

**ASYMMETRIC SYNTHESIS TOWARDS BIOACTIVE
MOLECULES: LINEZOLID, EPEREZOLID, MOPROLOL,
TOLIPROLOL, BUNITROLOL VIA NITROALDOL
REACTION AND ORGANIC TRANSFORMATIONS OVER
COPPER FLUORAPATITE**

**A THESIS
SUBMITTED TO THE
UNIVERSITY OF PUNE
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
CHEMISTRY**

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February 2013

Dedicated to
Sarah, Shaista
&
My Parents
Zubeda & Mohammad Shafi





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CERTIFICATE

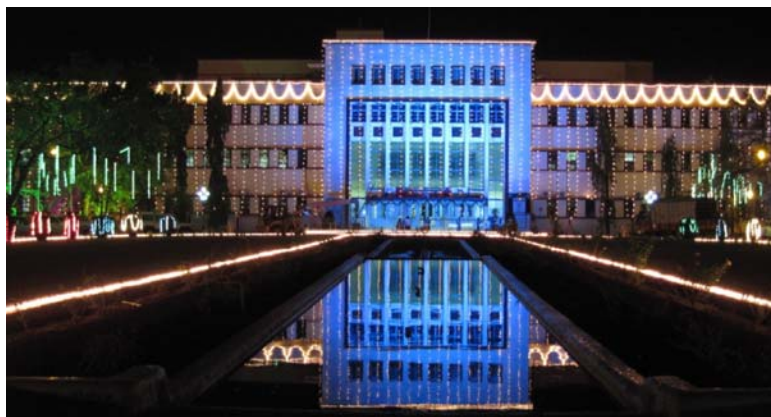
Certified that the work incorporated in the thesis entitled **“Asymmetric Synthesis towards Bioactive Molecules: Linezolid, Eperezolid, Moprolol, Toliprolol, Bunitrolol via Nitroaldol reaction and Organic Transformations Over Copper Fluorapatite”** was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

February 2013

(Dr. Shafeek A. R. Mulla)

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DECLARATION

I here by declare that the thesis entitled “**Asymmetric Synthesis towards Bioactive Molecules: Linezolid, Eperezolid, Moprolol, Toliprolol, Bunitrolol via Nitroaldol reaction and Organic Transformations Over Copper Fluorapatite**” submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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ABBREVIATIONS

Ac	Acetyl
Ac ₂ O	Acetic anhydride
AD	Asymmetric Dihydroxylation
Aq	Aqueous
Ar	Aryl
Bmim	1- <i>n</i> -butyl, 3-methyl imidazoles
Bn	Benzyl
Boc	<i>tert</i> -Butoxy carbonyl
brs	Broad singlet
Bu	Butyl
<i>t</i> -Bz	<i>tert</i> -Butyl
Bz	Benzoyl
ca.	Calculated
cat.	Catalytic/catalyst
Cbz	Benzyloxy carbonyl
CDCl ₃	Deuterated chloroform
CHCl ₃	Chloroform
CH ₂ Cl ₂	Dichloromethane
conc.	Concentrated
CuFAP	Copper fluorapatite
d	Doublet
dd	Doublet of doublet
de	Diastomeric excess
(DHQ) ₂ PHAL	1,4-Bis(dihydroquinin-9-O-yl)phthalazine
(DHQD) ₂ PHAL	1,4-Bis(dihydroquinidin-9-O-yl)phthalazine
DMAP	N,N-(Dimethylamino)pyridine
DMF	N, N-(Dimethyl)formamide
DMSO	N,N-Dimethyl formamideDimethyl sulfoxide

ee	Enantiomeric excess
equiv.	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
Et ₃ N	Triethyl amine
gm	Gram
GLC	Gas liquid chromatography
HCl	Hydrochloric acid
h or hrs	Hours
HPLC	High pressure liquid chromatography
H ₂ SO ₄	Sulfuric acid
Hz	Hertz
<i>i</i> -Pr	Isopropyl
Im	Imidazole
KOH	Potassium hydroxide
K ₂ CO ₃	Potassium carbonate
IL	Ionic liquid
IR	Infrared
L	ligand
Me	Methyl
MeOH	Methanol
m	Multiplate
mg	Miligram
min	Minutes
mL	Mililiter
mmol	Milimole
M ⁺	Molecular ion
M. P.	Melting point
Ms	Methansulfonyl
NaOH	Sodium hydroxide
Na ₂ CO ₃	Sodium carbonate

Na ₂ SO ₄	Sodium Sulfate
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
Pet. ether	Petroleum ether
Pd/C	Palladium on carbon
Ph	Phenyl
ppm	Parts per million
<i>p</i> -TSA	<i>p</i> -Toluene sulfonic acid
Py	Pyridine
RT	Room temperature
<i>R_f</i>	Retention factor
s	Singlet
SAD	Sharpless asymmetric dihydroxylation
satd.	Saturated
t	Triplet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsCl	<i>p</i> -Toluene sulfonyl chloride
TFA	Trifluoro acetic acid

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.
3. Organic Layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 and 230-400 mesh)
5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active F-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1} .
7. ^1H and ^{13}C NMR spectra were recorded on Bruker FT AV-200, AV-400 and AV-500 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet and dd = doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations recorded on JASCO-181 digital polarimeter at 25 °C using sodium D light.
10. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
11. Elemental analysis was done on Carlo ERBA EA 110B instrument.
12. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.
13. Copper fluorapatite catalyst was prepared as per literature procedure.
14. The ligands C_2 -Symmetric Chiral Piperazine was prepared as per literature procedures and Chiral Trianglamine was procured.

ABSTRACT

The thesis entitled “**Asymmetric Synthesis towards Bioactive Molecules: Linezolid, Eperezolid, Moprolol, Toliprolol, Bunitrolol via Nitroaldol reaction and Organic transformation over Copper Fluorapatite**” is divided into four chapters.

The title of the thesis clearly specify the objective to synthesize an enantiomerically pure bioactive molecules Linezolid, Eperezolid, Moprolol, Toliprolol, Bunitrolol and the development of synthetic methodologies over heterogeneous recyclable copper fluorapatite catalyst. **Chapter 1** deals with an enantioselective synthesis of Linezolid and Eperezolid via nitroaldol reaction over copper fluorapatite catalyst in the presence of C_2 -symmetric chiral piperazine ligand. **Chapter 2** describes an enantioselective synthesis of three β -blockers namely (S) Moprolol, (S)-Toliprolol and (S)-Bunitrolol via nitroaldol reaction over copper fluorapatite catalyst in the presence of chiral triethylamine ligand. **Chapter 3** deals with the synthetic methodologies for the synthesis of diaryl ethers over heterogeneous, reusable copper fluorapatite catalyst. **Chapter 4** describes the synthetic methodologies for the synthesis of β -nitroalcohols and amides from aldehydes using copper fluorapatite as heterogeneous and reusable catalyst.

Chapter 1

Enantioselective synthesis of Linezolid and Eperezolid via nitroaldol reaction over copper fluorapatite catalyst in the presence of chiral C_2 -symmetric piperazine ligand

The chapter includes the preparation of copper fluorapatite catalyst and details about biological action and comprehensive literature on synthesis of Linezolid and Eperezolid. Both Linezolid and Eperezolid are the new class of the antibacterial agents that can

inhibit the bacterial growth by a novel mechanism involving the early inhibitions of bacterial protein synthesis prior to chain initiation (**Fig. 1**).

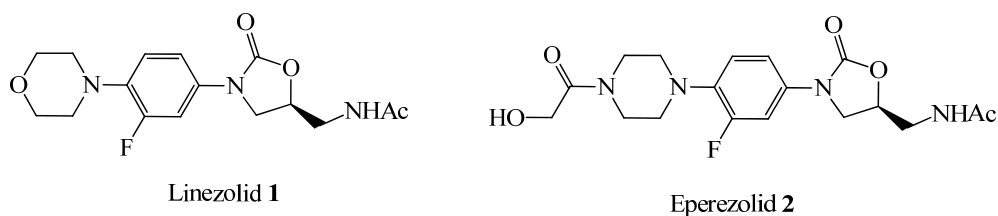


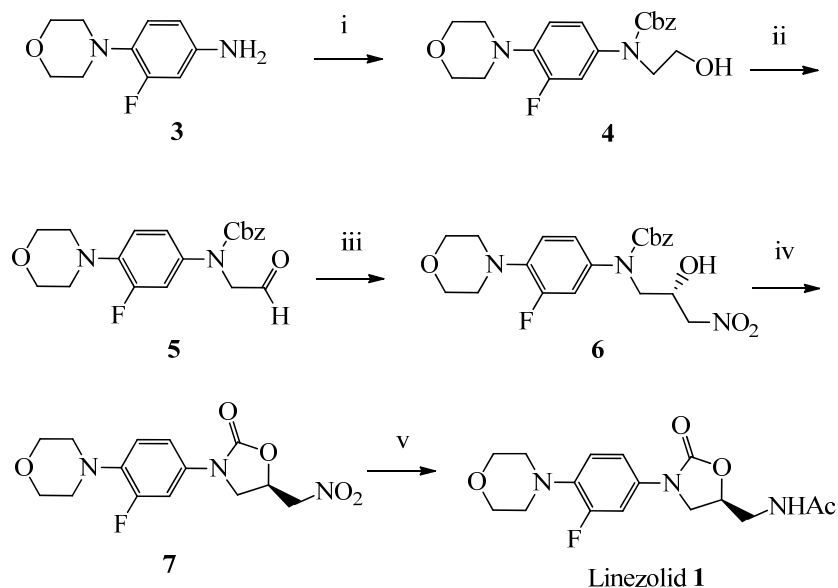
Fig. 1. Structure of Linezolid **1** and Eperezolid **2**.

The 3-aryl-2-oxazolidinones are a relatively new class of synthetic antibacterial agents having a new mechanism of action which involves early inhibition of bacterial protein synthesis. Linezolid **1**, the first and only oxazolidinone belongs to a new class of synthetic antibacterial drugs and is available for intravenous or oral treatment of gram-positive infections caused by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus faecalis* (VRE).¹ However, Linezolid **1** displays modest activity against RTI-causative gram-negative bacteria such as *Haemophilus influenzae*, and resistance against Linezolid has already been observed in gram-positive bacteria such as *S. aureus*² and *Enterococcus faecium*.³⁻⁷

Enantioselective synthesis of Linezolid

The synthesis was started with the 3-fluoro, 4-morpholinyl aniline **3** (**scheme 1**), which was prepared from 3,4-difluoronitrobenzene with excess amount of morpholine under nucleophilic aromatic displacement at the para position, selectively gave the *p*-substituted nitrobenzene followed by reduction of nitro group using 10 % Pd/C as catalyst and ammonium formate as hydrogen donor gave amine **3**. 3-fluoro, 4-morpholinyl aniline **3**

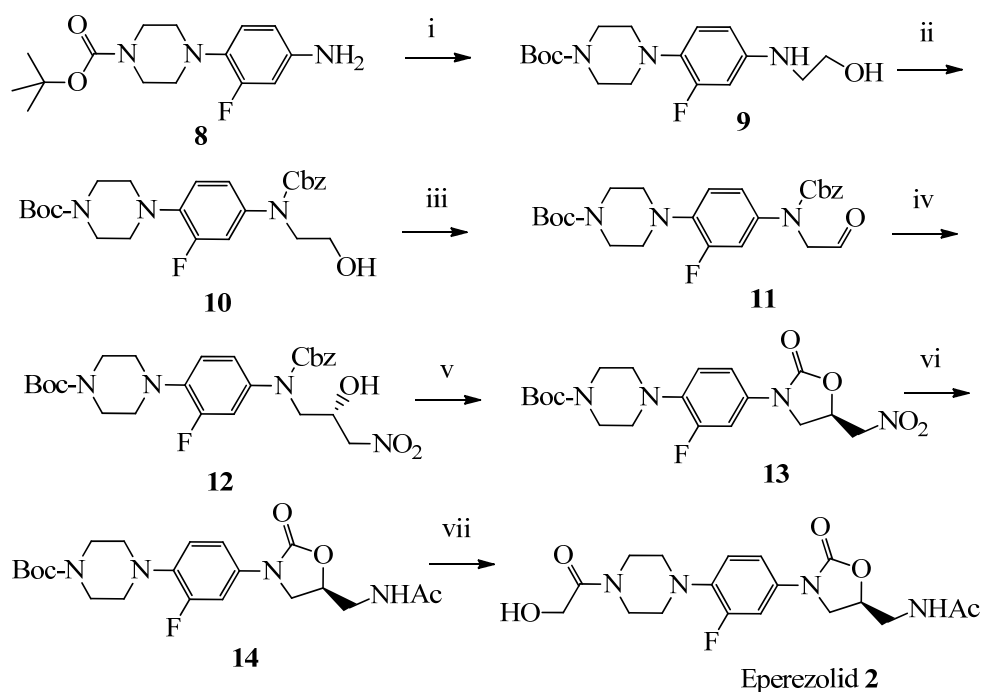
was treated with 2-chloroethanol in an *n*-butanol in the presence of molecular iodine catalyst and then followed by the protection of amine with Cbz-Cl in a DCM solvent at room temperature provided amine protected alcohol **4**. Amine protected alcohol **4** on Swern oxidation to give an aldehyde **5** as intermediate, which on an asymmetric nitroaldol reaction with nitromethane catalysed by copper fluorapatite in the combination with chiral C_2 -symmetric piperazine ligand gives β -nitro alcohol **6** as a key step product for the synthesis of Linezolid. The β -nitroalcohol **6** under goes cyclisation with anhydrous K_2CO_3 in a methanol solvent to give nitro oxazolidinone product **7**. The nitro oxazolidinone product **7** was reduced to amine by H_2 in the presence of Pd/C catalyst and acylated with acetic anhydride to give Linezolid **1**.



Scheme 1: *Reagents and reactions conditions:* (i) (a) 2-Chloroethanol, I_2 , *n*-butanol, Reflux 8 h, 97 % (b) Cbz-Cl, $NaHCO_3$, DCM, 96 % (ii) $(COCl)_2$, DMSO, Et_3N , CH_2Cl_2 , -78 to -60 °C, 96 %; (iii) CuFAP, Ligand, nitromethane, 24 h, 88 % (iv) K_2CO_3 , dry methanol, 0-RT, 12 h, 92 % (v) (a) 10 % Pd/C, H_2 (1 atm), EtOAc, 12 h, (b) Ac_2O , Py, 89 %.

Enantioselective synthesis of Eperezolid

The synthesis was started with the 3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl] aniline **8** (scheme 2), which was prepared from 3, 4-difluoronitrobenzene with excess amount of piperazine under nucleophilic aromatic displacement at the para position, selectively gave the *p*-substituted nitrobenzene. The protection of secondary amine of piperazine with BOC- anhydride gave the protected amine followed by reduction of nitro group using 10 % Pd/C as catalyst and ammonium formate as hydrogen donor gave amine **8**.



Scheme 2: Reagents and reactions conditions: (i) 2-Chloroethanol, I₂, butanol, Reflux 8 h, 93 %; (ii) Cbz-Cl, NaHCO₃, DCM, 95 %; (iii) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 to -60 °C, 93 %; (iv) CuFAP, Ligand, nitromethane, 24 h, 85 %; (v) K₂CO₃, dry methanol, 0-RT, 12 h, 88 %; (vi) 10 % Pd/C, H₂ (1 atm), EtOAc, 12 h then Ac₂O, Py, 92 %; (vii)(a)TFA, RT, 8 h (b) HOCH₂COCl, TEA, DCM, 0-RT, 4 h, 86 %.

3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl]aniline **8** was treated with 2-chloroethanol in a *n*-butanol in the presence of molecular iodine catalyst gives **9** and then followed by

the protection of amine **9** with Cbz-Cl in a DCM solvent at room temperature provided amine protected alcohol **10**. Amine protected alcohol **10** by Swern oxidation to give an aldehyde **11** as intermediate, which on an asymmetric nitroaldol reaction with nitromethane catalysed by copper fluorapatite in the combination with chiral C₂-symmetric piperazine ligand gives β -nitro alcohol **12** as a key step product for the synthesis of eperezolid. The β -nitroalcohol **12** under goes cyclisation with anhydrous K₂CO₃ in a methanol solvent to give nitro oxazolidinone product **13**. The nitro oxazolidinone product **13** was reduced to amine by H₂ in the presence of Pd/C catalyst and acylated with acetic anhydride to give Boc protected eperezolid **14**. Deprotection of Boc and finally acetylation of amine with 2-hydroxy acetyl chloride to gave Eperezolid **2**.

Chapter 2

Enantioselective synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol via nitroaldol reaction over copper fluorapatite catalyst in presence of chiral trianglamine ligand

This chapter includes the details about biological action and comprehensive literature on synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol (**Fig. 2**). All three β -adrenergic blocking agents are (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol, which posses antihypertensive, antianginal and sympatholytic properties.

These β -Adrenergic blocking agents are important drugs widely used for the treatment of hypertension, angina pectoris, glaucoma, anxiety and obesity. The three fundamental goals of cardiovascular drugs are lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart

muscle tone (cardiotonics).⁸ Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.⁹

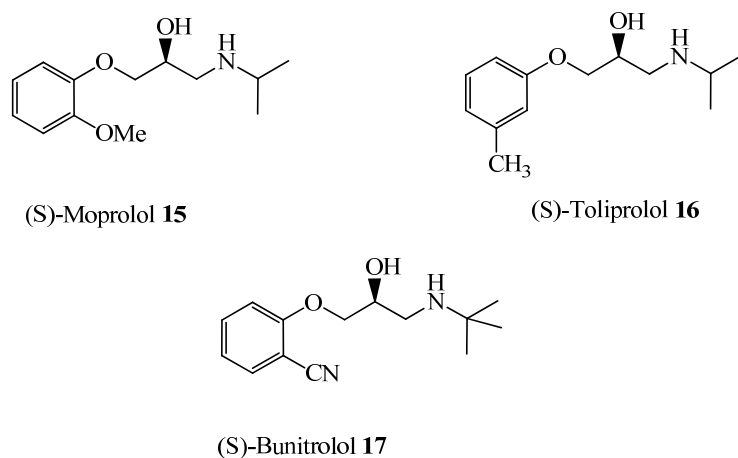
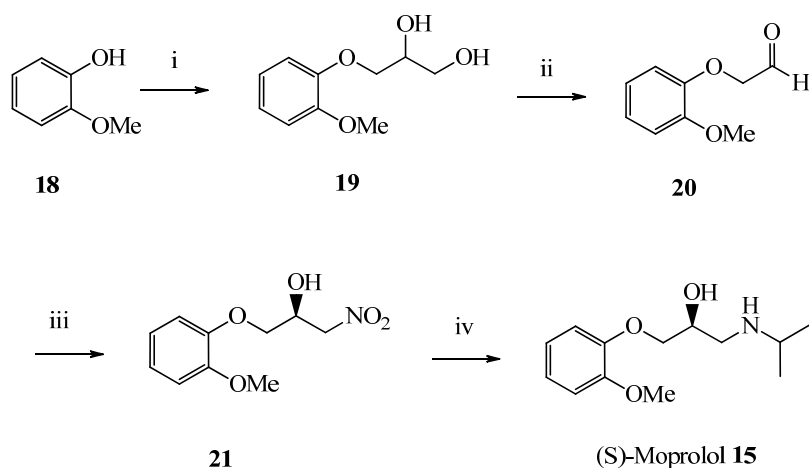


Fig. 2. Structure of (S)-Moprolol **15**, (S)-Toliprolol **16** and (S)-Bunitrolol **17**

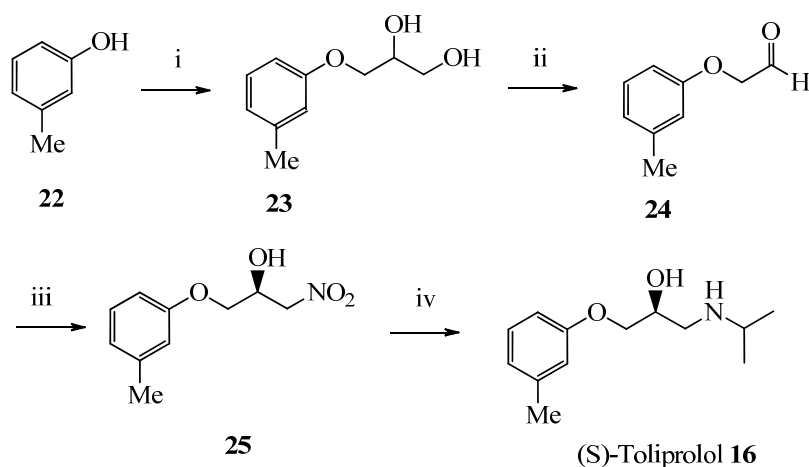
Enantioselective synthesis of (S)-Moprolol



Scheme 3: *Reagents and reactions conditions:* (i) NaOH, 3-chloro,1-2-propanediol, reflux, 8 h, 90 % (ii) NaIO₄, H₂O 0-5 °C, 90 % (iii) CuFAP, nitromethane, chiral triethylamine ligand, 84 % (iv) (a) H₂, Pd/C, methanol (b) isopropyl bromide, reflux, 88 %.

The synthesis was started with the commercially available guaiacol **18** (**scheme 3**). Guaiacol **18** was treated with 3-chloro, propane-1, 2-diol in a 10 % NaOH solution at refluxed condition for 8 h provided diol compound **19**. The oxidation of diol **19** with NaIO₄ at 0-5 °C, gives aldehyde **20**. The aldehyde **20** was subjected to nitroaldol reaction using CuFAP catalyst in the presence of chiral trianglamine ligand, gives β-nitro alcohol **21** as a key step product. Finally, the nitro group of **21** was reduced using H₂ in the presence of Pd/C catalyst in a methanol to provide amine and then followed by alkylation with isopropyl bromide at refluxed condition gives (S)-Moprolol **15**.

Enantioselective synthesis of (S)-Toliprolol



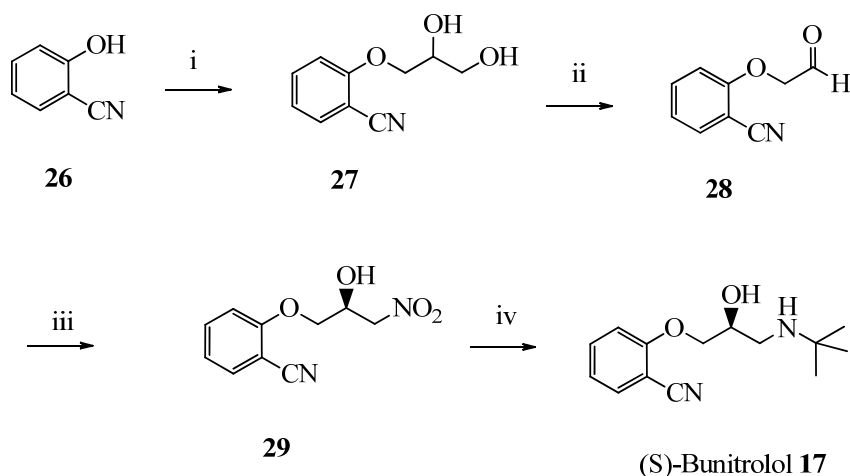
Scheme 4: Reagents and reactions conditions: (i) NaOH, 3-chloro,1-2-propanediol, 8 h, 94 % (ii) NaIO₄, H₂O 0-5 °C, 93 % (iii) CuFAP, nitromethane, chiral trianglamine ligand, 84 % (iv) (a) H₂, Pd/C methanol (b) isopropyl bromide, reflux, 83 %.

The synthesis was started with the commercially available *m*-Cresole **22** (**scheme 4**). The *m*-Cresole **22** was treated with 3-chloro, propane-1,2-diol in a 10 % NaOH solution at refluxed condition for 8 h, provided diol compound **23**. The oxidation of diol **23** with NaIO₄ at 0-5 °C, gives aldehyde **24**. The aldehyde **24** was subjected to nitroaldol reaction

using CuFAP catalyst in the presence of chiral triethylamine ligand, gives β -nitro alcohol **25** as a key step product. Finally, the nitro group of **25** was reduced using H_2 , in the presence of Pd/C catalyst in a methanol to provide amine and then followed by alkylation with isopropyl bromide at refluxed condition gives (S)-Toliprolol **16**.

Enantioselective synthesis of (S)-Bunitrolol

The synthesis was started with the commercially available *o*-cyanophenol **26** (scheme 5). The *o*-cyanophenol **26** was treated with 3-chloro, propane-1, 2-diol in a 10 % NaOH solution at refluxed condition provided diol compound **27**. The oxidation of diol **27** with $NaIO_4$ at 0-5 °C, gives aldehyde **28**. The aldehyde **28** was subjected to nitroaldol reaction using CuFAP catalyst in the presence of chiral triethylamine ligand, gives β -nitro alcohol **29** as a key step product. Finally, the nitro group of **29** was reduced using H_2 , in the presence of Pd/C catalyst in a methanol to provide amine and then followed by alkylation with *tert*-butyl bromide at refluxed condition gives (S)-Bunitrolol **17**.



Scheme 5: Reagents and reactions conditions: (i) NaOH, 3-chloro,1-2-propanediol, 8 h, 92 % (ii) $NaIO_4$, H_2O , 0-5 °C, 96 % (iii) CuFAP, nitromethane, chiral triethylamine ligand, 90 % (iv) (a) H_2 , Pd/C methanol (b) *tert*-Butyl bromide, reflux, 79 %.

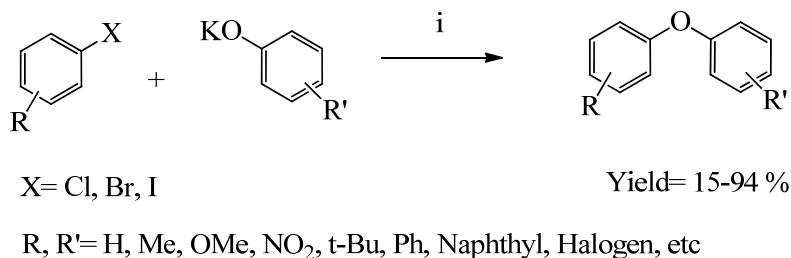
Chapter 3

Copper fluorapatite catalysed ligand-free synthesis of diaryl ethers

The chapter describes introduction, literature survey and the applications of heterogeneous reusable copper fluorapatite catalyst for synthesis of diaryl ethers. The chapter is divided into two sections.

Section I: Synthesis of diaryl ethers from phenols and aryl halides

Diaryl ether motifs are presents in the natural products and medicinally important compounds.¹⁰ Diaryl ethers molecules are not only important in biological systems but also key moieties in pharmaceutical, agricultural, polymer, industrial and life science.¹¹ The classical copper catalysed Ullmann coupling reaction for ether synthesis has been extensively used for the formation of diaryl ether on industrial scale in polar solvents. However application on industrial scale synthesis has been limited due to harsh reaction conditions such as high reaction temperature (125-300 °C), longer reaction time at which many functional groups are unstable hence lower yield to desire product. In addition, requirement of excess or stoichiometric quantities of copper complexes leads to problem of waste disposal.

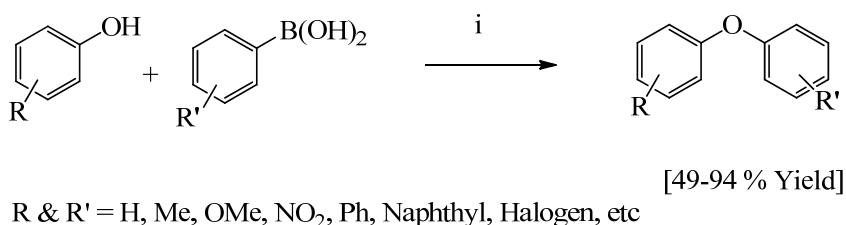


Scheme 6: *Reagents and reactions conditions:* (i) Haloarenes (1 mmol), substituted potassium phenoxide (1.1 mmol), CuFAP (100 mg), NMP (1 mL), 120 °C, 5-12 h.

Developed, a novel ligand free, highly efficient, an inexpensive and general method for the synthesis of diaryl ethers in a good to excellent yield from the cross coupling reactions of a wide range of electron-deficient, electronically neutral and electron-rich aryl halides with the various substituted potassium salts of phenols over ecofriendly, heterogeneous reusable copper fluorapatite (CuFAP) catalyst in the presence of *N*-Methyl 2-pyrrolidone as a solvent at 120 °C (**Scheme 6**).

Section II: Base promoted synthesis of diaryl ethers by cross-coupling of phenols with arylboronic acids

This section describes highly efficient synthesis of diaryl ethers from phenols and aryl boronic acids over copper fluorapatite using Cs_2CO_3 as a base and methanol as a solvent at ambient reaction temperature.



Scheme 7: Reagents and reactions conditions: (i) Phenols (1 mmol), arylboronic acid (1.1 mmol), CuFAP (100 mg), methanol (1 mL), RT, 5-12 h.

A mild, general, and highly efficient protocol has been developed for the synthesis of diaryl ethers in good to excellent yield under mild and ligand-free conditions. This is first example using recyclable, heterogeneous copper fluorapatite catalyzed arylation of substituted phenols with substituted arylboronic acids at room temperature in the presence of Cs_2CO_3 as base and methanol as a solvent. The catalyst was recovered and reused several time without loss of catalytic activity (**Scheme 7**).

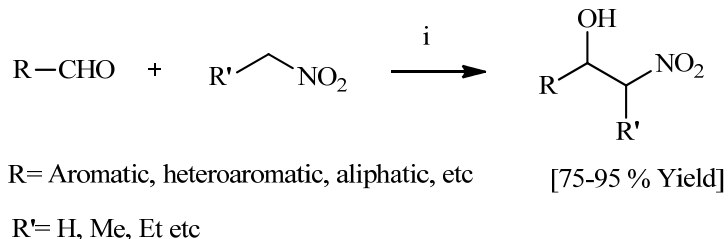
Chapter 4

Synthesis of β -nitroalcohols and amides over copper fluorapatite catalyst

The chapter describes introduction, detail literature survey on β -nitroalcohols, amides and their industrial applications. The chapter is divided into two sections.

Section I: Base-free synthesis of β -nitroalcohols from aldehydes and nitroalkanes at ambient reaction temperature

The Henry reaction is one of the most useful carbon-carbon bond forming reactions and has wide synthetic applications in organic synthesis by which β -nitroalcohols were synthesized on treatment of carbonyl derivatives with nitroalkanes in the presence of a basic catalyst. From last few decades various methods has been developed for the synthesis of β -nitroalcohols using varieties of reagent and catalysts in combination with the various ligands such as organic, inorganic bases like metal hydroxides or alkoxides^{12,13} are reported. Other catalysts such as phosphonium salts,¹⁴ phosphine-metal complexes,¹⁵ ionic liquid,¹⁶ simple amines,¹⁷ ammonium salts,¹⁸ guanidine derivatives,¹⁹ lithiumaluminum hydride,²⁰ Mg-Al-HT,²¹ and Amberlyst-21²² also have been reported. All the above mentioned methods can be applied for the synthesis of β -nitroalcohols but still suffering from limitations and drawbacks such as harsh reaction conditions, moisture sensitive and toxic catalyst and also the formation of the side product with poor yield to desired product. In this respect, there is still a need to develop mild and efficient methods for the synthesis of β -nitroalcohols. Hence, we developed a heterogeneous, highly efficient, eco-friendly and base-free catalyst system for Henry reaction by using CuFAP catalyst under neat reaction conditions (**Scheme 8**).



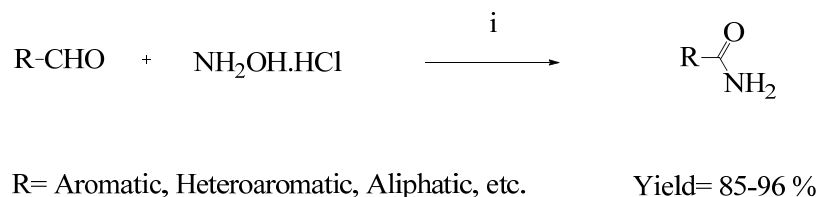
Scheme 8: Reagents and reactions conditions: (i) Aldehyde (1 mmol), nitromethane (1 mL), CuFAP (100 mg), RT, 5-18 h.

Section II: A direct synthesis of amides from aldehydes and hydroxylamine hydrochloride in solvent free conditions

Amides are key intermediates in organic synthesis as well as raw material in industrial applications such as detergents, lubricants and pharmaceuticals. Amides are commonly synthesized by the reaction of acid chlorides, acid anhydrides, or esters with amines. However, due to generation of waste and toxic material in the process, the synthesis of amide with high atom economical is great challenge in pharmaceutical industry. Beckmann rearrangement has been recognized as versatile method for the preparation of amides at high temperature using a strong Bronsted or Lewis acids as catalyst. The various methods for the synthesis of amides from aldehyde using varieties of reagent and catalysts with the precious metal compounds such as Ir, Rh, Ru, Ag/ Au, Pd, anhydrous oxalic acid, chloral, sulfamic acid, cyanuric chloride/DMF, ethyl chloroformate/boron trifluoride etherate, and chlorosulfonic acid have been reported.

Although, so far reported protocols have their own drawbacks and limitations such as the use of toxic solvents, expensive reagents, and formation of unwanted side products, prolonged reaction timings, tedious workup procedures and low yields to desire product.

We developed a one pot, an efficient, simple, general and convenient protocol for the synthesis of amides in good to excellent yields from various substituted aldehydes and utilizing readily available inexpensive hydroxylamine hydrochloride in a solvent-free condition at 100 °C (**Scheme 9**).



Scheme 9: Reagents and reactions conditions: (i) Aldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), CuFAP (100 mg), 100 °C.

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Chapter I

Enantioselective Synthesis of Linezolid and Eperezolid via Nitroaldol reaction over Copper fluorapatite catalyst in presence of Chiral C_2 -Symmetric Piperazine Ligand

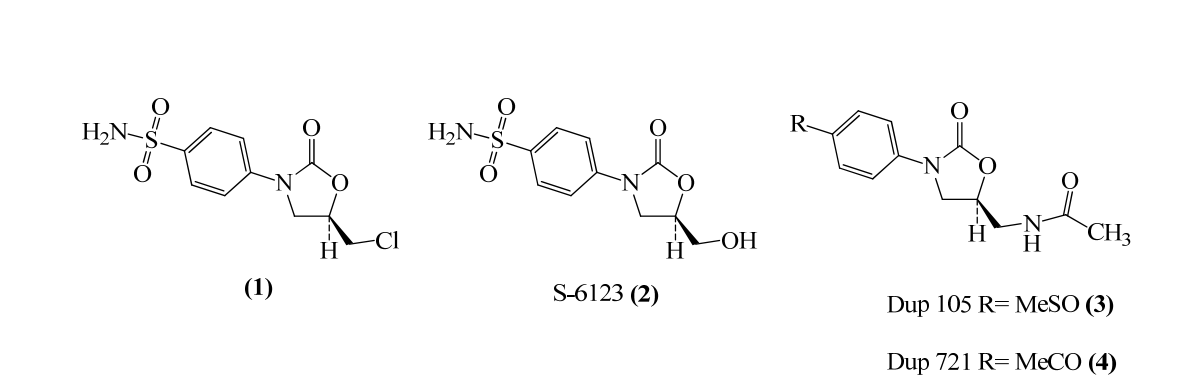
Enantioselective Synthesis of Linezolid and Eperezolid via Nitroaldol reaction over Copper fluorapatite catalyst in presence of Chiral C₂-Symmetric Piperazine Ligand

1.1 Introduction

Because of the complexities in the modern human life, along with the unhygienic conditions such as lack of proper sanitation, air and water pollution led to various bacterial infectious diseases. However, some of the bacteria are resistant to various antibacterial drugs, which is one of the key challenge to the researchers to develop new antibiotic classes that are unaffected by the bacterial resistance. The various antibacterial drugs and/or reagents are playing very important role in the human life to cure the various bacterial infections diseases. Therefore, world wide researcher have their objectives and interest in the search of new antibacterial agents that can inhibit the bacterial growth by a novel mechanism involving the early inhibitions of bacterial protein synthesis prior to chain initiation.

A series of 5-halomethyl-3-aryl-2-oxazolidinones **1** (**Fig.1**) were reported to have activity against certain plant pathogens. The subsequent chemical formulation of **1** eventually led to analogues such as (5*R*)-hydroxymethyl-3-aryl-2-oxazolidinone, S-6123 **2**¹ have been patented in a 1978 by DuPont de Nemours and Co. Inc.,² which showed weak *in vitro* antibacterial activity against human pathogens.³ In the year 1987, the researchers from DuPont Company formally reported the structure and antibacterial activity profiles of two new antibacterial agents such as Dup-105 **3** and DuP-721 **4** in Inter-science Conference on Antimicrobial Agents and Chemotherapy (ICAAC),⁴ which was obtained from further

The oxazolidinones compounds have a novel and unique mechanism of action by which an early inhibition of bacterial protein synthesis occurs prior to chain initiation.⁵ The compound **4** demonstrated potent activity against gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA),⁶ gram-negative anaerobes, and *Mycobacterium tuberculosis*.⁷ The *in-vitro* development of bacterial resistance to either compound **3** or compound **4** could not be demonstrated.⁸



The oxazolidinone moieties in Linezolid **5** and Eperezolid **6** were not only emerge as a new class with a novel mechanism of action but also significantly unaffected by existing

resistance in gram-positive pathogens and were orally active. Linezolid **5** was approved to use in humans clinical trials in the U.S. by the Food and Drug Administration (FDA) in April 2000, subsequently well performed in human clinical trials as compared to other marketed antibiotics drugs. Recent advancements have been done by replacing oxygen with sulphur in several pharmacophores, which led to improvements in efficiency and lowers the toxicity in a drug candidate. Besides antibacterials, these heterocyclic units are also used as intermediates for the synthesis of polymers and agricultural chemicals.

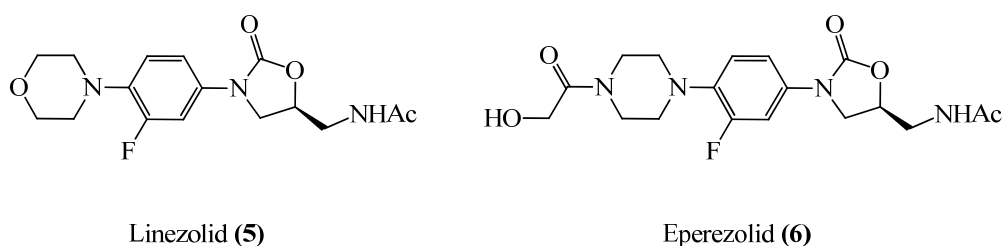


Fig. 2: Structures of Linezolid **5** and Eperezolid **6**

1.2 Pharmacology of linezolid and eperezolid

As shown in the **Fig.3**, structural-activity relationships (SAR) of oxazolidinone compounds were developed through systematic medication of various ring positions have identified certain optimum substitution pattern. Especially active analogues were with suitable electron-donating amino substituents on the phenyl ring can confer excellent antibacterial activity while helping to maintain a good safety profile. Another important result of this investigation was the identification of the potentiating effect of one or two fluorine atoms flanking the morpholine or piperazine ring system.

Among oxazolidinone compounds, Linezolid **5** is the first and only oxazolidinone belongs to a new class of synthetic antibacterial drugs, which is available for intravenous

or oral treatment of gram-positive infections caused by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus faecalis* (VRE).¹² However, Linezolid **5** displays modest activity against RTI-causative gram-negative bacteria such as *Haemophilus influenzae*, and resistance against gram-positive bacteria such as *S. aureus* and *Enterococcus faecium*.

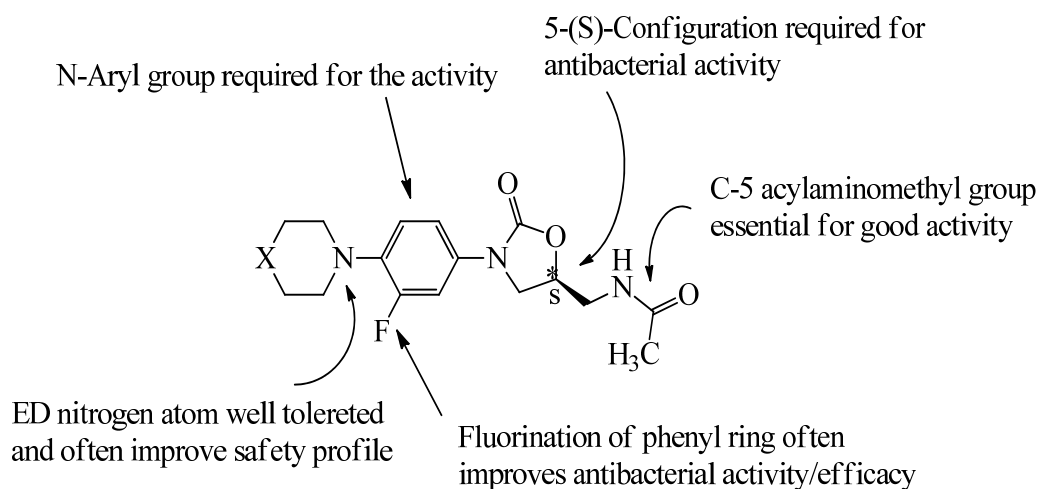


Fig. 3: Structural activity relationships of oxazolidinone compound

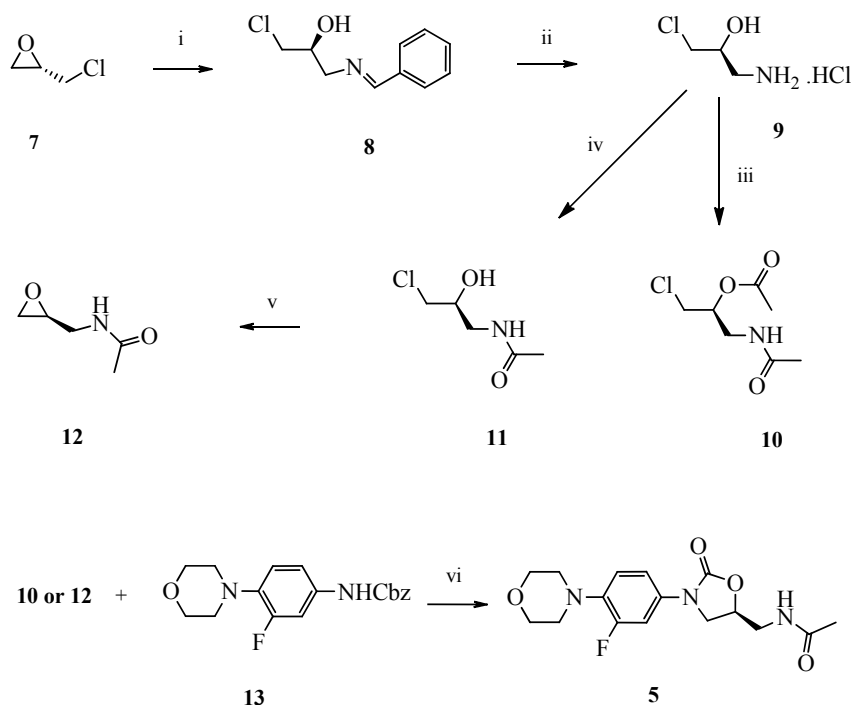
1.3 Review of Literature

There are several reports available for the asymmetric synthesis of linezolid **5** and eperezolid **6**¹³⁻¹⁹ in the literature. However, almost all the methods reported for the asymmetric synthesis of linezolid and eperezolid involve either classical resolution of racemates or a chiral pool approach which are described below.

Perrault's approach¹³

In this approach, (S)-epichlorohydrin **7** was converted to N-[(2S)-2-(acetyloxy)-3-chloropropyl] acetamide **10** and epoxide **12** via the common intermediate (2S)-1-amino-

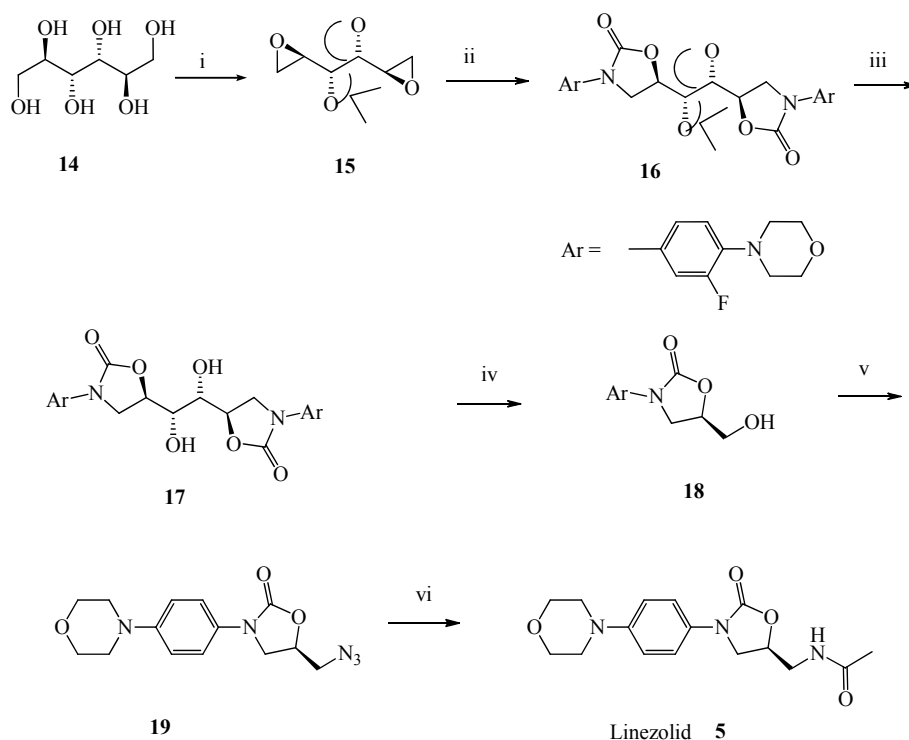
3-chloro-2-propanol hydrochloride **9**. Finally, coupling of acetamide **10** or epoxide **12** with 1.3 equiv of the benzyl carbamate **13** gave linezolid **5** in 81 % yield (**Scheme 1**).



Scheme 1: Reagents and reaction conditions: (i) NH_3 (aq), PhCHO , 25°C (ii) HCl (aq), 25°C , 76 % (iii) 2 eqv. Ac_2O , pyridine, 25°C , 83 % (iv) 1 eqv. Ac_2O , pyridine, 25°C (v) 1 eqv. KO^tBu , THF, -20°C , 97 % (vi) 3 eqv. LiOMe , 2 eqv. MeOH , DMF, 25°C , 81 %.

Lohray's approach¹⁴

In this approach, D-mannitol **14** was converted into C_2 -bis-epoxide **15** (**Scheme 2**) and used as a key intermediate. The C_2 -symmetric bis-epoxide **15** was reacted readily with 3-fluoro-4-substituted aniline in isopropyl alcohol at $80\text{--}85^\circ\text{C}$ to give the crude adduct which was reacted with carbonyldiimidazole in dichloromethane at 25°C to furnish the bis-oxazolidinone **16** in 70 % yields. The acetonide group was selective removed by treatment with 2N HCl to obtain the diol **17**. The oxidative cleavage of diol **17** with lead tetra acetate to obtained aldehyde which on in-situ reduction with sodium borohydride gave alcohol **18**. The alcohol **18** was converted into azide **19** and finally to linezolid **5**.

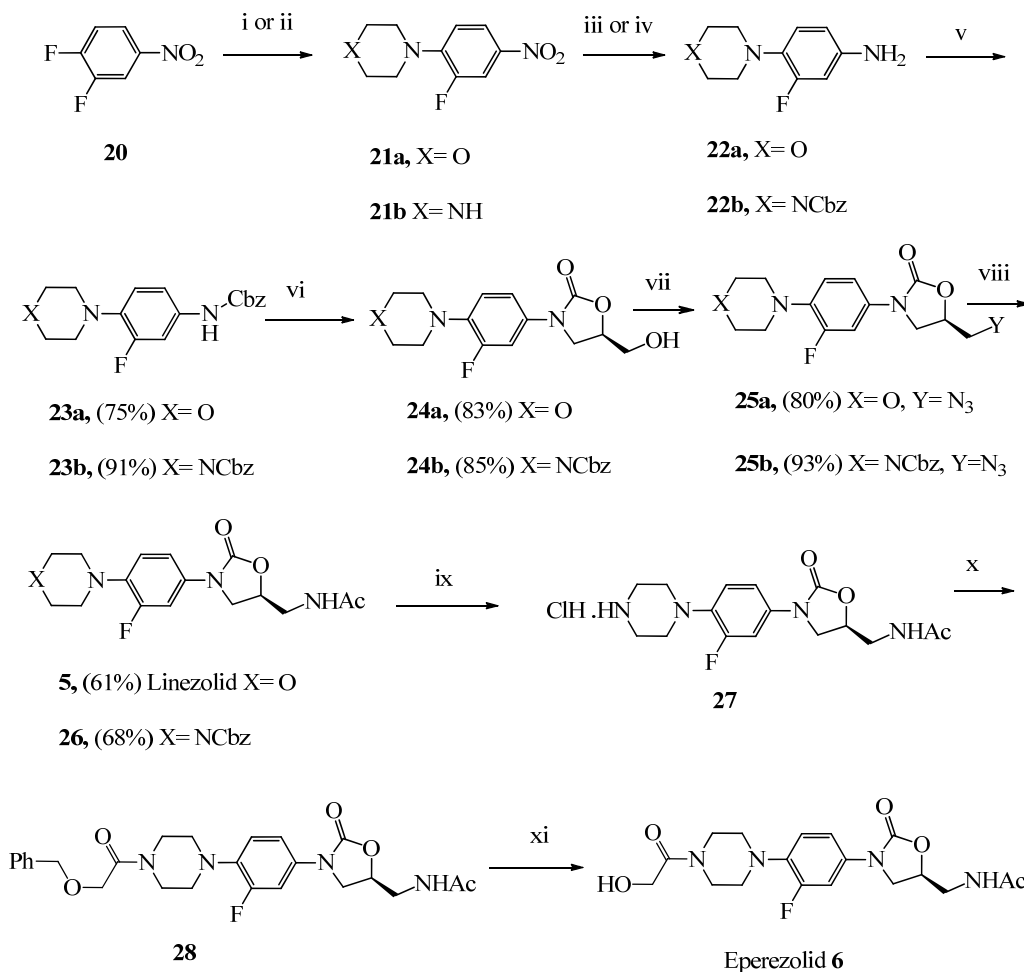


Scheme 2: Reagents and reaction conditions: (i) Ref. 15 (ii) (a) ArNH_2 , isopropyl alcohol, reflux (b) $(\text{Im})_2\text{-CO}$, CH_2Cl_2 , 70 % (iii) dil. HCl , 95 % (iv) (a) $\text{Pb}(\text{OAc})_4$, THF (b) NaBH_4 , MeOH , 95 % (v) a) MeSO_2Cl , Et_3N b) NaN_3 , DMSO , 80 °C, 84 % (vi) MeCOSH , 25 °C.

Brickner's approach¹⁶

In this approach, Linezolid **5** and Eperezolid **6** were synthesized by common route, as shown in **Scheme 3**. The nucleophilic substitution of 3, 4-difluoro nitrobenzene **20** with morpholine or piperazine, gave the *p*-substituted nitrobenzene **21a-b**. The nitro group of **21a-b** was reduced to amino compound **22a-b** followed by protection of amine group with Cbz-Cl to give carbamate **23a-b**. The carbamate **23a-b** in THF was reacted with (R)-glycidyl butyrate in presence of *n*-BuLi to give the corresponding (5*S*)-hydroxymethyl-oxazolidinone **24a-b** in 98 % ee is a key step. Linezolid **5** and the Cbz-piperazine **26** were obtained by known sequence of standard reactions: (i) azidation of alcohol **24a-b**, (ii) reduction of azide **25a-b** to amine using H_2 , Pd/C and in-situ

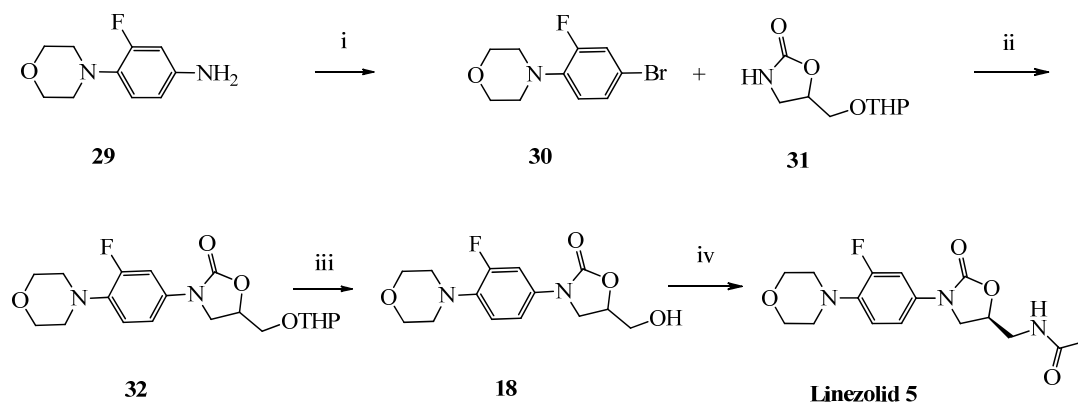
acetylation of amine by Ac₂O provided linezolid **5** and N- acetylation eperezolid **26**. The catalytic hydrogenolysis of **26** provided the piperazine HCl salt **27**, which was acylated with (benzyloxy) acetyl chloride. Finally, benzylic hydrogenolytic cleavage of **28** gave Eperezolid **6** in 99.7 % ee.



Scheme 3: Reagents and reaction conditions: (i) Morpholine / Piperazine, CH₃CN, reflux or (ii) (*i*-Pr)₂EtN, EtOAc (iii) H₂, 5 % Pd/C, THF or (iv) HCO₂NH₄, 10 % Pd/C, THF/MeOH. (v) Cbz-Cl, NaHCO₃, acetone-H₂O (vi) (a) *n*-BuLi, THF -78 °C (b) (R)-glycidyl butyrate. (vii) (a) MsCl, Et₃N, CH₂Cl₂. (b) potassium phthalimide, CH₃CN, H₂O, reflux (c) NaN₃, DMF, 75 °C (d) Aqueous MeNH₂, EtOH, reflux. (viii) (a) 10 % Pd/C, H₂, EtOAc. (b) Ac₂O, Py. (ix) Pd/C, H₂, MeOH-CH₂Cl₂. (x) ClCOCH₂OCH₂Ph, Et₃N, CH₂Cl₂, 0 °C. (xi) 10 % Pd/C, H₂, MeOH-CH₂Cl₂.

Trehan's approach¹⁷

In this approach, the aniline compound **29** was converted to aryl bromide **30** via Sandmeyer reaction. The key step in this approach was the coupling of aryl bromide **30** with oxazolidinone **31** using Buchwald's amination protocol. The oxazolidinone **31** was prepared from racemic 5-(hydroxymethyl)-2-oxazolidinone. Deprotection of **32** using Pyridinium *p*-toluenesulfonate (PPTS) in boiling ethanol gave alcohol **18**. The azidation of alcohol **18** followed by reduction of azide to amine using H₂, Pd/C and insitu acetylation of amine by Ac₂O was converted to racemic linezolid (**Scheme 4**).

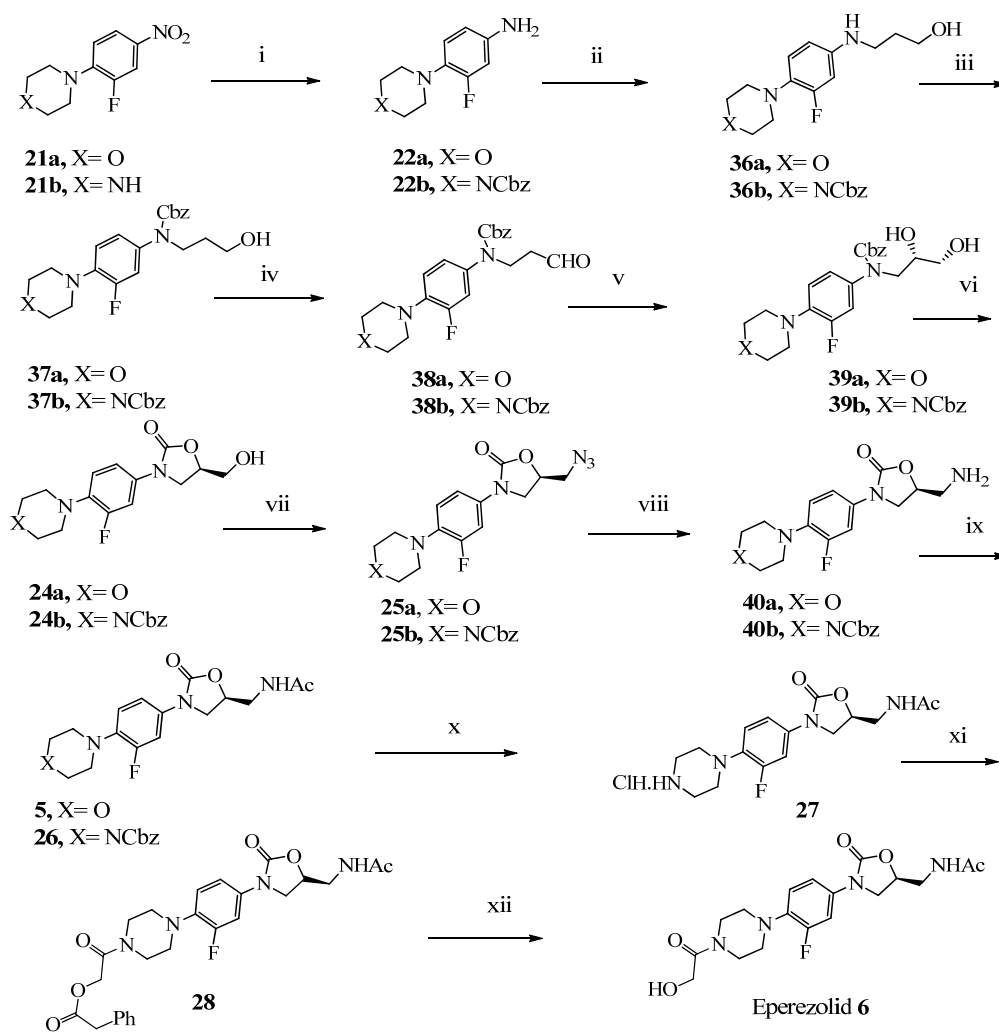


Scheme 4: Reagents and reaction conditions: (i) HNO₂, CuBr, HBr 47 % (ii) CuI (5 mol %), (±)-*trans*-1,2-diaminocyclohexane (10 mol %), dioxane, K₂CO₃, 110 °C, 15 h (iii) PPTS, EtOH, reflux, 1 h (iv) (a) CH₃SO₂Cl, Et₃N, CH₂Cl₂, 0-25 °C, 1 h. (b) NaN₃, DMF, 70 °C, 2 h. (c) CH₃COSH, 25 °C, 15 h.

A. Sudalai Approach¹⁸

In this approach, key intermediate formation of asymmetric diol **39a-b** via D-proline catalysed alpha-aminoxylation of the corresponding aldehyde **38a-b**. The regioselective intra-molecular cyclisation of diol **39a-b** using NaH to furnish oxazolidinone **24a-b** and then was converted into corresponding azide **25a-b**. The azide **25a-b** was reduced to amine **40a-b** by H₂, Pd/C and finally converted to linezolid **5** by reacting with acetic

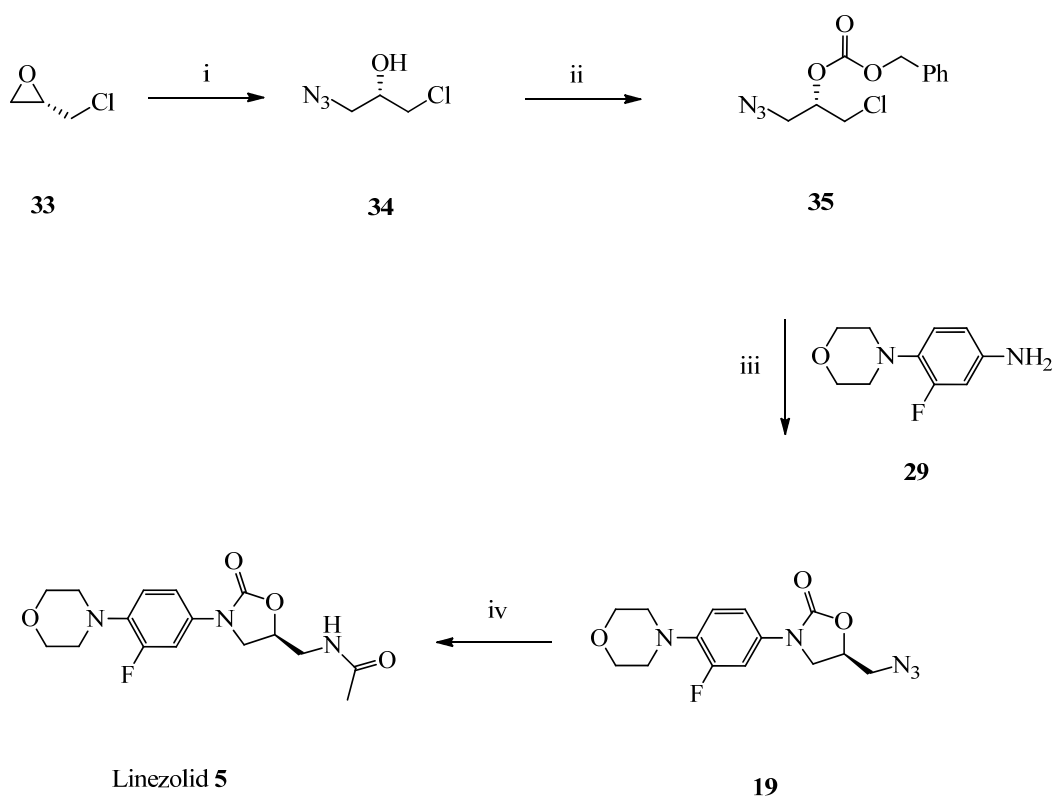
anhydride. The catalytic hydrogenolysis of **26** provided the piperazine HCl salt **27**, which was acylated with (benzyloxy) acetyl chloride. Finally, benzylic hydrogenolytic cleavage of **28** gave Eperezolid **6** in 99 % ee (**Scheme 5**).



Scheme 5: Reagents and reaction conditions: (i) CoCl_2 , NaBH_4 , MeOH, 60 °C, 95 % (ii) (a) $\text{TsO}-(\text{CH}_2)_3\text{-OH}$, NaI, Na_2CO_3 , DMF, 65 °C (iii) Cbz-Cl, NaHCO_3 , acetone- H_2O , 79 % (over two steps) (iv) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C to -60 °C, 94 % (v) (a) PhNO, D-proline (25 mol %), -20 °C, 24 h then MeOH, NaBH_4 (b) CuSO_4 (30 mol %), MeOH, 82 % (over two steps) (vi) NaH, THF, 0 °C, 94 % (vii) (a) MsCl, Et_3N , CH_2Cl_2 , 0 °C, 4 h (b) NaN_3 , DMF, 75 °C, 89 % (over two steps) (viii) 10 % Pd/C, H_2 (1 atm), MeOH- CH_2Cl_2 (3:1), 97 % (ix) PPh_3 , THF- H_2O , 12 h then Ac_2O , Py, 96 % (x) 10 % Pd/C, H_2 (1 atm), MeOH- CH_2Cl_2 (3:1), 89 % (xi) $\text{ClCOCH}_2\text{OCH}_2\text{Ph}$, Et_3N , CH_2Cl_2 , 0 °C, (xii) 10 % Pd/C, H_2 (1 atm), MeOH- CH_2Cl_2 (3:1), 89 %.

Madhusudhan's approach¹⁹

The key step in this approach was the regioselective opening of commercially available (S)-epichlorohydrin with sodium azide to obtained azido alcohol **34** in 65 % yields. Protection of alcohol **34** using phenyl chloroformate gave the corresponding product **35**, which was coupled with amine **29** to give azide **19**. Finally the azide **19** was converted into linezolid **5** in 86 % yields with thioacetic acid (**Scheme 6**).



Scheme 6: Reagents and reaction conditions: (i) NaN_3 , NH_4Cl , H_2O , EtOH , $0-25^\circ\text{C}$, 65 % (ii) $\text{PhCH}_2\text{OCOCl}$, Py , CH_2Cl_2 , 0°C , 91 % (iii) K_2CO_3 , $\text{Bn-NEt}_3^+ \text{Cl}^-$ (cat.), DMF , 80°C (iv) CH_3COSH , neat, 25°C .

1.4 Present Work

1.4.1 Objectives

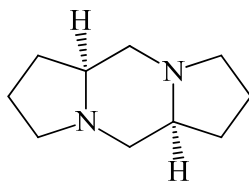
Due to high medicinal value of Linezolid **5** and Eperezolid **6** several synthetic routes developed by various researchers have been documented in the literature, which involves either chiral pool approach or the classical resolution of racemates. However, many of these reported synthetic routes suffer one/or other limitations and drawbacks such as low overall yields, use of expensive enzymes and resolving agents, low optical purity, the need for separation of diastereomers and the use of expensive chiral catalysts. Therefore, development of recoverable, reusable inexpensive catalysts as well as synthetic route for the synthesis of Linezolid **5** and Eperezolid **6** to achieve high overall yield with high optical purity is still challenging and active research area. Interestingly, a catalytic route for asymmetric synthesis of Linezolid **5** and Eperezolid **6** using heterogeneous catalyst with chiral ligand has not been reported so far. Hence we report the a catalytical route for asymmetric synthesis of Linezolid **5** and Eperezolid **6** with good optical purity and yield using asymmetric nitroaldol reaction catalysed by recyclable, heterogeneous copper fluorapatite catalyst in the presence of C_2 -symmetric chiral piperazine ligand which is a key step and source of chirality for the formation of β -nitroalcohols from the respective aldehydes under solvent free conditions. The results are described in this chapter.

1.4.2 Asymmetric nitroaldol reaction

In recent years, much attention has been focused on the catalytic asymmetric synthesis. In 1994, Shibasaki *et al.*²⁰ has found that lanthanum-lithium-(R)-BINOL [(R)-LLB] catalysed nitroaldol reaction as a key step for the synthesis of Pindolol. The catalytic asymmetric nitroaldol reaction of the aldehyde with nitromethane was examined under

the reaction conditions using 10 mol equivalents of nitromethane at -50 °C in the presence of 10 mol % of (R)-LLB catalyst; the reaction gave 76 % yield of nitroaldol in 92 % ee.

Development of a new general synthetic route for the synthesis of two antibacterial agents namely, Linezolid **5** and Eperezolid **6** with good optical purity and yield, *via* asymmetric nitroaldol reaction over heterogeneous, reusable copper fluorapatite catalyst in the presence of C_2 -symmetric chiral piperazine ligand (L^*)²¹ (**Fig. 4**) from corresponding aldehydes under solvent free conditions as the key step and source of chirality.



(S, S)- C_2 -Symmetric Chiral Piperazine (L^*)

Fig. 4: Chiral C_2 -symmetric piperazine ligand for nitroaldol reaction

1.5 Results and discussion

The retro-synthetic analysis for the synthesis of Linezolid **5** and Eperezolid **6** is presented in **Fig. 5**. Both the compounds show structural similarities. Linezolid **5** and Eperezolid **6** could be prepared from the corresponding β -nitroalcohols **45** and **54** by using asymmetric nitroaldol reaction over copper fluorapatite catalyst in the presence of C_2 -symmetric chiral piperazine ligand from the corresponding aldehydes **44** and **53**. The aldehydes **44** and **53** could be readily obtained from starting material by simple functional group transformations.

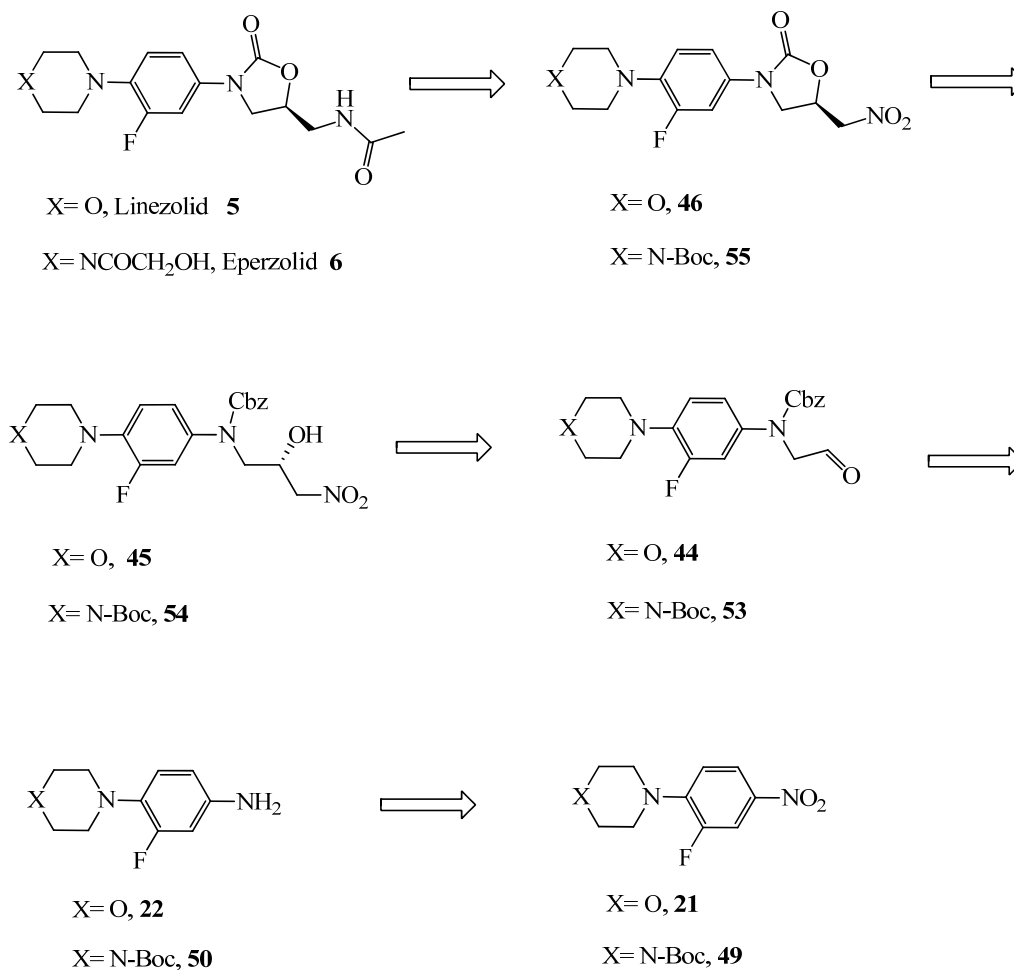
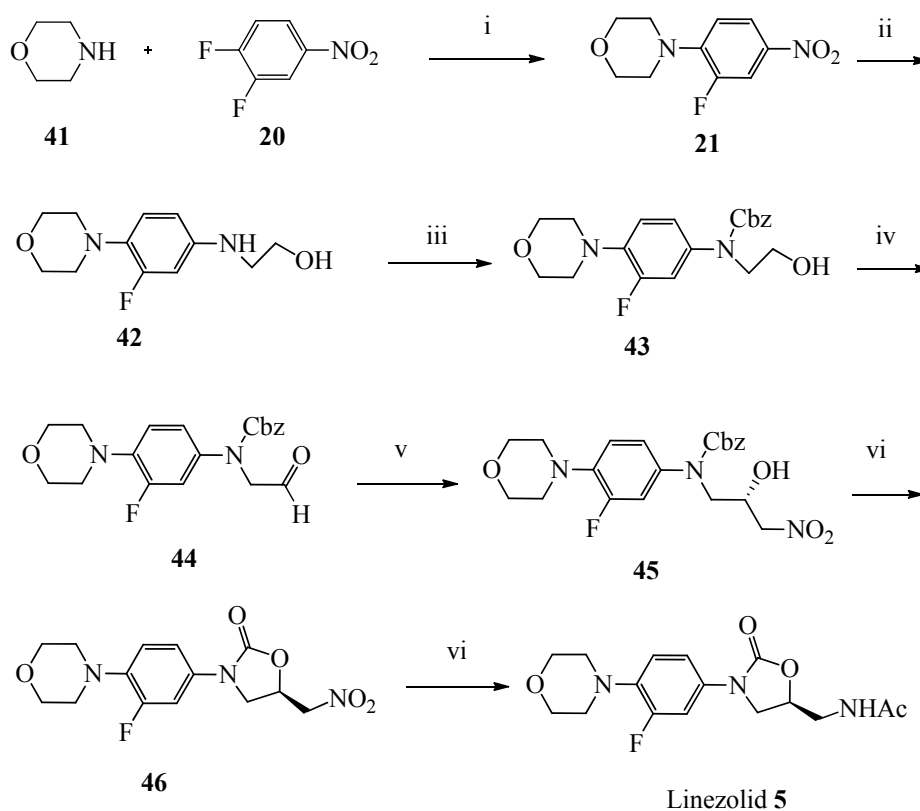


Fig. 5: Retrosynthetic analysis of linezolid **5** and eperzolid **6**

In our synthetic approach, the synthesis of linezolid **5** and eperzolid **6** are based on the retro- synthesis analysis, which leads to two chiral synthons (β -nitroalcohols **45** and **54**), both of which can be easily achieved by asymmetric nitroaldol reaction over copper fluorapatite catalyst in presence of C_2 -symmetric chiral piperazine ligand from their corresponding aldehydes **44** and **53**. The general synthetic route employed for the synthesis of Linezolid **5** and Eperzolid **6** are shown in **Scheme 7** and **8** respectively.

1.5.1 Enantioselective synthesis of Linezolid



Scheme 7: Reagents and reaction conditions: (i) acetonitrile Reflux, 99 % (ii) (a) Pd/C, ammonium formate, MeOH: THF (b) 2-Chloroethanol, I₂, butanol, Reflux 8 h, 97 % (iii) Cbz-Cl, NaHCO₃, DCM, 96 % (iv) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 to -60 °C, 96 %; (v) CuFAP, C₂-symmetric chiral piperazine, nitromethane, 24 h, 88 % (vi) K₂CO₃, dry methanol, 0-RT, 12 h, 92 % (vi) 10 % Pd/C, H₂(1 atm), EtOAc, 12 h then Ac₂O, Py 89 %.

3, 4-difluoronitrobenzene **20** was condensed with morpholine **41** in acetonitrile gave the selectively *p*-substituted nitrobenzene **21** in 99 % yield. The presence of the morpholine ring on the aromatic system was confirmed by ¹H NMR which shows the two triplets at δ 3.27 and 3.84 due to the methylene protons of –CH₂NCH₂– and –CH₂OCH₂– respectively (Fig. 6). The ¹³C-NMR showed signals at δ 49.80 and 66.54 for morpholine aliphatic carbons.

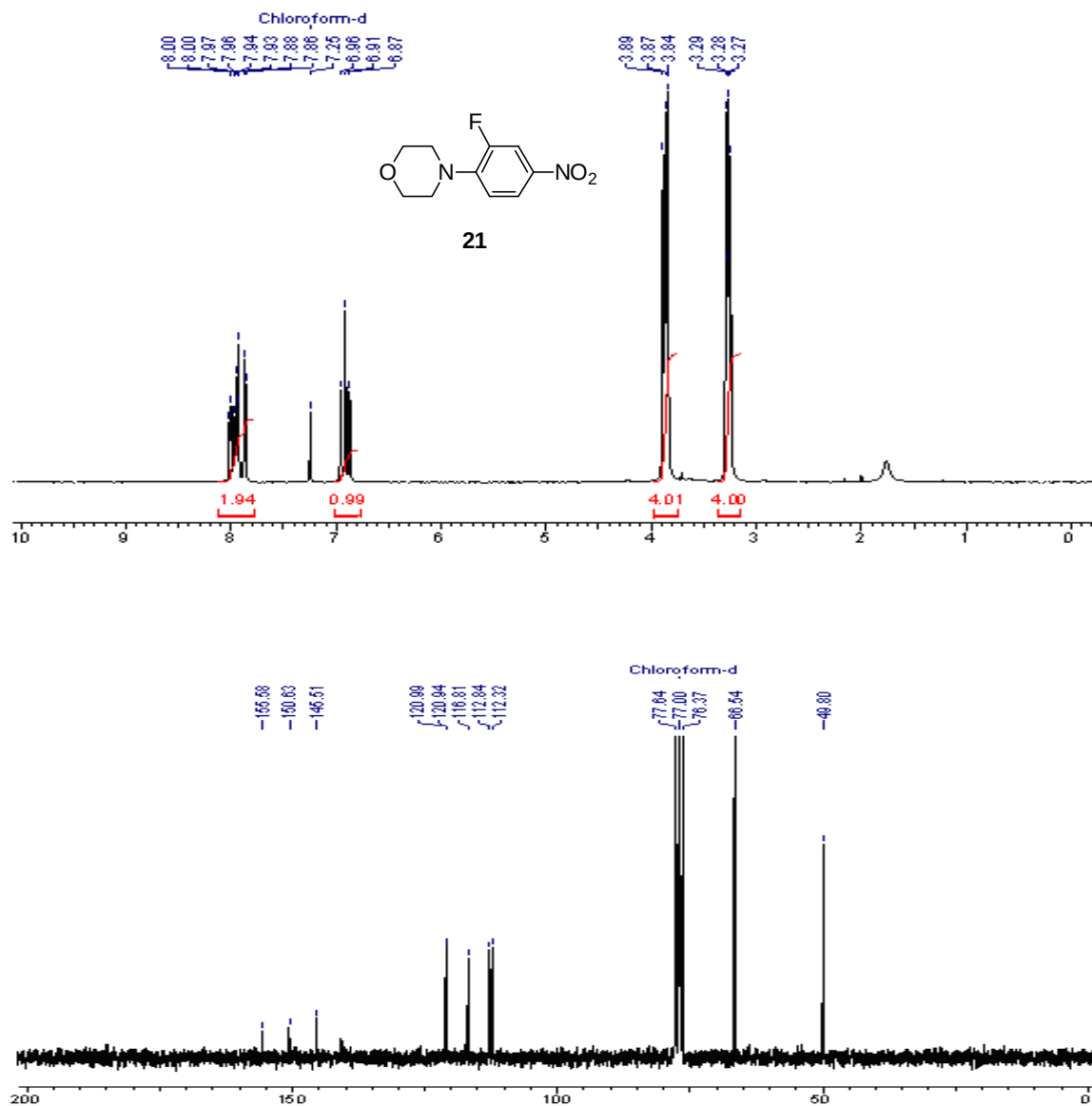


Fig. 6: ¹H and ¹³C-NMR spectrum of 3-fluoro-4-morpholinyl nitrobenzene **21**

The nitro group of the compound **21** was reduced to amine in 96 % yield by using 5 % Pd/C as a catalyst and ammonium formate as hydrogen donor source.

¹H NMR spectrum of the amine shows the broad singlet at δ 3.35 due to the presence of –NH₂ group (**Fig. 7**).

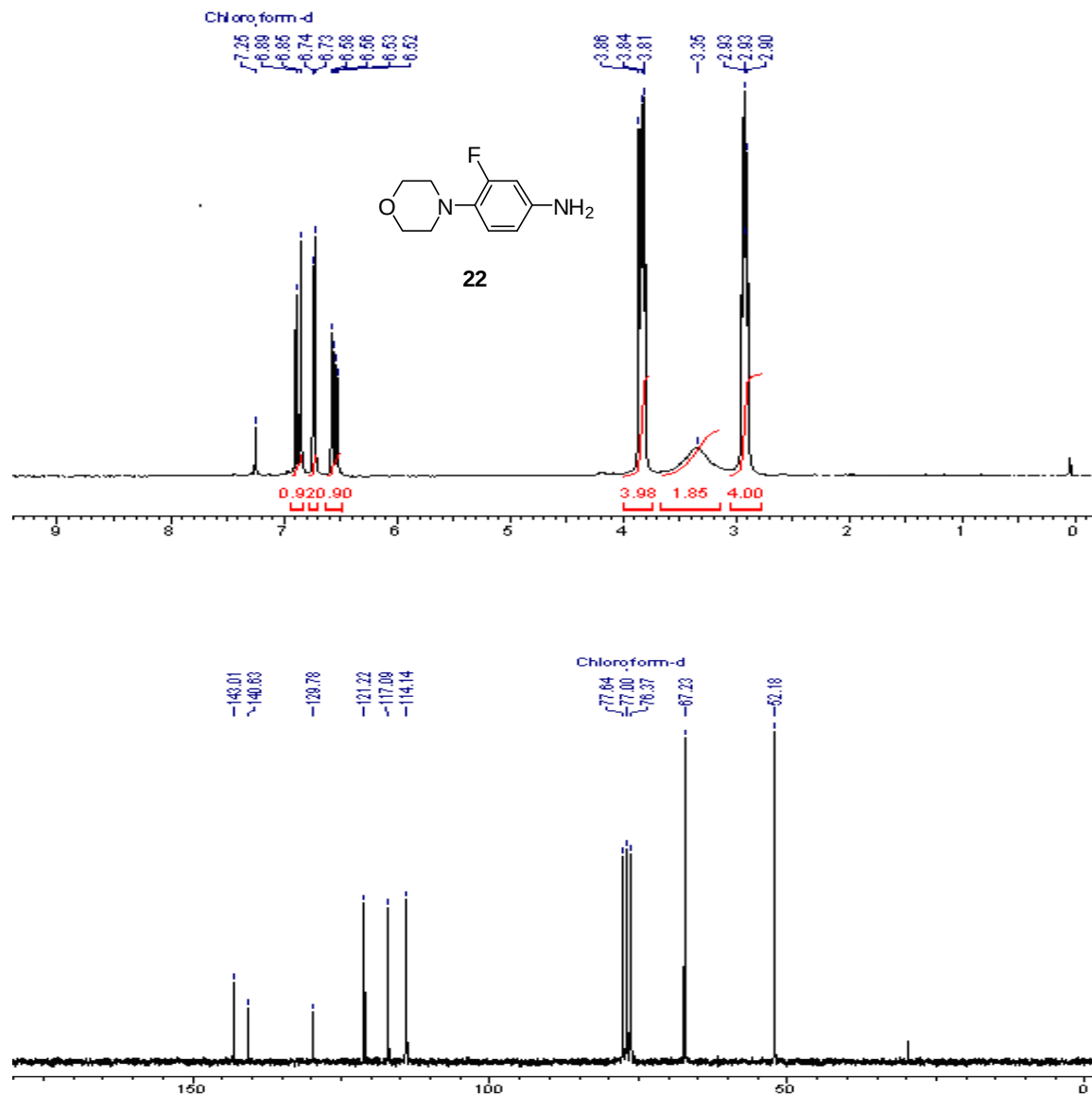


Fig. 7: ¹H and ¹³C-NMR spectrum of 3-fluoro-4-morpholinyl aniline **22**

The treatment of aryl amine with the chloroethanol in *n*-butanol catalysed by iodine gave secondary aminoalcohol **42**.²²

¹H NMR shows the two triplets at δ 3.19-3.24 and 3.76-3.80 due to the methylene protons of $\text{-NCH}_2\text{-CH}_2\text{OH}$ linkage and a broad singlet for -OH group at δ 3.13. The ¹³C-NMR

showed signals at δ 46.55 and 60.84 indicating the presence of $-\text{CH}_2-\text{CH}_2\text{OH}$ linkage (Fig. 8).

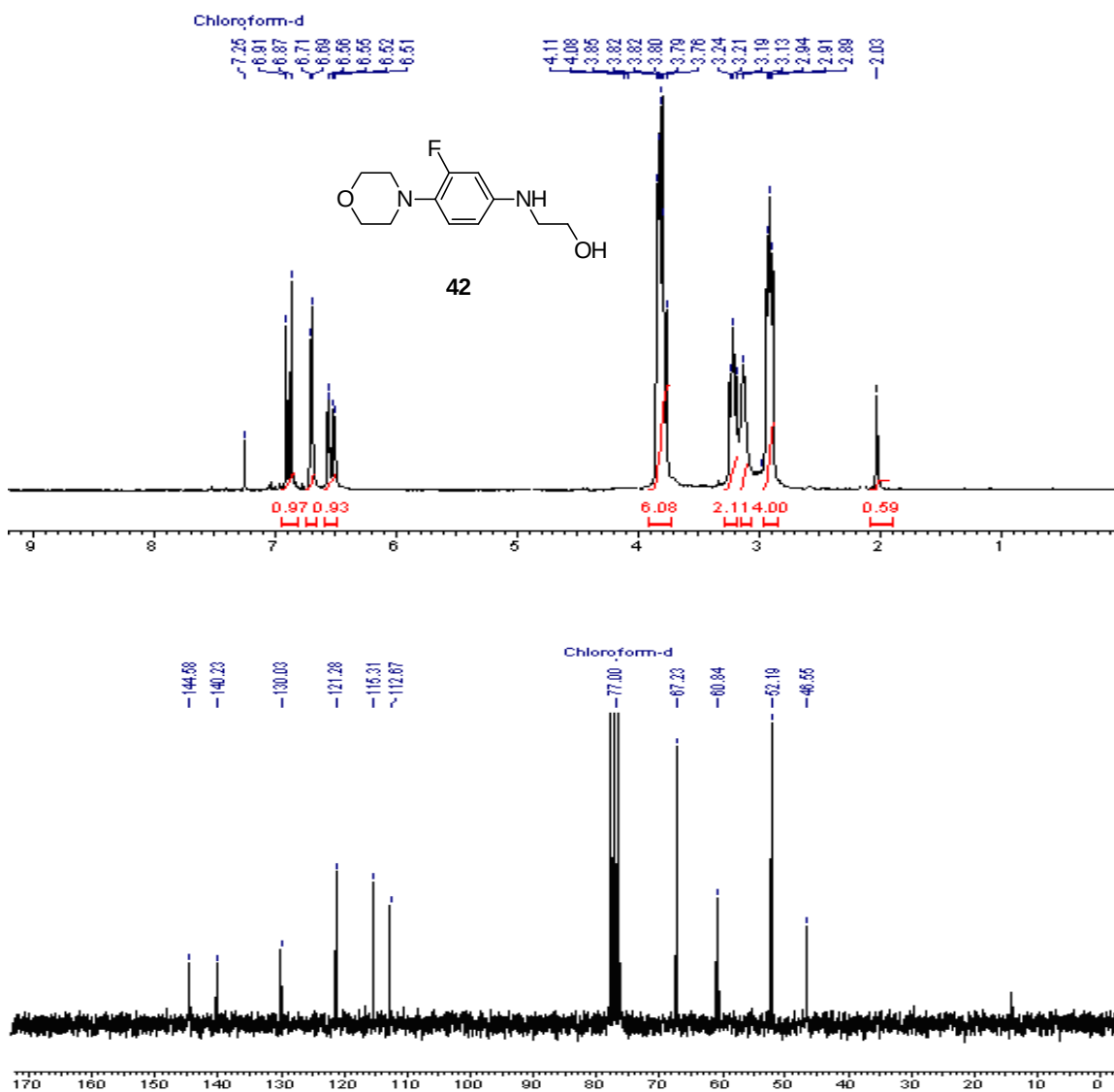


Fig. 8: ¹H and ¹³C-NMR spectrum of 3-fluoro-4-morpholinophenyl-2-ethanol amine **42**

The secondary amine group of **42** was protected by Cbz-Cl to give N-Protected alcohol **43** in 95 % yields.

The formation of alcohol **43** was confirmed by appearance of singlet at δ 5.10 for the benzylic proton and five aromatic protons at δ 7.27-7.33 in ¹H NMR spectrum (Fig. 9).

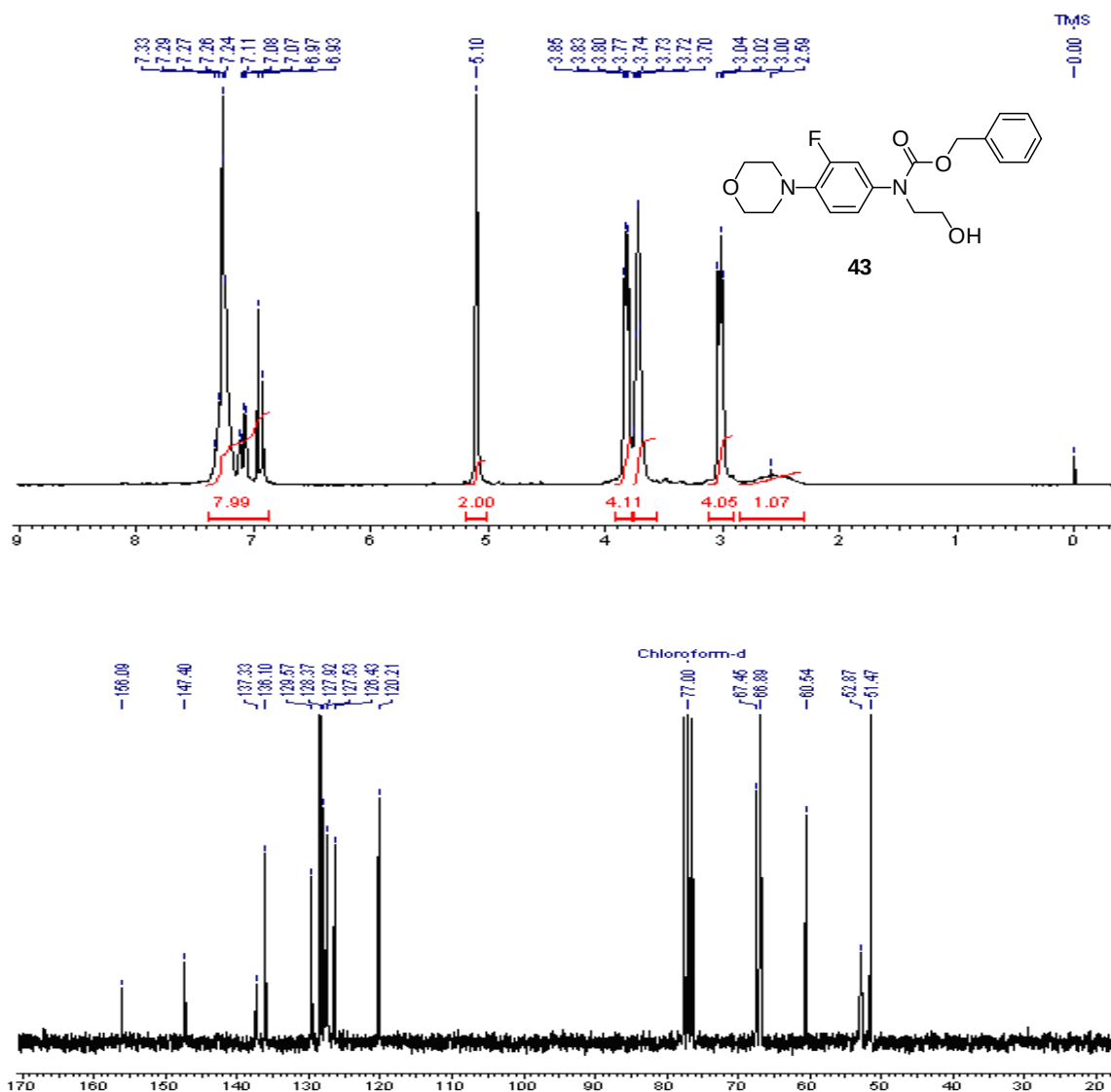


Fig. 9: ¹H and ¹³C-NMR spectrum of benzyl (3-fluoro-4-morpholinophenyl)(2-hydroxyethyl)carbamate **43**

The alcohol **43** was then subjected to oxidation to gave aldehyde **44** by using Swern oxidation method.²³

¹H NMR shows the disappearance of two triplets of methylene and appearance of new singlet for two protons at δ 4.38 adjacent to aldehyde group. Singlet at δ 9.65 for

aldehyde proton and the ^{13}C NMR spectrum shows typical signal at δ 196.81 for aldehyde confirmed the formation of product **44** (Fig. 10).

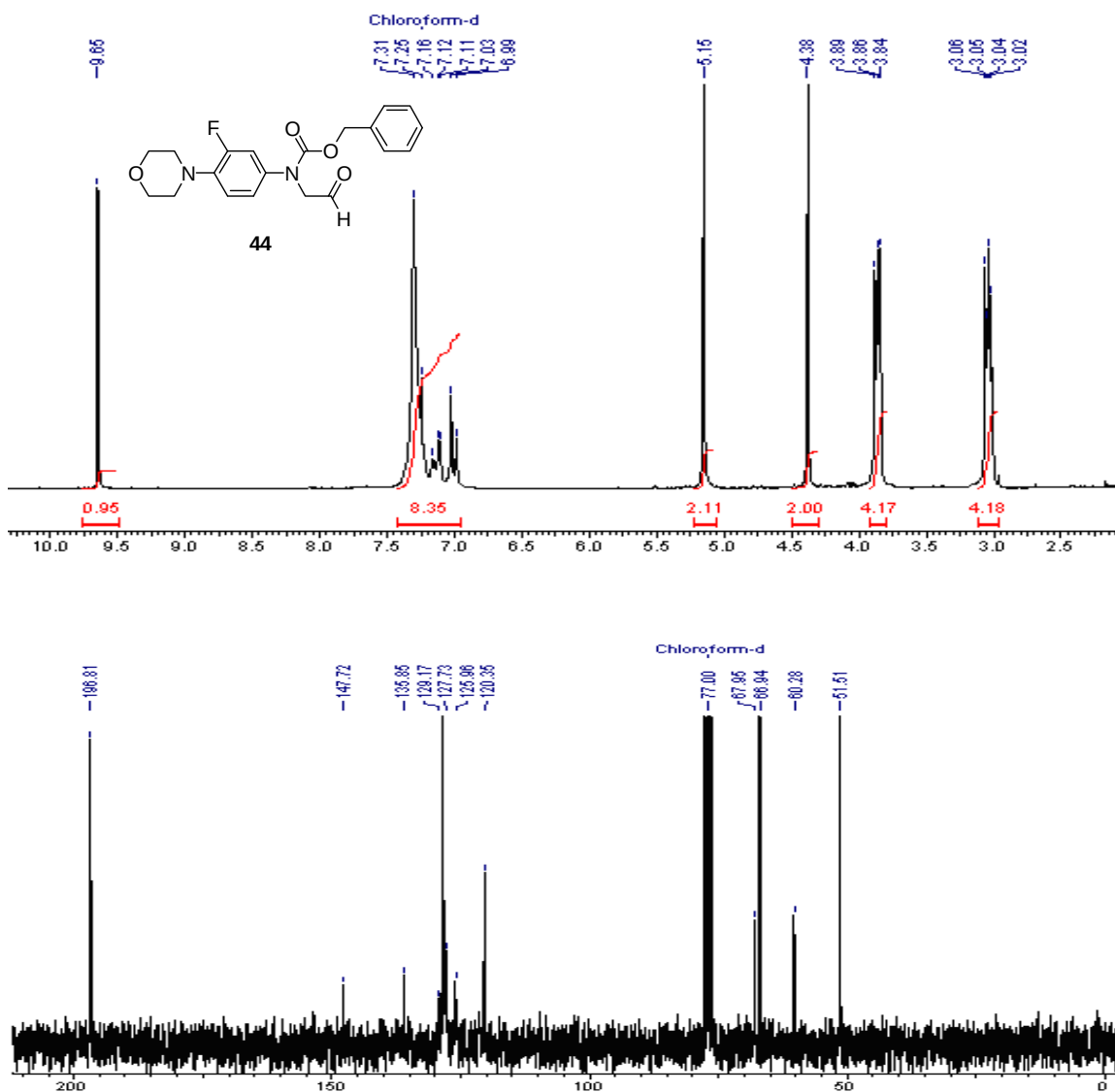


Fig. 10: ^1H and ^{13}C -NMR spectrum of benzyl (3-fluoro-4-morpholinophenyl) (2-ethanal) carbamate **44**

The aldehyde **44** was subjected to the asymmetric nitroaldol reaction with nitromethane catalysed by copper fluorapatite in the presence of C_2 -symmetric chiral piperazine ligand to obtain the β -nitroalcohol compound **45**. ^1H NMR shows the

disappearance of aldehyde proton and appearance of three multiplets for five protons at δ 3.70, 4.36 and 4.45. and the ^{13}C NMR spectrum shows typical signal at δ 78.52 for methylene group adjacent to nitro group and other signals at δ 53.64, 67.99 and 78.57 for the aliphatic carbons confirmed the formation of **45** (Fig. 11).

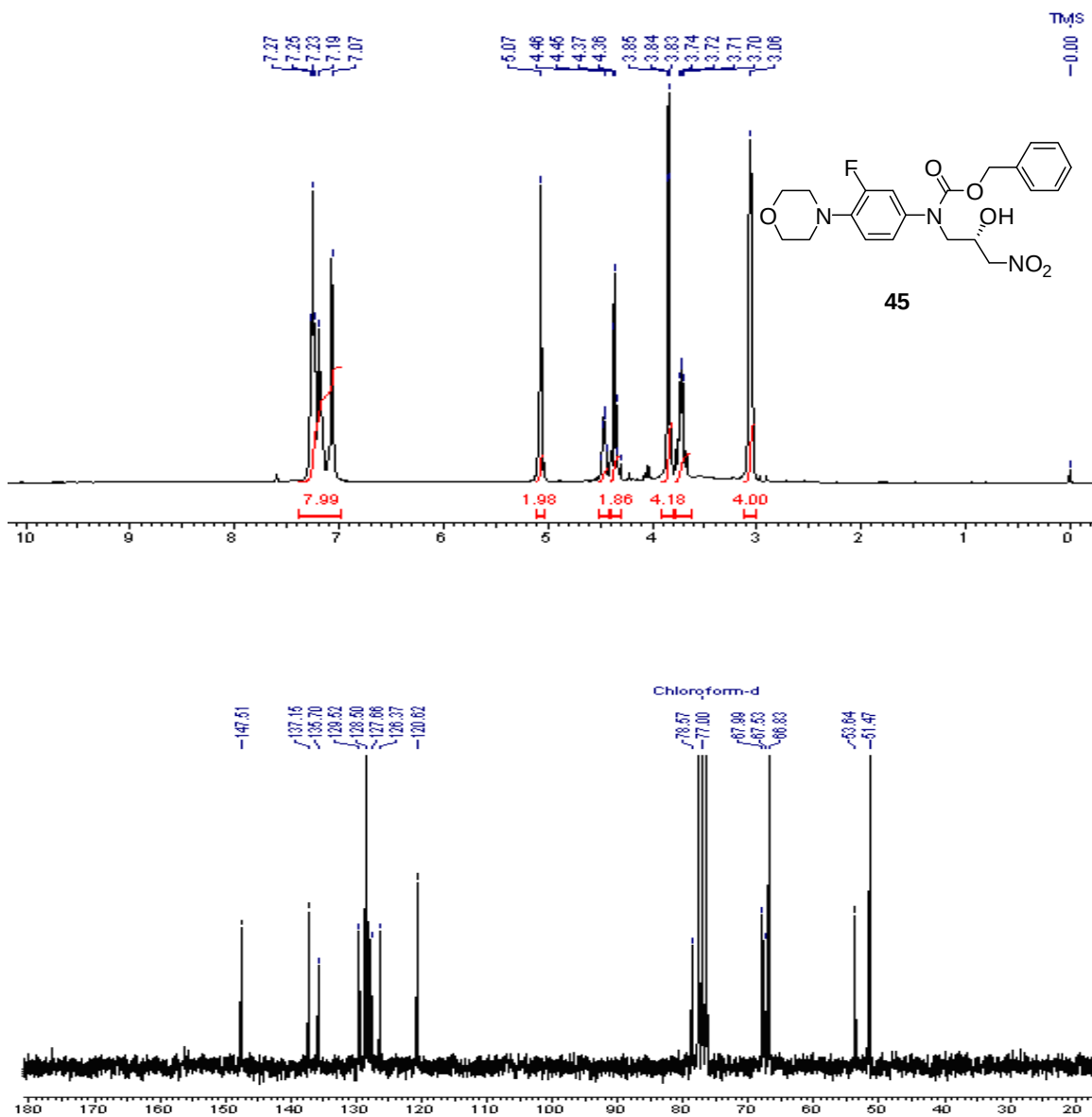


Fig. 11: ^1H and ^{13}C -NMR spectrum of (S)-benzyl (3-fluoro-4-morpholinophenyl)(2-hydroxy-3-nitropropyl)carbamate **45**

The regioselective intramolecular cyclisation²⁴ of β -nitroalcohol **45** with K_2CO_3 in dry methanol at 0 °C gave the desired oxazolidinone compound **46** in 92 % yields. The disappearance of benzylic protons at δ 5.07 and phenyl protons at δ 7.27 in 1H NMR confirmed the intramolecular cyclisation to obtained the oxazolidinone compound **46**, the typical signal at 154.86 in its ^{13}C NMR spectrum confines the presence of oxazolidinone carbonyl (**Fig. 12**).

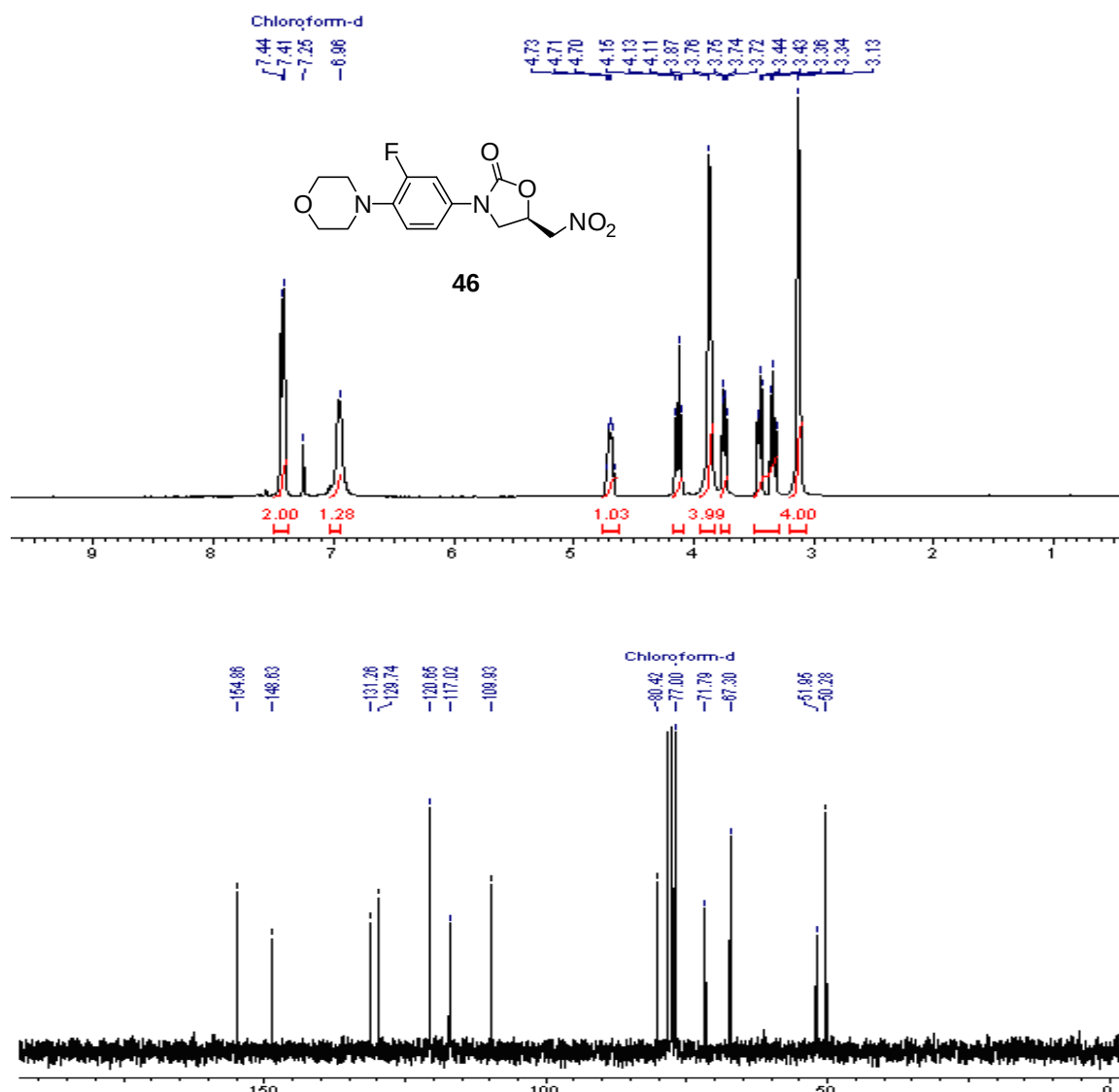


Fig. 12: 1H and ^{13}C -NMR spectrum of (S)-3-(3-fluoro-4-morpholinophenyl)-5-(nitromethyl)-oxazolidin-2-one **46**

Finally, the nitro group of the compound **46** was reduced with H₂ (1 atm) using 5 % Pd/C to furnish the crude amine, which was insitu acylated using acetic anhydride and pyridine to give linezolid **5** in 89 % yield.

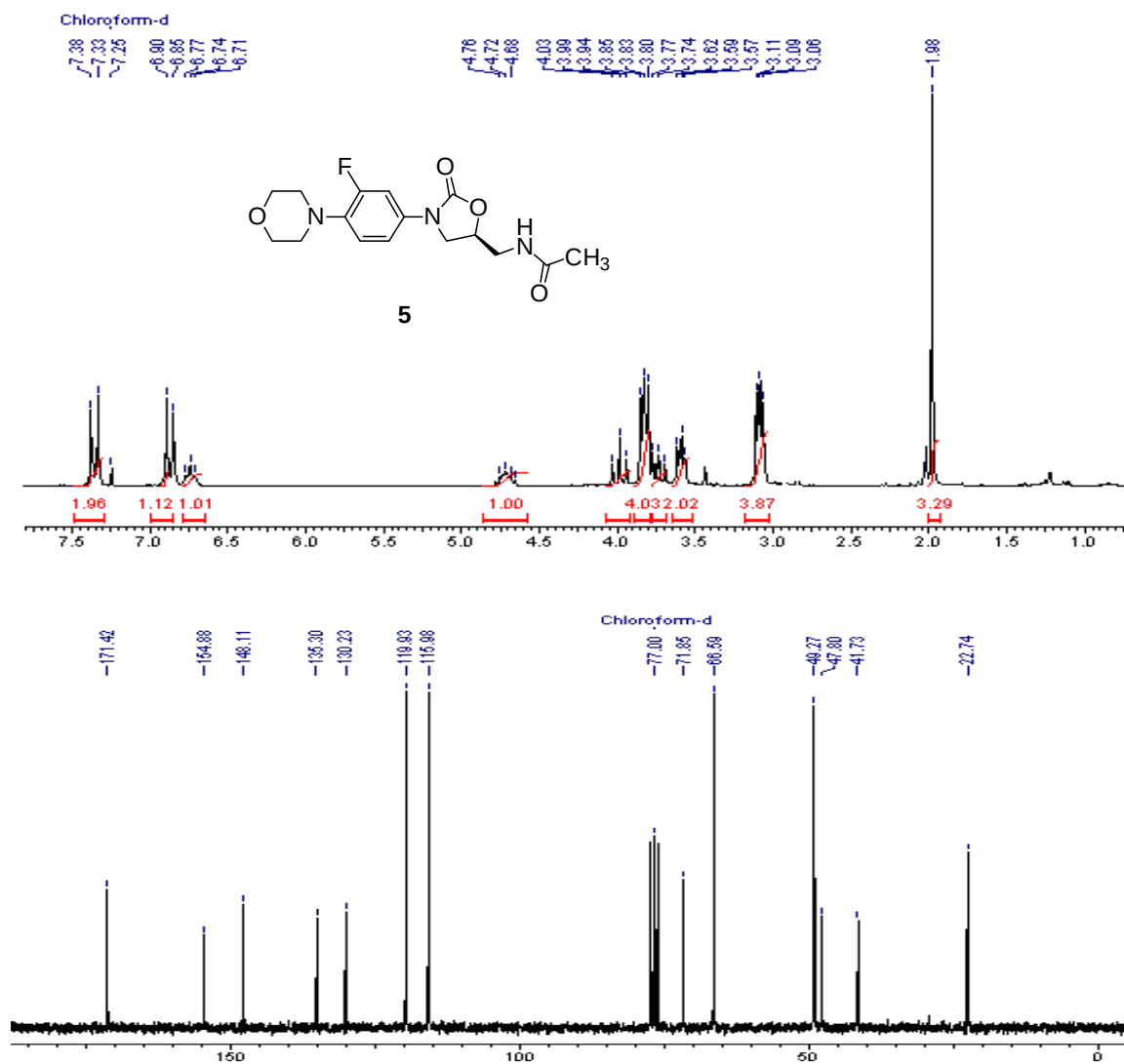
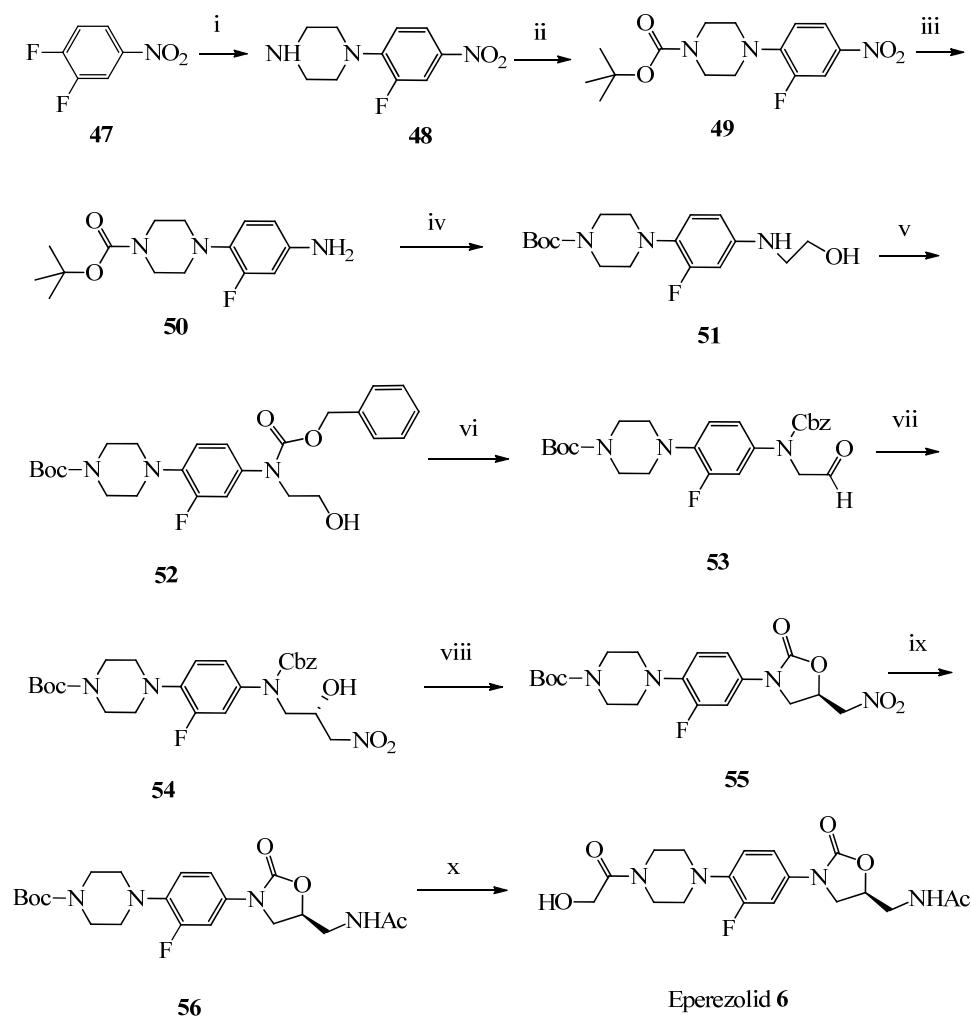


Fig. 13: ¹H and ¹³C-NMR spectrum of (S)-N-[[3-(3-fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl} acetamide (Linezolid) **5**

The ¹H NMR spectrum of linezolid **5** showed a singlet at δ 1.98 for three protons of methyl (-COCH₃) and a characteristic triplet at δ 6.74 for amine (NH) protons respectively indicating the presence of acetamide (NHAc) moiety (**Fig. 13**).

1.5.2 Enantioselective synthesis of Eperezolid



Scheme 8: Reagents and reaction conditions: (i) Piperazine, acetonitrile, TEA, Reflux, (ii) BOC-anhydride, Na_2CO_3 , THF, 96 % (iii) Pd/C, ammonium formate, MeOH: THF (iv) 2-Chloroethanol, I_2 , butanol, Reflux 8 h, 93 % (v) Cbz-Cl, NaHCO_3 , DCM, 95 % (vi) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78 to -60 °C, 93 % (vii) CuFAP, Ligand, nitromethane, 24 h, 85 % (viii) K_2CO_3 , dry methanol, 0-RT, 12 h, 88 % (ix) 10 % Pd/C, H_2 (1 atm), EtOAc, 12 h then Ac_2O , Py, 92 % (x)(a)TFA, RT, 8 h (b) HOCH_2COCl , TEA, DCM, 0-RT, 4 h, 86 %.

3, 4-difluoronitrobenzene was condensed with piperazine in acetonitrile gave the selectively *p*-substituted nitrobenzene **48** in 95 % yield. The presence of the piperazine ring on the aromatic system was confirmed by ^1H NMR which shows the two triplets at δ

3.01 and 3.12 due to the methylene protons of $-\text{CH}_2\text{NCH}_2-$ and $-\text{CH}_2\text{NHCH}_2-$ respectively while a broad singlet at δ 1.64 for secondary amine of piperazine. ^{13}C -NMR showed signals at δ 45.83 and 51.80 for aliphatic carbon of piperazine (**Fig. 14**).

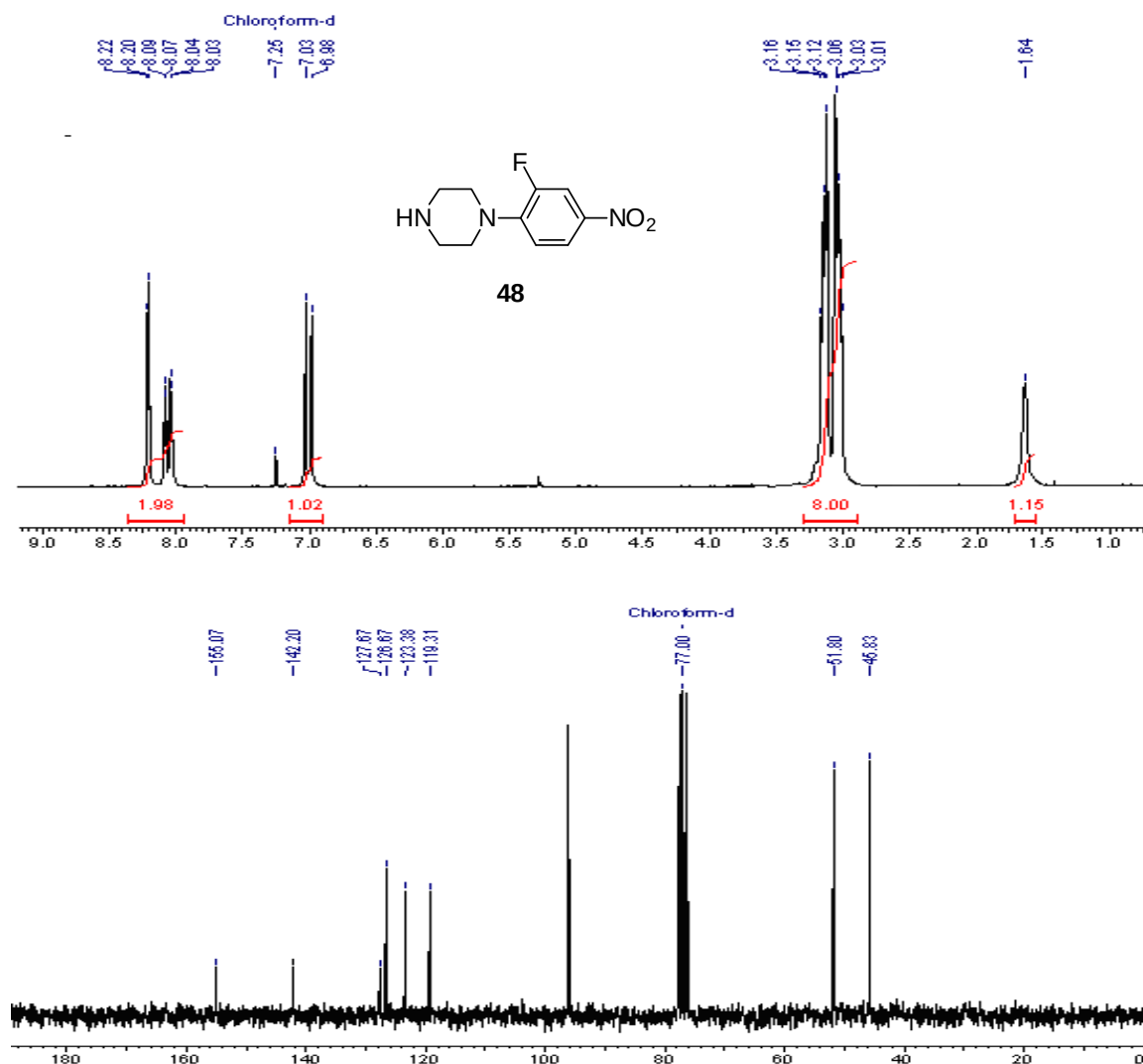


Fig. 14: ^1H and ^{13}C -NMR spectrum of 3-fluoro-4-piperazinyl nitrobenzene **48**

The secondary amine of the piperazine **48** was protected by BOC using di-*ter*-butyl dicarbonate (BOC- anhydride) in THF solvent to obtain the compound **49** in 97 % yields.

^1H NMR which shows the sharp singlet for nine protons of three $-\text{CH}_3$ groups at δ 1.45 due to the ter-butyl group and ^{13}C -NMR showed signals at δ 28.46 for three $-\text{CH}_3$ groups and 80.14 for quaternary carbon of ter-butyl group while δ 154.60 for carbonyl carbons confirms the BOC protection of secondary amine **49** (Fig. 15).

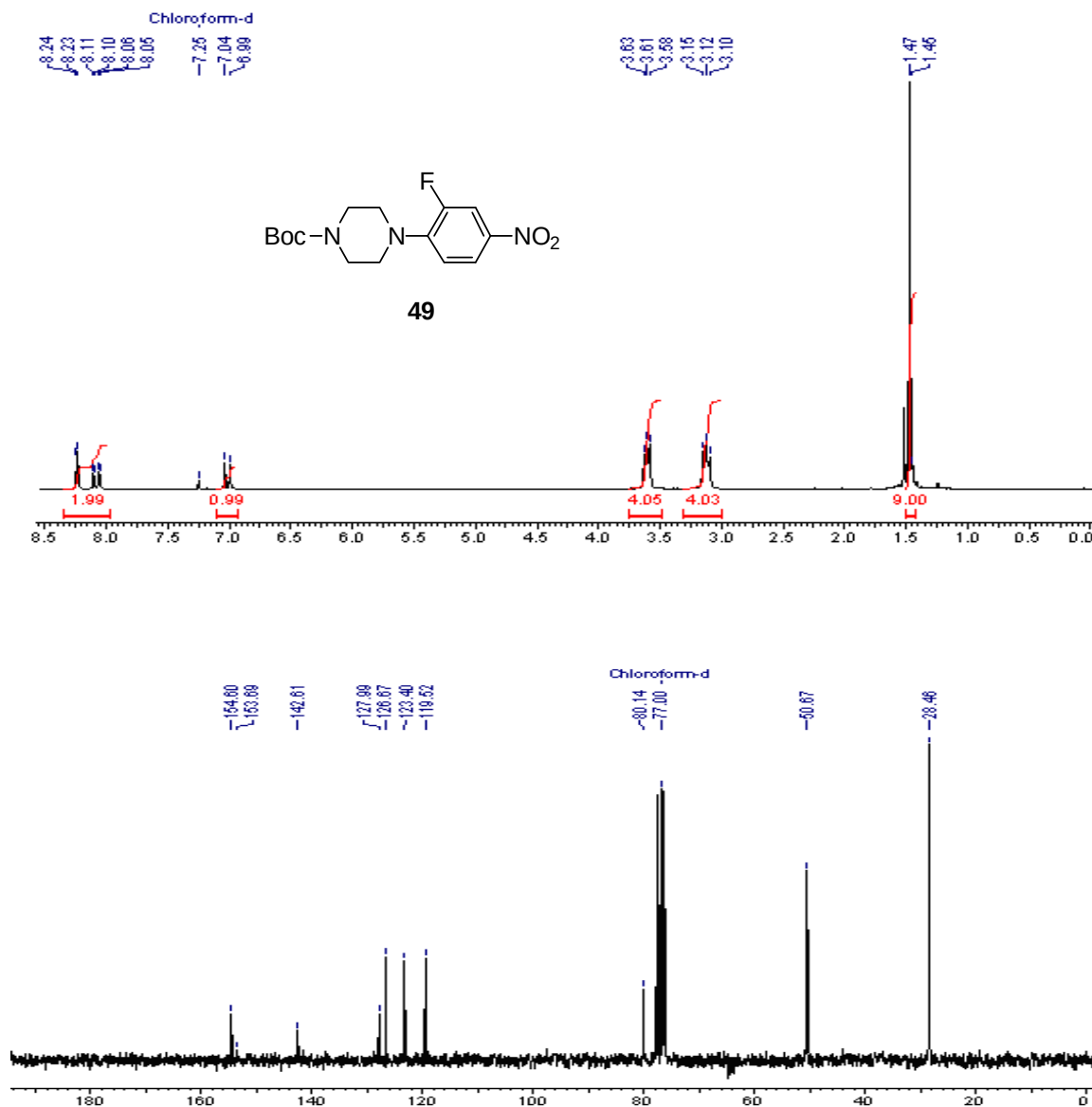


Fig. 15: ^1H and ^{13}C -NMR spectrum of 3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl]-nitrobenzene **49**

The nitro group of **49** was reduced to amine **50** in 94 % yield by using 10 % Pd/C as a catalyst and ammonium formate as hydrogen donor source. ^1H NMR spectrum of the amine **50** shows the broad singlet at δ 3.15 due to the presence of $-\text{NH}_2$ group (**Fig. 16**).

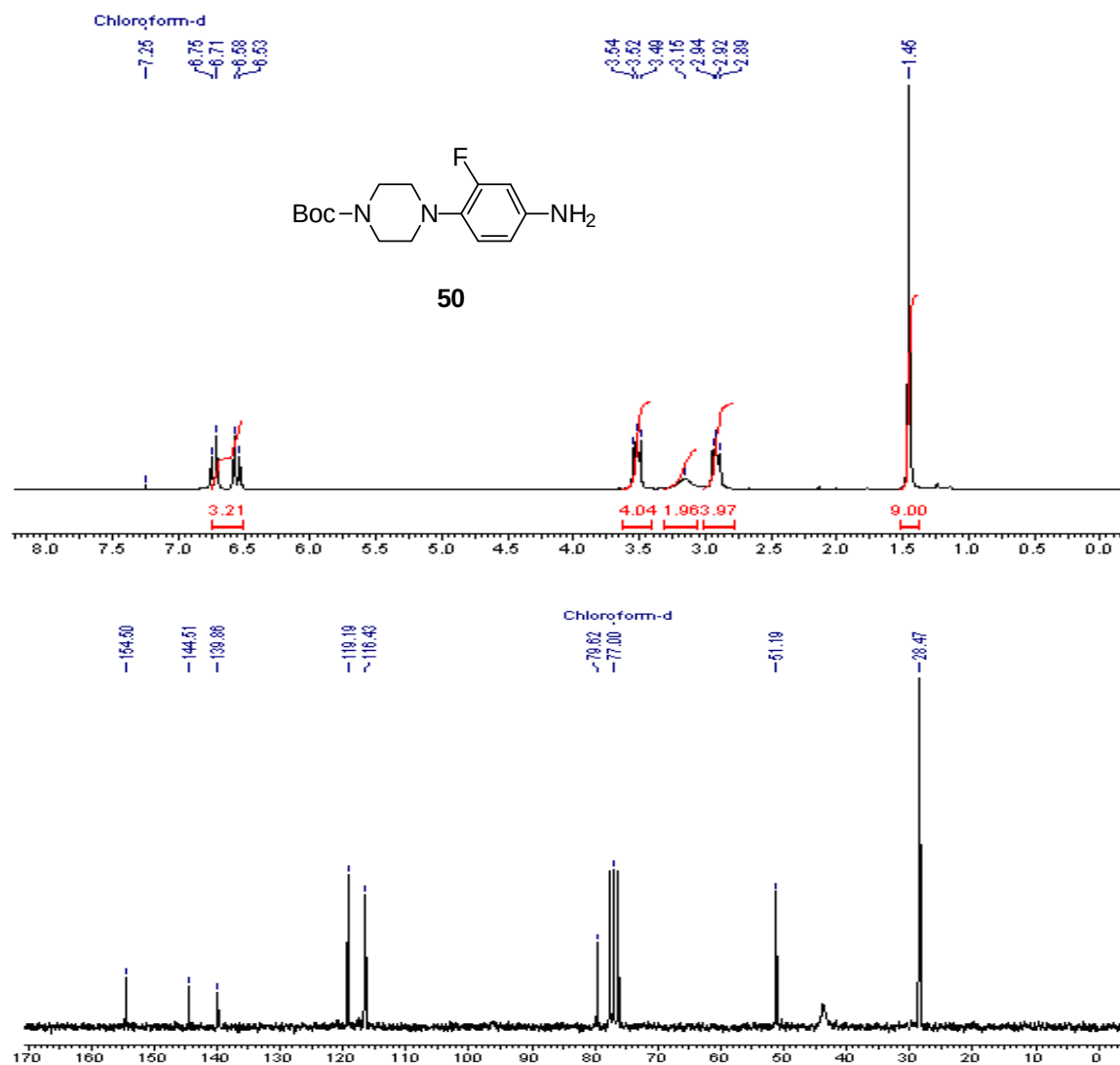


Fig. 16: ^1H and ^{13}C -NMR spectrum of 3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl] aniline **50**

The treatment of aryl amine **50** with the chloroethanol in *n*-butanol catalysed by iodine gave secondary amine **51**. ^1H NMR shows the two triplets at δ 3.13 and 3.71 due to the

methylene protons of $\text{-NCH}_2\text{-CH}_2\text{OH}$ linkage and a broad singlet for -OH group at δ 3.18. The ^{13}C -NMR showed signals at δ 46.63 and 60.60 indicating the presence of $\text{-NCH}_2\text{-CH}_2\text{OH}$ linkage (Fig. 17).

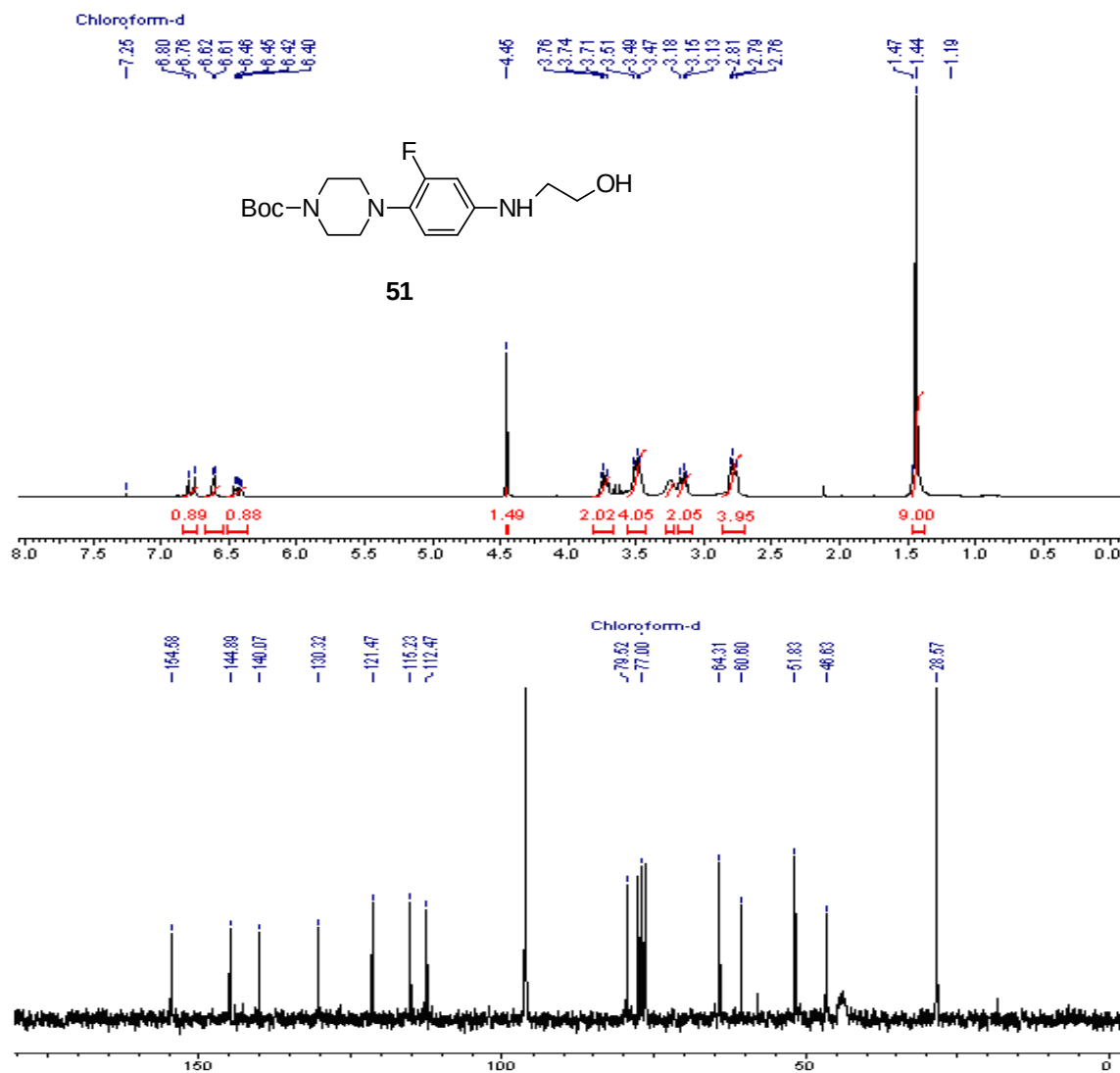


Fig. 17: ^1H and ^{13}C -NMR spectrum of *N*-{3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl] aniline}-2-hydroxy ethane **51**

The amine **51** was then N-protected by Cbz-Cl to give alcohol **52** in 95 % yield. The formation of alcohol **52** was confirmed by appearance of singlet at δ 5.04 for the benzylic proton and five aromatic protons at δ 7.18-7.23 in ^1H NMR spectrum (Fig. 18).

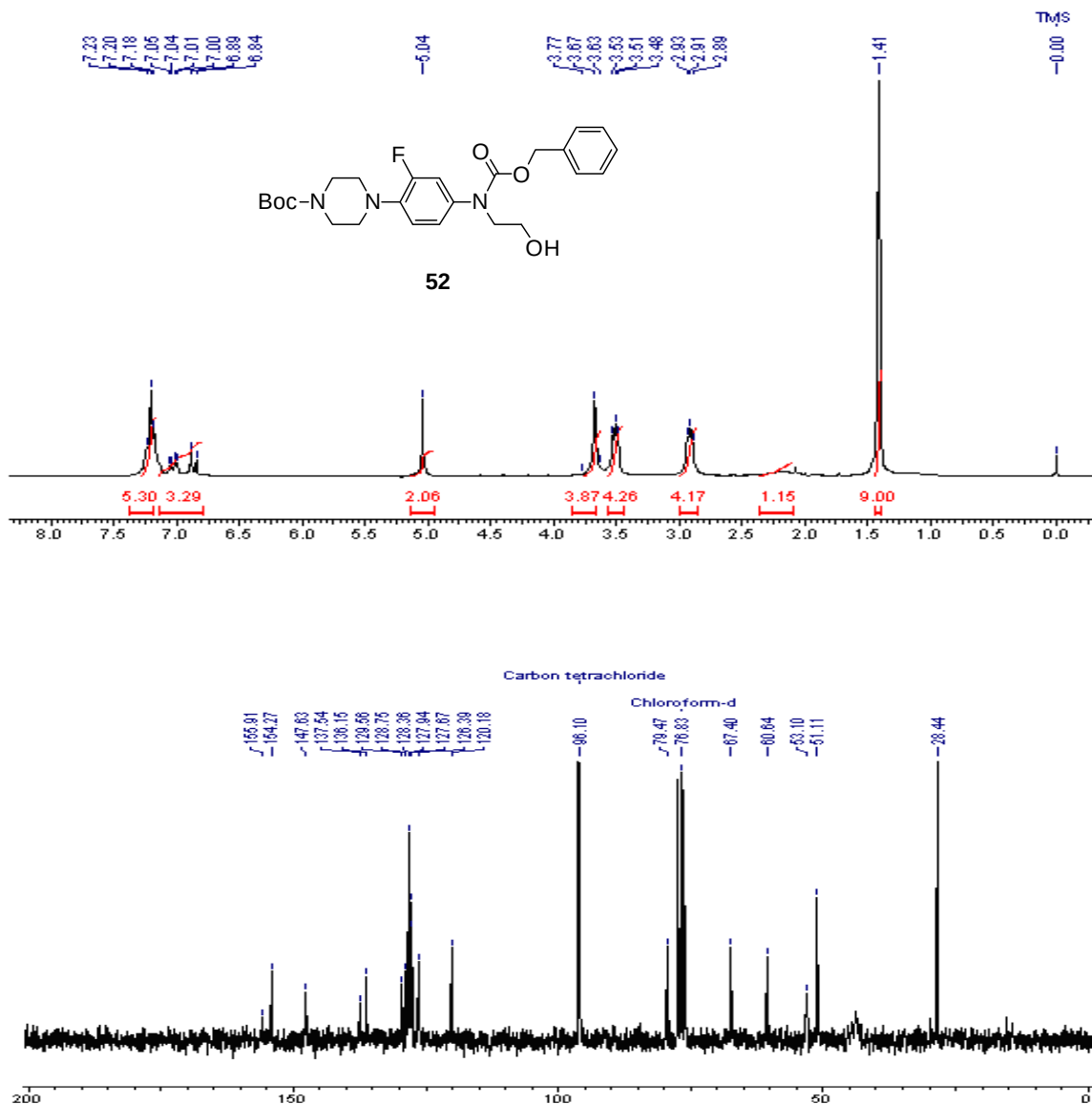


Fig. 18: ¹H and ¹³C-NMR spectrum of benzyl {3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl]-2-hydroxyethyl} carbamate **52**

The alcohol **52** was then subjected to oxidation using Swern oxidation method²³ to give aldehyde **53**.

¹H NMR shows of **53** the disappearance of two triplets of methylene and appearance of new singlet for two protons $-\underline{\text{CH}}_2$ adjacent to aldehyde group at δ 4.33 and also sharp

singlet at δ 9.62 for aldehyde proton. ^{13}C NMR spectrum shows typical signal at δ 196.11 for carbonyl carbon of aldehyde confirmed the formation of aldehyde **53** (Fig. 19).

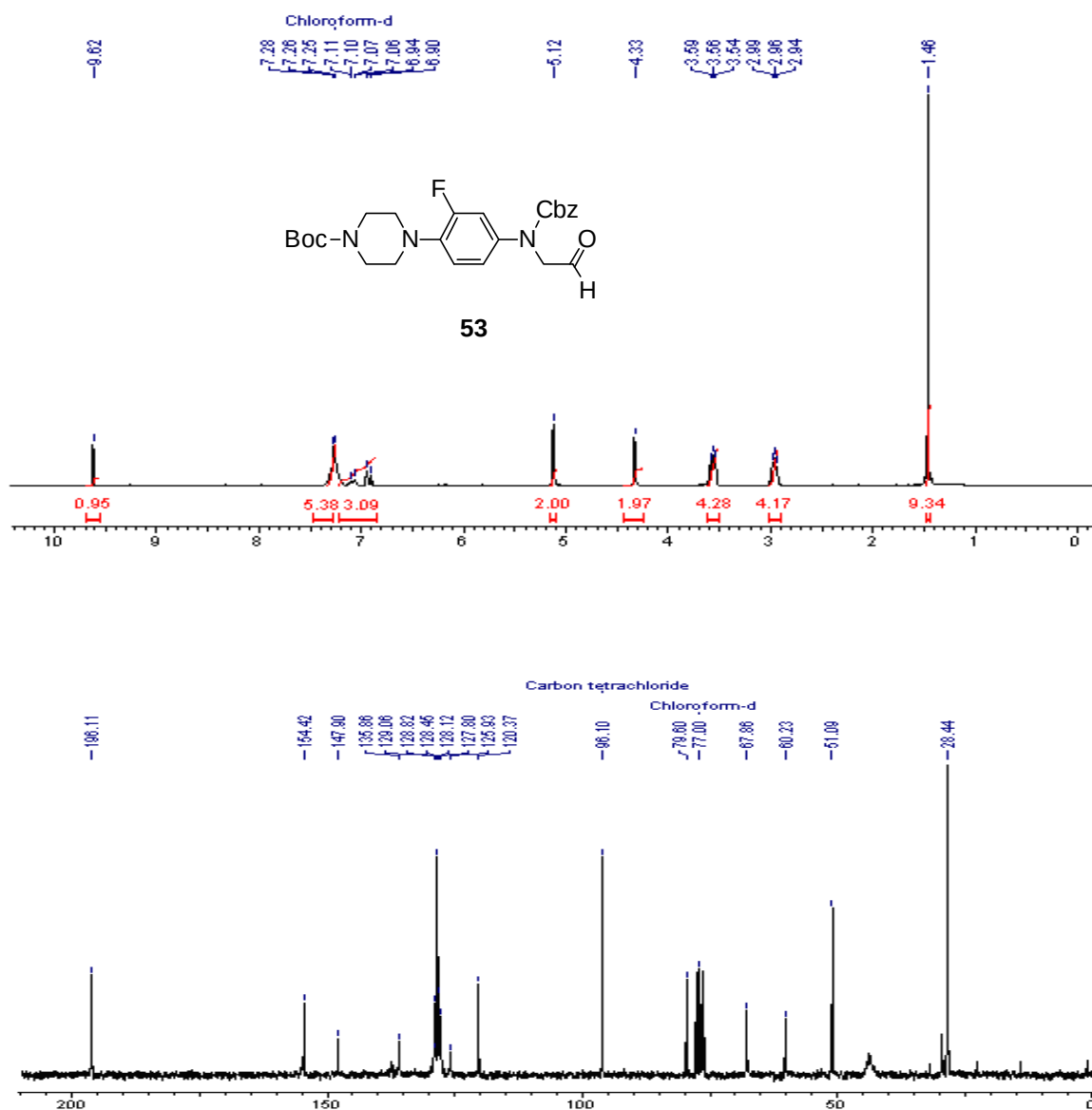


Fig. 19: ^1H and ^{13}C -NMR spectrum of benzyl {3-fluoro-4-[4- (*t*-butoxycarbonyl)-piperazinyl]-2-ethanal} carbamate **53**

The aldehyde **53** was subjected to the asymmetric nitroaldol reaction catalysed by copper fluorapatite in the presence of C_2 -symmetric chiral piperazine ligand to obtain the β -nitroalcohol **54**.

^1H NMR of **54** shows the disappearance of aldehyde proton and appearance of three multiplets at δ 3.72, 4.36 and 4.47 for five aliphatic protons. ^{13}C NMR spectrum shows typical signal at δ 79.65 for methylene group adjacent to nitro group and other signals at δ 53.73, 67.36 and 67.78 for the three aliphatic carbons confirmed the formation of product **54** (Fig. 20).

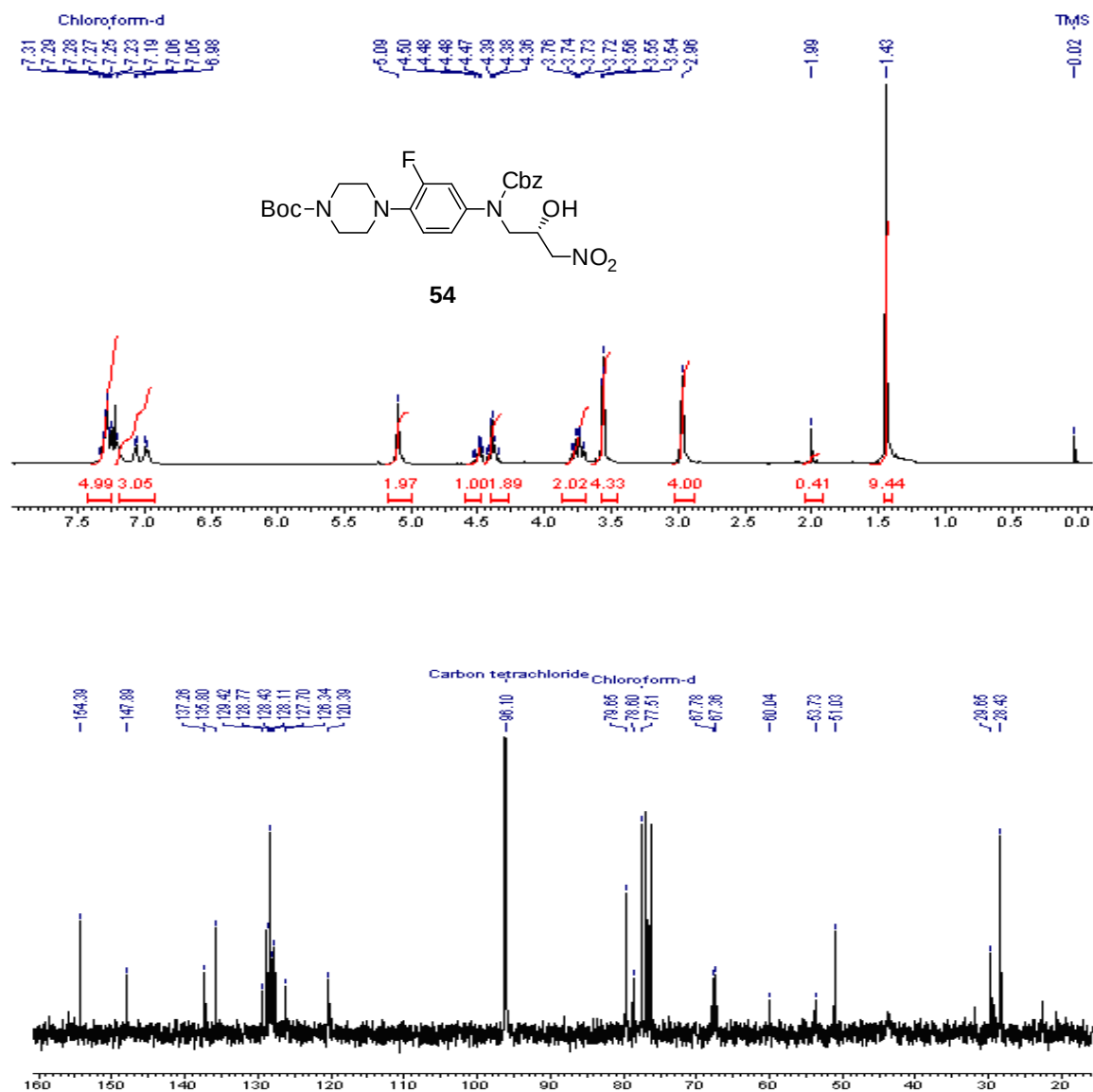


Fig. 20: ^1H and ^{13}C -NMR spectrum of (S)-benzyl {3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl]-2-hydroxy-3-nitropropyl} carbamate **54**

The regioselective intramolecular cyclisation²⁴ of β -nitroalcohol **54** in anhydrous K_2CO_3 in dry methanol at room temperature gave the desired oxazolidinone compound **55** in 88 % yields. The disappearance of benzylic $-\underline{CH}_2$ protons at δ 5.09 and five protons of phenyl ring at δ 7.27-7.31 in 1H NMR confirmed the intramolecular cyclisation to obtain the oxazolidinone compound **55**, the typical signal at 154.65 in its ^{13}C NMR spectrum confines the presence of oxazolidinone carbonyl (**Fig. 21**).

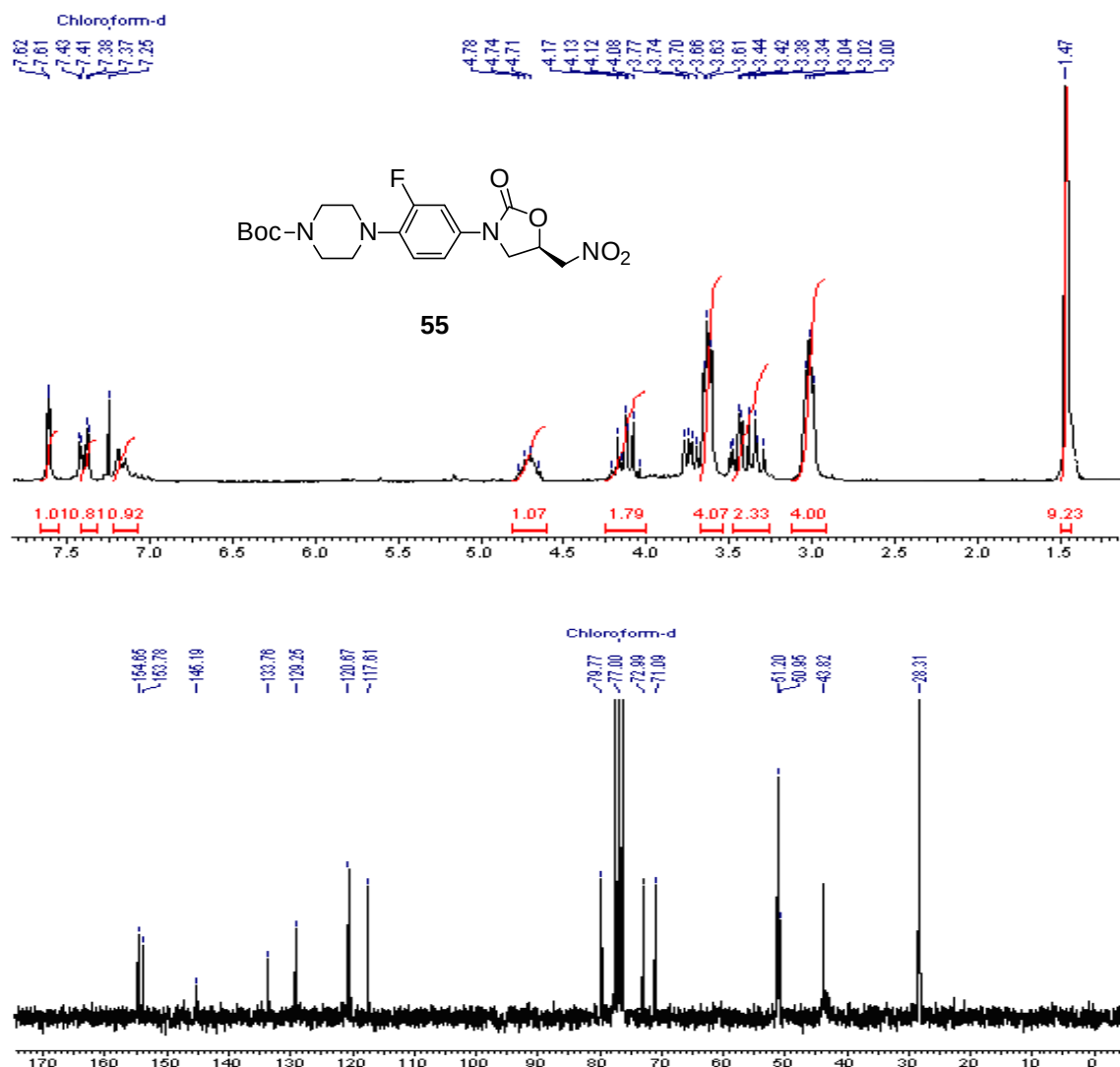


Fig. 21: 1H and ^{13}C -NMR spectrum of (S)-3-fluoro-4-[4-(*t*-butoxycarbonyl)-piperazinyl]-5-(nitromethyl)-oxazolidin-2-one **55**

The nitro group of the compound **55** was reduced with H₂ (1 atm.) using 5 % Pd/C to furnish the crude amine, which was insitu acylated using acetic anhydride in presence of pyridine as base to obtained N-Boc protected Eperezolid **56** in 92 % yield over two steps. The ¹H NMR spectrum of N-Boc protected Eperezolid **56** showed a singlet at δ 2.0 for three protons of methyl (-COCH₃) and a characteristic triplet at δ 6.55-6.61 for amine (NH) protons respectively indicating the presence of acetamide (NHAc) moiety (**Fig. 22**).

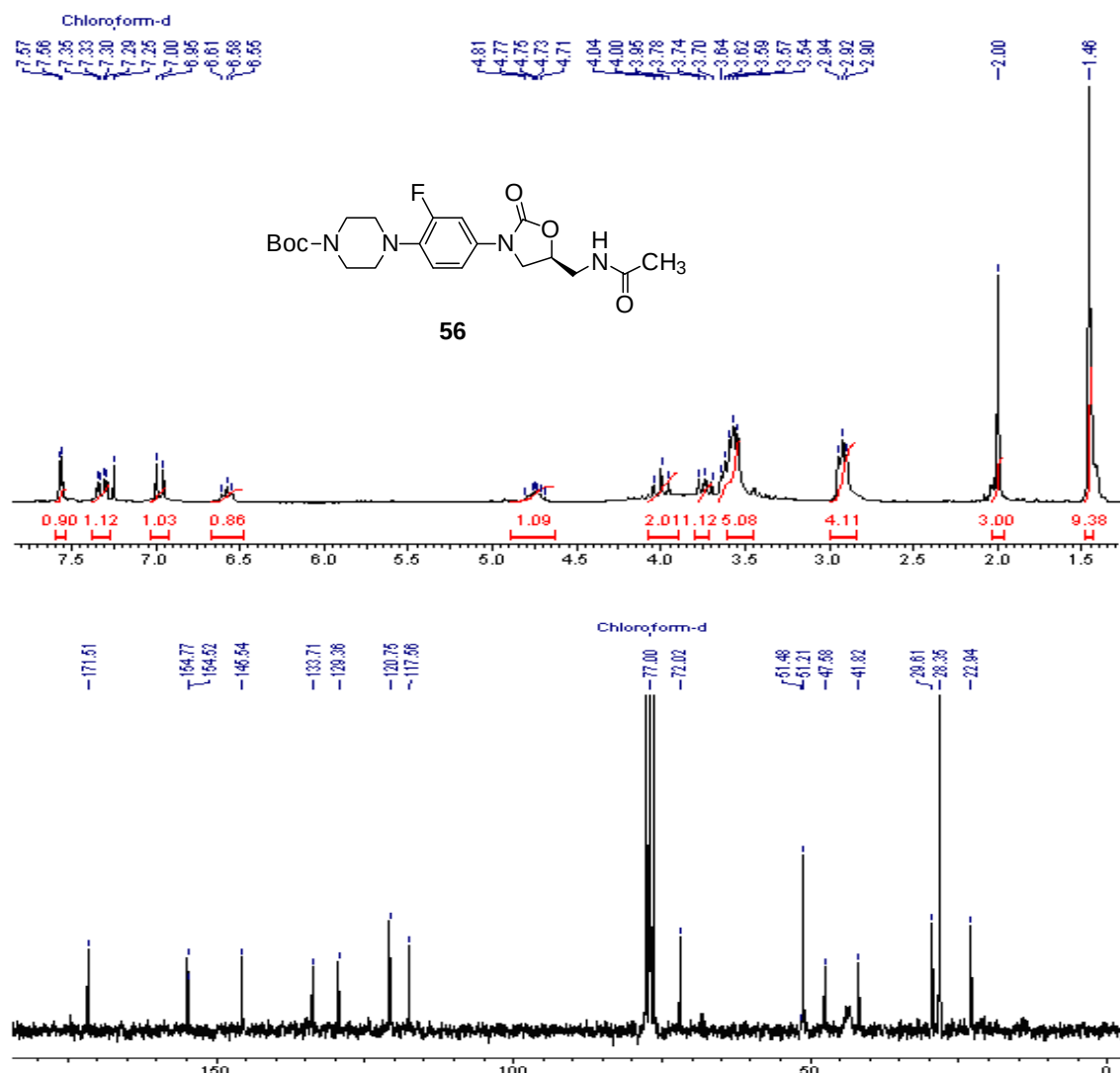


Fig. 22: ¹H and ¹³C-NMR spectrum of (S)-N-{[3-(3-fluoro-(4-*t*-butoxycarbonyl)-piperazinyl) phenyl-2-oxo-5-oxazolidinyl] methyl} acetamide **56**

Finally, the BOC protection of the piperazine was removed by the treatment of trifluoroacetic acid (TFA) in DCM and insitu acetylated with 2-hydroxy acetyl chloride to give eperezolid **6** in 86 % yields.

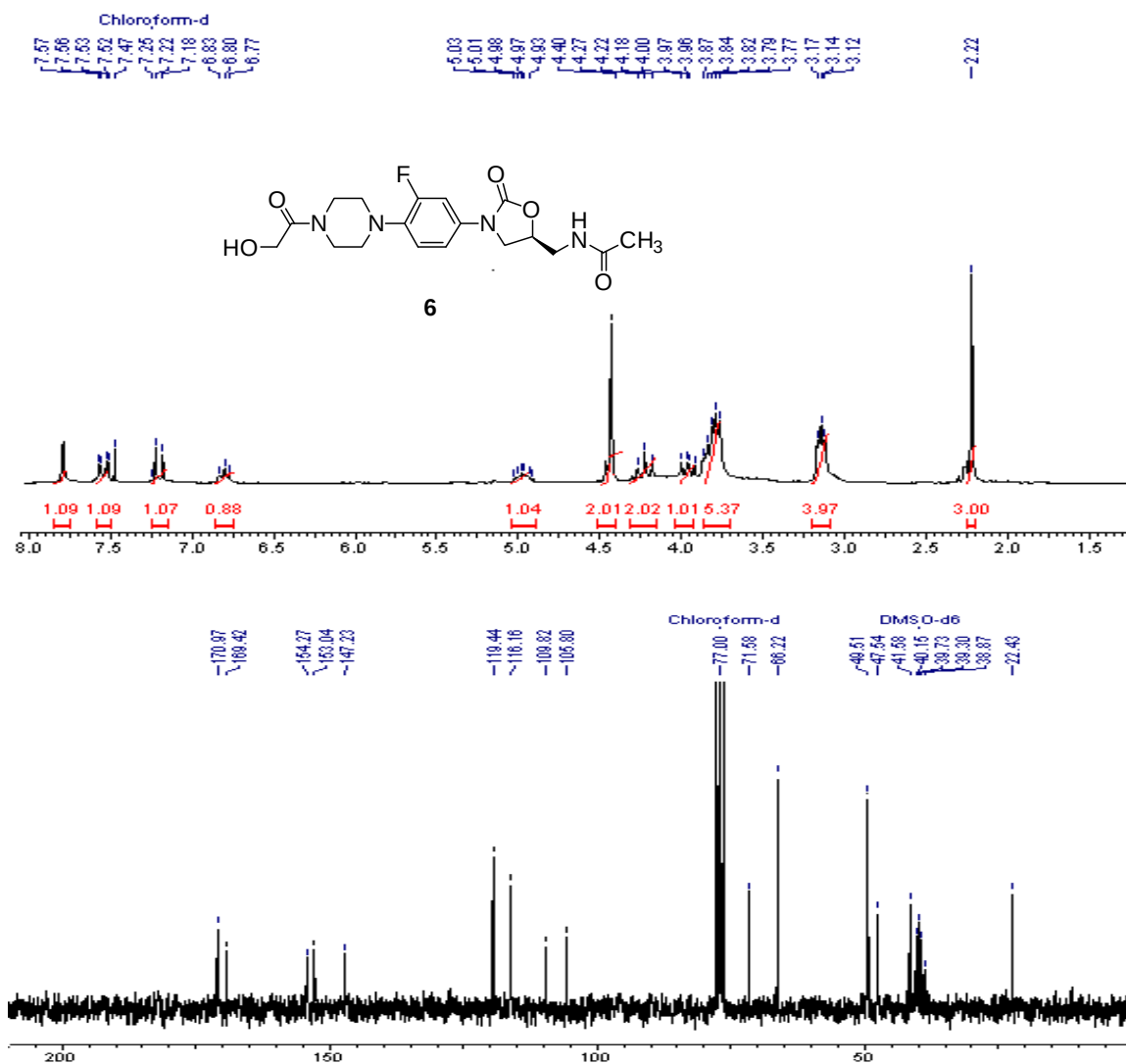


Fig. 23: ¹H and ¹³C-NMR spectrum of (S)-N-{[3-[3-fluoro-4-[4- N-1-(4-hydroxyacetyl)-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl] methyl} acetamide (Eperezolid) **6**

¹H NMR shows the disappearance of strong singlet for the three methyl groups (-CH₃) of *ter*-butyl at δ 1.46 and appearance of singlet for the two protons δ 4.40 for -CH₂OH

adjacent to carbonyl group confirms the formation of eperezolid **6**. ^{13}C NMR spectrum shows typical signal at δ 169.42 and 170.97 for presence of amide group also confirmed the formation of final Eperezolid **6** (**Fig. 23**).

1.6 Conclusion

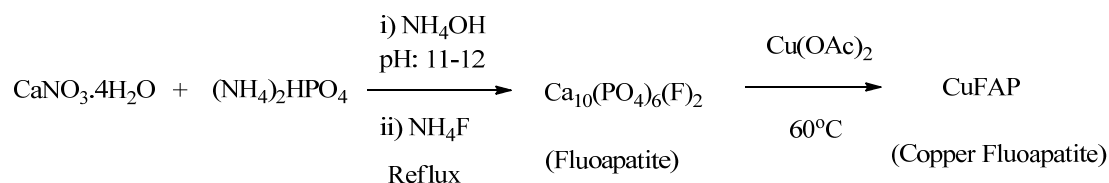
In conclusion, we have developed highly efficient, versatile, ecofriendly, and inexpensive asymmetric approach for the enantioselective synthesis of the antibacterial antibiotics, Linezolid **5** (overall yield 65.7 %) and Eperezolid **6** (overall yield 50.63 %) using asymmetric nitroaldol reaction catalysed by heterogeneous, recyclable copper fluorapatite catalyst in the presence of C_2 -symmetric chiral piperazine ligand from aldehyde as the key step and source of chirality. The salient features of this synthetic approach are its simplicity, clean, environmental friendly procedures, rapid, efficient and mild reaction conditions. The protocol is very general and it may work well for the synthesis of other oxazolidinone compounds affording good to excellent yields.

1.7 Experimental section

1.7.1 Preparation copper fluorapatite catalyst as per literature method²⁵

The copper fluorapatite catalyst was prepared by co-precipitation method in two steps.

The detail of the preparation procedure is described in **scheme 9**



Scheme 9: Preparation procedure of copper fluorapatite (CuFAP) catalyst

Step I: Preparation of fluorapatite [FAP, $\text{Ca}_{10}(\text{PO}_4)_6(\text{F})_2$]

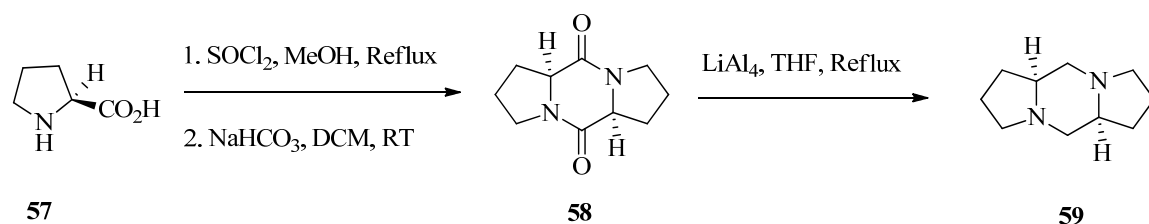
A mixture of $(\text{NH}_4)_2\text{HPO}_4$ (13.2 g, 0.1 mol) and NH_4F (1.6 g, 0.044 mol) in 416 mL of water, maintained at a pH greater than 12 by addition of NH_4OH (32 mL), was introduced into 150 mL of a solution of $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (37.76 g, 0.16 mol) under constant stirring. The suspension was refluxed for 4 h. The FAP crystallites were filtered, washed with water, dried overnight at 80 °C and calcined in air at 500 °C for 30 min.

Step II: Preparation of copper exchanged fluorapatite (CuFAP)

FAP (1 g) were stirred with aqueous $\text{Cu}(\text{OAc})_2$ (0.400 g, 2 mmol) in 25 mL water at 60 °C for a period of 10 h. The obtained slurries were filtered, washed with water and dried over night at 80 °C yielding copper exchanged fluorapatite (CuFAP) as a light blue powder (Cu content by means of ICP-MS: $\text{CuFAP} \cdot 0.73 \text{ mmol g}^{-1}$).

1.7.2. Preparation of the chiral C_2 -Symmetric piperazine ligand

The C_2 -Symmetric piperazine ligand was prepared as per literature procedure²¹ in two steps. The detail of the preparation procedure is described in **scheme 10**.



Scheme 10: Preparation procedure of C_2 -Symmetric piperazine ligand

Step I: (5S,10S)-(-)-octahydrodipyrrolo[1,2-;1',2'-]pyrazine-5,10-dione (58)

Dropwise Thionyl chloride (10.6 mL, 0.145 mol) was added to a suspension of L-proline 57 (8.0 g, 0.069 mol) in a methanol (65 mL) over a period of 1 h at -5 °C. This solution

was allowed to warm to RT and stirred for 2 h and then refluxed for 2-3 h. The solvent was evaporated under reduced pressure and residue obtained was subjected to repeat the above procedure 3 times to obtain HCl salt of L-proline methyl ester as yellow oil. The HCl salt of L-proline methyl ester was dissolved in CH₂Cl₂ (65 mL), followed by neutralization with sodium hydrogen carbonate (35 g, 0.417 mol). The residue obtained was removed by filtration and the filtrate was evaporated under reduced pressure. Then the neat filtrate was stirred at RT for 4-5 days. The filtrate was dissolved in CH₂Cl₂ and washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The concentrated products was purified by recrystallization from ethyl acetate, provided the desired **58** (5.4 g) as colorless solid.

Step II: (5S,10S)-decahydrodipyrrolo[1,2:1',2'-d]pyrazine ((S,S)-59, DHPP)

A solution of **58** (1.60 g, 8.3 mmol) in THF (10 mL) was added to a suspension of LiAlH₄ (1.56 g, 41.1 mmol) in THF (10 mL). After the complete addition the solution was refluxed for 5 h and quenched in the solution of H₂O (1.6 mL) and then 15 % aq. NaOH (1.6 mL) solution followed by addition of H₂O (4.8 mL). This solution was dried over K₂CO₃ to obtain dry precipitated. The precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to give (S,S) **59** (1 g) as colorless thick liquid which turn white solid on standing for long time.

1.7.3. Synthetic procedures

3-fluoro-4-morpholinyl nitrobenzene 21

3, 4-difluoronitrobenzene (15.9 g, 0.10 mol) in 25 mL acetonitrile, was added slowly to a stirred solution of morpholine (9.57 g, 0.11 mol) and triethylamine (20.2 g, 0.20 mol) in acetonitrile (150 mL). After the complete addition the reaction mixture was heated to

reflux for 4 hrs with vigorous stirring. The completion of reaction was monitored by TLC. After completion of the reaction, a mixture of 50 mL water and 50 mL ethyl acetate was added. The organic layer was separated and water layer was extracted with ethyl acetate (50 mL*3), the combined organic portions were dried over anhyd. Na₂SO₄ and concentrated to give crude product which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **21** (22.26 g, 98.59 % yield) as a yellow solid.

Yield: 99 %, yellow solid; m.p.: 112-113 °C, (lit.¹⁶ 111-112 °C); ¹H NMR (200 MHz, CDCl₃): δ 3.27 (t, 4H), 3.84 (t, 4H), 6.87 (dd, *J* = 4, 5 Hz, 1H), 7.86 (dd, *J* = 2, 5 Hz, 1H), 7.96 (dd, *J* = 2, 4 Hz, 1H); ¹³C NMR (200 MHz, CDCl₃): δ 49.80, 66.54, 112.32, 112.84, 116.81, 120.94, 120.99, 145.51, 150.63, 155.58.

3-fluoro-4-morpholinylaniline 22

Ammonium formate (9.45 g, 0.15 mmol) was added to a stirred solution of nitro compound **21** (11.3 g, 0.05 mol) in THF (15 mL) and MeOH (60 mL). The flask was alternately flushed with nitrogen and then 10 % Pd/C (0.132 g) was added, and the system was again flushed with nitrogen and stirring was continue for 4 h, The completion of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite and washed with ethylacetate (20 mL). The filtrate was evaporated on rotavapour then the mixture of water (40 mL) and EtOAc (60 mL) were added and the phases separated, and the aqueous portion was extracted with EtOAc (3 × 50 mL). The combined organic portions were washed with brine, dried over anhyd. Na₂SO₄, and concentrated to give crude product which was purified by column

chromatography using ethyl acetate-Petroleum ether for elution to get the pure product (9.4 g, 96 % yield) as a brown solid.

Yield: 96 %; light brown solid; mp: 134-136 °C; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.9 (t J = 3, 4H), 3.35 (brs, 2H), 3.81 (t, J = 3 Hz, 4H), 6.52 (dd, J = 6, 2 Hz, 1H), 6.73 (dd, J = 4, 2 Hz, 1H), 6.85 (d, J = 4 Hz, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 52.18, 67.23, 114.14, 117.09, 121.22, 129.78, 140.63, 143.01.

3-fluoro-4-morpholinophenyl-2-ethanol amine 42

2-chloroethanol (6 g, 0.075 mol) was added to a stirred solution of 3-Fluoro-4-morpholinylaniline (10.6 g, 0.05 mol) in *n*-butanol (50 mL), anhydrous K_2CO_3 (13.8 g, 0.1 mol) and Iodine (1 g). The flask was alternately flushed with nitrogen and then refluxed at 115-120 °C under nitrogen and stirring was continuing for 12 h. The completion of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure then the mixture of water (50 mL) and EtOAc (50 mL) were added and the phases separated, and the aqueous portion was extracted with EtOAc (3 $\times$ 50 mL). The combined organic portions were washed with brine, dried over anhyd. Na_2SO_4 , and concentrated to give crude product which was purified by column chromatography using ethyl acetate-Petroleum ether for elution to get the pure product (12.2 g, 95 % yield) as a brown syrup.

Yield: 95 %; Brown oil; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.03 (s, 1H), 2.89 (t, J = 5 Hz, 4H), 3.13 (brs, 1H), 3.19-3.24 (t, J = 6 Hz, 2H), 3.76-3.85 (m, 6H), 6.51 (dd, J = 2, 4 Hz, 1H), 6.69 (d, J = 2 Hz, 1H), 6.87 (d, J = 4 Hz, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 46.55, 52.19, 60.84, 67.23, 112.67, 115.31, 121.28, 130.03, 140.23, 144.58.

Benzyl (3-fluoro-4-morpholinophenyl)(2-hydroxyethyl) carbamate 43

To a stirred solution of alcohol **42** (3 g, 11.7 mmol) in dichloromethane (25 mL) and K_2CO_3 (3.22 g, 23.4 mmol) was cool to 0 °C and benzyl chloroformate 50 % solution in toluene (5.96 g, 17.5 mmol) was added slowly under nitrogen atmosphere. Stirring was continued for 4 h, progress of the reaction was monitored by TLC. After completion of the reaction, the mixture of water (50 mL) and dichloromethane (50 mL) were added and the phases separated, and the aqueous portion was extracted with dichloromethane (3 × 25 mL). The combined organic portions were washed with brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated to give crude product which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **43** (4.41 g, 95 % yield) as a thick oil.

Yield: 95 %; thick oil; ; 1H NMR (200 MHz, $CDCl_3$): δ 2.59 (brs, 1H), 3.0 (t, J = 4 Hz, 4H), 3.70 (t, J = 4 Hz, 4H), 3.80-3.85 (t, J = 5 Hz, 4H), 5.10 (s, 2H), 6.93 (d, J = 4 Hz, 2H), 7.08 (dd, J = 4 Hz, 1H), 7.27-7.33 (m, 5H) ; ^{13}C NMR (200 MHz, $CDCl_3$): δ 51.47, 52.87, 60.54, 66.89, 67.45, 120.21, 126.43, 127.53, 127.92, 128.37, 129.57, 136.10, 137.33, 147.40, 156.09.

Benzyl (3-fluoro-4-morpholinophenyl)(2-ethanal)carbamate 44**Swern oxidation method:**

To a stirred solution of oxalyl chloride, $(COCl)_2$ (5.04 g, 40 mmol) in dichloromethane (50 mL) at -78 °C, was added a solution of DMSO (3.12 mL, 40 mmol). The reaction mixture was stirred for 30 min. Alcohol **43** (3.74 g, 10 mmol) in dichloromethane (25 mL) was added slowly. After stirring for 45 h min. at -78 °C, the reaction was quenched by the addition of Et_3N (8.08 g, 40 mmol) and water (50 mL). The organic phase was

separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL), dried over anhyd. Na₂SO₄ and concentrated to give the crude aldehyde **44** which was purified by column chromatography using ethyl acetate: Petroleum ether for elution to get the pure product (3.58 g, 96 % yield) as yellow oil.

Yield: 96 %; yellow oil; ; **IR** (CHCl₃): 3032, 2958, 2855, 2824, 1706, 1603, 1557, 1496, 1449, 1416, 1219, 1115, 920, 754 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 3.02 (t, *J* = 4 Hz, 4H), 3.84 (t, *J* = 5 Hz, 4H), 4.38 (s, 2H), 5.15 (s, 2H), 6.99(dd, *J* = 2, 4 Hz, 2H), 7.11 (d, *J* = 5 Hz, 1H), 7.25 (m, 5H), 9.65 (s, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 51.51, 60.28, 66.94, 67.95, 120.35, 125.96, 127.73, 129.17, 135.85, 147.72, 196.81.

(S)-Benzyl (3-fluoro-4-morpholinophenyl)(2-hydroxy-3-nitropropyl)carbamate 45

CuFAP (100 mg) and the C₂-symmetric chiral piperazine ligand (L*) (3 mol %) in 10 mL nitromethane was taken into the 50 mL round bottomed flask and stirred at room temperature for 30 minutes. The reaction mixture was cooled to 0-10 °C and then aldehyde **44** (4 mmol) dissolved in 2 mL nitromethane was added, reaction was continued till the completion at 10 °C for 24 h. After completion of the reaction, a mixture of DCM and water (1:1, 100 mL) was added. Separate the organic layer and aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layer was washed with water (2 x 50 mL), brine, dried over anhydrous Na₂SO₄, filtered and concentrated on rotary evaporator under reduced pressure. Resulting residue was purified by column chromatography (silica gel) using EtOAc-petroleum ether (10:90) as eluant, affording the β -nitroalcohols **45** pale yellow liquid in 88 % yield.

Yield: 1.53 g, 88.4 %; pale yellow oil; $[\alpha]_D^{25}$ = -12.3 (*c* 1.09, CHCl₃); **IR** (CHCl₃): 3567.

3058, 2862, 2847, 1703, 1552, 1495, 1362, 1289, 1121, 926, 773 cm^{-1} ; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.06 (t, $J = 2$ Hz, 4H), 3.70 (m, 2H), 3.83 (t, $J = 2$ Hz, 4H), 4.36 (m, 2H), 4.45 (m, 1H), 5.07 (s, 2H), 7.07-7.27 (m, 8H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 51.47, 53.64, 66.83, 67.53, 67.99, 78.57, 120.62, 126.37, 127.66, 128.50, 129.52, 135.70, 137.15, 147.51.

(S)-3-(3-Fluoro-4-morpholinophenyl)-5-(nitromethyl) oxazolidin-2-one 46

To a stirred solution of β - hydroxy nitro compound **45** (1.29 g, 3 mmol) in dry methanol (25 mL) was added K_2CO_3 [0.828 g, 6 mmol] at 25 $^\circ\text{C}$ and the mixture was stirred for 10 h. The reaction mixture was filter to remove the K_2CO_3 and concentrated to give residue, the mixture of water (25 mL) and dichloromethane (25 mL) was added. The organic phase was separated and was extracted with CH_2Cl_2 (3×50 mL), washed with brine solution (20 mL), dried over anhyd. Na_2SO_4 and concentrated to give crude product, which was purified by column chromatography using ethyl acetate: Petroleum ether for elution to get the pure nitro-oxazolidinone compound **46** (0.898 g, 92 % yield) as a yellow oil.

Yield: 92 %; yellow oil; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.13 (t, 4H), 3.34-3.44 (m, 2H), 3.72 (t, 1H) 3.87 (t, $J = 4$ Hz, 4H), 4.11 (t, $J = 4$ Hz, 1H), 4.70 (m, 1H), 6.96 (m, 1H), 7.41 (m, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 50.28, 51.95, 67.30, 71.79, 80.42, 109.93, 117.02, 120.65, 129.74, 131.26, 148.63, 154.86.

(S)-N-{[3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-oxazolidinyl] methyl} acetamide:

Linezolid 5

To a stirred solution of nitro-oxazolidinone **46** (0.325 g, 1 mmol) in EtOAc (20 mL) was added 10 % Pd/C (0.10 g), and the system was alternately flushed and filled with

nitrogen, then hydrogen was introduced via a balloon system, and the mixture was stirred 4 h. The reaction mixture was then flushed with nitrogen and cooled to 0 °C and pyridine (0.128 g, 2 mmol) and acetic anhydride (0.255 g, 2.5 mmol) was added. The mixture was stirred for 10 min and then removed from the ice bath and stirred at room temperature for 3 h. The reaction mixture was filtered through a celite bed and concentrated under reduced pressure to give the crude product, which was purified by column chromatography with silica gel using MeOH: EtOAc as eluant to give linezolid **5** (0.30 g, 89 % yield) as a colorless solid.

Yield: 89 %; colorless solid; mp: 180-182 °C, {lit.¹⁶ 181.5-182.5 °C}; $[\alpha]_D^{25} = -8.6$ (c 0.919, CHCl₃), {lit.²⁰ $[\alpha]_D^{25}$: -9.0 (c 0.919, CHCl₃)}; **IR** (CHCl₃): 3323, 3013, 2967, 2859, 1745, 1664, 1564, 1518, 1485, 1450, 1413, 1377, 1305, 1227, 1120, 930, 825, 755, 666 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 1.98 (s, 3H), 3.06 (t, *J* = 5 Hz, 4H), 3.57 (m, 2H), 3.74 and 3.94 (m, 2H), 3.80 (t, *J* = 5 Hz, 4H), 4.68 (m, 1H), 6.71 (t, *J* = 4 Hz, 1H), 6.85 (dd, *J* = 4 Hz, 2 Hz, 1H), 7.33 (dd, *J* = 4, 2 Hz, 2H); **¹³C NMR** (200 MHz, CDCl₃): δ 22.74, 41.73, 47.80, 49.27, 66.59, 71.85, 115.98, 119.93, 130.23, 135.30, 148.11, 154.88, 171.42; **Analysis**: C₁₆H₂₀FN₃O₄ requires C, 56.97; H, 5.98; N, 12.46, F, 5.63%; found C, 56.86; H, 5.96; N, 12.50; F, 5.62%.

3-fluoro-4-piperazinyl nitrobenzene **48**

4-chloro-3-fluoronitrobenzene **47** (9.6 g, 50 mmol) in acetonitrile 25 mL was added slowly to a stirred solution of piperazine (17.5 g, 201 mmol) in acetonitrile (150 mL). After the complete addition the reaction mixture was heated to reflux for 8 h with vigorous stirring. The completion of reaction was monitored by TLC. After completion of the reaction, solvent was evaporated and a mixture of 50 mL water and 50 mL ethyl

acetate was added. The organic layer was separated and water layer was extracted with ethyl acetate (3 × 50 mL), the combined organic portions were dried over anhyd. Na₂SO₄ and concentrated to give crude product which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **48** (11.9 g, 95 % yield) as a brown solid.

Yield: 95 %, brown solid; mp: 67-69 °C, (lit.¹⁶ 68.5-71 °C); ¹H NMR (200 MHz, CDCl₃): δ 1.64 (brs, 1H), 3.01 (t, *J* = 5 Hz, 4H), 3.12 (t, *J* = 4 Hz, 4H), 6.98 (d, *J* = 5 Hz, 1H), 8.03-8.22 (m, 2H); ¹³C NMR (200 MHz, CDCl₃): δ 45.83, 51.80, 119.31, 123.38, 126.67, 127.67, 142.20, 155.07.

3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl] nitrobenzene 49

To a stirred solution of amine **48** (11.3 g, 50 mmol) in THF (100 mL) was added Na₂CO₃ (10.6 g, 100 mmol) in 60 mL water and stirred for 20 min. The mixture was cool to 0-10 °C and was added BOC anhydride (13 g, 60 mmol) in 25 mL THF slowly then the reaction was brought to room temperature and stirred for 2 h. The progress of reaction was monitored by TLC. After completion of the reaction, solvent was evaporated and ethyl acetate (100 mL) was added for phase separation. The organic layer was separated and water layer was extracted with ethyl acetate (3 × 50 mL), the combined organic portions were dried over anhyd. Na₂SO₄ and concentrated to give crude product which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **49** (15.5 g, 97 % yield) as a yellow solid.

Yield: 97 %, brown solid; mp: 121 °C; ¹H NMR (200 MHz, CDCl₃): δ 1.47 (s, 9H), 3.10 (t, *J* = 5 Hz, 4H), 3.58 (t, *J* = 5 Hz, 4H), 6.99 (d, *J* = 5 Hz, 1H), 8.05 (dd, *J* = 6, 2 Hz, 1H), 8.23 (d, *J* = 2 Hz, 1H); ¹³C NMR (200 MHz, CDCl₃): δ 28.46, 50.67, 80.14, 119.52,

123.40, 126.67, 127.99, 142.61, 153.69, 154.60.

3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl] aniline 50

Ammonium formate (7.32 g, 120 mmol) was added to a stirred solution of nitro compound **49** (13 g, 40 mmol) in THF (20 mL) and MeOH (80 mL). The flask was alternately flushed with nitrogen and then 10 % Pd/C (0.5 g) was added, and the system was again flushed with nitrogen and stirring was continue for 3 h, The progress reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered through a celite, washed with ethylacetate (25 mL). The filtrate was evaporated on rotavapour then the mixture of water (100 mL) and EtOAc (100 mL) were added and the phases separated, and the aqueous portion was extracted with EtOAc (3 × 50 mL). The combined organic portions were washed with brine, dried over anhyd. Na₂SO₄, and concentrated to give crude product which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **50**.(11.16 g, 94 % yield) as a light brown solid.

Yield: 94 %; light brown solid; mp: 87-90 °C; ¹H NMR (200 MHz, CDCl₃): δ 1.45 (s, 9H), 2.89 (t, *J* = 5 Hz, 4H), 3.15 (brs, 2H), 3.49 (t, *J* = 5 Hz, 4H), 6.53-6.75 (m, 3H); ¹³C NMR (200 MHz, CDCl₃): δ 28.47, 51.19, 79.62, 116.43, 119.19, 139.86, 144.51, 154.50.

N-{3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl] aniline}-2-hydroxy ethane 51

To a stirred solution of 3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl] aniline **50** (11.8 g, 4 mmol) in *n*-butanol (50 mL), anhydrous K₂CO₃ (11 g, 8 mmol) and Iodine (1.1 g) was added 2-chloroethanol (6.4 g, 8 mmol). The flask was alternately flushed with nitrogen and then refluxed at 115-120 °C under nitrogen and stirring was continue for 12 h, the reaction was monitored by TLC. After completion of the reaction, the reaction mixture

was concentrated under reduced pressure then the mixture of water (50 mL) and EtOAc (50 mL) were added and the phases separated, and the aqueous portion was extracted with EtOAc (3×50 mL). The combined organic portions were washed with brine, dried over anhyd. Na_2SO_4 , and concentrated to give crude product which was purified by column chromatography using ethyl acetate-Petroleum ether for elution to get the pure product **51** (12.6 g, 93 % yield) as a brown syrup.

Yield: 93 %; dark brown oil; ^1H NMR (200 MHz, CDCl_3): δ 1.44 (s, 9H), 2.76 (t, $J = 5$ Hz, 4H), 3.13 (t, $J = 5$ Hz, 2H), 3.18 (brs, 1H), 3.47 (t, $J = 4$ Hz, 4H), 3.71 (t, $J = 5$ Hz, 2H), 4.45 (s, 1H), 6.4 (dd, $J = 6, 2$ Hz, 1H), 6.61 (d, $J = 2$ Hz, 1H), 6.76 (dd, $J = 4, 2$ Hz, 1H); ^{13}C NMR (200 MHz, CDCl_3): δ 28.57, 46.63, 51.83, 60.60, 64.31, 79.52, 112.47, 115.23, 121.47, 130.32, 140.07, 144.89, 154.58.

Benzyl-[3-fluoro-4[4-(*t*-butoxycarbonyl)-piperazinyl]-2-hydroxyethanyl] carbamate **52**

To a stirred solution of alcohol **51** (10.17 g, 30 mmol) in dichloromethane (100 mL) and K_2CO_3 (8.28 g, 60 mmol) was cool to 0°C and benzyl chloroformate 50 % solution in toluene (15.13 g, 45 mmol) was added slowly under nitrogen atmosphere. Stirring was continued for 3 h, progress of the reaction was monitored by TLC. After completion of the reaction, the mixture of water (50 mL) and dichloromethane (50 mL) were added and the phases separated, and the aqueous portion was extracted with dichloromethane (3×25 mL). The combined organic portions were washed with brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated to give crude product which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **52** (13.5 g, 95 % yield) as a thick oil.

Yield: 86 %; thick oil; ; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 1.41 (s, 9H), 2.32 (brs, 1H), 2.89 (t, $J = 4$ Hz, 4H), 3.48(t, $J = 5$ Hz, 4H), 3.63-3.77 (m, 4H), 5.04 (s, 2H), 6.84-7.05 (m, 3H), 7.18-7.23 (m, 5H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 28.44, 51.11, 53.10, 60.64, 67.40, 79.47, 120.18, 126.39, 127.67, 127.94, 128.36, 128.75, 129.56, 136.15, 137.54, 147.63, 154.27, 155.91.

Benzyl {3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl]-2-ethanal} carbamate **53**

Swern oxidation method:

To a stirred solution of oxalyl chloride, $(\text{COCl})_2$ (10 g, 80 mmol) in dichloromethane (75 mL) at -78°C , was added a solution of DMSO (6.24 g, 80 mmol). The reaction mixture was stirred for 30 min. Alcohol **52** (9.46 g, 20 mmol) in dichloromethane (25 mL) was added slowly. After stirring for 45 h min. at -78°C , the reaction was quenched by the addition of Et_3N (16.1 g, 32 mmol) and water (50 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated to give the crude aldehyde **53** which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product (8.8 g, 93 % yield) as a yellow oil.

Yield: 87 %; yellow oil; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 1.46 (s, 9H), 2.94 (t, $J = 5$ Hz, 4H), 3.54 (t, $J = 5$ Hz, 4H), 4.33 (s, 2H), 5.12 (s, 2H), 6.90-7.10 (m, 3H), 7.11-7.28 (m, 5H), 9.62 (s, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 28.44, 51.09, 60.23, 67.86, 79.60, 120.37, 125.93, 127.80, 128.12, 128.45, 128.82, 129.06, 135.86, 147.90, 154.42, 196.11.

(S)-Benzyl {3-fluoro-4-[4-(t-butoxycarbonyl)-piperazinyl]-2-hydroxy-3-nitropropyl} carbamate **54**

CuFAP (100 mg) and the C_2 -symmetric chiral piperazine ligand (L^*) (3 mol %) in 10 mL nitromethane was taken into the 50 mL round bottomed flask and stirred at room temperature for 30 minutes. Reaction mixture was cooled to 0-10 °C and aldehyde **53** (1.88 g, 4 mmol) dissolved in 2 mL nitromethane was added, reaction was continued till the completion of the reaction at 10 °C for 24 hrs. After completion of the reaction, a mixture of DCM and water (1:1, 100 mL) was added. Separate the organic layer and aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layer was washed with water (2 x 50 mL), brine, dried over anhydrous Na_2SO_4 , filtered and concentrated on rotary evaporator under reduced pressure. Resulting residue was purified by column chromatography (silica gel) using EtOAc-petroleum ether (20:80) as an eluent, affording the β -nitroalcohols in 85 % yield **54** yellow oil.

Yield: 1.80 g, 85 %; pale yellow oil; $[\alpha]_D^{25} = -10.4$ (c 0.78, $CHCl_3$); 1H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.99 (s, 1H), 2.95 (t, $J = 4$ Hz, 4H), 3.54 (t, $J = 3$ Hz, 4H), 3.72-3.76 (m, 2H), 4.36 (m, 2H), 4.47 (m, 1H), 5.09 (s, 2H), 6.98-7.06 (m, 3H), 7.19-7.32 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 28.43, 29.65, 51.03, 53.73, 60.04, 67.36, 67.78, 79.65, 120.39, 126.34, 127.70, 128.11, 128.43, 128.77, 129.42, 135.80, 137.26, 147.89, 154.39.

(S)-3-fluoro-4-[4-(t-butoxycarbonyl)-piperazinyl]-5-(nitromethyl)-oxazolidin-2-one **55**

To a stirred solution of beta hydroxy nitro compound **54** (1.59 g, 3 mmol) in dry methanol (25 mL) was added K_2CO_3 [0.828 g, 6 mmol] at 25 °C and the mixture was

stirred for 12 h. The reaction mixture was filter to remove the K_2CO_3 and concentrated to give residue, the mixture of water (25 mL) water and dichloromethane (25 mL) was added. The organic phase was separated and was extracted with CH_2Cl_2 (3×50 mL), washed with brine solution (20 mL), dried over anhyd. Na_2SO_4 and concentrated to give crude product, which was purified by column chromatography using ethyl acetate – Petroleum ether for elution to get the pure product **55** (1.12 g, 88 % yield) as a yellow oil.

Yield: 88 %; yellow oil; 1H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 3.0 (t, $J = 4$ Hz, 4H), 3.38-3.44 (m, 2H), 3.61 (t, $J = 5$ Hz, 4H), 4.08-4.17 (m, 2H), 4.71 (m, 1H), 7.37 (d, $J = 2$ Hz, 1H), 7.41 (dd, $J = 4, 2$ Hz, 1H), 7.61 (d, $J = 2$ Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 28.31, 43.82, 50.95, 51.20, 71.09, 72.99, 79.77, 117.61, 120.67, 129.25, 133.76, 145.19, 153.78, 154.65.

(S)-N-{[3-(3-fluoro-(4-*t*-butoxycarbonyl)-piperazinyl) phenyl-2-oxo-5-oxazolidinyl] methyl} acetamide **56**

To a stirred solution of nitro-oxazolidinone **55** (1 g, 2.35 mmol) in EtOAc (20 mL) was added 10 % Pd/C (0.10 g), and the system was alternately flushed and filled with nitrogen, then hydrogen was introduced via a balloon system, and the mixture was stirred 6 h. The reaction mixture was then flushed with nitrogen and cooled to 0 °C and pyridine (0.372 g, 4.71 mmol) and acetic anhydride (0.480 g, 4.715 mmol) was added. The mixture was stirred for 10 min and then removed from the ice bath and stirred at room temperature for 2 h. The reaction mixture was filtered through a celite bed and concentrated under reduced pressure to give the crude product, which was purified by

column chromatography with silica gel using MeOH: EtOAc as eluant to give crude N-Boc protected Eperezolid **56** (0.95 g, 92 % yield) as a gum.

Yield: 92 %, gum; **IR** (CHCl₃): 3445, 3336, 3018, 2980, 2929, 2851, 2400, 1751, 1676, 1501, 1424, 1367, 1317, 1216, 1168, 1130, 1033, 928, 850, 756, 668 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 1.46 (s, 9H), 2.0 (s, 3H), 2.90 (t, J = 4 Hz, 4H), 3.54-3.64 (t, J = 10 Hz, 4H), 3.70-3.78 (m, 2H), 3.95 (m, 2H), 4.71-4.81 (m, 1H), 6.55 (t, J = 6 Hz, 1H), 6.95 (d, J = 5 Hz, 1H), 7.29 (dd, J = 6, 2 Hz, 1H), 7.56 (d, J = 2 Hz, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 22.94, 28.35, 29.61, 41.82, 47.58, 51.21, 51.48, 72.02, 117.56, 120.75, 129.36, 133.71, 145.54, 154.52, 154.77, 171.51.

(S)-N-{{3-[3-fluoro-4-[4- N-1-(4-hydroxyacetyl)-piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl)methyl}acetamide, Eperezolid 6

N-Boc protected Eperezolid **56** (0.5 g, 1.146 mmol) was dissolved in dichloromethane (2 mL) and cool to 0 °C was added TFA (2 mL) and the system was alternately flushed and filled with nitrogen then removed from the ice bath and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was evaporated on rotavapour. The mixture 10 % NaHCO₃ (15 mL) in water and dichloromethane (25 mL) was added. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (30 mL), dried over anhyd. Na₂SO₄ and concentrated to give the crude amine. The amine was dissolved in dichloromethane and cooled to 0 °C and was added TEA (0.232 g, 2.3 mmol) followed by addition of 2-hydroxy acetyl chloride (0.216 g, 2.3 mmol) in 5 mL dichloromethane. The mixture was stirred for 10 min and then removed from the ice bath and stirred at room temperature for 3 h. The progress of the

reaction was monitored by TLC, after completion of the reaction, mixture of water (20 mL) water and dichloromethane (20 mL) was added. The organic phase was separated and was extracted with dichloromethane (3×20 mL), washed with brine solution (20 mL), dried over anhyd. Na_2SO_4 and concentrated to give crude product, which was purified by column chromatography using ethyl acetate – methanol for elution to get the pure Eperezolid **6** (0.38 g, 86 % yield over two steps) as a white solid.

Yield: 86 %, white solid; mp: 174-175 °C, $[\alpha]_{\text{D}}^{25}$: -18.9 (c 0.853, DMSO), {lit.¹⁶ $[\alpha]_{\text{D}}^{25}$: -21 (c 0.853, DMSO)}; **IR** (CHCl_3): 3455, 3290, 2854, 2810, 1732, 1652, 1527, 1243, 1150, 1019, 852, 667 cm^{-1} ; **^1H NMR** (200 MHz, $\text{CDCl}_3 + \text{DMSO } d_6$): δ 2.22 (s, 3H), 3.12-3.17 (t, $J = 5$ Hz, 4H), 3.77-3.82 (t, $J = 5$ Hz, 4H), 3.84-3.87 and 3.96-4.0 (m, 2H), 4.18-4.27 (m, 2H), 4.40 (s, 2H), 4.93-5.03 (m, 1H), 6.77-6.83 (t, $J = 6$ Hz, 1H), 7.18(d, $J = 7$ Hz, 1H), 7.47(dd, $J = 9, 2$ Hz, 1H), 7.56(d, $J = 2$ Hz, 1H); **^{13}C NMR** (200 MHz, $\text{CDCl}_3 + \text{DMSO } d_6$): δ 22.43, 38.87, 39.30, 39.73, 40.15, 41.58, 47.54, 49.51, 66.22, 71.58, 105.80, 109.82, 116.16, 119.44, 147.23, 153.04, 154.27, 169.42, 170.97; **Analysis**: $\text{C}_{18}\text{H}_{23}\text{FN}_4\text{O}_5$ requires C, 54.82; H, 5.88; N, 14.21, F, 4.82 %; found C, 54.63; H, 5.90; N, 14.13; F, 4.98 %.

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Chapter II

Enantioselective synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol via nitroaldol reaction over copper fluorapatite catalyst in presence of chiral trianglamine ligand

Enantioselective synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol via nitroaldol reaction over copper fluorapatite catalyst in presence of chiral trianglamine ligand

2.1 Introduction

The β-adrenergic blocking agents are known as β-blockers, which belong to a larger class of medicines and also called as adrenergic inhibitors. The propranolol **1**, the first clinically useful β-blocker, which was invented by Scottish pharmacologist Sir James W. Black in early 1950s in Eli Lilly Laboratories.¹ This invention revolutionized the medical management of angina pectoris and is considered to be one of the most important contributions to clinical medicine and pharmacology of 20th century.² For this invention, in 1988 Sir James W. Black was awarded Nobel Prize in Medicine. The some of representative β-blockers are shown in (**Fig. 1**).

The main three actions of β-adrenergic blocking agents and/or drugs are; lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the improvement of the heart muscle tone (cardiotonics).³ Also the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.⁴

The β-blockers are play key role to block only catecholamines hormones in brain, heart, and blood vessels that results the heart beats more slowly with less force. In addition, blood vessels relax and widen so that blood flows through them more easily. Both of these actions are most important to reduce the blood pressure during heart-attack.

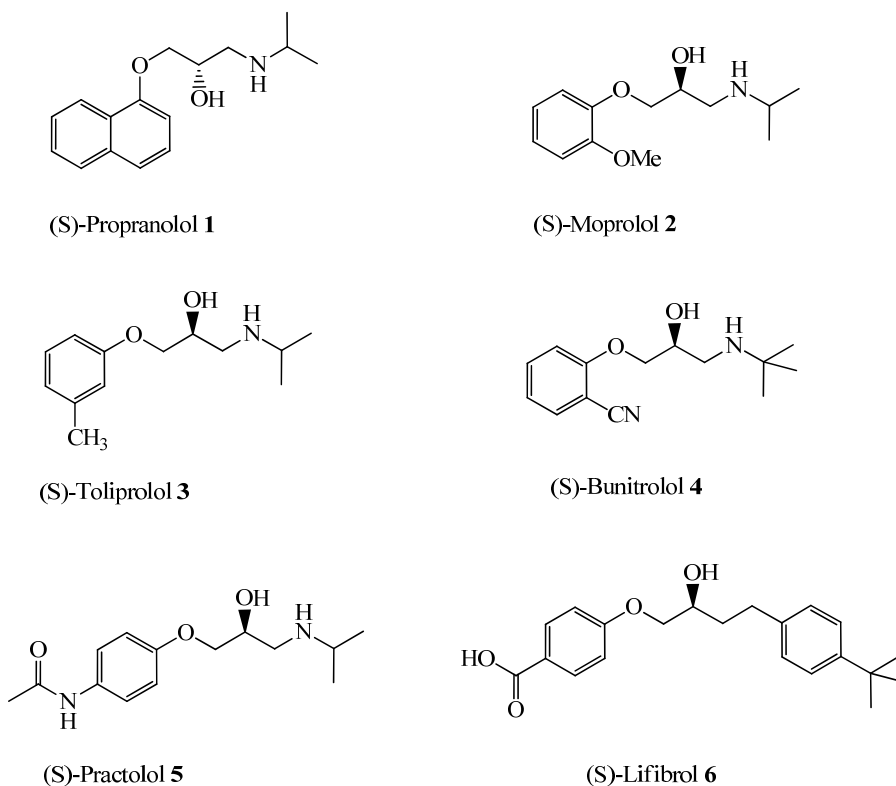


Fig. 1: Structures of the β -adrenergic blocking agents

There are three types of β -adrenergic receptor namely β_1 , β_2 and β_3 , which control several functions based on their location in the body.⁵

- 1) β_1 -adrenergic receptors are located only in the heart and in the kidneys.⁶
- 2) β_2 -adrenergic receptors are located only in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle.
- 3) β_3 -adrenergic receptors are located in fat cells.⁷

The stimulation of β_1 receptors by epinephrine induces a positive chronotropic and inotropic effect on the heart that increases cardiac conduction velocity and automaticity.⁸

The stimulation of β_1 receptors on the kidney causes renin release.⁹ The stimulation of β_2 receptors induces smooth muscle relaxation¹⁰ as well as tremor in skeletal muscle¹¹ and

increases glycogenolysis in the liver, skeletal muscle.¹² The stimulation of β_3 receptors induces lipolysis.¹³

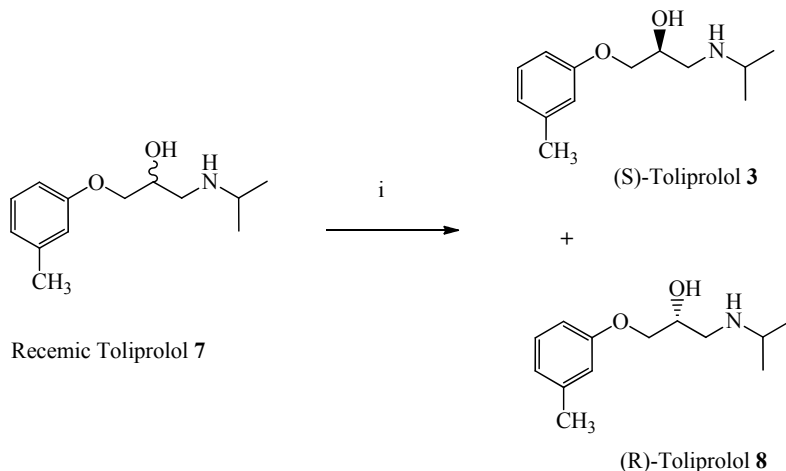
The blocking of β -receptor system reduces the overall activity of the sympathetic nervous system and hence, β -blockers are used to increase life expectancy after the heart attack. It is well established that the desirable therapeutic activities reside mainly in the (*S*)-enantiomers and not (*R*)-enantiomer¹⁴, which display undesirable side effects and/or inactive. Presently, many of the pharmaceuticals are marketing these antihypertensive drugs in the racemic forms, even though (*S*)-isomers are known to be 100-500 fold more effective than the (*R*)-isomer.¹⁵ To avoid undesirable side effects and/or toxicity to an organism caused by the (*R*)-isomers, the cost effective synthesis of optically pure (*S*)-isomer is challenge to researchers. However, considerable efforts have been made in recent years for the preparation in enantiomerically pure (*S*)-form via classical resolution and asymmetric syntheses or biotransformation. This chapter describes the enantioselective synthesis of three β -adrenergic blocking agents, (*S*)-Moprolol **2**, (*S*)-Toliprolol **3** and (*S*)-Bunitrolol **4** using heterogeneous, reusable catalyst with chiral ligand, which possesses antihypertensive, antianginal and sympatholytic properties.

2.2 Review of Literature

Literature search revealed that there are few reports available for the synthesis of β -blocker namely, (*S*)-Moprolol **2**, (*S*)-Toliprolol **3** and (*S*)-Bunitrolol **4**. However, most of the synthetic methods reported in the literature¹⁷⁻²² for the asymmetric synthesis of these β -blockers involve either a chiral pool approach or classical resolution of racemates, which are described below.

2.2.1 Howe's approach¹⁶

In this approach, Howe *et al.* synthesized (S)-Toliprolol **3** by resolution of their racemates. 1-isopropylamino-3-(3-tolyloxy)-2-propanol **7** were resolved using (-)-O, O-di-*p*-toluoyltartaric acid followed by the fractional crystallization in methanol water system to obtain the pure (S) isomer **3** (Scheme 1).

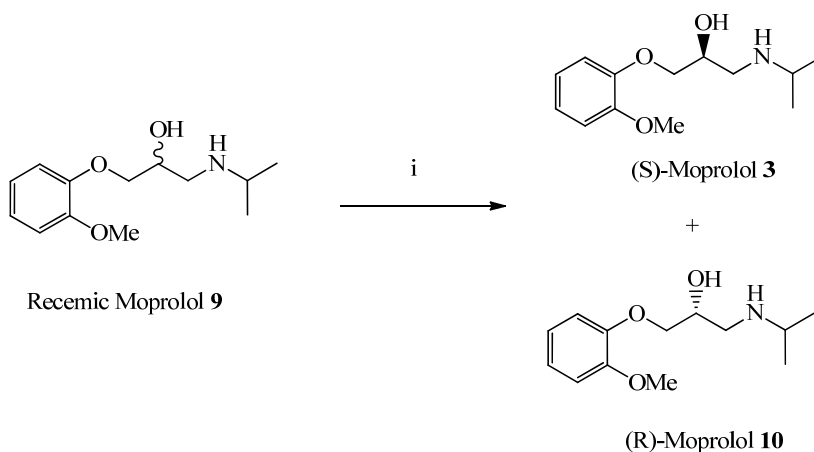


Scheme 1: Reagents and reaction conditions: (i) (-)-O, O-di-*p*-toluoyltartaric acid, MeOH, H₂O, fractional crystallization.

2.2.2 Ferrari's approach¹⁷

In this approach, Ferrari *et al.* developed a process for the separation of racemic Moprolol **9** into its two optical pure isomers. The racemic moprolol **9** was treated with equimolar quantity of L-(+)-glutamic acid in an alcohol: water mixtures, after solvent evaporation the mixture of the two optically active salts were obtained. This mixture of salt was then treated with isopropanol/ methanol/ water in the ratio 80/15/5 to yield a crystalline solid which is optically pure L-(+)-glutamic (+)-Moprolol salt. While other isomer was isolated from the filtrate by evaporation of mother liquor to dryness to get crude product which was further purified by crystallization with isopropanol/ methanol in a 95/5 ratio to

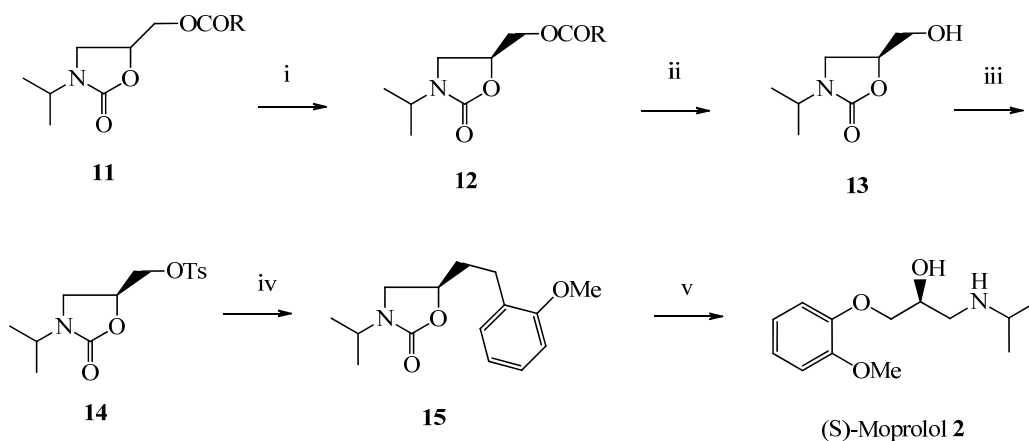
get optically pure L-(+)-glutamic (-)-Moprolol salt. The treatment of this salt with aqueous NaOH provided pure (S)-Moprolol **3** in a crystalline form (**Scheme 2**).



Scheme 2: Reagents and reaction conditions: (i) L-(+)-Glutamic acid, MeOH, Isopropanol, water.

2.2.3 Kazunori's approach¹⁸

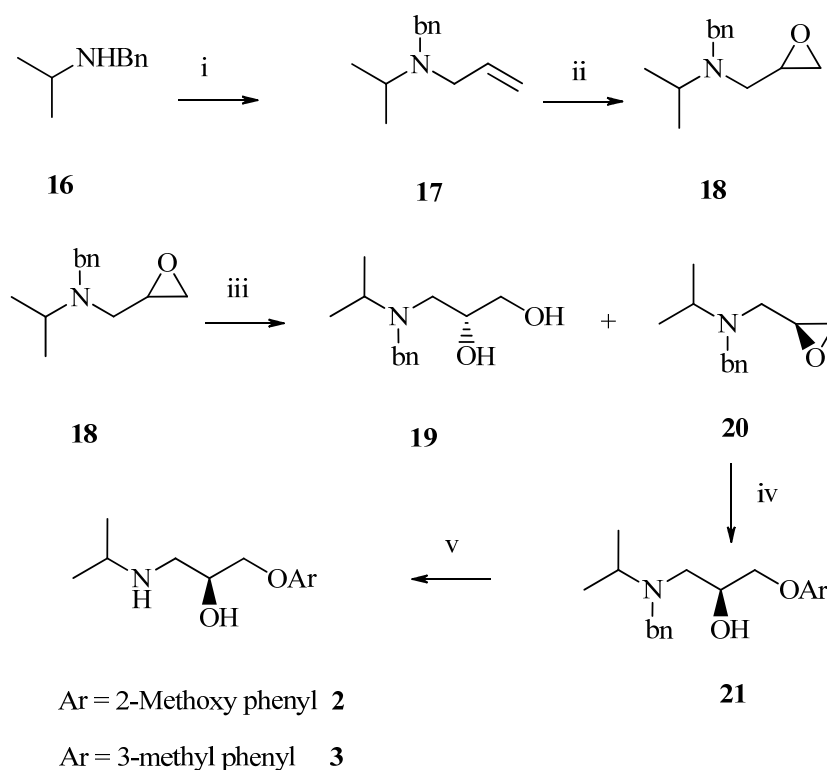
In this approach, Kazunori *et al.* have reported the synthesis of (S)-Moprolol **3** via asymmetric hydrolysis of racemic oxazolidinone **11** lipoprotein lipase Amano 3 (L.P.L. Amano 3, origin: *Pseudomonas aeruginosa*) enzyme obtained (S)-**12** in 99 % ee as key intermediate. This intermediate compound was then converted to (S)-Moprolol **2** by organic transformations as shown in **Scheme 3**.



Scheme 3: Reagents and reaction conditions: (i) lipase Amano 3 (ii) chemical hydrolysis (iii) TsCl, Et₃N, CH₂Cl₂ (iv) ArOH (Ar = 2-OMe-C₆H₄), NaH (v) NaOH, EtOH, H₂O.

2.2.4 Hou's approach¹⁹

Hou and co-workers synthesized various β -blockers including (*S*)-Moprolol **2** and (*S*)-Toliprolol **3**. In this approach they synthesized racemic epoxide **18** from substituted allyl amine **17** with Li_2PdCl_4 , cupric chloride followed by sodium sulfide. The epoxide **18** then Jacobsen hydrolytic kinetic resolution catalyzed by (*S,S*)-salen Co(III)OAc afforded chiral diol **19** and chiral epoxide **20**. The epoxide **20** on opening with various phenols followed by hydrogenation afforded β -blockers **2** and **3** (Scheme 4).

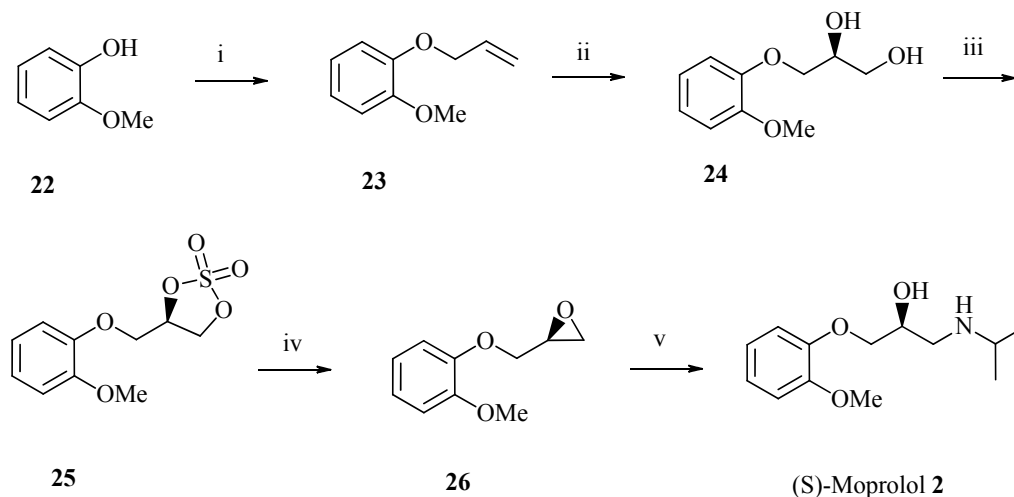


Scheme 4: *Reagents and reaction conditions:* (i) Allyl bromide, NaOH, DMF (ii) Li_2PdCl_4 , CuCl_2 , DMF, -10°C , then $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (iii) (*S,S*)-salen Co(III)OAc, H_2O (iv) ArOH, Et_3N , reflux; (v) 10 % Pd/C, H_2 , EtOH.

2.2.6 Sudalai's approach²⁰

In this approach, Sudalai and co-workers synthesized various β -blockers including (*S*)-Moprolol **2**. The synthesis was started with Sharpless asymmetric dihydroxylation of allyl

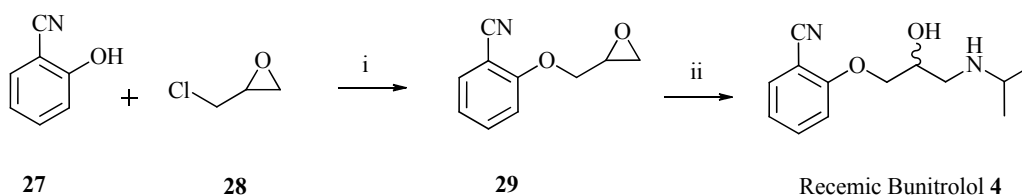
ethers **23** catalysed by (DHQD)₂-PHAL. The resultant diols **24** then converted to epoxides **26** *via* cyclic sulfate. The epoxides on treatment with amines afforded β-blockers (Scheme 5).



Scheme 5 *Reagents and reaction conditions:* (i) Allyl bromide, K₂CO₃, acetone, reflux, 12 h; (ii) cat. OsO₄, (DHQD)₂-PHAL, K₃Fe(CN)₆, K₂CO₃, *t*-BuOH/H₂O, 0 °C, 12 h; (iii) (a) SOCl₂, Et₃N, CH₂Cl₂, 0 °C, 40 min.; (b) cat. RuCl₃·3H₂O, NaIO₄, CH₃CN:H₂O, 0 °C, 30 min.; (iv)(a) LiBr, THF, 25 °C, 2-3 h (b) 20 % H₂SO₄, Et₂O, 25 °C, 10 h; (c) K₂CO₃, MeOH, 0 °C, 2 h; (v) R-NH₂, H₂O (cat.), reflux, 2 h.

2.2.5 Zhenya's approach²¹

Zhenya *et al.* have reported the synthesis of racemic Bunitrolol **4** by etherification of salicylnitrile with racemic epichlorohydrin **28** to give epoxide **29**. Thus, epoxide **29** on treatment with *ter*-butylamine afforded racemic Bunitrolol **4** in 35.7 % overall yield (Scheme 6).



Scheme 6: *Reagents and reaction conditions:* (i) NaOH, water (ii) *ter*-BuNH₂

2.3 Present Work

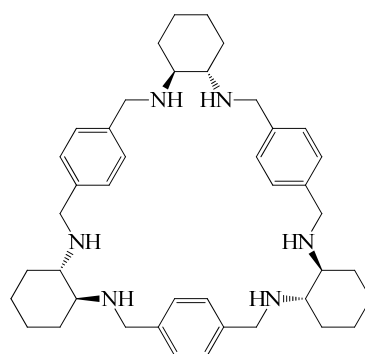
2.3.1 Objectives

The racemic as well as enantioselective synthesis for the β -blockers have been reported in literature. However, the reported methods described above for the synthesis of (S)-Moprolol **2**, (S)-Toliprolol **3** and (S)-Bunitrolol **4**, were based on classical resolution via diastereomers, chromatographic separation of enantiomers, enzymatic resolution, kinetic resolution and asymmetric synthesis *via* chiral pool strategy. The main drawback of the hydrolytic kinetic resolution is use of expensive reagents and/or wastage of half the material. Moreover, all these reported synthetic methods suffer from disadvantages such as low overall yields, use of expensive enzymes and resolving agents, low optical purity, the need for separation of diastereomers and the use of expensive chiral catalysts.

The nitroaldol reaction is one of the versatile C-C bond forming reaction in organic synthesis for the formation of β -hydroxynitroalkanes.²² Optically active β -hydroxynitroalkanes are useful intermediates for the synthesis of various pharmacologically important compounds.²³ Recently, much attention has been paid for the development of catalytic asymmetric nitroaldol reaction.²⁴⁻²⁶ However, these catalysts still have some limitations and drawbacks such as moisture or air sensitivity, need for strong bases and low temperature, low enantioselectivity and difficulties in the preparation of catalyst.

Due to the potential biological activity of the (S)-isomer of β -adrenergic blockers, researchers have their goals and/or aim to develop synthetic route, which will provide enantiomerically pure (S)-isomers only which shows higher affinity to β -receptors. Hence the asymmetric synthesis of β -blockers starting from prochiral substrates using catalytic

enantioselective reactions is still very much attractive. Therefore, we decided to develop a new strategy, which will be cost effective for the asymmetric synthesis of β -adrenergic blockers with good optical purity and yield using asymmetric nitroaldol reaction over heterogeneous, reusable copper fluorapatite catalyst in presence of chiral trianglamine ligand (L^*)²⁷ (**Fig. 2**), from readily available starting materials.



(S,S,S,S,S,S)-(+)-L*

L* = Chiral trianglamine ligand

Fig. 2: Chiral trianglamine ligand for nitroaldol reaction.

2.4 Results and discussion

The retro-synthetic analyses for the synthesis of these homochiral β -adrenergic blocking agents are presented in **Fig. 3**. All the compounds exhibit structural similarities. The compounds (S)-Moprolol **2**, (S)-Toliprolol **3** and (S)-Bunitrolol **4** could be prepared from the corresponding β -nitro alcohol compounds **32**, **36** and **39** respectively. The β -nitro alcohol compounds **32**, **36** and **39** could be achieved from the aldehydes **31**, **35** and **38** by asymmetric nitroaldol reaction by using copper fluorapatite catalyst in presence of chiral trianglamine ligand (L^*) while these aldehydes **31**, **35** and **38** could be readily obtained from **25**, **33** and **22** respectively by simple functional group transformations.

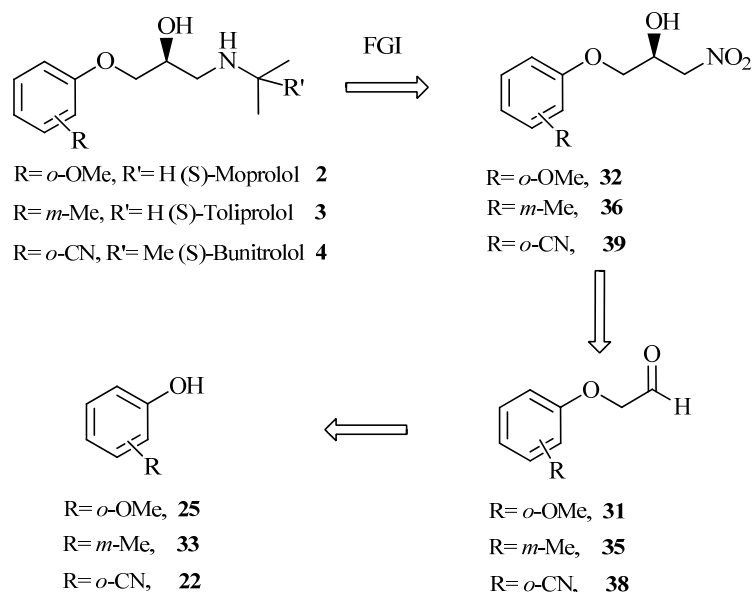
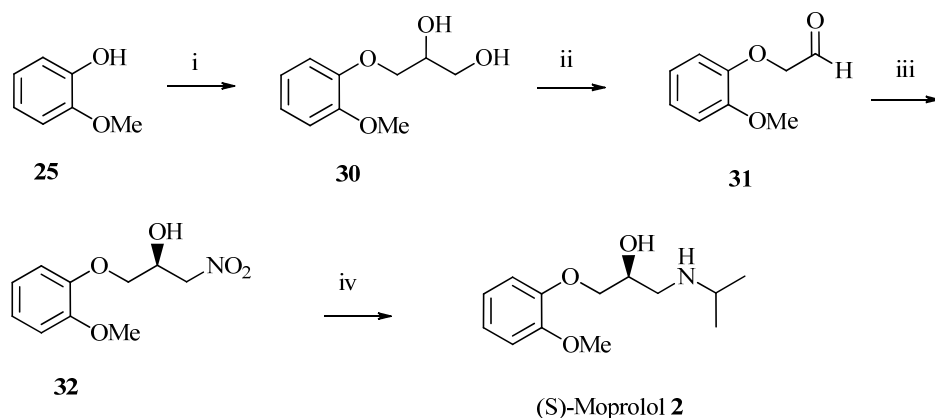


Fig. 3: Retrosynthetic analysis of Moprolol **2**, Toliprolol **3** and Bunitrolol **4**

Thus, our synthesis of (S)-Moprolol **2**, (S)-Toliprolol **3** and (S)-Bunitrolol **4** started from commercially available starting material namely, guaiacol **25**, *m*-cresole **33** and *o*-cynophenole **22**.

2.4.1 Enantioselective synthesis of (S)-Moprolol

The synthetic scheme employed for (S)-Moprolol **2** is presented in the **Scheme 7**.



Scheme 7: *Reagents and reaction conditions:* (i) NaOH, H₂O, 3-chloro,1-2-propanediol, reflux, 8 h (ii) NaIO₄, H₂O, 0-5 °C (iii) CuFAP, nitromethane, chiral triethylamine ligand (L*) (iv) (a) H₂, 10 % Pd/C methanol (b) isopropyl bromide.

As per retrosynthetic analysis (**Fig. 3**), we initiated a synthesis from commercially available guaiacol **25**. The guaiacol was reflux with aqueous NaOH solution and 3-chloro, 1-2-propan-di-ol for 8 h furnished diol **30**²⁸ in 96 % yield. The ¹H-NMR spectrum showed multiplets in the region of δ 3.76-3.80 and 4.02-4.09 for five protons and broad singlet at δ 3.37 confirmed the formation of the diols.

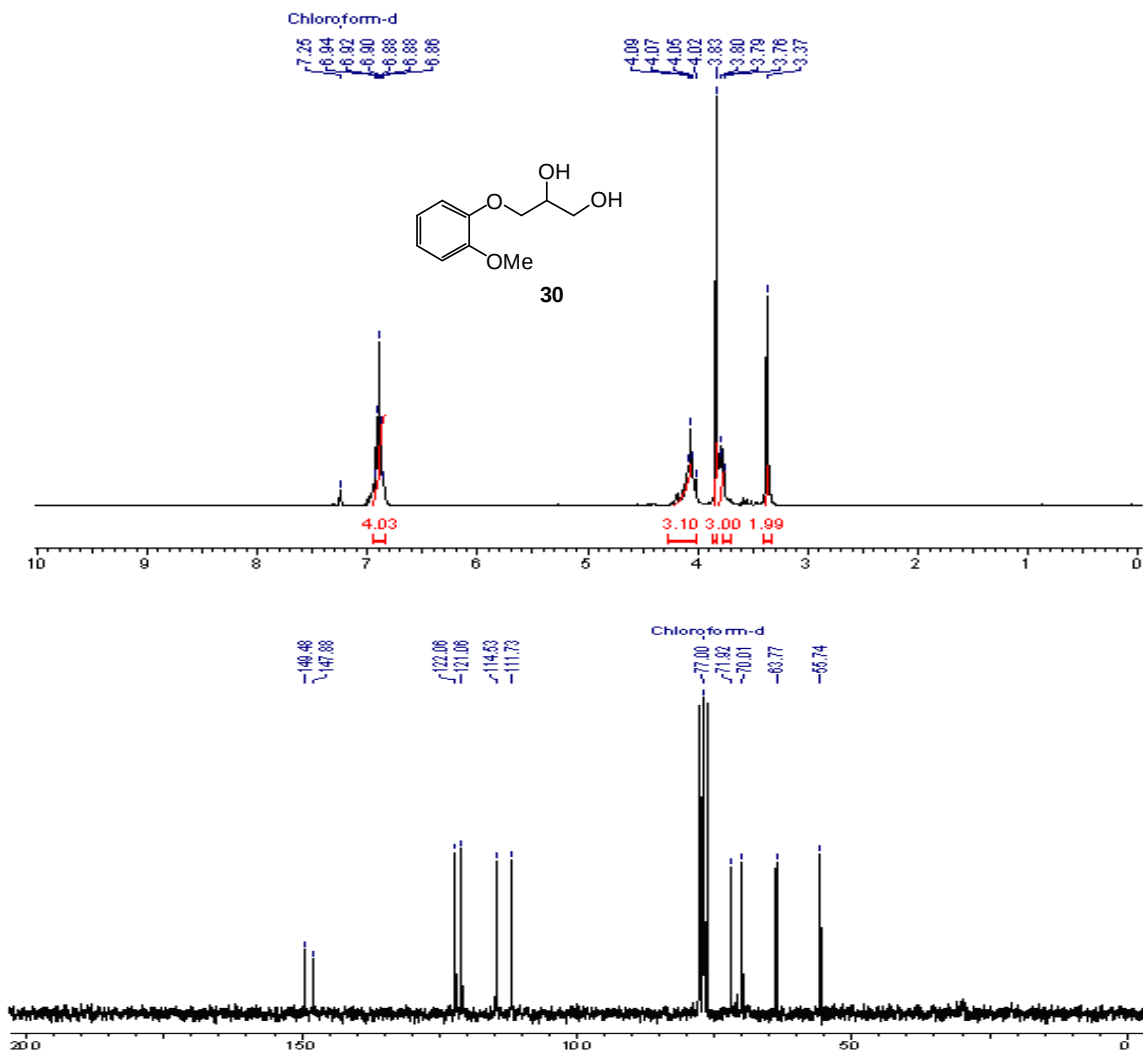


Fig. 4: ¹H and ¹³C NMR spectrum of 3-(2-Methoxyphenoxy) propane-1, 2-diol **30**

The ¹³C-NMR showed signals at δ 55.74 for aromatic -OCH₃ group and at δ 63.77, 70.01 and 71.92 for the three aliphatic carbons bearing oxo-functionality (**Fig. 4**). The IR

spectrum of these diols showed a broad band in the region of 3300-3600 cm^{-1} indicating the presence of hydroxyl functionality in the molecules **30**.

The oxidative cleavage²⁸ of diol **30** was carried out with NaIO_4 in water at 0-5 °C affording aldehydes **31** in 90 % yields. The ^1H -NMR spectrum of aldehyde showed disappearance of aliphatic multiplets and appearance of singlet for $-\text{OCH}_2-$ at δ 4.59 and another sharp singlet for the aldehyde proton at δ 9.98, confirmed the formation of the aldehyde **31**.

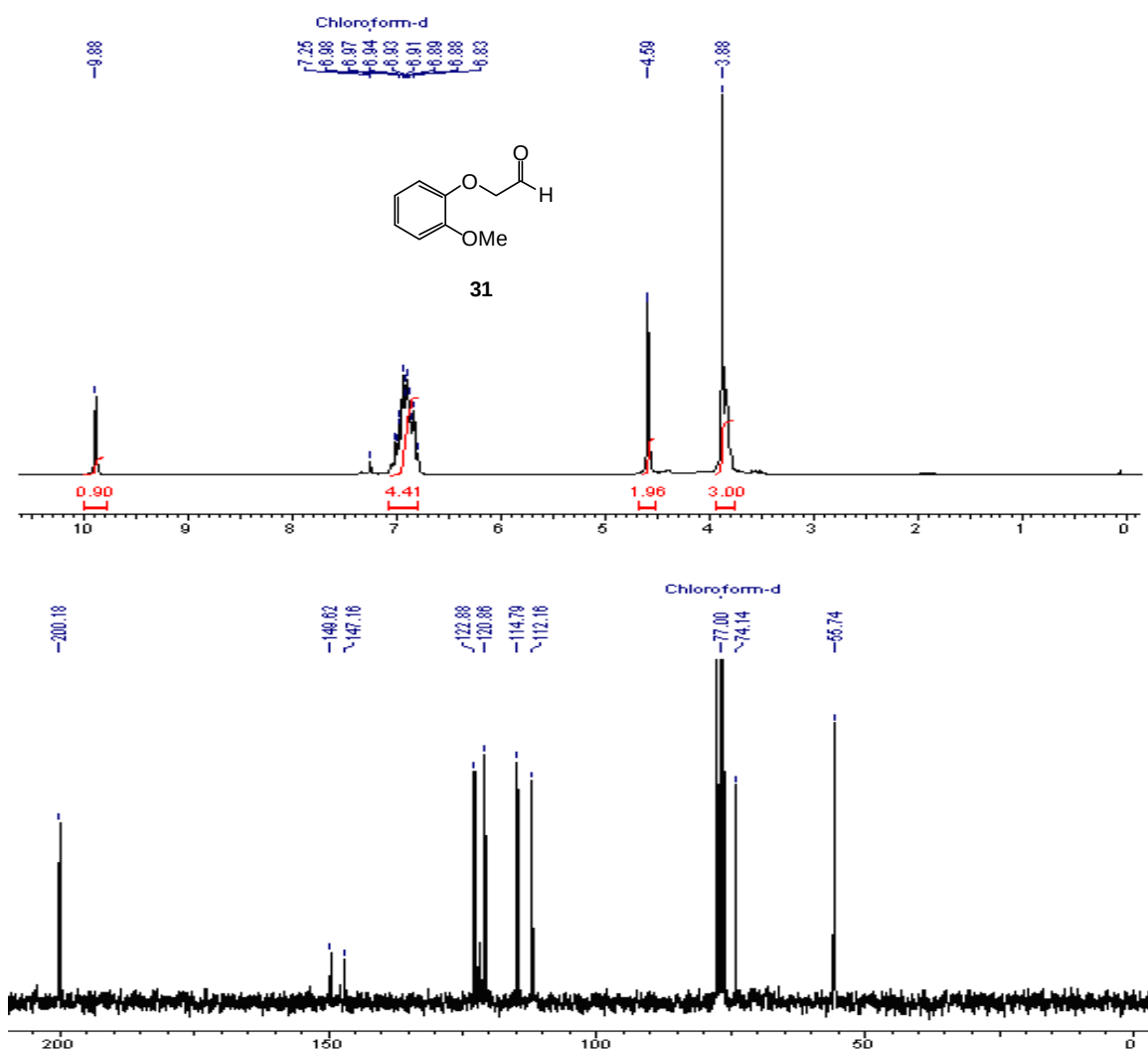


Fig. 5: ^1H and ^{13}C NMR spectrum of 2-(2-Methoxy phenoxy) ethanal **31**

The ^{13}C -NMR showed only two aliphatic signals at δ 55.74 for aromatic $-\text{OCH}_3$ group and at δ 74.14 for $-\text{OCH}_2-$ aliphatic carbons adjacent to aldehyde functionality (**Fig. 5**). The IR spectrum of aldehyde showed disappearance of a broad band in the region of $3300\text{--}3600\text{ cm}^{-1}$ indicating the absence of hydroxyl functionality in the molecules and appearance of new signal at 1737 cm^{-1} for carbonyl group of aldehyde **31**. Aldehydes **31** was then subjected to asymmetric nitroaldol reaction catalysed by copper fluorapatite in presence of chiral triethylamine ligand at $0\text{--}10^\circ\text{C}$ for 24 h to obtained the β -hydroxy nitro compound **32** in 92 % yield.

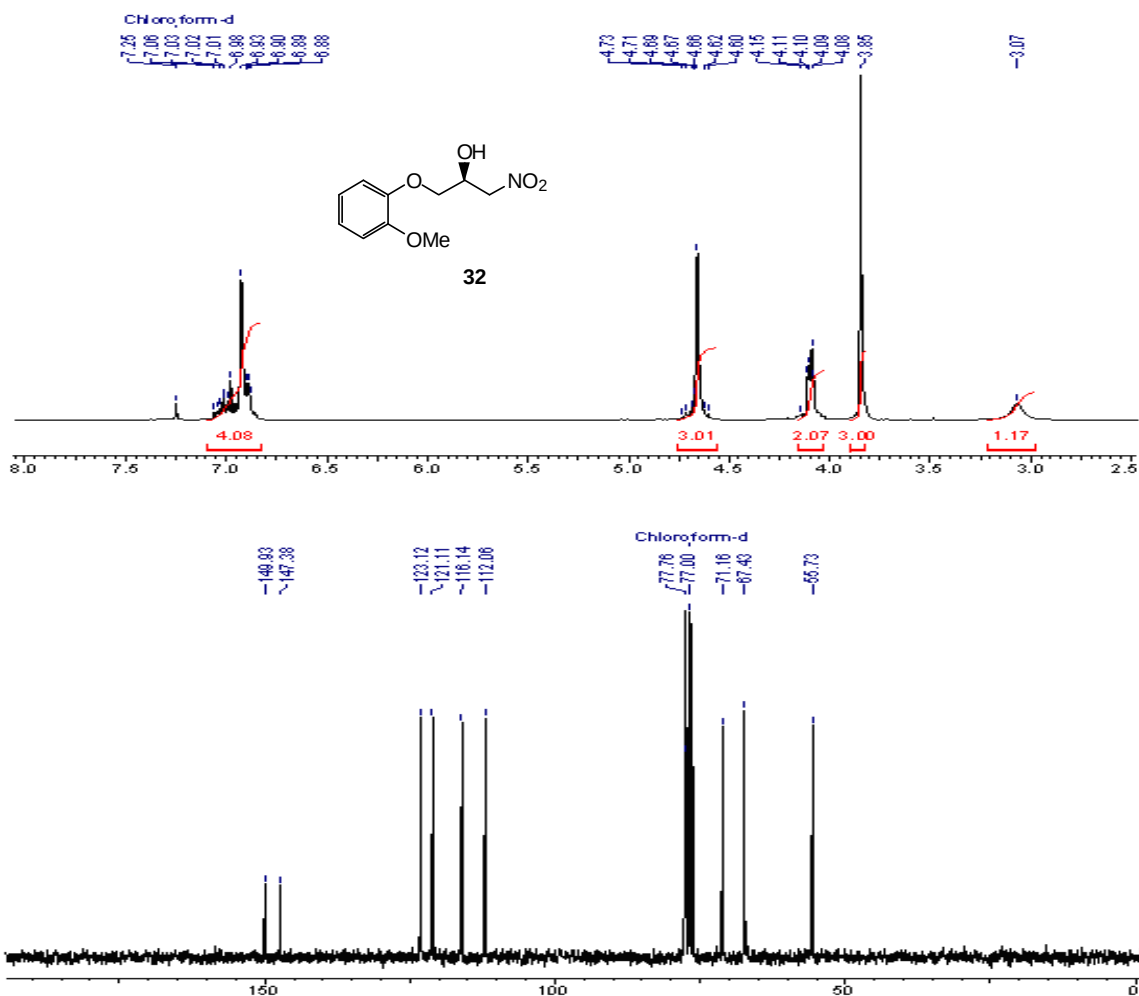


Fig. 6: ^1H and ^{13}C NMR spectrum of (S)-1-(2-methoxyphenoxy)-3-nitropropane-2-ol **32**

The ^1H -NMR spectrum of β -hydroxy nitro compound **32** showed disappearance of aldehyde proton and the appearance of new aliphatic multiplet at δ 4.08-4.15 for $-\text{O}-\underline{\text{CH}_2}-$ and other multiplet at δ 4.60-4.73 for $-\underline{\text{CHOH}}-\underline{\text{CH}_2}-\text{NO}_2$ adjacent to the nitro group and a broad singlet at δ 3.07 for the hydroxy proton confirms the β -hydroxy nitro compound **32**. The ^{13}C -NMR showed signals at δ 55.73 for aromatic $-\text{OCH}_3$ group, δ 77.76 for $-\underline{\text{CH}_2}-\text{NO}_2$ aliphatic carbon adjacent to nitro group and δ 67.43, 71.16 for the two aliphatic carbons bearing oxo-functionality (**Fig. 6**). The IR spectrum of β -hydroxy nitro compound showed a broad band in the region of $3300\text{--}3600\text{ cm}^{-1}$ indicating the presence of hydroxyl functionality in the molecules.

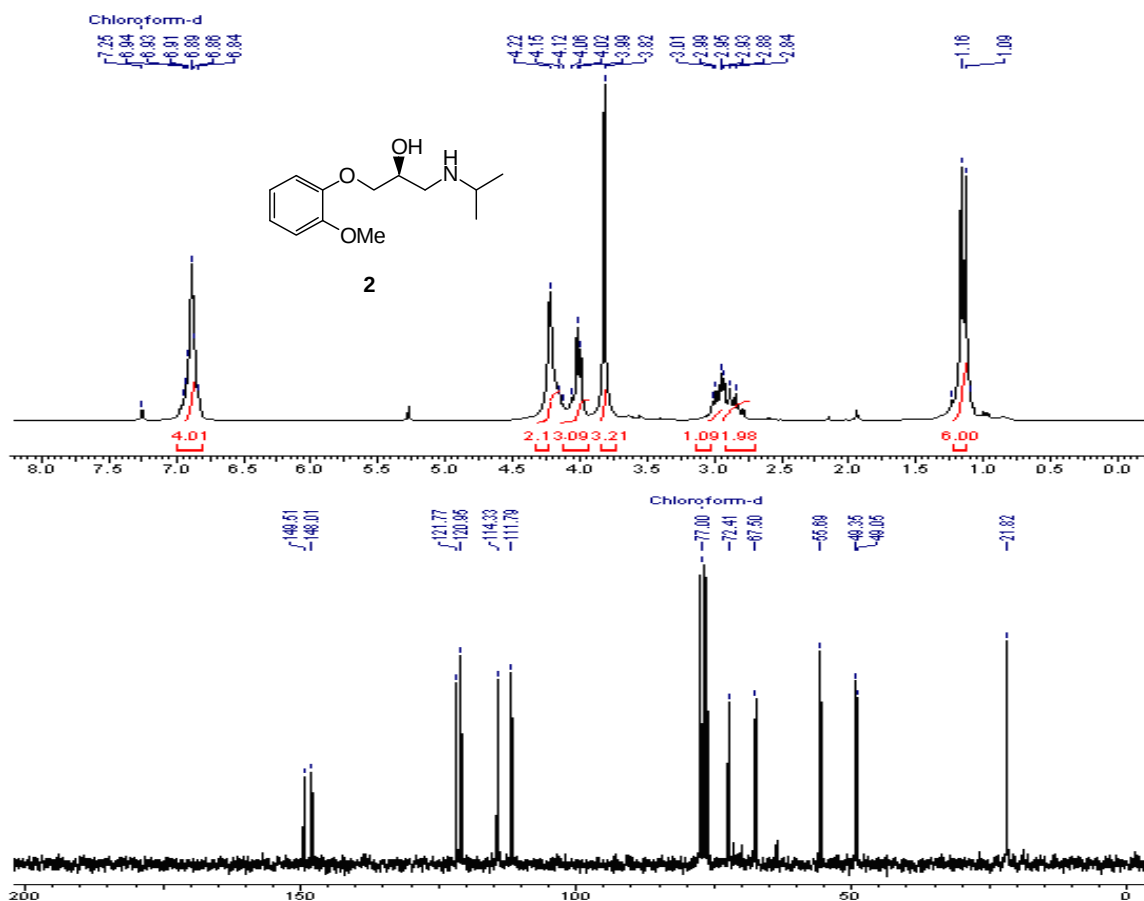
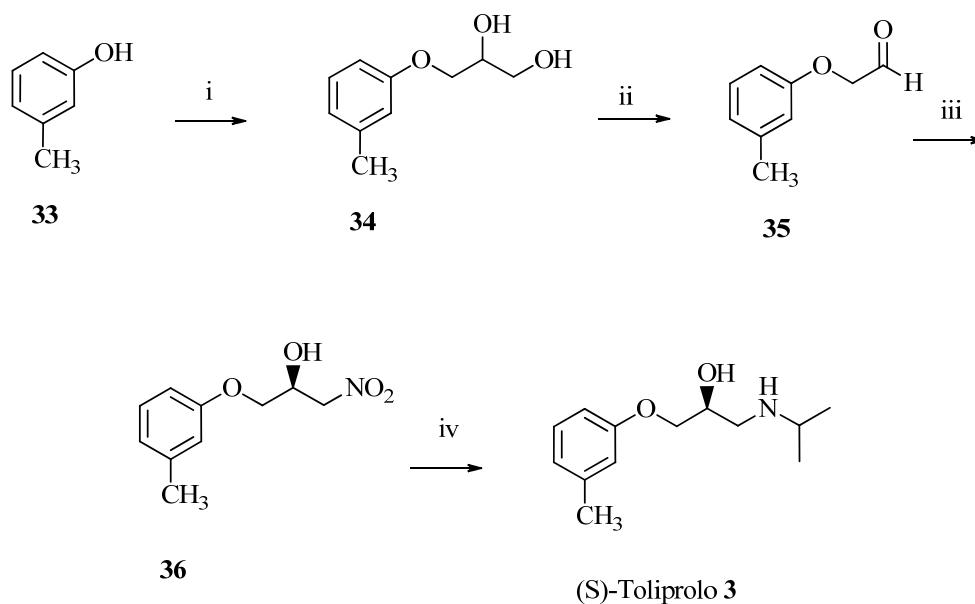


Fig. 7: ^1H and ^{13}C NMR spectrum of Moprolol **2**

Finally, β -hydroxy nitro compound **32** was subjected to Pd/C catalyzed hydrogenolysis to obtain amine; the amine was subjected insitu alkylation with isopropyl bromide in alcohol to obtain the (S)-Moprolol **2** in 88 % yields over two steps. The $^1\text{H-NMR}$ spectrum of Moprolol **2** showed a doublet at δ 1.09 for two methyl proton of isopropyl group and multiplets in the region δ 2.84-3.01 and δ 3.99-4.22 confirming the formation of (S)-Moprolol **2** (Fig. 7).

2.4.2 Enantioselective synthesis of (S)-Toliprolol

The synthetic scheme employed for the synthesis of (S)-Toliprolol **3** is presented in the scheme 8



Scheme 8: Reagents and reaction conditions: (i) NaOH, H₂O, 3-chloro-1,2-propanediol, reflux, 8 h (ii) NaIO₄, H₂O, 0-5 °C (iii) CuFAP, nitromethane, chiral triethylamine ligand (L*) (iv) (a) H₂, 10 % Pd/C methanol (b) isopropyl bromide.

As per retrosynthetic analysis Fig. 3, we initiated a synthesis from commercially available *m*-cresol **33**. The *m*-Cresol **33** was reflux with aqueous NaOH solution, and 3-chloro, 1-2-propan-di-ol for 8 h furnished diol **34**²⁸ in 90 % yield.

The ^1H -NMR spectrum showed multiplets in the region of δ 3.64-3.75 and δ 3.90-4.04 for five protons and a broad singlet at δ 3.60 confirmed the formation of the diols. The ^{13}C -NMR showed signals at δ 21.43 for aromatic $-\text{CH}_3$ group and at δ 63.56, 68.74 and 70.50 for the three aliphatic carbons bearing oxo-functionality (**Fig. 8**). The IR spectrum of these diols showed a broad band in the region of $3300\text{--}3600\text{ cm}^{-1}$ indicating the presence of hydroxyl functionality in the molecules.

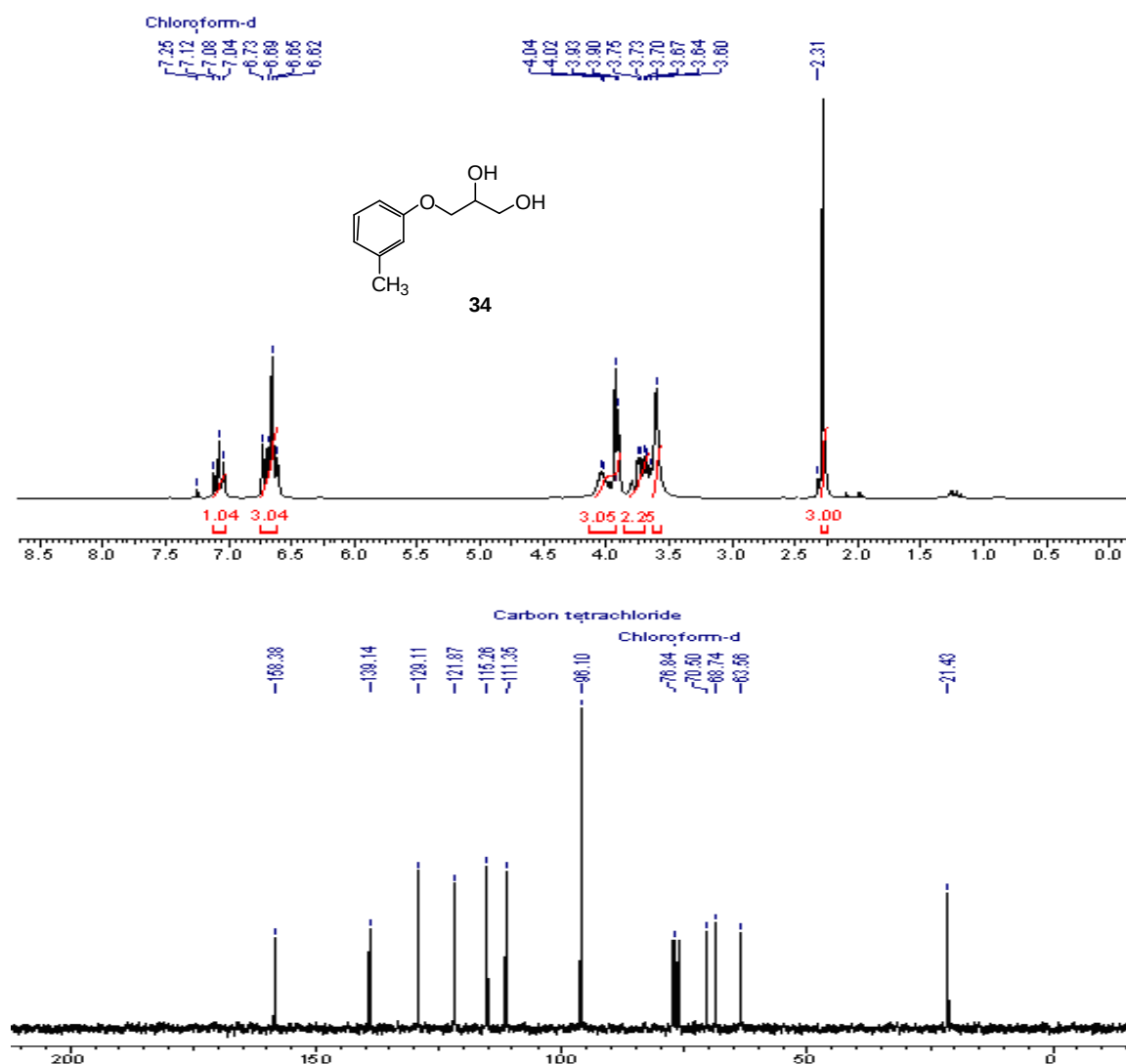


Fig. 8: ^1H and ^{13}C NMR spectrum of 3-(3-Methylphenoxy) propane-1, 2-diol **34**

The oxidative cleavage²⁸ of diol **34** was carried out with NaIO₄ in water at 0-5 °C affording aldehydes **35** in 93 % yields.

The ¹H-NMR spectrum of aldehyde showed disappearance of aliphatic multiplets and appearance of singlet for -OCH₂- at δ 4.48 and another sharp singlet for the aldehyde proton at δ. 9.83 confirmed the formation of the aldehyde **35**. The ¹³C-NMR showed only two aliphatic signals at δ 21.60 for aromatic -OCH₃ group and at δ 72.39 for -OCH₂- aliphatic carbons adjacent to aldehyde functionality carbons and the carbonyl carbon of aldehyde at δ 199.23 (**Fig. 9**). The IR spectrum of aldehyde **35** showed appearance of new signal at 1739 cm⁻¹ for carbonyl group of aldehyde **35**.

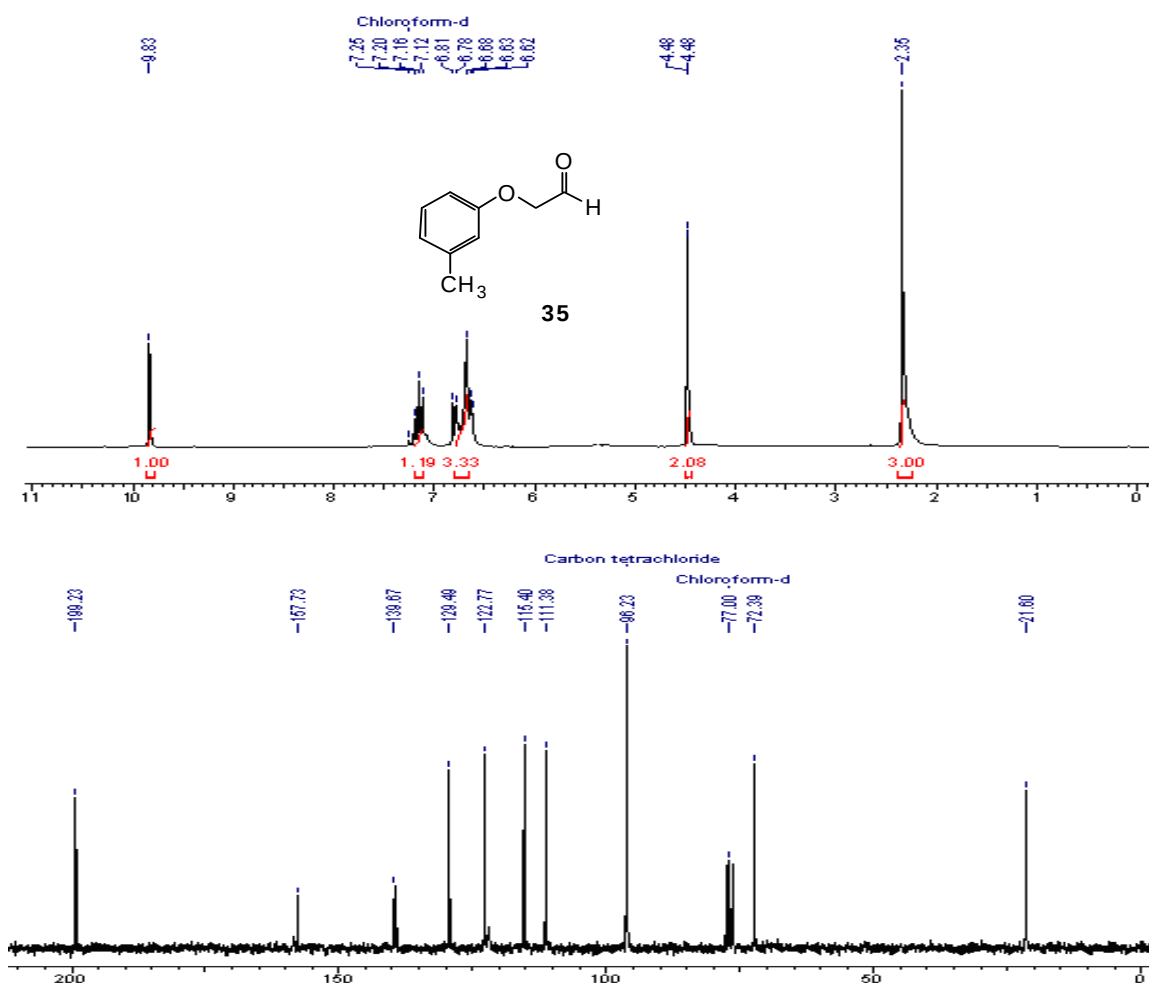


Fig. 9: ¹H and ¹³C NMR spectrum of 2-(3-Methylphenoxy) ethanal **35**

The aldehyde **35** was then subjected to asymmetric nitroaldol reaction catalysed by copper fluorapatite in the presence of chiral triethylamine ligand at 0-10 °C for 24 h to obtain the β-hydroxy nitro compound **36** in 84 % yield. The ¹H-NMR spectrum of β-hydroxy nitro compound showed disappearance of aldehyde proton and the appearance of new aliphatic multiplet for two protons at δ 3.94-3.97 for $-\underline{\text{CH}}_2-$ and other multiplet for three protons at δ 4.51-4.59 for $-\underline{\text{CHOH}}-\underline{\text{CH}}_2-\text{NO}_2$ adjacent to the nitro group and broad singlet at δ 2.97 for the hydroxy proton confirms the formation of β-hydroxy nitro compound **36**.

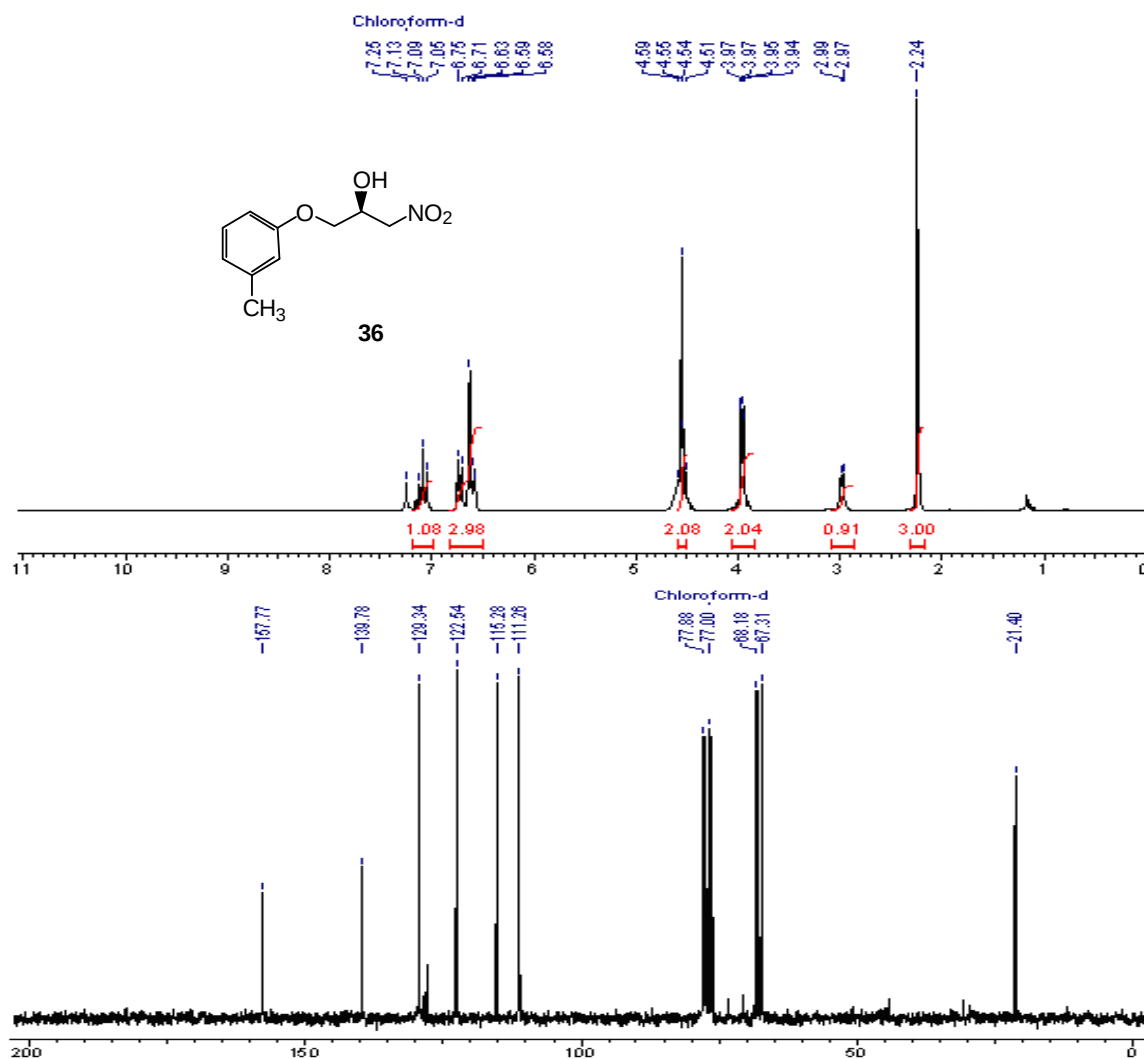


Fig. 10: ¹H and ¹³C NMR spectrum of (S)-1-(3-methylphenoxy)-3-nitropropane-2-ol **36**

The ^{13}C -NMR showed signals at δ 21.40 for aromatic $-\text{CH}_3$ group, δ 77.88 is for $-\text{CH}_2-$ NO_2 aliphatic carbon adjacent to nitro group and δ 67.31, 68.18 are for the two aliphatic carbons bearing oxo-functionality (**Fig. 10**). The IR spectrum of β -hydroxy nitro compound **36** showed abroad band in the region of $3300\text{--}3500\text{ cm}^{-1}$ indicating the presence of hydroxyl functionality in the molecules.

Finally, the β -hydroxy nitro compound **36** was subjected to Pd/C catalyzed hydrogenolysis to obtain amine; the amine was subjected in-situ alkylation with isopropyl bromide in alcohol to obtain the (*S*)-Toliprolol **3** in 83 % yields over two steps.

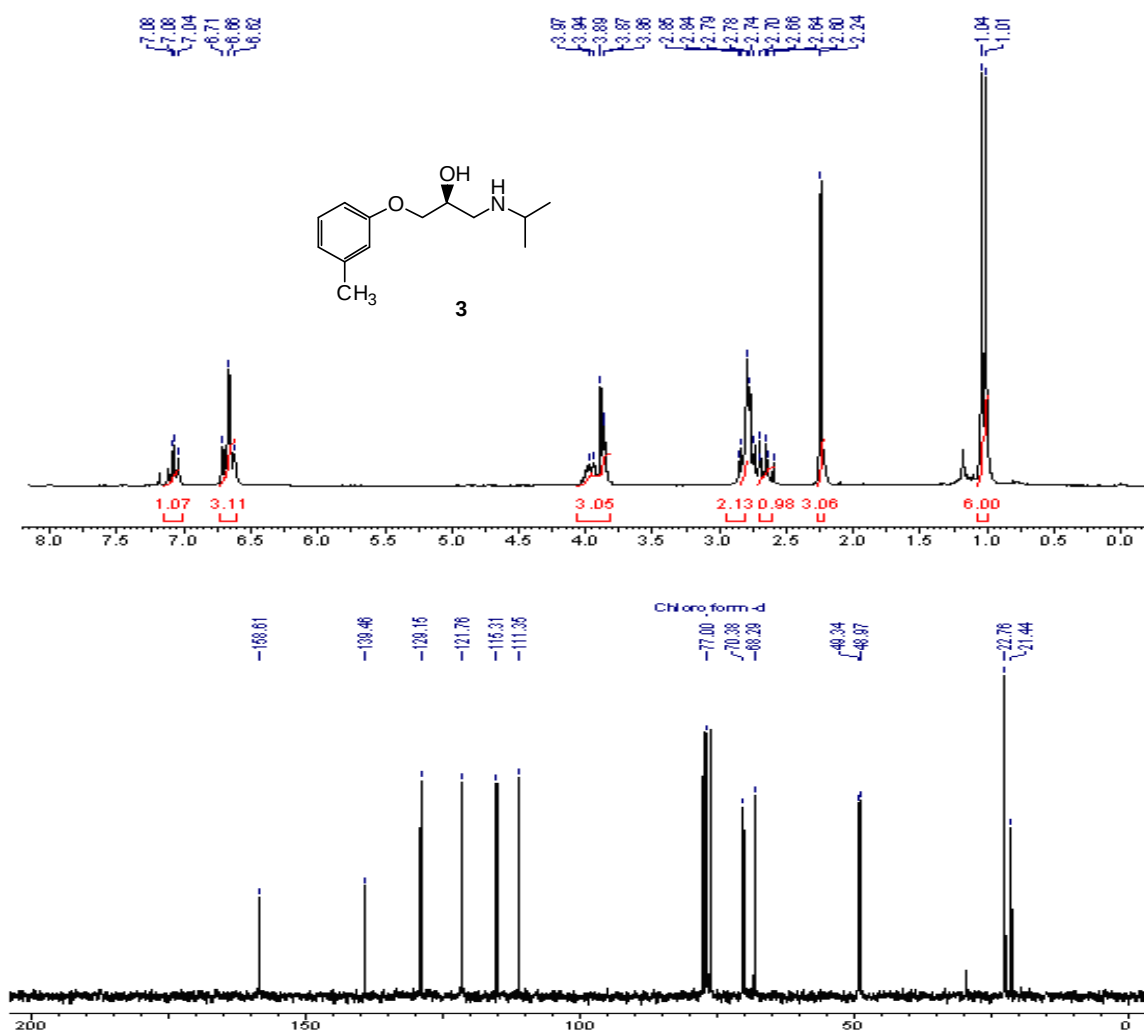
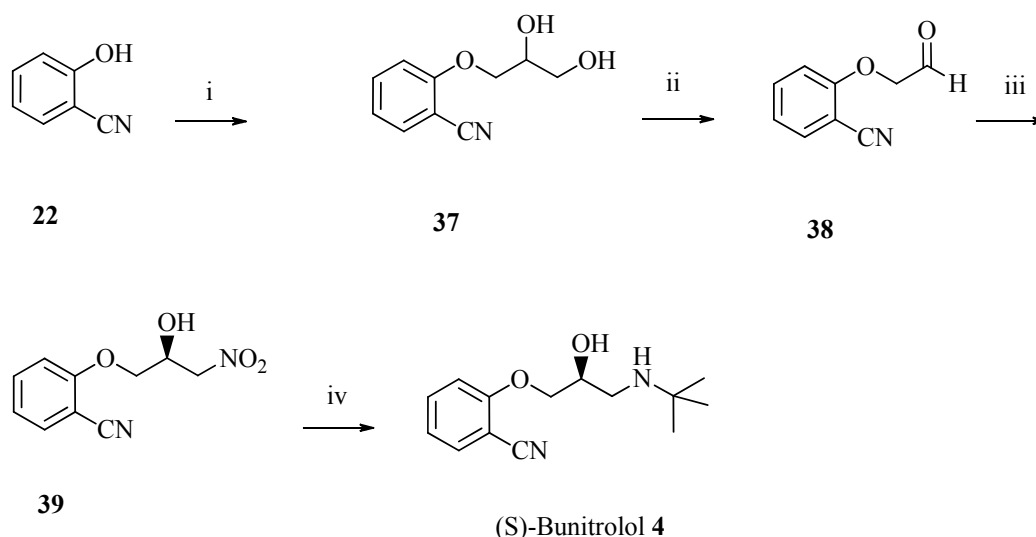


Fig. 11: ^1H and ^{13}C NMR spectrum of Toliprolol **3**

The ^1H -NMR spectrum of **3** showed a doublet at δ 1.01-1.04 for two methylene proton of isopropyl group and multiplets in the region δ 2.64-2.85 and δ 3.86-3.97 confirming the formation of (S)-Toliprolol **3** (Fig. 11).

2.4.3 Enantioselective synthesis of (S)-Bunitrolol

The synthetic scheme employed for the synthesis of (S)-Bunitrolol **4** is presented in the scheme 9



Scheme 9: Reagents and reaction conditions: (i) 3-chloro,1-2-propanediol, 8 h (ii) NaIO_4 , H_2O , 0-5 $^\circ\text{C}$ (iii) CuFAP, nitromethane, L-Proline (iv) (a) H_2 , 10 % Pd/C methanol (b) *ter*-Butyl bromide.

As per retrosynthetic analysis Fig. 3, we initiated a synthesis from commercially available *o*-cynophenole **22**. The *o*-cynophenole **22** was reflux with aqueous NaOH solution, and 3-chloro, 1-2-propan-di-ol for 8 h furnished diol **37**²⁸ in 92 % yield. The ^1H -NMR spectrum of **37** showed multiplets for two protons in the region of δ 3.28-3.69 for two protons and δ 3.71-4.04 for three protons confirmed the formation of the diols. The ^{13}C -NMR showed signals at δ 115.38 for aromatic nitrile carbon δ 44.30, 49.63, and 69.10 for the three aliphatic carbons bearing oxo-functionality (Fig. 12). The IR spectrum

of these diols showed a broad band in the region of 3300-3600 cm^{-1} indicating the presence of hydroxyl functionality in the molecules.

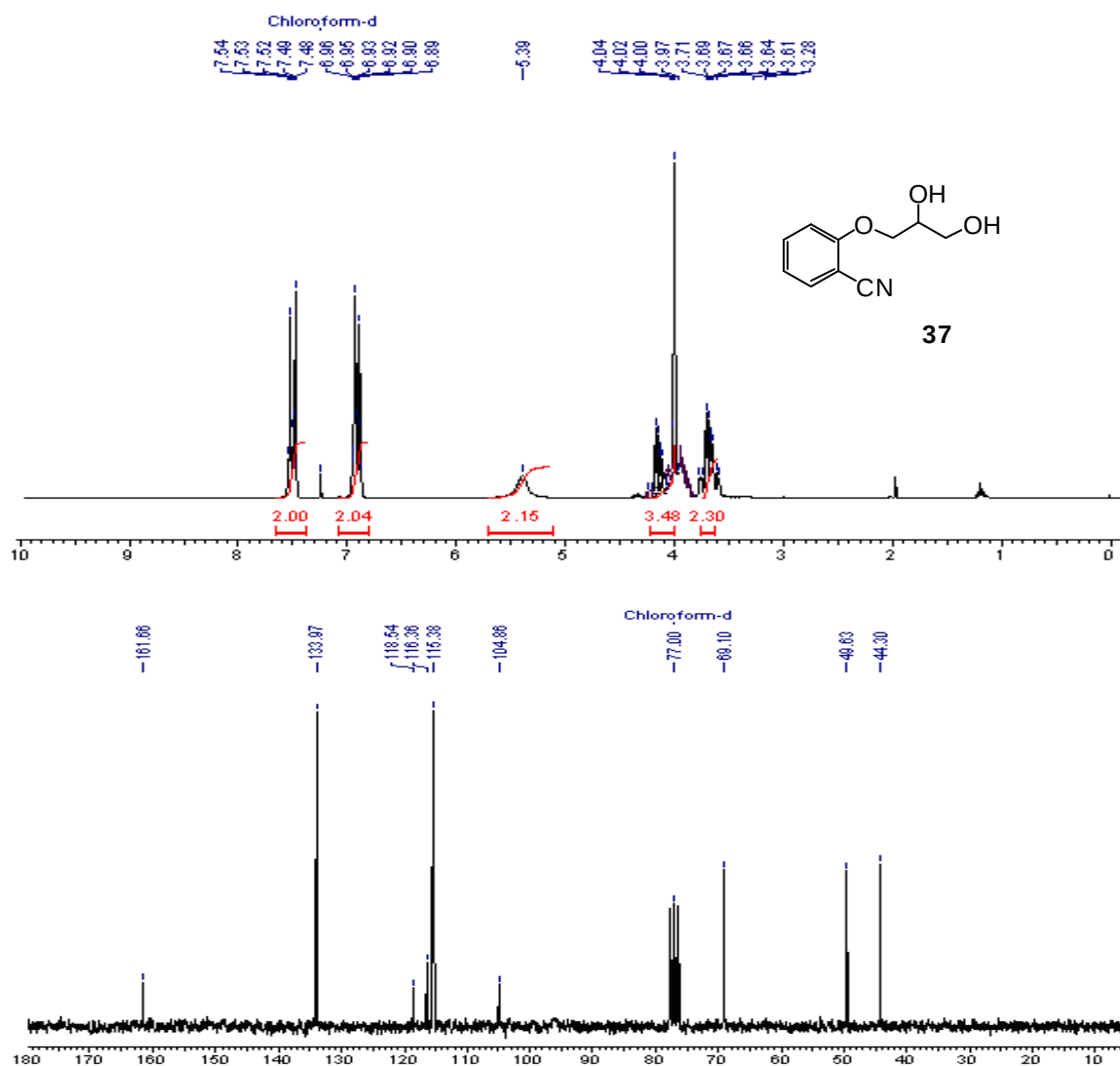


Fig. 12: ^1H and ^{13}C NMR spectrum of 3-(2-cynolphenoxy) propane-1, 2-diol **37**

The oxidation²⁸ of diol **37** was carried out with NaIO_4 in water at 0-5 $^\circ\text{C}$ affording aldehydes **38** in 96 % yields. The ^1H -NMR spectrum of aldehyde showed disappearance of aliphatic multiplets and appearance of singlet for $-\text{OCH}_2-$ at δ 4.61 and sharp singlet for the aldehyde proton at δ 9.81, confirmed the formation of the aldehyde **38**. The ^{13}C -

NMR showed δ 115.29 for aromatic nitrile carbon only one aliphatic signals at δ 72.41 for $-\text{OCH}_2-$ aliphatic carbons adjacent to aldehyde functionality (**Fig. 13**).

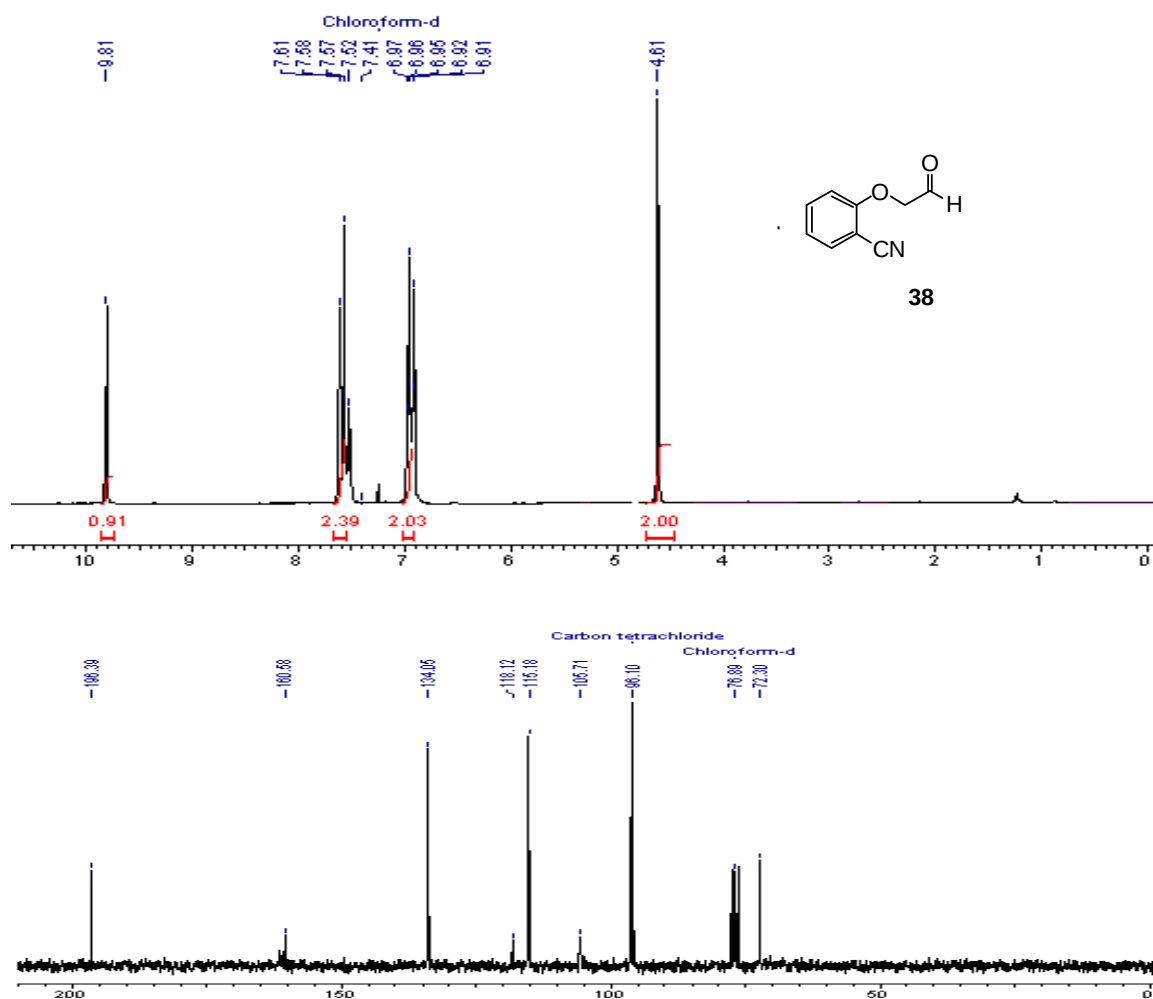


Fig. 13: ^1H and ^{13}C NMR spectrum of 2-(2-cyano phenoxy) ethanal **38**

The IR spectrum of aldehyde showed disappearance of a broad band in the region of $3300\text{--}3600\text{ cm}^{-1}$ indicating the absence of hydroxyl functionality in the molecules and appearance of a new signal at 1723 cm^{-1} for the carbonyl group of aldehyde.

Aldehyde **38** was then subjected to asymmetric nitroaldol reaction catalysed by copper fluorapatite in the presence of a chiral triethylamine ligand at $0\text{--}10^\circ\text{C}$ for 24 h to obtain

the β-hydroxy nitro compound **39** in 90 % yield. ¹H-NMR spectrum of β-hydroxy nitro compound showed disappearance of aldehyde proton and the appearance of new aliphatic multiplets for five protons at δ 3.55-4.68. The ¹³C-NMR showed signals at δ 115.19 for aromatic nitrile group, δ 78.14 for –CH₂–NO₂ aliphatic carbon adjacent to nitro group and δ 66.67, 68.86 for the two aliphatic carbons bearing oxo-functionality (**Fig. 14**). The IR spectrum of β-hydroxy nitro compound showed a broad band in the region of 3300-3600 cm⁻¹ indicating the presence of hydroxyl functionality in the molecules **39** which shows 97 % ee by chiral HPLC analysis (**Fig. 15**).

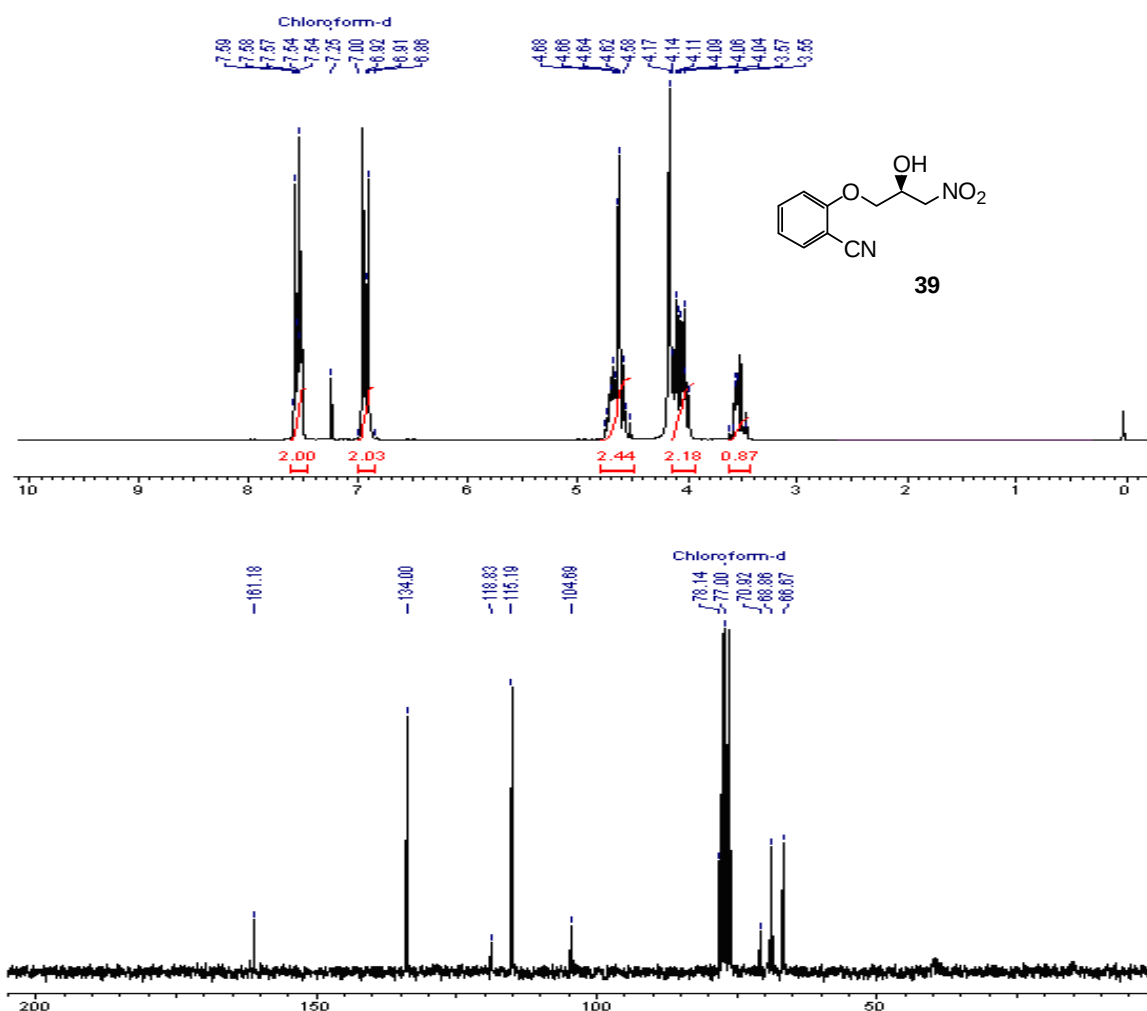
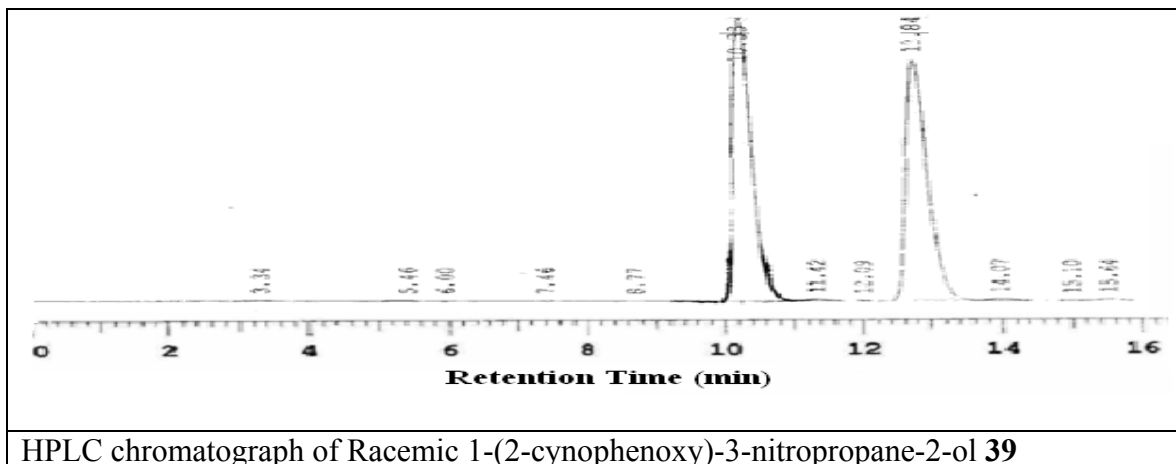


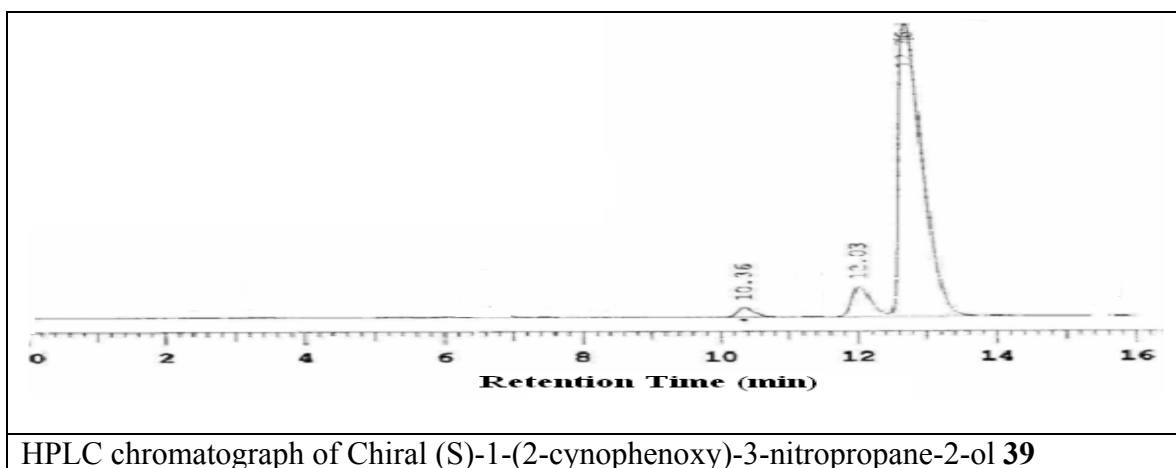
Fig. 14: ¹H and ¹³C NMR spectrum of (S)-1-(2-cynophenoxy)-3-nitropropane-2-ol **39**

Chiral HPLC Analysis of (S)-1-(2-cynophenoxy)-3-nitropropane-2-ol **39**

Column : Chiral Sep OJ
 Mobile phase : *n*-Hexane+ *i*-Propyl alcohol (80:20) mixture
 Wavelength : 254 nm
 Flow rate : 0.5 ml/min
 Injection Volume : 5 μ l



PK #	Retention Time (min)	Area	Area %	Height %
1	10.33	12920763	49.055	49.055
2	12.84	13115557	49.794	49.794



PK #	Retention Time (min)	Area	Area %	Height %
1	10.36	442830	1.934	2.17
2	12.76	19953627	97.82	97.82

Fig. 15: HPLC Analysis of (S)-1-(2-cynophenoxy)-3-nitropropane-2-ol **39**

The nitro compound **39** was subjected to Pd/C catalyzed hydrogenolysis to obtain amine. The amine was subjected in-situ alkylation with *ter*-butyl bromide in alcohol to obtain the (*S*)-Bunitrolol **4** in 79 % yields over two steps. The ^1H -NMR spectrum of **4** showed a sharp singlet at δ 1.19 for three methylene proton of *ter*-butyl group and multiplets in the region δ 2.68-2.98 for two protons and δ 3.98-4.15 for three proton and a broad singlet at 3.55 for hydroxy group confirming the formation of (*S*)-Bunitrolol **4** (Fig. 16).

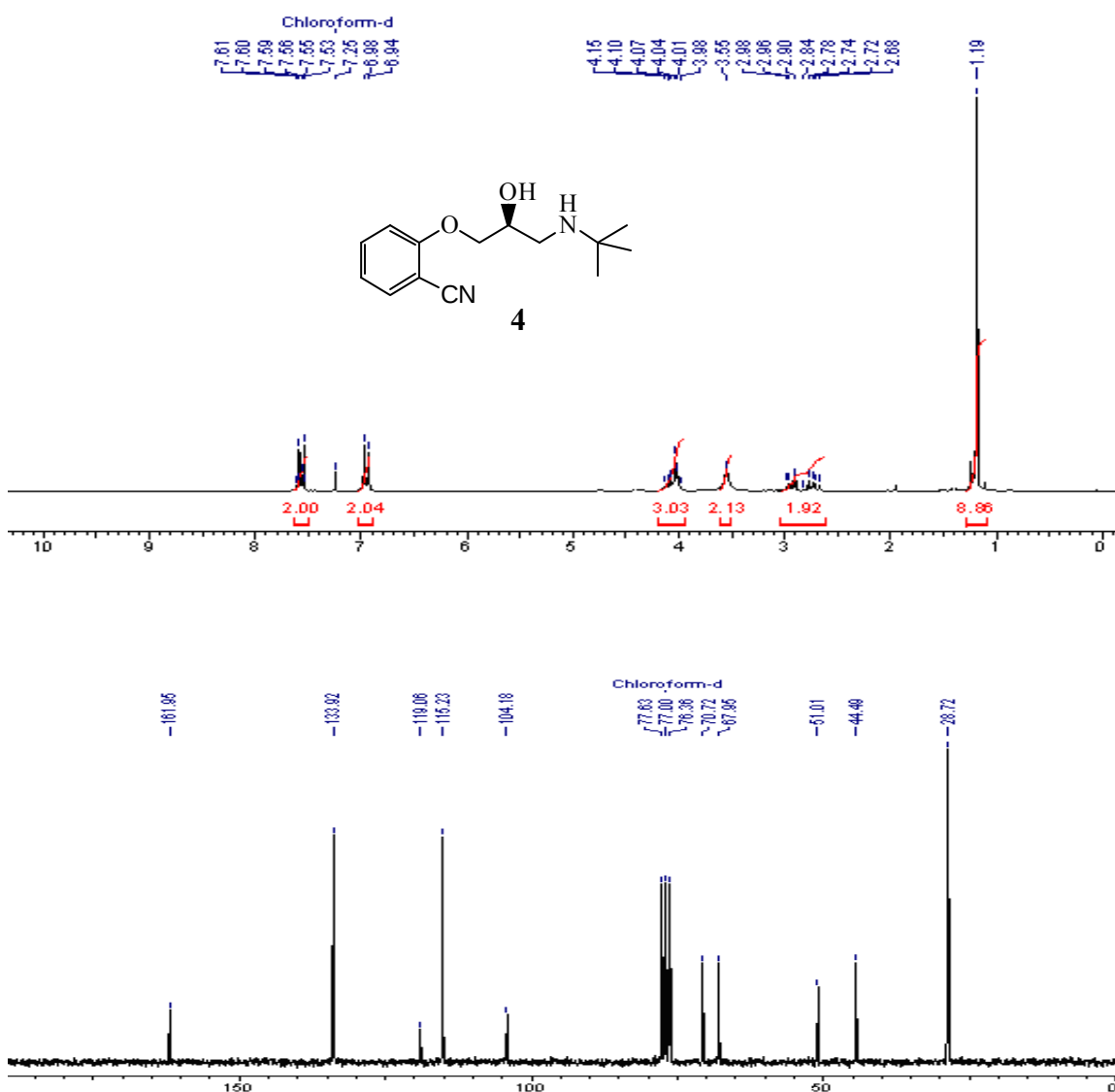


Fig. 16: ^1H and ^{13}C NMR spectrum of Bunitrolol **4**

2.5 Conclusion

In conclusion, we have developed highly efficient, versatile, ecofriendly, inexpensive, nontoxic, synthetic route for the enantioselective synthesis of the β -adrenergic blockers: (*S*)-Moprolol **2**, (*S*)-Toliprolol **3** and (*S*)-Bunitrolol **4** using reusable, heterogeneous copper fluorapatite catalyst in the presence of chiral triethylamine ligand *via* asymmetric nitroaldol reaction from the corresponding aldehydes as key step and source of chirality. The protocol is very general, simple, clean, efficient, rapid, and mild and it works well for the synthesis of β -adrenergic blockers affording good to excellent yields.

2.6 Experimental Section

Preparation of 3-(Aryloxy) propane-1, 2-diol (30, 34, 37)

3-chloro-1, 2-propanediol (3.056 g, 22 mmol) was added to a stirring solution of substituted phenol **25/33/22** (20 mmol) in 20 % aqueous NaOH solution (20 mL). After refluxing for 8 h, the reaction mixture cooled to room temperature and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layer was washed with water (2 x 50 mL) brine, dried over anhydrous Na₂SO₄, filtered and concentrated on rotary evaporator under reduced pressure. Resulting residue was purified by column chromatography (silica gel 60-120 mesh) using EtOAc-petroleum ether (10:90) as an eluent, affording the 3-(Aryloxy) propane-1, 2-diol **30/34/37** in 90-96 % yield.

3-(2-Methoxyphenoxy) propane-1, 2-diol 30

Yield: 3.81 g (96 %); white crystals; m.p.101-103 °C; **IR** (CHCl₃): 3435, 3018, 2933, 2840, 2401, 1734, 1594, 1505, 1455, 1329, 1254, 1216, 1125, 1028, 930, 837, 758, 669 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 3.37 (bs, 2H), 3.76-3.80 (m, 2H), 3.83 (s, 3H), 4.02-4.05 (m, 2H), 4.07-4.09 (m, 1H), 6.86-6.94 (m, 4H), **¹³C NMR** (200 MHz, CDCl₃):

δ 55.74, 63.77, 70.01, 71.92, 111.73, 114.53, 121.06, 122.06, 147.88, 149.48 ppm; Anal. Calcd for C₁₀H₁₄O₄: C, 60.59; H, 7.12. Found: C, 60.30; H, 7.27 %.

3-(3-Methylphenoxy) propane-1, 2-diol 34

Yield: 3.27 g (90 %); white crystals; m.p. 60-62 °C; **IR** (CHCl₃): 3399, 3018, 2930, 2878, 2400, 1602, 1585, 1490, 1458, 1291, 1259, 1216, 1172, 1160, 1119, 1048, 930, 877, 857, 785, 690, 669 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 2.31 (s, 3H), 3.60 (brs, 2H), 3.64-3.75 (m, 2H), 3.90-4.04 (m, 3H), 6.62-6.73 (m, 3H), 7.04-7.012 (m, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 21.43, 63.56, 68.74, 70.50, 76.84, 111.35, 115.26, 121.87, 129.11, 139.14, 158.38 ppm; MS: m/z = 204.98 (M⁺ + Na); Anal. Calcd for C₁₀H₁₄O₃: C, 65.92; H, 7.74. Found: C, 65.89; H, 7.71 %.

3-(2-cynolphenoxy) propane-1, 2-diol 37

Yield: 3.55 g (92 %); white crystals; m.p. 140-141 °C; **IR** (CHCl₃): 3420, 3015, 2232, 1602, 1495, 1445, 1287, 1205, 783 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 3.61-3.71 (m, 2H), 3.97-4.04 (m, 3H), 5.39 (brs, 2H), 6.89-6.95 (m, 2H), 7.48-7.54 (m, 2H); **¹³C NMR** (200 MHz, CDCl₃): δ 44.30, 49.63, 69.10, 104.86, 115.38, 116.36, 118.54, 133.97, 161.66 ppm; Anal. Calcd for C₁₀H₁₁NO₃: C, 62.17; H, 5.73; N, 7.25; Found: C, 62.10; H, 5.74; N, 7.30 %.

Preparation of 2-(Aryloxy) ethanals (31, 35, 38)

To a solution of sodium periodate (4.7 mmol) in water (100 mL) cooled to 0-5 °C was added 1,2-diols **30/34/37** (4.5 mmol) portion wise under vigorous stirring in about 90 min and keeping the temperature under 10 °C. After 1 h at 10 °C, excess NaIO₄ was decomposed with ethylene glycol (0.15 g). The reaction mixture was stirred for thirty minutes later at room temperature then the reaction mixture was filtered and collected

precipitates. The precipitate was suspended again in cool demineralized water (50 mL) and stirred for a further 30 min and filtered again to give aldehydes **31/35/38** which was air dried affording a 90-96 % yield and used in the next step without further purification

2-(2-Methoxy phenoxy) ethanal 31

Yield: 0.672 g (90 %); white crystals; m.p. 57-58 °C; **IR** (CHCl₃): 3020, 2927, 2400, 1737, 1595, 1504, 1456, 1400, 1254, 1216, 1126, 1029, 757, 669 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 3.88 (s, 3H), 4.59 (s, 2H), 6.83-6.98 (m, 4H), 9.88 (s, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 55.74, 74.14, 112.16, 114.79, 120.86, 122.88, 147.16, 149.62, 200.18 ppm; Anal. Calcd for C₉H₁₀O₃: C, 65.05; H, 6.07. Found: C, 64.93; H, 6.17 %.

2-(3-Methylphenoxy)ethanal 35

Yield: 0.627 g (93 %); yellow oil; **IR** (CHCl₃): 3443, 3019, 2925, 1739, 1603, 1586, 1490, 1457, 1383, 1291, 1261, 1216, 1161, 1117, 1065, 935, 757, 689, 668 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 2.35 (s, 3H), 4.48 (s, 2H), 6.62-6.81 (m, 3H), 7.12-7.20 (m, 1H), 9.83 (s, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 21.60, 72.39, 111.38, 115.40, 122.77, 129.49, 139.67, 157.73, 199.23 ppm; MS: *m/z* = 174.1 (M⁺ + Na); Anal. Calcd for C₉H₁₀O₂: C, 71.98; H, 6.71, Found: C, 71.96; H, 6.68 %.

2-(2-cyno phenoxy)ethanal 38

Yield: 0.695 g (96 %); Pale yellow oil; **IR** (CHCl₃): 3313, 3017, 2895, 1722, 1671, 1584, 1433, 1457, 1383, 1161, 1117, 1065, 935, 753, 699, 665 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 4.61 (s, 2H), 6.91-6.97 (m, 2H), 7.52-7.61 (m, 2H), 9.81 (s, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 72.30, 115.18, 118.12, 134.05, 160.58, 196.39 ppm; Anal. Calcd for C₉H₇NO₂: C, 67.07; H, 4.38. Found: C, 67.12; H, 4.29 %.

Preparation of β-nitroalcohols (32, 36, 39)

CuFAP (100 mg) and the chiral triethylamine ligand (L*) (3 mol %) in 10 mL nitromethane was taken into the 50 mL round bottomed flask and stirred at room temperature for 30 minutes. Reaction mixture was cooled to 0-10 °C and aldehyde **31/35/38** (4 mmol) dissolved in 2 mL nitromethane was added, reaction was continued at 10 °C till the completion of the reaction (28-36 h). After completion of the reaction, a mixture of DCM and water (1:1,100 mL) was added. The organic layer was separated and aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layer was washed with water (2 x 50 mL) brine, dried over anhydrous Na₂SO₄, filtered and concentrated on rotary evaporator under reduced pressure. Resulting residue was purified by column chromatography (silica gel 60-120 mesh) using EtOAc-petroleum ether (10:90) as an eluent, affording the β-nitroalcohols **32/36/39** in 84-92 % yield.

(S)-1-(2-methoxyphenoxy)-3-nitropropane-2-ol 32

Yield: 0.835 g (92 %), gum, $[\alpha]_D^{25} = -7.9$ (*c* 1.06, CHCl₃); **IR** (CHCl₃): 3433, 3019, 2932, 1594, 1557, 1505, 1456, 1383, 1255, 1217, 1179, 1125, 1028, 756, 668 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 3.07 (brs, 1H), 3.85 (s, 3H), 4.08-4.15 (m, 2H), 4.60-4.73 (m, 3H), 6.88-7.06 (m, 4H); **¹³C NMR** (200 MHz, CDCl₃): δ 55.73, 67.43, 71.16, 77.76, 112.06, 116.14, 121.11, 123.12, 147.36, 149.93 ppm; MS: *m/z* = 249.02 (M⁺ + Na); Anal. Calcd for C₁₀H₁₃NO₅: C, 52.86; H, 5.7, N, 6.16. Found: C, 52.6; H, 5.76, N, 6.23 %

(S)-1-(3-methylphenoxy)-3-nitropropane-2-ol 36

Yield: 0.709 g (84 %), gum, $[\alpha]_D^{25} = -12.3$ (*c* 1.1, CHCl₃); **IR** (CHCl₃): 3410, 3019, 2927, 2400, 1603, 1585, 1558, 1490, 1459, 1421, 1382, 1291, 1259, 1216, 1160, 1049, 929, 759, 669 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 2.24 (s, 3H), 2.97-2.99 (d, 1H), 3.94-

3.97 (m, 2H), 4.51-4.61 (m, 3H), 6.58-6.75 (m, 3H), 7.05-7.13 (m, 1H); ¹³C NMR (200 MHz, CDCl₃): δ 21.40, 67.31, 68.18, 77.88, 111.26, 115.28, 122.54, 129.34, 139.78, 157.77 ppm; Anal. Calcd for C₁₀H₁₃NO₄: C, 56.86; H, 6.2; N, 6.63. Found: C, 57.04; H, 6.30; N, 6.9 %.

(S)-1-(2-cynophenoxy)-3-nitropropane-2-ol 39

Yield: 0.800 g (90 %), Colorless oil; [α]²⁵_D = -5.69 (c 0.85, CHCl₃); 97 % ee by chiral HPLC analysis; IR (CHCl₃): 3416, 3025, 2912, 1590, 1567, 1525, 1445, 1373, 1252, 1217, 1179, 1121, 1022, 749, 659 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 3.55-3.57 (m, 1H), 4.04-4.17 (m, 3H), 4.58-4.68 (m, 2H), 6.86-7.0 (m, 2H), 7.54-7.59 (m, 2H); ¹³C NMR (200 MHz, CDCl₃): δ 66.67, 68.86, 70.92, 78.14, 104.69, 115.19, 118.83, 134.00, 160.18 ppm; Anal. Calcd for C₁₀H₁₀N₂O₄: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.1; H, 4.52; N, 12.59 %.

Preparation of Moprolol 2 and Toliprolol 3

To a solution of the β-nitroalcohols **32/36** (1 mmol) in methanol (10 mL) was added 10 % Pd/C (50 mg). The solution was then stirred under a hydrogen atmosphere for 6 h at RT. The progress of reaction was monitored by TLC. After complete reduction of nitro group to amine, Triethyl amine (2 mmol) and isopropyl bromide (3 mmol) was added and reaction was continued for further 12 h. The reaction mixture was filtered through a pad of Celite and washed thoroughly with methanol. The filtrate was concentrated and the residue thus obtained was purified by silica gel column to obtain (S)-Moprolol **2** and (S)-Toliprolol **3**, 88 and 83 % yields respectively.

Moprolol 2

Yield: 0.209 g (88 %), white solid, m.p. 82-83 °C; $[\alpha]_D^{25} = -5.21$, 93 % ee (*c* 4.54, EtOH) {Lit.²⁰ $[\alpha]_D^{25} = -5.6$ (*c*, 4.5, EtOH)}; **IR** (CHCl₃): 3307, 2964, 1593, 1505, 1455, 1384, 1330, 1254, 1225, 1179, 1125, 1027, 745, 618 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 1.09-1.16 (d, *J*= 7Hz 6H), 2.84-3.01 (m, 3H), 3.82 (s, 3H), 3.99-4.15 (m, 3H), 4.22 (bs, 2H); **¹³C NMR** (200 MHz, CDCl₃): δ 21.82, 49.05, 49.35, 55.69, 67.50, 72.41, 111.79, 114.33, 120.95, 121.77, 148.01, 149.51 ppm; MS: *m/z* = 238.97 (*M*⁺ + 1); Anal. Calcd for C₁₃H₂₁NO₃: C, 65.25; H, 8.84, N, 5.85. Found: C, 65.19; H, 8.78, N, 5.73 %.

Toliprolol 3

Yield: 0.184 g (83 %), white solid, mp 117-119 °C; $[\alpha]_D^{25} = -9.3$ (*c* 0.82, EtOH), 94 % ee; {Lit.²⁰ $[\alpha]_D^{25} = -9.9$ (*c*, 0.83, EtOH)}; **IR** (CHCl₃): 3369, 3019, 2968, 2927, 2400, 1602, 1490, 1458, 1384, 1258, 1215, 1159, 1048, 929, 759, 669 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 1.01-1.04 (d, *J*= 3Hz 6H), 2.24 (s, 3H), 2.64-2.74 (m, 1H), 2.78-2.85 (m, 2H), 3.86-3.89 (m, 2H), 3.94-3.97 (m, 1H), 6.62-6.71 (m, 3H), 7.04-7.08 (m, 1H); **¹³C NMR** (200 MHz, CDCl₃): δ 21.44, 22.76, 48.97, 49.34, 68.29, 70.38, 111.35, 115.31, 121.76, 129.15, 139.46, 158.61 ppm; MS: *m/z* = 224.06 (*M*⁺ + 1); Anal. Calcd for C₁₃H₂₁NO₂: C, 69.92; H, 9.48; N, 6.27 Found: C, 65.89; H, 9.41; N, 6.29 %.

Preparation of Bunitrolol 4

To a solution of the β-nitroalcohol **39** (1 mmol) in methanol (10 mL) was added 10 % Pd/C (50 mg). The solution was then stirred under a hydrogen atmosphere for 6 h at RT. The progress of reaction was monitored by TLC. After complete reduction of nitro group to amine, Triethyl amine (2 mmol) and *tert*-Butyl bromide was added and reaction was continued for further 12 h. The reaction mixture was filtered through a pad of Celite and

washed thoroughly with methanol. The filtrate was concentrated and the residue thus obtained was purified by silica gel column to give (S)-Bunitrolol **4** in 79 % yield.

Yield: 0.184 g (79 %), white solid, mp 160-163 °C; $[\alpha]_D^{25} = -15.6$ (*c* 1.4, EtOH), 96 % ee; **IR** (CHCl₃): 3410, 3019, 2978, 2937, 2400, 1564, 1490, 1458, 1384, 1258, 1215, 1159, 1049, 969, 759, 663 cm⁻¹; **¹H NMR** (200 MHz, CDCl₃): δ 1.19 (s, 9H), 2.68-2.98 (m, 2H), 3.55 (brs, 2H), 3.98-4.15 (m, 3H), 6.94-6.98 (m, 2H), 7.53-6.61 (m, 2H); **¹³C NMR** (200 MHz, CDCl₃): δ 28.72, 44.49, 51.01, 67.95, 70.72, 104.18, 115.23, 119.06, 133.92, 161.95 ppm; MS: *m/z* = 24.16 (M⁺ + 1); Anal. Calcd for C₁₄H₂₀N₂O₂: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.69; H, 8.14; N, 11.29 %.

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Chapter III

Copper fluorapatite Catalysed Ligand-free Synthesis of Diaryl ethers

i) “Ligand free, highly efficient synthesis of diaryl ether over copper fluorapatite as heterogeneous reusable catalyst” Shafeek A. R. Mulla, Suleman M. Inamdar, Mohsinkhan Y. Pathan, Santosh S. Chavan. ***Tetrahedron Lett.* 2012, 53, 1826-1829.**

This article also highlighted in ***Synfacts*, 2012, 8(6), 0691.**

ii) “Base promoted highly efficient copper fluorapatite catalyzed coupling of phenols with arylboronic acids under mild and ligand-free conditions” Shafeek A. R. Mulla, Suleman M. Inamdar, Mohsinkhan Y. Pathan, Santosh S. Chavan. ***RSC-adv.* 2012, 2, 12818.**

Section-I

Synthesis of diaryl ether from phenols and aryl halides

3.1.1 Introduction

Diaryl ether motifs are presents in the natural products and medicinally important compounds.¹ Diaryl ethers molecules are not only important in biological systems but also key moieties in pharmaceutical, agricultural, polymer, industrial, and life science.² However, carbon-carbon and carbon-heteroatom bond forming reaction catalysed by transition metals are an important fundamental transformation in the synthetic chemistry.³ The most simplest and straight forward way to synthesized diaryl ethers involves the direct formation of aryl-oxygen bond from an aryl halide.⁴ The classical copper catalysed Ullmann coupling reaction for ether synthesis has been extensively used for the formation of diaryl ether on industrial scale in polar solvents (pyridine, DMF, collidine).⁵ However, application on industrial scale synthesis has been limited due to harsh reaction conditions such as high reaction temperature (125-300 °C), longer reaction time at which many functional groups are unstable hence lower yield to desire product. In addition, the requirement of excess or stoichiometric quantities of copper complexes leads to the problem of waste disposal.⁶

Owing to the importance of diaryl ether moieties in life sciences, pharmaceutical, agricultural, polymer, the world-wide efforts have been made in the last few decades to develop the various methods for the synthesis of Ullmann diaryl ethers using varieties of reagents. The catalysts in combination with the various ligands have been reported catalytically processes,⁷⁻⁹ a palladium catalyzed coupling reaction in the presence of ligand between sodium phenoxide and electron deficient aryl bromide,¹⁰ microwave

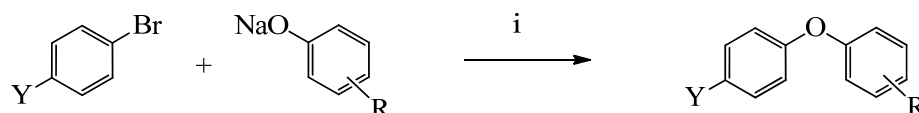
assisted Cu(0)-nano particles,^{11a} Nano Ceria,^{11b} KF/supported on natural nano-porous Zeolite,^{12a} Ullmann and Goldberg reactions,^{12b} copper¹³⁻¹⁴ and palladium complexes¹⁵ in the presence of ligands. Moreover, phosphines-palladium complexes are air sensitive and other complexes with palladium are expensive compare to copper or copper complexes.

3.1.2 Review of literature

Litrature survey revels that there are many methods available for the synthesis of diaryl ethers from the reaction of substituted haloarenes with substituted phenols in the presence of various ligands, bases and solvent at different reaction temperatures, which are described below.

Hartwig approach¹⁰

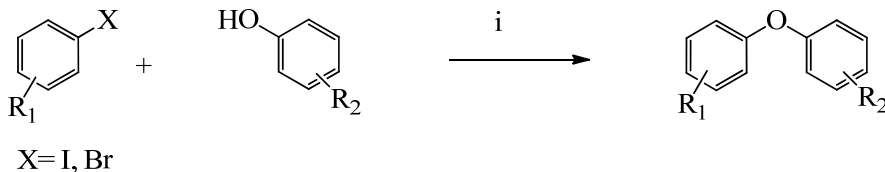
In this approach, sodium salts of the phenols was reacted with bromoarenes over Cu₂O and Pd(DBA)₂ catalysts in the presence of base at 110-120 °C (**Scheme 1**)



Scheme 1: Reagents and reaction conditions: (i) Aryl bromide (1 mmol), ArOH (1.1 mmol), Cs₂CO₃ (2 mmol), ligand (5-10 mol %) Pd(DBA)₂, DPPF (6-11 mol %), toluene:THF, reflux, 6-30 h

Taillefer approach^{12b}

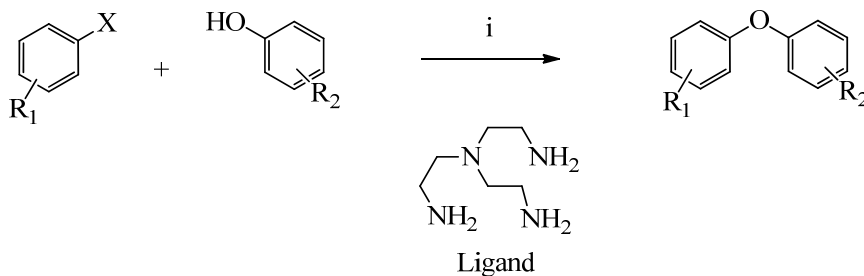
In this approach, Taillefer *et al.* treated various iodo or bromoarenes with substituted phenols in the presence of Cu₂O catalyst in combination with the ligands to achieve the diaryl ethers (**Scheme 2**).



Scheme 2: Reagents and reaction conditions: (i) Phenol (0.5 mmol), Aryl halide (0.6 mmol), K_3PO_4 (0.6 mmol), CuI (0.05 mmol), ligand (0.05 mmol), 80 °C, 24 h.

Shingare M. S. approach^{13h}

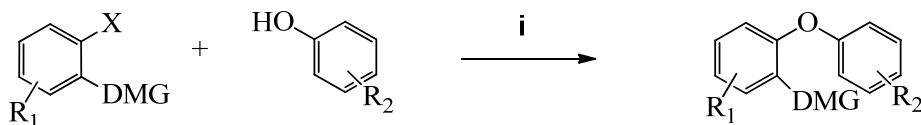
Shingare *et al* treated haloarenes with various phenols over CuI with amine as ligand in a dioxane solvent at 110 °C in the presence of base (**Scheme 3**).



Scheme 3: Reagents and reaction conditions: (i) Aryl halide (1 mmol), ArOH (1 mmol), Cs_2CO_3 (2 mmol), ligand (15 mol %), 1,4-Dioxane, 110 °C, 24 h

Snieckus approach^{14a}

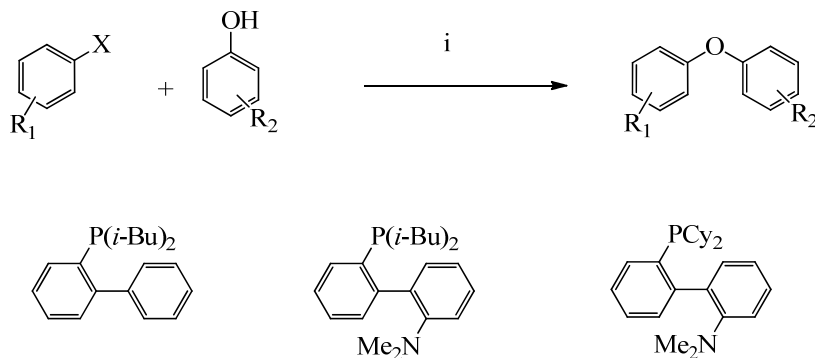
In this approach, Snieckus *et al.* reacted various haloarenes having electron withdrawing DMG on the ortho position with substituted phenols in the $CuPF_6$ (4MeCN) as a catalyst to achieve the diaryl ethers (**Scheme 4**).



Scheme 4: Reagents and reaction conditions: (i) Aryl chloride (1 mmol), ArOH (1.2 mmol), Cs_2CO_3 (2 mmol), ligand (5 mol %), toluene/xylene, reflux, 5-45 h

Buchwald approach^{15b}

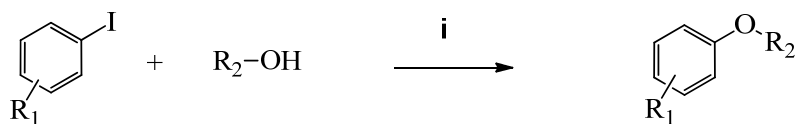
In this approach, Buchward *et al.* reacted various haloarenes with substituted phenols using Pd(OAc)₂ as a catalyst in the presence of three ligands and base in a toluene solvents to achieve the diaryl ethers (**Scheme 5**).



Scheme 5: Reagents and reaction conditions: (i) 1.0 equiv aryl halide, 1.2 equiv phenol, 1.4 equiv NaH or 2.0 equiv K₃PO₄, 2.0 mol % Pd(OAc)₂, 3.0 mol % ligand, toluene (3 mL), 100 °C, 14-24 h.

Buchwald approach^{15c}

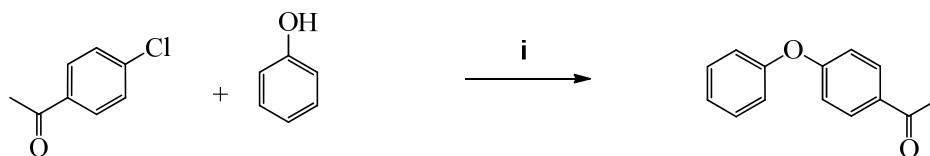
This method reports, the reaction of substituted iodobenzene with alcohols in the presence of copper iodide and 1,10-Phenanthroline ligand at 110 °C in the presence of base to yield aryl ethers (**Scheme 6**).



Scheme 6: Reagents and reaction conditions: (i) Aryl halide (1 mmol), Phenol (1 mL), 5 mol % CuI, Cs₂CO₃ (2 mmol), Ligand 5 mol %, 110 °C, 18-24 h.

Matthias Beller approach^{15d}

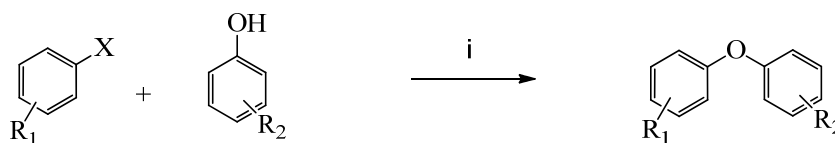
In this approach, 4-chloroacetophenone was treated with phenol in Pd(OAc)₂ in the presence of various ligands and base in toluene solvents (**Scheme 7**).



Scheme 7: Reagents and reaction conditions: (i) Aryl chloride (1 mmol), ArOH (1.2 mmol), K₃PO₄ (2 mmol), ligand (1 mol %), toluene (3 mL), 120 °C, 20 h.

Wang Q. approach^{15e}

This method reports, the reaction of haloarenes with phenols in the DMSO solvent under microwave irradiation conditions to yield diaryl ethers (**Scheme 8**).



Scheme 8: Reagents and reaction conditions: (i) Aryl halide (10 mmol), Phenol (12 mmol), anhy. K₂CO₃ (20 mmol), DMSO (50 mL).

3.1.3 Present Work

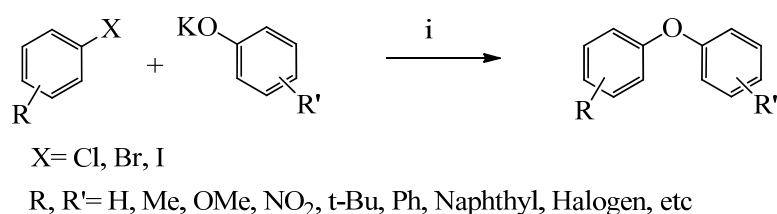
3.1.3.1 Objectives

Even though the significant improvement achieved, almost all these methods reported so far are lack of general applicability. The use of metals and/ or noble metal as catalysts with highly expensive ligands along with harsh reaction conditions limits to implement their application for the commercial-scale productions. However, the development of more general and cost effective ligand free catalysts for O-arylation of phenol, which is

equally applicable to electron-deficient, electronically neutral, and electron-rich aryl halides is still challenging and an active research area, which enable aryl ether formation under much milder, more efficient, environment friendly conditions compared to the classical Ullmann and Goldberg reactions.^{12b} This section describes a novel ligand free, highly efficient, an inexpensive and general method for the synthesis of diaryl ethers in a good to excellent yield from the cross coupling reactions of a wide range of electron-deficient, electronically neutral and electron-rich aryl halides with the various substituted potassium salts of various substituted phenols over ecofriendly, heterogeneous reusable copper fluorapatite (CuFAP) catalyst in the presence of N-Methyl 2-pyrrolidone (NMP) as a solvent at 120 °C (**Scheme 9**).

3.1.4 Results and discussion

We have developed the protocol for the Ullmann cross-coupling reactions, bromobenzene and potassium salt of phenol catalyzed by CuFAP was selected as a model reaction for optimizing the reaction conditions. Initially, we studied the effect of solvent on the cross coupling reaction.



Scheme 9: *Reagents and reaction conditions:* (i) substituted aryl halide (1 mmol), substituted potassium phenoxide (1.1 mmol), NMP (1 mL), CuFAP (100 mg), 120 °C, 3-16 h.

The reactions were carried out in various solvents at a different temperature by taking bromobenzene (1 mmole) and potassium salt of phenol (1.1 mmole) in the presence of

100 mg CuFAP catalyst, however, only NMP at 120 °C gives the cross-coupling product in a 93 % isolated yield (**Table 1**, entry **8**) whereas DMF, DMSO and Diglyme gives 8 %, 10 % and 15 % yields (**Table 1**, entries **5-7**), respectively. The desired cross coupling product formation was not observed during the reaction in THF, CH₃CN, toluene, and dioxane (**Table 1**, entries **1-4**).

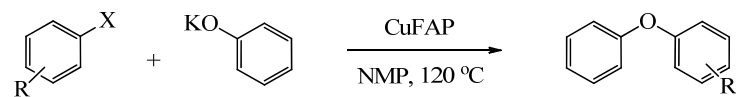
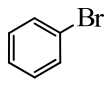
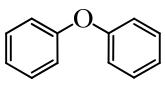
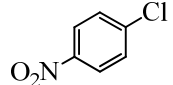
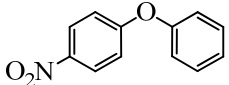
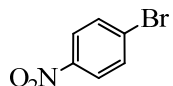
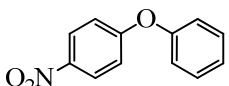
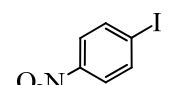
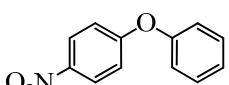
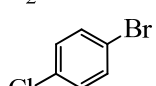
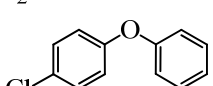
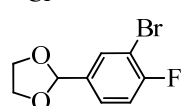
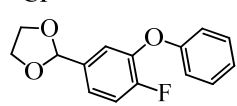
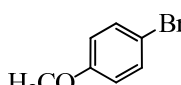
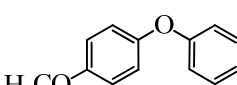
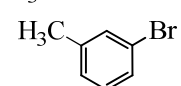
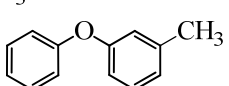
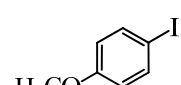
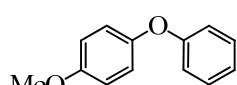
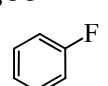
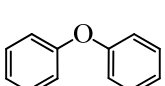
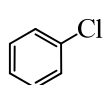
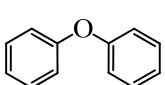
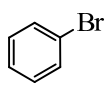
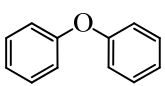
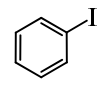
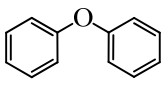
Table 1: Effect of solvent on the Ullmann diaryl etherification^a

Entry	Solvent	Temperature (°C)	Yield ^b (%)
1	THF	70	N.R.
2	CH ₃ CN	80	N.R.
3	Toluene	110	N.R.
4	Dioxane	100	N.R.
5	DMF	140	8
6	DMSO	150	10
7	Diglyme	150	15
8	NMP	120	93

^a Reaction conditions: bromobenzene (1 mmol), potassium phenoxide (1.1 mmol), solvent (1 mL), CuFAP (100 mg); ^bIsolated yields.

Results on the cross coupling product of bromobenzene and potassium salt of phenol in NMP solvent using CuFAP catalyst encourages us to investigate scope of CuFAP catalyst for Ullmann diaryl etherification. Therefore, a variety of electron-deficient, electron-rich and electronically neutral substituted haloarenes (fluoro, chloro, bromo and iodo) possessing a wide range of the functional group reacted with potassium phenoxide in NMP to obtained cross-coupling product in good to excellent yield; the results are shown in **Table 2**. The formation of desired cross-coupling product was not observed in absence CuFAP catalyst (**Table 2**, entry **1**).

Table 2: Diaryl etherification of potassium phenoxide with chloro, bromo or iodoarenes^a

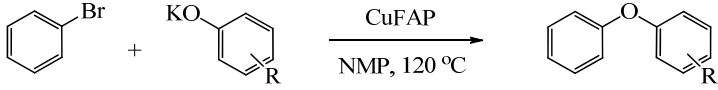
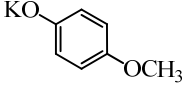
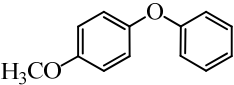
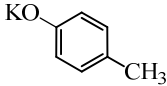
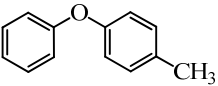
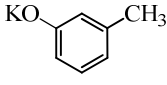
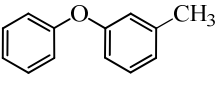
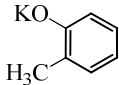
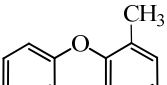
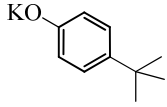
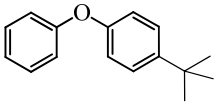
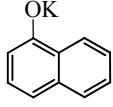
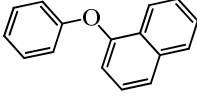
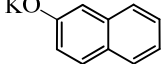
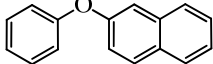
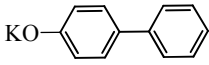
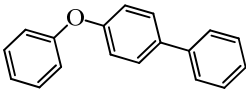
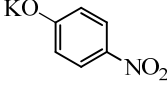
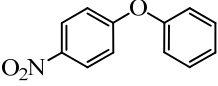
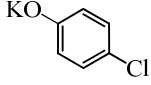
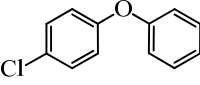
				
Entry	Aryl Halide	Product	Time (h)	Yield ^b (%)
1			8	N.R. ^c
2			5	91
3			4	94
4			3	94
5			3	93
6			5	92
7			5	87
8			5	90
9			4	89
10			15	N. R.
11			15	18
12			5	93
13			4	93

^a Reaction conditions: aryl halide (1 mmol), potassium phenoxide (1.1 mmol), NMP (1 mL), CuFAP (100 mg), 120 °C;

^b Isolated yields;

^c No reaction without CuFAP catalyst

Table 3: Ullmann diaryl etherification of bromobenzene with substituted potassium phenoxides^a

				
Entry	Phenoxide	Product	Time(h)	Yield ^b (%)
1			4	93
2			5	92
3			6	90
4			5	87
5			5	88
6			6	89
7			6	86
8			4	87
9			16	15
10			6	82

^a Reaction conditions: bromobenzene (1 mmol), substituted potassium phenoxide (1.1 mmol), NMP (1 mL), CuFAP (100 mg), 120 °C

^b Isolated yields

The electron-deficient aryl halide such as 4-nitrochlorobenzene, 4-nitrobromobenzene, 4-nitroiodobenzene, 4-chlorobromobenzene, and 3-bromo, 4-fluoro benzaldehydeacetal (**Table 2**, entries **2-6**) reacted with potassium phenoxide to provide an excellent yield to the desired cross coupling product in the short reaction time.

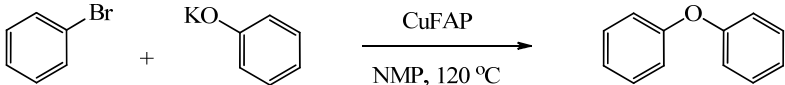
However, the electron-rich and electronically neutral aryl halides such as 4-bromoanisole, 3-bromotoluene, 4-iodoanisole (**Table 2**, entries **7-9**) and bromobenzene, iodobenzene, (**Table 2**, entry **12 and 13**) respectively, coupled with potassium phenoxide without any difficulties to obtain the corresponding cross coupling product in moderate to good yield with longer reaction time; while chlorobenzene provides very poor yield (**Table 2**, entry **11**) fluorobenzene gave no coupled product (**Table 2**, entry **10**).

To explore the scope of this methodology over CuFAP catalyst for electron-deficient, electronically neutral and electron-rich potassium salt of various substituted phenols such as 4-methoxy phenol, 4-methylphenol, 3-methylphenol, 2-methylphenol, 4-*tert*-butylphenol, α -naphthol, β -naphthol, 4-phenylphenol, 4-nitrophenol, 4-chlorophenol were successfully coupled with bromobenzene to give the corresponding diaryl ethers in good to excellent yields (**Table 3**, entries **1-10**), however, poor yield was obtained in case of potassium salt of 4-nitro phenol in long reaction time (**Table 3**, entry **9**).

The recyclability of CuFAP catalyst for the Ullmann diaryl etherification was investigated using bromobenzene and potassium phenoxide as substrate in NMP solvent at 120 °C, results are summarized in **Table 4**. The catalyst was recovered quantitatively by filtration, washed, dried and reused for several times without loss of catalytic activity (**Table 4**, entries **1-5**). The isolated yield obtained for cross coupling product even after fourth recycle of CuFAP catalyst (**Table 4**, entries **2-5**) is very much consistent with

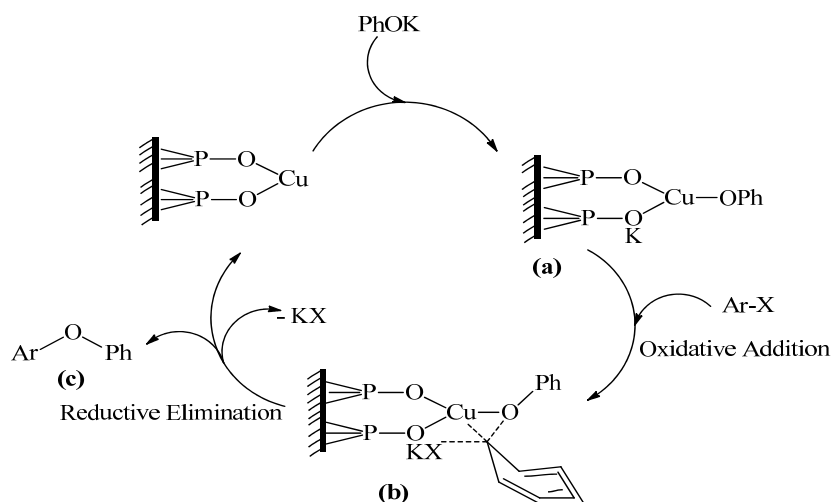
fresh catalyst (**Table 4**, entry **1**). These results clearly indicate that the reused CuFAP catalyst shows excellent performance for the Ullmann diaryl etherification.

Table 4: Recyclability studies of CuFAP catalyst for the Ullmann diaryl etherification^a

	
Entry	Yield ^b (%)
1	93
2	92
3	92
4	91
5	90

^a Reaction conditions: bromobenzene (1 mmol), potassium phenoxide (1.1 mmol), NMP (1 mL), CuFAP (100 mg), 120 °C, 5 h, Catalyst Recovery (%) = 97 ± 2

^b Isolated yields.



Scheme 10: Possible mechanism for the Ullmann diaryl etherification reaction over CuFAP catalyst.

According to the previous research work over CuFAP catalyst for the N-arylation of heterocycles,¹⁶ the possible mechanism proposed in **Scheme 10** for O-arylation may involve the CuFAP catalyzed nucleophilic substitution that proceeds via the formation of

the complex **(a)** with potassium phenoxide and then subsequently onto the oxidative addition of aryl halide via the formation of another complex **(b)** followed by the instantly in situ reductive elimination to release the diaryl ether product **(c)** as well as CuFAP catalyst in its original form (to recycle again).

3.1.5 Conclusion

In conclusion, a novel ligand free, highly efficient and an inexpensive method has been developed by using ecofriendly, heterogeneous reusable copper fluorapatite (CuFAP) catalyst for the synthesis of Ullmann diaryl ethers from the cross coupling reaction of the various substituted aryl halides with potassium salts of various substituted phenols in the presence of *N*-Methyl 2-pyrrolidone (NMP) as a solvent at 120 °C. The protocol obtained corresponding cross coupling products in good to excellent yield. The CuFAP catalyst recovered by simple filtration of the reaction mixture and reused several times without loss of catalytic activity.

3.1.6 Experimental section

3.1.6.1 General experimental procedure for Ullmann diaryl etherification:

Arylhalide (1 mmol), potassium salt of phenol (1.1 mmol), NMP (1 mL) and CuFAP catalyst (100 mg) were taken in 10 mL round bottom flask and stirred in nitrogen atmosphere at 120 °C for 3-16 h (**Table 2** and **3**) and progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was cooled to room temperature and diluted with 20 mL ethyl acetate followed by filtration to recover the catalyst. The filtrate was concentrate in vacuo to get the crude product which was further purified by column chromatography on silica gel (hexane/ ethyl acetate: 80/ 20) to afford diaryl ethers product.

Section II

Base promoted synthesis of diaryl ethers by cross-coupling of phenols with arylboronic acids

3.2.1 Introduction

Diaryl ethers are key structural motifs (**Fig. 1**) found in a variety of naturally occurring biologically and medicinally active compounds such as perrottetine (**1**),¹⁷ riccardin B (**2**),¹⁸ and K-13 (**3**).¹⁹ The importance of diaryl ether motifs in cyclic peptide formation has been reviewed by Rama Rao et al.²⁰ The diaryl ether structural motifs play a vital role not only in life science but also in agriculture to prevent various weed-killing chemicals.²¹

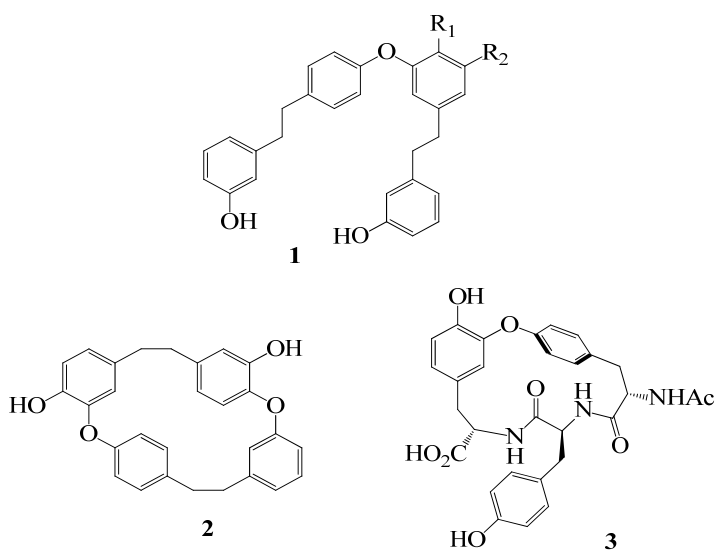


Fig. 1: Examples of the diaryl ether motif in natural products R₁ and R₂ in **1**= H, OH, OMe

The classic Ullmann coupling reaction for the synthesis of diaryl ethers has been extensively reported. However, its wide application for the synthesis of biologically active molecules containing diaryl ether motifs has been restricted because of the high reaction temperature (125–300 °C) and the long reaction time at which many functional

groups are unstable and/or the racemization of the amino acid moieties occurs, resulting in a lower yield of the desired product. Also, the requirement for copper complexes in excess quantities leads to the problem of waste disposal.²² Although, significant progress has been achieved,^{23–30} almost all of the reported methods are not practical approaches for the synthesis of biologically active compounds possessing sensitive functional groups.

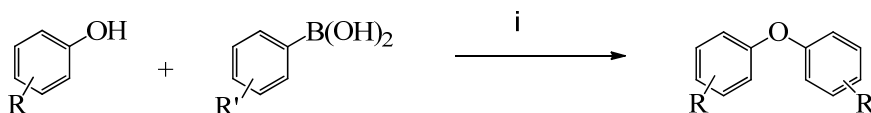
Arylboronic acid is used to introduce a phenyl ring to various biologically active compounds.³¹ Also, carbon–heteroatom bond forming reactions of arylboronic acids with amines,³² N-hydroxyphthalimides,³³ amides, imides,³⁴ and N-heterocycles,³⁵ to give the corresponding products have been reported in the literature.

3.2.2 Review of literature

To the best of our knowledge so far only two researcher, Evan *et al.*^{36a} and Chan *et al.*^{36b} have been reported the arylation of phenol with arylboronic acid over $\text{Cu}(\text{OAc})_2$ catalyst in presence of triethyl amine or pyridine as base and/or as ligand and DCM as solvent.

Evan's approach^{36a}

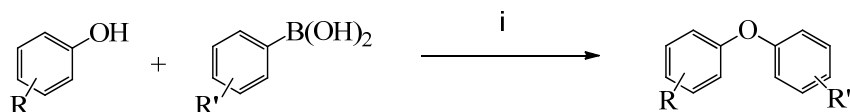
In this approach, Evan *et al.* synthesized the thyroxine derivative via diaryl ethers synthesis from the various substituted phenols and aryl boronic acids over stoichiometric amount of $\text{Cu}(\text{OAc})_2$ catalyst and an excess of triethylamine as base and/ or ligand at room temperature (**Scheme 11**).



Scheme 11: Reagents and reaction conditions: (i) Phenol (2 equiv), boronic acid (1 equiv), TEA (5 equiv), $\text{Cu}(\text{OAc})_2$ (2–3 equiv), DCM, RT, 18 h.

Chan's approach^{36b}

In this approach, Chan *et al.* synthesized the diaryl ethers from the various substituted phenols and aryl boronic acids over stoichiometric amount of $\text{Cu}(\text{OAc})_2$ catalyst and an excess of triethylamine/ Pyridine as base and/ or ligand at room temperature(**Scheme 12**).



Scheme 12: Reagents and reaction conditions: (i) Phenol (2 equiv), boronic acid (1 equiv), TEA/ Pyridine (5-10 equiv), $\text{Cu}(\text{OAc})_2$ (2-3 equiv), DCM, RT, 24-72 h.

3.2.3 Present work

3.2.3.1 Objectives

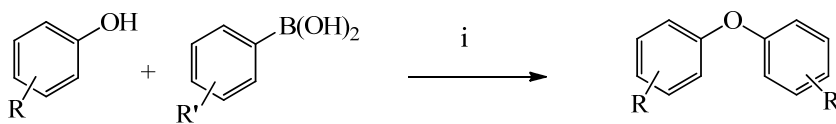
There are only two methods available in the literature for the O-arylation of phenols with aryl boronic acids, which suffer from the various drawbacks such as use of stoichiometric/excess amount of the catalyst as well as organic base (triethylamine or pyridine), long reaction time and hence, economically not feasible to implement their application for the commercial-scale productions. With the objective to overcome drawbacks of the reported methods, the section describes the O-arylation of phenols with aryl boronic acids in the presence of Cs_2CO_3 as base over copper fluorapatite as a heterogeneous and recyclable catalyst under mild reaction conditions.

3.2.4 Results and discussion

Being that diaryl ether motifs are key constituent of the structural backbone of many pharmaceutical compounds, the construction of their structural units under mild and

ligand-free reaction conditions compared to those of the classic Ullmann and Goldberg arylation³⁷ has attracted the attention of researchers world wide. Hence, this section describes the first report of a recyclable, heterogeneous copper fluorapatite catalyzed coupling reaction of phenols with arylboronic acids in the presence of Cs_2CO_3 as a base under mild and ligand-free reaction conditions.

As part of our continuous efforts to develop green, ecofriendly, general and cost effective method for organic transformation,³⁸ we have reported highly efficient, cost effective, general and milder method for the synthesis of diaryl ethers in good to excellent yield from the cross coupling reactions of a wide range of substituted phenols with substituted arylboronic acids over ecofriendly, heterogeneous, reusable, ligand-free copper fluorapatite (CuFAP) catalyst in the presence of Cs_2CO_3 in methanol solvent at ambient reaction conditions (**Scheme 13**).



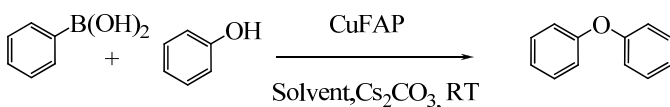
R & R' = H, Me, OMe, NO_2 , Ph, Naphthyl, Halogen, etc

Scheme 13: *Reagents and reaction conditions:* (i) substituted phenyl boronic acid (0.50 mmol), substituted phenols (0.55 mmol), Cs_2CO_3 (0.75 mmol), Methanol (3 mL), CuFAP (50 mg), room temperatures, 8 h

To develop a protocol for C-O cross coupling reactions, the reaction of phenol and phenyl boronic acid was initially catalyzed by the CuFAP catalyst in the presence of Cs_2CO_3 as a base in a methanol solvent under ambient conditions to give a 90 % yield of biphenyl ether. The results on this substrate under ambient conditions using the ligand-

free CuFAP catalyst, prepared as per the literature procedure³⁹ allowed us to select it as a model reaction to optimize the reaction conditions. In order to optimize the reaction conditions, the C-O coupling reaction was performed in various solvents such as methanol, ethanol, dichloromethane, dichloroethane, ethyl acetate, and acetonitrile. Methanol resulted in a high yield of the cross-coupling product, which may be due to it having the most polar and protic character (**Table 5**, entry **6**) as compared to ethanol, dichloromethane, dichloroethane, ethyl acetate, and acetonitrile as solvents, which result in a moderate yield (**Table 5**, entries **1- 5**).

Table 5: Effect of solvents on the diaryl etherification of phenol with phenyl boronic acid^a

		
Entry	Solvent	Yield ^b (%)
1	Acetonitrile	67
2	Ethyl acetate	54
3	Dichloromethane	31
4	Dichloroethane	28
5	Ethanol	79
6	Methanol	90

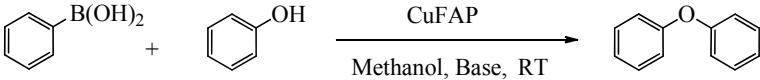
^a Reaction conditions: Phenyl boronic acid (0.50 mmol), Phenol (0.55 mmol), Cs₂CO₃ (0.75 mmol), solvent (3 mL), catalyst (50 mg), at room temperatures, 8 h.

^b Isolated yields.

After achieving a high yield in the methanol solvent, studies focused on the investigation of the influence of various bases on the C-O coupling reaction, with Cs₂CO₃ found to be the most effective base to achieve a high yield (**Table 6** entry **7**) as compared to NaOH, KOH, Na₂CO₃, and K₂CO₃ (**Table 6**, entries **3-6**). The high product yield when using Cs₂CO₃ as the base may be due to the increasing electropositive of group IA cations in the order Cs > K > Na, which facilitates the deprotonation of the phenol through the

increasing electronegativity of the carbonate salt in the solvent as well as the high solubility of Cs_2CO_3 in the methanol solvent (**Table 6**). However, no reaction (N. R.) was observed when using organic bases such as Et_3N and pyridine (**Table 6**, entry **1** and **2**). The promising results on the optimized reaction condition using Cs_2CO_3 as a base in methanol solvent over the ligand free CuFAP catalyst encourage us to investigate the feasibility of this methodology to wide range of substituted phenol and substituted arylboronic acid for the diaryl etherification.

Table 6: Effect of the base on the diaryl etherification of phenol with phenyl boronic acid and the solubility of inorganic bases in methanol^a

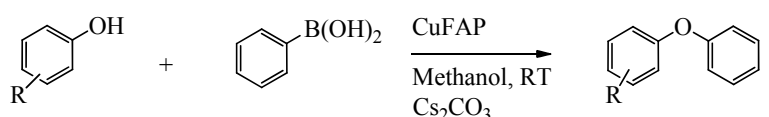
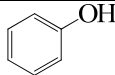
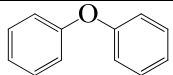
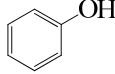
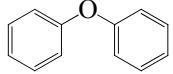
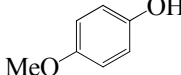
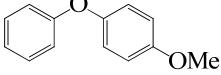
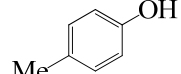
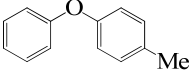
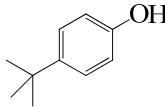
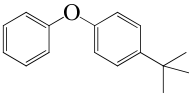
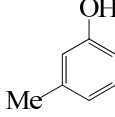
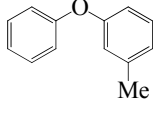
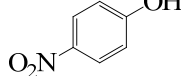
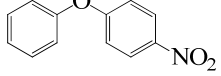
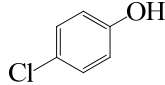
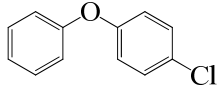
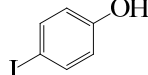
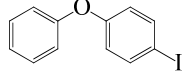
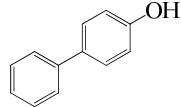
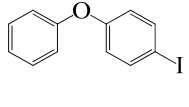
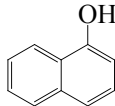
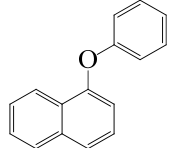
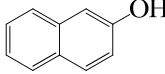
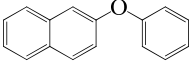
			
Entry	Base	Solubility in MeOH (g per 100 mL) at RT	Yield ^b (%)
1	Triethyl amine	-	N.R.
2	Pyridine	-	N.R.
3	NaOH	23.8 ^{42a}	24
4	KOH	28.17 ^{42b,c}	31
5	Na_2CO_3	0.17 ^{42c}	53
6	K_2CO_3	4.84 ^{42c,d}	69
7	Cs_2CO_3	44.52 ^{42c}	90

^a Reaction conditions: phenyl boronic acid (0.50 mmol), phenol (0.55 mmol), base (0.75 mmol), methanol (3 mL), CuFAP (50 mg), room temperature, 8 h.

^b Isolated yields. ^c Converted from g per 100 g to g per 100 mL

As shown in **Table 7**, a variety of the substituted phenols possessing a variety of the functional group reacted with phenyl boronic acid with Cs_2CO_3 as a base in methanol solvent to get diaryl ether as product in moderate to excellent yield. No desired cross-coupling product was obtained during the same reaction condition in the absence of CuFAP (**Table 7**, entry **1**).

Table 7: Diaryl etherification of substituted phenols with phenyl boronic acid^a

				
Entry	Substituted Phenols	Product	Time (h)	Yield ^b (%)
1			24	N.R. ^c
2			8	90
3			6	96
4			6	94
5			7	92
6			8	87
7			24	49
8			12	80
9			12	84
10			10	86
11			10	84
12			10	82

^a Reaction conditions: Phenyl boronic acid (0.50 mmol), substituted phenols (0.55 mmol), Cs₂CO₃ (0.75 mmol), Methanol (3 mL), catalyst (50 mg), at room temperatures, 8 h.

^b Isolated yields.

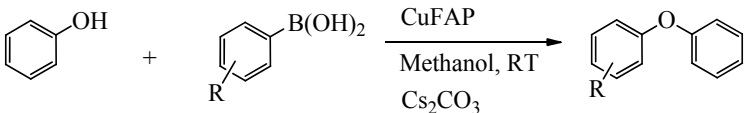
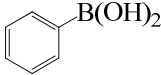
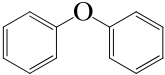
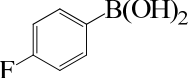
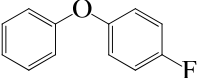
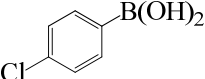
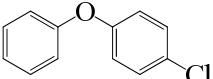
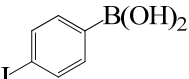
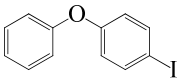
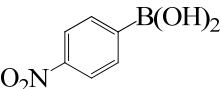
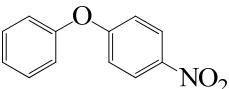
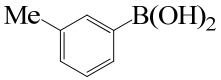
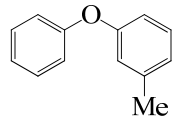
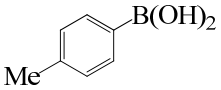
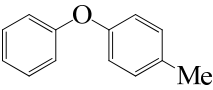
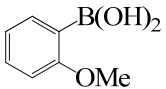
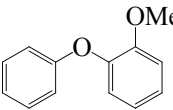
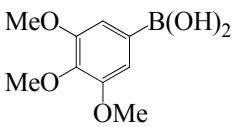
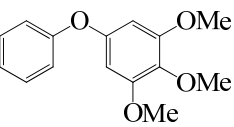
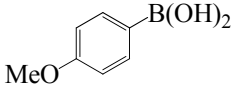
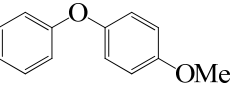
^c No reaction with CuFAP catalyst without base (Cs₂CO₃) and vice a versa

The phenols with electron donating group such as, 4-methoxy phenol, 4-methyl phenol, 4-*ter*-butyl phenol, (**Table 7**, entries **3-5**) provided an excellent yield as compare to phenol and 3-methylphenol (**Table 7**, entry **2** and **6**) while phenols with electron withdrawing group such as 4-chlorophenol and 4-Iodophenol provided moderated yields after long reaction time (**Table 7**, entry **8** and **9**) except in the case of 4-nitrophenol (**Table 7**, entry **7**) whereas 4-phenyl phenol, α -naphthol and β -naphthol also provided moderated yields (**Table 7**, entries **10-12**).

To widen the scope of the methodology using the ligand-free CuFAP catalyst for O-arylation, the coupling of various substituted arylboronic acids with phenol have been investigated; the results are summarized in **Table 8**. The substituted phenyl boronic acids with electron withdrawing group such as 4-fluorophenyl boronic acid, 4-chlorophenyl boronic acid, 4-iodophenyl boronic acid and 4-nitrophenyl boronic acid (**Table 8**, entries **2-5**) provided an excellent yield as compare to phenyl boronic acid (**Table 8**, entry **1**). However, substituted phenyl boronic acids with electron donating group such as 3-methylphenyl boronic acid, 4-methylphenyl boronic acid, 2-methoxyphenyl boronic acid, 3,4,5-trimethoxyphenyl boronic acid and 4-methoxyphenyl boronic acid were successfully coupled with phenol to give the corresponding diaryl ethers in moderated yield (**Table 8**, entries **6-10**).

The results in **Tables 7** and **8** indicate that the O-arylation cross coupling reaction is applicable to a large number of substrates having sensitive functional groups; however, the reaction time and the yield obtained are dependent on the nature of the substituents on the phenol as well on the arylboronic acids.

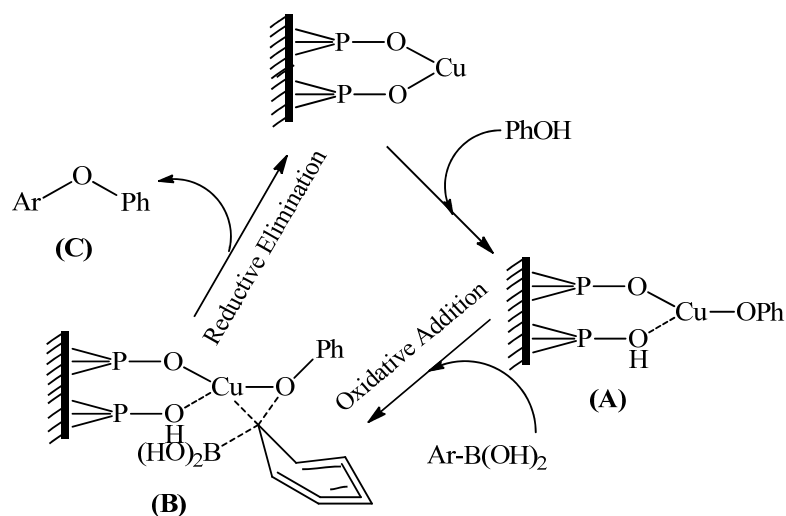
Table 8: Diaryl etherification of phenol with substituted arylboronic acids^a

				
Entry	Aryl boronic acids	Product	Time (h)	Yield ^b (%)
1			8	90
2			6	94
3			7	92
4			8	91
5			8	91
6			9	88
7			10	84
8			10	82
9			12	80
10			10	80

^a Reaction conditions: Aryl boronic acid (0.50 mmol), phenols (0.55 mmol), Cs₂CO₃ (0.75 mmol), Methanol (3 mL), catalyst (50 mg), at room temperatures, 8 h.

^b Isolated yields.

According to previous research work using the CuFAP catalyst for O-arylation,^{38a} N-arylation of heterocycles with chloro- and fluoroarenes³⁹ and N-arylation of heterocycles with bromo- and iodoarenes in the presence of base (K_2CO_3)^{40,41} the possible mechanism proposed in **Scheme 14** for the C-O cross coupling reaction may involve base promoted CuFAP catalyzed nucleophilic substitution that proceeds *via* the formation of the complex **(A)** and then the subsequent oxidative addition of phenyl boronic acid via the formation of another complex **(B)** followed by instant in situ reductive elimination to release the diaryl ether product **(C)** as well as the CuFAP catalyst in its original form to be recycled.

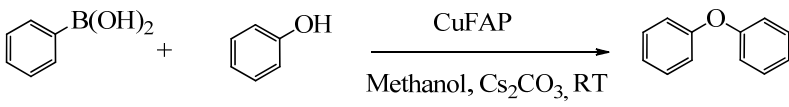


Scheme 14: Possible mechanism over ligand free CuFAP catalyst for the diaryl etherification.

The recyclability of the ligand-free CuFAP catalyst in the C–O cross coupling reaction was assessed using phenol and phenyl boronic acid with Cs_2CO_3 as a base in methanol solvent at room temperature; the results are summarized in **Table 9**. After the completion of the reaction, the catalyst was recovered quantitatively by filtration and recycled several

times, however, no loss of catalytic activity was observed even after the fourth cycle (**Table 9**, entry 5). The catalytic activity of the reused catalyst is very much comparable with that of the fresh catalyst (**Table 9**, entry 1), which clearly shows that no loss and/or leaching of copper occurred during the course of the reaction and the reused catalyst exhibits an excellent performance.

Table 9: Recyclability studies of ligand-free CuFAP catalyst for diaryl etherification of phenol with phenyl boronic acid^a

	
Entry	Yield (%) ^b
1	90
2	90
3	88
4	90
5	89

^a Reaction conditions: Phenyl boronic acid (0.50 mmol), Phenol (0.55 mmol), Base (0.75 mmol), methanol (3 mL), catalyst (50 mg), at room temperatures, 8 h.

^b Isolated yields.

3.2.5 Conclusion

In conclusion, a highly efficient method for the synthesis of diaryl ethers in good to excellent yields from the cross coupling reaction of substituted phenols with substituted aryl boronic acids has been developed over an inexpensive, ligand-free, recyclable, ecofriendly, heterogeneous copper fluorapatite (CuFAP) catalyst in the presence of Cs_2CO_3 as a base in a methanol solvent under ambient reaction conditions. The developed method is mild, general, simple, clean and applicable to a large number of substrates with sensitive functional groups. The CuFAP catalyst was recovered by filtration and recycled several times without loss of catalytic activity.

3.2.6 Experimental section

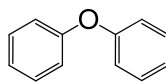
All chemicals and reagents were procured from commercial suppliers and used without further purification. The products were characterized using ^1H NMR and ^{13}C NMR spectra. NMR spectra of the products were obtained using a Bruker AC-200 MHz spectrometer with TMS as the internal standard. Column chromatography was performed using silica gel, Merck grade 60–120 mesh size. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F₂₅₄).

3.2.6.1 General experimental procedure for diaryl etherification:

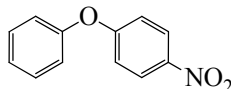
Arylboronic acid (0.50 mmol), phenol (0.55 mmol), Cs₂CO₃ (0.75 mmol), +methanol (3 mL) and CuFAP catalyst (50 mg) were taken in 10 mL round bottomed flask and stirred in nitrogen atmosphere at room temperature for 6-24 h (**Table 7** and **8**) and the progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was diluted with 10 mL methanol followed by filtration to recover the catalyst. The filtrate was concentrated in vacuo to get the crude product, which was further purified by column chromatography on silica gel using hexane/ethyl acetate mixture 90:10 to obtain diaryl ether product.

3.2.6.2 Spectral data for the diaryl ether compounds

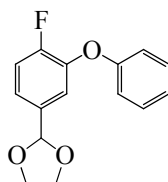
Diphenylether:



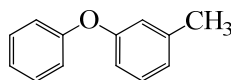
Colorless liquid; ^1H NMR (200 MHz, CDCl₃): δ 7.32-7.24 (m, 4H), 7.08-6.93 (m, 6H). ^{13}C NMR (200 MHz, CDCl₃): δ 157.21, 129.71, 123.19, 118.86. IR: 660, 725, 1240, 1498, 1610, 3021 cm⁻¹; GC-MS: 170, 94, 77, 65, 51.

1-nitro-4-phenoxybenzene:

Yellow solid; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 8.22 (d, $J=5\text{Hz}$ 2H), 7.47-7.25 (m, 3H), 7.10-6.98 (m, 4H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 163.36, 154.66, 142.59, 130.30, 125.92, 125.40, 120.53, 117.05; **IR**: 750, 858, 1250, 1370, 1495, 1604, 3058 cm^{-1} ; GC-MS: 215, 138, 122, 76, 51.

2-(4-fluoro-3-phenoxyphenyl)-1,3-dioxolane:

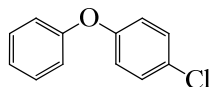
$^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.68 (s, 1H), 7.29-7.17 (m, 3H), 7.07-6.82 (m, 4H), 5.68(s, 1H), 4.07-3.90(m, 4H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 156.64, 154.41, 134.79, 131.96, 129.80, 126.93, 123.59, 120.00, 118.32, 114.65, 102.52, 65.34; **IR**: 650, 1090, 1250, 1509, 2091 cm^{-1} ; GC-MS: 261, 188, 110, 94, 73, 51.

1-Methyl-3-phenoxybenzene:

Colorless liquid; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.60-7.49 (m, 4H), 7.36-7.14 (m, 5H), 2.58 (s, 3H). $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 157.14, 139.90, 129.67, 124.02, 123.06, 119.54, 118.82, 115.87, 21.38; **IR**: 698, 738, 1260, 1487, 1607, 3049 cm^{-1} ; GC-MS: 184,

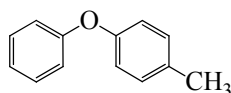
107, 93, 92, 76, 51.

1-Chloro-4-phenoxybenzene:



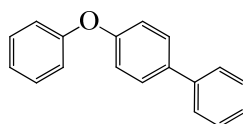
Colorless liquid; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.3-7.21 (m, 4H), 7.06 (m, 1H), 6.96-6.86 (m, 4H). $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 156.84, 155.92, 129.69, 128.16, 123.61, 120.01, 118.91; **IR**: 693, 784, 1235, 1496, 1581, 2932 cm^{-1} ; GC-MS: 204, 171, 94, 73, 50.

1-Methyl-4-phenoxybenzene:

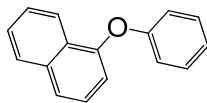


Colorless liquid; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.26-7.18 (m, 2H), 7.03 (m, 2H), 6.85 (m, 5H), 2.24 (s, 3H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 157.16, 154.04, 132.24, 129.58, 128.99, 122.14, 118.47, 117.68, 20.05; **IR**: 698, 740, 810, 1258, 1495, 1690, 3049 cm^{-1}

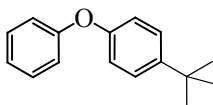
4-phenoxy-1,1'-biphenyl:



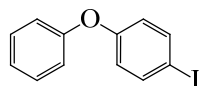
$^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.52-7.46 (m, 4H), 7.36-7.25 (m, 5H), 7.05-6.96 (m, 5H). $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 157.10, 156.81, 140.52, 136.24, 129.78, 128.77, 128.41, 126.88, 123.36, 119; **IR**: 712, 752, 1523, 1627, 3042 cm^{-1} ; GC-MS: 246, 169, 153, 93, 74, 65, 51.

1-phenoxynaphthalene:

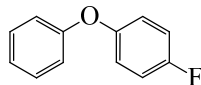
¹H NMR (200 MHz, CDCl₃): δ 8.16-8.11 (d, $J=5$ Hz 1H), 7.82-7.78 (d, $J=4$ Hz 1H), 7.57 (m, 1H), 7.43 (m, 2H), 7.17 (m, 1H), 7.03-6.86 (m, 6H); **¹³C NMR** (200 MHz, CDCl₃): δ 157.21, 156.57, 152.36, 134.27, 129.14, 127.10, 125.93, 122.48, 121.44, 117.89, 112.86; **IR**: 670, 790, 1370, 1506, 1619, 3058 cm⁻¹

1-(tert-butyl)-4-phenoxybenzene:

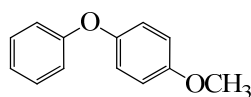
Colorless liquid; **¹H NMR** (200 MHz, CDCl₃): δ 7.25-7.36 (m, 4H), 6.96-7.01(m, 4H), 6.90 (m, 1H), 2.34 (s, 9H). **¹³C NMR** (200 MHz, CDCl₃): δ 157.56, 154.67, 146.10, 129.63, 126.52, 122.89, 118.43, 34.29, 31.48; **IR**: 700, 748, 1245, 1501, 1605, 2979 cm⁻¹

1-Iodo-4-phenoxybenzene:

Colorless liquid; **¹H NMR** (200 MHz, CDCl₃): δ 7.96 (m, 2H), 7.17 (m, 2H), 7.03 (m, 1H), 6.77 (m, 4H); **¹³C NMR** (200 MHz, CDCl₃): δ 162.68, 154.15, 142.12, 129.7, 129.09, 125.31, 124.79, 119.94, 118.29, 116.46.

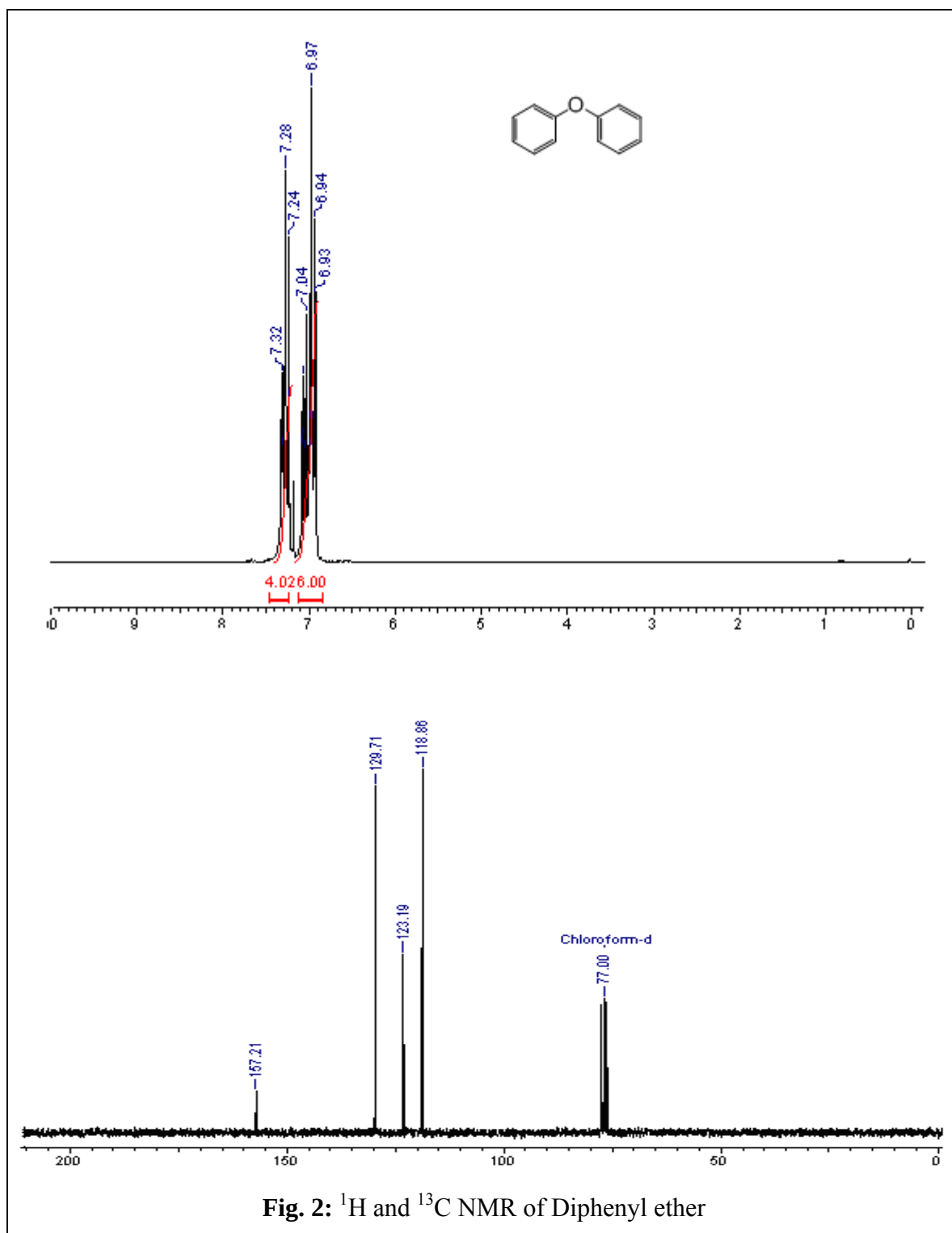
1-Fluoro-4-phenoxybenzene:

Colorless liquid; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.52 (m, 4H), 7.18 (m, 5H), $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 156.57, 129.08, 122.56, 118.22.

1-Methoxy-4-phenoxybenzene:

Colorless liquid; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.63 (m, 3H), 7.42 (m, 2H), 7.29 (m, 4H), 3.81 (s, 3H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 157.79, 154.68, 132.88, 130.21, 129.62, 122.77, 119.1, 118.31, 52.15.

3.2.7 Spectral data



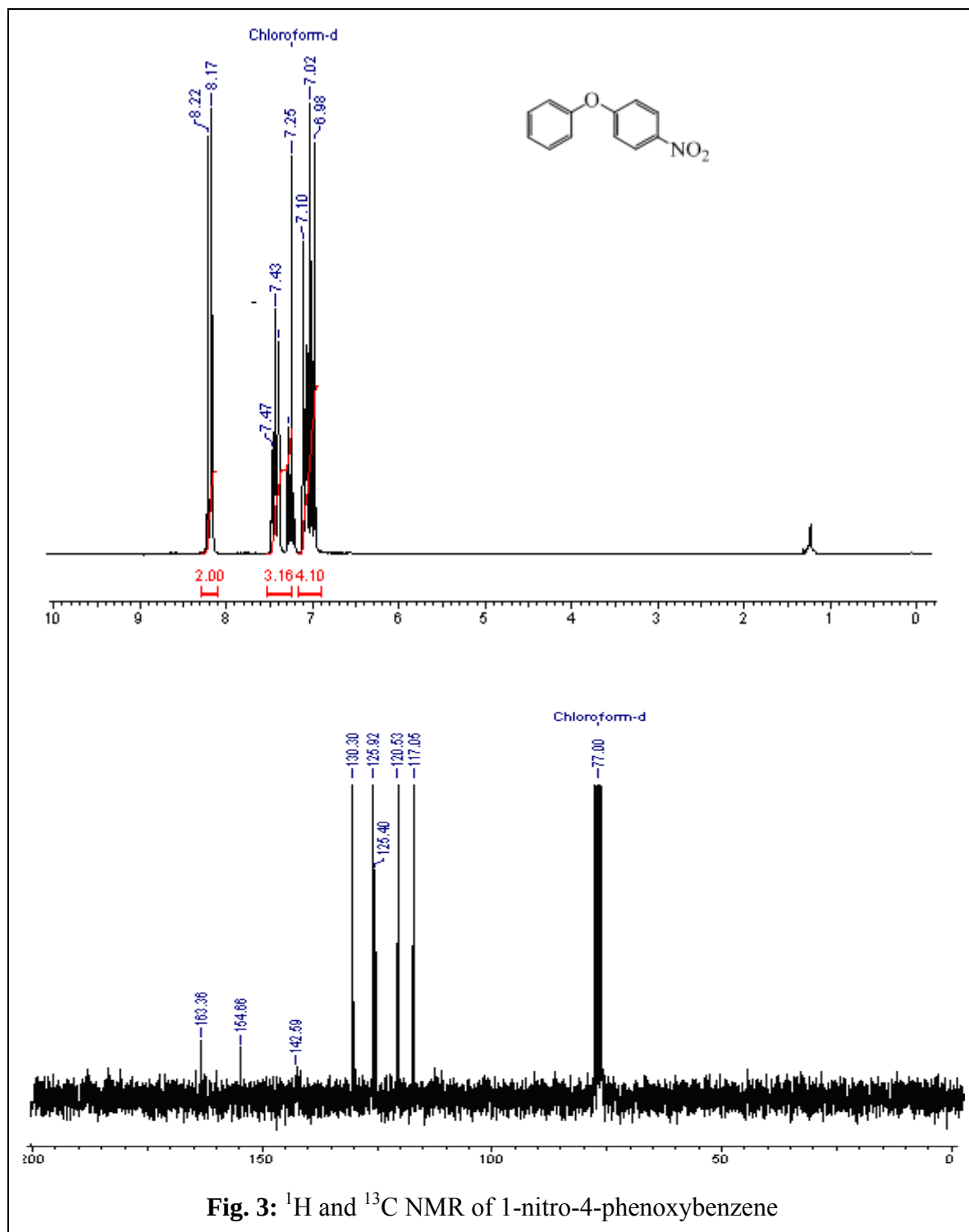


Fig. 3: ^1H and ^{13}C NMR of 1-nitro-4-phenoxybenzene

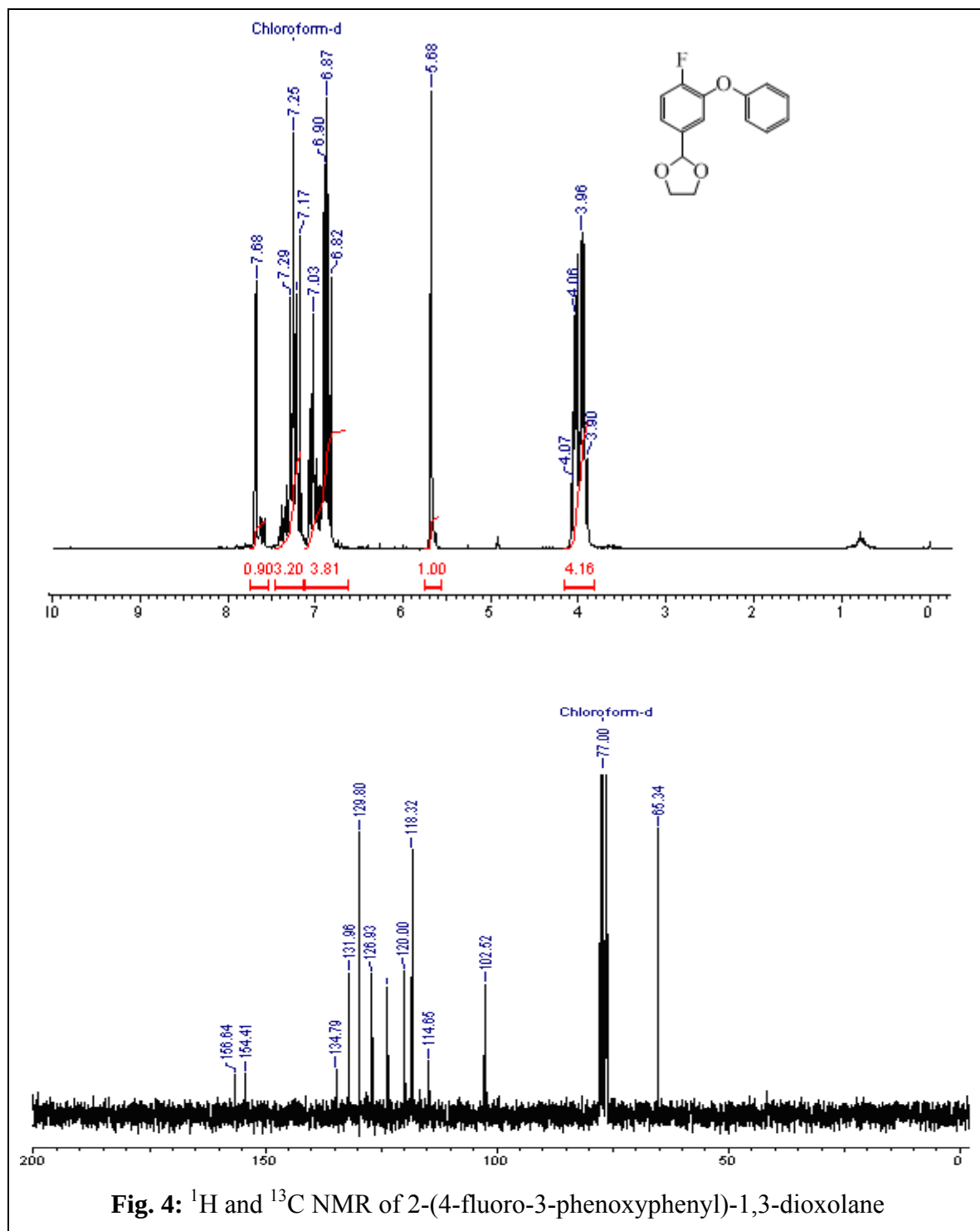
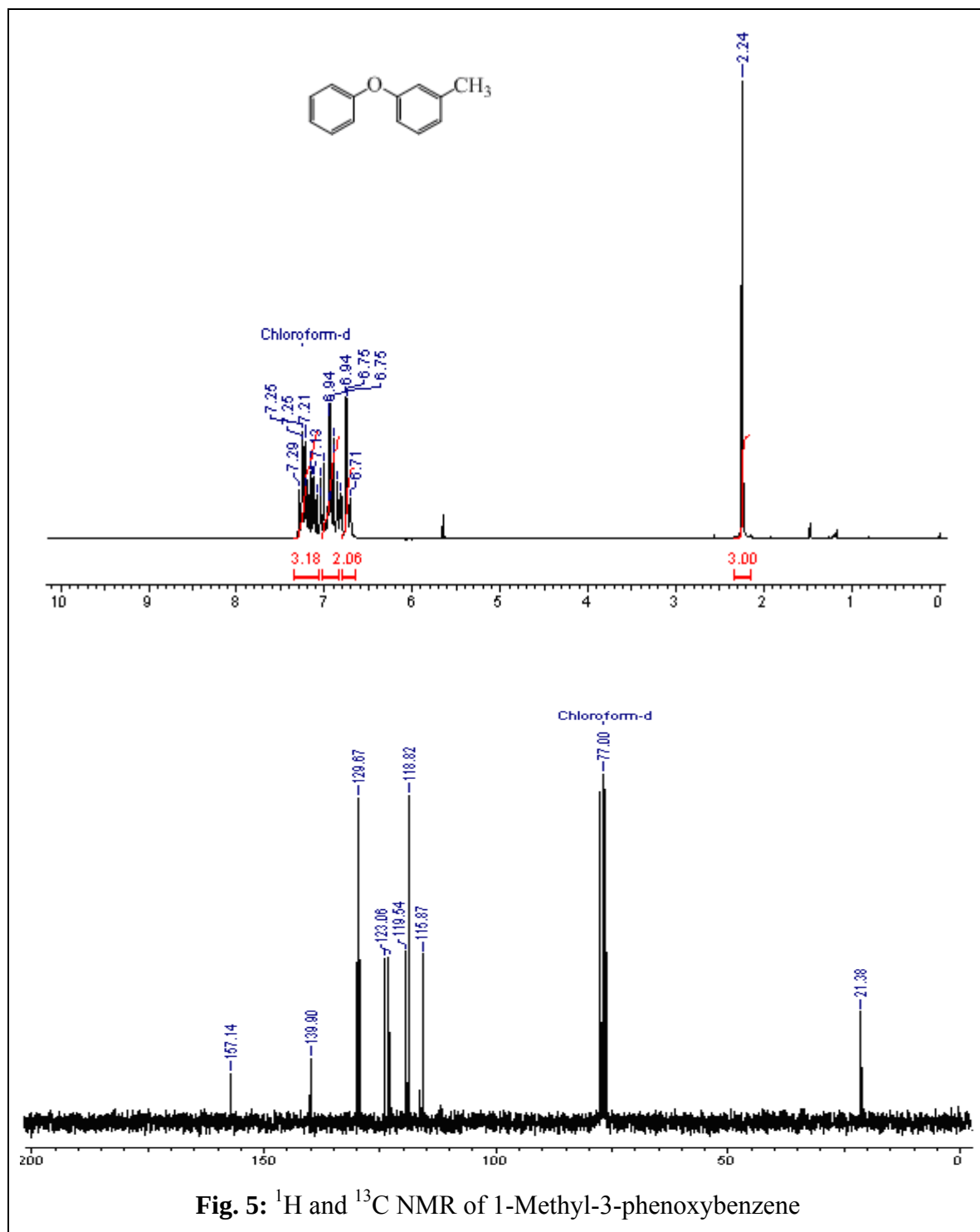
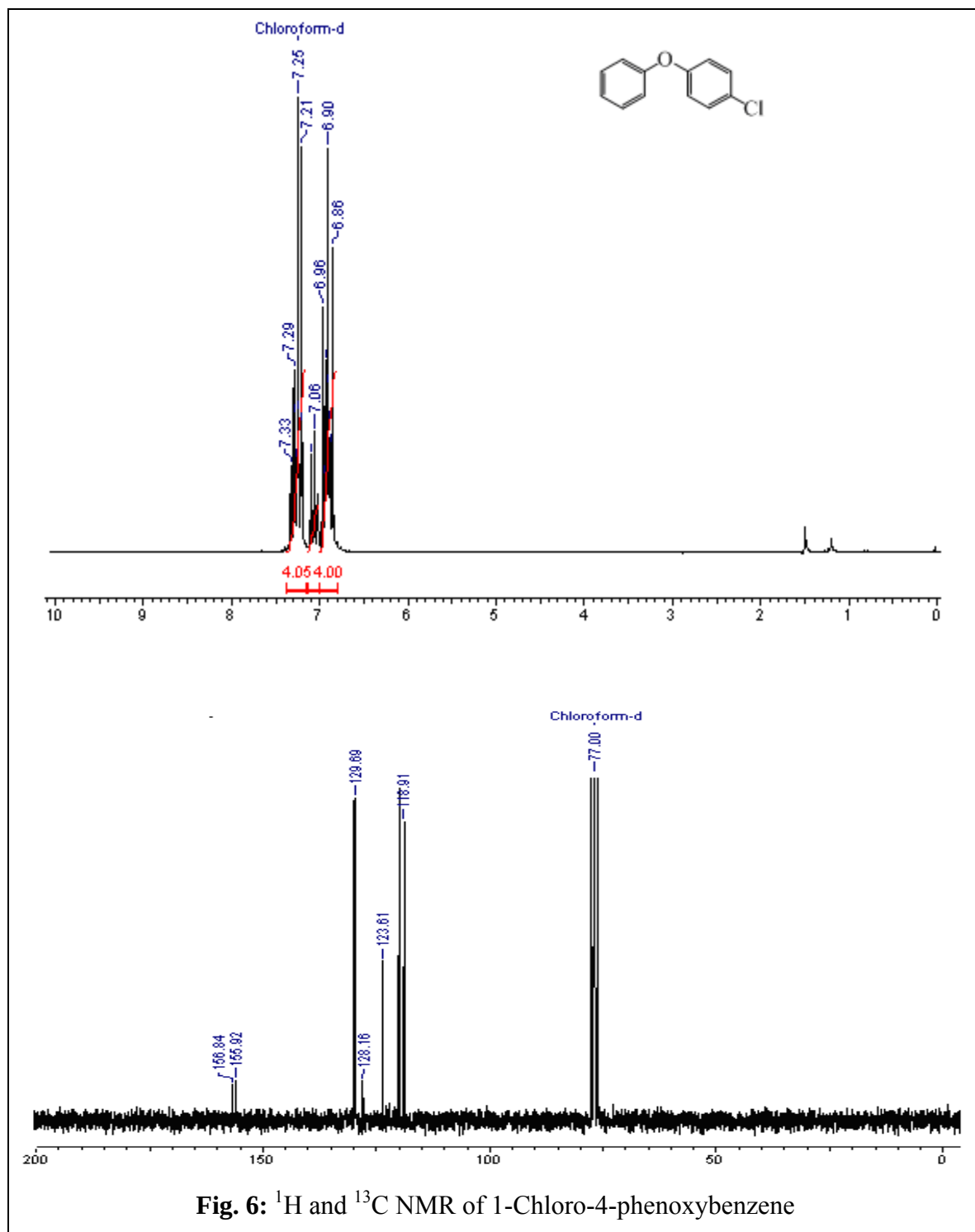
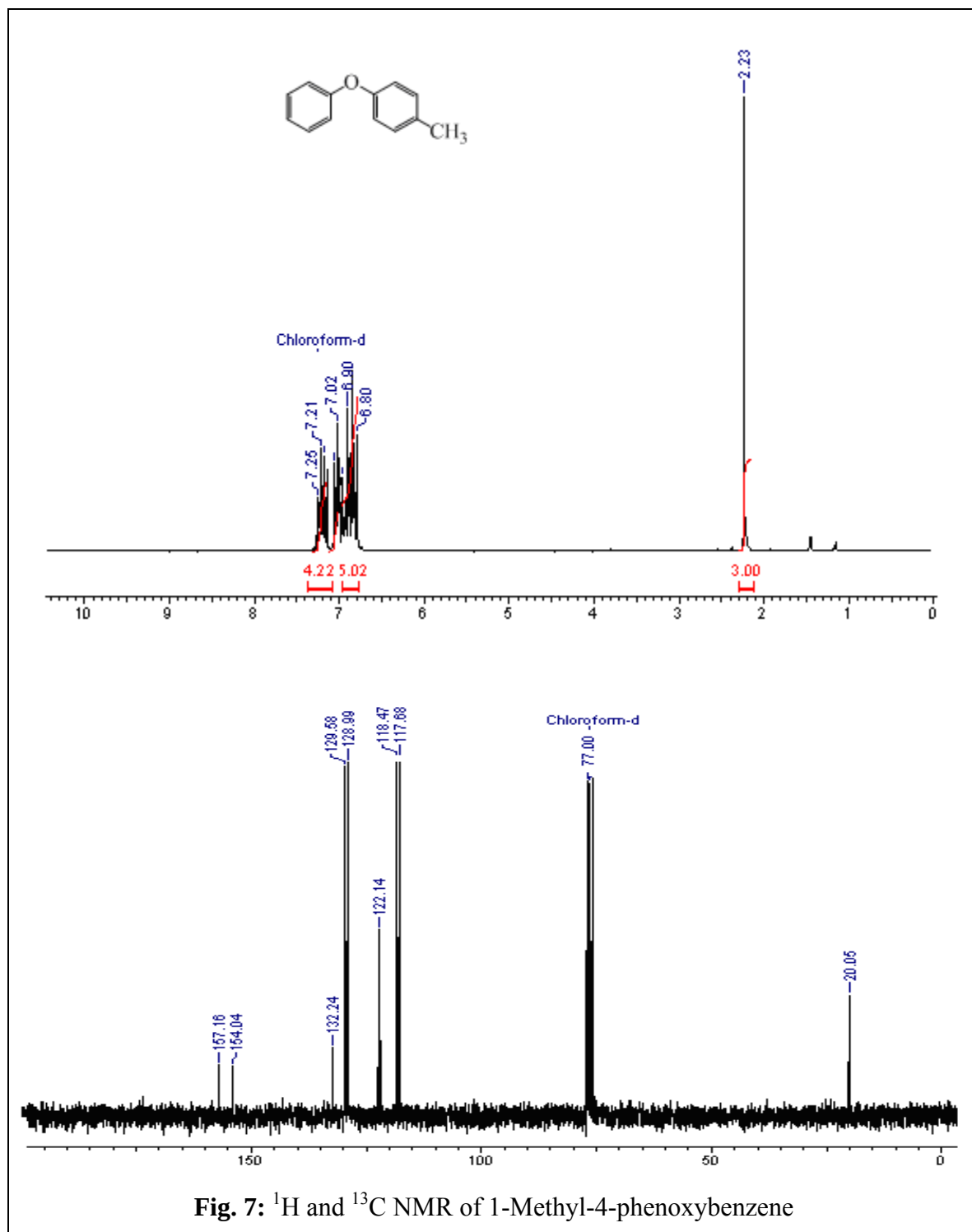
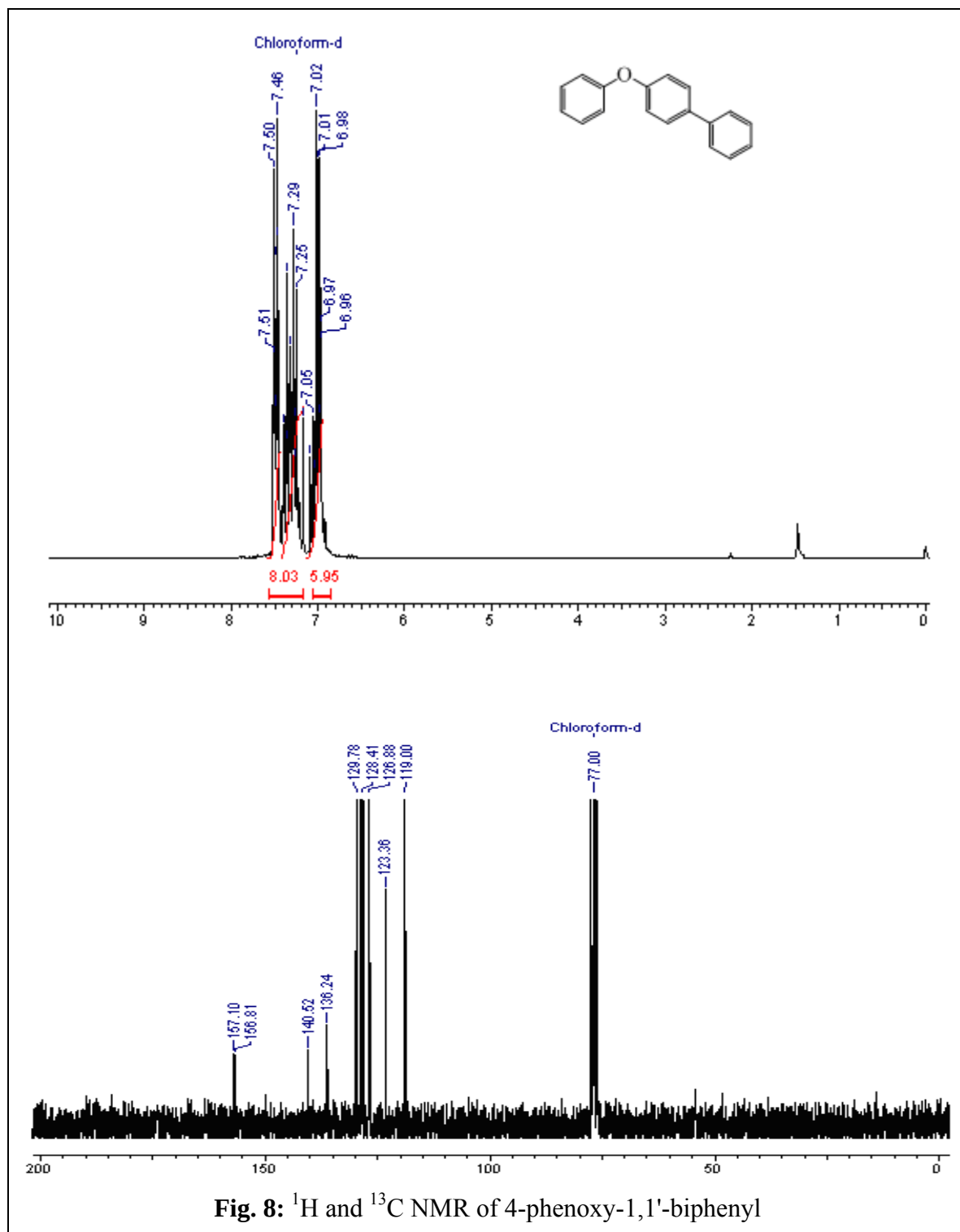


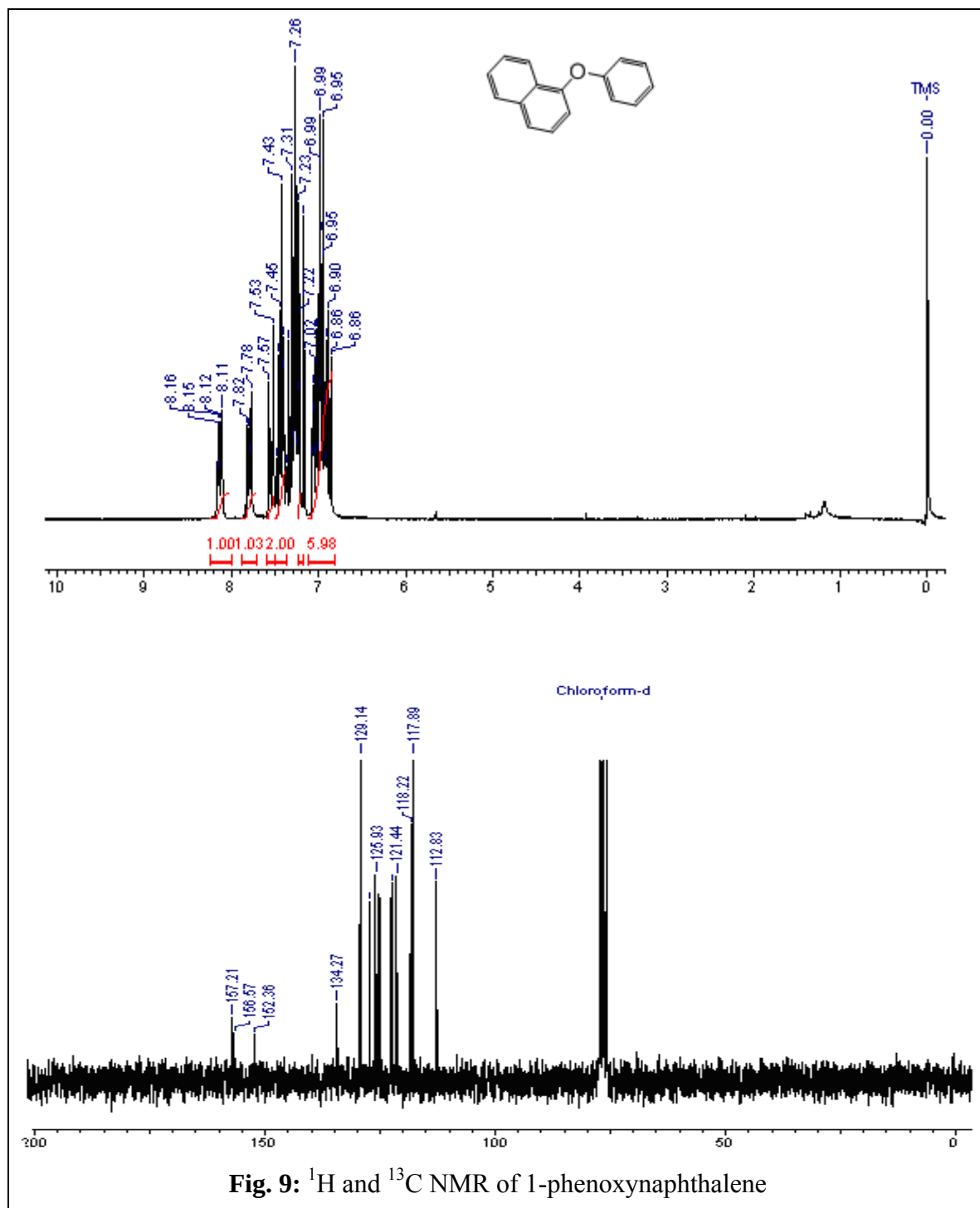
Fig. 4: ^1H and ^{13}C NMR of 2-(4-fluoro-3-phenoxyphenyl)-1,3-dioxolane

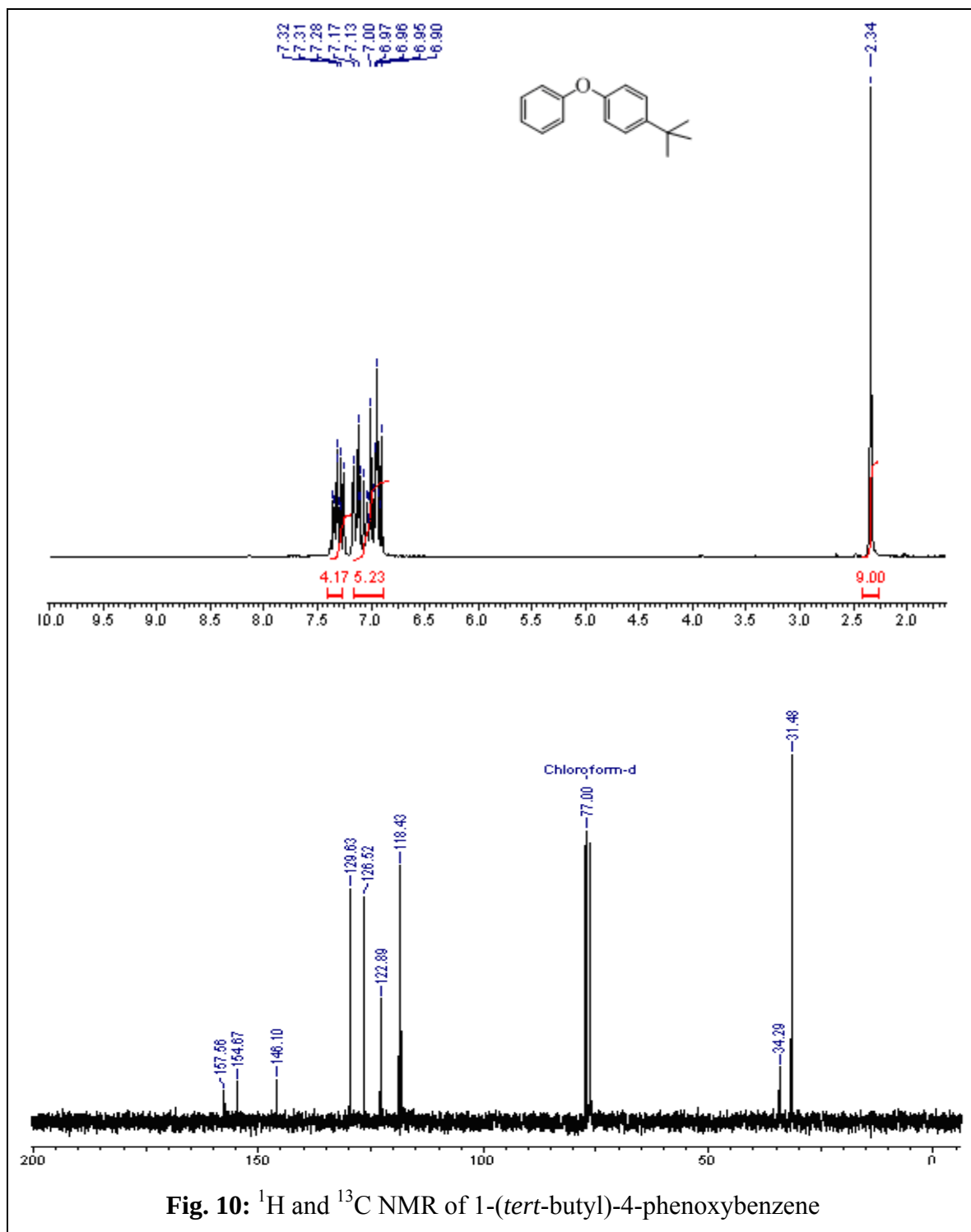


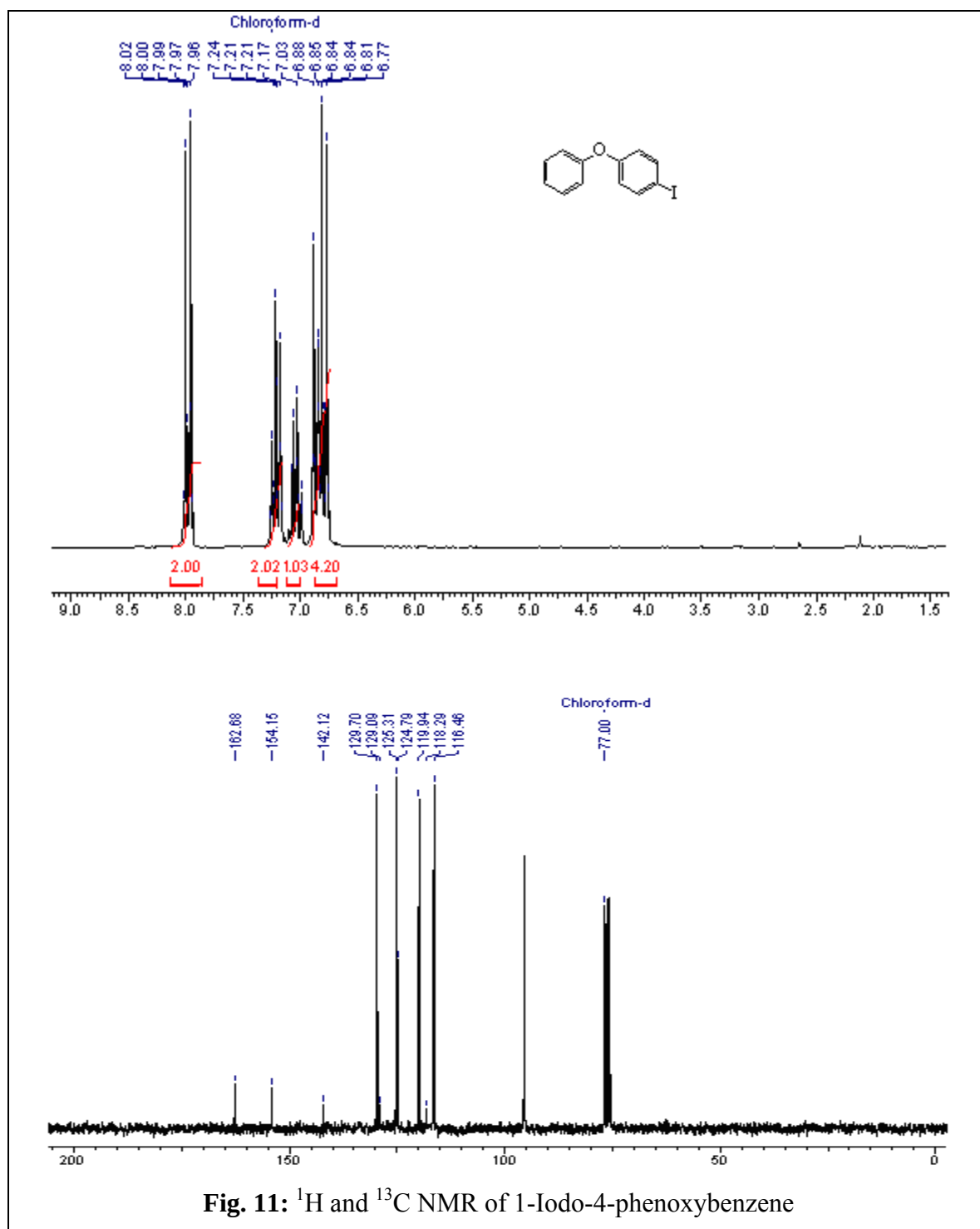


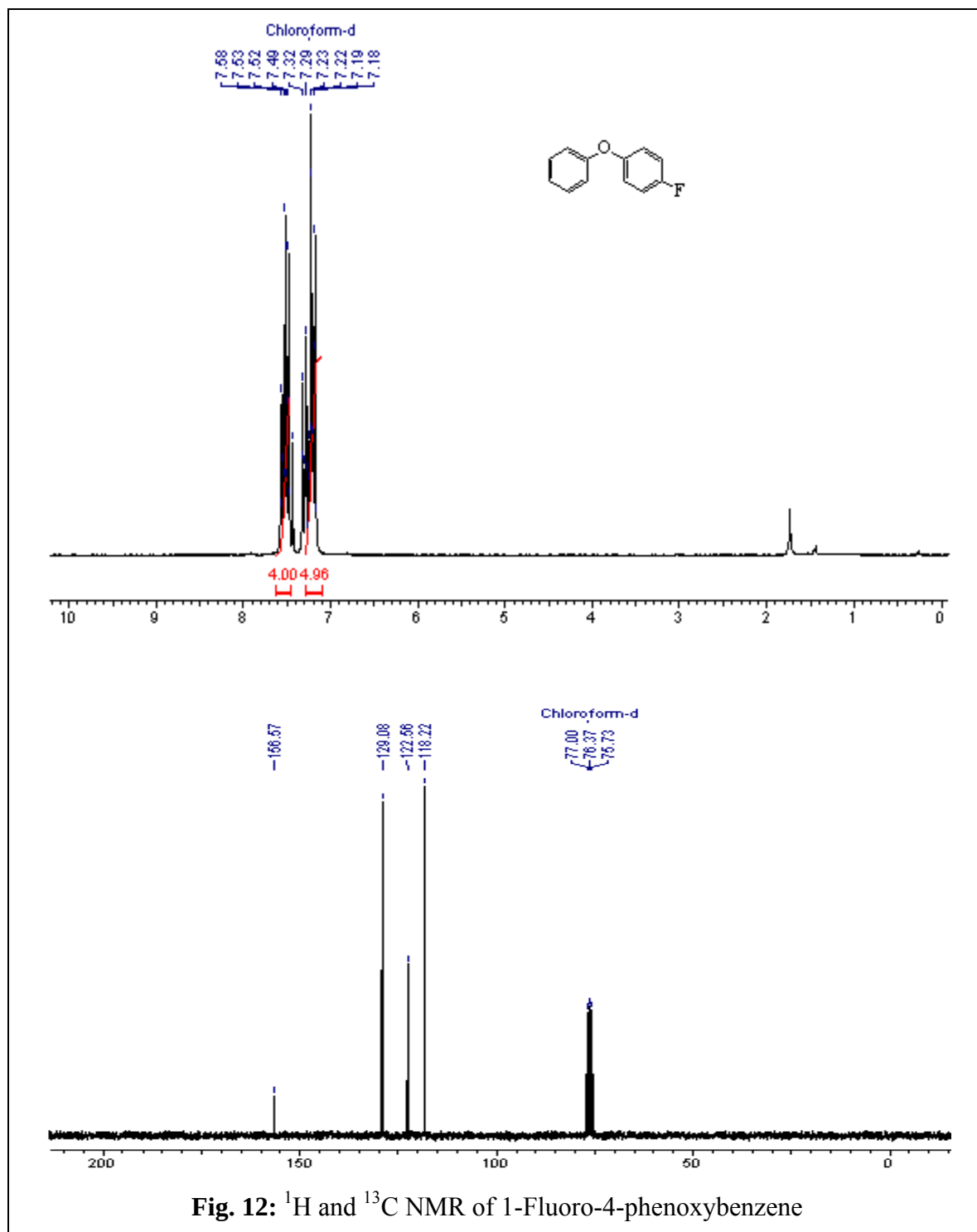


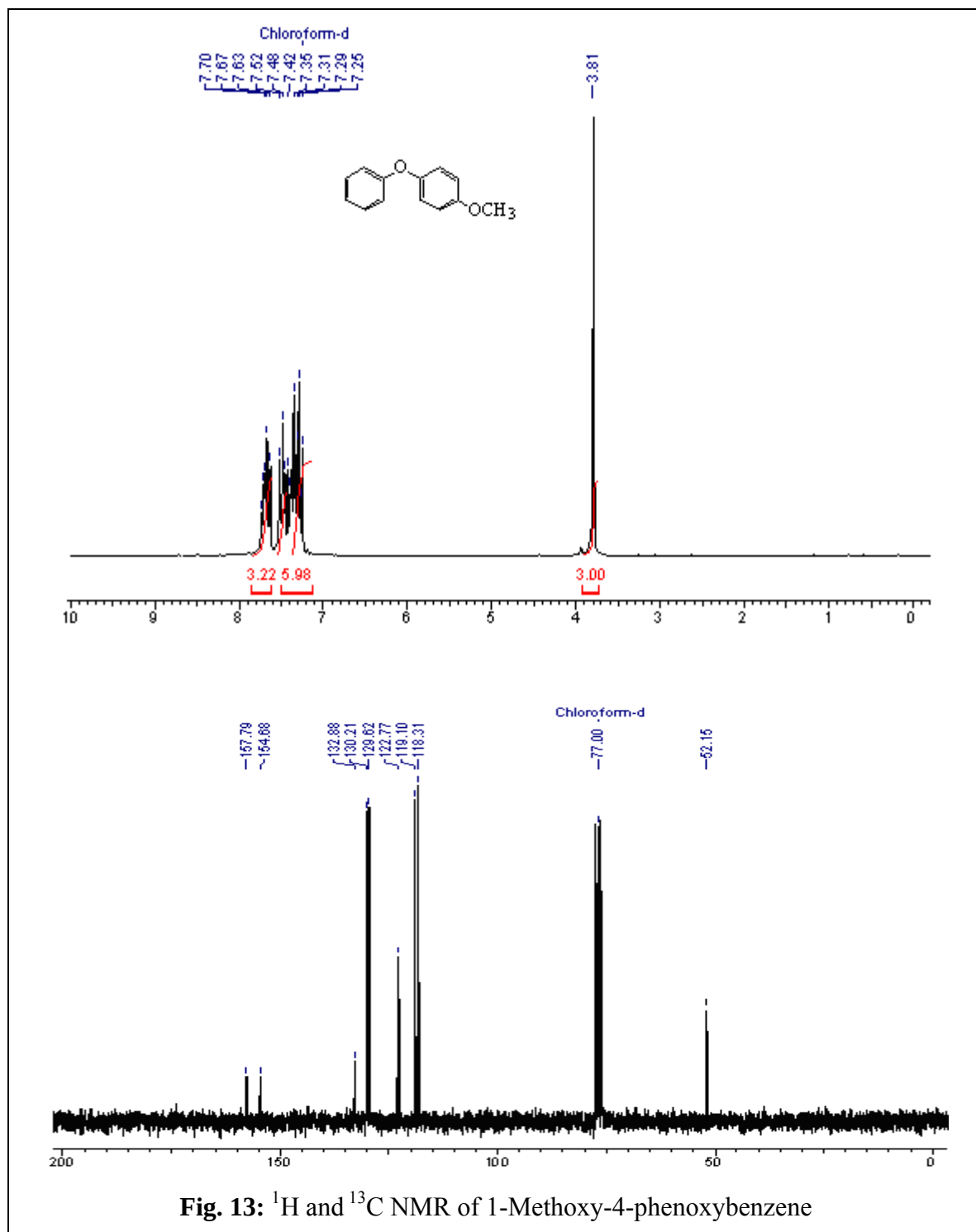












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Chapter IV

Synthesis of β -nitroalcohols and amides over Copper fluorapatite

Catalyst

Section-I

Base-free synthesis of β -nitroalcohols from aldehydes and nitroalkanes at ambient reaction temperature

4.1.1 Introduction

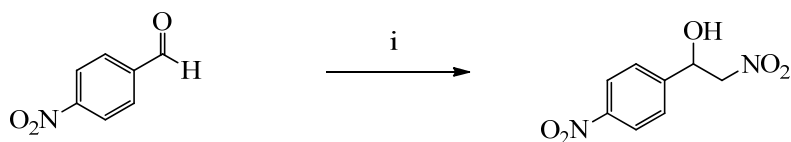
The Henry reaction is a classic and one of the most useful carbon-carbon bond forming reactions, that has wide synthetic applications in organic synthesis by which β -nitroalcohols were synthesized on treatment of carbonyl derivatives (aldehyde or ketone) with nitroalkanes in the presence of a basic catalyst.¹ The nitroalcohols are highly valuable products for the preparation of useful intermediates in the organic chemistry such as nitroalkenes, α -nitroketones, and β -aminoalcohols and their derivatives as ephedrine and norephedrine.² However, such transformation has been also demonstrated using enzymes³ and Cinchona alkaloids.⁴ A nitroaldol reaction catalysed by proazaphosphatranes was reported by Verkade and Kisanga.⁵ Owing to the importance of nitroalcohols as key intermediate for the synthesis of high medicinal value natural product, the world wide efforts have been made in the last few decades to develop various methods for the synthesis of β -nitroalcohols using varieties of reagents and catalysts in combination with the various ligands have been reported including organic, inorganic bases like metal hydroxides or alkoxides.^{6,7} Also, some of other catalysts such as phosphonium salts,⁸ phosphine-metal complexes,⁹ ionic liquid,¹⁰ simple amines,¹¹ ammonium salts,¹² guanidine derivatives,¹³ lithiumaluminum hydride,¹⁴ Mg-Al-HT,¹⁵ Amberlyst-21,¹⁶ and Zn(OTf)₂¹⁷ also have been reported. Moreover, asymmetric synthesis of this reaction to obtained chiral products were reported by Shibasaki *et al.*¹⁸

4.1.2 Review of literature

Literature survey reveals that, there are several methods available for the synthesis of β -nitroalcohols from the reaction of substituted aldehydes and/or ketones with nitroalkanes in the presence of the various ligands, bases and solvent at different reaction temperatures, however, few of them are described below.

Chisholm approach⁹

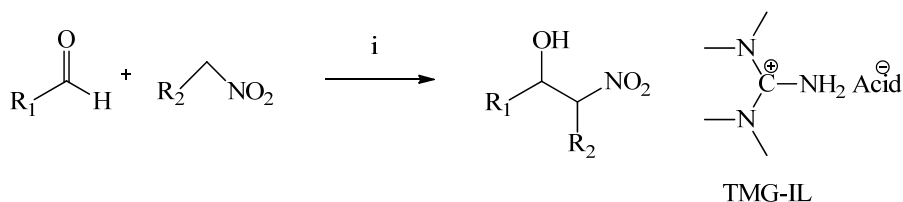
In this approach, Chisholm *et al.* treated various 4-nitro benzaldehydes with nitromethane in presence of Rhodium catalyst with various phosphine ligands (**Scheme 1**).



Scheme 1: Reagents and reaction conditions: (i) Aldehyde (1 equiv), nitromethane (5 equiv), Ligand (10 mol %), RT, 24 h.

Tao Jiang approach¹⁰

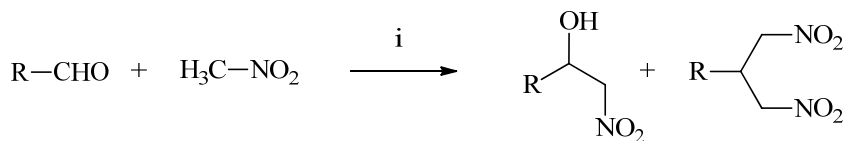
In this approach, Tao Jiang *et al.* treated various aldehydes with nitroalkanes in presence of tetramethyl guanidine based ionic liquid under mild reaction conditions (**Scheme 2**).



Scheme 2: Reagents and reaction conditions: (i) Aldehyde (5 mmol), nitromethane (100 mmol), TMG-IL (1 gm), RT, 6-24 h.

Cwik approach^{15b}

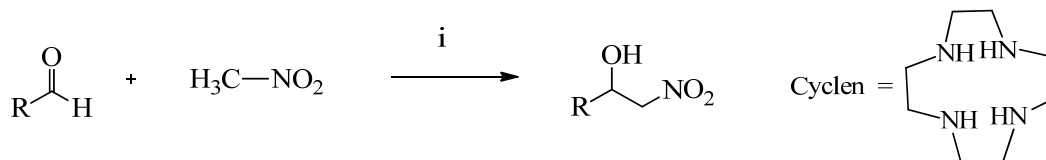
In this approach, Cwik *et al.* treated various aldehydes with nitromethane in presence of Mg-Al-HT as heterogeneous catalyst under mild conditions (**Scheme 3**).



Scheme 3: Reagents and reaction conditions: (i) Aldehyde (5 mmol), nitromethane (10 mmol), catalyst (0.13 gm), RT, 5 h.

Christophe Darcel approach¹⁹

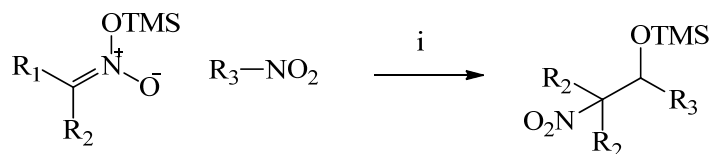
In this approach, Christophe Darcel *et al.* treated various aldehydes with nitromethane in presence of Cyclen as homogeneous catalyst under mild conditions (**Scheme 4**).



Scheme 4: Reagents and reaction conditions: (i) Aldehyde (1 mmol), nitromethane (2 mmol), cyclene (2-10 mol %), THF, RT, 24 h.

Ian Pottie approach²⁰

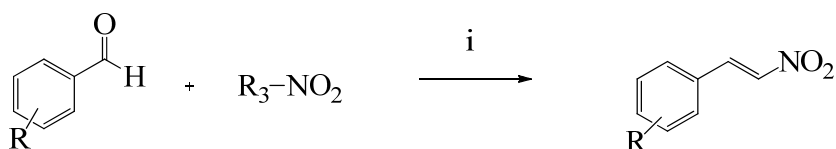
In this approach, trimethylsilyl methylenenitronate reacts with both aliphatic and aromatic aldehydes in the presence of catalytic amounts of scandium (III) triflate to form the Henry reaction products in low yields (**Scheme 5**).



Scheme 5: Reagents and reaction conditions: (i) Aldehyde (2 mmol), nitromethane (2.6 mmol), *n*-BuLi (2.6 mmol), TMSCl (2.6 mmol), THF, -78 °C, 18-120 h.

Dharmaraj approach²¹

In this approach, Dharmaraj *et al.* treated various aldehydes with nitromethane in presence of Ni-HAp as heterogeneous catalyst under microwave irradiation (**Scheme 6**).



Scheme 6: Reagents and reaction conditions: (i) Aldehyde (1 mmol), nitromethane (2 mmol), Ni-Hap catalyst (50 mg), 160 °C, 5 h.

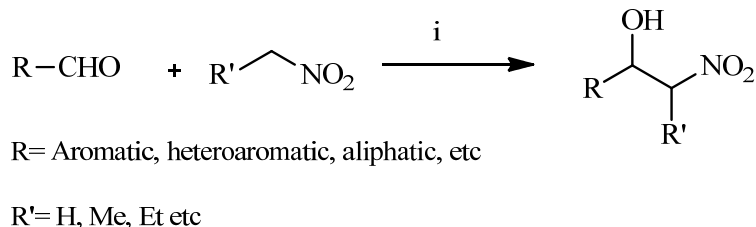
4.1.3 Present Work

4.1.3.1 Objectives

Even though the significant progress have been achieved for the synthesis of β -nitroalcohols, almost all these methods so far reported are in use of very expensive metals in combination with strong bases and/or ligands. All the above methods suffering from limitations and drawbacks such as harsh reaction conditions, moisture sensitive and toxic catalyst, formation of the side product and poor yield of the desired product. In this respect, there is still a need to develop improved process, which will be mild, general, cost effective and efficient methods for the synthesis of β -nitroalcohols.

4.1.4 Results and discussion

We have developed the protocol for the synthesis of β -nitroalcohols from various aldehydes and nitroalkanes catalysed by copper fluorapatite (CuFAP) without base under ambient conditions in good to excellent yields (**Scheme 7**).



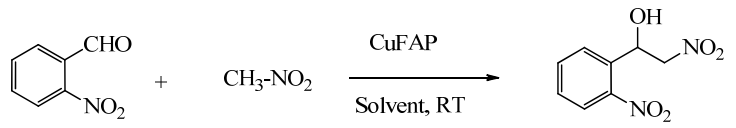
Scheme 7: *Reagents and reaction conditions:* (i) Aldehyde (1 mmol), nitroalkane (1 mL), CuFAP (100 mg), RT, 5-18 h.

The carbon-carbon bond forming reaction of the various aldehydes with nitroalkanes over a heterogeneous, highly efficient, eco-friendly and base-free CuFAP catalyst generated the corresponding β -nitroalcohols as product in good to excellent yield. The copper fluorapatite catalyst is basic in nature, due to that no additional base is required for the reaction.

The copper fluorapatite catalysed synthesis of β -nitroalcohols from 2-nitrobenzaldehyde and nitromethane was selected as a model reaction for optimizing the reaction conditions. Initially, we studied the effect of the various solvents on the coupling reaction, however, only neat reaction in the presence of nitromethane as substrate and solvent gives the cross-coupling product in good to excellent yield while other solvents such as ethyl acetate, THF, methanol, ethanol, dichloromethane, dichloroethane and acetonitrile provided poor yields. The results are summarized in **Table 1**.

At optimized reaction conditions, the scope of the nitroaldol reaction was explored using various substituted aldehyde and nitroalkanes. The various substituted aromatic aldehyde, aliphatic aldehyde possessing a wide range of the functional group reacts with nitroalkanes in the presence of CuFAP catalyst to get β -nitroalcohols as product. The results are summarized in **Table 2**.

Table 1: Effect of solvent on the nitroaldol reaction of 2-nitrobenzaldehyde^a

			
Entry	Solvent	Time (h)	Yield ^b (%)
1	Ethylacetate	12	73
2	THF	12	63
3	Methanol	12	76
4	Ethanol	12	70
5	DCM	12	62
6	DCE	12	65
7	CH ₃ CN	12	78
8	Nitromethane	5	94 ^c

^a Reaction conditions: 2-nitrobenzaldehyde (1 mmol), nitromethane (1.5 mmol), solvent (1 mL), CuFAP (100 mg), RT.

^b Isolated yields.

^c Nitromethane (1 mL)

In comparison, benzaldehyde having electron withdrawing group such as, 2-nitrobenzaldehyde, 3-bromo,4-fluorobenzaldehyde, 4-chlorobenzaldehyde, and 4-bromobenzaldehyde (**Table 2**, entries **2-5**) provided an excellent yields in short reaction time as compare to benzaldehyde (**Table 2**, entry **6**) while benzaldehyde with electron donating group such as, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde 2,4-dimethoxybenzaldehyde and piperonal (**Table 2**, entries **7-13**) provided an moderated yields in long reaction time. In case of the aliphatic aldehyde such as, cinnamaldehyde, propinaldehyde and isobutyraldehyde provided poor yields (**Table 2**, entries **14-16**). Dialdehyde such as 4-formylbenzaldehyde and glutaraldehyde (**Table 2**, entry **17 and 18**) provided poor yields while hetero-aromatic aldehydes such as, thiophene-2-aldehyde and

furfural (**Table 2**, entry **19** and **20**) provided excellent yields as compare to the benzaldehyde (**Table 2**, entry **6**).

Table 2: CuFAP catalysed nitroaldol reaction of aldehydes with nitroalkanes^a

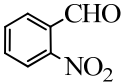
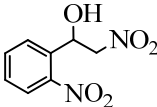
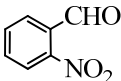
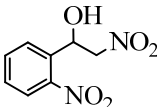
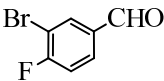
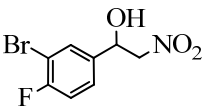
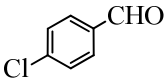
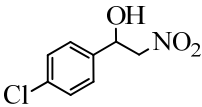
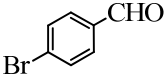
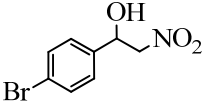
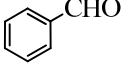
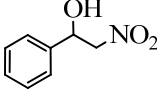
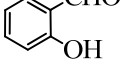
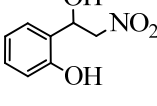
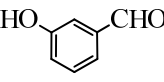
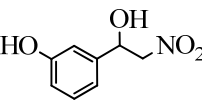
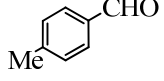
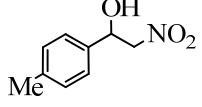
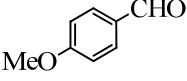
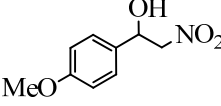
$\text{R}-\text{CHO} + \text{R}'-\text{CH}_2-\text{NO}_2 \xrightarrow[\text{Neat, RT}]{\text{CuFAP}} \text{R}-\text{CH}(\text{OH})-\text{CH}(\text{NO}_2)-\text{R}'$				
Entry	Aldehyde	Product	Time(h)	Yield ^b
1			12	N.R. ^c
2			5	94
3			5	95
4			8	90
5			9	92
6			10	88
7			12	85
8			12	83
9			12	86
10			15	84

Table 2 (Continued)

11			18	83
12			18	82
13			12	85
14			12	85
15			15	75
16			15	79
17			12	78
18			18	76
19			12	93
20			12	90
21			6	92
22			6	89

^a Reaction conditions: Aldehyde (1 mmol), nitroalkane (1 mL), CuFAP (100 mg). RT.^b Isolated yields.^c No reaction without catalyst

To expand the scope of the methodology, we further applied this catalyst system for the nitroaldol reaction of 2-nitrobenzaldehyde with various nitroalkanes such as, nitro-ethane and nitro-propane provided the corresponding β -nitroalcohols as product in good yields (**Table 2**, entry **21** and **22**). No desired alkylation product was obtained during the same reaction condition without CuFAP catalyst (**Table 2**, entry **1**).

The recyclability of CuFAP catalyst was investigated for the nitroaldol reaction of the 2-nitrobenzaldehyde with nitromethane under neat condition at room temperature. The results are summarized in **Table 3**. The catalyst was recovered quantitatively by filtration, washed and recycled for several times (**Table 3**, entries **2-4**) for the synthesis of β -nitroalcohols as product in 92-93 % yield, which is almost comparable with fresh catalyst (**Table 3**, entry **1**). This result clearly shows that the reused CuFAP catalyst shows excellent performance without loss of its catalytic activity.

Table 3: Recyclability study of CuFAP catalyst for the nitroaldol reaction^a

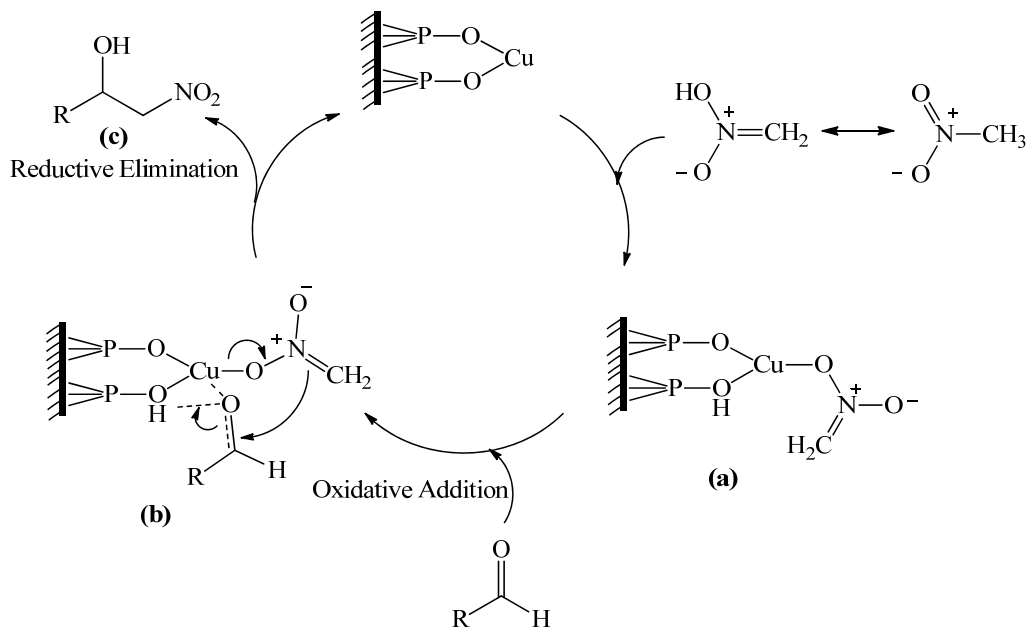
Entry	Yield ^b (%)
1	94
2	93
3	92
4	92

^a Reaction conditions: 2-nitrobenzaldehyde (1 mmol), nitromethane (1 mL), CuFAP (100 mg). RT, 5 h.

^b Isolated yields.

According to the previous research work over CuFAP catalyst for the N-arylation of heterocycles²² and O-arylation of phenols²³ the possible mechanism proposed in (**Scheme 8**) for nitroaldol reaction may involve the nucleophilic substitution that proceeds presence

of CuFAP catalyst via the formation of the complex **(a)** with nitromethane followed by the oxidative addition of aldehyde *via* the formation of another complex **(b)** and then the instantly in situ reductive elimination to release the β -nitroalcohol product **(c)** as well as CuFAP catalyst in its original form to recycle again.



Scheme 8: Proposed mechanism for the nitroaldol reaction over CuFAP catalyst.

4.1.5 Conclusion

In conclusion, we have developed the copper fluorapatite (CuFAP) a heterogeneous, reusable highly efficient green and eco-friendly catalyst for the synthesis of β -nitroalcohols in good to excellent yield at room temperature by the cross-coupling reaction of the various substituted aldehydes with nitroalkanes. The developed protocol is simple, clean, rapid and in the absence of base. The catalyst can be reused several times without loss of catalytic activity.

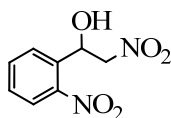
4.1.6 Experimental Section

4.1.6.1 General experimental procedure for the CuFAP catalysed Henry reaction:

Aldehyde (1 mmol), nitroalkane (1 mL) and CuFAP catalyst (100 mg) were taken in 10 mL round bottomed flask and stirred in nitrogen atmosphere at room temperature for 5-18 h (**Table 2**) and the progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was diluted with 20 mL ethyl acetate followed by filtration to recover the catalyst. The filtrate was concentrated in vacuo to get the crude product, which was further purified by column chromatography on silica gel using hexane/ethyl acetate mixture 90:10 to obtain β -nitroalcohols as product.

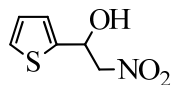
4.1.6.2 Spectral data for β -nitroalcohol

1-(2-nitrophenyl)-2-nitroethanol:



Yield: 94 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 8.08 (m, 1H), 7.92 (m, 1H), 7.74 (m, 1H), 7.54 (m, 1H), 6.01 (m, 1H), 4.9-4.48 (m, 2H), 2.78 (brs, 1H). $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 147.06, 134.39, 129.65, 128.66, 124.96, 80.03, 66.72. **IR** (CHCl_3): 751, 859, 1096, 1216, 1346, 1376, 1526, 1559, 1610, 3025, 3547 cm^{-1}

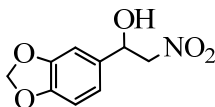
1-(thiophen-2-yl)-2-nitroethanol:



Yield: 93 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 4.62 (m, 2H), 5.43 (m, 1H), 6.36 (m, 2H), 7.4 (t, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 64.78, 78.37, 108.14, 110.62, 143.14, 150.7;

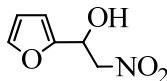
IR (CHCl_3): 668, 755, 884, 928, 1015, 1069, 1217, 1328, 1377, 1426, 1504, 1557, 1630, 1630, 2401, 2925, 3022, 3126, 3568 cm^{-1}

1-(benzo[1,3]dioxol-5-yl)-2-nitroethanol:



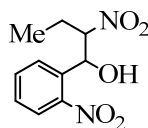
Yield: 85 %; **^1H NMR** (200 MHz, CDCl_3): δ 2.23 (brs, 1H), 4.42 (m, 2H), 5.33 (m, 1H), 5.97 (s, 2H), 6.77-6.88 (m, 3H); **^{13}C NMR** (200 MHz, CDCl_3): δ 70.8, 81.2, 101.37, 106.33, 108.6, 119.58, 131.97, 148.23; **IR** (CHCl_3): 486, 666, 706, 759, 814, 932, 1039, 1099, 1250, 1377, 1446, 1503, 1555, 1609, 2905, 3022, 3547 cm^{-1}

1-(furan-2-yl)-2-nitroethanol:



Yield: 90 %; **^1H NMR** (200 MHz, CDCl_3): δ 2.49 (brs), 4.68-4.84(m, 2H), 5.44 (m, 1H), 6.29-6.4(m, 2H), 7.38 (m, 1H); **^{13}C NMR** (200 MHz, CDCl_3): δ 65.48, 75.18, 108.83, 111.29, 143.82; **IR** (CHCl_3): 665, 747, 821, 1014, 1090, 1341, 1407, 1492, 1555, 1593, 1634, 2925, 3023, 3501 cm^{-1}

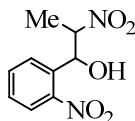
1-(2-nitrophenyl)-2-nitrobutanol:



Yield: 89 %; **^1H NMR** (200 MHz, CDCl_3): δ 1.02 (t, 3H), 1.74 (m, 1H), 2.13 (m, 1H),

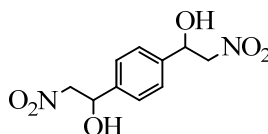
3.29 (brs, 1H), 4.79 (m, 1H), 5.71 (m, 1H), 7.52-8.04 (m, 4H); ^{13}C NMR (200 MHz, CDCl_3): δ 10.25, 10.36, 20.85, 24.03, 69.71, 69.92, 91.89, 93.96, 125.07, 128.61, 129.65, 134.05; IR (CHCl_3): 668, 755, 1061, 1216, 1310, 1347, 1440, 1529, 1554, 1610, 2401, 2883, 2940, 3023, 3542 cm^{-1}

1-(2-nitrophenyl)-2-nitropropanol:

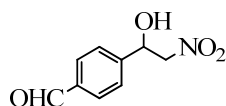


Yield: 92 %; ^1H NMR (200 MHz, CDCl_3): δ 1.5 (t, $J=3\text{Hz}$ 3H), 2.99 (brs, 1H), 4.95 (m, 1H), 5.69-6.09 (d, $J=15\text{Hz}$ 1H), 7.51-8.10 (m, 4H); ^{13}C NMR (200 MHz, CDCl_3): δ 11.91, 16.35, 69.23, 70.54, 84.72, 87.5, 124.96, 125.14, 128.83, 129.29, 129.41, 129.68, 134.06; IR (CHCl_3): 611, 659, 707, 752, 863, 991, 1049, 1132, 1346, 1448, 1526, 1610, 1699, 2415, 2904, 2996, 3109, 3543 cm^{-1}

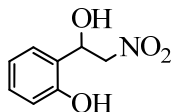
1,1'-(1,4-phenylene)bis(2-nitroethanol):



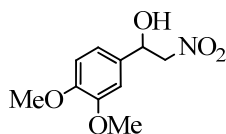
Yield: 78 %; ^1H NMR (200 MHz, CDCl_3): δ 4.56 (m, 4H), 5.42 (m, 2H), 7.48 (s, 4H); ^{13}C NMR (200 MHz, CDCl_3): δ 70.06, 81.38, 126.1, 127.85, 139.78; IR (CHCl_3): 499, 610, 625, 755, 860, 1061, 1110, 1148, 1216, 1310, 1347, 1440, 1528, 1552, 1610, 2401, 2883, 2940, 3023, 3536 cm^{-1}

1-(4-Formylphenyl)-2-nitroethanol:

Yield: 90 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.67 (brs, 1H), 4.51 (m, 2H), 5.49 (m, 1H), 7.54 (d, $J=4\text{Hz}$ 2H), 7.89 (d, $J=4\text{Hz}$ 2H), 10.1 (s, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 70.43, 80.77, 117.6, 126.59, 126.59, 130.32, 136.65, 144.48, 191.64; **IR** (CHCl_3): 667, 709, 768, 831, 921, 1016, 1170, 1214, 1306, 1377, 1419, 1554, 1609, 1701, 1932, 2402, 2744, 2840, 3023, 3480 cm^{-1}

1-(2-hydroxyphenyl)-2-nitroethanol:

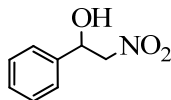
Yield: 85 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 4.51 (m, 2H), 5.28 (m, 1H), 7.15 (m, 2H), 7.52 (d, $J=3\text{Hz}$ 1H), 7.87 (d, $J=4\text{Hz}$ 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 70.32, 81.36, 112.52, 115.07, 116.79, 119.11, 120.64, 129.48, 138.85, 156.86; **IR** (CHCl_3): 597, 668, 751, 884, 1015, 1069, 1148, 1217, 1327, 1377, 1427, 1505, 1557, 1633, 1672, 2401, 2925, 3023, 3126, 3564 cm^{-1}

1-(3,4-dimethoxyphenyl)-2-nitroethanol:

Yield: 83 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.77 (s, 3H), 3.83 (s, 3H), 4.47 (m, 2H), 5.56 (m, 1H), 6.82 (d, $J=6\text{Hz}$ 2H), 7.03 (s, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 56.40,

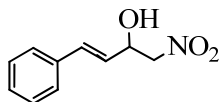
68.35, 80.39, 112.08, 113.76, 114.81, 127.47, 150.61, 154.61; **IR** (CHCl_3): 68, 758, 884, 1044, 1180, 1216, 1278, 1378, 1465, 1500, 1556, 2401, 2838, 2941, 3020, 3537. cm^{-1}

1-(phenyl)-2-nitroethanol:



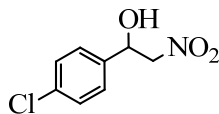
Yield: 88 %; **^1H NMR** (200 MHz, CDCl_3): δ 2.67 (brs, 1H), 4.57 (m, 2H), 5.48 (m, 1H), 7.41 (m, 5H); **^{13}C NMR** (200 MHz, CDCl_3): δ 69.57, 79.84, 124.87, 126.71, 127.37, 128.73, 133.7, 135.47; **IR** (CHCl_3): 699, 762, 895, 1066, 1090, 1217, 1287, 1377, 1495, 1554, 1633, 1958, 2922, 3029, 3547. cm^{-1}

1-nitro-4-phenylbut-3-en-2-ol:



Yield: 83 %; **^1H NMR** (200 MHz, CDCl_3): δ 2.44 (brs, 1H), 4.33 (m, 1H), 4.65 (m, 1H), 5.04 (m, 1H), 6.08 (dd, $J=3\text{Hz}$ 1H), 6.74 (d, $J=8\text{Hz}$ 1H), 7.31 (m, 5H); **^{13}C NMR** (200 MHz, CDCl_3): δ 70.97, 81.19, 125.91, 127.33, 128.97, 129.01, 129.57, 138.07; **IR** (CHCl_3): 666, 694, 755, 969, 1072, 1216, 1332, 1378, 1554, 1623, 1667, 1723, 1954, 2922, 3027, 3543. cm^{-1}

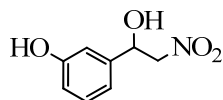
1-(4-chlorophenyl)-2-nitroethanol:



Yield: 90 %; **^1H NMR** (200 MHz, CDCl_3): δ 2.84 (brs, 1H), 4.35 (m, 2H), 5.33 (m, 1H),

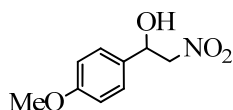
7.22-7.35 (m, 4H); ^{13}C NMR (200 MHz, CDCl_3): δ 69.68, 80.24, 122.31, 126.96, 129.74, 131.53, 136.4; IR (CHCl_3): 665, 759, 822, 969, 1090, 1259, 1341, 1407, 1555, 1636, 2926, 3022, 3489. cm^{-1}

1-(3-hydroxyphenyl)-2-nitroethanol:



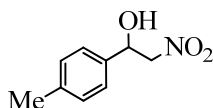
Yield: 83 %; ^1H NMR (200 MHz, CDCl_3): δ 3.11 (brs, 1H), 4.6 (m, 2H), 5.19 (m, 1H), 6.81-7.26 (m, 4H), 8.52 (brs, 1H); ^{13}C NMR (200 MHz, CDCl_3): δ 71.45, 82.62, 113.78, 115.82, 117.87, 130.43, 142.74, 158.46; IR (CHCl_3): 708, 974, 1076, 1276, 1350, 1381, 1464, 1557, 1639, 1723, 28.49, 2957, 3451 cm^{-1}

1-(4-methoxyphenyl)-2-nitroethanol:



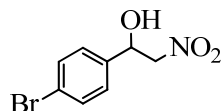
Yield: 84 %; ^1H NMR (200 MHz, CDCl_3): δ 2.51 (brs, 1H), 3.8 (s, 3H), 4.43 (m, 2H), 5.36 (m, 1H), 6.88 (dd, $J=1\text{Hz}$ 2H), 7.29 (dd, $J=1\text{Hz}$ 2H); ^{13}C NMR (200 MHz, CDCl_3): δ 55.31, 70.62, 81.22, 114.33, 127.25, 130.18, 159.96; IR (CHCl_3): 667, 791, 823, 1029, 1117, 1173, 1254, 1338, 1425, 1515, 1557, 1603, 1630, 1722, 1891, 2040, 2300, 2563, 2842, 2962, 3022, 3111, 3525 cm^{-1}

1-(4-methylphenyl)-2-nitroethanol:



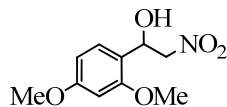
Yield: 86 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.31 (s, 3H), 2.52 (brs, 1H), 4.37 (m, 2H), 5.33 (m, 1H), 7.13 (m, 4H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 21.12, 70.83, 81.2, 125.83, 129.62, 135.13, 138.85; **IR** (CHCl_3): 667, 770, 812, 895, 969, 1078, 1181, 1339, 1415, 1507, 1556, 1631, 1716, 1799, 1908, 2302, 2402, 2593, 2924, 3024, 3111, 3547 cm^{-1} .

1-(4-bromophenyl)-2-nitroethanol:



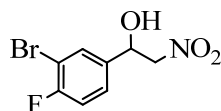
Yield: 90 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.94 (brs, 1H), 4.62 (m, 2H), 5.47 (m, 1H), 7.47-7.61 (m, 4H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 70.78, 82.21, 116.03, 129.13, 132.32, 140.56; **IR** (CHCl_3): 668, 767, 822, 1011, 1074, 1215, 1339, 1378, 1489, 1556, 1636, 2400, 2924, 3020, 3582 cm^{-1}

1-(2,4-dimethoxyphenyl)-2-nitroethanol:



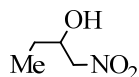
Yield: 82 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.96 (brs, 1H), 3.77 (s, 3H), 3.85 (s, 3H), 4.38 and 4.48 (m, 2H), 5.7 (m, 1H), 6.87 (m, 2H), 7.19 (m, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 55.76, 56.16, 66.78, 81.23, 112.2, 113.56, 114.09, 129.85, 150.5, 154.79; **IR** (CHCl_3): 666, 770, 1044, 1218, 1377, 1465, 1499, 1554, 3018, 3448 cm^{-1}

1-(3-Br, 4-F phenyl)-2-nitroethanol:



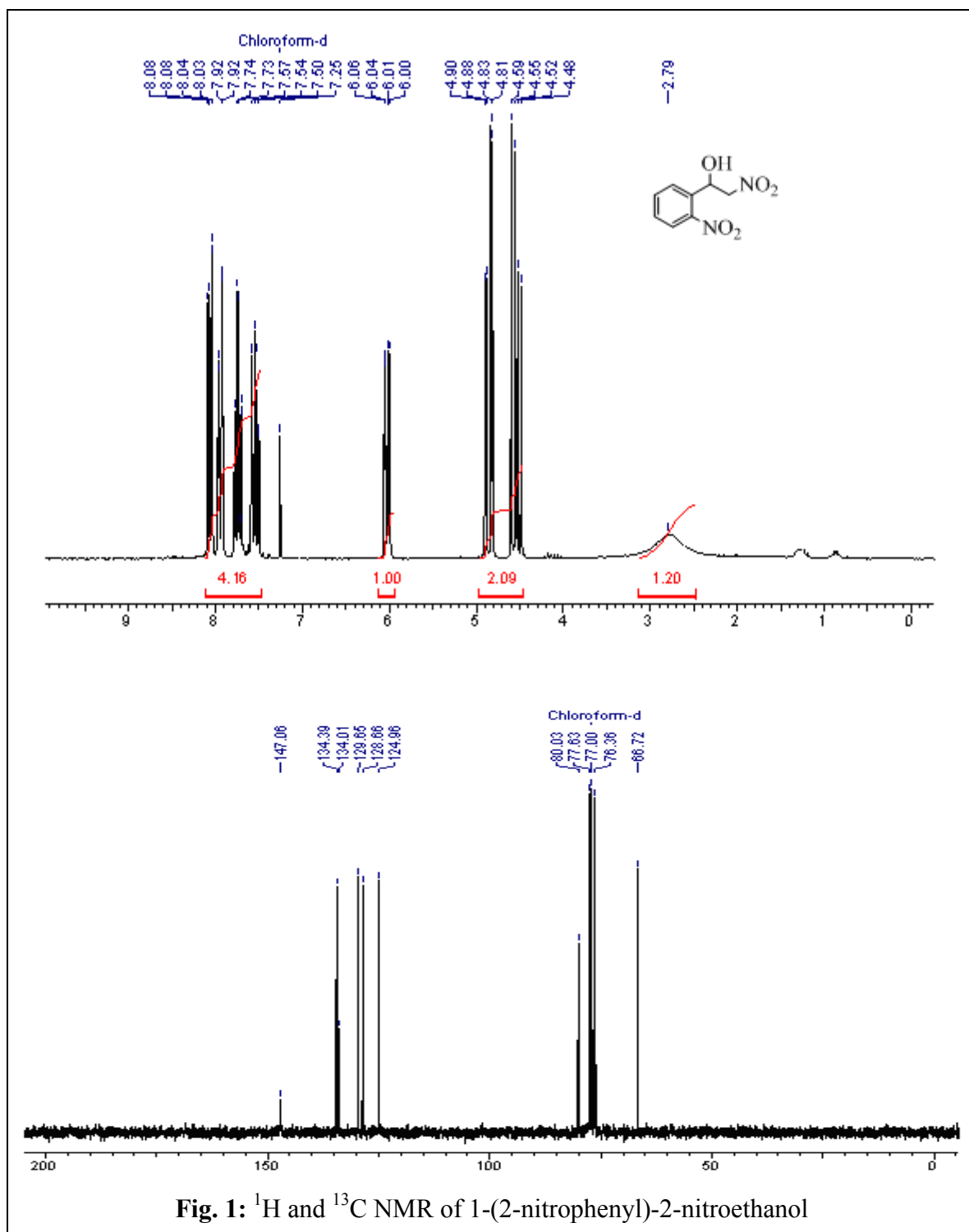
O=[N+]([O-])CC(O)CCC(O)CC[N+](=O)[O-]

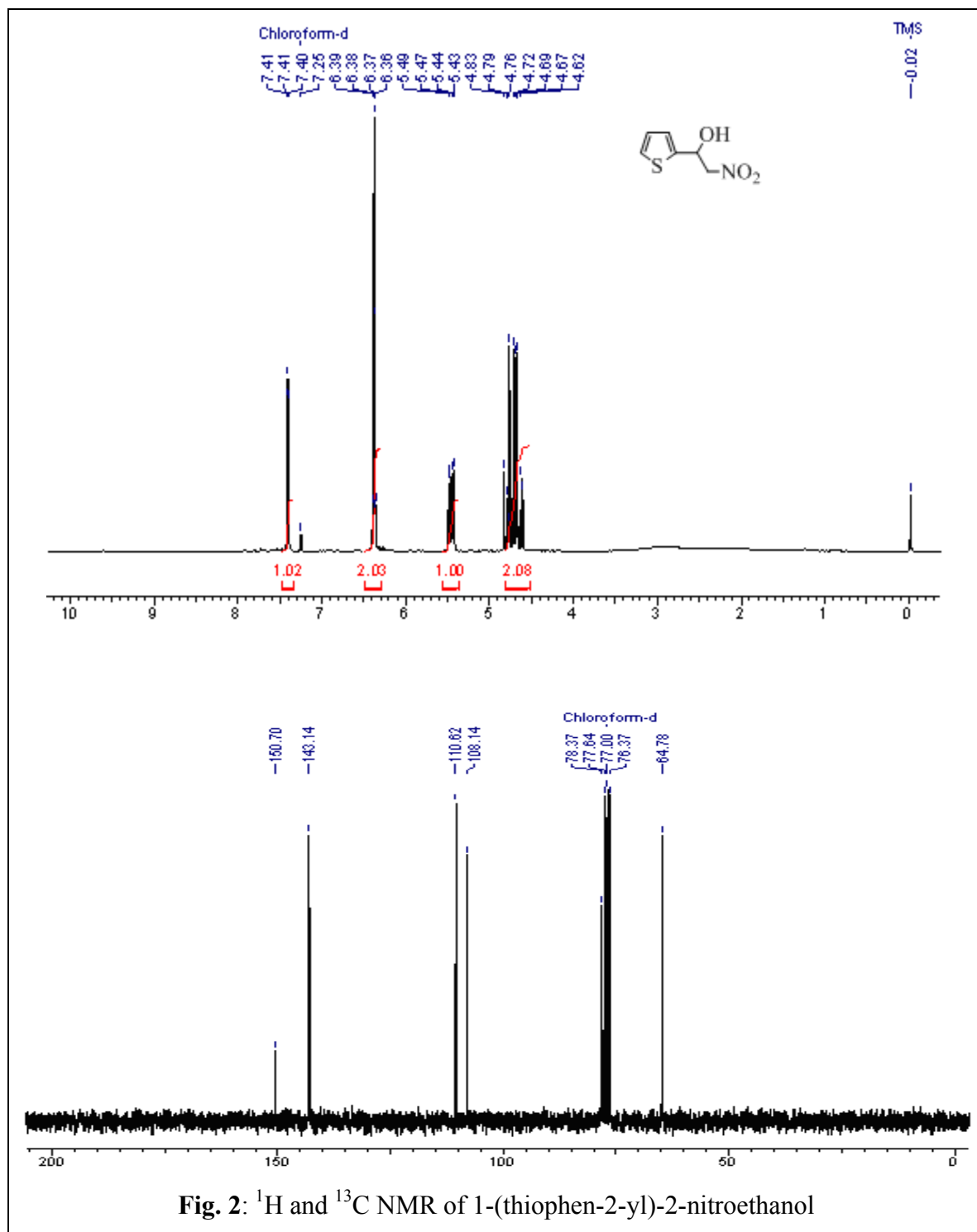
1-nitro-2-butanol:



Yield: 75 %; **¹H NMR** (200 MHz, CDCl₃): δ 0.94 (d, *J*=4Hz 3H), 1.47(t, *J*=4Hz 2H), 1.97 (brs, 1H), 3.84 (m, 1H), 4.36-4.58 (m, 2H); **¹³C NMR** (200 MHz, CDCl₃): δ 22.6, 29.66, 52.21, 67.25; **IR** (CHCl₃): 664, 756, 974, 1075, 1120, 1275, 1329, 1380, 1463, 1557, 1641, 1723,, 2820, 2967, 3455 cm⁻¹

4.1.7 Spectral data





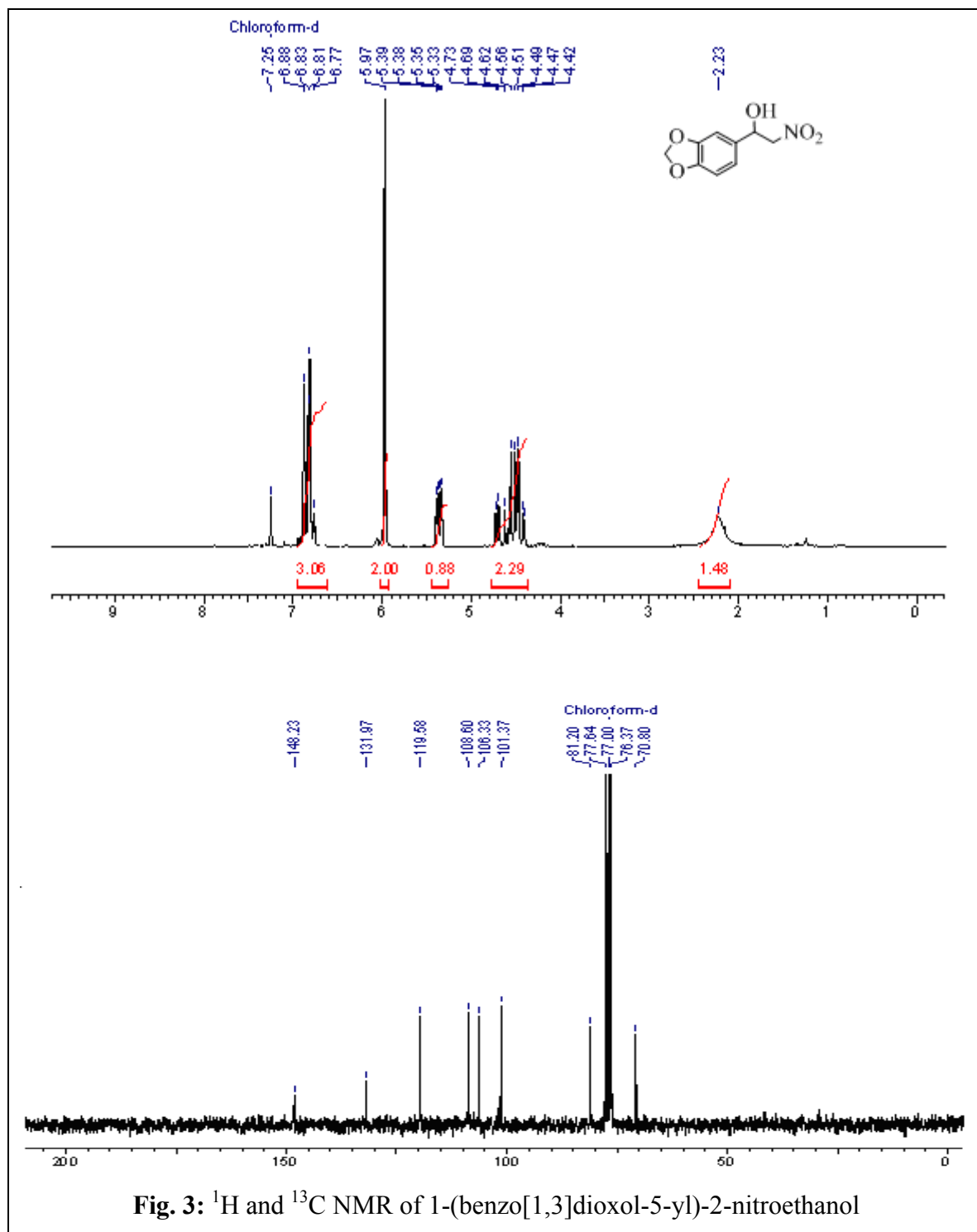


Fig. 3: ¹H and ¹³C NMR of 1-(benzo[1,3]dioxol-5-yl)-2-nitroethanol

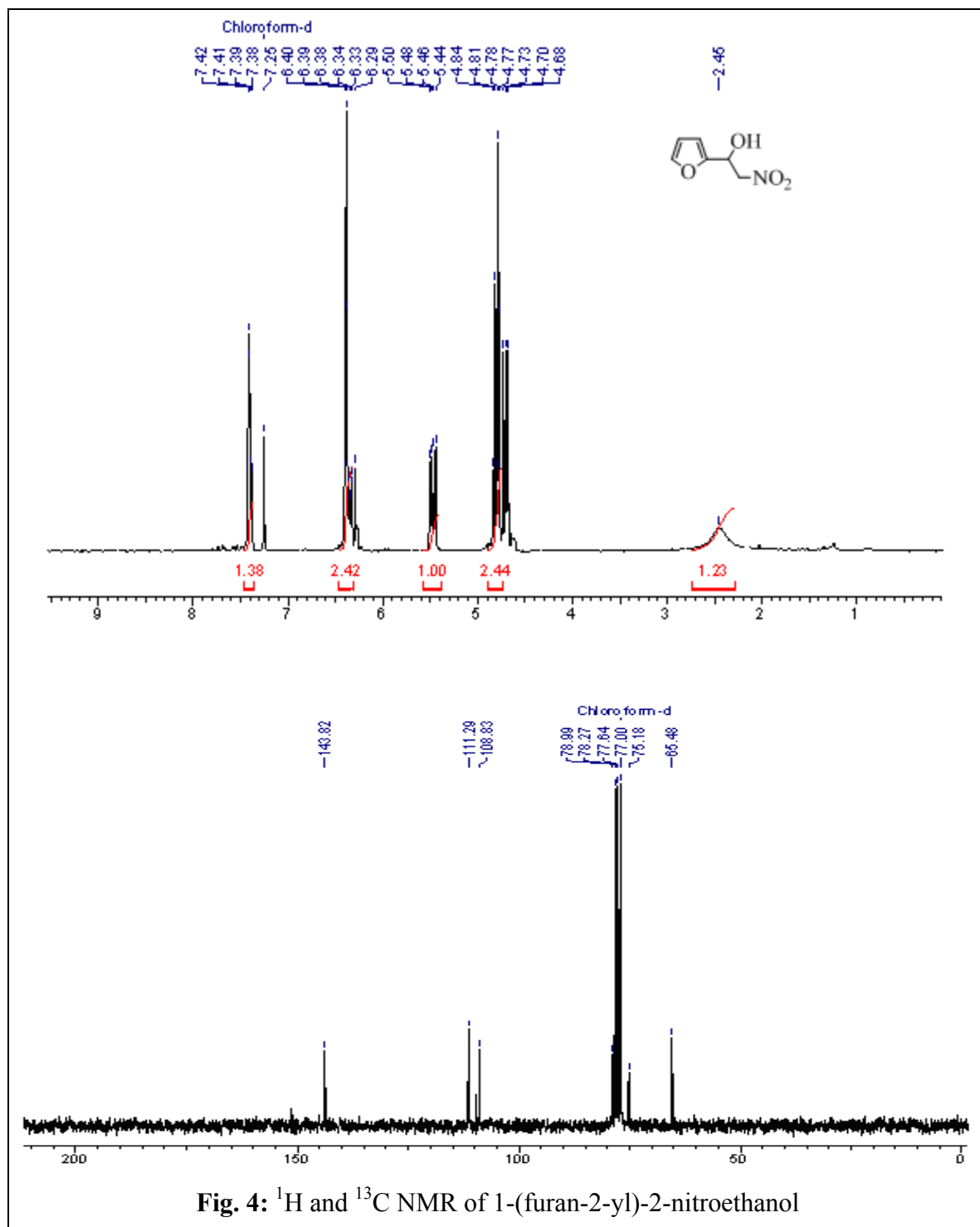


Fig. 4: ^1H and ^{13}C NMR of 1-(furan-2-yl)-2-nitroethanol

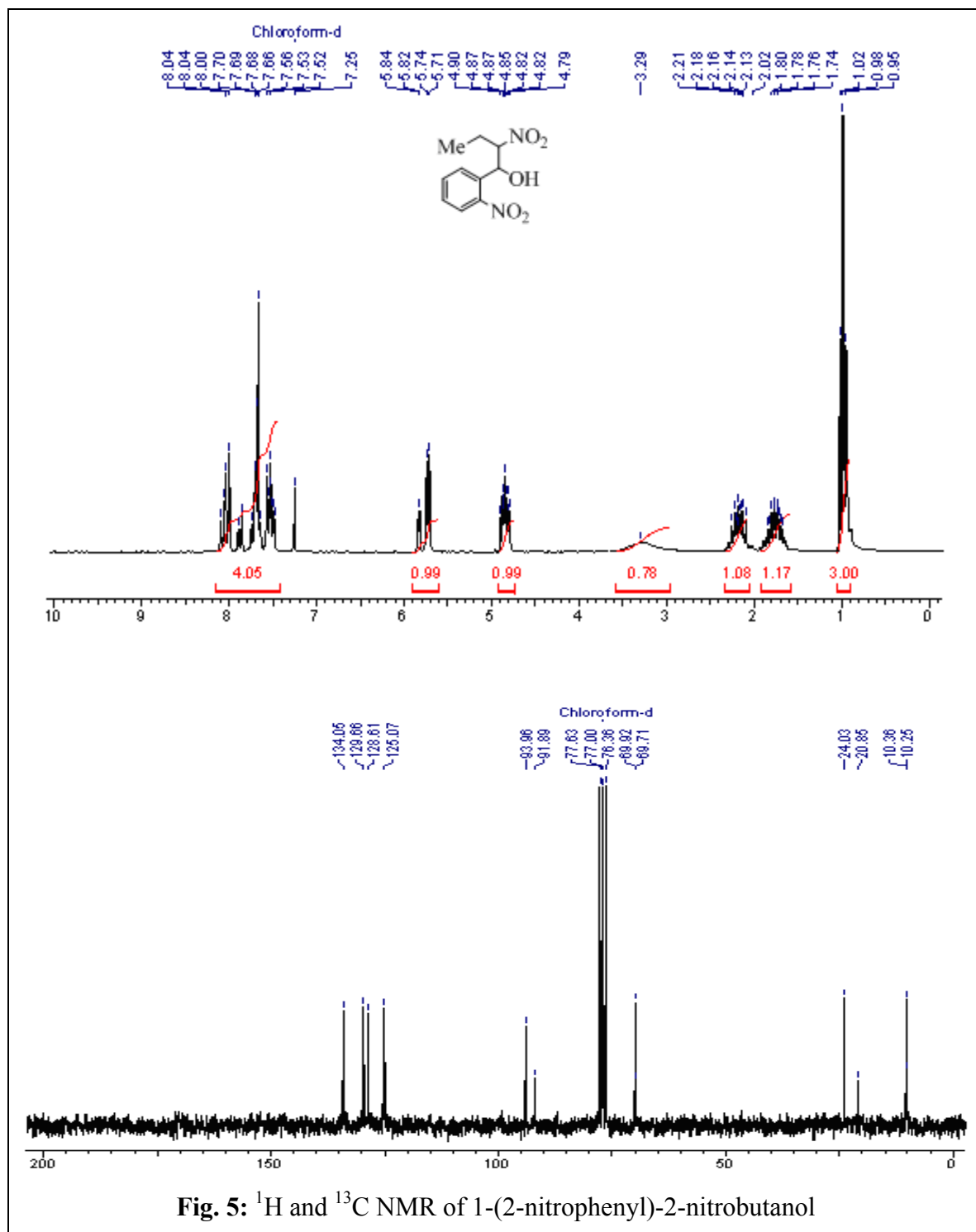
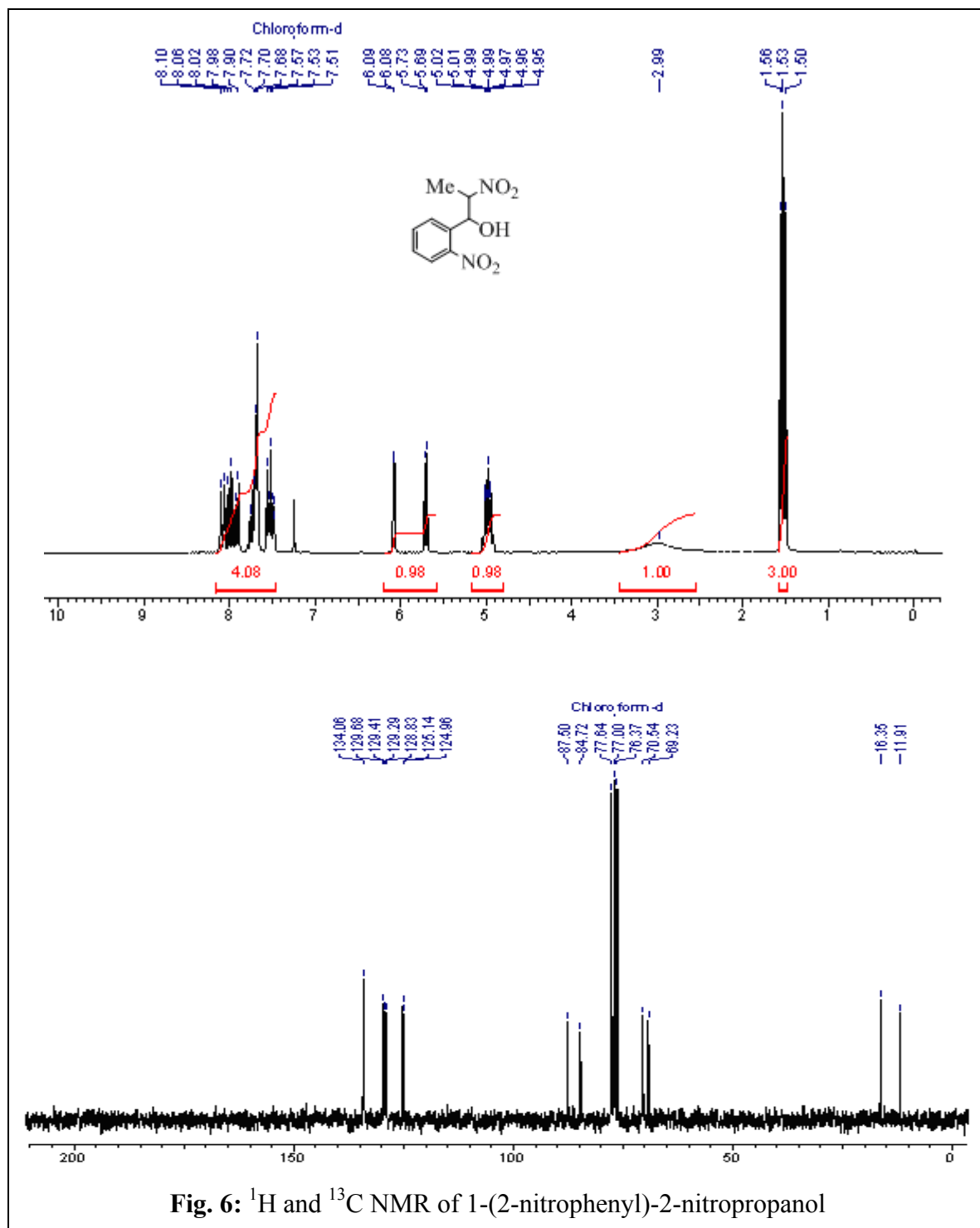
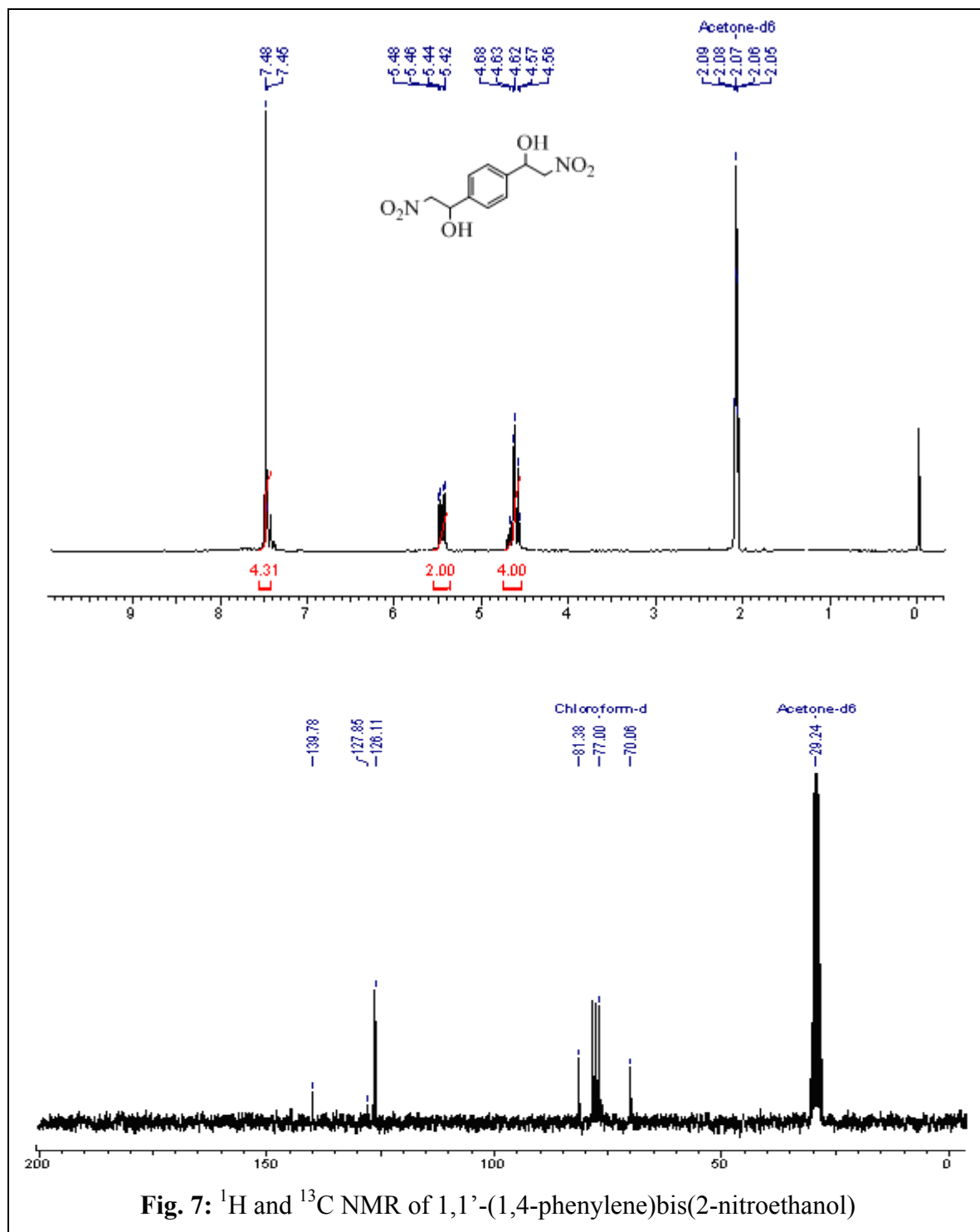
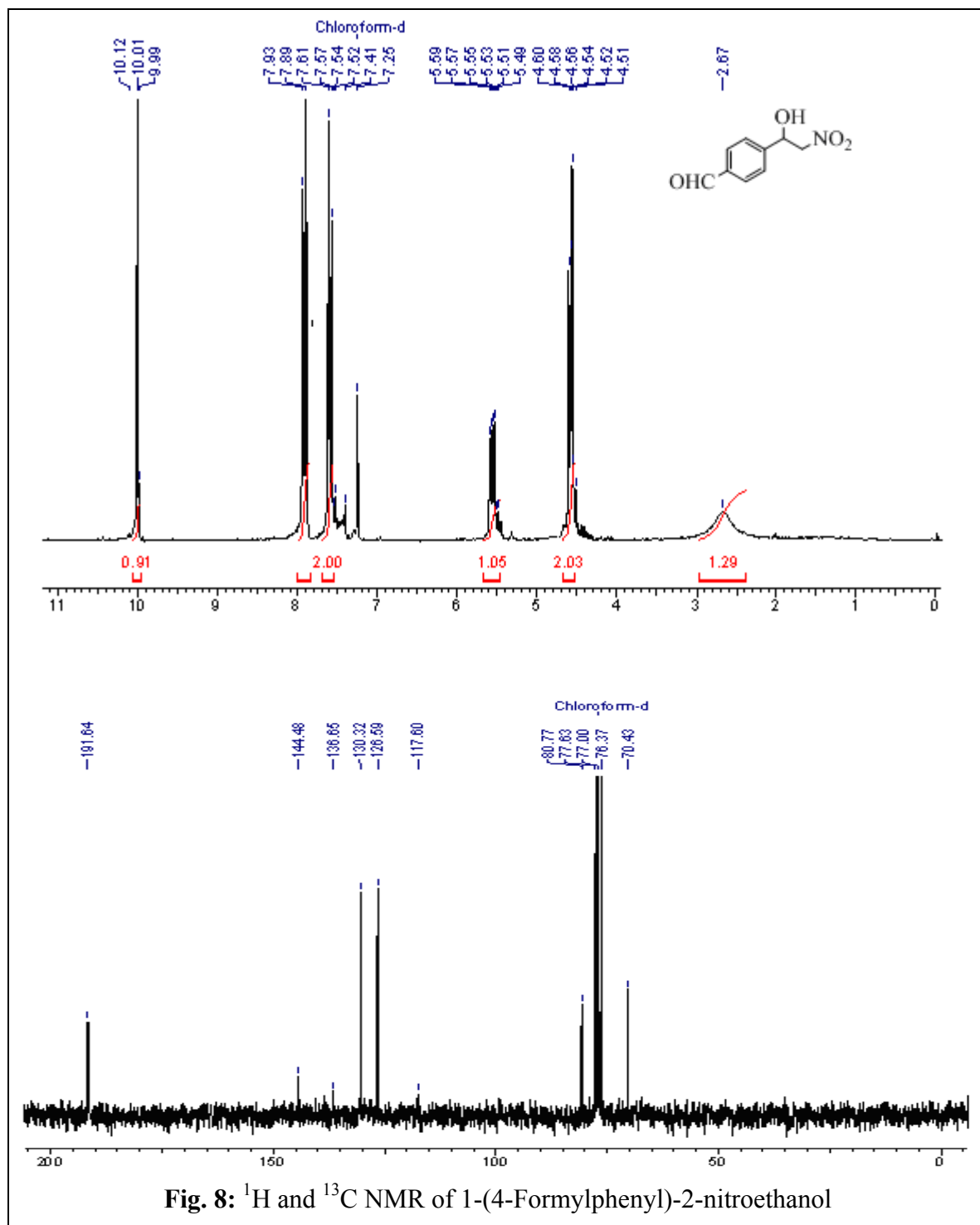
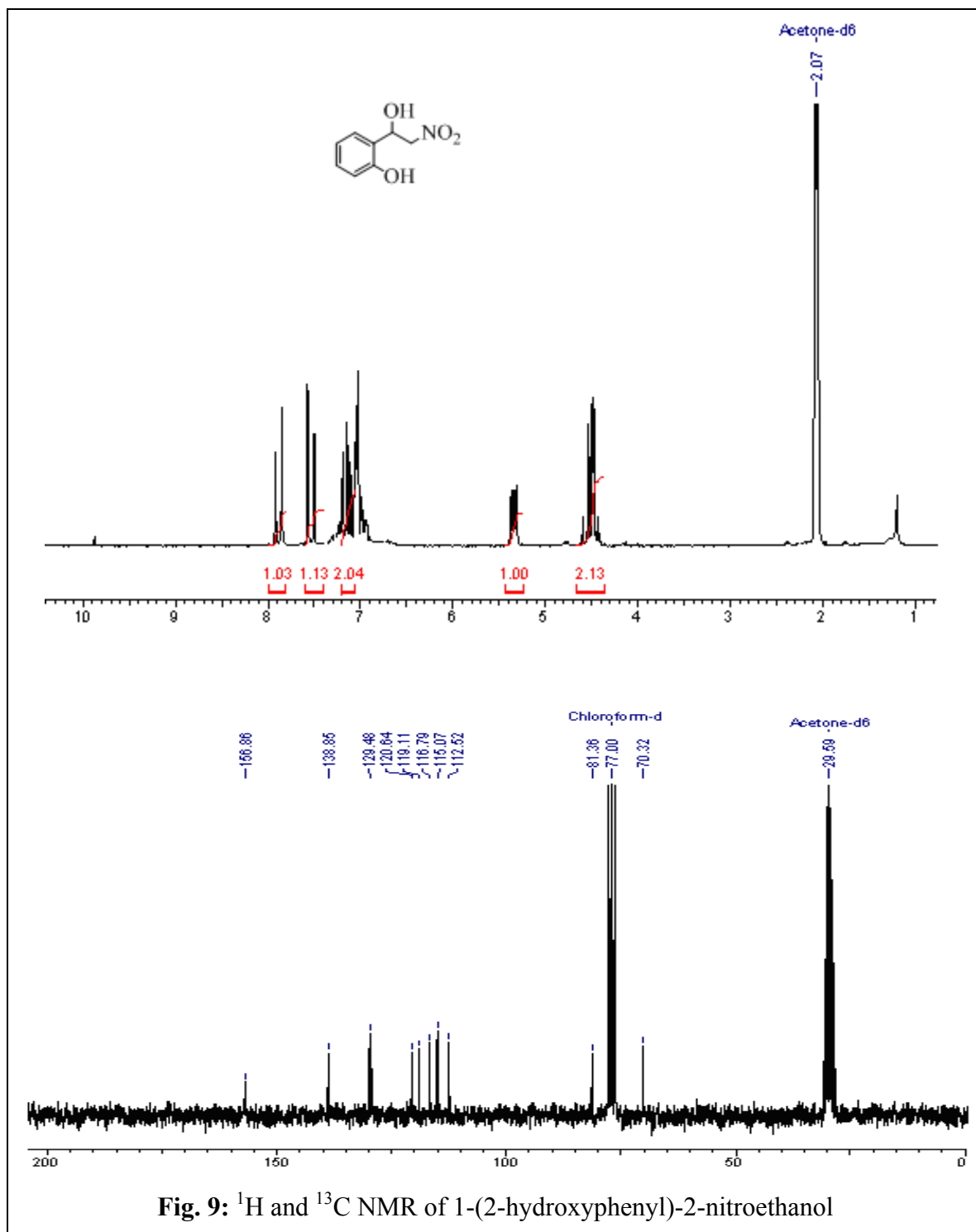


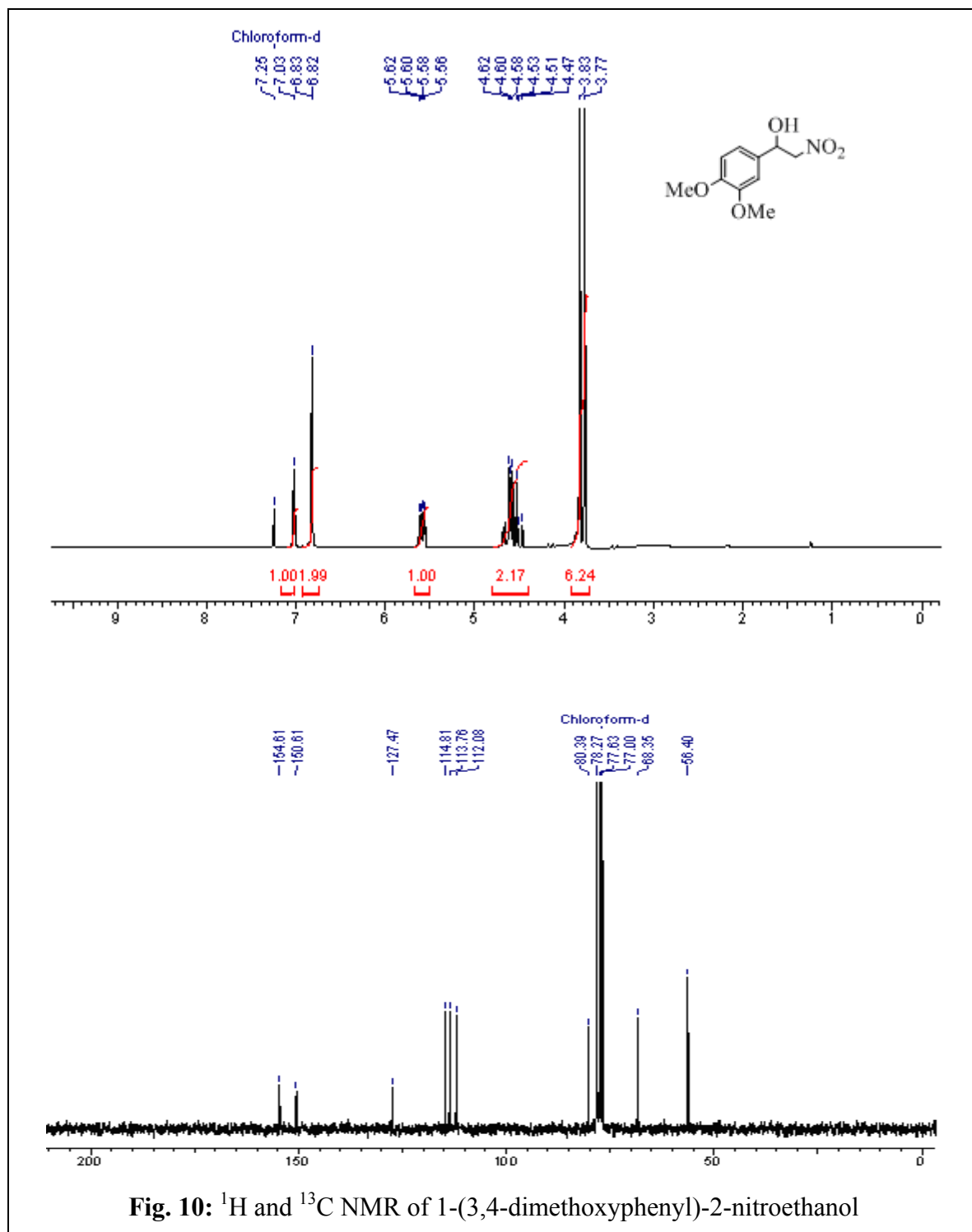
Fig. 5: ^1H and ^{13}C NMR of 1-(2-nitrophenyl)-2-nitrobutanol

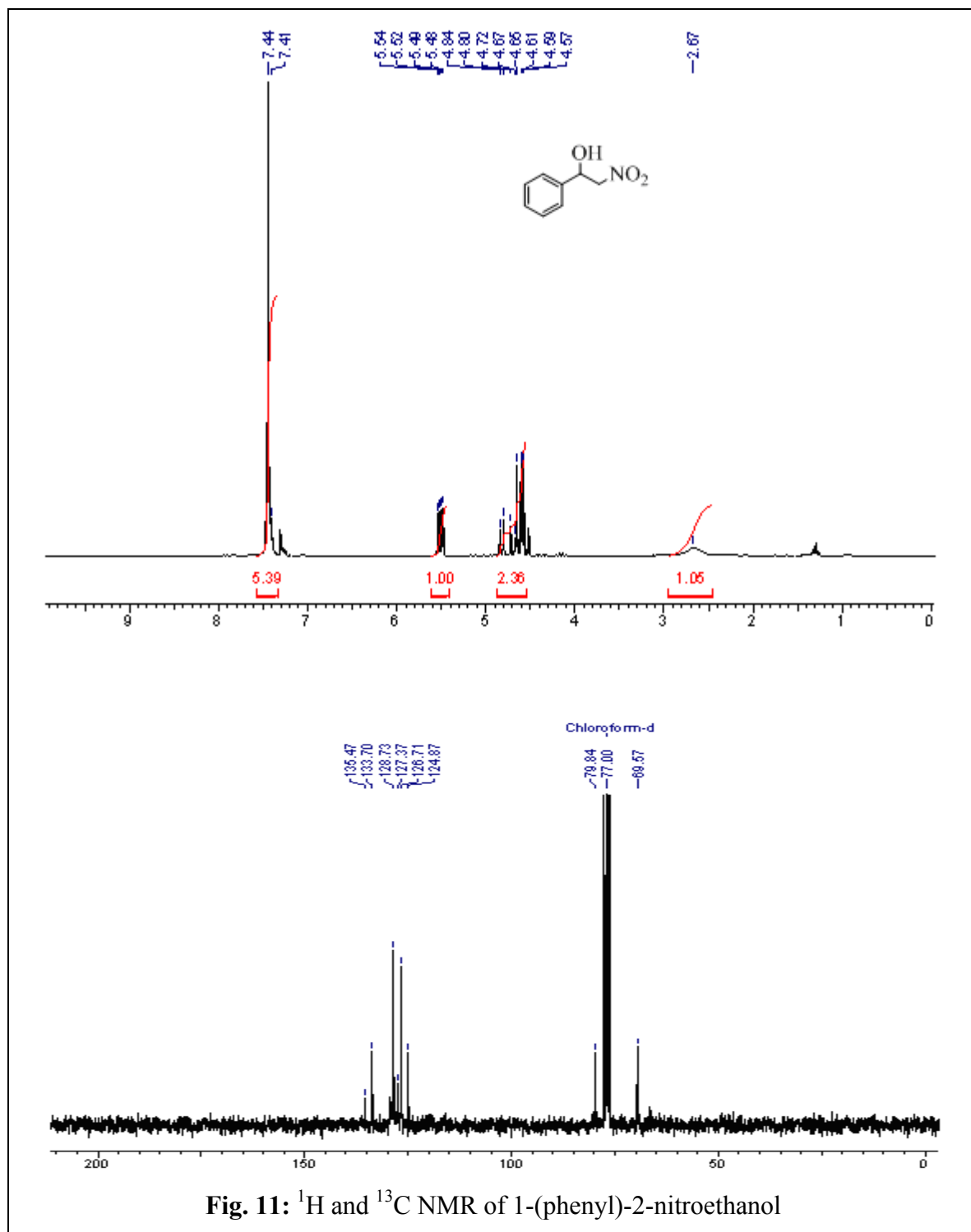


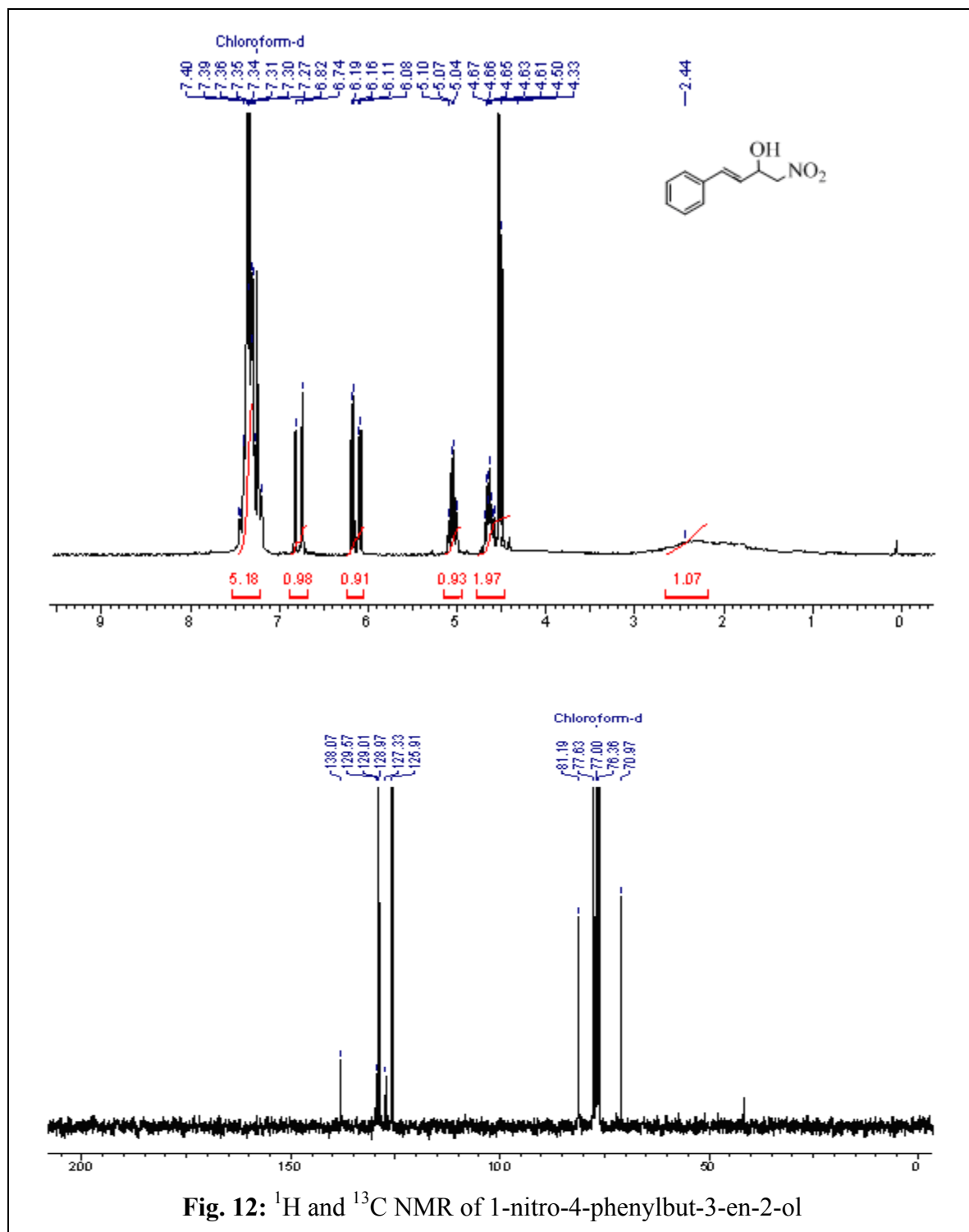


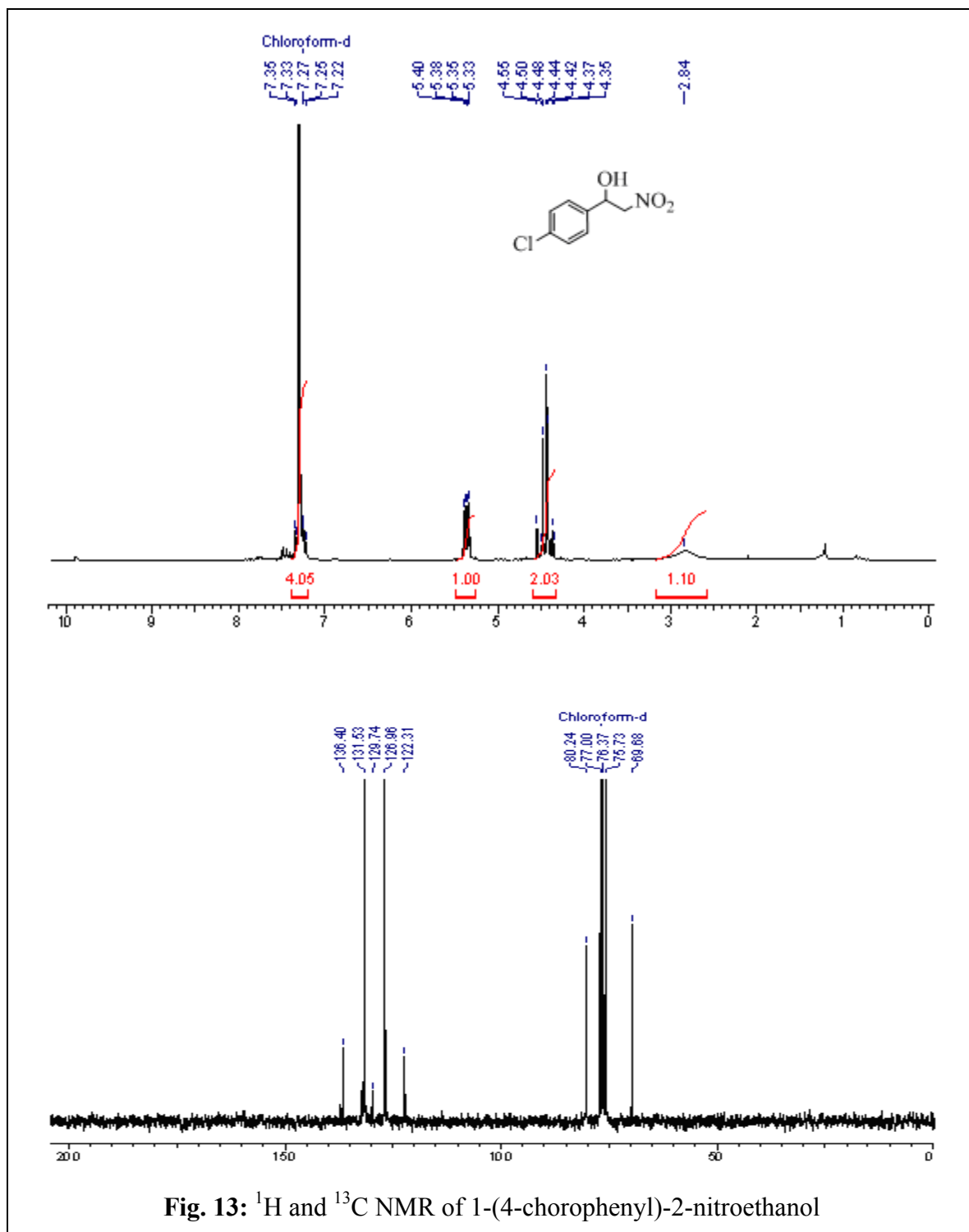












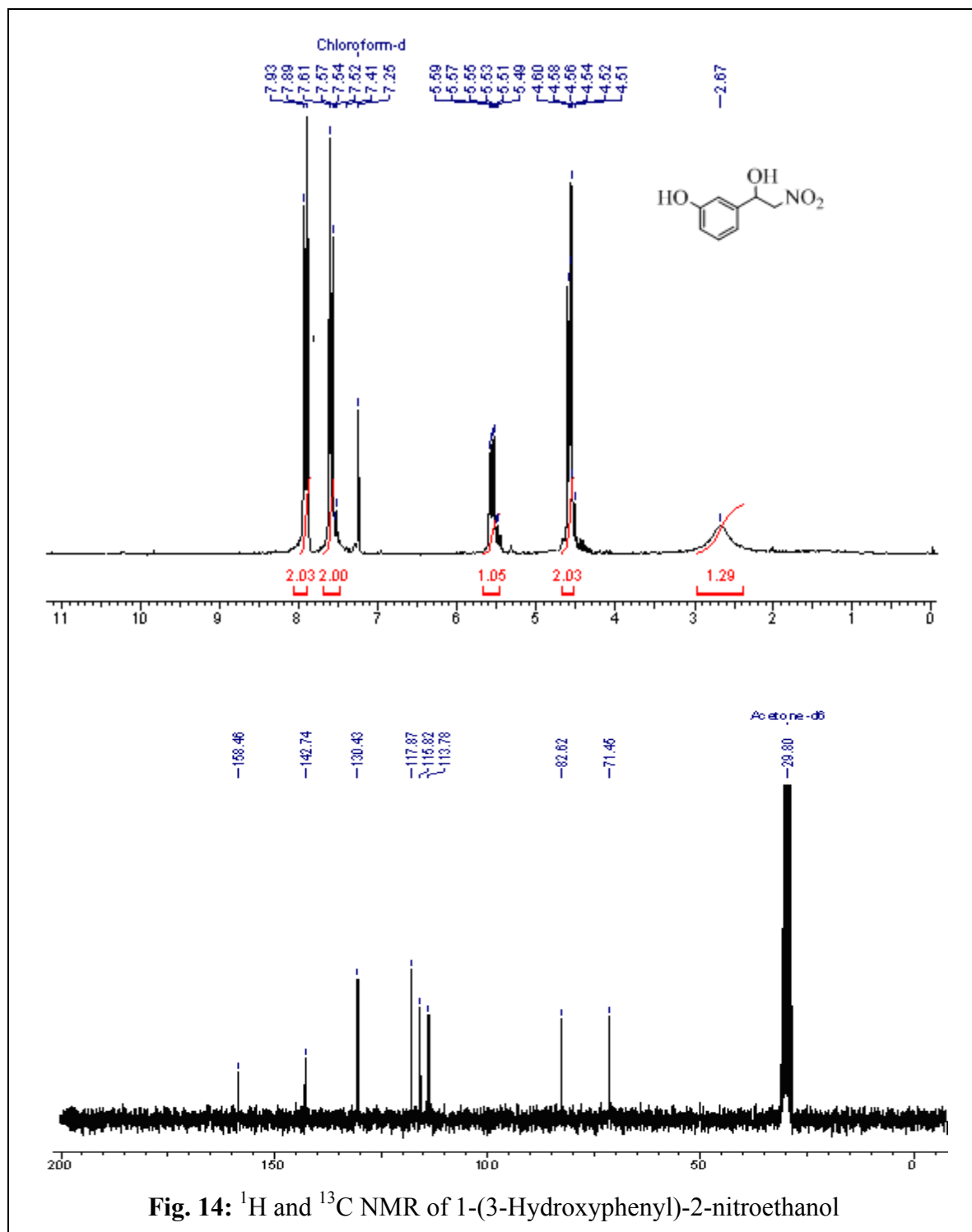


Fig. 14: ^1H and ^{13}C NMR of 1-(3-Hydroxyphenyl)-2-nitroethanol

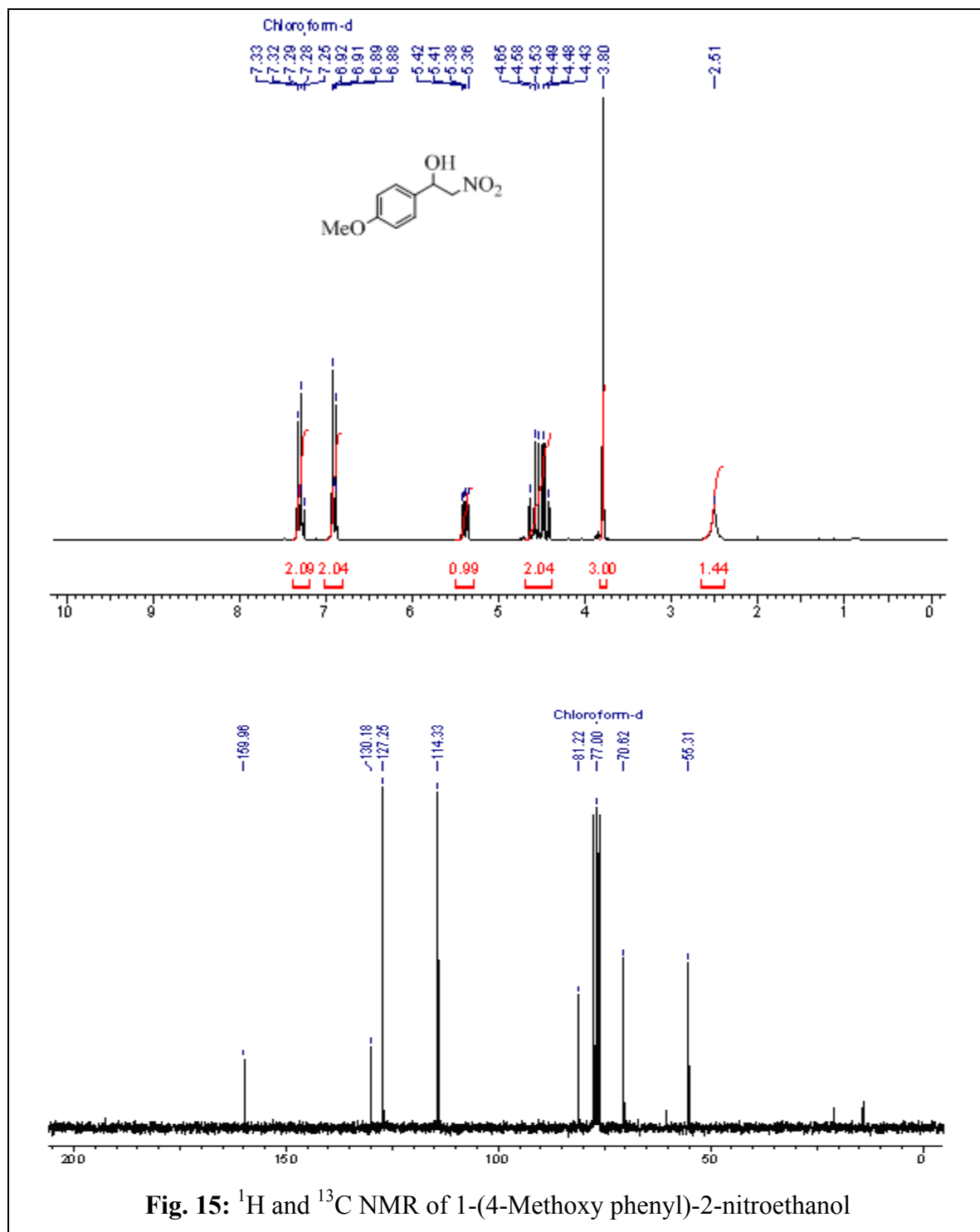


Fig. 15: ^1H and ^{13}C NMR of 1-(4-Methoxy phenyl)-2-nitroethanol

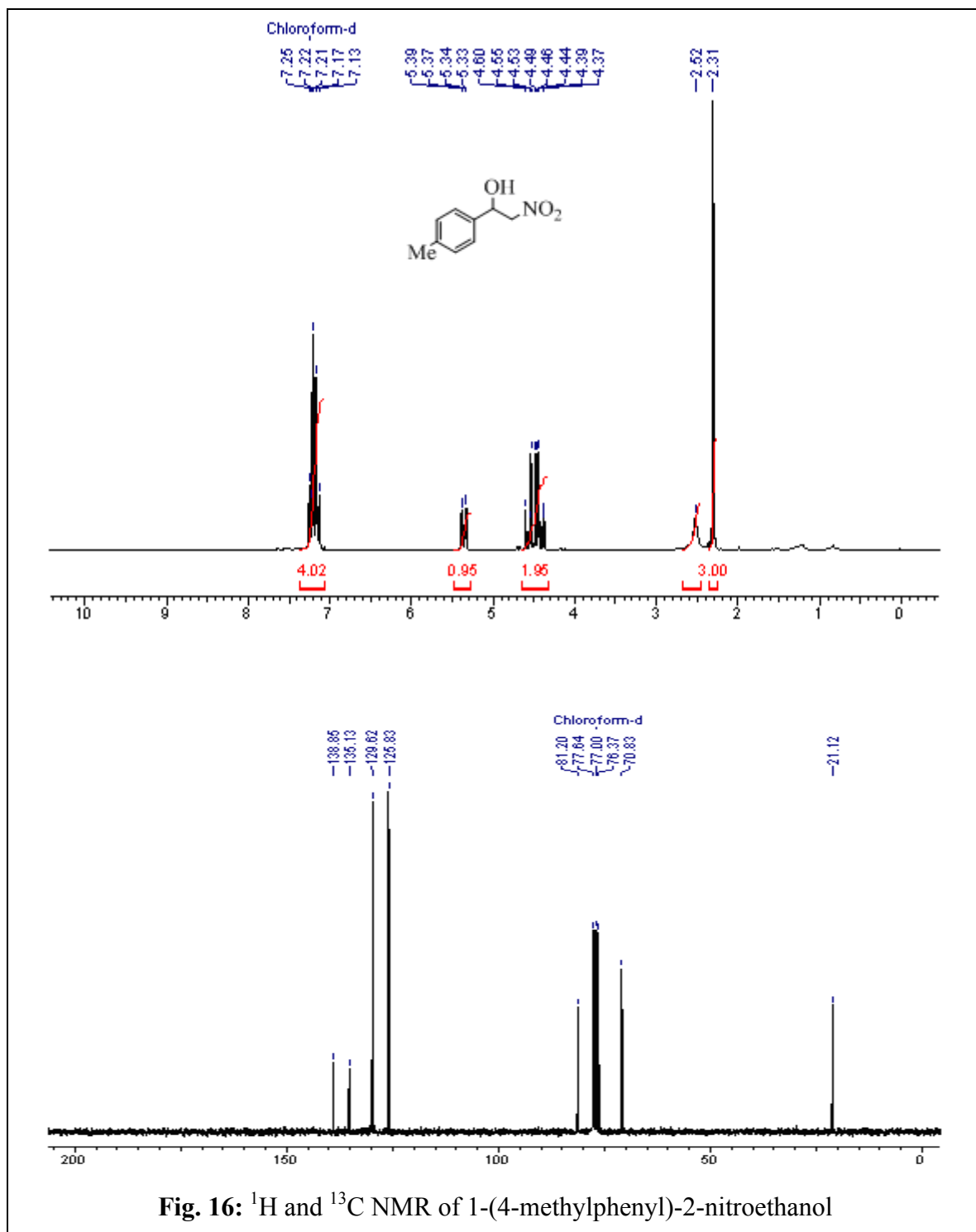


Fig. 16: ^1H and ^{13}C NMR of 1-(4-methylphenyl)-2-nitroethanol

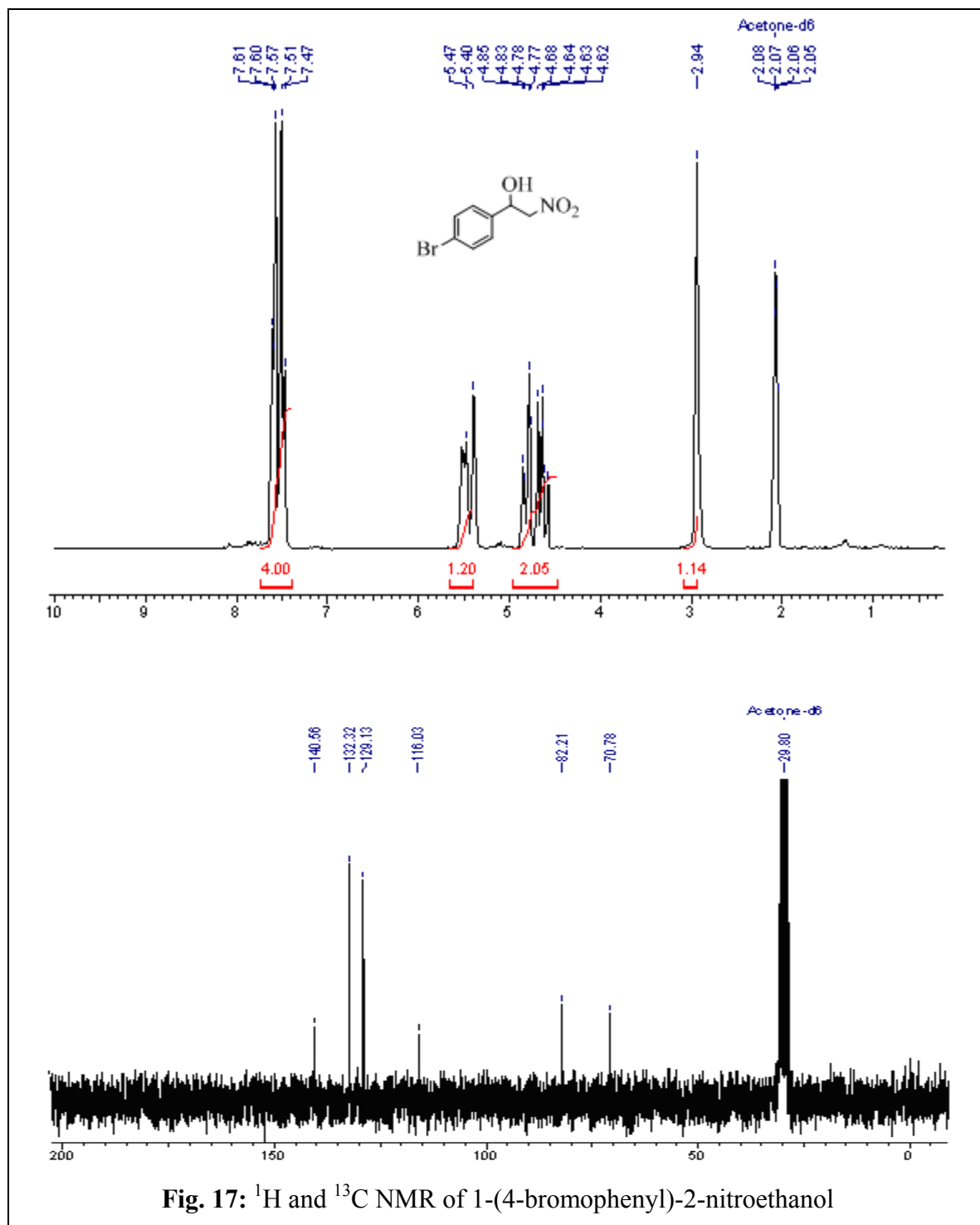
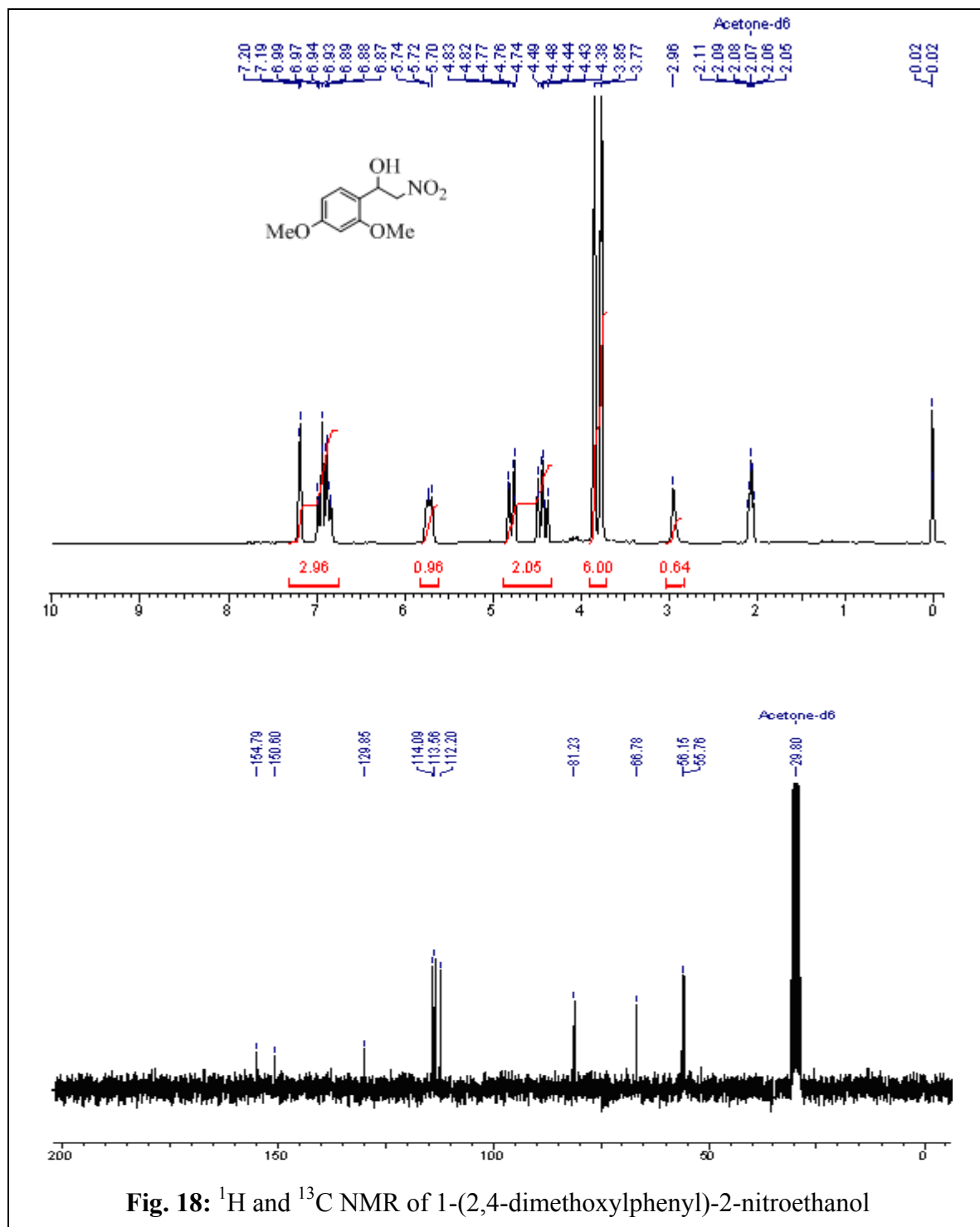
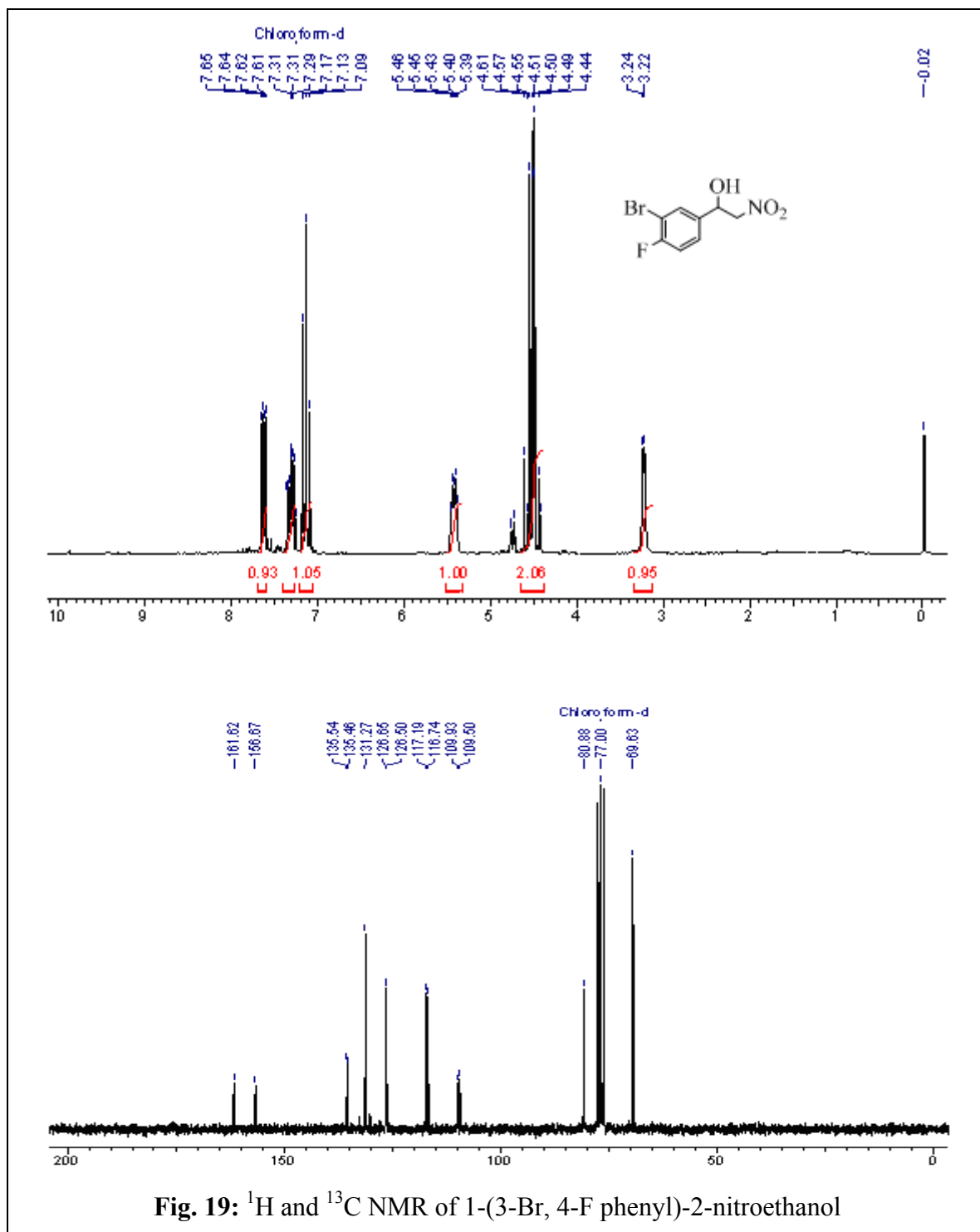
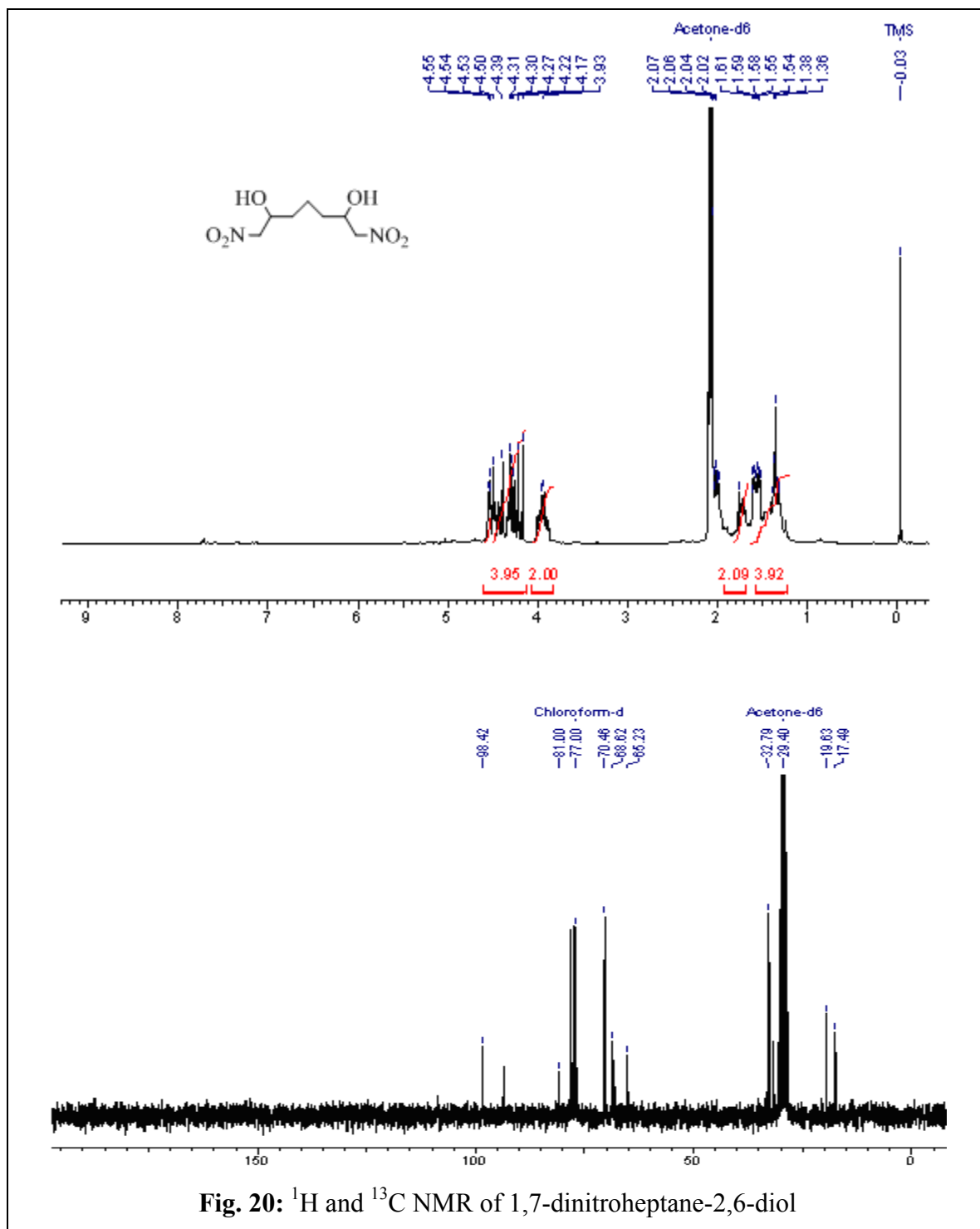


Fig. 17: ^1H and ^{13}C NMR of 1-(4-bromophenyl)-2-nitroethanol







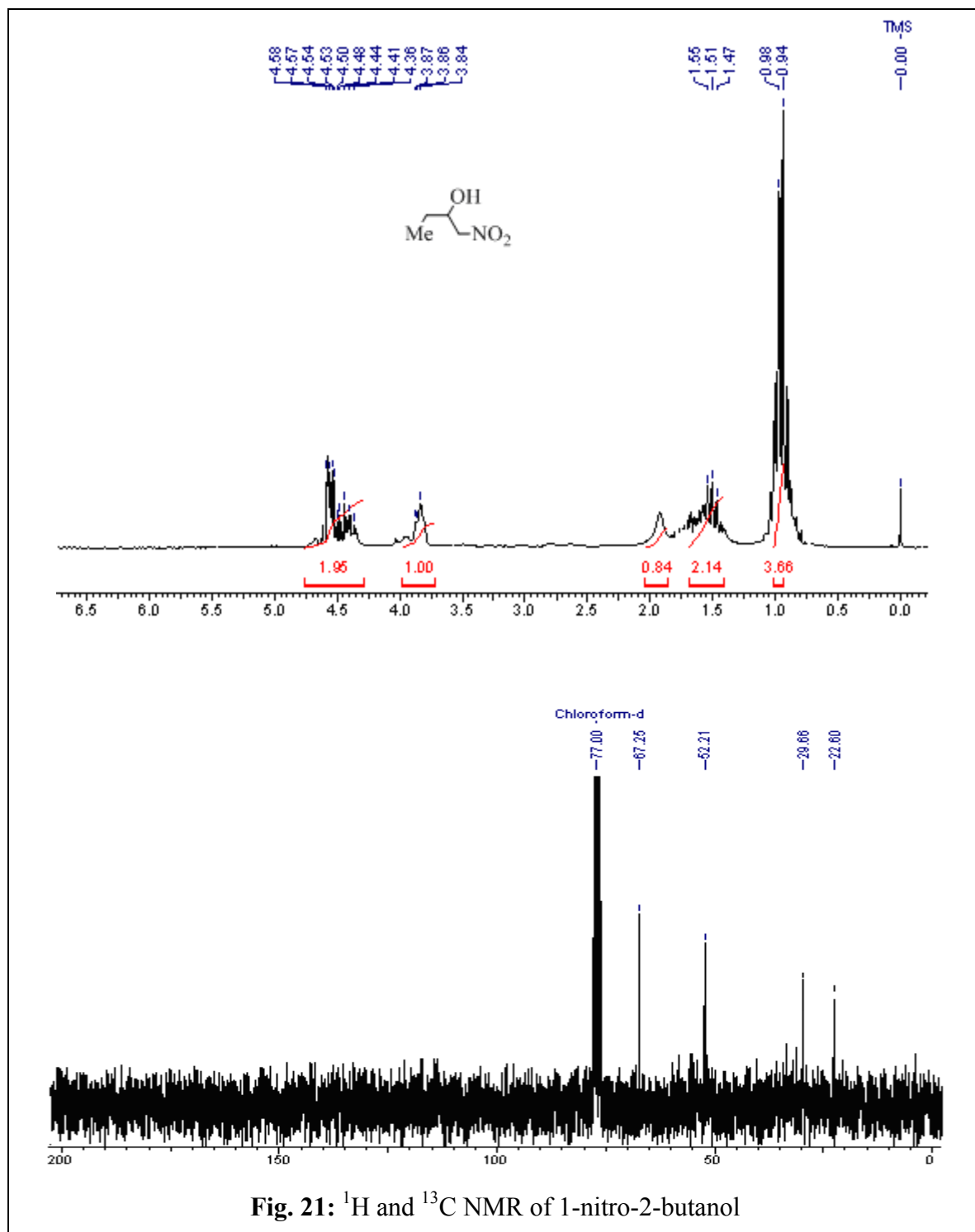


Fig. 21: ¹H and ¹³C NMR of 1-nitro-2-butanol

Section-II

A direct synthesis of amides from aldehydes and hydroxylamine hydrochloride in solvent free conditions

4.2.1 Introduction

Amides are valuable intermediates for wide variety of applications not only in organic synthesis but also in industrial scale of synthesis of detergents, lubricants and pharmaceuticals.²⁴ The conventionally amides are synthesized from the reaction of activated carboxylic acid derivatives (acid chlorides, acid anhydrides, or esters) with amines.^{25,26} However, the toxicity and waste generation involved in these synthetic method has made the researcher to have their objectives for the atom-economical synthesis of amides at high priority. Also amides are synthesized by enzymatic selective hydrolysis of nitriles as well lipase catalyzed amidation of acids and esters with ammonia. These approaches represent greener, however, serious drawbacks are prohibitive isolation costs as well as applicability to a limited range of substrates.²⁷ Beckmann rearrangement²⁸ is known to be an extremely valuable and versatile method for the synthesis of amides, which either require high temperature or the use of strong Bronsted or Lewis acids.²⁹ Apart from these methods, the various other methods for the synthesis of amides using varieties of reagent and precious metal catalysts such as Ir,³⁰ Rh,³¹ Ru,³² Ag/ Au,³³ Pd,³⁴ anhydrous oxalic acid,³⁵ chloral,³⁶ Sulfamic acid,³⁷ cyanuric chloride/DMF,³⁸ ethyl chloroformate/boron trifluoride etherate³⁹ and chlorosulfonic acid.⁴⁰ have been reported. Recently copper-catalyzed rearrangements of oxime to amide⁴¹ and bio glycerol-based carbon as a catalyst for the synthesis of amides from

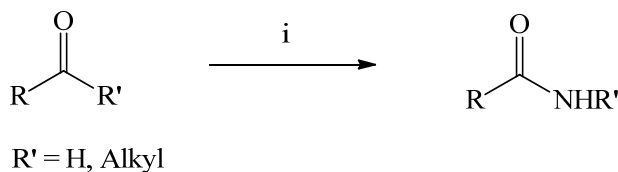
aldehydes have been also reported⁴² by J. M. J. Williams *et al.* and Y. V. D. Nageswar *et al.* respectively.

4.2.2 Review of literature

Literature survey reveals that there are several methods reported for the synthesis of amides from the reaction of various substituted aldehydes with hydroxylamine hydrochloride in the presence of various bases with or without ligands and solvent at different reaction temperatures. Few of them are described below.

Hashem Sharghi approach⁴³

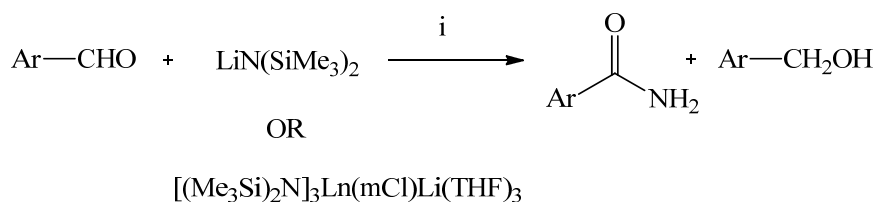
In this approach, various aldehydes were treated with hydroxylamine hydrochloride in the presence of titanium oxide catalyst under solvent-free reaction condition at high temperature (Scheme 9).



Scheme 9: Reagents and reaction conditions: (i) aldehyde (1 mmol), hydroxylamine hydrochloride (4.3 mmol) and TiO₂ (2 mmol), 140-170 °C, 1-9 h.

Shaowu Wang⁴⁴

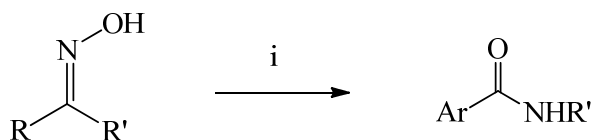
In this approach, aromatic aldehydes can be directly converted to the corresponding amides and alcohols in good to excellent yields by the treatment of aromatic aldehydes with lithium amide LiN(SiMe₃)₂ in the presence of catalytic lanthanide chlorides LnCl₃ or by the treatment of aromatic aldehydes with a stoichiometric amount of lanthanide amides [(Me₃Si)₂N]₃Ln(Cl)Li(THF)₃ at ambient temperature (Scheme 10).



Scheme 10: Reagents and reaction conditions: (i) aldehyde (2 mmol), $\text{LiN}(\text{SiMe}_3)_2$ (1.0 mmol), LnCl_3 (0.05 mmol), toluene (10 mL), RT, 2-3 days.

Robert Crabtree approach⁴⁵

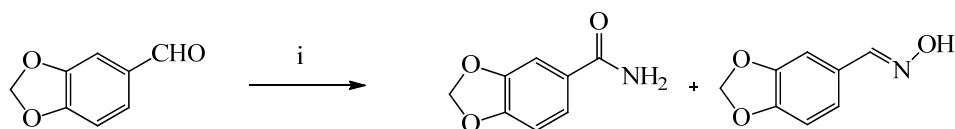
In this approach, various oximes were converted into amide in one pot in the presence of Rhodium catalyst were reported (**Scheme 11**).



Scheme 11: Reagents and reaction conditions: (i) oxime (2 mmol), $\text{TerpyRuPPh}_3\text{Cl}_2$ (0.02 mmol), toluene, reflux, 8 h.

Nemai Ganguly's approach⁴⁶

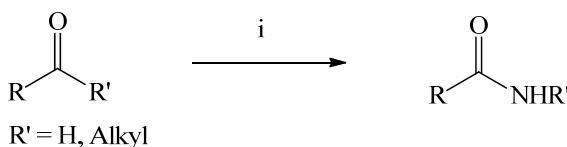
In this approach, various aldehyde was converted into amides in good to excellent yields has been accomplished employing hydroxylamine hydrochloride (1 mol equiv), sodium acetate (1.1 mol equiv), and copper sulfate pentahydrate (5 mol %) under neat conditions at 110 °C (**Scheme 12**).



Scheme 12: Reagents and reaction conditions: (i) Aldehyde (1 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1 mmol), NaOAc (1.1 mmol), $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (5 mol %), 110 °C, under air, 2-6 h.

Hashem Sharghi approach⁴⁷

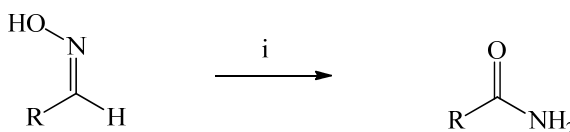
In this approach, various aldehydes were treated with hydroxylamine hydrochloride in the presence of Zinc oxide catalyst under solvent-free reaction condition at high temperature (Scheme 13).



Scheme 13: Reagents and reaction conditions: (i) aldehyde (1 mmol), hydroxylamine hydrochloride (4.3 mmol) and ZnO (2 mmol), 140-170 °C, 5-15 h.

Jonathan Williams's approach⁴⁸

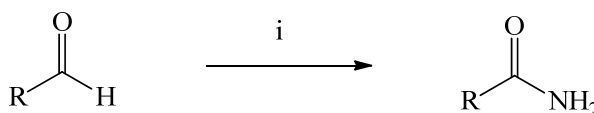
Jonathan Williams *et al* reported the rearrangement of oximes into primary amides catalyzed by $\text{Cu}(\text{OAc})_2$ in toluene solvent at 80 °C (Scheme 14).



Scheme 14: Reagents and reaction conditions: (i) oxime (3 mmol), $\text{Cu}(\text{OAc})_2$ (1-3 mmol), toluene, 80 °C, 24 h.

Robert Mebane approach⁴⁹

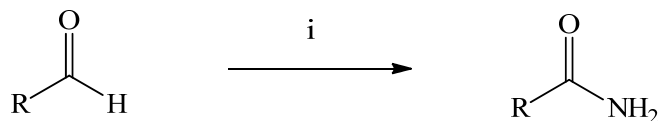
In this approach, various aldehydes were treated with hydroxylamine hydrochloride in the DMSO solvent at 100 °C and then addition of base and hydrogen peroxide to obtain the various amides (Scheme 15).



Scheme 15: Reagents and reaction conditions: (i) aldehyde (1 mmol), hydroxylamine hydrochloride (3.8 mmol), NaOH (5.6 mmol), H_2O_2 (2.5 mL), 100 °C, 1 h.

Hashem Sharghi approach⁵⁰

In this approach, various aldehydes were treated with hydroxylamine hydrochloride in the presence of Wet Alumina and mesetyl chloride without any organic solvents at 100 °C (Scheme 16).



Scheme 16: *Reagents and reaction conditions:* aldehyde (1 mmol), hydroxylamine hydrochloride (0.4 mmol), MeSO₂Cl (1 mL), wet Alumina (4.9 mmol), 100 °C, 1-3 h.

4.2.3 Present work

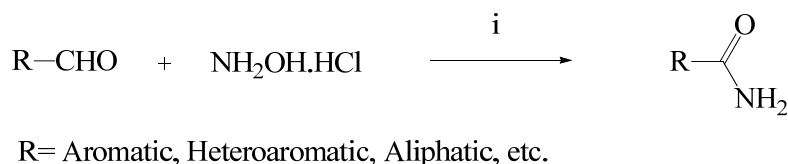
4.2.3.1 Objectives

Although various protocols⁵¹ have been reported in the literature, however, all the reported protocols have their own drawbacks and limitations such as the use of toxic solvents, expensive reagents, and formation of unwanted by products, prolonged reaction timings, tedious workup procedures and low yields.⁵² Therefore, aim and objective of the protocol is to develop a more general and cost effective catalysts for the synthesis of amides, which is equally applicable to electron-deficient, electronically neutral and electron-rich aldehydes and enable amide formation under much milder, more efficient, environment friendly conditions.

4.2.4 Results and discussion

Recently, the development of solvent-free protocols has become the center of interest for organic reaction^{53, 54} due to not only an environmental point of view but also in the view of simplicity of the reaction protocol. As part of our continuous efforts to explore the

further application of copper fluorapatite (CuFAP)²³ as heterogeneous, reusable catalyst for organic synthesis, we have now describe in this chapter, an efficient, general and solvent-free protocol for the one pot synthesis of amides from the various aldehydes utilizing an inexpensive and readily available hydroxylamine hydrochloride at 100 °C in good to excellent yields (**Scheme 17**).



Scheme 17: *Reagents and reaction conditions:* (i) Aldehyde (1 mmol), NH₂OH.HCl (1.2 mmol), CuFAP (100 mg), 100 °C, 2-5 h.

The copper fluorapatite (CuFAP) catalysed synthesis of benzamide from benzaldehydes and hydroxylamine hydrochloride was selected as a model reaction for optimizing the reaction conditions. Initially, we decided to study the effect of the various solvents on this reaction. The results are summarized in **Table 4**. The solvent-free reaction gives the product in 92 % yield at 100 °C whereas at reflux condition, however, other solvents such as ethyl acetate, THF, methanol, ethanol, Toluene, dichloroethane and acetonitrile provided poor yields to the desire product.

The results on the solvent effect show that benzaldehyde (1 mmol) reacts with hydroxylamine hydrochloride (1.2 mmol) over 100 mg CuFAP catalyst in a solvent-free condition at 100 °C to obtained benzamide as product in 92 % yield. The results on this substrate using CuFAP catalyst, prepared as per literature procedure²² made us to select as a model reaction to optimize the reaction conditions.

Table 4: Effect of solvent for the synthesis of benzamide from benzaldehyde^a

$\text{C}_6\text{H}_5\text{CHO} + \text{NH}_2\text{OH.HCl} \xrightarrow[\text{Without Solvent, 100 } ^\circ\text{C}]{\text{CuFAP}} \text{C}_6\text{H}_5\text{CONH}_2$			
Entry	Solvent	Temperature	Yield ^b (%)
1	Ethylacetate	70	23
2	THF	65	40
3	Methanol	70	28
4	Ethanol	85	52
5	Toluene	110	67
6	DCE	84	37
7	CH ₃ CN	85	49
8	Solvent-free	100	92 ^c

^a Reaction conditions: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), CuFAP (100 mg), solvent (10 mL), 6 h.

^b Isolated yields.

^c Reaction time 2 h.

The promising results on the optimized reaction condition using CuFAP catalyst encourage us to investigate the feasibility of this methodology to wide range of substituted aldehydes for the synthesis of amides. As shown in **Table 5**, a variety of the substituted aldehydes possessing a variety of the functional group reacted with hydroxylamine hydrochloride in the presence of CuFAP catalyst at 100 °C under solvent-free conditions to obtain amides as product in good to excellent yield (**Table 5**, entries 2-21). No desired product was obtained during the same reaction condition in absence of CuFAP catalyst (**Table 5**, entry 1).

Benzaldehyde with electron donating group such as 3,4-dimethoxybenzaldehyde, 2-hydroxy,3-methoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 4-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-

methylbenzaldehyde, 4-isopropylbenzaldehyde and piperonal (**Table 5**, entries **3-12**) reacted with hydroxylamine hydrochloride took longer reaction time and provided moderate yields as compare benzaldehyde (**Table 5**, entry **2**) whereas, benzaldehyde

Table 5: CuFAP catalyzed conversion of aldehydes to amides under neat conditions^a

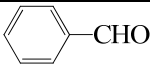
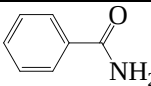
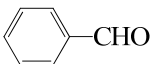
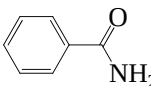
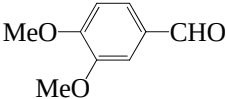
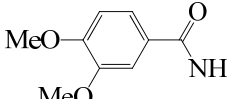
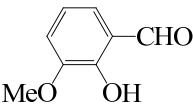
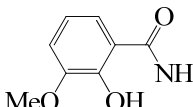
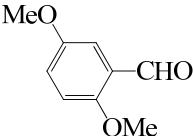
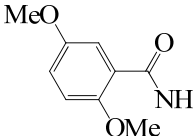
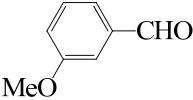
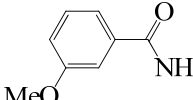
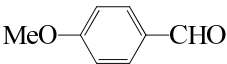
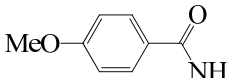
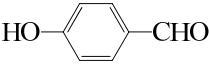
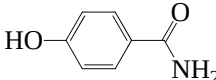
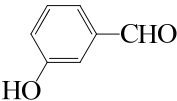
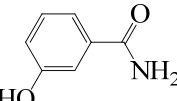
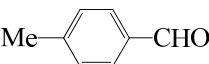
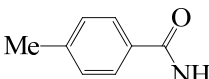
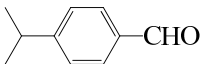
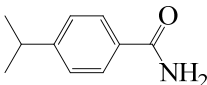
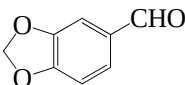
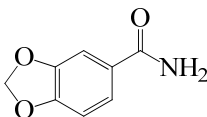
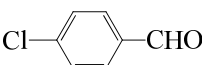
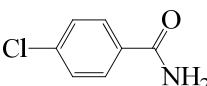
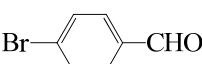
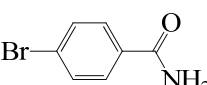
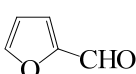
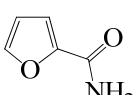
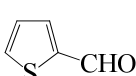
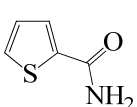
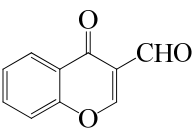
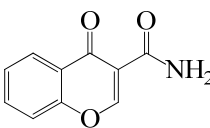
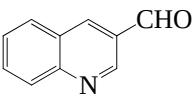
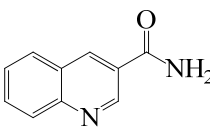
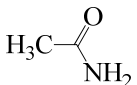
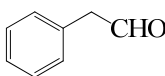
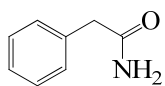
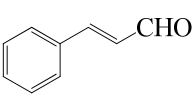
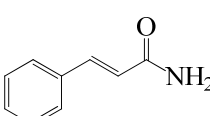
$\text{R-CHO} + \text{NH}_2\text{OH.HCl} \xrightarrow[\text{Without Solvent, 100 } ^\circ\text{C}]{\text{CuFAP}} \text{R}-\overset{\text{O}}{\underset{\text{NH}_2}{\text{C}}}$				
Entry	Aldehyde	Amide	Time(h)	Yield ^b (%)
1			12	N.R. ^c
2			2	92
3			4	86
4			4	85
5			4	89
6			3	91
7			4	90
8			4	89
9			3	91
10			3	88

Table 5 (Continued)

11			4	86
12			4	88
13			2	96
14			2	94
15			2	94
16			2	96
17			2	93
18			3	93
19	$\text{H}_3\text{C}-\text{CHO}$		5	83
20			5	86
21			5	88

^a Reaction conditions: Aldehyde (1 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.2 mmol), CuFAP(100 mg), 100 °C.

^b Isolated yield.

^c No Reaction without CuFAP

with electron withdrawing group such as 4-chlorobenzaldehyde and 4-bromobenzaldehyde (**Table 5**, entry **13** and **14**) as well as heteroaromatic aldehydes such

as 2-furfural, Thiophen-2-aldehyde, 3-chromonyl and 3-quinoline (**Table 5**, entries **15-18**) provided excellent yields. The acetaldehyde, phenyl acetaldehyde, and cinnamaldehyde (**Table 5**, entries **19-21**) provided poor yields as compare to benzaldehyde (**Table 5**, entry **2**). The results in the **Table 5** clearly indicate that the reaction is applicable to large number of substrate having sensitive functional groups; however, the reaction time and the yield obtained are dependent on the nature of substituents on the aldehydes.

Table 6: Recyclability study of CuFAP catalyzed conversion of benzaldehyde to benzamide^a

$\text{C}_6\text{H}_5\text{CHO} + \text{NH}_2\text{OH.HCl} \xrightarrow[\text{Without Solvent, 100 } ^\circ\text{C}]{\text{CuFAP}} \text{C}_6\text{H}_5\text{CONH}_2$	
Entry	Yield ^b (%)
1	92
2	92
3	90
4	91

^a Reaction conditions: benzaldehyde (1 mmol), NH₂OH.HCl (1.2 mmol), CuFAP(100 mg), 100 °C, 2 h

^b Isolated yields.

The recyclability of the CuFAP catalyst for the synthesis of amides was investigated using benzaldehyde and hydroxylamine hydrochloride under solvent-free conditions at 100 °C. The results are summarized in **Table 6**. After the completion of the reaction, the catalyst was recovered quantitatively by filtration and recycled several times, however, no loss of catalytic activity was observed even after third recycle (**Table 6**, entries **2-4**). The catalytic activity of reused catalyst is very much comparable with fresh catalyst (**Table 6**, entry **1**), which is clearly shows no loss and/ or leaching of copper take place during the course of reactions and reused catalyst shows excellent performance.

4.2.5 Conclusion

In conclusion, highly efficient protocol has been developed over non expensive, ligand free, recyclable, ecofriendly, heterogeneous copper fluorapatite (CuFAP) catalyst under solvent-free conditions for the synthesis of amides from the reaction of various aldehydes with hydroxylamine hydrochloride in good to excellent yield. The developed protocol is general and applicable to large number of substrate having sensitive functional groups. The CuFAP catalyst was recovered by filtration and recycled several times without loss catalytic activity.

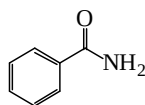
4.2.6 Experimental section

4.2.6.1 General experimental procedure for the CuFAP catalysed synthesis of amides:

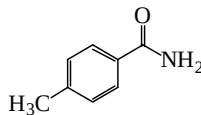
Aldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol) and CuFAP catalyst (100 mg) were taken in 10 mL round bottomed flask and stirred at 100 °C for 2-5 h (**Table 5**) and the progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was diluted with 20 mL methanol followed by filtration to recover the catalyst. The filtrate was concentrated in vacuo to get the crude product, which was further purified by column chromatography on silica gel using hexane/ethyl acetate mixture 70:30 to obtain amide as product.

4.2.6.2 Spectral data for amides

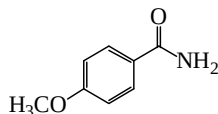
Benzamide:



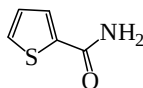
Yield: 92 %; **¹H NMR** (200 MHz, CDCl₃): δ 3.17 (brs, 2H), 7.42 (m, 3H), 7.95 (m, 2H);
¹³C NMR (200 MHz, CDCl₃): δ 128.29, 129.05, 132.09, 135.20, 169.1

4-Methyl benzamide:

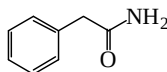
Yield: 88 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.37 (s, 3H), 2.92 (brs, 2H), 7.29 (d, 2H), 7.82 (d, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 21.28, 128.42, 129.65, 142.31, 168.85

4-Methoxy benzamide:

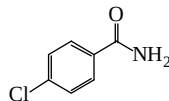
Yield: 90 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.0 (brs, 2H), 3.85 (s, 3H), 6.95 (d, 2H), 7.91 (d, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 65.71, 114.22, 127.42, 130.25, 163.15

Thiophenyl-2-amide:

Yield: 96 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.94 (brs, 2H), 7.11 (m, 1H), 7.67 (m, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 128.52, 129.36, 131.42, 163.8

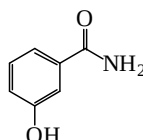
2-Phenyl acetamide:

Yield: 86 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.5 (s, 2H), 7.32 (m, 5H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 43.25, 127.22, 129.05, 130.0, 137.3, 173.05

4-Chloro benzamide:

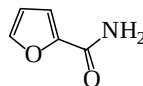
Yield: 96 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.18 (brs, 2H), 7.49 (dd, 2H), 7.95 (dd, 2H);

$^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 129.21, 130.14, 132.13, 133.97, 137.67, 167.88

3-Hydroxy benzamide:

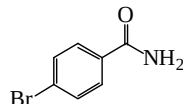
Yield: 91 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.15 (brs, 2H), 6.80 (m, 1H), 7.29 (m, 3H),

8.76 (brs, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 115.45, 119.12, 130.14, 158.33, 169.49.

Furanyl-2-amide:

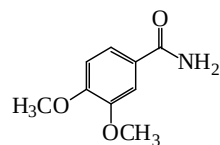
Yield: 94 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.0 (brs, 2H), 6.58 (t, 1H), 7.08 (d, 1H),

7.68 (d, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 112.59, 114.46, 145.34, 149.45, 160.18

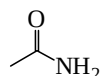
4-Bromo benzamide:

Yield: 94 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 7.48 (d, 2H), 7.94 (d, 2H); $^{13}\text{C NMR}$ (200

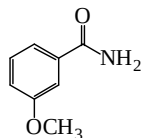
MHz, CDCl_3): δ 129.22, 130.16, 134.02, 137.69, 167.85

3,4-Dimethoxy benzamide:

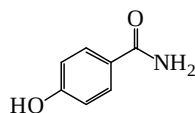
Yield: 86 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.87 (s, 3H), 3.9 (s, 3H), 7.03 (d, 1H), 7.54 (dd, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 56.08, 111.66, 113.27, 124.4, 136.97, 139.87, 168.11

Acetamide:

Yield: 83 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 1.86 (s, 3H), 3.02 (brs, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 22.44, 172.64

3-Methoxy benzamide:

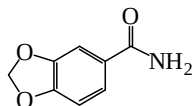
Yield: 91 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.04 (brs, 2H), 3.89 (s, 3H), 7.0 (d, 2H), 7.94 (d, 2H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 54.94, 113.45, 126.65, 129.48, 162.38

4-Hydroxy benzamide:

Yield: 89 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.22 (brs, 2H), 6.88 & 7.32(m, 4H), 8.84

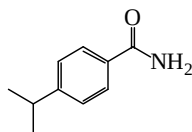
(brs, 1H); ^{13}C NMR (200 MHz, CDCl_3): δ 115.45, 119.28, 130.15, 158.34.

Piperonylamide:



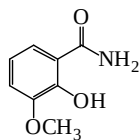
Yield: 88 %; ^1H NMR (200 MHz, CDCl_3): δ 2.91 (brs, 2H), 6.04 (d, 2H), 6.85 (t, 1H), 7.03 (dd, 1H), 7.17 (dd, 1H); ^{13}C NMR (200 MHz, CDCl_3): δ 102.33, 102.64, 105.79, 108.41, 108.95, 123.06, 148.87, 174.19

4-Isopropyl benzamide:

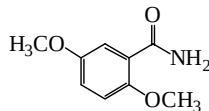


Yield: 86 %; ^1H NMR (200 MHz, CDCl_3): δ 1.23 (d, 6H), 2.06 (s, 2H), 2.9 (m, 1H), 7.31 (d, 2H), 7.86 (d, 2H); ^{13}C NMR (200 MHz, CDCl_3): δ 22.25, 24.43, 30.19, 44.78, 119.81, 129.47, 135.53, 137.77, 168.43

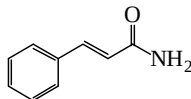
2-Hydroxy, 3-methoxybenzamide:



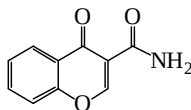
Yield: 85 %; ^1H NMR (200 MHz, CDCl_3): δ 2.95 (brs, 2H), 3.84 (s, 3H), 6.84-7.03 (m, 3H), 8.37 (s, 1H); ^{13}C NMR (200 MHz, CDCl_3): δ 56.33, 114.24, 116.43, 120, 122.18, 151.24, 170.25.

2,5-di-methoxybenzamide:

Yield: 89 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.92 (brs, 2H), 3.95 (s, 6H), 6.89 (dd, 1H), 7.58 (d, 1H), 7.74 (dd, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 29.65, 55.98, 110.29, 112.27, 121.7, 124.54, 148.65, 153.67, 171.6

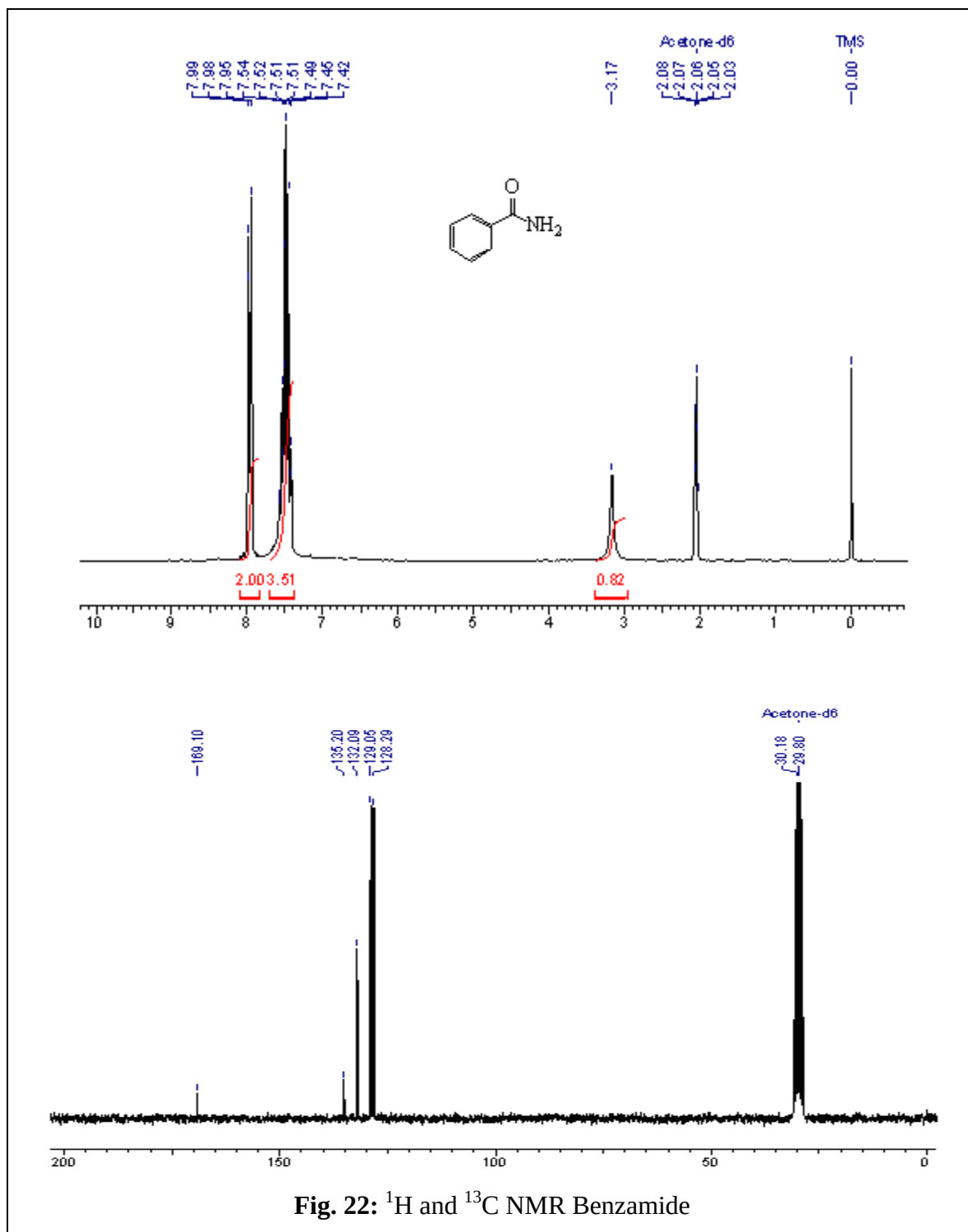
Cinnamamide:

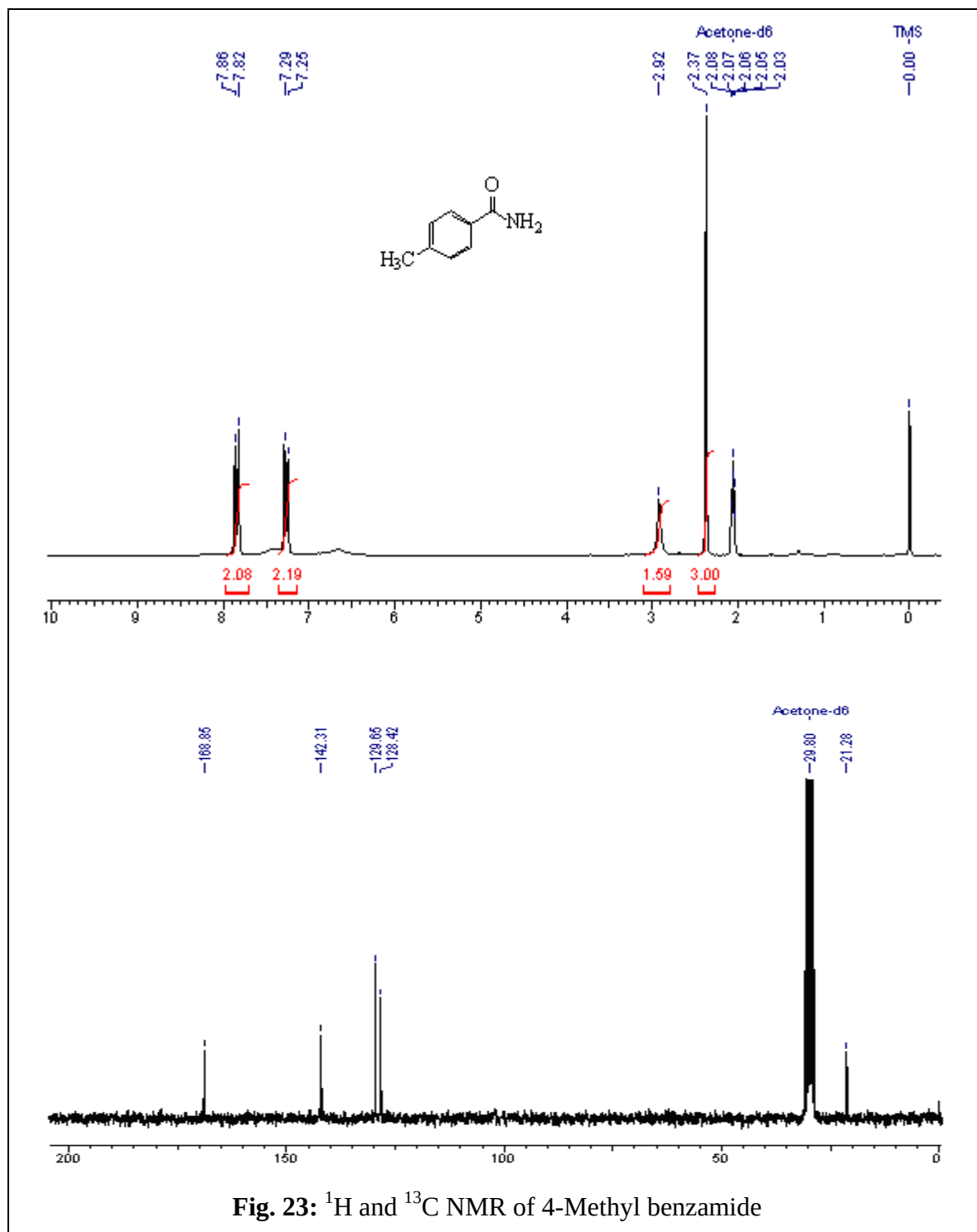
Yield: 88 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 2.98 (brs, 2H), 6.72 (d, 1H), 6.72 (m, 6H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 128.48, 129.66, 130.24, 136.16, 140.92, 167.92.

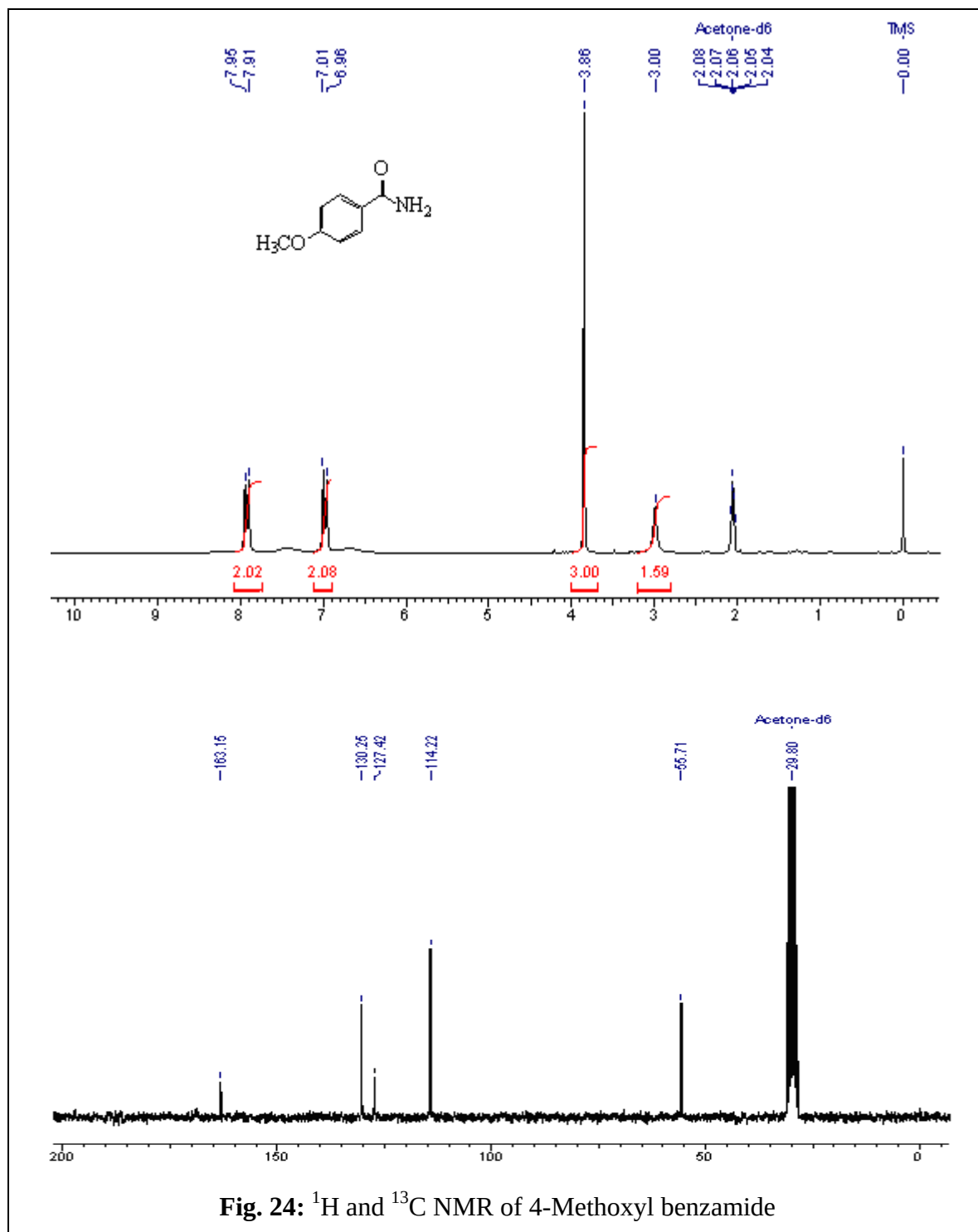
4-oxo-3-chromenylamide:

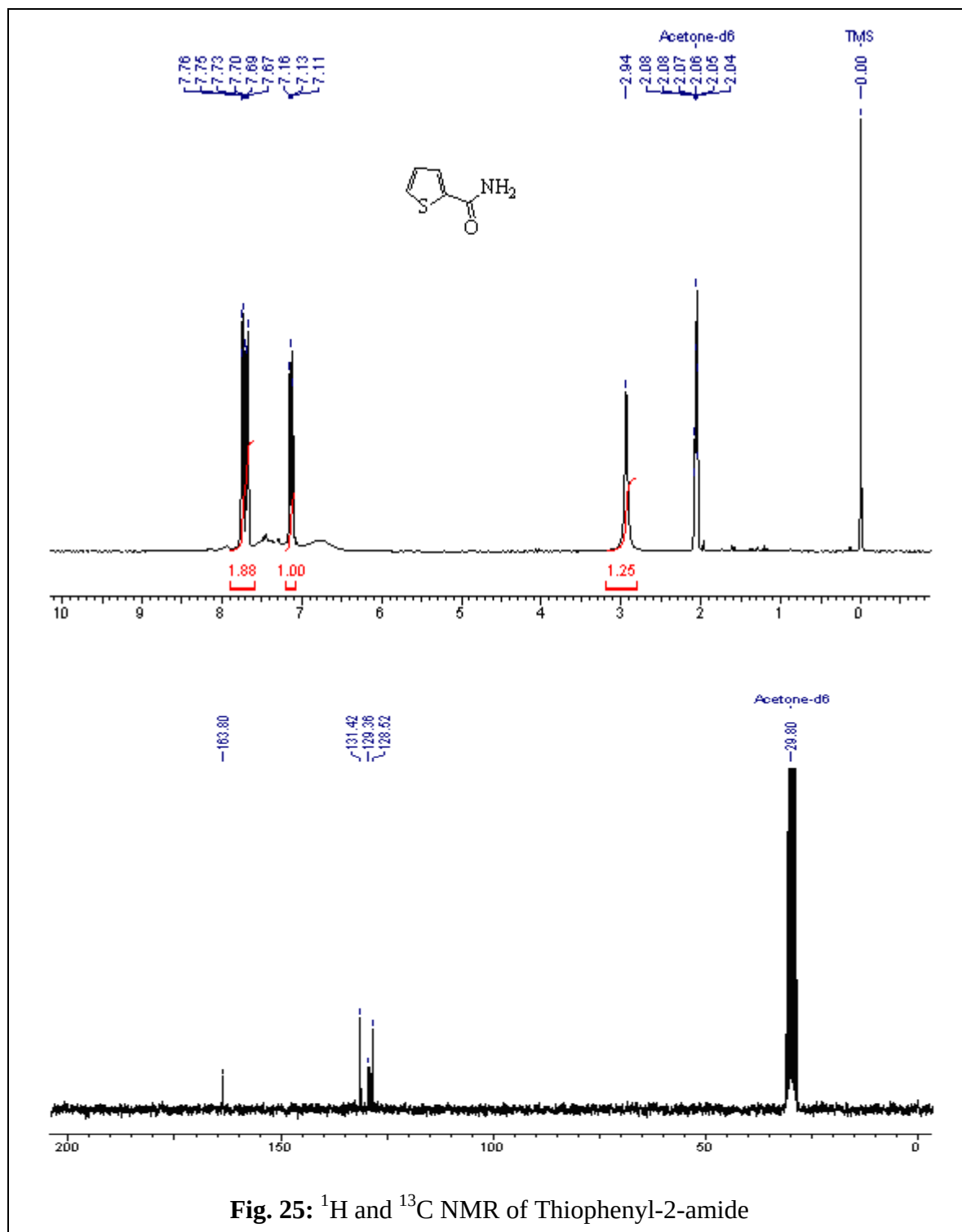
Yield: 93 %; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 3.02 (brs, 2H), 7.4 (m, 2H), 7.69 (m, 2H), 8.1 (m, 1H); $^{13}\text{C NMR}$ (200 MHz, CDCl_3): δ 117.24, 125.68, 126.13, 126.73, 134.23, 166.52, 188.79.

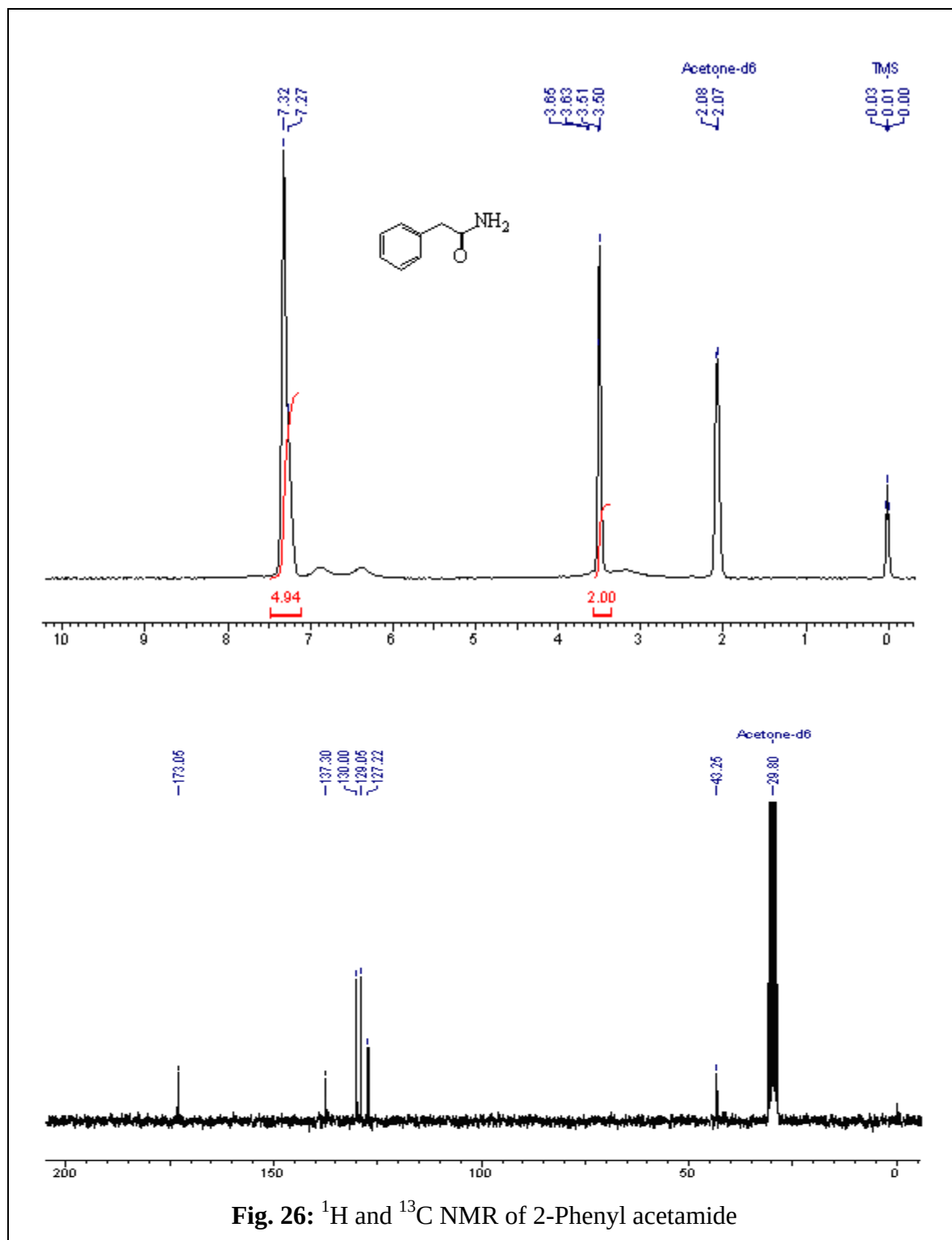
4.2.7 Spectral data











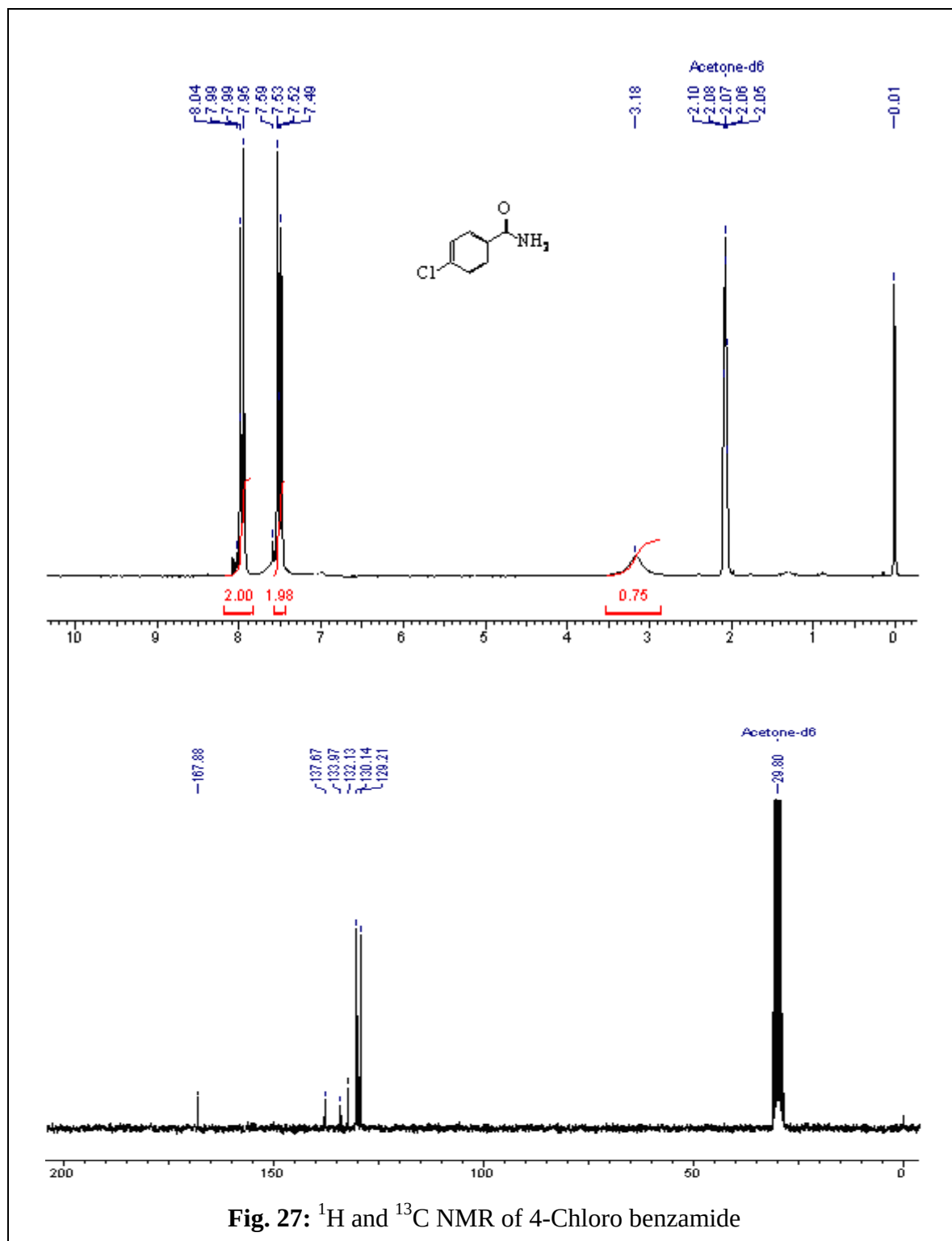


Fig. 27: ^1H and ^{13}C NMR of 4-Chloro benzamide

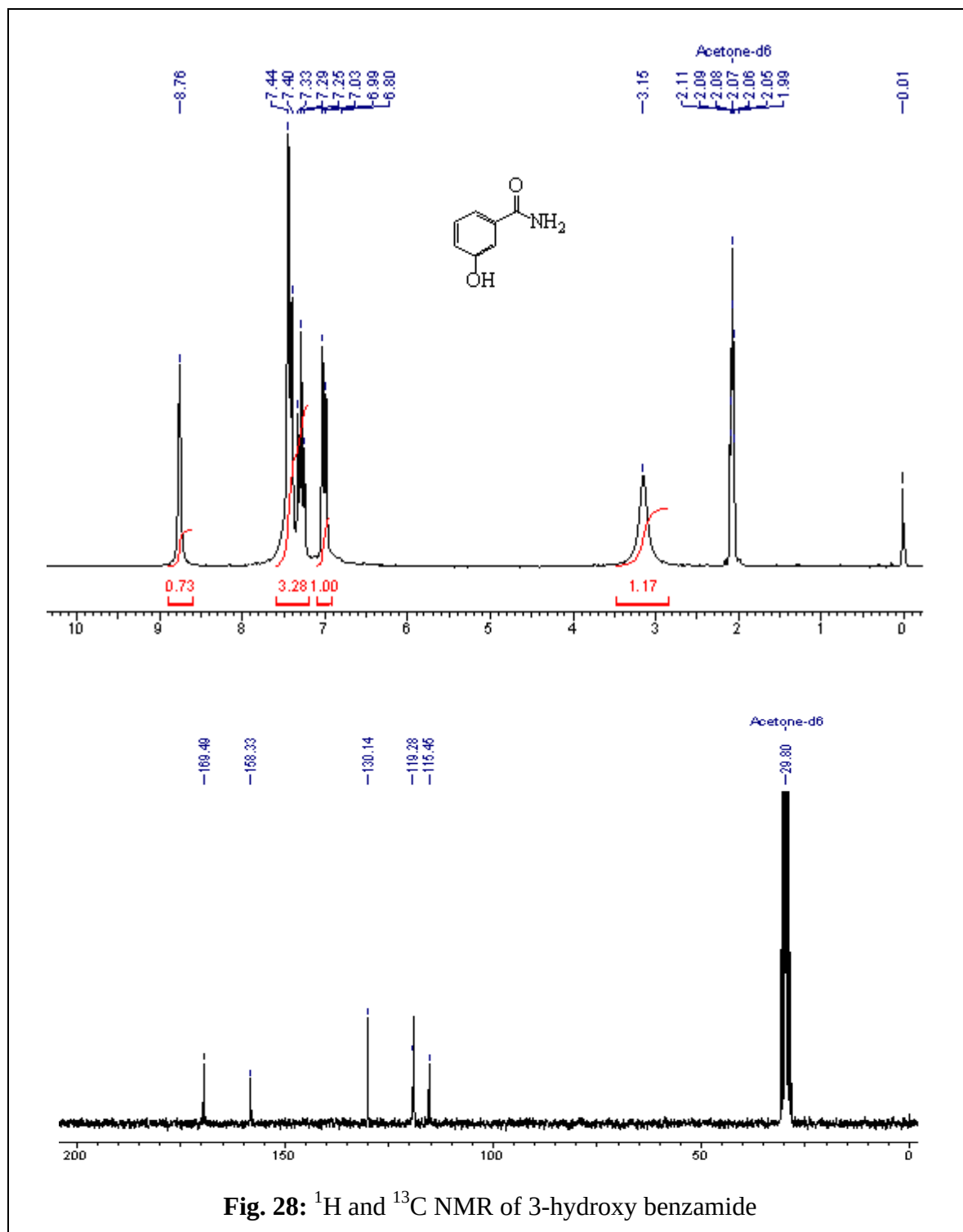
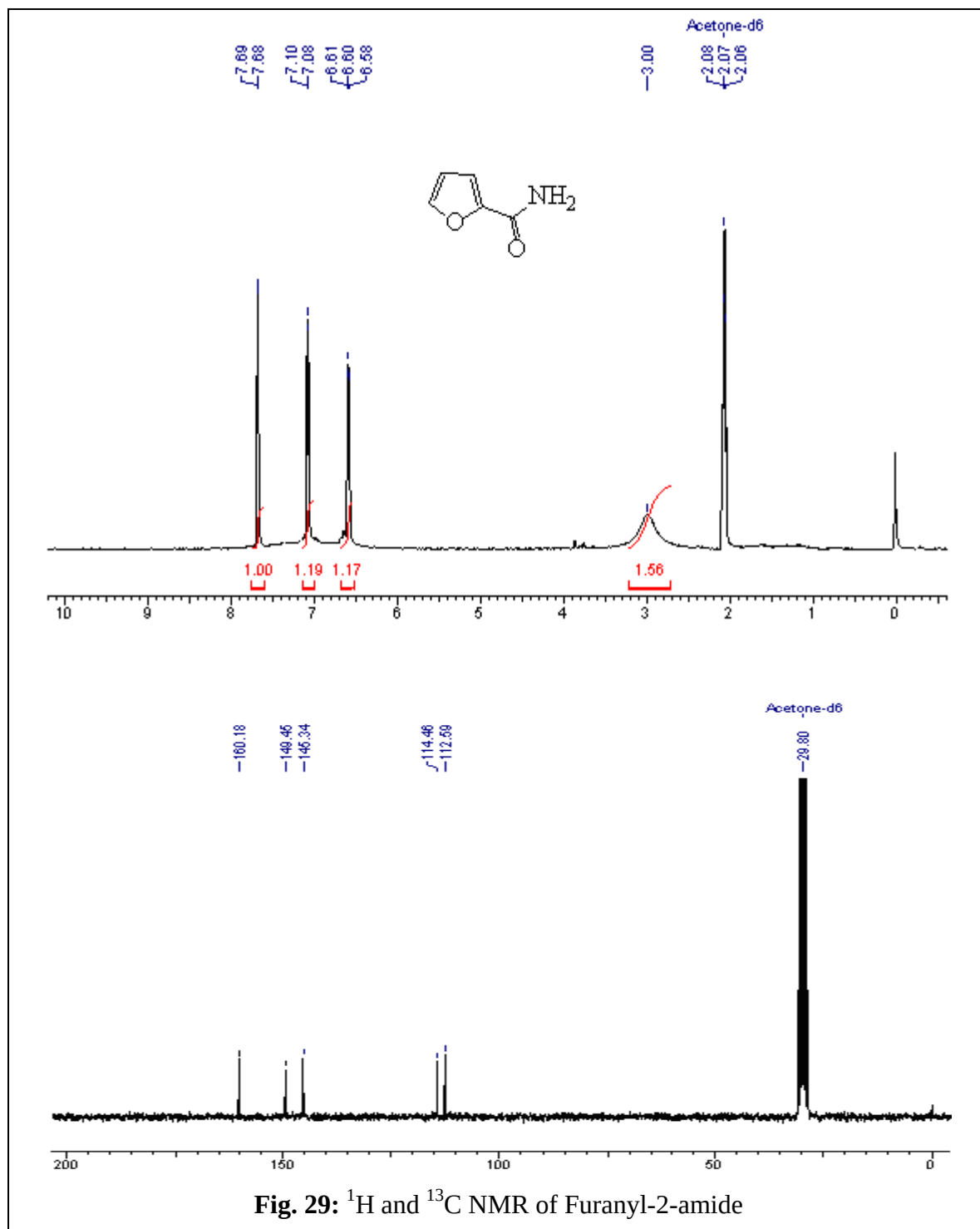
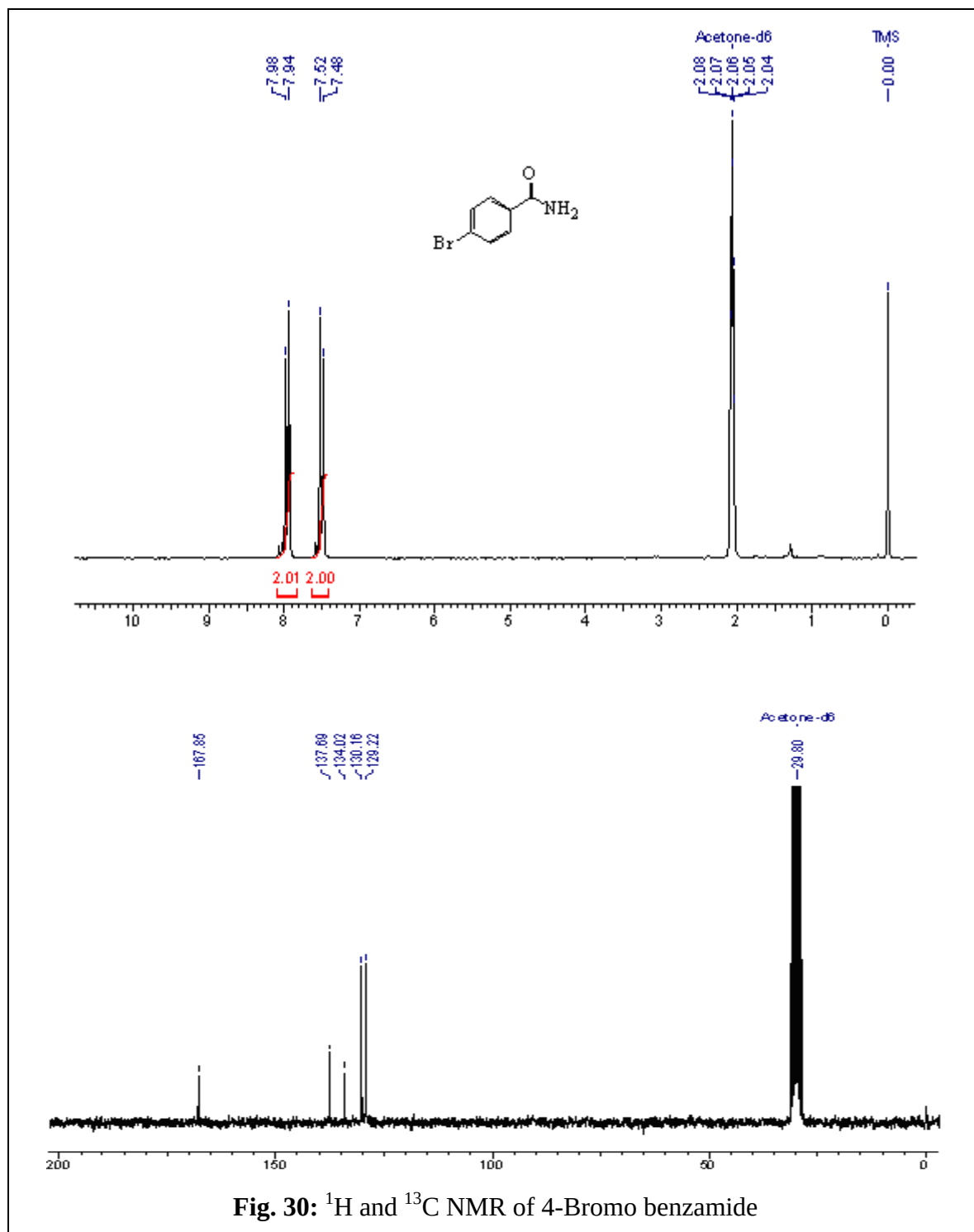
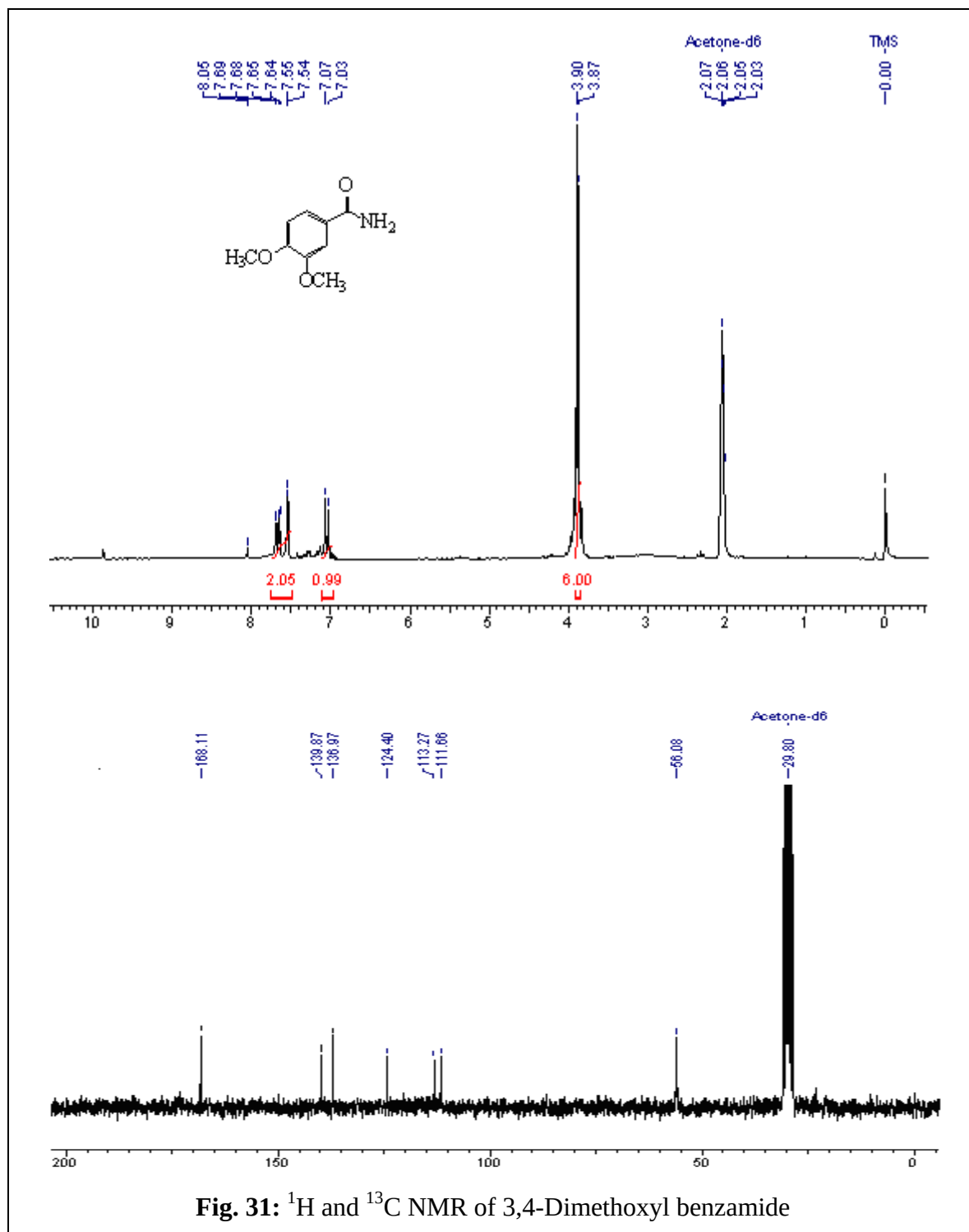
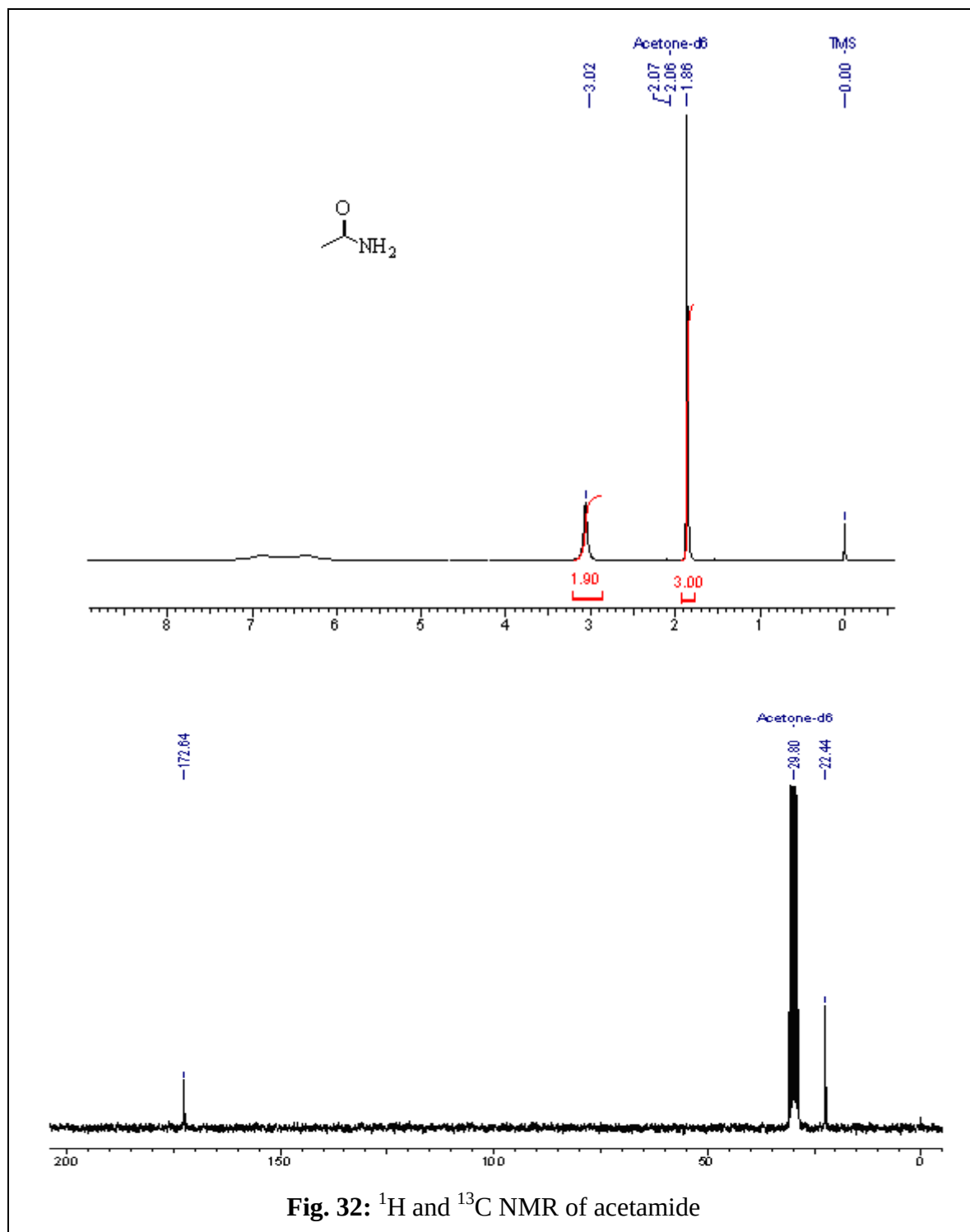


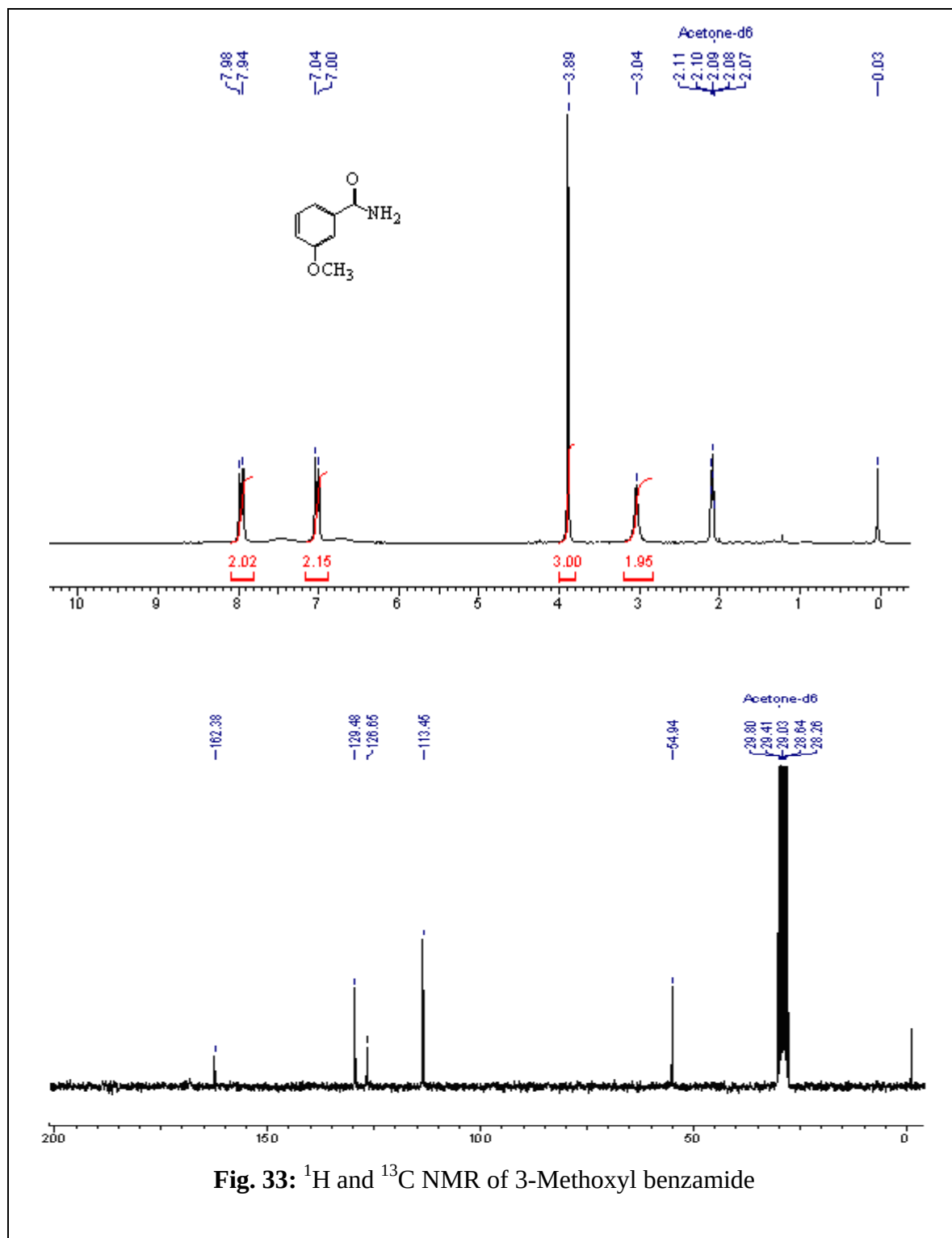
Fig. 28: ^1H and ^{13}C NMR of 3-hydroxy benzamide

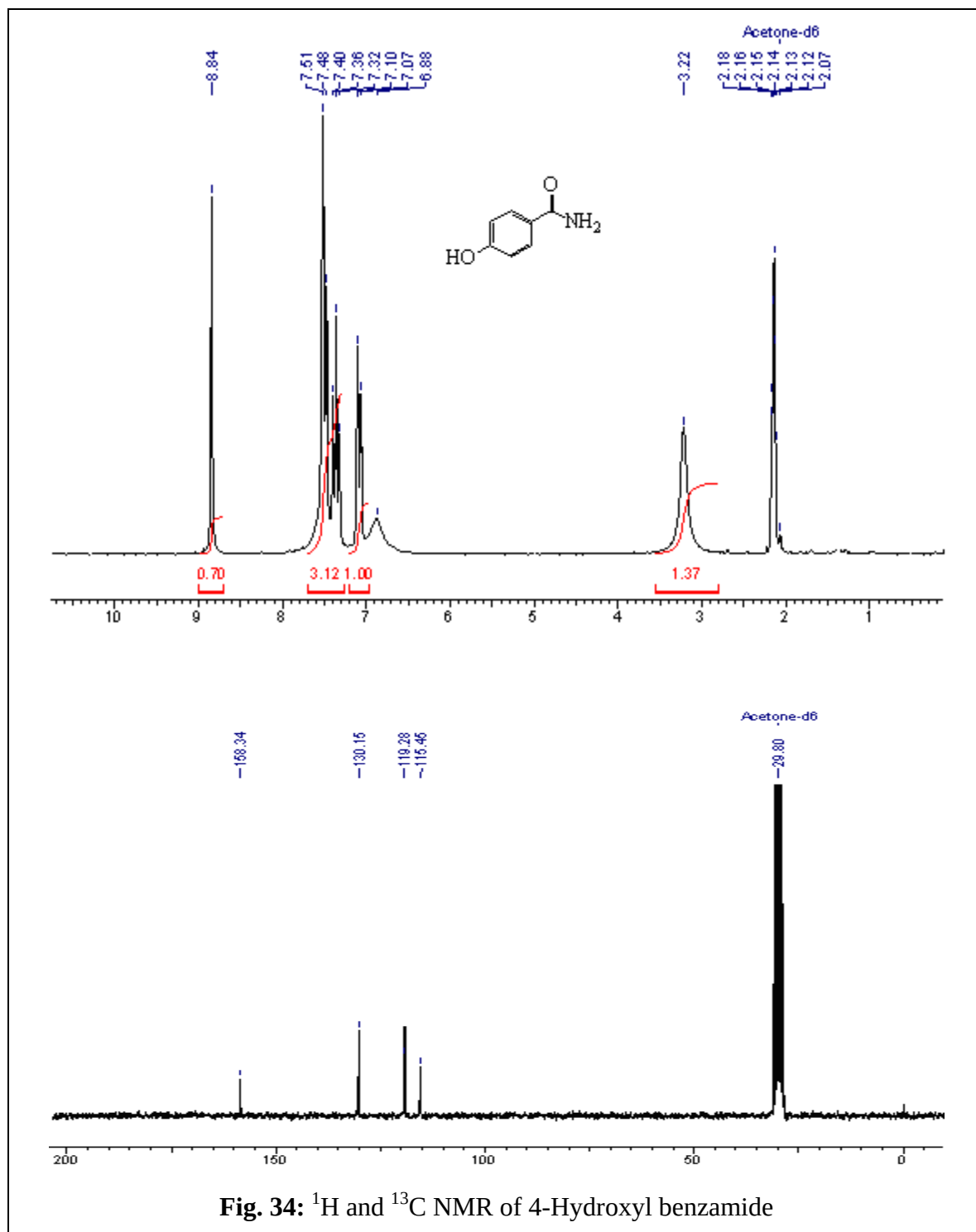


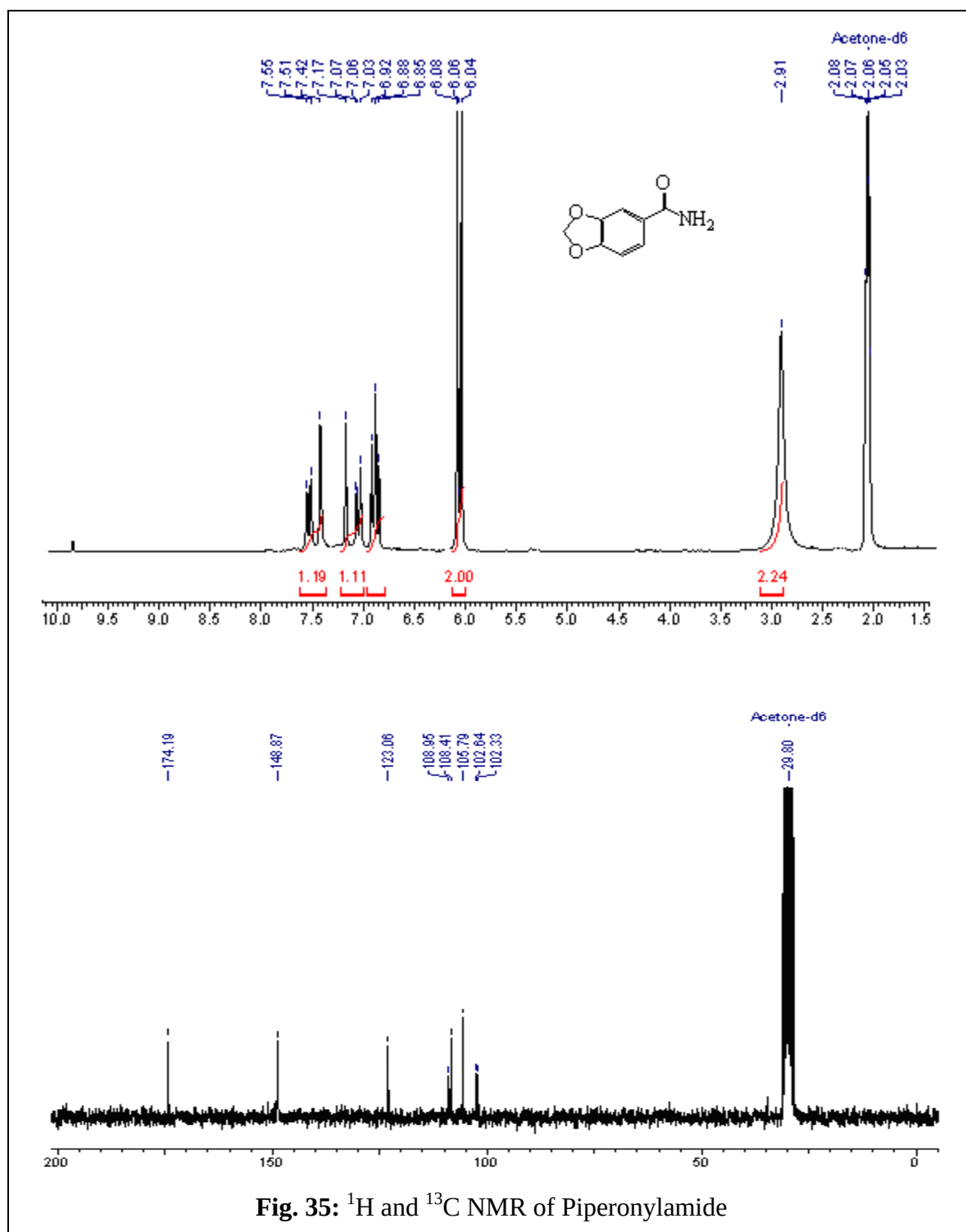












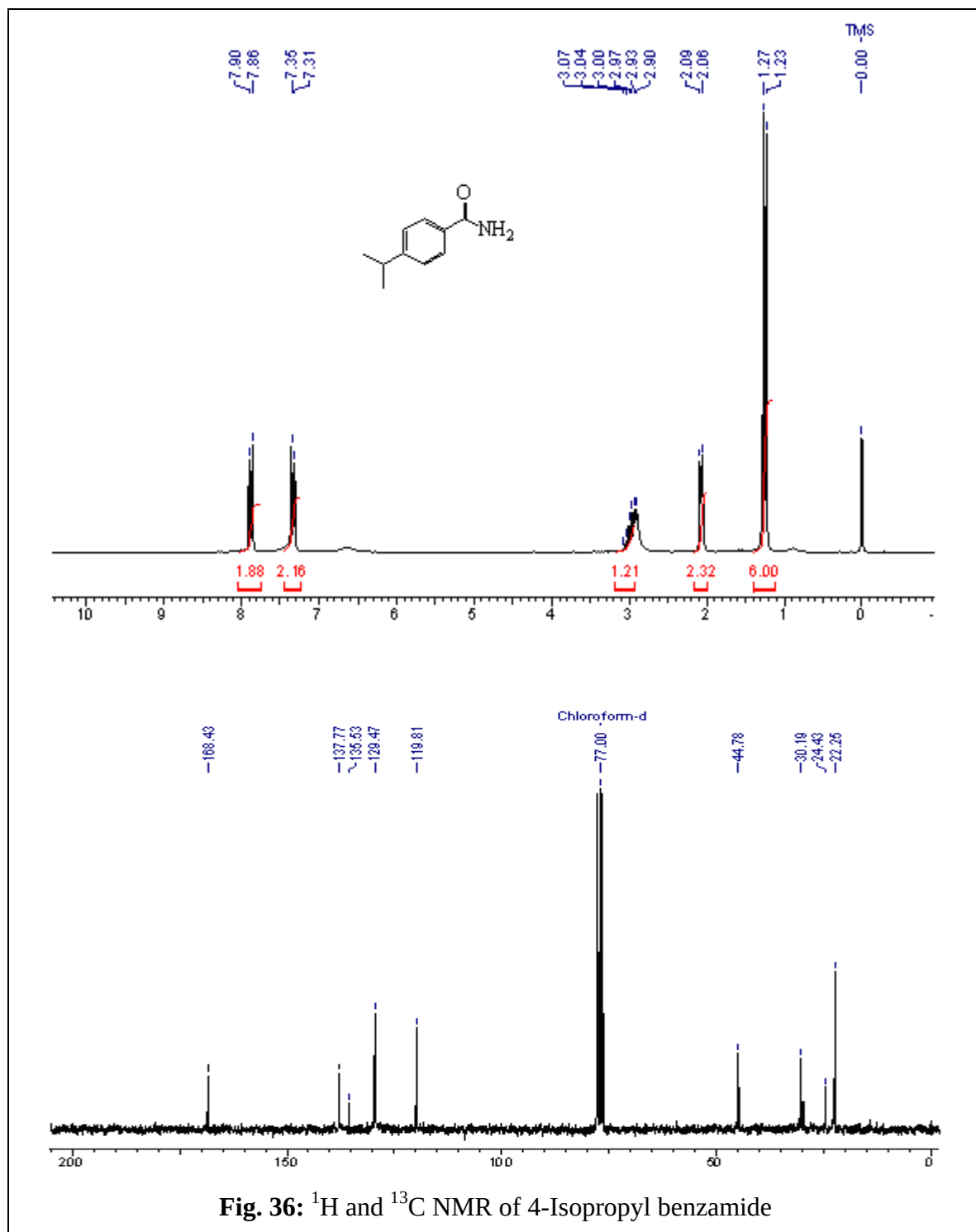
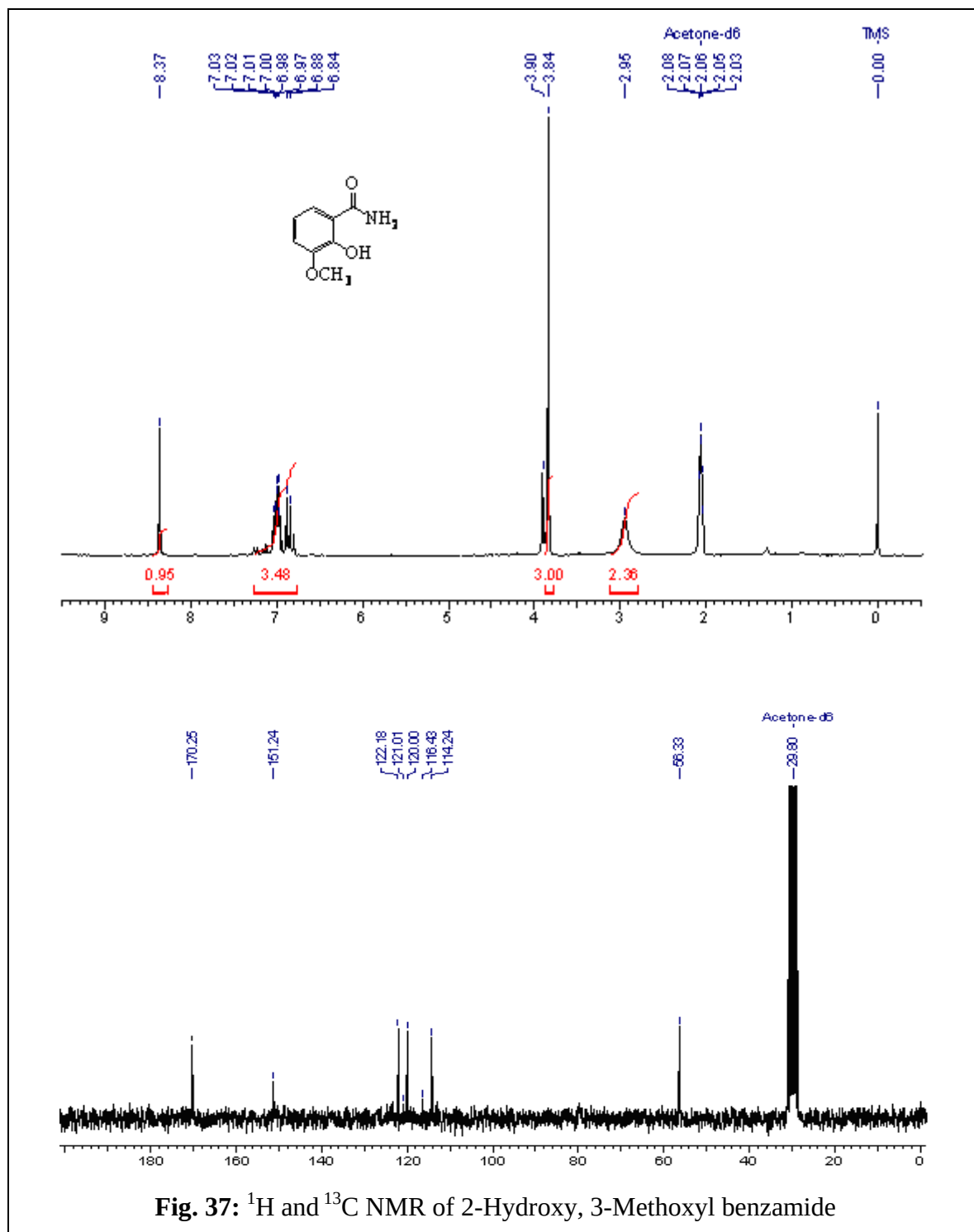


Fig. 36: ^1H and ^{13}C NMR of 4-isopropyl benzamide



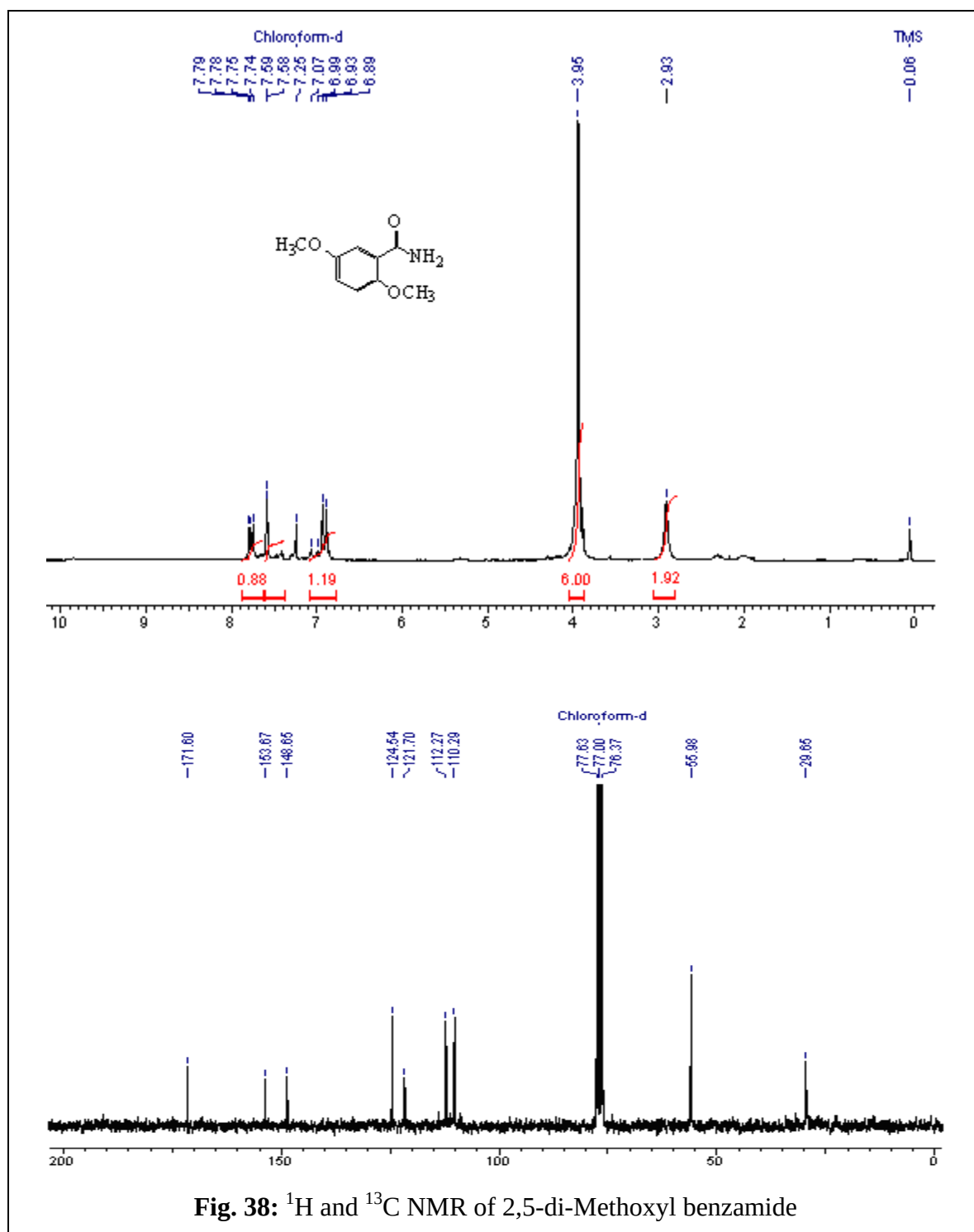
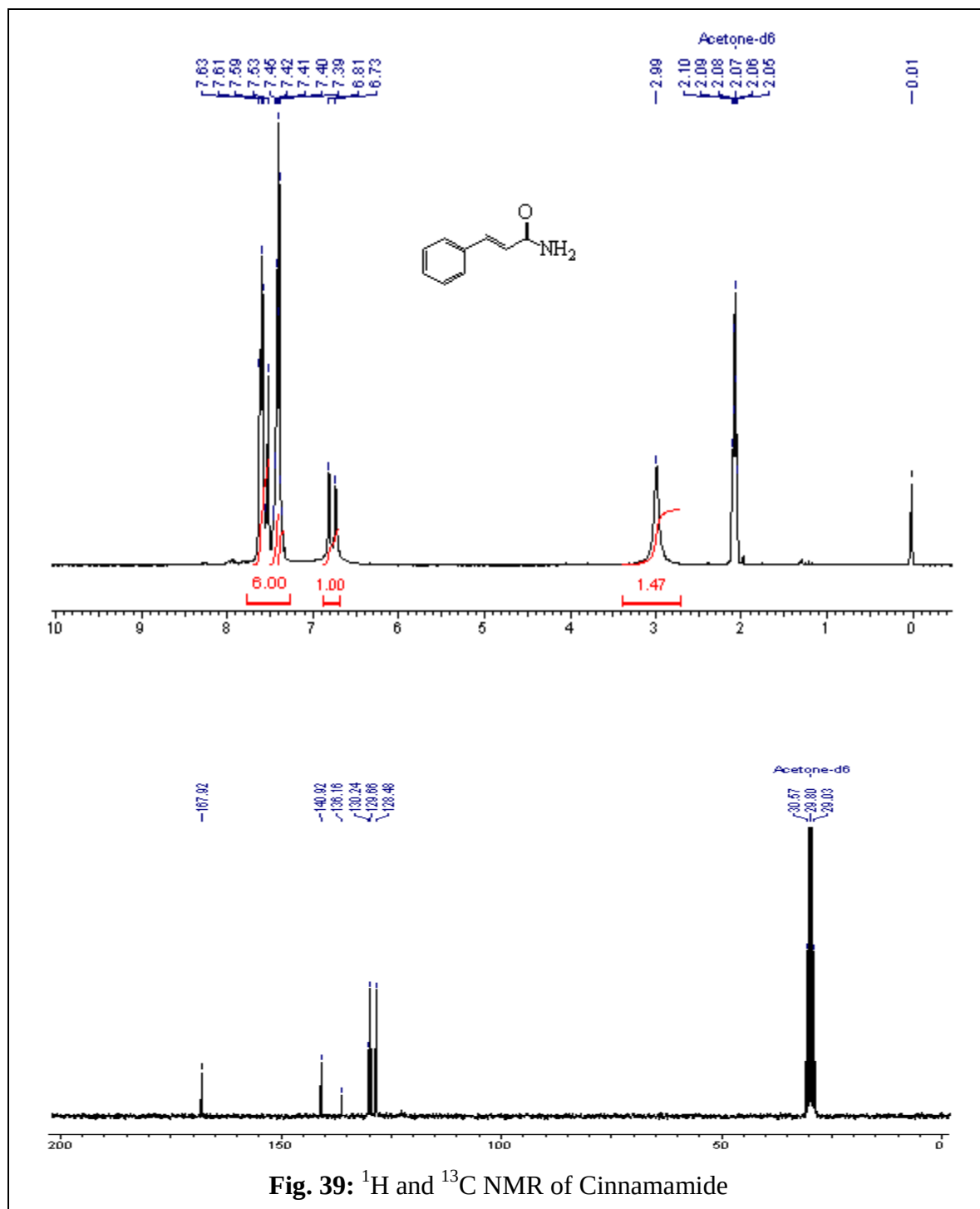
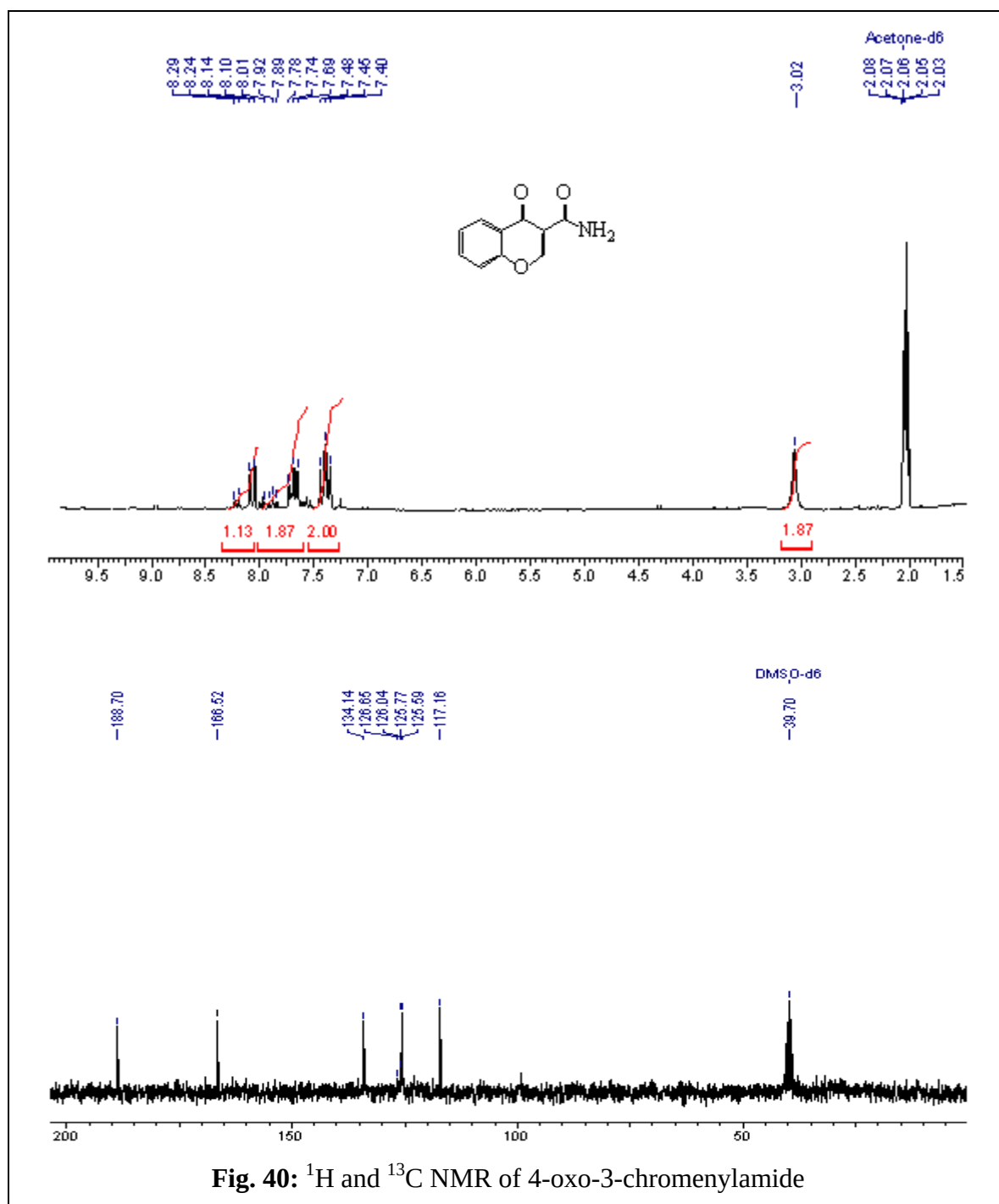


Fig. 38: ^1H and ^{13}C NMR of 2,5-di-Methoxyl benzamide





4.2.8 References

- 1 (a) Luzzio, F. A. *Tetrahedron*, **2001**, 57, 915; (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley–VCH: New York, **2001**.
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List of Publications:

- 1 Ligand free, highly efficient synthesis of diaryl ether over copper fluorapatite as heterogeneous reusable catalyst. Shafeek A. R. Mulla, Suleman M. Inamdar, Mohsinkhan. Y. Pathan, Santosh. S. Chavan, *Tetrahedron Lett.* **2012**, 53, 1826-1829.
- 2 Ullmann diaryl etherification with copper fluorapatite. Shafeek A. R. Mulla, Suleman M. Inamdar, Mohsinkhan. Y. Pathan, Santosh. S. Chavan. Highlighted in *Synfacts*, **2012**, 8(6), 0691.
- 3 Base promoted highly efficient copper fluorapatite catalyzed coupling of phenols with arylboronic acids under mild and ligand-free conditions. Shafeek A. R. Mulla, Suleman M. Inamdar, Mohsinkhan. Y. Pathan, Santosh. S. Chavan, *RSC-adv.*, **2012**, 2, 12818-12823.
- 4 Efficient, rapid synthesis of bis-(indolyl) methane using ethyl ammonium nitrate as an ionic liquid. Shafeek A. R. Mulla, A. Sudalai, Mohsinkhan. Y. Pathan, Shafi. A. Siddique, Suleman M. Inamdar, Santosh. S. Chavan, Santosh. Reddy, *RSC-adv.*, **2012**, 2, 3525-3529.
- 5 Solvent free, highly efficient one-pot multi-component synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols catalyzed by ethylammonium nitrate as reusable ionic liquid under neat reaction condition at ambient temperature. Shafeek A. R. Mulla, Tarek, A. Salama, Mohsinkhan. Y. Pathan, Suleman M. Inamdar, Santosh. S. Chavan, *Tetrahedron Lett.* **2013**, 54, 672-675.
- 6 Highly Efficient Cobalt (II) Catalyzed O-acylation of alcohols and phenols under solvent-free Conditions. Shafeek A. R. Mulla, Suleman M. Inamdar, Mohsinkhan.

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- 7 Novel, enantioselective synthesis of Linezolid and Eperezolid *via* asymmetric nitroaldol reaction over copper fluorapatite in the presence of C_2 -symmetric chiral piperazine ligand. Shafeek A. R. Mulla, Suleman M. Inamdar, ***Manuscript to be communicated.***
- 8 Short, efficient enantioselective synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol *via* asymmetric nitroaldol reaction over copper fluorapatite in the presence of chiral triethylamine ligand. Shafeek A. R. Mulla, Suleman M. Inamdar, ***Manuscript to be communicated.***
- 9 Base-free Synthesis of β -Nitroalcohols over Copper fluorapatite as Heterogeneous, Recyclable Catalyst at ambient temperature. Shafeek A. R. Mulla, Suleman M. Inamdar, ***Manuscript to be communicated.***
- 10 Copper fluorapatite Catalyzed a Direct Synthesis of Amides from Aldehydes in solvent free conditions. Shafeek A. R. Mulla, Suleman M. Inamdar, ***Manuscript to be communicated.***
- 11 Silzic catalysed general, mild and efficient one pot, three-component synthesis of β -amido ketone libraries. Shafeek A. R. Mulla, Suleman M. Inamdar, Tarek, A. Salama. ***Manuscript to be communicated.***
- 12 An efficient synthesis of amides from ketones over silzic as heterogeneous reusable catalyst under solvent-free conditions. Shafeek A. R. Mulla, Suleman M. Inamdar, Tarek, A. Salama. ***Manuscript under preparation.***