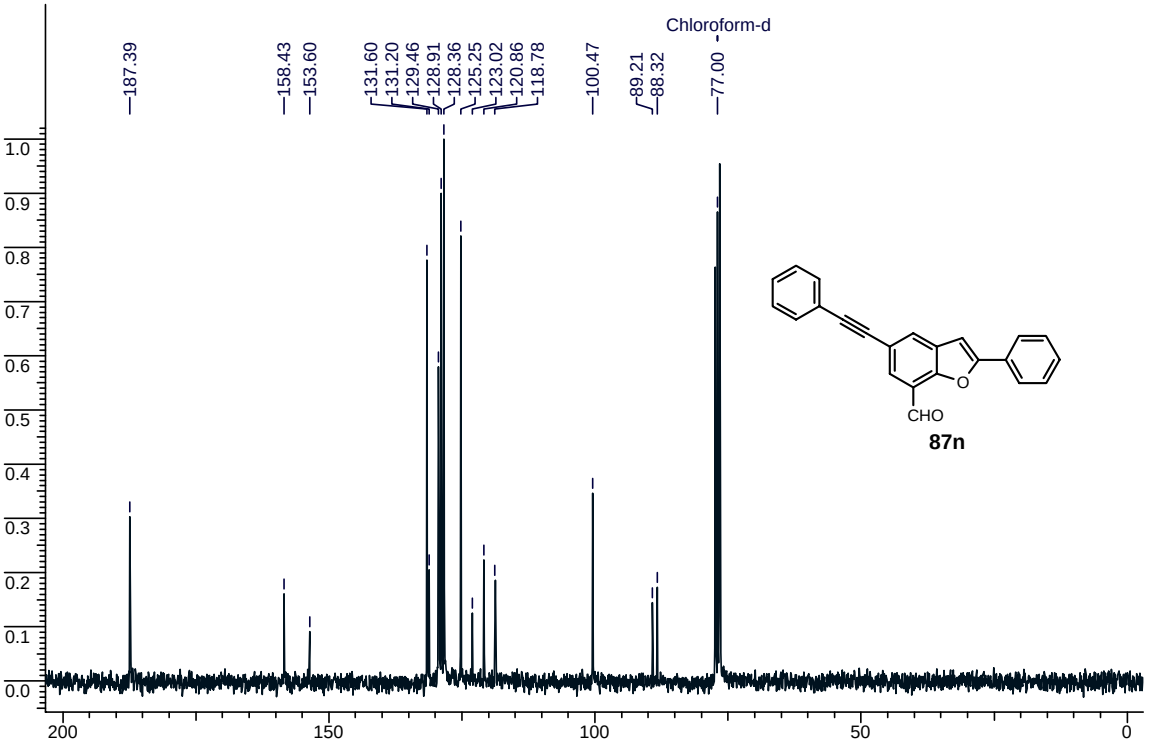
^{13}C NMR of **87k**



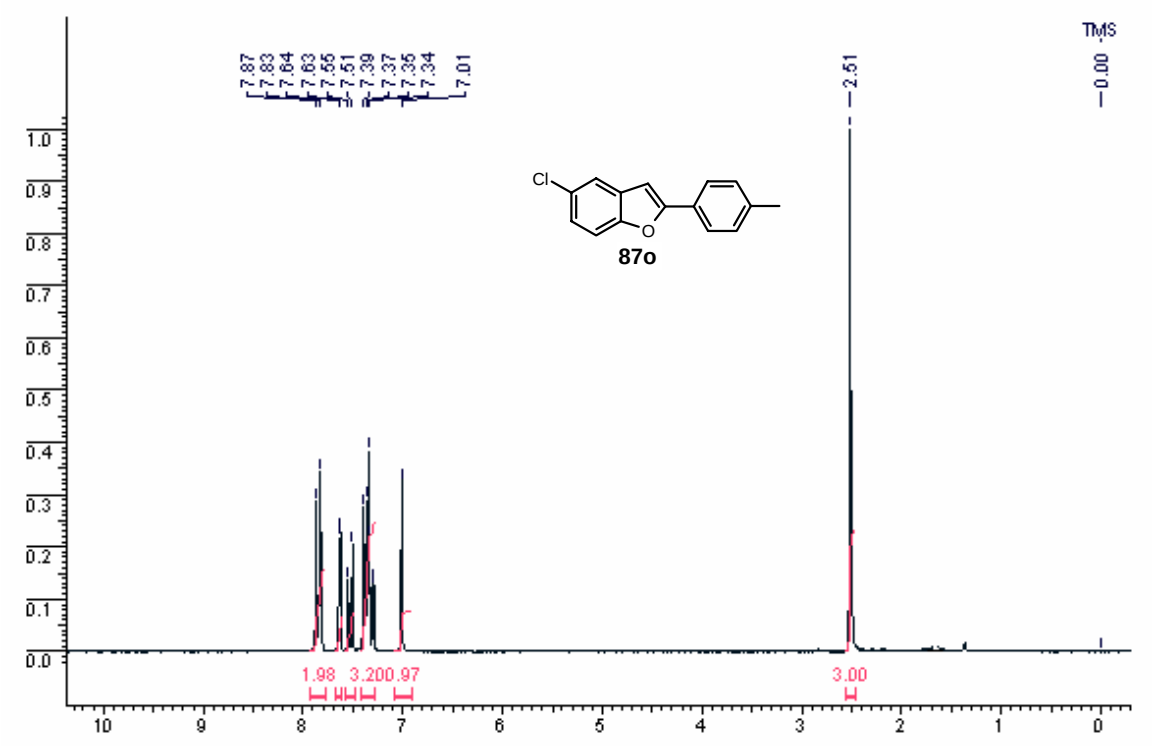
^{1}H NMR of **87n**



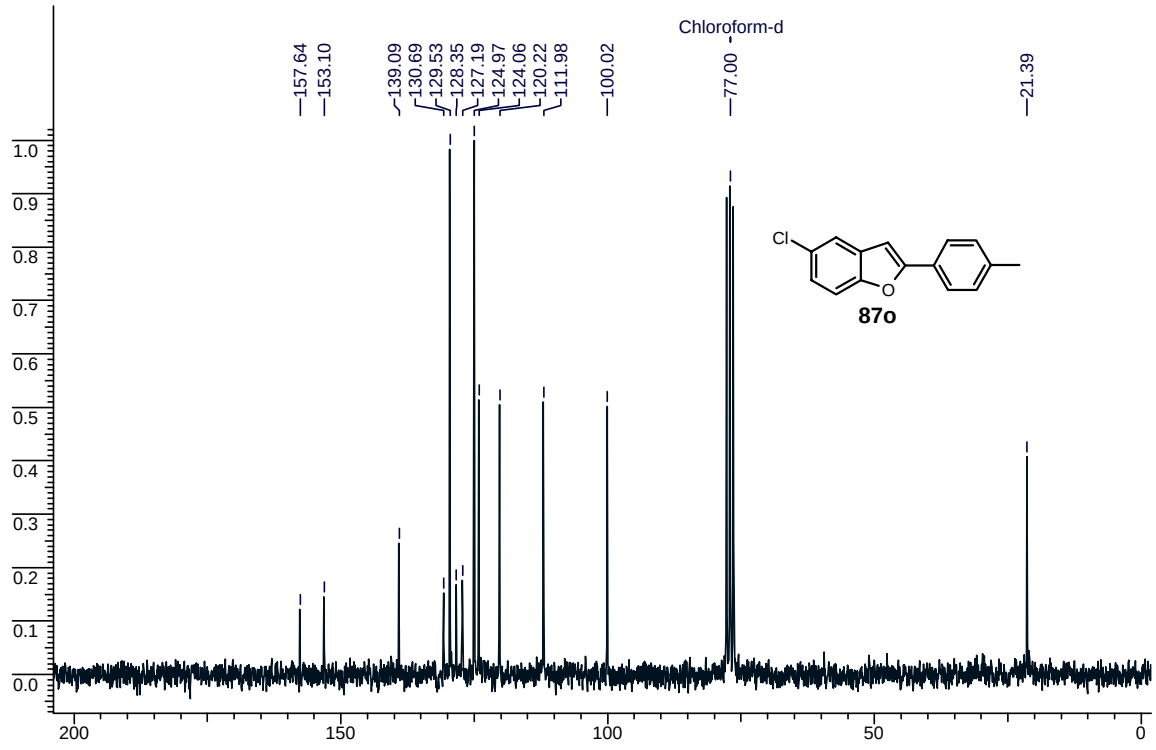
^{13}C NMR of **87n**



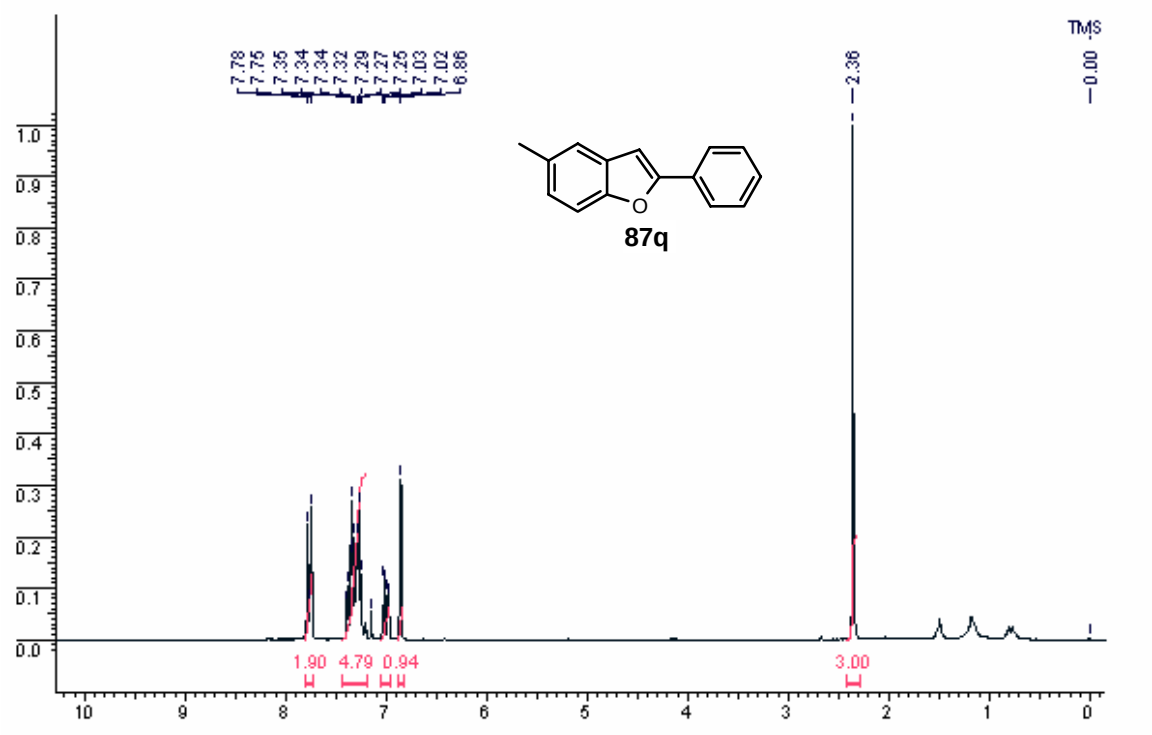
^{1}H NMR of **87o**



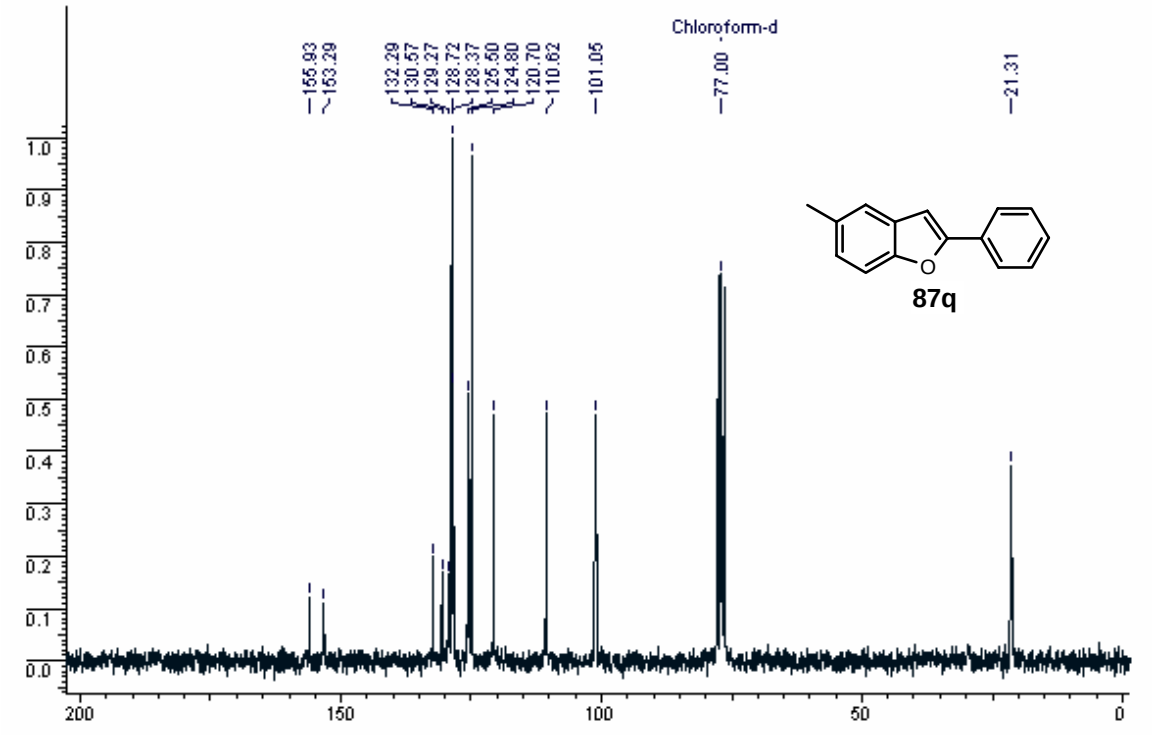
^{13}C NMR of **87o**



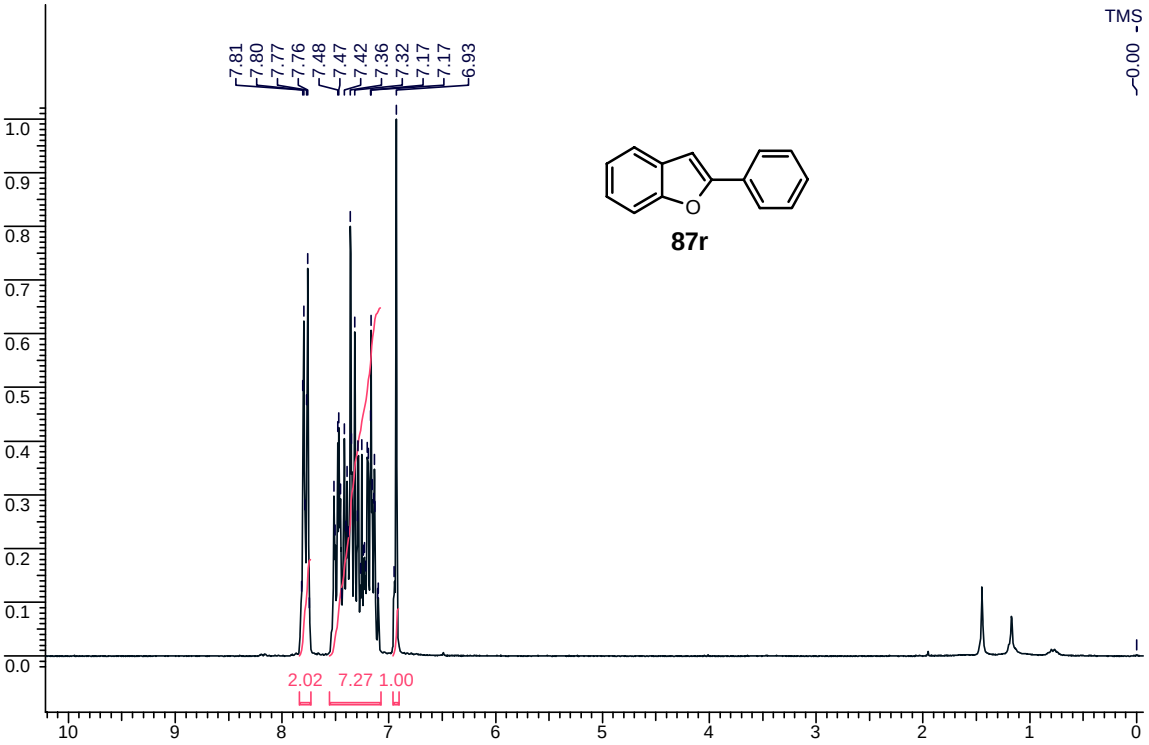
^{1}H NMR of **87q**



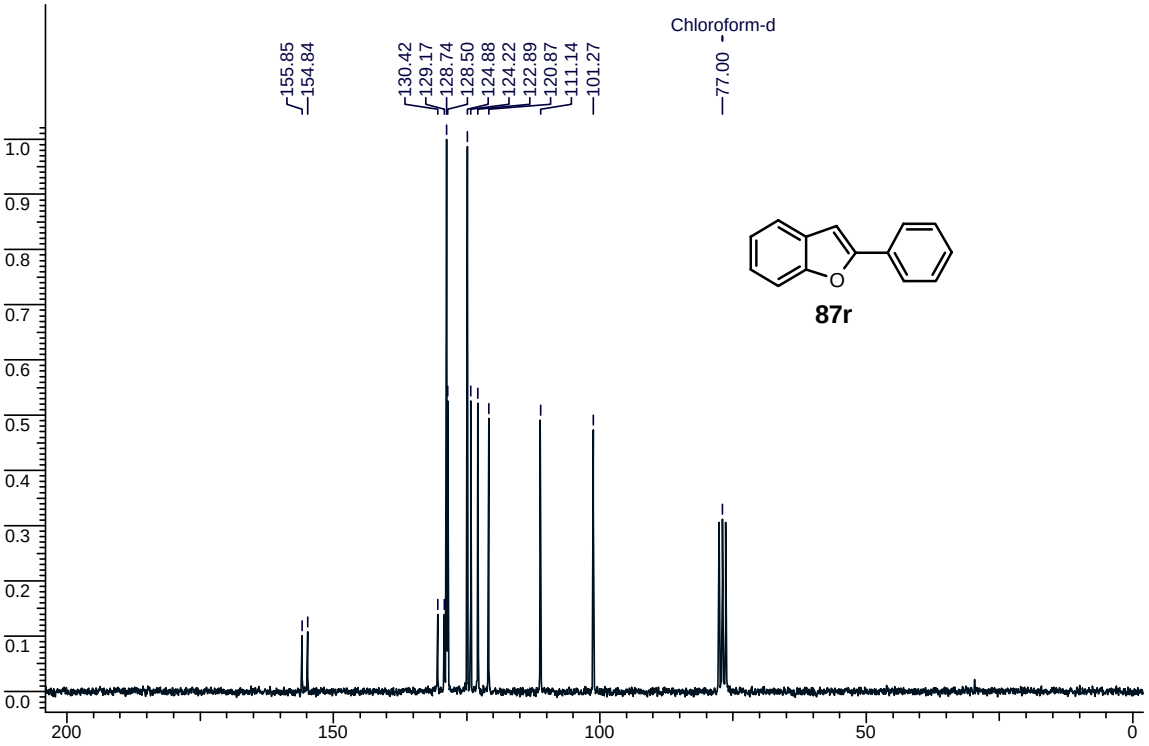
^{13}C NMR of **87q**



^{1}H NMR of **87r**



^{13}C NMR of **87r**



3.3.8 References

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List of Publications

1. Ionic Liquid-Promoted Regiospecific Friedlander Annulation: Novel Synthesis of Quinolines and Fused Polycyclic Quinolines
   Sanjay S. Palimkar, S.A. Siddiqui, Thomas Daniel, Rajgopal. J. Lahoti, and Kumar.V. Srinivasan*, ***J. Org. Chem.* 68 (2003) 9371-9378.**

2. Ligand-, copper-, and amine-free one-pot synthesis of 2-substituted indoles *via* Sonogashira coupling 5-*endo*-*dig*-cyclization
   Sanjay S. Palimkar, P. Harish Kumar, Rajgopal J. Lahoti and Kumar V. Srinivasan*, ***Tetrahedron* 62 (2006) 5109-5115.**

3. Copper-, ligand- and solvent-free synthesis of ynones by coupling acid chlorides with terminal alkynes
   Sanjay S. Palimkar, P. Harish Kumar, Nivrutti R. Jogdand, Thomas Daniel, Rajgopal J. Lahoti and Kumar V. Srinivasan*, ***Tetrahedron Lett.,* 47 (2006) 5527-5530.**

4. A novel one-pot three-component synthesis of 2,4-disubstituted-3*H*- Benzo-[*b*][1,4]diazepines in water
   Sanjay S. Palimkar, Rajgopal J. Lahoti and Kumar V. Srinivasan*, ***Green Chem.,* 9 (2007) 146-152.**

5. A novel synthesis of an indole containing KDR kinase inhibitor using tandem Sonogashira coupling - 5 - *endo* - *dig* - cyclization as the key step
   Sanjay S. Palimkar, Vijaykumar S. More, P. Harish Kumar and Kumar V. Srinivasan* ***Tetrahedron* (Article in press)**

6. Ultrasound-promoted *copper-, ligand-* and *amine-free* synthesis of benzo[*b*]furans/nitro benzo[*b*]furans *via* Sonogashira coupling-5-*endo-dig*-cyclization
   Sanjay S. Palimkar, Vijaykumar S. More and Kumar V. Srinivasan* ***Ultrasonics Sonochem*. (**Accepted**)**

7. A Simple and Efficient One-Pot Three-Component *Solvent-Free* Synthesis of β-Enaminones *via* Sonogashira Coupling-Michael Addition Sequences
   Sanjay S. Palimkar, Vijaykumar S. More and Kumar V. Srinivasan* ***Synth. Commun***. (Accepted).