ENANTIOSELECTIVE SYNTHESIS OF PHORACANTHOLIDE I, MEXILETINE, ENCIPRAZINE, ESMOLOL, ATENOLOL, XIBENOLOL VIA α-AMINOXYLATION OF ALDEHYDE AND APPLICATION OF RECYCLABLE CATALYSIS IN ORGANIC TRANSFORMATION

A THESIS

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IN

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BY

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(RESEARCH GUIDE)

CHEMICAL ENGINEERING AND PROCESS DEVELOPMENT

DIVISION, NATIONAL CHEMICAL LABORATORY,

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APRIL 2014

Dedicated

To

My Parents

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CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Enantioselective Synthesis of Phoracantholide I, Mexiletine, Enciprazine, Esmolol, Atenolol, Xibenolol via α- Aminoxylation of Aldehyde and Application of Recyclable Catalysis in Organic Transformation"** 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.

April 2014 **(Dr. Shafeek. A. R. Mulla)**

Pune **Research Guide**

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled "**Enantioselective Synthesis of Phoracantholide I, Mexiletine, Enciprazine, Esmolol, Atenolol, Xibenolol via α-Aminoxylation of Aldehyde and Application of Recyclable Catalysis in Organic Transformation"** 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.

April 2014
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Mohsinkhan Yaseenkhan Pathan

ABBREVIATIONS

Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
AD	Asymmetric Dihydroxylation
Aq	Aqueous
Ar	Aryl
Bmim	1-*n*-butyl, 3-methyl imidazoles
Bn	Benzyl
BnBr	Benzyl bromide
Boc	*tert*-Butoxy carbonyl
bp	Boiling point
brs	Broad singlet
Bu	Butyl
t-Bz	*tert*-Butyl
BuLi	Butyl lithium
ca.	Calculated
cat.	Catalytic/catalyst
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
conc.	Concentrated
d	Doublet
dd	Doublet of doublet
de	Diasteromeric excess
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
$(DHQ)_2PHAL$	1,4-Bis(dihydroquinin-9-O-yl)phthalazine

$(DHQD)_2PHAL$	1,4-Bis(dihydroquinidin-9-O-yl)phthalazine
DMAP	N,N-(Dimethylamino)pyridine
DMF	N, N-(Dimethyl)formamide
DMSO	N,N-Dimethyl formamideDimethyl sulfoxide
DTP/SiO_2	Dodecatungustophosphoric acid supported on silica
EAN	Ethylammonium nitrate
ee	Enantiomeric excess
equiv.	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3N	Triethyl amine
gm	Gram
HCl	Hydrochloric acid
h or hrs	Hours
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
Hz	Hertz
IBX	2-iodoxybenzoic acid
i-Pr	Isopropyl
KOH	Potassium hydroxide
K_2CO_3	Potassium carbonate
IL	Ionic liquid
IR	Infrared
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
m-CPBA	m-chloroperbenzoic acid
Me	Methyl
MeOH	Methanol
m	Multiplate
mg	Miligram

min	Minutes
mL	Mililiter
mmol	Milimole
M^+	Molecular ion
mp	Melting point
Ms	Methansulfonyl
NaOH	Sodium hydroxide
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium Sulfate
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Pet. ether	Petrolium ether
Pd/C	Palladium on carbon
Ph	Phenyl
ppm	Parts per million
p-TSA	*p*-Toluene sulfonic acid
Py	Pyridine
RT	Room tempareture
R*f*	Retention factor
s	Singlet
SAD	Sharpless asymmetric dihydroxylation
satd.	Saturated
t	Triplet
TBSCl	Tert-Butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
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)
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. ^{1}H 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. DTP/SiO_2 and EAN was prepared as per litrature procedure.

ABSTRACT

The thesis entitled **"Enantioselective Synthesis of Phoracantholide I, Mexiletine, Enciprazine, Esmolol, Atenolol, Xibenolol via α-Aminoxylation of Aldehyde and Application of recyclable Catalysis in Organic Transformation"** is divided into four chapters.

Chapter 1 is divided into two sections, section I and section II deals with an enantioselective synthesis of (*S*)-Phoracantholide I and (*R*)-Mexiletine, respectively, via α-aminoxylation of aldehyde catalyzed by L-proline. **Chapter 2** describes an enantioselective synthesis of (*S*)-Enciprazine, (*S*)-Esmolol, (*S*)-Atenolol and (*S*)-Xibenolol via α-aminoxylation of aldehyde catalyzed by L-proline. **Chapter 3** describes the synthetic methodologies in the presence of silica supported dodecatungstophosphoric acid (DTP/SiO_2) and divided into three sections. Section I deals with highly efficient one-pot multi-component synthesis of α -aminophosphonates and bis-α –aminophosphonates derivatives from one-pot three-component condensation of aldehydes, amines and di or tri alkylphosphite and their bioevaluation, whereas section II deals with a novel and efficient synthesis of azaarene-substituted 3-hydroxy-2-oxindoles from sp3 C-H functionalization of substituted azaarenes with various isatin, and section III deals with a facile and highly efficient one-pot multi-component synthesis of azaarene-substituted 3-substituted-2-oxindoles from one-pot three-component condensation of azaarenes/(2-azaaryl)methanes, isatin and malononitrile/ethylcynoacetate via sp3 C-H functionalization of azaarene/(2-azaaryl)methanes. **Chapter 4** describes the synthetic methodologies using ethylammonium nitrate (EAN) as an ionic liquid and divided into two sections. Section I deals with solvent free, highly efficient one-pot multi-component

synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols from one-pot three-component condensation of various aldehydes, amides/carbamates/urea, and naphthols/phenols under neat reaction condition at ambient temperature, whereas section II deals with an efficient, rapid synthesis of bis(indolyl)methanes from various substituted indoles and various substituted aldehydes at room temperature.

Chapter 1

Enantioselective synthesis of (*S*)-Phoracantholide I and (*R*)-Mexiletine via α-aminoxylation of aldehyde catalyzed by L-proline

The chapter includes the details about biological action and comprehensive literature on synthesis of (*S*)-Phoracantholide I and (*R*)-Mexiletine (**Fig.1**). The chapter is divided into two sections.

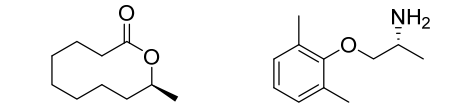
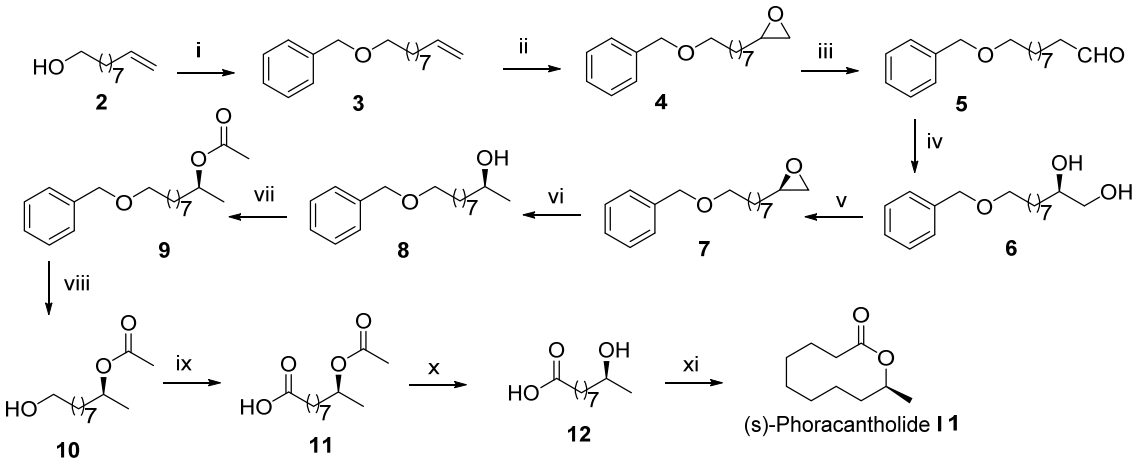


Fig. 1. Structure of (*S*)-Phoracantholide I **1** and (*R*)-Mexiletine **13**

Section I: Enantioselective synthesis of (*S*)-Phoracantholide I

(S)-phoracantholide I **1** (**Fig. 1**) was isolated from various natural sources as natural products[1] as well as a defensive secretion from the metasternal gland of the eucalypt longicorn Phoracantha synonyma beetles and (*R*)-enantiomer is considered as the natural isomer.[2] As (S)-phoracantholide I **1** is natural product, development of its synthetic methodology is center of interest among world-chemist. Hence, this section describes an enantioselective synthesis of (*S*)-phoracantholide I **1** via α-aminoxylation of aldehyde catalyzed by L-proline as key step and source of chirality.

The synthesis was started with the commercially available 9-decen-1-ol **2** (**Scheme 1**). The protection of alcohol with benzyl bromide using sodium hydride in a THF solvent at room temperature, gives the benzyl protected allylic ether compound **3**. The protected allylic ether compound **3** was subjected to an epoxidation using meta-chloroperbenzoic acid (m-CPBA) in a DCM solvent at room temperature, gives racemic epoxide **4**. An epoxide **4** was converted to corresponding aldehyde **5** using silica supported dodecatungstophosphoric acid (DTP/SiO_2) in chloroform solvent at room temperature under the Meinwald rearrangement condition. The aldehyde **5** was subjected to the α-aminoxylation condition catalyzed by L-proline in a DMSO followed by sodiumborohydride catalyzed in situ reduction and deprotection, gives the chiral diol **6**.



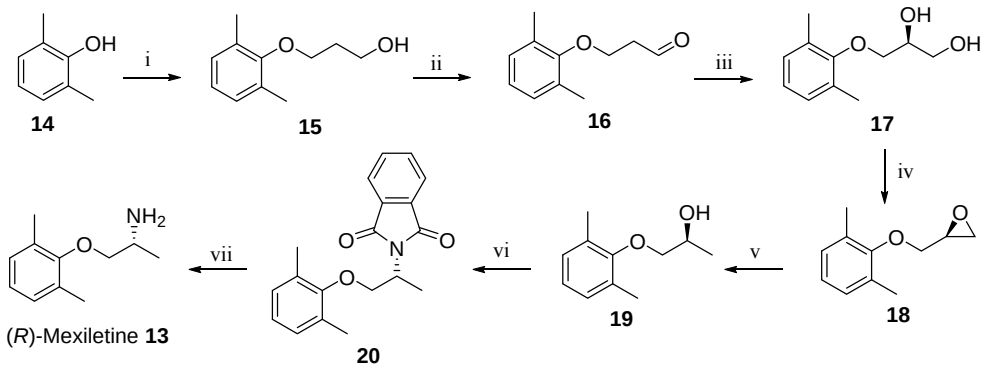
Scheme 1: *Reagents and reaction conditions*: (i) BnBr, NaH, THF, 0 ^{o}C-RT, 4 h, 92 %; (ii) m-CPBA, DCM, 0 ^{o}C-RT, 8 h, 95 %; (iii) DTP/SiO_2, $CHCl_3$, RT, 2 h, 78 %; (iv) (a) Nitrosobenzene (PhNO), L-proline, DMSO, 25 min, RT then $NaBH_4$, MeOH, 1 h; (b) $CuSO_4$, MeOH, RT, 12 h, over two step, 66 %; (v) PPh_3, Diethylazadicaroxylate (DEAD), reflux, 5 h, 89 %; (vi) LAH, THF, 0 ^{o}C-RT, 1 h, 98 %; (vii) Acetic anhydride, Et_3N, DMAP, DCM, 0 ^{o}C-RT, 2 h, 93 %; (viii) 10 % Pd/C, EtOH, H_2, RT, 14 h, 96 % (ix) H_5IO_6, PCC, MeCN, RT, 6 h, 90 %; (x) K_2CO_3, MeOH, RT, 2 h, 96 %; (xi) 2, 4, 6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 14 h, 72 %.

The chiral diol **6** was subjected to Mitsunobu reaction condition in the presence of diethylazodicarboxylate (DEAD) and triphenylphosphine (PPh_3), gives chiral epoxide **7**. The reduction of an epoxide **7** using lithium aluminium hydride (LAH) in a THF solvent gives secondary alcohol **8**, which was protected using acetic anhydride in the presence of triethylamine as a base in a DCM solvent at room tempreture, gives acetyl protected compound **9**. The selectively benzyl deprotection of compound **9** using Pd/C under the H_2 atmosphere in an ethanol solvent, gives primary alcohol **10**. The pyridinium chlorochromate (PCC) mediated oxidation of the compound **10**, gives the corresponding acid **11**. The acetyl deprotection of **11** in the presence of potassium carbonate, gives compound **12**, which was subjected to Yamaguchi lactonization, gives the target (S)-phoracantholide I **1**.

Section II: Enantioselective synthesis of (*R*)-Mexiletine

In 1980's, mexiletine is first developed clinical drug, which belong to the group Ib sodium channel blockers.[3] Mexiletine also clinically used as an antiarrhythmic, antimyotonic, analgesic, and pain relief oral drug in its racemic form.[4] However use of racemic mexiletine for clinical treatment is limited due to its side effect. Being (*R*)-mexiletine **13** (**Fig. 1**) potent important than (S)-mexiletine as clinical drugs in life sciences, therefore an enantiomerically pure synthesis of (R)-mexiletine **13** is highly challenging and active research area. Hence, this section describes the synthesis of (*R*)-mexiletine via α-aminoxylation of aldehyde catalyzed by L-proline as key step and source of chirality.

As illustrated in **Scheme 2**, the synthesis started with commercially available 2, 6 di-methylphenol **14**. The 2, 6 di-methylphenol **14,** was treated with base K_2CO_3 and 3-bromopropanol, afforded primary alcohol **15**. The oxidation of primary alcohol **15** using 2-iodoxybenzoic acid (IBX) as an oxidizing agent in a DMSO solvent at room tempreture, gives the corresponding aldehyde **16**. The aldehyde **16** was subjected to α-aminoxylation catalyzed by L-proline in an acetonitrile, followed by reduction with $NaBH_4$ and Pd/C catalyzed hydrogenolysis under the H_2 atmosphere in a methanol solvent afforded chiral diol **17.** The chiral diol under Mitsunobu reaction conditions afforded corresponding chiral epoxide **18**. The reduction of an epoxide **18** using LAH in a THF solvent, gives the chiral secondary alcohol **19**, which on reaction with phthalimide under Mitsunobu reaction condition, gives phthalate protected compound **20**. Finally deprotection of phthalate **20**, gives (*R*)-mexiletine **13**.



Scheme 2: *Reagents and reaction conditions:* (i) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 11 h, 96 %; (ii) IBX, DMSO, RT, 6 h, 92 %; (iii) (a) PhNO, L-proline, MeCN, -20 ^oC 12 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 12 h, over two steps, 71 %; (iv) PPh_3, Diisopropyl azodicarboxylate (DIAD), THF, reflux, 6 h, 83 %; (v) LAH, THF, 0 ^oC-RT, 2 h, 96 %; (vi) Ph_3P, phthalimide, DIAD, THF, RT, 5 h, 84 %; (vii) $N_2H_4.H_2O$, EtOH, reflux, 3 h, 83 %.

Chapter 2

Enantioselective synthesis of (*S*)-Enciprazine, (*S*)-Esmolol, (*S*)-Atenolol and (*S*)-Xibenolol via α-aminoxylation of aldehyde catalyzed by L-proline

This chapter includes the details about biological action and comprehensive literature on synthesis of (*S*)-Enciprazine, (*S*)-Esmolol, (*S*)-Atenolol and (*S*)-Xibenolol (**Fig. 3**). All four β-adrenergic blocking agents are (*S*)-Enciprazine, (*S*)-Esmolol, (*S*)-Atenolol and (*S*)-Xibenolol, which posse's antihypertensive, antianginal and sympatholytic properties.

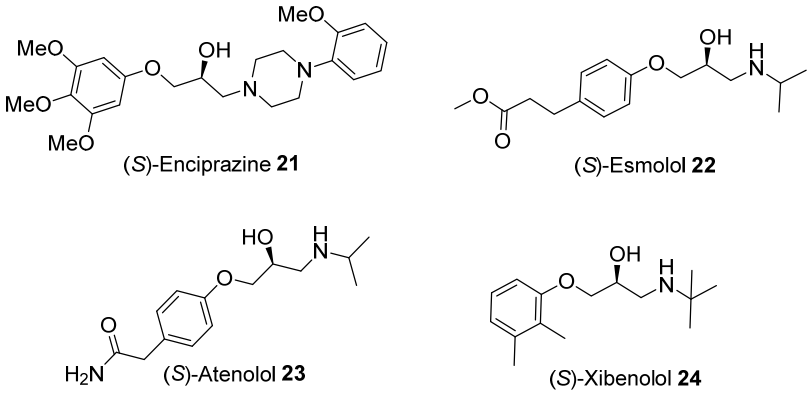


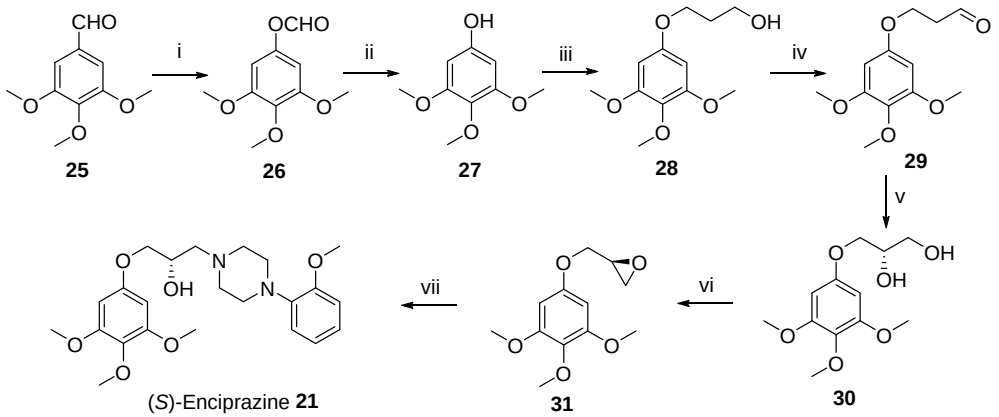
Fig. 2 Structure of (S)-Enciprazine **21**, (S)-Esmolol **22,** (S) Atenolol **23** and (S)-Xibenolol **24**

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).[5] 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.[6]

Enantioselective synthesis of (*S*)-Enciprazine 21

The synthesis of 3, 4, 5-trimethoxyphenol **27** was started with the commercially available

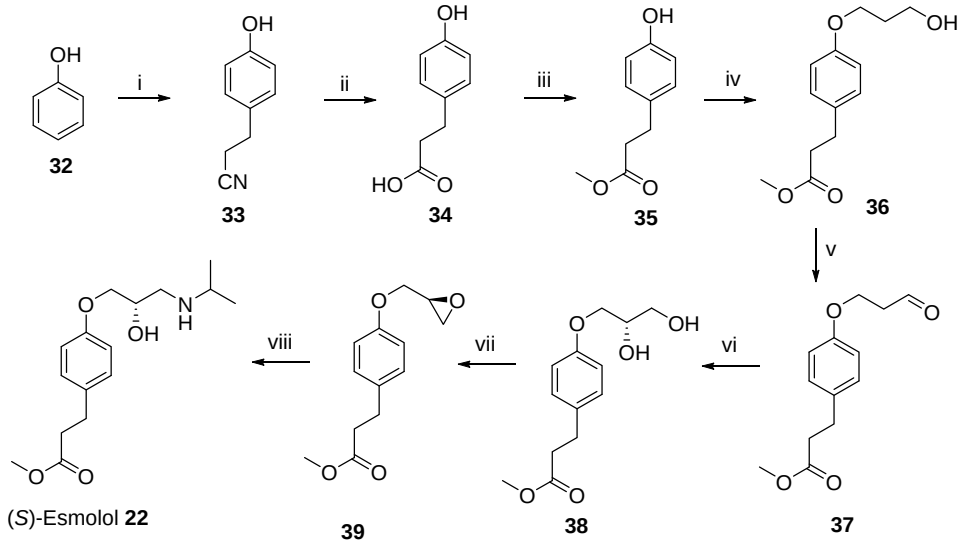
3, 4, 5-trimethoxybenzaldehyde **25** (**Scheme 3**). The 3, 4, 5-trimethoxybenzaldehyde was converted into the corresponding 3,4,5 trimethoxy phenyl formate **26** using meta-chloroperbenzoic acid (m-CPBA) in a dichloromethane solvent at room temperature, which was treated with KOH in a methanol solvent, gives the 3, 4, 5-trimethoxy phenol **27**. The 3, 4, 5-trimethoxy phenol **27** was treated with K_2CO_3 and 3- bromopropanol in an acetone solvent, afforded corresponding primary alcohol **28**. The oxidations of primary alcohol **28** using IBX as an oxidizing agent in a DMSO solvent at room tempreture, gives the corresponding aldehyde **29**. The aldehyde **29** was subjected to the α-aminoxylation catalyzed by L-proline in an acetonitrile, followed by reduction with $NaBH_4$ and Pd/C catalyzed hydrogenolysis under the H_2 atmosphere in a methanol solvent, afforded chiral diol **30.** The chiral diol **30** under Mitsunobu reaction conditions using PPh_3 and diethylazodicarboxylate (DEAD) afforded corresponding chiral epoxide **31.** Finally an epoxide **31** was treated with 1-(2-methoxyphenyl)piperazine in the refluxing isopropanol, gives (*S*)-Enciprazine **21**.



Scheme 3: *Reagents and reaction conditions:* (i) m-CPBA, CH_2Cl_2, RT., 8 h; (ii) KOH, MeOH, RT., 30 min, 91 %; over two step (iii) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 14 h, 94 %; (iv) IBX, DMSO, RT, 3 h, 90 %; (v) (a) PhNO, L-proline, MeCN, -20 ^oC 20 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 14 h, over two step, 73 %; (vi) PPh_3, DEAD, 1, 4 Dioxan, reflux, 4 h, 80 %; (vii) 1-(2-methoxyphenyl)piperazine, i-PrOH, reflux, 18 h, 95 %.

Enantioselective synthesis of (*S*)-Esmolol 22

The synthesis started with the commercially available phenol **32** (**Scheme 4**). The phenol was treated with an acrylonitrile and $AlCl_3$ under the Friedel-Craft reaction condition, gives compound **33**, which on hydrolysis using aq. NaOH, gives 4-hydroxy phenyl propanoic acid **34**. The estrification of 4-hydroxy phenyl propanoic acid **34** using catalytic amount of sulphuric acid in a methanol solvent under the reflux condition, gives desired ester **35**. The treatment of **35** with K_2CO_3 and 3- bromopropanol in an acetone solvent, afforded alcohol **36**.



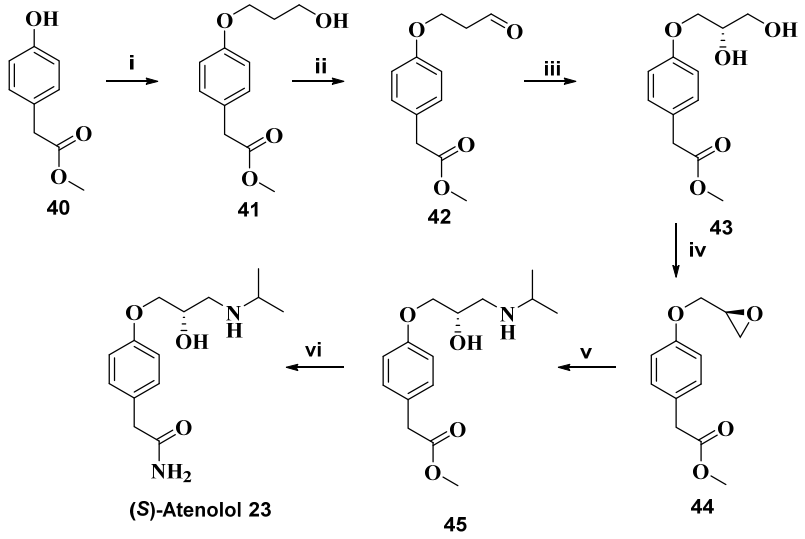
Scheme 4: *Reagents and reaction conditions:* (i) acrylonitrile, $AlCl_3$, RT-105 ^oC, 7 h; (ii) aq. NaOH, Reflux, 6 h; (iii) MeOH, H_2SO_4, Reflux, 4 h, over three step 76 %; (iv) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 12 h, 84 %; (v) IBX, DMSO, RT, 6 h, 92 %; (vi) (a) PhNO, L-proline, MeCN, -20 ^oC 22 h, then $NaBH_4$, MeOH, 30 min; (b) 10 % Pd/C, MeOH, H_2, RT, 10 h, over two step, 77 %; (vii) PPh_3, DIAD, 1, 4 Dioxan, reflux, 5 h, 88 %; (viii) isopropyl amine, water , reflux, 6 h, 81 %.

The oxidations of alcohol **36** using IBX as an oxidizing agent in a DMSO solvent at room tempreture, gives the corresponding aldehyde **37**. The aldehyde **37** was subjected to the α-aminoxylation condition catalyzed by L-proline in an acetonitrile, followed by

reduction with $NaBH_4$, and Pd/C catalyzed hydrogenolysis under the H_2 atmosphere in a methanol solvent, afforded chiral diol **38** as a key step product**.** The chiral diol **38** under Mitsunobu reaction conditions using triphenylphosphine (PPh_3) and diisopropyl azadicarboxilate (DIAD), afforded chiral epoxide **39**. Finally an epoxide **39** was converted to (S)-Esmolol **22** using iso-propyl amine in a catalytic amount of water at reflux condition.

Enantioselective synthesis of (*S*)-Atenolol 23

The synthesis started with the commercially available methyl 2-(4-hydroxyphenyl)acetate **40** (**Scheme 5**).



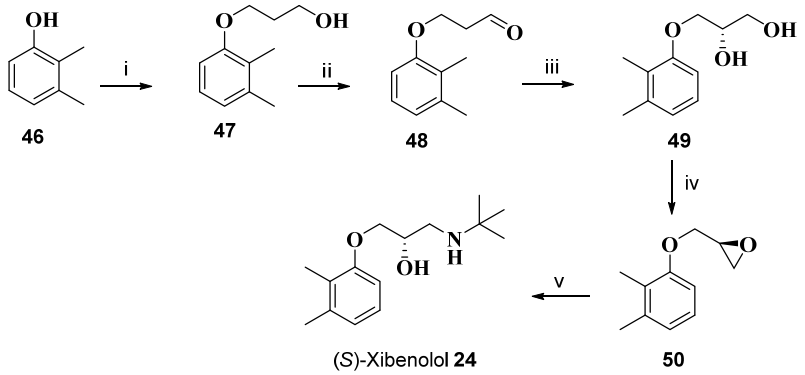
Scheme 5: *Reagents and reaction conditions:* (i) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 11 h, 90 %; (ii) IBX, DMSO, RT, 8 h, 89 %; (iii) (a) PhNO, L-proline, MeCN, -20 ^oC 24 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 16 h, over two step, 74 %; (iv) PPh_3, DIAD, 1, 4 Dioxan, reflux, 8 h, 82 %; (v) isopropyl amine, water , RT, 6 h, 70 %; (vi) NH_4OH–methanol, RT, 26 h, 75 %.

The compound **40** was treated with K_2CO_3 and 3- bromopropanol, afforded alcohol **41**. The oxidations of alcohol **41** using IBX as an oxidizing agent in a DMSO solvent at room tempreture, gives the corresponding aldehyde **42**. The aldehyde **42** was subjected to the α-aminoxylation condition catalyzed by L-proline in an acetonitrile, followed by

reduction with $NaBH_4$ and Pd/C catalyzed hydrogenolysis under the H_2 atmosphere in a methanol solvent, afforded chiral diol **43** as a key step product**.** The chiral diol **43** under Mitsunobu reaction conditions, afforded chiral epoxide **44**. The chiral epoxide **44** was treated with iso-propyl amine in a catalytic amount of water at room tempreture, gives amine compound **45**, which was finally converted to the target (*S*)-Atenolol **23** using ammonium hydroxide in a methanol solvent at room tempreture.

Enantioselective synthesis of (*S*)-Xibenolol 24

The synthesis started with the commercially available 2, 3-dimethyl phenol **46** (**Scheme 6**). The 2, 3-dimethyl phenol **46** was treated with K_2CO_3 and 3- bromopropanol in an acetone solvent at reflux condition, gives the corresponding alcohol **47**. The oxidations of alcohol **47** using IBX as an oxidizing agent in a DMSO solvent at room tempreture, gives the corresponding aldehyde **48**. The aldehyde **48** was subjected to the α-aminoxylation condition catalyzed by L-proline in an acetonitrile, followed by reduction with $NaBH_4$ and Pd/C catalyzed hydrogenolysis under the H_2 atmosphere in a methanol solvent afforded chiral diol **49** as a key step product**.** The chiral diol **49** under Mitsunobu reaction



Scheme 6: *Reagents and reaction conditions:* (i) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 6 h, 97 %; (ii) IBX, DMSO, RT, 3 h, 90 %; (iii) (a) PhNO, L-proline, MeCN, -20 ^oC 22 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 14 h, over two step, 68 %; (iv) PPh_3, DIAD, 1, 4 Dioxan, reflux, 4 h, 80 %; (v) tert-butyl amine, water, RT, 7 h, 98 %.

conditions, afforded a chiral epoxide **50**. Finally an epoxide **50** was treated with tert-butyl amine in a catalytic amount of water at room tempreture, gives (*S*)-Xibenolol **24**.

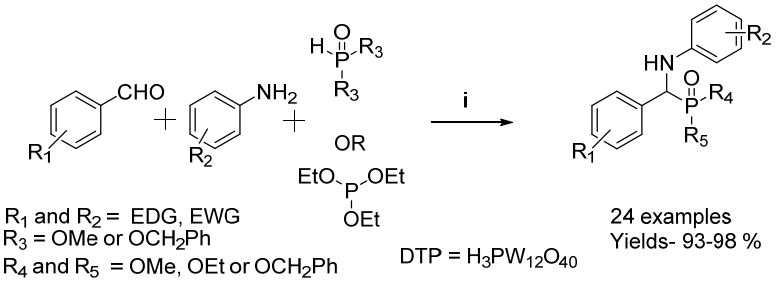
Chapter 3

Synthetic methodologies in the presence of silica supported dodecatungstophosphoric acid (DTP/SiO_2)

The chapter describes introduction, litrature survey, preparation of heterogeneous reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) catalyst and its application in organic transformations. The chapter is divided into three sections.

Section I: Highly efficient heterogeneous reusable silica supported dodecatungstophosphoric acid catalyzed one-pot multi-component synthesis of α -aminophosphonates and bis-α –aminophosphonates and their bioevaluation

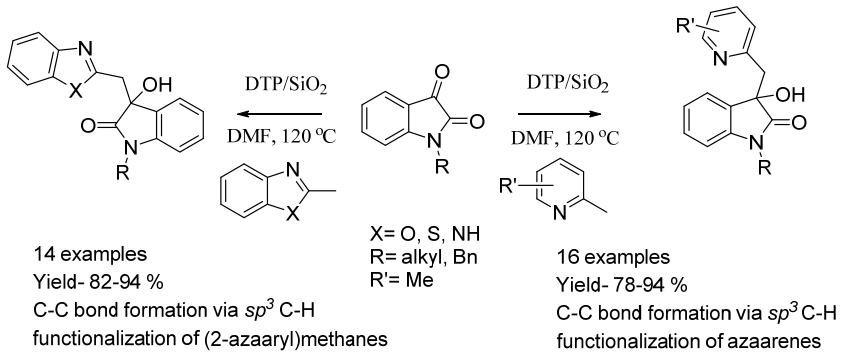
The α-aminophosphonates are structural resemblance of natural α-amino acids and α-aminophosphoric acids achieve significance important as a key moieties having wide application not only in the agriculture but also in the industrial, biological, and medicinal chemistry.[7] Being α-aminophosphonates motifs are key constituent of the structural backbone of many pharmaceutical and agricultural compounds, cost effective one-pot synthesis of their structural units under much milder, more efficient, environment friendly reaction conditions using recyclable benign catalysts is still challenging and an active research area. Therefore, this section describes highly efficient heterogeneous reusable silica supported dodecatungstophosphoric acid catalyzed one-pot multi-component synthesis of α-aminophosphonates and bis-α –aminophosphonates derivatives in excellent yields from various aldehyde, amine and di or tri alkyl phosphite at ambient temperature in a short reaction time (**Scheme 7**) and their bioevaluation.



Scheme 7: *Reagents and reaction conditions:* Aldehyde (1 mmol), amine (1mmol), DTP/SiO_2 (50 mg), CH_3CN (5 mL), RT, 1 h.

Section II: A novel and efficient synthesis of azaarene-substituted 3-hydroxy-2-oxindoles via sp^3 C-H functionalization of 2-methyl azaarenes and (2-azaaryl)methanes over heterogeneous, reusable silica-supported dodecatungstophosphoric acid catalyst

The oxindole units are key structural constituent not only found in a wide range of alkaloid, natural products but also in the biologically potential drugs such as convolutamydines-A, SM-130686, maremycin-B, maremycin-A, dioxibrassinine, donaxaridine, which cover a wide spectrum of biological and/ or medicinal activities such as anti-HIV, anti-cancer, anti-tubercular, anti-oxidant, neuroprotective etc.[8] Owing to the important application of the azaarene-substituted 3-hydroxy-2-oxindoles in the life sciences to construct and design potent drugs, its cost effective, efficient synthesis of various architecture units via sp^3 C-H functionalization of 2-methylazaarenes under environment friendly reaction conditions using recyclable benign catalysts is still challenging and an active research area. Therefore, this section describes a heterogeneous reusable DTP/SiO_2 catalyzed sp^3 C-H functionalization of 2-methylazaarenes and (2-azaaryl)methanes with isatin for the rapid and efficient synthesis of azaarene-substituted 3-hydroxy-2-oxindoles in excellent yields (**Scheme 8**).

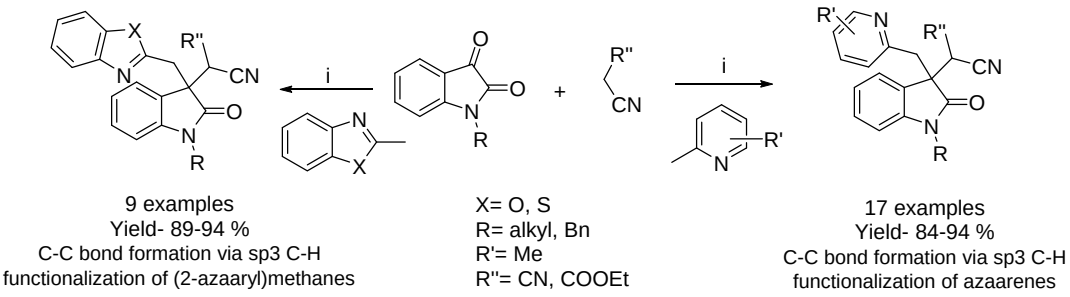


Scheme 8: *Reagents and reaction conditions:* Isatin (1 mmol), azaarene (2 mmol), DTP/SiO_2 (50 mg), DMF (5 mL), 120 °C, 8 h.

Section III: A facile and highly efficient one-pot multi-component synthesis of azaarene-substituted 3- substituted -2-oxindoles *via* sp^3 C-H functionalization of 2-methyl azaarenes and (2-azaaryl)methanes over reusable silica-supported dodecatungstophosphoric acid catalyst

The C-H functionalization via sp^3 C-H bond activation as well as C-C bond formation reactions have been well reported over transition metals,[9] Lewis and Bronsted acid catalysts.[10] Moreover, all these C-H functionalization approaches reported using either costly transition metals or moisture sensitive, toxic, and corrosive homogeneous (Lewis and Bronsted acid) catalysts in excess or stoichiometric quantity, which leads to the problems of toxic waste disposal[11] besides long reaction time, high temperature. The 3-substituted-3-hydroxy-2-oxindoles being the potent biological, and pharmaceutical value and also its biological activity known to be varying with substituent on the C-3 position, hence substitution of the various functional groups at C-3 position of 3-substituted 3-hydroxy-2-oxindoles to design and develop potent biological azaarene-substituted 3-substituted-2-oxindoles is highly challenging and active research area. Therefore, this section describes, highly efficient heterogeneous reusable silica-supported dodecatungstophosphoric acid catalyzed one-pot multi-component synthesis of azaarene-

substituted 3- substituted -2-oxindoles in excellent yields from 2-methyl azaarenes/ (2-azaaryl)methanes, isatin and malononitrile/ ethylcynoacetate via sp^3 C-H functionalization (**Scheme 9**).



Scheme 9: *Reagents and reaction conditions:* Isatin (1 mmol), 2-methyl azaarenes/ (2-azaaryl)methanes (2 mmol), malononitrile/ ethylcynoacetate (1.2 mmol), DTP/SiO_2 (50 mg), DMF (5 ml), 120 ^oC, 8 h.

Chapter 4

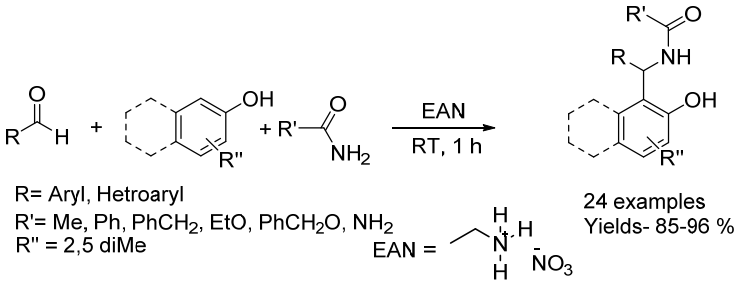
Synthetic methodologies using ethylammonium nitrate (EAN) as an ionic liquid

The chapter describes introduction, literature survey, preparation of ethylammonium nitrate (EAN) as an ionic liquid and its application in organic transformations. The chapter is divided into two sections.

Section I: 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

A variety of natural products containing 1,3-amino-oxygenated functional groups act as potential drugs, as antibiotic,[12] antitumor,[13] antimalarial,[14] antianginal,[15] antihypertensive,[16] antirheumatics,[17] and HIV protease inhibitors.[18a] The bradycardiac effects of these motifs have also been reported.[18b] Owing to the biological and/ or medicinal as well as pharmacological importance of 1-amidoalkyl-2-naphthols

derivatives, the development of efficient, cost effective, and general protocol over a recyclable, benign catalyst for the synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols is still possibility to explore. Therefore, this section describes a solvent-free, environmentally clean, mild, and simple one-pot multi-component protocol for efficient synthesis of 1-amido- and 1-carbamato-alkyl naphthols/ phenols in excellent yield via one-pot three-component condensation of various aldehydes, amides/carbamates/urea and naphthols/phenols using ethylammonium nitrate (EAN) as reusable ionic liquid as catalyst under neat reaction condition at ambient temperature (**Scheme 10**).

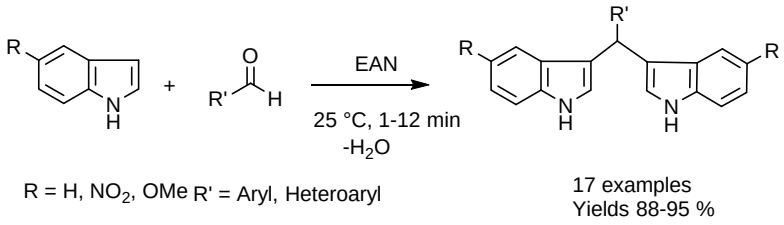


Scheme 10: *Reagents and reaction conditions:* Aldehyde (6 mmol), beta-naphthol/phenol (1 mmol), amide/urea/carbamate (1.1 mmol), EAN (0.8 mmol), RT, 1 h.

Section II: Efficient, rapid synthesis of bis(indolyl)methane using ethyl ammonium nitrate as an ionic liquid

Several bis(indolyl)alkanes and their derivatives have been isolated from plant and marine sources.[19] Among the various derivatives of indoles, bis(indolyl)methanes have wide medicinal applications such as to induce apoptosis in human cancer cell and normalize abnormal cell growth associated with cervical dysplasia, to promote beneficial estrogen metabolism in both women and men, to prevent the breast cancer and also to increase the natural metabolism of body's hormones.[20] Due to vast biological activity of

bis(indolyl)methanes and their wide medicinal applications, the development of efficient, cost effective, and general protocol for its synthesis over recyclable, environmentally benign catalyst is still possibility to explore. Therefore, this section describes a simple and rapid protocol for an efficient synthesis of bis(indolyl) methane in excellent yields using ethyl ammonium nitrate (EAN) as reusable ionic liquid at room temperature (**Scheme 11**).



Scheme 11: *Reagents and reaction conditions:* Indole (2 mmol), aldehyde (1 mmol), EAN (2 mmol), 25 ^{o}C.

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Chapter I

Enantioselective synthesis of (S)-Phoracantholide I and (R)-Mexiletine via a-aminoxylation of aldehyde catalyzed by L-proline

Section-I

Enantioselective synthesis of (*S*)-Phoracantholide I

1.1.1 Introduction

In the last few years, the worldwide efforts have been made by various researchers to isolate substituted lactones from various natural sources as natural products.[1] The substituted lactones such as Phoracantholide I **1**, Phoracantholide J **2**, Phoracantholide K **3**, Phoracantholide M **4** and Phoracantholide O **5** have been isolated as a defensive secretion from the metasternal gland of the eucalypt longicorn Phoracantha synonyma beetles[2] (**Fig. 1**).

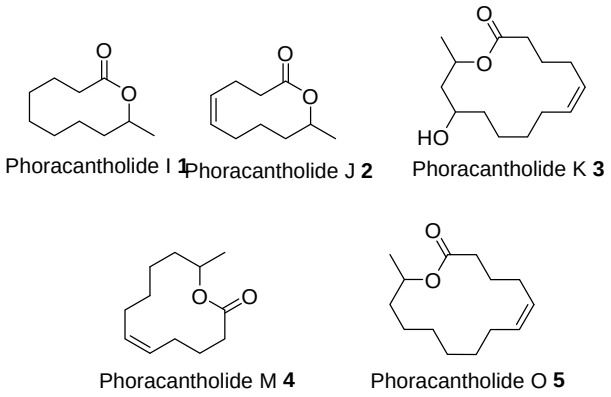


Fig. 1: Derivatives of Phoracantholide

Among the phoracantholide derivatives, Phoracantholide I **1** and Phoracantholide J **2** are ten member methyl-substituted lactones. However, Phoracantholide I **1** has a saturated ring system in its structure where as Phoracantholide J **2** consist one double bond in its structure (**Fig. 1**). Being (*S*)- and (*R*)- Phoracantholide I are natural product (**Fig. 2**), development of their synthetic methodology are center of interest among world-chemist. Therefore, various synthetic methods for synthesis of racemic form of Phoracantholide I (**Fig. 2**) were reported in the literature.

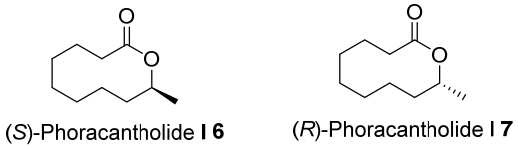


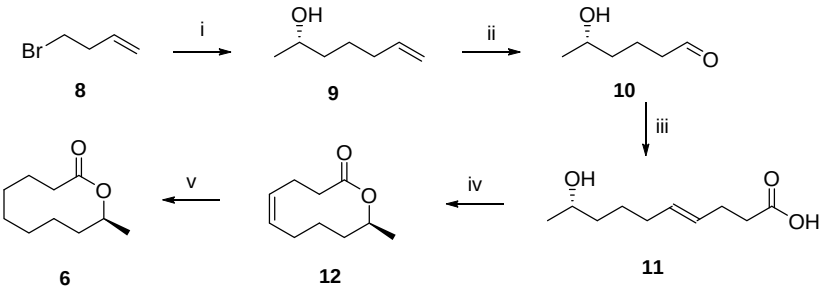
Fig. 2: Phoracantholide I

1.1.2 Review of Literature

In the literature, there are few reports available for the asymmetric synthesis of Phoracantholide I **1**.[3-8] However, almost all of the methods reported for the asymmetric synthesis of Phoracantholide I **1** involve either classical resolution of racemates or a chiral pool approach or use of inaccessible costly and toxic metal catalyst which are described below.

Schulz's approach[3]

In this approach, the alcohol **9** was obtained by the reaction of homoallyl bromide (4-bromo-1-butene) **8** with (*S*)-propylene oxide. The Lemieux-Johnson oxidation of double bond of **9** furnishes the aldehyde **10**. The aldehyde **10** was converted to hydroxyl acid **11** by Wittig reaction with (3-carboxypropyl)triphenylphosphonium ylide. The cyclization of hydroxyl acid **11** by Corey-Nicolaou method gives the compound (*S*)-phoracantholide J

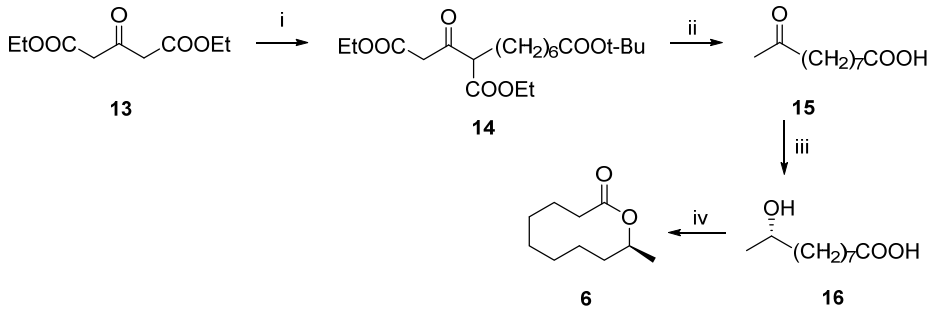


Scheme 1: *Reagents and reaction conditions*: (i) (*S*)-propylene oxide, Mg, Et_2O CuCN, 0 ^oC, 12 h, 91 %; (ii) K_2OsO_4, $NaIO_4$, dioxane, H_2O, 0 ^oC, 2 h, 71 %; (iii) nBuLi, NaHMDS, $[Ph_3P(CH_2)_3COOH]Br$, THF, -78 ^oC to RT, 2 h, 69 %; (iv) Dipyridiyldisulfide, $AgClO_4$, toluene, reflux, 14 h, 26 %; (v) H_2, 10 % Pd/C, MeOH, 5 h, 75 %.

12. Finally hydrogenation of **12** furnishes the (*S*)-phoracantholide I **6** in a 75 % yield (**Scheme 1**).

Naoshima's approach[4]

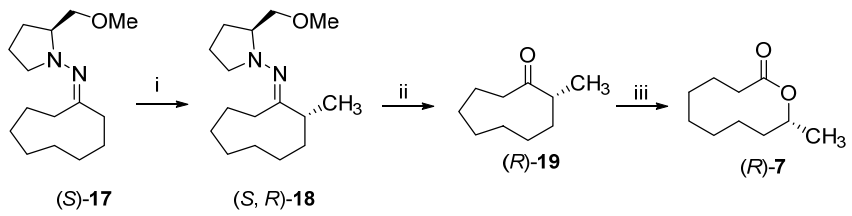
In this approach, the diethyl 3-oxoglutarate **13** was alkylated regioselectively with t-butyl 7-bromoheptanoate to give the monoalkylated 3-oxoglutarate **14**, which was converted to keto acid **15** by a decarboxylative hydrolysis. The **15** was subjected to a microbial asymmetric reduction in the aqueous solution of KCl using baker's yeast to give an optically pure (*S*)-alcohol **16** in a 46 % yield. The lactonization of (*S*)-alcohol **16** furnished (*S*)-phoracantholide I **6** in a 44 % yield (**Scheme 2**).



Scheme 2: *Reagents and reaction conditions*: (i) t-Butyl 7-Bromoheptanoate, $Mg(OEt)_2$, 88 %; (ii) 15 % NaOH, Reflux, 15 h, 89 %; (iii) baker's yeast, D-glucose, 2 % KCl, 46 %; (iv) triphenylphosphine, dipyridyl disulfide, $AgClO_4$, Benzene, Reflux, 8 h, 44 %.

Enders's approach[5]

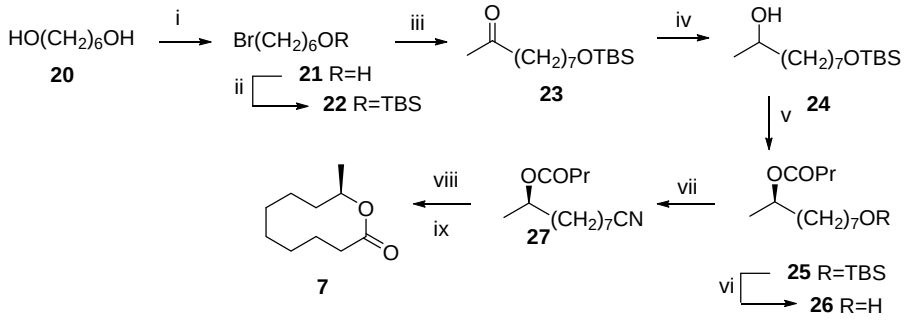
In this approach, (*R*)-phoracantholide I **7** was synthesized from the chiral (*S*)-1-amino-2-(methoxymethyl) pyrrolidine hydrazone of cyclononanone **17**. The low-temperature alkylation of compound **17** with methyl iodide gave α-substituted hydrazone (*S*, *R*)-**18** in 84 % yield. The ozonolysis of (*S*, *R*)-**18** in CH_2Cl_2 at -78 ^oC afforded the chiral ketone (*R*)-**19**. The oxidation of (*R*)-**19** with *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature furnished the (*R*)-phoracantholide I **7** in 74 % yield (**Scheme 3**).



Scheme 3: *Reagents and reaction conditions*: (i) a) LDA, THF, 0 ^{o}C, 4 h; b) MeI, -100 ^{o}C, 16 h 85 %; (ii) O_3, CH_2Cl_2, -78 ^{o}C, 70 %; (iii) m-CPBA, 4 days, 74 %.

Chattopadhyay's approach[6]

In this approach, the hexane 1, 6 diol compound **20** was partially brominated to give the compound **21**, which on silylation furnished the silylated compound **22**. α-alkylation of methyl acetoacetate with silylated compound **22** followed by alkaline hydrolysis afforded the ketone **23**. The reduction of ketone **23** with $NaBH_4$ afforded the key carbinol synthon **24**. Which was subjected to the porcine pancreatic lipase (PPL) catalyzed trans-acieration gives acierated product **25**, which on distillation gives alcohol compound **26**. The tosylation of compound **26** followed by reaction with KCN afforded the cynohydrin compound **27**. The cynohydrine on acidic hydrolysis, deesterification with alkali and subsequent acidification furnished the (*R*)-phoracantholide I **7** (**Scheme 4**).

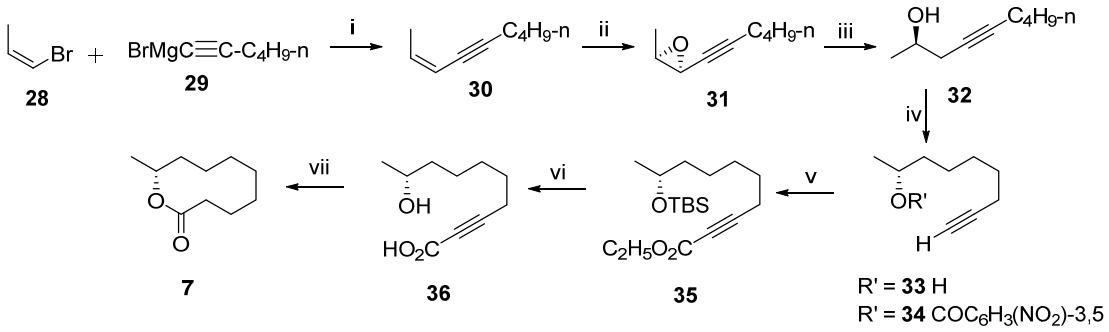


Scheme 4: *Reagents and reaction conditions*: (i) 48 % HBr, benzene, reflux, 30 h, 60 %; (ii) TBSCl, triethylamine, DMAP, CH_2Cl_2, RT, 14 h, 88 %; (iii) $CH_3COCH_2CO_2Me$, NaOMe, MeOH, Aqueous NaOH, 2N HCl, 18 h, 48 %; (iv) $NaBH_4$, MeOH, RT, 1 h, 78 %; (v) PPL, TFEB, diisopropyl ether, RT, 18 h, 26 %; (vi) Bu_4NF, THF, RT, 15 h, 84 %; (vii) *p*-

TsCl, pyridine, CH_2Cl_2, KCN, DMSO, 20 h, 68 %; (viii) Conc. HCl, reflux, 16 h; (ix) Alcoholic KOH, 16 h, 61 %.

Katsuki's Approach[7]

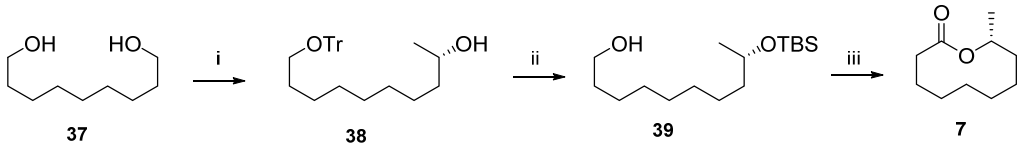
In this approach, a key intermediate is chiral epoxide, which was prepared by the epoxidation of alkyne compound **30**. The compound **30** on epoxidation using Mn-salen catalyst in the presence of NaClO gives chiral epoxide **31**. The chiral epoxide **31** was reduced by Lithium aluminium hydride (LAH) to give homopropargylic alcohol **32**. The homopropargylic alcohol **32** was treated with potassium 3-aminopropylamide (KAPA) furnished the terminal acetylene compound **33**, which was converted to the dinitrobenzoate **34**. The protection of dinitrobenzoate by t-butyldimethyl silyl (TBS) ether and subsequent ethoxycarbonylation of terminal acetylene gave the ester compound **35**. The hydrogenation followed by desilylation and hydrolysis of ester compound **35** afforded the hydroxyl acid **36**. Finally the hydroxyl acid **36** was converted to the (*R*)-phoracantholide I **7** using Yamaguchi method in a 41 % yield (**Scheme 5**).



Scheme 5: *Reagents and reaction conditions*: (i) $Pd(PPh_3)_4$, -78 ^oC, 35 % (ii) Mn-salen , NaClO, 80 % (iii) LAH, THF, O ^oC, 81 % (iv) $KNH(CH_2)_3NH_2$, 79 % (v) (a) TBSCl, imidazole, 94 % (b) BuLi, $ClCOOC_2H_5$, 70 % (vi) (a) H_2, Pd/C, 0 ^oC, 96 % (b) Bu_4NF, THF, 95 % (c) THF, aq. NaOH, 92 % (vii) 3, 4, 5-$Cl_3C_6H_2COCl$, DMP, 41 %.

Jone's approach[8]

The key step in this approach is to introduce chirality using a chiral arene chromium tricarbonyl based catalyst to mediate the addition of dimethyl zinc to a functionalized aldehyde. The synthesis was started with the mono trityloxy protection of 1, 9-nonanediol **37** followed by oxidation using dess-martin periodinane to gives aldehyde, the addition of dimethyl zinc to the aldehyde using chiral arene chromium tricarbonyl based catalyst furnished the chiral secondary alcohol **38**. The secondary alcohol **38** was protected with t-butyldimethyl silyl (TBS) ether followed by deprotection of trityloxy group using boron trichloride gives the protected chiral secondary alcohol **39**. The exposed alcohol **39** was transformed to the carboxylic acid followed by deprotection of chiral secondary alcohol and macrolactonisation afforded the (*R*)-phoracantholide I **7** in a 75 % yield (**Scheme 6**).



Scheme 6: *Reagents and reaction conditions*: (i) a) TrCl, Et_3N, DMF, 98 % b) Dess-martin periodinane, CH_2Cl_2, 99 % c) Me_2Zn, chromium catalyst, toluene 0 ^oC, 84 % (ii) a) TBSOTf, 2, 6 lutidine, 97 % b) BCl_3, CH_2Cl_2, 96 % (iii) a) PCC, DMF, RT, 95 % b) HF-Py, 100 % c) Ph_3P, Aldrithiol d) $AgClO_4$, 75 %.

1.1.3 Present Work

1.1.3.1 Objectives

(*S*)-Phoracantholide I **6** is being natural product and isolated from fermoral gland of Mantellid Frogs[3] by Dennis Poth et al. in 2012. Therefore, the development of its synthetic methodology is center of interest among researcher world-wide. However, so

far the synthesis of (*S*)-phoracantholide I **6** from ethyl (*S*)-3-hydroxybutyrate and asymmetric reduction of 9-oxononanoic acid using immobilized baker's yeast[9] have been reported by Kitahara et al. and Naoshima et al., respectively. These two reported synthetic routes suffer one/or other limitations and drawbacks such as lengthy process, use of toxic expensive reagents, chemical and catalysts as well as harsh and moisture sensitive reaction conditions, which affect overall yield and optical purity. Therefore, development of short and inexpensive synthetic route for the synthesis of (*S*)-phoracantholide I **6** to achieve high overall yield with high optical purity is still challenging and active research area. Hence, this section describes a synthetic route for asymmetric synthesis of (*S*)-phoracantholide I **6** with good optical purity and yield via L-proline catalyzed α-aminoxylation of aldehyde as a key step and source of chirality.

1.1.3.2 Proline-catalyzed α-aminoxylation

Proline is unique amino acid, which acts as a "Universal catalyst" because of its use in variety of organic transformation. It is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compaire to

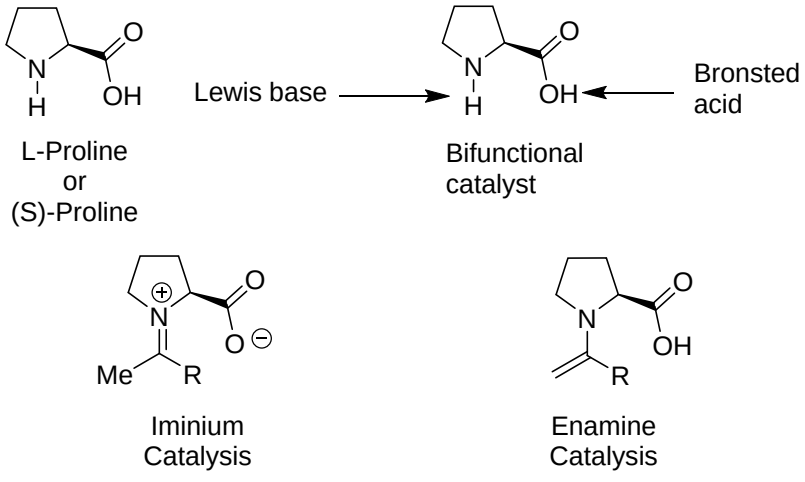


Fig. 3: Different form of proline as a catalyst

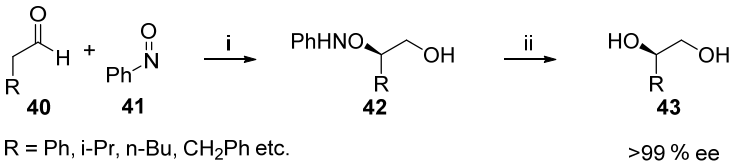
the other amino acids. Because of the secondary amine functionality, proline acts as a bifunctional catalyst as secondary amine acts as Lewis base where as the carboxylic acid group acts as Bronsted acid and it also acts as nucleophils to carbonyl group as an iminium intermediate or Michael acceptor as an enamine (**Fig. 3**).

Proline being bifunctional catalyst, its application in the various name reaction such as Mannich reaction,[10] Michael addition,[11] aldol condensation,[12] and Diels-Alder reaction[13] have been well documented. However, recently proline catalyzed α-aminoxylation[14] and α-amination[15] of carbonyl compounds have emerged as powerful methods for the synthesis of chiral building materials from easily available non-chiral materials.

The chiral 1, 2-diols synthesized from optically active α-hydroxy aldehyde or ketones are key intermediates for the synthesis of natural and bio-active molecules. Owing to the importance of chiral 1, 2-diols, world-wide efforts have been made by researcher and developed various methods for its synthesis. Among the developed methods, Sharpless dihydroxylation,[16] Davis oxaziridine,[17] Shi epoxidation[18] and Mn-salen catalyzed epoxidation[19] are prominent and well established methods. Even though significant improvement have been achieved to establish some prominent method for the synthesis of chiral 1, 2 diol, almost all methods reported so far requires complex starting material which is difficult to synthesize, inaccessible, toxic and costly metal used as catalyst in an equimolar or excess amount, long reaction time and harsh reaction conditions with low optical purity and also there is no direct method for the synthesis of chiral 1, 2 diol.

Recently, proline has been found to be unique an excellent and most promising asymmetric catalyst to synthesize chiral 1, 2-diol from carbonyl compound via α-aminoxylation. When an aldehyde **40** without substitution at α-position was reacted with

nitrosobenzene **41** in the presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety **42** undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **43** in very high enantioselectivities with good yield (**Scheme 7**).



Scheme 7: *Reagents and reaction conditions*: (i) (a) L-Proline (20 mol %), DMSO, 25 ^oC; (b) $NaBH_4$, MeOH; (ii) Pd/C, H_2 or $CuSO_4$ (30 mol %).

1.1.3.3 Possible Mechanism for L-proline catalyzed asymmetric α-aminoxylation of aldehyde

The mechanism of L-Proline catalyzed α-aminoxylation reaction of aldehyde is shown in **Fig. 4**.

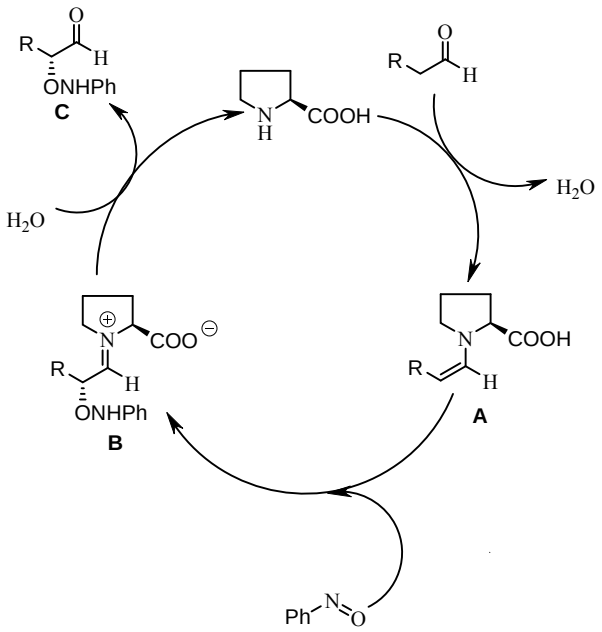


Fig. 4: Plausible mechanism for L-proline catalyzed asymmetric α-aminoxylation of aldehyde

The L-proline reacted with carbonyl carbon of aldehyde by libration of water to form an enamine **A**. The oxygen atom of nitrosobenzene approaches from the less hindered side of an enamine **A** to form a chair transition state (**Fig. 5**), which provide the chiral α-aminoxyaldehyde **B** with *R* configuration.

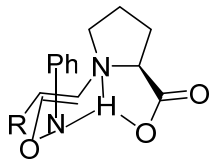


Fig. 5: Proposed chair transition state.

When α-aminoxyaldehyde **B** was reacted with water gives the secondary alcohol protected by an *O*-aminophenyl group **C**, which on insitu reduction with the $NaBH_4$ and followed by deprotection of *O*-aminophenyl group over Pd/C or $CuSO_4$ in the presence of H_2, give the *R* or *S* chiral 1, 2 diol by using either (*R*)- or (*S*)- proline, respectively, which is commercially available in both enantiopure form.[20]

1.1.4 Results and discussion

The retro-synthetic analysis for the synthesis of (*S*)-phoracantholide I **6** is presented in **Fig. 6**. The (*S*)-phoracantholide I **6** can be prepared from the corresponding hydroxyl acid **44** using the Yamaguchi lactonization. The hydroxyl acid **44** can be easily obtained from the corresponding acetyl protected alcohol **45**. The compound **45** can be obtained from corresponding chiral epoxide **46.** The chiral epoxide **46** can be obtained from 1, 2 chiral diol **47** with simple functional group transformations. The 1, 2 chiral diol **47** can be obtained *via* L-proline catalyzed α-aminoxylation of simple aldehyde **48**. The key starting material aldehyde **48** was obtained *via* simple organic transformations from the allylic compound **49**, which can be easily prepared from the commercially available 9-decen-1-ol **50**.

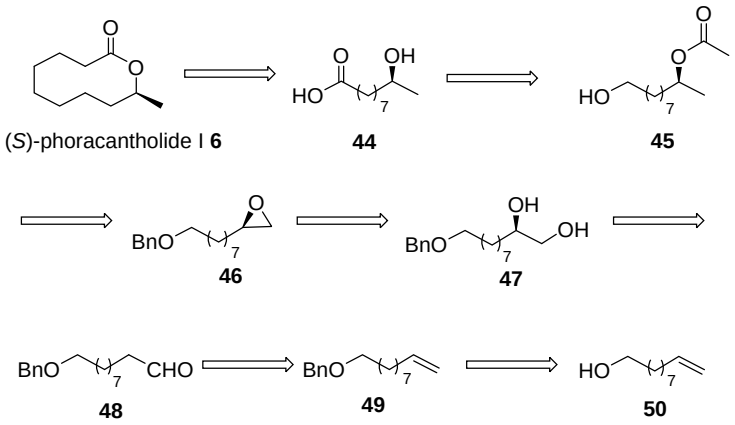
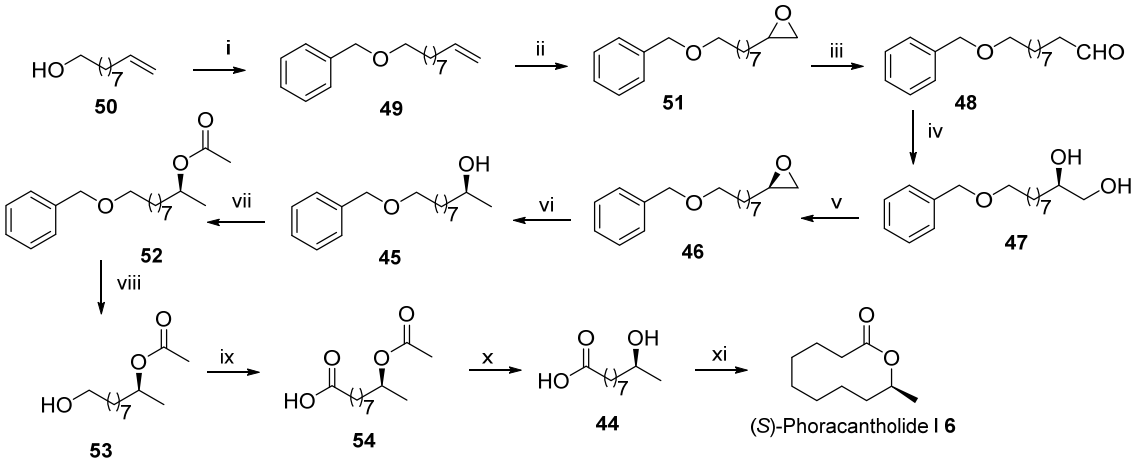


Fig 6: Retrosynthetic analysis for (*S*)-Phoracantholide I **6**

In our synthetic approach, the synthesis of (*S*)-phoracantholide I **6** is based on the retro-synthetic analysis; the chiral synthons (1, 2-diol **47**) can be easily achived by L-proline catalyzed asymmetric α-aminoxylation of aldehyde **48.** The general synthetic route employed for the synthesis of (S)-phoracantholide I **6** is shown in the **scheme 8**.

1.1.4.1 Enantioselective synthesis of Phoracantholide I



Scheme 8: *Reagents and reaction conditions*: (i) BnBr, NaH, THF, 0 ^{o}C to RT, 4 h, 92 %; (ii) m-CPBA, DCM, 0 ^{o}C-RT, 8 h, 95 %; (iii) DTP/SiO_2, $CHCl_3$, RT, 2 h, 78 %; (iv) (a) Nitrosobenzene (PhNO), L-proline, DMSO, 25 min, RT then $NaBH_4$, MeOH, 1 h; (b) $CuSO_4$, MeOH, RT, 12 h, over two step, 66 %; (v) PPh_3, Diethylazadicaroxylate (DEAD), reflux, 5 h, 89 %; (vi) LAH, THF, 0 ^{o}C-RT, 1 h, 98 %; (vii) Acetic anhydride, Et_3N, DMAP, DCM, 0 ^{o}C-RT, 2 h, 93 %; (viii) 10 % Pd/C, EtOH, H_2, RT, 14 h, 96 % (ix) H_5IO_6, PCC, MeCN, RT, 6 h, 90 %; (x) K_2CO_3, MeOH, RT, 2 h, 96 %; (xi) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 14 h, 72 %.

The synthesis was started with the commercially available 9-decen-1-ol **50** (**Scheme 8**). The protection of 9-decen-1-ol **50** with benzyl bromide, using sodium hydride in THF at room temperature gives the benzyl protected allylic ether compound **49** in a 92 % yield.[21]

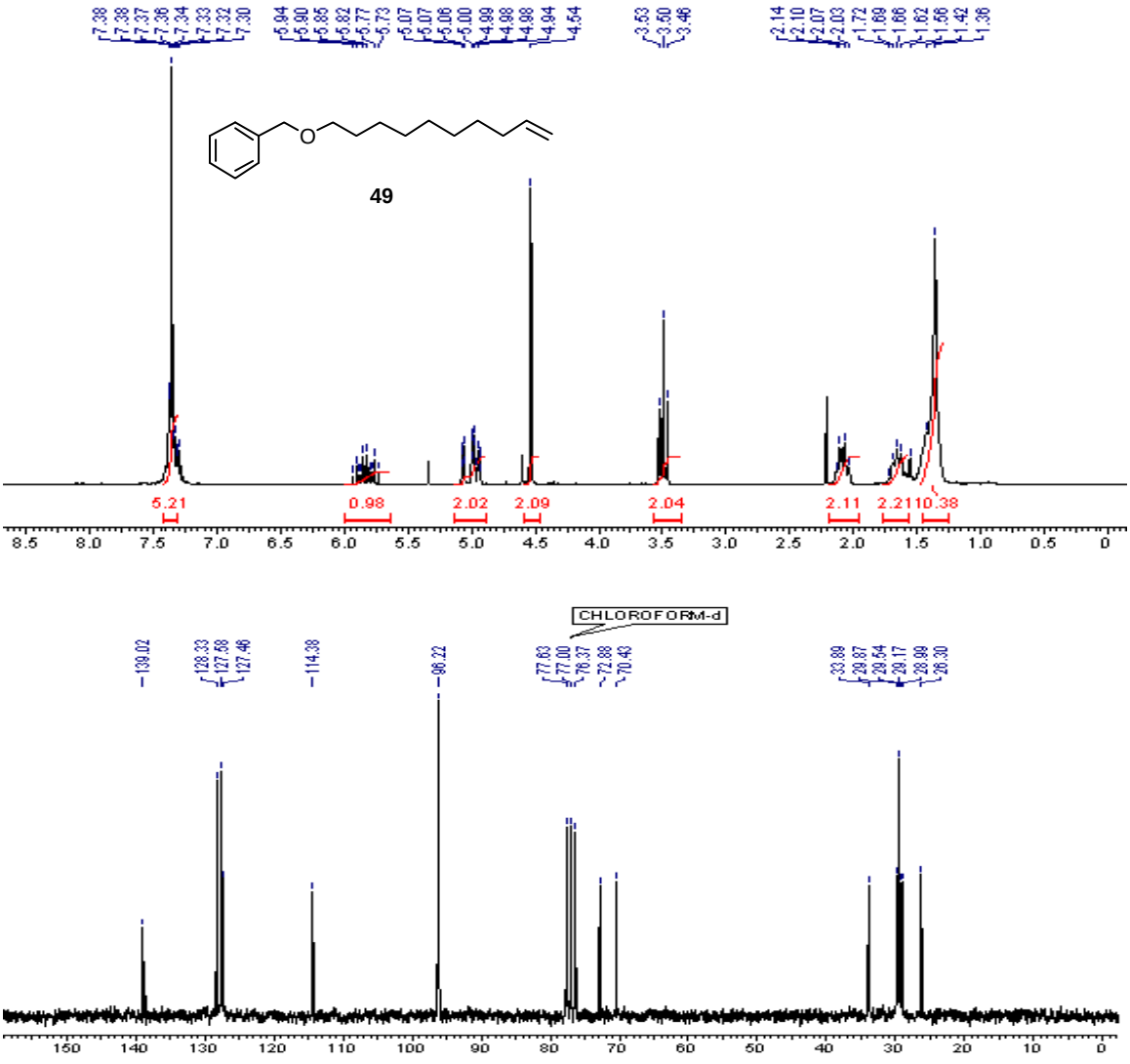


Fig. 7: ^{1}H & ^{13}C-NMR spectrum of ((dec-9-enyloxy)methyl)benzene **49**

The presence of benzyl group was confirmed by ^{1}H NMR spectrum which shows the singlet at δ 4.54 for two benzylic proton and multiplet at δ 7.30-7.38 for five aromatic

protons which confirmed the benylic group and multiplet at δ 5.77-5.94 for vinylic proton confirm the benzyl protected compound **49** (**Fig. 7**). The ^{13}C NMR spectrum showed signals at δ 114.38 and 139.02 for the carbon having terminal alkyne group and the signals at δ 127.46, 127.58 and 128.33 confirms the aromatic ring.

The protected allylic ether compound **49** was subjected to an epoxidation using meta-chloroperbenzoic acid (m-CPBA) in DCM at room temperature for 8 h gives racemic epoxide **51** in a 95 % yield.[21]

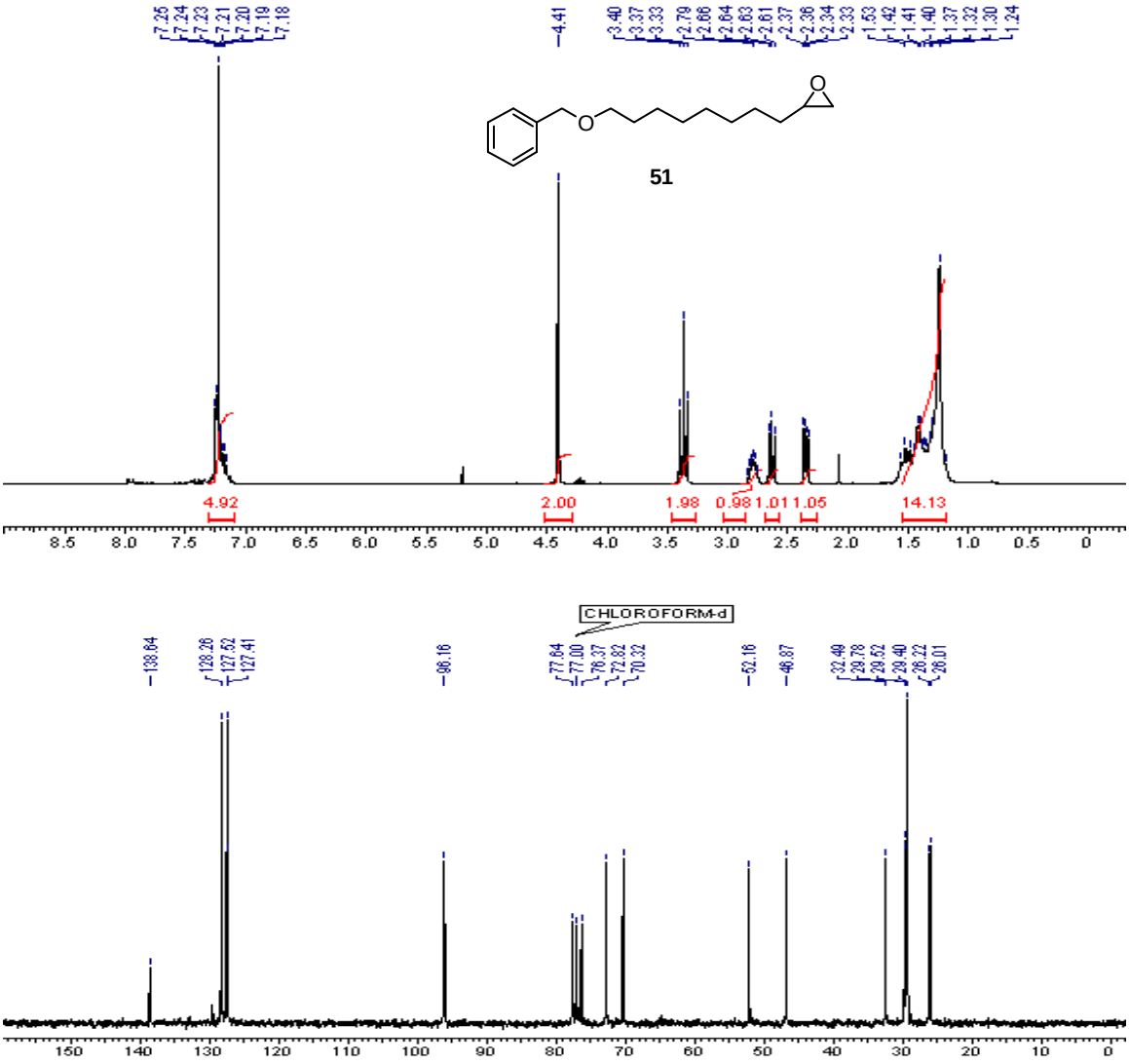


Fig. 8: ^{1}H & ^{13}C-NMR spectrum of 2-(8-(benzyloxy)octyl)oxirane **51**

^{1}H NMR spectrum of an epoxide shows disappearance of the vinylic protons and appearance of new multiplet at δ 2.64-2.79 for the tertiary proton of an epoxide. The ^{13}C NMR spectrum showed signals at δ 46.87 and 52.16 for the two carbon of an epoxide group (**Fig. 8**).

An epoxide **51** was converted to corresponding aldehyde **48** in a 78 % yield under the Meinwald rearrangement condition using silica supported dodecatungstophosphoric acid (20 % DTP/SiO_2) in chloroform solvent at room temperature for 2 h.

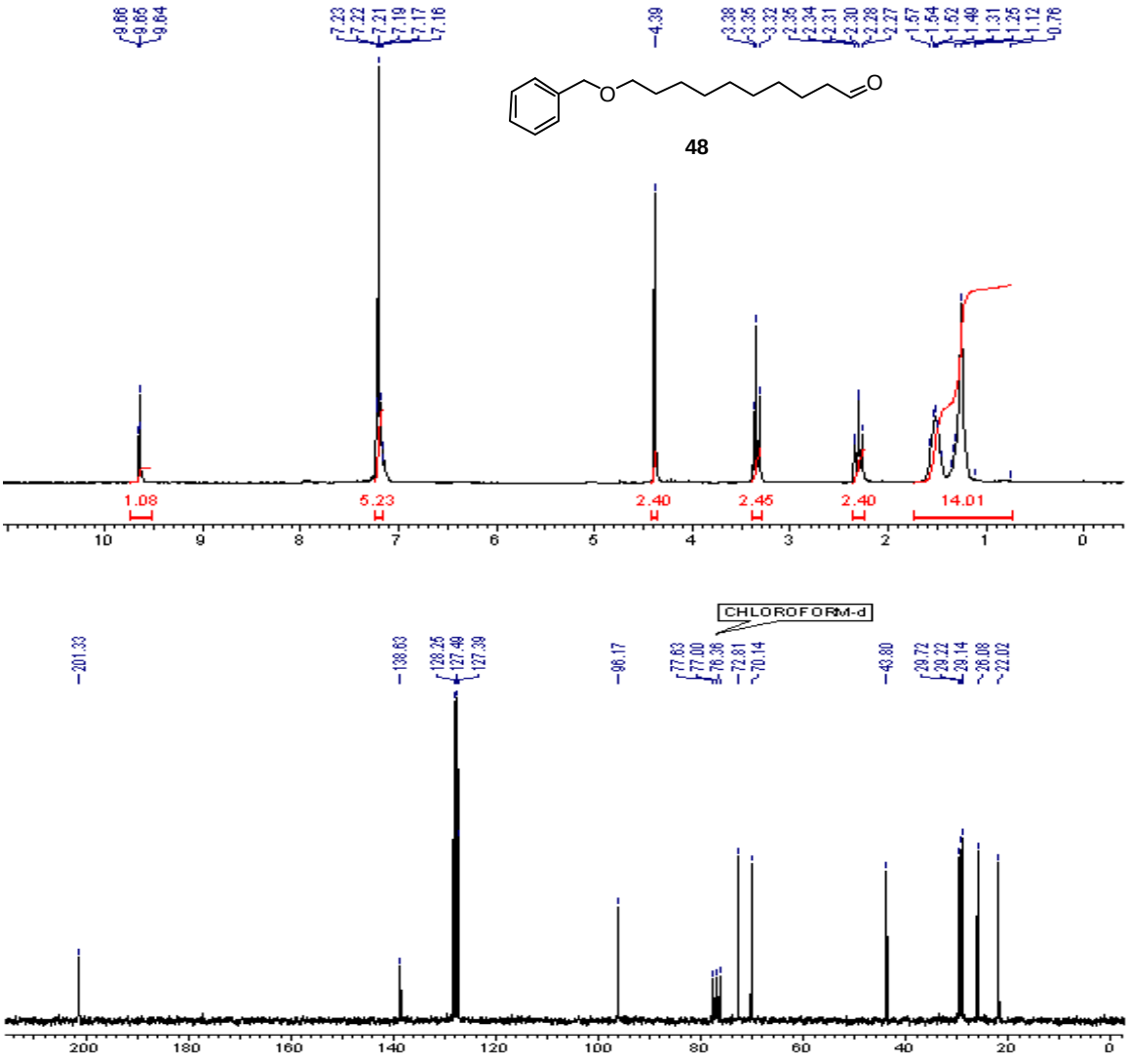


Fig. 9: ^{1}H & ^{13}C-NMR spectrum of 10-(benzyloxy)decanal **48**

^{1}H NMR spectrum shows the triplets at δ 9.65 due to the aldehyde protons and the singlet at δ 4.39 for two benzyl proton. The ^{13}C NMR spectrum showed characteristic signals at δ 201.33 for the carbonyl carbon of aldehyde confirm the formation of aldehyde (**Fig. 9**). Aldehyde **48** was then subjected to L-proline (20 mol %) catalyzed asymmetric α-aminoxylation with nitrosobenzene in dimethyl sulfoxide for 25 min and subsequently reduction was carried out with $NaBH_4$ in a methanol for 1 h. The crude aminoxy intermediates without purification was subjected to $CuSO_4$ catalyzed deprotection in a methanol at room tempreture to obtain diol **47** in a 66 % yields over two steps.

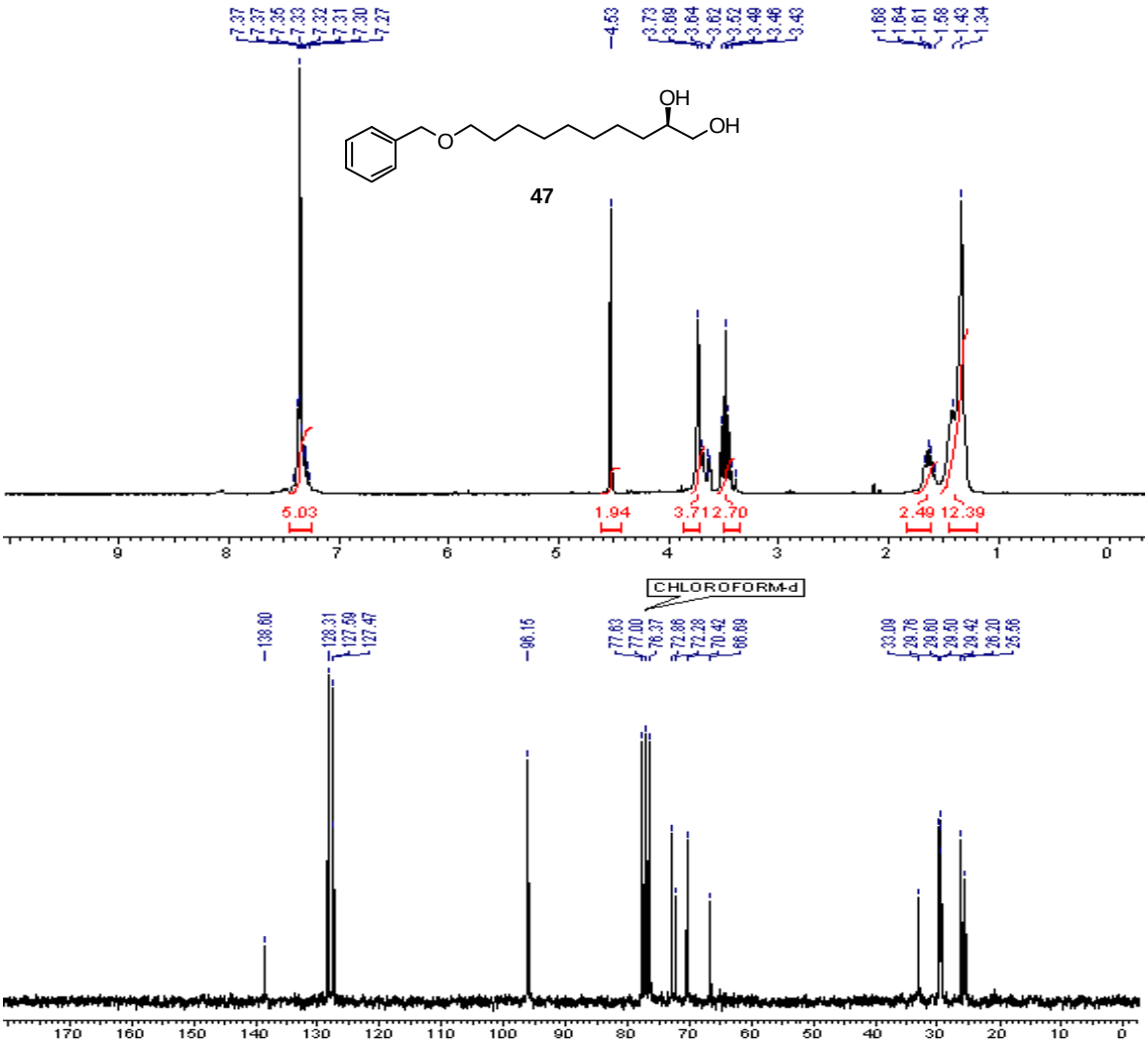


Fig. 10: ^{1}H & ^{13}C-NMR spectrum of (*R*)-10-(benzyloxy)decane-1,2-diol **47**

The formation of diol **47** was confirmed by appearance of multiplet at δ 3.62-3.73 and disappearance of aldehyde triplets at δ 9.65 in ^{1}H NMR spectrum. The ^{13}C NMR spectrum shows signal at δ 72.28 for the quaternary carbon having the hydroxyl group and disappearance of signal from δ 201.33 for the carbonyl carbon of aldehyde, which confirmed the formation of chiral 1, 2 diol **47** (**Fig. 10**).

The diol **47** was then converted to an epoxide **46** in a 89 % yield[22] under Mitsunobu reaction conditions using PPh_3 and DEAD in a 1, 4-dioxane solvent at reflux condition for 5 h in one step.

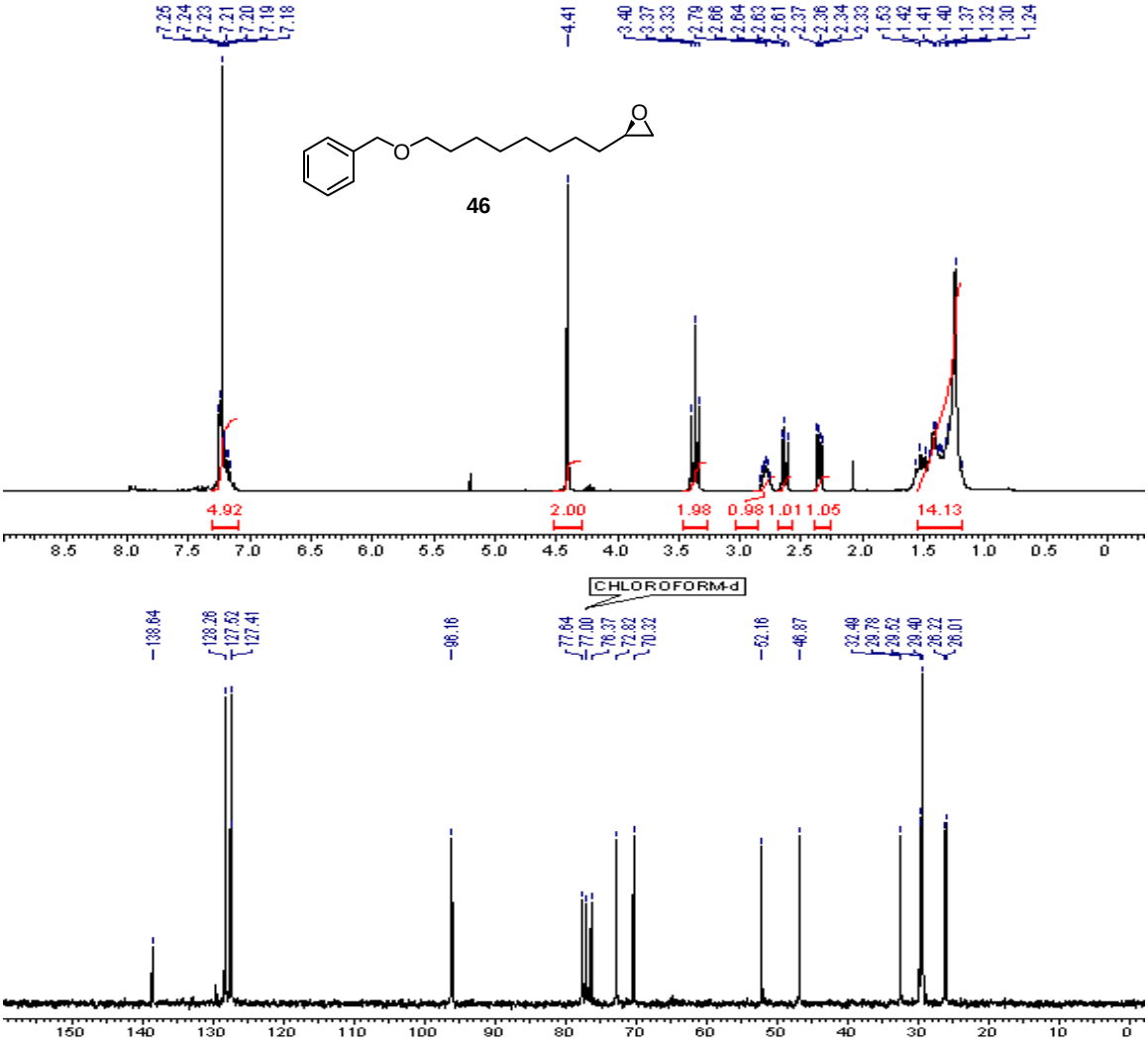


Fig. 11: ^{1}H & ^{13}C-NMR spectrum of (*R*)-2-(8-(benzyloxy)octyl)oxirane **46**

^{1}H NMR spectrum of an epoxide shows disappearance of peaks from δ 3.62 and appearance of new multiplet at δ 2.64-2.79 for the tertiary proton of an epoxide. The ^{13}C NMR spectrum showed signals at δ 46.87 and 52.16 for the two carbon of an epoxide group (**Fig. 11**).

The chiral epoxide **46** was subjected to the reduction using lithium aluminium hydride (LAH) as a hydride donor in THF at 0 ^{o}C to RT for 1 h, afforded the chiral secondary alcohol **45** in a 98 % yield.[21]

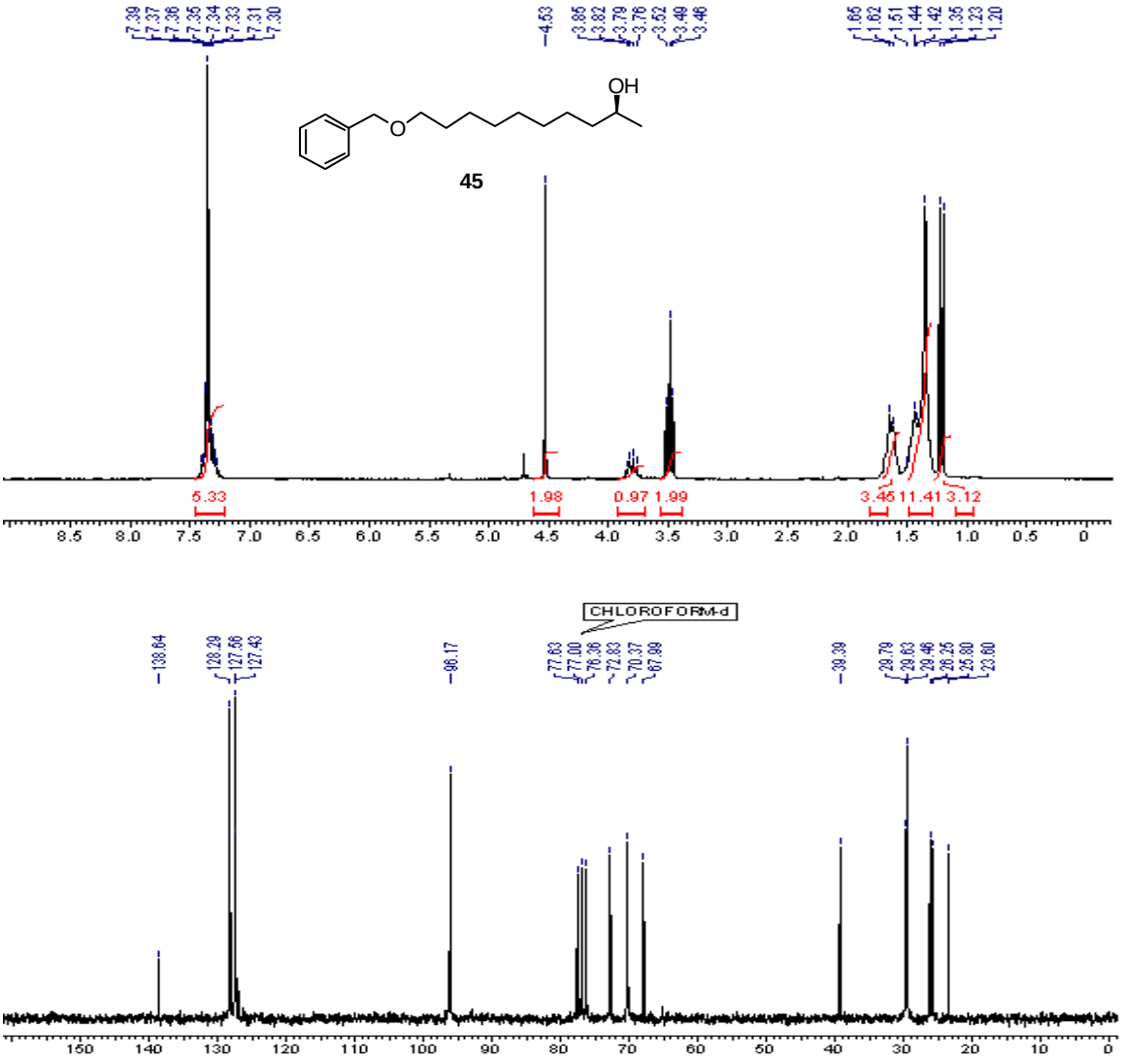


Fig. 12: ^{1}H & ^{13}C-NMR spectrum of (*S*)-10-(benzyloxy)decan-2-ol **45**

^{1}H NMR spectrum shows the characteristic doublet of methyl proton at δ 1.20 for three methyl protons and the multiplet for one proton at δ 3.76-3.85 for the quaternary carbon bearing the secondary hydroxyl group. ^{13}C NMR spectrum shows the signal at δ 23.60 and δ 67.99 for the terminal CH_3 group and the quaternary carbon having the hydroxyl group confirmed the formation of product **45** (**Fig. 12**).

The secondary alcohol **45** was protected using acetic anhydride in the presence of triethylamine as a base and catalytic amount of 4-dimethylaminopyridine (DMAP) in a DCM solvent at room tempreture for 2 h gives acetyl protected compound **52** in a 93 % yield.

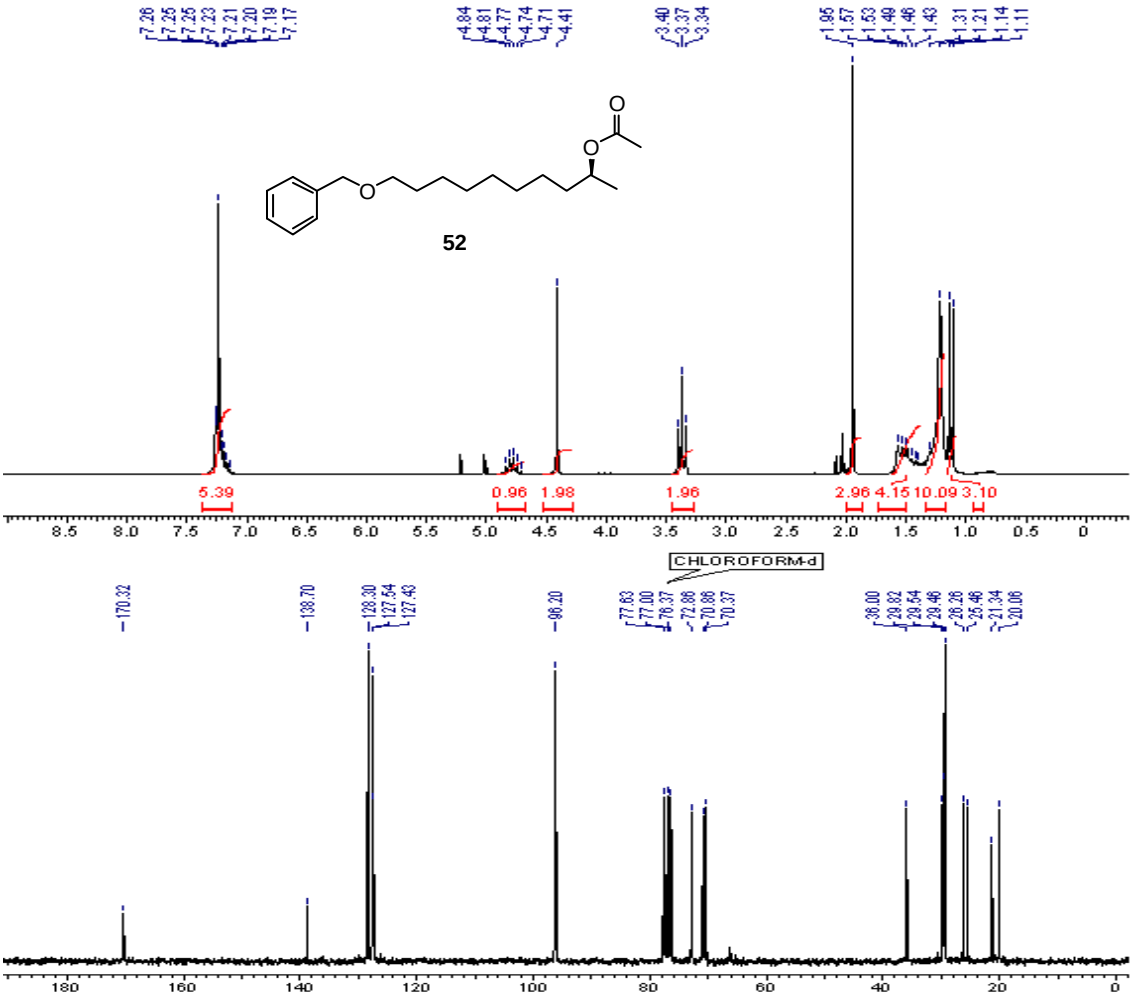


Fig. 13: ^{1}H & ^{13}C-NMR spectrum of (*S*)-10-(benzyloxy)decan-2-yl acetate **52**

^{1}H NMR spectrum shows the new singlet for the three methyl proton of acetyl group at δ 1.95 and the multiplet for one proton at δ 4.71-4.84. ^{13}C NMR spectrum shows typical signal at δ 21.34 for methyl group as well as the characteristic peak for the carbonyl carbon of acetyl group at δ 170.32 confirmed the acetyl protected compound **52** (**Fig. 13**). The acetyl protected compound **52** was subjected for the selectively benzyl deprotection using 10 % Pd/C in the presence of H_2 in an ethanol solvent at room tempreture for 14 h, afforded primary alcohol **53** in a 96 % yield.

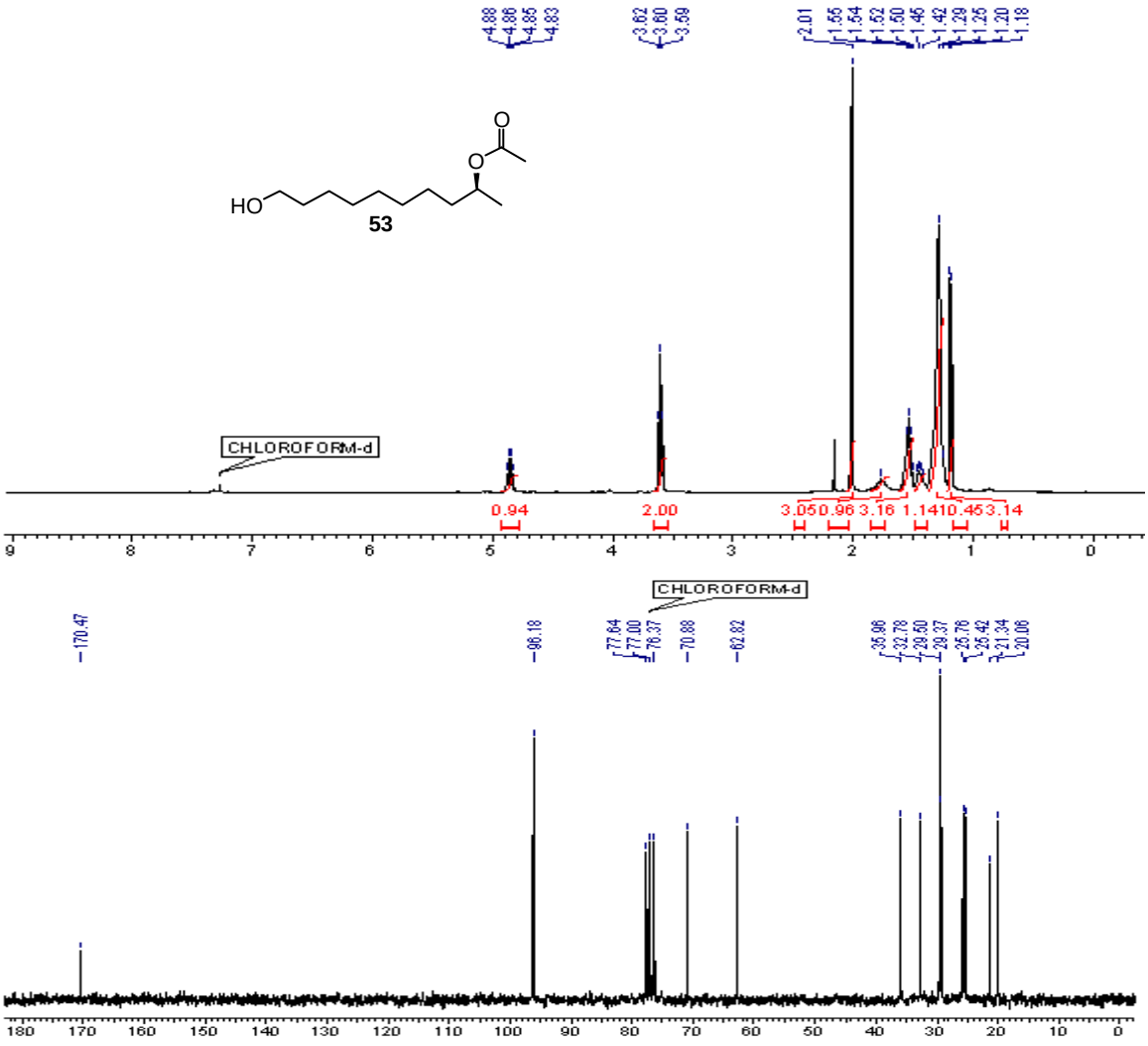


Fig. 14: ^{1}H & ^{13}C-NMR spectrum of (*S*)-10-hydroxydecan-2-yl acetate **53**

^{1}H NMR spectrum shows the disappearance of multiplet for five protons in the aromatic region as well as disappearance of singlet for two benzyl protons from δ 4.41 and appearance of broad singlet for one proton of primary hydroxyl group at δ 1.55. ^{13}C NMR spectrum shows disappearance of signals from the aromatic region confirmed the formation of **53** (**Fig. 14**).

The primary hydroxyl compound was subjected to the oxidation using sodiumperiodate and catalytic amount of pyridinium chlorochromate (PCC) in an acetonitrile at room tempreture for 6 h to get the oxidized acid **54** compound in a 90 % yield.[23]

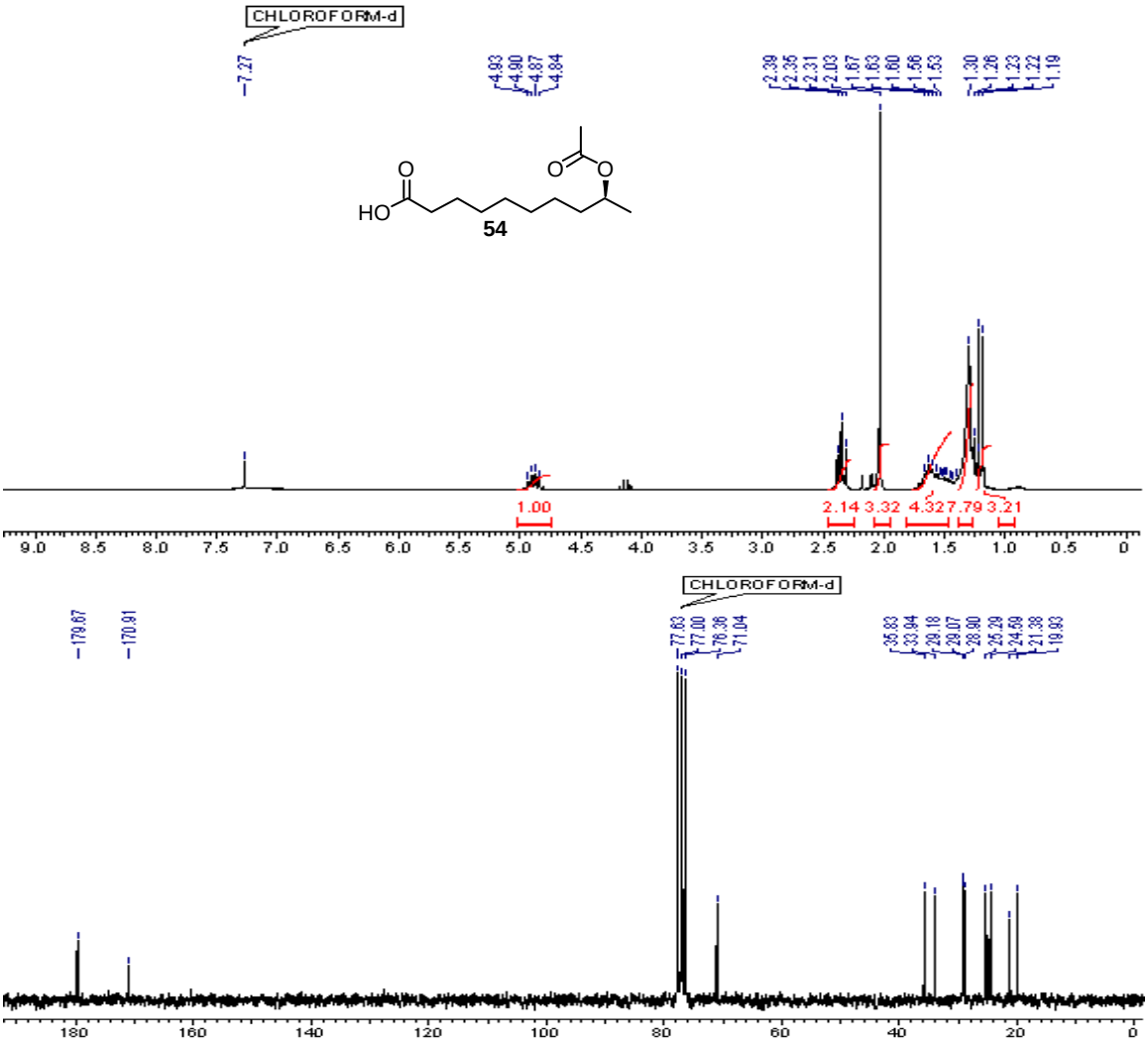


Fig. 15: ^{1}H & ^{13}C-NMR spectrum of (*S*)-9-acetoxydecanoic acid **54**

The ^{1}H NMR spectrum of acid shows the disappearance of triplet for two protons adjacent to the primary hydroxyl group from δ 3.60. ^{13}C NMR spectrum shows the signal at δ 179.67 and δ 170.91 for the two carbonyl carbons of acid group and acetyl group respectively, which confirm the formation of acid **54** (**Fig. 15**).

The acetyl deprotection of compound **54** was carried out using potassium carbonate in a methanol solvent at room tempreture for 2 h, afforded the compound **44** in a 96 % yield.

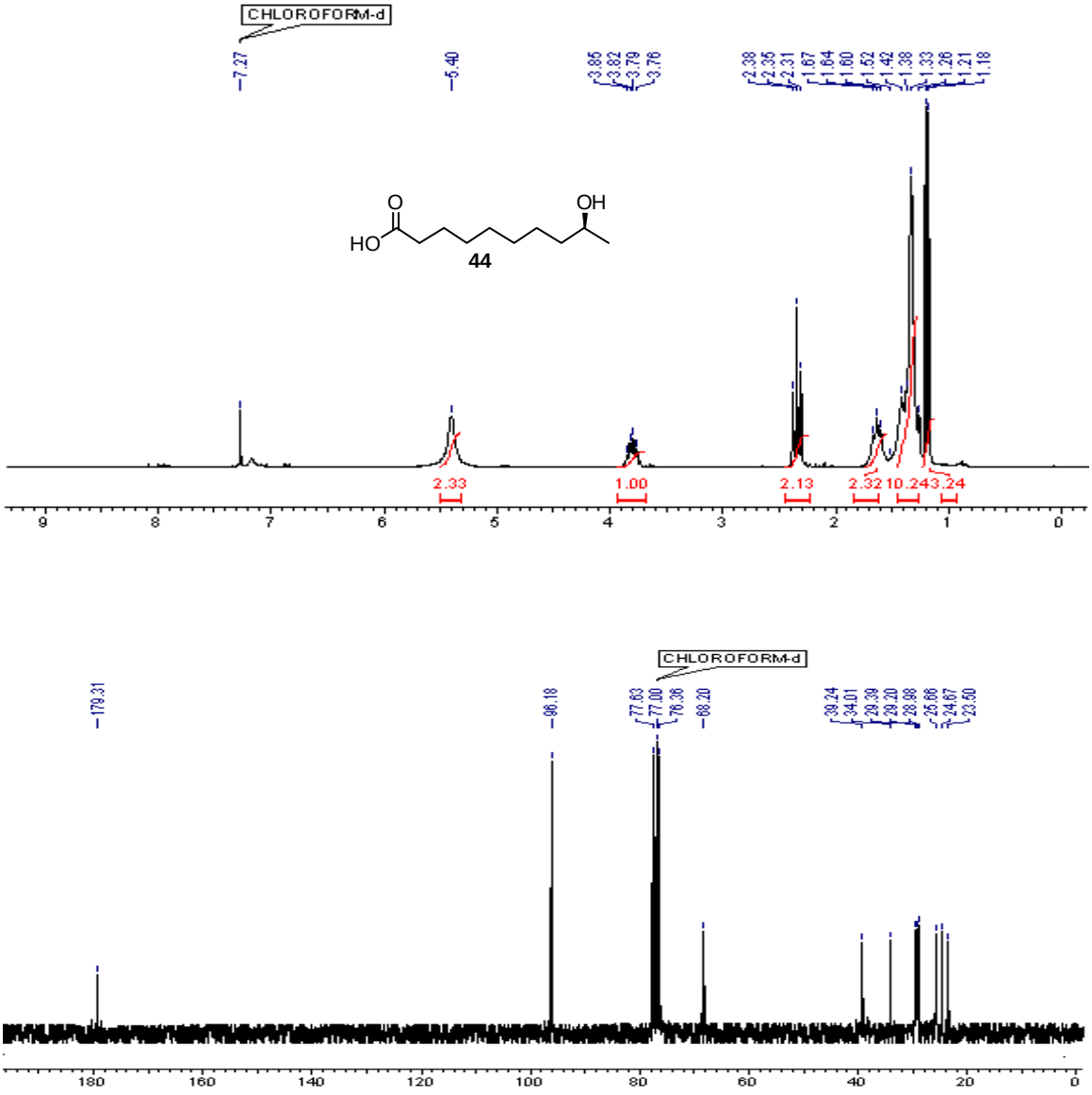
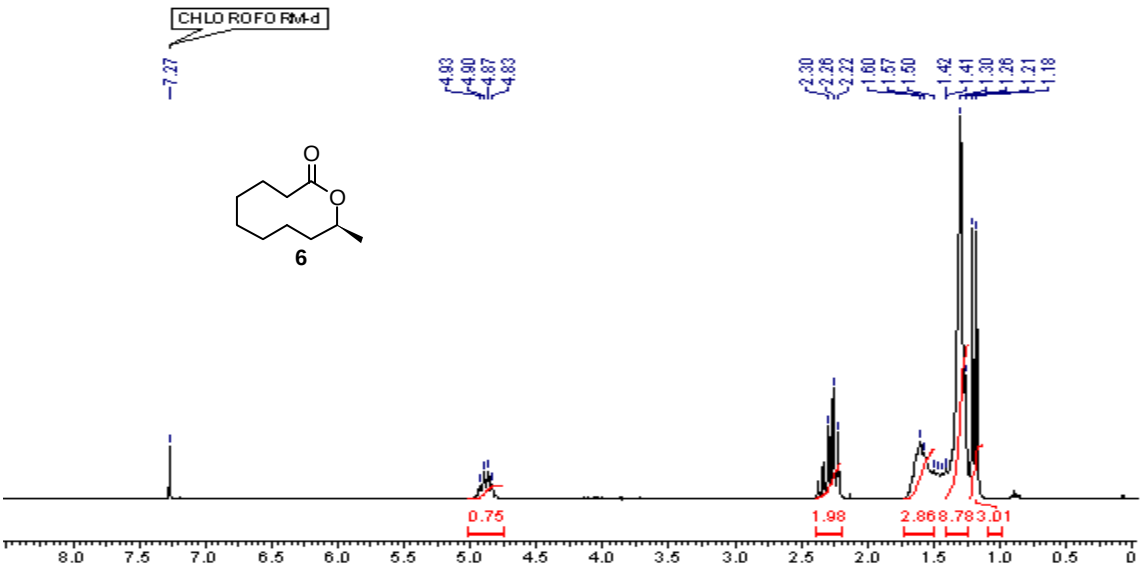


Fig. 16: ^{1}H & ^{13}C-NMR spectrum of (*S*)-9-hydroxydecanoic acid **44**

The ^{1}H NMR spectrum of compound shows the disappearance of singlet for three methyl protons of acetyl group from δ 1.67 and appearance of broad singlet at δ 5.40 for hydroxyl group of acid and alcohol. ^{13}C NMR spectrum shows the disappearance of signal from δ 170.91 for the carbonyl carbon of acetyl group confirms the formation of acid **44** (**Fig. 16**).

Finally, the (*S*)-9-hydroxydecanoic acid **44** was subjected to the Yamaguchi lactonization in the presence of 2, 4, 6-trichlorobenzoyl chloride, triethyl amine using catalytic amount of 4-dimethylaminopyridine (DMAP) in a toluene solvent at reflux tempreture for 14 h, afforded the desired target molecule (*S*)-Phoracantholide I **6** in a 72 % yield.[21]

The formation of (*S*)-Phoracantholide I **6** was confirmed by ^{1}H and ^{13}C NMR. ^{1}H NMR spectrum shows the multiplet for one proton at δ 4.83-4.93 for the quaternary proton and doublet at δ 1.21 for the three methyl protons. ^{13}C NMR spectrum shows the signal at δ 70.66 and 173.32 for the quaternary and carbonyl carbon, respectively, confirm the formation of (*S*)-phoracantholide I **6** (**Fig. 17**).



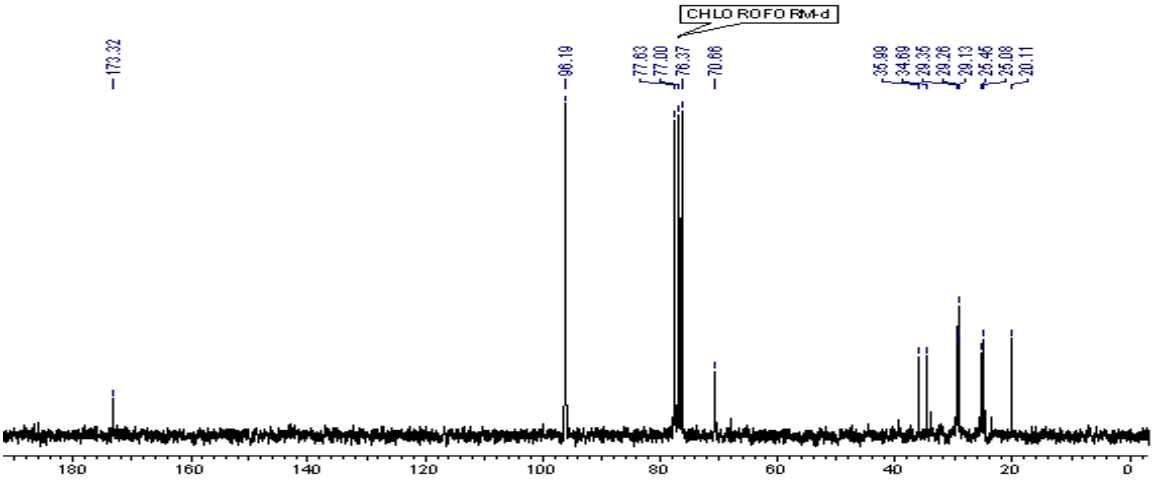


Fig. 17: ^{1}H & ^{13}C-NMR spectrum of (*S*)-Phoracantholide I **6**

1.1.5 Conclusion

In conclusion, highly efficient and straight forward asymmetric approach for an enantioselective synthesis of (*S*)-phoracantholide I **6** has been developed via α-aminoxylation of aldehyde catalyzed by L-proline as a key step and source of chirality. The salient features of this synthetic approach are its simplicity, clean, environmental friendly procedures, and efficient, rapid and mild reactions conditions. The protocol is very general and it may works well for the synthesis of other lactones compound affording good to excellent yields.

1.1.6 Experimental section

1.1.6.1 Synthetic procedures and Spectral data

((dec-9-enyloxy)methyl)benzene 49

To the solution of 9-decen-1-ol (5 g, 32 mmol) in 25 mL THF at 0 ^{o}C, NaH (60 %) (1.5 g, 38 mmol) was added portion wise under the nitrogen atmosphere. After completion of

NaH addition the reaction mixture was stirred at same temperature for 15 min. Then Benzyl bromide (3.8 mL, 32 mmol) taken in 10 mL THF was added drop wise to the reaction mixture and reaction mixture was stirred for 30 min. at same temperature followed to stirred reaction for 4 h at room tempreture. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched by 10 mL water at 0 ^{o}C, extracted by ethyl acetate (3*25 mL), the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue obtained was purified using ethyl acetate- petroleum ether as eluent by column chromatography over silica gel (60-120 mesh), afforded the allyl ether **49** (7.2 g, 92 % yield) as colorless liquid.

Yield: 92 %, colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.36-1.56 (m, 10H), 1.66 (t, *J*=7 Hz, 2H), 2.08 (q, *J*=7 Hz, 2H), 3.50 (t, *J*=2 Hz, 2H), 4.54 (s, 2H), 4.94-5.07 (m, 2H), 5.73-5.94 (m, 1H), 7.30-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 26.30, 28.99, 29.17, 29.54, 29.87, 33.89, 70.43, 72.88, 114.38, 127.46, 127.58, 128.33, 139.02.

2-(8-(benzyloxy)octyl)oxirane 51

To the solution of allyl ether **49** (5 g, 20 mmol) in 50 mL dichloromethane, the meta-chloroperbenzoic acid (m-CPBA 47 %) (8.9 g, 24 mmol) was added portion wise over the period of 30 min. The reaction mixture was stirred at room temperature until it shows the completion of the reaction by TLC (8 h). Then the reaction mixture was quenched by 20 % sodium bicarbonate and extracted with DCM (3*20 mL), the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue obtained was purified using ethyl acetate-petroleum ether as eluent by column chromatography over silica gel (60-120 mesh), afforded an epoxide **51** as colorless liquid (5 g, 95 %).

Yield: 95 %, colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.24-1.53 (m, 14H), 2.36

(dd, *J*=3 Hz, 2H), 2.64 (dd, *J*=4 Hz, 1H), 2.66-2.79 (m, 1H), 3.37 (t, *J*=6 Hz, 2H), 4.41 (s, 2H), 7.18-7.25 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 26.01, 26.22, 29.40, 29.52, 29.78, 32.49, 46.87, 52.16, 70.32, 72.82, 127.41, 127.52, 128.26, 138.64.

10-(benzyloxy)decanal 48

To the solution of an epoxide **51** (1 g, 3.8 mmol) in 20 mL chloroform, 20 % DTP/SiO_2 (50 mg) was added and reaction mixture was stirred at room temperature for 2 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered and washed with chloroform (2*10 mL). The filtrate was evaporated under the reduced pressure and product was purified using ethyl acetate-petroleum ether as eluent by column chromatography over silica gel (60-120 mesh), afforded the aldehyde **48** as colorless liquid (780 mg, 78 %).

Yield: 78 %, colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.25-1.57 (m, 14H), 2.34 (tt, *J*=7 Hz, 2H), 3.35 (t, *J*=6 Hz, 2H), 4.39 (s, 2H), 7.16-7.23 (m, 5H), 9.65 (t, *J*=2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 22.02, 26.08, 29.14, 29.22, 29.72, 43.80, 70.14, 72.81, 127.39, 127.49, 128.25, 138.63, 201.33.

(*R*)-10-(benzyloxy)decane-1, 2-diol 47

To a solution of aldehyde **48** (2.6 g, 10 mmol) and L-proline (230 mg, 2 mmol) in 10 mL DMSO at room temperature, nitrosobenzene (1.1 g, 10 mmol) was added portion wise and the reaction mixture stirred for 1 h. To this reaction mixture, MeOH (10 mL) and $NaBH_4$ (190 mg, 5 mmol) was added and stirring was continued for 30 min. After addition of water (10 mL) to the reaction mixture, the resulting mixture was extracted with ethyl acetate (3*50 mL) and the organic layer was dried over anhydrous sodium sulphate, and concentrated under the reduced pressure, afforded crud aminoxy alcohol.

To the crude aminoxy alcohol in MeOH, $CuSO_4$ (477 mg, 3 mmol) was added and stirred at room temperature for 8 h. The completion of the reaction was checked by TLC, and then the reaction mixture was filtered through a Celite pad. The filtrate was concentrated to get the crude product, which was purified using ethyl acetate-petroleum ether as eluent over the column chromatography using silica gel (60-120 mesh), gives diol **47** (1.87 g, 66 %).

Yield: 66 %, semi solid; $[\alpha]_D^{25}$ = +7.2 (c, 0.8, MeOH) (lit.[24] $[\alpha]_D^{25}$ = +7.2 (c, 0.8, MeOH, >99 % ee); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.34-1.58 (m, 12H), 1.64 (t, *J*=6 Hz, 2H), 3.43-3.52 (m, 3H), 3.62-3.73 (m, 4H), 4.52 (s, 2H), 7.27-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 25.56, 26.20, 29.42, 29.50, 29.60, 29.76, 33.09, 66.69, 70.42, 72.28, 72.86, 127.47, 127.59, 128.32, 138.61.

(*R*)-2-(8-(benzyloxy)octyl)oxirane 46

To the solution of diol **47** (2.8 g, 10 mmol), and PPh_3 (3.9 g, 15 mmol) in THF (30 mL), DEAD (2.4 mL, 15 mmol) in 10 mL THF was added drop wise under the N_2 atmosphere. The reaction mixture was stirred at room temperature till the completion of reaction (5 h), which was monitored by TLC. After the completion of reaction, the reaction mixture was evaporated under the reduced pressure and product was purified using ethyl acetate-petroleum ether as eluent by column chromatography over silica gel (60-120 mesh), afforded an epoxide **46** as colorless liquid (2.3 g, 89 %); $[\alpha]_D^{25}$ = +5.7 (c, 1, $CHCl_3$).

(*S*)-10-(benzyloxy)decan-2-ol 45

To a solution of an epoxide **46** (2.62 g, 10 mmol) in THF (15 mL), Lithium aluminum hydride (380 mg, 10 mmol) portion wise was added at 0 ^oC with stirring under the N_2 atmosphere. The completion of reaction was monitored by TLC (1 h). After completion

of reaction, the reaction mixture was quenched with 2 mL of 15 % NaOH solution and the stirred for 20 min. The inorganic white precipitate obtained was filtered, washed with ethyl acetate (2*10 mL). The filtrate was concentrated under the reduced pressure, afforded crud residue as product. The residue was purified using ethyl acetate-petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives alcohol **45** (2.5 g, 98 %).

Yield: 98 %, Colorless liquid; $[\alpha]_D^{25}$ = +4.7 (c, 1, $CHCl_3$) ; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.22 (d, *J*=6 Hz, 3H), 1.35-1.51 (m, 12H), 1.62-1.65 (m, 3H), 3.49 (t, *J*=6 Hz, 2H), 3.76-3.85 (m, 1H), 4.53 (s, 2H), 7.30-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 23.60, 25.80, 26.24, 29.46, 29.63, 29.79, 39.39, 67.99, 70.37, 72.83, 127.43, 127.56, 128.29, 138.64.

(*S*)-10-(benzyloxy)decan-2-yl acetate 52

To the solution of alcohol **45** (2.64 g, 10 mmol) and triethylamine (2.9 mL, 20 mmol) in a dichloromethane (25 mL), DMAP (250 mg, 2 mmol) was added and stirred for 5 min at 0 ^oC, to this reaction mixture, acetic anhydride (2 mL, 20 mmol) in DCM (5 mL) was added drop wise and then the reaction mixture was stirred at room temperature for 2 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was washed with water followed by separation of organic layer. The organic layer was concentrated under the reduced pressure to obtain crude residue as product. The residue was purified using ethyl acetate-petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives product **52** (2.84 g, 93 %).

Yield: 93 %, Colorless liquid; $[\alpha]_D^{25}$ = +6.2 (c, 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.12 (d, *J*=6 Hz, 3H), 1.21-1.31 (m, 10H), 1.49-1.57 (m, 4H), 1.95 (s, 3H), 3.37 (t, *J*=6

Hz, 2H), 4.41 (s, 2H), 4.71-4.84 (m, 1H), 7.17-7.26 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 20.06, 21.34, 25.46, 26.26, 29.46, 29.54, 29.82, 36.00, 70.37, 70.86, 72.86, 127.43, 127.54, 128.30, 138.70, 170.32.

(*S*)-10-hydroxydecan-2-yl acetate 53

To the solution of **52** (3 g, 9.8 mmol) in an ethanol (20 mL), 10 % Pd/C was added and the reaction mixture was stirred at room temperature under the H_2 atmosphere using H_2 filled balloon. The completion of reaction was monitored by TLC (14 h). After completion of reaction, the reaction mixture was filtered though the Cilitte pad. The filtrate was concentrated under the reduced pressure to obtained crud residue as product. The residue was purified using ethyl acetate-petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives product **53** (2.1 g, 96 %).

Yield: 96 %, Colorless liquid; $[\alpha]_D^{25}$ = +9.6 (c, 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.18 (d, *J*=6 Hz, 3H), 1.25-1.45 (m, 12H), 1.50-1.54 (m, 3H), 1.55 (s, 1H), 2.01 (s, 3H), 3.60 (t, *J*=6 Hz, 2H), 4.83-4.88 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 20.06, 21.34, 25.42, 25.76, 29.37, 29.50, 32.78, 35.96, 62.82, 70.88, 170.47.

(*S*)-9-acetoxydecanoic acid 54

Periodic acid (5 g, 22 mmol) was added to the acetonitrile (25 mL) and stirred the mixture at room temperature for 15 min, followed by cooling of reaction mixture in ice bath. To this reaction mixture the alcohol **53** (2.16 g, 10 mmol) in an acetonitrile (5 mL) was added drop wise and followed the addition of PCC (430 mg, 2 mmol), the resulting reaction mixture was stirred at room temperature for 6 h. After the reaction shows completion by TLC, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with brine (25 mL). The organic layer was separated and concentrated under the

reduced pressure, to obtained crud residue as product. The residue was purified using ethyl acetate-petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives compound **54** (2.1 g, 90 %).

Yield: 90 %, Colorless liquid; $[\alpha]_D^{25}$ = +8.2 (c, 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.18 (d, *J*=6 Hz, 3H), 1.23-1.30 (m, 8H), 1.53-1.67 (m, 4H), 2.03 (s, 3H), 2.35 (t, *J*=7 Hz, 2H), 4.84-4.93 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 19.93, 21.38, 24.59, 25.28, 28.90, 29.07, 29.18, 33.94, 35.83, 71.04, 170.91, 179.68.

(*S*)-9-hydroxydecanoic acid 44

Potassium carbonate (K_2CO_3) (5.5 g, 40 mmol) was added to the methanol (20 mL) and stirred the reaction mixture at room tempreture for 5 min. To this reaction mixture acid **54** (2.3 g, 10 mmol) in methanol (5 mL) was added drop wise, the resulting reaction mixture was stirred at room temperature till it shows complete conversion by TLC (4 h). After the completion of reaction, the reaction mixture was concentrated under the reduced pressure to obtain the crud residue. The crud residue was dissolved in ethyl acetate (50 mL), the inorganic material was separated by filtration, and the filtrate was concentrated under the reduced pressure to obtain the crud product. The crud product was purified using ethyl acetate-petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives product **44** (1.8 g, 96 %).

Yield: 96 %, Colorless liquid; $[\alpha]_D^{25}$ = +8.1 (c, 0.4, $CHCl_3$) (lit.[4] $[\alpha]_D^{22}$ = +8.14 (c, 0.41, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.20 (d, *J*=6 Hz, 3H), 1.26-1.52 (m, 10H), 1.64 (t, *J*=7 Hz, 2H), 2.35 (t, *J*=7 Hz, 2H), 3.76-3.85 (m, 1H), 5.40 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 23.50, 24.67, 25.66, 28.98, 29.20, 29.39, 34.01, 39.24, 68.20, 179.31.

(*S*)-10-methyloxecan-2-one 6

To the solution of acid **44** (1.1 g, 5.8 mmol) in THF (5 mL), Et_3N (0.9 g, 9 mmol) was added at room temperature. To this reaction mixture 2, 4, 6-trichlorobenzoyl chloride (2.1 g, 8.8 mmol) was added and the resulting reaction mixture was stirred at room temperature for 2 h. After the reaction shows completion by TLC, the reaction mixture was diluted with toluene (5 mL), the resulting solution was added drop wise to the solution of DMAP (714 mg, 5.8 mmol) in a toluene (15 mL) at 110 ^oC. The resulting reaction mixture was reflux until it shows completion of reaction by TLC (3 h). After the completion of reaction, reaction mixture was concentrated under the reduced pressure to obtain the residue as product. The residue was purified using ethyl acetate-petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives (*S*)-phoracantholide I **6** (710 mg, 72 %).

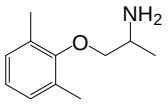
Yield: 72 %, Colorless liquid; $[\alpha]_D^{25}$ = +38.9 (c, 0.7, $CHCl_3$) (lit.[4] $[\alpha]_D^{22}$ = +38.8 (c, 0.68, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.18 (d, *J*=6 Hz, 3H), 1.26-1.42 (m, 9H), 1.50-1.60 (m, 3H), 2.28 (ddt, 2H), 4.81-4.93 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 20.11, 25.08, 25.45, 29.13, 29.26, 29.35, 34.69, 35.99, 70.66, 173.32.

Section-II

Enantioselective Synthesis of (*R*)-Mexiletine

1.2.1 Introduction

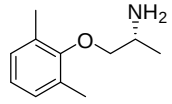
In 1980's, mexiletine **55** (**Fig. 18**) is first developed clinical drug, since then racemic form[25] of mexiletine is available in the market under the trade name Mixitil, which is clinically used as pain relief oral drug in the treatment of an antiarrhythmic, antimytonic, analgesic, and myotonic syndromes, and it belong to the group of Ib sodium channel blockers.[26]



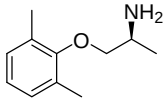
Mexiletine **55**

Fig. 18: Mexiletine **55**

However use of racemic form of mexiletine **55** for clinical treatment is limited due to its side effect. Moreover, in last few decades structure activity studies reveals that mexiletine enantiomers are differ in both pharmacodynamic and pharmacokinetic properties and hence (-)-(*R*)-mexiletine **56** is more potent in binding studies on cardiac sodium channels, as well as in blocking skeletal muscle sodium channels than (+)-(*S*)-mexiletine **60** in experimental arrhythmias (**Fig. 19**).[27]



(-)-(*R*)-Mexiletine **56**



(+)-(*S*)-Mexiletine **57**

Fig. 19: Isomer of Mexiletine **55**

Being (-)-(*R*)-mexiletine **56** is more potent as cardiovascular drug in life sciences, its demand is growing rapidly for enantiomerically pure form, and hence effort have been

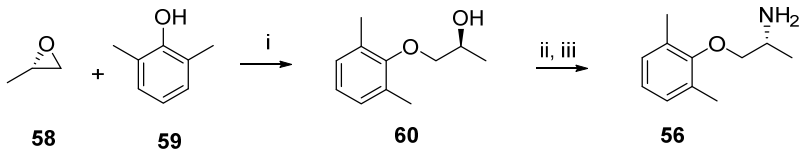
made by many researcher to develop the various strategies for synthesis of optically pure (-)-(*R*)-mexiletine **56** was reported in the literature. However, so far the strategy employed to prepare this compound is use of chiral pool approach and resolution of racemic mexiletine using enzymes as well as some chiral material.

1.2.2 Review of Literature

There are several reports available for the asymmetric synthesis of (*R*)-mexiletine **56** in the literature. However, almost all the methods reported for the asymmetric synthesis of Mexiletine involve either classical resolution of racemates using chiral material/ enzymes or a chiral pool approach which are described below.

Khan's approach[28]

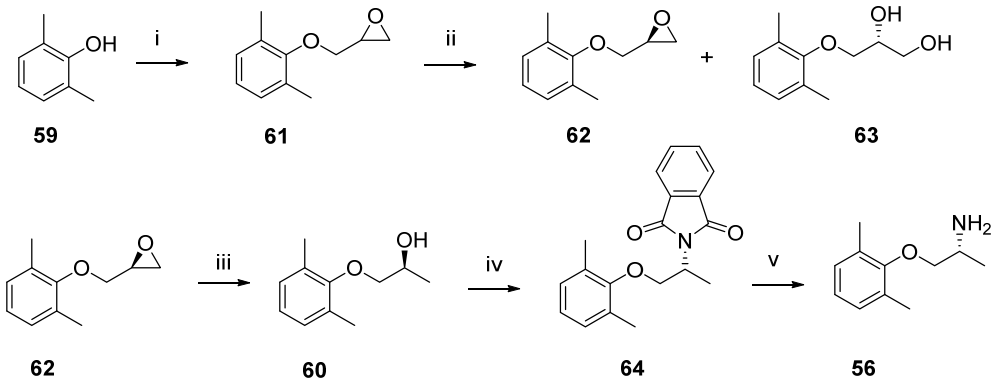
In this approach, Khan *et al*. have used the chiral pool approach for the synthesis of (*R*)-mexiletine **56**. The synthesis started with the (*S*)-propyline oxide **58**, which on treatment with the 2, 6-dimethyl phenol **59** using the bismuth triflate in a dichloromethane solvent, afforded the chiral secondary alcohol **60**. The alcohol **60** was converted to the phthalate derivative under the mitsunobu reaction condition. The phthalate was reduced using hydrazine hydrate, afforded the target (*R*)-mexiletine **56** in a 85 % yield (**Scheme 9**).



Scheme 9: *Reagents and reaction conditions*: (i)) bismuth triflate, CH_2Cl_2, 6 h, RT, 86 %; (ii) PPh_3, phthalimide, Diisopropyl azadicarboxilate (DIAD), THF, RT, 4 h, 80 %; (iii) N_2H_4, H_2O, EtOH, reflux, 3 h, 85 %.

Muthukrishnan's approach[29]

In this approach, Muthukrishnan *et al.* have used the hydrolytic kinetic resolution of terminal epoxide using Co-salen complex as a key step for the synthesis of (*R*)-Mexiletine **56**. The epoxide compound **61** was prepared from the reaction of 2, 6 dimethyl phenol **59** with epichlorohydrine. The aryl epoxide **61** was resolved using Co-salen complex into the chiral (*S*)-epoxide **62** and the undesired 1, 2-dio **63** *via* HKR protocol. The chiral (*S*)-epoxide **62** was reduced using LAH in a THF solvent, afforded the chiral secondary alcohol **60**. The alcohol **60** was protected by phthalate using triphenyl phosphine and DIAD in a THF solvent, afforded the phthalate protected compound **64**. The compound **64** was reduced using hydrazine hydrate; gives (*R*)-mexiletine **56** in a 86 % yield (**Scheme 10**).

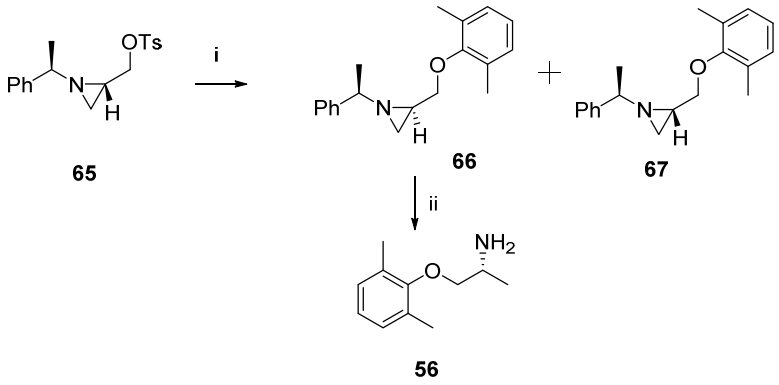


Scheme 10: *Reagents and reaction conditions*: (i) (±)-epichlorohydrin, K_2CO_3, acetone, reflux, 20 h, 80 %; (ii) (*R,R*) salen Co(III), 0 ^oC– RT, 30 h; (iii) $LiAlH_4$, THF, 0 ^oC, 30 min, 91 %; (iv) Ph_3P, phthalimide, DIAD, THF, RT, 4 h, 83 %; (v) $N_2H_4.H_2O$, EtOH, reflux, 3 h; 86 %.

Hyun-Joon & Lee approach[30]

In this approach, Hyun-Joon *et al*. have reported the nucleophilic substitution of (sulfonyloxymethyl)aziridine **66** with 2, 6-dimethylphenol **59** for the synthesis of (*R*)-Mexiletine **56** as shown in the **Scheme 11**. The aziridine **65** was transformed into aziridines **66** and **67** upon treatment with 2, 6-dimehtylphenol **59**. The two diastereomers

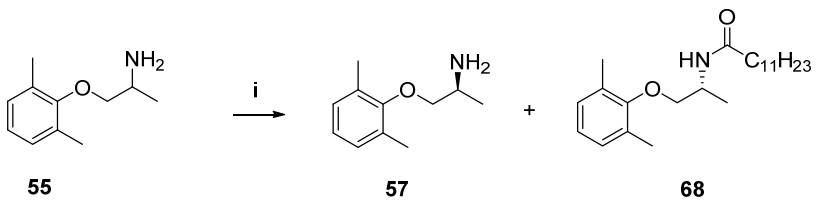
2*R*- and 2*S*-aziridines **66** and **67** respectively, obtained in the ratio 84:16 where as 76 % yield to the 2*R*-aziridines **66**. The major diastereomers **66** was isolated using the colum chromatography and converted into (*R*)-(-)-Mexiletine **56** upon treatment with H_2 in a MeOH solvent in the presence of $Pd(OH)_2$ in a 87 % yield.



Scheme 11: *Reagents and reaction conditions*: (i) 2, 6-dimethylphenol **59**, Acetone/DMF (1:1), K_2CO_3, reflux, 4 h, 76 %; (ii) H_2 (1 atm), $Pd(OH)_2$, MeOH, RT, 87 %.

Bertrand, Gastaldi and Gil approach[31]

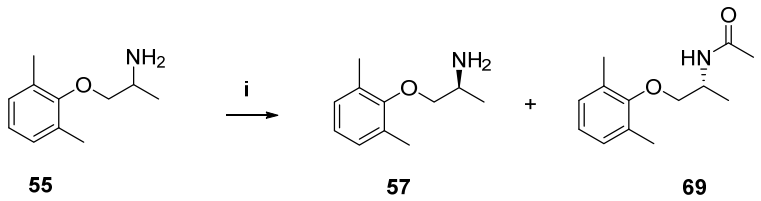
In this approach, Gill *et al*. have reported the resolution of the racemic mexiletine **55.** The resolution was carried out using enantioselective N-acylation using lauric acid catalyzed by *Candida antartica* lipase-B (CAL-B), which is more selective towards (*R*)-enantiomer for acylation. Thus, the acylated (*R*)-enantiomer **68** can be easily separated from the (*S*)-enantiomer **57**, afforded the protected (*R*)-mexiletine **68** with good optical purity (**Scheme 12**).



Scheme 12: *Reagents and reaction conditions*: (i) Lauric acid, CAL-B, heptane, 80 °C, 7 h.

Rebolledo's approach[32]

In this approach, Rebolledo *et al*. have reported the use of *Candida antartica* lipase CAL-B (Novozym 435) enzyme for resolution of the racemic mexiletine **55** *via* enantioselective acylation with ethyl acetate as the acylating reagent as well as a solvent. Under this reaction condition only the (*R*)-isomer of mexiletine **55** was acylated preferentially and the (*S*)-isomer remains **57** as it is. Thus, the resulting (*R*)-acetamide **69** and the unreacted (*S*)-isomer **57** was easily separated due to the difference in their polarity and afforded the acylated (*R*)-mexiletine **69** (**Scheme 13**).

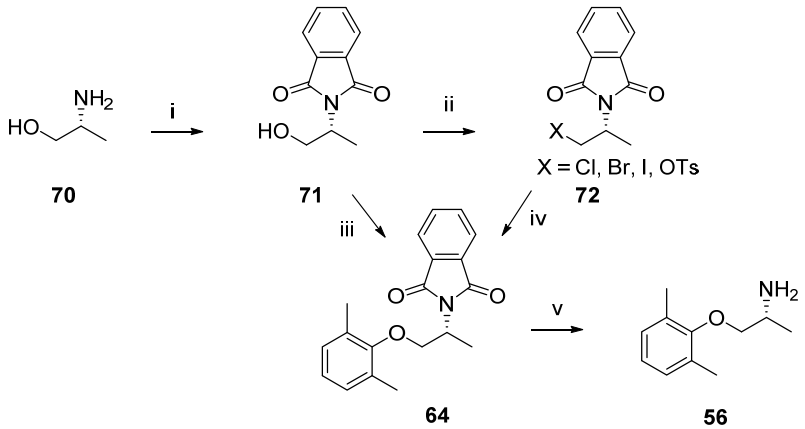


55 **57** **69**

Scheme 13: *Reagents and reaction conditions*: (i) CAL-B, EtOAc, 28 ^{o}C, 200 rpm, 21 h.

Lentini's Approach[33]

In this approach, Lentini *et al.* have synthesized (*R*)- Mexiletine **56** from chiral chiral (*R*)-(-)-2-amino-1-propanol **70**. The compound **70** on treatment with phthalimide, gives the phthalate compound **71**. The phthalate compound **71** treated with 2, 6-dimethylphenol **59** under the mitsunobu etherification followed by hydrozonalysis, afforded the final product (*R*)-mexiletine **56** (**Scheme 14**).

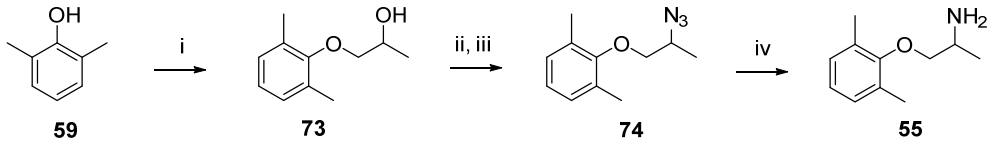


70 **71** **72** **64** **56**

Scheme 14: *Reagents and reaction conditions*: (i) phthalimide, Et_3N, 130 °C, 78 %; (ii) Toluene, HBr (g) or HI(g)/-5 ^oC- RT, 18 h, 80 ^oC, 2h (when X = Br or I); THF, $SOCl_2$, Py, 60 ^oC, 6 h (when X = Cl) (iii) 2, 6-xylenol **62**, Ph_3P, DEAD (or) DIAD, THF, RT, 24 h, 65 %; TsCl, Py, RT, 18 h (when X = OTs); (iv) 2, 6-xylenol **62**, DMF, Na_2CO_3, 24 h; (v) N_2H_4, AcOH, EtOH, reflux, 2 h.

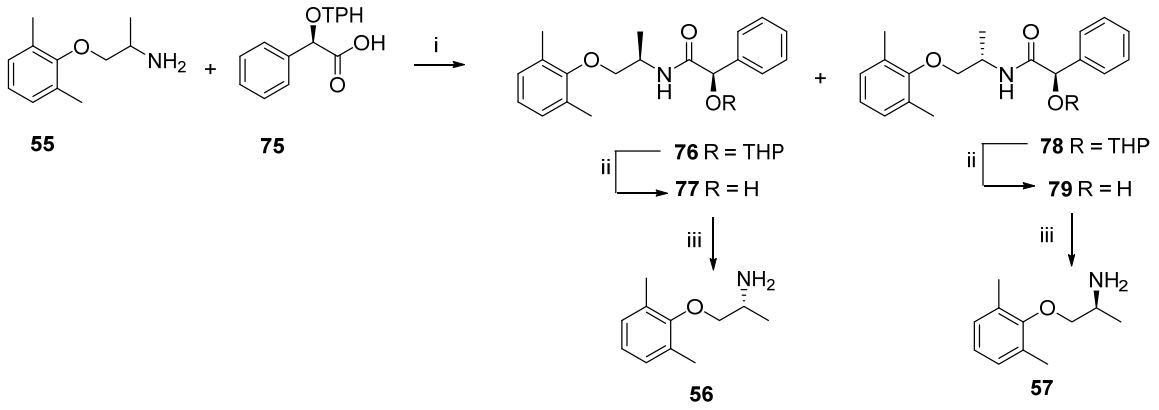
Martin's approach[34]

In this approach, Martin *et al.* have employed resolution strategy for the synthesis of the both the isomer of mexiletine by chiral derivatization in the presence of tetrahydropyranyl-protected (*R*)-Mandelic acid (THPMA) **75**. For this, the *rac*-mexiletine **55** was synthesized from coupling of 2, 6-dimethylphenol **59** with (±)propylene oxide in the presence of sodium hydroxide to afford aryloxy ether **73**. Subsequently, compound **73** was transformed to azide **74** as a key intermediate and it was subjected to Raney-Nickel catalyzed reduction of azide functionality to afford *rac*- Mexiletine **55** (**Scheme 15**).



Scheme 15: *Reagents and reaction conditions*: (i) propylene oxide, NaOH, H_2O, 60 ^oC, 6 h, 91 %; (ii) MsCl, Py, 0 ^oC- RT, 98 %; (iii) NaN_3, DMF, 100 ^oC, 2.5 h, 84 %; (iv) Ra-Ni, H_2 (1 atm), 5 h, 86 %.

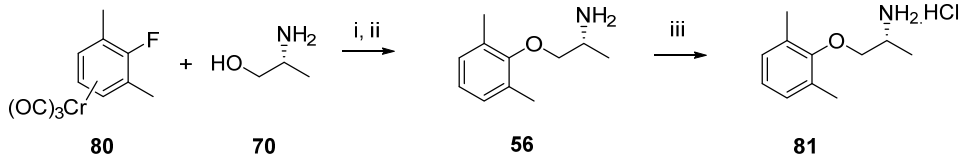
The racemic mexiletine **55** was transformed to diastereomeric mixture of the amide **76** and **77** with tetrahydropyranyl-protected (THPMA) **75** and subsequent hydrolytic cleavage of the tetrahydropyranyl (THP) protecting group led to **77** and **79**. Thus, the diastereomeric mixture **77** and **79** were separated by column chromatography with diastereomeric purities greater than 98 %. The amide functionality in **77** and **79** were subjected to hydrolysis using sulfuric acid in a 1, 4-dioxane solvent, giving rise to enantiomerically pure (*R*)-Mexiletine **56** and (*S*)-mexiletine **57**, respectively (**Scheme 16**).



Scheme 16: *Reagents and reaction conditions*: (i) N, N'-dicyclohexylcarbodiimide (DCC), EtOAc, 0 ^{o}C- RT, 2 h, 97 %; (ii) HCl, MeOH/H_2O, 85 %; (iii) H_2SO_4, H_2O/Dioxane, 80 ^{o}C, 72 h, 88 %.

Loughhead's approach[35]

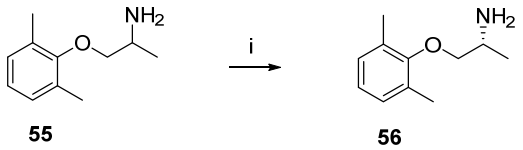
In this approach, Loughhead *et al.* have synthesized (*R*)-Mexiletine **56** *via* aromatic nucleophilic substitution of a $Cr(CO)_3$-complexed aromatic Fluoride **80** with (*S*)-(+)-2-amino-1-propanol **70** using the NaH as a base. The chromium complex was decomposed using the molecular iodine, afforded the (*R*)-Mexiletine **56** as shown in the **Scheme 17**. This on treatment with 1 M HCl in Et_2O gives crystalline (*R*)-Mexiletine hydrochloride salt **81**.



Scheme 17: *Reagents and reaction conditions*: (i) NaH, THF, RT; (ii) I_2; (iii) 1M HCl, Et_2O, 32 %.

Turgeon's approach[36]

In this approach, Turgeon *et al.* have reported the chemical resolution of racemic Mexiletine **55** using (+)-Di-*p*-toluoyl-D-tartaric acid, afforded the (*R*)-mexiletine **56** (**Scheme 18**).

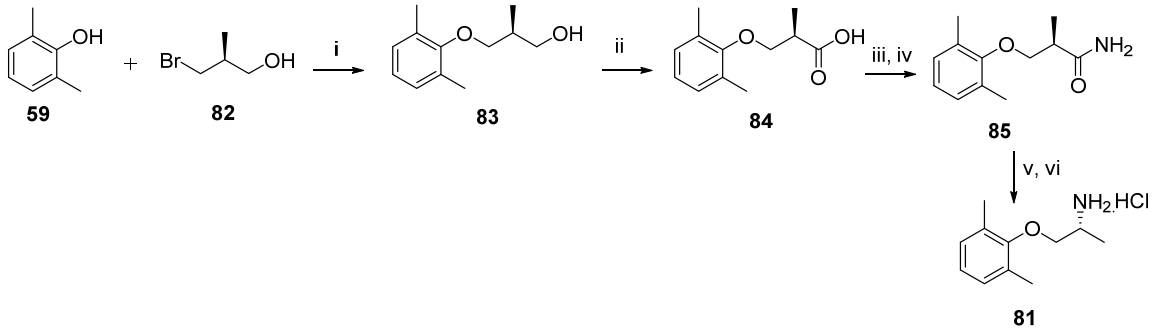


55 56

Scheme 18: *Reagents and reaction conditions*: (i) di-*p*-toluoyl-tartaric acid.

Lentini's approach[37]

In this report, Lentini *et al*. have reported the synthesis of (*R*)-Mexiletine **56** starting from (+)-(*S*)-3-bromo-2-mehtyl-1-propanol **82**. The 2, 6-dimethylphenol **59** was alkylated with (+)-(*S*)-3-bromo-2-mehtyl-1-propanol **82** to afforded alcohol **83** in a 40 % yield. The oxidation of alcohol **83** to the propionic acid **84** was carried out using catalytic amount of ruthenium dioxide in the presence of $NaIO_4$ as a co-oxidant. The carboxylic group of compound **84** reacted with thionyl chloride followed by conc.NH_4OH to furnish the amide **85**. The amide **85** was treated under classic Hofmann degradation condition using NaOBr and NaOH to furnish (*R*)-Mexiletine **56** which was treated with 40 % HCl gives the hydrochloric salt **81** (**Scheme 19**).



59 82 83 84 85 81

Scheme 19: *Reagents and reaction conditions*: (i) 10 % NaOH, RT, 3 h, 40 %; (ii) Cat.RuO_2, 10 % $NaIO_4$, EtOAc, 2 days, 75%; (iii) $SOCl_2$, reflux, 1 h; (iv) conc. NH_4OH, 0 °C- RT, 60 %; (v) NaOBr, NaOH, 80 °C, 3-4 min; (vi) HCl, 40 %.

1.2.3 Present Work

1.2.3.1 Objectives

Owing to the high medicinal value of (*R*)-mexiletine **56** as cardiovascular drugs in the life science, compared to its racemate and/or the (*S*)-mexiletine **57**, few synthetic routes for its synthesis developed by various researchers have been well documented in the literature. All the synthetic routes reported in the literature involve either chiral pool approach or the classical resolution of racemates or the enzymatic process. However, many of these reported synthetic routes suffer one/or other limitations and drawbacks such as low overall yields, use of expensive inaccessible enzymes and resolving agents, low optical purity, the need for separation of diastereomers and the use of expensive chiral catalysts. Therefore, development of inexpensive, economically viable synthesis of (*R*)-mexiletine **56** to achieve high overall yield with high optical purity is still challenging and active research area. Hence this section describes the catalytical route for asymmetric synthesis of (*R*)-mexiletine **56** *via* the α-aminoxylation of aldehyde catalyzed by L-proline, as key step and source of chirality to obtain chiral 1, 2 diol as a key intermediate for the synthesis of (*R*)-mexiletine **56**.

1.2.4 Results and discussion

The retro-synthetic analysis for the synthesis of (*R*)-mexiletine **56** is outlined in **Fig. 20**. The (*R*)-mexiletine **56** could be prepared from the corresponding chiral secondary alcohol **60**. The alcohol **60** was prepared by the reduction of chiral epoxide **62**, which was obtained from the (*S*)-1, 2 aryl diol **86** via Mitsunobu reaction**.** The (*S*)-1, 2 aryl diol **86** was easily obtained from the corresponding aldehyde **87** *via* L-proline catalyzed α-aminoxylation. The aldehydes **87** could be easily obtained from 2, 6-dimethyl phenol **59**

by simple functional group transformations.

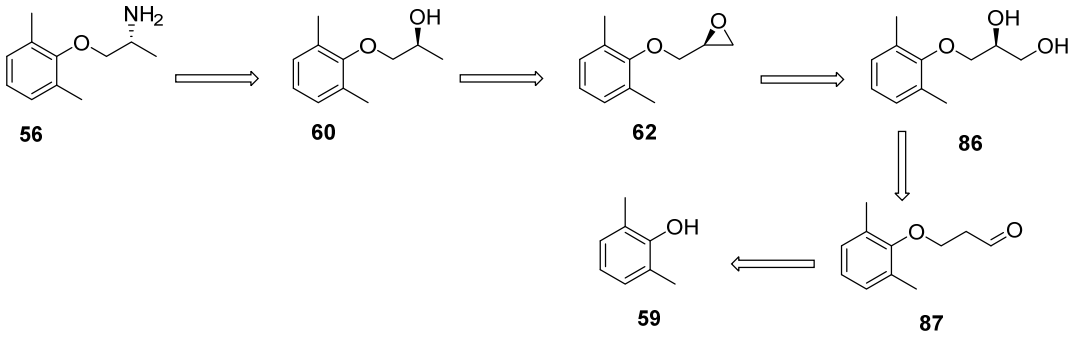
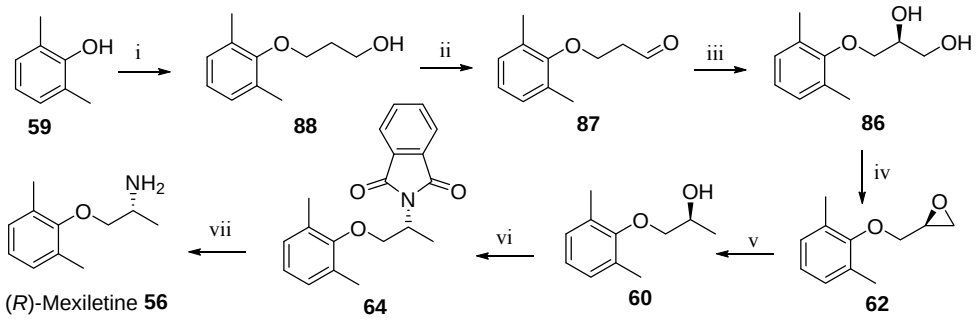


Fig. 20: Retrosynthetic analysis of (*R*)-Mexiletine **56**

In our synthetic approach, the synthesis of (*R*)-mexiletine **56** are based on the retro-synthesis analysis, which leads to chiral synthons (1, 2-diol **86)**, which can be easily achieved by asymmetric L-proline catalyzed α-aminoxylation of aldehyde **87**. The general synthetic route employed for the synthesis of (*R*)-mexiletine **56** is outlined in **Scheme 20**.

1.2.4.1 Enantioselective synthesis of Mexiletine



Scheme 20: *Reagents and reaction conditions*: (i) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 11 h, 96 %; (ii) IBX, RT, 6 h, 92 %; (iii) (a) PhNO, L-proline, MeCN, -20 ^oC 12 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 12 h, for two steps, 71 %; (iv) PPh_3, DIAD, THF, reflux, 6 h, 83 %; (v) LAH, THF, 0 ^oC-RT, 2 h, 96 %; (vi) Ph_3P, phthalimide, DIAD, THF, RT, 5 h, 84 %; (vii) $N_2H_4.H_2O$, EtOH, reflux, 3 h, 83 %.

The synthesis started with the easily and cheaply available 2, 6-dimethylphenol **59** (**Scheme 20**). The 2, 6-dimethylphenol **59** was condensed with 3-bromopropanol in an acetone solvent using potassium carbonate as a base gave the primary alcohol **88** in a 96 % yield. The presence of the aliphatic alcohol attached to the aromatic ring was confirmed by ^{1}H NMR spectrum, which shows the pentate at δ 2.04 and broad singlet at 2.19 due to the methylene protons of $–CH_2C\underline{H}_2CH_2-$ and $–CH_2CH_2O\underline{H}-$ respectively (**Fig. 21**).

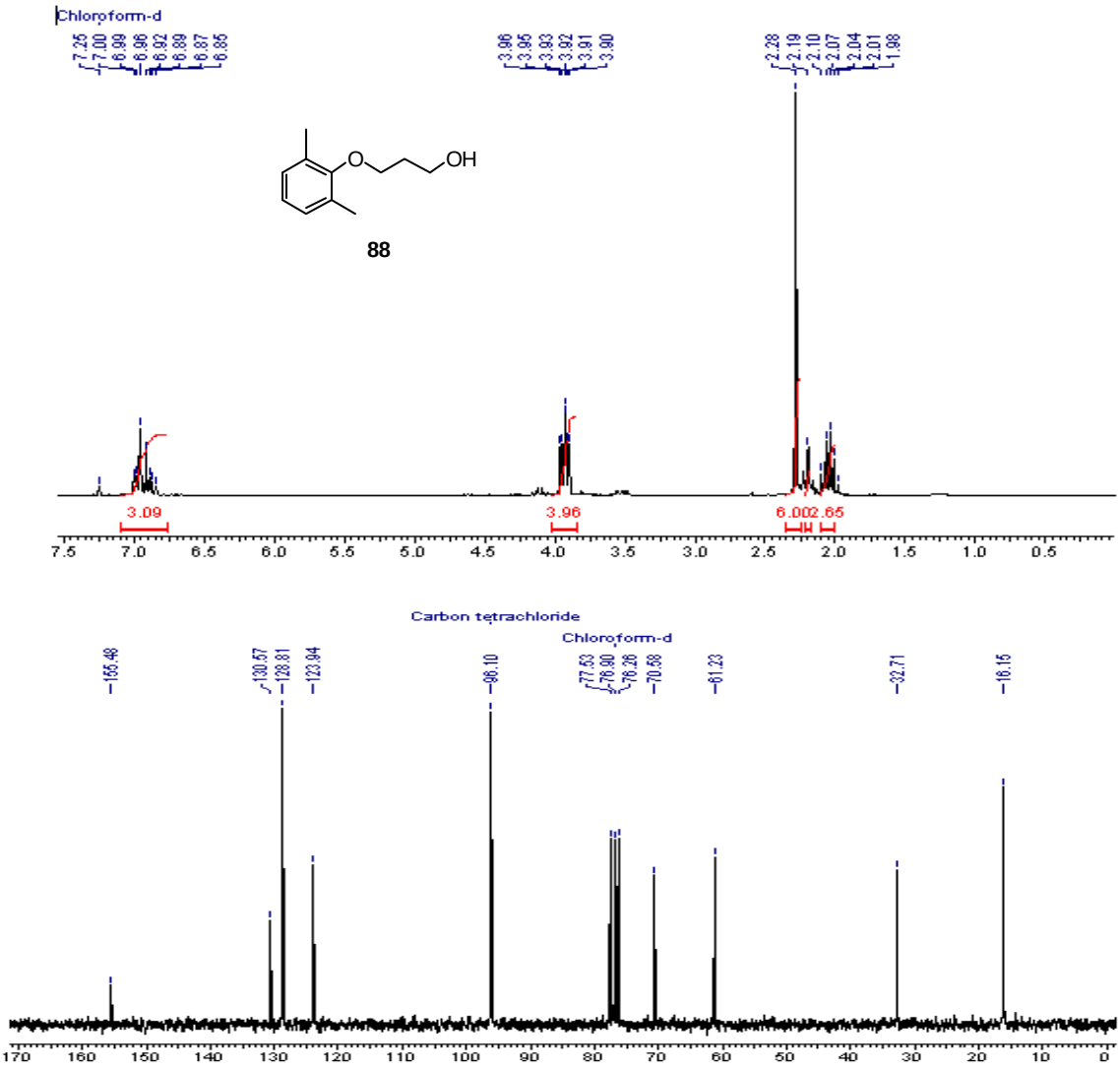


Fig. 21: ^{1}H and ^{13}C-NMR spectrum of 3-(2, 6-dimethylphenoxy)propan-1-ol **88**

The ^{13}C NMR spectrum showed signals at δ 32.71, 61.23 and 70.58 for side chain aliphatic carbons.

The primary alcohol of the compound **88** was oxidized in the presence of 2-iodoxybenzoic acid (IBX) as an oxidizing agent in a DMSO solvent at room tempreture for 6 h,[38] afforded aldehyde **87** in a 92 % yield.

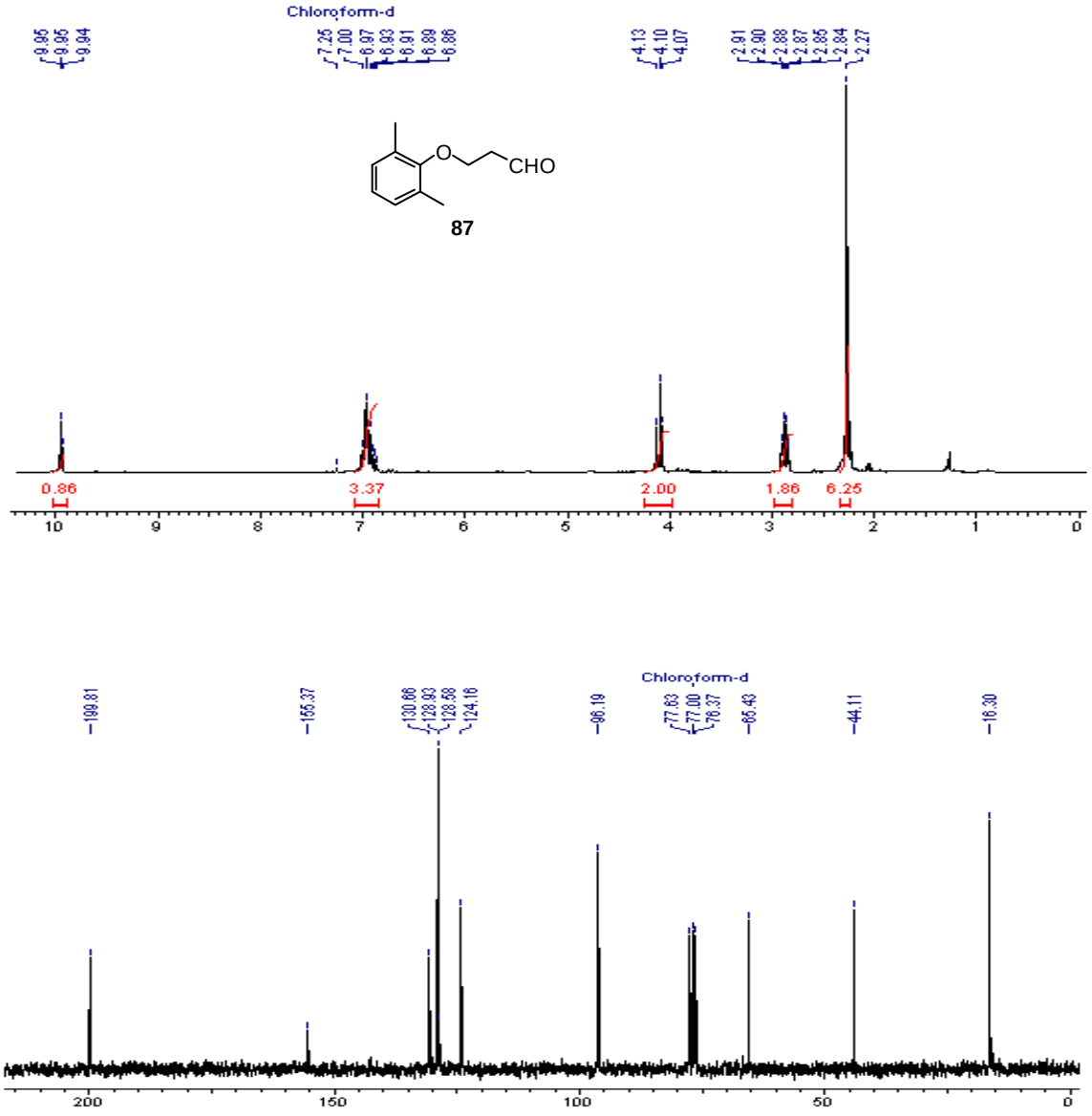


Fig. 22: ^{1}H and ^{13}C-NMR spectrum of 3-(2, 6-dimethylphenoxy)propanal **87**

^{1}H NMR spectrum of the aldehyde **87** shows the characteristic triplet at δ 9.95 due to the presence of –CHO group (**Fig. 22**). The ^{13}C NMR spectrum showed signals at δ 199.81 for carbonyl carbon of aldehyde.

The aldehyde **87** was subjected to L-proline catalyzed α-aminoxylation in an acetonitrile solvent at -20 ^{o}C for 12 h, followed by in situ reduction using sodium borohydride, which on deprotection using Pd/C under the H_2 atmosphere, gives the key intermediate chiral 1, 2-diol **86**.[39]

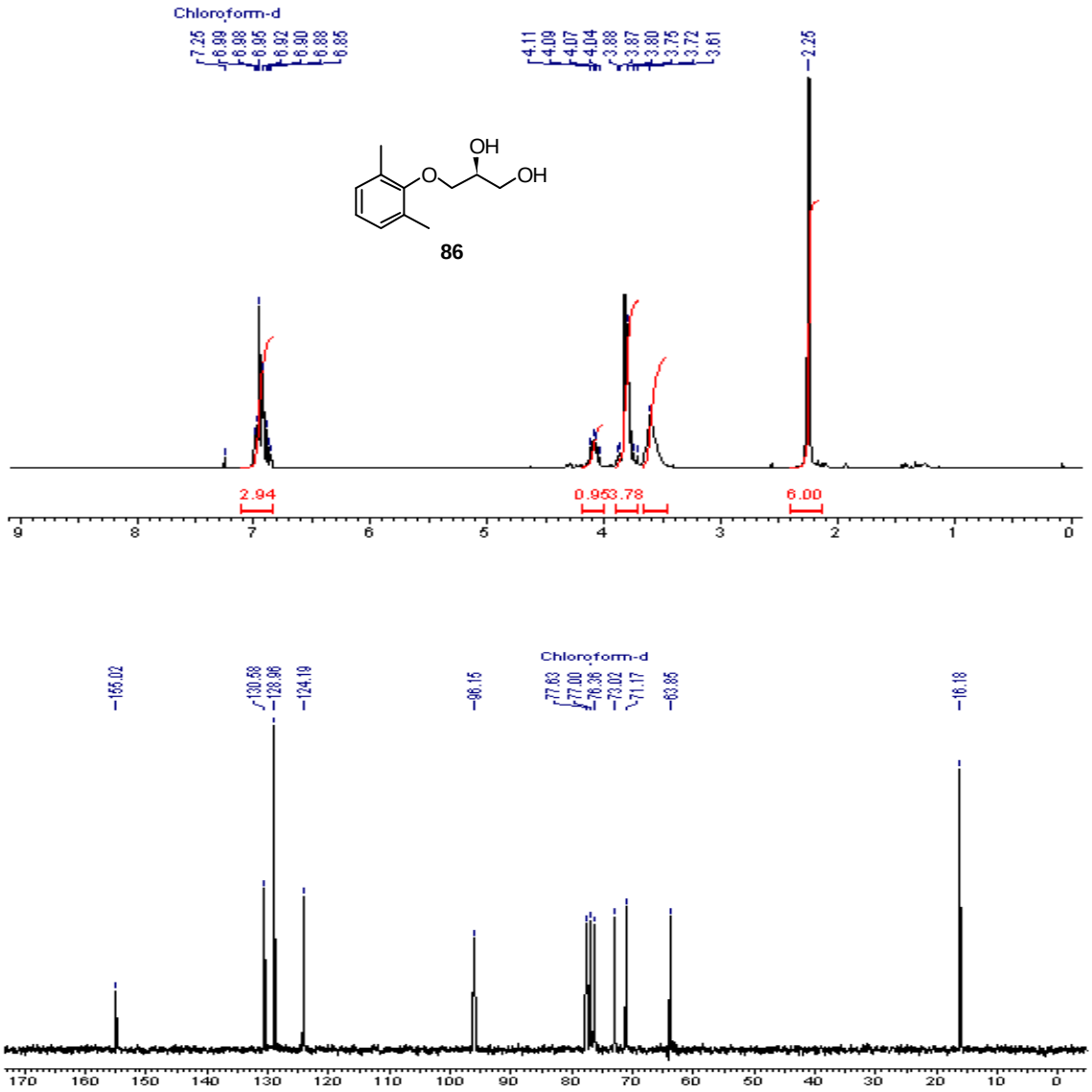
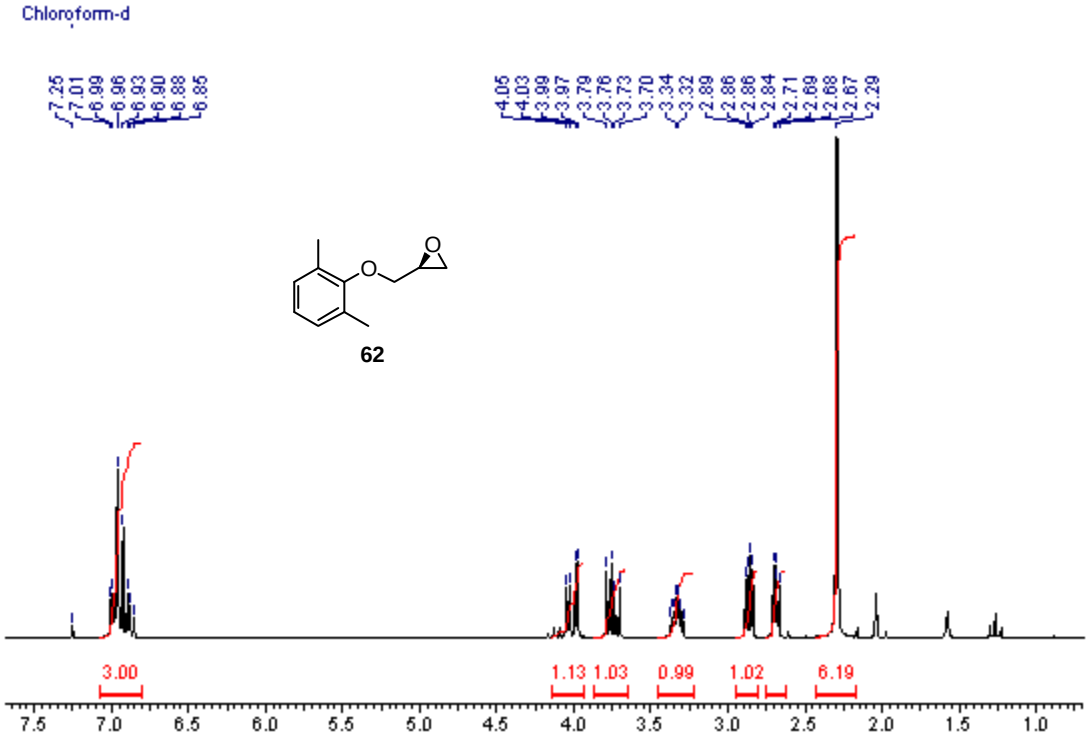


Fig. 23: ^{1}H and ^{13}C-NMR spectrum of (*S*)-3-(2, 6-dimethylphenoxy)propane-1,2-diol **86**

^{1}H NMR spectrum shows the multiplet at δ 4.04-4.11 due to the quaternary protons of -CH_2-C<u>H</u>-CH_2OH linkage and a broad singlet for two –OH group at δ 3.61. The ^{13}C NMR spectrum showed signals at δ 63.85, 71.17 and 73.02 indicating the presence of –<u>C</u>H_2-<u>C</u>H-<u>C</u>H_2OH linkage (**Fig. 23**).

The chiral 1, 2-diol **86** was subjected to the Mitsunobu reaction condition using triphenyl phosphine and diisopropyl azadicarboxilate in a THF solvent for 6 h, afforded the corresponding an epoxide **62** in a 83 % yield.[40]

The formation of an epoxide **62** was confirmed by appearance of multiplet at δ 3.32-3.34 for the quaternary proton in ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed signals at δ 50.46 and 44.44 indicating the presence of –CH_2-<u>C</u>H-<u>C</u>H_2O (epoxide) linkage (**Fig. 24**).



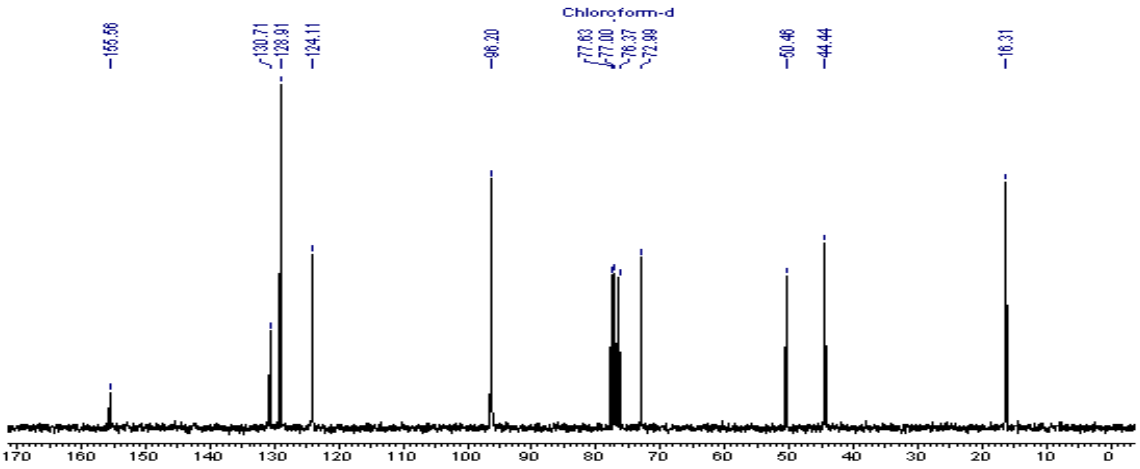
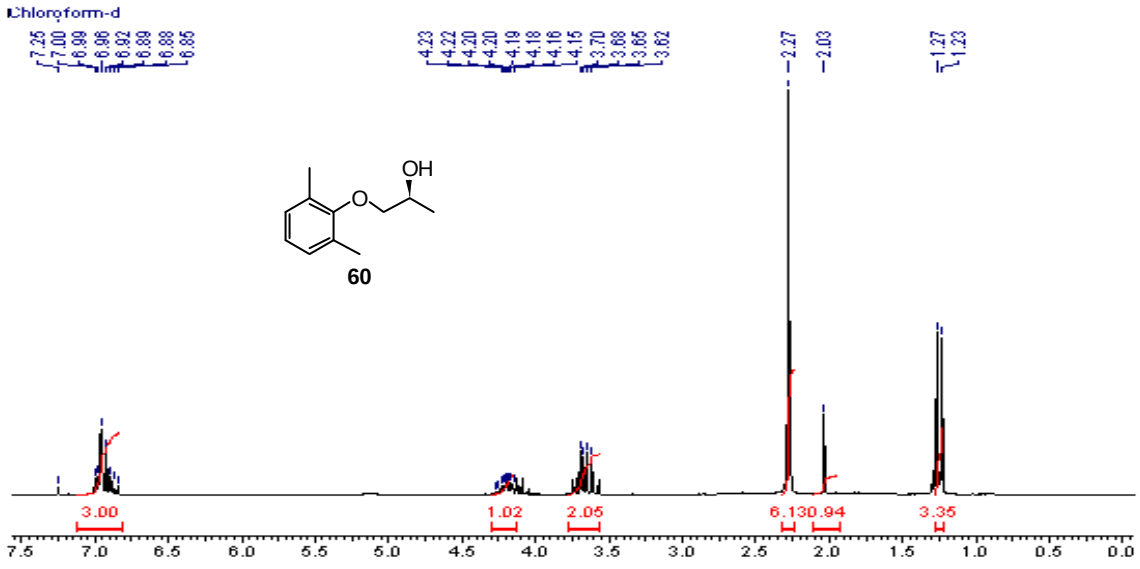


Fig. 24: ^{1}H and ^{13}C-NMR spectrum of (*S*)-2-((2, 6-dimethylphenoxy)methyl)oxirane **62**

The chiral epoxide **62** was reduced using lithium aluminium hydride in a THF solvent at 0 ^{o}C and then at room temperature for 1 h, afforded a sec-alcohol **60**.[29] ^{1}H NMR spectrum shows the disappearance of two doublets of doublet for the methylene proton and appearance of new doublet for three protons at δ 1.25 for three methyl protons and multiplet at δ 4.15-4.23 for the quaternary proton. ^{13}C NMR spectrum shows typical signal at δ 18.64 for terminal methyl group, confirmed the formation of compound **60** (**Fig. 25**).



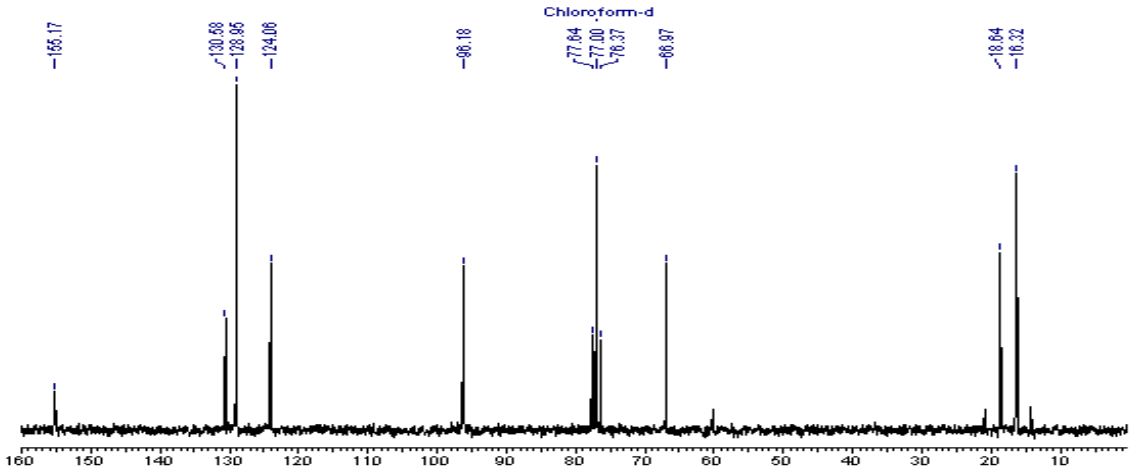
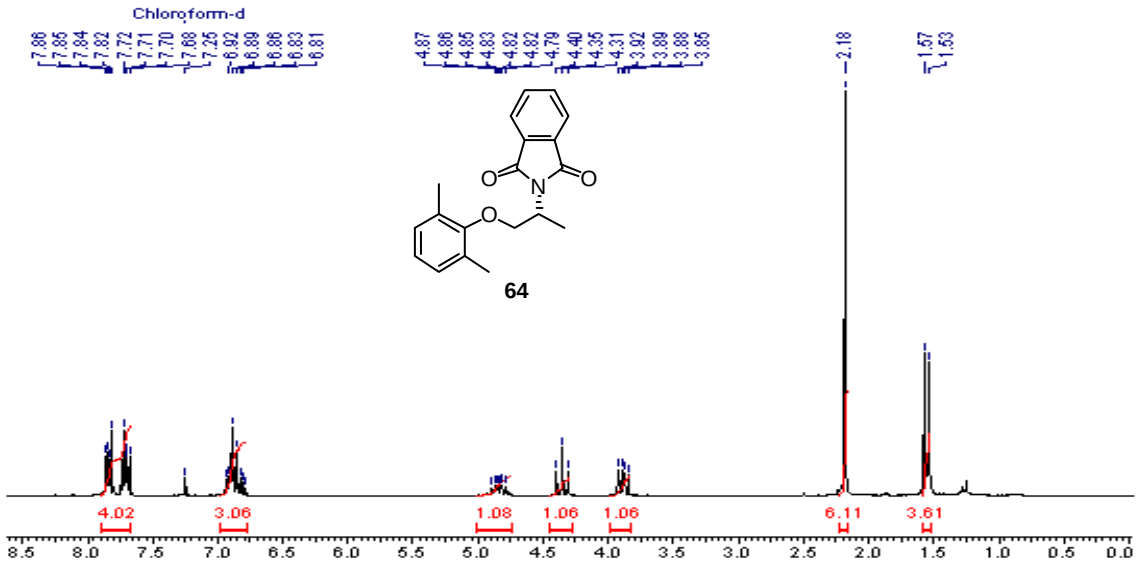


Fig. 25: ^{1}H and ^{13}C-NMR spectrum of (*S*)-1-(2, 6-dimethylphenoxy)propan-2-ol **60**

The alcohol **60** was subjected to the Mitsunobu reaction condition using phthalimide, triphenyl phosphine and diisopropyl azadicarboxilate (DIAD) in a THF solvent for 5 h at room temperature, gives phthalate protected compound **64**.[29]

^{1}H NMR spectrum shows the disappearance of alcohol proton and appearance of multiplet for four aromatic protons at δ 7.68-7.86.



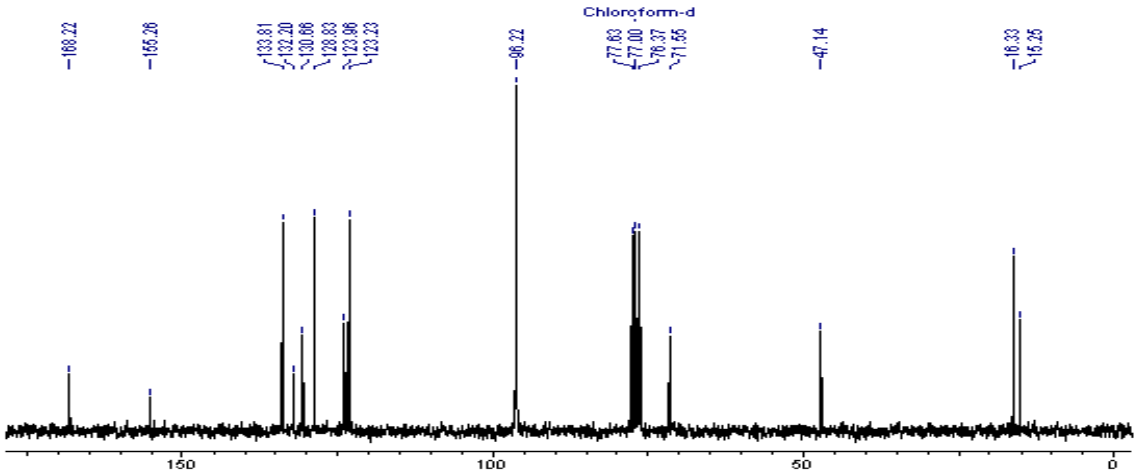
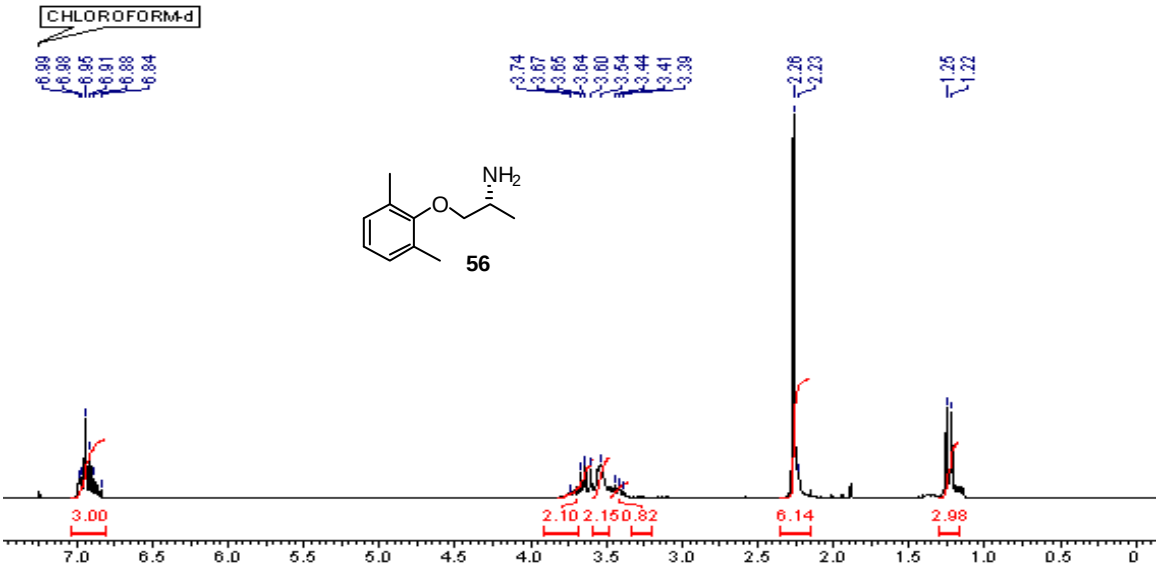


Fig. 26: ^{1}H and ^{13}C-NMR spectrum of (*R*)-2-(1-(2, 6-dimethylphenoxy)propan-2-yl)isoindoline-1,3-dione **64**

The ^{13}C NMR spectrum shows typical signal at δ 168.22 for two carbonyl group of phthalate adjacent to nitrogen, confirmed the formation of compound **64** (**Fig. 26**).

Finally, the Phthalate group of the compound **64** was deprotected using hydrazine hydrate in an ethanol solvent at reflux condition for 3 h to give (*R*)- Mexiletine **56** in a 83 % yield.[41]



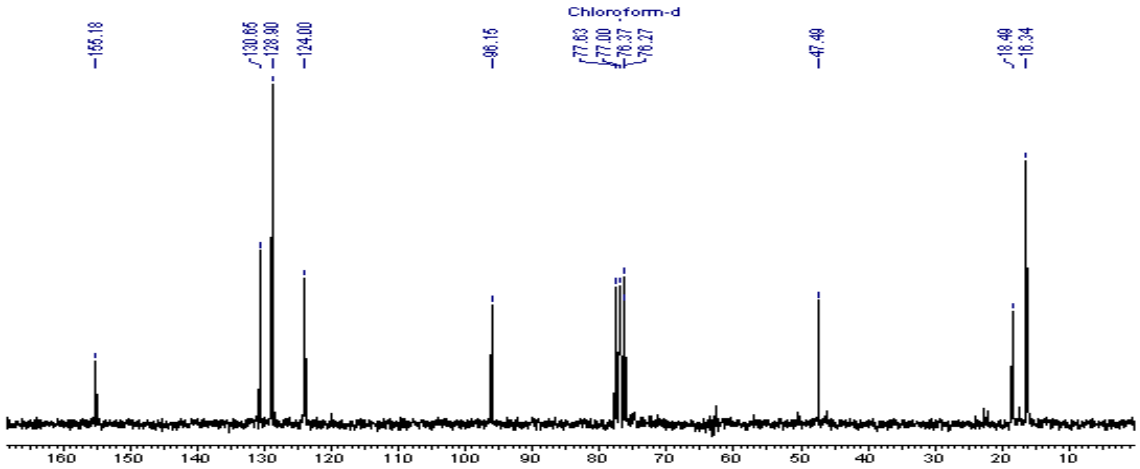


Fig. 27: ^{1}H and ^{13}C-NMR spectrum of (*R*)-1-(2, 6-dimethylphenoxy)propan-2-amine ((*R*)-Mexiletine) **56**

The ^{1}H NMR spectrum of (*R*)-mexiletine **56** showed a doublet at δ 1.25 for three protons of methyl (-CC$\underline{H}_3$) and a characteristic broad singlet at δ 3.54 for amine (N$\underline{H}_2$) protons, respectively, indicating the presence of primary amine (CH-NH_2) moiety and the aromatic ring was confirmed by the multiplet at δ 6.84-6.99 for three aromatic protons. ^{13}C NMR spectrum shows signal at δ 16.34 for the two methyl group attached to the aromatic ring and the signal at δ 47.49 for the quaternary carbon bearing the amine (**Fig. 27**).

1.2.5 Conclusion

In conclusion, we have developed highly efficient, versatile, ecofreindly, and inexpensive asymmetric approach for the enantioselective synthesis of the IB anti-arrhythmic drug, (*R*)-mexiletine **56** (overall yield 34.8 %) using asymmetric α-aminoxylation of aldehyde catalyzed by L-proline as the key step and source of chirality. The salient features of this synthetic approach are its simplicity, clean, environmental friendly procedures, efficient and mild reactions conditions. The protocol is very general and it may works well for the synthesis of other natural product and drug molecules in good to excellent yields.

1.2.6 Experimental section

1.2.6.1 Synthetic procedures and Spectral data

3-(2, 6-dimethylphenoxy)propan-1-ol 88

To the stirred solution of 2, 6-dimethylphenol **59** (5 g, 41 mmol) and K_2CO_3 (11.3 g, 82 mmol) in an acetone (50 mL), 3-bromopropan-1-ol (6.8 g, 49 mmol) in a 5 mL acetone, was added drop wise. After the complete addition, the reaction mixture was heated to reflux for 11 hrs with vigorous stirring. The completion of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and washed with an acetone (3*20 mL). The filtrate was concentrated under the reduced pressure to give crude product, which was purified by column chromatography using ethyl acetate – petroleum ether as an eluent by column chromatography over silica gel (60-120 mesh), afforded alcohol compound **88** as a colorless liquid (7.1 g, 96 %).

Yield 96 %, colorless liquid, bp 140-141^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.04 (pent, *J*=6 Hz, 2H), 2.19 (s, 1H), 2.28 (s, 6H), 3.92 (tt, *J*=6 Hz, 4H), 6.85-7.00 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 16.26, 32.71, 61.23, 70.58, 123.94, 128.81, 130.57, 155.48.

3-(2, 6-dimethylphenoxy)propanal 87

To a solution of alcohol **88** (2 g, 11.1 mmol) in a dimethyl sulfoxide (DMSO) (15 mL), 2-iodoxybenzoic acid (IBX) (4.66 g, 16.7 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The completion of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (20 mL) followed by separation of organic layer. The organic layer was separated and concentrated under the reduced pressure to obtained crud residue as product. The residue was purified using ethyl acetate – petroleum ether as an

eluent by column chromatography using silica gel (60-120 mesh), gives compound **87** as a colorless liquid (1.8 g, 92 %).

Yield 92 %, colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.27 (s, 6H), 2.88 (tt, *J*=6 Hz, 2H), 4.10 (t, *J*=6 Hz, 2H), 6.86-7.00 (m, 3H), 9.95 (t, *J*=1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 16.30, 44.11, 65.43, 124.16, 128.58, 128.93, 130.66, 155.37, 199.81.

(*S*)-3-(2, 6-dimethylphenoxy)propane-1, 2-diol 86

To a solution of aldehyde **87** (2 g, 11.2 mmol) and L-proline (258 mg, 2.2 mmol) in an acetonitrile (40 mL) solvent at -20 ^oC, nitrosobenzene (1.2 g, 11.2 mmol) was added portion wise and the reaction mixture stirred for 24 h. To this reaction mixture, MeOH (20 mL) and $NaBH_4$ (212 mg, 5.6 mmol) was added and stirring was continued for 30 min. After addition of water (10 mL), the resulting reaction mixture was extracted with ethyl acetate (3*50 mL) and the organic layer was dried over anhydrous sodium sulphate, which was concentrated under the reduced pressure, afforded crud aminoxy alcohol. To this crude aminoxy alcohol in a MeOH solvent, 10 % Pd/C (50 mg) was added under the hydrogen atmosphere and stirred at room tempreture for 10 h. The completion of reaction was checked by TLC, and the reaction mixture was filtered through a Celite pad and concentrated to give the crude product, which was purified using ethyl acetate – petroleum ether as eluent over the column chromatography using silica gel (60-120 mesh), gives diol **86** (1.58 g, 71%).

Yield 71 %, semi solid, $[\alpha]_D^{25}$= -2.8 (c 2, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.25 (s, 6H), 3.61 (s, 2H), 3.72-3.88 (m, 4H), 4.04-4.11 (m, 1H), 6.85-6.99 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 16.18, 63.85, 71.17, 73.02, 124.19, 128.96, 130.58, 155.02.

(*S*)-2-((2, 6-dimethylphenoxy)methyl)oxirane 62

To a stirred solution of diol **86** (1 g, 5.1 mmol), and PPh_3 (2 g, 7.65 mmol) in a anhydrous THF (20 mL), diethyl azodicarboxylate (1.3 g, 7.65 mmol) in 15 mL of THF solvent was added drop wise at room temperature. The reaction mixture was stirred at room temperature till the completion of reaction (3 h), which was monitored by TLC. After the completion of reaction, the reaction mixture was evaporated under the reduced pressure and the product was purified using ethyl acetate – petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), afforded an oxirane compound **62** (756 mg, 83 %) as a colorless liquid.

Yield 83 %, Colorless liquid, $[\alpha]_D^{25}$= +2.4 (c 2, $CHCl_3$) (lit.[29] $[\alpha]_D^{25}$= +2.5 (c 2, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.29 (s, 6H), 2.69 (dd, *J*=2 Hz, 1H), 2.86 (dd, *J*=4 Hz, 1H), 3.32-3.34 (m, 1H), 3.75 (dd, *J*=6 Hz, 1H), 3.99 (dd, *J*=3 Hz, 1H), 6.85-7.01 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 16.31, 44.44, 50.46, 72.99, 124.11, 128.91, 130.71, 155.56.

(*S*)-1-(2, 6-dimethylphenoxy)propan-2-ol 60

To a solution of an epoxide **62** (1 g, 5.6 mmol) in THF (10 mL), Lithium aluminum hydride (212 mg, 5.6 mmol) was added portion wise under the N_2 atmosphere at 0 ^oC and the reaction mixture was stirred for 2 h at room temperature. The completion of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was quenched with 2 mL of 15 % NaOH solution and the stirred for 20 min. The inorganic white precipitate obtained was filtered, washed with ethyl acetate (2*10 mL). The filtrate was concentrated under the reduced pressure, afforded crud residue as product. The residue was purified using ethyl acetate – petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), gives alcohol **60** (1 g, 96 %).

Yield 96 %, Colorless liquid; $[\alpha]_D^{25}$= -1.4 (c 5, $CHCl_3$) (lit.[29] $[\alpha]_D^{25}$= -1.3 (c 5, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.25 (d, *J*=6 Hz, 3H), 2.03 (s, 1H), 2.27 (s, 6H), 3.62-3.70 (m, 2H), 4.15-4.23 (m, 1H), 6.85-7.00 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 16.32, 18.64, 66.97, 124.06, 128.95, 130.58, 155.17.

I-2-(1-(2, 6-dimethylphenoxy)propan-2-yl)isoindoline-1, 3-dione 64

To the solution of alcohol **60** (0.8 g, 4.4 mmol), phthalimide (0.78 g, 5.3 mmol) and triphenylphosphine (1.26 g, 4.8 mmol) in a THF solvent (20 mL), diisopropyl azodicarboxylate (1 mL, 4.8 mmol) in a THF solvent (15 mL) was added drop wise under the nitrogen atmosphere at room tempreture. The reaction mixture was stirred at room temperature till the completion of reaction (5 h), which was monitored by TLC. After the completion of reaction, the reaction mixture was evaporated under the reduced pressure to obtain crude residue as product. The crud product was purified using ethyl acetate – petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), afforded phthalate protected compound **64** (1.15 g, 84 %).

Yield 84 %, Pale Yellow liquid, $[\alpha]_D^{25}$= -57 (c 2.5, $CHCl_3$) (lit.[42] $[\alpha]_D^{25}$= -55 (c 2.2, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.57 (d, *J*=7 Hz, 3H), 2.18 (s, 6H), 3.88 (dd, *J*=6 Hz, 1H), 4.35 (t, *J*=9 Hz, 1H), 4.79-4.87 (m, 1H), 6.81-6.92 (m, 3H), 7.68-7.72 (m, 2H), 7.82-7.86 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 15.25, 16.33, 47.14, 71.55, 123.23, 123.96, 128.83, 130.66, 132.20, 133.81, 155.26, 168.22.

(R)-Mexiletine 56

To a stirred solution of **64** (1 g, 3.2 mmol) in a ethanol solvent (15 mL), hydrazine hydrate (80 %) solution (1.5 mL, 24 mmol) was added. The resulting reaction mixture was refluxed till the completion of reaction (3 h), which was monitored by TLC. After

the completion of reaction, solid precipitated was observed. The solid precipitated was filtered and washed with ethanol (10 mL), the filtrate was evaporated under the reduced pressure. The resulting residue was dissolved in a diethyl ether (25 mL) and extracted with 2 N HCl (2*50 mL), and the aqueous phase was treated with 2 M NaOH until pH >12. The resulting aqueous phase was extracted with diethyl ether (3*20 mL), and the combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to obtain crude residue as product. The crud product was purified using ethyl acetate – petroleum ether as eluent by column chromatography using silica gel (60-120 mesh), afforded I-mexiletine **56** as colorless oil (480 mg, 83 %).

Yield 83 %, colorless oil, $[\alpha]_D^{25}$= -2.3 (c 5, $CHCl_3$) (lit.[29] $[\alpha]_D^{25}$= -2.4 (c 5, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.25 (d, *J*=6 Hz, 3H), 2.26 (s, 6H), 3.44-3.48 (m, 1H), 3.54 (s, 2H), 3.60-3.69 (m, 2H), 6.84-6.99 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 16.34, 18.49, 47.49, 76.27, 124.00, 128.90, 130.65, 155.18.

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Chapter II

Enantioselective synthesis of (S)-Enciprazine, (S)-Esmolol, (S)-Atenolol and (S)-Xibenolol via a-aminoxylation of aldehyde catalyzed by L-proline

Enantioselective synthesis of (S)-Enciprazine, (S)-Esmolol, (S)-Atenolol and (S)-Xibenolol via α-aminoxylation of aldehyde catalyzed by L-proline

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 revolutionalized 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.

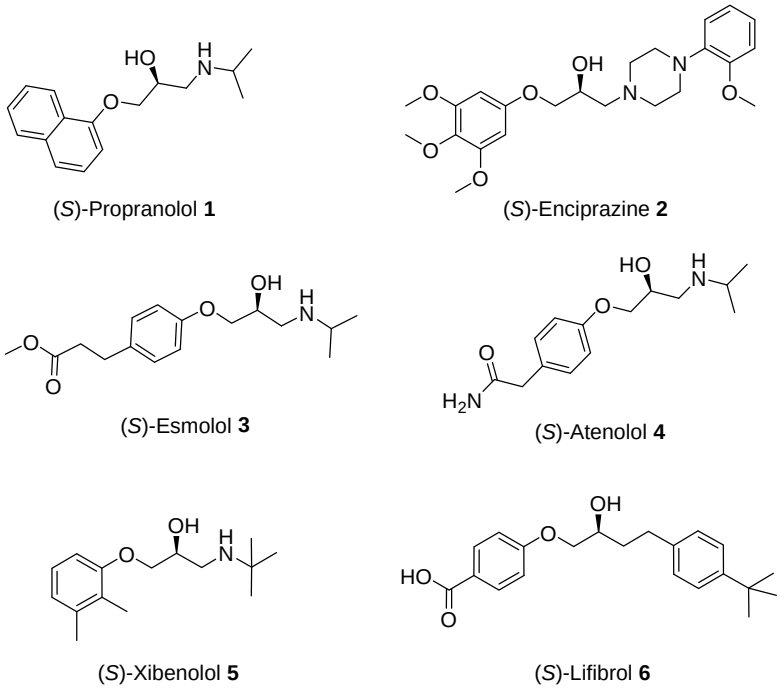


Fig. 1: Structures of the β-adrenergic blocking agents

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 relaxation[10] as well as tremor in skeletal muscle[11] 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 I-enantiomer,[14] 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 I-isomer**.**[15] To avoid undesirable side effects and/or toxicity to an organism caused by the I-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 four β-adrenergic blocking agents, (*S*)-Enciprazine **2**, (*S*)-Esmolol **3,** (*S*)-Atenolol **4** and (*S*)-Xibenolol **5** *via* α-aminoxylation of aldehyde catalyzed by L-proline as a key step and the source of chirality.

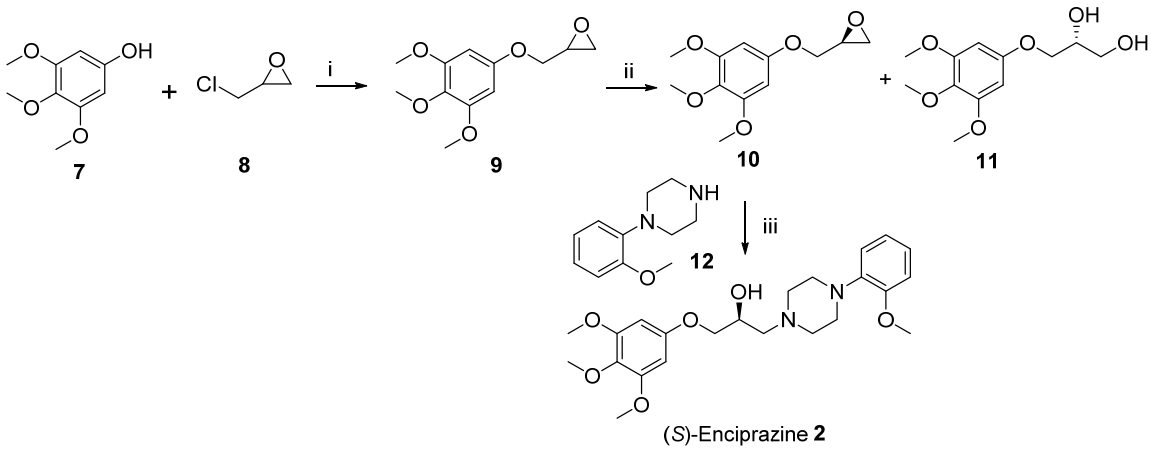
2.2 Review of Literature

Literature search revealed that there are few reports available for the synthesis of β-blocker namely, (*S*)-Enciprazine **2**, (*S*)-Esmolol **3**, (*S*)-Atenolol **4**, and (*S*)-Xibenolol **5**. However, most of the synthetic methods reported in the literature[16-22] for the asymmetric synthesis of these β-blockers involve either a chiral pool approach or classical resolution of racemates, which are described below.

Narsaiah's approach[16]

In this approach, Narsaiah *et al.* was synthesized (*S*)-Enciprazine **2**, using hydrolytic kinetic resolution protocol. In this approach they synthesized racemic epoxide **9** from 3,

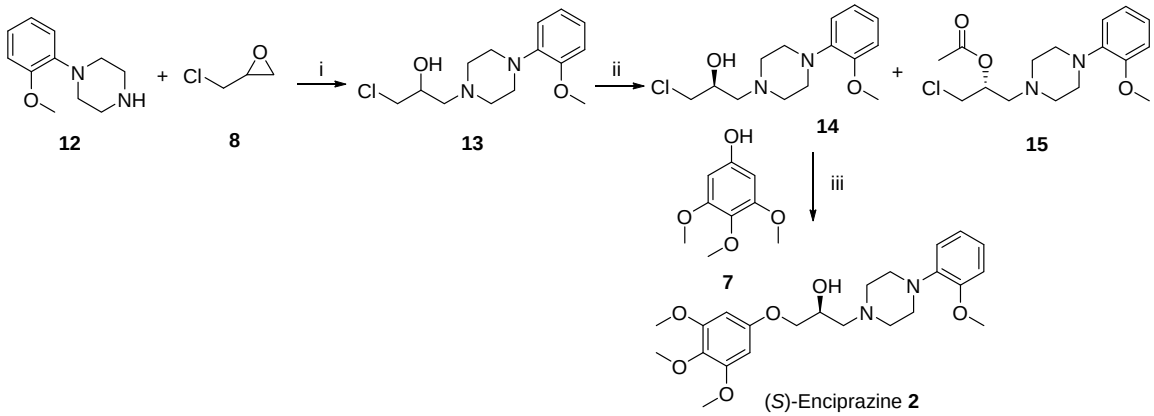
4, 5-trimethoxy phenol **7** and epichlorohydrine **8** in the presence of K_2CO_3 as a base. The epoxide **9** was resolved using Jacobsen hydrolytic kinetic resolution catalyzed by (*S, S*)-salen Co(III)Oac, afforded chiral epoxide **10** and chiral diol **11**. An epoxide **10** treated with 1-(2-Methoxyphenyl)piperazine **12** in an iso-propanol, afforded (*S*)-Enciprazine **2** (**Scheme 1**).



Scheme 1: *Reagents and reaction conditions*: (i) K_2CO_3, tetrabutylammonium bromide (TBAB), MeCN, Reflux, 6 h; (ii) (*R*,*R*)-salen–Co(III) catalyst, H_2O, 0 °C to RT, 10 h; (iii) *i*-PrOH, reflux, 15 h.

Banerjee's approach[17]

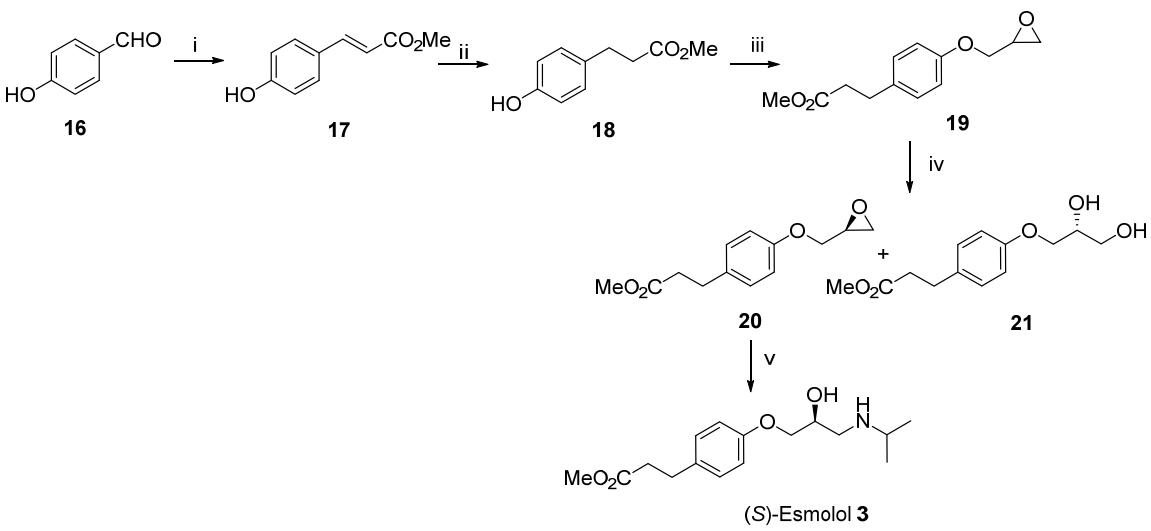
In this approach, Banerjee *et al.* have synthesized the intermediate compound **13** from the1-(2-Methoxyphenyl)piperazine **12** and epichlorohydrine **8** in the presence of LiBr in water at room temperature. The intermediate **13** was resolved in (*S*)-isomer **14** and acylated product **15** *via* enzymatic resolution using the lipase enzyme and vinyl acetate. The (*S*)-isomer **14** was converted to the (*S*)-Enciprazine **2** by reaction with 3, 4, 5-trimethoxy phenol **7** in the presence of K_2CO_3 in an acetonitrile solvent (**Scheme 2**).



Scheme 2: *Reagents and reaction conditions*: (i) LiBr, water, RT; (ii) Lipase, vinyl acetate, toluene, RT; (iii) K_2CO_3, MeCN, reflux.

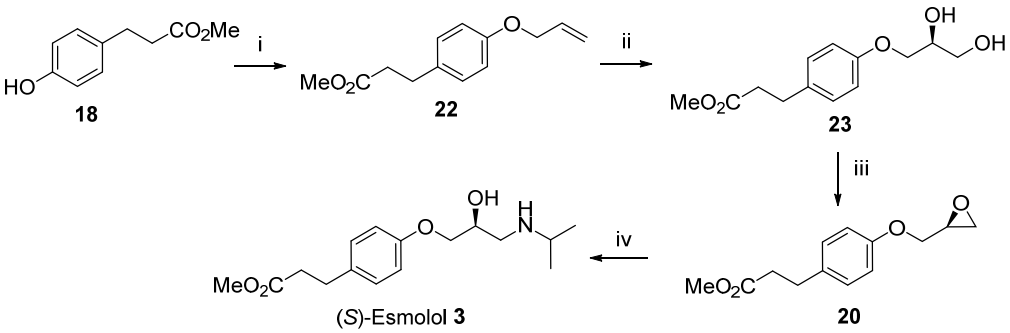
Narsaiah's approach[18]

In this approach, Narsaiah *et al.* have reported the synthesis of (*S*)-Esmolol **3** *via* Jacobsen hydrolytic kinetic resolution catalyzed by (*S, S*)-salen Co(III)Oac. First they synthesize the compound **18** from the 4-hydroxy benzaldehyde **16** *via* the witting reaction fallowed by hydrogenation using Pd/C in the presence of H_2 atmosphere at room temperature for 12 h. The compound **18** was treated with epichlorohydrine **8** in the presence of K_2CO_3, gives the racemic epoxide **19**, which upon the Jacobsen hydrolytic kinetic resolution gives the chiral epoxide **20** and chiral diol **21**. The chiral epoxide **20** was converted to the target molecule **3** by treating with isopropyl amine as shown in **Scheme 3**.



Scheme 3: *Reagents and reaction conditions*: (i) Wittig ylide, room temperature, 6.0 h; (ii) 10 % Pd/C, ethylacetate, hydrogen atmosphere, room temperature, 12 h; (iii) epichlorohydrine **8**, K_2CO_3, CH_3CN, reflux, 6 h; (iv) *R,R*-salen Co(III) catalyst, H_2O, 0 ^oC to room temperature, 8 h, 46 % of *S*-epoxide and 48 % *R*-diol; (v) isopropyl amine, H_2O, reflux, 5 h.

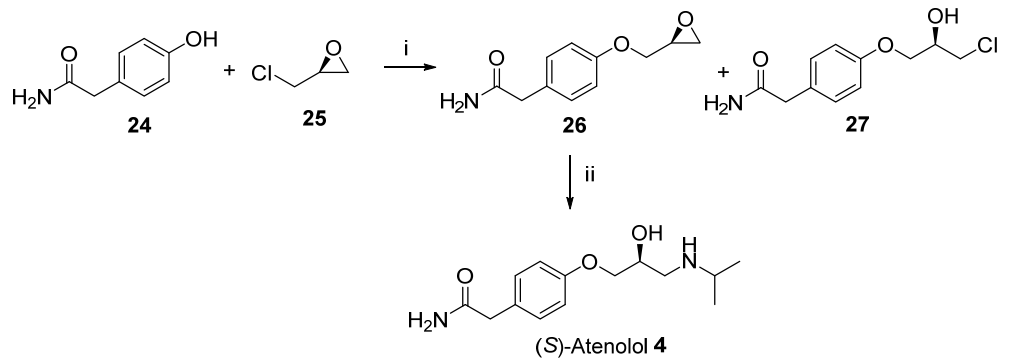
Narsaiah et al. have also describe the synthesis of (*S*)-Esmolol **3** *via* the Sharpless asymmetric dihydroxylation protocol. The compound **18** was treated with allyl bromide to furnish the allylic compound **22**. The allylic compound **22** was subjected to the Sharpless asymmetric dihydroxylation using Hydroquinine 1, 4-phthalazinediyl diether $(DHQ)_2$-PHAL ligand and AD-mix-α in the tert-butanol solvent to get the chiral diol **23**. The chiral diol **23** was subjected to the mitsunobu reaction conditions using triphenyl phosphine (PPh_3) and diethyl azodicarboxylate (DEAD) in the benzene solvent for 18 h gives chiral epoxide **20**. The chiral epoxide **20** was converted to the target molecule (*S*)-Esmolol **3** using isopropyl amine as shown in **Scheme 4**.



Scheme 4: *Reagents and reaction conditions*: (i) Allyl bromide, K_2CO_3, CH_3CN, reflux, 7 h; (ii) $(DHQ)_2$-PHAL, AD-mix-α, t-BuOH, H_2O, 0 ^oC, 3 h; (iii) TPP-DEAD, benzene, reflux, 18 h; (iv) isopropyl amine, H_2O, reflux, 5 h.

Kitaori's approach[19]

In this approach, Kitaori et al. have synthesized (*S*)-Atenolol **4** via chiral pool protocol. They synthesize chiral epoxide **26** from compound **24** and (*S*)-epichlorohydrine **25**, gives the mixture of chiral epoxide **26** and compound **27**. The chiral epoxide **26** treated with excess of isopropyl amine, afforded the (*S*)-Atenolol **4** (**Scheme 5**).

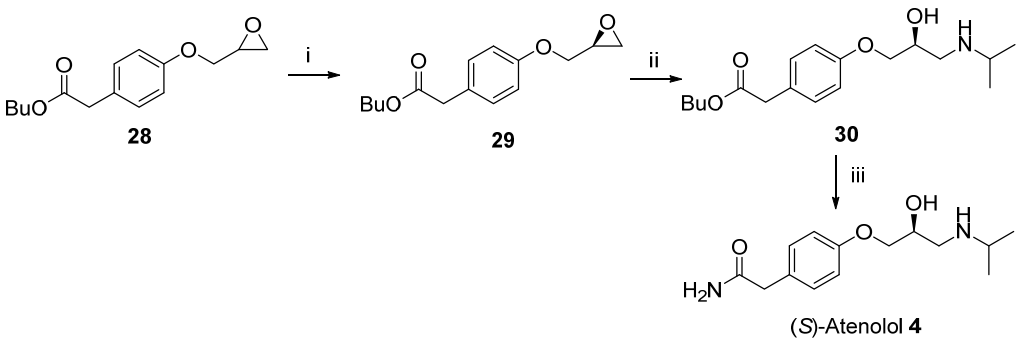


Scheme 5: *Reagents and reaction conditions*: (i) NaOH, benzyltrimethyl ammonium chloride (BTA), H_2O; (ii) isopropyl amine.

Kim's approach[20]

In this approach, Kim *et al.* have reported the synthesis of different cobalt salen type complexes and its application for the resolution of terminal epoxide. The synthesis started with the resolution of racemic an epoxide **28** using the cobalt-salen type catalyst; give the

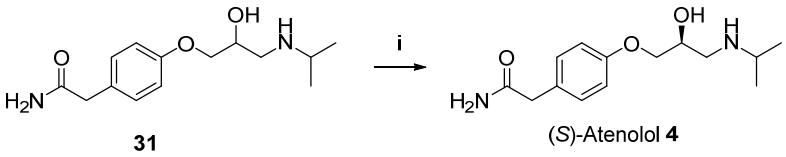
chiral epoxide **29** in 40 % yields with 98 % ee. The chiral epoxide **29** was treated with excess amount of isopropyl amine and catalytic amount of water to afford the amine compound **30**. Finally the ester was converted to amide using ammonium hydroxide in a methanol to get the target molecule (*S*)-Atenolol **4** as shown in **Scheme 6**.



Scheme 6: *Reagents and reaction conditions*: (i) Co-salen catalyst, H_2O, RT, 8 h; (ii) isopropyl amine, H_2O, reflux, 5 h; (iii) NH_4OH, MeOH, RT, 12 h.

Salunkhe's approach[21]

In this approach, Salunkhe *et al.* have reported the synthesis (*S*)-Atenolol **4** and (*S*)-Propranolol **1** *via* chemoenzymetic resolution. In this report, racemic Atenolol **31** was resolved using lipase and vinyl acetate to the (*S*)-Atenolol **4** and corresponding ester as shown in **Scheme 7**.

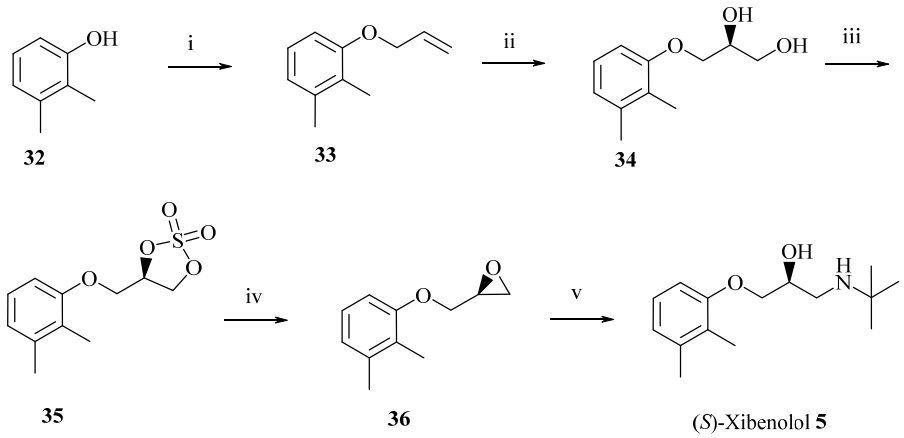


Scheme 7: *Reagents and reaction conditions*: (i) lipase PS-D, vinyl acetate, THF, RT, 10 h.

Sudalai's approach[22]

In this approach, Sudalai and co-workers have synthesized various β-blockers including (*S*)-Xibenolol **5** via Sharpless asymmetric dihydroxylation protocol. The 2, 3 dimethyl phenol **32** was treated with allyl bromide in the presence of K_2CO_3 in an acetone solvent

for 12 h, afforded the allylic compound **33**. The allyl ethers **33** was subjected to the Sharpless asymmetric dihydroxylation by using $(DHQD)_2$-PHAL catalyst in a tert butanol and water mixture for 12 h, afforded the chiral diol **34**. The resultant diol **34** then converted to chiral epoxides **36** *via* cyclic sulfate **35**. An epoxide **36** treated with tert-butyl amine and catalytic amount of water for 2 h, afforded (*S*)-Xibenolol **5** (**Scheme 8**).



Scheme 8: *Reagents and reaction conditions*: (i) Allyl bromide, K_2CO_3, acetone, reflux, 12 h; (ii) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C, 12 h; (iii) (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 40 min.; (b) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0 °C, 30 min.; (iv) (a) LiBr, THF, 25 °C, 2-3 h; (b) 20 % H_2SO_4, Et_2O, 25 °C, 10 h; (c) K_2CO_3, MeOH, 0 °C, 2 h; (v) tert-butyl amine, H_2O (cat.), reflux, 2 h.

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*)-Enciprazine **2**, (*S*)-Esmolol **3**, (*S*)-Atenolol **4** and (*S*)-Xibenolol **5** 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 and inaccessible

reagents and/or wastage of half the material and/or the undesired isomer. 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 and toxic chiral catalysts.

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 and/or achiral 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 from readily available achiral starting materials with good optical purity and high yield via α-aminoxylation of aldehyde catalyzed by L-proline as key step and source of chirality.

2.4 Results and discussion

The retro-synthetic analyses for the synthesis of these homochiral β-adrenergic blocking agents are presented in **Fig. 2**. All these compounds exhibit structural similarities. The compounds (*S*)-Enciprazine **2**, (*S*)-Esmolol **3**, (*S*)-Atenolol **4** and (*S*)-Xibenolol **5** could be prepared from the corresponding chiral 1, 2-diol compounds **38**, **23**, **39** and **34** via the corresponding an epoxide **10, 20, 37** and **36,** respectively. The chiral 1, 2-diol **38**, **23**, **39** and **34**, respectively, could be achieved from the corresponding aldehydes **40**, **41**, **42** and **43** via α-aminoxylation of aldehyde catalyzed by L-proline as a key step and source of chirality. These aldehydes **40**, **41**, **42** and **43** could be readily obtained from corresponding primary alcohols **44**, **45**, **46** and **47**, respectively, by oxidation using 2-

iodoxybenzoic acid (IBX). The corresponding primary alcohols could be obtained from the simple phenols **7**, **18**, **48** and **32** via simple functional group transformations.

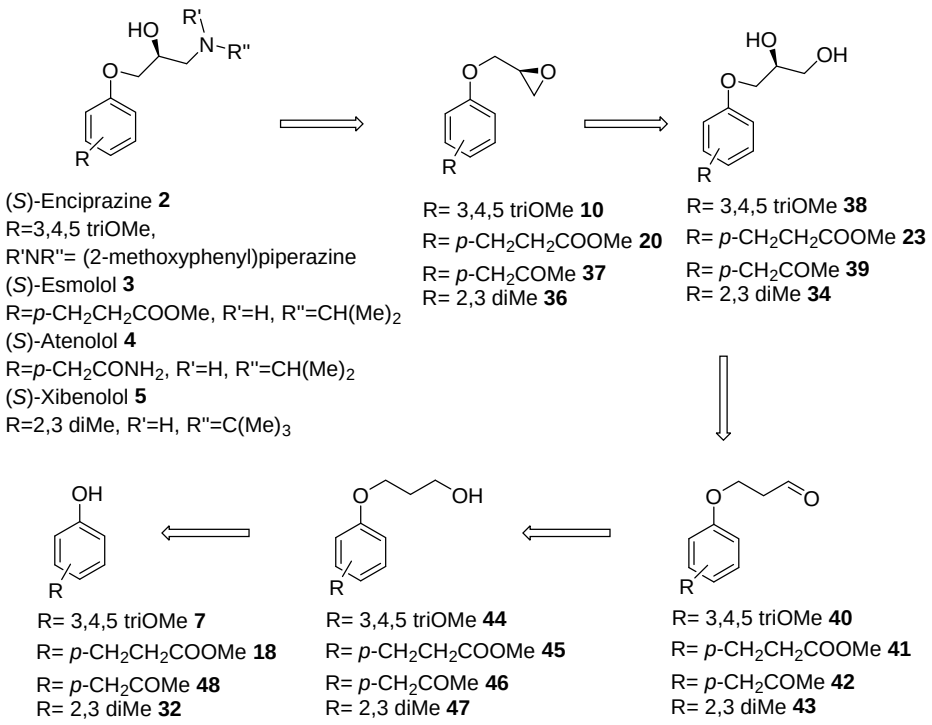
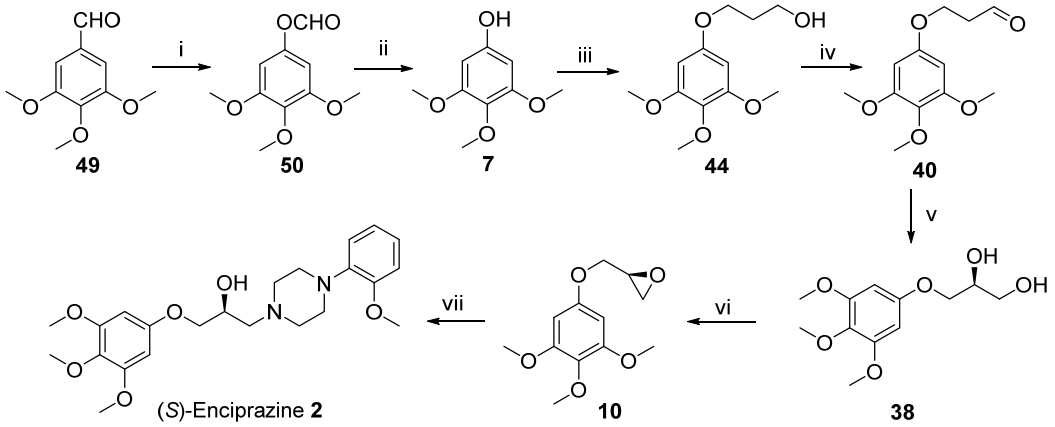


Fig. 2: Retrosynthetic analysis of (*S*)-Enciprazine **2**, (*S*)-Esmolol **3**, (*S*)-Atenolol **4** and (*S*)-Xibenolol **5**

As per our retro-synthetic analysis, synthesis of (*S*)-Enciprazine **2**, (*S*)-Esmolol **3**, (*S*)-Atenolol **4** and (*S*)-Xibenolol **5**, started from corresponding phenols **7**, **18**, **48**, and **32**, respectively, as starting materials.

2.4.1 Enantioselective synthesis of Enciprazine

The synthetic scheme employed for (*S*)-Enciprazine **2** is outlined in the **Scheme 9**.



Scheme 9: *Reagents and reaction conditions*: (i) m-CPBA, CH_2Cl_2, RT, 8 h; (ii) KOH, MeOH, RT, 30 min, 91 %; over two step (iii) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 14 h, 94 %; (iv) IBX, DMSO, RT, 3 h, 90 %; (v) (a) PhNO, L-proline, MeCN, -20 ^oC 20 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 14 h, over two step, 73 %; (vi) PPh_3, DEAD, 1, 4 Dioxan, reflux, 4 h, 80 %; (vii) 1-(2-methoxyphenyl)piperazine **12**, i-PrOH, reflux, 18 h, 95 %.

As per cofreindly ic analysis (**Fig. 2)**, we initiated a synthesis of 3, 4, 5-trimethoxy phenol **7** from the commercially available 3, 4, 5-trimethoxybenzaldehyde **49** as shown in the **scheme 9**. The 3, 4, 5-trimethoxybenzaldehyde **49** was converted into the corresponding 3, 4, 5-trimethoxy phenyl formate **50** using meta-chloroperbenzoic acid (m-CPBA) in a dichloromethane solvent at room temperature for 8 h, which was treated with KOH in a methanol solvent gives the 3, 4, 5-trimethoxy phenol[16] **7** in 91 % yield over the two step. The ^1H NMR spectrum showed singlet of nine protons at δ 3.79 for the three $–OCH_3$ attached to the aromatic ring. The aromatic ring was confirmed by the singlet at δ 6.09 for two aromatic protons, which confirmed the formation of the 3, 4, 5-trimethoxy phenol **7**. The ^{13}C NMR spectrum showed signals at δ 55.97 for two $–OCH_3$, attached to the aromatic ring at meta position and signal at δ 61.10 for one $–OCH_3$ attached to the aromatic ring at para position. The signal at δ 92.90 represents the aromatic ring carbon (**Fig. 3**).

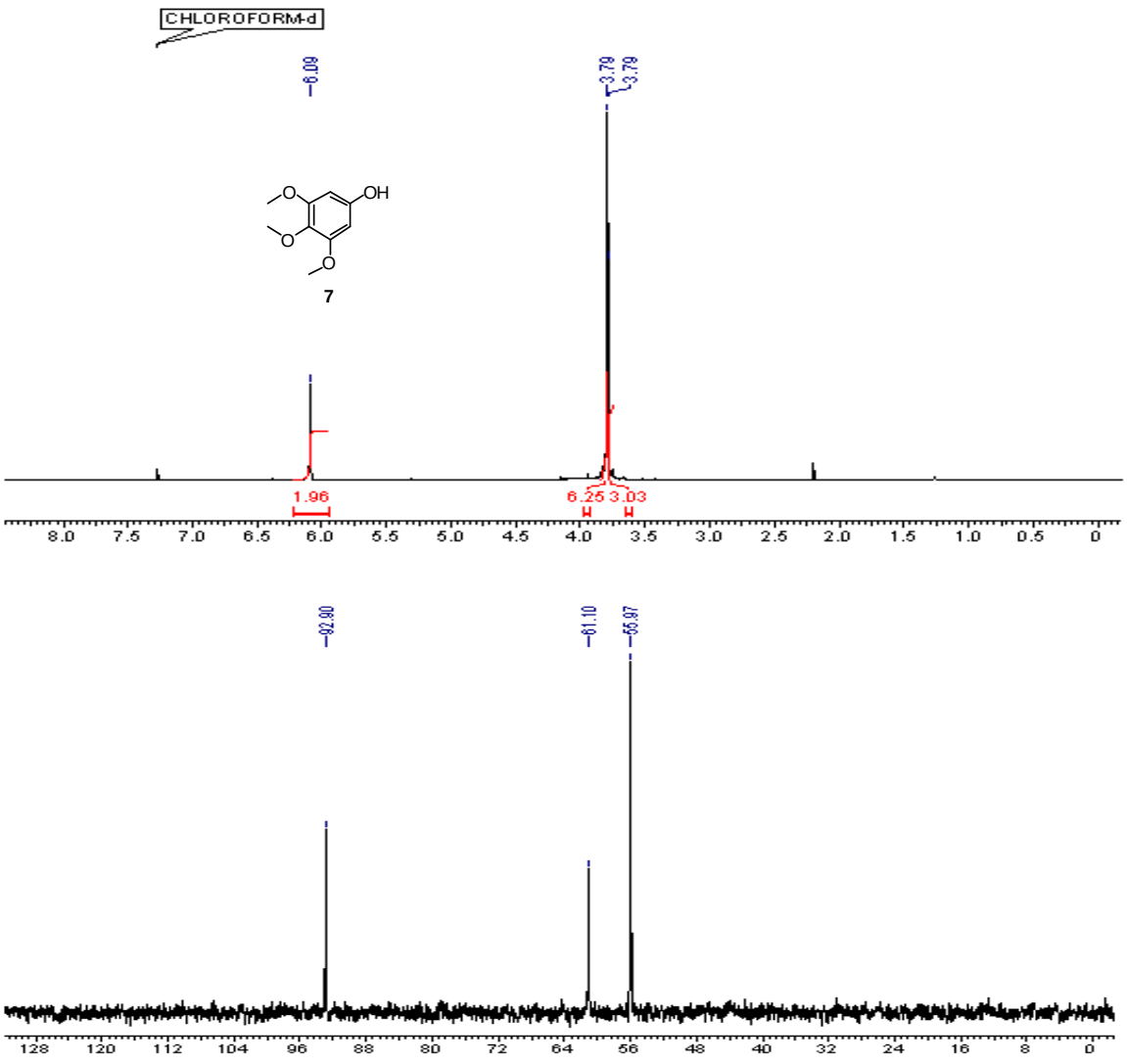


Fig. 3: ^{1}H and ^{13}C NMR spectrum of 3, 4, 5- trimethoxyphenol **7**

The O-alkylation of 3, 4, 5- trimethoxy phenol **7** with 3-bromo-1-propanol using K_2CO_3 as a base in an acetone solvent at reflux condition, affording the primary alcohol **44** in a 94 % yield. The ^{1}H NMR spectrum of alcohol **44** showed appearance of broad singlet for aliphatic alcohol at δ 1.93, multiplet for $–CH_2-\underline{CH_2}-CH_2-$ at δ 1.99-2.05 and appearance of triplet for $–O\underline{CH_2}-$ at δ 4.08 and another two sharp singlet's at δ 3.77 and 3.88 for the three $–OCH_3$ attached to the aromatic ring, confirmed the formation of the primary alcohol **44**.

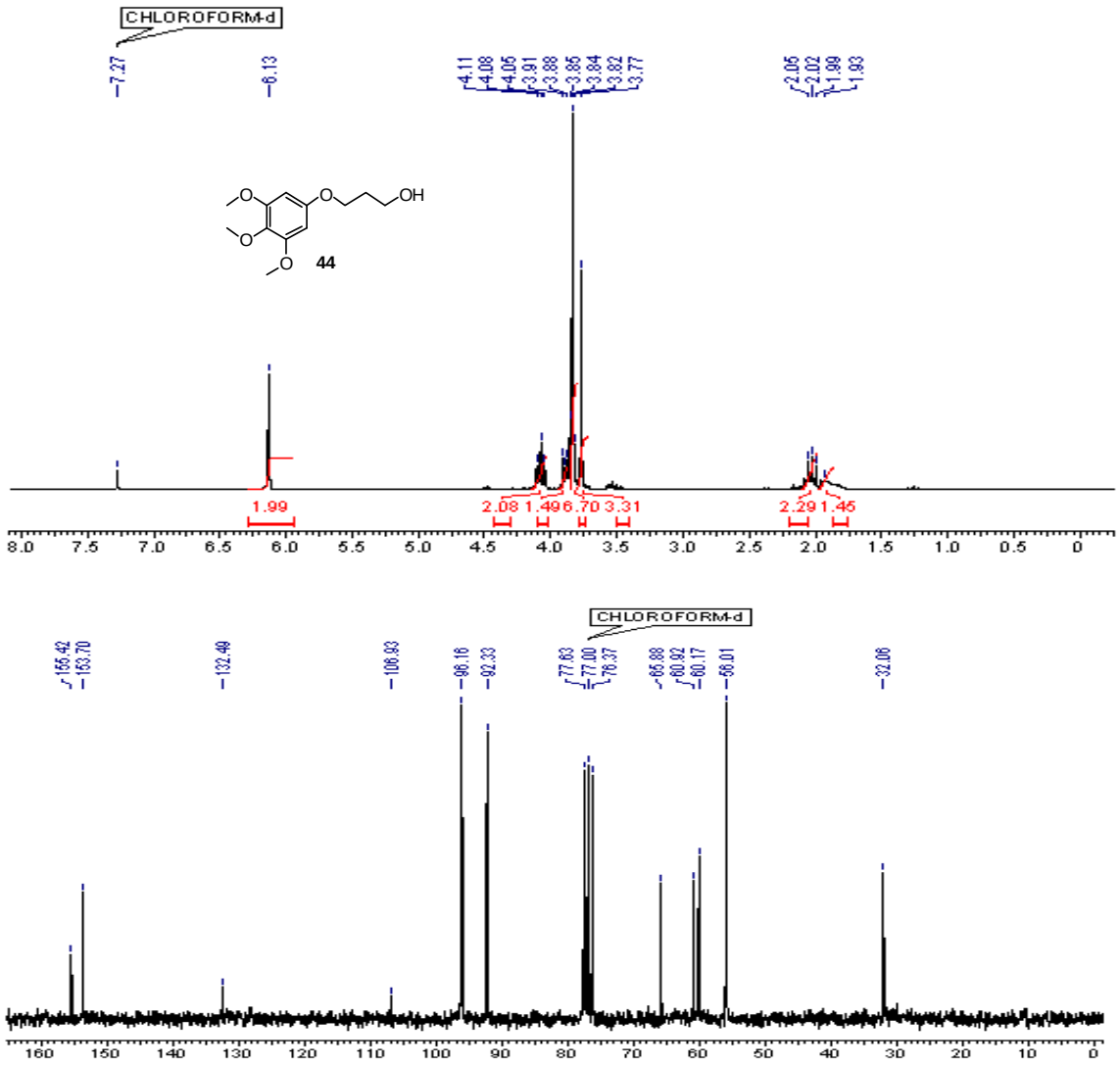


Fig. 4: ^{1}H and ^{13}C NMR spectrum of 3-(3, 4, 5-trimethoxy phenoxy) propan-1-ol **44**

The ^{13}C NMR spectrum showed only three new aliphatic signals at δ 32.06 for –OCH_2-$\underline{CH_2}$-CH_2-OH carbon, signal at δ 60.17 for –OCH_2-CH_2-$\underline{CH_2}$-OH carbons adjacent to hydroxy group and signal at δ 65.88 for –$O\underline{CH_2}$-CH_2-CH_2-OH carbon. These three signals confirm the aliphatic alcohol attached to the oxygen of phenol (**Fig. 4**).

The primary alcohol **44** was then subjected to the oxidation using 2-iodoxy benzoic acid (IBX) in a DMSO solvent at room tempreture for 3 h, afforded the aldehyde[23] **40** in a 90 % yield.

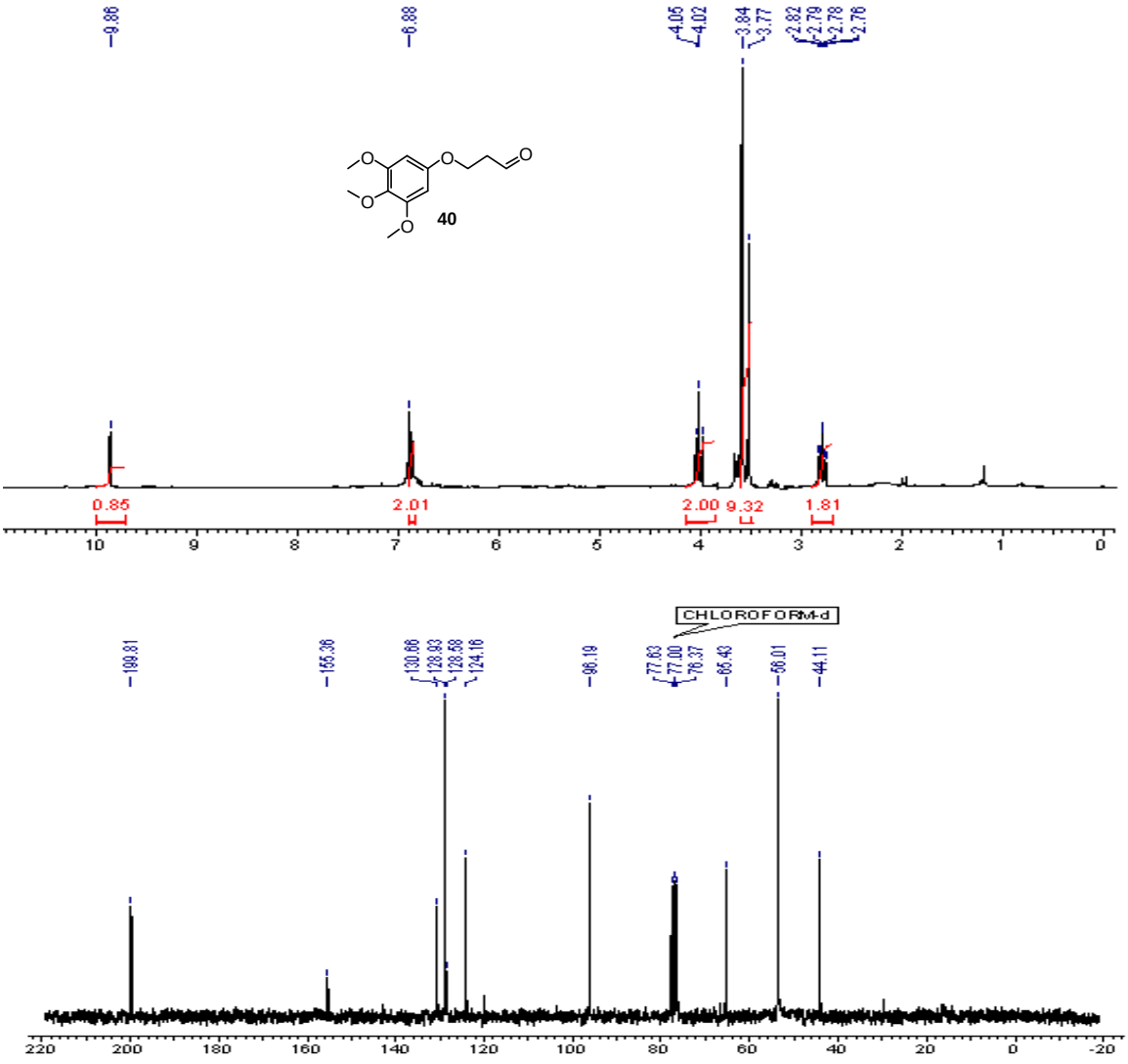


Fig. 5: ^{1}H and ^{13}C NMR spectrum of 3-(3, 4, 5-trimethoxy phenoxy) propanal **40**

The ^{1}H NMR spectrum of aldehyde **40** showed disappearance of aliphatic multiplet for –CH_2-$\underline{CH_2}$-CH_2- at δ 1.99-2.05 and appearance of sharp singlet for the aldehyde proton at δ 9.86 confirmed the formation of the aldehyde **40**. The ^{13}C NMR spectrum showed signal at δ 199.81 for carbonyl carbon of an aldehyde confirms the aldehyde functionality (**Fig. 5**).

Aldehyde **40** was then subjected to L-proline (20 mol %) catalyzed asymmetric α-aminoxylation with nitrosobenzene in an acetonitrile solvent at -20 °C for 24 h and

subsequently reduction was carried out with $NaBH_4$ in a methanol solvent. The crude aminoxy intermediates without purification was subjected to 10 % Pd/C catalyzed hydrogenolysis to obtain chiral 1, 2-diol[24] **38** in a 73 % yields over two steps.

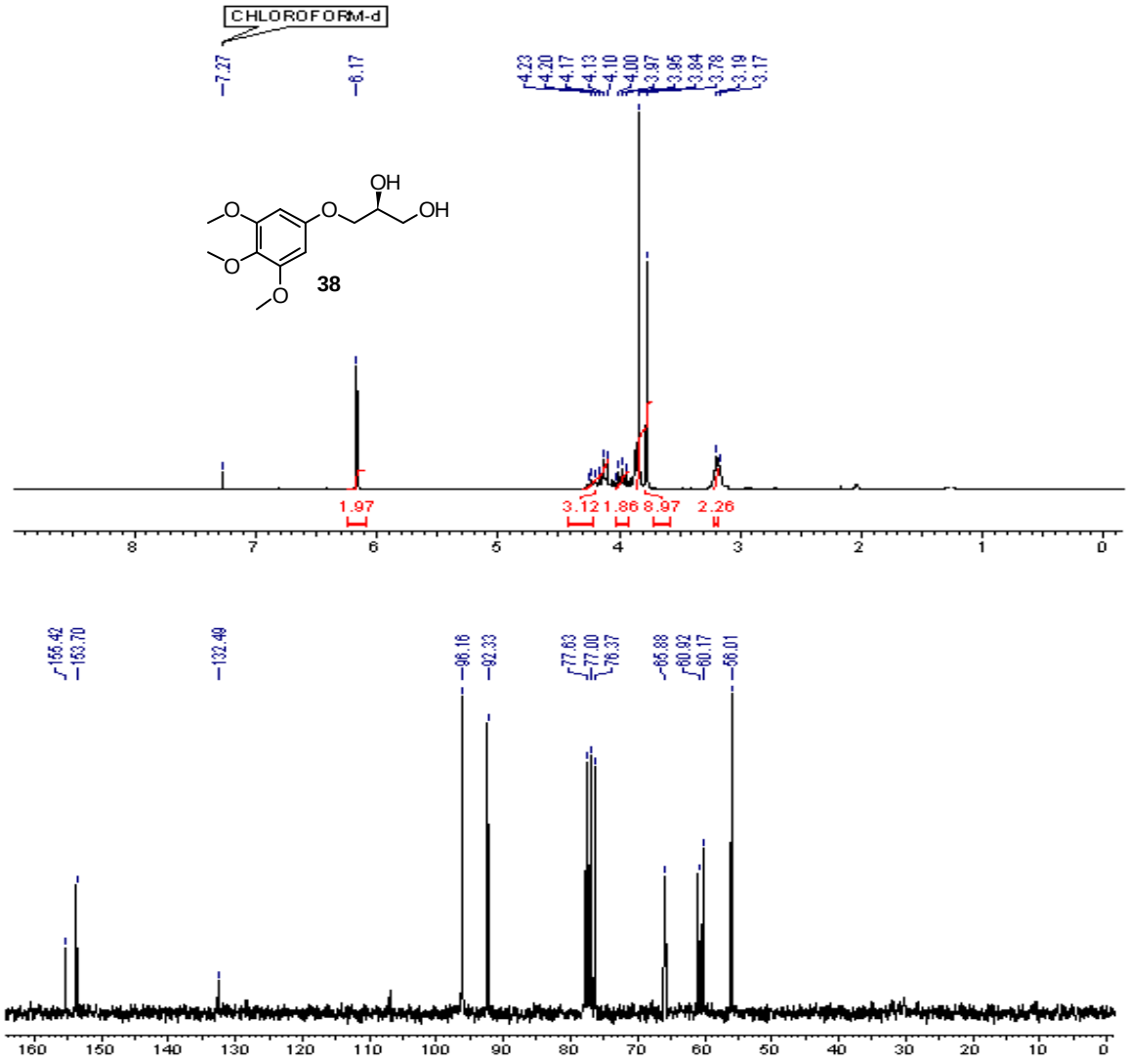


Fig. 6: ^{1}H and ^{13}C NMR spectrum of (*S*)-3-(3, 4, 5-trimethoxyphenoxy)propane-1,2-diol **38**

The ^{1}H NMR spectrum of diol compound **38** showed disappearance of aldehyde proton and the appearance of new aliphatic multiplet at δ 3.95-4.00, along with this broad singlet at δ 3.17 for the two hydroxyl group, confirms the diol compound **38**. The ^{13}C NMR spectrum showed signals at δ 56.01 for $–OCH_3$ group attached to the aromatic ring, and

signal at δ 60.17, 60.92 for aliphatic carbon adjacent to hydroxyl group and δ 65.88 for the –CH_2-CHOH-CH_2-OH carbon bearing secondary hydroxy group (**Fig. 6**).

The chiral diol **38** was then converted to chiral epoxide **10** under Mitsunobu reaction conditions using triphenyl phosphine (PPh_3) and diethyl azodicarboxylate (DEAD) using 1, 4-dioxane as a solvent at reflux condition for 4 h, afforded chiral epoxide **10**[25] in one step with a 80 % yield.

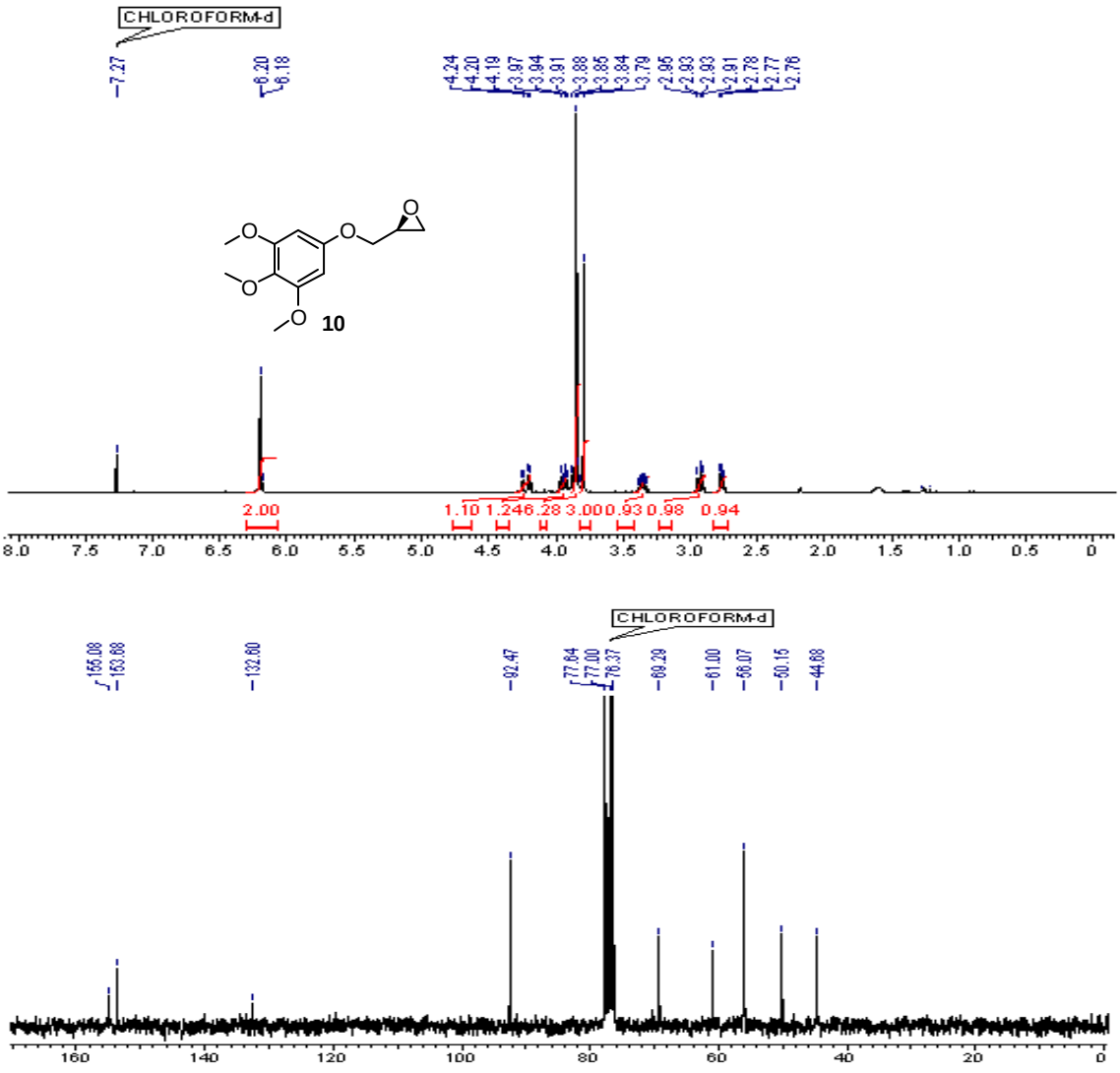


Fig. 7: ^{1}H and ^{13}C NMR spectrum of (*S*)-2-((3,4,5-trimethoxyphenoxy)methyl)oxirane **10**

The ^{1}H NMR spectrum of epoxide compound **10** showed disappearance of broad singlet for two hydroxyl groups and the appearance of new aliphatic multiplet at δ 2.93-2.95 for the quaternary proton of an epoxide. The ^{13}C NMR spectrum showed signals at δ 44.68, 50.15 and 69.29 for aliphatic carbon of the epoxide functionality, along with two signals for the –OCH_3 attached to the aromatic ring at δ 56.07 and 61.00, which confirm an epoxide formation (**Fig. 7**).

Finally, the chiral epoxide **10** was subjected to the reaction with 1-(2-methoxyphenyl)piperazine[16] **12** in an isopropanol solvent at reflux condition for 18 h to

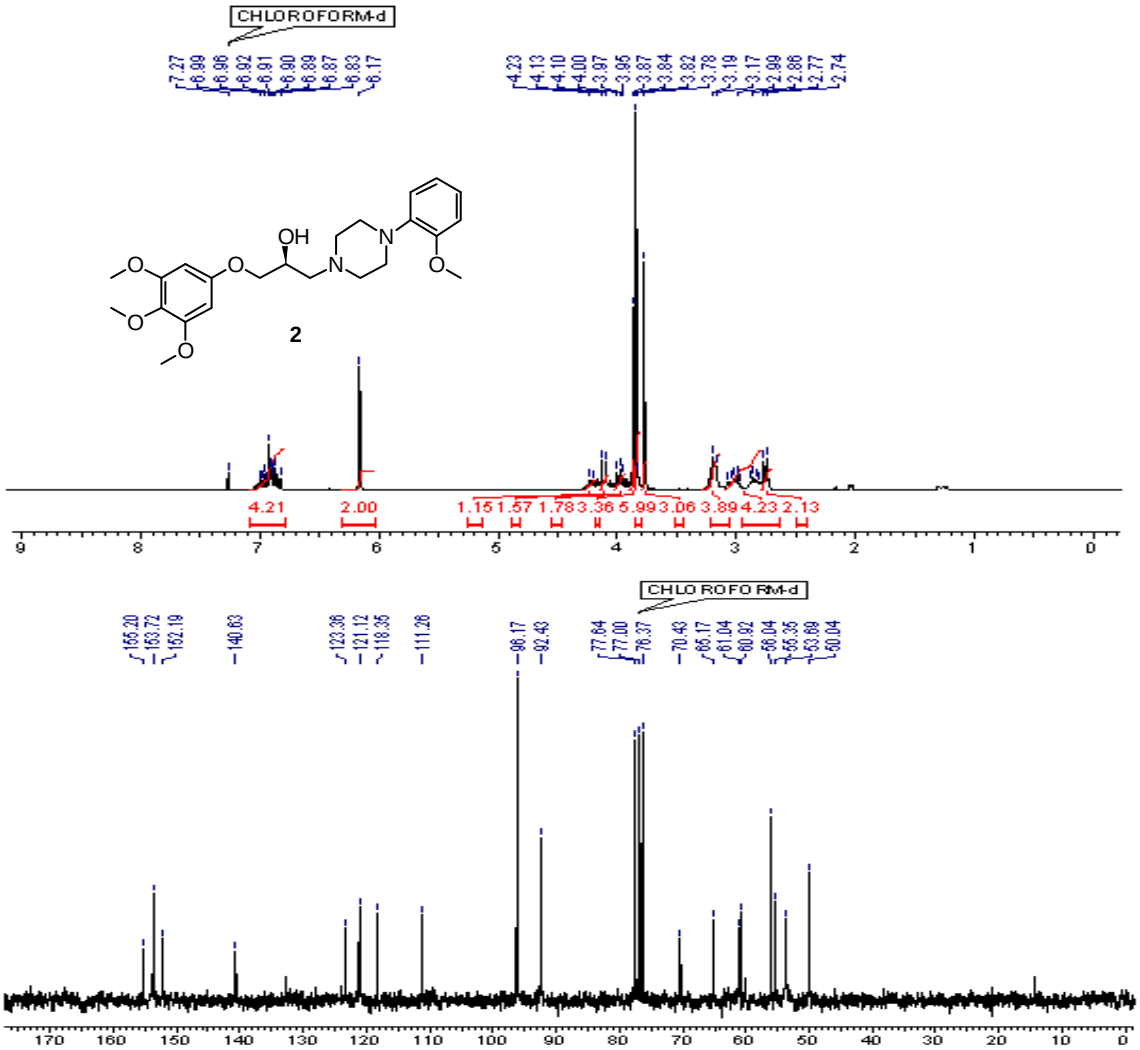


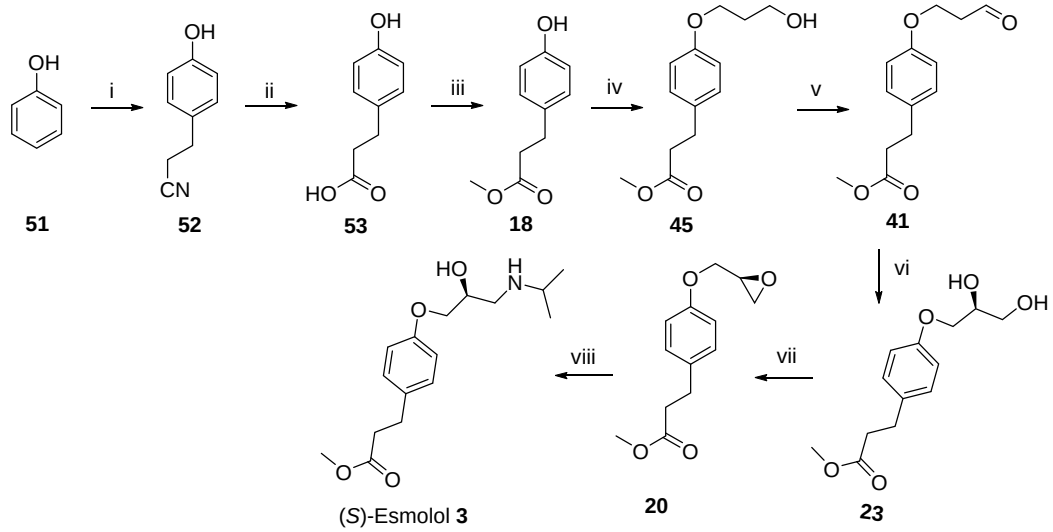
Fig. 8: ^{1}H and ^{13}C NMR spectrum of (*S*)-Enciprazine **2**

furnish the desired target molecule (*S*)-Enciprazine **2** in a 95 % yield.

The ^{1}H NMR spectrum of (*S*)-Enciprazine **2** showed two multiplets at δ 2.74-2.86 and δ 3.17-3.19 each of four protons for the total eight piperazine protons. Along with this one additional singlet at δ 3.87 for –OCH_3 protons attached to the aromatic ring and the multiplet in aromatic region for four protons at δ 6.83-6.99. ^{13}C NMR spectrum shows signal at δ 65.17 for the carbon bearing the secondary alcohol group and signal at δ 60.92 and 61.04 for the carbon of piperazine ring, confirming the formation of (*S*)-Enciprazine **2** (**Fig. 8**).

2.4.2 Enantioselective synthesis of Esmolol

The synthetic scheme employed for the synthesis of (*S*)-Esmolol **3** is presented in the **scheme 10.**



Scheme 10: *Reagents and reaction conditions*: (i) acrylonitrile, $AlCl_3$, RT-105 ^{o}C, 7 h; (ii) aq. NaOH, Reflux, 6 h; (iii) MeOH, H_2SO_4, Reflux, 4 h, over three step 76 %; (iv) 3-bromopropanol, K_2CO_3, Acetone, Reflux, 12 h, 84 %; (v) IBX, DMSO, RT, 6 h, 92 %; (vi) (a) PhNO, L-proline, MeCN, -20 ^{o}C 22 h, then $NaBH_4$, MeOH, 30 min; (b) 10 % Pd/C, MeOH, H_2, RT, 10 h, over two step, 77 %; (vii) PPh_3, DIAD, 1, 4 Dioxan, reflux, 5 h, 88 %; (viii) isopropyl amine, water , reflux, 6 h, 81 %.

As per cofreindly ic analysis (**Fig. 2**), the synthesis of (*S*)-Esmolol **3** was started from the Methyl 3-(4-(3-hydroxypropoxy)phenyl) propanoate **18**, which was synthesized from the commercial available phenol **51**. The phenol **51** under goes the Friedel-craft reaction with acrylonitrile using $AlCl_3$ as a catalyst at RT to 105 ^oC for 7 h, gives the cyno product **52**. The crude cyno compound **52** was reflux with aqueous NaOH solution for 6 h to furnish the acid **53**.[26] The crud acid **53** was subjected to the estrification in a methanol solvent using catalytic amount of H_2SO_4 for 4 h furnished the desired ester **18** in a 76 % yield over the three steps (**Scheme 10**).

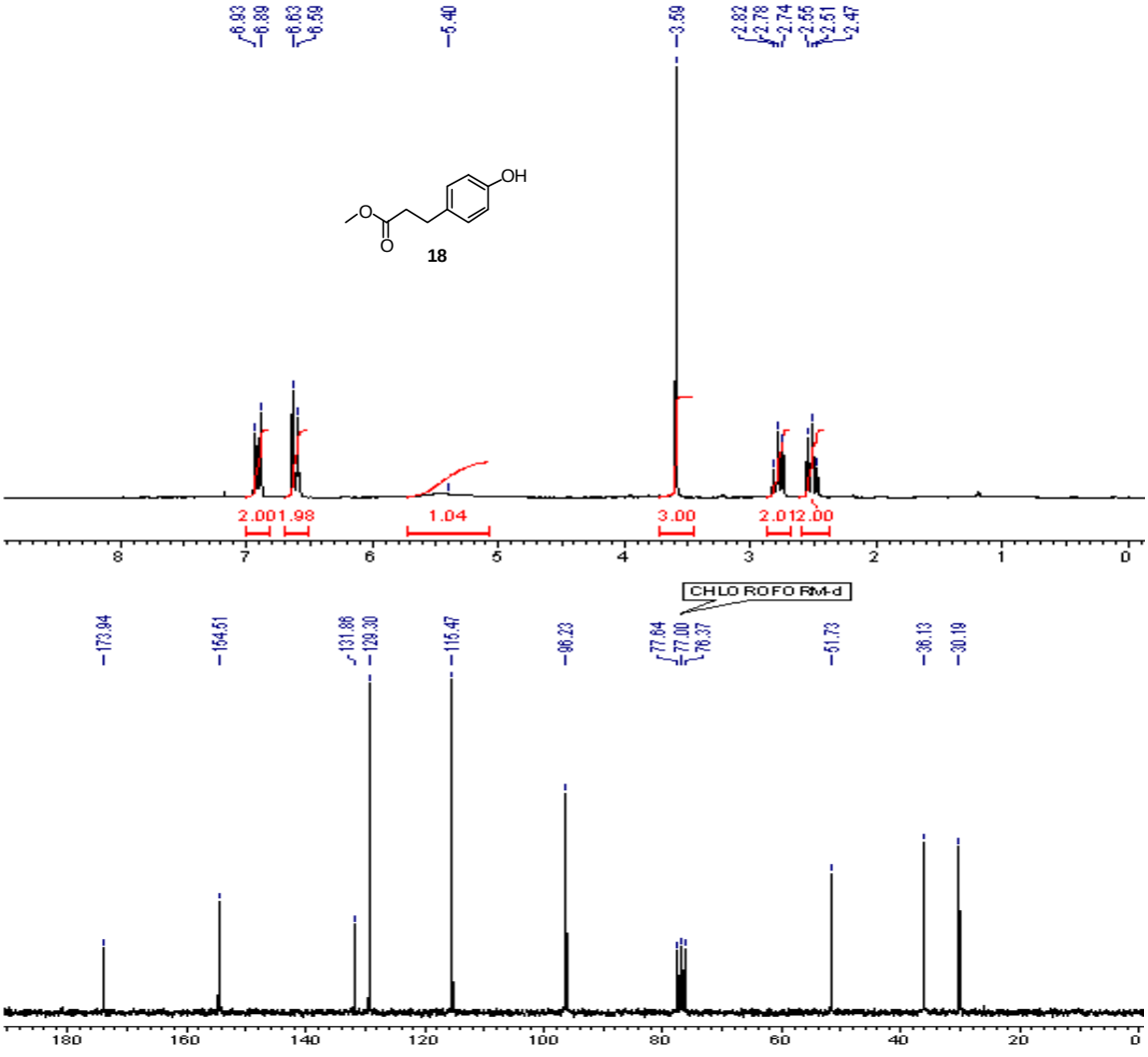


Fig. 9: ^1H and ^{13}C NMR spectrum of Methyl 3-(4-hydroxyphenyl)propanoate **18**

The ^{1}H NMR spectrum showed two triplets at δ 2.51 and δ 2.78 for $–CH_2-\underline{CH_2}-CO-$ proton and $–\underline{CH_2}-CH_2-CO–$ protons, respectively. The singlet at δ 3.59 for three protons represent the ester $–CH_2-CO-O\underline{CH_3}$ protons, which confirmed the formation of the desired ester **18**. The ^{13}C NMR spectrum showed signals at δ 30.19 and 36.13 for the two aliphatic $–CH_2–$ group and at δ 173.94 for the carbonyl carbon of ester **18** (**Fig. 9**).

The O-alkylation of substituted phenol **18** with 3-bromo-1-propanol in the presence of K_2CO_3 as a base in an acetone solvent at reflux condition affording the primary alcohol **45** in 84 % yield.

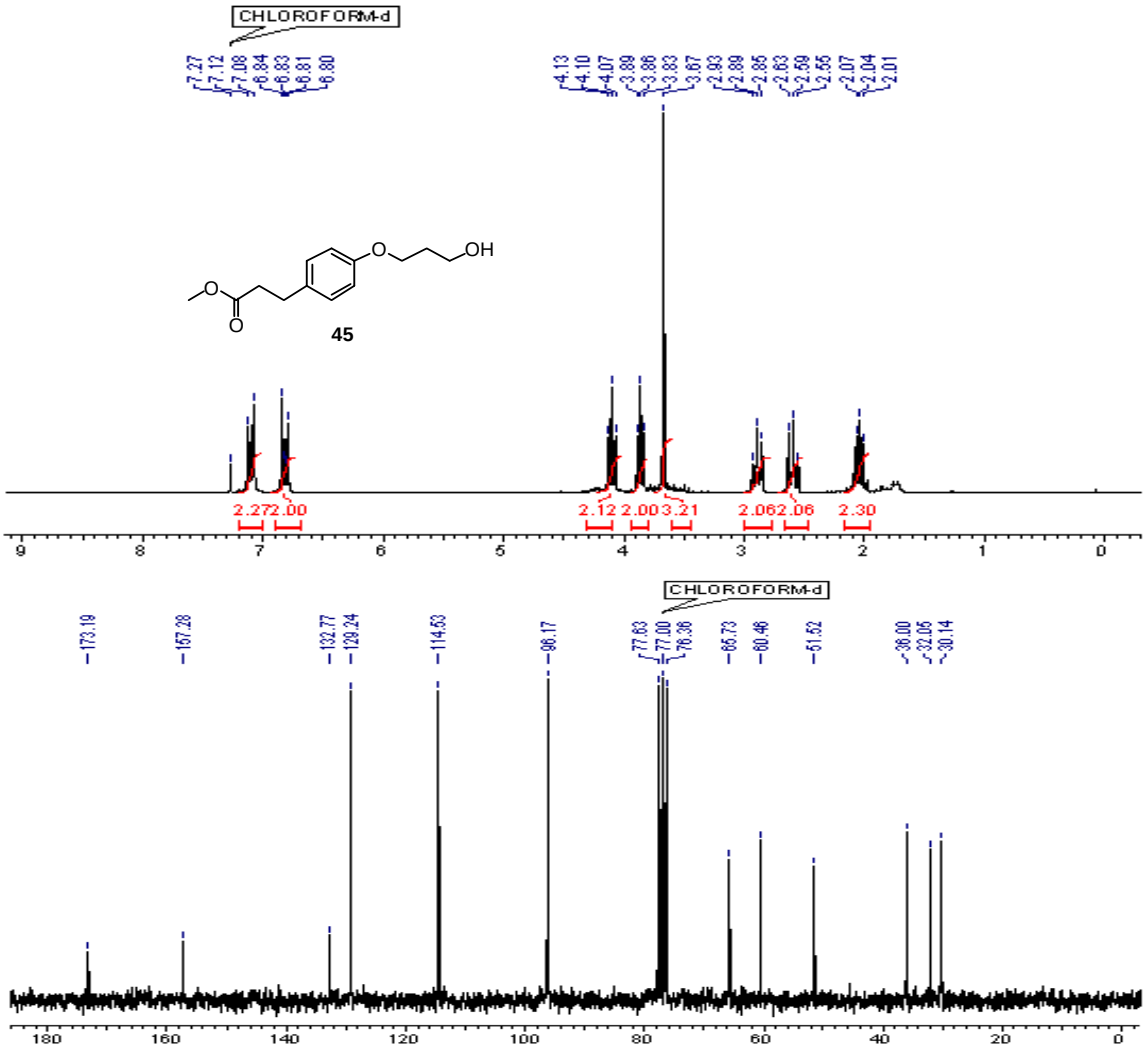
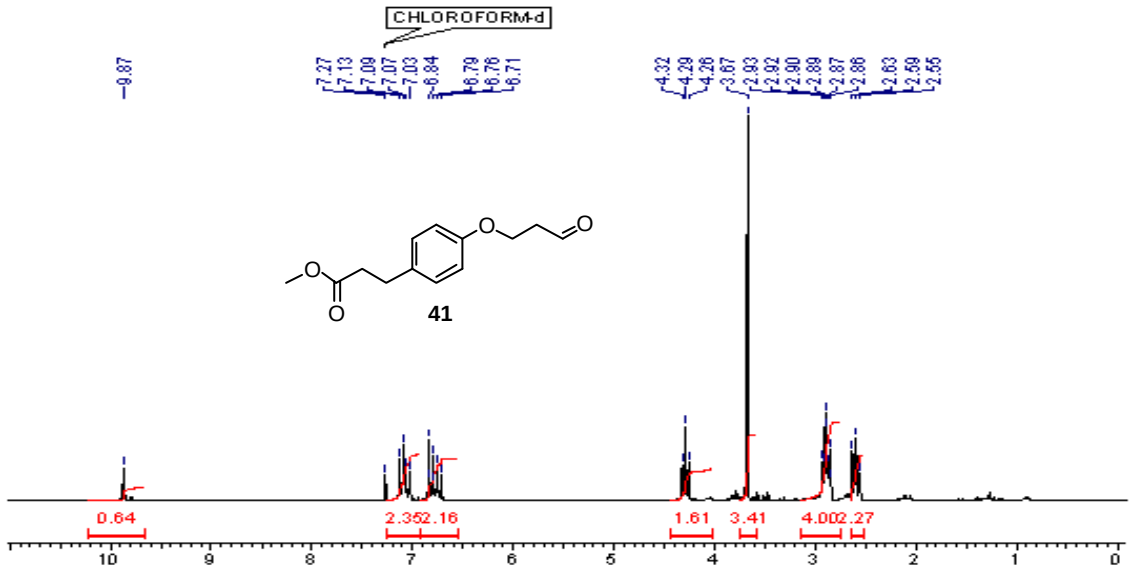


Fig. 10: ^{1}H and ^{13}C NMR spectrum of Methyl 3-(4-(3-hydroxypropoxy)phenyl) propanoate **45**

The ^{1}H NMR spectrum of alcohol **45** showed appearance of pentate at δ 2.04, for –CH_2-$\underline{CH_2}$-CH_2- attached hydroxy group. The two triplets at δ 3.86 and 4.10 represent the –$\underline{CH_2}$-CH_2-$\underline{CH_2}$- linkage attached to oxygen of phenol and hydroxy group, respectively. The sharp singlet's for the ester –CH_2-CO-O$\underline{CH_3}$ at δ 3.67, confirmed the formation of the primary alcohol **45**. The ^{13}C NMR spectrum showed characteristic three signals for –CH_2-CH_2-CH_2- linkage at δ 32.05, 60.46 and 65.73 (**Fig. 10**).

The primary alcohol **45** was then subjected to the oxidation using 2-iodoxy benzoic acid (IBX) in a DMSO solvent at room tempreture for 6 h, afforded the aldehyde **41** in a 92 % yield.[23] The ^{1}H NMR spectrum of aldehyde **41** showed disappearance of aliphatic pentate for –CH_2-$\underline{CH_2}$-CH_2– at δ 2.04 and appearance of sharp singlet for the aldehyde proton at δ 9.87 confirmed the formation of the aldehyde **41**. The ^{13}C NMR spectrum showed signal at δ 199.84 for carbonyl carbon of aldehyde confirms the aldehyde functionality (**Fig. 11**).



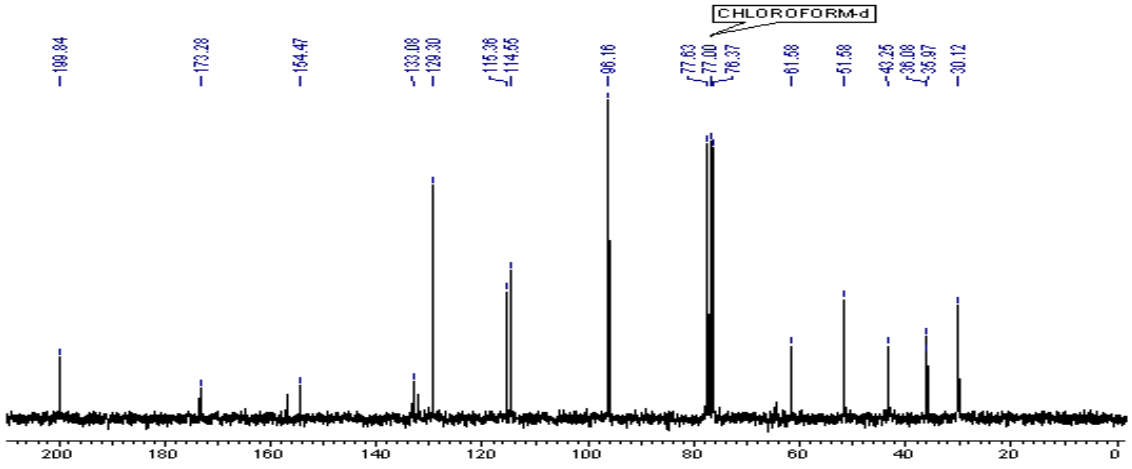
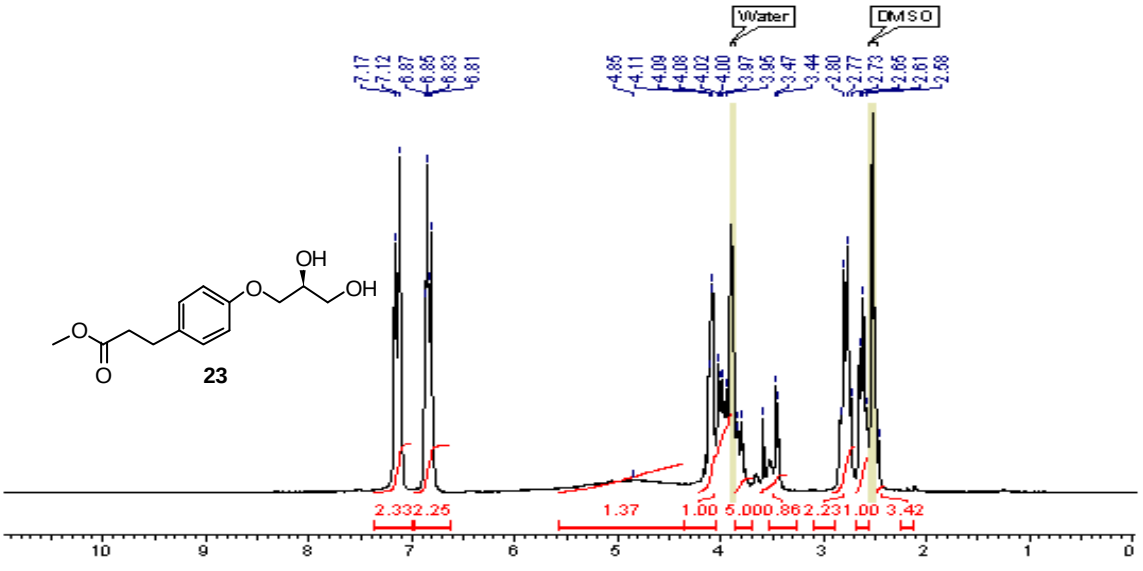


Fig. 11: ^{1}H and ^{13}C NMR spectrum of Methyl 3-(4-(3-oxopropoxy)phenyl)propanoate **41**

An aldehyde **41** was then subjected to L-proline (20 mol %) catalyzed asymmetric α-aminoxylation with nitrosobenzene in an acetonitrile solvent at -20 °C for 24 h and subsequently reduction was carried out with $NaBH_4$ in a methanol solvent. The crude aminoxy intermediates without purification was subjected to 10 % Pd/C catalyzed hydrogenolysis to obtain chiral diol[24] **23** in a 72 % yields over two steps.



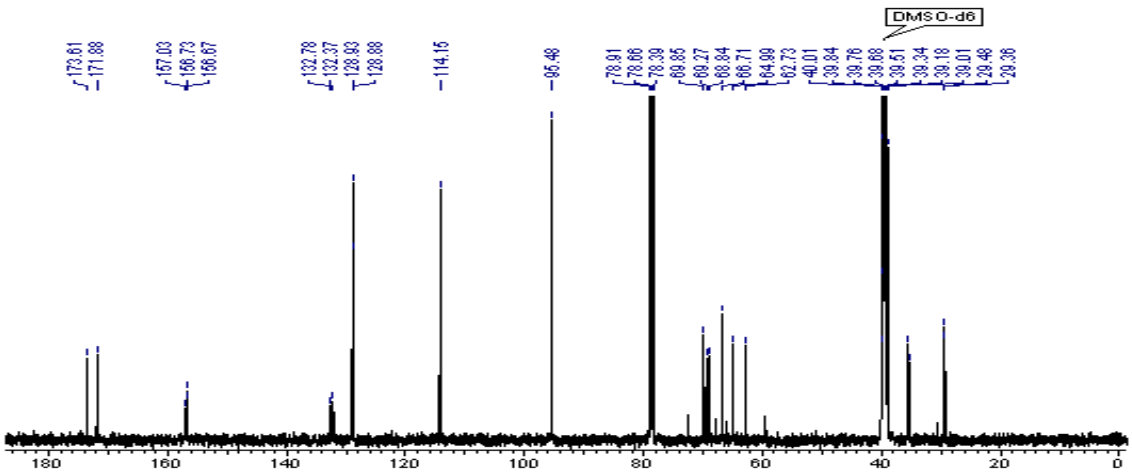


Fig. 12: ^{1}H and ^{13}C NMR spectrum of (*S*)-methyl 3-(4-(2,3-dihydroxypropoxy)phenyl)propanoate **23**

The ^{1}H NMR spectrum of diol **23** shows disappearance of aldehyde proton and the appearance of new aliphatic multiplet in the region at δ 3.44-4.11 for six protons. The ^{13}C NMR spectra shows disappearance of aldehyde signal from δ 199.84 and appearance of new signal in aliphatic region at δ 66.71, 69.27, and 69.85, confirm the formation of diol compound **23** (**Fig. 12**)**.**

The chiral diol **23** was then converted to chiral epoxide **20** under Mitsunobu reaction conditions using triphenylphosphine (PPh_3) and diisopropyl azodicarboxilate (DIAD) using 1, 4-dioxane as a solvent at reflux condition for 5 h, afforded the chiral epoxide[25] **20** in one step with a 88 % yield. The ^{1}H NMR spectrum of chiral epoxide **20** compound showed appearance of multiplet of one proton at δ 3.34-3.35 and two doublets of doublets for one protons each at δ 3.97 and 4.15. The ^{13}C NMR spectrum shows the signal at δ 50.10 for quaternary carbon of epoxide and signal at δ 173.20 represent the carbonyl carbon of ester, which confirmed the formation of epoxide compound **20** (**Fig. 13**).

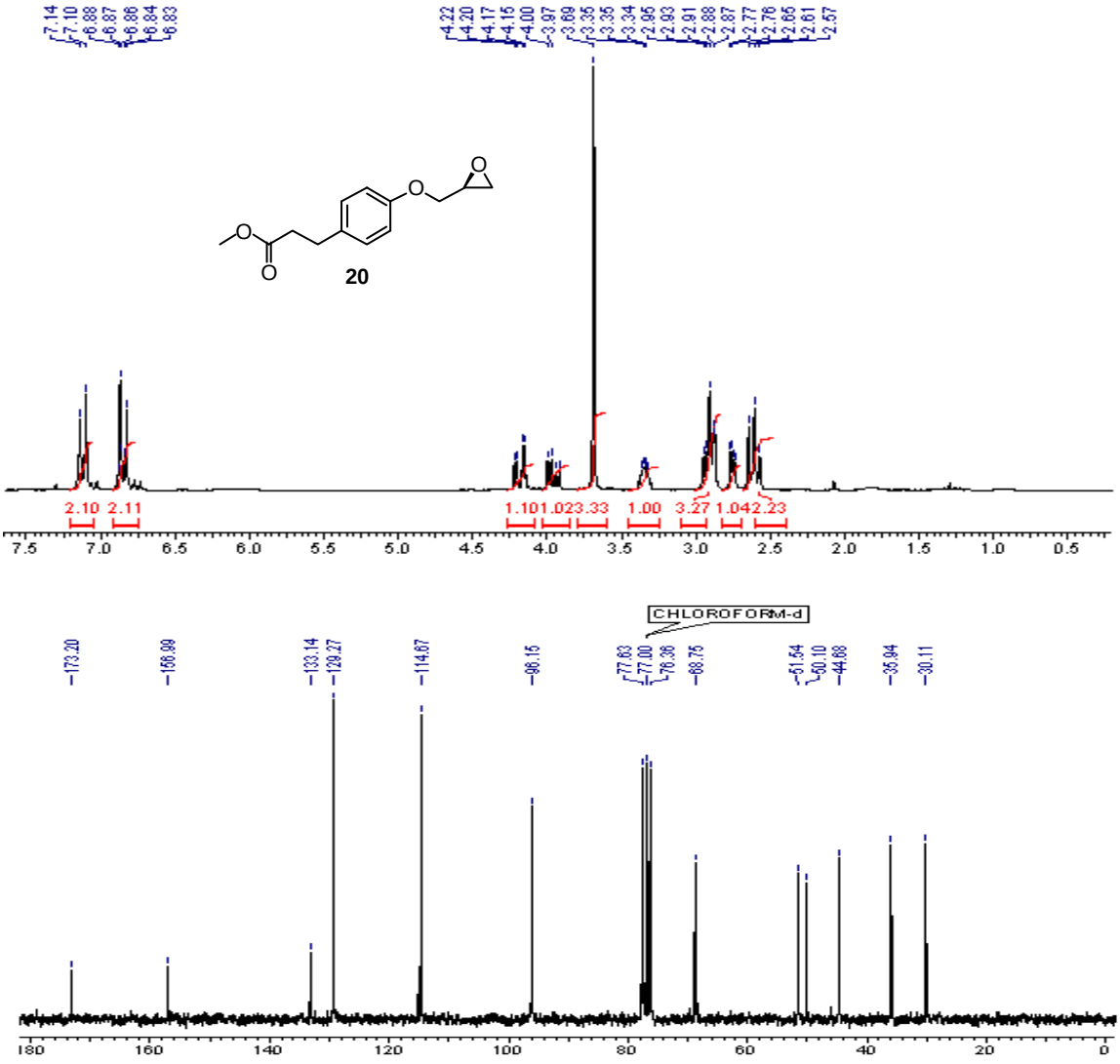


Fig. 13: ^{1}H and ^{13}C NMR spectrum of (*S*)-methyl 3-(4-(oxirane-2-ylmethoxy)phenyl) propanoate **20**

Finally, the chiral epoxide **20** was subjected to the reaction with excess of isopropyl amine and catalytic amount of water at reflux condition for 6 h to furnish the target molecule (*S*)-Esmolol[18] **3** in a 81 % yield. The formation of (*S*)-Esmolol **3** was confirmed by ^{1}H NMR spectrum, which shows doublet of six proton at δ 1.17 and the multiplet of one proton between δ 4.02-4.17, which are the characteristic peaks of target molecule. The ^{13}C NMR spectra shows the signal at δ 19.10 for the two methyl group of amine and

the signal for quaternary carbon at δ 51.37, which confirm the formation of (*S*)-Esmolol **3** (**Fig. 14**).

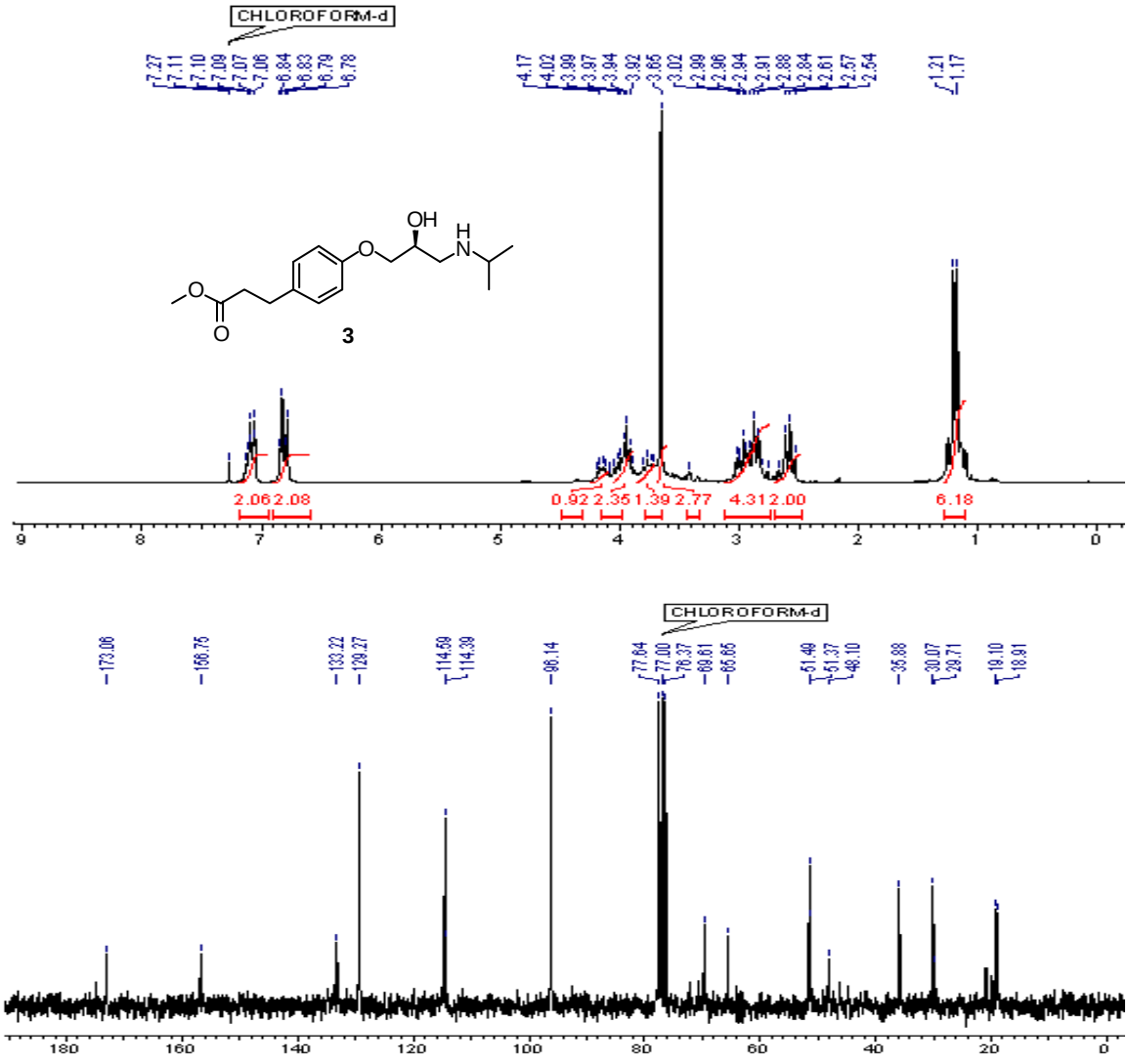
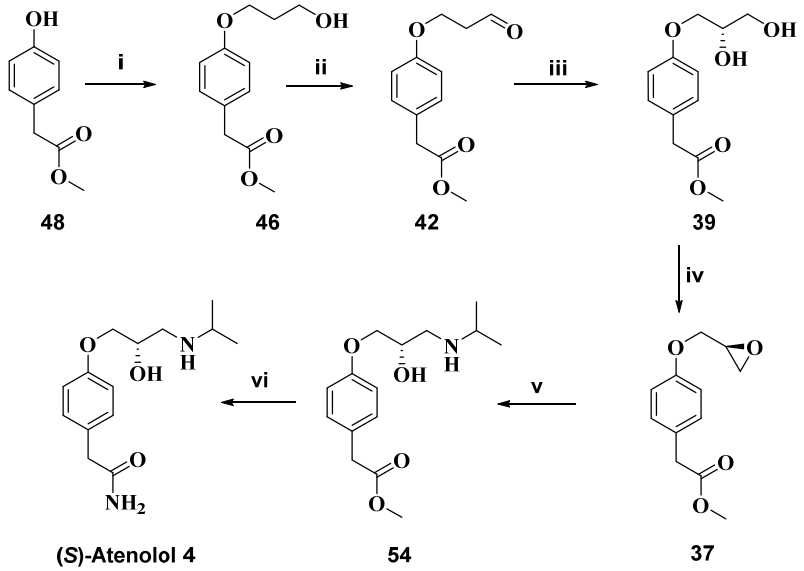


Fig. 14: ^{1}H and ^{13}C NMR spectrum of (*S*)-Esmolol **3**

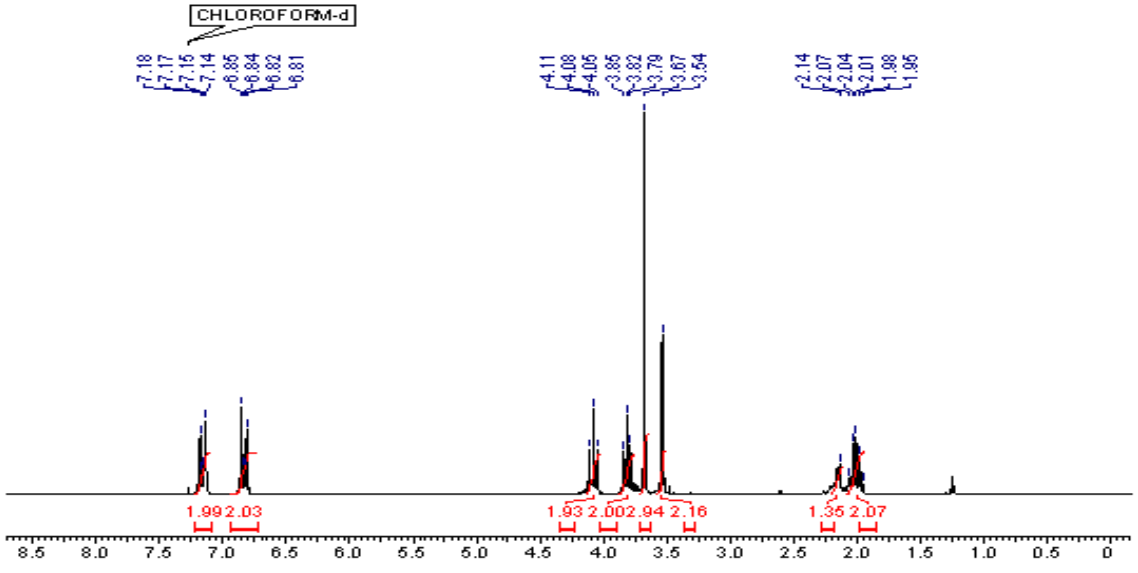
2.4.3 Enantioselective synthesis of Atenolol

The synthetic scheme employed for the synthesis of (*S*)-Atenolol **4** is presented in the **scheme 11**.



Scheme 11: *Reagents and reaction conditions:* (i) 3-bromopropanol, K_2CO_3, acetone, reflux, 11 h, 90 %; (ii) IBX, DMSO, RT, 8 h, 89 %; (iii) (a) PhNO, L-proline, MeCN, -20 ^oC 24 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, rt, 16 h, over two step, 74 %; (iv) PPh_3, DIAD, 1, 4 Dioxan, reflux, 8 h, 82 %; (v) isopropyl amine, water , RT, 6 h, 70 %; (vi) NH_4OH–methanol, RT, 26 h, 75 %.

As per retro-synthetic analysis **Fig. 2**, we initiated a synthesis from commercially available methyl 2-(4-hydroxyphenyl)acetate **48**. The methyl 2-(4-hydroxyphenyl)acetate **48** was reflux with 3-bromopropanol in the presence of K2CO$_3$ for 11 h in an acetone solvent furnished primary alcohol **46** in a 90 % yield.



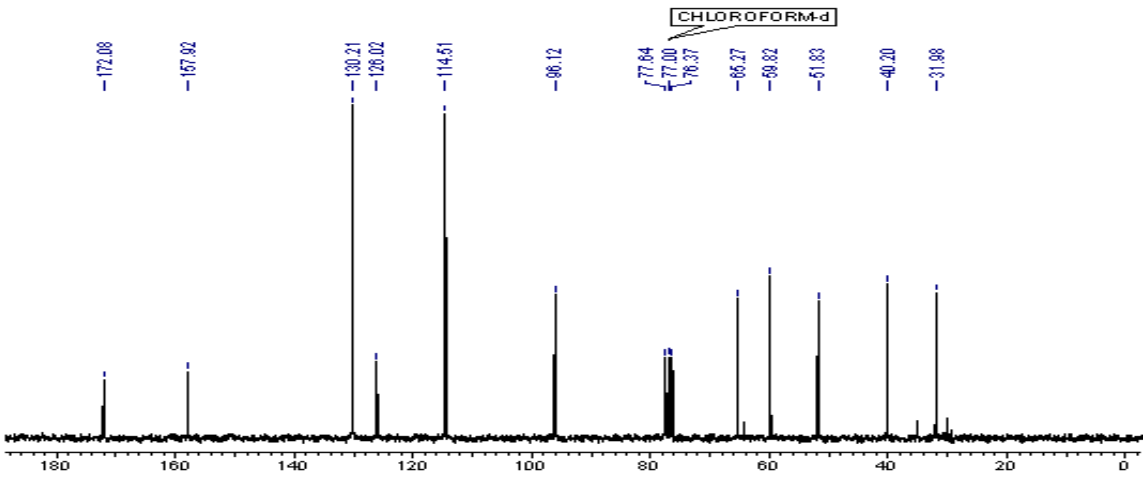
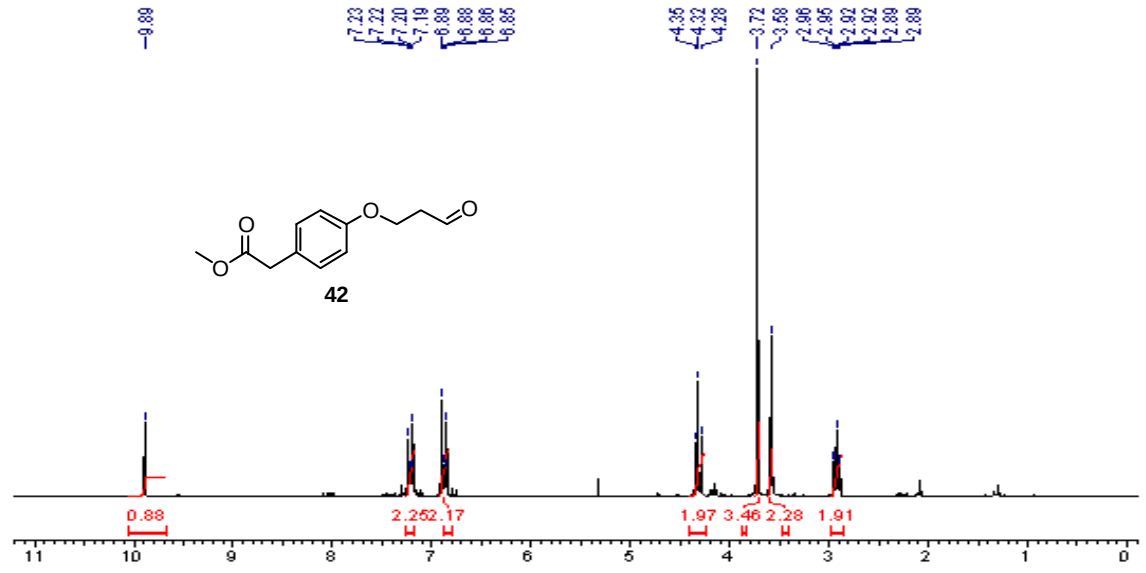


Fig. 15: ^{1}H and ^{13}C NMR spectrum of Methyl 2-(4-(3-hydroxypropoxy)phenyl)acetate **46**

The ^{1}H NMR spectrum of **46** showed pentate at δ 2.01 for two protons and singlet at δ 2.14 for one proton of primary hydroxyl group, confirmed the formation of the primary alcohol **46**. The ^{13}C NMR spectrum showed signals at δ 31.98, 59.82, and 65.27 for the three aliphatic carbons bearing primary hydroxyl group (**Fig. 15**).

The oxidation[23] of primary alcohol **46** was carried out with 2-iodoxy benzoic acid (IBX) in a DMSO solvent at room tempreture for 8 h, afforded the corresponding aldehydes **42** in a 89 % yields.



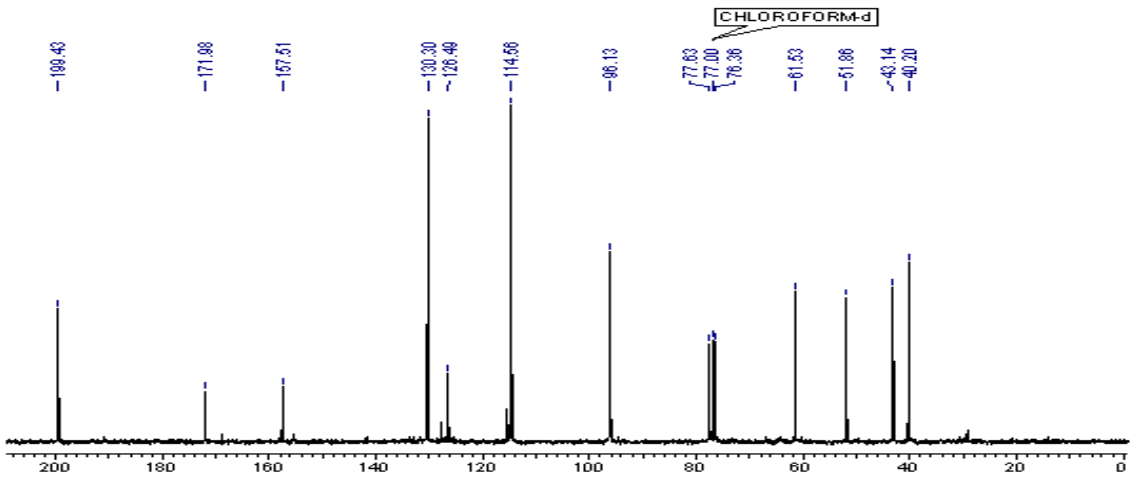


Fig. 16: ^{1}H and ^{13}C NMR spectrum of Methyl 2-(4-(3-oxopropoxy)phenyl)acetate **42**

The ^{1}H NMR spectrum of aldehyde **42** showed disappearance of pentate for two protons and appearance of sharp singlet for the aldehyde proton at δ 9.89, confirmed the formation of the aldehyde **42**. The ^{13}C NMR showed signals at δ 199.43 which is the characteristic peak for the carbonyl carbon of aldehyde functionality present in the compound (**Fig. 16**).

Aldehyde **42** was then subjected to L-proline (20 mol %) catalyzed asymmetric α-aminoxylation with nitrosobenzene in an acetonitrile solvent at -20 °C for 24 h and subsequently reduction was carried out with $NaBH_4$ in a methanol solvent. The crude aminoxy intermediates without purification was subjected to 10 % Pd/C catalyzed hydrogenolysis to obtain chiral diol[24] **39** in a 74 % yields over two steps.

^{1}H NMR spectrum of chiral diol compound showed disappearance of aldehyde proton and the appearance of new aliphatic multiplets for four protons at δ 3.77-4.03, and the broad singlet for two hydroxyl group of diol at δ 4.83. The ^{13}C NMR spectrum showed signals at δ 70.00 and 62.78 for two carbon bearing hydroxyl groups. Also the disappearance of signal for the carbonyl carbon of aldehyde and appearance of peak at δ

173.22 for the carbonyl carbon of ester, confirms the formation of diol **39** (**Fig. 17**).

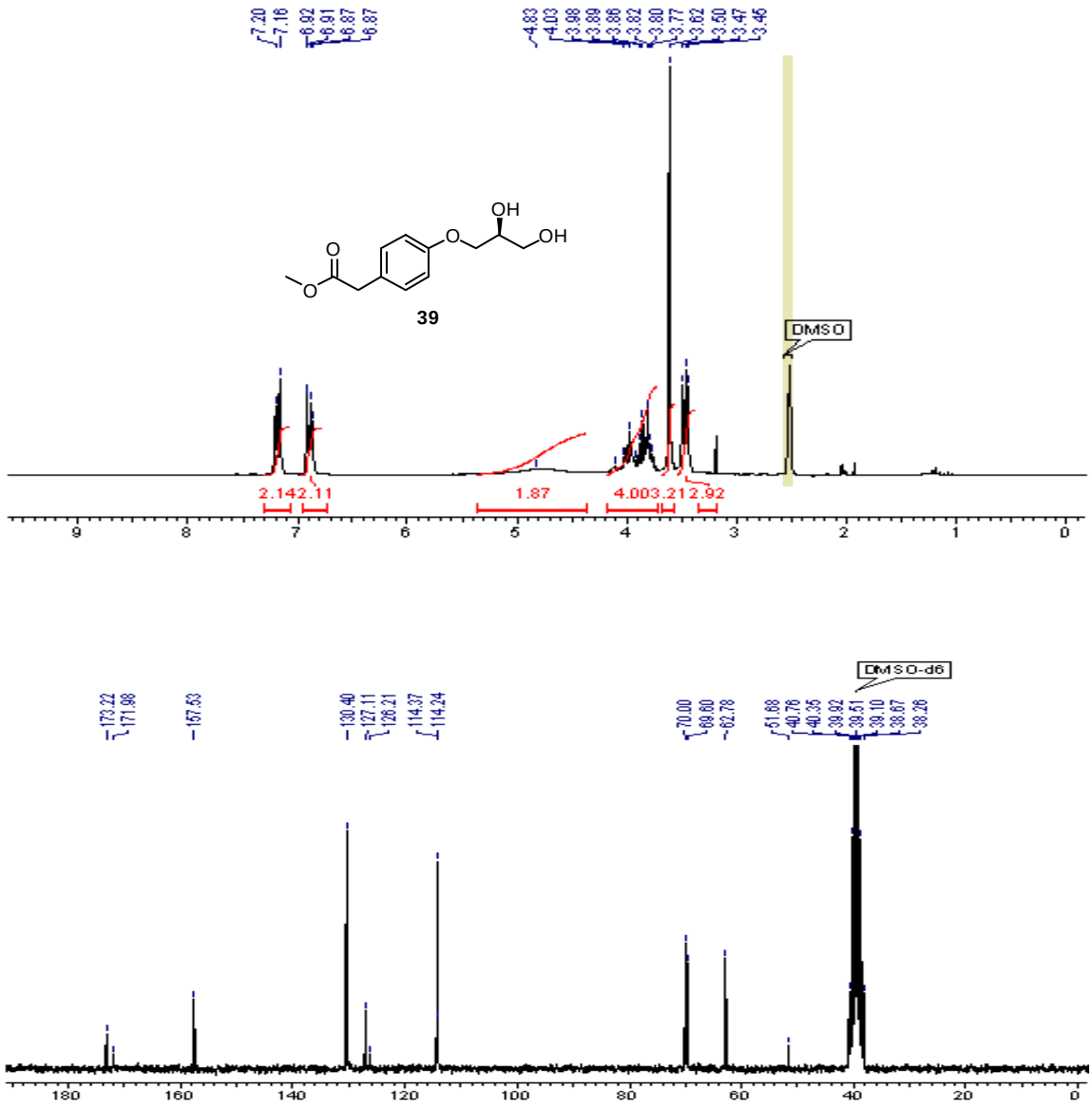


Fig. 17: ^{1}H and ^{13}C NMR spectrum of (*S*)-methyl 2-(4-(2, 3-dihydroxypropoxy)phenyl) acetate **39**

The chiral diol **39** was then converted to an epoxide **37** under Mitsunobu reaction conditions[25] using PPh_3 and DIAD using 1, 4-dioxane as a solvent at reflux condition for 8 h, gives chiral epoxide **37** in one step with a 82 % yield.

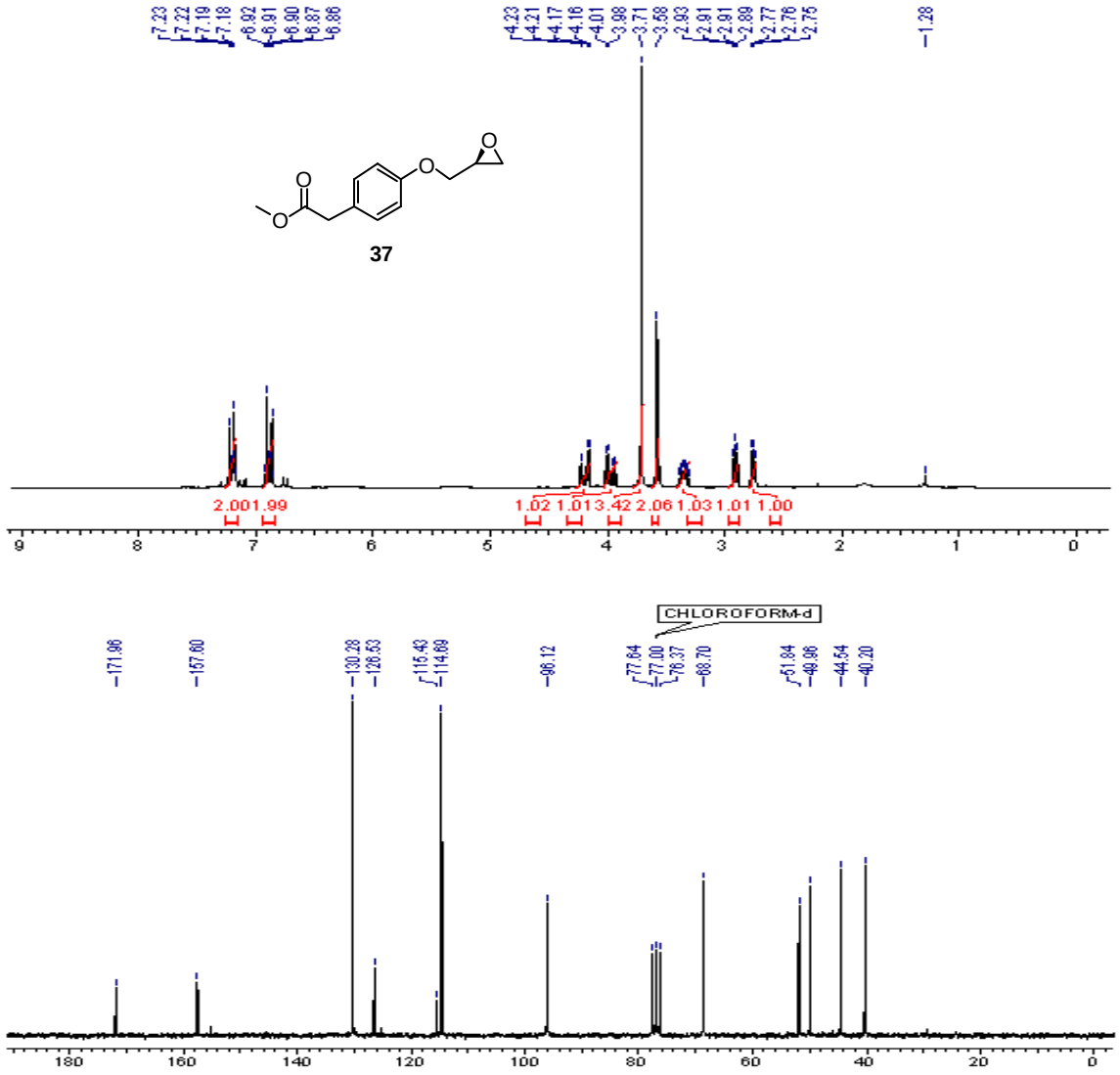


Fig. 18: ^{1}H and ^{13}C NMR spectrum of (*S*)-methyl 2-(4-(oxirane-2-ylmethoxy)phenyl) acetate **37**

The ^{1}H NMR spectrum of an epoxide compound showed appearance of multiplet of one proton at δ 2.89-2.93 and two doublets of doublets for one proton each at δ 3.98 and 4.16 and the disappearance of singlet for two hydroxyl proton. The ^{13}C NMR spectrum shows the signal at δ 49.96 for tertiary carbon of epoxide and signal at δ 171.96 represent the carbonyl carbon of ester, which confirmed the formation of epoxide compound **37** (**Fig**. **18**).

The chiral epoxide **37** was opened with the excess of isopropyl amine and catalytic amount of water at ambidant tempreture for 6 h, afforded the desired amino compound[27] **54** in a 70 % yield.

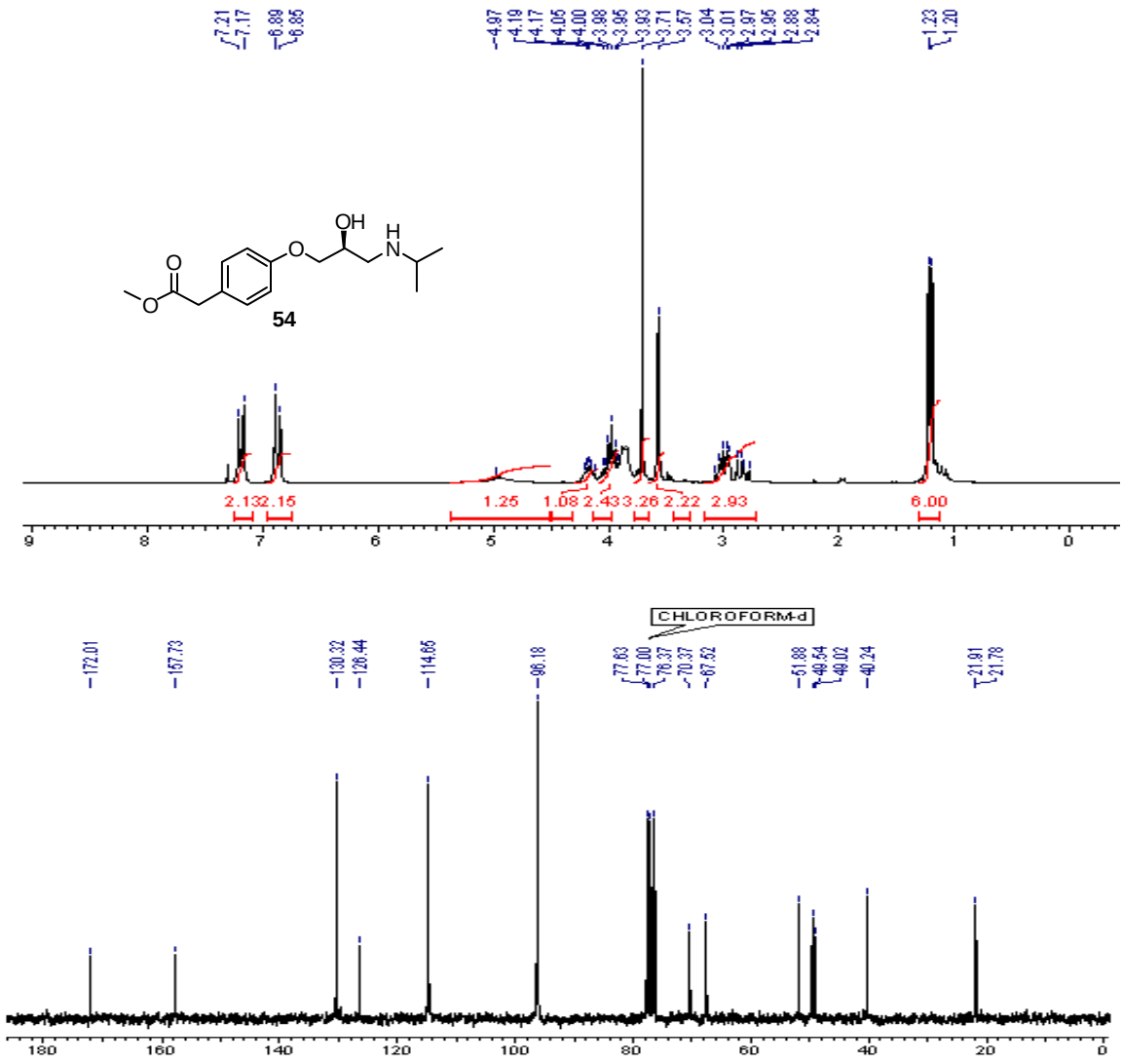


Fig. 19: ^{1}H and ^{13}C NMR spectrum of (*S*)-methyl 2-(4-(2-hydroxy-3-(isopropylamino)propoxy)phenyl) acetate **54**

The formation of amine **54** was confirmed by ^{1}H NMR spectrum, which shows doublet of six protons at δ 1.20 and broad singlet at δ 4.97 for the hydroxyl group. The ^{13}C NMR spectra shows the signal at δ 21.78 and 21.91 for the two methyl group of amine and the signal for quaternary carbon at δ 51.88 (**Fig. 19**).

Finally the ester group of amine **54** was converted to the amide using ammonium hydroxide in methanol for 26 h at room tempreture, afforded the desired target molecule (*S*)-atenolol[27] **4** in a 75 % yield.

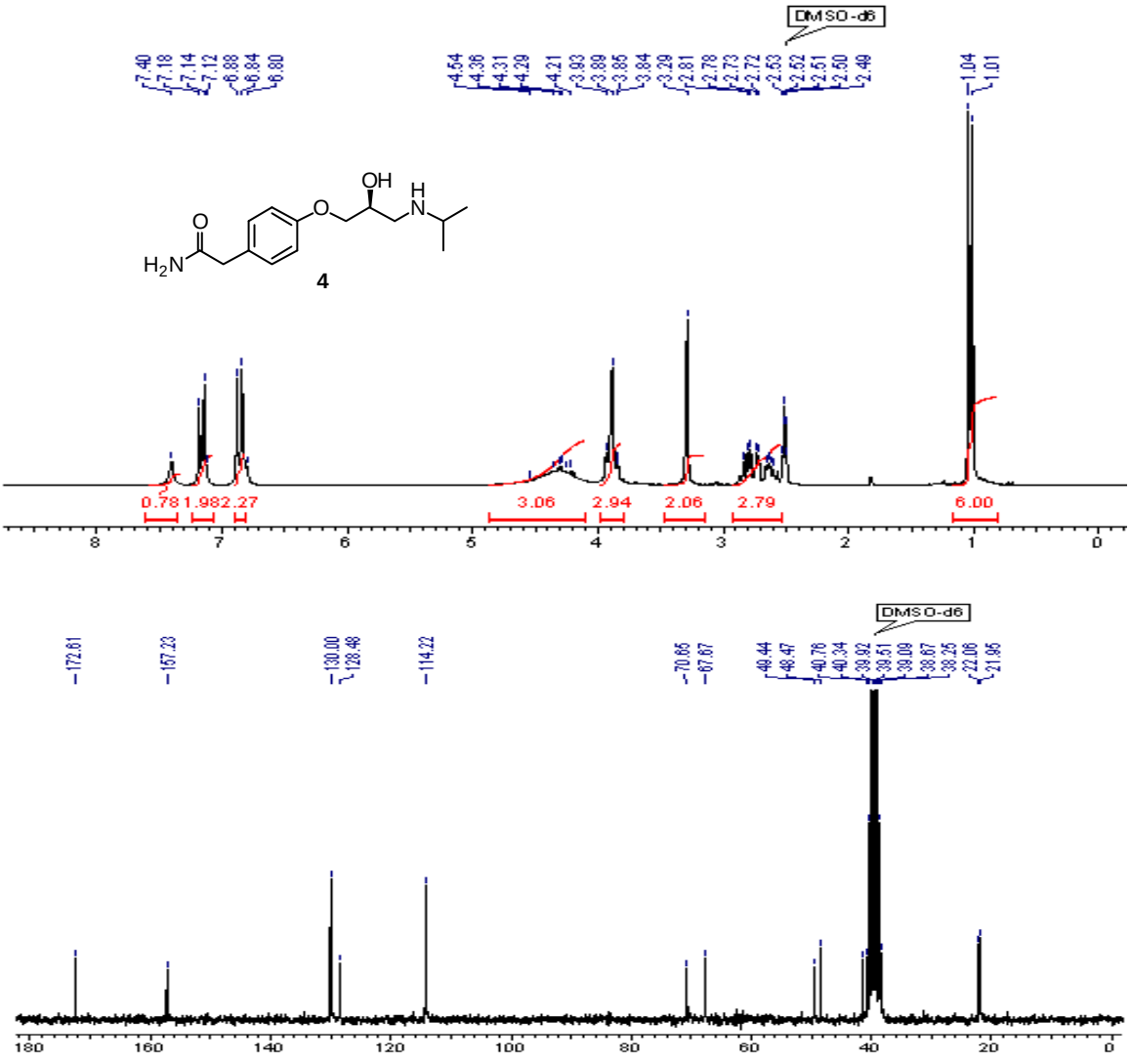


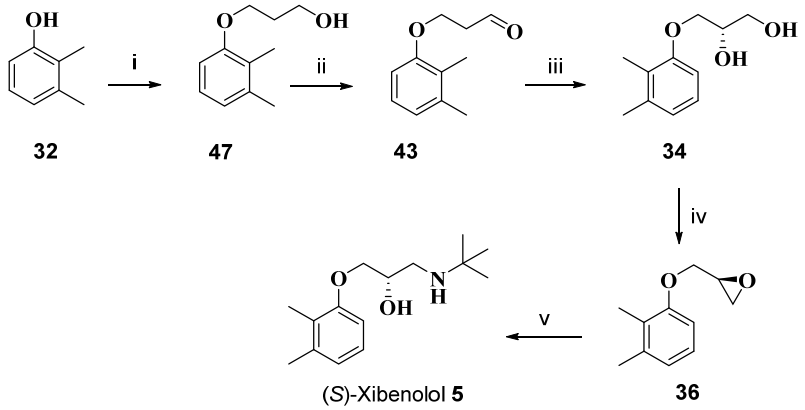
Fig. 20: ^{1}H and ^{13}C NMR spectrum of (*S*)-Atenolol **4**

The ^{1}H NMR spectrum of (*S*)-Atenolol **4** showed a sharp singlet at δ 3.29 for two benzyl proton of amide group and doublet for six protons at δ 1.01 and multiplate in the region δ 4.31-4.54 for three proton and a broad singlet at 7.40 for the –NH proton, confirming the

formation of (*S*)-Atenolol **4**. The ^{13}C NMR Spectrum shows the signal at δ 172.61 for the carbonyl carbon of amide (**Fig. 20**).

2.4.4 Enantioselective synthesis of Xibenolol

The synthetic scheme employed for the synthesis of (*S*)-Xibenolol **5** is presented in the **scheme 12.**



Scheme 12: *Reagents and reaction conditions:* (i) 3-bromopropanol, K_2CO_3, acetone, reflux, 6 h, 97 %; (ii) IBX, DMSO, RT, 3 h, 90 %; (iii) (a) PhNO, L-proline, MeCN, -20 ^oC 22 h, then $NaBH_4$, MeOH, 1 h; (b) 10 % Pd/C, MeOH, H_2, RT, 14 h, over two step, 68 %; (iv) PPh_3, DIAD, 1, 4 Dioxan, reflux, 4 h, 80 %; (v) tert-butyl amine, water, RT, 7 h, 98 %.

As per cofreindly ic analysis **Fig. 2**, we initiated a synthesis from commercially available 2, 3-dimethyl phenol **32**. The 2, 3-dimethyl phenol **32** was reflux with K_2CO_3, and 3-bromopropanol in an acetone solvent for 6 h furnished primary alcohol **47** in a 97 % yield.

The ^1H NMR spectrum showed multiplet in the region of δ 2.05-2.13 for two protons and two triplets for two protons each at δ 3.89 and δ 4.11, confirmed the formation of the –CH_2-CH_2-CH_2- linkage. The ^{13}C NMR spectrum showed signals at δ 11.78 and δ 20.20 for two –CH_3 group attached to the aromatic ring and at δ 32.26, 60.79 and 66.11 for the three aliphatic carbons bearing hydroxy functionality (**Fig. 21**).

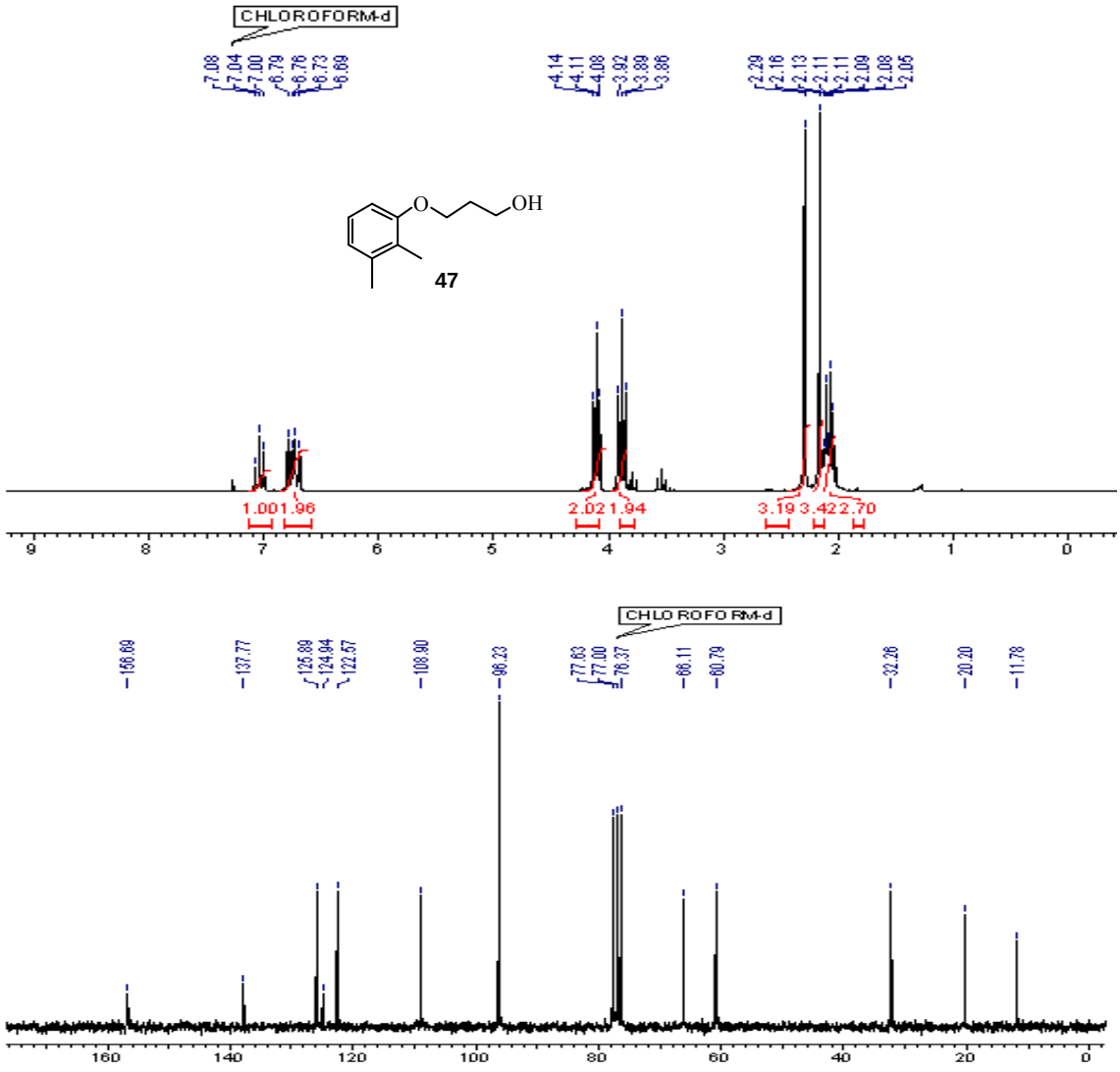


Fig. 21: ^{1}H and ^{13}C NMR spectrum of 3-(2, 3-dimethylphenoxy)propan-1-ol **47**

The oxidation[23] of primary alcohol **47** was carried out with 2-iodoxy benzoic acid (IBX) in a DMSO solvent at room tempreture for 3 h, affording aldehydes **43** in a 90 % yield. The ^{1}H NMR spectrum of aldehyde **43** showed disappearance of aliphatic multiplets and appearance of sharp triplet for the aldehyde proton at δ 9.90, confirmed the formation of the aldehyde **43**. The ^{13}C NMR spectrum showed only two signals at δ 43.43 and 62.04 for –O-$\underline{C}H_2$-$\underline{C}H_2$-CHO aliphatic carbons adjacent to aldehyde functionality and the carbonyl carbon of aldehyde at δ 199.83 (**Fig. 22**).

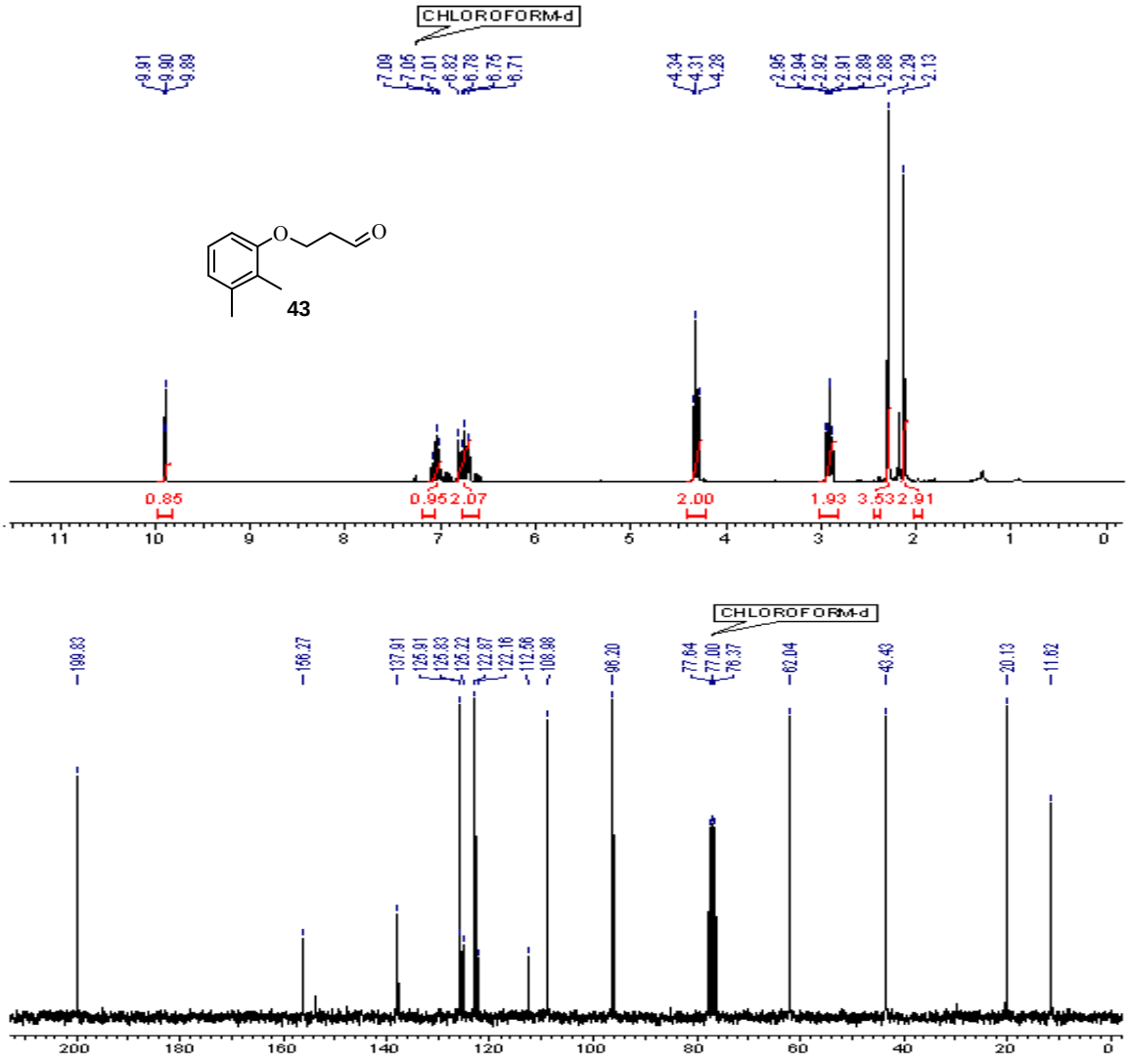


Fig. 22: ^{1}H and ^{13}C NMR spectrum of 3-(2, 3-dimethylphenoxy)propanal **43**

Aldehyde **43** was then subjected to L-proline (20 mol %) catalyzed asymmetric α-aminoxylation with nitrosobenzene in an acetonitrile solvent at -20 °C for 22 h and subsequently reduction was carried out with $NaBH_4$ in a methanol solvent. The crude aminoxy intermediates without purification was subjected to 10 % Pd/C catalyzed hydrogenolysis to obtain chiral diol[24] **34** in a 68 % yields over two steps.

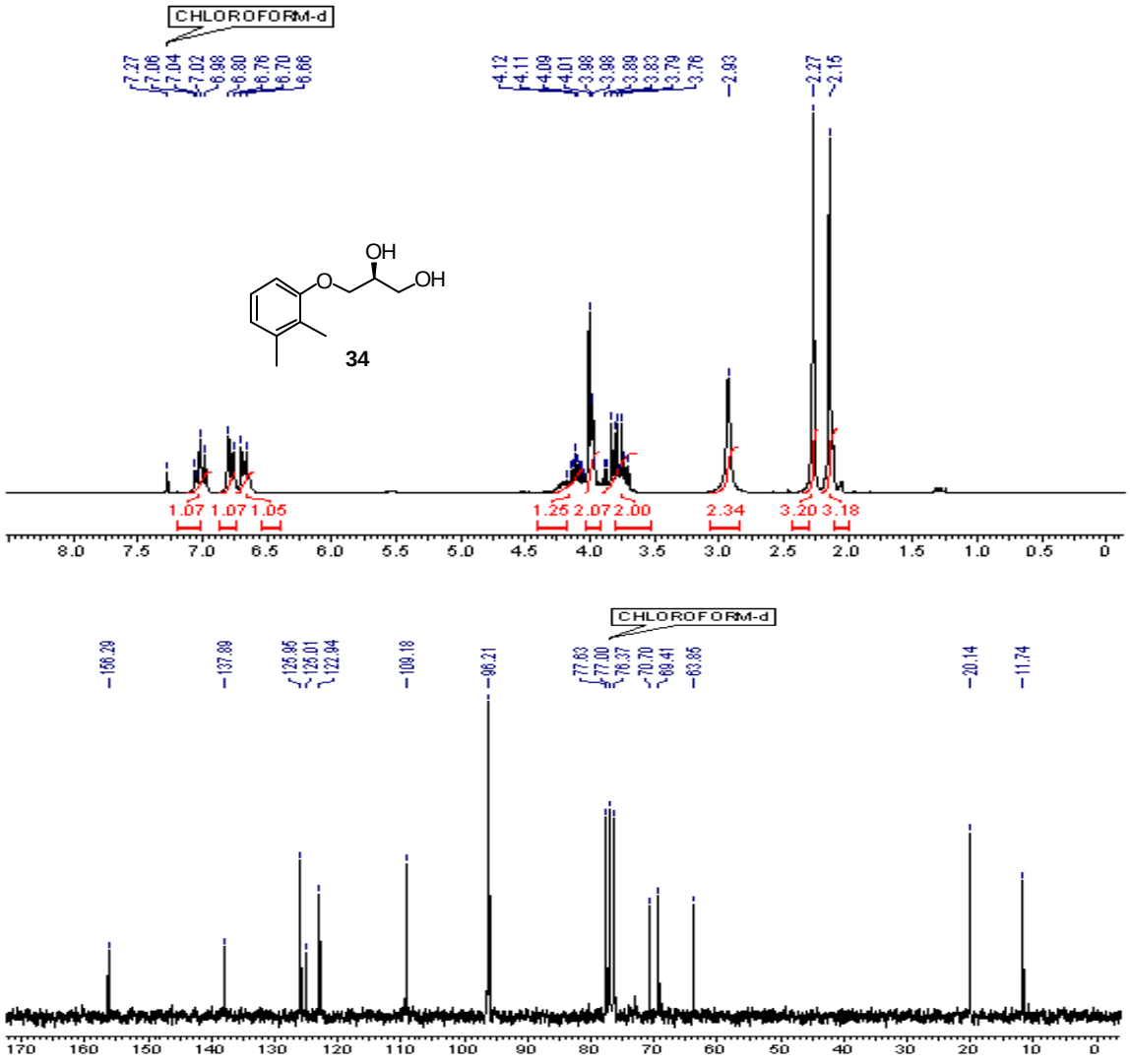


Fig. 23: ^{1}H and ^{13}C NMR spectrum of (*S*)-3-(2, 3-dimethylphenoxy)propane-1, 2-diol **34**

^{1}H NMR spectrum of chiral diol compound **34** showed disappearance of aldehyde proton and the appearance of new aliphatic multiplet at δ 3.76-4.12, and the broad singlet for two hydroxyl group of diol at δ 2.93. The ^{13}C NMR spectrum showed signals at δ 11.74 and 20.14 for two –CH_3 attached to the aromatic ring. The peak appearance at δ 70.70 for the tertiary carbon bearing hydroxy group and the disappearance of signal for the carbonyl carbon of aldehyde, confirms the formation of chiral diol **34** (**Fig. 23**).

The chiral diol **34** was then converted to an epoxide **36** under Mitsunobu reaction conditions[25] using triphenyl phosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD) in 1, 4-dioxane as a solvent at reflux condition for 4 h, afforded a 80 % yield. The ^{1}H NMR spectrum of an epoxide **36** compound showed disappearance of singlet for the hydroxyl group and appearance of multiplet of one proton at δ 2.91-2.93. The ^{13}C NMR spectrum shows the signal at δ 11.74, and 20.16 for two $-CH_3$ attached to the aromatic ring and signal at δ 50.26 for tertiary carbon of an epoxide, which confirmed the formation of an epoxide compound **36** (**Fig. 24**).

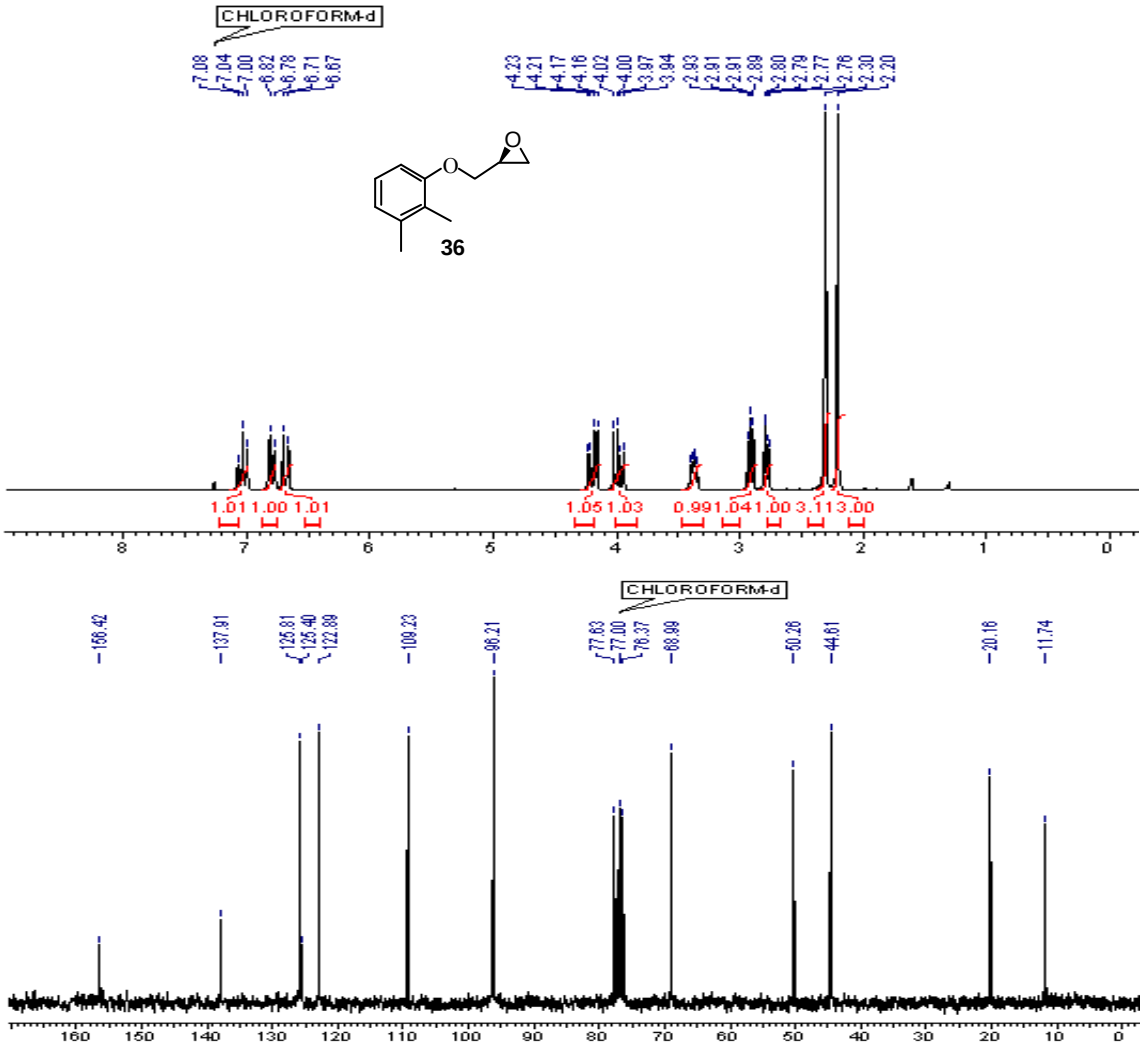


Fig. 24: ^{1}H and ^{13}C NMR spectrum of (S)-2-((2, 3-dimethylphenoxy)methyl)oxirane **36**

Finally, an epoxide **36** was treated with excess of tert-butyl amine in the presence of catalytic amount of water at room tempreture for 7 h, afforded the (*S*)-Xibenolol **5** in a 98 % yields. The ^{1}H NMR spectrum of **5** showed a singlet at δ 1.26 for nine methyl proton of tert-butyl group and two singlet for three proton each at δ 2.14 and δ 2.27, respectively, for the two methyl group attached to the aromatic ring. The multiplet in the region δ 2.85-3.05 for the one proton represents the carbon bearing the secondary hydroxy group.

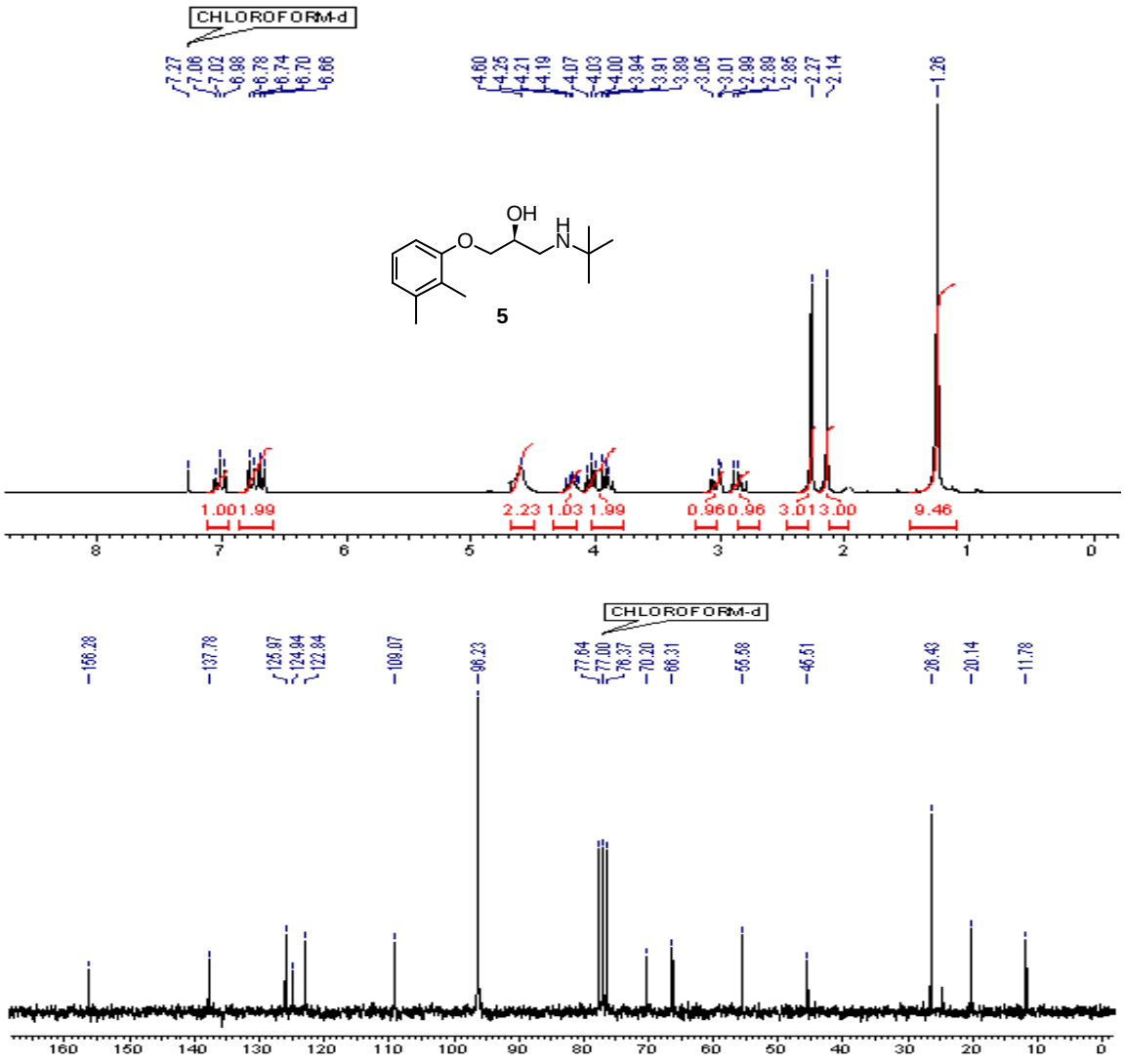


Fig. 25: ^{1}H and ^{13}C NMR spectrum of (*S*)-xibenolol **5**

^{13}C NMR spectrum shows signal at δ 26.43 for the three methyl group of amine and signal at δ 45.51 for quaternary carbon attached to –NH, confirming the formation of (*S*)-xibenolol **5** (**Fig. 25**).

2.5 Conclusion

In conclusion, we have developed highly efficient, versatile, cofreindly, inexpensive, nontoxic, synthetic route for an enantioselective synthesis of the β-adrenergic blockers: (*S*)-Enciprazine **2**, (*S*)-Esmolol **3,** (*S*)-Atenolol **4** and (*S*)-Xibenolol **5** *via* asymmetric α-aminoxylation of aldehyde catalyzed by L-proline as key step and source of chirality. The protocol is very general, simple, clean, efficient, rapid, and mild and it may works well for the synthesis of other β-adrenergic blockers affording good to excellent yields.

2.6 Experimental Section

2.6.1 Synthetic Procdures and Spectral data

Preparation of 3, 4, 5-trimethoxy phenol 7

To the solution of 3, 4, 5-trimethoxybenzaldehyde **49** (5 g, 25.5 mmol) in anhyd dichloromethane (50 mL), the *m*-CPBA (6.6 g, 38.3 mmol) was added in portion wise over the period of 30 min at 0 °C. After 1 h, cooling was removed and the mixture was stirred at RT until it shows the completion of reaction by TLC (8 h). After the completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (80 mL) and washed with sat. $NaHCO_3$ (3*20 mL). The organic layer was washed with brine (25 mL), dried over sodium sulphate (Na_2SO_4), and concentrated under reduced pressure. The crude product was obtained as red syrup **50**. To the solution of crude **50** in a MeOH (25 mL), solid KOH (1.25 g, 24 mmol) was added at 0 ^oC. The resulting reaction mixture was stirred at room temperature for 30 min. After the completion of reaction by TLC, the solvent was

removed under the reduced pressure to obtain the solid residue; the residue was washed with petroleum ether (50 mL). The residual solid was dissolved in H_2O (50 mL) and acidified with dilute HCl to give the product **7**, which was filtered and dried.

Yield: 3.92 g (91 %), white solid, mp 144-146 ^oC (lit.[16] 143-145 ^oC) **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 3.79 (s, 9H), 6.09 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 55.97, 61.10, 92.90.

Preparation of Methyl 3-(4-hydroxyphenyl)propanoate 18

To the solution of phenol **51** (10 g, 106 mmol) and acrylonitrile (6.8 g, 128 mmol), $AlCl_3$ (8.7 g, 53 mmol) was added in portion wise at room temperature over 30 min. The resulting reaction mixture was stirred for 3 h at room tempreture, and additional 6 h at 105 ^oC, then bring the reaction mixture to 70 ^oC, the hot reaction mixture was poured into 100 mL of cold water followed by stirring for 30 min at 70 ^oC, and then layer was separated. The organic layer was washed with hot water till the aqueous layer shows neutral pH on pH paper. The organic layer was concentrate to dryness under the reduced pressure to obtain the residue **52**. The residue **52** was dissolved in water (75 mL), and sodium hydroxide (5 g) was added in the portion wise for 30 min. The resulting reaction mixture was refluxed and monitored by TLC (6 h) for its completion. After the completion of reaction, reaction mixture was cool to room tempreture and acidified with conc. HCl at 10 ^oC. The solid precipitated was obtained, which was filtered and dried in the oven to get the crud acid **53**. The crud solid product **53** was dissolved in a methanol (50 mL), and a H_2SO_4 (0.5 mL) was added. The reaction mixture was reflux for the 4 h until it shows the completion of reaction by (TLC). Then the methanol was evaporated under the reduced pressure and product was purified using ethyl acetate-petroleum ether

as eluent by column chromatography using silica gel (60-120 mesh), afforded pure ester **18**.

Yield: 14.55 g (76 %); colorless oil; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.51 (t, *J*=7 Hz, 2H), 2.78 (t, *J*=7 Hz, 2H), 3.59 (s, 3H), 5.40 (brs, 1H), 6.60 (d, *J*=8 Hz, 2H), 6.90 (d, *J*=8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 30.19, 36.13, 51.73, 115.47, 129.30, 131.86, 154.51, 173.94.

Preparation of 3-(Aryloxy) propan-1-ol (44, 45, 46, 47)

A solution of phenol **7**/**18**/**48**/**32** (20 mmol) in 30 mL acetone (30 mL) at room tempreture, K_2CO_3 (40 mmol) was added. After the addition of K_2CO_3 the reaction mixture was stirred at same temperature 15 min. Then 3-bromopropan-1ol (22 mmol) was added drop wise to the reaction mixture followed by reflux the reaction mixture for (6-12 h). The completion of reaction was monitored by TLC. After the completion of reaction, reaction mixtures were cool to room temperature and filter and wash with acetone (2*10 mL). The filtrate was evaporated under the reduced pressure. The residue obtained was purified using ethyl acetate-petroleum ether as eluent by column chromatography over silica gel (60-120 mesh), afforded the 3-(Aryloxy) propan-1-ol **44**/**45**/**46**/**47** in a 84-97 % yield.

3-(3, 4, 5-trimethoxy phenoxy) propan-1-ol 44

Yield: 4.55 g (94 %); colorless liquid; bp 174-176 ^oC **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.93 (s, 1H), 2.02 (pent, *J*=6 Hz, 2H), 3.77 (s, 3H), 3.82 (s, 6H), 3.88 (t, *J*=3 Hz, 2H), 4.05 (t, *J*=6 Hz, 2H), 6.13 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 32.06, 56.01, 60.17, 60.92, 65.88, 92.33, 132.49, 153.70, 155.42; Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.52; H, 7.46 %.

Methyl 3-(4-(3-hydroxypropoxy)phenyl)propanoate 45

Yield: 4.0 g (84 %); Colorless liquid; bp 326-328 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.04 (t, *J*=6 Hz, 2H), 2.59 (t, *J*=8 Hz, 2H), 2.89 (t, *J*=8 Hz, 2H), 3.67 (s, 3H), 3.86 (t, *J*=6 Hz, 2H), 4.10 (t, *J*=6 Hz, 2H), 6.80-6.84 (m, 2H), 7.08 (d, *J*=8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 30.14, 32.05, 36.00, 51.52, 60.46, 65.73, 114.53, 129.24, 132.77, 157.28, 173.19; Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.52; H, 7.66 %.

Methyl 2-(4-(3-hydroxypropoxy)phenyl)acetate 46

Yield: 4.03 g (90 %); Colorless oil; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.98 (pent, *J*=6 Hz, 2H), 2.14 (s, 1H), 3.54 (s, 2H), 3.67 (s, 3H), 3.82 (t, *J*=6 Hz, 2H), 4.08 (t, *J*=6 Hz, 2H), 6.81-6.85 (m, 2H), 7.15 (dd, *J*=2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 31.98, 40.20, 51.83, 59.82, 65.27, 114.51, 126.02, 130.21, 157.92, 172.08; Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.17 %.

3-(2,3-dimethylphenoxy)propan-1-ol 47

Yield: 3.49 g (97 %); Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.08 (pent, 2H), 2.16 (s, 3 H), 2.29 (s, 3H), 3.89 (t, *J*=6 Hz, 2H), 4.11 (t, *J*=6 Hz, 2H), 6.71 (d, *J*=7 Hz, 1H), 6.78 (d, *J*=7 Hz, 1H), 7.04 (t, *J*=8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 11.78, 20.20, 32.26, 60.79, 66.11, 108.90, 122.57, 124.94, 125.89, 137.77, 156.69; Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.27; H, 8.97 %.

Preparation of 2-(Aryloxy) propanals (40, **41**, **42**, **43)**

To a solution of alcohol **44**/**45**/**46**/**47** (15 mmol) in dimethyl sulfoxide (15 mL) was added 2-iodoxy benzoic acid (IBX) (4.9g, 17.5 mmol) and stirring the reaction mixture for 3-8 h at room tempreture. The completion of reaction was monitored by TLC. After

the completion of the reaction, the reaction mixture was diluted with water (10 mL), and then with ethyl acetate (100 mL) and filter through bed of celite. The filtrate was washed with water (2*50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated under the reduced pressure. The residue obtained was purified using ethyl acetate-petroleum ether as eluent by column chromatography over silica gel (60-120 mesh), to yield 2-(Aryloxy) propanals **(40, 41, 42, 43)**

3-(3, 4, 5-trimethoxyphenoxy)propanal 40

Yield: 3.24 g (90 %); Colorless liquid; bp 149-152 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.76-2.82 (m, 2H), 3.77 (s, 3H), 3.84 (s, 6H), 4.02 (t, *J*=6.06 Hz, 2H), 6.88 (s, 2H), 9.86 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 44.11, 56.01, 65.43, 124.16, 128.58, 130.66, 155.36, 199.81; Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.06; H, 6.68 %.

Methyl 3-(4-(3-oxopropoxy)phenyl)propanoate 41

Yield: 3.28 g (92 %); Colorless liquid; bp 187-189 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.59 (t, *J*=8 Hz, 2H), 2.86-2.93 (m, 4H), 3.67 (s, 3H), 4.29 (t, *J*=6 Hz, 2H), 6.71-6.84 (m, 2H), 7.03-7.13 (m, 2H), 9.87 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 30.12, 35.97, 36.08, 43.25, 51.58, 61.58, 114.55, 115.36, 129.30, 154.47, 173.28, 199.84; Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.13; H, 6.79 %.

Methyl 2-(4-(3-oxopropoxy)phenyl)acetate 42

Yield: 2.96 g (89 %); Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.89 (tt, *J*=1 Hz, 2H), 3.58 (s, 2H), 3.72 (s, 3H), 4.32 (t, *J*=6 Hz, 2H), 6.86 (dd, *J*=2 Hz, 2H), 7.19 (dd, *J*=2 Hz, 2H), 9.89 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 40.20, 43.14, 51.86, 61.53, 114.56, 126.49, 130.30, 157.51, 171.98, 199.43; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35.

Found: C, 64.83; H, 6.39 %.

3-(2, 3-dimethylphenoxy)propanal 43

Yield: 2.40 g (90 %); Colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.13 (s, 3 H), 2.29 (s, 3H), 2.91 (tt, *J*=6 Hz, 2H), 4.31(t, *J*=6 Hz, 2H), 6.71 (d, *J*=7 Hz, 1H), 6.80 (d, *J*=7 Hz, 1H), 7.05 (t, *J*=8 Hz, 1H), 9.90 (t, *J*=2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 11.62, 20.13, 43.43, 62.04, 108.98, 112.56, 122.87, 125.83, 137.91, 156.27, 199.83; Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 7.93 %.

Preparation of 3-(aryl) propane-1, 2-diol (38, 23, 39, 34)

To a solution of aldehyde **40**/**41**/**42**/**43** (10 mmol) and L-proline (230 mg, 2 mmol) in an acetonitrile (40 mL) solvent at -20 ^oC, nitrosobenzene (1.1g, 10 mmol) was added portion wise and the reaction mixture was stirred at the same temperature for 20 h. To this reaction mixture, MeOH (20 mL) and $NaBH_4$ (212 mg, 5.6 mmol) was added and stirring was continued for 1 h. After addition of water (10 mL) to the reaction mixture, the resulting reaction mixture was extracted with ethyl acetate (3*50 mL) and an organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under the reduced pressure, afforded crud aminoxy alcohol. To this crude aminoxy alcohol in a MeOH solvent, 10 % Pd/C (50 mg) was added under the hydrogen atmosphere and stirred at room tempreture for 14 h. The completion of reaction was checked by TLC, the reaction mixture was filtered through a celite pad and concentrated to afford the crude product, which was purified using ethyl acetate-petroleum ether as eluent over the column chromatography using silica gel (60-120 mesh), gives chiral diol **38, 23, 39, 34**.

(*S*)-3-(3, 4, 5-trimethoxyphenoxy)propane-1,2-diol 38

Yield: 1.88 g (73 %); semi solid; $[\alpha]_D^{25}$= +3.7 (c 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 3.17, (s, 2H), 3.84 (s, 9H), 3.95-4.00 (m, 2H), 4.10 (d, *J*=5.6 Hz, 2H), 4.17-4.23 (m, 1H), 6.17(s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 56.01, 60.17, 60.92, 65.88, 92.33, 132.49, 153.70, 155.42; Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03. Found: C, 55.83; H, 7.00 %.

(*S*)-methyl 3-(4-(2,3-dihydroxypropoxy)phenyl)propanoate 23

Yield: 1.95 g (77 %); Colorless liquid; $[\alpha]_D^{25}$= +4.8 (c 1, $CHCl_3$) (lit.[28] $[\alpha]_D^{25}$= +4.6 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.65 (dd, *J*=2 Hz, 1H), 2.80 (dd, *J*=4 Hz, 1H), 3.44-3.47 (m, 1H), 3.95 (s, 2H), 3.97 (s, 3H), 4.08 (dd, *J*=5 Hz, 1H), 4.11 (dd, *J*=3 Hz, 1H), 6.85 (dd, *J*=2 Hz, 2H), 7.15 (dd, *J*=2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 29.36, 29.48, 62.73, 64.99, 66.71, 68.84, 69.27, 69.85, 114.15, 128.88, 128.93, 132.37, 132.78, 156.73, 171.88, 173.61; Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.38; H, 7.15 %.

(*S*)-methyl 2-(4-(2, 3-dihydroxypropoxy)phenyl)acetate 39

Yield: 1.77 g (74 %); Colorless liquid; $[\alpha]_D^{25}$= +6.9 (c 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 3.45 (t, *J*=5.8 Hz, 3H), 3.62 (s, 3H), 3.77-3.89 (m, 2H), 3.98-4.03 (m, 2H), 4.83 (s, 2H), 6.89 (dd, *J*=7 Hz, 2H), 7.17 (d, *J*=8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 51.68, 62.78, 69.60, 70.00, 114.24, 114.37, 126.21, 127.11, 130.40, 157.53, 171.98, 173.22; Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.96; H, 6.76 %.

(*S*)-3-(2, 3-dimethylphenoxy)propane-1,2-diol 34

Yield: 1.33 g (68 %); Colorless solid; mp 103-105 ^oC (lit.[22] 104-105 ^oC) $[\alpha]_D^{25}$= +6.16 (c 1, $CHCl_3$) (Lit.[22] $[\alpha]_D^{25}$= +4.25 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.15 (s, 3 H), 2.27 (s, 3H), 2.93 (s, 2H), 3.76-3.89 (m, 2H), 4.01 (d, *J*=6 Hz, 2H), 4.09-4.12 (m,

1H), 6.70 (d, *J*=7 Hz, 1H), 6.76 (d, *J*=7 Hz, 1H), 7.06 (t, *J*=8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 11.74, 20.14, 63.85, 69.41, 70.70, 109.18, 122.94, 125.08, 125.95, 137.89, 156.29; Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.19 %.

Preparation of 3-(aryl) propane- oxirane/(epoxide) (10, 20, 37, 36)

To a stirred solution of chiral diol **38**/**23**/**39**/**34** (5 mmol) in anhydrous 1, 4 dioxane (20 mL) solvent, PPh_3 (2 g, 7.5 mmol) was added and stirred for 10 min. To this reaction mixture diisopropyl azodicarboxylate (1.3 g, 7.65 mmol) in 15 mL of 1, 4-dioxane was added drop wise at room temperature. The resulting reaction mixture was stirred at 80 ^oC up to the completion of reaction, which was monitored by TLC (4-8 h). After the completion of reaction, the reaction mixture was diluted and washed with water. The organic layer was dried over sodium sulphate, filtered, and evaporated under the reduced pressure to afford the residue. The crud residue was purified using ethyl acetate-petroleum ether as eluent over the column chromatography using silica gel (60-120 mesh), gives oxirane **10, 20, 37, 36**

(*S*)-2-((3, 4, 5-trimethoxyphenoxy)methyl)oxirane 10

Yield: 960 mg (80 %); Colorless liquid; $[\alpha]_D^{25}$= +3.5 (c 1, $CHCl_3$) (lit.[16] $[\alpha]_D^{21}$= +3.5 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.76 (dd, *J*=2 Hz, 1H), 2.91 (dd, *J*=4 Hz, 1H), 2.93-2.95 (m, 1H), 3.79 (s, 3H), 3.84 (s, 6H), 3.91 (dd, *J*=3 Hz, 1H), 4.19 (dd, *J*=3 Hz, 1 H), 6.18 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 44.68, 50.15, 56.07, 61.00, 69.29, 92.47, 132.60, 153.68, 155.08; Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.02; H, 6.72 %.

(*S*)-methyl 3-(4-(oxirane-2-ylmethoxy)phenyl)propanoate 20

Yield: 1.03 g (88 %); Colorless liquid; $[\alpha]_D^{25}$= +4.6 (c 1, $CHCl_3$) (lit.[18] $[\alpha]_D^{25}$= +4.42 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.61 (t, *J*=8 Hz, 2H), 2.76 (dd, *J*=2 Hz, 1H), 2.87-2.95 (m, 3H), 3.34-3.37 (m, 1H), 3.69 (s, 1H), 3.97 (dd, *J*=3 Hz, 1H), 4.17 (dd, *J*=3 Hz, 1H), 6.83-6.88 (m, 2H), 7.12 (d, *J*=8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 30.11, 35.94, 44.68, 50.09, 51.53, 68.75, 114.67, 129.27, 133.14, 157.00, 173.20; Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.05; H, 6.87 %.

(*S*)-methyl 2-(4-(oxirane-2-ylmethoxy)phenyl)acetate 37

Yield: 910 mg (82 %); Colorless liquid; $[\alpha]_D^{25}$= +5.6 (c 1, $CHCl_3$) (lit.[27] $[\alpha]_D^{25}$= +5.7 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.76 (dd, *J*=2 Hz, 1H), 2.89 (dd, *J*=4 Hz, 1H), 3.25-3.33 (m, 1H), 3.52 (s, 2H), 3.66 (s, 3H), 3.98 (dd, *J*=5 Hz, 1H), 4.16 (dd, *J*=3 Hz, 1H), 6.90 (dd, *J*=2 Hz, 2H), 7.19 (dd, *J*=2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 40.20, 44.54, 49.96, 51.84, 68.70, 114.69, 115.43, 126.53, 130.28, 157.60, 171.96; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.84; H, 6.37%.

(*S*)-2-((2,3-dimethylphenoxy)methyl)oxirane 36

Yield: 700 mg (80 %); Colorless liquid; $[\alpha]_D^{25}$= -10.42 (c 2.6, $CHCl_3$) (lit.[22] $[\alpha]_D^{25}$= -6.52 (c 2.3, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.20 (s, 3H), 2.30 (s, 3H), 2.80 (dd, *J*=2 Hz, 1H), 2.91-2.93 (m, 1H), 3.94-4.02 (m, 1H), 4.16 (dd, *J*=5 Hz, 1H), 4.21 (dd, *J*=3 Hz, 1H), 6.71 (d, *J*=8 Hz, 1H), 6.82 (d, *J*=7 Hz, 1H), 7.04 (t, *J*=8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 11.74, 20.16, 44.61, 50.26, 68.99, 109.23, 122.89, 125.40, 125.81, 137.91, 156.42; Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 7.89%.

Preparation of (*S*)-Enciprazine 2

To the solution of an epoxide **10** (720 mg, 3 mmol) in anhyd *i*-PrOH (10 mL), 1-(2-methoxyphenyl)piperazine **12** (576 mg, 3 mmol) was added at room temperature. The

resulting reaction mixture was refluxed and monitored by TLC (18 h) for its completion. After the completion of reaction, the solvent was evaporated under the reduced pressure to obtain crude residue as product. The obtained residue was purified by using ethyl acetate-petroleum ether as eluent over the column chromatography using silica gel (60-120 mesh), to furnish (*S*)-Enciprazine **2** in a 95 % yield.

(*S*)-Enciprazine 2

Yield: 1.23 g (95 %); semi solid; $[\alpha]_D^{25}$= +32.16 (c 0.5, EtOH) (lit.[17] $[\alpha]_D^{25}$= +29 (c 05, EtOH for 95 % ee); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 2.74-2.86 (m, 4H), 2.97-3.05 (m, 2H), 3.17 (t, *J*=4 Hz, 4H), 3.78 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 3.95 (t, *J*=5 Hz, 2H), 4.10-4.23 (m, 1H), 6.17 (s, 2H), 6.83-6.99 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 50.04, 53.69, 55.35, 56.04, 60.92, 65.17, 70.43, 92.43, 111.26, 118.35, 121.12, 123.36, 140.63, 152.20, 153.72, 155.20; Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.87; H, 7.46; N, 6.48. Found: C, 63.84; H, 7.42; N, 6.51 %.

Preparation of (*S*)-Esmolol 3, (*S*)-Atenolol 4 and (*S*)-Xibenolol 5

The chiral epoxide **20**/**37**/**36** (2 mmol) was dissolved in an appropriate amines (10 mL). The resulting reaction mixture was refluxed in the presence of catalytic amount of water (0.2 mL) for 6-7 h. The completion of reaction was monitored by TLC. After the completion of reaction, excess of amine was removed under reduced pressure to afford **3**, **54** and **5** as a residue. The obtained residue was purified using ethyl acetate-petroleum ether as eluent over the column chromatography using silica gel (60-120 mesh), to obtain the pure product **3**, **5**.

(*S*)-Atenolol **4** was synthesis by adding crud **54** in the mixture of MeOH (20 mL) and NH_4OH (10 mL). The resulting reaction mixture was stirred for 24 h at room

temperatures. The completion of reaction was monitored by TLC. After the completion of reaction, reaction mixture was concentrated under the reduced pressure and the crude product was purified by using methanol-dichloromethane as eluent over the column chromatography using silica gel (60-120 mesh) to obtain the pure (*S*)-Atenolol **4**.

(*S*)-Esmolol 3

Yield: 455 mg (81 %); white solid; $[\alpha]_D^{25}$= +4.7 (c 1, $CHCl_3$) (lit.[18] $[\alpha]_D^{25}$= +4.5 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.17 (d, *J*=8 Hz, 6H), 2.57 (t, *J*=7 Hz, 2H), 2.84-3.02 (m, 4H), 3.65 (s, 3H), 3.75 (s, 1H), 3.92-3.97 (m, 2H), 4.02-4.17 (m, 1H), 6.78-6.84 (m, 2H), 7.06-7.11 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 18.91, 19.10, 30.07, 35.88, 51.49, 65.65, 69.61, 114.59, 129.27, 133.22, 156.75, 173.06; Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.08; H, 8.52; N, 4.80 %.

(*S*)-Atenolol 4

Yield: 372 mg (75 %); white solid; mp 152-153 ^oC (lit.[27] 148-150 ^oC) $[\alpha]_D^{25}$= -17.1 (c 1, 1N HCl) (Lit.[27] $[\alpha]_D^{25}$= -17 (c 1, 1N HCl); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.01 (d, *J*=6 Hz, 6H), 2.51-2.81 (m, 3H), 3.29 (s, 2H), 3.89 (t, *J*=9 Hz, 3H), 4.31-4.54 (s, 3H), 6.84 (d, *J*=8 Hz, 2H), 7.18 (d, *J*=8 Hz, 2H), 7.40 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 21.95, 22.06, 48.47, 49.44, 67.67, 70.65, 114.22, 128.48, 130.00, 157.23, 172.61; Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.06; H, 8.32; N, 10.48%.

(*S*)-Xibenolol 5

Yield: 515 mg (98 %); white sticky solid; $[\alpha]_D^{25}$= -25.81 (c 1, $CHCl_3$) (lit.[29] $[\alpha]_D^{25}$= -25.4 (c 1, $CHCl_3$)); **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 1.26 (s, 9H), 2.14 (s, 3H), 2.27 (s, 3H), 2.85 (dd, *J*=8 Hz, 1H), 3.01 (dd, *J*=3 Hz, 1H), 3.91 (dd, *J*=6 Hz, 1H), 4.19 (dd, *J*=5 Hz, 1H), 4.60 (s, 2H), 6.66 (d, *J*=8 Hz, 1H), 6.74 (d, *J*=7 Hz, 1H), 7.02 (t, *J*=8 Hz, 1H); **^{13}C**

NMR (50 MHz, $CDCl_3$): **δ** 11.78, 20.14, 26.43, 45.51, 55.58, 66.31, 70.20, 109.07, 122.84, 124.94, 125.97, 137.78, 156.28; Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.71; H, 10.07; N, 5.49 %.

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Chapter III

Synthetic methodologies in the presence of silica supported dodecatungstophosphoric acid (DTP/SiO_2)

i) "Highly efficient one-pot multi-component synthesis of α-aminophosphonates and bis-α-aminophosphonates catalyzed by heterogeneous reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) at ambient temperatire and their antitubercular evaluation against *Mycobactrium* Tuberculosis" Shafeek A. R. Mulla, Mohsinkhan Y. Pathan, Santosh S. Chavan, Suwarna P. Gample and Dhiman Sarkar. ***RSC Adv*. 2014, *4*, 7666-7672.**

ii) "A novel and efficient synthesis of azaarene-substituted 3-hydroxy-2-oxindoles via sp^3 C-H functionalization of 2-methyl azaarens and (2-azaaryl)methanes over a heterogeneous, reusable silica-supported dodecatungstophosphoric acid catalyst" Shafeek A. R. Mulla, Mohsinkhan Y. Pathan, Santosh S. Chavan. ***RSC Adv*. 2013, *3*, 20281-20286.**

Section-I

Highly efficient heterogeneous reusable silica supported dodecatungstophosphoric acid catalyzed one-pot multi-component synthesis of α -aminophosphonates and bis-α –aminophosphonates and their bioevaluation

3.1.1 Introduction

The synthesis of α-aminophosphonates has become the center of interest among world researchers due to their wide spectrum of biological and/ or medicinal activities and structural analogy to natural α-amino acids and α-aminophosphoric acids. They have achieved a significant importance as a key moieties having wide applications not only in agriculture but also in the biological/ medicinal chemistry, as anti-cancer agents,[1a-1c] inhibitors of synthase,[1d] HIV protease,[1e] antibiotics,[1f] enzyme inhibitors,[1g] anti-thrombotic agents,[1h] cytotoxicity,[1c] antibacterial activity,[1i] antifungal activity,[1j] antiproliferative activity,[1j] inhibitors of protein tyrosine phosphatases,[1k] herbicides, fungicides,[1l] insecticides,[1m] plant growth regulators,[1n] and as substrates in the synthesis of phosphonopeptides. Owing to the potential importance of α-aminophosphonate derivatives as a key moieties in life sciences, pharmaceuticals, agriculture, the world-wide efforts have made in the last few decades by researchers and various protocol have been developed for their synthesis using various catalysts such as $SnCl_4$,[2] $SnCl_2$,[3] $ZnCl_2$,[4] $BF_3.OEt_2$,[5] $InCl_3$,[6] $Mg(ClO_4)_2$,[7] $M(OTf)_3$,[8] $AlCl_3$,[9] CF_3CO_2H,[10] Montmorillonite Clay-MW,[11] TiO_2,[12] scandium (tris-dodecyl sulfate),[13] I_2,[14] Nano Fe_3O_4,[15] EAN,[16] H-beta zeolite,[17] Nano ZnO,[18] AIKIT-5,[19] $ZrOCl_2.8H_2O$,[20] $SbCl_3/Al_2O_3$[21] and Amberlyst-15,[22]

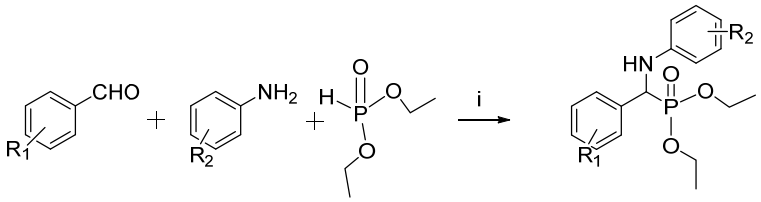
which have been reported in the literature.

3.1.2 Review of literature

Literature survey revels that, there are several methods available for the synthesis of α-aminophosphonates from the reaction of various substituted aldehydes, amines with di or trialkyl phosphite in the presence of various catalyst and solvent at different reaction conditions, however, few of them are described below.

Pawar approach[16]

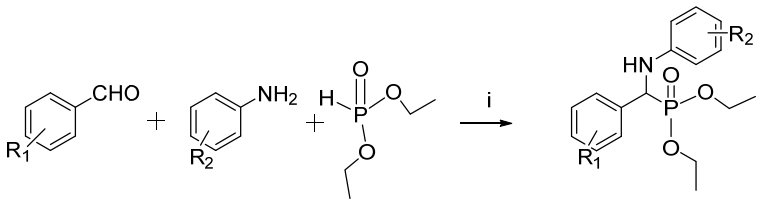
In this approach, Pawar *et al.* have treated various aromatic aldehydes and various aromatic amines with diethyl phosphite in ethylammonium nitrate ionic liquid at room temperature (**Scheme 1**).



Scheme 1: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), amine (1 mmol), diethyl phosphite (1 mmol), ethylammonium nitrate (2 mL), RT.

Reddy approach[15]

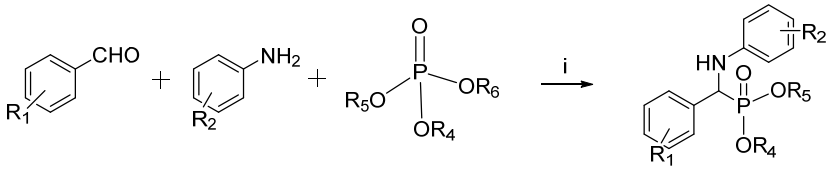
In this approach, Reddy *et al.* have treated various aromatic aldehydes and various aromatic amines with diethyl phosphite using Nano-Fe_3O_4 as a catalyst at 50 ^oC under neat reaction condition (**Scheme 2**).



Scheme 2: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), amine (1 mmol), diethyl phosphite (1.2 mmol), nano-Fe_3O_4 (0.05 mmol) at 50 ^oC.

Chakraborti approach[7]

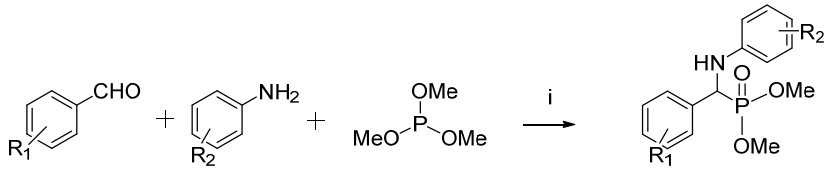
In this approach, Chakraborti *et al.* have treated various aromatic aldehydes and various aromatic amines with di or trialkyl phosphite in the presence of magnesium perchlorate as a catalyst at room temperature or 80 ^{o}C under neat reaction condition (**Scheme 3**).



Scheme 3: *Reagents and reaction conditions*: (i) Aldehyde (2.5 mmol), amine (2.5 mmol), di or tri alkyl phosphite (2.5 mmol), $Mg(ClO_4)_2$ (5 mol %) at RT-80 ^{o}C.

Tajbakhsh approach[22]

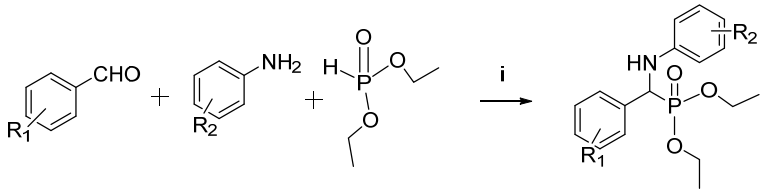
In this approach, Tajbakhsh *et al.* have treated various aromatic aldehyde and various aromatic amines with trimethyl phosphite using Amberlyst-15 as a catalyst in an acetonitrile solvent at room temperature (**Scheme 4**).



Scheme 4: *Reagents and reaction conditions*: (i) Aldehyde (2 mmol), amine (2.2 mmol), trimethyl phosphite (2.2 mmol), amberlite-15 (0.2 g), acetonitrile (4 mL) at RT.

Hosseini-Sarvari approach[12]

In this approach, Hosseini-Sarvari *et al.* have treated various aromatic aldehydes and various aromatic amines with diethyl phosphite using TiO_2 as a catalyst at 50 ^{o}C under the neat reaction condition (**Scheme 5**).



Scheme 5: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), amine (1 mmol), diethyl phosphite (1 mmol), TiO_2 (20 mol %), at 50 ^oC.

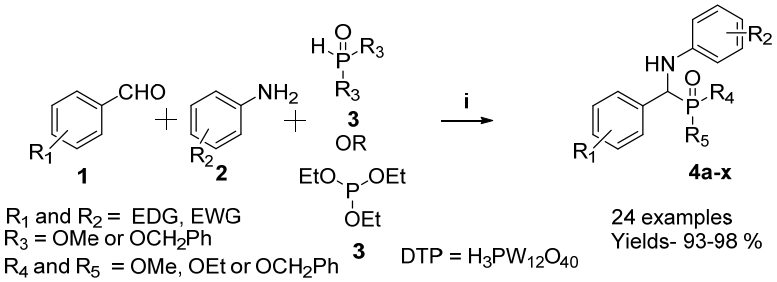
3.1.3 Present Work

3.1.3.1 Objectives

Even though significant improvements and/ or developments using either homogeneous or heterogeneous catalysts have been achieved, almost all of the methods reported in the literature so far lack of general applicability and commercial scale implementation, and suffer from one or more limitations such as the use of excess or stoichiometric quantity, moisture sensitive, toxic, corrosive, expensive catalysts, which are non-recoverable and/ or recoverable with tedious separation procedure involving lots of toxic waste generation besides a long reaction time, high temperature and low yield for the desired product.

As α-aminophosphonate derivatives are the key constituent and the structural backbone of many pharmaceutical and agricultural compounds, the development of more general and cost effective, one-pot multi-component protocols for their synthesis under much milder, more efficient, environment friendly conditions using recyclable, eco friendly catalysts is still a possibility to explore. Therefore, this section describes highly efficient, cost effective, general, and much milder one-pot multi-component protocol for the synthesis of α-aminophosphonates and bis-α–aminophosphonates derivatives in excellent yields via one-pot three component condensation of various aldehydes, amines and di or tri alkyl phosphites using a heterogeneous reusable silica supported

dodecatungstophosphoric acid catalyst at ambient temperature in a short reaction time (**Scheme 6**).



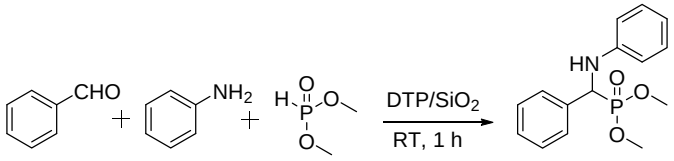
Scheme 6: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), amine (1 mmol), di/tri alkyl phosphite (1 mmol), DTP/SiO_2 (50 mg), acetonitrile (5 mL), RT, 1 h.

TB is a chronic infectious disease[23] and a serious threat to the public health worldwide. The world health organization (WHO) declared[24] TB as an international public health crisis and appealed to develop the anti-TB drug or vaccine, which could be licensed by 2020. Even though α-aminophosphonate derivatives, which are constituents of various potent drugs,[1a-1k] and their bioevaluation for anticancer activity are well reported,[1a-1c] surprisingly its antitubercular (TB) activity has not reported so far. Therefore, herein we report for first time the preliminary results on the antitubercular activity of α-aminophosphonate derivatives against *Mycobactrium Tuberculosis* H37Ra (MTB) strain.

3.1.4 Results and discussion

To develop a one-pot multi-component protocol for synthesis of α-aminophosphonate derivatives, benzaldehyde (10 mmol), aniline (10 mmol), and dimethylphosphite (10 mmol), catalyzed by 50 mg (0.35 mol %) 20 % DTP/SiO_2 catalyst in a 5 mL solvent at ambient temperature for 1 h was selected as a model reaction to optimized the reaction conditions.

Table 1: Optimizations of reaction conditions for the synthesis of α–aminophosphonate[a]



Entry	Solvent	Catalyst	Yield (%)[b]
1	Methanol	DTP/SiO_2	74
2	Ethanol	DTP/SiO_2	78
3	Dichloromethane	DTP/SiO_2	40
4	Acetonitrile	DTP/SiO_2	98
5	Dimethylformamide	DTP/SiO_2	N.R.
6	Water	DTP/SiO_2	N.R.
7	Acetonitrile	-	N.R.
8	Acetonitrile	DTP/SiO_2 (25 mg)	84
9	Acetonitrile	DTP/SiO_2 (100 mg)	98
10[c]	Acetonitrile	10 % DTP/SiO_2	76
11[d]	Acetonitrile	30 % DTP/SiO_2	98

[a]Reaction condition: Benzaldehyde (10 mmol), aniline (10 mmol), dimethylphosphite (10 mmol), catalyst 20 % DTP/SiO_2: 25-100 mg (0.18- 0.7 mol % of DTP) in 5 mL solvent, room temperature 1 h.

[b]Isolated yields after column chromatography.

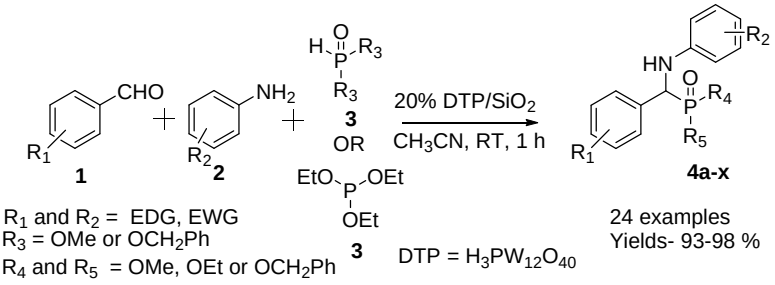
[c]50 mg = 0.17mol %; [d]50 mg = 0.52 mol %.

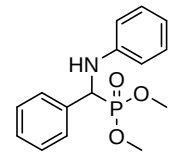
Initially, the screening of different solvents such as methanol, ethanol, dichloromethane, acetonitrile, dimethylformamide and water were performed. However, the acetonitrile solvent gives the desired α-aminophosphonate product in a 98 % yield (**Table 1**, entry **4**) whereas methanol, ethanol, and dichloromethane gives 74 %, 78 %, and 40 % yields, respectively (**Table 1**, entries **1-3**). The formation of the desired product was not observed using dimethylformamide or water as the solvent (**Table 1**, entry **5** and **6**) and also in the absence of catalyst in an acetonitrile solvent (**Table1**, entry **7**). The promising results using an acetonitrile as a solvent over DTP/SiO_2 catalyst allowed us to further optimize the DTP loading and catalyst loading, and the results in **Table 1** (entry **8-11**)

reveals that the catalyst with 20 % DTP loading and 50 mg catalyst shows excellent catalytic activity (**Table 1**, entry **4**). The excellent yield, using 20 % DTP/SiO_2 in an acetonitrile solvent, motivated us to investigate the scope of the one-pot multi-component protocol for the synthesis of the α-aminophosphonates and bis-α–aminophosphonates derivatives from various substituted aldehydes, amines and di or tri alkyl phosphites in the presence of DTP/SiO_2 catalyst at optimized reaction conditions. To establish the general applicability, a variety of substituted aldehydes, substituted amines and di/tri alkyl phosphites were subjected for a three-component condensation (Kabachnik-Fields) reaction. Interestingly, a wide range of aryl/heteroaromatics aldehydes, and amines possessing various electron donating and electron withdrawing functional groups reacted smoothly with di or tri alkyl phosphites over a DTP/SiO_2 catalyst at ambient temperature for 1 h to give the desired products in excellent yields (**Table 2**, entries **4a-x**).

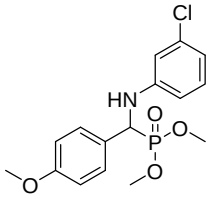
The aromatic/heteroaromatics aldehydes such as benzaldehyde, 4-methoxy benzaldehyde, 4-chloro benzaldehyde, 4-methyl benzaldehyde, 2, 5-dimethoxy benzaldehyde, and furfural reacted well with aniline/ 3-chloroaniline/ 2, 4, 6- trimethylaniline/ 1-naphthylamine/ 4-nitroaniline/ 4-methoxyaniline, and dimethylphosphite to produce the corresponding α-aminophosphate in excellent yields (**Table 2**, entries **4a-o**). To further elaborate the scope of one-pot multi component protocol over a DTP/SiO_2 catalyst, the substituted aromatic amines such as aniline, 3-chroloaniline and 1-naphthylamine reacted smoothly with benzaldehyde/ 3, 4, 5- trimethoxybenzaldehyde/ 4-chloro benzaldehyde/ 4-methylbenzaldehyde/ 4-methoxy benzaldehyde, and dibenzylphosphite/ triethylphosphite to obtain the corresponding α-aminophosphonate in an excellent yields (**Table 2**, entries **4p-u**).

Table 2: Substrate scope for one-pot three-component condensation reaction for the synthesis of α-aminophosphonate derivatives[a, b]

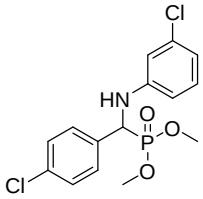




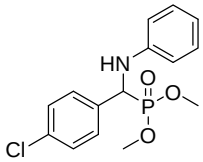
4a 98%



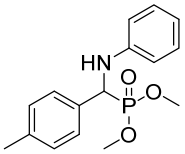
4b 98%
12.8[f]



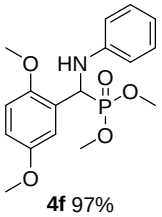
4c 97%
8.7[e]



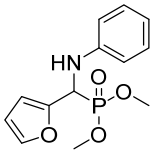
4d 98%



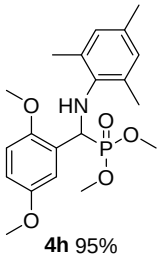
4e 98%



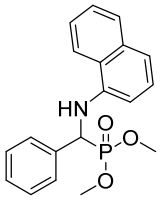
4f 97%



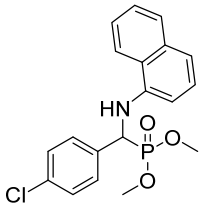
4g 97%



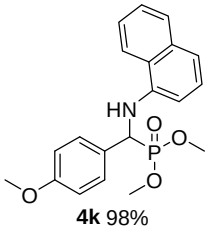
4h 95%



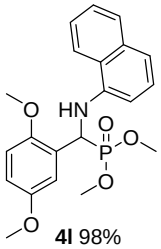
4i 98%



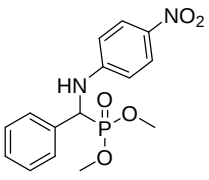
4j 97%



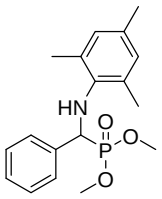
4k 98%



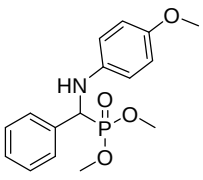
4l 98%



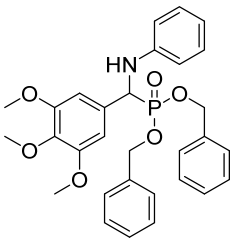
4m 95%



4n 97%
8.62[d]

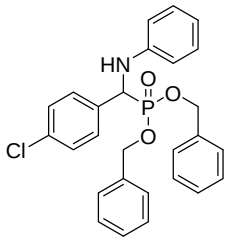


4o 98%



4p 93%
19[e]

Table 2 (*continued*)



4q 96%
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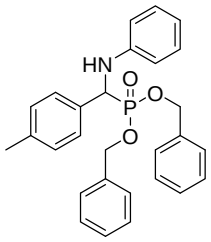
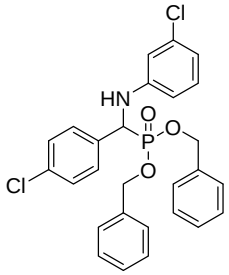
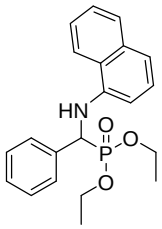


4r 95%
11.8[e]



4s 96%
18.3[e]



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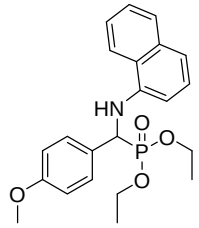

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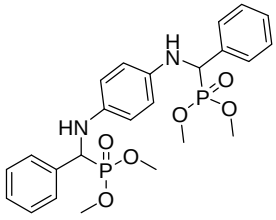
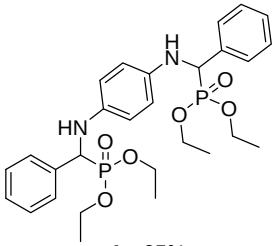
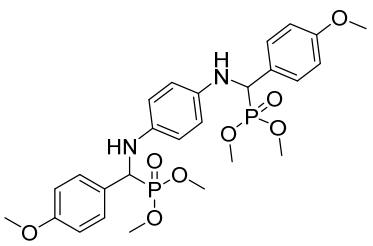


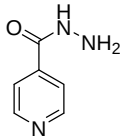
4v 96%
7.51[d]



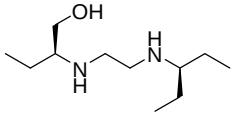
4w 95%



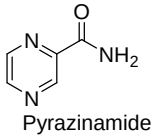
4x 96%



Isoniazid
4y 0.125[c]



Ethambutol
4z 0.8[c]



Pyrazinamide
4aa >10[c]

[a]Reaction conditions: Aldehyde (10 mmol), amine (10 mmol), phosphite (10 mmol), DTP/SiO_2 (50 mg) in 5 mL CH_3CN , room temperature 1 h.

[b]Isolated yields after column chromatography.

[c]IC_{90} for stander drugs.

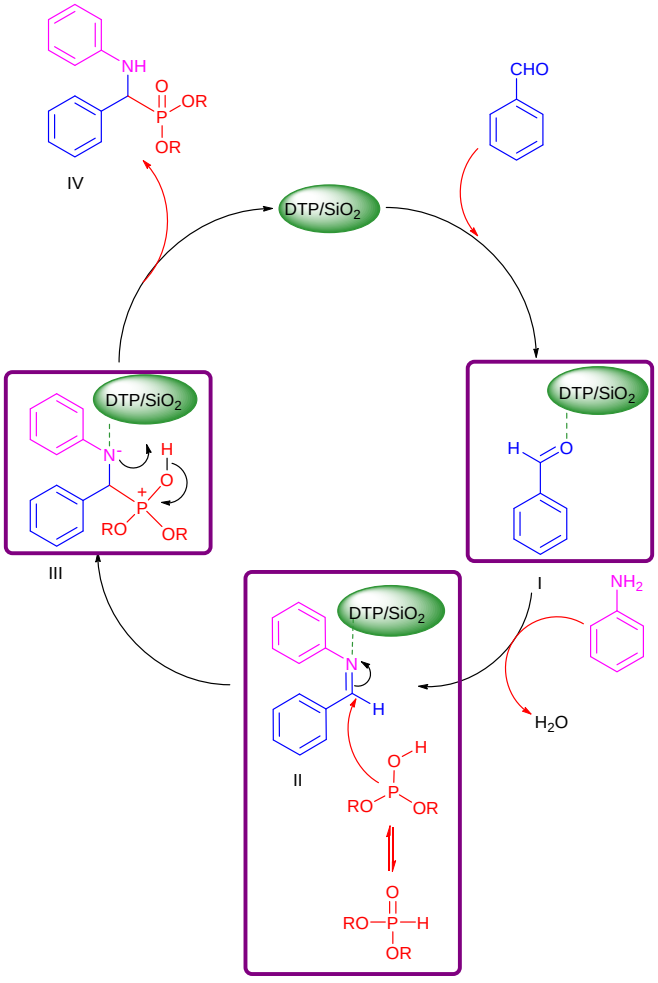
[d]IC_{50} against M. tuberculosis H37Ra for antitubercular activity.

[e]IC_{50} against THP 1 cell line for cytotoxicity.

The excellent performance of the DTP/SiO_2 catalyst for the synthesis of α-aminophosphonate derivatives from the various combinations of aryl/heteroaromatics aldehydes/ substituted aldehydes, amines/substituted amines and di or tri alkyl phosphites made us excited to investigate the dimer formation of α–aminophosphonates. Amazingly, benzaldehyde/4-methoxy benzaldehyde (20 mmol) reacted very well with dimethyl phosphite/ triethylphosphite (20 mmol) and 4-amino aniline (10 mmol) to

provide the corresponding bis-α–aminophosphonate as a dimer in a high yield (**Table 2** entries **4v-x**). The results in the **Table 2** clearly reveal that the one-pot three-component condensation reactions over the DTP/SiO_2 catalyst shows a remarkable and excellent performance irrespective to the presence of an electron donating/ electron withdrawing groups on the aromatic/ heterocyclic aldehydes and /or amines and hence the one-pot three-component protocol is highly effective, promising, and general for the synthesis of α-aminophosphonate and bis- α–aminophosphonate derivatives.

A per earlier literature[3] a probable mechanism is shown in **Scheme 7** for the synthesis of

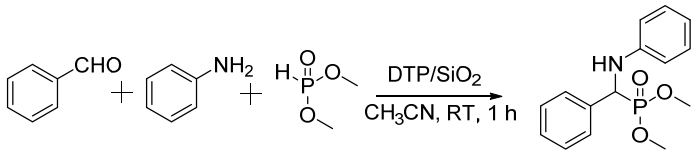


Scheme 7: A possible mechanism for the synthesis of α- aminophosphonates over a DTP/SiO_2 catalyst

α-aminophosphonate. The mechanism involves the activation of the carbonyl group of aldehyde by DTP/SiO_2 (**I**) followed by the nucleophilic addition of amine to afford the imine (**II**) by the removal of water. The subsequent activation of imine (**II**) by DTP/SiO_2 facilitated the addition of phosphite to give an activated phosphonium intermediate (**III**), which then gave the desired product **IV** (**Scheme 7**).

The recyclability and recovery of the DTP/SiO_2 catalyst was investigated for the synthesis of α–aminophosphonates by a one-pot three-component condensation of benzaldehyde and aniline with dimethyl phosphite as a model substrate in an acetonitrile solvent at room temperature for 1 h, and the results are provided in **Table 3**. The DTP/SiO_2 catalyst was recovered quantitatively from reaction mixture by filtration and reused several times without the loss of catalytic activity (**Table 3**, entries **2-6**).

Table 3: The recyclability of a DTP/SiO_2[a]



Cycles	Yield (%)[b]
1	98
2	98
3	97
4	98
5	96
6	97

[a]Reaction conditions: Benzaldehyde (10 mmol), aniline (10 mmol), dimethylphosphite (10 mmol), 20 % DTP/SiO_2 in 5 mL CH_3CN , room temperature, 1 h.

[b]Isolated yields after column chromatography.

The isolated yield obtained for the product at the end of 5th recycle (**Table 3**, entry **6**) is very much consistent with the fresh DTP/SiO_2 catalyst (**Table 3**, entry **1**). The consistent

catalytic activity of the recovered and reused DTP/SiO_2 catalyst indicates that the reused catalyst shows an excellent performance for the synthesis of α–aminophosphonates.

All of the synthesized α-aminophosphonates and bis-α-aminophosphonate derivatives (**4a-x**) were screened using 100 µg/mL concentrations for their in vitro antitubercular activity against the *M. tuberculosis* H37Ra (ATCC 25177) strain by XTT reduction menadione assay. As shown in the **Fig. 1**, the **4e**, **4f**, **4g**, **4i**, **4j**, **4n**, **4o** and **4v** α–aminophosphonate derivatives were exhibited inhibition. However, only **4n** and **4v** derivatives exhibited more than 90 % inhibition, and they were further screened using various concentrations for their *in vitro* antitubercular activity to achieve IC_{50}, which is compared with standard drugs such as isoniazid, ethambutol and pyrazinamide (**Table 2**, entry **4y-aa**). The **4n** and **4v** α–aminophosphonate derivatives exhibited half maximal

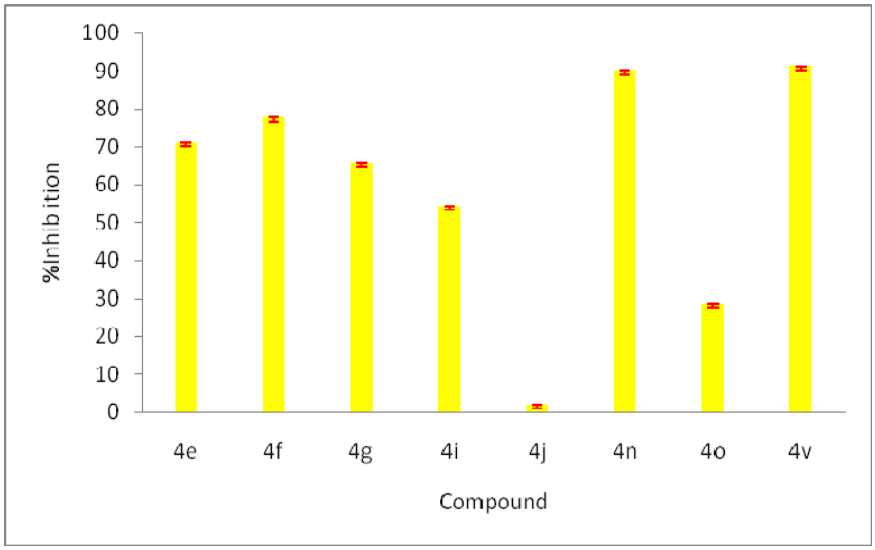


Fig. 1: Analysis of antitubercular activity of compounds by using XTT Reduction menadione assay. The 100 µg/ml compounds were added in 2 M. tuberculosis culture at 0 day after inoculation. Cells growth was estimated by monitoring the extent of XTT reduction after 8 day of incubation with respect to DMSO vehicle control and media as blank. Percent inhibition of compounds is as shown in graph. Further details are provided in experimental section. The result is average of three identical experiments ± standard deviation.

concentration (IC_{50}) values of 8.62 and 7.51 µg/mL (**Table 2** entry **4n** and **4v**), respectively, which indicate that the compounds are promising antitubercular agents. These findings inspired us to evaluate their cytotoxicity. Hence, all of the α-aminophosphonate derivatives (**4a-x**) were evaluated for their cytotoxicity using a THP 1 (Human acute monocytic leukemia cell line) in *vitro* MTT assay. Surprisingly, the **4n** and **4v** compounds were found to be non active towards cytotoxicity. However, a few compounds **4b**, **4c**, **4p**, **4q**, **4r**, and **4s** (**Table 2**) showed a good cytotoxicity.

The selectiveness of the **4n** and **4v** compounds towards antitubercular activity made us enthusiastic to evaluate these compounds for their antimicrobial activity. The **4n** and **4v** were evaluated for their antimicrobial activity against gram-negative (Escherichia coli) and gram-positive (Staphylococcus aureus and Bacillus) bacteria (**Table 4**). Miraculously, **4n** and **4v** shows no antibacterial activity towards gram-negative and gram-positive bacteria. The evaluation data on cytotoxicity using the THP 1 (Human acute monocytic leukemia) cell line (**Table 2**), antimicrobial activity against gram-positive and gram-negative bacteria (**Table 4**) clearly shows that **4n** and **4v** are highly selective towards antitubercular activity against the *M. tuberculosis* H37Ra (MTB) strain and were found to be promising antitubercular agents for further drug discoveries.

Table 4: The antibacterial screening of **4n** and **4v** against gram-positive and gram-negative bacteria.

Compounds	Concentration (µg/mL)	% Inhibition		
		E. coli	S. aureus	Bacillus
4n	100	0.8	35	87.3
4v	100	10.1	-10.3	2.5

3.1.5 Conclusion

In conclusion, a novel, environment friendly, highly efficient, cost effective, one-pot multi-component protocol has been developed for the efficient synthesis of α–aminophosphonate derivatives in excellent yields via a one-pot three-component condensation of various substituted aldehydes, substituted amines and di or tri alkyl phosphites using an ecofriendly, heterogeneous, reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) catalyst at ambient temperature in a short reaction time. The one-pot multi-component condensation reactions (MCR) over the DTP/SiO_2 catalyst shows a remarkable and excellent performance irrespective of the presence of electron donating/ electron withdrawing groups on the aromatic/ heterocyclic aldehydes and /or amines and hence the one-pot three-component protocol is highly effective, promising and general for the synthesis of α-aminophosphonate and bis-α–aminophosphonate derivatives.

The catalyst was recycled several times without the loss of catalytic activity. These α–aminophosphonate derivatives were evaluated for the first time for the antitubercular activity against M. tuberculosis H37Ra (MTB) strain by using an XTT reduction menadione assay (XRMA) protocol. However, the **4n** and **4v** α-aminophosphonate derivative exhibited half maximal concentration (IC_{50}) values of **8.62** and **7.51** μg/mL, respectively. An evaluation of the data on the cytotoxicity and antimicrobial activity shows that **4n** and **4v** are highly selective towards antitubercular activity against *M. tuberculosis* H37Ra (MTB) strain and were found to be promising antitubercular agents for further drug discoveries.

3.1.6 Experimental Section

3.1.6.1 General Procedure for the preparation of DTP/SiO_2

DTP impregnated SiO_2 (20 % DTP/SiO_2) catalyst was prepared by an incipient wetness technique[25] as follows.

The 2 g of dry dodecatungstophosphoric acid (DTP) was weighed accurately. This was dissolved in 8 mL of methanol. The solution was added in small aliquots of 1 mL each time to the silica with constant stirring with a glass rod properly. The solution was added at time intervals of 2 min. Initially on addition of the DTP solution, silica was in a powdery form but on complete addition it formed a paste. The paste on further kneading for 10 min resulted in a free flowing powder. The performed catalyst was dried at 120 ^oC for removal of water and other occluded volatiles and subsequently calcined at 285 ^oC for 3 h.

3.1.6.2 A typical experimental procedure for synthesis of α-aminophosphonates over the 20 % DTP/SiO_2

The reaction mixture of aldehyde (10 mmol), amine (10 mmol) and di/tri alkyl phosphite (10 mmol) was stirred in a 10 mL round bottom flask containing 5 mL acetonitrile solvent in the presence of 50 mg DTP/SiO_2 catalyst at room temperature for 1 h. The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (10 mL) and the catalyst was recovered by filtration. The filtrate was washed with aqueous $NaHCO_3$ and then with water followed by separation of an aqueous layer and organic layer. The organic layer is dried over anhydrous Na_2SO_4 and concentrate in a vacuum to gives the crude product. The crude product was purified by silica gel column chromatography using a 70:30 ratio

of petroleum ether:ethyl acetate to afford the pure α-amino phosphonate. The products obtained were characterized by NMR

3.1.6.3 Antitubercular testing using XTT Reduction menadione assay protocol

M. *tuberculosis* H37Ra (ATCC 25177) were grown to logarithmic phase ($O.D._{59}$5~1.0) in a defined medium *(M. pheli* medium). The stock culture was maintained at -70 ^{o}C and sub-cultured once in *M. pheli* medium before inoculation into experimental culture. Isoniazid, ethambutol and pyrazinamide were procured from Sigma. Drugs were solubilized in dimethyl sulfoxide (DMSO) and stored in aliquots at -20 °C. XTT sodium salt powder (Sigma) was prepared as a 1.25 mM stock solution in sterile Ix PBS and used immediately. Menadione (Sigma) was always freshly prepared as a 6 mM solution in DMSO before use. Compounds were screened for their inhibitory effect on MTB by following XTT Reduction Menadione Assay (XRMA) protocol published earlier. Briefly, 2.5 μL of these inhibitor solutions were added in a total volume of 250 μL of *M. pheli* medium consisting of 1x 10^6 bacilli. The incubation was terminated on the 8th day for MTB cultures. The XRMA was then carried out to estimate viable cells present in different wells of the assay plate. For that, in all wells of assay plate 200 μM XTT was added as a final concentration and incubated at 37 ^{o}C for 20 minutes. Then 60 μM Menadione was added as a final concentration and incubated at 37 ^{o}C for 40 minutes. The optical density was read on a micro plate reader (Spectramax plus 384 plate reader, Molecular Devices Inc) at 490 nm filter against a blank prepared from cell-free wells. Absorbance given by cells treated with the vehicle alone was taken as 100 % cell growth. All experiments were performed in triplicates and the quantitative value was expressed as the average ± standard deviation and IC_{50} values were calculated from their dose

response curves. For details: Sarkar D., Sing U., *J. Micro. Methods*, **211**, 84, 202.

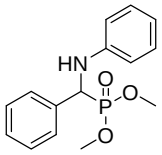
3.1.6.4 Cytotoxicity evaluation using MTT Reduction menadione assay protocol

Cytotoxicity of compounds was tested for their inhibitory effect on THP 1 (Acquired from NCCS). In case of THP 1, cells were grown in RPMI medium. About 10,000 cells were taken per well in 96-well tissue culture plates and treated with different concentrations of test samples for 72 h. Vehicle control [dimethyl sulfoxide (DMSO), 1 %] were run simultaneously. Cell viability was assessed with 10 mL from 5 mg/mL stock solution of tetrazolium salt (MTT) dissolved in cell culture medium and subsequently incubated for additional 1 h at 37 °C, 5 % of CO_2 and 95 % humidity in incubator. The violet colored formazan crystals formed were solubilized in 200 mL of isopropanol and incubated for another 4 h. The optical density was read on a micro plate reader at 49 nm filter against a blank prepared from cell-free wells.

All experiments were carried out in triplicate, and the quantitative value was expressed as the average + standard deviation.

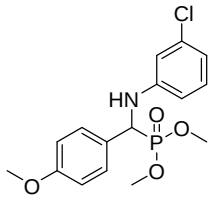
3.1.6.5 Spectral data

Dimethyl phenyl(phenylamino)methylphosphonate (4a)



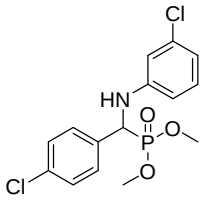
Yield: 98 %; White solid; mp: 91-93 °C; **^{1}H NMR** (200 MHz, Acetone d_6): **δ** 7.37-7.36 (m, 2H), 7.24-7.19 (m, 3H), 6.97-6.93 (m 2H), 6.56-6.45 (m, 3H), 4.80 (br s, 1H), 4.72 (d, *J*=24 Hz, 1H), 3.68 (d, *J*=10 Hz, 3H), 3.34 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, Acetone d_6): **δ** 148.5, 138.1, 130.1, 129.5, 128.8, 118.7, 115.0, 57.4, 54.3.

Dimethyl (((3-chlorophenyl)amino)(4-methoxyphenyl)methylphosphonate (4b)



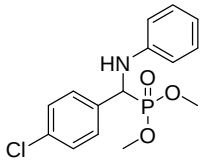
Yield: 98 %; Yellow solid; mp: 92-94 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.45-7.27 (m, 4H), 6.66-6.49 (m, 4H), 4.70 (d, *J*=24 Hz, 1H), 4.25 (br s, 1H), 3.75 (d, *J*=10 Hz, 3H), 3.65 (s, 3H), 3.45 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 153.4, 140.8, 140.4, 136.4, 136.3, 129.2, 128.6, 128.5, 128.4, 115.9, 115.3, 58.7, 55.9, 54.2.; **MALDI TOF/TOF** m/z calcd for $C_{16}H_{19}ClNO_4P$ [M+] 355.07, observed 354.91.

Dimethyl ((4-chlorophenyl)(3-chlorophenyl)amino)methyl)phosphonates (4c)



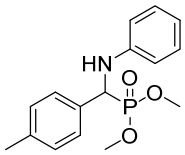
Yield: 97 %; Yellow solid; mp: 134-136 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.41-7.40 (m, 1H), 7.39-7.30 (m, 2H), 7.10-7.05 (m, 2H), 6.70-6.56 (m, 1H), 6.56-6.50 (m, 2H), 4.80 (br s, 1H), 4.69 (s, 1H), 3.78 (d, *J*=10 Hz, 3H), 3.54 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 151.9, 151.7, 137.0, 134.0, 127.6, 127.2, 127.1, 126.9, 124.7, 111.3, 54.9, 52.8, 52.6.

Dimethyl (4-chlorophenyl) (phenylamino)methylphosphonate (4d)



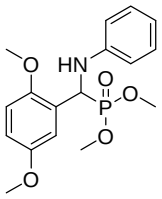
Yield: 98 %; White solid; mp: 112-114 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.42-7.28 (m, 4H), 7.08-7.04 (m, 2H), 6.69 (t, *J*=7.02 Hz, 1H), 6.55-6.50 (m, 2H), 4.78 (br s, 1H), 4.67 (d, *J*=21 Hz, 1H), 3.79 (d, *J*=10 Hz, 3H), 3.55 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 145.9, 134.3, 129.3, 129.2, 129.0, 118.9, 113.9, 56.8, 53.8.

Dimethyl (phenylamino)(p-tolyl)methylphosphonate) (4e)



Yield: 98 %; White solid; mp: 122-124 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.34-7.30 (m, 2H), 7.14-7.03 (m, 4H), 6.69-6.52 (m, 3H), 4.79 (s, 1H), 4.77 (d, *J*=21 Hz, 1H), 3.75 (d, *J*=10 Hz, 3H), 3.45 (*d*, *J*=10 Hz, 3H), 2.32 (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 146.0, 137.6, 132.6, 129.5, 129.2, 127.8, 118.6, 113.9, 57.0, 53.8, 21.3; **MALDI TOF/TOF** m/z calcd for $C_{16}H_{20}NO_3P$ $[M + K^+]$ 344.12, observed 344.02.

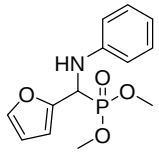
Dimethyl (2,5-dimethoxy phenyl)(phenylamino)methylphosphonate (4f)



Yield: 97 %; White solid; mp: 134-136 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.11-7.01 (m, 3H) 6.79-6.55 (m, 5H) 5.40 (d, *J*=24 Hz, 1H), 4.78 (br s, 1H), 3.90 (s, 3H), 3.84 (d, *J*=10 Hz, 3H), 3.71 (s, 3H), 3.46 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 146.2, 145.90, 135.7, 129.0, 128.6, 127.8, 118.4, 113.7, 57.1, 54.1, 53.5; **MALDI TOF/TOF**

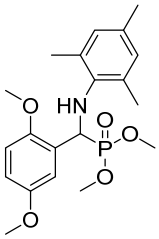
m/z Calcd for $C_{17}H_{22}NO_5P$ [M + K^+] 390.12, observed 390.02.

Dimethyl (furan-2-yl)(phenylamino)methylphosphonate) (4g)



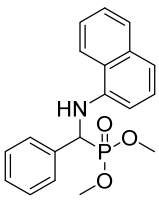
Yield: 97 %; Black solid; mp: 102-105 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.30 (s, 1H), 7.04-6.67 (m, 2H), 6.64-6.54 (m, 3H), 6.31-6.22 (m, 2H), 4.88 (d, *J*=24 Hz, 1H), 4.54 (br s, 1H), 3.75 (d, *J*=10 Hz, 3H), 3.55 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 149.1, 145.7, 142.4, 129.1, 118.9, 133.8, 110.7, 108.9, 53.7, 53.4, 51.3, 48.1.

Dimethyl (mesitylamino)(2,5-dimethoxyphenyl)methylphosphonate (4h)



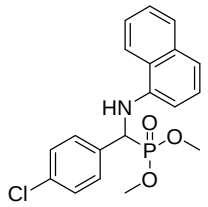
Yield: 95 %; White solid; mp: 109-111 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 6.82-6.72 (m, 5H), 5.01 (d, *J*=23 Hz, 1H), 4.29 (br s, 1H), 3.86-3.67 (m, 9H), 3.46 (d, *J*=10 Hz, 3H), 2.24-2.14 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 153.8, 141.9, 130.5, 129.5, 128.9, 128.3, 114.4, 112.2, 56.4, 55.5, 29.8, 20.6, 18.6.

Dimethyl (napthalen-1-ylamino)(phenyl)methylphosphonate (4i)



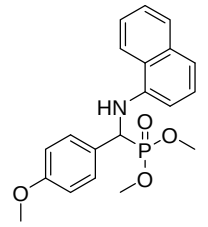
Yield: 98 %; White solid; mp: 128-130 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 8.00-7.52 (m, 1H), 7.56-7.49 (m,1H), 7.48-7.47 (m, 4H), 7.33-7.29 (m, 3H), 7.18-7.13 (m, 2H), 6.36 (d, *J*=8 Hz, 1H), 5.00 (d, *J*=24 Hz, 1H), 3.82 (d, *J*=10 Hz, 3H), 3.52 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 159.5, 141.3, 134.3, 128.7, 126.9, 126.2, 125.8, 125.1, 124.1, 120.1, 118.8, 114.2, 106.6, 56.8, 55.00.

Dimethyl (4-chlorophenyl)(naphthalene-1-ylamino)methylphosphonate (4j)



Yield: 97 %; White solid; mp: 127-129 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.96 (d, *J*=7 Hz, 1H), 7.78-7.74 (m, 1H), 7.44-7.42 (m, 4H), 7.32-7.13 (m, 4H), 6.32 (d, *J*=7 Hz, 1H), 5.40 (s, 1H), 4.94 (d, *J*=24 Hz, 1H), 3.80 (d, *J*=10 Hz, 3H), 3.58 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 140.7, 134.1, 129.0, 128.9, 128.8, 125.9, 125.3, 124.1, 119.9, 119.2, 106.7, 57.1, 54.1; **MALDI TOF/TOF** m/z Calcd for $C_{19}H_{19}ClNO_3P$ [M +] 375.07, observed 375.02.

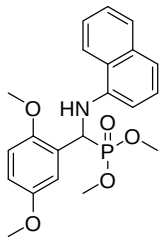
Dimethyl (4-methoxyphenyl)(naphthalene-1-ylamino)methylphosphonate (4k)



Yield: 98 %; White solid; mp: 113-115 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.98-7.91 (m, 1H), 7.76-7.12 (m, 1H), 7.53-7.38 (m, 4H), 7.25-7.09 (m, 2H), 6.83 (d, *J*=8 Hz, 2H), 6.38

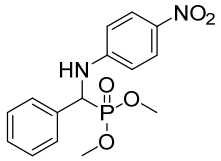
(d, *J*=8 Hz, 1H), 4.90 (d, *J*=23 Hz, 1H), 3.78 (d, *J*=10 Hz, 3H), 3.75 (s, 3H), 3.51 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 159.5, 141.3, 134.3, 128.7, 126.9, 126.2, 125.8, 125.1, 124.1, 120.1, 118.8, 114.2, 106.6, 56.8, 55.0, 53.7

Dimethyl (2,5-dimethoxyphenyl)(naphthalene-1-ylamino)methylphosphonate (4l)



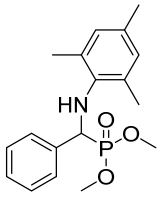
Yield: 98 %; White solid; mp: 130-132 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 8.03-7.91 (m, 1H), 7.77-7.72 (m, 1H), 7.55-7.40 (m, 2H), 7.20-7.05 (m, 3H), 6.88-6.70 (m, 2H), 6.48-6.43 (m, 1H), 5.55 (d, *J*=24 Hz, 1H), 3.94 (s, 3H), 3.87 (d, *J*=10 Hz, 3H), 3.65 (s, 3H), 3.49 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 154.1, 151.5, 141.0, 134.3, 128.6, 126.4, 125.7, 125.0, 123.9, 120.2, 118.6, 114.1, 113.5, 111.8, 105.9, 56.4, 55.4, 53.7, 49.9, 46.8.

Dimethyl (4-nitrophenylamino)(phenyl)methylphosphonate (4m)



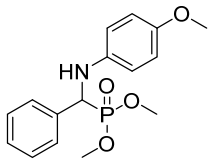
Yield: 95 %; Yellow solid; mp: 124-126 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO d_6): **δ** 7.90 (d, *J*=9 Hz, 2H), 7.45-7.20 (m, 5H), 6.70 (d, *J*=9 Hz, 2H), 4.90 (dd, 1H), 4.40 (br s, 1H), 3.69 (d, *J*=10 Hz, 3H), 3.46 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50MHz, $CDCl_3$+DMSO d_6): **δ** 151.9, 137.1, 133.9, 127.6, 127.1, 124.7, 111.3, 54.9, 52.7, 51.9.

Dimethyl (mesitylamino)(phenyl)methylphosphonate (4n)



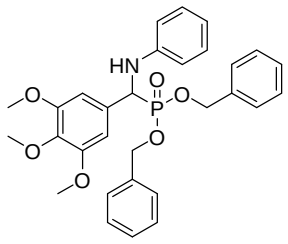
Yield: 97 %; Yellow solid; mp: 93-95 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.44-7.30 (m, 2H), 7.25-7.17-7.19 (m, 3H), 6.61 (s, 2H), 4.73 (s, 1H), 4.37 (d, *J*=22 Hz, 1H), 3.74 (d, *J*=10 Hz, 3H), 3.34 (d, *J*=10 Hz, 3H), 2.09 (s, 3H), 2.06 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 141.4, 136.9, 131.1, 130.1, 129.6, 129.1, 128.4, 60.8, 57.8, 53.8, 29.7, 20.6, 18.7; **MALDI TOF/TOF** m/z calcd for $C_{18}H_{24}NO_3P$ [M + K^+] 372.14, observed 372.03.

Dimethyl (4-methoxyphenylamino)(phenyl)methylphosphonate (4o)



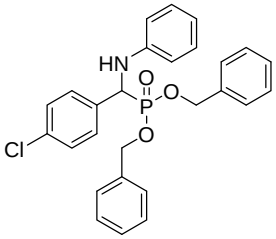
Yield: 98 %; White solid; mp: 85-87 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.45-7.23 (m, 5H), 6.64 (d, *J*=9 Hz, 2H), 6.51 (d, *J*=9 Hz, 2H), 4.75 (d, *J*=24 Hz, 1H), 4.22 (br s, 1H), 3.79 (d, *J*=10 Hz, 3H), 3.65 (s, 3H), 3.47 (d, *J*=10 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 152.7, 139.8, 135.8, 128.6, 128.0, 127.9, 127.8, 115.2, 114.7, 58.1, 55.3, 53.6; **MALDI TOF/TOF** m/z calcd for $C_{16}H_{20}NO_4P$ [M +] 321.11, observed 321.04.

Dibenzyl (phenylamino)(3,4,5-trimethoxyphenyl)methylphosphonate (4p)



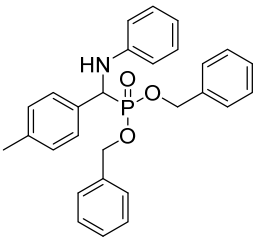
Yield: 93 %; White solid; mp: 103-105 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.34-7.29 (m, 8H), 7.17-7.10 (m, 4H), 6.74 (t, *J*=7 Hz, 1H), 6.64 (d, *J*=2 Hz, 2H), 6.60 (d, *J*=7 Hz, 2H), 5.09-5.04 (m, 2H), 4.93 (dd, *J*=7 Hz, 1H), 4.77-4.65 (m, 2H), 3.85 (s, 3H), 3.76 (s, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 153.4, 146.2, 131.1, 129.2, 128.6, 128.5, 128.2, 127.9, 118.8, 113.9, 104.8, 104.6, 68.6, 60.7, 58.2, 55.9; **MALDI TOF/TOF** m/z calcd for $C_{30}H_{32}NO_6P$ [M + K^+] 572.19, observed 572.06.

Dibenzyl (4-chlorophenyl)(phenylamino)methylphosphonate (4q)



Yield: 96 %; Yellow solid; mp: 131-133 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.37-7.26 (m, 12H), 7.11-7.07 (m, 4H), 6.73 (t, J=7 Hz, 1H), 6.50 (d, J=7 Hz, 2H), 5.07-4.68 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 145.9, 134.3, 129.2, 128.8, 128.6, 128.2, 128.1, 118.8, 113.9, 68.9, 57.3, 54.3; **MALDI TOF/TOF** m/z calcd for $C_{27}H_{25}ClNO_3P$ [M + K^+] 516.12, observed 515.98.

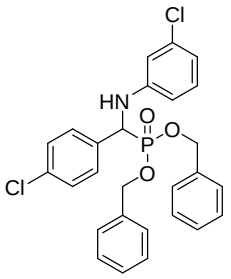
Dibenzyl (phenylamino)(p-tolyl)methylphosphonate (4r)



Yield: 95 %; Greenish solid; mp: 137-139 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.38-7.30

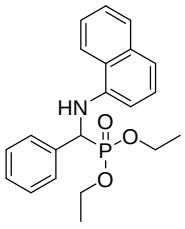
(m, 10H), 7.18-7.07 (m, 6H), 6.73 (t, *J*=7 Hz, 1H), 6.58 (d, *J*=7 Hz, 2H), 5.07-4.58 (m, 5H), 2.37(s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 146.1, 137.5, 136.1, 132.6, 129.4, 129.1, 128.5, 127.9, 127.8, 118.5, 113.9, 68.5, 57.5, 54.5, 21.3; **MALDI TOF/TOF** m/z Calcd for $C_{28}H_{28}NO_3P$ [M + K^+] 496.18, observed 496.05.

Dibenzyl ((4-chlorophenyl)((3-chlorophenyl)amino)methyl)phosphonates (4s)



Yield: 96 %; Yellow solid; mp: 99-101 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.30-7.32 (m, 11H), 7.21-7.18 (m, 3H), 7.17-6.90 (m, 1H), 6.52-6.39 (m, 3H), 4.99 (br, s 1H), 4.95-4.55 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$): **δ** 147.0, 135.4, 134.8, 133.6, 130.1, 129.1, 128.9, 128.6, 128.1, 128.0, 127.8, 118.7, 113.7, 111.9, 68.8, 56.3, 54.8; **MALDI TOF/TOF** m/z Calcd for $C_{27}H_{24}Cl_2NO_3P$ [M + K^+] 550.08, observed 549.98.

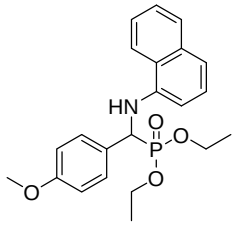
Diethyl (naphthalene-1-ylamino)(phenyl)methylphosphonate (4t)



Yield: 98 %; White solid; mp: 114-116 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.96-6.99 (m, 11H), 6.25 (dd, *J*=7 Hz, 1H), 5.39 (br s, 1H), 4.87 (d, *J*=24 Hz, 1H), 3.53-4.12 (m, 4H), 1.20 (t, *J*=7 Hz, 3H), 1.05 (t, *J*=7 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 159.4, 141.5,

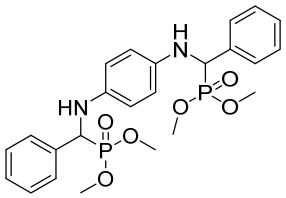
134.4, 128.7, 127.4, 126.2, 125.7, 125.0, 124.1, 120.1, 118.6, 114.0, 106.6, 63.2, 57.2, 54.9, 54.2, 16.5.

Diethyl (4-methoxyphenyl)(phenylamino)methylphosphonate (4u)



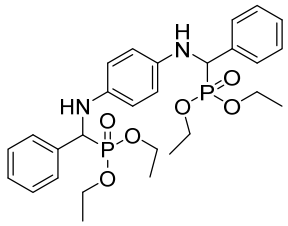
Yield: 98 %; White solid; mp: 96-98 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 7.92 (d, *J*=7 Hz, 1H), 7.67-7.62 (m, 1H), 7.40-7.29 (m, 4H), 7.08-7.04 (m, 2H), 6.75 (d, *J*=8 Hz, 2H), 6.31 (dd, *J*=7 Hz, 1H), 4.78 (d, *J*=23 Hz, 1H), 4.10-3.83 (m, 4H), 3.67 (s, 3H), 1.22 (t, *J*=7 Hz, 3H), 1.09 (t, *J*=7 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 141.4, 135.7, 134.4, 128.6, 127.9, 127.7, 126.1, 125.7, 125.0, 124.1, 120.1, 118.7, 106.5, 63.2, 57.8, 54.8, 16.5.

Tetramethyl((1,4-phenylenebis(azanediyl))bis(phenylmethylene))bis(phosphonates) (4v)



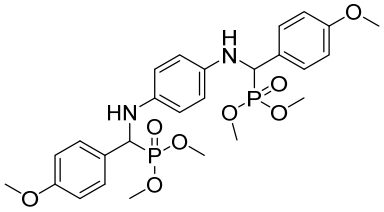
Yield: 96 %; Brown solid; mp: 178-180 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO d_6): **δ** 7.38-7.20 (m, 10H), 6.38 (s, 4H), 4.62 (d, *J*=24 Hz, 2H), 3.65 (d, *J*=10 Hz, 6H), 3.38 (d, *J*=10 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$+DMSO d_6): **δ** 132.7, 128.4, 124.3, 117.7, 112.7, 53.3, 52.7, 49.2, 28.7; **MALDI TOF/TOF** m/z Calcd for $C_{24}H_{30}N_2O_6P_2$ [M + K^+] 543.15, observed 543.07.

Tetraethyl ((1,4-phenylenebis(azanediyl))bis(phenylmethylene))bis(phosphonates) (4w)



Yield: 95 %; White solid; mp: 152-154 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO d_6): **δ** 7.34-7.17 (m, 10H), 6.28 (s, 4H), 4.44 (d, *J*=24 Hz, 2H), 4.03 (s, 2H), 4.01-3.56 (m, 8H), 1.19 (t, *J*=7 Hz, 6H), 1.01 (t, *J*=7 Hz, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO d_6): **δ** 158.7, 128.7, 127.5, 114.9, 113.4, 54.5, 52.7, 29.1.

Tetramethyl ((1,4-phenylenebis(azanediyl))bis((4-methoxyphenyl)methylene)) bis (phosphonates) (4x)



Yield: 96 %; White solid; mp: 161-163 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO d_6): **δ** 7.32-7.26 (m, 4H), 6.80-6.76 (m, 4H), 6.40 (s, 4H), 4.62 (d, *J*=24 Hz, 2H), 4.23 (br s, 2H), 3.73 (s, 6H), 3.67 (d, *J*=10 Hz, 6H), 3.46 (d, *J*=10 Hz, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO d_6): **δ** 136.4, 128.5, 128.0, 127.9, 115.5, 62.9, 16.5, 16.4, 16.3.

3.1.7 Spectra

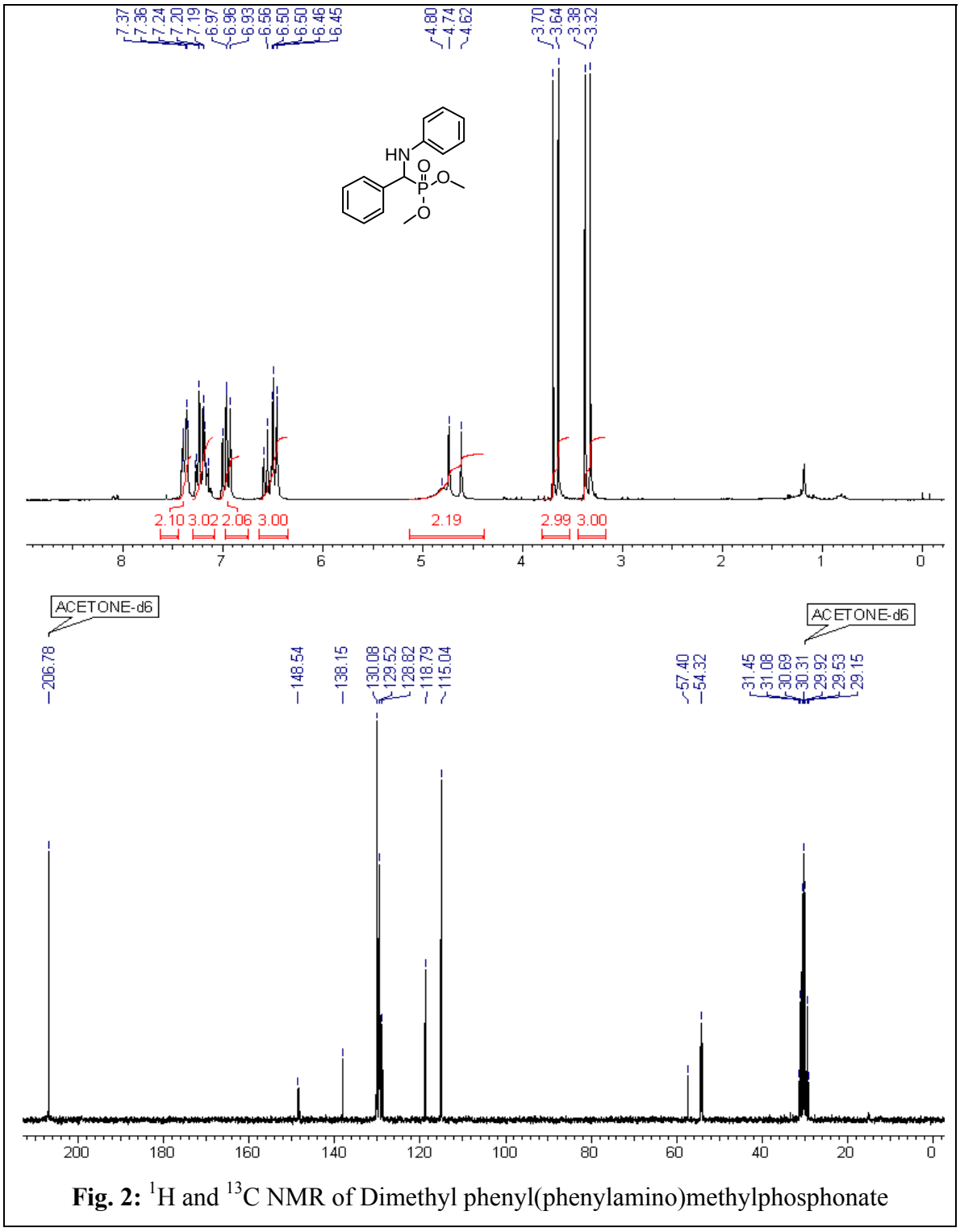


Fig. 2: ^{1}H and ^{13}C NMR of Dimethyl phenyl(phenylamino)methylphosphonate

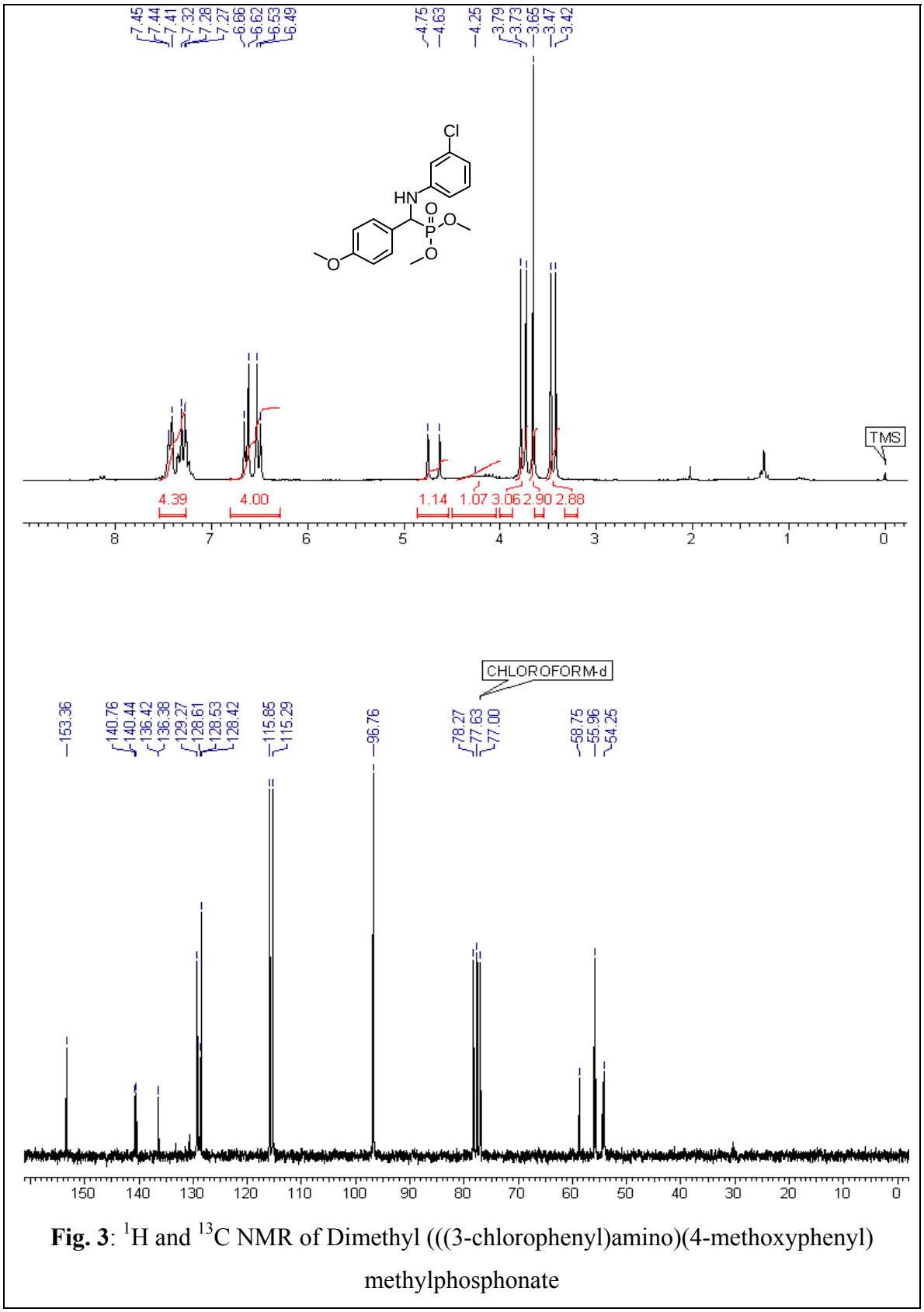


Fig. 3: ^{1}H and ^{13}C NMR of Dimethyl (((3-chlorophenyl)amino)(4-methoxyphenyl) methylphosphonate

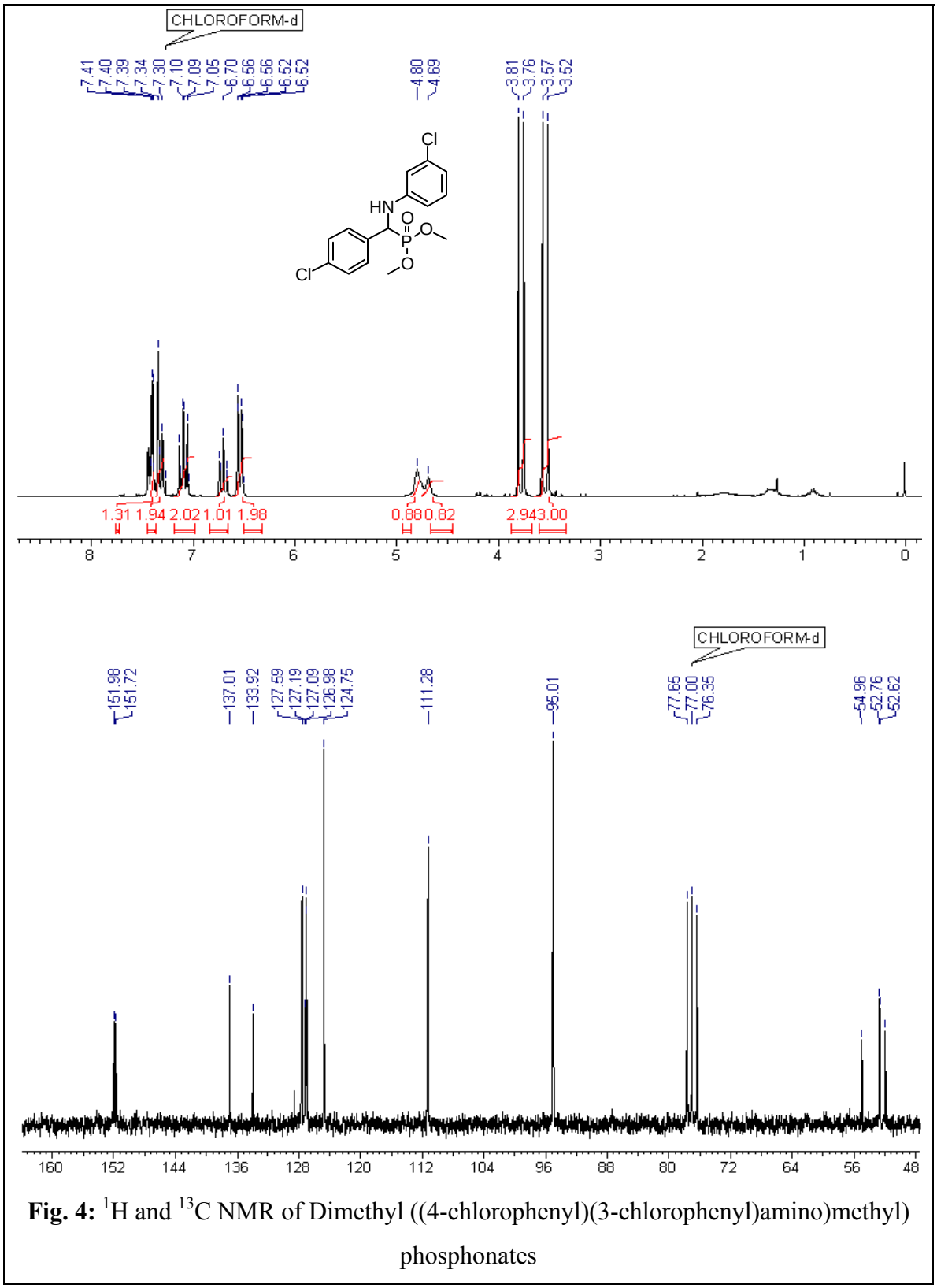


Fig. 4: ^{1}H and ^{13}C NMR of Dimethyl ((4-chlorophenyl)(3-chlorophenyl)amino)methyl) phosphonates

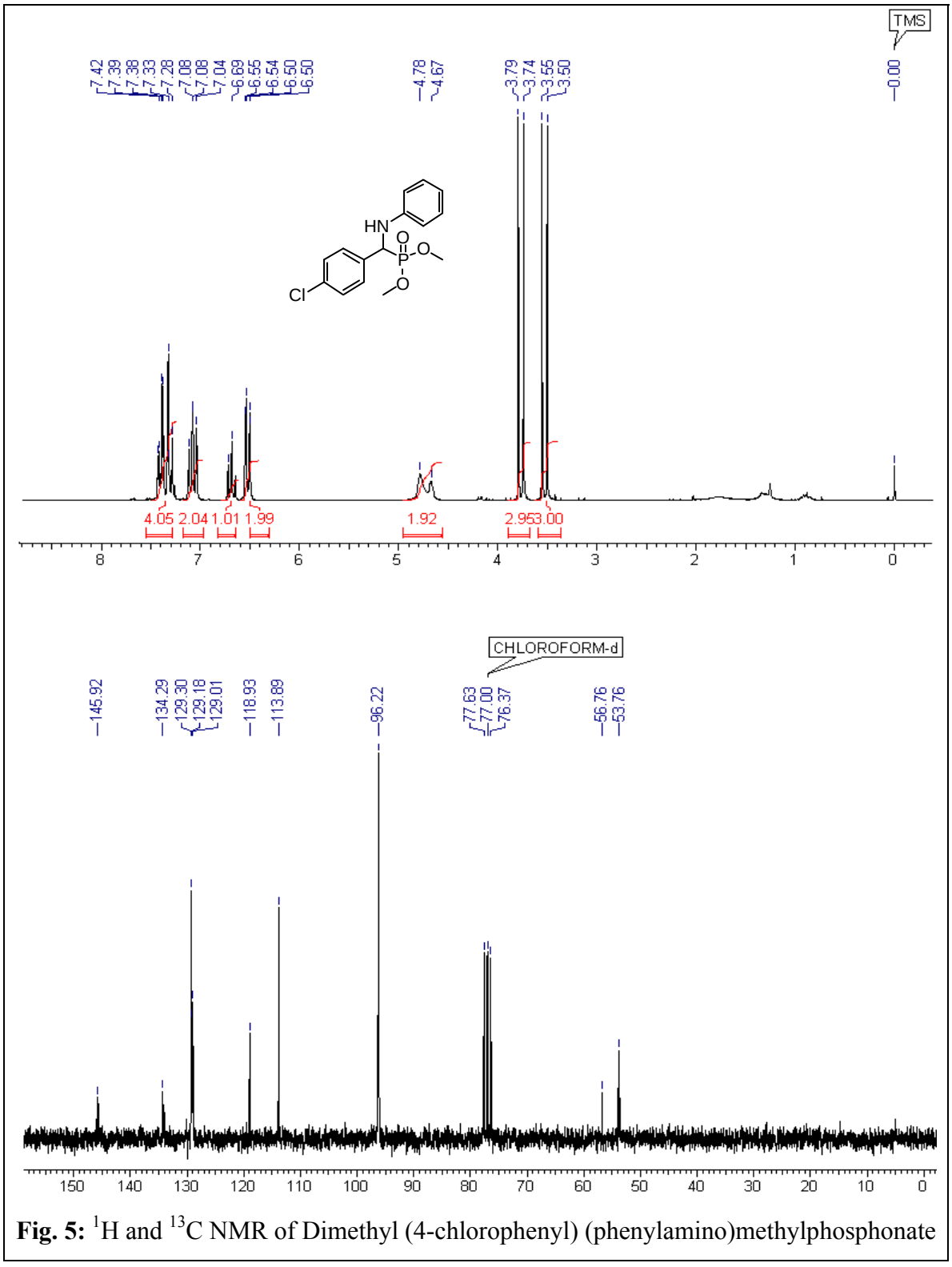


Fig. 5: ^{1}H and ^{13}C NMR of Dimethyl (4-chlorophenyl) (phenylamino)methylphosphonate

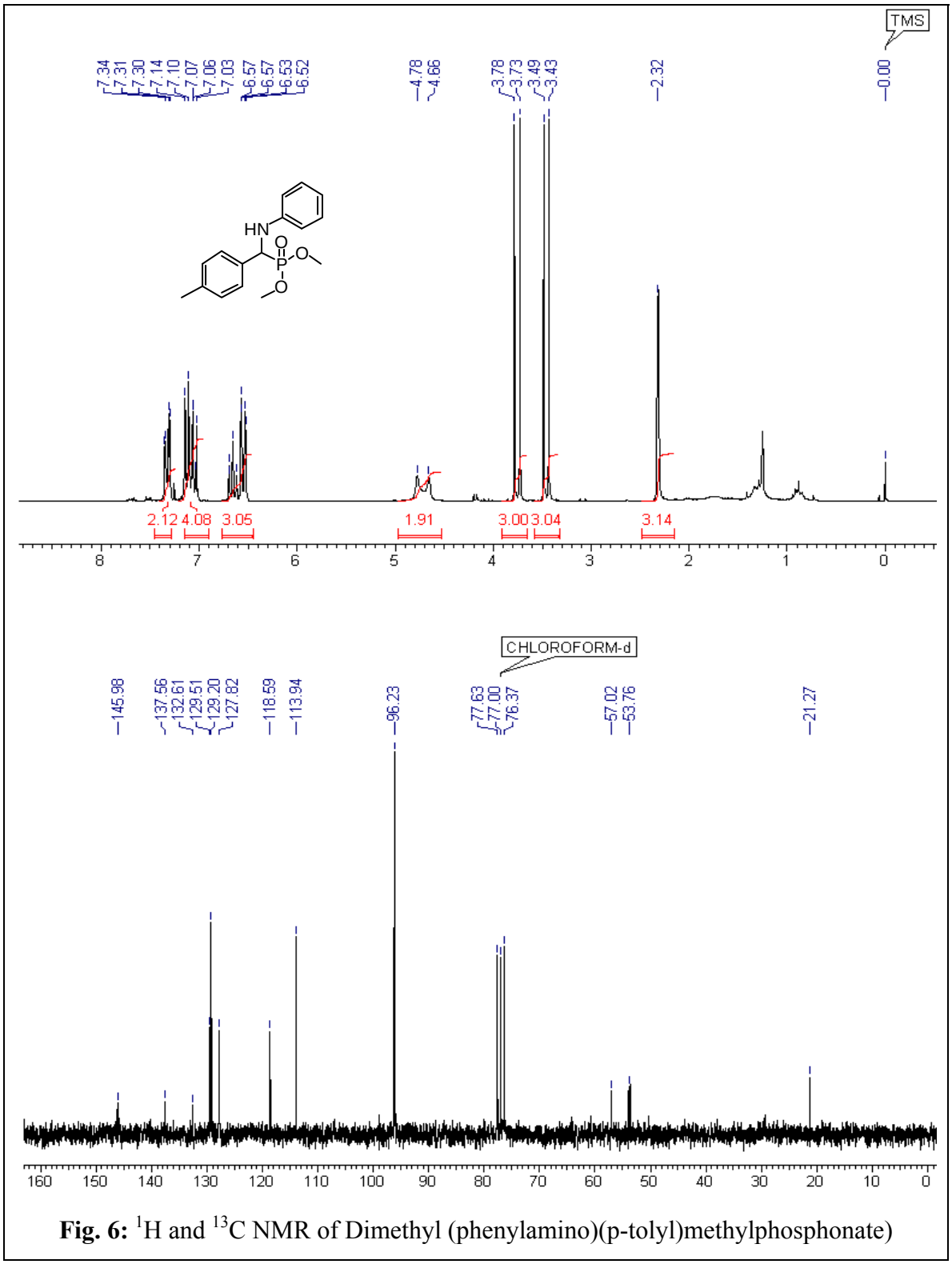


Fig. 6: ^{1}H and ^{13}C NMR of Dimethyl (phenylamino)(p-tolyl)methylphosphonate)

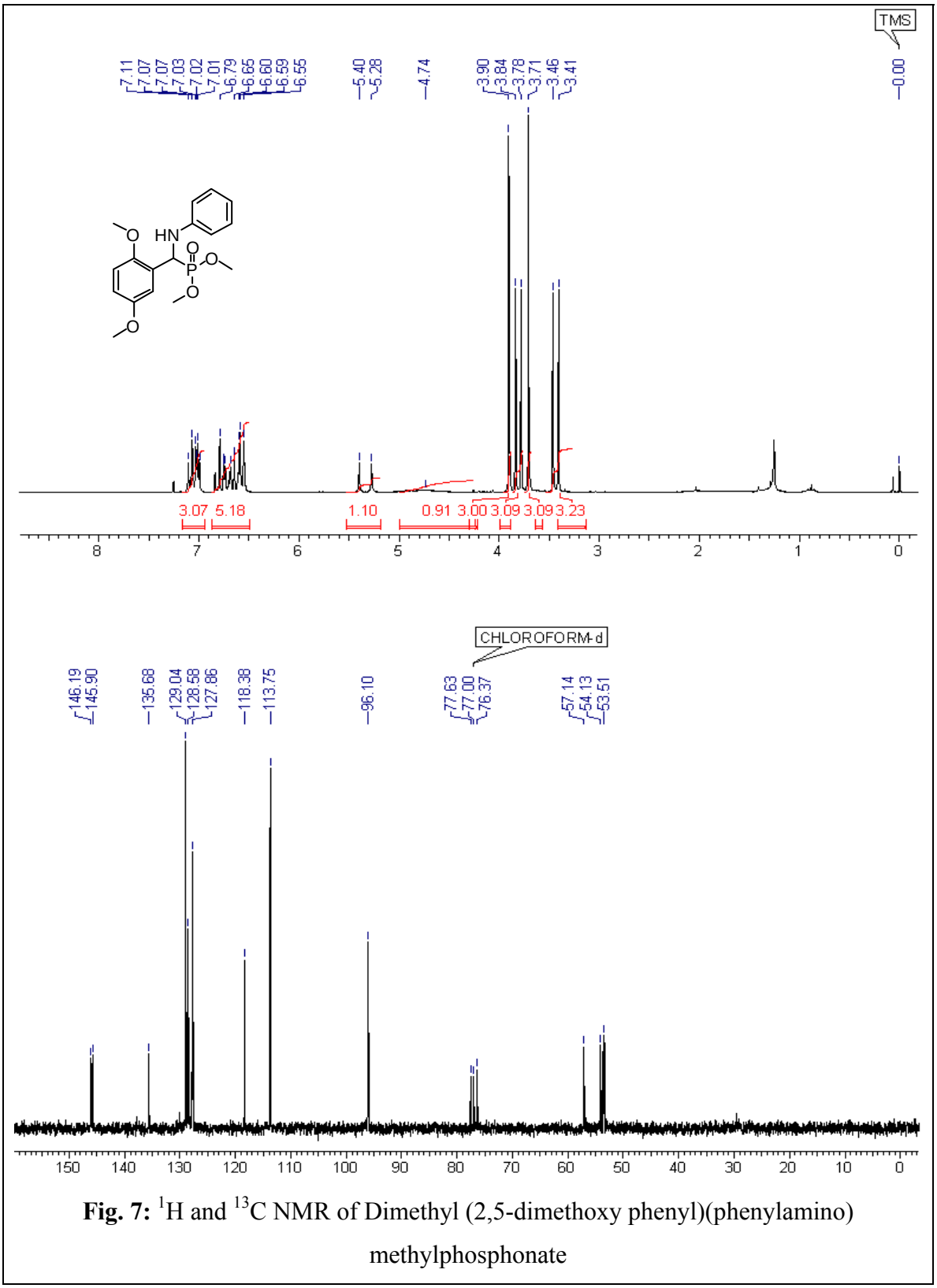


Fig. 7: ^{1}H and ^{13}C NMR of Dimethyl (2,5-dimethoxy phenyl)(phenylamino) methylphosphonate

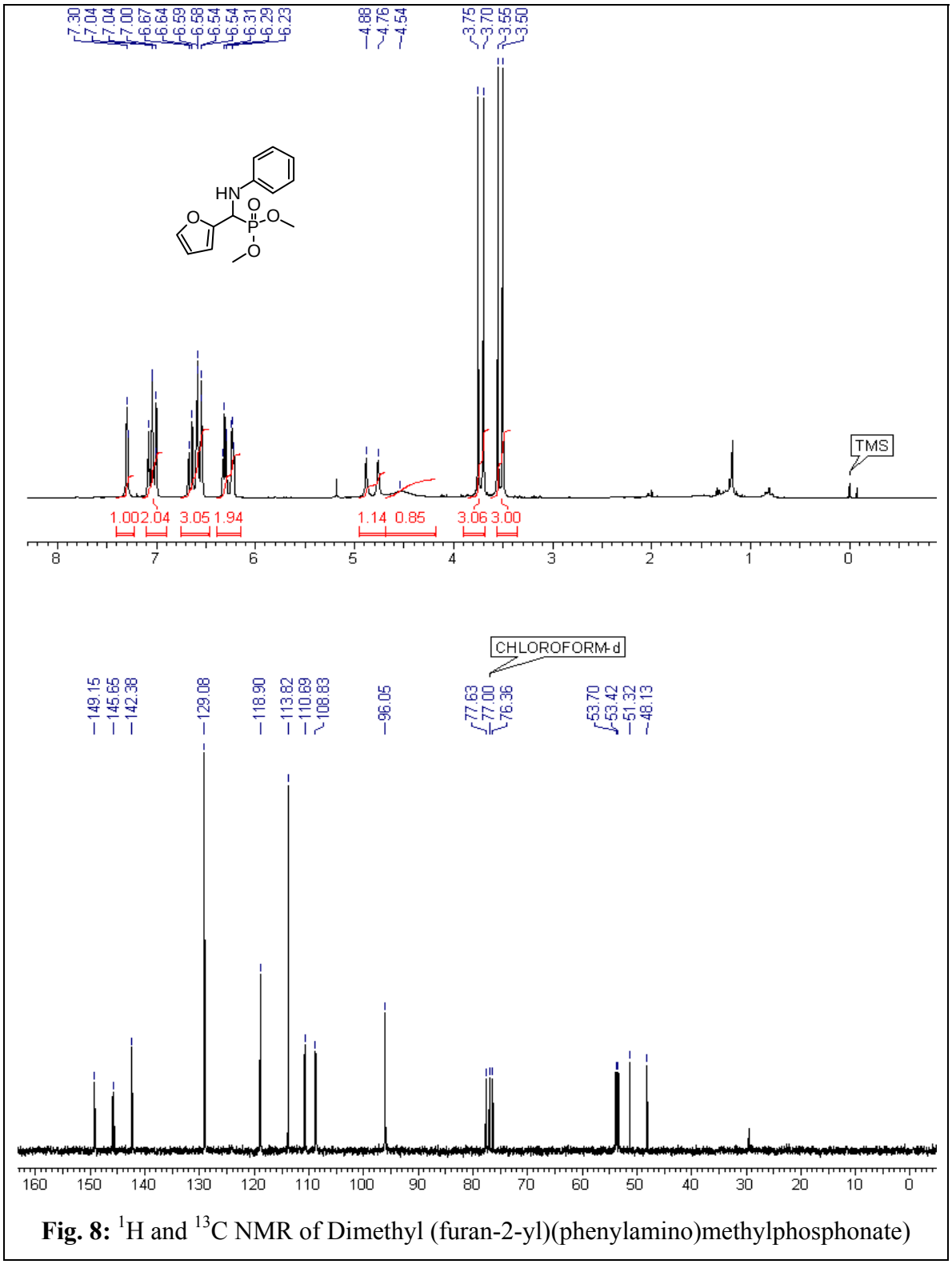


Fig. 8: ^{1}H and ^{13}C NMR of Dimethyl (furan-2-yl)(phenylamino)methylphosphonate)

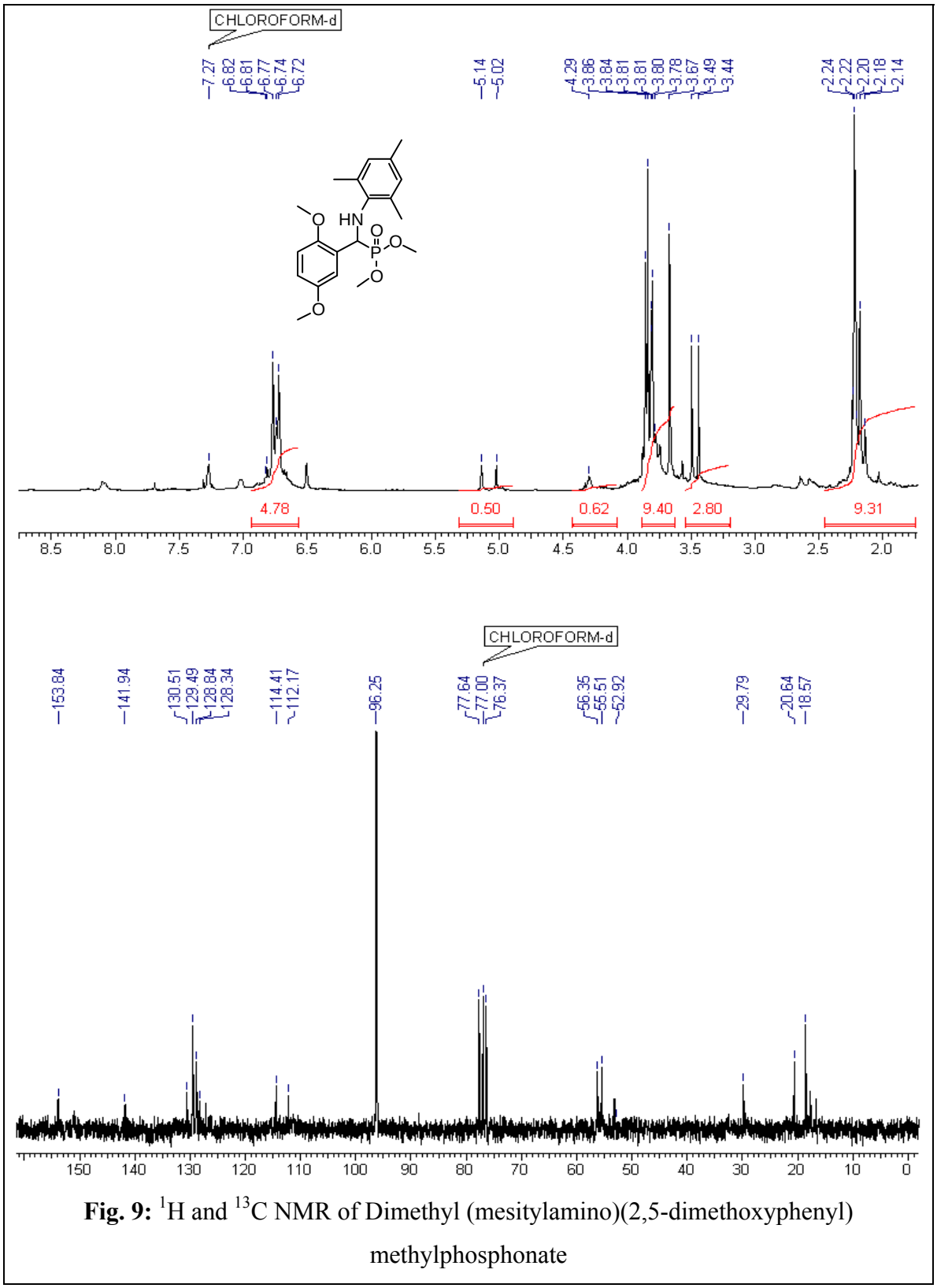


Fig. 9: ^{1}H and ^{13}C NMR of Dimethyl (mesitylamino)(2,5-dimethoxyphenyl) methylphosphonate

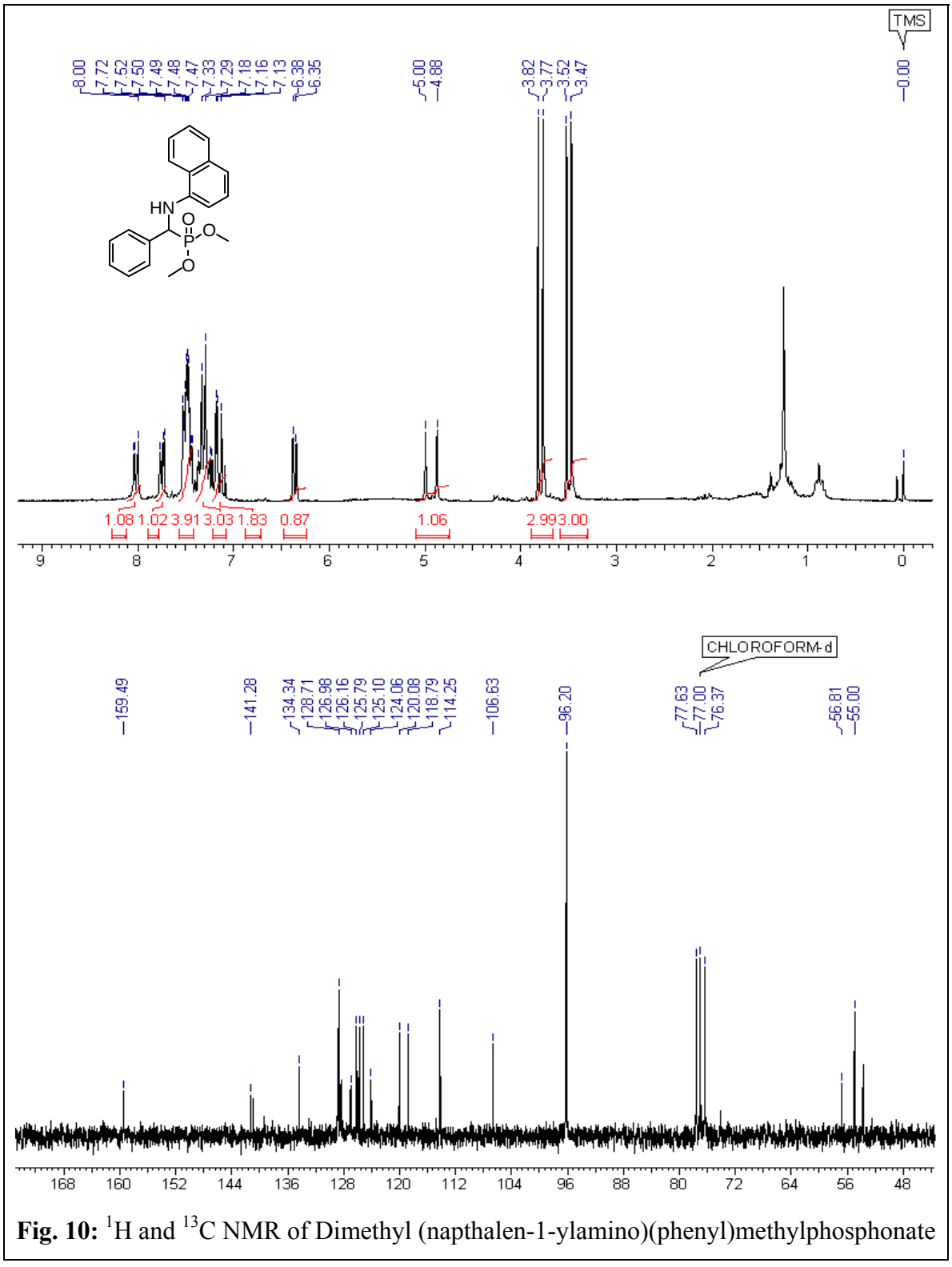


Fig. 10: ^{1}H and ^{13}C NMR of Dimethyl (napthalen-1-ylamino)(phenyl)methylphosphonate

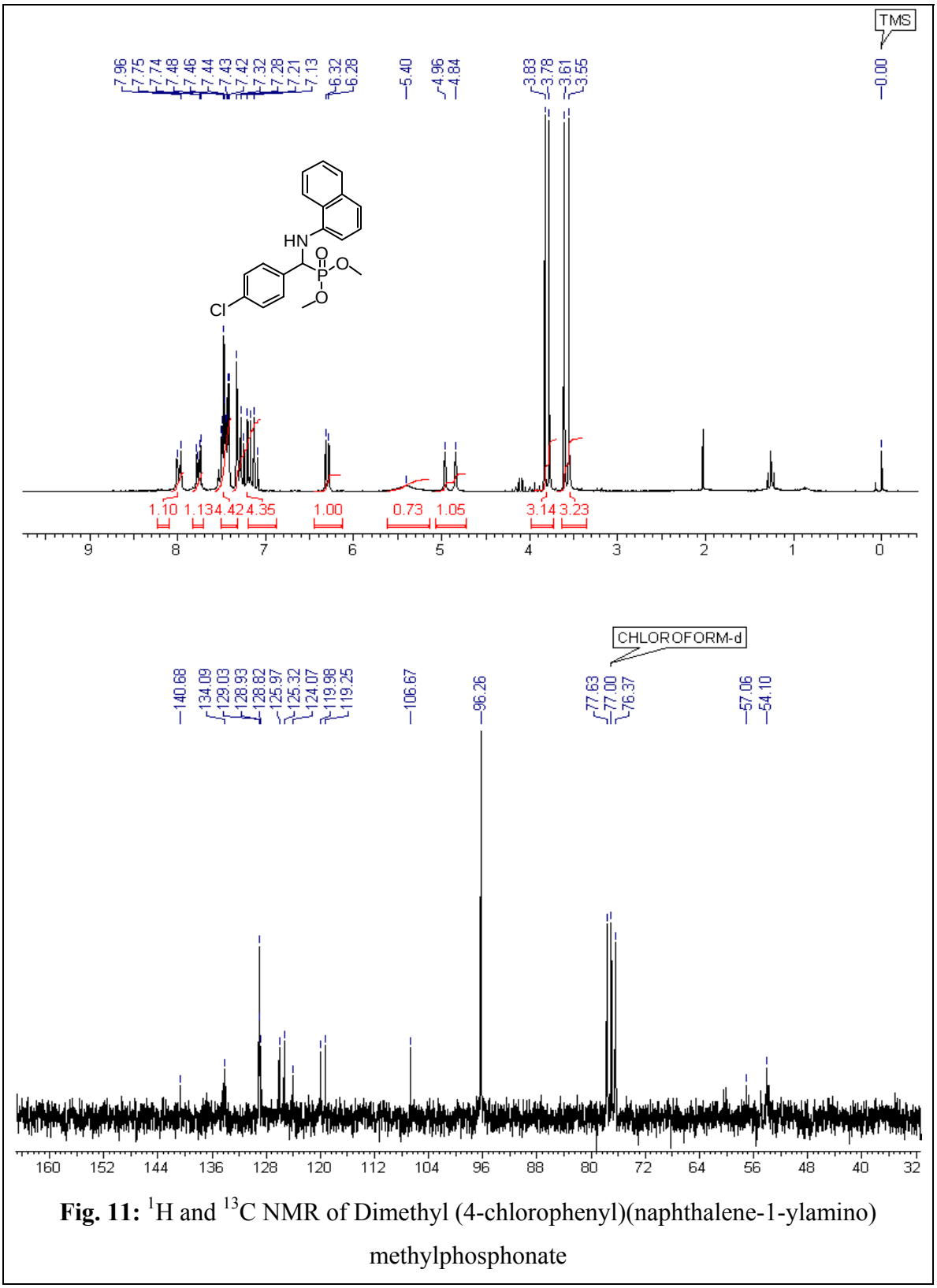


Fig. 11: ^{1}H and ^{13}C NMR of Dimethyl (4-chlorophenyl)(naphthalene-1-ylamino) methylphosphonate

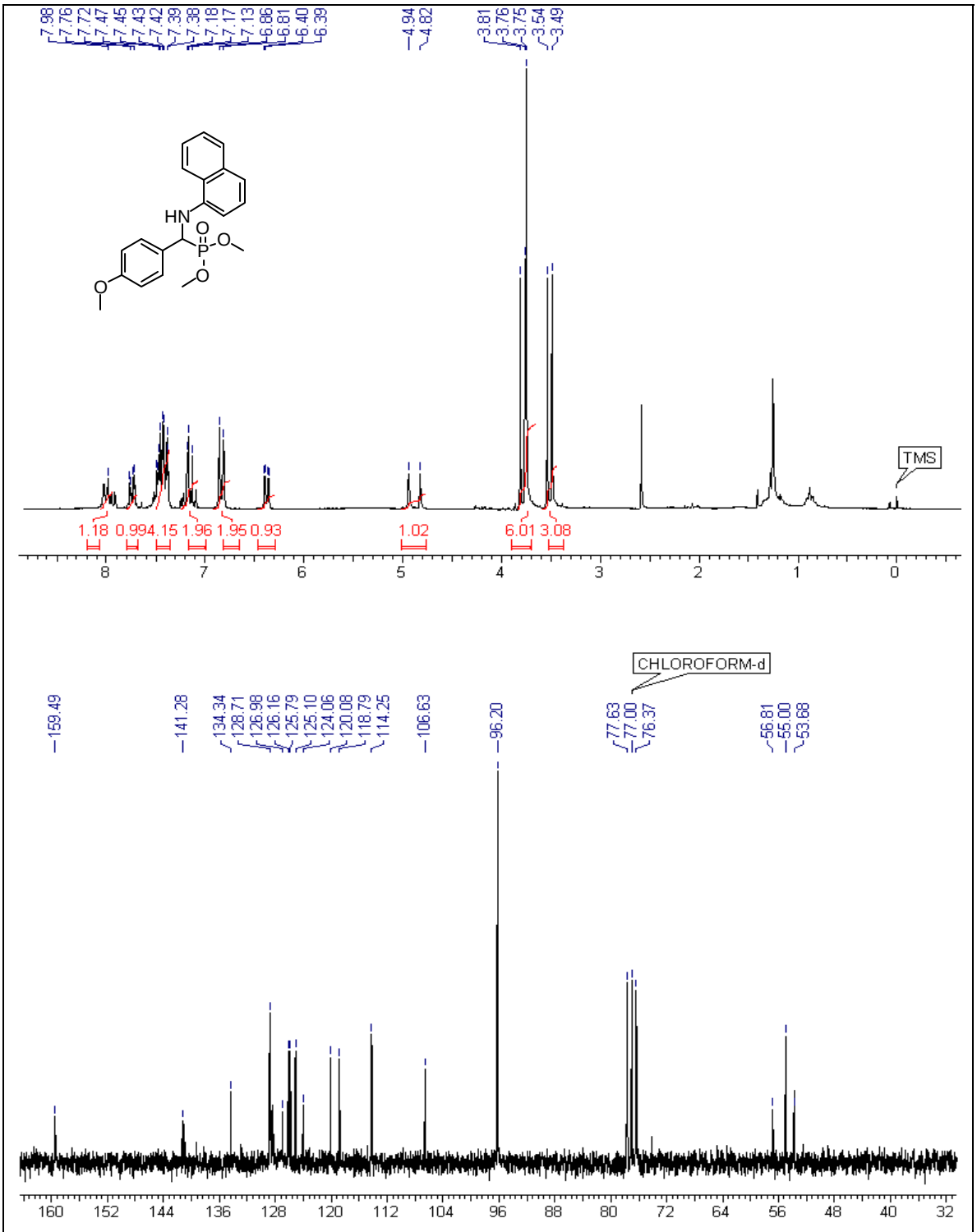


Fig. 12: ^{1}H and ^{13}C NMR of Dimethyl (4-methoxyphenyl)(naphthalene-1-ylamino) methylphosphonate

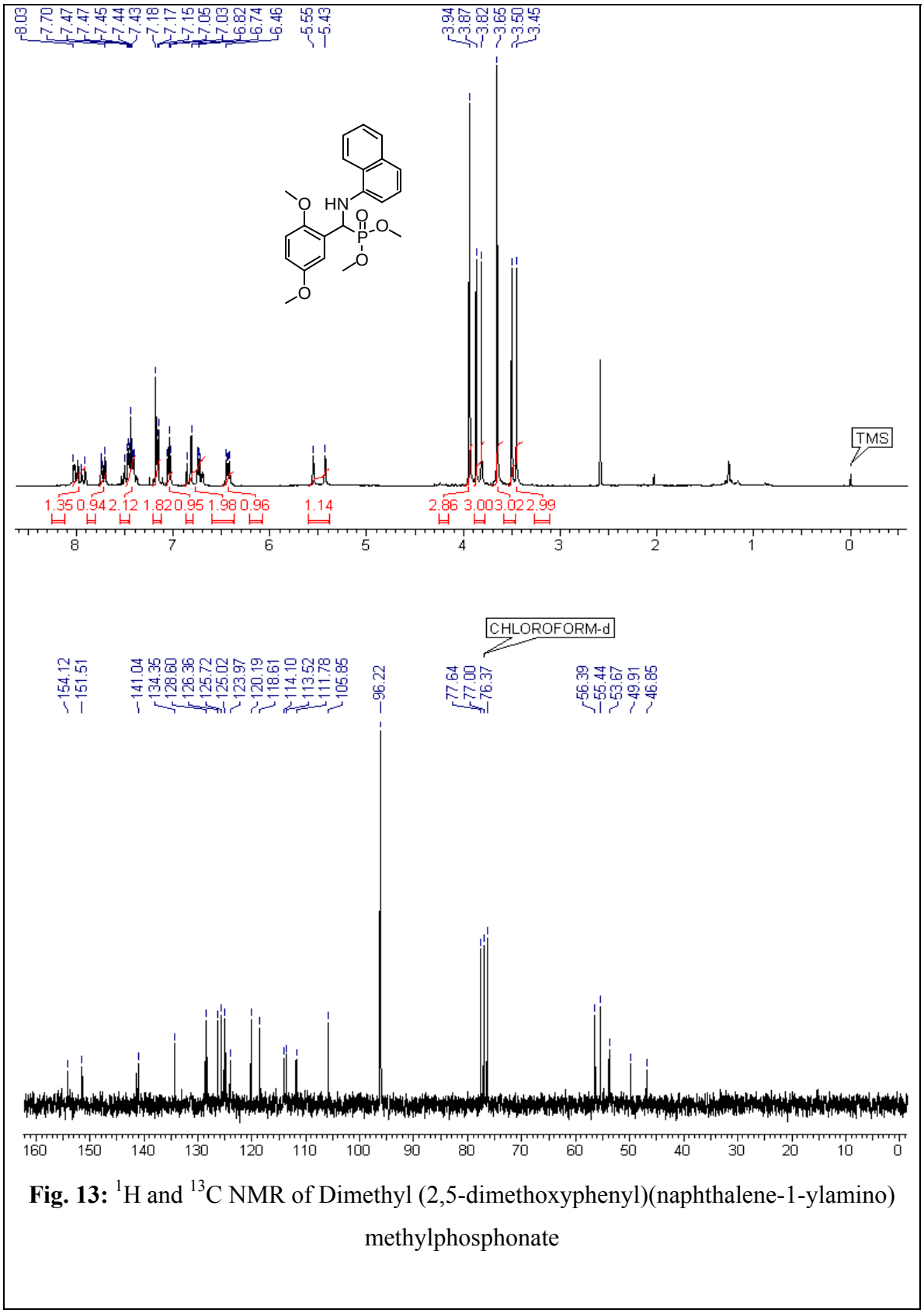


Fig. 13: ^{1}H and ^{13}C NMR of Dimethyl (2,5-dimethoxyphenyl)(naphthalene-1-ylamino) methylphosphonate

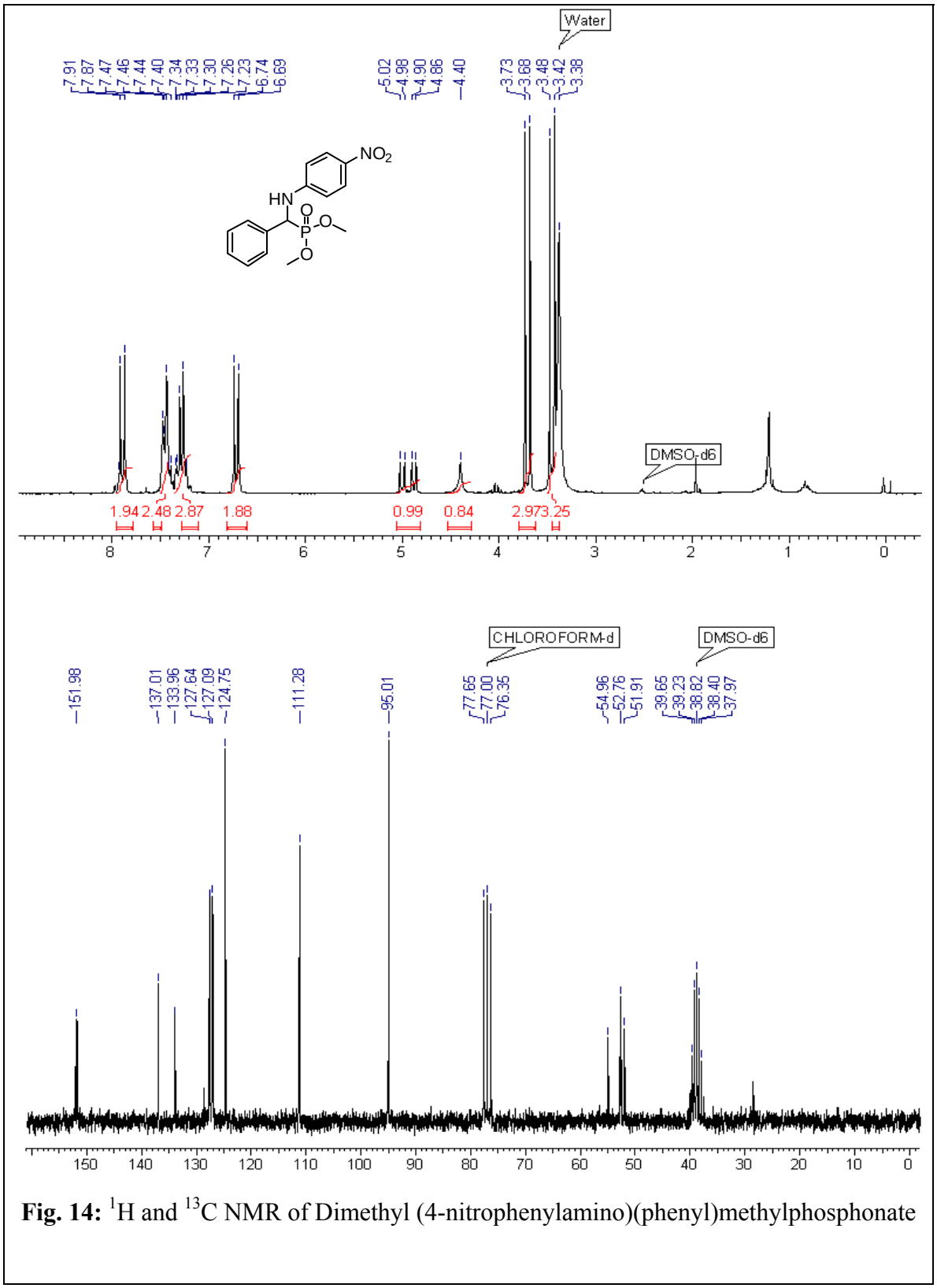


Fig. 14: ^{1}H and ^{13}C NMR of Dimethyl (4-nitrophenylamino)(phenyl)methylphosphonate

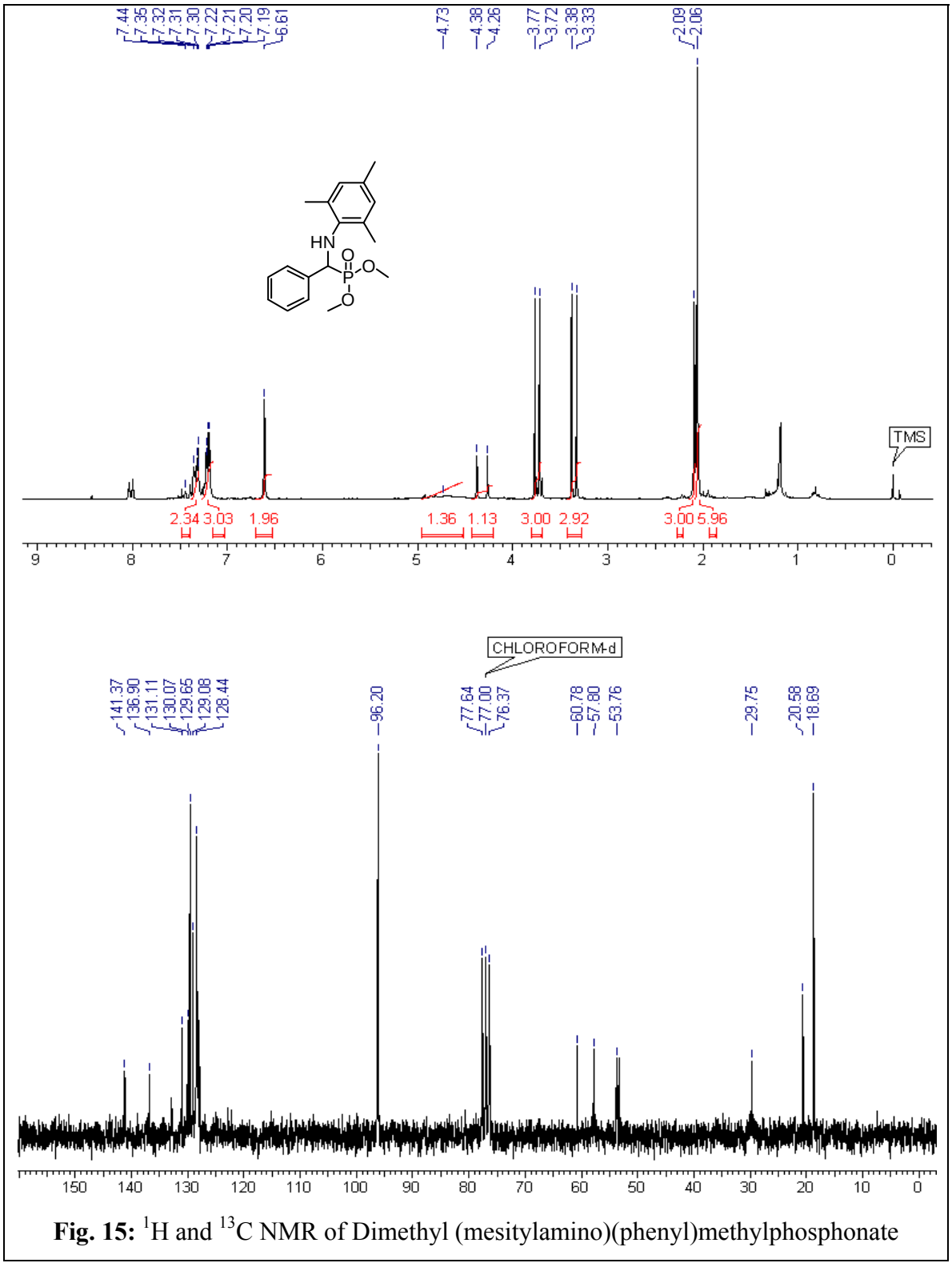


Fig. 15: ^{1}H and ^{13}C NMR of Dimethyl (mesitylamino)(phenyl)methylphosphonate

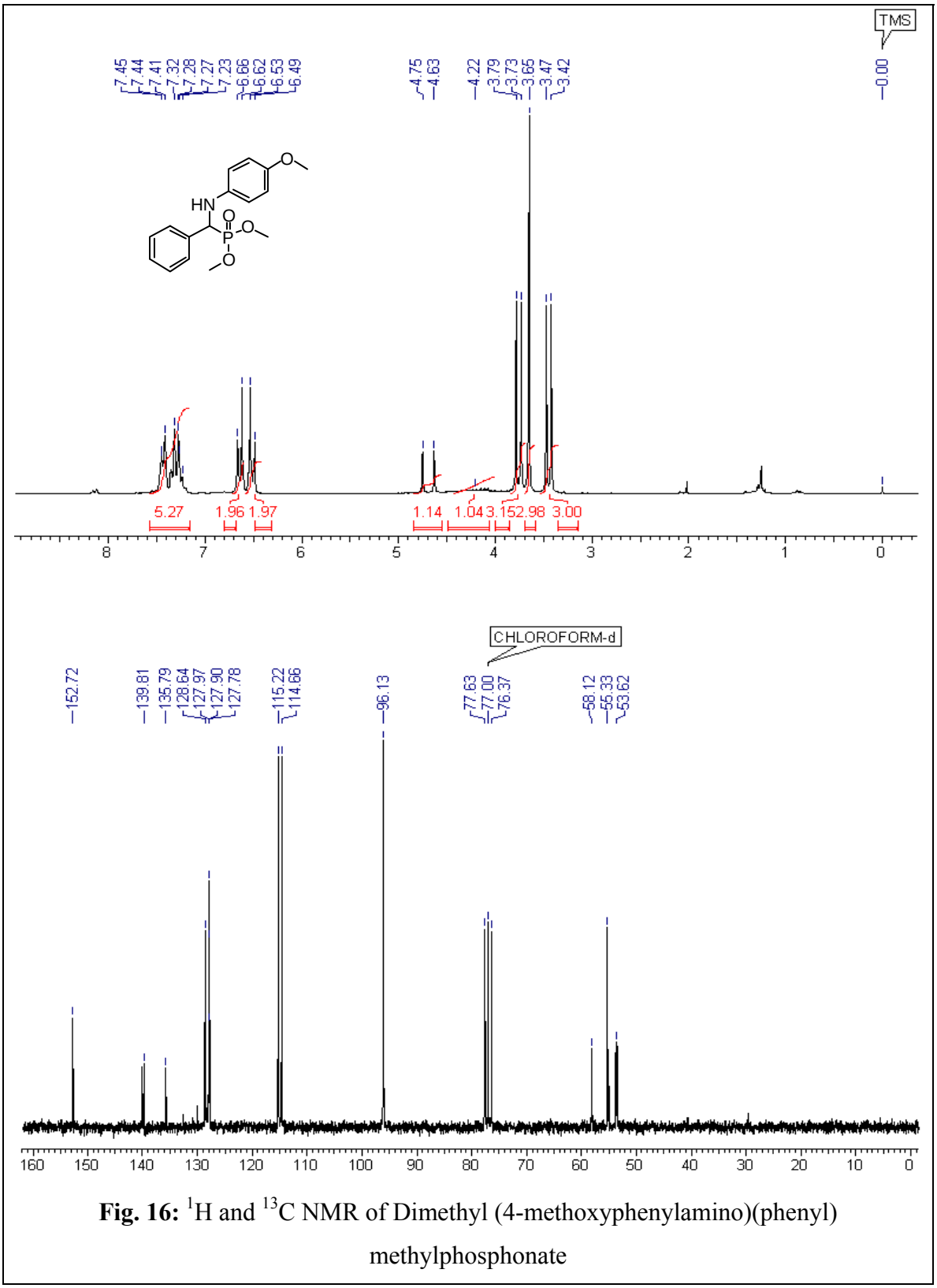


Fig. 16: ^{1}H and ^{13}C NMR of Dimethyl (4-methoxyphenylamino)(phenyl) methylphosphonate

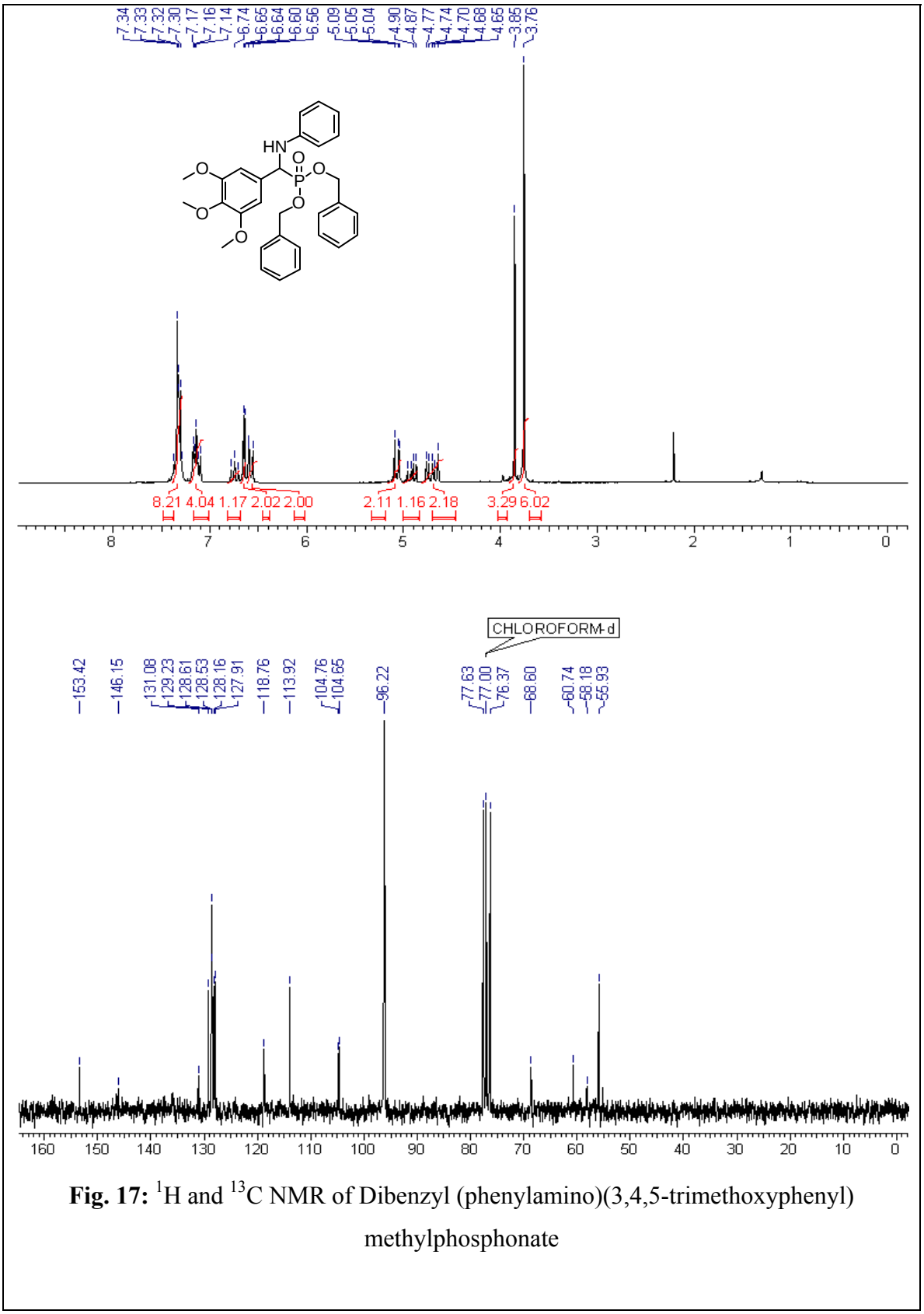


Fig. 17: ^{1}H and ^{13}C NMR of Dibenzyl (phenylamino)(3,4,5-trimethoxyphenyl) methylphosphonate

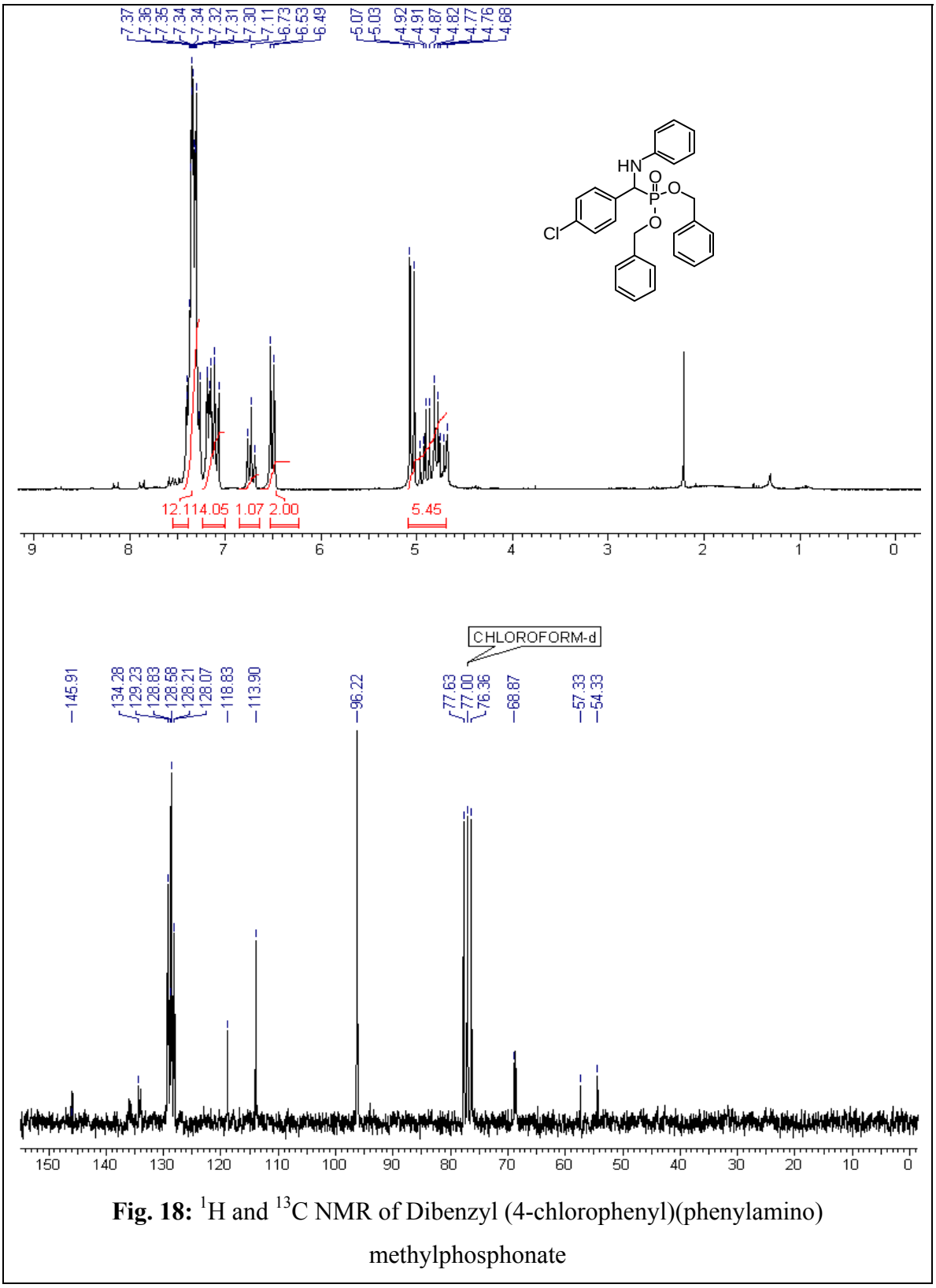


Fig. 18: ^{1}H and ^{13}C NMR of Dibenzyl (4-chlorophenyl)(phenylamino) methylphosphonate

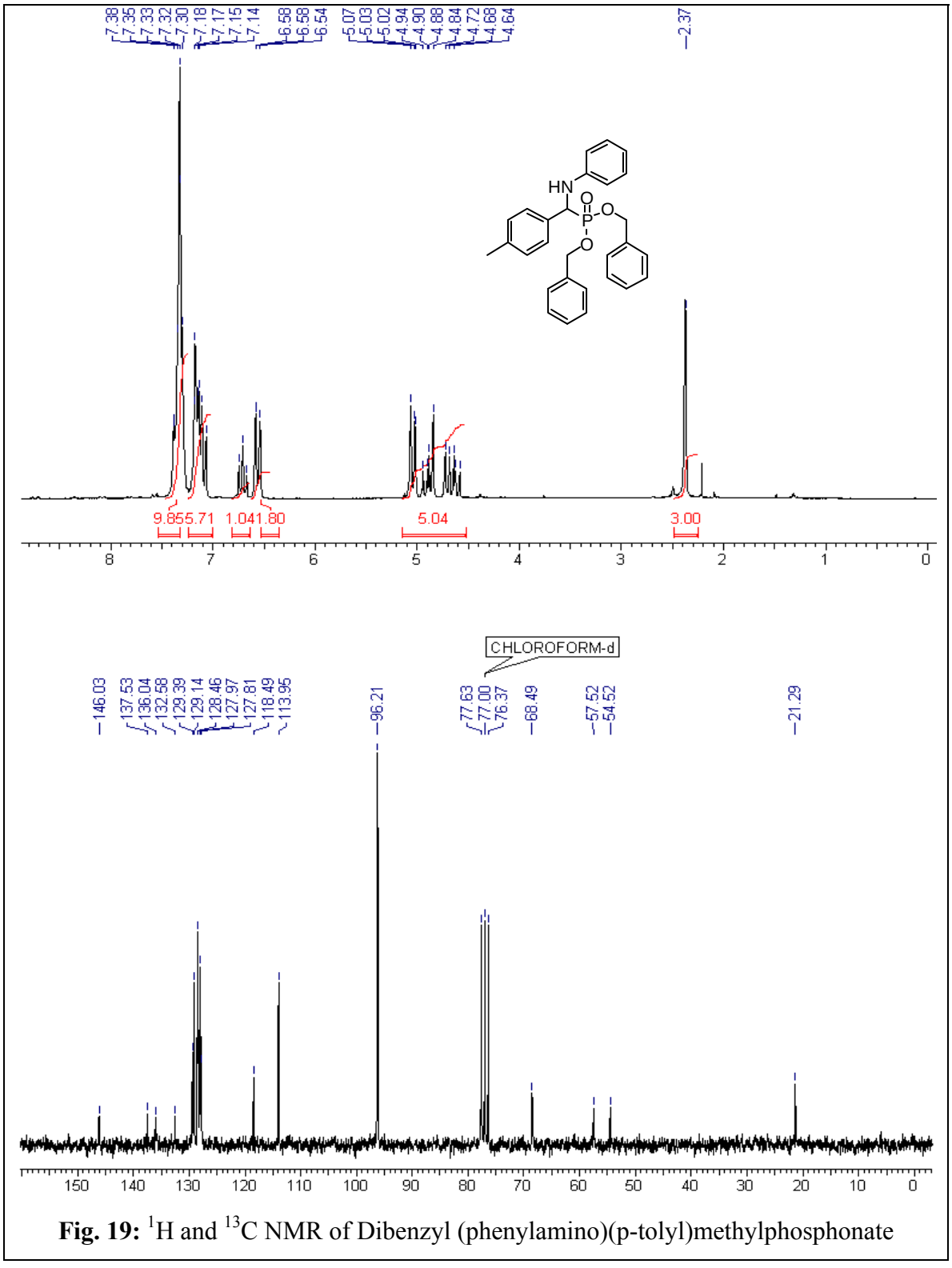


Fig. 19: ^{1}H and ^{13}C NMR of Dibenzyl (phenylamino)(p-tolyl)methylphosphonate

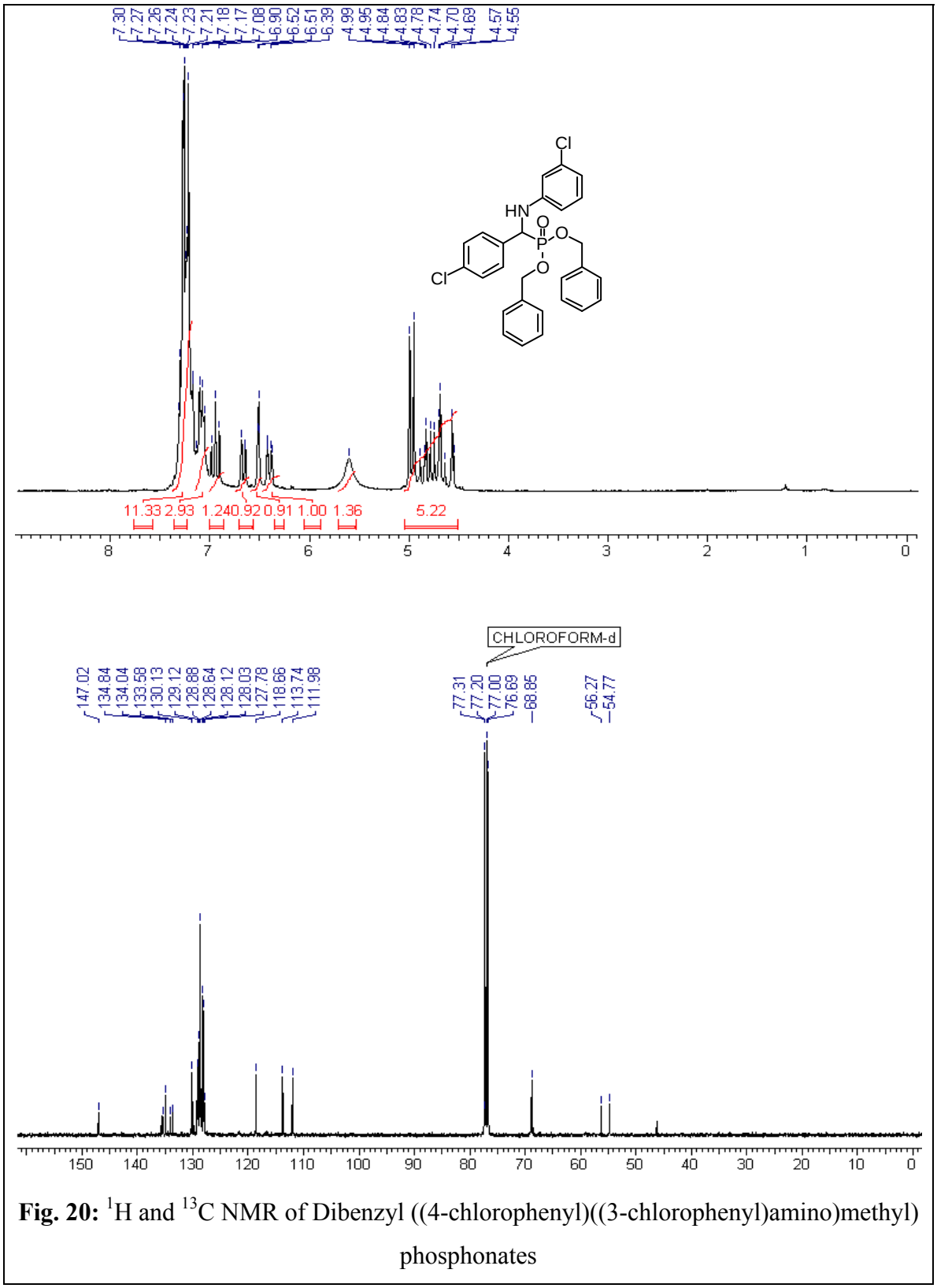


Fig. 20: ^{1}H and ^{13}C NMR of Dibenzyl ((4-chlorophenyl)((3-chlorophenyl)amino)methyl) phosphonates

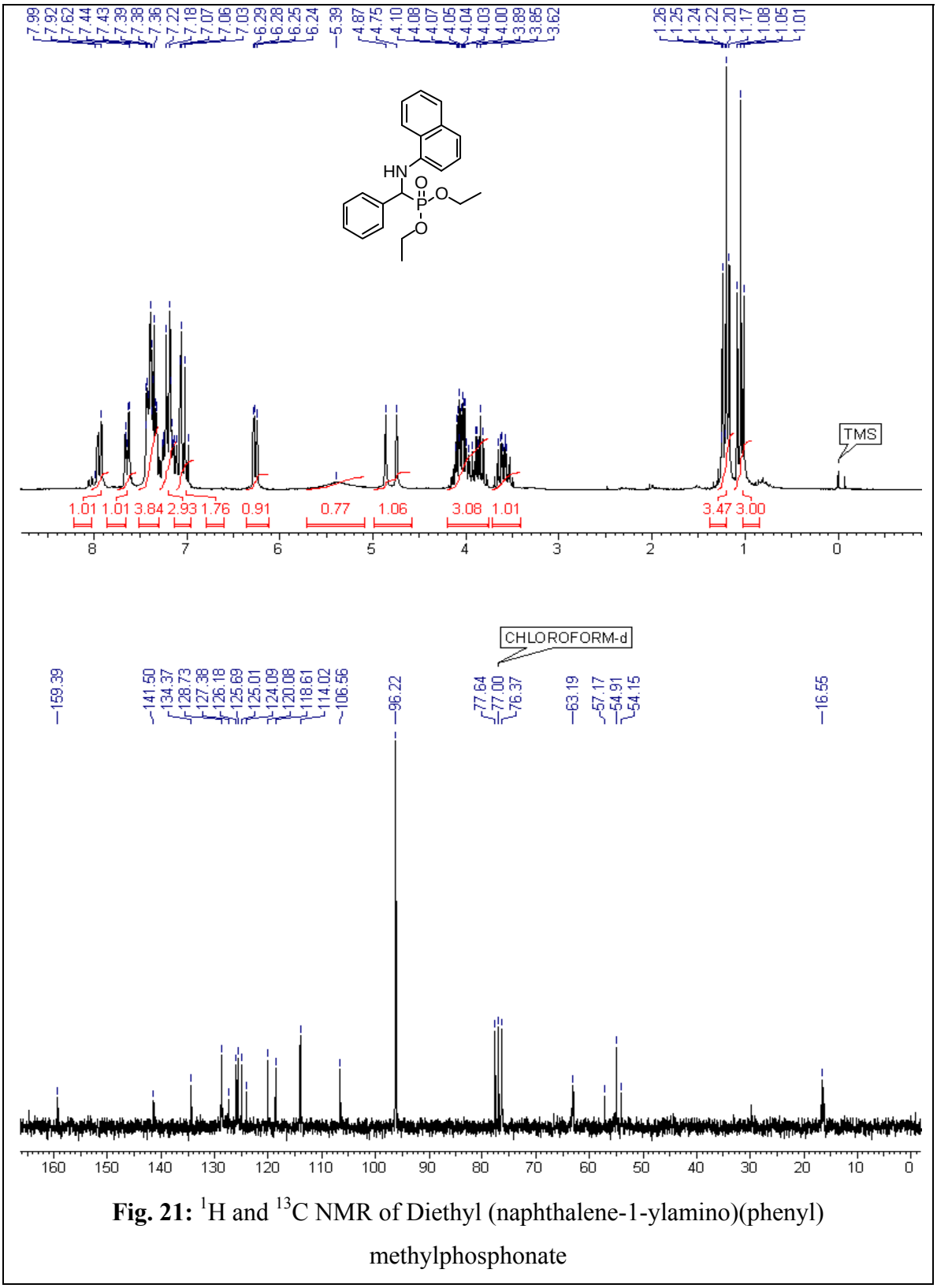


Fig. 21: ^{1}H and ^{13}C NMR of Diethyl (naphthalene-1-ylamino)(phenyl) methylphosphonate

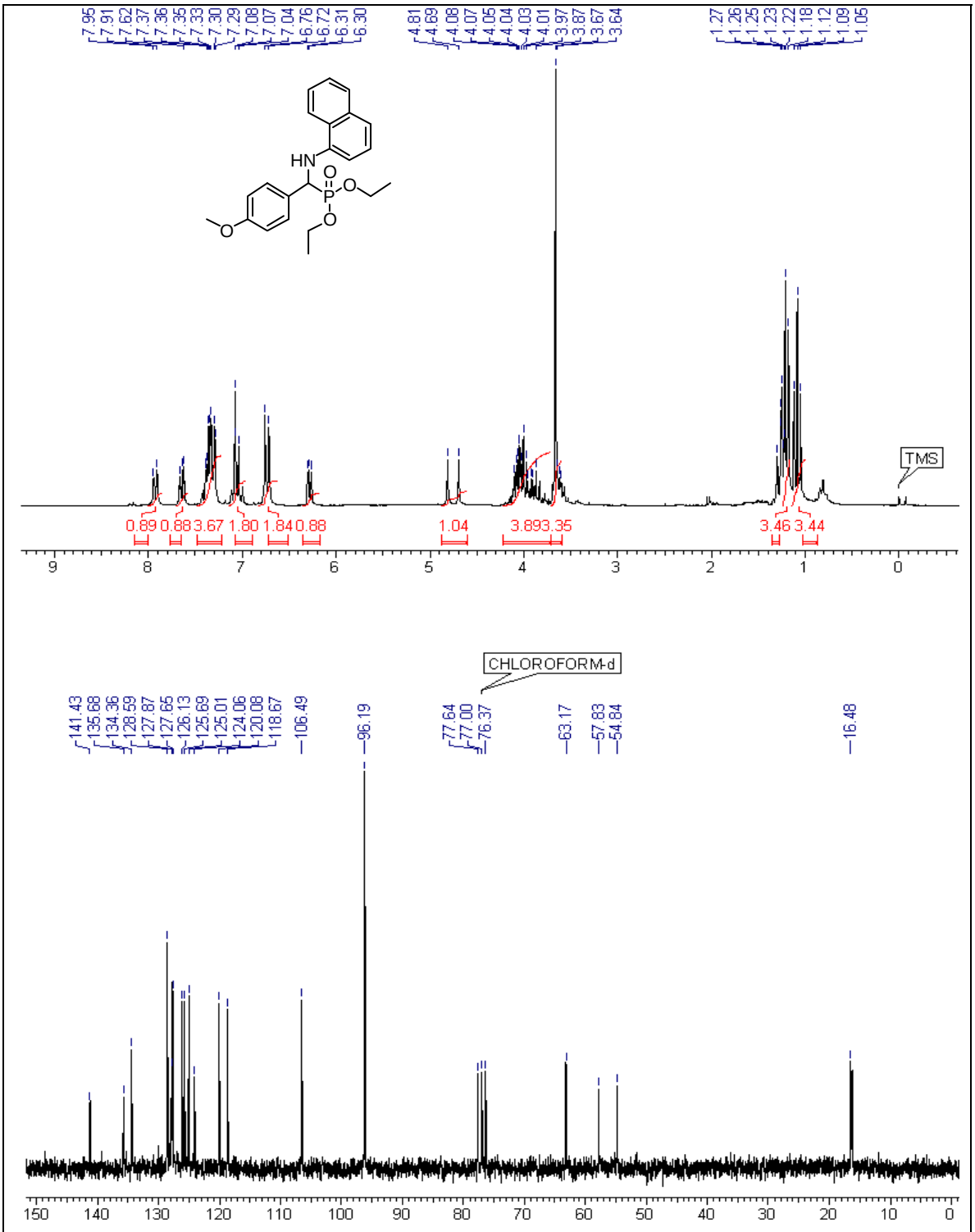


Fig. 22: ^{1}H and ^{13}C NMR of Diethyl (4-methoxyphenyl)(phenylamino) methylphosphonate

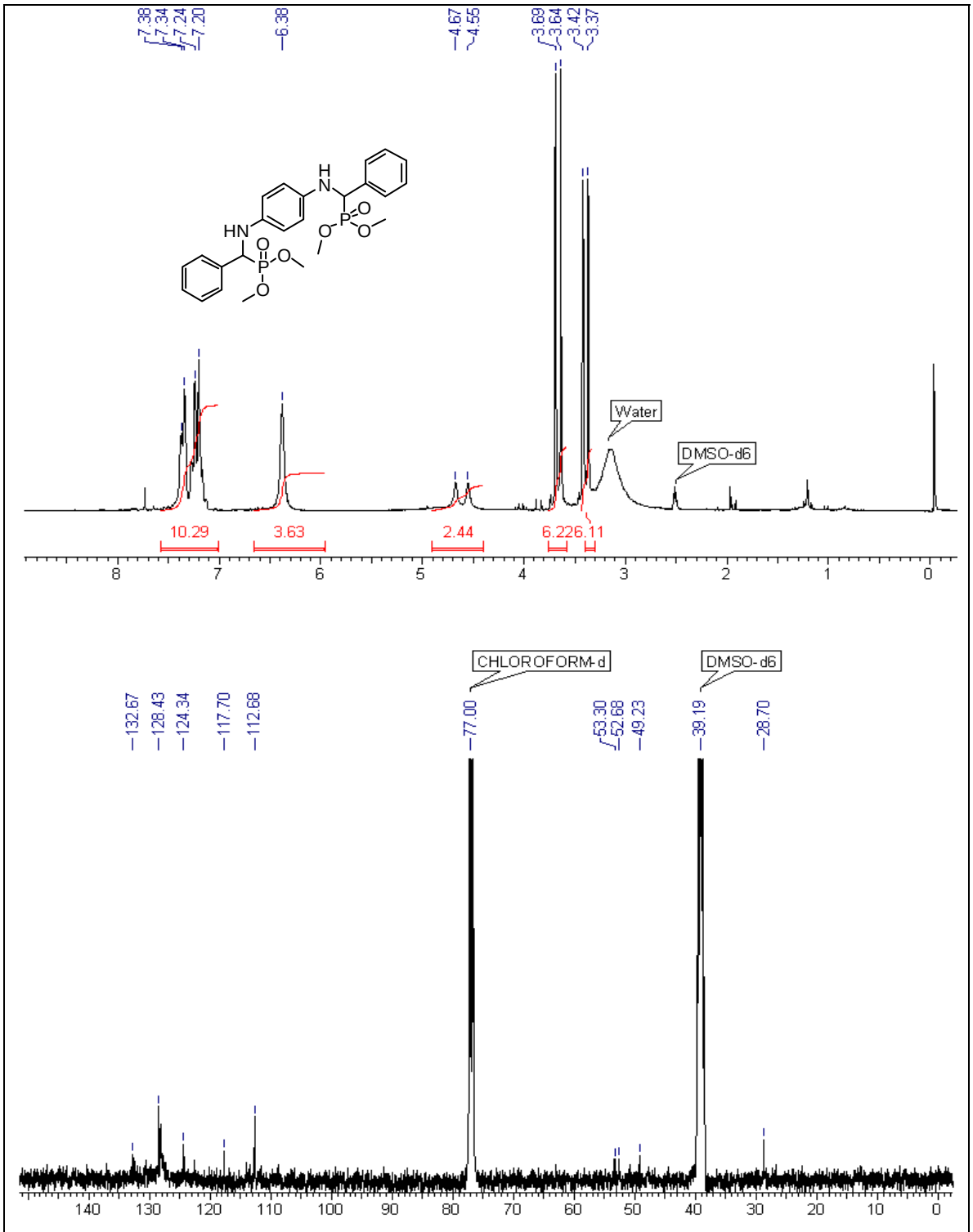


Fig. 23: ^{1}H and ^{13}C NMR of Tetramethyl ((1,4-phenylenebis(azanediyl)) bis(phenylmethylene))bis(phosphonates)

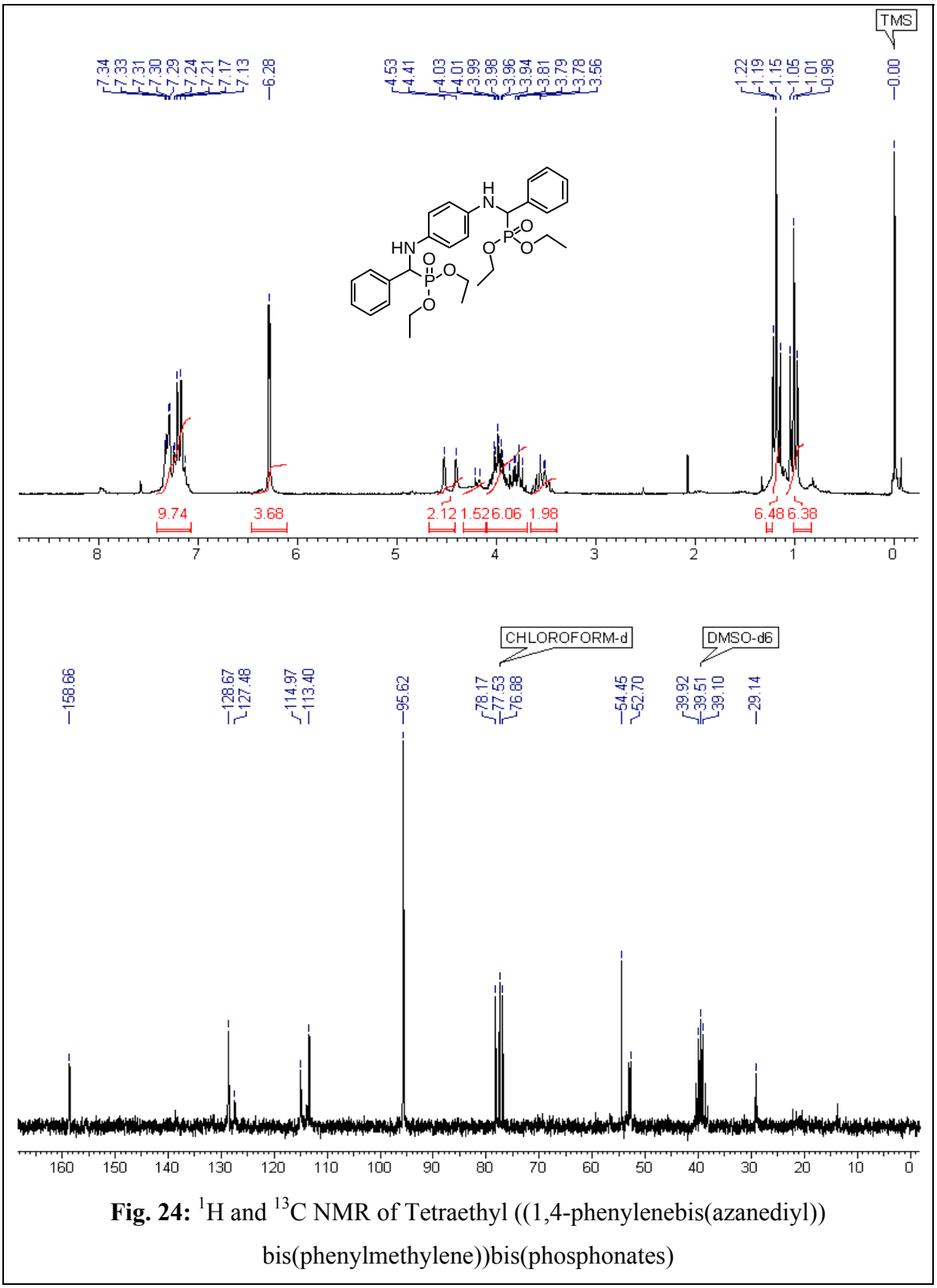


Fig. 24: ^{1}H and ^{13}C NMR of Tetraethyl ((1,4-phenylenebis(azanediyl)) bis(phenylmethylene))bis(phosphonates)

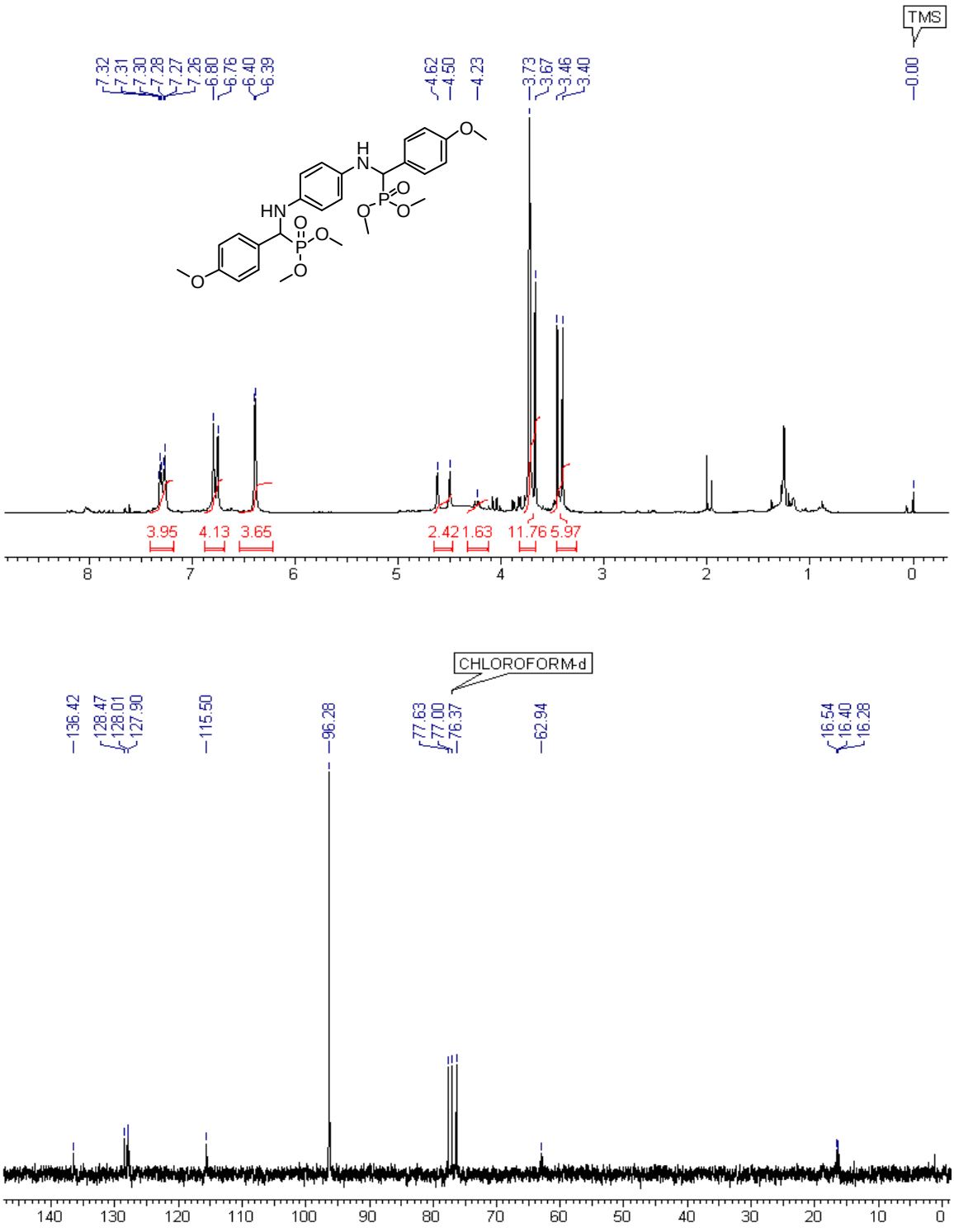


Fig. 25: ^{1}H and ^{13}C NMR of Tetramethyl ((1,4-phenylenebis(azanediyl))bis((4-methoxyphenyl)methylene)) bis(phosphonates)

Section-II

A novel and efficient synthesis of azaarene-substituted 3-hydroxy-2-oxindoles via sp^3 C-H functionalization of 2-methyl azaarenes and (2-azaaryl)methanes over heterogeneous, reusable silica-supported dodecatungstophosphoric acid catalyst

3.2.1 Introduction

The oxindole units are key structural constituent not only found in a wide range of alkaloid, natural products but also in biologically potential drugs such as

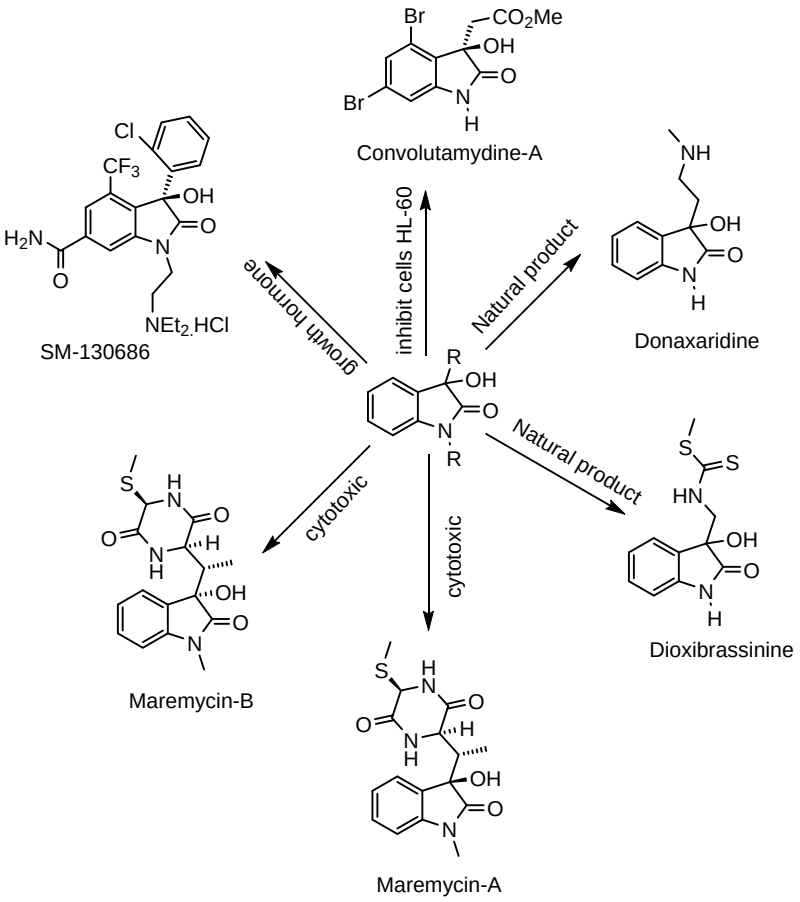


Fig. 26: Biological important of 3-hydroxy-2-oxindole

convolutamydines-A, SM-130686, maremycin-B, maremycin-A, dioxibrassinine, donaxaridine, (**Fig. 26**) which covers a wide spectrum of biological and/ or medicinal activities such as anti-HIV, anti-cancer, anti-tubercular, anti-oxidant, neuroprotective etc.[26] 3-substituted-3-hydroxy-2-oxindoles being the potent biological, and pharmaceutical value and also its biological activity known to be vary with substituent on the C-3 position, world wide efforts have been made by many researchers to design and develop the various strategies for its synthesis such as cyclization of ortho-prefunctionalized R-ketoanilides[27] or R-ketoamides,[28] hydroxylation of oxindoles,[29] catalytic arylation,[30] alkylation,[31] Friedel-Crafts reactions,[32] and organocatalyzed aldol[33] or Morita-Baylis-Hillman[34] in which isatin act as electrophiles to synthesize only 3-aryl/alkyl substituted-3-hydroxy-2-oxindoles. However, the synthesis of a complex organic molecule *via* C-H functionalization has gained considerable interest due to its exceptional advantages as easy access to form building block for the synthesis of a complex organic compounds using cheap and readily available starting materials with good atom economy.[35] As the C-H functionalization has exceptional advantages besides straightforward and convenient strategies, the C-H functionalization *via* sp^3 C-H bond activation as well C-C bond formation reactions have been well reported over transition metal,[36] Lewis and Bronsted acid catalyst.[37] Moreover, all these C-H functionalization approaches reported using either costly transition metal or moisture sensitive, toxic, and corrosive homogeneous (Lewis and Bronsted acid) catalysts in excess or stoichiometric quantity, which is leads to the problems of toxic waste disposal[38] long reaction time, high temperature and low yield for the desired product, hence the lack of commercial scale implementation.

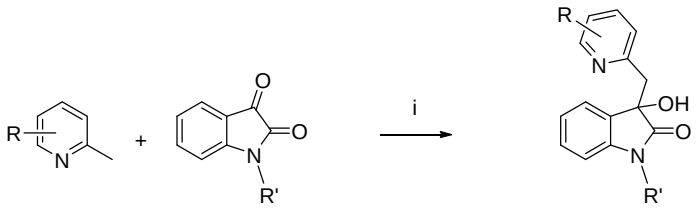
Even though the azaarenes-substituted 3-hydroxy-2-oxindoles are one of the highly promising intermediate of various potent drugs, surprisingly so far only few approaches of its synthesis *via* sp^3 C-H functionalization of 2-methyl azaarenes have been reported in literature.

3.2.2 Review of literature

Litrature survey revels that, the synthesis of azaarenes substituted 3-hydroxy-2-oxindoles from the reaction of 2-substituted azaarenes with isatin in the presence of trifluoromethanesulfonic acid (TfOH),[39] Iodine (I_2)[40] as catalyst and also in michrowave[41] have been reported in literature, which are described below.

Xingwei Li approach[39]

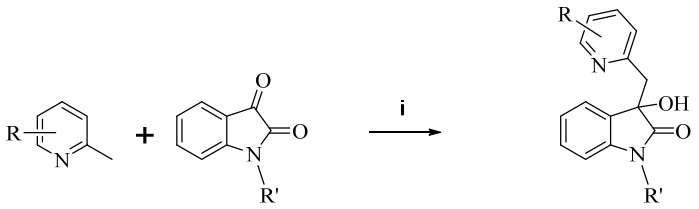
In this approach, Xingwei Li *et al.* have treated various 2-substituted azaarenes with various isatin in the presence of TfOH at 120 ^oC using 1, 4 Dioxane as a solvent in the pressure tube for 48 h (**Scheme 8**).



Scheme 8: *Reagents and reaction conditions*: (i) Isatin (0.3 mmol), azaarene (1.2 mmol), TfOH (10 mol%), 1, 4-dioxane (1 mL), 120 ^oC, 48 h.

Rok Lee approach[40]

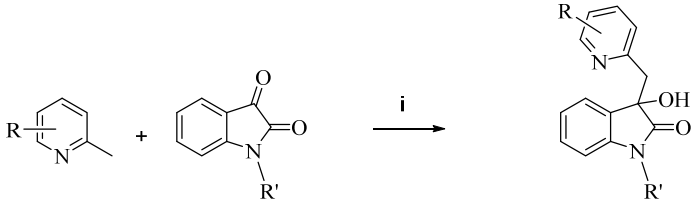
In this approach, Rok Lee *et al.* have treated various 2-substituted azaarenes with various isatin in a 1, 4-dioxane as solvent in the presence of I_2 as a catalyst under the reflux condition for 8 h (**Scheme 9**).



Scheme 9: *Reagents and reaction conditions*: (i) Isatin (1 mmol), azaarene (2.5 mmol), I_2 (20 mol%), 1, 4-dioxane (1 mL), reflux, 8 h.

Meshram approach[41]

In this approach, Meshram *et al.* have treated various 2-substituted azaarenes with various isatin in the presence of water under the microwave irradiations for 10 min, afforded desired product in a low yield (**Scheme 10**).



Scheme 10: *Reagents and reaction conditions*: (i) Isatin (1 mmol), azaarene (3 mmol), water (2 mL), microwave (MW), 10-15 min.

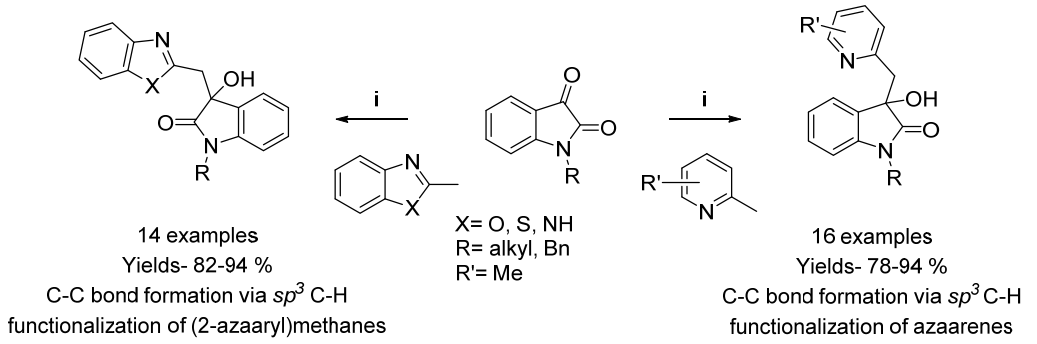
3.2.3 Present Work

3.2.3.1 Objectives

Nonetheless, these approaches reported in the literature so far lack general applicability or practical approach and hence suffer from one or other limitations such as use of excess or stoichiometric quantity, toxic, corrosive homogeneous catalysts involving tedious separation procedure as well the main drawback is incompatibility of catalysts in which unprotected isatin either reacts or decompose in the presence of it, causes occurrence of undesired reaction, hence poor yield to desired product.

Owing to the important application of the azaarenes substituted 3-hydroxy-2-oxindoles in

the life sciences to construction and design potent drugs, its cost effective, efficient synthesis of various architecture units *via* sp^3 C-H functionalization of 2-methyl azaarenes under environment friendly reaction conditions using recyclable benign catalysts is still challenging and an active research area. To the best of our knowledge, so far no report on the sp^3 C-H functionalization of 2-methyl azaarenes and (2-azaaryl)methanes using heterogeneous, reusable catalyst has been published in the literature. Hence, this section describes general, cost effective, rapid, environmentally friendly synthesis of azaarene-substituted 3-hydroxy-2-oxindoles via sp^3 C-H functionalization of 2-substituted azaarenes and (2-azaaryl)methanes with isatin over the 20 % DTP/SiO_2 as a heterogeneous reusable catalyst in DMF at 120 ^oC for 8 h (**Scheme 11**).



Scheme 11: *Reagents and reaction conditions*: (i) Isatin (1 mmol), azaarene (2 mmol), 20 % DTP/SiO_2 (50 mg), DMF (5 mL) at 120 ^oC, 8 h.

3.2.4 Results and discussion

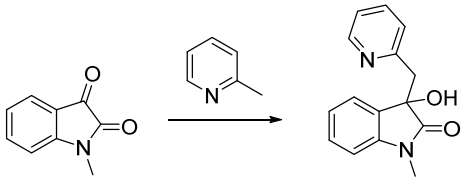
To develop protocol for synthesis of azaarene-substituted 3-hydroxy-2-oxindoles *via* sp^3 C-H functionalization, N-methyl isatin(1 mmol), 2-picoline(2 mmol), catalyzed by 50 mg 20 % DTP/SiO_2 catalyst in a 5 mL solvent was selected as model reaction to optimized reaction conditions. Initially, the screening of different solvents such as

dimethylformamide, toluene, 1, 4-dioxane, THF, and acetonitrile were carried out at different temperature. However, DMF solvent (**Table 5**, entry **2**) gives the desired product in a 93 % isolated yield in 8 h, whereas neat reaction condition, toluene and 1,4-dioxane solvent gives 90 %, 60 % and 86 % yield, respectively (**Table 5**, entries **1, 3** and **4**) in 24 h. The formation of desired product was not observed in THF and acetonitrile solvents (**Table 5**, entry **5** and **6**).

The promising results using DMF as a solvent over DTP/SiO_2 catalyst, made us enthusiastic to develop and/ or explore the scope of various acid catalysts for the synthesis of azaarene- substituted 3-hydroxy-2-oxindoles *via* sp^3 C-H functionalization of 2-methyl azaarenes. Various supported and unsupported acid catalysts were screened at 120 ^oC in DMF solvent. However, silica supported dodecatungstophosphoric acid catalyzed *via* sp^3 C-H functionalization of 2-methyl azaarenes provided excellent yield to the desired product (**Table 5**, entry **2**) as compared to unsupported and supported acid catalysts such as $MgCl_2$, $ZnCl_2$ and $ZnCl_2$/silica, sulphated zirconia, respectively (**Table 5**, entries **9-12**). The formation of desired product was not observed in the absence of catalyst as well on pure silica even after 30 h (**Table 5**, entry **7** and **8**).

Delighted with the results of catalyst screening made us to further optimized DTP loading, catalyst loading, interestingly, increasing the DTP loading from 10 to 20 % resulted in a dramatic enhancement in the yield from 72 % to 93 % (**Table 5**, entry **13, 2**), however, no improvement in the yield was observed by further increasing 30 % DTP loading (**Table 5**, entry **14**). By taking 20 % as an optimal DTP loading, the increasing catalyst loading from 25 mg to 50 mg resulted in a drastic increase in the yield from 58 % to 93 % (**Table 5**, entry **15** and **2**); moreover, no further increase in yield was observed

Table 5: Optimization of reaction condition for the reaction of N-methyl isatin and picoline[a]



Entry	Solvent	Catalyst	Temp (^{o}C)	Time (h)	Yield (%)[b]
Effect of solvent					
1	2-Picoline	DTP/SiO_2	120	24	90
2	DMF	DTP/SiO_2	120	08	93
3	Toluene	DTP/SiO_2	110	24	60
4	1,4-dioxane	DTP/SiO_2	100	24	86
5	THF	DTP/SiO_2	66	24	NR[c]
6	Acetonitrile	DTP/SiO_2	82	24	NR[c]
Catalyst screening					
7	DMF	-	120	30	NR[c]
8	DMF	SiO_2	120	30	NR[c]
9[d]	DMF	$MgCl_2$	120	8	58
10[d]	DMF	$ZnCl_2$	120	8	47
11	DMF	$ZnCl_2/SiO_2$	120	8	38
12	DMF	Sulphated Zirconia	120	8	52
Effect of DTP Loading					
13[e]	DMF	DTP/SiO_2	120	8	72
14[f]	DMF	DTP/SiO_2	120	8	93
Effect of catalyst loading					
15	DMF	DTP/SiO_2 (25 mg)	120	8	58
16	DMF	DTP/SiO_2 (100 mg)	120	8	93
Effect of temperature					

Table 5 (*Continued*)

17	DMF	DTP/SiO_2	80	16	NR[c]
18	DMF	DTP/SiO_2	100	10	67
19	DMF	DTP/SiO_2	150	8	78
Effect of time					
20	DMF	DTP/SiO_2	120	6	68
21	DMF	DTP/SiO_2	120	10	93

[a]Reaction conditions: N-methyl isatin (1 mmol), 2-picoline (2 mmol), solvent (5 mL), catalyst (50 mg).

[b]Isolated yields after chromatographic purification.

[c]No reaction.

[d]20 mol % catalyst was used.

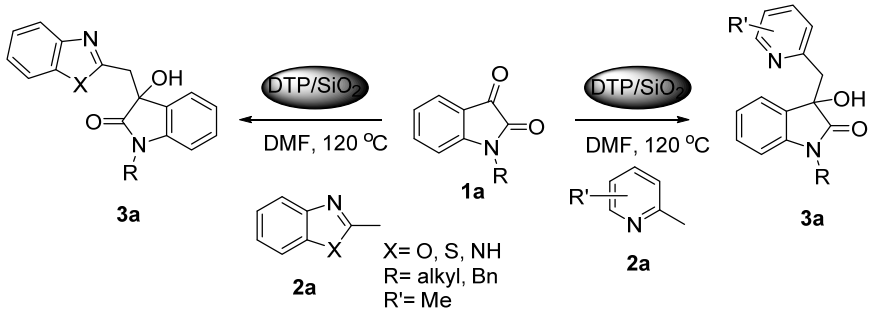
[e]10 % DTP/SiO_2 was used.

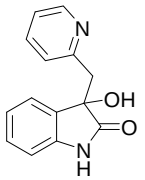
[f]30 % DTP/SiO_2 was used.

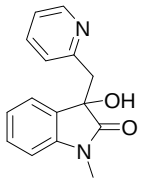
by increasing catalyst loading by 100 mg (**Table 5**, entry **16**). Finally, studies were undertaken to optimize the reaction temperature and time, increasing the reaction temperature from 80-150 ^oC, resulted no reaction at 80 ^oC (**Table 5**, entry **17**), whereas the yield of desired product was increased with increasing temperature from 100-120 ^oC (**Table 5**, entry **18** and **2**).

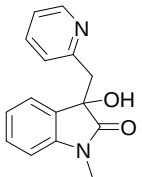
However, yield of desired product decreased by further increasing reaction temperature (**Table 5**, entry **19**). The yield of desired product was increased with increasing reaction time from 6 h to 8 h (**Table 5**, entry **20** and **2**) and remains unaltered by further increasing reaction time (**Table 5**, entry **21**). The studies of optimization reaction condition (**Table 5**, entry **1-21**) reveals that catalyst with 20 % DTP loading and 50 mg catalyst concentration shows excellent catalytic activity at 120 ^oC in 8 h. (**Table 5**, entry**2**). The excellent performance of DTP/SiO_2 catalyst at optimized reaction condition, encourage us to establish general applicability and/ or compatibility of DTP/SiO_2 catalyst with various substrate, the reaction of various N-substituted isatin with various 2-

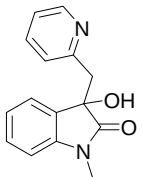
Table 6: Synthesis of azaarene-substituted 3-hydroxy-2-oxindoles via sp^3 C-H functionalization of 2-methyl azaarenes and (2-azaaryl)methanes with isatin catalyzed by DTP/SiO_2[a, b]

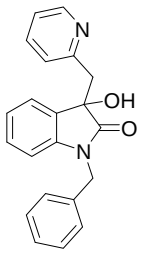


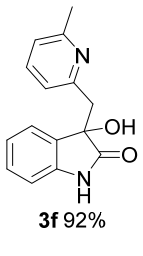

3a 90%


3b 93%


3c 92%


3d 91%


3e 92%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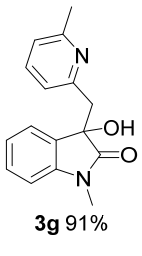
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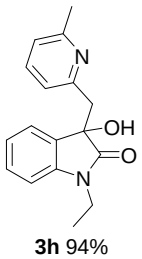
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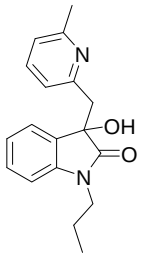
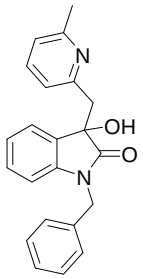

3i 90%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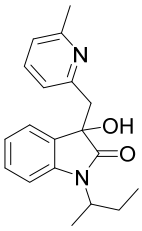
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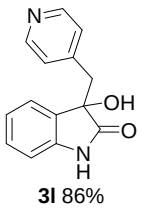
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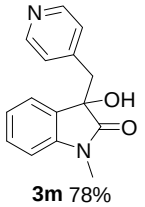
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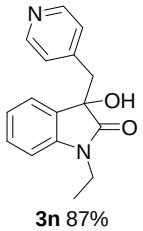
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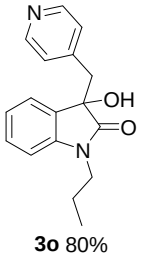
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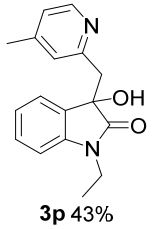
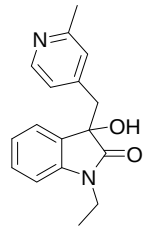

3p 43%

Table 6 (*Continued*)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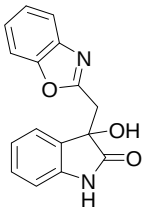
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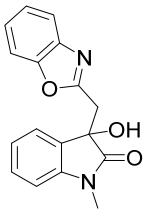
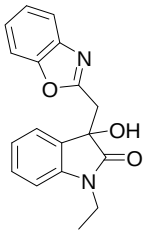

3s 94%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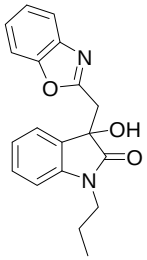
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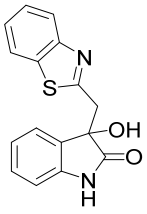
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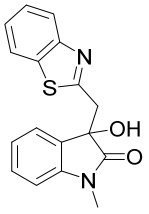
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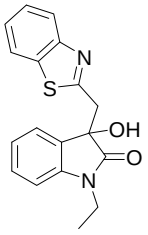
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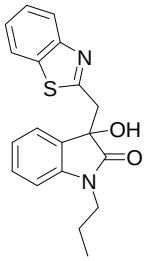
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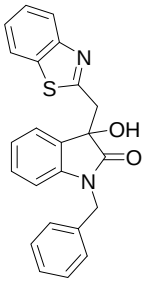
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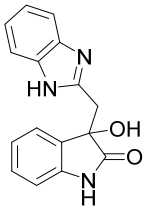
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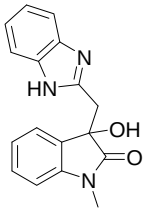
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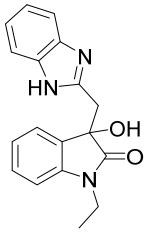
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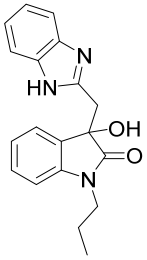
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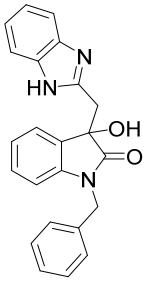

3ae 85%

[a]Reaction conditions: Isatin (1 mmol), azaarene (2 mmol), 20 % DTP/SiO_2 (50 mg) in DMF (5 mL) at 120 ^oC for 8 h.

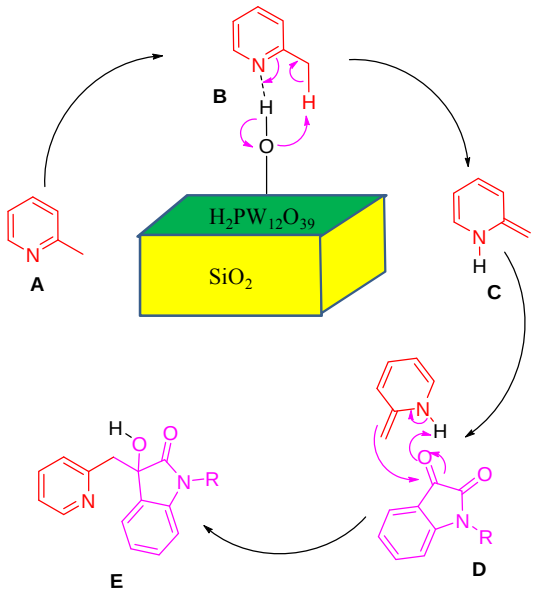
[b]Isolated yields after chromatographic purification.

substituted azaarenes have been investigated and results are illustrate in **Table 6**. Interestingly, various N-substituted isatin was reacted smoothly with 2-substituted azaarenes in the presence of DTP/SiO_2 catalyst at optimized reaction conditions and gave the corresponding desired product in good to excellent yield (**Table 6**, entries **3a-ae**).

The *N*-unprotected and protected isatin such as NH protic, N-methyl, -ethyl, -propyl, -isobutyl, -benzyl isatin were reacted smoothly without any problems with 2-picoline, 2, 6- lutidine gave 90-94 % isolated yields to desired product (**Table 6**, entries **3a-k**), whereas 4-picoline gave 78-87 % yields (**Table 6**, entries **3l-o**). However, *N*-ethyl isatin reacted with 2, 4-lutidine, gives comparable yields to the corresponding 2-substituted and 4-substituted products as 43 % and 39 %, respectively (**Table 6**, entries **3p-q**). The achievement of an excellent results on various 2-substituted azaarenes with *N*-substituted isatin, develop a keen interest to further elaborate the scope to (2-azaaryl)methanes (2-methylbenzoxaxole/2-methylbenzothiazole/2-methylbenzimidazole) under the optimized reaction condition. Surprisingly, NH protic, N-methyl, -ethyl, -propyl and/or -benzyl, isatin was successfully reacted with 2-methylbenzoxaxole/ 2-methylbenzothiazole/2-methylbenzimidazole, provided 82-94 % isolated yields to desired products (**Table 6**, entries **3r-ae**). From these results, it is very much clear that DTP/SiO_2 catalyst show amazing performance irrespective of the protected/ unprotected isatin and/ or 2-substituted azaarenes and hence developed approach is highly effective, promising, and general for the synthesis of variety of azaarene-substituted 3-hydroxy-2-oxindoles derivatives *via* sp^3 C-H functionalization of 2-substituted azaarene with isatin in the presence of DTP/SiO_2 catalyst.

As per earlier reported in the literatures,[26d, 39] the probable mechanism proposed for the synthesis of azaarene-substituted 3-hydroxy-2-oxindoles is shown in **Scheme 12**. As shown in **Scheme 12**, the predicted mechanism involves the protonation of 2-picoline over the DTP/SiO_2 catalyst as shown in **B** followed by C-H bond cleavage give enamine **C**, which then add as nucleophile to isatin as shown in **D** to release instantly

corresponding desired product **E** by formation of C-C bond.



Scheme 12: Plausible DTP/SiO_2 catalysed sp^3 C-H functionalization of 2-methylazaarenes

The recovery and recyclability of catalysts is highly demandable world wide in near future to achieve environmental sustainable and economical viable processes. Hence, the recyclability and recovery of DTP/SiO_2 catalyst was investigated for the synthesis of

Table 7: Recoverability and reusability of DTP/SiO_2[a]

Entry	Run	Yield (%)
1	Fresh	93
2	Run-1	93
3	Run-2	92
4	Run-3	93
5	Run-4	93

[a]Reaction conditions: N-methyl isatin (1 mmol), picoline (2 mmol), DTP/SiO_2 (50 mg) in DMF (5 mL) at 120 ^oC for 8 h.

[b]Isolated yields after chromatographic purification.

azaarene-substituted 3-hydroxy-2-oxindoles by the reaction of N-methyl isatin with picoline at optimized reaction condition, and results are given in **Table 7**. The DTP/SiO_2 catalyst was recovered quantitatively and recycled again several times without loss of catalytic activity (**Table 7**, entries **2-5**). The isolated yield obtained at end of 4^{th} recycle of DTP/SiO_2 catalyst (**Table 7**, entry **5**) is very much consistent as of fresh DTP/SiO_2 catalyst (**Table 7**, entry **1**).

The consistent catalytic activity of reused DTP/SiO_2 catalyst indicates that the reused catalyst shows excellent performance for the synthesis of azaarene-substituted 3-hydroxy-2-oxindoles.

3.2.5 Conclusion

In conclusion, a novel, general, cost effective approach over heterogeneous reusable DTP/SiO_2 catalyzed sp^3 C-H functionalization of 2-substituted azaarenes and (2-azaaryl)methanes with isatin for the rapid and efficient synthesis of azaarene-substituted 3-hydroxy-2-oxindoles in good to excellent yield at short reaction time has been developed. The DTP/SiO_2 catalyst was recovered by simple filtration from the reaction mixture and reused several times without the loss of catalytic activity. The described protocol is simple, clean, and environmentally friendly and may be applicable for various C-H functionalization reactions, hence further studies are in progress.

3.2.6 Experimental Section

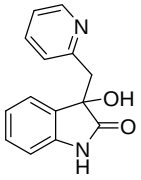
3.2.6.1 A typical experimental procedure for synthesis of azaarene-substituted 3-hydroxy-2-oxindole over the 20 % DTP/SiO_2:

A mixture of isatin (1 mmol), picoline (2 mmol) in a 5 mL DMF solvent was stirred at 120 ^oC for 8 h in the presence of 50 mg DTP/SiO_2 catalyst. The completion of the

reaction was monitored by TLC. After completion of reaction, reaction mixture was diluted with ethyl acetate (10 mL) and catalyst was recovered by filtration. The filtrate was washed with aqueous $NaHCO_3$ and then with water followed by separation of aqueous layer and organic layer. The organic layer is dried over anhydrous Na_2SO_4 and concentrate in vacuum to gives the crude product. The crude product was purified by silica gel column chromatography using 70 : 30 ratio of petroleum ether-ethyl acetate to afford the pure azaarene-substituted 3-hydroxy-2-oxindole (**Table 6**). All the isolated reaction products were characterized and confirmed by NMR

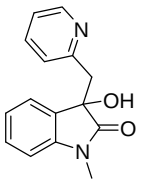
3.2.6.2 Spectral data

3-hydroxy-3-(pyridine-2-ylmethyl)indolin-2-one (3a)



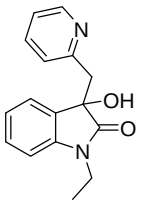
Yield: 90 %; white solid; mp: 152-154 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 3.24 (d, *J*=13.01 Hz, 1H), 3.36 (d, *J*=13.13 Hz, 1H), 6.37 (s, 1H), 6.70 (d, *J*=7.70 Hz, 1H), 6.84-6.99 (m, 2H), 7.10-7.21 (m, 3H), 7.59-7.68 (m, 1H), 8.35 (d, *J*=4.55 Hz, 1H), 10.20 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 45.31, 75.87, 109.44, 121.28, 121.84, 124.53, 124.78, 128.97, 131.17, 136.01, 141.82, 148.50, 156.29, 178.78.

3-hydroxy-1-methyl-3-(pyridine-2-ylmethyl)indolin-2-one (3b)



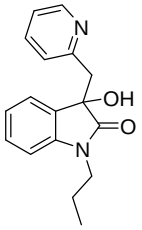
Yield: 93 %; Yellow solid, mp: 135-137 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.05 (d, *J*=14.78 Hz, 1H), 3.10 (s, 3H), 3.25 (d, *J*=14.78 Hz, 1H), 6.71-6.78 (m, 2H), 6.86 (t, *J*=7.45 Hz, 1H), 7.0 (d, *J*=7.71 Hz, 1H), 7.15 – 7.25 (m, 2H), 7.60 (t, *J*=7.71 Hz, 1H), 8.49 (d, *J*=4.81 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.09, 42.64, 76.06, 108.20, 122.34, 122.68, 123.85, 124.85, 129.32, 130.76, 137.34, 142.82, 147.72, 157.13, 176.74.

1-ethyl-3-hydroxy-3-(pyridine-2-ylmethyl)indolin-2-one (3c)



Yield: 92 %; Yellow solid, mp: 94-96 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J*=7.20 Hz, 3H), 3.10 (d, *J*=14.53 Hz, 1H), 3.26 (d, *J*=14.53 Hz, 1H), 3.64 (q, *J*=7.2 Hz, 2H), 6.73-6.90 (m, 3H), 7.00 (d, *J*=7.71 Hz, 1H), 7.14-7.26 (m, 2H), 7.57-7.66 (m, 1H), 8.50 (d, *J*=4.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.49, 34.61, 42.67, 76.03, 108.34, 122.51, 124.09, 124.91, 129.30, 131.09, 137.45, 141.97, 147.67, 157.25, 176.24.

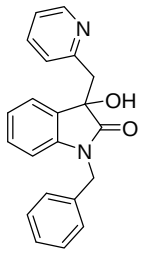
3-hydroxy-1-propyl-3-(pyridine-2-ylmethyl)indolin-2-one (3d)



Yield: 91 %; Off white solid, mp: 102-104 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J*=7.45 Hz, 3H), 1.74 (q, *J*=7.32 Hz, 2H), 3.20 (d, *J*=14.65 Hz, 1H), 3.35 (d, *J*=14.65 Hz,

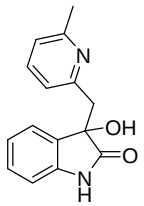
1H), 3.68 (sextet, 2H), 6.85 (d, *J*=7.83 Hz, 1H), 6.94-7.01 (m, 2H), 7.13 (d, *J*=7.71 Hz, 1H), 7.25-7.37 (m, 2H), 7.73 (t, *J*=7.71 Hz, 1H), 8.61 (d, *J*=4.80 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.28, 20.55, 41.40, 42.77, 75.97, 108.47, 122.37, 122.46, 124.00, 124.91, 129.25, 130.96, 137.46, 142.31, 147.61, 157.78, 176.58.

1-benzyl-3-hydroxy-3-(pyridine-2-ylmethyl)indolin-2-one (3e)



Yield: 92 %; Brown solid, mp: 111-113^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.18 (d, *J*=14.65 Hz,1H), 3.30 (d, *J*=14.65 Hz, 1H), 4.70 (d, *J*=15.66, 1H), 4.85 (d, *J*=15.66, 1H), 6.60 (d, *J*=7.71 Hz, 1H), 6.87 (t, *J*=6.7 Hz, 2H), 7.03-7.28 (m, 8H), 7.61-7.68 (m, 1H), 8.51 (d, *J*=4.67 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 42.66, 43.63, 76.03, 109.26, 122.81, 123.99, 125.17, 127.23, 127.56, 128.72, 129.30, 130.80, 135.57, 137.83, 141.94, 147.33, 156.83, 176.69.

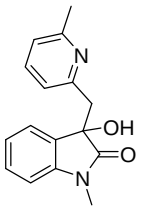
3-hydroxy-3-((6-methylpyridin-2-yl)methyl)indolin-2-one (3f)



Yield: 92 %; Red solid, mp: 178-180 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 2.34 (s, 3H), 3.15 (d, *J*=13.26 Hz, 1H), 3.32 (d, *J*=13.39 Hz, 1H), 6.43 (s, 1H), 6.73 (d, *J*=7.58

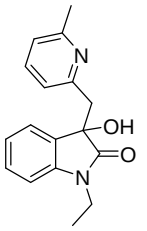
Hz, 1H), 6.87-7.18 (m, 5H), 7.53 (t, *J*=7.71 Hz, 1H), 10.21 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 23.96, 44.84, 75.80, 109.38, 121.14, 121.35, 124.76, 128.92, 131.37, 136.36, 141.91, 155.69, 156.54, 178.81.

3-hydroxy-1-methyl-3-((6-methylpyridin-yl)methyl)indolin-2-one (3g)



Yield: 91 %; Yellow solid, mp: 126-127 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ δ 2.67 (s, 3H), 2.99 (d, *J*=14.53 Hz, 1H), 3.22 (s, 3H), 3.30 (d, *J*=14.53 Hz, 1H), 6.83-7.01 (m, 4H), 7.18-7.35 (m, 2H), 7.62 (t, *J*=7.45 Hz, 1H), 8.01 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.96, 26.08, 42.10, 75.98, 108.14, 122.03, 122.63, 123.80, 129.23, 131.16, 137.66, 142.8, 156.61, 176.63.

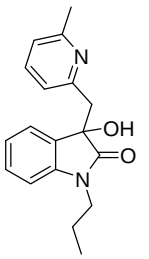
1-ethyl-3-hydroxy-3-((6-methylpyridin-2-yl)methyl)indolin-2-one (3h)



Yield: 94 %; Yellow solid, mp: 126-127 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (t, *J*=7.07 Hz, 3H), 2.57 (s, 3H), 3.16 (d, *J*=14.53 Hz, 1H), 3.20 (d, *J*=14.53 Hz, 1H), 3.65 (q, *J*=7.20 Hz, 2H), 6.74-6.90 (m, 3H), 7.08-7.32 (m, 2H), 7.53 (t, *J*=7.46 Hz, 1H), 7.90 (s, 1H),; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.54, 23.84, 34.61, 42.12, 75.93, 108.32,

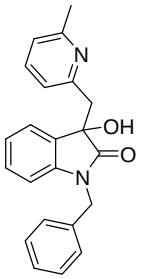
122.49, 124.10, 129.22, 131.38, 137.8, 141.92, 156.82, 176.17.

3-hydroxy-3-((6-methylpyridin-2-yl)methyl)-1-propylindolin-2-one (3i)



Yield: 90 %; Yellow solid, mp: 101-103 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J*=7.45 Hz, 3H), 1.75 (q, *J*=7.32 Hz, 2H), 2.64 (s, 3H), 3.08 (d, *J*=14.65 Hz, 1H), 3.32 (d, *J*=14.65 Hz, 1H), 3.68 (sextet, *J*=5.30 Hz, 2H), 6.83-6.98 (m, 4H), 7.19 (d, *J*=7.71 Hz,1H), 7.31 (t, *J*=7.71 Hz, 1H), 7.59 (t, *J*=7.71 Hz, 1H), 7.99 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.25, 20.55, 24.01, 41.35, 42.38, 75.94, 108.41, 121.66, 121.95, 122.36, 123.93, 129.11, 131.26, 137.55, 142.26, 156.98, 176.59.

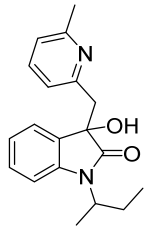
1-benzyl-3-hydroxy-3-((6-methylpyridin-2-yl)methyl)indolin-2-one (3j)



Yield: 90 %; Yellow solid, mp: 176-178 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.58 (s, 3H), 3.30 (m, 2H), 4.74 (d, *J*=15.66 Hz, 1H), 4.86 (d, *J*=15.66 Hz, 1H), 6.62 (d, *J*=7.71 Hz, 1H), 6.85 (s, 3H), 7.04-7.24 (m, 8H), 7.55 (t, *J*=7.58 Hz, 1H), 7.88 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.22, 42.18, 43.61, 75.97, 109.24, 122.33, 122.79, 124.00, 127.57,

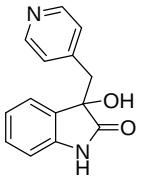
128.74, 129.22, 131.14, 135.63, 138.11, 141.88, 156.83, 176.63.

1-Sec-butyl-3-hydroxy-3-((6-methylpyridin-2-yl)methyl)indolin-2-one (3k)



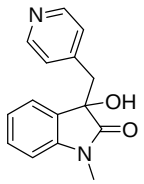
Yield: 93 %; Red Gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.79-0.86 (m, 3H), 1.38 (d, *J*=7.08 Hz, 3H), 1.62-1.71 (m, 1H), 2.59 (s, 3H), 3.12 (s, H), 4.14-4.31 (m, 1H), 6.82-6.88 (m, 4H), 7.08-7.19 (m, 2H), 7.54 (t, *J*=7.70 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.29, 17.79, 26.25, 26.40, 42.60, 49.85, 75.60, 109.74, 124.28, 129.04, 131.67, 137.86, 141.83, 156.84, 176.66.

3-hydroxy-3-(pyridine-4-ylmethyl)indolin-2-one (3l)



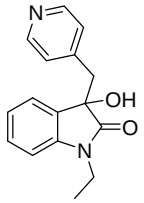
Yield: 86 %; Red solid, mp: 183-1185 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 3.04 (d, *J*=12.51 Hz, 1H), 3.25 (d, *J*=12.38 Hz, 1H), 6.32 (s, 1H), 6.7 (d, *J*=7.71 Hz, 1H), 6.94-7.01 (m, 3H), 7.14 – 7.24 (m, 2H), 8.36 (d, *J*=4.29 Hz, 2H), 10.21 (s, 1H),; **^{13}C NMR** (50 MHz, DMSO-d6): δ 42.60, 76.03, 109.48, 121.40, 124.54, 125.54, 129.16, 130.48, 141.51, 144.15, 148.76, 178.37.

3-hydroxy-1-methyl-3-(pyridin-4-ylmethyl)indolin-2-one (3m)



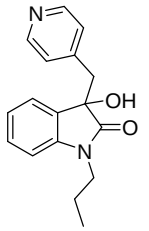
Yield: 78 %; Yellow solid, mp: 201-203 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.92 (s, 3H), 3.08 (d, *J*=12.51 Hz, 1H), 3.24 (d, *J*=12.63 Hz, 1H), 4.87 (s, 1H), 6.58 (d, *J*=7.71 Hz, 1H), 6.90 (d, *J*=5.05 Hz, 1H), 7.00 (d, *J*=7.33 Hz, 1H), 7.1 (d, *J*=6.32 Hz, 1H), 7.20 (t, *J*=7.58 Hz, 1H), 8.22 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.95, 43.91, 76.58, 108.43, 123.03, 124.19, 128.89, 129.92, 142.87, 145.11, 147.71, 177.32.

1-ethyl-3-hydroxy-3-(pyridine-4-ylmethyl)indolin-2-one (3n)



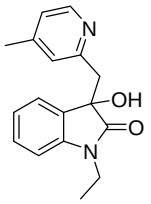
Yield: 87 %; Brawn solid, mp: 171-173 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J*=7.2 Hz, 3H), 3.12 (d, *J*=12.51 Hz, 1H), 3.26 (d, *J*=12.51 Hz, 1H), 3.31-3.66 (m, 2H), 4.58 (s, 1H), 6.60 (d, *J*=7.45 Hz, 1H), 6.86 (d, *J*=6.06 Hz, 2H), 7.01 (t, *J*=7.96 Hz, 1H), 7.17-7.25 (m, 2H), 8.21 (d, *J*=6.06 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.10, 34.54, 44.21, 76.59, 108.60, 122.94, 124.35, 125.92, 129.00, 130.02, 142.08, 145.16, 147.64, 176.71.

3-hydroxy-1-propyl-3-(pyridine-4-ylmethyl)indolin-2-one (3o)



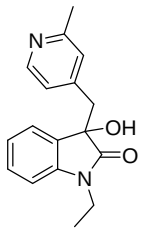
Yield: 80 %; White solid, mp: 164-166 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ δ 0.69 (t, *J*=7.58 Hz, 3H), 1.29 (q, *J*=7.32 Hz, 2H), 3.08-3.54 (m, 4H), 5.07 (s, 1H), 6.56 -6.60 (m, 1H), 6.82-6.85 (m, 2H), 6.99 (t, *J*=6.7 Hz, 1H), 7.15-7.23 (m, 2H), 8.15 (d, *J*=5.94 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.14, 20.35, 41.43, 43.96, 76.54, 108.64, 122.76, 124.27, 125.68, 129.14, 129.78, 142.57, 144.34, 148.18, 177.28.

1-ethyl-3-hydroxy-3-((4-methylpyridin-2-yl)methyl)indolin-2-one (3p)



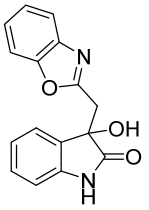
Yield: 43 %; Brawn solid, mp: 98-100 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (t, *J*=7.30 Hz, 3H), 2.25 (s, 3H), 2.95 (d, *J*=14.64 Hz, 1H), 3.24 (d, *J*=14.64 Hz, 1H), 3.66 (q, *J*=7.20 Hz, 2H), 6.73-8.89 (m, 4H), 7.02 (d, *J*=4.17 Hz, 1H), 7.14-7.22 (m, 1H), 8.35 (d, *J*=5.05 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.51, 21.07, 34.58, 42.42, 76.13, 108.28, 122.45, 123.25, 124.08, 125.47, 129.18, 131.38, 137.67, 141.99, 147.62, 148.52, 157.30, 176.37.

1-ethyl-3-hydroxy-3-((2-methylpyridin-4-yl)methyl)indolin-2-one (3q)



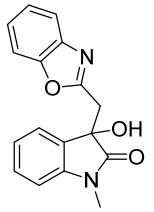
Yield: 39 %; White solid, mp: 109-111 °C; **^{1}H NMR (**200 MHz, $CDCl_3$): δ 0.94 (t, *J*=7.33 Hz, 3H), 2.46 (s, 3H), 3.12 (d, *J*=12.51 Hz, 1H), 3.26 (d, *J*=12.51 Hz, 1H), 3.43 (q, *J*=7.07 Hz, 2H), 6.64 (d, *J*=7.83 Hz, 1H), 6.78 (d, *J*=4.93 Hz, 1H), 7.02 (t, *J*=7.33 Hz, 1H), 7.20 (t, *J*=7.20 Hz, 3H), 8.14 (d, *J*=5.56 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 12.15, 22.80, 34.57, 44.21, 76.55, 108.61, 122.92, 124.37, 126.00, 128.87, 130.06, 142.07, 146.27, 156.46, 176.59.

3-(benzo[*d*]oxazol-2-ylmethyl)-3-hydroxyindolin-2-one (3r)



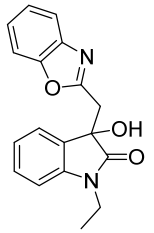
Yield: 88 %; Yellow solid, mp: 157-159 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 3.58 (d, *J*=14.15 Hz,1H), 3.72 (d, *J*=14.15 Hz, 1H), 6.61 (s,1H), 6.80 (d, *J*=7.71 Hz, 1H), 6.94 (t, *J*=6.94 Hz, 1H), 7.13 (d, *J*=6.69 Hz, 1H), 7.19-7.27 (m, 1H), 7.38 – 7. 54 (m, 2H), 7.89 – 7.94 (m, 1H), 8.03-8.07 (m, 1H), 10.39 (s, 1H); 13C **NMR** (50 MHz, DMSO-d6): δ 42.15, 74.69, 109.92, 121.79, 122.04, 122.45, 124.70, 125.11, 126.04, 129.72, 130.52, 135.31, 142.08, 152.07, 165.43, 178.00.

3-(benzo[*d*]oxazol-2-ylmethyl)-3-hydroxy-1-methylindolin-2-one (3s)



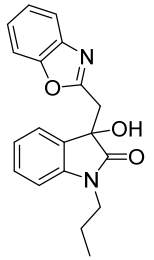
Yield: 94 %; White solid, mp: 102-104 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.22 (s, 3H), 3.55 (d, *J*=15.28 Hz, 1H), 3.75 (d, *J*=15.16 Hz, 1H), 5.43 (s, 1H), 6.83 (d, *J*=7.83 Hz, 1H), 6.95- 7.13 (m, 2H), 7.27 -7.54 (m, 3H), 7.87 (t, *J*=6.69 Hz, 1H), 8.05 (d, *J*=7.83 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.29, 40.90, 75.22, 108.44, 121.50, 122.75, 123.09, 124.28, 125.39, 126.37, 129.57, 129.94, 134.61, 143.16, 151.82, 166.17, 176.00.

3-(benzo[*d*]oxazol-2-ylmethyl)-1-ethyl-3-hydroxyindolin-2-one (3t)



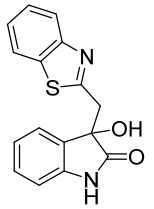
Yield: 91 %; Red solid, mp: 112-114 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J*=7.20 Hz, 3H), 2.90 (s, 1H), 3.56 (d, *J*=15.03 Hz, 1H), 3.72 (d, *J*=15.03 Hz, 1H), 3.78 (q, *J*=7.33 Hz, 2H), 6.84 (d, *J*=7.83 Hz, 1H), 7.00 (t, *J*=7.45 Hz, 1H), 7.13 (d, *J*=7.45 Hz, 1H), 7.26 -7.56 (m, 3H), 7.83-7.89 (m, 1H), 8.04 (d, *J*=7.45 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.49, 34.80, 41.14, 75.27, 108.53, 121.43, 122.88, 124.48, 125.25, 126.23, 129.86, 134.77, 142.29, 152.30, 165.74, 175.67.

3-(benzo[*d*]oxazol-2-ylmethyl)-3-hydroxy-1-propylindolin-2-one (3u)



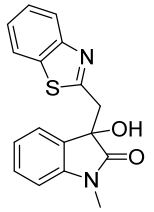
Yield: 89 %; Red Thick Gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96 (t, *J*=7.45 Hz, 3H), 1.72 (q, *J*=7.20 Hz, 2H), 3.52-3.77 (m, 4H), 5.47 (s, 1H), 6.82 (d, *J*=7.83 Hz, 1H), 6.94-7.13 (m, 2H), 7.33-7.54 (m, 3H), 7.82-8.05 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.39, 20.65, 41.27, 41.63, 75.25, 108.68, 121.41, 122.81, 122.96, 124.40, 124.67, 125.17, 126.14, 129.81, 134.85, 142.68, 152.59, 165.58, 176.08.

3-(benzo[*d*]thiazol-2-ylmethyl)-3-hydroxyindolin-2-one (3v)



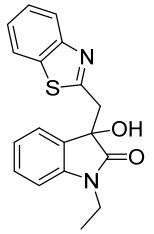
Yield: 86 %; Brawn solid, mp: 117-119 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 3.58 (d, *J*=14.15 Hz, 1H), 3.75 (d, *J*=14.15 Hz, 1H), 6.62 (s, 1H), 6.80 (d, *J*=7.71 Hz, 1H), 6.95 (t, *J*=7.45 Hz, 1H), 7.13-7.28 (m, 2H), 7.39-7.55 (m, 2H), 7.90-8.08 (m, 2H), 10.40 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 41.92, 74.39, 109.63, 121.72, 121.83, 124.55, 125.78, 129.33, 130.24, 135.39, 141.82, 151.81, 152.90, 165.09, 166.58, 177.71.

3-(benzo[*d*]thiazol-2-ylmethyl)-3-hydroxy-1-methylindolin-2-one (3w)



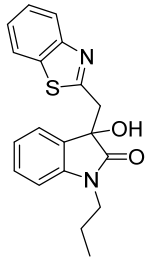
Yield: 90 %; Reddish solid, mp: 113-115 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.21 (s, 3H), 3.42 (d, *J*=15.16 Hz, 1H), 3.64 (d, *J*=15.16 Hz, 1H), 6.72 (d, *J*=7.71 Hz, 1H), 6.84-7.00 (m, 2H), 7.17-7.43 (m, 4H), 7.75-7.80 (m, 1H), 7.93-7.97 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.32, 40.99, 75.31, 108.44, 121.48, 123.09, 124.29, 125.31, 126.29, 129.94, 143.21, 165.87, 176.05.

3-(benzo[*d*]thiazol-2-ylmethyl)-1-ethyl-3-hydroxyindolin-2-one (3x)



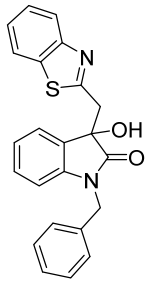
Yield: 89 %; Red solid, mp: 109-111 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16 (t, *J*=6.95 Hz, 3H), 3.41 (d, *J*=15.03 Hz, 1H), 3.58-3.76 (m, 3H), 6.72 (d, *J*=7.83, 1H), 6.87 (t, *J*=6.69 Hz, 1H), 7.01 (d, *J*=7.33 Hz, 1H), 7.15-7.41 (m, 3H), 7.76 (d, *J*=6.82 Hz, 1H), 7.92 (d, *J*=8.46 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 12.49, 34.78, 41.14, 75.29, 108.54, 121.42, 122.87, 124.45, 125.21, 126.18, 129.70, 129.85, 142.24, 152.47, 165.63, 175.72.

3-(benzo[*d*]thiazol-2-ylmethyl)-3-hydroxy-1-propylindolin-2-one (3y)



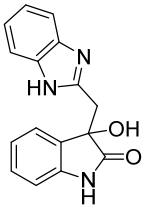
Yield: 89 %; Red solid, mp: 102-104 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96 (t, *J*=7.45 Hz, 3H), 1.70 (q, *J*=7.20 Hz, 2H), 3.45-3.77 (m, 4H), 6.82 (d, *J*=7.83 Hz, 2H), 6.97-7.02 (m, 2H), 7.25-7.51 (m, 4H), 7.82-8.05 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.74, 14.59, 21.00, 30.06, 42.01, 75.65, 109.07, 114.06, 121.77, 123.23, 124.74, 125.58, 125.79, 126.54, 129.92, 130.19, 142.98, 176.51.

3-(benzo[*d*]thiazol-2-ylmethyl)-1-benzyl-3-hydroxyindolin-2-one (3z)



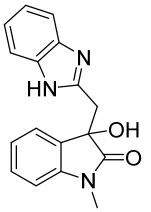
Yield: 89 %; Red solid, mp: 122-124 °C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.50-3.73 (m, 2H), 4.67 (d, *J*=15.66 Hz, 1H), 4.94 (d, *J*=15.54 Hz, 1H), 6.58 (d, *J*=7.58 Hz, 1H), 6.88 (t, *J*=7.58 Hz, 1H), 7.05-7.14 (m, 6H), 7.26-7.46 (m, 4H), 7.74 (d, *J*=8.08 Hz, 1H), 7.95 (d, *J*=7.71 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 41.37, 43.97, 75.47, 109.60, 121.53, 123.08, 124.37, 125.32, 126.29, 127.20, 128.81, 129.96, 135.34, 148.25, 152.52, 176.21.

3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxyindolin-2-one (3aa)



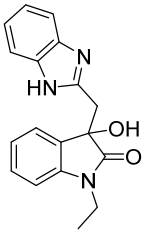
Yield: 89 %; Off white solid, mp: 192-194 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 3.26 (d, *J*=14.40 Hz, 1H), 3.45 (d, *J*=14.27 Hz, 1H), 6.57 (s, 1H), 6.83 (d, *J*=7.71 Hz, 1H), 6.90-6.99 (m, 2H), 7.16-7.25 (m, 3H), 7.50-7.56 (m, 2H), 10.43 (s, 1H), 12.16 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 36.56, 74.39, 109.52, 121.04, 121.20, 121.35, 124.28, 129.09, 131.01, 149.95, 151.23, 178.12.

3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxy-1-methylindolin-2-one (3ab)



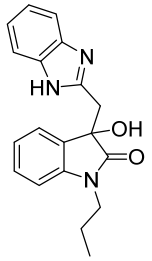
Yield: 86 %; Off white solid, mp: 162-164 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 2.93-3.43 (m, 5H), 6.62-7.55 (m, 8H), 12.22 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 26.84, 48.74, 74.11, 108.40, 121.03, 122.02, 123.82, 129.22, 130.39, 143.26, 149.63, 151.29, 176.44.

3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-ethyl-3-hydroxyindolin-2-one (3ac)



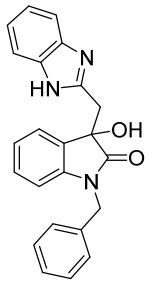
Yield: 84 %; Red solid, mp: 147-149 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 1.12 (t, *J*=7.07 Hz, 3H), 3.20-3.44 (m, 2H), 3.58-3.77 (m, 2H), 6.49 (s, 1H), 6.87-7.10 (m, 5H), 7.21 (t, *J*=7.45 Hz, 1H), 7.39-7.43 (m, 2H), 12.03 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 12.07, 33.85, 36.77, 74.18, 108.39, 121.03, 12.79, 123.99, 129.19, 130.57, 142.29, 149.62, 162.32, 176.03.

3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxy-1-propylindolin-2-one (3ad)



Yield: 82 %; Yellow solid, mp: 105-107 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 0.86 (t, *J*=7.45 Hz, 3H), 1.57 (q, *J*=7.07 Hz, 2H), 3.25 (d, *J*=14.27 Hz, 1H), 3.40 (d, *J*=14.27 Hz, 1H), 3.48-3.71 (m, 2H), 6.51 (s, 1H), 6.86-7.13 (m, 5H), 7.17-7.25 (m, 1H), 7.40-7.44 (m, 2H), 12.03 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 11.27, 20.18, 36.78, 40.76, 74.14, 108.56, 121.78, 123.96, 129.18, 130.44, 142.83, 149.63, 162.32, 176.46.

3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-benzyl-3-hydroxyindolin-2-one (3ae)



Yield: 85 %; Red solid, mp: 132-134 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 3.42-

3.56 (m, 2H), 4.72 (d, *J*=16.17 Hz, 1H), 5.04 (d, *J*=16.04 Hz, 1H), 6.62 (s, 1H), 6.93 (t, *J*=8.08 Hz, 1H), 7.107-7.15 (m, 4H), 7.20-7.32 (m, 6H), 7.42-7.47 (m, 2H), 12.10 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d6): δ 36.56, 42.69, 74.38, 109.05, 122.14, 124.03, 127.01, 127.15, 128.44, 129.12, 130.40, 136.10, 142.43, 149.47, 176.55.

3.2.7 Spectra

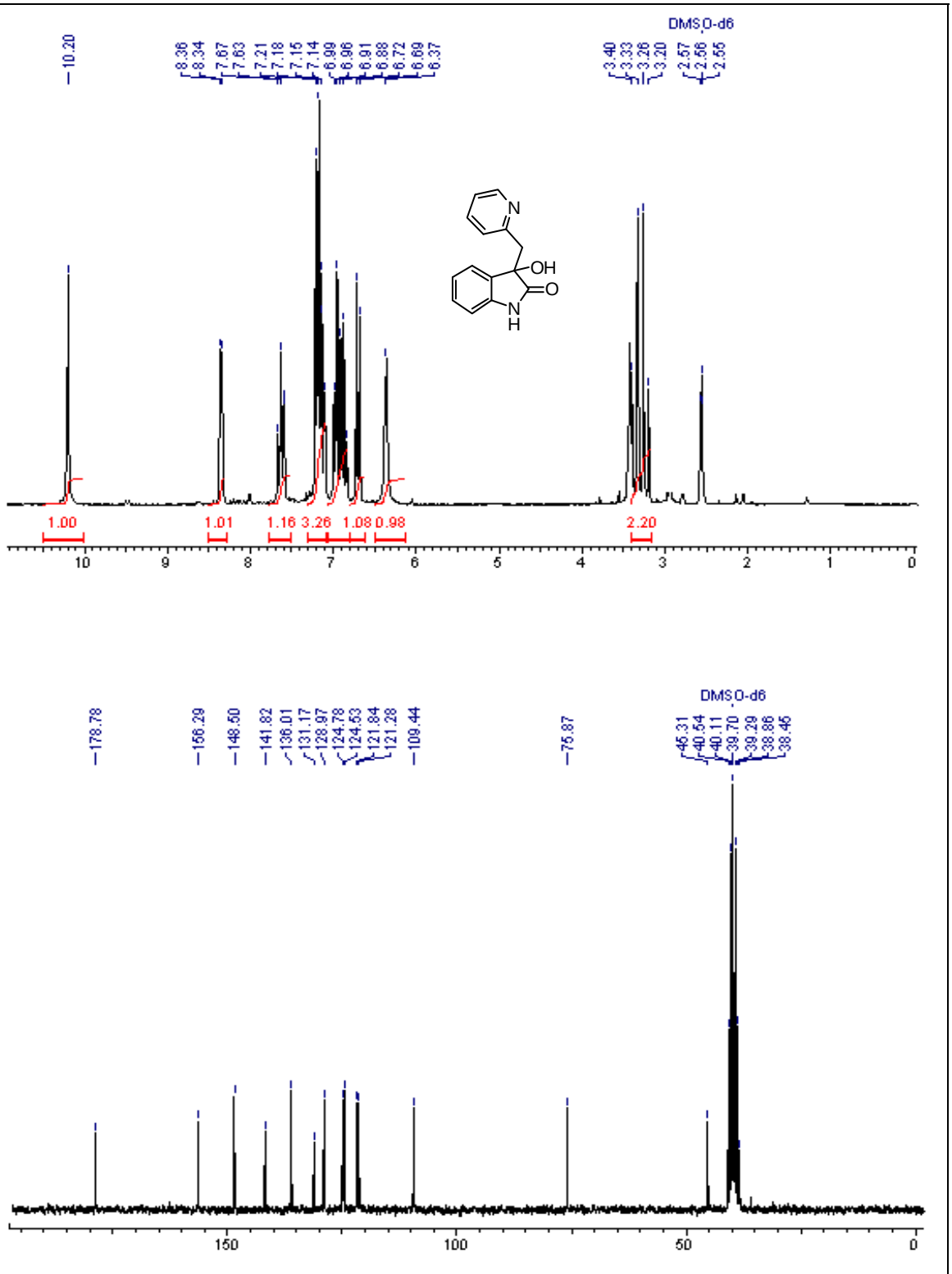


Fig. 27: ^{1}H and ^{13}C NMR of 3-hydroxy-3-(pyridine-2-ylmethyl)indolin-2-one

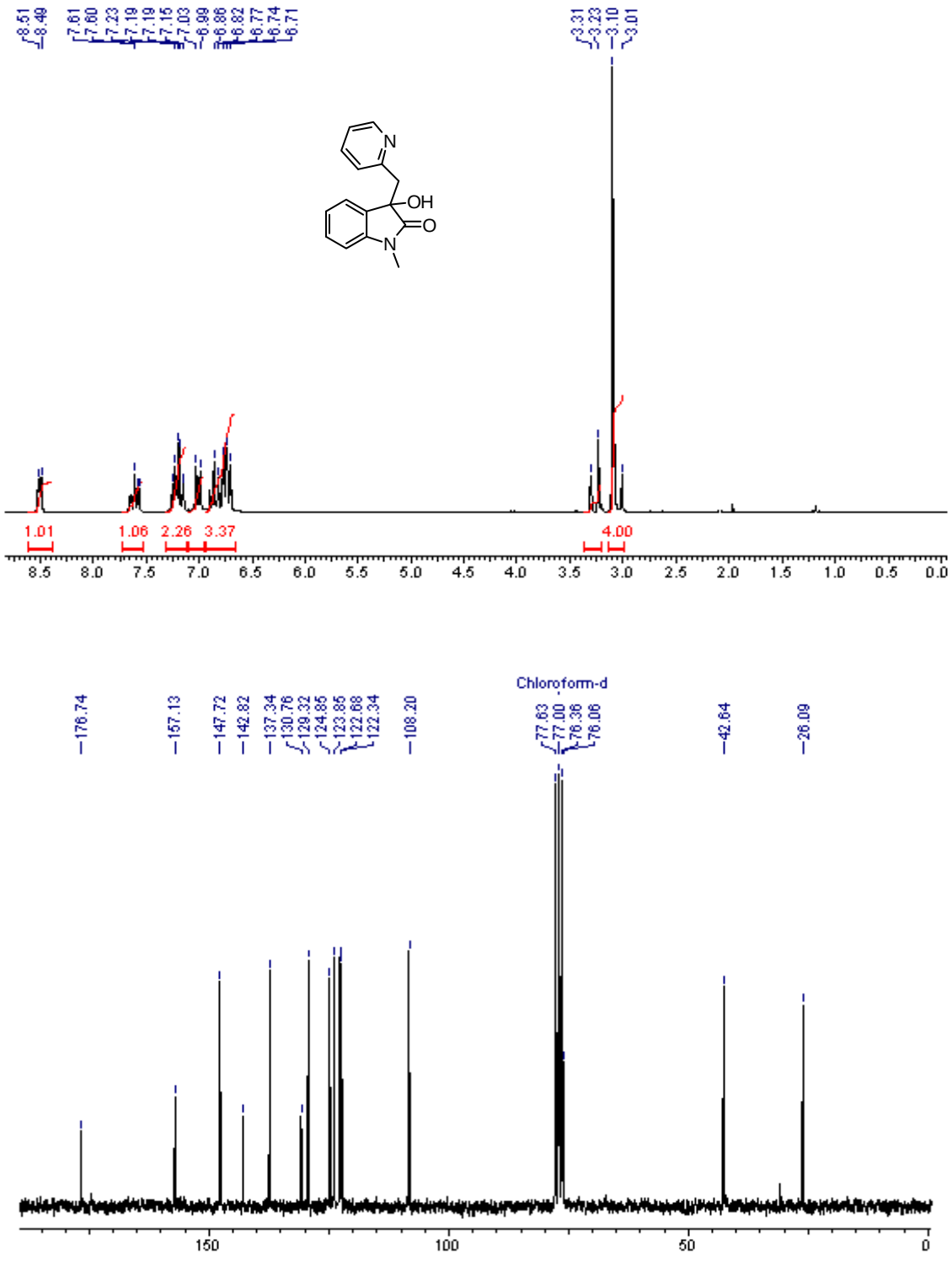


Fig. 28: ^{1}H and ^{13}C NMR of 3-hydroxy-1-methyl-3-(pyridine-2-ylmethyl)indolin-2-one

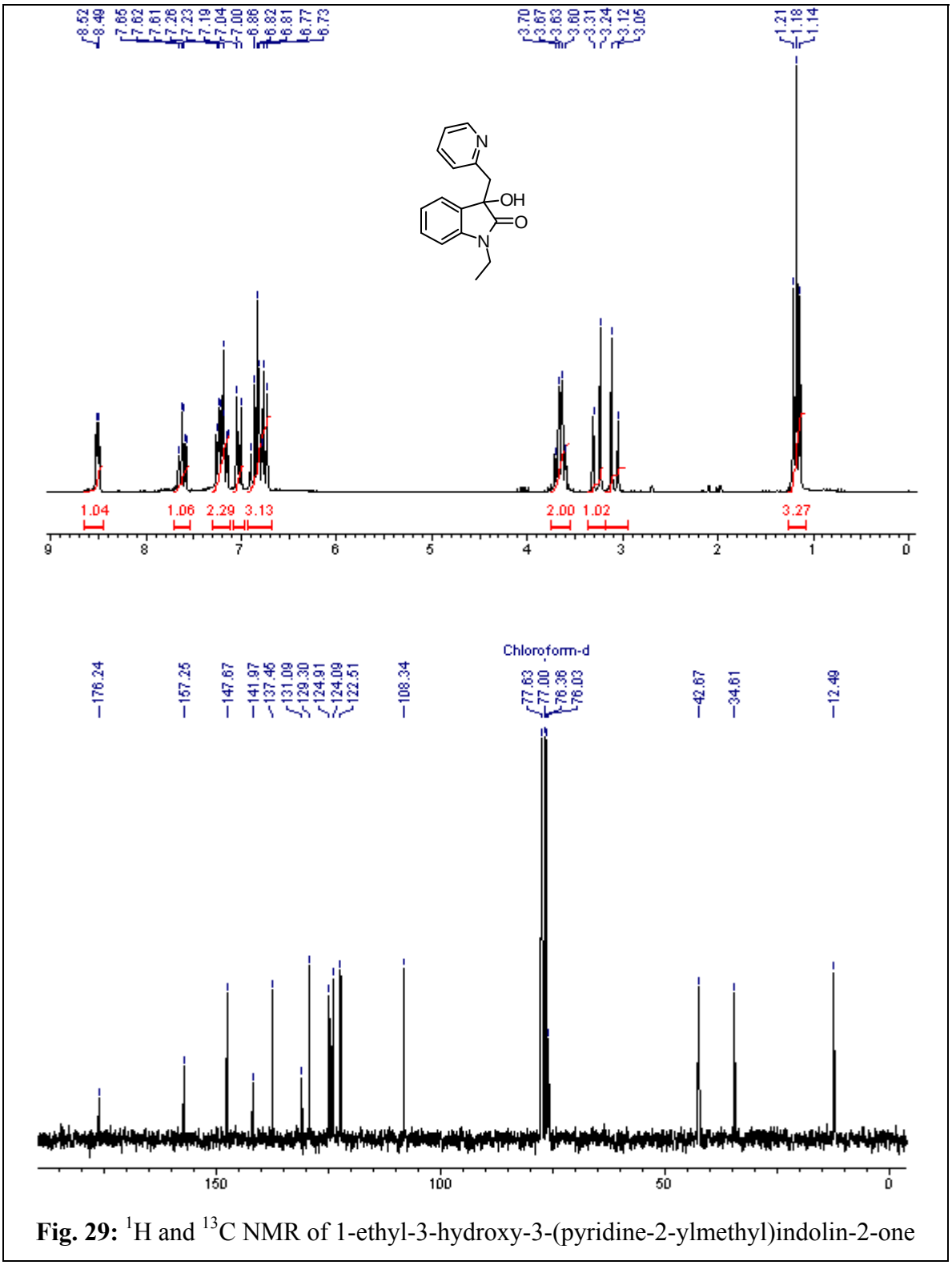


Fig. 29: ^{1}H and ^{13}C NMR of 1-ethyl-3-hydroxy-3-(pyridine-2-ylmethyl)indolin-2-one

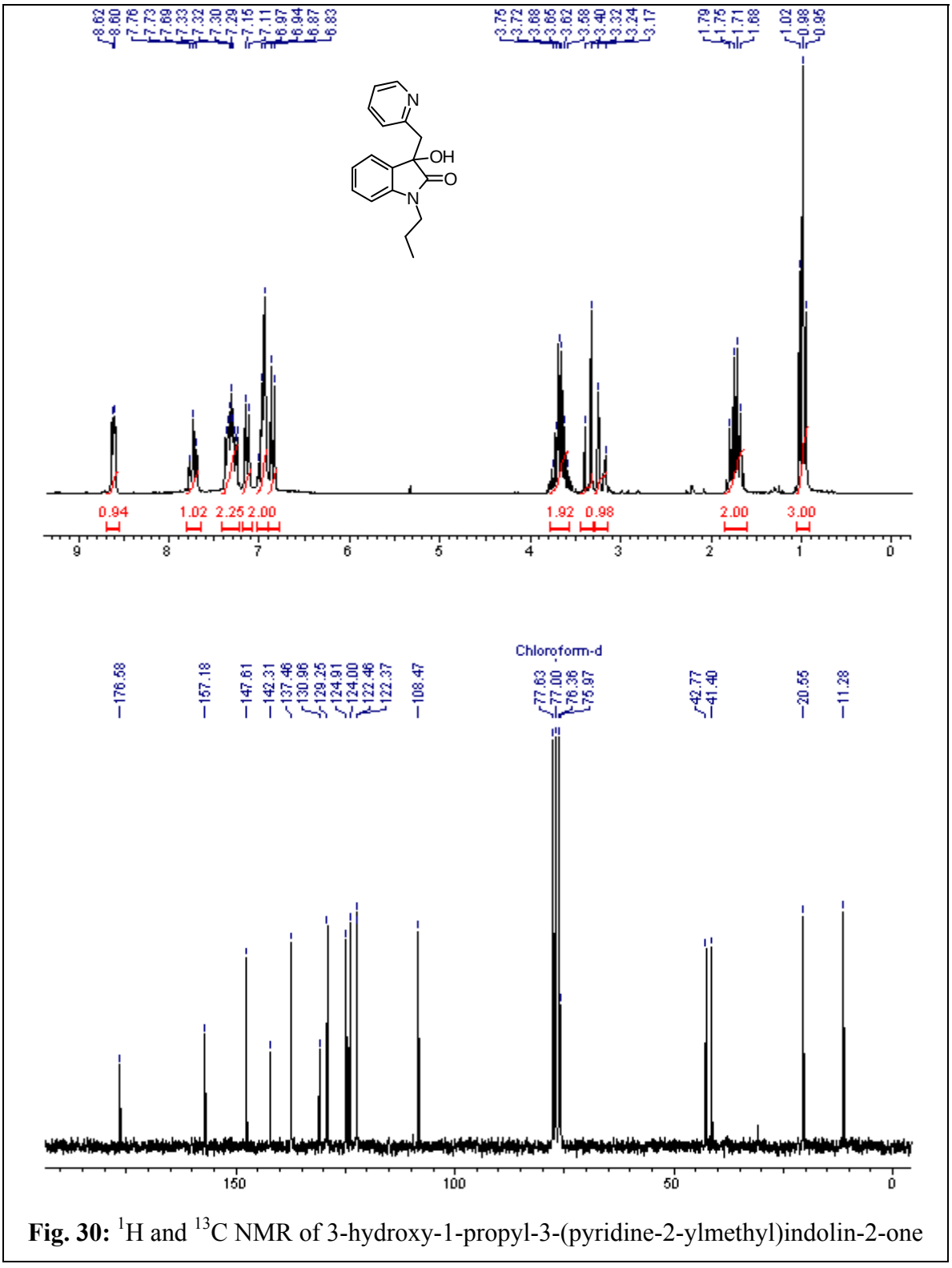


Fig. 30: ^{1}H and ^{13}C NMR of 3-hydroxy-1-propyl-3-(pyridine-2-ylmethyl)indolin-2-one

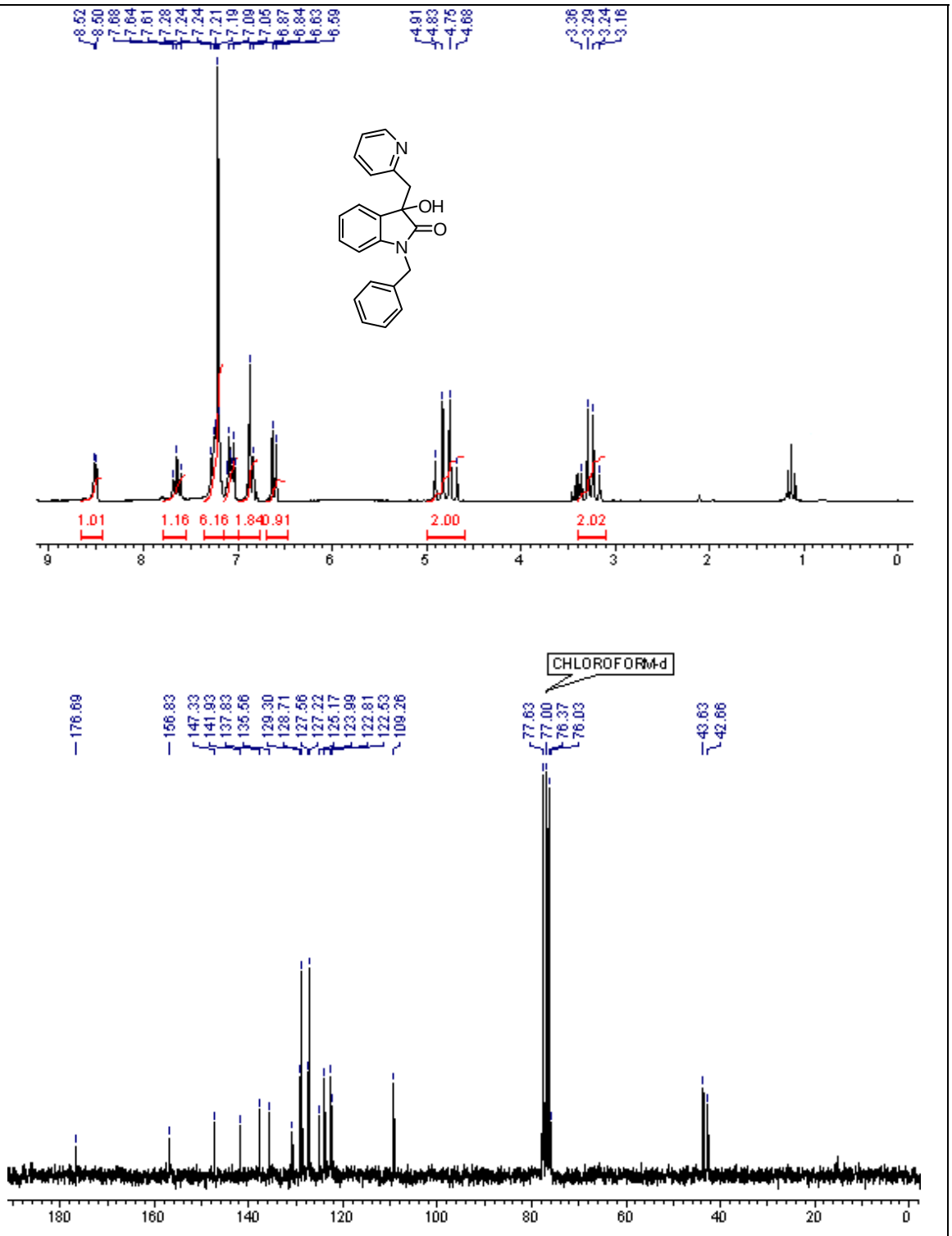


Fig. 31: ^{1}H and ^{13}C NMR of 1-benzyl-3-hydroxy-3-(pyridine-2-ylmethyl)indolin-2-one

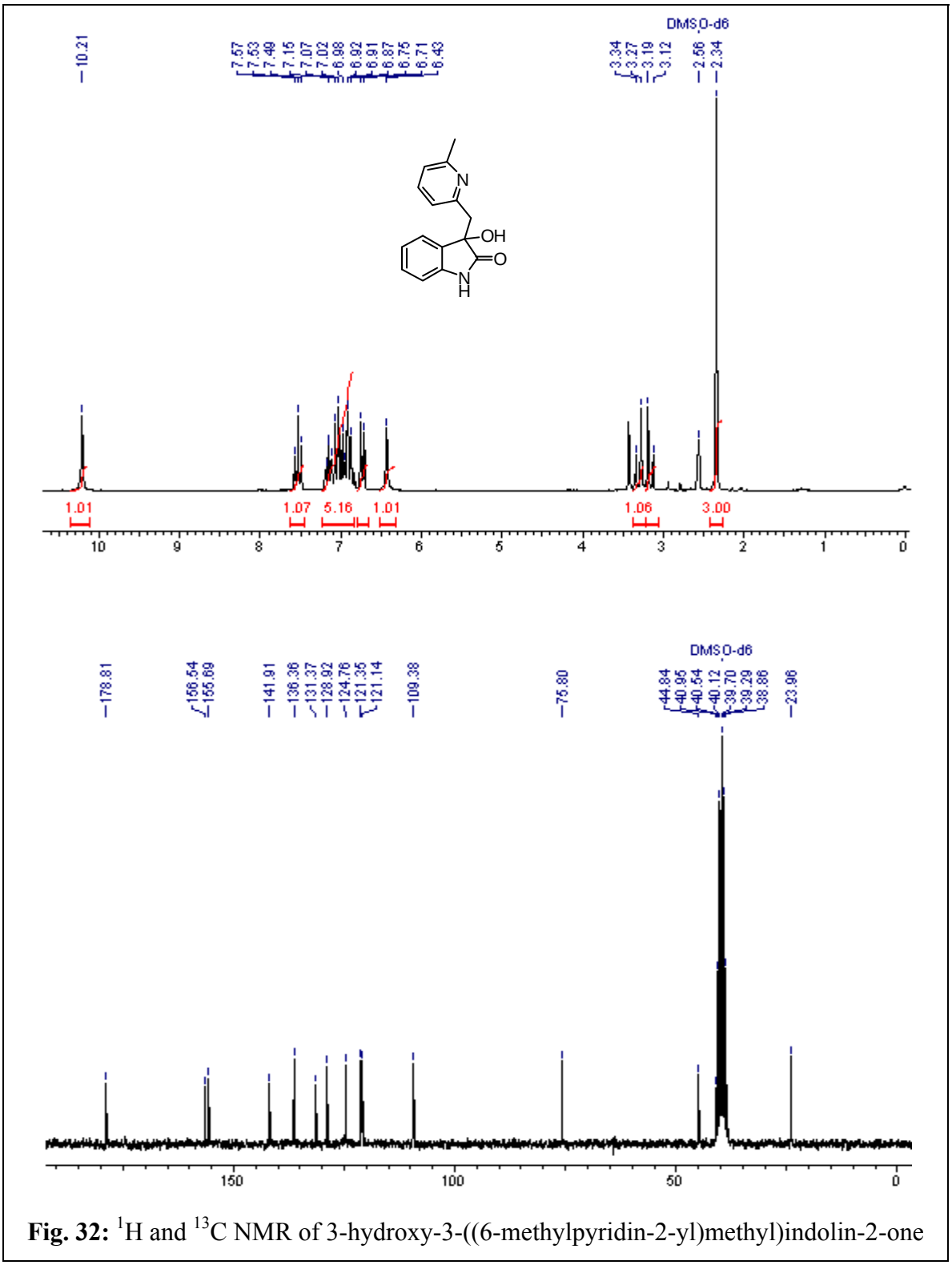


Fig. 32: ^{1}H and ^{13}C NMR of 3-hydroxy-3-((6-methylpyridin-2-yl)methyl)indolin-2-one

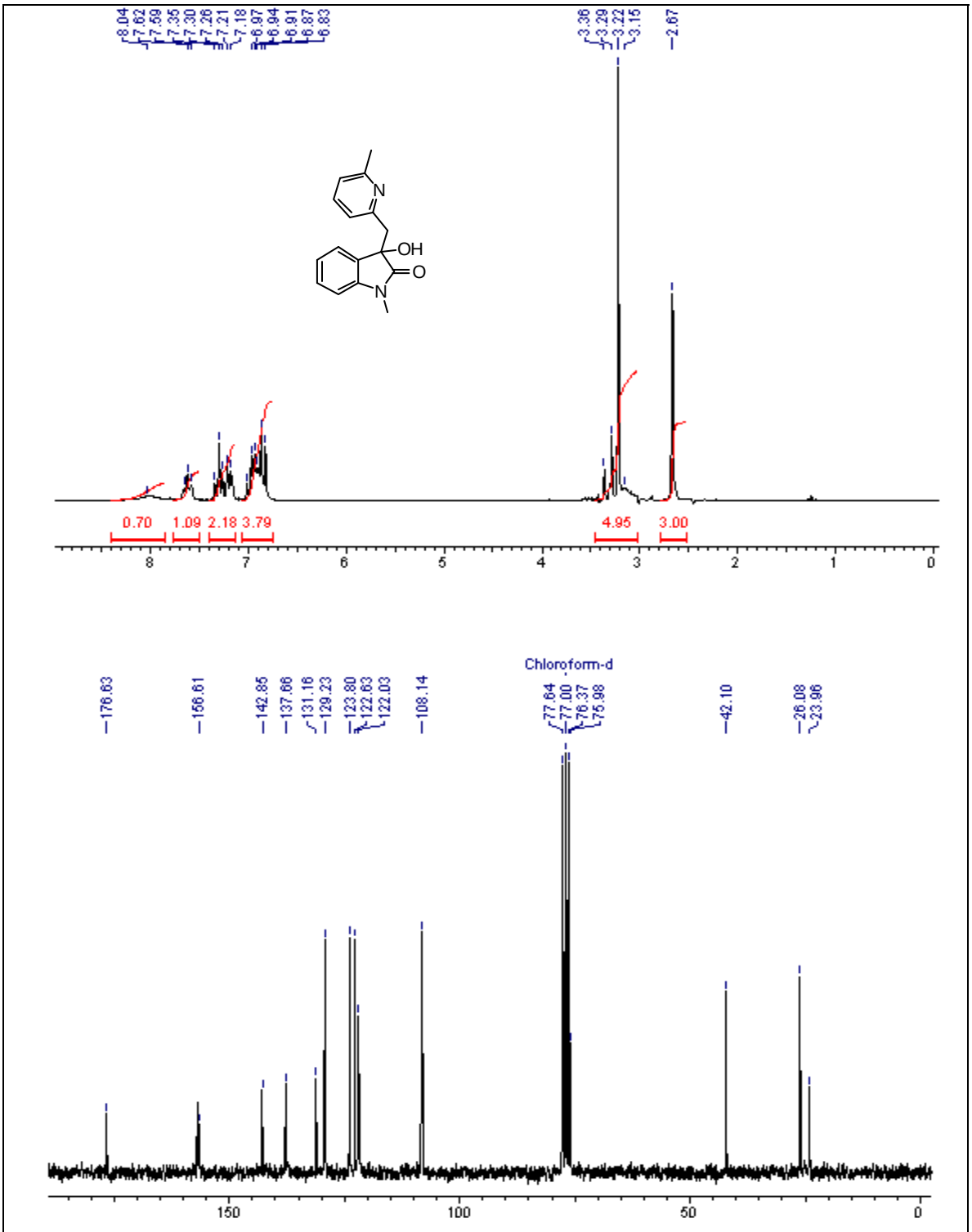


Fig. 33: ^{1}H and ^{13}C NMR of 3-hydroxy-1-methyl-3-((6-methylpyridin-yl)methyl)indolin-2-one

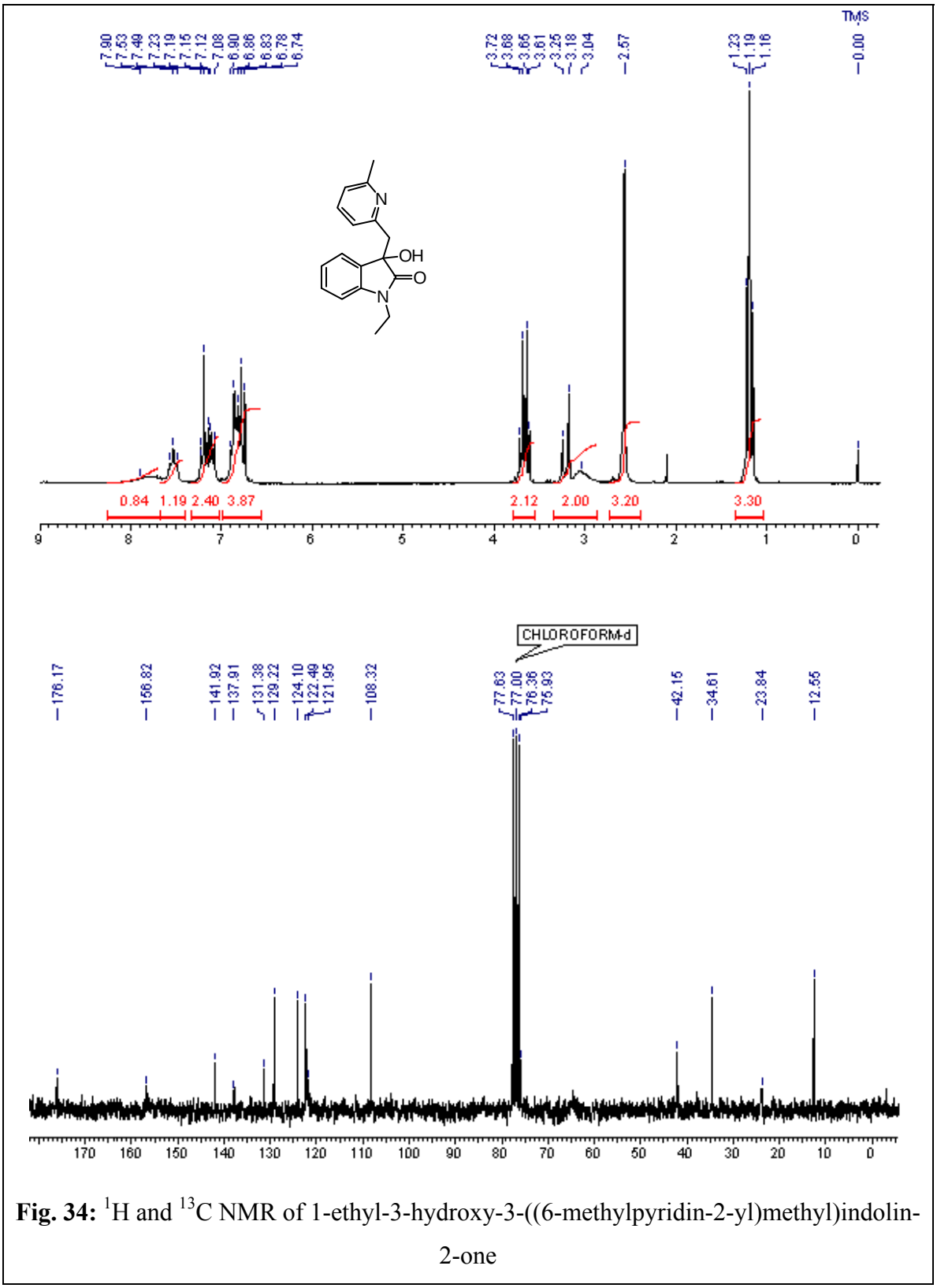


Fig. 34: ^{1}H and ^{13}C NMR of 1-ethyl-3-hydroxy-3-((6-methylpyridin-2-yl)methyl)indolin-2-one

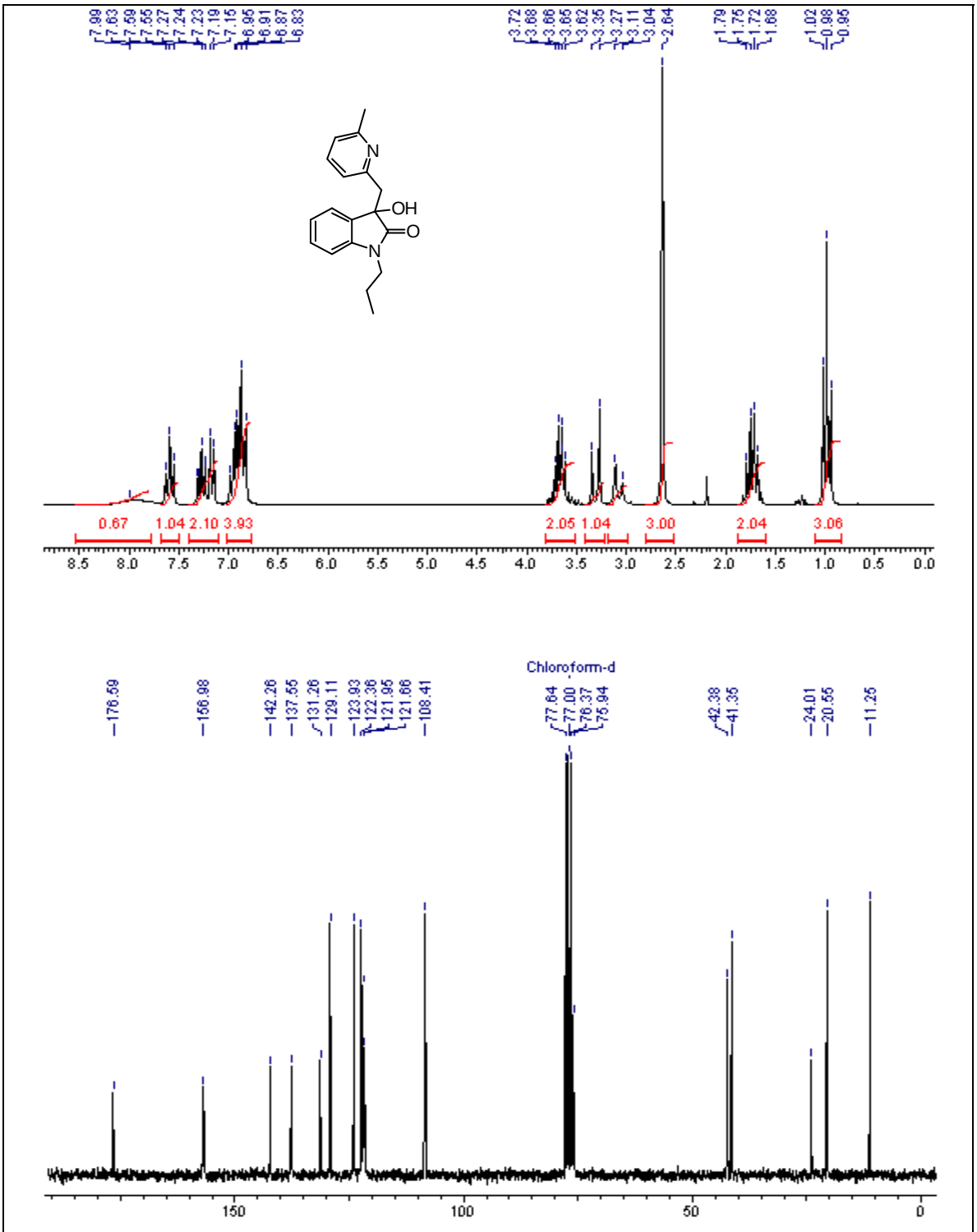


Fig. 35: ^{1}H and ^{13}C NMR of 3-hydroxy-3-((6-methylpyridin-2-yl)methyl)-1-propylindolin-2-one

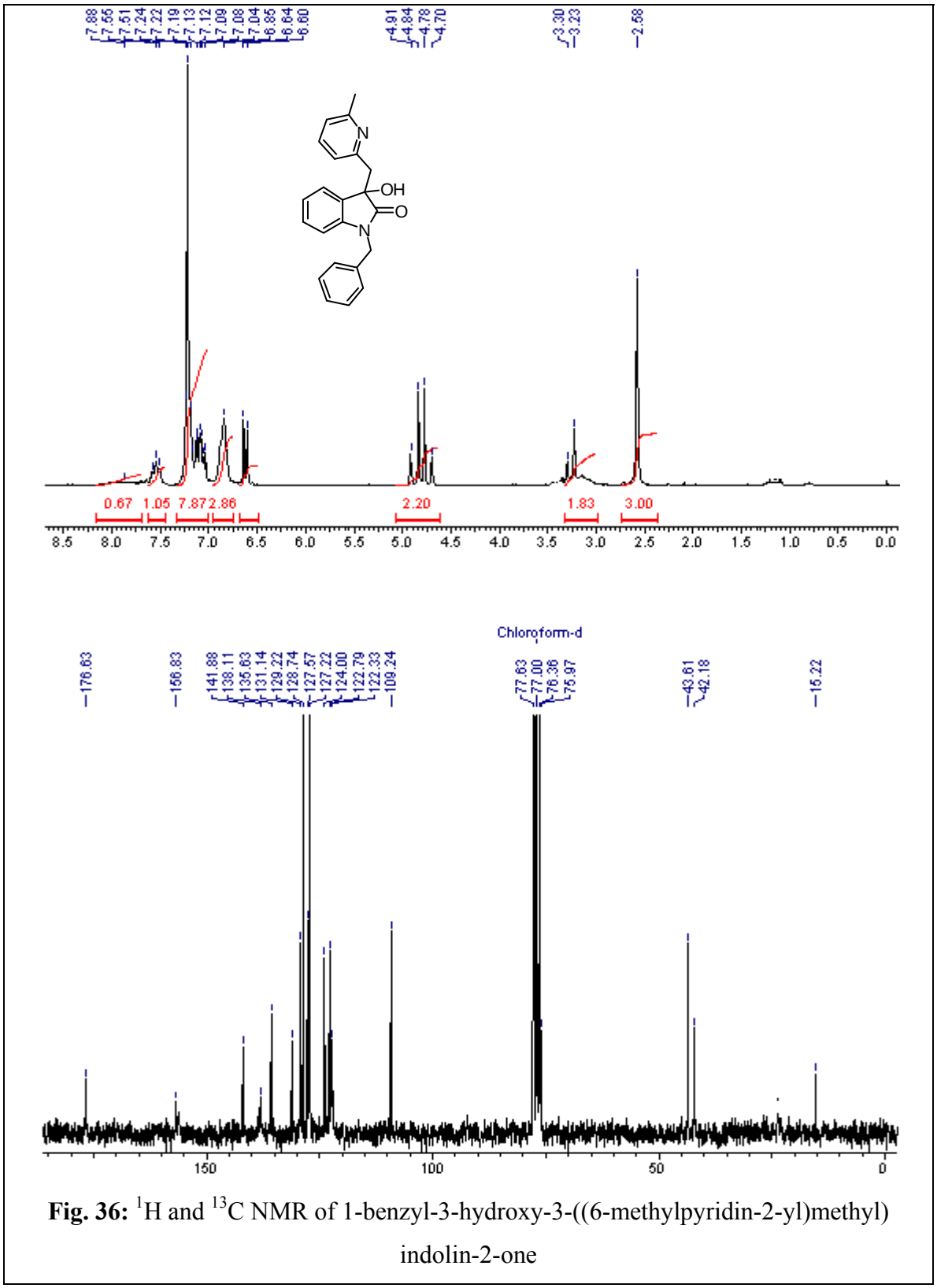


Fig. 36: ^{1}H and ^{13}C NMR of 1-benzyl-3-hydroxy-3-((6-methylpyridin-2-yl)methyl) indolin-2-one

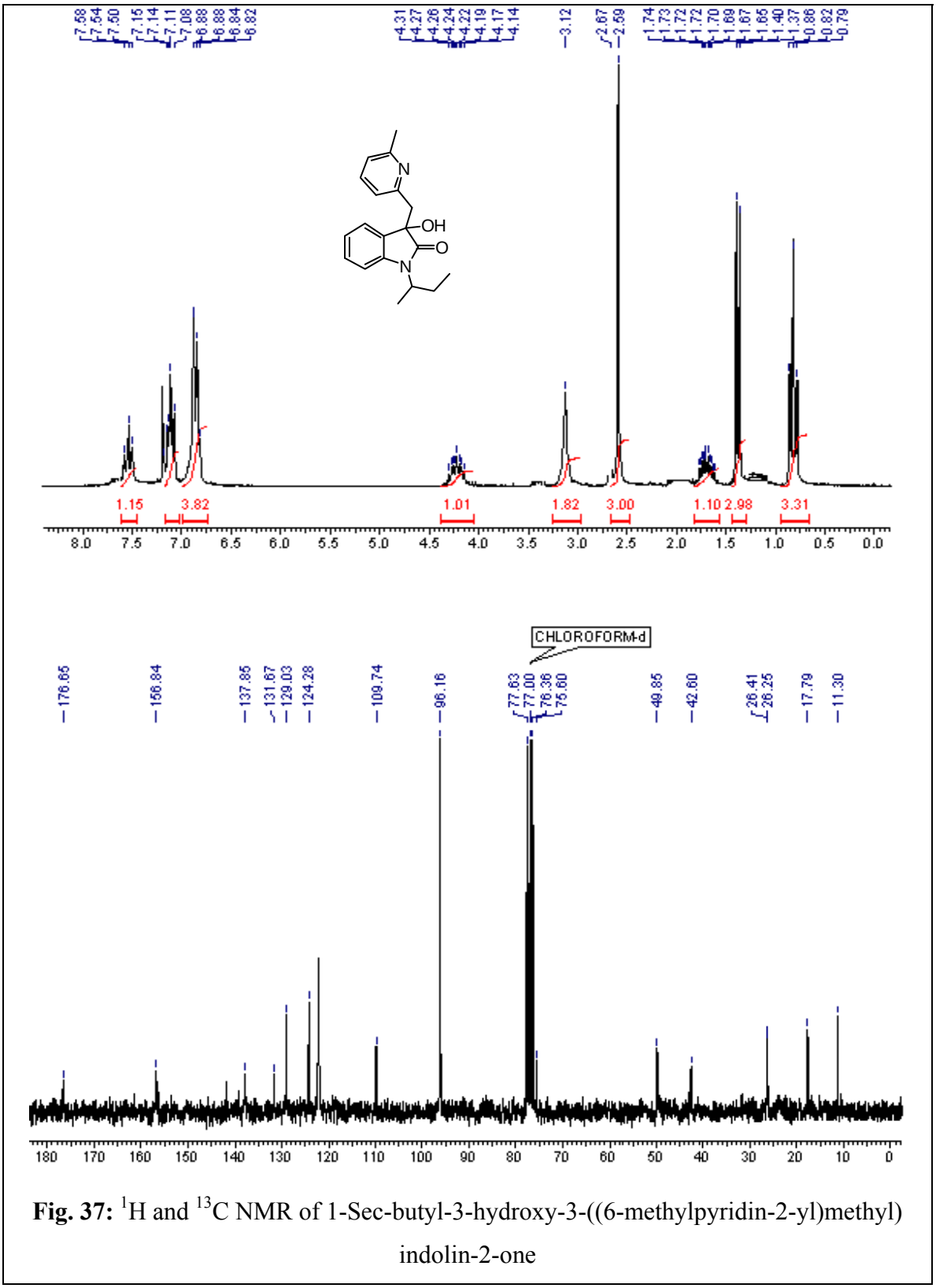


Fig. 37: ^{1}H and ^{13}C NMR of 1-Sec-butyl-3-hydroxy-3-((6-methylpyridin-2-yl)methyl) indolin-2-one

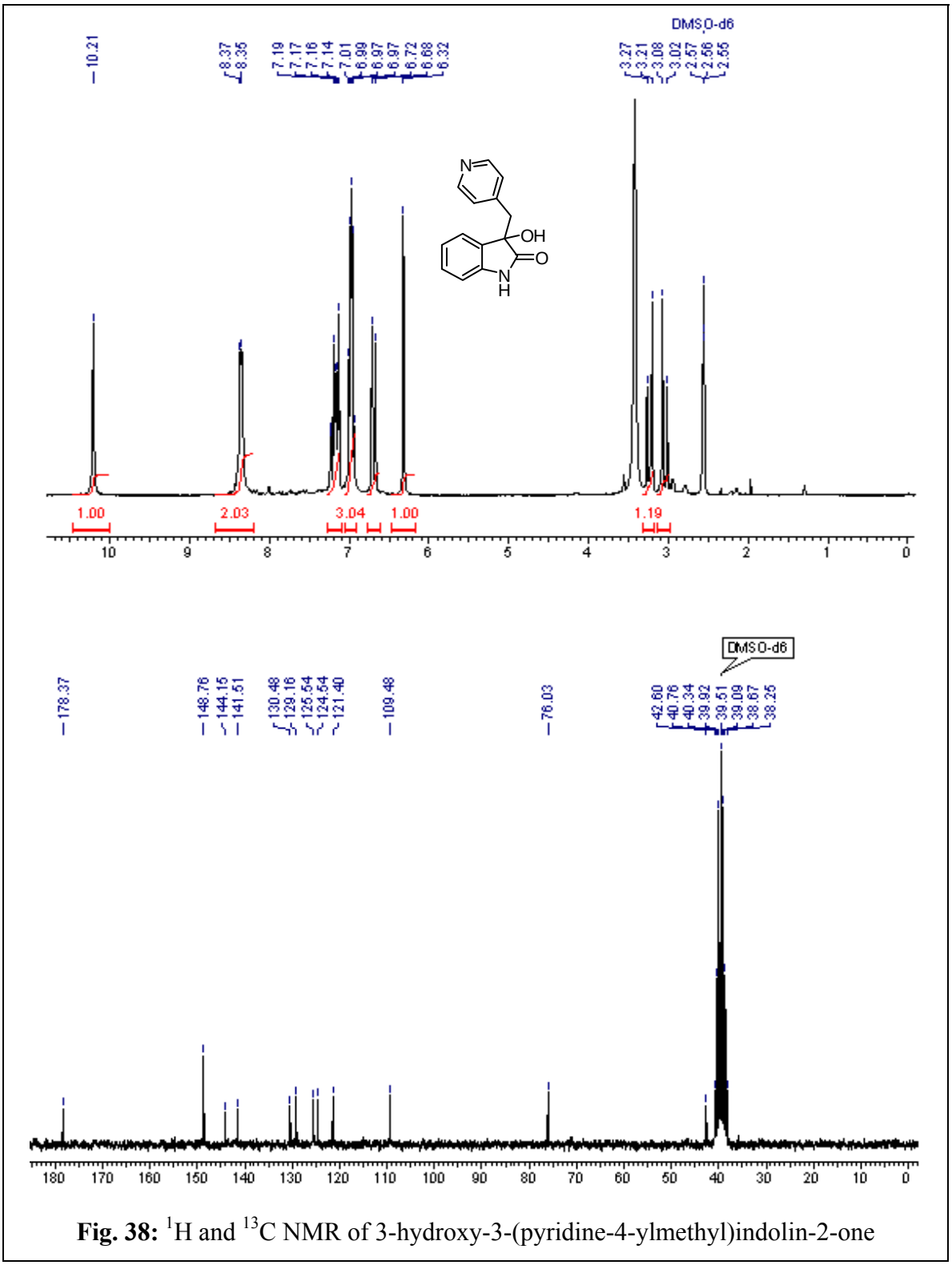


Fig. 38: ^{1}H and ^{13}C NMR of 3-hydroxy-3-(pyridine-4-ylmethyl)indolin-2-one

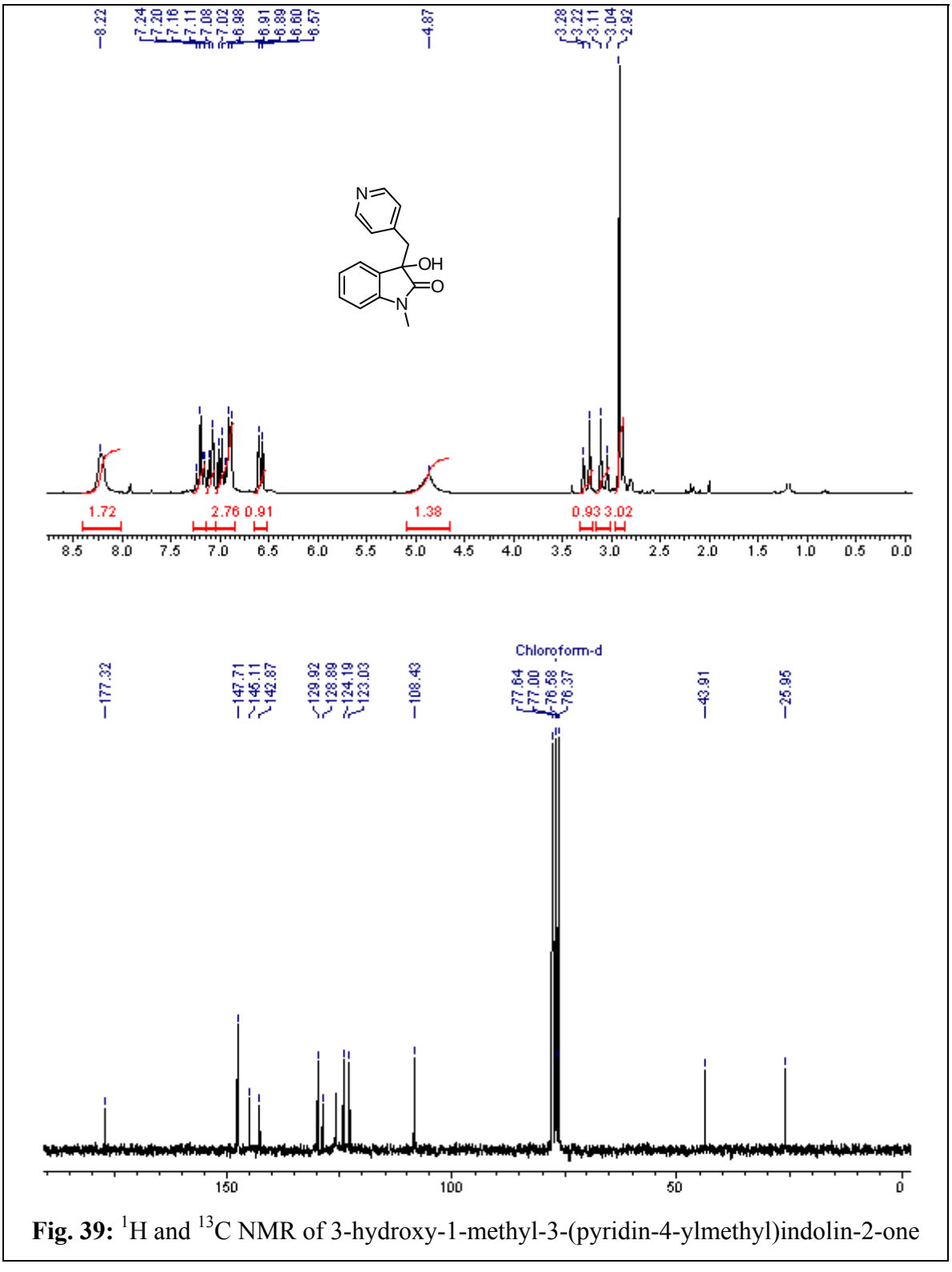


Fig. 39: ^{1}H and ^{13}C NMR of 3-hydroxy-1-methyl-3-(pyridin-4-ylmethyl)indolin-2-one

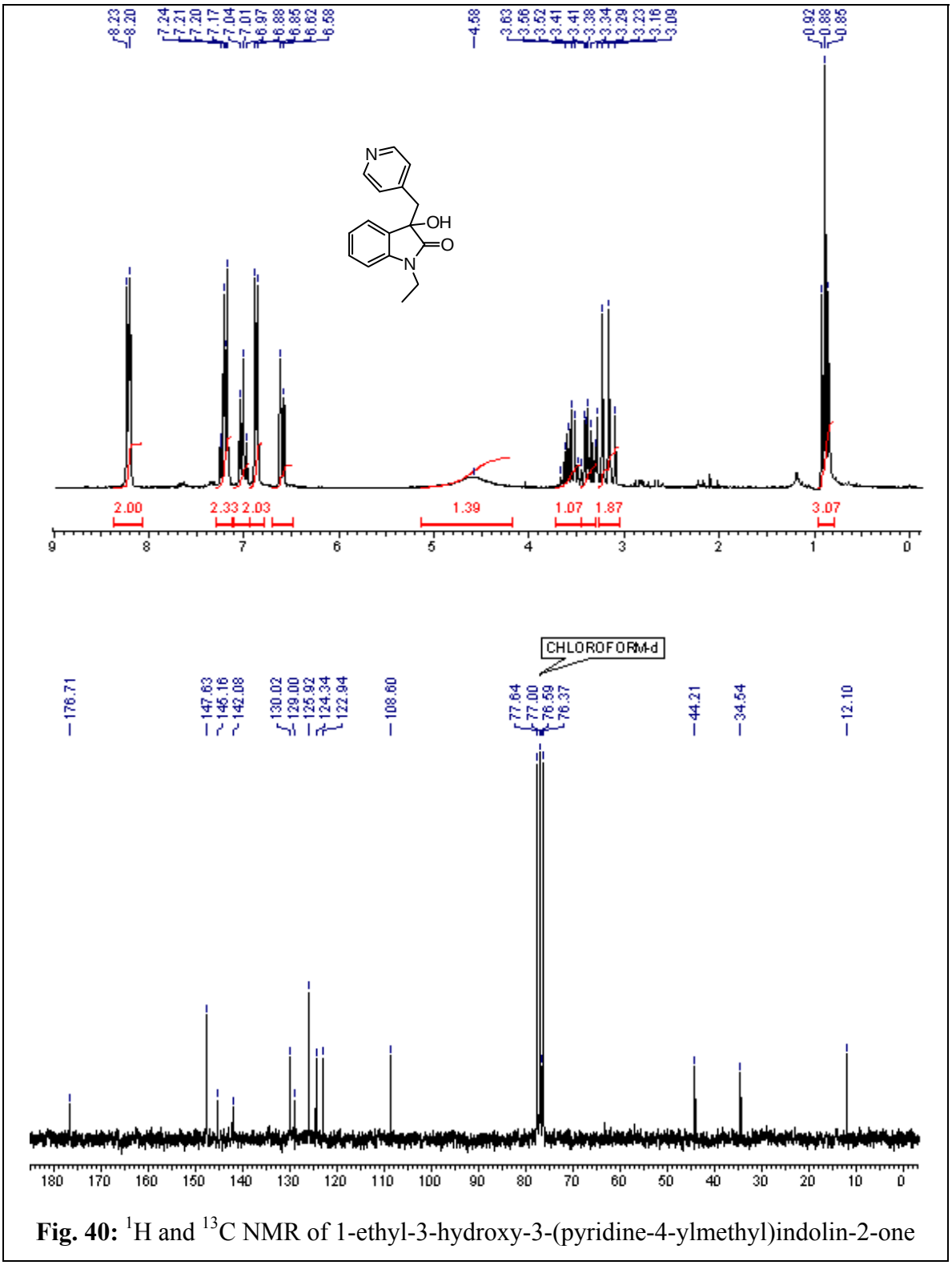


Fig. 40: ^{1}H and ^{13}C NMR of 1-ethyl-3-hydroxy-3-(pyridine-4-ylmethyl)indolin-2-one

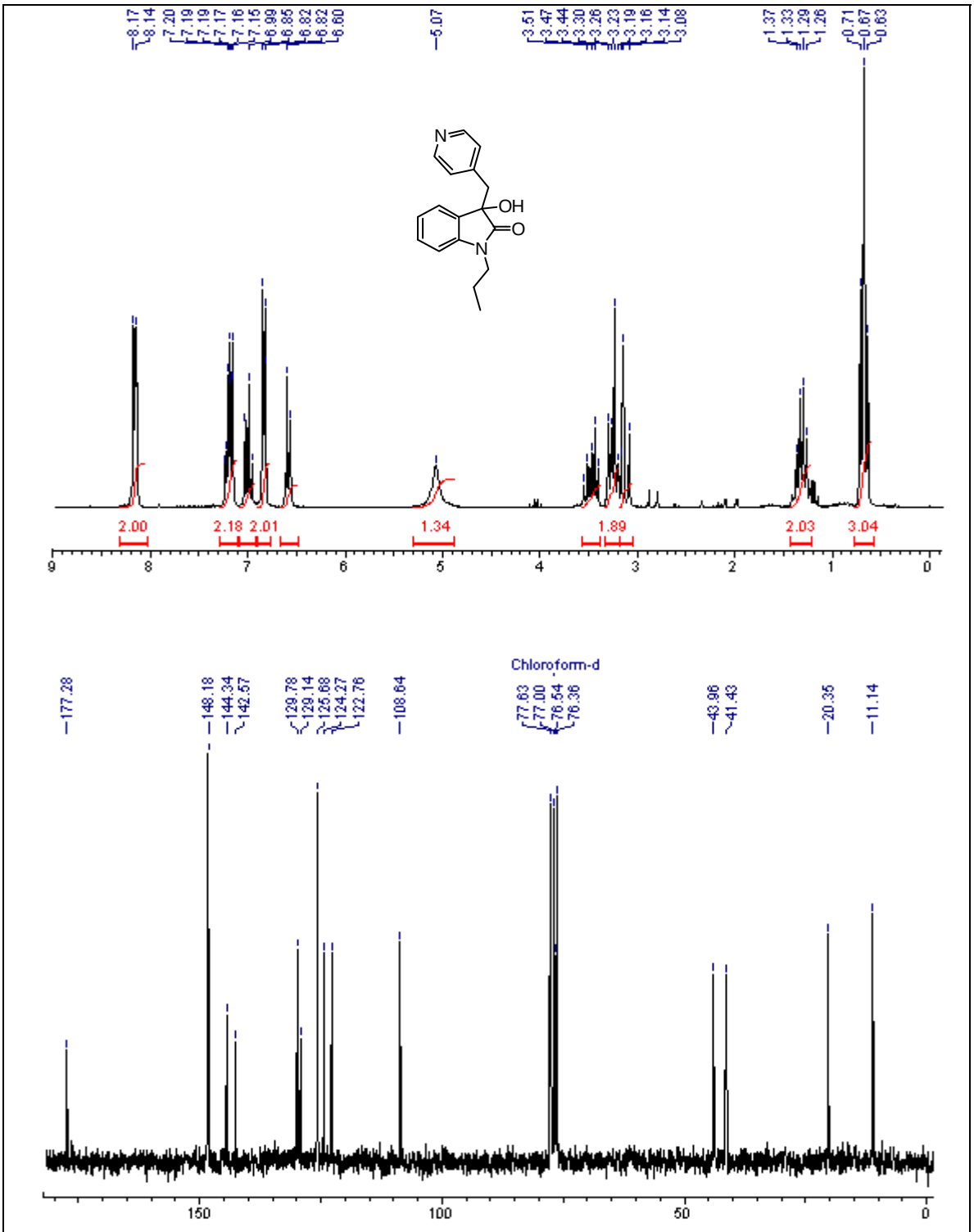


Fig. 41: ^{1}H and ^{13}C NMR of 3-hydroxy-1-propyl-3-(pyridine-4-ylmethyl)indolin-2-one

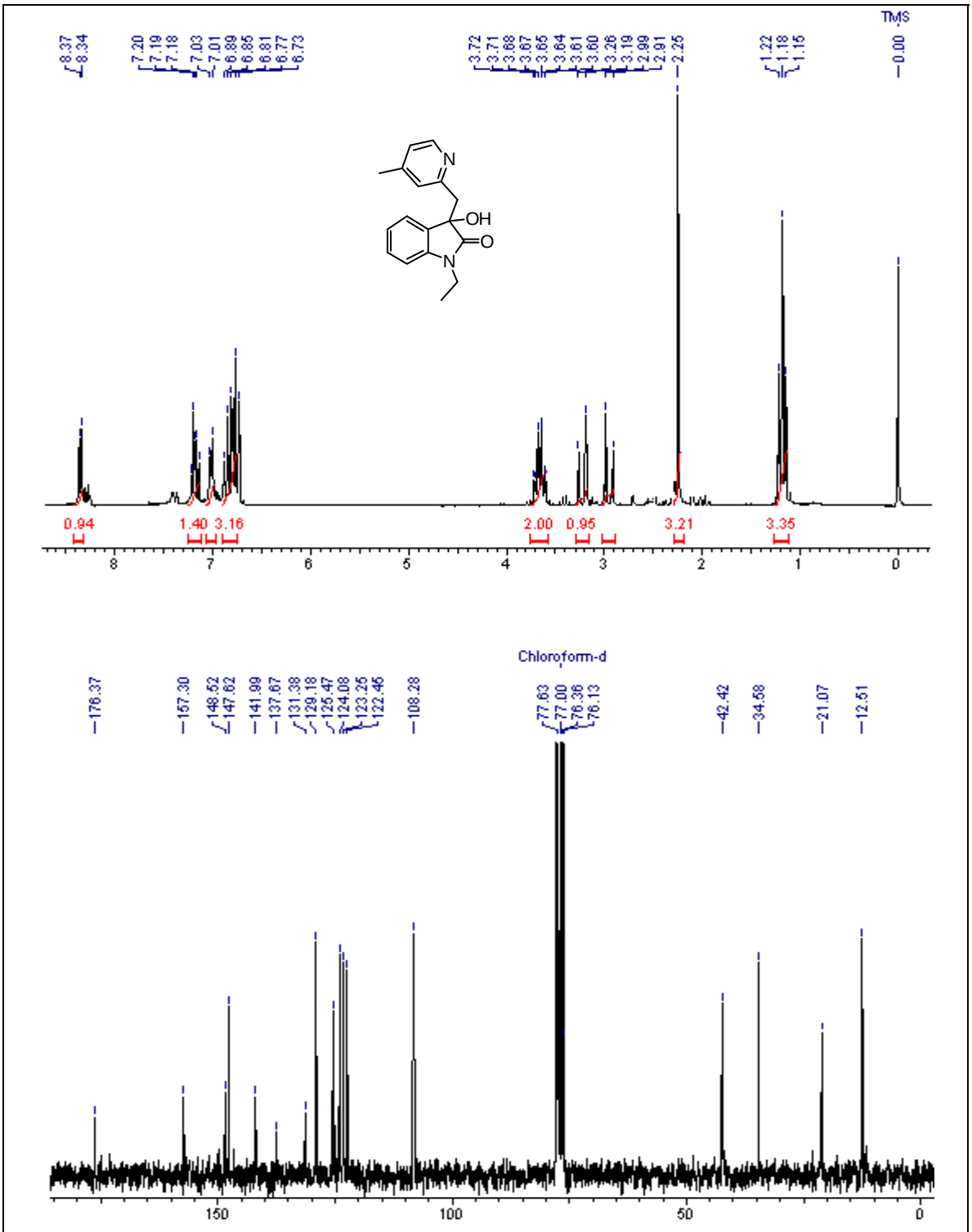


Fig. 42: ^{1}H and ^{13}C NMR of 1-ethyl-3-hydroxy-3-((4-methylpyridin-2-yl)methyl)indolin-2-one

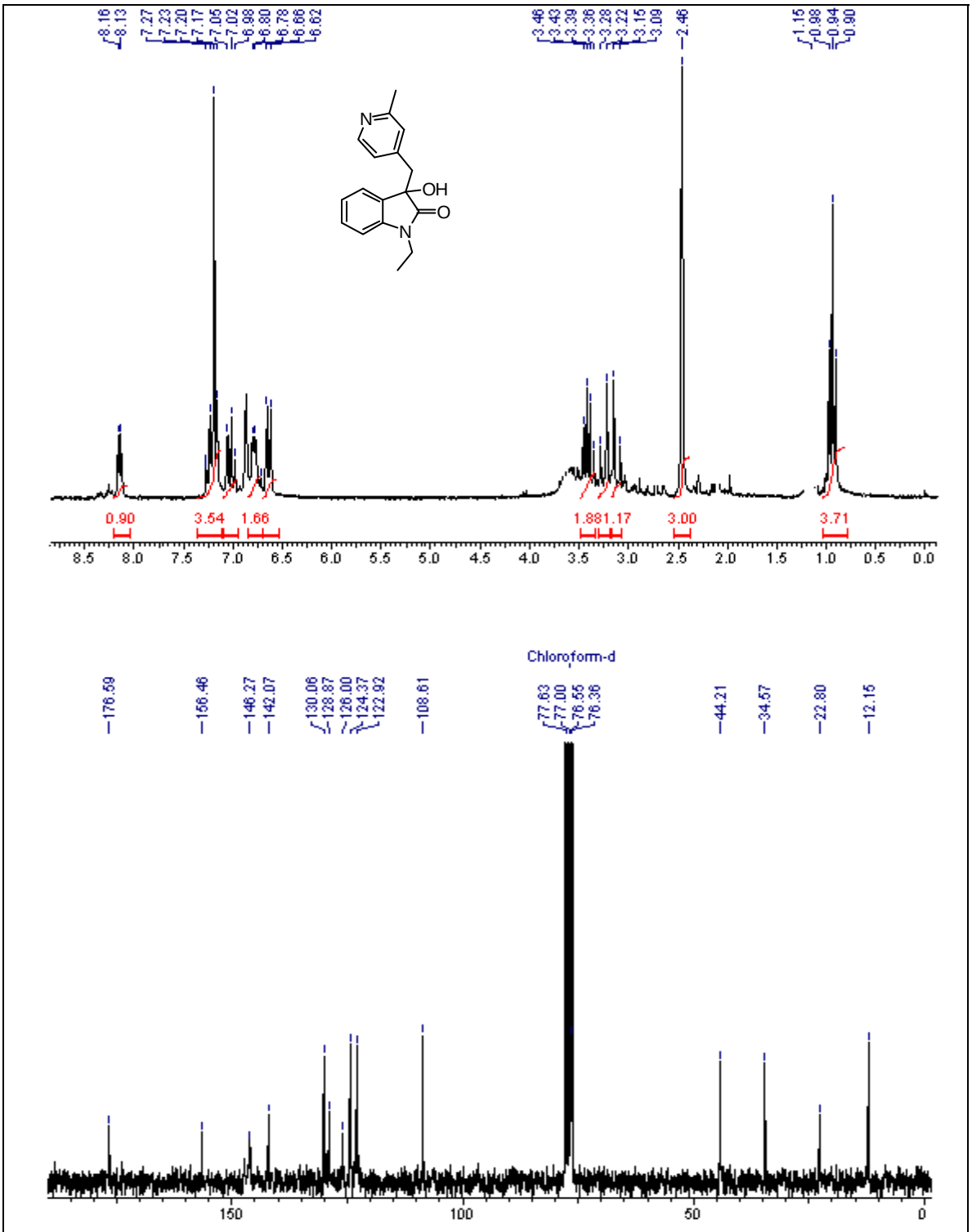


Fig. 43: ^{1}H and ^{13}C NMR of 1-ethyl-3-hydroxy-3-((2-methylpyridin-4-yl)methyl)indolin-2-one

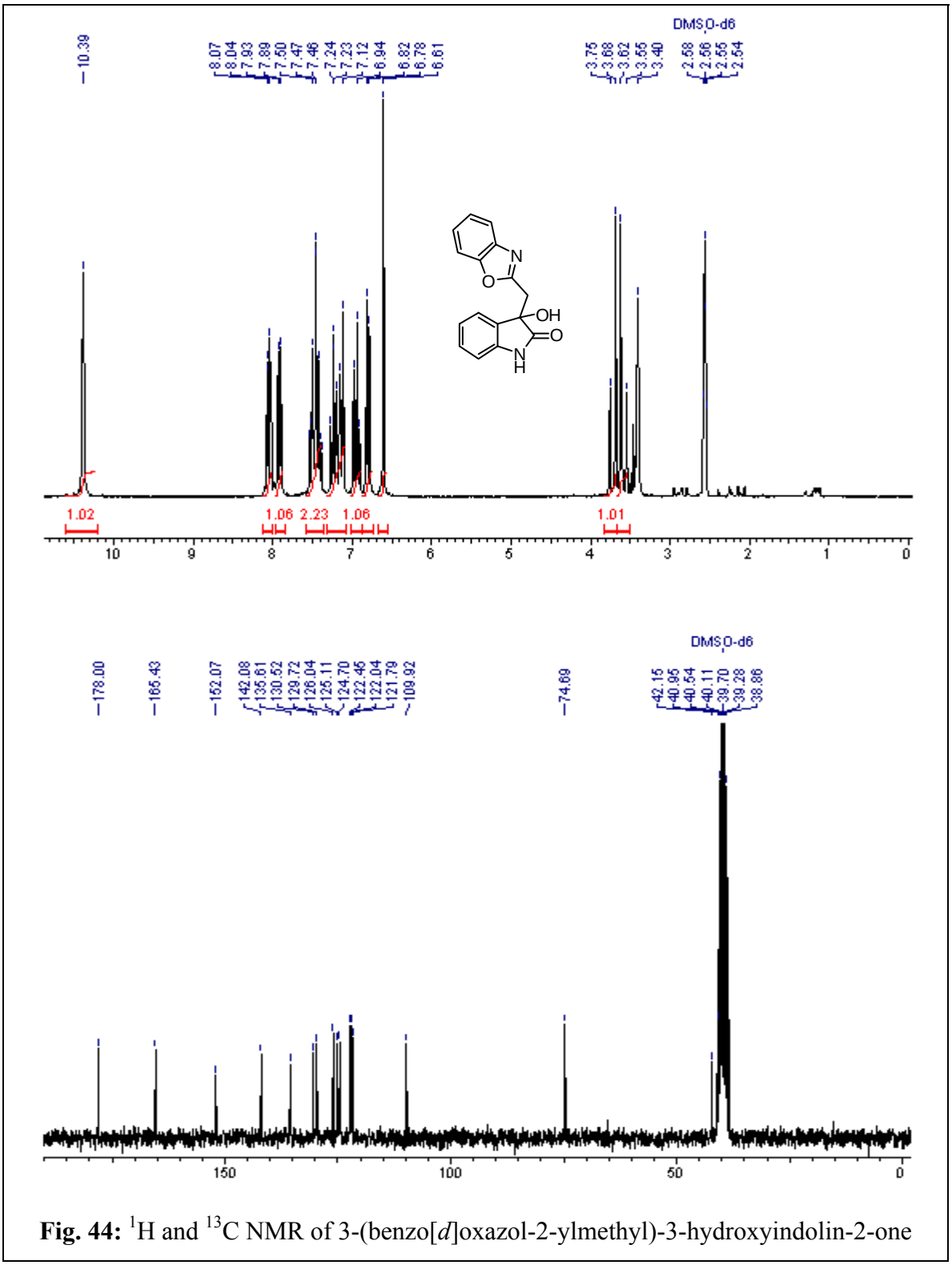


Fig. 44: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]oxazol-2-ylmethyl)-3-hydroxyindolin-2-one

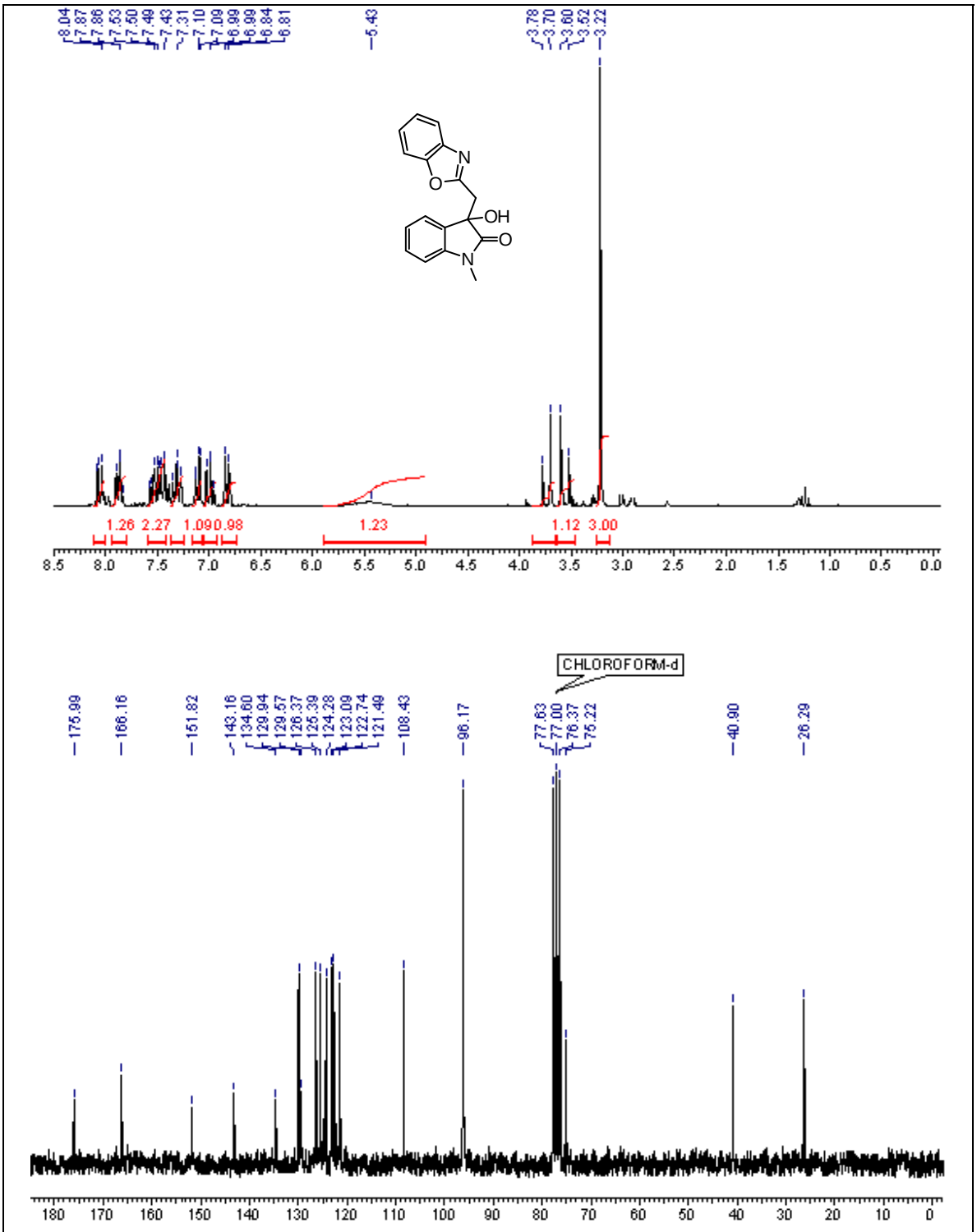


Fig. 45: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]oxazol-2-ylmethyl)-3-hydroxy-1-methylindolin-2-one

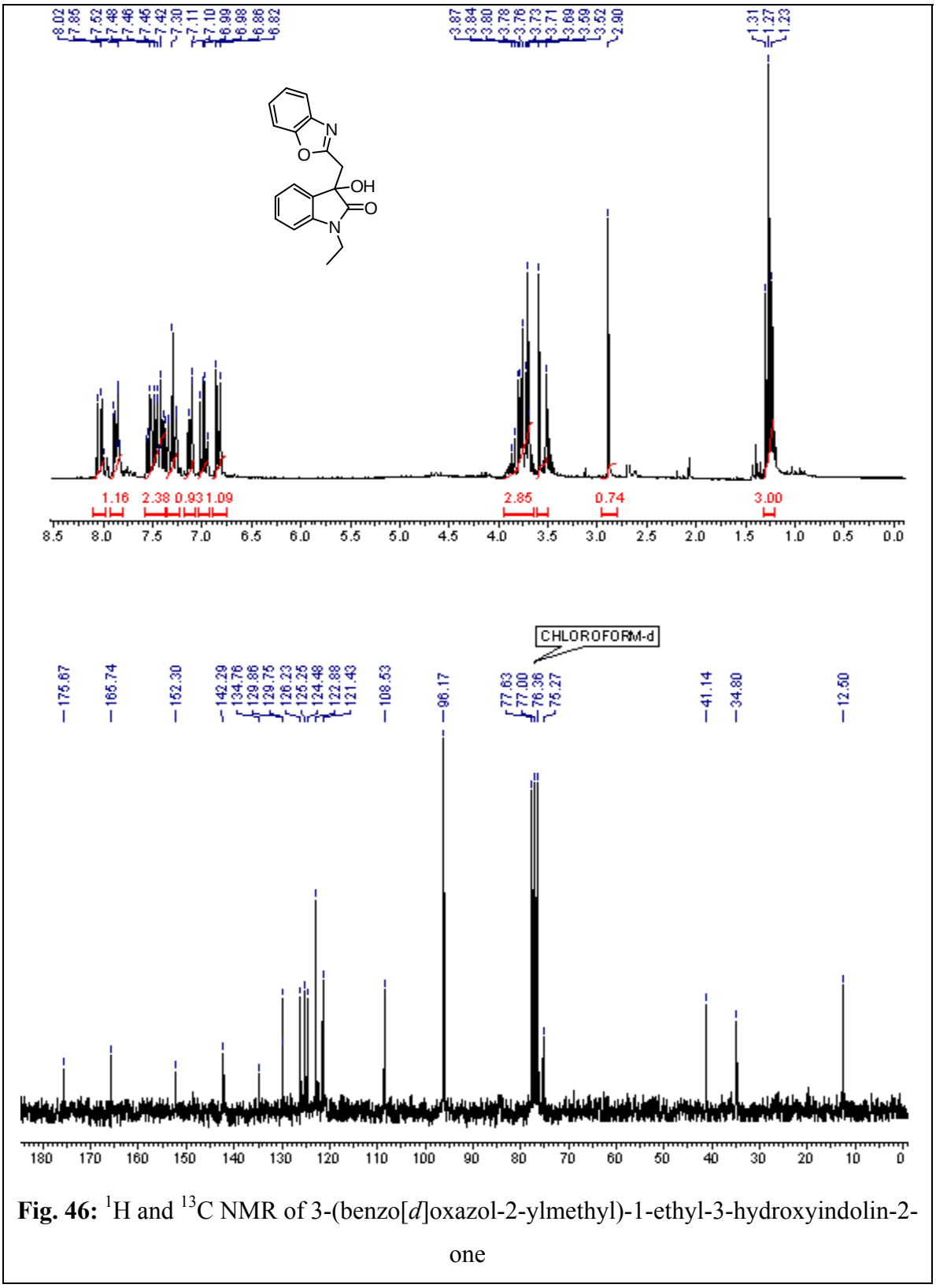


Fig. 46: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]oxazol-2-ylmethyl)-1-ethyl-3-hydroxyindolin-2-one

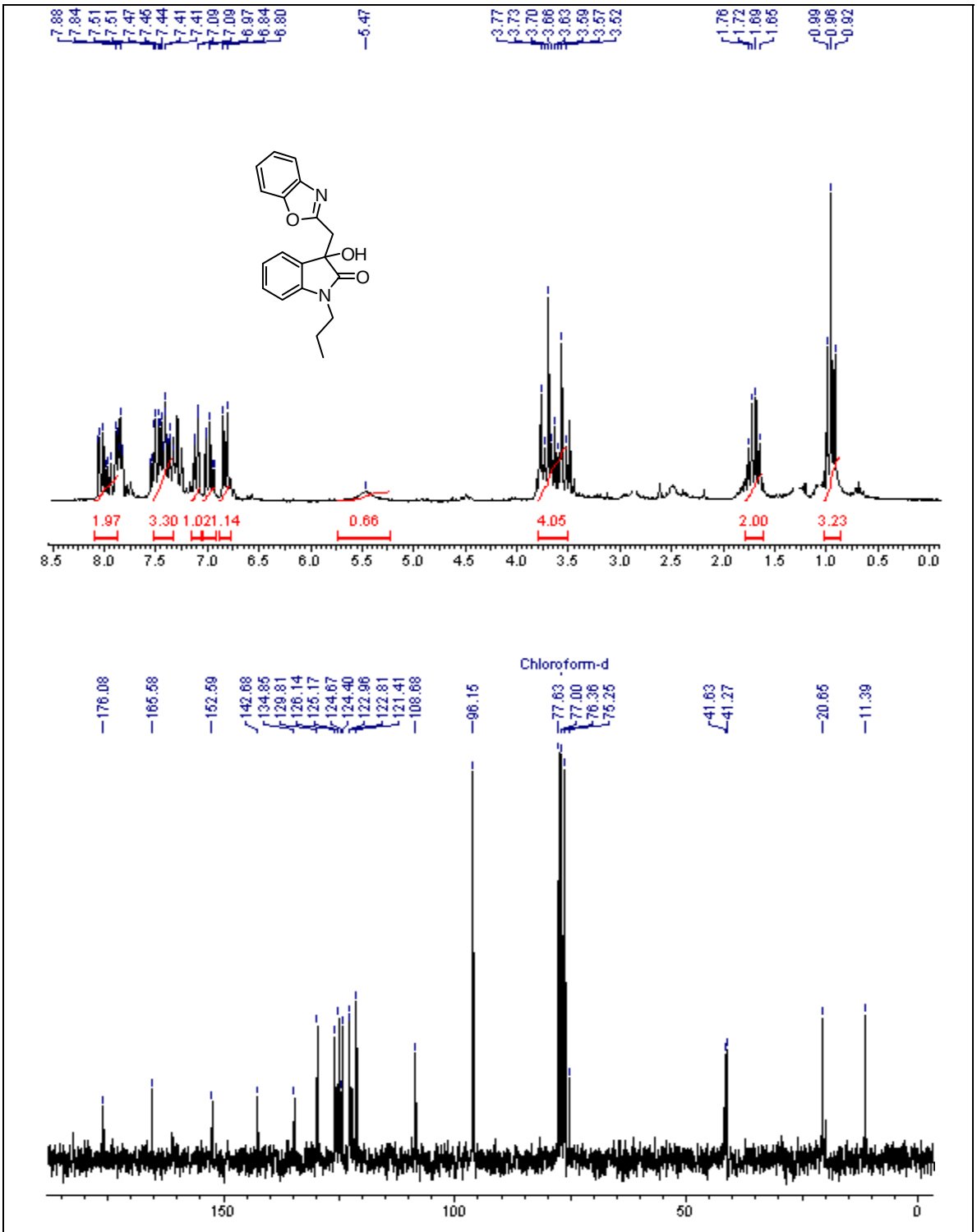


Fig. 47: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]oxazol-2-ylmethyl)-3-hydroxy-1-propylindolin-2-one

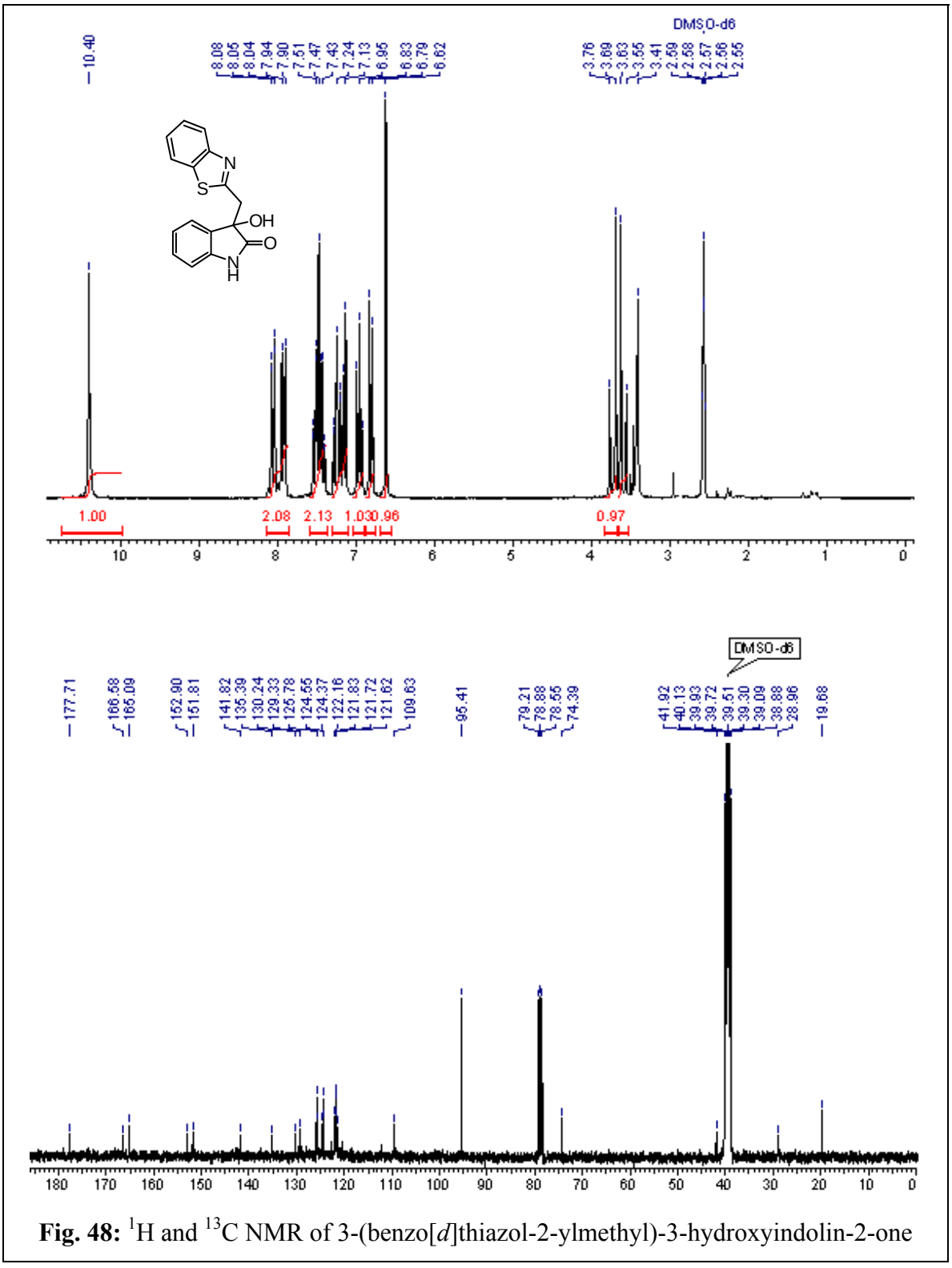


Fig. 48: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]thiazol-2-ylmethyl)-3-hydroxyindolin-2-one

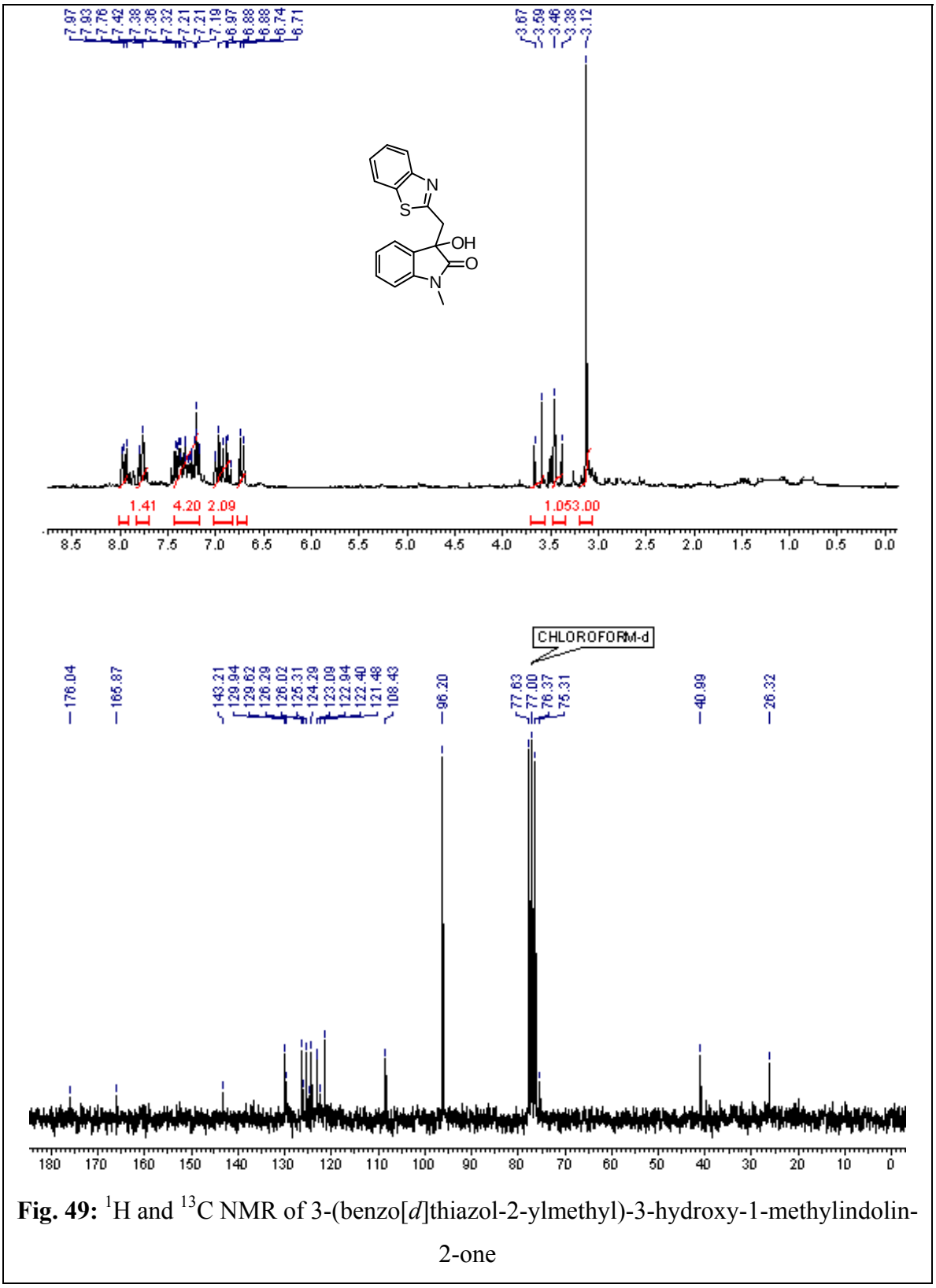


Fig. 49: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]thiazol-2-ylmethyl)-3-hydroxy-1-methylindolin-2-one

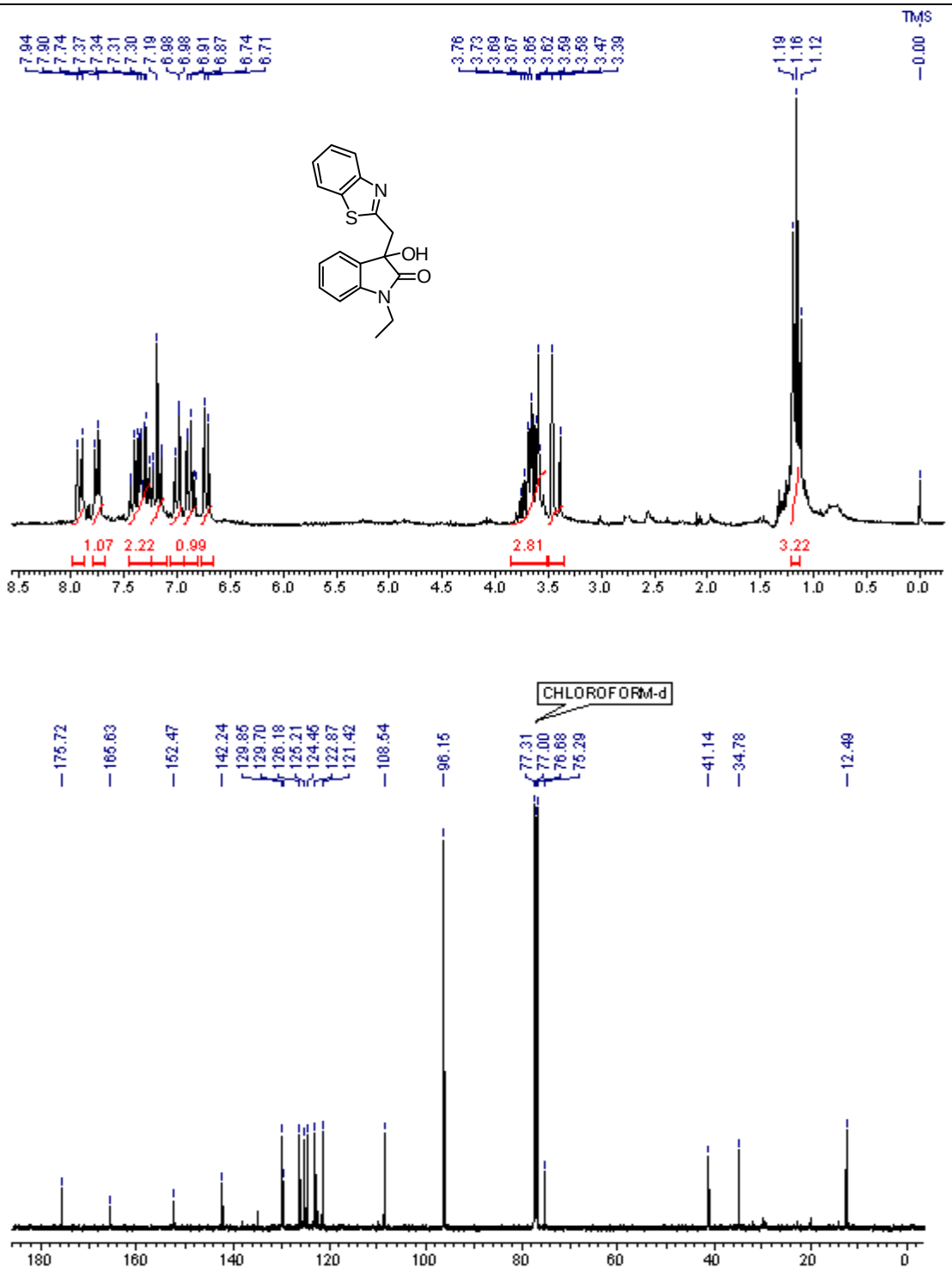


Fig. 50: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]thiazol-2-ylmethyl)-1-ethyl-3-hydroxyindolin-2-one

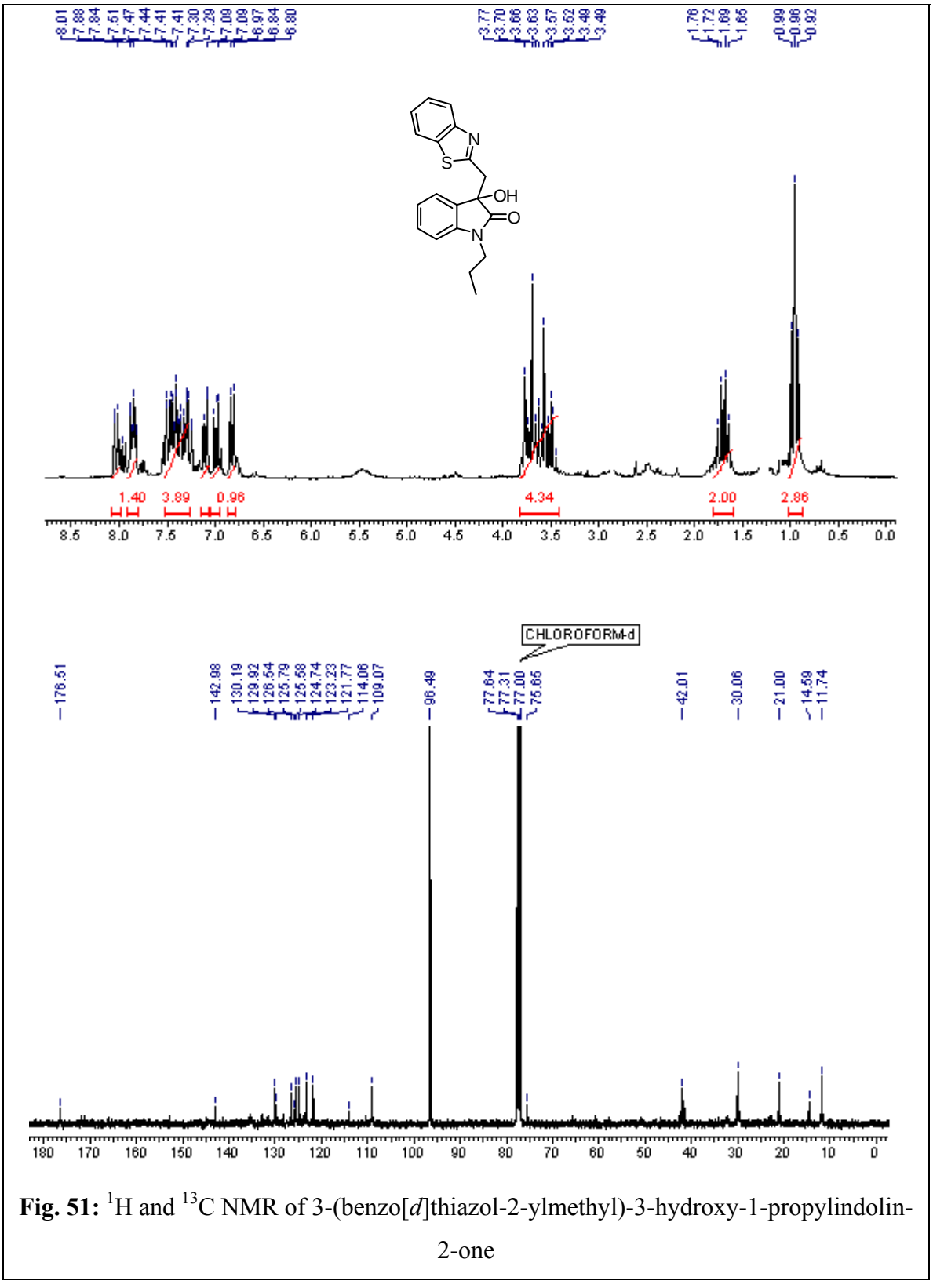


Fig. 51: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]thiazol-2-ylmethyl)-3-hydroxy-1-propylindolin-2-one

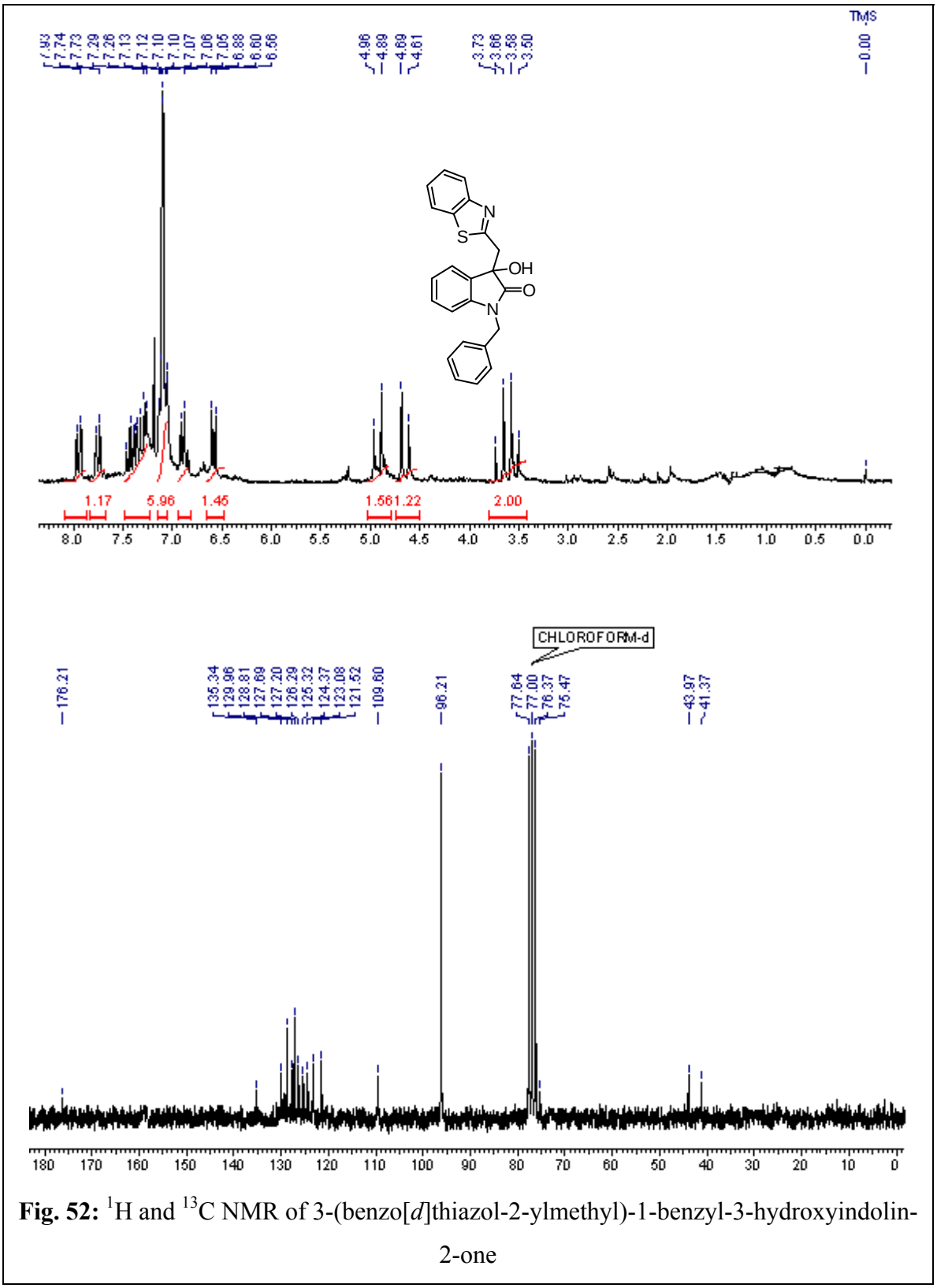


Fig. 52: ^{1}H and ^{13}C NMR of 3-(benzo[*d*]thiazol-2-ylmethyl)-1-benzyl-3-hydroxyindolin-2-one

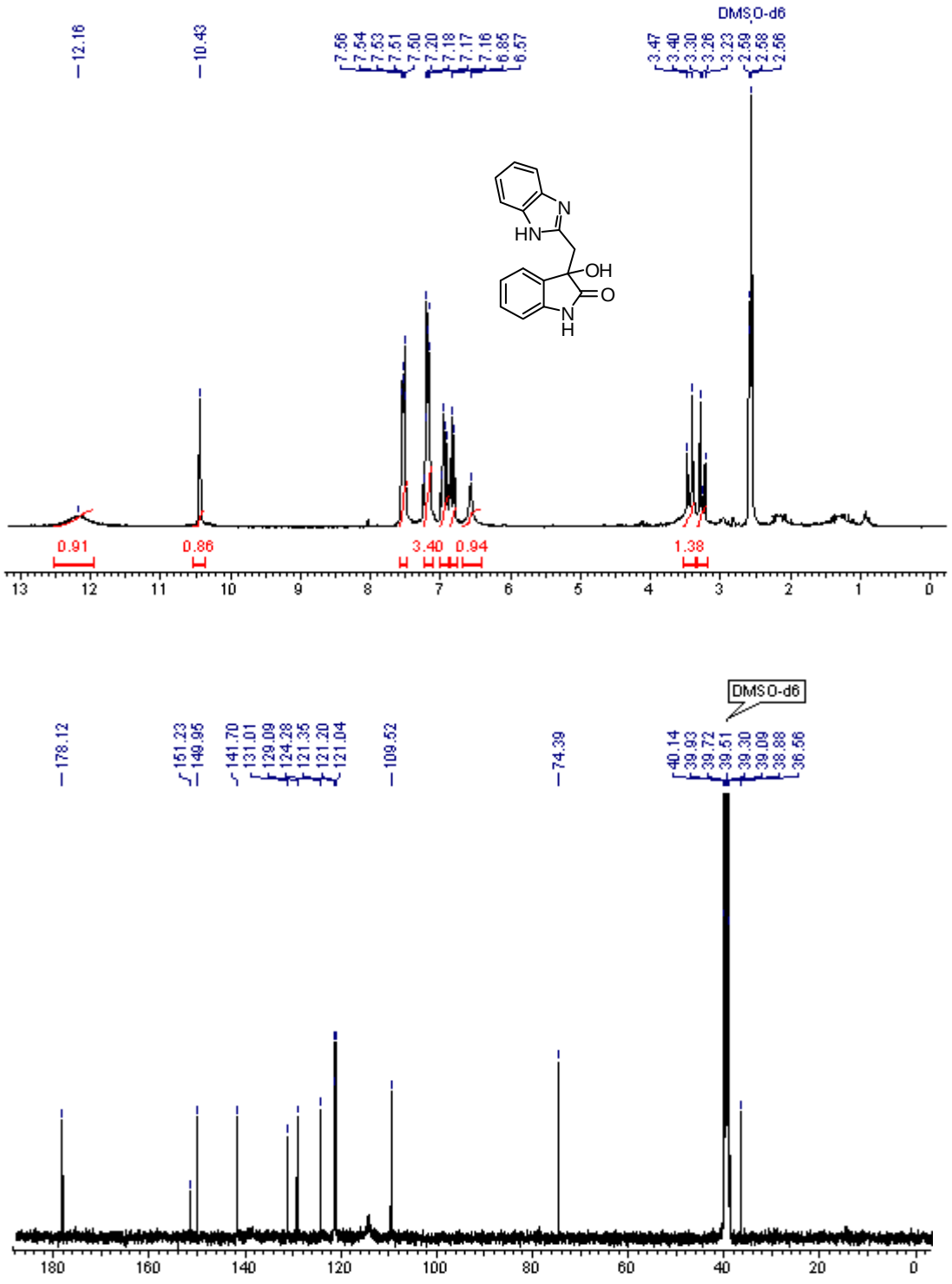


Fig. 53: ^{1}H and ^{13}C NMR of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxyindolin-2-one

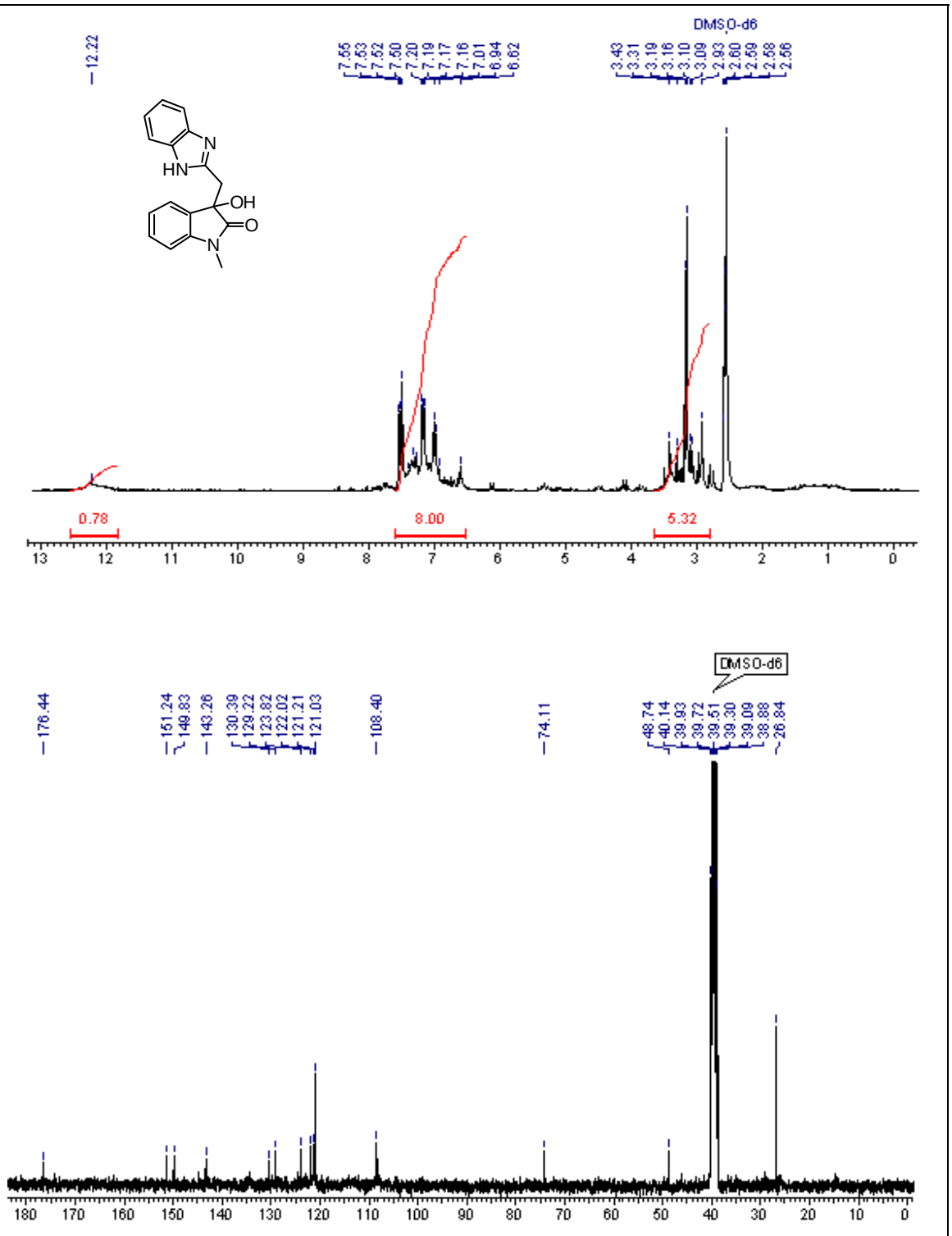


Fig. 54: ^{1}H and ^{13}C NMR of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxy-1-methylindolin-2-one

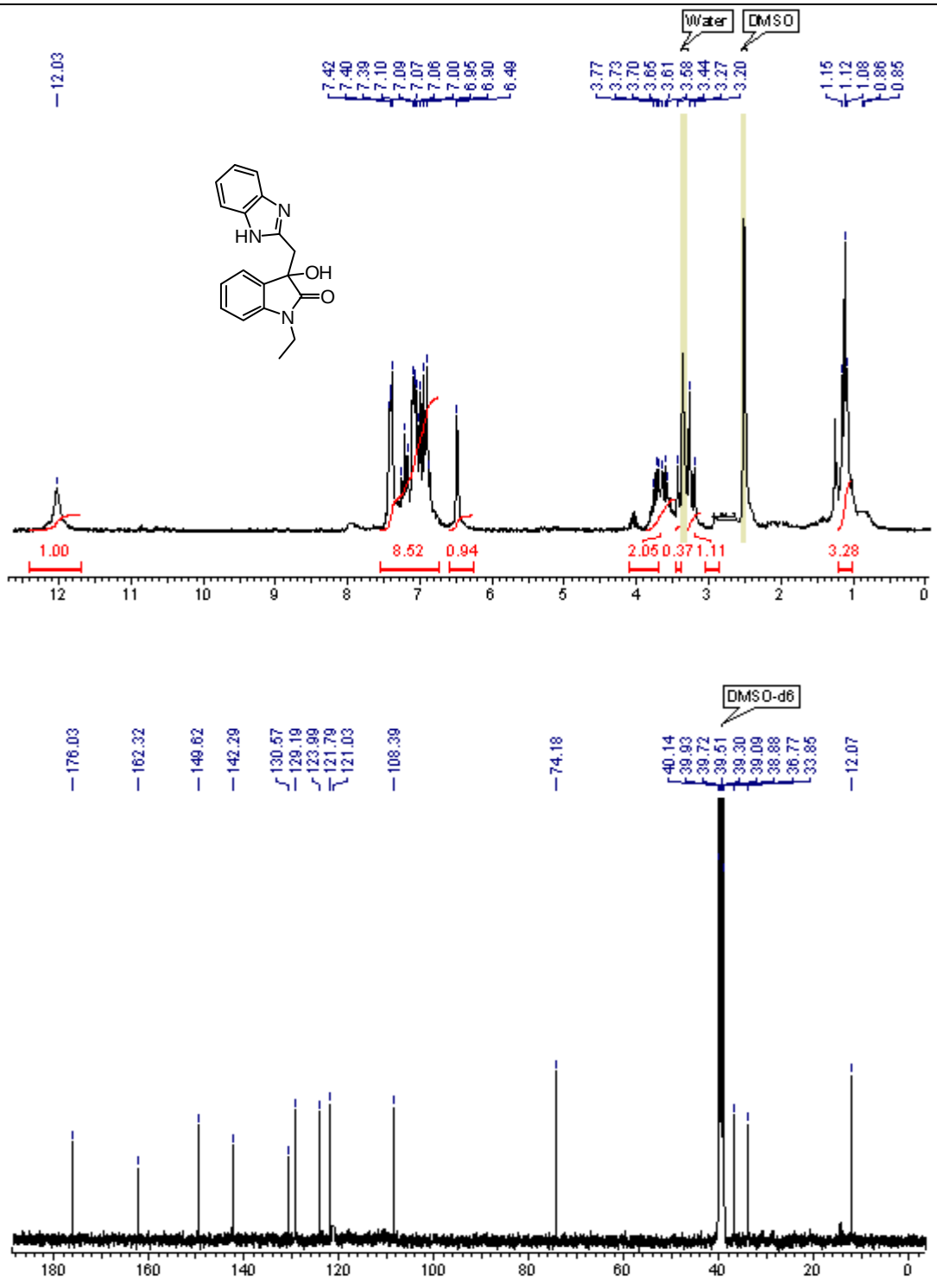


Fig. 55: ^{1}H and ^{13}C NMR of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-ethyl-3-hydroxyindolin-2-one

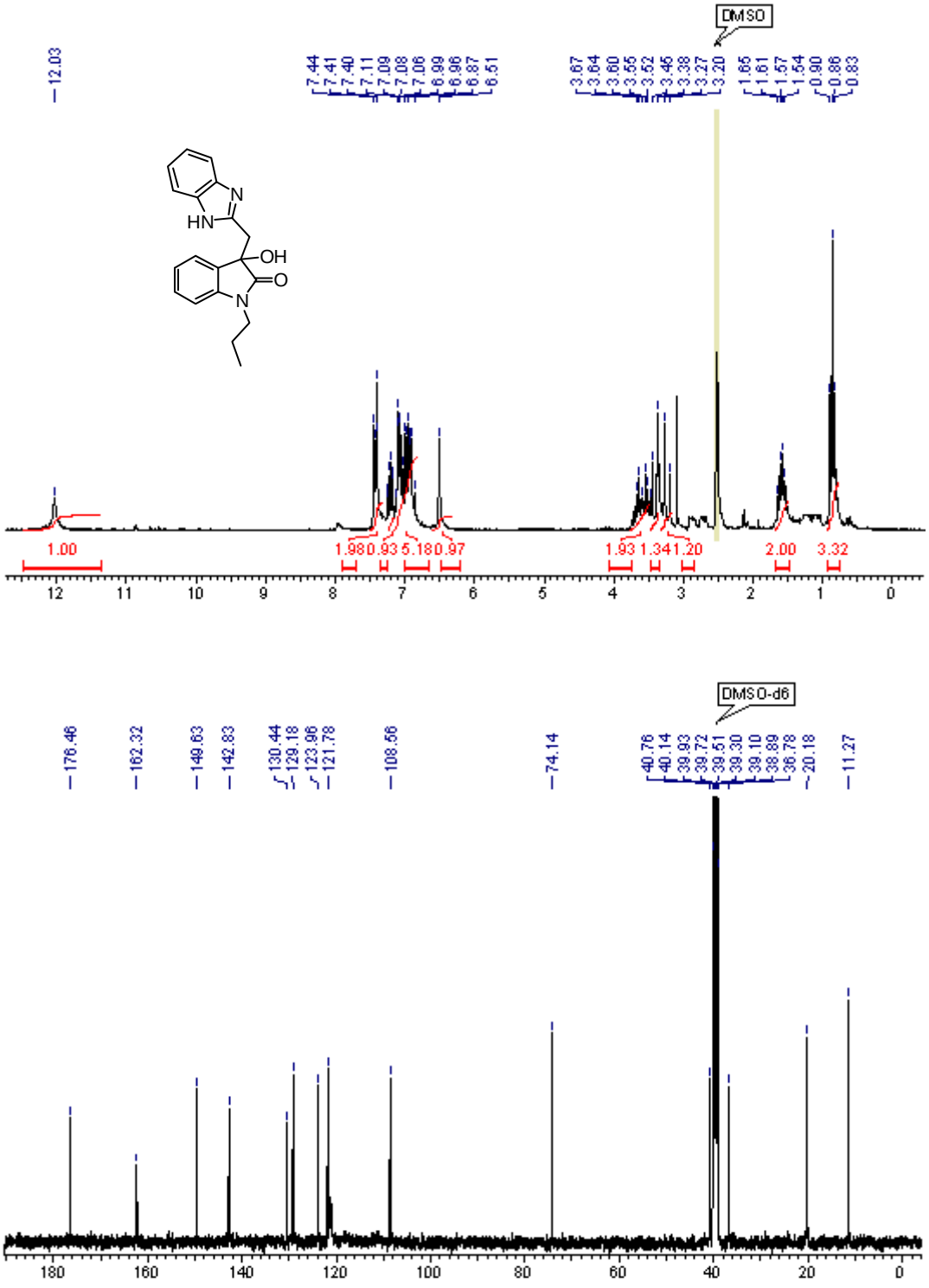


Fig. 56: ^{1}H and ^{13}C NMR of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-3-hydroxy-1-propylindolin-2-one

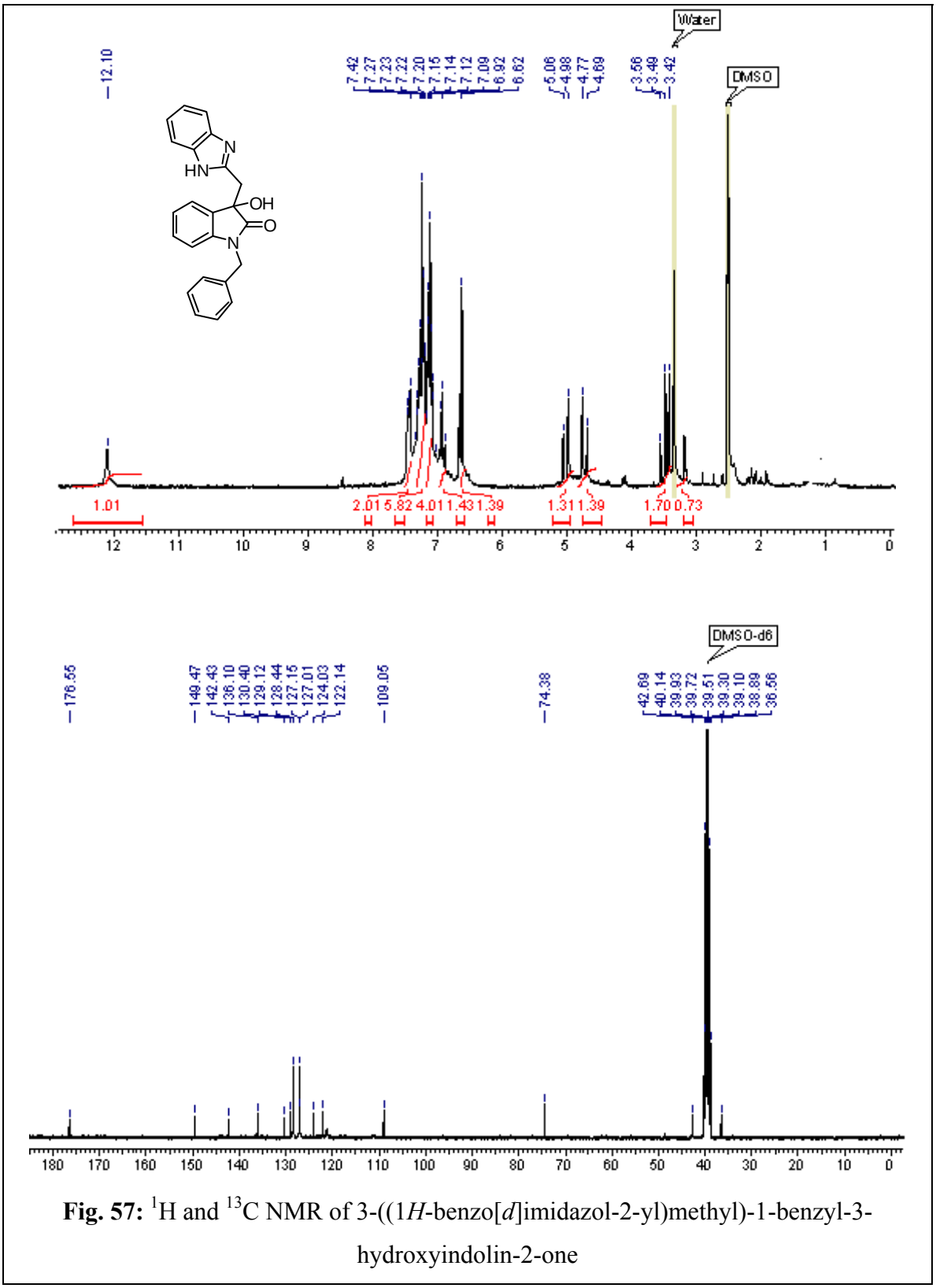


Fig. 57: ^{1}H and ^{13}C NMR of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-benzyl-3-hydroxyindolin-2-one

Section-III

A facile and highly efficient one-pot multi-component synthesis of azaarene-substituted 3- substituted -2-oxindoles *via* sp^3 C-H functionalization of 2-methyl azaarenes and (2-azaaryl)methanes over reusable silica-supported dodecatungstophosphoric acid catalyst

3.3.1 Introduction

The spirocyclic oxindoles motifs are densely functionalized hetrocyclic rings (**Fig. 58**) not only main structural constituents found in numerous natural alkaloids but also in a variety of pharmacophore substances, which exibits wide range of biological activities such as antibacterial, antiflammatory, antimalarial, anti cancer and laxative drugs.[42]

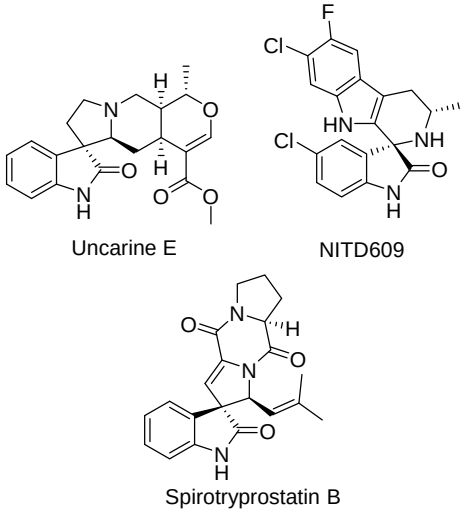


Fig. 58: Biologically active densely functionalized spirooxindoles

Being potent biological and pharmaceutical values of spirooxindole motifs, worldwide researcher are keenly interested to understands its molecular architecture. However, recently, structural activity relation (SAR) reveals that its biological activity[43, 26a] know to be vary with varying substituent on the C-3 position of oxindole. As a result, C-3 position

of oxindole is key characteristic position and/or a central framework at which a variety of spiro rings can be attached to achieve densely functionalized spirooxindoles, which will represent one of the privileged scaffolds library design and drug discovery.[44] Owing to the important of spirocyclic oxindoles and 3-substituted 2-oxindoles in the life sciences, the demand of these motif are increasing rapidly for drug discoveries and hence, the development of conventional and concise synthetic routs, which will be highly efficient, cost effective and economically viable for the synthesis of spirooxindoles and 3-substituted 3-oxindoles are a major challenge and interesting field in the synthetic chemistry.

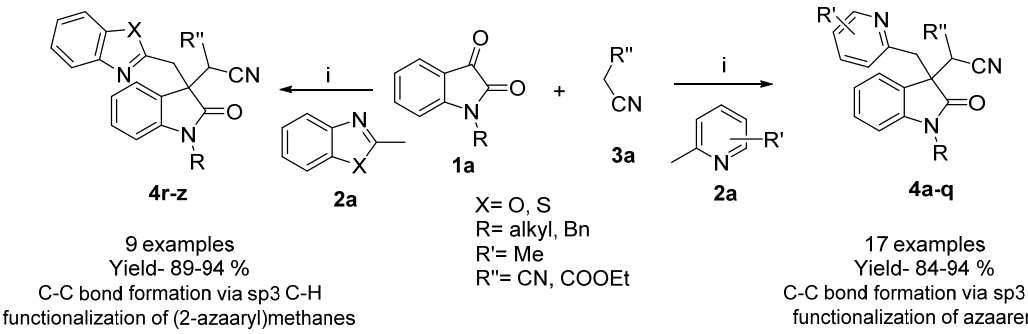
Recently, direct C-H functionalization has emerged as powerful tools in the synthetic organic chemistry,[45] to synthesize complex organic molecules such as alkaloids, pharmacophore substances, spirooxindoles and/or 3-substitted 2-oxindoles etc. Azaarenes being core structural motif of varies bioactive, pharmaceutical compounds, functionalization of its C-H bond via C(sp2)-H and C(sp3)-H bond activation has attracted more attention of the world chemist due to its added advantages such as easy access to form building block for the synthesis of a complex organic compounds using cheap and readily available starting materials with good atom economy over traditional process.[46] In this context, the considerable achievement have been made since last decade for the C-H functionalization in which nucleophilic addition of azaarenes towards aldehydes, Isatins, N-sulfonyl aldimines, substituted chalcones and benzylic arylation of 2-methyl azaarenes have been established.[47] Although, reducing number of steps towards the formation of desired chemical bond is a major concern for the chemist from an atom-economical and environmental point of view. Under this concept, in recent year more

systematic C-H activation is utilized in multi-component reactions. The interesting aspects of C-H activation in multi-component reactions are fascinating area of modern day's synthetic organic and medicinal chemistry.

3.3.2 Present Work

3.3.2.1 Objectives

The C-H functionalization via sp^3 C-H bond activation as well as C-C bond formation reactions have been well reported over transition metals,[36] Lewis and Bronsted acid catalysts.[37] Moreover, all these C-H functionalization approaches reported using either costly transition metals or moisture sensitive, toxic, and corrosive homogeneous (Lewis and Bronsted acid) catalysts in excess or stoichiometric quantity, which leads to the problems of toxic waste disposal[38] besides long reaction time, high temperature. The 3-substituted-3-hydroxy-2-oxindoles being the potent biological, and pharmaceutical value and also its biological activity known to be varying with substituent on the C-3 position, hence incorporation of the various functional groups at C-3 position of 3-substituted 3-hydroxy-2-oxindoles to design and develop potent biological azaarene-substituted 3-substituted-2-oxindoles is highly challenging and active research area. Therefore, this section describes, highly efficient heterogeneous reusable silica-supported dodecatungstophosphoric acid catalyzed one-pot multi-component synthesis of azaarene-substituted 3- substituted -2-oxindoles in excellent yields from 2-methyl azaarenes/ (2-azaaryl)methanes, isatin and malononitrile/ ethylcynoacetate via sp^3 C-H functionalization (**Scheme 13**).



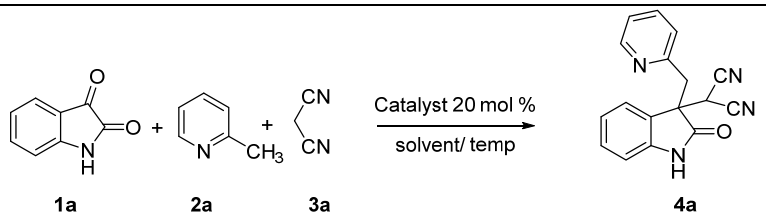
Scheme 13: *Reagents and reaction conditions*: (i) Isatin (1 mmol), azaarene (1.5 mmol), malononitrile/ethylcynoacetate (1.2 mmol), 20 % DTP/SiO_2 (50 mg), DMF (5 mL) at 120 ^oC, 8 h.

3.3.3 Results and discussion

To develop one-pot multi-component protocol for the synthesis of azaarene-substituted 3-substituted-2-oxindole via sp3 C-H functionalization, isatin (1 mmol) **1a**, 2-picoline (1.5 mmol) **2a** and malononitrile (1.2 mmol) **3a** catalyzed by 50 mg of 20 % DTP/SiO_2 in 5 mL solvent was selected as model reaction to optimized reaction conditions. Initially, the screening of different solvents such as Toluene, 1, 4-dioxane, acetonitrile, THF and DMF were carried out at different temperature. However, DMF solvent (**Table 8**, entry **7**) gives the desired product in a 87 % isolated yield in 7 h, whereas toluene, 1,4-dioxane, neat reaction condition gives 60 %, 71 %, and 34 % yield, respectively (**Table 8**, entries **1-3**) in 8 h. The formation of desired product was not observed in acetonitrile, THF solvent as well as in the absence of catalyst at 120 ^oC for 12 h in a DMF solvent (**Table 8**, entries **4-6**), The promising results using 50 mg of 20 % DTP/SiO_2 as a catalyst in a DMF solvent, made us enthusiastic to develop the scope of various catalysts for the synthesis of azaarene-substituted 3-substituted-2-oxindole via sp3 C-H functionalization of 2-picoline. Therefore, various catalysts were screened in a DMF solvent at 120 ^oC and results are shown in **Table 8**. Results in **Table 8** reveals that 20 % DTP/SiO_2 catalyst shows

excellent performance to desired product via C(sp3)-H functionalization of 2-picoline (**Table 8**, entry **7**) compared to sulfated zirconia, $ZnCl_2$, $InCl_3$, Iodine (**Table 8**, entry **8-9**, **15-16**).

Table 8: Optimization of the reaction conditions[a]



1a **2a** **3a** **4a**

Sr. No.	Solvent	Catalyst	Temp. (^oC)	Time (h)	Yield (%)[b]
1	Toluene	DTP/SiO_2	110	8	60
2	1,4 Dioxan	DTP/SiO_2	101	8	71
3	Neat	DTP/SiO_2	110	8	34
4	Acetonitrile	DTP/SiO_2	82	8	NR[c]
5	THF	DTP/SiO_2	66	8	NR[c]
6	DMF	No catalyst	120	12	NR[c]
7	**DMF**	**DTP/SiO_2**	**120**	**7**	**87**
8	DMF	$Zr(SO_4)_2(H_2O)_4$	120	8	40
9	DMF	$ZnCl_2$	120	8	73
10	DMF	$Cu(OAc)_2$	120	8	NR[c]
11	DMF	$FeCl_3$	120	8	NR[c]
12	DMF	$AlCl_3$	120	8	NR[c]
13	DMF	$MgCl_2$	120	8	NR[c]
14	DMF	$CuCl_2$	120	8	NR[c]
15	DMF	$InCl_3$	120	8	24
16	DMF	Iodine	120	8	30

[a]Reaction conditions: Isatin (1 mmol), 2- picoline (1.5 mmol), malononitrile (1.2 mmol), 20 % DTP/SiO_2 (50 mg), /lewis acid catalyst (20 mol%) in solvent (5 mL).

[b]Isolated yield after column chromatography.

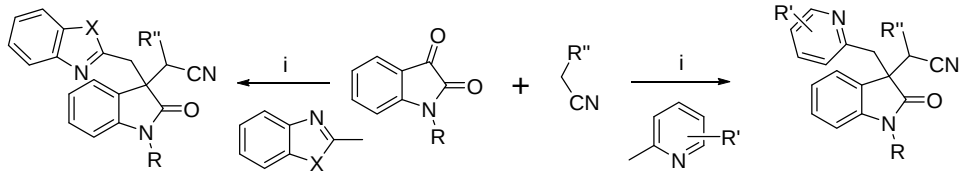
[c]No reaction.

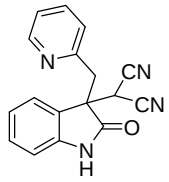
However, formation of desired product was not observed using $Cu(OAc)_2$, $FeCl_3$, $AlCl_3$, $MgCl_2$, and $CuCl_2$ as catalyst (**Table 8**, entries **10-14**).

Having an established optimized reaction conditions in hand, the substrate scope of one-pot multi-component reaction has been investigate using isatin, active methylene compounds and various azaarenes and results are shown in **Table 9**.

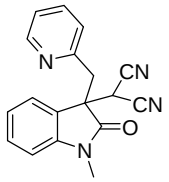
Initially isatin and various protected isatins such as NH, N-methyl, ethyl, benzyl were reacted smoothly with 2-picoline and malononitrile under the optimized reaction conditions to give the desired product in a 87-90 % isolated yields (**Table 9**, entries **4a-d**), whereas 2, 6-lutidine gave desired product in excellent (91-94 %) yields (**Table 9**, entries **4e-h)**. However, 4-picoline also reacted smoothly with the isatin, protected isatin, and malononitrile gives the desired product in a 83-86 % yield (**Table 9**, entries **4i-l**). The achievement of an excellent result on various azaarenes isatin with malononitrile, develop a keen interest to elaborate the scope to ethylcynoacetate by replacing malononitrile with ethylcynoacetate under the optimized reaction conditions. Surprisingly, various azaarenes (2-picoline, 4-picoline and 2, 6 lutidine)/ isatin were reacted successfully with ethylcynoacetate, and provided a 82-89 % yield to the corresponding desired product (**Table 9**, entries **4m-q**). Impressed by these results, the scope of one-pot multi-component reactions was further elaborated to (azaaryl)methanes by substituting it at the C-3 positions of isatins to achieve variety of azaarene-substituted 3-substituted -2-oxiindoles, which pusses unique biological activities and application in a wide range of biologically active natural products.[48, 49] Interestingly, various protected isatins reacted smoothly with (azaaryl)methane and malononitrile, gave unprecedented azaarene substituted 3-substituted -2-oxiindoles in a 85-94 % yields (**Table 9**, entries **4r-z**). From

Table 9: Substrate scope for the synthesis of azaarene-substituted 3-substituted -2-oxiindoles[a,b]

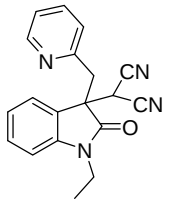




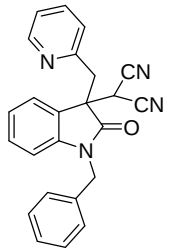
4a 87 %



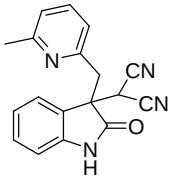
4b 90 %



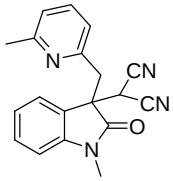
4c 88 %



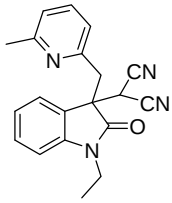
4d 90 %



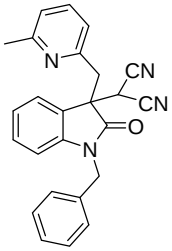
4e 91 %



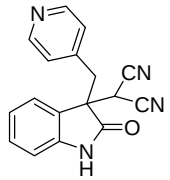
4f 92 %



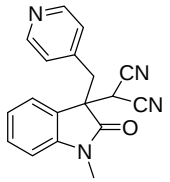
4g 92 %



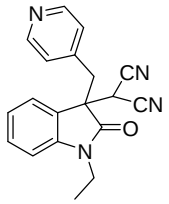
4h 94 %



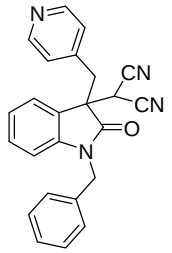
4i 84 %



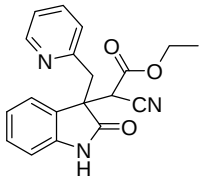
4j 83 %



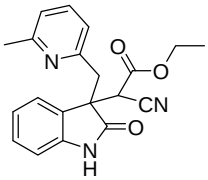
4k 86 %



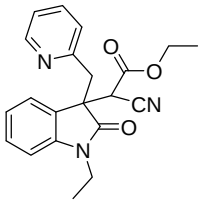
4l 85 %



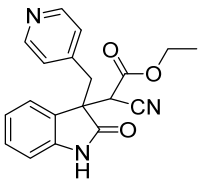
4m 86 %



4n 89 %

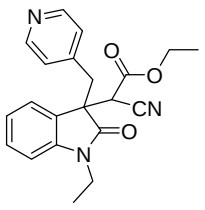


4o 82 %

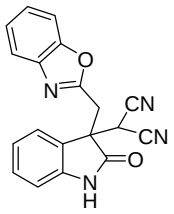


4p 82 %

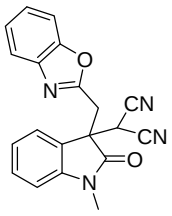
Table 9 (*Continued*)



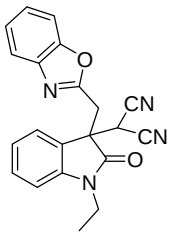
4q 89 %



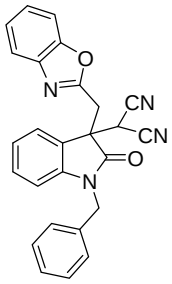
4r 91 %



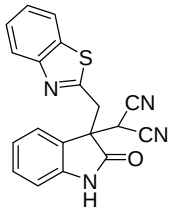
4s 94 %



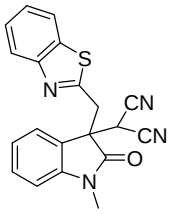
4t 92 %



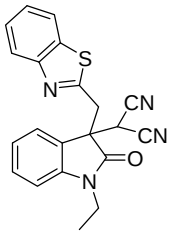
4u 90 %



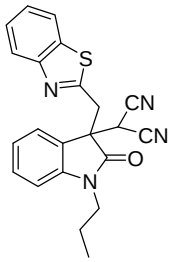
4v 89 %



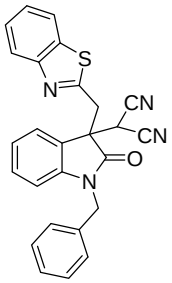
4w 93 %



4x 94 %



4y 92 %



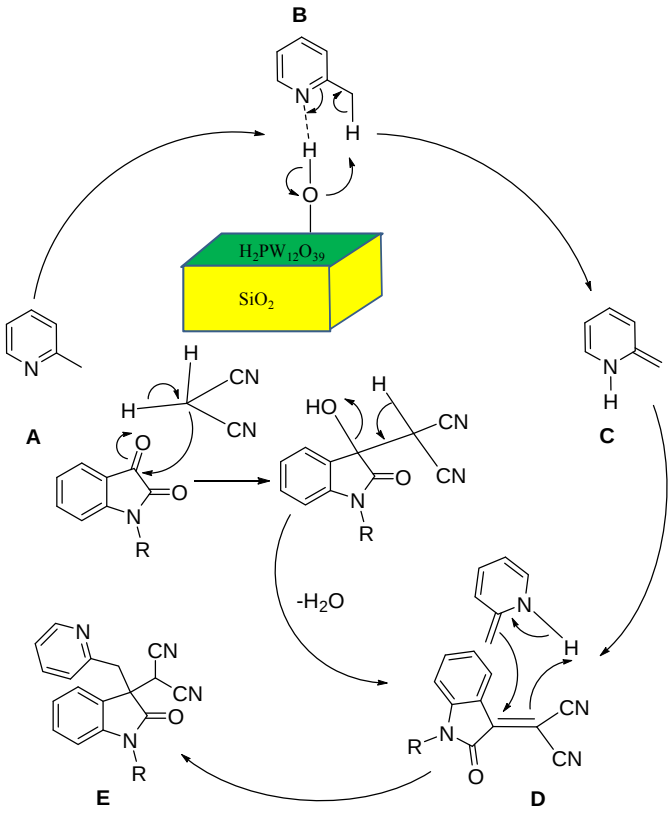
4z 91 %

[a]Reaction conditions: Isatin (1 mmol), azaarene (2 mmol), malononitrile/ethylcynoacetate (1.2 mmol), 20 % DTP/SiO_2 (50 mg) in DMF (5 mL) at 120 ^oC for 8 h.

[b]Isolated yields after chromatographic purification.

these results, it is very much clear that DTP/SiO_2 catalyst shows excellent performance irrespective to protected/unprotected isatin/substituted azaarene/(azaaryl)methane with malononitrile/ethylcynoacetate and hence developed MCR protocol is highly efficient, promising and general for the synthesis of azaarene-substituted -3-substituted -2-oxiindoles.

A possible mechanism for the synthesis of azaarene-substituted-3-substituted- 2-oxindoles is outlined in **Scheme 14**, which is proposed on the basis of previous reported literature. [50, 26d, 39]



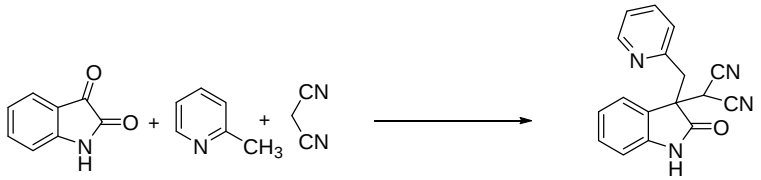
Scheme 14: Proposed mechanism for three-component SP^3 C-H functionalization

As shown in **Scheme 14**, the predicted mechanism involves the protonation of 2-picoline **A** over DTP/SiO_2 catalyst as shown in **B** followed by C-H bond cleavage gives enamine **C**, which then add as nucleophile to the insitu generated Knoevenagel adduct **D** to release instantly corresponding desired product **E** by formation of C-C bond.

The recovery and recyclability of catalyst is highly demandable world wide in near future to achieve environmental sustainable and economical viable processes. Hence, the recyclability and recovery of DTP/SiO_2 catalyst was investigated for the synthesis of azaarene-substituted 3-substituted -2-oxiindoles by the reaction of isatin, 2-picoline with malononitrile under the optimized reaction conditions, and results are given in **Table 10**. The DTP/SiO_2 catalyst was recovered quantitatively by simple filtration from the reaction

mixture and recycled again several times without loss of catalytic activity (**Table 10**, entries **2-5**). The isolated yield obtained at the end of 4th recycle of DTP/SiO_2 catalyst (**Table 10**, entry **5**) is very much consistent as of fresh DTP/SiO_2 catalyst (**Table 10**, entry **1**). The consistent catalytic activity of reused DTP/SiO_2 indicates that the reused catalyst shows excellent performance for the synthesis of azaarene-substituted 3-substituted -2-oxiindoles via the sp3 C-H functionalization.

Table 10: The recyclability study of DTP/SiO_2[a, b]



Entry	Run	Yield (%)
1	Fresh	87
2	Run-1	87
3	Run-2	86
4	Run-3	85
5	Run-4	87

[a]Reaction Conditions: Isatin (1 mmol), 2-picoline (2 mmol), malononitrile (1.2 mmol) in DMF (5 mL) at 120 ^oC for 8 h.

[b]Isolated yield after column chromatography.

3.3.4 Conclusion

In conclusion, we have developed unprecedented one-pot multi-component (MCR) protocols for the synthesis of biologically relevant novel azaarene-substitute 3-disubstituted-2-oxindoles over heterogeneous, recyclable DTP/SiO_2 catalyst. The developed MCR protocol is an efficient, environmentally clean, general, atom-economical, and strategy occurring via C(sp^3)-H functionalization, Knoevenagel

condensation, and Michel addition in one-pot to rationalize the complex molecule synthesis. Applications of developed MCR protocol for various substrates scope and the synthesis of biological/medicinal/ or pharmaceutical valuable compounds are under progress in our research group. The catalyst DTP/SiO_2 was recovered by simple filtration from the reaction mixture and reused several times without the loss of catalytic activity.

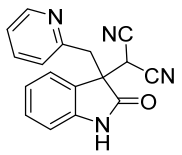
3.3.5 Experimental Section

3.3.5.1 A typical experimental procedure for synthesis of azaarene-substitute 3-substituted-2-oxindoles over the 20 % DTP/SiO_2

A mixture of isatin (1 mmol), malononitrile/ ethylcynoacetate (1.2 mmol) in a 5 mL DMF solvent was stirred for 15 min at room tempreture, to this azaarene (2 mmol) was added and the reaction mixture was heated at 120 ^{o}C for 8 h in the presence of 50 mg 20 % DTP/SiO_2 catalyst. The completion of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was diluted with ethyl acetate (10 mL) and catalyst was recovered by filtration. The filtrate was washed with aqueous $NaHCO_3$ and then with water followed by separation of aqueous layer and organic layer. The organic layer is dried over anhydrous Na_2SO_4 and concentrate in a vacuum to gives the crude product. The crude product was purified by silica gel column chromatography using 70:30 ratio of pet ether/ethyl acetate to afford the pure azaarene substituted 3-hydroxy-2-oxindole (**Table 9**). All the isolated desired reaction products were characterized and confirmed by NMR.

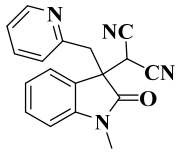
3.3.5.2 Spectral data

2-(2-oxo-3(pyridine-2-ylmethyl)indolin-3-yl)malononitrile (4a)



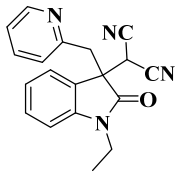
Yield: 87 %; Off White solid, mp: 152-154 ^{o}C; **^{1}H NMR** (DMSO-d_6): **δ** 10.94 (s, 1H), 8.34 (d, *J*=4.80 Hz, 1H), 7.60 (dt, *J*=7.71 Hz, 1H), 7.26-7.13 (m, 3H), 7.08-6.93 (m, 2H), 6.80 (d, *J*=8.34 Hz, 1H), 5.83 (s, 1H), 3.50 (d, *J*=1.77 Hz, 2H); **^{13}C NMR** (DMSO-d_6): **δ** 175.2, 154.8, 148.7, 142.4, 136.4, 129.9, 125.8, 124.4, 124.2, 122.2, 121.9, 111.9, 110.0, 51.5, 40.8, 29.8.

2-(1-methyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)malononitrile (4b)



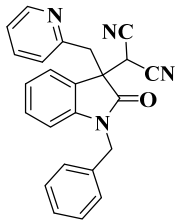
Yield: 90 %; Off White solid, mp: 98-100 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 8.42 (d, *J*=4.04 Hz, 1H), 7.57-7.49 (m, 1H), 7.40-7.30 (m, 2H), 7.15-6.96 (m, 3H), 6.83 (d, *J*=7.83 Hz, 1H), 5.06 (s, 1H), 3.50 (s, 2H), 3.23 (s, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 173.5, 154.5, 149.00, 143.8, 136.4, 130.4, 125.3, 124.3, 124.2, 123.4, 122.4, 111.1, 108.8, 52.0, 41.3, 29.9, 26.7.

2-(1-ethyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)malononitrile (4c)



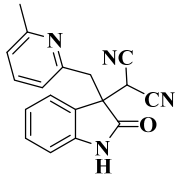
Yield: 88 %; Off White solid, mp: 124-126 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 8.31 (d, *J*=4.93 Hz, 1H), 7.48-7.35 (m, 2H), 7.26-7.19 (m, 1H), 7.07-6.89 (m, 3H), 6.75 (d, *J*=7.83 Hz, 1H), 4.89 (s, 1H), 3.68 (q, 2H), 3.45 (s, 2H), 1.14 (t, *J*=7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 173.1, 154.4, 148.9, 142.8, 136.4, 130.4, 125.4, 124.0, 123.2, 122.3, 111.1, 109.9, 108.9, 51.8, 41.3, 35.2, 30.1, 12.1.

2-(1-benzyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)malononitrile (4d)



Yield: 90 %; Off white solid, mp: 132-134 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 8.26 (d, *J*=4.80 Hz, 1H), 7.45-7.35 (m, 2H), 7.23-7.11 (m, 6H), 7.06-6.94 (m, 2H), 6.88 (d, *J*=7.71 Hz, 1H), 6.61 (d, *J*=7.71 Hz, 1H), 4.93 (s, 1H), 4.83 (d, *J*=15.79 Hz, 2H), 3.50 (s, 2H); **^{13}C NMR** ($CDCl_3$): **δ** 173.6, 154.2, 148.9, 143.0, 136.7, 134.7, 130.4, 128.8, 127.8, 127.4, 124.4, 124.3, 123.4, 122.4, 111.1, 110.1, 110.0, 52.1, 44.5, 41.4, 30.3.

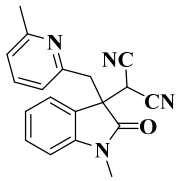
2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile (4e)



Yield: 91 %; Off White solid, mp: 201-203 ^{o}C; **^{1}H NMR** (DMSO-d_6): **δ** 10.92 (s, 1H), 7.48 (t, *J*=7.71 Hz, 1H), 7.27-7.14 (m, 2H), 6.99 (t, *J*=7.71 Hz, 2H), 6.87-6.81 (m, 2H), 5.80 (s, 1H), 3.43 (d, *J*=14.15 Hz, 2H), 2.31 (s, 3H); **^{13}C NMR** (DMSO-d_6): **δ** 175.4,

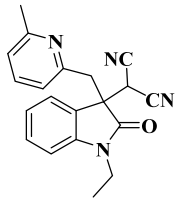
156.9, 153.9, 142.6, 136.6, 129.8, 126.1, 124.3, 121.7, 121.3, 120.8, 112.0, 109.9, 51.3, 40.2, 29.7, 23.6.

2-(1-methyl-3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile (4f)



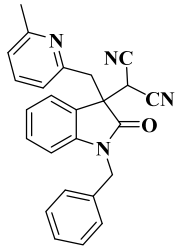
Yield: 92 %; White solid, mp: 112-114 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.55-7.30 (m, 3H), 7.16-7.02 (m, 2H), 6.91-6.87 (m, 2H), 5.06 (s, 1H), 3.57 (s, 2H), 3.30 (s, 3H), 2.49 (s, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 173.6, 157.4, 153.4, 143.9, 137.1, 130.3, 125.5, 124.2, 123.3, 122.00, 121.2, 108.7, 51.7, 40.7, 30.0, 26.6, 24.1.

2-(1-ethyl-3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile (4g)



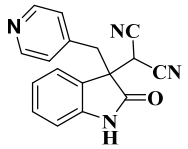
Yield: 92 %; Brown solid, mp: 111-113 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.37-7.19 (m, 3H), 7.04-6.89 (m, 2H), 6.76 (t, *J*=7.71 Hz, 2H), 4.93 (s, 1H), 3.85-3.54 (m, 2H), 3.41 (s, 2H), 2.36 (s, 3H), 1.16 (t, *J*= 7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 173.2, 157.7, 153.6, 142.9, 136.7, 130.7, 130.3, 125.7, 124.5, 123.1, 121.8, 121.2, 109.9, 108.8, 51.7, 41.1, 35.3, 30.1, 24.3, 12.4.

2-(1-benzyl-3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile (4h)



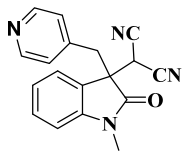
Yield: 94 %; White solid, mp: 141-143 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.32 (t, *J*=8.21 Hz, 2H), 7.18-7.11 (m, 6H), 7.00 (d, *J*=7.45 Hz, 1H), 6.89 (d, *J*=7.83 Hz, 1H), 6.70 (d, *J*=7.58 Hz, 1H), 6.60 (d, *J*=7.83 Hz, 1H), 5.01 (s, 1H), 4.90 (d, *J*=15.79 Hz, 1H), 4.72 (d, *J*=15.66 Hz, 1H), 3.45 (d, *J*=5.18 Hz, 2H), 2.34 (s, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 173.6, 157.7, 153.4, 142.9, 136.8, 134.7, 130.2, 128.8, 127.8, 127.2, 125.4, 124.3, 123.3, 121.9, 121.3, 109.8, 51.9, 44.4, 41.4, 29.9, 24.2.

2-(2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)malononitrile (4i)



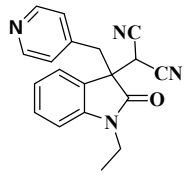
Yield: 84 %; Brown solid, mp: 169-171 ^{o}C; **^{1}H NMR** (DMSO-d_6): **δ** 10.93 (s, 1H), 8.30 (d, *J*=5.94 Hz, 2H), 7.68 (d, *J*=7.20 Hz, 1H), 7.29 (t, *J*=7.71 Hz, 1H), 7.16 (t, *J*=7.33 Hz, 1H), 6.85 (d, *J*=5.94 Hz, 2H), 6.75 (d, *J*=7.58 Hz, 1H), 5.83 (s, 1H), 3.46 (d, *J*=12.51 Hz, 1H), 3.35 (d, *J*=12.51 Hz, 1H); **^{13}C NMR** (DMSO-d_6): **δ** 174.5, 149.1, 142.8, 142.1, 130.4, 124.9, 124.6, 122.5, 110.3, 52.6, 38.2, 29.7.

2-(1-methyl-2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)malononitrile (4j)



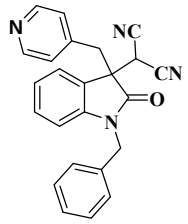
Yield: 83 %; Red solid, mp: 116-118 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 8.35 (d, *J*=6.06 Hz, 2H), 7.76 (d, *J*=6.57 Hz, 1H), 7.47-7.25 (m, 3H), 6.80 (d, *J*=6.19 Hz, 2H), 4.44 (s, 1H), 3.43 (d, *J*=12.51 Hz, 1H), 3.34 (d, *J*=12.38 Hz, 1H), 3.05 (s, 3H); ^{13}CNMR ($CDCl_3$) δ= 172.6, 149.4, 143.7, 141.8, 131.1, 124.8, 124.0, 123.9, 110.6, 109.3, 53.4, 39.9, 30.2, 26.4.

2-(1-ethyl-2-oxo-3(pyridine-4-ylmethyl)indolin-3-yl)malononitrile (4k)



Yield: 86 %; Yellow solid, mp: 128-130 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 8.31 (d, *J*=4.93 Hz, 1H), 7.48-7.35 (m, 2H), 7.26-7.19 (m, 1H), 7.07-6.89 (m, 3H), 6.75 (d, *J*=7.83 Hz, 1H), 4.89 (s, 1H), 3.68 (q, 2H), 3.45 (s, 2H), 1.14 (t, *J*=7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 173.1, 154.4, 148.9, 142.8, 136.4, 130.4, 125.4, 124.0, 123.2, 122.3, 111.1, 109.9, 108.9, 51.8, 41.3, 35.2, 30.1, 12.1.

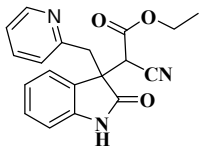
2-(1-benzyl-2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)malononitrile (4l)



Yield: 85 %; Off white solid, mp: 121-123 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 8.20 (d, *J*=6.06 Hz, 2H), 7.75-7.71 (m, 1H), 7.25-7.14 (m, 5H), 6.78-6.53 (m, 5H), 4.75 (d, *J*=15.79 Hz, 1H), 4.55 (d, *J*=15.92 Hz, 1H), 4.50 (s, 1H), 3.46 (d, *J*=12.51 Hz, 1H), 3.28 (d, *J*=12.51 Hz, 1H); **^{13}C NMR** ($CDCl_3$): **δ** 172.6, 148.9, 143.1, 142.5, 133.8, 131.2, 128.9, 127.9, 126.6,

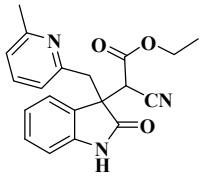
125.2, 123.9, 123.8, 110.6, 109.5, 53.3, 44.3, 39.9, 30.7.

Ethyl 2-cyano-2-(2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)acetate (4m)



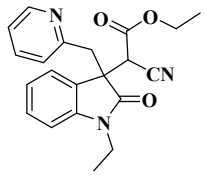
Yield: 86 %; Orange solid, mp: 167-169 ^{o}C; mixture of two diastereoisomers (dr 60/40); **^{1}H NMR** ($CDCl_3$): **δ** 10.57 (s, 1H), 10.49 (s, 1H), 8.35-8.26 (m, 2H), 7.57-7.42 (m, 3H), 7.17-6.85 (m, 8H), 6.67-6.61 (m, 2H), 5.08 (s, 1H), 4.95 (s, 1H), 4.08-3.90 (m, 3H), 3.57-3.33 (m, 3H), 0.90 (t, *J*=7.20 Hz, 5H); **^{13}C NMR** ($CDCl_3$): **δ** 173.9, 162.8, 152.1, 143.5, 129.9, 126.0, 125.2, 123.9, 122.9, 121.2, 114.7, 108.5, 63.0, 51.0, 43.9, 34.9, 11.8.

Ethyl 2-cyano-2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)acetate (4n)



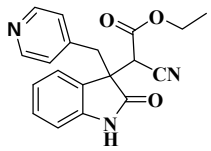
Yield: 89 %; White solid, mp: 93-95 ^{o}C; mixture of two diastereoisomers (dr 60/40); **^{1}H NMR** ($CDCl_3$): **δ** 10.54 (s, 1H), 10.46 (s, 1H), 7.46-7.37 (m, 2H), 7.20-6.85 (m, 8H), 6.75-6.63 (m, 4H), 5.04 (s, 1H), 4.91 (s, 1H), 4.09-3.90 (m, 4H), 3.45-3.39 (m, 4H), 2.23 (s, 6H), 1.04-0.90 (m, 6H); **^{13}C NMR** ($CDCl_3$): **δ** 176.6, 176.1, 163.8, 163.5, 156.5, 154.6, 154.1, 142.5, 136.1, 128.9, 127.7, 124.5, 123.8, 121.1, 121.0, 120.9, 115.8, 109.3, 62.2, 51.7, 44.2, 42.8, 23.7, 13.3.

Ethyl 2-cyano-2-(1-ethyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)acetate (4o)



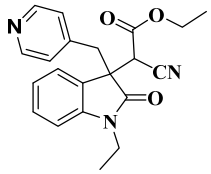
Yield: 82 %; Pink solid, mp: 130-132 ^{o}C; mixture of two diastereoisomers (dr 70/30); **^{1}H NMR** ($CDCl_3$): **δ** 8.38-8.32 (m, 1H), 7.72-7.56 (m, 1H), 7.47-6.85 (m, 5H), 6.75-6.61 (m, 1H), 4.48 (s, 1H), 4.07-3.92 (m, 2H), 3.80-3.48 (m, 4H), 1.30-0.99 (m, 6H); **^{13}C NMR** ($CDCl_3$): **δ** 174.6, 162.7, 154.1, 148.3, 143.0, 136.0, 129.4, 129.2, 126.9, 124.4, 124.0, 122.4, 122.0, 114.9, 107.9, 62.7, 51.6, 43.9, 34.7, 13.5, 11.9.

Ethyl 2-cyano-2-(2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)acetate (4p)



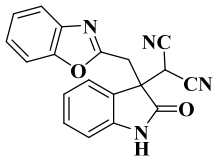
Yield: 82 %; Orange solid, mp: 167-169 ^{o}C; mixture of two diastereoisomers (dr 65/35); **^{1}H NMR** ($CDCl_3$): **δ** 10.56 (s, 1H), 8.27 (t, *J*=4.29 Hz, 3H), 7.60 (d, *J*=7.20 Hz, 1H), 7.21.7.17 (m, 1H), 6.83-6.76 (m, 3H), 5.07 (s, 1H), 3.96 (q, 2H), 3.16-3.09 (m, 2H), 0.90 (t, *J*=7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 177.30, 175.69, 163.29, 148.97, 144.13, 141.80, 129.52, 126.64, 125.10, 121.82, 117.31, 115.60, 109.66, 62.31, 52.42, 50.49, 44.21, 35.79, 30.78, 24.69, 13.28.

Ethyl 2-cyano-2-(1-ethyl-2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)acetate (4q)



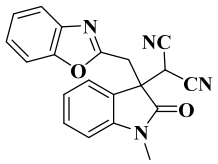
Yield: 89 %; Pink solid, mp: 144-146 ^{o}C; mixture of two diastereoisomers (dr 80/20); **^{1}H NMR** ($CDCl_3$): **δ** 8.29 (d, *J*=6.06 Hz, 2H), 7.75 (d, *J*=7.58 Hz, 1H), 7.35-7.27 (m, 1H), 7.16 (t, *J*=7.58 Hz, 1H), 6.81-6.72 (m, 2H), 6.62 (d, *J*=7.74 Hz, 1H), 4.38 (s, 1H), 4.05-3.94 (m, 2H), 3.63-3.40 (m, 4H), 1.01 (t, *J*=7.07 Hz, 3H), 0.86 (t, *J*=7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 174.0, 162.3, 148.2, 143.3, 129.9, 126.1, 125.3, 123.6, 122.8, 114.5, 108.5, 62.9, 51.9, 43.9, 42.0, 34.7, 13.5, 11.6.

2-3(-(benzo[d]oxazol-2-ylmethyl)-2-oxoindolin-3-yl)malononitrile (4r)



Yield: 91 %; Off White solid, mp: 188-190 ^{o}C; **^{1}H NMR** (DMSO-d_6): **δ** 11.11 (s, 1H), 8.00-7.86 (m, 2H), 7.55-7.27 (m, 4H), 7.10 (t, *J*=7.45 Hz, 1H), 6.87 (d, *J*=7.71 Hz, 1H), 5.92 (s, 1H), 4.00 (d, *J*=14.53 Hz, 1H), 3.86 (d, *J*=14.65 Hz, 1H); **^{13}C NMR** (DMSO-d_6): **δ** 174.4, 163.7, 152.0, 142.7, 134.9, 130.7, 126.2, 125.3, 125.0, 124.6, 122.5, 122.1, 111.8, 111.4, 110.4, 51.2, 36.9, 29.8.

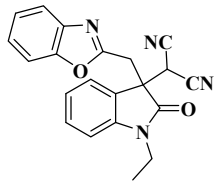
2-(3-(benzo[d]oxazol-2-ylmethyl-2-oxoindolin-3-yl)malononitrile (4s)



Yield: 94 %; White solid, mp: 158-160 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.87 (d, *J*=7.71 Hz, 1H), 7.70 (d, *J*=7.58 Hz, 1H), 7.46-7.19 (m, 4H), 7.06 (t, *J*=7.45 Hz, 1H), 6.82 (d, *J*=7.83 Hz, 1H), 5.05 (s, 1H), 3.84 (d, *J*=15.28 Hz, 1H), 3.70 (d, *J*=15.41 Hz, 1H), 3.21 (s, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 172.7, 162.6, 152.8, 144.0, 134.9, 131.0, 126.3, 125.5, 124.5, 124.3,

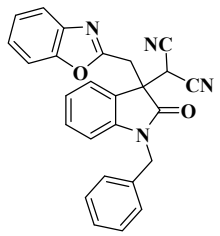
123.8, 123.2, 121.4, 110.6, 109.2, 51.6, 37.4, 30.1, 26.9.

2-(3-(benzo[d]oxazol-2-ylmethyl)-1-ethyl-2-oxoindolin-3-yl)malononitrile (4t)



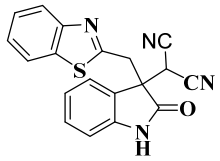
Yield: 92 %; White solid, mp: 154-156 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.94 (d, *J*=7.58 Hz, 1H), 7.76 (d, *J*=7.71 Hz, 1H), 7.57 (d, *J*=8.2 Hz, 1H), 7.49-7.32 (m, 3H), 7.13 (t, *J*=7.58 Hz, 1H), 6.90 (d, *J*=7.83 Hz, 1H), 5.04 (s, 1H), 3.90 (d, *J*=15.16 Hz, 1H), 3.84-3.74 (m, 3H), 1.25 (t, *J*=7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 172.3, 162.5, 152.8, 143.1, 134.9, 130.9, 126.3, 125.5, 124.4, 123.6, 123.2, 121.4, 110.6, 109.3, 51.4, 37.4, 35.4, 30.3, 12.2.

2-(3-(benzo[d]oxazol-2-ylmethyl)-1-benzyl-2-oxoindolin-3-yl)malononitrile (4u)



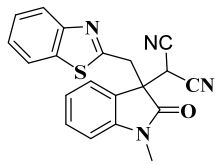
Yield: 90 %; White solid, mp: 154-156 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.82 (d, *J*=8.34 Hz, 1H), 7.66 (d, *J*=7.45 Hz, 1H), 7.54 (d, *J*=7.45 Hz, 1H), 7.42-7.16 (m, 3H), 7.09-6.97 (m, 6H), 6.62 (d, *J*=7.58 Hz, 1H), 5.37 (s, 1H), 4.94 (d, *J*=15.79 Hz, 1H), 4.76 (d, *J*=15.79 Hz, 1H), 3.88 (s, 2H); **^{13}C NMR** ($CDCl_3$): **δ** 172.3, 162.1, 152.0, 142.8, 134.6, 133.9, 130.4, 128.1, 127.2, 126.5, 125.6, 124.9, 123.7, 123.1, 122.6, 120.9, 109.8, 51.0, 43.9, 37.2, 29.8.

2-(3-(benzo[d]thiazol-2-ylmethyl)-2-oxoindolin-3-yl)malononitrile (4v)



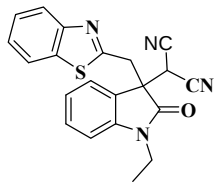
Yield: 89 %; Off White solid, mp: 188-190 ^{o}C; **^{1}H NMR** (DMSO-d_6): **δ** 11.11 (s, 1H), 8.00-7.86 (m, 2H), 7.55-7.27 (m, 4H), 7.10 (t, *J*=7.45 Hz, 1H), 6.87 (d, *J*=7.71 Hz, 1H), 5.92 (s, 1H), 4.00 (d, *J*=14.53 Hz, 1H), 3.86 (d, *J*=14.65 Hz, 1H); **^{13}C NMR** (DMSO-d_6): **δ** 174.4, 163.7, 152.0, 142.7, 134.9, 130.7, 126.2, 125.3, 125.0, 124.6, 122.5, 122.1, 111.8, 111.4, 110.4, 51.2, 36.9, 29.8.

2-(3-(benzo[d]thiazol-2-ylmethyl-2-oxoindolin-3-yl)malononitrile (4w)



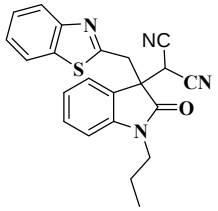
Yield: 93%; Off white solid, mp: 153-155 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.94 (d, *J*=7.78 Hz, 1H), 7.78 (d, *J*=7.79 Hz, 1H), 7.52-7.35 (m, 4H), 7.13 (t, *J*=7.78 Hz, 1H), 6.90 (d, *J*=8.24 Hz, 1H), 5.11 (s, 1H), 3.90 (d, *J*=15.57 Hz, 1H), 3.75 (d, *J*=15.11 Hz, 1H), 3.29 (s, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 172.7, 162.7, 152.7, 143.9, 134.9, 131.0, 126.4, 125.6, 124.3, 123.8, 123.2, 121.5, 110.6, 109.3, 51.6, 37.3, 30.1, 26.9.

2-(3-(benzo[d]thiazol-2-ylmethyl)-1-ethyl-2-oxoindolin-3-yl)malononitrile (4x)



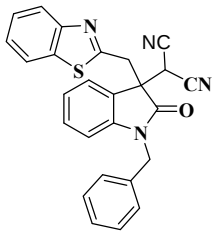
Yield: 94 %; Off white solid, mp: 153-155 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.84 (d, *J*=8.59 Hz, 1H), 7.68 (d, *J*=7.20 Hz, 1H), 7.46 (d, *J*=7.45 Hz, 1H), 7.36-7.19 (m, 3H), 7.04 (t, *J*=7.45 Hz, 1H), 6.70 (d, *J*=7.85 Hz, 1H), 4.95 (s, 1H), 3.85-3.64 (m, 4H), 1.17 (t, *J*=7.20 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 172.3, 162.6, 152.6, 143.1, 134.9, 131.0, 126.3, 125.5, 124.5, 123.6, 123.1, 110.6, 109.3, 51.4, 37.3, 35.5, 30.3, 12.2.

2-(3-(benzo[d]thiazol-2-ylmethyl)-2-oxo-1-propylindolin-3-yl)malononitrile (4y)



Yield: 92 %; Off white solid, mp: 153-155 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.93 (d, *J*=7.58 Hz, 1H), 7.76 (d, *J*=7.07 Hz, 1H), 7.54 (d, *J*=7.45 Hz, 1H), 7.48-7.32 (m, 3H), 7.13 (t, *J*=7.58 Hz, 1H), 6.89 (d, *J*=7.83 Hz, 1H), 5.07 (s, 1H), 3.92-3.65 (m, 4H), 1.70 (q, *J*=7.33 Hz, 2H), 0.93 (t, *J*=7.33 Hz, 3H); **^{13}C NMR** ($CDCl_3$): **δ** 172.6, 162.6, 152.6, 143.6, 134.9, 130.9, 126.3, 125.5, 124.4, 123.6, 123.1, 121.4, 110.7, 109.63, 109.5, 51.5, 42.4, 37.4, 30.2, 20.6, 11.5.

2-(3-(benzo[d]thiazol-2-ylmethyl)-1-benzyl-2-oxoindolin-3-yl)malononitrile (4z)



Yield: 91 %; Off white solid, mp: 153-155 ^{o}C; **^{1}H NMR** ($CDCl_3$): **δ** 7.85 (d, *J*=7.58 Hz, 1H), 7.68 (d, *J*=8.08 Hz, 1H), 7.52 (d, J=6.69 Hz, 1H), 7.42-7.17 (m, 4H), 7.13-6.99 (m,

6H), 6.64 (d, *J*=7.58 Hz, 1H), 4.97-4.73 (m, 3H), 3.90-3.71 (m, 2H); **^{13}C NMR** ($CDCl_3$): **δ** 172.7, 162.4, 152.7, 143.3, 135.1, 134.3, 131.1, 128.8, 127.9, 127.1, 126.3, 125.6, 124.3, 123.9, 123.4, 121.5, 110.5, 109.6, 51.8, 44.7, 37.8, 30.4.

3.3.6 Spectra

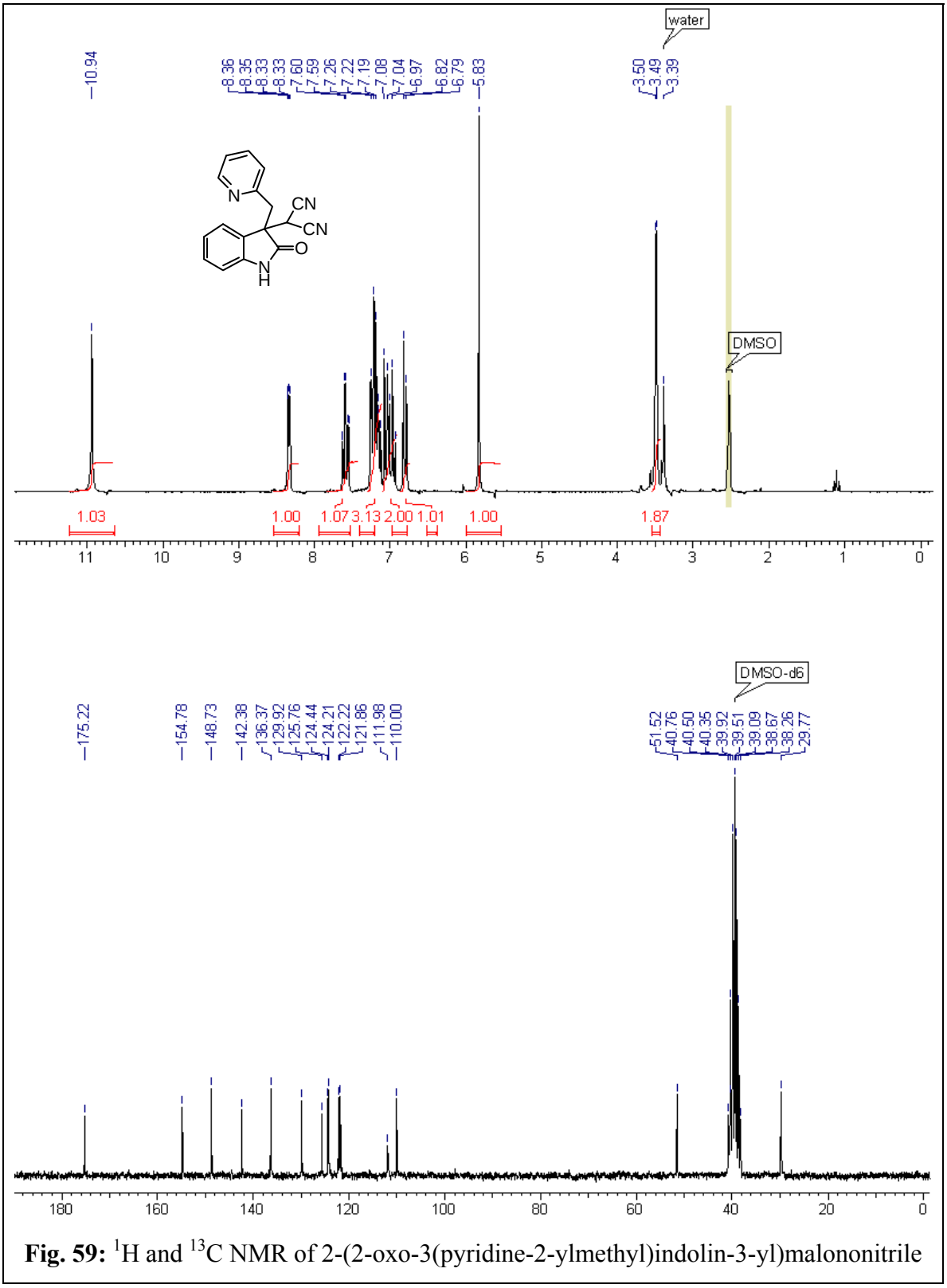


Fig. 59: ^{1}H and ^{13}C NMR of 2-(2-oxo-3(pyridine-2-ylmethyl)indolin-3-yl)malononitrile

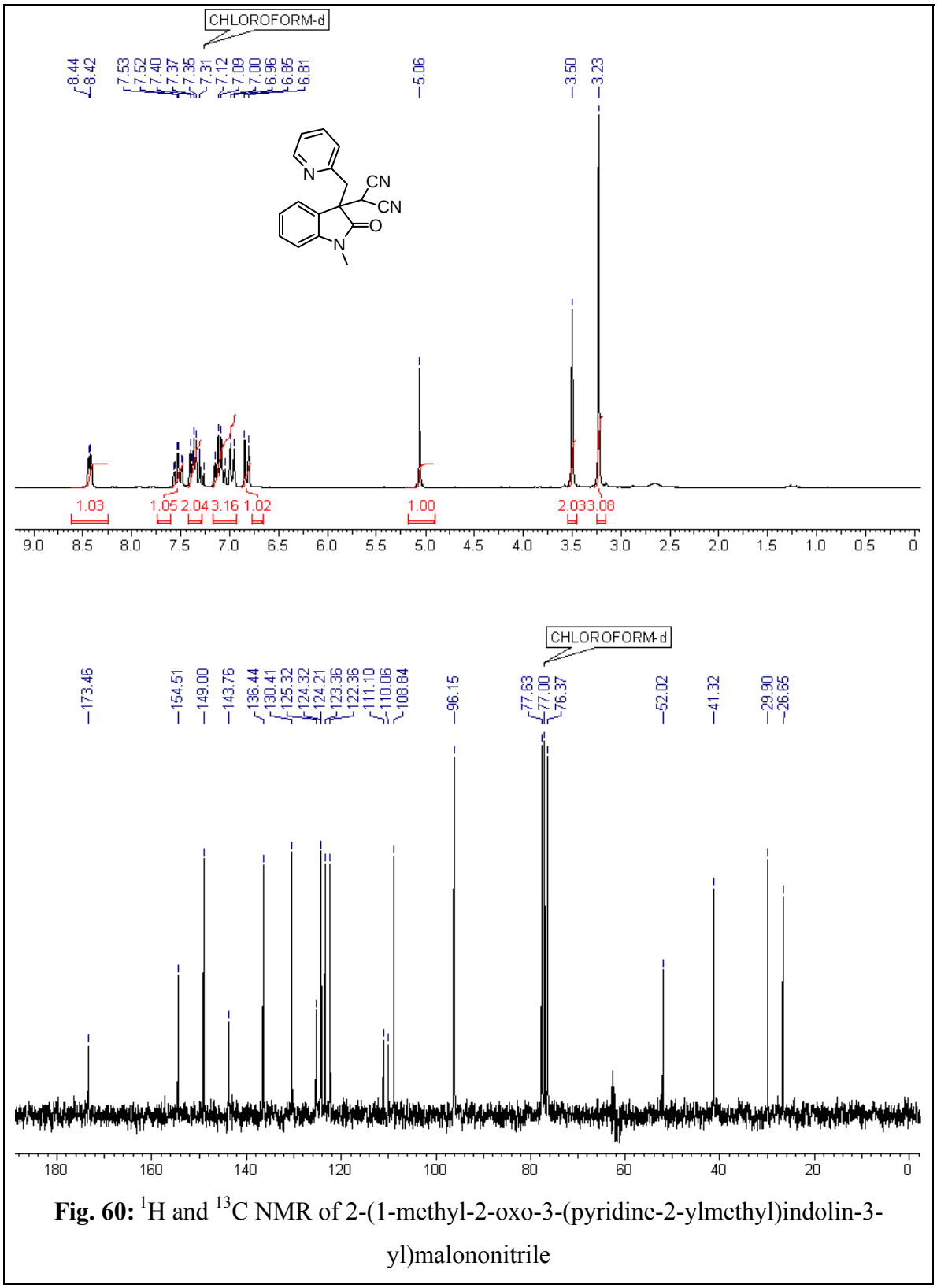


Fig. 60: ^{1}H and ^{13}C NMR of 2-(1-methyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)malononitrile

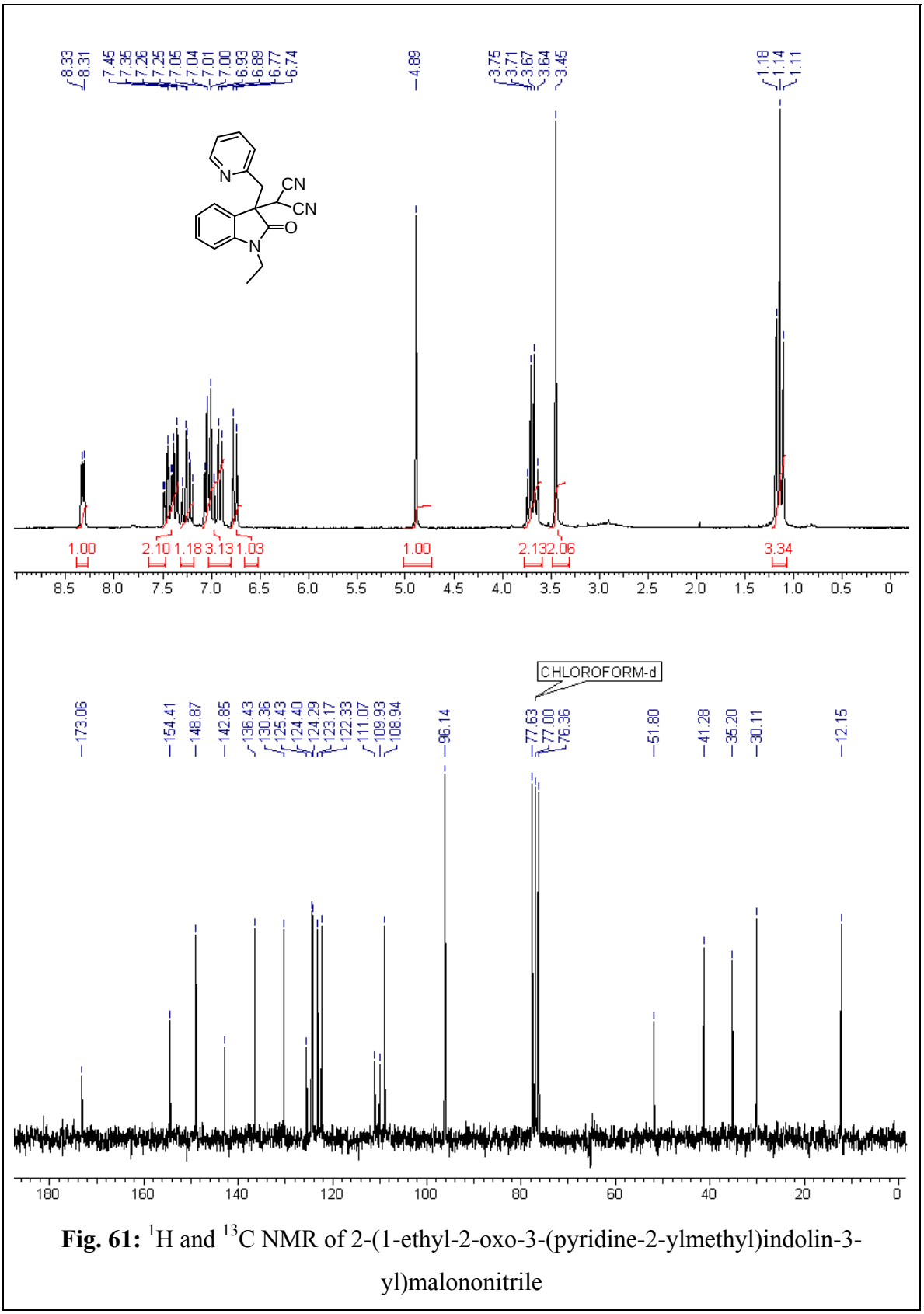


Fig. 61: ^{1}H and ^{13}C NMR of 2-(1-ethyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)malononitrile

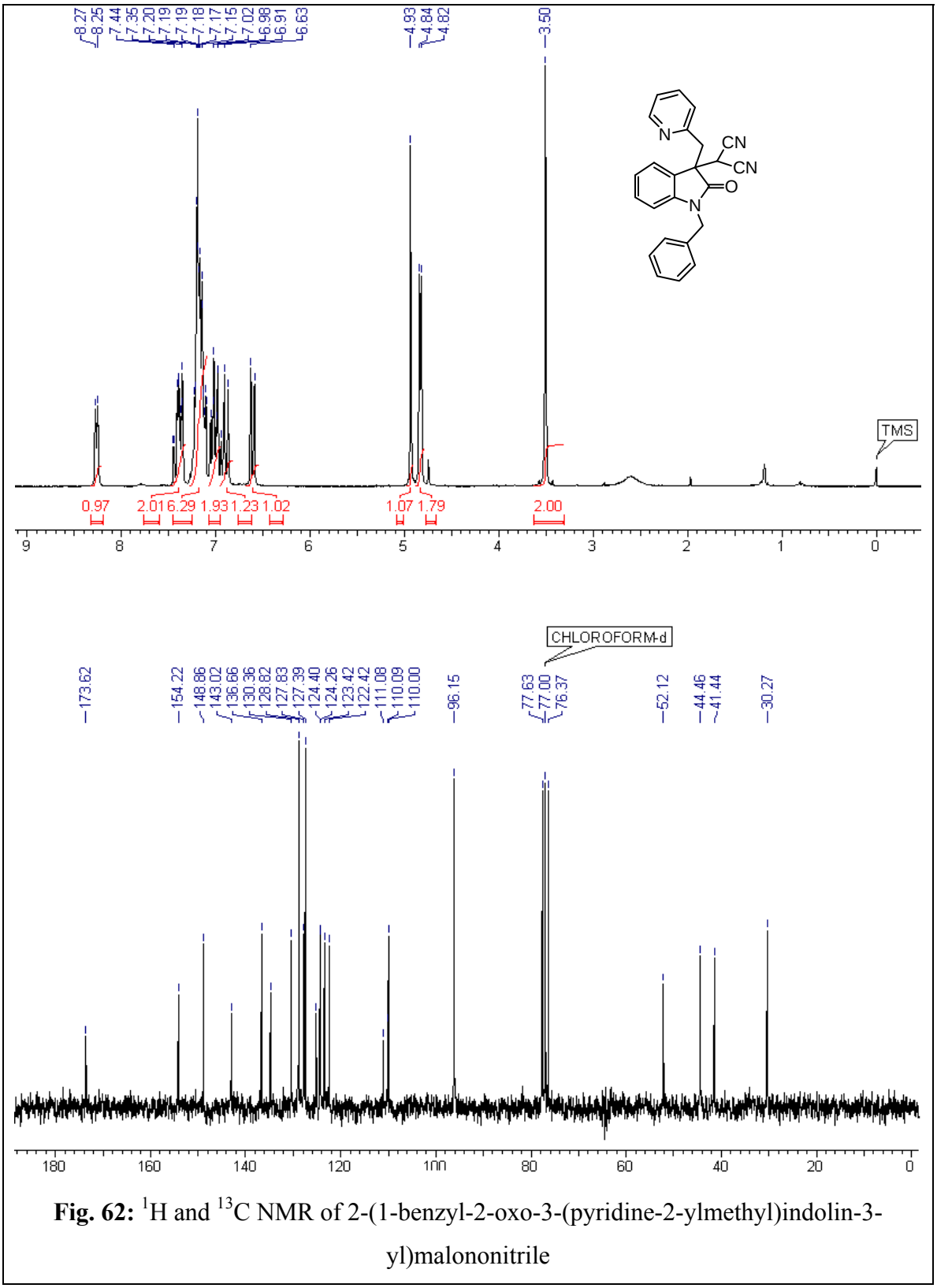


Fig. 62: ^{1}H and ^{13}C NMR of 2-(1-benzyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)malononitrile

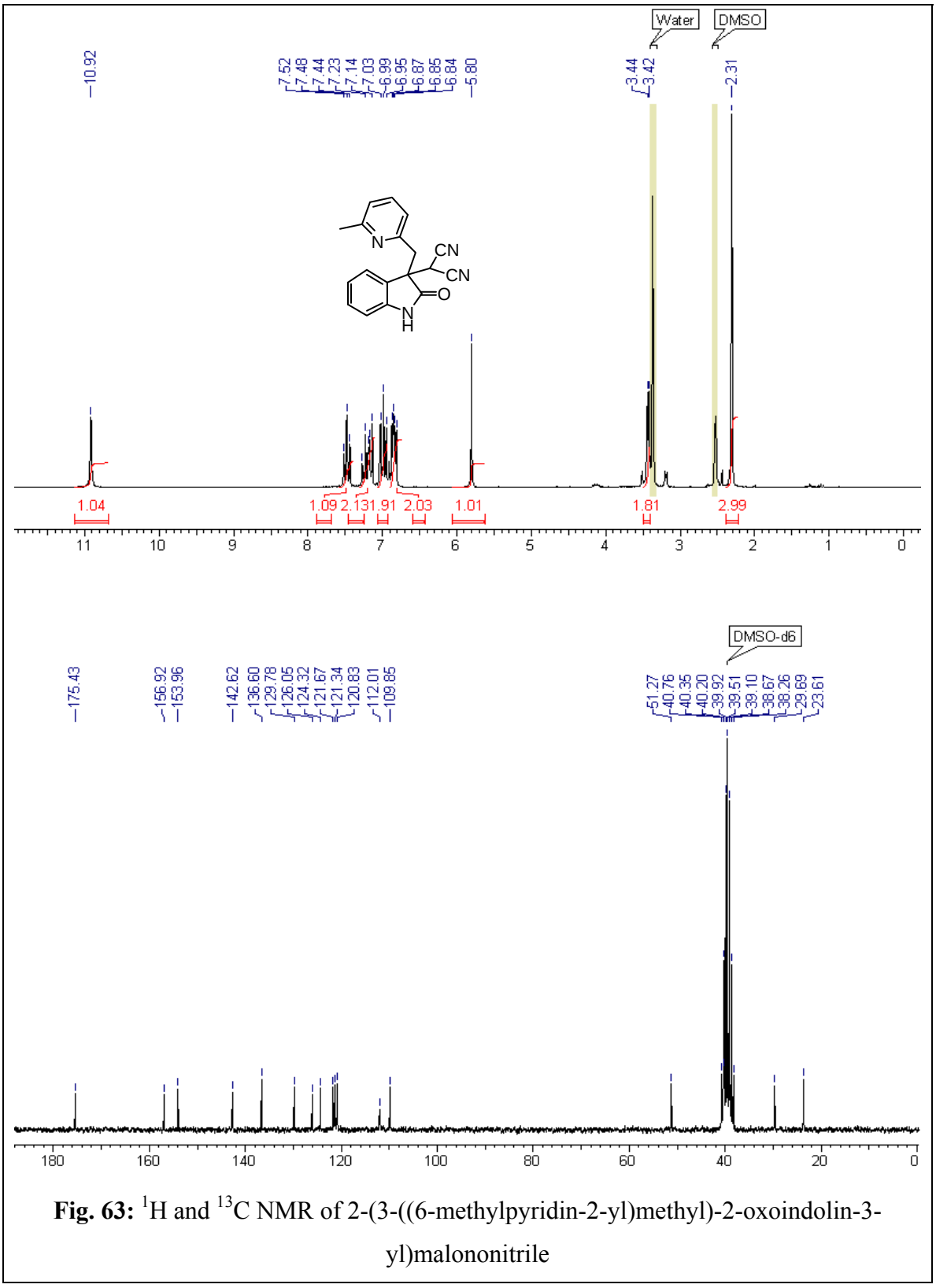


Fig. 63: ^{1}H and ^{13}C NMR of 2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile

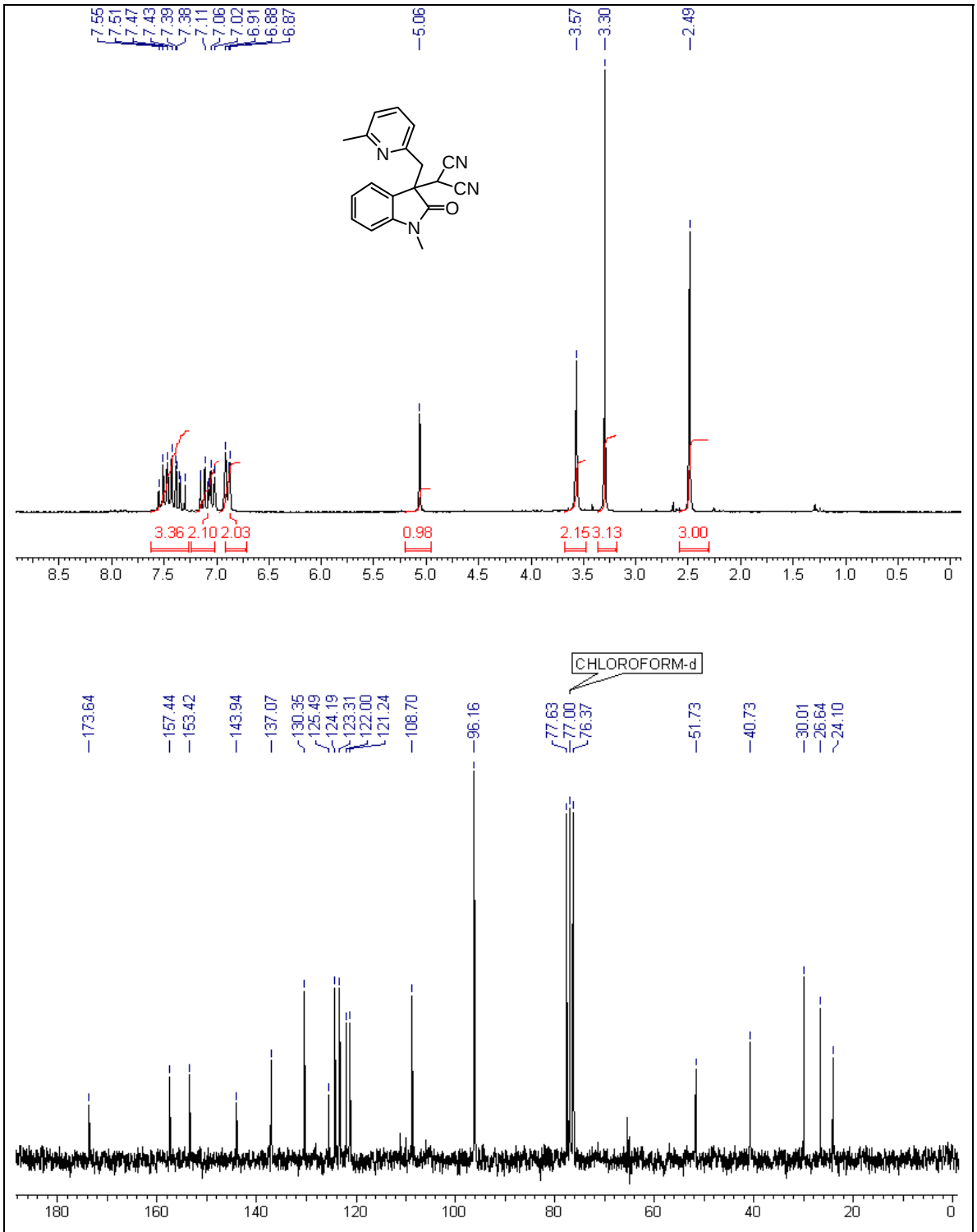


Fig. 64: ^{1}H and ^{13}C NMR of 2-(1-methyl-3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile

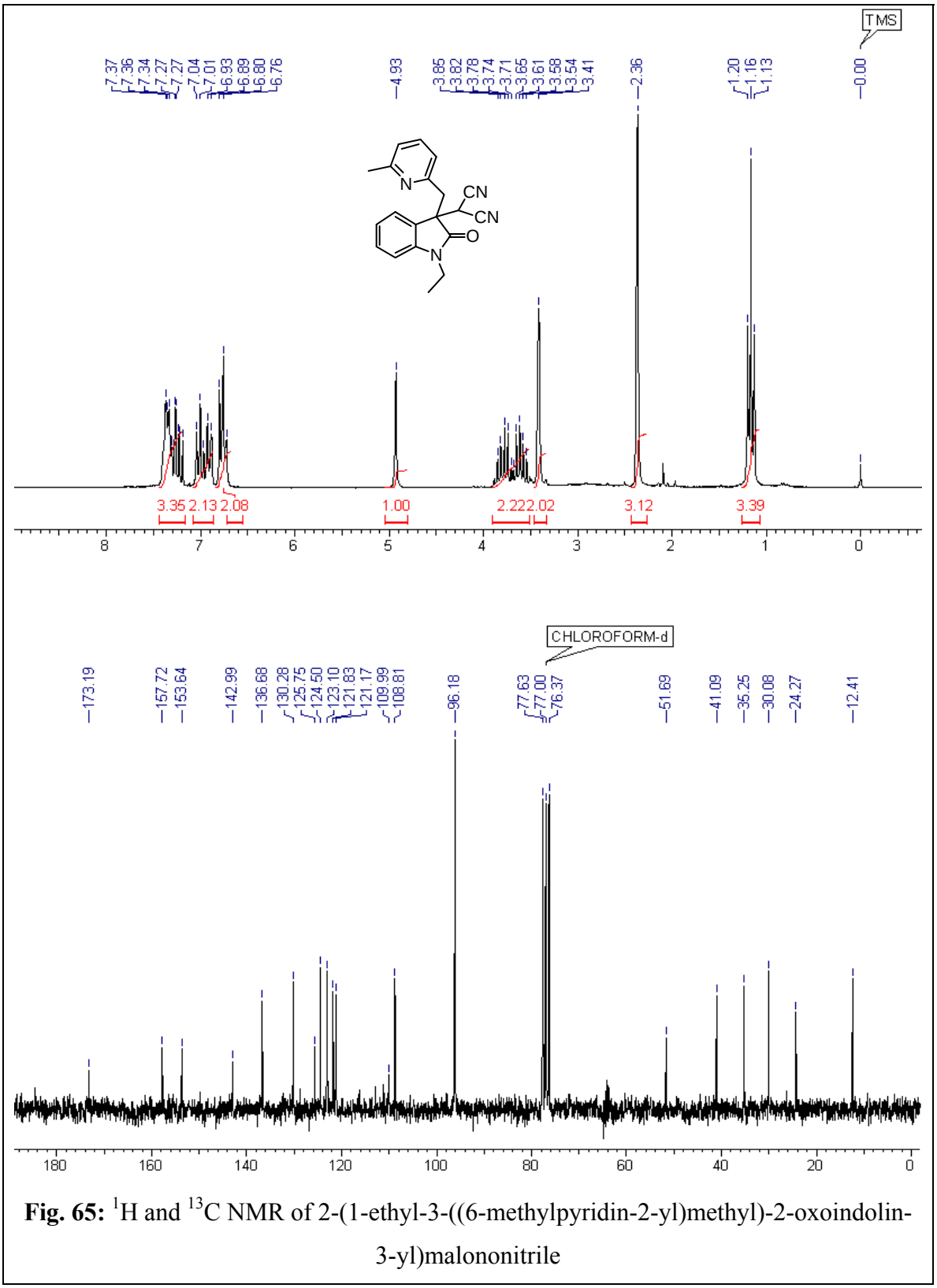


Fig. 65: ^{1}H and ^{13}C NMR of 2-(1-ethyl-3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile

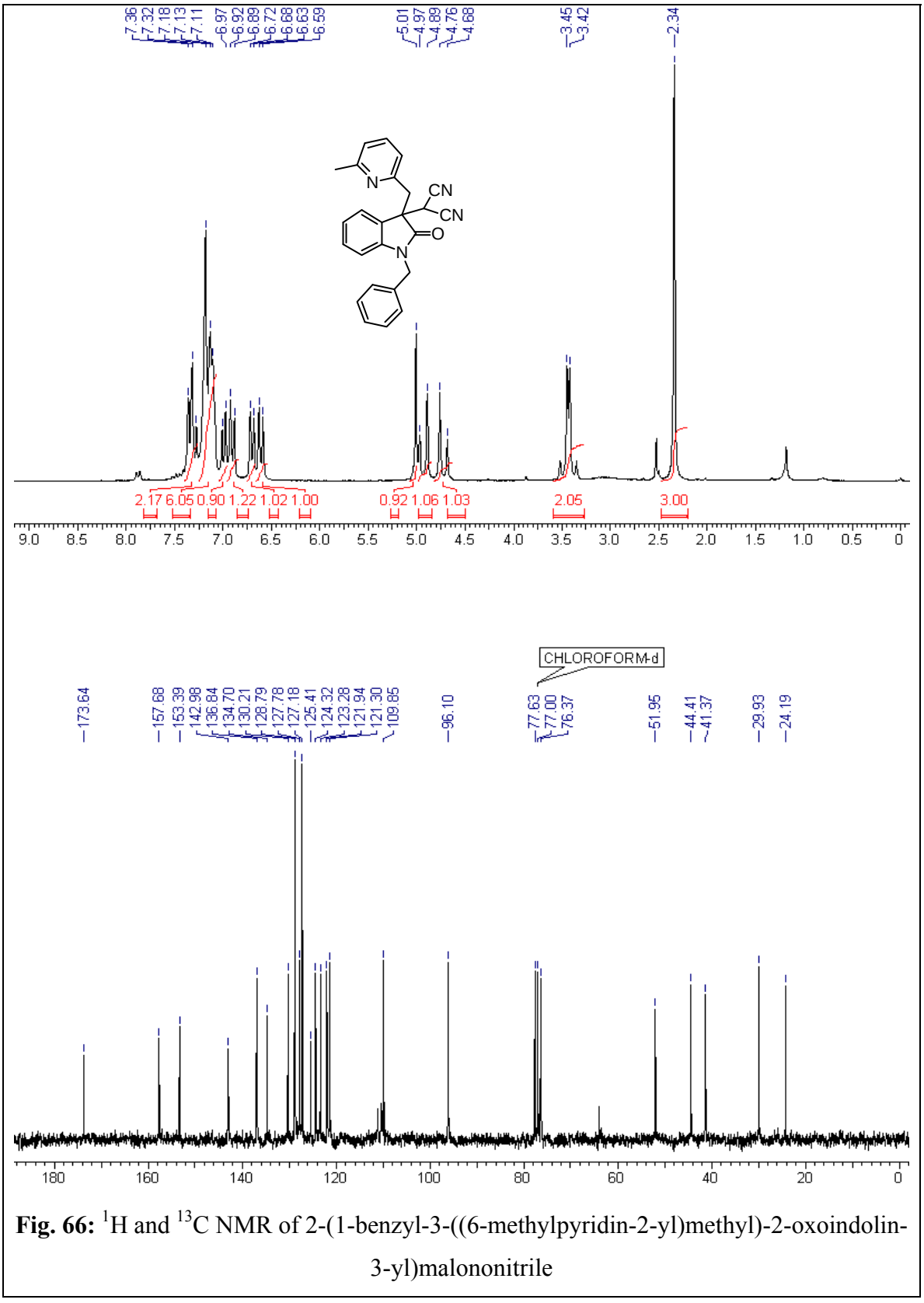


Fig. 66: ^{1}H and ^{13}C NMR of 2-(1-benzyl-3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)malononitrile

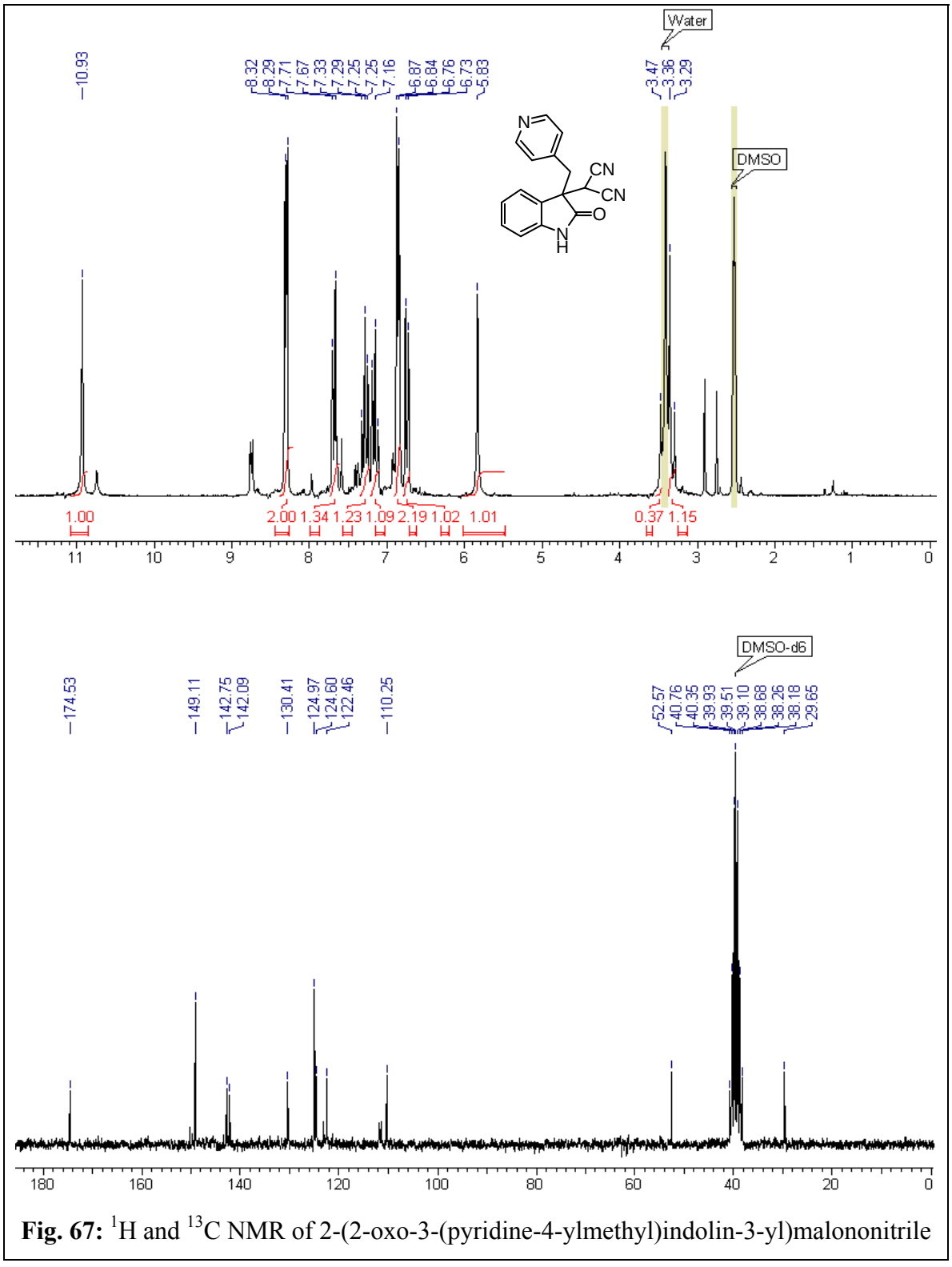


Fig. 67: ^{1}H and ^{13}C NMR of 2-(2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)malononitrile

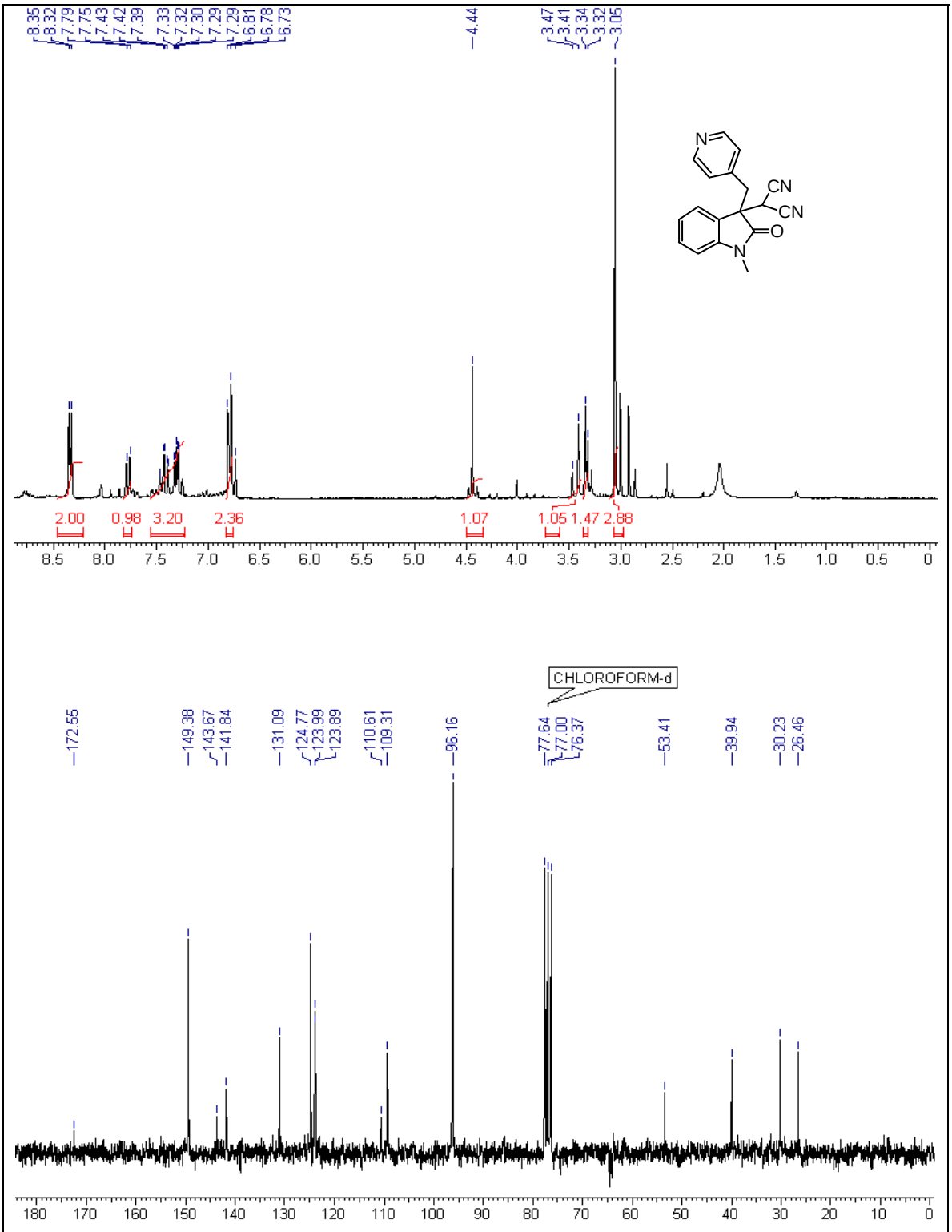


Fig. 68: ^{1}H and ^{13}C NMR of 2-(1-methyl-2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)malononitrile

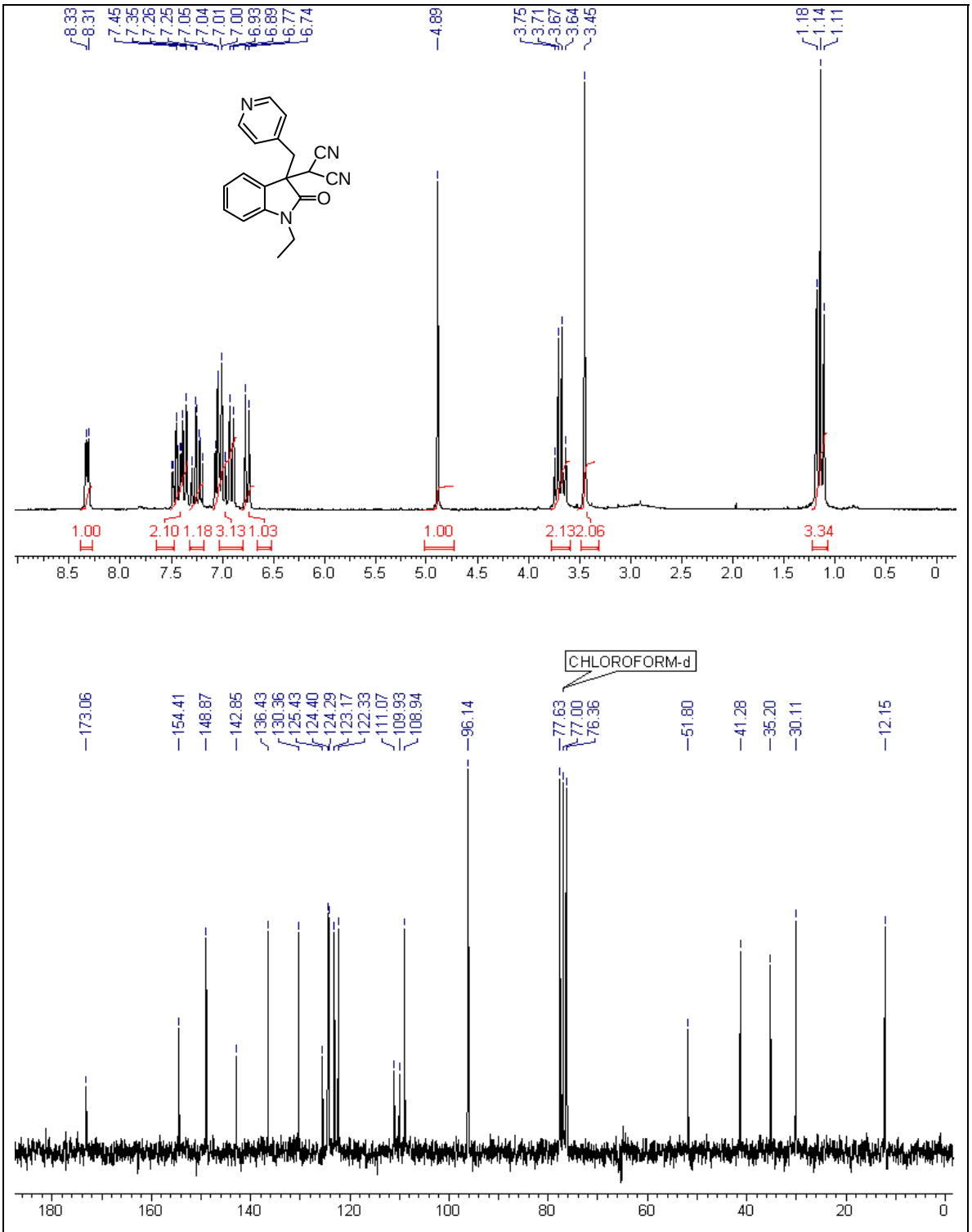


Fig. 69: ^{1}H and ^{13}C NMR of 2-(1-ethyl-2-oxo-3(pyridine-4-ylmethyl)indolin-3-yl)malononitrile

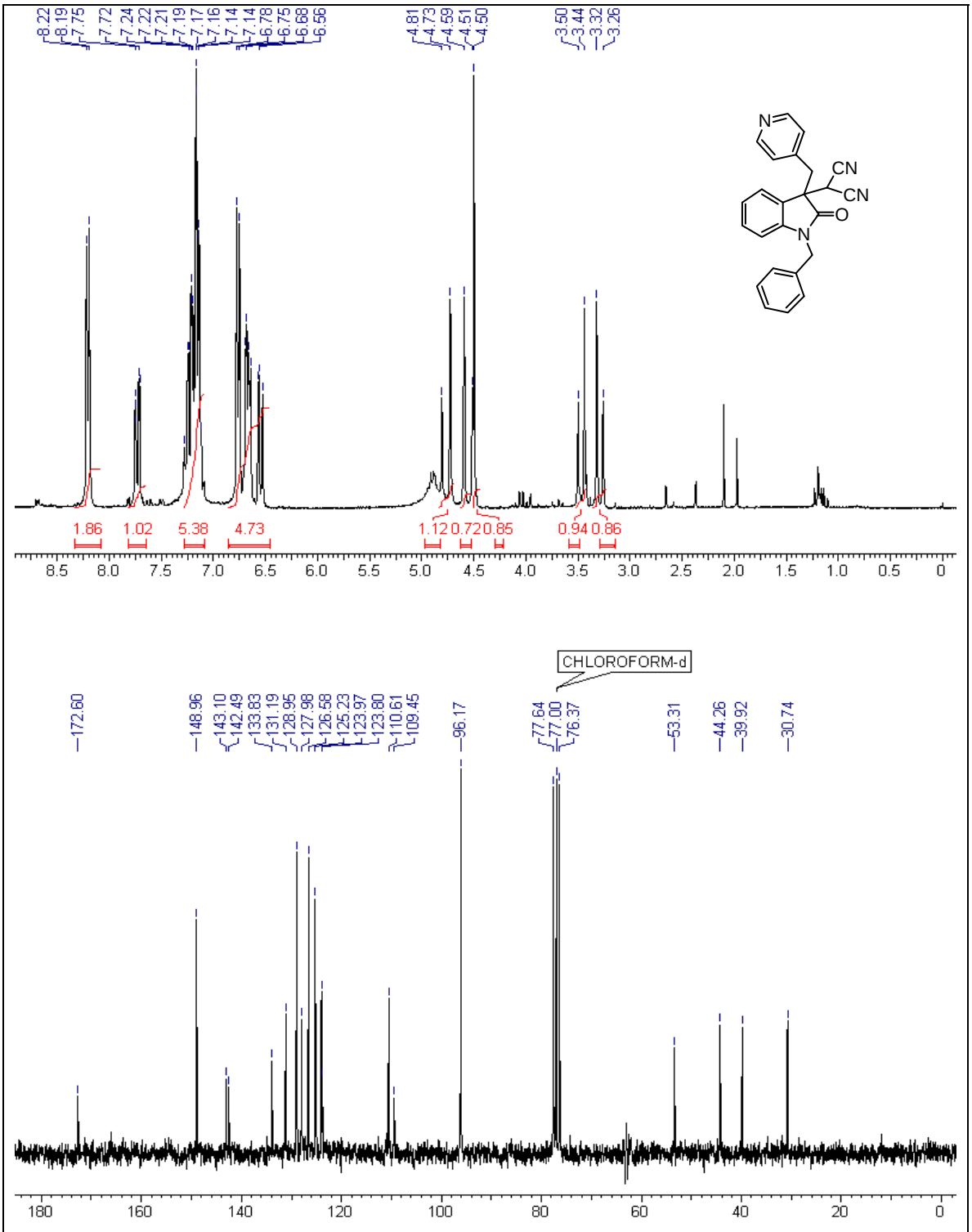


Fig. 70: ^{1}H and ^{13}C NMR of 2-(1-benzyl-2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)malononitrile

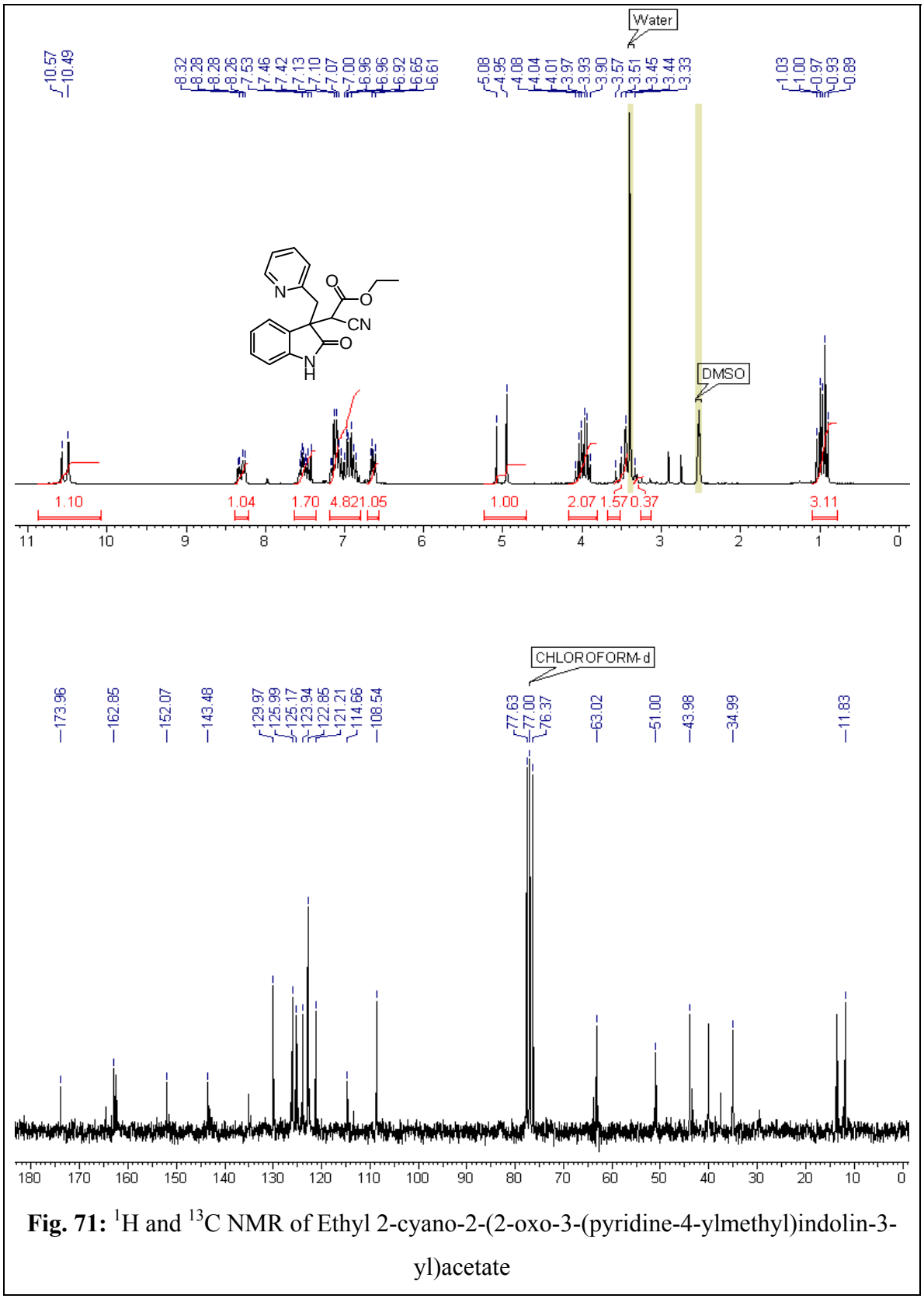


Fig. 71: ^{1}H and ^{13}C NMR of Ethyl 2-cyano-2-(2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)acetate

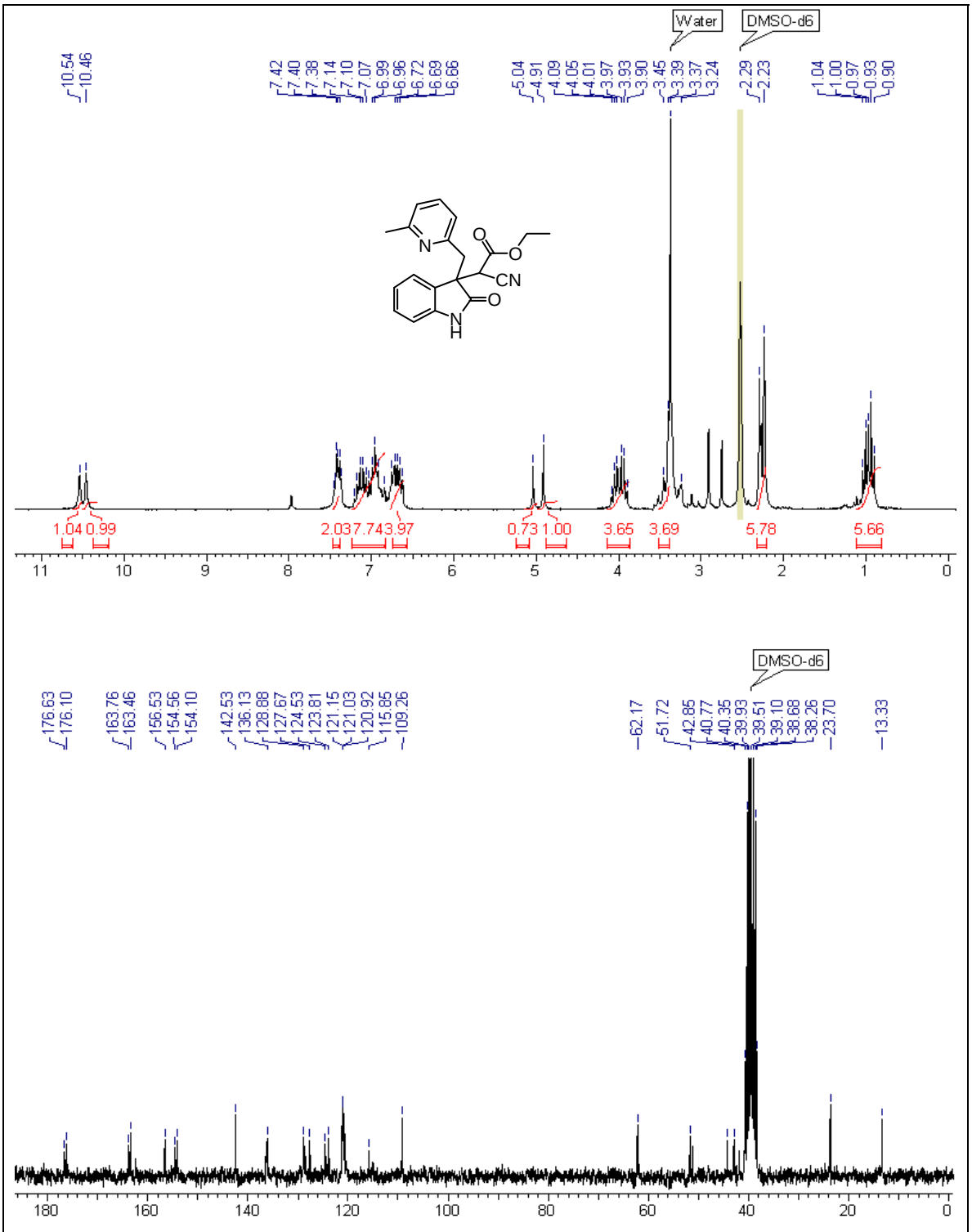


Fig. 72: ^{1}H and ^{13}C NMR of Ethyl 2-cyano-2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoindolin-3-yl)acetate

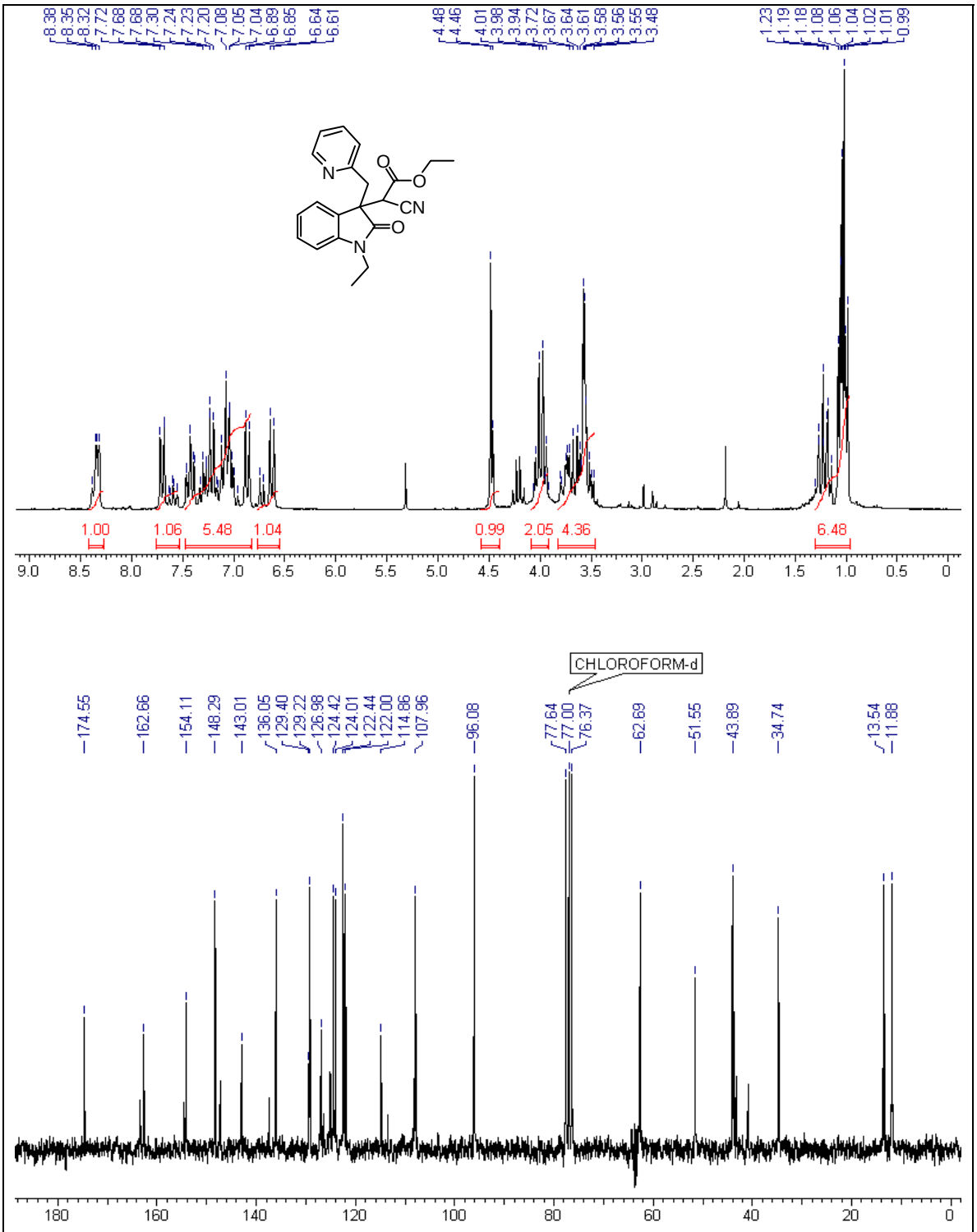


Fig. 73: ^{1}H and ^{13}C NMR of Ethyl 2-cyano-2-(1-ethyl-2-oxo-3-(pyridine-2-ylmethyl)indolin-3-yl)acetate

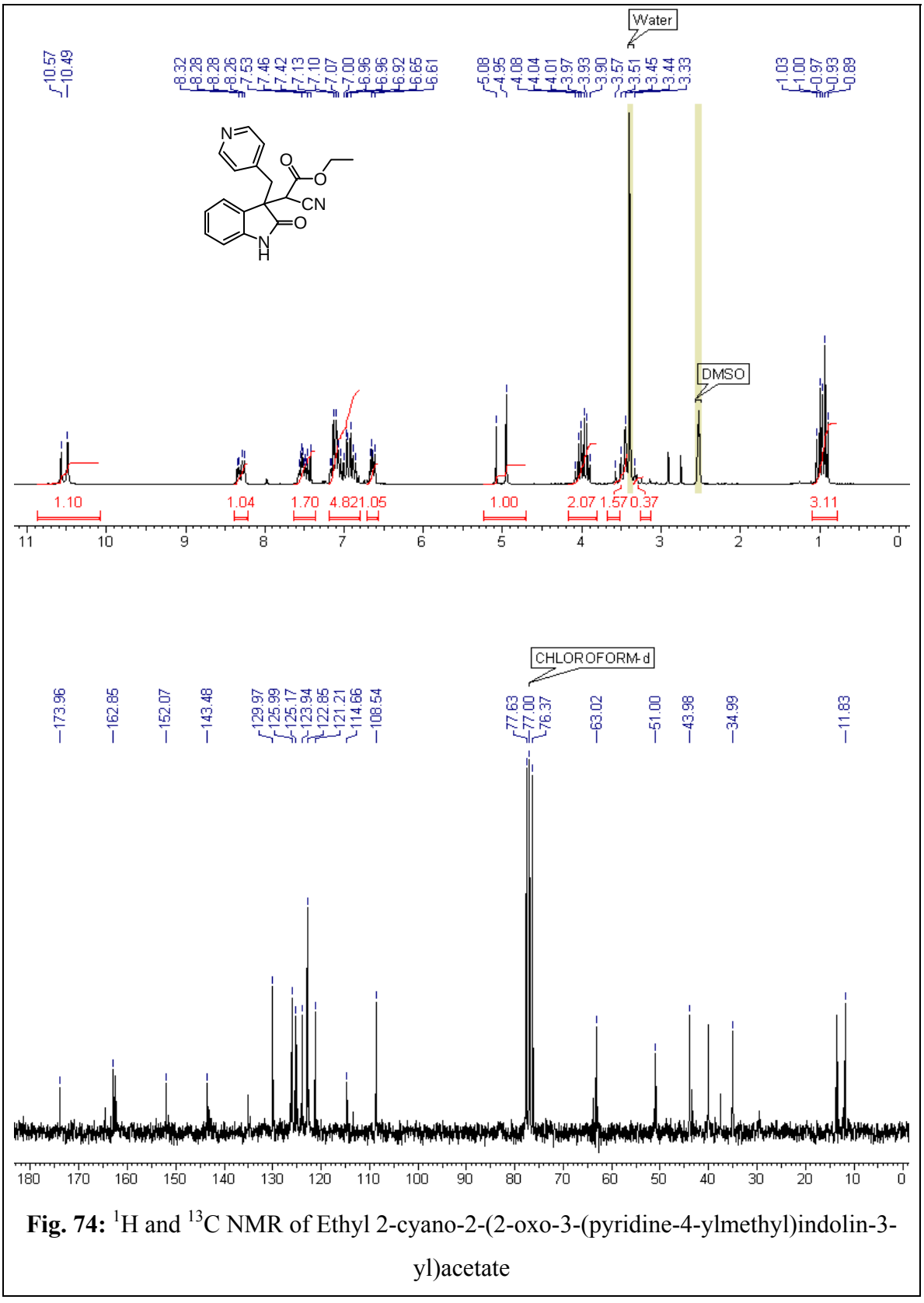


Fig. 74: ^{1}H and ^{13}C NMR of Ethyl 2-cyano-2-(2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)acetate

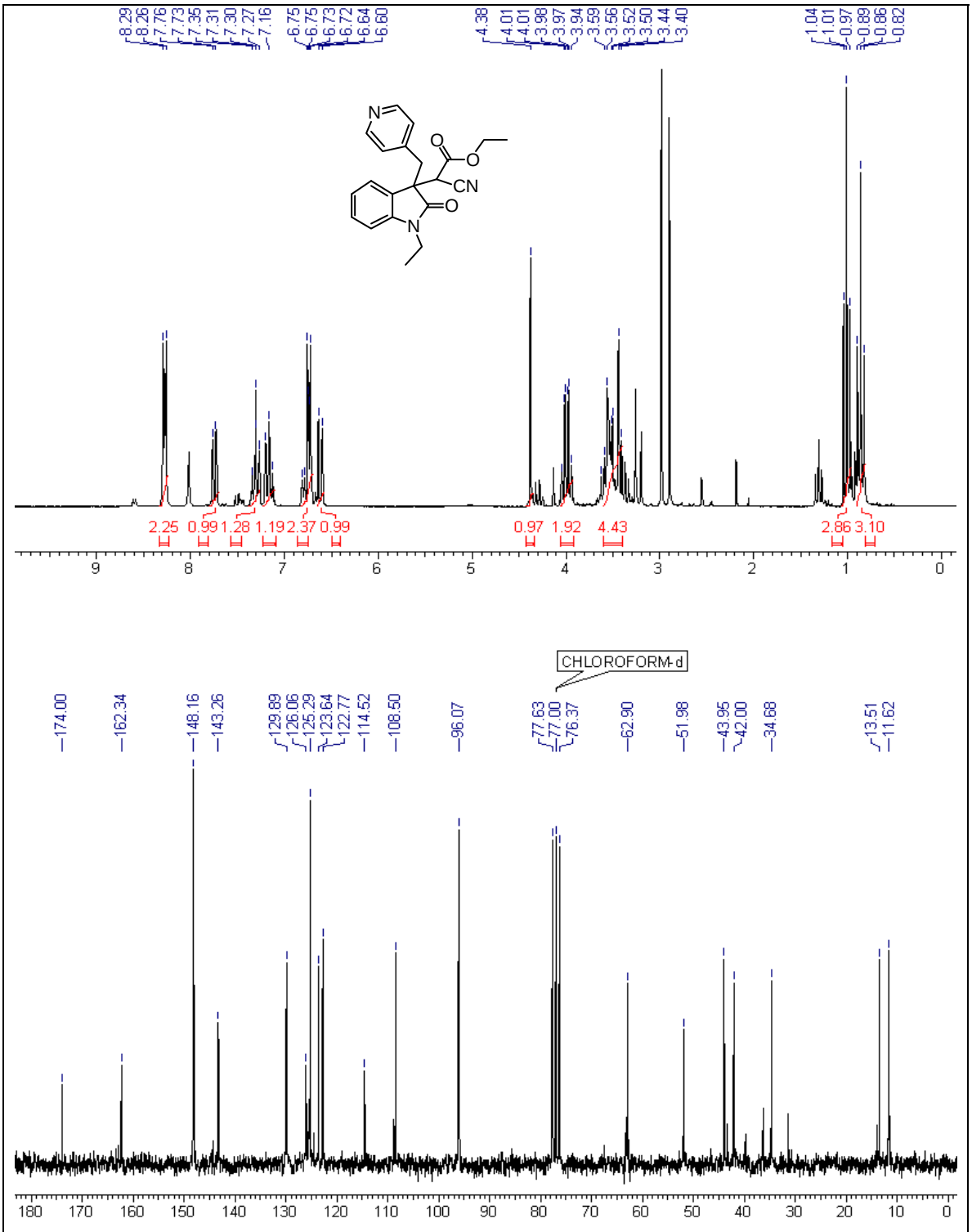


Fig. 75: ^{1}H and ^{13}C NMR of Ethyl 2-cyano-2-(1-ethyl-2-oxo-3-(pyridine-4-ylmethyl)indolin-3-yl)acetate

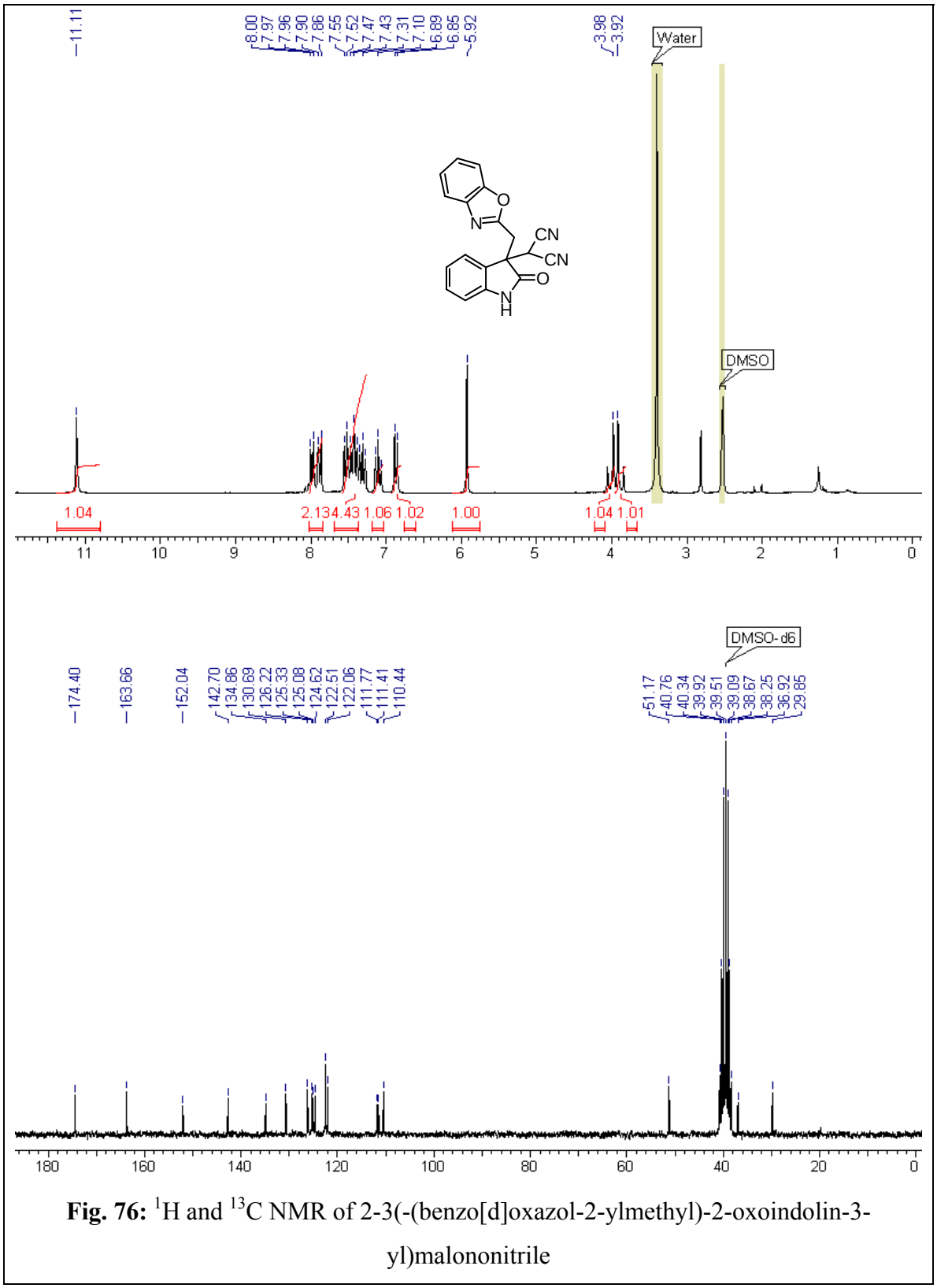


Fig. 76: ^{1}H and ^{13}C NMR of 2-3(-(benzo[d]oxazol-2-ylmethyl)-2-oxoindolin-3-yl)malononitrile

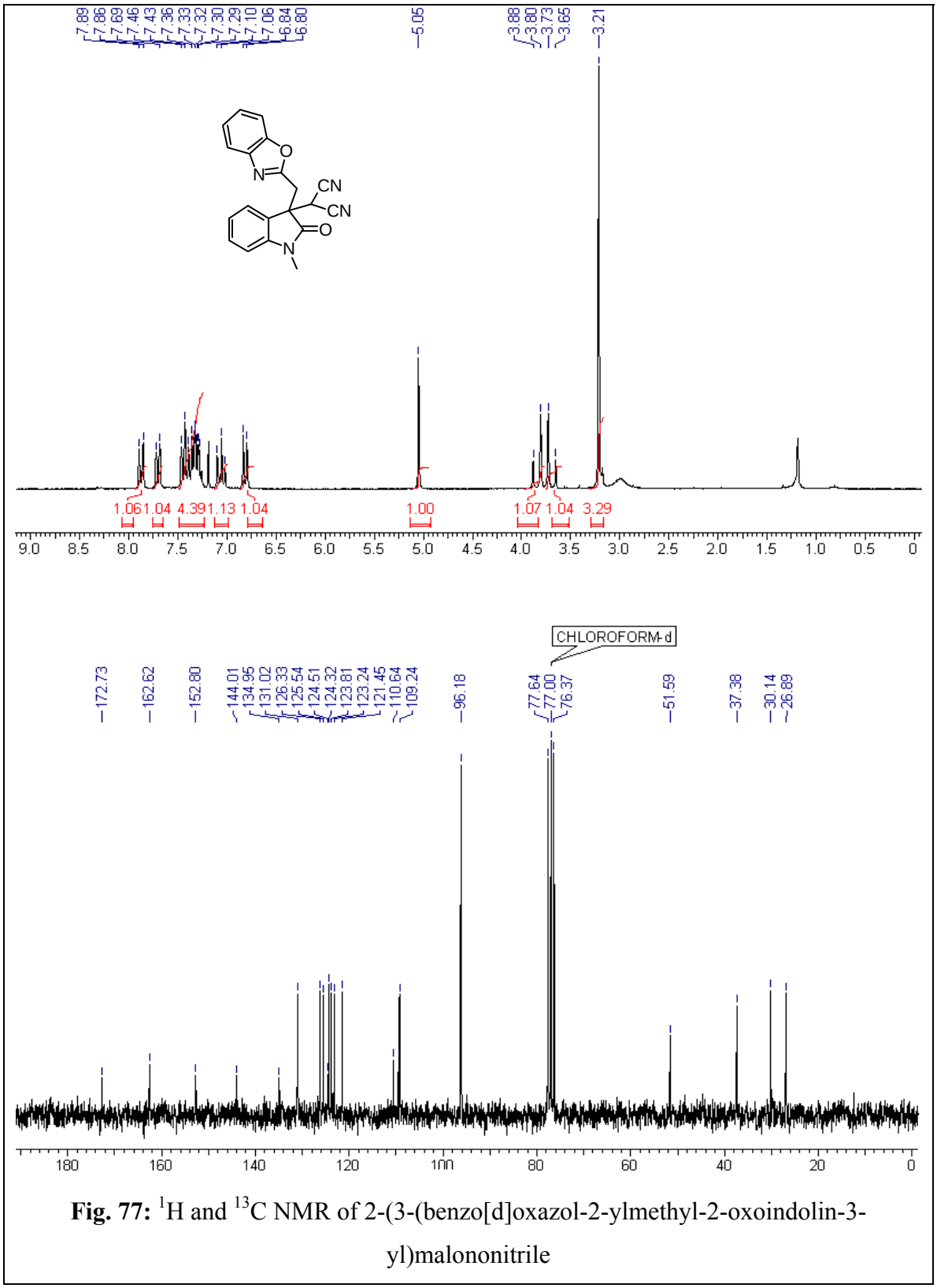


Fig. 77: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]oxazol-2-ylmethyl-2-oxoindolin-3-yl)malononitrile

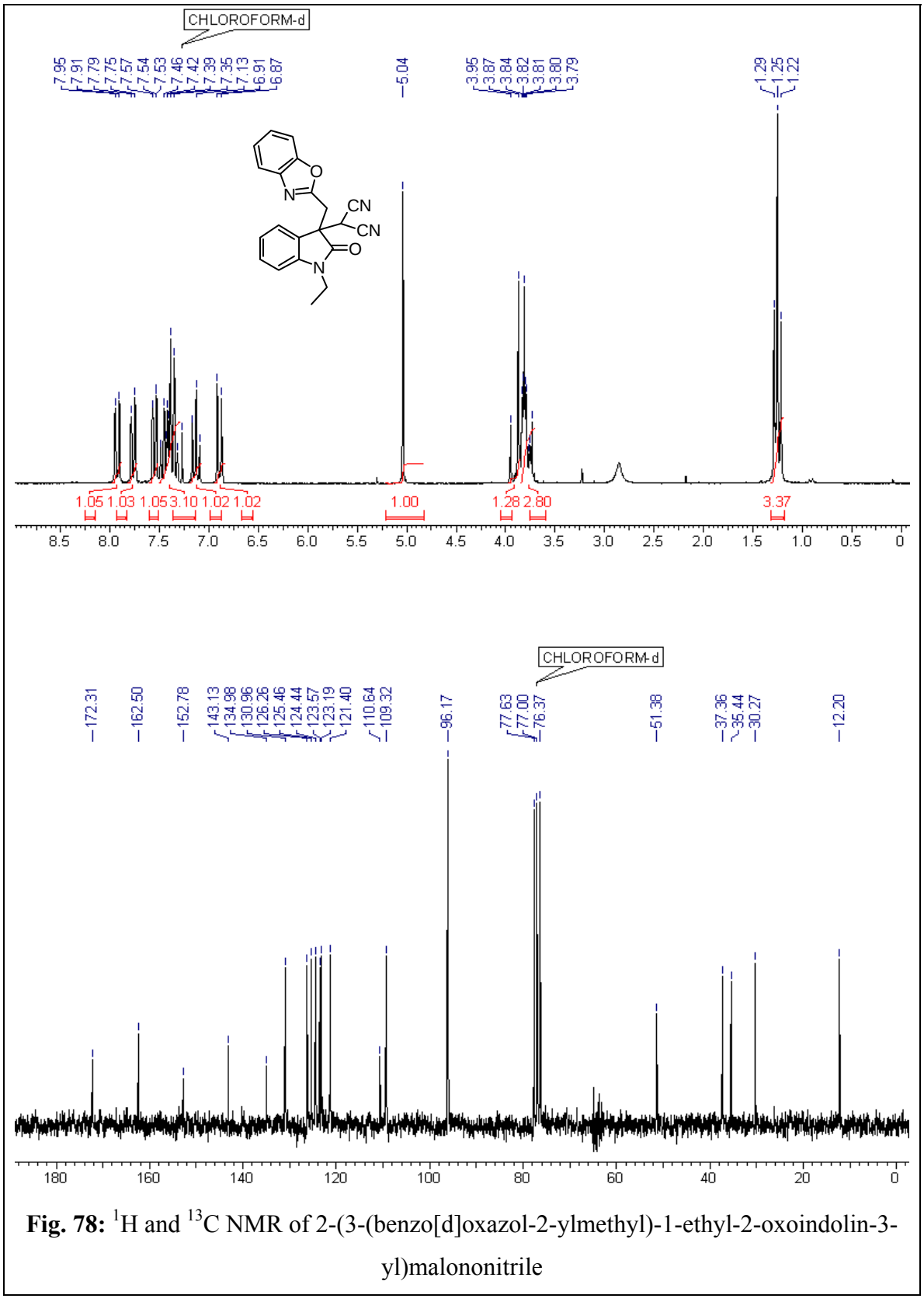


Fig. 78: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]oxazol-2-ylmethyl)-1-ethyl-2-oxoindolin-3-yl)malononitrile

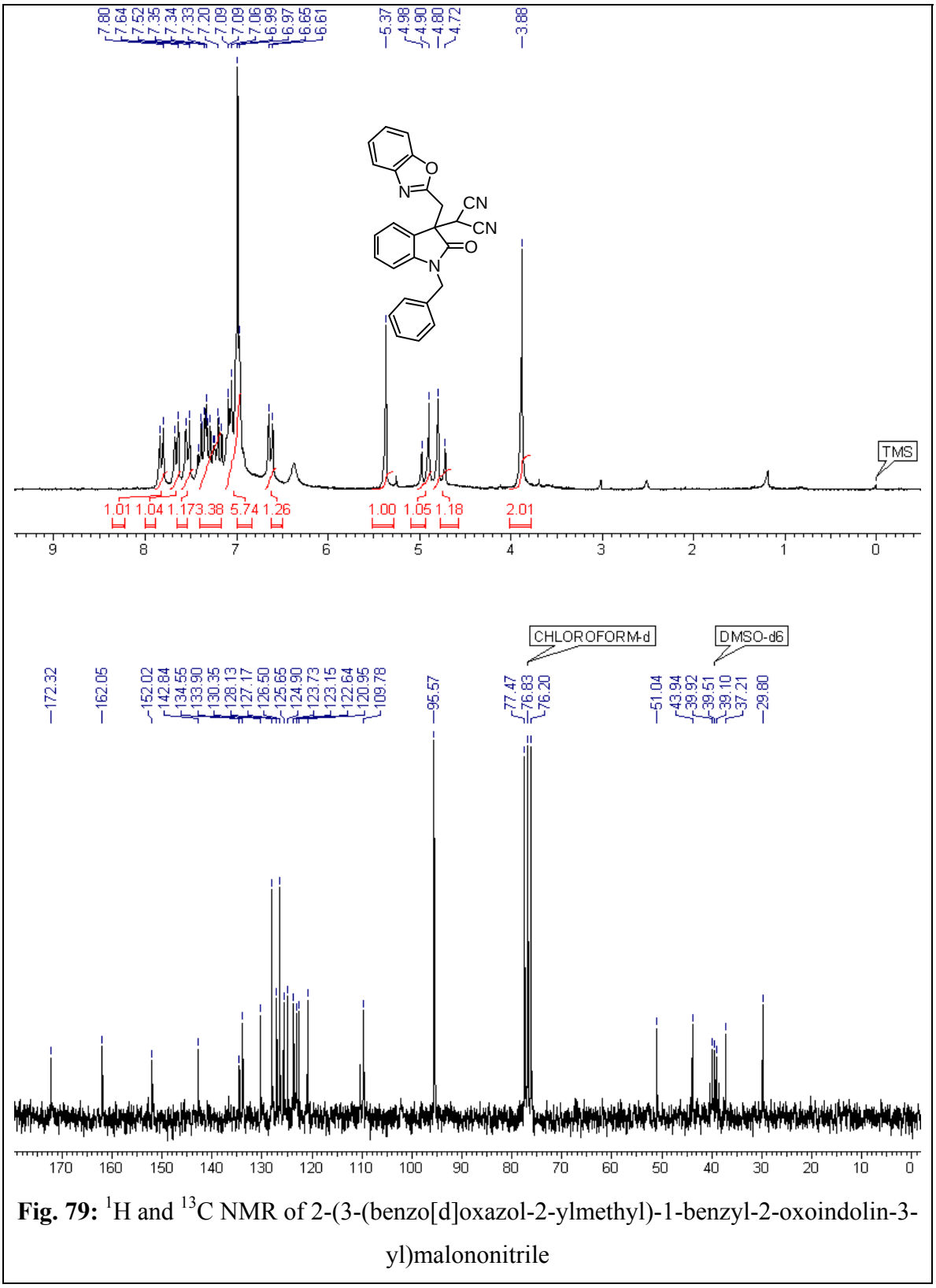


Fig. 79: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]oxazol-2-ylmethyl)-1-benzyl-2-oxoindolin-3-yl)malononitrile

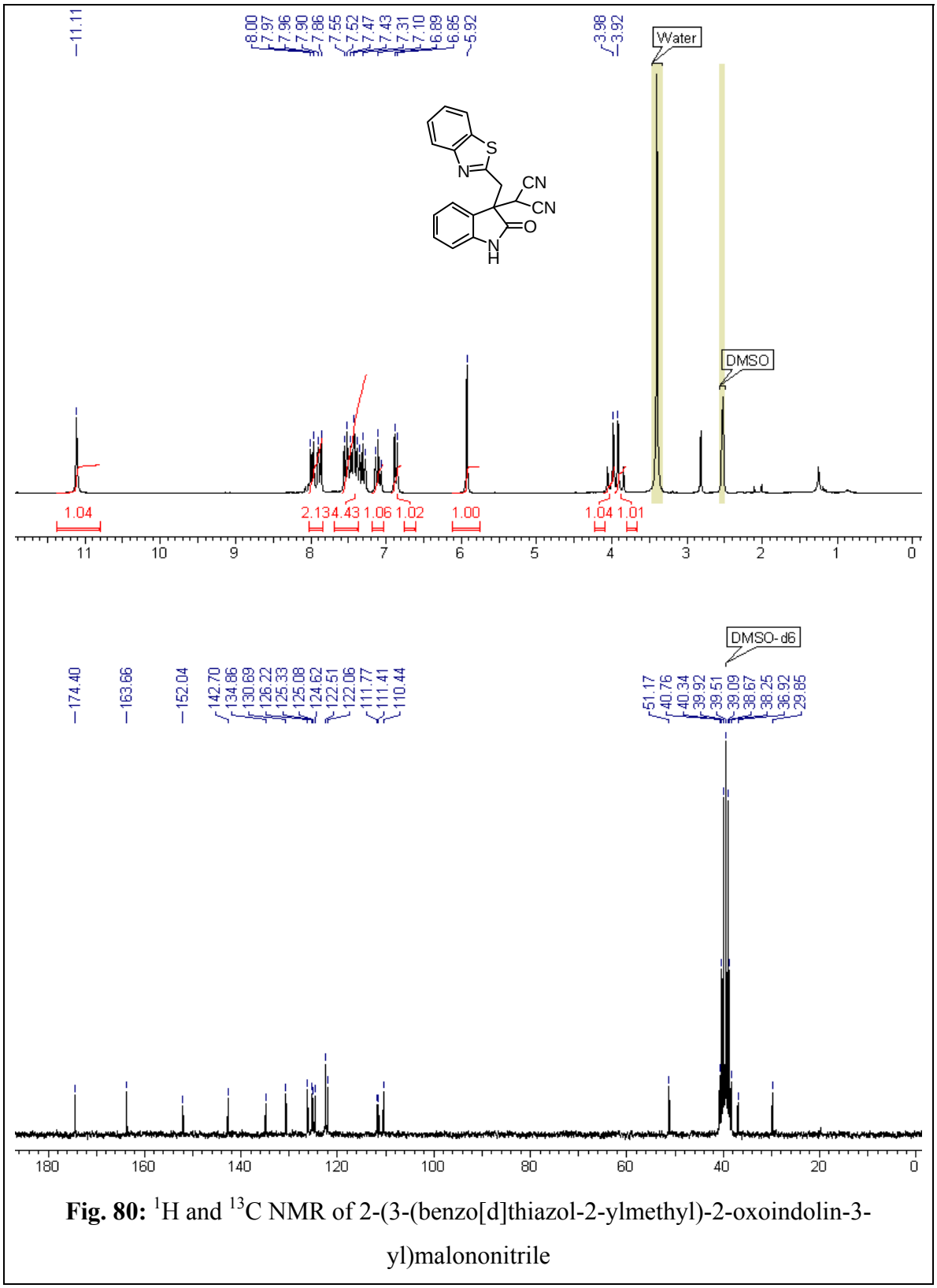


Fig. 80: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]thiazol-2-ylmethyl)-2-oxoindolin-3-yl)malononitrile

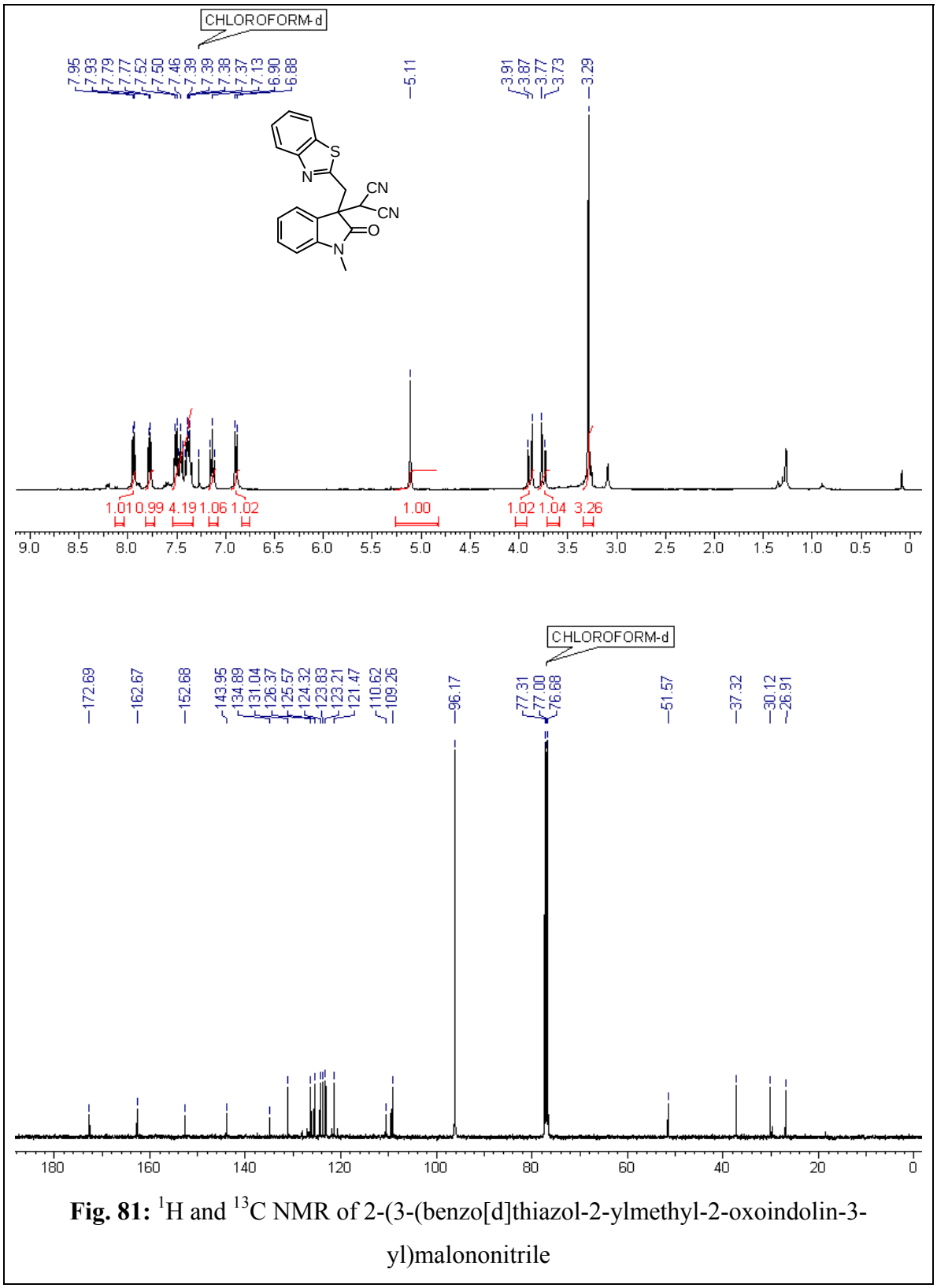


Fig. 81: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]thiazol-2-ylmethyl-2-oxoindolin-3-yl)malononitrile

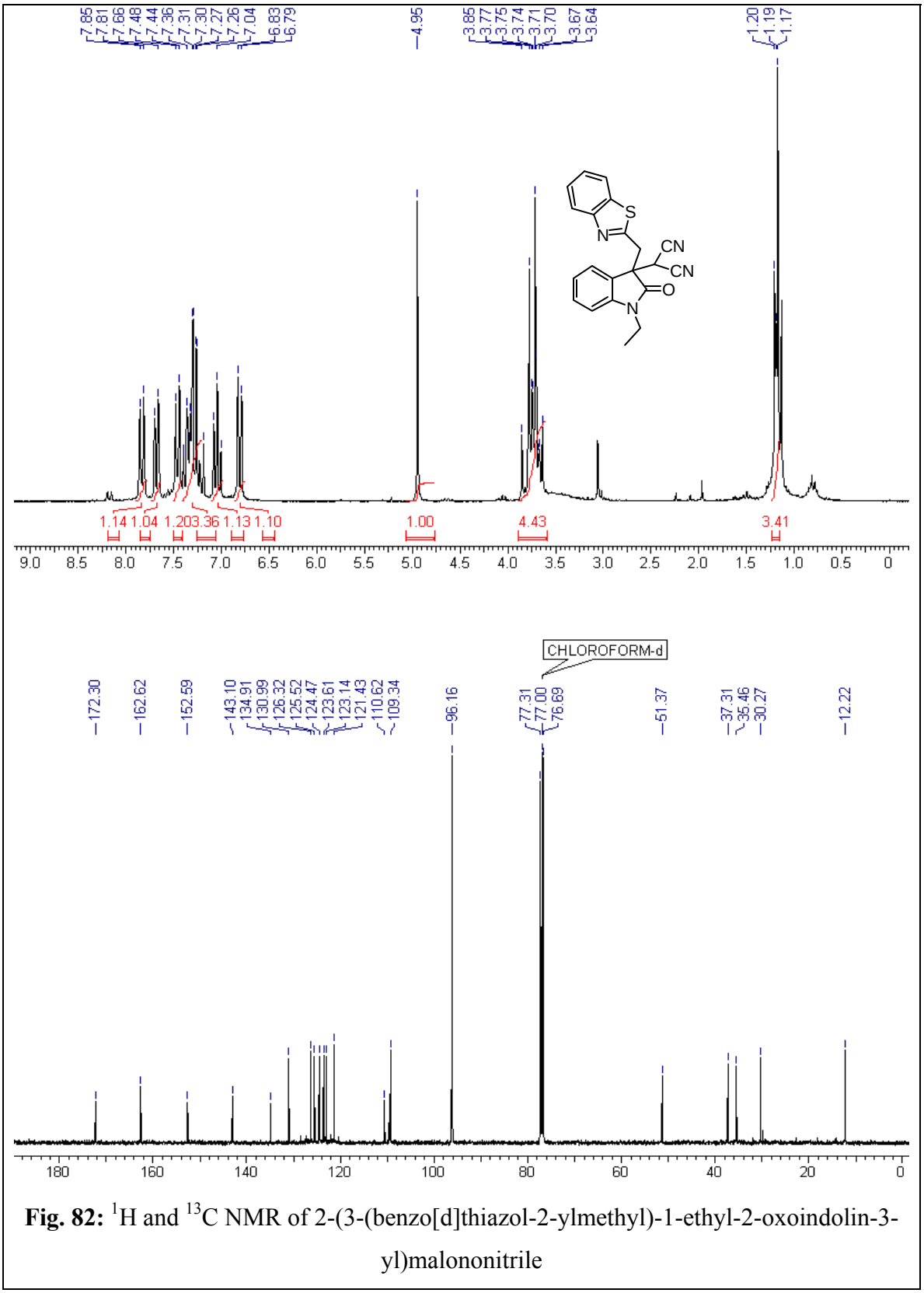


Fig. 82: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]thiazol-2-ylmethyl)-1-ethyl-2-oxoindolin-3-yl)malononitrile

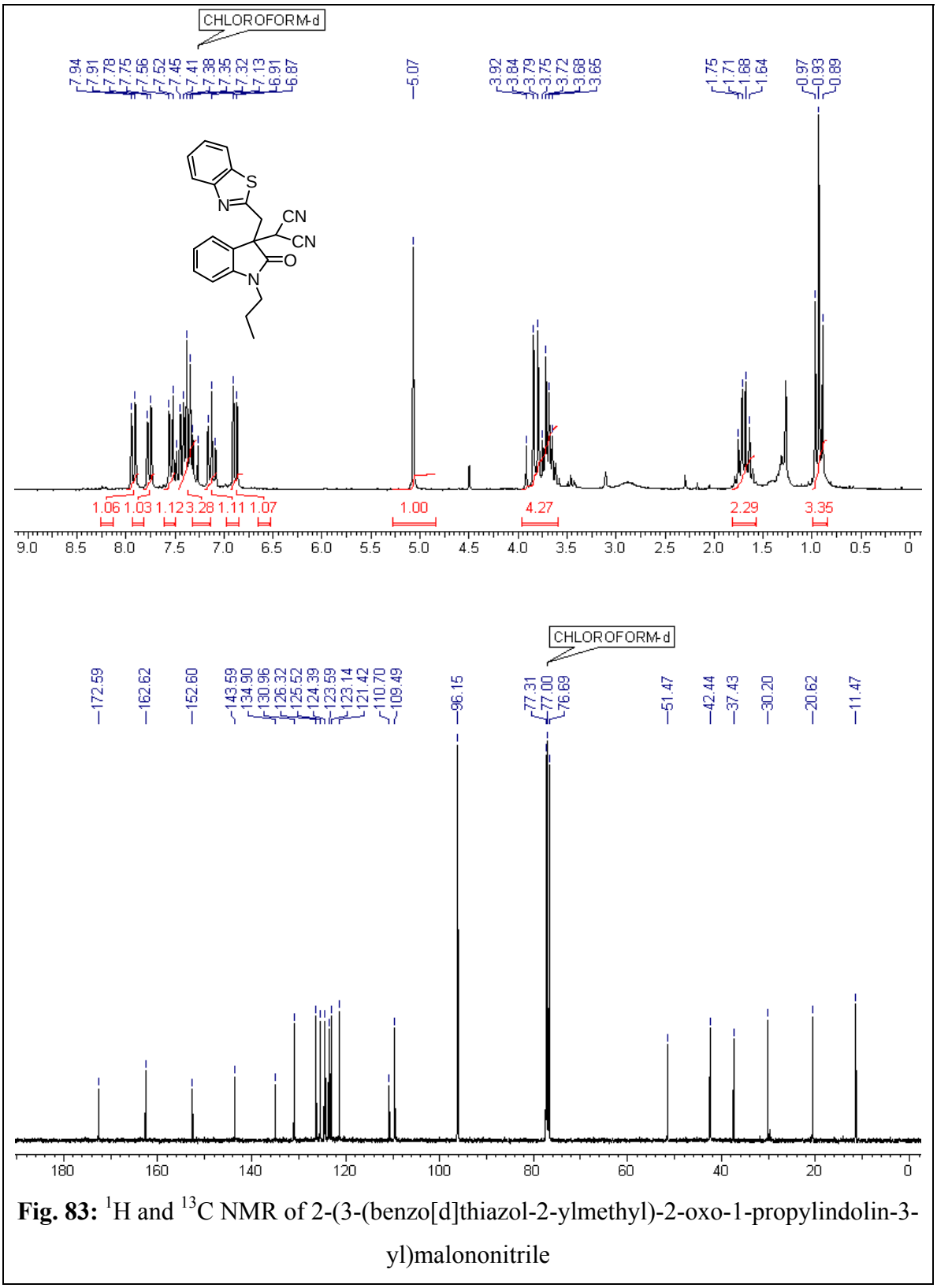


Fig. 83: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]thiazol-2-ylmethyl)-2-oxo-1-propylindolin-3-yl)malononitrile

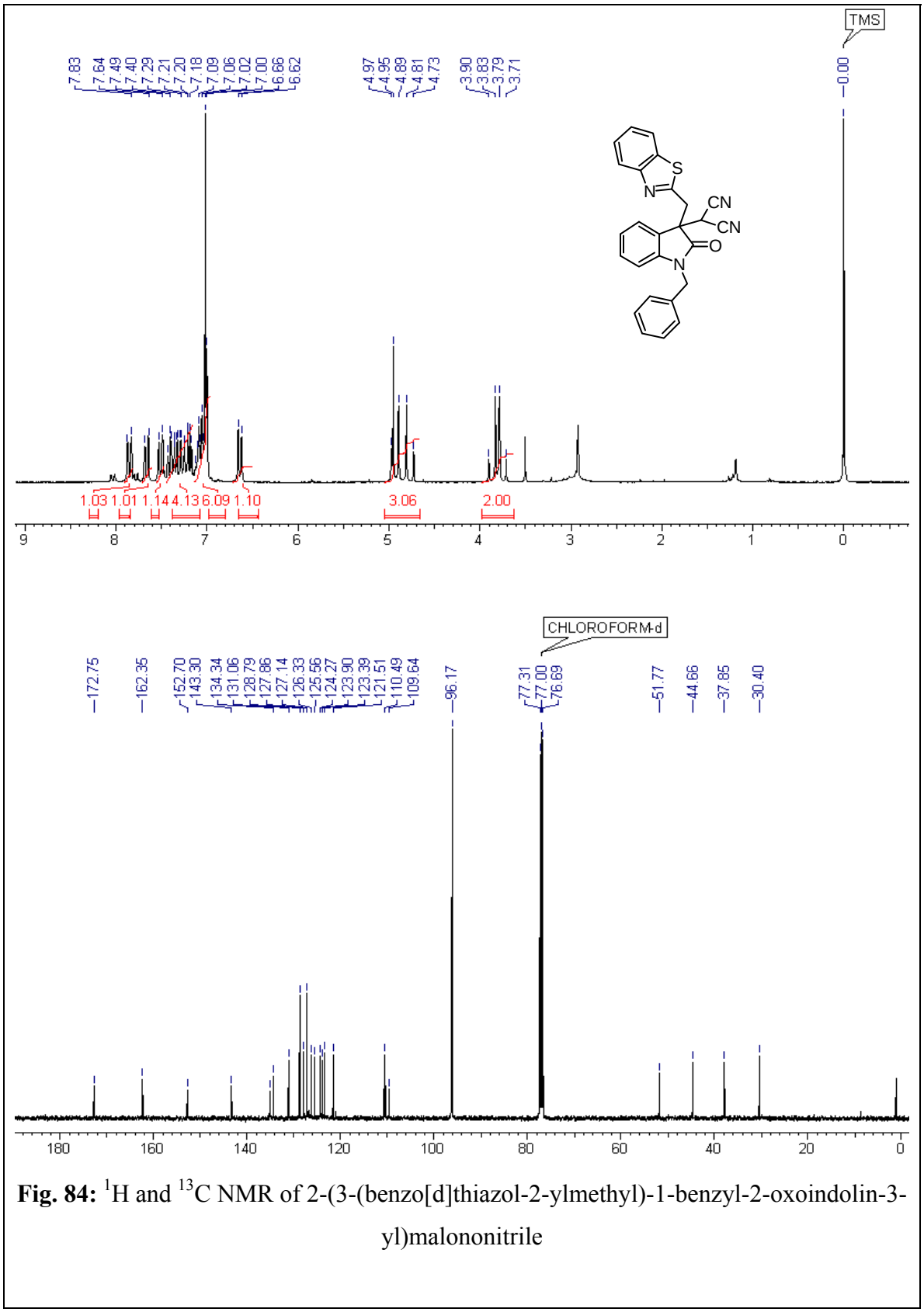


Fig. 84: ^{1}H and ^{13}C NMR of 2-(3-(benzo[d]thiazol-2-ylmethyl)-1-benzyl-2-oxoindolin-3-yl)malononitrile

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Chapter IV

Synthetic methodologies using ethylammonium nitrate (EAN) as an ionic liquid

i) "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 and Santosh S. Chavan. ***Tetrahedron Lett.* 2013, 54, 672-675.**

ii) "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 and R. Santosh Reddy. ***RSC Adv*. 2012, 2, 3525-3529.**

Section-I

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

4.1.1 Introduction

A variety of natural products containing 1,3-amino-oxygenated functional groups act as potential drugs, as antibiotic,[1] antitumor,[2] antimalarial,[3] antianginal,[4] antihypertensive,[5] antirheumatics,[6] and HIV protease inhibitors.[7a] The bradycardiac effects of these motifs have also been reported.[7b] Owing to the biological and/ or medicinal as well pharmacological importance of 1-amidoalkyl-2-naphthols derivatives, efforts have been made by the various researchers in developing multi-component coupling reactions (MCRs) for the synthesis of 1-amidoalkyl-2-naphthols from aldehydes, beta-naphthols and amides/ carbamates and/ or urea under thermal and/ or heating or sonication conditions using various catalysts such as montmorillonite K10,[8] *p*-TSA,[9] iodine,[10] $Fe(HSO_4)_3$,[11] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[12] $HClO_4$–SiO_2,[13] cationexchange resins,[14] silica sulfuric acid,[15] thiamine hydrochloride,[16] zwitterionic salts[17] and supported acid catalyst,[18] and ionic liquids.[19]

Recently, use of ionic liquids in organic synthesis has become the center of interest due to their dual role as catalyst and media along with their unique properties such as hydrophobicities/ hydrophilicities, good solvating capability, easy recoverability, reusability, high thermal stability and non-flammability with almost no vapour pressure.[20]

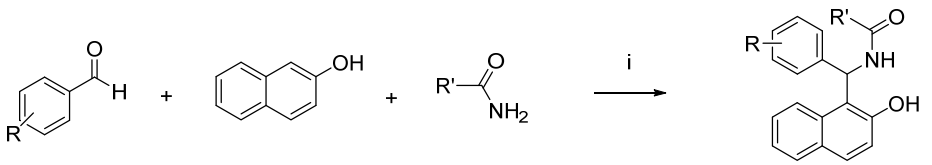
Due to novel properties of ionic liquids, their use in MCRs for name reactions such as Kabachnik-Field reaction,[21] Biginelli reaction,[22] Ugi reaction,[23] and Mannich reaction[24] have been well documented. However, the developed MCRs protocol for the synthesis 1-amidoalkyl-2-naphthols using ionic liquids[19] reported at higher temperature is not compatible with sensitive functional groups and hence limits their application for the commercial exploitation as catalysts and/ or reaction media to achieve high yield of the products. A cost effective construction of its structural unit (1-amidoalkyl-2-naphthols) using MCRs protocol under much milder, more efficient, environment friendly conditions using recyclable, ecofreindly ionic liquid as green catalyst is still a possibility to explore.

4.1.2 Review of literature

Literature survey revels that, there are several methods available for the synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols from the reaction of various substituted aldehydes, amides/ carbamates/ urea/ nitrile with 2-naphthols/phenols in the presence of the various catalysts and solvents at different reaction conditions, however, few of them are described below.

Mishra's approach[18e]

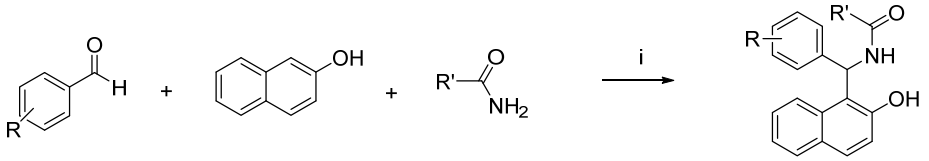
In this approach, Mishra *et al.* have treated various aromatic aldehydes and 2-naphthol with benzamide or urea in the presence of MoZr catalyst at 80 ^{o}C under the neat reaction condition (**Scheme 1**).



Scheme 1: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), 2-naphthol (1 mmol), amide/urea (1.1 mmol), MoZr (100 mg), 80 ^{o}C, 1-2 h.

Tamaddon approach[18d]

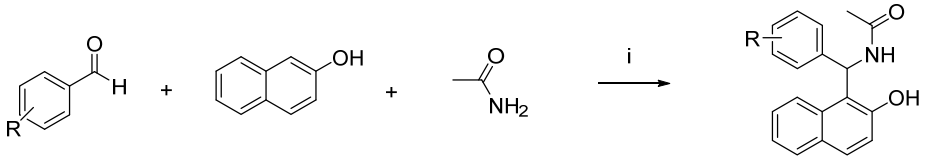
In this approach, Tamaddon *et al.* have treated various aromatic aldehydes and 2-naphthol with amide or urea in the presence of $[MeC(OH)_2]^+ClO_4^-$ as a super acidic ionic liquid in ethyl acetate at room temperature or neat reaction condition at 80 ^oC (**Scheme 2**).



Scheme 2: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), 2-naphthol (1 mmol), amide/urea (1 mmol), $[MeC(OH)_2]^+ClO_4^-$ (1 mol %), EtOAc/ neat, RT/ 80 ^oC, 8-35 min.

Kohansal approach[18f]

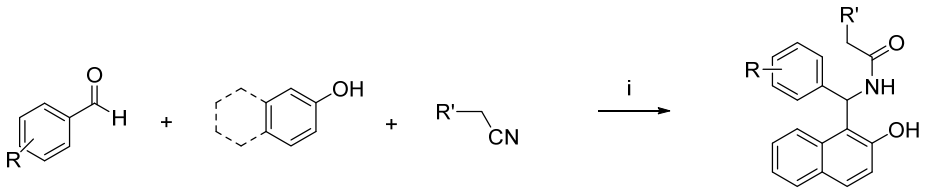
In this approach, Kohansal *et al.* have treated various aromatic aldehydes and 2-naphthols with acetamide in the presence of $KAl(SO_4)_2.12H_2O$ as a heterogeneous catalyst at 85 ^oC under neat reaction condition (**Scheme 3**).



Scheme 3: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), 2-naphthol (1 mmol), acetamide (1 mmol), and $KAl(SO_4)_2.12H_2O$ (0.35 mmol), 85 ^oC, 10-25 min.

Perumal approach[18g]

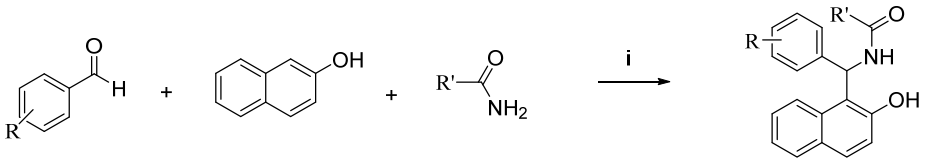
In this approach, Perumal *et al*. have treated various aromatic aldehydes and 2-naphthol/phenols with various nitriles in the presence of I_2 and acetyl chloride for 3-14 h at room temperature (**Scheme 4**).



Scheme 4: *Reagents and reaction conditions*: (i) Aldehyde (10 mmol), 2-naphthol/phenol (10 mmol), Iodine (0.4 mmol), acetyl chloride (2.8 mmol), and nitrile (10 mmol), RT, 3-14 h.

Hajipour approach[19e]

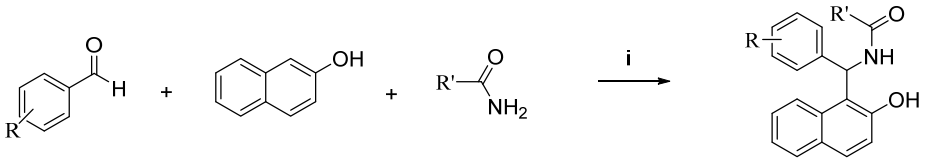
In this approach, Hajipour *et al.* have treated various aromatic aldehydes and 2-naphthol with amide or urea in the presence of ionic liquid [TEBSA] [HSO_4] at 120 ^oC for 10 min. (**Scheme 5**).



Scheme 5: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), 2-naphthol (1 mmol), amide/urea (1.2 mmol), [TEBSA] [HSO_4] (5 mol %), 120 ^oC, 10 min.

Lihong Hu approach[16]

In this approach, Lihong Hu *et al.* have treated various aromatic aldehydes and 2-naphthol with amide or urea in the presence of Thiamine hydrochloride (VB_1) at 80 ^oC for 4 h in alcohol (**Scheme 6**).

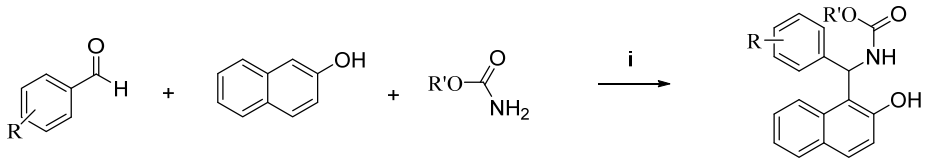


Scheme 6: *Reagents and reaction conditions*: (i) Aldehyde (5 mmol), 2-naphthol (5 mmol), amide/urea (5.5 mmol), VB_1 (10 mol %), 80 ^oC, 4 h.

Shaterian approach[13]

In this approach, Shaterian *et al.* have treated various aromatic aldehydes and 2-naphthol

with carbamates in the presence of SiO_2-$NaHSO_4$ at 100 ^oC under neat reaction condition (**Scheme 7**).

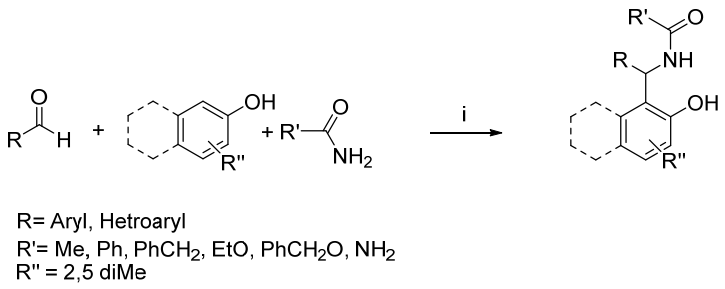


Scheme 7: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), 2-naphthol (1 mmol), carbamate (1.1 mmol), SiO_2-$NaHSO_4$ (50 mg), 100 ^oC, 3-30 min.

4.1.3 Present Work

4.1.3.1 Objectives

All these methods reported in the literature so far lack general applicability and suffer from one or other limitations such as high reaction temperature, longer reaction time, and lower yield of the desire product, tedious work-up and use of toxic reagents. Therefore, the development of more general and cost effective MCRs protocol for the synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols is still challenging and an active research area. As compared to other ionic liquids, ethylammonium nitrate (EAN) with acidic properties (pH=5)[25] is cheap, easily recoverable and reusable at room temperature. Therefore, this section describes a highly efficient, cost effective, general and much milder MCRs protocol for the synthesis of 1-amido- and 1-carbamato-alkyl-2-naphthols/phenols in good to excellent yields via one-pot three-component condensation of various aldehydes, amides/ carbamates /urea and naphthols/phenols using ethylammonium nitrate as reusable ionic liquid catalyst under neat reaction conditions at ambient temperature **(Scheme 8)**.



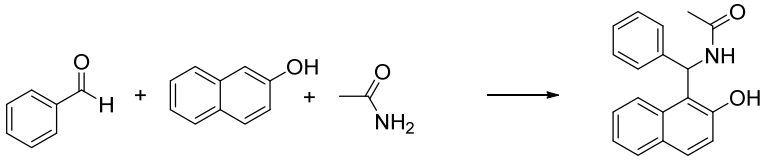
Scheme 8: *Reagents and reaction conditions*: (i) Aldehyde (6 mmol), beta-naphthol/phenol (1 mmol), amide/urea/carbamate (1.1 mmol) in EAN (0.8 mmol) RT 1 h.

4.1.4 Results and discussion

To investigate the optimal reaction conditions for the solvent-free MCRs protocol, the reaction was initially carried out by stirring the mixture of benzaldehyde (6 mmol), beta-naphthol (1 mmol) and acetamide (1.1 mmol) as model reaction in the presence of various loading of EAN (0.2-1 mmol) at room temperature for 1 h. The results obtained are shown in **Table 1**. Interestingly, increasing the molar concentration of EAN from 0.2 mmol to 0.8 mmol resulted in a dramatic improvement in the yield from 37 % to 93 % (**Table 1**, entries **2-5**). However, further increase to 1mmol concentration of EAN (**Table 1**, entry **6**) did not improve the yield. In the absence of EAN (**Table 1**, entry **1**), the desired product formation was not observed even after heating. These results clearly indicate that the EAN shows excellent performance under optimized reaction conditions (**Table 1**, entry **5**).

The promising results on benzaldehyde, beta-naphthol and acetamide using 0.8 mmol EAN as catalyst at the optimized reaction conditions encouraged us to investigate the feasibility of solvent-free MCRs protocol to a wide range of substituted aldehydes, amides/ carbamates / urea and naphthols/phenols for the synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols. A variety of aromatic/hetrocyclic aldehydes, amides/

Table 1: Influence of ethylammonium nitrate for the reaction of benzaldehyde, beta-naphthol and acetamide.[a]



Entry	Ethylammonium nitrate (mmol)	Yield[b] (%)
1	00	00
2	0.2	37
3	0.4	68
4	0.6	88
5	0.8	93
6	1.0	93

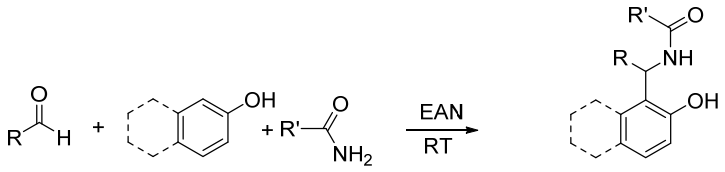
[a] Reaction conditions: Benzaldehyde (6 mmol), beta-naphthol (1 mmol), acetamide (1.1 mmol), RT, 1 h.

[b] Isolated yields after column chromatography.

carbamates/urea possessing various electron donating and electron withdrawing functional groups reacted smoothly with naphthols/phenols under neat reaction conditions to give desired products in excellent yields over EAN at ambient temperature (**Table 2**, entries **1-24**).

The results in **Table 2** illustrate that the one-pot three component condensation reactions show excellent performance irrespective of the presence of electron withdrawing or electron donating groups on aromatic/ hetrocyclic aldehydes and hence solvent-free MCRs protocol is highly effective, promising and general for the synthesis of 1-amido- and 1-carbamato-alkyl-2-naphthols/ phenols. The substituted aromatic aldehydes with electron withdrawing and electron donating groups reacted with beta-naphthol and acetamide/ benzamide/benzylamide provided desired products in excellent yields (**Table2**, entries **2-4** and entries **7-12**), whereas heterocyclic aldehydes such as furfural

Table 2: EAN mediated one-pot three-component reaction of aldehydes with beta-naphthol/phenol and amide/carbamate/urea giving the corresponding 1-amido- and 1-carbamato-alkyl naphthols /phenols.[a]



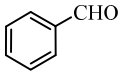
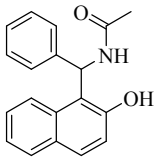
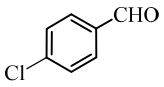
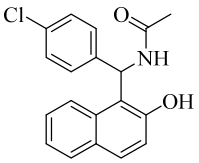
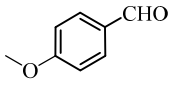
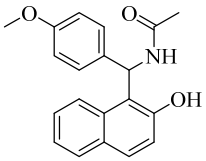
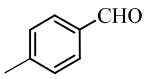
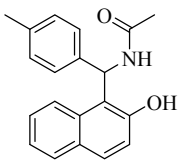
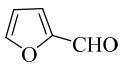
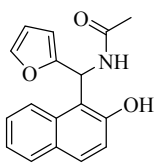
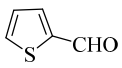
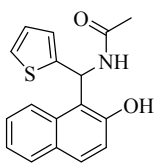
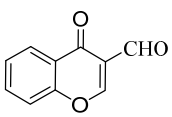
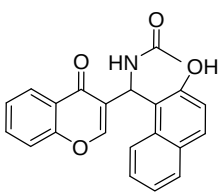
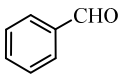
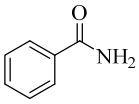
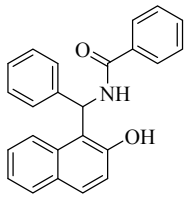
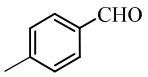
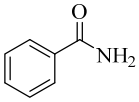
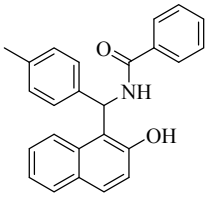
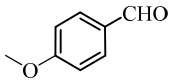
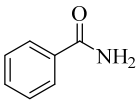
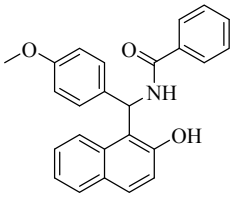
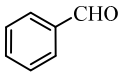
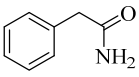
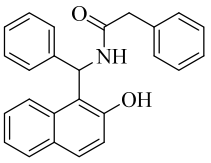
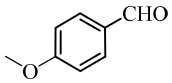
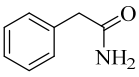
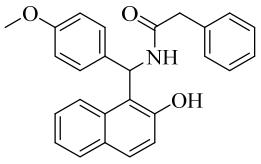
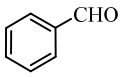
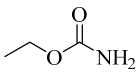
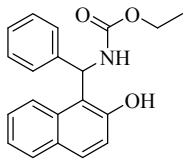
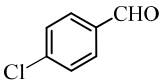
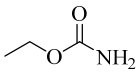
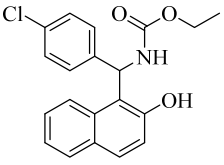
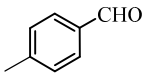
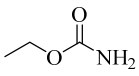
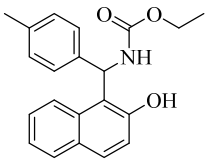
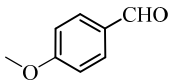
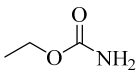
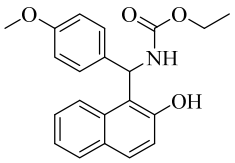
Entry	Aldehyde	Amide/Carbamate/Urea	Product	Yield[b] (%)
1				93
2*				95
3				91
4				95
5				87
6				85
7*				91

Table 2 (*Continued*)

8				94
9				95
10				91
11				92
12				90
13				90
14				94
15				93
16				88

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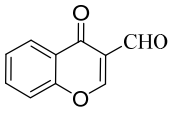
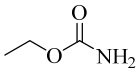
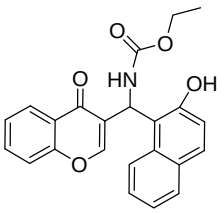
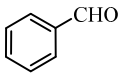
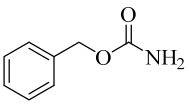
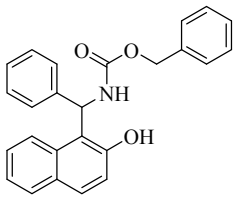
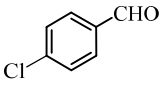
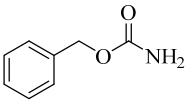
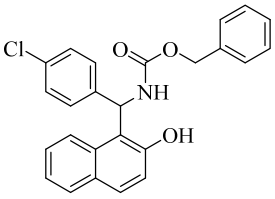
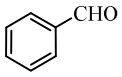
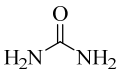
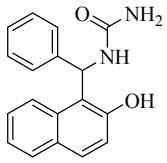
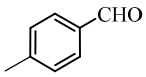
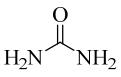
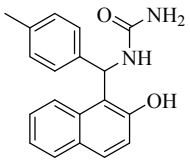
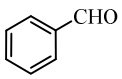
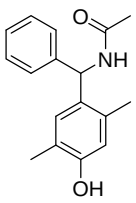
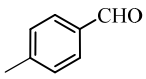
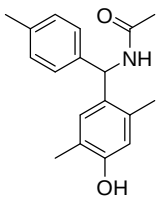
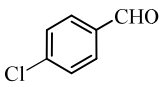
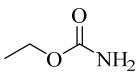
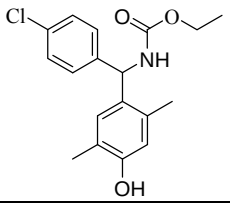
17				85
18				91
19				90
20				96
21				93
22				93
23				94
24				95

[a] Aldehyde (6 mmol), beta-naphthol/phenol (1 mmol), amide/urea/carbamate (1.1 mmol) in EAN (0.8 mmol), RT, 1 h.

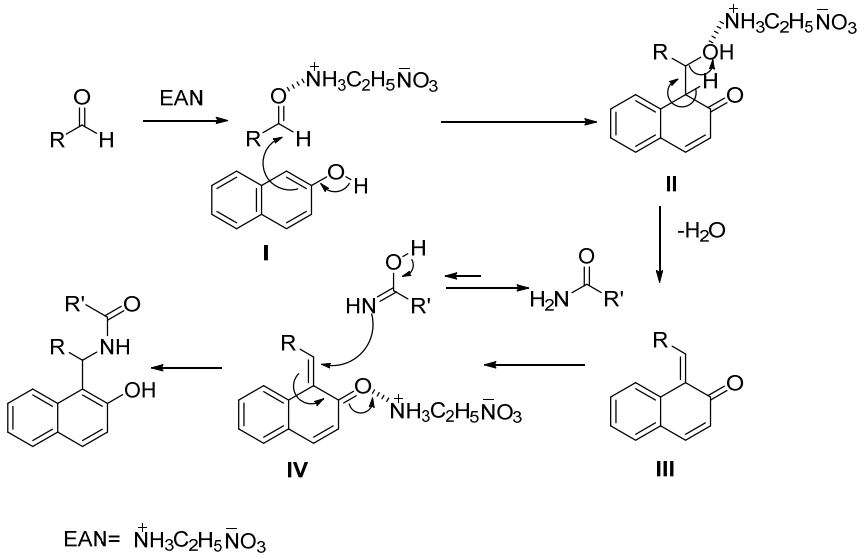
[b] Isolated yields after column chromatography.

Note: * Excess EAN is used in case of 4-chlorobenzaldehyde and 3-formyl chromones.

Note: 2-naphthol was used in entry 1-21 and 2, 5 di-methyl phenol was used in entry 22-24.

and thiophene 2-carbaldehyde reacted with beta-naphthols and acetamide provided high yields (**Table 2**, entries **5-6**). However, the condensation of aromatic aldehydes, carbamates /urea with beta-naphthol provided desired products in good to excellent yields (**Table 2**, entries **13-21**). Interestingly, 3-formyl chromone reacted smoothly with beta-naphthols and acetamide/ ethylcarbamate to give expected product in excellent/good yield (**Table 2**, entries **7** and **17**). To study the scope of this protocol with phenol, a reaction of benzaldehyde / 4-methylbenzaldehyde / 4-chlorobenzaldehyde and acetamide/ ethylcarbamate were carried out with 2, 5-dimethylphenol under optimized reaction conditions, which provided the corresponding 1-amido- and 1-carbamato-alkyl phenols in excellent yields (**Table 2**, entries **22-24**). However, in all the cases 1-amido- and 1-carbamato-alkyl naphthols/phenols were the exclusive products. The results in **Table 2** clearly indicate that solvent-free MCR protocol over EAN under neat reaction conditions at ambient temperature is applicable to large number of substrates having different functional groups; however, the yield obtained are dependent on the nature of substituents on aromatic/ heterocyclic aldehydes, amides/ carbamates as well on the phenols.

As per earlier reported literatures[9,14] the probable mechanism proposed in **scheme 9** for the synthesis of 1-amidoalkyl naphthol involves the activation of carbonyl group of aldehyde by EAN to form the activated intermediate **I** then subsequently nucleophilic addition of beta-naphthol to obtain complex **II** followed by removal of water from the

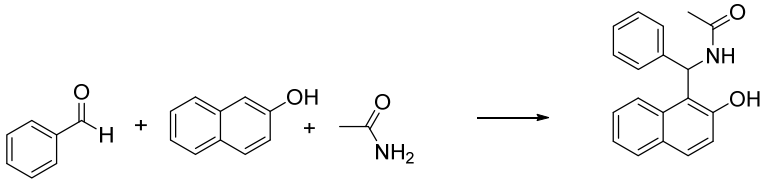


Scheme 9: Possible mechanism for the synthesis of 1-amidoalkyl naphthol.

complex **II** produce intermediate **III** as a *ortho*-quinone methide then subsequently activation by EAN to generate intermediate **IV** as a Michael acceptor, which leads to in-situ Michael addition of amide or carbamate or urea to release instantly the corresponding products (**Table 2**, entries **1-24**).

The recovery and recyclability of EAN was investigated for the synthesis of 1-amidoalkyl naphthols by one-pot three component condensations of benzaldehyde, beta-naphthol and acetamide as model substrates in the presence of EAN under neat reaction condition at ambient temperature for 1 h, and the results are summarized in **Table 3**. EAN was recovered quantitatively from the reaction mixture by extracting the organic compound by ethyl acetate and the insoluble EAN were reused for several times without loss of activity (**Table 3**, entries **1-5**). The isolated yield obtained for the product even after the fourth recycle (**Table 3**, entries **2-5**) is very much consistent with fresh EAN (**Table 3**, entry **1**). The consistent activity of recovered and reused EAN indicates that the reused EAN also shows excellent performance for the synthesis of 1-amidoalkyl napthol.

Table 3: Recovery and recyclability of EAN.[a]



Cycles	Yield[b] (%)
1	93
2	93
3	92
4	91
5	92

[a] Reaction conditions: Benzaldehyde (6 mmol), beta--naphthol (1 mmol), acetamide (1.1 mmol) in EAN (0.8 mmol), RT, 1 h.

[b] Isolated yields after column chromatography.

EAN recovery (%) = 98±2

4.1.5 Conclusion

In conclusion, a solvent-free, environmentally clean, much milder, inexpensive, general and simple one-pot multi-component protocol has been developed for efficient synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols in good to excellent yield via one-pot three component condensation of various aldehyde, amide/urea/carbamate and naphthols/phenols using ethylammonium nitrate (EAN) as reusable ionic liquid catalyst under neat reaction condition at ambient temperature. The present method is convenient and applicable to a wide variety of aldehydes, naphthols, phenols and amides or urea or carbamates for the synthesis of corresponding 1-amido- and 1-carbamato-alkyl naphthols /phenols. EAN was recovered and recycled several times without loss of catalytic activity.

4.1.6 Experimental Section

4.1.6.1 A typical procedure for the synthesis of Ethyl ammonium nitrate (EAN) ionic liquid

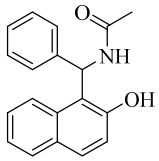
The ethyl ammonium nitrate used was synthesized according to the procedures reported in the literature.[21] The aqueous solution of ethylamine (70 %, 100 mL) was taken in a 1 Lit. round bottom flask, which was maintained below 10 ^{o}C using an ice-water bath. To this cold solution, nitric acid (30 %, 330 mL) was added slowly drop-wise with vigorous stirring to attain a pH of the mixture of 7.3, the addition was stopped and the mixture was stirred further for 0.5 h. The water from the mixture was removed in a rotary evaporatior in a boiling water bath at a pressure of 200 mmHg. The traces of water were removed at 100 ^{o}C and 1 mmHg pressure to afford the ethyl ammonium nitrate in quantitative yield (170 g).

4.1.6.2 A typical procedure for the synthesis of 1-amido- and 1-carbamato-alkyl naphthol/phenol using EAN

The reaction mixture of aldehyde (6 mmol), beta-naphthol/phenol (1 mmol) and amide/carbamate/urea (1.1 mmol) was stirred in presence of 0.8 mmol EAN at room temperature for 1 hour. The completion of reaction was monitored by TLC. On completion of reaction, the reaction mixture was extracted thrice with 10 mL ethyl acetate. The extract was dried over anhydrous sodium sulfate, evaporated under vacuum and the residue was purified by short column on silica gel (hexane/ethyl acetate, 70:30) to obtain pure 1-amido- and 1-carbamato-alkyl naphthols/phenols (**Table 2**). The recovered EAN was subjected to high vacuum at 80 ^{o}C to remove the water and then reused. All the isolated reaction products were characterized and confirmed by NMR.

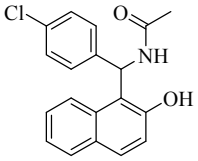
4.1.6.3 Spectral data

N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)acetamide



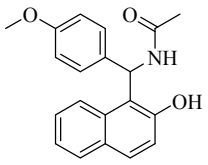
Yield: 93 %; white solid; mp: 240-242 °C **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.92 (s, 3H), 7.17-6.97 (m, 7H), 7.28 (t, *J*=7.58 Hz, 1H), 7.63-7.52 (m, 2H), 7.84 (d, *J*=8.47 Hz, 1H), 7.96 (d, *J*=8.96 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 22.99, 48.50, 118.72, 122.44, 126.09, 128.28, 128.40, 128.92, 132.30, 135.34, 139.02, 152.98, 169.14.

N-((4-chlorophenyl)(2-hydeoxynaphthalen-1-yl)methyl)acetamide



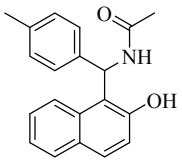
Yield: 95 %; white solid; mp: 224-226 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.00 (s, 3H), 7.05-7.35 (m, 7H), 7.59-7.70 (m, 2H), 7.90-8.05 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 22.26, 47.35, 117.44, 117.84, 121.84, 126.96, 127.65, 128.53, 130.74, 152.30, 168.56.

N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)acetamide



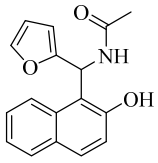
Yield: 91 %; white solid; mp: 208-210 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.04 (s, 3H), 3.74 (s, 3H), 6.87 (d, *J*=8.72 Hz, 2H), 7.16 (d, *J*=8.21 Hz, 3H), 7.32 (t, *J*=8.21 Hz, 2H), 7.43 (t, *J*=7.84 Hz, 1H), 7.80-7.95 (m, 3H), 8.52 (d, *J*=8.21 Hz, 1H), 10.07 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 22.91, 47.67, 55.19, 113.62, 118.72, 119.19, 122.57, 123.54, 126.45, 127.48, 128.68, 128.73, 129.31, 132.51, 134.61, 153.28, 157.89, 169.31.

N-((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)acetamide



Yield: 95 %; white solid; mp: 222-224 °C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d6): δ 2.04 (s, 3H), 2.25 (s, 3H), 6.98 (d, *J*=8.09 Hz, 2H), 7.08-7.29 (m, 5H), 7.38 (t, *J*=8.21 Hz, 1H), 7.63-7.74 (m, 2H), 7.98 (d, *J*=8.4 Hz, 1H), 8.10 (d, *J*=9.22 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 19.92, 22.24, 47.75, 117.98, 121.70, 125.35, 127.65, 128.18, 131.62, 134.60, 138.27, 152.24, 168.39.

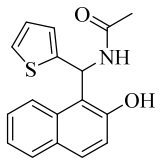
N-(furan-2-yl(2-hydroxynaphthalen-1-yl)methyl)acetamide



Yield: 87 %; Brown solid, mp: 226-228 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.98 (s, 3H), 6.15 (d, *J*=3.03 Hz, 1H), 6.40-6.42 (m, 1H), 7.13-7.54 (m, 5H), 7.84 (t, *J*=8.84 Hz, 2H), 8.03 (d, *J*=8.46 Hz, 1H), 8.66 (d, *J*=8.09 Hz, 1H), 10.09 (s, 1H); **^{13}C NMR** (50

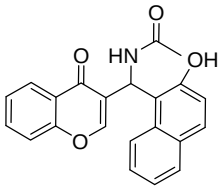
MHz, DMSO-d_6): δ 22.75, 43.66, 106.26, 110.56, 116.77, 118.60, 122.57, 126.45, 128.55, 128.69, 129.62, 132.61, 141.87, 153.51, 155.06, 169.11.

N-((2-hydroxynaphthalen-1-yl)(thiophen-2-yl)methyl)acetamide



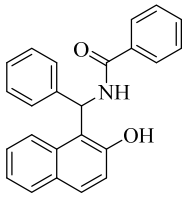
Yield: 85 %; Brown solid, mp: 208-210 ^oC; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.98 (s, 3H), 6.14-6.42 (m, 2H), 7.14-7.54 (m, 5H), 7.79-8.06 (m, 4H), 8.66 (d, *J*=8.09 Hz, 1H), 10.10 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 22.31, 43.24, 105.81, 110.11, 116.35, 118.17, 122.13, 122.81 126.00, 128.12, 128.24, 129.17, 132.17, 141.42, 153.07, 154.63, 168.67.

N-((2-hydroxynaphthalen-1-yl)(4-oxo-4H-chromen-3-yl)methyl)acetamide



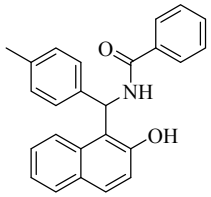
Yield: 91 %; Yellow solid, mp: 211-213 ^oC; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.96 (s, 3H), 7.08-7.25 (m, 3H), 7.46-7.58 (m, 2H), 7.72-7.92 (m, 6H), 8.33-8.48 (m, 2H), 10.04 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 22.47, 47.79, 111.72, 116.62, 118.43, 124.85, 125.17, 128.10, 129.04, 133.85, 136.95, 150.23, 153.48, 154.68, 168.49, 175.27, 188.53.

N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)benzamide



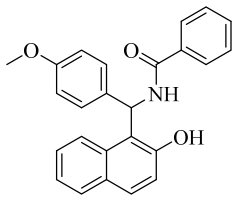
Yield: 94 %; White solid, mp: 230-232 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 7.13-7.51 (m, 14H), 7.66-7.84 (m, 4H), 8.02 (d, *J*=8.46 Hz, 1H), 8.19 (d, *J*=8.59 Hz, 1H), 8.80 (d, *J*=8.97 Hz, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 49.30, 118.61 , 122.18, 122.65, 126.20, 126.74, 127.74, 128.09, 129.35, 130.92, 132.14, 141.99, 152.70, 165.92.

N-((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)benzamide



Yield: 95 %; White solid, mp: 187-189 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.25 (s, 3H), 6.98 (d, *J*=8.09 Hz, 2H), 7.17-7.44 (m, 10H), 7.64-7.86 (m, 4H), 8.15 (d, *J*=8.59 Hz, 1H), 8.78 (d, *J*=8.97 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 20.71, 49.32, 118.71, 122.72, 126.33, 126.84, 128.53, 130.94, 152.73, 165.98.

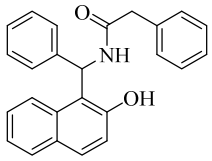
N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)benzamide



Yield: 91 %; White solid, mp: 209-211 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ

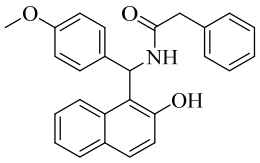
3.74 (s, 3H), 6.90 (d, *J*=8.72 Hz, 2H), 7.26-7.61 (m, 9H), 7.83-7.94 (m, 4H), 8.15 (d, *J*=8.47 Hz, 1H), 9.12 (d, *J*=8.46 Hz, 1H), 10.43 (s, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 48.78, 54.85, 112.87, 113.66, 118.37, 121.84, 122.32, 126.40, 127.23, 127.81, 131.21, 189.

N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)-2-phenylacetamide



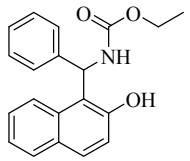
Yield: 92 %; Brown solid, mp: 180-182 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.70 (d, *J*=7.70 Hz, 2H), 7.14-7.50 (m, 13H), 7.82-7.94 (m, 3H), 8.68 (d, *J*=8.33 Hz, 1H), 10.13 (s, 1H); **^{13}C NMR** (200 MHz, DMSO-d_6): δ 48.14, 48.86, 118.77, 120.58, 122.60, 125.98, 126.62, 128.67, 128.82, 129.10, 132.50, 134.97, 141.50, 153.06, 158.85.

N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)-2-phenylacetamide



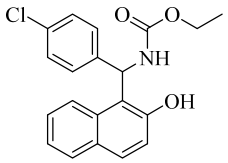
Yield: 90 %; Brown solid, mp: 192-194 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.69-3.74 (m, 5H), 6.86 (d, *J*=8.72 Hz, 2H), 7.10 (d, *J*=8.59 Hz, 3H), 7.26-7.45 (m, 8H), 7.80-7.97 (m, 3H), 8.62 (d, *J*=8.46 Hz, 1H), 10.06 (s, 1H); **^{13}C NMR** (200 MHz, DMSO-d_6): δ 42.41, 47.83, 55.20, 113.63, 118.88, 122.60, 126.60, 127.43, 128.45, 129.40, 132.46, 134.43, 136.62, 153.29, 157.92, 170.06.

Ethyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate



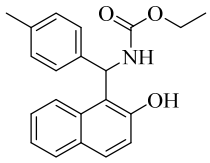
Yield: 90 %; white solid, mp: 186-188 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.22 (t, *J*=6.95 Hz, 3H), 4.08 (q, *J*=6.95 Hz, 2H), 6.90 (d, *J*=8.97 Hz, 1H), 7.21-7.48 (m, 8H), 7.65 (d, *J*=7.96 Hz, 1H), 7.85 (t, *J*=8.72 Hz, 2H), 7.96 (d, *J*=8.59 Hz, 1H), 10.18 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 15.16, 50.74, 60.63, 118.97, 123.06, 126.51, 126.87, 128.63, 129.08, 129.81, 132.56, 142.95, 153.38, 156.65.

Ethyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methylcarbamate



Yield: 94 %; white solid, mp: 162-164 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.23 (t, 3H), 4.08 (q, 2H), 6.90 (d, *J*=8.97 Hz, 1H), 7.24-7.50 (m, 7H), 7.69-7.97 (m, 4H), 10.21 (s, 1H); **^{13}C NMR** (200 MHz, DMSO-d_6): δ 14.97, 59.52, 60.54, 118.77, 122.95, 127.01, 128.25, 128.41, 128.54, 128.68, 129.87, 131.27, 132.29, 139.60, 141.88, 153.28, 157.16.

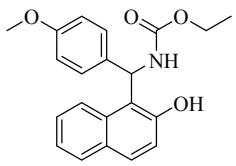
Ethyl ((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)carbamate



Yield: 93 %; white solid, mp: 171-173 ^{o}C; **^{1}H NMR** (200 MHz, Acetone-d_6): δ 1.19 (t,

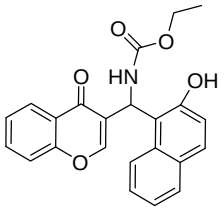
J=7.07 Hz, 3H), 2.25 (s, 3H), 4.08 (q, 2H), 6.94-7.36 (m, 9H), 7.48 (t, *J*=7.32 Hz, 1H), 7.82 (t, *J*=9.09 Hz, 2H), 8.10 (d, *J*=8.59 Hz, 1H); **^{13}C NMR** (200 MHz, Acetone-d_6): δ 15.07, 21.02, 51.71, 54.69, 61.22, 98.51, 119.38, 120.65, 123.66, 123.87, 127.11, 127.77, 129.63, 129.86, 130.07, 130.40, 133.54, 136.76, 140.74, 153.64, 157.26.

Ethyl ((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)carbamate



Yield: 88 %; white solid, mp: 169-171 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.22 (t, *J*=6.95 Hz, 3H), 3.41 (s, 3H), 4.06 (q, *J*=6.82 Hz, 2H), 6.90 (d, *J*=8.97 Hz, 1H), 7.24-7.48 (m, 9H), 7.65 (d, *J*=7.96 Hz, 1H), 7.85 (t, *J*=8.72 Hz, 2H), 7.96 (d, *J*=8.59 Hz, 1H), 10.18 (s, 1H); **^{13}C NMR** (200 MHz, Acetone-d_6): δ 14.95, 51.59, 54.57, 61.10, 119.26, 120.53, 123.76, 126.99, 127.65, 129.74, 130.28, 133.43, 136.64, 140.62, 153.53, 157.15.

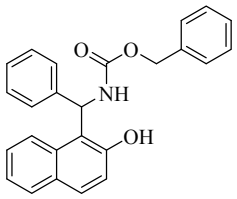
Ethyl(2-hydroxynaphthalen-1-yl)(4-oxo-4H-chromen-3-yl)methylcarbamate



Yield: 85 %; Yellow solid, mp: 181-183 ^{o}C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.21 (t, 3H), 4.03 (q, 2H), 7.01 (b, 1H), 7.43-7.17 (m, 2H), 7.69-7.50 (m, 4H), 7.82-7.71 (m, 3H), 8.07-8.03 (d, J=9 Hz, 1H), 8.43 (d, 2H), 8.54 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 19.92, 22.24, 47.75, 117.98, 121.70, 125.35, 127.53, 127.65, 128.18,

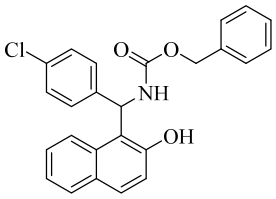
131.62, 134.60, 138.27, 152.24, 168.39.

Benzyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate



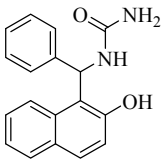
Yield: 91 %; White solid, mp: 173-175 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 5.12 (d, *J*=4.04 Hz, 2H), 6.95 (d, *J*=8.84 Hz, 1H), 7.22-7.52 (m, 14H, 7.81-7.99 (m, 4H), 10.18 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 50.34, 65.67, 118.43, 118.80, 122.50, 126.36, 127.79, 128.11, 128.34, 128.55, 129.33, 132.04, 137.00, 142.31, 152.90, 156.04.

Benzyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methylcarbamate



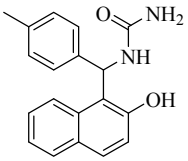
Yield: 90 %; White solid, mp: 154-156 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 5.12 (d, *J*=3.54 Hz, 2H), 6.94 (d, *J*=8.72 Hz, 1H), 7.25-7.47 (m, 12H), 7.79-7.96 (m, 4H), 10.21 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 49.89, 65.75, 118.36, 122.57, 123.06, 126.59, 127.82, 127.91, 128.06, 128.35, 128.61, 129.56, 130.93, 131.93, 136.93, 141.43, 152.97, 156.07.

1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)urea



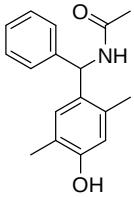
Yield: 96 %; White solid, mp: 173-175 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 5.92 (s, 2H), 6.99-7.10 (m, 6H), 7.26-7.50 (m, 3H), 7.80-7.90 (m, 3H), 10.01 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 55.19, 113.62, 118.72, 119.19, 122.57, 126.45, 127.48, 128.73, 129.31, 132.51, 134.61, 153.28, 157.89, 169.31.

1-((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)urea



Yield: 93 %; White solid, mp: 118-120 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.28 (s, 3H), 5.91 (s, 2H), 6.98-7.11 (m, 6H), 7.25-7.49 (m, 3H), 7.79-7.89 (m, 3H), 10.00 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 20.77, 48.86, 118.77, 120.58, 122.60, 125.98, 128.67, 128.82, 129.10, 132.50, 134.97, 141.50, 153.06, 158.85.

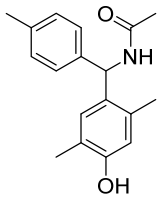
N-((4-hydroxy-2,5-dimethylphenyl)(phenyl)methyl)acetamide



Yield: 93 %; White solid, mp: 178-180 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.94 (s, 3H), 2.07 (s, 3H), 2.32 (s, 3H), 6.16 (d, *J*=8.46 Hz, 1H), 6.63 (s, 1H), 6.82 (s, 1H), 7.08-

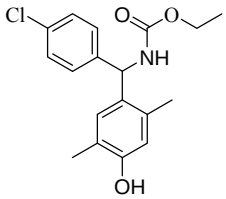
7.19 (m, 5H), 8.56 (d, *J*=8.58 Hz, 1H), 9.18 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 16.45, 19.35, 23.12, 52.33, 116.92, 121.37, 127.73, 129.36, 130.18, 131.58, 134.25, 136.21, 140.38, 154.62, 168.73.

N-((4-hydroxy-2,5-dimethylphenyl)(p-tolyl)methyl)acetamide



Yield: 94 %; White solid, mp: 184-186 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.89 (s, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 2.27 (s, 3H), 6.10 (d, *J*=8.46 Hz, 1H), 6.58 (s, 1H), 6.77 (s, 1H), 7.10 (q, *J*=8.22 Hz, 4H), 8.50 (d, *J*=8.58 Hz, 1H), 9.12 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 15.19, 18.10, 19.98, 21.87, 51.08, 115.67, 120.12, 126.48, 128.11, 128.93, 130.33, 133.00, 134.96, 139.13, 153.37, 167.48.

Ethyl (4-chlorophenyl)(4-hydroxy-2,5-dimethylphenyl)methylcarbamate



Yield: 95 %; White solid, mp: 166-168 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.19 (t, *J*=6.95 Hz, 3H), 2.06 (s, 3H), 2.19 (s, 3H), 4.04 (q, *J*=7.07 Hz, 2H), 5.96 (d, *J*=8.97 Hz, 1H), 6.62 (s, 1H), 6.88 (s, 1H), 7.26 (d, *J*=8.46 Hz, 2H), 7.42 (d, *J*=8.47 Hz, 2H), 8.04 (d, *J*=9.09 Hz, 1H), 9.20 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 14.44, 15.60, 18.53, 53.34, 59.67, 116.04, 120.78, 127.94, 128.80, 129.34, 130.22, 131.02, 133.23, 141.60, 153.97, 155.50.

4.1.7 Spectra

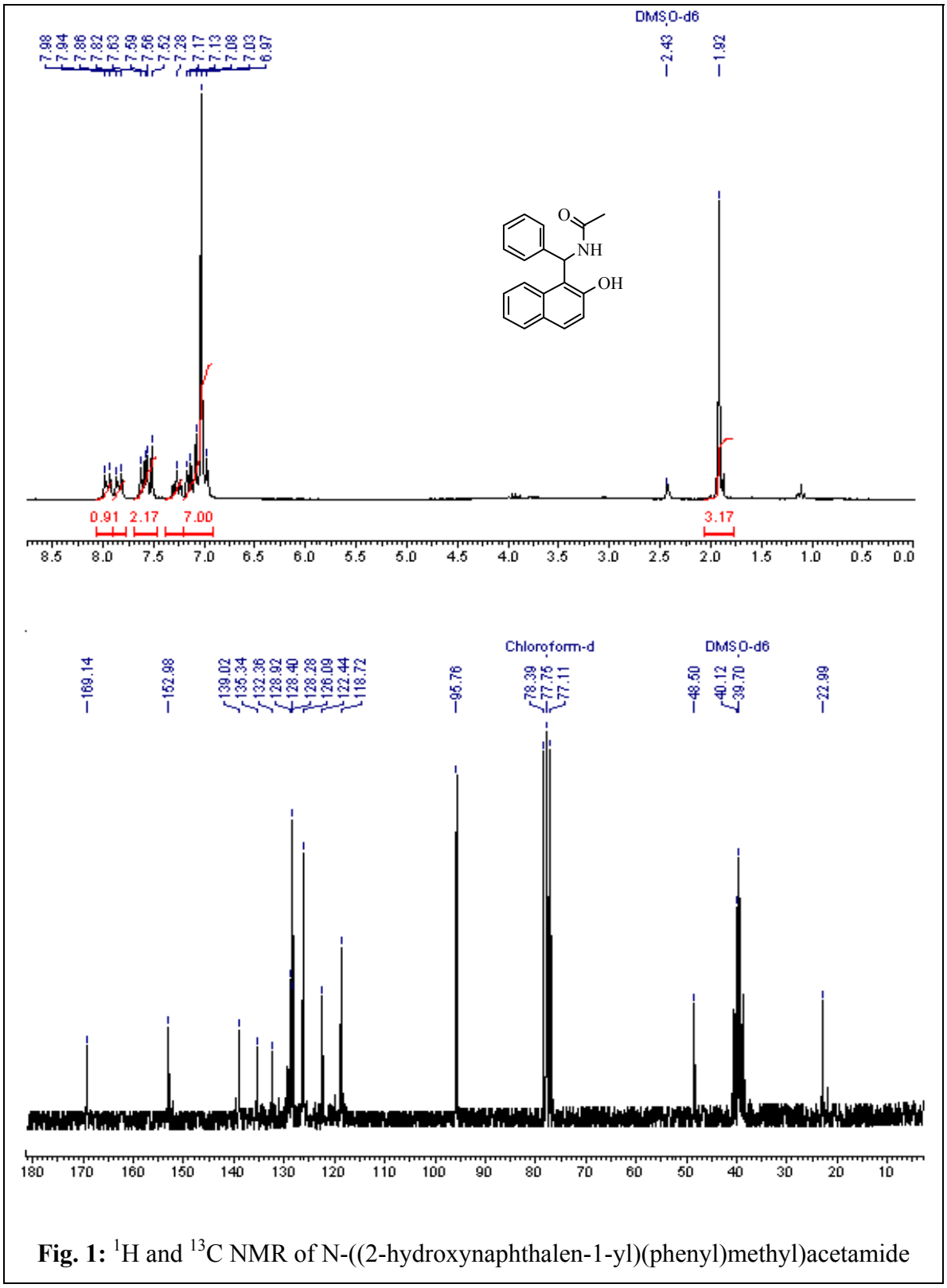


Fig. 1: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)acetamide

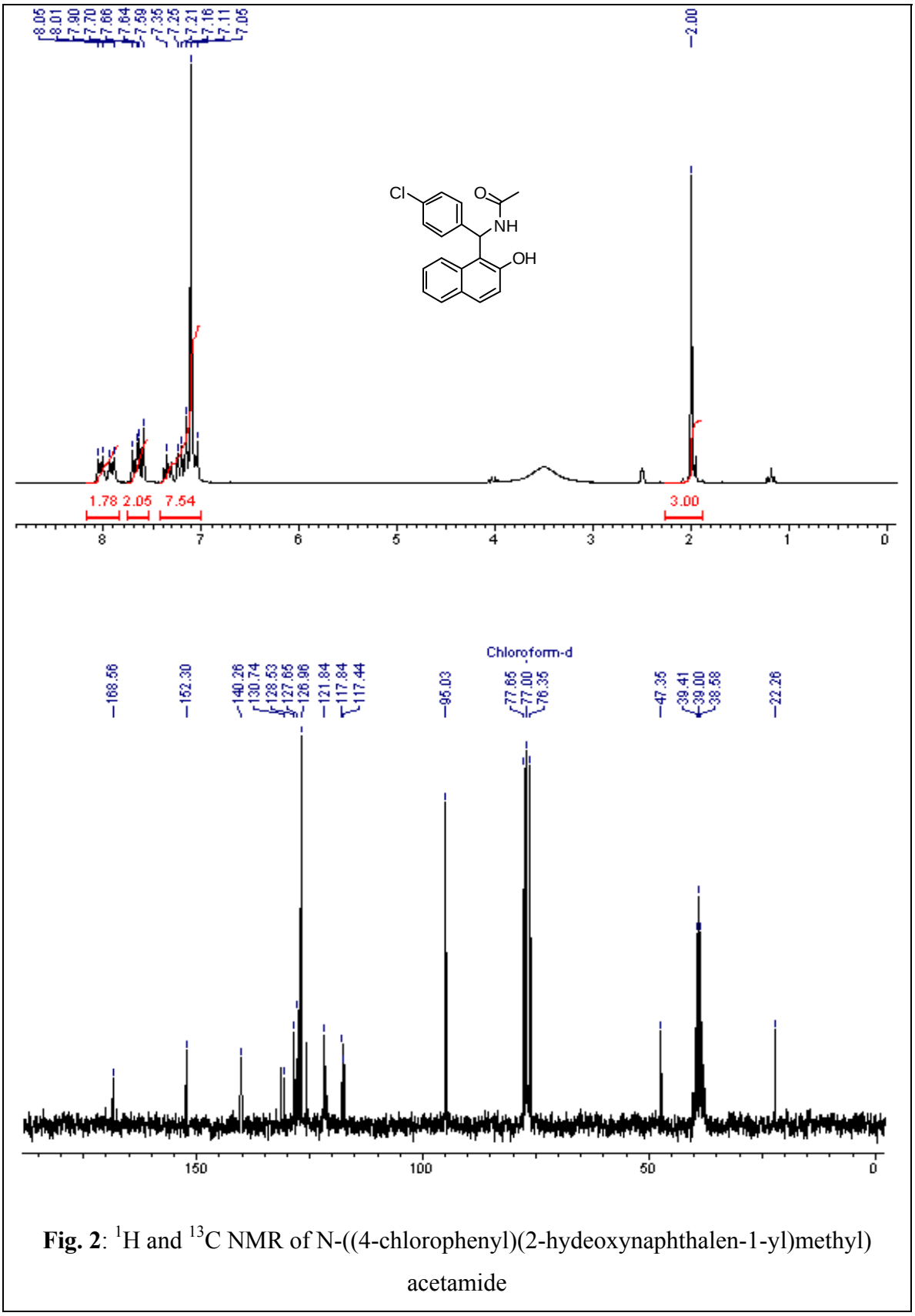


Fig. 2: ^{1}H and ^{13}C NMR of N-((4-chlorophenyl)(2-hydeoxynaphthalen-1-yl)methyl) acetamide

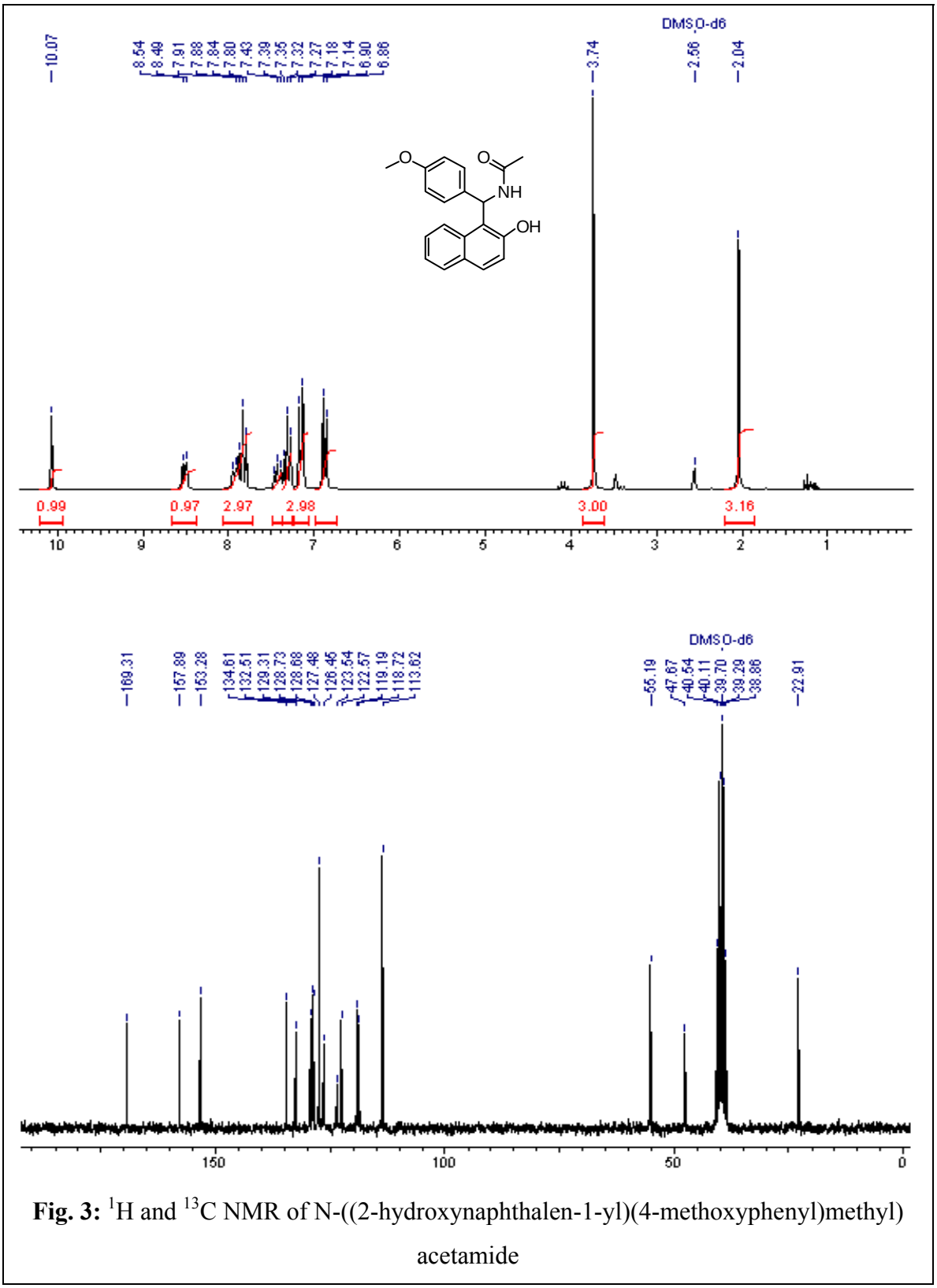


Fig. 3: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl) acetamide

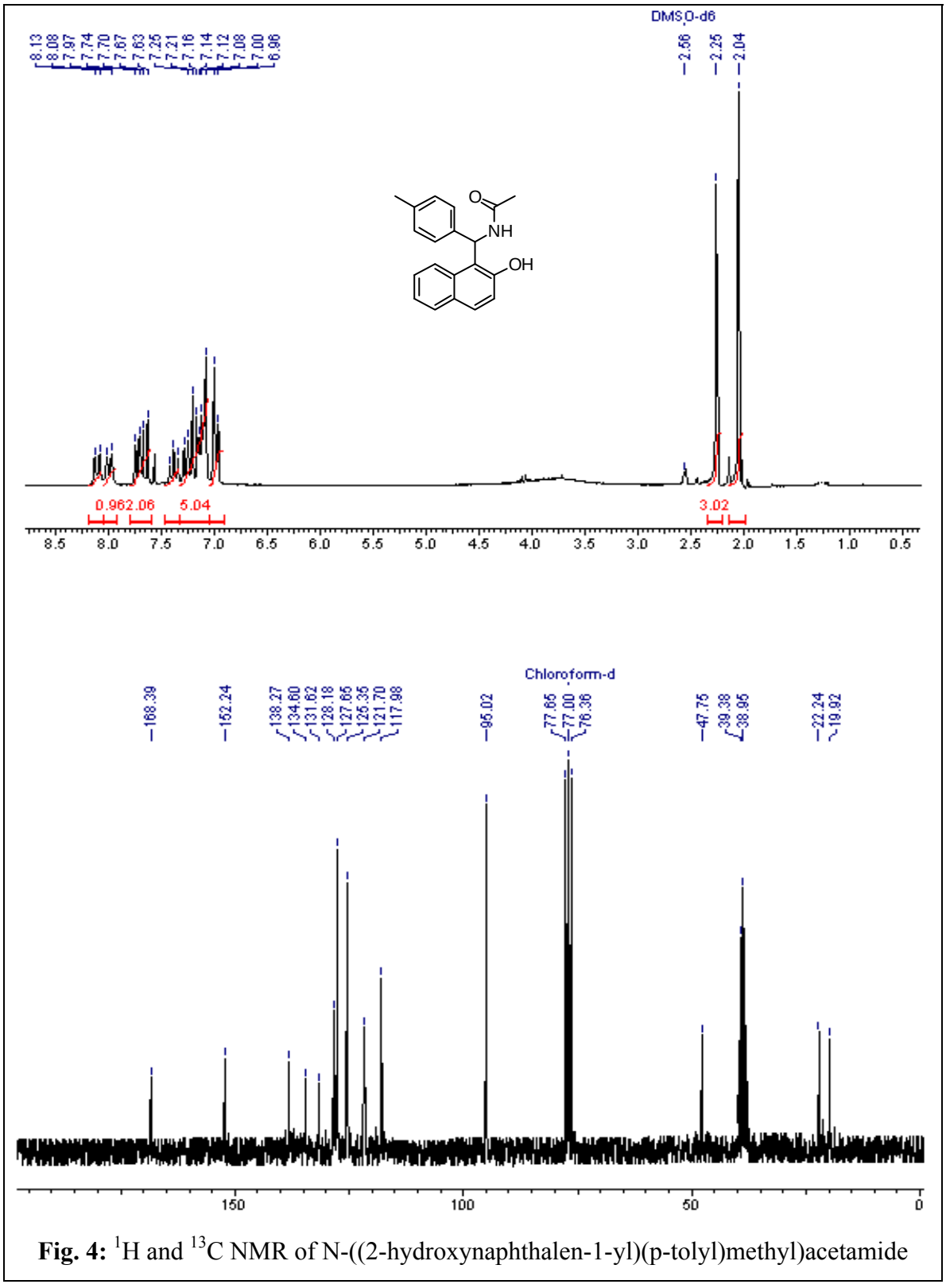


Fig. 4: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)acetamide

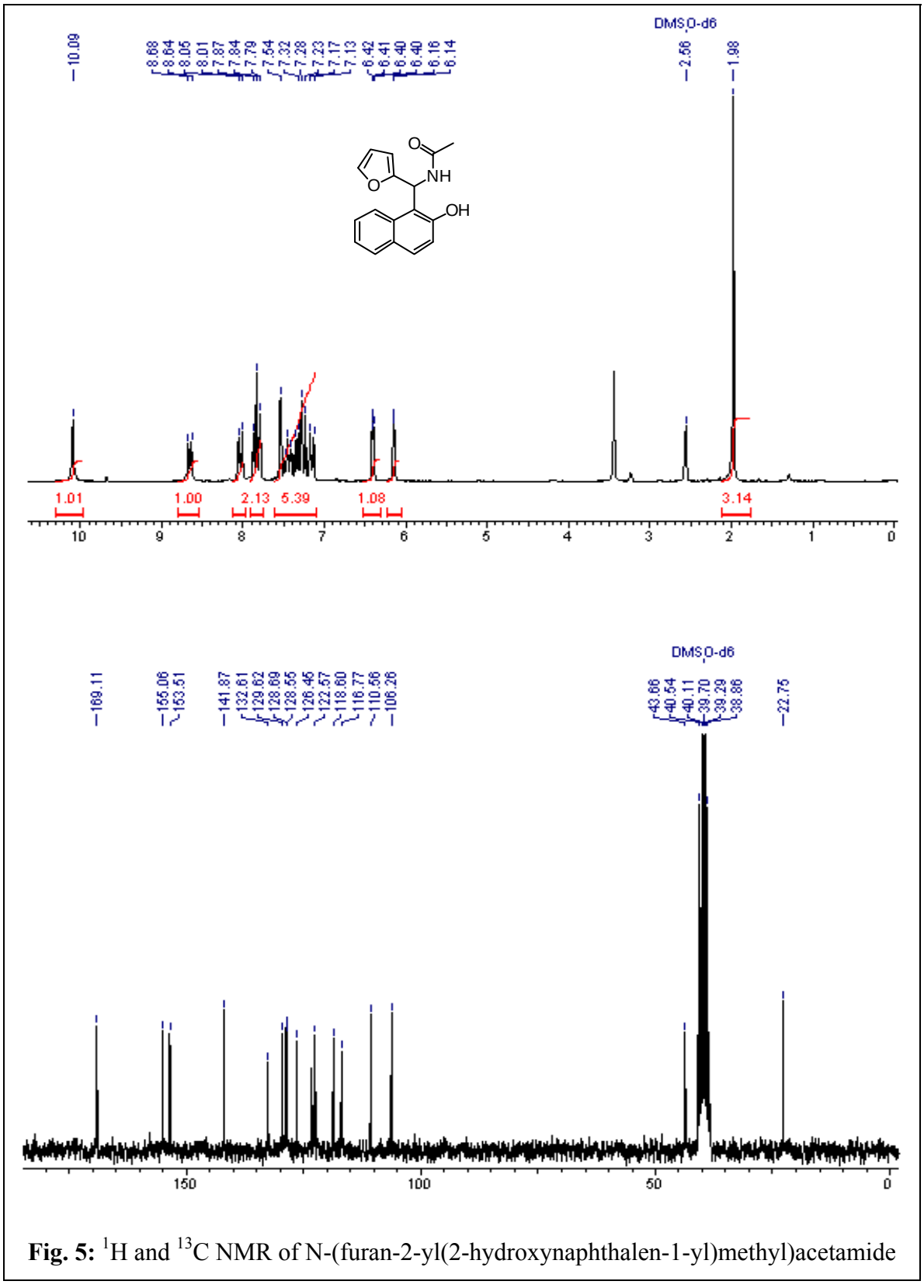


Fig. 5: ^{1}H and ^{13}C NMR of N-(furan-2-yl(2-hydroxynaphthalen-1-yl)methyl)acetamide

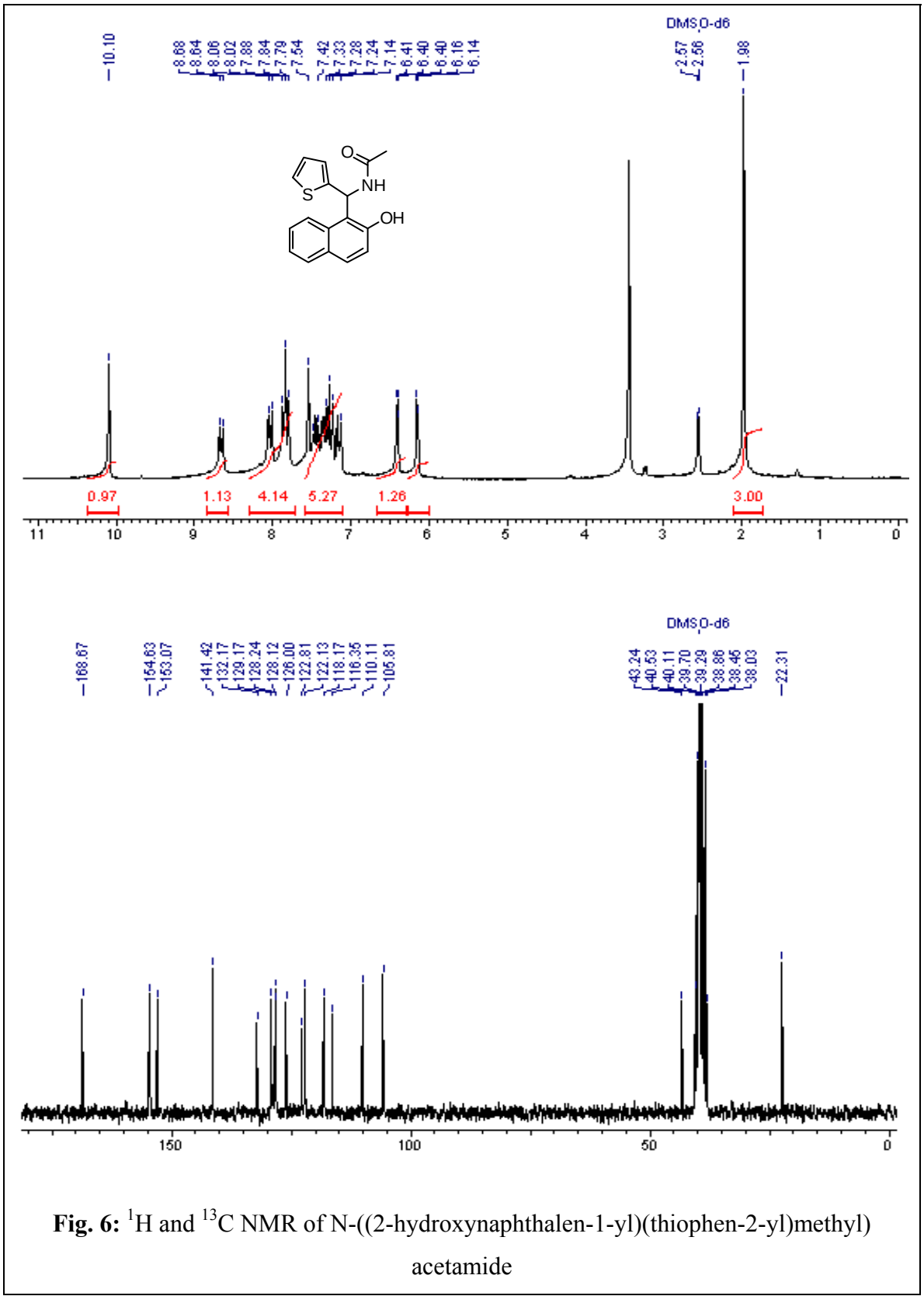


Fig. 6: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(thiophen-2-yl)methyl) acetamide

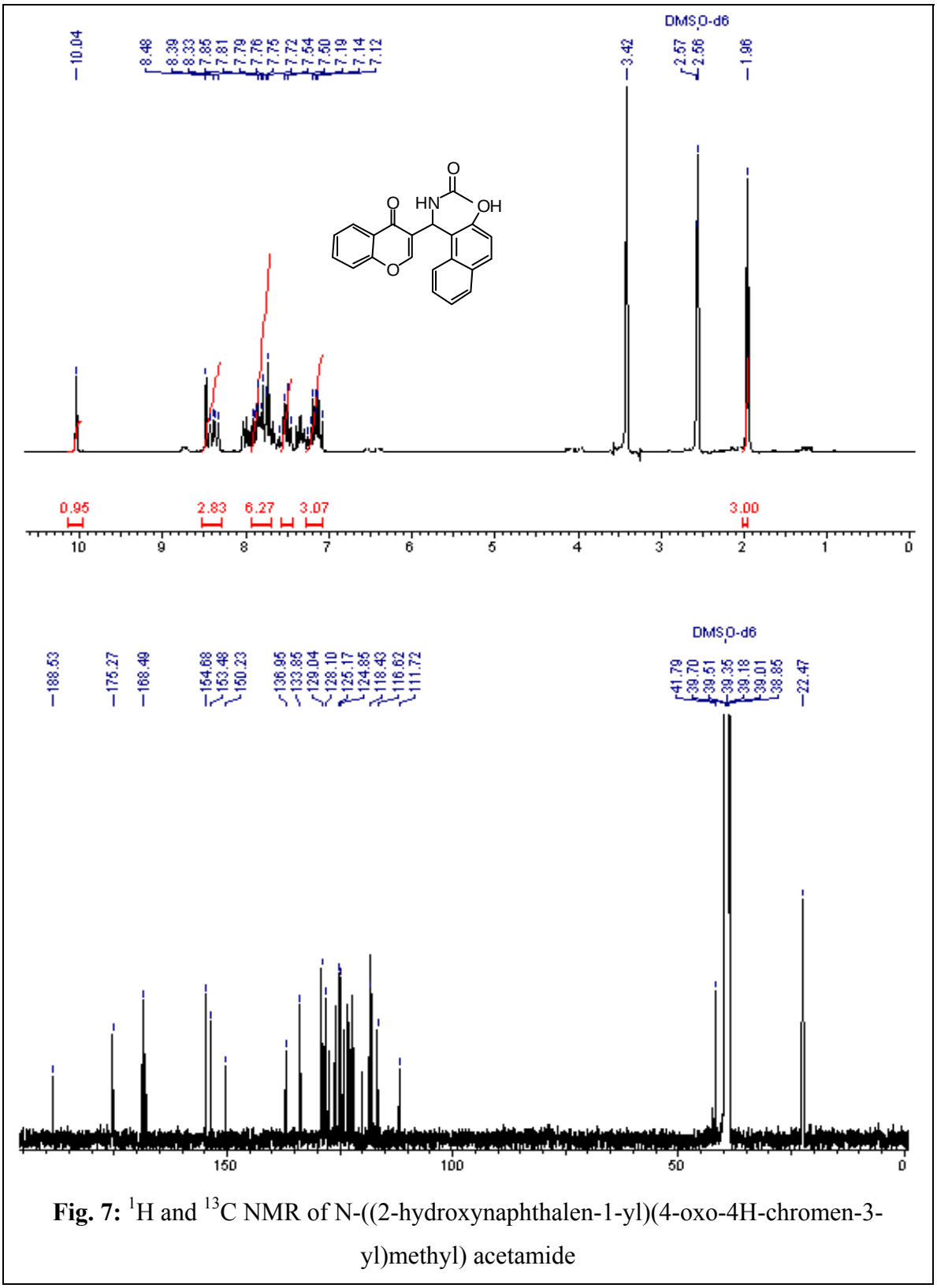


Fig. 7: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(4-oxo-4H-chromen-3-yl)methyl) acetamide

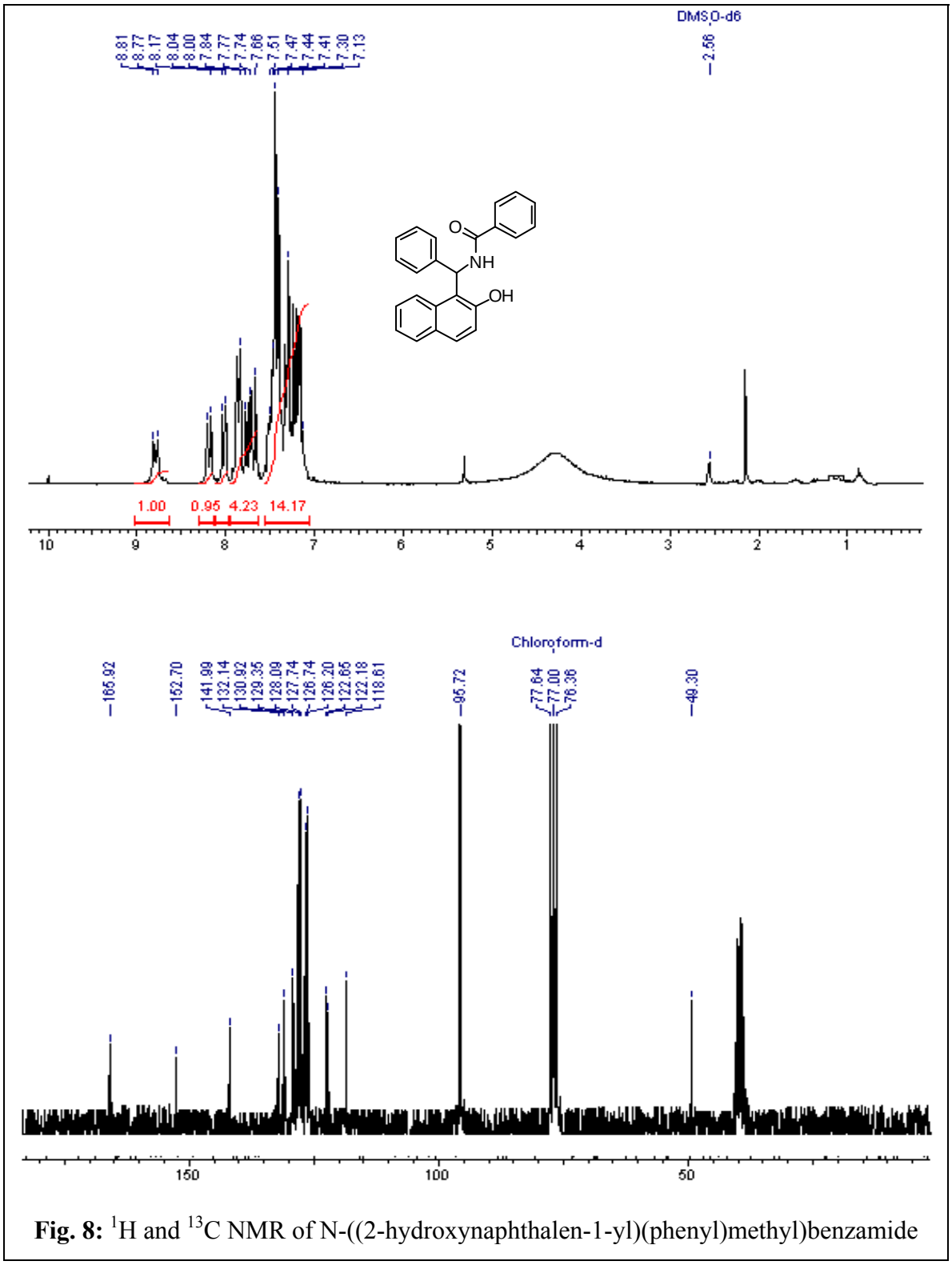


Fig. 8: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)benzamide

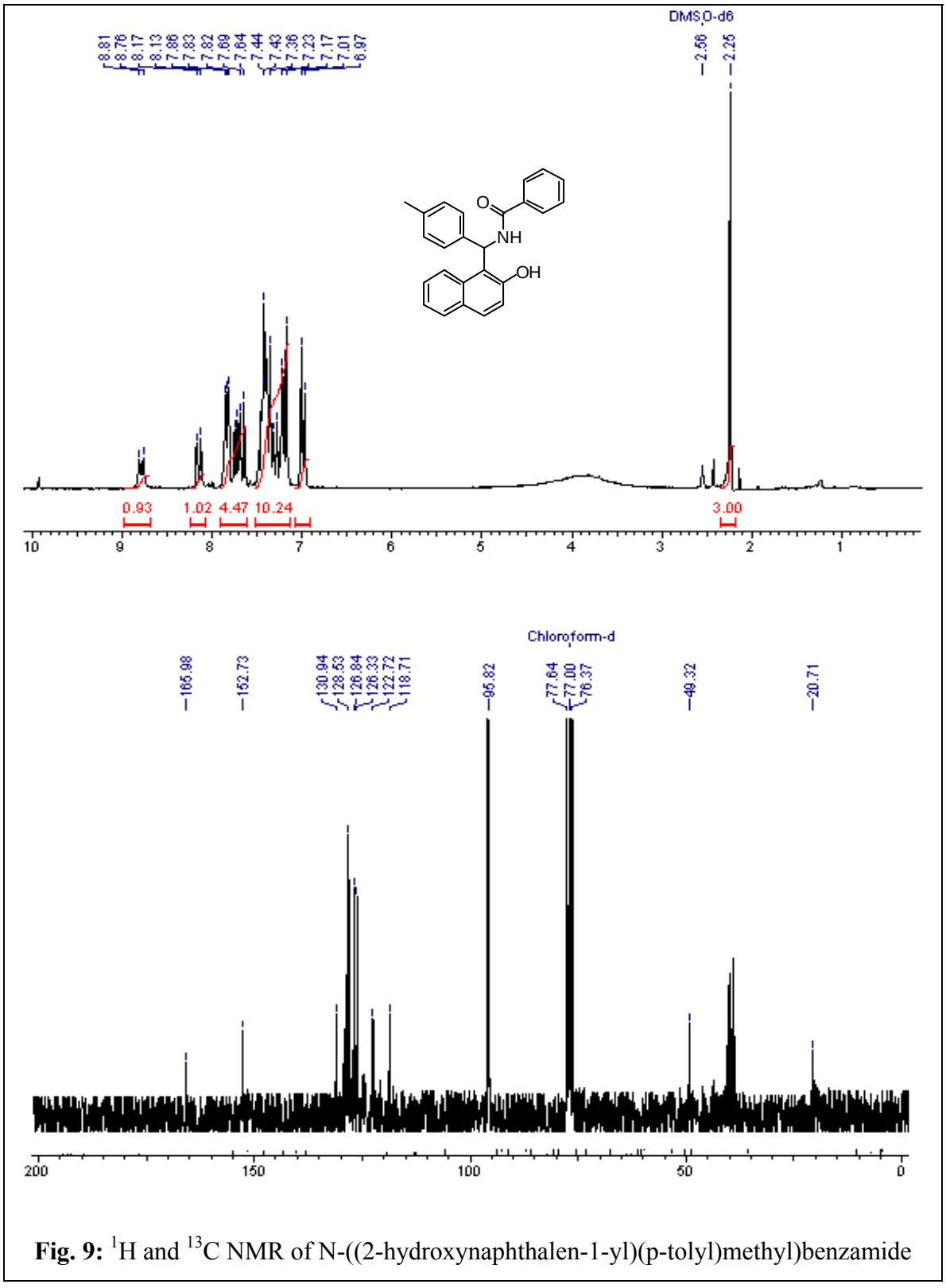


Fig. 9: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)benzamide

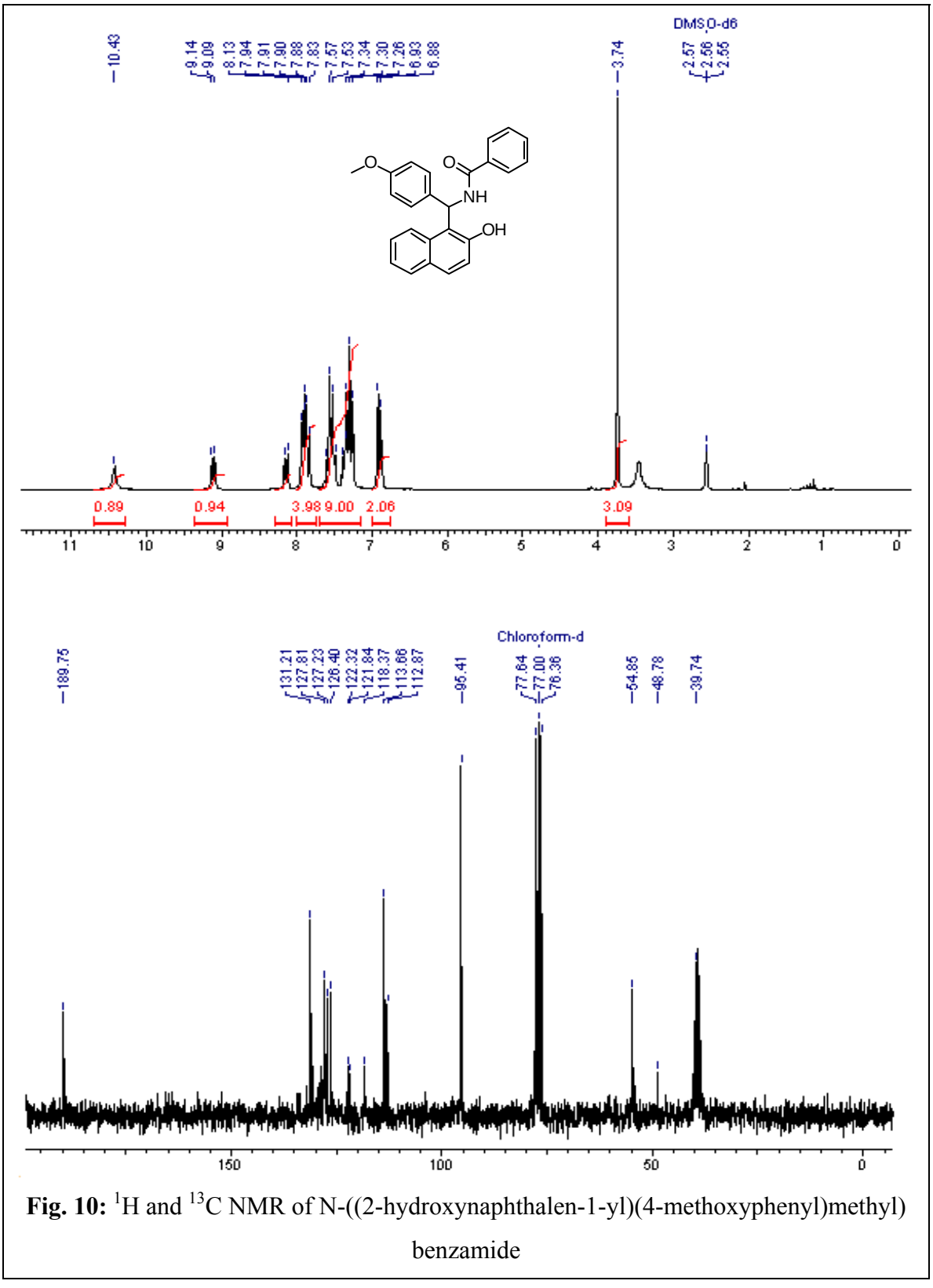


Fig. 10: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl) benzamide

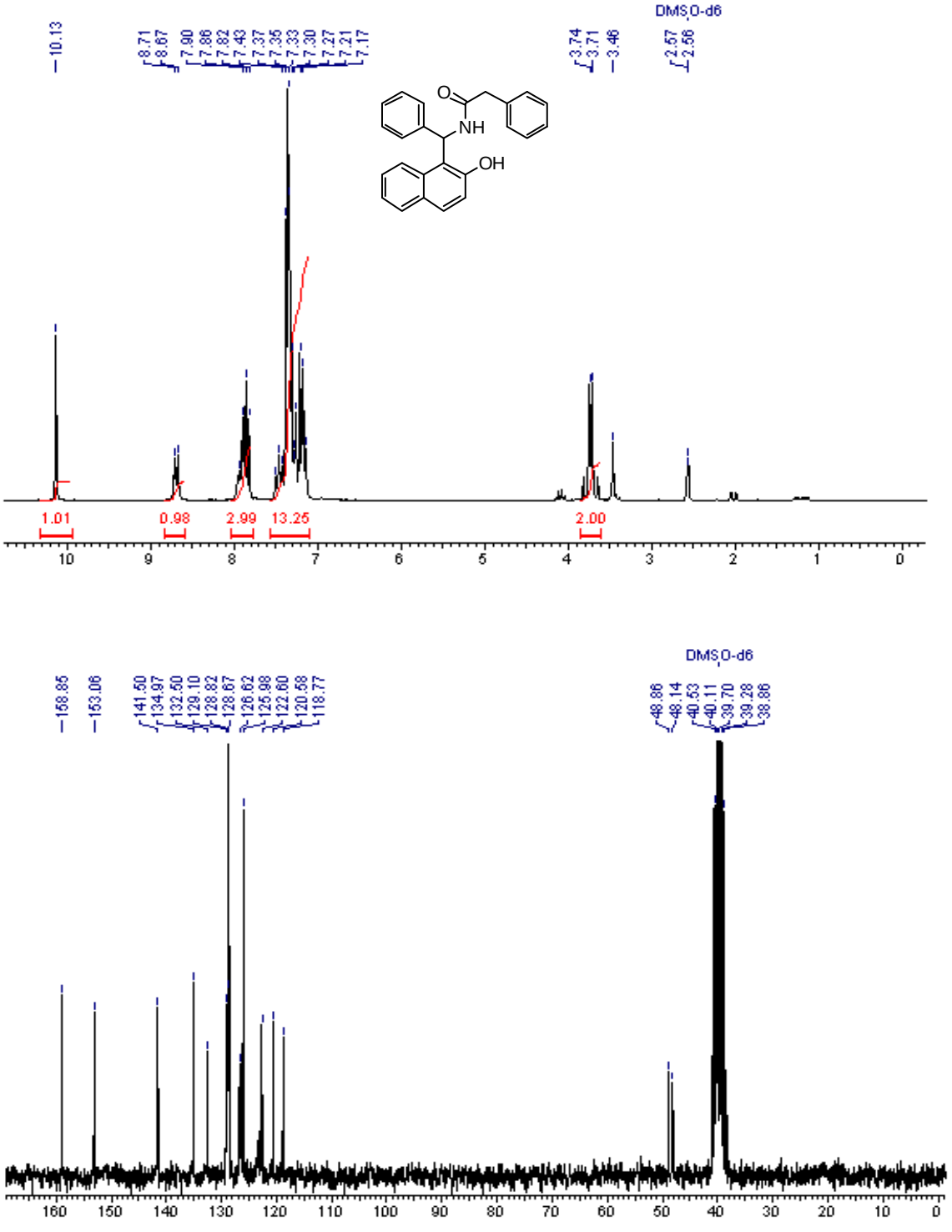


Fig. 11: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)-2-phenylacetamide

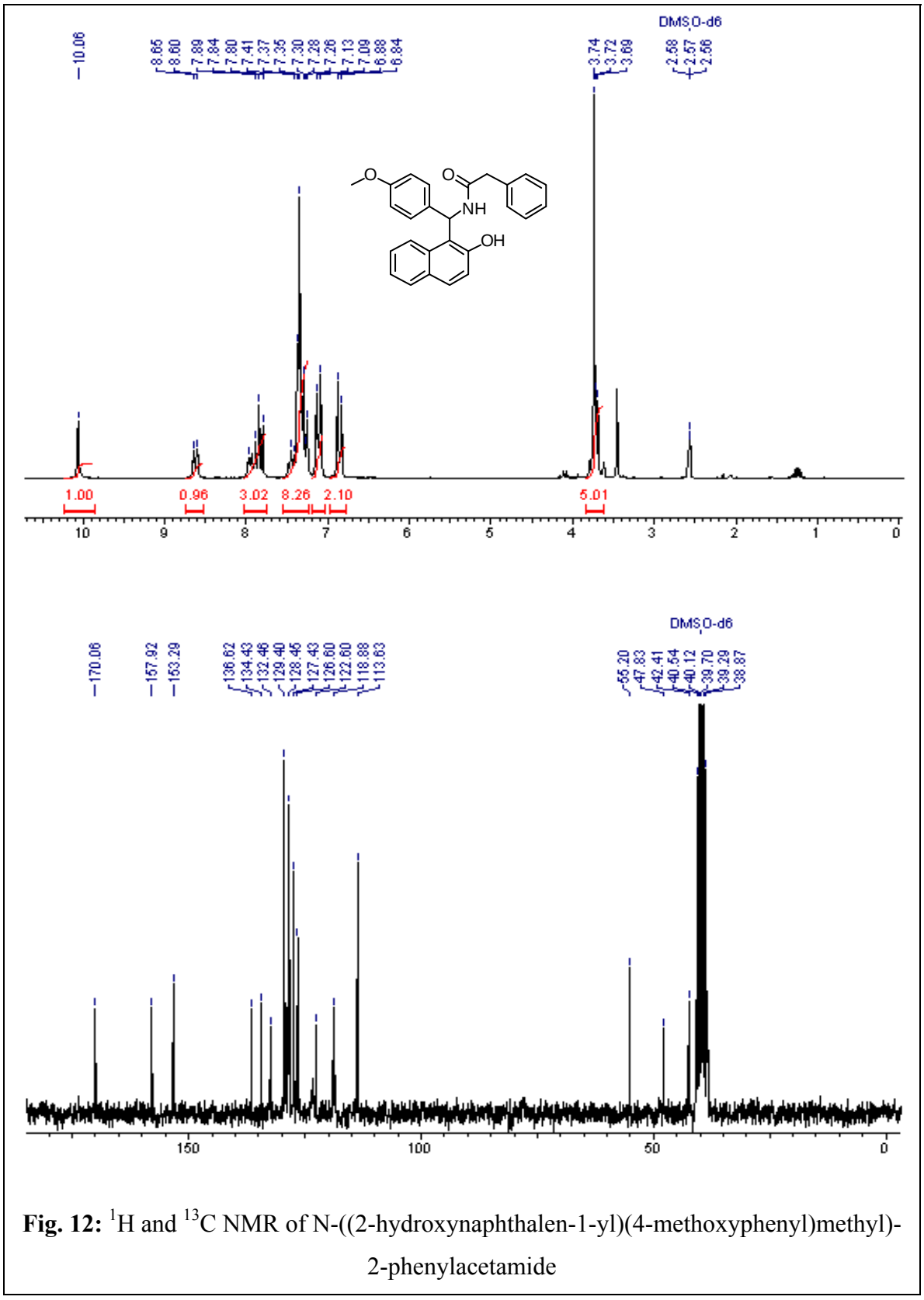


Fig. 12: ^{1}H and ^{13}C NMR of N-((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)-2-phenylacetamide

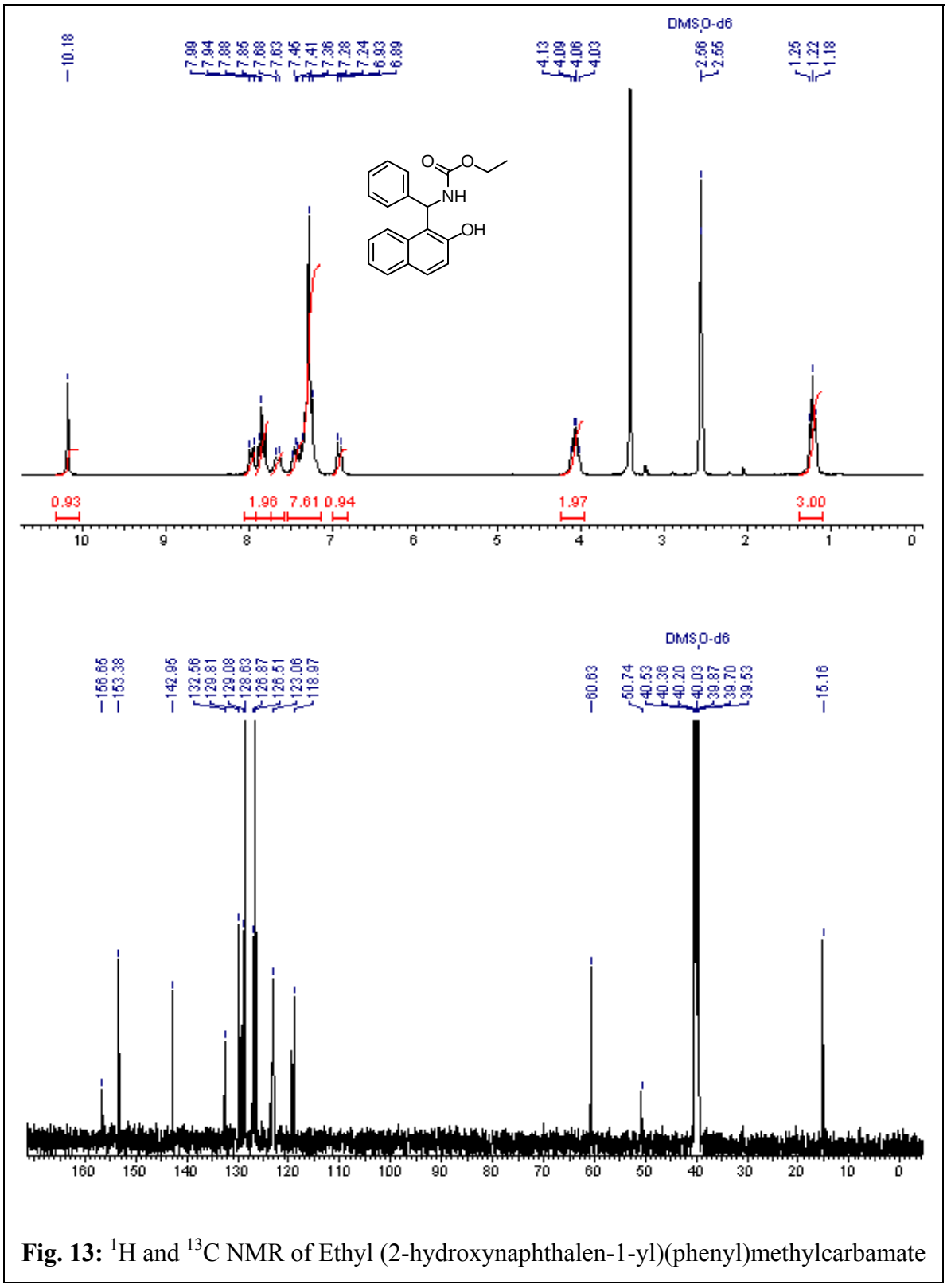


Fig. 13: ^{1}H and ^{13}C NMR of Ethyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate

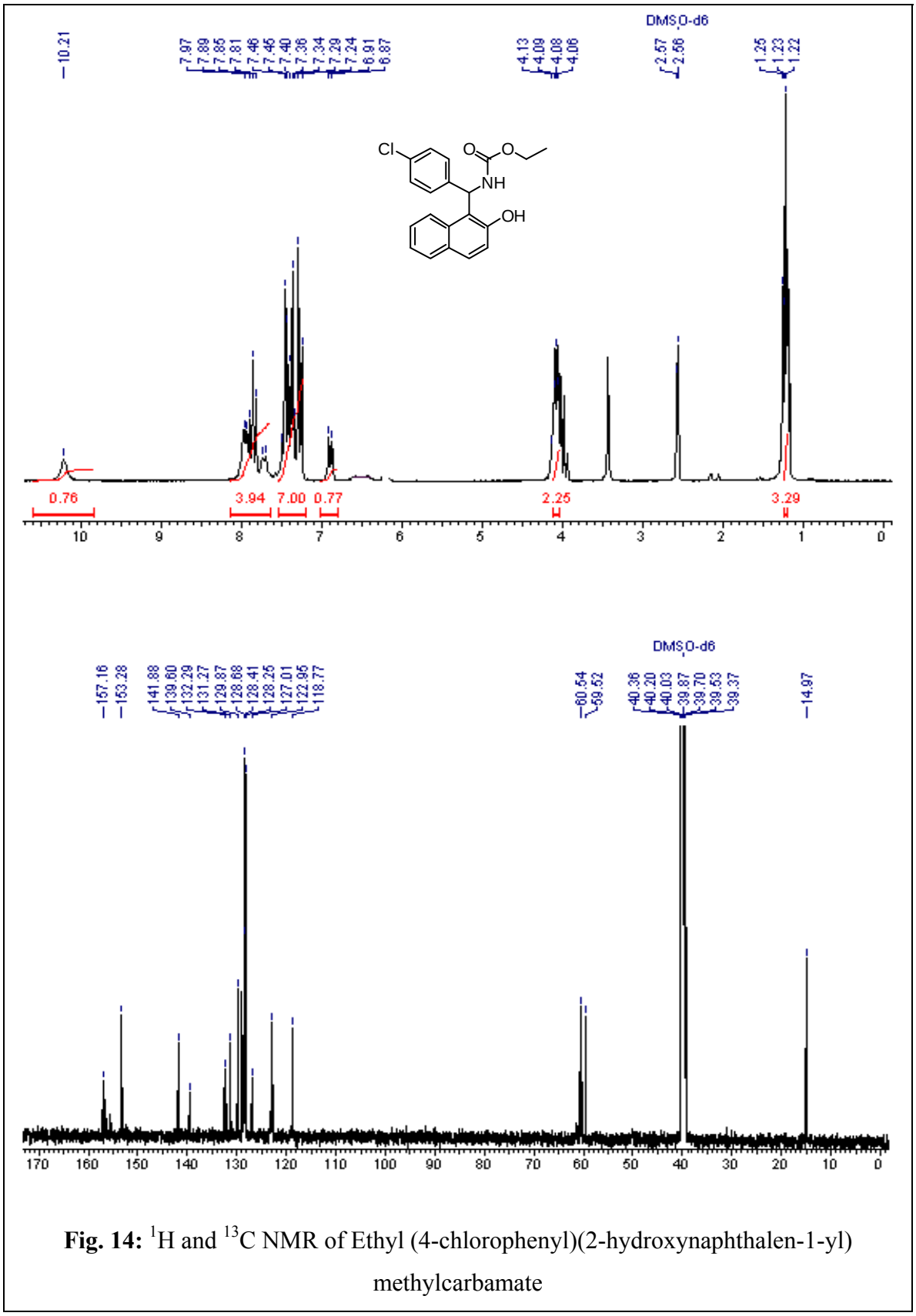


Fig. 14: ^{1}H and ^{13}C NMR of Ethyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl) methylcarbamate

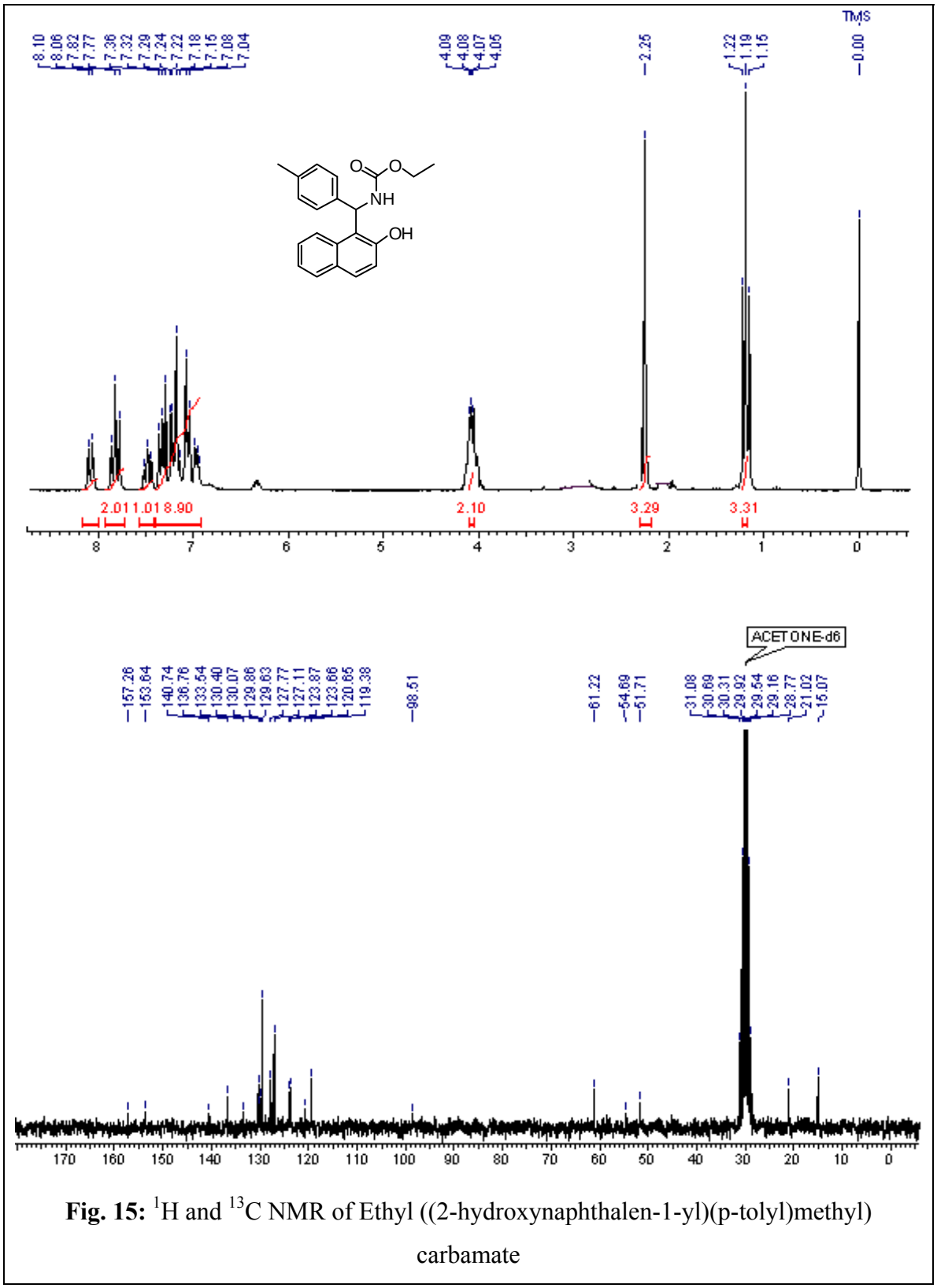


Fig. 15: ^{1}H and ^{13}C NMR of Ethyl ((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl) carbamate

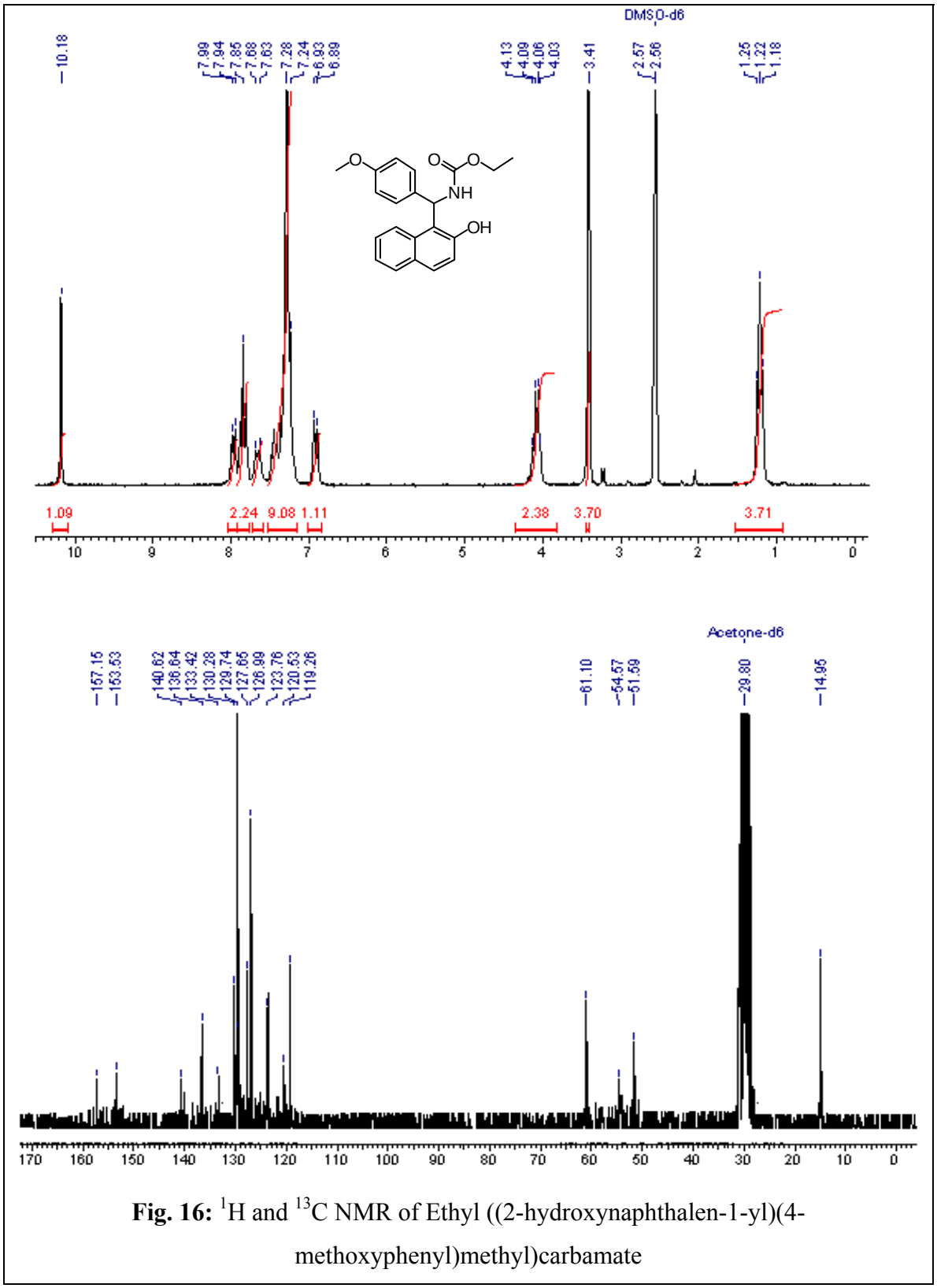


Fig. 16: ^{1}H and ^{13}C NMR of Ethyl ((2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl)carbamate

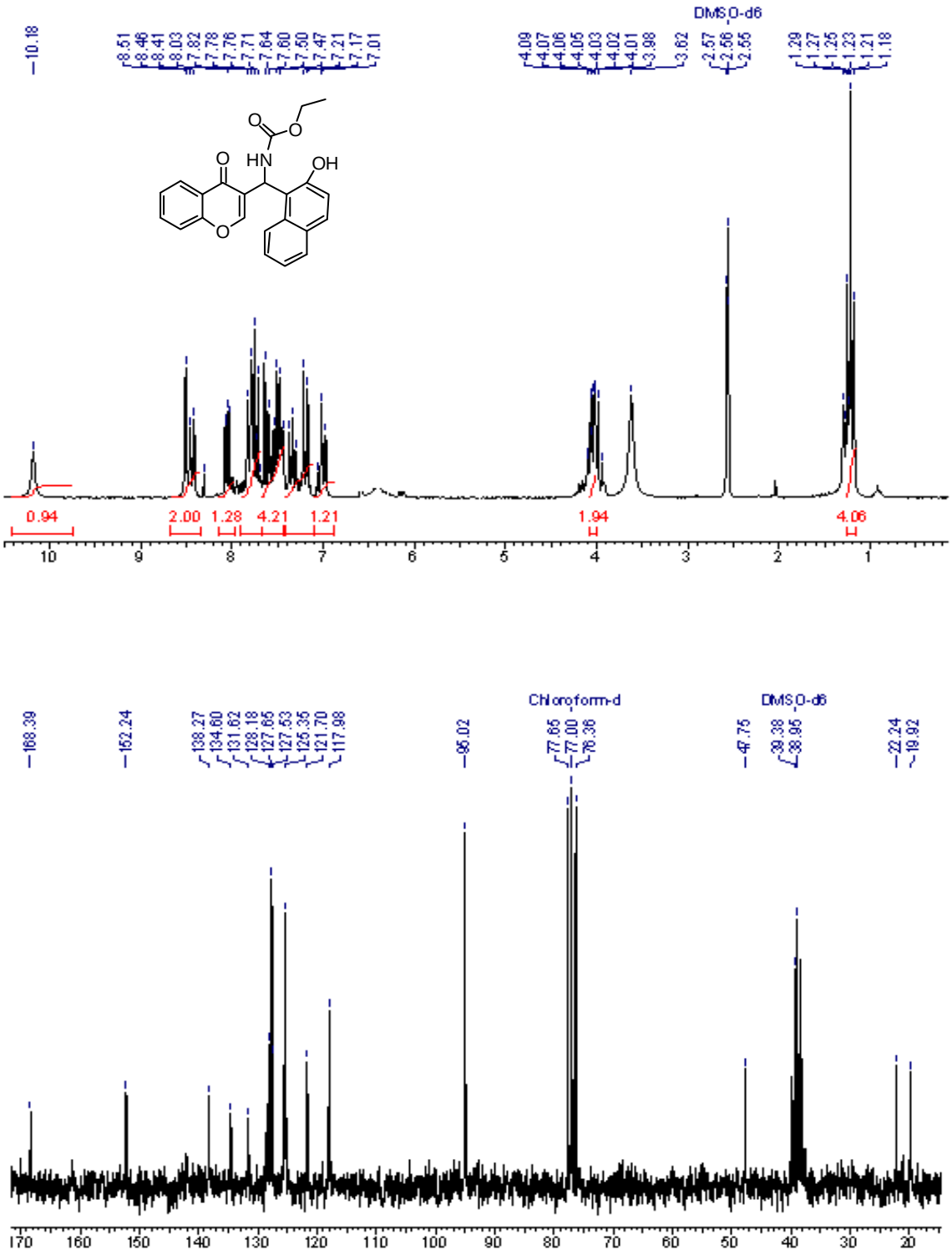


Fig. 17: ^{1}H and ^{13}C NMR of Ethyl(2-hydroxynaphthalen-1-yl)(4-oxo-4H-chromen-3-yl) methylcarbamate

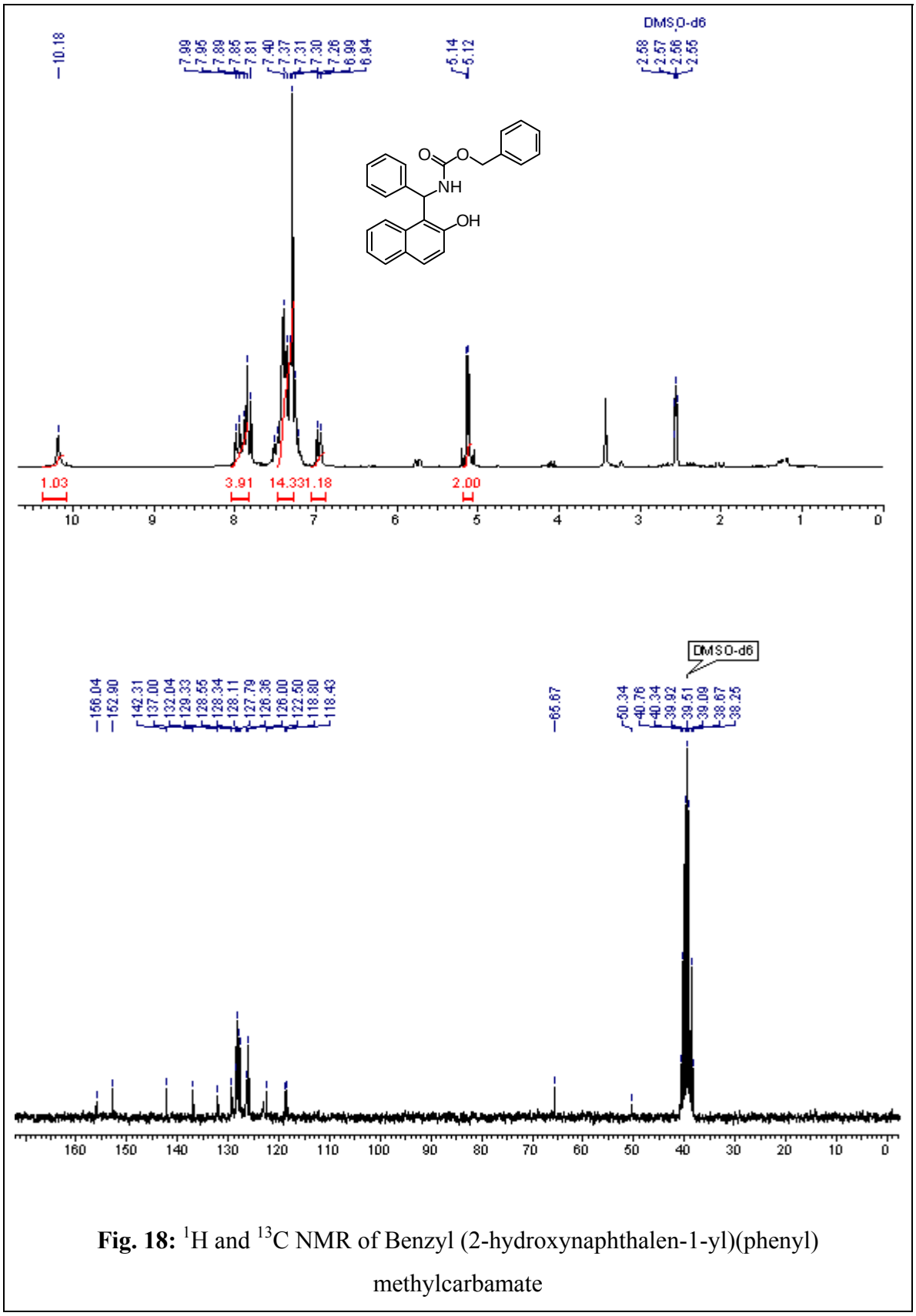


Fig. 18: ^{1}H and ^{13}C NMR of Benzyl (2-hydroxynaphthalen-1-yl)(phenyl) methylcarbamate

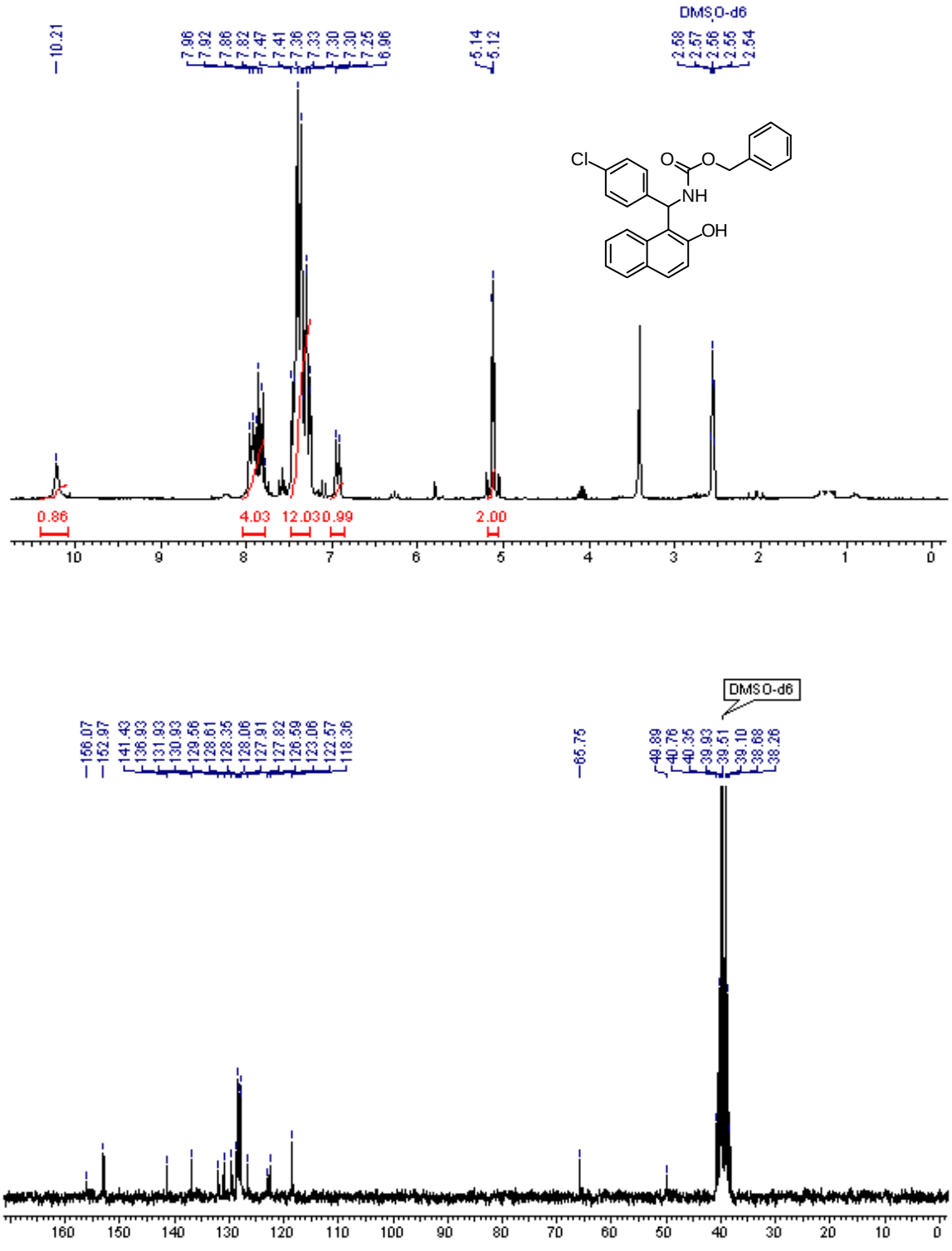


Fig. 19: ^{1}H and ^{13}C NMR of Benzyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl) methylcarbamate

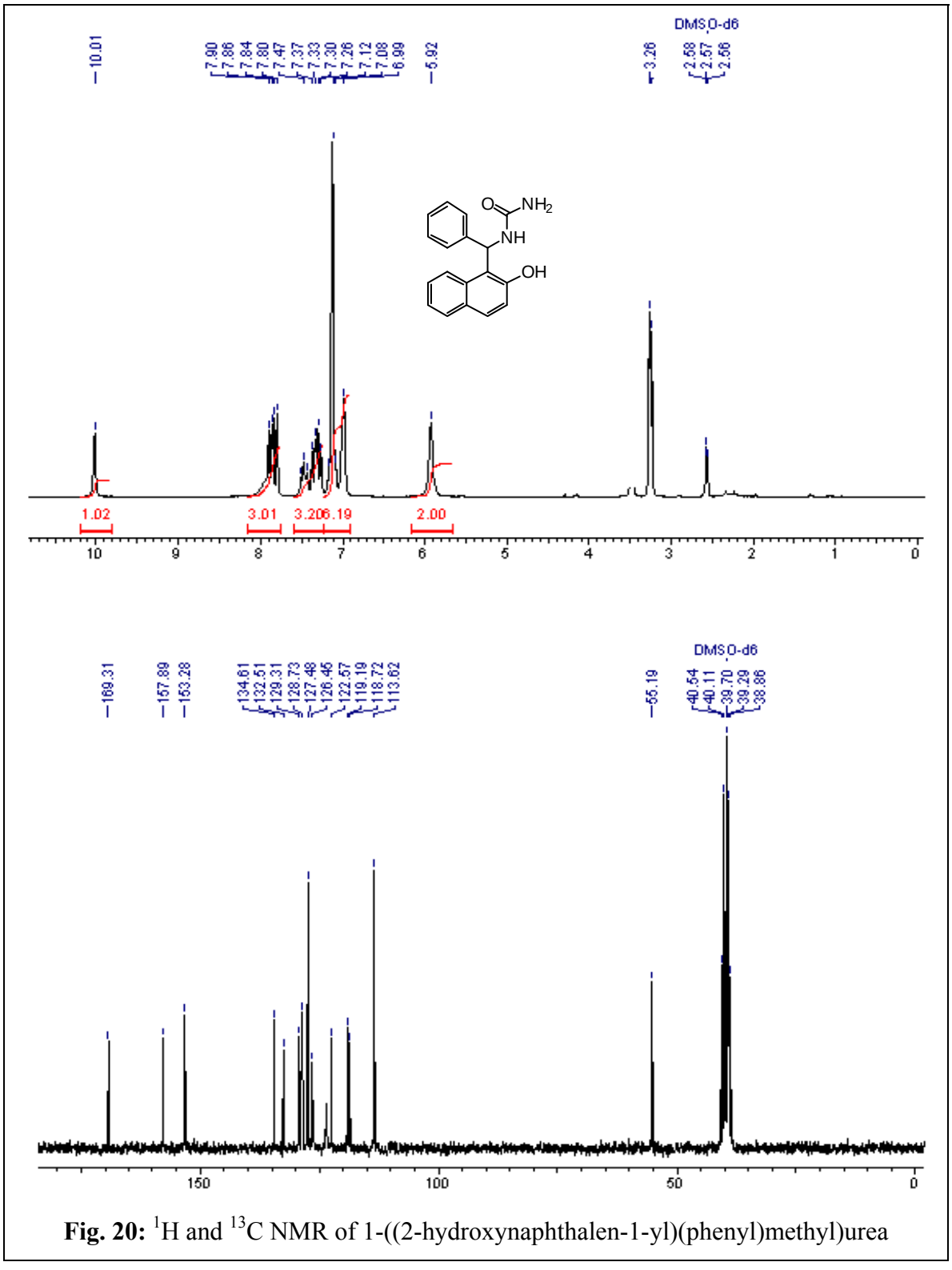


Fig. 20: ^{1}H and ^{13}C NMR of 1-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)urea

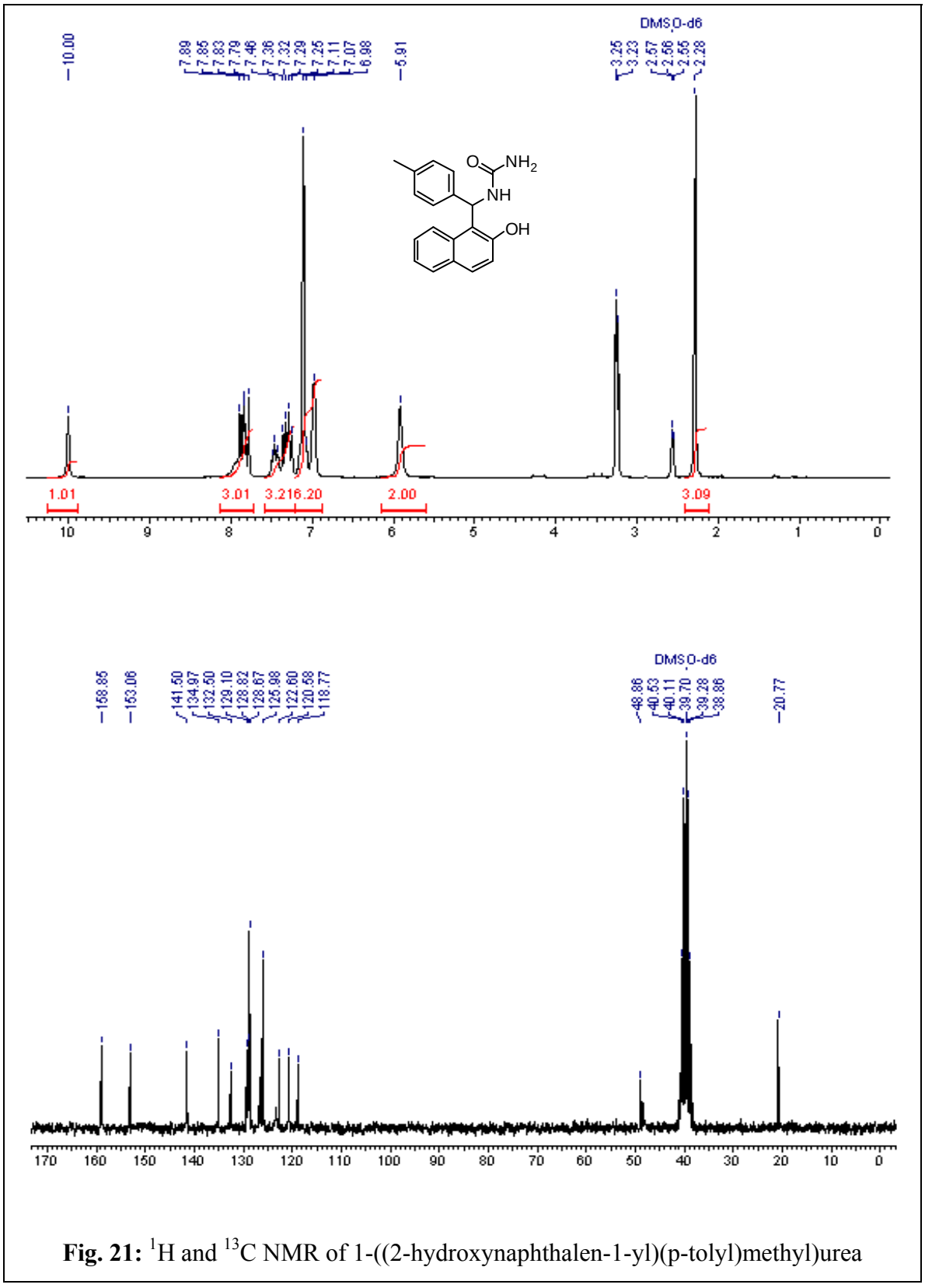


Fig. 21: ^{1}H and ^{13}C NMR of 1-((2-hydroxynaphthalen-1-yl)(p-tolyl)methyl)urea

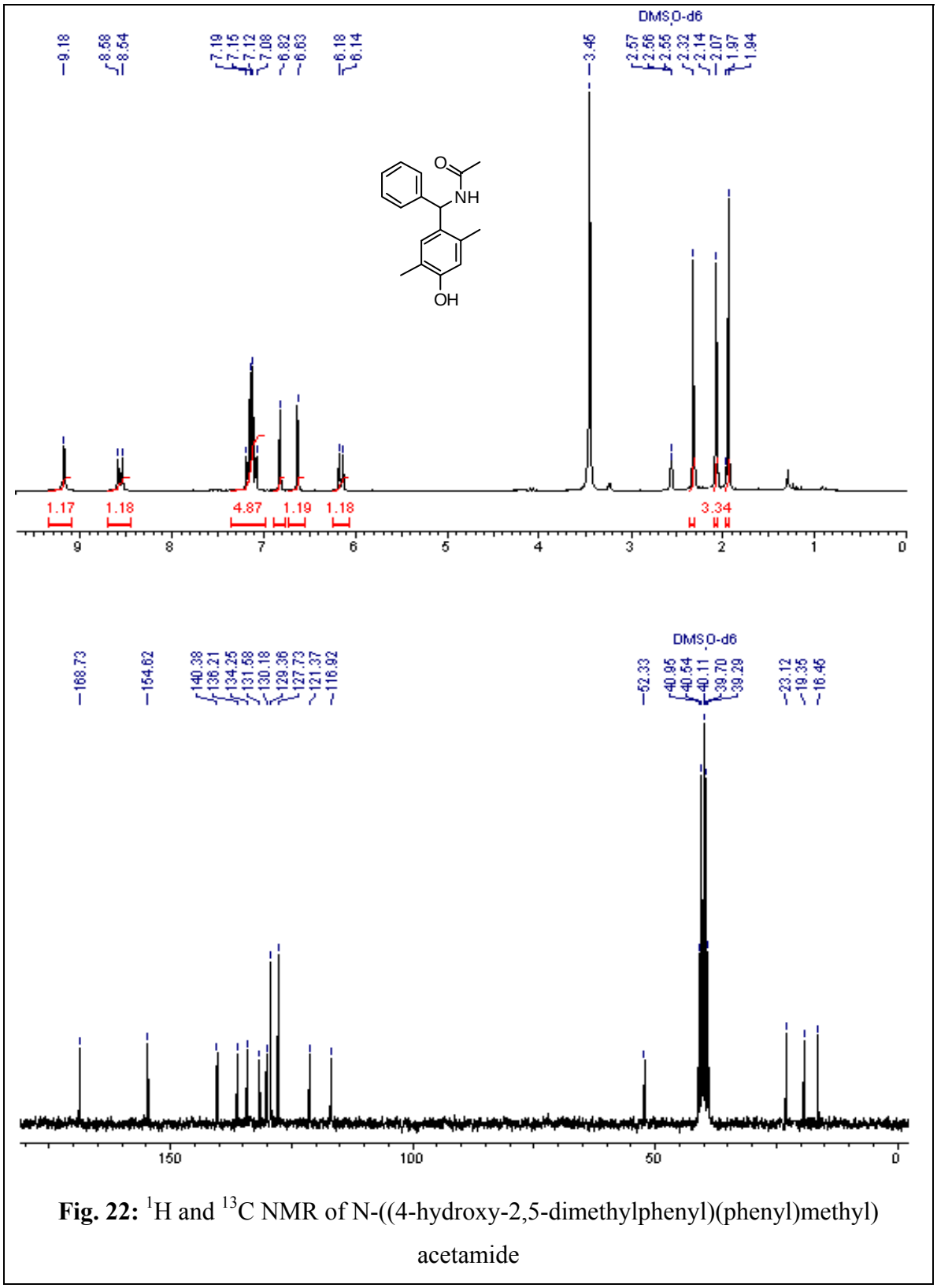


Fig. 22: ^{1}H and ^{13}C NMR of N-((4-hydroxy-2,5-dimethylphenyl)(phenyl)methyl) acetamide

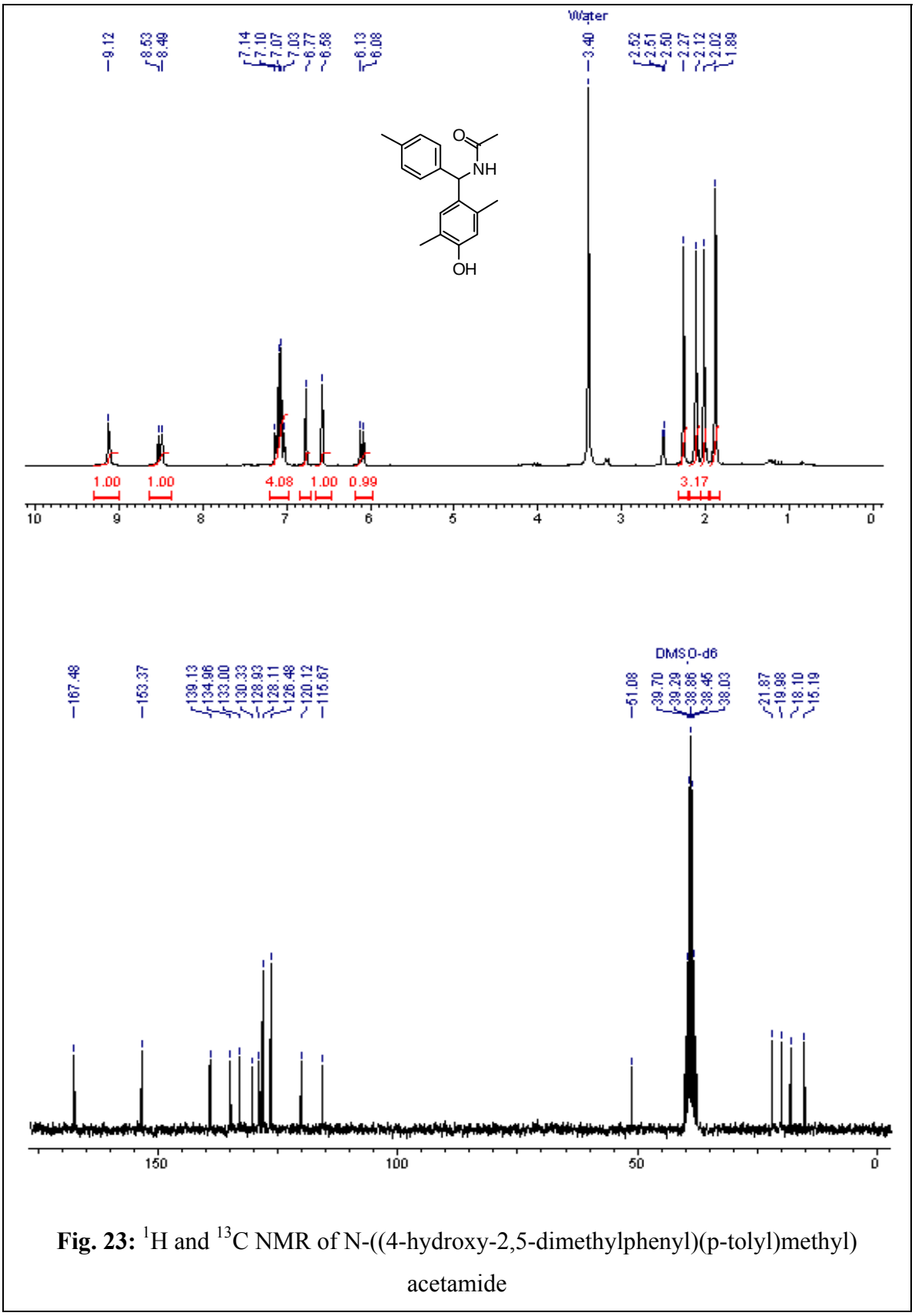


Fig. 23: ^{1}H and ^{13}C NMR of N-((4-hydroxy-2,5-dimethylphenyl)(p-tolyl)methyl) acetamide

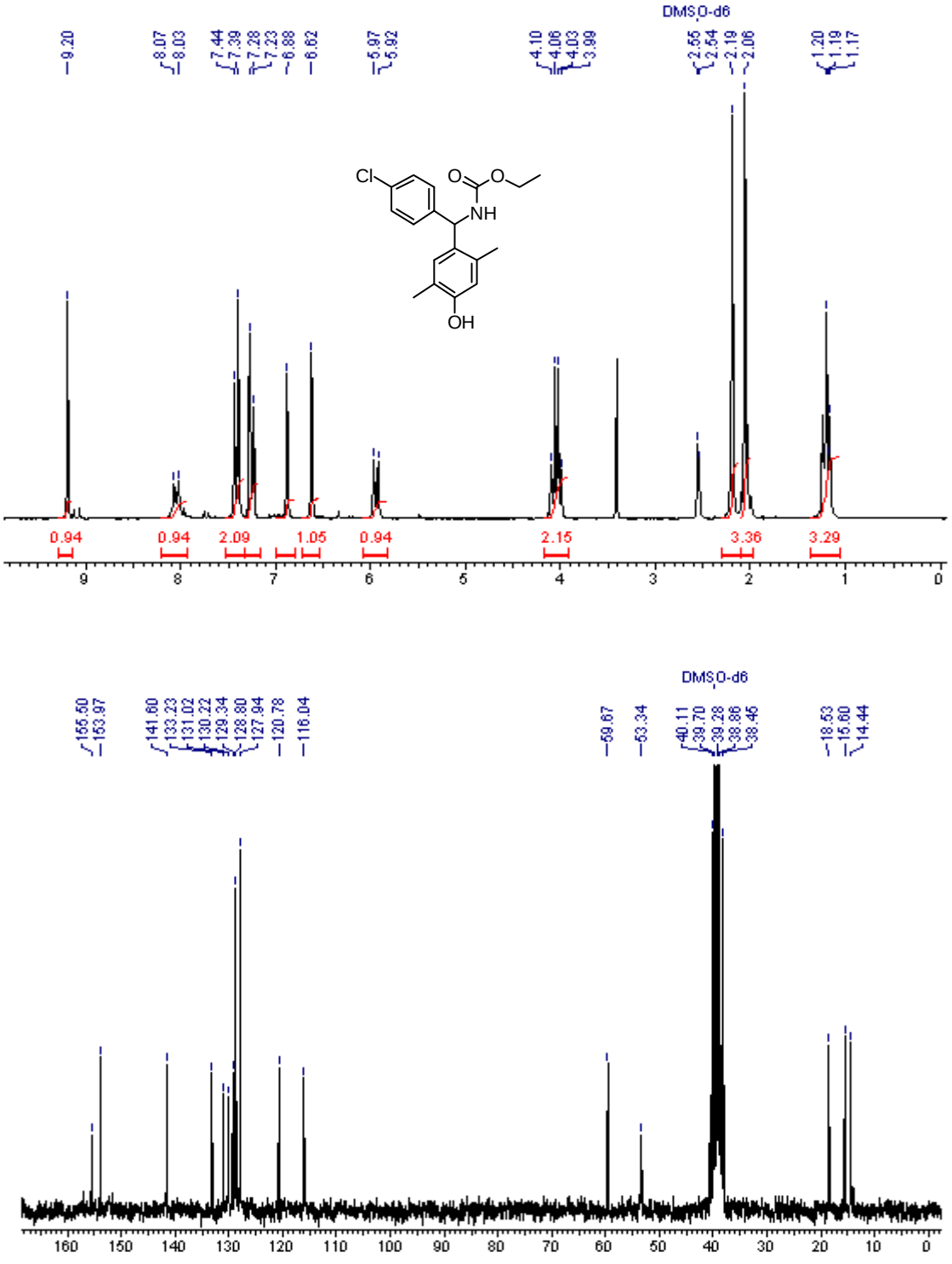


Fig. 24: ^{1}H and ^{13}C NMR of Ethyl (4-chlorophenyl)(4-hydroxy-2,5-dimethylphenyl) methylcarbamate

Section-II

Efficient, rapid synthesis of bis(indolyl)methane using ethyl ammonium nitrate as an ionic liquid

4.2.1 Introduction

Several bis(indolyl)alkanes and their derivatives have been isolated from plant and marine sources.[26] Among the various derivatives of indoles, bis(indolyl)methanes have wide medicinal applications such as to induce apoptosis in human cancer cell and normalize abnormal cell growth associated with cervical dysplasia,[27] to promote beneficial estrogen metabolism in both women and men, to prevent the breast cancer[28] and also to increase the natural metabolism of body's hormones.[29] Due to vast biological activity of bis(indolyl)methanes and their wide medicinal applications, various methods of their synthesis have been reported in the literature. However, almost all the methods have employed conventional Lewis acids as well as protic acids as catalysts to promote electrophilic substitution reaction of indoles with various aldehydes or carbonyl compounds.[30] A variety of other catalysts such as H-Y zeolite,[31] sulphamic acid,[32] $In(OTf)_3$,[33] $LiClO_4$,[34] bis(cyclopentadienyl)$ZrCl_2$,[35] $CuBr_2$,[36] $ZrCl_4$,[37] $Zn(HSO_4)_2$,[38] polyindole salt,[39] CAN,[40] N-tert-butanesulfinyl aldimines,[41] ion exchange resin,[42] acetic acid,[43] $InCl_3$,[44] InF_3,[45] $Dy(OTf)_3$,[46] $Ln(OTf)_3$,[47] $FeCl_3.6H_2O$,[48] $V(HSO_4)_3$,[49] SBA-15/SO_3H,[50] oxalic acid,[51] TBBDA,[52] silica bonded S-sulfonic acid,[53] $Bi(NO_3)_3$,[54] $Cu(BF_4)_2.SiO_2$,[55] vanadomolybdophosphoric acid,[56] Ph-PMO-SO_3H,[57] glycerin and $CeCl_3$,[58] $B(C_6F_5)_3$,[59] $H_6P_2W_{18}O_{62}$,[60] phosphated zirconia,[61] Ph_3CCl,[62] have been reported for synthesis of bis(indolyl)methanes. However, these methods suffer from drawbacks, such as toxic metal ions, expensive solvents, long reaction times, tedious work-up, low

product yields, higher catalyst loading and formation of large amounts of wastes.[63-65]

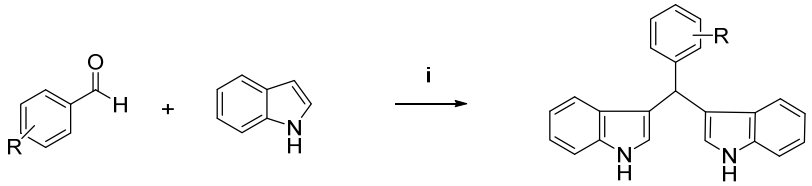
Due to unique properties of ionic liquids as described in section I, their application for the synthesis of heterocyclic compounds.[66] and the synthesis of bis(indolyl)methane using [bmim]BF_4,[67] [bmim]PF_6,[67] [acmim]Cl, [hmim]HSO_4[68] and TMGT,[69] at room temperature have been reported in the literature.

4.2.2 Review of literature

Literature survey revels that, there are several methods available for the synthesis of bis(indolyl)methanes from the reaction of indoles with a variety of aldehydes in the presence of the various catalyst and solvent at different reaction conditions, however, few of them are described below.

Dubey approach[50]

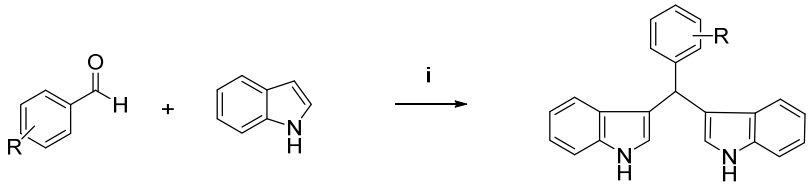
In this approach, Amit Dubey *et al.* have treated various aromatic aldehydes with indole in the presence of SBA-15/SO_3H catalyst at 60 ^oC in a carbon tetrachloride solvent for 24 h (**Scheme 10**).



Scheme 10: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), indole (2 mmol), SBA-15/SO_3H (100 mg), CCl_4, 60 ^oC, 24 h.

Niknam approach[53]

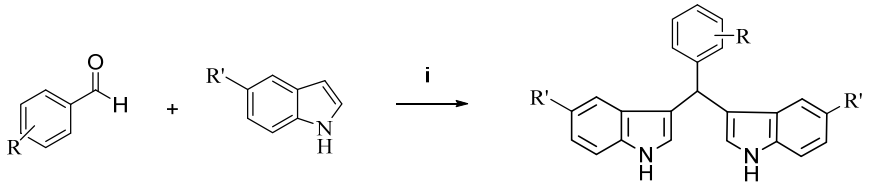
In this approach, Niknam *et al.* have treated various aromatic aldehydes with indole in the presence of silica bonded S-sulfonic acid (SBSSA) as a catalyst in an acetonitrile solvent at room temperature (**Scheme 11**).



Scheme 11: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), indole (2 mmol), SBSSA (100 mg), CH_3CN, RT.

Heravi approach[60]

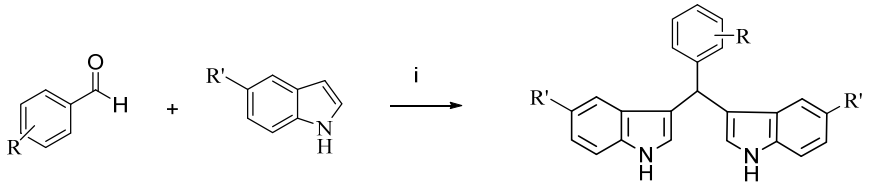
In this approach, Heravi *et al.* have treated various aromatic aldehydes with various indoles in the presence of diphosphooctadecatungstic acid ($H_6P_2W_{18}O_{62}$) as a catalyst at 110 ^oC under neat reaction conditions (**Scheme 12**).



Scheme 12: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), indole (2 mmol), $H_6P_2W_{18}O_{62}$ (0.7 mol %), 110 ^oC.

Hagiwara approach[69]

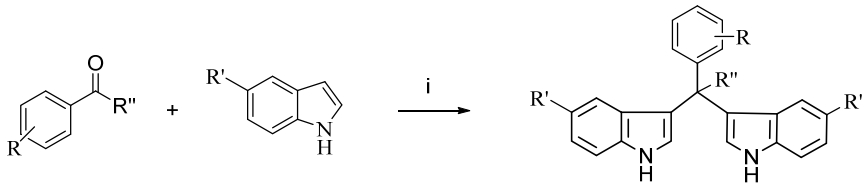
In this approach, Hagiwara *et al.* have treated various aromatic aldehydes with various indoles in the presence of acidic ionic liquid immobilized on silica (ILIS) as a catalyst at room temperature in an acetonitrile solvent (**Scheme 13**).



Scheme 13: *Reagents and reaction conditions*: (i) Aldehyde (0.3 mmol), indole (0.5 mmol), ILIS (0.05 mmol), MeCN (3 mL), RT.

Yadav's approach[66]

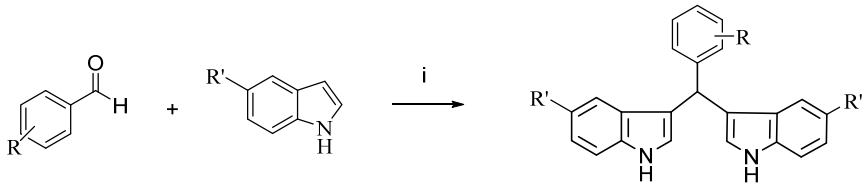
In this approach, Yadav *et al.* have treated various aromatic aldehydes/ketones with various indoles in the presence of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquid as a catalyst as well as reaction medium at room temperature for 3-5 h (**Scheme 14**).



Scheme 14: *Reagents and reaction conditions*: (i) Aldehyde (1 mmol), indole (2 mmol), [bmim]BF_4 or [bmim]PF_6 (3 mL), RT, 3-5 h.

Teck-Peng Loh approach[48]

In this approach, Teck-Peng Loh *et al.* have treated various aromatic aldehydes with various indoles in the presence of $FeCl_3.6H_2O$ as a catalyst at room temperature in a 1-methyl-3-octylimidazolium hexafluorophosphate ([omim]PF_6) ionic liquid as a solvent (**Scheme 15**).

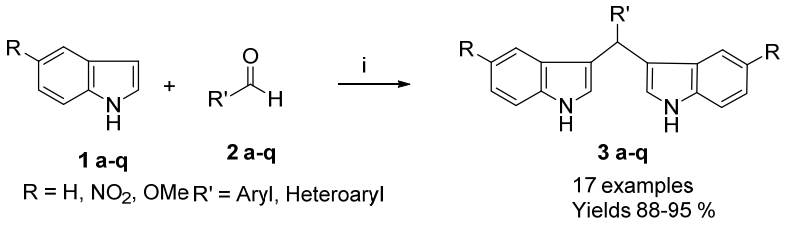


Scheme 15: *Reagents and reaction conditions*: (i) Aldehyde (0.25 mmol), indole (0.5 mmol), $FeCl_3.6H_2O$ (5 mol%), [omim]PF_6 (0.5 mL), RT.

4.2.3 Present Work

4.2.3.1 Objectives

All these methods reported in the literatures suffer certain disadvantages such as very long reaction times and lower product yields as well as use of toxic metal ions, expensive solvents, tedious work-up, higher catalyst loading and formation of large amounts of wastes. Due to wide medicinal application of bis(indolyl)methanes in life sciences, the development of more general and cost effective, an elegant, rapid and efficient protocol for the synthesis of bis(indolyl)methanes is still challenging and an active research area. As part of our continuous efforts to explore the possibility to develop green, and economical viable protocol for organic transformation, this section describes the use of ethyl ammonium nitrate $[C_2H_5NH_3]NO_3$ as a media as well as catalyst in the electrophilic substitution of indoles with a variety of aldehydes to provide bis(indolyl)methanes at ambient conditions (**Scheme 16**).



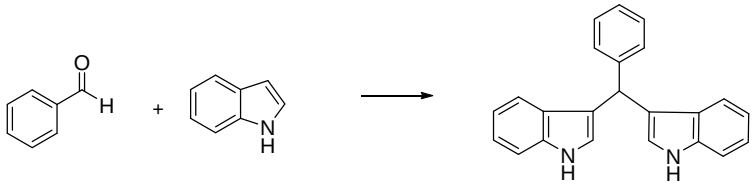
Scheme 16: *Reagents and reaction conditions*: (i) Indole (2 mmol), Aldehyde (1 mmol), Ethylammonium nitrate (EAN) (2 mmol) at 25 ^oC for 1-12 min.

4.2.4 Results and discussion

Using indole and benzaldehyde as test substrates, the reaction parameters were optimized to determine the optimal condition for the synthesis of bis(indolyl)methanes and results are shown in **Table 4**. When Indole (2 mmol) was treated with benzaldehyde (1 mmol)

for 5 h in ethylammonium nitrate (EAN) (0.2 mmol) as an ionic liquid without solvent at 25 °C, the corresponding bis(indolyl)methane (**3a**) was obtained in 30 % yield (**Table 4**, entry **2**). When we carried out the same reaction in absence of EAN no reaction took place even at higher temperature (85 °C) (**Table 4**, entry **1**); however the yield and reaction time could be significantly improved to 60 % yield in 1.5 h when 0.8 mmol of EAN was used (**Table 4**, entry **5**). Interestingly, increasing the molar ratio of EAN (2 mmol) resulted in a dramatic improvement in the yield of **3a** (95 %) in 3 min (**Table 4**, entry **7**).

Table 4: Influence of ethyl ammonium nitrate for the reaction of benzaldehyde and indole[a]



Entry	Ethyl ammonium Nitrate (mmol)	Reaction Time (min)	Yield (%)[b]
1	0	300	0
2	0.2	300	30
3	0.4	300	45
4	0.6	210	50
5	0.8	90	60
6	1.0	10	90
7	2.0	03	95

[a] Reaction conditions: Indole (2 mmol), Benzaldehyde (1 mmol), Ethylammonium nitrate at 25 °C.

[b]Isolated yields after chromatographic purification.

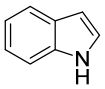
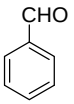
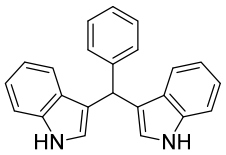
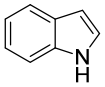
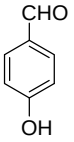
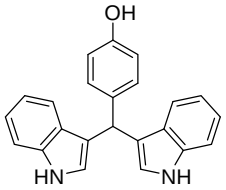
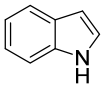
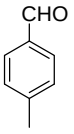
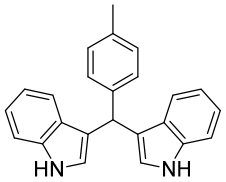
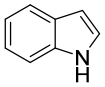
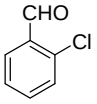
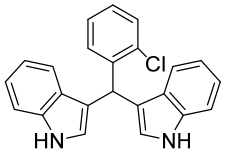
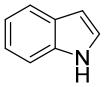
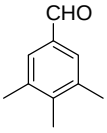
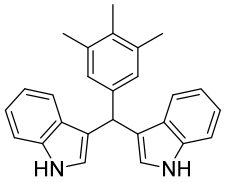
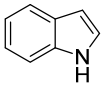
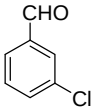
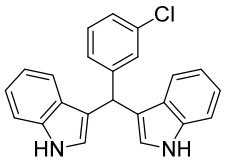
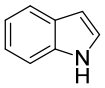
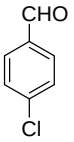
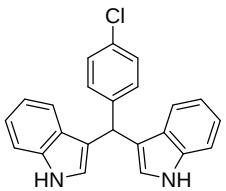
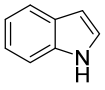
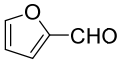
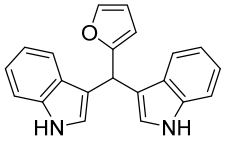
In general, higher EAN concentration (2 mmol) gave better yields in shorter time. These results clearly indicate that the EAN acts as catalyst as well as a green reaction media. To

gauze the scope of this methodology, a variety of substituted aldehydes (**2a-q**) were reacted with indoles (**1a-q**) in the presence of 2 mmol of EAN at 25 °C to produce the corresponding bis(indolyl)methanes and results are shown in **Table 5**.

The nature of substitution on the aromatic ring showed some effect on product yields and reactions times. Aromatic aldehydes with electron-withdrawing groups at *o*- and *p*-positions, provided products in excellent yields with shorter reactions time (**Table 5**, entry **d**, **g** and **i**), the reaction is extremely fast often completing in < 3 min. However, in case of the 3-chlorobenzaldehyde, a low yield of the corresponding product was obtained in longer reaction time (**Table 5**, entry **f**). Substrates with electron-donating groups took longer time with moderate yields (**Table 5**, entry **b**, **c** and **e**). In the case of 3,4,5-trimethylbenzaldehyde, rate of reaction is found to be very slow, due to presence of three electron donating methyl groups (**Table 5**, entry **e**). Also, similar effect is observed in case of 5-methoxy indole with 4-methyl and 4-methoxy benzaldehyde (**Table 5**, entry **p** and **q**). This clearly indicates that the position and nature of the substitutions on aromatic ring play a key role on the rate of reaction. Heterocyclic aldehydes reacted smoothly with indole to give the corresponding product in excellent yield (**Table 5**, entry **h** and **j**). Furthermore aliphatic aldehydes also react smoothly with the indole to give the corresponding products in good yields (**Table 5**, entry **k** and **l**).

To further elaborate the scope of this protocol with substituted indole, a reaction of 5-nitro indole and 5-methoxy indole was carried out with different aromatics as well as aliphatic aldehyde, which provided the corresponding bis(indolyl)methanes in good to moderate yields (**Table 5**, entries **m**-**q**).

Table 5: EAN mediated synthesis of bis(indole) methane at 25 $^{o}C^{a}$

Entry	Indole (**1**)	Aldehyde (**2**)	Product (**3**)	Time (min)	Yield (%)[b]
a				03	95
b				05	92
c				08	91
d				03	92
e				10	90
f				10	88
g				01	95
h				03	92

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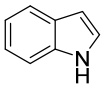
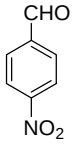
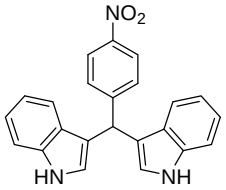
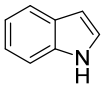
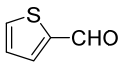
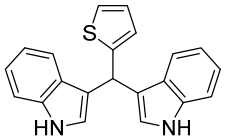
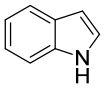
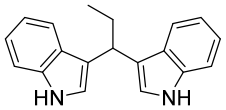
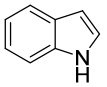
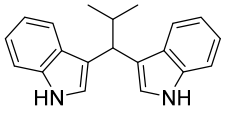
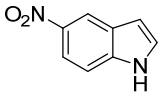
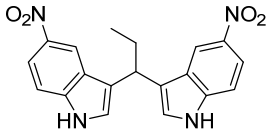
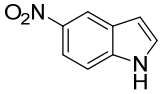
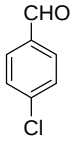
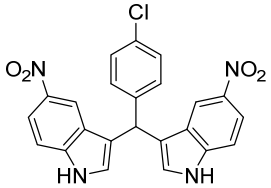
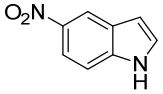
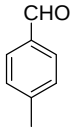
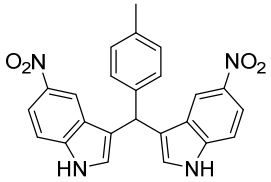
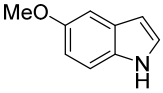
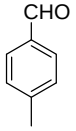
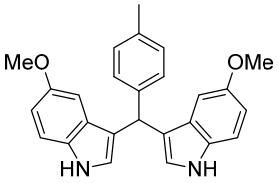
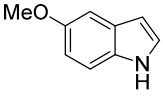
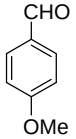
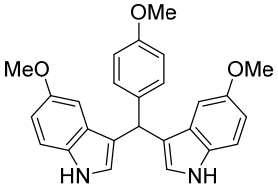
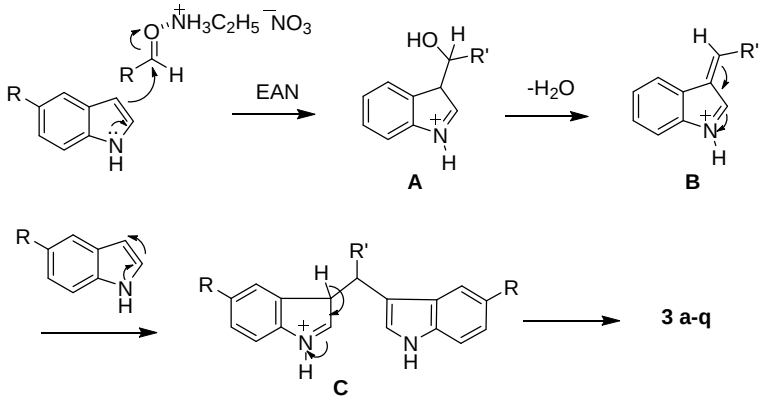
i				01	95
j				04	93
k				02	93
l				02	89
m				08	87
n				08	86
o				05	94
p				11	87
q				12	83

[a] Reaction conditions: Indole (2 mmol), Aldehyde (1 mmol), Ethylammonium nitrate (2 mmol) at 25 °C.

[b] Isolated yields after chromatographic purification.

A probable mechanism is shown in **Scheme 17** for synthesis of bis(indolyl) methanes. The mechanism involves activation of the carbonyl group by EAN followed by nucleophilic addition of indole to aldehyde proceeds to afford the intermediate **A**. The subsequent dehydration of **A** gave **B** which on nucleophilic addition of another mole of indole gave **C,** followed by aromatization to give the product **3a-q** (**Scheme 17**).



Scheme 17: Plausible reaction mechanism for synthesis of bis(indolyl) methane over EAN

Recyclability of Ethyl ammoniumnitrate

The EAN was recovered from aqueous layer by removal of water at 70 ^{o}C under reduced pressure and recycled several times with almost no loss of activity and results are shown in **Table 6,** Run**1**-**4**.

Table 6: Recoverability and reusability of ethyl ammonium nitrate[a]

No. of cycles	Fresh	Run 1	Run 2	Run 3	Run 4
Yield (%)[b]	95	95	94	94	93
EAN (%)Recovery	>98	>97	>96	>96	>95

[a] Reaction conditions: Indole (2 mmol), Benzaldehyde (1 mmol), Ethylammonium nitrate (2 mmol) at 25 ^{o}C.

[b]Isolated yields after chromatographic purification.

The efficacy of EAN for the synthesis of bis(indolyl)methanes as compared to other acid catalysts and ionic liquids (ILs) reported in the literature can be understood from the results shown in **Table 7**.

The high rate can be rationalized due to high acidity associated with it (pH=5) coupled with its ability to absorb water formed during the reaction in the synthesis of bis(indolyl)methanes.

Table 7: Comparison between EAN and acid catalysts/ionic liquid used in synthesis of bis(indolyl)methanes.

Sr. No.	Reaction Condition	Time	Catalyst	Yield (%)[Reff.]
1	EAN, RT	03 min	EAN	95
2	Ionic liquid , 1 mL , RT	15 min	TMGT	93[69]
3	Microwave oven, 450 W	05 min	[bmim] [HSO_4]	93[68]
4	Acetonitrile 3 mL, RT	5.5 h	Acidic Ionic Liquid Immobilized on Silica (ILIS)	97[70]
5	Ionic liquid 1 mL, RT	1.5 h	$FeCl_3 \cdot 6H_2O$	98[48]
6	[bmim]BF_4 or [bmim]PF_6 2 mL, RT	4.5 h		87[67]
7	Ionic liquid 1 mL, RT	15 min	$In(OTf)_3$	90[33]

4.2.5 Conclusion

In conclusion, this section describes EAN mediated an efficient, rapid synthesis of bis(indolyl) methane from indoles and aldehydes in excellent yields at room temperature in shorter reaction time. Novel EAN acts as catalyst and green media for the reaction, making this method cheaper, simple, convenient, and environmentally friendly process for the synthesis of substituted bis(indolyl)methanes.

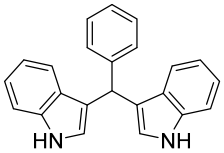
4.2.6 Experimental Section

4.2.6.1 A typical procedure for the synthesis of bis(indolyl)methane using EAN

A mixture of indole (2 mmol), benzaldehyde (1 mmol) and EAN (2 mmol) was stirred at room temperature. The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted by water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum to get crude product**.** The crude product was purified by column chromatography. All the isolated reaction products were characterized and confirmed by NMR.

4.2.6.2 Spectral data

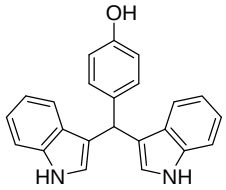
3,3'-(phenylmethylene)bis(1H-indole)



Yield: 95 %; Red solid; mp: 124-126 ^{o}C (lit.[36] 123-125 ^{o}C) **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 5.60 (s, 1H), 6.67 (s, 2H), 7.04 (t, 2H), 7.18-7.27 (m, 3H), 7.29-7.32 (m, 2H), 7.35-7.46 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 41.1, 110.4, 119.8, 120.1, 121.5, 123.8, 126.5,

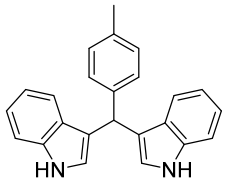
127.1, 128.6, 136.4, 144.4.

4-(di(1 H-indol-3-yl)methyl)phenol



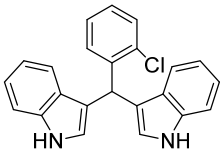
Yield: 92 %; white solid; mp: 222-224 °C (lit.[36] 124-125 °C); **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 4.67 (brs, 1H), 5.82 (s, 1H), 6.64 (s, 2H), 6.74-6.99 (m, 4H), 7.14-7.23 (m, 4H), 7.38 (t, *J*=9.2 Hz, 4H), 7.93 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 59.9, 110.6, 114.2, 117.8, 118.9, 119.2, 120.8, 123.1, 126.6, 128.7, 134.5, 136.4, 154.4.

3, 3‘-(p-tolylmethylene)bis(1H-indole)



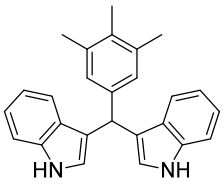
Yield: 91 %; Yellow solid; mp: 98-100 °C (lit.[36] 96-98 °C); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 5.86 (s, 1H), 6.73 (d, *J*=2.5 Hz, 2H), 7.05 (t, *J*=8.1 Hz, 2H), 7.13 (d, *J*=8.0 Hz, 2H), 7.30-7.42 (m, 6H), 7.46 (d, *J*=8.1 Hz, 2H), 7.89 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.91, 47.67, 55.19, 113.62, 118.72, 119.19, 122.57, 123.54, 126.45, 127.48, 128.68, 128.73, 129.31, 132.51, 134.61, 153.28.

3,3’-((2-chlorophenyl)methylene)bis(1H-indole)



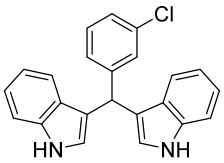
Yield: 92 %; Pinck solid; mp: 71-73 °C (lit.[36] 72-74 °C); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.51 (s, 1H), 6.62 (s, 2H), 7.03 (t, 2H), 7.2-7.6 (m, 11H), 7.89 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.4, 111.9, 120.5, 122.1, 123.8, 127.0, 128.3, 130.4, 131.5, 137.1, 142.5.

3,3'-((3,4,5-trimethylphenyl)methylene)bis(1H-indole)



Yield: 90 %; White solid, mp: 223-225 °C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.46 (s, 6H), 5.81 (s, 1H), 6.73 (d, *J*=2.5 Hz, 2H), 7.02-7.13 (m, 6H), 7.30-7.42 (m, 2H), 7.41 (d, *J*=8.1 Hz, 2H), 7.89 (s, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 39.4, 43.66, 106.26, 110.56, 116.77, 118.60, 122.57, 126.45, 128.55, 128.69, 129.62, 132.61, 141.87.

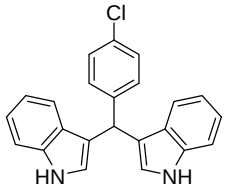
3,3'-((3-chlorophenyl)methylene)bis(1H-indole)



Yield: 88 %; Brown solid, mp: 218-220 °C; **^{1}H NMR** (200 MHz, DMSO-d6): δ 5.87 (s, 1H), 6.49 (s, 2H), 6.88 (t, *J*=7.8 Hz, 2H), 7.26 (t, *J*=7.8 Hz, 2H), 7.30-7.41 (m, 8H), 8.13

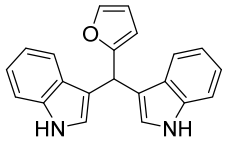
(br, s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.6, 111.6, 120.1, 122.4, 123.5, 127.2, 128.6, 130.1, 131.8, 136.9, 142.

3,3‘-((4-chlorophenyl)methylene)bis(1H-indole)



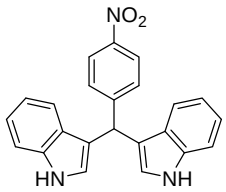
Yield: 95 %; Pink solid, mp: 78-80 ^{o}C (lit.[36] 76-77 ^{o}C); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.89 (s, 1H), 6.53 (s, 2H), 6.98 (t, *J*=7.8 Hz, 2H), 7.24 (t, *J*=7.8 Hz, 2H), 7.30-7.41 (m, 8H), 8.23 (br, s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.6, 111.6, 120.1, 122.4, 123.5, 127.2, 128.6, 130.1, 131.8, 136.9, 142.

3,3’-(furan-2-ylmethylene)bis(1H-indole)



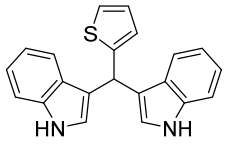
Yield: 92 %; Black solid; mp: 321-322 °C (lit.[36] 320-323 ^{o}C); **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 5.83 (s, 1H), 5.96 (d, *J*=3.4 Hz, 1H), 6.32 (d, *J*=2.2 Hz, 1H), 6.76 (d, *J*=2.4 Hz, 1H), 7.02 (t, 2H), 7.15 (t, 2H), 7.23-7.45 (m, 5H), 8.65 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 35.1, 107.2, 109.5, 111.1, 117.6, 119.4, 122.1, 124.1, 126.5, 136.5, 141.0.

3,3’-((4-nitrophenyl)methylene)bis(1H-indole)



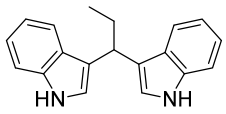
Yield: 95 %; Brown solid; mp: 220-222 °C (lit.[36] 221-223 °C); **^{1}H NMR** (200 MHz, $CDCl_3$+DMSO-d_6): δ 5.96 (s, 1H), 6.78 (d, *J*=2.4 Hz, 2H), 6.9 (t, 2H), 7.1 (t, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 7.38 (d, *J*=8.1 Hz, 2H), 7.56 (d, *J*=8.1 Hz, 2H), 8.10 (d, *J*=8.1 Hz, 2H), 10.41 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 49.32, 118.71, 122.72, 126.33, 126.84, 128.53, 130.94, 152.73.

3,3'-(thiophen-2-ylmethylene)bis(1H-indole)



Yield: 93 %; Red solid; mp: 189-191 °C (lit.[30b] 188-190 °C); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.17 (s, 1H), 6.84 (s, 2H), 6.91-6.97 (m, 2H), 7.08 (t, *J*=7.5 Hz, 2H), 7.16 (d, *J*=5.1 Hz, 1H), 7.14 (t, *J*=7.5 Hz, 2H), 7.31 (t, *J*=8 Hz, 2H), 7.49 (d, *J*=8 Hz, 2H), 8.02 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.8, 111.7, 119.4, 120.36, 122.1, 123.8, 124.1, 125.8, 126.4, 127.3, 136.5, 149.2.

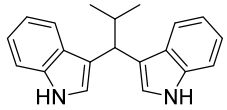
3,3'-(propane-1, 1-diyl)bis(1H-indole)



Yield: 93 %; Brown gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.08 (t, *J*=7.2 Hz, 3H), 2.26-2.31(m, 2H), 4.45 (t, *J*=7.2 Hz, 1H), 6.93 (s, 2H), 7.08 (t, *J*=7.3 Hz, 2H), 7.20-7.37 (m,

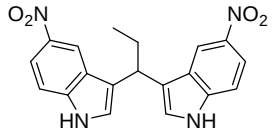
4H), 7.63 (d, *J*=7.8 Hz, 2H), 7.89 (s, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 13.2, 28.7, 36.3, 111.1, 119.4, 119.8, 120.4, 121.6, 121.9, 127.5, 136.7.

3,3‘-(2-methylpropane-1, 1-diyl)bis(1H-indole)



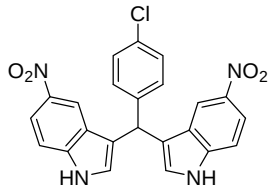
Yield: 89 %; White solid, mp: 66-68 ^{o}C; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.01 (d, *J* = 6.6 Hz, 6H,), 2.61-2.68 (m, 1H), 4.24 (d, *J* = 8.1 Hz, 1H,), 6.99-7.13 (m, 6H), 7.25-7.29 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 2H,), 7.85 (s, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 21.8, 32.9, 41.1, 111.1, 118.9, 119.3, 119.5, 121.4, 121.7, 127.4, 136.0.

3,3’-(propane-1, 1-diyl)bis(5-nitro-1H-indole)



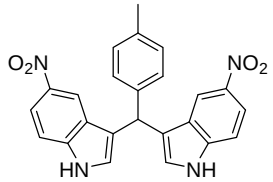
Yield: 87 %; white gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.05 (t, *J*=6.95 Hz, 3H), 2.31-2.25 (m, 2H), 4.36-4.39 (m, 1H), 7.31-7.38 (m, 4H), 7.90 (d, 2H), 8.34 (s, 2H), 140.97 (br, s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.16, 50.74, 60.63, 118.97, 123.06, 126.51, 126.87, 128.63, 129.08, 129.81, 132.56, 142.95, 153.38, 156.65.

3,3’-((4-chlorophenyl)methylene)bis(5-nitro-1H-indole)



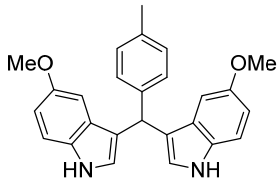
Yield: 86 %; Yellow solid, mp: 142-144 ^{o}C; **^{1}H NMR** (200 MHz, DMSO-d_6): δ): δ 5.96 (s, 1H), 6.78 (d, *J*=2.4 Hz, 2H), 6.9 (t, 2H), 7.1 (t, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 7.38 (d, *J*=8.1 Hz, 2H), 8.10 (d, *J*=8.1 Hz, 2H), 10.41 (s, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 49.32, 118.71, 122.72, 126.33, 126.84, 128.53, 130.94, 152.73.

3,3‘-(p-tolylmethylene)bis(5-nitro-1H-indole)



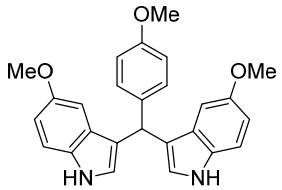
Yield: 94 %; Brown solid, mp: 215-216 ^{o}C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 5.7 (s, 1H), 6.64-6.77 (m, 6H), 7.03-7.09 (m, 2H), 7.19-7.25 (m, 4H), 10.6 (br, s, 2H); **^{13}C NMR** (200 MHz, DMSO-d_6): δ 15.33, 21.28, 51.97, 61.48, 119.64, 120.91, 123.92, 127.37, 128.03, 130.66, 133.80, 137.02, 141.03.

3,3’-(p-tolylmethylene)bis(5-methoxy-1H-indole)



Yield: 87 %; Brown solid, mp: 215-216 ^{o}C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 3.60 (s, 6H), 5.64 (s, 1H), 6.64-6.77 (m, 6H), 7.03-7.07 (m, 2H), 7.19-7.25 (m, 4H), 10.59 (br, s, 2H); **^{13}C NMR** (200 MHz, DMSO-d_6): δ 20.58, 55.08, 101.25, 110.33, 111.75, 117.69, 124.08, 126.85, 128.07, 128.36, 131.71, 134.32, 141.72, 152.50.

3,3’-((4-methoxyphenyl)methylene)bis(5-methoxy-1H-indole)



Yield: 83 %; Brown solid, mp: 198-200 ^{o}C; **^{1}H NMR (**200 MHz, DMSO-d6): **δ** 3.62 (s, 6H), 3.73 (s, 3H), 5.81 (s, 1H), 6.63-6.76 (m, 8H), 7.15-7.21 (m, 4H), 10.03 (br, s, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): **δ** 54.46, 54.99, 101.09, 110.33, 111.41, 112.79, 117.90, 124.00, 126.71, 128.91, 131.64, 152.47, 157.07.

4.2.7 Spectra for selected compounds

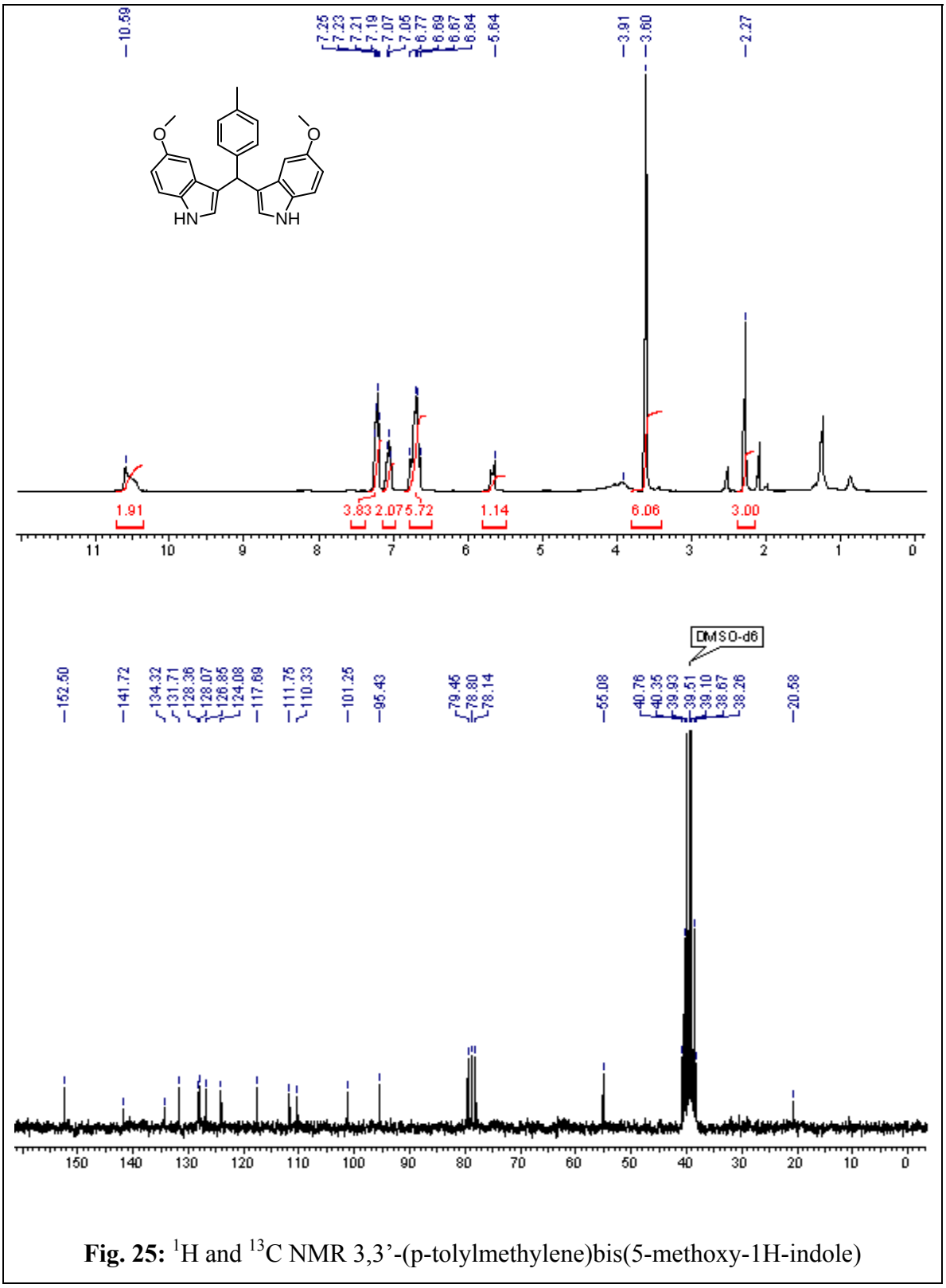


Fig. 25: ^{1}H and ^{13}C NMR 3,3'-(p-tolylmethylene)bis(5-methoxy-1H-indole)

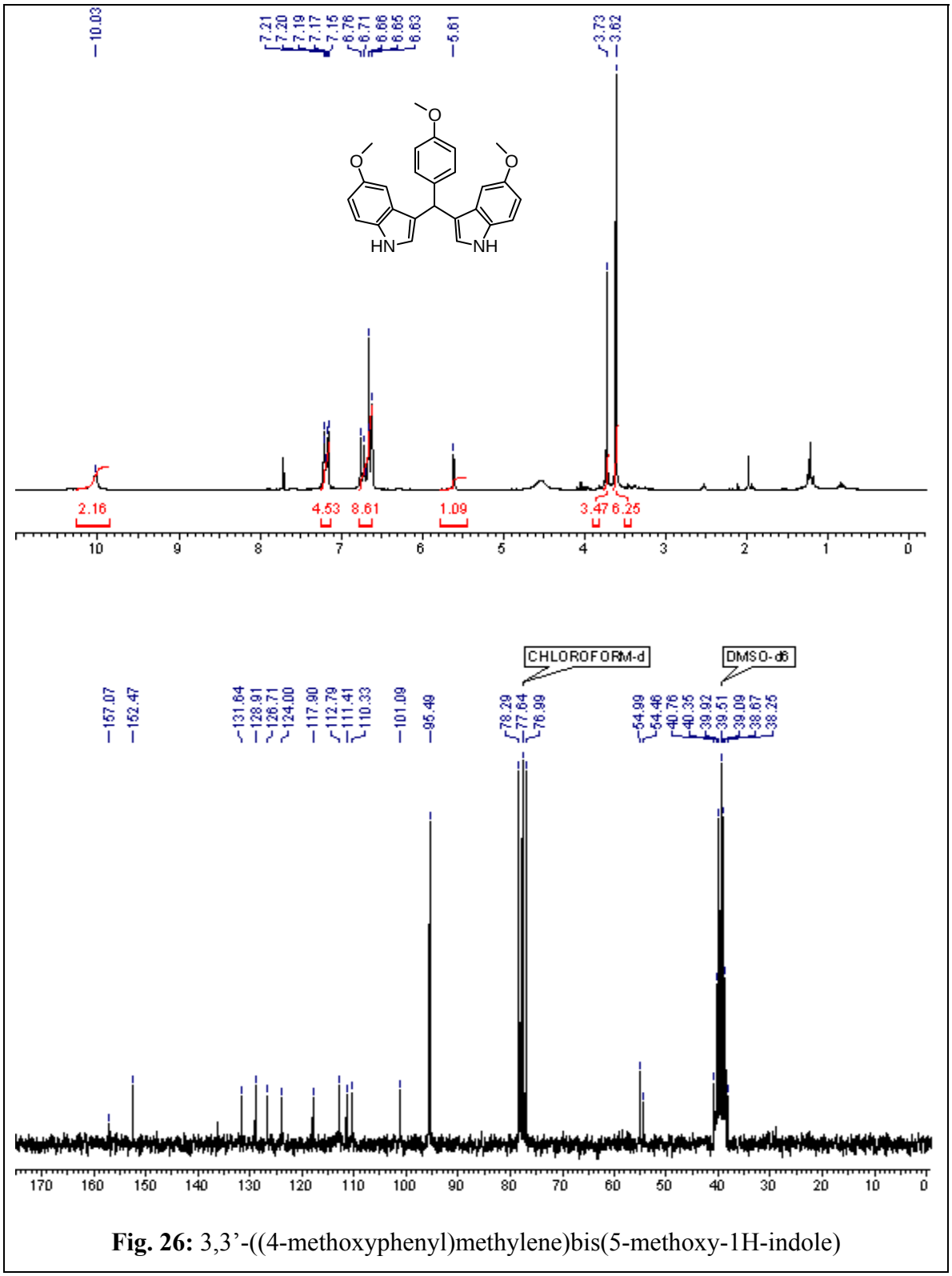


Fig. 26: 3,3'-((4-methoxyphenyl)methylene)bis(5-methoxy-1H-indole)

4.2.8 References

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List of Publications:

1 Shafeek A. R. Mulla, Mohsinkhan Y. Pathan, Santosh S. Chavan, Suwarna P. Gample and Dhiman Sarkar "Highly efficient one-pot multi-component synthesis of α-aminophosphonates and bis-α-aminophosphonates catalyzed by heterogeneous reusable silica supported dodecatungstophosphoric acid (DTP/SiO_2) at ambient temperature and their antitubercular evaluation against *Mycobactrium* Tuberculosis" *RSC Adv.* **2014**, *4*, 7666-7672.

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