NOVEL ORGANIC TRANSFORMATIONS USING ULTRASOUND, IONIC LIQUID AND THEIR APPLICATION TOWARDS THE SYNTHESIS OF BIOLOGICAL ACTIVE MOLECULES/INTERMEDIATES

A Thesis

Submitted to the

UNIVERSITY OF PUNE

For the degree of

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

Sanjay P. Borikar

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE 411008, INDIA

OCTOBER, 2010

Dedicated to

my parents, lovely wife
and
my adorable son Aarnav

NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Division of organic chemistry
Phone: +91-20-25902574
Fax: +91-20-25893614

Dr. Thomas Daniel
Scientist

CERTIFICATE

This is to certify that the work presented in the thesis entitled **"NOVEL ORGANIC TRANSFORMATIONS USING ULTRASOUND, IONIC LIQUID AND THEIR APPLICATION TOWARDS THE SYNTHESIS OF BIOLOGICAL ACTIVE MOLECULES/INTERMEDIATES"** submitted by **Mr. Sanjay P. Borikar** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such material as obtained from other sources has been duly acknowledged in the thesis.

Dr. THOMAS DANIEL **19th October 2010**
(Research Supervisor)

CANDIDATE'S DECLARATION

I hereby declare that the work presented in the thesis entitled **"NOVEL ORGANIC TRANSFORMATIONS USING ULTRASOUND, IONIC LIQUID AND THEIR APPLICATION TOWARDS THE SYNTHESIS OF BIOLOGICAL ACTIVE MOLECULES/INTERMEDIATES"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, Pune, India under the supervision of **Dr. THOMAS DANIEL.** 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.

Sanjay P. Borikar
Date: 19th October 2010
Division of Organic Chemistry
National Chemical Laboratory
Pune 411 008.

Acknowledgement

First of all I wish to express my deep sense gratitude and respect to my research supervisor ***Dr. Thomas Daniel,*** *for introducing me the fascinating field of Organic chemistry, his valuable guidance and helpful suggestions throughout my Ph.D. programme.*

It is my pleasant duty to express my grateful and sincere thanks to Dr. Vincent Paul and Dr. D. D. Sawaikar for their valuable co-operation during this work.

I am also thankful to Dr. M. K. Gurjar (former head, OCT), Dr. Ganesh Pandey (Head, Division of Organic Chemistry) and Dr. S. Sivaram (Director, NCL) for permitting me to work in NCL.

I extend my gratitude to Dr. R. A. Joshi, Dr. (Mrs) R. R. Joshi, Dr. H. B. Borate, Dr. Gumaste, Mr. I. Shivakumar, Dr. Muthukrishnan, Dr. Mohapatra, Dr. J. M. Gajbhiye, Dr. (Mrs) S. R. Deshpande, Dr. U. R. Kalkote and all other scientists of NCL.

I would also like to acknowledge all the staff members of GC-MS, HPLC, IR, NMR, Mass, Microanalysis, X-ray analysis, Library, Administration and technical divisions of NCL for their assistance during the course of my work.

I take this opportunity to thank to my seniors as well as present labmates is gratefully acknowledged. They made working in the lab enjoyable. I wish to thank division office staff, Mrs. Catherine, Mrs. Kulkarni, Mr. Fernandis, Mr. Ranawade, Mr. R. Tikhe, and Mr. Sayyad for their help whenever needed.

My thanks are due to all my friends of NCL as well as out of NCL for their sincere co-operation. I am also thankful to my parents, family members, relatives and teachers who have contributed a lot for me to reach this stage. The love and support from my wife Mrs. Manjusha and son Mast. Aarnav for the healthy and inspiring environment with out whom I would not been able to stand out as a person and my deep sense of gratitude remains forever. The thesis is a form to pay respect to their attributes.

Last but not least, I am thankful to NCL, CSIR, New Delhi for this opportunity.

NCL, Pune ***Sanjay P. Borikar***

CONTENTS

Section B: Synthesis and characterization of novel ILs based on *n*-alkyl-3-methylpyridinium salts

Section C: Synthesis and characterization of 1,3-di-*n*-butylimidazolium based ionic liquids

Chapter 2: Some useful organic transformations

Section A: Regioselective bromination of anilines and phenols using [BMPy]Br_3 and [BBIm]Br_3 ILs

Chapter 3: Synthesis of biological active molecules

Section A: Total synthesis of (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one: an anticancer agent

Section B: Synthesis of *S*-(-)-Rivastigmine as an acetylcholinesterase inhibitor

ABBREVIATIONS

AcOH	Acetic acid
Ac_2O	Acetic anhydride
$AgBF_4$	Silver tetrafluoroborate
$AlCl_3$	Aluminium chloride
$BnNH_2$	Benzyl amine
brs	Broad (signal)
Bp	Boiling point
BMPy	1-Butyl-3-methylpyridinim
Br_2	Bromine
C_2H_5OH or EtOH	Ethanol
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated chloroform
CH_2Cl_2 or DCM	Dichloromethane
CH_3CN	Acetonitrile
CH_3OH or MeOH	Methanol
COSY	2D-Correlation spectroscopy
$CuCl_2$	Copper chloride
d	Doublet
DDMPy	1-Dodecyl-3-methylpyridinim
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
Et_3N	Triethylamine
$[EtNH_3]NO_3$	Ethylammonium nitrate
g	Grams
GC	Gas chromatography
h	Hours
HBr	Hydrobromic acid

HF	Hydrogen fluoride
HMIm	1-H-3-Methylimidazolium
HMPy	1-Hexyl-3-methylpyridinim
IL	Ionic liquid
IR	Infra red
K_2CO_3	Potassium carbonate
m	Multiplet
Mp	Melting point
M^+	Molecular ion
mg	Milligrams
min	Minute
mL	Millilitre
mmol	Millimole
$NaBH_4$	Sodium borohydrate
NaOAc	Sodium acetate
Na_2SO_4	Sodium sulphate
NMR	Nuclear Magnetic Resonance
P_c	Critical pressure
ppm	Part per million
p-TSA or PTSA	*p*-Toluenesulfonic acid
q	Quartet
r.t. or RT	Room temperature
RTILs	Room temperature ionic liquids
s	Singlet
$SnCl_3$	Tin chloride
t	Triplet
T_c	Critical temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethysilane
VOC	Volatile organic compound

General remarks

- Progress of the reaction was monitored by TLC and visualized by UV absorption by florescence quenching or I_2 staining or by both.
- Solvents for anhydrous reactions were dried by standard procedures. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi rotary evaporator. Silica gel for column chromatography was 60-120 mesh and 230-400 mesh.
- Optical measurements were recorded on a JASCO digital polarimeter.
- All the temperatures are in ^oC (degree celsius). All the melting points and boiling points are in ^oC and are uncorrected. Melting points were recorded on Buchi B-540 melting point apparatus.
- IR spectra were recorded on a Perkin-Elmer infra-red spectrometer model 599-B and model 1620 FT-IR (ν_{max} in cm^{-1}).
- Unless otherwise stated, ^{1}H-NMR spectra were recorded using TMS as internal reference on Bruker AC-200, AC-300, and 400 instruments using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million (ppm) downfield from TMS. The coupling constants (*J* values) are reported in Hertz (Hz*).*
- ^{13}C-NMR spectra were recorded on Bruker AC-200, AC-300, and 400 instruments operating at 50 MHz, 75 MHz and 125 MHz respectively.
- Mass spectra were recorded on Shimadzu GCMS-QP5050 or Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
- GC analysis was carried out on Agilent 6890N; unless otherwise stated.
- Microanalysis was carried out in the micro-analytical section of NCL.
- The compound numbers, scheme numbers and references given in each section separately refer to that particular section only.

Thesis Abstract

Thesis Title

"Novel Organic Transformations Using Ultrasound, Ionic Liquid and Their Application Towards the Synthesis of Biological Active Molecules/Intermediates"

Thesis is divided into three chapters:

CHAPTER-1: Synthesis and characterization of novel ionic liquids (ILs).
CHAPTER-2: Some useful organic transformations.
CHAPTER-3: Synthesis of biological active molecules.

CHAPTER-1: Synthesis and characterization of novel ionic liquids (ILs).

This chapter is divided into three sections. Section A deals with the brief introduction to ionic liquids. Section B and Section C describes the synthesis and their characterization of novel ILs based on *N*-alkyl-3-methylpyridinium and 1,3-di-*n*-butylimidazolium salts.

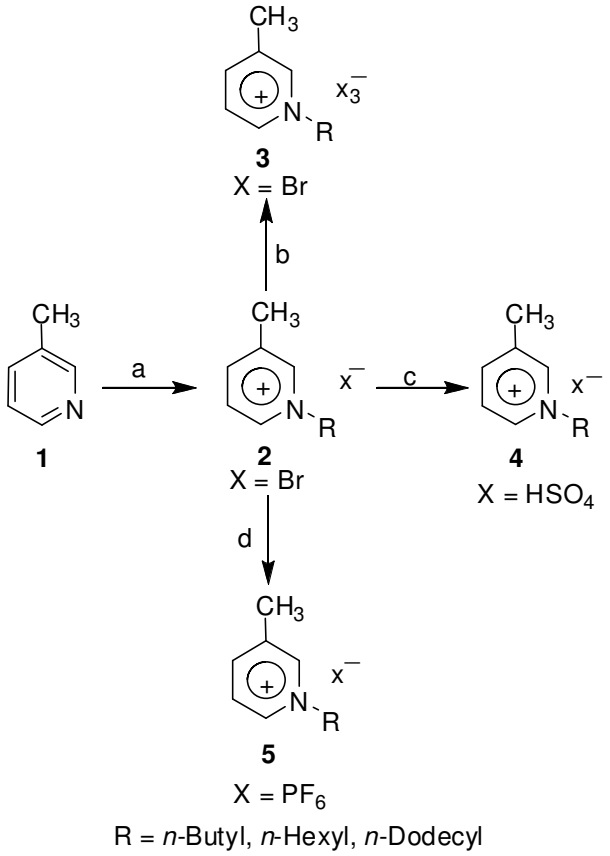
Section A: ***Brief introduction to ionic liquids (ILs):***

The quaternary salts, whose melting point below 100 ^{o}C are commonly called as "ionic liquid". In particular, the salts those are liquid at room temperature are called room-temperature ionic liquids or RTILs. In the past few years, the evolution of a new era in chemical research has entered by ionic liquids as potential 'Green Designer Solvents'[1] as new replacement for volatile organic solvents (VOCs). In recent years, the tremendous growth in research of ionic liquids has resulted in the development of a large number of novel ionic liquids as well as many associated applications in organic reactions, which is useful for organic chemist. Ionic liquids have the potential to increase chemical reactivity, selectivity and thus lead to more efficient processes. They are non-

flammable and due to their low vapor pressure, less toxic than conventional solvents. A brief history of ionic liquids and their emergence as environmentally benign solvents, general method for their synthesis, list of cations and anions reported in the literature, their physico-chemical properties and dependence of it on their structure is described in this section in details. A variety of organic reactions preformed in ionic liquids have been summarized. The new emerging concepts in ILs such as task-specific ionic liquid (TSIL),[2] supported ionic liquid catalysis (SILC) and chiral ionic liquid (CIL)[3] is discussed in this section.

Section B: ***Synthesis and characterization of novel ILs based on N-alkyl-3-methyl pyridinium salts:***

In this section, synthesis and characterization of various ionic liquids based on pyridinium cations has been described. A series of *N*-alkyl substituted -3-methylpyridinium salts (ILs) have been synthesized as shown in **Scheme 1**.



Scheme 1.

Reagents and conditions: (a) RBr, 90 ^{o}C, 5 h, 96%; (b) Br_2, 0 ^{o}C, 2 h, 95%; (c) 97% H_2SO_4, DCM, Reflux, 48 h, 98%; (d) KPF_6, H_2O, RT, 5 h, 92%.

In this series, the anionic groups (X) are kept the same and alkyl group (R) is altered and vice versa. The different tribromide, hydrogen sulphate and hexafluorophosphate salts were synthesized and characterized by spectral and elemental analyses. The density and viscosity of 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 temperature were measured by using TG-DTA techniques.

Table 1: List of ILs synthesized and characterized

Sr. No.	Ionic Liquid	Sr. No.	Ionic Liquid	Sr. No.	Ionic Liquid
1	[BMPy]Br	5	[HMPy]Br	9	[DDMPy]Br
2	[BMPy]HSO_4	6	[HMPy]HSO_4	10	[DDMPy]HSO_4
3	[BMPy]PF_6	7	[HMPy]PF_6	11	[DDMPy]PF_6
4	[BMPy]Br_3	8	[HMPy]Br_3	12	[DDMPy]Br_3

Section C: ***Synthesis and characterization of 1,3-di-n-butylimidazolium based ILs:***

The section deals with the synthesis and physio-chemical properties of 1,3-di-*n*-butylimidazolium [BBIm] based ionic liquids with different anions as shown in **Figure 1**.

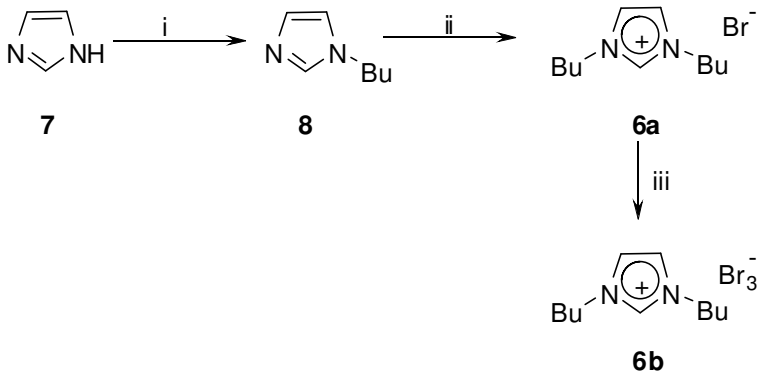
6

X = Br, Br_3, PF_6

Figure 1. 1,3-di-*n*-butylimidazolium [BBIm] based ionic liquids

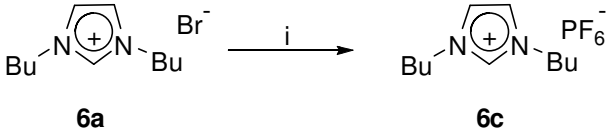
1,3-Di-*n*-butylimidazolium tribromide [BBIm]Br_3 **6b** have been synthesized as shown in **Scheme 2**. The metathesis reaction is generally carried out in water. To the aqueous solution of the 1,3-di-*n*-butylimidazolium bromide **6a**, potassium hexafluorophosphate in water added with stirring. The solution become turns milky immediately due to the precipitation of salt. After 10 h of stirring, the layer containing the ILs with the PF_6 anion separate out and was extracted with ethyl acetate. The organic

layer was washed with water, dilute hydrochloric acid and finally with brine. The removal of solvent gave [BBIm]PF_6 **6c** in high purity (**Scheme 3**).



Scheme 2.

Reagents and conditions: (i) *n*-BuBr, KOH, CH_3CN, 7 h, 93%; (ii) *n*-BuBr, 80 ^oC, 12 h, 96%; (iii) Br_2, 0 ^oC to RT, 2 h, 96%.



Scheme 3.

Reagents and conditions: (i) KPF_6, H_2O, RT, 10 h, 95%.

CHAPTER-2: Some useful organic transformations.

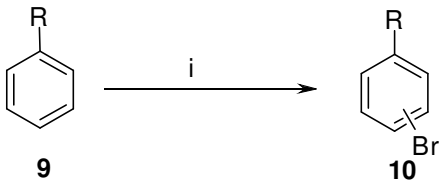
This chapter is divided into four sections. Section A and Section B deals with the bromination of aromatic activating and deactivating substrates such as anilines, phenols, aldehydes and ketones. Section C describes synthesis of 1,1-diacetates under ultrasonic irradiations and Section D deals with *p*-TSA mediated *N*-nitrosation of secondary amines.

Section A: ***Regioselective bromination of anilines and phenols using [BMPy]Br_3 and [BBIm]Br_3 ILs:***

Bromination of anilines and phenols has continued to attract synthetic chemists as the brominated products constitute the subunits of many biologically active molecules.[4] Apart from bromine in presence of ionic liquid as solvent and reagent, a popular and

versatile reagent commonly used for aromatic bromination is tribromide ILs. The different methods reported for aromatic bromination using tribromide ILs such as [BMIm]Br_3,[5] [HMIm]Br_3,[6] pentylpyridinium tribromide,[7] pyridinium tribromide [PHP][8] conferring good regio-selectivities.

We have developed an efficient, rapid and regioselective useful method for bromination of anilines and phenols by reaction of different anilines and phenols with novel 1-butyl-3-methylpyridinium tribromide [BMPy]Br_3[9] and 1,3-Di-*n*-butylimidazolium tribromide [BBIm]Br_3[10] under solvent-free conditions. The reaction conditions are mild and selective bromination of anilines and phenols (**Scheme 4**). In comparison with reported protocols, this method avoids the use of expensive reagents and use of organic solvents. This novel ionic liquid is safer and easier to use. It displayed improved selectivity and better reaction conditions as compared to current bromination techniques. The new functional ionic liquids can be easily recovered and recycled and eliminates toxic bromine vapors.



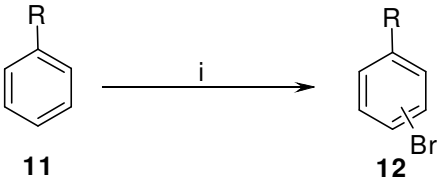
Scheme 4.

Reagents and conditions: (i) [BMPy]Br_3 or {BBIm]Br_3, RT, solvent-free, 88-98 %.

Section B: *Bromination of aromatic aldehydes and ketones using [BMPy]Br_3 and [BBIm]Br_3 ILs*

Brominated aromatic aldehyde and ketone are important compounds that can be used as precursors of natural products.[11] Tribromide ILs are used for the bromination of various aldehydes and ketones instead of bromine, which is harmful and hazardous. Generally, the direct bromination of aromatic aldehydes and ketones has several limitations. Recently, the bromination of aromatic aldehydes catalyzed by ceric ammonium nitrate and silica gel was reported.[12]

This section describes the bromination of aryl aldehydes and ketones in $[BMPy]Br_3$ and $[BBIm]Br_3$ ILs as solvent as well as reagent with good conversion and high selectivity (**Scheme 5**). The reaction completed in less than one hour gave monobrominated product.



R = CHO, COR'

Scheme 5.

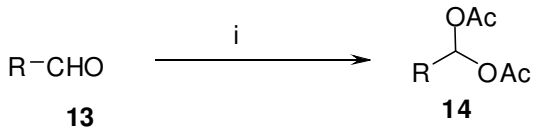
Reagents and conditions: (i) $[BMPy]Br_3$ or $\{BBIm\}Br_3$, RT, solvent-free, 80-98 %.

Section C: ***Synthesis of 1, 1-diacetates under ultrasonic irradiation:***

It covers the introduction to sonochemistry, physicochemical properties, factors influencing sonochemical process, sonochemistry in ionic liquids and the phenomenon of cavitation.[13] Application of ultrasound in chemical transformations may be termed as sonochemistry. The ultrasound mediated reactions in ionic liquids are reviewed. The role of ultrasound in synthetic organic chemistry using catalyst has been well documented in the literature. Sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse.[14]

Acylals (1,1-diacetates) is one of the most frequently and extensively used selective protecting groups for aldehydes in organic synthesis.[15] The standard synthesis of acylals involves the reaction of aldehydes with acetic anhydride using sulfuric acid[16] and a wide range of solvents and catalysts.

This section deals with the synthesis of acylals of a variety of aldehydes with acetic anhydride in IL, 1-butyl-3-methylpyridinium hydrogen sulfate ($[BMPy]HSO_4$) at ambient temperature (30 ^oC) under ultrasonic irradiation (**Scheme 6**).

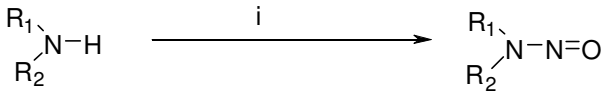


13 **14**

Scheme 6.

Reagents and conditions: (i) $[BMPy]HSO_4$)))), RT, solvent-free, 85-97 %.

Section D: ***p-TSA mediated N-nitrosation of secondary amines:***



15 **16**

Scheme 7.

Reagents and conditions: (i) *p*-TSA, $NaNO_2$, CH_2Cl_2, RT, 85-97 %.

N-Nitrosation of secondary amine is an important unit process in industry and interesting area for mechanistic organic and biological chemists.[17] An effort has been made to combine both the synthetic and mechanistic aspects of nitrosation and trans-nitrosation.[18] These compounds are useful synthetic intermediates for the preparation of various *N*,*N*-bonded functionalities.

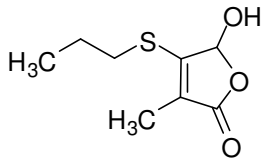
Among the nitrosating agent employed, metal nitrites, either alone or supported on solid matrices enjoyed considerable importance. *N*-Nitrosation of secondary amine using alumina-methanesulfonic acid/$NaNO_2$[19] and tungstate sulfuric acid/$NaNO_2$[20] as nitrosating agent is reported recently. Excellent chemo-selectivities were found to be obtained when the reaction was carried out at ambient conditions.

p-Toluenesulfonic acid would be a superior proton source to all of the reported acidic solid supports or acidic resins for running reactions under mild conditions. *N*-Nitrosation of secondary amines using *p*-toluenesulfonic acid-$NaNO_2$ as nitrosating agent under mild conditions was studied. This method proved excellent chemo-selectivity product and made attractive for large-scale operations.

CHAPTER III: Synthesis of biological active molecules

Section A: ***Total synthesis of (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5H-furan-2-one: an anticancer agent:***

(±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **17,** a biologically active natural product is recently isolated as white solid from the methanolic extracts of cultivated plant *Allium cepa* (green onion) by Parkin and co-workers in 2007 (**Figure 2**).[21] It shows potential cancer chemopreventive constituents directed by the quinone reductase (QR) induction bioassay using murine hepatoma (Hepa 1c1c7) cells. Organosulfur compounds have been shown to induce Phase II enzymes, which is responsible for protection against cancer.



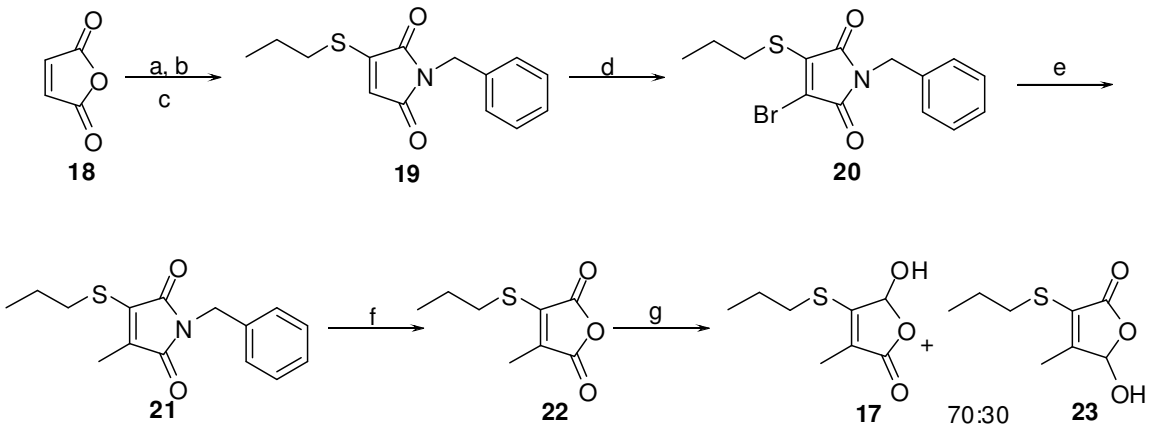
5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one (**17**)

Figure 2.

(±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **17** was found to have potent anticancer activity and exhibited QR and GST activity. The structure was assigned from spectral analysis and molecular formula, ($C_8H_{12}O_3S$ by HRMS). It is a γ-hydroxybutenolide moiety with one sulfur group and one methyl group. The stereochemistry was not assigned by spectral data and no X-ray crystallographic analysis was reported.

Approach I:

According to our first approach for the synthesis of compound **17**, thiomaleimide **19** was prepared in 25% yield from commercially available maleic anhydride **18** as shown in **Scheme 8**. Thiomaleimide **19** was brominated using bromine to furnish bromo thiomaleimide **20**. The resulted compound **20** underwent replacement of methyl group using Gilman reagent (Me_2CuLi) furnished the methyl thiomaleimide **21.**



Scheme 8.

Reagents and conditions: (a) Benzyl amine (1.0 equiv.), glac. AcOH, reflux, 2 h; (b) NaOAc (1.0 equiv.), Br_2 (1.0 equiv.), 0 ^oC to r.t., 2 h; (c)1-propanethiol (1.5 equiv.), DMF, 90 ^oC, 4 h; (d) Br_2 (1.2 equiv.), Et_3N (1.2 equiv.), DCM, 0 ^oC to r.t., 1 h; (e) CuI (1.2 equiv.), 1.6 M MeLi in hexane, dry THF, -78 ^oC, 4 h; (f) 5 N KOH, ethanol, reflux, 2 h; (g) $NaBH_4$ (0.5 equiv.), MeOH, r.t., 10 min.

Alkaline hydrolysis of methyl thiomaleimide **21** using 5N KOH gave anhydride **22**. The anhydride **22** was selectively reduced by $NaBH_4$ in methanol to furnish the ratio of 70-30 target molecule (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **17** as a major isomer and (±)-5-hydroxy-4-methyl-3-propylsulfanyl-5*H*-furan-2-one **23** as minor isomer. The compound **17** was confirmed by X-ray crystallography (**Figure 3**).

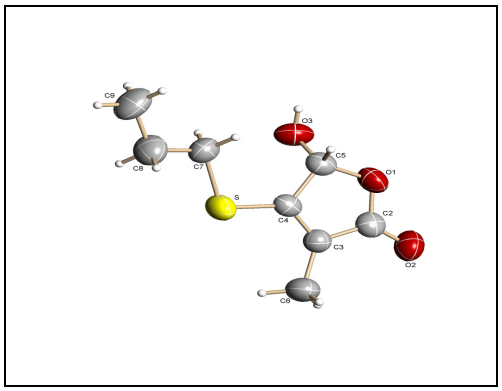
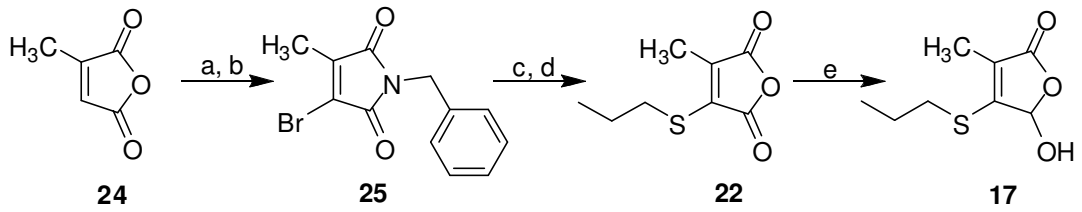


Figure 3. ORTEP diagram of compound **17**

Approach II:

After the synthesis of racemic 5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **17** employing Gilman strategy, it was thought to develop an alternative route using mild reaction conditions. The bromo methylmaleimide **25** was prepared from commercially available citraconic anhydride **24** by bromination as shown in **Scheme 9**. The treatment of **25** with 1-propanethiol and alkaline hydrolysis using 5N KOH as the base in ethanol furnished anhydride **22,** which on selectively reduced by $NaBH_4$ to furnish the desired target molecule **17** as a major isomer.

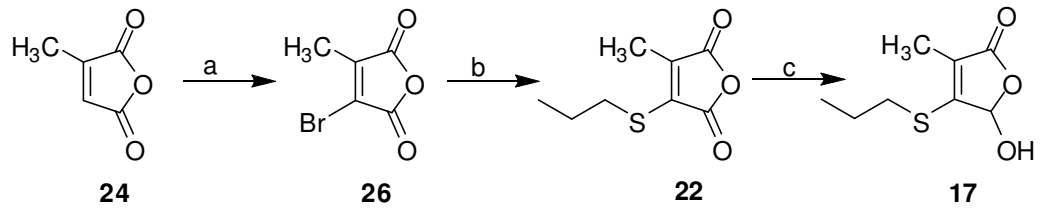


Scheme 9.

Reagents and conditions: (a) Benzyl amine (1.0 equiv.), glac. AcOH, reflux, 2 h; (b) NaOAc (1.0 equiv.), Br_2 (1.0 equiv.), 0 ^oC to r.t., 2 h; (c) 1-propanethiol (1.5 equiv.), DMF, 90 ^oC, 4 h; (d) 5 N KOH, ethanol, reflux, 2 h; (e) $NaBH_4$ (0.5 equiv.), MeOH, r.t., 10 min.

Approach III:

The short route for the synthesis of (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **17** was synthesized in only three steps.



Scheme 10.

Reagents and conditions: (a) Br_2, r.t., 7days; (b) 1-propanethiol (1.5 equiv.), DMF, 90 ^oC, 4 h; (c) $NaBH_4$ (0.5 equiv.), MeOH, r.t., 10 min.

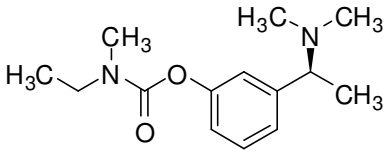
In conclusion, three different synthetic routes for (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **17** have been achieved successfully**.**

Section B: ***Synthesis of S-(-)-Rivastigmine as an acetylcholinesterase inhibitor:***

Rivastigmine hydrogen tartarate **34** is an acetyl cholinesterase inhibitor with brain-region selectivity[22] and a long duration of action and is a "pseudo-irreversible" cholinesterase inhibitor due to slow dissociation of a carbamoyl derivative from the esteratic site of acetyl cholinesterase. It was approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's disease (AD) on April 21, 2000.

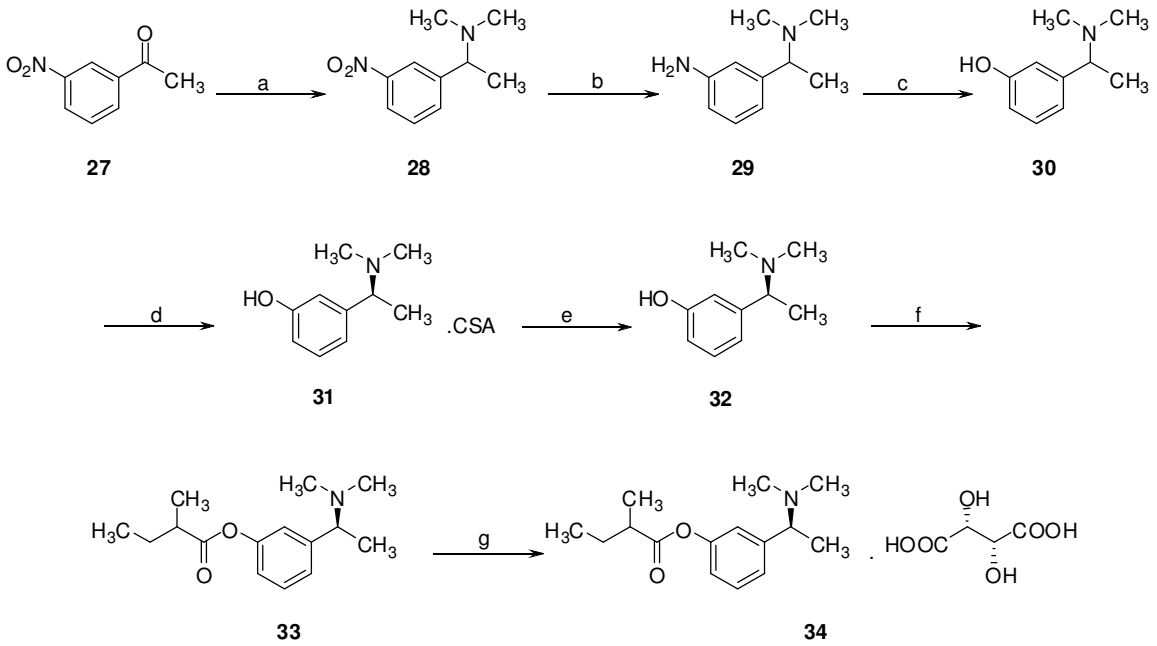
Originally, rivastigmine **33** (**Figure 4**) was synthesized by resolving the racemic rivastigmine with (+)-di-*O,O'*-p-toluoyl tartaric acid monohydrate.[23] However, this method involves three or more recrystallizations to achieve increased enantiomeric excess. Accordingly, the total yield is low and high enantiomeric excess cannot be ensured. Later, several other syntheses of rivastigmine have been reported.[24]

The synthesis of *S*-(-)-Rivastigmine **33** is outlined in the **Scheme 11**. Thus, the reductive amination of 3′-nitroacetophenone **27** using dimethylamine in methanol gave imine product which was reduced to afford 3-(1-(dimethylamino)ethyl)nitrobenzene **28.** The hydrogenation of compound **28** using Raney Ni under pressure at room temperature afforded compound **29**. The diazotization of **29** to the racemic compound **30** was carried out by using 95% H_2SO_4 and $NaNO_2$ in good yields. The compound **30** was then converted to CSA salt **31** using D-10-camphorsulfonic acid monohydrate in EtOH, which was released with Na_2CO_3 to afford chiral compound **32**. Finally, the synthesis of *S*-(-)-rivastigmine **33** was achieved by the condensation of chiral compound **32** with *N*-ethyl-*N*-methyl carbamoyl chloride (EMCC) in good yield and enantiomeric excess, which was treated with L-tartaric acid gave tartarate salt **34.**



S-(-)-Rivastigmine (**34**)

Figure 4.



Scheme 11.

Reagents and conditions: (a) Me_2NH in CH_3OH (2.0 equiv.), $Ti(OiPr)_4$ (2.0 equiv.), r. t., 10 h; $NaBH_4$, r. t., 10 h; (b) Raney Ni, H_2 (pressure 60 psi), r. t., 3 h, CH_3OH; (c) 95% H_2SO_4 (3.3 equiv.), H_2O, $NaNO_2$ (1.1 equiv.), 0 ^oC, 30 min then boiled 1 h; (d) D-10-CSA (1.02 equiv.), C_2H_5OAc, C_2H_5OH, mixed at 80-90 ^oC then cooled; (e) Na_2CO_3 (1.9 equiv.), H_2O-EtOAc (1:1), r. t., 10 min; (f) *N*-ethyl-*N*-methyl carbamoyl chloride (EMCC) (1.2 equiv.), K_2CO_3 (1.2 equiv.), acetone, reflux, 18 h; (g) L-(+)-Tartaric acid (1.0 equiv.), acetone, reflux, 1 h and then cooled.

References:

1. Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391.
2. Sang-gi, L. *Chem. Commun.* **2006**, 1049.
3. Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281.
4. Kuroboshi, M.; Waki, Y.; Tanaka, H. *J. Org. chem.* **2003**, *68*, 3938.
5. Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, *17*, 2809.
6. Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun*. **2004**, *22*, 2536.
7. Salazar, J.; Dorta, R. *Synlett* **2004**, *7*, 1318.
8. Reeves, W. P.; King, R. M. *Synthetic Commun.* **1993**, *23*, 855.
9. Borikar, S. P.; Daniel, T.; Paul, V. *Tetrahedron Lett*. **2009**, *50*, 1007.
10. Borikar, S. P.; Daniel, T.; Paul, V. *Synthetic Commun.* **2010**, *40*, 647**.**

11. Léo, P. -M.; Morin, C.; Philouze, C. *Org. Lett.* **2002**, *4*, 2711.
12. Patwari, S. B.; Baseer, M. A.; Vibhute, Y. B.; Bhusare, S. R. *Tetrahedron Lett.* **2003**, *44*, 4893.
13. (a) Adewuyi, Y. G. *Ind. Eng. Chem. Res.* **2001**, *40*, 4681; (b) Ultrasonics, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Wiley NewYork, **1983**, *23*, 462.
14. Lorimer, J.; Mason, T. *Chem. Soc. Rev.* **1987**, *16*, 239.
15. Kochhar, K. S.; Bal, B. S.; Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. *J. Org. Chem.* **1983**, *48*, 1765.
16. Gregory, M. J. *J. Chem. Soc.* **1970**, 1201.
17. (a) Williams, D. L. H.; *Cambridge University Press: Cambridge,* **1988**, 77; (b) Williams, D. L. H.; *John Wiley & Sons Ltd, New York,* **1996**, 665.
18. Garcia-Rio, L.; Leis, J. R.; Moreira, J. A.; Norberto, F. *J. Org. Chem.* **2001**, *66*, 381.
19. Niknam, K.; Zolfigol, M. A. *Synthetic Commun.* **2006**, *36*, 2311.
20. Karami, B.; Montazerozohori, M.; Habibi, M. H. *Bull Korean Chem. Soc*. **2005**, *26*, 1125.
21. Parkin, K. L.; Xiao, H. *Phytochemistry* **2007**, *68,* 1059.
22. Polinsky, R. J. *Clin. Therapeutic* **1998**, *20,* 634.
23. Enz, A. GB Patent 2203040, **1987**.
24. (a) Abhay, G.; Mangesh, M.; Sanjay, P. R. WO2005061446, **2005**; (b) Boeaio, A. A.; Pytkowicz, J.; Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260; (c) Hana, S.; Josef, H.; Stanislav, S. WO2004037771, **2004**; (d) Ma, D. W.; Pan, Q. B.; Pan, S. WO2007025481, **2007**; (e) Garrido, M.; Vicente, J.; Montserrat, A.; Miquel, J. M. J. WO2007014973, **2007**; (f) Hu, M.; Zhang, F. -L.; Xie, M. -H. *Synthetic Commun.* **2009**, *39*, 1527; (g) Mangas-Sanchez, J.; Rodríguez-Mata, M.; Busto, E.; Gotor-Fernandez, V.; Gotor V. *J. Org. Chem.* **2009**, *74*, 5304.

Chapter I

Synthesis and characterization of novel ionic liquids (ILs)

Section-A

Brief introduction to ionic liquids (ILs)

1.1.1 Introduction

'Green chemistry' or 'Sustainable technology' 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 or processes such as use of ionic liquids - some old and some new.[1]

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

Chemistry undeniably plays an important part of our daily lives. Food and drink has been made safe to consume; the whole area of pharmaceuticals has allowed the development and synthesis of new cures for illnesses and diseases; the development of cosmetics has enabled us to beautify and admire our appearances; all as a result of chemistry. However, in the chemical industry, hundreds of tones of hazardous waste are released to the air, water, and land every hour of every day. In particular, solvents are used in large quantities in fine-chemical and pharmaceutical industries. Therefore, solvent define a major role of the environmental performance of a process and also impact on safety and health issues. The continuously increasing air pollution has brought about changes in the global climate. The drive towards clean technology in the chemical industry with increasing emphasis on waste reduction at source will require a high level of innovation and new technology. The idea of "green" solvents expresses the goal to minimize the environmental impact resulting from the use of solvents in chemical production. Recently, four directions towards the green solvents have been developed: (i) substitution of hazardous solvents with ones that show better EHS (environmental, health and safety) properties, such as increased biodegradability or reduced ozone depletion potential;[2-4] (ii) use of "bio-solvents" i.e. solvents produced with renewable resources such as ethanol produced by fermentation of sugar-containing feeds, starchy feed

materials or lignocelluloses materials[5] (this substitution of petrochemically fabricated solvents leads to an avoidance of fossil resource use and fossil fuel CO_2 emissions to the environment); (iii) substitution of organic solvents either with supercritical fluids that are environmentally harmless (e.g. the use of supercritical CO_2 in polymer processing[6-9] avoids the use of chlorofluorocarbons, and thus reduces ozone depletion); (iv) use of non-volatile and thermally stable ionic liquids as solvents in place of traditional industrial solvents, most of which are volatile organic compounds (VOCs). Replacement of conventional solvents by ionic liquids would prevent the emission of VOCs, a major source of environmental pollution. Ionic liquids can be designed to be environmentally benign, with large potential benefits for sustainable chemistry.

The ideal solvent should have negligible vapor pressure, high boiling point and be non-toxic. They must have capacity to dissolve wide range of organic, inorganic and organometallic compounds. It should be chemically and physically stable, recyclable, reusable, inexpensive and easy to handle. In addition, solvents that allow more selective and rapid transformations will have a significant impact.

1.1.2 Alternative reaction media to ionic liquids

The use of these alternative reaction media is mainly aimed at replacing the toxic volatile organic solvents to have a negative impact on the environment.

1.1.2.1 Solvent-free synthesis

It seems that the easiest way to prevent any form of solvent emission is to use no solvent at all. There have been many attempts to perform various reactions using no solvent at all.[10] Advantages of solvent-free synthesis include reduced pollution, low costs, easy handling and simple processes. These advantages are quite important especially for industry. However, there are many disadvantages in performing solvent-free synthesis, for one strong exotherms can occur which can be difficult to deal with.

1.1.2.2 Perfluorinated (fluorous) solvents

The perfluorinated hydrocarbons are recently found application in organic chemistry as a useful class of solvents. The fluorous compounds were defined as being

compounds that are highly fluorinated and based upon sp^3-hybridized carbons. Perfluorinated solvents such as perfluoroalkenes, perfluoroalkyl ethers and perfluoroalkyl amines are generally chemically benign and environment-friendly. Their physical properties make them unique for their use as reaction media. Since, perfluorocarbons are immiscible with many common organic solvents; they are suitable for the formation of biphasic systems. This overview describes the utilization of perfluorocarbons as reaction media in many organic and catalytic reactions.[11-12]

Perfluorinated molecules have unique properties, such as high density, a very low solubility both in water and in most organic solvents, high stability (mainly due to the stability of the C-F bond) and low solvent strength,[13] although they are miscible at higher temperature. The poor solubility of perfluorinated solvents can be explained based on their low surface tensions, very weak van-der-Waals interactions, high densities and low dielectric constants.

1.1.2.3 Supercritical fluids

A supercritical fluid (SCF) is defined as a material which can be either liquid or gas, used in a state above the critical temperature (T_c) and critical pressure (P_c); where gases and liquids can co-exist. It shows unique and tunable physicochemical properties that are different from those of either gases or liquids under standard conditions. In recent years, supercritical carbon dioxide ($scCO_2$) has been receiving increasing demand as an alternative reaction medium. Several features of $scCO_2$ make it an interesting solvent in the context of green chemistry and catalysis. The critical pressure and temperature for carbon dioxide are moderate (73 atm and 31.1 ºC) and these conditions are easily achieved in laboratory.

The advantages related to the use of $scCO_2$ are numerous and were clearly addressed in a recent article[14]: CO_2 is non-flammable and less toxic than most organic solvents; it is relatively inert towards reactive compounds and is a natural, unregulated solvent, with high availability; it can be easily removed by depressurization, which renders it an easy separation from the products of a reaction. Other advantages include high gas solubility, weak solvation, high diffusion rates and good mass transfer. Furthermore, the selectivity of a reaction can be dramatically changed, when conducted

in a supercritical fluid as compared to traditional organic solvents. Supercritical fluids have also been used to describe as new solvents for organic and catalytic reactions.[15-16] 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.

1.1.2.4 Poly(ethylene glycol) – PEG

Poly(ethylene glycol) is the linear polymer formed from the polymerization of ethylene oxide. PEG usually indicates the polyether of molecular weight less than 20,000 and is known to be inexpensive, thermally stable, recoverable, biologically compatible and non-toxic.[17] Furthermore, PEG and its monomethylethers have a low vapor pressure, non-flammable, simple work-up procedures and recyclable. For this reason, PEG is considered to be an environmentally benign alternative media for organic reactions.

Recently, PEG is used as green solvent in many organic reactions[18] with low molecular weights (< 2000) because it is either liquid at room temperature or has a low melting point. Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter its properties can not be easily tuned. One of the major drawbacks in its use in organic reactions that also applies to ionic liquids is the inconvenience of using organic solvents to extract the products, even though $scCO_2$ can also be used in both cases. Probably due to the popularity of other alternative solvents, especially ionic liquids, there are only a few examples in the literature that uses PEG as solvent in organic reactions.

1.1.2.5 Water

Water is a universally greener solvent in terms of availability, low cost, safety and environmentally benign. In the early 1980s, Breslow[19] and Grieco[20] have worked on the use of water as solvent limited to hydrolysis reaction because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., organometallics). Since then, many reactions have reported in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results. For instance, the rates and stereo-selectivities of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. The use of organic co-

solvents or surfactants helps to increase the solubility of non-polar reactants in water by disrupting the strong hydrogen-bond network of pure water.[21] The discovery that Lewis acids, especially some metal triflates, can efficiently catalyze reactions in water also contributed to popularize it as solvent in organic reactions.[22]

1.1.2.6 Ionic liquids (ILs)

In the past three decades, ionic liquids have been used as "green solvents" for many organic transformations such as transition metal catalysis rather than traditional organic solvents. Ionic liquids (ILs) are a liquid containing only ions (cations and anions), but it is different from molten salts.[23] Recently, molten salts and ionic liquids has been distinguished on the basis of melting point criterion. Molten salts are usually defined as a high melting, highly viscous and highly corrosive liquid, while ionic liquids are defined as pure compounds, consisting only of cations and anions (i. e. salts), which melt at or below 100 ^{o}C and have lower viscocities.[24] Free-flowing ionic liquid at room temperature are called room temperature ionic liquids (RTILs).

The great interest for such compounds relies on the fact that they posses several attractive properties such as negligible vapor pressure, chemical and thermal stability, non-flammability, high ionic conductivity, wide electrochemical potential window and moreover the ability to act as catalysts. In addition, many of their physicochemical properties are changed substantially by variation of the cation and the anion; thus, they are "tunable" to the desired reaction. For this reason, they have been referred to as "designer solvents''.[25]

1.1.3 Brief history of Ionic Liquids

The history of ionic liquids began in 1914; Walden reported the first synthesis of room temperature molten salt (i. e., ethylammonium nitrate salt).[26] He reported the physical properties of ethylammonium nitrate, $[EtNH_3]NO_3$, which has a melting point of 8 ºC, formed by the reaction of ethylamine with concentrated nitric acid. This salt is liquid at room temperature; but usually it contains a small amount of water (200-600 ppm).

Hurley and Weir[27] have developed the first ionic liquid with chloroaluminate ions such as ethyl pyridinium bromide/$AlCl_3$ for their use in electroplating aluminium in 1948 at the Rice Institute. It was prepared by mixing and warming 1-ethylpyridinium bromide with aluminum chloride ($AlCl_3$). The use of chloroaluminate ionic liquids as electrolyte attracted interest from both fundamental and applied research. In 1967, Swain *et al.* described the use of tetra-*n*-hexylammonium benzoate as a solvent for kinetic and electrochemical investigation.[28] Room temperature ionic liquids (RTILs) were more popular in general audience with the reopening of development in this area by the groups of Osteryoung *et al.*[29] and Hussey *et al.*[30] in 1970s and 1980s respectively. They carried out extensive research on organic chloride-aluminium chloride room temperature ionic liquids and the first major review on room temperature ionic liquids was written by Hussey.[31] The ionic liquids based on $AlCl_3$ can be regarded as the first generation of ionic liquids.

The first report in which ionic liquids were described as new reaction media and catalyst for Friedel–Crafts reaction in 1986.[32] In 1990, the use of ionic liquids as solvents for homogeneous transition metal catalysts was described for the first time by Chauvin *et al.*, who reported the dimerisation of propene by nickel complexes dissolved in acidic chloroaluminate melts[33] and Osteryoung *et al.* reported the polymerization of ethylene by Ziegler–Natta catalysts.[34]

The hygroscopic nature of $AlCl_3$ based ionic liquids has delayed the progress in their use in applications of organic reactions; since, they must be prepared and handled under inert gas atmosphere. Thus, the synthesis of air and moisture stable ionic liquids, which are considered as the second generation of ionic liquids, attracted further interest in the use of ionic liquids in various fields. In 1992, Wilkes and Zaworotko[35] reported the first air and moisture stable ionic liquids based on 1-ethyl-3-methylimidazolium cation with either tetrafluoroborate or hexafluorophosphate as anions. Unlike the chloroaluminate ionic liquids, these ionic liquids could be prepared and safely stored outside of an inert atmosphere. Generally, these ionic liquids are water insensitive; however, the exposure to moisture for a long time can cause some changes in their physical and chemical properties. This is due to the formation of HF as a result of decomposition of the ionic liquid in presence of water. Therefore, ionic liquids based on

more hydrophobic anions such as trifluoromethanesulfonate ($CF_3SO_3^-$), bis-(trifluoromethanesulfonyl)imide [$(CF_3SO_2)_2N^-$] and tris-(trifluoromethanesulfonyl) methide [$(CF_3SO_2)_3C^-$] have been developed.[36–38] These ionic liquids have received extensive attention not only because of their low reactivity with water but also because of their large electrochemical windows. Usually, these ionic liquids can be well dried with the water contents below 1 ppm under vacuum at temperatures between 100-150 ºC.

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

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

Welton has published many papers dealing with the applications of ionic liquids as solvents for synthesis and catalysis. He focuses on how the ionic liquids interact with solute species to affect their reactivity and he works on replacing environmentally damaging solvents with more benign alternatives. He is also the author of one of the most cited papers,[39] which was cited 3307 times up to october 2010.

Wasserscheid is an active member of the ionic liquid community and focuses on the preparation and characterization of ionic liquids for use in the biphasic catalysis. For example, he could show that the use of hexafluorophosphate ionic liquids allows selective, biphasic oligomerization of ethylene to 1-olefins. Together with Welton, he edited a very important book entitled “Ionic Liquids in Synthesis” which presents the synthesis and physicochemical properties of ionic liquids as well as their use in catalysis, polymerization, and organic and inorganic synthesis.[40]

MacFarlane works on the synthesis of new air and water stable ionic liquids with the purpose of employing such ionic liquids as indicators for sensing and displaying environmental parameters such as humidity. This process is controlled by the color

change of the ionic liquids where they are synthesized with either a colored cation or anion, so that the ionic liquids themselves are sensors. Also, he has published many papers on the use of ionic liquids in electropolymerization and in batteries.

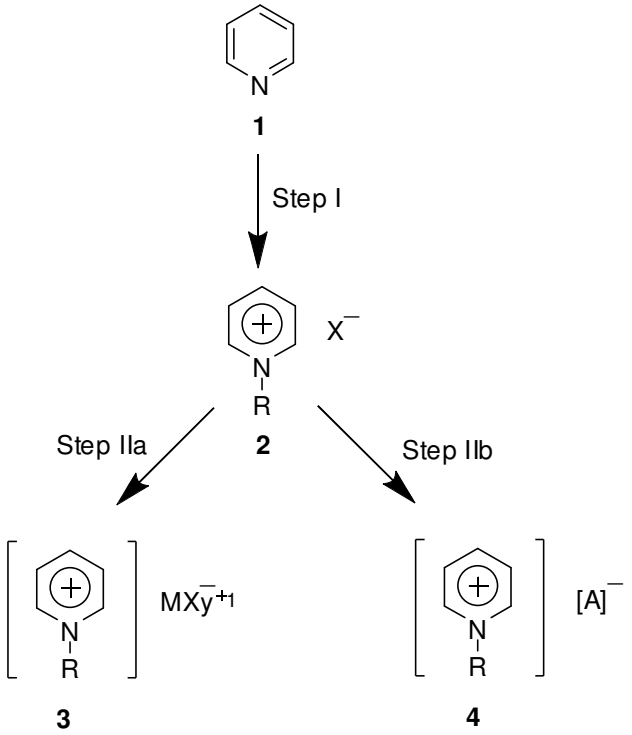
Ohno concentrates his work on the synthesis of a series of polymerizable ionic liquids and their polymerization to prepare a new class of ion conductive polymers. For example, he prepared polymer electrolytes with high ionic conductivity and good elasticity by mixing nitrite rubber [poly(acrylonitrile-cobutadiene) rubber] with the ionic liquid *N*-ethylimidazolium bis(trifluoromethanesulfonyl)imide. Recently, he edited a book titled "Electrochemical Aspects of Ionic Liquids" which introduces some basic and advanced studies on ionic liquids in the field of electrochemistry.[41]

Davis, Jr. introduced the concept of ''task-specific ionic liquids'' (TSILs) in the field of ionic liquids. TSILs are ionic liquids in which a functional group is incorporated enabling the liquid to behave not only as a reaction medium but also as a reagent or catalyst in some reactions or processes.[42]

Abbott has recently developed a range of ionic compounds, which are fluid at room temperature. These ionic liquids are based on simple precursors such as choline chloride (vitamin B_4); which is cheap and produced on a multitonne scale and hence these ionic liquids can be applied to large scale processes for the first time. Recently, he edited a book titled "Electrodeposition from Ionic Liquids" which introduces the applications of ionic liquids on electrodeposition of metals.[43]

1.1.4 Synthesis of Ionic Liquids

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



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

Figure 1. General synthetic paths for pyridinium based ILs

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

1.1.5 Cations

Innovations in the field of ILs are being reported continuously in the form of novel cation and anion combinations. The cations are generally bulky, unsymmetrical

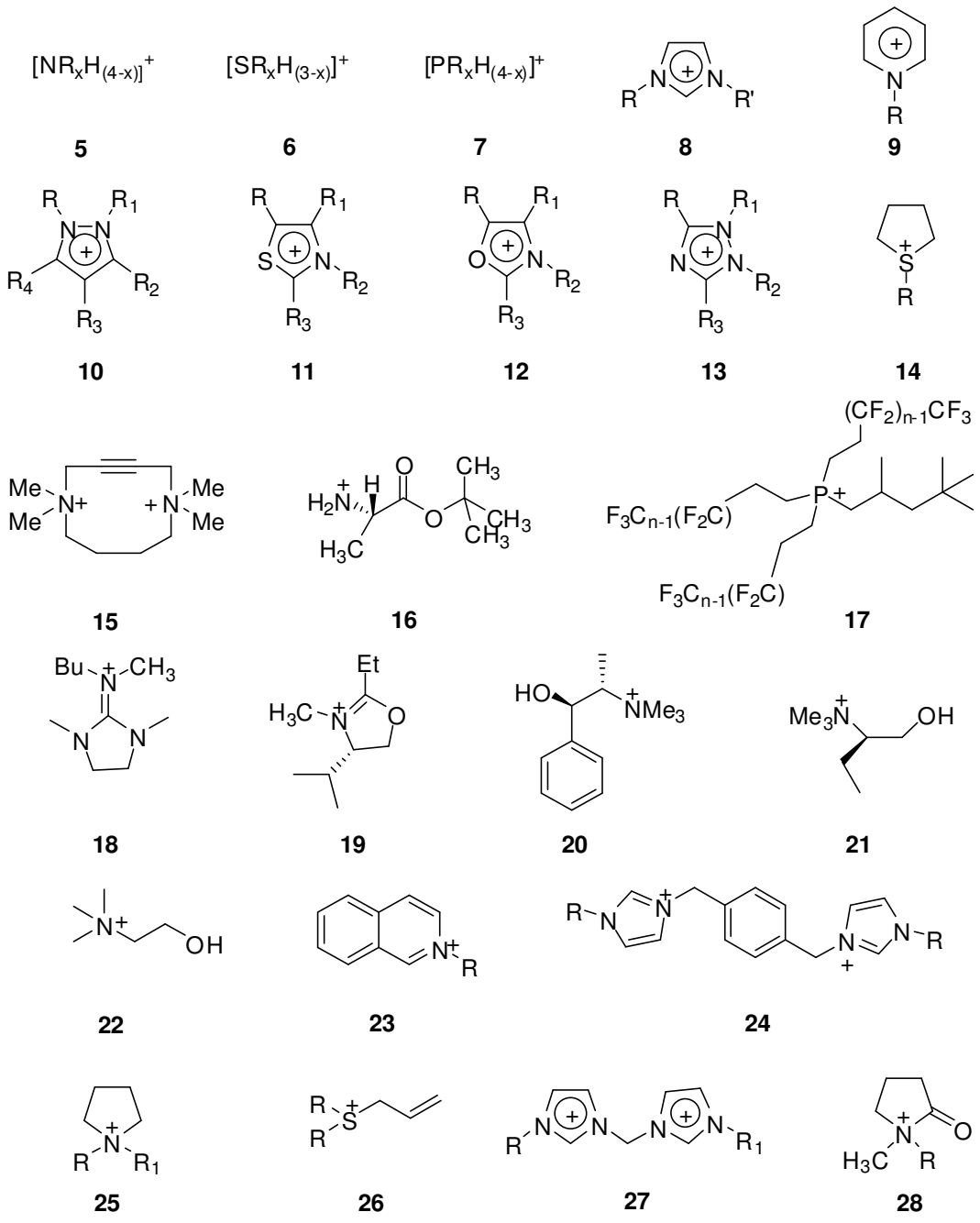


Figure 2. Different types of organic cations in ILs

ammonium or phosphonium salts, or heteroaromatics, with low symmetry, weak intermolecular interactions and lower charge densities. Those described in the literature are based on tetraalkylammonium (**5**),[44] trialkylsulphonium (**6**),[45] tetraalkylphosphonium (**7**),[46] 1,3-dialkylimidazolium (**8**),[47] *N*-alkylpyridinium (**9**),[48] *N*,*N*-dialkylpyrazolium

(**10**),[49] *N*-alkylthiazolium (**11**),[50] *N*,*N*-dialkyloxazonium (**12**),[51] *N*,*N*-dialkyltriazolium (**13**),[52] *S*-alkylthiolanium (**14**),[53] organic polycations such as (**15**)[54] and (**27**),[55] Warner's chiral cation (**16**),[56] highly fluorinated phosphonium (**17**),[57] cyclic hexaalkylguanidinium (**18**),[58] Wasserscheid's chiral cations (**19**, **20** and **21**),[59] cholinium (**22**),[60] isoquinolinium (**23**),[61] dimeric imidazolium (**24**),[62] *N*,*N*-dialkylpyrrolidinium (**25**),[63] sulfonium (**26**) [64] and pyrrolidonium (**28**)[65] (**Figure 2**).

Besides organic cations based ionic liquids, lithium salts are increasingly being developed particularly for secondary batteries and for storage of energy. They have often lower lattice energy and therefore, lower melting points than their neighboring elements in the periodic table. As an example the mixture of LiCl and $EtCl_2$ gives a liquid, on a large range of composition, at temperatures lower than 0 ºC.[66]

1.1.6 Anions

The anion chemistry has a large influence on the properties of IL. The most commonly employed IL anions are polyatomic inorganic species. The introduction of different anions has become more popular as an increasing number of alternatives are being discovered. In the future, list of cations and anions will be extended to a nearly limitless number. Various combinations of cations and anions have provided finely designed ionic liquids for different applications. Various anions reported in the literature are listed in **Table 1**.

Table 1. A list of some anions in ILs and their references

Sr. No.	Anions	Ref.	Sr. No.	Anions	Ref.
1	$AuCl_4$	67	18	$AlCl_4$	76
2	$CF_3OCF_2CF_2BF_3$ [TFSA]	68	19	$ZnCl_3$	40
3	HBr_2	69	20	$CuCl_2$	40
4	H_2Br_3	69	21	$SnCl_3$	40
5	Br_3	70	22	$N(EtSO_2)$	40
6	SbF_6	72	23	$N(FSO_2)$	77
7	CH_3CO_2	35	24	$C(CF_3SO_2)_3$	77
8	NO_3	35	25	CH_3SO_3	40

9	NO_2	35	26	$N(CN)_2$	78
10	CF_3SO_3	36	27	halides	79
11	$(CF_3SO_2)_2N$ [NTf_2]	71	28	Al_2Cl_7	40
12	CF_3CO_2	36	29	Al_3Cl_{10}	40
13	$B(Et_3Hex)$	73	30	Au_2Cl_7	40
14	OTs	74	31	Fe_2C_{17}	40
15	Carborane anion	75	32	Sb_2F_{11}	40
16	BF_4	35	33	(Glycerol)borate anion	80
17	PF_6	81	34	HSO_4	82

1.1.7 Purity of ionic liquids

The physico-chemical properties of ionic liquids can change by the presence of impurities arising from their preparation.[83] Purity of ILs is a major factor, when using ILs as reaction media, especially for transition metal catalysis. Although, a very few reports are available on "distillable ionic liquid",[84] in most of these reported methods neither the ILs were distilled nor they were recrystallized. Also, the purification of ILs via column chromatography is tricky. As a consequence, once the ILs has formed in the course of the synthesis, purification can become a nuisance. The main contaminations in ILs are halide anions, organic bases that are generally produced from unreacted starting material and water.[85] A colorimetric method has been recently developed to determine the level of unreacted alkyl imidazole (<0.2 mol%) in the ionic liquid.[85] Halide impurities can have a detrimental effect on transition metal catalyzed reactions. Halide impurities can be removed by washing of ILs with water and also by titration with $AgBF_4$ which can also be, of course quite expensive and may lead to silver impurities in ILs. Alternatively, methods of preparations have been proposed to avoid the use of halide containing starting materials.

Gallo *et al.*[86] have systematically studied the influence of halide impurities on catalytic Michael addition reactions. They have found that the system is strongly sensitive to the amount of halides present in the ILs, inhibiting the activity of the transition metal catalyst. Furthermore, the total amount of halide impurities in different IL batches is variable even if the same synthetic protocol is followed. For a palladium-

catalyzed copolymerization of styrene and carbon monoxide, Klingshirn *et al.*[87] came to the same conclusions. Daguenet and Dyson[88] explained this fact as a consequence of the extremely weak interactions between the halide anion and the imidazolium cation, through which the dissociation of the halide from a transition metal complex can become thermodynamically disfavored in ILs.

The second major purity problem is "color." Most ILs are colorless in pure form, but in reality, they are more likely to be pale yellow to dark orange. The origin of this is still somewhat unclear, since these (often trace) impurities are not detectable via NMR or IR spectroscopy. Most likely, the color is due to degradation of the starting material. By taking some precautions, colourless ILs can be obtained by (1) using freshly distilled starting material for the synthesis; (2) performing the alkylation step at the most modest temperatures possible (i.e., avoiding overheating) under a protective atmosphere, and (3) by cleaning the final IL product through stirring with activated charcoal.[89]

The third issue regarding the purity is the amount of water present in the ILs. This is not only a problem for running reactions with water-sensitive compounds, but the amount of water can change the physical properties of an IL dramatically.[90] Therefore, it is always advisable to dry ILs at elevated temperature in high vacuum with vigorous stirring overnight before using them. Stirring is crucial here because of high viscosities and because the water desorption takes place only via the surface of the liquid phase. In critical cases, the amount of water present can additionally be checked by IR spectroscopy[90] or, of course, by standard Karl Fischer titration. In some cases, e.g. PF_6 based salts; traces of water can generate the decomposition of the anion and the formation of HF. Organic solvents are usually purified by distillation before use, this method is not suitable to clean up ionic liquids, due to their non-volatile nature. Due to these reasons, the highest purity possible must be attained during synthesis itself.

1.1.8 Physicochemical properties of ILs

A fundamental understanding must be established for the chemical and physical properties of new solvent before incorporation into an industrial application. Optimal physical properties would include low viscosity to facilitate mixing and a large density difference in comparison to other process fluids to hasten phase separation. Chemically,

the solvent would have a high capacity for the solute. To encourage widespread use of the solvent, it would be inexpensive to produce, recyclable, and robust solvents to endure various processing environments.

The physical properties such as melting point, boiling point, density, surface tension and viscosity are related to the mechanics and engineering components associated with a process. For example, density, viscosity and surface tension will determine important parameters including rates of liquid–liquid phase separation, mass transfer, power requirements of mixing and pumping. Other physical properties, such as refractive index are related to certain chemical properties despite providing a bulk property description. Chemical properties such as the structuredness, polarity, and relative hydrogen bonding, donating and accepting ability are more obviously related to the molecular chemistry of their application.[91] Due to intermolecular interactions, these parameters measure, these chemical properties are believed to play a major role in determining solubilities, partition constants, and reaction rates.

The physico-chemical properties of ILs can be varied by the selection of suitable cations and anions. Thus their properties can be adjusted to suit the requirements of a particular process. Because of this reason, the ILs has been referred to as "designer" solvents.

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

1.1.8.1 Melting point

The most important property of the IL is the melting point. The melting point of IL lies below 100 °C. With a given cation the choice of anion has a strong effect on the melting point.[92] The coordinating and hydrophilic anions like halides lead to high melting points, whereas weakly coordinating and hydrophobic anions result in low melting points. Also increase in size of the anion with same charge leads to a decrease in melting points (**Table 2**).

Both cations and anions contribute to the low melting points of the ILs. Cation size and symmetry make an important impact on the melting points of ILs. Symmetrically substituted cations can crystallize easily and therefore often lead to ionic solids with high melting point. Low symmetry in substitution can prevent easy crystallization, resulting in low melting points.

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

Entry	**Pyridinium/Imidazolium salts**	**MP (^{o}C)**	**Ref.**
1	[EMIm][Cl]	87	30[a]
2	[EMIm][NO_2]	55	34
3	[EMIm][NO_3]	38	34
4	[EMIm][BF_4]	15	30c
5	[EMIm][PF_6]	62	30c
6	[EMIm][$(CF_3SO_2)_2N$]	-3	30c
7	[BMPy][$N(CN)_2$]	5	93
8	[BMPy][PF_6]	42	94
9	[BPy][Cl]	130-131	95
10	[BPy][Br]	105	96
11	[BPy][BF_4]	15	97
12	[HPy][Br]	46	a
13	[HPy][NTf_2]	0	96
14	[EPy][Cl]	116-118	95
15	[EPy]Br]	117-121	b
16	[EPy][PF_6]	103	98
17	[BPy][PF_6]	71-73	98
18	[HPy][PF_6]	42	98
19	[OPy][PF_6]	65	98
20	[HDPy][PF_6]	117-119	98
21	[BnPy][PF_6]	103	98

[a]Merck Chemical Company, [b]Acros Organics

By variation of the alkyl chain length in the cation, fine-tuning of the melting point can be achieved. Longer the alkyl chain, lower is the melting point, but only up to a certain extent (rule of thumb for pyridinium cations: C_8 gives the lowest melting points) (**Table 3, entry 3**).[94] Beyond that, prolongation of the alkyl chain raises the melting point again. In addition to this, a good distribution of charge in cation and weak intermolecular interaction such as weak hydrogen bonding are also responsible for the lowering of melting points of ILs. Comparison of the melting points of different salts clearly illustrate that, cation size, symmetry, charge distribution and alkyl chain length affects the melting points of ILs (**Table 3**).

Table 3. Melting points of various salts.

Entry	**Salts**	**Melting point (^oC)**
1	NaCl	803
2	KCl	772
3	[OPy]Br	28-30
4	[DPy]Br	30-32
5	[DDPy]Br	73-75
6	[TDPy]Br	58-60
7	[HDPy]Br	63
8	[ODPy]Br	65-67
9	[Epy]Br	73-75
10	[MMIm]Cl	125
11	[EMIm]Cl	87
12	[BMIm]Cl	65

1.1.8.2 Viscosity

Viscosity is a key property of ionic liquids. Ionic liquids tend to have higher viscosities than conventional solvents, but the value of the viscosity varies tremendously with chemical structure, composition, temperature and the presence of solutes of impurities. Viscosities are ranging from 10 mPa·s to about 500 mPa·s at room temperature A high viscosity may produce a reduction in the rate of many organic

reactions and a reduction in the diffusion rate of the redox species. Current research for new and more versatile IL is driven, in part, by the need for materials with low viscosity. The viscosity of ILs is determined by van der Waals forces and hydrogen bonding. In *n*-butylmethylimidazolium IL, when triflate anion was displaced with $(n\text{-}C_4F_9SO_3)^-$ ion and from the trifluoroacetate ion to $(n\text{-}C_3H_7COO)^-$ ions. Comparison of the viscosities of $[BMIm]CF_3SO_3^-$ with $[BMIm](CF_3SO_2)_2N^-$, reveals a lower viscosity despite stronger van der Waals interactions for ILs with $(CF_3SO_2)_2N^-$ ion as shown in **Table 4**. In this case, the complete suppression of hydrogen bonding over compensates for the expected increase in viscosity. Electrostatic forces may also play an important role. Alkyl chain lengthening in the cation and fluorination in the cation/anion leads to an increase in viscosity.[99] This is due to stronger van der Waals forces between cations leading to increase in the energy required for molecular motion. Also, the ability of anions to form hydrogen bonding has a pronounced effect on viscosity.

Table 4. Viscosity of different pyridinium and imidazolium based ILs at 25 ^oC.

Entry	Ionic Liquid	Viscosity (mPa·s)
1	$[BMPy][NTf_2]$	63
2	$[HMPy][NTf_2]$	85
3	$[OMPy][NTf_2]$	112
4	$[BMIm][CF_3SO_3]$	90
5	$[BMIm][n\text{-}C_4F_9SO_3]$	373
6	$[BMIm][CF_3CO_2]$	73
7	$[BMIm][n\text{-}C_3F_7CO_2]$	182
8	$[BMIm][PF_6]$	450
9	$[BMIm][BF_4]$	233
10	$[BMIm][NTf_2]$	52
11	$[BPy][BF_4]$	66
12	$[BPy][NTf_2]$	35
13	$[HPy][NTf_2]$	48
14	$[OPy][NTf_2]$	63

The fluorinated anions such as NTf_2^- and PF_6^- form viscous ionic liquids due to the formation of hydrogen bonding. In general, all ionic liquids show a significant decrease in viscosity as the temperature increases.[100] As is evident from **Table 4**, viscosity increases with increasing alkyl chain length, also fluorination in anions causes increases in viscosity. Strength of hydrogen bonding decreases in the order $[PF_6]^-$ >$[BF_4]^-$ >$[NTf_2]^-$ which results in decrease in viscosity.

1.1.8.3 Density

Density is one of the basic and important physical properties of ILs. In general, IL is denser than water with values ranging from 1 to 1.6 g cm^{-3}.

Table 5. Densities of pyridinium and imidazolium salt of ILs at 25 ^oC

Entry	Ionic Liquids	Density (g/ml)
1	[BPy][BF_4]	1.22
2	[HPy][BF_4]	1.16
3	[BMPy][BF_4]	1.18
4	[BMPy][OTf]	1.28
5	[BMPy][$N(CN)_2$]	1.05
6	[BMIm][Cl]	1.08
7	[HMIm][Cl]	1.03
8	[OMIm][Cl]	1.00
9	[BMIm][I]	1.44
10	[BMIm][BF_4]	1.12
11	[BMIm][PF_6]	1.36
12	[BMIm][Tf_2N]	1.43
13	[BMIm][CF_3CO_2]	1.209
14	[BMIm][CF_3SO_3]	1.29

The density of an ionic liquid depends on the length and type of substituents in the cation, and also on the kind of the anion as shown in **Table 5**. The molar mass of the anion,[101] alkyl chain length and bulkiness in the cation significantly affects the overall

density of ILs. The density of ionic liquid is also temperature dependent. As temperature changes from 293 to 313 K, the density of [BMIm][BF_4] decreases linearly as the temperature increases.[91]

1.1.8.4 Vapor pressure and thermal stability

These are unique properties of ionic liquids. They have negligible vapor pressure. This is a great advantage from a process engineering viewpoint, since separation by distillation of a reaction mixture becomes more effective as a method of product isolation. The well-known problem of azeotrope formation between the solvent and the products does not arise.

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

Table 6. Thermal decomposition temperature for different ILs

Entry	Ionic Liquid	Decomposition temp. (^oC)
1	[EPy]Br	268 [102]
2	[PPy]Br	259
3	[BPy]Br	237
4	[HPy]Br	238
5	[OPy]Br	236
6	[OMPy]Br	233
7	[OMPy]BF_4	374
8	[OMPy]Tf_2N	394
9	[BMPy]Br	235
10	[BMPy]BF_4	364
11	[BMPy]Tf_2N	397
12	[EPy]$EtSO_4$	303
13	[EMPy]$EtSO_4$	281

Recently, TGA of pyridinium salts have been described and noted that the thermal decomposition is heavily dependent on the salt structure. It indicates that the experiments performed under N_2 or air produces the same results. The onset of thermal decomposition is nearly similar for the different cations but appears to decrease as the anion hydrophilicity increases. It has been suggested that the stability dependence on the anion is $[PF_6]^-$>$[NTf_2]^-$~$[BF_4]^-$>halides.[99] Halide anions dramatically reduce the thermal stability with the onset of decomposition occurring at least 100 °C below the corresponding ILs with non-halide anions. An increase in cation size from 1-ethyl to 1-octyl, [EPy] to [OPy], does not appear to have a large effect as shown in **Table 6**.

1.1.8.5 Polarity

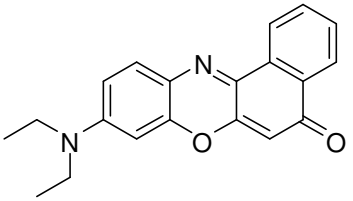
Polarity is a key feature of a liquid. For molecular solvents, this is commonly recorded as the 'polarity' of the pure liquid, and is generally expressed by its dielectric constant. Actually, this scale is unable to provide adequate correlations with many experimental data and the quantitative characterization of the 'solvent polarity'.

Empirical polarity parameter scales were described by observing the effect of the solvent on solvent-dependent processes, such as the rate of chemical reactions, the absorption of light by solvatochromic dyes and partition methods.[103] These approaches have been applied to ILs, both solvatochromic and fluorescent dyes, and also partition coefficients. They have been utilized to determine the polarity of these new solvents.

ILs-solvatochromic probe interactions: The solvatochromic probes are generally easy to perform, and they may be convenient if the interpretation is carefully considered. Generally, each probe is sensitive to a particular kind of interaction (hydrogen bonding, dipolarity/polarizability, etc.); but solvent polarity arises from the sum of all possible intermolecular interactions, and therefore different probes can give different polarity scales.

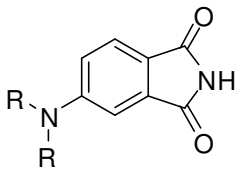
Neutral probes: Nile red and aminophthalimides. The first experiment using a solvatochromic dye, in particular Nile red (**Fig. 3**), was carried out by Carmichael and Seddon[104] on a series of 1-alkyl-3-methylimidazolium ILs. The visible absorption band for Nile red displays one of the largest solvatochromic shifts known. This probe is most likely sensitive to changes in solvent dipolarity/polarizability, although exactly which

factors dominate the shift in its absorption maximum is unclear. The values found for a number of 1-alkyl-3-methylimidazolium ILs shows that the polarity of these salts is comparable to that of short-chain alcohols.[105]



29

Nile red



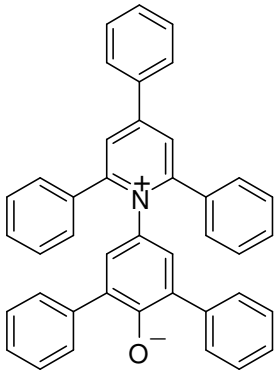
30

30a AP : R = H
30b DAP: R = Me

Figure 3. Solvatochromoc dyes

The data on polarity obtained using other neutral solvatochromic dyes show some variability. For example, a different polarity trend has been found when two fluorescent neutral probes, 4-aminophthalimide (AP) **30a** and *N*, *N*'-dimethyl-4-aminophthalimide (DAP) **30b** (**Fig. 3**) have been used with a series of ILs.[106] According to these latter probes, pyridinium salts is more polar than acetonitrile and less polar than methanol. The pyridinium salts are less polar than imidazolium salts.

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



31

Figure 4. Reichardt's dye

Because of its structure (**Fig. 4**), the solvatochromic shift of this probe is strongly affected by the hydrogen-bond donor ability of the solvent, which stabilizes the ground state more than the excited state. The $E_{T(30)}$ scale is therefore largely, but not exclusively, a measure of hydrogen-bonding acidity of the solvent system. The E_N^T values of several ILs are reported in **Table 7**.

Table 7. E_N^T values of several ILs

Entry	Pyridinium salts	E_N^T	Ref.
1	[PPy][BF_4]	0.661	107
2	[BPy][BF_4]	0.639	107
3	[BPy][NTf_2]	0.648	107
4	[OPy][NTf_2]	0.588	108
5	[PMPy][BF_4]	0.670	107
6	[BMPy][BF_4]	0.630	107
7	[BMPy][NTf_2]	0.588	108
8	[OMPy][NTf_2]	0.576	108

1.1.8.6 Solubility in water

The hydrophilic/hydrophobic behavior of IL is important for the solvation properties. It is necessary to dissolve reactants, but it is also relevant for the recovery of products by solvent extraction. Furthermore, the water content of ILs can affect the rates and selectivity of reactions. The solubility of ILs in water is an important factor for the industrial application of these solvents. Extensive data are available on the miscibility of pyridinium ILs with water. The solubility of these ILs in water depends on the nature of the anion, temperature and the length of the alkyl chain on the pyridinium cation. The ILs which is not water soluble tends to adsorb water from the atmosphere. On the basis of IR studies, water molecules absorbed from the air are mostly present in the free state.[89] It has been bonded via H-bonding with $[PF_6]^-$ $[BF_4]^-$ $[SbF_6]^-$ $[HSO_4]^-$ $[ClO_4]^-$ $[CF_3SO_3]^-$ and $[NTf_2]^-$ with a concentration of the dissolved water in the range 0.2-1.0 mol $dm.^{-3}$ Most of the water molecules should exist in symmetrical 1:2 type H-bonded complexes:

anion…HOH…anion. The strength of H-bonding between anion and water increases in the order $[PF_6]^- < [SbF_6]^- < [BF_4]^- < [NTf_2]^- < [ClO_4]^- < [NO_3]^- < [CF_3CO_2]^-$.

1.1.8.7 Surface tension

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

In general, liquid/air surface tension values for ILs are somewhat higher than those for conventional solvents [$(3.3\text{-}5.7) \times 10^{-4}$ N cm^{-1}]. Surface tension values vary with temperature and affected by the alkyl chain length.

1.1.8.8 Conductivity

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

1.1.8.9 Electrochemical window

The electrochemical window is an important property and plays a key role in using ionic liquids in electro-deposition of metals and semiconductors. The

electrochemical window is defined as the electrochemical potential range over which the electrolyte is neither reduced nor oxidized at an electrode. This value determines the electrochemical stability of solvents. The electro-deposition of elements and compounds in water is limited by its low electrochemical window of only about 1.2 V. On the contrary, ionic liquids have significantly larger electrochemical windows. In general, the wide electrochemical windows of ionic liquids have opened the door to electro-deposit metals and semiconductors at room temperature which were formerly obtained only from high temperature molten salts.

1.1.9 Salient features of ILs, which makes so attractive:

Some of the salient features of ILs are as follows:

1. They show low or negligible vapor pressure and non-flammable.
2. They have high thermal stability.
3. They serve as a good medium to solubilize gases such as H_2, CO, O_2 and CO_2 and many reactions are now being performed using ionic liquids and supercritical CO_2.
4. Their ionic character enhances the reaction rates to a great extent in many reactions including microwave assisted and ultrasound promoted organic synthesis.
5. Their ability to dissolve a wide range of inorganic, organic, organometallic compounds and even polymeric materials.
6. Highly polar yet non-coordinating solvents.
7. Most of the ionic liquids may be stored without decomposition for a long period of time.
8. They exhibit Brønsted, Lewis and Franklin acidity, as well as superacidity.
9. They are immiscible with a number of organic solvents and provide a non-aqueous, polar alternative for two-phase systems. Hydrophobic ionic liquids can also be used as immiscible polar phases with water.
10. Because of their non-volatile nature, products could be easily isolated by vacuum distillation, leaving behind the IL pure enough for recycling after the reaction.
11. They are relatively cheap, and easy to prepare.
12. ILs may be termed as “designer” and ‘neoteric’ solvents since their properties can be adjusted to suit for the particular process by changing anion/cation or both.

1.1.10 Applications of ionic liquids

Ionic liquid is a wide concept in modern synthetic organic chemistry. Recently, ILs has been generating enormous interest in organic synthesis due to their unique properties, in combination with their tunability. Applications of ILs are concentrated in two directions: 1. to replace organic solvents with ionic liquids; due to their unique solvent properties and 2. to replace liquid acid with ionic liquid due to their variable acidity. The former applications include Diel-Alder reaction, Heck reaction and Morita–Baylis–Hillman reaction, while the latter include coupling reactions and Friedel–Crafts reactions. ILs are widely used in organic synthesis especially in transition metal catalyzed reaction as reaction media, reagent or catalyst. In most of the cases, ILs enhance rate of reactions, yields, selectivities in comparison to conventional organic solvents. Some of the applications of ionic liquids as solvent and catalyst are recorded in **Table 8**.

Table 8. Examples of applications of ionic liquids as solvent and catalyst

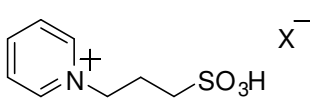
Reaction	**Nature of the ILs**	**Catalyst**	**Ref.**
Diels-Alder reaction	[EtPy][BF_4],	–	109
	[EtPy][CF_3COO]		
	[MePy][OTf]	$Er(OTf)_3$	110
	[BuPy][Cl]/$AlCl_3$	–	111
Diels-Alder cycloaddition	[PrPy]Br	–	112
Intramolecular Diels-Alder	[BuPy][BF_4],	–	113
reaction	[BuPy][NTf_2],		
	[HePy][NTf_2]		
Morita–Baylis–Hillman	[EtPy][BF_4],	DABCO or HMTA	114
reaction	[BuPy][NO_3]		
Heck reaction	[HePy][BF_4],	$Pd(OAc)_2$, base	115
	[HePy][Cl]	$PdCl_2$	
	[BuPy][BF_4]	Pd	116
Three-component	[BuPy][BF_4]	–	117
condensation			

Knoevenagel condensation	[BuPy][NO_3]	NH_4Ac	118
	[BuPy][Cl]·$AlCl_3$	–	119
Synthesis of peptide	[EFPy][BF_4]	base	120
Bromination reaction	[BMPy][Br_3]	–	121
	[PrPy][Br_3	–	122
Arylation	[EtPy][Tf]	–	123
Acylation of β-D glucose	[BuPy][BF_4], [PrPy][BF_4]	CAL-B	124
Reduction of aldehydes and ketones	[BuPy][BF_4]	$NaBH_4$	125
Cycloaddition of CO_2 to butyl glycidyl ether	_	[BuPy][Cl]	126
Beckmann rearrangement	[BuPy][BF_4]	$POCl_3$ or PCl_5	127
Aromatic benzoylation	[BuPy][Cl]/$AlCl_3$	–	128
Fisher Indole synthesis	[BuPy][Cl]/$AlCl_3$	–	129
Friedel-crafts alkylation	[EtPy][BF_4], [EtPy][CF_3COO]	$FeCl_3$	130
Friedel-Crafts acylation	[EtPy][BF_4], [EtPy][CF_3COO]	–	131
Friedel-crafts reaction	[BuPy][Cl]-$AlCl_3$	[BuPy][Cl]-$AlCl_3$	132
Alkylation reactions	[BuPy][BF_4]	–	133
Vinyl acetate hydroformylation	[BuPy][$N(SO_2CF_3)_2$]	$Rh(CO)_2(acac)$	134
Etherification	[BMPy][Br]	[BMPy][Br]	95
Michael Reaction	[BMPy][BF_4]	PTC	135
	[BMPy][$N(CN)_2$]	Organocatalyst	136
Copolymerization of styrene and CO	[HePy][NTf_2]	$(bipy)Pd(OAc)_2$	137
Hydrosilylation of styrene	[EtPy][PF_6], [BuPy][PF_6], [HePy][PF_6],	$Rh(PPh_3)_3Cl$	98

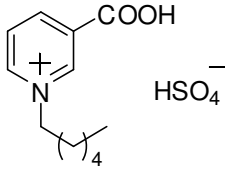
	[OctPy][PF_6], [HeDePy][PF_6], [BnPy][PF_6]		
Demethylation	[PyH][Cl]	–	138
Suzuki cross-coupling	[C_3CNPy][NTf_2], [BuPy][NTf_2]	Pd complex	139
Stille coupling	[C_3CNPy][NTf_2], [BuPy][$N(SO_2CF_3)_2$]	Pd complex	139
Sonogashira reaction	[BuPy][BF_4], [BuPy][PF_6], [BuPy][NO_3]	$Pd(OAc)_2$, $PdCl_2$	140
	[BMPy]BF_4	Pd complex	141
Mizoroki–Heck reactions	[BMPy]BF_4	Pd complex	141
Fischer esterification	[Py][CH_3SO_3], [Py][*p*-TSA]	–	142
Esterification	[PSPy][HSO_4]	[PSPy][HSO_4]	143
	[Bupy][HSO_4]	[Bupy][HSO_4]	144
	[PSPy][BF_4], [PSPy][HSO_4], [PSPy][H_2PO_4], [PSPy][*p*-TSA]	[PSPy][BF_4], [PSPy][HSO_4], [PSPy][H_2PO_4], [PSPy][*p*-TSA]	145
	[Etpy][CF_3CO_2]	[Etpy][CF_3CO_2]	146
Synthesis of 1,5-Benzodiazepine	[Bupy][HSO_4]	[Bupy][HSO_4]	147
Aromatic nitration	[BMPy][NTf_2]	–	148
Kinetic resolution of amino acid esters	[Etpy][CF_3CO_2]	–	149
Iodination of arenes	[BuPy][BF_4]	F-TEDA-BF_4	150

1.1.11 Task Specific Ionic Liquids [TSILs]

Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the ILs. These ILs can act as reagents or catalysts in organic reactions. Recently, many attempts have been made to explore functional ionic liquids through incorporation of additional functional groups as a part of the cation and/or anion. Recently, various types of ''task-specific ionic liquids'' (TSILs) have been designed and synthesized for specific purposes such as catalysis, organic synthesis, separation of specific materials as well as for the construction of nanostructure materials and ion conductive materials etc.[151] Many of them were focused on the incorporation of functionality into a branch appended to the cation, especially pyridinium cation (**Fig. 5**).[148]



32



33

32a: [PSPy][BF_4], X = BF_4
32b: [PSPy][H_2PO_4], X = H_2PO_4
32c: [PSPy][HSO_4], X = HSO_4
32d: [PSPy][*p*-TSA], X = *p*-$CH_3C_6H_4SO_3$

Figure 5. Task specific ionic liquids

It is well known that polar compounds or compounds containing strong proton donor functionality (such as phenols, carboxylic acids, diols as well as ionised compounds) interact strongly with ILs.[40] Compounds such as ketones, aldehydes and esters with weak proton donor/accepter functionality interact with ILs through induced ion dipole or weak van der Walls interactions.[40]

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

defined as a TSIL since the functionalized pyridinium salt become integral elements of the overall ionic liquid solution and can introduce a functional group into the liquid.

1.1.12 Chiral Ionic Liquids [CILs]

Chiral ionic liquids present the most complex application area of ionic liquids. Chirality in solvent is hard to achieve with simple molecular solvents, but it is an issue with complex liquids. There are few review articles which discuss chirality in the cations and the anions in the ionic liquid.[152] In addition very few review articles reported on the applications of chiral ionic liquids in organic reactions.[153] It is speculated that a high molecular order might have a beneficial effect on asymmetric induction in ILs compared to the traditional solvent systems. There are no real evidence to support that chirality in solvent would induce asymmetry in reactions.[153]

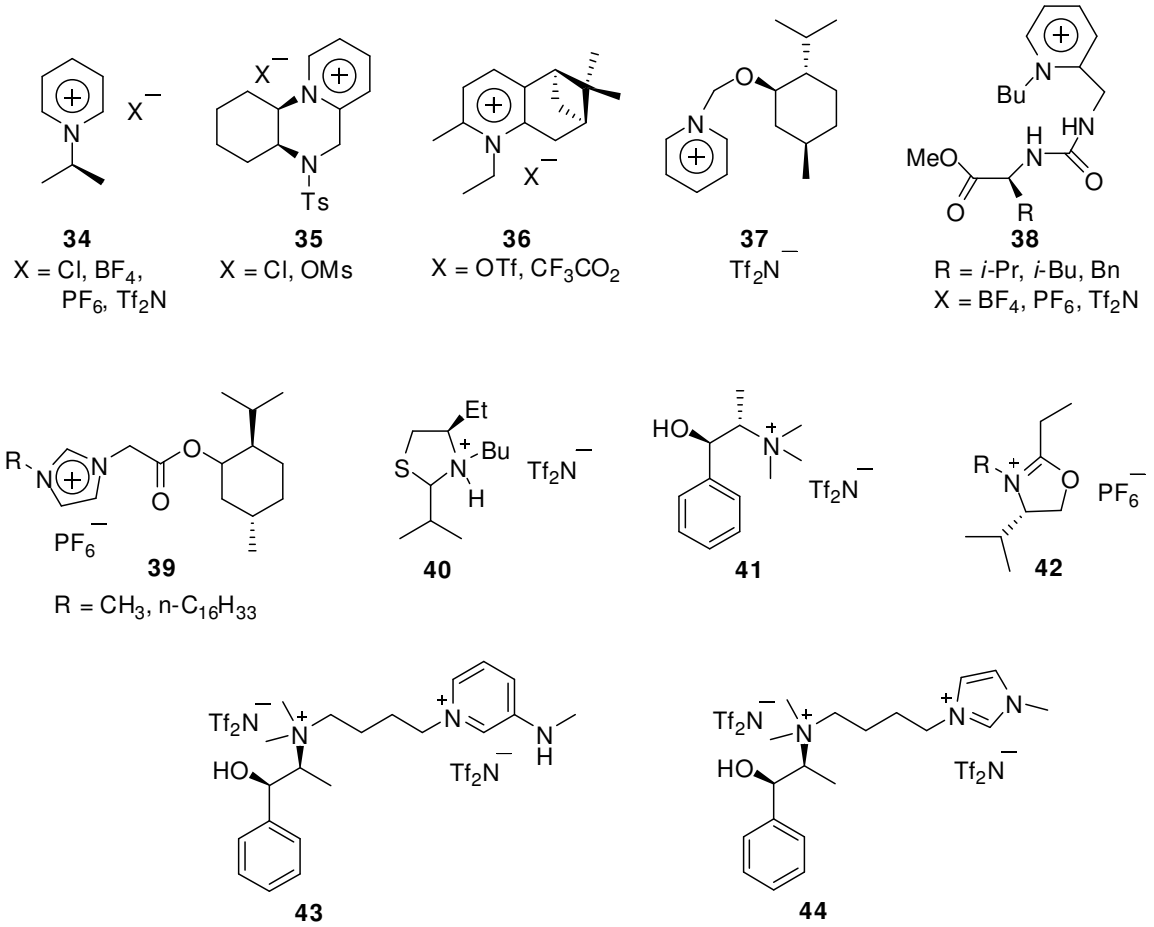


Figure 6. Representative examples of some of the chiral ILs

If an ionic liquid has a free hydroxy group it is possible to lock the reactant in certain conformation around the IL. The free hydroxy would act as a chiral catalyst which is built into the solvent.[154]

In the first report chiral ionic liquid lactate is used as anion. This still remains one of the few examples where chirality is induced in an anion.[155]

Some chiral pyridinium and imidazolium cations have also been used as a cation in chiral ILs (**Fig. 6**). Asymmetry in pyridinium salts has been in the alkyl-chain attached to nitrogen (Menthyl group). Chiral pyridinium derivatives could be constructed so that pyridinium is part of the bigger ring system.

Chiral ionic liquids are quite attractive for their potential application to chiral discrimination including asymmetric synthesis and optical resolution of racemates. Novel chiral ionic liquids, directly derived from the 'chiral pool', have been synthesized and are interesting solvents for enantioselective reactions and useful in chiral separation techniques.[59] Some representative examples are shown in **Fig. 6**.

Due to their ease of synthesis and their peculiar properties, these new chiral solvents should play a central role in enantioselective organic synthesis and hopefully expand the scope of chiral solvents. Most reports deal with the synthesis and properties of the new chiral ILs and only a few deals with their application in organic reactions.[153]

1.1.13 Supported ionic liquids (SILs)

Supported ionic liquid catalysis (SILC) is a concept which combines the advantages of ionic liquids with those of heterogeneous support materials.[156] In a very early example of supported ionic liquid catalysis an eutectic mixture of palladium chloride/copper chloride was supported on a porous silica gel and investigated for the partial oxidation of olefin (Wacker catalysis). Although the melting point of this supported molten salt (423 K) was slightly higher than of room temperature ionic liquids. The potential of such supported ionic systems was recognized thereby contributing to their further exploration. Furthermore the related field of supported aqueous phase catalysis was investigated at the same time and further helped to advance the area of supported catalysis.

The first supported Lewis acidic ionic liquid systems were prepared and explored for catalysis applications.[156] A solid support material was impregnated with a pre-formed ionic liquid which was also the catalytically active species. Most commonly these ionic liquids consisted of aluminum chloride derivatives and were largely tested for Friedel–Crafts reactions.[157] Although, most of the research focused on alkylation reaction; some work was also carried out to evaluate the acylation of arene complexes.[158]

When a substantial amount of an ionic liquid is immobilized on a porous solid support material, the formation of multiple layers of free ionic liquid on the carrier may act as an inert reaction phase to dissolve various homogeneous catalysts. Although such supported ionic liquid-phase (SILP) catalysts appear as solids, the active species dissolved in the ionic liquid phase on the support maintain the attractive features of ionic liquid homogeneous catalysts such as, e.g. high specificity and dispersion of molecular entities. A schematic diagram of SILP hydroformylation catalyst is as shown in **Figure 7.**

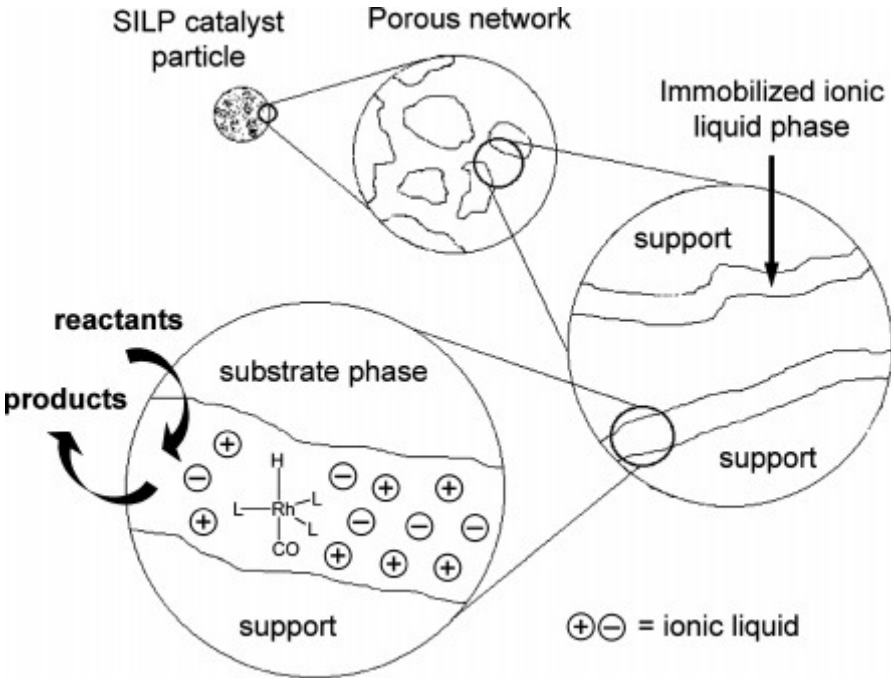
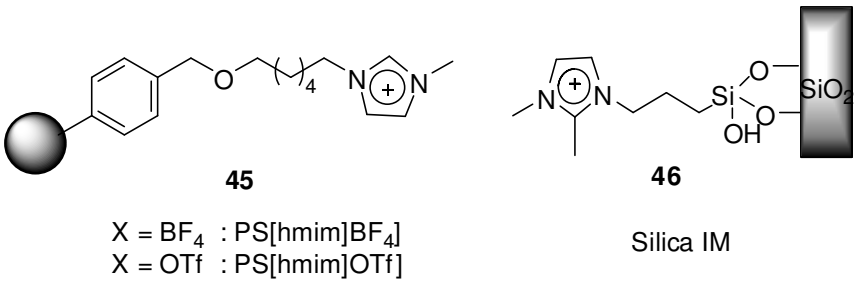


Figure 7. Schematic drawing of a supported ionic liquid-phase (SILP) catalyst.

By supporting ionic liquids, the required amount of the ionic phase can be significantly reduced and it opens the possibility to use fixed-bed reactor systems. Due to the low volatility of the ionic liquids these supported catalysts are especially attractive for

gas-phase reactions. Furthermore by using structured supports like membranes or large pore-size zeolites, novel catalyst systems can be designed and prepared which combine the advantages of homogeneous and heterogeneous catalysis. The recent advances in supported ionic liquid catalysis have showed a tremendous potential and will help to accelerate their introduction into commercial processes. Some of the supported ionic liquid catalysis is as shown in **Fig. 8**.



45 **46**

X = BF_4 : PS[hmim]BF_4]
X = OTf : PS[hmim]OTf]

Silica IM

Figure 8. Representative examples of SILCs

1.1.14 Biodegradability of ionic liquids

The physicochemical properties of ionic liquids have been studied intensively since their discovery. Diverse modifications of cations and anions have provided ionic liquids with desired properties for many technical applications.[159] Yet, the design of an ionic liquid with suitable properties for a specific application in view is not enough and more attention needs to be paid to the total life-cycle impacts of ionic liquids. Studies on the biodegradation of ionic liquids and their potential accumulation in the environment have begun only recently.[160] Degradation of organic compounds can be either aerobic or anaerobic. In both processes micro-organisms require a source of nitrogen and other essential nutrients in order to decompose an organic substrate into carbon dioxide and water. A difference of the processes is that an aerobic treatment requires a source of oxygen and an anaerobic treatment requires an electron acceptor such as Fe^{3+}.[3c].

1.1.15 Recycling of ionic liquids

Environmental considerations require the recovery of ionic liquids after their use. Ionic liquids are quite expensive, and hence their recycling is also necessary due to economic reasons. A review by Olivier-Bourbigou and Magna indicates that ILs have

been successfully recycled in many reactions.[161] Several procedures for recycling ionic liquids have been reported, and the efficiency of the recycling varies from poor to very good recovery.

Recyclability requires rates and yields to be maintained at a reasonable level after repeated reactions. In particular, reactions containing a transition metal catalyst immobilized into the ionic liquid of a biphasic reaction system have proved to be recyclable. Generally, recycling is based on the non-volatile nature of ionic liquids and the solubility differences between ionic liquids, organic compounds and water. Products can be extracted from ionic liquids with a non-polar solvent or they can be separated by distillation. A water immiscible ionic liquid can be washed with water to get a water soluble product or side products out of the reaction mixture.

1.1.16 Benign ionic liquids

Until now, research on ionic liquids has mainly focused on imidazolium and pyridinium-based ionic liquids because they have good, adjustable properties for many applications and they are easy to prepare. Growing concerns about environmental issues have led the design of ionic liquids into a direction where more attention is paid to eco-toxicology. New anion candidates have been suggested on the basis of the first toxicological and eco-toxicological studies. These anions form non-toxic, readily biodegradable and water-soluble ionic liquids. Combining these anions with non-toxic, biodegradable cations, e.g. butyryl choline, could result in new ionic liquids with benign properties. The need remains for poorly coordinating, hydrophobic anions that could replace commonly used fluorous anions such as $[PF_6]^-$ and $[NTf_2]^-$, until now, no potential candidates have been discovered.

1.1.17 Summary and Conclusions

The unique physico-chemical properties of ILs should increase the clean technology development in organic synthesis, pharmaceuticals, biocatalysis, and biotransformation, especially in industrial catalytic processes. The possibility to adjust the properties of ILs such as the hydrophobicity, viscosity, density, thermal stability, polarity and solubility to suit to the particular process is one of their key advantages and

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

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

1.1.18 References

1. (a) Lancaster, M. *Green Chemistry: An Introductory Text,* Royal Society of Chemistry, Cambridge, **2002**; (b) Matlack, A. S. *Introduction to Green Chemistry*, Marcel Dekker, New York, **2001**; (c) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice,* Oxford University Press, Oxford, **1998**.
2. Curzons, A.; Constable, C. C.; Cunningham, V. L. *Clean Prod. Process.* **1999**, *1*, 82.
3. Curran, P.; Maul, J.; Ostrowski, P.; Ublacker, G.; Linclau, B. *Topics in Current Chemistry*, Springer-Verlag, Berlin, Heidelberg, **1999**, vol. *206*, pp. 79.
4. Gani, R.; Jiménez-Gonzalez, C.; Kate, A.; Crafts, A. P.; Jones, M.; Powell, L.; Atherton, H. J.; Cordiner, L. J. *Chem. Eng.* **2006**, *1*, 30.
5. Savaiko, B. *World Ethanol and Biofuels Report* **2004**, *2*, 20.
6. Noyori, R. *Chem. Rev.* **1999**, *99*, 353.
7. Nalawade, S.; Picchioni, F.; Janssen, L. *Prog. Polym. Sci.* **2006**, *31*, 19.
8. Behles, J.; DeSimone, J. *Pure Appl. Chem.* **2001**, *73*, 1281.
9. Tomasko, D.; Li, H.; Liu, D.; Han, X.; Wingert, M.; Lee, J.; Koelling, K. *Ind. Eng. Chem. Res.* **2003**, *42*, 6431.
10. Tanaka, K.; Kaupp, G. *Solvent-free Organic Synthesis*, Wiley-VCH, Weinheim, **2009** and references cited therein.
11. Knochel, P. Betzemeier, B. *Modern Solvents in Organic Synthesis*, Springer-Verlag, Berlin, **1999,** vol. *206*, pp. 60.
12. Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475.
13. Zhu, D. W. *Synthesis* **1993**, 953.
14. Beckman, E. J. *J. Supercrit. Fluids* **2004**, *28*, 121.
15. McHugh, M. A.; Krukonis, V. J. *Supercritical Fluid Extraction: Principles & Practice,* Butterworth-Heinemann, Boston, **1994**.
16. (a) Darr, J. A.; Poliakoff, M. *Chem. Rev.* **1999**, *99*, 495; (b) Eckert, C. A.; Knutson, B. L.; Debendetti, P. G. *Nature* **1996**, *383*, 313; (c) Jessop, P. G.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231.
17. (a) Harris, J. M. *Polyethylene Glycol Chemistry. Biotechnological and Biomedium Applications;* Plenum Press: New York, **1992**, 3; (b) Harris, J. M.;

Zalipsky, S. *Poly(ethylene glycol): Chemistry and Biological Applications;* ACS Books: Washington, DC, **1997**.

18. (a) Kouznetsov, V. V.; Merchan Arenas, D. R.; Romero Boho´rquez, A. R. *Tetrahedron Lett.* **2008**, *49*, 3097; (b) Kumar, R.; Chaudhary, P.; Nimesh, S.; Chandra, R. *Green Chemistry*, **2006**, *8*, 356; (c) Andrade, C. K. Z.; Takada, S. C. S.; Suarez, P. A. Z.; Alves, M. B. *Synlett* **2006**, *10*, 1539.
19. (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816; (b) Breslow, R.; Maitra, U.; Rideout, D. C. *Tetrahedron Lett.* **1983**, *24*, 1901; (c) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239.
20. (a) Grieco, P. A.; Garner, P.; He, Z. *J. Org. Chem*. **1983**, *25*, 1807; (b) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem*. **1983**, *48*, 3137.
21. Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751.
22. (a) Corma, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307; (b) Li, C. -J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68.
23. Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351.
24. Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed*. **2000**, *39*, 3772.
25. Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391.
26. Walden, P. *Bull. Acad. Imper. Sci.* **1914**, *1*, 1800.
27. Hurley, F. H.; Weir, T. P. *J. Electrochem. Soc*. **1951**, *98*, 207.
28. Swain, C. G.; Ohno, A.; Roe, D. K.; Brown, R.; Maugh, T. *J. Am. Chem. Soc.* **1967**, *89*, 2648.
29. (a) Chum, H. L.; Koch, V. R.; Miller, L. L.; Osteryoung, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 3264; (b) Robinson, J.; Osteryoung, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 323.
30. (a) Wilkes, J. S.; Levisky, J. A.; Wilson, R. A.; Hussey, C. L. *Inorg. Chem.* **1982**, *21*, 1263; (b) Scheffler, T. B.; Hussey, C. L.; Seddon, K. R.; Kear, C. M.; Armitage, P. D. *Inorg. Chem.* **1983**, *22*, 2099; (c) Appleby, C. D.; Hussey, C. L.; Seddon, K. R.; Turp, J. E. *Nature* **1986**, *323*, 614.
31. Hussey, C. L. *Adv. Molten Salt Chem.* **1983**, *5*, 185.
32. Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480.

33. Chauvin, Y.; Gilbert, B.; Guibard, I. *J. Chem. Soc. Chem. Commun.* **1990**, 1715.
34. Carlin, R. T.; Osteryoung, R. A. *J. Mol. Catal.* **1990,** *63*, 125.
35. Wilkes, J. S.; Zaworokto, M. J. *J. Chem. Soc. Chem. Commun.* **1992**, 965.
36. Bonhôte, P.; Dias, A.; Papageorgiou, N.; Kalyanasundaram, K.; Grätzel, M. *Inorg. Chem*. **1996**, *35*, 1168.
37. Fuller, J.; Carlin, R. T. *in Molten Salts,* ed. Trulove, P. C.; De Long, H. C.; Stafford, G. R.; Deki, S. PV 98-11, The Electrochemical Society Proceedings Series, Pennington, NJ, **1998**, 227.
38. MacFarlane, D. R.; Meakin, P.; Sun, J.; Amini, N.; Forsyth, M. *J. Phys. Chem. B*, **1999**, *103*, 4164.
39. Welton, T. *Chem. Rev*. **1999**, *99*, 2071.
40. Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*, Wiley-VCH, Weinheim, **2007**; and references cited therein.
41. Ohno, Y. *Electrochemical Aspects of Ionic Liquids*, John Wiley & Sons, Inc., New Jersey, **2005**.
42. Sang-gi, L. *Chem. Commun.* **2006**, 1049.
43. Endres, F.; MacFarlane, D.; Abbott, A. *Electrodeposition from Ionic Liquids,* John Wiley & Sons, Inc., New Jersey, **2008**.
44. Sun, J.; Forsyth, M.; Mac Farlana, D. R. *J. Phys. Chem. B* **1998**, *102*, 8858.
45. Miyatake, K.; Yamamoto, K.; Endo, K.; Tsuchida, E. *J. Org. Chem.* **1998**, *63*, 7522.
46. King, J. A. General Electric Company, US Patent 5 705 696, **1998**.
47. Bonhôte, P.; Dias, A.; Papageorgiou, N.; Kalyanasundaram K.; Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168.
48. Tait, S.; Osteryoung, R. A. *Inorg. Chem.* **1984**, *23*, 4352.
49. Mamantov, G. J. C.; Dunstan, T. D. J. Electrochemical Systems, Inc. US Patent 5552241, **1996**.
50. Davis, J. H.; Forrester, Jr. K. J. *Tetrahedron Lett.* **1999**, *40*, 1621.
51. Tomoharu, N. Sanyo Chem. Ind. Ltd. JP 11273734, **1999**.
52. Vestergaard, B. B.; Petrushina, N. J. I.; Hjuler, H. A.; Berg, R.W.; Begtrup, M. *J. Electrochem. Soc.* **1993**, *140*, 3108.

53. Zhang, H. Q.; Yang, L.; Fang, S. H.; Peng, C. X.; Xuo, H. J. *Chinese Sci. Bull.*, **2009**, *54*, 1322.
54. Lall, S.; Mancheno, D.; Castro, S.; Behaj, V.; Cohen, J. I.; Engel, R. *Chem. Commun.* **2000**, 2413.
55. Varma, R. S.; Namboodiri, V. V. *Chem. Commun.* **2001**, 643.
56. Bwambok, D. K.; Marwani, H. M.; Fernand, V. E.; Fakayode, S. O.; Lowry, M.; Negulescu, I.; Strongin, R. M.; Warner, I. M. *Chirality* **2008**, *20*, 151.
57. Tindale, J. J.; Ragogna, P. J. *Chem. Commun.* **2009**, 1831.
58. Xie, H.; Zhang, S.; Duan, H. *Tetrahedron Lett.* **2004**, *45*, 2013.
59. Wasserscheid, P.; Boesmann, A.; Bolm, C. *Chem. Commun.* **2002**, 200.
60. Petkovic, M.; Ferguson, J. L.; Nimal Gunaratne, H. Q.; Ferreira, R.; Leitão, M. C.; Seddon, K. R.; Rebelo, L. P. N.; Pereira, C. S. *Green Chem.* **2010**, *12*, 643.
61. Visser, A. E.; Holbrey, J. D.; Rogers, R. D. *Chem Commun.* **2001**, 2484.
62. Ganesan, K.; Alias, Y. *Int. J. Mol. Sci.* **2008**, *9*, 1207.
63. MacFarlane, D. R.; Meakin, P.; Sun, J.; Amini, N.; Forsyth, M. *J. Phys. Chem. B,* **1999**, *103*, 4164.
64. Zhao, D.; Fei, Z.; Hi, A. W.; Dyson, P. J. *Int. J. Mol. Sci.* **2007**, *8*, 304.
65. Zhang, H. B.; Zhou, X. H.; Dong, J. F.; Zhang, G. Y.; Wang, C. X. *Sci. China Ser B-Chem.* **2007**, *50*, 238.
66. Chauvin, Y.; Olivier, H.; De Souza, R. F. Institut Francais du Pétrole, US patent, 5723712, **1998**.
67. Hasan, M.; Kozhevnikov, I. V.; Siddiqui, M. R. H.; Steiner, A.; Winterton, N. *Inorg. Chem.* **1999**, *38*, 5637.
68. Terasawa, N.; Tsuzuki, S.; Umecky, T.; Saitoc, Y.; Matsumoto, H. *Chem. Commun.* **2010**, *46*, 1730.
69. Driver, G.; Johnson, K. E. *Green Chemistry* **2003**, *5*, 163.
70. Salazar, J.; Dorta, R. *Synlett* **2004**, *7*, 1318.
71. Dhanalakshmi, K.; Vaultier, M. *Tetrahedron* **2003**, *59*, 9907.
72. Chauvin, Y.; Oliver-Bourbigon, H. *Chem. Tech.* **1995,** 26.
73. Ford, W. T.; Hauri, R. J.; Hart, D. J. *J. Org. Chem.* **1973**, *38*, 3916.

74. Karodia, N.; Guise, S.; Newlands, C.; Andersen, J. -A. *Chem. Commun.* **1998**, 2341.
75. Larsen, A. S.; Holbrey, J. D.; Tham, F. S.; Reed C. A. *J. Am. Chem. Soc.* **2000**, *122*, 7264.
76. Fannin, A. A.; Floreani, D. A.; King, L. A.; Landers, J. S.; Piersma, B. J.; Stech, D. J.; Vaughn, R .L.; Wilkes, J. S.; Williams, J. L. *J. Phys. Chem.* **1984**, *88*, 2614.
77. Koch, V. R.; Dominey, L. A.; Nanjundiah, C.; Ondrechen, M. J. *J. Electrochem. Soc.* **1996**, *143*, 798.
78. MacFarlane, D.; Golding, J.; Forsyth, S.; Forsyth, M.; Deacon, G. B. *Chem. Commun.* **2001**, 1430.
79. Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097.
80. Chiappe, C.; Signori, F.; Valentini, G.; Marchetti, L.; Pomelli, C. S.; Bellina, F. *J. Phys. Chem. B* **2010**, *114,* 5082.
81. Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D. *J. Chem. Soc. Chem. Commun.* **1994**, 299.
82. Keim, W.; Korth, W.; Wasserscheid, P. **2000,** WO 2000016902, [(2000). Chem. Abstr. 132, P238691].
83. Seddon, K. R.; Stark, A; Torres, M, -J. *Pure Appl. Chem.* **2000**, *72*, 2275.
84. Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Molecules* **2004**, *9*, 387.
85. Holbrey, J. D.; Seddon, K. R.; Wareing, R. *Green Chem.* **2001**, *3*, 33.
86. Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. P. *J. Chem. Soc., Dalton. Trans.* **2002**, 2133.
87. Klingshirn, M. A.; Broker, G. A.; Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. *Chem. Commun.* **2002**, 1394.
88. Daguenet, C.; Dyson, P. J. *Organometallics* **2004**, *23*, 6080.
89. Cammarata, L.; Kazarian, S. G.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5192.
90. Holbrey, J. D.; Seddon, K. R. *J. Chem. Soc., Dalton. Trans.* **1999**, 2133.

91. Noda, A.; Hayamizu, K.; Watanabe, M. *J. Phys. Chem. B* **2001**, *105*, 4603.
92. Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772.
93. Bandre´s, I.; Giner, B.; Gasco´n, I.; Castro, M.; Lafuente, C. *J. Phys. Chem. B* **2008**, *112*, 12461.
94. Marek, J.; Stodulka, P.; Cabal, J.; Soukup, O.; Pohanka, M.; Korabecny, J.; Musilek, K.; Kuca, K. *Molecules* **2010**, *15*, 1967.
95. Nardi, J. C.; Hussey, C. L.; King, L. A.; Carpio, R. A. US Patent 4,115,390, **1978**.
96. Crosthwaite, J. M.; Muldoon, M. J.; Dixon, J. R.; Anderson, J. L.; Brennecke, J. F. *J. Chemical Thermodynamics* **2005**, *37*, 559.
97. Noda, A.; Watanabe, M. *Electrochimica Acta.* **2000**, *45*, 1265.
98. (a) Peng, J. J.; Li, J. Y.; Bai, Y.; Qiu, H. Y.; Jiang, K.; Jiang, J.; Lai, G. Q. *Catal. Commun.* **2008**, *9*, 2236; (b) Peng, J. J.; Li, J. Y.; Bai, Y.; Gao, W. H.; Qiu, H. Y.; Wu, H.; Deng, Y.; Lai, G. Q. *J. Mol. Catal. A: Chemical* **2007**, *278*, 97.
99. Crosthwaite, J. M.; Muldoon, M. J.; Dixon, J. K.; Anderson, J. L.; Brennecke, J. F. *J. Chem. Thermodynamics* **2005**, *37*, 559.
100. Fuller, J.; Carlin, R. T.; Osteryoung, R. A. *J. Electrochem. Soc.* **1997**, *144*, 3881.
101. (a) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, *3*, 156; and references cited therein; (b) Ye, C.; Shreeve, J. M. *J. Phys. Chem. A* **2007**, *111,* 1456.
102. Tong, B.; Liu, Q. –S.; Tan, Z. –C.; Welz-Biermann, U. *J. Phys. Chem. A* **2010**, *114,* 3782.
103. Reichard C. *Solvents and Solvent Effects in Organic Chemistry* (2nd ed.), VCH: Weinheim, **1990**.
104. Charmichael, A. J.; Seddon, K. R. *J. Phys. Org. Chem.* **2000**, *13*, 591.
105. (a) van de Broeke, J.; Stam, M.; Lutz, M.; Kooijman, H.; Spek, A. L.; Deelman, B. -J.; van Koten, G. *Eur. J. Inorg. Chem.* **2003**, *26*, 2798; (b) Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002**, *43*, 4657.
106. Aki S. N. V. K.; Brennecke, J. F.; Samanta, A. *Chem. Commun.* **2001**, *5*, 413.

107. Reichardt, C. *Green Chem.* **2005**, *7*, 339.
108. Lee, J. –M.; Ruckes, S.; Prausnitz, J. M. *J. Phys. Chem. B* **2008**, *112,* 1473.
109. Xiao, Y.; Malhotra, S. V. *Tetrahedron Lett.* **2004**, *45*, 8339.
110. Bortolini, O.; Nino, A. D.; Garofalo, A.; Maiuolo, L.; Procopio, A.; Russo, B. *Appl. Catal. A: General* **2010**, *372*, 124.
111. Lee, C. W. *Tetrahedron Lett.* **1999**, *40,* 2461.
112. Fuentes, A.; Martinez-Palou, R.; Jimenez-Vazquez, H. A.; Delgado, F.; Reyes, A.; Tamariz, J. *Monatsh. Chem.* **2005,** *136*, 177.
113. Tiwari, S.; Khupse, N.; Kumar, A. *J. Org. Chem.* **2008**, *73*, 9075.
114. Zhao, S.; Zhang, H.; Feng, L.; Chen, Z. *J. Mol. Catalysis A: Chemical* **2006**, *258*, 251.
115. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett*. **1999**, *1*, 997.
116. Hamill, N. A.; Hardacre, C.; Jane McMath, S. E. *Green Chem.* **2002**, *4*, 139.
117. Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Chinese Chem. Lett.* **2005**, *16*, 155.
118. Li, Y. Q.; Xu. X. M.; Zhou, M. Y. *Chinese Chem. Lett.* **2003**, *14*, 448.
119. Hariani, J. R.; Nara, S. J.; Salunkhe, M. M. *Tetrahedron Lett.* **2002**, *43,* 1127.
120. Li, P.; Xu, J. C. *Chinese Chem. Lett*. **2000**, *11*, 377.
121. Borikar, S. P.; Daniel, T.; Paul, V. *Tetrahedron Lett.* **2009**, *50,* 1007.
122. Salazar, J.; Dorta, R. *Synlett* **2004**, 1318.
123. Velazquez, C. A.; Lynn, G. M.; Kumar, V.; Keefer, L. K.; Malhotra, S. V. *Synthetic Commun.* **2010**, *40*, 1322.
124. Park, S.; Kazlauskas, R. J. *J. Org. Chem.* **2001**, *66*, 8395.
125. Xu, D. Q.; Luo, S. P.; Liu, B. Y.; Xu, Z. Y.; Shen, Y. C. *Chinese Chem. Lett.* **2004**, *15*, 643.
126. Ju, H. –Y.; Ahn, J. –Y.; Manju, M. D.; Kim, K. H.; Park, D. –W. *Korean J. Chem. Eng*. **2008**, *25*, 471.
127. Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 403.
128. Rebeiro, G. L.; Khadilkar, B. M. *Synthetic Commun.* **2000**, *30*, 1605.
129. Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370.
130. Xiao, Y.; Malhotra, S. V. *J. Mol. Catal. A: Chemical* **2005**, *230*, 129.

131. Xiao, Y.; Malhotra, S. V. *J. Organomettalic Chem.* **2005**, *690*, 3609.
132. Wang, Z. W.; Wang, L. S. *Green Chemistry* **2003**, *5*, 737.
133. Su, C.; Chen, Z. -C.; Zheng, Q. -G. *Synthetic Commun.* **2003**, *33*, 2817.
134. Williams, D. B. G.; Ajam, M.; Ranwell, A. *Organometallics* **2007**, *26*, 4692.
135. Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44,* 5351.
136. Mečiarová, M.; Toma, Š.; Šebesta, R. *Tetrahedron Asymmetry* **2009**, *20*, 2403.
137. Klingshirn, M. A.; Broker, G. A.; Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. *Chem. Commun.* **2002**, 1394.
138. Schmid, C. R.; Beck, C. A.; Cronin, J. S.; Staszak, M. A. *Org. Proc. Res. & Dev.* **2004**, *8,* 670.
139. Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 15876.
140. de Lima, P. G.; Antunes, O. A. C. *Tetrahedron Lett.* **2008**, *49*, 2506.
141. Rahman, M. T.; Fukuyama, T.; Ryu, I.; Suzuki, K.; Yonemura, K.; Hughesc, P. F.; Nokiharab, K. *Tetrahedron Lett.* **2006**, *47*, 2703.
142. Ganeshpure, P. A.; Das, J. *React. Kinet. Catal. Lett.* **2007**, *92*, 69.
143. Gui, J.; Cong, X.; Liu, D.; Zhang, X.; Hu, Z.; Sun, Z. *Catal. Commun.* **2004**, *5*, 473.
144. Arfan, A.; Bazureau, J. P. *Org. Proc. Res. & Dev.* **2005**, *9*, 743.
145. Xing, H.; Wang, T.; Zhou, Z.; Dai, Y. *Ind. Eng. Chem. Res.* **2005**, *44*, 4147.
146. Zhao, H.; Malhotra, S. V. In *Catalysis of Organic Reactions*; Morrell, D.; Ed.; Marcel Dekker: New York, **2002**, *83*, 667.
147. Du, Y.; Tian, F.; Zhao, W. *Synthetic Commun.* **2006**, *36*, 1661.
148. (a) Chowdhury, S.; Mohan, R. S.; Scott, J. L. Tetrahedron **2007**, *63*, 2363; and references cited therein; (b) Wang, Z.; Wang, C.; Bao, W.; Ying, T. *J. Chem. Res.* **2005**, *6*, 388.
149. Zhao, H.; Malhotra, S. V. *Biotechnol. Lett.* **2002**, *24*, 1257.
150. Chiappe, C.; Pieraccini, D. *ARKIVOC* **2002**, *xi*, 249.
151. Lee, S. -G. *Chem. Commun.* **2006**, 1049.

152. (a) Baudequin, C.; Bregon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.; Gaumont, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3921; (b) Ding, J.; Armstrong, D. W. *Chirality* **2005**, *17*, 281.

153. (a) Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, *19*, 3235; (b) Winkel, A.; Reddy, P. V. G.; Wilhelm, R. *Synthesis* **2008**, *7*, 999; (c) Truong, T. K. T.; Vo-Thanh, G. *Tetrahedron*, **2010,** *66*, 5277**.**

154. Thanh, G. V.; Pegot, B.; Loupy, A. *Eur. J. Org. Chem.* **2004**, *5*, 1112.

155. Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chemistry* **1999**, *1*, 23.

156. Mehnert, C. P. *Chem. Eur. J.* **2005**, *11*, 50.

157. (a) deCastro, C.; Sauvage, E.; Valkenberg, M. H.; Hölderich, W. F. *J. Catal.* **2000**, *196*, 86; (b) Valkenberg, M. H.; Sauvage, E.; Castro-Moreira, C. P.; Hölderich, W. F. WO 01/32308, **2001**.

158. Valkenberg, M. H.; deCastro, C.; Hölderich, W. F. *Appl. Catal. A: Chemical* **2001**, *215*, 185.

159. Kamal, A.; Chouhan, G. *Adv. Synth. Catal.* **2004**, *346*, 579.

160. (a) Zhang, C.; Wang, H.; Malhotra, S. V.; Dodge, C. J.; Francis, A. J. *Green Chem.* **2010**, *12*, 851; (b) Coleman, D.; Gathergood, N. *Chem. Soc. Rev.* **2010**, *39*, 600; (c) Docherty, K. M.; Dixon, J. K.; Kulpa Jr. C. F. *Biodegradation* **2007**, *18*, 481.

161. Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chemical* **2002**, *182-183*, 419.

Section-B

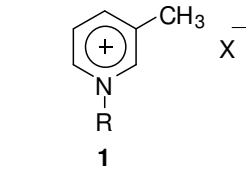
Synthesis and characterization of novel ILs based on n-alkyl-3-methylpyridinium salts

1.2.1 Introduction

In the previous section-A, description and a brief introduction of ionic liquids is given. This includes the definition of ILs, brief history of ILs and their characteristic physico-chemical properties. The salient features of ILs, stability of ILs, biodegradation of ILs and applications of ILs have been thoroughly discussed. The new concepts in ILs such as task specific ionic liquids (TSILs), supported ionic liquids (SILs) and chiral ionic liquids (CILs) have been discussed briefly. The ionic liquids are organic salts, invariably possessing a high degree of asymmetry that makes packing and thus inhibits crystallization. Moreover, the ILs based upon pyridinium cation has good thermal stability, large electrochemical window; most of them are liquids at room temperature, low viscosity and high polarity as compared to other ILs. Thus considering these important features of ILs based upon pyridinium cations, we have synthesized several ILs based upon this class of cations with different anions of varying basicity and studied their efficiency in various important organic transformations. The inherent brønsted acidity of pyridinium ring protons and Lewis acidity of pyridinium nucleus arising due to positive charge delocalization prompted us to explore their use in various organic transformations catalyzed by both Lewis and Brønsted acids. The permutation and combination of anions and cations can result in numerous ILs with varied chemical and physical properties. This section deals with the synthesis and characterization of novel ionic liquids based upon *n*-alkyl-3-methyl pyridinium cations with different anions of varying basicity.

1.2.2 Present work

A very few reports[1-6] are published on the synthesis and physiochemical properties of pyridinium based ionic liquids, but not much effort was taken on the synthesis of 3-methylpyridinium (i. e. *β*-picoline) based ionic liquids. This prompted us to synthesize the novel ionic liquids based upon *n*-alkyl-3-methylpyridinium cations. 3-Picoline is an important intermediate in the synthesis of nicotinic acid and its derivatives, has been rarely used as a starting material for ILs. Thus, a series of *n*-alkyl substituted 3-methylpyridinium salts based ILs have been synthesized with varying anions and cations as shown in **Figure 1**.



1

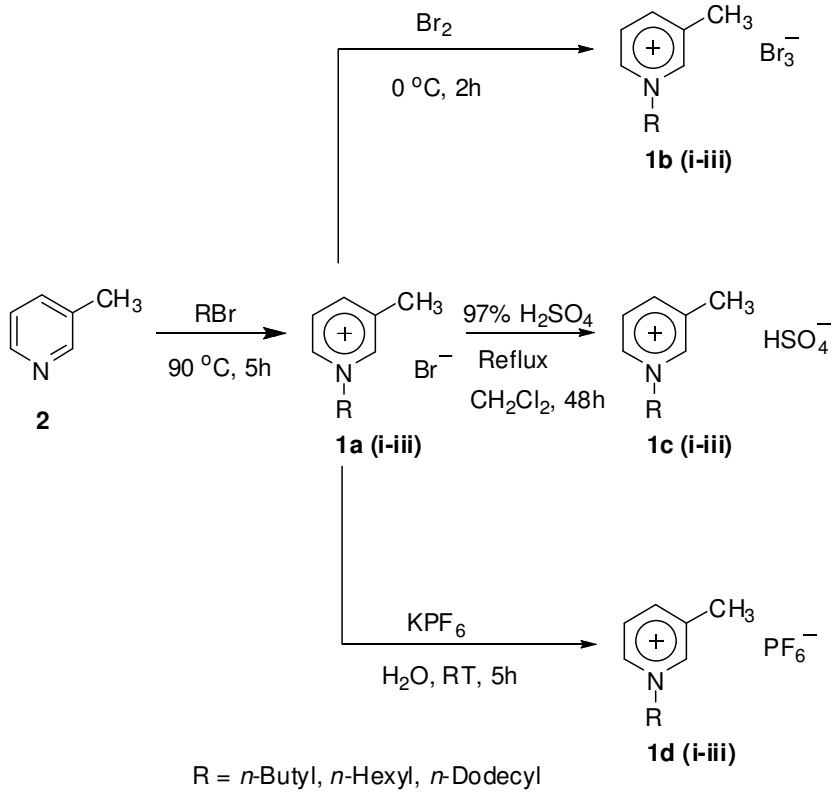
X = Br, Br_3, HSO_4, PF_6
R = *n*-butyl, *n*-hexyl, *n*-dodecyl

Figure 1. Structure of *n*-alkyl-3-methylpyridinium based ionic liquids

1.2.3 Results and discussion

1.2.3.1 Synthesis of Ionic Liquids

The different *n*-alkyl-3-methylpyridinium based ILs **1** were synthesized from an inexpensive, cheap starting material such as β-picoline **2**. The *n*-alkylation and direct quarternization of β-picoline **2** with different alkyl bromides under neat and refluxing conditions at 90 ^{o}C for a appropriate time afforded *n*-alkyl-3-methylpyridinium bromide **1a** in excellent yield (96%). A viscous liquid was obtained with a brownish color. The color can be removed to a certain extent by charcoal



R = *n*-Butyl, *n*-Hexyl, *n*-Dodecyl

Scheme1. Synthesis of *n*-alkyl-3-methylpyridinium salt of ionic liquids

treatment. Further, the bromination of *n*-alkyl-3-methylpyridinium bromide **1a** using molecular bromine at 0 ^{o}C to afford *n*-alkyl-3-methylpyridinium tribromide **1b** in good yield as red colored liquid. Excess bromine was removed completely by applying high vacuum. The metathesis of *n*-alkyl-3-methylpyridinium bromide **1a** with 97% sulfuric acid afforded *n*-alkyl-3-methylpyridinium hydrogen sulphate **1c** in excellent yield as a viscous brownish colored liquid.

Similarly, the metathesis of *n*-alkyl-3-methylpyridinium bromide **1a** with potassium hexafluorophosphate in water at room temperature gave *n*-alkyl-3-methylpyridinium hexafluorophosphate **1d** as shown in **Scheme 1**. During the reaction, the solution became milky immediately due to the precipitation of their respective salts. In all 3-methylpyridinium salt of ionic liquids, where R is different alkyl groups such as *n*-butyl, *n*-hexyl and *n*-dodecyl; this phenomena was observed. These ILs were fully characterized by their spectral and elemental analyses. The list of ionic liquids synthesized is given **Table 1**.

Table 1. List of *n*-alkyl-3-methylpyridinium salt of ionic liquids

Sr. No.	Ionic Liquid	Sr. No.	Ionic Liquid	Sr. No.	Ionic Liquid
1	[BMPy]Br	5	[HMPy]Br	9	[DDMPy]Br
2	[BMPy]HSO_4	6	[HMPy]HSO_4	10	[DDMPy]HSO_4
3	[BMPy]PF_6	7	[HMPy]PF_6	11	[DDMPy]PF_6
4	[BMPy]Br_3	8	[HMPy]Br_3	12	[DDMPy]Br_3

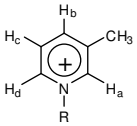
1.2.3.2 Characterization of Ionic Liquids

1.2.3.2.1 NMR study of Ionic Liquids

The proton NMR study of various ionic liquids showed that the chemical shifts of pyridinium protons (i.e. H_a, H_b, H_c and H_d) depends on the anions and concentrations. It is well known that the formation of hydrogen bonding causes a downfield chemical shift of proton. Hydrogen bonding in pyridinium ring depends on the basicity of anion. This effect is strong for H_a proton and weaker for H_c proton. This effect can be explained by two phenomena i) H-bonding and ii) ring stacking. It is observed that H_a proton is less electron rich than H_b, H_c and H_d because it is attached to a carbon atom in between one electronegative nitrogen atom and one methyl group. Thus, H_a proton is more prone for H-bonding with counter anion than

others. This is shown in chemical shifts of H_a proton (**Table 2**). In the case of more electronegative and basic Br^-, the chemical shift is at 9.4 ppm. But in the case of less electronegative and basic anion PF_6^-, the chemical shift is at 8.5 ppm. Hence, it can be concluded that PF_6^- salts are more covalently bonded than its Br^- counterpart. This is also agreeing with the solubility of these salts in water. PF_6 salts are hydrophobic and Br salts are hydrophilic and hygroscopic in nature. This characteristic property can be made use of in designing ILs of different solubilities in water.

Table 2. ^{1}H NMR values of protons of *n*-alkyl-3-methylpyridinium cation

 **Ionic Liquids**		**Chemical shift, δ (ppm)**			
		H_a	**H_b**	**H_c**	**H_d**
R = butyl	[BMPy]Br	9.42	9.23	7.99	8.23
	[BMPy]Br_3	8.66	8.59	7.74	8.11
	[BMPy]HSO_4[a]	8.47	8.44	7.70	8.11
	[BMPy]PF_6	8.53	8.48	7.85	8.26
R =Hexyl	[HMPy]Br	9.45	9.26	8.02	8.25
	[HMPy]Br_3	8.96	8.90	8.04	8.31
	[HMPy]HSO_4[a]	8.54	8.47	7.77	8.18
	[HMPy]PF_6	8.54	8.50	7.89	8.22
R = dodecyl	[DDMPy]Br	9.48	9.29	8.04	8.26
	[DDMPy]Br_3	8.75	8.27	8.04	8.32
	[DDMPy]HSO_4[a]	8.68	8.62	7.88	8.33
	[DDMPy]PF_6	8.52	8.49	7.89	8.22

[a] ^{1}H NMR was recorded in D_2O.

1.2.3.2.2 Density of Ionic Liquids

The density of ILs can be changed by changing either the pressure or the temperature. It also depends on the molar mass of anion. The contribution of the larger hydrophobic anions decreases the density of the ILs. This may be due to weaker molecular attraction and weak hydrogen bonding between them, which decreases molecular agglomeration.

Table 3. Density of *n*-alkyl-3-methylpyridinium salt of ILs

Ionic Liquids	**Density (g/cm^3)[a]**
[BMPy][Br]	1.21
[BMPy][Br_3]	1.75
[BMPy][HSO_4]	1.27
[HMPy][Br_3]	1.81
[HMPy][HSO_4]	1.15
[HMPy][PF_6]	1.24
[DDMPy][Br_3]	1.89
[DDMPy][HSO_4]	1.31

[a]Density was determined at 28 ^oC

1.2.3.2.3 Viscosity of Ionic Liquids

This is a most important physical property of ionic liquids. The ability of ionic liquid used as a solvent in the reaction depends on its viscosity. The viscosity measurement indicates that ionic liquids became less viscous with increasing water content. It is desired for the ionic liquid to have only small changes in viscosity in the normal operating temperature range. The previous studies have shown that the viscosity of ILs is mainly controlled by hydrogen bonding, van der Waals forces, molecular weight and mobility. It also depends on the atmospheric temperature.

Table 4. Viscosity of 3-methylpyridinium salt of ILs

Ionic Liquids	**Viscosity (cP)[a]**
[BMPy][Br]	251.4
[BMPy][Br_3]	55.4
[BMPy][HSO_4]	124.5
[HMPy][Br_3]	61.7
[HMPy][HSO_4]	112.1
[HMPy][PF_6]	91.5
[DDMPy][Br_3]	67.3
[DDMPy][HSO_4]	99.1

[a]Viscosity was determined at 28 ^oC

The viscosity of ILs is on a higher side when more basic anion is present. This has been clearly demonstrated from the data presented in **Table 4**. In tribromide based ILs, the van der Walls forces dominates over the H-bonding due to better charge delocalization. This will reduce the viscosity of the IL, whereas in case of Br based ILs, because of basic anion and smaller size, the van der Waals forces dominate over the H-bonding due to less charge delocalization. This increases the viscosity of the IL.

1.2.3.2.4 Thermal analysis of ionic liquids

The decomposition of ionic liquids on heating results in the low or negligible vapor pressure. In general, the ILs hitherto reported are thermally stable up to 400 ^{o}C after which it tends to decompose at around 480 ^{o}C completely. Usually the complete weight loss should occur with the absorption of heat, which will result in an endotherm. The tribromide ILs evolves the bromine gas during the decomposition. The decomposition temperatures of ILs are listed in **Table 5**, where both the temperature of decomposition onset (T_{onset}) and start temperature for the decomposition (T_{start}) are given.

Table 5. Onset (T_{onset}) and start (T_{start}) of the thermal decomposition temp. for ILs

ILs	T_{start}/ ^{o}C	T_{onset}/ ^{o}C
[BMPy]Br	200	299
[BMPy]HSO_4	213	362
[BMPy]PF_6	202	340
[BMPy]Br_3	180	305
[HMPy]Br	195	310
[HMPy]HSO_4	214	361
[HMPy]PF_6	208	343
[HMPy]Br_3	181	315
[DDMPy]Br	198	308
[DDMPy]HSO_4	205	370
[DDMPy]PF_6	214	340
[DDMPy]Br_3	185	312

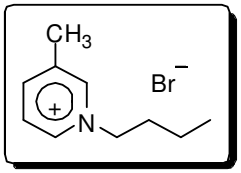
Our experimental result showed that the halide ions suddenly decrease the thermal stability by almost 80 ^{o}C, whereas tribromides and hydrogen sulfate salts

decrease slowly. The decomposition of tribromides ILs starts at around 180 ^{o}C and it fully decomposes at around 320 ^{o}C. In the case of HSO_4 salts, decomposition starts at 214 ^{o}C, and at 360 ^{o}C complete weight loss was observed. The thermal analysis of ionic liquid depended on the components of the ionic liquid such as cations and anions.

1.2.4 Experimental Section

Preparation and characterization of *n*-alkyl-3-methylpyridinium salt of ILs:

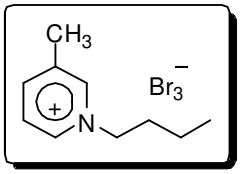
(1) 1-Butyl-3-methylpyridinium bromide [BMPy]Br [1a(i)]:



To a stirred solution of 3-picoline (10.0 g, 0.1 mol) and *n*-butyl bromide (13.84 mL, 0.128 mol) was heated and refluxed at 90 ^{o}C for 4 h. After completion of the reaction, excess n-butyl bromide was distilled off at 80 ^{o}C under reduced pressure (10 mm Hg) over 4 h leaving behind the product [BMPy]Br as a brownish viscous liquid (24.06 g; 97.8 %).

Molecular formula	**:**	$C_{10}H_{16}BrN$
Nature	**:**	Brownish viscous liquid
IR (nujol)	**:**	3428, 3043, 2961, 2874, 1633, 1505, 1466, 1384, 1252, 1157, 1049, 811, 687 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.87 (t, J = 7.20 Hz, 3H), 1.24-1.39 (m, 2H), 1.88-2.03 (m, 2H), 2.57 (s, 3H), 4.85 (t, J = 7.45 Hz, 2H), 7.99 (t, J = 6.57 Hz, 1H), 8.23 (d, J = 8.09 Hz, 1H), 9.23 (d, J = 5.81 Hz, 1H), 9.42 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 12.86, 17.90, 18.57, 33.10, 60.54, 127.14, 138.90, 141.60, 143.88, 145.05 ppm.
Anal. Calcd. for $C_{10}H_{16}BrN$	**:**	Calcd.: C, 52.19; H, 7.01; N, 6.09. Found: C, 52.10; H, 7.09; N, 6.51.
MS (EI) (*m/z*)	**:**	150 (M - X).

(2) 1-Butyl-3-methylpyridinium tribromide [BMPy]Br_3 [1b(i)]:



Molecular bromine (0.22 mL, 0.436 mmol) was added slowly to 1-butyl-3-methylpyridinium bromide [BMPy]Br (1.0 g, 0.436 mmol) at ice-cooled temperature under stirring to give a deep red liquid. The stirring was continued for another 2 h. The excess bromine was removed under reduced pressure over 5 h at 60 ^oC gave pure [BMPy]Br_3 as a red oil (1.62 g; 95.4%).

Molecular formula : $C_{10}H_{16}Br_3N$

Nature : Red oil

IR (nujol) : 3401, 3020, 1633, 1505, 1466, 1215, 1157, 1045, 758, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.72 (t, J = 7.20 Hz, 3H), 1.07-1.22 (m, 2H), 1.68-1.84 (m, 2H), 2.38 (s, 3H), 4.41 (t, J = 7.58 Hz, 2H), 7.74 (t, J = 7.83 Hz, 1H), 8.07 (d, J = 8.09 Hz, 1H), 8.59 (d, J = 6.07 Hz, 1H), 8.66 (s, 1H, merge) ppm.

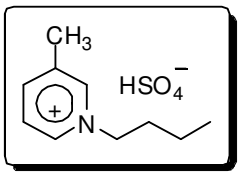
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 12.86, 18.23, 18.76, 32.81, 61.36, 127.34, 139.41, 141.10, 143.36, 145.47 ppm.

Anal. Calcd. for $C_{10}H_{16}Br_3N$: Calcd.: C, 30.80; H, 4.14; N, 3.59.
Found: C, 31.01; H, 4.13; N, 3.35.

MS (EI) (*m/z*) : 150 (M - X_3).

---

(3) 1-Butyl-3-methylpyridinium hydrogen sulphate [BMPy]HSO_4 [1c(i)]:



To a stirred solution of 1-butyl-3-methylpyridinium bromide [BMPy]Br (5.0 g, 86.9 mmol) in 25 mL of dry CH_2Cl_2 at 0 ^oC, 97 % H_2SO_4 (1.15 mL, 86.9 mmol) was added dropwise in 10 mins. The resulting solution was refluxed for 48 h and the solution was washed with water. The organic layer was dried over anhyd. Na_2SO_4. The solvent CH_2Cl_2 was distilled off under reduced pressure to gave pure IL [BMPy]HSO_4 as blackish viscous liquid (5.3 g; 98.7 %).

Molecular formula : $C_{10}H_{17}NO_4S$

Nature : Blackish viscous liquid

IR (nujol) : 3428, 3043, 2961, 2874, 1633, 1505, 1466,

1384, 1252, 1157, 1049, 811, 687 cm^{-1}.

^{1}H NMR (D_2O, 200 MHz) : δ0.71 (t, *J* = 7.32 Hz, 3H), 1.03-1.22 (m, 2H), 1.68-1.83 (m, 2H), 2.32 (s, 3H), 4.33 (t, *J* = 7.33 Hz, 2H), 7.70 (t, *J* = 7.08 Hz, 1H), 8.11 (d, *J* = 7.83 Hz, 1H), 8.44 (d, *J* = 6.06 Hz, 1H), 8.47 (s, 1H merge) ppm.

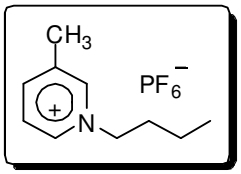
^{13}C NMR (D_2O, 50 MHz) : δ 12.55, 17.52, 18.57, 32.43, 61.32, 127.23, 139.68, 141.14, 143.60, 145.73 ppm.

Anal. Calcd. for $C_{10}H_{17}NO_4S$: Calcd.: C, 48.57; H, 6.93; N, 5.66.
Found: C, 48.60; H, 6.81; N, 5.64.

MS (EI) (*m/z*) : 150 (M - X).

---

(4) 1-Butyl-3-methylpyridinium hexafluorophosphate [BMPy]PF_6 [1d(i)]:



To a stirred solution of [BMPy]Br (1.0 g, 3.89 mmol) in 10.0 mL of H_2O, potassium hexafluorophosphate (KPF_6) (0.787 g, 4.28 mmol) was added. The resulting solution was stirred at room temperature for 5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to obtain desired [BMPy]PF_6 ionic liquid as yellow solid (1.22 g, 97.13 %).

Molecular formula : $C_{10}H_{16}F_6NP$

Nature : Yellow solid

Mp : 50-52 ^oC

IR (nujol) : 3683, 2966, 2401, 1635, 1508, 1252, 1159, 758, 558 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ0.87 (t, *J* = 7.20 Hz, 3H), 1.26-1.41 (m, 2H), 1.85-2.00 (m, 2H), 2.51 (s, 3H), 4.47 (t, *J* = 7.45 Hz, 2H), 7.85 (t, *J* = 7.19 Hz, 1H), 8.26 (d, *J* = 7.83 Hz, 1H), 8.48 (d, *J* = 6.06 Hz, 1H), 8.53 (s, 1H merge) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.15, 18.06, 19.12, 33.08, 61.82, 127.73, 140.22, 141.13, 143.73, 146.12 ppm.

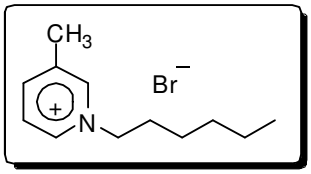
Anal. Calcd. for $C_{10}H_{16}F_6NP$: Calcd.: C, 40.69; H, 5.46; N, 4.74.

Found: C, 40.45; H, 5.50; N, 4.81.

MS (EI) (*m/z*) : 150 (M - X).

---

(5) 1-Hexyl-3-methylpyridinium bromide [HMPy]Br [1a(ii)]:



A stirred solution of 3-picoline (20.0 g, 0.214 mol) and *n*-hexyl bromide (36.17 mL, 0.257 mol) was heated and refluxed at 90 ^{o}C for 5 h. Excess *n*-hexyl bromide was distilled off at 80 ^{o}C under reduced pressure (10 mm Hg) over 6 h leaving behind the product [HMPy]Br as a yellow liquid (54.1 g; 98.0%).

Molecular formula : $C_{12}H_{20}BrN$

Nature : Yellow liquid

IR (nujol) : 3401, 3018, 2933, 2861, 2451, 1634, 1592, 1505, 1467, 1384, 1243, 1216, 1155, 1048, 753, 687, 661 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.83 (t, J = 6.82 Hz, 3H), 1.20-1.39 (m, 6H), 1.94-2.05 (m, 2H), 2.63 (s, 3H), 4.92 (t, J = 7.45 Hz, 2H), 8.02 (t, J = 7.83 Hz, 1H), 8.25 (d, J = 7.96 Hz, 1H), 9.26 (d, J = 6.07 Hz, 1H), 9.45 (s, 1H) ppm.

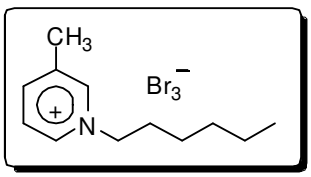
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.55, 18.27, 21.92, 25.25, 30.70, 31.53, 61.20, 127.50, 139.20, 141.88, 144.20, 145.32 ppm.

Anal. Calcd. for $C_{12}H_{20}BrN$: Calcd.: C, 55.82; H, 7.81; N, 5.42.
Found: C, 55.90; H, 7.61; N, 5.35.

MS (EI)(*m/z*) : 178 (M - X).

---

(6) 1-Hexyl-3-methylpyridinium tribromide [HMPy]Br_3 [1b(ii)]:



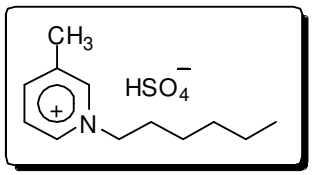
Molecular bromine (0.199 mL, 3.89 mmol) was added slowly to 1-hexyl-3-methylpyridinium bromide [HMPy]Br (1.0 g, 3.89 mmol) under stirring and cooling in a ice-bath resulted in a deep red liquid. The stirring was continued for further 2 h. The excess bromine was removed under reduced pressure over 5 h at 60 ^{o}C to afford pure [HMPy]Br_3 as a red oil (1.52 g; 94.4 %).

Molecular formula : $C_{12}H_{20}Br_3N$

Nature	**:**	Red oil
IR (nujol)	**:**	3401, 3055, 2957, 2859, 1634, 1592, 1504, 1465, 1382, 1322, 1249, 1217, 1154, 1048, 802, 754, 685, 665 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.87 (t, *J* = 7.20 Hz, 3H), 1.26-1.45 (m, 6H), 2.00-2.11 (m, 2H), 2.69 (s, 3H), 4.78 (t, *J* = 7.45 Hz, 2H), 8.03 (dd, *J* = 6.07, 7.83 Hz, 1H), 8.30 (d, *J* = 7.96 Hz, 1H), 8.92 (d, *J* = 6.07 Hz, 1H), 8.95 (s, 1H merge) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.10, 18.56, 19.05, 32.95, 61.94, 127.79, 139.82, 141.46, 143.66, 145.59 ppm.
Anal. Calcd. for $C_{12}H_{20}Br_3N$	**:**	Calcd.: C, 34.48; H, 4.82; N, 3.35. Found: C, 34.25; H, 4.68; N, 3.26.
MS (EI) (*m/z*)	**:**	178 (M - X_3).

---

(7) 1-Hexyl-3-methylpyridinium hydrogen sulphate [HMPy]HSO_4 [1c(ii)]:

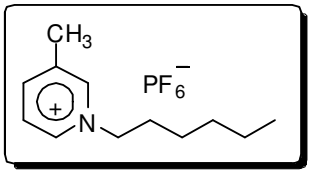


To a stirred solution of 1-hexyl-3-methylpyridinium bromide ([HMPy]Br) (10.0 g, 0.0389 mol) in 50 mL of dry CH_2Cl_2 at 0 ^oC, 97% H_2SO_4 (2.07 mL, 0.0389 mol) was added dropwise in 10 mins. The resulting solution was then refluxed for 47 h. The solution was washed with water (3 x 10 mL), collected the organic layer, and dried over anhydrous Na_2SO_4. The solvent DCM was distilled off under reduced pressure to afford [HMPy]HSO_4 as a viscous oil (10.55 g; 98.6%).

Molecular formula	**:**	$C_{12}H_{21}NO_4S$
Nature	**:**	Viscous oil
IR (nujol)	**:**	3435, 3019, 2931, 1594, 1403, 1216, 1053, 758, 669 cm^{-1}.
^{1}H NMR (D_2O, 200 MHz)	**:**	δ 0.58 (t, *J* = 6.95 Hz, 3H), 0.96-1.10 (m, 6H), 1.67-1.77 (m, 2H,), 2.29 (s, 3H), 4.30 (t, *J* = 7.33 Hz, 2H), 7.67 (t, *J* = 7.70 Hz, 1H), 8.12 (d, *J* = 8.08 Hz, 1H), 8.40 (d, *J* = 6.06 Hz, 1H), 8.44 (s, 1H, merge) ppm.

^{13}C NMR (D_2O, 50 MHz)	**:**	δ 13.08, 17.51, 21.56, 24.70, 30.17, 30.34, 61.54, 127.23, 139.67, 141.12, 143.51, 145.74 ppm.
Anal. Calcd. for $C_{12}H_{21}NO_4S$	**:**	Calcd.: C, 52.34; H, 7.69; N, 5.09. Found: C, 52.18; H, 7.72; N, 5.28.
MS (EI) (*m/z*)	**:**	178 (M - X).

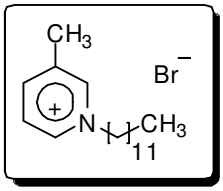
(8) 1-Hexyl-3-methylpyridinium hexafluorophosphate [HMPy]PF_6 [1d(ii)]:



To a stirred solution of 1-hexyl-3-methylpyridinium bromide (1.0 g, 3.89 mmol) in 10.0 mL of H_2O, KPF_6 (0.787 g, 4.28 mmol) was added. The resulting mixture was stirred at room temperature for 6 h. The immiscible layer was separated out and then the solution was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated on vacuum under reduced pressure to obtain desired [HMPy]PF_6 ionic liquid as faint yellow liquid (1.22 g, 97.13 %).

Molecular formula	**:**	$C_{12}H_{20}F_6NP$
Nature	**:**	Faint yellow liquid
IR (nujol)	**:**	3673, 3593, 3435, 3098, 2932, 2862, 2004, 1909, 1860, 1812, 1758, 1634, 1594, 1505, 1470, 1384, 1296, 1253, 1204, 1157, 1038, 954, 839, 687 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.86 (t, *J* = 6.69 Hz, 3H), 1.24-1.38 (m, 6H), 1.90-2.05 (m, 2H), 2.58 (s, 3H), 4.52 (t, *J* = 7.58 Hz, 2H), 7.89 (dd, *J* = 6.06, 7.83 Hz, 1H), 8.23 (d, *J* = 7.96 Hz, 1H), 8.50 (d, *J* = 7.58 Hz, 1H merge), 8.54 (s, 1H) ppm.
^{13}C NMR (D_2O, 50 MHz)	**:**	δ 13.14, 17.61, 21.44, 24.79, 30.12, 30.65, 61.12, 127.03, 139.19, 140.86, 143.25, 145.20 ppm.
Anal. Calcd. for $C_{12}H_{20}F_6NP$	**:**	Calcd.: C, 44.59; H, 6.24; N, 4.33. Found: C, 44.15; H, 6.07; N, 4.42.
MS (EI) (*m/z*)	**:**	178 (M - X).

(9) 1-Dodecyl-3-methylpyridinium bromide [DDMPy]Br [1a(iii)]:

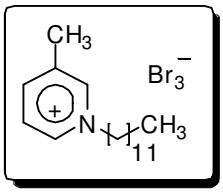


To a stirred solution of 3-picoline (5.0 g, 0.053 mol) and 1-bromo dodecane (12.89 mL, 0.053 mol) was heated and refluxed at 90 ^{o}C for 4-5 h. Excess 1-bromo dodecane was distilled off at 80 ^{o}C under reduced pressure (10 mm Hg) over 2 h to afford [DDMPy]Br as a yellow solid (25.06 g, 96.0 %).

Molecular formula	**:**	$C_{18}H_{32}BrN$
Nature	**:**	Yellow solid
Mp	**:**	55-57 ^{o}C
IR (nujol)	**:**	3666, 3429, 3017, 2855, 2453, 1634, 1591, 1505, 1466, 1378, 1321, 1245, 1153, 1049, 921, 807, 753, 687, 661 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.85 (t, *J* = 6.32 Hz, 3H), 1.21-1.30 (m, 18H), 1.95-2.09 (m, 2H), 2.64 (s, 3H), 4.93 (t, *J* = 7.32 Hz, 2H), 8.02 (dd, *J* = 6.06, 7.96 Hz, 1H), 8.24 (d, *J* = 8.09 Hz, 1H), 9.27 (d, *J* = 6.06 Hz, 1H), 9.46 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.87, 18.43, 22.39, 25.81, 28.84, 29.04, 29.31, 31.60, 31.78, 61.41, 127.63, 139.35, 142.04, 144.37, 145.38 ppm.
Anal. Calcd. for $C_{18}H_{32}BrN$	**:**	Calcd.: C, 63.15; H, 9.42; N, 4.09. Found: C, 63.28; H, 9.21; N, 4.26.
MS (EI) (*m/z*)	**:**	262 (M - X).

---

(10) 1-Dodecyl-3-methylpyridinium tribromide [DDMPy]Br_3 [1b(iii)]:



Molecular bromine (0.299 mL, 5.84 mmol) was added slowly to 1-dodecyl-3-methylpyridinium bromide (2.0 g, 5.84 mmol) under stirring at 0 ^{o}C to room temperature for 2 h to produce a deep red liquid. The liquid was left in vacuo overnight to furnish [DDMPy]Br_3 as a red liquid (2.8 g, 95.27%).

Molecular formula	**:**	$C_{18}H_{32}Br_3N$
Nature	**:**	Red liquid
IR (nujol)	**:**	3054, 2923, 2.52, 1591, 1465, 1384, 1046, 757,

684 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ0.87 (t, *J* = 6.69 Hz, 3H), 1.25-1.38 (m, 18H), 2.02-2.20 (m, 2H), 2.70 (s, 3H), 4.72 (t, *J* = 7.70 Hz, 2H), 8.03 (t, *J* = 6.19 Hz, 1H), 8.32 (d, *J* = 7.95 Hz, 1H), 8.75 (d, *J* = 6.19 Hz, 2H) ppm.

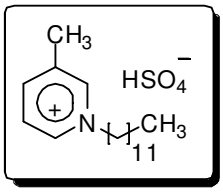
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 14.00, 19.07, 22.52, 26.12, 28.89, 29.18, 29.36, 29.45, 31.73, 62.70, 128.10, 140.31, 141.49, 143.78, 146.13 ppm.

Anal. Calcd. for $C_{18}H_{32}Br_3N$: Calcd.: C, 43.05; H, 6.42; N, 2.79.
Found: C, 43.21; H, 6.34; N, 2.83.

MS (EI) (*m/z*) : 262 (M – X_3).

---

(11) 1-Dodecyl-3-methylpyridinium hydrogen sulphate [DDMPy]HSO_4 [1c(iii)]:



To a solution of 1-dodecyl-3-methylpyridinium bromide (2.0 g, 5.8 mmol) in 20.0 mL of dry CH_2Cl_2 at 0 ^oC for 10 mins was stirred and added dropwise 97 % Conc. H_2SO_4 (0.31 mL, 5.8 mmol). The resulting solution was then refluxed for 48 h. The solution was washed with water (1 x 10 mL), collected the organic layer, and dried over anhydrous Na_2SO_4. The organic layer distilled off under reduced pressure to afford pure IL [DDMPy]HSO_4 as a viscous oil (10.55 g, 98.6 %).

Molecular formula : $C_{18}H_{33}NO_4S$

Nature : Viscous oil

IR (nujol) : 3012, 1635, 1466, 1164, 1052, 852, 688, 579 cm^{-1}.

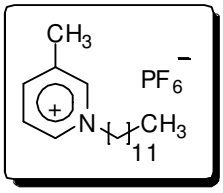
^{1}H NMR (D_2O, 200 MHz) : δ 0.52 (t, *J* = 6.57 Hz, 3H), 0.92-1.09 (m, 18H), 1.68-1.86 (m, 2H), 2.34 (s, 3H), 4.42 (t, *J* = 7.07 Hz, 2H), 7.79 (dd, *J* = 6.06, 7.96 Hz, 1H), 8.23 (d, *J* = 8.09 Hz, 1H), 8.56 (d, *J* = 6.19 Hz, 1H), 8.58 (s, 1H, merge) ppm.

^{13}C NMR (D_2O, 50 MHz) : δ 13.68, 17.79, 22.44, 25.85, 29.06, 29.27, 29.42, 29.61, 31.13, 31.76, 61.48, 127.69, 139.89, 141.48, 143.66, 146.23 ppm.

Anal. Calcd. for $C_{18}H_{33}NO_4S$: Calcd.: C, 60.13; H, 9.25; N, 3.90.

		Found: C, 60.24; H, 9.17; N, 3.85.
MS (EI) (*m/z*)	**:**	262 (M - X).

(12) 1-Dodecyl-3-methylpyridinium hexafluorophosphate [DDMPy]PF_6 [1d(iii)]:



To a stirred solution of [DDMPy]Br (1.0 g, 2.9 mmol) in 10.0 mL of H_2O, KPF_6 (0.59 g, 3.2 mmol) was added. The resulting solution was stirred at room temperature for 6 h. The immiscible layer was separated out and then the solution was extracted with dichloromethane (3 x 10 mL). Collected the organic layer, dried over anhydrous sodium sulphate and concentrated on vacuum under reduced pressure to afford [DDMPy]PF_6 ionic liquid as faint yellow solid (1.62 g, 95.4 %).

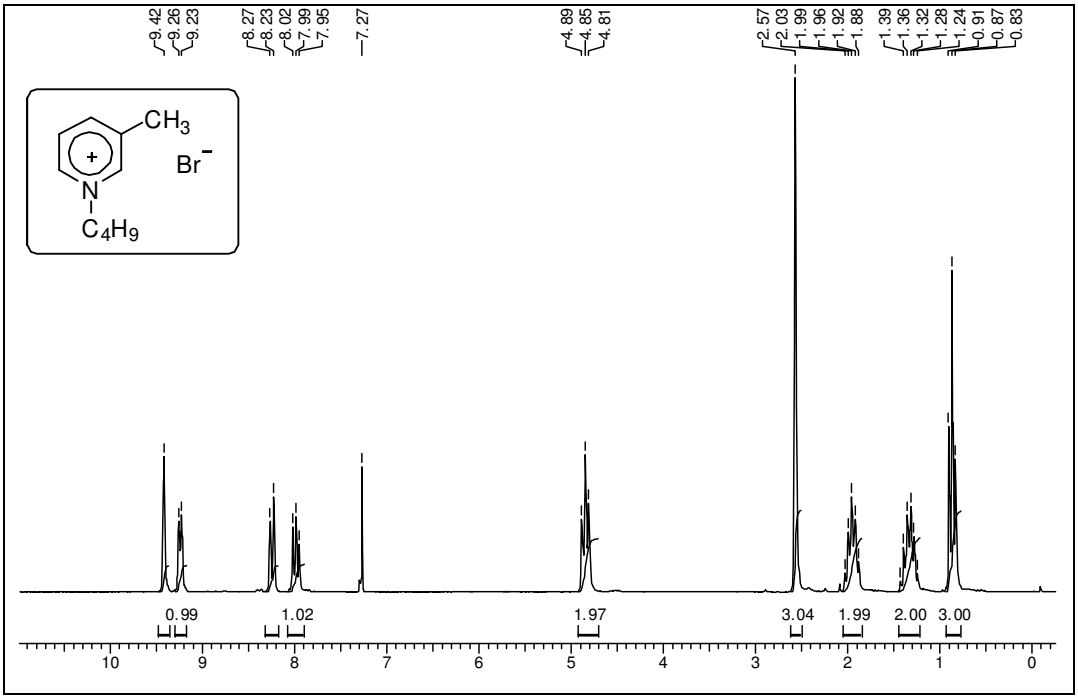
Molecular formula	**:**	$C_{18}H_{32}F_6NP$
Nature	**:**	Faint yellow solid
Mp	**:**	49-50 ^oC
IR (nujol)	**:**	3091, 3046, 2856, 1636, 1594, 1507, 1467, 1378, 1322, 1252, 1155, 1049, 841, 687 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.88 (t, J = 6.06 Hz, 3H), 1.24 (m, 18H), 1.97 (m, 2H), 2.58 (s, 3H), 4.52 (t, J = 7.45 Hz, 2H), 7.89 (dd, J = 6.06, 7.84 Hz, 1H), 8.22 (d, J = 7.95 Hz, 1H), 8.53 (d, J = 6.06 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 14.07, 18.28, 22.62, 25.96, 28.87, 29.27, 29.44, 29.54, 31.43, 31.83, 62.22, 127.77, 140.16, 141.17, 143.68, 145.91 ppm.
Anal. Calcd. for $C_{18}H_{32}F_6NP$	**:**	Calcd.: C, 53.06; H, 7.92; N, 3.44. Found: C, 52.98; H, 7.69; N, 3.48.
MS (EI)(*m/z*)	**:**	262 (M - X).

1.2.5 Spectral data

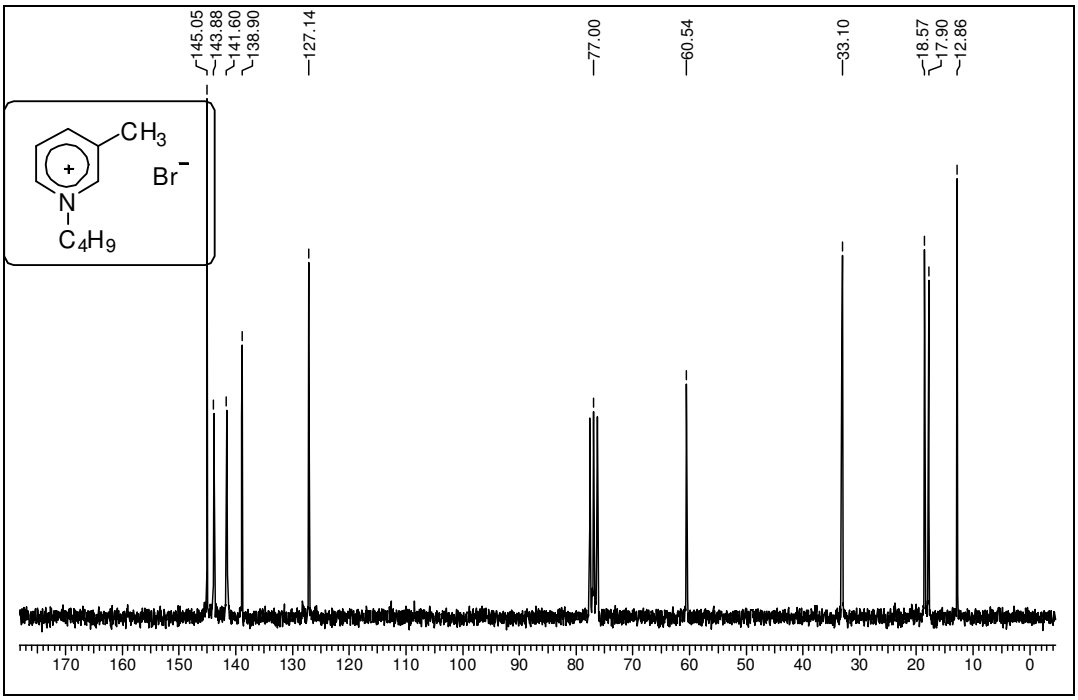
Table 6. ^{1}H and ^{13}C NMR spectrum of some selected ILs are given below:

Sr. No.	Spectra
1	^{1}H NMR and ^{13}C NMR spectra of [BMPy]Br
2	^{1}H NMR and ^{13}C NMR spectra of [BMPy]Br_3
3	^{1}H NMR and ^{13}C NMR spectra of [BMPy]HSO_4
4	^{1}H NMR and ^{13}C NMR spectra of [BMPy]PF_6
5	^{1}H NMR and ^{13}C NMR spectra of [HMPy]Br
6	^{1}H NMR and ^{13}C NMR spectra of [HMPy]HSO_4
7	^{1}H NMR and ^{13}C NMR spectra of [HMPy]PF_6
8	^{1}H NMR and ^{13}C NMR spectra of [DDMPy]Br
9	^{1}H NMR and ^{13}C NMR spectra of [DDMPy]Br_3
10	^{1}H NMR and ^{13}C NMR spectra of [DDMPy]HSO_4
11	^{1}H NMR and ^{13}C NMR spectra of [DDMPy]PF_6

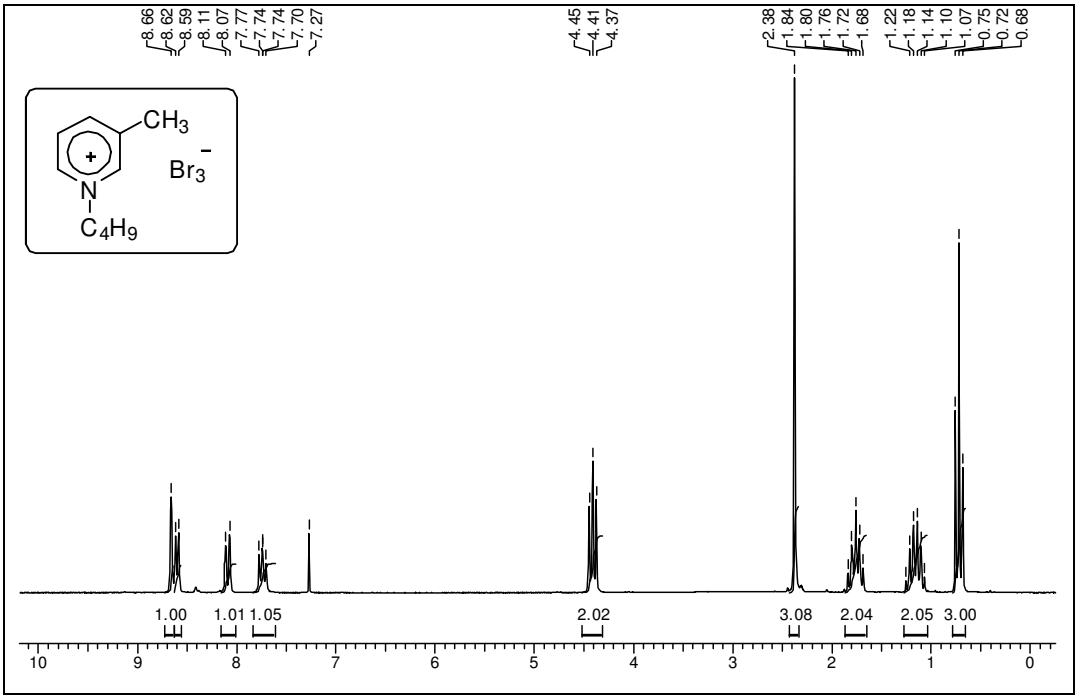
(1) ^{1}H NMR spectra of [BMPy]Br [**1a(i)**]:



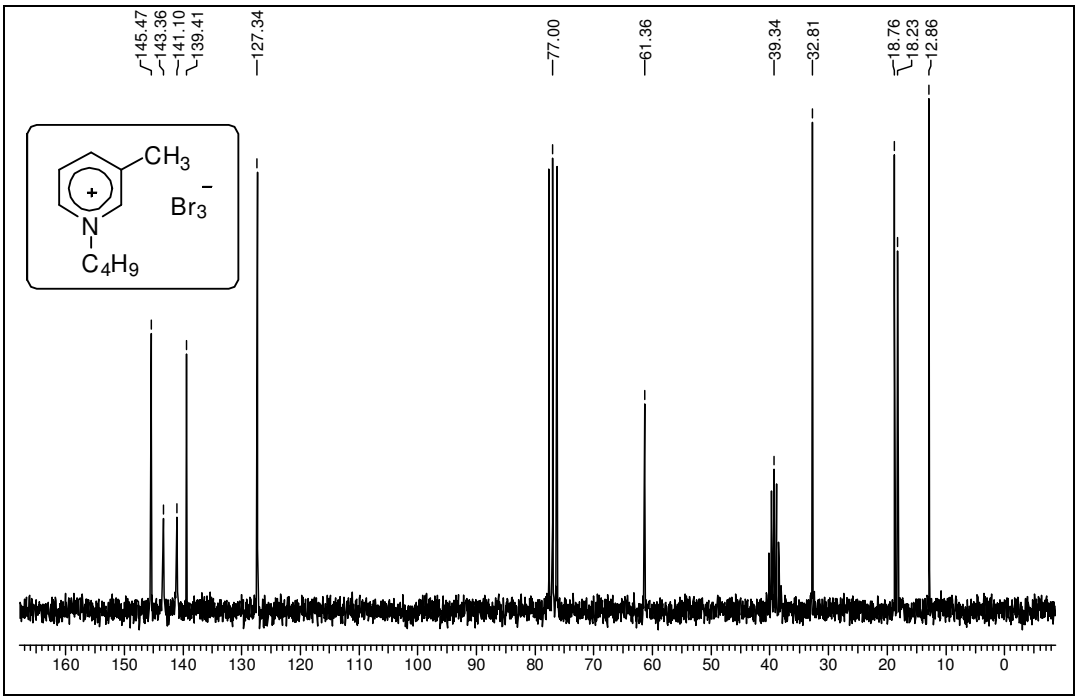
(1) ^{13}C NMR spectra of [BMPy]Br [**1a(i)**]:



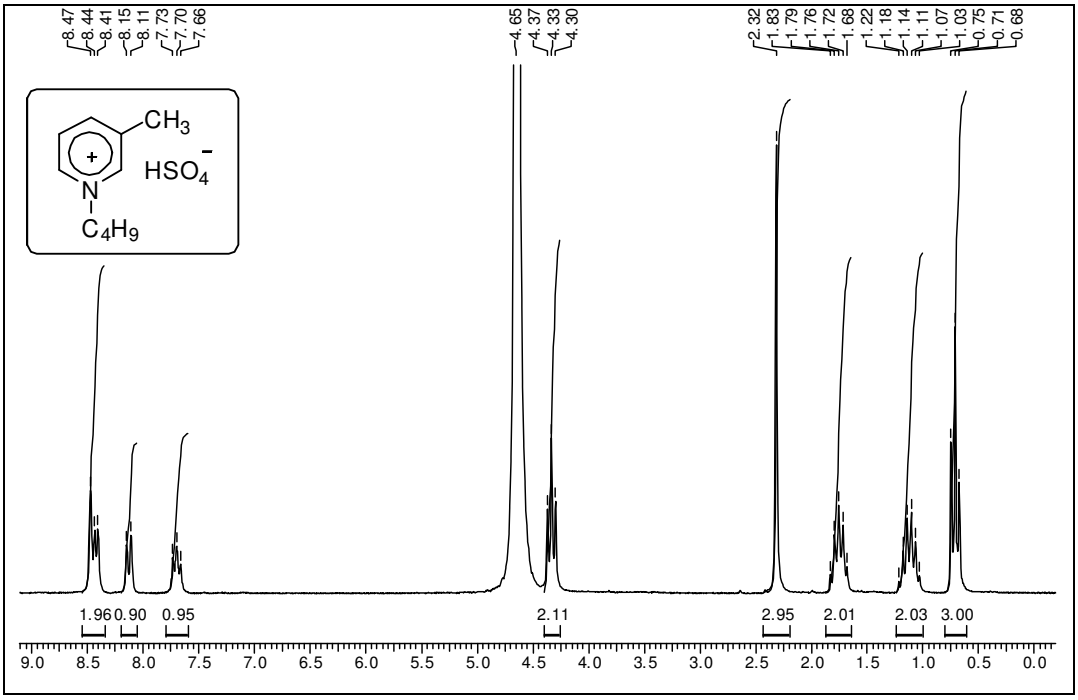
(2) ^{1}H NMR spectra of [BMPy]Br_3 [**1b(i)**]:



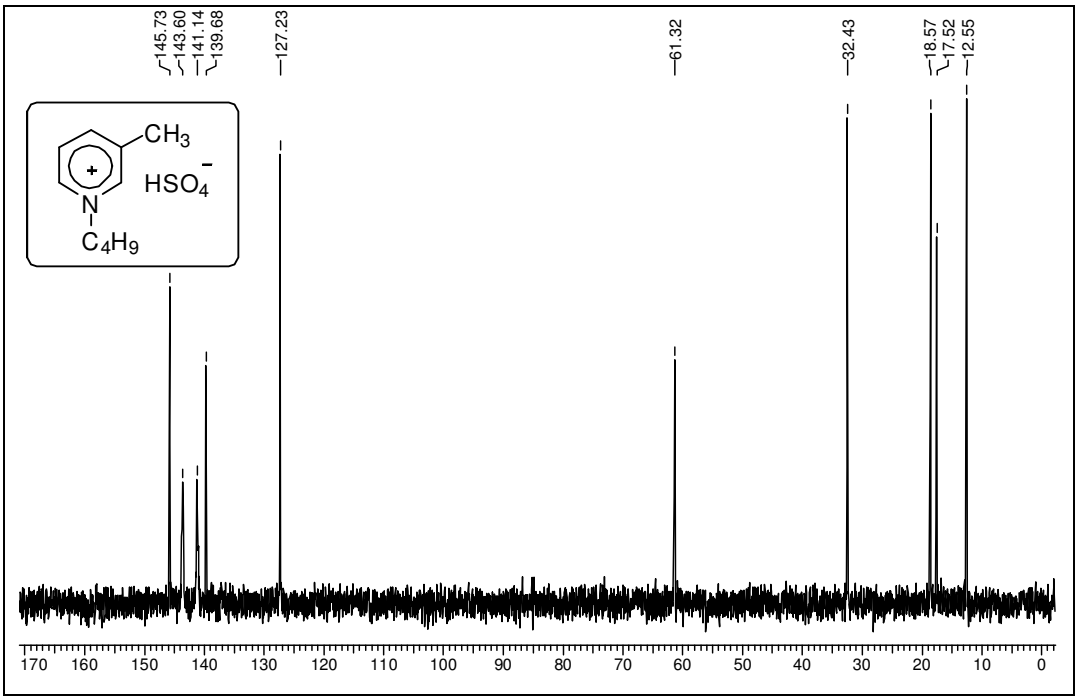
(2) ^{13}C NMR spectra of [BMPy]Br_3 [**1b(i)**]:



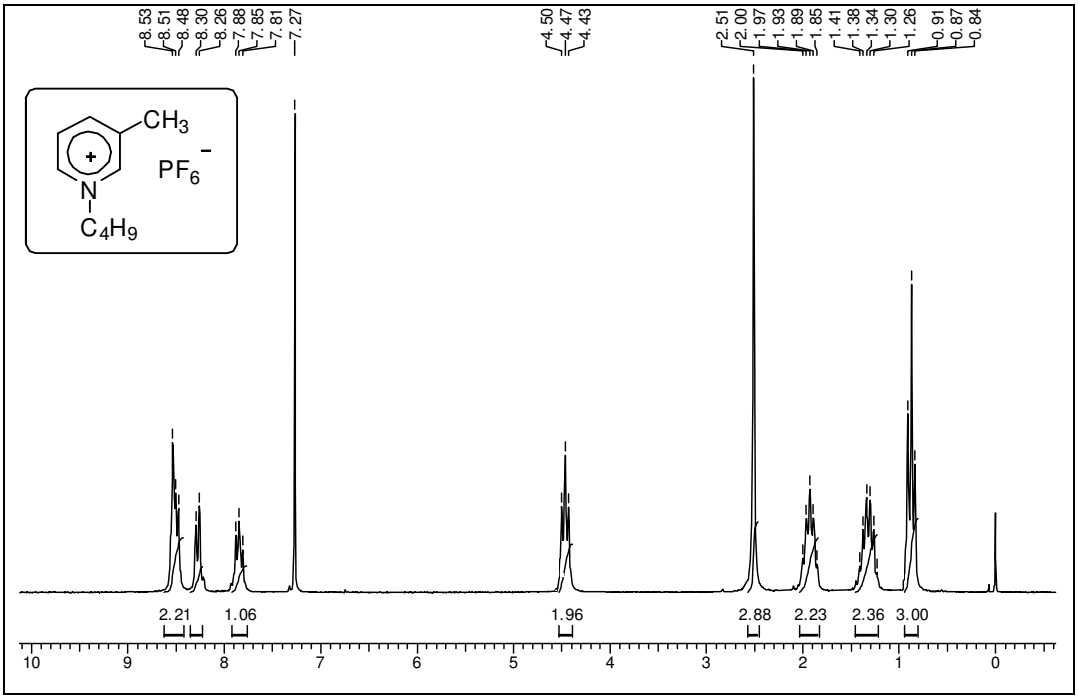
(3) ^{1}H NMR spectra of [BMPy]HSO_4 [**1c(i)**]:



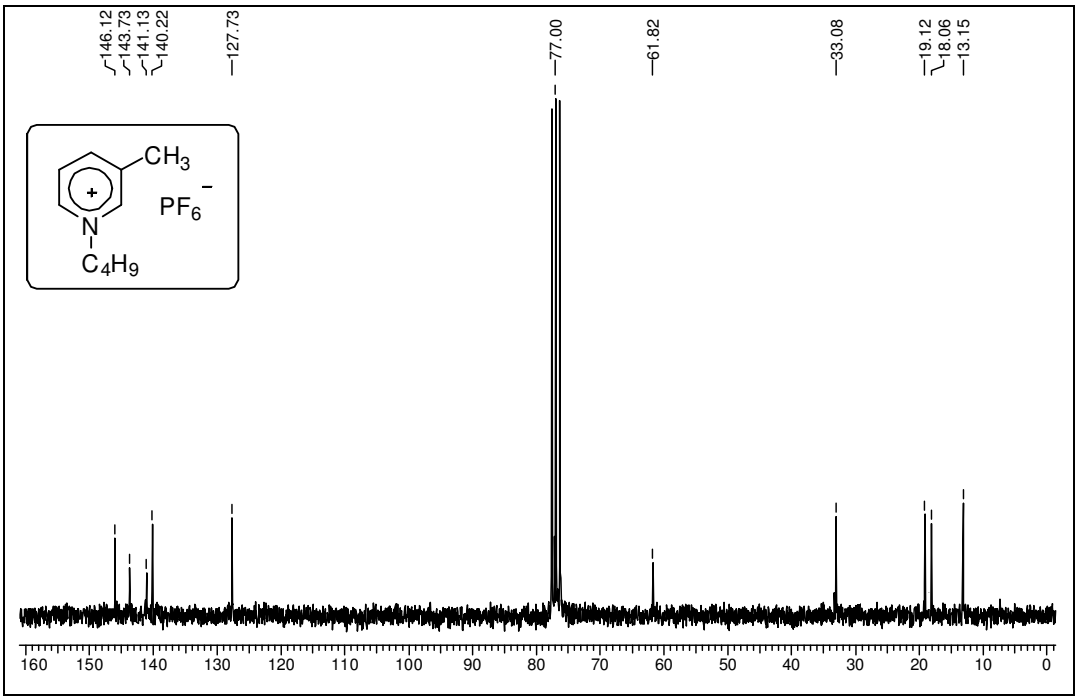
(3) ^{13}C NMR spectra of [BMPy]HSO_4 [**1c(i)**]:



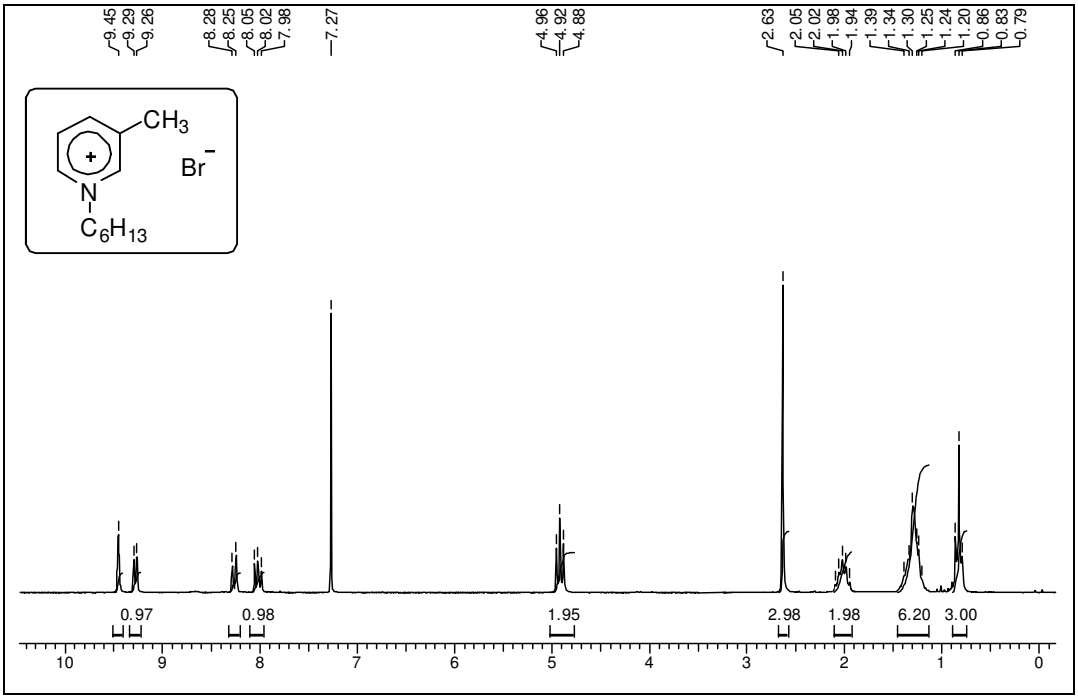
(4) ^{1}H NMR spectra of [BMPy]PF_6 [**1d(i)**]:



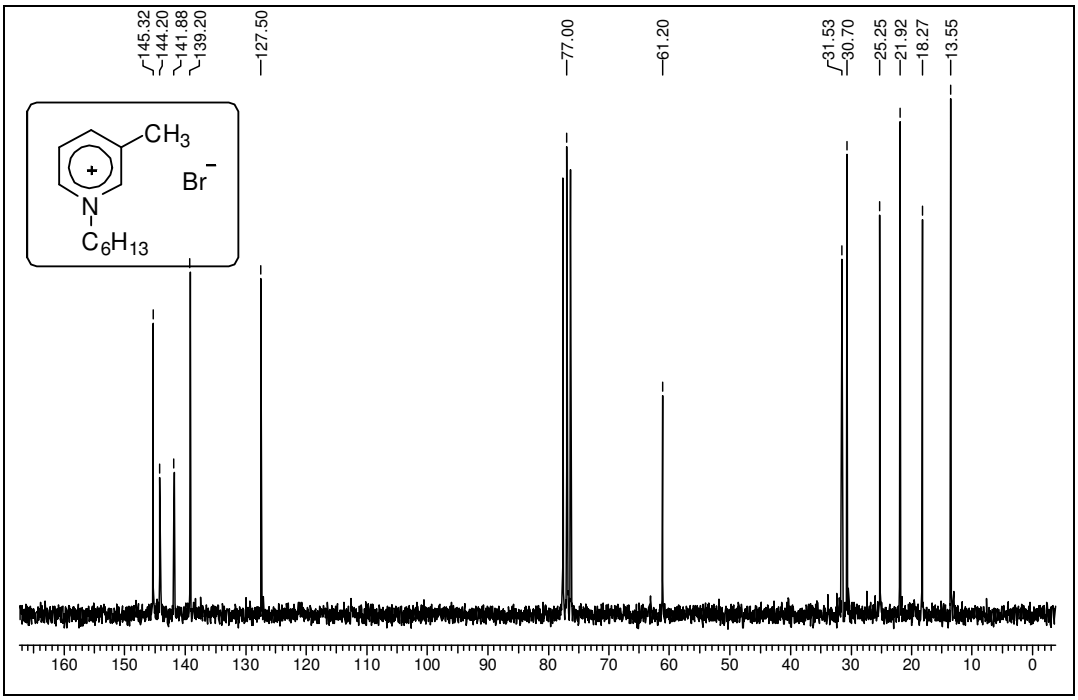
(4) ^{13}C NMR spectra of [BMPy]PF_6 [**1d(i)**]:



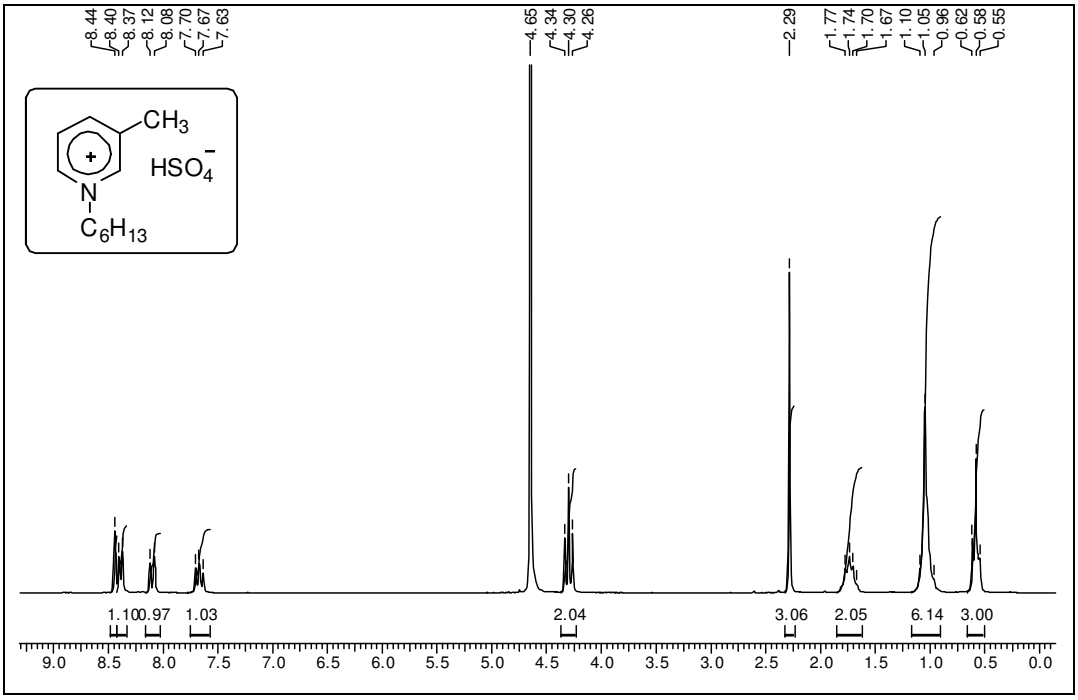
(5) ^{1}H NMR spectra of [HMPy]Br [**1a(ii)**]:



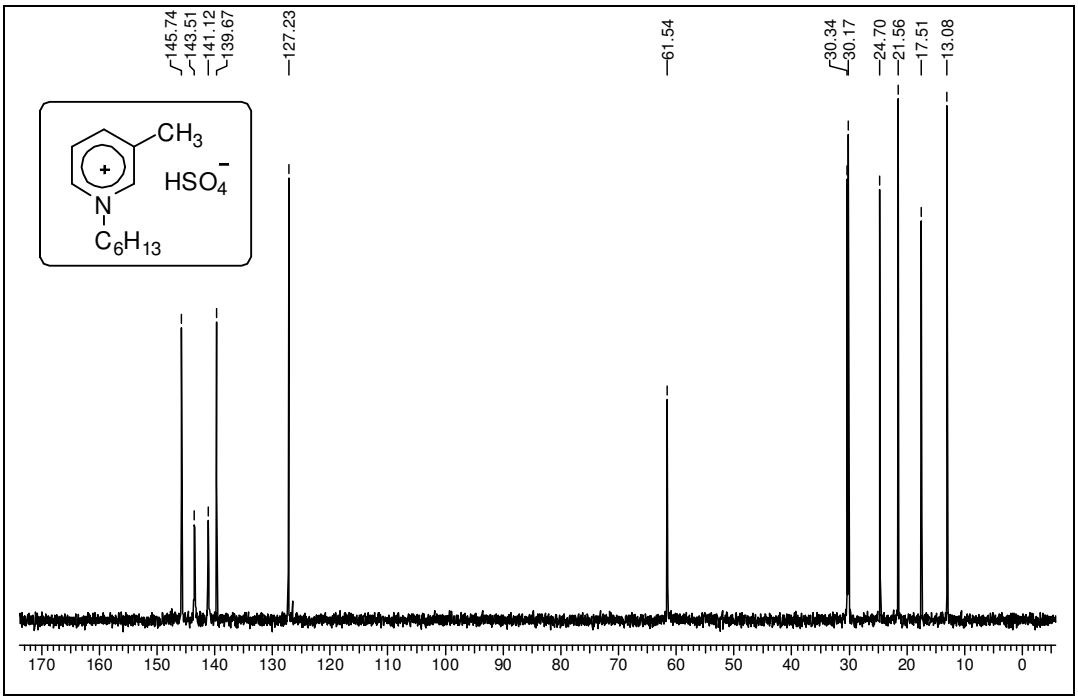
(5) ^{13}C NMR spectra of [HMPy]Br [**1a(ii)**]:



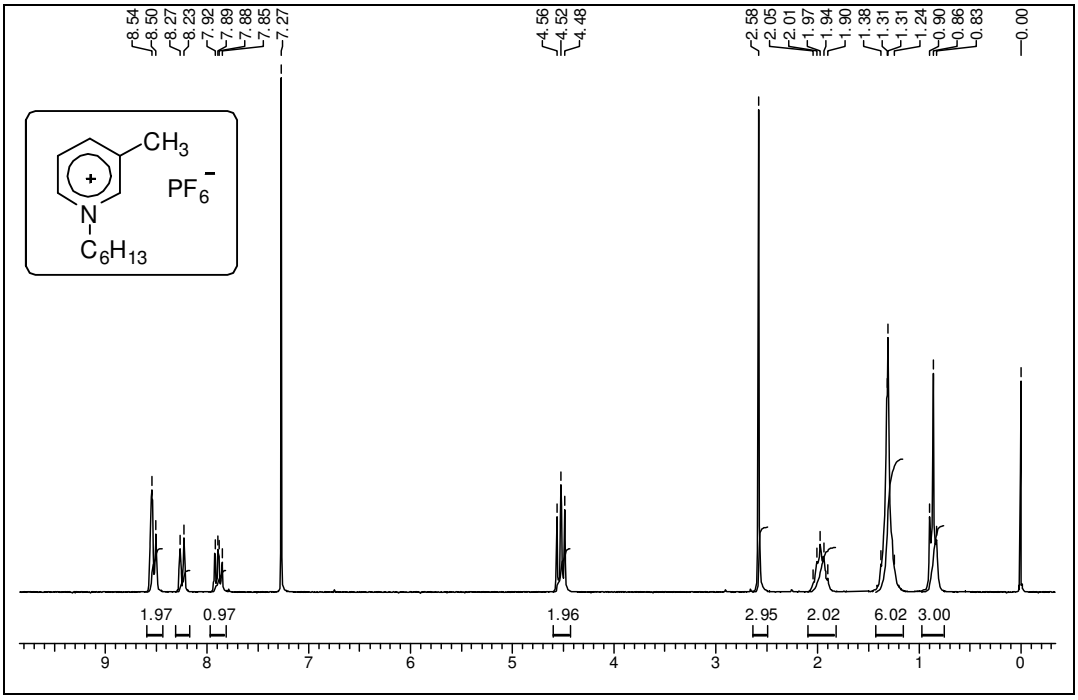
(6) ^{1}H NMR spectra of [HMPy]HSO_4 [**1c(ii)**]:



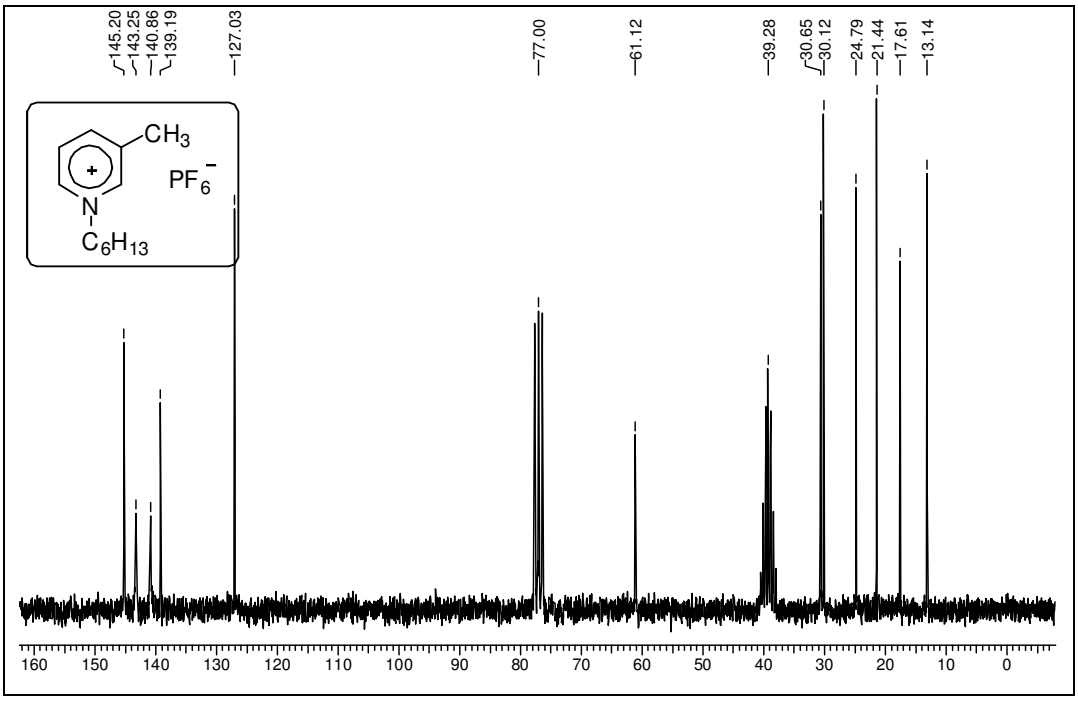
(6) ^{13}C NMR spectra of [HMPy]HSO_4 [**1c(ii)**]:



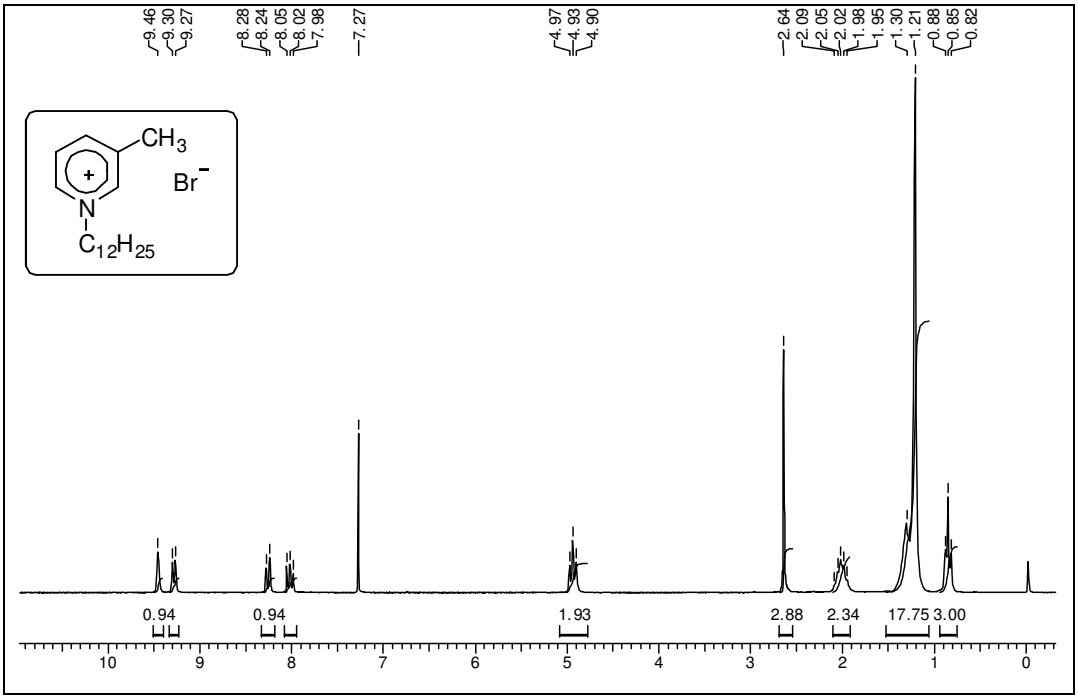
(7) ^{1}H NMR spectra of [HMPy]PF_6 [**1d(ii)**]:



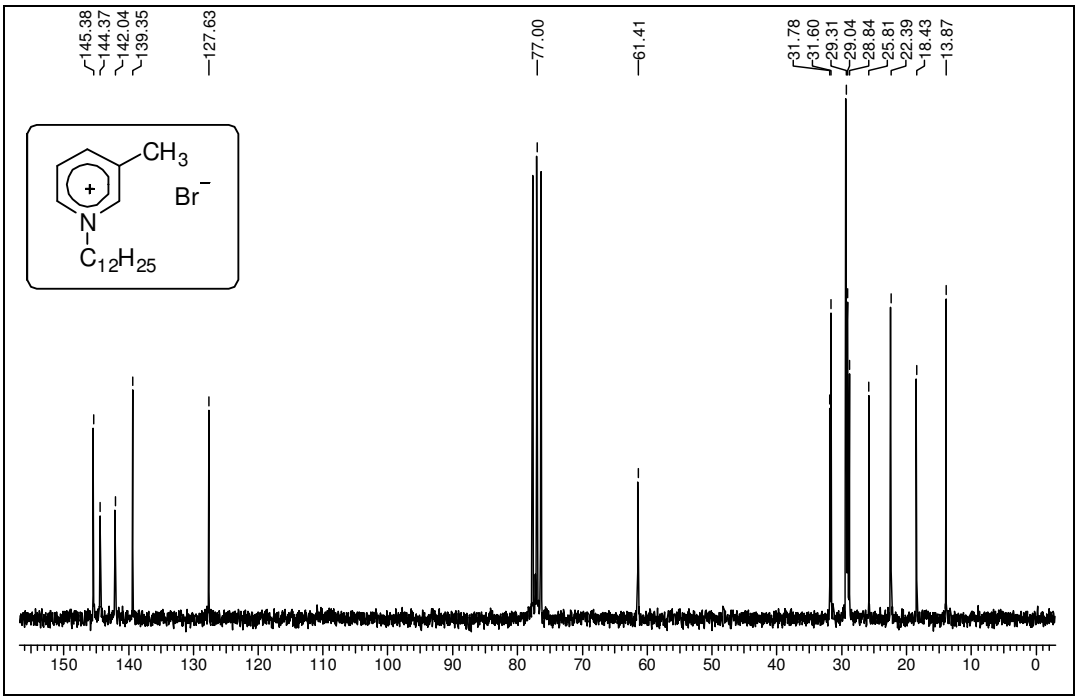
(7) ^{13}C NMR spectra of [HMPy]PF_6 [**1d(ii)**]:



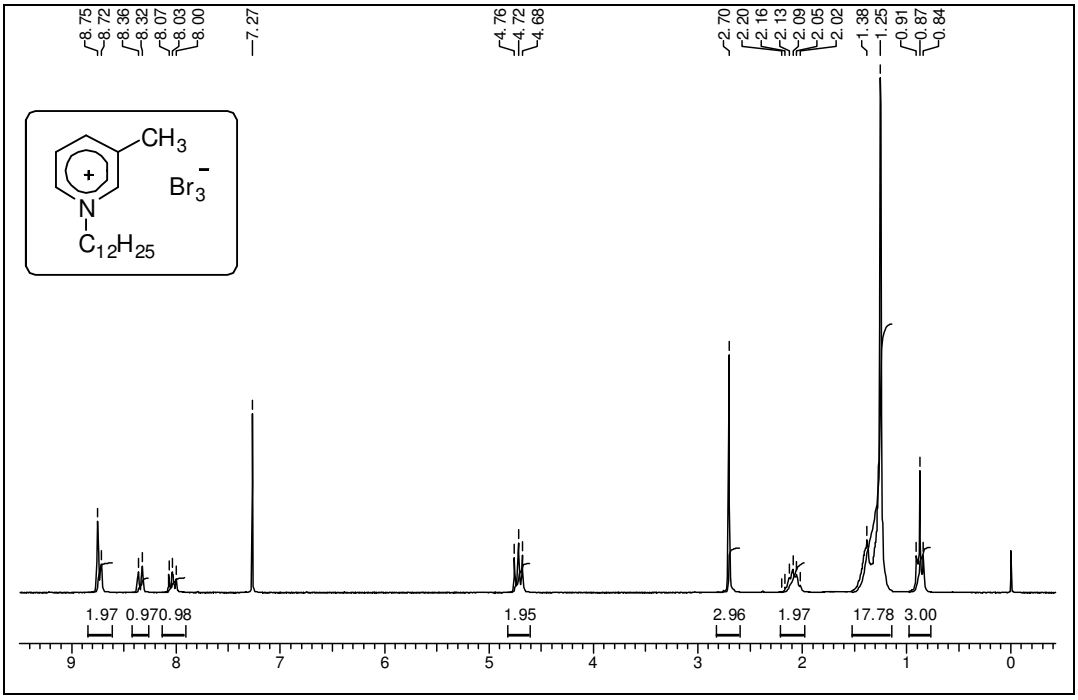
(8) ^{1}H NMR spectra of [DDMPy]Br [**1a(iii)**]:



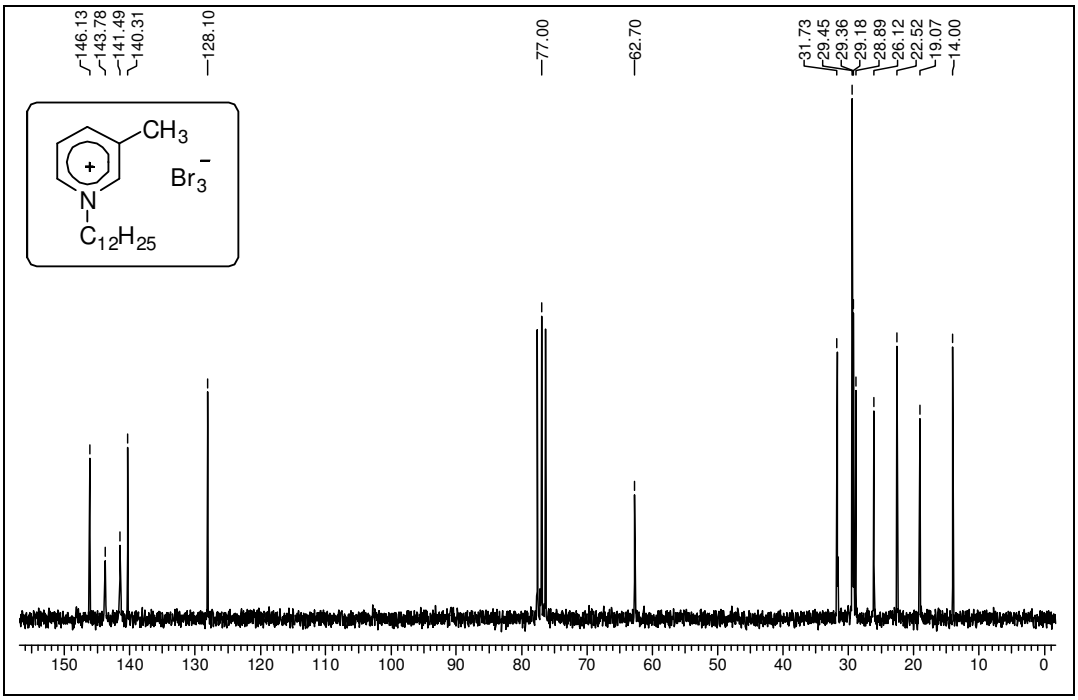
(8) ^{13}C NMR spectra of [DDMPy]Br [**1a(iii)**]:



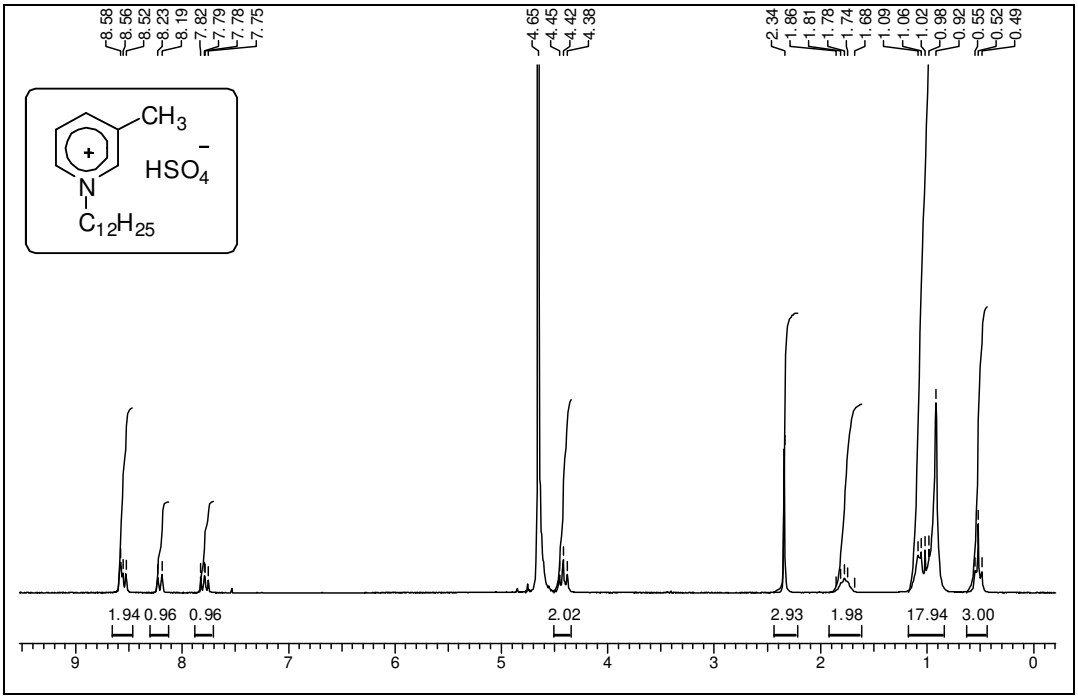
(9) ^{1}H NMR spectra of [DDMPy]Br_3 [**1b(iii)**]:



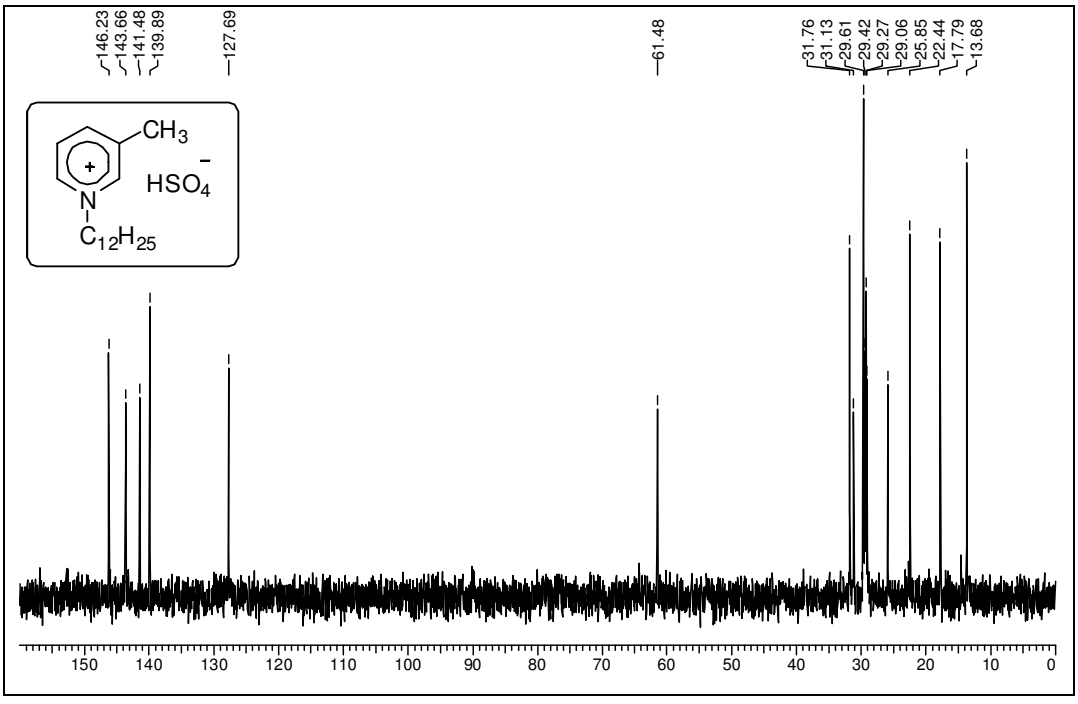
(9) ^{13}C NMR spectra of [DDMPy]Br_3 [**1b(iii)**]:



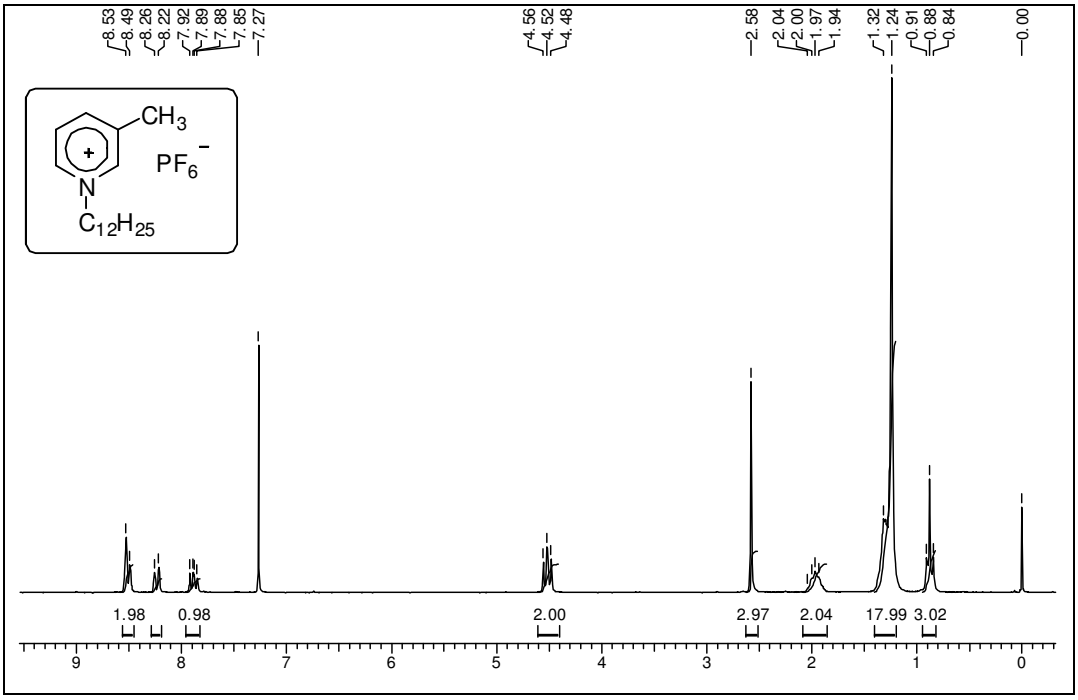
(10) ^{1}H NMR spectra of [DDMPy]HSO_4 [**1c(iii)**]:



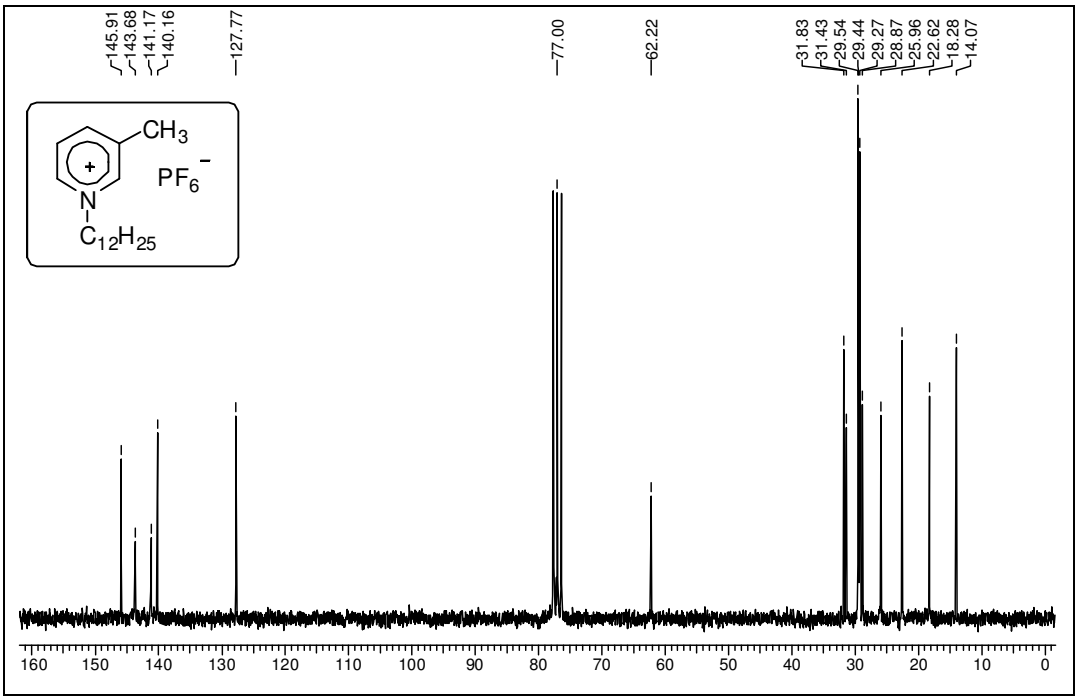
(10) ^{13}C NMR spectra of [DDMPy]HSO_4 [**1c(iii)**]:



(11) ^{1}H NMR spectra of [DDMPy]PF_6 [**1d(iii)**]:



(11) ^{13}C NMR spectra of [DDMPy]PF_6 [**1d(iii)**]:



1.2.6 References

1. Duan, Z.; Gu, Y.; Zhang, J.; Zhu, L.; Deng, Y. *J. Mol. Catal. A: Chemical* **2006**, *250*, 163.
2. Zhao, D.; Fei, Z.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 15876.
3. Ding, J.; Armstrong, D. W. Chirality 2005, 17, 281.
4. Truong, T. K. T.; Vo-Thanh, G. *Tetrahedron* **2010**, *66*, 5277.
5. Harjani, J. R.; Singer, R. D.; Garcia, M. T.; Scammells, P. J. *Green Chem.* **2009**, *11*, 83.
6. Gómeza, E.; Calvara, N.; Domínguez, A.; Macedo, E. A. *J. Chem. Thermodynamics* **2010**, *42*, 1324.

Section-C

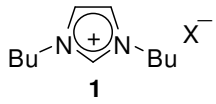
Synthesis and characterization of 1,3-di-n-butylimidazolium based ionic liquids

1.3.1 Introduction

There have been many studies in the structure of ILs with different anions and their properties. Larsen *et al.* conducted a detailed study of the liquid character of highly ionic compounds, by single crystal XRD. 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. The interaction between the cation and anion in the same ionic liquid salts are decreased essentially to the level of van der Waals or very weak hydrogen bonding type forces leading to packing inefficiency resulting in the disorder. This section deals with the synthesis and characterization of imidazolium based ionic liquids.

1.3.2 Present work

A lot of literature[1-5] is available on the synthesis and physio-chemical properties of unsymmetrical imidazolium based ionic liquids, but not much effort has been taken on the synthesis and physio-chemical properties of symmetrical imidazolium based ionic liquid.[6-10] This section deals with the synthesis and physio-chemical properties of 1,3-di-*n*-butylimidazolium [BBIm]X based ionic liquids with different anions as shown in **Figure 1**.



1

X = Br, Br_3, PF_6

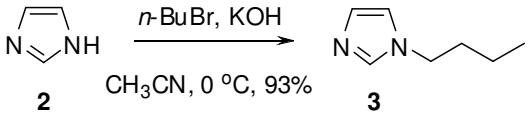
Figure 1. Structure of 1,3-di-*n*-butylimidazolium based ionic liquids

1.3.3 Results and discussion

1.3.3.1 Synthesis of Ionic Liquids

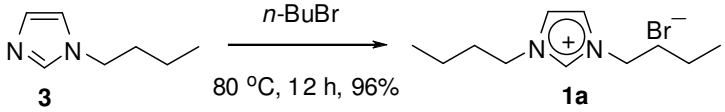
Our research interest in this area is focused mainly on the development of new ionic liquids based on symmetrical 1,3-di-*n*-butylimidazolium [BBIm]X salts **1** and exploring their use as efficient reagent and solvent (reaction media) in the organic transformations. There are several methods available in the literature for the synthesis of ionic liquids but they suffer from several drawbacks such as multistep synthesis, lower yield, harsh reaction conditions and longer reaction time.

In this section, we have focused mainly on the synthesis of these ILs. For the synthesis of ILs, the required starting material, 1-*n*-butylimidazole **3** was prepared. Imidazole **2** on treatment with 1-butyl bromide using potassium hydroxide at 0 ^{o}C produced 1-*n*-butylimidazole **3** as shown in **Scheme 1.**



Scheme 1.

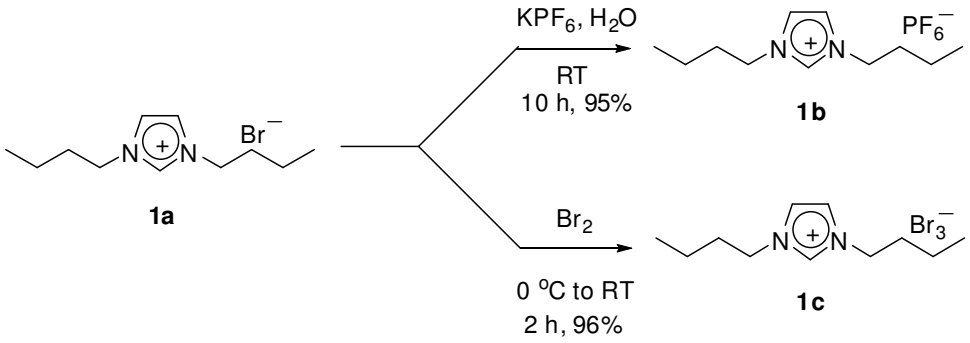
The desired IL, 1,3-di-*n*-butylimidazolium bromide ([BBIm]Br) **1a** was generated by direct alkylation and quarternization on nitrogen atom by reacting 1-*n*-butylimidazole **3** with 1-butyl bromide at 80 ^{o}C for 12 h without any solvent (**Scheme 2**). The reaction was carried out in an inert atmosphere (N_2, argon). 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. ILs should be heated carefully; otherwise excess of heat formed during the reaction generates a colored product indicating impurities might have been formed in the solvent.



Scheme 2.

The rest of ILs based on [BBIm] cation with different anion which could not easily accessible by direct alkylation. It was prepared by direct anion-anion exchange from the desired acid or salt in the second step. This process is referred as metathesis. The metathesis reaction is generally carried out in water. To the aqueous solution of 1,3-di-*n*-butylimidazolium bromide **1a**, potassium hexafluorophosphate (KPF_6) in water was added with stirring. The solution turned milky immediately due to the precipitation of salt. After 10 h of stirring, the layer containing the ILs with the PF_6 anion separated out; which was extracted with ethyl acetate. The organic layer was washed with water, dilute hydrochloric acid, and finally with brine. The excess

solvent was distilled off under reduced pressure to give [BBIm]PF_6 **1b** in high purity as shown in **Scheme 3**.



Scheme 3.

The bromination of 1,3-di-*n*-butylimidazolium bromide **1a** using molecular bromine at 0 °C to room temperature under stirring produced 1,3-di-*n*-butylimidazolium tribromide ([BBIm]Br_3) **1c** in good yield as red colored liquid. Excess bromine was removed completely by applying high vacuum.

1.3.3.2 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 H_a and H_b. This effect can be explained by two phenomena i) H-bonding and ii) ring stacking.

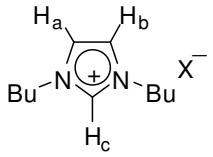


Table 1. ^{1}H NMR values of imidazolium cation

IL	ILs		Chemical Shift (δ ppm)[a]		
	Cation	Anion	H_a	H_b	H_c
1a	[BBIm]	Br	7.66	7.65	10.41
1b	[BBIm]	PF_6	7.32	7.32	8.57
1c	[BBIm]	Br_3	7.44	7.43	8.99

[a.] ^{1}H NMR was recorded in $CDCl_3$ using TMS as internal 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 anions. It is clear that H_c proton is less electron rich than H_a and H_b because it is directly attached to a carbon atom in between two electronegative nitrogen atoms. So that H_c proton is more prone for H-bonding with counter anion than others. This is shown in the NMR shifts of H_c proton. In the case of more electronegative and basic Br^-, the shift is at 10.41 ppm. But in the case of less electronegative and basic anion PF_6^- and Br_3^- the shift is at 8.57 and 8.99 ppm as shown in **Table 1**. From this it can be proved that PF_6 and Br_3 salts are more covalently bonded than its Br counterpart. This is also agreeing with the solubility of these salts in water. PF_6 and Br_3 salts are hydrophobic while Br salt is hydrophilic and hygroscopic in nature. This characteristic property can be made use of in designing ILs of different solubilities in water.

1.3.3.3 Density of Ionic Liquids

The density of IL 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 2**).

Table 2. Density of [BBIm]X ILs

IL	ILs		Density [a]
	Cation	Anion	g/cm^3
1a	[BBIm]	Br	1.23
1b	[BBIm]	PF_6	1.22
1c	[BBIm]	Br_3	1.55

[a.] Density was determined at 28 ^oC.

1.3.3.4 Viscosity of Ionic Liquids

It is the most important property for initially determining the process ability of a solvent or reagent. 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. In the previous

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

Table 3. Viscosity of [BBIm]X ILs

IL	ILs		Viscosity [a]
	Cation	Anion	(cP)
1a	[BBIm]	Br	373.1
1b	[BBIm]	PF_6	132.0
1c	[BBIm]	Br_3	59.5

[a.] Viscosity was determined at 28 ^oC.

Viscosity is on a higher side for ILs with more basic anion. In PF_6 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 Br based ILs because of more basic anion and smaller size, the van der Waals forces dominates over the H-bonding due to less charge delocalization. This will increase the viscosity of the IL (**Table 3**).

1.3.3.5 Thermal Analysis of Ionic Liquids

The ILs has negligible vapor pressure and therefore it decomposes on heating. In general, the ILs are thermally stable up to 400 ^oC after which it tends to decompose and at around 480 ^oC it completely decomposes. It was clear from our experiments that halide ions suddenly decrease the thermal stability by almost 100 ^oC. Decomposition started at around 220 ^oC and the IL fully decomposed at around 330 ^oC. In the case of PF_6 salts, decomposition started at 335 ^oC and at 480 ^oC complete weight loss was observed. However, decomposition of 1,3-di-*n*-butylimidazolium ionic liquids are started at around 130 ^oC.

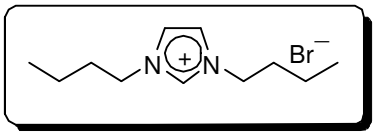
Usually the complete weight loss should occur with the absorption of heat, which will result in an endotherm. The tribromide ILs was liberated bromine gas during the decomposition. In the case of PF_6 salts, there may be some side reaction, which can result in a more thermodynamically stable product. From the weight loss calculated from the exact decomposition temperature, it can be concluded that the

decomposition of PF_6 species into more stable Br^- species may have resulted in the endotherm.

1.3.4 Experimental Section

Preparation and characterization of different ionic liquids (ILs):

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

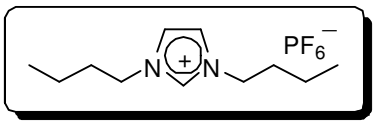


To a mixture of 1-*n*-butylimidazole (2.5 g, 0.02 mol) and *n*-butyl bromide (3.01 g, 0.022 mol) was heated with stirring at 80 °C for 12 h. Excess *n*-butyl bromide was distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [BBIm]Br as colourless viscous liquid (5.04 g; 96.0%).

Molecular formula	**:**	$C_{11}H_{21}BrN_2$
Nature	**:**	Colourless viscous liquid
IR (nujol)	**:**	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.97 (t, J = 7.20 Hz, 6H), 1.33-1.45 (m, 4H), 1.86-2.01 (m, 4H), 4.39 (t, J = 7.33 Hz, 4H), 7.65 (d, J = 1.64 Hz, 2H), 10.41 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 12.86, 18.82, 31.60, 49.11, 121.92, 135.99 ppm.
Anal. Calcd. for $C_{11}H_{21}BrN_2$	**:**	Calcd.: C, 50.57; H, 8.05; N, 10.73. Found: C, 50.24; H, 7.91; N, 10.54.
MS (EI) (*m/z*)	**:**	181 (M - X).

---

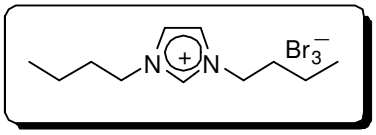
(2) 1, 3-Di-*n*-butylimidazolium hexafluorophosphate [BBIm]PF_6 (1b):



To a solution of 1,3-di-*n*-butylimidazolium bromide (10.0 g, 0.038 mol) in water (50 mL) was added to a solution of potassium hexafluorophosphate (8.46 g, 0.045 mol) in water (25 mL), and the mixture was stirred at room temperature for 10 h. The ionic liquid [BBIm]PF_6 separated out as an immiscible layer. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with water, dil. HCl and finally with brine. Then, it was dried over anhydrous sodium sulphate. The solvent ethyl acetate was distilled off under reduced pressure leaving behind the pure IL [BBIm]PF_6 as a viscous oil (11.5 g; 92.0%).

Molecular formula	**:**	$C_{11}H_{21}F_6N_2P$
Nature	**:**	Viscous oil
IR (nujol)	**:**	3603, 3146, 2936, 1565, 1466, 1166, 1091, 754, 623 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.95 (t, *J* = 7.33 Hz, 6H), 1.26-1.41 (m, 4H), 1.78-1.93 (m, 4H), 4.17 (t, *J* = 7.45 Hz, 4H), 7.32 (d, *J* = 1.64 Hz, 2H), 8.57 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.23, 19.31, 31.80, 49.85, 122.24, 135.10 ppm.
Anal. Calcd. for $C_{11}H_{21}F_6N_2P$	**:**	Calcd.: C, 40.61; H, 6.46; N, 8.61. Found: C, 40.56; H, 6.31; N, 8.52.
MS (EI) (*m/z*)	**:**	181 (M - X).

(3) 1, 3-Di-*n*-butylimidazolium tribromide [BBIm]Br_3 (1c):



Molecular bromine (1.956 mL, 0.038 mol) was added slowly to 1,3-di-*n*-butylimidazolium bromide **1a** (10.0 g, 0.038 mol) under stirring and cooled in a ice-bath resulted a deep red liquid. The stirring was continued for 2 h. Excess bromine was removed under reduced pressure over 5 h at 60 ^oC to get pure [BBIm]Br_3 **1c (**15.5 g, 96.1%**).**

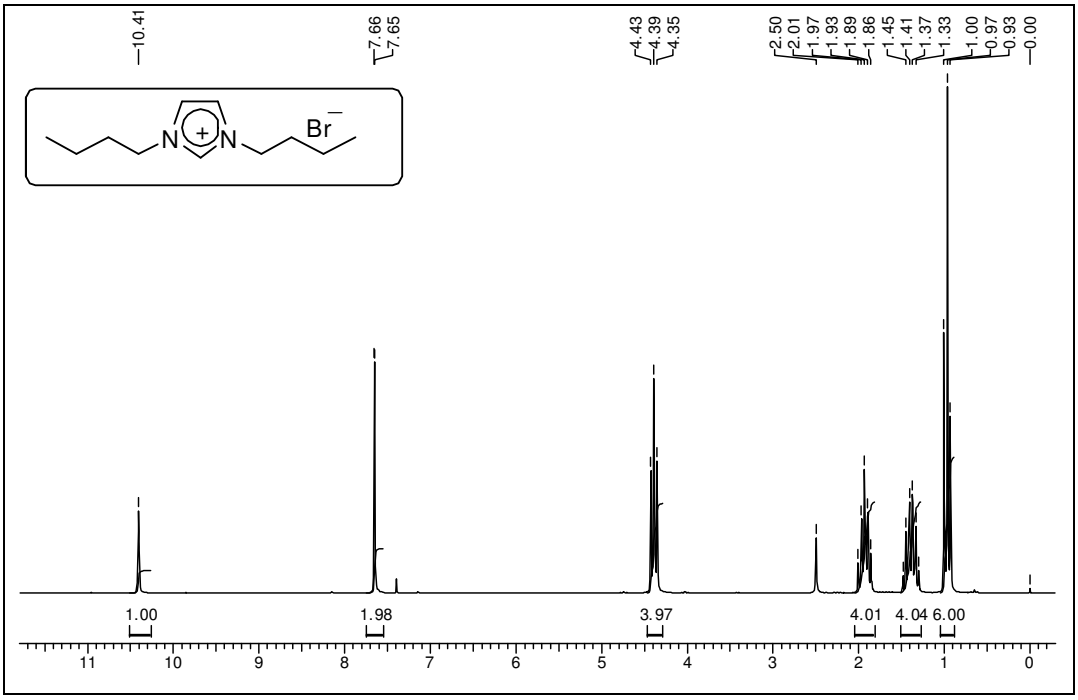
Molecular formula	**:**	$C_{11}H_{21}Br_3N_2$
Nature	**:**	Red oil
IR (nujol)	**:**	3401, 3067, 2874, 1635, 1563, 1465, 1167, 753 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.01 (t, *J* = 7.20 Hz, 6H), 1.36-1.51 (m, 4H), 1.89-2.05 (m, 4H), 4.34 (t, *J* = 7.58 Hz, 4H), 7.43 (d, *J* = 1.64 Hz, 2H), 8.99 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.21, 19.23, 31.78, 50.05, 122.40, 134.82 ppm.
Anal. Calcd. for $C_{11}H_{21}Br_3N_2$	**:**	Calcd.: C, 31.38; H, 5.03; N, 6.65. Found: C, 31.31; H, 4.93; N, 6.50.
MS (EI) (*m/z*)	**:**	181 (M – X_3).

1.3.5 Spectral data

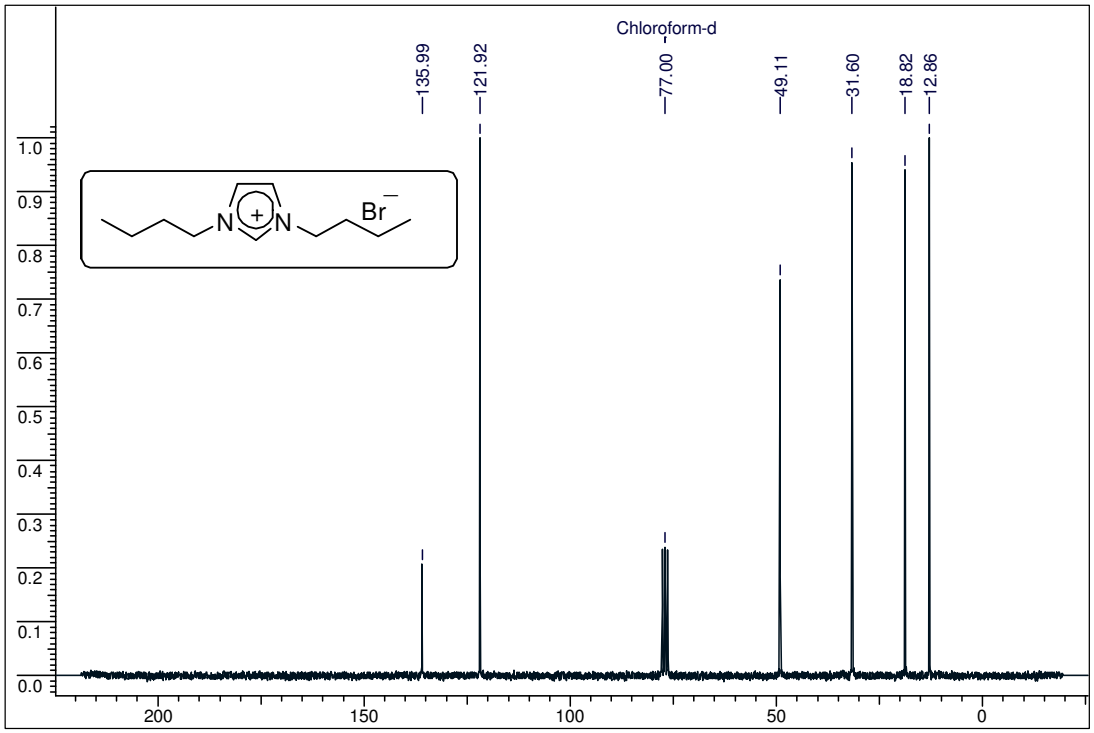
Table 4. ^{1}H and ^{13}C NMR spectrum of imidazolium ionic liquids are given below:

Sr. No.	Spectra
1	^{1}H NMR and ^{13}C NMR spectra of **[BBIm]Br**
2	^{1}H NMR and ^{13}C NMR spectra of **[BBIm]PF_6**
3	^{1}H NMR and ^{13}C NMR spectra of **[BBIm]Br_3**

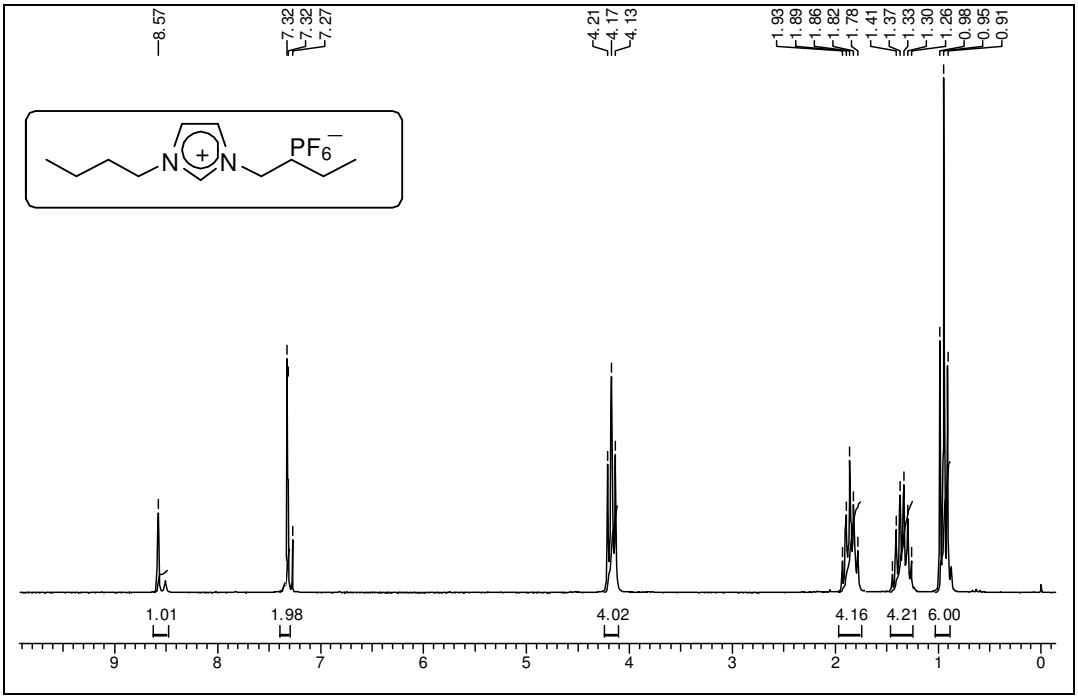
1. ^{1}H NMR spectra of [BBIm]Br (1a):



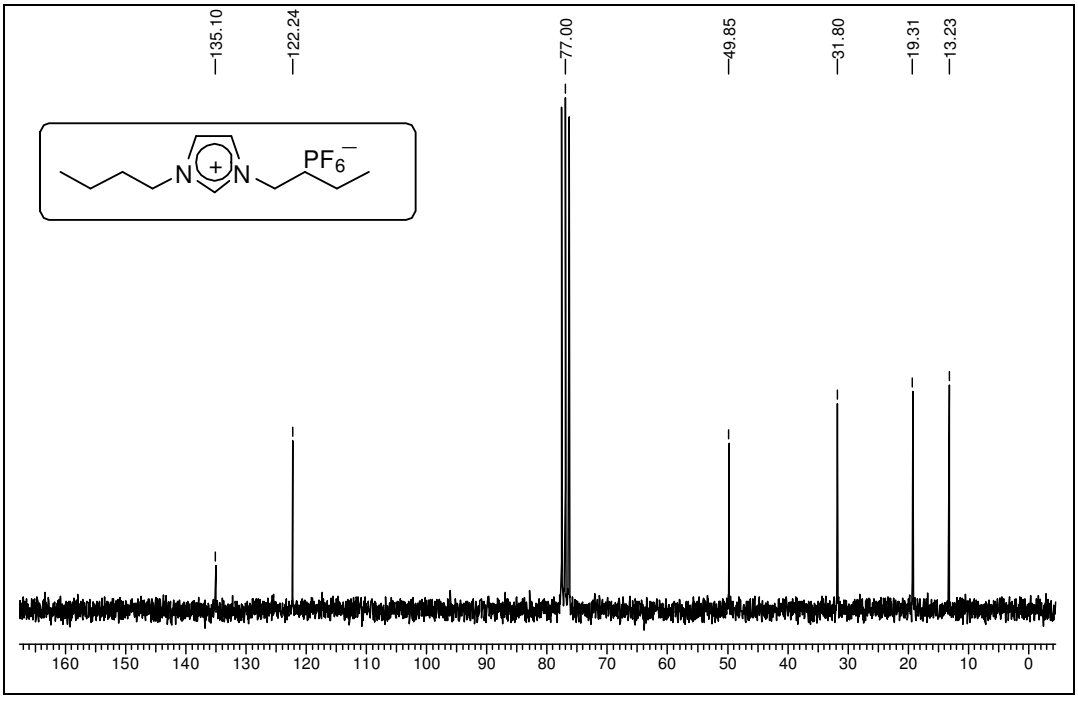
1. ^{13}C NMR spectra of [BBIm]Br (1a):



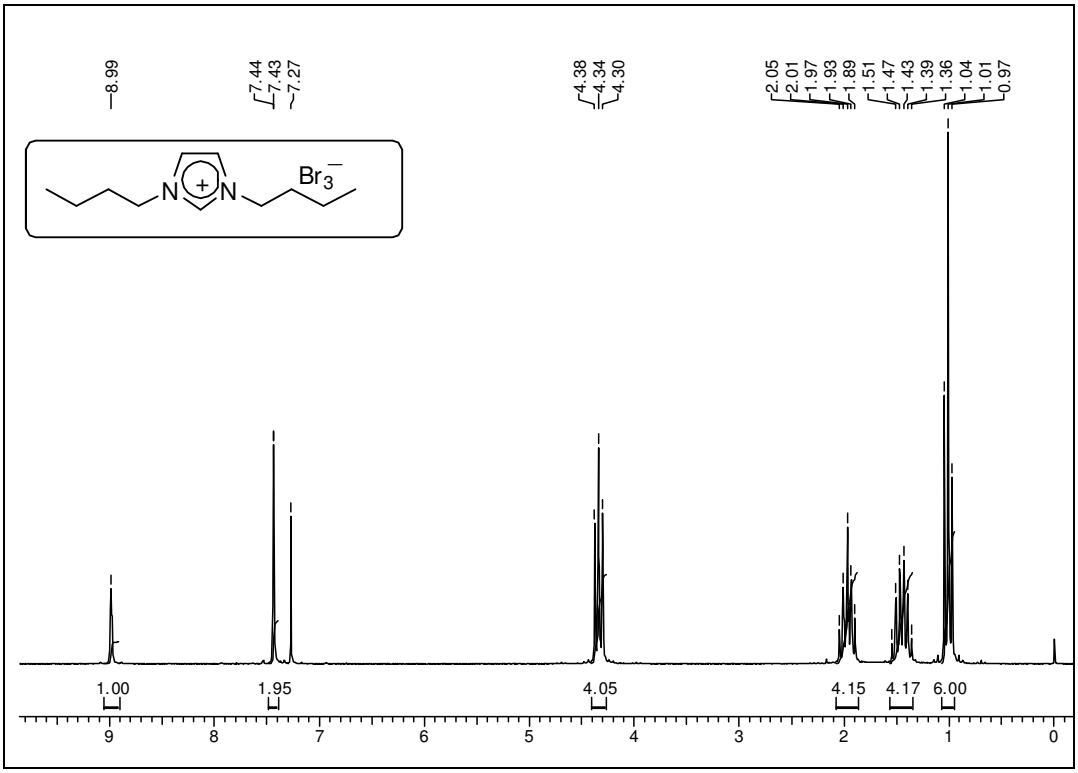
2. ^{1}H NMR spectra of [BBIm]PF_6 (1b):



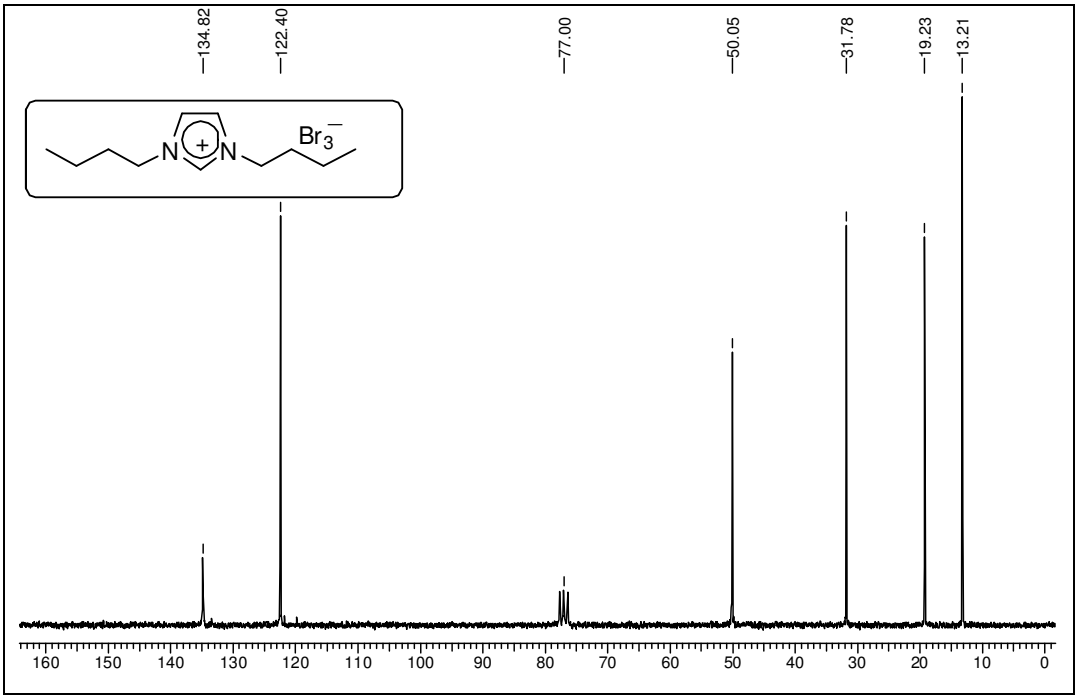
2. ^{13}C NMR spectra of [BBIm]PF_6 (1b):



3. ^{1}H NMR spectra of [BBIm]Br_3 (1c):



3. ^{13}C NMR spectra of [BBIm]Br_3 (1c):



1.3.6 References

1. Aupoix, A.; Pégot, B.; Vo-Thanh, G. *Tetrahedron* **2010**, *66*, 1352.
2. Dzyuba, S. V.; Kollar, K. D.; Sabnis, S. S. *J. Chem. Educ.* **2009**, *86*, 856.
3. Linder, T.; Sundermeyer, J. *Chem. Commun.* **2009**, 2914.
4. Myles, L.; Gore, R.; Špulák, M.; Gathergood, N.; Connon, S. J. *Green Chem.* **2010**, *12*, 1157.
5. Burrell, A. K.; Del Sesto, R. E.; Baker, S. N.; McCleskey, T. M.; Baker, G. A. *Green Chem*. **2007**, *9*, 449.
6. Pal, S. K.; Kumar, S. *Tetrahedron Lett.* **2006**, *47*, 8993.
7. LaFrate, A. L.; Bara, J. E.; Gin, D. L.; Noble, R. D. *Ind. Eng. Chem. Res.* **2009**, *48,* 8757.
8. Holbrey, J. D.; Matthew, R. W.; Swatloski, R. P.; Broker, G. A.; Pitner, W. R.; Seddon, K. R.; Rogers, R. D. *Green Chemistry* **2002**, *4*, 407.
9. Pernak, J.; Sobaszkiewicz, K.; Foksowicz-Flaczyk, J. *Chem. Euro. J.* **2004**, *10*, 3479.
10. Dzyuba, S. V.; Bartsch, R. A. *Chem. Commun.* **2001**, 1466.

Chapter II

Some useful organic transformations

Section-A

Regioselective bromination of anilines and phenols using $[BMPy]Br_3$ and $[BBIm]Br_3$ ILs

2.1.1 Introduction

Halogenated aromatic compounds are an important class of molecules in the synthetic organic chemistry. The bromination of aromatic substrates is one of the important and routinely utilized transformations in organic synthesis, especially in the synthesis of biological active molecules such as potent antitumour, antibacterial, antifungal, antiviral, and antioxidizing agents.[1] Bromination reactions of unsaturated molecules involving additions or electrophilic substitutions are common in organic synthesis. Typically, they are performed in batch processes by dissolving the substrate and the brominating reagent in a common solvent. This area has received significant interest in recent years due to the increasing commercial importance of bromo-organics. Bromo-organics are used in the synthesis of a large number of natural products as well as in the manufacture of pharmaceuticals, agrochemicals and other specialty chemicals. Bromo-organics are key intermediates in the preparation of organometallic reagents and play vital roles in transition metal coupling reactions.[2] Despite a number of precedents, new efficient methodologies for rapid and regioselective aromatic bromination of anilines and phenols are still in great demand.

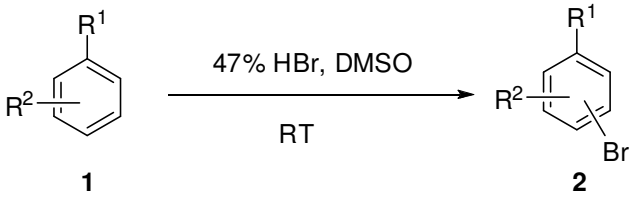
2.1.2 Review of literature

Bromine has been the most commonly used brominating reagent in the presence of an acidic or basic catalyst.[3] However, bromine is a hazardous and corrosive reagent which is difficult to manipulate due to its toxicity and high vapor pressure. The most commonly employed other reagents for this purpose are NBS in the combination of NBS-H_2SO_4-CF_3CO_2H,[4] NBS-PTSA,[5] NBS-NaOH,[6] NBS-SiO_2,[7] NBS-Amberlyst,[8] NBS-HZSM-5,[9] NBS-NH_4OAc,[10] NBS-[BMIm]Br or dioxane[11], NBS-CH_3CN,[12] NBS-solid acid,[13] and NBS-PEG-400[14]. Apart from bromine and NBS in the presence of acidic or basic catalyst, other brominating reagents such as LDH-CO_3^{2-} Br_3^-,[15] $ZrBr_4$/diazene,[16] tetrabutylammonium tribromide (TBATB),[17] IBX/TEAB,[18] LiBr/$Cu(OAc)_2$,[19] boric acid/KBr,[20] KBr/poly(4-vinylpyridine)-supported peroxodisulfate,[21] KBr with green oxidant,[22] bromodimethylsulfonium bromide (BDMS)[23] etc. have also been reported. Recently, a popular and versatile reagent commonly used for aromatic bromination is

tribromide ILs. The different methods have reported for aromatic bromination using tribromide ILs such as tridecylmethylphosphonium tribromide,[24] [BMIm]Br_3,[25] pentylpyridinium tribromide,[26] [HMIm]Br_3,[27] pyridinium tribromide [PHP],[28] tetraalkylphosphonium trihalide,[29] ethylenebis(*N*-methylimidazolium) ditribromide (EBMIDTB)[30] etc.. Nevertheless, there is still a great demand for tribromide ILs to brominate the anilines and phenols under mild conditions with excellent regio-selectivities. This section explains about some of the numerous methods reported recently in the literature for the aromatic bromination of anilines and phenols.

Chauhan *et al.* (1996)[31]

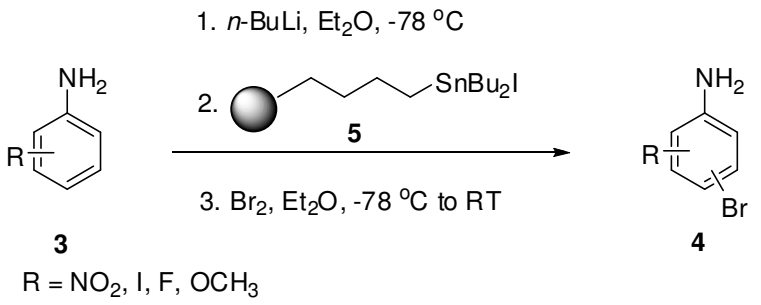
Chauhan and co-workers reported aqueous hydrobromic acid (HBr) in DMSO as an extremely powerful brominating reagent for the regiospecific bromination of benzene derivatives **1** under ambient temperature afforded brominated product **2** in good yield (**Scheme 1**). The general efficiency of this reaction was evident from the variety of monosubstituted and disubstituted benzene derivatives such as NO_2, CHO, NH_2, OH and CH_3 groups being monobrominated within a short time and regiospecifically.



Scheme 1.

Chrétien *et al.* (2005)[32]

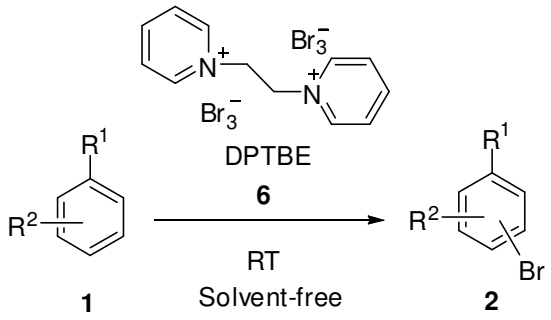
Chrétien *et al.* reported polymer-supported organotin reagent **5** for regioselective halogenation of aromatic amines **3** gave brominated product **4** in excellent yields (**Scheme 2**).



Scheme 2.

Kavala *et al.* (2005)[33]

Kavala *et al.* described 1,2-Dipyridiniumditribromide-ethane (DPTBE) **6** as new recyclable crystalline ditribromide reagent. The bromination of aromatic compounds **1** containing phenols, anilines and amides were performed under solvent-free conditions into the corresponding brominated products **2** using DPTBE in good selectivity (**Scheme 3**). The spent reagent can be recovered, regenerated, and reused without any significant loss.

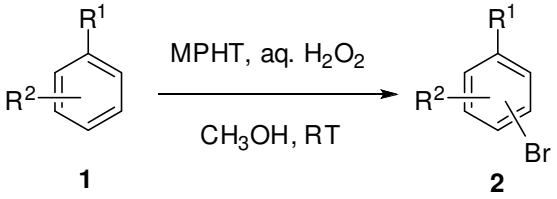


Scheme 3.

Sain *et al.* (2006)[34]

Sain and co-workers reported the regioselective bromination of various aromatic compounds **1** by using *N*-methylpyrolidin-2-one hydrotribromide (MPHT) and aqueous hydrogen peroxide (aq. H_2O_2) afforded brominated product **2** in good yields (**Scheme 4**).

The use of MPHT alone as brominating agent gave poor yields; while the addition of aq. H_2O_2 enhanced the reaction rate and in shorter reaction times.

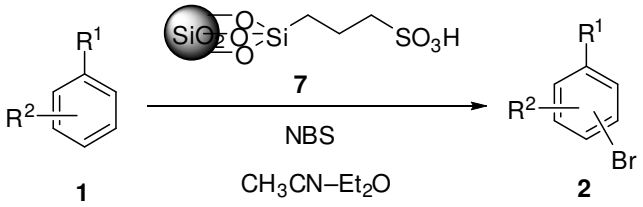


R^1 = OH, NH_2, CHO
R^2 = H, CH_3, Cl, NO_2, OCH_3, CH_3, $COCH_3$, Ph

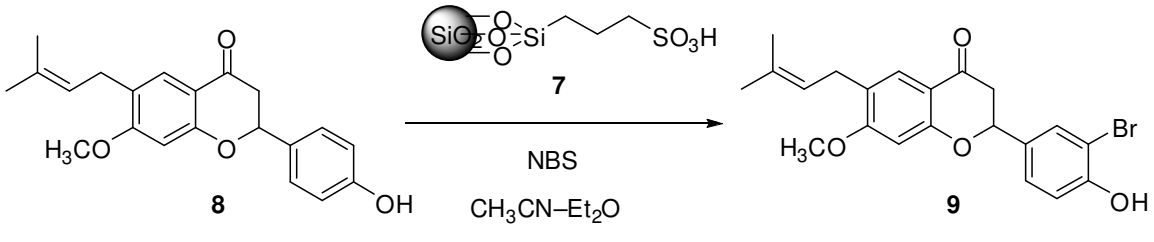
Scheme 4.

Das *et al.* (2006)[35]

Das *et al.* described sulfonic-acid-functionalized silica **7**, a heterogeneous recyclable catalyst. The nuclear bromination of aromatics **1** and heteroaromatics **8** using NBS as brominating agent catalyzed by **7** at room temperature in CH_3CN-H_2O system has been reported (**Scheme 5**). A wide variety of aromatic amines, aromatic and hetero-aromatic phenols, and some containing acid sensitive groups also underwent smooth



R^1 = OH, NH_2, OCH_3
R^2 = H, Br, CH_3, NO_2, Cl, CHO, $COCH_3$, Ph, OCH_3

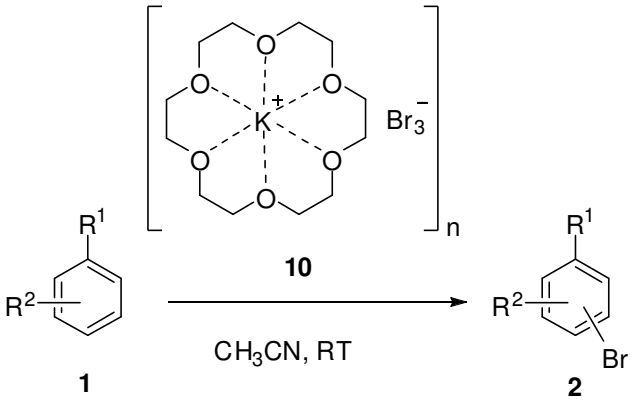


Scheme 5.

nuclear bromination. This protocol was not suitable for bromination of aromatics containing methyl group.

Zolfigol *et al.* (2007)[36]

Zolfigol and co-workers described a unique tribromide salt **10** with a nano-tube like structure ({[K.18-crown-6]Br_3}$_n$) as reagent for bromination of aromatic compounds **1** in acetonitrile at room temperature afforded brominated product **2** with good yields. (**Scheme 6**).

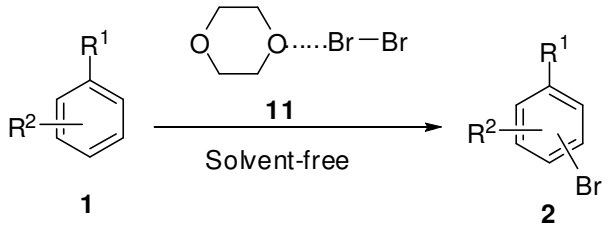


R^1 = OH, NR_2, OCH_3
R^2 = H, OCH_3, CH_3, Br, Cl

Scheme 6.

Bhar *et al.* (2007)[37]

Bhar *et al.* reported the regioselective ring bromination of aromatic compounds **1** using dioxane dibromide (DD) **11** under solvent-free conditions gave brominated products **2** with high yields and good purity (**Scheme 7**).

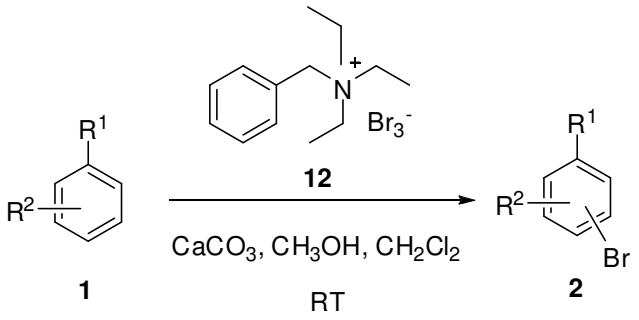


R^1 = OH, OCH_3, NH_2, NHCO
R^2 = H, Br, $COOCH_3$, CHO,

Scheme 7.

Pourmousavi *et al.* (2009)[38]

Pourmousavi *et al.* described novel benzyl triethyl ammonium tribromide (BTEAT) **12** as brominating ionic liquid. This can be used for bromination of aromatics **1** to the corresponding brominated compounds **2** at room temperature in good to excellent yields (**Scheme 8**). The tribromide ionic liquid could be recycled and reused.

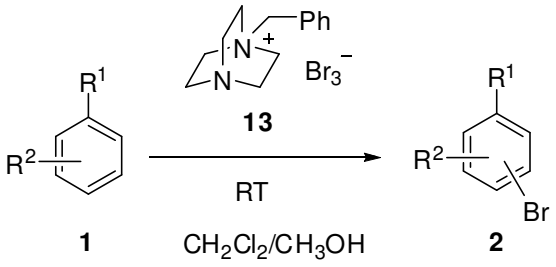


R^1 = OH, NH_2, OCH_3
R^2 = H, CH_3, NO_2, Cl, CHO, Ph

Scheme 8.

Moghaddam *et al.* (2009)[39]

Moghaddam and co-workers used *N*-benzyl-DABCO tribromide **13** as a bromine source and solid organic ammonium tribromide. The bromination of aromatic compound **1** was carried out in CH_2Cl_2 or CH_3OH at room temperature afforded corresponding brominated compound **2** (**Scheme 9**).

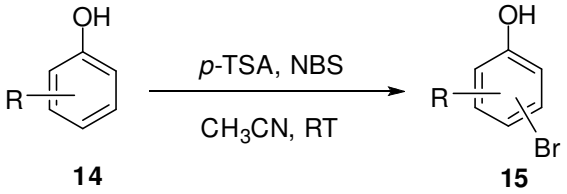


R^1 = OH, NH_2, OCH_3
R^2 = H, CH_3, NO_2, Ph, Cl, CHO

Scheme 9.

Bovonsombat *et al.* (2010)[40]

Bovonsombat and co-workers reported *para*-regioselective monobromination of phenol and its analogues **14**, promoted by *p*-toluenesulfonic acid (*p*-TSA) was achieved with high to excellent yields at room temperature using *N*-bromosuccinimide (NBS) (**Scheme 10**).

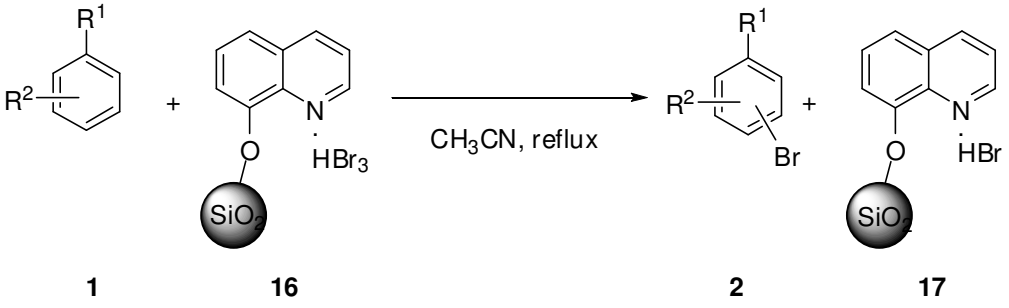


R = OCH_3, $COCH_3$, Br, CHO, CH_3, $COOCH_3$

Scheme 10.

Li *et al.* (2010)[41]

Li *et al.* synthesized silica-supported quinolinium tribromide (SQTB) **16** as recoverable solid brominating reagent and applied for regioselective monobromination of aromatic amines **1** includes primary, secondary and tertiary amines as well as amides and heterocycles (**Scheme 11**).



R^1 = NH_2, NR_2, NHCO
R^2 = H, CH_3, NO_2, Cl, COOH, OCH_3, Ph

Scheme 11.

2.1.3 Present work

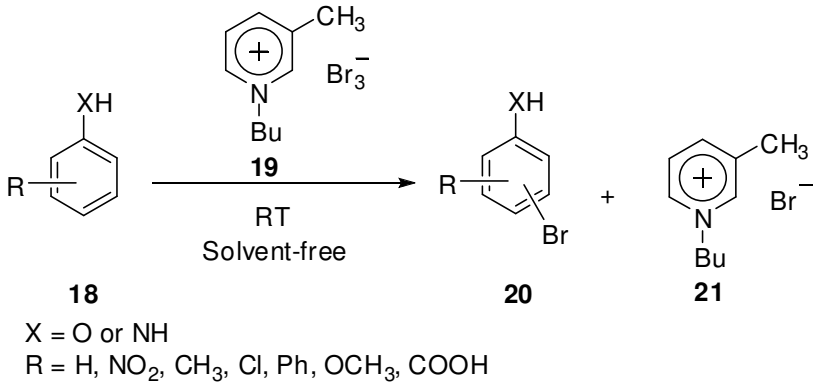
Organic reaction using conventional organic solvents especially chlorinated hydrocarbons have posed a serious threat to the environment owing to their toxicity and volatile nature. Therefore, it is imperative to perform organic reactions under solvent-free conditions. In this regard organic reactions in ionic liquids has received tremendous attention in recent times.[42]

The application of ionic liquids especially tribromides, as effective brominating reagent for organic transformation have received considerable interest in the recent decades due to their unique chemical and physical properties such as non-volatility, non-inflammability, thermal stability, eliminates toxic bromine vapors, and ease of recyclability. There has been considerable interest in developing green chemistry[43] for organic synthesis due to environmental demand and sustainability.

Despite a number of precedents, new efficient methodologies for aromatic bromination of anilines and phenols are still in strong demand. We have successfully demonstrated the [BMPy]Br_3[44] and [BBIm]Br_3[45] as a new reagent/solvent for the regioselective bromination of different anilines and phenols under mild conditions. The methodology developed by us covers all the above mentioned drawbacks since the non-volatile IL can be efficiently recovered and reused and the process does not require any additional catalyst since the IL itself promotes the reaction.

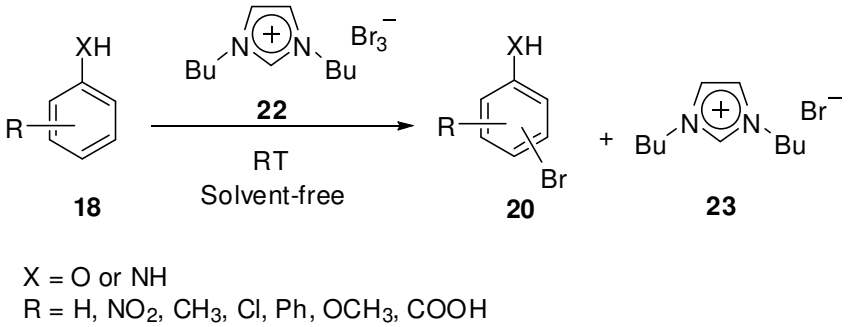
2.1.4 Results and discussion

A variety of anilines and phenols **18** including primary and tertiary amines were subjected to the regioselective nuclear bromination in IL, 1-butyl-3-methylpyridinium tribromide ([BMPy]Br_3) **19** as the brominating reagent as well as solvent at ambient temperature (30 ^oC) under solvent-free conditions afforded monobrominated products **20** (**Scheme 12**).



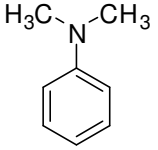
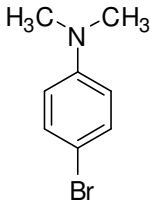
Scheme 12.

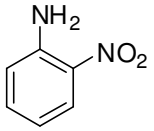
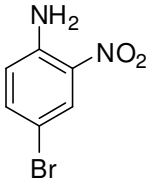
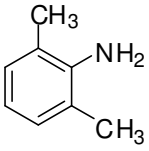
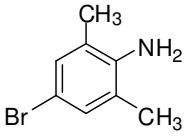
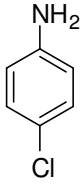
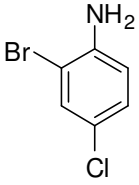
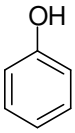
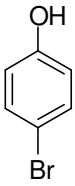
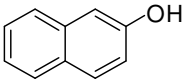
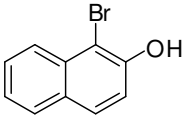
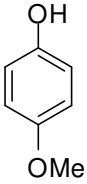
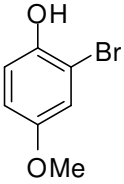
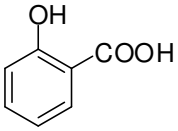
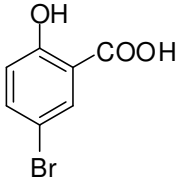
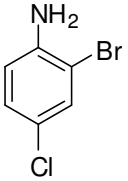
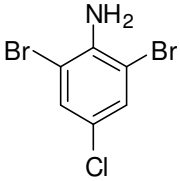
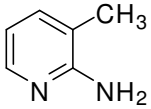
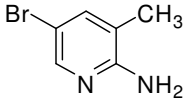
Similarly, the bromination of phenols and anilines **18** were performed in IL, 1,3-di-*n*-butylimidazolium tribromide ([BBIm]Br_3) **22** as brominating reagent and solvent at room temperature under solvent-free conditions afforded corresponding brominated compounds **20** (**Scheme 13**) and the results are summarized in **Table 1**.

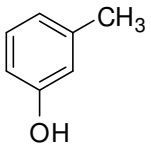
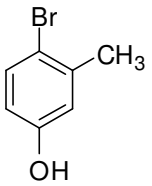
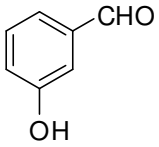
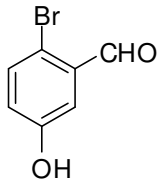
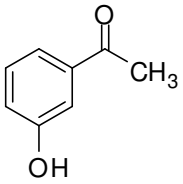
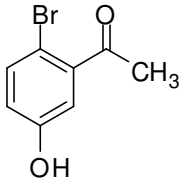
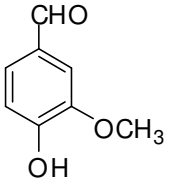
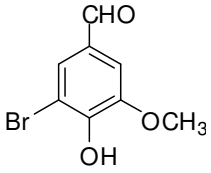
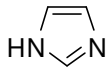
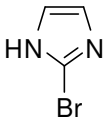


Scheme 13.

Table 1. Regioselective aromatic bromination of anilines and phenols using [BMPy]Br_3 and [BBIm]Br_3 at room temperature

Entry	**Substrate**	**Product**	**Time (min)**		**Yield (%)**	
			IL 19	**IL 22**	**IL 19**	**IL 22**
1			6	5	92	98

2			Imm.	15	98	95
3			Imm.	Imm.	98	97
4			Imm.	Imm.	97	98
5			Imm.	Imm.	96	97
6			45	3	97	98
7			12	15	98	91
8			60	-	89	-
9			2	-	98	-
10			Imm.	-	97	-

11			30	-	88	-
12			15	-	92	-
13			15	-	90	-
14			10	Imm .	98	98
15			5	-	91	-

2-Nitroaniline was monobrominated immediately by using [BMPy]Br_3 **19**; whereas it took 15 mins by using [BBIm]Br_3 **22** (entry **2**). Phenol was cleanly monobrominated under solvent-free conditions at room temperature by both the IL **19** and **22** separately, affording exclusively *p*-bromophenol (entry **5**). α-Naphthol being a bulky molecule took 45 minutes for monobromination in [BMPy]Br_3 IL; whereas in [BBIm]Br_3, it took just 3 mins. (entry **6**). Imidazole underwent monobromination to afford 2-bromoimidazole in 5 minutes (entry **15**).

The process tolerates anilines and phenols containing both electron donating and electron withdrawing substituents. The electron donating groups afforded the *para*-brominated products, when the *para*-position is blocked the *ortho*-brominated product was obtained exclusively. Whereas, when the electron withdrawing substrates were used in the bromination reaction the bromination at *meta*-position was observed. The longer reaction time afforded the dibrominated products.

All the reactions were carried out at room temperature in air, adding 1.0 eq. of IL **19** and **22** to equimolar amount of substrate without any solvent. Although the reactions were slightly exothermic, no special precautions were taken for cooling. They were monitored by TLC and stopped after the disappearance of the substrate. The time taken for complete conversion and the isolated yields are recorded in **Table 1**. All the isolated products are known compounds reported in the literature. They were well characterized by their physical constants such as boiling points and melting points. Their IR, NMR and mass spectral were in conformity with their structures.

All the reactions were quenched by adding water. This caused precipitation of the products as solids or oils, which were readily separated by extraction with ethyl acetate and washed with fresh portions of water and then dried (either with sodium sulfate or in v*acuo*). The aqueous phase containing highly water soluble ionic liquids (i. e. [BMPy]Br **21**, [BBIm]Br) **23** were easily concentrated in *vacuo* to recycle it. The recyclable ionic liquids could be used to regenerate tribromide room temperature ionic liquids **19** and **22** with the addition of bromine.

2.1.5 Conclusion

In conclusion, a new room temperature ionic liquid bromine analogue was synthesized, characterized, which is safer, easier to use; which displayed improved selectivity and better reaction condition, as compared to the current bromination techniques. This new functional RTIL [BMPy]Br_3 and [BBIm]Br_3 may be classified as "green" for the following reasons: (1) it eliminates toxic bromine vapors; (2) the bromine carrier [BMPy]Br and [BBIm]Br can be easily recovered and recycled and (3) avoids the use of conventional solvents such as ethyl acetate, $CHCl_3$, etc.. Furthermore, both the ILs **19** and **22** afforded good to excellent yields for a wide variety of anilines and phenols at room temperature.

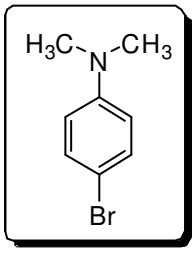
2.1.6 Experimental Section

General procedure for regioselective monobromination of anilines and phenols:

To a stirred mixture of anilines or phenols (3.3 mmol) was added 1-butyl-3-methylpyridinium tribromide [BMPy]Br_3 (3.3 mmol) or 1,3-di-*n*-butylimidazolium tribromide [BBIm]Br_3 (3.3 mmol) at room temperature for appropriate time. After completion of the reaction as indicated by TLC, water (10 mL) was added into the reaction mixture to quench IL. The resulting reaction mixture was extracted with diethyl ether (3 x 10 mL), separated the organic layer, dried over sodium sulphate and concentrated to afford pure monobromo anilines or monobromo phenols.

2.1.6.1 Characterization data:

4-Bromo-*N*,*N*-dimethylaniline:



Molecular formula : $C_8H_{10}BrN$

Nature : White solid

Mp : 50-52 ^oC

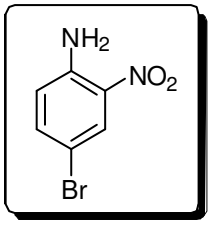
IR ($CHCl_3$, υ_{max}) : 3090, 1592, 1500, 1355, 1223, 1063, 805 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ2.92 (s, 6H), 6.61 (d, J = 9.09 Hz, 2H), 7.32 (d, J = 9.22 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ40.21, 108.50, 114.10, 131.59, 149.24 ppm.

MS (EI) (*m/z*) : 199 (M^+), 201 (M+2).

4-Bromo-2-nitroaniline:



Molecular formula : $C_6H_5BrN_2O_2$

Nature : Orange solid

Mp : 111-112 ^oC

IR ($CHCl_3$, υ_{max}) : 3472, 3351, 3092, 1636, 1591, 1558, 1499, 1455, 1402, 1337, 1248, 1102, 881, 815, 762, 703, 626, 521 cm^{-1}.

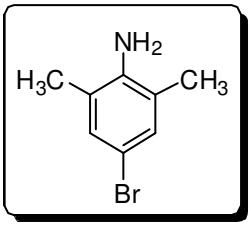
^1H NMR ($CDCl_3$, 200 MHz) : δ 6.06 (brs, 2H), 6.70 (d, J = 8.91 Hz, 1H), 7.41 (dd, J = 8.91, 2.30 Hz, 1H), 8.25 (d, J = 2.45 Hz,

1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 108.21, 120.85, 128.72, 132.99, 138.92, 144.17 ppm.

MS (EI) (*m/z*) : 216 (M^+), 218 (M+2).

4-Bromo-2,6-xylidine:



Molecular formula : $C_8H_{10}BrN$

Nature : Brown solid

Mp : 49-50 ^oC

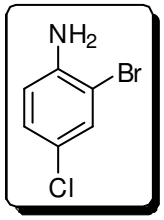
IR ($CHCl_3$, υ_{max}) : 3497, 3427, 2975, 2928, 2859, 1632, 1468, 1224, 854, 682 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.16 (s, 6H), 3.55 (s, 2H), 7.08 (s, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 17.37. 109.35, 123.59, 130.49, 141.83 ppm.

MS (EI) (*m/z*) : 199 (M^+), 201 (M+2).

2-Bromo-4-chloroaniline:



Molecular formula : C_6H_5BrClN

Nature : Pale brown solid

Mp : 65-66 ^oC

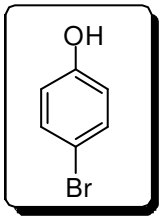
IR ($CHCl_3$, υ_{max}) : 3485, 3018, 2923, 2860, 1634, 1222, 852, 687 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.09 (brs, 2H), 6.67 (d, J = 8.92 Hz, 1H), 7.09 (dd, J = 8.92, 2.11 Hz, 1H), 7.42 (d, J = 2.11 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 108.95, 116.07, 122.68, 128.15, 131.57, 142.70 ppm.

MS (EI) (*m/z*) : 207 (M^+), 209 (M+2).

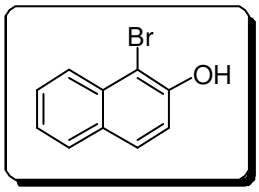
4-Bromophenol:



Molecular formula : C_6H_5BrO

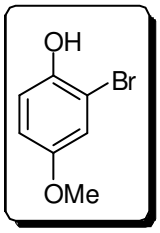
Nature	**:**	Pinkish brown solid
Mp	**:**	61-63 ^{o}C
IR ($CHCl_3$, υ_{max})	**:**	3340, 1885, 1588, 1487, 1433, 1240, 1217, 1173, 1068, 1005, 823, 808, 602 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 5.46 (s, 1H), 6.80 (d, *J* = 8.91 Hz, 2H), 7.40 (d, *J* = 8.91 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 112.79, 117.11, 132.47, 155.02 ppm.
MS (EI) (*m/z*)	**:**	172 (M^+), 174 (M+2).

1-Bromo-2-naphthol:



Molecular formula	**:**	$C_{10}H_7BrO$
Nature	**:**	Brownish crystal
Mp	**:**	77-80 ^{o}C
IR ($CHCl_3$, υ_{max})	**:**	3407, 3059, 1625, 1360, 816, 749 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 5.93 (s, 1H), 7.29 (d, *J* = 8.97 Hz, 1H), 7.39 (t, *J* = 8.08 Hz, 1H), 7.57 (t, *J* = 8.34 Hz, 1H), 7.76 (t, *J* = 8.08 Hz, 2H), 8.05(d, *J* = 8.97 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 106.06, 117.11, 124.05, 125.25, 127.75, 128.13, 129.23, 129.58, 132.22, 150.52 ppm.
MS (EI) (*m/z*)	**:**	222 (M^+), 224 (M+2).

2-Bromo-4-methoxyphenol:

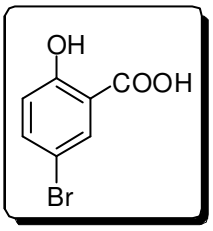


Molecular formula	**:**	$C_7H_7BrO_2$
Nature	**:**	Faint yellow solid
Mp	**:**	59–60 ^{o}C
IR ($CHCl_3$, υ_{max})	**:**	3420, 2927, 1652, 1497, 1209, 1032, 736 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 3.70 (s, 3H), 5.26 (brs, 1H), 6.81 (dd, *J* = 8.91, 2.83 Hz, 1H), 6.93 (d, *J* = 8.91 Hz, 1H), 7.01 (d, *J* = 2.81 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 55.92, 110.08, 115.21, 116.35, 116.79, 146.51, 153.76 ppm.

MS (EI) (*m/z*) : 202 (M^+), 204 (M+2).

5-Bromosalicylic acid:



Molecular formula : $C_7H_5BrO_3$

Nature : White solid

Mp : 163-165 ^oC

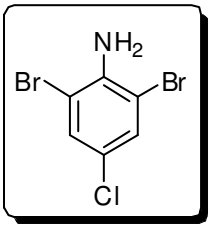
IR ($CHCl_3$, υ_{max}) : 3621, 3054, 2864, 1699 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 5.74 (s, 1H), 6.96 (d, J = 8.82 Hz, 1H), 7.62 (dd, J = 8.82, 2.45 Hz, 1H), 8.07 (d, J = 2.45 Hz, 1H), 10.41 (brs, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 109.72, 114.98, 119.84, 132.05, 137.90, 159.96, 170.82 ppm.

MS (EI) (*m/z*) : 216 (M^+), 218 (M+2).

2,6-Dibromo-4-chloroaniline



Molecular formula : $C_6H_4Br_2ClN$

Nature : White solid

Mp : 94-96 ^oC

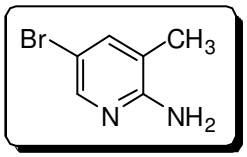
IR ($CHCl_3$, υ_{max}) : 2495, 3318, 1618, 1458, 858, 732 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 5.02 (brs, 2H), 7.41 (s, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 108.94, 123.02, 132.56, 141.32 ppm.

MS (EI) (*m/z*) : 285 (M^+), 287 (M+2).

2-Amino-5-bromo-3-picoline



Molecular formula : $C_6H_7BrN_2$

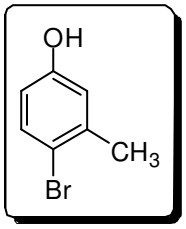
Nature : Faint white solid

Mp : 92-94 ^oC

IR ($CHCl_3$, υ_{max}) : 3467, 3296, 2924, 1635, 1582, 1469, 1440, 1379,

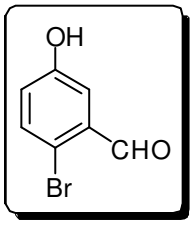
		1325, 1267, 1197, 1042, 886, 542 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 2.11 (s, 3H), 4.48 (brs, 2H), 7.39 (d, *J* = 1.26 Hz, 1H), 7.97 (d, *J* = 2.01 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 16.99, 108.25, 118.03, 139.65, 145.99, 155.90 ppm.
MS (EI) (*m/z*)	**:**	186 (M^+), 188 (M+2).

4-Bromo-3-methylphenol:



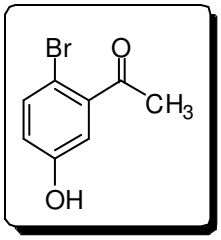
Molecular formula	**:**	C_7H_7BrO
Nature	**:**	White solid
Mp	**:**	58-60 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3523, 2929, 1639, 1491, 1195, 1031, 741 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 2.29 (s, 3H), 5.27 (brs, 1H), 6.56 (dd, *J* = 8.62, Hz, 1H), 6.72 (d, *J* = 2.81 Hz, 1H), 7.32 (d, *J* = Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 20.68, 108.91, 115.89, 130.21, 131.45, 151.04, 133.15 ppm.
MS (EI) (*m/z*)	**:**	186 (M^+), 188 (M+2).

2-Bromo-5-hydroxybenzaldehyde:



Molecular formula	**:**	$C_7H_5BrO_2$
Nature	**:**	White solid
Mp	**:**	130-132 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3505, 1698, 1606, 1394, 1158, 1088 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 7.02 (d, *J* = 8.89 Hz, 1H), 7.44-7.50 (m. 2H), 10.32 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 114.68, 115.75, 117.61, 123.68, 134.90, 155.79, 192.48 ppm.
MS (EI) (*m/z*)	**:**	200 (M^+), 202 (M+2).

6-Bromo-3-hydroxyacetophenone:



Molecular formula : $C_8H_7BrO_2$

Nature : White solid

Mp : 75-76 ^oC

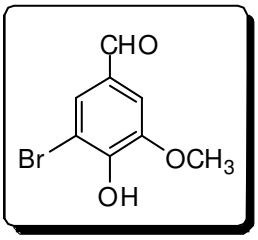
IR ($CHCl_3$, υ_{max}) : 3498, 2990, 1697, 1360, 1157, 1059, 687 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 2.61 (s, 3H), 6.78- 6.88 (m, 2H), 7.45 (d, J = 8.86 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 30.19, 108.78, 115.99, 119.45, 134.76, 142.01, 155.39, 202.69 ppm.

MS (EI) (*m/z*) : 214 (M^+), 216 (M+2).

5-Bromo-4-hydroxy-3-methoxybenzaldehyde:



Molecular formula : $C_8H_7BrO_3$

Nature : White solid

Mp : 165-167 ^oC

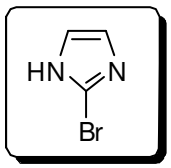
IR ($CHCl_3$, υ_{max}) : 3314, 2976, 2945, 2848, 1685, 1588, 1511, 1429, 1358, 1291, 1158, 1055, 682 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 3.98 (s, 3H), 6.55 (brs, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.63 (d, J = 1.4 Hz, 1H), 9.80 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ56.91, 108.34, 108.40, 130.25, 130.36, 147.82, 149.01, 189.64 ppm.

MS (EI) (*m/z*) : 230 (M^+), 232 (M+2).

2-bromo-1*H*-imidazole:



Molecular formula : $C_3H_3BrN_2$

Nature : Off-white solid

Mp : 198-200 ºC

IR ($CHCl_3$, υ_{max}) : 3156, 3097, 2901, 1546, 1444, 1294, 1072, 834, 756 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ7.12 (d, J = 6.54 Hz, 1H), 7.66 (d, J = 6.96 Hz,

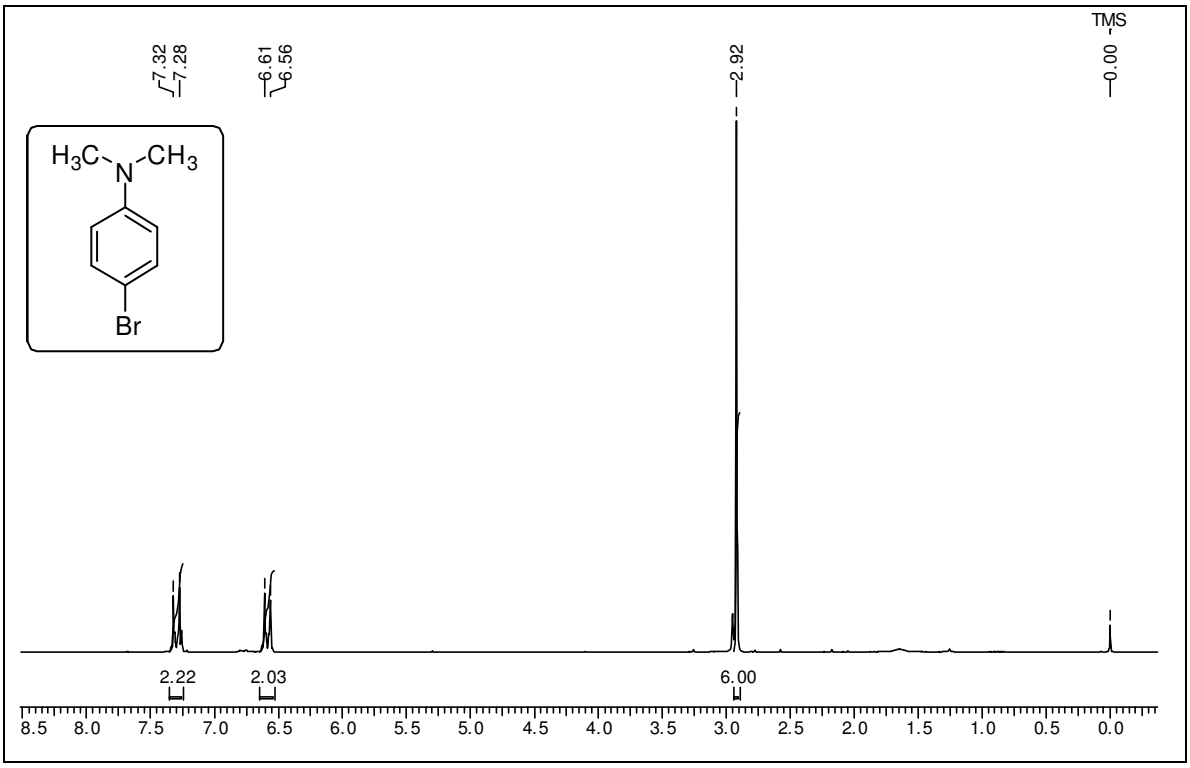
		1H), 10.52 (brs, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 117.24, 121.92, 137.66 ppm.
MS (EI) (*m/z*)	**:**	146 (M^+), 148 (M+2).

2.1.7 Spectral data

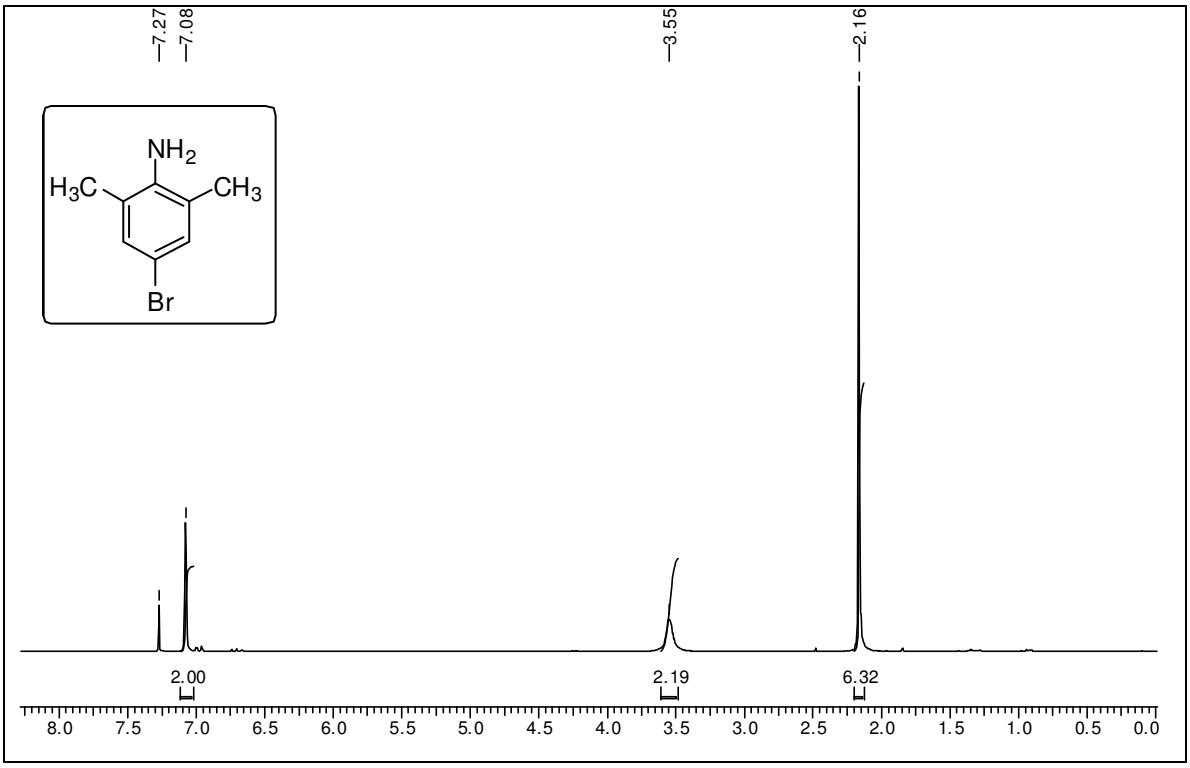
Table 2: ^{1}H and ^{13}C NMR spectrum of some selected compounds are given below:

Sr. No.	Spectra
1	^{1}H NMR spectra of 4-Bromo-*N*,*N*-dimethylaniline
2	^{1}H NMR spectra of 4-Bromo-2,6-xylidine
3	^{1}H NMR spectra of 1-Bromo-2-naphthol
4	^{13}C NMR spectra of 1-Bromo-2-naphthol
5	^{1}H NMR spectra of 2-Amino-5-bromo-3-picoline
6	^{1}H NMR spectra of 2-bromo-4-chloroaniline
7	^{13}C NMR spectra of 2-bromo-4-chloroaniline

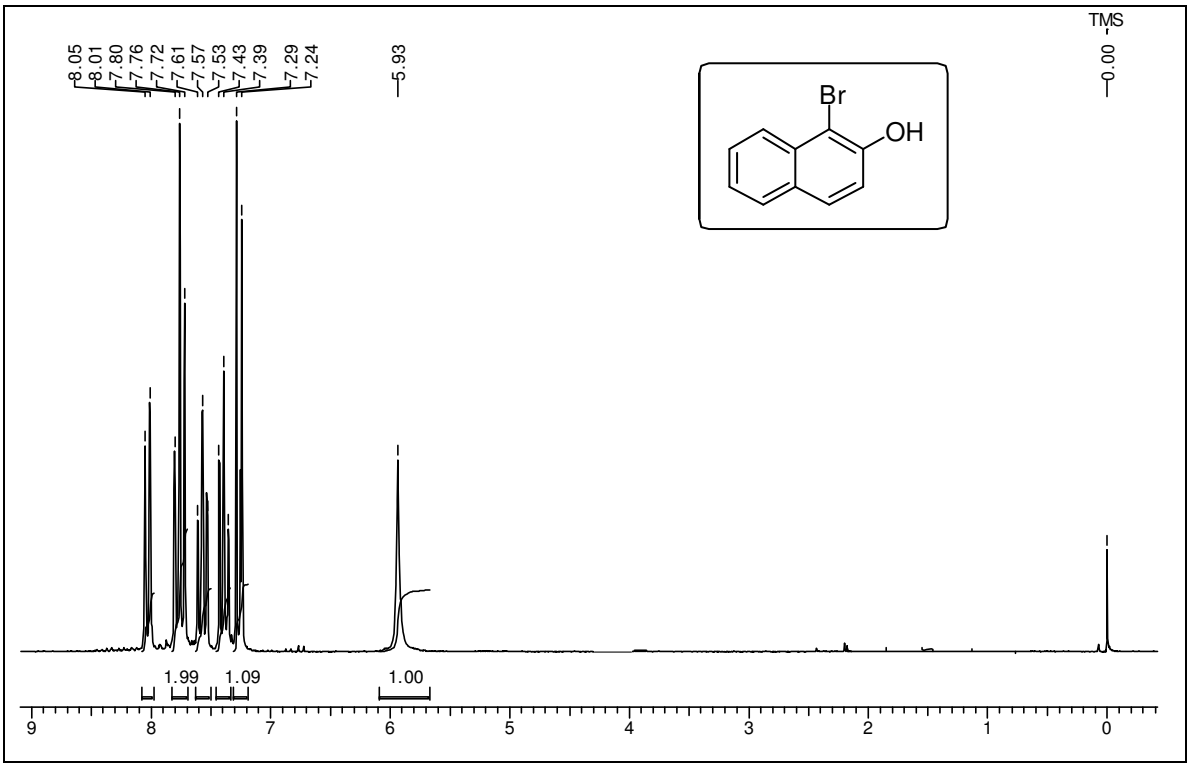
1. ^{1}H NMR spectra of 4-Bromo-*N*,*N*-dimethylaniline:



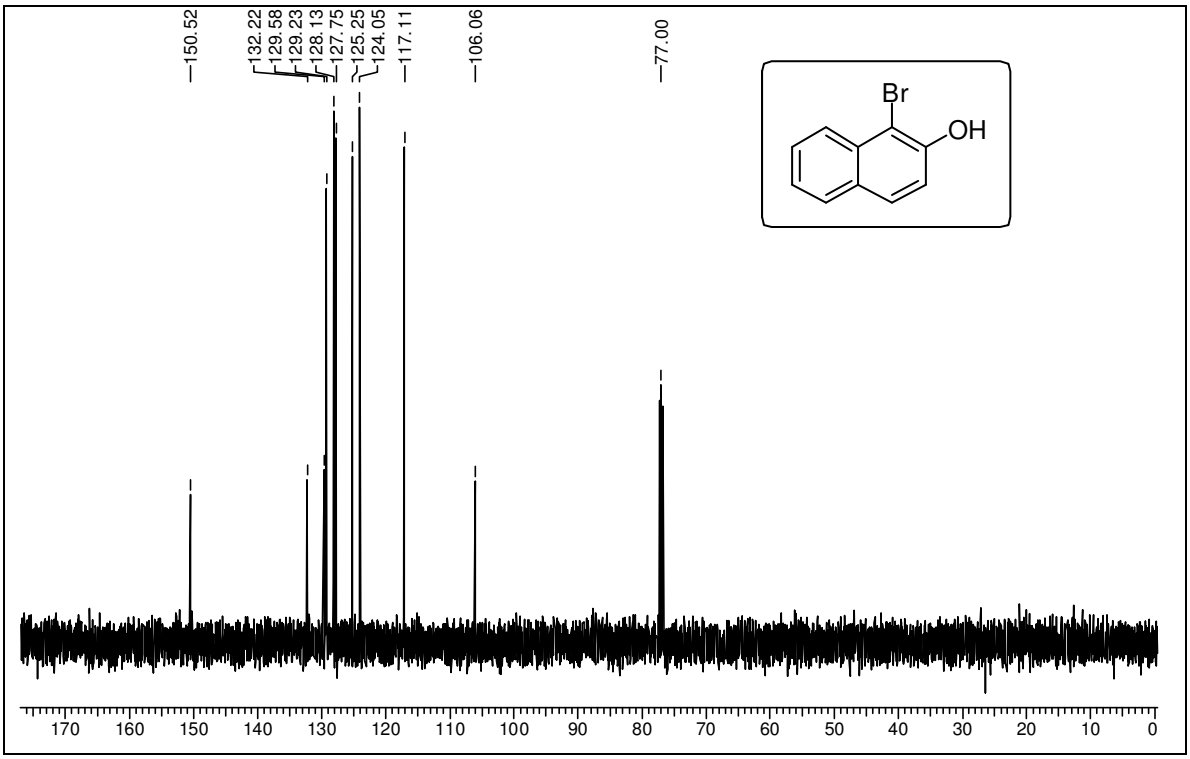
2. ^{1}H NMR spectra of 4-Bromo-2,6-xylidine:



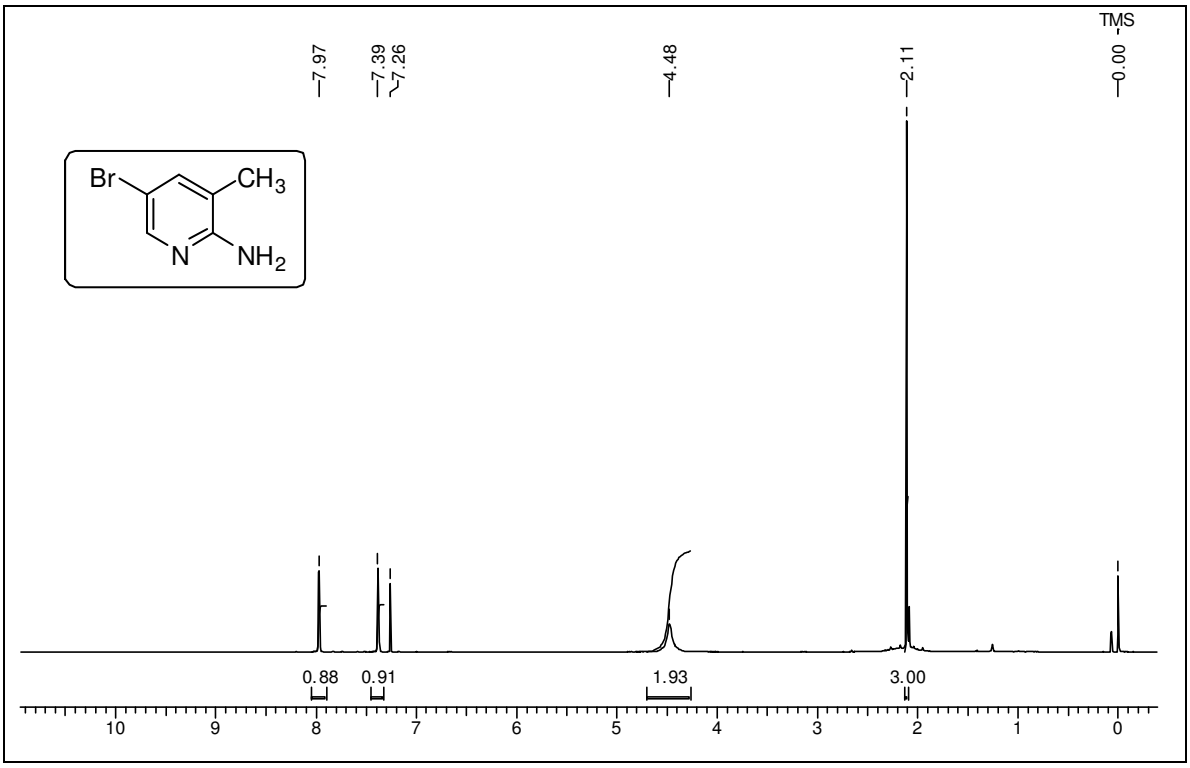
3. ^{1}H NMR spectra of 1-Bromo-2-naphthol:



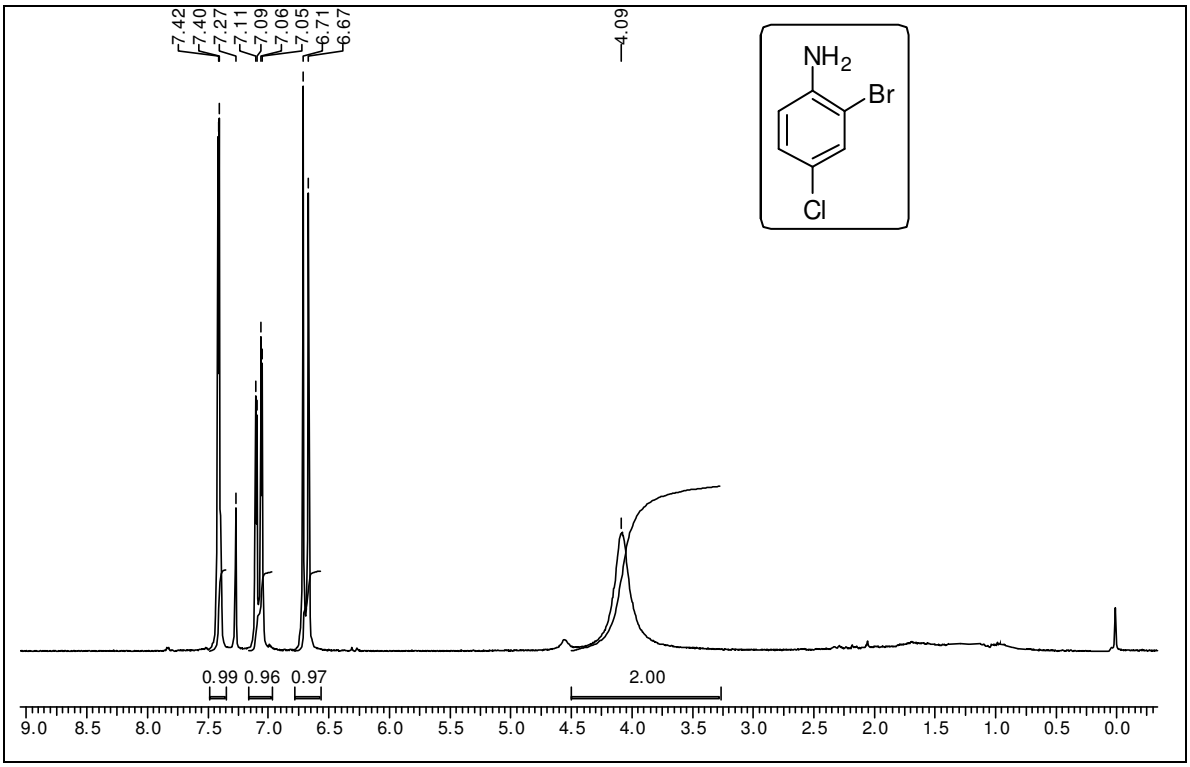
4. ^{13}C NMR spectra of 1-Bromo-2-naphthol:



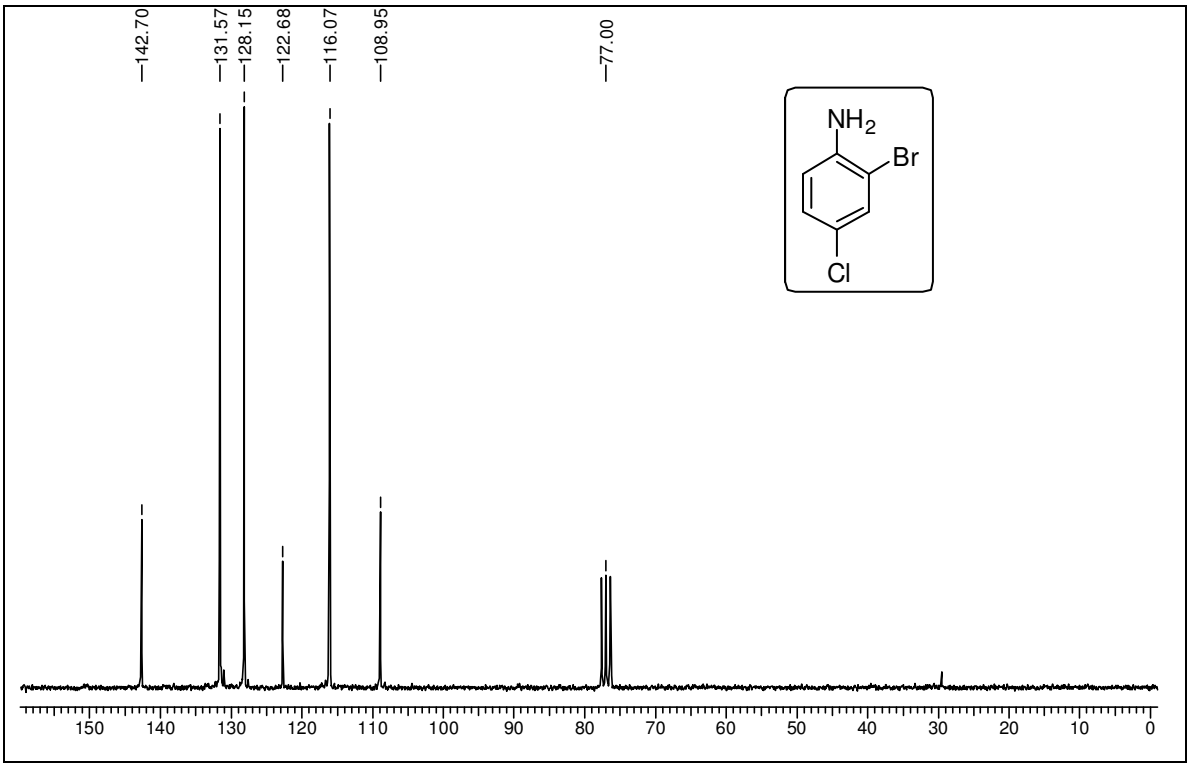
5. ^{1}H NMR spectra of 2-amino-5-bromo-3-picoline**:**



6. ^{1}H NMR spectra of 2-bromo-4-chloroaniline:



7. ^{13}C NMR spectra of 2-bromo-4-chloroaniline:



2.1.8 References

1. (a) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335; (b) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141; (c) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937; (d) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937; (e) Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740; (f) Larock, R. C. *Comprehensive organic transformation*, VCH, New York, **1989**, 315.
2. (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009; (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2; (c) Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed.* **1994**, *33*, 2379.
3. (a) Wang, L.; Jing, H. W.; Bu, X. L.; Chang, T.; Jin, L. L.; Liang, Y. M. *Catal. Commun.* **2007**, *8*, 80; (b) Jiang, X. F.; Shen, M. H.; Tang, Y.; Li, C. Z. *Tetrahedron Lett.* **2005**, *46*, 487; (c) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **2005**, *46*, 4465; (d) Heravi, M. M.; Abdolhosseini, N.; Oskooie, H. A. *Tetrahedron Lett.* **2005**, *46*, 8959; (e) Esakkidurai, T.; Kumarraja, M.; Pitchumani, K. *Catal. Lett.* **2004**, *92*, 169; (f) Smith, K.; Bahzad, D. *J. Chem. Soc., Chem. Commun.* **1996**, 467; (g) Ranu, B. C.; Sarkar, D. C.; Chakraborty, R. *Synthetic Commun.* **1992**, *22*, 1095; (h) Schmid, H. *Helv. Chim. Acta.* **1946**, *29*, 1144.
4. Duan, J.; Zhang, L. H.; Dolbier, W. R., Jr. *Synlett* **1999**, 1245.
5. Adhikari, M. V.; Samant, S. D. *Ultrason. Sonochem.* **2002**, *9***,** 107.
6. Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett.* **1993**, *34*, 931.
7. Konishi, H.; Aritomi, K.; Okano, T.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 591.
8. Goldberg, Y.; Alper, H. *J. Mol. Catal.* **1994**, *88*, 377.
9. Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 7055.
10. Das, B.; Venkateswarlu, K.; Majhi, A.; Siddaiah, V.; Reddy, K. R. *J. Mol. Catal. A: Chemical* **2007**, *267*, 30.
11. Pingali, S. R. K.; Madhav, M.; Jursic, B. S. *Tetrahedron Lett.* **2010**, *51*, 1383.
12. Chhattise, P. K.; Ramaswamy, A. V.; Waghmode, S. B. *Tetrahedron Lett.* **2008**, *49*, 189.

13. Libo, R.; Feng, L.; Wenhua, O.; Haifang, M.; Xianhua, P. *Acta Chimica Sinica* **2010**, *68*, 713.
14. Venkateswarlu, K.; Suneel, K. *Synthetic Commun.* **2009**, *39*, 215.
15. Ghiaci, M.; Sedaghat, M. E.; Ranjbari, S.; Gil, A. *Appl. Catal. A: General* **2010**, *384*, 18.
16. Stropnik, T.; Bombek, S.; Kočevar, M.; Polanc, S. *Tetrahedron Lett.* **2008**, *49*, 1729.
17. Bernard, A.; Kumar, A.; Jamir, L.; Sinha, D.; Sinha, U. B. *Acta. Chim. Slov.* **2009**, *56*, 457.
18. Bhalerao, D. S.; Mahajan, U. S.; Akamanchi, K. G. *Synthetic Commun.* **2008**, *38*, 2814.
19. Menini, L.; Da Cruz Santos, J. C.; Gusevskaya, E. V. *Adv. Synth. Catal.* **2008**, *350*, 2052.
20. Nath, J.; Chaudhuri, M. K. *Green Chem. Lett. Reviews* **2008**, *1*, 223.
21. (a) Tajik, H.; Mohammadpoor-Baltork, I.; Hassan-Zadeh, P.; Rafiee Rashtabadi, H. *Russian J. Org. Chem.* **2007**, *43*, 1282; (b) Tajik, H.; Mohammadpoor-Baltork, I.; Albadi, J. *Synthetic Commun.* **2007**, *37*, 323.
22. Podgoršek, A.; Zupan, M.; Iskra, J. *Angew Chem. Int. Ed.* **2009**, *48*, 8424; and references cited therein.
23. Choudhury, L. H.; Parvin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513; and references cited therein.
24. Ma, K.; Li, S.; Weiss, R. G. *Org. Lett.* **2008**, *10*, 4155.
25. Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, *17*, 2809.
26. Salazar, J.; Dorta, R. *Synlett* **2004**, *7*, 1318.
27. Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* **2004**, 2536.
28. Reeves, W. P.; King, R. M. *Synthetic Commun.* **1993**, *23*, 885.
29. Cristiano, R.; Ma, K.; Pottanat, G.; Weiss, R. G. *J. Org. Chem.* **2009**, *74*, 9027.
30. Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Lasemi, Z. *Synthetic Commun.* **2010**, *40*, 868.
31. Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P. *Chem. Commun.* **1996**, *23*, 2679.

32. Chrétien, J. -M.; Zammattio, F.; Le Grognec, E.; Paris, M.; Cahingt, B.; Montavon, G.; Quintard, J. -P. *J. Org. Chem.* **2005**, *70*, 2870; and references cited therein.
33. Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267.
34. Singhal, S.; Jain, S. L.; Sain, B. *J. Mol. Catal. A*: *Chemical* **2006**, *258*, 198; and references cited therein.
35. Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, *47*, 8693.
36. Zolfigol, M. A.; Chehardoli, G.; Salehzadeh, S.; Adams, H.; Ward, M. D. *Tetrahedron Lett.* **2007**, *48*, 7969.
37. Chaudhari, S. K.; Roy, S.; Saha, M.; Bhar, S. *Synthetic Commun.* **2007**, *37*, 579.
38. Pourmousavi, S. A.; Salehi, P. *Acta Chim. Slov.* **2009**, *56*, 734.
39. Moghaddam, F. M.; Zargarani, D. *Synthetic Commun.* **2009**, *39*, 4212.
40. Bovonsombat, P.; Ali, R.; Khan, C.; Leykajarakul, J.; Pla-on, K.; Aphimanchindakul, S.; Pungcharoenpong, N.; Timsuea, N.; Arunrat, A.; Punpongjareorn, N. *Tetrahedron* **2010**, *66*, 6928; and references cited therein.
41. Li, Z.; Sun, X.; Wang, L.; Li, Y.; Ma, Y. *J. Braz. Chem. Soc.* **2010**, *21*, 496; and references cited therein.
42. Gordon, C. M. *Applied Catalysis A: General* **2001**, *222*, 101; (b) Pavlinac, J.; Zupan, M.; Laali, K.; Stavber, S. *Tetrahedron* **2009**, *65*, 5625; (c) Greaves, T. L.; Drummond, C. J. *Chem. Rev.* **2008,** *108*, 206.
43. Horvath, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169.
44. Borikar, S. P.; Paul, V.; Daniel, T. *Tetrahedron Lett.* **2009**, *50*, 1007.
45. Borikar, S. P.; Paul, V.; Daniel, T. *Synthetic Commun.* **2010**, *40*, 647.

Section-B

Bromination of aromatic aldehydes and ketones using $[BMPy]Br_3$ and $[BBIm]Br_3$ ILs

2.2.1 Introduction

Modern organic chemistry is usually measured by availability of simple, highly functionalized building blocks that can be used in the preparation of larger molecules with diverse properties and applications.[1] The bromination of aromatic substrates has been the subject of a great interest in recent years due to the commercial importance of brominated compounds in the synthesis of natural products, as well as in the manufacturing of pharmaceuticals and agrochemicals. Bromoarenes[2] are starting points for the preparation of a diverse array of building blocks.[3] The preparation of brominated aromatic compounds with molecular bromine is a well-known reaction in organic chemistry.[4] This reaction requires transition metal-based catalysts and the side product generated in the course of these reactions is corrosive and toxic.

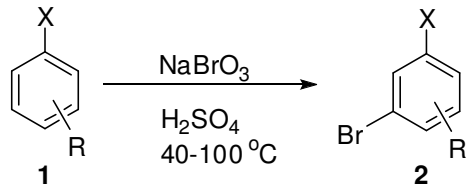
Bromo derivatives of aromatic aldehydes are important intermediates that can be used as precursors of natural products[5] and of salen-type ligands are widely used in asymmetric catalysis.[6] The bromination of deactivating aromatic ring is in great demand, because it is difficult to perform as compared to the bromination of activating aromatic ring.

2.2.2 Review of literature

This section describes some of the recent methodologies reported in the literature for bromination of deactivated aromatic rings. Some of the recent elegant methods are described below. Bromine trifluoride (BrF_3) in a mixture with elemental bromine can be used as a brominating agent for deactivated aromatic compounds.[7,8]

Groweiss *et al.* (2000)[9]

Groweiss *et al.* reported sodium bromate ($NaBrO_3$) as an efficient brominating agent for aromatic substrates with one or two deactivating groups. Addition of a strong acid such as conc. H_2SO_4 into a stirred aqueous solution of the aromatic substrate **1** and sodium bromate at 40-100 °C, leads to the decomposition of the bromate ions and production of the active brominating species afforded brominated product **2** (**Scheme 1**).

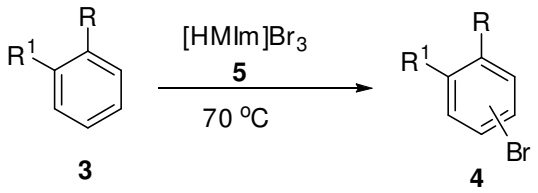


R = H, F, Cl, etc.
X = NO_2, COOH, COOMe, CHO, F, CF_3, etc.

Scheme 1.

Chiappe *et al.* (2004)[10]

Chiappe and co-workers used acidic ionic liquid, 3-methylimidazolium tribromide ([HMIm]Br_3) as highly efficient reagent/ solvent for the bromination of non-activated aromatic compounds such as aldehydes and ketones. Aromatic bromination of aldehydes or ketones **3** using [HMIm]Br_3 ionic liquid at 70 °C under solvent-free conditions afforded brominated product **4** in good yield (**Scheme 2**).

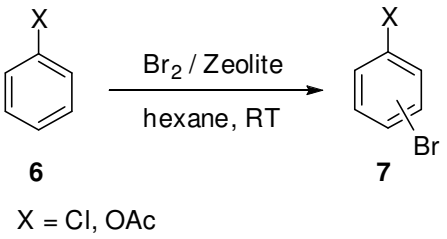


R = CHO, R^1 = CH_3
R = $COCH_3$, R^1 = H

Scheme 2.

Esakkidurai *et al.* (2004)[11]

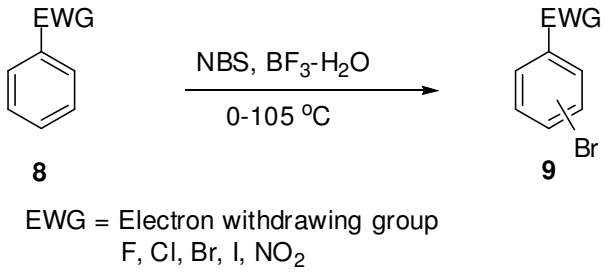
Esakkidurai and co-workers reported bromination of aromatic substrates **6** such as chlorobenzene, phenyl acetate etc. by using molecular bromine in the presence of reusable zeolite in hexane at room temperature gave bromo compounds **7** in good selectivity and yield (**Scheme 3**).



Scheme 3.

Prakash *et al.* (2004)[12]

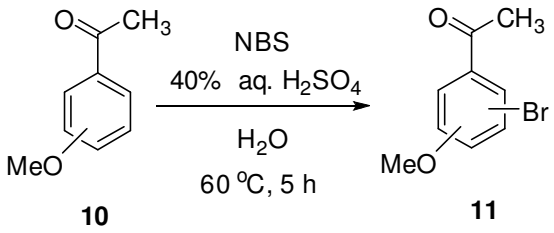
Prakash *et al.* described the method for bromination of deactivated aromatic compounds **8** using *N*-bromosuccinimide (NBS) in boron trifluoride monohydrate (BF_3-H_2O) system at room temperature (**Scheme 4**). Halogenation of more deactivated systems were also achieved by varying the reaction conditions such as raising the temperature, prolonged reaction time, and increased amount of BF_3-H_2O. In all cases, the formation of monobrominated product **9** in high selectivity and good yield was observed under the reaction conditions.



Scheme 4.

Pravst *et al.* (2006)[13]

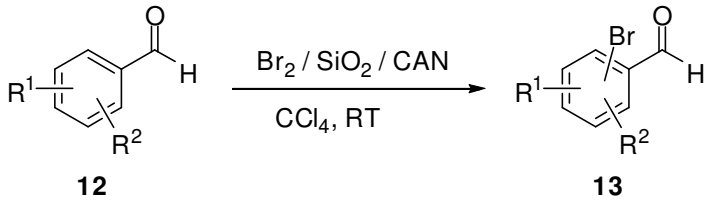
Pravst and co-workers reported the ring bromination of methoxy substituted aromatic ketones **10** in water using NBS at 60 °C for 5 h to afford bromo methoxy substituted product **11** (**Scheme 5**). They have also reported α-bromination of methoxy substituted aromatic ketones using NBS under solvent-free conditions.



Scheme 5.

Wang *et al.* (2007)[14]

Wang and co-workers reported the bromination of various substituted aromatic aldehydes **12** by bromine and silica gel using catalytic amount of ceric ammonium nitrate (CAN) at room temperature in tetrachloromethane gave brominated aldehydes **13** in good yields (**Scheme 6**).

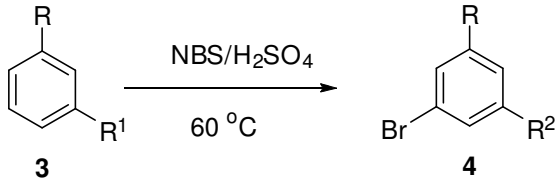


R^1 = OH, H, etc.
R^2 = NO_2, OCH_3, CH_3, etc.

Scheme 6.

Saiganesh *et al.* (2007)[15]

Saiganesh *et al.* reported simple and efficient method for the bromination of highly deactivated aromatic substrates **3**, which contain at least two electron-deactivating substituents such as CHO, COOH, CN, NO_2. This was achieved by NBS in conc. sulfuric acid (H_2SO_4) at 60 °C gave the bromo compound **4** (**Scheme 7**).

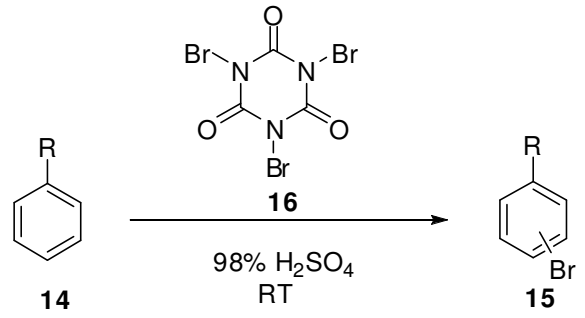


R, R^1 = Electron Withdrawing Groups
CHO, COOH, CN, NO_2

Scheme 7.

Esteves *et al.* (2009)[16]

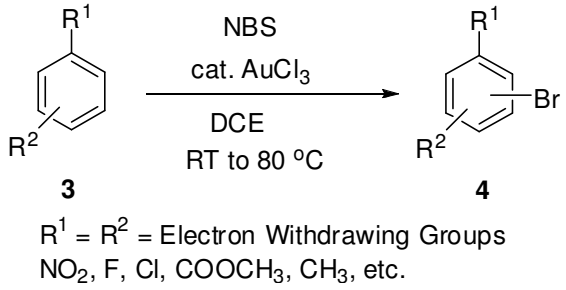
Esteves and co-workers reported superelectrophilic bromination of deactivated aromatic rings **14** such as nitrobenzene, acetophenone, etc. with tribromoisocyanuric acid **16** (TBCA) in 98% H_2SO_4 at room temperature produced bromoarenes **15** in good to excellent yields (**Scheme 8**).



Scheme 8.

Wang *et al.* (2010)[17]

Wang and co-workers reported gold catalyzed bromination of aromatic rings by *N*-bromosuccinimide (NBS). Aromatic bromination of various deactivated aromatic compounds **3** using NBS catalyzed by $AuCl_3$ in dichloroethane (DCE) at room temperature to 80 ^oC afforded bromo aromatic compounds **4** in high yields (**Scheme 9**).



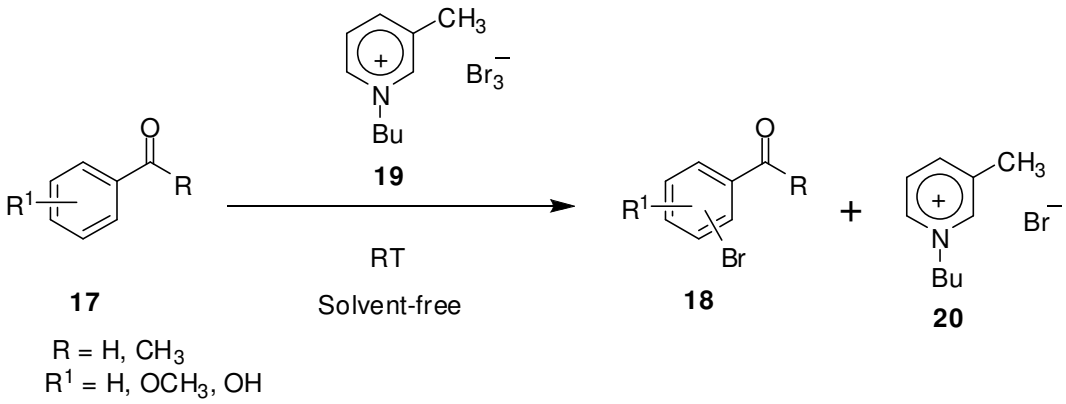
Scheme 9.

2.2.3 Present work

In the previous Section-A, a brief description of the regioselective bromination of activated aromatic ring such as anilines and phenols using novel ionic liquids [BMPy]Br_3 and [BBIm]Br_3 was given. Although, the ionic liquids are same; but the bromination of deactivated ring such as aromatic aldehyde and ketone by using this IL is novel. The nuclear bromination of activated ring is easy; whereas it is difficult for the deactivated ring. Hence, there are very few reports in the literature. This prompted us to study the bromination of deactivated rings. In this section, we have described a highly efficient, simple, and eco-friendly method for the monobromination of aromatic aldehydes and ketones using [BMPy]Br_3 and [BBIm]Br_3 under solvent-free conditions at room temperature.

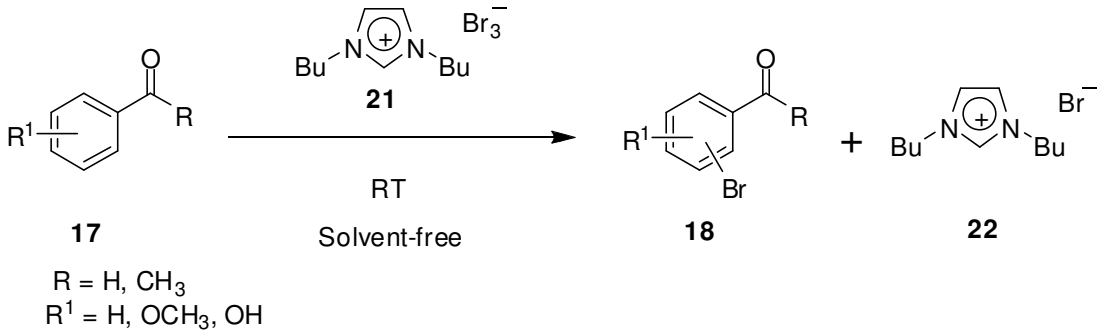
2.2.4 Results and discussion

A variety of aromatic aldehydes and ketones **17** were monobrominated using [BMPy]Br_3 IL **19** at room temperature under solvent-free conditions afforded brominated product **18** in good yield (**Scheme 10**).



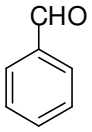
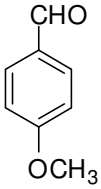
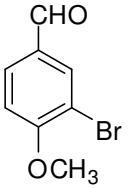
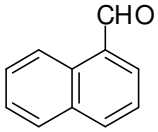
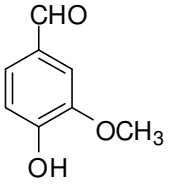
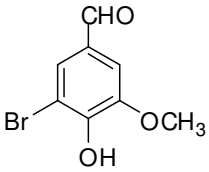
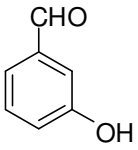
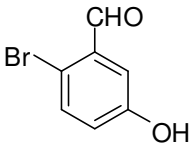
Scheme 10.

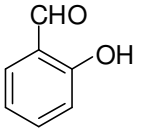
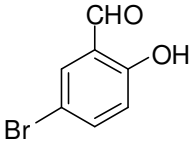
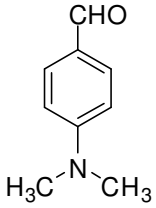
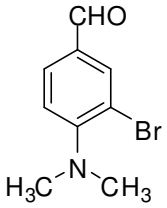
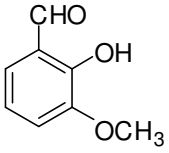
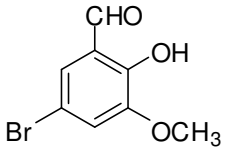
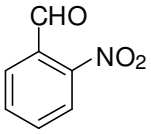
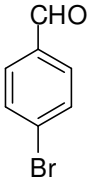
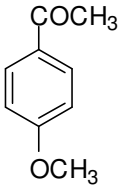
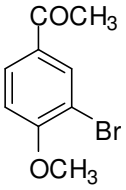
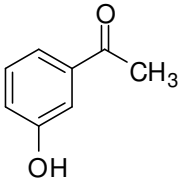
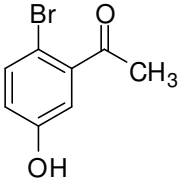
Similarly, the aromatic bromination of aromatic aldehydes and ketones **17** were performed using [BBIm]Br_3 **21** as the brominating reagent at room temperature under solvent-free conditions afforded monobrominated product **18** (**Scheme 11**). The results are summarized in **Table 1**.



Scheme 11.

Table 1. Aromatic bromination of aldehydes and ketones using [BMPy]Br_3 and [BBIm]Br_3 at room temperature

Entry	Substrate	Product	Time (min)		Yield (%)	
			[BMPy]Br_3	**[BBIm]Br_3**	**[BMPy]Br_3**	**[BBIm]Br_3**
1		No reaction	120	120	0	0
2			15	25	86	91
3		No reaction	120	120	0	0
4			10	Imm.	98	98
5			15	8	92	95

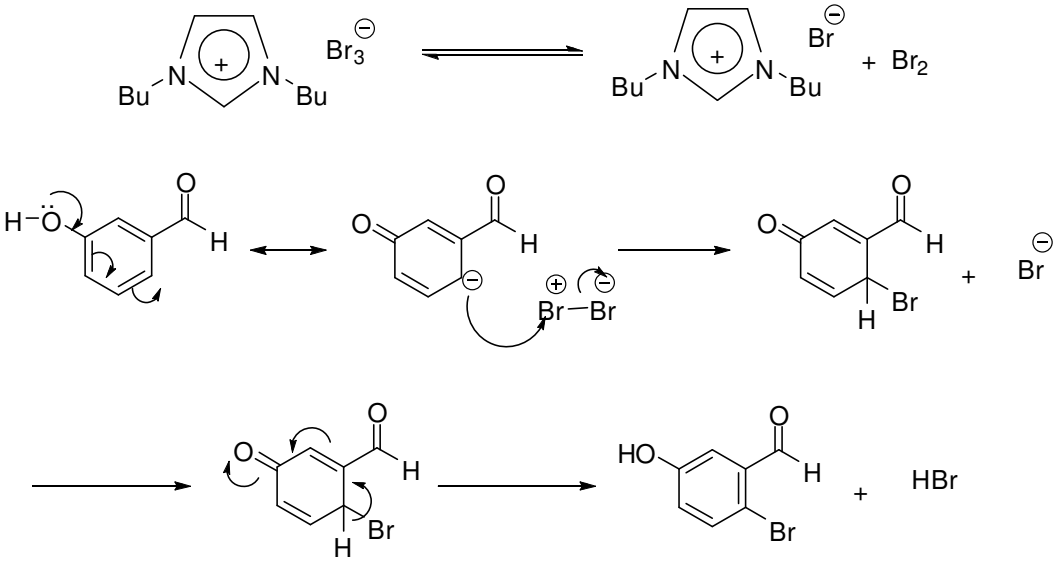
6			25	30	96	95
7			4	8	85	90
8			-	2	-	95
9		No reaction	120	120	0	0
10		No reaction	120	120	0	0
11			20	35	89	83
12			15	10	90	91

Both tribromide ILs are an efficient brominating reagent for the selective bromination of various aryl aldehydes and ketones with complete selectivity and excellent yields. The results are summarized in **Table 1**. 3-Hydroxybenzaldehyde underwent monobromination in 8 min by using [BBIm]Br_3, whereas it took 15 min using [BMPy]Br_3 (entry 5). 2-hydroxybenzaldehyde was brominated in 25 and 30 min by using

ILs **19** and **21** (entry 6). The aromatic aldehydes containing two activating groups have more activity (entries 4 and 8); than that containing only one activating group have less activity (entries 2, 5 and 6). The substrate containing deactivating groups have no activity (entries 1, 3, 9 and 10) due to its lower electron density of benzene ring. Similarly, a variety of substituted ketones underwent selective monobromination (entries 11-12).

All the reactions were quenched by adding water. This caused precipitation of the products as solids or oils, which were readily separated and washed with fresh portions of water and then dried. The aqueous phase containing highly water soluble IL was easily concentrated in *vacuo* to recycle [BBIm]Br or [BMPy]Br, which then could be used to regenerate [BBIm]Br_3 or [BMPy]Br_3 with bromine. The regeneration and reusable property is a great feature of ionic liquids.[18] Our bromination method using tribromide ILs **19** and **21** were better because it took short reaction time at room temperature and gave good yield than reported method.[10]

The plausible mechanism is shown in **Scheme 12**. [BBIm]Br_3 exists in a rapid equilibrium with imidazolium bromide and bromine in solution.



Scheme 12. Plausible mechanism

All the reactions were carried out at room temperature in air, adding 1.0 eq. of IL **19** and **21** to equimolar amount of substrate without any solvent. Although the reactions were slightly exothermic, no special precautions were taken for cooling. They were

monitored by TLC and stopped after the disappearance of the substrate. All the isolated products are known compounds and reported in the literature. The compounds synthesized were well characterized by IR, ^{1}H-NMR and mass spectral analysis and compared with the reported literature data.

2.2.5 Conclusion

In conclusion, a simple and practical method for selective bromination of aromatic aldehydes and ketones using room temperature ionic liquid [BMPy]Br_3 and [BBIm]Br_3 has been explored. The advantages of this method are high conversions, short reaction time, mild reaction conditions and simple workup with good yield. Moreover, the ionic liquids are re-usable and re-cyclable.

2.2.6 Experimental Section

General procedure for regioselective monobromination of anilines and phenols:

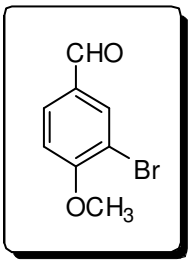
To a stirred mixture of aromatic aldehydes or ketones (2.5 mmol) was added 1-butyl-3-methylpyridinium tribromide (2.5 mmol) or 1,3-di-*n*-butylimidazolium tribromide (2.5 mmol) at room temperature. After completion of the reaction as indicated by TLC, water was added into the reaction mixture to quench the IL. The resulting reaction mixture was extracted with diethyl ether, separated from the organic layer, dried over sodium sulfate and concentrated to afford pure monobromo aldehydes or monobromo ketones. All compounds were characterized based on their spectroscopic data and by comparison with those reported in the literature.

Regeneration of tribromide ionic liquids:

After the addition of water into the reaction mixture, the water soluble ionic liquid [BMPy]Br or [BBIm]Br were recovered by evaporation of the aqueous solution and washing with diethyl ether in each case. The recovered ionic liquid [BMPy]Br or [BBIm]Br were dried and treated with molecular bromine under stirring and cooling in a ice-bath to regenerate [BMPy]Br_3 or [BBIm]Br_3 ionic liquid and reused for the next reaction without loss of activity.

2.2.6.1 Characterization data:

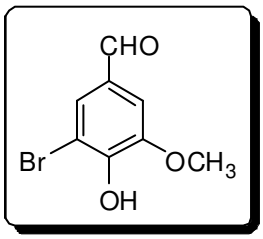
3-Bromo-4-methoxybenzaldehyde:



Molecular formula	**:**	$C_8H_7BrO_2$
Nature	**:**	White solid
Mp	**:**	52-53 ^oC
IR ($CHCl_3$, υ_{max})	**:**	2927, 2861, 1690, 1594, 1465 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	**:**	δ 3.94 (s, 3H), 6.95(d, *J* = 3.98 Hz, 1H), 7.79 (d, *J* = 6.42 Hz, 1H), 8.05 (s, 1H), 9.80 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 56.62, 111.59, 112.71, 130.85, 130.99, 134.54, 161.01, 189.58 ppm.

MS (EI) (*m/z*) : 214 (M^+), 216 (M+2).

5-Bromo-4-hydroxy-3-methoxybenzaldehyde:



Molecular formula : $C_8H_7BrO_3$

Nature : White solid

Mp : 165-167 ^oC

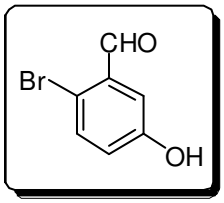
IR ($CHCl_3$, υ_{max}) : 3314, 2976, 2945, 2848, 1685, 1588, 1511, 1429, 1358, 1291, 1158, 1055, 682 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 3.98 (s, 3H), 6.55 (brs, 1H), 7.35 (d, J = 1.4 Hz, 1H), 7.63 (d, J = 1.4 Hz, 1H), 9.80 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 56.91, 108.34, 108.40, 130.25, 130.36, 147.82, 149.01, 189.64 ppm.

MS (EI) (*m/z*) : 230 (M^+), 232 (M+2).

6-Bromo-3-hydroxybenzaldehyde:



Molecular formula : $C_7H_5BrO_2$

Nature : White solid

Mp : 130-132 ^oC

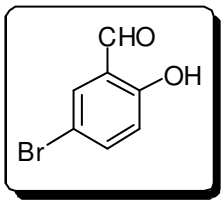
IR ($CHCl_3$, υ_{max}) : 3505, 1698, 1606, 1394, 1158, 1088 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ7.02 (d, J = 8.89 Hz, 1H), 7.44-7.50 (m. 2H), 10.32 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 114.68, 115.75, 117.61, 123.68, 134.90, 155.79, 192.48 ppm.

MS (EI) (*m/z*) : 200 (M^+), 202 (M+2).

5-Bromo-2-hydroxybenzaldehyde:



Molecular formula : $C_7H_5BrO_2$

Nature : White solid

Mp : 103-105 ^oC

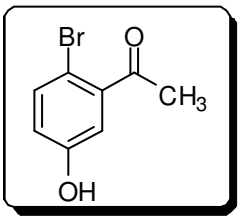
IR ($CHCl_3$, υ_{max}) : 3498, 1695, 1608, 1396, 1157, 1085 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 6.88 (d, *J* = 8.74 Hz, 1H), 7.57 (dd, *J* = 8.74, 2.41 Hz, 1H), 7.64 (d, *J* = 2.41 Hz, 1H), 9.81 (s, 1H), 10.9 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 111.65, 120.12, 122.07, 135.91, 139.94, 160.81, 195.73 ppm.

MS (EI) (*m/z*) : 200 (M^+), 202 (M+2).

6-Bromo-3-hydroxyacetophenone:



Molecular formula : $C_8H_7BrO_2$

Nature : White solid

Mp : 75-76 ^oC

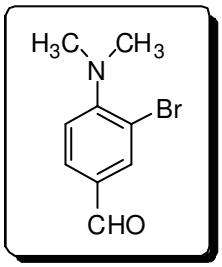
IR ($CHCl_3$, υ_{max}) : 3498, 2990, 1697, 1360, 1157, 1059, 687 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.61 (s, 3H), 6.78- 6.88(m, 2H), 7.45 (d, *J* = 8.86 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 30.19, 108.78, 115.99, 119.45, 134.76, 142.01, 155.39, 202.69 ppm.

MS (EI) (*m/z*) : 214 (M^+), 216 (M+2).

3-Bromo-4-(*N*,*N*-dimethylamino)benzaldehyde:



Molecular formula : $C_9H_{10}BrNO$

Nature : White solid

Mp : 102-104 ^oC

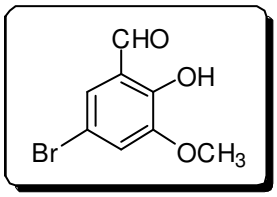
IR ($CHCl_3$, υ_{max}) : 2908, 2832, 1694, 1604, 1392, 1156, 1086 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.95 (s, 6H), 7.05 (d, *J* = 7.98 Hz, 1H), 7.71 (dd, *J* = 7.98, 2.03 Hz, 1H), 8.03 (d, *J* = 2.03 Hz, 1H), 9.81 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 43.02, 115.99, 119.03, 129.67, 130.47, 135.43, 156.41, 189.38 ppm.

MS (EI) (*m/z*) : 227 (M^+), 229 (M+2).

5-Bromo-2-hydroxy-3-methoxybenzaldehyde:



Molecular formula : $C_8H_7BrO_3$

Nature : Yellowish solid

Mp : 120-121 ^oC

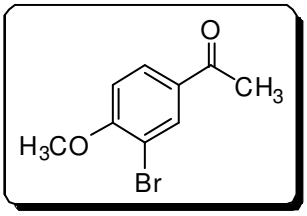
IR ($CHCl_3$, υ_{max}) : 3292, 2981, 1643, 1586, 1514, 1430, 1359, 1293, 1160, 1057, 684 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 3.92 (s, 3H), 7.17 (d, J = 2.14 Hz, 1H), 7.31 (d, J = 2.28 Hz, 1H), 9.86 (s, 1H), 11.01 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 56.38, 110.89, 120.52, 121.16, 125.92, 149.09, 150.68, 195.26 ppm.

MS (EI) (*m/z*) : 230 (M^+), 232 (M+2).

3-Bromo-4-methoxyacetophenone:



Molecular formula : $C_9H_9BrO_2$

Nature : White solid

Mp : 85-87 ^oC

IR ($CHCl_3$, υ_{max}) : 3065, 2992, 2925, 2851, 1672, 1592, 1498, 1357, 1168, 659 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 2.56 (s, 3H), 3.98 (s, 3H), 6.94 (d, J = 8.41 Hz, 1H), 7.91 (d, J = 8.41 Hz, 1H), 8.17 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ26.19, 56.41, 111.05, 111.71, 129.44, 131.13, 133.76, 159.49, 195.56 ppm.

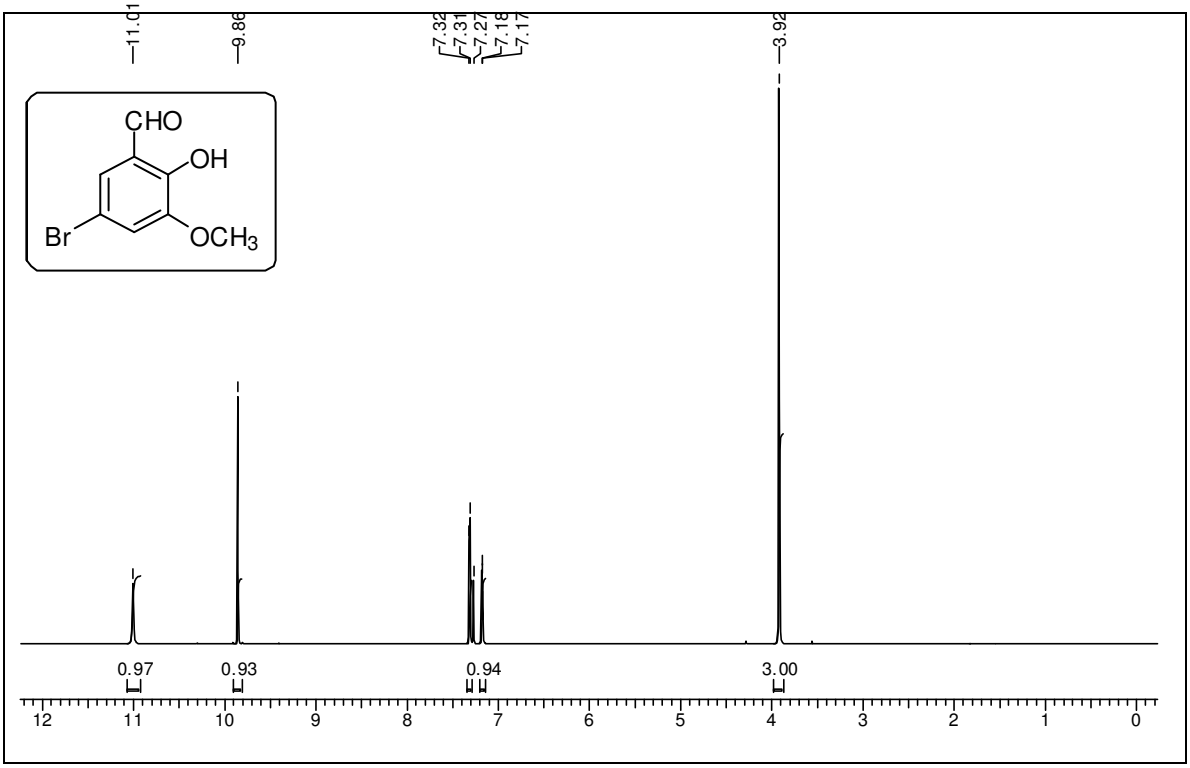
MS (EI) (*m/z*) : 228 (M^+), 230 (M+2).

2.2.7 Spectral data

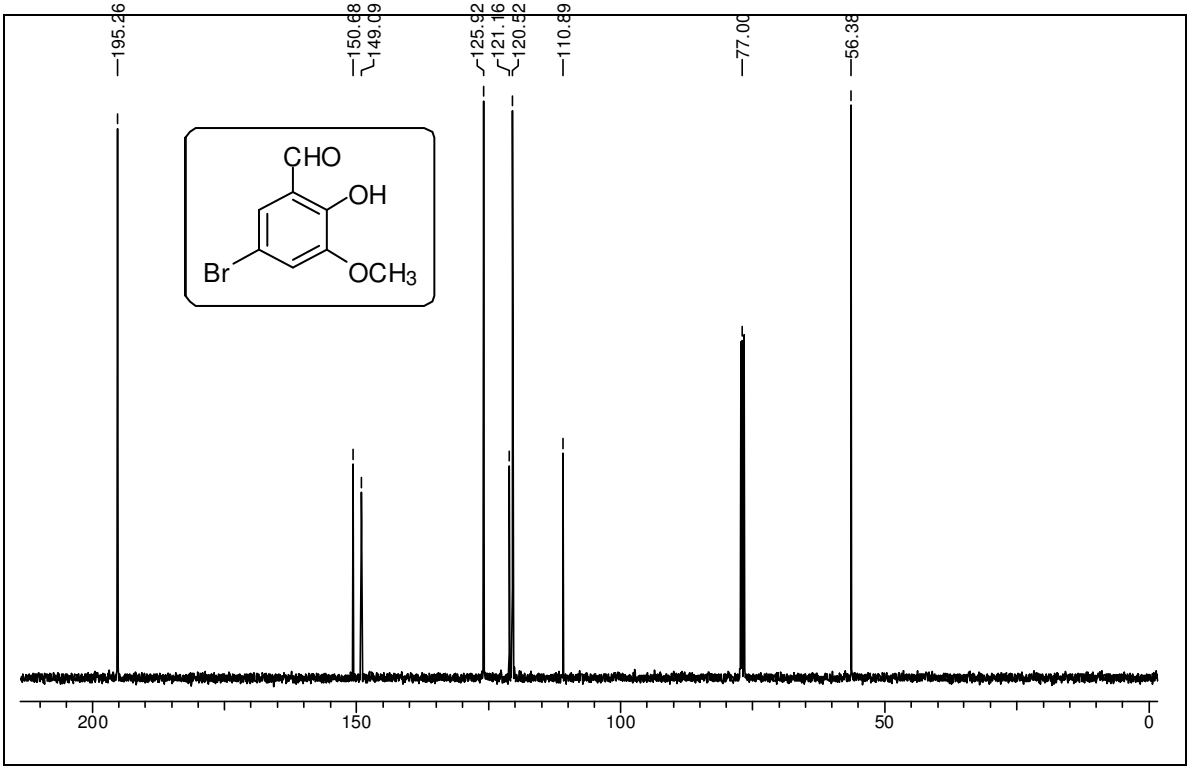
Table 2: ^{1}H, ^{13}C NMR and mass spectrum of some selected compounds are given below:

Sr. No.	Spectra
1	^{1}H NMR spectra of 5-Bromo-2-hydroxy-3-methoxybenzaldehyde
2	^{13}C NMR spectra of 5-Bromo-2-hydroxy-3-methoxybenzaldehyde
3	Mass spectra of 5-Bromo-2-hydroxy-3-methoxybenzaldehyde
4	^{1}H NMR spectra of 3-Bromo-4-(*N*,*N*-dimethylamino)benzaldehyde
5	^{13}C NMR spectra of 3-Bromo-4-(*N*,*N*-dimethylamino)benzaldehyde
6	Mass spectra of 3-Bromo-4-methoxybenzaldehyde

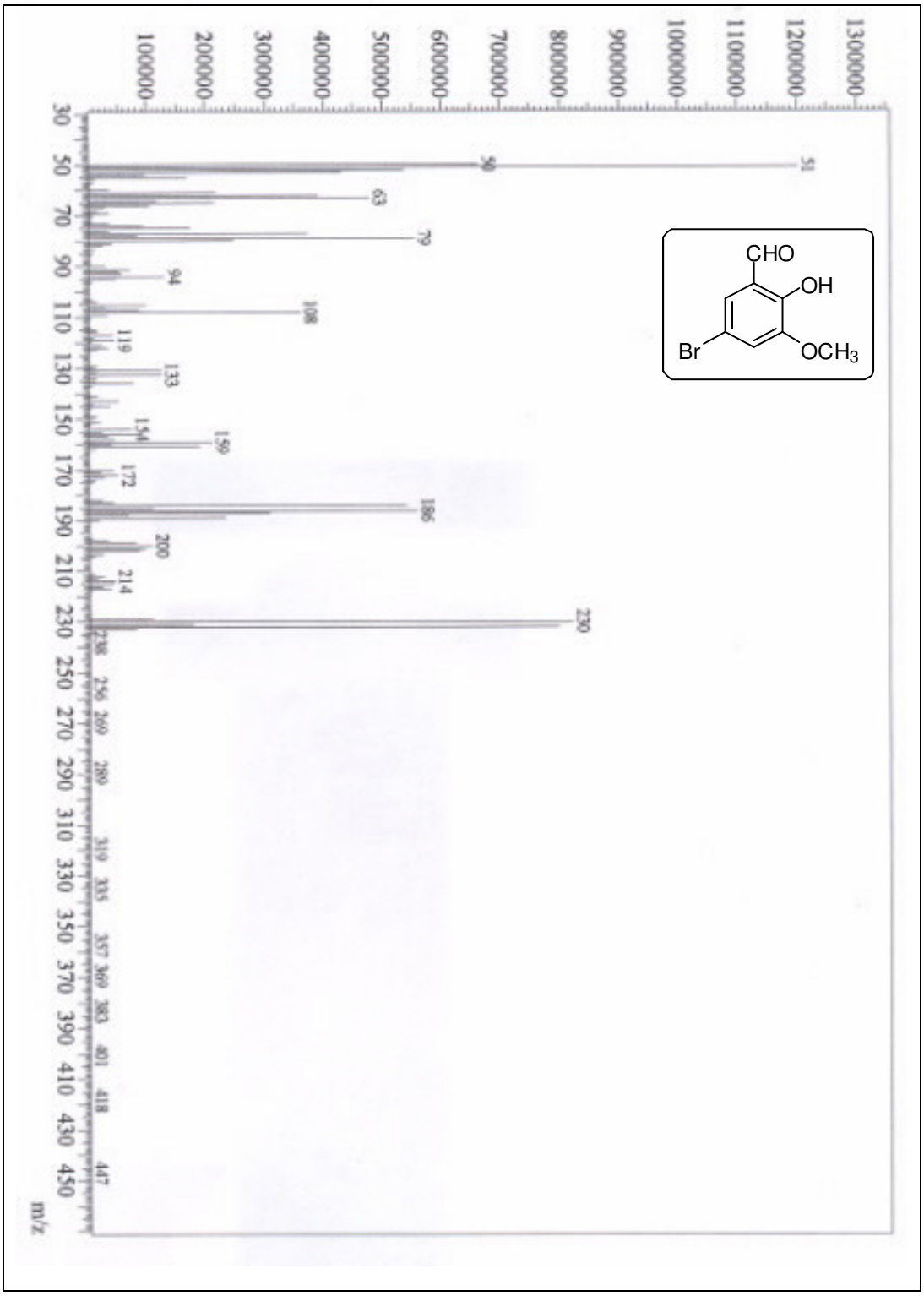
1. ^{1}H NMR spectra of 5-Bromo-2-hydroxy-3-methoxybenzaldehyde:



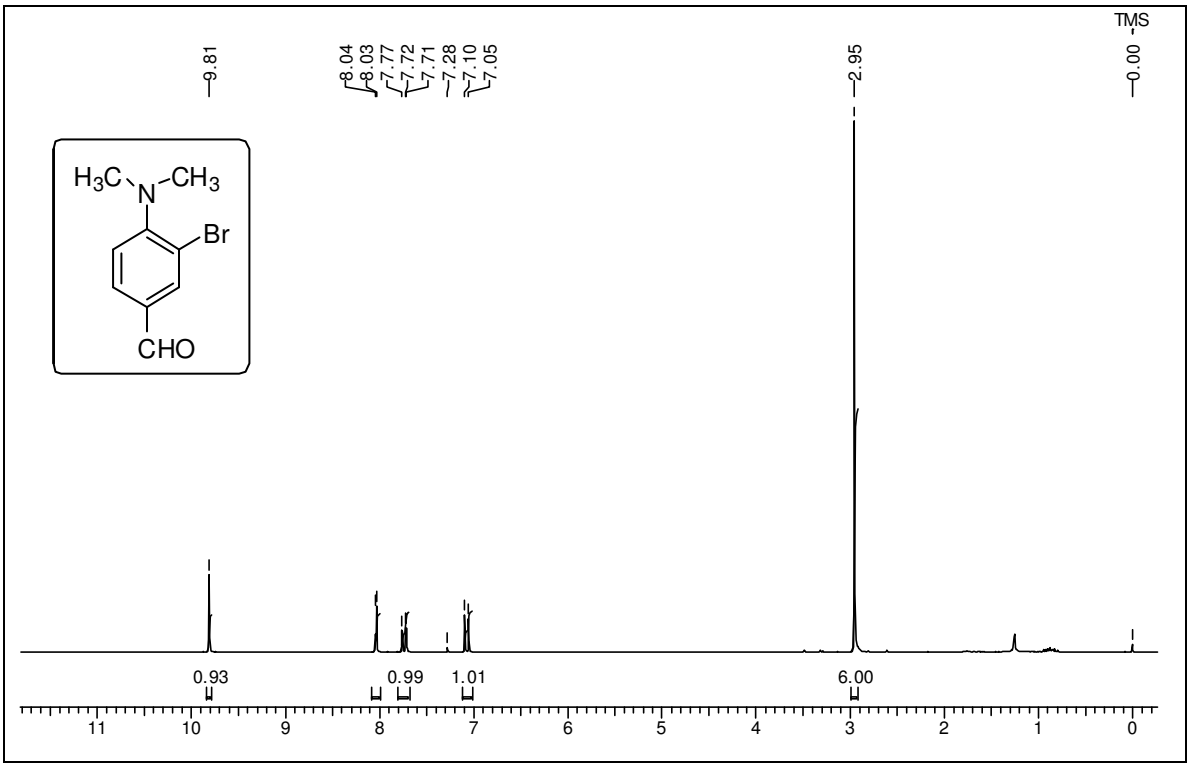
2. ^{13}C NMR spectra of 5-Bromo-2-hydroxy-3-methoxybenzaldehyde:



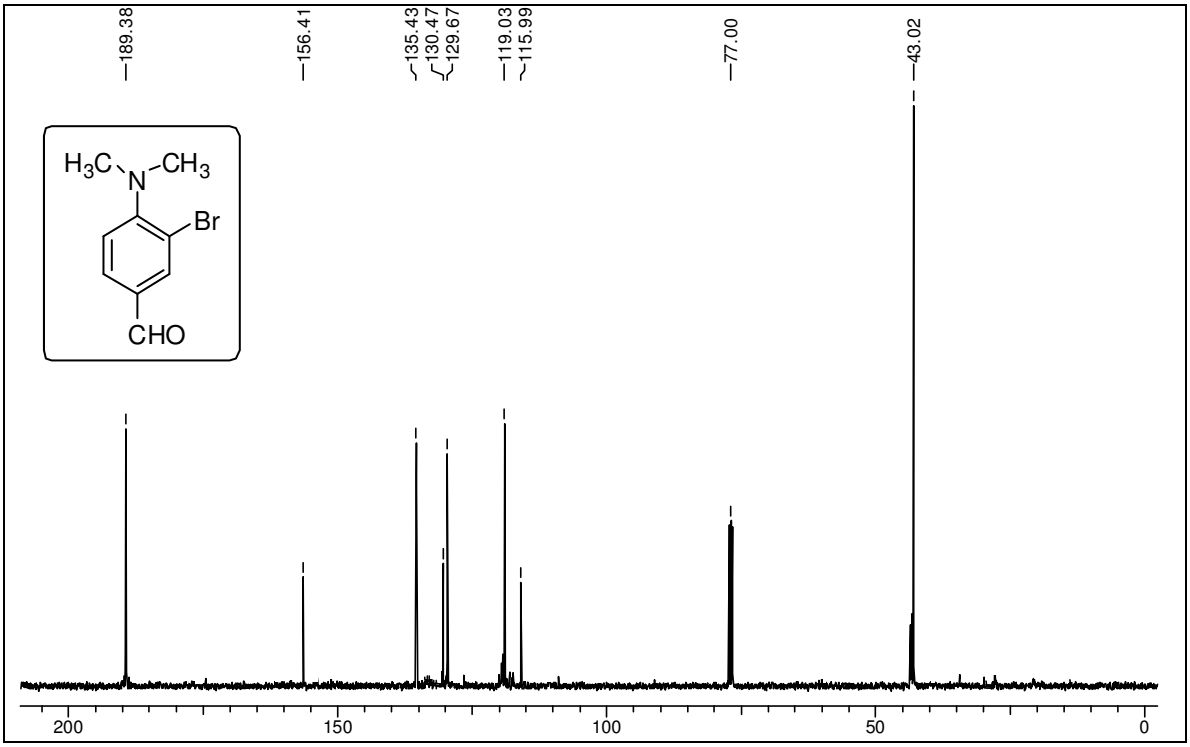
3. Mass spectra of 5-Bromo-2-hydroxy-3-methoxybenzaldehyde:



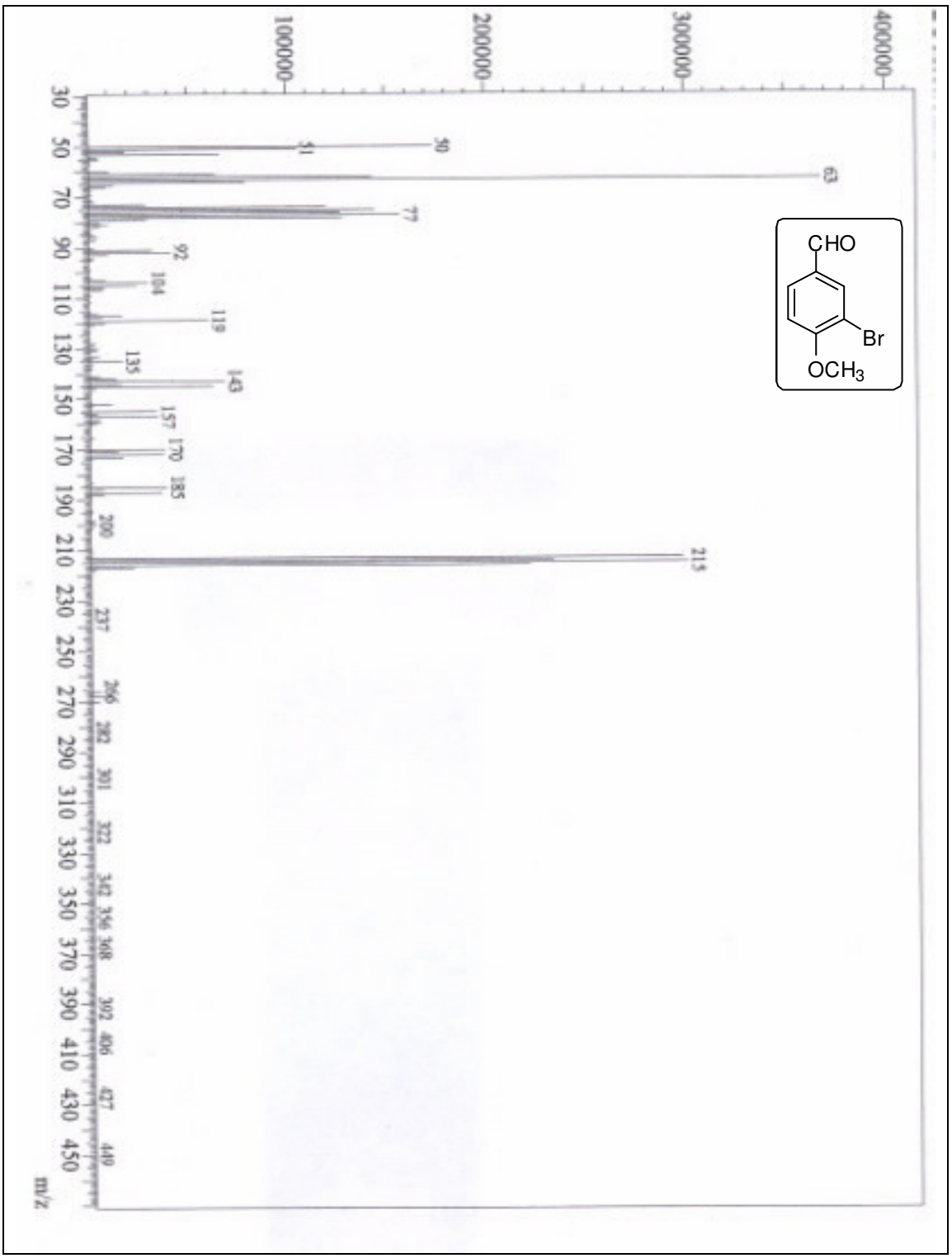
4. ^{1}H NMR spectra of 3-Bromo-4-(*N*,*N*-dimethylamino)benzaldehyde:



5. ^{13}C NMR spectra of 3-Bromo-4-(*N*,*N*-dimethylamino)benzaldehyde:



6. Mass spectra of 3-Bromo-4-methoxybenzaldehyde:



2.2.8 References

1. Szmant, H. H. *Organic Building Blocks of the Chemical Industry*; Wiley: New York, **1989**.
2. Stanforth, S. P. *Sci. Synth.* **2007**, *31a*, 121.
3. (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534; (b) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447; (c) Brennfuehrer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114; (d) de Meijere, A.; Stulgies, B.; Albrecht, K.; Rauch, K.; Wegner, H. A.; Hopf, H.; Scott, L. T.; Eshdat, L.; Aprahamian, I.; Rabinovitz, M. *Pure Appl. Chem.* **2006**, *78*, 813.
4. Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* **2003**, *44*, 8781.
5. (a) Léo, P. -M.; Morin, C.; Philouze, C. *Org. Lett.* **2002**, *4*, 2711; (b) Tatsuta, K.; Ozeki, H.; Yamaguchi, M.; Tanaka, M.; Okui, T. *Tetrahedron Lett.* **1990**, *31*, 5495; (c) Willem, A. L., Otterlo, V.; Michael, J. P.; Fernandes, M. A.; Koning, C. B. *Tetrahedron Lett.* **2004**, *45*, 5091.
6. (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939; (b) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105***,** 1563.
7. Lerman, O.; Rozen, S. *J. Fluorine Chem.* **1989**, *45*, 104.
8. Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.
9. Groweiss, A. *Org. Process Res. Dev.* **2000**, *4*, 30.
10. Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* **2004**, 2536.
11. Esakkidurai, T.; Kumarraja, M.; Pitchumani, K. *Catal. Lett.* **2004**, *92*, 169.
12. Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.
13. Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2006**, *47*, 4707.
14. Wang, L.; Jing, H.; Bu, X.; Chang, T.; Jin, L.; Liang, Y. *Catal. Commun.* **2007**, *8*, 80.
15. Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867.
16. de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. *Tetrahedron Lett.* **2009**, *50***,** 3001.

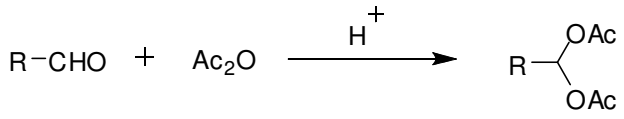
17. Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 2028; and references cited therein.
18. Kaushik, M. P.; Polshettiwar, V. *Indian J. Chem.* **2006**, *45B*, 2542.

Section-C

Synthesis of 1,1-diacetates under ultrasonic irradiation

2.3.1 Introduction

Selective protection and deprotection of aromatic or aliphatic carbonyl groups are extremely important in organic chemistry, essentially because of its application in various multistep syntheses.[1-4] In various ketones, the chemospecific protection of one carbonyl in 1,3-diones has great importance because of its involvement in various natural product syntheses.[1-4] Protection of carbonyl groups mainly involves the formation of acetals or ketals in the presence of an acid.[5-7] A carbonyl group can be protected by converting it into dioxolanes, diacetates, thiacetals, or oxathiolanes.[8] In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations. One prominent protection and deprotection of carbonyl group that produces an interesting class of oxygen heterocycles is the acylals synthesis. In 1905, Knoevenagel reported the first strong proton acid catalyzed acylals synthesis of aldehydes with acetic anhydride.[9]



1 **2**

Scheme 1. Acylals (1,1-diacetates) synthesis

In the 20th century, the scope of the original synthesis of acylals shown in **Scheme 1** was gradually extended by variation of acidic catalyst.[10-14] 1,1-Diacetate (acylals) are stable under both neutral and basic media as well as under acidic conditions[14] and undergo easy conversion into parent aldehydes.[15-16] Further, they are used as substrates in nucleophilic substitution reactions[17] and are precursors of 1-acetoxydienes[18] for Diels-Alder reactions. Compounds bearing the acylals functionality find industrial applications as cross linking agent for cellulose in cotton[19] and activators in the composition of bleaching mixture for wine-stained fabrics.[20]

Ionic liquids (ILs) act as environmentally benign green solvents and catalysts in many modern synthetic organic chemistry rather than classical organic solvents.[21,22] Ionic liquids have many advantages such as low vapor pressure, high thermal stability, able to

dissolve wide range of organic, inorganic and organo-metallic compounds, high polarity, reusability.[23] Due to this ionic liquid has been successfully applied in several classical organic reactions.[24,25] Recently, ionic liquids have been successfully employed as dual reagent (solvents + catalytic activity) for a variety of reactions, their use as catalyst under solvent-free conditions need to be given more attention.[26] Ionic liquids with acidic counter anions involving 1-hexyl-3-methylimidazolium hydrogen sulfate [hmim]HSO_4,[27] phenyl butyl ethyl selenonium tetrafluoroborate [pbeSe]BF_4,[28] 1-methylimidazolium tetrafluoroborate [hmim]BF_4,[29] 1-methyl-3-(3-sulfopropyl)-imidazolium hydrogen sulfate [HSO_3-pmim]HSO_4[30] can be used as acid catalysts. Due to high polarity, it can be used under solvent-free conditions.

Recently, ultrasonic irradiations (US) has become an established tool in organic synthesis,[31-34] because of the rate enhancements, higher yields, shorter reaction time and improved selectivity with respect to conventional reaction conditions. In addition, solvent-free ultrasonic irradiation processes are also clean and efficient. Moreover, it has received increasing attention.[35-36]

Introduction to Sonochemistry

Ultrasound is generally defined as sound of a frequency beyond that to which the human ear can respond. It is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and 40 kHz because this is the range employed in common laboratory equipment. However, since acoustic cavitation

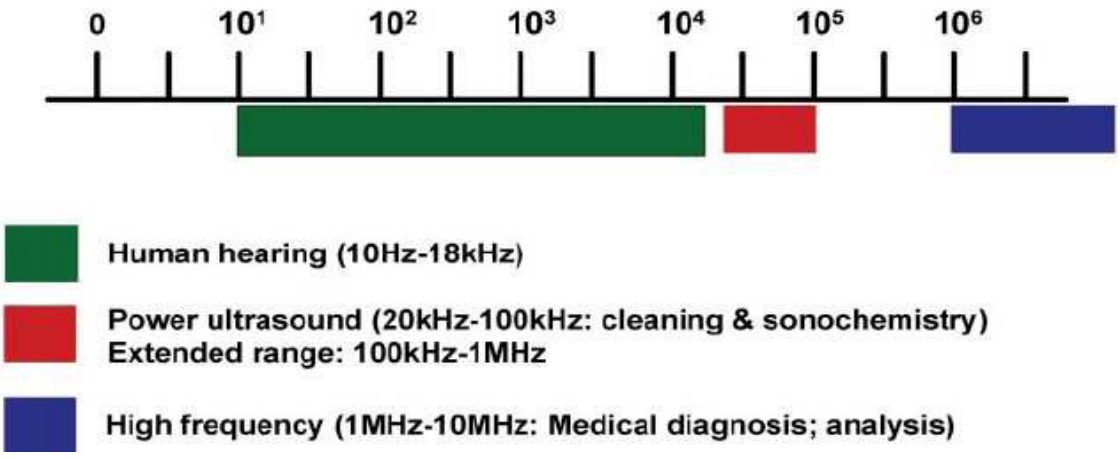


Figure 1. Sound frequencies (in Hz)

can be generated well above these frequencies, recent researches into sonochemistry use a much broader range (**Figure 1**). High frequency ultrasound from around 5 MHz and above does not produce cavitation and this is the frequency range used in medical imaging.

Cavitation is a phenomenon, in which the formation, growth and collapse of bubbles occur in the liquid, when the ultrasonic energy is applied to the liquid.[37,38] Ultrasounds are waves at frequencies above the hearing range.

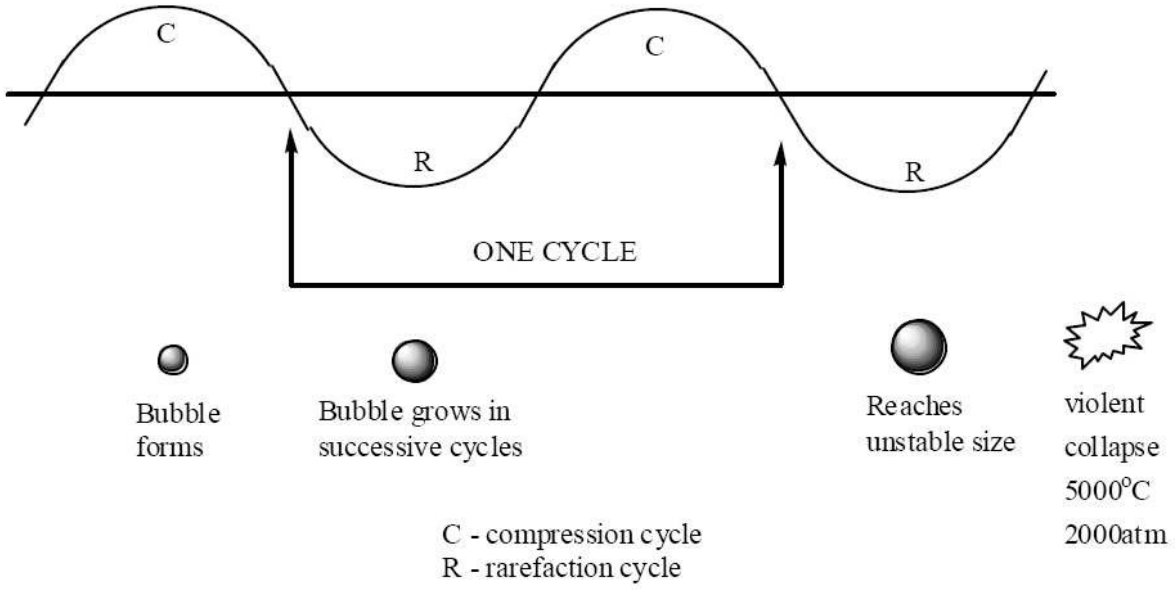


Figure 2. Sound propagation in a liquid

Ultrasonic energy (high frequency sound waves) produces an alternative adiabatic compression and rarefaction of the liquid media being irradiated (**Figure 2**). In the rarefaction part of the ultrasonic wave, micro-bubbles form because of reduced pressure. These micro-bubbles contain vaporized liquid or gas that was previously dissolved in the liquid. The micro-bubble can be either stable about their average size for many cycles (stable cavitation) or transient when they grow to certain size and violently collapse or implode during the compression part of the wave (transition cavitation). The energy releasing phenomena of the bubble formation and collapse is termed as acoustic cavitation.[39-41]

The application of ultrasound to chemical transformations may be termed as sonochemistry. Sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse.[42]

The physical effects of ultrasound can enhance the reactivity of a catalyst by enlarging its surface area or accelerate a reaction by proper mixing of reagents. The chemical effects of ultrasound enhance reaction rates because of the formation of highly reactive radical species formed during cavitation.[43] Homogeneous sonochemistry examines, mainly in the liquid phase, the activity of radicals or excited species formed in the bubble gas phase during the violent implosion and their possible release into the liquid. In heterogeneous sonochemistry, the mechanical effects of cavitation resulting from the erosion action of microjets formed during the asymmetric collapse of bubbles at the vicinity of interfaces are also important.[44]

Sonochemistry in ionic liquid

The driving energy for sonochemical organic reaction is provided by phenomenon of acoustic cavitation which is initiation, propagation and implosive collapse of the bubbles under adiabic conditions generating intercavity temperatures >5000 K and pressure up to 1200 bars. Since these micro-bubbles are unstable and collapse over a very short period of time, ca. 10^{-5} to 10^{-7} seconds, there is no bulk heating of the medium. The atmosphere of the bubbles, which contains gases, vapors of the solvent and of the volatile solutes, is compressed and heated leading to pyrolytic reactions. The resulting species, generally free radicals and other reactive intermediates are injected into the bulk medium, which remain at ambient temperature. A thermal quenching of the species occurs, followed by diverse reactions with other molecules. Thus, only volatile molecules which can penetrate the bubbles will undergo the extreme conditions produced during the collapse. In most cases, the low volatility of the substrates/ solutes used and relatively higher volatility of the molecular solvents used which exerts a cushioning effect, limit the efficiency of cavitation. To overcome this, high boiling solvents such as dodecane have been used to maximize temperature within the cavity but this resulted in carbon contamination of the products due to sonochemical degradation of the solvent.

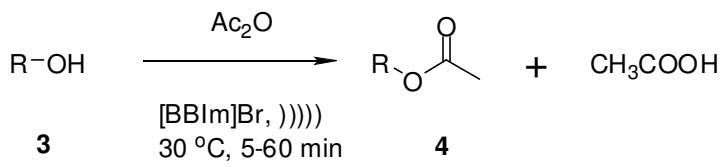
Complementarily, ILs are thermally stable non-volatile media, with a polar character favoring reaction which develops charges at some stage of the pathway. A logical conclusion is that cavitation bubbles in ILs should contain essentially molecules of the solutes, leading to their preferential activation without participation of the solvent. This activation should result in increased rates of the thermolytic processes, if the whole reaction occurs inside the cavity. Moreover, this increased intensity of cavitation leads to high intensity micro-streaming enhancing mass and heat transfer in the IL which in turn can generate reactive intermediates, nano-particles etc. On the other hand it is also possible that the strong polarity of the ILs should stabilize charges in reaction intermediates, broadening thus the domain of sonochemistry to polar pathways, of low sensitivity to sonication up to now. It is worth noting here that so far Sonochemistry is a method whose privileged domain is that of reactions proceeding via radicals or radical ions.

From the above presentation of both the physical aspects of sonochemistry and the properties of ILs, it can be deduced that sonochemistry in ILs should offer a number of advantages which was indeed found to be the case as can be seen in the following examples.

Ultrasound assisted some organic reactions

***O*-acetylation of alcohols**[45]

The *O*-acetylation of a variety of alcohols with acetic anhydride to the corresponding esters has been achieved by Srinivasan *et al.* in short reaction times with excellent isolated yields. This reaction was carried out under ambient conditions without any additional catalyst by the combined use of ultrasonic irradiation and a room temperature ionic liquid as a reaction medium and promoter (**Scheme 2**).

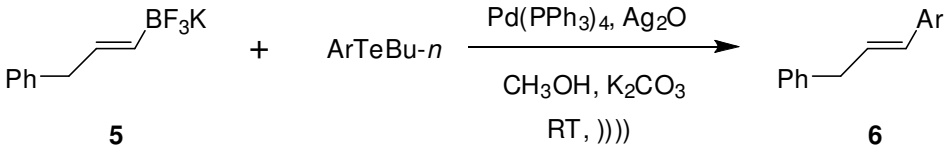


Scheme 2.

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

Suzuki cross-coupling[46]

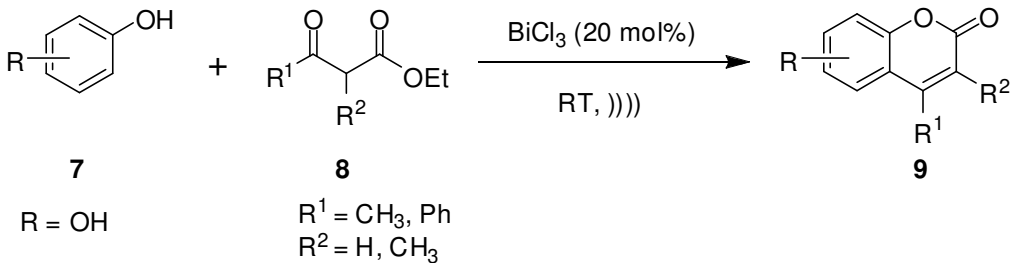
The ultrasound assisted Suzuki cross-coupling reactions of organotellurides (ArTeBu-*n*) with potassium organotriflouroborate salts were carried out in methanol. This reaction was catalyzed by palladium (0) and varieties of stilbenes containing functional group were prepared in good to excellent yields (**Scheme 3**). Silver oxide (Ag_2O) was used in the reaction as an additive.



Scheme 3.

Pechmann condensation[47]

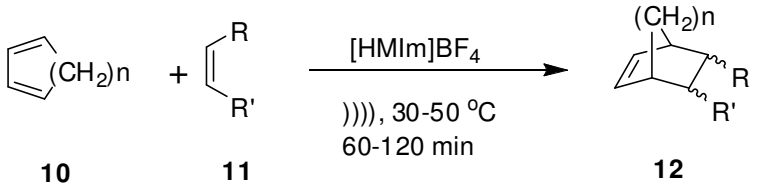
Samant *et al.* reported the condensation of phenol with *β*-ketoester in the presence of $BiCl_3$ as a Lewis acid under ultrasonic irradiation at ambient temperature to afford coumarins in good yields (**Scheme 4**). In the absence of ultrasound, under the same conditions, the reaction was found to be slow. A variety of *β*-ketoesters were applied in the reaction.



Scheme 4.

Cycloaddition[48]

Bravo and co-workers described a series of sonochemical cycloadditions involving cyclopentadiene **10** or 1,3-cyclohexadiene with carbonyl dienophiles in an imidazolium-based [HMIm]BF_4 ionic liquid as reaction medium (**Scheme 5**).

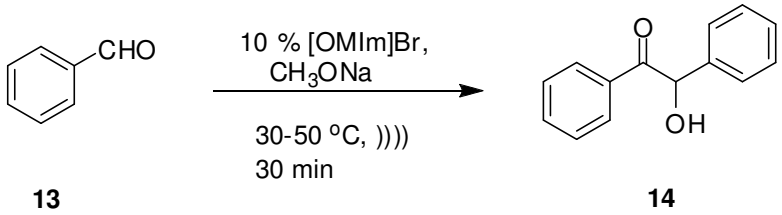


Scheme 5.

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

Benzoin condensation[49]

Benzoin condensation in ionic liquid [OMIm]Br at low frequency ultrasound irradiation without catalyst such as thiamin, triazolium, or thiazolium salts was carried out by Lévêque and co-workers.[49] No product formation was observed at silent condition. It was observed that the yield of product decreased drastically when only 2% of ionic liquid was used for the reaction (**Scheme 6**).



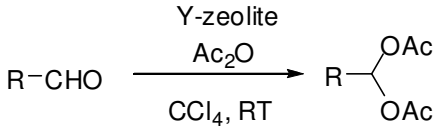
Scheme 6.

2.3.2 Review of literature

This section describes about some of the recent elegant methods reported in literature for the synthesis of 1,1-diacetates (acylals). In particular, the synthesis of acylals from the aldehydes with different reagents such as alum [$KAI(SO_4)_2 12H_2O$],[50] H_2SO_4-silica,[51] sulphated zirconia (SZ),[52] H_2NSO_3H,[53] preyssler heteropolyacid $H_{14}[NaP_5W_{29}MoO_{110}]$,[54] P_2O_5/Al_2O_3,[55] $HClO_4$-SiO_2,[56] saccharin sulfonic acid (SS),[57] $H_3PW_{12}O_{40}$ (PW)/MCM-41,[58] $NbCl_5$,[59] and copper methanesulfonate (CMS)-HOAc[60] and acetic anhydride has been obtained exclusively.

Gigante *et al.* (1995)[61]

Gigante and co-workers reported the Y-zeolite as inorganic heterogeneous catalyst. The preparation of 1,1-diacetates **2** from the corresponding aldehydes **1** by using Y-zeolite as catalyst and tridecane (internal standard) in good yields (**Scheme 7**). The catalyst could be re-generated and re-used.



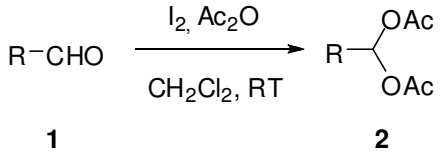
1 **2**

R = aromatic or aliphatic

Scheme 7.

Sarma *et al.* (1997)[62]

Sarma *et al.* used iodine as catalyst for the preparation of 1,1-diacetates **2** from the corresponding aldehydes **1** in good to excellent yields (**Scheme 8**).



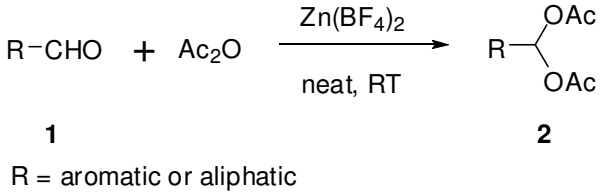
1 **2**

R = aryl or alkyl

Scheme 8.

Ranu *et al.* (2003)[63]

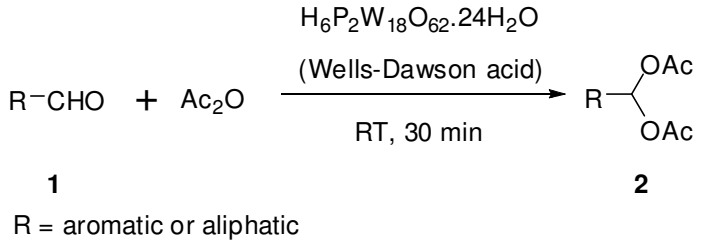
Ranu *et al.* described the aqueous solution (40 wt.%) of zinc tetrafluoroborate [$Zn(BF_4)_2$] catalyzed efficient conversion of corresponding aldehydes **1** to the respective geminal diacetates **2** in good to excellent yields (**Scheme 9**).



Scheme 9.

Autino *et al.* (2003)[64]

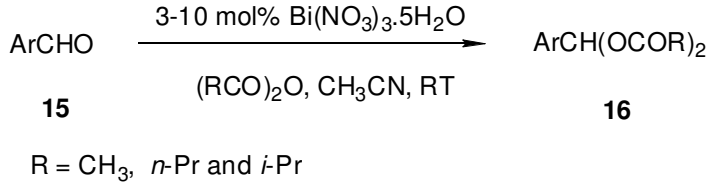
Autino and co-workers reported solvent-free catalytic preparation of 1,1-diacetates (acylals) **2** from aromatic and aliphatic aldehydes **1** using a Well-Dawson acid ($H_6P_2W_{18}O_{62}.24H_2O$) under mild conditions (**Scheme 10**).



Scheme 10.

Mohan *et al.* (2004)[65]

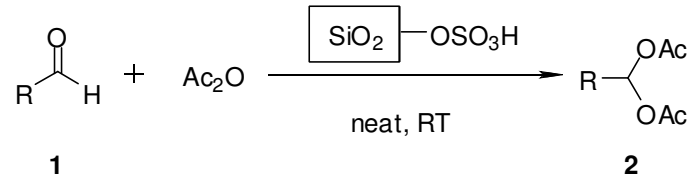
Mohan *et al.* have used bismuth nitrate ($Bi(NO_3)_3.5H_2O$) as catalyst for the chemoselective synthesis of acylals **16** from the corresponding aryl aldehydes **15** in good yields (**Scheme 11**). Ketones are not affected under the reaction conditions.



Scheme 11.

Desai *et al.* (2006)[66]

Desai and co-workers reported silica sulfuric acid (SSA) as a reusable solid acid catalyst. An efficient method has been developed for the chemoselective synthesis of acylals **2** from aldehydes **1** and acetic anhydride in the presence of silica sulfuric acid under solvent-free conditions (**Scheme 12**). The deprotection of acylals has also been achieved using SSA in methanol medium.



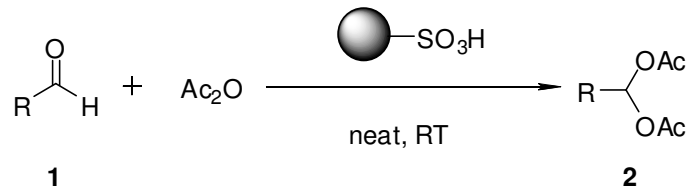
1 **2**

R = alkyl, aryl, heteroaryl

Scheme 12.

Wang *et al.* (2007)[67]

Wang *et al.* described PEG-supported sulfonic acid as an efficient and recyclable catalyst. An environmentally benign synthesis of 1,1-diacetate **2** in good yields by reaction of different aldehydes **1** with acetic anhydride in the presence of PEG-supported sulfonic acid under solvent-free conditions was described (**Scheme 13**).



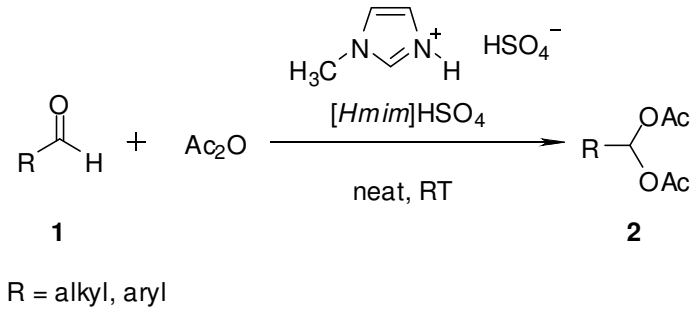
1 **2**

R = alkyl, aryl

Scheme 13.

Hajipour *et al.* (2008)[68]

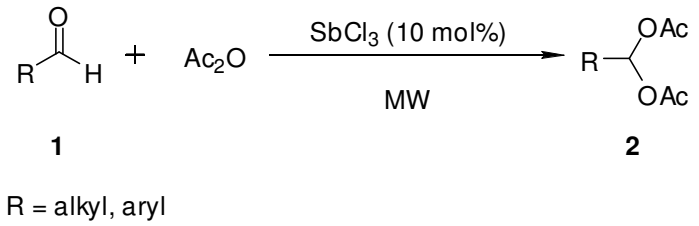
Hajipour and co-workers have reported 1-H-3-methylimidazolium hydrogen sulfate ([HMIm]HSO_4) as a brönsted acidic ionic liquid. The synthesis of 1,1-diacetates **2** from aldehydes **1** by using ([HMIm]HSO_4) as a catalyst under mild and solvent-free conditions at room temperature have been employed (**Scheme 14**).



Scheme 14.

Zhang *et al.* (2009)[69]

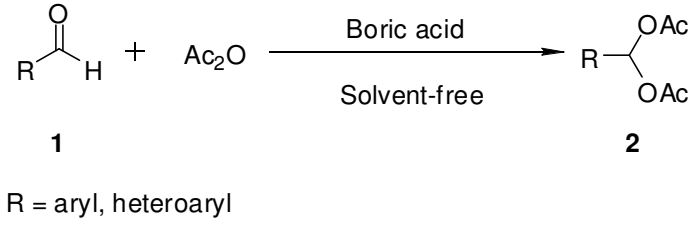
Zhang *et al.* reported microwave-assisted solvent-free synthesis of 1,1-diacetates **2** catalyzed by 10 mol% $SbCl_3$ as a Lewis acid. In this reaction, the corresponding aromatic aldehydes were converted to acylals in good yields (**Scheme 15**).



Scheme 15.

Shingare *et al.* (2009)[70]

Shingare and co-workers reported solvent-free synthesis of 1,1-diacetates using boric acid (BO_3H_3), an inexpensive, efficient and mild catalyst. Various aromatic and heteroaryl aldehydes were converted to corresponding diacetates at room temperature. The present method does not involve any hazardous organic solvents or catalysts. This

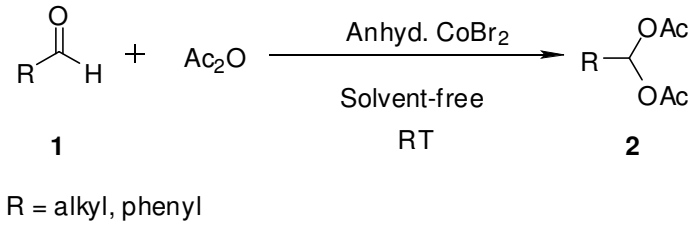


Scheme 16.

method gives notable advantages such as excellent chemoselectivity, mild reaction condition, short reaction times and excellent yield (**Scheme 16**).

Meshram *et al.* (2010) [71]

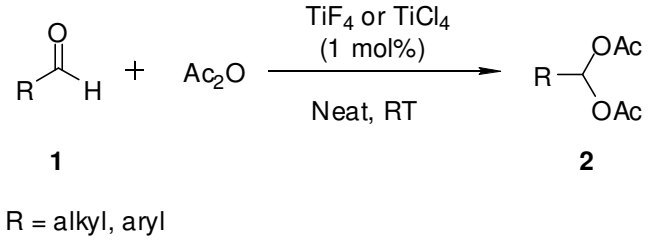
Meshram and co-workers described synthesis of 1,1-diacetates using anhyd. $CoBr_2$, a highly efficient catalyst under solvent-free condition at room temperature. This method gives notable advantages such as mild reaction conditions, ease of catalyst handling, short reaction time and excellent yield (**Scheme 17**).



Scheme 17.

Jung *et al.* (2010)[72]

Jung and co-workers reported a novel, mild and chemoselective method for the preparation of gem-diacetates **2** from aldehydes **1** catalyzed by titanium (IV) fluoride (TiF_4) and titanium (IV) chloride ($TiCl_4$) under solvent-free conditions at room temperature (**Scheme 18**). The reaction showed a high chemoselectivity toward aldehydes in the presence of ketones.



Scheme 18.

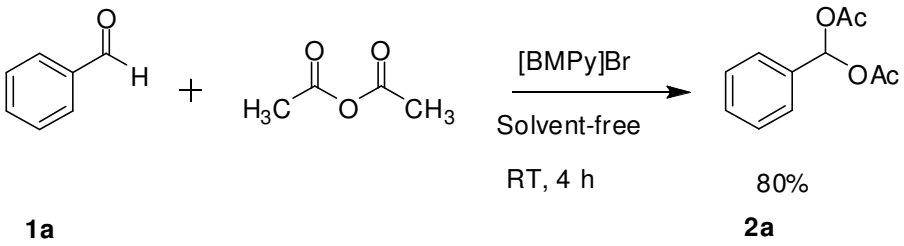
2.3.3 Present work

Many catalytic methods are available in the literature for synthesis of 1,1-diacetates (acylals). However, many of the methods reported above use expensive catalysts, strong acidic conditions, and higher temperatures and require longer reaction times. Some of the methods resulted in unsatisfactory yields and involved cumbersome product isolation procedures. Consequently, we thought, there is scope for further innovation towards milder reaction conditions, short reaction times and better yields. This is possible by a combination of 'Green' room temperature ionic liquids (ILs) as catalysts as well as solvent and ultrasound (ultrasonic irradiation) as energy source for the synthesis of acylals.

The use of ultrasound in these ILs, which have no vapor pressure, change should considerably the characteristics of cavitation in the bulk and force even less volatile substrates to undergo the cavitational activation. Continuing our investigations in this area, we have evaluated a synthesis of 1,1-diacetate promoted by the combined use of ultrasound and the IL, 1-butyl-3-methylpyridinium hydrogen sulfate, [BMPy]HSO_4 under ambient conditions in excellent isolated yields in short reaction times.

2.3.4 Results and discussion

In a model study, a mixture of benzaldehyde and acetic anhydride was stirred in ionic liquid [BMPy]Br at room temperature for 4 h under solvent-free condition. The product 1,1-diacetoxy-1-phenyl methane, **2a** was isolated by dilution with water and extracted with ethyl acetate and characterized (**Scheme 19**).



Scheme 19.

The formation of 1,1-diacetoxy-1-phenyl methane, **2a** was confirmed by spectral data (^{1}H, ^{13}C-NMR, IR, and MS spectroscopy). The IR spectrum of the compound **2a** showed typical absorption band in the region 1755 and 1245, 1065 cm^{-1} for ester C=O and ester C–O stretching frequencies respectively. The ^{1}H-NMR spectrum exhibits acetal proton signal at δ 7.67 ppm and singlet signals at δ 1.92 ppm suggesting acetal protons and acetate group present in the molecule. The ^{13}C-NMR spectra showed typical acetal proton and ester carbonyl carbon signals at δ 89.76 and 168.64 ppm respectively confirming the formation of **2a**.

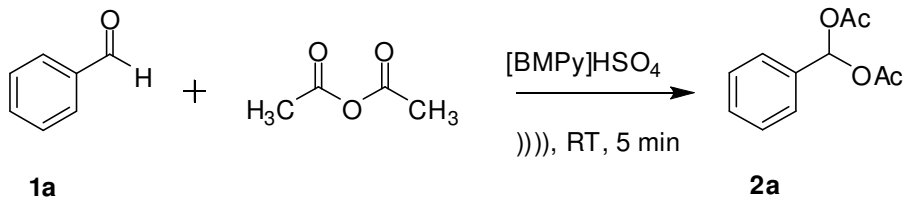
As we have synthesized several ionic liquids (ILs) based on 1-alkyl-3-methylpyridinium salts [RMPy]X. Obviously, our next target was to find out the best ionic liquid among them for the synthesis of acylals. Several ILs belonging to the [RMPy] series were screened for the typical reaction of benzaldehyde with acetic anhydride at room temperature under solvent-free condition to afford 1,1-diacetoxy-1-phenyl methane **2a.** The results are presented in **Table 1**.

Table 1. Acylals reaction of benzaldehyde with acetic anhydride in various ILs

Entry	Ionic liquid	Time (h)	Yield (%)
1	[BMPy]Br	4	80
2	[BMPy]HSO_4	4	95
3	[BMPy]PF_6	4	79
4	[HMPy]Br	4	78
5	[HMPy]HSO_4	4	84
6	[HMPy]PF_6	4	82
7	[DDMPy]Br	4	81
8	[DDMPy]HSO_4	4	86
9	[DDMPy]PF_6	4	82

Evidently, the IL [BMPy]HSO_4 afforded the best results. Encouraged by this result, we sonicated the mixture of benzaldehyde and acetic anhydride at ambient

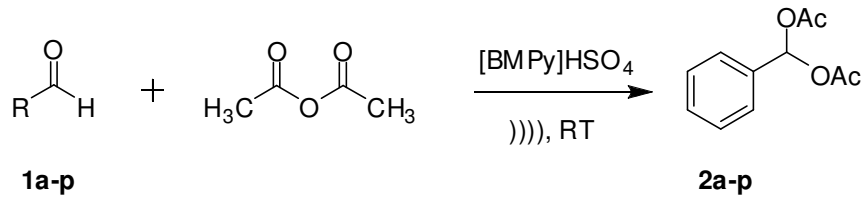
temperature in IL, [BMPy]HSO_4. The product 1,1-diacetoxy-1-phenyl methane, **2a** was easily synthesized in a very short time (**Scheme 20**).



Scheme 20.

The role of ultrasound in promoting the synthesis of acylals is evident from the fact that the corresponding reactions under stirring conditions without ultrasound (silent reactions) needed much longer time to the complete conversion. In many cases it ended in lowered yields.

Consequently, a variety of aldehydes including aromatic, aliphatic and cinnamyl aldehydes were subjected with freshly distilled acetic anhydride using IL [BMPy]HSO_4 as the reaction medium as well as catalyst under ultrasonic irradiation as shown in the **Scheme 21**.



Scheme 21.

All the reactions were monitored by TLC and taken to completion. The results are summarized in **Table 2**. All the compounds were well characterized by melting point, IR, ^{1}H-NMR and ^{13}C-NMR spectral data. For the known compounds, the values were in agreement with those reported in literature. It can be observed that, all the aldehydes have reacted in short reaction times under ultrasonic irradiation to afford 1,1-diacetate in very good to excellent isolated yields.

Table 2. Preparation of 1,1-diacetate using $[BMPy]HSO_4$ under ultrasonic irradiation

Entry	Aldehyde R	Product	Time (min)	Yield (%)	Mp (^oC)
1	Ph	**2a**	5	97	43-44
2	2-$NO_2C_6H_4$	**2b**	8	94	84-86
3	3-$NO_2C_6H_4$	**2c**	7	91	64-65
4	4-ClC_6H_4	**2d**	4	95	81-83
5	4-FC_6H_4	**2e**	6	92	49-51
6	4-BrC_6H_4	**2f**	5	94	92-94
7	3-HOC_6H_4	**2g**	15	91	77-78
8	3,4,5-$(MeO)_3C_6H_2$	**2h**	8	92	113-115
9	4-$MeOC_6H_4$	**2i**	6	92	63-64
10	Cinnamyl	**2j**	7	96	85-86
11	5-Me-furyl	**2k**	10	95	89-91
12	4,4-$Me_2NC_6H_4$	**2m**	120	0	-
13	Hexyl	**2n**	5	85	-
14	Piperonyl	**2o**	25	92	78-91
15	Acetophenone	**2p**	120	0	-

The process tolerates aromatic aldehydes containing both electron donating and electron withdrawing substituents except 4-(Dimethylamino)benzaldehyde **1m,** which may be due to the more electron donating of dimethylamino group. In the case of 3-hydroxybenzaldehyde **1g**, we observed both carbonyl and phenolic –OH groups acylated. No diacetate formation was observed for acetophenone **1p**. The acid sensitive substrate like 5-methylfurfural **1k** was also protected as gem-diacetate in good yield which may be due to mild acidic conditions. In some cases, an exothermic reaction took place after the addition of Ac_2O to the reaction mixture, which enhances the completion of the reaction. The reaction rate was found to be dependent on steric crowding surrounding the aldehydes group. Thus, the combined steric effects of the peri hydrogen and the 4-methoxy group made the reaction faster than the 2, 3, 4-trimethoxy benzaldehyde **1i**. The substituted aromatic, heterocyclic as well as aliphatic aldehydes all produced significantly improved yields as compared to the classical acylals protocol.

The products were easily isolated by dilution with water and extracted with ethyl acetate, dried and concentrated to afford 1,1-diacetates **2**. It was pure enough for all practical purposes. However, they were subjected to further purification by recrystallization for characterization. The combined aqueous filtrate was then subjected to distillation at 80 °C/10 mmHg for 4 h to remove water leaving behind [BMPy]HSO_4 in near quantitative yield. The IL, thus recovered could be used at least 2 - 3 times for the synthesis of **2a** without loss in activity.

Mechanism

The mechanism of this reaction may be involved either intermolecular or intramolecular transfer of the second acetate group after initial attack by acetic anhydride as shown in **Figure 3**. Probably, the role of catalyst i.e. IL here is to protonate the carbonyl group of aldehydes and increases the electrophilicity of the functional group.

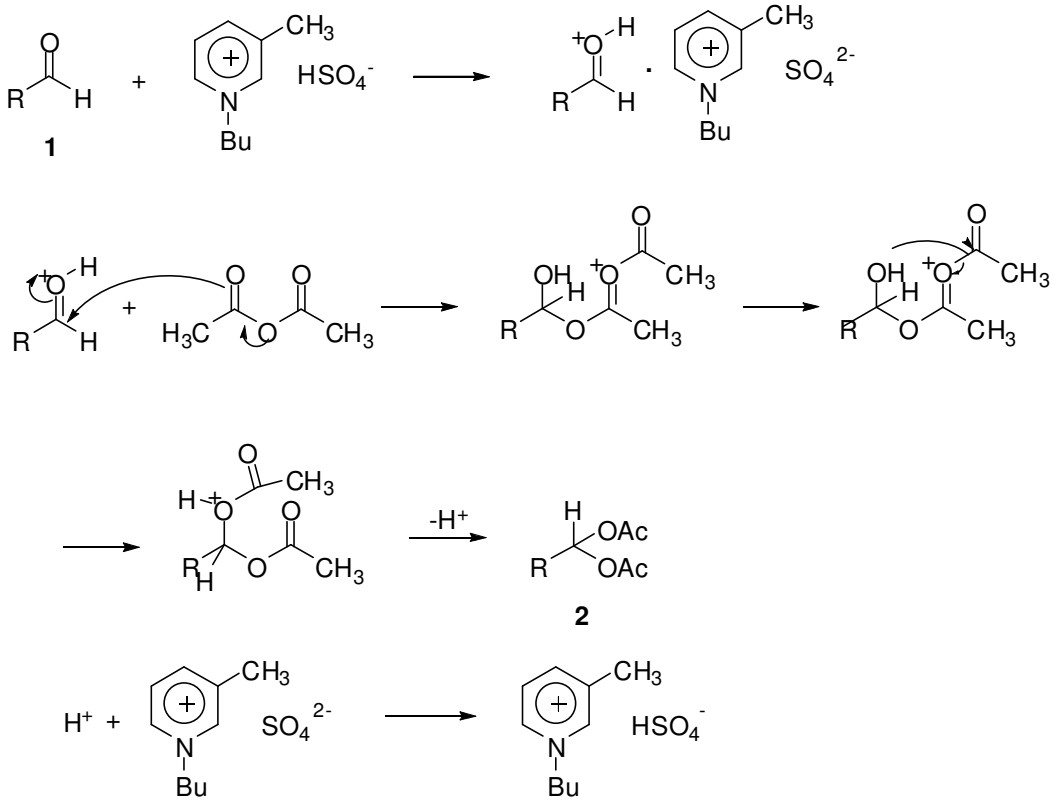


Figure 3. Plausible mechanism

2.3.5 Conclusion

In conclusion, we have demonstrated a simple and efficient method for the conversion of aldehydes to acylals using brønsted acidic ionic liquid under ultrasonic irradiation, solvent-free conditions. Ionic liquid acts as both solvent and catalyst. Thus, the synthesis of 1,1-diacetates promoted by the synergy of combined use of novel IL and ultrasound offers an easy access to substituted 1,1-diacetates in excellent yields. The advantages include recycle and reuse of ILs, low cost, short reaction time, excellent yields, and high selectivity. The use of an inexpensive and relatively non-toxic acidic ionic liquid is another advantage of this method.

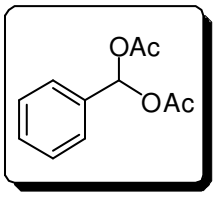
2.3.6 Experimental Section

General procedure for the synthesis of 1,1-diacetates under ultrasonic irradiation

A mixture containing respective aldehyde **1a-p** (10 mmol), freshly distilled Ac_2O (30 mmol) and 1-butyl-3-methylpyridinium hydrogen sulphate [BMPy]HSO_4 (5 mol %) was sonicated at ambient conditions in a thermostate (30 ± 1 °C) ultrasonic cleaning bath. The completion of the reaction was monitored by TLC and then added H_2O to quench the ionic liquid. The resulting solution was extracted with ethyl acetate. The combined organic layer was washed with aq. $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the corresponding 1, 1-diacetates **2a-p**. The combined aqueous filtrate was subjected to distillation at 80 °C under reduced pressure (10 mmHg) over 4 h to leave behind the IL in near complete recovery, pure enough for recycle.

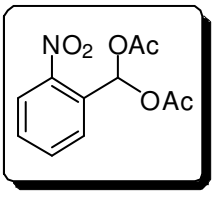
2.3.6.1 Characterization data:

1,1-Diacetoxy-1-phenylmethane (2a):



Molecular formula	**:**	$C_{11}H_{12}O_4$
Nature	**:**	White crystalline solid
Mp	**:**	43-44 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3060, 1755, 1605, 1470, 1375, 1245, 1205, 1065, 1010, 760, 700 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.92 (s, 6H), 7.29-7.45 (m, 5H), 7.67 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 20.74, 89.76, 126.65, 128.61, 129.69, 135.65, 168.64 ppm.
MS (EI) (*m/z*)	**:**	209 (M + 1).

1,1-Diacetoxy-1-(2-nitrophenyl)methane (2b):



Molecular formula	**:**	$C_{11}H_{11}NO_6$
Nature	**:**	Yellow solid
Mp	**:**	84-86 ^oC

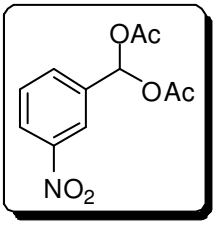
IR ($CHCl_3$, υ_{max}) : 3019, 1763, 1534, 1374, 1216, 757, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.15 (s, 6H), 7.55-7.63 (m, 1H), 7.70-7.73 (m, 2H), 8.04 (d, *J* = 8.46 Hz, 1H), 8.21 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ20.38, 85.88, 124.90, 127.79, 130.40, 133.47, 147.69, 168.11 ppm.

MS (EI) (*m/z*) : 254 (M + 1).

1,1-Diacetoxy-1-(3-nitrophenyl)methane (2c):



Molecular formula : $C_{11}H_{11}NO_6$

Nature : Faint yellow solid

Mp : 64-65 ^oC

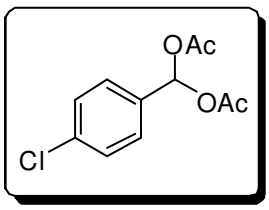
IR ($CHCl_3$, υ_{max}) : 3090, 1755, 1530, 1350, 1230, 1200, 1085, 1040, 950, 815, 730 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ2.16 (s, 6H), 7.61 (t, *J* = 7.96 Hz, 1H), 7.73 (s, 1H), 7.82 (d, *J* = 7.70 Hz, 1H), 8.25 (d, *J* = 8.21 Hz, 1H), 8.40 (t, *J* = 7.96 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ20.63, 88.23, 121.76, 124.46, 129.69, 132.86, 137.42, 148.22, 168.51 ppm.

MS (EI) (*m/z*) : 254 (M + 1).

1,1-Diacetoxy-1-(4-chlorophenyl)methane (2d):



Molecular formula : $C_{11}H_{11}ClO_4$

Nature : White solid

Mp : 81-83 ^oC

IR ($CHCl_3$, υ_{max}) : 3060, 3020, 1760, 1605, 1480, 1210, 1010, 780, 620 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ2.13 (s, 6H), 7.36-7.49 (m, 4H), 7.64 (s, 1H) ppm.

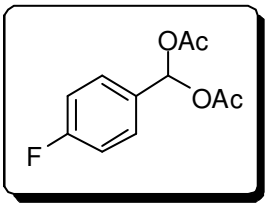
^{13}C NMR ($CDCl_3$, 50 MHz) : δ20.51, 88.97, 128.07, 128.69, 133.85, 135.62,

---

168.61 ppm.

MS (EI) (*m/z*) : 244 (M + 2).

1,1-Diacetoxy-1-(4-fluorophenyl)methane (2e):



Molecular formula : $C_{11}H_{11}FO_4$

Nature : Faint yellow solid

Mp : 39-41 ^oC

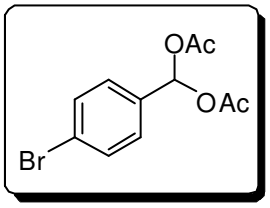
IR ($CHCl_3$, υ_{max}) : 3014, 2913, 1764, 1749, 1609, 1477, 1370, 1237, 1201, 1037, 795, 675 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 2.10 (s, 6H), 6.91-7.23 (m, 2H), 7.29-7.41 (m, 2H), 7.60 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.68, 89.01, 115.47, 128.70, 131.49, 163.25, 168.92 ppm.

MS (EI) (*m/z*) : 227 (M +1).

1,1-Diacetoxy-1-(4-bromophenyl)methane (2f):



Molecular formula : $C_{11}H_{11}BrO_4$

Nature : White solid

Mp : 92-94 ^oC

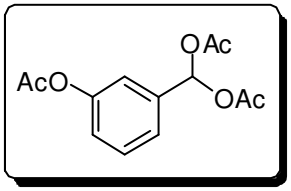
IR ($CHCl_3$, υ_{max}) : 3093, 1758, 1549, 1488, 1372, 1250, 1205, 942, 828 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 2.13 (s, 6H), 7.38 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.63 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.69, 88.99, 123.83, 128.32, 131.68, 134.39, 168.57 ppm.

MS (EI) (*m/z*) : 288 (M + 2).

1,1-Diacetoxy-1-(3-acetoxyphenyl)methane (2g):



Molecular formula : $C_{13}H_{14}O_6$

Nature : White solid

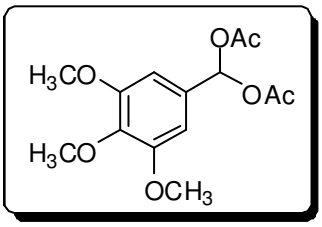
Mp : 77-78 ^{o}C

IR ($CHCl_3$, υ_{max}) : 3051, 2985, 1745, 1441, 1610, 1529, 1490, 1250, 1208, 750 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.12 (s, 6H), 2.32 (s, 3H), 7.15 (d, J = 7.07 Hz, 1H), 7.39-7.42 (m, 3H), 7.68 (s, 1H) ppm.

MS (EI) (*m/z*) : 266 (M^+).

1,1-Diacetoxy-1-(3,4,5-trimethoxyphenyl)methane (2h):



Molecular formula : $C_{14}H_{18}O_7$

Nature : Brownish solid

Mp : 113-115 ^{o}C

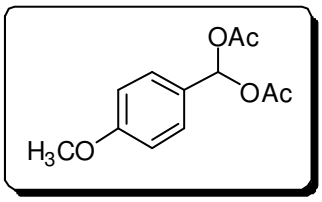
IR ($CHCl_3$, υ_{max}) : 1750 3029, 2945, 2801, 1759, 1608, 1501, 1380, 1226, 1205, 1015, 789, 719 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.14 (s, 6H), 3.89 (d, J = 7.35 Hz, 9H), 6.76 (s, 2H), 7.60 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.67, 55.93, 60.55, 89.57, 103.56, 130.67, 138.74, 153.15, 168.58 ppm.

MS (EI) (*m/z*) : 298 (M^+).

1,1-Diacetoxy-1-(4-methoxyphenyl)methane (2i):



Molecular formula : $C_{12}H_{14}O_5$

Nature : Colourless solid

Mp : 63-64 ^{o}C

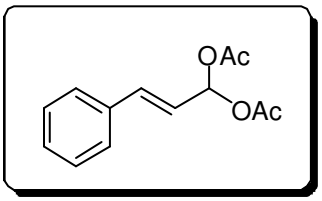
IR ($CHCl_3$, υ_{max}) : 3029, 2945, 2801, 1759, 1608, 1501, 1380, 1226, 1205, 1015, 789, 719 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.13 (s, 6H), 3.85 (s, 3H), 6.94 (d, J = 8.59 Hz, 2H), 7.46 (d, J = 8.59 Hz, 2H), 7.60 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 21.45, 55.70, 90.05, 114.23, 127.92, 128.31, 160.74, 168.93 ppm.

MS (EI) (*m/z*) : 238 (M^+).

1,1-Diacetoxy-3-phenylprop-2-ene (2j):



Molecular formula : $C_{13}H_{14}O_4$

Nature : White solid

Mp : 85-86 ^oC

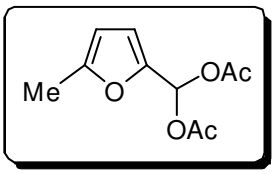
IR ($CHCl_3$, υ_{max}) : 3085, 2930, 1760, 1655, 1610, 1495, 1375, 1240, 1205, 1110, 1005, 940, 750, 690 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 2.15 (s, 6H), 6.24 (dd, J = 15.4, 6.80 Hz, 1H), 6.83 (d, J = 15.4 Hz, 1H), 7.28-7.34 (m, 5H), 7.39 (d, J = 6.9 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 20.85, 89.76, 121.83, 127.03, 128.66, 128.82, 135.21, 135.59, 168.59 ppm.

MS (EI) (*m/z*) : 234 (M^+).

1,1-Diacetoxy-1-(5-methylfuryl)methane (2k):



Molecular formula : $C_{10}H_{12}O_5$

Nature : Blackish solid

Mp : 89-91 ^oC

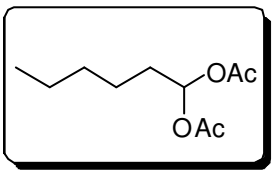
IR ($CHCl_3$, υ_{max}) : 3101, 2939, 1758, 1573, 1376, 1244, 1201, 1022, 958 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 2.14 (s, 6H), 2.33 (s, 3H), 5.99 (d, J = 3.1 Hz, 1H), 6.42 (d, J = 3.1 Hz, 1H), 7.58 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.72, 20.11, 106.12, 106.29, 109.61, 152.21, 155.78, 168.81 ppm.

MS (EI) (*m/z*) : 212 (M^+).

1,1-Diacetoxyhexane (2n):

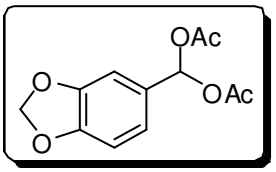


Molecular formula : $C_{10}H_{18}O_4$

Nature : Colourless oil

IR ($CHCl_3$, υ_{max})	**:**	2970, 1755, 1460, 1375, 1235, 1205, 1090, 1020, 990, 650 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.02 (t, J = 5.56 Hz, 3H), 1.29-1.83 (m, 8H), 2.04 (s, 6H), 6.61 (t, J = 5.5 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.92, 20.69, 22.53, 23.13, 31.47, 33.26, 90.74, 169.07 ppm.
MS (EI) (*m/z*)	**:**	202 (M^+).

1,1-Diacetoxy-piparane (2o):



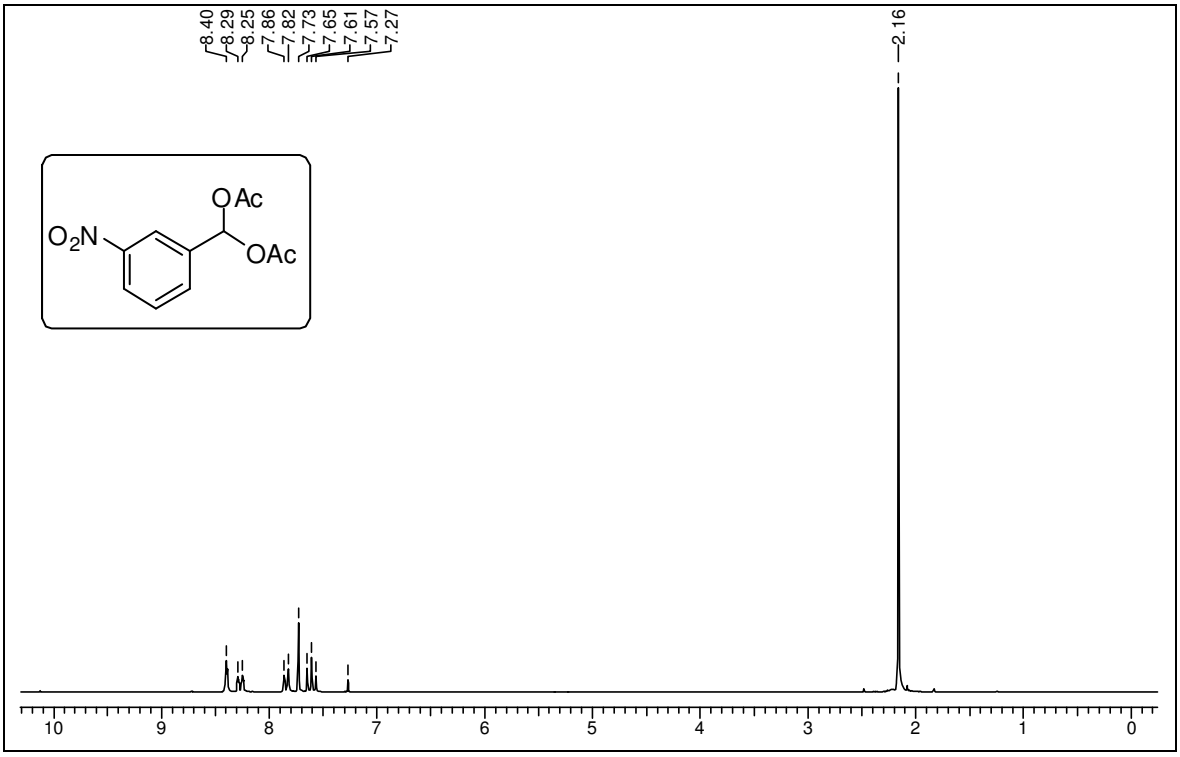
Molecular formula	**:**	$C_{12}H_{12}O_6$
Nature	**:**	White solid
Mp	**:**	78-79 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3098, 2910, 1760, 1605, 1496, 1439, 1360, 1229, 1198, 1030, 969, 790 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 2.11 (s, 6H), 5.98 (s, 2H), 6.82 (d, J = 8.46 Hz, 1H), 6.95-7.02 (m, 2H), 7.56 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 20.54, 89.40, 101.19, 106.70, 107.88, 120.68, 129.09, 147.65, 148.48, 168.46 ppm.
MS (EI) (*m/z*)	**:**	252 (M^+).

2.3.7 Spectral data

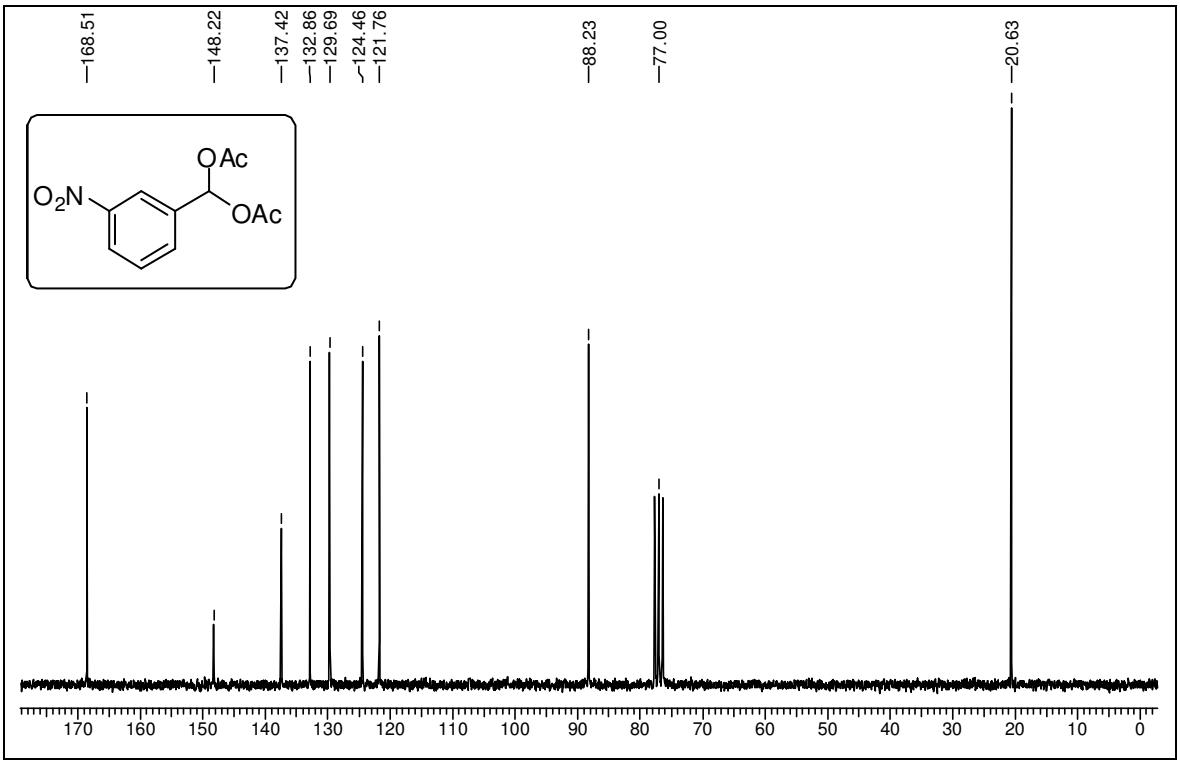
Table 3: ^{1}H and ^{13}C NMR spectrum of some selected compounds are given below:

Sr. No.	Spectra
1	^{1}H NMR and ^{13}C NMR spectra of **2b**
2	^{1}H NMR and ^{13}C NMR spectra of **2h**
3	^{1}H NMR and ^{13}C NMR spectra of **2f**
4	^{1}H NMR and ^{13}C NMR spectra of **2o**

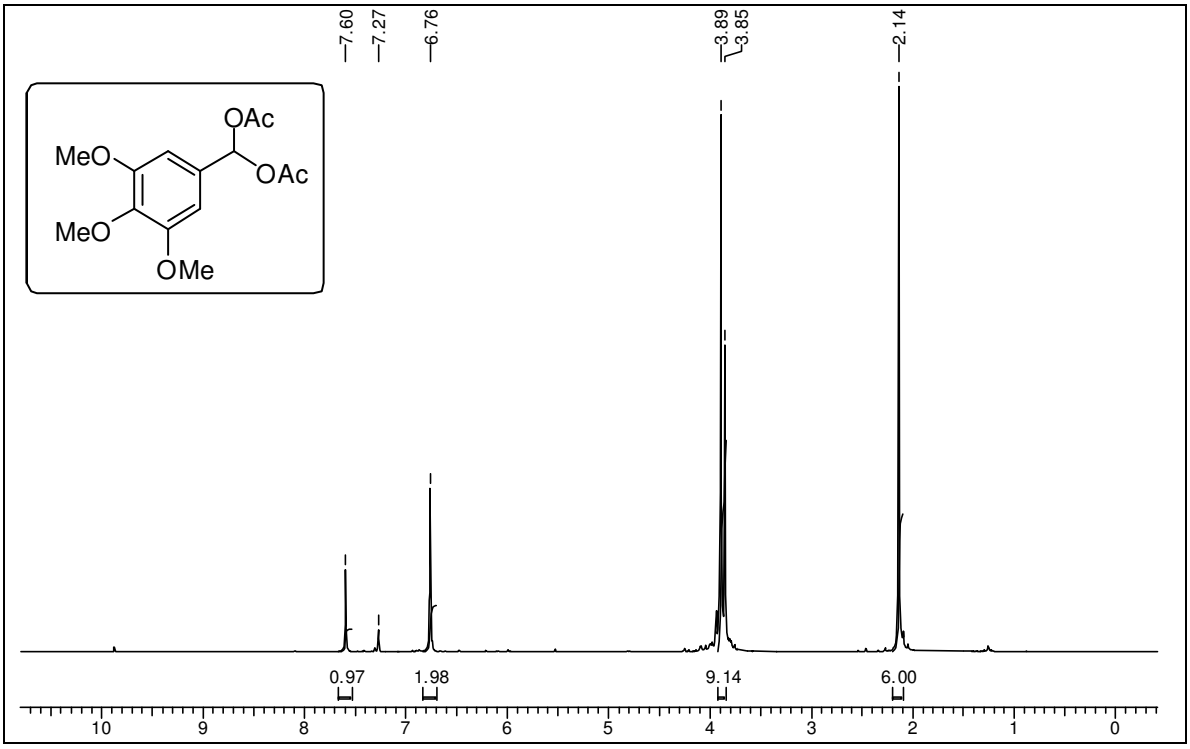
1. ^{1}H NMR spectra of 1,1-diacetoxy-1-(3-nitrophenyl)methane (**2b**):



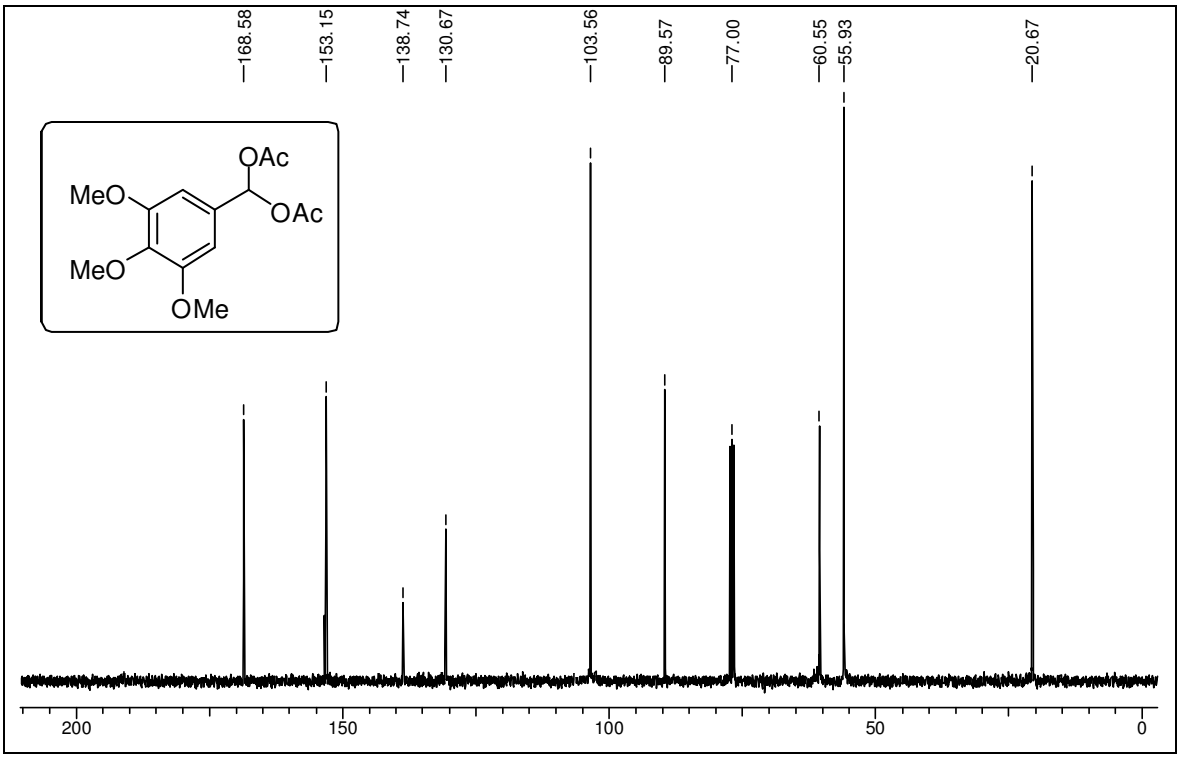
1. ^{13}C NMR spectra of 1,1-diacetoxy-1-(3-nitrophenyl)methane (**2b**):



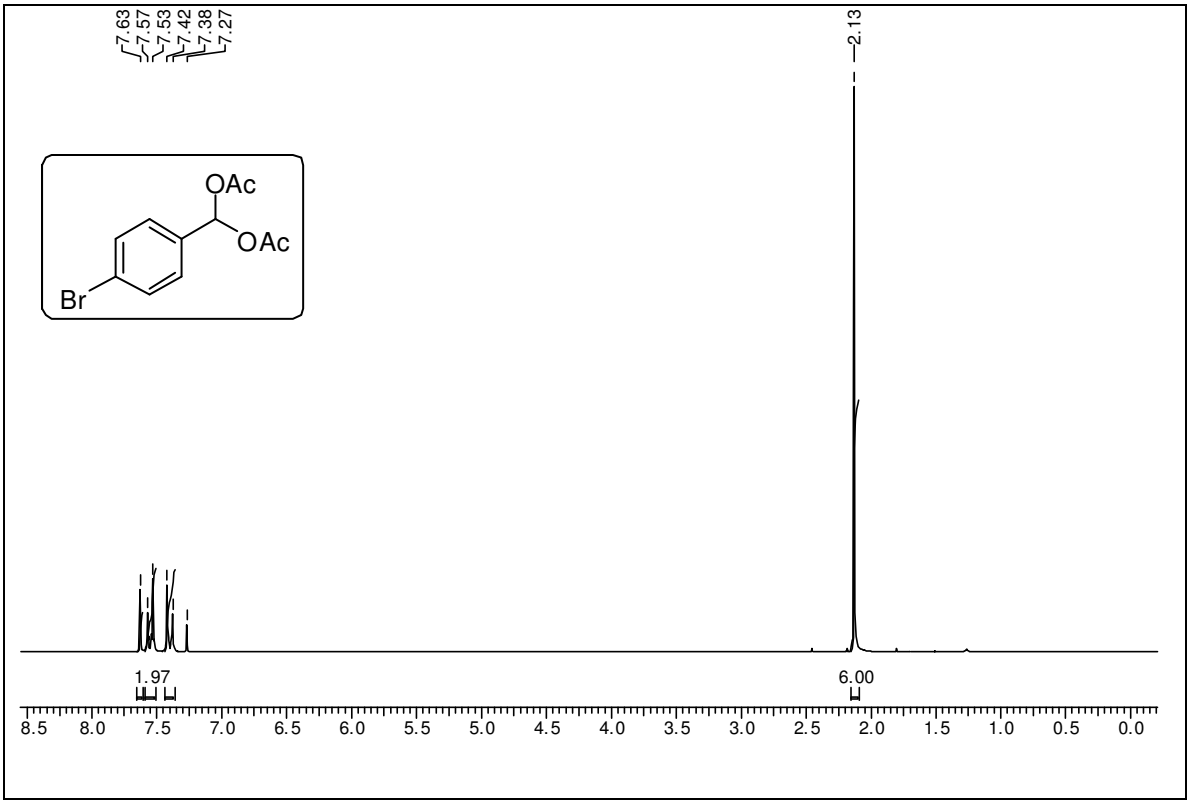
2. ^{1}H NMR spectra of 1,1-diacetoxy-1-(3,4,5-trimethoxyphenyl)methane (**2h**):



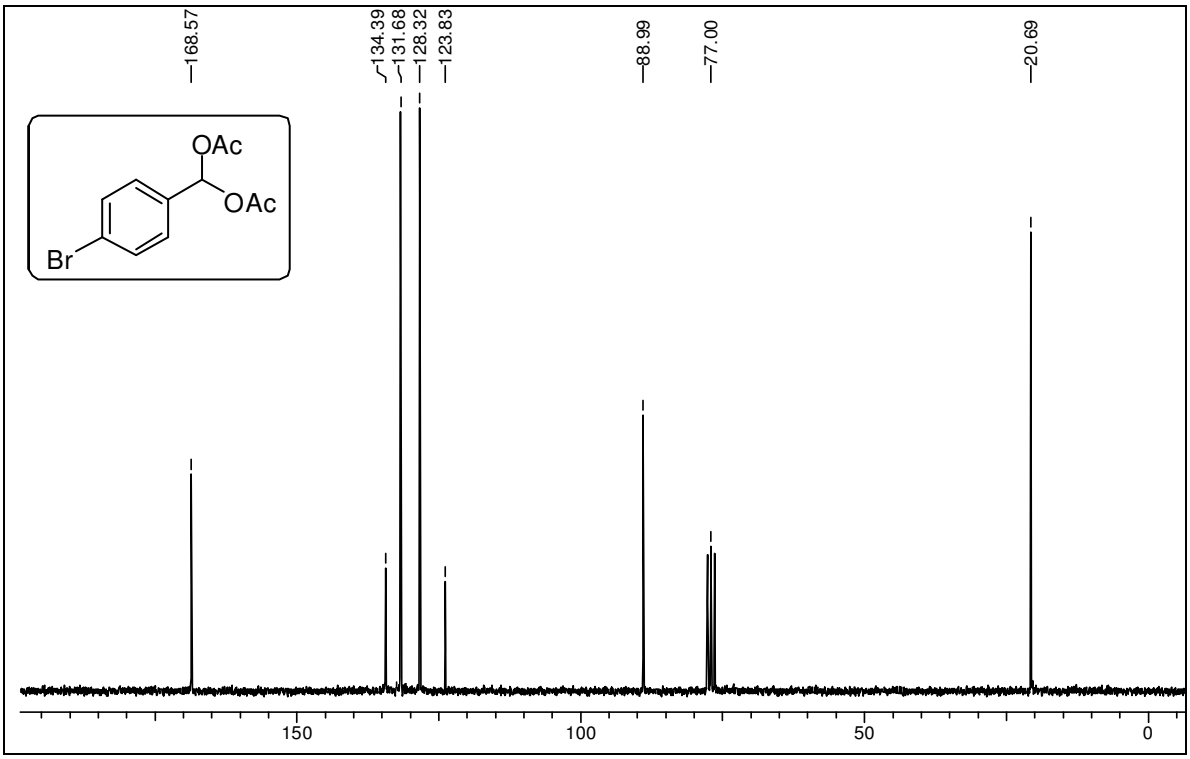
2. ^{13}C NMR spectra of 1,1-diacetoxy-1-(3,4,5-trimethoxyphenyl)methane (**2h**):



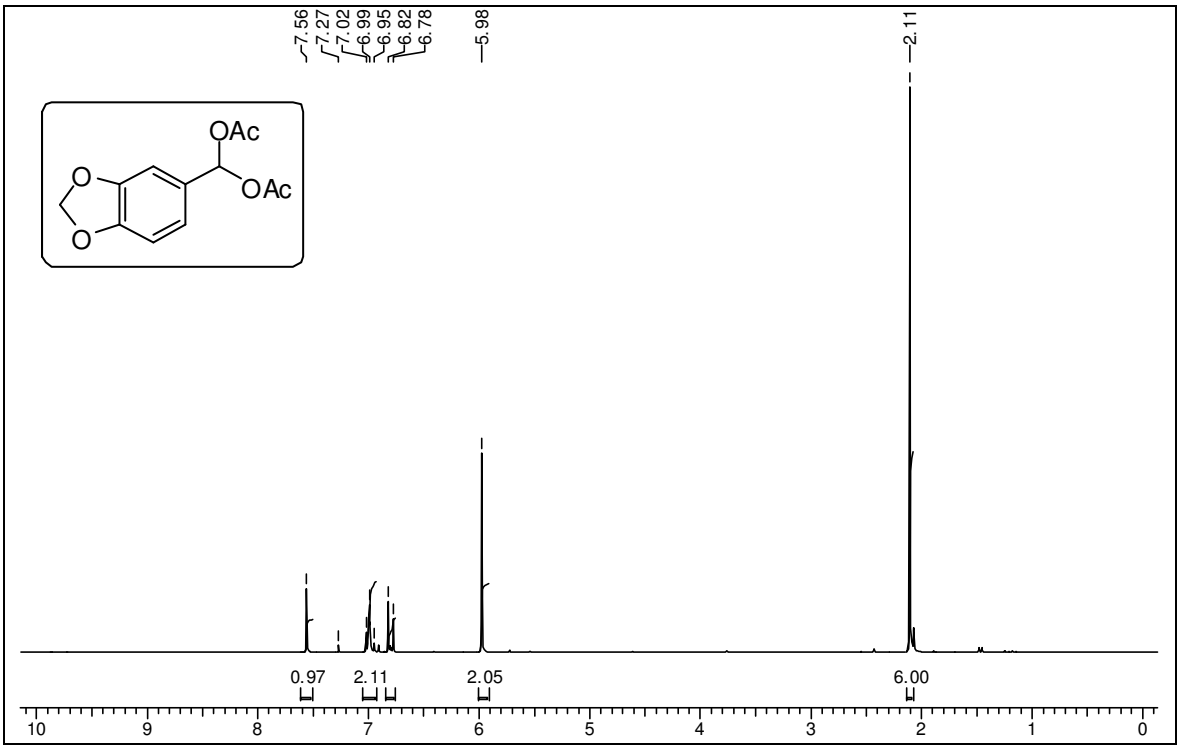
3. ^{1}H NMR spectra of 1,1-diacetoxy-1-(4-bromophenyl)methane (**2f**):



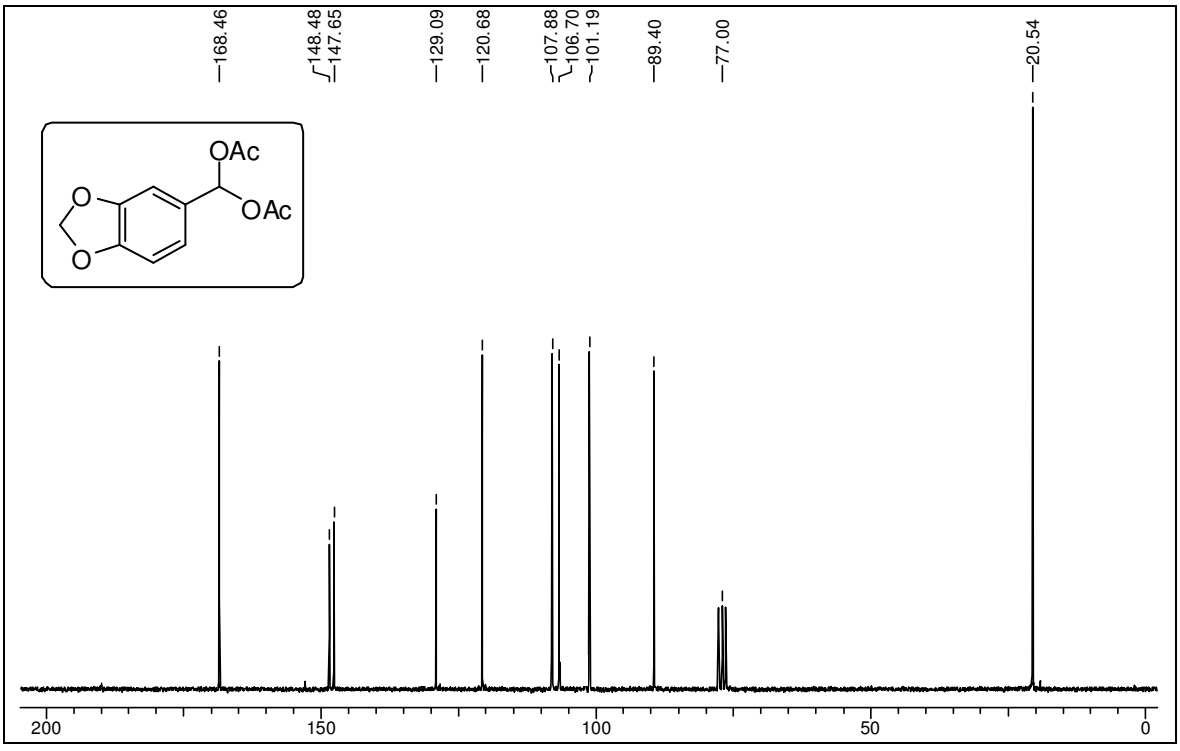
3. ^{13}C NMR spectra of 1,1-diacetoxy-1-(4-bromophenyl)methane (**2f**):



4. ^{1}H NMR spectra of 1,1-Diacetoxy-piparane (**2o**):



4. ^{13}C NMR spectra of 1,1-Diacetoxy-piparane (**2o**):



2.3.8 References

1. Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**, 188.
2. Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: Stuttgart, **1994**, 156.
3. Tormokangas, O. P.; Toivola, R. J.; Kaninen, E. K.; Koskinen, A. M. P. *Tetrahedron* **2002**, *58*, 2175.
4. Raju, N.; Rajagopalan, K.; Swaminathan, S. A. *Tetrahedron Lett.* **1980**, *21*, 1577.
5. Lee, S. H.; Lee, J. H.; Yoon, C. M. *Tetrahedron Lett.* **2002**, *43*, 2699.
6. Verma, S. K.; Sathe, M.; Kaushik, M. P. *Synthetic Commun.* **2010**, *40*, 1701.
7. Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett.* **2002**, *43*, 2843.
8. Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199; and references cited therein.
9. Knoevenagel, E. *Justus Liebigs Ann. Chem.* **1905**, *402*, 111.
10. Freeman, F.; Karchevski, E. M. *J. Chem. Eng. Data* **1977**, *22*, 355.
11. Scriabine, I. *Bull. Soc. Chim. Fr.* **1961**, 1194.
12. Cockerille, F. O. *US patent* 2264789, **1941**; C. A. **1942**, *36*, 1620.
13. Michie, J. K.; Miller, J. A. *Synthesis* **1981**, 824.
14. Kochhar, K. S.; Bal, B. S.; Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. *J. Org. Chem.* **1983**, *48*, 1765.
15. Varma, R. S.; Chatterjee, A. K.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 3207.
16. Jin, T. S.; Sun, X.; Li, T. S. *J. Chem. Res. (s)* **2000**, 128.
17. Yadav, J. S.; Subha Reddy, B. V.; Kiran Kumar Reddy, G. S. *Tetrahedron Lett.* **2000**, *41*, 2695.
18. Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, T. R.; Ullah, W. J. *J. Chem. Soc. Perkin Trans.* **1981**, *1*, 1096.
19. Frick Jr., J. G.; Harper Jr., R. J. *J. Appl. Polym. Sci.* **1984**, *29*, 1433.
20. Sanderson, W. R. *Eur. Pat. Appl. EP* 125,781.
21. Welton, T. *Chem. Review* **1999**, *99*, 2071; and references cited therein.
22. Parvulescu, V. I.; Hardacre, C. *Chem. Review* **2007**, *107*, 2615; and references cited therein.
23. Kwan, J.; Kim, M. J. *J. Org. Chem*. **2002**, *67*, 6845.

24. Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis Jr, J. H. *J. Am. Chem. Soc.* **2002**, *124*, 5962.
25. Morrison, D. W.; Forbes, D. C.; Davis Jr., J. H. *Tetrahedron Lett.* **2001**, *42*, 6053.
26. Li, T. S.; Zhang, Z. H.; Yang, F.; Fu, C. G. *J. Chem. Res*. **1998**, *1*, 38.
27. Hajipour, A. R.; Khazdooz, L.; Ruoho, A. E. *Catal. Commun*. **2008**, *9*, 89.
28. Lenardão, E. J.; Feijó, J. D. O.; Thurow, S.; Perin, G.; Jacob, R. G.; Silveira, C. C. *Tetrahedron Lett.* **2009**, *50*, 5215.
29. Zhu, H. -P.; Yang, F.; Tang, J.; He, M. -Y. *Green Chemistry* **2003**, *5*, 38.
30. Li, H.; Yu, S.; Liu, F.; Xie, C.; Li, L. *Catal. Commun*. **2007**, *8*, 1759.
31. Machado, P.; Lima, G. R.; Rotta, M.; Bonacorso, H. G.; Zanatta, N.; Martin, M. A. P. *Ultrasonics Sonochemistry* **2011**, *18*, 293.
32. Wang, S. Y.; Ji, S. J. *Tetrahedron* **2006**, *62*, 1527.
33. Zhou, W. J.; Ji, S. J.; Shen, Z. L. *J. Organomettalic Chem.* **2006**, *691*, 1356.
34. Nikpassand, M.; Mamaghani, M.; Shirini, F.; Tabatabaeian, K. *Ultrasonics Sonochemistry* **2010,** *17*, 301.
35. Wang, S. X.; Li, Z. Y.; Zhang, J. C.; Li, J. T. *Ultrasonics Sonochemistry* **2008**, *15*, 677.
36. Li, X.; Lin, Q.; Ma, L. *Ultrasonics Sonochemistry* **2010**, *17*, 752.
37. Adewuyi, Y. G. *Ind. Eng. Chem. Res.* **2001**, *40*, 4681.
38. Ultrasonics, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Wiley NewYork, **1983**, *23*, 462.
39. Witekowa, S. *Acta. Chim.* **1972**, *17*, 97.
40. Mason, T. J.; Lorimer, J. P. *Sonochemistry: Theory, Application and Uses,* Ellis Horwood Ltd., Chichester, U.K., **1988**.
41. Hua, I.; Hoffmann, M. R. *Eniviron. Sci. Technol.* **1997**, *31*, 2237.
42. Boucher, R. M. G. *Br. Chem. Engin.* **1970**, *15*, 363.
43. Serpone, N.; Colarusso, P. *Res. Chem. Intermed.* **1994**, *20*, 635.
44. Luche, J. -L. *Synthetic Organic Sonochemistry*, Plenum Press, New York, **1998**.
45. Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2003**, *5*, 693.
46. Cella, R.; Stefani, H. A. *Tetrahedron* **2006**, *62*, 5656.

47. Patil, S. B.; Bhat, R. P.; Raje, V. P.; Samant, S. D. *Synthetic Commun.* **2006**, *36*, 525.
48. Bravo, J. L.; López, I.; Cintas, P.; Silvero, G.; Arévalo, M. J. *Ultrason. Sonochem.* **2006**, *13*, 408.
49. Estager, J.; Lévêque, J. –M.; Turgis, R.; Draye, M. *Tetrahedron Lett.* **2007**, *48*, 755.
50. Shelke, K.; Sapkal, S.; Kategaonkar, A.; Shingate, B.; Shingare, M. S. *S. Afr. J. Chem.* **2009**, *62*, 109.
51. Pourmousavi, S. A.; Zinati, Z. *Turk. J. Chem.* **2009**, *33*, 385.
52. Palacios-Grijalva, L. N.; Cruz-González, D. Y.; Lomas-Romero, L.; González-Zamora, E.; Ulibarri, G.; Negrón-Silva, G. E. *Molecules* **2009**, *14*, 4065.
53. Jin, T. S.; Sun, G.; Li, Y. W.; Li, T. S. *Green Chemistry* **2002**, *4*, 255.
54. Romanelli, G.; Ruiz, D.; Vázquez, P.; Thomasa, H.; Autino, J. C. *Chem. Eng. J.* **2010**, *161*, 355.
55. Hajipour, A. R.; Zarei, A.; Ruoho, A. E. *Tetrahedron Lett.* **2007**, *48*, 2881.
56. Khan, A. T.; Choudhury, L. H.; Ghosh, S. *J. Mol. Catal. A.: Chemical* **2006**, *255*, 230.
57. Shirini, F.; Mamaghani, M.; Mostashari-Rad, T.; Abedini, M. *Bull. Korean Chem. Soc.* **2010**, *31*, 2399.
58. Jermy, R. B.; Pandurangan, A. *Catal. Commun.* **2008**, *9*, 577.
59. Gao, S. T.; Zhao, Y.; Li, C.; Ma, J. J.; Wang, C. *Synthetic Commun.* **2009**, *39*, 2221.
60. Wang, M.; Gong, H.; Jiang, H.; Wang, Z. *Synthetic Commun.* **2009**, *36*, 1953.
61. Pereira, C.; Gigante, B.; Marcelo-Curto, M. J.; Carreyre, H.; Pérot, G.; Guisnet, M. *Synthesis* **1995**, 1077.
62. Deka, N.; Kalita, D. J.; Borah, R.; Sarma, J. C. *J. Org. Chem.* **1997**, *62*, 1563.
63. Ranu, B. C.; Dutta, J.; Das, A. *Chem. Lett.* **2003**, *32*, 366.
64. Romanelli, G. P.; Thomas, H. J.; Baronetti, G. T. Autino, J. C. *Tetrahedron Lett.* **2003**, *44*, 1301.
65. Aggen, D. H.; Arnold, J. N.; Hayes, P. D.; Smoter, N. J.; Mohan, R. S. *Tetrahedron* **2004**, *60*, 3675.

66. Desai, U. V.; Thopate, T. S.; Pore, D. M.; Wadgaonkar, P. P. *Catal. Commun.* **2006**, *7*, 508.
67. Wang, Q. -Y.; Sheng, S. -R.; Wei, M. -H.; Xie, Z. -L.; Liu, X. -L. *Synthetic Commun.* **2007**, *37*, 1019.
68. Hajipour, A. R.; Khazdoor, L.; Ruoho, A. E. *Catal. Commun.* **2008**, *9*, 89.
69. Xu, R.; Zhang, J.; Yian, Y.; Zhou, J. *J. Iran. Chem. Soc*. **2009**, *6*, 443.
70. Shelke, K. F.; Sapkal, S. B.; Kakade, G. K.; Shinde, P. V.; Shingate, B. B.; Shingare, M. S. *Chinese Chem. Lett.* **2009**, *20*, 1453.
71. Meshram, G. A.; Patil, V. D. *Synthetic Commun.* **2010**, *40*, 442.
72. Jung, M.; Yoon, J.; Kim, H. S.; Ryu, J. –S. *Synthesis* **2010**, *16*, 2713.

Section-D

p-TSA mediated N-nitrosation of secondary amines

2.4.1 Introduction

N-Nitrosation chemistry of amines is an important and well-established reaction in organic synthesis.[1] Nitrosation is a unit process of great industrial importance generating commercially valuable intermediates. *N*-Nitrosation reaction serves to introduce one or more nitroso groups into reacting molecules. *N*-Nitrosamines have drawn considerable interest in recent years mainly due to their strong mutagenic and carcinogenic properties.[2] The nitrosation of amines is of particular interest as the corresponding *N*-nitrosamines obtained are found to be biologically active and show activities such as vasodilatation, platelet aggregation, inflammation and neuronal plasticity.[3] Nitroso compounds are used as pesticides, lubricant and antioxidants.[4] The *N*-nitrosamino group is used in the synthesis of various α-amino compounds and as synthetic intermediates with an NO activating group.[5] They are also useful synthetic intermediates for the preparation of various *N-N* bonded functionalities. A hindered rotation about the *N-N* bond, being a consequence of a partial double bond character between two adjacent nitrogens, results in many intriguing stereochemical features in this class of compounds.[6,7] Nitrosation of primary, secondary or tertiary amines has long been a very active and rewarding area of research for mechanistic organic and biological chemists. Some efforts have also been made to combine both the synthetic and mechanistic aspects of nitrosation or trans-nitrosation.[8] Nitrosation of amines is of considerable commercial importance, as nitrosated compounds find utility as pharmaceuticals and dyes.

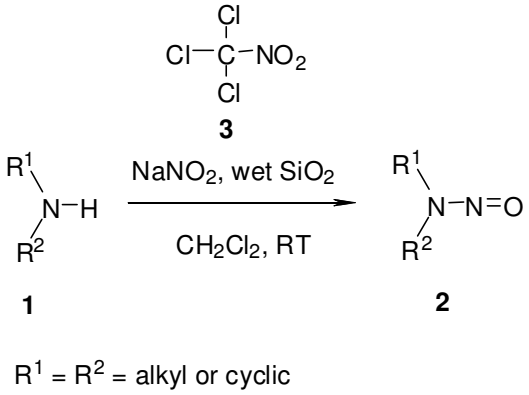
2.4.2 Review of literature

This section briefs about some of the recent developments reported in literature for the *N*-nitrosation of secondary amines. In particular, *N*-nitrosation of secondary amines with solid acid reagent such as oxalic acid dihydrate,[9] inorganic acidic salts,[10] hydrolysable chloride salts,[11] alumina-methanesulfonic acid (AMA),[12] molybdatophosphoric acid (MPA),[13] citric acid,[14] silica sulfuric acid,[15] Nafion-H®,[16] tungstate sulfuric acid (TSA),[17] and 1,3,5-triazine-2,4,6-triyltrisulfamic acid (TTSA)[18] with sodium nitrite has been extensively studied to obtain various *N*-nitroso derivatives.

A heterogeneous reaction condition was observed in most of the methods. Although numerous methods to achieve nitrosation are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. Some of the recent elegant methods are described below.

Demir *et al.* (1992)[19]

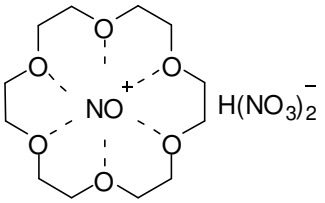
Demir *et al.* used trichloro nitromethane **3** in combination with sodium nitrite ($NaNO_2$) in the presence of wet SiO_2 as an effective *in situ* generation of HNO_2 for the *N*-nitrosation of secondary amines **1** afforded *N*-nitroso compounds **2** in good yields (**Scheme 1**). This was completely heterogeneous system.



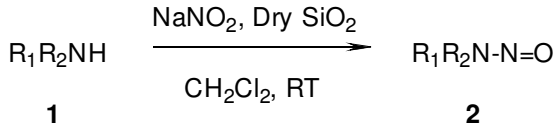
Scheme 1.

Zolfigol *et al.* (2001)[20]

Zolfigol and co-workers reported novel [$NO^{\cdot}$·Crown·$H(NO_3)_2^{-}$] complex **4** as a nitrosonium ion (NO^{-}) source. This could be further used in combination with sodium nitrite in the presence of dry SiO_2 to convert variety of secondary amines **1** to the corresponding *N*-nitroso compounds **2** under mild and homogeneous conditions gave quantitative yields (**Scheme 2**). The 18-Crown-6 can be recycled and reused.



4



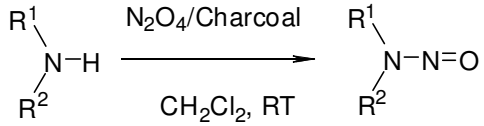
1 **2**

$R_1 = R_2$ = alkyl or cyclic

Scheme 2.

Iranpoor *et al.* (2005)[21]

Iranpoor *et al.* performed dinitrogen tetroxide (N_2O_4) impregnated on activated charcoal mediated *N*-nitrosation of secondary amines **1** to afford the corresponding *N*-nitroso derivatives **2** in high yields (**Scheme 3**). They have also reported *N*-nitrosation of tertiary amine.



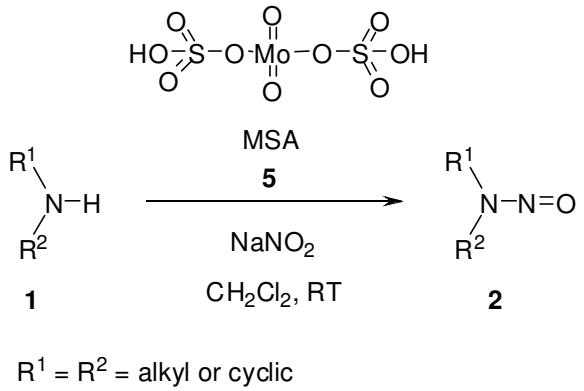
1 **2**

$R^1 = R^2$ = alkyl or cyclic

Scheme 3.

Montazerozohori *et al.* (2006)[22]

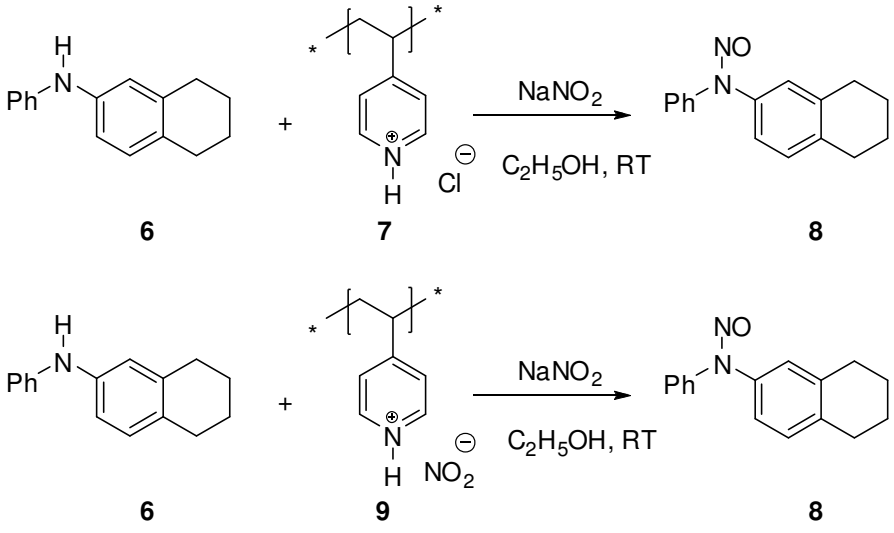
Montazerozohori and co-workers reported new solid acid reagent i.e. wet molybdate sulfuric acid (MSA) **5** as a H^+ source, which can be used in combination with sodium nitrite to transform a variety of secondary amines **1** to the corresponding *N*-nitroso compounds **2** under heterogeneous conditions gave high yields (**Scheme 4**). The reagent (MSA) can be readily removed by filtration and re-used, without loss of activity.



Scheme 4.

Zarchi *et al.* (2007)[23]

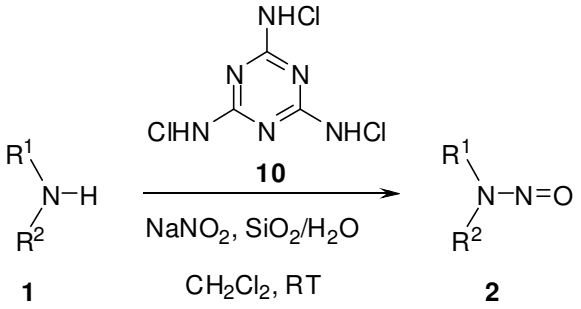
Zarchi *et al.* reported crosslinked poly(4-vinylpyridinium)chloride [P_4-H]Cl **7** or quaternized crosslinked poly(*N*-methyl-4-vinylpyridinium)-nitrite [P_4-Me]NO_2 **9** as effective nitrosating agents. The *N*-nitrosation of secondary amines **6** with sodium nitrite under mild conditions at room temperature in ethanol has carried out using these catalysts (**Scheme 5**). This method includes a lot of unique merits namely, chemoselectivity, contamination of *C*-nitrosation side products avoided and simple work-up procedure. Polymeric reagent could be re-generated and re-used for further reaction. This protocol was applicable to wide spectrum of secondary amines bearing various functionalities.



Scheme 5.

Bamoniri *et al.* (2007)[24]

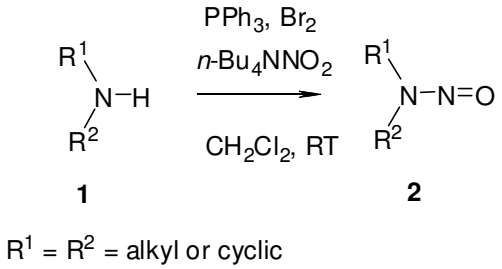
Bamoniri *et al.* described the use of trichloromelamine **10** in combination with sodium nitrite in the presence of wet silica gel as effective nitrosating agent for the transformation of secondary amines **1** into the corresponding *N*-nitrosamines **2** under mild conditions in good to excellent yields (**Scheme 6**). The nitrosation did not occur in the absence of wet silica gel.



Scheme 6.

Iranpoor *et al.* (2008)[25]

Iranpoor *et al.* reported the combination of $PPh_3/Br_2/n\text{-}Bu_4NNO_2$ as a new reagent system for the efficient preparation of *N*-nitrosamines **2** from the corresponding secondary amines **1** (**Scheme 7**).

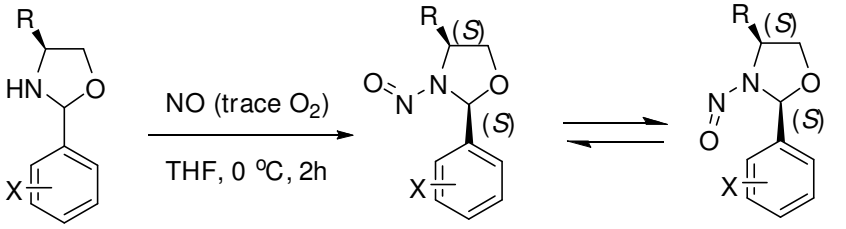


Scheme 7.

Wu *et al.* (2008)[26]

Wu and co-workers reported nitric oxide with traces of oxygen as a nitrosating agent for the *N*-nitrosation of compound **11** afforded highly diastereoselective product **12**

in good yield (**Scheme 8**). The general efficiency of this reaction is evident from the variety of amine compounds including heterocyclic amines being nitrosated within a very short time.



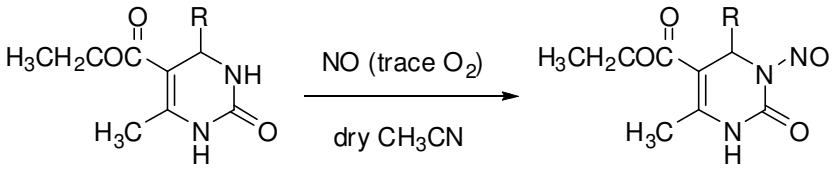
11 **12** **12**

E-(2*S*, 4*S*) *Z*-(2*S*, 4*S*)

Scheme 8.

Shen *et al.* (2009)[27]

Shen *et al.* reported *N*-nitrosation of dihydropyrimidinones **13** with nitric oxide (NO) occurred regioselectively, giving the corresponding *N*-(3)-nitrosamides **14** in high yields (**Scheme 9**). The reaction most likely took place by a nucleophilic attack. Aprotic and polar solvents, such as acetonitrile and tetrahydrofuran greatly favored the reaction, whereas protic solvents with high dielectric constant, such as methanol and water, disfavored it.



13 **14**

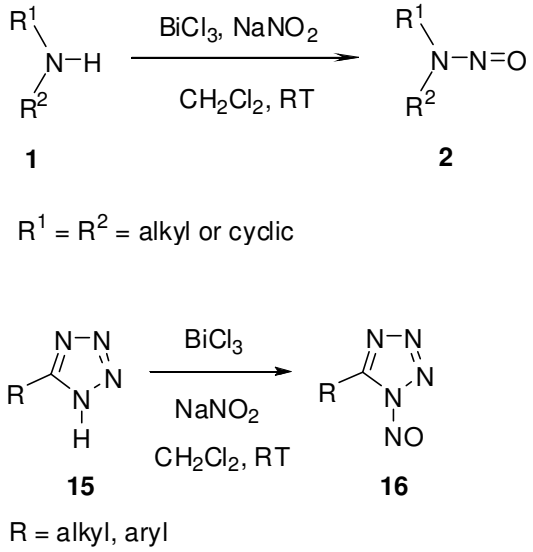
R = alkyl, aryl

Scheme 9.

Chaskar *et al.* (2009)[28]

Chaskar *et al.* described bismuth (III) chloride ($BiCl_3$) and sodium nitrite as a mild and efficient nitrosating reagent for the *N*-nitrosation of secondary amines **1** and

tetrazoles **15** under ambient conditions to the corresponding *N*-nitrosamines **2** and *N*-nitroso tetrazoles **16** respectively in good to excellent yields (**Scheme 10**).



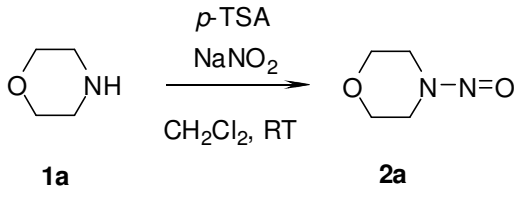
Scheme 10.

2.4.3 Present work

Although several reagents are known in the literature for the *N*-nitrosation of secondary amines, these are associated with certain drawbacks such as substrate generality, harsh reaction conditions, stoichiometric amounts of the catalyst, use of toxic gases etc. This provides scope for development of milder conditions for *N*-nitrosation of secondary amines. The generation of nitrosonium ion (NO^+) in the nitrosation reaction is the well-known key step. We have found that *p*-toluenesulfonic acid a cheap, commercially and readily available reagent used in many organic synthesis and transformations.[29] The utility of *p*-toluenesulfonic acid and the absence of reports about their exploration for *N*-nitrosation of secondary amines prompted us to undertake the present work. Therefore, we have decided to apply *p*-toluenesulfonic acid-sodium nitrite as the novel nitrosating agent for *N*-nitrosation of secondary amines. We wish to explain a simple and chemo-selective method for the *N*-nitrosation of secondary amines. In this section, we describe *p*-toulenesulfonic acid (*p*-TSA) as a proton source mediated *N*-nitrosation of secondary amines under mild and heterogeneous conditions.

2.4.4 Results and discussion

In our study, for the preparation of *N*-nitrosamines **2**, we visualized *p*-toluenesulfonic acid mediated *N*-nitrosation of secondary amines **1** with $NaNO_2$ could be achieved. Thus, we subjected *p*-toluenesulfonic acid-mediated *N*-nitrosation of morpholine **1a** with $NaNO_2$ under mild condition at room temperature, corresponding *N*-nitrosomorpholine **2a** in 97% yield (**Scheme 11**).



Scheme 11.

Encouraged by this result, we screened various solvents like CH_2Cl_2, CH_3CN, CH_3OH, $CHCl_3$, diethyl ether etc. with different equivalent of *p*-TSA ranging from 0.5 to

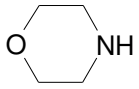
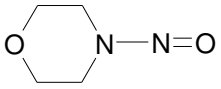
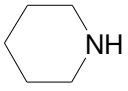
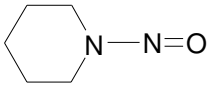
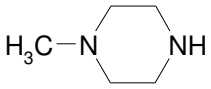
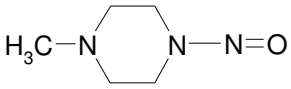
2; we found that CH_2Cl_2 at ambient temperature is the best solvent system for the *N*-nitrosation.

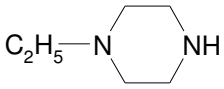
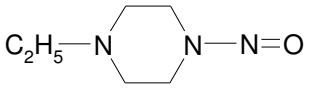
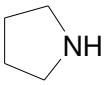
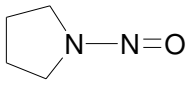
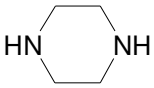
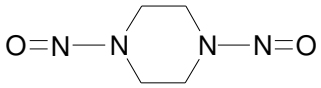
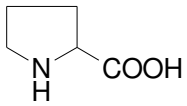
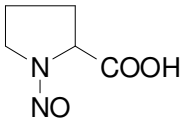
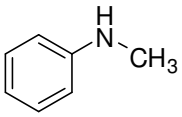
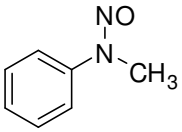
Table 1. *N*-Nitrosation of morpholine **1a** using various solvents

Entry	Solvent	Yield (%)
1	CH_3CN	92
2	CH_3OH	88
3	$CHCl_3$	91
4	CH_2Cl_2	97
5	Diethyl ether	85
6	THF	51
7	Acetone	70

To generalize the scope of reaction, various cyclic secondary amines were subjected to *N*-nitrosation. We found that *N*-nitrosation of substituted cyclic secondary amines underwent smoothly giving high yields of *N*-nitrosamines with good selectivity, the results and reaction conditions of which are summarized in **Table 2**.

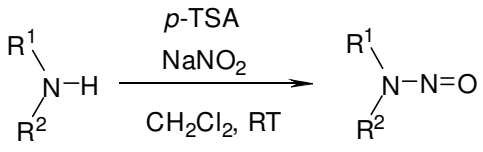
Table 2. *N*-Nitrosation of cyclic secondary amines

Entry	Substrate (1a-h)	Product (2a-h)	Time (mins)	Yield (%)
1	 **1a**	 **2a**	5	97
2	 **1b**	 **2b**	3	92
3	 **1c**	 **2c**	20	95

4	 **1d**	 **2d**	15	85
5	 **1e**	 **2e**	5	97
6	 **1f**	 **2f**	5	95[c]
7	 **1g**	 **2g**	720	90
8	 **1h**	 **2h**	4	91

Remarkably, *C*-nitrosation was not at all observed even in the activated aromatic ring such as of *N*-methyl aniline **1h**. This can be explained from the fact that *p*-toluenesulfonic acid is superior proton source to activate the nitrogen sites of the secondary amines by the formation of nitrosonium ion (NO^+) with sodium nitrite and thus deactivating the aromatic ring for nucleophilic nitrosation. Only in the case of piperazine **1f**, we observed selective dinitrosation product **2f**. Thus, it can be seen from **Table 1**, cyclic secondary amines (piperidine, *N*-substituted piperazine, pyrrolidine and L-proline) underwent *N*-nitrosation to give the corresponding *N*-nitrosamines **2a-h** in high yields.

It was also interested to examine *N*-nitrosation reaction of alkyl amines. Thus, *p*-toluenesulfonic acid mediated *N*-nitrosation of secondary amines **1** was carried out with sodium nitrite which gave *N*-nitrosamines **2** in good yields (**Scheme 12**).

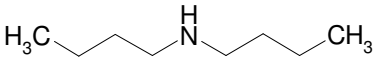
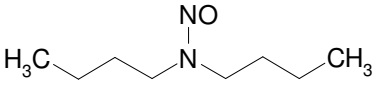


$R^1 = R^2$ = ethyl, isopropyl, dicyclohexyl

Scheme 12.

As can be seen from **Table 3,** secondary alkyl amines gave *N*-nitrosation in 93-95% yields. However, dicyclohexylamine **1k** and dibutylamine **1l** gave *N*-nitrosodicyclohexylamine **2k** and *N*-nitrosodibutylamine **2l** 95% yield respectively, in very short time.

Table 3. *N*-Nitrosation of alkyl amines

Entry	Substrate (15a-d)	Product (16a-d)	Time (mins)	Yield (%)
1	Et_2NH	$Et_2N—N=O$	20	93
	1i	**2i**		
2	(*iso*-Pr)$_2$NH	(*iso*-Pr)$_2$N—N=O	90	95
	1j	**2j**		
3	(c-C_6H_{11})$_2$NH	(c-C_6H_{11})$_2$N—N=O	2	95
	1k	**2k**		
4			4	95
	1l	**2l**		

Mechanism

In the first step, the *p*-TSA reacts with sodium nitrite forming sodium salt and nitrous acid. The nitrosonium electrophile is formed, when *p*-toluenesulfonic acid is reacts with nitrous acid and eliminate water. The nitrosonium ion thus formed further reacts with secondary amines **1** in the presence of water to afford *N*-nitrosamines **2**.

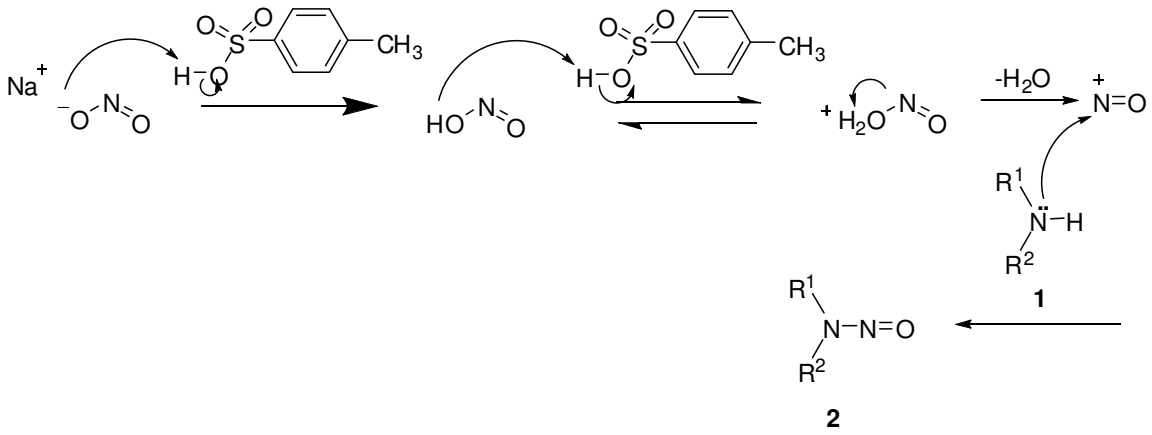
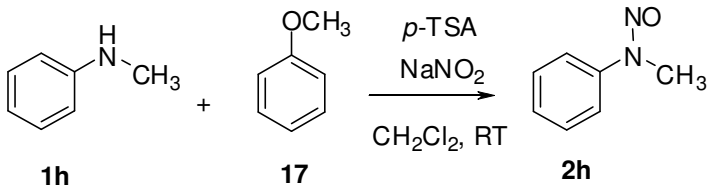


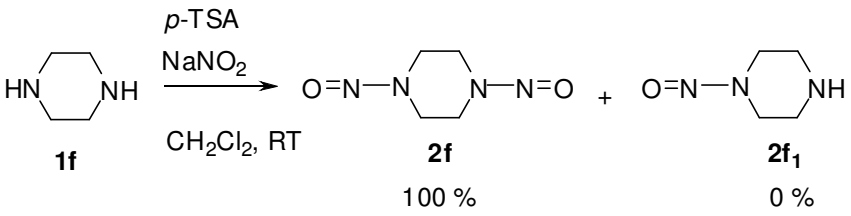
Figure 1. Mechanism for *p*-TSA mediated *N*-nitrosation of secondary amine

We were interested to access the chemoselectivity of this method; a competitive reaction was performed between *N*-methyl aniline **1h** and anisole **17**. It was observed that the secondary amine nitrosation occurred exclusively, whereas anisole remained intact in the reaction mixture after 1 h. The nitrosation reaction of *N*-methyl aniline **1h** further shows the chemoselectivity of the method as *N*-nitroso-*N*-methyl aniline **2h** is the only product. Thus, this system behaves differently to some other reported methods, the nitrosonium ion (NO^+) attacks only the nitrogen sites of the secondary amines even where an aromatic moiety is connected directly to nitrogen atom (**Scheme 13**).



Scheme 13.

Dinitrosation of piperazine **1f** occurred easily using 1:1.1 molar ratio of the reagent and at different conditions, but unfortunately mononitrosation could not be achieved even after altering molar ratio of the reactant and reagent and at different conditions (**Scheme 14**).



Scheme 14.

The *N*-nitrosation of L-proline **1g** furnished *N*-nitroso-L-proline **2g** in good yield and the chiral centre remained intact. This reaction was very slow as compared to others.

2.4.5 Conclusion

In conclusion, we have developed a simple and efficient methodology for *N*-nitrosation of secondary amines employing an inexpensive, commercially and readily available *p*-toluenesulfonic acid. In terms of handling and availability; *p*-toluenesulfonic acid (*p*-TSA) is superior proton source compared to other proton sources known. The procedure is easy to operate, simple work-up, excellent yield, highly chemo and regio-selective and avoids *C*-nitrosation side products. Our method works very well with variety of aliphatic and cyclic secondary amines and tolerates various functional groups.

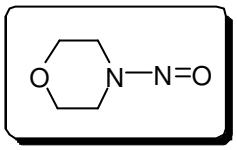
2.4.6 Experimental Section

General procedure for *N*-nitrosation of secondary amines:

To a stirred suspension of sodium nitrite (6.0 mmol), secondary amine (5.7 mmol) in dichloromethane (10 mL) was added slowly *p*-toluenesulfonic acid (6.0 mmol) at room temperature. The reaction mixture was efficiently stirred for appropriate time and the completion of the reaction was monitored by TLC (SiO_2; pet ether/EtOAc). After completion of the reaction, the insoluble solid was removed by filtration and washed with CH_2Cl_2. The filtrate was dried over Na_2SO_4, concentrated under reduced pressure to afford *N*-nitrosamines.

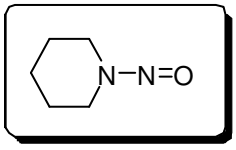
2.4.6.1 Characterization data:

***N*-Nitrosomorpholine (2a):**



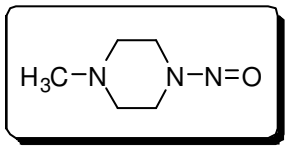
Molecular formula	:	$C_4H_8N_2O_2$
Nature	:	Pale yellow powder
Mp	:	29-30 ^oC (Low melting solid)
IR ($CHCl_3$, υ_{max})	:	2982, 1456, 1355, 1034 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ 3.63 (t, J = 5.18 Hz, 2H), 3.81-3.90 (m, 4H), 4.28 (t, J = 5.18 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ 42.15, 62.55 ppm.
MS (EI) (*m/z*)	:	116 (M^+).

***N*-Nitrosopiperidine (2b):**



Molecular formula	:	$C_5H_{10}N_2O$
Nature	:	Light yellow liquid
IR ($CHCl_3$, υ_{max})	:	2945, 2851, 1449, 1345, 1089 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ 1.46-1.58 (m, 2H), 1.74-1.77 (m, 4H), 3.73 (t, J = 5.94 Hz, 2H), 4.15 (t, J = 5.69 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ 21.87, 23.91, 44.05 ppm.
MS (EI) (*m/z*)	:	114 (M^+).

***N*-Nitroso-*N*-methylpiperazine (2c):**



Molecular formula : $C_5H_{11}N_3O$

Nature : Light yellow liquid

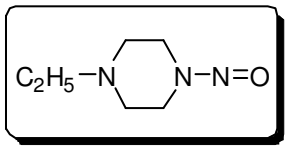
IR ($CHCl_3$, υ_{max}) : 2975, 1449, 1351, 1043 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.35-2.40 (s and t merge, 5H), 2.61 (t, *J* = 5.31 Hz, 2H), 3.84 (t, *J* = 5.81 Hz, 2H), 4.27 (t, *J* = 5.55 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ42.55, 42.98, 53.14 ppm.

MS (EI) (*m/z*) : 129 (M^+).

***N*-Nitroso-*N*-ethylpiperazine (2d):**



Molecular formula : $C_6H_{13}N_3O$

Nature : Dark yellow liquid

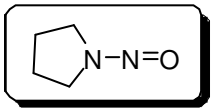
IR ($CHCl_3$, υ_{max}) : 2981, 1425, 1349, 1045 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ1.12 (t, *J* = 7.20 Hz, 3H). 2.39-2.54 (m, 4H), 2.65 (t, *J* = 5.18 Hz, 2H), 3.84 (t, *J* = 5.30 Hz, 2H), 4.27 (t, *J* = 5.31 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 13.39, 46.51, 42.07, 52.88 ppm.

MS (EI) (*m/z*) : 143 (M^+).

***N*-Nitrosopyrrolidine (2e):**



Molecular formula : $C_4H_8N_2O$

Nature : Yellow oil

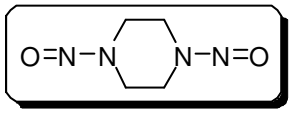
IR ($CHCl_3$, υ_{max}) : 2983, 1445, 1305, 1050 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ1.98-2.11 (m, 4H), 3.58 (t, *J* = 7.20 Hz, 2H), 4.28 (t, *J* = 6.32 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ21.36, 22.78, 44.12, 48.64 ppm.

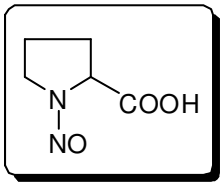
MS (EI) (*m/z*) : 100 (M^+).

***N,N*-DiNitrosopiperazine (2f):**



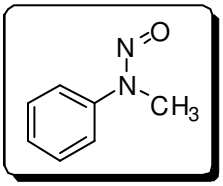
Molecular formula	:	$C_4H_8N_4O_2$
Nature	:	Yellow solid
Mp	:	154-155 ^oC
IR ($CHCl_3$, υ_{max})	:	2932, 1430, 1350, 1050 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ 3.82 (s, 2H), 4.05 (t, J = 5.44 Hz, 2H), 4.42 (t, J = 5.44 Hz, 2H), 4.57 (s, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ 37.20, 40.55, 46.61, 49.24 ppm.
MS (EI) (*m/z*)	:	144 (M^+).

***N*-Nitroso-L-proline (2g):**



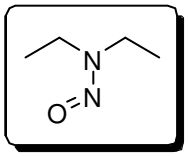
Molecular formula	:	$C_5H_8N_2O_3$
Nature	:	Faint yellow solid
Mp	:	106-108 ^oC
IR ($CHCl_3$, υ_{max})	:	1730, 1450 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ 2.28 (m, 4H), 3.71 (t, J = 7.56 Hz, 1H), 4.40 (t, J = 7.71 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ 20.97, 29.85, 51.05, 58.15, 172.49 ppm.
MS (EI) (*m/z*)	:	144 (M^+).

***N*-Methyl-*N*-nitrosoaniline (2h):**



Molecular formula	:	$C_7H_8N_2O$
Nature	:	Yellow oil
IR ($CHCl_3$, υ_{max})	:	3070, 2973, 1595, 1450, 1320, 1091, 1050, 758, 704 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	:	δ 3.46 (s, 3H), 7.32-7.58 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ 30.51, 118.58, 126.62, 128.80, 141.75 ppm.
MS (EI) (m/z)	:	136 (M^+).

***N*-Nitrosodiethylamine (2i):**



Molecular formula : $C_4H_{10}N_2O$

Nature : Pale yellow liquid

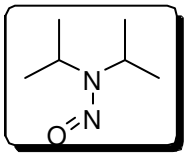
IR ($CHCl_3$, υ_{max}) : 2973, 1451, 1375, 1223, 1058 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.11 (t, *J* = 6.82 Hz, 3H). 1.42 (t, *J* = 6.82 Hz, 3H), 3.55 (q, *J* = 6.82, 2.71 Hz, 2H), 4.10 (q, *J* = 6.82, 2.71 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 11.3, 14.1, 38.4, 46.9 ppm.

MS (EI) (*m/z*) : 102 (M^+).

***N*-Nitrosodiisopropylamine (2j):**



Molecular formula : $C_6H_{14}N_2O$

Nature : Pale yellow solid

Mp : 46-48 ^oC

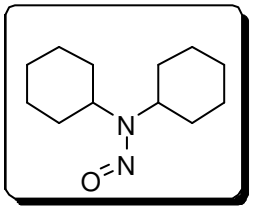
IR ($CHCl_3$, υ_{max}) : 2962, 1466, 1382, 1120 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.14 (d, *J* = 6.82 Hz, 6H). 1.49 (d, *J* = 6.82 Hz, 6H), 4.14-4.34 (m, 1H), 4.89-5.10 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 18.66, 47.02 ppm.

MS (EI) (*m/z*) : 130 (M^+).

***N*-Nitrosodicyclohexylamine (2k):**



Molecular formula : $C_{12}H_{22}N_2O$

Nature : Yellow oil

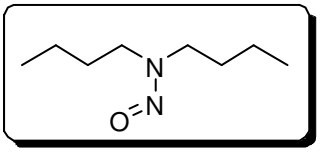
IR ($CHCl_3$, υ_{max}) : 2973, 1451, 1223, 1058 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.11-1.96 (m, 20H), 3.71 (m, 1H), 4.88 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 24.44, 24.60, 28.63, 53.32 ppm.

MS (EI) (*m/z*) : 210 (M^+).

***N*-Nitrosodibutylamine (2l):**



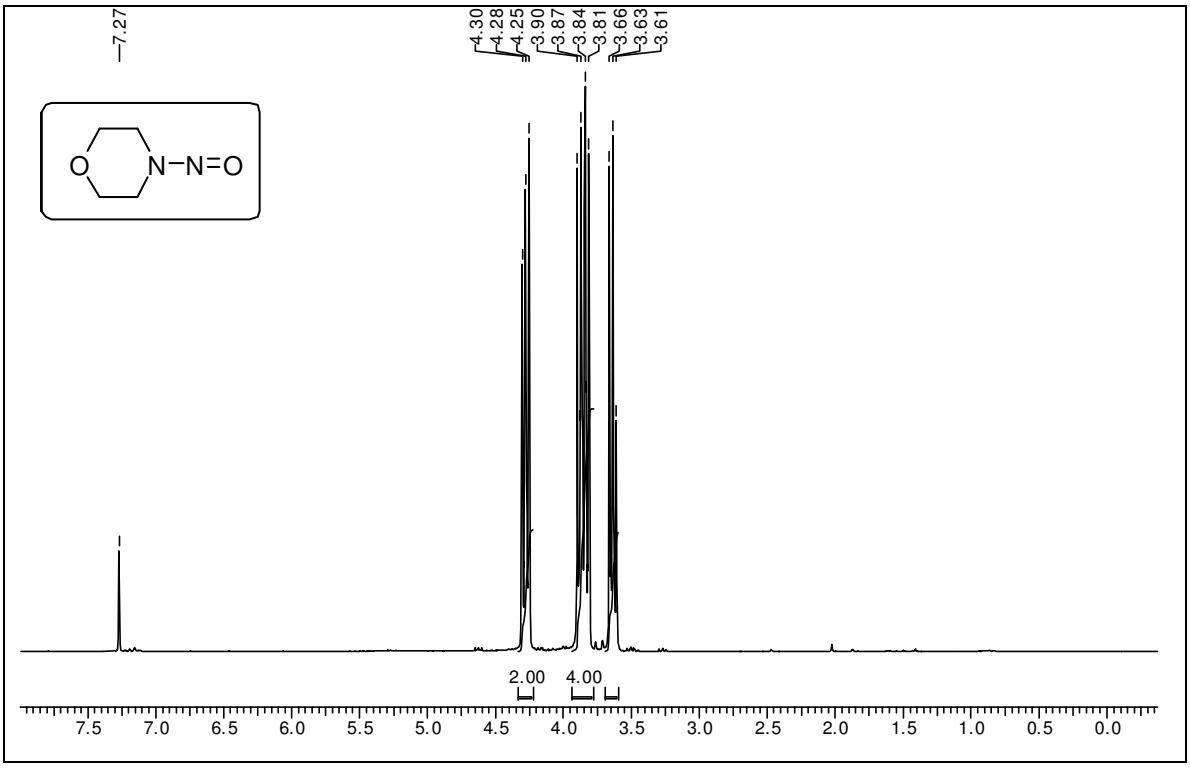
Molecular formula	**:**	$C_8H_{18}N_2O$
Nature	**:**	Yellow liquid
IR ($CHCl_3$, υ_{max})	**:**	2978, 1449, 1382, 1070 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ0.92 (t, *J* = 7.20 Hz, 3H), 0.98 (t, *J* = 7.20 Hz, 3H), 1.20-1.55 (m, 6H), 1.66-1.81 (m, 2H), 3.53 (t, *J* = 7.20 Hz, 2H), 4.07 (t, *J* = 7.20 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.51, 13.66, 19.74, 20.40, 28.15, 30.41, 43.49, 52.08 ppm.
MS (EI) (*m/z*)	**:**	158 (M^+).

2.4.7 Spectral data

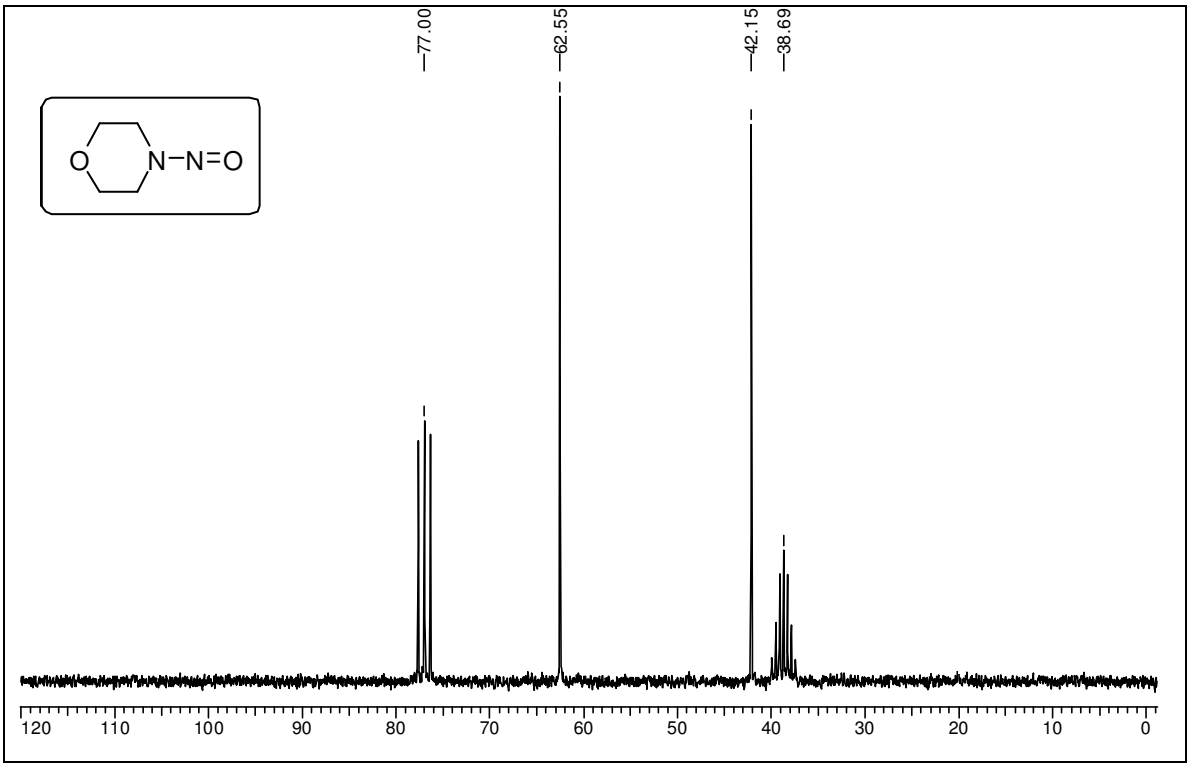
Table 4: ^{1}H and ^{13}C NMR spectrum of some selected compounds are given below:

Sr. No.	Spectra
1	^{1}H NMR and ^{13}C NMR spectra of **2a**
2	^{1}H NMR and ^{13}C NMR spectra of **2e**
3	^{1}H NMR and ^{13}C NMR spectra of **2j**
4	^{1}H NMR and ^{13}C NMR spectra of **2k**

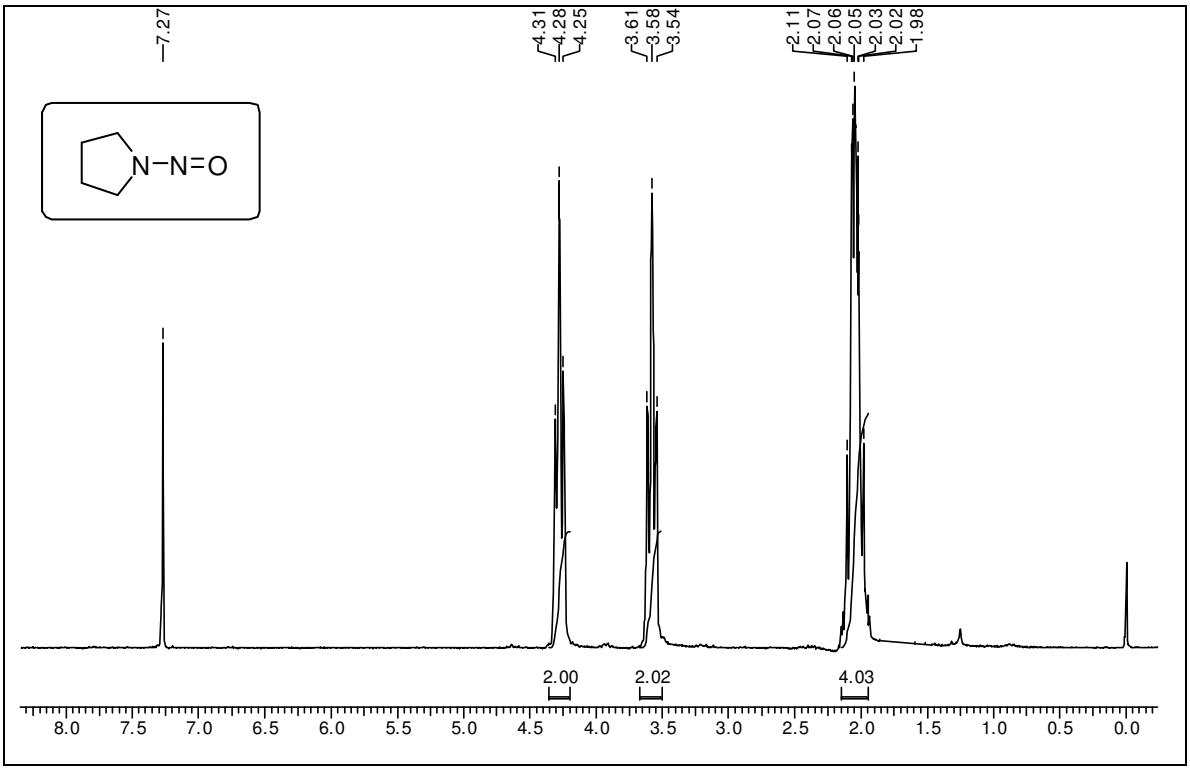
1. ^{1}H NMR spectra of *N*-Nitrosomorpholine (**2a**):



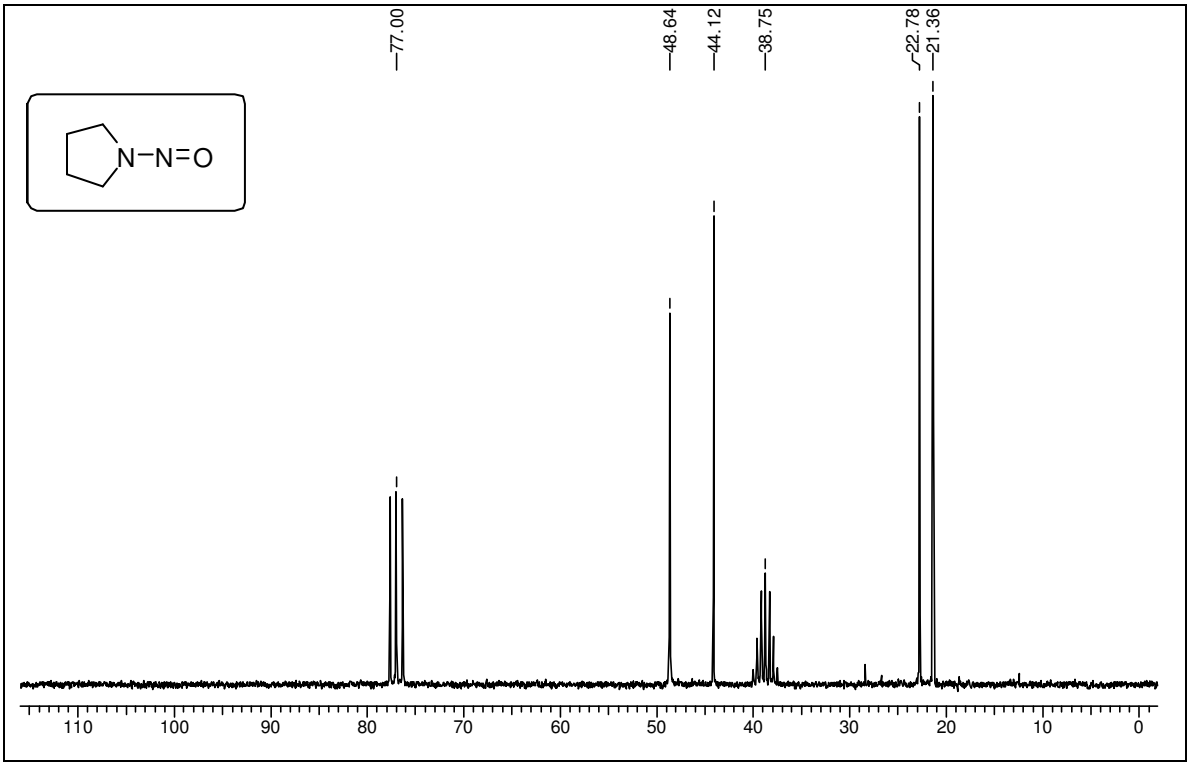
1. ^{13}C NMR spectra of *N*-Nitrosomorpholine (**2a**):



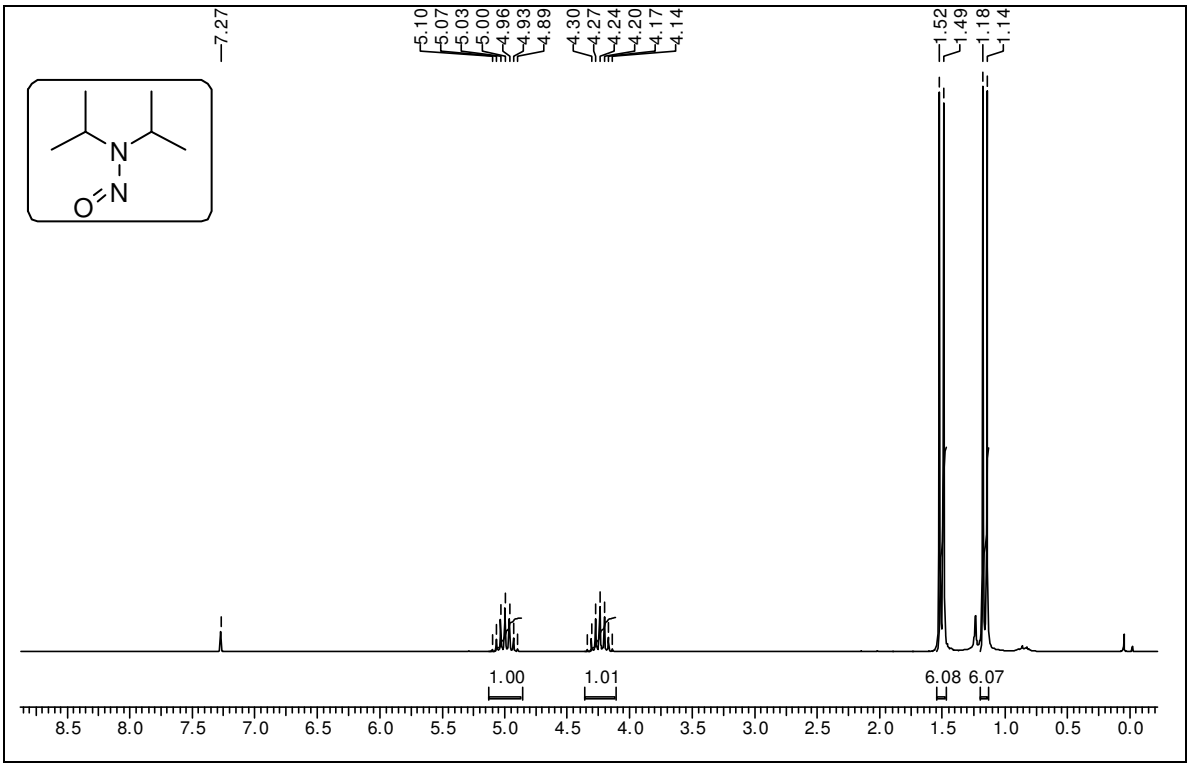
2. ^{1}H NMR spectra of *N*-Nitrosopyrrolidine (**2e**):



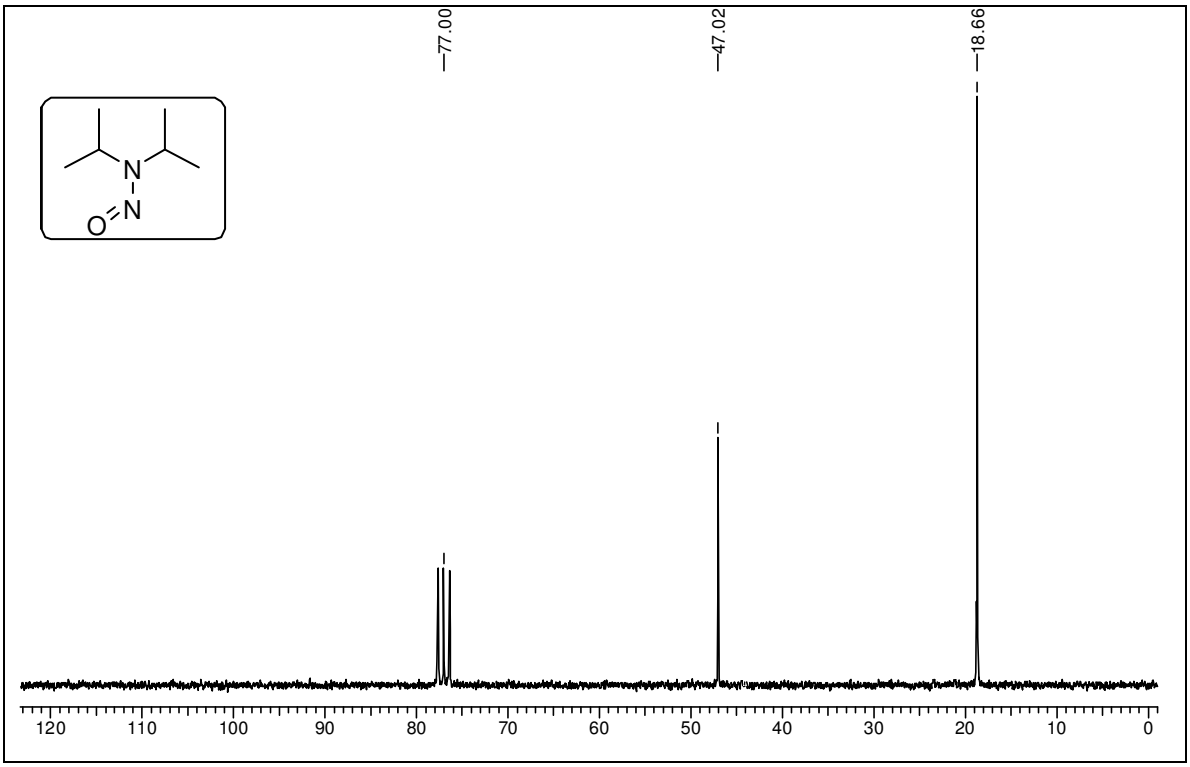
2. ^{13}C NMR spectra of *N*-Nitrosopyrrolidine (**2e**):



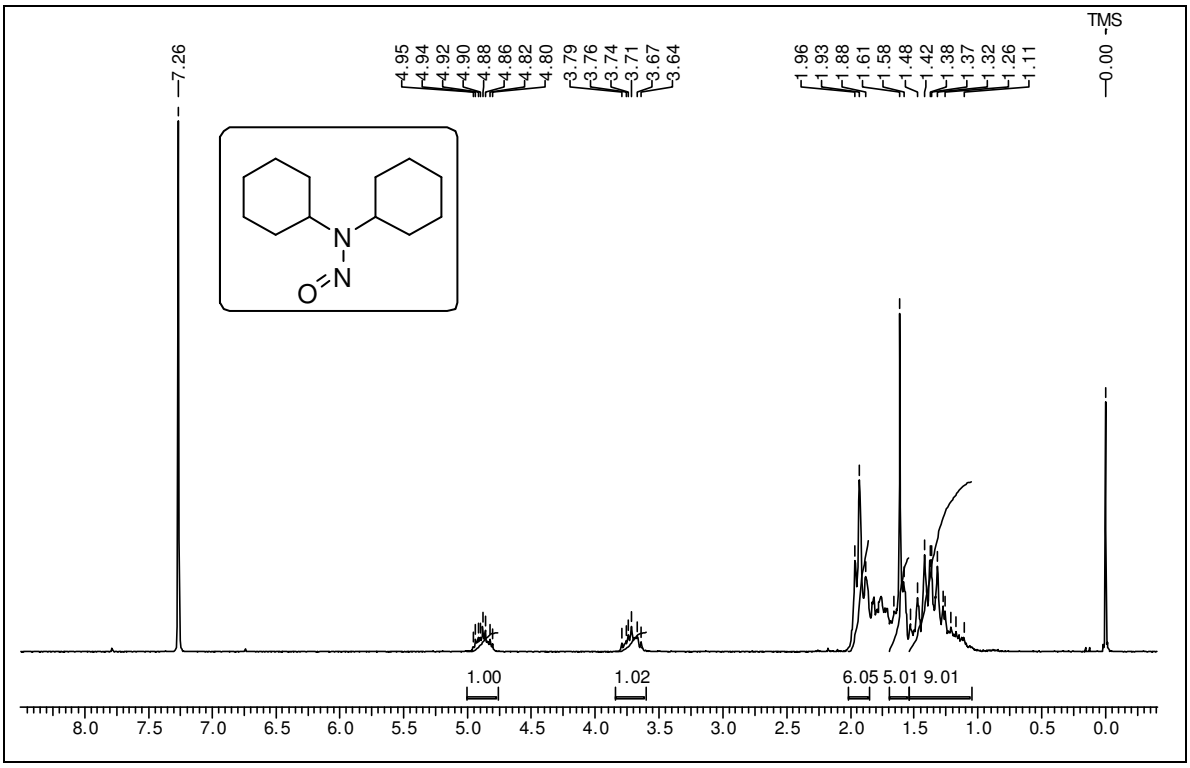
3. ^{1}H NMR spectra of *N*-Nitrosodiisopropylamine (**2j**):



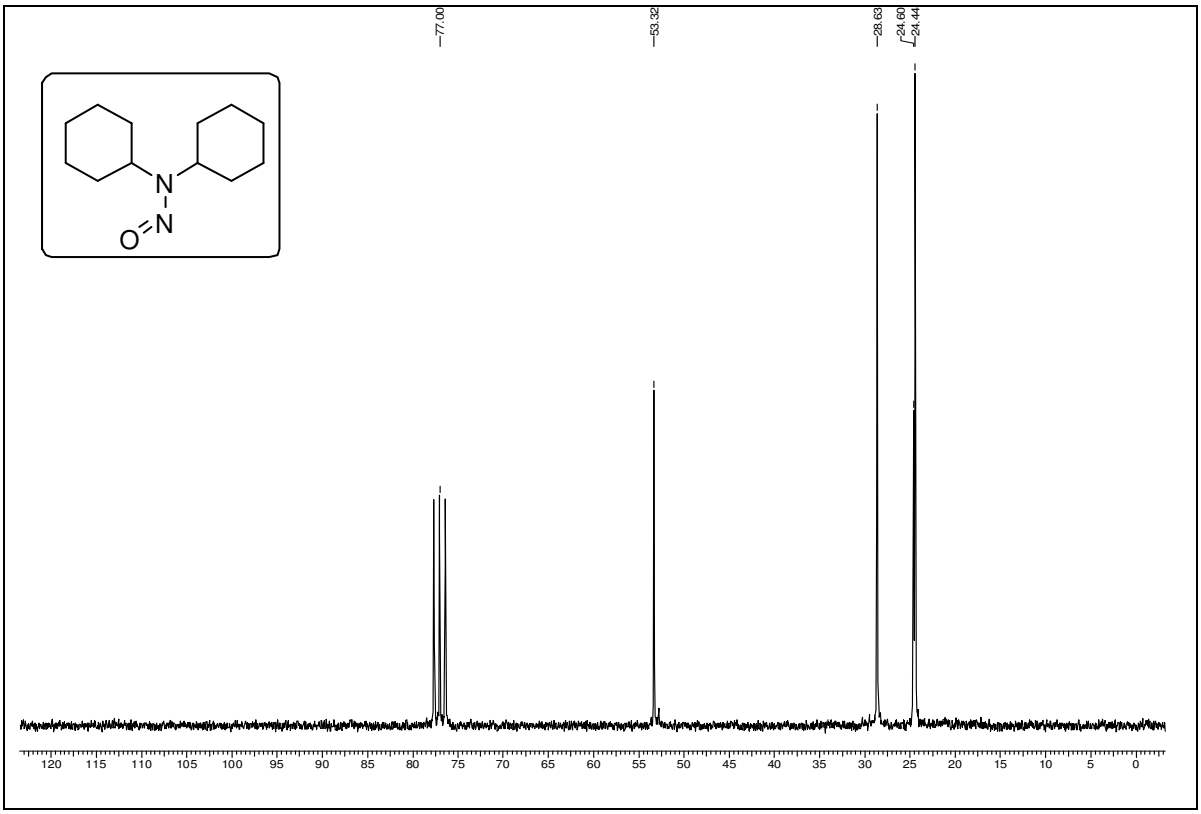
3. ^{13}C NMR spectra of *N*-Nitrosodiisopropylamine (**2j**):



4. ^{1}H NMR spectra of *N*-Nitrosodicyclohexylamine (**2k**):



4. ^{13}C NMR spectra of *N*-Nitrosodicyclohexylamine (**2k**):



2.4.8 References

1. (a) Williams, D. L. H. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Supplement F2: John Wiley & Sons Ltd.: New York, **1996**, 665; (b) Keefer, L. K.; Williams, D. L. H. *Methods in Nitric Oxide Research*; John Wiley & Sons Ltd.: New York, **1996**, 509; (c) Williams, D. L. H. *Nitrosation*, Cambridge University Press: Cambridge, UK, **1988**, 77.
2. Garcia-Rio, L.; Leis, J. R.; Issglesias, E. *J. Org. Chem.* **1997**, *62*, 4712.
3. Moncada, S.; Palmer, R. M.; Higgs, E. A. *Pharmacol. Rev.* **1991**, *43*, 109.
4. Nudelman, N. S.; Bonatti, A. E. *Synlett* **2000**, 1825.
5. Kostyukovskii, Y. L.; Melamed, D. B. *Russ. Chem. Rev.* **1988**, *57*, 350.
6. Zolfigol, M. A.; Shirini, F.; Choghamarani, A. G.; Taqian-Nasab, A.; Keypour, H.; Salehzadeh, S. *J. Chem. Res. Synop.* **2000**, *9*, 420.
7. Rivera, A.; Gallo, G. I.; Joseph-Nathan, P. *Synthetic Commun*. **1997**, *27*, 163.
8. Garcia-Rio, L.; Leis, J. R.; Moreira, J. A.; Norberto, F. *J. Org. Chem.* **2001**, *66*, 81.
9. Zolfigol, M. A. *Synthetic Commun*. **1999**, *29*, 905.
10. Zolfigol, M. A.; Ghaemi, E.; Madrakian, E.; Kiany-Borazjani, M. *Synthetic Commun*. **2000**, *30*, 2057.
11. Zolfigol, M. A.; Shirini, F.; Choghamarani, A. G.; Taqian-Nasab, A.; Keypour, H.; Salehzadeh, S. *J. Chem. Res. Synop.* **2000**, *9*, 420.
12. Niknam, K.; Zolfigol, M. A. *Synthetic Commun*. **2006**, *36*, 2311.
13. Zolfigol, M. A.; Niknam, K.; Nazari, F. *J. Chinese. Chem. Soc.* **2006**, *53*, 669.
14. Ghorbani-Choghamarani, A.; Goudarziafshar, H.; Rezaee, S.; Mortazavi, S. S. *Chinese Chem. Lett.* **2009**, *20*, 415.
15. Zolfigol, M. A.; Bamoniri, A. *Synlett* **2002**, *10*, 1621.
16. Zolfigol, M. A.; Habibi, D.; Mirjalili, B. F.; Bamoniri, A. *Tetrahedron Lett*. **2003**, *44*, 3345.
17. Karami, B.; Montazerozohori, M.; Habibi, M. H. *Bull. Korean Chem. Soc,* **2005**, *26*, 1125.
18. Chehardoli, G.; Zolfigol, M. A.; Faal-Rastegar, T.; Mallakpour, S.; Ghorbani-Choghamarani, A. *J. Chem. Sci.* **2009**, *121*, 441.

19. Demir, A. S.; Mahasneh, A. S.; Aksoy, H.; Gercek, Z.; *Synthetic Commun*. **1992**, *22*, 2607.
20. Zolfigol, M. A.; Zebarjadian, M. H.; Chehardoli, G.; Keypour, H.; Salehzadeh, S.; Shamsipur, M. *J. Org. Chem.* **2001**, *66*, 3619.
21. Iranpoor, N.; Firouzabadi, H.; Pourali, A. R. *Synthetic Commun*. **2005**, *35*, 1517.
22. Montazerozohori, M.; Karami, B. *Helv. Chim. Acta*. **2006**, *89*, 2922.
23. Zarchi, M. A. K.; Noei, J. *J. Appl. Poly. Science* **2007**, *104*, 1064.
24. Bamoniri, A.; Zolfigol, M. A.; Mirjalili, B. F.; Fallah, F. *Russian J. Org. Chem.* **2007**, *43*, 1393.
25. Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron Lett*. **2008**, *49*, 4242.
26. Peng, L.; Wang, J.; Sun, C.; Liu, Z.; Wu. L. *Tetrahedron Asymmetry* **2008**, *19*, 2078.
27. Shen, Y.; Liu, Q.; Wu, G.; Wu, L. *Tetrahedron Lett*. **2009**, *49*, 1220.
28. Chaskar, A. C.; Langi, B. P.; Deorukhkar, A.; Deokar, H. *Synthetic Commun*. **2009**, *39*, 604.
29. (a) Le-Bras, G.; Hamze, A.; Messaoudi, S.; Provot, O.; Le-Calvez, P. -B.; Brion, J. -D.; Alami, M. *Synthesis* **2008**, *10*, 1607; (b) Amere, M.; Blanchet, J.; Lasne, M. -C.; Rouden, J. *Tetrahedron Lett*. **2008**, *49*, 2541; (c) Shi, D. -Q.; Dou, G. -L. *Synthetic Commun*. **2008**, *38*, 3329; (d) Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Plaon, K.; Krause, M. M.; Khanthapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett*. **2009**, *50*, 2664.

Chapter III

Synthesis of biological active molecules

Section-A

Total synthesis of (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5H-furan-2-one: an anticancer agent

3.1.1 Introduction

Cancer is the third leading cause of death worldwide and the total number of cases globally is increasing by 45% from 2007 to 2010.[1] Cancers of the lung, breast, colon/ rectum and prostate are no longer largely confined to Western industrialized countries but are among the most common cancers worldwide. Lung cancer has been the most common cancer in the world since 1985.[2] Liver cancer is the fifth most common cancer in men and the eighth most common in women.[1] Like tobacco, obesity and sedentary life style are established causes of several types of cancer.

Cancer is a class of diseases in which a group of cells display uncontrolled growth of abnormal body tissues, invasion (intrusion and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body *via* lymph or blood). Cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents.

Cancer is the foremost killer disease in western countries and India. Tumor is a general term indicating any normal mass or growth of tissues that is not necessarily life threatening. A "cancerous tumor" is malignant neoplasm of potential danger. Cancer can arise in any organ of the body even though some sites are more prone than others. This disease has attracted worldwide attention and search for reliable methods to cure it is continuously going on.[3]

Chemotherapy is the treatment of cancer with drugs and it is often used in combination with other types of therapies such as surgery, radiation or immunotherapy, chemotherapy and combined modality therapy, out of which, surgery and radiation are generally successful only if the cancer is found at an early localized stage. But once the disease has progressed to local advanced cancer or metastatic cancer, these therapies are less successful. Then the only tool in oncologist's hand to fight against cancer, to save the patient is chemotherapy alone, or in combination with radiation therapy and surgery.

In early 1940, chemotherapeutic drugs were developed. Physicians found that "combination of drugs" may cure leukemias, lymphomas and testicular cancers.

Unfortunately, the majority of the most common cancers like breast, lung, colorectal and prostate cancers are not yet curable with chemotherapy alone.

Combined modality therapy requires the efforts of wide assortment of specialists, oncologists, surgeons, pathologists and radiologists. Most approaches to cancer chemotherapy have centered on the idea that cytotoxic drugs can be used to eradicate proliferating neoplastic cells. Chemotherapy has curative potential in patients with various hematological malignancies, testicular cancer and germ cell tumors. A major advantage of chemotherapy is its ability to treat widespread or metastatic cancer, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas. Despite improvements in the treatment of most metastatic solid tumors, these remain largely incurable. Reasons for this are insufficient tumor selectivity of anti-cancer agents and poor penetration within the tumor mass.[4,5] The main disadvantage of cancer chemotherapy is the toxicity of the drugs used.

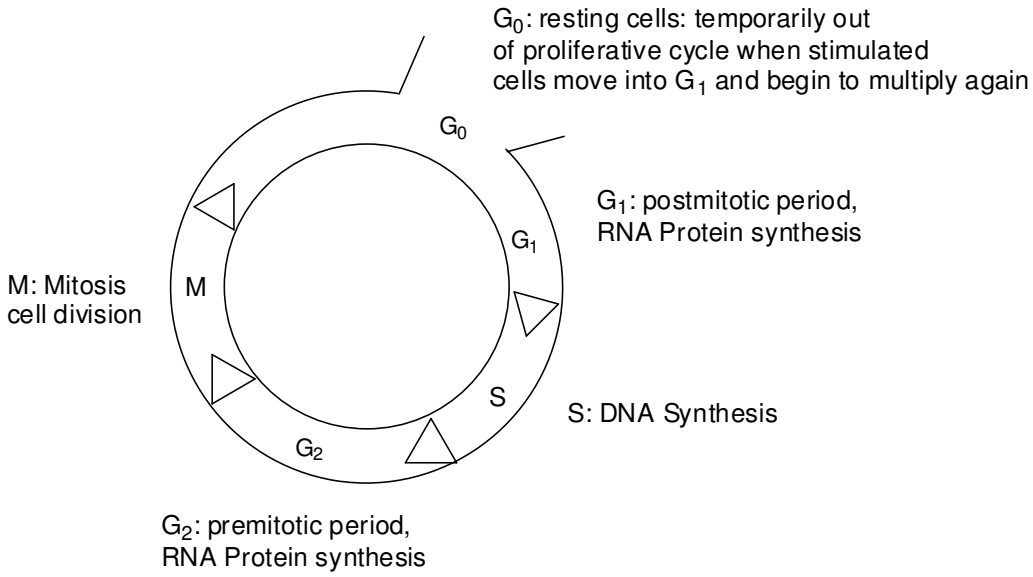


Figure 1. Proliferative cell cycle of normal cell

The main objective of chemotherapeutic drugs is to destroy cancer cells without harming healthy normal cells, therefore it is necessary to understand the life cycle of a cell. Normal cells divide and replicate in controlled manner (**Figure 1**), while cancerous cells divide and replicate in uncontrolled manner. Therefore, targeting some aspect of the

cell growth cycle seems to be reasonable. Fast growing cells would be affected the most and slow growing cells the least is the basis for many chemotherapies.

A large number of anticancer drugs, possessing diverse molecular structures, are being used presently. Further, many are undergoing clinical trials. Some of the antineoplastic agents although efficient are not specifically cytotoxic to tumor cells as they also kill normal cells. Most of the anticancer agents in use affect the function or the synthesis of DNA and are therefore more active in rapidly proliferating cell population.

Figure 2 represents exercise of anticancer agents, according to biochemical transformations that occur during phase cycle of the cells. Thus by understanding the biochemical process of phase cycle of normal and cancer cells, type of actual treatment of cancer is decided.[6]

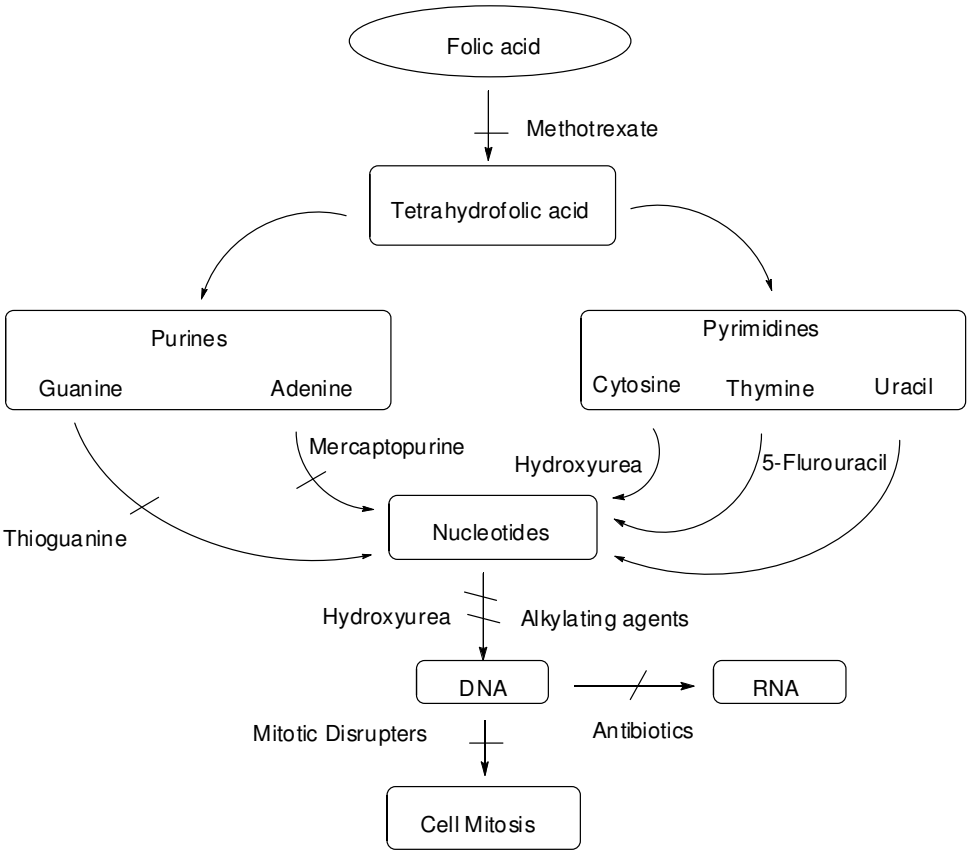


Figure 2. Mechanism of chemotherapy according to cell cycle

Chemotherapy varies with type of cancer and stage of its development and mode of action of anticancer agents. Reactions between DNA enzymes and anticancer agents are irreversible and shut down the functioning of the enzymes, leading to ultimate death of cell.

The anticancer agents are divided into six main categories according to their mode of action. The main categories of anticancer agents are

1) Alkylating agents
2) Anti-metabolites
3) Mitotic inhibitors
4) Topoisomerase inhibitors
5) Antiestrogens
6) Enzyme inhibitors

1) Alkylating agents:

Alkylating agents are one of the earliest and most commonly used chemotherapeutic agents for cancer treatments. Their use in cancer treatments started in early 1940s with nitrogen mustards. Alkylating agents behave as strong electrophiles through the formation of carbonium ion intermediate under physiological conditions. The various alkylating agents are nitrosoureas (CCNU, BCNU, fotemustine **1** and stroptozotocin), mustards [chlorambucil, melphalan, mechlorethamine, cyclophosphamide and ifosamide **2**], platinum complexes (cisplatin **3**, carboplatin, etc.), tetrazines (Procarbazine **4**, dacarbazine, mitozolomide, temozolomide) and cyclopropylindoles (adoxelesin, carzelesin). Thiotepa, altretamine and busulfan are other alkylating agents (**Figure 3**).

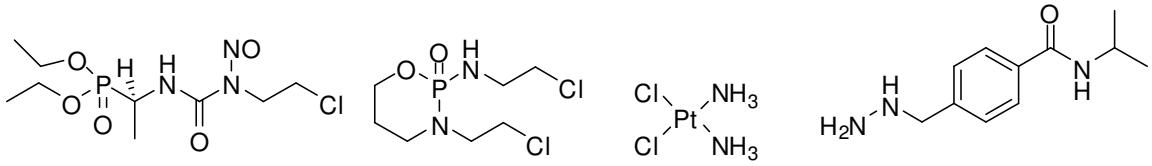


Figure 3.

These agents work directly on the DNA and prevent the cell division process by cross-linking the DNA strands and causing abnormal base pairing. When a DNA is altered in this manner, undesired cellular activity comes to a halt and the cell cannot multiply. Alkylating chemotherapy drugs are effective during all phases of cell cycle. Therefore, they are used to treat a large number of cancers. However, they are more effective in treating slow-growing cancers such as solid tumors and leukemia.

2) Anti-metabolites:

The compounds which interfere in varying ways with the synthesis of DNA are known as antimetabolites. All drugs in this category affect the cell during the "S" phase of the cell cycle. Antimetabolites inhibit the growth of the most rapidly proliferating cells in the body. There are three categories of antimetabolites: folic acid analogues (methotrexate, edatrexate, raltitrexed **5** etc.), pyrimidine analogues (5-fluorouracil, cytosine arabinoside, gemcitabine **6** etc.), purine analogues (6-mercaptopurine, 6-thioguanine, fludarabine **7** etc.) as shown in **Figure 4**.

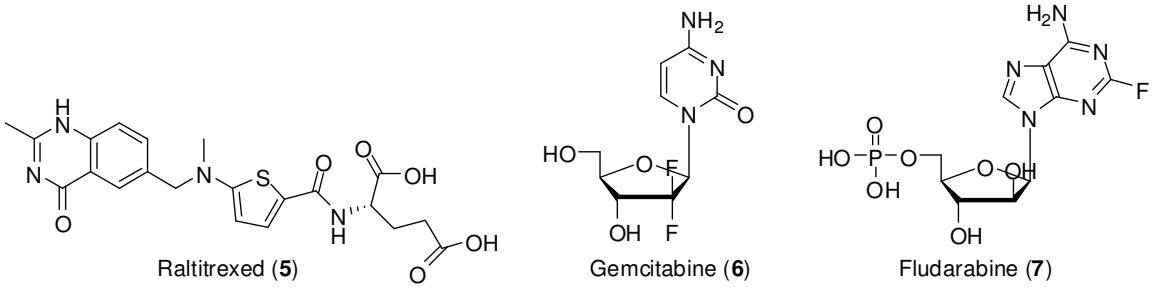
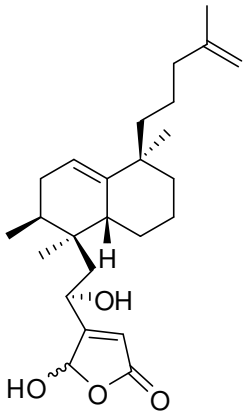


Figure 4.

3) Mitotic inhibitors:

A mitotic inhibitor is a type of drug derived from natural substances such as plant alkaloids and used in the treatment of cancer. The M-phase or mitosis is the most important part of the cell division cycle and includes condensation of nuclear chromatin and disruption of the nuclear envelope, organization of a mitotic spindle, and chromosome segregation. The key player within cell cycle, namely cyclin-dependent kinase (CDKs), microtubule and microtubule associated proteins (MAPs), have been selected as targets for the discovery of new antimitotic cancer drugs.

Cdc25 (cell division cycle) is a dual specificity protein tyrosine phosphatase that regulates activation of CDKs (cyclin-dependent kinases) through the dephosphorylation of both threonine and tyrosine residues of CDKs. As a result of their unique substrate selectivity and their essential functions in cell cycle control, cdc25 phosphatases represent attractive screening targets to identify new antimitotic compounds. Dysidiolide **8** is the first natural product inhibitor of cdc25A and was isolated from the Caribbean sponge *Dysidea etheria* (**Figure 5**). It inhibited the dephosphorylation of *p*-nitrophenol phosphate by cdc25A phosphatase with an IC_{50} of 9.4 μM.[7] Because of its unusual structure and interesting biological activity, a number of synthetic chemists undertook efforts directed toward the total synthesis of dysidiolide, from which some important structure-activity relationship information was obtained.[8] Dysidiolide and its analogs exhibited antitumoural properties (**Figure 5**).[9]



Dysidiolide (**8**)

Figure 5.

Microtubules are protein polymers that are responsible for various aspects of cellular shape and movement. The major component of microtubules is the polymer tubutin, a protein containing two nonidentical subunits (alpha and beta). The antimitotic agents act by affecting the equilibrium between free tubulin dimers and assembled polymers. Microtubule interactive agents (MIAS) act by affecting the equilibrium between free tubulin and assembled polymers, which inhibit polymerization in cells undergoing mitosis, leading to arrest at metaphase and consequently result in death of the cells.

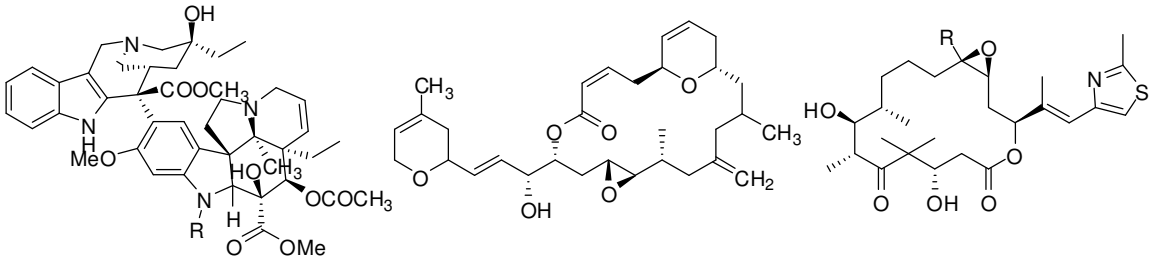


Figure 6. Tubulin polymerization inhibitors

The two major classes of natural products and derived antimitotic agents that act through inhibition of tubulin polymerization are those that bind to *β*- tubulin at colchicine site and those that bind to vinca-domain. A large number of naturally occurring ligands that inhibit tubulin polymerization have been reported (**Figure 6**) in the literature and there has been a continuing discovery of new agents with pronounced structural diversity.[10]

There are a variety of synthetic compounds that also demonstrate efficient inhibition of tubulin polymerization.

Some of the semisynthetic and synthetic microtubule inhibitors:

There are a number of semisynthetic or synthetic compounds which inhibit microtubule assembly. Paclitaxel **14** is one of the ligand, which inhibits microtubule system. Paclitaxel was isolated from the bark of pacific yew *Taxus brevifolia* (**Figure 7**).[11]

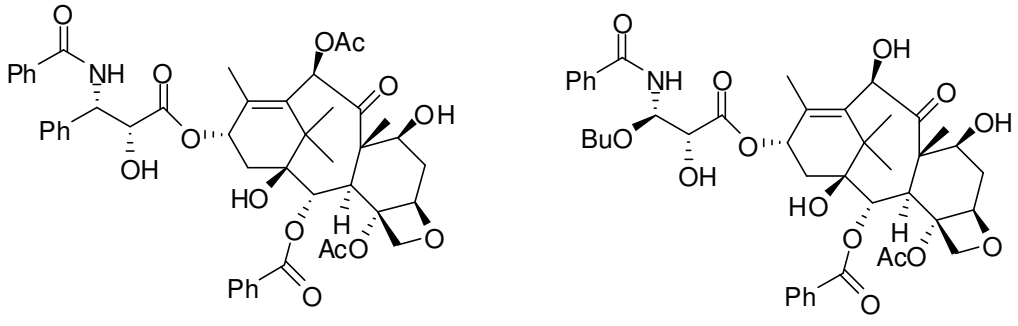


Figure 7.

The docetaxel **15**, a semisynthetic analogue of paclitaxel **14**, vinblastine **9** and vincristine **10** are standard agents in cancer therapy. The clinical use of paclitaxel **14** and docetaxel **15** are restricted mainly by oral bioavailability, although they are highly potent and effective cancer drugs. Numerous new semisynthetic analogues of paclitaxel are under clinical study. Bristol-Myers-Squibb, the company which developed paclitaxel, have reported two paclitaxel analogues BMS-184476 and BMS-188797,[12] which are in phase – I and II clinical trials and they displayed similar or superior efficacy in nude mice xenograft models.

Two taxane analogues in clinical development by Aventis Pharma, i. e. TXD-258 and RPR-109881A,[13,14] have been reported to be effective against various human tumor xenografts, including multidrug-resistance-positive (MDR) and taxane-resistant models.

4) Antibiotics (Topoisomerase inhibitors):[15]

Topoisomerase inhibitors are a class of enzymes involved in the regulation of DNA super coiling. Type I toposiomerases change the degree of super coiling of DNA by causing single-strand breaks and re-ligation, whereas type II topoisomerases (such as bacterial gyrase) cause double-strand breaks. The different roles of DNA topoisomerase I and II may indicate an opposing pair of roles in the regulation of DNA super coiling. Both activities are especially crucial during DNA transcription and replication, when the DNA helix must be unwound to allow proper function of large enzymatic machinery, and topoisomerases have indeed been shown to maintain both transcription and replication.

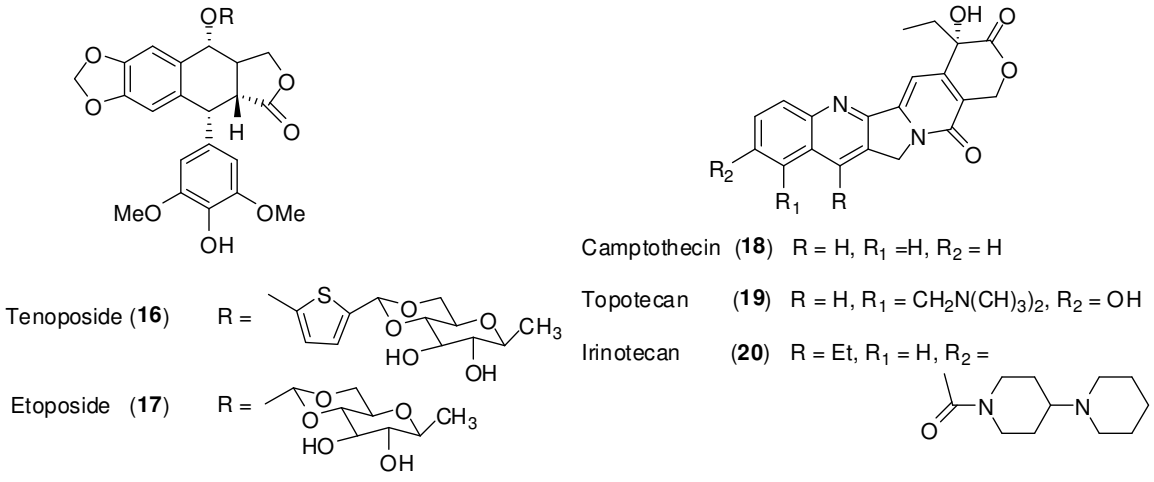


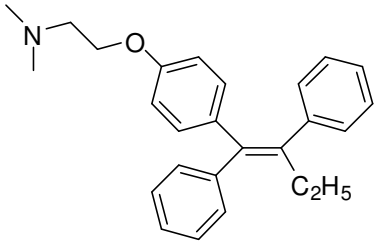
Figure 8.

Currently, topoisomerase I agent are directed the semisynthetic derivatives of podophyllotoxin such as tenoposide **16** and etoposide **17** and compounds derived from camptothecin **18** such as topotecan **19** and irinotecan **20** (**Figure 8**). Although, camptothecin **18** itself was originally isolated as a cytotoxin and the topoisomerase I activity was not discovered until later, these semisynthetic derivatives were synthesized in efforts to overcome the instability of the lactone ring and the innate insolubility of the parent compound, while maintaining topoisomerase I inhibitory activity. Saintopin, doxorubicin, daunomycin are the examples of naphthacenedione and anthracyclines respectively; which exert their cytotoxic effects through interaction with topoisomerase enzymes.

Along with the topoisomerarse inhibitory activity, anthracyclines/ antraquinones also work by the formation of free oxygen radicals. These radicals result in DNA strand breaks and subsequent inhibition of DNA synthesis and function.

5) Antiestrogens:[16]

Tamoxifen **21** (**Figure 9**) is a competitive inhibitor of estradiol binding to the estrogen receptor. It is used in the treatment of metastatic breast cancer. It is used alone for palliation of advanced breast cancer in women with estrogen receptor-positive tumors. It is also used for adjuvant therapy in certain types of early stage disease depending on the patient's age, receptor status of the tumor and degree of nodal involvement.



Tamoxifen (**21**)

Figure 9.

6) Enzyme inhibitors:

Enzyme inhibitors are molecules that bind to enzymes and decrease their activity. The binding of an inhibitor can stop a substrate from entering the enzyme's active site

and/ or hinder the enzyme from catalyzing its reaction. Inhibitor binding is either reversible or irreversible. Irreversible inhibitors usually react with the enzyme and change it chemically. Reversible inhibitors bind to enzymes with non-covalent interactions such as hydrogen bonds, hydrophobic interactions and ionic bonds. Multiple weak bonds between the inhibitor and the active site combine to produce strong and specific binding.

Enzyme ribonucleotide reductase is closely related to proliferative status in cancer cells. Specifically, it inhibits ribonucleotide reductase to block deoxyribonucleotide formation and DNA synthesis. Hydroxyurea is S-phase specific drug; it inhibits DNA synthesis by reacting with enzyme ribonucleotide reductase.[17]

Phase I and II drug-metabolizing enzymes are an important system that the human body has developed to protect itself from environmental toxins. Organosulfur compounds can alter xenobiotic drug-metabolizing enzymes and inhibit the formation of carcinogen–DNA adduct.[18-19] Organosulfur compounds include oil-soluble constituents diallyl sulfide **22**, diallyl disulfide (DADS) **23**, diallyl trisulfide, dithiin and ajoene; water-soluble derivatives *S*-allyl cysteine (SAC) **24** and *S*-allyl mercaptocysteine (SAMC) **25** and metabolites allyl mercaptan (AM) and allyl methyl sulfide (**Figure 10**). Garlic organosulfur compounds also produce antiproliferative effects in cancer cells, leading to cell cycle arrest and/ or apoptosis.[20] Garlic, onions, leeks and other *Allium* vegetables have numerous purported health benefits, including anticancer properties.[21]

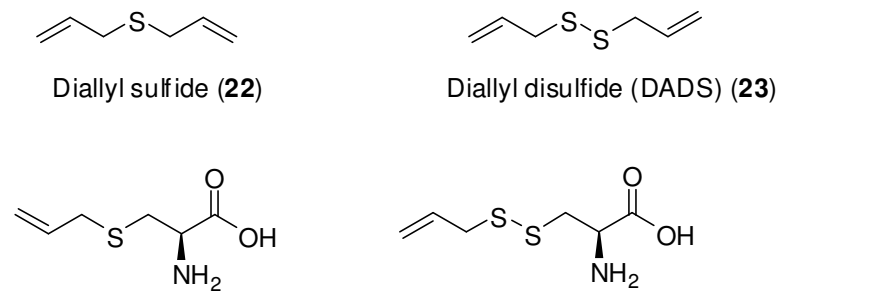
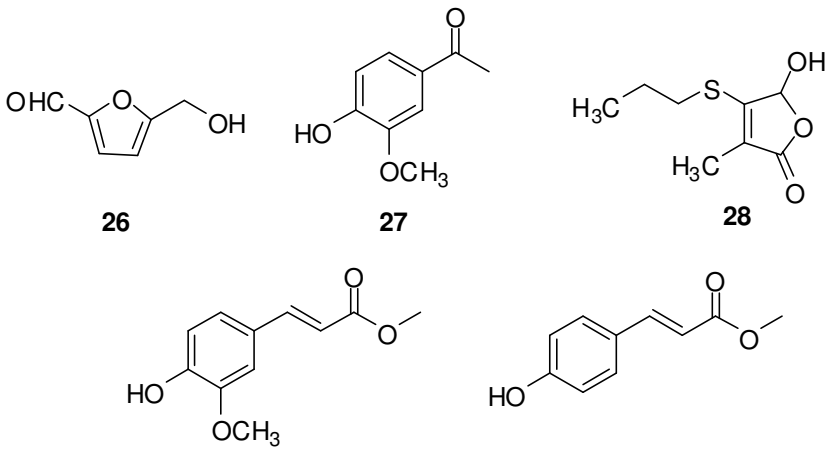


Figure 10. Some of the examples of organosulfur compounds

Xenobiotic metabolism by phase I enzymes (e.g., cytochrome P450s) may yield either inactive detoxification products or highly reactive, electrophilic carcinogens that may react with nucleophilic centers such as DNA to initiate carcinogenesis.[22] Products of

phase I metabolism can be substrates for phase II enzymes (e.g., NAD-(P)H: quinone reductase (QR), glutathione-*S*-transferase (GST), and UDP-glucuronosyl transferase (UGT) and transformed to easily excretable inert products.[23] An individual's risk of chemical carcinogenesis is largely controlled by the balance between phase I carcinogen-activating enzymes and phase II detoxifying enzymes.[24] The induction of xenobiotic metabolizing enzymes, particularly phase II enzymes, affords protection against neoplastic effects of chemical carcinogens[25] and phase II enzyme induction has emerged as an important strategy for chemoprevention.[26]

In recent years, the phase II enzymes from plants and vegetables have been received great deal of attention, because of peculiar structure with specific biological activities. Along this line, the genus *Allium* is a rich source of biologically active compounds. *Allium* is a genus of perennial bulbous plants that produce chemical compounds (mostly cysteine sulfoxide) that give them a characteristic onion or garlic taste and odor. Some of the *Allium* species are *A. cepa*, *A. oschaninii*, *A. ampeloprasum*, *A. ascalonicum A. sativum* and *A. schoenoprasum*. Among them *A. cepa* and *A. sativum* are the most well known. Recently, Parkin *et al*. reported[27] that the γ-hydroxybutenolide moiety alongwith other active agents (**Figure 11**) isolated from the cultivated plant *Allium cepa* (green onion) shows anticancer activity and exhibited QR and GST activity.

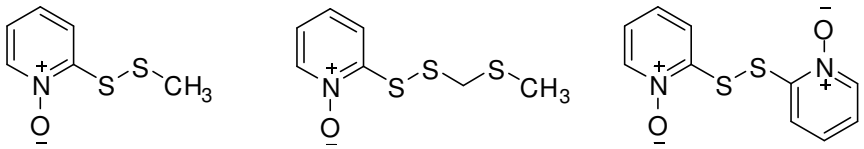


26 **27** **28**

29 **30**

Figure 11. Compounds isolated from *A. cepa*

O'Donnell *et al.* reported isolation of anticancer pyridine-*N*-oxide alkaloids possessing disulfide functional groups from *A. stipitatum*.[28] 2-(Methyldithio)pyridine-*N*-oxide **31** and 2-[(methylthiomethyl)dithio]pyridine-*N*-oxide **32** displayed potent anticancer activity against human cancer cell line with IC_{50} values ranging from 0.3 to 1.8 μM with a selectivity index of 2.3 when compared to a human somatic cell line (**Figure 12**).

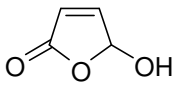


31 **32** **33**

Figure 12. Structures of pyridine-*N*-oxide alkaloids isolated from *A. stipitatum*

Likewise, Carotenuto *et al.* isolated the cytotoxic porrigenins A, B and agigenin from *Allium porrum*.[29] Porrigenin A and B are isomers of each other, and exhibited high antiproliferative activity and cytotoxicity (against IGR-1, J-744, WEHI 164, P-388 tumor cell lines in vitro).

A short review on *γ*-hydroxybutenolide derivatives



34

Figure 13.

γ-Hydroxybutenolide (5-hydroxy-2(5*H*)-furanone) **34** (**Figure 13**) derivatives[30] are becoming increasingly important moieties in organic chemistry, as they are present in an ever-growing number of biologically active natural products and medicinally important compounds. Many of these compounds have a wide variety of properties such as antibacterial, anti-inflammatory, cytotoxic, anti-feedant, ichthyotoxicity, or antimicrobial activities; some of them are phospholipase A_2 (PLA_2), protein kinase C (PKC) inhibitors. A numbers of methodologies have been developed for their synthesis.

Naturally occurring 5-membered hydroxy lactones

Natural products containing five-member framework are found in plants, marine sponges[30] and insects. They originate from natural sources. Vertinolide is one of the oldest natural product possessing hydroxy lactone framework isolated in 1981 from *Verticillium intertextum*.[31] Desacetylnimbinolide **35** and desacetylisonimbinolide **36** were isolated as new tetranortriterpenoids from *Azadzrachta indica* (**Figure 14**).[32]

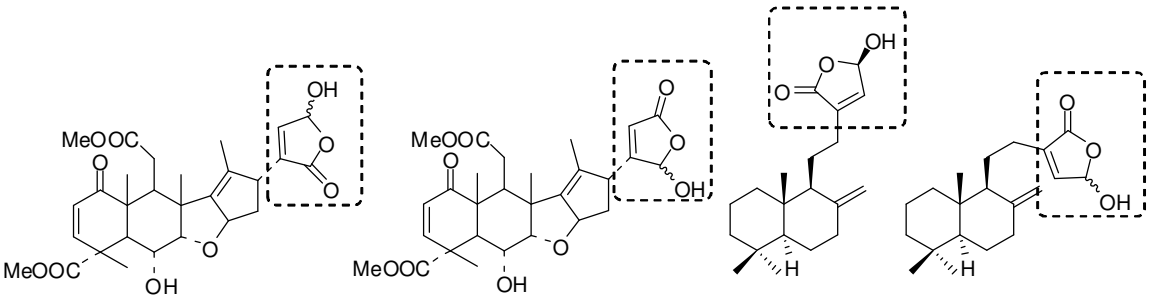


Figure 14.

In 1988, Itokawa *et al.* isolated[33] labdane-type diterpenes coronarin C **37** and D **38** from the rhizomes of *Hedychium coronarium* cultivated in Brazil, showing cytotoxic activity against Chinese hamster V-79 cells (**Figure 14**).

Cacospongionolide A-F **39-44**, six new metabolites were isolated from the marine sponge *Fasciospongia cavernosa*.[34] Cacospongionolide F **43** exhibited antimicrobial activity; whereas cacospongionolide B **40** and E **43** possess cytotoxic as well as antimicrobial activities. Further pharmacological screening revealed that they displayed antiinflammatory properties and inhibited phospholipase A_2 (PLA_2). Other analogs of cacospongionolide A, C and D possess cytotoxic activity (**Figure 15**).

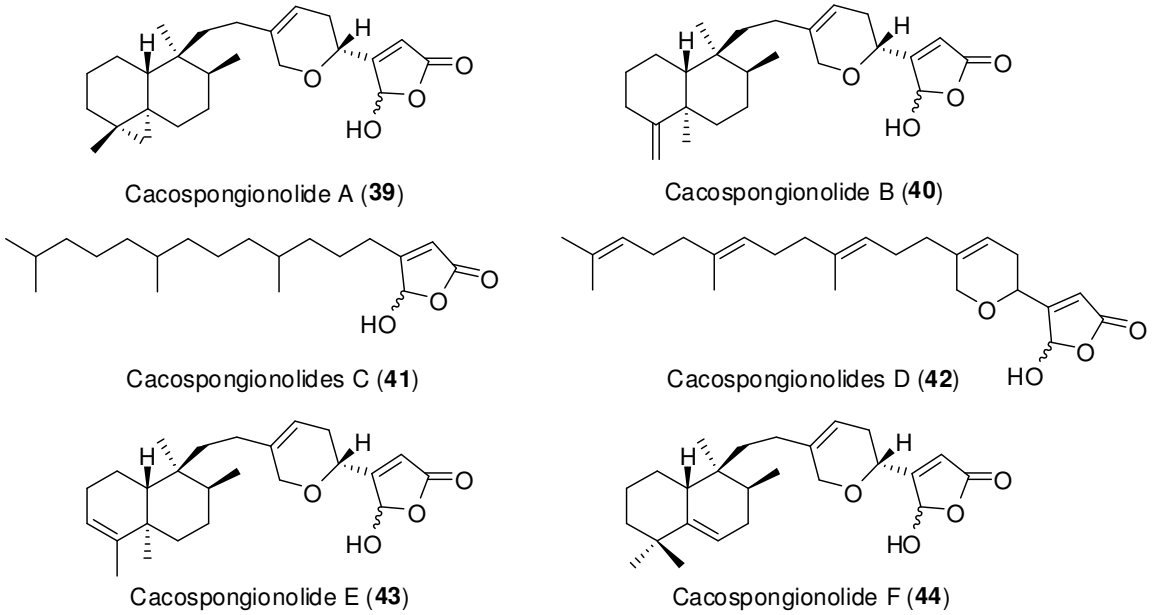


Figure 15.

A new ring B-*seco* limonoids, turrapubesins D-G along with turraflorin D and E were isolated from the twigs and leaves of *Turraea pubescens* and have cytotoxic activity against the P-388 and A-549 cells.[35] More recently, two new andirobin-type limonoids[36] such as moluccensins N **45** and O **46** were isolated from seeds of an Indian mangrove, *Xylocarpus moluccensis* and bear *γ*-hydroxybutenolide moiety (**Figure 16**).

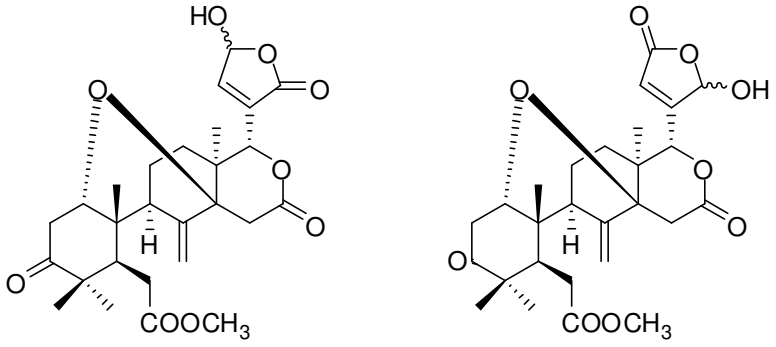
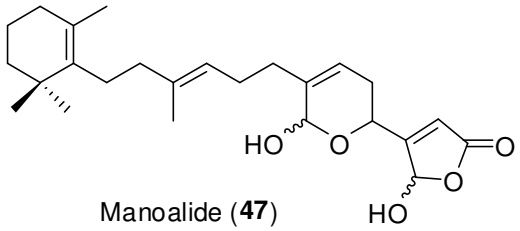


Figure 16.

Manoalide **47** is the parent compound of a series of marine sponge metabolites belonging to the sesterterpene class.[37] Manoalide was first reported in 1980 by Scheuer *et al.* from the marine sponge *Luffariella variabilis* (**Figure 17**).

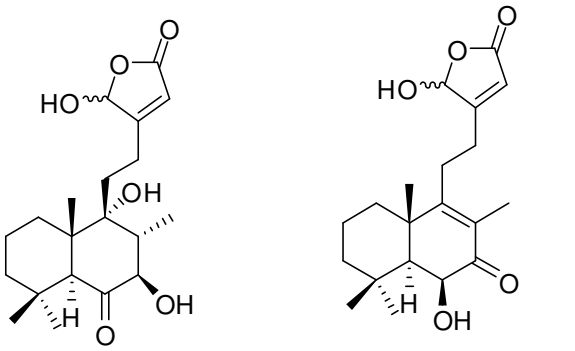


Manoalide (**47**)

Figure 17.

Manoalide is a potent PLA_2 inhibitor; and one year later, three congeners of manoalide were obtained from the same sponge,[38] of which secomanoalide is more potent against bovine pancreatic PLA_2.[39] Both displayed antibacterial and antiinflammatory activity against *Streptomyces pyogenes* and *Staphylococcus aureus*. Luffariellolide, from a Palauan *Luffariella* sp., also inhibited bee venom PLA_2 with an IC_{50} of 0.23 μM. Luffariellins A and B, isolated from *L. Variabilis* are very potent against bee venom PLA_2 with IC_{50} values of 56 and 62 nM, respectively.[40]

Sibiricinone A **48** and B **49**, new labdane diterpenes were isolated from the aerial parts of *Leonurus sibiricus*,[41] and exhibited antipyretic activity (**Figure 18**).



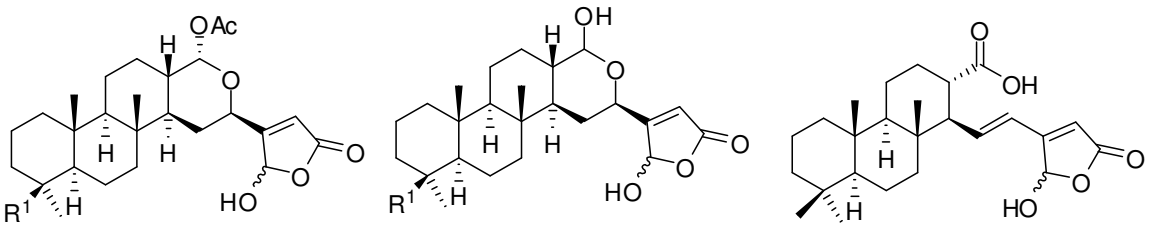
Sibiricinone A **(48)** Sibiricinone B **(49)**

Figure 18.

Two new *seco*-prezizaane-type sesquiterpenes,[42] 1,2-dehydroneomajucin and jiadifenin were isolated from the methanol extract of the pericarps of *Illicium jiadifengpi*, indigenous to the southern part of China. Jiadifenin and (2*S*)-hydroxy-3,4-dehydroneomajucin were found to have neurotrophic activity.

Petrosaspongiolides M-R **50-54**, sesterterpenes isolated from the New Caledonian sponge *Petrosaspongia nigra* and inhibited PLA_2 (**Figure 19**). The most potent analogue

(petrosaspongiolide M) inhibited human synovial and bee venom PLA_2 with IC_{50} values of 1.6 and 0.6 μM, respectively; while petrosaspongiolide P **52** inhibited human synovial PLA_2 (IC_{50} 3.8 μM). Petrosaspongiolides N **51**, Q **53**, and R **54** showed only weak activity.[44] Petrosaspongiolide M **50** possesses antiinflammatory activity.[45]



Petrosaspongiolide

PM (50) $R^1 = CH_3$
PN (51) $R^1 = CH_2OAc$

Petrosaspongiolide

PP (52) $R^1 = CH_3$
PQ (53) $R^1 = CH_2OAc$

Petrosaspongiolide R (**54**)

Figure 19.

Spongianolides A-E, sesterterpenes isolated from a sponge *Spongia* sp., inhibited PKC with IC_{50} values of 20-30 μM[46] and possesses potent cytotoxic activity.

Palinurin, originally isolated from the Mediterranean sponge *Ircinia variabilis*,[47] was inhibitory against PLA_2 with an IC_{50} value of 50 μM. Two sesterterpenes, palauolol and palauolide, isolated from a Palauan sponge *Fascaplysinopsis* sp. inhibited bee venom PLA_2 (85% and 82% inhibition at 0.8 μg/mL, respectively). They possess antimicrobial and antiinflammatory activity respectively.[48]

Luffarins A and C-E have been isolated from the Australian marine sponge *Luffariella geometrica*. They exhibited antimicrobial activity against *Staphylococcus aureus*, *Micrococcus* and *Saccharomyces cerevisiae*.[49]

Some of the synthetic 5-membered hydroxy lactones

There are a number of synthetic compounds, which are having hydroxy lactone as an important moiety. The sesterterpene dysidiolide **8** is an inhibitor of Cdc25A. The γ-hydroxybutenolide group present in the natural products is a major determinant of their phosphatase-inhibiting activity. On this basis, Koch and co-workers have synthesized several compounds as shown in **Figure 20**. The most potent compound **55** had an IC_{50}

value of 350 nM, which is significantly lower than the reported IC_{50} value for dysidiolide (9.4 μM). Two compounds **56** and **57** inhibited acetylcholinesterase (AChE) with IC_{50} values of 1.3 and 4.5 μM. A series of compounds with *γ*-hydroxybutenolide moiety were reported 11*β*-hydroxysteroid dehydrogenase *(*11*β*HSD) inhibitors.[50] The stereochemistry of these two compounds were not reported.

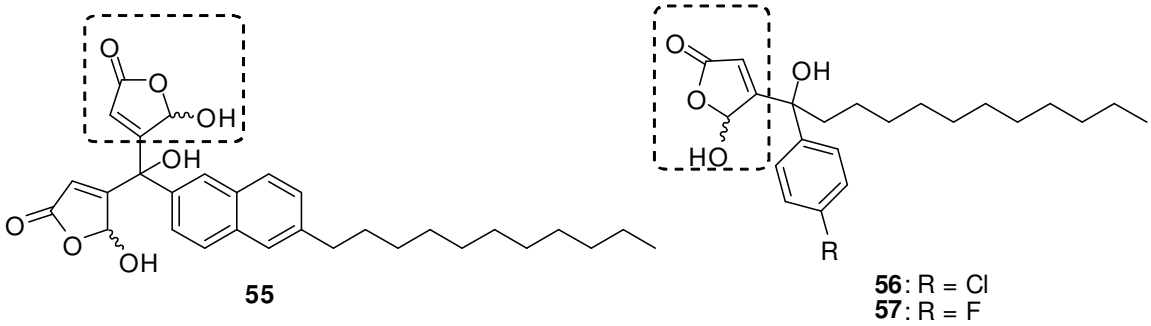
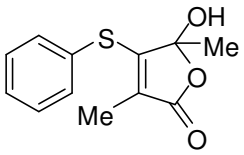


Figure 20.

Some of the synthetic compounds bearing *γ*-hydroxybutenolide moiety were reported[51] and nearly similar compound **58** was reported due to unique combination of sulfur with the butenolide moiety (**Figure 21**).[52]



58

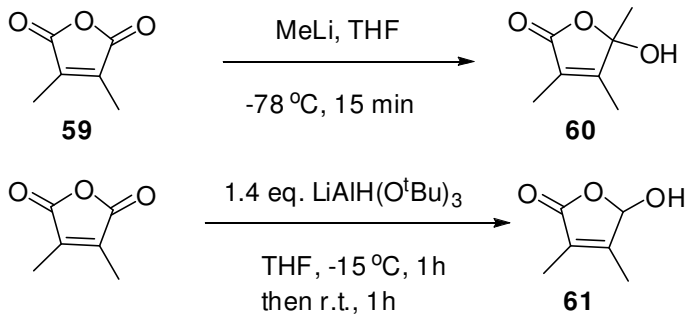
Figure 21.

Preparation of hydroxy lactones

Synthesis of hydroxybutenolides (hydroxyfuranones)

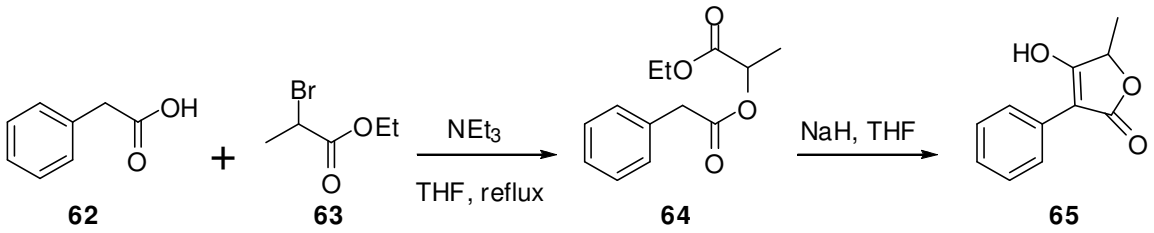
For the synthesis of compounds having cyclic double bond, different methods are documented in literature and these are summarized below.

De Kimpe and co-workers[53] reported the formation of hemiacetal **60** and 3,4-dimethyl,3-hydroxyfuranones **61** by the nucleophilic addition of methyllithium and reduction of cyclic anhydride **59** (**Scheme 1**).



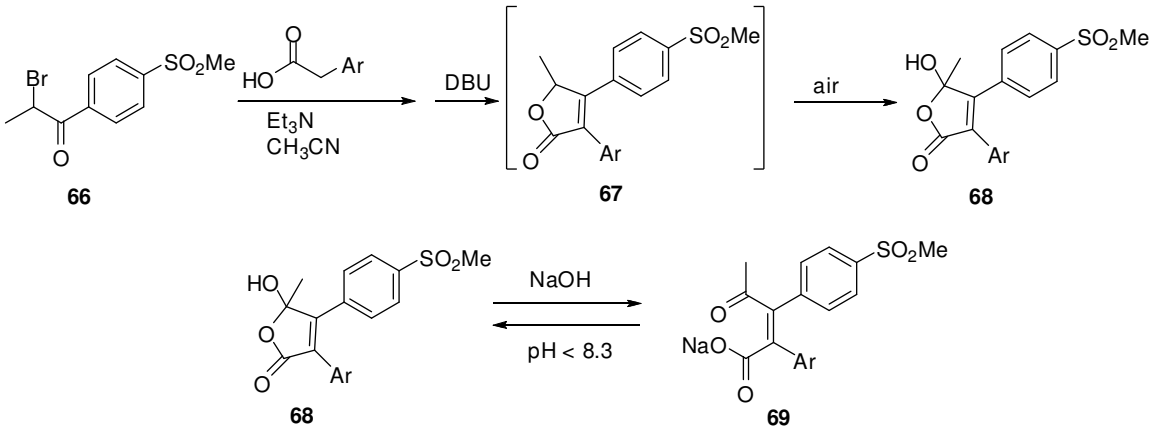
Scheme 1.

Weber *et al*. have reported[54] the various 3-and 4-hydroxy-2(5H)-furanones **65** as anti-oxidant and antiinflammatory agents. They were synthesized *via* alkaline cyclization of ethoxycarbonylmethyl phenylacetates **64** using sodium hydride in dry THF (**Scheme 2**). Intermediates were obtained by the condensation of a phenyl acetic acid **62** derivative with a suitable α-bromo carboxylic ester **63** in the presence of triethylamine.



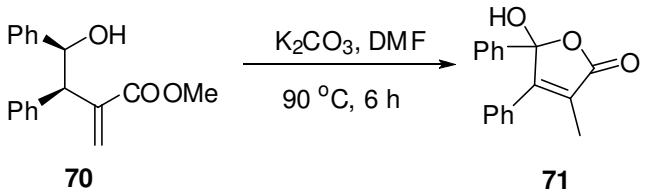
Scheme 2.

Black and co-workers reported[55] 5-hydroxy-5-methylfuranone derivatives **68** as orally-active inhibitors of cyclooxygenase-2 (COX-2). α-Bromo ketone **66** was displaced by the triethylammonium salt of aryl acetic acid to provide the corresponding ester, which underwent an intramolecular aldol condensation in the presence of DBU. If oxygen was vigorously excluded, the intermediate 5-methyl furanone **67** could be isolated. However, exposure to air in the presence of the base led to rapid oxidation of the ring, providing the desired hydroxyfuranone **68 (Scheme 3)**. The cyclization and oxidation were accomplished in one step by treating the ester with DBU followed by passing a stream of air through the dark solution using a gas diffusion tube.



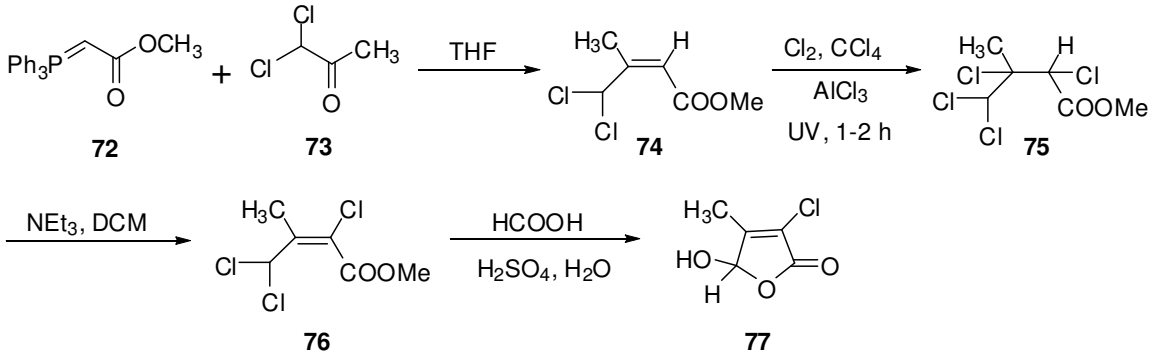
Scheme 3.

Kim *et al*. reported[56] one pot synthesis of γ-hydroxybutenolide **71** from Baylis-Hillman adduct *syn*-**70**, by aerobic oxidation with K_2CO_3 (30 mol%) in DMF produced **71** in good yield (**Scheme 4**).



Scheme 4.

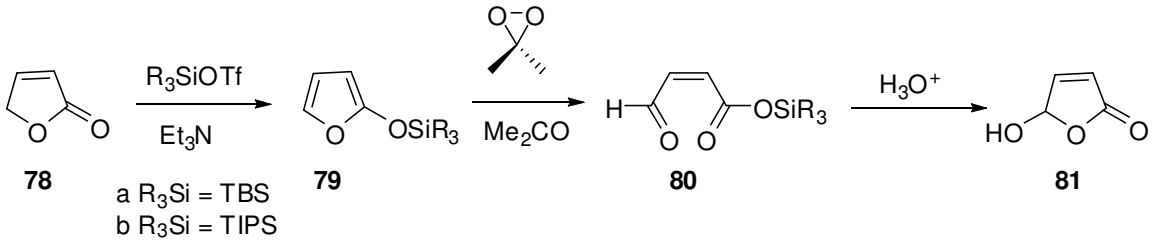
Franzen and co-workers[57] reported the synthesis of chlorinated hydroxy furanones **77** from chlorinated aldehydes or ketones **73**. The Wittig condensation of the chlorinated aldehyde **73** and propanones gave the olefinic ester **74**, which was then chlorinated with chlorine afforded dichloro compound 75. Chlorinated olefin 76 was quantitatively



Scheme 5.

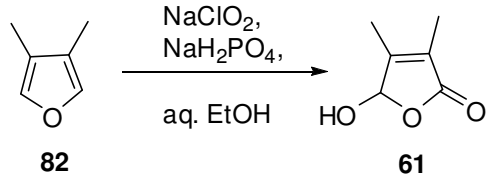
obtained upon triethylamine treatment of **75** in CH_2C1_2. Finally, the corresponding hydroxyfuranones **77** (**Scheme 5**) could be obtained by hydrolysis of chlorinated olefin **76** using formic acid / H_2SO_4 / H_2O in one step in 60-80% yield.

Boukouvalas *et al.*[58] reported a new, highly efficient synthesis of γ-hydroxybutenolide **81** from the readily available 2-trialkylsilyloxyfurans **79**. 2-Trialkylsilyloxyfurans reacts rapidly with dimethyldioxirane at -78 °C to provide trialkylsilyl (*Z*)-4-oxo-2-alkenoates **80**, whose hydrolysis delivers γ-hydroxybutenolides **81** with high efficiency (**Scheme 6**). This is a short synthesis of a naturally occurring monoterpene γ-hydroxybutenolides.

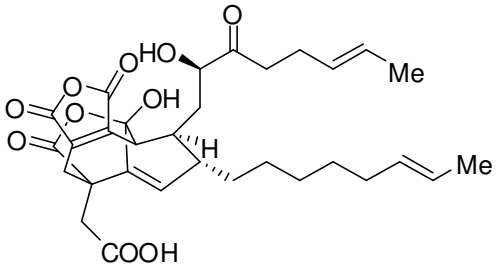


Scheme 6.

Clive and co-workers[59] reported the simple conversion of disubstituted furan **82** into γ-hydroxybutenolides **61** using sodium chlorite ($NaClO_2$) as oxidizing agent (**Scheme 7**). This methodology was applied to the synthesis of biologically active molecules CP-225,917 **83** (**Figure 22**).



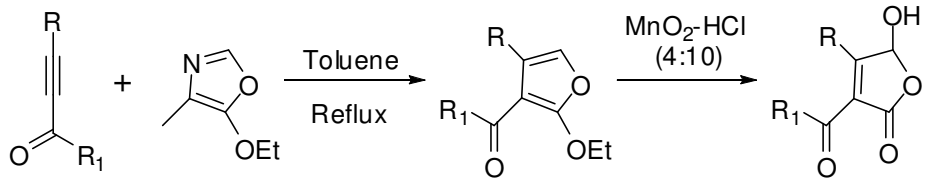
Scheme 7.



CP-225,917 (**83**)

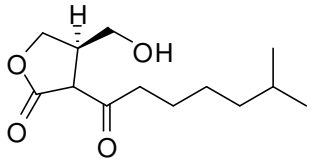
Figure 22.

Yadav *et al.* reported[60] regioselective synthesis of disubstituted hydroxy butenolides **87** from 4-aryl-3-carbethoxy-2-ethoxyfuran **86** by the oxidation with MnO_2-HCl, followed by the tandem Diels-Alder and retro Diels-alder cycloadditions of acetylenic dienophiles **84** with 4-methyl-5-ethoxyoxazole **85** in toluene (**Scheme 8**). Further, this methodology was applied to the total synthesis of (±)-A Factor **88** (**Figure 23**).



84 **85** **86** **87**

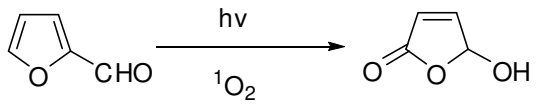
Scheme 8.



A-Factor (**88**)

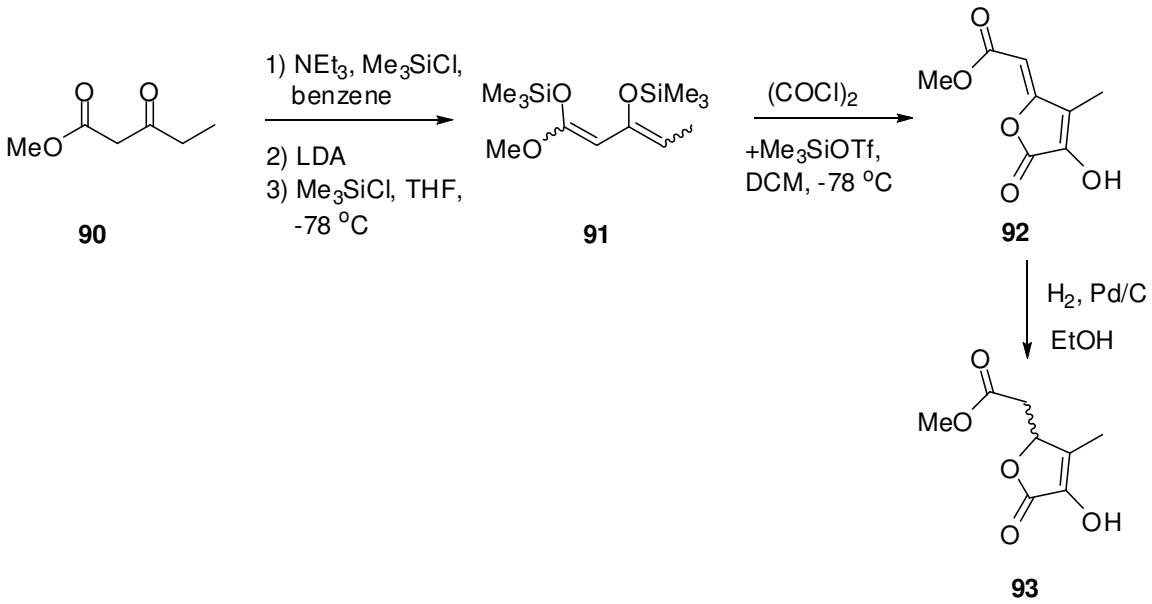
Figure 23.

Schenck and co-workers have reported[61] the photooxygenation of furfural **89** in methanol. Furfural on oxidation by photolysis afforded γ-hydroxybutenolide **81 (Scheme 9)**.



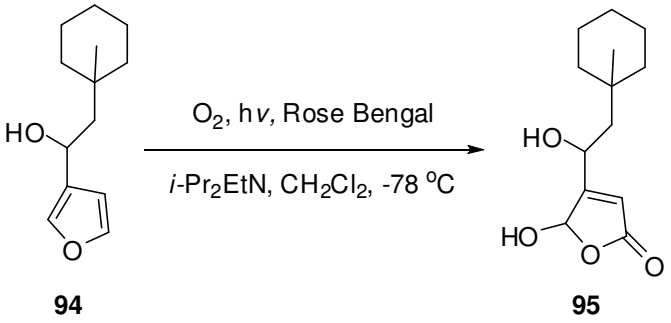
Scheme 9.

Langer and co-workers[62] reported the synthesis of racemic butenolides **93** from *β*-keto esters **90**. The cyclization of 1,3-bis-silyl enol ethers **91** prepared from **90** with oxalyl chloride afforded the *γ*-alkylidene butenolides **92**. Hydrogenation[63] of the latter gave racemic α-hydroxy butenolides **93** (**Scheme 10**).



Scheme 10.

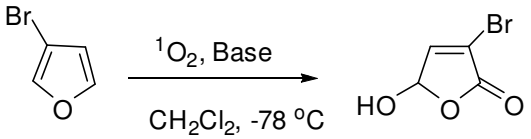
Takahashi *et al.* have reported[64] the monocyclic analogues of natural cdc25A inhibitor dysidiolide. It was prepared in racemic form from 1-methyl-1-cyclohexanecarboxylic acid. The photo-oxidation of furan ring **94** using Rose Bengal and triisopropylethyl amine as a base in dichloromethane at -78 °C afforded monocyclic analogue of dysidiolide **95** (**Scheme 11**).



94 **95**

Scheme 11.

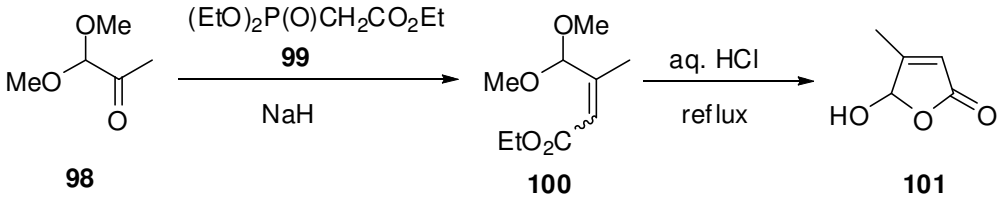
Aquino and co-workers[65] reported the base promoted regioselective photo-oxidation of 3-bromofuran **96** in dichloromethane at -78 °C gave 3-bromo- or 4-bromo-5-hydroxy-5H-furan-2-ones **97** in good yields (**Scheme 12**). They have tried several bases such as DBU, phosphazene, DIPEA, pempidine, 2,6-di-*tert*-Bu-pyr, $(TMS)_3N$.



96 **97**

Scheme 12.

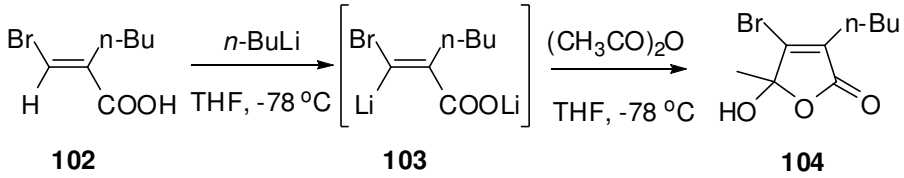
Pattenden *et al*. reported[66] the synthesis of monosubstituted γ-hydroxybutenolides **101** *via* Emmons–Horner reaction and cyclization. Emmons–Horner reaction of pyruvic aldehyde dimethyl acetal **98** with triethyl phosphonoacetate **99** in the presence of NaH gave an isomeric mixture (*E* : *Z* = 15 : 1) of the ester **100**. Cyclisation of ester with 6 M hydrochloric acid under reflux afforded the γ-hydroxy-β-methylbutenolide **101** in quantitative yield (**Scheme 13**).



98 **100** **101**

Scheme 13.

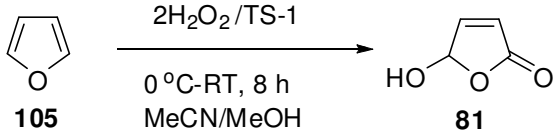
Descomps *et al.* reported[67] the preparation of γ-hydroxybutenolides moiety. The lithiation of acid **102** using *n*-BuLi in dry THF afforded substituted β-lithio carboxylate **103**, which was treated with acetic anhydride to produce bromo substituted γ-hydroxybutenolides **104** (**Scheme 14**).



102 **103** **104**

Scheme 14.

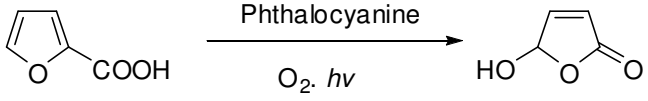
Kumar *et al.* have reported[68] efficient synthesis of 5-hydroxyfuranone using titanium silicate molecular sieves (TS-1) as heterogeneous catalyst. Furan **105** was treated with aq. H_2O_2 in acetonitrile in the presence of TS-1 wherein the corresponding hydroxy lactone **81** was obtained in excellent yields (**Scheme 15**).



105 **81**

Scheme 15.

Xu *et al.* reported[69] recyclable phthalocyanine based sensitizer for photooxygenation of 2-furoic acid **106** at 0 °C in CH_2Cl_2 to afford **81** (**Scheme 16**).



106 **81**

Scheme 16.

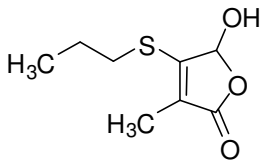
A large number of methods developed for the synthesis of γ-hydroxybutenolides demonstrate the importance of these molecules in organic and biochemistry.

3.1.2 Present Work

Allium is a group of flowering plants, some species of which are used as food and herbal medicine worldwide.[70] Majority of *Allium* species are native to the Northern hemisphere, mainly in Asia. A few species are native to Africa and Central and South America.[71] The approximately 750 species[72] of *Allium* available so far, are distinguished from one another and classified according to the color and shape of their fruiting bodies and leaves and by other morphological characteristics.

Allium cepa, a cultivated plant is effective against common cold to heart disease, diabetes, osteoporosis, and other diseases.[73] It contains biologically active compounds with antiinflammatory, anticholesterol, anticancer, and antioxidant properties such as quercetin. Reports on the isolation of biologically active agents from *Allium cepa*[74] have been few but have received attention due to the unique structures and specific biological activities of the metabolites. Thiosulphinates and α-sulphinyldisulphides, with antiasthmatic activity, are some of the interesting metabolites that have been previously isolated from *Allium cepa.*[75]

(±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **28,** a biologically active natural product is recently isolated as white solid from the methanolic extracts of cultivated plant *Allium cepa* (green onion) by Parkin and co-workers in 2007 (**Figure 11**).[27] It shows potential cancer chemopreventive constituents directed by the quinone reductase (QR) induction bioassay using murine hepatoma (Hepa 1c1c7) cells. Organosulfur compounds have been shown to induce Phase II enzymes, which is responsible for protection against cancer.[76]



28

(±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one

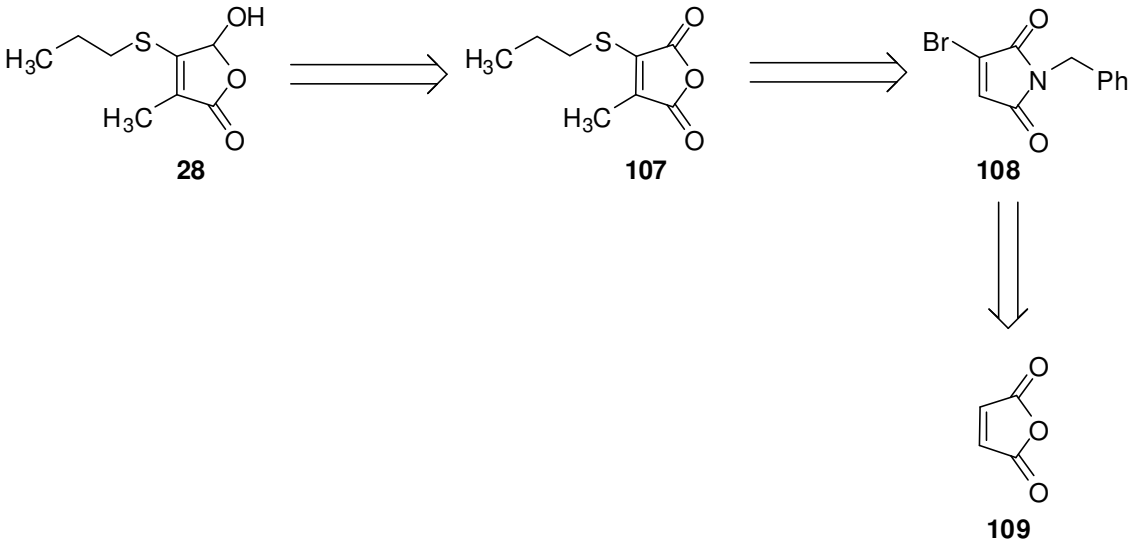
Figure 11.

(±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **28** was found to have potent anticancer activity and exhibited QR and GST activity.[27] The structure was assigned from spectral analysis and molecular formula, ($C_8H_{12}O_3S$ by HRMS). It is a *γ*-hydroxybutenolide moiety with one sulfur group and one methyl group. The stereochemistry was not assigned by spectral data and no X-ray crystallographic analysis was reported.[27]

From the introductory remarks, it is apparent that compound **28** containing *γ*-hydroxybutenolide moiety is of interest from both synthetic as well as from medicinal point of view. Since, there are no reports in the literature for the synthesis of **28** and also due to the structural relevance with the research, the synthesis of **28** was undertaken.

The present section primarily concerns with the synthesis of compound **28**, an organosulfur compound containing *γ*-hydroxybutenolide moiety, having anticancer activity. It was thought worthwhile to attempt the synthesis of compound **28** because of its structural novelty, including one chiral centre at C-5 position and our keen interest in the synthesis of five membered *γ*-hydroxybutenolide ring.

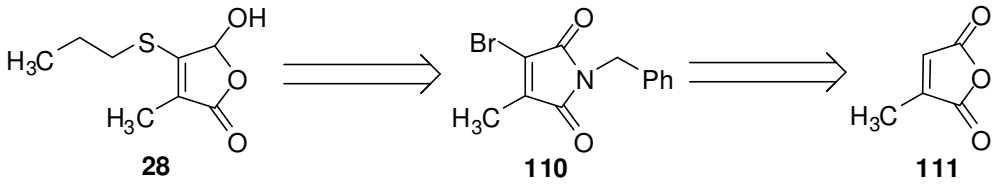
As per retrosynthetic approach I depicted in **Scheme 17**; it was envisioned that compound **28** could be obtained from commercially available maleic anhydride **109**. The 5-hydroxy functionality at C-5 position in compound **28** could be obtained from anhydride **107** *via* selective reduction of carbonyl group. Anhydride **107** could be



Scheme 17. Retrosynthetic approach I of compound **28**

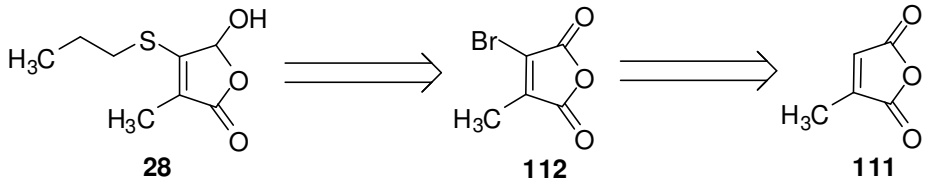
achieved from bromomaleimide **108** as a key intermediate, which could be obtained from maleic anhydride **109.**

The retrosynthetic approach II was planned as shown in **Scheme 18**. The target molecule **28** could be obtained from methyl bromomaleimide **110** *via* alkaline hydrolysis and finally, **110** could be achieved from commercially available citraconic anhydride **111**.



Scheme 18. Retrosynthetic approach II of compound **28**

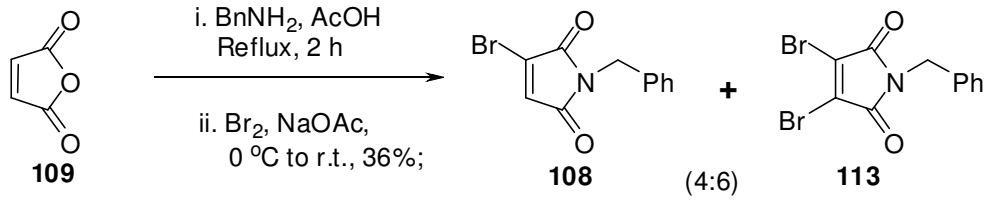
The retrosynthetic approach III was planned as shown in **Scheme 19**. The advantage of this approach is the earlier drawback from approach I and II avoided and depicted a short route for compound **28**. The target molecule **28** could be obtained from bromocitraconic anhydride **112** and it could be achieved from commercially available citraconic anhydride **111**.



Scheme 19. Retrosynthetic approach III of compound **28**

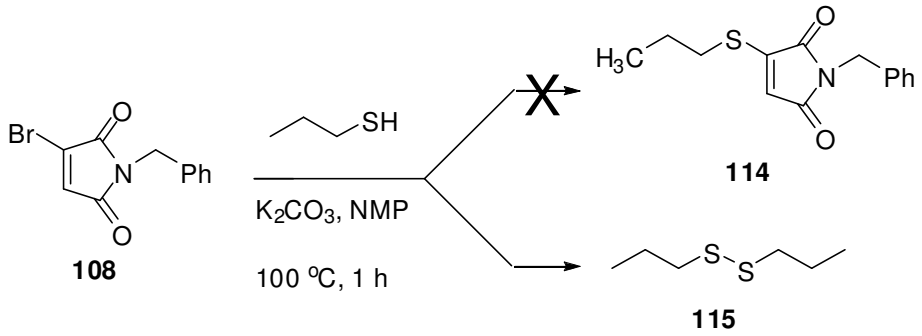
3.1.3 Results and discussion

According to retrosynthetic approach I (**Scheme 17**), the bromomaleimide **108** which is a key intermediate for compound **28,** was synthesized from commercially available maleic anhydride **109** as per the reported procedure[77] as shown in **Scheme 20**.



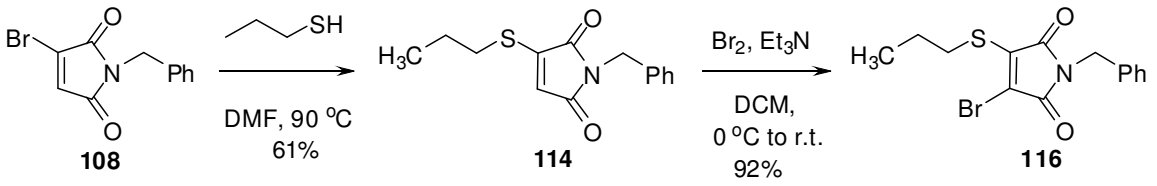
Scheme 20.

The bromomaleimide was treated with 1-propanethiol in the presence of 1.5 equivalents of K_2CO_3 in *N*-methyl-2-pyrrolidone (NMP) at room temperature for 2-3 h, but unfortunately it did not yield the desired product **114**. The starting material remains unchanged. Then, the same reaction was continued at reflux condition in an attempt to obtain the desired product **114**, but, it did not get the required product. Instead of **114**, self condensation of thiol **115** was observed (**Scheme 21**)**.**



Scheme 21.

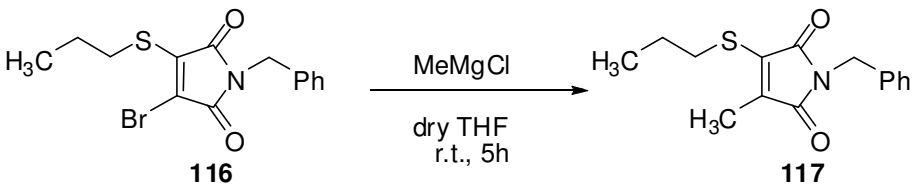
Having failed to obtain the desired product **114** by nucleophilic substitution reaction (**Scheme 21**), it was thought that the same reaction can be performed in dimethylformamide at room temperature. The reaction was monitored by TLC. After 48 h, the starting material disappeared and compound **114** was obtained in only 36% yield. To improve the yield, the reaction was heated at 90 °C for 4 h to afford **114** in 61% yield. ^{1}H NMR spectrum showed CH adjacent to carbonyl group (C=CH-CO) at δ 6.05 ppm, integrating for one proton whereas, ^{13}C NMR showed a peak at δ 117.2 ppm signifying CH adjacent to carbonyl group and a peak at δ 169.3 and 167.7 ppm for ketone carbonyl (CH-CO-N) and (C-CO-N) respectively. The mass spectrum (EI) exhibited molecular ion peak at 261 (M+1) (**Scheme 22**).



Scheme 22.

Subsequently, bromination of thiomaleimide with molecular bromine in the presence of Et_3N in dichloromethane at 0 °C to room temperature furnished the compound **116** in 92% yield (**Scheme 22**). In ^1H NMR spectrum showed no peak in the range of δ 5.5 to 6.5 ppm. In ^{13}C NMR spectrum, the carbon (C-Br) was shifted to downfield at δ 116.5 ppm. IR spectrum showed a peak at 665 cm^{-1} for C-Br bond. The mass spectrum (ESI) of **116** observed molecular ion peak at 340 (M+1).

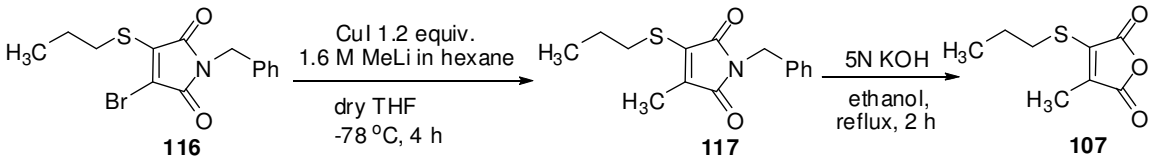
The next step was the incorporation of methyl group at the C-3 position in compound **116**, which was the key step for synthesis of target molecule **28**. The displacement of bromo group by methyl group of **116** using Grignard reagent (MeMgCl) in dry THF at room temperature afforded a complex reaction mixture and isolation of the desired product **117** was difficult (**Scheme 23**).



Scheme 23.

Hence, we planned to introduce methyl group using Gilman reagent. Freshly prepared Me_2CuLi[78] from CuI and 1.6 M MeLi in hexane at -78 °C was reacted with **116** in dry THF at -30 °C and -60 °C to give **117** in 25% and 47% yield respectively. The same reaction was subjected at -78 °C for 4 h afforded key intermediate **117** in 63% yield (**Scheme 24**). In ^1H NMR spectrum, the methyl group was observed as a singlet at δ 1.92 ppm. In ^{13}C NMR spectrum, the methyl group was observed at δ 9.56 ppm. In IR

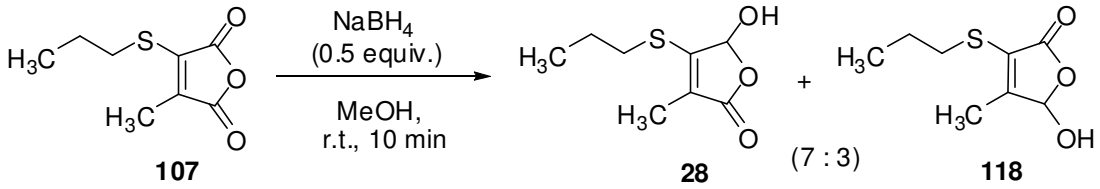
spectrum, no band was observed for C-Br bond in the range of 650-675 cm^{-1}. The mass spectrum (EI) showed molecular ion peak at 275 (M^+).



Scheme 24.

Alkaline hydrolysis of **117** with 5N KOH in absolute ethanol under reflux conditions furnished the cyclic anhydride **107** in 60% yield.[79] IR spectrum of anhydride and carbonyl group showed stretching at 1825 and 1766 cm^{-1}; while ^1H and ^{13}C NMR spectrum showed no peak in aromatic region. The mass spectrum (EI) exhibited molecular ion peak at 187 (M+1) (**Scheme 24**).

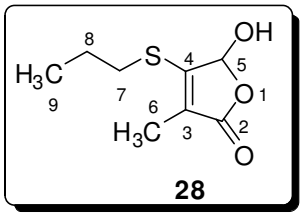
Finally, the selective reduction of carbonyl group at C-5 position in anhydride **107** with sodium borohydride in dry methanol at room temperature for 10 min gave mixture of two regio-isomers i.e. compound **28** and compound **118** with ratio 7:3; which were separated by flash silica gel column chromatography (**Scheme 25**). Compound **28** exhibited HRMS and ^{13}C NMR spectral data is in full agreement with those reported in the literature.[27]



Scheme 25.

Compound **28** was characterized by all spectral means. IR spectrum showed carbonyl absorption at 1766 cm^{-1} indicating the presence of carbonyl function. ^1H NMR spectrum exhibited various peaks in accordance with the structure. A triplet at δ 1.05 ppm integrating for three protons was attributed to methyl group ($C\underline{H}_3$-CH_2-CH_2-S-), while other triplet at δ 3.08 ppm integrating for two protons was assigned to methylene protons

adjacent to sulfur (C<u>H</u>$_2$-S). One multiplet was observed at δ 1.71 ppm corresponding to methylene protons in between other methylene and methyl group (CH_3-C<u>H</u>$_2$-CH_2). A sharp singlet at δ 1.84 ppm appeared for another three protons corresponding to the methyl group directly attached to the ring. Hydroxyl proton appeared as a broad singlet at δ4.27 ppm, while H5 proton adjacent to OH group appeared as a singlet at δ6.06 ppm.



28

The structure assigned was further supported by the ^{13}C NMR spectrum, which showed 8 signals. Carbon C5 adjacent to hydroxyl group (C-OH) appeared at δ 96.49 ppm. Carbon C3 attached to methyl group in the ring was observed at δ 122.55 ppm, while C4 attached to sulfur appeared at δ 157.75 ppm. Carbonyl carbon C2 appeared at δ 170.94 ppm. HRMS showed molecular ion peak at 188.05072, which confirmed the molecular formula $C_8H_{12}O_3S$ of **28**. Finally, the structure was confirmed by X-ray crystallography. Compound **28** was recrystallized from petroleum ether-ethyl acetate by diffusion method. The crystal data of **28**: $C_8H_{12}O_3S$, M. W. 188.24, crystal system: Orthorhombic, space group: Pbca, Unit cell dimensions: a = 11.1790(8) Å, α = 90°.; b = 8.0910(6) Å, β = 90°.; c = 21.1200(15) Å, γ = 90°, V = 1910.3(2) Å^3 Z = 8, Density (calculated) = 1.309 Mg/m^3 and other characteristic spectral information confirmed the structure; which is presented in experimental section and elucidated structure is presented in **Figure 24**.

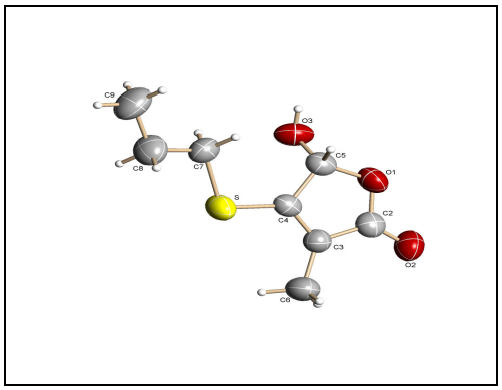
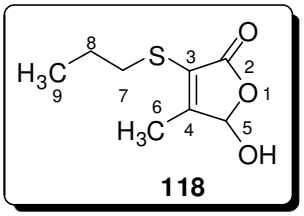


Figure 24. ORTEP diagram of compound **28**

Thus, the first total synthesis of (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one **28** was achieved by incorporation of methyl group *via* Gilman reagent and selective reduction of carbonyl group of anhydride functionality at C-5 position.



118

^{1}H NMR spectrum of **118** showed a triplet at δ 0.99 ppm integrating for three protons that was assigned to methyl group (C<u>H</u>$_3$-CH$_2$-CH$_2$-S-), while methylene protons adjacent to sulfur (C<u>H</u>$_2$-S) assigned at δ 2.97 ppm. One multiplet observed at δ 1.58 ppm corresponding to methylene protons in between other methylene and methyl group (CH$_3$-C<u>H</u>$_2$-CH$_2$). A sharp singlet at δ 2.11 ppm appeared for another three protons corresponding to the methyl group directly attached to the ring. H5 proton adjacent to OH group appeared as a singlet at δ 5.93 ppm. Thus, the characteristic splitting pattern of ^{1}H NMR spectrum revealed the structure of **118**. It was observed that protons of **28** appeared downfield as compared to the protons of **118**.

Further, confirmation of **118** was accomplished on the basis of ^{1}H NMR, ^{13}C NMR, ^{13}C DEPT spectral data.

The peak assignment was done on the basis of ^{1}H-^{1}H COSY experiments. The splitting pattern observed for compound **118** in ^{1}H NMR for H6 (methyl) was due to its long range coupling with proton at C5 through four bonds (**Figure 25**).

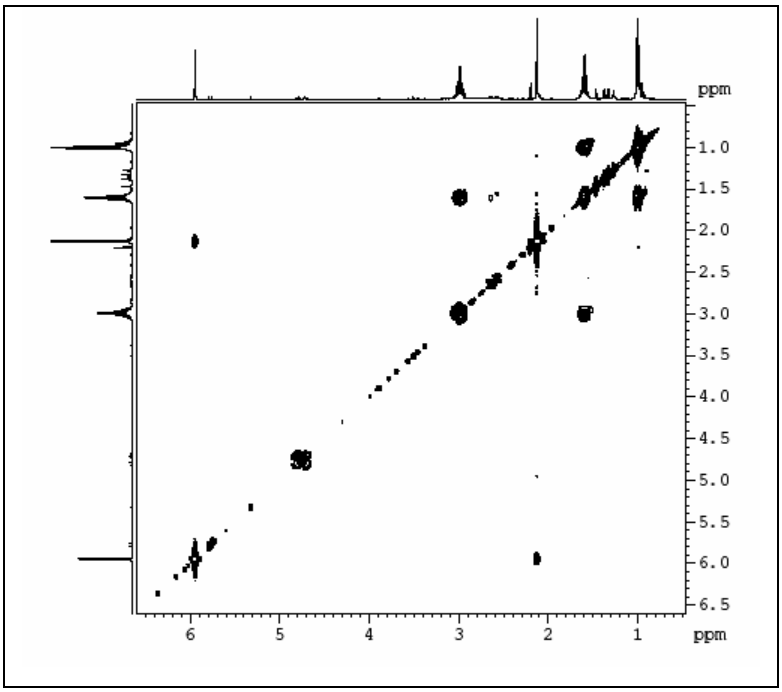


Figure 25. ^{1}H-^{1}H COSY Spectrum of compound **118**

Important COSY correlations:

H9 δ 0.99 ppm	with	H8 δ 1.59 ppm
H8 δ 1.59 ppm	with	H9 δ 0.99 and H7 δ 2.97 ppm
H6 δ 2.11 ppm	with	H5 δ 5.93 ppm
H7 δ 2.97 ppm	with	H7 δ 1.59 ppm
H5 δ 5.93 ppm	with	H6 δ 2.11 ppm

Further, compound **118** was confirmed by ^{1}H-^{13}C HMBC spectrum. In which H9 proton correlated with C7 and C8, whereas H8 correlated with C7 and C9. H6 (methyl) proton was mild correlation with C7 through five bonds and C2 of carbonyl through four bonds. H6 proton strongly correlated with C3, C4 and C5 through two or three bonds. H5 proton was strongly correlated with C4 and C2 and mild with C6. From the HMBC

spectrum, we concluded that the methyl group was placed in between hydroxyl group and sulfur group with strong bond (**Figure 26**).

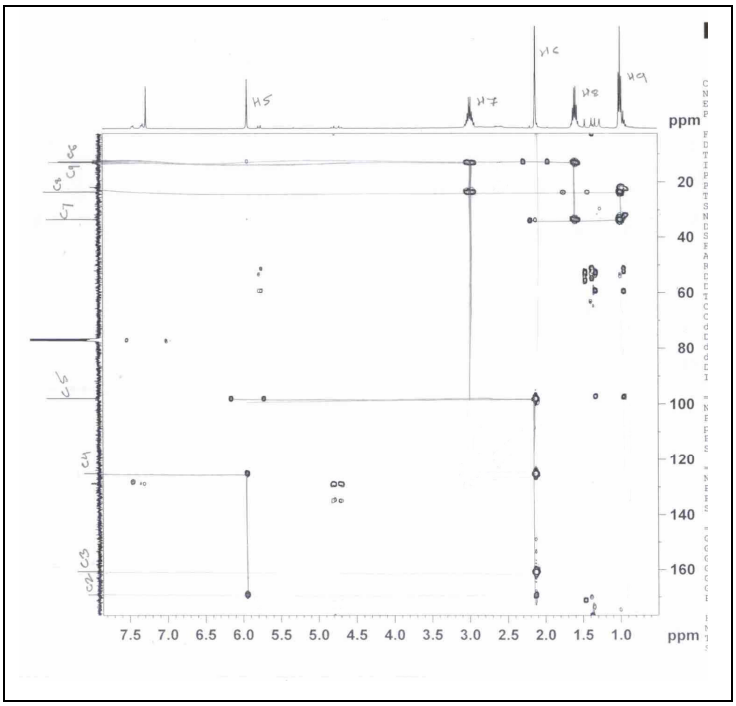
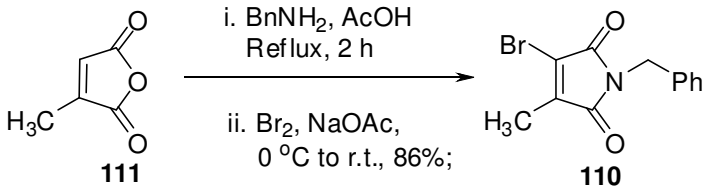


Figure 26. ^{1}H-^{13}C HMBC spectrum of compound **118**

Important ^{1}H-^{13}C HMBC correlations:

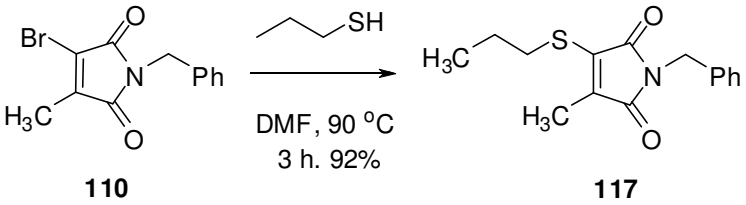
H9 δ 0.99 ppm	with C8 δ 23.51 and C7 δ 33.32 ppm
H8 δ 1.59 ppm	with C9 δ 13.01 and C7 δ 33.32 ppm
H6 δ 2.11 ppm	with C7 δ 33.32, C5 δ 98.07, C4 δ 125.22, C3 δ 160.71 and C2 δ 169.71 ppm
H7 δ 2.97 ppm	with C8 δ 23.51 and C9 δ 13.01 ppm
H5 δ 5.93 ppm	with C6 δ 12.73, C4 δ 125.22 and C2 δ 169.71 ppm

After completion of total synthesis **28** by employing Gilman strategy, it was decided to develop an alternative route involving mild reaction conditions. According to retrosynthetic approach II (**Scheme 18**), the methyl bromomaleimide **110** synthesized from commercially available citraconic anhydride **111** as per the reported procedure[80] as shown in **Scheme 26**.



Scheme 26.

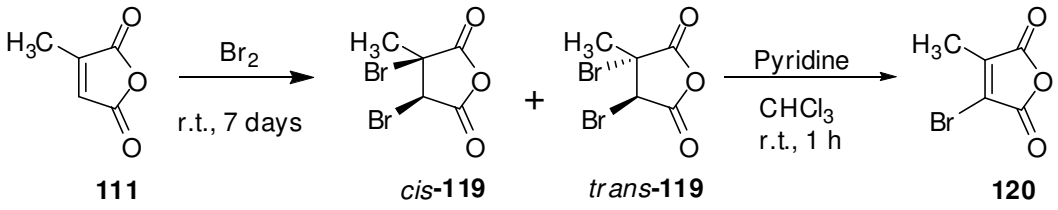
The nucleophilic substitution reaction of **110** with 1-propanethiol (1.5 equiv.) in DMF at 90 °C for 3 h afforded compound **117** in 92% yield (**Scheme 27**).



Scheme 27.

Alkaline hydrolysis of **117** and the subsequent reduction with $NaBH_4$ is described earlier for complete synthesis of **28**.

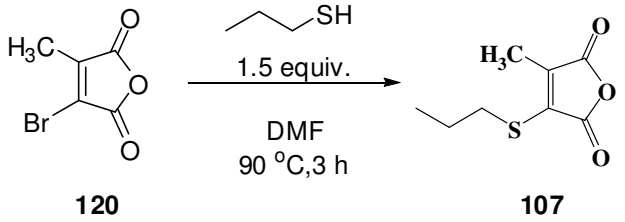
A short alternative route for the synthesis of **28** is described according to retrosynthetic approach III (**Scheme 19**). Bromination of **111** using molecular bromine at room temperature for 7 days afforded a mixture of *cis*- and *trans*- 2,3-dibromo-2-methyl succinic anhydride **119** and then treated with pyridine in chloroform at room temperature for 1 h to afford 3-bromo-4-methyl maleic anhydride **120** as shown in **Scheme 28**.[80]



Scheme 28.

The nucleophilic substitution reaction of **120** with 1-propanethiol in dimethylformamide at 90 °C for 3 h afforded anhydride **107** in 87% yield **(Scheme 29)**

and finally, the reduction of anhydride with $NaBH_4$ in methanol gave the target molecule **28**.



120 **107**

Scheme 29.

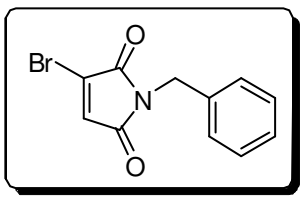
3.1.4 Conclusion

In conclusion, we have described a total synthesis of (±)-5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one by three different approaches. In the first approach, we have employed Gilman strategy and selective reduction of carbonyl group of anhydride functionality. In the second approach, we have avoided Gilman reagent for the synthesis of **28** and in the third approach, we have described the short route. A simple protocol for the synthesis of racemic 5-Hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one is represented.

3.1.5 Experimental Section

3.1.5.1 Procedure and Characterization data:

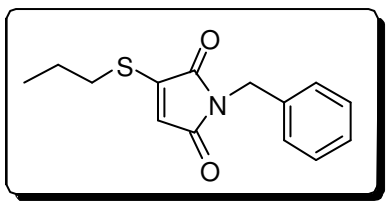
(A) Preparation of 3-bromo-1-benzyl-1*H*-pyrrole-2,5-dione (108):



A stirred mixture of maleic anhydride **109** (5.0 g, 51.0 mmol) and benzyl amine (5.55 mL, 51.0 mmol) in glacial acetic acid (50 mL) was refluxed for 2 h. After the solution was cooled to 0 °C, bromine (2.6 mL, 51.0 mmol) and sodium acetate (4.18 g, 51.0 mmol) were added. Further, the reaction mixture was stirred for 2 h at 0 °C to room temperature. Then ice-water (100.0 g) was added and extracted with dichloromethane (3 x 30 mL). The organic layer was separated and washed with water (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 2% ethyl acetate in petroleum ether, afforded compound **108** as yellow solid (4.9 g, 36%).

Molecular formula	**:**	$C_{11}H_8BrNO_2$
Nature	**:**	Yellow solid
Mp	**:**	51-52 °C
IR ($CHCl_3$, υ_{max})	**:**	3059, 2938, 2848, 1955, 1907, 1776, 1651, 1600, 1494, 1402, 1288, 925 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 4.63 (s, 2H), 6.79 (s, 1H), 7.18-7.28 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 42.27, 128.03, 128.51, 128.70, 131.36, 131.84, 135.56, 164.93, 168.09 ppm.
MS (EI) (*m/z*)	**:**	266 (M+1).

(B) Preparation of 1-benzyl-3-(propylthio)-1*H*-pyrrole-2,5-dione (114):

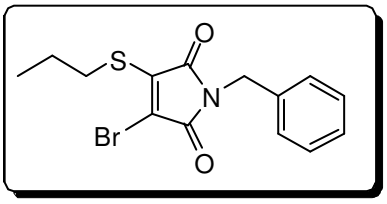


To a stirred solution of **108** (5.0 g, 18.79 mmol) in DMF (50 mL) was added 1-propanethiol (2.55 mL, 28.19 mmol). The resulting mixture was then heated at 90 °C for 4 h. Water (20 mL) was added to the reaction mixture and extracted with ethyl acetate (3 x 30 mL). The organic layer was separated, washed with water (2 x 10 mL), dried over Na_2SO_4 and then concentrated under vacuo to afford

the residue, which was purified by silica gel column chromatography using 2% ethyl acetate in petroleum ether to afford compound **114** (3.0 g, 61%) as pale yellow crystal.

Molecular formula	**:**	$C_{14}H_{15}NO_2S$
Nature	**:**	Pale yellow crystal
Mp	**:**	94-95 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3444, 3143, 3032, 2926, 2962, 2873, 1762, 1704, 1556, 1497, 1456, 1433, 1397, 1354, 1241, 1141, 1054 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.07 (t, *J* = 7.32 Hz, 3H), 1.76 (m, 2H), 2.88 (t, *J* = 7.20 Hz, 2H), 4.67 (s, 2H), 6.05 (s, 1H), 7.28-7.37 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 13.38, 21.10, 33.62, 41.59, 117.15, 127.73, 128.40, 128.57, 136.18, 151.64, 167.62, 169.26 ppm.
MS (EI) (*m/z*)	**:**	263 (M+2).

(C) Preparation of 1-benzyl-3-bromo-4-(propylthio)-1*H*-pyrrole-2,5-dione (116):

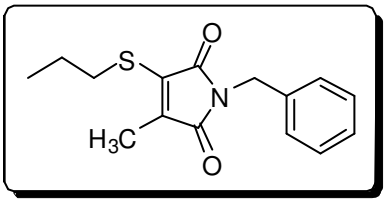


To a stirred solution of **114** (2.69 g, 10.3 mmol) in dichloromethane (30 mL) at 0 ^oC was added bromine (0.63 mL, 12.36 mmol) dropwise. The resulting solution was stirred for 5 min at 0 ^oC, and Et_3N (1.72 mL, 12.36 mmol) was added. After addition, the reaction mixture was brought to room temperature and stirred for additional 1 h. The progress of the reaction was monitored by TLC. Water (15 mL) was added to the reaction mixture and extracted with dichloromethane (3 x 20 mL). The organic layer was separated, washed with water (2 x 15 mL), dried over Na_2SO_4 and concentrated to afford the residue, which was purified by silica gel column chromatography using 1% ethyl acetate in petroleum ether, to afford compound **116** (3.2 g, 91.7 %) as yellow solid.

Molecular formula	**:**	$C_{14}H_{14}BrNO_2S$
Nature	**:**	Yellow solid
Mp	**:**	44-45 ^oC

IR ($CHCl_3$, υ_{max})	**:**	2900, 1750, 1715, 1530, 1432, 1391, 1200, 1177, 1080, 1040, 759, 665 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.04 (t, *J* = 7.20 Hz, 3H), 1.70 (m, 2H), 3.36 (t, *J* = 7.46 Hz, 2H), 4.69 (s, 2H), 7.26-7.36 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 12.98, 23.84, 32.69, 42.56, 116.51, 128.00, 128.56, 128.70, 135.70, 143.54, 164.02, 165.65 ppm.
MS (EI) (*m/z*)	**:**	341 (M+1).

(D) Preparation of 1-benzyl-3-methyl-4-(propylthio)-1*H*-pyrrole-2,5-dione (117):

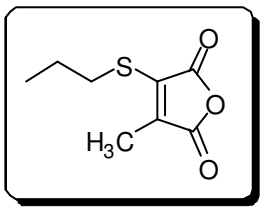


The following reaction was carried out under inert atmosphere. To a stirred solution of CuI (0.7 g, 3.68 mmol) in dry THF (20 mL) at -78 ^oC was added 1.6 M MeLi in hexane (5.75 mL, 9.2 mmol). The solution became dark black. The resulting mixture was stirred for 1 h. To the above solution, compound **116** (1.0 g, 3.06 mmol) in dry THF (5 mL) was added dropwise and stirred for 4 h at -78 ^oC. The progress of the reaction was monitored by TLC. The reaction mixture was quenched by the addition of saturated solution of NH_4Cl (20 mL) and extracted with diethyl ether (3 x 25 mL). The organic layer was separated, washed with water (2 x 10 mL), dried over Na_2SO_4 and concentrated under vacuo to afford yellow residue, which was purified by silica gel flash column chromatography using 1% ethyl acetate in petroleum ether to afford compound **117** (0.51 g, 63.0 %) as yellow oil.

Molecular formula	**:**	$C_{15}H_{17}NO_2S$
Nature	**:**	Pale yellow liquid
IR ($CHCl_3$, υ_{max})	**:**	3367, 2932, 1704, 1603, 1400, 1348, 1070 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.93 (t, *J* = 7.33 Hz, 3H), 1.56 (m, 2H), 1.92 (s, 3H), 3.16 (t, *J* = 7.45 Hz, 2H), 4.57 (s, 2H), 7.19-7.28 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 9.56, 13.04, 23.91, 33.28, 41.77, 127.73, 128.38, 128.61, 135.92, 136.42, 138.29, 167.90, 169.70 ppm.
MS (EI) (*m/z*)	**:**	275 (M^+).

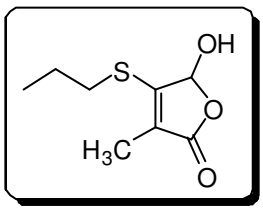
(E) Preparation of 3-methyl-4-(propylthio)furan-2,5-dione (107):



To a stirred solution of **117** (0.1 g, 0.36 mmol) in absolute ethanol (5 mL) was added dropwise aq. 5N KOH (10 mL) solution. The resulting mixture was then refluxed for 2 h with stirring. The reaction mixture was concentrated and the residue was cooled to 0 ^oC and acidified with 2N HCl, then extracted with ethyl acetate (3 x 15 mL). The organic layer was separated, washed with water (2 x 5 mL), dried over Na_2SO_4, filtered and evaporated. Purification by column chromatography using 5% ethyl acetate in petroleum ether afforded **107** as dark yellow liquid (0.040 g, 60%).

Molecular formula	**:**	$C_8H_{10}O_3S$
Nature	**:**	Dark yellow liquid
IR ($CHCl_3$, υ_{max})	**:**	3342, 2986, 2306, 1825, 1766, 1712, 1600, 1421, 1265, 1021, 896, 739, 705, 665 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.03 (t, J = 7.33 Hz, 3H), 1.68 (m, 2H), 2.05 (s, 3H), 3.31 (t, J = 7.46 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 9.99, 12.86, 23.76, 33.04, 136.00, 142.43, 161.95, 163.84 ppm.
MS (EI) (*m/z*)	**:**	187 (M+1).

(F) Preparation of (±)-5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one (28):

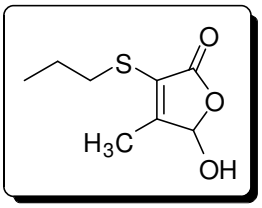


To a stirred solution of compound **107** (0.05 g, 0.268 mmol) in dry MeOH (1 mL), was added sodium borohydride (0.005 g, 0.0134 mmol) at 0 ^oC and stirred for 10 minutes. The reaction was monitored by TLC. After the reaction was complete, ice water (5 mL) was added and extracted with ethyl acetate (3 x 10 mL). The organic phase was washed with water, dried over Na_2SO_4, filtered and concentrated in

vacuo to afford the crude product, which was purified by silica gel flash column chromatography using 10% ethyl acetate in petroleum ether to afford racemic **28** (0.032 g, 63.5%) as white crystalline solid, and racemic **118** (0.014 g, 27.5%) as pale yellow liquid.

Molecular formula	**:**	$C_8H_{12}O_3S$
Nature	**:**	White crystalline solid
Mp	**:**	64-66 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3432, 2984, 1735, 1446, 1374, 1246, 939, 757 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.05 (t, *J* = 7.3 Hz, 3H), 1.71 (m, 2H), 1.84 (s, 3H), 3.08 (m, 2H), 4.27 (s, 1H), 6.06 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	**:**	δ 9.12, 13.16, 23.39, 32.32, 96.49, 122.55, 157.75, 170.94 ppm.
HR-MS (EI): $C_8H_{12}O_3S$	**:**	Calcd. : 188.05072, Found : 188.05071 [M^+].

(F) Preparation of (±)-5-Hydroxy-4-methyl-3-propylsulfanyl-5*H*-furan-2-one (118):

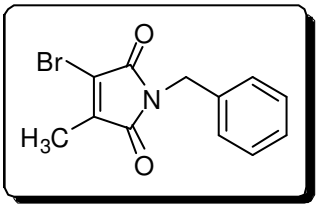


Molecular formula	**:**	$C_8H_{12}O_3S$
Nature	**:**	Pale yellow liquid
IR ($CHCl_3$, υ_{max})	**:**	3393, 2965, 2932, 2873, 1746, 1707, 1635, 1456, 1381, 1339, 1294, 1128, 1087, 1009, 946, 755, 699 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.99 (t, *J* = 7.34 Hz, 3H), 1.59 (m, 2H), 2.11 (s, 3H), 2.97 (t, *J* = 7.45 Hz, 2H), 5.93 (s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	**:**	δ 12.73, 13.01, 23.51, 33.32, 98.07, 125.22,

160.71, 169.19 ppm.

MS (EI) (***m/z***) **:** 188 (M^+).

(G) Preparation of 1-Benzyl-3-bromo-4-methylmaleimide (110):



To a stirred solution of citraconic anhydride **111** (15.0 mL, 167 mmol) in glacial acetic acid (100 mL), was added benzylamine (18.0 mL, 167 mmol) dropwise in an ice-cooled bath. The mixture was then heated to reflux for 2-3 h. After cooling, sodium acetate (13.7 g, 167 mmol) and bromine (12.9 mL, 251 mmol) were added. The mixture was then heated to reflux for another 2-3 h. After cooling, the mixture was poured into ice-water (100 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over sodium sulfate, and solvent was removed to give the crude product, which was purified by recrystallization from ethyl acetate to afford compound **110** (40.2 g, 86.0 %).

Molecular formula **:** $C_{12}H_{10}BrNO_2$

Nature **:** Yellow solid

Mp **:** 60-62 ^oC

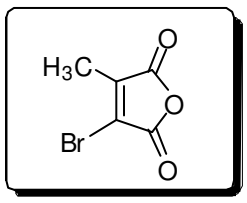
IR ($CHCl_3$, υ_{max}) **:** 3470, 3059, 2938, 2848, 1955, 1907, 1776, 1651, 1600, 1494, 1402, 1288, 925 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 2.02 (s, 3H), 4.68 (s, 2H), 7.26-7.35 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) **:** δ 10.55, 42.18, 124.86, 128.45, 128.59, 128.88, 135.76, 142.18., 165.04, 168.88 ppm.

MS (EI) (***m/z***) **:** 280 (M^+).

(H) Preparation of 3-bromo-4-methylmaleic anhydride (120):



A mixture of **111** (11.2 g, 1 mol) and molecular bromine (17.67 g, 1.1 mol) in a stoppered round bottom flask, was stirred at room temperature for a week. The progress of the reaction was monitored by ^{1}H NMR. The excess bromine was removed by bubbling nitrogen though the reaction mixture in a well ventilated hood, followed by evaporation

under reduced pressure until the clear mixture was only slightly red. ^{1}H NMR of the crude product showed that this was a 50:1 mixture of adduct and starting material by their olefinic signals. The product was a mixture of *trans*- and *cis*- 2,3-dibromo-2-methyl succinic anhydride **119**. To this crude adduct in chloroform (50 mL), cooled in an ice bath, was added pyridine (7.91 g, 1 mol) dropwise over a period of 10 min. with the internal temperature maintained below 20 ^{o}C throughout the addition. The resulting clear reaction mixture was stirred at room temperature for approximately 1 h. The reaction mixture was monitored by TLC until the reaction was completed. The reaction mixture was washed with water, dried over sodium sulfate and concentrated on rota vapor gave a crude product, which was recrystallized in pet ether to afford pure 3-bromo-4-methylmaleic anhydride **120** (16.5 g, 86.7%).

Molecular formula	**:**	$C_5H_3BrO_3$
Nature	**:**	White crystalline solid
Mp	**:**	74-75 ^{o}C
IR ($CHCl_3$, υ_{max})	**:**	1830, 1765, 1236, 1047, 906, 723, 677 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 2.17 (s, 3H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 11.30, 126.78, 145.43, 160.00, 163.42 ppm.
MS (EI) (***m/z***)	**:**	190 (M^+).

Table 1. Crystal data and structure refinement for compound **28**.

Empirical formula	$C_8H_{12}O_3S$	
Formula weight	188.24	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 11.1790(8) Å	α= 90°.
	b = 8.0910(6) Å	β= 90°.
	c = 21.1200(15) Å	γ = 90°.
Volume	1910.3(2) $Å^3$	
Z	8	
Density (calculated)	1.309 Mg/m^3	
Crystal size	0.38 x 0.21 x 0.03 mm^3	
Reflections collected	13976	
Completeness to theta = 25.00°	99.2 %	
Goodness-of-fit on F^2	1.102	
Final R indices [I>2sigma(I)]	R1 = 0.0674, wR2 = 0.1570	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound **28**. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	858(1)	4188(2)	825(1)	66(1)
O(1)	2925(2)	5646(3)	2259(1)	62(1)
O(2)	4778(2)	5607(3)	1881(1)	72(1)
O(3)	1013(2)	6602(3)	2087(1)	68(1)
C(4)	1952(3)	4771(4)	1355(2)	45(1)
C(3)	3122(3)	4818(4)	1228(2)	49(1)
C(5)	1732(3)	5248(4)	2028(2)	52(1)
C(2)	3721(3)	5369(4)	1796(2)	54(1)
C(7)	-524(3)	4246(5)	1270(2)	60(1)
C(6)	3772(3)	4379(6)	636(2)	74(1)
C(8)	-1496(3)	3516(6)	868(2)	80(1)
C(9)	-2686(3)	3506(6)	1198(3)	89(2)

Table 3. Bond lengths [Å] and angles [°] for compound **28**.

Bond lengths [Å]		**Bond angles [°]**	
S-C(4)	1.725(3)	C(4)-S-C(7)	105.14(17)
S-C(7)	1.809(3)	C(2)-O(1)-C(5)	109.1(2)
O(1)-C(2)	1.340(4)	C(5)-O(3)-H(3)	109.5
O(1)-C(5)	1.456(4)	C(3)-C(4)-C(5)	110.2(3)
O(2)-C(2)	1.211(4)	C(3)-C(4)-S	124.9(3)
O(3)-C(5)	1.365(4)	C(5)-C(4)-S	124.9(2)
O(3)-H(3)	0.8200	C(4)-C(3)-C(2)	107.2(3)
C(4)-C(3)	1.335(4)	C(4)-C(3)-C(6)	129.8(3)
C(4)-C(5)	1.493(5)	C(2)-C(3)-C(6)	123.0(3)
C(3)-C(2)	1.444(5)	O(3)-C(5)-O(1)	109.3(3)
C(3)-C(6)	1.490(5)	O(3)-C(5)-C(4)	113.0(3)
C(5)-H(5)	0.9800	O(3)-C(5)-C(4)	113.0(3)
C(7)-C(8)	1.500(5)	O(1)-C(5)-C(4)	103.0(2)
C(7)-H(7A)	0.9700	O(3)-C(5)-H(5)	110.4
C(7)-H(7B)	0.9700	O(1)-C(5)-H(5)	110.4
C(6)-H(6A)	0.9600	C(4)-C(5)-H(5)	110.4
C(6)-H(6B)	0.9600	O(2)-C(2)-O(1)	120.9(3)
C(6)-H(6C)	0.9600	O(2)-C(2)-C(3)	128.6(3)
C(8)-C(9)	1.501(5)	O(1)-C(2)-C(3)	110.5(3)
C(8)-H(8A)	0.9700	C(8)-C(7)-S	108.4(3)
C(8)-H(8B)	0.9700	C(8)-C(7)-H(7A)	110.0
C(9)-H(9A)	0.9600	S-C(7)-H(7A)	110.0
C(9)-H(9B)	0.9600	C(8)-C(7)-H(7B)	110.0
C(9)-H(9C)	0.9600	S-C(7)-H(7B)	110.0
		H(7A)-C(7)-H(7B)	108.4
		C(3)-C(6)-H(6A)	109.5
		C(3)-C(6)-H(6B)	109.5
		H(6A)-C(6)-H(6B)	109.5
		C(3)-C(6)-H(6C)	109.5
		H(6A)-C(6)-H(6C)	109.5
		H(6B)-C(6)-H(6C)	109.5
		C(7)-C(8)-C(9)	112.4(4)
		C(7)-C(8)-H(8A)	109.1
		C(9)-C(8)-H(8A)	109.1
		C(7)-C(8)-H(8B)	109.1
		C(9)-C(8)-H(8B)	109.1
		H(8A)-C(8)-H(8B)	107.9
		C(8)-C(9)-H(9A)	109.5
		C(8)-C(9)-H(9B)	109.5
		H(9A)-C(9)-H(9B)	109.5
		C(8)-C(9)-H(9C)	109.5
		H(9A)-C(9)-H(9C)	109.5
		H(9B)-C(9)-H(9C)	109.5

Table 4. Torsion angles [°] for compound **28**.

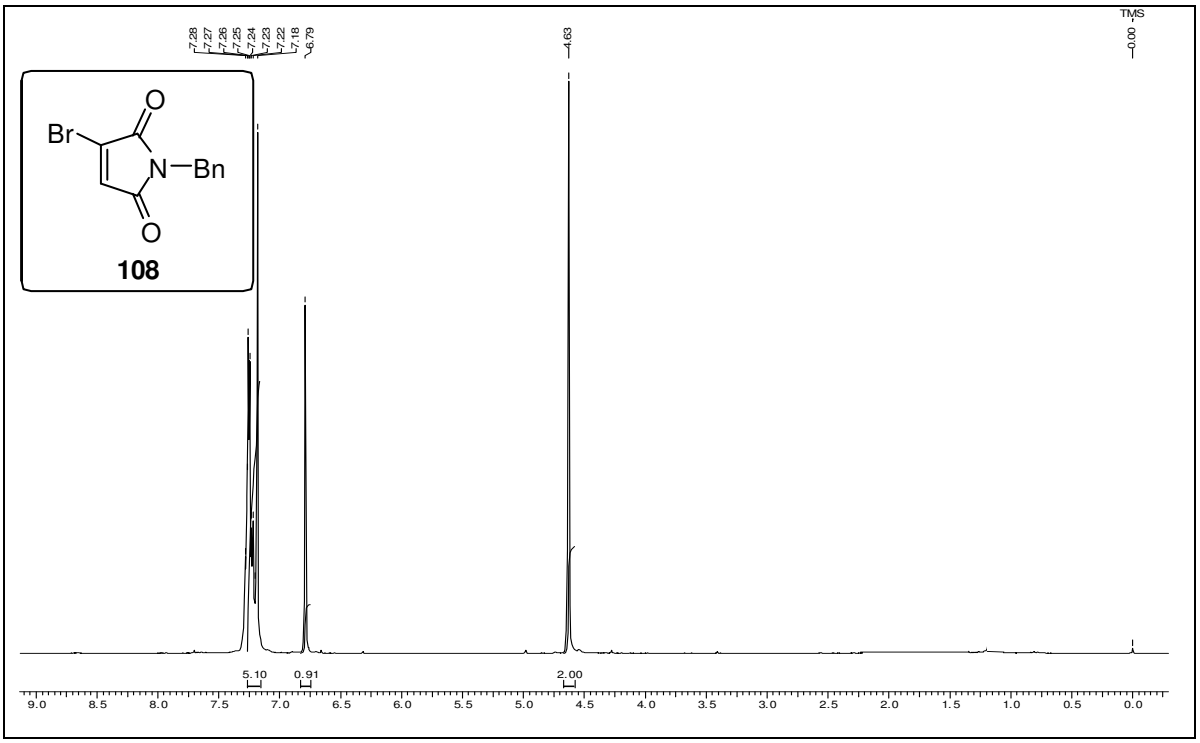
C(7)-S-C(4)-C(3)	176.7(3)
C(7)-S-C(4)-C(5)	-1.4(3)
C(5)-C(4)-C(3)-C(2)	-1.8(4)
S-C(4)-C(3)-C(2)	180.0(2)
C(5)-C(4)-C(3)-C(6)	177.1(4)
S-C(4)-C(3)-C(6)	-1.1(6)
C(2)-O(1)-C(5)-O(3)	-122.8(3)
C(2)-O(1)-C(5)-C(4)	-2.4(3)
C(3)-C(4)-C(5)-O(3)	120.4(3)
S-C(4)-C(5)-O(3)	-61.3(4)
C(3)-C(4)-C(5)-O(1)	2.5(4)
S-C(4)-C(5)-O(1)	-179.2(2)
C(5)-O(1)-C(2)-O(2)	-179.7(3)
C(5)-O(1)-C(2)-C(3)	1.5(4)
C(4)-C(3)-C(2)-O(2)	-178.6(3)
C(6)-C(3)-C(2)-O(2)	2.5(6)
C(4)-C(3)-C(2)-O(1)	0.2(4)
C(6)-C(3)-C(2)-O(1)	-178.8(3)
C(4)-S-C(7)-C(8)	-171.8(3)
S-C(7)-C(8)-C(9)	179.9(3)

3.1.6 Spectral data

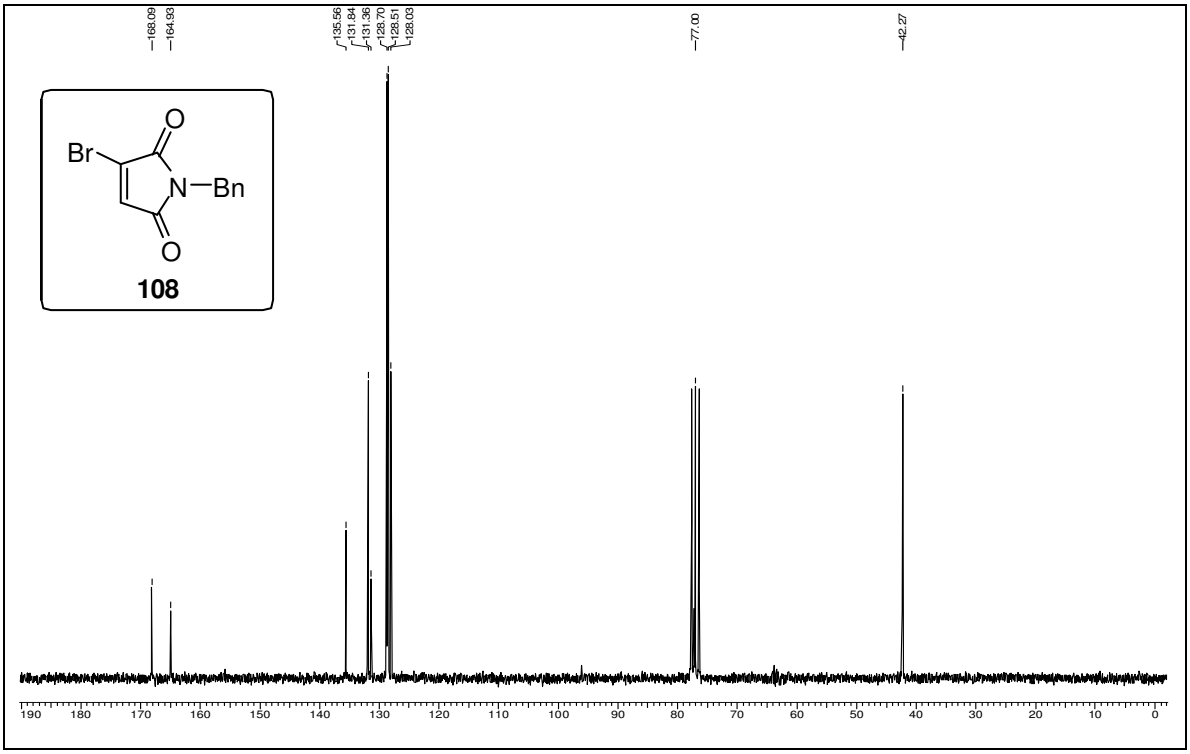
Table 5: ^{1}H and ^{13}C NMR spectrum of compounds are given below:

Sr. No.	Spectra
1	^{1}H NMR and ^{13}C NMR spectra of compound **108**
2	^{1}H NMR and ^{13}C NMR spectra of compound **114**
3	^{1}H NMR and ^{13}C NMR spectra of compound **116**
4	^{1}H NMR and ^{13}C NMR spectra of compound **117**
5	^{1}H NMR and ^{13}C NMR spectra of compound **107**
6	^{1}H NMR and ^{13}C NMR spectra of compound **28**
7	^{1}H NMR and ^{13}C NMR spectra of compound **118**
8	^{1}H NMR and ^{13}C NMR spectra of compound **110**
9	^{1}H NMR and ^{13}C NMR spectra of compound **120**

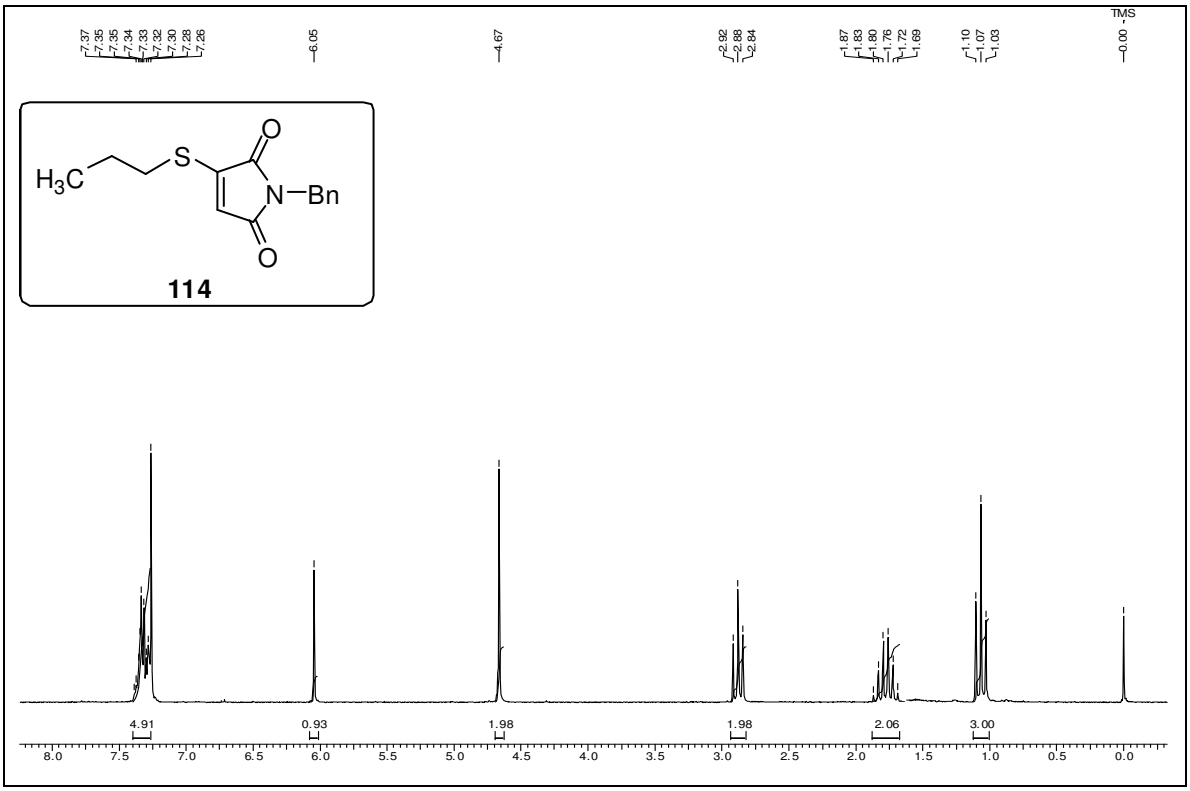
1. ^{1}H NMR spectra of compound **108**:



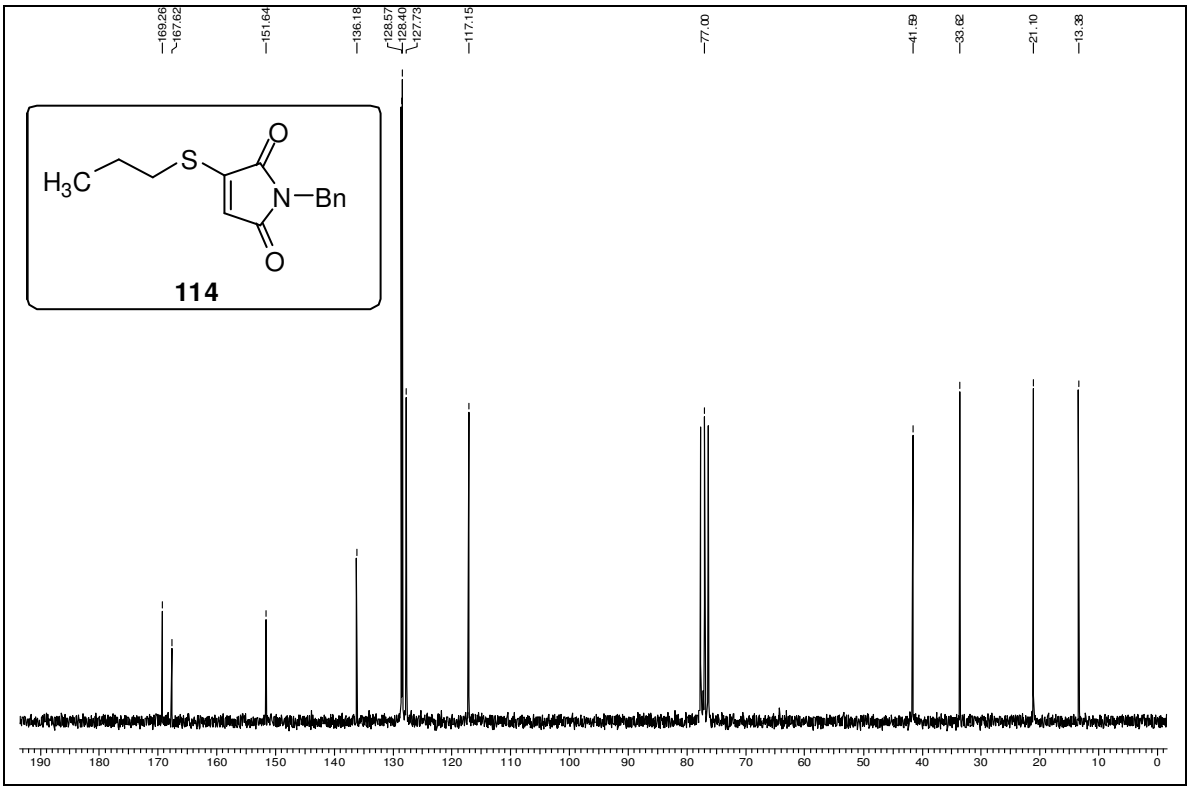
1. ^{13}C NMR spectra of compound **108**:



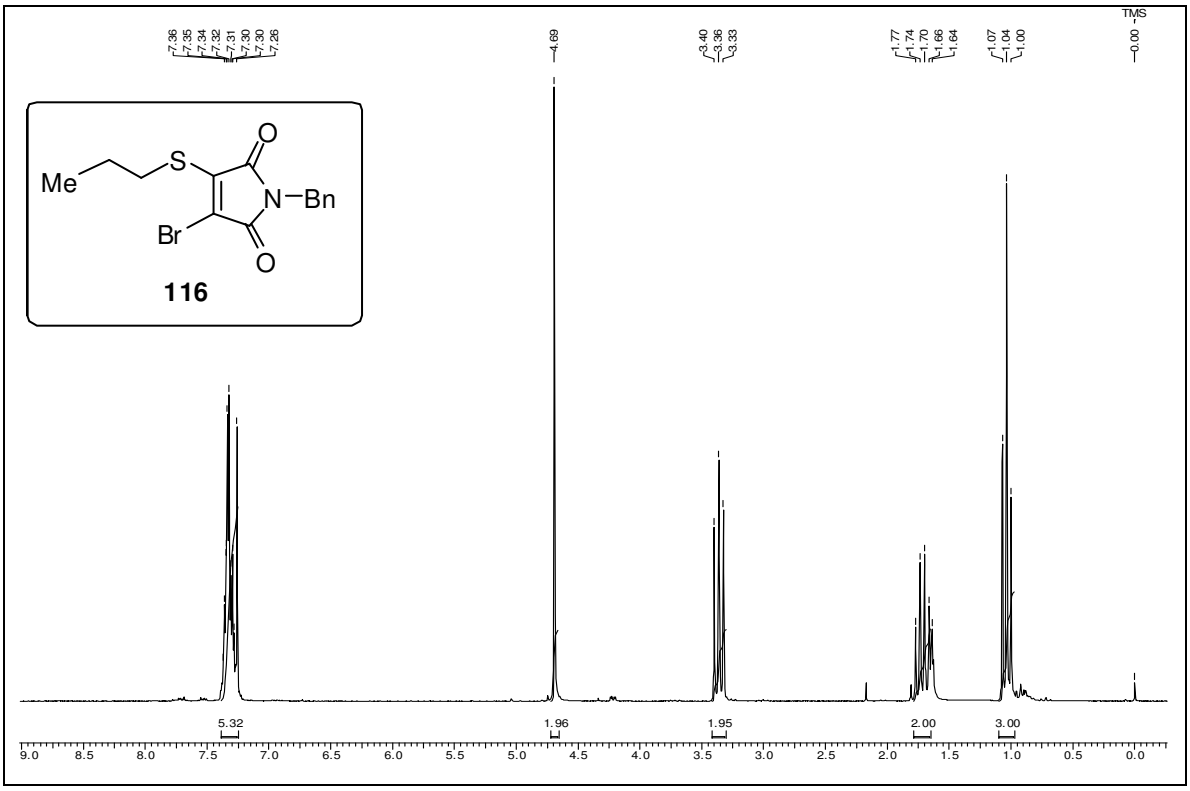
2. ^{1}H NMR spectra of compound **114**:



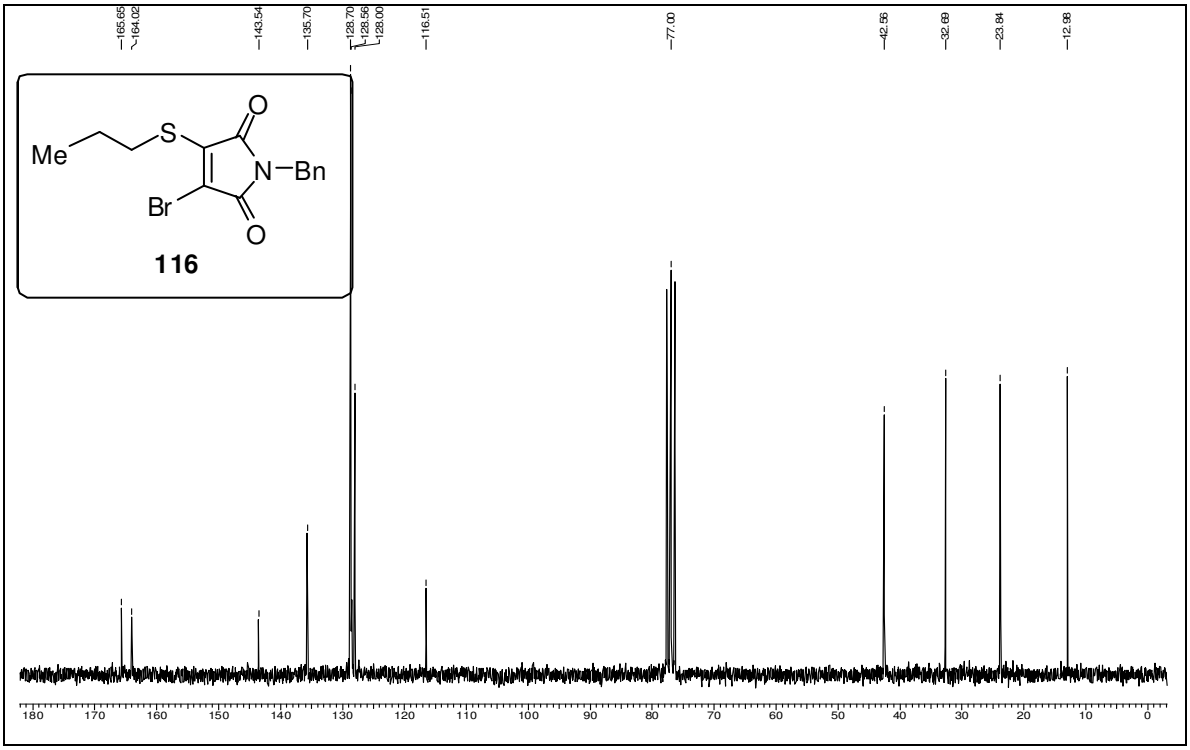
2. ^{13}C NMR spectra of compound **114**:



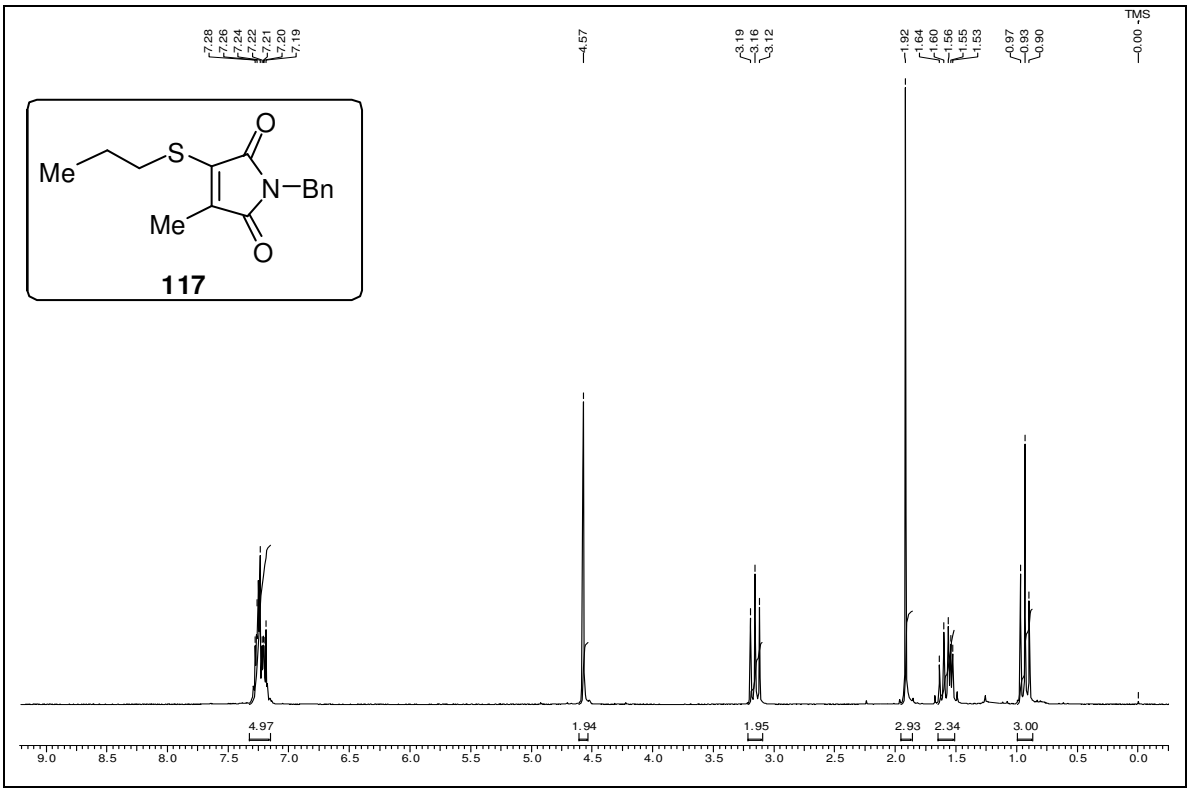
3. ^{1}H NMR spectra of compound **116**:



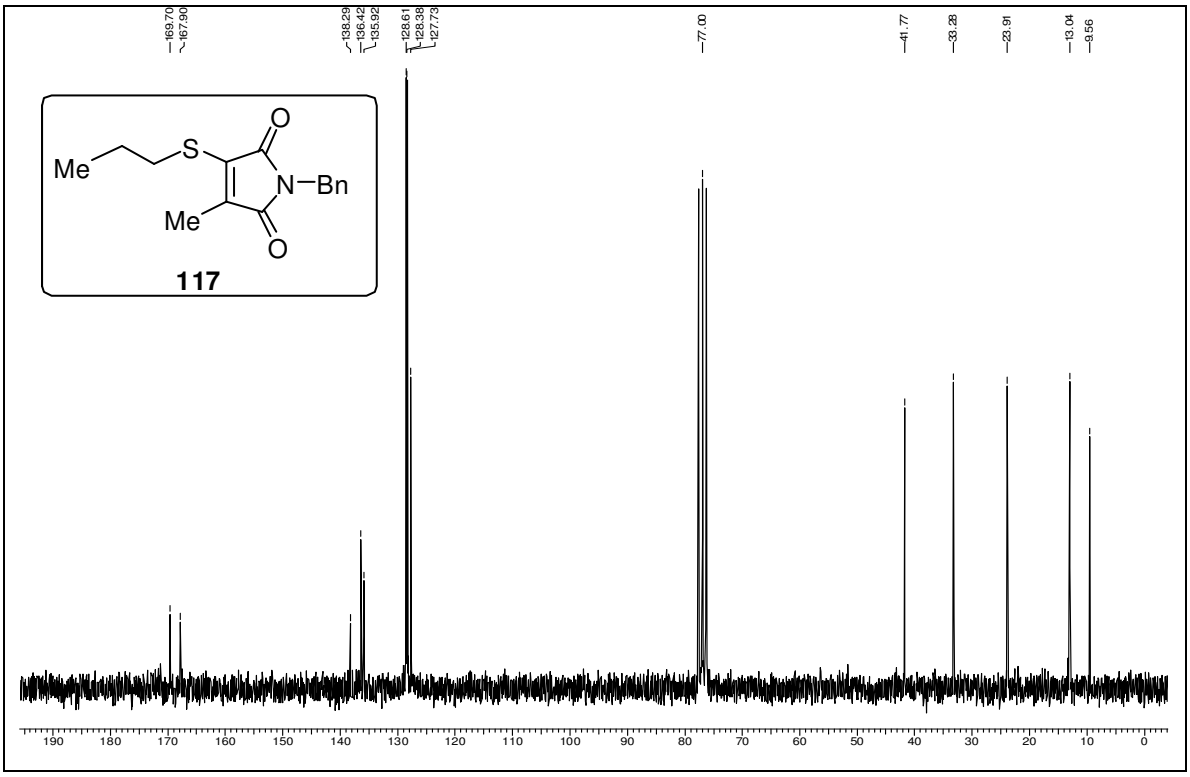
3. ^{13}C NMR spectra of compound **116**:



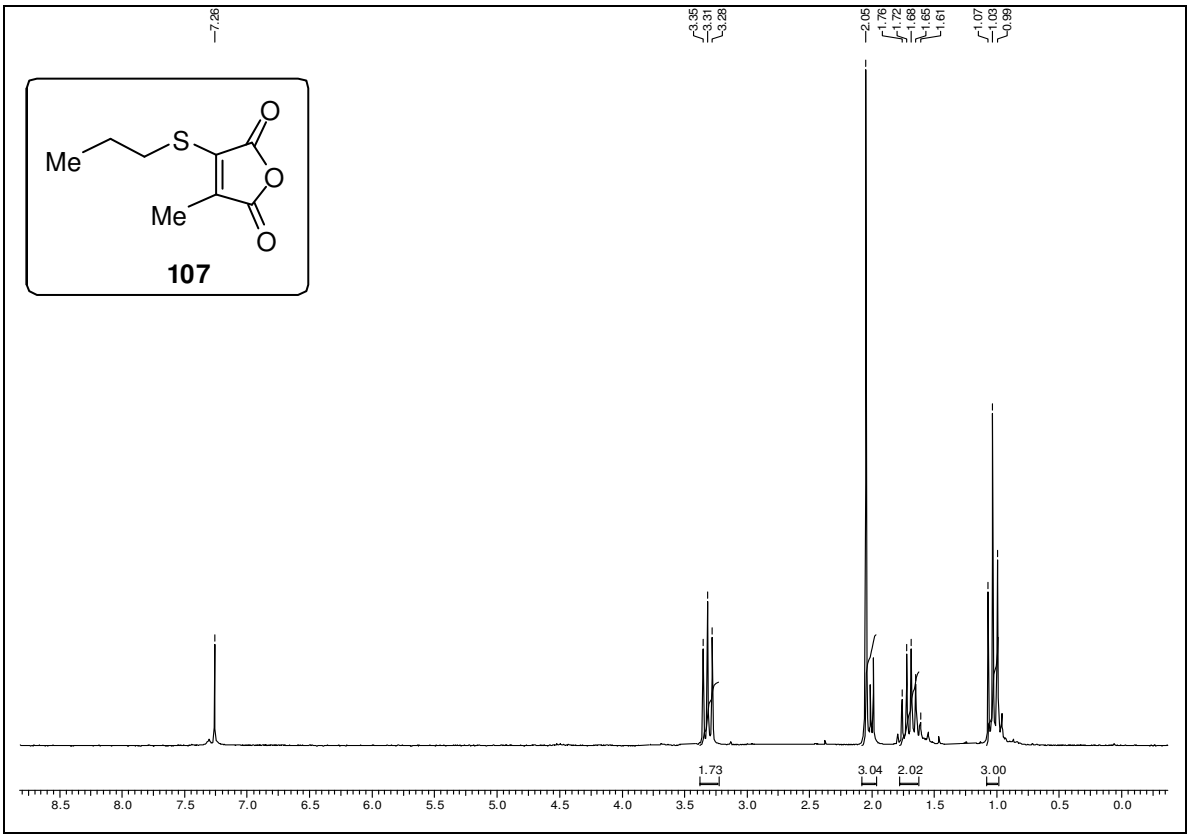
4. ^{1}H NMR spectra of compound **117**:



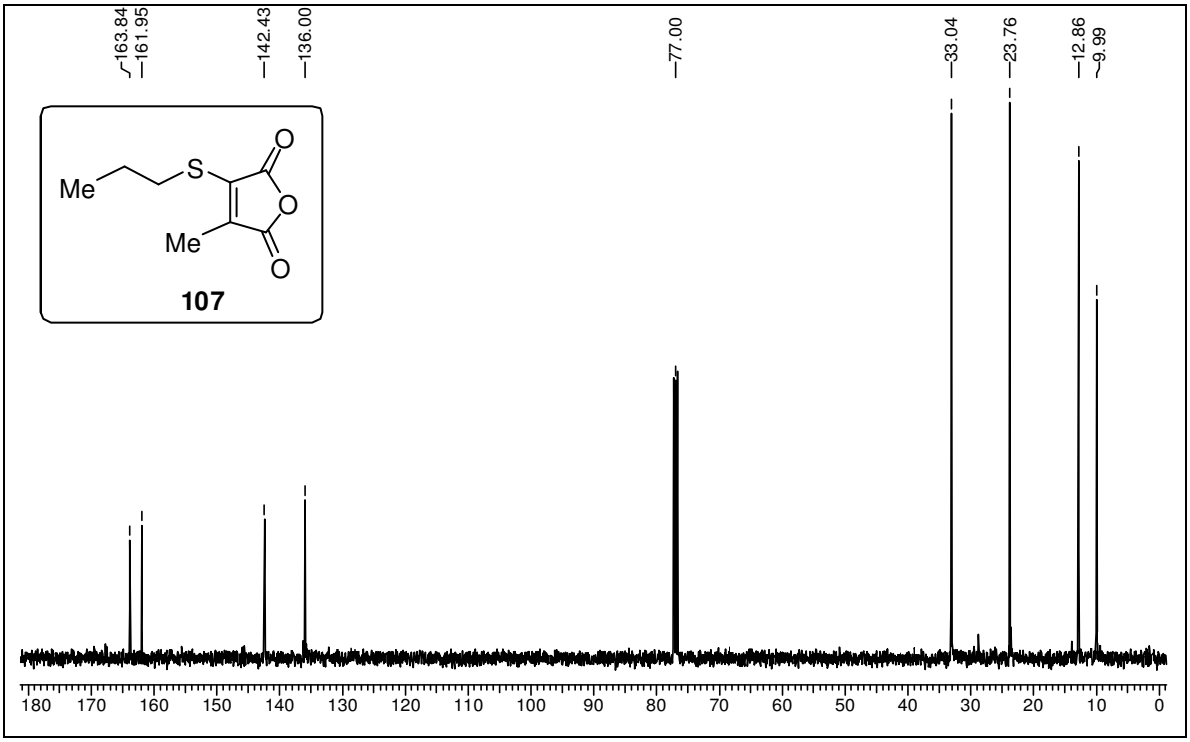
4. ^{13}C NMR spectra of compound **117**:



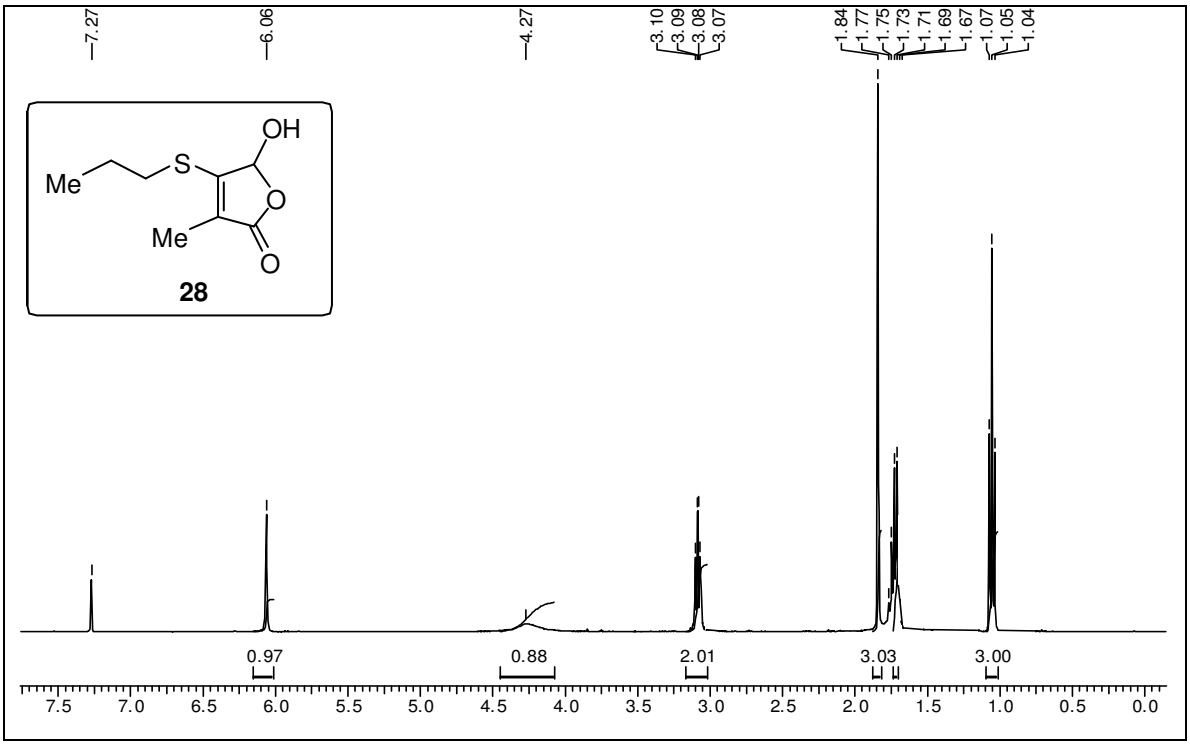
5. ^{1}H NMR spectra of compound **107**:



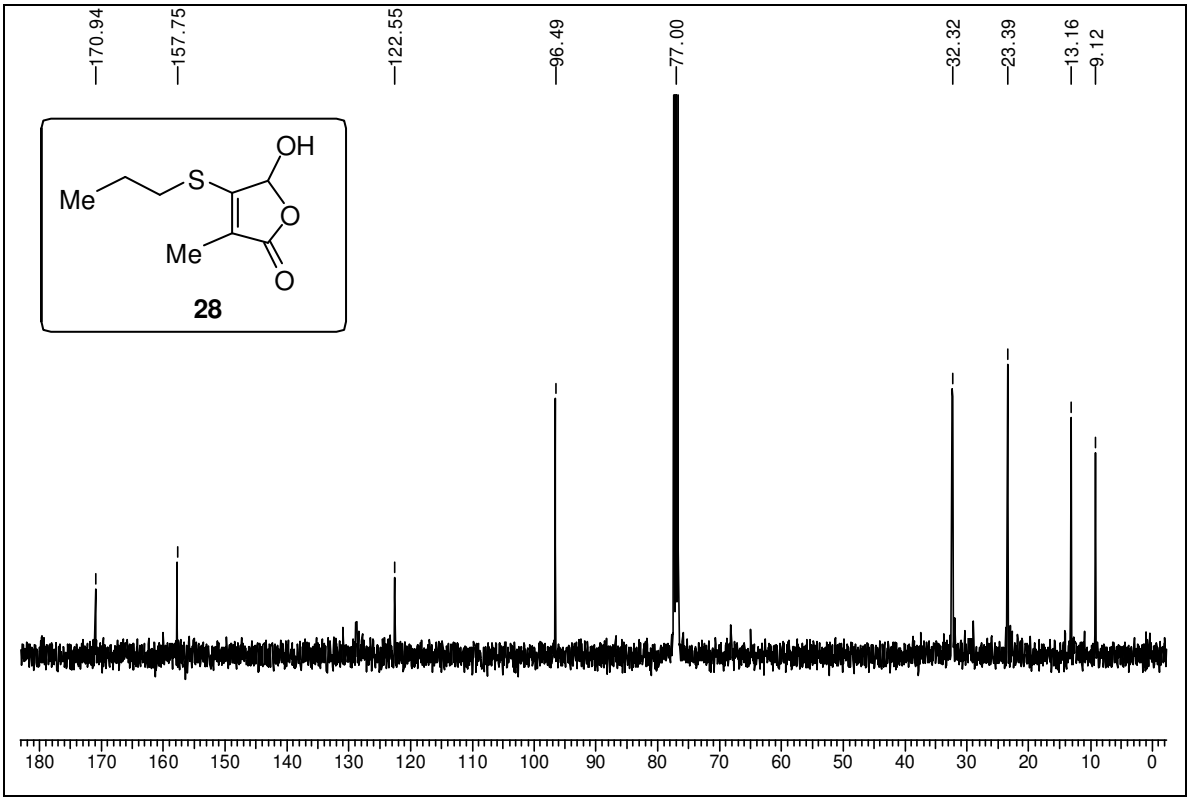
5. ^{13}C NMR spectra of compound **107**:



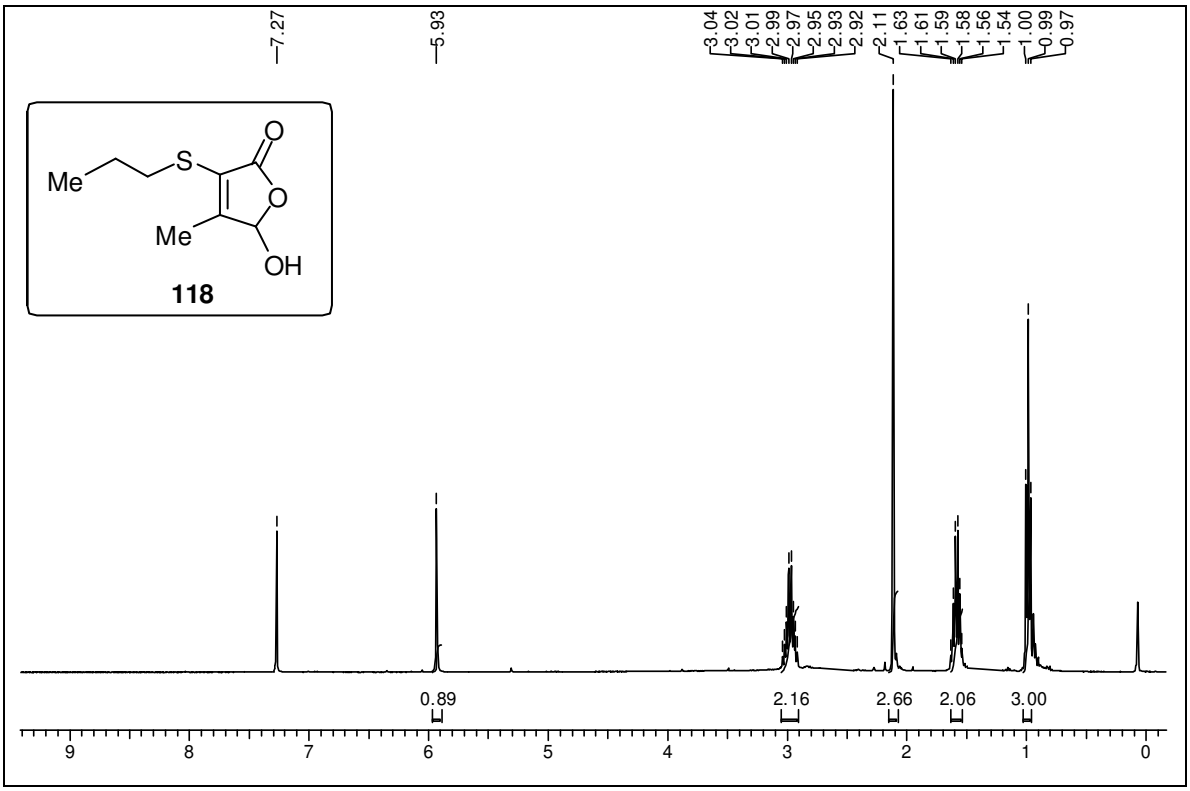
6. ^{1}H NMR spectra of compound **28**:



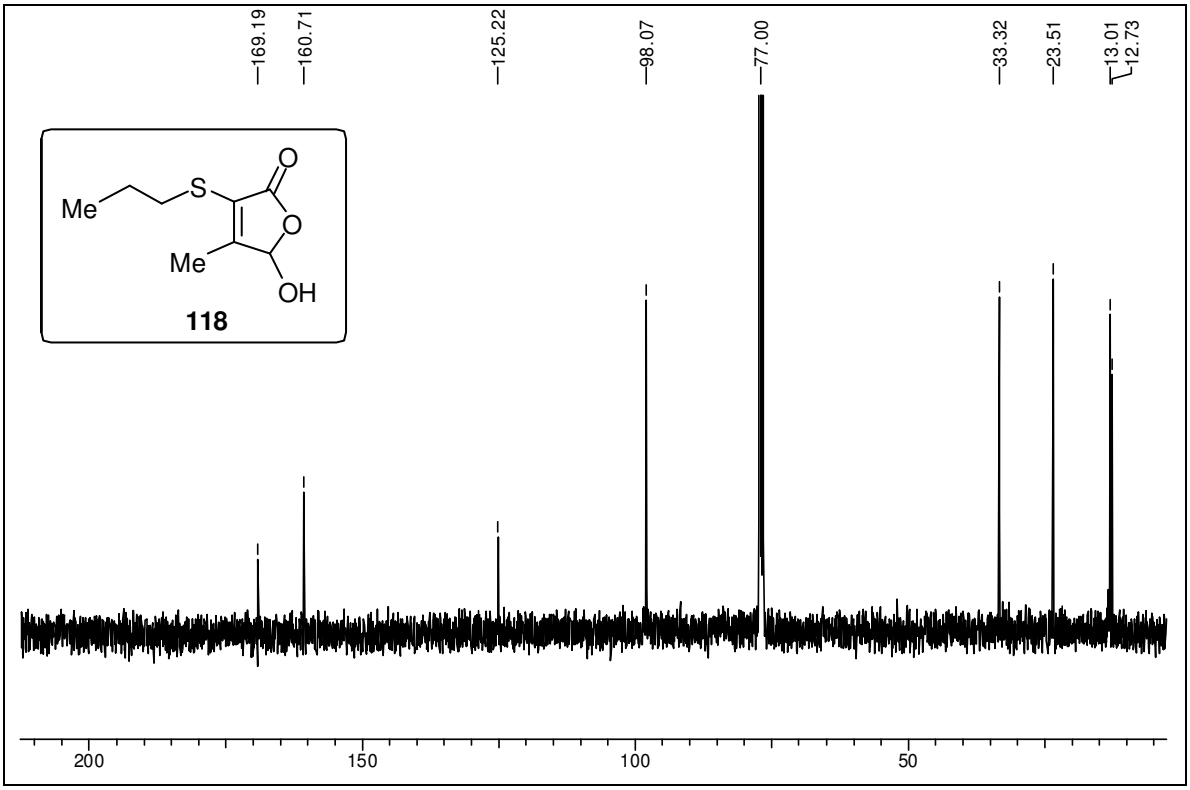
6. ^{13}C NMR spectra of compound **28**:



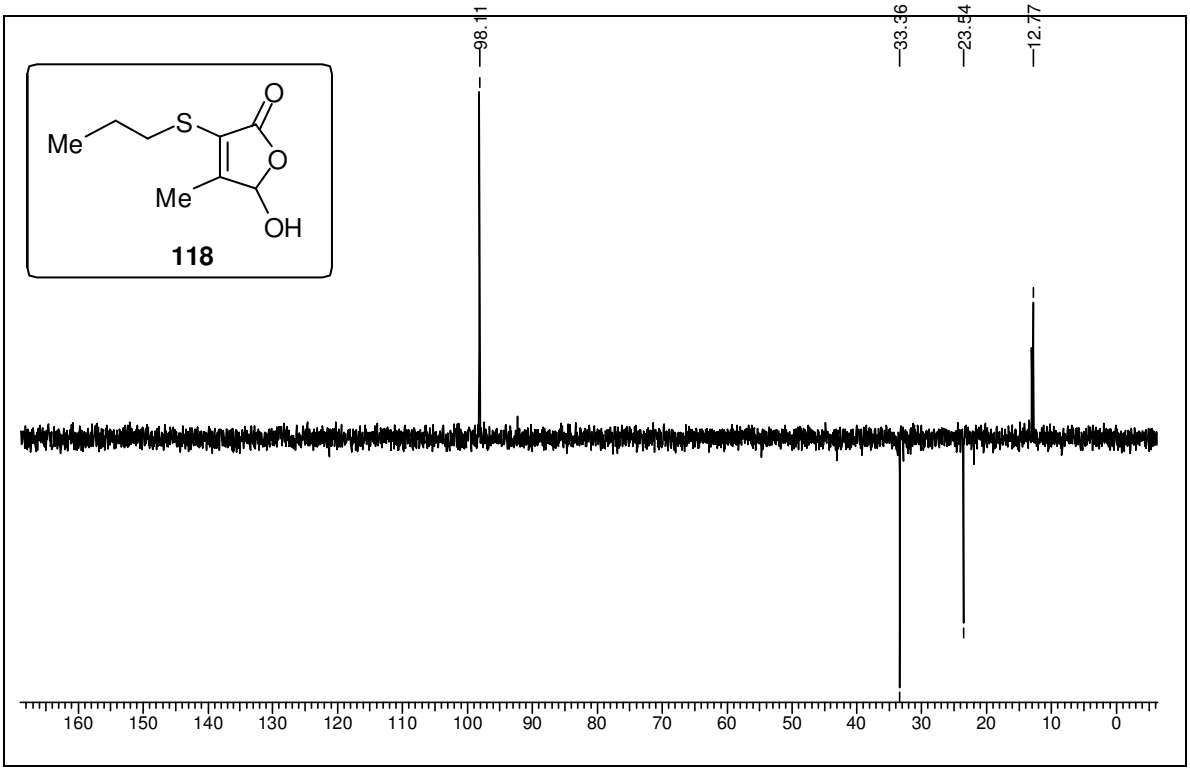
7. ^{1}H NMR spectra of compound **118**:



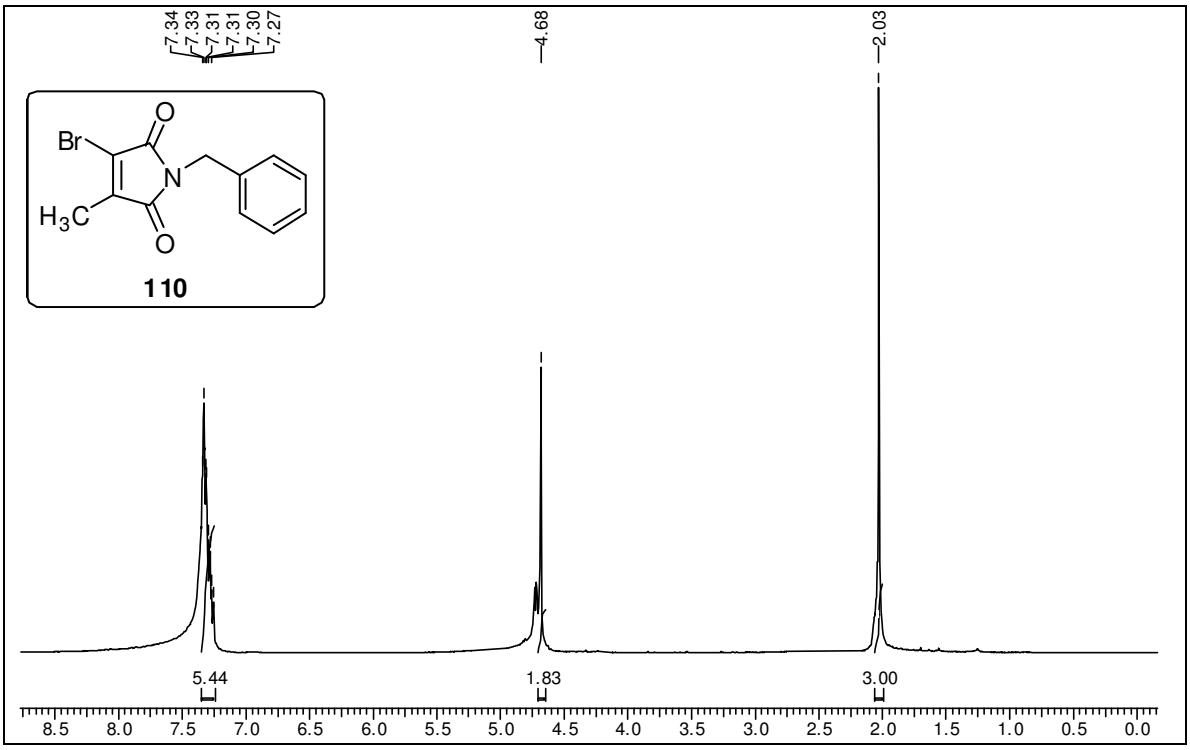
7. ^{13}C NMR spectra of compound **118**:



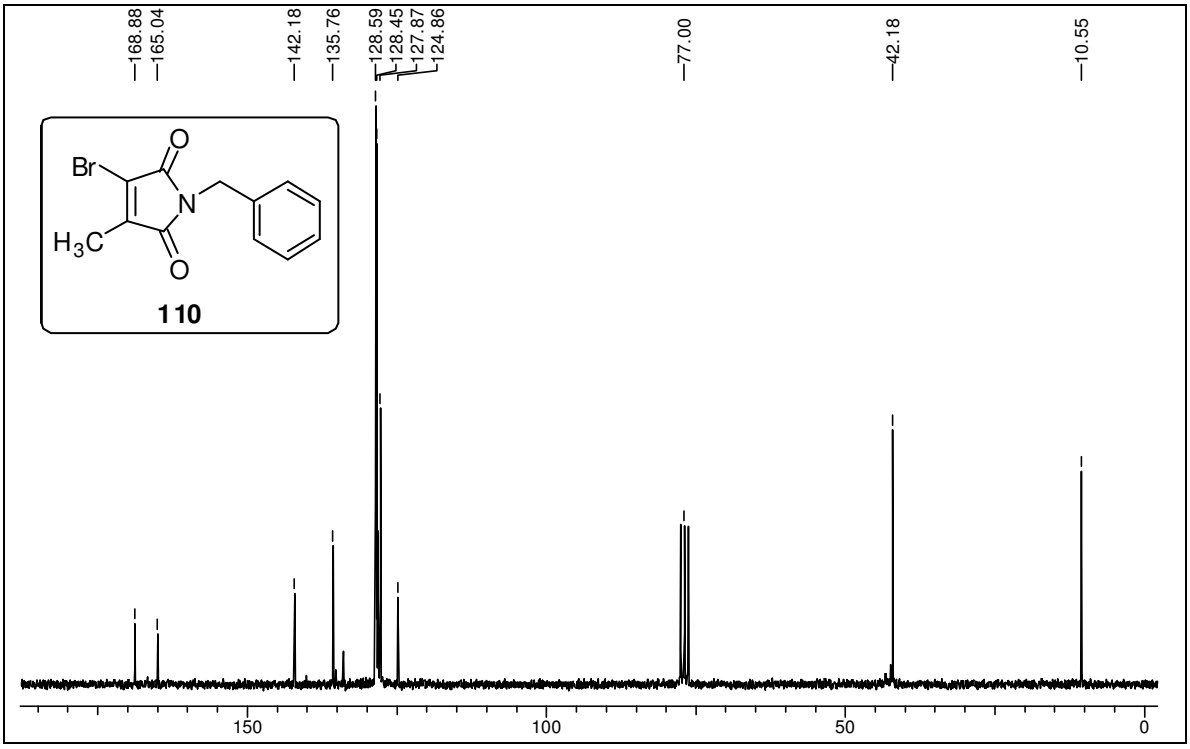
7. ^{13}C NMR DEPT spectra of compound **118**:



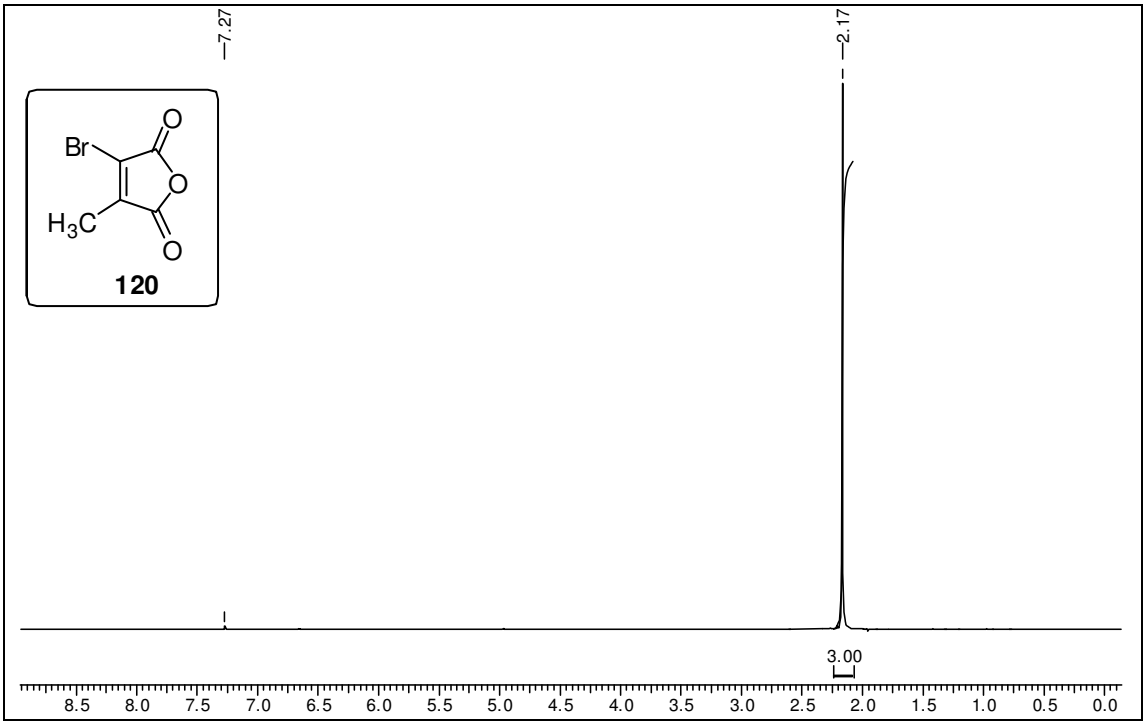
8. ^{1}H NMR spectra of compound **110**:



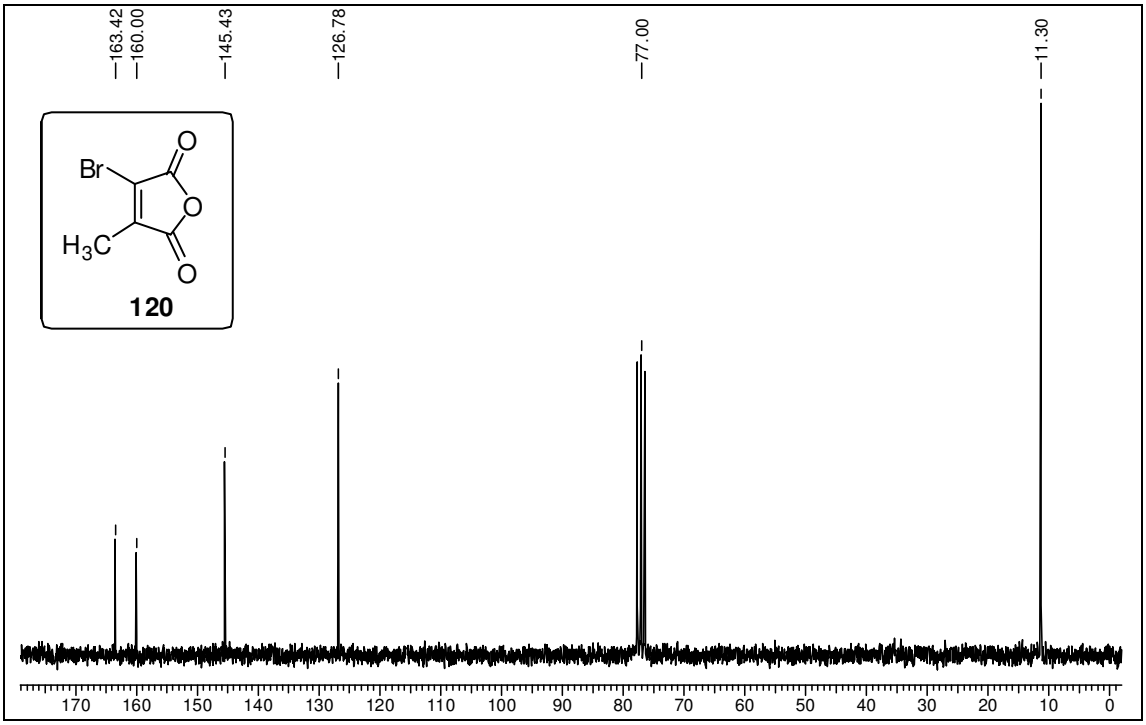
8. ^{13}C NMR spectra of compound **110**:



9. ^{1}H NMR spectra of compound **120**:



9. ^{13}C NMR spectra of compound **120**:



3.1.7 References

1. Atlanta, G. A. American Cancer Society, Global Cancer Facts & Figures, **2007.**
2. Parkin D. M. Global cancer statistics, **2002**. CA *Cancer J. Clin.* **2005**, *55*, 74.
3. Pettit, G. R.; Cragg, G. M.; Heralad, C. L. *Biosynthetic Products for Cancer Chemotherapy*, Elsevier, Amesterdam, **1984**, 4.
4. Jain, R. K. *Sci. Am.* **1994**, *271*, 58.
5. Jain, R. K. *Science* **1996**, *271*, 1079.
6. Barranco, S. C. Cancer and chemotherapy, (Academic press) **1981**, *1*, 123.
7. Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759.
8. (a) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425; (b) Boukouvalas, J.; Cheng, Y. -X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228; (c) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615; (d) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimoto, Y.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571; (e) Demeke, D.; Forsyth, C. J. *Org. Lett.* **2000**, *2*, 3177; (f) Brohm, D.; Metzger, S.; Bhargava, A.; Műller, O.; Lieb, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 307.
9. (a) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119***,** 12425; (b) Marcos, I. S.; Escola, M. A.; Moro, R. F.; Basabe, P.; Díez, D.; Sanz, F.; Mollinedo, F.; de la Iglesia-Vicente, J.; Bierra, B. G.; Urones, J. G. *Bioorg. Med. Chem.* **2007**, *15*, 5719.
10. Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2006**, *27*, 209.
11. Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc*. **1971**, *93*, 2325.
12. Altstadt, T. J.; Fairchild, C. R.; Golik, J.; Johnston, K. A.; Kadow, J. F.; Lee, F. Y.; Long, B. H.; Rose, W. C.; Vyas, D. M.; Wang, H.; Wu, M. J.; Wittman, M. D. *J. Med. Chem.* **2001**, *44*, 4577.
13. Vrignaud, P.; Lejeune, P.; Bissery, M. C. *Proc. Am. Assoc. Cancer Res*. **2001**, *42*, 1975.

14. Dykes, D. J.; Sarsat, J. P.; Bissery, M. C. *Proc. Am. Assoc. Cancer Res*. **2000**, *41*, 301.
15. Crooke, C. J. *Cancer and chemotherapy* (Academic press) **1981**, *3*, 112.
16. Jensen, E. V. *Cancer and chemotherapy* (Academic press) **1981**, *11*, 187.
17. Bolton, M. G.; Colvin, O. M.; Hilton, J. *Cancer research* **1991**, *51*, 2410.
18. Ameen, M.; Syed Musthapa, M.; Abidi, P.; Ahmad, I.; Rahman, Q. *J. Biochem. Mol. Toxicol.* **2003**, *17*, 366.
19. Chen, C.; Pung, D.; Leong, V.; Hebbar, V.; Shen, G.; Nair, S.; Li, W.; Kong, A. N. *Free Radic. Biol. Med.* **2004**, *37*, 1578.
20. (a) Herman-Antosiewicz, A.; Singh, S. V. *Mutat. Res.* **2004**, *555*, 121; (b) Sambucetti, L. C.; Fischer, D. D.; Zabludoff, S.; Kwon, P. O.; Chamberlin, H.; Trogani, N.; Xu, H.; Cohen, D. *J. Biol. Chem.* **1999**, *274*, 34940.
21. (a) Chen, C.; Kong, A. N. *Trends Pharmacol. Sci.* **2005**, *26*, 318; (b) Shukla, Y.; Kalra, N. *Cancer Lett.* **2007**, *247*, 167; (c) Ross, S. A.; Finley, J. W.; Milner, J. A. *J. Nutr.* **2006**, *136*, 852S; (d) Belloir, C.; Singh, V.; Daurat, C.; Siess, M. H.; Le Bon, A. M. *Food Chem. Toxicol.* **2006**, *44*, 827.
22. Miller, E. C.; Miller, J. A. In *Accomplishments in Cancer Research*; Rhoads, J. E., Ed.; Lippincott: Philadelphia, PA, **1980,** 63.
23. Conney, A. H. *Cancer Res.* **2003**, *63*, 7005.
24. Wilkinson, J.; Clapper, M. L. *Proc. Soc. Exp. Biol. Med.* **1997**, *216*, 192.
25. Talalay, P. *Adv. Enz. Reg*. **1989**, *28*, 237.
26. Talalay, P. *Biofactors* **2000**, *12*, 5.
27. Parkin, K. L.; Xiao, H. *Phytochemistry* **2007**, *68,* 1059.
28. O'Donnell, G.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. *J. Nat. Prod.* **2009**, *72*, 360.
29. Carotenuto, A.; Fattorusso, E.; Lanzotti, V.; Magno, S.; De Feo, V.; Carnuccio, R.; D'Acquisto, F. *J. Nat. Prod.* **1997**, *60*, 1003.
30. Ebada, S. S.; Lin, W.; Proksch, P. *Mar. Drugs* **2010**, *8*, 313.

31. (a) Trifonov, L. S.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Helv. Chim. Acta* **1981**, *64*, 1843; (b) Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Rast, D. M.; Hoesch, L. *Tetrahedron* **1982**, *38*, 397.
32. Siddiqui, S.; Mahmood, T.; Siddiqui, B. S.; Faizi, S. *J. Nat. Prod.* **1986**, *49*, 1068.
33. Itokawa, H.; Morita, H.; Katou, T.; Takeya, K.; Cavalheiro, A. J.; de Oliveira, R. C. B. *Planta Medica* **1988**, *54*, 311.
34. (a) De Rosa, S.; de Stefano, S.; Zavodnik, N. *J. Org. Chem.* **1988**, *53*, 5020; (b) De Rosa, S.; Crispino, A.; de Giulio, A.; Iodice, C.; Pronzato, R.; Zavodnik, N. *J. Nat. Prod.* **1995**, *58*, 1776; (c) De Rosa, S.; de Giulio, A.; Crispino, A.; Iodice, C.; Tommonaro, G. *Nat. Prod. Res.* **1997**, *10*, 267; (d) De Rosa, S.; Puliti, R.; Crispino, A.; de Giulio, A.; de Sena, C.; Iodice, C.; Mattia, C. A. *Tetrahedron* **1995**, *51*, 10731; (e) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Amodeo, P.; Tancredi, T. *J. Nat. Prod.* **1999,** *62,* 1316; (f) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Benrezzouk, R.; Terencio, M. C.; Ferrandiz, M. L.; Alcaraz, M. J.; Paya, M. *J. Nat. Prod.* **1998**, *61*, 931.
35. Wang, X. –N; Yin, S.; Fan, C. –Q.; Lin, L. –P.; Ding, J.; Yue, J. –M. *Tetrahedron* **2007**, *63*, 8234.
36. Wu, J.; Yang, S. –X.; Li, M. –Y.; Feng, G.; Pan, J. –Y.; Xiao, Q.; Sinkkonen, J.; Satyanandamurty, T. *J. Nat. Prod.* **2010**, *73*, 644.
37. (a) De Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611; (b) Potts, B. C. M.; Faulkner, D. J. *J. Nat. Prod.* **1992**, *55*, 1701.
38. De Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1981**, *22*, 3147.
39. (a) De Freitas, J. C.; Blankemeier, L. A.; Jacobs, R. S. *Experientia* **1984**, *40*, 864; (b) Lombardo, D.; Dennis, E. A. *J. Biol. Chem.* **1985**, *260*, 7234; (c) Glaser, K. B.; deCarvalho, M. S.; Jacobs, R. S.; Kernan, M. R.; Faulkner, D. J. *Mol. Pharmacol*. **1989**, *36*, 782.
40. Kernan, M. R.; Faulkner, D. J.; Jacobs, R. S. *J. Org. Chem.* **1987**, *52*, 3081.
41. Boalino, M. D.; McLean, S.; Reynolds, W. S.; Tinto, W. F. *J. Nat. Prod.* **2004**, *67***,** 714.
42. Yokoyama, R.; Huang, J. –M.; Yang, C. –S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65,* 527; and references cited therein.

43. (a) Jägers, E.; Steglich, W. *Angew. Chem.* **1981**, *93*, 1105; (b) Jägers, E.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1016.
44. Randazzo, A.; Debitus, C.; Minale, L.; Pastor, P. G.; Alcaraz, M. J.; Paya´, M.; Gomez-Paloma, L. *J. Nat. Prod.* **1998**, *61*, 571.
45. (a) Posadas, I.; Terencio, M. C.; Randazzo, A.; Gomez-Paloma, L.; Payá, M.; Alcaraz, M. J. *Biochem. Pharmacol.* **2003**, *65*, 887; (b) Fang, J. M.; Hsu, K. C.; Cheng, Y. S. *Phytochemistry* **1989**, *28*, 1173; (c) Randazzo, A.; Debitus, C.; Minale, L.; Pastor, P. G.; Alcaraz, M. J.; Payá, M.; Gomez-Paloma, L. *J. Nat. Prod.* **1998**, *61*, 571.
46. He, H.; Kulanthaivel, P.; Baker, B. J. *Tetrahedron Lett.* **1994**, *35*, 7189.
47. Altano, G.; Cimino, G.; DeStefano, S. *Experientia* **1979**, *35*, 1136.
48. Schmidt, E. W.; Faulkner, D. J. *Tetrahedron Lett.* **1996**, *37*, 3951.
49. Butler, M. S.; Capon, R. J. *Aust. J. Chem*. **1992**, *45*, 1705.
50. (a) Koch, M. A.; Waldmann, H. *Drug Discovery Today* **2005**, *10*, 471; (b) Koch, M. A.; Wittenberg, L. -O.; Basu, S.; Jeyaraj, D. A.; Gourzoulidou, E.; Reinecke, K.; Odermatt, A.; Waldmann, H. *Proc. Natl. Acad. Sci.* **2004**, *101*, 16721.
51. (a) Friesen, R. W.; Mancini, J. A. *J. Med. Chem.* **2008**, *51*, 4059; (b) Marcos, I. S.; Castañeda, L.; Basabe, P.; Díez, D.; Urones, J. G. *Tetrahedron* **2009**, *65*, 9256.
52. Takahashi, Y.; Hagiwara, H.; Uda, H.; Kosugi, H. *Heterocycles* **1981**, *15*, 225.
53. Surmont, R.; Verniest, G.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 5750.
54. Weber, V.; Rubat, C.; Duroux, E.; Lartigue, C.; Madesclaire, M.; Coudert, P. *Bioorg. Med. Chem.* **2005**, *13*, 4552.
55. Black, W. C.; Brideau, C.; Chan, C.; Charleson, S.; Cromlish, W.; Gordon, R.; Grimm, E. L.; Hughes, G.; Leger, S.; Li, C. –S.; Riendeau, D.; Thérien, M.; Wang, Z.; Xu, L. –J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1195.
56. Kim, K. H.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Lee, J. -E.; Kim, J. N. *Bull. Korean Chem. Soc.* **2009**, *30*, 1012.
57. Franzen, R.; Kronberg, L. *Tetrahedron Lett.* **1995**, *36*, 3905.
58. Boukouvalas, J.; Lachance, N. *Synlett* **1998**, *1*, 31.
59. Clive, D. L. J.; Minaruzzaman, O. L. *J. Org. Chem.* **2005**, *70*, 3318.

60. Yadav, J. S.; Valluri, M.; Rama Rao, A. V. *Tetrahedron Lett.* **1994**, *35*, 3609.

61. (a) Schenck, G. O. *Liebigs Ann. Chem.* **1953**, *584*, 156; (b) Schroeter, S.; Appel, H. R.; Brammer, R.; Schenck, G. O. *Liebigs Ann. Chem.* **1966**, *697*, 42.

62. (a) Langer, P.; Schneider, T.; Stoll, M. *Chem. Eur. J.* **2000**, *6*, 3204; (b) Langer, P.; Saleh, N. N. R.; Köhler, V. *Eur. J. Org. Chem.* **2002**, 1566.

63. (a) Marino, C.; Varela, O.; de Lederkremer, R. M. *Carbohydr. Res.* **1990**, *220*, 145; (b) Jerocic, L. O.; Varela, O. J.; Cirelli, A. F.; de Lederkremer, R. M. *Tetrahedron* **1984**, *40*, 1425.

64. (a) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41*, 2111; (b) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimotoa, Y.; Shiraic, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571.

65. Aquino, M.; Bruno, I.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2006**, *8*, 4831.

66. (a) Pattenden G.; Weedon B. C. L. *J. Chem. Soc. (C)* **1968**, 1984; (b) Yamano, Y.; Fujita, Y.; Mizuguchi, Y.; Nakagawa, K.; Okano, T.; Ito, M.; Wada, A. *Chem. Pharm. Bull.* ***2007****, 55***,** 1365.

67. Descomps, A. Master's thesis in organic chemistry, University of Tromso, **2008**.

68. Kumar, P.; Pandey, R. K. *Green Chemistry* **2000**, *2*, 29.

69. Xu, H.; Chan, W. K.; Ng, D. K. P. *Synthesis* **2009**, *11*, 1791; and references cited therin.

70. Sparreboom, A.; Cox, M. C.; Acharya, M. R.; Figg, W. D. *J. Clin. Oncology* **2004**, *22*. 2489.

71. Jiemei, X.; Kamelin, R. V. *Flora of China*, **2000**, *24*, 165.

72. Hirschegger, P.; Jaške, J.; Trontelj, P.; Bohanec. B. *Molecular Phylogenetics and Evolution* **2010**, *54***,** 488.

73. (a) Gates, M. A.; Tworoger, S. S.; Hecht, J. L.; De Vivi, I.; Rosner, B.; Hankinson, S. E. *Int. J. Cancer* **2007**, *121*, 2225; (b) Dorsch, W.; Ettl, M.; Hein, G. *Int. Arch. Allergy Appl. Immunol.* **1987**, *82*, 535; (c) Fukushima, S.; Takada, N.; Hori, T.; Wanibuchi, H. *J. Cell Biochem.* **1997**, *27*, 100; (d) Galeone, C.; Pelucchi, C.; Levi, F.; Negri, E.; Franceschi, S.; Talamini, R.; Giacosa, A.; La Vecchia, C. *Am. J. Clin. Nutr.* **2006,** *84*, 1027; (e) Sheela, C. G.; Kumud, K.;

Augusti, K. T. *Planta. Med.* **1995**, *61*, 356; (f) Wagner, H.; Dorsch, W.; Bayer, T.; *Prostaglandins Leukot Essent Fatty Acids*. **1990**, *39*, 59.

74. Augusti, K. *Indian J. Exp. Biol.* **1996**, *34*, 634.
75. Bayer, T.; Breu, W.; Seligmann, O.; Wray, V.; Wagner, H. Phytochemistry **1989**, *28*, 2373.
76. (a) Sumiyoshi, H.; Wargovich, M. *Cancer Res.* **1990**, *50,* 5084; (b) Iciek, M.; Kwiecień, I.; Wlodek, L. *Envirnmental and Mole. Mutagenesis* **2009**, *50*, 247.
77. Dubernet, M.; Caubert, V.; Guillard, J.; Viaud-Massuard, M. C. *Tetrahedron* **2005**, *61*, 4585.
78. Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
79. Xie, G.; Lown, J. W. *Tetrahedron Lett.* **1994**, *35*, 5555.
80. Choi, D. -S.; Huang, S.; Huang, M.; Barnard, T. S.; Adams, R. D.; Seminario, J. M.; Tour, J. M. *J. Org. Chem.* **1998,** *63,* 2646.

Section-B

Synthesis of S-(-)-Rivastigmine as an acetylcholinesterase inhibitor

3.2.1 Introduction

Alzheimer's disease (AD) is the commonest cause of dementia affecting older people. This incurable, degenerative and terminal disease was first described by German neurologist Alois Alzheimer in 1906 and was named after him.[1] Prevalence is 1-2% at age 65 years, but increases markedly to 35% or greater by age 85.[2] In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050.[3] Because of a demographic shift toward a more aged population; the percentage of affected individuals is rapidly increasing. This trend is expected to continue for the foreseeable future. Therefore, accurate and timely diagnosis and effective treatments are critical to optimal outcomes over the 8 to 10 years course of the illness. Incidence rates, or the number of new cases arising in a given population over time, also increase with age. Age is by far the greatest risk factor for developing Alzheimer's disease.

Alzheimer's disease is a physical disease affecting the brain. During the course of the disease, 'plaques' and 'tangles' develop in the structure of the brain,[4] leading to the death of brain cells. People with Alzheimer's also have a shortage of some important chemicals in their brains. These chemicals are involved with the transmission of messages within the brain. Alzheimer's is a progressive disease, which means that gradually, over time, more parts of the brain are damaged. As this happens, the symptoms become more severe.

Cholinesterase is a family of enzyme that catalyze the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation. There are two types of cholinesterase in the CNS—acetylcholinesterase and butyrylcholinesterase.

Acetylcholinesterase inhibitor (AChEI):

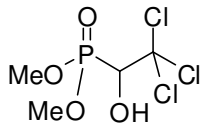
An acetylcholinesterase inhibitor is a chemical that inhibits the anionic site of the cholinesterase enzyme from breaking down acetylcholine, increasing both the level and duration of action of the neurotransmitter acetylcholine. Acetylcholinesterase inhibitors have recently been introduced as cognition-enhancing agents in the treatment of patients

with mild to moderate Alzheimer's disease (AD).[5] This inhibitors function as reversible of cholinesterases, and most likely to have therapeutic uses. They differ principally in the type of bond they form with acetylcholinesterase. These include different classes of agents:

1. Organophosphates
2. Piperidines
3. Phenanthrene derivatives
4. Carbamates
5. Acridines

1. Organophosphate:

The organophosphate acetylcholinesterase inhibitor is esters of phosphoric acids. It includes Metrifonate or trichlorfon (**Figure 1**). It has been proposed for use in treatment of Alzheimer's disease, but it's use for this purpose is not currently recommended.[6]



Metrifonate (**1**)

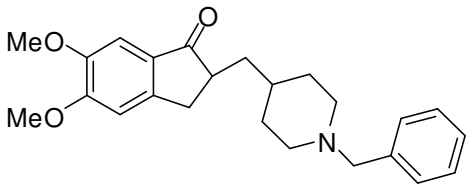
Figure 1.

Metrifonate **1** is a long-acting irreversible cholinesterase inhibitor, originally used to treat schistosomiasis. Its potential to enhance central nervous system cholinergic neurotransmission led to clinical trials for the treatment of people with Alzheimer's disease (AD). Metrifonate forms an irreversible covalent bond with the substrate.

2. Piperidines:

The acetylcholinesterase inhibitor contains piperidine as a core ring. Donepezil **2** is one of the drugs containing piperidine ring. It is a centrally acting reversible acetylcholinesterase inhibitor. Donepezil[7] is high-affinity, non-covalent inhibitor and has

non-competitive and competitive properties. Its main therapeutic use is in the treatment of Alzheimer's disease (AD); where it is used to increase cortical acetylcholine.



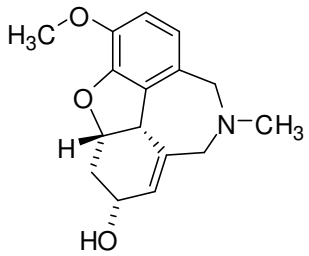
Donepezil (**2**)

Figure 2.

Donepezil is approved by US-FDA and Health Canada's Health Protection Branch in 1996-97 for symptomatic treatment of early to intermediate stage Alzheimer's disease (AD).[8] It has been readily accepted because it can be administered once a day, it has a half life of about 70 h. Half life is significantly long for other agents. Side effects, including nausea, diarrhea, abdominal discomfort, and some sleep disturbances have been reported and many of these occur with other agents as well.

3. Phenanthrene derivatives:

Galanthamine **3** is a natural product of phenanthrene alkaloid isolated from the Caucasian snow-drop (*Galanthus woronowii*) and from the bulbs of different species of the *Amaryllidaceae* family (**Figure 3**). It is a long-acting, selective, reversible, competitive acetylcholinesterase (AChE) inhibitor,[9] and an allosteric modulator of the neuronal nicotinic cholinergic receptor.[10] It reduces the action of AChE and therefore tends to increase acetylcholine release by activating presynaptic nicotinic receptors in the brain. Galanthamine, commercially available as Reminyl®, is the most recently approved



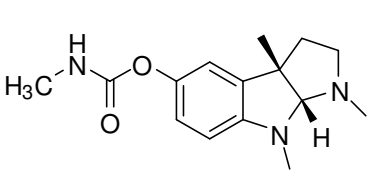
Galanthamine (**3**)

Figure 3.

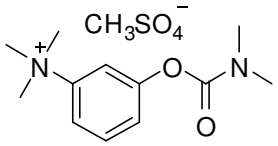
AChE inhibitor in USA by the FDA, and in Europe by the European registration bureau for the symptomatic treatment of Alzheimer's disease (AD).

4. Carbamates:

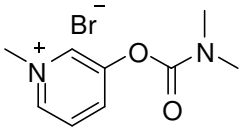
Carbamates are organic compounds which contains carbamic acid and carbamate ester functional groups. Some of the carbamate compounds acting as reversible acetylcholinesterase inhibitors, which includes Physostigmine **4**,[11] Neostigmine methyl sulfate **5**,[12] Pyridostigmine bromide **6**,[13] Ambenonium chloride **7**,[14] Rivastigmine **8**[15] and Demecarium bromide **9**[16]. These compounds exert their beneficial effect on intellectual functioning by blocking acetylcholinesterase and enhancing cholinergic function. They have been developed to improve the neuropsychological deficits of Alzheimer's disease (AD).



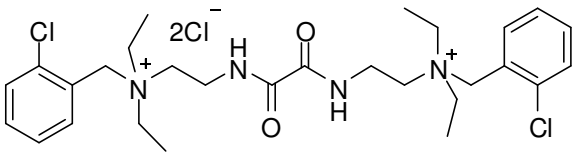
Physostigmine (**4**)



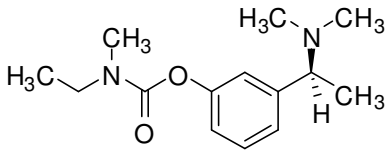
Neostigmine methyl sulfate (**5**)



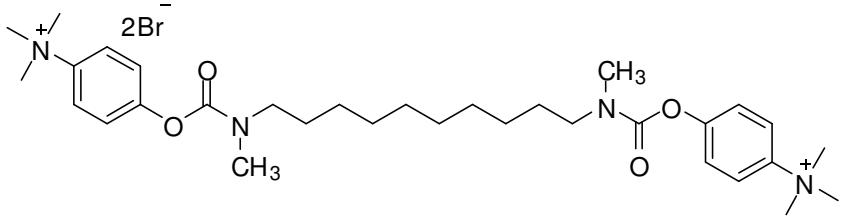
Pyridostigmine bromide (**6**)



Ambenonium chloride (**7**)



Rivastigmine **(8**)

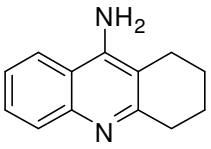


Demecarium bromide (**9**)

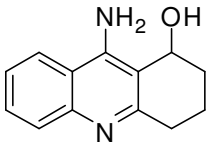
Figure 4.

5. Acridines:

Acridine is an organic compound with tricyclic ring having one nitrogen heteroatom. Some of the acridine compounds, which can act as reversible acetylcholinesterase inhibitors, which includes tacrine **10** and velnacrine **11**. These are high-affinity, non-covalent and non-competitive inhibitors. Tacrine **10** and velnacrine **11** are associated with a high frequency of hepatotoxicity.



Tacrine (**10**)

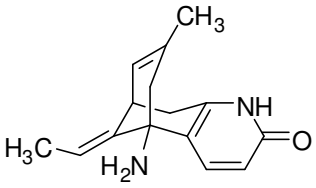


Velnacrine (**11**)

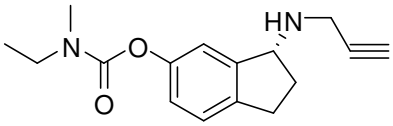
Figure 5.

In the early and mid 20th century, tacrine **10** was the first centrally-acting cholinesterase inhibitor to be approved by US-FDA for the treatment of Alzheimer's disease[17] and was marketed under the trade name Cognex. But it is no longer frequently used because of its short half-life requiring multiple daily dosing, up to four times a day, considerable adverse drug reactions, and systematic checking of liver enzymes at periodic intervals such that few patients could tolerate therapeutic doses.

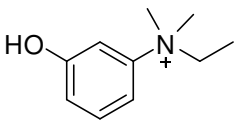
Some of the other agents such as huperzine A **12**,[18] ladostigil **13**[19] and edrophonium **14**[20] can act as reversible acetylcholinesterase inhibitor for the treatment of Alzheimer's disease.



Huperzine A (**12**)



Ladostigil (**13**)

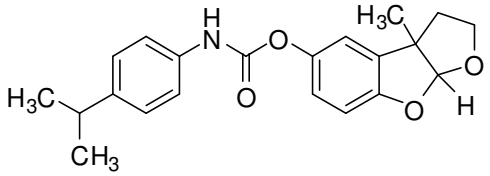


Edrophonium (**14**)

Figure 6.

Butyrylcholinesterase inhibitor (BuChEI):

Butyrylcholinesterase is an enzyme developed in human. It is very similar to the neuronal acetylcholinesterase, and is a non-specific cholinesterase found in the blood plasma. Butyrylcholinesterase inhibitor, efficiently catalyses the hydrolysis of numerous endogenous substances, including choline esters.[21] Butyrylcholine is a synthetic compound and does not occur in the body naturally. It is used as a tool to distinguish between acetyl- and butyrylcholinesterase. Although, it is predominantly associated with glial cells in human brain and affected by AD, such as in amygdala, hippocampus and thalamus. BuChE is involved in neural function like co-regulation of cholinergic and non-cholinergic neurotransmission in the brain. Tetrahydrofurobenzofuran cymserine (THFBFC) **15** is a potent butyrylcholinesterase inhibitor.[22]



Tetrahydrofurobenzofuran cymserine (THFBFC) (**15**)

Figure 7.

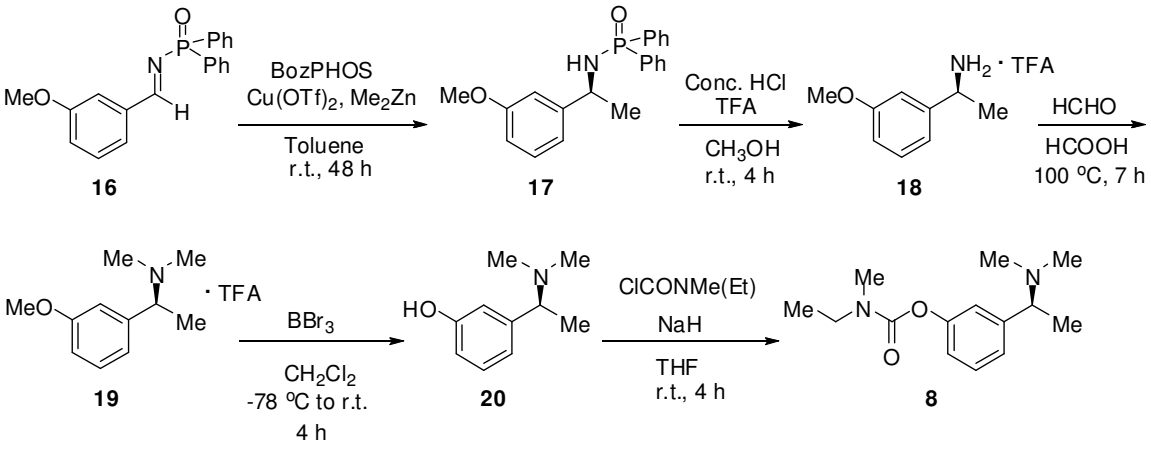
3.2.2 Review of Literature

In this section, we discussed in brief some of the more significant methods for the synthesis of (*S*)-rivastigmine. In the patented method, the (*S*)-rivastigmine has been synthesized from either 3′-methoxyacetophenone or 3′-hydroxyacetophenone. All of these methods have certain drawbacks, such as complex sequential operations, trace impurities of metals, or multiple crystallisation steps involving diastereomeric salts. It is observed that all the reported methods are cumbersome and expensive for a process scale preparation. This prompted us to initiate studies designed towards developing a novel and less hazardous synthetic route amenable for scale-up operations of rivastigmine.

Charette *et al.* (2003)[23]

Charette and co-workers synthesized (*S*)-rivastigmine **8** from *N*-phosphinoylimine **16** in five steps. The key step of this strategy was the copper-catalyzed addition of

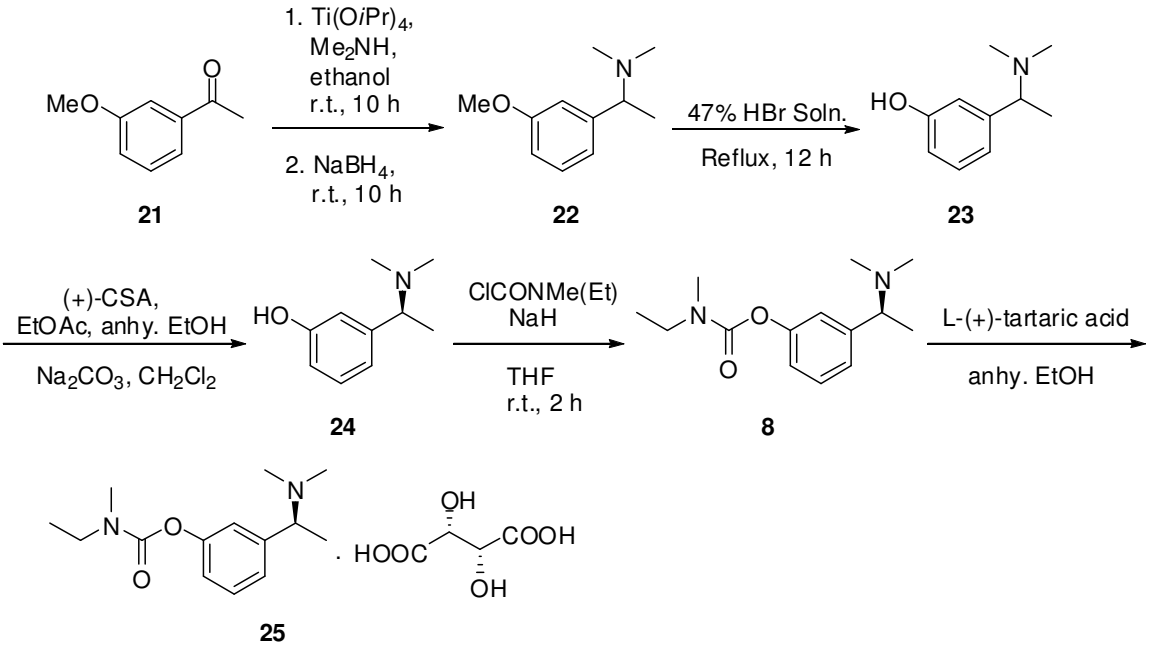
dimethylzinc to *N*-phosphinoylimine **16** in the presence of novel BozPHOS chiral ligand. A simple deprotection, methylation and carbamoylation of compound **17** furnished (*S*)-rivastigmine **8** in high yield (**Scheme 1**).[24]



Scheme 1.

Stepankova *et al.* (2004)[25]

Stepankova *et al.* devised an elegant synthesis of (*S*)-rivastigmine **8** and its

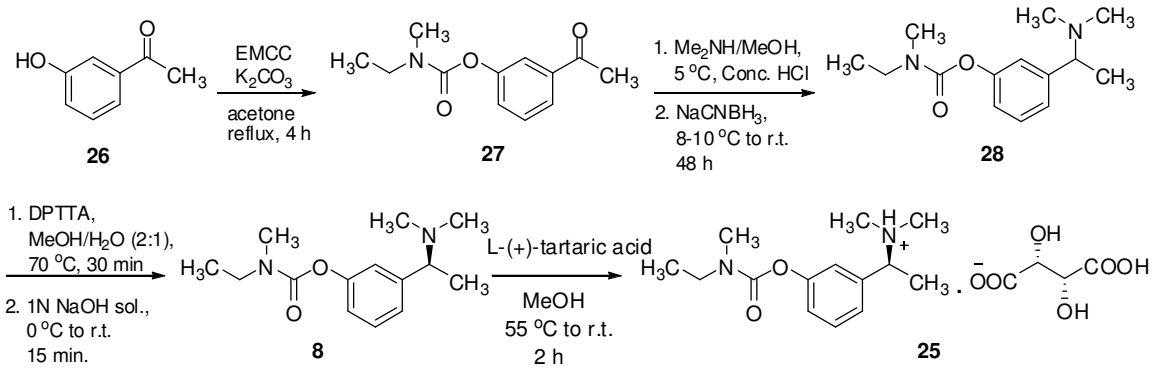


Scheme 2.

tartrate salt **25** started from 3′-methoxyacetophenone **21** in five steps and 8% overall yield. The key step involved in this synthesis was the resolution of racemic amine compound **23** by *S*-(+)-camphor-10-sulfonic acid (CSA) gave chiral amine **24** in poor yield (**Scheme 2**).

Gaitonde *et al.* (2005)[26,27]

Gaitonde *et al.* commenced their synthesis of rivastigmine from 3′-hydroxyacetophenone **26**, which underwent carbamoylation by *N*-ethyl-*N*-methylcarbamoyl chloride (EMCC) in the presence of base gave crude compound **27** in quantitative yield. The reductive amination of ketone **27** was performed by using 2M Me_2NH in methanol, conc. HCl and $NaCNBH_3$ furnished racemic rivastigmine **28** in 55.4% yield. The formation of tartrate salt of racemic rivastigmine **28** was achieved by using di-*p*-toluoyl tartaric acid (DPTTA) in the mixture of methanol and water, then the releasing of DPTTA salt by 1N NaOH solution to furnish (*S*)-(-)-rivastigmine in very less yield. Finally, the (*S*)-rivastigmine hydrogentartarate **25** was achieved by using L-(+)-tartaric acid in 77% yield. The key step of this strategy was the carbamoylation of 3′-hydroxyacetophenone **26 (Scheme 3)**.

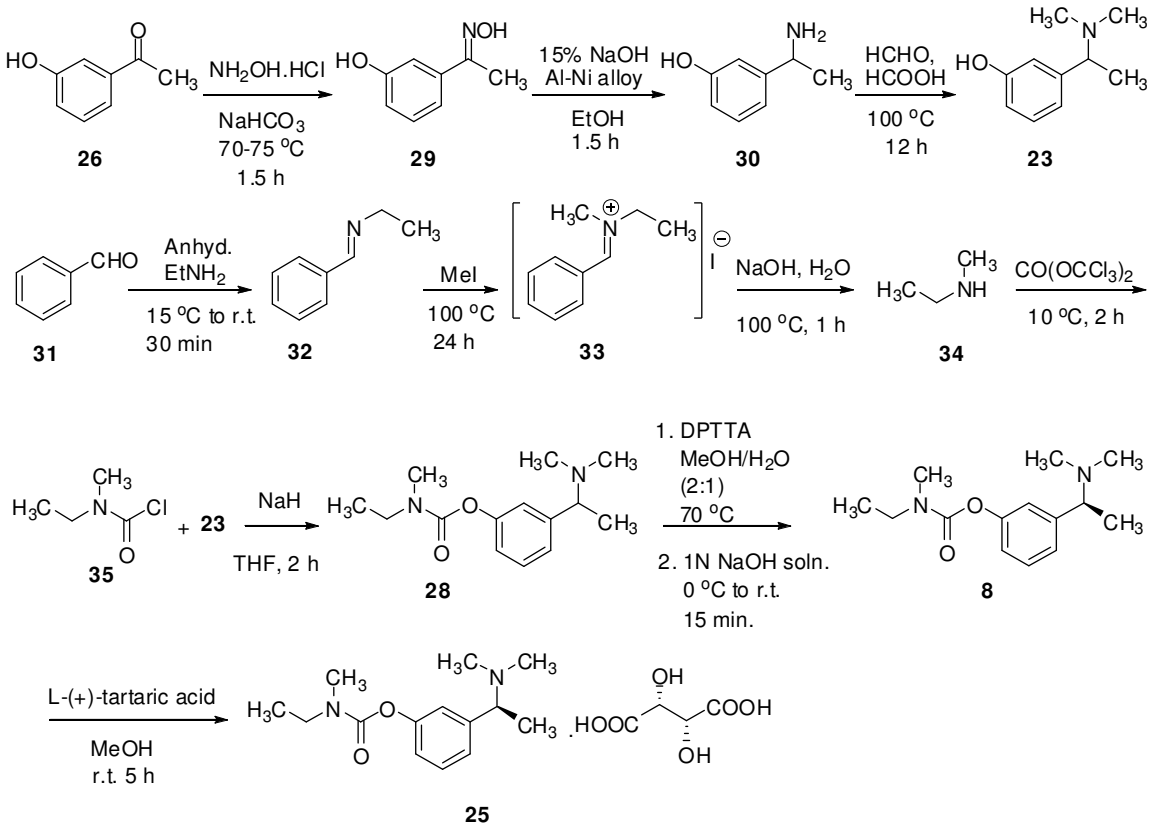


Scheme 3.

Feng *et al.* (2007)[28]

Feng and co-workers reported synthesis of rivastigmine hydrogentartarate (**Scheme 4**). Accordingly, the oxime **29** was achieved from **26** by using $NH_2OH.HCl$ in presence of base gave 98% yield, which was reduced with Al-Ni alloy in ethanol to

afford amine **30** in 78% yield. The *N*-methylation of **30** was carried out by using formic acid and formaldehyde at 100 °C to furnish racemic compound **23**. The *N*-ethyl-*N*-methylcarbamoyl chloride **35**[29] was prepared in four steps from benzaldehyde **31**. The carbamoylation of **23** was performed by using NaH in THF with **35** afforded racemic rivastigmine **28**. The formation of DPTTA salt of rivastigmine was achieved by using di-*p*-toluoyl tartaric acid (DPTTA), then the releasing of DPTTA salt by 1N NaOH solution furnished (*S*)-rivastigmine **8** in very less yield. Finally, the rivastigmine hydrogentartarate was achieved by using L-(+)-tartaric acid in 67% yield.

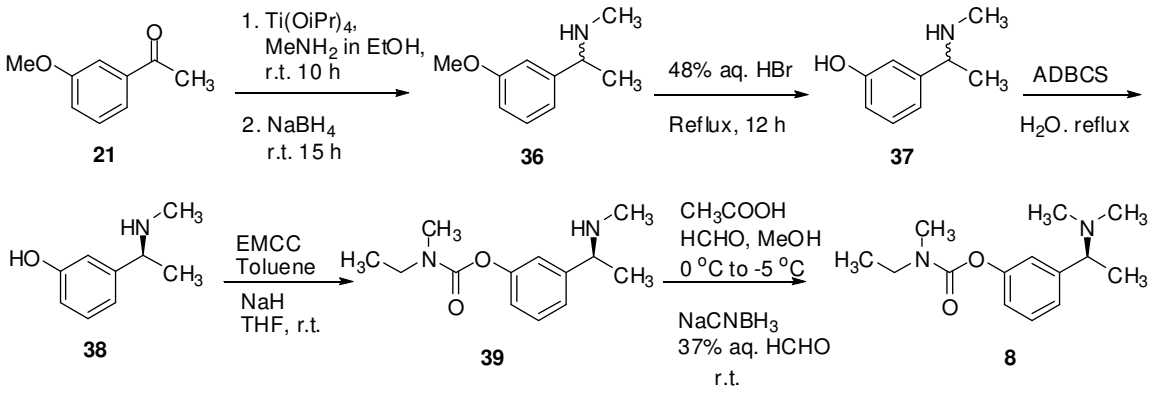


Scheme 4.

Garrido *et al.* (2008)[30]

The synthesis of rivastigmine was discribed by Garrido and co-workers; where they began from 3′-methoxyacetophenone **21 (Scheme 5)**. Compound **36** was achieved from **21** by reductive amination using methyl amine in ethanol and $NaBH_4$ at room temperature in 62% yield. The demethylation of **36** to racemic **37** was obtained using

48% aq. HBr solution. The resolution of racemic **37** was carried out by using ammonium *D*-bromocamphorsulfonate (ADBCS) furnished chiral amine **38**, which was carbamoylated with 0.5 M solution of EMCC in toluene at room temperature to afford compound **39**. Further, **39** was converted to (*S*)-rivastigmine **8** by using formaldehyde and acetic acid in methanol in 60% yield. The key step of this synthesis is the reductive amination and resolution of racemic amine by ADBCS.

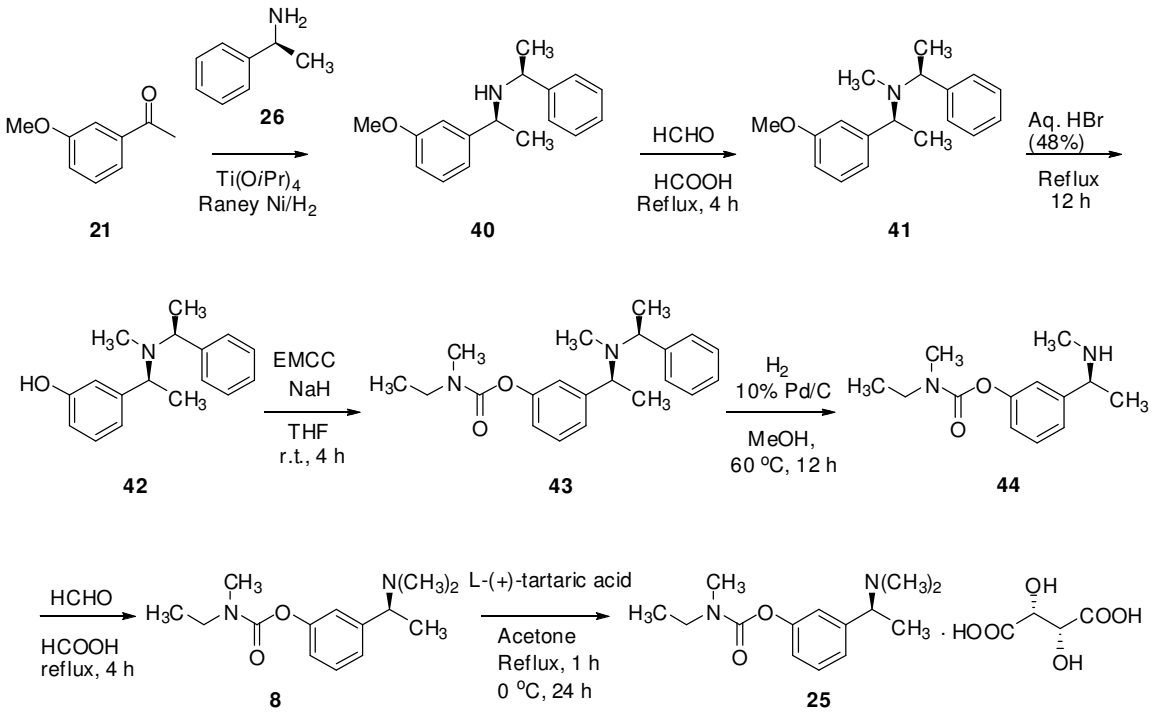


Scheme 5.

Hu *et al.* (2009)[31]

Hu *et al.* synthesized (*S*)-rivastigmine and its tartrate salt from commercially available 3′-methoxyacetophenone **(Scheme 6)**. The one-pot asymmetric reductive amination of **21** with (*S*)- or (*R*)-α-methylbenzylamine **26** using the combination of Ti(O*i*Pr)$_4$/Raney-Ni/H_2 afforded diastereomerically pure (*S*)-1-(3-methoxyphenyl)-*N*-[(*S*)-1-phenylethyl]ethanamine **40** (**Scheme 6**).[32]

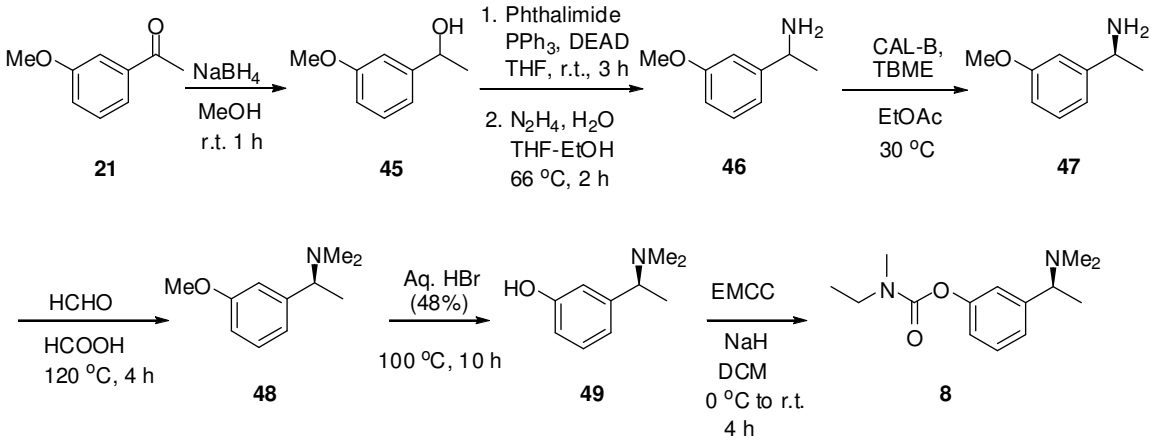
Compound **40** was subjected to *N*-methylation using formic acid and formaldehyde to afford (*S*)-1-(3-methoxyphenyl)-*N*- methyl- *N* -[(*S*)-1-phenylethyl]ethanamine **41**. Demethylation of **41** using HBr solution in water under refluxed condition gave compound **42**, which was treated with EMCC to afford compound **43**. The regioselective hydrogenolysis of **43** was achieved the desired product **44** in excellent yield. Further, the *N*-methylation of **44** gave (*S*)-rivastigmine, which was finally treated with L-(+)-tartaric acid to afford (*S*)-(-)-rivastigmine tartrate **25**.



Scheme 6.

Mangas-Sánchez *et al.* (2009)[33]

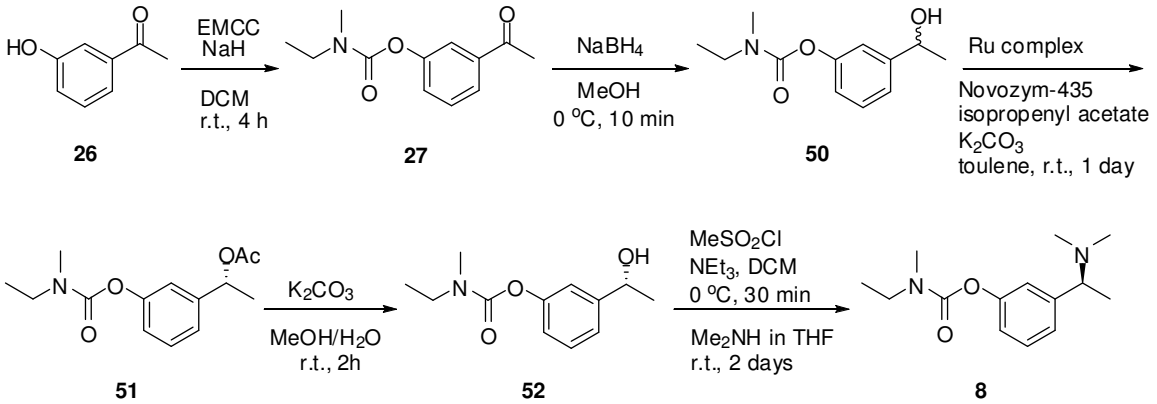
Mangas-Sánchez *et al.* synthesized (*S*)-rivastigmine from 3′-methoxyacetophenone in six steps (**Scheme 7**). 3′-methoxyacetophenone **21** was reduced to racemic alcohol **45** followed by protection and deprotection of amine by hydrazine to convert racemic amine **46**. The enzymatic resolution of **46** by *Candida antarctica* lipase type B (CAL-B) in *tert*-butyl methyl ether (TBME) afforded chiral amine **47**. The dimethylation of **47** was carried out by using formic acid and formaldehyde obtaining compound **48**. The cleavage of *O*-methyl bond using 48% HBr solution of in water afforded (*S*)-3-[1-(Dimethylamino)ethyl]phenol **49**. Finally, the carbamoylation of **49** with EMCC in the presence of sodium hydride in dichloromethane at room temperature gave enantiomerically pure (*S*)-rivastigmine in 80% yield. The key step of this strategy was the enzymatic resolution of **46** by CAL-B.



Scheme 7.

Kim *et al.* (2010)[34]

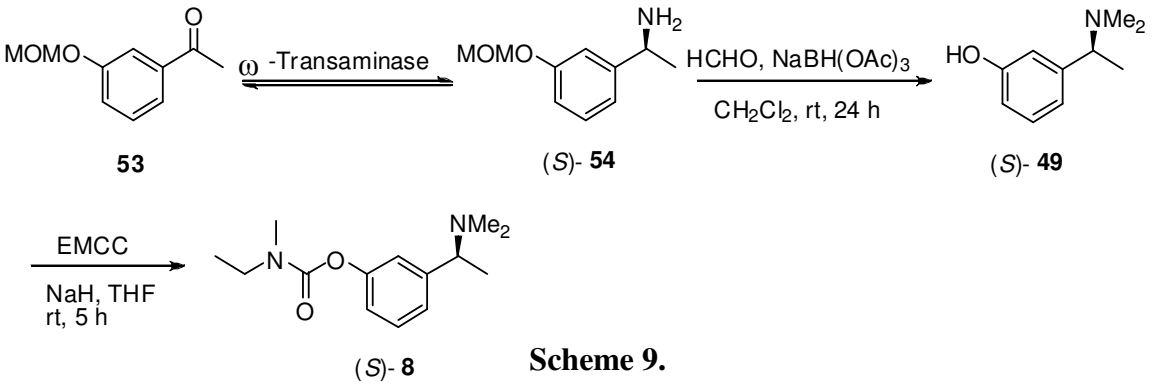
Kim and co-workers synthesized (*S*)-rivastigmine **8** from 3′-hydroxyacetophenone in five steps (**Scheme 8**). 3′-hydroxyacetophenone was condensed with EMCC in presence of sodium hydride (NaH) in CH_2Cl_2 followed by the reduction of carbonyl group afforded racemic compound **50**. The enzymatic dynamic kinetic resolution of **50** in the presence of combination of polymer supported ruthenium complex and a lipase at room temperature for 1 day gave acylated product **51**; which was hydrolyzed in alkaline solution to afford chiral hydroxy compound **52**. Finally, the mesylation and amination of **52** with mesyl chloride in CH_2Cl_2 and triethylamine as a base and dimethyl amine in THF at room temperature for 2 days afforded (*S*)-(-)-rivastigmine in overall 57% yield. The key step was dynamic kinetic resolution using a polymer supported ruthenium complex and a lipase.



Scheme 8.

Faber *et al.* (2010)[35]

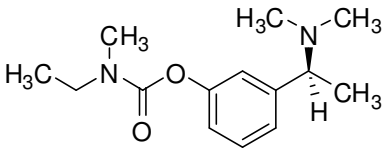
Faber *et al.* devised an elegant chemoenzymatic asymmetric total synthesis of (*S*)-rivastigmine using ω-transaminase started from MOM protective acetophenone **53** in four steps and 71% overall yield (**Scheme 9**). The key building block (*S*)-**54** was derived *via* enzyme catalyzed asymmetric transamination of a structurally tuned ketone using ω-transaminase. This method towards the synthesis of (*S*)-Rivastigmine represented the shortest route published to date.



Scheme 9.

3.2.3 Present work

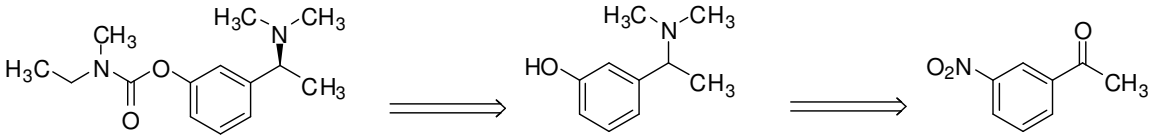
Rivastigmine **8** is a non-selective pseudo-irreversible carbamate type cholinesterase inhibitor that targets both acetylcholinesterase and butylcholinesterase. It is selective in the brain region and has a long duration of action.[36] (*S*)-Rivastigmine {(S)-3-[1-(dimethylamino)-ethyl]phenyl ethyl(methyl)carbamate}**8** has been approved by the FDA in 2000 and supported by several pivotal trials, including a randomized US trail (ENA 713 B352). In 2006, it became the first product approved globally for the treatment of mild to moderate dementia associated with Parkinson's disease (**Figure 4**).[37] Dementia represents an important medical problem, not only because of increased age population, but also a major cause by other conditions such as Lewy-body[38] disease or following strokes. This is a parasympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type. Now, its tartrate salt is marketed under brand name Exelon.



(*S*)-(-)-Rivastigmine (**8**)

Figure 4.

The present section deals with the synthesis of (*S*)-(-)-rivastigmine **8**, possessing carbamate moiety at one end and chiral centre at the other end, having acetylcholinesterase inhibitor. It was thought to attempt the synthesis of **8** with the simple route as shown in the retrosynthetic analysis (**Scheme 10**).



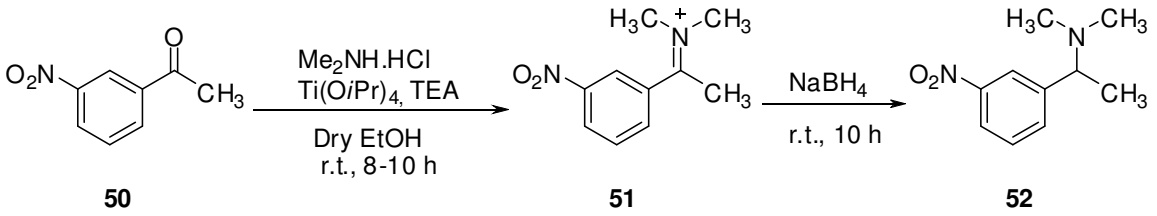
8 **23** **50**

Scheme 10. Retrosynthetic analysis

As per retrosynthetic analysis depicted in **scheme 10**, it was envisioned that (*S*)-rivastigmine could be obtained from racemic hydroxy compound **23** *via* resolution of **23** and condensation with EMCC; while **23** could be achieved from 3′-nitroacetophenone **50** *via* reductive amination, reduction and diazotization reaction.

3.2.4 Results and discussion

According to retrosynthetic analysis, the reductive amination of 3′-nitroacetophenone **50** using dimethylamine hydrochloride in dry ethanol in the presence of titanium tetraisopropoxide (Ti(O*i*Pr)$_4$) and triethylamine as a base for 8 to 10 h at room temperature gave imine product **51**, which was reduced by $NaBH_4$ afforded 3-(1-(dimethylamino)ethyl)nitrobenzene **52** in poor yield (35%) (**Scheme 11**).

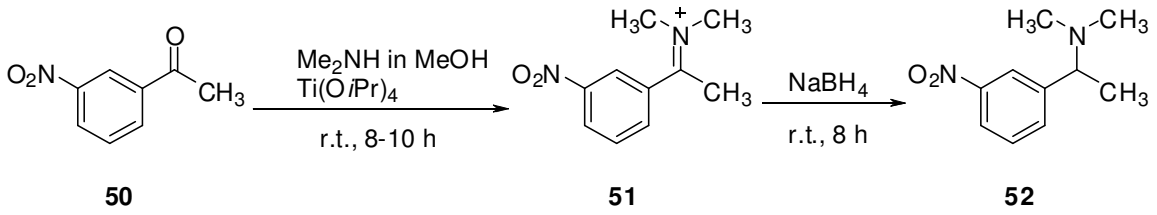


50 **51** **52**

Scheme 11.

The formation of **52** was confirmed by spectral analysis. ^{1}H NMR spectrum displayed the doublet and singlet at δ 1.36 and 2.20 ppm corresponding to three and six protons respectively indicating the presence of methyl and dimethyl amino group. Quartrate at δ 3.36 ppm for one proton was observed which was assigned to CH proton adjacent to methyl group. The aromatic protons were observed as multiplet at δ 7.44 to 8.19 ppm. ^{13}C NMR spectrum showed peak at δ 19.26 ppm signifying methyl group adjacent to CH carbon; whereas peaks at δ 42.57 and 64.76 ppm for dimethyl amino group and CH carbon adjacent to methyl group. The mass spectrum exhibited molecular ion peak at 194 (M^+).

The same reaction was performed again to improve the yield. The reductive amination of **50** was carried out using dimethylamine in ethanol instead of hydrochloride salt of dimethylamine in the presence of Ti(O*i*Pr)$_4$, without base at room temperature for 8 to 10 h afforded **51** and on reduction with $NaBH_4$ gave **52** in good yield (67%). But, when methanol was used as a solvent instead of ethanol in reductive amination reaction, excellent yield (92%) was obtained (**Scheme 12**).

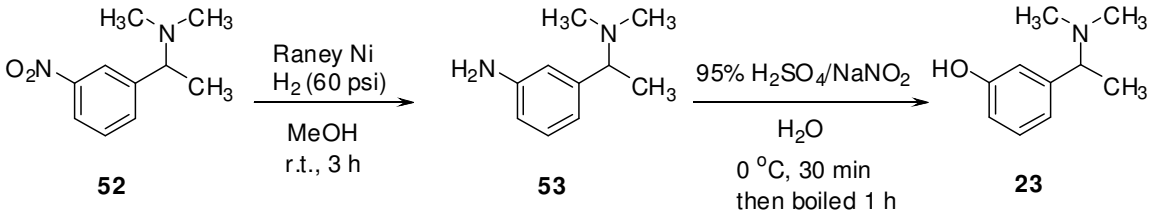


50 **51** **52**

Scheme 12.

The hydrogenation of **52** using Raney Ni under hydrogen pressure (60 *psi*) at room temperature for 3 h in methanol afforded 3-(1-(dimethylamino)ethyl)aniline **53**. The diazotization of **53** was carried out by using 95% H_2SO_4 and $NaNO_2$ in H_2O at 0 ^{o}C

for 30 min, the resulting mixture was boiled for 1 h to yield racemic compound **23** in good yield (**Scheme 13**).

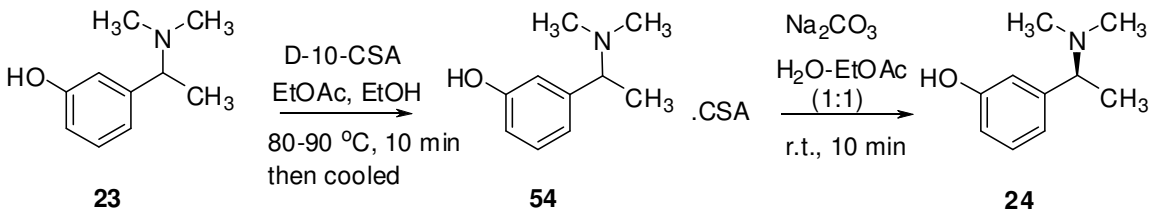


Scheme 13.

^{1}H NMR spectrum of compound **53** showed a broad singlet of two protons at δ 3.63 ppm for amino group. IR spectrum showed strong band at 3421 cm^{-1} for amino group. In its mass spectrum (ESI), molecular ion peak was observed at 164 (M^+).

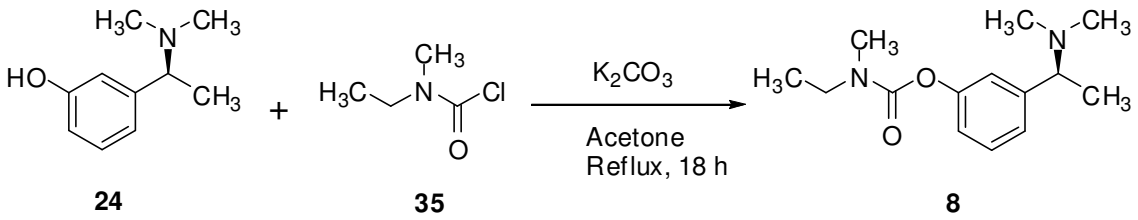
^{1}H NMR spectrum of compound **23** showed a broad singlet of one proton at δ 5.30 ppm for phenolic OH group. IR spectrum of phenolic OH group showed a broad band at 3300 cm^{-1}.

The next step was the resolution of hydroxy compound **23**. The formation of (+)-CSA salt **54** was carried out using D-10-camphorsulfonic acid monohydrate (CSA) in methanol and ethyl acetate at 70 °C for 10 min. But the reaction solution after cooling did not separate the solid. Hence, it was decided to change the solvent for the formation of CSA salt. Compound **23** was treated with D-(10)-CSA at 80-90 °C for 10 min in ethanol and ethyl acetate, then cooled the solution to obtain (+)-CSA salt **54** in good yield with optical rotation $[\alpha]^{25}_D$ = + 12.65° (*c* = 2.0, MeOH). The salt **54** was treated with Na_2CO_3 in (1:1) mixture of water and ethyl acetate at room temperature for 10 min afforded chiral hydroxy compound **24** with optical rotation $[\alpha]^{25}_D$ = -55.05° (*c* = 1.55, MeOH) (**Scheme 14**).



Scheme 14.

Finally, the synthesis of *S*-(-)-rivastigmine was achieved by the condensation of **24** with EMCC in the presence of base. The condensation reaction was optimized using different reagents and conditions (**Table 1**).



24 **35** **8**

Scheme 15.

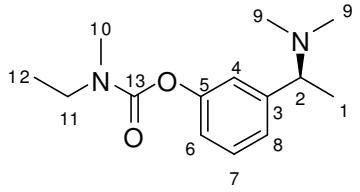
Table 1. Optimization of condensation reaction

Sr. No.	Reagent	Reaction Condition	Time	Yield[a]
1.	NaH/THF	RT	24 h	45-50%
2.	K_2CO_3/DMSO	RT	24 h	No reaction
		Reflux	6 h	40%
3.	K_2CO_3/DMSO/PTC	Reflux	16 h	20%
4.	K_2CO_3/Acetone	RT	24 h	13-20%
5.	K_2CO_3/Acetone	Reflux	18 h	75-80%
			16 h	73%
			9 h	52%
			5 h	37%

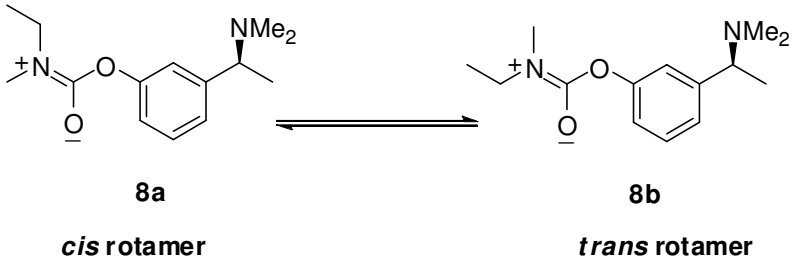
[a] Yields determined *via* GC-analysis.

The condensation of **24** with *N*-ethyl-*N*-methyl carbamoyl chloride (EMCC) using NaH in THF at room temperature for 24 h afforded only 45-50% product **8**. The same reaction failed when K_2CO_3 in DMSO was used at room temperature for 24 h; but at reflux condition for 6 h, 40% product **8** was obtained. The condensation reaction was carried out using phase transfer catalyst such as benzyltriethylammonium chloride (BTAC) using K_2CO_3 in DMSO gave poor yield after refluxing for 16 h. In acetone instead of DMSO, only 13-20% product was obtained by the condensation reaction of **24**

with **35** at room temperature for 24 h. The same reagent was used at reflux condition and the reaction was monitored by gas chromatography (GC). The good result was found after 18 h in 75-80 % yield with >99% ee (**Scheme 15**) (**Table 1**).



^{1}H NMR spectrum of compound **8** showed the multiplet in the range of δ 1.12-1.23 ppm corresponds to three protons indicated the presence of methyl proton ($C\underline{H_3}$-CH_2-N). It showed two rotamers of methyl proton i.e. *cis* and *trans* form. One doublet was observed at δ 1.33 ppm for three protons, which was assigned to methyl proton ($C\underline{H_3}$-CH-N). The dimethyl amino group ($C\underline{H_3}$-N-$C\underline{H_3}$) was observed as a singlet at δ 2.19 ppm corresponds to six protons. The methyl group ($C\underline{H_3}$-N-CO) was observed as a singlet in the form of *cis* and *trans* rotamer at δ 2.93 and 3.05 ppm. The multiplet was observed for CH_2 and CH protons (CH_3-$C\underline{H_2}$-N, N-$C\underline{H}$-CH_3) at δ 3.33-3.48 ppm for two and one proton respectively. The aromatic protons were observed as multiplet at δ 6.94 to 7.09 ppm; whereas one proton showed triplet at δ 7.24 ppm. In ^{13}C NMR spectrum, carbon C12 showed rotamer at δ 12.27 and 13.03 ppm corresponds to methyl carbon ($\underline{C}H_3$-CH_2-N). Carbon C1 was observed a peak at δ 19.29 ppm. C10 showed a rotamer at δ 33.60 and 34.01 ppm corresponds to methyl group directly attached to N ($\underline{C}H_3$-N-CO). Carbonyl carbon was observed as a rotamer at δ 154.15 and 154.34 ppm. Mass spectrum showed a molecular ion peak at 250 and the optical rotation was $[\alpha]^{25}_{D} = -33.2^{o}$ (*c* = 2.0, EtOH).



8a **8b**

***cis* rotamer** ***trans* rotamer**

Figure 8. Structure of *cis* and *trans* rotamer

The diastereomeric excess was confirmed by ^{1}H NMR spectroscopy. Interestingly, when sample was scanned at room temperature, ^{1}H NMR spectra showed two rotamers, i.e. *cis* and *trans* isomers, owing to restricted rotation about the *N*-CO bond

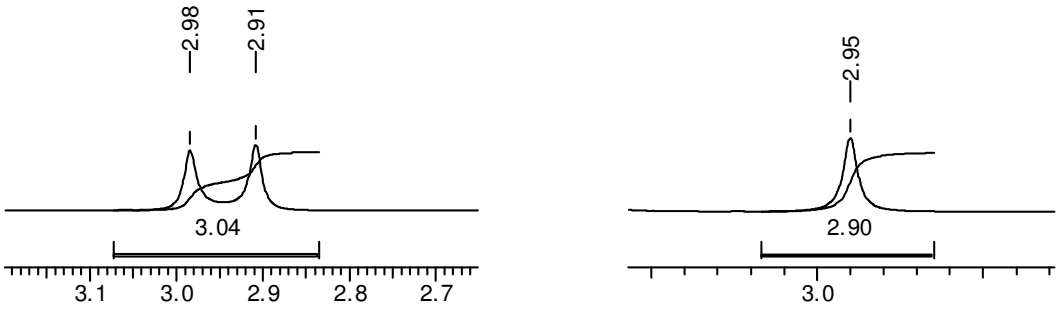
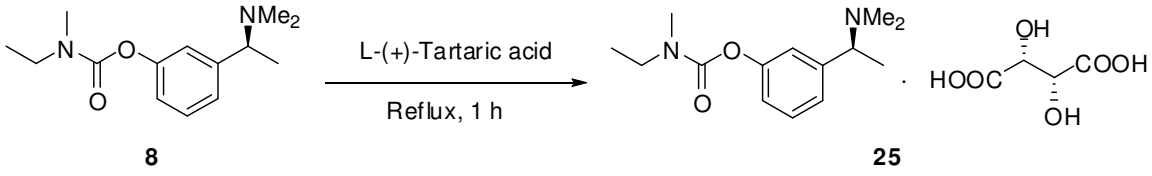


Figure 9. *cis* and *trans* rotamers in ^{1}H NMR spectra at room temperature and singlet of methyl group at 70 ^{o}C.

of carbamate (**Figure 9**). To confirm the diastereoselectivity of compound **8**, we had recorded NMR spectrum at high temperature (70 ^{o}C), the spectroscopic measurement showed only one diastereomer and d.e. was estimated to be >98%.

Since, rivastigmine is marketed as tartrate salt under the brand name Exelon. So we made tartrate salt as well. The tartrate salt **25** was achieved by the treatment of L-(+)-tartaric acid in acetone with **8** in reflux condition for 1 h (**Scheme 16**). It was a white crystalline solid with optical rotation $[\alpha]^{25}_D = +4.32^o$ (c = 3.0, EtOH).



8 **25**

Scheme 16.

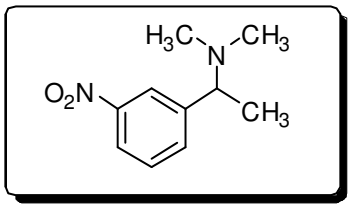
3.2.5 Conclusion

In summary, we have developed a simple and concise five-step organic transformation for the synthesis of (*S*)-(-)-rivastigmine **8** and its tartrate salt **25**.

3.2.6 Experimental Section

3.2.6.1 Procedure and Characterization data:

(A) [1-(3-nitrophenyl) ethyl] dimethylamine (52):

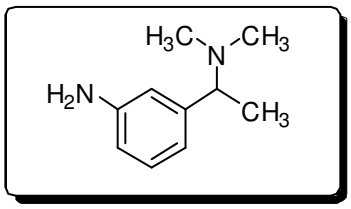


Titanium isopropoxide (86.14 g, 0.303 mol) was added slowly under inert atmosphere to a solution of dimethylamine (13.6 g, 0.303 mol) in dry methanol (80 mL), cooled it to 10 ^{o}C in a water-ice bath. Then we added 3-nitroacetophenone (25.0 g, 0.15 mol) slowly into the reaction mixture. The addition of titanium isopropoxide is slightly exothermic. The reaction mixture is then stirred at room temperature for 8-10 h. During the reaction period, the mixture becomes slightly turbid. After said period, sodium borohydride (8.6 g, 0.227 mol) was added slowly and carefully to the reaction mixture and stirred at room temperature for 8-10 h. The reaction mixture thickens into slurry and foams and it needs to be mixed very vigorously. The temperature was maintained at 25-30 ^{o}C by mild cooling with ice-water. The aqueous solution of ammonium hydroxide was slowly poured into the reaction mixture to quench the reaction. The fine white crystals of the inorganic material were sucked away and washed with methanol. The filtrate was evaporated in vacuo. The resulting residue was diluted with water and extracted with ethyl acetate. The combined organic layer was washed once with water and then extract with 2N HCl. The acidic aqueous extracts combined and basified with 20% NaOH to pH 12-14 and further extracted with EtOAc. The organic fraction was washed with water and brine, dried over Na_2SO_4 and concentrated to obtain crude product, which was further purified by column chromatography on silica gel (pet. ether/EtOAc = 90/10) to afford compound **52** as a dark yellow liquid (30.46 g, 46%).

Molecular formula	**:**	$C_{10}H_{14}N_2O_2$
Nature	**:**	Dark yellow liquid
IR ($CHCl_3$, υ_{max})	**:**	3091, 2594, 2055, 1556, 1345, 1216, 1120, 1025, 761 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.36-1.39 (d, J = 6.69 Hz, 3H), 2.20 (s, 6H), 3.33-3.43 (q, J = 6.70, 13.39 Hz, 1H), 7.48 (t, J = 7.83 Hz, 1H), 7.65 (d, J = 7.71 Hz, 1H), 8.08 (d, J = 8.09 Hz, 1H), 8.18 (s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 19.26, 42.57, 64.76, 121.56, 121.92, 128.85, 133.34, 146.86, 148.14 ppm.
Elemental Analysis	**:**	Calcd: C, 61.84; H, 7.27; N, 14.42.
$C_{10}H_{14}N_2O_2$ (194)		Found: C, 61.59; H, 7.33; N, 14.65.
MS (EI) ***(m/z)***	**:**	194 (M^+).

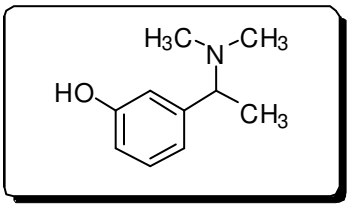
(B) [1-(3-aminophenyl) ethyl] dimethylamine (53):



A solution of compound **52** (5.0 g, 0.03 mol) in methanol (10 mL) was stirred over Raney-Nickel (6 mL slurry) under H_2 pressure (Parr Shaker; 60-psi pressure) for 3 h at room temperature. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel using pet. ether/EtOAc solvent system to yield compound **53** (3.3 g, 78%) as a reddish liquid.

Molecular formula	**:**	$C_{10}H_{16}N_2$
Nature	**:**	Reddish liquid
IR ($CHCl_3$, υ_{max})	**:**	3321, 3055, 2601, 2061, 1602, 1452, 1221, 1155, 1021, 762 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.32-1.35 (d, J = 6.57 Hz, 3H), 2.20 (s, 6H), 3.06-3.16 (q, J = 6.70, 13.39 Hz, 1H), 3.63 (s, 2H), 6.56-6.59 (m, 1H), 7.65-7.69 (m, 2H), 7.09 (t, J = 8.08 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 20.26, 43.27, 66.03, 113.63, 113.91, 117.81, 128.91, 145.54, 146.28 ppm.
Elemental Analysis	**:**	Calcd: C, 73.13; H, 9.82; N, 17.06.
$C_{10}H_{16}N_2$ (164)		Found: C, 73.01; H, 9.96; N, 16.88.
MS (EI) ***(m/z)***	**:**	164 (M^+).

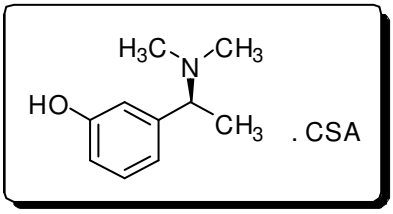
(C) Racemic 3-(1-(dimethylamino)ethyl)phenol (23):



To a mixture of compound **53** (1.0 g, 0.6 mmol) in H_2O (20 mL) was added 95% H_2SO_4 (1.97 mL). This mixture was diazotized with solution of $NaNO_2$ (0.53 g, 7.7 mmol) in H_2O (2 mL) at 0 ^oC. The mixture was stirred for 30 min and poured into the H_2O (2 mL). The reaction mixture was boiled for about 1 h to give brown tar. The reaction was monitored by TLC. The crude product was extracted with ethyl acetate and purified by column chromatography to obtain compound **23** as a faint yellow solid (0.936 g, 93%).

Molecular formula	**:**	$C_{10}H_{15}NO$
Nature	**:**	Faint yellow solid
Mp	**:**	85-86 ^oC
IR ($CHCl_3$, υ_{max})	**:**	3396, 2945, 2833, 2597, 2042, 1642, 1450, 1217, 1114, 1030, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.35-1.39 (d, J = 6.67 Hz, 3H), 2.23 (s, 6H), 3.18-3.31 (q, J = 6.67, 13.27 Hz, 1H), 5.32 (s, 1H), 6.70-6.80 (m, 3H), 7.14 (t, J = 7.58 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 19.01, 43.20, 67.11, 116.41, 116.73, 120.55, 130.15, 144.60, 158.15 ppm.
Elemental Analysis	**:**	Calcd: C, 72.69; H, 9.15; N, 8.48.
$C_{10}H_{15}NO$ (165)		Found: C, 72.46; H, 9.37; N, 8.46.
MS (EI) ***(m/z)***	**:**	165 (M^+).

(D) (*S*)-3-(1-(dimethylamino)ethyl)phenol (1*S*)-(+)-10-camphorsulfonic acid salt, monohydrate (54):

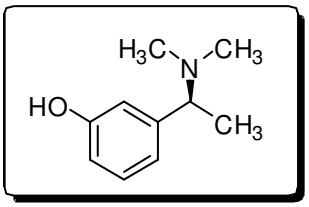


The racemic phenol **23** (10.0 g, 0.060 mol) was dissolved in ethyl acetate (50 mL). In a separate vessel, (1*S*)-(+)-10-camphorsulfonic acid (CSA) (15.48 g, 0.0618 mol) was dissolved in ethanol (6 mL). Upon complete dissolution of the solid, the (*S*)-CSA/EtOH solution was transferred to the phenol/EtOAc solution. The mixture was heated at 80-90

^{o}C to dissolve any solids. After dissolution of solids, the solution was cooled to room temperature over 12-18 h. The slurry was filtered to collect the solids and the filter-cake washed with ethyl acetate and dried. A total of 6.2 g (31.5%) of the desired (*S*)-CSA (*S*)-phenol salt, monohydrate was obtained with an enantiomeric excess of 99% as determined by GC analysis [Chiral GC analysis: CP-Cyclodextrin (0.25µm x 0.30 mm x 30 m)]; $[\alpha]^{25}_{D}$ = + 12.65^{o} (*c* = 2.0, MeOH).

Molecular formula	**:**	$C_{20}H_{31}NO_5S$
Nature	**:**	Faint yellow solid
Mp	**:**	176-178 ^{o}C
IR ($CHCl_3$, υ_{max})	**:**	3350, 3018, 2914, 2399, 1741, 1604, 1462, 1217, 1037, 769, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 0.67 (s, 3H), 0.92 (s, 3H), 1.16-1.28 (m, 1H), 1.56-1.59 (d, *J* = 6.94 Hz, 3H), 1.76-1.90 (m, 3H), 2.09-2.22 (m, 1H), 2.50 (d, *J* = 4.92 Hz, 3H), 2.69 (d, *J* = 4.55 Hz, 3H), 3.11-3.18 (brs, 5H), 4.00-4.13 (m, 1H), 6.66-6.76 (m, 2H), 6.88 (s, 1H), 7.07 (t, *J* = 7.83 Hz, 1H), 10.22 (brs, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 14.51, 17.63, 18.06, 22.23, 24.54, 40.21, 40.38, 44.83, 45.27, 56.21, 63.02, 113.68, 114.56, 117.15, 128.10, 134.56, 155.86, 214.27 ppm.

(E) (*S*)-3-(1-(dimethylamino)ethyl)phenol (24):

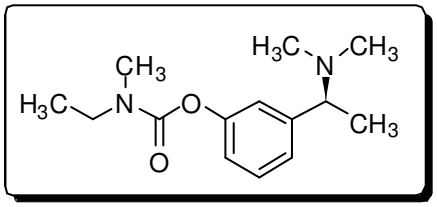


Sodium carbonate (0.29 g, 2.7 mmol) was dissolved in water (5 mL) under stirring. The CSA salt of phenol **54** (0.59 g, 1.4 mmol) is added into the solution of saturated sodium carbonate under stirring and stirred further for 5 min at room temperature. To this reaction mixture was added ethyl acetate (5 mL) and again stirred for 5 min. Then, the layers were separated. The aqueous layer was extracted twice with ethyl acetate (95 mL). The combined organic fractions washed with water, dried over Na_2SO_4 and concentrated to afford brownish white solid **24** (0.225 g, 96%). $[\alpha]^{25}_{D}$ = -

55.05° (*c* = 1.55 MeOH) {Lit. $[\alpha]^{25}_D$ = -55.7° (*c* = 1.55 MeOH)}; ee > 99% [Chiral GC analysis: CP-Cyclodextrin (0.25µm x 0.30 mm x 30 m)].

Molecular formula	**:**	$C_{10}H_{15}NO$
Nature	**:**	Brownish white solid
Mp	**:**	116.5-118.5 °C
IR ($CHCl_3$, υ_{max})	**:**	3398, 2945, 2833, 2596, 2042, 1641, 1450, 1217, 1114, 1030, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	**:**	δ 1.36-1.39 (d, *J* = 6.69 Hz, 3H), 2.22 (s, 6H), 3.19-3.29 (q, *J* = 6.69, 13.26 Hz, 1H), 5.30 (s, 1H), 6.81 (m, 3H), 7.15 (t, *J* = 7.58 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	**:**	δ 18.93, 42.37, 65.47, 115.10, 115.63, 119.24, 129.25, 142.73, 157.10 ppm.
Elemental Analysis	**:**	Calcd: C, 72.69; H, 9.15; N, 8.48
$C_{10}H_{15}NO$ (165)		Found: C, 72.46; H, 9.37; N, 8.46.
MS (EI) ***(m/z)***	**:**	165 (M^+).

(F) (*S*)-(-)-Rivastigmine (8):



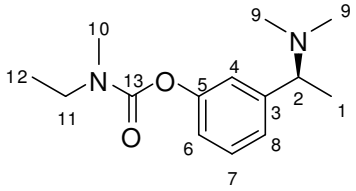
To a stirred solution of chiral phenol **24** (0.1 g, 0.60 mmol) in acetone (5 mL) was added K_2CO_3 (0.1 g, 0.72 mmol) at room temperature for 30 min. Then *N*-ethyl-*N*-methyl carbamoyl chloride (0.088 g, 0.72 mmol) was added and refluxed for 16-18 h. The resulting reaction was monitored by TLC and GC. The reaction mixture was cooled gradually to room temperature and filtered. The filtrate was quenched in ice-water mixture and then extracted with CH_2Cl_2. The organic layer was washed with 1N NaOH, dried over Na_2SO_4, concentrated to afford (*S*)-rivastigmine **8** as a colourless liquid (6.4 g, 84%).

Molecular formula	**:**	$C_{14}H_{22}N_2O_2$
Nature	**:**	Pale yellow liquid
$[\alpha]^{25}_D$	**:**	-33.2° (*c* = 2.0, EtOH)
IR ($CHCl_3$, υ_{max})	**:**	2917, 2851, 2253, 2126, 1706, 1643, 1462, 1399,

1240, 1026, 826, 765 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.13-1.18 (m, 3H, H_{12}, 2 rotamers), 1.29 (d, J = 6.69 Hz, 3H), 2.17 (s, 6H), 2.95 (2 x s, 3H, H_{10}, 2 rotamers), 3.39-3.42 (m, 3H, H_2 & H_{11} merge), 6.97 (d, J = 7.81 Hz, 1H), 7.06 (s, 1H), 7.13 (d, J = 7.24 Hz, 1H), 7.29 (t, J = 7.71 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100MHz) :



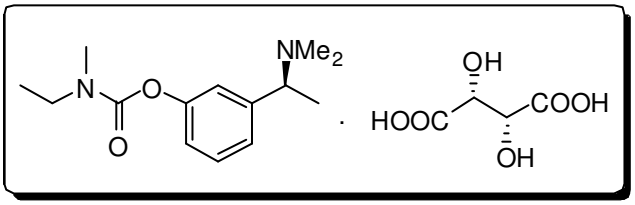
δ 12.27 (C_{12}, rotamer 1), 13.03 (C_{12}, rotamer 2), 19.29 (C_1), 33.60 (C_{10}, rotamer 1), 34.01 (C_{10}, rotamer 2), 42.39 (C_9), 43.85 (C_{11}), 65.27 (C_2), 120.57 (C_4), 120.87 (C_6, rotamer 1), 120.94 (C_6, rotamer 2), 124.32 (C_8), 128.88 (C_7), 143.49 (C_5, rotamer 1), 143.67 (C_5, rotamer 2), 151.39 (C_3), 154.15 (C=O, rotamer 1), 154.34 (C=O, rotamer 2) ppm.

Elemental Analysis : Calcd: C, 67.20; H, 8.80; N, 11.20.

$C_{14}H_{22}N_2O_2$ (250) Found: C, 67.15; H, 8.81; N, 11.18.

MS (EI) ***(m/z)*** : 250 (M^+).

(G) (*S*)-(-)-Rivastigmine tartrate (25):



(*S*)-(-)-Rivastigmine **8** (4.72 g, 18.9 mmol) was dissolved in acetone (30 mL) and L-(+)-tartaric acid (2.83 g, 18.9 mmol) was added. The reaction mixture was refluxed for 1 h and allowed to cool to room temperature slowly and kept overnight at room tempeature. The precipitated white crystalline solid was filtered off and washed with cold acetone and dried to afford (*S*)-rivastigmine tartrate **25** (6.4 g, 84%).

Molecular formula : $C_{18}H_{28}N_2O_8$

Nature : White crystalline solid

Mp : 123-124 ^oC

$[\alpha]^{25}_D$: +4.32^o (c = 3.0, EtOH)

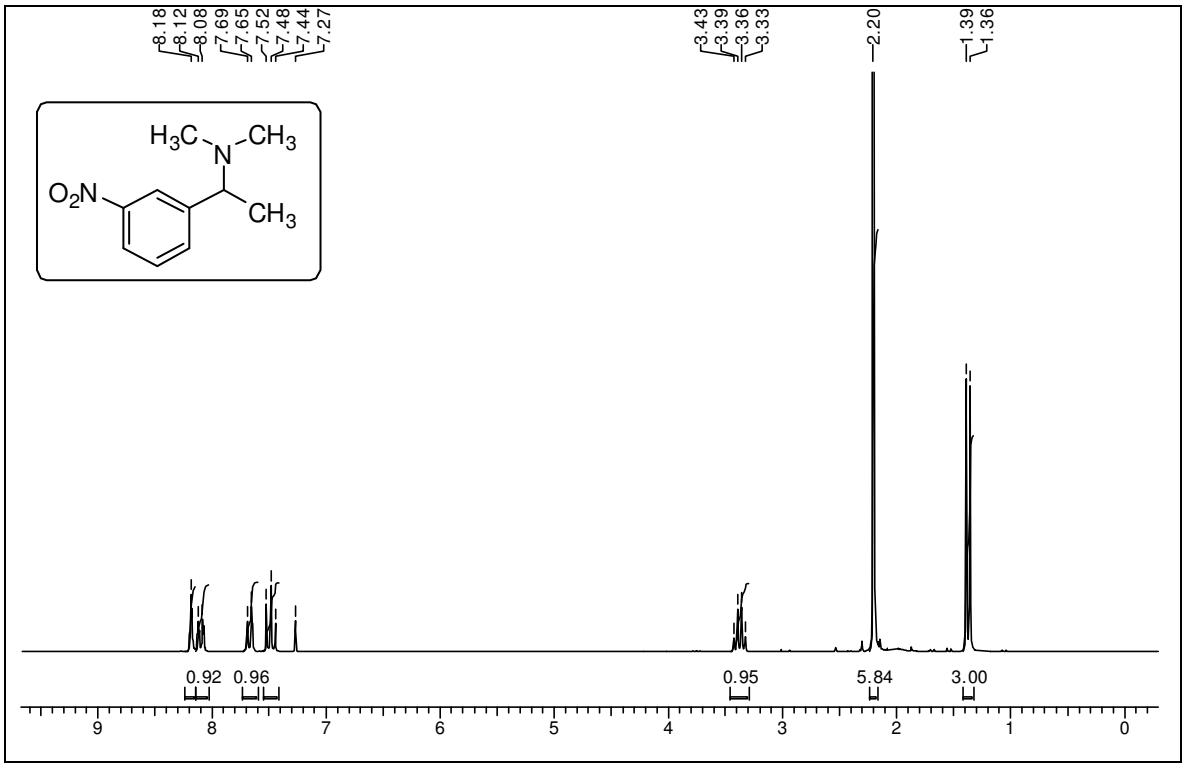
IR ($CHCl_3$, υ_{max})	**:**	3320, 2979, 2936, 2875, 1717, 1591, 1403, 1305, 1134, 1068, 789, 679 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200MHz)	**:**	δ 1.11-1.25 (m, 3H, H_{12}, 2 rotamers), 1.64 (d, J = 5.68 Hz, 3H), 2.63 (s, 6H), 2.94 (2 x s, 3H, H_{10}, 2 rotamers), 3.31-3.47 (m, 2H), 4.33 (d, 1H), 4.49 (s, 2H), 6.97-7.42 (m, 8H) ppm.
^{13}C NMR ($CDCl_3$, 50MHz)	**:**	δ 12.23 (C_{12}, rotamer 1), 13.03 (C_{12}, rotamer 2), 16.24, 33.70 (C_{10}, rotamer 1), 34.08 (C_{10}, rotamer 2), 40.15, 43.97, 64.78, 72.69, 122.52, 122.87, 126.13, 129.85, 135.17, 151.51, 154.04 (C=O, rotamer 1), 154.20 (C=O, rotamer 2), 176.15 ppm.
Elemental Analysis	**:**	Calcd: C, 53.99; H, 7.05; N, 7.0.
$C_{18}H_{28}N_2O_8$ (251)		Found: C, 53.98; H, 7.15; N, 6.95.

3.2.7 Spectral data

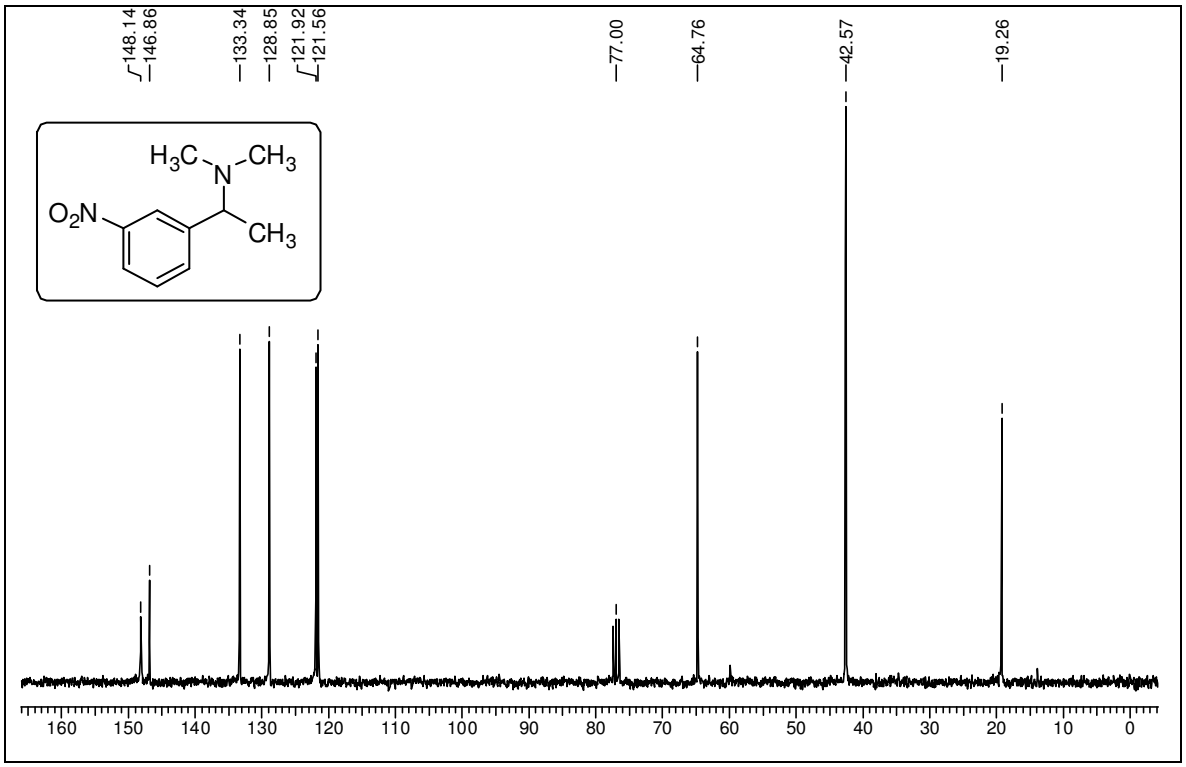
Table 2. ^{1}H, ^{13}C and ^{13}C DEPT NMR spectrum of some selected compounds are given below:

Sr. No.	Spectra	
1	^{1}H and ^{13}C NMR spectra of compound	**52**
2	^{1}H and ^{13}C NMR spectra of compound	**53**
3	^{1}H and ^{13}C NMR spectra of compound	**54**
4	^{1}H and ^{13}C NMR spectra of compound	**24**
5	^{1}H, ^{13}C and DEPT NMR spectra of compound	**8**
6	^{1}H, ^{13}C and DEPT NMR spectra of compound	**55**

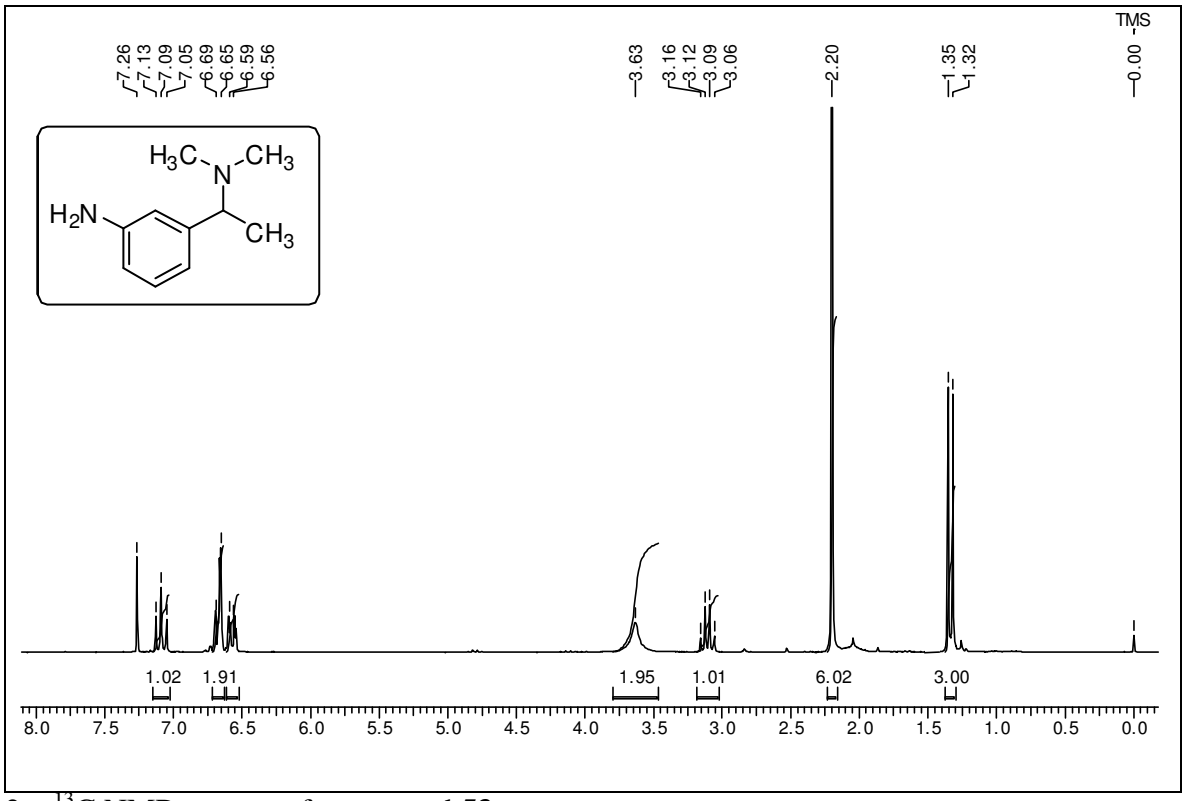
1. ^{1}H NMR spectra of compound **52**:



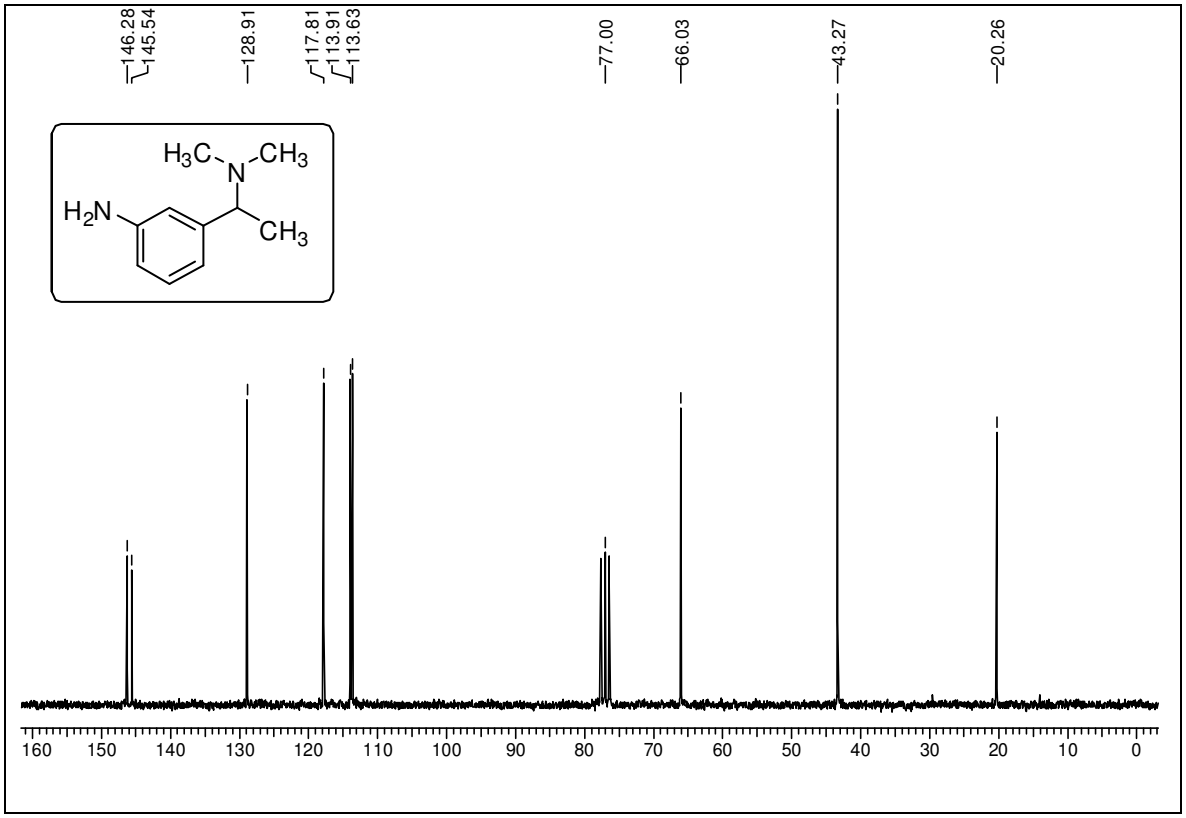
1. ^{13}C NMR spectra of compound **52**:



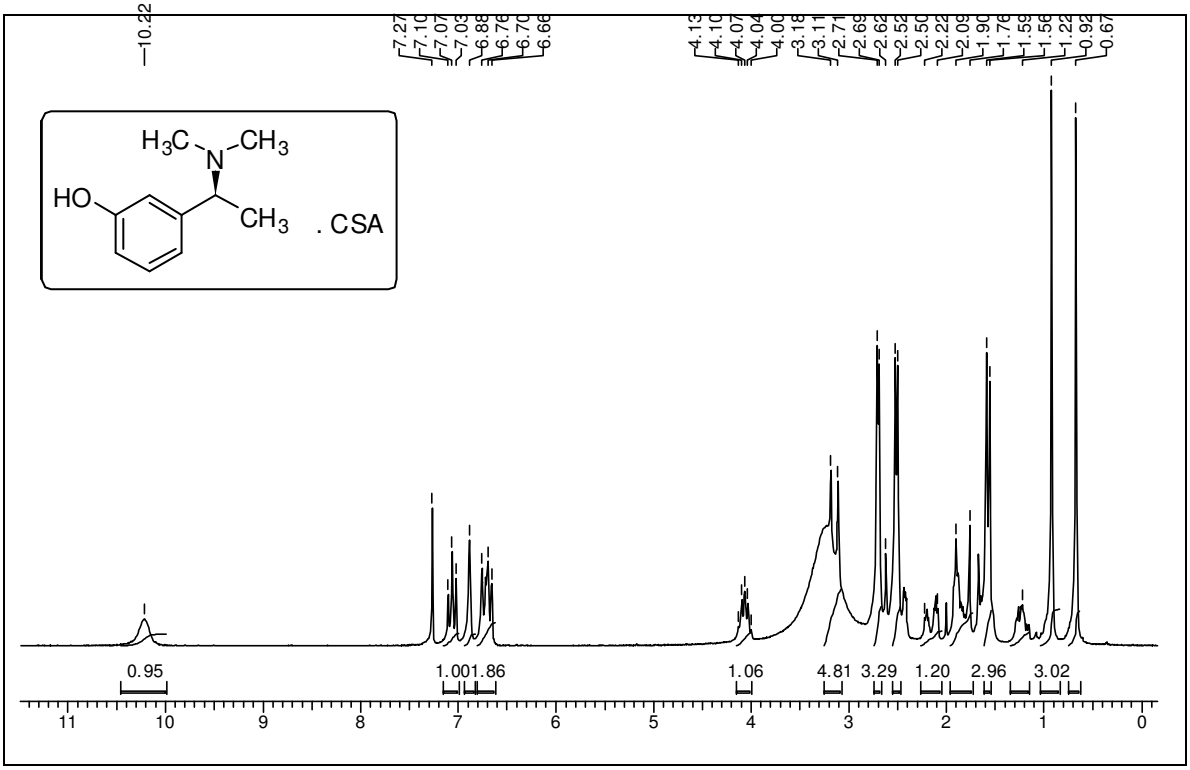
2. ^{1}H NMR spectra of compound **53**:



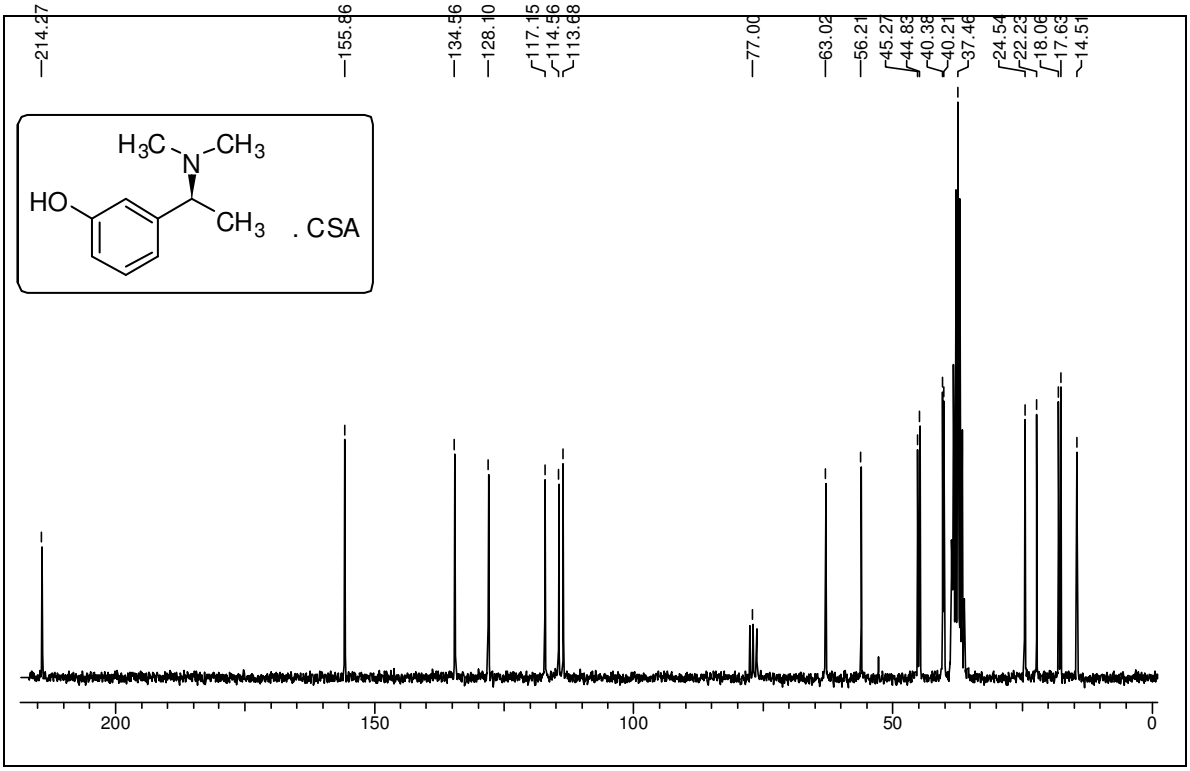
2. ^{13}C NMR spectra of compound **53**:



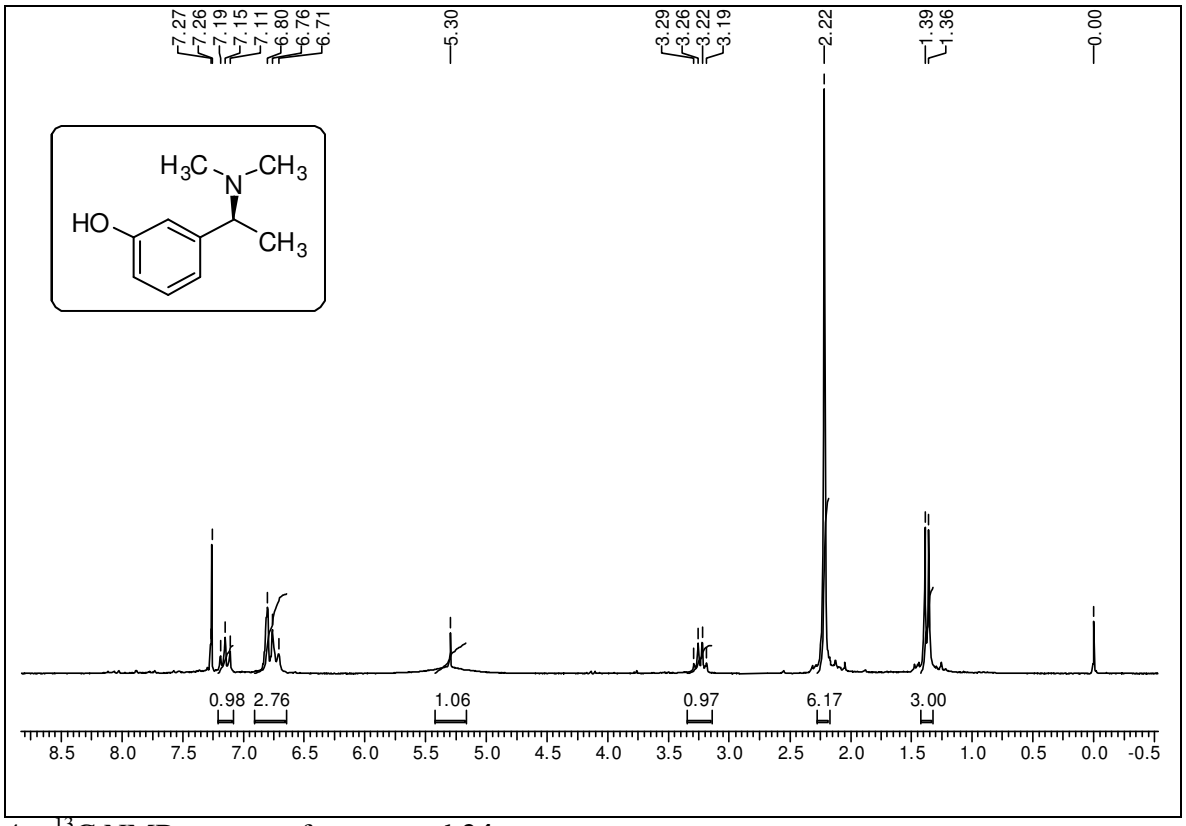
3. ^{1}H NMR spectra of compound **54**:



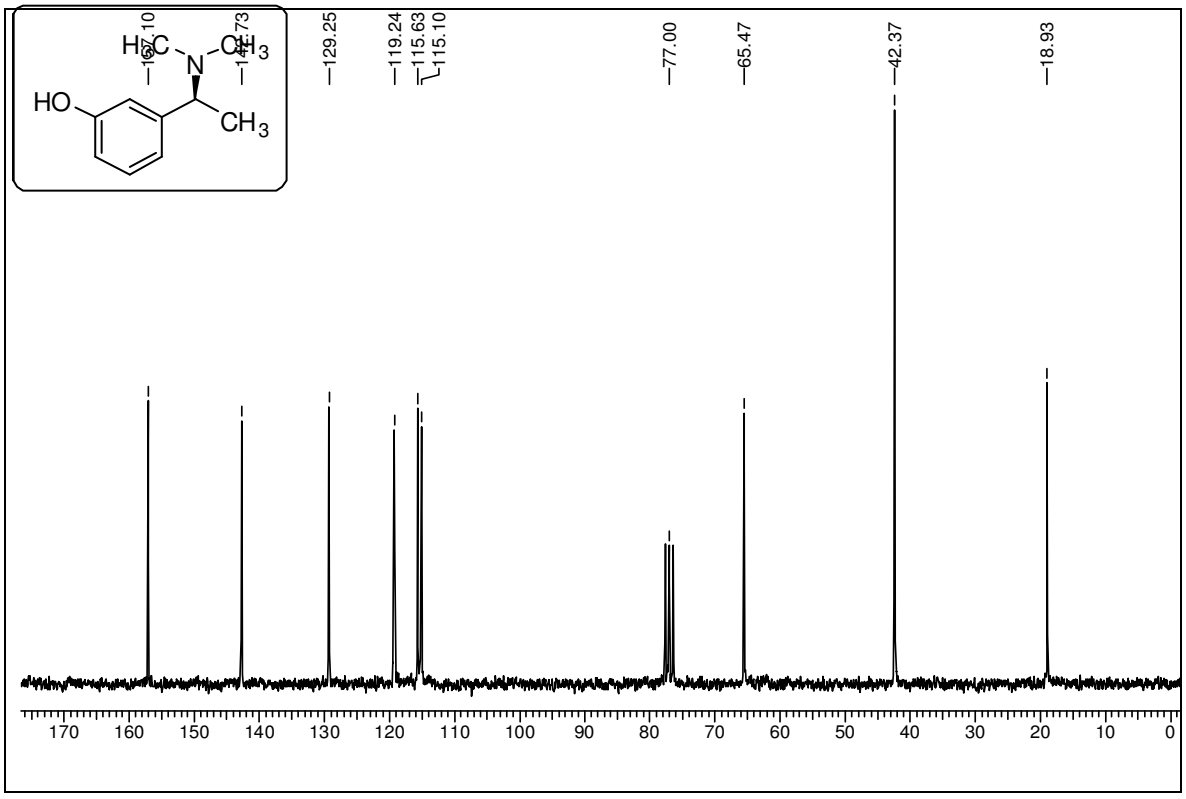
3. ^{13}C NMR spectra of compound **54**:



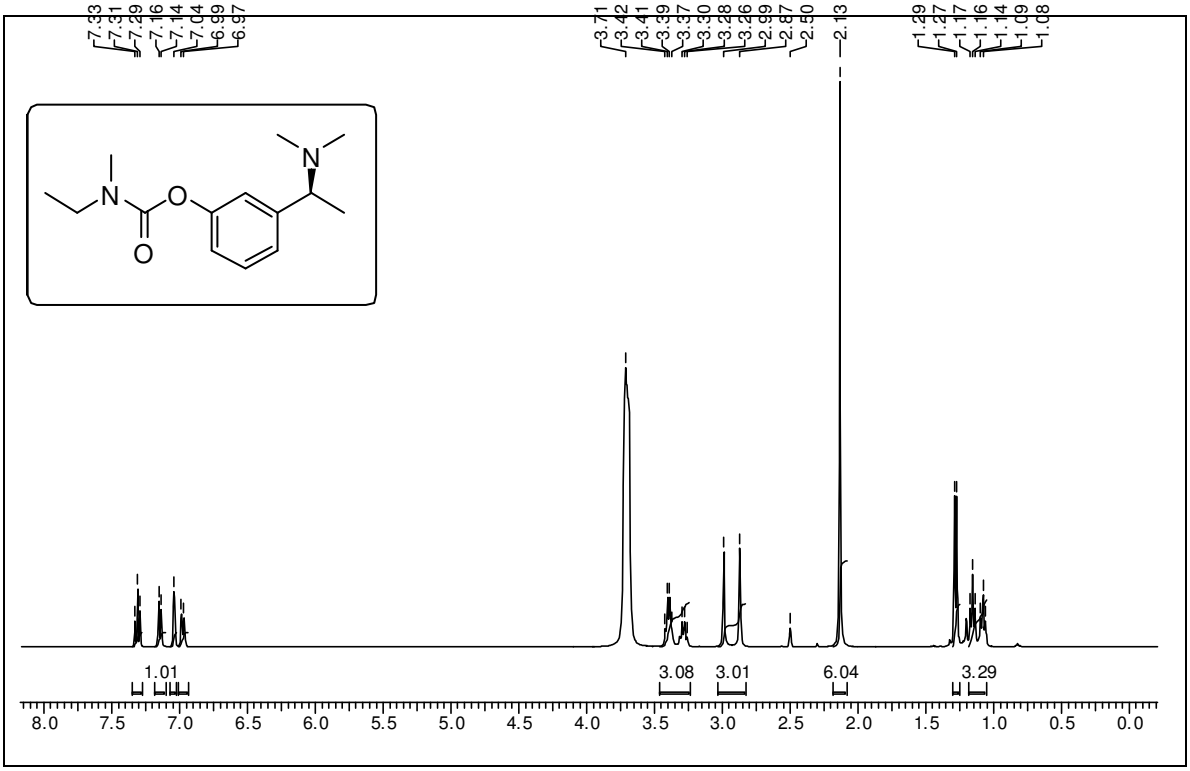
4. ^{1}H NMR spectra of compound **24**:



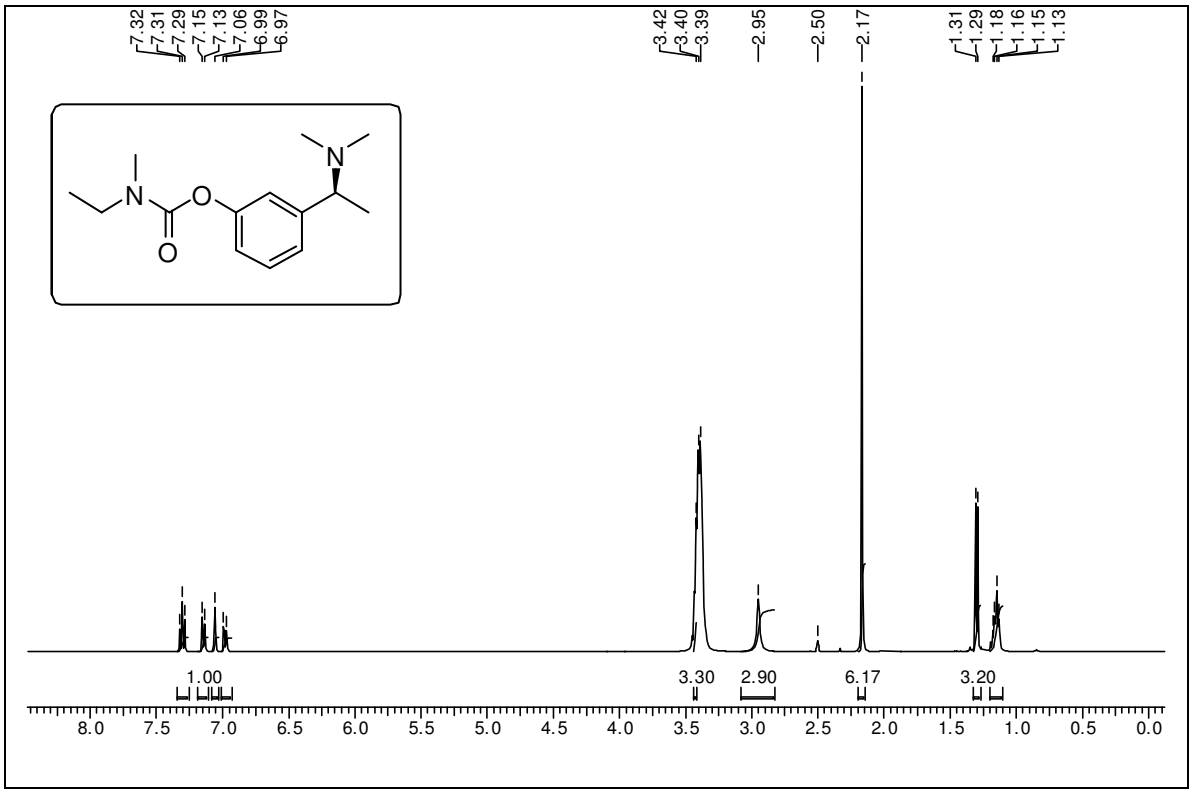
4. ^{13}C NMR spectra of compound **24**:



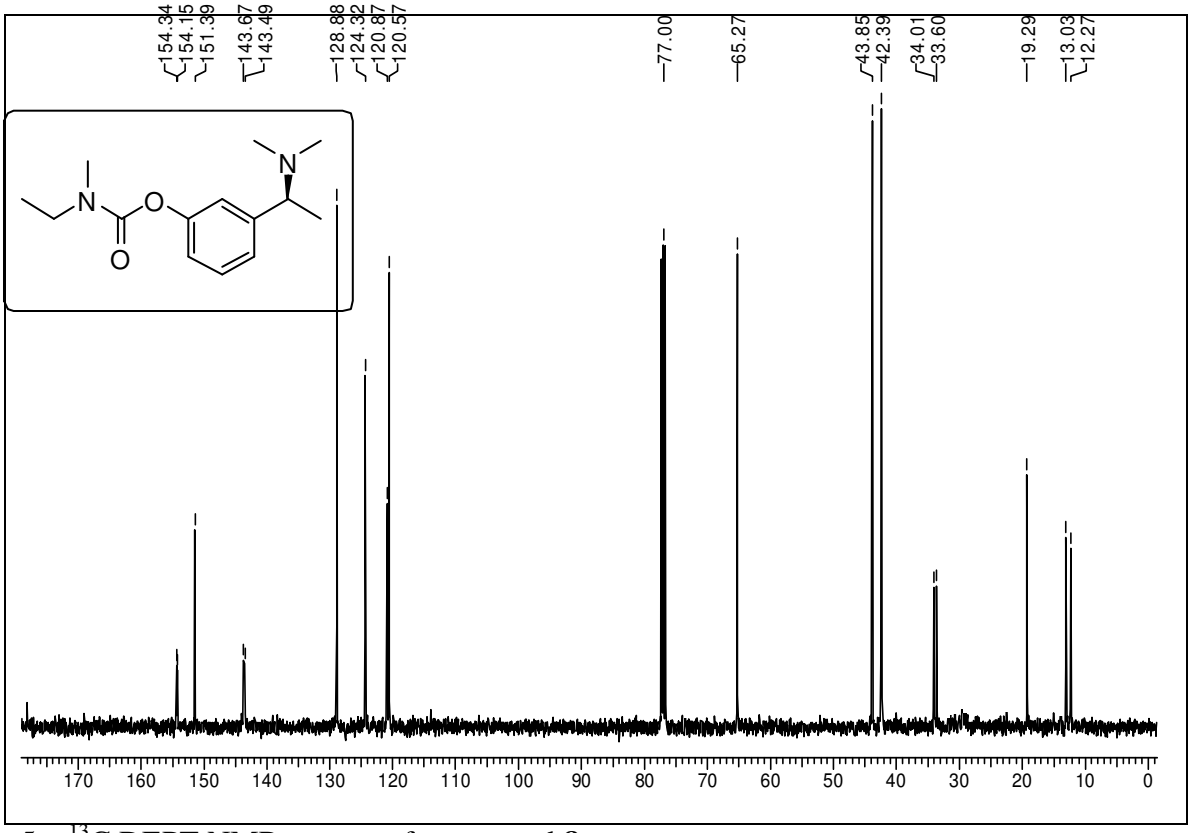
5. ^{1}H NMR spectra of compound **8** at room temperature:



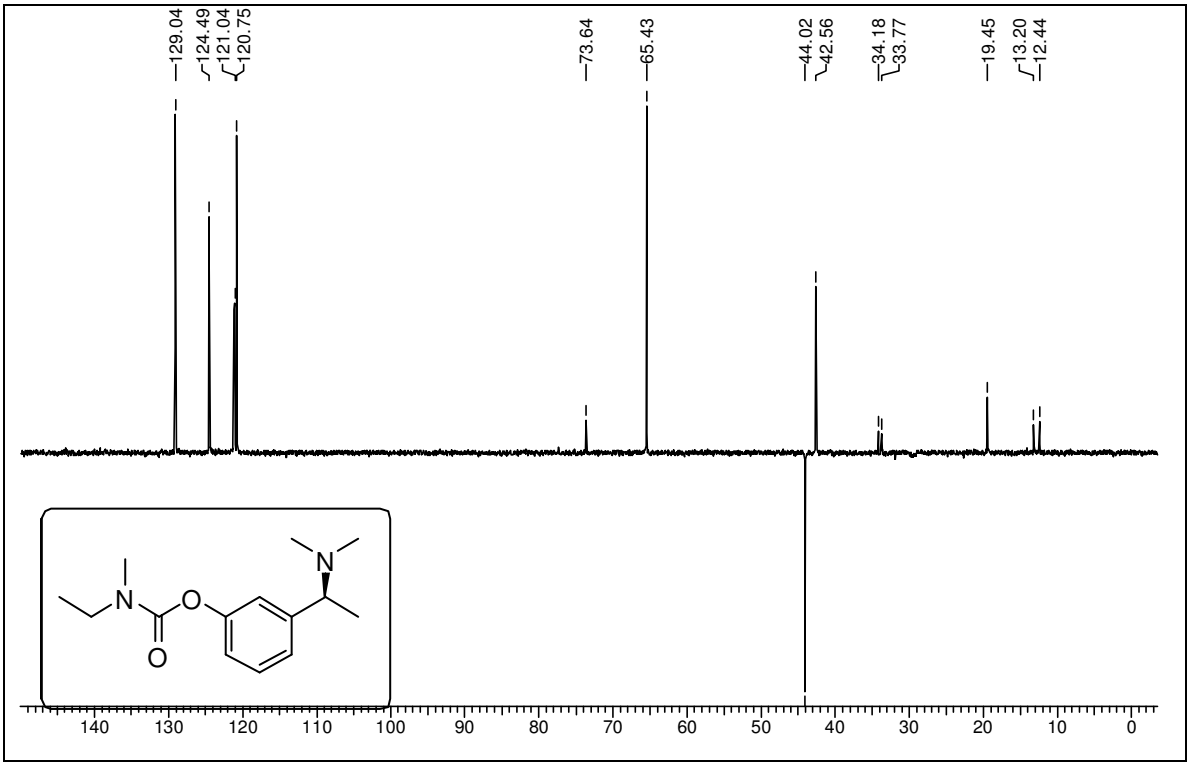
5. ^{1}H NMR spectra of compound **8** at 70 ^{o}C:



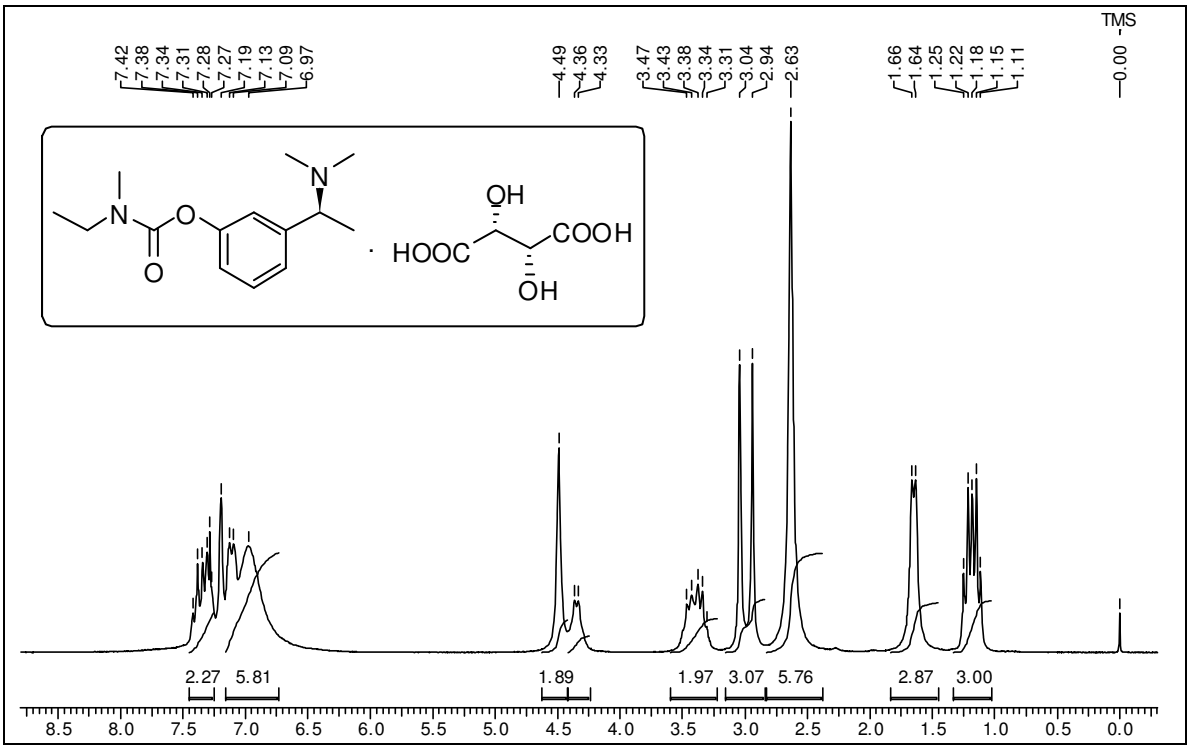
5. ^{13}C NMR spectra of compound **8** at room temperature:



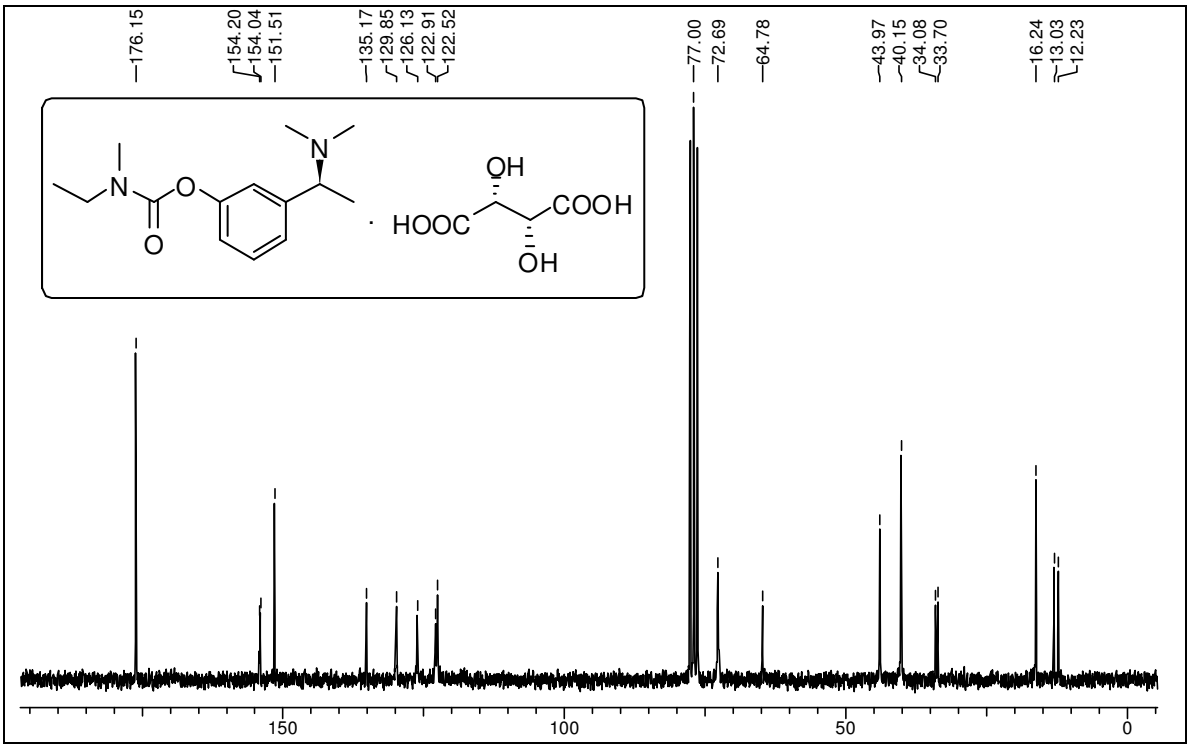
5. ^{13}C DEPT NMR spectra of compound **8**:



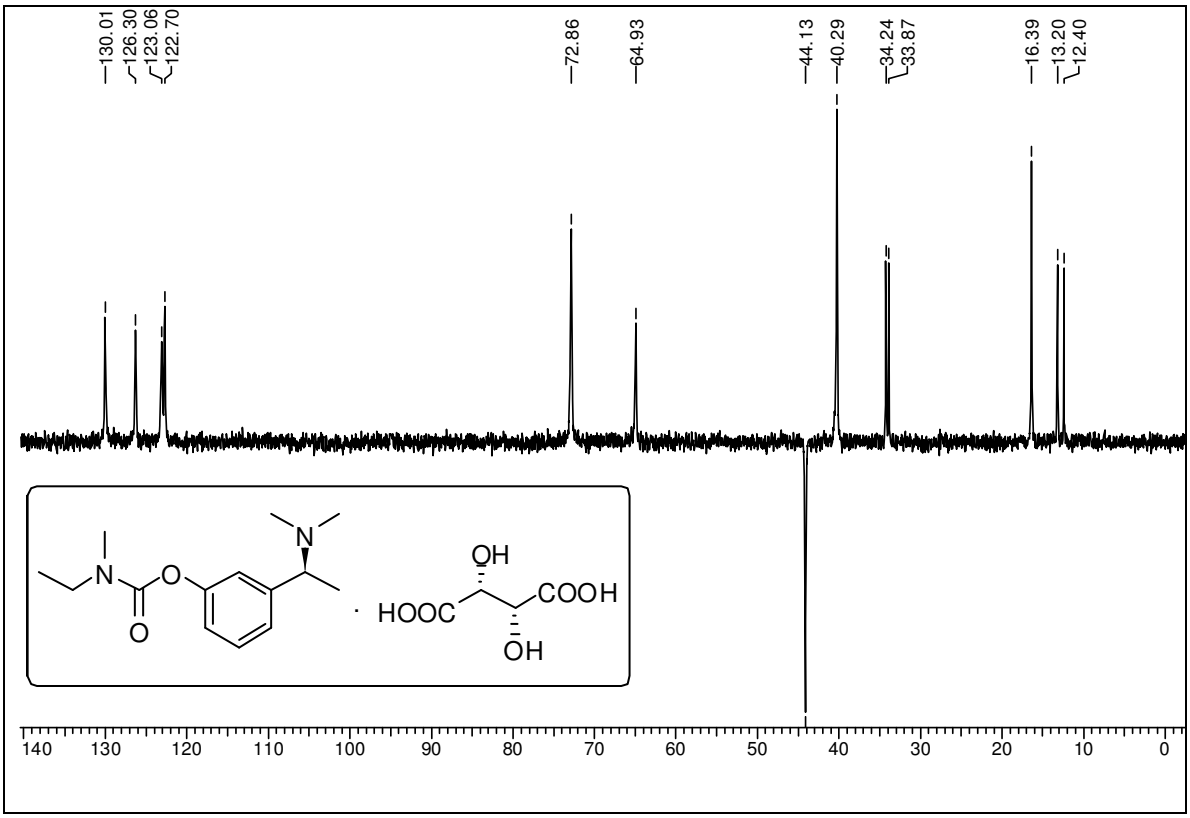
6. ^{1}H NMR spectra of compound **55**:



6. ^{13}C NMR spectra of compound **55**:



6. ^{13}C DEPT NMR spectra of compound **55**:



3.2.8 References:

1. Berchtold, N. C.; Cotman, C. W. *Neurobiology of Aging* **1998**, *19*, 173.
2. Brookmeyer, R.; Gray, S.; Kawas, C. *Am. J. Public Health* **1998**, *88*, 1337.
3. Brookmeyer, R.; Johnson, E.; Ziegler-Graham, K.; Arrighi, H. M. *Alzheimer's and Dementia* **2007**, *3*, 186.
4. Tiraboschi, P.; Hansen, L. A.; Thal, L. J.; Corey-Bloom, J. *Neurology* **2004**, *62*, 1984.
5. Cummings, J. L. *Am. J. Psychiatry* **2000**, *157*, 4.
6. López-Arrieta, J.; Schneider, L. *Cochrane Database of Systematic Reviews* **2009**, *4*.
7. (a) Enz, A.; Amstutz, R.; Boddeke, H.; Gmelin, G.; Malanowski, J. *Prog. Brain Res.* **1993**, *98*, 431; (b) Millard, C. B.; Broomfield, C. A. *Neurochemistry* **1995**, *64*, 1909; (c) Bryson, H. M.; Benfield, P. *Drugs Aging* **1997**, *10*, 234; (d) Dooley, M.; Lamb, H. M. *Drugs Aging* **2000**, *16*, 199.
8. Kosasa, T.; Kuriya, Y.; Matsui, K.; Yamanishi, Y. *Eur. J. Pharmacology* **1999**, *386*, 7.
9. Bores, G. M.; Kosley, R. W. *Drugs Future* **1996**, *21*, 621.
10. Lilienfeld, S. *CNS Drug Rev.* **2002**. *8*, 159.
11. Julian, P. L.; Pikl, J. *J. Am. Chem. Soc.* **1935**, *57*, 755.
12. Aeschlimann, J. A.; Reinert, M. *J. Pharmacol.* **1931**, *43*, 413.
13. Yu, Q. -S.; Holloway, H. W.; Luo, W.; Lahiri, D. K.; Brossi, A.; Greig, N. H. *Bioorg. Med. Chem.* **2010**, *18*, 4687.
14. (a) Hodge, A. S.; Humphrey, D. R.; Rosenberry, T. L. *Mol. Pharmacol.* **1992**, *41***,** 937; (b) Bolognesi, M. L.; Cavalli, A.; Andrisano, V. *Farmaco* **2003**, *58*, 917.
15. Camps, P.; Munoz-Torrero, D. *Med. Chem.* **2002**, *2*, 11.
16. Ward, D.; Abney, K.; Oliver, J. *Vet. Ophthalmol.* **2003**, *6*, 23.
17. Crismon, M. L. *Ann. Pharmacother.* **1994**, *28*, 744.
18. Wang, B. -S.; Wang, H.; Wei, Z. -H.; Song, Y.; Zhang, L.; Chen, H. -Z. *J. Neural Transmission* **2009**, *116***,** 457.
19. Weinstock, M.; Bejar, C.; Wang, R. H. *J. Neural Transmission* **2000**, *60*, 157.

20. Leonetti, F.; Catto, M.; Nicolotti, O.; Pisani, L.; Cappa, A.; Stefanachi, A.; Carotti, A. *Bioorg. Med. Chem.* **2008**, *16*, 7450.
21. Darvesh, S.; Hopkins, D. A. *J. Comp. Neurol.* **2003**, *463*, 25.
22. Kamal, M. A.; Qu, X.; Yu, Q. -S.; Tweedie, D.; Holloway, H. W.; Li, Y.; Tan, Y.; Greig, N. H. *J. Neural. Transm.* **2008**, *115*, 889.
23. Boezio, A. A.; Pytkowicz, J.; Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260.
24. Amstutz, R.; Enz, A.; Marzi, M.; Boelsterli, J.; Walkinshaw, M. *Helv. Chim. Acta* **1990**, *73*, 739.
25. Stepankova, H.; Hajicek, J.; Simek, S. PCT, WO 2004/037771 A1, **2004.**
26. Gaitonde, A.; Mangle, M. GB 2005/2409453, **2005**.
27. Gaitonde, A.; Mangle, M.; Pawar, S. PCT, WO 2005/061446, **2005.**
28. Feng, J.; Chen, W. M.; Sun, P. H. *Nan Fang Yi Ke Da Xue Xue Bao* **2007**, *27*, 177.
29. Wawzonck, S.; Mckillip, W.; Peterson, C. J. *Org. Synth.* **1964**, *44*, 75.
30. Garrido, M.; Vicente, J.; Montserrat, A.; Miquel; Jorge, M. J. PCT, WO 2007/014973, **2007**.
31. Hu, M.; Zhang, F. L.; Xie, M. H. *Synthetic Commun,* **2009**, *39*, 1527.
32. Hu, M.; Zhang, F. L.; Xie, M. H. *Lett. Org. Chem.* **2007**, *4*, 126.
33. Mangas-Sánchez, J.; Rodriguez-Mata, M.; Busto, E.; Gotor-Fernández, V.; Gotor, V. *J. Org. Chem.* **2009**, *74*, 5304.
34. Han, K.; Kim, C.; Park, J.; Kim, M. -J. *J. Org. Chem.* **2010**, *75*, 3105.
35. Fuchs, M.; Koszelewski, D.; Tauber, K.; Kroutil, W.; Faber, K. *Chem. Commun*. **2010**, *46*, 5500.
36. Polinsky, R. J. *Clin. Ther.* **1998**, *20*, 634.
37. Rosler, M.; anand, R.; Cicin-Sain, A.; Gauthier, S.; Agid, Y.; Dal-Bianco, P.; Stahelin, H. B.; Hartman, R.; Gharabawi, M. *Brit. Med. J.* **1999**, *318*, 633.
38. Reading, P. J.; Luce, A. K.; McKeith, I. G. *Movement Disord.* **2001**, *16*, 1171.

List of publications:

A. Papers published/communicated/to be communicated based on the present work:

1. **Borikar, S. P**.; Daniel, T.; Paul V. "An efficient, rapid, and regioselective bromination of anilines and phenols with 1-butyl-3-methylpyridinium tribromide as a new reagent/solvent under mild conditions." *Tetrahedron Lett.* **2009**, *50*, 1007.
2. **Borikar, S. P.**; Daniel, T.; Paul V. "A mild, efficient and regioselective monobromination of arylamines and phenols using [BBIm]Br_3 as a new reagent" *Synthetic Commun*. **2010,** *40*, 647.
3. **Borikar, S. P.**; Paul V. "*N*-Nitrosation of secondary amines using *p*-TSA-$NaNO_2$ as a novel nitrosating agent under mild conditions" *Synthetic Commun*. **2010,** *40*, 654.
4. **Borikar, S. P**. *et al*. "A convenient and efficient protocol for the synthesis of acylals catalyzed by brønsted acidic ionic liquid under ultrasonic irradiation" communicated to *Ultrasonics Sonochemistry.*
5. **Borikar, S. P**. *et al*. "Aromatic Bromination of Aldehydes and Ketones using 1,3-Di-*n*-butylimidazolium Tribromide [BBIm]Br_3 Ionic Liquids under Solvent-Free Conditions" communicated to *Journal of Iranian Chemical Society.*
6. **Borikar, S. P**. *et al*. "Formal synthesis of 5-hydroxy-3-methyl-4-propylsulfanyl-5H-furan-2-one" (to be communicated).
7. **Borikar, S. P.;** *et al*. "The first total synthesis of 5-hydroxy-3-methyl-4-propylsulfanyl-5*H*-furan-2-one as potential anticancer agent derived from *Allium cepa*" (to be communicated.)

B. Posters presented in Conferences/Workshop:

8. An efficient, rapid, and regioselective bromination of anilines and phenols with 1-butyl-3-methylpyridinium tribromide as a new reagent/solvent under mild conditions **S. P. Borikar,** Thomas Daniel, and Vincent Paul **19th National Symposium on catalysis** , (CATSYMP-19) Poster No. 66, 18-21 Jan 2009 National Chemical Laboratory ,Pune 411008

9. An efficient, rapid, and regioselective bromination of anilines and phenols with 1-3-dibutyl-Imidazolium tribromide as a new reagent/solvent under mild conditions. **S. P. Borikar,** Thomas Daniel, and Vincent Paul **11th CRSI National Symposium in Chemistry** at NCL Pune Feb 6-8 2009.
10. 1,3-Di-*N*-butyl-2-MethylImidazolium tribromide as a new reagent for regioselective bromination of anilines and phenols under solvent free conditions" **S. P. Borikar,** Thomas Daniel, and Vincent Paul Poster present ed at National Seminar on Emerging Trends in Chemical Science Research (**NSETCSR**) on Jan 20-21, 2009 at Dept of Chemistry ,Sardar Patel University , Vallabh Vidyanagar, Gujarat 38812.

C. List of patents:

11. "Process for the preparation of racemic 1-[4-[2-(allyloxy)ethyl]phenoxy]-3-isopropylamino-2-propanol and its use in the preparation of racemic betaxolol." **Borikar, S. P.** *et al.* **2006**, *US* 2006094903.
12. "RS 1-{4-{2-(allyloxy)-ethyl} phenoxy}-3-isopropylamino propan-2-ol, process for preparation thereof and process for preparation of RS betaxolol." **Borikar, S. P.** *et al.* **2004**, *IN* 2004DE02311.
13. "Preparation of S-(-)-1-[4-[2-(allyloxy) ethyl]phenoxy]-3-isopropylaminopropan-2-ol as an intermediate for (S)-Betaxolol." **Borikar, S. P.** *et al.* **2004**, *US* 6989465.
14. "S-(-)-1-{4-[2-allyloxy)-ethyl] phenoxy}-3-isopropylamino propan-2-ol and process for preparation thereof and process for the preparation of S-(-)-betaxolol." **Borikar, S. P.** *et al.* **2004**, *IN* 2004DE02310.
15. "Process for preparation of S-(-)-betaxolol and salts thereof." **Borikar, S. P.;** *et al.* **2006**, *US* 2006004109.
16. "Process for preparation of s-(-)-betaxolol hydrochloride." **Borikar, S. P**. *et al.* **2004** *IN* 2004DE01215.

Erratum