SYNTHESIS AND STUDY OF IONIC LIQUIDS FOR BIOLOGICALLY ACTIVE HETEROCYCLES AND ASYMMETRIC SYNTHESIS

A Thesis

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By

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"SYNTHESIS AND STUDY OF IONIC LIQUIDS FOR BIOLOGICALLY ACTIVE HETEROCYCLES AND ASYMMETRIC SYNTHESIS"*** submitted by **Mr. S. A. Siddiqui** 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.

Division Of Organic Chemistry: Technology, **Dr. K. V. Srinivasan**

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31st July, 2007

CANDIDATE'S DECLARATION

I hereby declare that the work presented in the thesis entitled ***"SYNTHESIS AND STUDY OF IONIC LIQUIDS FOR BIOLOGICALLY ACTIVE HETEROCYCLES AND ASYMMETRIC SYNTHESIS"*** submitted for Ph. D. degree to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune, India, under the supervision of Dr. K. V. Srinivasan. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University. In keeping with the general practice, due acknowledgements have been made, wherever the work described is based on the findings of other investigators. Any inadvertent omissions that might have occurred due to oversight or error in judgment are regretted.

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Shafi A. Siddiqui

DEDICATED

TO

MY PARENTS,

BROTHERS & SISTERS

CONTENTS

Chapter 2 *Study of ionic liquids as reaction media cum promoters in the synthesis of biologically active heterocycles*

ABBREVATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
Aq.	Aqueous
AD	Asymmetric dihydroxylation
Bbim	1,3-di-*n*-butyl imidazolium
Bn	Benzyl
Boc	*tert*-Butoxy carbonyl
brs	Broad singlet
Bu	Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
ca.	Calculated
cat.	Catalytic/ catalyst
$CDCl_3$	Deuterated chloroform
conc.	Concentrated
d	Doublet
dd	Doublet of doublet
de	Diasteromreic excess
$(DHQ)_2PHAL$	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	1,4-Bis(dihydroquinidin-9-*O*-yl)phthalazine
DMAP	*N,N*-(Dimethylamino)pyridine
DMF	*N,N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
Ee	Enantiomeric excess
equiv	Equivalents
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
g	Gram
GLC	Gas liquid chromatography

h or hrs	Hours
HPLC	High pressure liquid chromatography
Hbim	1-*n*-butyl imidazolium
Hz	Hertz
i-Pr	Isopropyl
Im	Imidazole
IL	Ionic liquid
IR	Infrared
LC-MS	Liquid chromatography mass spectrometry
m-CPBA	*m*- Chloroperbenzoic acid
Me	Methyl
mg	Miligram
min	Minutes
mL	Mililiter
mmol	Milimole
M.P.	Melting point
Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
NMO	N-Methyl morpholine N-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PMB	*p*-Methoxybenzyl
ppm	Parts per million
p-TSA	*p*-Toluene sulfonic acid
Pyr	Pyridine
rt	Room temperature
Red-Al$^{@}$	Bis(2-methoxyethoxy)aluminum hydride
R_f	Retention factor
s	Singlet
SAD	Sharpless asymmetric dihydroxylation
satd.	Saturated

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsCl	*p*-Toluene sulfonyl
TFA	Trifluoro acetic acid

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometers.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- The ligands DHQD and $(DHQ)_2$-PHAL, were purchased from Aldrich.

ABSTRACT

SYNTHESIS AND STUDY OF IONIC LIQUIDS FOR BIOLOGICALLY ACTIVE HETEROCYCLES AND ASYMMETRIC SYNTHESIS"

The title of the thesis clearly indicates the objective that is to interface synthetic organic chemistry for the development of new methodologies and synthesize enatiomerically pure bio-active entities. The thesis is divided into three chapters. The first chapter is divided into two sections, Section A deals with the brief introduction of ionic liquids and Section B describes the synthesis and characterization of new ionic liquids. Second chapter provides study of the application of ionic liquids in the synthesis of biologically active heterocycles. It is divided into five sections, each section describing the details of the synthesis of one family of heterocyclic skeleton. Third chapter is divided into three sections; Section A deals with a brief introduction of Sharpless asymmetric dihydroxylation and cyclic sulfite chemistry and Section B and Section C describes the enantioselctive synthesis of (*S, S*)-Reboxetine and (*S*)-Dapoxetine respectively.

CHAPTER 1: Synthesis and characterization of Ionic Liquids.

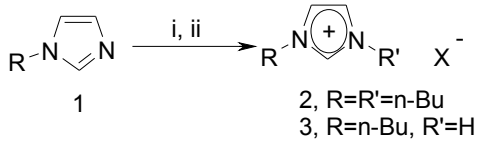
This chapter is divided into two sections, Section A deals with a brief introduction and physiochemical properties of ionic liquids while Section B deals with the synthesis and characterization of new ionic liquids.

Section A: ***Ionic liquid (IL)-a brief introduction***

The past few years has witnessed the evolution of a new era in chemical research by the entry of ionic liquids as potential 'Green Designer Solvents' as novel replacements for volatile organic compounds traditionally used as industrial solvents.[1] Ionic liquids are systems consisting of salts that are liquid at ambient conditions. A brief history of ionic liquids and their emergence as environmentally benign solvents have been discussed in this section. Various types of ILs and their nomenclature are covered. The unique property of this ionic species, which gives liquid character to it, has been discussed in detail. A wide variety of reactions performed in ionic liquids have been summarized.

Section B: ***Synthesis and characterizations of new ionic liquids***

A series of N,N-dialkyl substituted imidazolium and 1-alkyl imidazolium based ILs have been synthesized (**Scheme 1**).



Scheme 1. Reaction conditions; i) RBr, 90 ^{0}C, 12 h, 90 %; b) HX, 0 ^{0}C, 2-8 h, 90%

The alkyl chain length (R and R') are kept the same and anionic part (X) are altered. All ILs were characterized by NMR, IR and Mass spectrometry and elemental analysis. Density, viscosity and polarity of all ILs were also evaluated. The variation of both density and viscosity has been correlated to the change in the basicity of the anion. Melting and decomposition temperatures were measured using TG-DTA techniques.

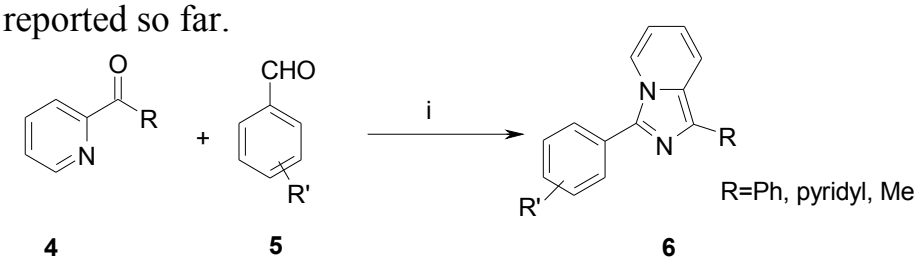
CHAPTER 2: Study of ionic liquids as reaction media cum promoters in the synthesis of biologically active heterocycles

Knowledge of heterocyclic chemistry is useful in biosynthesis and in drug metabolism as well. Nucleic acids are important in biological processes of heredity and evolution. There are a large number of synthetic heterocyclic compounds with other important applications and many are valuable intermediates in synthesis. Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. This chapter is subdivided into five sections.

Section A: ***Synthesis of 1-substituted imidazo[1,5-a]pyridines***

Imidazo[1,5-*a*]pyridine skeleton is a basic structure of synthetic drugs such as Pirmogrel, with human clinical applications as effective platelet aggregation and thromboxane synthase inhibitors. Syntheses of imidazo[1,5-*a*]pyridines are well documented.[3] This section deals with the study of room

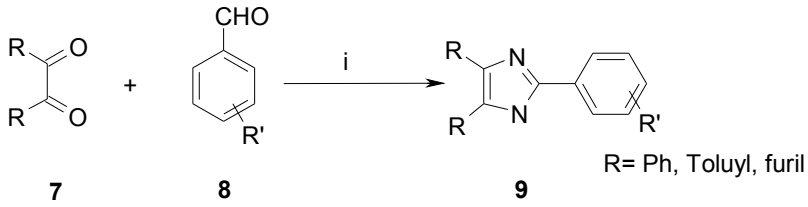
temperature ionic liquids for efficient synthesis of several substituted imidazo[1,5-*a*]pyridines (**Scheme 2**) under milder conditions and enhanced reaction rates than those reported so far.



Scheme 2. Reaction conditions; i) NH_4OAc, $[Hbim]BF_4$, 100 ^{0}C, 1-3 h, 95%

Section B: ***Synthesis of 2,4,5-triaryl imidazoles***

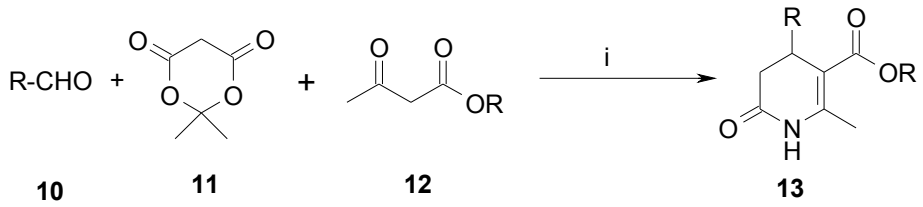
Over the century, the importance of imidazoles in biological system has attracted much interest due to their chemical and biochemical properties. Even today, 147 years later, research in imidazole chemistry continues unabated. Compounds with imidazole ring system have many pharmacological properties and play important roles in biochemical processes such as many of the substituted imidazoles are known as inhibitors of P38 MAP kinase, fungicides and herbicides, plant growth regulators and therapeutic agents. This section deals with the study of room temperature ionic liquid for the synthesis of several substituted 2,4,5-triaryl imidazoles (**Scheme 3**). Several ILs were screened for this synthesis and their efficacy is discussed in this section.



Scheme 3. Reaction conditions; i) NH_4OAc, $[Hbim]BF_4$, 100 ^{0}C, 1-3 h, 95%

Section C: Synthesis of 4-aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyidones

The research on the dihydropyridines systems is of current interest due to their exceptional properties as calcium channel antagonists. Substitution on the dihydropyidones ring has been widely studied due to the important effects of some substituents on their biological activities. This section describes room temperature ionic liquid promoted efficient synthesis of several 4-aryl substituted 5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones (**Scheme 4**).

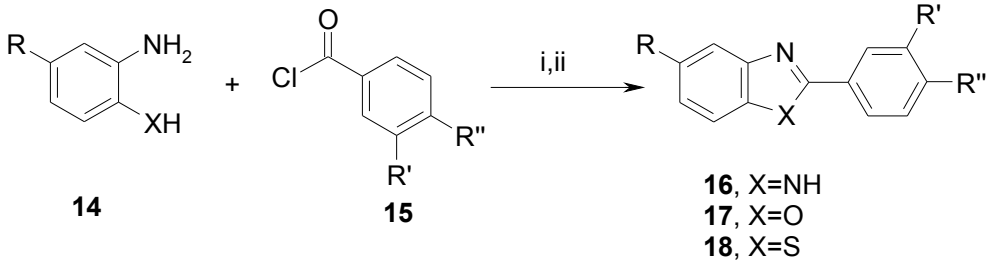


10 11 12 13

Scheme 4. Reaction conditions; i) $[Hbim]BF_4$, NH_4OAc, 100^0C.

Section D: ***Synthesis of 2-substituted benzimidazoles/benzoxazoles and benzthiazoles***

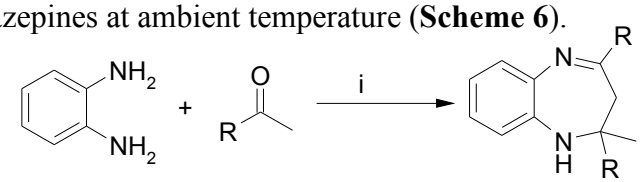
The heterocycles 2-aryl benzimidazoles, benzoxazoles and benzthiazoles have received considerable attention in diverse areas of chemistry. These nuclei are found in a variety of naturally occurring compounds and are of significant importance in medicinal chemistry. In this section, a regioselective one-pot synthesis of 2-aryl benzimidazoles, benzoxazoles and benzthiazoles (**Scheme 5**) using the ionic liquids, 1-butylimidazolium tetraflouroborate ($[Hbim]BF_4$) and 1,3-di-*n*-butylimidazolium tetrafluoroborate ($[bbim]BF_4$) has been described.



Scheme 5. Reaction conditions; i) [bbim]Br, rt, 1-2 h, 90% or ii) $[Hbim]BF_4$, 10-20 min., 90%.

Section E: ***Synthesis of 1,5-benzodiazepines***

The benzodiazepine nucleus is a well-studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various sedative hypnotic, muscle relaxant, anxiolytic, antistaminic, and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 35 years ago the research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. This section describes a room temperature ionic liquid promoted simple and effective method for the synthesis of several 1,5-benzodiazepines at ambient temperature (**Scheme 6**).



19 20 21

Scheme 6. Reaction conditions; i) [bbim]Br, 50 min., rt.

It is important to note that in all the syntheses of bio-active heterocycles described so far, the reactions were performed in the absence of any added catalyst with the recyclable ILs themselves acting as promoters.

CHAPTER 3: Enationselective synthesis of (*S, S*)-Reboxetine and (*S*)-Dapoxetine using Sharpless asymmetric dihydroxylation

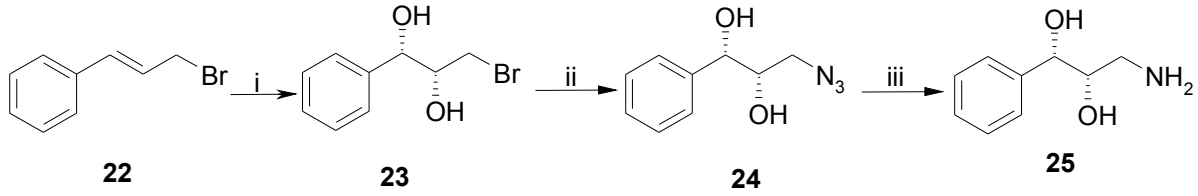
Section A: *Brief introduction to the Sharpless asymmetric dihydroxylation and cyclic sulfite.*

Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetry inducing agents. Especially useful is the carbon-heteroatom bond forming reactions, since the resulting functionality can be readily manipulated to produce many important classes of compounds. The Sharpless Asymmetric Dihydroxylation (SAD) reaction is one such reaction developed in early 1990. [7] It has evolved as one of the most powerful methods for enantioselective oxidation of olefins to optically active vicinal diols that are versatile and convenient building blocks in the synthesis of bioactive compounds. In this chapter, the development of SAD reaction from stoichiometric to catalytic version, the mechanism, reaction conditions and varied ligands used along with recent applications will be covered. In our synthetic endeavors we have employed the chiral diol compounds obtained by SAD reaction towards the synthesis (*S, S*)-Reboxetine and (*S*)-dapoxetine. To bring about the functional group changes we have also employed the chemistry of cyclic sulfites/sulfates as intermediates.

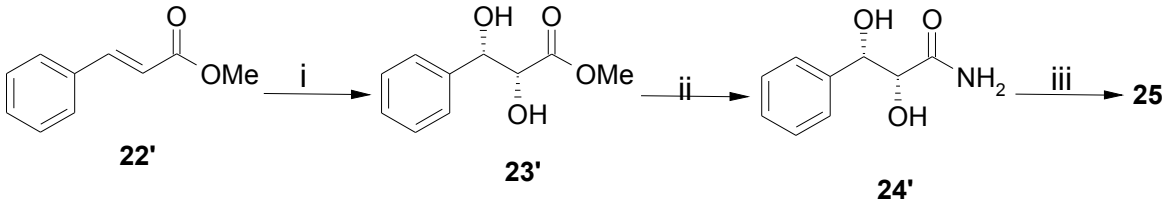
Section B: *Enantioselctive synthesis of (S, S)-Reboxetine*

Reboxetine is a classical example of α-aryloxybenzyl derivatives having a mixture of (*2R, 3R) and (2S,3S)*-2[α-(2-ethoxyphenoxy)phenylmethyl]-morpholine, known to be a potent selective norepinephrine reuptake inhibitor (NRI). Reboxetine has been marketed as a mixture of two enantiomers, (*S,S*) and (*R,R*) under the brand name Edronax^{TM}, for the

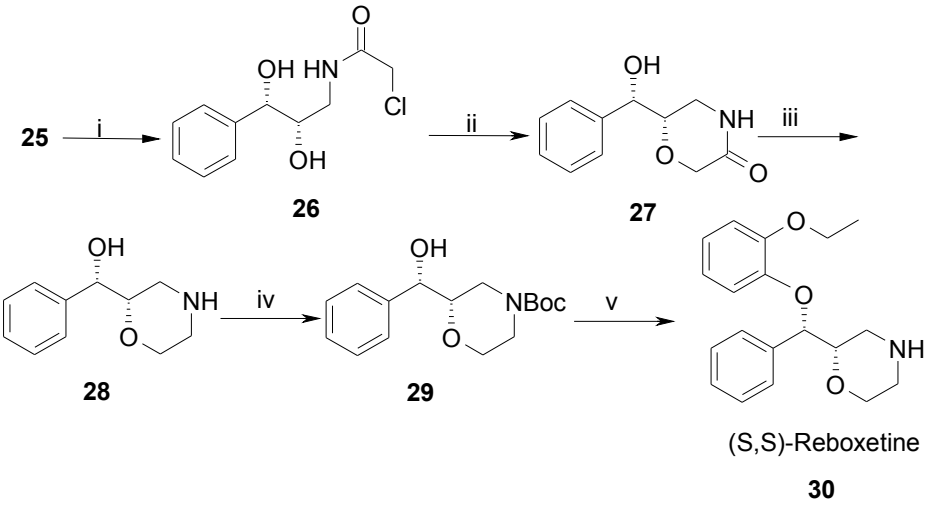
treatment of depressive illness in several European countries. In this section we have investigated, the enantioselective synthesis of (*S, S*)-reboxetine starting with *trans* cinnamyl bromide **22** which on subjecting to asymmetric dihydroxylation under Sharpless condition gave (1*S, 2R*)-3-bromo-1-phenylpropane-1,2-diol **23** in 84 % yield. Nucleophilic displacement of the bromo group by sodium azide furnished the azido alcohol **24**, which was reduced by Pd/C in MeOH under hydrogen atmosphere to afford the amine **25** (Scheme 7). The amine **25** was also synthesized from cinnamyl ester **22'** under SAD condition in IL:*t*-BuOH:H_20 gave **23'** in 88% yield with ee. The enantiomer **23'** on reaction with ammonia in refluxing methanol gave **24'** which on reduction by Red-Al afford **25** (Scheme 8). The free amine **25** was protected with chloro acetyl chloride to furnish the amide **26** in 70 % yield, which was readily cyclized to compound **27** using potassium *tert*-butoxide in *t*-BuOH. This cyclic amide was reduced using a solution of Red-Al® at 0 ^{0}C, which gave the morpholine intermediate **28** in 83% yield. The secondary amine of **28** was protected with $(Boc)_2O$ to get the known intermediate **29**. The free hydroxyl group was coupled with chromium complex of 2-ethoxy fluorobenzene followed by cleavage of Boc group by TFA to give the target compound **30** (**Schemes 7-9**).



Scheme 7. Reaction conditions: i) $DHQ)_2PHAL$ (1 mol%), OsO_4 (0.1 mol%), $K_3Fe(CN)_6$ (3 equ.), K_2CO_3 (3equ.), $NaHCO_3$ (3 equ.), $MeSO_2NH_2$ (1 equ.), H_2O:*t*-BuOH (1:1), 0 ^{0}C, 24 h. ii) NaN_3 (5 equ.) DMF, 68 ^{0}C, 16 h. iii) 10% palladium on carbon, H_2 (1 atmp.), rt, 12 h.



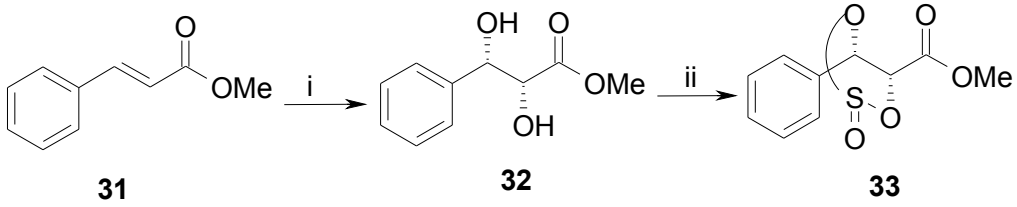
Scheme 8. Reaction conditions: i) $(DHQ)_2PHAL$ (1 mol%), OsO_4 (0.1 mol%), $K_3Fe(CN)_6$ (3 equ.), K_2CO_3 (3 equ.), $MeSO_2NH_2$ (1 equ.), H_2O:*t*-BuOH:IL (1:1:1), rt, 24 h. b) MeOH, NH_4OH, reflux, 8 h. c) dry THF, Red-Al® (2 equ.), 0 ^{0}C to rt, 4 h.

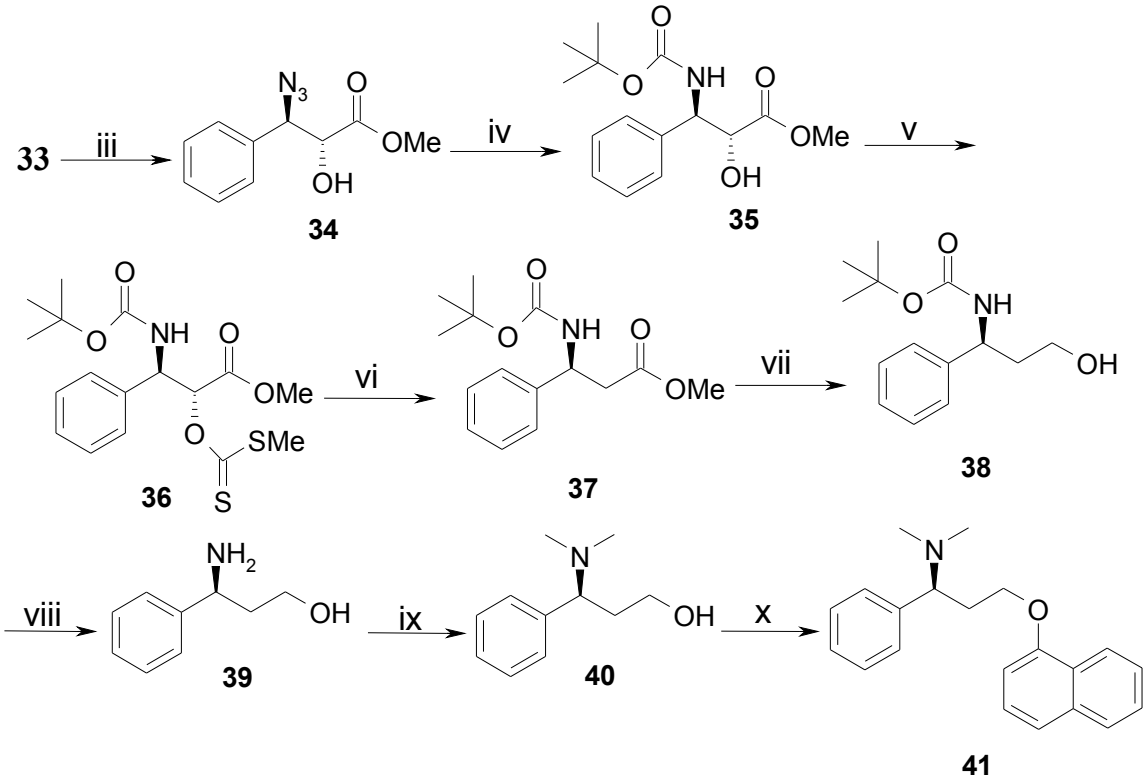


Scheme 9. Reaction conditions: i) $ClCOCH_2Cl$, Et_3N, DCM at -10 ^{0}C- rt, 6 h; ii) ^{t}BuOK (2 equ.), *t*-BuOH, rt, 4 h; iii) Red-Al, THF, 0 ^{0}C; iv) $(Boc)_2O$, NaOH, DCM:$H_2$0, 0 ^{0}C to rt; v) i) NaH (1.5 equ.), DMF, rt, 1 h, **Cr-complex** 2 h; ii) I_2, 0 ^{0}C, THF. iii) CF_3COOH (1.5 equ.), DCM, 0 ^{0}C to rt, 2 h.

Section C: ***Enantioselective synthesis of (S)-Dapoxetine***

The enantiomer (*S*)-(+)-N,N-dimethyl-α-N,N-dimethyl-α-[2-(1-naphthalenyloxy)ethyl] benzenemethanamine [(*S*)-dapoxetine] is a potent serotonin re-uptake inhibitor for treating depression and other disorders as bulimia or anxiety. Moreover, (S)-dapoxetine is currently being tested as a treatment for premature ejaculation in men. In this section we will discuss enationselective synthesis of (*S*)-dapoxetine (**Scheme 10**). The cinnamyl ester **31** on Sharpless asymmetric dihydroxylation condition gave chiral diol **32**, which was protected with $SOCl_2$ to generate the cyclic sulfate **33** which on reaction with sodium azide gave azido alcohol **34** with inversion. The azide **34** was reduced and protected by $(Boc)_2O$ in one step to obtain **35**, the secondary alcohol of **35** was removed by Barton-Mc-Combie deoxygenation method to give **37** . The Boc protected ester **37** was reduced by LAH in THF to give the primary alcohol **38**. Boc group was deprotected with TFA in DCM at rt to give the amino alcohol **39.** The compound **39** was methylated using formaldehyde in formic acid to give the *N,N*-dimethyl derivative **40** which on Mitsonibu reaction afforded the target molecule (*S*)-dapoxetine **41** in an overall yield of 11.4%.





Scheme 10. Reaction conditions; i) $(DHQ)_2PHAL$ (5 mol %), OsO_4, NMO , *t*-BuOH, rt, 16 h, 80%; ii) CH_2Cl_2, Et_3N (2.2 mmol), $SOCl_2$ (1.2 mmol), 0 ^{0}C to rt, 1 h, 95%; iii) NaN_3 (5 equ.), DMF, 80 ^{0}C, 24 h, 80%; iv) H_2/Pd-C, EtOAC, rt, 24 h, $(Boc)_2O$, Et_3N, 80%; v) NaH (2 mmol), MeI (2 mml), CS_2 (2 mmol), THF, 12 h, 82 %; vi) n-Bu_3SnH (2 mmol) ,AIBN, toluene, reflux, 12 h, 75%; vii) $LiAlH_4$ (2 equ.), THF, rt, 12 h, 82%; viii) TFA, DCM, rt, 78%; ix) HCHO, HCOOH, 83%; x) Ph_3P (2mmol), DEAD (2 mmol), 1-napthol (1.2 mmol) , THF, rt, 72 %.

CHAPTER-1

SYNTHESIS AND CHARACTERIZATION OF IONIC LIQUIDS

SECTION-A

Ionic Liquid

A Brief Introduction

1.1 Introduction

Green chemistry is the universally accepted term to describe the movement towards more environmentally acceptable chemical processes and products. Green chemistry encompasses education, research and commercial application across the entire supply chain for chemicals. Green chemistry can be achieved by applying environmentally friendly technologies-some old and some new.[1]

Hundreds of tones of hazardous waste are released to the air, water, and land by industry every hour of every day. The chemical industry is the biggest source of such waste. The present day challenge for chemists is to develop new products, processes and services that achieve the societal, economic and environmental benefits. This requires a new approach which sets out to reduce the materials and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemicals in the environment, maximize the use of renewable resources and extend the durability and recyclability of products. The drive towards clean technology in the chemical industry with an increasing emphasis on the reduction of waste at source will require a high level of innovation and new technology. Solvents constitute a major factor in deciding the efficacy of an environmental friendly technology. The ideal solvent should have a very low volatility, it should be chemically and physically stable, recyclable and reusable, and eventually easy to handle. In addition, solvents that allow more selective and rapid transformations will have a significant impact.

1.1.1 Innovations in Solvents

Water as solvent

Water has been successfully used as a solvent in some biphasic industrial metal catalyzed reactions since last 30 years.[2-4] However, its application is still limited due to (i) low miscibility of organic substrates in water, giving rise to low reaction rates; (ii) water is protic coordinating solvent and so it can react with halo organics and more vigorously with organometallic complexes by halide-carbon or metal-carbon bond hydrolysis; (iii) from an environmental perspective, trace amount of organic compounds in water are very difficult to remove.

Perflourinated solvents

More recently, perfluorinated solvents have proven their utility for many organic and catalytic reactions.[5-6] Nevertheless, specific ligands must be designed to solubilize catalyst in the perfluorinated phase. Moreover, the decomposition of fluorous solvents at high temperature leads to formation of toxic compounds. Moreover, fluorous compounds are often detected in the organic phase.

Supercritical fluids

Supercritical fluids have also been used described as new solvents for organic and catalytic reactions.[7-8] Their physical properties and chemical stability make them eligible to be called as green solvents. Unfortunately, critical conditions needed for their handling is still a limitation.

Ionic liquids

Since last two decades, Ionic liquids (ILs) have seen come up as a novel class of solvents.[9-10] The history of IL started from the first ionic compound which is a liquid at room temperature viz. ethyl ammonium nitrate ($[EtNH_3]^+[NO_3]^-$) was synthesized by Walden, in 1914 from the reaction of ethylamine with concentrated nitric acid.[11] This IL had a melting point of 12-14 ^{0}C. These early studies on liquid salts did not lead to an explosion of interest in ionic liquids and it was not before the late 1940's that the next ionic liquids were discovered by Hurley and Wier. While looking for an inexpensive and facile method for aluminum electroplating they noted that by mixing powdered alkylpyridinium chlorides with $AlCl_3$ a reaction took place resulting in the formation of a liquid.[12] These ionic liquids incorporate organic cations, i.e. the type of cations used in the ionic liquids that now form the basis of modern synthetic applications, and chloroaluminate anions. While such anions are still being used in synthesis and catalysis, they have become less popular than other more inert anions. This is mainly due to their sensitivity towards air and moisture and the fact that extraction of certain organic products may result in the destruction of these particular ionic liquids.

Osteryoung, Wilkes, Hussey and Zaworotko working on electrochemical aspects of the chloroaluminates were largely responsible for bringing ionic liquids to the attention of a wider scientific community.[13] They were studying chloroaluminates as solvents for

transition metal complexes[14] and as reaction media for stoichiometric organic synthesis.[15] Chauvin and Osteryoung independently combined these two features, i.e. that ionic liquids could dissolve transition metal complexes and support organic chemistry. Chauvin showed that nickel complexes dissolved in acidic chloroaluminate ionic liquids represent an excellent system for the dimerisation of alkenes[16] while Osteryoung used Ziegler-Natta catalysts in acidic chloroaluminates to polymerise ethylene.[17] It was Zaworotko who made the next leap forward, this being the synthesis of water-stable ionic liquids that contain tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate anions.[18]

However, one person who stands out as having made a considerable contribution to the field, looking at both the fundamental properties and applications of ionic liquids is K. Seddon at the University of Belfast. He is perhaps the person who has done most to popularize ionic liquids resulting in such intensive research activity around the world. Ionic liquids have since been utilized as in separation processes[19] as extractants for heavy metals with potential applications in the nuclear processing industry[20] as lubricants[21] as matrices in MALDI mass spectrometry[22] and even as propellants for small satellites.[23] The first industrial process using ionic liquid technology in chemical synthesis has also been reported [24] and numerous others are expected to follow.

They also find additional use in enzyme catalysis or in multiphase bio-process operations. In the present work, emphasis will be given to second generation and third generation ionic liquids i.e. dialkylimidazolium and 1-alkylimidazloium salts rather than the air and moisture sensitive first generation ones (chloroaluminates). Processes based on these stable ionic liquids have been stressed and a brief account of the various features of ionic liquids as designer solvents are presented.

1.1.2 Introduction to ionic liquids

Generally IL refers to molten salts, which contain ions. Only those liquids, which are non-corrosive, and have low viscosity, are chosen to be called as Ionic Liquids. So classes belonging to molten inorganic salts viz. molten sodium chloride will not be considered under the heading IL.

Room temperature Ionic Liquids (RTILs) are emerging as novel replacements for volatile organic compounds (VOCs) traditionally used as industrial solvents. These

solvents are often liquids at room temperature and consist entirely of ionic species. They have many fascinating properties since both the thermodynamics and kinetics of reactions in IL are different to those in conventional molecular solvents. These "Designer Solvents" aptly named-consists of an anionic and a cationic part, which can be varied for a particular end use or to possess a particular set of properties.

1.1.3 Classification

ILs are classified into two categories.

i. Binary ionic liquids – salts where equilibrium is involved.

ii. Simple salts – made of single anion and cation.

The first category, the first generation ILs, contains a mixture of metal halide and dialkylimidazolium chloride. These contain several ionic species and their melting point and other properties depend on the mole fractions of the individual components. The second class, generally termed as second generation ILs, consists of simple cation and anion e.g. ethyl ammonium nitrate ($[EtNH_3]^+[NO_3]^-$), dialkylimidazolium ILs [bmim]Br. The third generation ILs consist of chiral ILs made from either chiral cations or anions, mono-alkyl imidazoluim ILs and task specific ILs.

ILs generally are composed of relatively large organic cations and inorganic or organic anions and have a melting range of –96 ^{0}C to 100 ^{0}C. Cations are mainly alkyl quaternary ammonium or phosphonium moiety which may be a part of a heterocyclic ring.

1.1.4 Recent developments in cations and anions

In the literature, it has been mentioned a large number of cation–anion associations are able to yield room temperature ionic liquid, unlike the inorganic salts. They are composed solely of ions (cations and anions) but they are liquid at low temperature (melting point typically below 100 ^{0}C). Different cation-anion combinations are developed and studied for their suitability to be used as ILs.

Cations

The cations are generally organic components with low symmetry and bulk in size. Those described until now are based on ammonium **1,**[25-27] sulfonium **2,**[28] phosphonium **3,**[29] imidazolium **4,**[30-33] pyridinium **5,**[34-36] pyrrolidinium **6,**[37] thiazolium **7,**[38] triazolium **8,**[39]

oxazolium **9,**[40] and pyrazolium **10** [41] differently substituted (**Fig. 1**). Of particular interest are the salts based on the *N*,*N*-dialkylimidazolium cation **4** because of the wide spectrum of physico-chemical properties available in that class. Liquid imidazolium salts are generally obtained by anion exchange from imidazolium halide precursors.

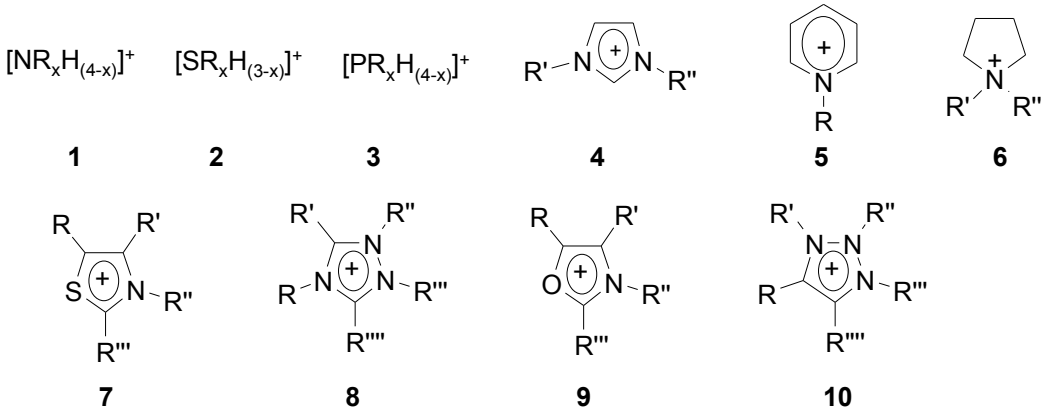


Fig. 1. Examples of cations described in ionic liquids.

It has very often been assumed that non-symmetrical *N*,*N*-dialkylimidazolium cations give lower melting point salts. Very surprisingly, however, the symmetrical 1,3-dialkylimidazolium hexafluorophosphates with dibutyl, dipentyl, dioctyl, dinonyl and didecyl substituents are found to be liquids at room temperature.[42]

The alkyl chain on the imidazolium can also bring a fluorocarbon tail.[43] In that way, the fluorinated salts, when added to a conventional ionic liquid, can act as surfactants and facilitate the emulsification of per-fluorocarbons in ionic liquids. It can also include task-specific functional groups.[44]

Besides the *N*,*N*-dialkylimidazolium cations, pyrrolidinium cations **6** have gained attention first as plastic crystal former with anions such as BF_4 or NTf_2. These low melting salts exhibit interesting ionic conductivity and, therefore, have received attention for use as electrolytes in a range of applications including solar cells and batteries.[45] Other recently developed cations are the planar trialkylsulfonium ones such as **2**. When combined with the NTf_2 anion, they give low melting salts with very high conductivity and the lowest viscosity of all the NTf_2 based room temperature ionic liquids ($[SEt_3][NTf_2]$: mp = 35 ^{0}C and 30mPas at 25 ^{0}C). Their high conductivity can be ascribed to a little stronger degree of

association between SEt_3^+ and NTf_2. than that of 1-ethyl-3-methylimidazolium (EMI^+) and NTf_2 salt.[46]

In most chemical applications of ionic liquids, cations influence the physical properties of the medium. However, a chemical effect of the cation is also possible.

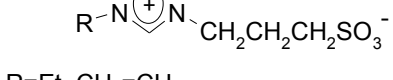
Anions

Concerning the anions, they can be classified in two parts; those which give polynuclear anions, e.g. Al_2Cl_7, Al_3Cl_{10}, Au_2Cl_7, Fe_2Cl_7, Sb_2F_{11}. These anions are formed by the reaction of the corresponding Lewis acid, e.g. $AlCl_3$ with the mononuclear anion, e.g. $AlCl_4$. They are particularly air and moisture sensitive. The second class of anions corresponds to mononuclear anions which lead to neutral, stoichiometric ionic liquids, e.g. Cl, Br, ClO_4, BF_4, PF_6, SbF_6, $ZnCl_3$, $CuCl_2$, $SnCl_3$, $N(CF_3SO_2)_2$, $N(C_2F_5SO_2)_2$, $N(FSO_2)_2$, $C(CF_3SO_2)_3$, CF_3CO_2, CF_3SO_3, CH_3SO_3, CH_3COO, NO_3, OTs etc. Of particular interest is the trifluoromethylsufonylamide anion [NTf_2],[47-48] which gives particularly thermally stable salts (up to 400 ^{0}C).

Salts based on this anion can be easily prepared by anion exchange reactions using the commercially available lithium trifluoromethylsufonylamide. Because of the delocalization of the negative charge, the anion is probably less associated with the cation and then more mobile than the triflate one. For reasons that are not completely elucidated, this imide anion strongly lower the melting points of salts such as quaternary ammonium such as Et_4N^+ ([Et_4N][NTf_2]). $LiNTf_2$ and $LiCTf_3$ salts are considered as attractive alternatives to $LiPF_6$ in high voltage ion cells due to the hydrolytic instability of $LiPF_6$.[49]

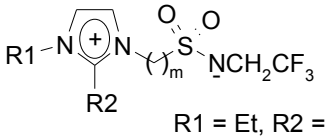
Zwitterionic-type ionic liquids

A series of zwitterionic-type ionic liquids consisting of an imidazolium cations containing a covalently bound counter anionic sites, such as a sulfonate **11** or a sulfonamide **12** group have been prepared (**Fig. 2**). They act as an excellent ion conductive matrix, in which only added ions can migrate.



R=Et, CH_2=CH-

11



R1 = Et, R2 = H, m = 3
R1 = Me, R2 = Me, m=2

12

Fig. 2. Examples of zwitterionic salts.

1.1.5 What features make ionic liquids so attractive?

The versatility of their chemical and physical properties

Besides their very low vapor pressure, which makes ionic liquids good alternatives to volatile organic solvents, they display a large operating range (typically from -40 to 450 ^{0}C), a good thermal stability,[52] high ionic conductivity[53] and large electrochemical window.[54] However, the key property of these solvents is the possibility to tune their physical and chemical properties by varying the nature of the cations and anions.[55,56] The spectrum of their physical and chemical properties is much larger than that of organic solvents. Some typical physical characteristics of the more currently used salts are given in Table 1.

Table 1. Physical characteristics of 1-butyl-3-methylimidazolium ionic liquids.

Anion	M.P (^{0}C)	Density (g/cm^3)	Viscosity (mPas)	Conductivity (Sm^{-1})
BF_4^-	-82/-83	1.17(30 ^{0}C)	233 (30 ^{0}C)	0.173 (25 ^{0}C)
PF_6^-	-61	1.37 (30 ^{0}C)	312 (30 ^{0}C)	0.146 (25 ^{0}C)
$CF_3SO_3^-$	16	1.29 (20 ^{0}C)	90 (20 ^{0}C)	0.37 (20 ^{0}C)
$CF_3CO_2^-$	-50/-30	1.209 (21 ^{0}C)	73 (20 ^{0}C)	0.32 (20 ^{0}C)
NTf_2^-	-4	1.429 (19 ^{0}C)	52 (20 ^{0}C)	0.39 (20 ^{0}C)

It has recently been demonstrated that the viscosity of 1-alkyl-3-methylimidazolium salts can be decreased by using highly branched and compact alkyl chain but more importantly by changing the nature of the anion.[57] For the same cation the viscosity decreases as follows: $Cl > PF_6 > BF_4 > NO_3 > NTf_2$.

An illustration of their versatility is given by their exceptional solubility characteristics[58] which make them good candidates for multiphasic catalysis. For example, their solubility with water depends on the nature of the anions, temperature and length of the alkyl chain on the dialkylimidazolium cation. For the same 1-butyl-3-methylimidazolium cation, the BF_4, CF_3SO_3, CF_3CO_2, NO_3, and halide salts display a complete miscibility with water at 25 ^{0}C. However, upon cooling the [BMI][BF_4]/water solution to 4 ^{0}C, a water-rich phase separates. In a similar way, changing the [BMI] cation

for the longer chain [HMI] (1-hexyl-3-methylimidazolium) leads to a BF_4 salt, which presents a low co-miscibility with water at room temperature. On the other hand, the PF_6, SbF_6, NTf_2, BR_4 show a very low miscibility with water. But for the PF_6 based melt, the shorter symmetric substituted 1,3-dimethylimidazolium PF_6 salt becomes water-soluble. Salts based on 1,3-dialkylimidazolium cation remain preferred as they generally interact weakly with the anions and are more thermally stable than other quaternary ammonium cations. Huddleston et al. demonstrated that water content, density, viscosity, surface tension, melting point, and thermal stability were affected by changes in alkyl chain length of the imidazolium cations and by the nature of the anion. As expected, the anion mainly determines water miscibility and has the most dramatic effect on the properties. For a series of 1-alkyl-3-methylimidazolium cations, increasing the alkyl chain length from butyl to octyl increases the hydrophobicity and the viscosity of the ionic liquid, whereas densities and surface tension values decrease. As a result, one could expect that modifications of alkyl substituents of the imidazolium ring can give rise to different and very tunable solvent properties.

How do ionic liquids compare with conventional solvents?

At the present time, there is still only an empirical knowledge of these media mainly developed on the basis of their solvent effect on organic reactions compared to that of well-known conventional solvents. The challenge would be to be able to predict their properties in order to optimize the choice for a given application.

Solvent polarity has often a strong influence on the outcome of reactions. However, the exact meaning of polarity is already complex, but becomes even more complicated in the case of ionic liquids, as many varied interactions can be involved. Different investigations of solvent–solute interactions in ionic liquids using solvatochromic dyes have been reported.[59-60] The data indicate that polarities of 1,3-dialkylimidazolium salts based on the PF_6, BF_4, CF_3SO_3 and NTf_2 anions can be compared to that of short chain primary alcohol with a little lower polarity for the NTf_2 anion. The ionic liquid nucleophilicity is dependant on the anions and is much lower than that of polar solvents, which makes ionic liquids highly polar but yet non-coordinating which in a unique property.

Following properties make ILs an attractive substitute for molecular solvents in chemical processes.

[1] Ionic liquids do not evaporate as they have no detectable vapour pressure. Since reducing the emissions of volatile organic compounds is viewed as one of the most important ways of reducing pollution from the chemical industry it is perhaps this property of ionic liquids that makes them so attractive as potentially benign replacements to organic solvents.

[2] Many metal catalysts (notably salts), organic compounds (especially polar compounds), gases and biocatalysts dissolve in ionic liquids, allowing homogeneously catalyzed reactions to be performed.

[3] Ionic liquids are immiscible with many organic solvents and compounds, which lends themselves to biphasic or multiphasic catalytic reactions. Most are also immiscible with fluorous phases and some are immiscible with water.

[4] Ionic liquids have polarities comparable to alcohols, which are amongst the most widely used solvents in which to conduct homogeneously catalyzed reactions. In contrast to alcohols, however, many ionic liquids are non-nucleophilic, which can have a pronounced effect on a catalyzed reaction. The non-nucleophilic environment presented by many ionic liquids is also less likely to deactivate a catalyst and can lead to increased turnover numbers, which is essential in biphasic processes where catalyst recycling and reuse is required.

[5] Ionic liquids have favorable thermal stabilities and operate over large temperature ranges. Many of the commonly used ionic liquids melt below room temperature and melting points as low as –80 ^{0}C or below are not unusual. On the other hand they often only start to decompose above 350 ^{0}C, providing a large temperature range in which to conduct synthesis compared to molecular solvents.

[6] It is not always necessary to modify a catalyst for use in ionic liquids, and expensive ligands that modify the solubility properties of a catalyst are not necessarily required. Many catalysts are salts and in general these are very well retained in ionic liquids, and where necessary, ligands that anchor a catalyst in an ionic liquid phase are available.

[7] Functional ionic liquids, often referred to as task-specific ionic liquids, can be prepared by incorporating functional groups on the organic cation, or using functional anions. These ionic liquids have specific chemical properties and combined with a greater understanding of the factors controlling the physical properties of ionic liquids. The ability to design an ionic liquid for a specific process is essential as there seems to be essentially no limit to the number of different ionic liquids that can be made.

[8] While very little toxicity data are available it would appear that many ionic liquids do not represent an immediate threat to health if handled properly. Indeed, at the most they may be as toxic as methanol.

1.1.6 Fundamental principles of the formation and development of RTILs.

The objective of this section is to provide light into the nature and properties of the ionic liquids, which will be useful in defining the ionic liquids as solvents and applications for industrially important processes and catalytic reactions leading to clean technology.

The melting point of a salt is related to its lattice energy. For e.g. a plot of lattice energy of group 1 halides against the melting point in Kelvin will give a straight line. The relationship was first studied by Kapustinskii, who coined the equation popularly known as Kapustinskii equation.[61] (Equation 1)

It can be seen that by using larger anionic and cationic components (increasing the value of r_0 (ionic radii)) in the salt, it is possible to lower this energy and therefore reduce the melting point.

$$U = \frac{287.2 v Z^{+} Z^{-}}{r_0} \left(1 - \frac{0.345}{r_0} \right) \qquad \text{---------- Equ. 1}$$

U = lattice energy; v = number of ions per molecule

r_0 = sum of the ionic radii; Z^{+}, Z- = charge of the ionic species

From this it is clear that as we increase both the size of the anion as well as that of the cation, the melting point decreases. From the Kapustinskii equation an increase in the ionic charge will tend to increase the lattice energy of the crystal. However, the effect on

melting point is complicated by the fact that according to Fajan's rules an increasing charge also results in increasing covalency particularly for small cations and large anions.

It is also possible to reduce lattice energy by increasing the size of cation. In the case of organic cations, the length of alkyl chain can be considered as the basis of the size of particular cation. So to decrease the lattice energy, the alkyl chain length should be increased thereby increasing the number of ionic liquids.

One can observe that there is a maximum chain length allowed before other forms of bonding begin to dominate and the melting point increases. The melting point below 0 ^{0}C can be glass transition temperature rather than the true melting point. The significant variation in melting point which can be induced by simply changing the anion from [$C_n$mim]Cl to the [$C_n$mim]PF_6 and [$C_n$mim]BF_4 ionic liquids have been well documented e.g. [C_4mim]PF_6 melts at 5 ^{0}C whereas [C_4mim]Cl has a melting point of 84 ^{0}C. These lower melting point liquids with shorter alkyl chain length lead to much more fluid and easily managed liquid.[62-64]

1.1.7 Synthesis of Ionic Liquids

The number of available ionic liquids continues to grow at an ever increasing rate, however only few are used by the wider community. The majority of the ionic liquids in use are prepared via salt metathesis reactions and one of the greatest challenges in the field of ionic liquids concerns their synthesis in high purity. Until ionic liquids of well-defined purity are commercially available at acceptable prices, the reliability of the data reported will remain somewhat ambiguous and catalyst performance in these new media must be compared with some caution. At present, many research groups working in the field prepare their solvents themselves, inevitably leading to variations in quality and purity data are seldom provided.

Literature of ionic liquid shows that small amounts of (mainly halide or water) impurities can exert a huge effect on the outcome of a catalyzed reaction. Also examples, where results could not be reproduced and different conclusions are reached, are not uncommon. Having given this warning it is also clear that the field is moving at an incredible pace and new synthetic routes and purification procedures are being developed

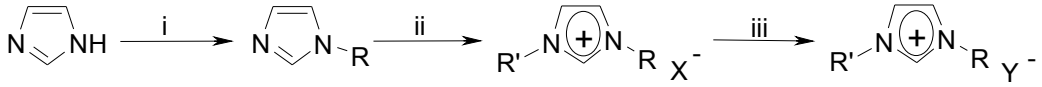
all the time, and in general the quality of ionic liquids used presently is superior to those employed just a few years ago.

Ideally, ionic liquids should be colorless, clear, odorless and free flowing liquids. While colored impurities may subjectively appear more disturbing, they usually cause less problems then the less obvious halide contaminants. Especially hydrophilic ionic liquids comprised of e.g. $[BF_4]^-$ or $[OTf]^-$ are likely to contain some residual halide. If such ionic liquids are prepared via the commonly employed metathesis route, careful washing of a solution in, for example, dichloromethane with water is essential until addition of $AgNO_3$ to the water-phase does not lead to a positive reaction for silver halide. While this does not mean that there is no halide left in the ionic liquid, it could at least be regarded as a minimum standard that ought to be fulfilled. While halide impurities are easier to extract from hydrophobic ionic liquids, those based on $[PF_6]$, and to a lesser degree also those based on $[BF_4]$, are susceptible towards anion degradation and formation of HF. It is increasingly common to check the results for possible interference from the various impurities.

Numerous examples report on the beneficial effects when catalysis is performed in an ionic liquid be it increased rate, selectivity, recycling potential or even the accessibility of products that were not available otherwise. Are all these results to be questioned due to insufficiently purified ionic liquids? Certainly not, rather the contrary is true. While ionic liquids of poor quality are likely to afford inferior results, it is only in few cases that the contaminant can be held responsible for any observed catalytic activity. An example is acid-catalyzed reactions where HF from degradation of the anion could act as the catalyst.

Thus, while the absolute value of reported turnover frequencies and selectivities are likely to be subject to change, it appears that with increasing solvent quality results will change for the better, not the worse. Publications, which report significant improvements in ionic liquids relative to conventional solvents, can in most cases be taken for the real thing. Whether it makes sense to run a given reaction in an ionic liquid both from an economical as well as an ecological point of view is a different question and has to be decided in each individual case. The most widely used synthetic approach used to prepare ionic liquids is summarized in **Scheme 1**. The scheme depicts the preparation of

imidazolium-based ionic liquids although the method is widely applicable to other types of cations, notably pyridinium systems.



Scheme 1. Reaction conditions; i) BuBr, KOH, CH_3CN, 0 ^{0}C to rt; ii) BuBr, 80 ^{0}C; iii) HY, methanol, rt.

In the first step an alkyl halide (chloride, bromides and iodides) reacts with imidazole to form 1-alkyl imidazole which again reacts with alkyl halide to form the imidazolium halide.[65-66] In many cases solvent is not required during the reaction. The imidazolium halide on further metathesis gave the desired ionic liquid.

An increasing number of ionic liquids are no longer based on tetrafluoroborate or hexafluorophosphate anions, although these remain the most widely studied as solvents for catalysis. Alkylation with appropriate precursors that simultaneously generate the anion represents the most effective method. Alkylation of the 1-alkylimidazole derivatives are carried out in trichloroethane, a solvent chosen for its stability toward strongly alkylating agents, its moderately high boiling point, and the insolubility of the imidazolium salts in this medium.[67] Alternative activation sources have also been applied to the synthesis of ionic liquids, notably, the use of ultrasound[68] and microwave dielectric heating, which not only reduces the reaction time, but can also increase the conversion.[69-70]

1.1.8 The importance of the purity of ionic liquids

The physical and chemical properties of ionic liquids can be altered by the presence of impurities arising from their preparation.[71] Purification of the ionic liquids is then essential. The main contaminants are halide anions or organic base that generally emanate from unreacted starting material and water.[72] A colorimetric method has been recently developed to determine the level of unreacted alkylimidazole (<0.2 mol%) in the ionic liquid. As halide impurities can have a detrimental effect on transition metal catalyzed reactions, alternative methods of preparations have been proposed to avoid the use of halide containing starting materials. Examples are given by the direct alkylation of alkylimidazole derivatives.[73-75] Even hydrophobic ionic liquids can accommodate water.[76] Ionic liquids are usually dried by heating under vacuum. However, water is difficult to

remove completely probably due to the existence of hydrogen bonding. The presence of water can not only reduce the density and the viscosity but can also modify the chemical properties. In some cases, e.g. PF_6 based salts, traces of water can generate the decomposition of the anion and the formation of HF.

1.1.9 Properties of Ionic Liquids

The special structural make up of IL is that the physical and chemical properties can be tuned by the careful selection of cations and anions.

Melting point

The most interesting and most debated property of the IL is the melting point. Recent literature reveals the complexity in correlating structure and chemical composition with melting points. Table 2 provides MPs of some salts with chloride anion.[77]

Table 2. Melting points of various chlorides

Salt	M.P. (^{0}C)
NaCl	803
KCl	772
$[MMIM]^+Cl^-$	125
$[EMIM]^+Cl^-$	87
$[BMIM]^+Cl^-$	65

In comparison with inorganic salts these have a low symmetry,[78] weak intermolecular interactions[79-80] and good charge distribution in both cations and anions.[81] Increase the size of anions also decreases the MPs. They used a weakly coordinating anion i.e carborane and varied the alkyl chain length in the imidazolium moiety. They concluded that the positional disorder of the cations in the crystal structures, which is a direct indicator of packing inefficiency, is the reason behind the low melting of these ILs having larger anions. If the cation/anion interactions are reduced to the level of van der Waals or very weak hydrogen bonding type forces, then the disorder reflects packing inefficiency.

Vapors Pressure and Thermal Stability

ILs have no measurable vapor pressure. This feature is advantageous from engineering point of view as the reactants and products can be easily distilled off from the reaction mixture, which makes for a more effective method for isolation. Moreover azeotrope formation between the solvent and the products does not arise.

Thermal stability of ILs is higher than other molecular solvents. It depends on the strength of heteroatom-carbon and heteroatom-hydrogen bonds. ILs synthesized by direct protonation of an amine or a phosphane show restricted thermal stability. ILs obtained by alkylation of an amine or phosphane have a tendency to undergo thermally induced transalkylation or dealkylation which will depend on the nature of anion. Dialkylimidazolium based ILs have been shown to exhibit very high thermal stability upto 400 ^{0}C[33] and in some cases it may be more than 450 ^{0}C.

Density

Density is an important property particularly used in fluid flow calculations and the design of liquid/liquid two phase mixer-settler units. It can be generalized that the density of ILs depend on the bulkiness of anion.[33] It has been observed that changes in the structure of cation also can have slight changes in the density of IL.

Viscosity

The viscosity of ILs is essentially governed by their tendency to form hydrogen bonding and by the strength of their van der Waals interactions.[33] Comparison of the viscosity of different dialkylimidazolium based ILs emphasizes the interplay between van der Waals interactions and hydrogen bonding e.g. an increase in viscosity was observed for butylmethylimidazolium IL when triflate anion is displaced with n-$C_4F_9SO_3^-$ ion and from the trifluoroacetate ion to n-$C_3H_7COO^-$ ion. This is due to increased van der Waals interactions in the case of n-$C_4F_9SO_3^-$ and n-$C_3F_7COO^-$ ions. Comparison of the viscosities of [bmim]CF_3SO_3 with [bmim]$(CF_3SO_2)_2N$, reveals a lower viscosity despite stronger van der Waals interactions for ILs with $(CF_3SO_2)_2N^-$ ion. In this case, the almost complete suppression of hydrogen bonding overcompensates for the expected increase in viscosity.

The structure of cation also influences viscosity of ILs. Increasing the chain length or with fluorinated alkyl chains will result in higher viscosity. The viscosity of ILs can be lowered drastically in some cases, by only slight increase in temperature[81] or by the addition of small amounts of organic cosolvents.[82]

Polarity and Solvent properties

Solvent polarity is the most commonly used criterion for solvent classification. Even when considering molecular solvents it is poorly understood and often confused. Terms such as polar, apolar, and nonpolar are used indiscriminately to apply to values of dielectric constants, dipole moments, and polarizabilities, even though none of these are directly correlated in a simple way. The simplest qualitative definition is that a polar solvent is one that will dissolve and stabilize dipolar or charged solutes. It is widely thought, though yet to be generally demonstrated, that under this definition, ionic liquids will be highly polar solvents. The longest wavelength absorption band of Reichardt's dye (2,4,6-triphenylpyridinium N-4-(2,6-diphenylphenoxide) betaine shows one of the largest solvatochromic shifts known (375 nm between diphenylether and water).[83] It can register effects arising from the solvent dipolarity, hydrogen bonding, and Lewis acidity and is considered to be a good general polarity scale. The E_T^N values of a small number of alkyl ammonium nitrate,[84] thiocyanate,[84] and sulfonate[85] salts have been recorded. Values of ca. 0.95-1.01 for monoalkyl ammonium nitrates and thiocyanates are close to that of water (1.00, by definition), whereas quaternary ammonium sulfonates give lower values of ca. 0.45-0.65 which are more typical of polar organic solvents such as DMSO. An attempt was also made to separate dipole-dipole polarizability effects from hydrogen-bonding effects by using the π^* scale of dipolarity/ polarizability, the R scale of hydrogen bond donor acidity, and the 0, scale of hydrogen bond basicity.[85] Although some difference was seen between the π^* values for monalkylammonium salts and the quaternary ammonium salts, the difference in the hydrogen-bond acidities and basicities was far more marked.

The solvent properties of these ionic liquids have also been investigated using chromatographic techniques.[84-86] It was generally found that the ionic liquids could be considered to be polar phases with the solvent properties being largely determined by the ability of the salt to act as a hydrogen-bond donor and/or acceptor and the degree of

localization of the charge on the anions. However, the ammonium and phosphonium salts that were used would not exhibit large differences in the delocalization of charge on the cation, and this may be an important effect for other salts, such as the pyridinium- and imidazolium based ionic liquids. Furthermore, it was found that increasing the chain length of alkyl substituents on both cations and anions leads to greater lipophilicity of the ionic liquids.[85,87] Also, the influence of hydrogen bonding can be diminished by fluorinating the ionic liquids.[88]

Handling and availability

The handling of ionic liquids depends essentially on the stability of the anion towards hydrolysis. Whereas ionic liquids with nitrate, benzenesulfonate, and [bis(trifluormethylsulfonyl]amide ions, for example, are air and water stable and can even be synthesized in water, systems with chloroaluminate anions must be classified as extremely hygroscopic and labile towards hydrolysis. More difficulties arise when traces of water in chloroaluminate melts react with the anions of the melt to release super acid protons. These cause unwanted side reactions and possess a considerable potential for corrosion. To sum up: the handling and stability of ionic liquids cannot be easily assessed, but it is mainly dependent on the nature of the anion. The commercial availability of ionic liquids was very limited until recently. Only a small number of systems could be purchased from chemical distributors in small quantities (up to 25 g).[89] Since the end of 1999, a large variety of ionic liquids is now commercially available in up to 5 liter scale.[90] If demand for ionic liquids grows further, it is supposed that in the near future particularly producers of ionic liquid precursor compounds (such as amines) will enter the market. In such a case it is expected a drastic decrease in prices for ionic liquids should be possible. It should be specifically noted here that after most applications the used ionic liquid can be easily recovered, cleaned up - if necessary - and reused repeatedly. In an ideal case the cost for the ionic liquid can be therefore regarded as a one-time investment.

Toxicological and Environmental Concerns

The toxicological and environmental properties of ionic liquids are slowly emerging, but are becoming increasingly needed, as ionic liquids are beginning to be employed in larger quantities. While ionic liquids are classified as non-toxic and ‘green’

this is not necessarily the case and such generalization must be taken with extreme caution. It would appear that many ionic liquids are more toxic than commonly used organic solvents. A strategy for the risk-assessment of ionic liquids has been developed [91] and the aquatic biodegradation of both imidazolium cations and a range of anions have been investigated.[92] It was found that 1-butyl-3-methylimidazolium based ionic liquids with a range of different anions (those currently widely used in catalysis) are essentially poorly biodegradable. However, with a modified cation, viz. the 3-methyl-1- (propoxy methyl carbonyl)-imidazolium cation, the analogous series of ionic liquids were considerable more prone to biodegradation, indicating again how designer ionic liquids can overcome specific problems.[93] Likewise, ionic liquids containing the octyl sulfate anion, which is cheap, widely available and has a well-documented toxicology, have been developed and are probably amongst the greenest available.[94] Despite being prepared via the conventional metathesis route they are readily isolated in halide free form and are now prepared on the ton scale.

Ionic liquids have been shown to exhibit both antimicrobial and antifungal activities.[95] In general, if the alkyl groups are short then they are not active, but with C8 chains and above activities become comparable to effective reagents. The implication here is that if an ionic liquid can enter microbial or fungal cells then it is likely that they could also enter mammalian cells, exhibiting toxicity or potentially being mutagenic. In fact, preliminary assays using human cells have been reported.[96,97] However, the great advantage of ionic liquids is that they are non-volatile and therefore cannot be ingested by inhalation. So as long as they are handled properly and fully removed from organic products, their exposure to humans should approach zero and therefore not present a serious health risk.

1.1.10 Applications of Ionic Liquid

Numerous literature material is available which shows the importance of ILs e.g. a number of excellent books[10] and recent general reviews[9] as well as those covering specific topics such as catalysis (including biocatalysis) in ionic liquids,[98] synthesis of organometallic complexes in ionic liquids,[99] biphasic systems and supported ionic liquids,[100] solvent properties,[101] ionic liquids with fluorine containing anions,[102] analytical

applications of ionic liquids,[103] chiral ionic liquids,[104] electrochemistry in ionic liquids,[105] and physical properties of ionic liquids are available.[106] In addition, a number of special issues[107,108] have appeared covering a range of topics including ionic liquids as green solvents,[109] physical and thermodynamic data,[110] and organometallic chemistry in ionic liquids.[111] The 'non-innocent' nature of some specific ionic liquids has been addressed by Dupont and Spencer.[112]

1.1.11 Summary and Conclusion

Ionic liquid chemistry is at an incredibly exciting area of development. The unique properties of these liquids and the possibility to tailor properties by choice of cation, anion and substituents, open the door to a variety of processing options. In many applications ionic liquids with weakly coordinating anions and suitable substituted cations are attractive alternative "solutions" to commonly used solvents. They give rise to increased solubility of reactants/products, increase in rate and selectivity of reactions, biphasic catalysis, homogeneous catalysis etc. The liquid crystalline properties of some ionic liquids can result in a very highly ordered solvent environment for various end uses such as transition metal catalysis.

The following points are to be addressed in the future for their effective utilization towards the evolution of cost effective green technologies.

[1] Fundamental knowledge for the design of ionic liquids – effect of cation, anion and substituents on its physical and chemical properties.

[2] Quantitative Structure-Property Relationship (QSPR) modeling, which make use of the statistical link between the physicochemical properties of a compound and a set of molecular descriptors, that can be used in the correlation of toxicity and corrosivity.

[3] Detailed study on toxicology of ILs.

[4] Ease of separation in their pure form and recyclability.

[5] Cost of ionic liquids.

1.1.12 References

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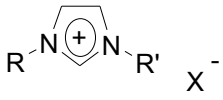
SECTION-B

Synthesis and Characterization of Ionic Liquids

The previous section provided an insight into the importance of the peculiar character and some of the applications of ionic liquids. Ionic liquids are organic salts, invariably possessing a high degree of asymmetry that frustrates packing and thus inhibits crystallization. The permutation and combination of anions and cations can result in numerous ILs with varied chemical and physical properties A search for a substitute for expensive butylmethylimidazolium hexaflourophosphate [bmim]PF_6, which should have similar physical and chemical characteristics was inevitable.

This section deals with the synthesis and characterization of ionic liquids based on structure **13**.



13

1.2.1 Introduction

Very few detailed studies have been reported on the physical and chemical properties of imidazolium based ionic liquids with respect to their changing the anions. Mainly, the structure of ILs with respect to the change in the anions and their properties have been stressed in detail. Larsen *et al.* conducted a detailed examination of the liquidus character of the highly ionic compounds, by single crystal XRD studies of dialkylimidazolium salts with the very weakly coordinating anion. They concluded that the positional disorder, which induces packing inefficiency in the crystal lattice is the main cause of the low melting point of these species despite presence of large anions. Cation/anion interactions are decreased essentially to the level of van der Waals or very weak hydrogen bonding-type forces leading to packing inefficiency resulting in disorder.

1.2.2 Present Work

1.2.2.1 Objective

As lot of literature available on the synthesis and physiochemical properties of unsymmetrical imidazolium ionic liquids, but not much effort was taken on the synthesis and physicochemical properties of symmetrical dialkyl and monoalkyl imidazolium ionic liquid. This section deals with the synthesis and physicochemical properties of 1,3-dibutyl imidazolium i.e. [bbim]X and mono-butyl imidazolium i.e. [Hbim]X ionic liquids.

Synthesis of ionic liquid

The ionic liquids based on structure **13** were synthesized by us.

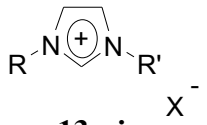


Table 3. List of ILs synthesized. **13a-j**

IL	R	R'	X	IL	R	R'	X
13a	n-C_4	n-C_4	Cl	**13f**	n-C_4	H	Cl
13b	n-C_4	n-C_4	Br	**13g**	n-C_4	H	Br
13c	n-C_4	n-C_4	BF_4	**13h**	n-C_4	H	BF_4
13d	n-C_4	n-C_4	PF_6	**13i**	n-C_4	H	PF_6
13e	n-C_4	n-C_4	ClO_4	**13j**	n-C_4	H	ClO_4

Ionic liquids were purified by column chromatography. Density, viscosity, thermal stability, polarity, NMR and IR were recorded. The properties are correlated with the change in structure of cation and anion of ILs. All the alkyl groups are straight chain.

Characterization of ionic liquids

NMR

NMR spectra were recorded on Bruker AC 200 spectrometer for bbim series using TMS as internal standard whereas for Hbim series $CDCl_3$ was used as external lock and NMR spectra was recorded on Brucker AC 500.

Infrared Spectroscopy

Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer.

Density measurements

Density determination is based on measuring the period of oscillation T of a vibrating U – shaped sample tube (2mm i.d) which is filled with the sample liquid. The introduction of liquid or gas in the tube changes the frequency of oscillation and hence the density. The following relationship exists between the period T and density d where ρw is he density of calibrating substance (water), Tρ is the period of oscillation of calibrating

substance (water), Tρx is the period of oscillation for unknown sample and To is the period for vacuum.

Air and distilled water were used as standard fluids. Temperature of the cells was controlled within ± 0.01 K by thermostat water circulated around the cells. The density of an unknown liquid sample was obtained by introducing the sample in one cell and water as reference into the other cell. After measuring T, d was calculated using equation 2.

$$d = \left(\frac{\rho_w}{\left(T_\rho / To \right)^2 - 1} \right) \left(\left(\frac{T_{\rho x}}{T_o} \right) - 1 \right) \qquad \text{---------- Equ. 2}$$

Viscosity

Viscosity was measured in Brookfield Digital viscometer, Model DV-I at room temperature (30 ^{0}C).

Thermo gravimetric analysis

TG-DTA was done using machine MODEL No. PG-320, Seiko, Japan. Argon is used as carrier gas. Weight of sample = 20mg.

Polarity

Solvent polarity has a powerful influence on the outcome of chemical reactions and on the features observed with spectroscopic techniques. As a result, the choice of the solvent for a particular application must be made with great care and thought. To aid such decisions, a number of parameters are available for guidance, e.g. dielectric constant, refractive index and dipole moment. However, solvent polarity cannot simply be defined using these terms, since specific solvent–solute interactions are not taken into account. This has led to the development of empirical scales of solvent polarity. A common approach to the development of such scales has been to use solvatochromic dyes, that is, compounds for which the absorption or emission band maxima shift according to the polarity of the medium in which they are dissolved. Although solvent effects on organic reactivity and spectroscopic transitions have been studied for more than a century, the concept of solvent polarity, while easily grasped in a qualitative sense, eludes rigorous and precise definition.

The IUPAC recommendation for the definition of solvent polarity specifies, "*that the polarity is sum of all possible, non-specific and specific, intermolecular interactions between the solute ions or molecules and solvent molecules, excluding such interactions leading to definite chemical alterations of the ions or molecules of solute".*

Because these manifold intermolecular forces include Coulomb interactions, directional interactions between dipoles (and quadrapoles or higher multipole moments), inductive, dispersive, hydrogen-bonding, and charge-transfer forces, as well as solvophobic interactions, not surprisingly single macroscopic physical parameters (e.g. dielectric constants, dipole moments, refractive indices0 or functions thereof cannot adequately describe solvent polarity. This inadequacy, coupled with the lack of comprehensive theoretical expressions, has led to the introduction of empirical solvent polarity scales based on solvent interactions with a reference solute.

Several polarity scales, based on solvatochromic probes, have been devised over the years, including the *Y*-scale introduced by Winstein, Dong and Winnik's *Py*-scale, Kosower's *Z*-scale, Dubois *Φ*-scale, the Reichardt $E_T(30)$ scale, Gutmann's donor (DN) and acceptor numbers (AN), and the linear solvation energy relationship (LSER) developed by Kamlet and Traft. Polarity in terms of E_T values of both series of ionic liquid was recorded on UV spectrometer using Reichardt's betain dye. The sample was prepared by dissolving 1 mg of Reichardt's betain dye in 5 mL of IL.

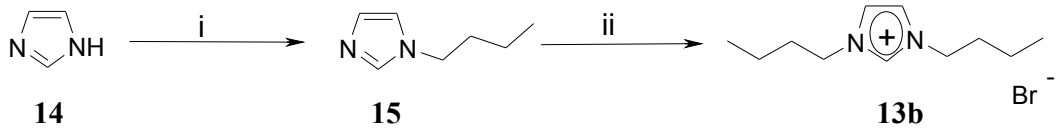
1.2.3 Results and Discussions

1.2.3.1 Synthesis of Ionic Liquids

There are several methods available for the synthesis of ionic liquids but they suffer from several drawbacks such as multistep synthesis, lower yield, harsh reaction conditions and long reaction time.

The different 1,3-di-*n*-butylimidazolium ILs **13a-e** (**Scheme 2**) are prepared by the quarternization of previously prepared 1-*n*-butylimidazole **15** with the respective alkyl bromide resulting in the bromo IL. This is converted into BF_4, PF_6 and ClO_4 salt by the metathesis reaction with sodium tetrafluoroborate, hexafluorophospahte and perchloic acid respectively. The imidazolium bromide salt is obtained quantitatively in a neat reaction of alkyl bromide with 1-n-butylimidazole at 70 ^{0}C under inert atmosphere (**Scheme 2**). A

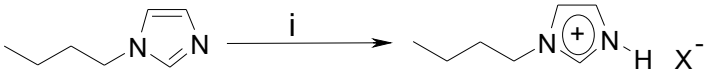
very viscous liquid (consistency of honey) was obtained with a yellowish color. The color can be removed to a certain extent by charcoal treatment. The metathesis reaction is generally carried out in water. To the aqueous solution of the IL, sodium tetrafluoroborate/ hexafluorophospahte/ perchloric acid solution in water is added with stirring. The solution turns milky immediately due to the precipitation of respective salt. After 10 h of stirring, the layer containing the ILs with the BF_4, PF_6, ClO_4 anion separates out and was extracted with ethyl acetate (**Scheme 2**). The organic layer was washed with water, dilute hydrochloric acid, sodium bicarbonate solution, finally with brine and removal of solvent furnished the respective ILs containing the anion BF_4, PF_6 and ClO_4 in high purity.



14 **15** **13b**

Scheme 2. Reaction conditions; i) BuBr, KOH, CH_3CN, 0 ^{0}C to rt; ii) BuBr, 80 ^{0}C

The different 1-*n*-butylimidazolium ILs **13f-j** were prepared by the direct quarternization of previously prepared 1-*n*-butylimidazole **15** with the respective hydazoic anion (**Scheme 3**) to obtain the respective ILs with the anions Br^-, Cl^-, BF_4^-, PF_6^- and ClO_4^- .



15 **13f-j**

Scheme 3. Reaction conditions; i) HX, 0 ^{0}C.

Water was removed from the reaction mixture by subjecting it to evaporation for 4h at 80 ^{0}C under reduced pressure (10mm Hg) to give the respective 1-*n*-butylimidazolium ILs.

1.2.3.2 NMR study of Ionic Liquids

From the ^{1}H NMR values of various ILs it is clear that chemical shifts of imidazolium protons (i.e. H_a, H_b and H_c) depend on anion and concentration. This effect is strong for H_c proton and weaker for Ha and Hb. This effect can be explained by two phenomena i) H-bonding and ii) ring stacking.

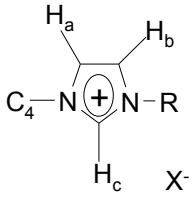


Table 4. ^{1}H NMR values of protons of imidazolium cation and –NH proton.

IL	ILs		Ha [a]	Hb [a]	Hc [a]	-NH [b]
			δ ppm	δ ppm	δ ppm	δ ppm
	R	X				
13a	C_4	Cl	7.46(s)	7.46(s)	10.76(s)	-
13b	C_4	Br	7.54(s)	7.54(s)	10.41(s)	-
13c	C_4	BF_4	7.74(s)	7.74(s)	9.20(s)	-
13d	C_4	PF_6	7.33(s)	7.33(s)	8.79(s)	-
13e	C_4	ClO_4	7.42(s)	7.42(s)	9.03(s)	-
13f	H	Cl	7.11(s)	7.47(s)	8.69(s)	12.17(brs)
13g	H	Br	7.39(s)	7.64(s)	9.18(s)	12.22(brs)
13h	H	BF_4	7.12(s)	7.12(s)	8.16 (s)	14.59(brs)
13i	H	PF_6	7.18(s)	7.18(s)	8.56(s)	12.61(brs)
13j	H	ClO_4	7.15(s)	7.42(s)	8.57(s)	11.83(brs)

[a]: ^{1}H NMR was recorded in $CDCl_3$ using TMS as internal standard.
[b]: ^{1}H NMR was recorded neat using $CDCl_3$ as external lock (standard).

It is well known that the formation of H-bonds causes a downfield chemical shift of proton. Hydrogen bonding in imidazolium ring depends on the basicity of anion. It is logical to assume that H_c proton is less electron rich than H_a and H_b because it is attached to a carbon atom in between two electronegative nitrogen atoms. So H_c proton is more prone for H-bonding with counter anion than others. This is so the case as evidenced from NMR shifts of H_c proton. In the case of more electronegative and basic Br^-, the shift is at 10. But in the case of less electronegative and basic anion BF_4^- the shift is at 8.8 ppm. From this it can be proved that BF_4 salts are more covalently bonded than its Br counterpart. This is also agreeing with the solubility of these salts in water. BF_4 salts are hydrophobic and Br salts are hydrophilic in nature. This characteristic property can be made use of in designing ILs of different polarities and solubilities in water.

When we took ^{1}H NMR of [Hbim]X series of ILs in $CDCl_3$ as deuterated solvent no –NH proton shift (as –NH bond is very moisture sensitive) was observed (it may be due to moisture in $CDCl_3$). So we performed the ^{1}H NMR of the [Hbim]X neat using $CDCl_3$ as

external lock ($CDCl_3$ was filled in capillary and it was blocked and inserted into neat compound) and we found that –NH proton of [Hbim]BF_4 went to 14.59 δ ppm. It can be observed from the chemical shifts recorded in Table 4, that with increasing basicity of the anion (increasing p*K*a of the corresponding acid) there is a progressive shifting of the –NH proton toward downfield region. As the sample was neat and viscous no splitting in butyl chain was observed giving rise to only broad signals (Table 4).

1.2.3.3 Density of Ionic Liquids

The overall density of IL heavily depends on the molar mass of anion. The contribution of the larger hydrophobic anions decreases the density of the IL This may be due to weaker molecular attraction and weak hydrogen bonding which decreases molecular agglomeration.

Table 5. Density of [bbim]X and [[Hbim]X ILs

IL	IL			Density [a]
	R	R'	X	g/cm^3
13a	n-C_4	n-C_4	Cl	1.02
13b	n-C_4	n-C_4	Br	1.23
13c	n-C_4	n-C_4	BF_4	1.15
13d	n-C_4	n-C_4	PF_6	1.23
13e	n-C_4	n-C_4	ClO_4	1.19
13f	n-C_4	H	Cl	1.11
13g	n-C_4	H	Br	1.21
13h	n-C_4	H	BF_4	1.20
13j	n-C_4	H	ClO_4	1.29

[a]: Density was determined at 28 ^{0}C

1.2.3.4 Viscosity of Ionic Liquids

Viscosity is probably the most important physical property for initially determining the processability of a solvent. Ideally one would like the viscosity of a fluid to be as low as possible allowing the fluid to be pumped easily. In addition it is desired for the fluid to have only small changes in viscosity in the normal operating temperature range. Previous

studies show that the viscosity of ILs is mainly controlled by hydrogen bonding, van der Waals forces, molecular weight and mobility.

Table 6. Viscosity of [bbim]X and [[Hbim]X ILs

IL	IL			Viscosity [a] (cP)
	R	R'	X	
13a	n-C_4	n-C_4	Cl	1179.6
13b	n-C_4	n-C_4	Br	373.1
13c	n-C_4	n-C_4	BF_4	105.6
13d	n-C_4	n-C_4	PF_6	132.0
13e	n-C_4	n-C_4	ClO_4	57.6
13f	n-C_4	H	Cl	149.6
13g	n-C_4	H	Br	98.6
13h	n-C_4	H	BF_4	68.8
13j	n-C_4	H	ClO_4	28.2

[a]: Viscosity was determined at 28 ^{0}C

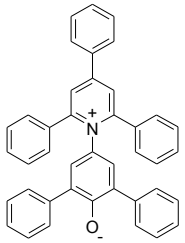
Viscosity is on a higher side for ILs with more basic anion. This is clearly demonstrated from the data recorded as shown in Table 6. In BF_4 based ILs because of less basic anion, the van der Waals forces dominates over the H-bonding due to better charge delocalization. This will reduce the viscosity of the IL, whereas in Cl based ILs because of more basic anion and smaller size, the he van der Waals forces dominates over the H-bonding due to less charge delocalization. This will increase the viscosity of the IL.

1.2.3.5 Polarity of Ionic Liquids

The E_T(30) scale, based on the large negative solvatochromic shift of the long-wavelength intermolecular л-л* charge transfer (CT) absorption band of Reichardt's pyridinium N-phenoxide betaine dye (historically, the dye numbered 30 in the first publication by Reichardt *et al. Leibigs Ann. Chem.,* **1963**, *661*,1), is one of the most popular empirical solvent polarity scales. Weight of Reichardt's betain dye in 5 ml of ionic liquid = 1 mg.

The procedure involves the dissolving of 1 mg of the Reichardt's betain dye in 5 mL of IL, recording the wavelength maxima of the CT band of Reichardt's betain dye 30 and calculating the $E_T(30)$ values from the equation 3. The values for the various ILs and some molecular solvents are recorded in Table 7.

$$E_T\ (30)\ (\text{kcal mol}^{-1}) = \frac{28591}{\lambda_{max}\ (\text{nm})} \qquad \textbf{Equ. 3}$$



Reichardt's betain dye

Table 7. E_T (30) values of IL [bbim]X and [Hbim]X at 28 ^{0}C

Sr. No.	ILs	λ_{max} nm	E_T (30) (kcal mol^{-1})
1	[bbim]Cl	415	68.89
2	[bbim]Br	430	66.49
3	[bbim]BF_4	377.5	75.73
4	[bbim]ClO_4	374.5	76.34
5	[Hbim]Cl	388.5	73.59
6	[Hbim]Br	388	73.68
7	[Hbim]BF_4	384.5	74.35
8	[Hbim]ClO_4	448	63.82
10	Acetonitrile	620 (630)	46.11 (45.38)
11	MeOH	514 (515)	55.62 (55.51)
12	DCM	607 (700)	42.65 (40.84)
13	EtOH	546 (546)	52.36 (52.36)
14	DMSO	(630)	(45.38)
15	H_20	(450)	(63.53)

[a]: Value in parenthesis is reported in literature.

1.2.3.6 Thermal Analysis of Ionic Liquids

The ILs has no distinguishable vapour pressure and as a result it decomposes on heating. In general the ILs hitherto reported are thermally stable up to 400 ^{0}C after which it tends to decompose and at around 480 ^{0}C it completely decomposes. From our experiments, it was clear that halide ions dramatically decrease the thermal stability by almost 100 ^{0}C. Decomposition started at around 220 ^{0}C and the IL fully decomposed at

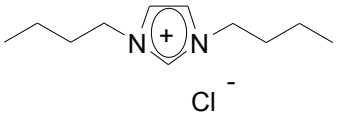
around 330 ^{0}C. In the case of BF_4 salts, decomposition started at 335 ^{0}C and at 480 ^{0}C complete weight loss was observed. However decomposition of 1-*n*-butyl imidazolium ionic liquids are started at around 130 ^{0}C.

Usually the complete weight loss should occur with the absorption of heat, which will result in an endotherm. In the case of BF_4^- salts, there may be some side reaction, which can result in a more thermodynamically stable product. From the weight loss calculated from the exact decomposition temperature, it can be concluded that the decomposition of BF_4^- species into more stable BF_3 and F^- may have resulted in the endotherm.

1.2.4. Experimental

1.2.4.1 Synthesis of Ionic Liquids.

1,3-di-*n*-butylimidazolium Chloride [bbim]Cl (13a)



A mixture of 1-*n*-butylimidazole (12.4g, 1 mmol) and *n*-butyl chloride (10.17g, 1.1 mmol) was refluxed in toluene for 8 h.

Toluene and excess *n*-butyl chloride were distilled off at 80 ^{0}C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [bbim]Cl as a viscous oil.

Yield : 20.61g, (95 %)

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

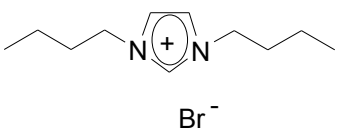
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.85-0.92 (t, *J*= 7.2 Hz, 6H), 1.20-1.40 (m, 4H), 1.66-1.92 (m, 4H), 4.22 (t, *J*= 7.0 Hz, 4H), 7.48 (s, 2H), 10.76 (s, 1H).

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

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

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

1,3-di-*n*-butylimidazoliumBromide [bbim]Br (13b)



A mixture of 1-*n*-butylimidazole (12.4g, 1 mmol) and *n*-butyl bromide (15g, 1.1 mmol) was heated with stirring at 70 ^{0}C for 4 h.

Excess *n*-butyl bromide was distilled off at 80 ^{0}C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [bbim]Br as colourless viscous liquid.

Yield **:** 24.9g, (96%)

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

^{1}H NMR **:** δ 0.85-0.93 (t, *J*= 7.1 Hz, 6H), 1.26-1.33 (m, 4H), 1.82-1.89,

(200 MHz, $CDCl_3$): (m, 4H), 4.28-4.35 (t, *J*= 7.2 Hz, 4H), 7.54 (s, 2H),10.41 (s,1H).

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

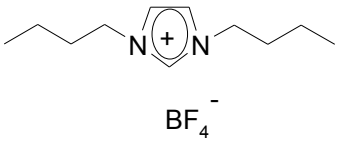
(50 MHz, $CDCl_3$)

MS **:** 181 (M – X), 165, 138, 124, 97, 81, 68, 57.

Elemental Analysis **: $C_{11}H_{21}N_2Br$** Calcd. C, 50.57; H, 8.05; N, 10.73.

Found C, 50.24; H, 7.91; N, 10.54.

1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim]BF_4 (13c)



To a solution of 1,3-di-*n*-butylimidazolium bromide([bbim]Br) (10g, 1 mmol) in water (50 mL) was added a solution of sodium tetrafluoroborate (5.11g, 1.2 mmol) in water (25 mL).

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

Yield **:** 9.89g, (86%)

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

^{1}H NMR **:** δ 1.12-1.20 (t, *J*= 7.2 Hz, 6H), 1.49-1.63 (m, 4H), 2.03-2.18

(200 MHz, $CDCl_3$) (m, 4H), 4.43-4.50 (t, *J*= 7.6 Hz, 4H), 7.74 (s, 2H), 9.20 (s, 1H).

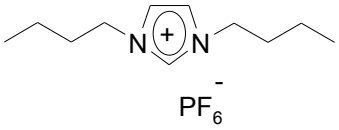
^{13}C NMR **:** δ 13.1, 19.1, 31.8, 49.5, 122.3, 135.4.

(50 MHz, $CDCl_3$)

MS **:** 181 (M – X), 165, 151, 124, 97, 81, 68, 57.

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

1,3-di-*n*-butylimidazolium hexafluorphosphate [bbim]PF_6 (13d)



To a solution of 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) (10g, 1 mmol) in water (50 mL) was added hexafluorophosphoric acid (65% water solution) (20.43g, 1.4 mol) in water (25 mL), and the mixture was stirred at room temperature for 5 h. The ionic liquid [bbim]PF_6 separated out as an immiscible layer. The mixture was extracted with dichloromethane (3 X 30 mL). The combined organic layer was separated, washed with water and brine, dried over anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure leaving behind the pure IL [bbim]PF_6 as a viscous oil.

Yield **:** 11.5 g, (92%)

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

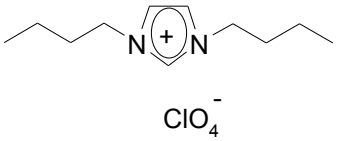
^{1}H NMR (200 MHz, $CDCl_3$) **:**δ 0.92-1.0 (t, *J*= 7.0 Hz, 6H), 1.27-1.44 (m, 4H), 1.79-1.94 (m, 4H), 4.15-4.23 (t, *J* = 7.5 Hz, 4H), 7.33 (s, 2H), 8.79 (s, 1H).

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

MS **:** 181 (M – X), 165, 138, 124, 97, 81, 68, 57.

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

1,3-di-*n*-butylimidazolium perchlorate [bbim]ClO_4 (13e)



To a solution of 1,3-di-*n*-butylimidazolium bromide([bbim]Br) (10g, 1 mmol) in water (50 mL) was added a solution of perchloric acid (5.11g, 1.2 mmol) in water (25 mL), and the mixture was stirred at room temperature for 5 h. The ionic liquid [bbim]ClO_4 separated out as an immiscible layer. The mixture was extracted with dichloromethane (3 X 30 mL). The combined organic layer was separated, washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure leaving behind the pure IL [bbim]ClO_4 as a viscous oil.

Yield **:**10.4g, (98%)

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

^{1}H NMR **:δ** 0.89-0.97 (t, *J*= 7.4 Hz, 6H), 1.25-1.40 (m, 4H), 1.79-1.94

(200 MHz, $CDCl_3$) (m, 4H), 4.19-4.26 (t, *J*= 7.3 Hz, 4H), 7.42 (s, 2H), 9.03 (s, 1H).

^{13}C NMR **:δ** 13.2, 19.2, 31.8, 49.8, 122.4, 135.5.

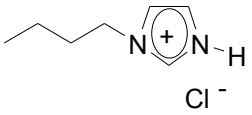
(50 MHz, $CDCl_3$)

MS **:** 181 (M - X,) 165, 151, 124, 107, 81, 68, 57.

Elemental Analysis : **$C_{11}H_{21}N_2ClO_4$** Calcd. C, 46.97; H, 7.47; N, 9.96.

Found C, 46.74; H, 7.21; N, 9.87.

1-*n*-butylimidazolium chloride [Hbim]Cl (13f)



Hydrochloric acid (3.6g, 1 mmol) as 35% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (12.4g, 1 mmol) at 0 ^{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 ^{0}C under reduced pressure (10mm Hg) to give the product [Hbim]Cl as a viscous oil.

Yield **:** 15.7 g, (98%).

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

^{1}H NMR **:δ** 0.48 (brs, 3H), 0.88 (brs, 2H), 1.42 (brs, 2H), 4.00 (brs, 2H), 7.11

($CDCl_3$ as external lock) (s, 1H), 7.47 (s, 1H), 8.69 (s, 1H), 12.17 (brs, 1H, NH).

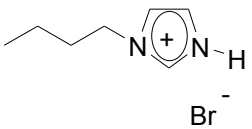
^{13}C NMR **: δ** 11.7, 17.7, 30.9, 45.7, 118.3, 123.7, 134.7.

MS **:** 124 (M-X), 109, 97, 81, 68, 55.

Elemental Analysis **: $C_7H_{13}N_2Cl$** Calcd. C, 52.17; H, 8.07; N, 17.39.

Found C, 52.02; H, 7.92; N,17.18.

1-*n*-butylimidazolium bromide [Hbim]Br (13g)



Hydrobromic acid (8.1g, 1 mmol) as 40% aqueous solution was added slowly over a period of 30 min to 1-butylimidazole (12.4g, 1 mmol) at 0 ^{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 ^{0}C under reduced pressure (10mm Hg) to give the product [Hbim]Br as viscous oil.

Yield **:** 19.7g, (98%)

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

^{1}H NMR **: δ** 0.21 (brs, 3H), 0.64 (brs, 2H), 1.31 (brs, 2H), 4.03 (brs, 2H),

($CDCl_3$ as external lock) 7.39 (s, 1H), 7.64 (s, 1H), 9.18 (s, 1H), 12.22 (brs, 1H, NH).

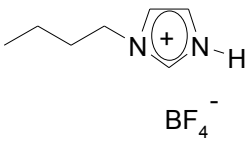
^{13}C NMR **:δ** 13.1, 19.1, 32.4, 47.3, 120, 124.7, 136.1.

(50 MHz, $CDCl_3$)

MS **:** 124 (M-X), 109, 97, 81, 68, 55.

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

1-*n*-butylimidazolium Tetrafluoroborate [Hbim]BF_4 (13h)



Tetrafluoroboric acid (8.7g, 1 mmol) as 40% aqueous solution was added slowly over a period of 30 min. to 1-butylimidazole (12.4g, 1 mmol) at 0 ^{0}C under stirring.

The reaction mixture was stirred for an additional period of 2 h at the same temperature. Water from the reaction mixture was removed by subjecting it to evaporation for 4 h at 80 ^{0}C under reduced pressure (10mm Hg) to give the product [Hbim]BF_4 as a viscous oil.

Yield **:** 20.2 g, (96%)

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

^{1}H NMR **: δ** 0.56 (brs, 3H), 0.95 (brs, 2H), 1.47 (brs, 2H,), 3.87 (s, 2H),

($CDCl_3$ as external lock) 7.12 (s, 2H), 8.16 (s, 1H), 14.59 (brs, 1H, NH).

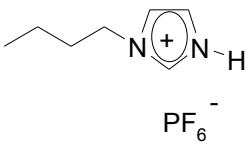
^{13}C NMR **:δ** 13.1, 19.2, 32.1, 48.5, 120.9, 122.2, 135.2.

(50 MHz, $CDCl_3$)

MS **:** 124 (M - X), 109, 97, 81, 68, 55.

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

1-*n*-butylimidazolium hexaflouorphosphate [Hbim]PF_6 (13i)



Hexafluorophosphoric acid (14.59g, 1 mmol) as 65% aqueous solution was added slowly over a period of 30 min to 1- butylimidazole (12.4g, 1 mmol) at 0 ^{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 ^{0}C under reduced pressure (10mm Hg) to give the product [Hbim]PF_6 as a viscous oil.

Yield **:**26.3g, (98%)

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

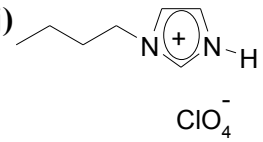
^{1}H NMR **: δ** 0.42 (brs, 3H), 0.84 (brs, 2H), 1.43 (brs, 2H), 3.96 (brs, 2H), **($CDCl_3$ as an external lock)** 7.18 (s, 2H), 8.56 (s, 1H), 12.91 (brs, 1H).

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

MS **:** 124 (M-X), 109, 97, 81, 68, 55.

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

1-*n*-butylimidazolium perchlorate [Hbim]ClO_4 (13j)



Viscous oil

Yield **:** 98%

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

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

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

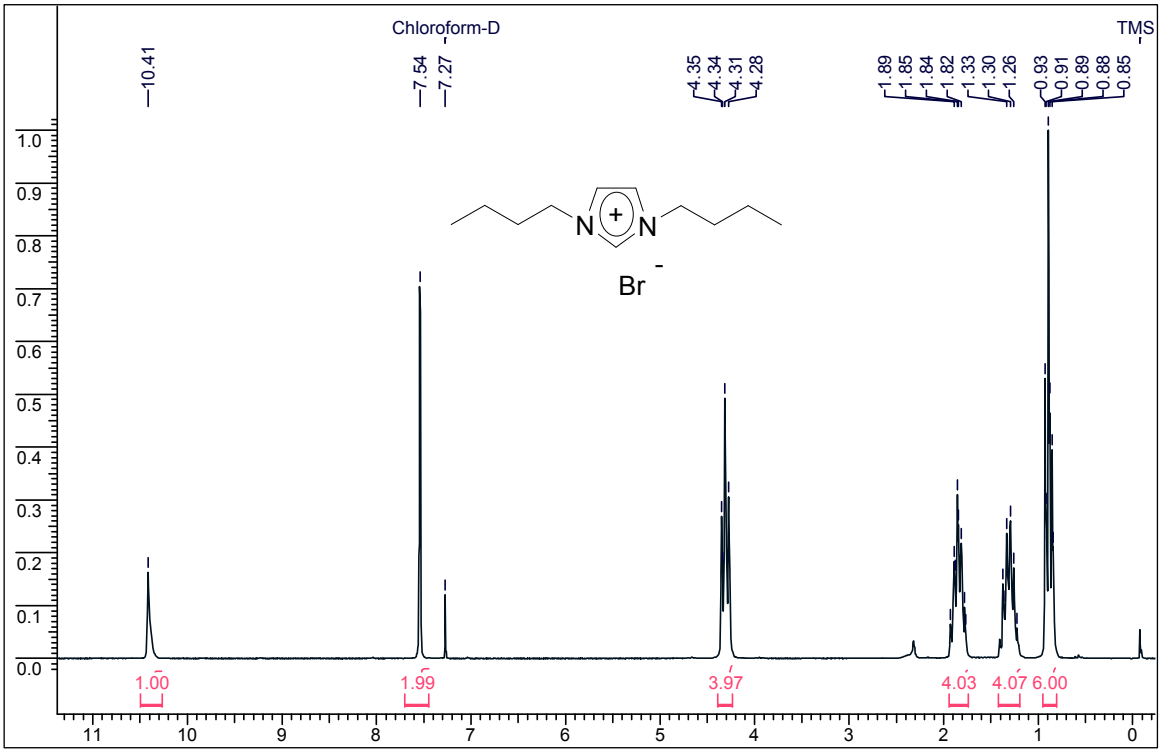
MS **:** 124 (M-X), 109, 97, 81, 68, 55.

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

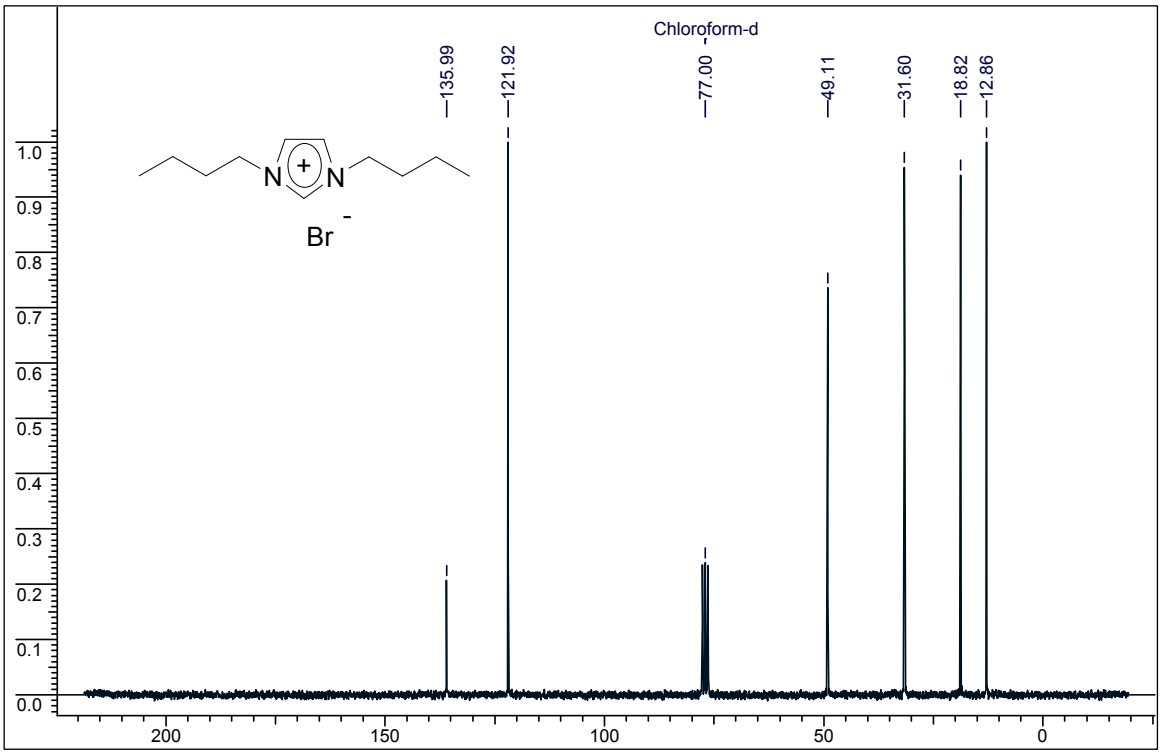
1.2.5 Spectra

[1] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13b**
[2] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13c**
[3] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13d**
[4] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13e**
[5] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13f**
[6] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13g**
[7] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13h**
[8] ^{1}H NMR and ^{13}C NMR Spectra of **IL 13j**

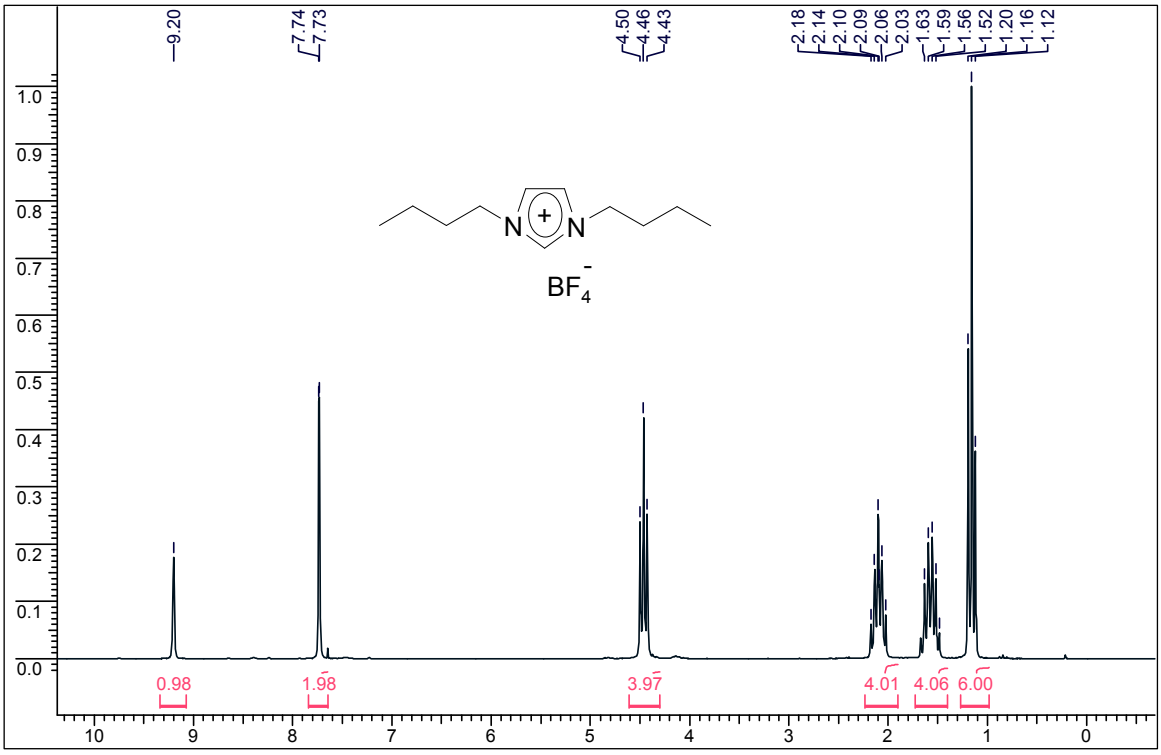
[1] ^{1}H NMR spectra of IL 13b



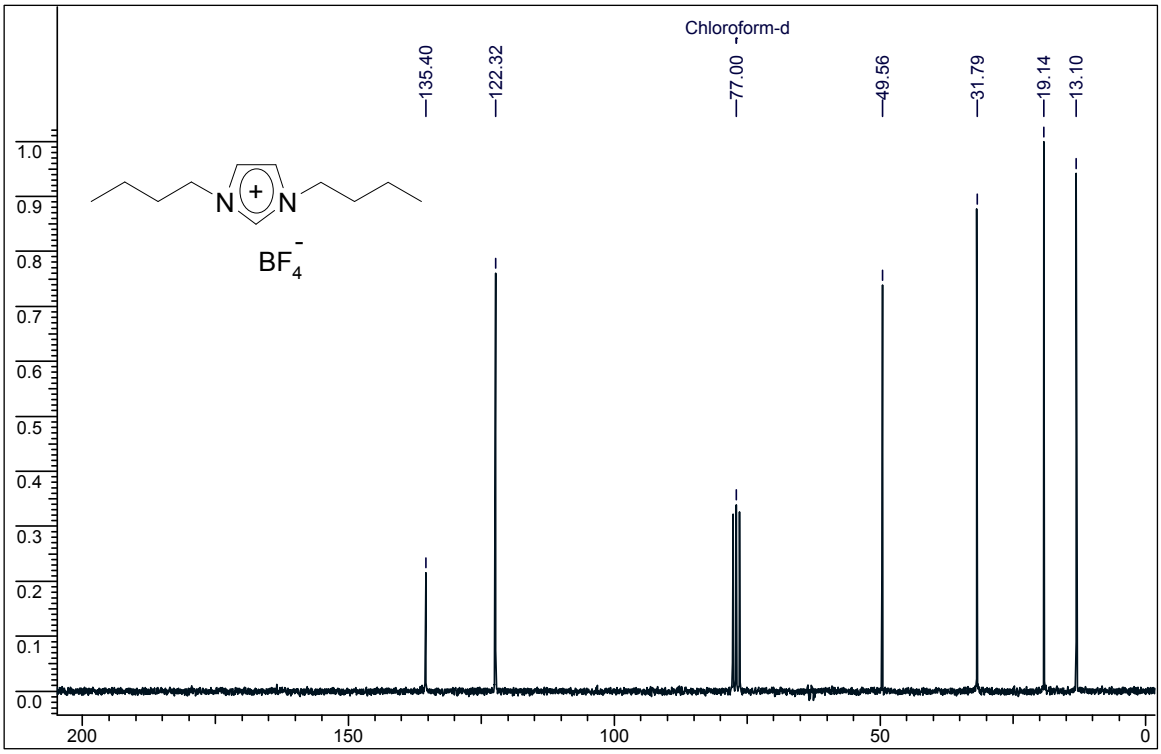
[1] ^{13}C NMR spectra of IL 13b



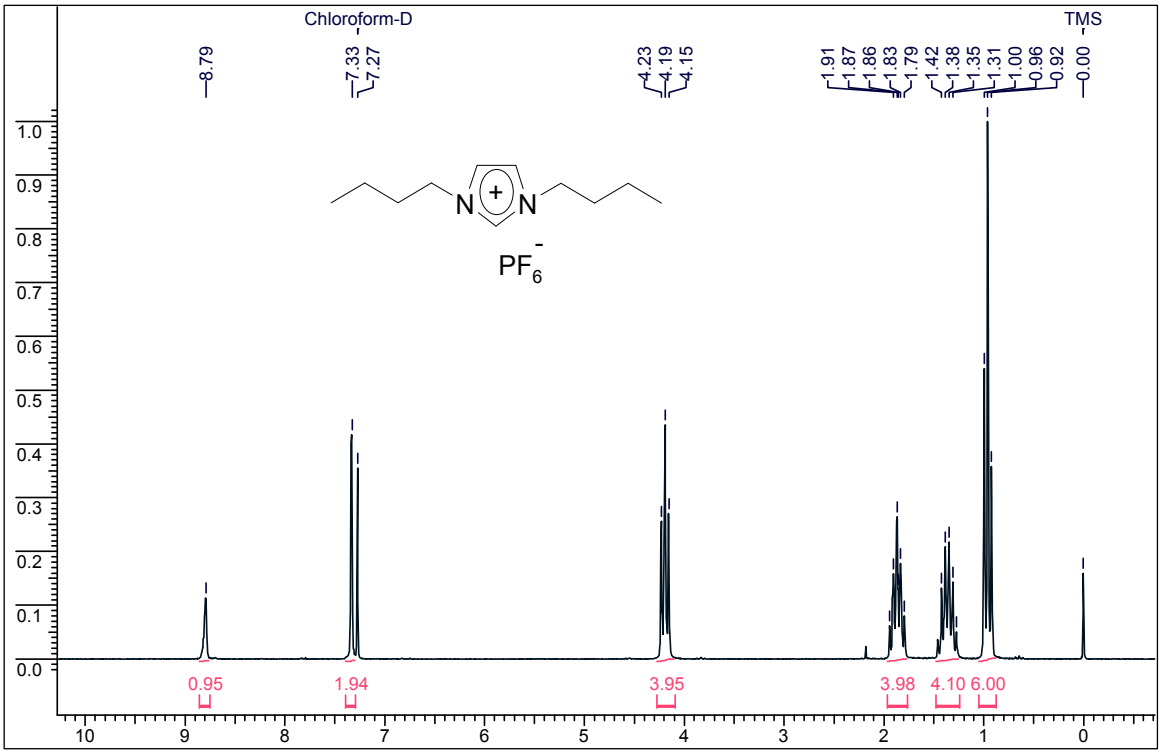
[2] **^{1}H NMR spectra of IL 13c**



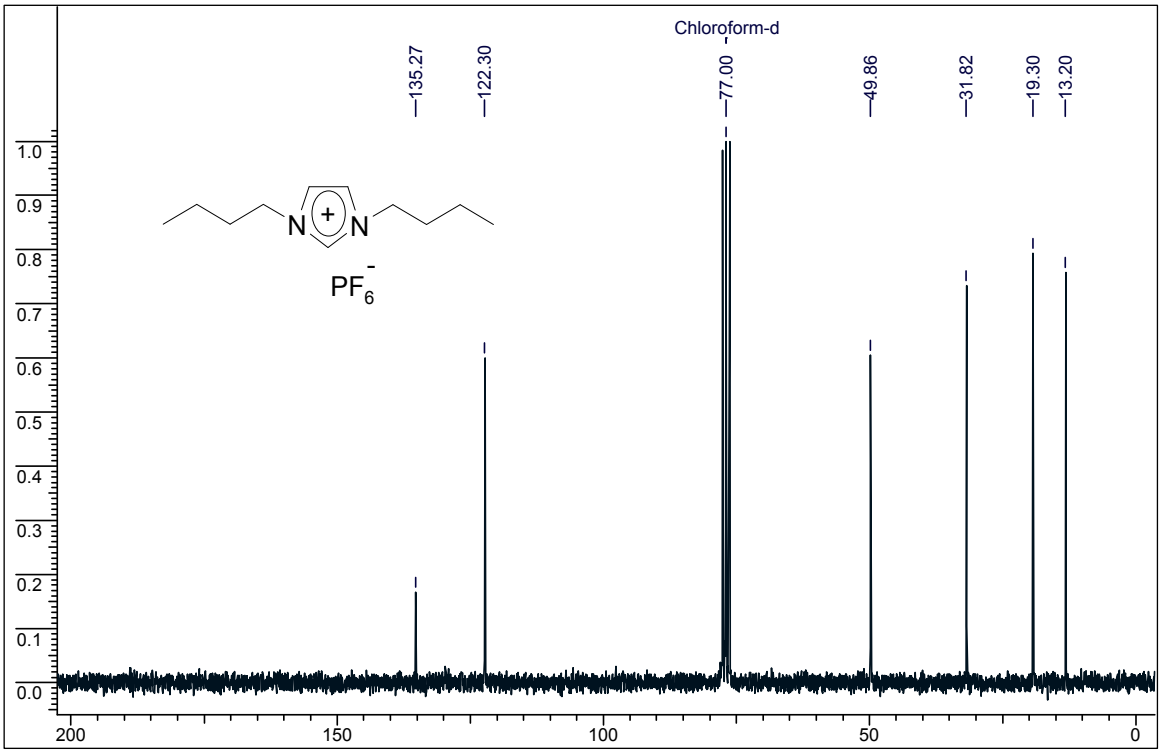
[2] **^{13}C NMR spectra of IL 13c**



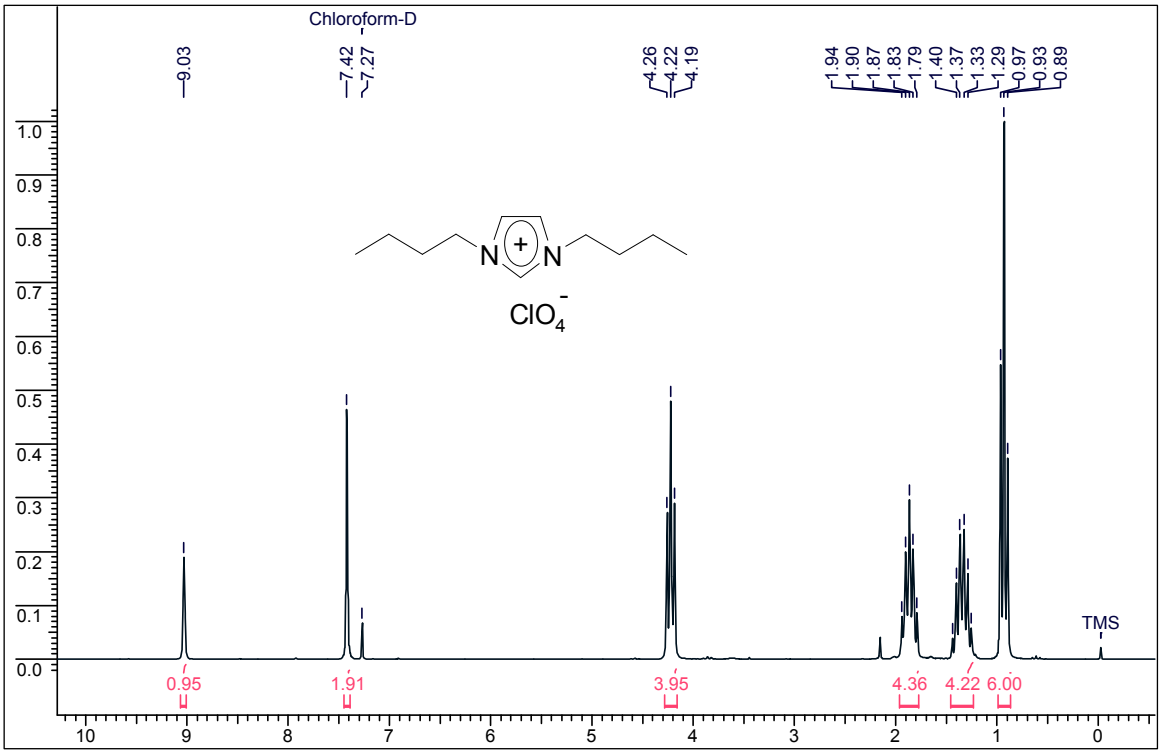
[3] ^{1}H NMR spectra of IL 13d



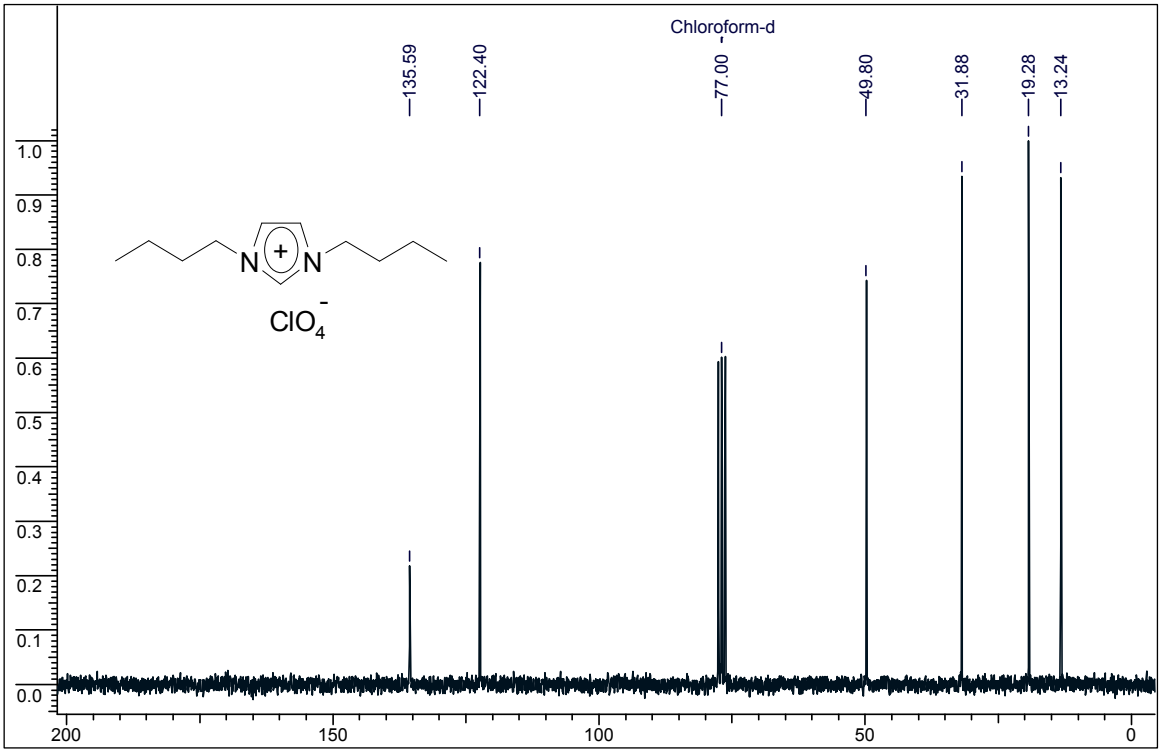
[3] ^{13}C NMR spectra of IL 13d



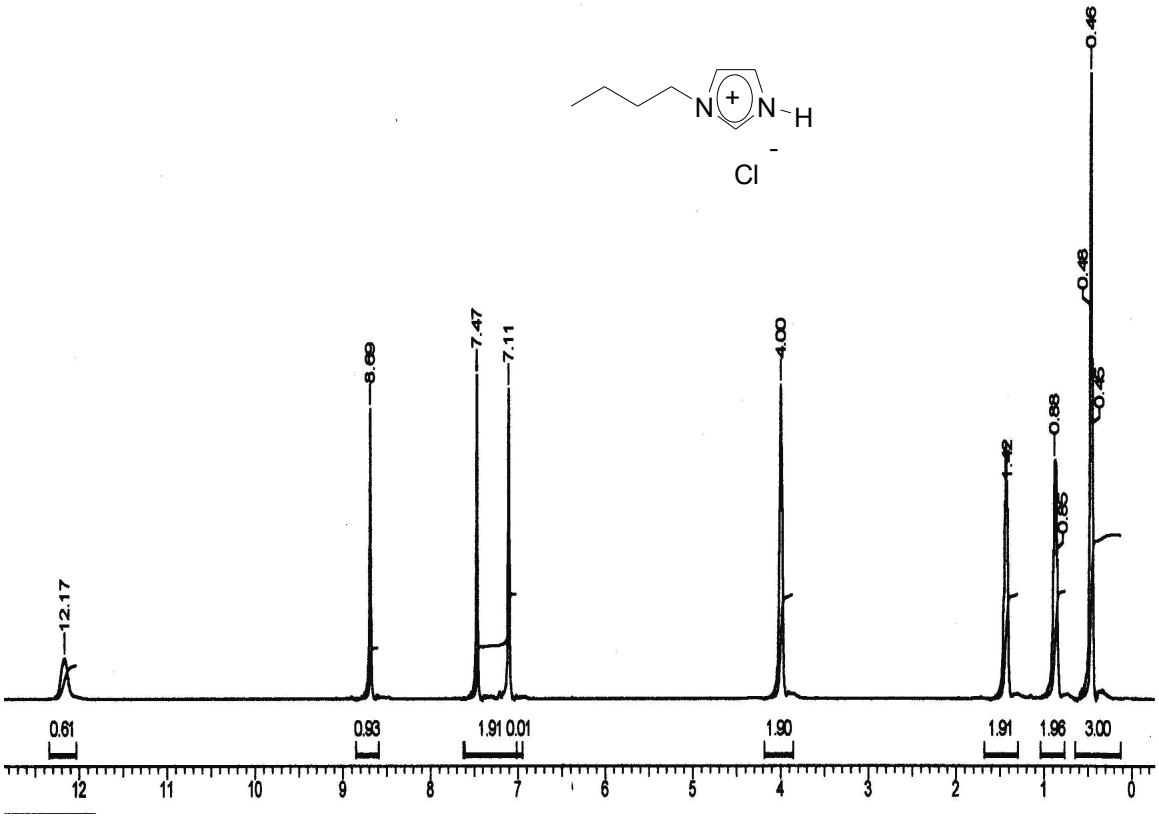
[4] ^{1}H NMR spectra of IL 13e



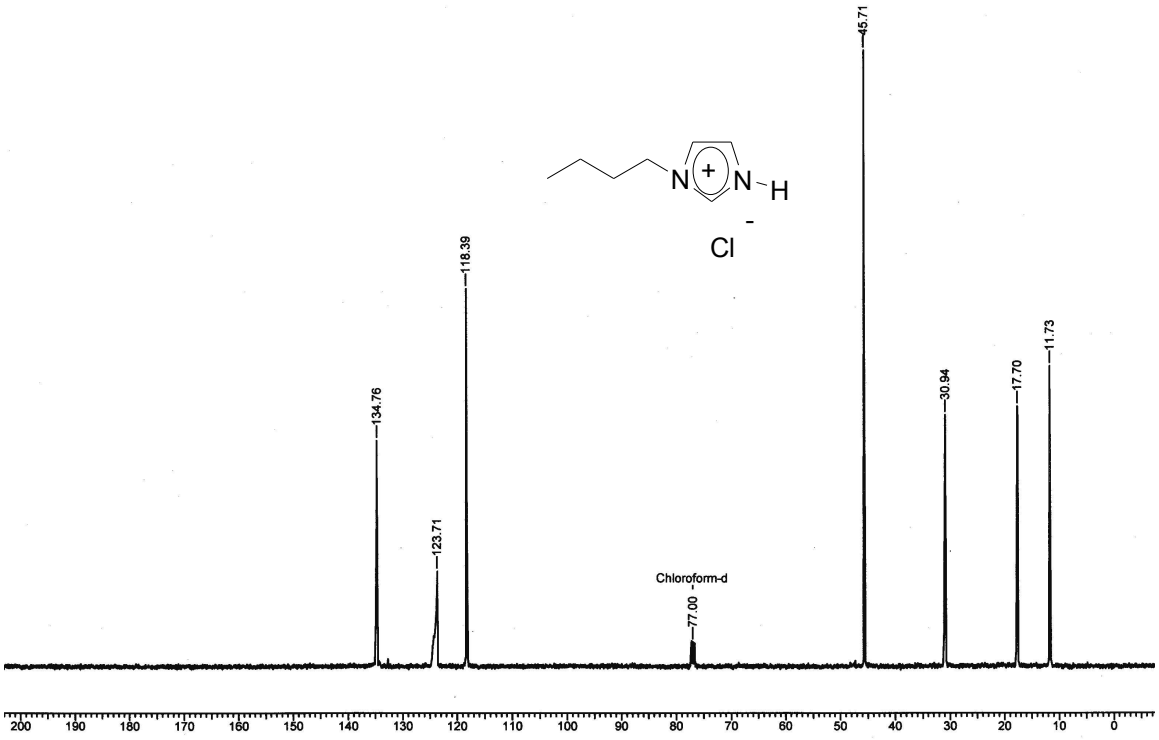
[4] ^{13}C NMR spectra of IL 13e



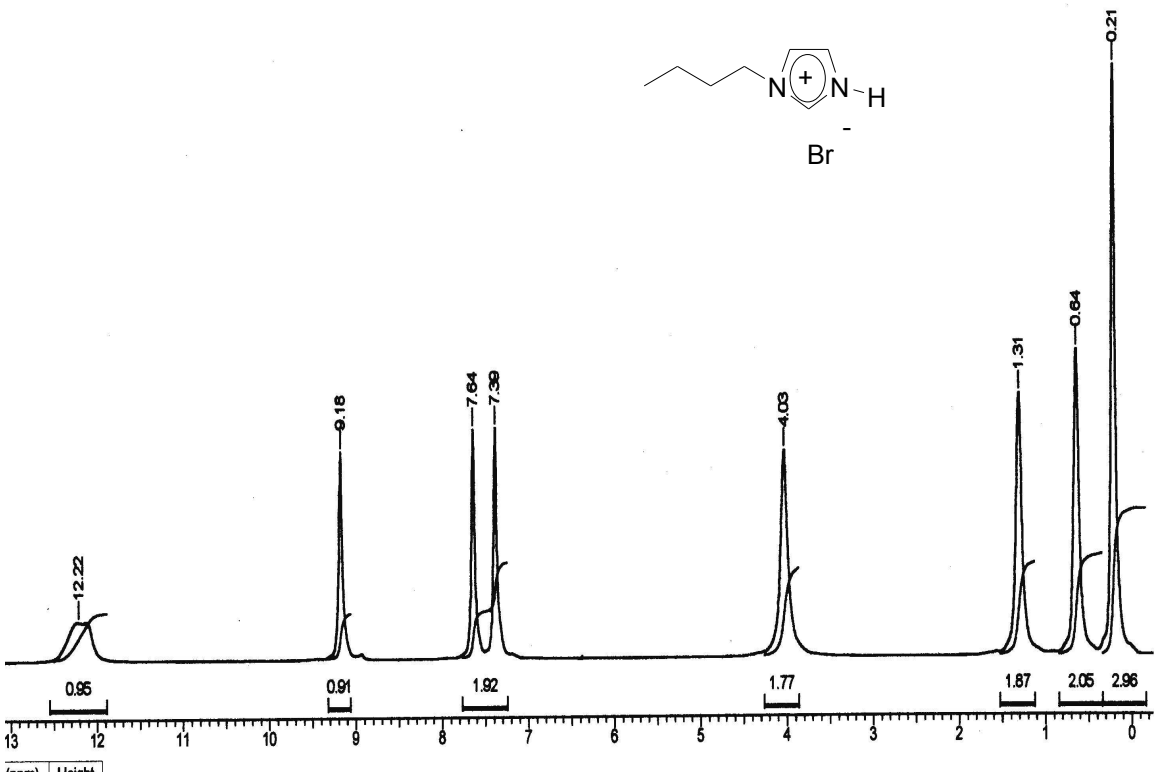
[5] ^{1}H NMR ($CDCl_3$ as external lock) spectra of IL 13f



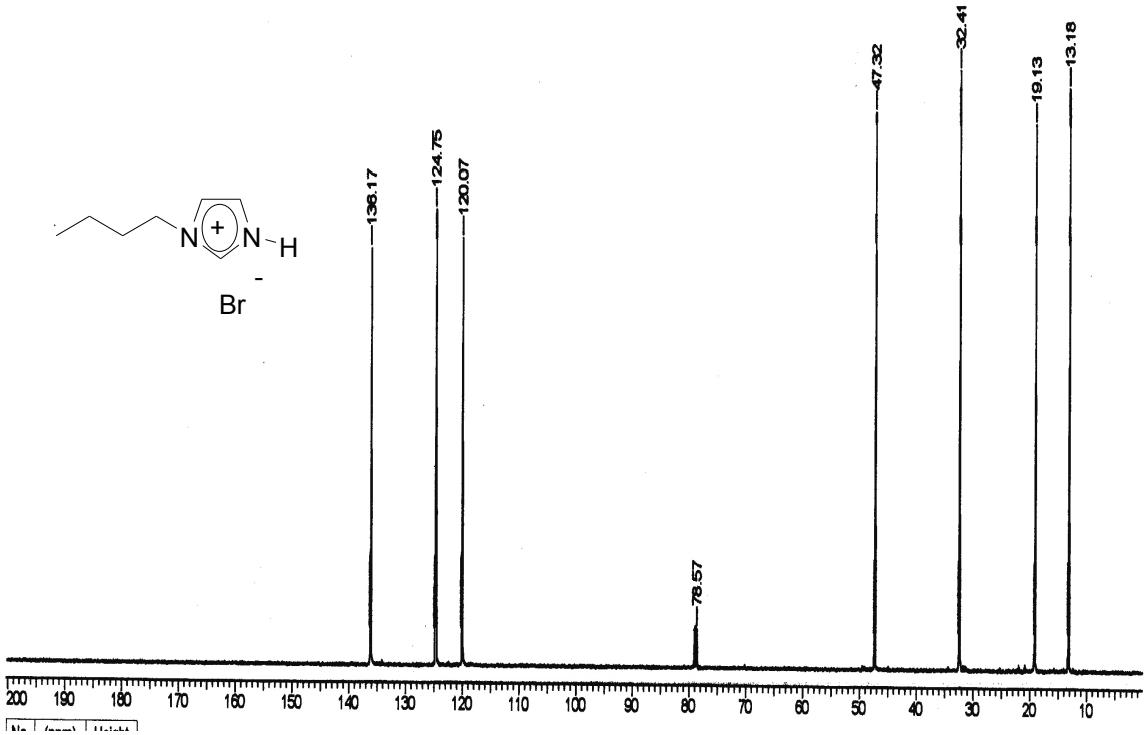
[5] ^{13}C NMR spectra of IL 13f



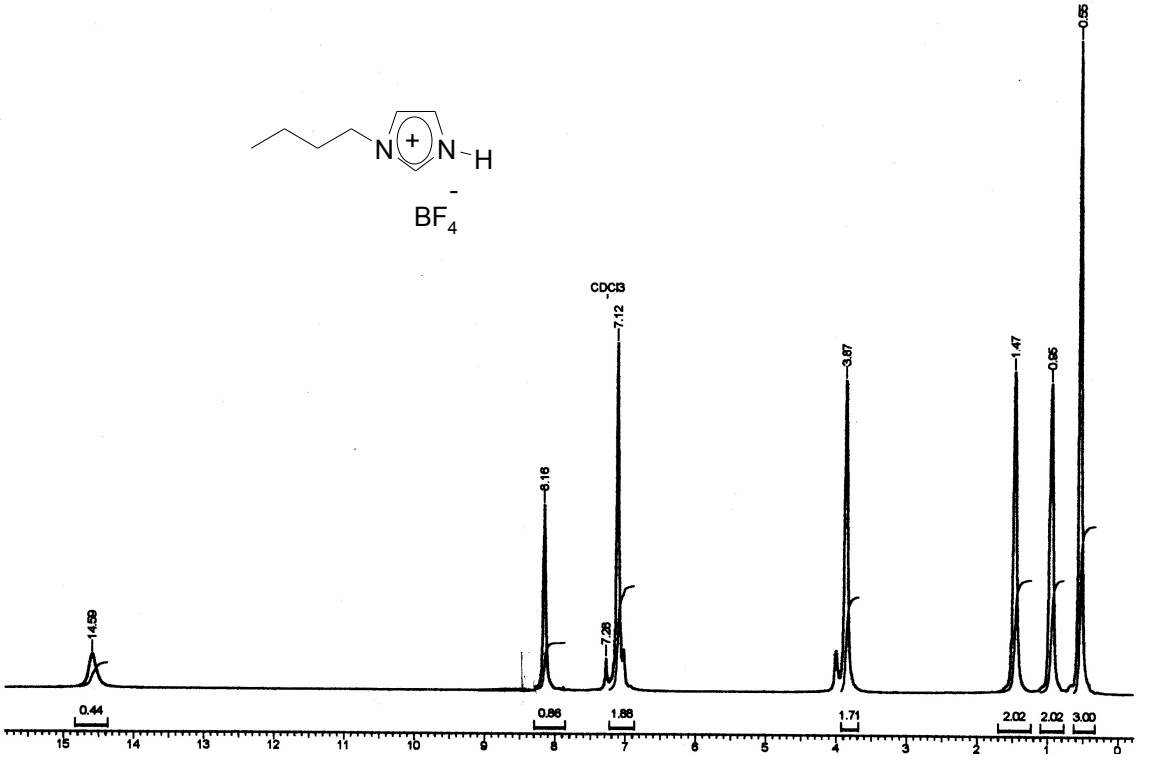
[6] ^{1}H NMR ($CDCl_3$ as external lock) spectra of IL 13g



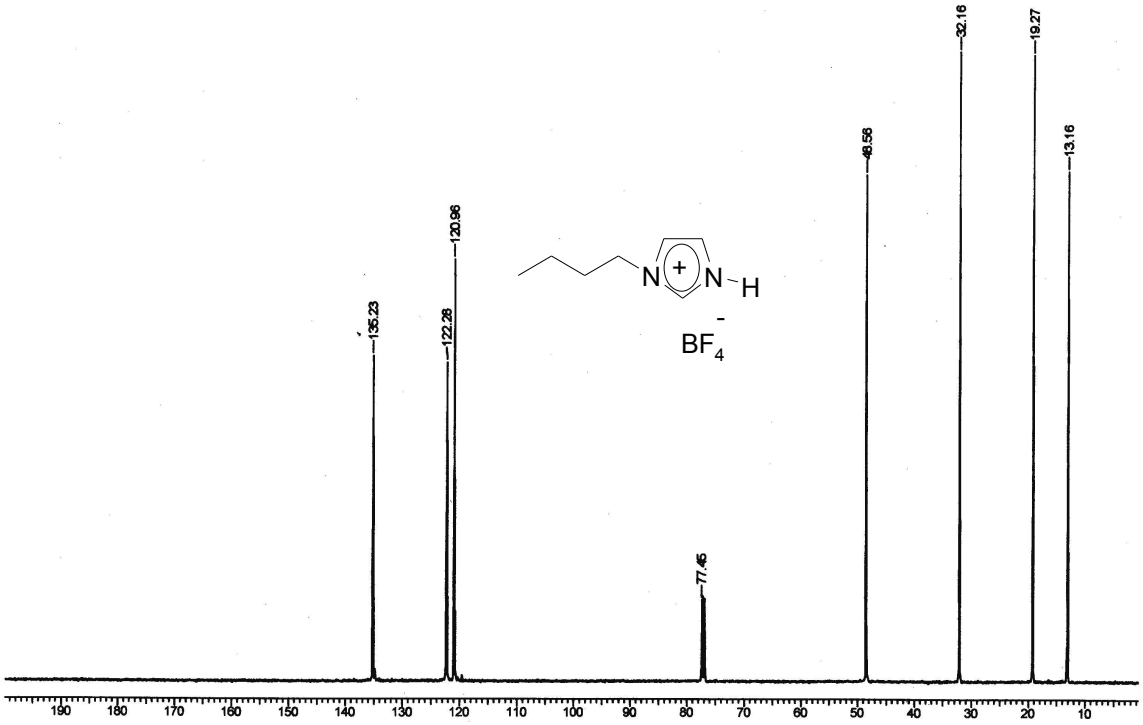
[6] ^{13}C NMR spectra of IL 13g



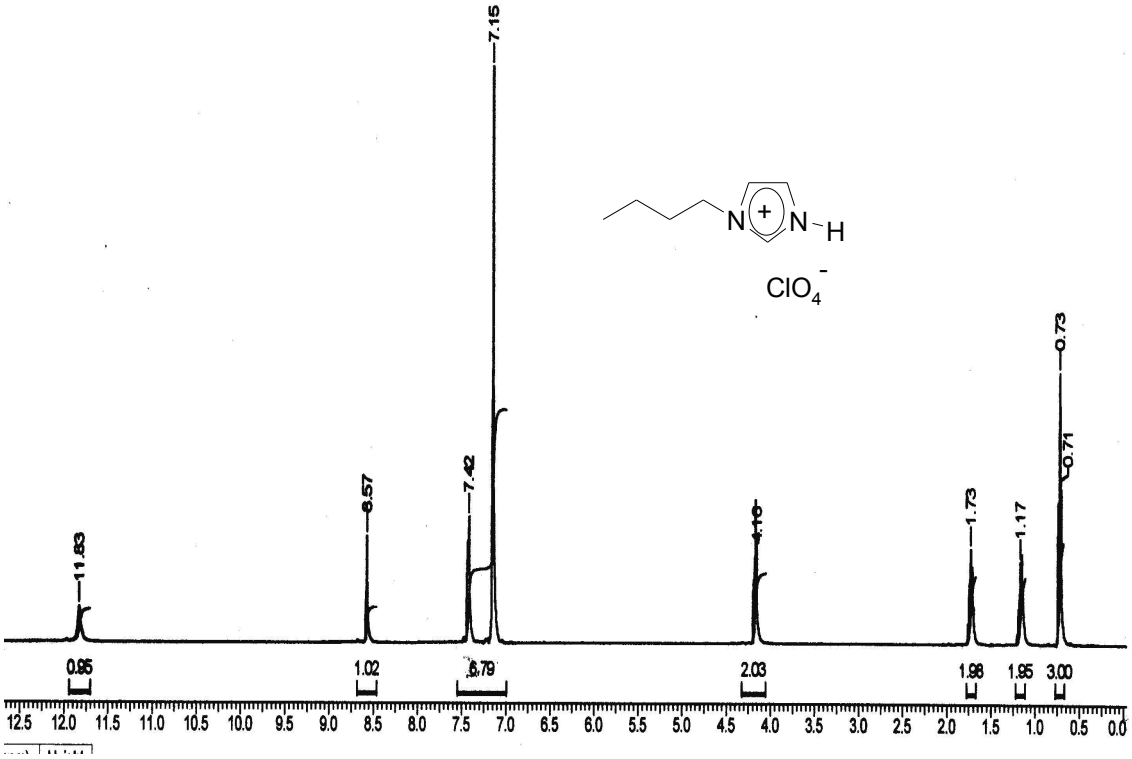
[7] ^{1}H NMR ($CDCl_3$ as external lock) spectra of IL 13h



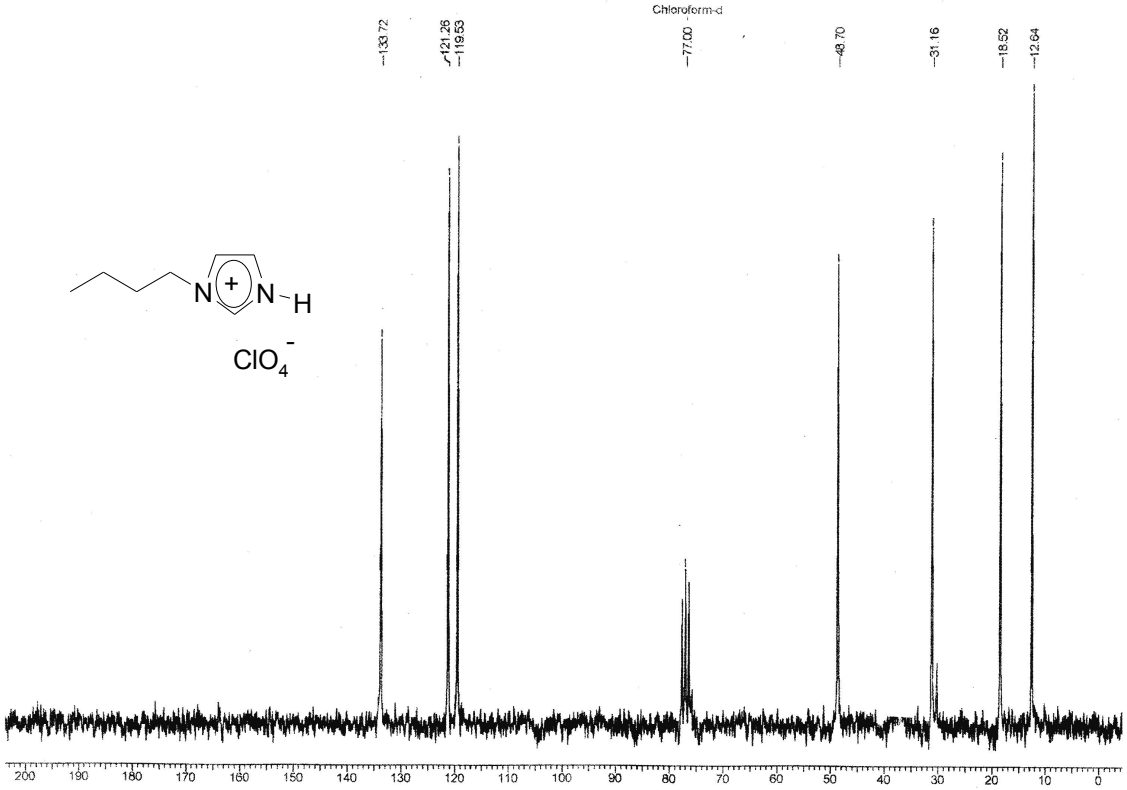
[7] ^{13}C NMR spectra of IL 13h



[8] ^{1}H NMR ($CDCl_3$ as external lock) spectra of IL 13j



[8] ^{13}C NMR spectra of IL 13j



CHAPTER-2

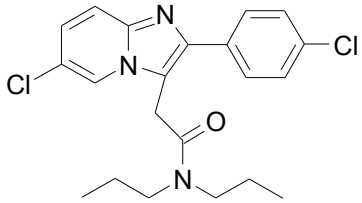
STUDY OF IONIC LIQUIDS AS REACTION MEDIA CUM PROMOTERS IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLES

SECTION-A

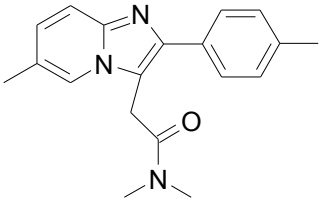
Synthesis of 1-substituted imidazo[1, 5-a]pyridines

2. 1.1 Introduction

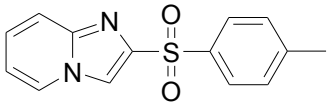
Fused bicyclic heterocycles with nitrogen atom in the five-membered ring, are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds. Imidazopyridine ring systems represent an important class of compounds not only for their theoretical interest but also from a pharmacological point of view, which have been shown to possess a broad range of useful pharmacological activities,[1] including anti gastric antisecretory,[2] local anesthetic,[3] antiviral,[4] antianxiety,[5] antibacterial, antifungal, anthelmintic, antiprotozoal, anticonvulsant, gastrointestinal, antiulcer (Zolmidine), anxiolytic (Alpidem), hypnotic (Zolpidem) and immunomodulatory activities.[6-9] Some of these drugs are Zolpidem (Stilnox®, Ambien®, Myslee®) sold by Sanofi-Synthelabo, is a non-benzodiazepine hypnotic of the imidazopyridine class, leader of the international market with a blockbuster status for the treatment of sleep disorders. The nature and the position of the substituents on the pyridinic moiety influence these pharmacological activities



Alpidem (A)



Zolpidem (B)

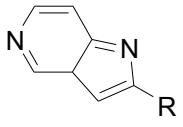


Zolmidine (C)

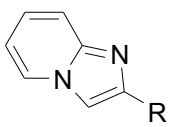
Fig. 1

These imidazo pyridine heterocyclic structures form part of the skeleton of natural alkaloids,[10] neuromuscular blocking agents,[11] reversible inhibitors of the H^+, K^+-ATPase enzyme[12] with a potent antisecretory activity [13] and of sedative hypnotics of the nervous system.[14]

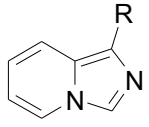
There are several imidazo pyridines which are present as natural products. Following are the structures of the imidazo pyridines (**Fig. 2**) which are found in nature. The nomenclature of imidazo pyridines depend on the position of nitrogen atom in the heteroaromatic ring.



imidazo[1,4-*c*]pyridine (D)



imidazo[1,2-*a*]pyridine (E)



imidazo[1,5-*a*]pyridine (F)

Fig. 2

Imidazo[1,5-*a*]pyridines possess synthetically challenging scaffold skeleton and is a basic structure of synthetic drugs such as Pirmogrel, with human clinical applications as effective platelet aggregation and thromboxane synthase inhibitors,[15] and have been screened as selective inhibitors of aromatase estrogen production suppressors,[16] as potential positive inotropic agents.[17]

In particular, 1-pyridyl imidazo[1,5-*a*]pyridines possess a bidentate structural feature with a pyridyl unit directly next to a fused imidazole heterocycles are a desirable class of compounds in the pursuit of structural diversity for property performance and have emerged as a new class of ligands for numerous organic transformations.[16-20]

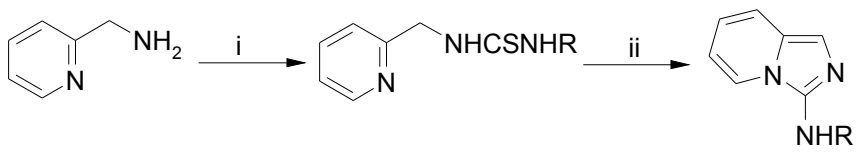
These imidazopyridines also undergo nitration, acylation, formylation and other transformations[23] to afford valuable intermediates in the construction of several other pharmacologically active heterocyclic compounds.

2.1.2 Review of literature.

Imidazo pyridines are not only pharmacologically potent but very important in material chemistry due to its scaffold skeleton. Numerous methods are found in literature for the synthesis of imidazo pyridines. In this section we describe some of the more important synthetic methods described in literature for the synthesis of [1,5-*a*]pyridines or related heterocycles.

Bourdais's approach (1980)[24]

A series of 3-substituted aminoimidazo[1,5-*a*]pyridine derivatives **3** were synthesized by cyclodesulfurization of a variety of *N*'-substituted-*N*-(2-pyridylmethyl)thioureas **2** with dicyclohexyl carbodimide (DCC). The substituted thioureas **2** were prepared by reacting 2-aminomethylpyridine **1** with the appropriate alkyl, aryl or aralkylisothiocyanic ester in benzene at 20-50 ^{0}C. The cyclodesulfurization of these thiourea derivatives was achieved by refluxing with excess of DCC in anhydrous benzene or toluene affording product **3** in moderate to good yields (**Scheme 1**).

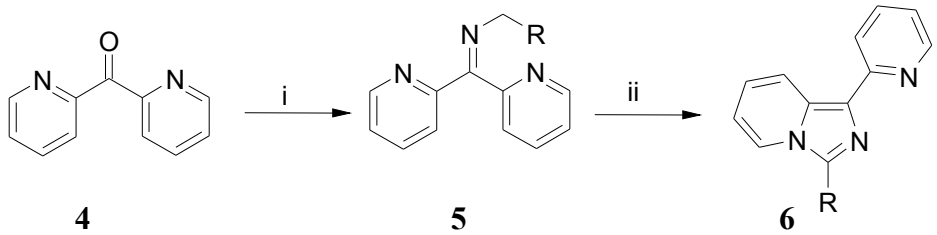


1 **2** **3**

Scheme 1. Reaction conditions**:** i) alkyl isothiocyanic ester, benzene, 50 ^{0}C, 52-80%; ii) DCC, anhydrous toluene, reflux, 2-7 h, 51-82%.

Krapcho's approach (1986)[25]

Krapcho *et al.* reported the synthesis of 1,3-disubstituted imidazo [l,5-*a*lpyridines **6** from ketimines **5,** which was obtained from the condensation of di-2-pyridyl ketone **4** with respective amine under acidic condition. Ketimines **5** on further treatment with base (LDA) and benzophenone in THF at -78 ^{0}C gave **6** in moderate yield (**Scheme 2**).

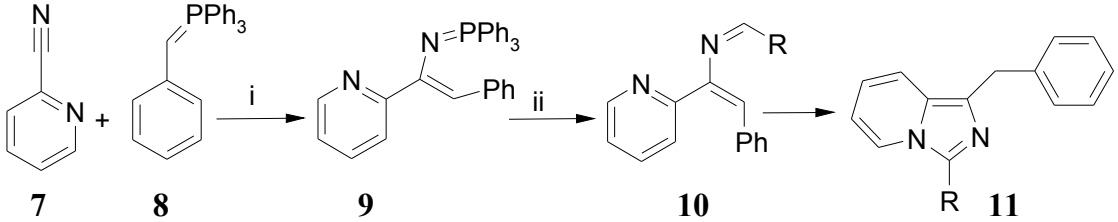


4 **5** **6**

Scheme 2. Reaction conditions**:** i) alkyl, aryl amine; ii) LDA, benzophenone, -78 ^{0}C, THF, 65-80%.

Francisco's approach (1995) [26]

Francisco *et al.* reported the synthesis of substituted imidazo[1,5-*a*]pyridines from 2-cyanopyridine **7**. The reaction of 2-cyanopyridine **7**, with phosphorous ylide **8** in the presence of strong base (MeLi) under anhydrous condition gave unstable intermediate *N*-vinylic phosphazene **9** in excellent yield, which was stirred in chloroform at room temperature converted to thermodynamically stable heterocyle **11** (**Scheme 3**).



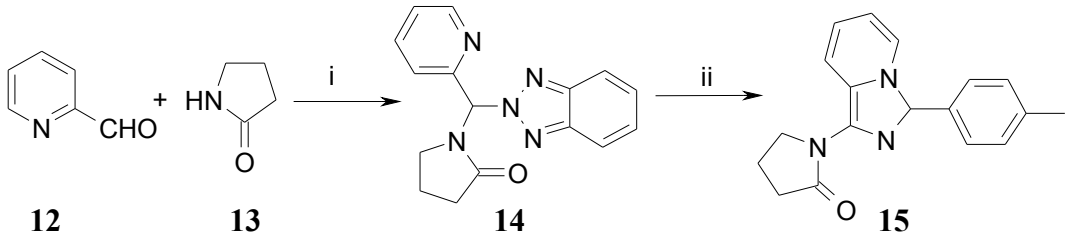
7 **8** **9** **10** **11**

Scheme 3. Reaction conditions**:** i) MeLi, benzene, rt, 80%, 24 h; ii) $CHCl_3$, rt, 52-70%.

Katritzky's approach (2001)[27]

Katritzky *et al.* synthesized 1-amido-3-aryl-and-alkylimidazo[1,5-*a*]pyridines **15**. A mixture of 2-pyridine carboxyldehyde **12**, pyrrolidin-2-one **13** and benzotriazole was subjected to condensation reaction in the presence of catalytic amount of *p*-TSA in refluxing toluene to give intermediate **14** in excellent isolated yield after 12 h, which on

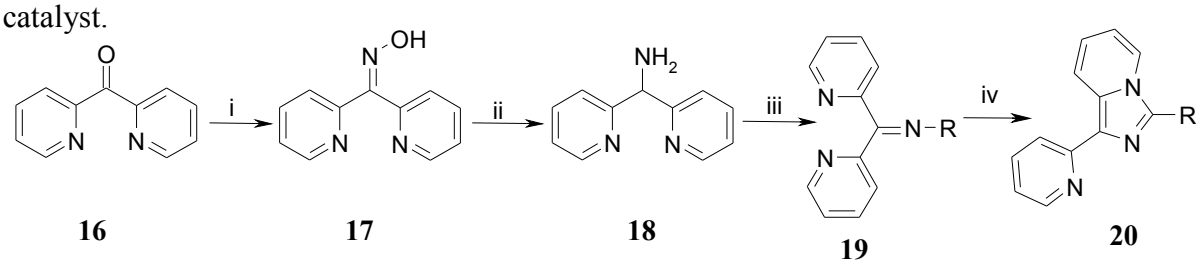
further treatment with *p*-methyl phenyl cyanide in DCM using catalytic amount of Lewis acid ($TiCl_4$) at elevated temperature (60 ^{0}C) afforded **15** in 92% yield (**Scheme 4**).



Scheme 4. Reaction conditions**:** i) benzotriazole, *p*-TSA, 95%; ii) *p*-methyl phenyl cyanide, $TiCl_4$, 4 h.

Doring's approach (2002)[28]

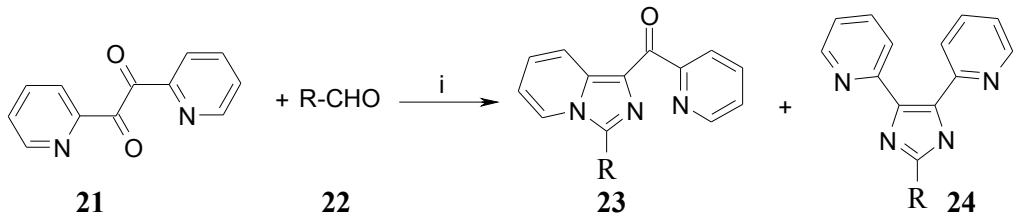
Doring *et al.* demonstrated the synthesis of structurally challenging 1-pyridyl imidazo[1,5-*a*]pyridines from 2,2'-dipyridyl ketone **16,** which on condensation with hydroxyl amine hydrochloride gave oxime intermediate **17** in good yield. The oxime was reduced by Zn dust in acetic acid which gave amine **18** in quantitatively yield**.** Under acidic condition the amine **18** was reacted with aldehyde to afford imine **19**, which on further reaction with $CuCl_2$ and sodium hydroxide in the presence of air in methanolic solution at reflux temperature gave compound **20** in poor to moderate yields (**Scheme 5**). The selective oxidation of the imine **19** was achieved by molecular oxidation using copper ions as catalyst.



Scheme 5. Reaction conditions**:** i) NH_4OH, 80%; ii) Zn dust, acetic acid, reflux, 70%; iii) aldehyde, acetic acid, 70%; iv) NaOH, $CuCl_2$, MeOH, reflux 7 h, NH_4OAc, 45%.

Bu's approach (2003)[29]

Bu *et al.* reported very good one-pot synthetic method for the synthesis of imidazo-[1,5-*a*]pyridines **24** from 1,2-dipyridyl diketone **21**. The diketone **21** on condensation with aromatic aldehydes **22** and ammonium acetate in acetic acid at 110 ^{0}C gave mixture of **23** and **24** in moderate isolated yield. Ammonium acetate plays a very important role for the regioslectivity of the desired product formation in this process (**Scheme 6**).

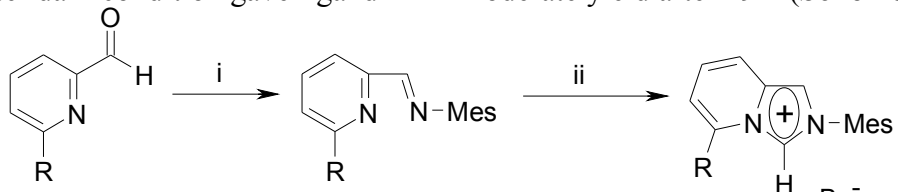


21 **22** **23** **24**

Scheme 6. Reaction conditions*:* i) NH_4OAc, acetic acid, 6 h, 50 %.

Burstein's approach (2005)[30]

Burstein *et al.* reported the synthesis of substituted 2H-imidazo[1,5-*a*]pyridin-4-ium bromides **27**. These salts are found to be precursor for a new class of *N*-heterocyclic carbene ligands. As a consequence of their bicyclic geometry, these ligands are capable of influencing the coordination sphere of a carbene bound metal. Reaction of 2-pyridinecarboxaldehyde **25** with 2,4,6-trimethyl aniline (Mes) in EtOH at 90 ^{0}C affords intermediate **26**, which on further reaction with AgOTf, chloro methyl pivalate in DCM at 40 ^{0}C under dark condition gave ligand **27** in moderate yield after 19 h (**Scheme 7**).

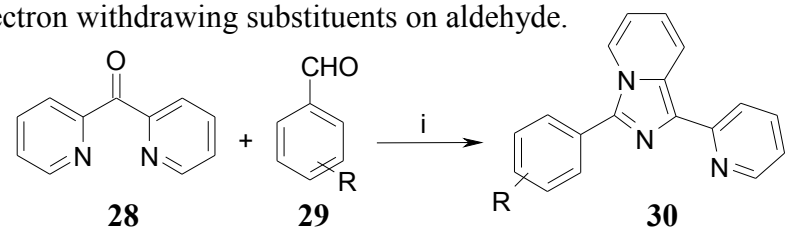


25 **26** **27**

Scheme 7. Reaction conditions: i) 2, 4, 6-trimethyl aniline, EtOH, 90 ^{0}C, 30 min; 90% ii) AgOTf, 53%.

Bu's approach (2005)[31]

Bu *et al.* reported synthesis of series of substituted 1-pyridyl imidazo[1,5-*a*]pyridines, a class of ligands possessing an *N,N*-bidentate feature, in good to moderate yields from condensation of aromatic aldehydes **29** with 2,2'-dipyridyl ketone **28** and ammonium acetate as a nitrogen source in acetic acid at 110 ^{0}C (**Scheme 8**). Author modified his previous method by choosing appropriate starting material to get the desired product. The novelty of this methodology, it is straight far ward and tolerates electron donating as well as electron withdrawing substituents on aldehyde.

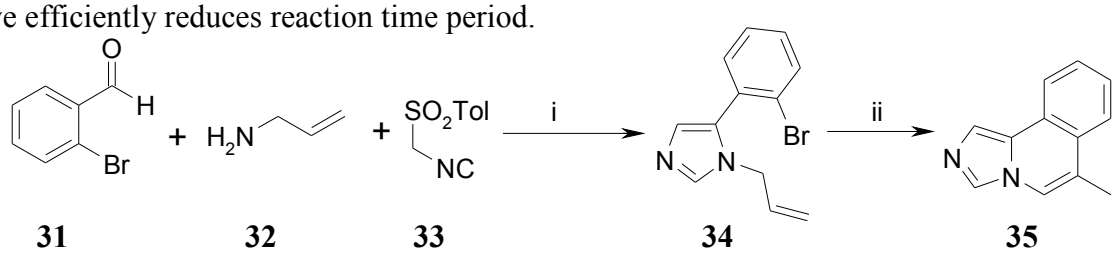


28 **29** **30**

Scheme 8. Reaction conditions: i) NH_4OAc, acetic acid, 110 ^{0}C, 6 h, 50-69%.

Beebe's approach (2006)[32]

Fused imidazo-pyridine derivatives were synthesized using a sequential van Leusen/ intramolecular Heck protocol by Beebe *et. al*. The combination of a multi component reaction followed by an intramolecular carbon–carbon bond forming reaction generates heterocycles **35** of significant molecular complexity in just two steps (**Scheme 9**). Micro-wave efficiently reduces reaction time period.

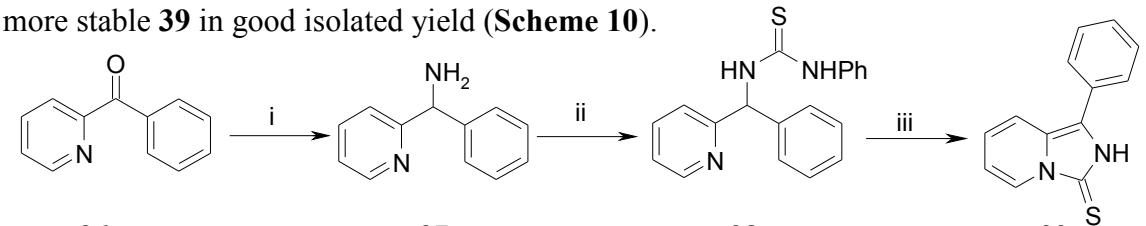


31 **32** **33** **34** **35**

Scheme 9. Reaction conditions**:** i) K_2CO_3, MeOH, DME, rt, overnight, 55%; ii) $Pd(OAc)_2$, Et_3N, (*o*-tol)$_3$P, 125 ^{0}C, MW, 1 h, 42%.

Kim's approach (2007)[33]

Very recently Kim *et al.* reported the synthesis of 1-substituted-imidazo[1,5-*a*]pyridine-3(2*H*)-thione derivatives, from phenyl-2-pyridyl ketone **36** which on treatment with hydroxyl amine hydrochloride gave oxime followed by reduction using Zn dust in acetic acid gave intermediate **37** in good yield. The amine on treatment with phenyl isothiocyanate led to the thiourea **38** which on elevated temperature in xylene converted to more stable **39** in good isolated yield (**Scheme 10**).



36 **37** **38** **39**

Scheme 10. Reaction conditions: i) NH_3, HCl, Zn, acetic acid, 110 ^{0}C. ii) PhNCS, Et_3N, MeOH. iii) xylene, reflux, 75-85%.

Some other important methods involving the synthesis of substituted imidazo[1,5-a]pyridines can be found in the literature.[34-44]

2.1.3 Present Work

2.1.3.1 Objectives

Imidazo[1,5-*a*]pyridines have synthetically challenging skeleton and possess very potent pharmacological activities. Although many synthetic protocols are reported for the preparation of imidazo[1,5-*a*]pyridines, most of these suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged reaction times, or use of hazardous, moisture sensitive and often expensive acid catalysts. Moreover, the synthesis of these heterocycles is usually carried out in polar solvents leading to complex isolation and recovery procedures. These processes also generate waste containing both catalyst and solvent, which have to be recovered, treated, and disposed of.

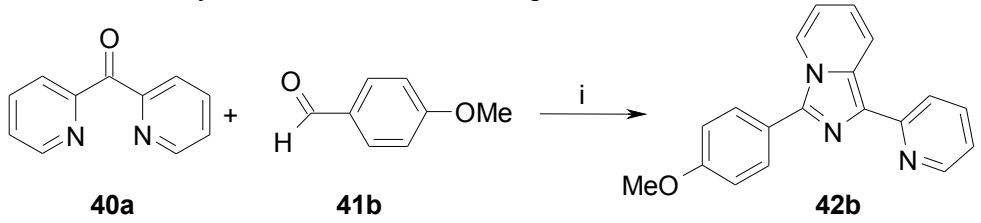
Ionic liquids are salts that are generally liquid at room temperature, and have attracted much attention in recent years,1 since they (i) have a good solubility for a wide range of organic, inorganic and organometallic materials; (ii) enjoy novel properties such as high thermal stability, almost nonexistent vapor pressure, nonflammability as well as easy recycle; (iii) possess alterable hydrophobic or hydrophilic behavior via regulating the nature of their cations and anions; (iv) serve as good media for a variety of organic syntheses. Compared with volatile solvents that have a detrimental impact on the environment, ionic liquids are considered as environmentally friendly green solvents (for more details see chapter 1).

2.1.3.2 Results and Discussion

As the imidazo[1,5-*a*]pyridines are synthetically challenging scaffold skeleton and posses very potent pharmacological activities, we decided to synthesize the imidazo[1,5-*a*]pyridines in ionic liquid in an environment friendly manner.[45] The literature survey and plausible mechanism clearly indicates that formation of [1,5-*a*]pyridines requires either acid catalyst or/and acidic solvents. As we had discussed in Chapter 1, the ionic liquids particularly those belonging to [Hbim] series synthesized by us possess inherent Bronsted and Lewis acidity as characterized by ^{1}H NMR (using $CDCl_3$ as external lock) and also high polarity as determined by Reichardt's betain dye in the $E_T(30)$ scale.

Initially we performed the reaction of 1,2-dipyridyl ketone (**40a)**, anisaldehyde (**41b)** and ammonium acetate in ionic liquid for 24 h at ambient temperature (**Scheme 11**).

A new spot was observed on TLC, which was isolated by column chromatography and found to be merely 9% which was non-acceptable.



40a **41b** **42b**

Scheme 11. Reaction conditions. i) NH_4OAc, $[Hbim]BF_4$, rt, 24 h

The IR spectra of **42b** shows absorption at 1603 cm^{-1} confirms C=N and absence of peaks corresponding to 1,2-dipyridyl ketone. The ^1H NMR spectra of **42b** shows singlet of three protons for methoxy group at δ 3.75 and other values are identical with the known compound.

Our next challenge was to increase the yield and find out optimum condition for the synthesis of library of 1-substituted imidazo[1,5-*a*]pyridines. We have done a systematic study for the optimization of the reaction conditions for the formation of imidazopyridines. In this regard first we did the study of the effect of reaction temperature on formation of the imidazopyridine **42b** (Table 1).

Table 1. Study of temperature effect on the formation of **42b** in $[Hbim]BF_4$

Entry	Temperature (^{0} C)	Time (h)	Yield [b] (%)
1	RT [a]	24	09
2	40	24	20
3	60	24	35
4	80	24	45
5	90	24	45
6	100	1	93

[a]: Room temperature (27 ^{0}C); [b]: Isolated yield after column chromatography.

A rate enhancement with higher yield 20% (entry 2) was observed when temperature was increased to 40 ^{0}C. Slowly we increased the temperature further to 60 ^{0}C,

80 ^{0}C and 90 ^{0}C respectively. An increase in the formation of yield of product was observed but it was not beyond 45% even after prolonged reaction time. However at 100 ^{0}C there was complete conversion and at the same time drastic fall in reaction time were observed (1h) 93% yield (Table 1, entry 5). At higher temperature 130 ^{0}C no further cut down in reaction time period was observed. At higher temperature IL was also found to give some unknown black material indicating a partial decomposition. Hence a reaction temperature of 100 ^{0}C was found to be optimum.

As we had synthesized several ionic liquids (ILs) based on 1,3-di-*n*-butyl imidazolium salts [bbim]X and 1-*n*-butyl imidazolium salts [Hbim]X and fully characterized in terms of physical parameters. Obviously, our next target was to find out the best ionic liquid among them and then to correlate their efficacy in term of their inherent Bronsted/Lewis acidity and polarity. Result of this study would give an insight to select the best IL among synthesized ones for reactions in focus.

Various ionic liquids were screened with varying basicity of anions as solvents cum promoters for the typical reaction of 1,2-dipyridylketone with *p*-anisaldehyde in different ILs without any added catalyst to afford 1-(2-pyridyl)-3-(4-methoxy phenyl)-imidazo[1,5-*a*]pyridines **(42b)** at 100 ^{0}C for 12 h, the results are recorded in Table 2.

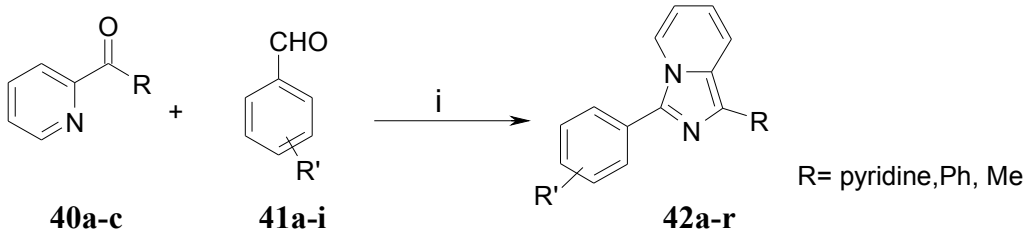
Table 2. Synthesis of **42b** in [bbim] and [Hbim] X

ILs	**pK$_a$** [a]	**–NH proton δ ppm**	**E_T(30) (kcal mol^{-1})** [b]	**Yield** [c] **(%)**
[bbim]ClO_4	-11	--	76.34	38
[bbim]Br	-9	--	66.49	53
[bbim]Cl	**-7**	**--**	**68.89**	**55**
[bbim]BF_4	**0.5**	**--**	**75.73**	**55**
[Hbim]ClO_4	-11	11.83	63.82	69
[Hbim]Br	-9	12.17	73.68	76
[Hbim]Cl	-7	12.22	73.59	82
[Hbim]BF_4	**0.5**	**14.59**	**74.35**	**93**[d]

[a:] The pK$_a$ values of the parent acids of the anions; [b:] Polarity of ILs determined by Reichardt's dye; [c:] Isolated yield after column chromatography; [d]: reaction time 1 h.

The pK_a values are those of the parent acid of the anions and taken from literature.[46] The polarity of different ionic liquids based on 1,3-di-*n*-butyl imidazolium salts and *N*-butyl imidazolium salts were evaluated in terms of E_T (30) values using Reichardt's dye as per the reported procedure.[47]

It becomes evident from these results (Table 2), the IL [Hbim]BF_4 afforded the best results. Consequently, all further studies were conducted at 100 ^{0}C using IL [Hbim]BF_4 as the reaction medium cum promoter to generate a library of 1-substituted imidazo[1,5-*a*]pyridines **(42a-j)** by the condensation of 1,2-dipyridylketone/2-benzoyl/2-acetyl pyridine (**40a-c**) with aryl aldehydes **(41a-i)**, and ammonium acetate as a nitrogen source (**Scheme 12**).



Scheme 12. Reaction conditions. i) [Hbim]BF_4, NH_4OAc, 100 ^{0}C

The results are recorded in Table 3. All the reactions proceed to completion at the time indicated in the Table 3 and the yield data are for the isolated products after column chromatography. All the compounds were well characterized by melting point, IR, ^{1}H NMR and ^{13}C NMR. Their elemental analyses were in conformity with their structures.

The 1-substituted imidazo[1,5-*a*]pyridines have been obtained in excellent isolated yields in relatively short reaction times in case of aromatic and heteroaromatic ketones. It was observed that the process tolerates both electron donating and electron withdrawing substituents on the aldehyde.

Furthermore, the versatility of the method was tested by subjecting 2-benzoyl and 2-acetyl pyridine respectively to the reaction protocol under identical conditions. The corresponding products (**42l-o)** from 2-benzoyl pyridine was obtained in excellent isolated yields (entry 11-14, Table 2) whereas the compounds **42p-r** from 2-acetyl pyridine was obtained in relatively lower yields after much longer reaction period (entry 15-17, Table 3).

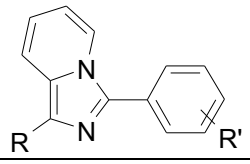
Ammonium acetate is a solid source of ammonia, which can be conveniently generated in situ by the dissociating it to ammonia and acetic acid. Usually, the amount of ammonium acetate used is loosely controlled. A large excess is often used for two reasons: one is other is that it is a neutral salt and not a significantly active species other than as an ammonia source and other is that it is water-soluble and any leftover can be easily removed during a workup.

It is important to note that in all the cases, 1-substituted imidazo[1, 5-*a*]pyridines were precipitated on dilution of the reaction mixture with water and were isolated by simple filtration. The dried product thus obtained showed a single spot on TLC and was pure enough for all practical purposes. The aqueous filtrate was then subjected to distillation at 80 ^{0} C under reduced pressure (10 mmHg) for 4 h to recover the IL almost completely. The IL, thus recovered could be reused three times without loss of activity for the typical reaction of **42b**.

The efficacy of the ILs to promote these heterocyclization reactions was correlated not only to the basicity of the anions but also with the polarity of ionic liquids. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (Table 2). This correlation was also evident when the yield of **42b** was compared with –NH proton chemical shifts of the ILs indicative of the Bronsted acidities of the [Hbim] ILs (Table 2). The yield of **42b** increases progressively not only with increasing Bronsted acidity of the ILs as indicated by the increasing downfield shift of the NH proton but also with increasing polarity of these ILs as indicated by their E_T (30) values.

Thus among the ILs screened, it is found that the IL, [Hbim]BF_4 efficiently promoted this heterocyclization reaction by virtue of its inherent Brønsted acidity conferred by the most acidic –NH hydrogen [chemical shift δ ppm = 14.6]. This makes the IL capable of bonding with the carbonyl oxygen increasing the reactivities of the parent carbonyl compounds without any added acid catalyst.

Table 3. Synthesis 1-substituted imidazo[1,5-*a*]pyridines **42a**–**r**

Entry				Time (h)	Yield [a] (%)
	R	**R'**	**42**		
1	Pyridine	H	42a	1	94
2	Pyridine	*p*-OMe	42b	1	93
3	Pyridine	*o*-Me	42c	1.1	91
4	Pyridine	*o*-OH	42d	1.2	93
5	Pyridine	*p*-OH	42e	2.3	92
6	Pyridine	*o*-Cl	42g	1.5	91
7	Pyridine	*m*-OMe, *p*-OH	42h	2	93
8	Pyridine	*m*-NO_2	42i	2	87
9	Pyridine	*m,di-tert*-Bu, *p*-OH	42j	1.3	94
10	Phenyl	H	42l	1.2	95
11	Phenyl	*o*-NH_2	42m	2.3	85
12	Phenyl	*p*-OMe	42n	1	93
13	Phenyl	*o*-OH, *m*-OMe	42o	1.5	95
14	Me	*H*	42p	6	60
15	Me	*p-OMe*	42q	6	45
16	Me	*o*-OH	42r	12	55

[a:] Isolated yield after column chromatography

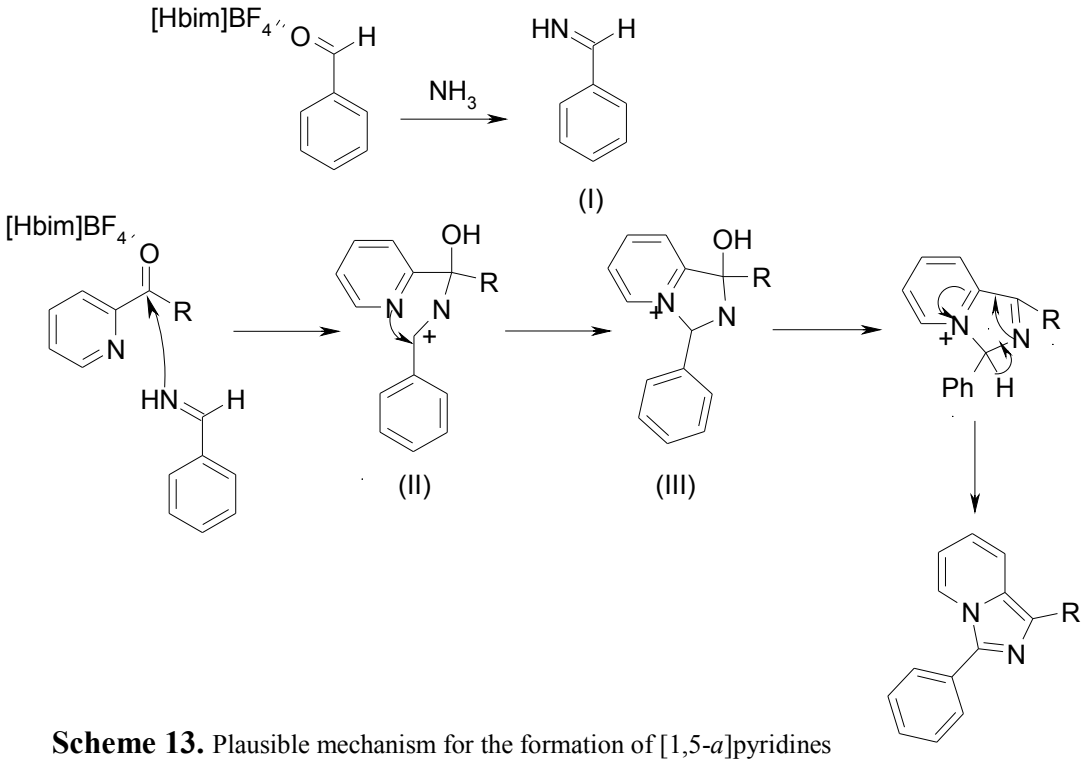
We also experimentally established (as shown in Table 4) that the synthesis of 1-(2-Pyridyl)-3-(4-metoxy-phenyl)imidazo[1,5-*a*]pyridine **42b** using molecular solvents such as toluene, acetonitrile, methanol and acetic acid afforded **42b** in low yields ranging from 17-70% over a much longer period of 12 h. Thus highlighting the role of the acidic IL [Hbim]BF_4 as a reaction medium cum promoter.

Table 4. Synthesis of **42b** in molecular solvents

Solvents	Reaction Temp (^{0}C)	Time (h)	Yield [b] (%)
Methanol	65 [a]	12	25
Ethanol	78 [a]	12	22
Acetic acid	**110**	**12**	**70**
Toluene	110	12	17
DMSO	110	12	20
DMF	110	12	28

[a:] Reflux temperature; [b:] Isolated yield of product after column chromatography.

2.1.4 Plausible mechanism for the formation of imidazo[1,5-*a*]pyridine



Scheme 13. Plausible mechanism for the formation of [1,5-*a*]pyridines

It is assumed that ionic liquid binds with the carbonyl oxygen increasing the reactivity of the parent carbonyl of aldehyde by virtue of its inherent acidity. Further facilitates the formation of the imine (I), and further increases the reactivity of carbonyl of 1-substituted pyridyl ketone. As a result, the imine is readily formed and the nucleophilic

attack of the imine nitrogen with the carbonyl group of the ketone is facilitated which results in the formation of (II) which is converted to intermediate (III) followed by dehydration at elevated temperature to afford 1-substituted imidazo[1,5-*a*]pyridine as yellow color solids.

2.1.5 Conclusion

In conclusion, we have developed a mild, simple, straight far ward, convenient and efficient protocol for the synthesis of a library of 1-substituted imidazo[1,5-*a*]pyridines via the condensation of di(pyridin-2-yl)methanone or phenyl(pyridin-2-yl)methanone or 1-(pyridin-2-yl)ethanone with aromatic aldehydes and ammonium acetate using a room temperature ionic liquid [Hbim]BF_4 as a recyclable medium cum promoter without any added catalyst. The process gives rise to excellent isolated yields of 1- substituted imidazo[1,5-*a*]pyridines in short reaction times (1-12 h). The reaction times achieved are shorter than those hitherto reported under thermal conditions excluding those wherein microwave assisted synthesis are carried out. The versatility of the method was established by conducting the reaction successfully with 2-benzoyl and 2-acetyl pyridines under identical conditions to afford the corresponding substituted imidazo[1,5-*a*]pyridines in good to excellent isolated yields. The corresponding reaction in molecular solvents under similar conditions in the absence of a catalyst is sluggish and poor yielding (Table 4), highlighting the role of the IL in promoting this novel one-pot methodology. The robust experimental procedure, simple isolation procedure, efficient recovery, and recycling of IL and the absence of a catalyst makes this an environmentally benign methodology amenable for scale up.

2.1.6 Experimental

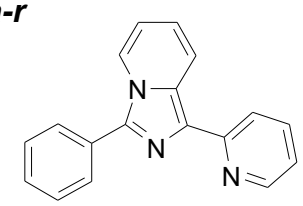
General procedure for synthesis of 1-substituted imidazo[1,5-*a*]pyridines from di(pyridin-2-yl)methanone

A mixture of di(pyridin-2-yl) methanone **(40a)** (4 mmol), substituted aldehydes **(41a-i)** (4 mmol), ammonium acetate (12 mmol) and [Hbim]BF_4 (8 mmol) was heated at 100 ^{0}C with vigorous stirring for the appropriate time mentioned in Table 3. After completion of reaction (the progress of reaction was monitored by TLC) the reaction

mixture was diluted with water (25 mL). The solid substituted imidazo[1,5-*a*]pyridine products, which separated out was filtered, dried under reduced pressure. The product (crude), thus isolated, were pure enough (single spot on TLC). They were subjected to further purification by chromatography through a column of silica gel using 25% EtOAc in petroleum ether as eluent to yield the desired substituted imidazo[1,5-*a*]pyridines in excellent yields of 84-96% and were fully characterized in terms of physical constant, IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and LC-MS.

2.1.6.1 Characterization data for compounds 42a-r

1-(2-Pyridyl)-3-phenylimidazo [1,5-*a*] pyridine (42a)



Yellow solid

M. P. (°C) **:** 91-92

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 646,761**,** 960, 1404, 1565, 1633, 2224, 2933.

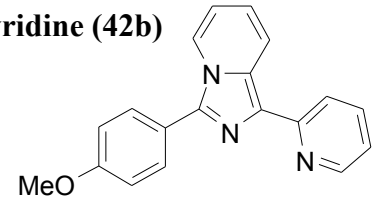
^{1}H NMR **:** **δ** 6.60 (t, *J*= 6.5 Hz, 1H), 6.88 (dd, *J*= 9.0, 6.2 Hz, 1H) 7.05 **(200 MHz, $CDCl_3$)** (t, *J*= 6.5 Hz**,** 1H), 7.42 (t, *J*= 7.5 Hz, 1H), 7.50 (t, *J*= 7.5 Hz, 2H), 7.67 (t, *J*= 7.5 Hz, 1H), 7.80 (d, *J*= 7.5 Hz, 2H), 8.21 (d, *J*= 7.5 Hz, 2H), 8.58 (d, *J*= 4.5 Hz, 1H), 8.66 (d, *J*= 9.0 Hz, 1H).

^{13}C NMR **:** **δ** 113.8, 119.8, 120.3, 120.9, 121.5, 121.6, 128.2, 128.8, 128.9, **(50 MHz, $CDCl_3$)** 129.9, 130.1, 130.4, 136.1, 137.9, 148.8, 154.8.

LC-MS **:** 272.13 (M+H), 252.13, 208.14, 148.07.

Elemental Analysis : **$C_{18}H_{13}N_3$** Calcd**.** C, 79.68; H, 4.83; N, 15.49.
Found C, 79.55; H, 4.69; N, 15.27.

1-(2-Pyridyl)-3-(4-metoxy-phenyl) imidazo [1,5-*a*] pyridine (42b)



Yellow solid

M. P. (°C) **:** 120-121.

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 765**,** 850, 1050, 1321, 1509, 1633, 2248, 2850.

^{1}H NMR **:** **δ** 3.80 (s, 3H), 6.57 (t, *J*=7.7 Hz, 1H), 6.85 (dd, *J*= 9, 6.4 Hz, 1H) **(200 MHz, $CDCl_3$)** 6.96-7.04 (m, 3H), 7.69-7.59 (m, 3H), 8.17 (dd, *J*= 8.1, 7.0 Hz, 2H), 8.56 (d, *J*= 5.8 Hz, 1H), 8.61 (d, *J*= 9.3 Hz, 1H).

^{13}C NMR **:** **δ** 55.3, 113.6, 114.4, 119.8, 120.2, 120.8, 121.5, 122.4, 122.6,

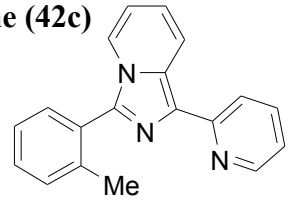
(50 MHz, $CDCl_3$) 129.7, 129.8, 130, 136.2, 138, 148.8, 154.9, 160.

LC-MS **:** 302.13 (M+H), 274.12, 248.12, 208.14, 148.07.

Elemental Analysis : **$C_{19}H_{15}N_3O$** Calcd. C, 75.73; H, 5.02; N, 13.94.

Found C, 75.51; H, 4.89; N, 13.81.

1-(2-Pyridyl)-3-(2-methyl-phenyl) imidazo [1,5-*a*] pyridine (42c)



Yellow solid

M. P. (°C) **:** 114-115 .

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 725, 810, 900, 1050, 1520, 1635, 1862, 2840, 3021.

^{1}H NMR **:** **δ** 2.21 (s, 3H), 6.54 (t, *J*= 6.5 Hz, 1H), 6.86 (dd, *J*= 9, 6.3 Hz, 1H),

(200 MHz, 7.03 (t, *J*= 6.5 Hz, 1H), 7.21-7.38 (m, 3H), 7.45 (d, *J*= 7.5 Hz, 1H),

$CDCl_3$/ DMSO-d_6) 7.57 (d, *J*= 7.5 Hz, 1H), 7.65 (t, *J*= 8.0 Hz, 1H), 8.19 (d, *J*= 8.0 Hz, 1H), 8.58 (d, *J*= 4.5 Hz, 1H), 8.66 (d, *J*= 9.0 Hz, 1H).

^{13}C NMR **:** **δ** 19.8, 113.6, 119.9, 120.4, 121, 121.6, 121.7, 126.2, 129, 129.7

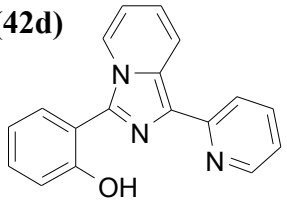
(50 MHz, $CDCl_3$/ DMSO-d_6) 129.9, 130.6, 130.9, 136.3, 137.8, 138.6, 139.1, 149, 152.5.

LC-MS **:** 286.13 (M+H), 248.12, 212.08, 188.09, 183.12.

Elemental Analysis **:** **$C_{19}H_{15}N_3$** Calcd. C, 79.98; H, 5.30; N, 14.73.

Found C, 79.72; H, 5.19; N, 14.68.

1-(2-Pyridyl)-3-(2-hydroxy-phenyl) imidazo [1,5-*a*] pyridine (42d)



Pale yellow solid

M. P. (°C) **:** 195-196.

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 759, 964, 1260, 1315, 1630, 2400, 3450.

^{1}H NMR **:** **δ** 7.18 (t, *J*= 6.8 Hz, 1H), 7.34-7.54 (m, 4H), 7.76 (t, *J*= 8 Hz, 1H)

(200 MHz, 8.16 (d, *J*= 7.9 Hz, 1H), 8.52 (d, *J*= 7.7 Hz, 1H), 8.66

$CDCl_3$/ DMSO-d_6) **(**d**,** *J*= 6.7 Hz, 1H), 9.0 (d, *J*= 4.5 Hz, 1H), 9.12 (d, *J*= 9.2 Hz, 1H).

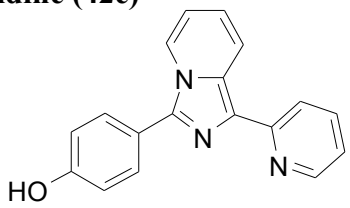
^{13}C NMR **:** **δ** 112.5, 113.8, 114.8, 117.3, 118, 118.9, 119.9, 120.6, 128.2,

(50 MHz, $CDCl_3$/ DMSO-d_6) 128.6, 129.4, 134.8, 136.4, 147.3, 153.3, 156.5.

Elemental Analysis **:** **$C_{18}H_{13}N_3O$** Calcd. C, 75.25; H, 4.56; N, 14.63.

Found C, 75.07; H, 4.27; N, 14.48.

1-(2-Pyridyl)-3-(4-hydroxy-phenyl) imidazo[1,5-*a*] pyridine (42e)



Yellow solid

M. P. (°C) **:** 195-196.

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 865, 908, 1210, 1368, 1635, 3460.

^{1}H NMR **: δ** 6.62 (t, *J*= 7.0 Hz, 1H), 6.60-6.64 (m,1H) 6.83-7.05 (m, 3H),

(200 MHz, 7.31 (dd, *J*= 9.0, 6.14 Hz, 1H), 7.54-7.7 (m, 3H), 8.12 (dd, *J*=

$CDCl_3$/ DMSO-d_6) 8.0, 7.2 Hz, 2H), 8.6 (d, *J*= 5.8 Hz, 1H), 8.8 (d, *J*= 9.0 Hz, 1H),

^{13}C NMR **: δ** 114.8, 117.3, 118, 118.9, 119.9, 120.6, 128.2, 128.6, 129.4, 134.8

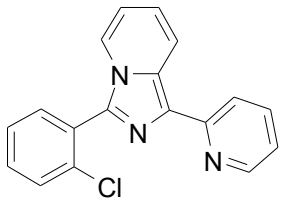
(50 MHz, $CDCl_3$/ DMSO-d_6) 136.4, 143.4, 147.3, 149.4, 155.4, 157.6.

LC-MS **:** 288.11 (M+H), 255.08, 211.12, 185.09.

Elemental Analysis : **$C_{18}H_{13}N_3O$** Calcd. C, 75.25; H, 4.56; N, 14.63.

Found C, 75.09; H, 4.19; N, 14.48.

1-(2-Pyridyl)-3-(2-chloro-phenyl) imidazo [1,5-*a*] pyridine (42f)



Bright yellow solid

M. P. (°C) **:** 178-179.

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 708, 821, 1052, 1453, 1635, 2469, 3080.

^{1}H NMR **: δ** 6.60-6.67 (m, 1H), 6.90-6.98 (m, 1H), 7.1-7.16 (m, 1H), 7.37-

($CDCl_3$, 200 MHz) 7.72(m, 6H), 8.19-8.24 (m, 1H), 8.6-8.63 (m, 1H), 8.69-8.74 (m, 1H).

^{13}C NMR **: δ** 113.4, 119.7, 120.3, 121.1, 121.4, 122.2, 127.2, 129.1, 129.7,

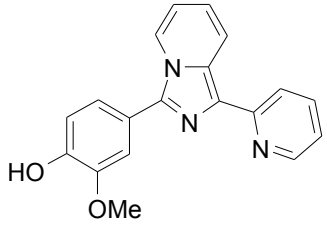
(50 MHz, $CDCl_3$) 129.8, 130.8, 133.2, 134.3, 135.5, 136.1, 148.9, 154.8.

LC-MS **:** 307.08 (M+H), 288.12, 248.09, 212.06, 185.09.

Elemental Analysis **: $C_{18}H_{12}N_3Cl$** Calcd. C, 70.47; H, 3.91; N, 13.70.

Found: C, 70.29; H, 3.71; N, 13.59.

1-(2-Pyridyl)-3-(3-methoxy-4-hydroxy-phenyl) imidazo [1,5-*a*] pyridine (42g)



Yellow solid

M. P. (°C) **:** 132-133.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 665, 755, 910, 1085, 1291, 1657, 3019, 3460.

^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) : **δ** 3.71 (s, 3H), 5.12 (brs, 1H), 6.41-6.47 (t, *J*= 9.0 Hz, 1H), 6.66-6.74 (m, 1H), 6.8-6.92 (m, 2H), 7.0-7.05 (m, 1H), 7.12-7.14 (m, 1H), 7.47-7.56 (m, 1H), 7.99-8.03 (d, *J*= 9.6 Hz, 2H). 8.39-8.44 (d, *J*= 8.4 Hz, 2H).

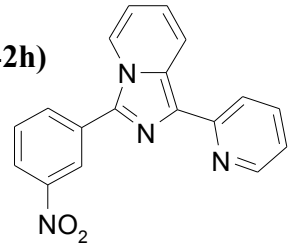
^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) : **δ** 55.2, 111.5, 113.1, 114.9, 119, 119.6, 120.2, 120.3, 120.4. 120.5, 121.8, 127.5, 128.6, 129.1, 135.7, 137, 146.8, 147.4, 153.9.

LC-MS : 318.12 (M+H), 288.05, 275.09, 271.02.

Elemental Analysis : **$C_{19}H_{15}N_3O_2$** Calcd. C, 71.91; H, 4.76; N, 13.24.

Found C, 71.74; H, 4.58; N, 13.09.

1-(2-Pyridyl)-3-(3-nitro-phenyl) imidazo [1,5-*a*] pyridine (42h)



Yellow solid

M. P. (°C) : 188-187

IR ($CHCl_3$, cm^{-1}) : υ_{max} 840, 914, 1210, 1335, 1560, 1620, 1810, 2100.

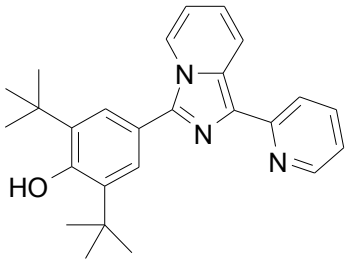
^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) : **δ** 6.81 (t, *J*= 7 Hz, 1H), 7.09 (t, *J*=7 Hz, 1H), 7.14 (t, *J*=7 Hz,1H) 7.79-7.8 (m, 2H), 8.10 (d, *J*= 8 Hz, 1H), 8.26 (d, *J*= 8 Hz, 1H), 8.34 (d, *J*= 8 Hz, 1H), 8.57-8.6 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) : **δ** 115.8, 120, 121.5, 121.8, 123.2, 123.3, 123.7, 124.0, 130.0, 131.0, 131.3, 131.8, 134.1, 136, 138.1, 149, 149.5, 155.

Elemental Analysis : **$C_{18}H_{12}N_4O_2$** Calcd. C, 68.35; H, 3.82; N, 17.71.

Found: C, 68.13; H, 3.59; N, 17.62.

1-(2-Pyridyl)-3-(3, 5-di-tertbutyl-4-hydroxy-phenyl) imidazo [1,5-*a*] pyridine (42i)



Yellow solid

M. P. (°C) : 212-213.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 669, 710, 1036, 1352, 1430, 1633, 2400, 3435.

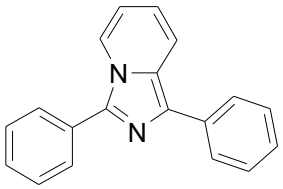
^{1}H NMR : **δ** 1.5 (s, 18H), 5.45 (brs, 1H), 6.84-6.92(m, 1H), 7.03-7.10 (m, 1H)

(200 MHz, $CDCl_3$) 7.58 (s, 2H), 7.66-7.74 (m, 1H), 8.12-8.16 (d, *J*= 7.2 Hz, 1H), 8.24-8.28 (d, *J*= 8.4 Hz, 1H), 8.60-8.71 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 30.2, 113.5, 119.9, 120.2, 120.7, 121.7, 125.6, 136.2.

Elemental Analysis : $C_{26}H_{29}N_3O$ Calcd. C, 78.16; H, 7.32; N, 10.52.
Found: C, 78.06; H, 7.19; N, 10.42.

1, 3-diphenylH-imidazo[1,5-*a*]pyridine (42j)



Yellow solid

M. P. (°C) **:** 122-123.

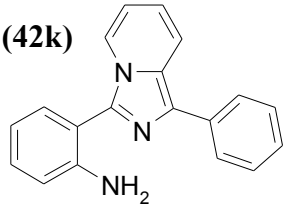
^{1}H NMR **: δ** 6.41 (m, 1H), 6.58 (m, 1H), 7.22-7.48 (m, 11H)
(200 MHz, $CDCl_3$) 7.88 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 119, 121.8, 126.3, 127.6, 128.2, 129.3, 130.7, 132.8, 144.

LC-MS **:** 271.12 (M+H), 248.07, 236.09, 211.11.

Elemental Analysis : $C_{19}H_{14}N_2$ Calcd. C, 84.42; H, 5.22; N, 10.36.
Found: C, 84.19; H, 5.14; N, 10.24.

2-(1-phenylH-imidazo[1, 5-*a*]pyridin-3-yl)benzenamine (42k)



Yellow solid

M. P. (°C) **:** 146-147.

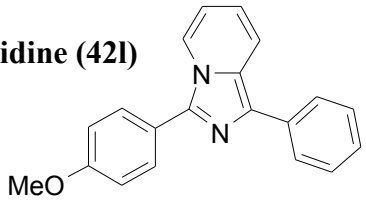
IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 700, 850, 920, 1120, 1635, 2100, 3405, 3487.

^{1}H NMR **: δ** 4.2 (brs, 2H), 5.78 (m, 1H) 6.12 (m, 1H), 6.52 (m, 2H),
(200 MHz, $CDCl_3$) 7.03 (m, 1H), 7.16 (m, 1H), 8.02 (d, *J*= 8.0 Hz, 1H).

^{13}C NMR **: δ** 109.2, 117.0, 118.9, 119.2, 122.2, 126.4, 127.5, 128.3, 128.8,
(50 MHz, $CDCl_3$) 129.3, 129.6, 130.2, 133.2, 143.9, 145.2.

Elemental Analysis : $C_{19}H_{15}N_3$ Calcd. C, 79.98; H, 5.30; N, 14.73.
Found C, 79.72; H, 5.19; N, 14.59.

3-(4-methoxyphenyl)-1-phenylH-imidazo[1, 5-*a*]pyridine (42l)



Yellow solid

M. P. (°C) **:** 148-149

^{1}H NMR **: δ** 3.83 (s, 3H), 6-44-6.51 (m, 1H), 6.65-6.73 (m, 1H), 7.24-7.31

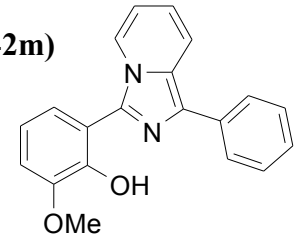
(200 MHz, $CDCl_3$) (m, 3H), 7.41-7.49 (m, 2H), 7.70-7.80 (m, 3H), 7.90-7.95 (m, 2H) 8.08-8.12 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 55.0, 112.7, 114.1, 118.6, 119.1, 126.1, 126.4, 127.0, 128.3, 129.4, 131.1, 134.6, 137.7, 159.6.

LC-MS : 301.13 (M+H), 288.13, 255.12, 188.09.

Elemental Analysis : **$C_{20}H_{16}N_2O$** Calcd. C, 79.98; H, 5.37; N, 9.33.
Found C, 79.72; H, 5.25; N, 9.19.

2-methoxy-6-(1-phenylH-imidazo[1,5-*a*]pyridin-3-yl)phenol (42m)



Yellow solid

M. P. (°C) : 172-173.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 690, 730, 835, 900, 1640, 1910, 2100, 2600, 3410.

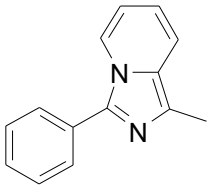
^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) : **δ** 3.92 (s, 3H), 6.64-6.71 (m, 1H), 6.85-7.05 (m, 3H), 7.21-7.31 (m, 2H), 7.41-7.49 (m, 2H), 7.86-7.91 (m, 2H), 8.07-8.1 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) : **δ** 56.2, 112.7, 117.4, 119, 121.2, 122.2, 124.3, 126.3, 127.5, 128.8, 129.3, 129.5, 130.2, 133.2, 143.9, 145.7, 151.9.

LC-MS : 317.12 (M+H), 302.09, 285.06, 245.12.

Elemental Analysis : **$C_{20}H_{16}N_2O_2$** Calcd. C, 75.93; H, 5.10; N, 8.86.
Found: C, 75.78; H, 5.02; N, 8.68.

1-methyl-3-phenylH-imidazo[1,5-*a*]pyridine(42n)



Yellow solid

M. P. (°C) : 105-106.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 690, 745, 850, 960, 1635, 1808, 1945, 3021.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 2.67 (s, 3H), 6.42 (m, 1H), 6.58 (m, 1H), 7.32-7.48 (m, 6H) 7.88 (m, 1H).

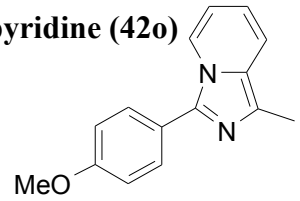
^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 17.0, 119.2, 122.0, 123.5, 126.3, 127.5, 128.8, 129.3, 130.2, 130.7, 136.2, 143.5.

LC-MS : 209.16 (M+H), 201.05, 188.09.

Elemental Analysis : **$C_{14}H_{12}N_2$** Calcd. C, 80.74; H, 5.81; N, 13.45.

Found: C, 80.58; H, 5.72; N, 13.32.

3-(4-methoxyphenyl)-1-methylH-imidazo[1,5-*a*]pyridine (42o)



Yellow solid

M. P. (°C) **:** 122-123

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 660, 850, 960, 1235, 1640, 1808, 1945, 2850, 3120.

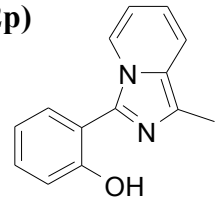
^{1}H NMR (200 MHz, $CDCl_3$) **:** **δ** 2.56 (s, 3H), 3.73 (s, 3H), 6.48 (m, 1H), 6.62 (m, 1H), 6.83 (m, 2H), 7.34-7.37 (m, 3H), 7.88 (m, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** **δ** 17.0, 55.9, 115.0, 119.2, 122.3, 123.0, 126.5, 128.3, 130.1, 135.0, 143.5, 160.7.

LC-MS **:** 238.18 (M+H), 233.09, 205.12, 189.09

Elemental Analysis **:** **$C_{15}H_{14}N_2O$** Calcd. C, 75.61; H, 5.92; N, 11.76.
Found: C, 75.48; H, 5.82; N, 11.60.

2-(1-methylH-imidazo[1,5-*a*]pyridin-3-yl)phenol (42p)



Yellow solid

M. P. (°C) **:** 149-151.

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 735, 860, 964, 1235, 1318, 1635, 1945, 2850, 3410.

^{1}H NMR (200 MHz, $CDCl_3$) **:** **δ** 2.29 (s, 3H), 6.63 (m, 1H), 6.81 (m, 1H), 7.08 (m, 1H), 7.38-7.42 (m, 2H), 7.89 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) **:** **δ** 17.0, 116.4, 118.5, 119.2, 121.9, 122.3, 123, 126.3, 129.0, 130.2, 135.6, 143.7, 155.0.

LC-MS **:** 224.10 (M+H), 205.08, 196.11, 145.07.

Elemental Analysis **:** **$C_{14}H_{12}N_2O$** Calcd. C, 74.98; H, 5.39; N, 12.49.
Found: C, 74.82; H, 5.12; N, 12.32.

2.1.6.2 Spectra's of some representative compounds

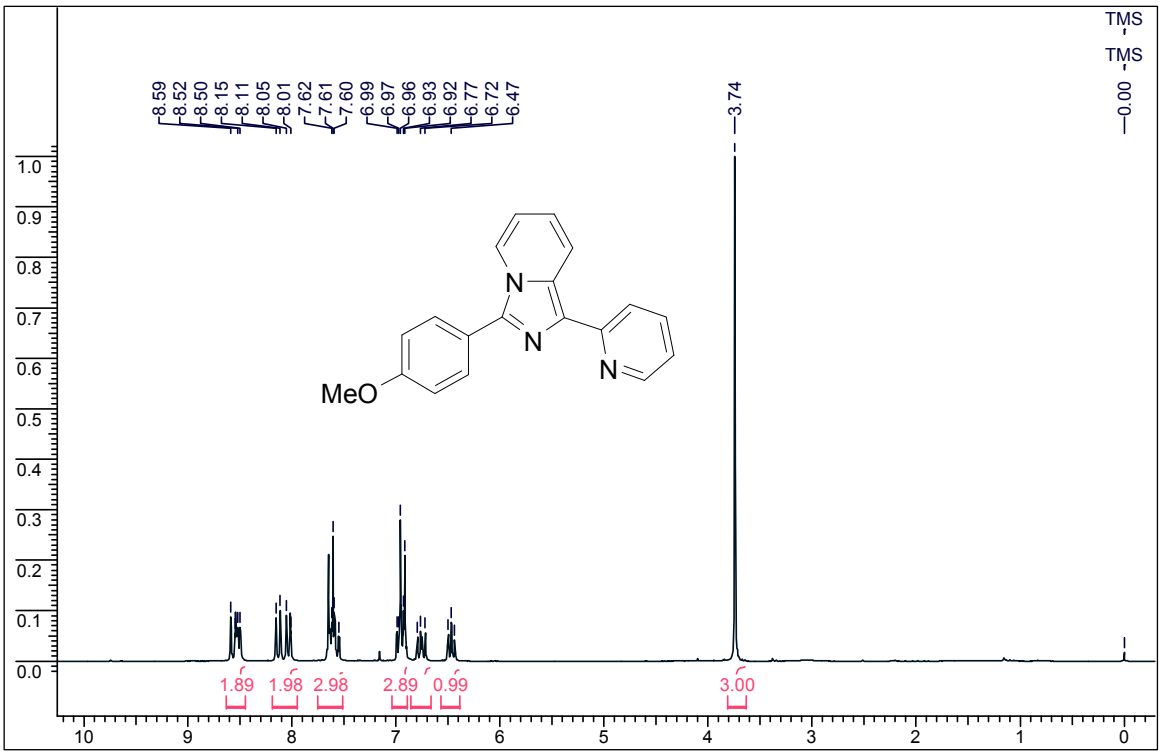
[1] ^{1}H NMR and ^{13}C NMR spectra of **42b**

[2] ^{1}H NMR and ^{13}C NMR spectra of **42g**

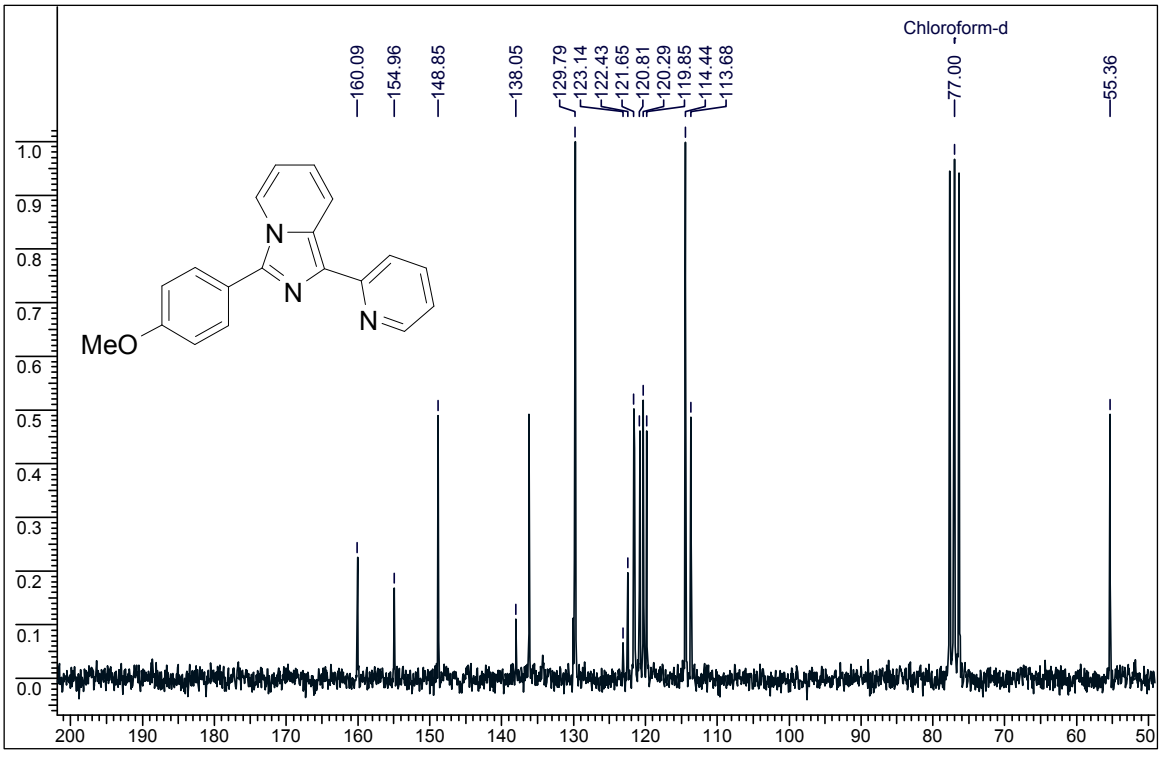
[3] ^{1}H NMR and ^{13}C NMR spectra of **42i**

[4] ^{1}H NMR and ^{13}C NMR spectra of **42l**

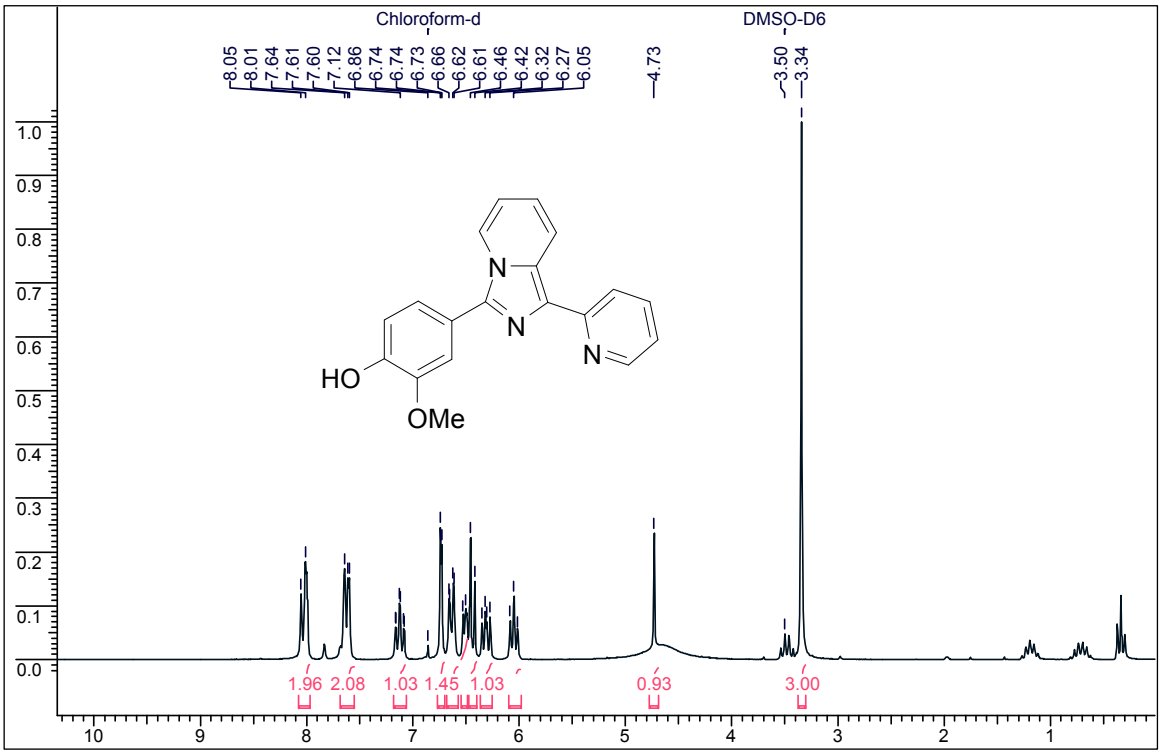
[1] ^{1}H NMR spectra of 42b



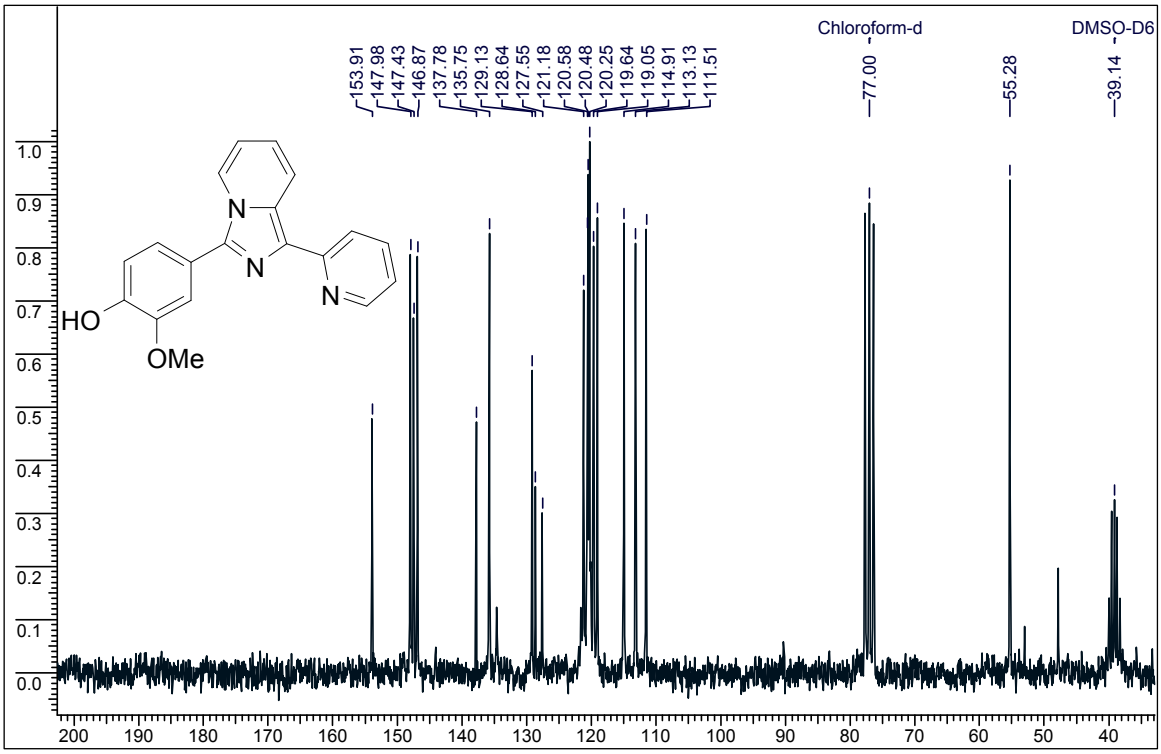
[1] ^{13}C NMR spectra of 42b



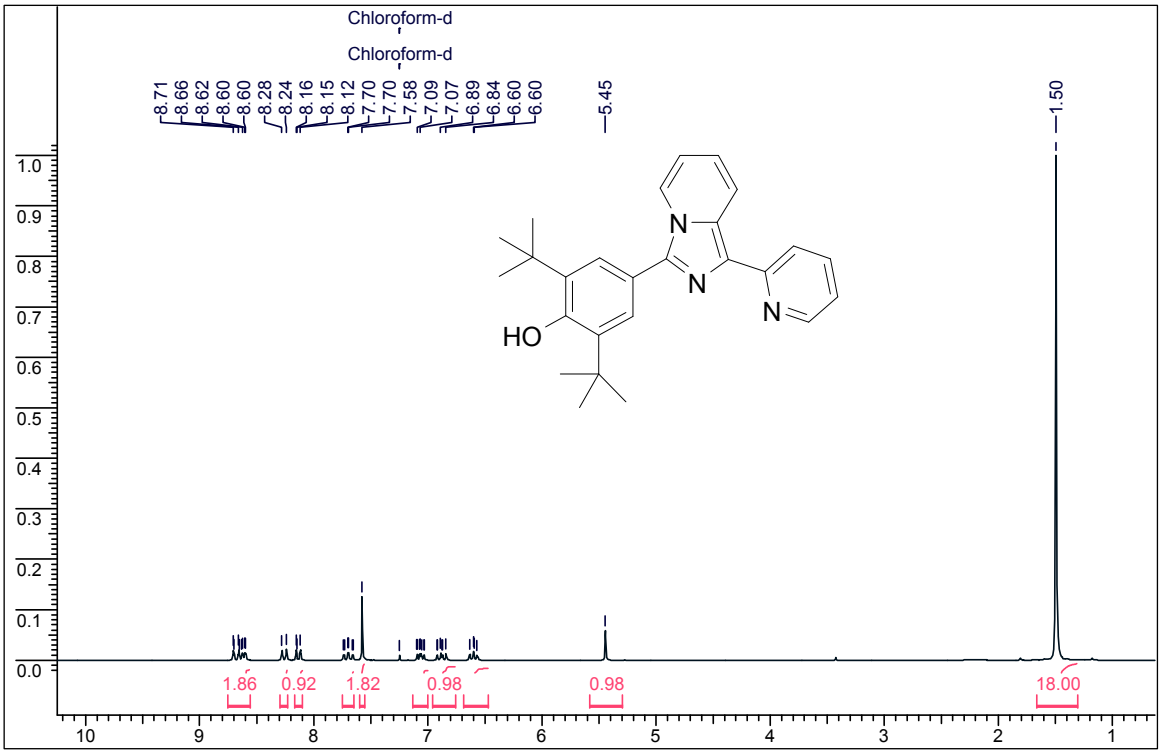
[2] ^{1}H NMR spectra of 42g



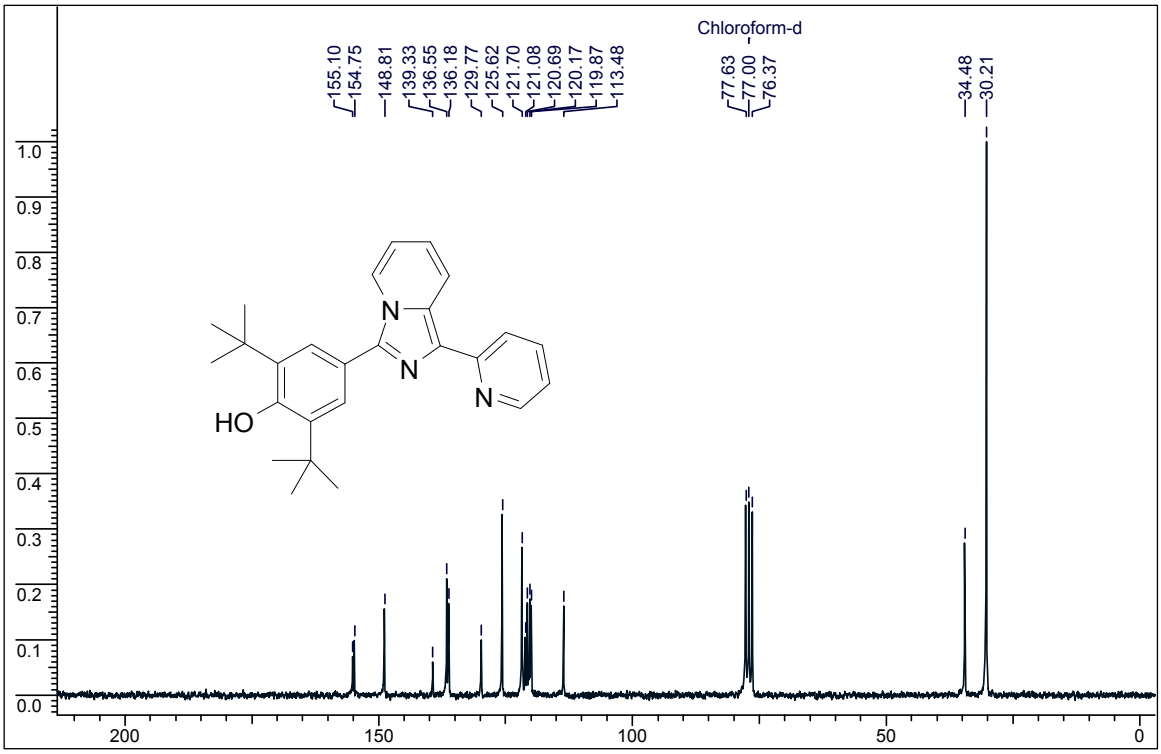
[2] ^{13}C NMR spectra of 42g



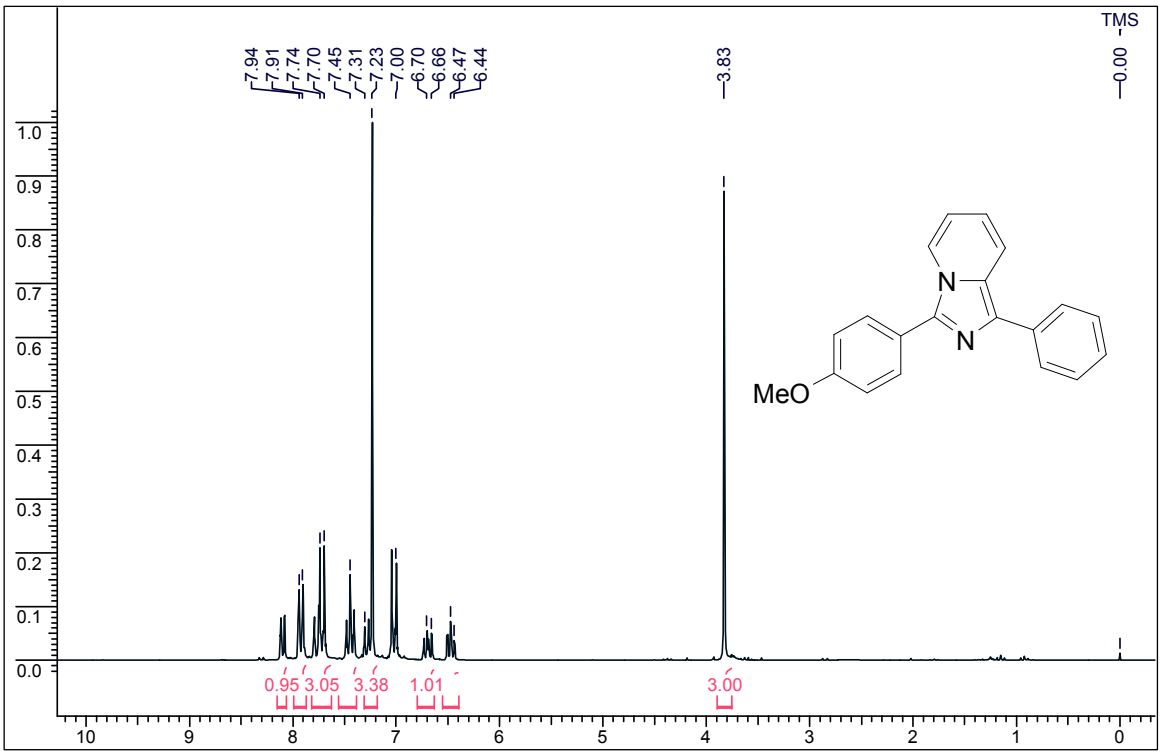
[3] ^{1}H NMR spectra of 42i



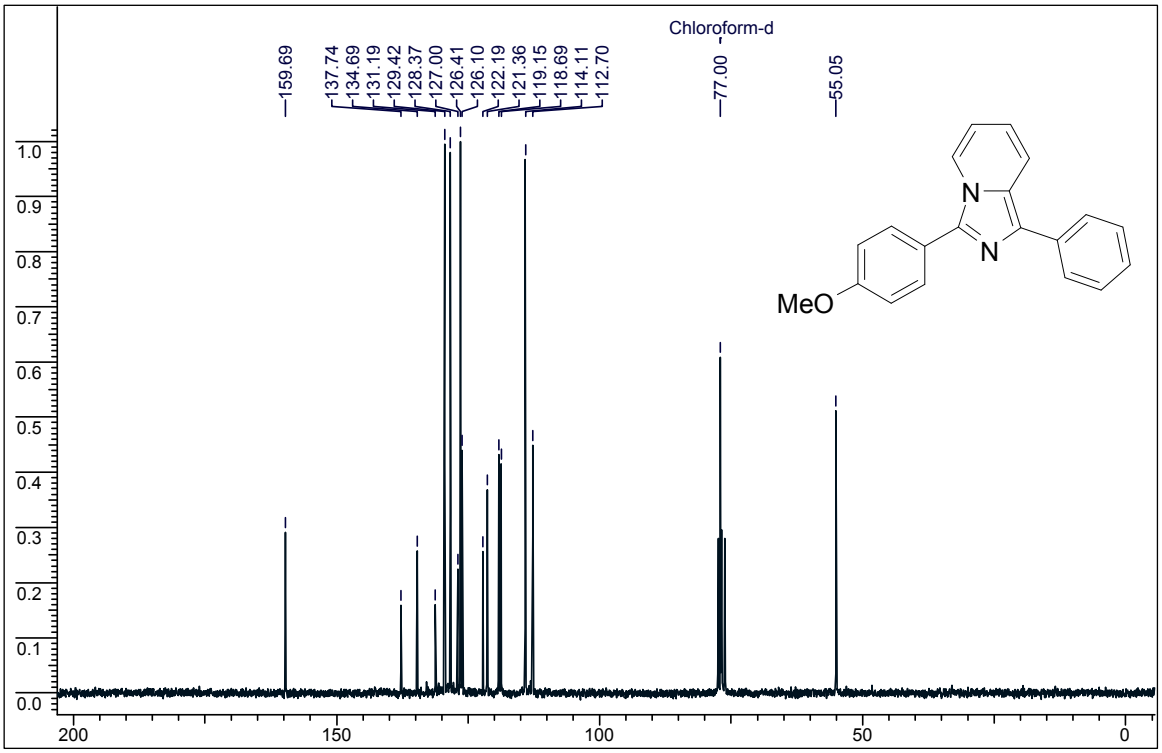
[3] ^{13}C NMR spectra of 42i



[4] ^{1}H NMR spectra of 42l



[4] ^{13}C NMR spectra of 42l



2.1.7 References

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SECTION-B

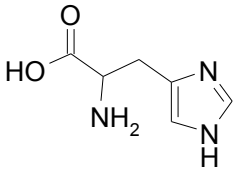
Synthesis of

2,4,5-trisubstituted imidazoles

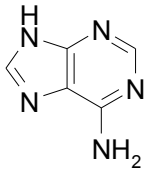
2.2.1 Introduction

Imidazole or imidazoline is an azapyrrole, five-membered heterocyclic system with three carbon atoms and two nitrogen atoms separated by one of the carbon atoms, nitrogen atoms are at the positions 1 and 3, as a result also named as 1,3-diazole. Imidazole was earlier also called as glyoxaline as it was first prepared in 1858 from glyoxal and ammonia by Debus that pioneered a novel synthetic route to imidazole.[1]

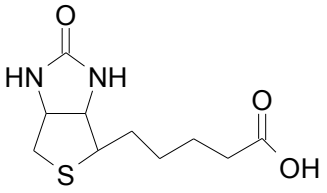
Imidazoles are common scaffolds in highly significant biomolecules, including the essential amino acid histidine **G** (involved in the biochemical reactions of living systems), purine **H** (forming bases of nucleic acid), histamine, the pilocarpine alkaloids.[2] The reduced form of the imidazole ring is also present in naturally occurring biotin (vitamin H) **I** (**Fig. 3**) and other alkaloids, which have been shown to exhibit interesting biological activities such as antimicrobial, anticryptococcal, inhibition of nitric oxide synthase, and cytotoxic activities.[3]



Histidine (G)



Purine (H)

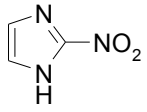


Biotin (I)

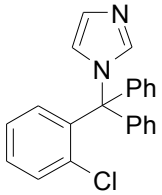
Fig. 3

Members of this class of diazoles are known to possess NO synthase inhibition,[4] antibiotic,[5] antifungal,[6] antiulcerative activities,[7] inhibitors of 5-lipoxygenase[8] and substances with CB1 receptor,[9] VEGF receptor I and II,[10] and neuropeptide Y antagonistic activities.[11]

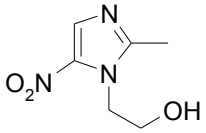
Moreover, compounds with imidazole nucleus have many pharmacologically significant properties and play important roles in biochemical processes some important drugs with their activities are giving as below (**Fig. 4**).



Azomycin-Antibiotic
[2-Nitroimidazole]



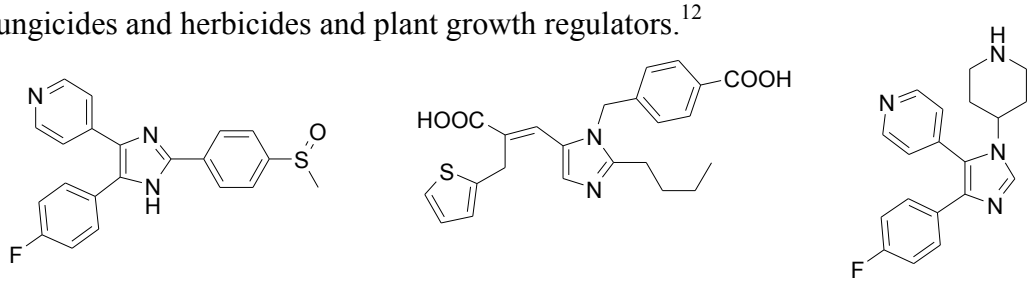
Clotrimazole-Anticancer



Matronidazole-Anticancer

Fig. 4

Many of substituted imidazoles are known as inhibitors of p38 MAP kinase, fungicides and herbicides and plant growth regulators.[12]



Potent and selective p38 kinase inhibitors

Fig. 5

Recent advances in green chemistry, organometallic chemistry and coordination chemistry have extended the boundary of imidazoles to the synthesis and applications of a large class of imidazoles as imidazole related N-heterocyclic carbenes (NHC) and as ionic liquids novel, green alternative for volatile organic solvents (**Fig. 6**).[13,14]

Ionic Liquid (J) **NHC (K)**

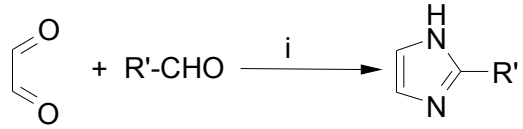
Fig. 6

2.2.2 Review of literature

Literature search revealed that there are nemorus methods are for the synthesis of imidazole library. Here in this section we covered some recent and some of the more significant methods for the synthesis of 2, 4, 5-trisubstituted-*1*H-imidazoles.

Debus approach (1858)[1]

Debus pioneered the chemical synthesis of imidazoles **45**, from glyxol **43**, acetaldehyde **44** and ammonia solution in acetic acid and water gives imidazole in moderate to good yield (**Scheme 14**). It was also called as glyxoline.

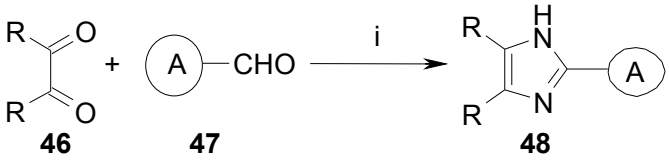


43 **44** **45**

Scheme 14. Reaction conditions: i) ammonia solution, acetic acid.

Mjalli's approach (1996)[15]

Mjalli *et al.* reported the synthesis of highly substituted imidazole libraries on solid support. Condensation of an aldehyde **47** and 1,2-dione **46** in the presence of ammonium acetate in acetic acid at 100 ^{0}C gave substituted imidazole **48** with good to moderate isolated yield after 4-8 h. The synthesis was accomplished by attaching the aldehyde component to Wang resin via ester or ether linkages (**Scheme 15**).

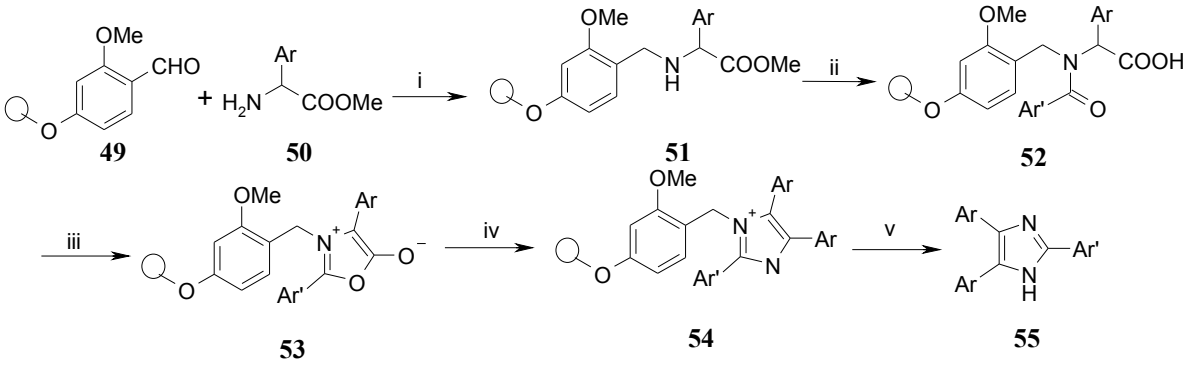


46 **47** **48**

Scheme 15. Reaction conditions: i) NH_4OAc, AcOH, 55-75%.

Bilodeau's approach (1998)[16]

2,4,5-triaryl-1H-imidazoles **55** has been prepared in moderate to excellent isolated yield by the reaction of the resin-bound munchnones **49** with tosylimines in dichloromethane in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), followed by release of the imidazoles from the polymer-linked derivatives **54** by acidic treatment. Munchnones **53** were synthesized via cyclization of compounds **52**, which was obtained by acylation of compounds **51** which in turn was prepared from the commercially available polystyrene-poly(ethylene glycol) graft copolymer resin **49** and the amino acid methyl esters **50** (**Scheme 16**)

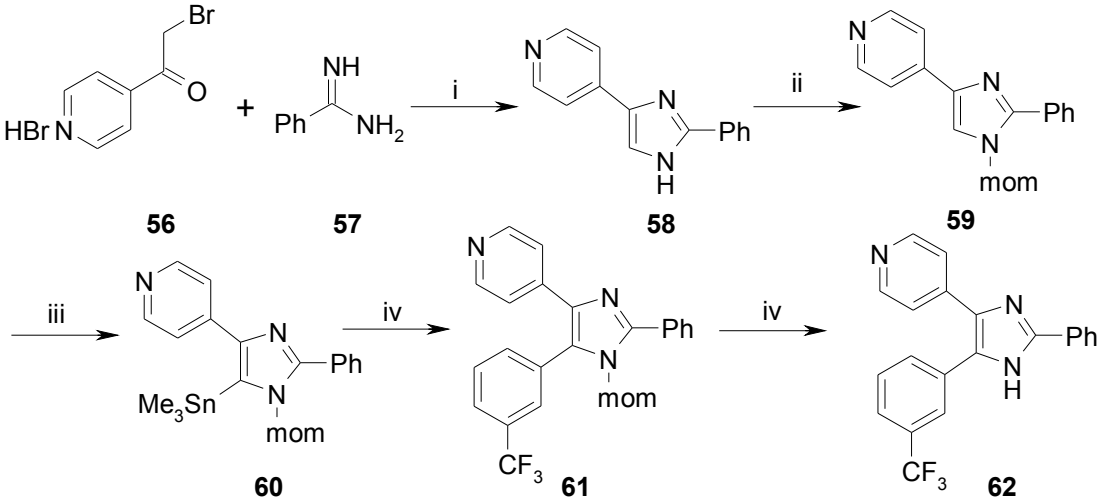


Scheme 16. Reaction conditions: i) $NaB(OAc)_3H$, AcOH, DMF; ii) ArCOCl, i-Pr_2NEt, DCM, KOH, dioxane, H_2O; iii) EDC, DCM; iv) *N*-tosyl imines; v) AcOH, CF_3COOH, H_2O, 100 ^{0}C.

Liverton's approach (1999)[17]

A Stille-type coupling was used as a key step in the synthesis of 2,4,5-triaryl-*1*H-imidazole **62** from 4-(bromoacetyl) pyridine hydrobromide **56,** and benzamidine **57** in DMF gave **58**.

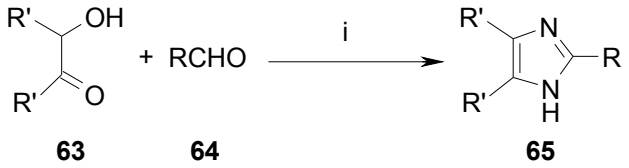
Amine of compound **58** was proteced by MOM gave **59** and the 5-position of **59** was functionalized by treatment with butyl lithium and subsequent reaction with chlorotrimethyltin gives the intermediate **60**.The resulting organometallic derivative **60** underwent Pd-catalyzed Stille coupling with 3-iodo-(trifluoromethyl) benzene to give the imidazole derivative **61**. Finally, deprotection by treatment with aqueous hydrochloric acid furnished the 2,4,5-triaryl-*1*H-imidazole **62** (**Scheme 17**).



Scheme 17. Reaction conditions: i) DMF, 40 ^{0}C, 80%; ii) NaH, THF, 0 ^{0}C, MOMCl, 57%; iii) BuLi, THF, -78 ^{0}C, Me_3SnCl; iv) 3-$CF_3C_6H_4I$, DMF, $Pd(PPh_3)_4$, 80 ^{0}C, 72%; v) 6 M HCl, reflux, 54%.

Guo's approach (2004)[18]

Guo *et al.* reported the solvent–free microwave-assisted synthesis of trisubstituted imidazoles **65** by the condensation of α-hydroxyketone **63** with different aldehydes **64** and ammonium acetate over silica gel or alumina impregnated as the solid support in short reaction time with 80-95% yield (**Scheme 18**).

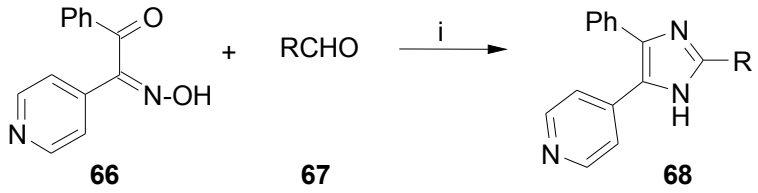


Scheme 18. Reaction conditions**:** i) NH_4OAc, SiO_2 or Al_2O_3, MW.

Comb's approach (2004)[19]

Combs *et al.* synthesized 2,4,5-trisubstituted-imidazoles **68** from keto-oxime **66**, aldehyde **67** and ammonium acetate via cyclization to the *N*-hydroxyimidazole and an

unprecedented in situ thermal reduction of the N-O bond upon microwave irradiation at 200 ^{0}C for 20 min in the presence of catalytic amount of acetic acid (**Scheme 19**).

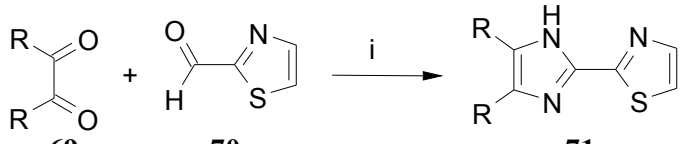


66 **67** **68**

Scheme 19. Reaction conditions: i) AcOH, 200 ^{0}C, MW, 20 min.

Bu's approach (2004)[20]

Bu *et al.* reported a new class of two-photon absorbing Y-shaped molecules possessing an imidazole–thiazole core **71** and a stilbene-type conjugation pathway with either nitro or sulfonyl as terminal electron-accepting group resulting from the condensation of 1,2-diketones **69** with sulphur containing heterocycles **70** in acetic acid as solvent with ammonium acetate as nitrogen source at 110 ^{0}C in good to moderate isolated yield (**Scheme 20**).

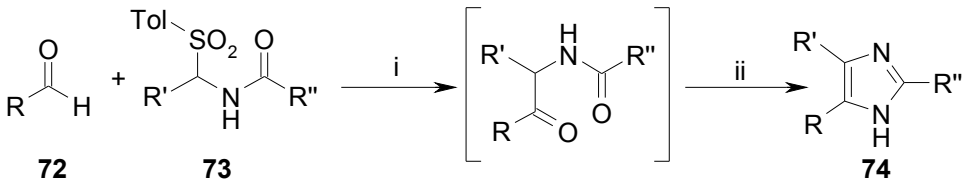


69 **70** **71**

Scheme 20. Reaction conditions: i) NH_4OAc**,** AcOH, 6 h, 55-80%.

Frantz's approach (2004)[21]

Frantz and co-workers described a methodology that allows the one-pot synthesis of substituted 2,4,5-triaryl-*1*H-imidazoles **74**. The cornerstone of this methodology is the thiazolium-catalyzed addition of an aryl aldehyde **72** to an acylimine **73** to generate the corresponding α-ketoamide and the subsequent addition of an appropriate amine, followed by ring closure to the imidizole derivative (**Scheme 21**).

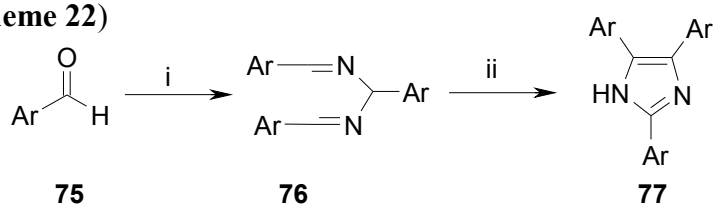


72 **73** **74**

Scheme 21. Reaction conditions: i) thiazolium organocatalyst 5 mol%, Et_3N, THF, 60 ^{0}C, ii) NH_4OAc**.**

Chou's approach (2004)[22]

2,4,5-triaryl-1H-imidazoles **77** were synthesized in 40–90% yield by heating the corresponding triaryl-2,4-diazapentadienes **76** with a stoichiometric amount of potassium *tert*-butoxide in DMSO in the presence of air or oxygen. Compounds **76** were synthesized by the condensation of the corresponding aryl aldehydes **75** with a solution of ammonia in ethanol (**Scheme 22**)

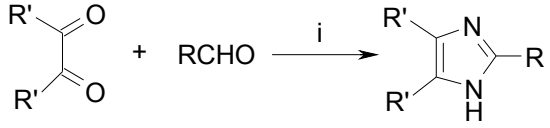


75 **76** **77**

Scheme 22. Reaction conditions: i) NH_3, EtOH, reflux; ii) *t*-BuOK, DMSO, O_2, 140 ^{0}C

Sharma's approach (2006)[23]

Author reported synthesis of 2,4,5-trisubstituted imidazoles in good yields using $ZrCl_4$ as a heterogeneous catalyst at room temperature in acetonitrile. A variety of aromatic, aliphatic, and terpenoidal aldehydes **79** underwent condensation with 1,2-diketones **78** and ammonium acetate to afford the 2,4,5-trisubstituted imidazoles **80** (**Scheme 23**).

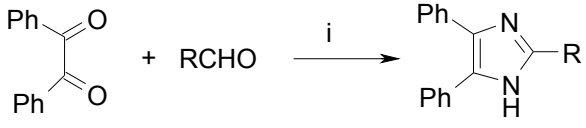


78 **79** **80**

Scheme 23. Reaction conditions: i) NH_4OAc, $ZrCl_4$, CH_3CN, rt, 0.75-10 h.

Heravi's approach (2007)[24]

Very recently author has reported, the synthesis of 2,4,5-triaryl-imidazoles **83** from benzil **81**, aldehydes **82** and ammonium acetate as a nitrogen source, in the presence of catalytic amount of $NiCl_2{\cdot}6H_2O$ supported onto acidic alumina in very good yields in the range 86-92% under heterogeneous catalytic conditions (**Scheme 24**).



81 **82** **83**

Scheme 24. Reaction conditions**:** i) NH_4OAc, $NiCl_2{\cdot}6H_2O$, EtOH, reflux, 25-120 min.

Several other methods involving the synthesis of various 2,4,5-trisubstituted imidzoles can be found in the literature.[25-35]

2.2.3 Present work

2.2.3.1 Objective

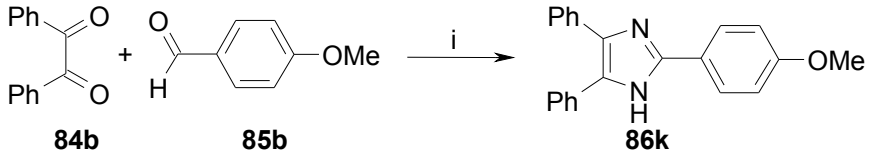
Even today, 148 years later, the importance of imidazoles in biological system (chemical and biochemical properties) and recent advances in green chemistry, organometallic chemistry, research in imidazole chemistry continues unabated. Moreover, many of the synthetic protocols for imidazoles reported so far suffer from several disadvantages such as i) harsh reaction conditions; ii) poor isolated yield; ii) prolonged time period; iv) use of hazardous and often expensive acid catalysts; v) formation of side products.

The development of a simple, efficient and general synthetic method for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. With the currently growing trend toward increased environmental responsibility, there is considerable incentive to find new catalytic systems that are efficient, recyclable and environmentally friendly. In recent years, room-temperature RTILs[12] have attracted growing interest because of their useful properties such as thermal stability, high ionic conductivity, negligible vapor pressure, tolerance towards air and moisture, low corrosive nature and a large electrochemical window. The present work describes the use of room temperature ILs as reaction media cum promoter for the synthesis of a variety of 2,4,5-trisubstituted imidzoles

2.2.3.2 Results and Discussion

In a model study, in the presence of IL[13] [Hbim]BF_4, the mixture of 1, 2-diphenyl-ethane-1, 2-dione (**84b**), *p*-methoxy benzaldehyde (**85b)** and ammonium acetate was heated at different temperatures i.e. rt, 40, 60, 80, and 90 ^{0}C. Even at 90 ^{0}C, the conversion does not go beyond 45 % even after 24 h. However when the temperature was raised to 100 ^{0}C, reaction was complete in 1 h, (progress of reaction monitored by TLC) wherein it was found that after 1 h all starting material had disappeared and showed a single product spot corresponding to (2-(4-methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole) **86k.** The pure product was isolated by column chromatography and fully characterized. From these results we found that, the heterocyclization reaction is facilitated by increasing the temperature and a reaction temperature of 100 ^{0}C was found to be optimum. At higher

temperature of 130 ^{0}C, no further decrease in reaction time period was observed and also at this higher temperature IL was found to give an unknown black material indicating its thermal instability at this temperature.



84b **85b** **86k**

Scheme 25. Reaction conditions: i) NH_4OAc, $[Hbim]BF_4$, 40-100 ^{0}C

The IR spectrum of **86k** showed absorption at 1565, 1638 and 3438 cm^{-1} corresponds to C=C, C=N, –NH respectively. The ^{1}H NMR spectrum of **86k** showed singlet of three protons at δ 3.85 corresponds to methoxy group, multiplet for ten protons in the region δ 7.25-7.59 for aromatic proton and 12.52 (brs, 1H) corresponds to –NH. The ^{13}C NMR spectrum showed peaks at δ 54.6 and 145.7 corresponding to methoxy carbon and C=N respectively, elemental data confirms with the structure of **86k** and corresponds to the known data (**Scheme 25**).

Thus, the present system is highly effective for synthesis of **86k**. But we had series of new ionic liquids based on 1,3-di-n-butyl imidazolium salts [bbim]X and *N*-butyl imidazolium salts [Hbim]X with varying basicity of anions.[36] So to find out the best ionic liquid we tested the different ionic liquids by carrying out the typical reaction of benzil with *p*-methoxy benzaldehyde **85b** in the absence of any added catalyst to afford 2-(4-methoxy-phenyl)-4,5-diphenyl-1*H*-imidazole (**86k**) (**Scheme 25**) at 100 ^{0}C for 24 h. The yield data are recorded in Table 5.

Table 5. Synthesis of imidazole **86k** in [bbim] and [Hbim]X

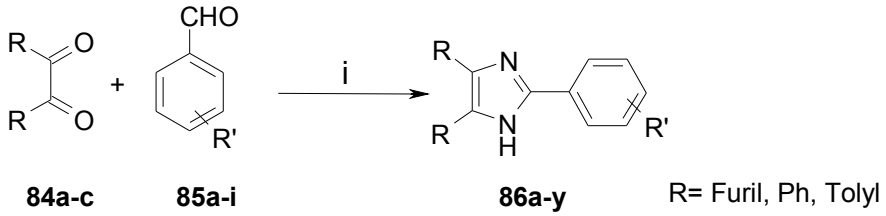
ILs	**pK$_a$** [a,]	***E*$_T$(30) (kcal mol^{-1})**	**Chemical shift -NH proton δ ppm**	**Yield** [b] **(%)**
[bbim]ClO_4	-11	76.34	--	21
[bbim]Br	-9	66.49	--	27
[bbim]Cl	-7	68.89	--	29
[bbim]BF_4	**0.5**	**75.73**	**--**	**43**
[Hbim]ClO_4	-11	63.82	11.83	61

[Hbim]Br	-9	73.68	12.17	81
[Hbim]Cl	-7	73.59	12.22	80
[Hbim]BF_4	0.5	74.35	14.59	95

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

The polarity of different ionic liquids based on 1,3-di-*n*-butyl imidazolium salts and 1-*n*-butyl imidazolium salts were evaluated using Reichardt's dye as per the reported procedure.[37] The pK_a values are those of the parent acid of the anions and taken from literature. From above results it was found that [Hbim]BF_4 is the most effective ionic liquid for heterocyclization reaction.

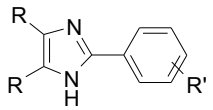
It becomes evident from these results, the IL [Hbim]BF_4 afforded the best results. Consequently, all further studies were conducted using this IL as the reaction medium and promoter to generate a variety of imidazoles **(86a-y)** by the reaction of 1,2-di-furan-2-yl-ethane-1,2-dione **(84a)**, 1,2-diphenyl-ethane-1,2-dione **(84b)** and 1,2-di-p-toluyl-ethane-1, 2-dione **(84c)** with aromatic aldehydes **(85a-i)** respectively in the presence of excess of ammonium acetate at 100 ^{0}C (**Scheme 26**).



Scheme 26. Reaction conditions: i) NH_4OAc, [Hbim]BF_4, 100 ^{0}C

The results are recorded in Table 6. All the reactions proceed to completion at the time indicated in the Table 6 and the yield data are for the isolated products after column chromatography. All the compounds were well characterized by melting point, IR, ^{1}H NMR and ^{13}C NMR. Their elemental analyses were in conformity with their structures. The 2,4,5-trisubstituted imidazoles have been obtained in excellent isolated yields in relatively short reaction times. It can be observed from the above results that heteroaromatic 1,2-diketones (furil) react faster to give substituted imidazole in excellent as isolated yields (entry 1-9) as compare to simple aromatic 1,2-diketones (entry 10-18) and substituted aromatic 1,2-diketones (entry 20-25). The electron donating group on diketones makes the reaction slightly sluggish, where as the process tolerates electron donating, halo substitution as well as electron withdrawing substituents on the aldehyde.

Table 6. Synthesis of imidazoles **86a-y** in $[Hbim]BF_4$ at 100 ^{0}C

Entry				Time (min.)	Yield [a] (%)
	R	R'	86a-y		
1	*o*-Furyl	H	86a	25	93
2	*o*- Furyl	*p*-OMe	86b	25	94
3	*o*- Furyl	*o*-OH	86c	35	92
4	*o*- Furyl	*p*-OH	86d	40	93
5	*o*- Furyl	*o*-Cl	86e	70	85
6	*o*- Furyl	*p*-Br	86f	65	92
7	*o*- Furyl	*o*-OH, *m*-OMe	86g	70	88
8	*o*- Furyl	*m*-OMe, *p*-OH	86h	75	85
9	*o*- Furyl	*p*-NO_2	86i	70	87
10	Phenyl	H	86j	60	95
11	Phenyl	*p*-OMe	86k	60	95
12	Phenyl	*o*-OH	86l	70	93
13	Phenyl	*p*-OH	86m	90	94
14	Phenyl	*o*-Cl	86n	70	96
15	Phenyl	*p*-Br	86o	65	95
16	Phenyl	*o*-OH, *m*-OMe	86p	60	95
17	Phenyl	*m*-OMe, *p*-OH	86q	70	87
18	Phenyl	*p*-NO_2	86r	60	94
19	*p*-Tolyl	H	86s	60	91
20	*p*-Tolyl	*p*-OMe	86t	60	88
21	*p*-Tolyl	*o*-OH	86u	70	90
22	*p*-Tolyl	*p*-OH	86v	100	93
23	*p*-Tolyl	*o*-Cl	86w	110	98
24	*p*-Tolyl	*p*-Br	86x	95	87
25	*p*-Tolyl	*o*-OH, *m*-OMe	86y	110	91

[a]: Isolated yield after column chromatography.

It is important to note that in all the cases, imidazoles were precipitated on dilution of the reaction mixtures with water and were isolated by a simple filtration. The dried product thus obtained showed a single spot on TLC and was pure enough for all practical purposes. The aqueous filtrate was then subjected to distillation at 80 ^{0}C under reduced pressure (10 mmHg) for 4 h to recover the IL almost completely. The IL, thus recovered could be reused three times without loss of activity for the typical reaction of **86k.**

To illustrate the efficacy of IL for synthesis of 2,4,5-trisubstuited imidazole (heterocyclization), a typical reaction of benzil **84b** with *p*-methoxy benzaldehyde **85b** was performed under identical conditions in different solvents such as ethanol, toluene, N,N-dimethyl formamide, dimethyl sulfoxide, sulfuric acid, polyphosphoric acid and acetic acid. The results are depicted in Table 7

Table 7. Synthesis of **86k** in different solvents

Entry	Solvent	Temperature (^{0}C)	Reaction Time (h)	Yield [a] (%)
1	Ethanol	75	24	Traces
2	DMF	100	24	10
3	DMSO	100	24	15
4	**Sulfuric acid**	**100**	**4**	**80**
5	PPA	100	4	75
6	**Acetic acid**	**110**	**6**	**80**
7	**[Hbim]BF_4**	**100**	**1**	**95**

[a]: Isolated yield after column chromatography

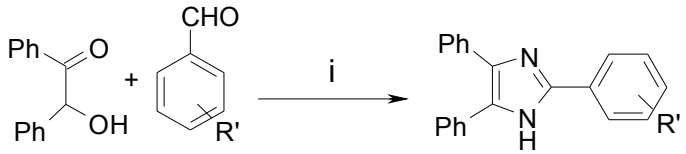
From the results of Table 7 it was observed that reaction in molecular solvents without any added catalyst are very sluggish and gave the corresponding products in the range of 10-15% isolated yield after prolonged reaction period (entry 1-3, Table 7). When reaction was performed in acids as solvent cum promoter, the reactions gave the desired imidazole in the very good isolated yields (entry 4-6, Table 7) after 4-6 h whereas [Hbim]BF_4 afforded the desired product in excellent yield (95%) just after 1 h. Thus these results highlight the role of IL in promoting the heterocyclization.

The efficacy of the ILs to promote these heterocyclization reactions was correlated to the basicity of the anions of the ILs as well as the polarity of ionic liquids. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (Table 5). This correlation was also evident when the yield of **86k** was compared with –NH proton chemical shifts of the ILs indicative of the Bronsted acidities of the [Hbim] ILs (Table 5). The yield of **86k** increases progressively not only with increasing Bronsted acidity of the ILs as indicated by the increasing downfield shift of the N***H*** proton but also with increasing polarity of these ILs as indicated by their E_T values.

The IL, $[Hbim]BF_4$ has promoted this heterocyclization reaction by virtue of its inherent Brønsted acidity conferred by the most acidic –N***H*** hydrogen [chemical shift δ ppm = 14.6].

Synthesis of 2,4,5-triaryl imidazoles from α-hydroxy ketone, benzoin

Although there are numerous literature available for the synthesis of trisubstituited imidazoles using 1,2-diketones, but very few reports found in the literature for the synthesis of trisubstituited imidazoles using α-hydroxyl–ketone as starting material.[18] In the literature reports where they are used there is an additional oxidation step to oxidize the imidazoline to imidazole. Under our condition we found that the reaction of benzoin with a variety of aromatic aldehyde gave 2,4,5-trisubstituited imidazoles in the absence of any added oxidizing agent (**Scheme 27**). The results are recorded in Table 7 (entry 10-18).



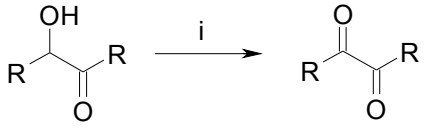
87 **85a-i** **86j-r**

Scheme 27. Reaction conditions: i) NH_4OAc, $[Hbim]BF_4$, 100 ^0C

As can be observed from Table 7, the process tolerates both electron donating and electron withdrawing substituents in the aromatic aldehyde however latter take marginally more time for completion of the reaction.

A probable mechanism as reported in literature where the procedures make use of an oxidizing agent for the formal oxidation of imidazoline to imdazole thereby introducing an additional oxidation step. In our case it was initially thought that the dissolved oxygen in the IL may have brought about the formal oxidation of the imidazoline to imidazole. However, this possibility was discounted by subjecting the IL to a degassing protocol using an ultrasonic cleaning bath (Transsonic Model T710DH) at 40 KHz in the degassing mode at a reduced pressure of 15 mmHg for 2 h. The degassed IL was well flushed with argon and the typical reaction of benzoin with benzaldehyde was performed in it using an inert atmosphere of argon. Even under such conditions, the triarylimidazole **86j** was obtained in excellent isolated yield (95%). It seems probable that apparently the fully conjugated nature of the product results in rapid oxidation in this case aided by the large electrochemical window and polarity of the IL. Alternatively, the probability of benzoin itself undergoing oxidation under these conditions to benzil was explored. Thus, a solution of benzoin in the degassed IL was heated at 100 ^{0}C for 1 h in an atmosphere of argon. To immense our surprise, benzoin was converted to benzil in 85% isolated yield. Alternatively, the probability that benzoin itself undergoes aerial oxidation to benzil under these conditions was explored. Thus, two sets of control reactions were carried out to confirm the aerial oxidation. To our surprise, benzoin was converted to benzil when heated with IL for 1 h whereas in absence of IL, only trace amounts of benzil were detected after 24 h. This shows that aerial oxidation of benzoin to benzil does not take place and it is in all probably the redox potential of the IL that has facilitated the transformation.

Further we explored this oxidation for different substrates as shown below in **Schemes 28 and 29**. The results are recorded in Table 9.

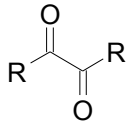


88a-d **89a-d**

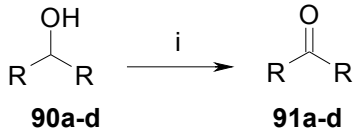
Scheme 28. Reaction conditions: i) [Hbim]BF_4, 100 ^{0}C

Strong electron donating substrate (entry 89c) takes more time to oxidize whereas hetroaromatic substrate (89d) easily oxidizes under identical condition.

Table 8. Oxidation of α-hydroxyl–ketone in $[Hbim]BF_4$ at 100 ^0C

Entry			Yield [a] (%)	Time (h)
	R	R		
89a	C_6H_5	C_6H_5	85	1
89b	*p*-MeC_6H_4	*p*-MeC_6H_4	90	1.5
89c	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	90	2
89d	Furil	Furil	90	1

[a]: Isolated yield after column chromatography



90a-d **91a-d**

Scheme 29. Reaction condition: i) $[Hbim]BF_4$, 100 ^0C

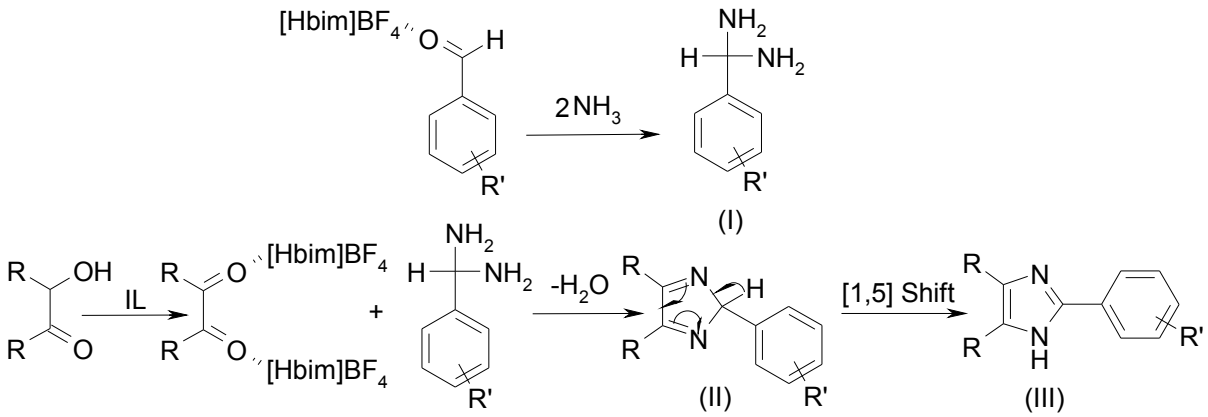
In order to broaden the scope of this observation, several hydroxy ketons were subjected to oxidation under identical conditions. The results are recorded in table 10. It was observed reaction takes more time to oxidize nitrogen containing hetero aromatic substrates (entry 91c) whereas aliphatic substrate (entry 91d) failed to undergo the oxidation which a limitation of this protocol. Based on the above observation, a plausible mechanism for this reaction may be as follows.

Table 9. Oxidation reaction in $[Hbim]BF_4$ at 100 ^0C

Entry			Yield [a] (%)	Time (h)
	R	R		
91a	C_6H_5	C_6H_5	90	2
91b	*p*-MeC_6H_4	*p*-MeC_6H_4	88	2.5
91c	C_6H_5	Pyridine	85	6
91d	**C_6H_5**	**H**	**No reaction**	**24**

[a]: Isolated yield after column chromatography

2.2.4 Plausible mechanism for the formation of 2,4,5-trisubstituted imidazole



Scheme 30. Plausible mechanism for the formation of 2,4,5-trisubstituted imidazole

Ionic liquid is capable of binding with the carbonyl oxygen of aldehyde, increasing the reactivity of the parent carbonyl compound. IL facilitates the formation of a diamine intermediate I, which under acidic IL condenses further with the carbonyl carbons of the 1,2-diketone followed by dehydration to afford the imino (iso-imidazole) intermediate II, which being thermodynamically unstable, rearranges *via* [1,5] sigmatropic shift to the thermodynamically stable 2,4,5-trisubstituted imidazole III.

2.2.5 Conclusion

In conclusion, we have developed a mild, convenient and efficient protocol for the synthesis of a library of biologically active 2,4,5-trisubstituted imidazoles via the condensation of 1,2-diketones and α-hydroxy ketones such as benzoin with aromatic aldehydes and ammonium acetate using a room temperature ionic liquid as a recyclable medium cum promoter. The process gives rise to excellent isolated yields of 2,4,5-trisubstituted imidazoles in short reaction times (25-120 min). The corresponding reactions in molecular solvents under similar conditions in the absence of a catalyst are sluggish and poor yielding, highlighting the role of the IL in promoting this novel one-pot methodology. The simple experimental procedure, isolation procedure, efficient recovery, and recycling of IL makes this an environmentally benign methodology amenable for scale up. The synthesized imidazoles are being tested for their anti-fungal and anti-bacterial properties. This work already peer reviewed and published in *Tetrahedron* **2005,** *61,* 3539.

2.2.6 Experimental

General procedure for synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketones:

A mixture of 1,2-diketones **84a**, **84b** or **84c** (4 mmol), substituted aldehydes **85a-i**, (4 mmol), ammonium acetate (24 mmol) and [Hbim]BF_4 (4 mmol) was heated at 100 ^{0}C with good stirring for the appropriate time mentioned in Table 6. After completion of reaction (progress of reaction was monitored by TLC), the reaction mixture was diluted with water. The solid imidazole products, which separated out, were filtered and dried under reduced pressure. The crude products, thus isolated, were pure enough (single spot on TLC). They were subjected to further purification by column chromatography using 25% EtOAc in petroleum ether as eluent to yield the desired 2,4,5-trisubstituted imidazoles in excellent yield and were fully characterized in the form of IR, ^{1}H, ^{13}C-NMR spectral and elemental analyses and mass spectroscopy.

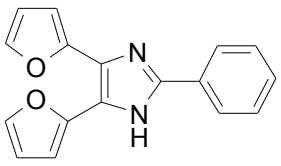
The aqueous layer consisting of the IL was subjected to distillation (80 ^{0}C at 10mmHg) for 4 h to remove water, leaving behind the IL [Hbim]BF_4 (recovery 98%), which was recycled without incurring loss in yield.

General procedure for synthesis of 1,2- diketone form α-hydroxyl–ketone in *[Hbim]BF_4*

α-hydroxyl–ketone (1 mmol) and [Hbim]BF_4 (2 mmol) was heated at 100 ^{0}C with good stirring for the appropriate time mentioned in Table 10. After completion of reaction (progress of reaction was monitored by TLC), the reaction mixture was diluted with water (10 ml). The solid 1,2-diketone products, which separated out, were filtered and dried under reduced pressure. The crude products, thus isolated, were pure (single spot on TLC).

2.2.6.1 Characterization data for compounds 86a-y

4,5-Difuran-2-yl-2-phenyl-1H-imidazole (86a)



Yellow solid

M. P. (°C) : 218-219

IR (Nujol, cm^{-1}) **:** υ_{max} 718, 890, 965, 1042, 1234, 1448, 1560, 1602, 3058, 3420.

^{1}H NMR **:** δ 6.13-6.18 (d, *J*= 7.5 Hz, 2H), 6.85-6.89 (d, *J*= 8.0 Hz, 2H),

(200 MHz, $CDCl_3$/ DMSO-d_6) 7.18 (s, 2H), 7.22-7.48 (m, 5H), 12.42 (brs, 1H).

^{13}C NMR **:** δ 106.9, 110.7, 123.9, 125.6, 127.7, 127.9, 128.9, 140.2, 146.1,

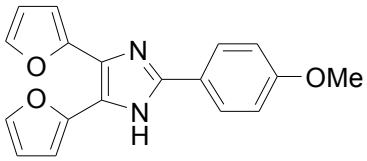
(50 MHz,$CDCl_3$/ DMSO-d_6) 146.3.

LC-MS **:** 277.29 (M+H), 254.12, 212.08, 189.19.

Elemental Analysis **: $C_{17}H_{12}N_2O_2$** Calcd. C, 73.91; H, 4.34; N, 10.14.

Found C, 73.62; H, 4.01; N, 9.82.

4,5-Difuran-2-yl-2(4-methoxy-phenyl-1H-imidazole (86b)



Yellow solid

M. P. (°C) **:** 198-199

IR (Nujol, cm^{-1}) **:** υ_{max} 635, 708, 880, 1050, 1230, 1508, 1570, 1610, 3105, 3419.

.**^{1}H NMR** **:** δ 3.75 (s, 3H), 6.14-6.19 (d, *J*= 8.0 Hz, 2H), 6.83-6.86

(200 MHz, (d, *J*= 8.5 Hz, 2H), 7.16 (s, 2H), 7.41 (d, *J*= 8.0 Hz, 2H),

$CDCl_3$/ DMSO-d_6) 7.79-7.82 (d, *J*= 8.0 Hz, 2H), 12.53 (brs, 1H).

^{13}C NMR **:** δ 55.2, 107.3, 111.6, 114.1, 121.9, 127, 141.2, 146.4, 147,

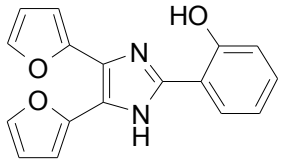
(50 MHz, $CDCl_3$/ DMSO-d_6) 160.3.

LC-MS **:** 307.10 (M+H), 289.12, 285.14, 218.09, 195.12.

Elemental Analysis **: $C_{18}H_{14}N_2O_3$** Calcd. C, 70.58; H, 4.61; N, 9.15.

Found C, 70.22; H, 4.32; N, 9.02.

2-(4,5-difuran-2-yl-1H-imidazole-2yl)-phenol (86c)



Pale yellow solid

M. P. (°C) : 235-236

IR (Nujol, cm^{-1}) : υ_{max} 718, 870, 965, 1120, 1210, 1416, 1570, 1615, 3108, 3428.

^{1}H NMR **:** δ 6.13-6.16 (d, *J*= 7 Hz, 2H), 6.18-6.23 (d, *J*= 8.3 Hz, 2H),

(200 MHz,$CDCl_3$/ DMSO-d_6) 6.85-7.15 (m, 4H) 7.16 (s, 2H), 12.38 (brs, 1H).

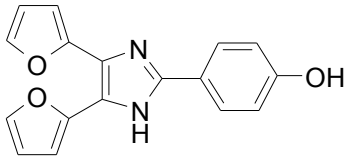
^{13}C NMR **:** δ 115.3, 121.6, 122.8, 124.5, 126.8, 127.3, 130.1, 135.1, 146.5.

(50 MHz,$CDCl_3$/ DMSO-d_6)

Elemental Analysis **: $C_{17}H_{12}N_2O_3$** Calcd. C, 69.86; H, 4.10; N, 9.58.

Found C, 69.38; H, 3.82; N, 9.13.

4-(4,5-difuran-2-yl-1H-imidazole-2yl)-phenol (86d)



Yellow solid

M. P. (°C) : 223-224

IR (Nujol, cm^{-1}) : υ_{max} 715, 860, 965, 1238, 1416, 1560, 1615, 3108, 3310, 3450.

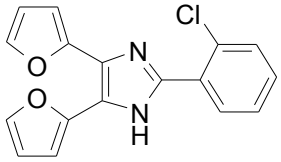
^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) : δ 6.14-6.18 (d, *J*= 8.0 Hz, 2H), 6.49-6.61 (d, *J*= 7.5 Hz, 2H) 6.85-6.89 (d, *J*= 7.0 Hz, 2H), 7.16 (s, 2H), 7.23-7.28 (d, *J*= 8.0 Hz, 2H), 12.41 (brs, 1H)

^{13}C NMR (50 MHz,$CDCl_3$/ DMSO-d_6) : δ 116.3, 121.6, 12.4, 130.1, 134.9, 146.4.

LC-MS : 293.29 (M+H), 278.13, 245.09, 188.08.

Elemental Analysis : **$C_{17}H_{12}N_2O_3$** Calcd. C, 69.86; H, 4.10; N, 9.58.
Found C, 69.48; H, 3.79; N, 9.13.

2-(2-chloro-phenyl) 4,5-difuran-1H-imidazole (86e)



Bright yellow solid

M. P. (°C) : 240-241

IR (Nujol, cm^{-1}) : υ_{max} 716, 865, 930, 1055, 1148, 1275,1420, 1570, 1618, 3416.

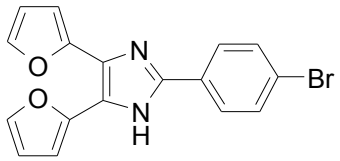
^{1}H NMR (200 MHz,$CDCl_3$/ DMSO-d_6) : δ 6.31-6.39 (d, *J*= 7.0 Hz, 4H), 7.31-7.40 (d, *J*= 7.0 Hz, 2H) 7.16-7.42 (m, 4H) 12.58 (brs, 1H).

^{13}C NMR (50 MHz,$CDCl_3$/ DMSO-d_6) : δ 105, 111.6, 122.1, 127.1, 128.1, 129.4, 129.9, 132.1, 135.5, 136.4, 142.2, 154.2.

LC-MS : 312.05 (M+H), 302.10, 258.12, 233.09.

Elemental Analysis : **$C_{17}H_{11}N_2O_2Cl$** Calcd. C, 65.59; H, 3.53; N, 9.00
Found C, 65.28; H, 3.29; N, 8.63.

2-(4-bromo-phenyl) 4,5-difuran-1H-imidazole (86f)



Yellow solid

M. P. (°C) : 228-229

IR (Nujol, cm^{-1}) : υ_{max} 708, 840, 945, 1060, 1248, 1416, 1580, 1608, 3108, 3385.

^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) : δ 6.28-6.33 (m, 4H), 7.3-7.4 (d, *J*= 7.0 Hz, 2H), 7.54-7.58 (d, *J*= 8.2 Hz, 2H), 8.02-8.06 (d, *J*= 8.6 Hz, 2H), 12.78 (brs, 1H).

^{13}C NMR **:** δ 105.8, 1161.6, 122.1, 127.1, 128.4, 129.4, 129.9, 132.1,

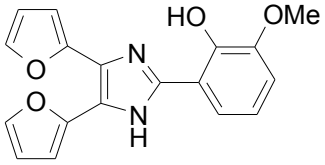
(50 MHz,$CDCl_3$/ DMSO-d_6) 135.5, 136.4, 142.2, 154.2.

LC-MS **:** 356.19 (M+H), 345.12, 312.08, 258.07.

Elemental Analysis **: $C_{17}H_{11}N_2O_2Br$** Calcd. C, 57.46; H, 3.09; N, 7.88.

Found, C, 57.12; H, 2.69; N, 7.53.

2-(4, 5-difuran-1H-imidazol-2-yl)-6-methoxy phenol (86g)



Yellow solid

M. P. (°C) **:** 238-239

IR (Nujol, cm^{-1}) **:** υ_{max} 715, 864, 910, 1210, 1416, 1575, 1610, 3130, 3420, 3600.

^{1}H NMR **:** δ 3.65 (s, 3H), 6.30-6.33 (m, 4H), 7.31-7.40 (m, 2H),

(200 MHz,$CDCl_3$/ DMSO-d_6) 7.55-7.58 (m, 3H), 12.71 (brs, 1H).

^{13}C NMR **:** δ 105.2, 111.6, 115.5, 120.2, 122.6, 124.2, 127.1, 140.1, 152.3,

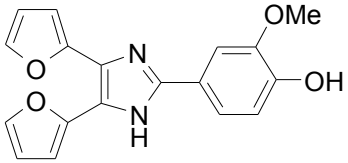
(50 MHz,$CDCl_3$/ DMSO-d_6) 156.2.

LC-MS **:** 323.10 (M+H), 302.19, 279.15, 245.18.

Elemental Analysis **: $C_{18}H_{14}N_2O_4$** Calcd. C, 67.08; H, 4.34; N, 8.69.

Found C, 66.68; H, 4.09; N, 8.32.

2-(4, 5-difuran-1H-imidazol-2-yl)-2-methoxy phenol (86h)



Bright yellow solid

M. P. (°C) **:** 225-226

IR (Nujol, cm^{-1}) : υ_{max} 715, 864, 930, 1155, 1240, 1416, 1585, 1610, 3360, 3600.

^{1}H NMR **:** δ 3.87 (s, 3H), 6.47-6.49 (d, *J*= 5.0 Hz, 2H), 7.30-7.40

(200 MHz,$CDCl_3$/ DMSO-d_6) (d, *J*= 7.0 Hz, 2H), 7.55-7.58 (m, 3H), 12.72 (brs, 1H).

^{13}C NMR **:** δ 105, 111.6, 115.5, 120.2, 122.6, 124.2, 127.1, 140.1, 152,

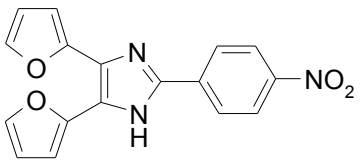
(50 MHz,$CDCl_3$/ DMSO-d_6) 156.

LC-MS **:** 323.08 (M+H), 298.18, 248.12, 215.09.

Elemental Analysis **: $C_{18}H_{14}N_2O_4$** Calcd. C, 67.08; H, 4.34; N, 8.69.

Found C, 66.28; H, 4.02; N, 8.32.

2- (4-nitro-phenyl) 4,5-difuran-1H-imidazole (86i)



Dark yellow solid

M. P. (°C) **:** 208-209 (decomposes).

IR (Nujol, cm^{-1}) : υ_{max} 718, 865, 930, 1165, 1258, 1408, 1565, 1605, 3120, 3410.

^{1}H NMR : δ 6.29-6.33 (m, 4H), 7.31-7.40 (d, *J*= 7.0 Hz, 2H), 7.78-7.79 (d,

(200 MHz, $CDCl_3$/ DMSO-d_6) *J*=9.0 Hz, 2H), 8.51-853 (d, *J*=9.0 Hz, 2H), 12.69 (brs, 1H).

^{13}C NMR : δ 105.3, 111.6, 122.3, 124.1, 127.9, 136.3, 142.3, 142.6,

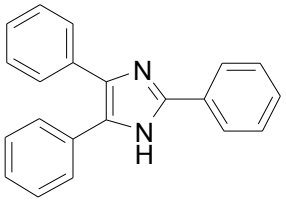
(50 MHz,$CDCl_3$/ DMSO-d_6) 148.4,154.4.

LC-MS : 322.08 (M+H), 308.15, 289.17.

Elemental Analysis : **$C_{17}H_{11}N_3O_4$** Calcd. C, 63.55; H, 3.42; N, 13.08.

Found C, 63.23; H, 3.28; N, 12.78.

2,4,5-triphenyl-1H-imidazole (86j)



Yellow solid

M. P. (°C) : 269-270

IR (Nujol, cm^{-1}) : υ_{max} 1216, 1580, 1638, 2470, 2993, 3434.

^{1}H NMR (200 MHz,$CDCl_3$/ DMSO-d_6): δ 7.42-8.12 (m, 15H), 12.61 (brs, 1H).

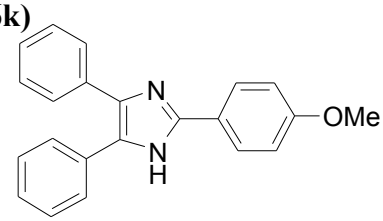
^{13}C NMR (50 MHz,$CDCl_3$/ DMSO-d_6) : δ 122.1, 127.2, 128.5, 129.1, 136.5.

LC-MS : 297.13 (M+H), 268.08, 245.12.

Elemental Analysis : **$C_{21}H_{16}N_2$** Calcd. C, 85.11; H, 5.44; N, 9.45.

Found C, 84.92; H, 5.28; N, 9.22.

2-(4-methoxy-phenyl)-4,5-diphenyl-1H-imidazole (86k)



Pale yellow solid

M. P. (°C) : 222-223

IR (Nujol, cm^{-1}) : υ_{max} 764, 829, 968, 1070, 1216, 1565,1636, 2465, 2893, 3428.

^{1}H NMR : δ 3.85 (s, 3H), 6.93-6.96 (d, *J*= 8.8 Hz, 2H), 7.25-7.59

(200 MHz,$CDCl_3$/ DMSO-d_6) (m, 10H), 8.02-8.05 (d, *J*= 8.8 Hz, 2H), 12.52 (brs, 1H).

^{13}C NMR : δ 54.6, 113.2, 122.7, 126.3, 126.5, 127.4, 127.6, 132.8, 145.7,

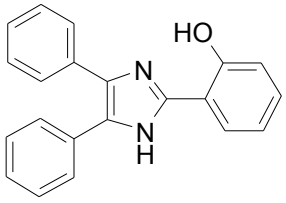
(50 MHz,$CDCl_3$/ DMSO-d_6) 159.1.

LC-MS : 327.15 (M+H), 314.10, 298.07, 233.05.

Elemental Analysis : **$C_{22}H_{18}N_2O$** Calcd. C, 80.96; H, 5.56; N, 8.58.

Found C, 80.75; H, 5.38; N, 8.23.

2-(4,5-diphenyl-1H-imidazol-2-yl)-phenol (86l)



Yellow solid

M. P. (°C) **:** 205-206

IR (Nujol, cm^{-1}) **:** υ_{max} 765, 830, 996, 1216, 1570, 1638, 2465, 2998, 3432, 3596

^{1}H NMR **:** δ 6.87-6.95 (d, *J*= 7.5 Hz, 2H), 6.97-7.01 (d, *J*= 8.1 Hz, 2H),

(200 MHz,$CDCl_3$/ DMSO-*d_6*) 7.17-7.23 (m, 10H), 12.74 (brs, 1H).

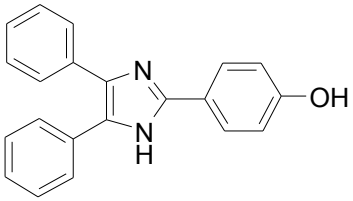
^{13}C NMR **:** δ 112.7, 116.4, 118.1, 124.8, 126.8, 127.4, 127.8, 129.1, 145.7,

(50 MHz,$CDCl_3$/ DMSO-*d_6*) 156.6.

Elemental Analysis **: $C_{21}H_{16}N_2O$** Calcd. C, 80.75; H, 5.16; N, 8.97.

Found C, 80.57; H, 4.88; N, 8.75.

4-(4,5-diphenyl-1H-imidazol-2-yl)-phenol (86m)



Yellow solid

M. P. (°C) **:** 233-234

IR (Nujol, cm^{-1}) **:** υ_{max} 758, 822, 915, 1216, 1570, 1638, 2465, 2998, 3432, 3596.

^{1}H NMR **:** δ 6.93-6.97 (d, *J*= 8.0 Hz, 2H), 7.52-7.87 (m, 10H), 7.88-7.92

(200 MHz,$CDCl_3$/ DMSO-*d_6*) (d, *J*= 8.5 Hz, 2H), 12.58 (brs, 1H).

^{13}C NMR **:** δ 113.7, 119.9, 125.1, 125.3, 126.1, 126.5, 144.7, 159.2.

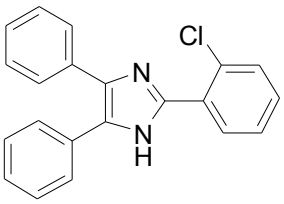
(50 MHz,$CDCl_3$/ DMSO-*d_6*)

LC-MS **:** 313.14 (M+H), 299.12, 285.14.

Elemental Analysis **: $C_{21}H_{16}N_2O$** Calcd. C, 80.75; H, 5.16; N, 8.97.

Found C, 80.68; H, 4.95; N, 8.88.

2-(2- chloro-phenyl)-4,5-diphenyl-1H-imidazole (86n)



Yellow solid

M. P. (°C) **:**188-189

IR (Nujol, cm^{-1}) **:** υ_{max} 1216, 1565,1638, 2470, 2993, 3434

^{1}H NMR **:** δ 7.27-7.37 (m, 10H), 7.45-7.49 (d, *J*= 9.0 Hz, 1H), 7.57-7.59

(200 MHz, (d, *J*= 8.0 Hz, 2H), 8.02-8.05 (d, *J*= 8.7 Hz, 1H),

$CDCl_3$/ DMSO-*d_6*) 12.50 (brs, 1H).

^{13}C NMR **:** δ 125.4, 125.6, 126.5, 126.9, 127.2, 128.4, 128.6, 128.8, 129.6,

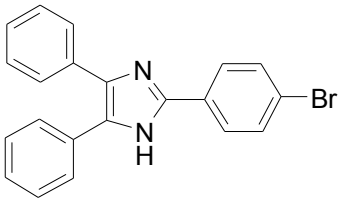
(50 MHz,$CDCl_3$/ DMSO-d_6) 130.1, 130.5, 142.2.

LC-MS **:** 332.09 (M+H), 308.12, 289.14, 267.09.

Elemental Analysis **: $C_{21}H_{15}ClN_2$** Calcd. C, 76.24; H, 4.57; N, 8.47.

Found C, 75.94; H, 4.39; N, 8.22.

2-(4-bromo-phenyl)-4,5-diphenyl-1H-imidazole (86o)



Yellow solid

M. P. (°C) **:** 248-249

IR (Nujol, cm^{-1}) **:** υ_{max} 1261, 1570, 1645, 2255, 2473, 3417.

^{1}H NMR **:** δ 7.25-7.48 (m, 10H), 7.50-7.52 (d, *J*= 8.0 Hz, 2H), 7.80-7.92

(200 MHz,$CDCl_3$/ $DMSOD_6$) (d, *J*= 8.6 Hz, 2H), 12.49 (brs, 1H).

^{13}C NMR **:** δ 120.1, 125.5, 126.3, 126.7, 127.1, 128.1, 129.5, 130.5, 143.3.

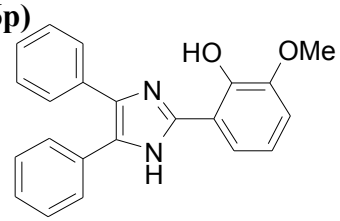
(50 MHz,$CDCl_3$/ $DMSOD_6$)

LC-MS **:** 376.17 (M+H), 358.09, 323.05, 298.15.

Elemental Analysis **: $C_{21}H_{15}BrN_2$** Calcd. C, 67.21; H, 4.03; N, 7.47.

Found C, 66.98; H, 3.85; N, 7.32.

2-(4,5-diphenyl-1H-imidazol-2-yl)-6-meyhoxy phenol (86p)



Yellow solid

M. P. (°C) **:** 170-171

IR (Nujol, cm^{-1}) **:** υ_{max} 770, 825, 996, 1048, 1565, 1654, 2925, 3412.

^{1}H NMR **:** δ 3.86 (s, 3H), 6.82-6.85 (m, 3H), 7.29-7.32 (m, 5H),

(200 MHz,$CDCl_3$/ DMSO-d_6) 7.53-7.55 (m, 5H), 12.50 (brs, 1H).

^{13}C NMR **:** δ 54.7, 110.9, 112.1, 115.6, 117.1 121.1, 126.2, 127.3, 127.4,

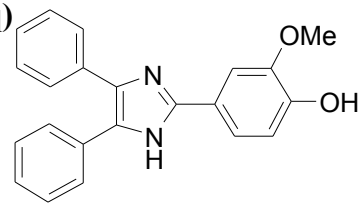
(50 MHz,$CDCl_3$/ DMSO-d_6) 129.8, 145.1, 146.1, 147.3.

LC-MS **:** 343.14 (M+H), 332.12, 302.09, 278.09.

Elemental Analysis **: $C_{22}H_{18}N_2O_2$** Calcd C, 77.17; H, 5.30; N, 8.18.

Found C, 76.93; H, 4.91; N, 7.92.

2-(4,5-diphenyl-1H-imidazol-2-yl)-2-meyhoxy phenol (86q)



Yellow solid

M. P. (°C) **:** 197-198

IR (Nujol, cm^{-1}) **:** υ_{max} 763, 1230, 1410, 1570, 1605, 2854, 2924, 3380, 3512.

^{1}H NMR **:** δ 3.80 (s, 3H), 6.75-6.69 (d, *J*= 8.2 Hz, 1H), 7.11-7.19

(200 MHz, 7.22-7.23 (d, *J*= 8.1 Hz, 1H), 7.40-7.45 (m, 5H),

$CDCl_3$/ DMSO-d_6) 7.55-7.56 (d, *J*= 8.0 Hz, 1H), 12.52 (brs, 1H).

^{13}C NMR **:** δ 55.1, 108.5, 114.6, 118.1, 121.1, 126.2, 127.3, 132.3, 146.3,

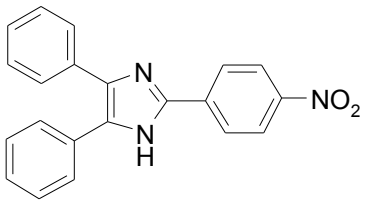
(50 MHz,$CDCl_3$/ DMSO-d_6) 146.8.

LC-MS **:** 343.08 (M+H), 312.19, 288.15.

Elemental Analysis **: $C_{22}H_{18}N_2O_2$** Calcd. C, 77.17; H, 5.30; N, 8.18.

Found C, 76.92; H, 4.91; N, 7.95.

2-(*p*-nitro-phenyl)-4,5-diphenyl-1H-imidazole (86r)



Dark yellow solid

M. P. (°C) **:** 196-197 (decomposes).

IR (Nujol, cm^{-1}) **:** υ_{max} 845, 1443,1522, 1540, 1570, 1602, 3056, 3425.

^{1}H NMR **:** δ 7.25-7.57 (m, 10H), 7.78 (d, *J*= 9.0 Hz, 2H), 8.50

(200 MHz,$CDCl_3$/ DMSO-d_6) (d, *J*= 9.0 Hz, 2H), 12.59 (brs, 1H).

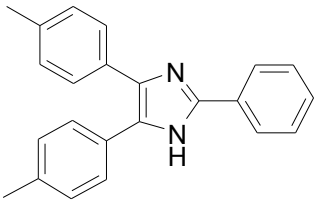
^{13}C NMR **:** δ 122.7, 124.2, 127.3, 132.8, 146.7, 160.8.

(50 MHz,$CDCl_3$/ DMSO-d_6)

Elemental Analysis **: $C_{21}H_{15}N_3O_2$** Calcd. C 73.88; H 4.43; N 12.31.

Found C 73.65; H 4.28; N 11.99.

2-phenyl-4, 5-di-*p*-tolyl-1H-imidazole (86s)



Yellow solid

M. P. ^{0}C **:** 254-255

IR (Nujol, cm^{-1}) **:** υ_{max} 629, 726, 878, 1216, 1570, 1638, 2465, 2998, 3432.

^{1}H NMR **:** δ 2.36 (s, 6H), 7.14-7.34 (m, 8H), 7.35-7.38 (m, 5H),

(200 MHz,$CDCl_3$/ DMSO-d_6) 12.56 (brs, 1H).

^{13}C NMR **:** δ 19.7, 124.1, 126.4, 127.1, 127.5, 127.7, 128.3, 129.1, 129.2,

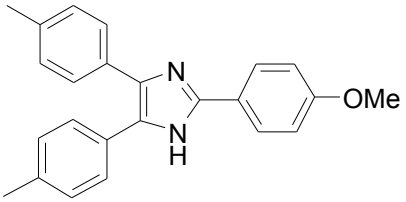
(50 MHz,$CDCl_3$/ DMSO-d_6) 135.1.

LC-MS **:** 325.17 (M+H), 302.15, 285.14.

Elemental Analysis **: $C_{23}H_{20}N_2$** Calcd. C, 85.15; H, 6.21; N, 8.63.

Found C, 84.92; H, 5.97; N, 8.51.

2-(4-methoxy-phenyl)-4,5-di-*p*-tolyl-1H-imidazole (86t)



Pale yellow solid

M. P. (°C) **:** 243-244

IR (Nujol, cm^{-1}) **:** υ_{max} 1216, 1560, 1638, 2475, 2988, 3430

^{1}H NMR **:** δ 2.37 (s, 6H), 3.86 (s, 3H), 6.94-6.96 (d, *J*= 8.2 Hz, 2H)

(200 MHz, 7.13-7.15 (m, 4H), 7.46-7.48 (m, 4H), 8.03-8.05

$CDCl_3$/ DMSO-d_6) (d, *J*= 8.2 Hz, 2H), 12.59 (brs, 1H).

^{13}C NMR **:** δ 20.2, 54.3, 112.9, 122.6, 126.1, 126.9, 128.1, 135.4, 145.1,

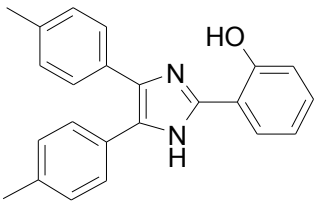
(50 MHz,$CDCl_3$/ DMSO-d_6) 158.6.

LC-MS **:** 355.18 (M+H), 329.12, 308.15, 289.09.

Elemental Analysis **: $C_{24}H_{22}N_2O$** Calcd. C, 81.33; H, 6.26; N, 7.90.

Found C, 80.91; H, 5.88; N, 7.58.

2-(4,5-di-*p*-tolyl-1H-imidazol-2-yl) phenol (86u)



Yellow solid

M. P. (°C) **:** 223

IR (Nujol, cm^{-1}) **:** υ_{max} 1216, 1555, 1638, 2465, 2998, 3432, 3596.

^{1}H NMR **:** δ 2.36 (s, 6H), 6.85-6.90 (t, *J*= 8.3 Hz, 1H), 6.95-6.98 (d,

(200 MHz, *J*= 8.0 Hz, 1H), 7.14-7.17 (m, 4H), 7.21-7.23(d, *J*= 7.3 Hz, 1H)

$CDCl_3$/ DMSO-d_6) 7.43-7.46 (m, 4H), 7.96-7.99 (d, *J*= 8.0 Hz, 1H), 12.84 (brs, 1H).

^{13}C NMR **:** δ 19.7, 114.2, 118.5, 126.1, 126.5, 126.8, 127.6, 127.7, 127.9,

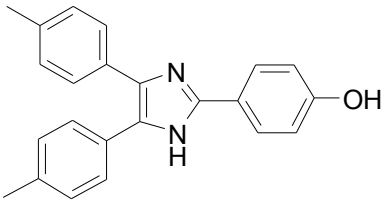
(50 MHz, $CDCl_3$/ DMSO-d_6) 127.9, 129.7, 135.5, 144.4, 157.2.

LC-MS **:** 341.16 (M+H), 312.09, 298.12, 248.05.

Elemental Analysis **: $C_{23}H_{20}N_2O$** Calcd C, 81.15; H, 5.92; N, 8.23.

Found C, 80.95; H, 5.71; N, 8.08.

4-(4,5-di-*p*-tolyl-1H-imidazol-2-yl) phenol (86v)



Yellow solid

M. P. (°C) **:** 218-219

IR (Nujol, cm^{-1}) **:** υ_{max} 1216, 1575, 1638, 2465, 2975, 3422, 3610.

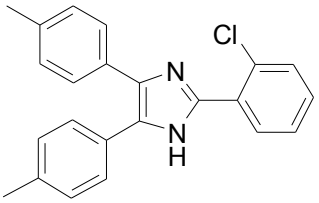
^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) **:** δ 2.38 (s, 6H), 6.88-6.92 (d, *J*= 8.6 Hz, 2H), 7.15-7.19 (m, 4H), 7.41-7.45 (m, 4H), 7.91-7.96 (d, *J*= 8.6 Hz, 2H), 12.77 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) **:** δ 19.7, 114.2, 118.5, 126.1, 126.5, 126.8, 127.6, 127.7, 127.9, 129.7, 135.5, 144.4, 157.2.

LC-MS **:** 341.16 (M+H), 322.12, 302.09, 288.12.

Elemental Analysis **:** **$C_{23}H_{20}N_2O$** Calcd C, 81.15, H, 5.92, N, 8.23.
Found C, 81.02, H, 5.85, N, 8.12.

2-(2-chlor-phenyl)-4,5-di-*p*-tolyl-1H-imidazole (86w)



Light yellow solid

M. P. (°C) **:** 195-196

IR (Nujol, cm^{-1}) **:** υ_{max} 1216, 1550, 1638, 2465, 2998, 3432

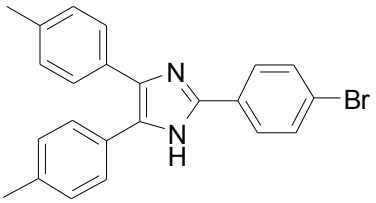
^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) **:** δ 2.39 (s, 6H), 7.27-7.37 (m, 8H), 7.45-7.49 (d, *J*= 9.0 Hz, 1H) 7.57-7.59 (m, 2H), 8.02-8.05 (d, *J*= 8.7 Hz, 1H), 12.54 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) **:** δ 19.6, 125.4, 125.6, 126.5, 126.9, 127.2, 128.4, 128.7, 128.8, 129.7, 130.1, 130.6, 130.6, 142.2.

LC-MS **:** 359.13 (M+H), 360.12, 305.19, 288.04.

Elemental Analysis **:** **$C_{23}H_{19}ClN_2$** Calcd. C, 76.98, H, 5.34, N, 7.81.
Found C, 76.72, H, 5.21, N, 7.72.

2-(4-bromo-phenyl)-4,5-di-*p*-tolyl-1H-imidazole (86x)



Yellow solid

M. P. (°C) **:** 215-216

IR (Nujol, cm^{-1}) **:** υ_{max} 665, 755, 935, 1115, 1216, 1560, 1638, 2465, 2978, 3432.

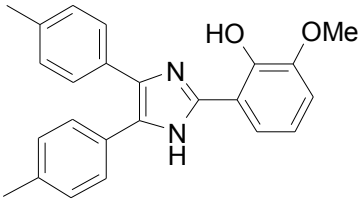
^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-d_6) : δ 2.35 (s, 6H), 7.11-7.15 (m, 4H), 7.42-7.46 (m, 4H), 7.54-7.58 (d, *J*= 8.2 Hz, 2H), 8.02-8.06 (d, *J*= 8.6 Hz, 2H), 12.78 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) : δ 19.4, 119.8, 125.4, 126.1, 127.3, 129.8, 134.7, 142.8.

LC-MS : 404.07 (M+H), 398.08, 378.12, 302.14.

Elemental Analysis : **$C_{23}H_{19}BrN_2$** Calcd. C, 68.49; H, 4.75; N, 6.95.
Found C, 68.32; H, 4.68; N, 6.82.

2-(4,5-di-*p*-tolyl-1H-imidazol-2-yl)-6-methoxy-phenol (86y)



Yellow solid

M. P. (°C) : 230-231

IR (Nujol, cm^{-1}) : υ_{max} 660, 758, 960, 1216, 1565, 1638, 2475, 2978, 3442, 3616.

^{1}H NMR (200 MHz,$CDCl_3$/ DMSO-d_6) : δ 2.36 (s, 6H), 3.79 (s, 3H), 6.82-6.85 (m, 3H), 7.31-7.34 (m, 4H), 7.55-7.58 (m, 4H), 12.71 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-d_6) : δ 19.4, 54.7, 110.9, 112.1, 115.6, 117.1, 126.3, 126.7, 127.3, 127.5, 132.3, 146.4, 146.9.

LC-MS : 371.17 (M+H), 355.12, 318.09, 289.14.

Elemental Analysis : **$C_{24}H_{22}N_2O_2$** Calcd. C, 77.81; H, 5.99; N, 7.56.
Found C, 77.78; H, 5.87; N, 7.47.

2.2.6.2 Spectra's of some selected compounds

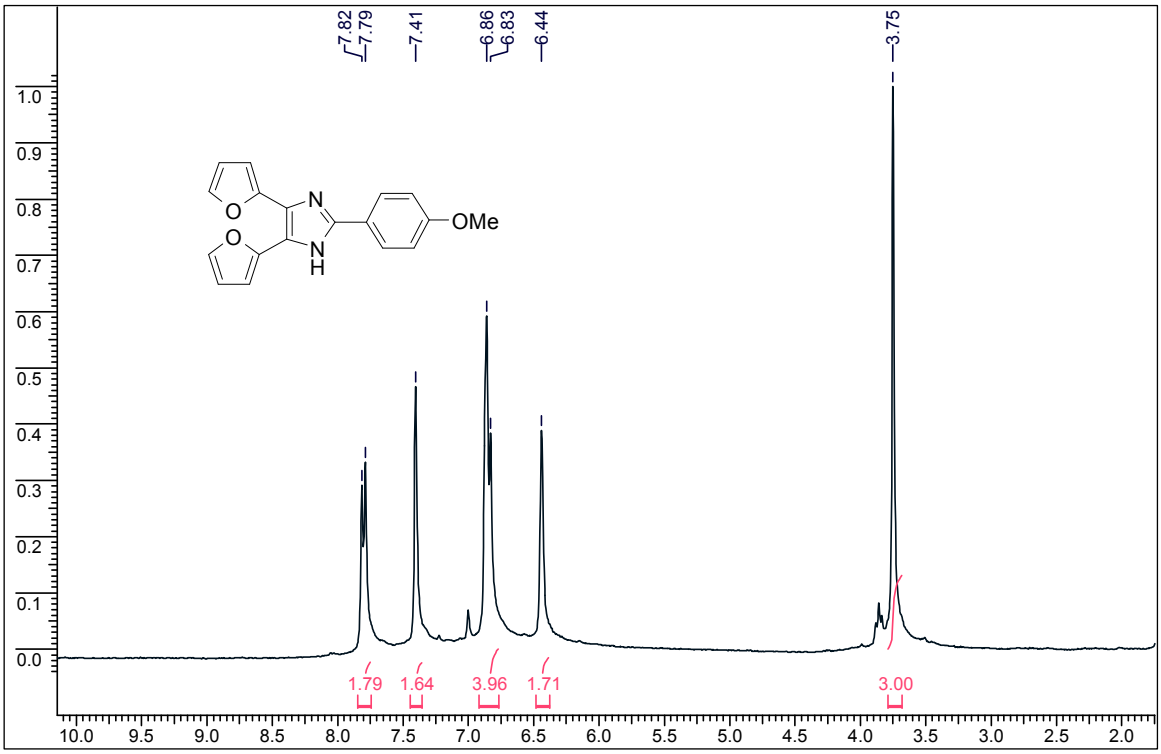
[1] ^{1}H NMR and ^{13}C NMR spectra of **86b**

[2] ^{1}H NMR and ^{13}C NMR spectra of **86k**

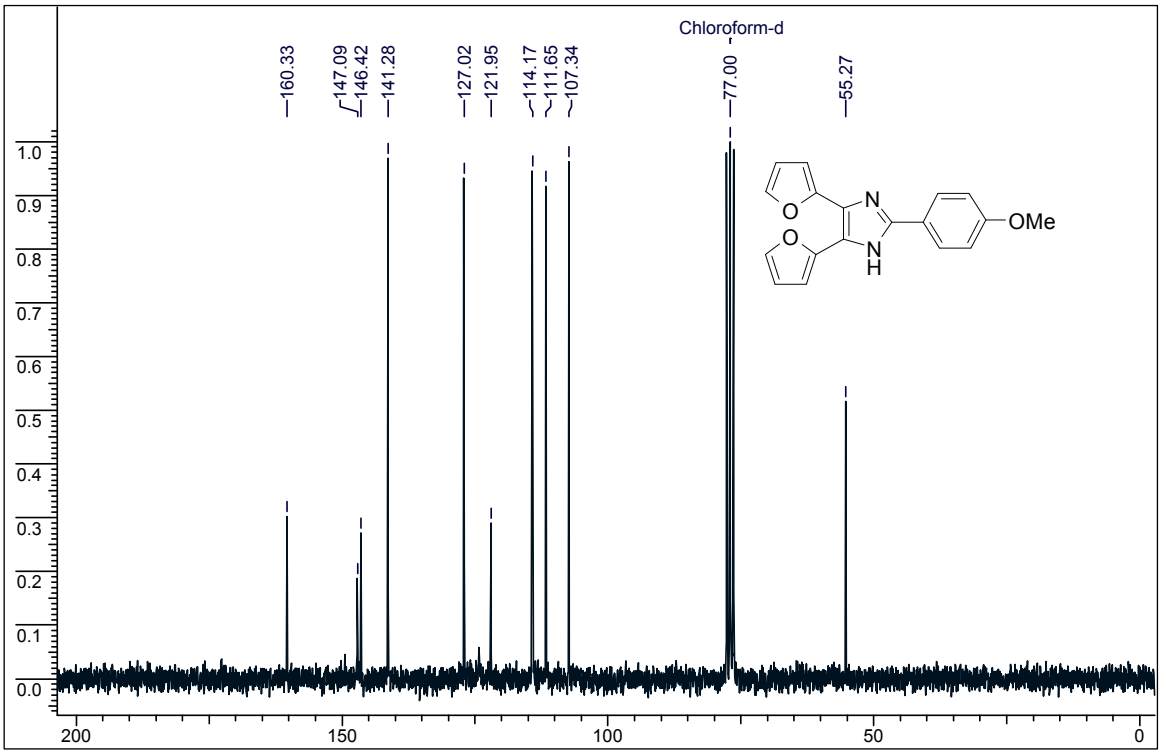
[3] ^{1}H NMR and ^{13}C NMR spectra of **86p**

[4] ^{1}H NMR and ^{13}C NMR spectra of **86t**

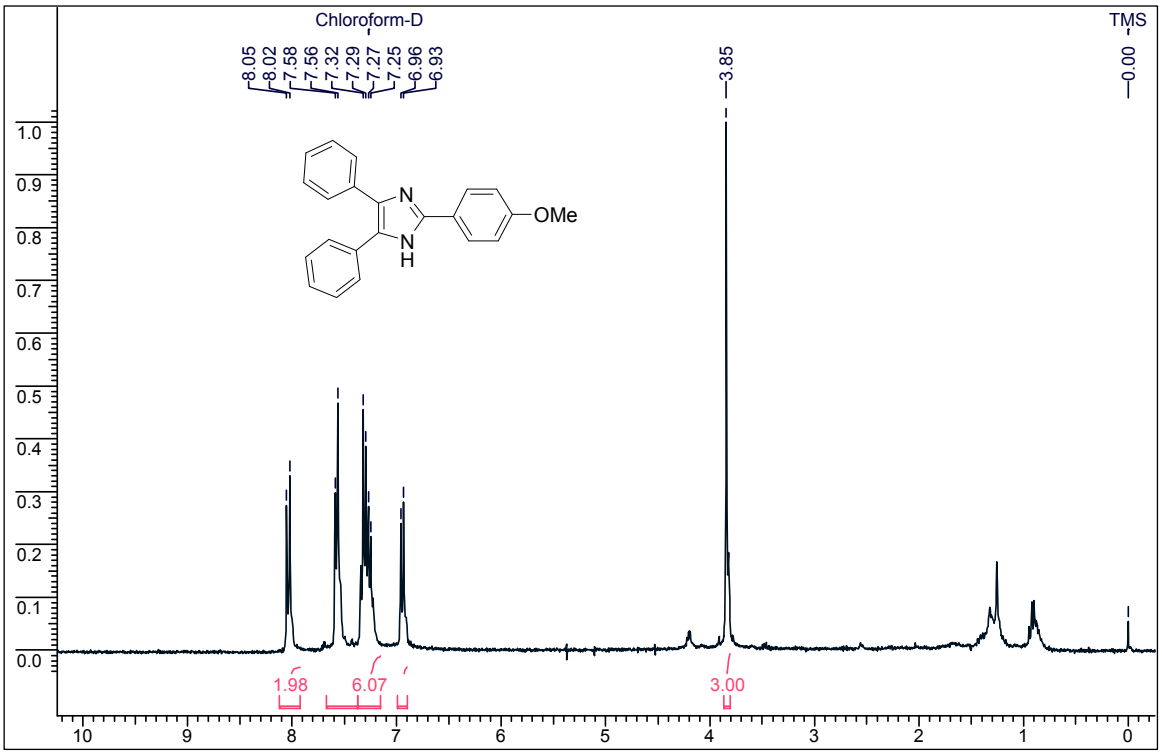
[1] ^{1}H NMR spectra of 86b



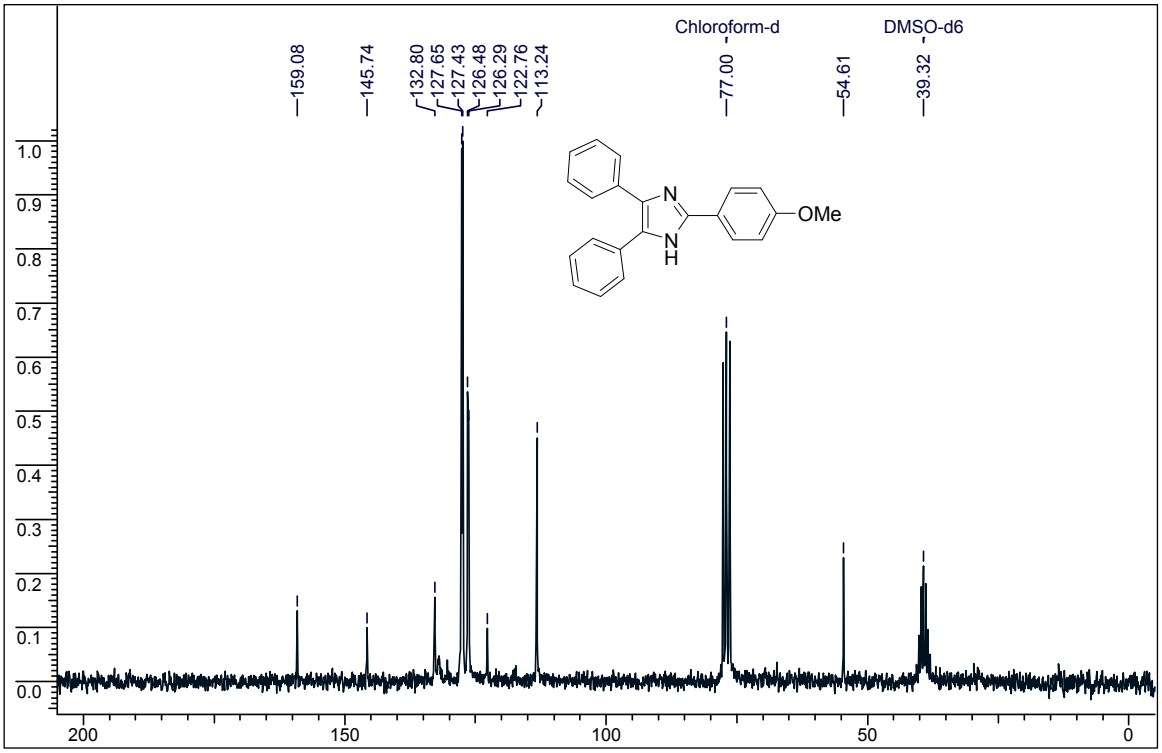
[1] ^{13}C NMR spectra of 86b



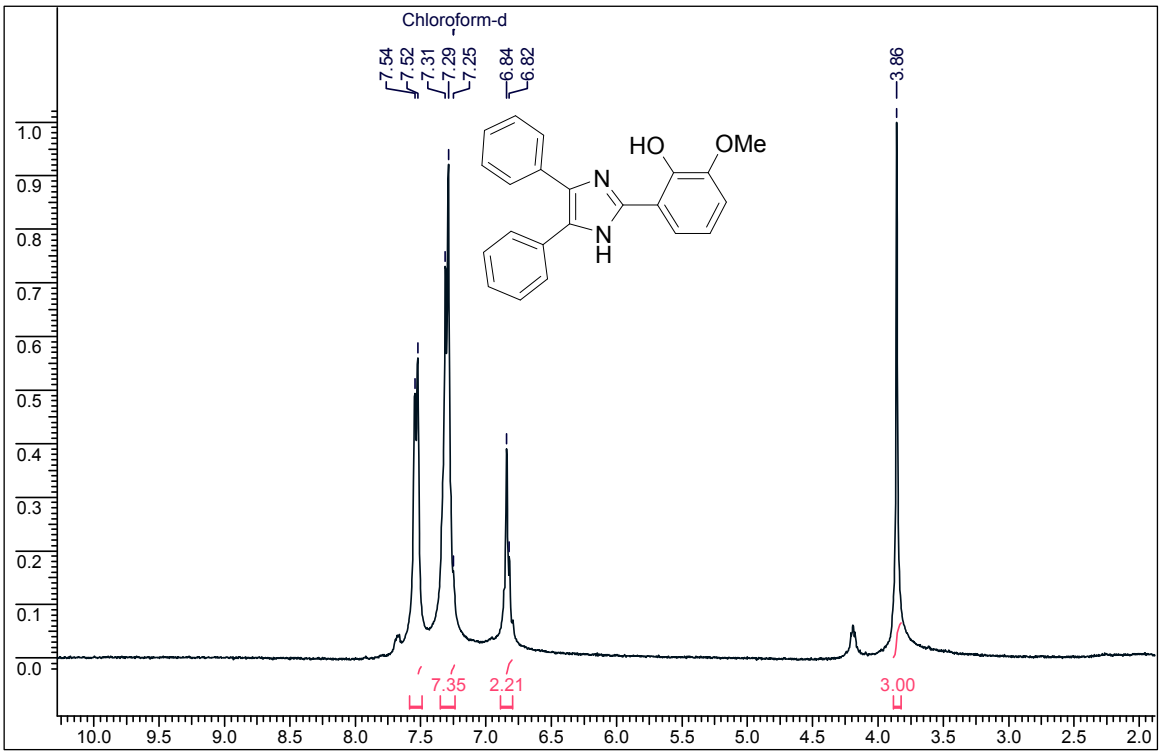
[2] ^{1}H NMR spectra of 86k



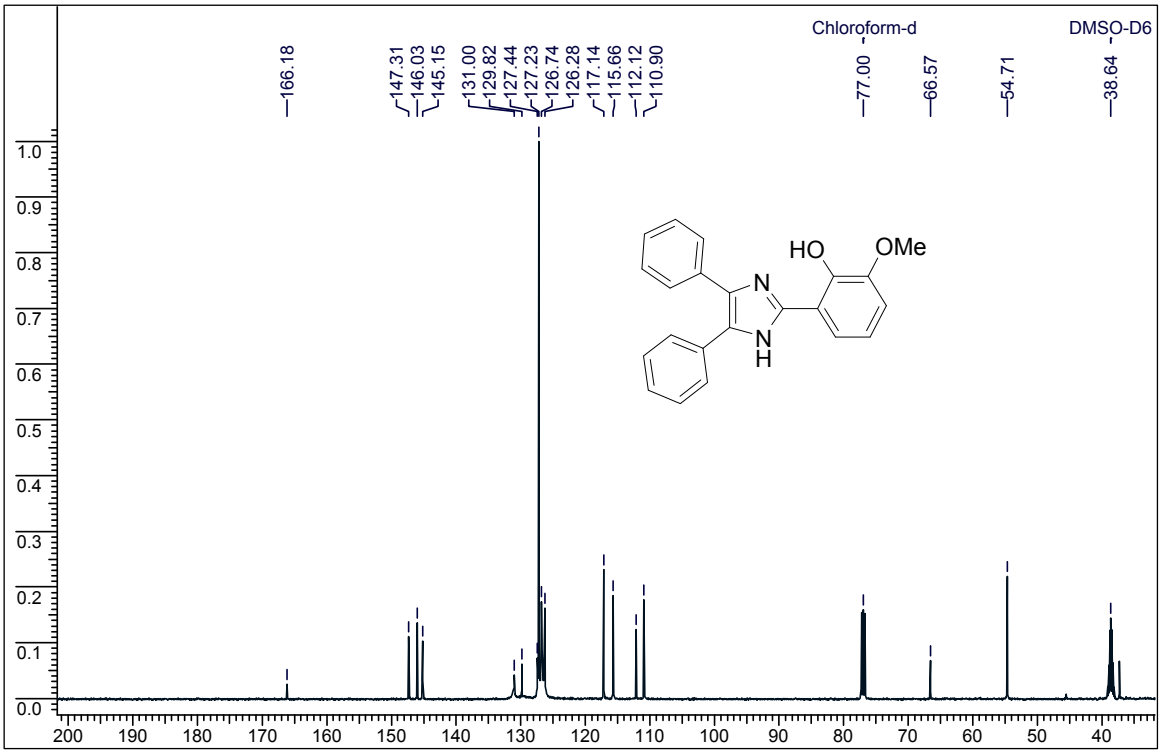
[2] ^{13}C NMR spectra of 86k



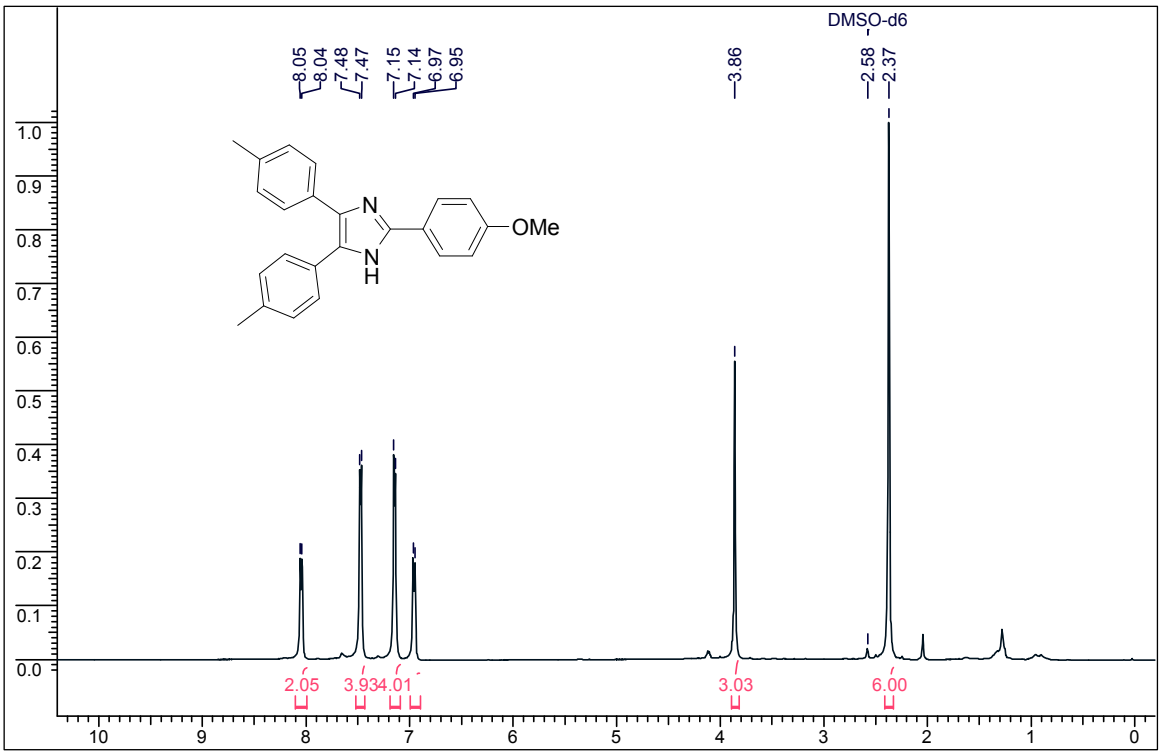
[3] ^{1}H NMR spectra of 86p



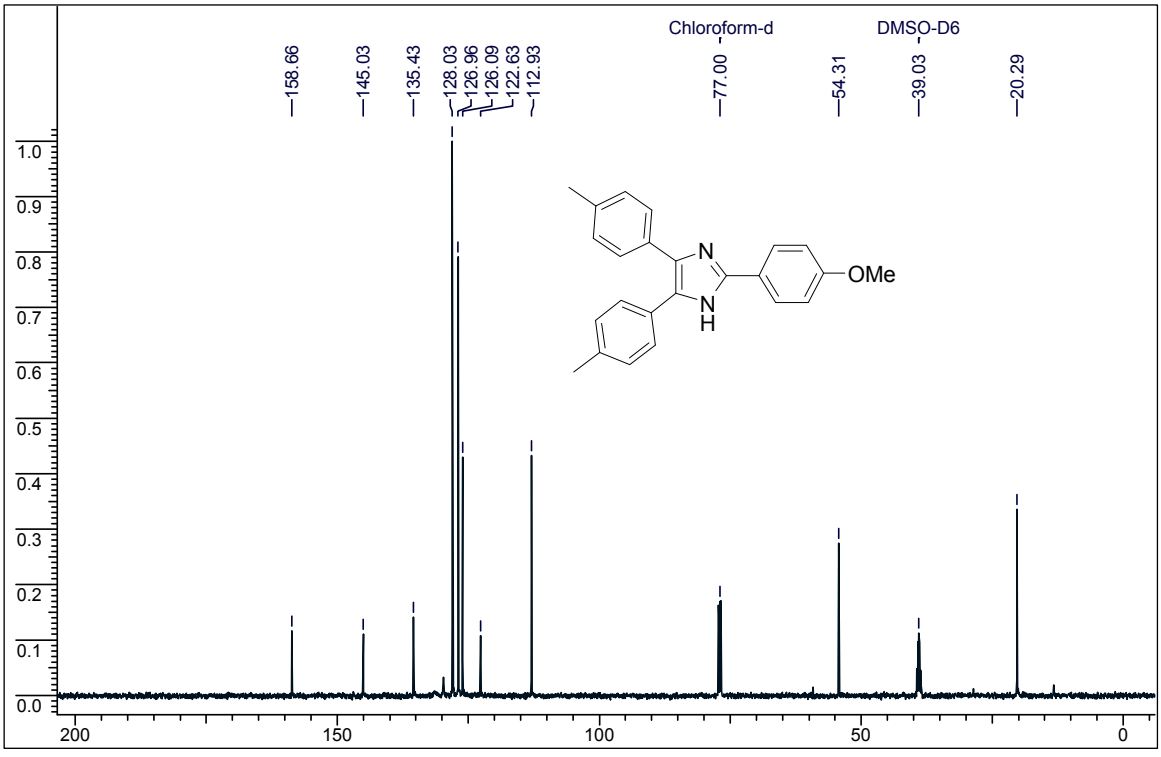
[3] ^{13}C NMR spectra of 86p



[4] ^{1}H NMR spectra of 86t



[4] ^{13}C NMR spectra of 86t



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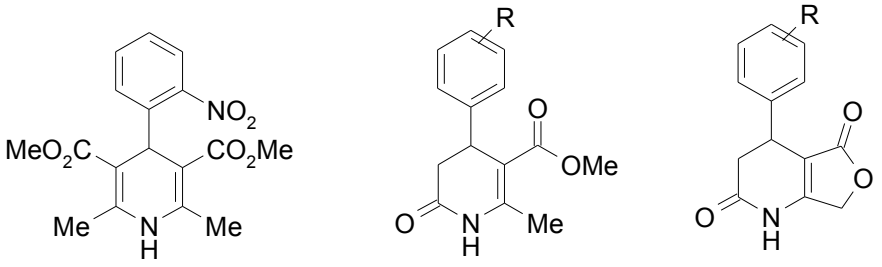
SECTION-C

Synthesis of 4-substituted aryl 5-alkoxy carbonyl-6-methyl-3, 4-dihydro-2-pyridones

2.3.1 Introduction

The piperidine structural motif is found as a constituent of numerous alkaloids, several of which possess significant pharmacological properties.[1] There is unabated interest in the study of 4-aryl-l,4-dihydropyridines (DHPs) as a consequence of their pharmacological activity as the most important class of calcium channels modulators.[2-4] Since the earlier crystallographic studies[5,6] directed to the definition of a structure-activity relationship for these types of compounds, a big effort has been devoted to the synthesis of differently substituted DHPs.[7] In addition to the chemical modification carried out on the periphery of the parent nifedipine (L).



L **M** **N**

Fig. 7

It has recently been proposed that the antagonist or agonist activity in DHPs is dependent on the absolute configuration at C-4 *(R- versus* S-enantiomer) acting as a molecular switch.[8] Other structural requirements are that the substituted phenyl ring occupies an axial position perpendicularly bisecting the boat-like DHP or DHPM ring with the substituents in a synperiplanar orientation. A *cis-carbonyl* ester orientation with respect to the olefinic double bond is also needed for a high activity. In principle, 2,3-dihydro-2-pyridones **M** present all the requirements needed for an antagonist behavior, since they are endowed with the essential substituents (ester and methyl groups) on the left hand side of the molecule, the substituents on the right-hand side being considered as nonessential (Fig. 7).[9-11] Similarly, compound **N** bearing the lactone ring with the carbonyl group *trans* to the olefinic double bond also exhibit an agonist effect.

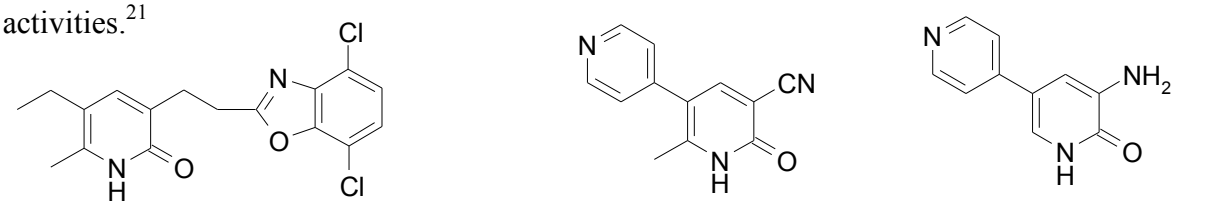
The 2 and 4-pyridones are six-membered nitrogen-containing heterocycles, either unsaturated (pyridones) or in their reduced forms (dihydropyridones and *δ*-lactams) (**Fig. 8**), have a long history of medicinal applications. Since pyridones can be assembled from a range of starting materials, ring substituents can be constructed in many different regiochemistries and with a great variety of functionalization.

2-Pyridone 3,4-Dihydro-2-pyridone 4-Pyridone δ-Lactam

Fig. 8

Particularly 3,4-dihydro-2-pyridones, which serve as valuable building blocks in the construction of piperidines, perhydroquinolones, indolizidines, quinolizidines and other alkaloid ring systems have gained importance and have a wide range of biological and pharmacological activities.[12] These 3,4-dihydropyridones compounds are important key intermediates for the preparation of *o*-chloroformyl 1,4-DHPs by the Vilsmeier Haack reaction, substances that can be further transformed in a wide variety of pyridine fused heterocyclic systems.[13,14]

Many naturally occurring and synthetic compounds containing the 2-pyridone[15] scaffold possess interesting pharmacological properties as they are identified as specific non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus-1 (HIV-1).[16] Milrinone, Amrinone[17]and their analogues[18] (**Fig. 9**) are cardiotonic agents for the treatment of heart failure. Some 2-pyridones are also reported to possess antitumor,[19] antibacterial,[20] antimicrobial, antiviral, antifungal, antihypertensive and other biological activities.[21]



Pyridone L-697,661 Milrinone WIN 47203 Amrinone WIN 40680

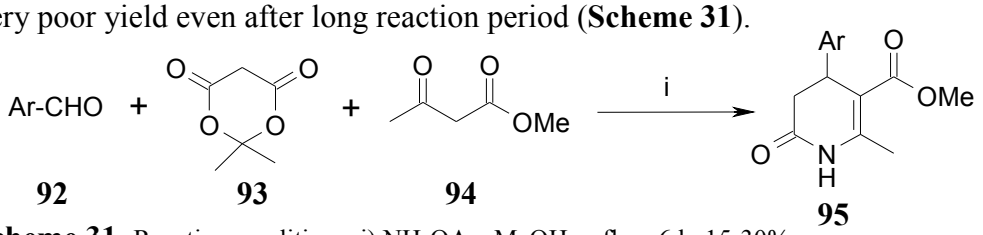
Fig. 9

2.3.2 Review of literature

A number of synthetic methods for the preparation of pyridones have been reported in the literature due to its broad spectrum biological activities and its skeleton. In this section we have reviewed some of the important synthetic methods for the preparation of 3,4-dihydro-2-pyridones which have appeared in the literature recently.

Svetlik's approach (1990)[22]

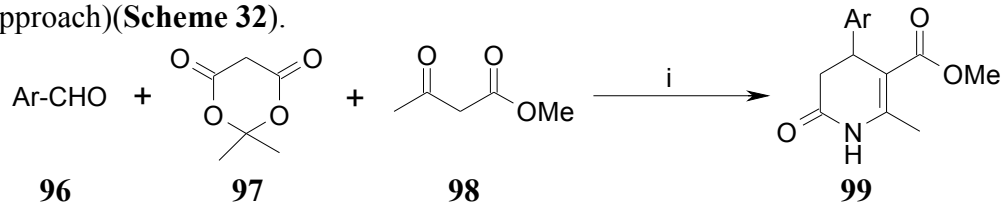
Svetlik *et al.* reported the synthesis of 4-substituted aryl-3,4-dihydropyridones **95,** from condensation of aromatic aldehyde **92**, Meldrum's acid **93**, methyl acetoacetate **94,** ammonium acetate and acetic acid in refluxing methanol which afforded desired product in very poor yield even after long reaction period (**Scheme 31**).



Scheme 31. Reaction conditions: i) NH_4OAc, MeOH, reflux, 6 h, 15-30%.

Seaone's approach (1996)[23]

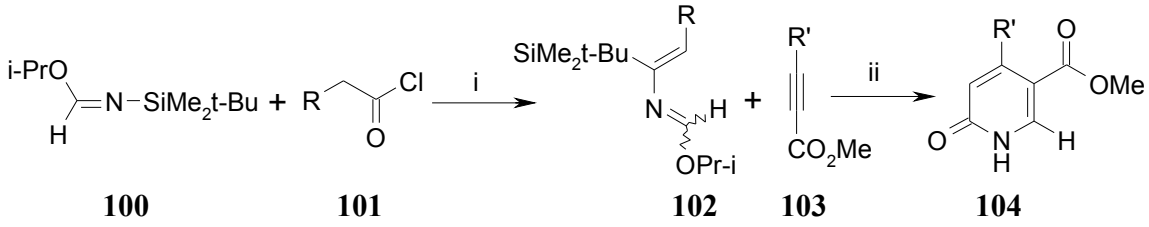
Seaone *et al.* reported very similar method to that of Svetlik's approach for the synthesis of 3,4-dihydropyridone **99,** wherein a mixture of aromatic aldehyde **96**, Meldrum's acid **97**, methyl acetoacetate **98** and ammonium acetate was heated in acetic acid at 110 ^{0}C which afforded desired product in better yield as compared to the earlier method (Svetilk's approach)(**Scheme 32**).



Scheme 32. Reaction conditions: i) NH_4OAc, AcOH, 110 ^{0}C, 10-14 h, 40-60%.

Ghosez's approach (1999)[24]

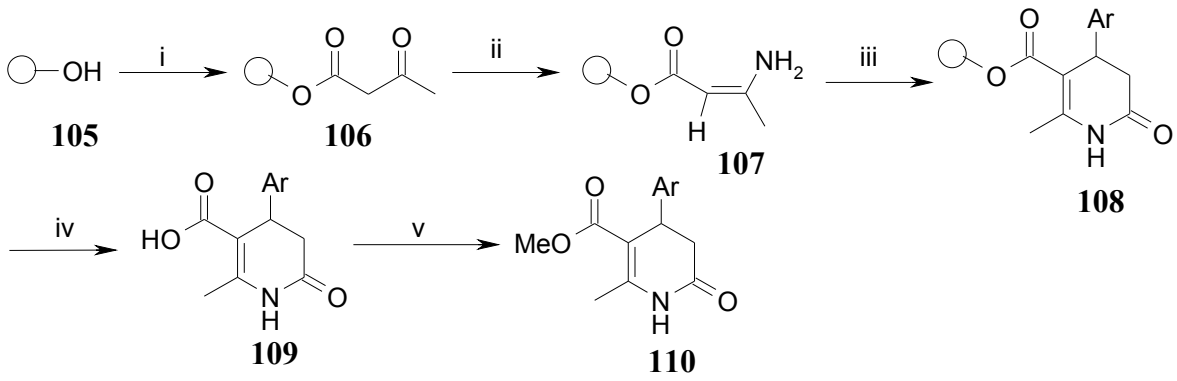
Ghosez *et al.* reported the synthesis of 2-pyridones via cycloaddition followed by aromatization using *N*-silylated iminoethers **100,** as a starting material which on reaction with 2-substituted acetyl chlorides **101** in presence of toluene and base triethyl amine gave the activated 2-azadienes **102** in good yield which on cycloaddition with dienophile **103** in toluene at 80 ^{0}C followed by treatment with methanol afforded 2-pyridones **104** as adduct in good to excellent isolated yields (**Scheme 33**).



Scheme 33. Reaction conditions: i) Et_3N, toluene, rt, 5 h; ii) toluene, 85 ^{0}C, 70-85%.

Rodriguez's approach (2002)[25]

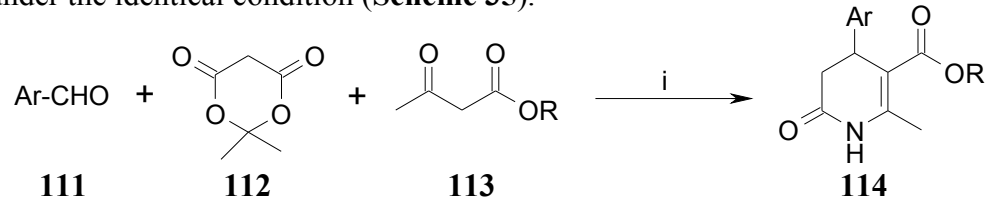
Substituted 3,4-dihydro-2-pyridones **110** was synthesized by solid-phase synthesis using Wang resin from the immobilized β-ketoester. The solid-phase synthesis of 2-pyridones starts from a synthesis of immobilized β-ketoesters **106**, which was prepared by simple acetoacetylation of hydroxyl functionalized polymers **105** (Wang resin) with 1,3-dioxin-4-one. Thus, the reaction of **106** with ammonium acetate in acetic acid at 118 ^{0}C after 6 h gave rise to the corresponding enamine **107**. The intermediate **107** was further reacted with Knovenagel derivatives in DMF at 150 ^{0}C after 5 h by a Hantzsch type heterocyclization afforded the immobilized 2-pyridones **108**. The desired products **109** and **110** were cleaved from the resin using TFA in DCM affording the products in good yield (**Scheme 34**).



Scheme 34. Reaction conditions: i) 1,3-Dioxin-4-one, toluene, 111 ^{0}C; ii) NH_4OAc, AcOH, 118 ^{0}C; iii) DMF, 150 ^{0}C; iv) TFA, 95% in DCM; v) TFA, 95% in DCM, MeOH, 71-85%.

Rodriguez's approach (2003)[26]

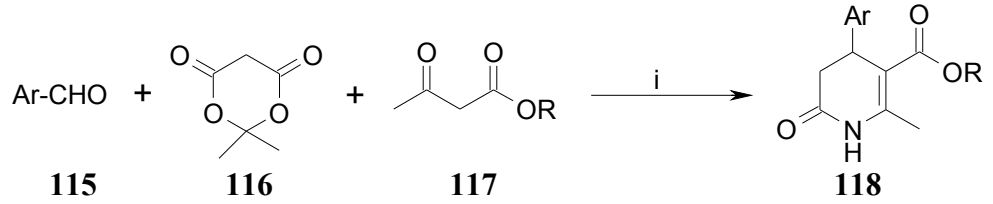
4-Aryl substituted-5-alkoxycarbonyl-6-methyl-3,4-dihydropyridones **114** have been synthesized in one-pot condensation from aromatic aldehyde **111**, Meldrum's acid **112**, methyl acetoacetate **113** and ammonium acetate under solvent free conditions using microwave irradiation as alternative to conventional heating. This rapid method produced pure products in excellent yields (81–91%) compared to conventional heating (17–28%) under the identical condition (**Scheme 35**).



Scheme 35. Reaction conditions: i) NH_4OAc, MW, 15 min., 81-91%.

Tu's approach (2003)[27]

Tu *et al.* reported very similar method to Rodriguez's approach. A series of 4-aryl-5-ethoxy-carbonyl-6-methyl-3,4-dihydro-2-pyridones **118** have been synthesized by the condensation of aromatic aldehyde **115**, Meldrum's acid **116**, β-keto ester **117** and ammonium acetate under solvent-free conditions and microwave irradiation (**Scheme 36**).

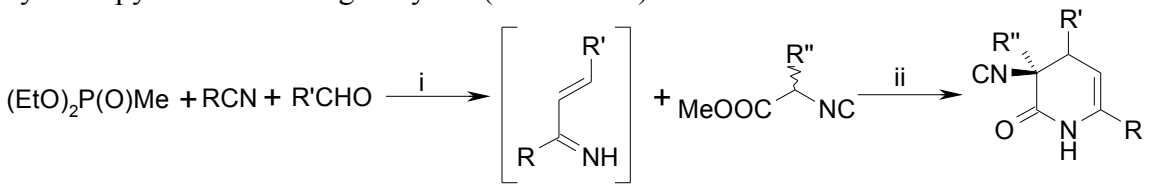


115 **116** **117** **118**

Scheme 36. Reaction conditions: i) NH_4OAc, MW, 75-88%.

Paravidino's approach (2006)[28]

Paravidino reported synthesis of functionalized 3-isocyano-3,4-dihydro-2-pyridones **124** from phosphonate **119**, nitriles **120**, aldehydes **121**. Reaction of phosphonate, nitrile and aldehyde and *n*-BuLi in THF at -78 ^{0}C to rt affords the 1-azadienes **122** which on further cycloaddition with methyl-2-isocyano-2-phenylacetate **123** in THF gave 3-isocyano-3,4-dihydro-2-pyridones **124** in good yield (**Scheme 37**) .

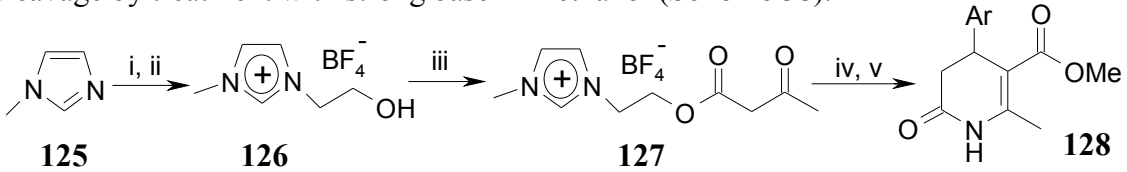


119 **120** **121** **122** **123** **124**

Scheme 37. Reaction conditions: i) *n*-BuLi, THF, -78 ^{0}C to rt, 5 h; ii) THF, rt, 18 h, 64%.

Feng-Ping's approach (2006)[29]

Recently Feng-Ping *et al.* synthesized task specific hydroxyl functionalized ionic liquid 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate **126** via microwave irradiation using methylimidazolium **125**, chlorohydrin and sodium tetrafluoroborate which was used for the synthesis of 3,4-dihydropyridones. Methyl acetoacetate on treatment with **126** gave intermediate **127** which on condensation with Meldrum acid, ammonium acetate and aromatic aldehyde afforded 3,4-dihydropyridones **128** in good yields 80-90% after cleavage by treatment with strong base in methanol (**Scheme 38**).

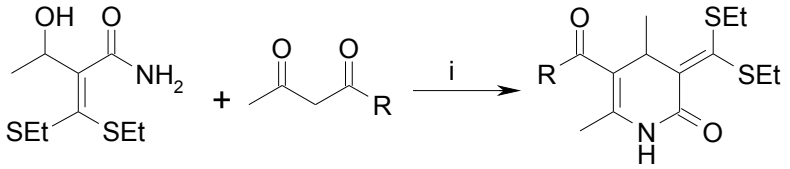


125 **126** **127** **128**

Scheme 38. Reaction conditions: i) chlorohydrin, MW; ii) $NaBF_4$, CH_3CN; iii) ethyl acetoacetate, MW, 10 min.; iv) Meldrum's acid, aldehyde, NH_4OAc, ethanol, reflux; v) CH_3ONa, methanol, rt, 5 h.

Li's approach (2007)[30]

Very recently Li reported synthesis of substituted 2-pyridones **131** from hydroxyketene-(*S*,*S*)-acetals **129,** which on condensation with active methylene compounds **130** in the presence of catalyst $BF_3 \cdot OEt_2$ gave **131** in moderate yield at 0 ^{0}C (**Scheme 39**).



129 **130** **131**

Scheme 39. Reaction conditions: i) BF_3.OEt, 0 ^{0}C, 2 h, 65-80%.

Several other methods of significance which involves the synthesis of 3,4-dihydro-2-pyridones can be found in the literature.[31-33]

2.3.3 Present Work

2.3.3.1 Objectives

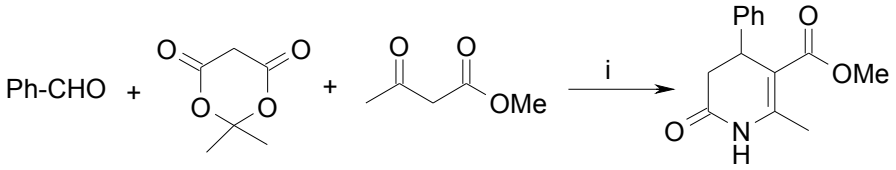
Since 3,4-dihydro-2-pyridones serve as valuable building blocks in the construction of piperidines, perhydroquinolones, indolizidines, quinolizidines and other alkaloid ring systems and have a wide range of biological and pharmacological activities.[11] The general and common methods towards 3,4-dihydro-2-pyridones require multistep synthesis,[12–14] usually via a combination of three steps: (1) a condensation, (2) a conjugate addition, and (3) an elimination. Most of these multi-step synthesis and suffer from other drawbacks such as use of acidic or and moisture sensitive catalysts, low yields, cumbersome isolation procedure, long reaction time period and specific starting material (synthesized from several steps).

Over the past decade, room temperature ionic liquids (RTILs)[45] have emerged as a new class of stable and inert solvents. Indeed, this family of ionic moieties presents several interesting properties compared to classical molecular solvents. They exhibit high thermal stability, high polarity due to their ionic nature and a great ability to solubilize polar and

non-polar organic compounds. Moreover, their immiscibility with molecular solvents and their very low vapor pressure make them very good solvents for both extraction and recyclability. The use of ionic liquids as solvents for chemical transformations is also of a topical interest in academia and industry according to the twelve principles ruling Green Chemistry.

2.3.3.2 Results and discussion

From our previous study of ionic liquid for the synthesis of biologically active heterocycles (see chapter 2, section A&B), we found that ionic liquid [Hbim]BF_4[36] is the best ionic liquid for heterocyclization reaction among series of ILs we had. For the model study, initially we performed the reaction of benzaldehyde (**132a**), meldrums acid (**133**), methyl acetoacetate (**134a)** and ammonium acetate in ionic liquid ([Hbim]BF_4) for 24 h at ambient temperature (**Scheme 40**) no progress in reaction was observed (monitored by TLC). As a plausible mechanism shows that the reaction will pass through a condensation followed by conjugate addition and decarboxylation and since the decarboxylation takes place very well at higher temperature condition, we performed the reaction in [Hbim]BF_4 at 100 ^{0}C and we observed that the reaction was complete within 30 min. (monitored by TLC). The reaction mixture was diluted with water and filtered off to give a solid product which was further purified by column chromatography and characterized.



132a **133** **134a** **135a**

Scheme 40. Reaction conditions i) [Hbim]BF_4, NH_4OAc, 100 ^{0}C, 30 min.

IR spectra of compound **135a** showed the NH group at 3210 cm^{-1} and the two carbonyl groups at 1675 and 1705 cm^{-1} respectively. The ^{1}H NMR spectra shows a doublet of doublets at δ 4.28-4.32 corresponding to the proton on C4 due to the splitting by coupling with the protons on C3 (J= 7.57 Hz and J= 1.50 Hz). The two methyl groups appear as singlet at δ 2.39 and 3.76 respectively. The ^{13}C NMR spectra of **135a** showed the signals of the olefinic carbons C5 (at δ 107) and C6 (at δ 145) respectively and carbonyl carbon of ester and amide were observed at δ 167 and 171 respectively.

As we had synthesized several ILs based on 1,3-di-*n*-butyl imidazolium salts [bbim]X and 1-*n*-butyl imidazolium salts [Hbim]X and fully characterized in terms of physical parameters. Obviously, our next thing on chart was to find out best ionic liquid and to correlate the results observed from experiments with the results obtained from physical chartectrization of ILs. Result of this study would give an insight to select the best IL among synthesized ones for reactions in focus.

Various ionic liquids were screened with varying basicity of anions as solvents and promoters for the typical reaction of benzaldehyde, Meldrum's acid, methyl acetoacetate and ammonium acetate at 100 ^{0}C for 6 h, in the absence of any added catalyst to afford 4-phenyl-3,4-dihydro-2-pyridone **(135a).** The results are recorded in Table 10.

Table 10. Synthesis of **135a** in [bbim] and [Hbim] X

ILs	pK_a [a]	–NH proton δ ppm	$E_T(30)$ (kcal mol^{-1}) [b]	Yield [c] (%)
[bbim]ClO_4	**-11**	**--**	**76.34**	**50**
[bbim]Br	-9	--	66.49	42
[bbim]Cl	-7	--	68.89	38
[bbim]BF_4	**0.5**	**--**	**75.73**	**46**
[Hbim]ClO_4	-11	11.83	63.82	52
[Hbim]Br	-9	12.17	73.68	76[d]
[Hbim]Cl	-7	12.22	73.59	82[d]
[Hbim]BF_4	**0.5**	**14.59**	**74.35**	**90[d]**

[a:] The pK_a values of the parent acids of the anions; [b:] Polarity of ILs determined by Reichardt's dye; [c:] Isolated yield after column chromatography; [d]: reaction time 30 min.

The pK_a values are those of the parent acid of the anions and taken from literature.[35] The polarity of different ionic liquids based on 1,3-di-*n*-butyl imidazolium salts and 1-*n*-butyl imidazolium salts were evaluated in terms of $E_T(30)$ values using Reichardt's dye as per the reported procedure.[36]

It becomes evident from these results (Table 10), the IL [Hbim]BF_4 afforded the best results. Consequently, all further studies were conducted at 100 ^{0}C using this IL as the reaction medium cum promoter to generate a variety of 4-aryl-3,4-dihydro-2-pyridones by

the reaction of aromatic aldehydes, Meldrum's acid, methyl or ethyl acetoacetate and ammonium acetate as a nitrogen source.

In all the cases, 4-aryl substituted-3,4-dihydro-2-pyridones were precipitated on dilution of the reaction mixture with water and were isolated by simple filtration. The dried product thus obtained showed a single spot on TLC. The aqueous filtrate was then subjected to distillation at 80 ^{0} C under reduced pressure (10 mmHg) for 4 h to recover the IL almost completely. The IL, thus recovered was reused three times with minimal loss in yield for the typical reaction of **135a**

Table 11. Synthesis of 4-substituted aryl-3,4-dihydro-2-pyridones **135a-l.**

Entry	R	Ar	Time (min.)	Yield [a] (%)
135a	Me	C_6H_5	45	90
135b	Me	4-OCH_3-C_6H_4	45	91
135c	Me	4-Cl-C_6H_4	60	88
135d	Me	2-F-C_6H_4	45	90
135e	Me	3-NO_2-C_6H_4	90	75
135f	Me	4-NO_2- C_6H_4	90	76
135g	Et	C_6H_5	45	90
135h	Et	4-OCH_3-C_6H_4	45	90
135i	Et	4-Cl-C_6H_4	90	85
135j	Et	2-F-C_6H_4	60	86
135k	Et	3-NO_2-C_6H_4	90	77
135l	Et	4-NO_2- C_6H_4	90	75

[a]: Isolated yield after column chromatography

The results are recorded in Table 11. All the compounds were well characterized by physical constant, IR, ^{1}H NMR and ^{13}C NMR. Their elemental analyses were in conformity with their structures.

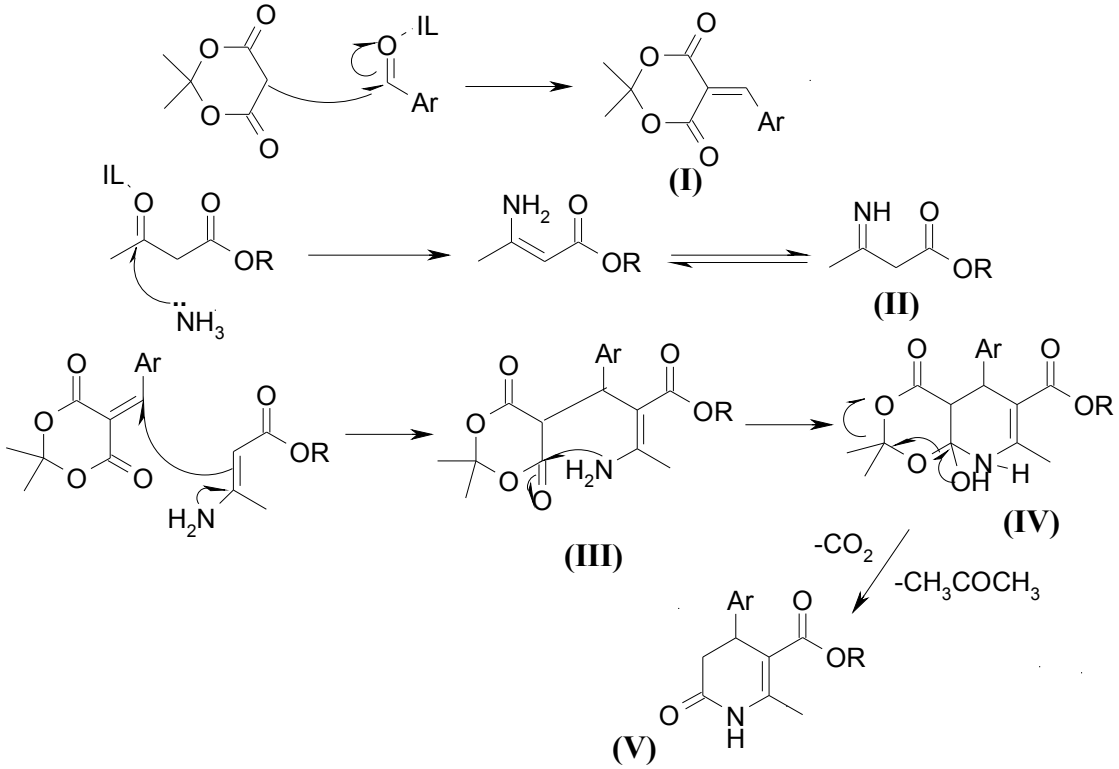
The 4-aryl substituted-3,4-dihydro-2-pyridones have been obtained in excellent isolated yields in relatively short reaction times. It was observed that the process tolerates

electron donating and halo substituents on the aldehyde whereas electron withdrawing substituents make reaction sluggish (entry 135e, f, k, l; Table 11)

The efficacy of the ILs to promote these heterocyclization reactions was correlated not only to the basicity of the anions but also with the polarity of ionic liquids. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield (Table 10). This correlation was also evident when the yield of **135a** was compared with –N*H* proton chemical shifts of the ILs indicative of the Bronsted acidities of the [Hbim] ILs (Table 10). The yield of **135a** increases progressively not only with increasing Bronsted acidity of the ILs as indicated by the increasing downfield shift of the NH proton but also with increasing polarity of these ILs as indicated by their E_T (30) values.

Thus among the ILs screened, it is found that the IL, [Hbim]BF_4 efficiently promoted this heterocyclization reaction by virtue of its inherent Bronsted acidity conferred by the most acidic –N***H*** hydrogen [chemical shift δ ppm = 14.6].

2.3.4 Plausible mechanism for the formation of 3,4-dihydro-2-pyridone



Scheme 41. Plausible mechanism for the formation of 3,4-dihydro-2-pyridone

The formation of compound is not straightforward and can be accounted for by considering the strong acidic properties of Meldrum's acid (p*K*a = 4.97) and ionic liquid which reacts with the aromatic aldehyde in presence of acidic ionic liquid to form the Knoevenagel product **(I)**. The nucleophilic addition of ammonia to β-keto ester in the presence of acidic ionic liquid generates the enaminone derivative **(II)** which reacts with **(I)** to yield the non isolated intermediate **(III)** which undergoes a 6-*exo-trig* cyclization leading to **(IV)**. At elevated temperature subsequent loss of acetone and carbon dioxide yields the 3,4-dihydro-2-pyridones **(V)** as a solid in good yield

2.3.5 Conclusion

In summary, we had developed a mild, concise and highly convergent approach towards the library of 4-substituted aryl 3,4-dihydro-2-pyridones from simple and readily accessible starting materials using a room temperature ionic liquid as a novel recyclable medium cum promoter without any added catalyst. This reaction is simple and runs under relatively mild conditions with short reaction times and higher selectivity using a recyclable catalyst. Moreover, this green strategy avoids the use of moisture-sensitive and heavy metal Lewis acids and also eliminates routine aqueous workup procedures for the isolation of required products.

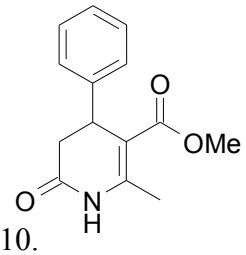
2.3.6 Experimental

Typical procedure for the synthesis of 4-substituted aryl-3,4-dihydro-pyrid-2-ones (135a-l)

A mixture of substituted aldehydes (**132a-f)** (4 mmol), Meldrum's acid **133** (4 mmol), ammonium acetate (12 mmol), β-keto ester (**134a-b)** (4 mmol) and [Hbim]BF_4 (8 mmol) was heated at 100 ^{0}C with vigorous stirring for the appropriate time mentioned in Table 12. After completion of reaction (the progress of reaction was monitored by TLC) the reaction mixture was diluted with water (25 mL). The solid products, which separated out were filtered, washed with water and dried under reduced pressure. They were subjected to further purification by chromatography through a column of silica gel using 25% EtOAc in petroleum ether as eluent to yield the desired 4-susbstituted aryl-3,4-dihydro-2-pyridones in excellent yields and were fully characterized.

2.3.6.1 Characterization data for compounds 135a-l

Methyl 1,4,5,6-tetrahydro-2-methyl-6-oxo-4-phenylpyridine-3-carboxylate (135a)



M. P. (^{0}C) : 197-198

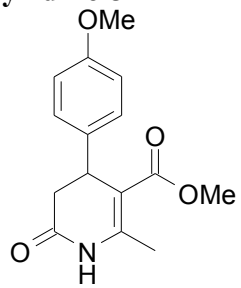
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1215, 1676, 1700, 2400, 3019, 3210.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.44 (s, 3H), 2.68-2.77 (dd, *J*= 16.8, 1.8 Hz, 1H), 2.90-3.02 (dd, *J*= 16.4, 7.8 Hz, 1H), 3.68 (s, 3H), 4.24-4.30 (t, 1H), 7.22-7.31 (m, 5H), 8.11 (s, 1H).

^{13}C NMR 50 MHz,$CDCl_3$) : δ 18.8, 37.6, 38.1, 51.3, 106.8, 126.5, 128.7, 141.8, 146.8, 167.3, 171.4.

Elemental Analysis : **$C_{14}H_{15}NO_3$** Calcd. C, 68.56; H, 6.16; N, 5.71.
Found C, 68.42; H, 5.98; N, 5.65.

Methyl-4-(4-methoxyphenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135b)



M. P. (^{0}C) : 188-189

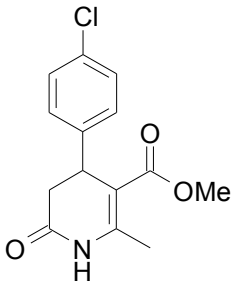
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1038, 1215, 1669, 1705, 3019, 3218.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.40 (s, 3H), 2.66-2.72 (dd, *J*= 16.5, 1.3 Hz, 1H), 2.91-3.03 (dd, *J*= 16.8, 7.5 Hz, 1H), 3.66 (s, 3H), 3.75 (s, 3H), 4.21-4.26 (t, 1H), 6.76-6.79 (d, *J*= 8.0 Hz, 2H), 7.08-7.09 (d, *J*= 7.8 Hz, 1H), 7.90 (brs, 1H)

^{13}C NMR (50 MHz,$CDCl_3$) : δ 18.8, 37.7, 38.4, 51.6, 55 7, 106.8, 114.3, 128.8, 133.5, 146.8, 158.0, 167.3, 170.2**.**

Elemental Analysis : **$C_{15}H_{17}NO_4$** Calcd. C, 65.44; H, 6.22; N, 5.09.
Found C, 65.34; H, 6.09; N, 4.98.

Methyl-4-(4-chlorophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135c)



M. P. (^{0}C) : 208-209

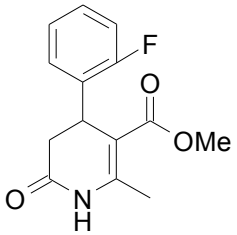
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1284, 1377, 1407, 1461, 1489, 1631, 1697, 2855, 2925, 3219.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.54 (s, 3H), 2.73-2.82 (dd, *J*= 15.0, 1.9 Hz, 1H), 2.90-3.03 (dd, *J*= 16.2, 7.5 Hz, 1H), 3.67 (s, 3H), 4.74-4.78 (t, 1H), 7.17-7.47 (m, 4H), 8.20 (s, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 18.9, 34.9, 36.3, 37.2, 37.9, 51.4, 105.7, 127.1, 128.1, 128.3, 128.9, 130.1, 133.2, 138.1, 147.7, 166.9, 170.7.

Elemental Analysis : **$C_{14}H_{14}ClNO_3$** Calcd. C, 60.11; H,5.04; N, 5.01.
Found C, 59.92; H, 4.88; N, 4.85.

Methyl-4-(2-florophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135d)



M. P. (^{0}C) : 148-149

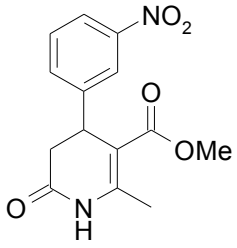
IR ($CHCl_3$, cm^{-1}) : υ_{max} 756, 1217, 1288, 1629, 1680, 1699, 3112, 3218.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.45 (s, 3H), 2.68-2.77 (dd, *J*= 16.4, 2.4 Hz, 1H), 2.90-3.03 (dd, *J*= 16.7, 8.1 Hz, 1H), 4.58-4.62 (t, 1H), 7.03-7.22 (m, 4H) 8.05 (brs, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 17, 26.9, 38.3, 52.3, 106.3, 115.4, 124.3, 127.2, 127.7, 129.4, 146, 160.3, 167.3, 169.8.

Elemental Analysis : **$C_{14}H_{14}FNO_3$** Calcd. C, 63.87; H, 5.36; N, 5.32.
Found C, 63.61; H, 5.22; N, 5.21.

Methyl-4-(3-nitrophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135e)



M. P. (^{0}C) : 204-205

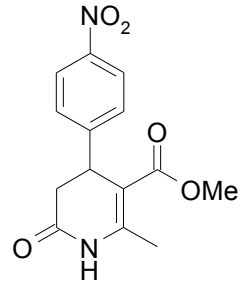
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1159, 1215, 1380, 1531, 1630, 1677, 1702, 2953, 3238.

^1H NMR (200 MHz, $CDCl_3$) : δ 2.37 (s, 3H), 2.61-2.72 (dd, *J*= 17.7, 3.6 Hz, 1H), 2.78-2.89 (dd, *J*= 15.7, 6.2 Hz, 1H), 3.64 (s, 3H), 3.71-3.72 (t, 1H), 7.33-7.41 (t, 1H), 7.55-7.65 (m, 1H), 7.96-8.08 (m, 2H), 8.2 (brs, 1H)

^{13}C NMR (50 MHz,$CDCl_3$) : δ 19.4, 36.4, 39.6, 51.1, 102.9, 121.3, 122.7, 128.7, 134.2, 145.2, 149.6, 151.4, 167.6.

Elemental Analysis : **$C_{14}H_{14}N_2O_5$** Calcd. C, 57.93; H, 4.86; N, 9.65.
Found C, 57.78; H, 4.78; N, 9.53.

Methyl-4-(4-nitrophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135f)



M. P. (^0C) : 208-209

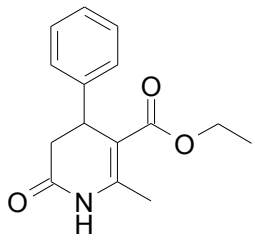
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1159, 1215, 1352, 1618, 1673, 1702, 2400, 2953, 3240.

^1H NMR (200 MHz, $CDCl_3$) : δ 2.45 (s, 3H), 2.63-2.72 (dd, *J*= 16.6, 3.0 Hz, 1H), 2.94-3.06 (dd, *J*= 15.1, 3.0 Hz, 1H) 3.65 (s, 3H), 4.34-4.37 (t, 1H), 7.37 (d, *J*= 8.2 Hz, 1H), 8.00 (brs, 1H), 8.14 (d, *J*= 8.0 Hz, 2H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 19.3, 37.6, 37.9, 65.1, 105.8, 124.1, 127.4, 147.3, 149.5, 166.8, 170.2.

Elemental Analysis : **$C_{14}H_{14}N_2O_5$** Calcd. C, 57.93; H, 4.86; N, 9.65.
Found C, 57.82; H, 4.78; N, 9.55.

Ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxo-4-phenylpyridine-3-carboxylate (135g)



M. P. (^0C) : 138-139

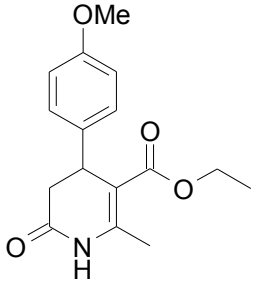
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1094, 1215, 1616, 1672, 1698, 2400, 3019, 3235.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.14-1.25 (t, 3H), 2.40 (s, 3H), 2.66-2.74 (dd, *J*= 14.1, 2.3 Hz, 1H), 2.88-3.00 (dd, *J*= 16.5, 8.1 Hz, 1H), 4.05-4.13 (m, 2H) 4.23-4.27 (t, 1H), 7.20-7.26 (m, 5H), 7.91 (s, 1H)

^{13}C NMR (50 MHz,$CDCl_3$) : δ 14.1, 19.1, 37.9, 60.2, 107.5, 126.7, 128.7, 142.2, 145.7, 166.8, 170.8.

Elemental Analysis : **$C_{15}H_{17}NO_3$** Calcd. C, 69.48; H, 6.61; N, 5.40.
Found C, 69.34; H, 6.56; N, 5.25.

Ethyl-1,4,5,6-tetrahydro-4-(4-methoxyphenyl)2-methyl-6-oxopyridine-3-carboxylate (135h)



M. P. (^{0}C) : 148-195

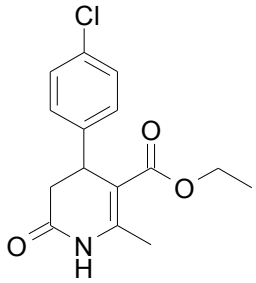
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1217, 1510, 1635, 1697, 3016, 3132, 3234.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.16-1.23 (t, 3H), 2.39 (s, 3H), 2.62-2.71 (dd, *J*= 16.3, 2.1 Hz, 1H), 2.84-2.96 (dd, *J*= 16.6, 7.7 Hz, 1H), 3.76 (s, 3H), 4.06-4.14 (m, 2H), 4.17-4.22 (t, 1H), 6.77-6.82 (d, *J*= 6.7 Hz, 2H), 7.08-7.12 (d, *J*= 6.7 Hz, 2H), 7.54 (brs, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 14.1, 19.1, 37, 38.1, 55.1, 60.1, 107.7, 114, 127.7, 134.2, 145.5, 158.4, 166.9, 170.9.

Elemental Analysis : **$C_{16}H_{19}NO_4$** Calcd. C, 66.42; H, 6.62; N, 4.84.
Found C, 66.32; H, 6.53; N, 4.75.

Ethyl-4-(4-chlorophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135i)



M. P. (^{0}C) : 203-204

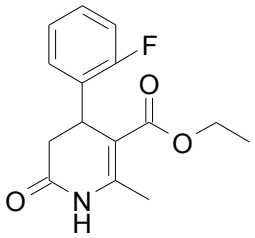
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1284, 1415, 1461, 1489, 1645, 1705, 2925, 3219.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.15-1.20 (t, 3H), 2.45 (s, 3H), 2.63-2.72 (dd, *J*= 16.6, 2.1 Hz, 1H), 2.84-2.96 (dd, *J*= 15.8, 8.0 Hz, 1H), 4.07-4.19 (m, 2H), 4.58-4.65 (t, 1H), 7.06 (d, *J*= 8.0 Hz, 2H), 7.23 (d, *J*= 7.5 Hz, 2H), 8.12 (brs, 1H)

^{13}C NMR (50 MHz,$CDCl_3$) : δ 15, 19.3, 36.8, 38.5, 56.2, 61, 105.8, 114.3, 128.4, 129, 134, 146.3, 156.3, 166.9, 168.7.

Elemental Analysis : **$C_{15}H_{16}ClNO_3$** Calcd. C, 61.33; H, 5.49; N, 4.77.
Found C, 61.18; H, 5.36; N, 4.58.

Ethyl-4-(2-fluorophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135j)



M. P. (^{0}C) : 137-138

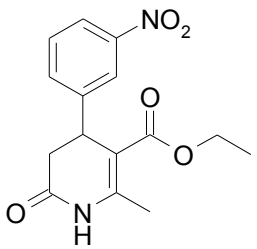
IR ($CHCl_3$, cm^{-1}) : υ_{max} 756, 1217, 1288, 1629, 1699, 3112, 3218.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.14-1.21 (t, 3H), 2.48 (s, 3H), 2.68-2.76 (dd, *J*= 16.5, 2.1 Hz, 1H), 2.90-3.03 (dd, *J*= 16.7, 8.1 Hz, 1H), 4.05-4.17 (m, 2H), 4.58-4.65 (t, 1H), 7.03-7.22 (m, 4H), 8.05 (s, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 14, 18.9, 31.5, 36.8, 60.1, 105.5, 115.4, 115.8, 124.1, 127.7, 128.7, 147, 157.9, 162.8, 166.5, 170.7.

Elemental Analysis : **$C_{15}H_{16}FNO_3$** Calcd. C, 64.97; H, 5.82; N, 5.05.
Found C, 64.82; H, 5.78; N, 4.85.

Ethyl-4-(3-nitrophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135k)



M. P. (^{0}C) : 205-206

IR ($CHCl_3$, cm^{-1}) : υ_{max} 1159, 1215, 1531, 1640, 1677, 1700, 1810, 2953, 3210.

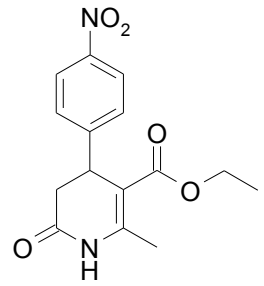
^{1}H NMR : δ 1.23-1.29 (t, 3H), 2.41 (s, 3H), 2.38-2.42 (dd, *J*= 16.5, 2 Hz, 1H)

(200 MHz, $CDCl_3$) 2.99-3.08 (dd, *J*= 15.8, 7.5 Hz, 1H), 4.17-4.22 (m, 2H), 4.35-4.38 (t, 1H), 7.47-7.51 (m, 2H), 8.01-8.05 (m, 2H), 8.12 (brs, 1H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 14.2, 15.4, 36.7, 38.3, 61.7, 104.5, 118.3, 123, 129.6, 133.9, 141.6, 147, 148.5, 166.8, 169.6.

Elemental Analysis : **$C_{15}H_{16}N_2O_5$** Calcd. C, 59.21; H, 5.30; N, 9.21.
Found C, 59.05; H, 5.21; N, 9.11.

Ethyl-4-(4-nitrophenyl)-1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylate (135l)



M. P. (^{0}C) : 248-249

IR ($CHCl_3$, cm^{-1}) : υ_{max} 1215, 1352, 1618, 1660, 1690, 2400, 3230.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.16-1.23 (t, 3H), 2.65-2.74 (dd, *J*= 16.4, 1.8 Hz, 1H), 2.95-3.06 (dd, *J*= 16.0, 8.2 Hz, 1H), 4.17-4.22 (m, 2H), 4.34-4.37 (t, 1H), 7.30 (d, *J*= 7.5 Hz, 1H), 8.10 (brs, 1H), 8.18 (d, *J*= 7.8 Hz, 2H).

^{13}C NMR (50 MHz,$CDCl_3$) : δ 15, 15.8, 37.7, 38.3, 62, 105.2, 121.4, 128.7, 145.6, 147.5, 148.8, 167.2, 170.

Elemental Analysis : **$C_{15}H_{16}N_2O_5$** Calcd. C, 59.21; H, 5.30; N, 9.21.
Found C, 59.08; H, 5.12; N, 9.11.

2.3.6.2 Spectral data of representative compounds

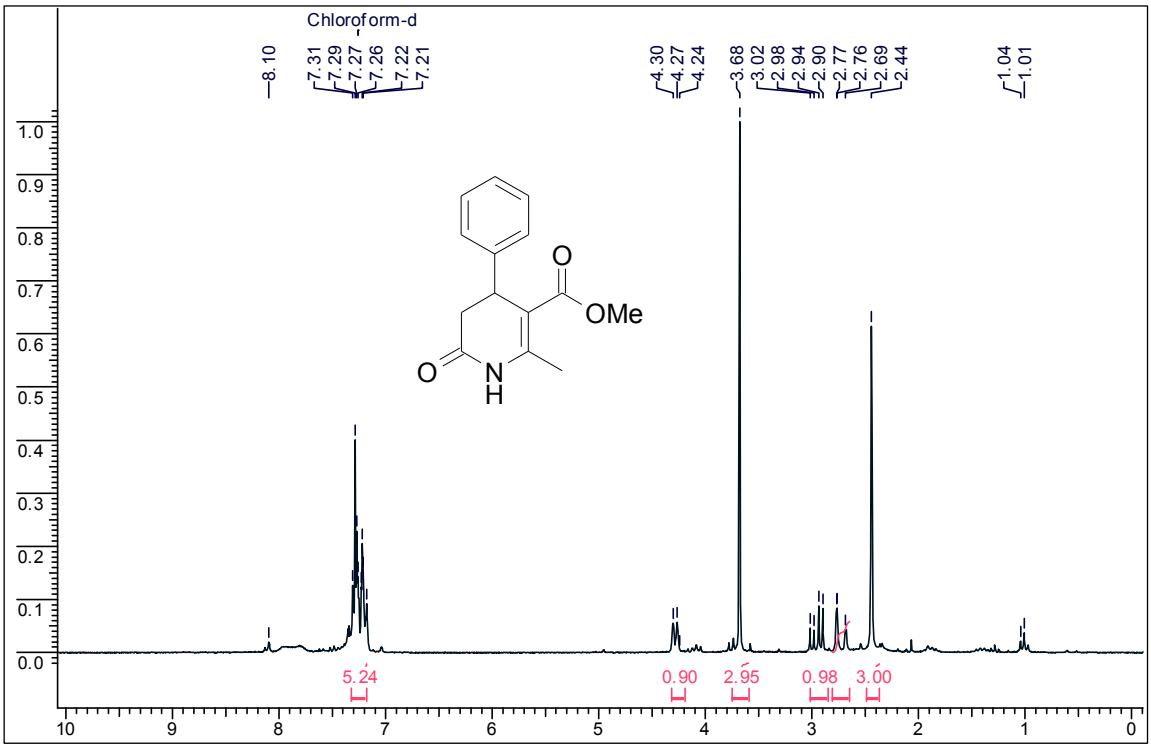
[1] ^{1}H NMR and ^{13}C NMR spectra of **135a**

[2] ^{1}H NMR and ^{13}C NMR spectra of **135c**

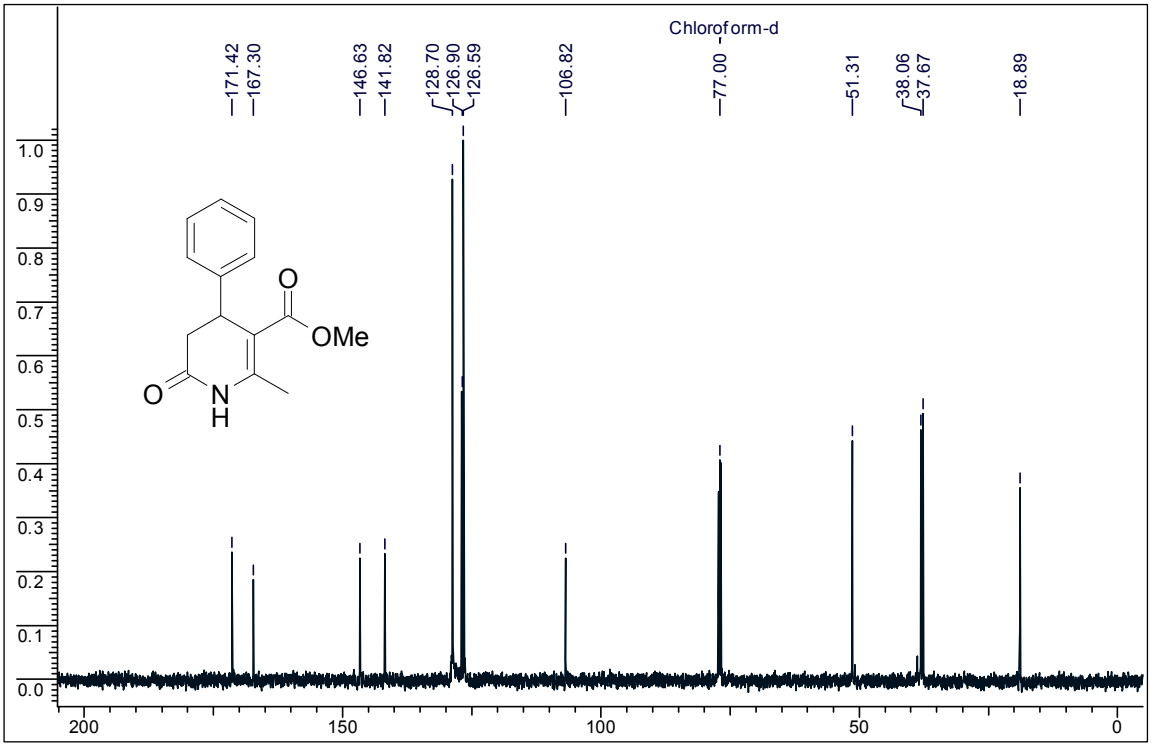
[3] ^{1}H NMR and ^{13}C NMR spectra of **135g**

[4] ^{1}H NMR and ^{13}C NMR spectra of **135h**

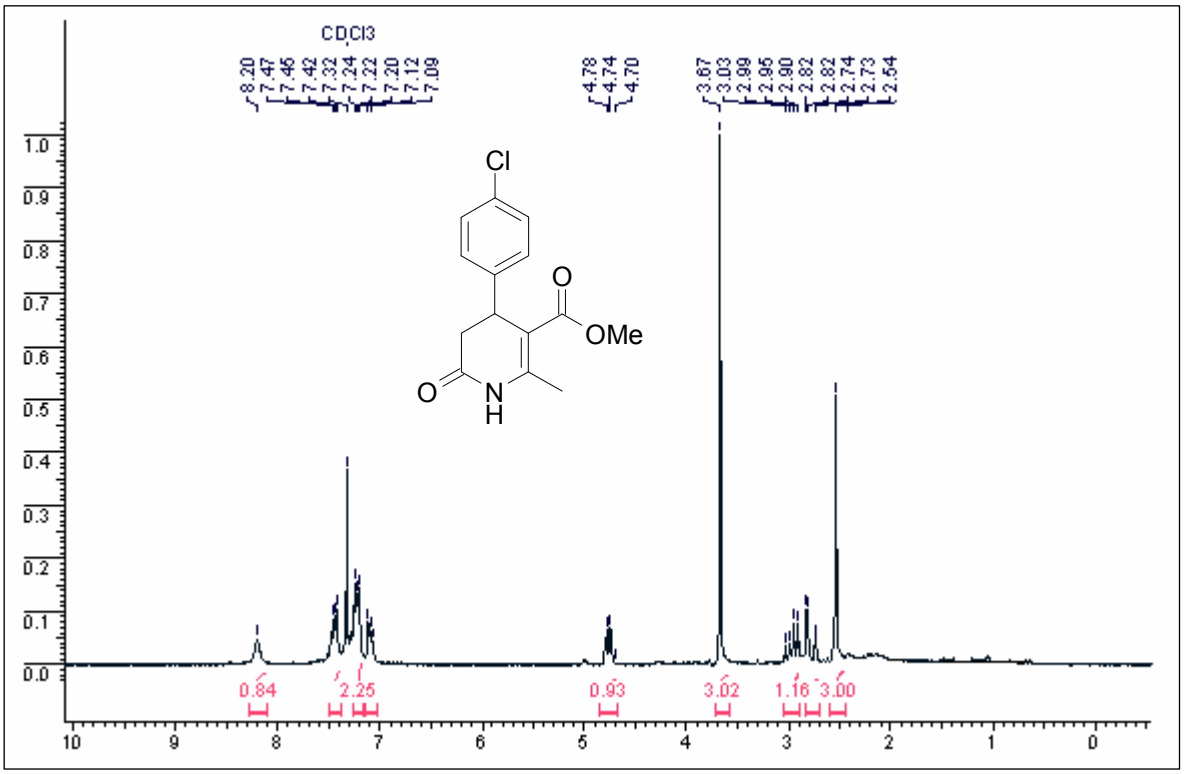
[1] ^{1}H NMR spectra of 135a



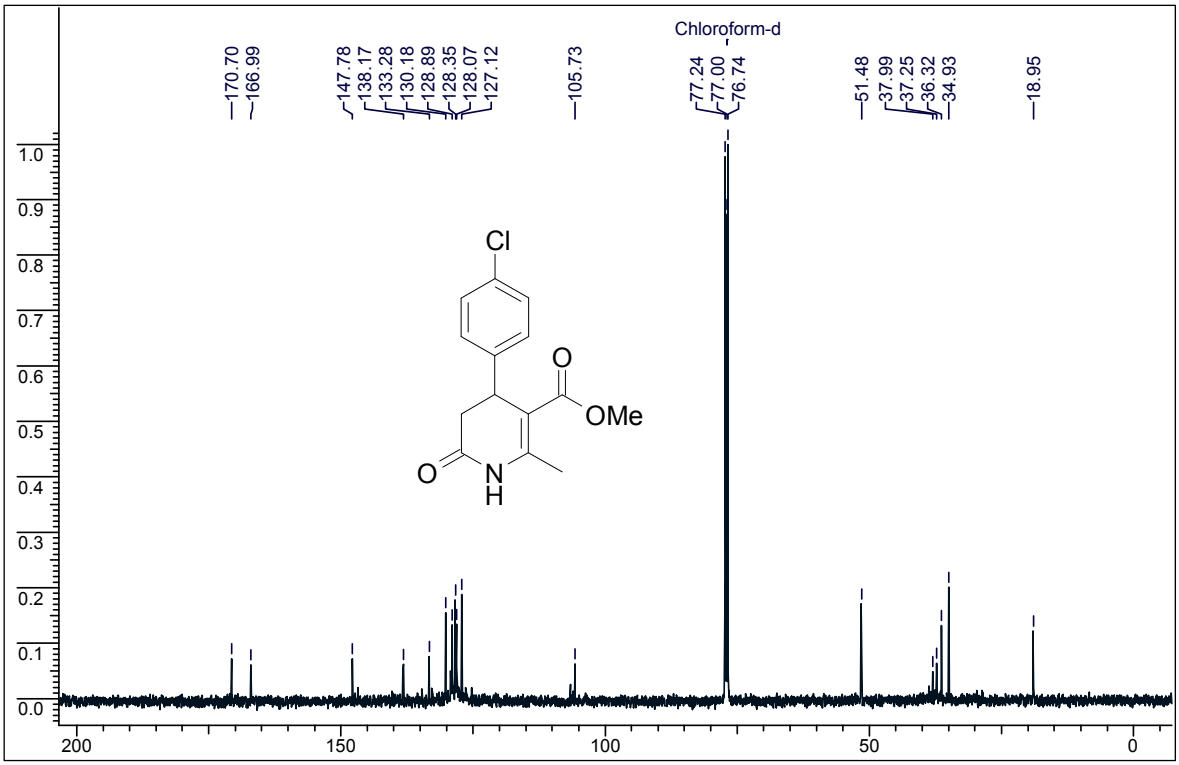
[1] ^{13}C NMR spectra of 135a



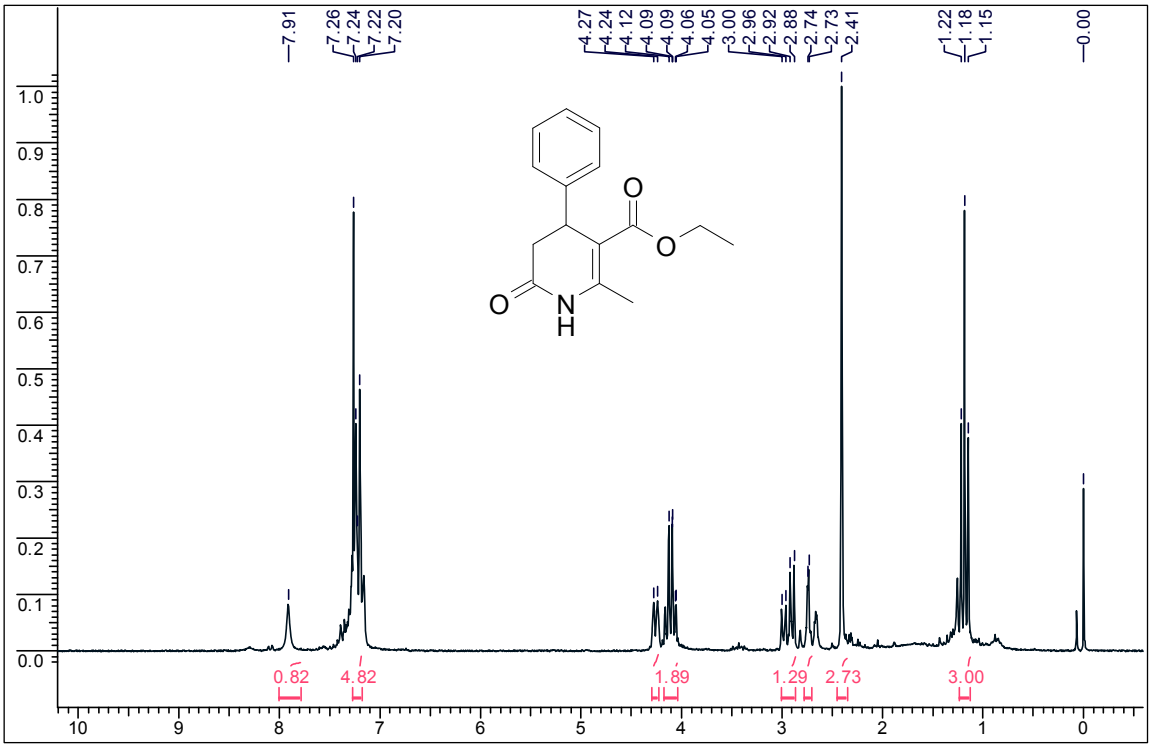
[2] ^{1}H NMR spectra of 135c



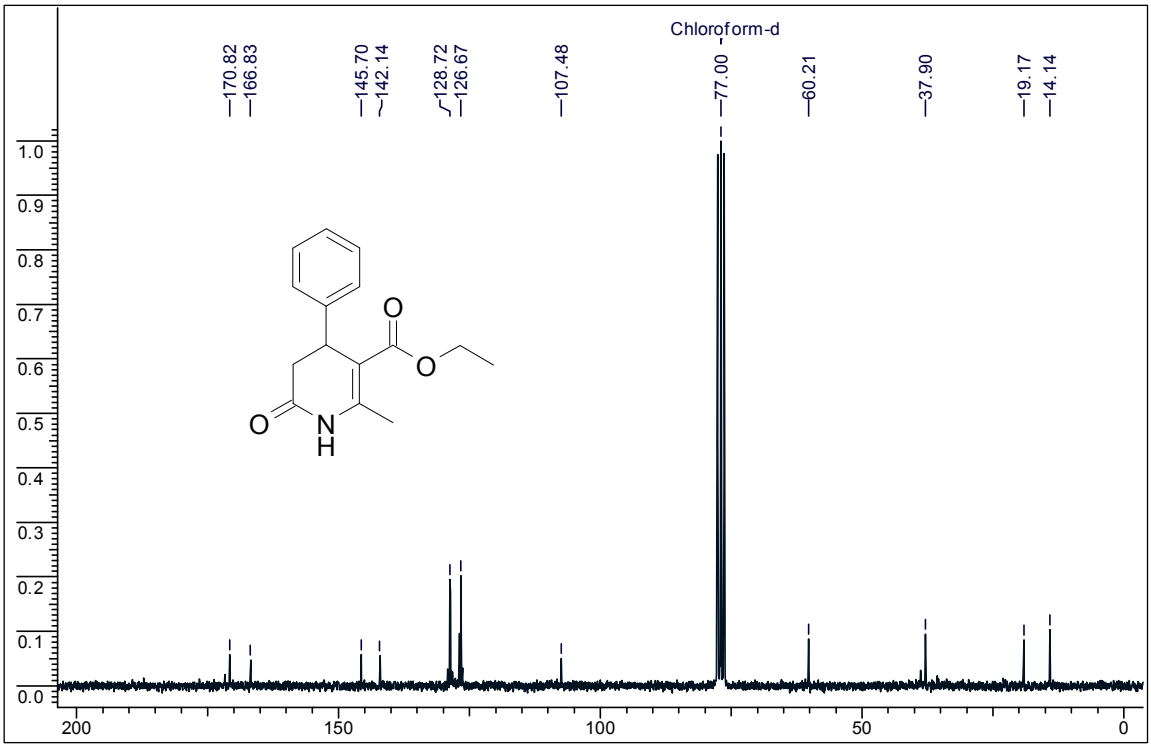
[2] ^{13}C NMR spectra of 135c



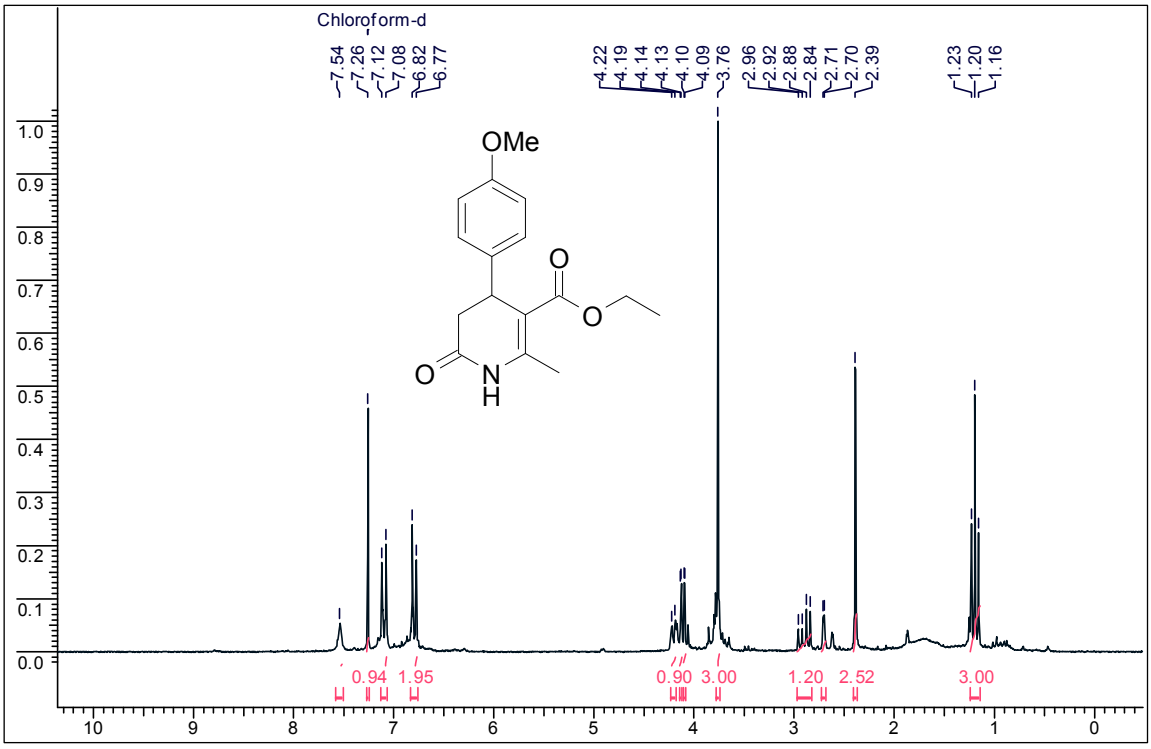
[3] ^{1}H NMR spectra of 135g



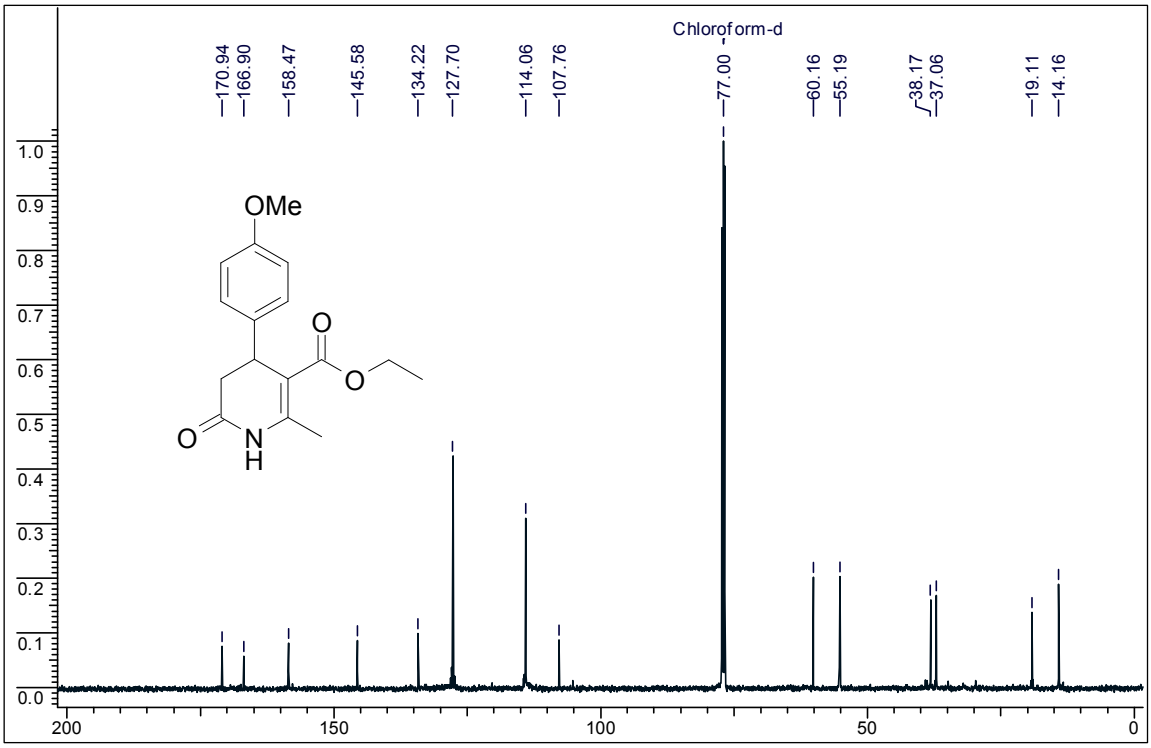
[3] ^{13}C NMR spectra of 135g



[4] ^{1}H NMR spectra of 135h



[4] ^{13}C NMR spectra of 135h



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SECTION-D

Synthesis of

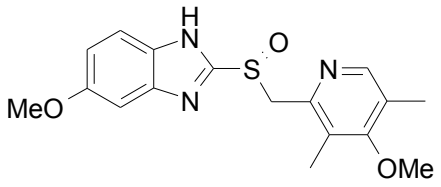
2-substituted benzimidazoles

/benzoxazoles/benzthiazoles

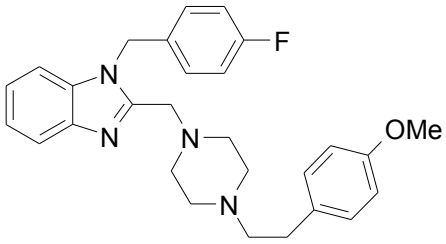
2.4.1 Introduction

Benzimidazole/benzoxazole/benzothiazoles are bicyclic compound having imidazole/oxazole/thiazole rings fused to benzene respectively.

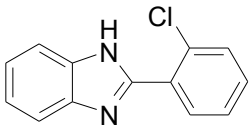
Benzimidazole nucleus is a part of the nucleotide portion of vitamin $B_{12,}$ in some drugs such as proton pump inhibitors, anthelmintic agents[1] and antirhino/enteroviral agents.[2] Benzimidazoles also exhibit significant activity against several viruses including HIV,[3] herpes (HSV-1),[4] RNA,[5] influenza[6] and human cytomegalovirus (HCMV). In recent years benzimidazoles have been reported to act as topoisomerase I inhibitors,[7] selective neuropeptide Y Y1 receptor antagonists,[8] angiotensin II (AII) inhibitors,[9] inhibitors of HCMV replication, potential antitumour agents,[10] antimicrobial agents,[11] smooth muscle cell proliferation inhibitors,[12] a treatment for interstitial cystitis,[13] antihistamine (astemiazole),[14] antifungal (chlorfenazol), anti-ulcerative (omeprazole)[15] (**Fig. 10**) anti-inflammatory activity[16] and in diverse areas of chemistry.[17]



Omeprazole



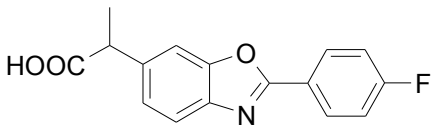
Astemizole



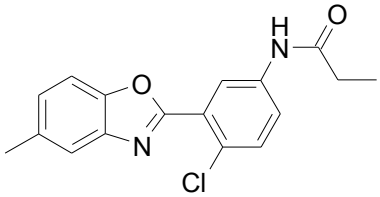
Chlorfenazol

Fig. 10

Benzoxazole is used primarily in industry and research as valuable precursors in many useful synthetic transformations.[18] Some of the substituted benzoxazole is a key intermediate of PPAR agonists for treatment of type 2 diabetes and dyslipidemic.[19] These also shows melatonin receptor agonist,[20] LPAAT-β,[21] cyclooxygenase inhibitory,[22] anticancer,[23] antimycobacterial,[24] elastase inhibitory[25] and VLA-4 antagonist[26] activities. It is also found within the chemical structures of pharmaceutical drugs such as flunoxaprofen (**Fig. 11**), constitute an important class of non-steroidal, anti-inflammatory drugs.[27] Benzoxazoles also find applications in material sciences as photo chromatic agents[28] and laser dyes.[29]



Flunoxaprofen

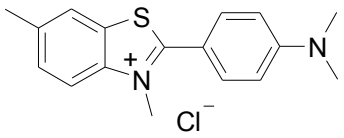


LPAAT-β inhibitor

Fig. 11

Benzothiazole derivatives are widely found in bioorganic and medicinal chemistry with applications in drug discovery and development for treatment of autoimmune and inflammatory diseases,[30] in the prevention of solid organ transplant rejection, epilepsy,[31] amyotrophic lateral sclerosis,[32] analgesia, tuberculosis, viral infections, and cancer.[33] They have also found applications in industry as antioxidants,[34] vulcanization accelerators,[35] and as a dopant in a light emitting organic electroluminescent device.[36]

Thiofalvin T (CI 49005) is a benzothiazole salt is used to visualize plaques composed of amyloid beta found in the brains of Alzheimer's disease patients. Riluzole is a drug used to treat amyotophic lateral sclerosis. It delays the onset of ventilator-dependence or tracheostomy in selected patients and may increase survival by approximately two months.



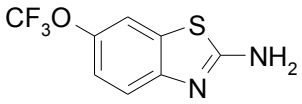


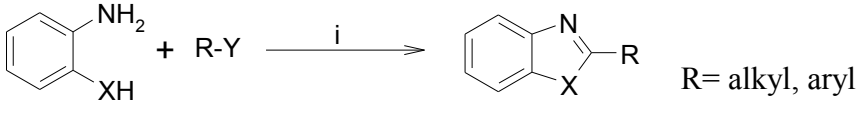
Fig. 12 **Thioflavin T** **Riluzole**

2.4.2 Review of literature

Alexandra Phillip was the first to synthesize benzimidazole by chemical method in 1930 and pioneered the synthetic preparatory methods for benzimdazole.[37] After that vast number of methods have been reported in the literature for the synthesis of these heterocycles due to their potent biological and material properties. This section summarizes some of the important synthetic methods for the synthesis of these heterocycles.

Hein's approach (1957)[38]

Hein and co-workers reported the preparation of 2-substituted benzimidazoles, benzoxazoles and benzothiazoles **138** by the condensation of a carboxylic acid, ester, amide or nitrile **137** with an *o*-amino, *o*-hydroxy or *o*-mercapto aryl amine **136** in the presence of poly phosphoric acid (PPA) as a solvent at high temperature (**Scheme 42**).

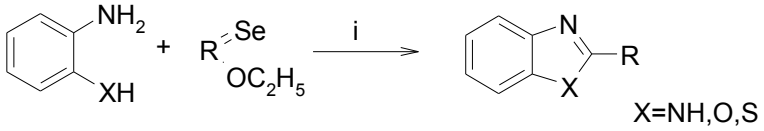


136 **137** **138**

Scheme 42. Reaction conditions; i) polyphosphoric acid (PPA), 250 ^{0}C, 4 h, 70-85%.

Cohen's approach (1977)[39]

Cohen *et al.* synthesized 2-susbstiuted benzimidazole, benzoxazole and benzothiazole **141** in moderate to good yield by reacting aliphatic selenoesters**140** with *o*-pheneylenediamine, *o*-aminophenol and *o*-aminothiophenol **139** respectively in ethanol (**Scheme 43**).

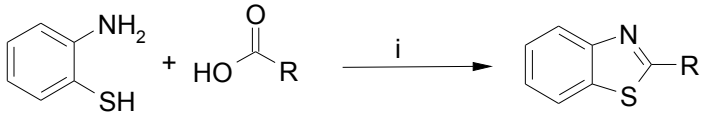


139 **140** **141**

Scheme 43. Reaction conditions; i) ethanol, 24 h, 50-70%.

Boger's approach (1978)[40]

Boger synthesized 2-substituted benzothiazoles **144** in good to moderate yield by the condensation of *o*-amino thiophenol **142** and respective acid **143** in the presence of catalytic amount of P_2O_5/CH_3SO_3H at elevated temperature (**Scheme 44**).

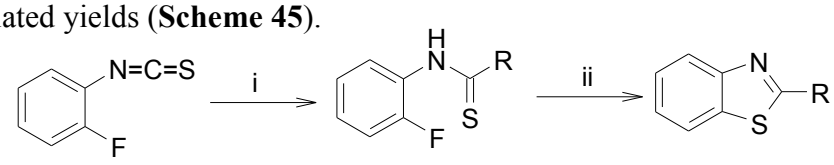


142 **143** **144**

Scheme 44. Reaction conditions; i) P_2O_5/CH_3SO_3H, 70 ^{0}C, 10 h, 55-70%.

Ares's approach (1991)[41]

Treatment of 2-fluorophenyiosthiocyanate **145** with Grignard reagent gave thioamide **146** which on treatment with base gave 2-susbtituted benzothiozoles **147** in good to excellent isolated yields (**Scheme 45**).



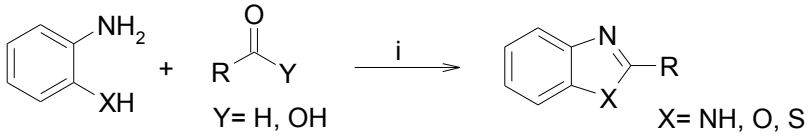
145 **146** **147**

Scheme 45. Reaction conditions; i) RMgX, THF, NH_4Cl; ii) NaH, toluene/DMF, 100 ^{0}C, 70-90%.

Souflaoui's approach (1998)[42]

Souflaoui reported *s*ynthesis of 2-substituted benzimidazole/benzoxazoles/benzothiazole **150** derivatives on mineral supports such as $Ca(OCl)_2$/ Al_2O_3 or MnO_2 / SiO_2 or by fusion in solvent free condition. The reactions are activated under microwave irradiation. The

reaction times are considerably shortened and the products are obtained in higher yields compare to conventional heating (**Scheme 46**).

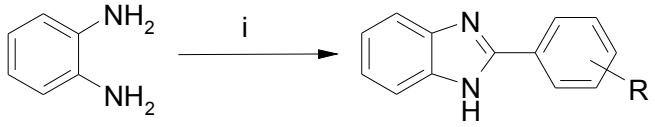


148 **149** **150**

Scheme 46. Reaction conditions: i) $Ca(OCl)_2$/ Al_2O_3 or MnO_2 / SiO_2, MW, 75-95%.

Beaulieu's approach (2003)[43]

Beaulieu *et al.* reported the rapid formation of benzimidazoles **152** by the addition of oxone® to a mixture of *o*-phenylenediamine **151** and substituted aromatic aldehydes in wet DMF at room temperature which affords benzimidazoles in excellent yield (**Scheme 47**).

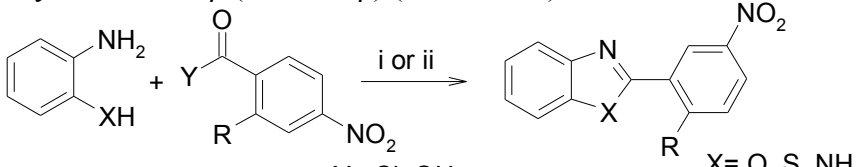


151 **152**

Scheme 47. Reagents and conditions: i) aromatic aldehyde, oxone, DMF: water, rt, 80-90%.

Klein's approach (2004)[44]

2-Arylbenzoxazoles, benzothiazoles and benzimidazoles **155** were synthesized from *o*-pheneylenediamine, *o*-aminophenol and *o*-aminothiophenol **153** which on reaction with benzoyl chloride or benzoic acid **154** in presence of base followed by treatment with acid catalyst delivered target molecules in good to excellent isolated yield. The target molecules were identified as new classes of potent, isoform specific inhibitors of lysophosphatidic acid acyltransferase-β (LPAAT-β) (**Scheme 48**).



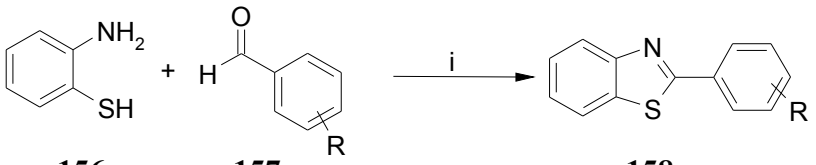
153 **154** **155**

Scheme 48. Reaction conditions: i) (a) Et_3N; (b) $_p$-TsOH, xylene, 110 ^{0}C; ii) PPA, 150 ^{0}C, 65-80%.

Ranu's approach (2004)[45]

Ranu *et al*. synthesized 2-arylbenzothiazoles **161** by condensing *o*-aminothiophenol **159** with aromatic aldehydes **160** in an ionic liquid, 1-pentyl-3-methylimidazolium bromide

([pmim]Br) using microwave irradiation under solvent and catalyst-free condition in excellent yield (**Scheme 49**).

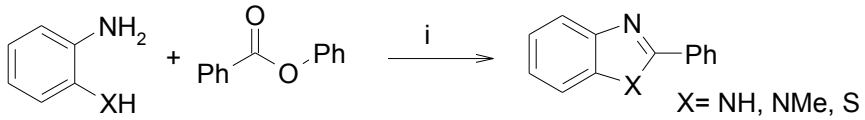


156 **157** **158**

Scheme 49. Reaction conditions: i) (a) [pmim]Br, MW or (b) [pmim]Br, 80 ^{0}C, 6 h, 80-95%.

Janda's approach (2004)[46]

Janda *et al.* synthesized different benzimidazoles and benzothiazoles **161** in excellent yield from polymer-bound esters **160** which was treated with *o*-aminothiophenols or *o*-phenylenediamines **159** in the presence of Lewis acid Et_2AlCl (**Scheme 50**).

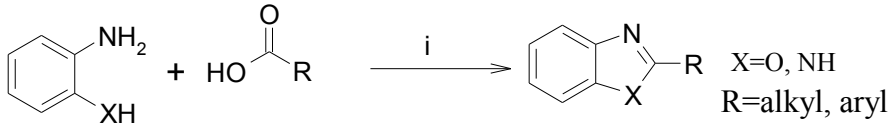


159 **160** **161**

Scheme 50. Reaction conditions: i) Lewis acid, toluene, reflux, 24 h, 75-90%.

Wang's approach (2006)[47]

Wang *et al.* synthesized 2-substituted benzoxazoles or benzimidazoles **164** by condensing a variety of carboxylic acids **163** with *o*-aminophenols or *o*-phenylenediamines **162** in presence of PS-PPh_3 resin combined under microwave irradiation in high yield (**Scheme 51**).

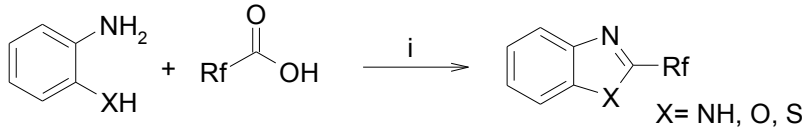


162 **163** **164**

Scheme 51. Reaction conditions; i) PS-PPh_3, CCl_3-CN, CH_3CN, MW, 150 ^{0}C., 85-95%.

Hao's approach (2007)[48]

Recently Hao and co-workers reported the synthesis of 2-trifluoromethyl and 2-difluoromethyl substituted benzimidazole, benzoxazole and benzothiazole derivatives **167**, through a one-pot reaction of trifluoroacetic acid and difluoroacetic acid **166**, respectively, with *o*-phenylenediamines, *o*-aminophenols, and *o*-aminobenzenethiols **165** in excellent yields (**Scheme 52**).

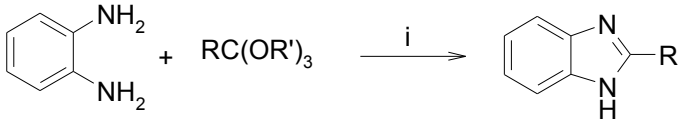


165 **166** **167**

Scheme 52. Reaction conditions: i) PPh_3, E_3N, CCl_4, refluxing, 80-90%.

Wang's approach (2007)[49]

Very recently Wang *et al.* reported the synthesis of benzimidazole derivatives **173** by the reaction of *o*-phenylenediamines **171** with orthoesters **172** in the presence of Lewis acids (**Scheme 53**).



168 **169** **170**

Scheme 53. Reaction conditions: i) Lewis acids, ethanol, rt, 75-90%.

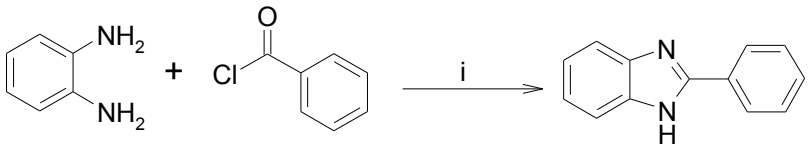
2.4.3 Present work

2.4.3.1 Objectives

The benzimidazole/benzoxazole/benzothiazoles nucleus is found in a variety of naturally occurring compounds. Interest in these structures stems from their widespread occurrence in molecules that display a plethora of useful biological properties such as antiulcer, anti-cancer and antiviral effects and is also a key feature in cardiotonic agents such as pimobenden, adibenden, potential antitumor agents. These compounds also possesses very good thermal stability and has been used as part of the backbone in high performance, high temperature polymers. Widely used traditional methods for their preparation involve the reaction of a carboxylic acid or its derivative with an appropriate *o*-phenylenediamine, *o*-aminophenol or *o*-aminothiophenol in the presence of a strong acid or cyclodehydration of mono-acylated product under acidic condition or by pyrolysis at 200–350 ^{0}C.

The preparatory methods reported in the literature for the synthesis of above heterocycles suffer from several drawbacks such as low yield, multiple reaction steps, tedious manipulations in the isolation of products and utilization of toxic reagents. The development of simple, efficient and environmentally benign chemical processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis.

2.4. 3.2 Results and discussion



171a **172a** **173a**

Scheme 54. Reaction conditions; i) $[Hbim]BF_4$, rt.

From previous study we found that IL $[Hbim]BF_4$ gives the best result compare to other ILs we have. Consequently to a clean mixture of *o*-phenylenediamine (**171a)** in $[Hbim]BF_4$ benzoyl chloride (**172a)** was added at room temperature and the reaction mixture was vigorously stirred. After the addition is over reaction mixture was stirred further and it complete in 10 min. (checked by TLC) and the product precipitated out as a solid. After completion of reaction, mixture was diluted with water and filtered off and dried under reduced pressure. The isolated product was further purified by column chromatography to give pure product **173a** in 93% yield which was fully characterized. The IR spectrum of **173a** shows absorption at 1640 and 3420 cm^{-1} corresponding to C=N and –NH functional group respectively. The ^1H NMR spectrum of **173a** showed broad singlet at δ 4.5 for –N*H* and multiplet of nine protons in the region of 7.32-8.19 for aromatic region. The elemental analysis and the physical constant were compare to the literature values of **173a**.

Generally the synthesis of benzimidazole proceeds through a two step process. First is the acylation followed by cyclization using acid catalyst at elevated temperature? In first step hydrochloric acid is librated as a by product during the reaction, we thought that this librated hydrochloric acid may facilate the further cyclization to deliver the target 2-phenyl benzimidazole **173a**. To check this we performed the reaction of **173a** in molecular solvent (acetonitrile) without any added catalyst, we got only the mono-acylated product exclusively with no trace of benzimidazole. This indicates that the librated hydrochloric acid is not taking part in the further cyclization step. As we wish to establish the role of IL as solvent to cum promoter for this heterocyclization, we performed another experiment for the synthesis of **176a** using IL $[Hbim]BF_4$. In this reaction we trapped the librated hydrochloric acid by addition of base potassium carbonate, however reaction proceeded to give the 2-phenyl benzimidazole as the sole product. These results confirmed that IL

[Hbim]BF_4 due to its large electrochemical window and inherent Brønsted acidity promoted this heterocyclization for the formation of target molecule 2-phenyl benzimidazole in excellent yield in a short reaction time.

We screened several imdazolium ILs synthesized by us along with two non-imidazolium ILs such as ethyl ammonium nitrate and *n*-butylpyridinium tetrafluoroborate as solvents and promoters for the typical reaction of 1,2-phenylendiamine (**171a)** with benzoyl chloride (**172a)** under ambient conditions in the absence of any added catalyst to afford 2-phenyl benzimidazole (**173a**). The time for complete conversion and yield data are recorded in Table 12.

Table 12. Synthesis of 2-phenyl benzimidazole (**173a**) in different ILs

ILs	pK_a [a]	–NH proton δ ppm	$E_T(30)$ (kcal mol^{-1}) [b]	Time (min.)	Yield [c] (%)
[bbim]ClO_4	-11	--	76.34	130	87
[bbim]Br	-9	--	66.49	40	90
[bbim]Cl	-7	--	68.89	45	93
[bbim]BF_4	**0.5**	**--**	**75.73**	**40**	**92**
[Hbim]ClO_4	-11	11.83	63.82	90	84
[Hbim]Br	-9	12.17	73.68	18	92
[Hbim]Cl	-7	12.22	73.59	18	92
[Hbim]BF_4	**0.5**	**14.59**	**74.35**	**10**	**95**
Et $^{\oplus}NH_3$ $^{\ominus}NO_3$	--	--	--	5.3 h	70
n-butyl pyridinium tetrafluoroborate	--	--	--	5.3 h	73

[a:] The pK_a values of the parent acids of the anions; [b:] Polarity of ILs determined by Reichardt's dye; [c:] Isolated yield after column chromatography;.

The IL [Hbim]BF_4 among the monoalkyl imidazolium and [bbim]BF_4 among the dialkyl imidazolium respectively afforded the best results. The efficacy of the ILs to promote these heterocyclization reactions was correlated not only to the basicity of the anions but also with the polarity of ionic liquids. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a

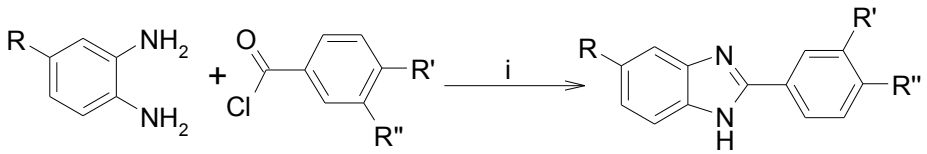
bearing on the acidity of the ILs. It is worth noting that the synthesis of 2-phenyl benzimidazole, the non-imidazolium ILs such as n-butyl pyridinium tetrafluoroborate (entry 12) and ethyl ammonium nitrate (entry 11) took much longer time (5.3 h) to afford **173a** in relatively lowered yields (70-73%).

The effect of mole ratio of the IL [Hbim]BF_4 with respect to the formation of **173a** was investigated (Table 13). It can be observed that a minimum of equimolar proportion of the IL is required for optimum result.

Table 13. Catalytic study of [Hbim]BF_4 for formation of **173a**

Entry	mole ratio of [Hbim]BF_4/benzoyl chloride	Yield[b] (%)	Time (h)
1	Nil[a]	00	12
2	0.2[a]	10	12
3	0.4[a]	25	12
4	0.6[a]	35	12
5	0.8[a]	75	1
6	1.0	93	0.1

[a]: Reaction condition; OPD (1 mmol), benzoyl chloride (1 mmol), acetonitrile solvent;
[b]: Isolated yield after purification.

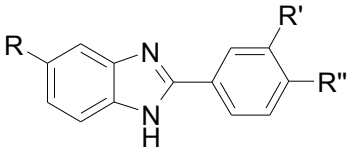


171a-c **172a-c** **173a-i**

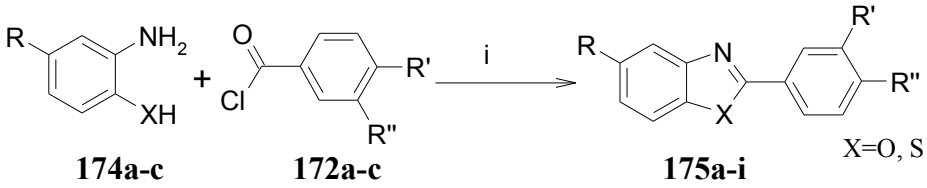
Scheme 55. Reaction conditions: i) [Hbim]BF_4, rt

It becomes evident from above results (Table 13 and 14), the IL [Hbim]BF_4 afforded the best results. Consequently, all further studies were conducted at room temperature using IL [Hbim]BF_4 to synthesizes different 2-susbtituted benzimidazole/benzoxazole/benzo thiazole. The results are recorded in Table 14.

Table 14. Data for the synthesis of benzimidazoles **173a-i**

Entry				Time (min.)	Yield [a] (%)
	173a-l				
	R	**R'**	**R''**		
173a	H	H	H	10	93
173b	H	H	NO_2	20	88
173c	H	F	CF_3	15	85
173d	Me	H	H	10	95
173e	Me	H	NO_2	20	89
173f	Me	F	CF_3	15	90
173g	COPh	H	H	20	94
173h	COPh	H	NO_2	30	83
173i	COPh	F	CF_3	25	91

[a]: Isolated yields after purification

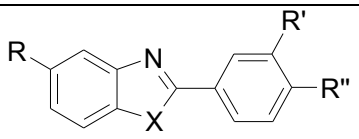


174a-c **172a-c** **175a-i**

Scheme 56. Reaction conditions: i) $[Hbim]BF_4$, rt

In a similar manner, the benzoxazole and benzthiazole was synthesized. The results are recorded in Table 15.

Table 15. Data for the synthesis of 2-substituted benzoxazole/benzthiazoles **175a-i**

Entry					Time (min.)	Yield [a] (%)
	175a-i					
	X	**R**	**R'**	**R''**		
175a	O	H	H	H	10	93

175b	O	H	H	NO_2	20	88
175c	O	H	F	CF_3	15	85
175d	O	Cl	H	H	10	95
175e	O	Cl	H	NO_2	25	89
175f	O	Cl	F	CF_3	15	90
175g	S	H	H	H	10	84
175h	S	H	H	NO_2	25	88
175i	S	H	F	CF_3	15	87

[a:] Isolated yields after purification

2.4.4 Conclusion

In conclusion, we have developed a novel one-pot synthesis of 2-susbtituted benzimidazoles/benzoxazoles/benzthiazoles in excellent isolated yields at ambient conditions using ionic liquid [Hbim]BF_4 as a reaction medium cum promoter. For this process, there was no need for any additional catalyst, which are generally required in the methodologies reported so far. The efficacy of the ILs to promote these heterocyclization reactions was correlated not only to the basicity of the anions but also with the polarity of ionic liquids. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there is a progressive increase in yield. The ambient reaction conditions, absence of a catalyst and recyclability of the non-volatile ILs makes this an environment friendly methodology amenable for scale up. This work already peer reviewed and published in *J. Mole. Cata. A*. **2004,** *214,* 155.

2.4.5 Experimental

Typical procedure for synthesis of 2-phenyl benzimidazole (173a) in [Hbim]BF_4 :

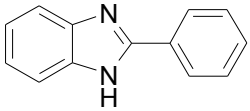
A mixture of *o*-phenylenediamine (4.6 mmol) and benzoyl chloride (4.6 mmol) in [Hbim]BF_4 (4.6 mmol) was stirred at room temperature. After completion of the reaction (progress of reaction was monitored by TLC), reaction mixture was diluted with water (10

mL) and the separated product was filtered and dried under reduced pressure. The product, thus isolated, was pure enough. It was subjected to further purification by column chromatography using 20% EtOAc in petroleum ether as eluent and fully characterized.

The aqueous layer consisting of the IL was subjected to distillation (80 ^{0}C at 10mm Hg) for 2 h to remove water, leaving behind the IL [Hbim]BF_4 (recovery 96%), which was recycled.

2.4.5.1 Characterization data

2-phenyl-1H-benzimidazole (173a)



M. P. (^{0}C) **:** 294-295

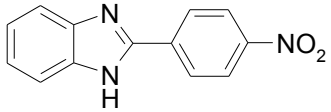
IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 735, 810, 1035, 1140, 1310, 1463, 1643, 3420.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.3 (brs, 1H), 7.32-8.19 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) **: δ** 112, 115.3, 121.7, 122.5, 126.4, 129, 130, 130.3, 134.9, 143.6, 151.6.

Elemental Analysis **: $C_{13}H_{10}N_2$** Calcd. C, 80.39; H, 5.19; N, 14.42.
Found C, 80.19; H, 5.05; N, 14.23.

2-(4-nitrophenyl)-1H-benzimidazole (173b)



M. P. (^{0}C) **:** 215-217 (decomposes)

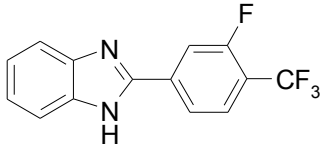
IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 718, 1279, 1348, 1461, 1524, 1635, 2925, 3441.

^{1}H NMR (200 MHz, $CDCl_3$/ DMSO-*d_6*) **: δ** 7.26-7.32 (m, 2H), 7.70-7.74 (m, 4H), 8.21-8.24 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$/ DMSO-*d_6*) **: δ** 115.4, 121.6, 123.3, 128.4, 136.8, 138.9, 148.4, 152.9.

Elemental Analysis **: $C_{13}H_9N_3O_2$** Calcd. C, 65.27; H, 3.79; N, 17.56.
Found C, 65.15: H, 3.62; N, 17.45.

2-(3-fluoro-4-(trifluoromethyl)phenyl)-1H-benzimidazole (173c)



M. P. (^{0}C) **:** 166-167

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 835, 1134, 1448, 503, 1641, 2923, 3413.

^{1}H NMR **: δ** 4.84 (brs, 1H), 7.19-7.68 (m, 6H), 8.09 (s, 1H),

(200 MHz, $CDCl_3$/ DMSO-d_6)

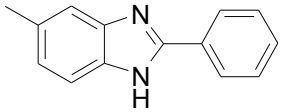
^{13}C NMR : **δ** 113.2, 115.2, 116.0, 119.1, 122.9, 123.0, 127.3, 136.0, 138.9,

(50 MHz, $CDCl_3$/ DMSO-d_6) 152.9, 158.0.

Elemental Analysis : **$C_{14}H_8F_4N_2$** Calcd. C, 60.01; H, 2.88; N, 10.00

Found C, 59.87; H, 2.61; N, 09.72.

5-methyl-2-phenyl-1H-benzimidazole (173d)



M. P. (^{0}C) : 235-236

IR ($CHCl_3$, cm^{-1}) : υ_{max} 835, 1134, 1448, 503, 1641, 2923, 3395.

^{1}H NMR : **δ** 2.19 (s, 3H), 3.4 (brs, 1H), 6.44-6.75 (m, 2H), 7.04-7.08 (m, 4H)

(200 MHz, $CDCl_3$) 7.38-7.47 (m, 3H), 7.93-7.97 (m, 2H).

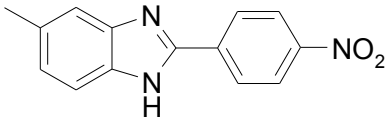
^{13}C NMR : **δ** 19.1, 116.26, 117.2, 120.2, 125.1, 126.5, 126.9, 130, 133.4, 135,

(50 MHz, $CDCl_3$) 138.3, 140.8

Elemental Analysis : **$C_{14}H_{12}N_2$** Calcd. C, 80.74; H, 5.81; N, 13.45.

Found C, 80.61; H, 5.64; N,13.28.

5-methyl-2-(4-nitrophenyl)-1H-benzimidazole (173e)



M. P. (^{0}C) : 240-241

IR ($CHCl_3$, cm^{-1}) : υ_{max} 708, 1035, 1140, 1279, 1318, 1450, 1534, 1645, 2925, 3421.

^{1}H NMR : **δ** 2.31 (s, 3H), 7.06 (m, 1H), 7.50-7.55 (m, 2H), 7.71-7.73

(200 MHz, $CDCl_3$/ DMSO-d_6) (d, *J*= 7.5 Hz, 2H), 8.25 (m, 2H)

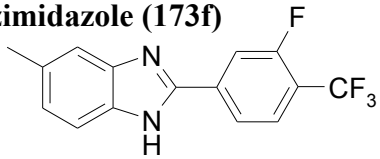
^{13}C NMR : **δ** 23, 114.8, 115.3, 121.6, 125.4, 128.6, 132.3, 136, 136.8, 138.8,

(50 MHz, $CDCl_3$/ DMSO-d_6) 148.4, 153.2.

Elemental Analysis : **$C_{14}H_{11}N_3O_2$** Calcd. C, 66.40; H, 4.38; N, 16.59.

Found C, 66.29; H, 4.29; N, 16.34 .

2-(3-fluoro-4-(trifluoromethyl)phenyl)-5-methyl-1H-benzimidazole (173f)



M. P. (^{0}C) : 174-175

IR ($CHCl_3$, cm^{-1}) : υ_{max} 752, 810, 945, 1123, 1322, 1418, 1645, 3430.

^{1}H NMR : **δ** 2.38 (s, 3H), 4.64 (brs, NH), 7.01-7.63 (m, 5H), 7.87 (s, 1H).

(200 MHz, $CDCl_3$)

^{13}C NMR **: δ** 24.3, 113.4, 115.2, 115.8, 116.3, 123.4, 125.3, 127.3, 132.2,

(50 MHz, $CDCl_3$) 135.3, 136.4, 138.9, 153, 158.3.

Elemental Analysis **: $C_{15}H_{10}F_4N_2$** Calcd. C, 61.23; H, 3.43; N, 9.52.

Found C, 61.13; H, 3.28; N, 9.40.

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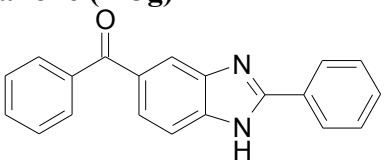
phenyl(2-phenyl-1H-benzimidazol-5-yl)methanone (173g)



M. P. (^{0}C) **:**221-222

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 810, 950, 1040, 1320, 1418, 1545, 1640, 1715, 3420.

^{1}H NMR **: δ** 4.52 (brs, 1H), 7.38-7.95 (m, 13H).

(200 MHz, $CDCl_3$/ DMSO-*d_6*)

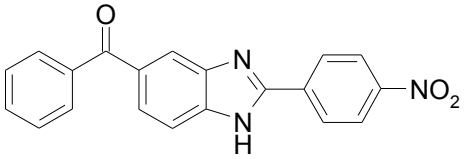
^{13}C NMR **: δ** 115.2, 121.9, 125.8, 127.3, 127.8, 128.8, 129.4, 129.7, 130.1,

(50 MHz, $CDCl_3$/ DMSO-*d_6*) 133.5, 135, 138, 146.8, 166.3, 194.2.

Elemental Analysis **: $C_{20}H_{14}N_2O$** Calcd. C, 80.52; H, 4.73; N, 9.39.

Found C, 80.28; H, 4.68; N, 9.15 .

(2-(4-nitrophenyl)-1H-benzimidazol-5-yl)(phenyl) methanone (173h)



M. P. (^{0}C) **:** 240-241

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 780, 960, 1148, 1250, 1418, 1545, 1645, 1710, 2810, 3415.

^{1}H NMR **: δ** 7.36-7.45 (m, 3H), 7.70-7.80 (m, 6H), 8.14-8.25 (m, 3H)

(200 MHz, $CDCl_3$/ DMSO-*d_6*)

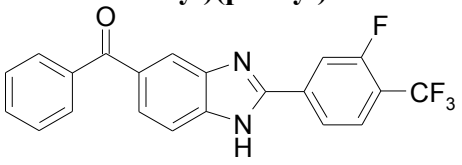
^{13}C NMR **: δ** 115, 119.2, 121.6, 125.2, 128.3, 128.7, 130.3, 131.2, 132.4, 136,

(50 MHz, $CDCl_3$/ DMSO-*d_6*) 138.3, 139.7, 141.3, 142.8, 148.6, 152.9, 195.8.

Elemental Analysis **: $C_{20}H_{13}N_3O_2$;** Calcd. C, 69.96; H, 3.82; N, 12.24.

Found C, 69.42; H, 3.29; N, 11.86.

(2-(3-fluoro-4-(trifluoromethyl)phenyl)-1H-benzimidazol-5-yl)(phenyl)methanone (173i)



M. P. **:** 226-227

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 1139, 1250, 1463, 1657, 1710, 2949, 3424.

^{1}H NMR **: δ** 7.12-7.49 (m, 6H), 7.73-7.81 (m, 3H), 8.14 (s, 1H)

(200 MHz, $CDCl_3$/ DMSO-*d_6*)

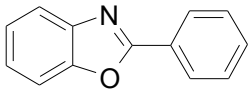
^{13}C NMR **: δ** 113.4, 115.2, 116.8, 118.7, 119, 123.4, 125.6, 127.5, 128.5,

(50 MHz, $CDCl_3$/ DMSO-*d_6*) 130.3, 131.2, 132.5, 135.4, 138.6, 139, 153, 158.2, 196.5.

Elemental Analysis **: $C_{21}H_{12}F_4N_2O$** Calcd. C, 65.63; H, 3.15; N, 7.29.

Found C, 65.21; H, 2.74; N, 6.89 .

2-phenyl benzoxazole (175a)



M. P. (^{0}C) **:** 102-103

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 668, 1010, 1453, 1528, 1634, 3019

^{1}H NMR(200 MHz, $CDCl_3$) : δ 7.27-7.83 (m, 7H), 8.25-8.30 (m, 2H).

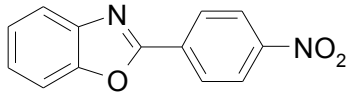
^{13}C NMR **: δ** 110.5, 119.2, 123.9, 124.4, 126.2, 127.5, 128.3, 129.4, 141.5,

(50 MHz, $CDCl_3$) 150.2, 162.8.

Elemental Analysis **: $C_{13}H_9NO$** Calcd. C, 79.98; H, 4.65; N, 7.17.

Found C, 79.75; H,4.58; N, 7.08.

2-(4-nitrophenyl)benzoxazole (175b)



M. P. (^{0} C) **:** 145-146

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 812, 1020, 1432, 1469, 1567, 1589.

^{1}H NMR **: δ** 7.30–7.35 (m, 5H), 7.53–7.60 (m, 2H), 8.22-8.26 (m, 2H),

(200 MHz, $CDCl_3$/ DMSO-*d_6*)

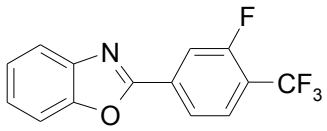
^{13}C NMR **: δ** 110.7, 119.2, 121.6, 123.9, 124.8, 127.9, 132.5, 141.4, 149,

(50 MHz, $CDCl_3$/ DMSO-*d_6*) 154.2.

Elemental Analysis **: $C_{13}H_8N_2O_3$** Calcd. C, 65.00; H, 3.66; N, 11.66.

Found C, 64.82; H, 3.48; N, 11.54.

2-(3-fluoro-4-(trifluoromethyl)phenyl)benzoxazole (175c)



M. P. (^{0} C) **:** 150-151

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 1019, 1258, 1513, 1593, 3394.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.12-7.49 (m, 7H)

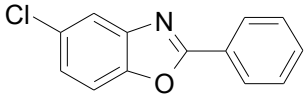
^{13}C NMR **: δ** 110.7, 113.4, 116.2, 119.5, 123.4, 123.8, 124.9, 127.3, 131.1,

(50 MHz, $CDCl_3$ 141.2, 150, 158.2, 162.7.

Elemental Analysis : $C_{14}H_7F_4N_2O$ Calcd. C, 59.80; H, 2.51; N, 4.98.

Found C, 59.68; H, 2.40; N, 4.72.

5-chloro-2-phenyl benzoxazole (175d)



M. P. (^{0}C) : 123-124

IR ($CHCl_3$, cm^{-1}) : υ_{max} 690, 750, 1460, 1565, 1620, 2800, 3070.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.25-7.51 (m, 8H)

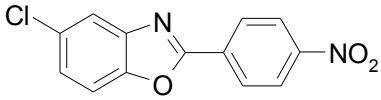
^{13}C NMR : **δ** 112.5, 117.7, 122.8, 126.2, 127.5, 128.3, 128.5, 129.3,

(50 MHz, $CDCl_3$) 142.9, 148.1, 162.7.

Elemental Analysis : $C_{13}H_8ClNO$ Calcd. C, 67.99; H, 3.51; N, 6.10.

Found C,67.85; H, 3.28; N, 5.98.

5-chloro-2-(4-nitrophenyl)benzoxazole (175e)



M. P. (^{0}C) : 178-179

IR ($CHCl_3$, cm^{-1}) : υ_{max} 690, 750, 1460, 1565, 1620, 2800, 3070.

^{1}H NMR : **δ** 7.20-7.27 (m, 3H), 7.73-7.75 (m, 2H), 8.24-8.27 (m, 2H)

(200 MHz, $CDCl_3$)

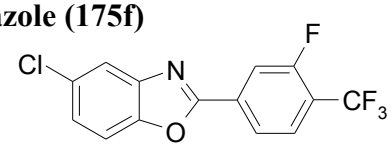
^{13}C NMR : **δ** 112.1, 118, 121.6, 122.8, 128.5, 132.3, 142.9, 148.2, 162.7.

(50 MHz, $CDCl_3$)

Elemental Analysis : $C_{13}H_7ClN_2O_3$ Calcd. C, 56.85; H, 2.57; N, 10.20.

Found C, 56.71; H, 2.38; N, 09.98.

5-chloro-2-(3-fluoro-4-(trifluoromethyl)phenyl)benzoxazole (175f)



M. P. (^{0} C) : 160-161

IR ($CHCl_3$, cm^{-1}) : υ_{max} 1019, 1258, 1513, 1593, 3394.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.15-7.49 (m, 6H)

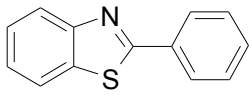
^{13}C NMR : **δ** 112.1, 113.4, 116.5, 117.4, 118.7, 122.9, 123.3, 127.3, 128.7,

(50 MHz, $CDCl_3$ 131.2, 142.9, 148.2, 158.3, 162.7.

Elemental Analysis : $C_{14}H_6ClF_4NO$ Calcd. C, 53.27; H, 1.92; N, 4.44.

Found C, 53.18; H, 1.73; N, 4.28.

2-phenyl benzthiazole (175g)



M. P. (^{0}C) : 102-103

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27-7.53 (m, 5H), 7.95-8.13 (m, 4H).

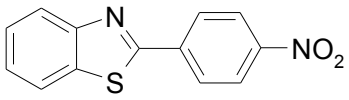
^{13}C NMR : **δ** 110.5, 119.2, 123.9, 124.4, 126.2, 127.5, 128.3, 129.4, 141.5,

(50 MHz, $CDCl_3$) 150.2, 162.8.

Elemental Analysis : **$C_{13}H_9NO$** Calcd. C, 79.98; H, 4.65; N, 7.17.

Found C,79.85; H, 4.58; N,7.08.

2-(4-nitrophenyl)benzthiazole (175h)



M. P. (^{0} C) : 145-146

IR ($CHCl_3$, cm^{-1}) : υ_{max} 750, 830, 1450, 1610, 2200.

^{1}H NMR(200 MHz, $CDCl_3$/ DMSO-d_6) : δ 7.55–7.74 (m, 4H), 8.12-8.26 (m, 4H),

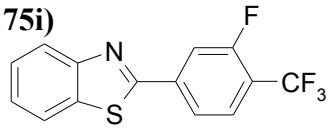
^{13}C NMR : **δ** 121.6, 121.8, 125.2, 125.9, 128.4, 135.8, 139.6, 148, 154.2,

(50 MHz, $CDCl_3$/ DMSO-d_6) 166.8.

Elemental Analysis : **$C_{13}H_8NO_2S$** Calcd. C, 60.93; H, 3.15; N, 10.93.

Found C, 60.75; H, 2.98; N, 10.64.

2-(3-fluoro-4-(trifluoromethyl)phenyl)benzthiazole (175i)



M. P. (^{0} C) : 167-168

IR ($CHCl_3$, cm^{-1}) : υ_{max} 810, 915, 1035, 1460, 1900, 215, 2200.

^{1}H NMR : **δ** 7.12-7.18 (m, 2H), 7.49-7.55 (m, 3H), 8.12-8.23 (m, 2H).

(200 MHz, $CDCl_3$)

^{13}C NMR : **δ** 113.4, 116.2, 118.5, 121.4, 121.8, 123.9, 124.3, 125.8,

(50 MHz, $CDCl_3$ 127.3, 134.2, 138.2, 154.4, 158.2, 166.6.

Elemental Analysis : **$C_{14}H_7F_4NS$** Calcd. C, 56.56; H, 2.37; N, 4.71.

Found C, 56.38; H, 2.20; N, 4.62.

2.4.5.2 Spectra's of some selected compounds

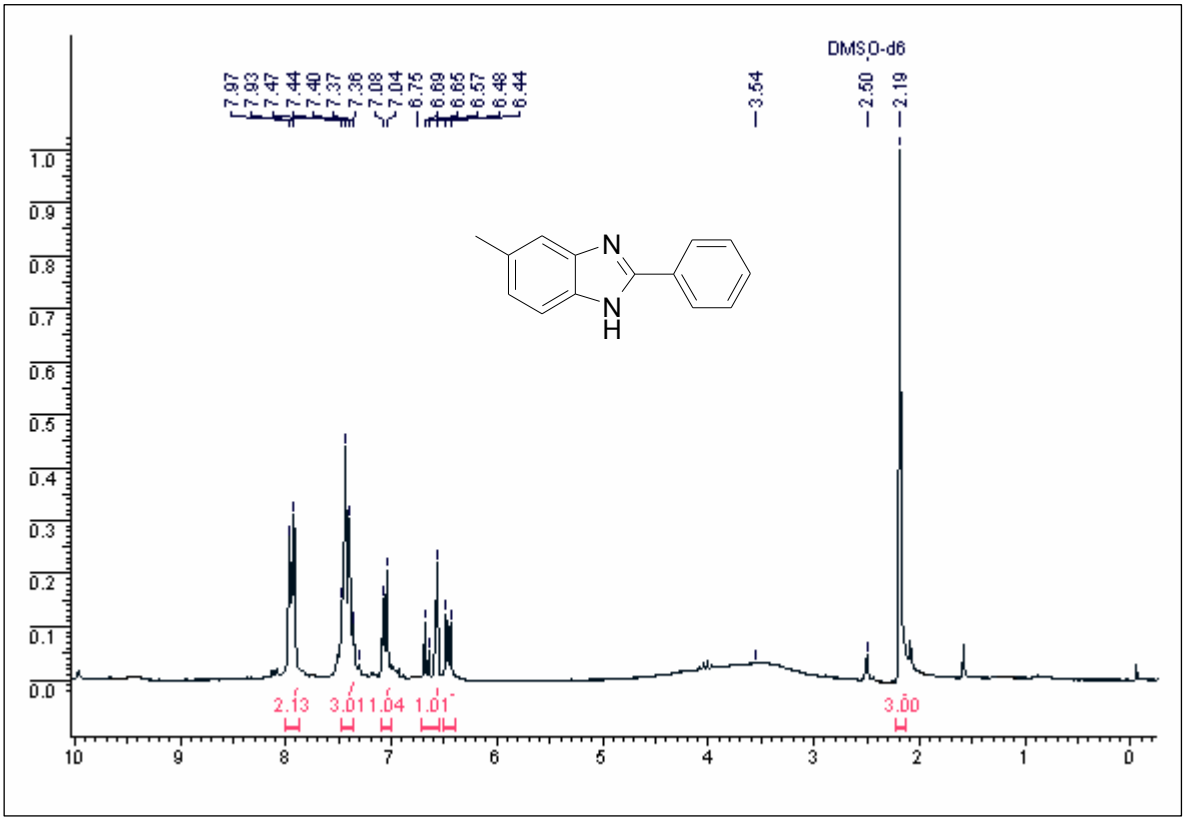
[1] ^{1}H NMR and ^{13}C NMR spectra of **173d**

[2] ^{1}H NMR and ^{13}C NMR spectra of **173g**

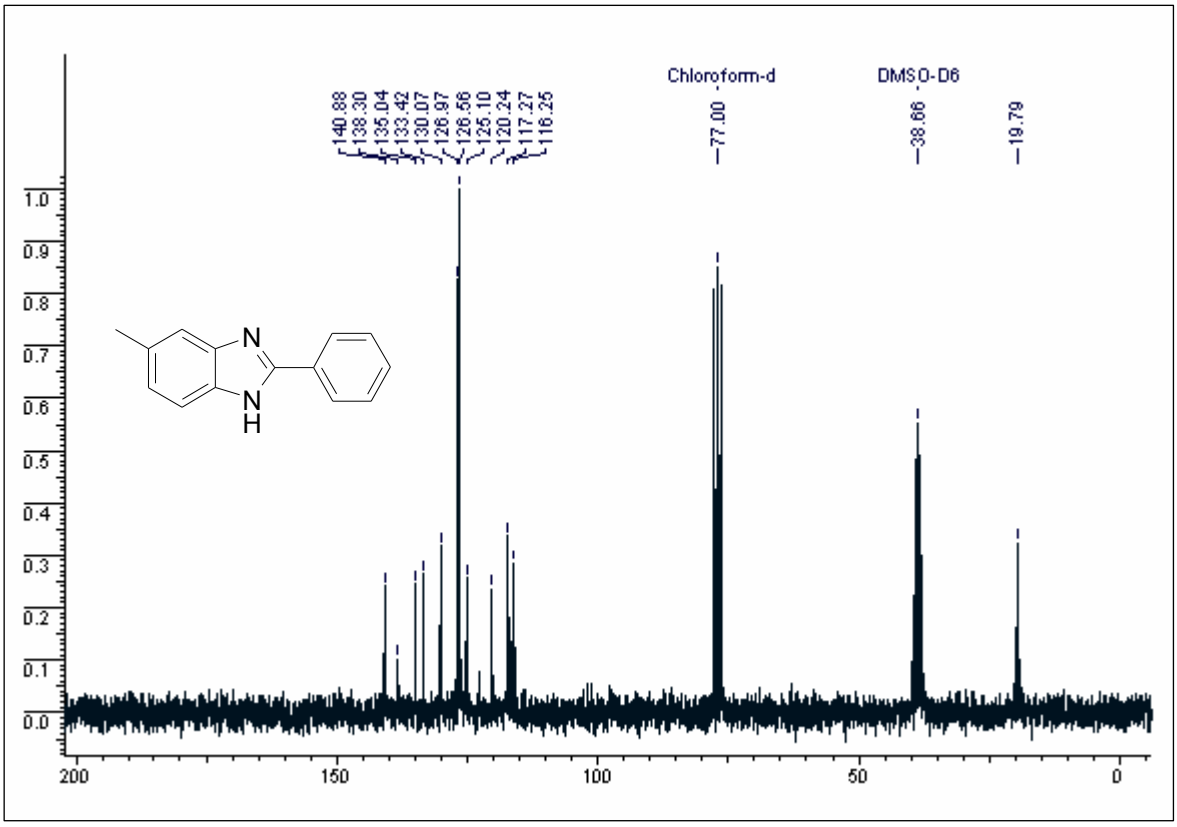
[3] ^{1}H NMR spectra of **175a**

[4] ^{1}H NMR spectra of **175g**

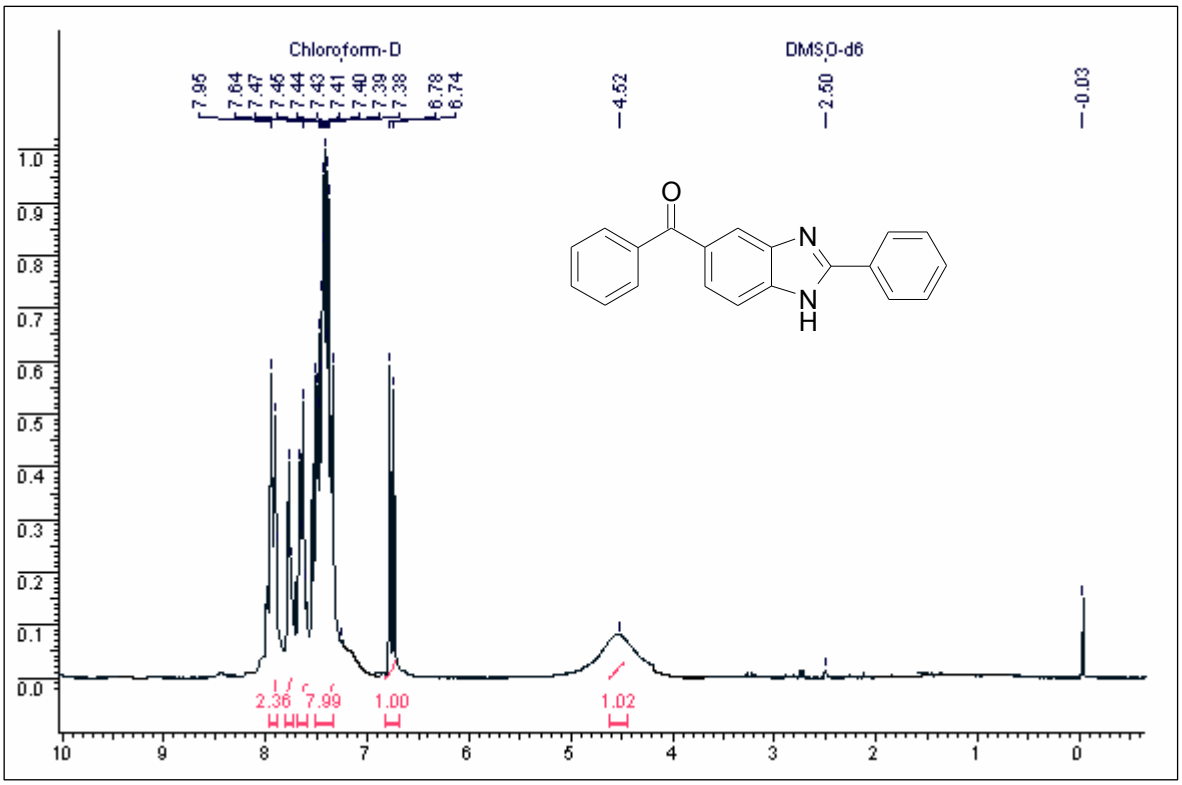
[1] ^{1}H NMR spectra of 173d



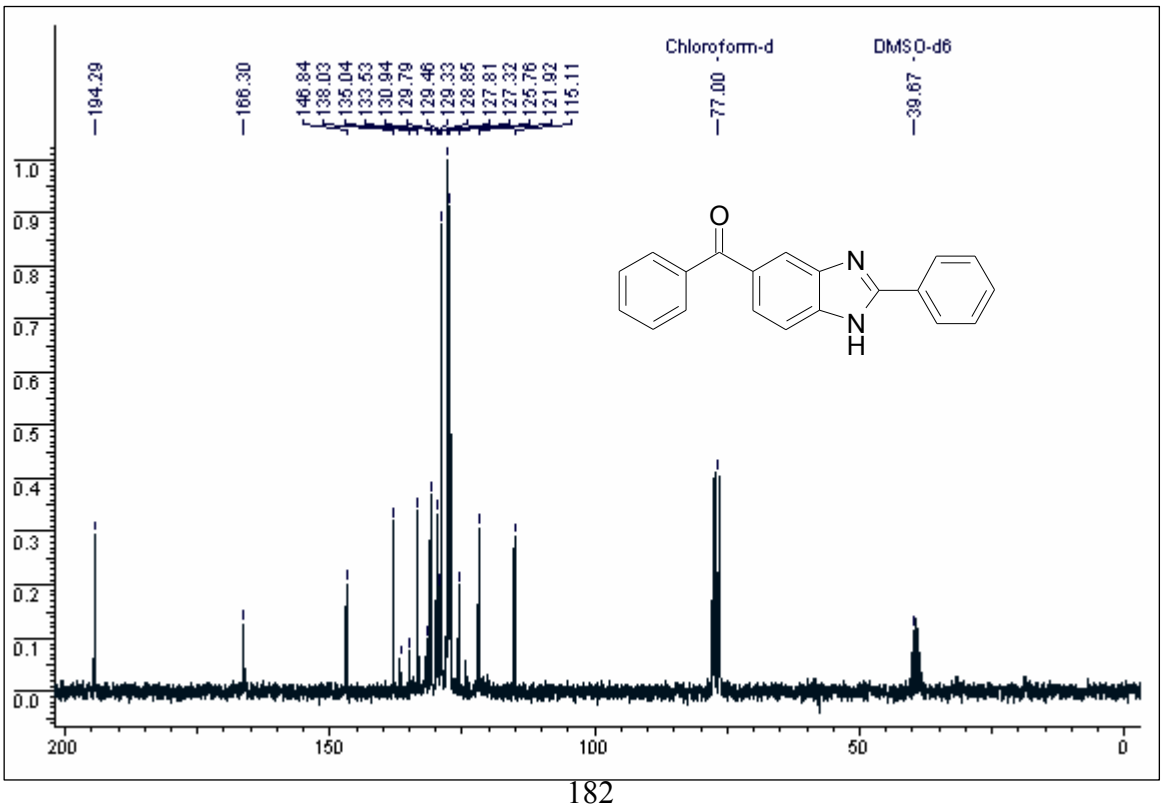
[1] ^{13}C NMR spectra of 173d



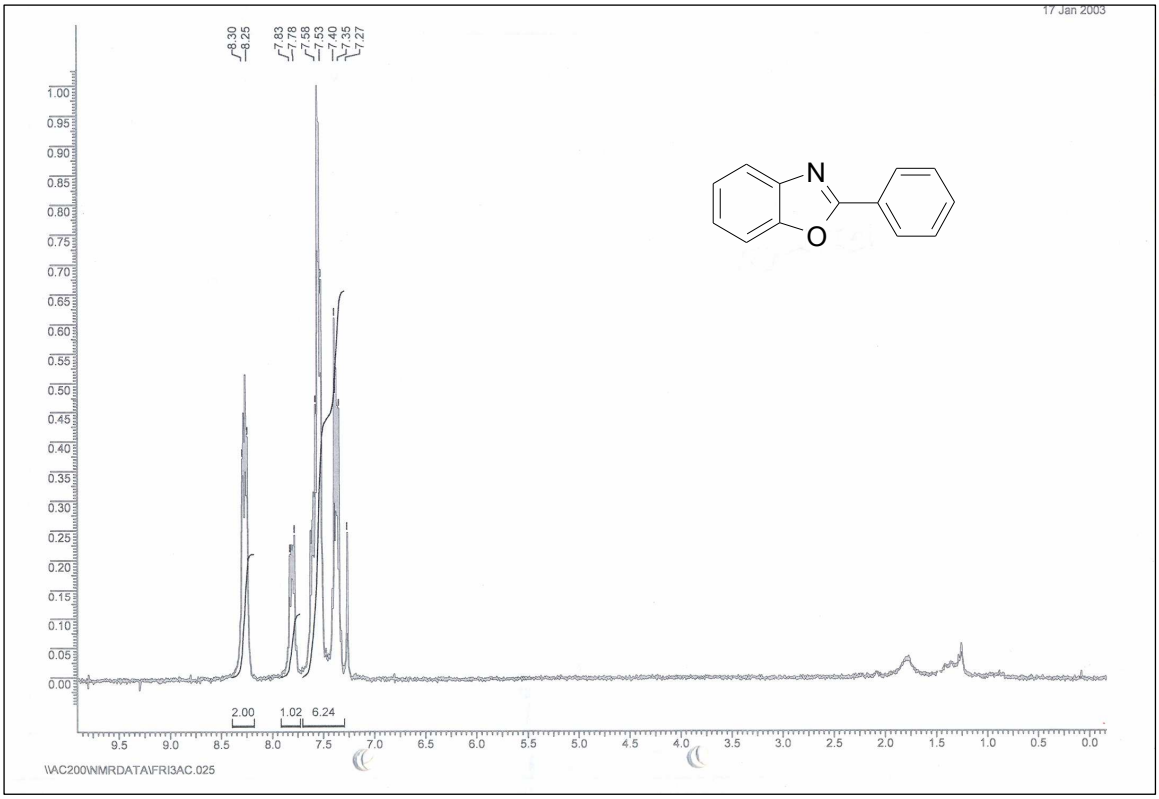
[2] ^{1}H NMR spectra of 173g



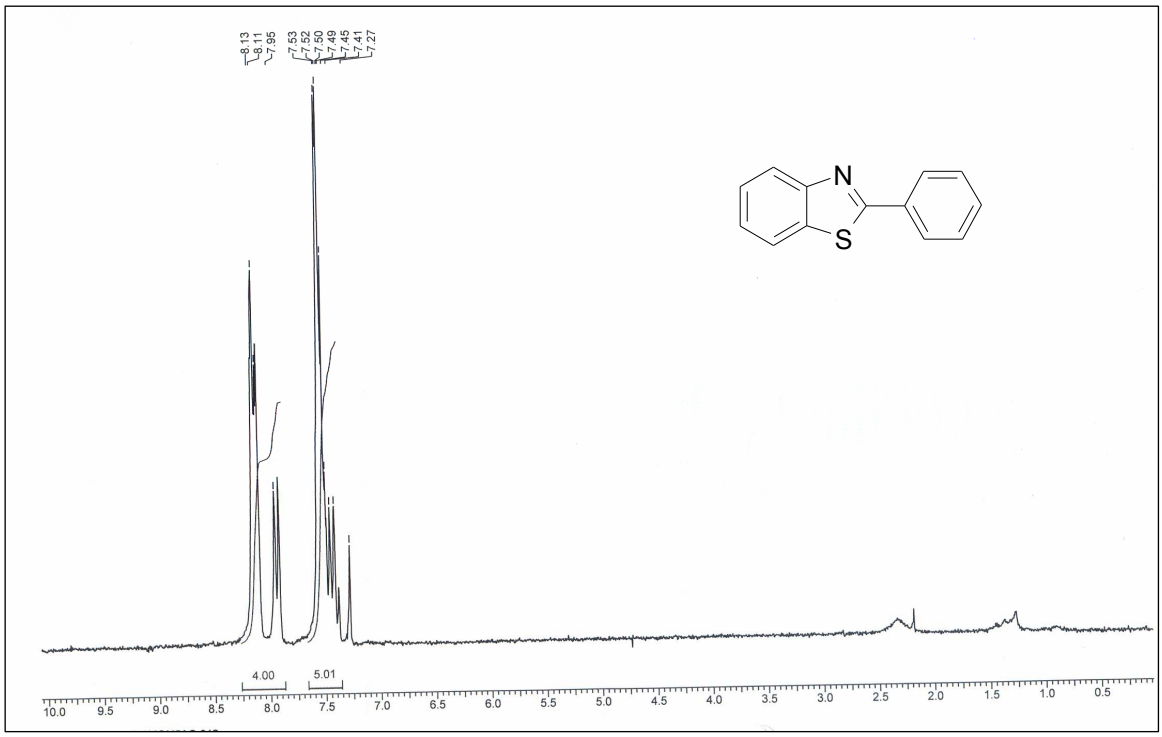
[2] ^{13}C NMR spectra of 173g



[3] ^{1}H NMR spectra of 175a



[4] ^{1}H NMR spectra of 175g



2.4.6 References

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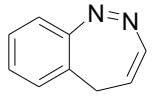
SECTION-E

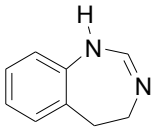
Synthesis of 1, 5-benzodiazepines

2.5.1 Introduction

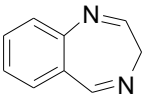
Benzodiazepines are bicyclic heterocyclic compounds having a benzene nucleus fused to a seven-membered ring containing two nitrogen atoms. The following six formulae represents the basic ring structures of benzodiazepines. The term benzodiazepine implies a maximum degree of instauration, i.e. a total of three double bonds in the seven-membered ring. The position of the odd hydrogen atom (even if occupied by another mono- or divalent substituents) is indicated by the term lH, 2H, 3H, etc.



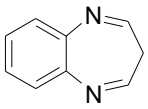
5H-1,2-benzodiazepines



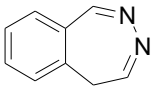
1H-1,3-benzodiazepines



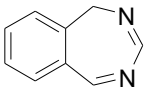
3H-1,4-benzodiazepines



3H-1,5-benzodiazepines



5H-2,3-benzodiazepines

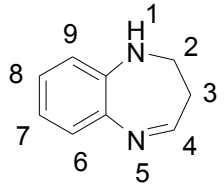


1H-2,4-benzodiazepines

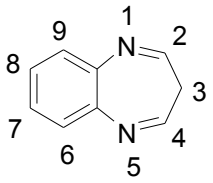
The 1,4 benzodiazepines form the most extensively explored group in this series, largely owing to the discovery of their interesting biological activity, which has led to the introduction of four drugs. The l,5-benzodiazepines have been thoroughly studied during a period of several decades, largely because of their relatively easy synthesis from common starting materials. The other four groups of benzodiazepines have so far failed to attract very much interest.

1,5-Benzodiazepines may exit in either of the tautomeric forms A or B (**Fig. 13**). While the 3*H* tautomer is, in general, thermodynamically preferred, mono protonation renders the 1*H* tautomer energetically more favorable, and most of the salts of 1,5-enzodiazepines occur in this form.

Fig. 13.



1H-1,5-Benzodiazepines (A)

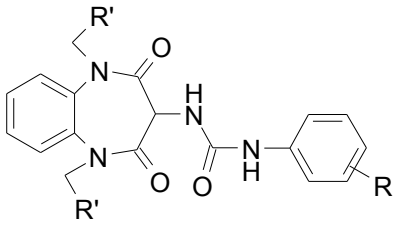


3H-1,5-Benzodiazepines (B)

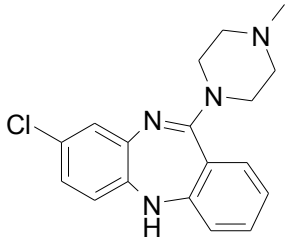
The benzodiazepine nucleus is a well-studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various sedative hypnotic, muscle relaxant,

anxiolytic, antistaminic, and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 35 years ago the research in this area is still very active and is directed toward the synthesis of compounds with enhanced pharmacological activity.

The discovery of diazepam followed by many other psychotropic agents sharing a 1,4-benzodiazepines skeleton has also promoted the studies on the isomeric 1,5-benzodiazepine ring system[1] along with the synthetic approaches to mono and diannelated 1,5-benzodiazepines[2] due to their accessibility, easy functionalization and potential pharmacological properties, mainly 1,5-benzodiazepines and 1,5-benzodiazepinone derivatives have received significant attention. Peripheral choleecystokinin receptor agonists,[3] CCK-B/gastrin receptor agonists,[4] arginine vasopressin antagonists,[5] CNS depressants,[6-7] antiamoebics[8] and antiproliferative agents[9] derived from 1,5-benzodiazepinones have been reported. Heterofused 1,5-benzodiazepinones have also been evaluated towards benzodiazepine receptor binding[10] or HIV reverse transcriptase inhibition[11] and found to possess anticonvulsant,[12] analgesic or anti-inflammatory,[13] anti psychotic (clozapine)[14] or PAF-induced aggregation inhibitory activities (**Fig. 14**).[15,16]



CCK-B/gastrin Receptor Antagonists



Clozapine

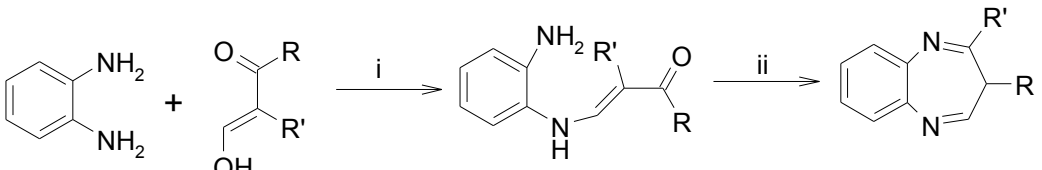
Fig.14

2.5.2 Review of Literature

Due to the wide range of application of 1,5-benzodiazepines from drugs to fibers to dyes, there are several synthetic methods reported in the literature for the synthesis of 1,5-benzodiazepines. In this section we have covered some of more significant and useful synthetic methods for the preparation of 1,5-benzodiazpeines.

Weissnfels approach (1967)[17]

Weissnfels and coworkers studied the condensation of *o*-phenylenediamine **176** with various α-hydroxymethyl ketones **177** to give the intermediate **178** which was further cyclized to 1,5-benzodiazepine **179** in good yield in the presence of perchloric acid (**Scheme 57**).

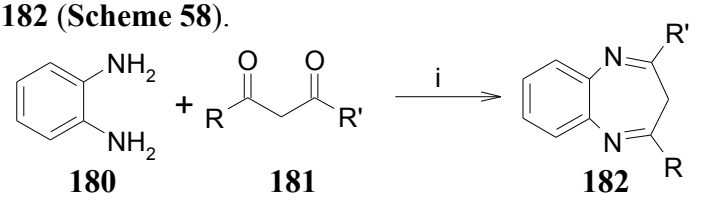


176 **177** **178** **179**

Scheme 57. Reaction conditions: i) 100 ^{0}C, 12 h; ii) $HClO_4$, EtOH, reflux, 70-80%.

Neumann's approach (1976)[18]

Neumann and workers synthesized 1,5-benzodiazepines **182** in good yield by condensation of *o*-pheneylenediamine **180** with pentane-2,4-dione **181** under acidic condition to give an unstable intermediate which spontaneously tautomerizes to the more stable 1,5-benzodiazpine **182** (**Scheme 58**).

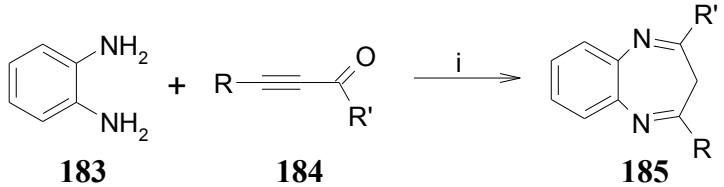


180 **181** **182**

Scheme 58. Reaction conditions: i) heat, HX.

Amey's approach (1976)[19]

Amey *et al.* reported synthesis of 1,5-benzodiazepines from *o*-phenylenediamine **183,** which on condensation with different acetylene ketones **184** in a hot mixture of acetic acid and ethanol gave benzodiazepines **185** in excellent isolated yield (**Scheme 59**).

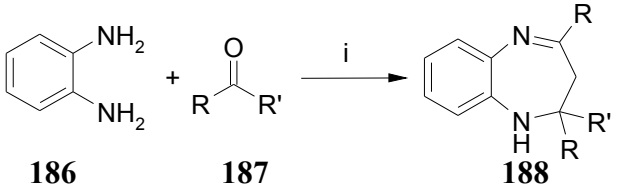


183 **184** **185**

Scheme 59. Reaction conditions: i) acetic acid, ethanol, reflux, 80-95%.

Jung's approach (1999)[20]

Jung *et al.* reported the synthesis of 1,5-benzodiazepines by the condensation of *o*-phenylenediamine **186** with different ketones **187** in the presence of polypohoshporic acid or SiO_2, which afforded the corresponding 1,5-benzodiazepines **188** in moderate yield (**Scheme 60**).

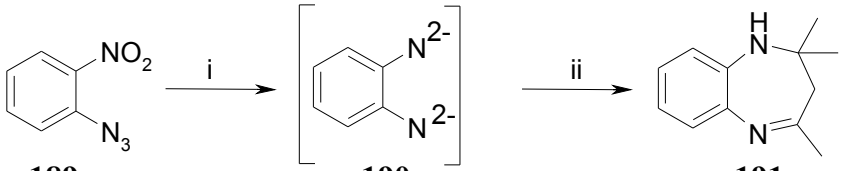


186 **187** **188**

Scheme 60. Reaction conditions: i) PPA or SiO_2, solvent, reflux, 75-93%.

Zhong's approach (2001)[21]

Zhong *et al.* synthesized 1,5-benzodiazepines **191** from *o*-nitro phenyl azide **189** which was treated with the low-valent titanium reagent (derived from the $TiCl_4$:Sm system) to give rise to the intermediate **190** in situ, which reacted with ketones to afford the 1,5-benzodiazepine **191** in high yields.

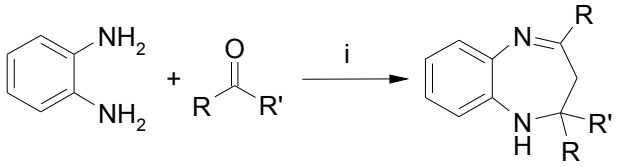


189 **190** **191**

Scheme 61. Reaction conditions: i) $TiCl_4$:Sm; ii) ketones 85-93%.

Curini's approach (2001)[22]

Curini *et al.* synthesized 1,5-benzodiazepines **194** in good yield by the condensation *o*-phenylenediamines **192** with different ketones **193** in the presence of a catalytic amount of Ytterbium triflate [$Yb(OTf)_3$] under solvent free conditions (**Scheme 62**).

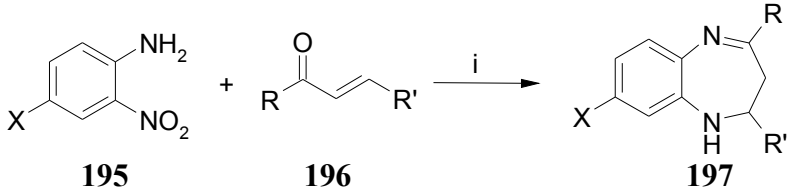


192 **193** **194**

Scheme 62. Reaction conditions: i) $Yb(OTf)_3$, solvent free, rt, 80-95%.

Ma's approach (2002)[23]

Ma *et al.* synthesized 1,5-benzodiazepine **197** from *o*-nitro anilines **195** and chalcones **196**, insitu reduction of nitro group of **195** by tin (Sm) followed by cyclization using low-valent titanium afforded target compound in excellent isolated yield (**Scheme 63**).



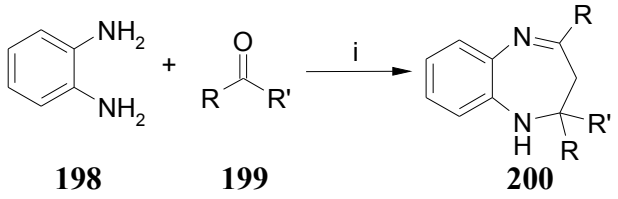
195 **196** **197**

Scheme 63. Reaction conditions: i) Sm, THF, rt, 60-75%.

Pozarentzi's approach (2002)[24]

Pozarentzi *et al.* synthesized library of 1,5-benzodiazepines **200** by condensing *o*-phenylenediamine **198** and different ketones **199** in the presence of a catalytic amount of

acetic acid under microwave irradiation which offers better results compare to conventional heating with respect to reaction time and yield (**Scheme 64**).

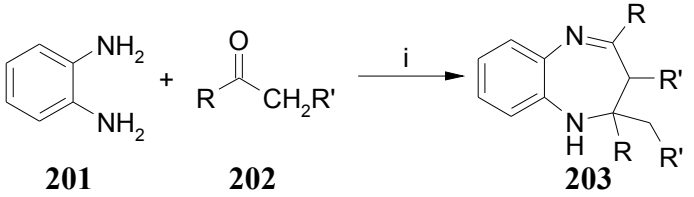


198 **199** **200**

Scheme 64. Reaction conditions: i) AcOH, MW, 80-95%.

Yadav's approach (2003)[25]

Yadav *et al.* reported the synthesis of 1,5-benzodiazepines **203** by the condensation of *o*-phenylenediamine **201** with ketones **202** in the presence of catalyst Amberlyst-15® in ionic liquid as a reaction media, which gave **203** in good yield at room temperature (**Scheme 65).**

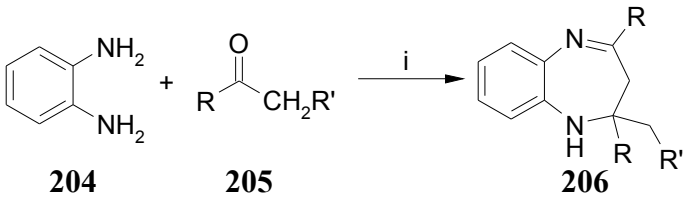


201 **202** **203**

Scheme 65. Reaction conditions: i) Ionic Liquid (**[**bmim]PF_6), Amberlyst-15®, 5 h, 85-95%.

Heravi's approach (2007)[26]

Very recently Heravi *et al.* reported synthesis of 1,5-benzodiazepines **206** by the condensation of *o*-phenylenediamine **204** and various ketones **205** in the presence of Preyssler heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$), as a heterogeneous catalyst in refluxing ethanol gave **206** in good yield (**Scheme 66**).



204 **205** **206**

Scheme 66. Reaction conditions: i) $H_{14}[NaP_5W_{30}O_{110}]$, ethanol, reflux.

Due to its wide range of applications in pharmacology, dyes, fibers and other areas numerous papers can be found in the literature for the synthesis of 1,5-benzodiazepines Some other general synthetic methods for the preparation of 1,5-benzodiazepines are also reported in the literature.[27-35]

2.5.3 Present Work

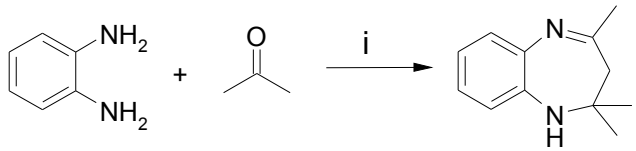
2.5.3.1 Objectives

1,5-benzodiazepines are useful precursors for the synthesis of some fused ring benzodiazepine derivatives, such as triazolo, oxadiazolo, oxazino, or furano benzodiazepines. Due to their wide range of applications these compounds have received a great deal of attention in connection with their synthesis. Although many reagents and preparatory method have been reported in the literature many of these methodologies are associated with several shortcomings such as long reaction times, expensive reagents, harsh reaction conditions, low-product yields, occurrence of several side products etc.

In recent years, ionic liquids have attracted intensive interest as possible alternatives to traditional solvents for organic reactions, particularly in the area of green chemistry. They have also been referred to as 'designer solvents' as their physical and chemical properties can be adjusted by the careful choice of cation and anion. These compounds also exhibit acidic properties. The use of ionic liquids as reaction media may offer a convenient solution to both the solvent-emission and catalytic-recycling problem.

2.3.4.2 Results and Discussion

Initially we performed reaction of *o*-phenylenediamine (OPD) with acetone in the ionic liquid [bbim]Br at room temperature for 12 h, after that TLC was checked, which shows complete disappearance of starting material and formation of the compound **209a** where its spectral data and physical constant were comparable to that reported in the literature for the known compound.



207a **208a** **209a**

Scheme 67. Reaction conditions: i) [bbim]Br, rt, 12 h

The IR spectra of 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **(209a)** shows absorption at 1638 and 3350 cm^{-1} corresponding to the C=N and –NH functional group respectively. The ^{1}H NMR spectra of **209a** showed singlet of six protons at δ 2.09 for two methyl groups, singlet of two protons at δ 2.09 for methylene group and broad singlet at δ 2.94 corresponding to –NH. The ^{13}C NMR-DEPT shows peak at 44.7

corresponding to methylene group which confirmed the compound formation. Elemental analysis and physical constants match with the literature data of **209a**.

Table 16. Catalytic study of ionic liquid for the synthesis of **209a**

Entry	mol% of [bbim]Br	Time (h)	Yield [a] (%)
1	**0**	**24**	**Nil**
2	30	12	30
3	60	12	55
4	80	3	70
5	**100**	**1**	**93**
6	200	1	93

[a]: Isolated yield after column chromatography

After that we performed the same reaction again to optimize the reaction condition and time for complete conversion. We found that starting material completely disappeared after 50 min. at room temperature (progress of reaction was monitored by TLC). No reaction was observed when OPD was reacted with acetone under similar conditions in the absence of the IL for 48 h (Table 16, entry 1), thus highlighting the role of the IL as a promoter. It was also ascertained that a minimum of an equimolar proportion of the IL with respect to the OPD is needed to achieve optimum conversion. Any excess of IL beyond this proportion did not show any further increase in conversion and yield (Table16, entry 6).

Table 17. Study of different ILs for synthesis of **209a** at 28 ^{0}C for 50 min**.**

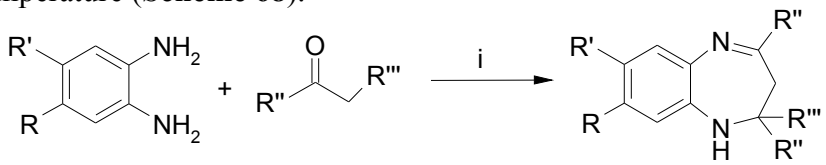
Entry	ILs	pKa[a]	Yield [b] (%)
1	n-butyl pyridinium tetrafluoroborate	--	Nil [c]
2	$EtNH_3NO_2$	--	53[d]
3	**[bbim]Br**	-7	**93**
4	**[bbim]Cl**	-9	**90**
5	**[bbim]BF_4**	0.5	**92**
6	[bbim]PF_6	--	68

7	[bbim]ClO_4	-11	60

[a]: The pK_a values of the parent acid of the anions; [b]: Isolated yield of after column chromatography; [c]: Reaction mixture was stirred for 12 h; [d]: Reaction mixture was stirred for 2 h.

The reaction of OPD with acetone was performed under similar conditions in the several ILs. It was found that n-butyl pyridinium tetrafluoroborate showed no conversion whereas the ethyl ammonium nitrate showed only 53% conversion (Table 17). The use of [bbim]BF_4 and [bbim]Cl gave similar results as for [bbim]Br (Table 17).

It is proved from these results (Table 17), the IL [bbim]BF_4 and [bbim]Br afforded the best results. Consequently, all further studies were conducted using the IL [bbim]Br as the reaction medium cum promoter to synthesize a variety of 1,5-benzodiazepines under ambient temperature (**Scheme 68**).

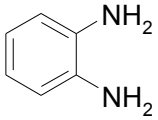
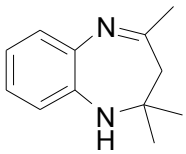
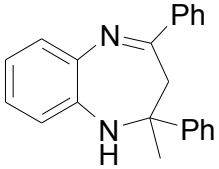


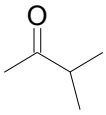
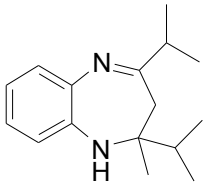
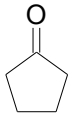
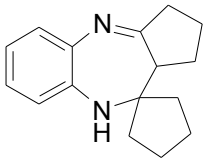
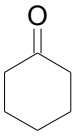
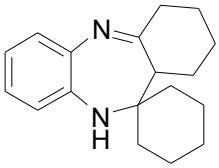
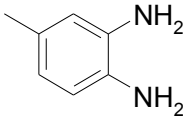
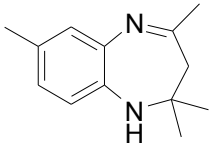
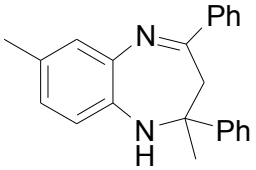
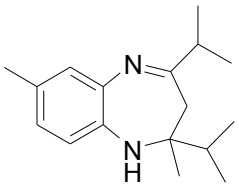
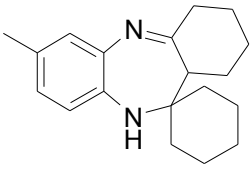
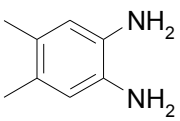
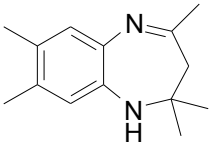
207a-d **208a-e** **209a-m**

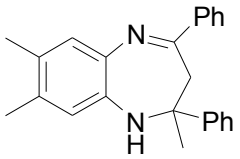
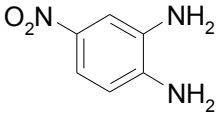
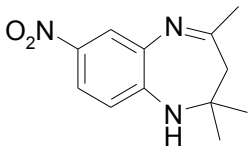
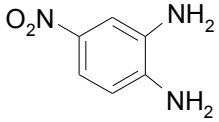
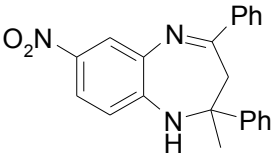
Scheme 68. Reaction conditions: i) [bbim]Br, rt, 50 min.

The results are summarized in Table 18. As is evident, the reactions in IL gave rise to excellent isolated yields of the 1,5-benzodiazepines in a relatively short reaction time (50 min) under ambient temperature. The isolated benzodiazepines **209a-m** were completely characterized by IR, ^1H and ^{13}C NMR analysis, and their melting points were also recorded. The elemental analysis was in agreement with their structures. The IL could be recovered and recycled at least three times for the reaction of the OPD with acetone without incurring any loss in yield of the benzodiazepine **209a** .

Table 18. Synthesis of 1,5-benzodiazpepines **209a-m** in [bbim]Br at 28 ^0C for 50 min.

Sr. No.	Diamine	Ketone	1,5-benzodiazpepines	Yield [a] (%)
1	 **A**	**CH_3COCH_3 A**	 **209a**	**93**
2	**A**	**$PhCOCH_3$ B**	 **209b**	**96**

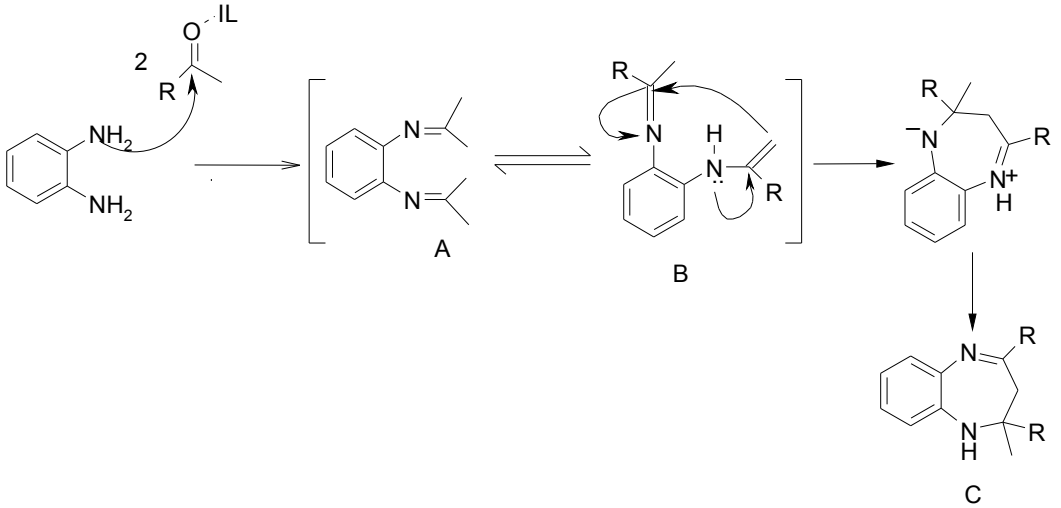
3	**A**	 **C**	 **209c**	**96**
4	**A**	 **D**	 **209d**	
5	**A**	 **E**	 **209e**	**90**
6	 **B**	**A**	 **209f**	**95**
7	**B**	**B**	 **209g**	**91**
8	**B**	**C**	 **209h**	**93**
9	**B**	**D**	 **209i**	**92**
10	 **C**	**A**	 **209j**	**93**

11	**C**	**B**	 **209k**	**90**
12	 **D**	**A**	 **209l**	**84**
13	 **D**	**B**	 **209m**	**86**

[a]: Isolated yield of products after column chromatography

Interestingly, cyclic ketones such as cyclopentanone, cyclohexanone and cycloheptanone also reacted well and equally efficiently with similar success to afford fused ring 1,5-benzodiazepines in high yields.

The enhanced reactivity for the synthesis of the benzodiazepines in the imidazolium IL even in the absence of a catalyst may be attributed to the inherent Brønsted and Lewis acidities of the ring hydrogen's H_2, H_4 and H_5 of the imidazolium cation in [bbim]Br. Previous studies involving multi-nuclear NMR spectroscopy and conductivity measurements for the imidazolium ions correlating their acidity characteristics support the above observations.



Scheme 69. Plausible mechanism for the formation of 1,5-benzodiazepines

The mechanism of the reaction probably involves an intramolecular imines–enamine cyclization promoted by IL as shown in **Scheme 69**. Amino group of o-phenylenediamine attacks carbonyl group of ketone giving the intermediate diimine A. 1,3-shift of the hydrogen attached methyl group then occurs to form an isomeric enamine B, which cyclizes to afford seven-membered ring C (1,5-benzodiazepines).

2.5.5 Conclusion

In conclusion we have developed a novel and efficient method for the synthesis of 1,5-benzodiazepines which not only afforded the products in excellent yields but also avoid the problems associated with catalyst cost, handling, safety and pollution. Ionic liquid can have acted as eco-friendly, non-volatile, recyclable, non-explosive, easy to handle, and thermally robust solvent. Importantly, the IL not only acts as a solvating medium but also as a promoter for the reaction giving rise to twin advantages of ambient temperature conditions and the non-requirement of a catalyst. This work already peer reviewed and published in *Tetrahedron Letters* **2003,** *44*, 1835.

2.5.6. Experimental

Typical procedure for the synthesis of 2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine

A mixture of *o*-phenylenediamine (**207a)** (4.62 mmol) and the ketone (**208a**) (9.72 mmol) in [bbim]Br (4.62 mmol) was stirred at ambient temperature. After completion of reaction (progress of reaction was monitored by TLC), the reaction mixture was diluted with water (25 ml) and the separated product was filtered and dried under reduced pressure. The product, thus isolated, was pure enough. It was further subjected to further purification by chromatography through a column of silica-gel using 20% EtOAc in petroleum ether as eluent and fully characterized.

The aqueous layer consisting of the IL was subjected to distillation (80°C at 10 mmHg) for 2 h to remove water, leaving behind the IL [bbim] Br (recovery 98%), which could be recycled.

2.5.6.1 Characterization data for 1,5benzodiazepines 209a-m

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (209a)

Pale yellow solid

M. P. (^{0} C) **:** 136–138

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 710, 945, 1051, 1245, 1456, 1638, 2110, 3350.

^{1}H NMR **:** **δ** 1.20 (s, 6H), 2.09 (s, 2H), 2.24 (s, 3H), 2.94 (brs, 1H),

(200 MHz, $CDCl_3$) 6.59–7.06 (m, 4H).

^{13}C NMR **:** **δ** 29.5. 30.1, 44.7, 68, 121.4, 121.6, 125.2, 126.4, 137.7, 140.3,

(50 MHz, $CDCl_3$) 172.1.

Elemental Analysis **:** **$C_{12}H_{16}N_2$** Calcd. C, 76.55; H, 8.57; N, 14.88.

Found C, 76.33; H, 8.50; N, 14.59.

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (209b)

Yellow crystal

M. P. (^{0} C) **:** 150–152

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 815, 1055, 1245, 1465, 1635, 2100, 3325.

^{1}H NMR **:** **δ** 1.80 (s, 3H), 2.95 (d, *J*= 12.8 Hz, 1H), 3.15 (d, *J*= 12.8 Hz, 1H)

(200 MHz, $CDCl_3$) 3.45 (brs, 1H), 6.55-7.0(m, 3H), 7.15-7.35 (m, 7H), 7.55-7.65 (m, 4H).

^{13}C NMR **:** **δ** 29.7, 42.9, 73.3, 121.2, 121.4, 125.2, 126.1, 126.8, 126.9, 127.8

(50 MHz, $CDCl_3$) 128.1, 128.5, 129.5, 137.9.

Elemental Analysis **:** **$C_{22}H_{20}N_2$** Calcd. C, 84.58; H, 6.45; N, 8.97.

Found C, 84.43; H, 6.37, N, 8.91

2-Diisopropyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (209c)

Yellow solid

M. P. (^{0} C) : 119-120

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 758, 980, 1150, 1456, 1665,1830, 2200, 3268.

^{1}H NMR **:** **δ** 0.93-1.19(d, *J*= 7.8 Hz, 6H), 1.23 (s, 3H), 1.24-1.28

(200 MHz, $CDCl_3$) (d, *J*= 7.2 Hz, 6H),1.93-1.96 (m, 1H), 2.16-2.22 (m, 1H), 2.30-2.80 (m, 2H), 3.31 (brs, 1H), 6.69-7.17 (m, 4H).

^{13}C NMR **:** **δ** 16.8, 17.9, 19.8, 23.1, 37.7, 39.4, 121.2, 121.3, 127.1, 138.1

(50 MHz, $CDCl_3$) 178.7.

Elemental Analysis : $C_{16}H_{24}N_2$ Calcd. C, 78.64, H, 9.90; N, 11.46.
Found C, 78.54; H, 9.75; N 11.31.

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydro-1H-dibenzo[b]-cyclopenta[e][1,4]-diazepine (209d)

Yellow solid

M. P. (^{0} C) : 138–139.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 850, 1050, 1245, 1640, 1670, 2150, 3338.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 1.3–1.92 (m, 12H), 2.30–2.61 (m, 3H), 4.54 (brs, 1H), 6.6–7.39 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 23.2, 24.1, 24.5, 28.7, 33.2, 34.4, 38.5, 39.3, 54.4, 66.7, 118.3, 119.4, 126.3, 128.6, 132.2, 139, 143.1, 178.

Elemental Analysis : $C_{16}H_{20}N_2$ Calcd. C, 79.96; H, 8.39; N, 11.66.
Found: C, 79.78; H, 8.24; N, 11.43.

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[1,5]diazepine (209e)

Pale yellow

M. P. (^{0} C) : 136–137.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 758, 945, 1150, 1640, 1850, 2100, 3290.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 1.23–1.85 (m, 16H), 2.30–2.70 (m, 3H), 4.45 (brs, 1H), 6.65–7.35 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 21.6, 21.7, 23.2, 24.5, 25.3, 33.2, 34.4, 39.3, 40.5, 52.4, 63.1, 121.3, 121.5, 126.3, 129.6, 138.1, 142.6, 178.9.

Elemental Analysis : $C_{18}H_{24}N_2$; Calcd. C, 80.55; H, 9.01; N, 10.44.
Found: C, 80.36; H, 8.84; N, 10.31.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (209f)

Yellow solid

M. P. (^{0} C) : 127–128.

IR ($CHCl_3$, cm^{-1}) : υ_{max} 710, 850, 945, 1150, 1450, 1665, 2200, 2800, 3325.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 1.30 (s, 6H), 2.19 (s, 2H), 2.23 (s, 3H), 2.80 (s, 3H), 6.65–6.75 (s, 1H), 6.70–6.80 (m, 1H), 7.05– 7.10 (m, 1H).

^{13}C NMR : **δ** 20.9, 29.6, 30.4, 30.8, 45.8, 67, 122.6, 126.6, 127, 136.7

(50 MHz, $CDCl_3$) 138.1, 174.3.

Elemental Analysis : **$C_{13}H_{18}N_2$**; Calcd. C, 77.18, H, 8.97, N, 13.85.
Found C, 77.10, H, 8.78, N, 13.72.

2-Methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (209g)

Yellow solid

M. P. (^{0} C) : 92-93

IR ($CHCl_3$, cm^{-1}) : υ_{max} 745, 850, 935, 1045, 1240, 1659, 2100, 2750, 3275.

^{1}H NMR : **δ** 1.8 (s, 3H), 2.41 (s, 3H), 2.98–3.03 (d, *J*= 13 Hz, 1H),
(200 MHz, $CDCl_3$) 3.13–3.17 (d, *J*= 13 Hz, 1H), 3.5 (brs, 1H), 6.70–7.69 (m, 13H).

^{13}C NMR : **δ** 20.9, 28.7, 45.9, 51, 113.5, 123.5, 125.7, 126.3, 127.4, 128.2,
(50 MHz, $CDCl_3$) 128.3, 128.5, 128.6, 129, 130.8, 131.2, 134, 136.9, 164.6.

Elemental Analysis : **$C_{23}H_{22}N_2$** Calcd. C, 84.63; H, 6.79; N, 8.58.
Found C, 84.51; H, 6.65; N, 8.42.

2-Diisopropyl-2-methyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (209h)

Pale yellow solid

M. P. (^{0} C) : 119-120

IR ($CHCl_3$, cm^{-1}) : υ_{max} 840, 930, 1145, 1280, 1668, 1820, 2300, 3253.

^{1}H NMR : **δ** 0.94 (d, *J*= 7.8 Hz, 6H), 1.12 (s, 3H), 1.42 (d, *J*= 7.2 Hz, 6H)
(200 MHz, $CDCl_3$) 1.85 (m, 1H), 2.1 (m, 1H), 2.3 (s, 3H), 2.47–2.55 (d, *J*= 15.5 Hz,
1H), 2.57–2.64 (d, *J*=16 Hz, 1H), 3.67 (brs, 1H), 6.64–7.35 (m, 4H).

^{13}C NMR : **δ** 14.7, 16.5, 20.9, 23.8, 29.2, 36.1, 40.4, 113.6, 118.2, 122.8,
(50 MHz, $CDCl_3$) 127.8, 132.8, 137, 164.6.

Elemental Analysis : **$C_{17}H_{26}N_2$** Calcd. C, 79.02, H, 10.14; N, 10.84.
Found C, 78.94; H, 10.02; N 10.69.

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1Hdibenzo[b,e][1,4] diazepine (209i)

Yellow solid

M. P. (^{0} C) : 142-143

IR ($CHCl_3$, cm^{-1}) : υ_{max} 810, 918, 1035, 1345, 1665, 1810, 2240, 3260.

^{1}H NMR : **δ** 1.96-2.75 (m, 19H), 2.95-3.29 (m, 4 H), 3.29 (t, *J*= 7.5 Hz,1H),

(200 MHz, $CDCl_3$) 4.99 (brs, 1H), 7-7.5 (m, 3H).

^{13}C NMR **: δ** 20.1, 20.9, 23.8, 26.7, 27.4, 33, 34.9, 43.7, 47.8, 113.5, 123.5,

(50 MHz, $CDCl_3$) 127.4, 128.5, 132.7, 134, 164.6.

Elemental Analysis **: $C_{19}H_{26}N_2$** Calcd. C, 80.80; H 9.28; N, 9.92.

Found C, 80.53; H, 9.02; N, 9.67.

2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (209j)

Yellow solid

M. P. (^{0} C) : 112–114

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 745, 850, 1035, 1240, 1635, 2230, 3290.

^{1}H NMR **: δ** 1.35 (s, 6H), 2.19 (s, 3H), 2.20 (s, 3H) 2.22 (s, 2H), 2.34

(200 MHz, $CDCl_3$) (s, 3H), 2.80 (brs, 1H), 6.52 (s, 1H), 6.39 (s, 1H).

^{13}C NMR **: δ** 18.9, 19.1, 29.8, 30.3, 30.4, 45.3, 67.7, 122.8, 127.8, 129.9,

(50 MHz, $CDCl_3$) 133.6, 135.5, 138.4, 171.3.

Elemnetal Analysis **: $C_{14}H_{20}N_2$** Calcd. C, 77.73; H, 9.32; N, 12.95.

Found C, 77.52; H, 9.15; N, 12.82.

2-Methyl-2,4-diphenyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (209k)

Pale yellow solid

M. P. (^{0} C) : 115–116

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 835, 940, 1050, 1130, 1635, 1950, 2200, 3285.

^{1}H NMR **: δ** 1.70 (s, 3H), 2.25 (s, 6H), 2.90 (d, *J*= 12.8 Hz, 1H), 3.10

(200 MHz, $CDCl_3$) (d, *J*= 12.8 Hz, 1H), 3.45 (brs, 1H), 6.6 (s, 1H), 7.15 (s, 1H),

7.30–7.18 (m, 6H), 7.50–7.60 (m, 4H).

^{13}C NMR **: δ** 18.6, 19.3, 29.7, 43.2, 73, 122.3, 125.4, 126.8, 126.9, 127.8,

(50 MHz, $CDCl_3$) 128.2, 129.4, 129.6, 134.8, 135.7, 137.6, 139.7, 147.8, 166.8.

Elemental Analysis **: $C_{24}H_{24}N_2$** Calcd. C, 84.67; H, 7.11; N, 8.23.

Found C, 84.42; H, 7.02; N, 8.15.

2,2,4-Tri-methyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine (209l)

Bright yellow solid

M. P. (^{0} C) : 113–114.

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 780, 945, 1055, 1245, 1645, 1890, 2350, 3280.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 4.00 (brs, 1H), 7.15 (s, 1H), 8.0–8.15 (m, 1H), 8.75–8.80 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 29.9, 30.0, 30.2, 45.6, 60.8, 118.3, 121.2, 126.2, 132.4, 137.9, 145.2, 170.7.

Elemental Analysis : **$C_{12}H_{16}N_3O_2$**; Calcd. C, 61.52; H, 6.88; N, 17.94. Found C, 61.25; H, 6.74; N, 17.73.

2-Methyl-2,4-diphenyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine (209m)

Dark yellow solid

M. P. (^{0} C) : 136–138

IR ($CHCl_3$, cm^{-1}) : υ_{max} 850, 970, 1085, 1250, 1430, 1651, 1950, 2150, 3300.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 1.80 (s, 3H), 3.05–3.15 (d, *J* =12.6 Hz, 1H), 3.35 (d, *J* = 12.6 Hz, 1H), 4.40 (brs, 1H), 6.80–7.95 (m, 13H).

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 29.2, 45.6, 60.8, 118.3, 121.2, 126.2, 128.6, 129, 130.8, 132.4, 136.9, 145, 168.4.

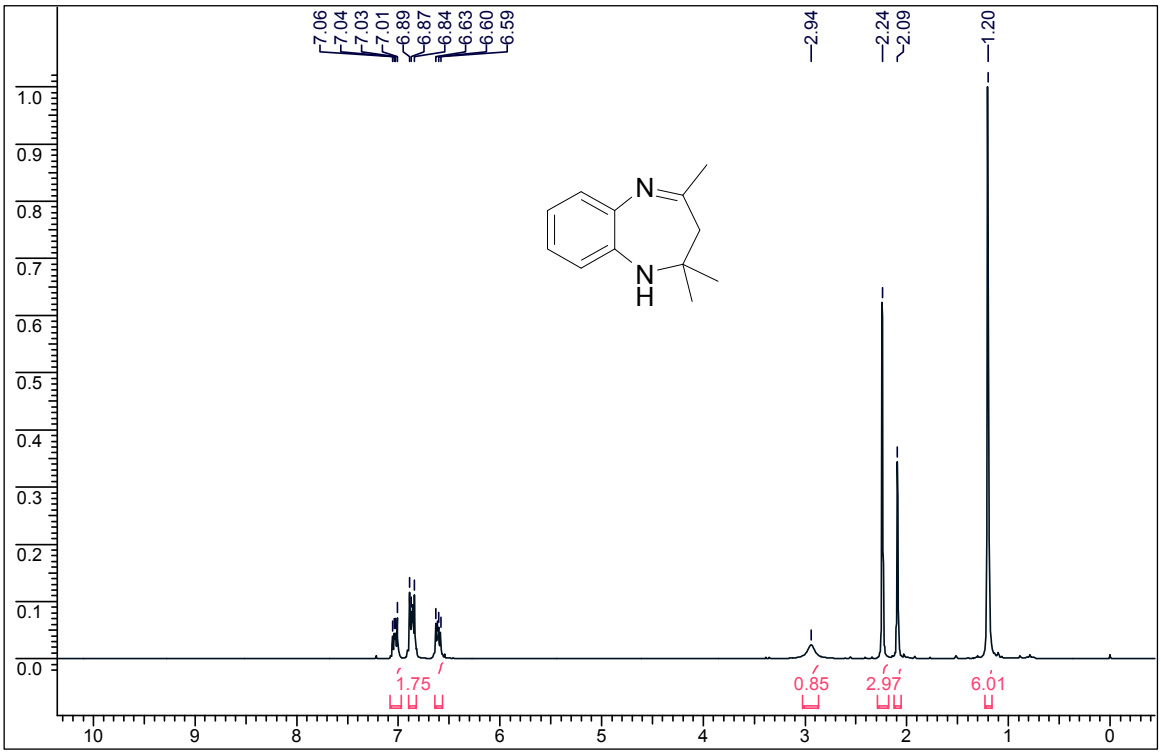
Elemental Analysis : **$C_{22}H_{20}N_3O_2$**; Calcd. C, 73.72; H, 5.62; N, 11.72. Found C, 73.62; H, 5.51; N, 11.53.

2.5.7 Spectra

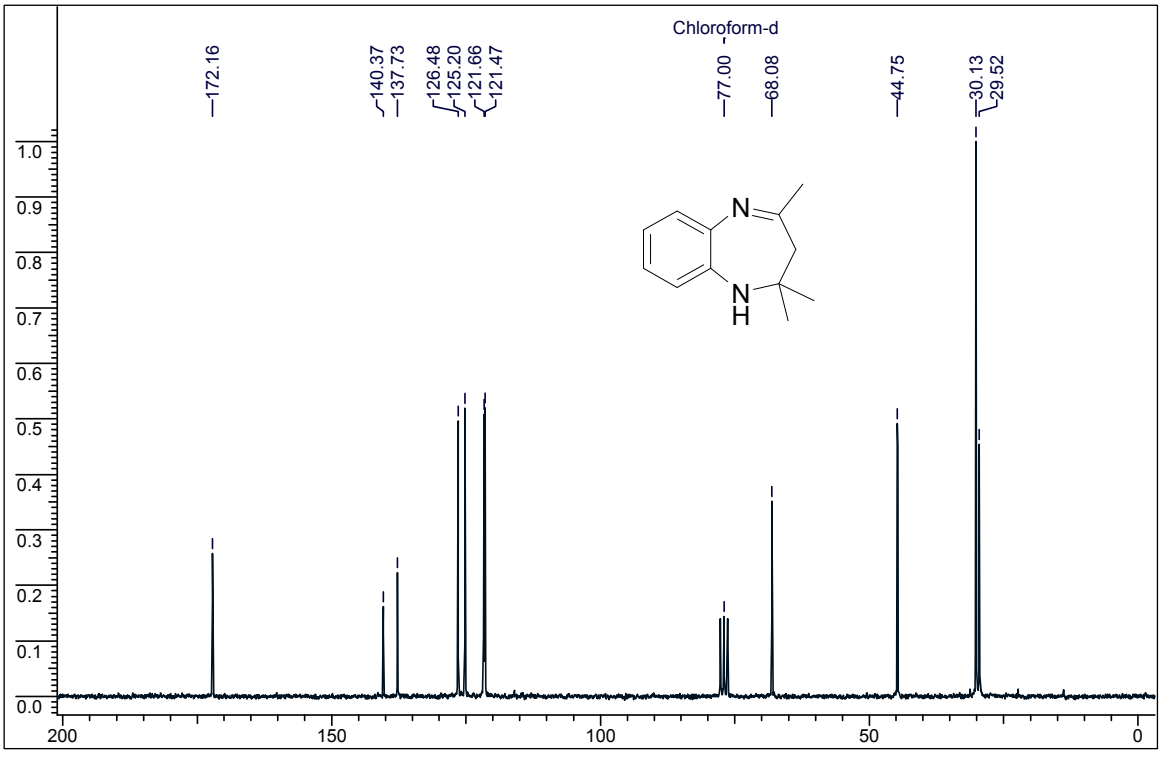
[1] ^{1}H NMR and ^{13}C NMR spectra of **209a**

[2] ^{1}H NMR and ^{13}C NMR spectra of **209b**

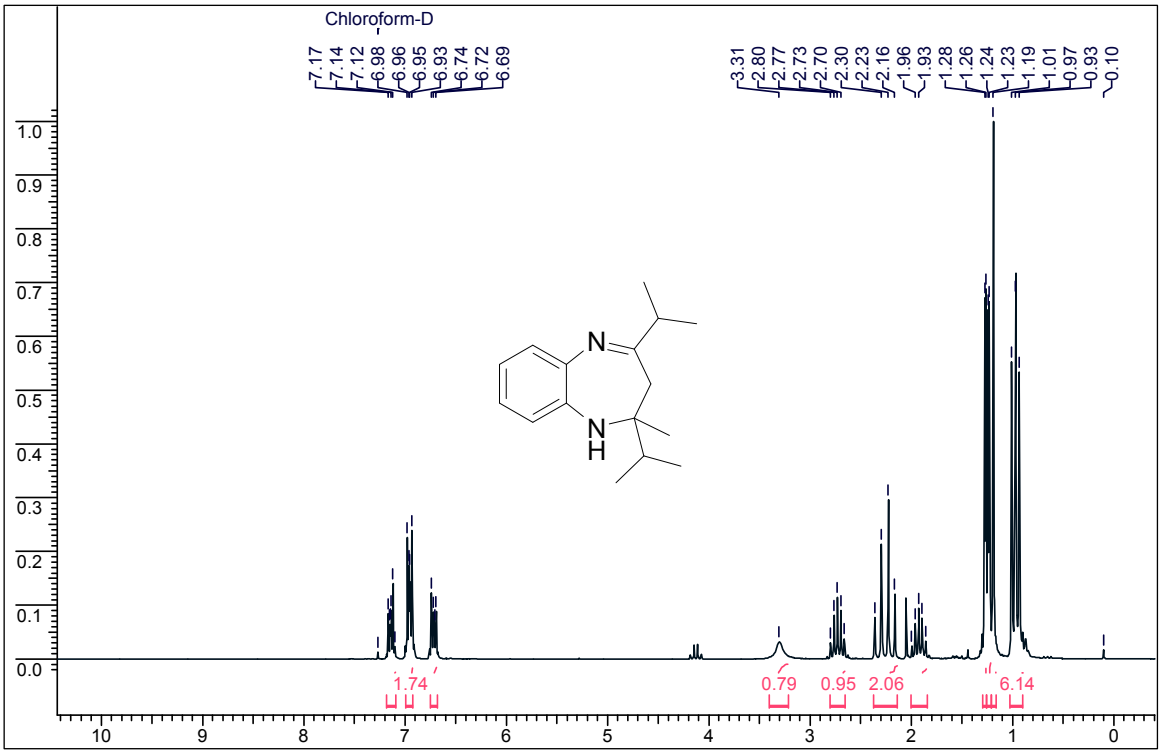
[1] ^{1}H NMR spectra of 209a



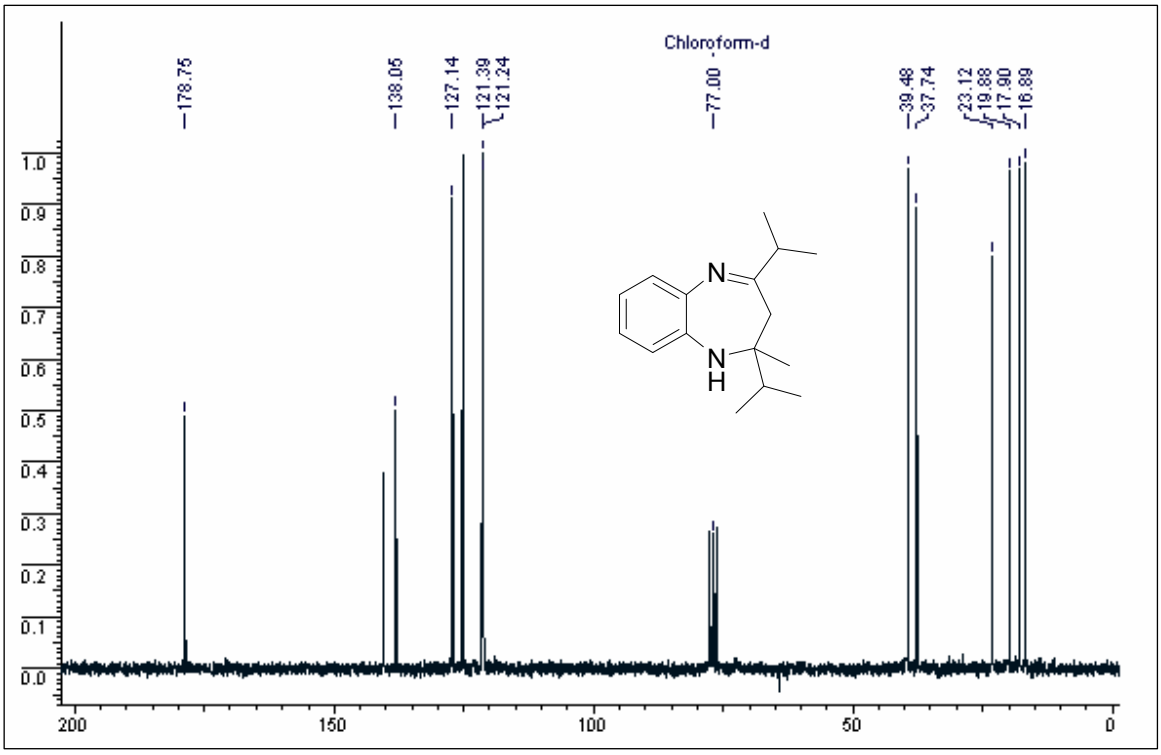
[1] ^{13}C NMR spectra of 209a



[2] ^{1}H NMR spectra of 209b



[2] ^{13}C NMR spectra of 209b



2.5.8 References

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CHAPTER-3

ENATIONSELECTIVE SYNTHESIS OF (*S*, *S*)-REBOXETINE AND (*S*)- DAPOXETINE USING SHARPLESS ASYMMETRIC DIHYDROXYLATION

SECTION-A

Sharpless Asymmetric Dihydroxylation(SAD)

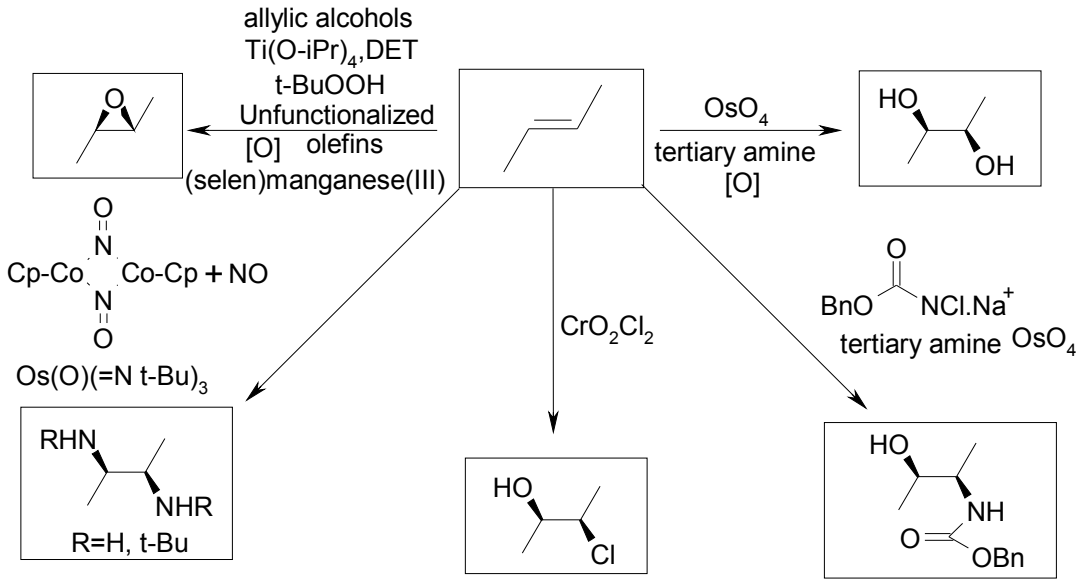
3.1.1 Introduction

Since the total synthesis of (*S, S*)-Reboxetine and (*S*)-Dapoxetine respectively in the present work employs Sharpless asymmetric dihydroxylation (SAD) and cyclic sulfite/sulfate chemistry, it is pertinent to describe how the salient features of both the above phenomena.

3.1.2 Sharpless asymmetric dihydroxylation

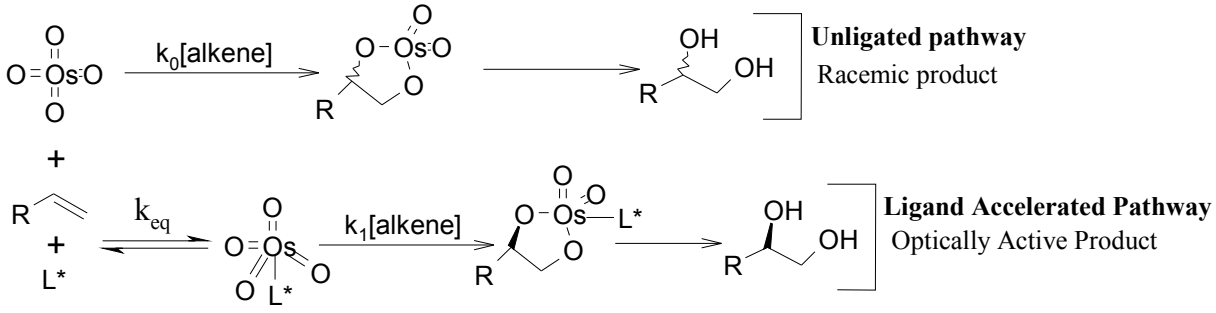
Nature, an architect par excellence, produces hundreds of compounds through a variety of biogenetic pathways and quite a few of them have attracted the synthetic organic chemist's attention due to their remarkable structural features and/or the conferred specific bioactivity. Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries and biotechnologies.

In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years (**Scheme 1**).



Scheme 1. Transition metal mediated suprafacial 1,2-difunctionalization of olefins.

A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and amino hydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of *ligand acceleration*,[7] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand (**Scheme 2**). This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo, regio, and stereo selectivity of the reaction in a profound way.



$$\text{Ligand Acceleration} = \frac{\text{Saturation Rate with Ligand}}{\text{Rate without Ligand}}$$

Scheme 2. Ligand accelerated catalysis-dihydroxylation of olefins

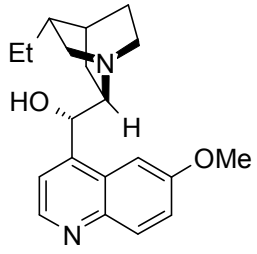
The osmium tetroxide-catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry. In his pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee[8] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[5b] Inorganic co-oxidants such as sodium or potassium chlorate[9a] or hydrogen peroxide,[9b,c] were among the first to be introduced, but in some cases diminished yields resulted due to over oxidation. Much better results were obtained with alkaline *t*-BuOOH, introduced by Sharpless and Akashi,[10] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[11] Tsuji *et al*.[12] demonstrated that $K_3Fe(CN)_6$ in the

presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

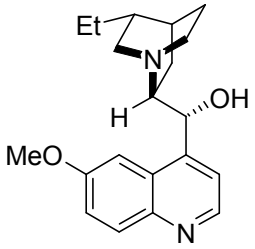
Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[13] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridine for further investigations due to their intrinsically higher affinity for OsO_4.[14] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[13]

Apart from the cinchona alkaloid catalyzed AD, there are a number of methods employing chiral monodentate[15] and bidentate diamine[16] ligands. Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os(VI) glycolate products and as a consequence prevent *in situ* recycling of the osmium (Os) and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand[16] (**Fig. 1**).

(a) Cinchona Alkaloid Ligands for AD under *Catalytic* Conditions[13,17,19,20]

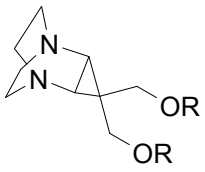


Dihydroquinidine
DHQD



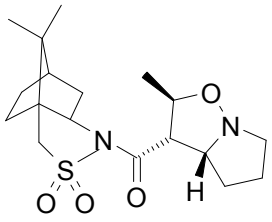
Dihydroquinine
DHQ

(b) Monodentate Ligands for AD under *Catalytic* Conditions



R=*t*-$BuPh_2Si$

Hirama *et al.*



Murahashai *et al.*

(c) Chiral Diamine Ligands for AD under *Stoichiometric* Conditions

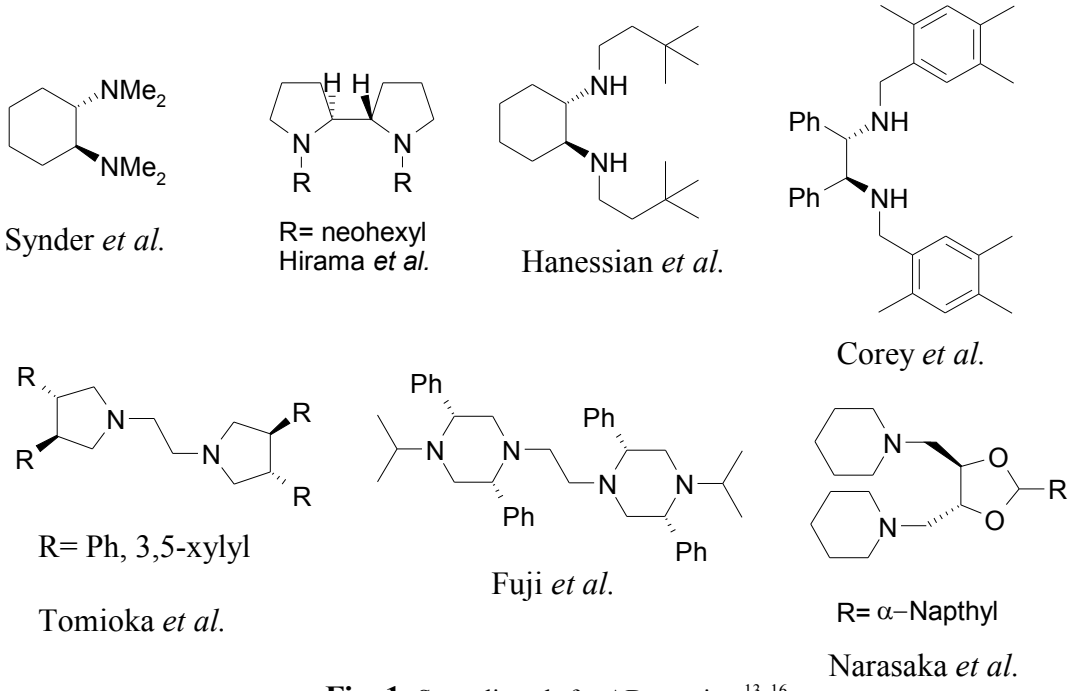


Fig. 1. Some ligands for AD reaction.[13, 16]

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless[17] found that the process became catalytic when NMO was employed as the co-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was initially lower than that produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle,[18] (**Fig. 2**) which exhibited only low or no enantioselectivity. Wai[18] discovered a partial remedy in slow addition of the olefin. Kwong[19] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os(VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (**Fig. 3**).

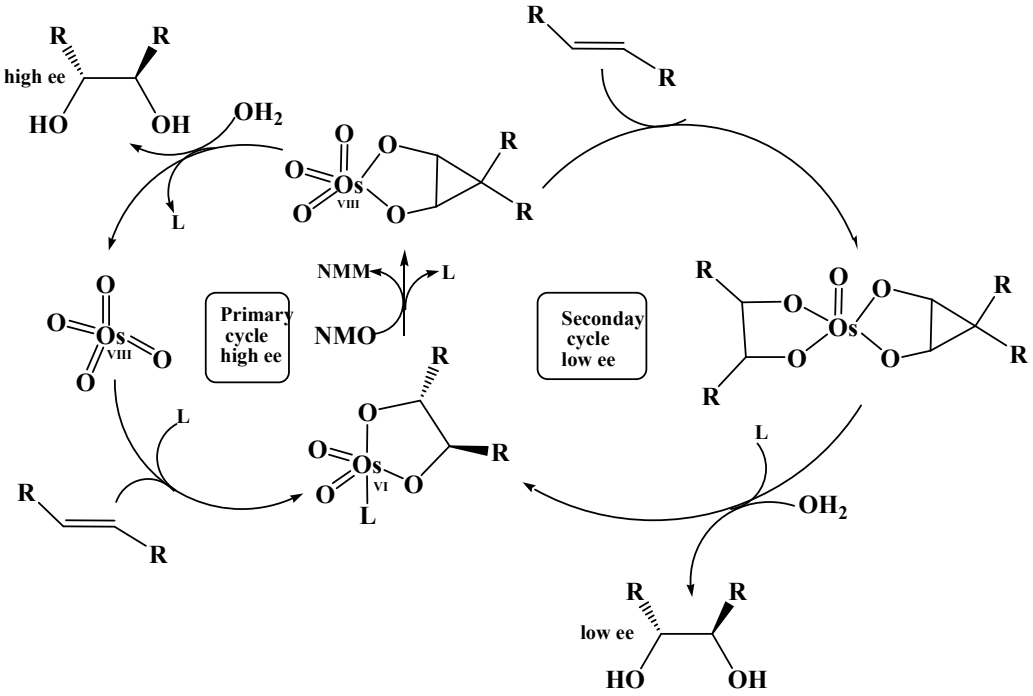


Fig. 2. Two catalytic cycles for the AD reactions using NMO as the co-oxidant.[18]

Sharpless *et al.*[20] found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0 ^{0}C rather than at room temperature, which may have beneficial influence on the selectivity.[21] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

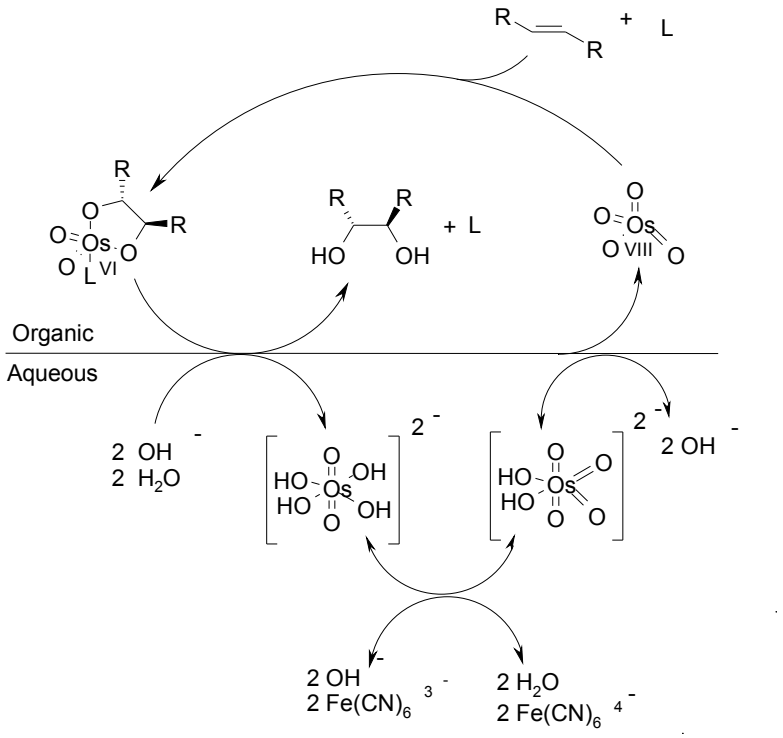


Fig. 3. Catalytic cycle for the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant. [18]

The discovery of ligands with two independent cinchona alkaloid units by Hartung[20] (phthalazine core) and Crispino[22] (diphenyl pyrimidine core) attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Fig. 4**).

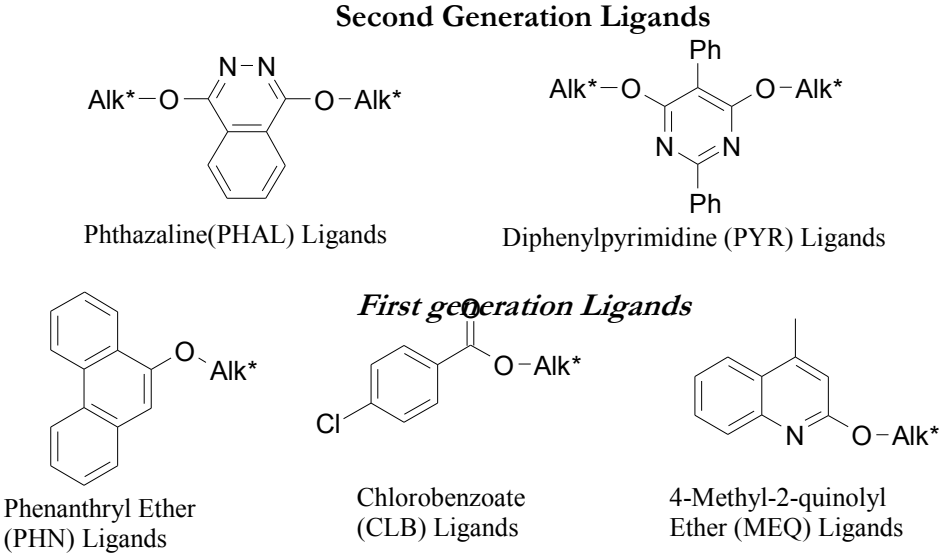
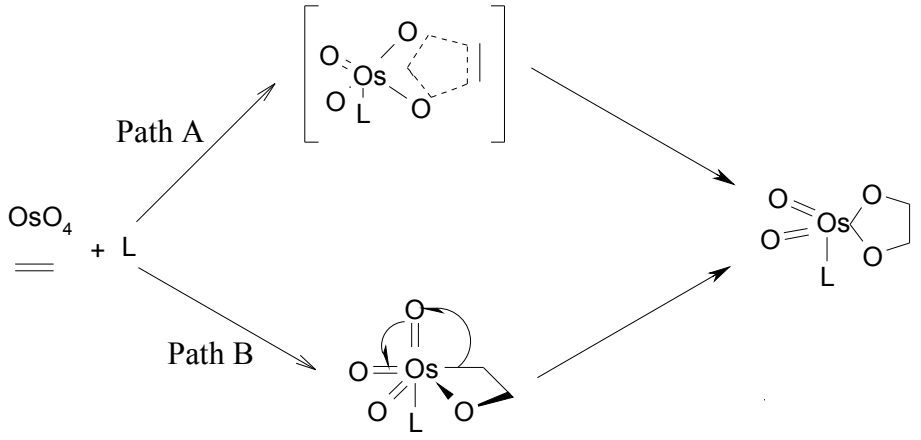


Fig. 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ)

3.1.3 The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken [23a] and Criegees originally proposed a concerted [3+2] pathway, (**Scheme 3**, **Path A**) while Sharpless *et al.*[23b] and Jorgensen *et al.*[23c] suggested a stepwise reaction which is initiated by a [2+2] like addition of the olefin across an Os=O bond (Path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product



Scheme 3. Schematic presentation of the concerted [3+2] mechanism (Path A) and the stepwise mechanism (Path B)

The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature[21] is consistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighted differently according to temperatures owing to their different activation parameters, DH and DS. Hence, this observation suggests that the stepwise [2+2] like mechanism is operative. High level *ab initio* calculations have indeed shown that osmaoxetanes are energetically accessible minima on the potential energy surface.[24]

3.1.3.1 Empirical Rules for Predicting the Face Selectivity

Despite the mechanistic uncertainties, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (**Scheme 4**).[25] The plane of the olefin is divided into four quadrants and the substituents are placed into three quadrants according to a simple set of rules. The SE (south east) quadrant is sterically inaccessible and, with few exceptions, no substituents other than hydrogen can be placed

here. The NW (north west) quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE (north east) quadrant appears to be quite spacious. The SW (south west) quadrant is special in that its preferences are ligand-dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[25c] An olefin, which is placed into this plane according to the above constraints, receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives.

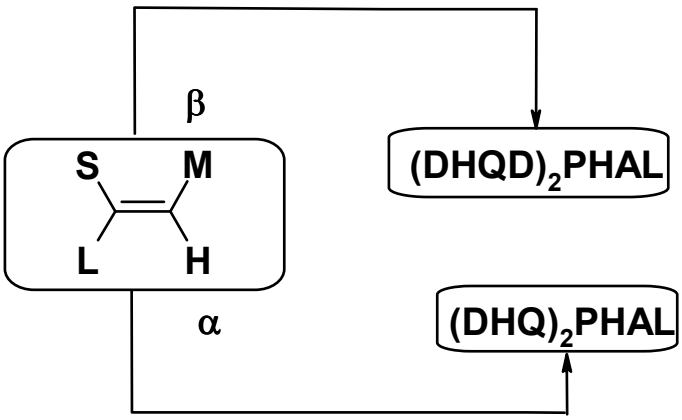


Fig. 5. Mnemonic diagram (S= small group, L= large group, M= medium group, H= proton)

Predictions for 1,1-disubstituted olefins using the empirical mnemonic device are not always unambiguous,[26] since it may be difficult to judge which of the two substituents prefer the attractive, SW quadrant. Along with steric size, the properties of the substituents have also to be taken into account and compared with the ligand-specific preferences for the SW quadrant. PHAL ligands show the following preferences for the SW quadrant: [25c,26-27] Aromatic groups >> *n*-alkyl > branched alkyl > oxygenated residues Recent studies have revealed that oxygenated residues[26,28] have very small preferences for ligands binding pocket (SW quadrant). Studies with 1,1-disubstituted olefins have shown that pyrimidine (PYR) ligands have very different preferences for SW quadrant [25c,27] and the steric size of a substituents is much more important than in the PHAL system. Thus, the following preference is observed: Branched alkyl > long *n*-alkyl (length ³3) > aromatic residues > short *n*-alkyl

A few exceptions mostly for terminal olefins have appeared in recent years. The AD of certain *ortho*-substituted allyl benzenes in the presence of PHAL ligands have been shown to give facial selectivities opposite to those predicted by the mnemonic device.[29] Furthermore, *trans*-olefins in the same series react with the expected face selectivity even with the PHAL ligands; thereby demonstrating that exceptions are so far limited to the class of terminal olefins.

Thus, the mnemonic device is a simple tool for predicting the facial selectivity of the AD reaction. However, reliable predictions require the intrinsic preference of each ligand to be taken into account. Thus, the SW quadrant is especially attractive for aromatic groups in the PHAL systems, while aliphatic groups are preferred in the PYR systems. PYR ligands are, therefore the ligands of choice for aliphatic and/or sterically congested olefins, while PHAL ligands are better for aromatic substrates. These simple rules allow the prediction of the face selectivities even in difficult cases and very few exceptions are known.

3.1.4. Reaction Conditions

Catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH. The olefin concentration in the *t*-BuOH/water mixture is usually 0.1M.[20] While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aq. layer),[30] it is possible to buffer the system with 3 equivalents of $NaHCO_3$ (pH 10.3, aq. layer). Buffering of the reaction has a beneficial effect on the yield when base-sensitive substrates are used or base-sensitive products are formed. Normally the reaction is performed with 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant. The key reagents used are the Os reagent and the ligands. Only 0.2 to 0.4 mol% of Os reagent, either OsO_4 or the nonvolatile $K_2OsO_2(OH)_4$ is added. The ligand concentration is 1 mol%. However it can be dropped in some cases without much loss in enantioselectivity. For e.g. stilbene still gives 96% ee when 1/100 of 1 mol% of $(DHQD)_2$-PHAL is used as compared to the 99.8% ee obtained under normal conditions.[20] Alternatively, the amount of OsO_4 can be increased to 1 mol% for accelerating the reaction rate of relatively unreactive olefins.

Additionally, the ligand can be recovered especially when large-scale reactions are carried out. For the PHAL ligands, the combined organic layers are extracted with 3% aq.

H_2SO_4 saturated with K_2SO_4 (ca. 40 mL/1 g of ligand), followed by a second extraction of the organic solution with saturated K_2SO_4 (ca. 40 mL/1 g of ligand). The ligand enters the aqueous phase as the hydrogen sulfate salt and the solution can be reused directly for the subsequent AD reactions without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base. Additionally, the amount of water should be decreased by the volume of aqueous ligand solution added to the reaction mixture. One equivalent of $MeSO_2NH_2$ should be added for all substrates other than terminal olefins to enhance hydrolysis of the osmate (VI) ester and hence the rate of catalytic turnover.

3.1.5. The Cinchona Alkaloid Ligands and their Substrate Preferences

Phthalazine (PHAL) ligands

The phthalazine ligands are most widely used, due to their ready availability and their broad substrate scope.[25b] This ligand class is used in the AD-mix formulation. PHAL ligands react especially well when aromatic groups are present, and remarkably high enantioselectivities are observed when the aromatic substituents appear in certain optimal locations/patterns.[25a] One such case is *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[31] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.[11] Recent developments have provided ligands with even broader scope than that of the PHAL derivatives.

Anthraquinone (AQN) ligands

The anthraquinone ligands are especially well suited for almost all olefins having aliphatic substituents.[32] Even diols derived from allyl halides or allyl alcohols can now be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[22]

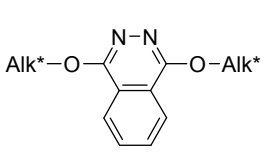
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PYR ligands.[33] Even *cis*-1,2-disubstituted olefins give improved face selectivities with these ligands. The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

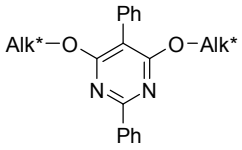
Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[34] However, in certain cases better results are obtained with the new second generation ligands.[32-33,35]

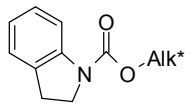
Table 1. Substrate Preferences of different Cinchona Alkaloid Ligands**.**



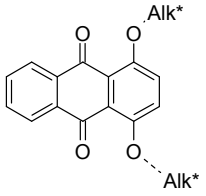
PHAL ligands



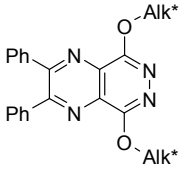
PYR ligands



IND ligands

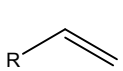
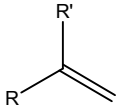
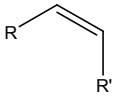
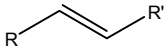
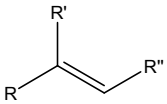
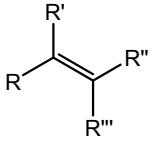


AQN ligands



DPP ligands

Alk* = cinchona alkaloid

Olefin Class						
	R=Aromatic	**R,R'=Aromatic**	**Acyclic**	**R,R'=Aromatic**	PHAL	PYR
	DPP, PHAL	DPP, PHAL	IND	DPP, PHAL	DPP	PHAL
Preferred	**R=Aliphatic**	**R,R'=Aliphatic**	**Cyclic**	**R,R'=Aliphatic**	AQN	
Ligand	AQN	AQN	PYR	AQN		
	R=Branched	**R,R'=Branched**	DPP			
	PYR	PYR	AQN			

3.1.6 Recent Applications of Sharpless Asymmetric Dihydroxylation (SAD) Reaction in Organic Synthesis

Asymmetric dihydroxylation offers some important advantages over the use of chiral pool materials in enantioselective synthesis.

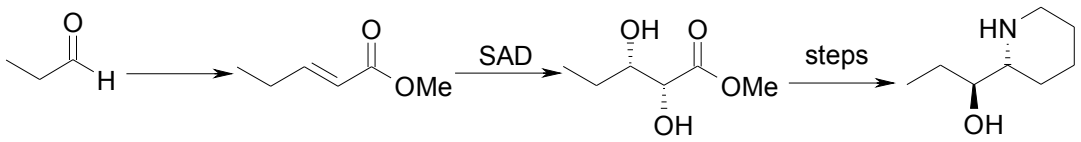
[1] SAD, catalytic in both OsO_4 and the chiral ligand, provides either enantiomer of the product.

[2] SAD is not limited to a certain number of standard starting materials (e.g. carbohydrates, tartrates, etc.), since virtually any olefin can be regarded as a substrate.

[3] Third, most enantiospecific syntheses from the chiral pool require an elaborate protecting group strategy. However with SAD, the diol can be carried through the synthesis "masked" as an olefin, ready to be released at any point.

In most instances, diols are not the final products and their synthetic elaboration requires some further transformations. Commonly, these involve the selective manipulation of one of the two OH groups either by protecting it or by converting it into a leaving group, suitable for displacement by a nucleophile. Over the last decade, several applications of SAD reaction in the syntheses of bioactive molecules and natural products have been documented in the literature. While most synthetic applications of SAD are covered in the review article by Sharpless *et al.*[5a] a few recent applications are documented below.

1. Kumar *et al.* [36] has employed SAD to synthesize (-)-α-conhydrine **(Scheme 4)**.

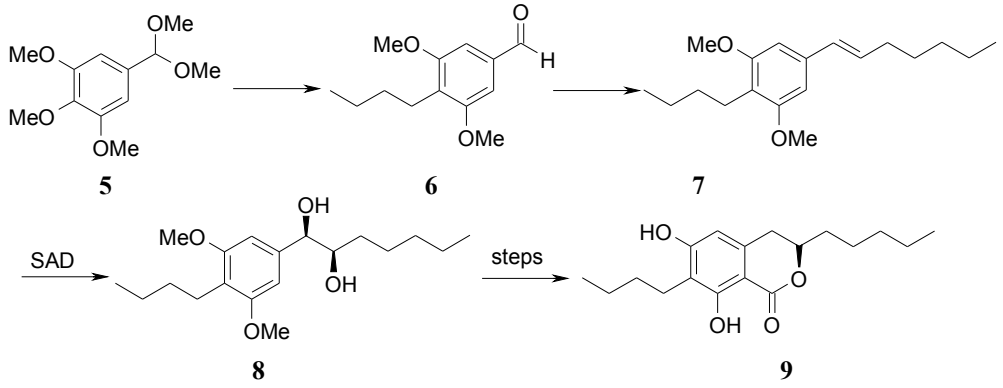


1 **2** **3** **4**

(-)-α-conhydrine

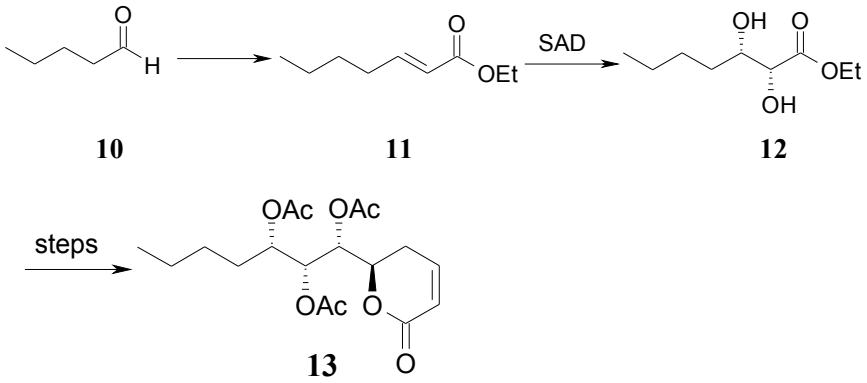
Scheme 4.

2. She *et al.*[37] has employed SAD to synthesize (R)-7-butyl-6,8-dihydroxy-3-pentylisochroman-1-one, an antimalerial agent **(Scheme 5).**



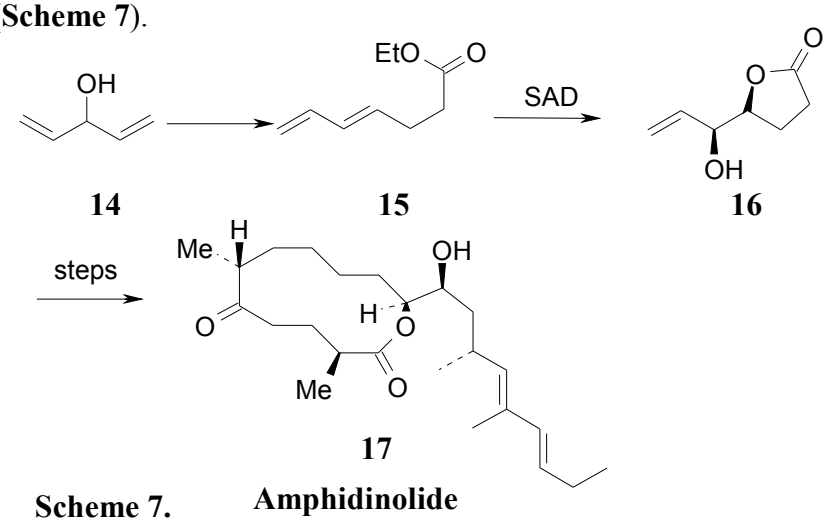
Scheme 5.

3. Naidu *et al.* [38] has employed SAD to synthesize Boronolide**,** is an α, β-unsaturated C-12 lactone isolated from the leaves and branches of *Tetradenia fruticosa* and from the leaves of *Tetradenia barberae*, which have been used as a local folk medicine in Madagascar and South Africa (**Scheme 6**).



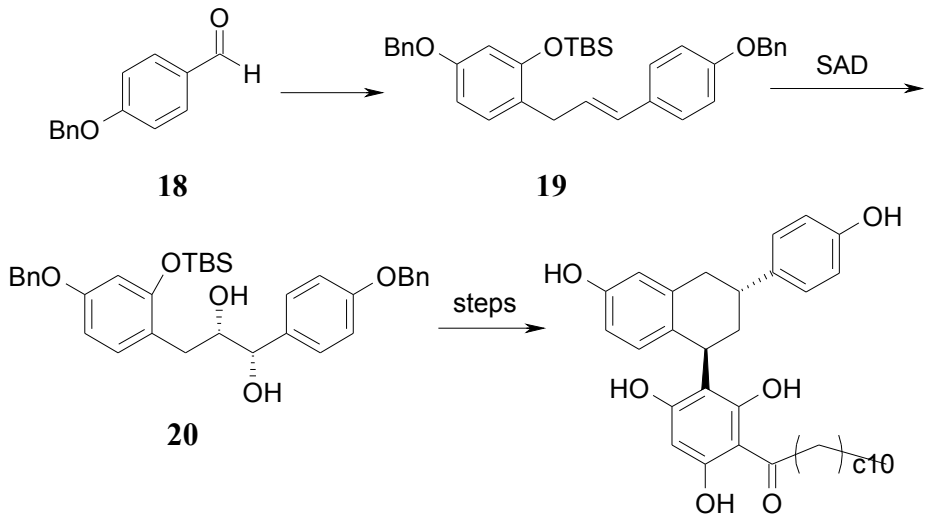
Scheme 6. **Boronolide**

4. Ghosh *et al.*[39] reported an enantioselective first total synthesis and structural revision of the cytotoxic natural product amphidinolide by employing SAD (**Scheme 7**).



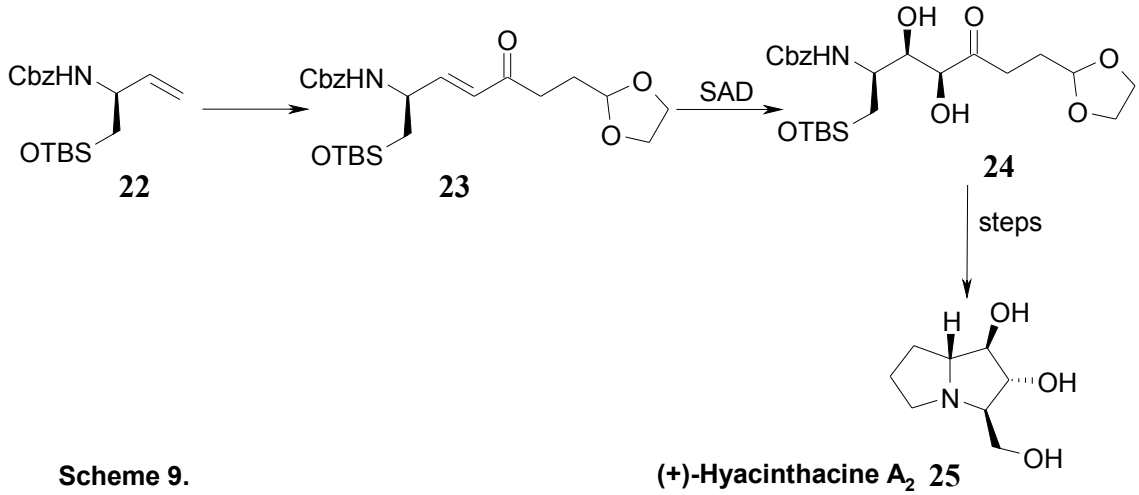
Scheme 7. **Amphidinolide**

5. Hetch *et al.*[40] synthesized (+)-Myristinin A, a naturally occurring DNA Polymerase *β*-Inhibitor and Potent DNA-Damaging Agent from *p*-hydroxy benzaldehyde by employing SAD (**Scheme 8**).



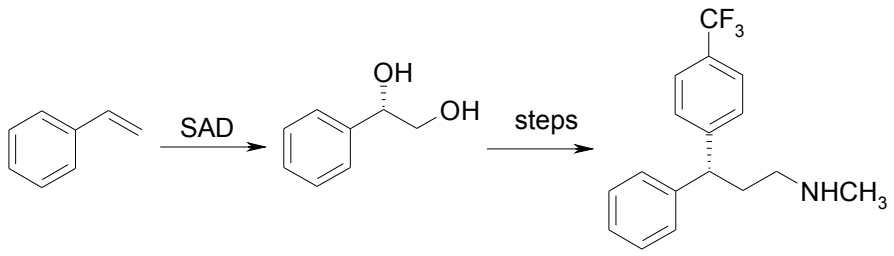
Scheme 8.

6. Belchert *et al.*[41] reported enantiospecific Synthesis of (+)-Hyacinthacine A_2 from (*S*)-*N*- Cbz-vinylgylcine by employing SAD (**Scheme 9**).



Scheme 9. **(+)-Hyacinthacine A_2 25**

7. Pandey *et al.* reported synthesis of Norfluoxetine and Fluoxetine important [42] drugs for psychiatric disorders are synthesized using SAD (**Scheme 10**).



26 **27** **28**

Fluoxetine

Scheme 10.

3.1.7 Conclusion

Thus, Sharpless asymmetric dihydroxylation has become a powerful tool for catalytic oxidation reaction. With the proper choice of ligands and the amount of primary oxidant, the catalytic oxidation reaction leading to chiral diols has proved very promising in terms of both yields and enantioselectivities. It has contributed to rapid advances in synthetic organic chemistry giving access to new molecules needed to investigate hitherto unexplained and undiscovered phenomena in the molecular world.

3.1.8 Introduction of cyclic sulfite/sulfates

Although cyclic sulfate esters have been known since 1932,[43] the lack of an efficient method for preparing cyclic sulfates limited their applications. The oxidation of cyclic sulfites with sodium periodate catalyzed by ruthenium tetroxide[44] represents an important development that has broadened the use of cyclic sulfate intermediates in synthesis. The advent of the catalytic asymmetric dihydroxylation reaction provides a route to chiral 1, 2-diols from a wide spectrum of olefins, which can be further elaborated to cyclic sulfates.[45] The significant role of cyclic sulfates in organic synthesis originates from several properties.

[1] They have high reactivity toward various nucleophiles and are more reactive than epoxides.

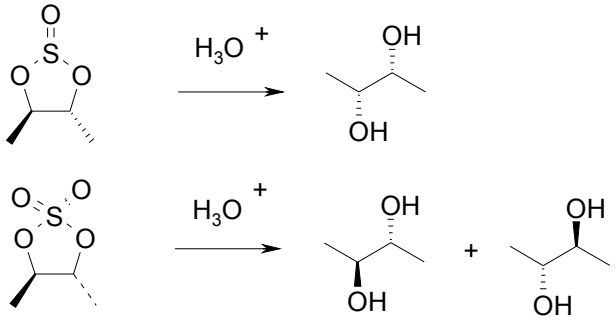
[2] They can activate nucleophilic attack at one position while serving as a protecting group at a second position; under more vigorous conditions they can serve as an activator for two sequential reactions.

[3] The reactions of five-membered cyclic sulfates with nucleophiles provide two contiguous stereo centers; moreover, a remote stereo center can be controlled by cyclic sulfates of 1, 3- and 1,4-diols.

Finally, since the intermediate of nucleophilic substitution is generally the salt form of a mono sulfate ester, separation of the product from the non salt by product is typically a facile process.

The carbon atoms in the cyclic sulfate moiety are highly reactive toward nucleophilic reagents. The enhanced reactivity relative to an acyclic sulfate may originate from two sources: (i) ring strain and (ii) partial double bond character between the ring oxygen atoms and the sulfur atom.[6a] Ring strain may arise from the difference in the internal O–S–O bond angle in the cyclic sulfate versus that in the pentacoordinate intermediate.

With cyclic sulfites, the presence of an unshared pair of electrons on sulfur partially represses the double-bond character of the sulfur atom and the ring oxygen atoms. Thus, cyclic sulfites and cyclic sulfates are expected to display different reactivities. In the nucleophilic substitution of cyclic sulfites, attack at the sulfur atom competes with substitution at carbon; however, in cyclic sulfates this competing reaction is only observed when the carbon centered SN_2 chemistry is severely hindered. For example, hydrolysis of the cyclic sulfite of d-(2)-2,3-butanediol (**Scheme 11**) takes place with retention of chirality, since water attacks the sulfur atom. In contrast, inversion takes place in the cyclic sulfate of the same butanediol, indicating that attack occurs mainly at the carbon atoms

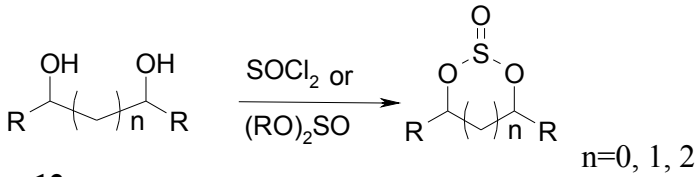


Scheme 11.

3.1.9 Synthesis of cyclic sulfites/sulfates

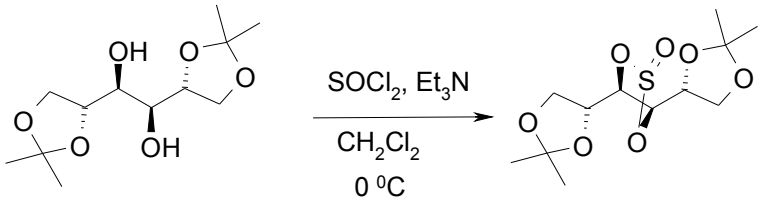
The most efficient synthesis of cyclic sulfites is the reaction of thionyl chloride with a diol [46] or trans esterification of a dialkyl sulfite with a diol (**Scheme 12**).[47] The neat

reaction of ethylene glycol with thionyl chloride furnished ethylene sulfite in moderate yields; however, the yield was improved by the addition of methylene chloride.



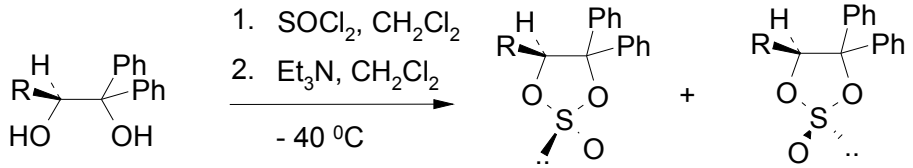
Scheme 12.

It is necessary to expel hydrogen chloride formed during the reaction by heating the reaction mixture[48] or by using a stream of nitrogen. In the reaction of thionyl chloride with substrates that contain an acid-labile functionality, a base such as triethylamine, imidazole, or pyridine is required to scavenge the hydrogen chloride liberated during the reaction.[49]



Scheme 13. 100 %

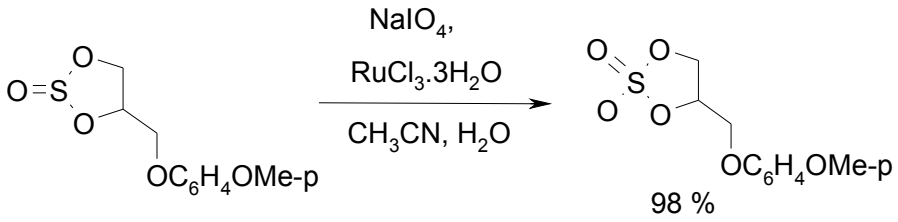
Since the sulfur atom in dialkyl sulfites has tetrahedral geometry, some sulfites are stereoisomeric.[16] Slow addition of triethylamine to a solution of thionyl chloride and (*S*)-1,1-diphenylpropane-1,2-diol in CH_2Cl_2 at 24 ^{0}C gave a 90:10 diastereomeric mixture of (2*R*,5*S*)-*trans*-4,4-diphenyl-5-methyl-1,3,2-dioxathiolane-2-oxide (***a***) and its epimer ***b*** (Scheme 14).[17] However, a change in the order of addition (adding $SOCl_2$ to (*S*)-1,1-diphenylpropane-1,2-diol and Et_3N at 24 ^{0}C) provided a 1:1 mixture of the two diastereomers.



Scheme 14.

Oxidation of cyclic sulfites to sulfates is another alternative. Use of stoichiometric amount of RuO_4 gave cyclic sulfates in satisfactory yield.[57] However; this procedure is limited to small scale preparations due to the expensive RuO_4. The discovery that a

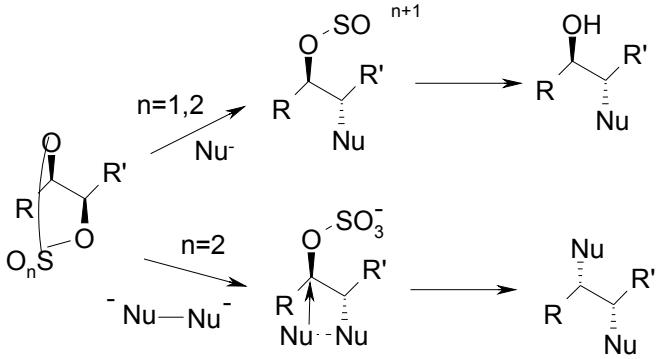
catalytic amount of RuO_4 is generated *in situ* by the reaction of $RuCl_3$ or RuO_2 with $NaIO_4$ made available an expedited route for the oxidation of cyclic sulfites to sulfates.[50]



Scheme 15.

3.1.10 Reactions of Cyclic Sulfites/Sulfates

Analogous to epoxides, cyclic sulfites/sulfates can be opened by attack of a nucleophile at either carbon center giving a sulfite/sulfate monoester. These monoesters allow some interesting transformations, which make the chemistry of cyclic sulfites/sulfates more versatile than of epoxides. Hydrolysis of the monoesters leads to hydroxy compounds that parallel those obtained from oxiranes.[50] However, the sulfate monoester can function as a leaving group, leading to disubstitution products.



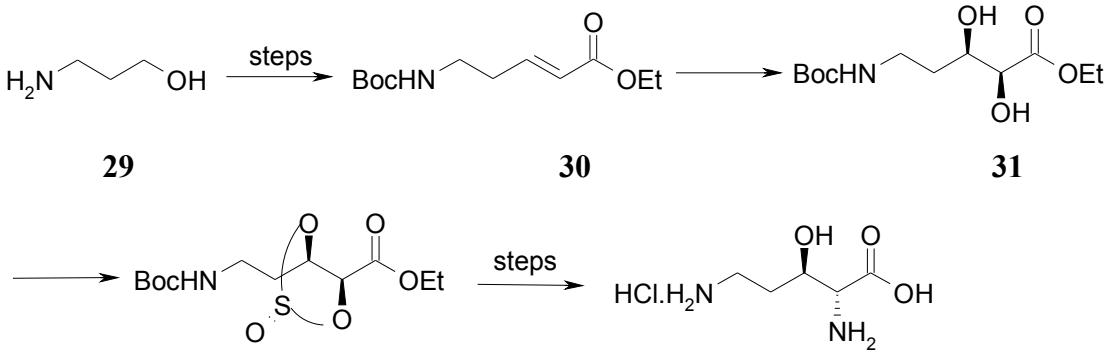
Scheme 16.

Cyclic sulfites and especially sulfates react with a variety of nucleophiles and a few examples are Cl(LiCl), Br(NH_4Br),[51] F($Et_4NF.2H_2O$, *n*-Bu_4NF),[52] N_3(LiN_3, NaN_3),[53-55] RNH_2,[56] $PhCO_2$($PhCO_2NH_4$),[52] ROH,[57] NO_3(*n*-Bu_4NNO_3),[50] SCN(NH_4SCN),[51] PhS(PhSNa),[58] AcS,[59] H($NaBH_4$, $NaBH_3CN$),[50] $PhCH_2$($PhCH_2MgBr$, Li_2CuCl_4),[50] RCºC-,($RCºCSiMe_3$ + MeLi),[60] $(RS)_2CH$(with 1,4-cyclic sulfates).[61]

3.1.11 Recent Applications of Cyclic Sulfites/Sulfates

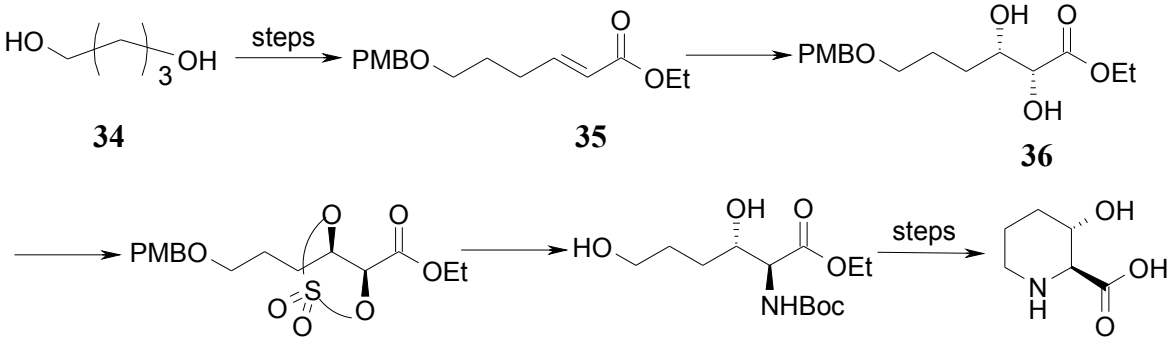
Several applications of cyclic sulfites/sulfates have been documented in the literature in the recent years. A few of them are described below.

1. Kumar *et al.*[62] reported the Enantioselective synthesis of (2R,3R) and (2S,3S)-β-hydroxyornithine synthesis using Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulfite as the key steps (**Scheme 17**).



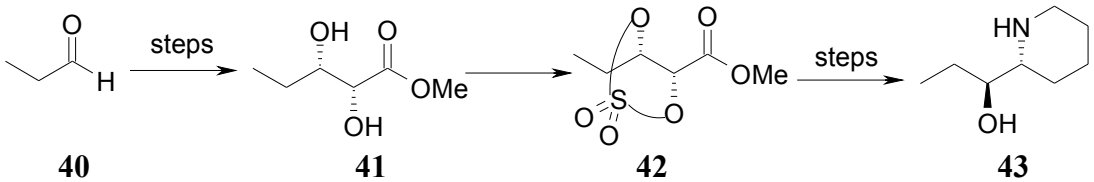
Scheme 17.

2. Bodas *et al.*[63] reported A concise enantioselective synthesis of (2S,3S)-3-hydroxypipecolic acid 1 starting from 1,4-butanediol using Sharpless asymmetric dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfate as the key steps (**Scheme 18**).



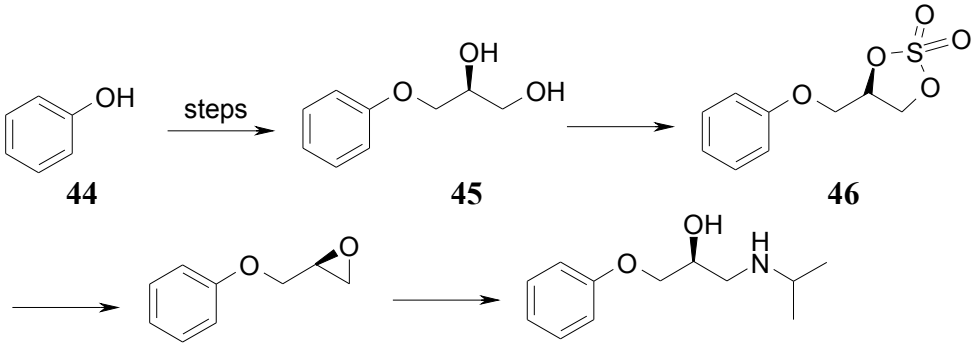
Scheme 18.

3. Kandula *et al.*[64] reported an asymmetric synthesis of (−)-conhydrine using the Sharpless asymmetric dihydroxylation and the regiospecific nucleophilic opening of a cyclic sulfate as the key steps (**Scheme 19**).



Scheme 19.

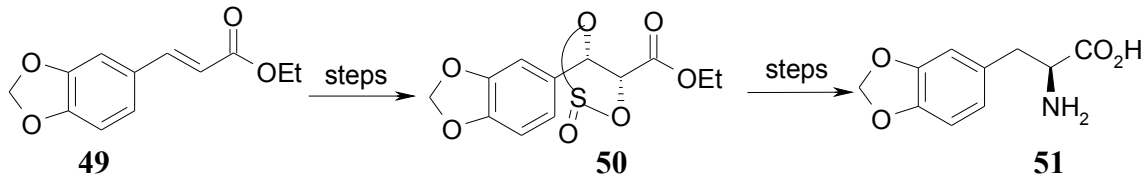
4. Sayyed *et al.*[65] reported a simple and effective procedure for the enantioselective synthesis of several β-adrenergic blocking agents incorporating the first asymmetric synthesis of celiprolol. The key steps are Sharpless asymmetric dihydroxylation of aryl allyl ethers to introduce chirality into the molecules and conversion of cyclic sulfates into the corresponding epoxides using a three-step procedure (**Scheme 20**).



44 **45** **46** **47** **48**

Scheme 20.

5. Sudlai *et al.*[66] reported a simple and effective procedure for the enantioselective synthesis of important neurotransmitter drug, (S)-3,4-dihydroxyphenylalanine by employing the Sharpless asymmetric dihydroxylation and cyclic sulfite as a key step (**Scheme 21**).



49 **50** **51**

Scheme 21.

3.1.12 Conclusion

Thus, given the vast chemistry associated with synthetic applications of epoxides, exploration of the chemistry of 1,2-cyclic sulfites/sulfates their hitherto neglected cousins in organic synthesis is proving fruitful today. The initial realization that these intermediates are epoxide like, but generally much more reactive has given synthetic chemists many ideas for their utility.

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SECTION-B

Enantioselective synthesis of (S, S)-Reboxetine

3.2.1 Introduction

The word "depression" comes from the Latin word, "deprimere", meaning to press down or depress. Depression is one of the most common and treatable of all mental illnesses. No one is immune from depression - it occurs in people of all social classes, all countries and all cultural settings. 80-90% of those who suffer from depression can be effectively treated, and nearly all people who receive treatment derive some benefit.[1]

There are three main classes of anti-depressant medications;

[1] Selective serotonin reuptake inhibitors (SSRIs)

[2] Tricyclic medications

[3] Monoamine oxidase inhibitors (MAOIs)

Selective serotonin reuptake inhibitors (SSRIs) affect the availability of neurotransmitters such as dopamine, norepinephrine, and serotonin, which are all involved in mood stabilization. The SSRIs are the most recent class of anti-depressants to have been developed, and these medications generally have fewer side effects than the MAOIs or tricyclics. Some of the SSRIs on the market include Paxil (Paroxetine), Zoloft (Sertraline), and Prozac (Fluoxetine) (**Fig. 6**).

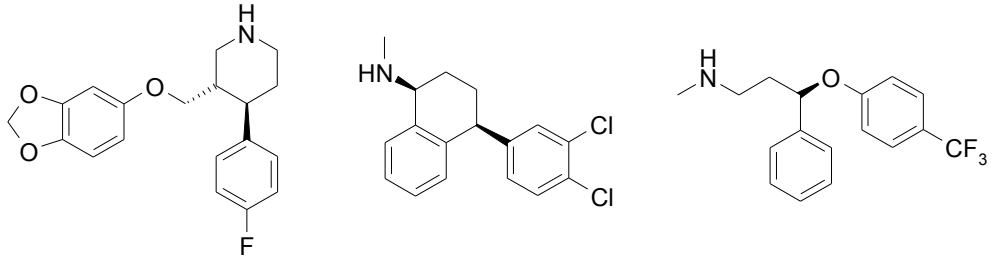


Fig. 6. Structures of Paxil, Zoloft and Prozac

Tricyclic anti-depressants have been in use since the 1950s. They stabilize chemical imbalances in the brain by acting on certain neurotransmitters. The common side effects associated with tricyclic anti-depressants include dry mouth, constipation, dizziness, drowsiness, and sexual dysfunction. Examples of tricyclic medications include Elavil (Amitriptyline), Tofranil (Imipramine), and Pamelor (Nortriptyline).

Monoamine oxidase inhibitors (MAOIs) work by inhibiting the metabolic degradation of the neurotransmitters serotonin, norepinephrine, and dopamine. While these medications do increase levels of these neurotransmitters in the brain, they also increase levels of an amine known as tyramine. This will, in turn, cause a sharp rise in blood

pressure, especially after a person has consumed certain foods. MAOIs are considered a last resort because of their harmful effects on blood pressure, and they are only used when a patient doesn't respond to any other type of medication. If a person is taking an MAOI, strict dietary guidelines are suggested to lower the risk. Nardil (Phenelzine) and Parnate (Tranylcyptomine) (**Fig. 7**) are couple of common MAOIs.

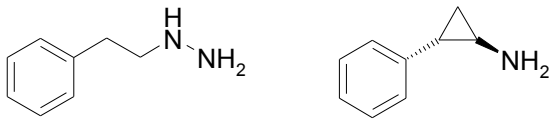
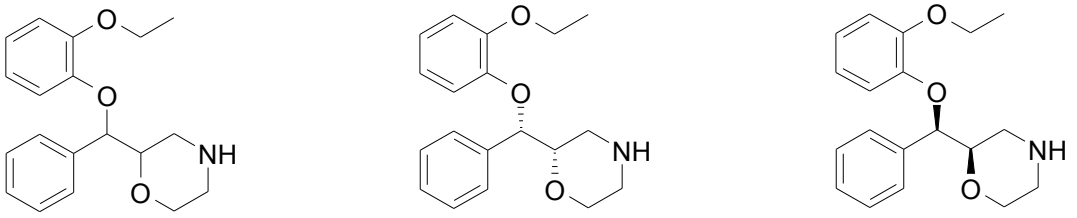


Fig. 7. Structures of Nardil and Parnate

3.2.2 Reboxetine and pharmacology

α-Aryloxybenzyl derivatives of morpholine are an important class of compounds owing to their impact on the central nervous system,[2] as well as potential treatments for depression and attention deficit/hyperactivity disorder (ADHD). Reboxetine is a classical example of such α-aryloxybenzyl derivatives having a mixture of (*2R, 3R)* and *(2S, 3S)*-[α-(2-ethoxyphenoxy)phenyl methyl]-morpholine, known to be a potent selective norepinephrine reuptake inhibitor (NRI) and widely studied for its pharmacological properties.[3-5]



(±)-Reboxetine **(S, S)-Reboxetine** **(R, R)-Reboxetine**

Fig. 8. Racemic, *(S, S) and (R, R)*-reboxetine

Reboxetine possesses two chiral centers; however, as a result of regio and stereo chemical constrains associated with key reactions in its synthesis, reboxetine exists as only the (*R, R*) and (*S*, *S*) enantiomers, it has been marketed as a mixture of two enantiomers (*S, S*) and (*R, R*) under the brand name Edronax®, Norebox® and Irenor®. It is approved for treatment of depression in over 50 countries worldwide and in many European countries.[6]

It is currently under clinical trials for the treatment of ADHD in adults[7] and cocaine dependence.[8]

It has comparable efficacy to that of imipramine, desipramine and fluoxetine (**Fig. 9**) e. g. in a study lasting up to eight weeks, reboxetine (4-10 mg daily) has shown similar efficacy (improvements in the HAMD, it is the Hamilton rating scale for depression) as compared to imipramine (150-200 mg daily), desipramine (150-200 mg daily) and fluoxetine (20-40 mg daily). In comparison with imipramine, reboxetine had a lower incidence of cardiovascular events, dry mouth and hypotension. Compared to fluoxetine, reboxetine had a lower cumulative risk of nausea, diarrhoea and somnolence but a higher incidence of constipation, dry mouth, hypotension, paraesthesia and urinary hesitancy. Reboxetine appears to have low toxicity in overdose and no symptoms of a withdrawal syndrome were seen on discontinuation of the drug.[9]

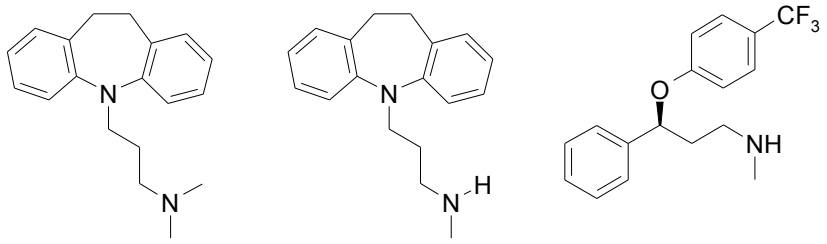


Fig. 9. ***Structures of imipramine, desipramine and fluoxetine***

However as discussed above currently used Reboxetine is a mixture of two enatiomers but it is found that (*S, S*)-reboxetine is approximately 24 times more potent than the (*R, R*)–reboxetine[10] and presents best affinity and selectivity for norepinephrine transporter (NET).[11]

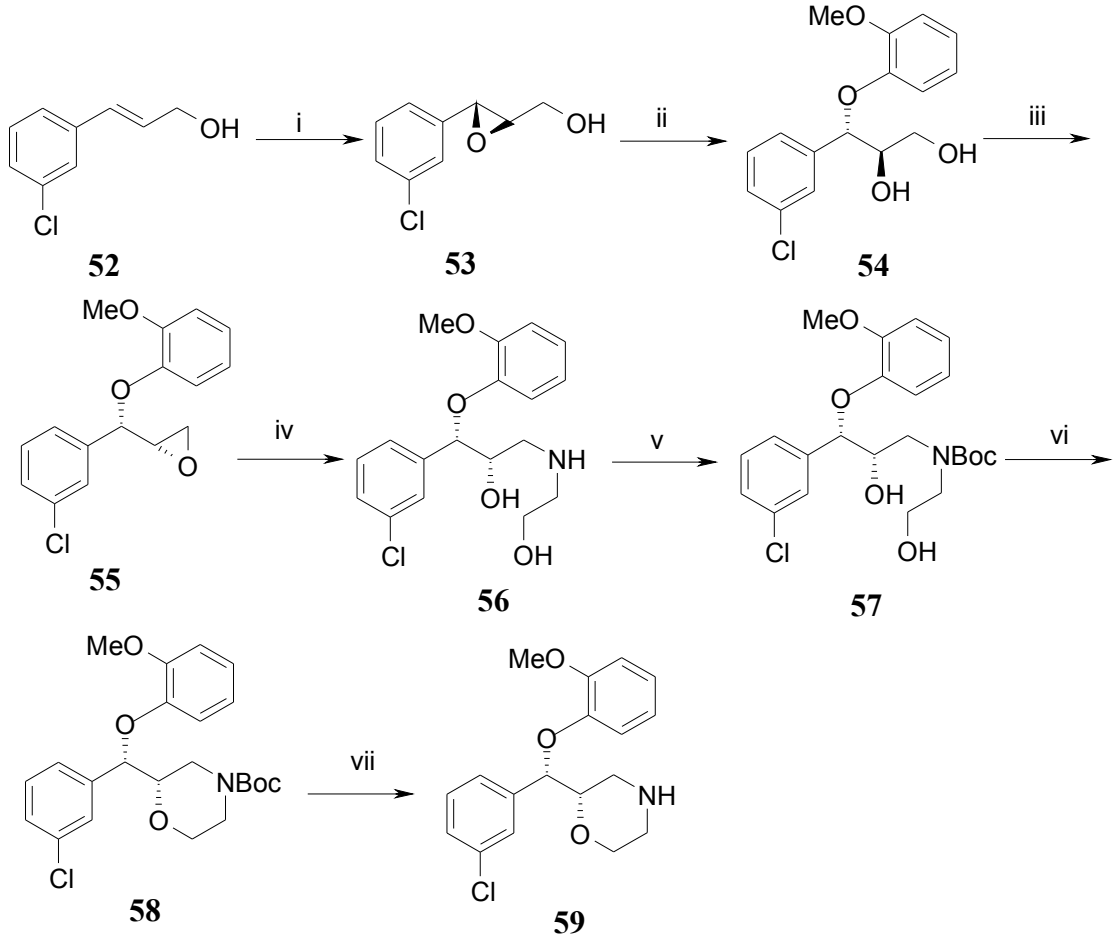
3.2.3 Review of literature

Melloni and co-workers[12] were the first to report the relative configuration of the two diastereoisomers of (+)-2-[N-(α-ethoxyphenoxy)benzylmorpholine which was determined by the synthesis involving regio and stereo specific reactions. (*RS, RS*) diastereoisomer FCE 20124 was separated into its (+) and (-) enantiomers both by crystallization of the optically active mandelate salt and by a multi-step synthesis from (+)-(2*S*, 3*R*)-3-phenylglycidic acid. Since then very few asymmetric synthesis of reboxetine

have been documented in the literature. Among many chemical routes, the most important employ the Sharpless asymmetric epoxidation, which is a stereo differentiating reaction.

Prisinzano's approach (2005)[13]

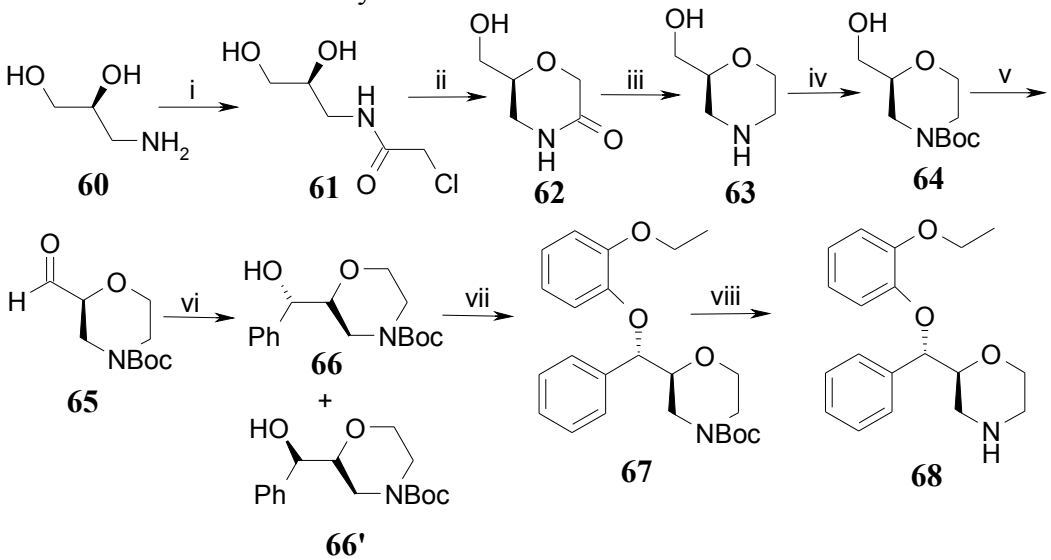
Prisinzano and coworkers very recently reported the synthesis of reboxetine by employing Sharpless asymmetric epoxidation (SAE) to get the chiral epoxide **53** in 85% ee. The chiral epoxide was cleaved with guaiacol to give the diol **54**. The secondary hydroxyl group was protected with methanesulfonyl chloride and the primary hydroxyl function exposed by the silyl ether with acid. The intermediate mesylate was converted to the epoxide **55** under phase transfer catalyzed condition in basic medium. Epoxide **55** on treatment with ethanolamine gave intermediate **56**. The free amine of **56** was protected with Boc_2O to give **57** which on further cyclization with tosyl imidazole gave morpholine ring **58**, deprotection of Boc group by TFA gave chloro-(*S, S*)-Reboxetine **59** in 93% yield.



Scheme 22. Reaction conditions**:** i) Ti(*i*-OPr)$_4$, cumene hydroperoxide, $_D$-DET, CH_2Cl_2, 4 A^0 mol. sieves, 72%, 85% ee. ii) Guaiacol, NaOH, CH_2Cl_2, 99%. iii) a) TMSCl, Et_3N, EtOAc. b) MsCl, Et_3N, EtOAc. c) 2N HCl. d) NaOH, toluene, methyltributylammonium chloride, 60%. iv) Ethanolamine, *i*-PrOH, reflux, 70%. v) Boc_2O, CH_2Cl_2, 83%. vi) NaH, TsIm, THF, 61%. vii) TFA, CH_2Cl_2, 93%.

Tamagnan's approach (2005)[14]

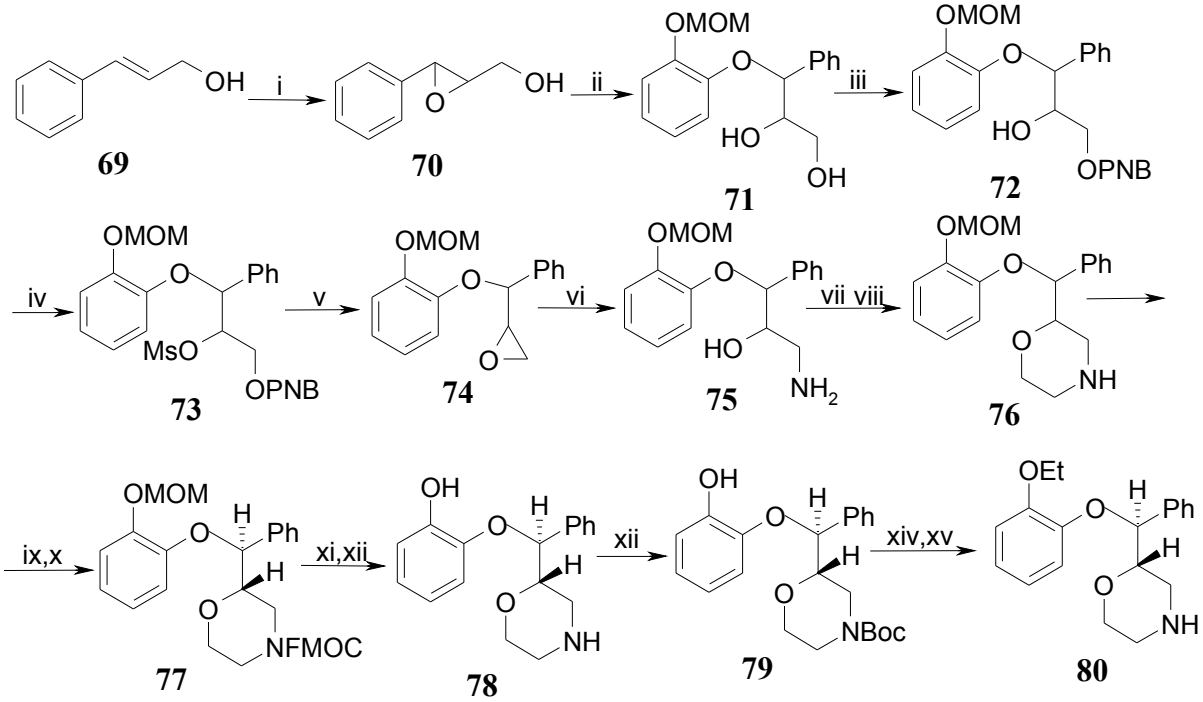
Tamagnan and co-workers recently reported the chiral pool synthesis of reboxetine from commercially available (*S*)-3-amino-1, 2-propanediol amine **60,** on protection with chloroacetyl chloride in a mixture of CH_3CN/MeOH solvent provided amide **61**. Conversion to morpholinone **62** was realized directly by addition of **61** to a solution of ^{t}BuOK in *t*-AmOH**.** Hydride reduction of amide **62** afforded (*S*)-2-(hydroxyl methyl) morpholine **63,** which on protection with $(Boc)_2O$ gave **64**. Slow addition of trichloro isocyanuric acid (TCIA) in EtOAc to a mixture of TEMPO and alcohol **64** in presence of $NaHCO_3$ lead to aldehyde **65**. Addition of diphenyl zinc to aldehyde **65** in THF at –10 ^{0}C gave distereomeric mixture of **66** and **66'** respectively. Sodium alkoxide of **66** in DMF was reacted with aryl chromium complex, which lead to the formation of **67** after oxidative dechromination with iodine. Finally, deprotection of Boc group in **67** by TFA provided (*S, S*)-reboxetine **68** in 98% isolated yield.



Scheme 23. Reaction conditions**:** i) $ClCH_2COCl$, Et_3N, CH_3CN/MeOH, 94%. ii) ^{t}BuOK, *t*-AmOH, 92%. iii) Red-Al, THF, 85%. iv) Boc_2O, NaOH, CH_2Cl_2/H_2O, 83%. v) TEMPO, TCIA, $NaHCO_3$, EtOAc, 89%. vi) Ph_2Zn, THF, 18 h, 60 & 19%. vii) NaH, DMF, Cr-Complex, 2 h, I_2, THF, 95%. viii) TFA, CH_2Cl_2, 98%.

Dileep Kumar's approach (2004)[15]

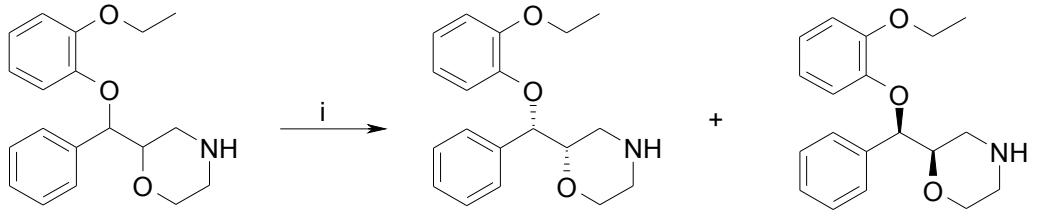
Dileep Kumar and co-workers reported the synthesis of reboxetine; there approach is similar to the approach of Melloni's work, from *trans*-cinnamyl alcohol **69,** which was converted to epoxide **70** using *m*CPBA. The opening of epoxide **70** with phenol in the presence of NaOH followed by basic work-up yielded diol **71**. The primary -OH group of alcohol **71** on protection with *p*-nitrobenzoyl chloride gave compound **72,** whereas secondary -OH group was protected with MsCl in the presence of triethylamine to afford **73** in nearly quantitative yield. Treatment of compound **73** with NaOH gave **74**. The ring opening of oxirane **74** with aqueous ammonia afforded **75,** protection of amine **75** with chloro acetyl chloride using triethyl amine gave intermediate which after work-up was dissolved in *t*-BuOH and added to a solution of ^{t}BuOK to give the amide. Reduction of amide by Red-Al® in toluene afforded **76**. The resolution of the amine **76** was achieved by (+) mandelic acid in absolute ethanol and subsequently protected by FMOC-Cl to afford **77**. The MOM group **77** was cleaved by catalytic amount of *p*-toluene sulfonic acid in methanol and FMOC group was cleaved by TBAF salt to give free amine **78,** which was again protected by Boc group to afford **79.** This on treatment with ethyl iodide in presence of ^{t}BuOK in DMF gave intermediate further deprotection of Boc group gave (2*S*, 3*S*) reboxetine **80**.



Scheme 24. Reaction conditions**:** i) *m*CPBA, CH_2Cl_2, 80%. ii) 2-methoxyphenol, aq. NaOH, 64%. iii) Pyridine, PNBCl, 65%. iv) Et_3N, MsCl, CH_2Cl_2, 90%. v) aq. NaOH, dioxane, 95%. vi) 30% NH_4OH, methanol, 88%. vii) a) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2; b) ^{t}BuOK, *t*-BuOH, 64%. viii) Red Al, toluene, 88%. ix) (+) mandelic acid, 75%, x) FMOC-Cl, Et_3N, ether, 75%. xi) *p*TSA, MeOH, 94%. xii) TBAF, H_2O, THF, 87%. xiii) Boc_2O, CH_2Cl_2, 87%. xiv) ^{t}BuOK, DMF, ethyl iodide. xv) TFA, 90%.

Raggi's approach (2002)[16]

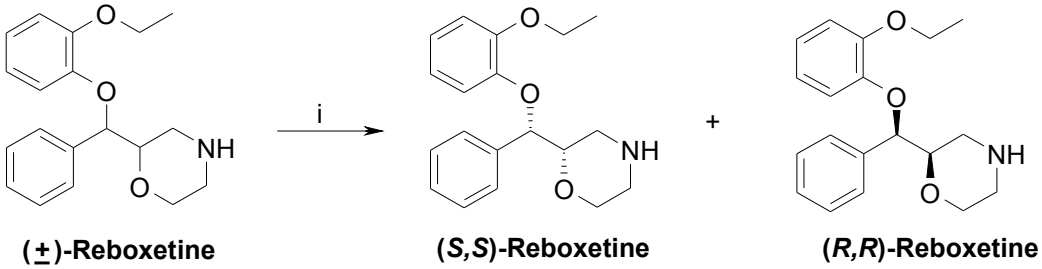
In this approach, Raggi *et al.* made use of capillary electrophoresis method to separate the enantiomers of racemic mixture of (*R, R*) and (*S, S*) reboxetine. Sulfobutyl ether β-cyclodextrin was chosen as the chiral selector using an uncoated fused silica capillary (**Scheme 25**).



Scheme 25. Reaction conditions**:** i) fused silica capillary (internal diameter 50 µm, total length 48.5 cm, effective length 40.0 cm), electrolyte pH 3.0, 100 mM phosphate buffer, 1.25 mM Sulfobutyl ether-β-cyclodextrin, 20 kV.

Ohman's approach (2002)[17]

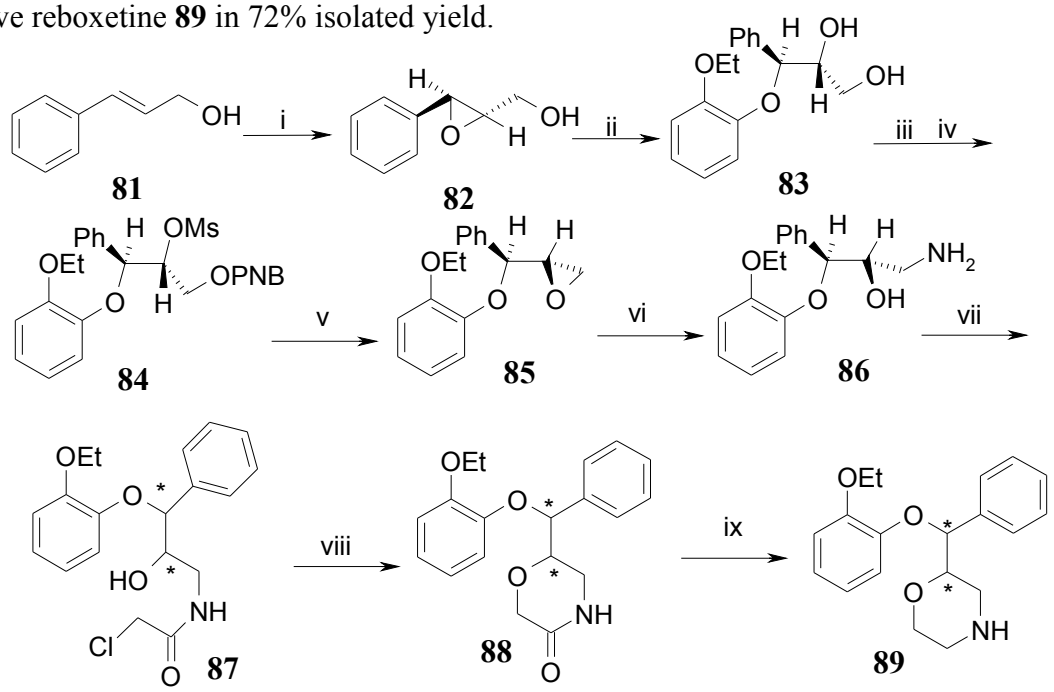
Ohman *et al.* reported, the separation of the racemic mixture of reboxetine was done using reversed-phase high-performance liquid chromatography using three different chiral columns, Chiral-AGP, Chiral Grom 2 and Chiral-CBH (**Scheme 26**).



Scheme 26. Reaction conditions**:** i) Chiral columns

Melloni approach (1985)[11]

Melloni and co-workers were credited first to synthesize reboxetine, starting from *trans*-cinnamyl alcohol **81** which on epoxidation gave **82,** which in turn was reacted with sodium 2-ethoxyphenate to give the diol **83** in regio and stereo specific way .The primary -OH group of **83** was protected using *p*-nitrobenzoyl chloride**,** where as secondary -OH was protected using mehanesulfonyl chloride gives **84** and the epoxide **85** was prepared in high yield by treatment of compound **84** with sodium hydroxide in an aqueous dioxane. The reaction of **85** with aqueous ammonia gave **86**, which was protected with chloroacetyl chloride to give **87** and was subsequently cyclized to **88**. Reduction of amide by Red-Al gave reboxetine **89** in 72% isolated yield.



Scheme 27. Reaction conditions**:** i) *m*CPBA, CH_2Cl_2, 80%. ii) 2-ethoxy phenol, aq. NaOH, 83%. iii) pyridine, PNBCl, 61%. iv) Et_3N, MsCl, CH_2Cl_2, 84%. v) aq. NaOH, dioxane, 95%. vi) 30% NH_4OH, methanol, 75%. vii) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2, 86%. vii) ^{t}BuOK, *t*-BuOH, 86%. ix) Toluene, Red-Al, 72%.

3.2.4 Present Work

3.2.4.1 Objectives

Due to its potent medicinal properties several syntheses of both (+) and (-)-reboxetine as well as racemic (±)-reboxetine are documented in the literature through varied synthetic routes, most involve a large number of steps or costly chiral auxiliaries

and resolving agents. Hence, interest in newer synthetic methods with fewer steps goes unabated. Moreover asymmetric synthesis of individual enantiomers is extremely important because (*S*) and (*R*)-isomers usually display very different pharmacological or physiological properties.

The Sharpless asymmetric dihydroxylation and subsequent transformation of the diol formed were envisioned as powerful tool offering considerable opportunities for synthetic manipulations. We envisaged enantioselctive synthesis of (*S, S)*-reboxetine from commercially available *trans*-cinnamyl bromide employing Sharpless asymmetric dihydroxylation procedure as the source of introducing chirality.[18]

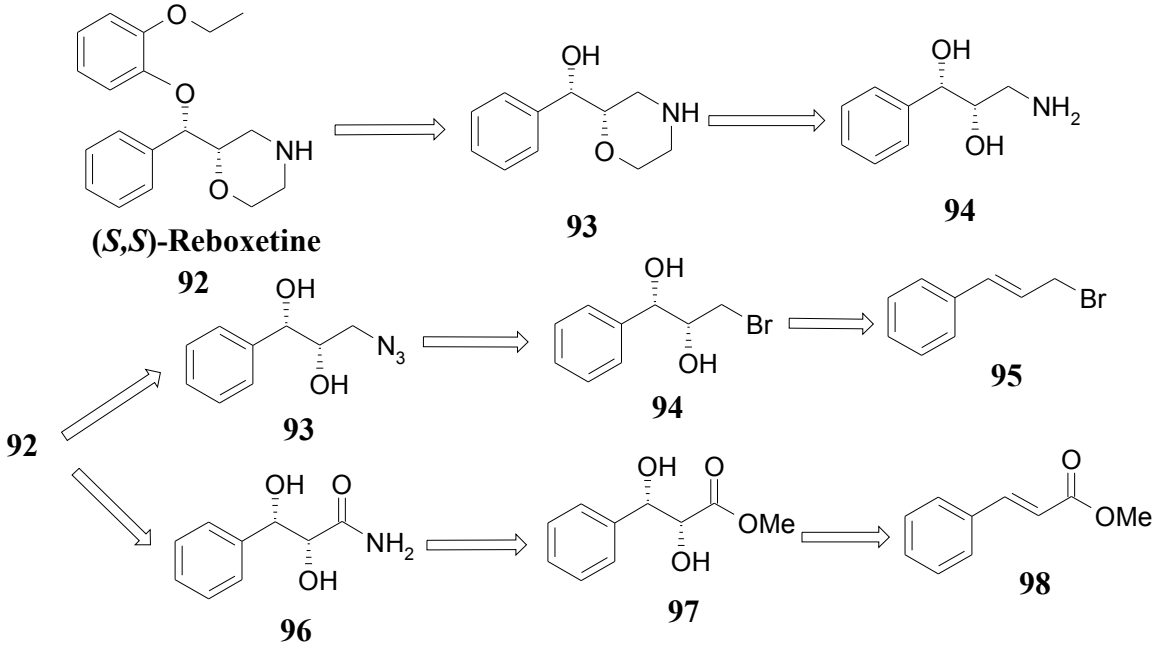
3.2.4.2 The retro synthetic strategy for (*S, S*)-reboxetine

The retro synthesis strategy for (*S, S*)-Reboxetine is outlined in **Scheme 28**. (*S, S*)-Reboxetine can be obtained from the morpholine derivative **91** which can be realized through amino alcohol **92** which in turn can be obtained from two routes:

(i) from the corresponding azido alcohol **93** or

(ii) reduction of amide **96**.

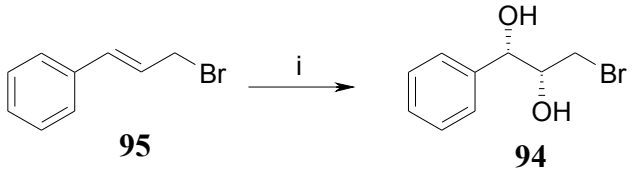
The azido alcohol **94** can be obtained from cinnamyl bromide **95** by Sharpless asymmetric dihydroxylation and the amide could be obtained from cinnamyl ester **98** by Sharpless asymmetric dihydroxylation



Scheme 28: Retro synthetic analysis for reboxetine.

3.2.4.3 Results and discussion

Route 1: Synthesis of amino alcohol 92 from *trans*-cinnamyl bromide 95

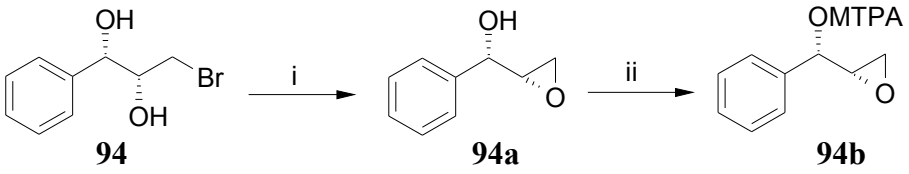


95 **94**

Scheme 29. Reaction conditions**:** i) $(DHQ)_2PHAL$ (1 mol%), OsO_4 (0.1 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $NaHCO_3$ (3 equiv.), $MeSO_2NH_2$ (1 equiv.), H_2O:*t*-BuOH (1:1), 0 ^{0}C, 24 h.

The enantioselective synthesis of (*S, S*)- reboxetine was started by subjecting the commercially available *trans* cinnamyl bromide **95** to asymmetric dihydroxylation under Sharpless protocol[18] using osmium tetraoxide and $K_3Fe(CN)_6$ as co-oxidant in the presence of catalytic amount of chiral ligand $(DHQ)_2PHAL$ and $NaHCO_3$ as a buffering agent[19] affording (1*S, 2R*)-3-bromo-1-phenylpropane-1,2-diol **94** in 84% yield with $[\alpha]_D^{25}$ –8.66 (*c* 1.16, EtOH) and 95% ee (**Scheme 29**). For the measurement of enantiomeric excess (ee), the diol **94** was converted into the epoxide which was further converted into the corresponding (*S*)-Mosher's ester[20] by reaction with (*R*)-(–)-α-methoxy-α-(trifluoromethyl) phenyl acetyl chloride (CH_2Cl_2–DMAP, Et_3N, 0 °C, 4 h, 90% yield) (**Scheme 31**) and ^{19}F spectra was recorded to find out the exact ratio [**Fig. 10.** ^{19}F spectra of **94b**]. The IR spectrum of **94** showed broad hydroxyl absorption at 3438 and 3564 cm^{-1}. In the ^1H NMR spectrum of **94**, disappearance of olefinic protons was observed whereas the hydroxyl protons appeared at δ 2.02 and 3.83 (broad singlets) and the chiral protons at 3.1-3.40 (multiplet, two protons), 4.05-4.16 (multiplet, one proton), 4.66-4.69 (doublet, one proton), and the five protons of aromatic region appeared as a singlet at δ 7.35. The asymmetric dihydroxylation reaction of cinnamyl bromide, which gave base sensitive product (**94**) was performed under buffered condition using $NaHCO_3$ (3 equiv.) as a buffering agent, which does not affect the ee of product (**94**) but it has a beneficial effect on the yield. Also the buffered condition, minimizes the formation of the byproduct epoxide and also increases the selectivity at 0 ^{0}C. When reaction was performed at ambient temperature instead of 0 ^{0}C epoxide was formed in considerable amount with a consequent decrease in selectivity. This is the reason the reaction was performed under buffer media at 0 ^{0}C, which in turn not

only gave excellent isolated yield but also excellent enantioselectivity of the Sharpless dihydroxylated product.



94 **94a** **94b**

Scheme 30. Reaction conditions**:** i) powdered NaOH, THF, 0 ^{0}C to rt, 12 h. ii) (-) MOSCl, DMAP, Et_3N, DCM, rt, 2 h.

Alternatively, the use of $(DHQD)_2PHAL$ in SAD gave (1*R, 2S*)-3-bromo-1-phenylpropane-1,2-diol **94'** with $[\alpha]_D^{25}$ +8.71 (*c* 1.16, EtOH).

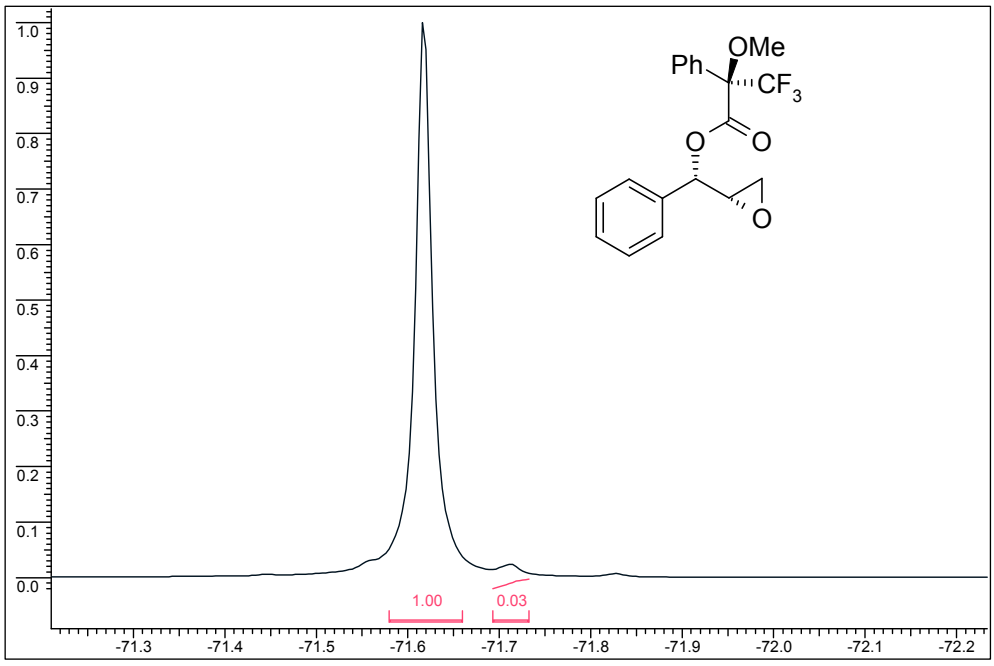
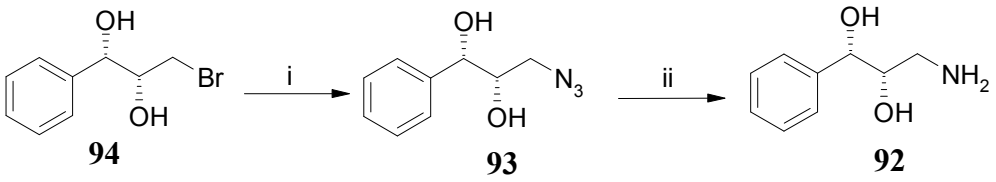


Fig. 10. ^{19}F spectra of 94b (for calculating ee of bromo diol **94**)



94 **93** **92**

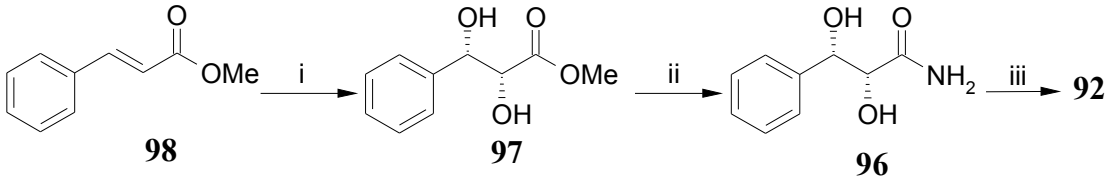
Scheme 31. Reaction conditions**:** i) NaN_3 (5 equiv.) DMF, 68 ^{0}C, 16 h. ii) 10% palladium on carbon, H_2 (1 atmp. balloon pressure), rt, 12 h.

Nucleophilic displacement of the bromo group by sodium azide in DMF furnished the azido alcohol **93** in 84% yield.[21] The IR spectrum of **93** showed prominent azide

absorption at 2098 cm^{-1}. The azide group was reduced using 10% Pd/C in MeOH under hydrogen atmosphere (1 atm., balloon pressure) giving rise to the amino alcohol **92**. The IR spectrum of **92** showed the amine absorption at 3368 cm^{-1} (**Scheme 31**) and no absorption at 2098 cm^{-1} corresponding to the azido group. The ^1H NMR spectrum of **92** showed broad peak at δ 2.77 for the primary amine.

Route 2: Synthesis of amino alcohol 92 from cinnamyl ester 98

The synthesis of amino alcohol **92** from cinnamyl ester is presented in **Scheme 32.**



Scheme 32. Reaction conditions**:** i) $(DHQ)_2PHAL$ (1 mol%), OsO_4 (0.1 mol%), $K_3Fe(CN)_6$ (3equiv.), K_2CO_3 (3equiv.), $MeSO_2NH_2$ (1 equiv.), H_2O:*t*-BuOH (1:1), rt, 24 h. ii) MeOH, NH_4OH, 8 h. iii) dry THF, Red-Al® 0 ^0C to rt, 4 h.

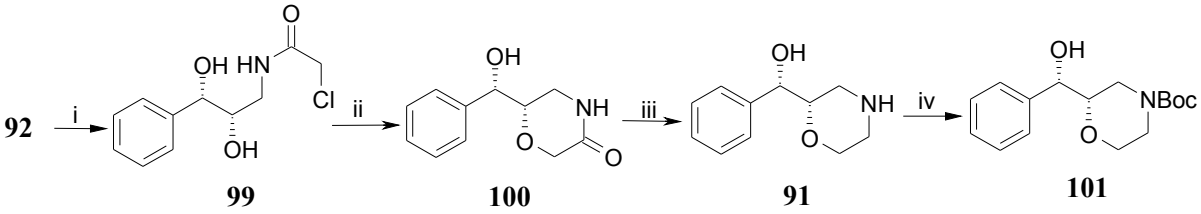
*Trans-c*innamyl methyl ester **98** was synthesized from commercially available *trans*-cinnamic acid using dry MeOH and catalytic amount of *p*TSA (10 mol%) under argon atmosphere at room temperature, which on subjecting to Sharpless asymmetric dihydroxylation conditions using catalytic amount of $(DHQ)_2PHAL$ as a chiral ligand gave "α" diol[22] with $[\alpha]_D^{25}$ +3.46 (*c* 1.14, EtOH). The IR spectrum of **97** shows absorption at 3468 cm^{-1} for hydroxyl group, ^1H NMR spectrum of **97** showed the broad singlet at δ 2.69 for hydroxyl group whereas the two chiral proton appeared at 4.30-4.31 (doublet, one proton), 4.94-4.96 (doublet, one proton). The ester on treatment with ammonium hydroxide in MeOH at reflux temperature after 6 h, gave the amide[23] in 94% isolated yield. The IR spectrum of **96** showed the amide absorption at 3420 cm^{-1}. ^1H NMR spectrum of **96** showed a broad singlet at δ 5.31 corresponds to amide protons and disappearance of peaks corresponding to methoxy group. Its ^{13}C NMR spectrum showed the amide carbonyl carbon at δ 174.9 (Scheme 32).

For the reduction of the amide group, we chose $LiAlH_4$ as reducing agent, which in refluxing THF gave very poor yield of **92** (40%) after long reaction span of 12 h. Finally,

we replaced the $LiAlH_4$ by the strong reducing agent Red-Al® at 0 ^{0}C which afforded the amino alcohol **92** in 80% yield.

Synthesis of (*S, S*)-Reboxetine starting from amino alcohol 92

The synthesis of (*S, S*)-Reboxetine, starting from amino alcohol is presented in **Scheme 33**.



Scheme 33. Reaction conditions**:** i) $ClCOCH_2Cl$, Et_3N, DCM at -10 ^{0}C to rt, 6 h. ii) ^{t}BuOK (2 equiv.), *t*-BuOH, rt, 4 h. iii) Red-Al, THF, 0 ^{0}C. iv) $(Boc)_2O$, NaOH, DCM:H_20, 0 ^{0}C to rt, 5 h

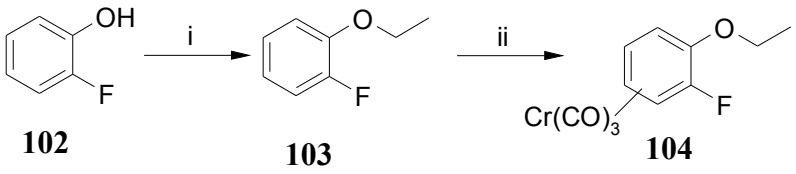
The free amine of **92** was acylated with freshly distilled chloro acetyl chloride in DCM which furnished the amide **99** in 70% yield, IR spectrum of **99** showed absorption at 1670 cm^{-1} attributable to the carbonyl function. The ^{1}H NMR spectrum of **99** showed peak at δ 6.98 (broad singlet) for acetyl amide proton whereas ^{13}C NMR spectrum of **99** showed the carbonyl carbon at δ 166. The compound **99** was readily cyclized to compound **100** using potassium *tert*-butoxide in *t*-BuOH in 80% yield. The ^{13}C NMR spectrum of **100** showed the carbonyl carbon at δ 169.

Another challenge was to reduce the carbonyl group of the cyclic amide. The reduction was tried with strong hydride transfer reagent such as $LiAlH_4$ in refluxing THF or ether but the procedure gave only 25-30% of the desired reduced compound. Yet again, we reduced the amide using a solution of Red-Al® at 0 ^{0}C, giving the morpholine intermediate **91** in 83% isolated yield. The IR spectrum of **91** showed disappearance of absorption corresponding to amide carbonyl at 1670 cm^{-1} and the ^{13}C NMR peak at δ 169 with DEPT showing methylene carbon at δ 67.5 in the later were confirming the product formation.

The secondary amine **91** was protected with $(Boc)_2O$ to get the known intermediate **101** in 83% yield, $[\alpha]_D^{25}$ +33.4 (*c* 1.24, $CHCl_3$) (lit.[14] +34 (*c* 1.24, $CHCl_3$). ^{1}H NMR spectrum of **101** showed the singlet of nine protons at δ 1.43 for *tert*-butyl group and doublet at δ 4.74 for benzylic protons. It's ^{13}C NMR spectrum showed at δ 79.8 and 154.2

for benzylic and carbonyl carbon respectively. The physical and spectroscopic data of intermediate **101** were in full agreement with literature data.[14]

2-Fluorophenol **102** on alkylation with ethyl bromide as an alkylating agent with K_2CO_3 as a base gave 2-ethoxy fluorobenzene **103** in 96% isolated yield (**Scheme 34**).

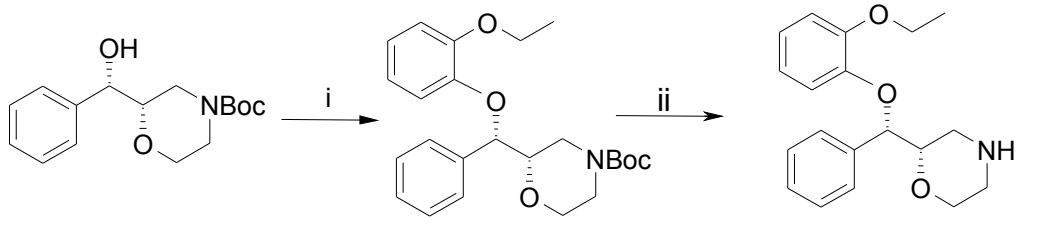


102 **103** **104**

Scheme 34. Reaction conditions**:** i) ethyl bromide, K_2CO_3, dry acetone, reflux, 20 h, 96%. ii) $Cr(CO)_6$, THF, di-n-butyl ether, 60 h, 49%

The IR spectrum of **103** showed disappearance of the hydroxyl absorption at 3560 cm^{-1} corresponding to 2-fluoro phenol. The ^1H NMR spectrum of 2-ethoxy flourobenzene **103** showed peaks at δ 1.23-1.30 (triplet, three protons) for methyl group and δ 3.85-3.95 (quartet, two protons) for methylene group respectively. The ^{13}C NMR-DEPT spectrum of 2-ethoxy fluoro benzene showed δ 64.9 for methylene carbon. The 2-ethoxy fluorobenzene **103** was reacted with chromium hexacarbonyl under standard condition in toluene under dark conditions protected from light (to avoid photo oxidation due to $Cr(CO)_6$) which gave aryl-chromium complex **104** in 45% isolated yield (**Scheme 34**).[24] The complex formed was purified by column chromatography and its characterization data was in full agreement with the literature data.

Converting the isomer **101** to ether **105** without affecting the stereochemistry was another challenge (**Scheme 35**). This was best achieved via an aromatic nucleophilic substitution



101 **105** **90 (*S,S*)-Reboxetine**

Scheme 35. Reaction conditions**:** i) a) NaH (1.5 equiv.), DMF, rt, 1 h, **104,** 2 h; b) I_2, 0 ^0C, THF. ii) CF_3COOH (1.5 equiv.), DCM, 0 ^0C to rt, 2 h.

Sodium alkoxide of **101** in DMF was reacted with aryl chromium **104** giving rise to a chromium complex, which led to **105** in 95% yield after oxidative dechromination with iodine. The IR spectrum of **105** showed absence of absorption at 3405 cm^{-1} corresponding to the hydroxyl group. ^{1}H NMR spectrum of **105** showed peaks at δ 3.75-3.96 (multiplet three protons) of methyl and 2.81-3.03 (multiplet, two protons) for methylene group respectively.

Finally, Boc group of **105** was eliminated by excess trifluoro acetic acid in DCM which gave (*S*, *S*)-Reboxetine **90** in 88% yield with $[\alpha]_D^{25}$ +12.81 (*c* 1.03, MeOH) (lit.[14] +13 (*c* 1.03, MeOH)). The IR spectrum of **90** showed absence of ester carbonyl absorption at 1760 but absorption at 3395 cm^{-1} corresponding to the –NH was observed. ^{1}H NMR spectrum of **90** showed signals at δ 1.41 (triplet, three protons) and 5.17 (doublet, one proton) corresponds to the methyl protons in ethoxy moiety and benzylic proton respectively. Its ^{13}C NMR spectrum displayed carbon signals at δ 14.6, 45.3 and 46.7 corresponds to the methyl group in the ethoxy moiety and methylene group in the morpholine moiety respectively and disappearance of characteristic carbonyl carbon peak at δ 155.09 of *tert*-butyl group which also confirmed the formation of **90** (**Scheme 35**).

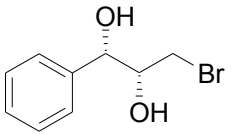
All the observed spectral data and specific rotation of **90** are in full accordance with the reported literature data.[11]

3.2.5 Conclusion

In conclusion, we had developed a relatively short and high yielding enantioselective synthesis of (+)-(*S*,*S*)-Reboxetine using Sharpless asymmetric dihydroxylation as the source of chirality and a chromium complex coupling in the final step without affecting stereochemistry of the parent compound which are key steps of this enantioselctive synthesis. Sharpless asymmetric dihydroxylation of cinnamyl bromide has been reported for the first time by us in this synthesis and it gave excellent enatioselectivity. Thus, the results described here constitute a short, straight forward and efficient synthesis of active isomer of reboxetine i.e. (*S, S*)-Reboxetine with an overall yield of 21% over nine linear steps with excellent yields in individual reaction steps. This work already peer reviewed and published in *Synlett* **2006,** 1771.

3.2.6 Experimental

(2*R*, 3*S*)-1-bromo-3-phenylpropane-2, 3-diol (94)

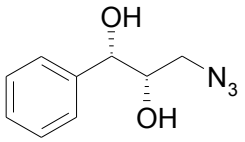


To a mixture of $K_3Fe(CN)_6$ (25.05g, 76.1 mmol), K_2CO_3 (10.5g, 76.1 mmol), $NaHCO_3$ (6.39g, 76.1 mmol) and $(DHQ)_2PHAL$ (197mg, 1 mol%) with respect to *trans*-cinnamyl bromide in *t*-BuOH-H_2O (1:1, 126 mL) cooled to 0 ^{0}C,

was added OsO_4 as a 0.1 M solution in toluene (0.3 mol% w/v) followed by methane sulfonamide (2.4g, 25.3 mmol). After stirring for 30 min at 0 ^{0}C, the *trans*-cinnamyl bromide (5g, 25.3 mmol) was added in one portion. The reaction mixture was stirred at 0 ^{0}C for 24 h (progress of reaction was monitored by TLC) and then quenched with solid sodium sulfite (40g). Stirring was continued for 45 min, and the solution was extracted with EtOAc (3 x 50 mL). The combined organic phase was separated, washed with brine, dried on $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography on silica gel with petroleum ether/EtOAc (8:2) which gave (2*R*, 3*S*)-1-bromo-3-phenylpropane-2, 3-diol (**94**) as a colorless syrupy liquid.

Yield	**:** 4.9g, (84%)
TLC	**:** Silica gel; petroleum ether/ethyl acetate (8:2); R_f= 0.56
$[\alpha]_D^{25}$	**:** –8.66 (*c* 1.16, EtOH).
IR ($CHCl_3$, cm^{-1})	**:** υ_{max} 702, 738, 1086, 1215, 1392, 1455, 1603, 2400, 2975, 3019, 3438, 3564.
^{1}H-NMR (200 MHz, $CDCl_3$)	**: δ** 2.02 (brs, 1H), 3.14-3.19 (dd, *J*= 5.4, 5.7 Hz, 1H), 3.33-3.40 (dd, *J*= 3.6, 4.1 Hz, 1H), 3.83 (brs, 1H), 4.05-4.16 (m, 2H), 4.66-4.69 (d, *J*= 6.3 Hz, 1H), 7.35 (m, 5H).
^{13}C-NMR (50 MHz, $CDCl_3$)	**: δ** 35.1, 74.7, 75.2, 126.5, 127.4, 128.1, 128.3, 128.4, 139.8.
LC-MS	: 231.07 (M+H), 210.11, 181.14, 168.07.
Elemental Analysis	**: ($C_9H_{11}BrO_2$)** Calcd. C, 46.78; H, 4.80; Br, 34.58. Found, C, 46.54; H, 4.65; Br, 34.11

(2*R*, 3*S*)-1-azido-3-phenylpropane-2, 3-diol (93)



To a solution of bromo diol **94** (5g, 2 mmol) in DMF (50 mL) was added NaN_3 (5.47g, 8.6 mmol) with stirring at 60 ^{0}C under argon.

Progress of the reaction was monitored by thin layer chromatography. After completion of reaction (24 h) solvent was evaporated under reduced pressure, the residue was dissolved in diethyl ether and filtered through silica gel and celite pad. The residue and filtrate was dissolved and extracted with ethyl acetate (2 × 20 mL). Organic layer was washed with water (3 × 20 mL), brine solution (20 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Further the product was purified by flash column chromatography on silica gel.

Yield **:** 3.52g, (84%).

TLC **:** Silica gel; petroleum ether/ethyl acetate (8:2); R_f= 0.5

$[\alpha]_D^{25}$ **:** -16.8 (*c* 2.34, MeOH)

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 764, 876, 924, 1157, 1494, 1603, 1810, 1889, 1959, 2098, 2518, 2924, 3032, 3087, 3401.

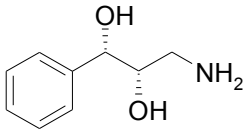
^{1}H-NMR (200 MHz, $CDCl_3$) **:** **δ** 3.08-3.11 (dd, *J*= 6.2, 6.3 Hz, 1H), 3.17-3.25 (dd, *J*= 3.2, 3.5 Hz 1H), 3.79-3.86 (m, 1H), 4.55-4.59 (d, *J*= 7.2 Hz, 1H), 7.29-7.40 (m, 5H).

^{13}C-NMR (50 MHz, $CDCl_3$) **:** **δ** 52.8, 74.9, 126.5, 128.2, 128.5, 139.9.

LC-MS **:** 194.07 (M+H), 168.07, 150.06, 137.51, 127.95.

Elemental Analysis **:** **($C_9H_{11}N_3O_2$)** Calcd. C, 55.95; H, 5.74; N, 21.75. Found, C, 55.72; H, 5.51; N, 21.56.

(2*S*, 3*S*)-1-amino-3-phenylpropane-2,3-diol (92)



To a mixture of azide **93** (3g, 1.5 mmol) in methanol (20 mL) was added Pd/C (10 mol%) and stirred under hydrogen atmosphere (1 atm. balloon pressure) at room temperature till completion of the reaction (24 h, monitored by TLC).

After completion, the reaction mixture was filtered through Whatmann filter paper, washed with methanol, filtrate was evaporated under reduced pressure gave amine as a yellow hygroscopic mass in excellent isolated yield. The product was pure enough.

Yield : 2.51g, (90%)

TLC : Silica gel; ethyl acetate/MeOH (8:2); R_f= 0.4

$[\alpha]_D^{25}$: -18.28 (*c* 1.27, EtOH)

IR ($CHCl_3$, cm^{-1}) : υ_{max} 1051, 1334, 1386, 1493, 1583, 2921, 3018, 3065, 3368, 3420.

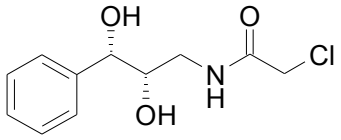
^{1}H-NMR (200 MHz, $CDCl_3$) : **δ** 2.77 (brs, 2H), 2.86 (brs, 2H), 3.01-3.1 (m, 1H), 3.17-3.19 (m, 1H), 3.74-3.81 (m, 1H), 4.53-4.58 (d, *J*= 5.4 Hz, 1H), 7.23- 7.34 (m, 5H).

^{13}C-NMR (50 MHz, $CDCl_3$) : **δ** 52.9, 75.1, 126.6, 128.3, 128.6, 140.3, 162.8.

LC-MS : 168.07 (M+H), 148.05, 132.05.

Elemental Analysis : **$C_9H_{11}NO_2$** Calcd. C, 64.65; H, 7.84; N, 8.38.
Found, C, 64.43; H, 7.63; N, 8.22.

2-chloro-*N*-((2*S*, 3*S*)-2, 3-dihydroxy-3-phenylpropyl)acetamide (99)



The amine **92** (1g, 6 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and Et_3N (0.735g, 7.2 mmol) added to the solution. The solution was kept at -10 ^{0}C. Freshly distilled chloro acetyl chloride (0.753g, 6.6 mmol) in CH_2Cl_2 (5 mL) was added slowly with stirring for 30 min. under argon at 0 ^{0}C and the stirring continued at same temperature for 45 min. After addition was over reaction mixture was allowed to attain room temperature (30 ^{0}C) and stirring was further continued for the next 14 h. After completion (progress of reaction was monitored by TLC), the reaction mass was quenched with ice-cold water (10 mL), extracted with CH_2Cl_2 (2 X 10 mL). Organic layer was separated, washed with water (2 X 5 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was practically pure enough to use directly for the next cyclization step.

TLC : Silica gel; petroleum ether/ethyl acetate (6:4); R_f= 0.4

$[\alpha]_D^{25}$: -4.38 (*c* 1.25, EtOH).

IR ($CHCl_3$, cm^{-1}) : υ_{max} 750, 840, 995, 1120, 1238, 1495, 1670, 2010, 3300, 3420.

^{1}H-NMR (200 MHz, $CDCl_3$) : **δ** 2.04 (brs, 1H), 4.0-4.14 (m, 5H) 5.73-5.76 (d, *J*= 6.9 Hz, 1H), 6.98 (brs, 1H), 7.33-7.38 (m, 5H).

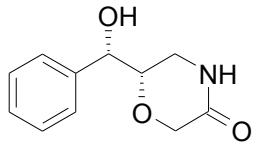
^{13}C-NMR : **δ** 40.8, 42.4, 79, 126.3, 127, 128.3, 128.6, 128.8, 129, 135.5,

(50 MHz, $CDCl_3$) 166.9.

LC-MS : 245.06 (M+H), 243.06, 212.08.

Elemental Analysis : **$C_{11}H_{14}ClNO_3$** Calcd. C, 54.22; H, 5.79; N, 5.75.
Found, C, 53.95; H, 5.58; N, 5.51.

(*S*)-6-(*S*)-hydroxy (phenyl) methyl)morpholine-3-one (100)



The crude product **99** (1g, 4.1 mmol) obtained in previous step was dissolved in *t*-BuOH (10 mL) and added to a solution of KO*t*Bu (1.01g, 8.2 mmol) in *t*-BuOH (5 mL). The solution was stirred for 6 h at room temperature (monitored by TLC) followed by quenching the reaction with water. The product was extracted with ethyl acetate (2 X 10 mL). The organic layer was separated, washed with water (2 X 5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Evaporation of the solvent afforded the crude product, which was further purified by flash column chromatography on silica gel affording **100** in 80% isolated yield.

Yield : 0.68g, (80%)

TLC **:** Silica gel; petroleum ether/ethyl acetate (6:4); R_f= 0.5

IR ($CHCl_3$, cm^{-1}) **:**υ_{max} 1118, 1215, 1346, 1431, 1454, 1680, 2360, 2925, 3200, 3396.

^{1}H-NMR **: δ** 2.17 (brs, 1H), 3.17-3.28 (m, 1H), 3.72-3.75 (m, 1H), 3.91-4.03 (m, 1H), 4.11-4.28 (m, 2H), 4.56-4.6 (d, *J*= 7.5 Hz, 1H), 6.97 (brs, 1H), 7.27-7.36 (m, 5H).

(200 MHz, $CDCl_3$)

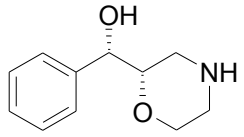
^{13}C-NMR **: δ** 42.8, 67.4, 72.5, 74.8, 126.7, 128, 128.4, 128.7, 138.6, 169.8.

(50 MHz, $CDCl_3$)

LC-MS : 208.09 **(**M+H), 198.06, 145.08.

Elemental Analysis : **$C_{11}H_{13}NO_3$** Calcd. C, 63.76; H, 6.32; N, 6.76.
Found, C, 63.48; H, 6.11; N, 6.58.

(*S*)-((*S*)-morpholine-2-yl)(phenyl)methanol (91)



A solution of Red-Al® (0.971g, 4.8mmol) in anhydrous toluene (10 mL) was slowly added to the amide **100** (0.5g,

2.4 mmol) dissolved in anhydrous toluene (20 mL) at room temperature (30 ^{0}C).

The mixture was stirred for 4 h at 30 ^{0}C and the excess Red-Al® was decomposed with 2N NaOH (10 mL). The reaction mixture was extracted with ethyl acetate (2 X 5 mL). The organic layer was separated, washed with water (2 X 5 mL), brine solution (5 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the separated crude product was purified by flash column chromatography on silica gel to afford compound **91** as viscous solid mass in 83% isolated yield.

Yield **:** 0.385g, (83%)

TLC **:** Silica gel; petroleum ether/ethyl acetate (6:4); R_f= 0.4

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 750, 997, 1078, 1154, 1250, 1453, 1595, 2915, 3031, 3405.

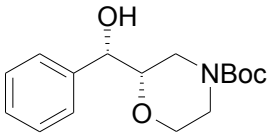
^{1}H-NMR (200 MHz, $CDCl_3$) **:** **δ** 2.8-4.13 (m, 7H), 4. 82 (d, *J*= 7.5 Hz, 1H), 7.3-7.41 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$) **:** **δ** 42.8, 48.1, 67.5, 75.2, 87.1, 126.7, 128.1, 128.5, 128.7, 138.6.

LC-MS : 194.24 (M+H), 188.08, 156.12.

Elemental Analysis **:** **$C_{11}H_{15}NO_2$** Calcd. C, 68.37; H, 7.82; N, 7.25.
Found, C, 68.24; H, 7.69; N, 6.98.

(*S*)-*tert*-butyl 2-((*S*)-hydroxy (phenyl)methyl) morpholine-4-carboxylate (101)



To a vigorously stirred solution of **91** (0.35g, 1.81 mmol) in a mixture of CH_2Cl_2 (10 mL) and water (5 mL) was added at room temperature NaOH (0.08g, 1.99 mmol) a 4N sodium hydroxide solution.

Di-*tert*-butyl bicarbonate (0.37g, 1.99 mmol) was then added drop wise to the reaction mixture. After 3 h, the mixture was extracted with CH_2Cl_2 (3 X 5 mL), the extracts were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with EtOAc/pet ether (50:50) to afford **101** as a white solid.

Yield **:** 0.31g, (82 %)

TLC **:** Silica gel; petroleum ether/ethyl acetate (7:3); R_f= 0.4

$[\alpha]_D^{25}$ **:** + 33.4 (*c* 1.23, $CHCl_3$).

M. P. (^{0}C) **:**103-104

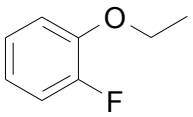
^{1}H-NMR **: δ** 1.41 (s, 9H), 3.2-4.13 (m, 8H), 4.74-4.78 (d, *J*= 7.3 Hz, 1H), **(200 MHz, $CDCl_3$)** 7.20-7.35 (m, 5H).

^{13}C-NMR **: δ** 28.2, 40.9, 47.4, 64.0, 73.2, 79.8, 125.9, 126.5, 127.2, 128.0, **(50 MHz, $CDCl_3$)** 128.3, 136.7, 154.9.

LC-MS : 294.16 (M+H)**,** 288.05, 234.09, 185.15.

Elemental Analysis **: $C_{16}H_{23}NO_4$** Calcd. C, 65.51; H, 7.90; N, 4.77.
Found C, 65.38; H, 7.76; N, 4.68.

1-ethoxy-2-flourobenzene (103)



A mixture of 2-fluorophenol (1g, 8.9 mmol), bromoethane (1.45g, 13.39 mmol) and K_2CO_3 (2.64 g, 17.85 mmol) in dry acetone (20 mL) was stirred under argon at 55 ^{0}C overnight (20 h).

After reaction was over (progress of reaction was monitored by TLC), the reaction mixture was filtered through a Buckner funnel and the solvent from the filtrate was evaporated under reduced pressure. This furnished 1-ethoxy-2-fluorobenzene as a colorless liquid in excellent isolated yield.

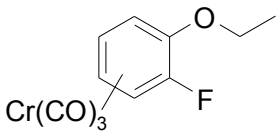
Yield **:** 1.2g, (96%)

TLC **:** Silica gel; petroleum ether/ethyl acetate (9:1); R_f= 0.6

^{1}H-NMR **: δ** 1.23-1.3 (t, 3H), 3.85-3.95 (q, 2H), 6.69-6.95 (m, 4H).
(200 MHz, $CDCl_3$)

^{13}C-NMR **: δ** 15.0, 64.9, 116, 116.3, 122.4, 125.0, 146.0, 153.0.
(50 MHz, $CDCl_3$)

(1-Ethoxy-2-fluorobenzene) tricarbonylchromium (104)



A mixture of 1-ethoxy-2-fluorobenzene **103** (1g, 7.14 mmol) and chromium hexacarbonyl (1.95g, 10.71 mmol) in di-*n*-butyl ether (25 mL) and THF (5 mL) was refluxed for 60 h under nitrogen in the dark.

After completion of the reaction, solvent was evaporated under reduced pressure, the crude product was purified by flash column chromatography on silica gel with EtOAc/hexane

Yield **:** 0.935g, (45%).

M. P. (^{0}C) **:** 78-79

TLC **:** Silica gel; petroleum ether/ethyl acetate (8.5/1.5); R_f= 0.5

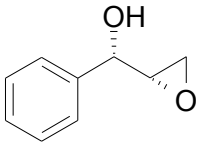
^{1}H-NMR **: δ** 1.48-1.51 (t, 3H), 3.95-4.15 (m, 2H), 5.02-5.63 (m, 5H).

(200 MHz, $CDCl_3$)

^{13}C-NMR **: δ** 15, 65.9, 79, 85.5, 90, 130, 146, 230.

(50 MHz, $CDCl_3$)

(*S*)-((*S*)-oxiran-2-yl)(phenyl) methanol (94a)



To a mixture of bromo diol (1g, 4.3 mmol) in dry THF (5 mL) at 0 ^{0}C was added powdered NaOH (0.347g, 8.6 mmol) in one portion and continued the stirring at 0 ^{0}C for overnight (12 h).

After completion of the reaction (progress of reaction was monitored by TLC), solvent was evaporated under reduced pressure. Residue was diluted with water (5 mL), extracted with ethyl acetate (2 X 5 mL). Organic layer was washed with water, brine, dried over $MgSO_4$, solvent was evaporated under reduced pressure to give crude epoxide, which was further purified by column chromatography using EtOAc /pet ether.

Yield **:** 0.639g, (98%)

TLC **:** Silica gel; petroleum ether/ethyl acetate (7:3); R_f= 0.5

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 700, 833, 926, 1044, 1093, 1215, 1454, 1495, 3019, 3451.

^{1}H-NMR **:** δ 2.74-2.82 (m, 2H), 2.95 (brs, 1H), 3.14-3.20 (m, 1H), 3.38-3.44

(200 MHz, $CDCl_3$) (m, 1H), 4.38-4.41 (d, *J*= 5.6 Hz, 1H), 7.3-7.37 (m, 5H).

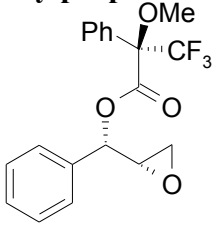
^{13}C-NMR **:** δ 45.3, 55.9, 74.4, 126.2, 126.6, 126.7, 128.1, 128.3, 128.5, 140.0.

(50 MHz, $CDCl_3$)

Elemental Analysis **: $C_9H_{10}O_2$** Calcd. C, 71.98; H, 6.71.

Found C, 71.72; H, 6.60.

(2R)-(S)-((S)-oxiran-2-yl)(phenyl)methyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (94b)



To a solution of (S)-((S)-oxiran-2-yl) (phenyl) methanol (50mg, 0.33 mmol) and catalytic amount of dimethylaminopyridine (2mg,

10 mol%) in CH_2Cl_2 (2 mL) at 0 ^{0}C under argon atmosphere, triethyl amine (67mg, 0.66 mmol) was added dropwise.

The reaction mixture was stirred for 30 min. and (*R*)-(-)-α-methoxy-α-trifluoro methylphenyl acetyl chloride (0.057 mL, 0.33 mmol) in CH_2Cl_2 (2 mL) was added drop-wise, stirred at 0 ^{0}C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give Mosher's ester of (S)-((S)-oxiran-2-yl) (phenyl) methanol.

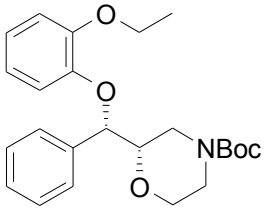
Yield **:** 0.639g, (98%)

TLC **:** Silica gel; petroleum ether/ethyl acetate (7:3); R_f= 0.5

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 700, 833, 926, 1044, 1093, 1215, 1454, 1495, 3019, 3451.

^{1}H-NMR (200 MHz, $CDCl_3$) **:** δ 2.81-2.85 (m, 1H), 2.90-2.94 (m, 1H), 3.37-3.44 (m, 1H), 3.68 (s, 3H), 5.63-5.67 (d, *J*= 7.5 Hz, 1H), 7.29-7.52 (m, 10H).

(*S*)-*tert*-butyl-2-((*S*)-(2-ethoxyphenoxy)-(phenyl)methyl)morpholine-4-carboxylate (105)



To a suspension of NaH (60% oil dispersion, 59mg, 1.46 mmol, washed once with hexane) in DMF (1 mL) was added drop wise **101** (0.287g, 9.79 mmol) in DMF (3 mL) at room temperature under nitrogen atmosphere.

After 1 h tricarbonylchromium complex **104** (0.405g, 1.46 mmol) in DMF (3 mL) was added to the mixture. The mixture was stirred for 2 h at room temperature and then cooled to 0 ^{0}C before addition of a solution of molecular Iodine (I_2) (1.49g, 5.87 mmol) in THF (5 mL) over 30 min. The whole mixture was stirred for 30 min at room temperature, and then $Na_2S_2O_3$ solution (20 mL of 10% (w/v)) was added. The mixture was extracted with ethyl acetate (3 X 5 mL), the organic extracts were combined and washed with water (2 X 5 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with EtOAc/pet ether (15:85)

Yield **:** 0.639g, (95%).

TLC : Silica gel; petroleum ether/ethyl acetate (8:2); R_f=0.6

$[\alpha]_D^{25}$: + 50.8 (*c* 1.01, $CHCl_3$).

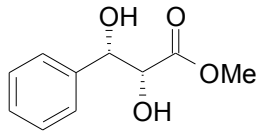
IR ($CHCl_3$, cm^{-1}) : υ_{max} 1122, 1148, 1254, 1499, 1693, 1760, 2952, 2977.

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.40 (s, 12H), 2.81-3 (m, 2H), 3.56-3.62 (m, 1H), 3.7-3.92 (m, 3H), 3.95-4.11 (m, 3H), 5. 21 (d, *J*= 4.0 Hz, 1H), 6.69-6.92 (m, 4H) 7.25-7.47 (m, 5H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 14.6, 28.6, 42.5, 45.3, 64.3, 65.5, 81.9, 114.7, 115.8, 116.1, 120.8, 124.2, 146.7, 150.2, 155.0.

Elemental Analysis : **$C_{24}H_{31}N_5O_2$** Calcd. C, 69.71; H, 7.56; N, 3.39.
Found C, 69.59; H, 7.18; N, 3.16.

(2*R*, 3*S*)-methyl 2,3-dihydroxy-3-phenylpropanoate (97)



A 100 ml round-bottomed flask was charged with $(DHQ)_2PHAL$ (0.120g, 0.5 mol%), *trans*-cinnamyl methyl ester (5g, 3 mmol), NMO (7.71 mL, 60% w/v in water), and *t*-BuOH (15.42 mL). OsO_4 (0.156 mL, 0.2 mol%) was added to the above mixture under stirring. The reaction mixture was stirred at room temperature until the completion of the reaction (24 h, progress of reaction was monitored by TLC) and then poured into a solution of sodium sulfite (6.66g) in water (22.2 mL). The mixture was stirred at room temperature for 2 h. The organic phase was separated and evaporated. The residue was dissolved in ethyl acetate (75 mL). The aqueous phase was extracted with ethyl acetate (2 X 25 mL). The organic phases were combined and washed with 5% aqueous HCl (3 X 10 mL) and dried over $MgSO_4$. Solvent was evaporated under reduced pressure. The crude diol was further purified by recrystallization from toluene as colorless needles in 83% isolated yield with 99% ee.

Yield : 5g, (83%).

TLC : Silica gel; petroleum ether: EtOAc, 8:2); R_f = 0.6

MP (^{0}C) : 86-87

$[\alpha]_D^{25}$: + 3.46 (*c* 1.14, EtOH).

IR($CHCl_3$,cm^{-1}) : υ_{max} 930, 1049, 1110, 1215, 1270, 1439, 1739, 3019, 3468.

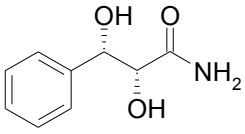
^{1}H NMR : **δ** 2.69 (brs, 2H), 3.74 (s, 3H), 4.30-4.31 (d, *J*= 2.9 Hz, 1H)

(200 MHz, $CDCl_3$) 4.94-4.96 (d, *J*= 3.0 Hz, 1H), 7.19-7.33 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$) **: δ** 52.5, 74.3, 74.8, 126.1, 127.8, 128.2, 139.7, 173.

Elemental Analysis **: $C_{10}H_{12}O_4$** Calcd C, 61.22; H, 6.16.
Found C, 61.18; H, 6.02.

(2*R*, 3*S*)-2, 3-dihydroxy-3-phenylpropanamide (96)



To a solution of ester **97** (0.5 g, 2.51 mmol) in methanol (5 mL) was added excess aqueous ammonium hydroxide (6 equiv.) and the mixture was stirred at 40 ^{0}C for 8 h. After the reaction was completed (monitored by TLC) MeOH was evaporated under reduced pressure and dried.

The product was pure enough for characterization and also for processing to the next step.

Yield **:** 0.435g, (94%).

M.P. ^{0}C **:** 135-136

TLC **:** Silica gel; petroleum ether: EtOAc (2:8); R_f =0.3

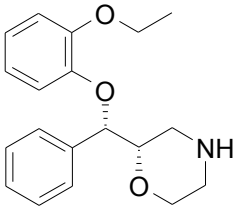
$[\alpha]_D^{25}$ **:** + 63.15 (*c* 0.61, MeOH).

^{1}H NMR (200 MHz, $CDCl_3$+DMSOD_6) **: δ** 3.91-4.0 (dd, *J*= 3.5, 3.9 Hz, 1H), 4.84-4.98 (dd, *J*= 3.5, 2.4 Hz, 1H), 5.31 (brs, 2H), 7.16-7.41(m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$ + DMSOD_6) **: δ** 73.0, 75.2, 126.0, 126.2, 126.5, 127.1, 127.3, 142.5, 174.9.

Elemental Analysis **: $C_9H_{11}NO_3$** Calcd. C, 59.66; H, 6.12; N, 7.73.
Found C, 59.38; H, 6.02; N, 7.58.

(+)-(*2S,3S*)-2-[α-(2-Ethoxyphenoxy)phenyl methyl]morpholine (90)



Trifluoroacetic acid (0.236g {0.74 mL}, 15 equiv) was added drop wise to a solution of **105** (50mg, 0.118 mmol) in dry CH_2Cl_2 (5 mL) at 0 ^{0}C. The reaction mixture was allowed to reach room temperature and stirred further for 1.5 h.

After reaction was over reaction mixture was cooled at 0 ^{0}C, then solution of 1M NaOH (5 mL) was added slowly at 0 ^{0}C and the mixture was extracted with EtOAc/MeOH (95:5) (3

X 5 mL). The extracts were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with MeOH/$CHCl_3$ (10:90)

Yield	**:** 0.034 g (92%)
TLC	**:** Silica gel; $CHCl_3$/MeOH (9:1); R_f=0.6
$[\alpha]_D^{25}$	**:** + 12.81 (*c* 1.03, MeOH).
IR ($CHCl_3$, cm^{-1})	**:** υ_{max} 997, 1040, 1150, 1260, 1468, 1500, 1605, 2100, 2920, 3100.
^{1}H-NMR	**:** δ 1.41-1.48 (t, 3H), 2.80-2.89 (m, 4H), 3.68-3.74 (m, 1H),
(200 MHz, $CDCl_3$)	4.01-4.13 (m, 4H), 5.17-5.20 (d, *J*= 5.5 Hz, 1H), 6.90-7.05 (m, 4H), 7.35-7.42 (m, 5H).
^{13}C-NMR	**:** δ 14.6, 45.3, 46.7, 64.6, 67.2, 84.1, 115.1, 118.6, 123, 128.5,
(50 MHz, $CDCl_3$)	130.7, 139, 146.7, 150.2.
LC-MS	: 314.17 (M+H), 308.05, 284.05, 192.08.
Elemental Analysis	**: $C_{19}H_{23}NO_3$** Calcd. C, 72.82; H, 7.40; N, 4.47. Found C, 72.62; H, 7.12; N, 4.18.

3.2.7 Spectra

[1] ^{1}H NMR and ^{13}C NMR Spectra of **94**

[2] ^{1}H NMR and ^{13}C NMR Spectra of **93**

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

[4] ^{1}H NMR and ^{13}C NMR Spectra of **99**

[5] ^{1}H NMR and ^{13}C NMR Spectra of **100**

[6] ^{1}H NMR Spectra of **94a**

[7] ^{1}H NMR Spectra of **94b**

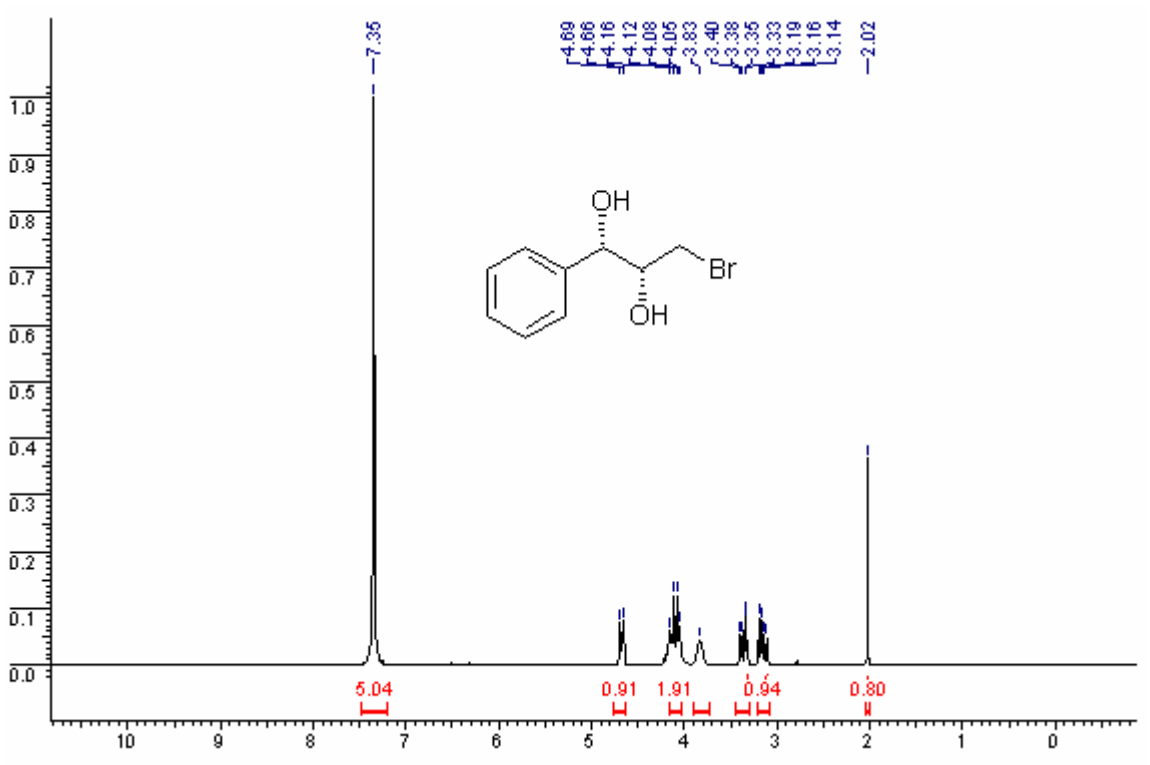
[8] ^{1}H NMR and ^{13}C NMR Spectra of **97**

[9] ^{1}H NMR and ^{13}C NMR Spectra of **96**

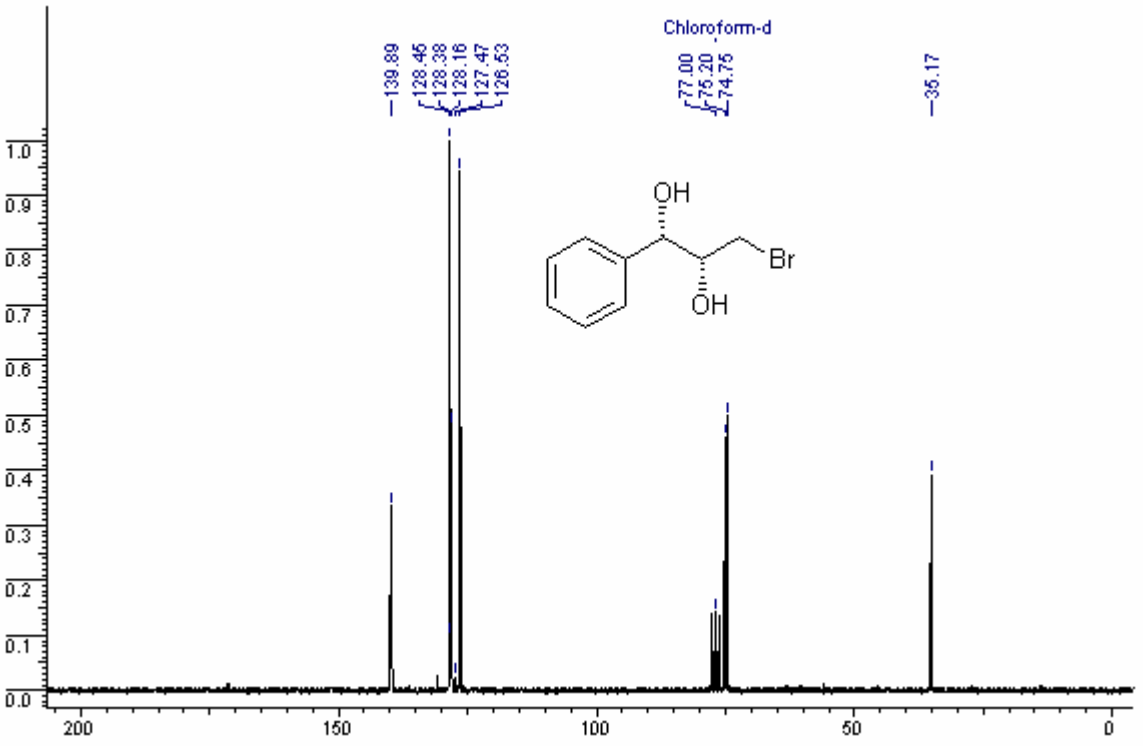
[10] ^{1}H NMR and ^{13}C NMR Spectra of **101**

[11] ^{1}H NMR and ^{13}C NMR Spectra of **90 [(*S, S*)-Reboxetine]**

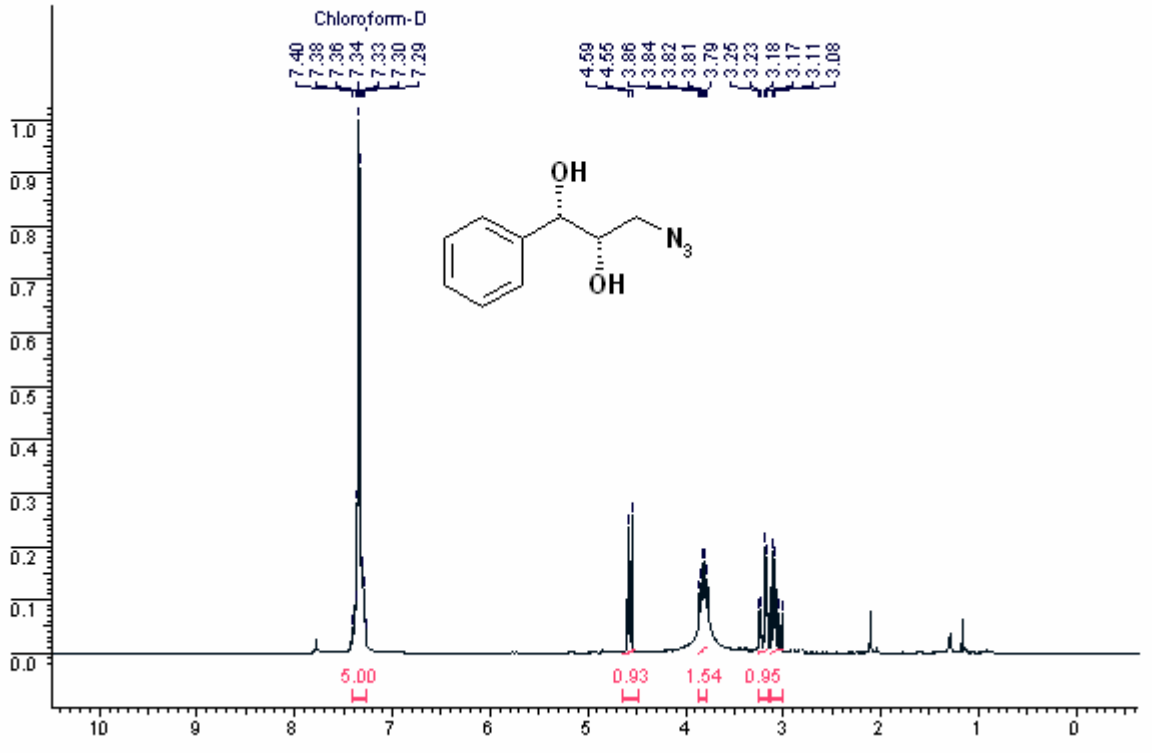
[1] ^{1}H NMR spectra of 94



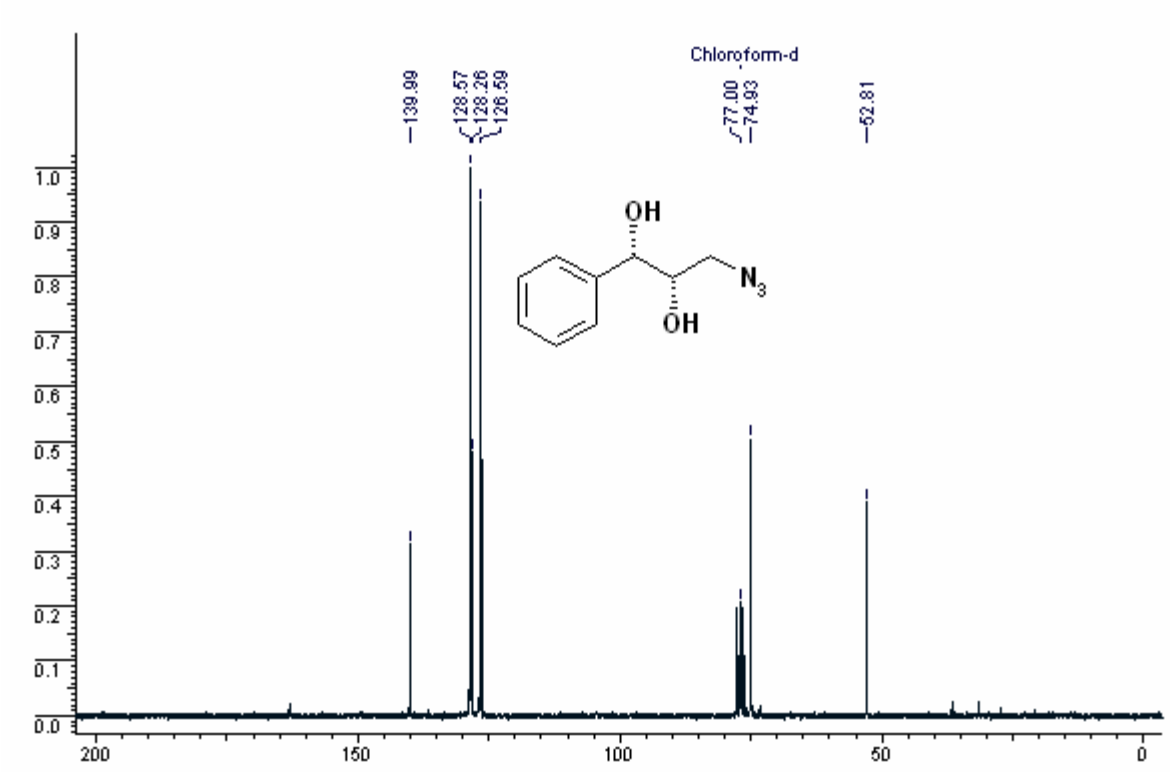
[1] ^{13}C NMR spectra of 94



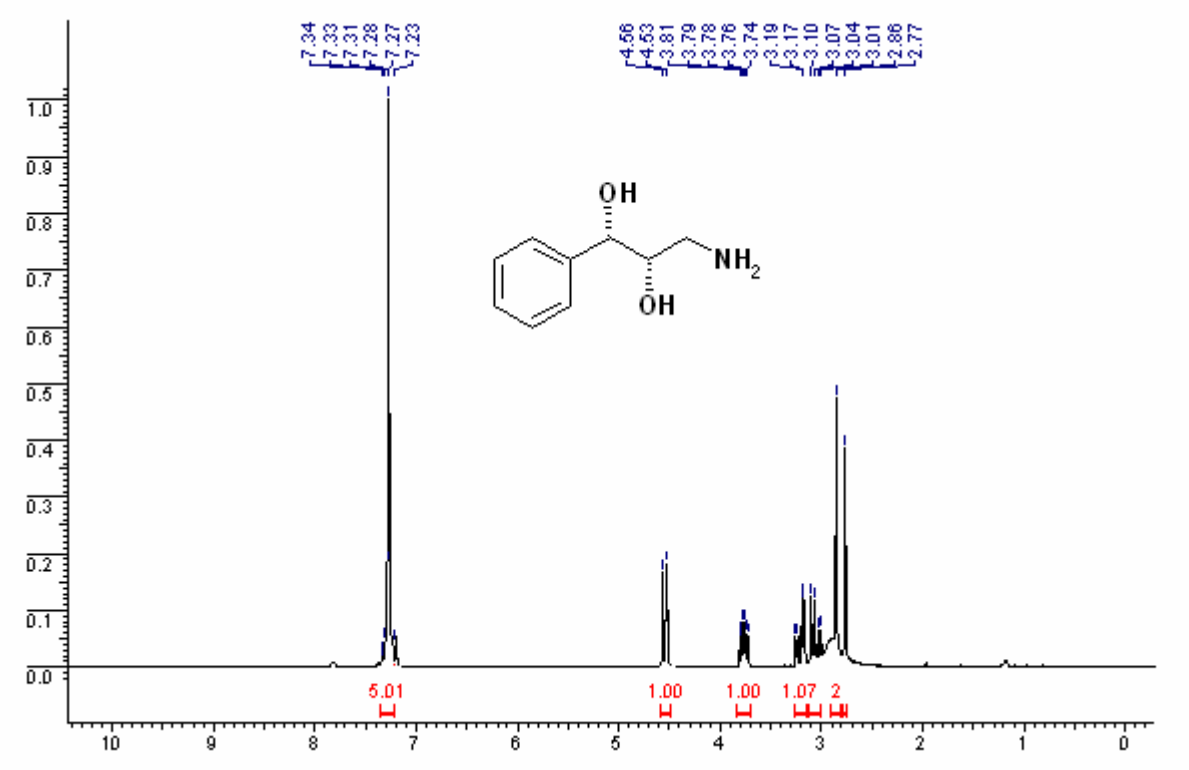
[2] ^{1}H NMR spectra of 93



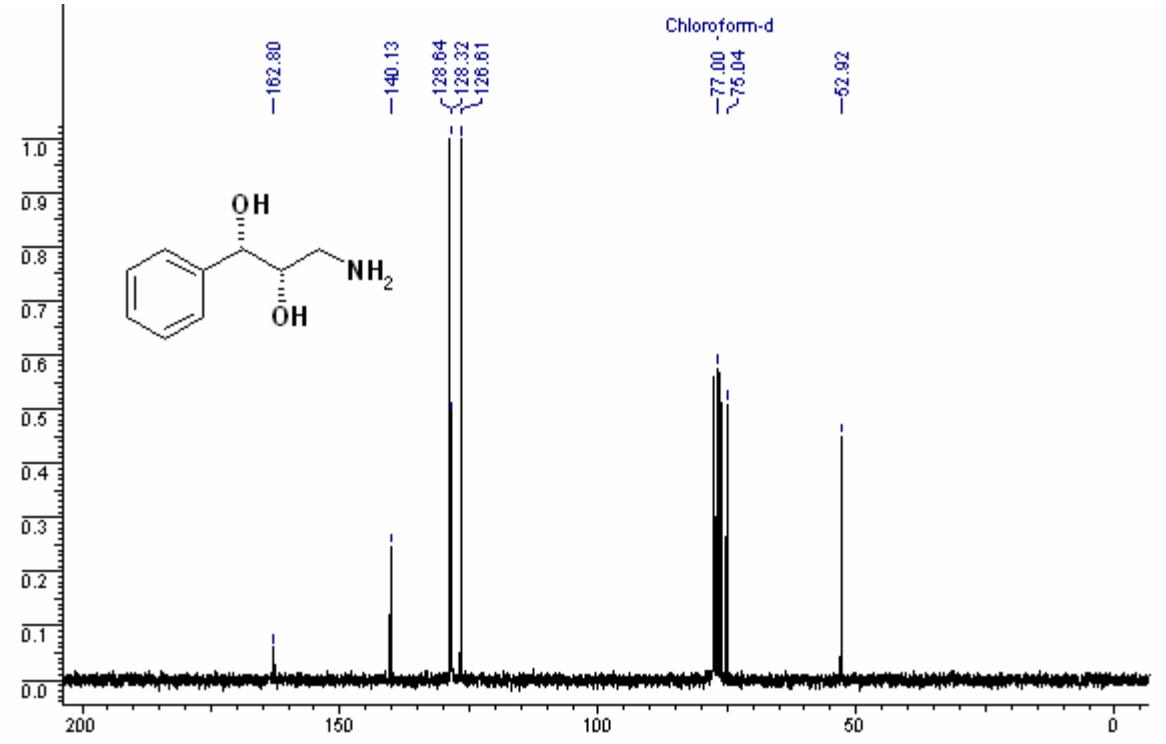
[2] ^{13}C NMR spectra of 93



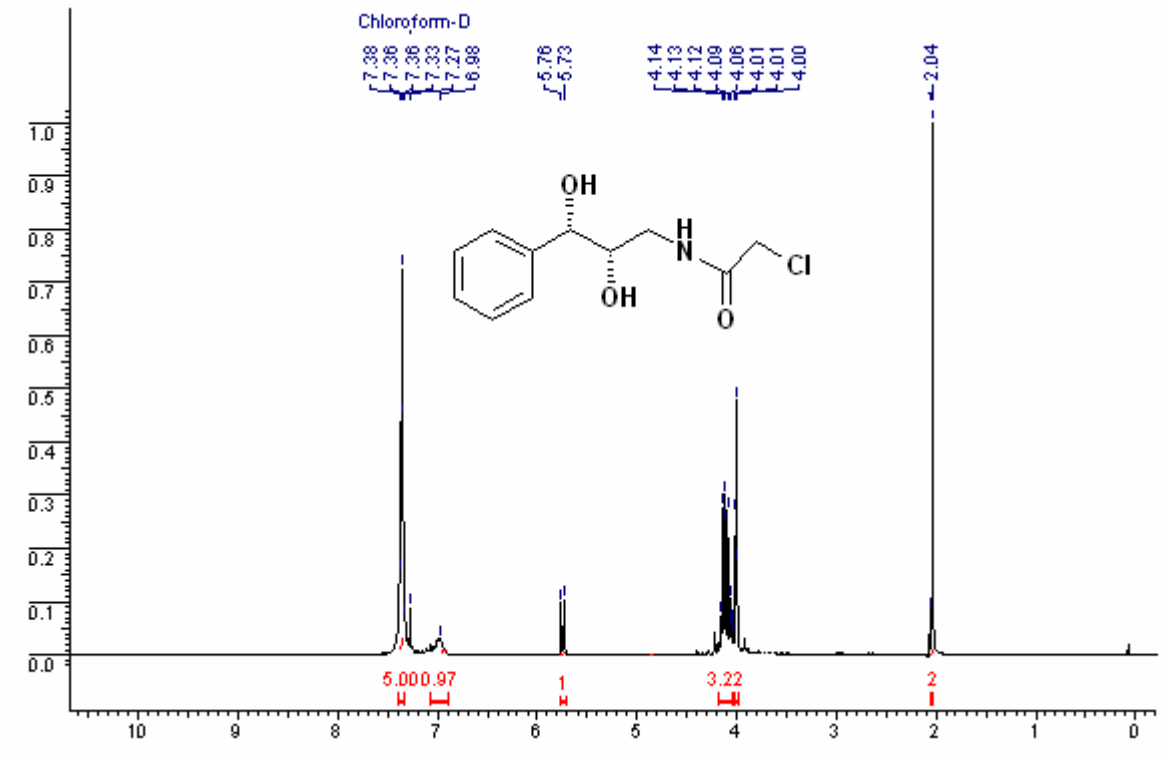
[3] ^{1}H NMR spectra of 92



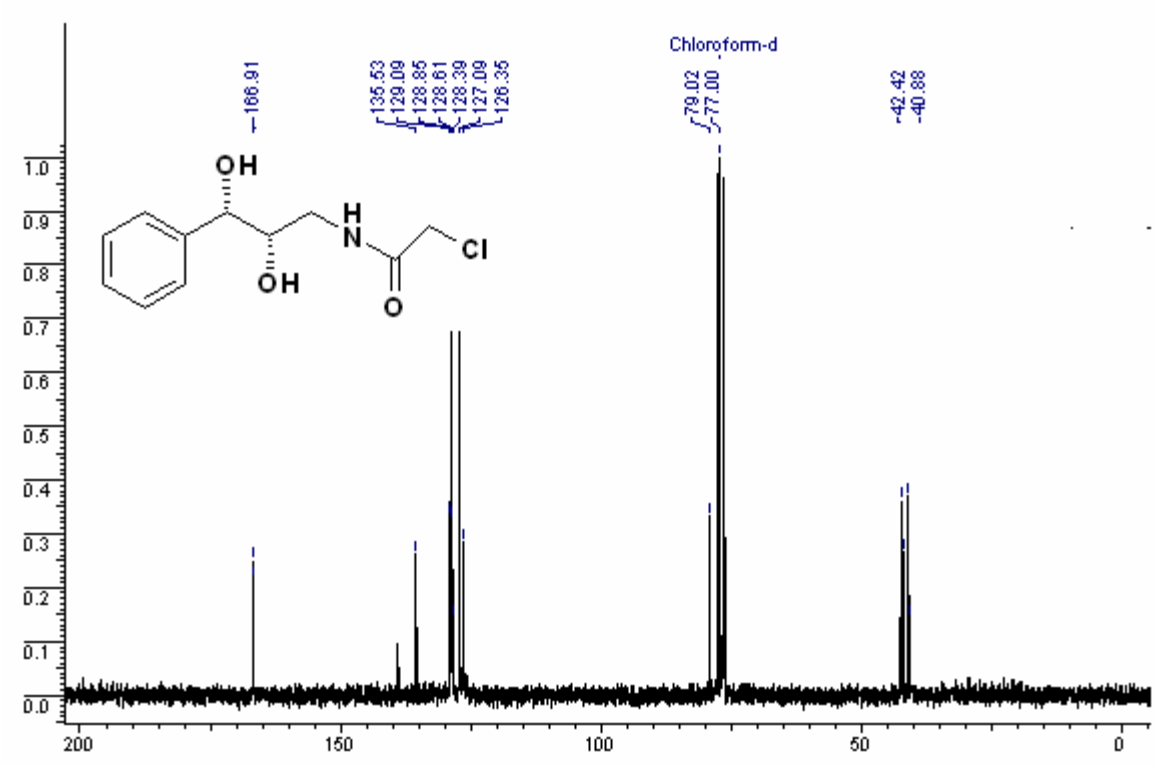
[3] ^{13}C NMR spectra of 92



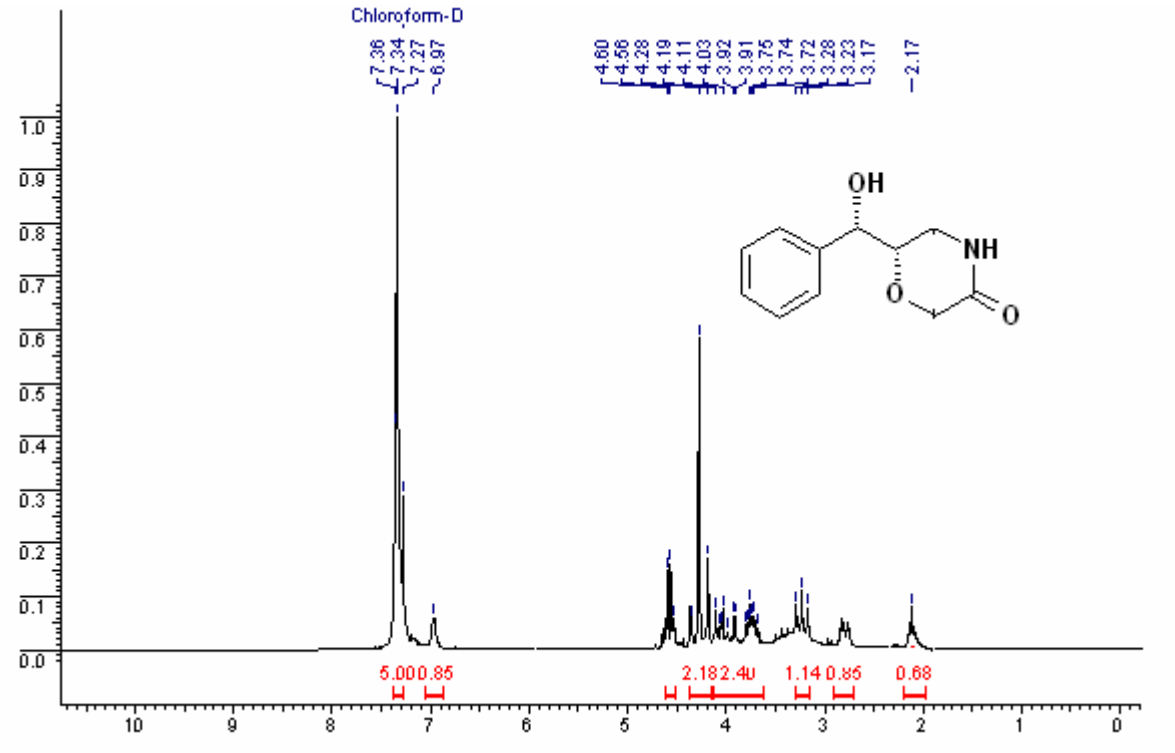
[4] ^{1}H NMR spectra of 99



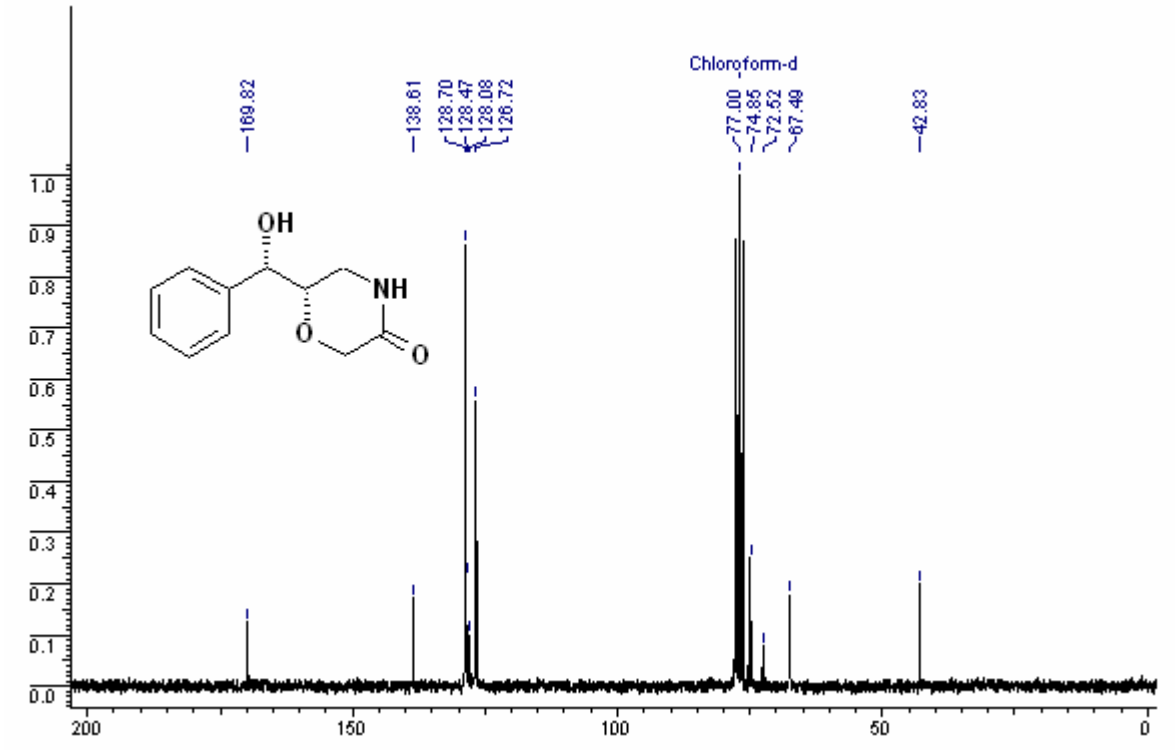
[4] ^{13}C NMR spectra of 99



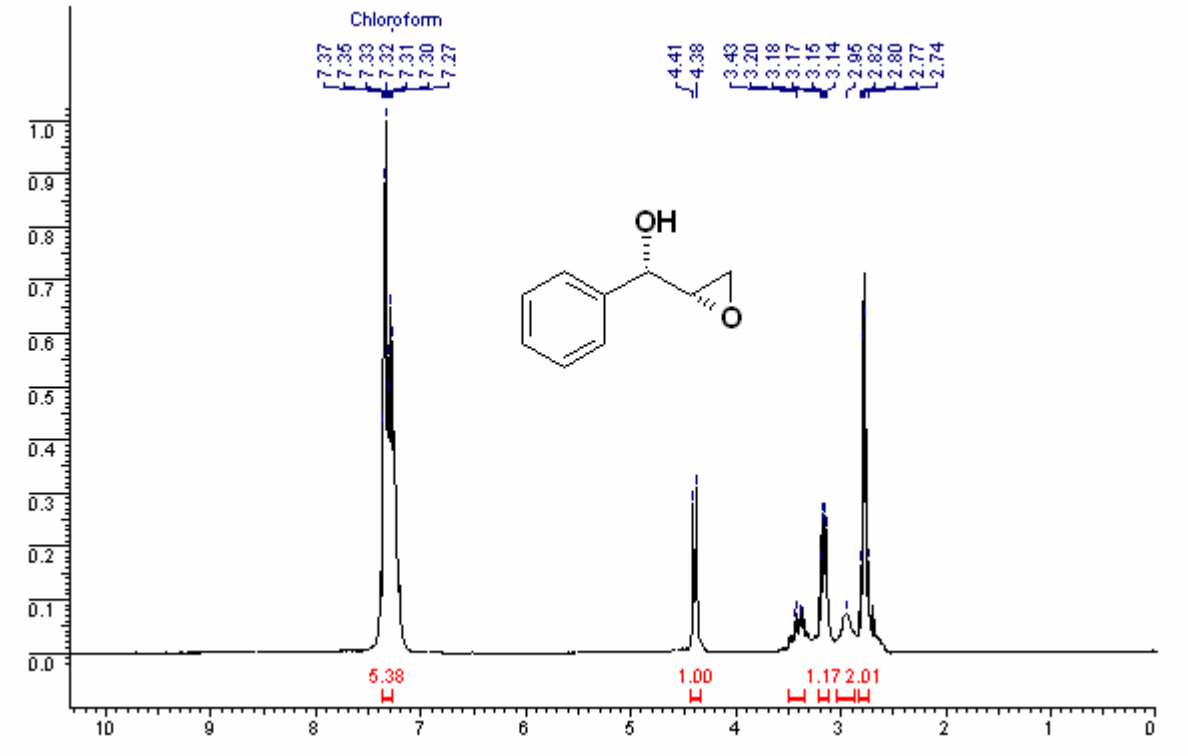
[5] ^{1}H NMR spectra of 100



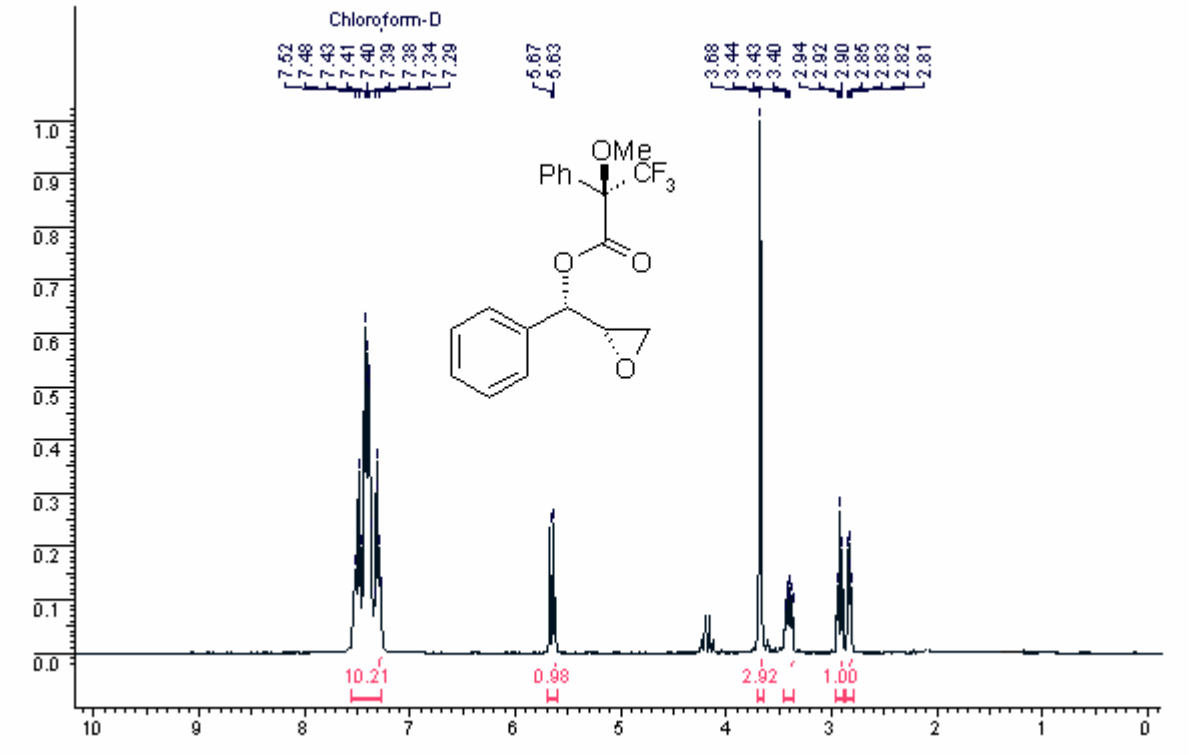
[5] ^{13}C NMR spectra of 100



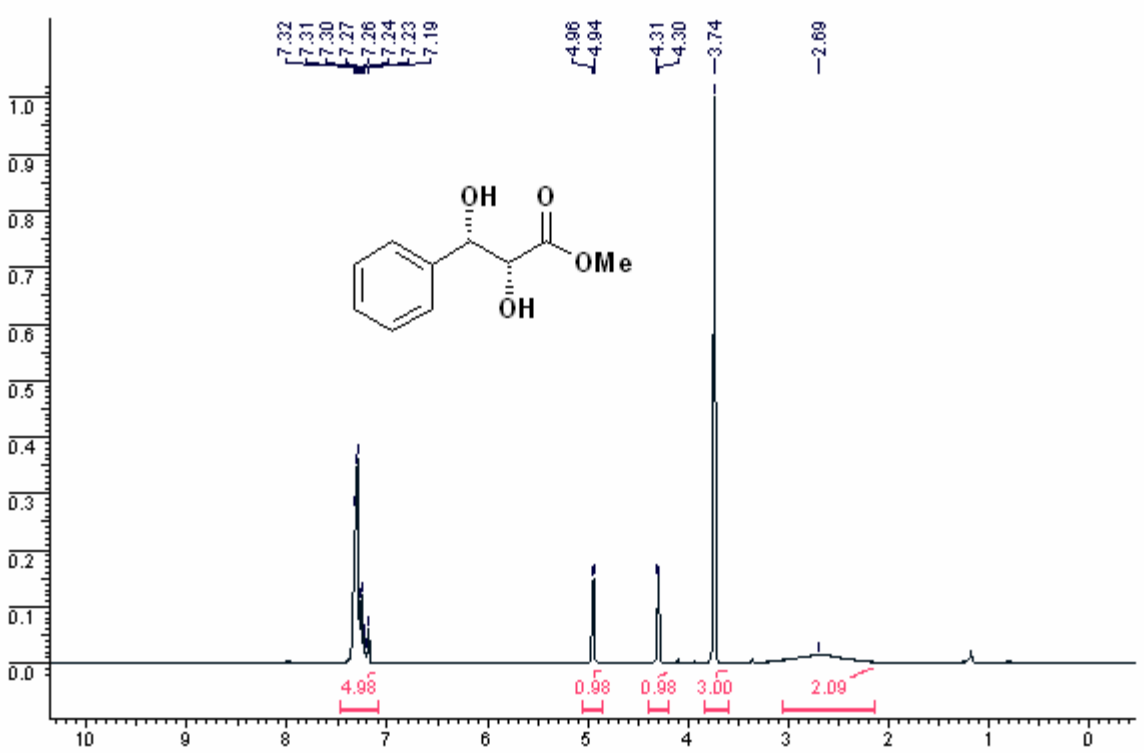
[6] ^{1}H NMR spectra of 94a



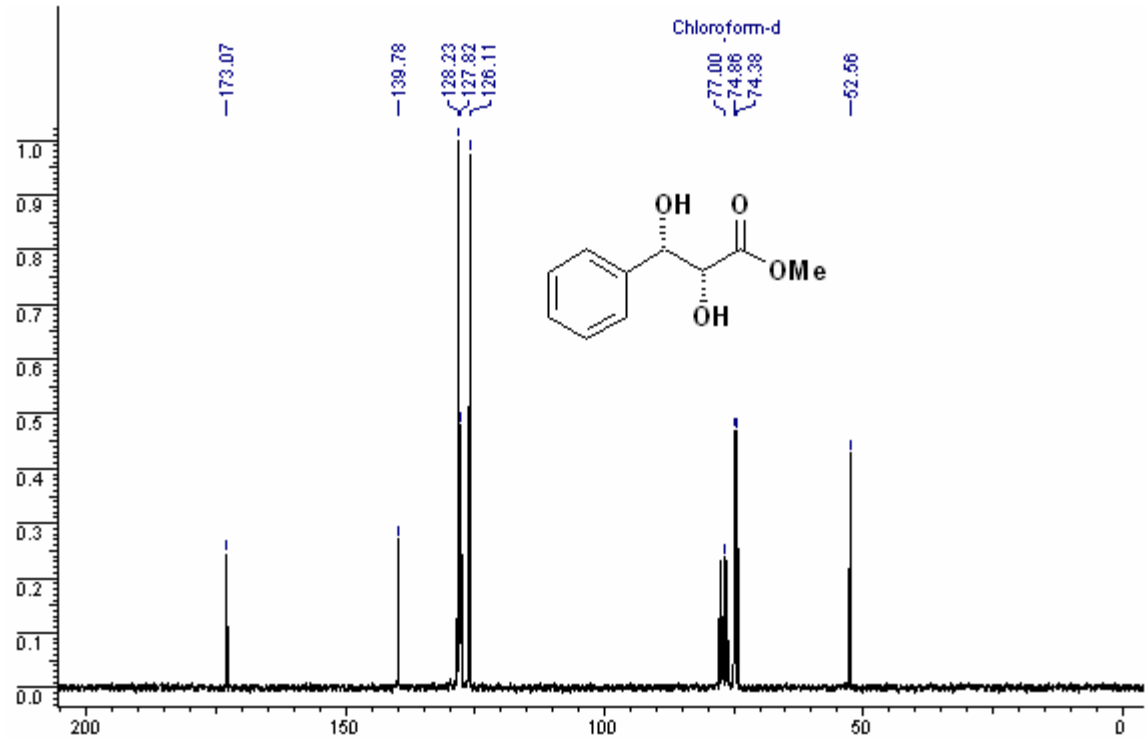
[7] ^{1}H NMR spectra of 94b



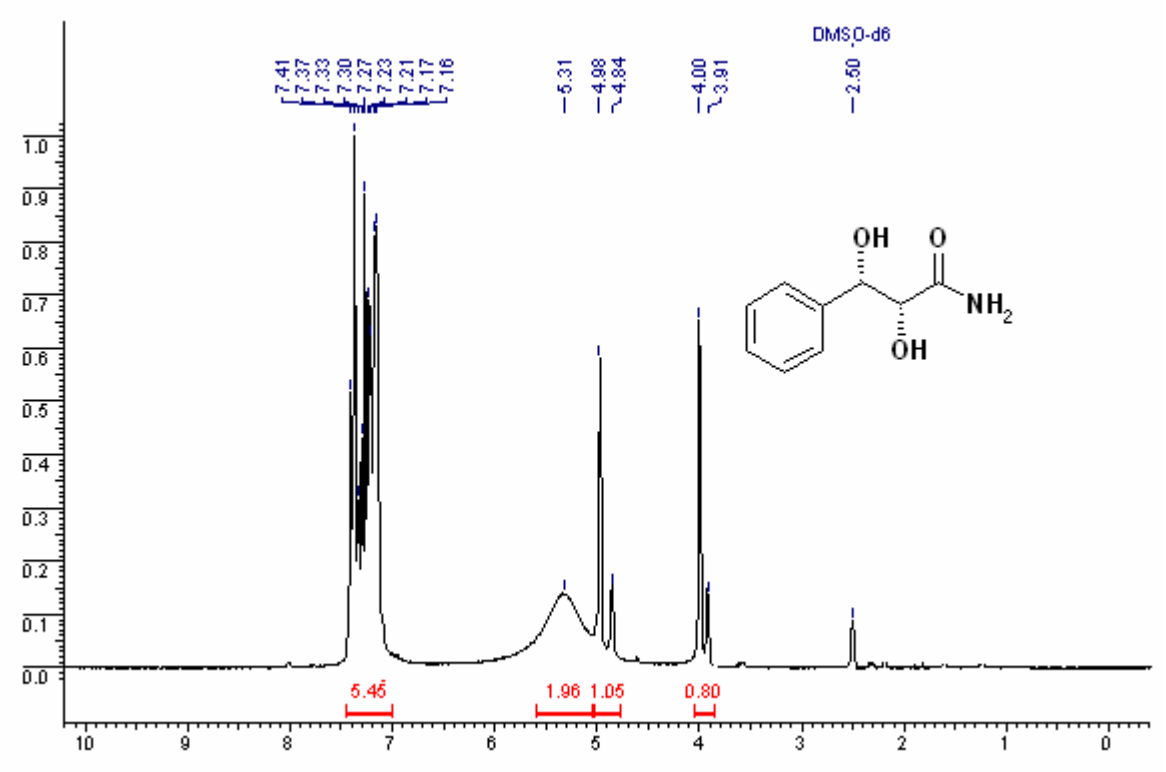
[8] ^{1}H NMR spectra of 97



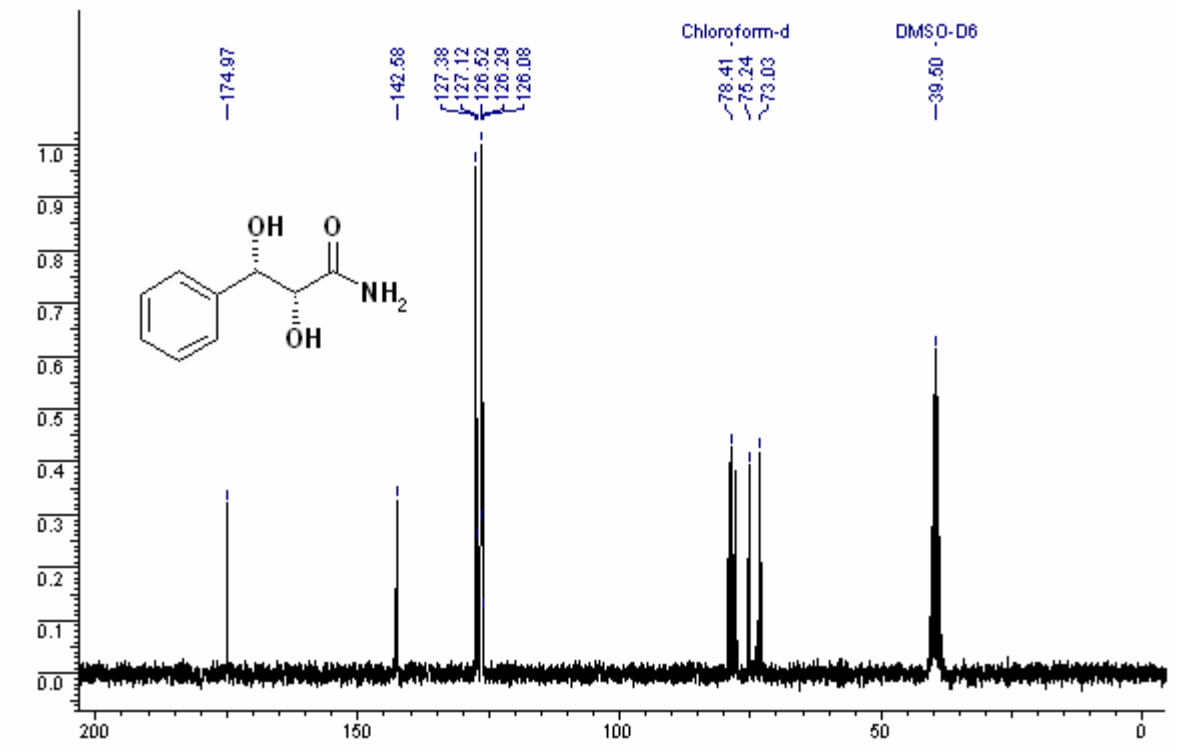
[8] ^{13}C NMR spectra of 97



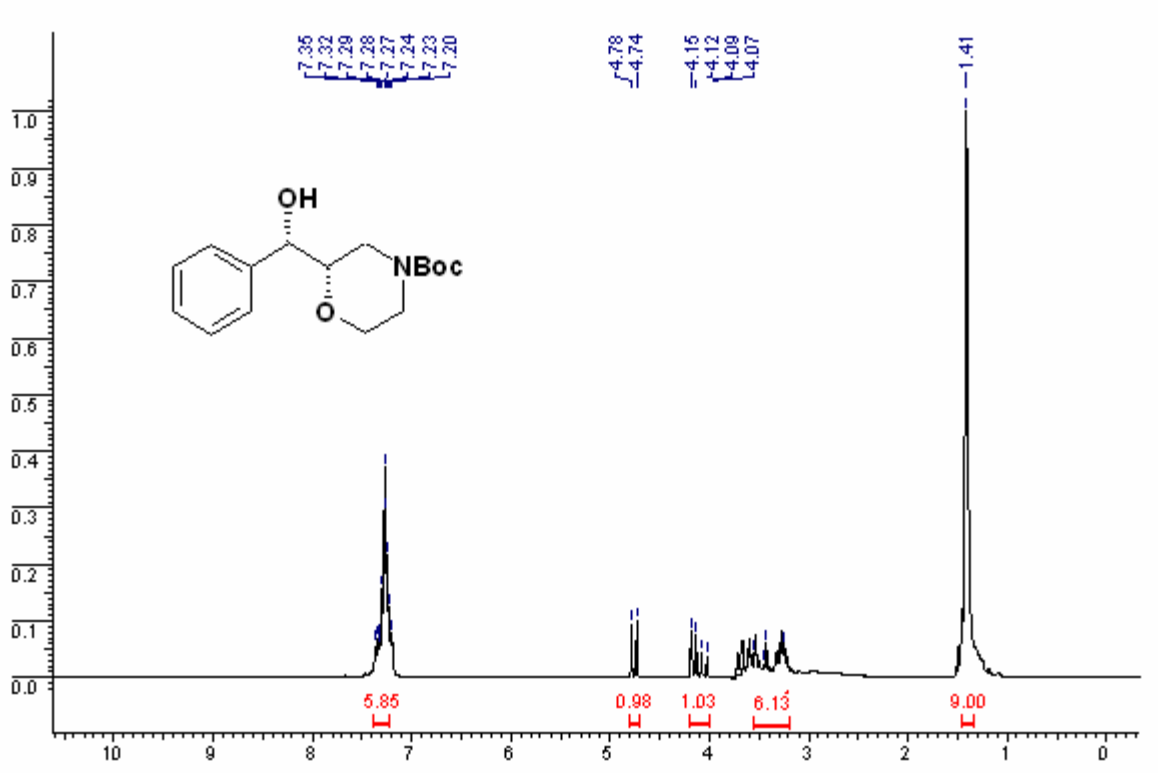
[9] ^{1}H NMR spectra of 96



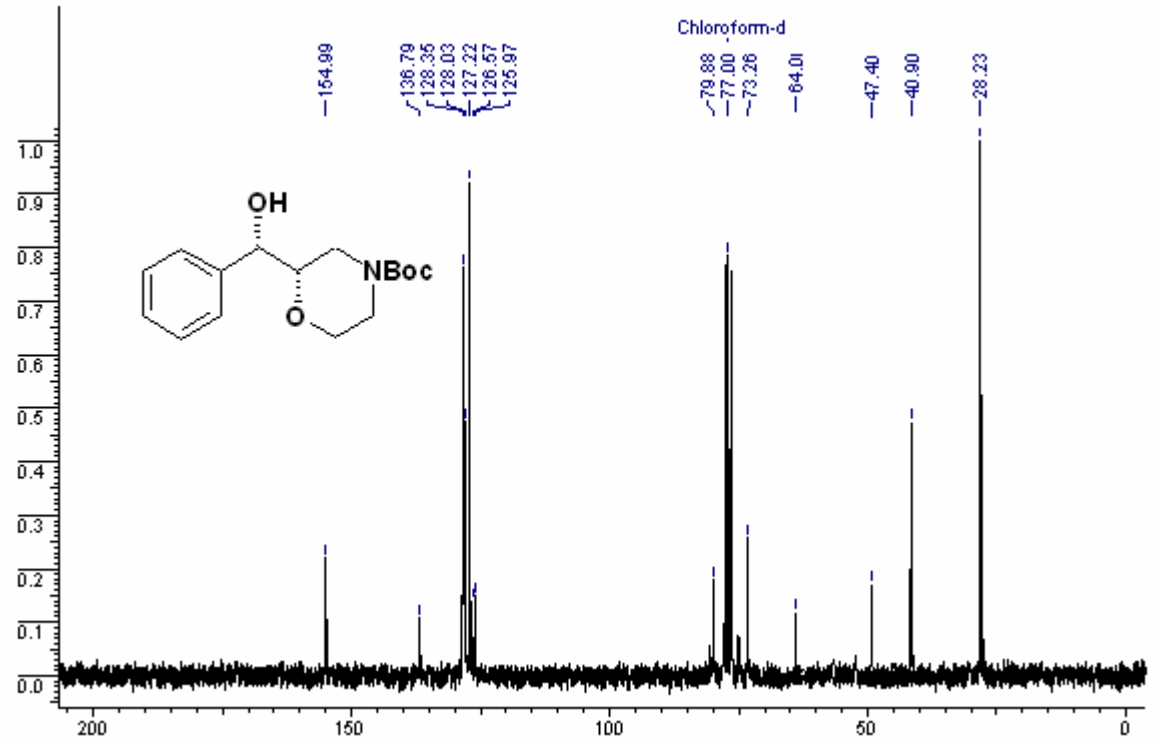
[9] ^{13}C NMR spectra of 96



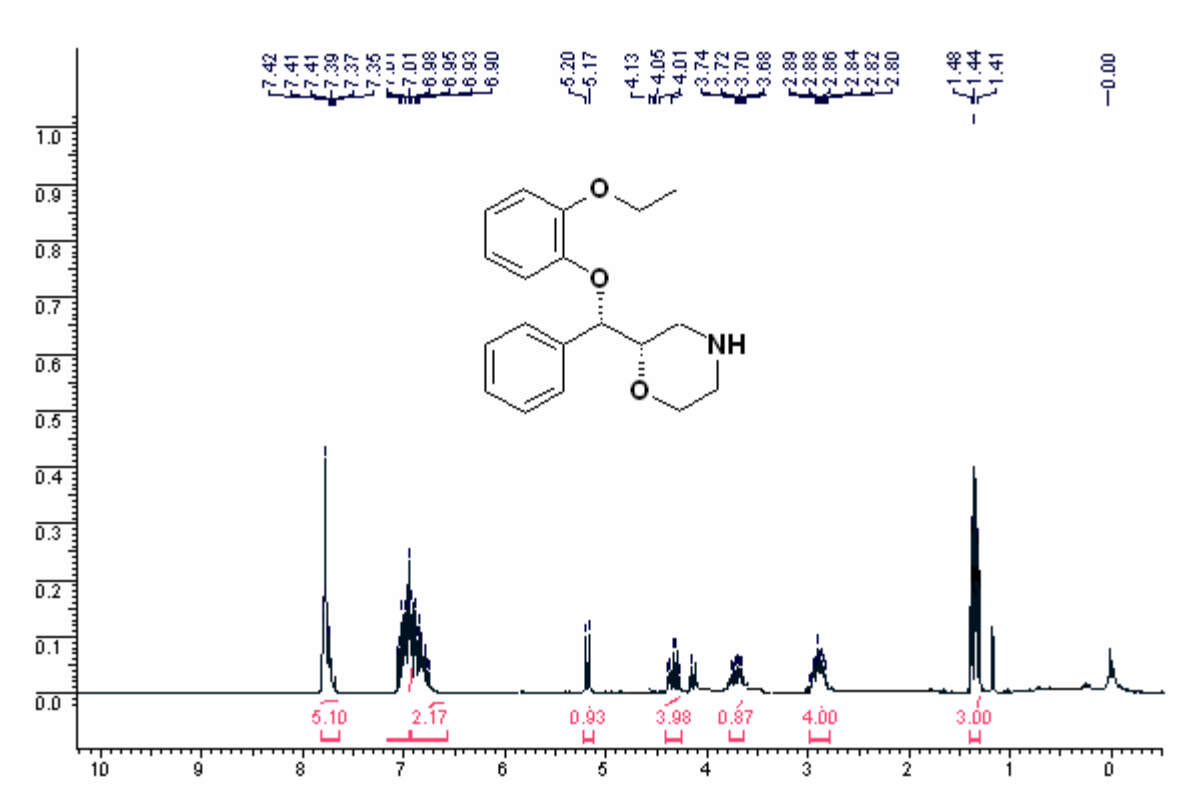
[10] ^{1}H NMR spectra of 101



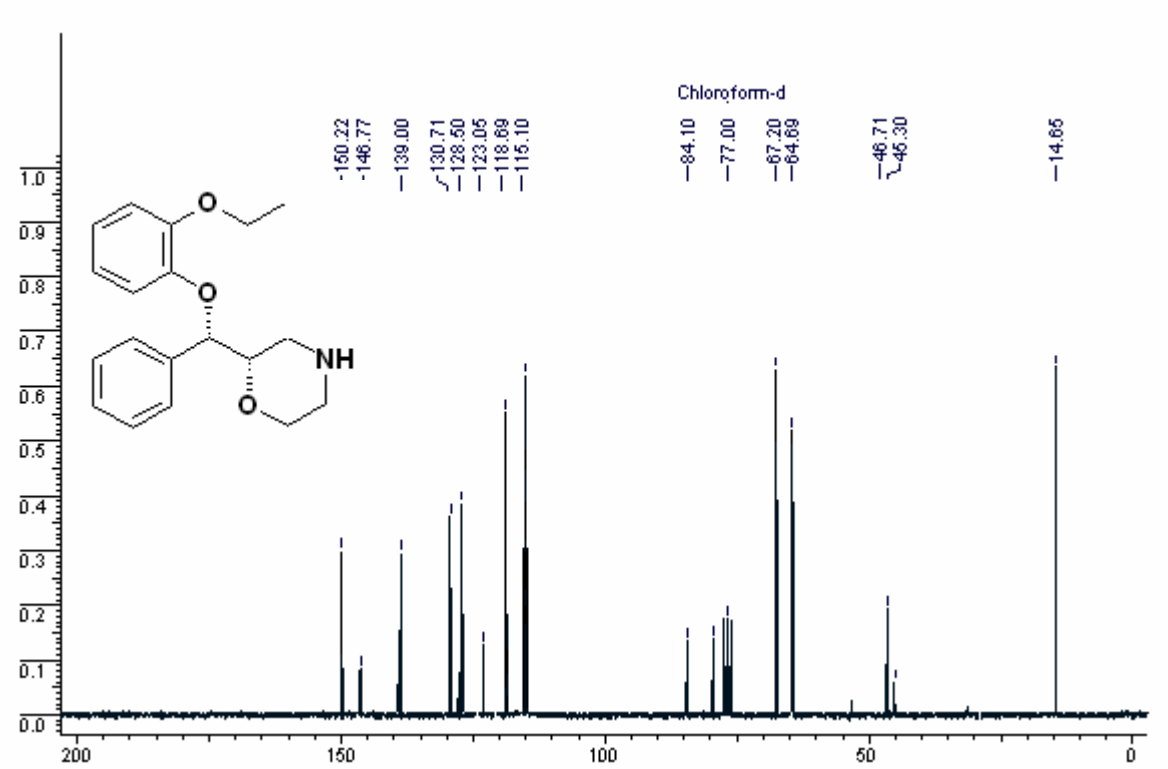
[10] ^{13}C NMR spectra of 101



[11] ^{1}H NMR Spectra of 90 [(*S, S*)-Reboxetine]



[11] ^{13}C NMR Spectra of 90 [(*S, S*)-Reboxetine]



3.2.8 References

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SECTION-C

Enantioselective synthesis of

(S) - Dapoxetine

3.3.1 Introduction

Depression is a common psychiatric disorder and one of the most frequent illnesses in the world-affecting people of all gender, ages and backgrounds. Depression has major effects on economic productivity, individual well being and social functioning, around the globe. It is a huge burden on individuals, families, and society.[1]

Nearly 121 million people worldwide suffer from depression. Depressive disorders are the 4th leading cause, worldwide, of life years lost due to disability (behind infectious diseases, heart disease and respiratory infections, and before HIV/AIDS), depressive disorders are expected to rank 2nd in global diseases by 2020 (after heart disease) and depression is the mental disorder most commonly leading to suicide.[2]

There are two main types of depression:

[A] Clinical depression (or major depression) and

[B] Bipolar disorder (also called manic depression).

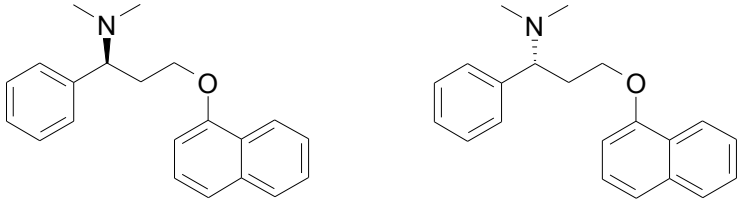
Both illnesses have mild, moderate and severe forms depending on the number and intensity of the symptoms. During a major depression, a person's general outlook on life can shift dramatically. Bipolar disorder is a less common form of depression. This illness involves cycles of depression alternating with a "high" known as mania.

Antidepressant medications are widely used effective treatments for depression. Existing antidepressant drugs are known to influence the functioning of certain neurotransmitters (chemicals used by brain cells to communicate), primarily serotonin, norepinephrine, and dopamine, known as monoamines. Older medications - tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) - affect the activity of both of these neurotransmitters simultaneously. Their disadvantage is that they can be difficult to tolerate due to side effects or, in the case of MAOIs, dietary and medication restrictions play an important part. Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs), have fewer side effects than the older drugs, making it easier for patients to adhere to treatment. Both generations of medications are effective in relieving depression, although some people will respond to one type of drug, but not another. Medications that take entirely different approaches to treating depression are now in development.

More than 80% of people with depression improve when they receive appropriate treatment with medication, psychotherapy, or the combination. Depression is the leading cause of psychiatric disability claims, generating up to $20 billion a year in direct costs.

Premature ejaculation is thought to be the most common male sexual dysfunction, with a prevalence of 21–33%.[3] It can be a source of distress for many men, although some are less affected or cope more effectively with the condition.[4-5] In men who are affected by this problem, premature ejaculation can adversely affect self-image, interfere with sexual satisfaction and the sexual relationship and negatively affect the overall quality of life of men and their partners.[6-7]

The asymmetric synthesis of individual enantiomers is extremely important because the (*S*) and (*R*)-isomers usually display very different pharmacological or physiological properties.[8] For example, the enantiomer (*S*)-(+)-*N,N*-dimethyl-α-[2-(1-naphthalenyloxy) ethyl] benzenemethanamine [(*S*)-dapoxetine] is a potent serotonin re-uptake inhibitor for treating depression and other disorders as bulimia or anxiety.



(*S*)-Dapoxetine **(*R*)-Dapoxetine**

Fig. 10. Structures of (*S*)-Dapoxetine and (*R*)-Dapoxetine

The enantiomer (*S*)-dapoxetine originally known as LY 210448 and credited to biochemist David T. Wong[9] of *Eli Lilly and Company*, is found to be a potent selective serotonin re-uptake inhibitor (SSRIs) but is slightly different from the SSRIs (such as (*S*)-Fluoxetine, (-)Paroxetine and Sertraline (**Fig. 11**)) widely prescribed for depression and other psychiatric disorders as bulimia or anxiety. Dapoxetine is very much structurally related to fluoxetine (Prozac) with antidepressant activity.

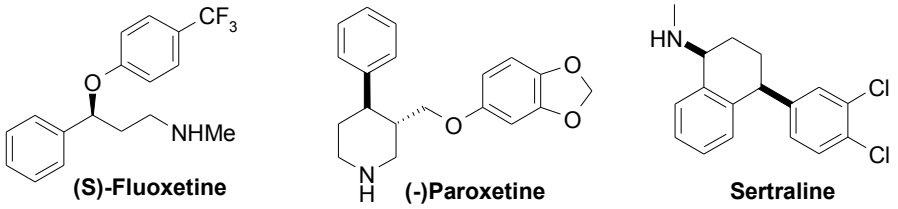


Fig. 11. Structures of (S)-Fluoxetine, (-) Paroxetine and Sertraline

Dapoxetine is the D-enantiomer of LY 243917 and found to be 3.5 times more potent as a serotonin reuptake inhibitor than the L-enantiomer of LY 243917. Dapoxetine would make it join the ranks of sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levittra®), the erectile dysfunction drugs and cabergoline (Dostinex ®) as a drug invented to improve male sexual health.[10]

3.3.2 Dapoxetine and Pharmacology

Delay in ejaculation is one of the side effects of serotonine-specific reuptake inhibitors (SSRIs) and TCAs that make them useful in the treatment of premature ejaculation (PE) with physiological rather than physical etiologies.[11] Although it has been found in the literature that premature ejaculation is more common among men with higher levels of education because of their interest in the sexual satisfaction of their partner.[12]

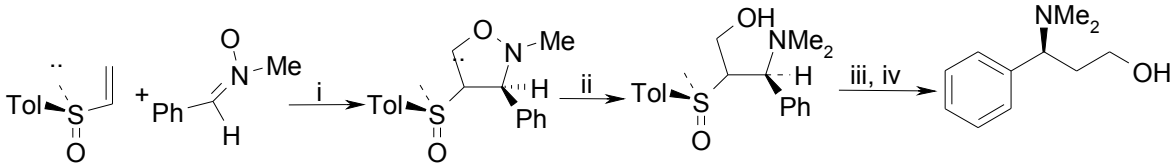
SSRI antidepressants have been shown to delay ejaculation in men treated for different psychiatry disorders. SSRIs are considered the most effective treatment currently available for PE. These include paroxetine, fluoxetine, sertraline and more. The use of these drugs that require chronic therapy is limited by the neuropsychiatric side effects. New SSRI drugs specifically targeted to treat premature ejaculation (e.g. dapoxetine) can be taken on an as needed basis and have recently shown positive results in large phase III studies. Nevertheless dapoxetine is not yet approved by any regulatory authority around the world. There is speculation that some of the associated effects are caused by lowered libido and blood pressure as well as lowered anxiety levels. Other pharmaceutical products known to delay male orgasm are; opioids, cocaine, and diphenhydramine.[13]

3.3.3 Review of literature

Koizumi approach (1982)[14]

Koizumi and co-workers synthesized (*S*)-(3)-*N,N*-dimethyl amino-3-phenylpropan-1-ol **110** foremost intermediate of target molecule (S)-dapoxetine, from (*R*)-(+)-*p*-tolyl vinyl sulfoxide **106** which on reaction with excess of *C*-phenyl-*N*-methylnitrone **107** in refluxing benzene gave 4-(*p*-tolyl sulfinyl)isoxazolidines **108** in 36% and 4% yield. The mixture of **108** was converted to (-)-3-(dimethyl-amino)-3-phenyl-1-propanol **109** by *N*-methylation,

reductive N-O cleavage and desulfuriazation as sequence of reactions. The optical purity of **109** was determined by use of $Eu(hfc)_3$. The absolute configuration of (-)-**109** was determined as *R* by the comparison of the optical rotation with (*S*)-(+)-**109** which was obtained from (-)-β-alanine ethyl ester. Thus the absolute configuration at C-3 in **108** was assigned as the *S* configuration. After the preparation of the crucial intermediate (**110**), the author has not carried out further elaboration of this intermediate to (*S*)-dapoxetine

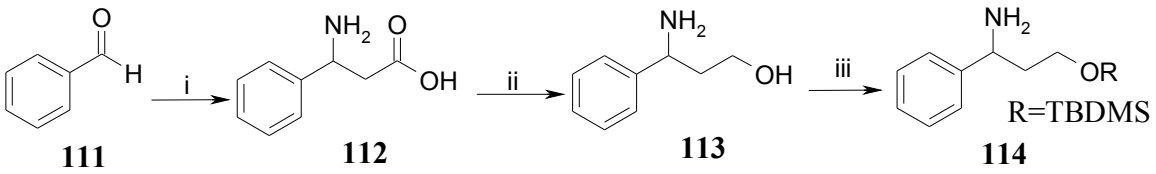


106 **107** **108** **109** **110**

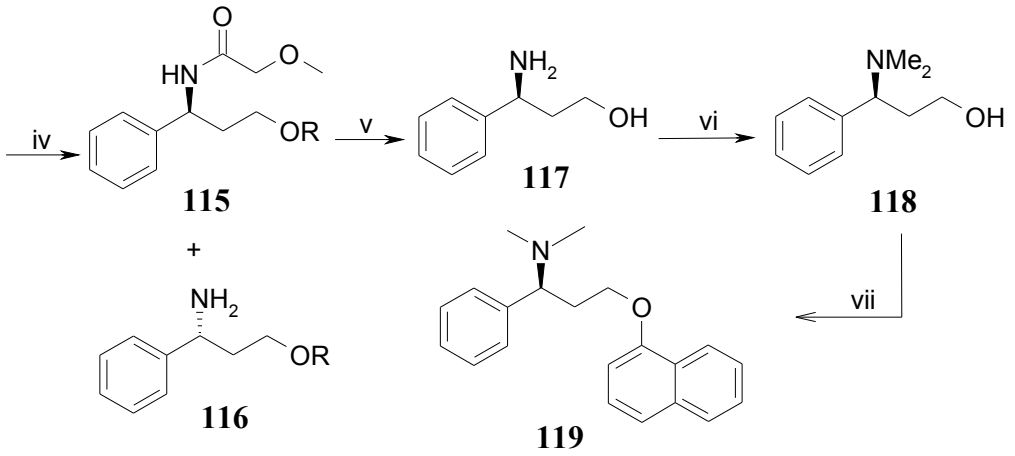
Scheme 36. Reaction conditions: i) benzene, reflux, 20 h, 40%; ii) (a) MeI; (b) Zn-AcOH, rt; iii) $TiCl_4$-AcOH-AcONa, rt; iv) Raney Ni-EtOH, rt.

Gotor approach (2006)[15]

Very recently Gotor and co-workers reported lipase catalyzed resolution of chiral 1, 3-amino alcohols, and its application in the asymmetric synthesis of (*S*)-dapoxetine. Their synthesis was starting from benzaldehyde **111** which on reaction with malonic acid, ammonium acetate in refluxing ethanol after 12 h gave intermediate **112** in 68% yield. The acid group of **112** was reduced by $LiAlH_4$ in THF at 65 ^{0}C in 3 h to give **113** in 77% isolated yield. The alcohol group was protected by *tert*-butyl dimethyl silyl chloride (TBDMSCl) using imidazole in DCM at ambient temperature which gave **114** in 95% yield. The amine **114** on enzymatic resolution using ethyl methoxyacetate as acyl donor, antarctica lipase type A as enzyme in TBME solvent after 47 h at 30 ^{0}C gave **115** in 93% ee and the hydrolyzed intermediate **116**. The intermediate **115** on treatment with 6M HCl at 50 ^{0}C gave **117** in 84% after 23 h, the primary amine of **117** was converted into tertiary amine **118** using formaldehyde and formic acid as hydride source in 83% yield, which on reaction with 1-napthol, triphenyl phosphine, DEAD in THF gave (*S*)-dapoxetine **119** in good yield with 93% ee after 15 h at room temperature.



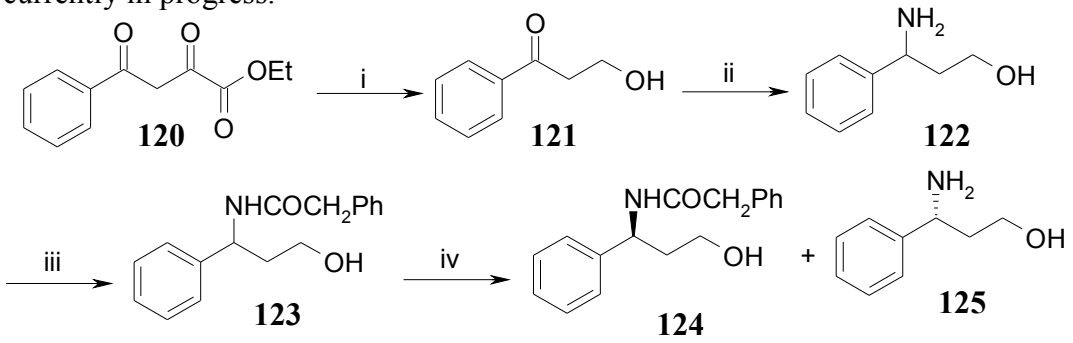
111 **112** **113** **114**



Scheme 37. Reaction conditions: i) $CH_2(COOH)_2$, NH_4OAc, EtOH, 80 ^{0}C,12 h; ii) $LiAlH_4$, THF, 65 ^{0}C, 3 h; iii) TBDMSCl, imidazole, CH_2Cl_2, rt; iv) Acyl donor, enzyme, solvent, 30 ^{0}C, 250 rpm; v) HCl 6M, 50 ^{0}C; vi) $(CH_2O)n$, HCOOH, rt, 83%; vii) PPh_3, DEAD, 1-napthol, THF, rt, 72%.

Fadnavis approach (2006)[16]

Fadnavis *et al.* also reported preparation of enantiomerically pure (*R*) and (*S*)-3-amino-3-phenyl-1-proanol prominent intermediate of the (*S*)-dapoxetine, via resolution with immobilized penicillin G acylase. Ethyl 2, 4-dioxo-4-phenylbutyrate **120** was converted to 3-oxo-3-phenyl-1-propanol **121** in 90% yield by reaction with baker's yeast. Reductive amination with sodium cyanoborohydride in the presence of ammonium acetate gave the racemic 3-amino-3-phenyl-1-propanol **122** in 65% yield. Enzymatic resolution of the corresponding *N*-phenyl acetyl derivative **123** with *penicillin G acylase,* immobilized on an epoxy resin gave (*S*)-amide **124** and (*R*)-amino alcohol **125** in high enantiomeric purity (ee >99%) and >45% yields for each enantiomer. Authors claimed in this publication that conversion of the crucial intermediate amino alcohol (**125**) to Dapoxetine is currently in progress.



Scheme 38. Reaction conditions: i) Bakers yeast, diisopropyl ether, 48 h ii) NH_4OAc, $NaBH_3CN$, EtOH, rt, 36 h, 65%. iii) $PhCH_2COCl$, NaOH, rt, 4 h, 80%. iv) *penicillin G acylase*, 4 h, water.

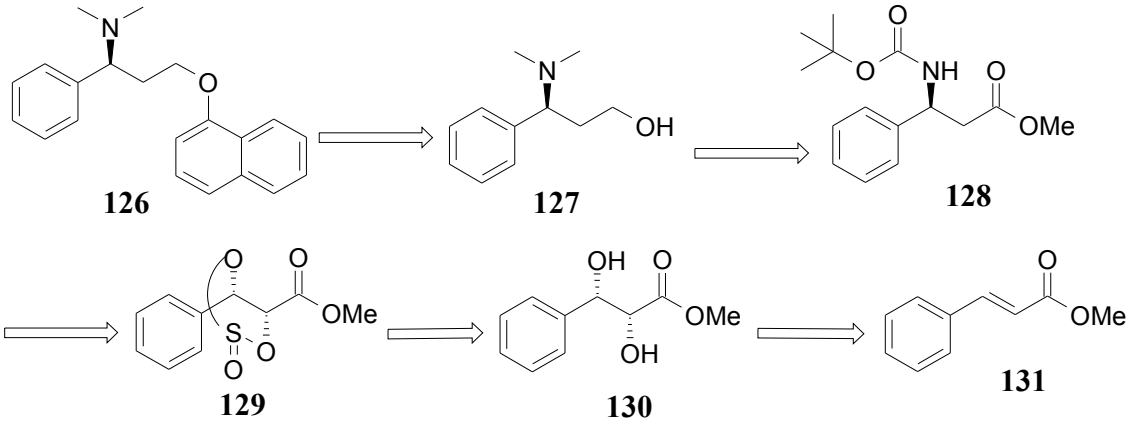
3.3.4 Present work

3.3.4.1 Objectives

To the best of our knowledge, there has been no chemical method reported so far which directly leads to the asymmetric synthesis of (+)-(*S*)-Dapoxetine from a chiral starting material. The literature for both (+) and (-)-Dapoxetine as well as racemic (±)-Dapoxetine through varied synthetic routes, mostly involve costly chiral auxiliaries and resolving agents. Hence, interest in newer synthetic methods with fewer steps, excellent yield and enantioselctivity goes unabated. Moreover asymmetric synthesis of individual enantiomers is extremely important because (*S*) and (*R*)-isomers usually display very different pharmacological or physiological properties.

Keeping important pharmacological properties of (*S*)-Dapoxetine in mind, the Sharpless asymmetric dihydroxylation[17] and subsequent transformation of the diols formed via cyclic sulfite[18] were envisioned as powerful tools offering considerable opportunities for synthetic manipulations to evolve a novel methodology.

3.3.4.2 The retro synthetic strategy for (*S*)-Dapoxetine



Scheme 39. Retro synthetic analysis of (*S*)-Dapoxetine

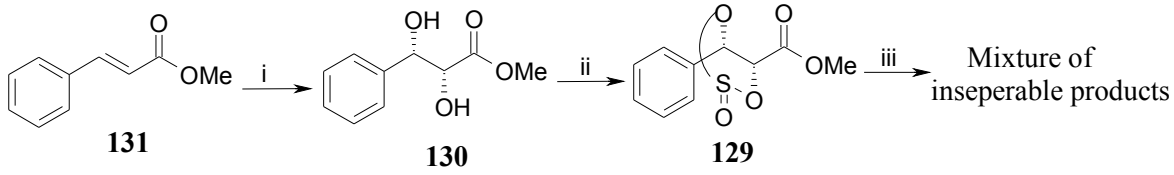
The retro synthesis strategy for (*S*)-Dapoxetine is outlined in Scheme **39**. (*S*)-Dapoxetine **126** can be obtained from *N,N*-dimethyl amino alcohol **127** which can be realized through Boc protected amino ester **128** which in turn could be obtained from cyclic sulfite **129.** The cyclic sulfite **129** could be formed from cinnamyl ester diol **130,**

followed by Sharpless asymmetric dihydroxylation of cinnamyl ester **131** as a source of chirality

3.3.4.3 Results and discussion

As shown in retro synthetic analysis (Scheme 39), the (*S*)-Dapoxetine can be realized from cinnamyl ester by Sharpless asymmetric dihydroxylation[19] and subsequent synthetic manipulations.

Attempt to synthesis of cyclic sulfate from cinnamyl ester 131



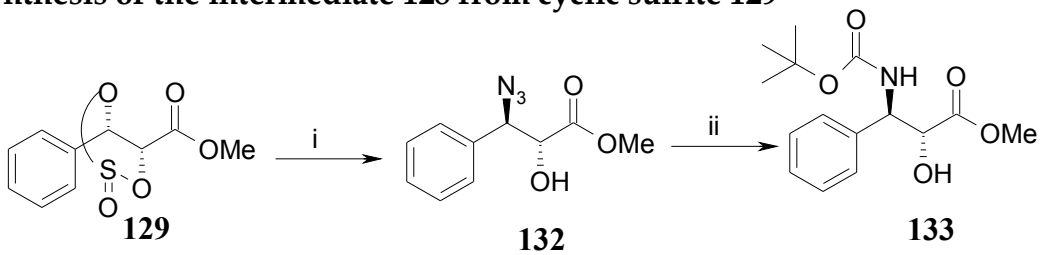
Scheme 40. Reaction conditions: i) $(DHQ)_2PHAL$ (1 mol%), OsO_4 (0.1 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), $MeSO_2NH_2$ (1 equiv.), H_2O:*t*-BuOH (1:1), rt, 24 h, 83%, 96% ee. ii) CH_2Cl_2, Et_3N, $SOCl_2$, 0 ^{0}C to rt, 1 h, 90%; iii) $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN-H_2O, 0 ^{0}C.

*Trans-c*innamyl methyl ester **131** on Sharpless asymmetric dihydroxylation protocol using $(DHQ)_2PHAL$ as a chiral ligand gave "α" diol[20] of cinnamyl ester **131** with $[\alpha]_D^{25}$ + 3.46 (*c* 1.14, EtOH). The IR spectrum of **131** showed absorption at 3468 cm^{-1} corresponding to hydroxyl group, ^{1}H NMR spectrum of **130** showed the peaks in the range δ 4.30-4.96 corresponds to methine protons and absence of olefinic proton signals. ^{13}C NMR spectrum of **130** shows signals at δ 74.38 and 74.86 corresponding to the carbon atoms bearing hydroxyl groups.

The vicinal diol **130** on treatment with $SOCl_2$ in presence of Et_3N in CH_2Cl_2 at 0 ^{0}C yielded the corresponding cyclic sulphite **129** in 88% isolated yield as a distereomeric mixture in a 1:1.4 ratio. The ^{1}H NMR spectrum of **129** showed the presence of a set of four doublets in the region δ 4.64-6.00 corresponding to a mixture of diastereomers (which is in a 1:1.4 ratio). The IR spectrum of **129** further showed the absence of hydroxyl absorption. As our target was to convert cyclic sulfite to cyclic sulfate and chopping of cyclic sulfate by hydride will gave hydroxyl group at C-*2* of aromatic ring, so that cyclic sulfite **129** was further subjected to oxidation with catalytic amount of $RuCl_3.3H_2O$ employing $NaIO_4$ as stoichiometric oxidant in acetonitrile-water system at 0 ^{0}C, but all attempts to isolate the

corresponding cyclic sulfate failed. Since the cyclic sulfates of cinnamate derivatives are extremely unstable, we obtained a mixture of inseparable products.

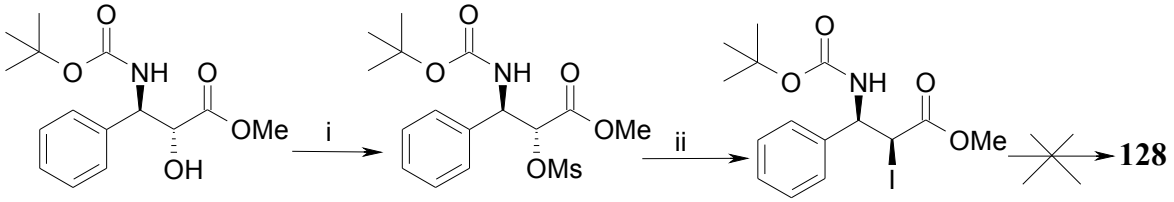
Synthesis of the intermediate 128 from cyclic sulfite 129



129 **132** **133**

Scheme 41. Reaction conditions: i) NaN_3, DMF, rt, 78%; ii) H_2/Pd-C, EtOAC, rt, $(Boc)_2O$, Et_3N; 80%;

As we failed to get the cyclic sulfate after several attempts, we changed our strategy and followed a new synthetic strategy as shown in Scheme 41. This was based on the presumption that the nucleophilic opening of cyclic sulfite **129** would occur in a regiospecific manner at the α-carbon atom. Indeed, the cyclic sulfite reacted with NaN_3 in DMF at higher temperature (80 ^{0}C), with apparent complete selectivity for attack at *C-2* to furnish azido alcohol **132** in 85% yield.[20] The aromatic ring must be responsible for the increased reactivity of the α-position and also destabilizes the transition state for *C-3* substitution. The formation of azido alcohol **132**, was confirmed by its IR spectrum showing strong absorption at 2106 and 3480 cm^{-1} which can be assigned to N_3 and OH groups respectively. ^{1}H NMR spectrum of **132** showed the appearance of doublets at δ 4.55 and 4.90 due to *C-2* carbon bearing OH and *C-3* carbon bearing N_3 functionalities respectively and disappearance of the diastereotopic peaks of cyclic sulfite in the region of δ 4.64-6.00. The azido alcohol on catalytic reduction by Pd/C (10%) followed by in situ protection by $(Boc)_2O$ in ethyl acetate and Et_3N affords **133**. The IR spectrum of **133** gave amine absorption at 3290 cm^{-1} and for the amide carbonyl at 1662 cm^{-1}. The ^{1}H NMR spectrum of **133** showed singlet peak of nine protons at δ 1.48 for *tert*-butyl group. The ^{13}C NMR spectrum of **133** showed peak at δ 154.99 corresponding to the carbonyl carbon of *tert*-butyl group.

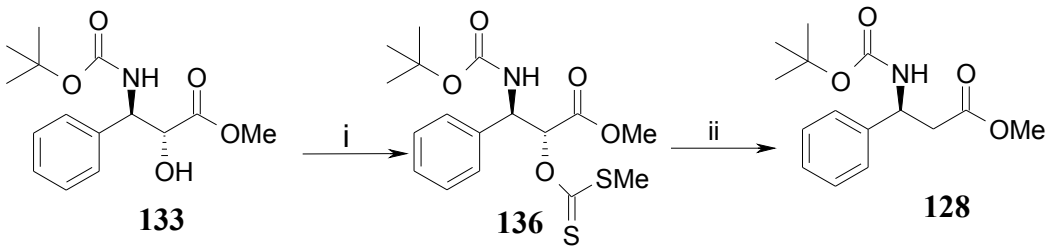


133 **134** **135**

Scheme 42. Reaction conditions: i) $MeSO_2Cl$, Et_3N, DCM, 0 ^{0}C to rt, 12 h, 85%; ii) NaI, acetone, reflux, 80%, 12 h.

Another challenge was the deoxygenation of secondary alcohol. First we converted secondary alcohol to good leaving group by reaction of alcohol with methanesulfonyl chloride using Et_3N to give **134** in 85% yield which on treatment with NaI in refluxing acetone gave intermediate **135**. The ^{1}H NMR spectrum of this intermediate showed the disappearance of methyl group of mesyl. However, the intermediate **135** on reaction with various hydride sources failed to gave the expected **128**.

This failure forced us to look through the literature for a good method. Finally we adopted the more conventional method of deoxygeation i. e. Barton-Mc-Combie deoxygenation protocol[21] (Scheme 43).

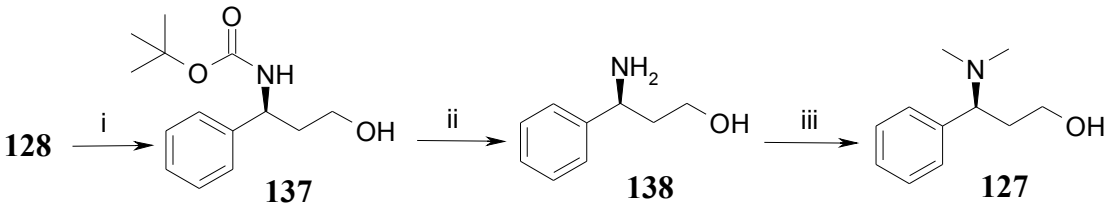


133 **136** **128**

Scheme 43. Reaction conditions: i) MeI, CS_2, Et_3N, CH_2Cl_2, 0 ^{0}C to rt, 12 h; ii) *n*-$(Bu)_3SnH$, AIBN, toluene, reflux.

Alcohol of **133** on treatment with CS_2, MeI in presence of Et_3N in DCM gave **136** in 82% isolated yield. The IR spectrum of **136** showed disappearance of hydroxyl group. ^{1}H NMR spectrum of **136** showed singlet for three protons at δ 2.46 for *S*-methyl, other peaks go to downfield region at 5.37 (doublet, one proton), 6.12-6.14 (doublet, one proton) corresponds to O-C-S-SMe. The intermediate **136** on reaction with hydride source (tri-*n*-butyl tinhydride) using catalytic amount of AIBN(as radical initiator) and imidazole in refluxing toluene under inert atmosphere gave **128** in 80% yield. The ^{1}H NMR spectrum of **128** displayed at δ 2.85 (doublet, two proton) for the methylene group, ^{13}C NMR spectrum of **128** showed signal at δ 40.7 for the methylene group which was conformed by DEPT.

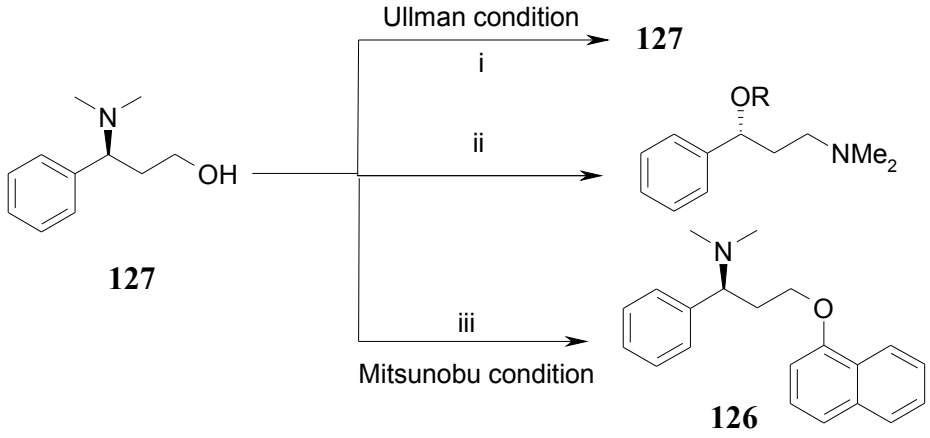
Enantioselctive synthesis of (*S*)-Dapoxetine from intermediate 128



Scheme 44. Reaction conditions**:** i) $LiAlH_4$, THF, rt, 12 h; ii) TFA, DCM, rt; iii) HCHO, HCOOH.

The ester group of **128** was reduced by LAH in THF to afford **137** in 81% yield. The IR spectrum of **137** showed absorption at 3410 cm^{-1} corresponding to primary alcohol. The ^1H NMR spectrum of **137** indicates absence of singlet at δ 3.61 for methoxy group. ^{13}C NMR of **137** also indicates absence of peak at δ 171.3 for carbonyl carbon of ester. The Boc group of **137** was deprotected by TFA in DCM at room temperature to give **138** in 85% yield as a hygroscopic product. The spectral data of **138** are in accordance with the literature data. The ^1H NMR spectrum of **138** showed absence of peaks at δ 1.44 for *tert*-butyl group.

The primary amine **138** was alkylated by using Clarke-Eschweiler protocol using formaldehyde and excess of formic acid as reducing reagent at reflux temperature followed by acidic workup and basic treatment gave **137** in 85% yield.[22] The ^1H NMR spectrum of **137** showed singlet of six protons corresponds to methyl group at δ 2.15. ^{13}C NMR spectrum of **137** showed signal at δ 32 for methyl group. This method is by far the best method for the conversion of a primary amine to a tertiary amine available in literature with excellent selectivity and yield (Scheme 45).



Scheme 45. Reaction conditions: i) CuCl, pyridine, 1-napthol; ii) a) Et_3N, MsCl, rt, 3 h; b) K_2CO_3, 1-napthol, reflux, 65 h. iii) Ph_3P, DEAD, 1-napthol, THF, rt, 72%;

The final reaction in the sequence was the coupling between the alcohol hydroxyl of **127** and 1-napthol for which we tried Ullmann protocol. Ullmann condensation of **127** with 1-iodonaphthalene as coupling partner using CuI or CuCl in the presence of methyl lithium and pyridine as a base, however only the starting material was recovered after 24 h. So we converted primary alcohol into good leaving group by reaction with Mscl on treatment with 1-napthol and K_2CO_3 as base gave rearranged product (*S*)-3-(N,N-dimethylamino)-1-phenylpropan-1-ol as the major product.

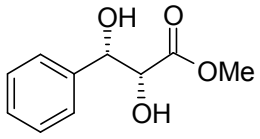
We ultimately opted for Mitsunobu reaction[23] by nucleophilic substitution conditions, using 1-naphthol in the presence of DEAD, PPh_3 and THF as solvent gave (+)-(*S*)-Dapoxetine **126** in 72% yield. The physical and spectral data are in full agreement with the literature data.

3.3.5 Conclusion

In conclusion, a short and high yielding enantioselective synthesis of (*S*)-Dapoxetine has been achieved which makes use of the Sharpless asymmetric dihydroxylation, cyclic sulfite, Clarke-Eschweiler and Mitsunobu reaction as the key steps for the first time. To the best of our knowledge this is the first report of the total chemical synthesis of (*S*)-Dapoxetine from an achiral starting material i.e. *trans* cinnamyl ester. In conclusion, we have developed an enantioselective total chemical synthesis of (+)-(*S*)-dapoxetine for the first time comprising of 10 steps in an overall yield of 17% and 96% ee.

3.3.6 Experimental

(2*R*, 3*S*)-methyl 2, 3-dihydroxy-3-phenylpropanoate (130)



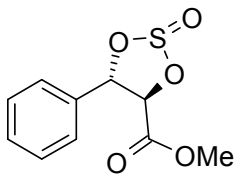
A 100 ml round-bottomed flask was charged with $(DHQ)_2PHAL$ (0.120g, 0.5 mol%), *trans*-cinnamyl methyl ester (5g, 3 mmol), NMO (7.71 mL, 60% w/v in water), and *t*-BuOH (15.42 mL).

Under stirring OsO_4 (0.156 mL, 0.2 mol%) was added. The reaction mixture was stirred at room temperature until completion of the reaction (progress of reaction was monitored by TLC, 24 h) and then poured into a solution of sodium sulfite (6.66g) in water (22.2 mL).

The mixture was stirred at room temperature for 2 h. The organic phase was separated and solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (2 X 25 mL). The organic phases were combined and washed with 5% aqueous HC1 (2 X 5 mL) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the crude diol was pure enough for processing in further steps (single spot on TLC) and was recrystallized from toluene to give **130** as colorless needles.

Yield	**:** 5g, (83%).
TLC	**:** Silica gel; petroleum ether: EtOAc (8:2); R_f = 0.6
$[\alpha]_D^{25}$	**:** +3.46 (*c* 1.14, EtOH).
M. P. (^{0}C)	**:** 86-87
IR($CHCl_3$, cm^{-1})	**:** υ_{max} 930, 1049, 1110, 1215, 1270, 1439, 1739, 3019, 3468.
^{1}H NMR (200 MHz, $CDCl_3$)	**:** δ 2.69 (brs, 2H), 3.74 (s, 3H), 4.3-4.31 (d, *J*= 2.9 Hz, 1H), 4.94-4.96 (d, *J*= 3.0 Hz, 1H), 7.19-7.32 (m, 5H)
^{13}C NMR (50 MHz, $CDCl_3$)	**:** δ 52.5, 74.3, 74.8, 126.1, 127.8, 128.2, 139.7, 173.
LC-MS	**:** 197.04 (M+H).
Elemental Analysis	**: $C_{10}H_{12}O_4$** Calcd. C, 61.22; H, 6.16. Found C, 61.18; H, 6.02.

Synthesis of compound 129



To a stirred solution of the diol (**130**) (1g, 0.5 mmol) in dry CH_2Cl_2 (10 mL) cooled at 0 ^{0}C were added Et_3N (2.34g, 1.2 mmol) and a solution of $SOCl_2$ (2.34g, 1.45 mL, 2.3 mmol) in CH_2Cl_2 (5 mL) was added over a period of 20 min.

After addition was over, the reaction mixture was continued for further 45 min. at 0 ^{0}C. After reaction was over (monitored by TLC), the reaction mixture was quenched by chilled water (10 mL) followed by addition of CH_2Cl_2 (10 mL). The organic layer was washed with water (3 X 5 mL), brine (5 mL), dried over $MgSO_4$, the mixture was filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure gave a yellow oily

liquid product (its mixture of distereomers 1:1), which was separated by flash column chromatography and characterized.

130

Yield **:** 1.1g, (90%).

TLC **:** Silica gel; petroleum ether: EtOAc (9:1); R_f = 0.5

$[\alpha]_D^{25}$ **:** -92.3 (*c* 1.1, CH_2Cl_2).

IR($CHCl_3$, cm^{-1}) **:** υ_{max} 1050, 1268, 1353, 1439, 1457, 1496,1749, 2958, 3025, 3584.

^{1}H NMR **:** **δ** 3.85 (s, 3H), 4.82-4.86 (d, *J*= 7.5 Hz, 0.5 H), 5.19-5.23 (d, *J*= 8.3 Hz, 0.5 H), 5.58-5.62 (d, *J*= 8.4 Hz, 0.5 H), 6.15-6.18 (d, *J*= 7.4 Hz, 0.5 H), 7.27-7.51 (m, 5H).

(200 MHz, $CDCl_3$)

^{13}C NMR **:** **δ** 53.2, 81.2, 87.8, 127.8, 129.0, 129.5, 133.9, 166.5.

(50 MHz, $CDCl_3$)

Elemental Analysis **:** **$C_{10}H_{10}O_5S$** Calcd. C, 49.58; H, 4.16; S, 13.24.
Found C, 49.22; H, 4.02.

129 A

TLC **:** Silica gel; petroleum ether: EtOAc (9:1); R_f = 0.5

$[\alpha]_D^{25}$ **:** -128.46 (*c* 0.72, acetone).

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 1050, 1268, 1353, 1439, 1457, 1496, 1749, 2958, 3025, 3584.

^{1}H NMR **:** **δ** 3.85 (s, 3H), 5.19-5.23 (d, *J*= 8.4 Hz, 1H), 5.58-5.62 (d, *J*= 8.4 Hz, 0.5H), 7.27 (m, 5H).

(200 MHz, $CDCl_3$)

^{13}C NMR **:** **δ** 53.3, 81.3, 87.8, 127.5, 129, 129.6, 133.9, 166.5.

(50 MHz, $CDCl_3$)

129B

TLC **:** Silica gel; petroleum ether: EtOAc (9:1); R_f = 0.4

$[\alpha]_D^{25}$ **:** -95 (*c* 0.97, acetone).

IR ($CHCl_3$, cm^{-1}) **:** υ_{max} 1216, 1268, 1353, 1439, 1457, 1496, 1749, 2958, 3025, 3584.

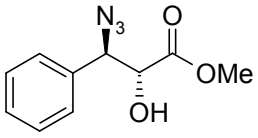
^{1}H NMR **:** **δ** 3.85 (s, 3H), 4.82-4.86 (d, *J*= 7.4 Hz, 1H), 6.14-6.18 (d, *J*= 7.3 Hz, 1H), 7.27-7.44 (m, 5H).

(200 MHz, $CDCl_3$)

^{13}C NMR **:** **δ** 53.2, 83, 83.3, 126.7, 127.4, 128.9, 129, 129.4, 129.7, 133.6, 167.3.

(50 MHz, $CDCl_3$)

(2*R*, 3*R*)-methyl 3-azido-2-hydroxy-3-phenylpropanoate (132)



To a solution of **129** (1g, 0.4 mmol) in DMF (10 mL), sodium azide (1.3g, 2 mmol) was added and the reaction mixture was stirred at 80 ^{0}C for 48 h (progress of reaction was monitored by TLC) under argon atmosphere.

After the completion of the reaction, the solvent was evaporated under reduced pressure. The resulting solid mass was dissolved in methanol (20 mL) and filtered through a pad of silcagel-celite mixture. Methanol was evaporated and the thick solid mass diluted by water (10 mL). The resulting suspension was stirred for 30 min. and was extracted with ethyl acetate (3 X 5 mL) organic layer was separated and washed with water (2 X 5 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure**.** The residue was further purified by flash column chromatography to afford **132** as a yellow liquid in 80% isolated yield.

Yield **:** 0.73g, (80%).

TLC **:** Silica gel; petroleum ether: EtOAc (8:2); R_f =0.4

$[\alpha]_D^{25}$ **:** -59.98 (*c* 4.44, EtOH).

IR($CHCl_3$, cm^{-1}) **:** υ_{max} 1586, 1742, 1887, 2104, 2498, 2824, 2955, 3031, 3065, 3476.

^{1}H NMR **:** **δ** 2.91 (brs, 1H), 3.74 (s, 3H), 4.55-4.57 (d, *J*= 4.3 Hz, 1H),

(200 MHz, $CDCl_3$) 4.90-4.92 (d, *J*= 4.3 Hz, 1H), 7.30-7.41 (m, 5H).

^{13}C NMR **:** **δ** 52.5, 67.1, 73.6, 126.5, 127.6, 128.5, 128.8, 134.2, 171.7.

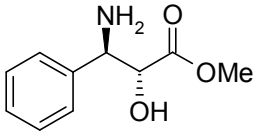
(50 MHz, $CDCl_3$)

LC-MS **:** 222.11 (M+H), 180.11, 168.08.

Elemental Analysis **:** **$C_{10}H_{11}N_3O_3$** Calcd. C, 54.29; H, 5.01; N, 19.00.

Found C, 54.10; H, 4.87; N, 18.88.

(2*R*, 3*R*)-methyl 3-amino-2-hydroxy-3-phenylpropanoate 132'



The hydroxyl azide ester **132** (1g, 4.52 mmol) was dissolved in methanol (20 mL) and reduced in the presence of 10% Pd-C under hydrogen atmosphere (1 atm. balloon pressure) at room temperature for 36 h.

After the reaction was over (progress of reaction was monitored by TLC). The reaction was filtered off and the residue washed with methanol (2 X 5 mL). The collected filtrate was evaporated under reduced pressure to give a thick solid mass which was purified by flash column chromatography to give a hygroscopic solid of the reduced amino product in 93% yield.

Yield **:** 0.79g, (93%).

TLC **:** Silica gel; petroleum ether: EtOAc (5:5); R_f =0.2

IR($CHCl_3$, cm^{-1}) **:** υ_{max} 689, 872, 916, 1024, 1120, 1251, 1586, 1742, 3357, 3400.

^{1}H NMR **:** **δ** 3.5 (s, 3H), 4.11-4.14 (d, *J*= 5.2 Hz, 1H), 4.26-4.28

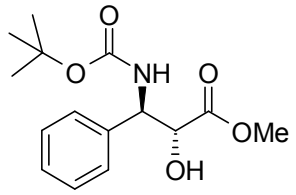
(200 MHz, $CDCl_3$/) (d, *J*= 4.9 Hz, 1H), 7.16-7.22 (m, 5H).

^{13}C NMR **:** **δ** 51.1, 56, 72.7, 125.4, 125.8, 126, 126.5, 128.6, 170.7.

(50 MHz, $CDCl_3$)

LC-MS **:** 195.22 (M+H), 186.08, 145.16.

***tert*-butyl (1*R*, 2*R*)-2-(methoxycarbonyl)-2-hydroxy-1-phenylethylcarbamate (133)**



To a solution of **132** (1.5g, 5.74 mmol) in EtOAc were added Et_3N (0.88 mL, 6.32 mmol), $(Boc)_2O$ (1.45 mL, 6.32 mmol) and 10 % Pd/C (0.05g). The mixture was stirred at room temperature under hydrogen atmosphere (1 atm. balloon pressure) for 12 h.

After completion of reaction (monitored by TLC), the reaction mixture was filtered off and concentrated under reduced pressure and the residue was further purified by flash column chromatography using light petroleum ether: EtOAc (3:1) as an eluent to afford pure **133** as a white solid in 88% isolated yield.

Yield **:** 1.761g, (88%).

TLC **:** Silica gel; petroleum ether: EtOAc (8:2); R_f =0.3

$[\alpha]_D^{25}$ **:** - 78.41 (*c* 1.91, Acetone)

M. P. (^{0}C) **:** 123-124

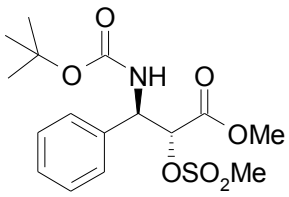
IR($CHCl_3$, cm^{-1}) **:** υ_{max} 1393, 1440, 1455, 1504, 1585, 1662, 2400, 2981, 3019, 3290.

^{1}H NMR **:** **δ** 1.31 (s, 9H), 3.33 (s, 3H), 5.25-5.29 (d, *J*= 9.2 Hz, 1H),

(200 MHz, $CDCl_3$) 5.49-5.53 (d, *J*= 8.9 Hz, 1H), 7.27-7.41 (m, 5H).

^{13}C NMR	**: δ** 27.5, 52.1, 60.6, 74.6, 84.3, 126.5, 128.5, 129.1, 134.9, 148.1,
(50 MHz, $CDCl_3$)	151.1, 165.8.
LC- MS	**:** 296.64 (M+H), 286.64, 254.62, 240.61, 222.60, 196.63.
Elemental Analysis	**: $C_{15}H_{21}NO_5$** Calcd. C, 61.00; H, 7.17; N, 4.74.
	Found C, 60.79; H, 7.02; N, 4.43.

***tert*-butyl-(1*R*,2*R*)-2-(methoxycarbonyl)-2-methylsulfonyl-1-phenylethylcarbamate (134)**

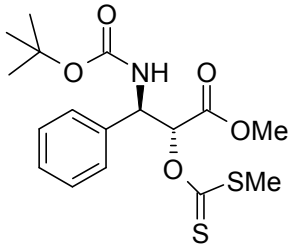


To a solution of **133** (0.425g, 1.44 mmol) in DCM (10 mL) at 0 ^{0}C was added Et_3N (0.16g, 1.58 mmol) followed by methane sulfonyl chloride (0.173g, 1.51 mmol) under argon atmosphere.

After addition was over stirring was continued for another 30 min. at 0 ^{0}C, then the reaction was allowed to reach ambient temperature and stirring was continued for further 12 h. When the reaction was completed (monitored by TLC), the solvent was evaporated under reduced pressure, solid mass left was quenched by ice-cold water (5 mL), and the resulting suspension was stirred for 30 min. The suspension was extracted with ethyl acetate (3 X 5 mL) organic layer was washed with water (2 X 5 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated under vacuum**.** The resulting crude mixture was purified by flash column chromatography using 10% ethyl acetate in petroleum ether as an eluent to afford the pure product.

Yield	**:** 0.51g, (95%).
TLC	**:** Silica gel; petroleum ether: EtOAc (8:2); R_f =0.6
^{1}H NMR	**: δ** 1.40 (s, 9H), 3.63 (s, 3H), 3.65 (s, 3H), 5.25-5.34 (d, *J*= 7.2 Hz,
(200 MHz, $CDCl_3$)	1H), 5.48-5.59 (d, *J*= 8.9 Hz, 1H), 7.21-7.34 (m, 5H).
^{13}C NMR	**: δ** 28.1, 38.8, 52.4, 52.6, 78.6, 125.9, 127.2, 127.5, 128.3, 128.7,
(50 MHz, $CDCl_3$)	135.3, 154.9, 167.
Elemental Analysis	**: $C_{16}H_{23}NO_7S$** Calcd. C, 51.56; H, 6.21; N, 3.75; S, 8.59.
	Found C, 51.28; H, 6.02; N, 3.63; S, 8.22

***tert*-butyl(1*R*,2*R*)-2-(methoxycarbonyl)-2-O-(*S*-methyldithiocarbonate)-1-phenylethylcarbamate (136)**

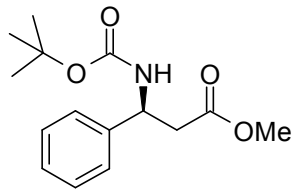


The reaction vessel is flushed with nitrogen and a nitrogen atmosphere is maintained during the ensuing steps. To a solution of **133** (0.315g, 1.06 mmol) in THF (10 mL) at 0 ^{0}C was added sodium hydride (50% oil dispersion, 0.053g, 2.2 mmol).

Vigorous gas evolution was observed. After the reaction mixture was stirred for 20 min. carbon disulfide (0.255g, 0.202 mL, 3.3 mmol) was added all at once. Stirring was continued for next 30 min. after which iodomethane (0.272g, 0.123 mL, 1.9 mmol) was added in a single portion. The reaction mixture was stirred for another 2 h (progress of reaction mixture was monitored by TLC). On completion glacial acetic acid (5 mL) was added dropwise to destroy excess sodium hydride. The solution was filtered and the filtrate was concentrated under reduced pressure. The semisolid residue was extracted with diethyl ether (3 X 5 mL) and the combined ether extracts were washed with saturated sodium bicarbonate (5 mL) solution and water (5 mL). The etheral solution was dried over anhydrous $MgSO_4$, the drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography which gave **136** as a pale yellow solid in 82% isolated yield.

Yield	**:** 0.337g, (82%).
TLC	**:** Silica gel; petroleum ether: EtOAc (8:2);R_f =0.5
$[\alpha]_D^{25}$	**:** -47.26 (*c* 1.13, Acetone)
M. P. (^{0}C)	**:** 118-119
IR($CHCl_3$, cm^{-1})	**:** υ_{max} 1311, 1433, 1513, 1692, 1745, 1826, 2976, 3032, 3064, 3398.
^{1}H NMR (200 MHz, $CDCl_3$)	**: δ** 1.43 (s, 9H), 2.56 (s, 3H), 3.62 (s, 3H), 5.37 (d, *J*= 7.1 Hz,1H), 6.12-6.14 (d, *J*= 7.0 Hz, 1H), 7.30-7.40 (m, 5H).
LC-MS	**:** 386.11 (M+H), 355.11, 288.11, 218.09.
Elemental Analysis	**: $C_{17}H_{23}NO_5S_2$** Calcd. C, 52.97; H, 6.01; N, 3.63; S, 16.64 Found C, 52.88; H, 5.84; N, 3.41; S, 16.26

***tert*-butyl (*S*)-2-(methoxycarbonyl)-1-phenylethylcarbamate (128)**



To a solution of **136** (0.2g, 0.519 mmol) in toluene (10 mL) tri-*n*-butyltin hydride (0.453g, 1.558 mmol) and catalytic amount of AIBN (0.1 mol% w/w based on **136**) were added at room temperature under inert atmosphere.

The reaction mixture was heated at reflux till completion of reaction (progress of reaction was monitored by TLC). During the course of the reaction, the solution of reaction mixture changes from deep yellow to nearly colorless. After the reaction was over, toluene was removed under reduced pressure to give a thick oily residue, which was partitioned between petroleum ether and acetonitrile. The acetonitrile layer was separated and washed with petroleum ether (3 X 5 mL). The acetonitrile was evaporated under reduced pressure. The crude product separating out was purified by flash column chromatography to afford **128** as a colorless solid in 80% isolated yield.

Yield **:** 0.116g, (80%).

TLC **:** Silica gel; petroleum ether: EtOAc (8:2); R_f =0.4

$[\alpha]_D^{25}$ **:** -31.49 (*c* 1.31, Acetone)

M. P. (^{0}C) **:** 95-96

IR($CHCl_3$, cm^{-1}) **:** υ_{max} 1374, 1446, 1478, 1735, 1889, 2088, 2256, 2479, 2984, 3449.

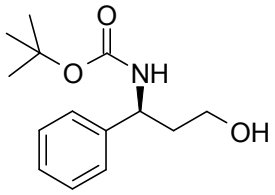
^{1}H NMR (200 MHz, $CDCl_3$) **:** **δ** 1.42 (s, 9H), 2.82-2.87 (q, 2H), 3.61 (s, 3H), 5.08-5.48 (t, 1H), 7.25-7.37 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$) **:** **δ** 28.2, 40.7, 51.6, 79.6, 126.1, 127.4, 128.5, 155.0, 171.3.

LC-MS **:** 280.15 (M+H), 268.11, 245.09, 198.07.

Elemental Analysis **:** **$C_{15}H_{21}NO_4$** Calcd. C, 64.50; H, 7.58; N, 5.01.
Found C, 64.33;H, 7.39; N, 4.89.

***tert*-butyl (*S*)-3-hydroxy-1-phenylpropylcarbamate (137)**

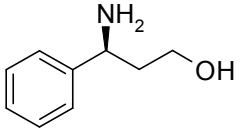


A solution of *tert*-butyl(*S*)-2-(methoxycarbonyl)-1-phenylethylcarbamate **128** (0.1g, 3.98 mmol) in dry THF (10 mL) was cooled to 0 ^{0}C and $LiAlH_4$ (0.06g, 15.9 mmol) added in small portions.

The reaction mixture was refluxed for 2 h following the complete disappearance of the starting material by TLC analysis. The reaction mixture was cooled to 0 ^{0}C, and the excess hydride was destroyed by chilled water (5 mL). The grey mixture was extracted by ethyl acetate (3 X 5 mL) and the organic phases were combined, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude mixture separating out was purified by flash column chromatography using petroleum ether and ethyl acetate as eluent which gave **137** as a white solid in 81% yield.

Yield	**:** 0.073g, (81%).
TLC	**:** Silica gel; petroleum ether: EtOAc (7:3); R_f =0.3
$[\alpha]_D^{25}$	**:** -53.03 (*c* 1.27, Acetone)
M. P. (^{0}C)	**:** 104-105
IR($CHCl_3$, cm^{-1})	**:** υ_{max} 1167, 1374, 1446, 1478, 1680, 2210, 2450, 2600, 3410, 3540.
^{1}H NMR	**: δ** 1. 44 (s, 9 H), 1.77-2.17 (m, 2H), 3.66-3.72 (m, 2H), 4.89-5.09
(200 MHz, $CDCl_3$)	(t, 1H) 7.27-7.39 (m, 5H)
^{13}C NMR	**: δ** 28.2, 39.3, 51.5, 58.9, 79.9, 126.3, 127.4, 128.7, 141.9, 156.3.
(50 MHz, $CDCl_3$)	
Elemental Analysis	**:** **$C_{14}H_{21}NO_3$** Calcd. C, 66.91; H, 8.42; N, 5.57.
	Found C, 66.75; H, 8.29; N, 5.28.

(*S*)-3-amino-3-phenylpropan-1-ol (138)



Trifluoroacetic acid (0.5 mL) was added drop wise to a solution of **137** (0.05g, 0.199 mmol) in dry CH_2Cl_2 (5 mL) at 0 ^{0}C. The reaction mixture was allowed to reach room temperature and stirred further for 6 h.

1M NaOH solution (15 mL) was then slowly added at 0 ^{0}C and the mixture was extracted with EtOAc/MeOH (95:5) (2 X 5 mL). The organic extracts were combined dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The separated crude product was purified by flash column chromatography on silica gel with $CHCl_3$/MeOH (9:1)

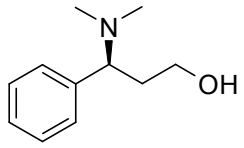
Yield **:** 0.03g, (85%)

TLC : Silica gel; $CHCl_3$/MeOH (9:1); R_f =0.3

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 2.1 (m, 2H), 3.54 (t, 2H), 3.97 (t, 1H), 7.08-7.22 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 39.4, 57.4, 56.4, 126.1, 128.2, 128.9, 139.9.

(*S*)-3-(*N, N*-dimethylamino)-3-phenylpropan-1-ol (127)



To a solution of (S)-3-amino-3-phenylpropan-1-ol (0.05g, 0.19 mmol) in formic acid (39 lL), was added a 30% aqueous solution of formaldehyde (78 lL, 1.05 mmol) and the mixture refluxed over 8 h when the reaction is complete as monitored by TLC.

After that the solution was acidified with conc. HCl to pH = 1 and basified with 4 N NaOH. The organic phases were combined, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude was purified by flash column chromatography.

Yield : 0.05g, (85%).

TLC : Silica gel; MeOH: EtOAc (8:2); R_f =0.3

$[\alpha]_D^{25}$: + 39.2 (*c* 0.6, $CHCl_3$).

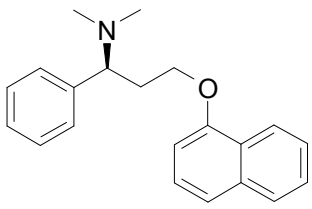
IR($CHCl_3$, cm^{-1}) : υ_{max} 733, 847, 914, 1047, 1167, 1265, 1345, 2310, 2445, 3410.

^{1}H NMR (200 MHz, $CDCl_3$) : **δ** 1.66-1.75 (m, 1H), 2.15 (s, 6H), 2.51-2.68 (m, 1H), 3.39-3.66 (m, 1H), 3.88-3.94 (m, 1H), 7.30-7.41 (m, 5H)

^{13}C NMR (50 MHz, $CDCl_3$) : **δ** 32.1, 36.4, 63.1, 67.5, 127.1, 127.8, 128.3, 128.8, 128.9, 136.1.

Elemental Analysis : **$C_{11}H_{17}NO$** Calcd. C, 73.70; H, 9.56; N, 7.81.
Found C, 73.58; H, 9.37; N, 7.75.

(*S*)-*N, N*-dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine (126)



To a solution of **137** (20mg, 0.11 mmol) in dry THF (2.4 mL) under nitrogen atmosphere was added 1-naphthol (32 mg, 0.22 mmol). The mixture was cooled to 0 ^{0}C and PPh_3 (0.22 mmol) and DEAD (lL, 0.22 mmol) were successively added.

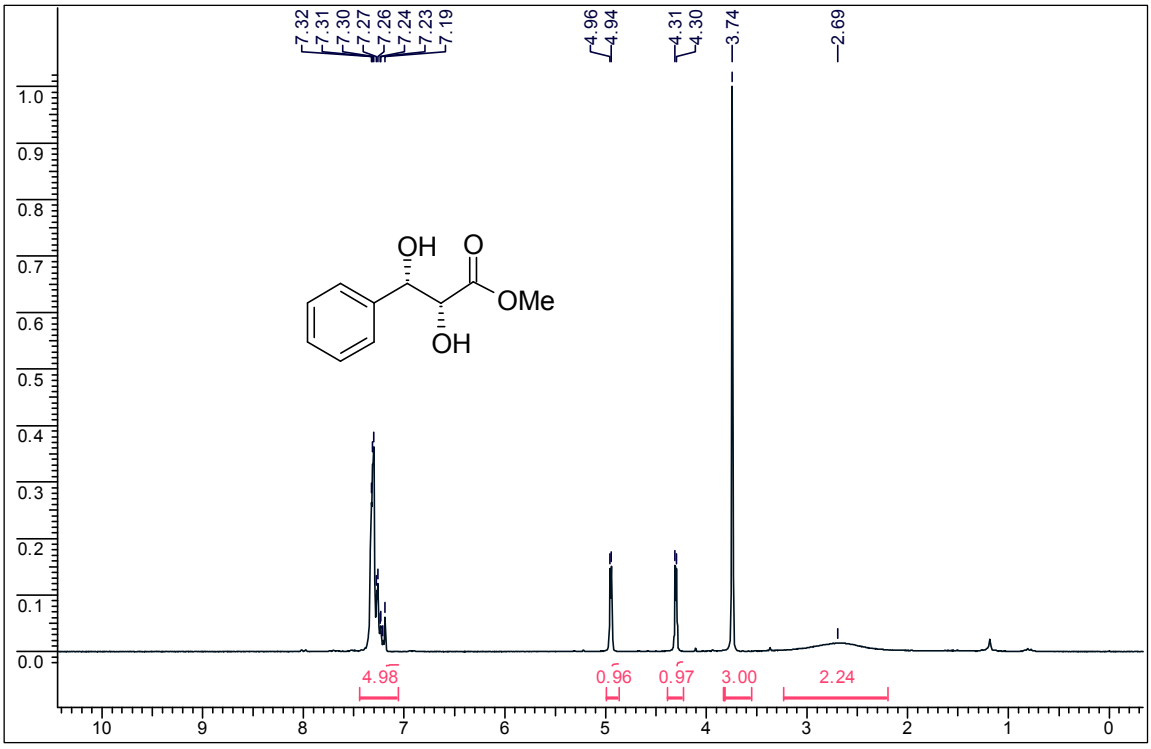
The solution was allowed to warm till room temperature and stirred further for 15 h. After reaction was completed (progress of reaction monitored by TLC). The solution was evaporated and the crude product was purified by flash column chromatography using EtOAc/ MeOH mixture which afforded (*S*)-dapoxetine as a colorless oil in 74% yield.

Yield	**:** 0.02g, (74%).
TLC	**:** Silica gel; EtOAc: MeOH (9:1); R_f =0.3
$[\alpha]_D^{25}$	**:** + 64.2 (*c* 0.3, $CHCl_3$).
IR($CHCl_3$, cm^{-1})	**:** υ_{max} 733, 847, 914, 1047, 1167, 1265, 1345, 1727, 1922, 2100, 2310, 2950, 2960.
^{1}H NMR (200 MHz, $CDCl_3$)	**: δ** 2.22 (s, 6H), 2.34-2.45 (m, 1H), 2.59-2.71 (m, 1H), 3.55-3.63 (m, 1H), 3.93-4.12 (m, 2H), 7.19-7.52 (m, 9H), 7.70-7.74 (m, 1H), 7.95-8.21 (m, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	**: δ** 32.0, 36.4, 63.1, 67.5, 104.5, 120.1, 127.1, 127.4, 127.8, 128.3, 128.9, 136.0, 138.1, 155.2.
LC-MS	**:** 306.18 (M+H), 285.16.
Elemental Analysis	**:** **$C_{21}H_{23}NO$** Calcd. C, 82.58; H, 7.59, N, 4.59 Found C, 82.19; H, 7.28; N, 4.21.

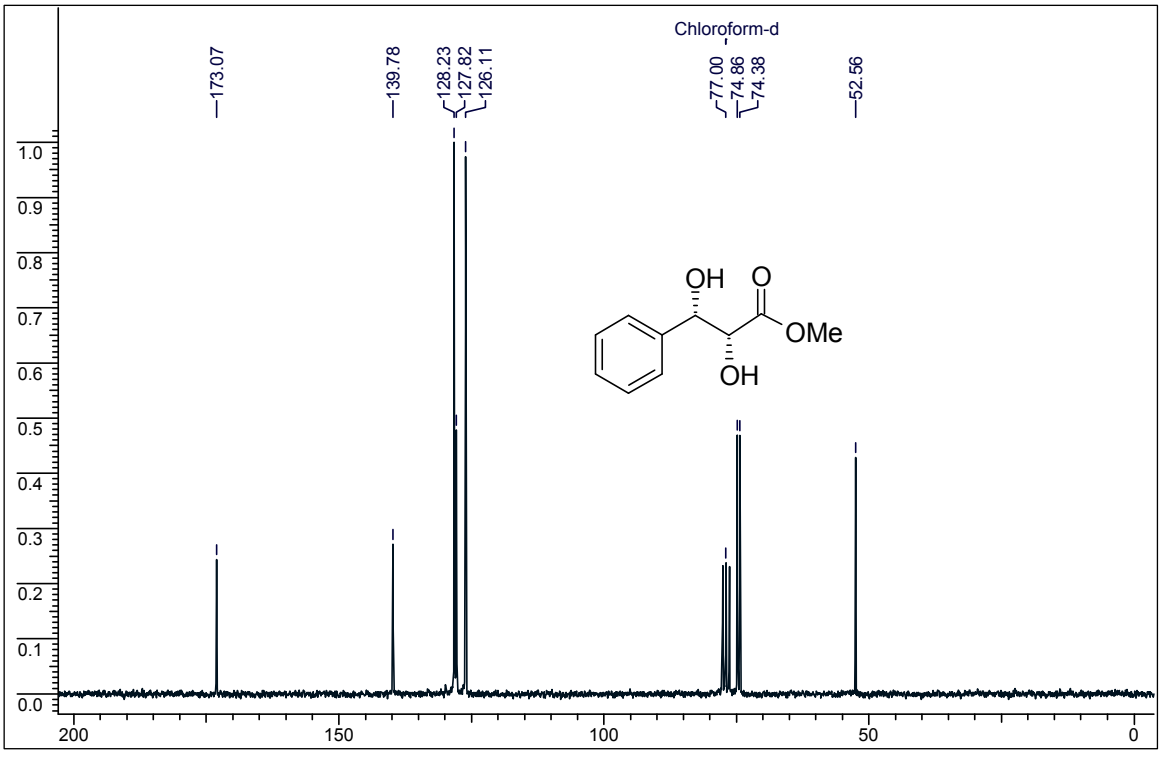
3.3.7 Spectra

[1]	^{1}H NMR and ^{13}C NMR Spectra of	**130**
[2]	^{1}H NMR and ^{13}C NMR Spectra of	**129**
[3]	^{1}H NMR Spectra of	**129 (A)**
[4]	^{1}H NMR Spectra of	**129(B)**
[5]	^{1}H NMR and ^{13}C NMR Spectra of	**132**
[6]	^{1}H NMR and ^{13}C NMR Spectra of	**133**
[7]	^{1}H NMR Spectra of	**136**
[8]	^{1}H NMR and ^{13}C NMR Spectra of	**128**
[9]	^{1}H NMR and ^{13}C NMR Spectra of	**137**
[10]	^{1}H NMR and ^{13}C NMR Spectra of	**127**
[11]	^{1}H NMR and ^{13}C NMR Spectra of	**126 (*S*-Dapoxetine)**

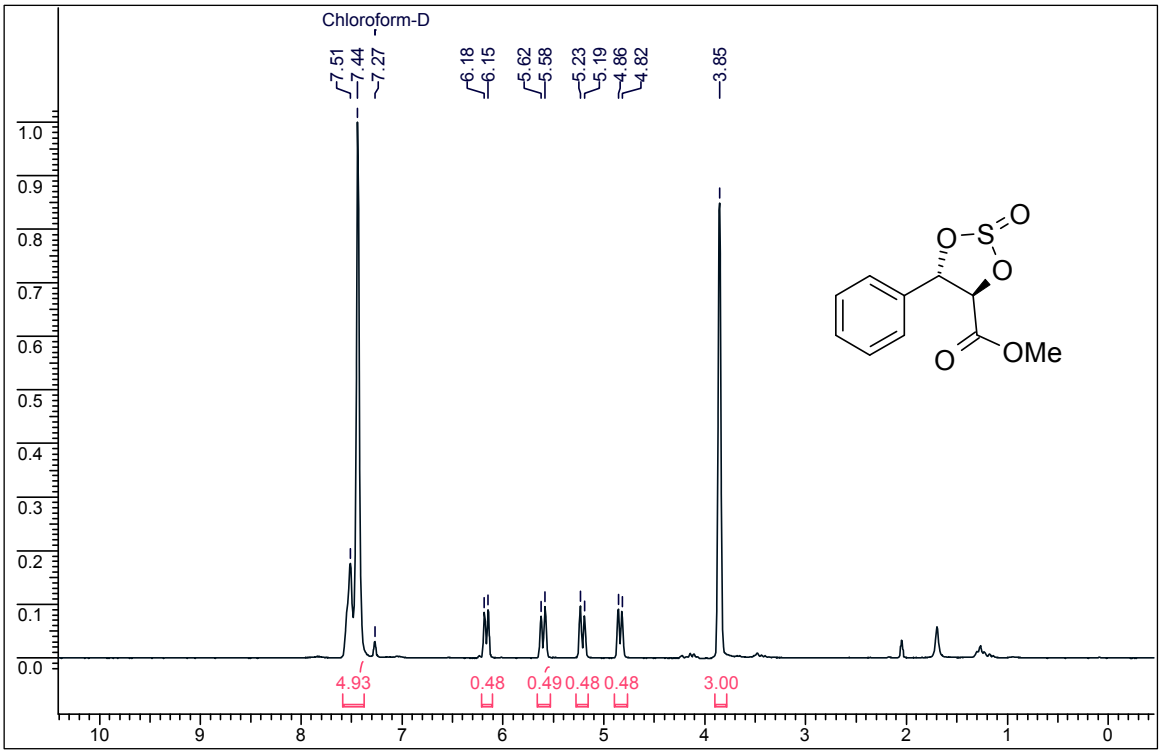
[1] ^{1}H NMR spectra of 130



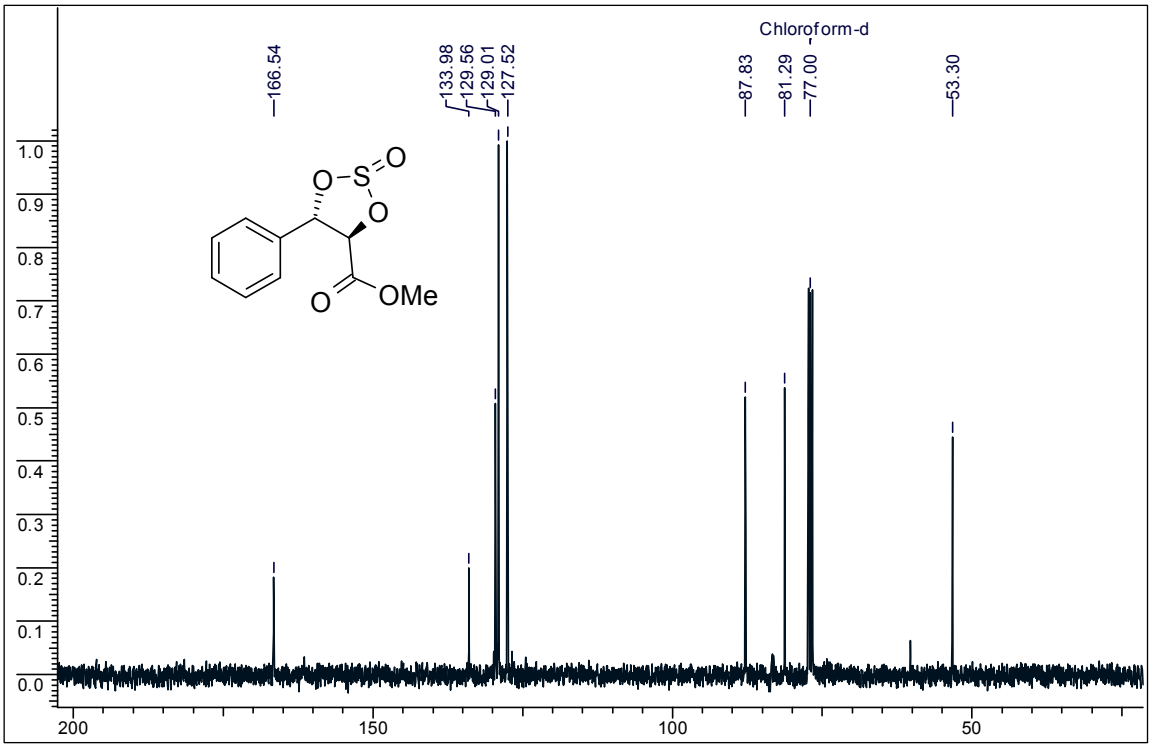
[1] ^{13}C NMR spectra of 130



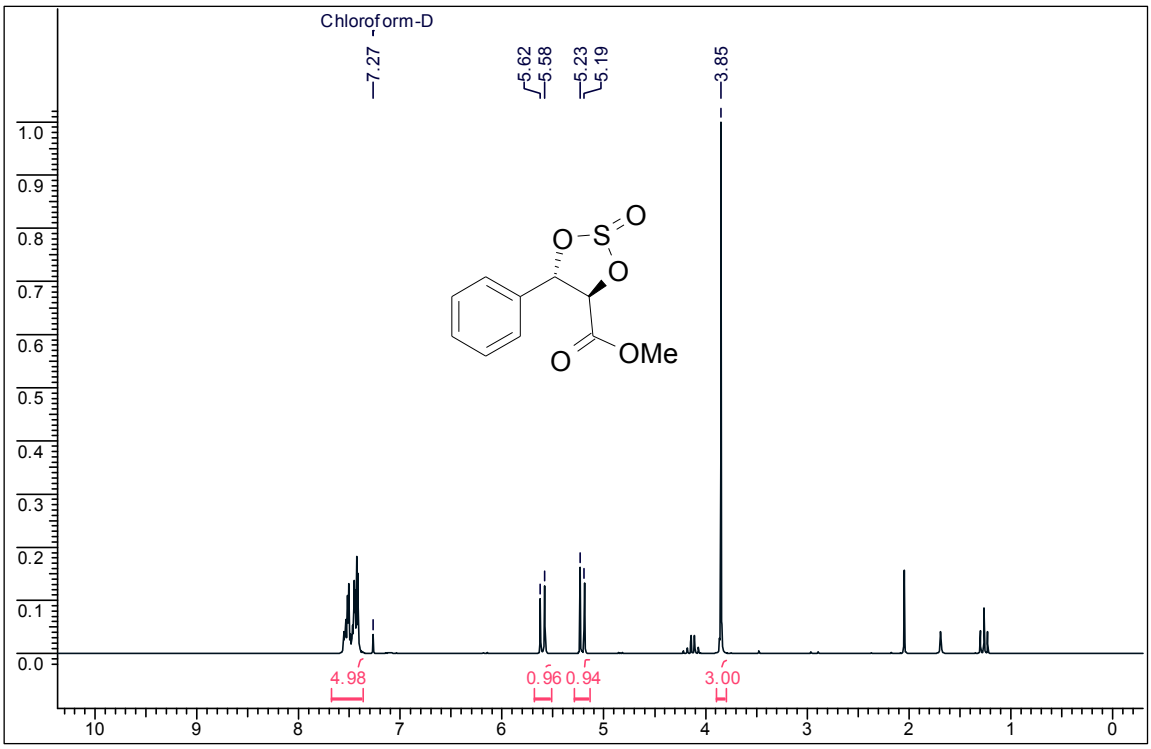
[2] ^{1}H NMR spectra of 129



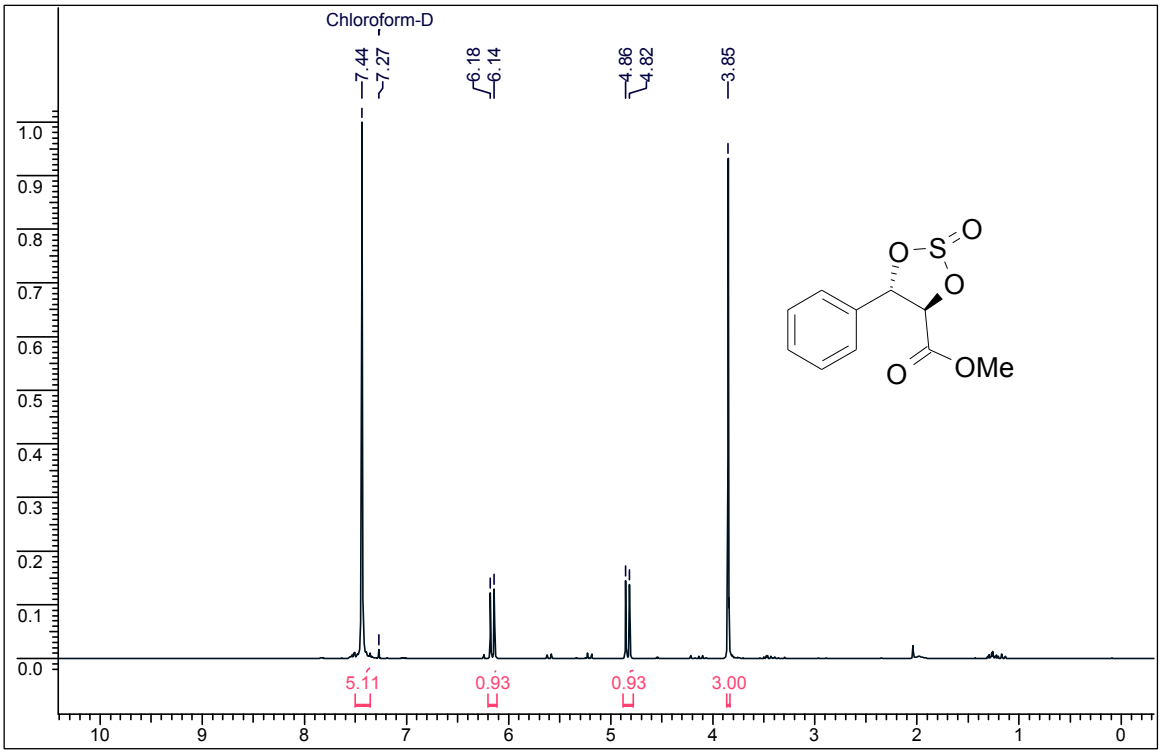
[2] ^{13}C NMR spectra of 129



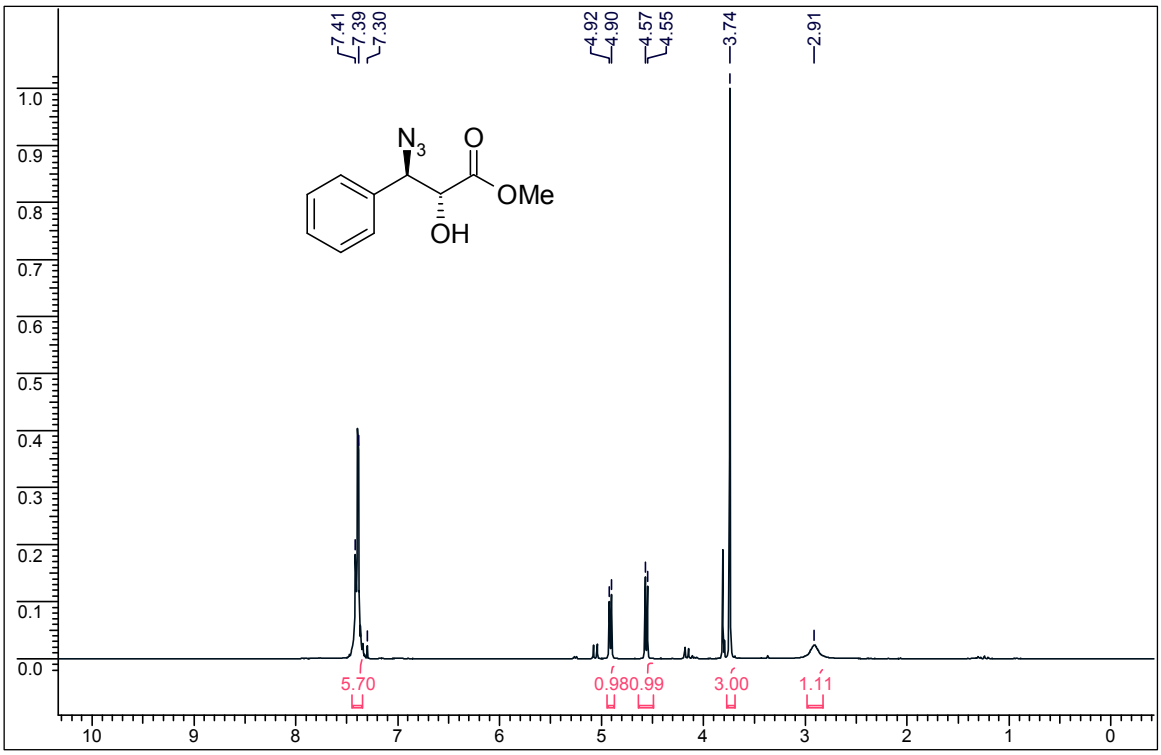
[3] ^{1}H NMR spectra of 129 (A)



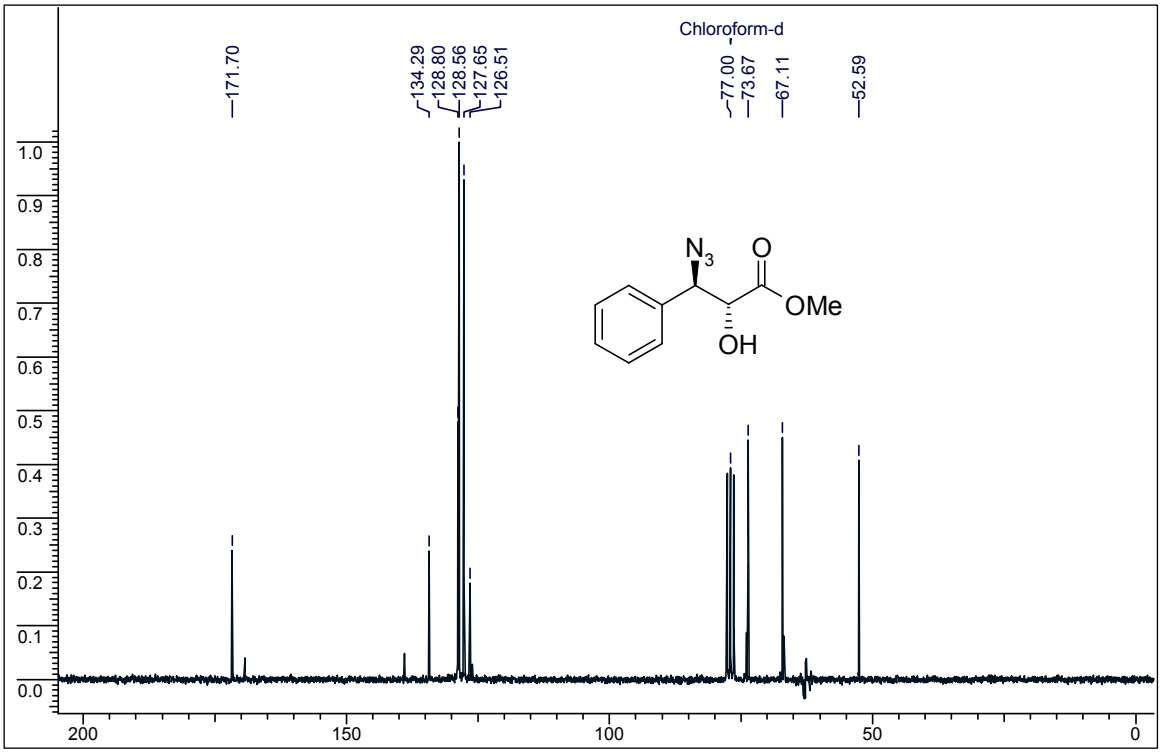
[4] ^{1}H NMR spectra of 129 (B)



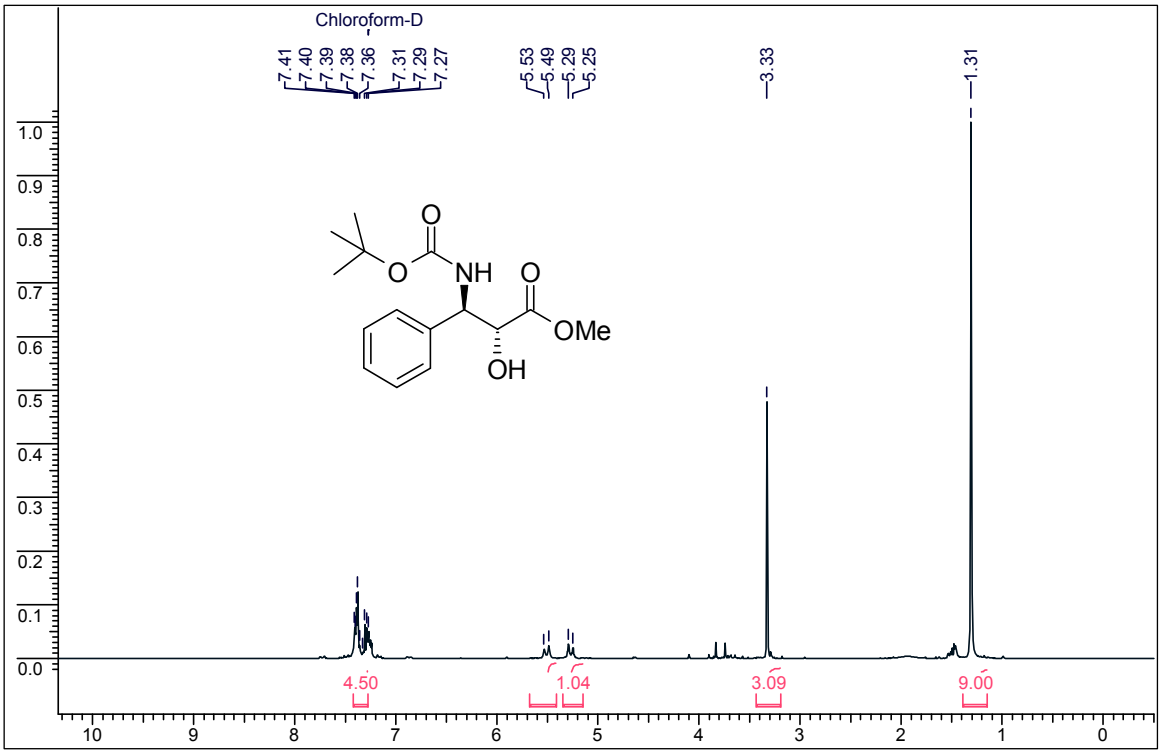
[5] ^{1}H NMR spectra of 132



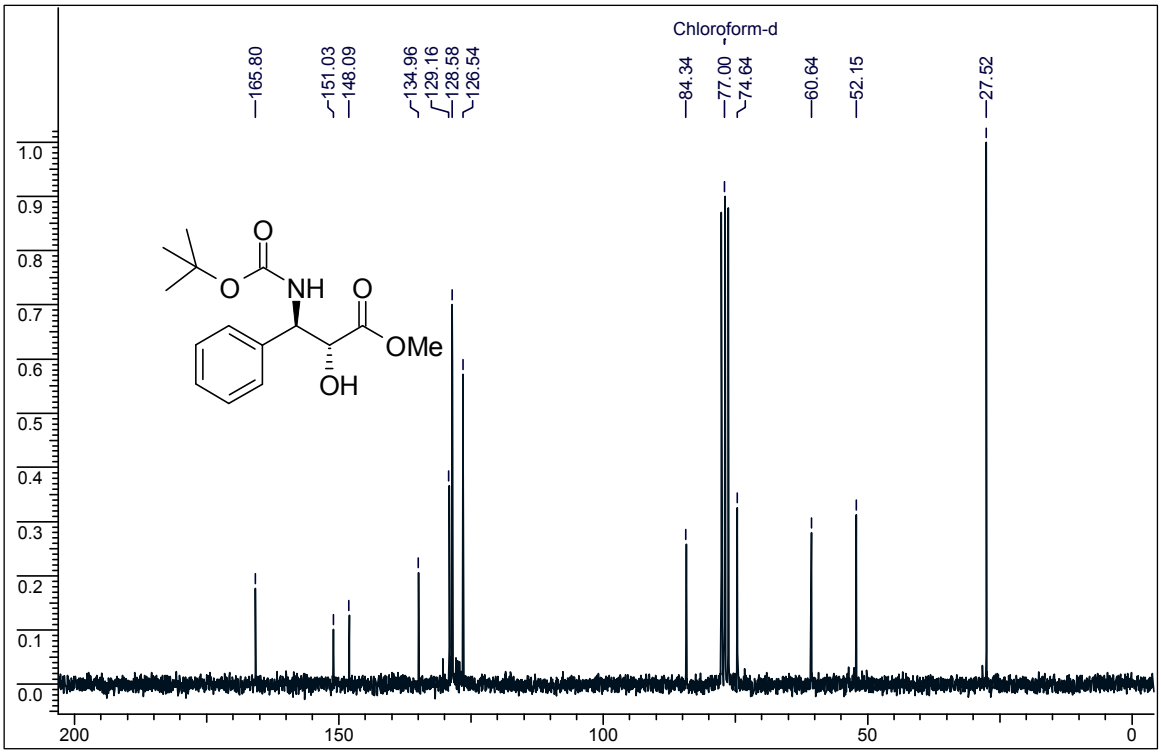
[5] ^{13}C NMR spectra of 132



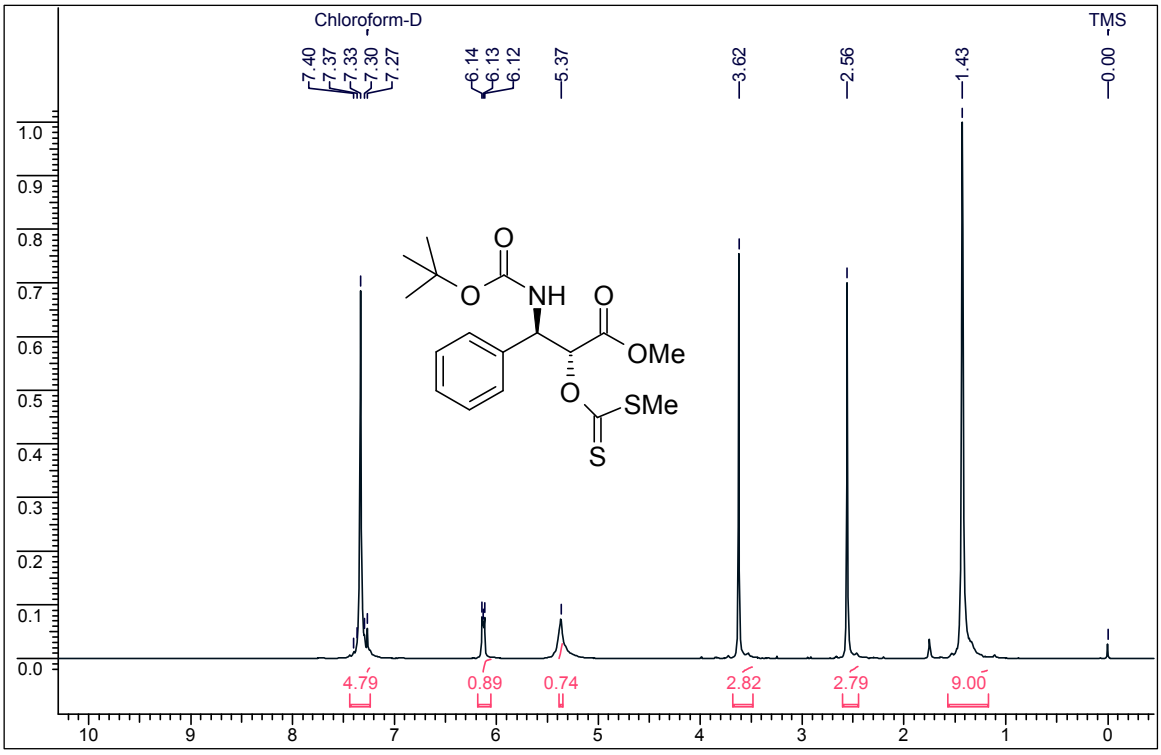
[6] ^{1}H NMR spectra of 133



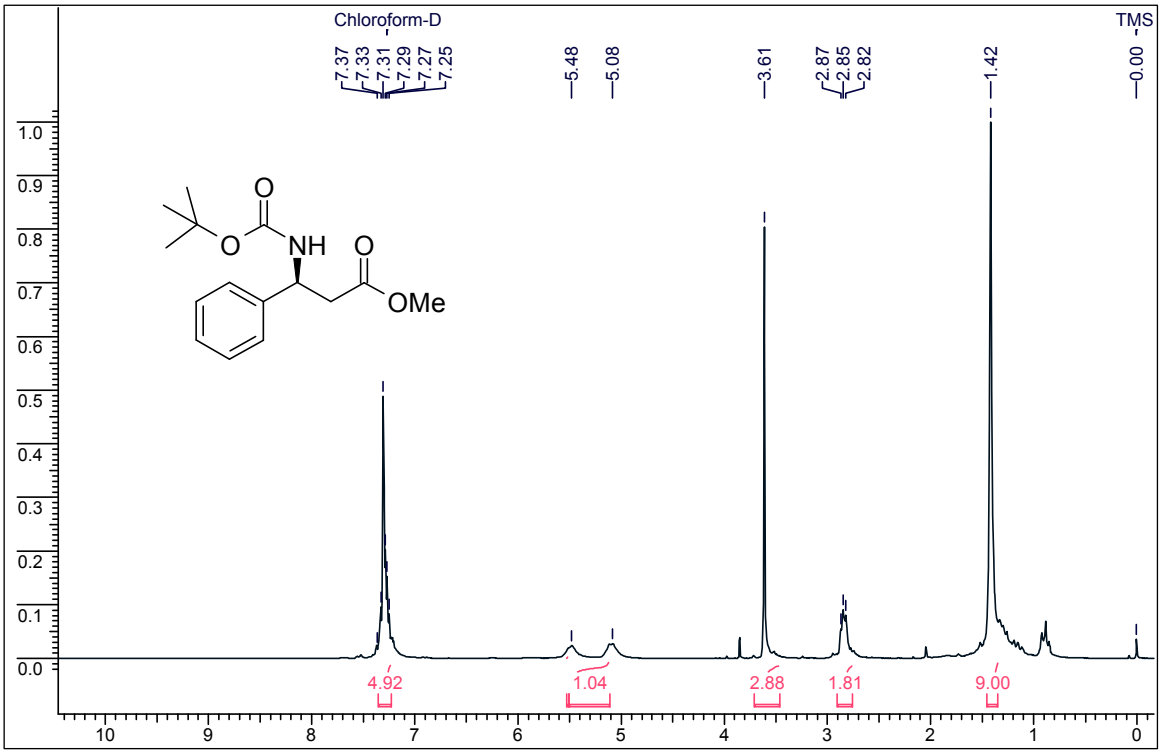
[6] ^{13}C NMR spectra of 133



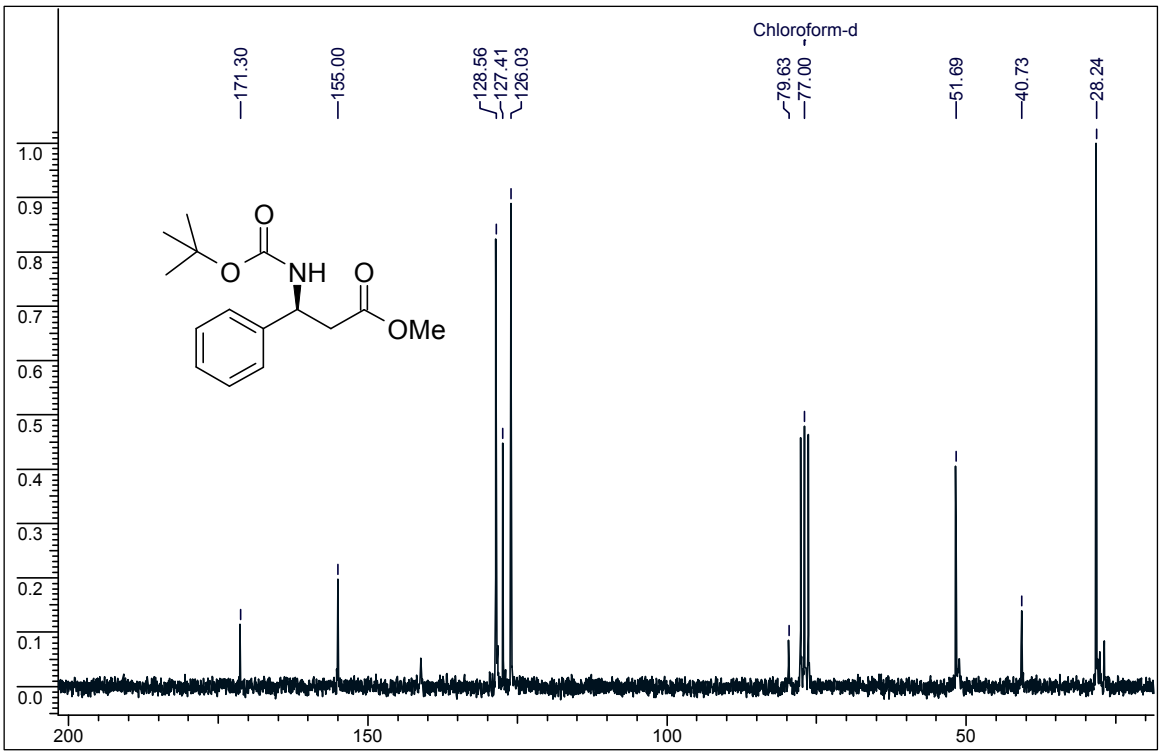
[7] ^{1}H NMR spectra of 136



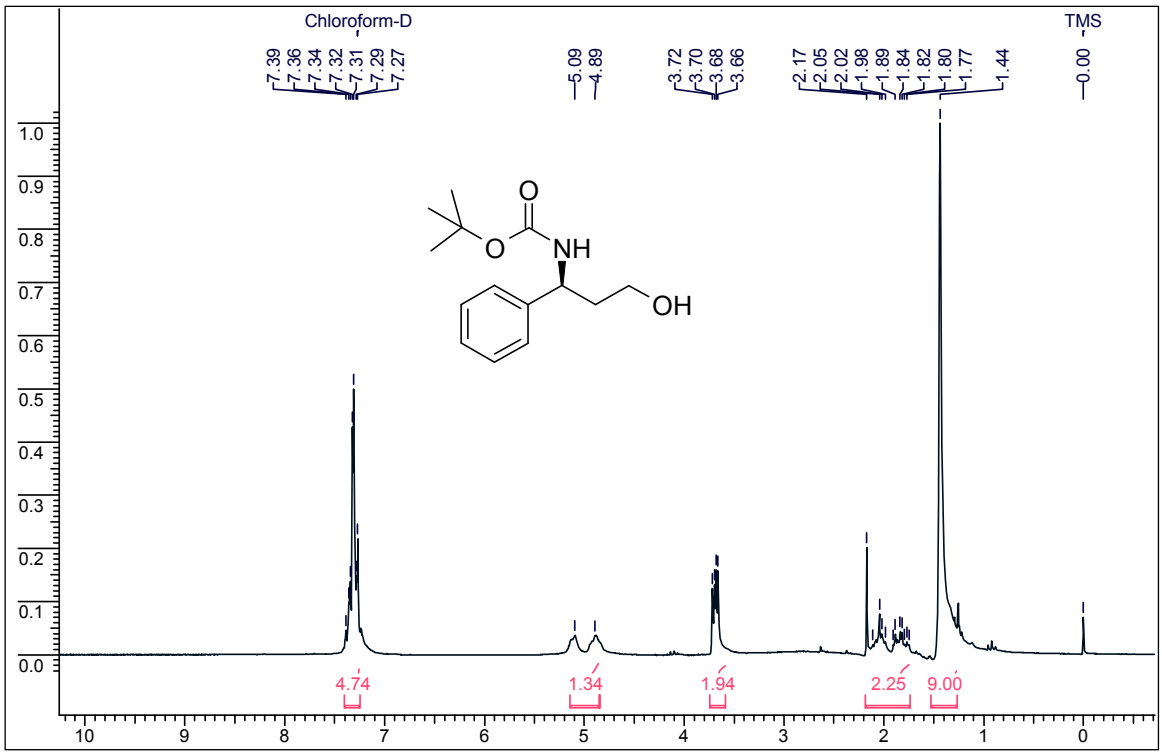
[8] ^{1}H NMR spectra of 128



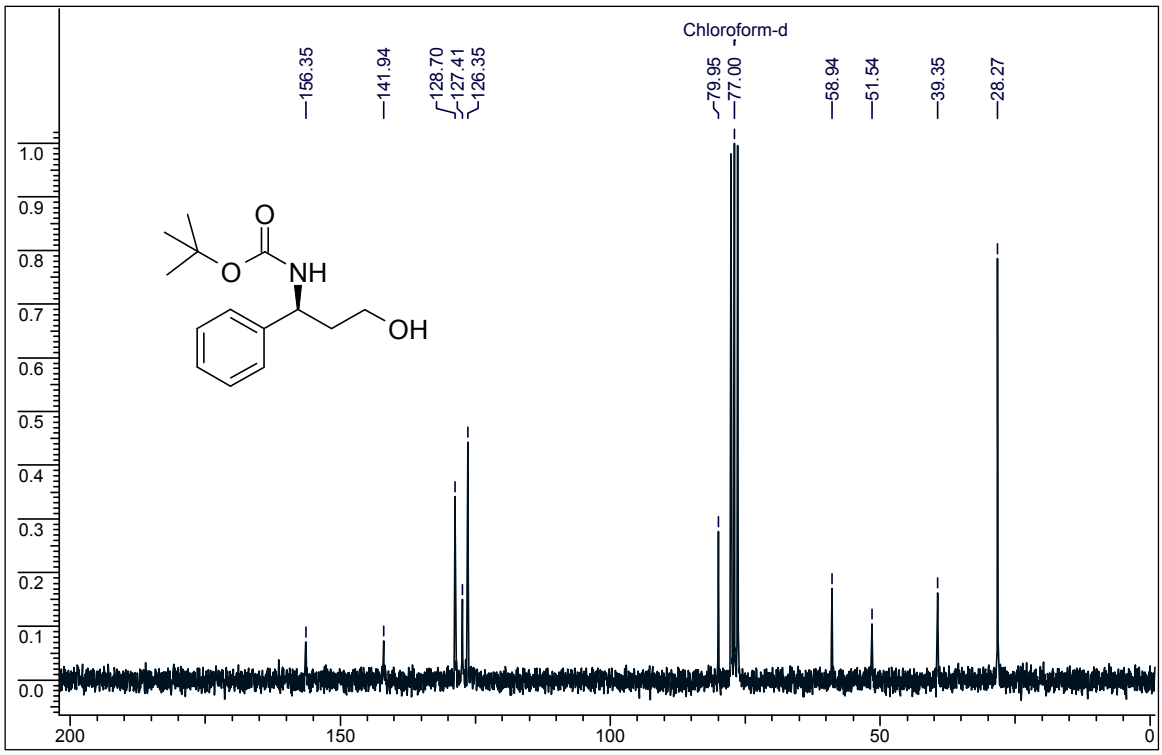
[8] ^{13}C NMR spectra of 128



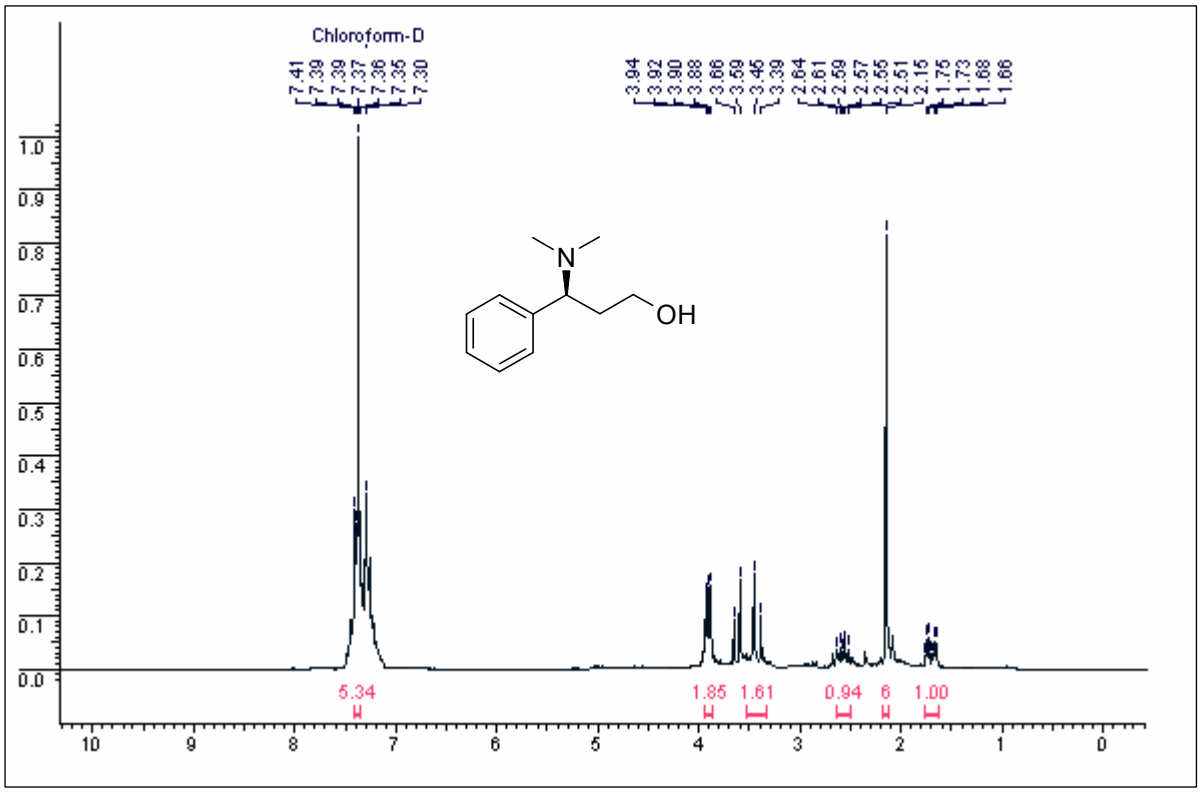
[9] ^{1}H NMR spectra of 137



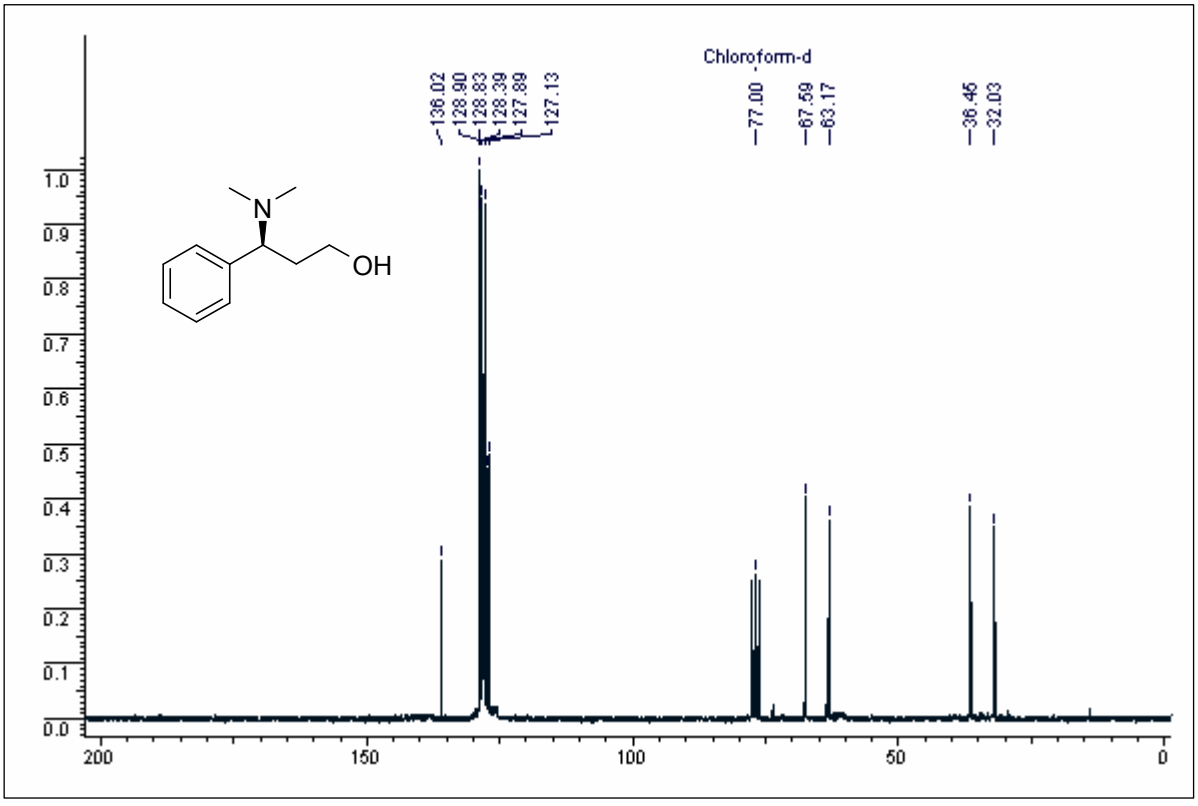
[9] ^{13}C NMR spectra of 137



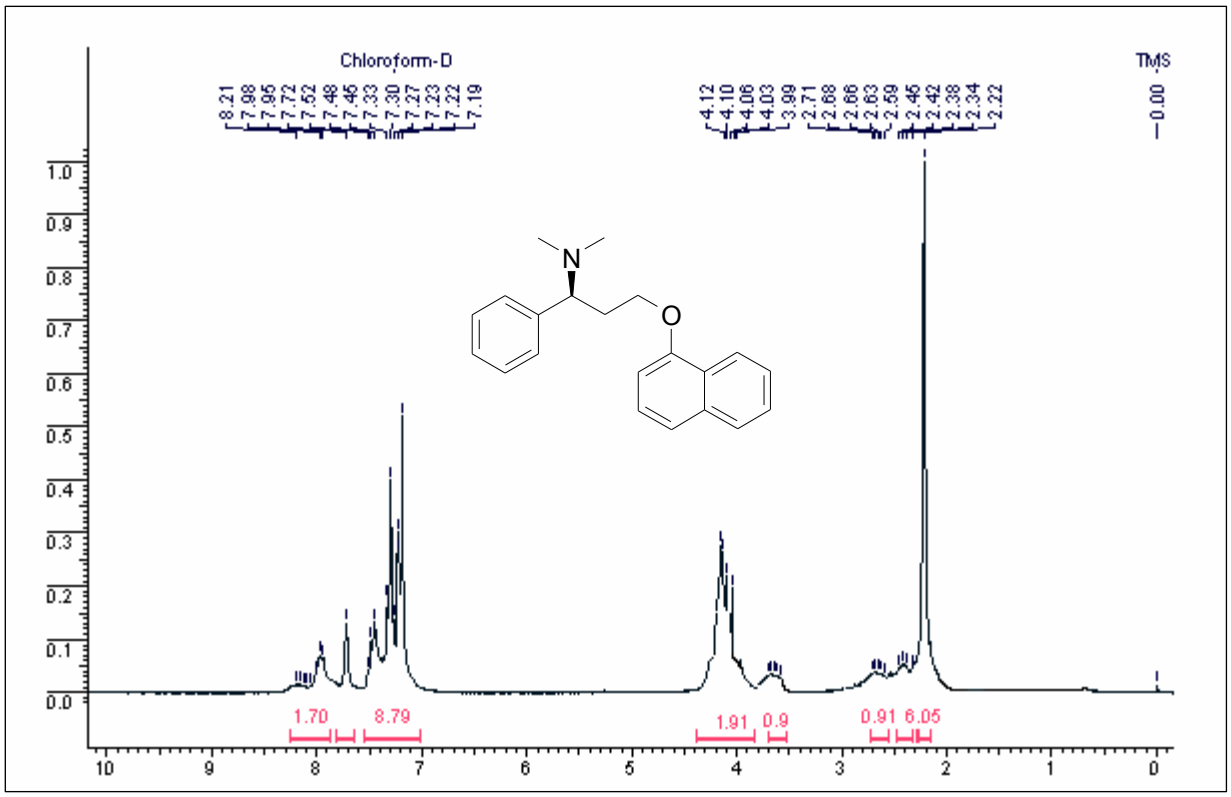
[10] ^{1}H NMR spectra of 127



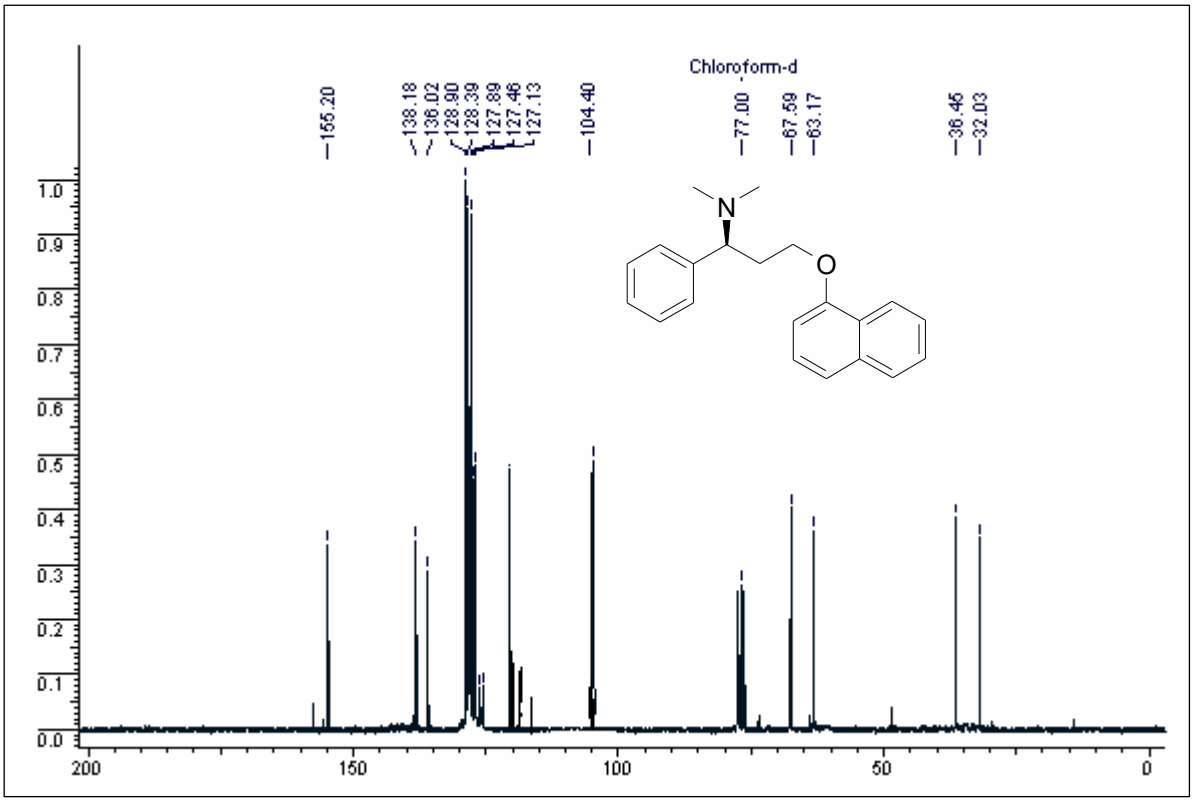
[10] ^{13}C NMR spectra of 127



[11] ^{1}H NMR spectra of 126



[11] ^{13}C NMR spectra of 126



3.3.8 References

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