ASYMMETRIC SYNTHESES OF PHARMACEUTICALLY IMPORTANT COMPOUNDS EMPLOYING HYDROLYTIC KINETIC RESOLUTION STRATEGY AND DEVELOPMENT OF NOVEL CHROMONE BASED DERIVATIVES AS POTENT ANTITUBERCULAR AGENTS

A THESIS SUBMITTED TO

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

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CERTIFICATE

This is to certify that the research work presented in the thesis entitled "**Asymmetric syntheses of pharmaceutically important compounds employing hydrolytic kinetic resolution strategy and development of novel chromone based derivatives as potent antitubercular agents**" has been carried out under my supervision and is a bonafide work of **Mr. Mohammad Mujahid**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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September 2013

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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Asymmetric syntheses of pharmaceutically important compounds employing hydrolytic kinetic resolution strategy and development of novel chromone based derivatives as potent antitubercular agents**" submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other University or Institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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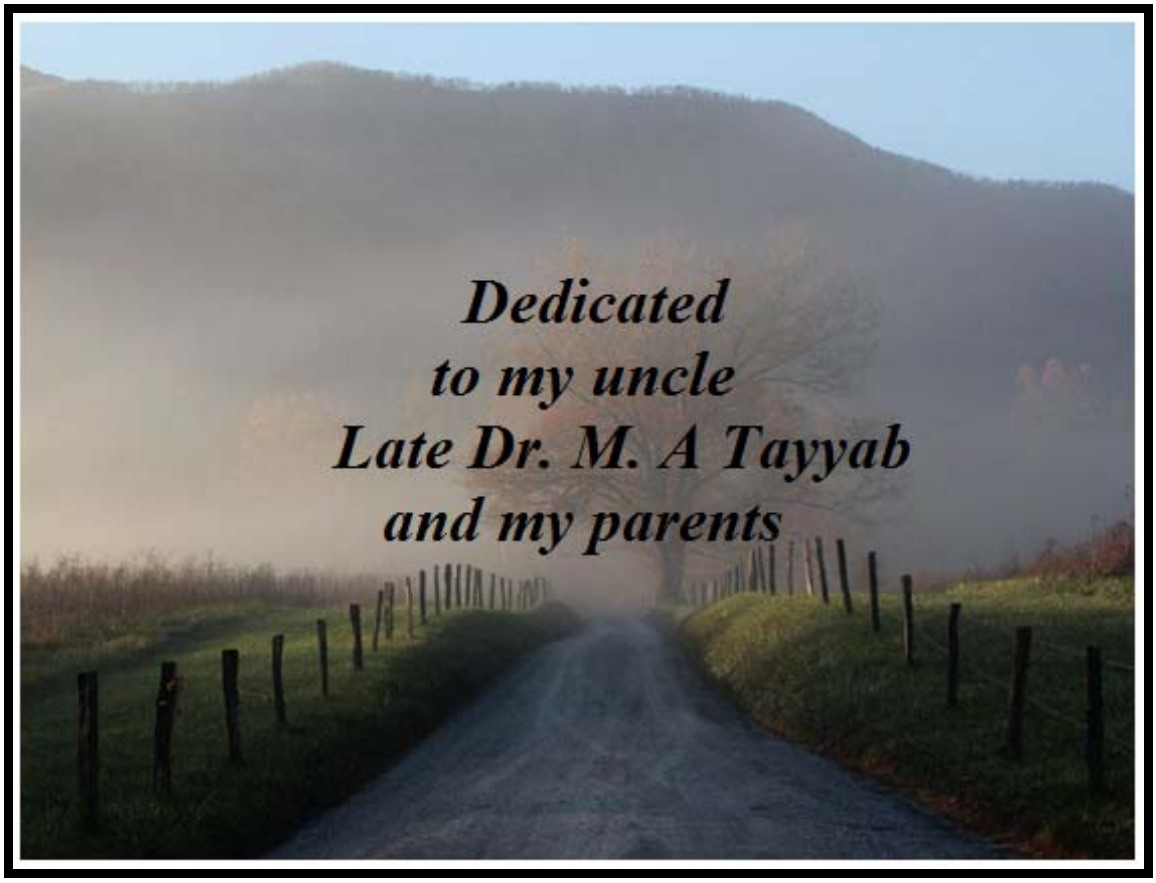
Dedicated
to my uncle
Late Dr. M. A Tayyab
and my parents

ACKNOWLEDGEMENT

First of all, I would like to thank my Almighty **"ALLAH"** *the most beneficent and merciful for giving me everything in my life.*

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The love and affection showered by my wife on me is magnanimous. The love, dedication, sacrifice, support and encouragement I received from my wife helped me to complete this work. I am thankful to my son Ashaaz and my sister's kids Umair and Fuzain for making my life more beautiful than it was.

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Mohammad Mujahid

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Chapter 4

Development of novel chromone based derivatives as potent antitubercular agents

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl Lithium
Bu_3P	-	Tributylphosphine
Cbz	-	Carboxybenzyl
CbzCl	-	Benzyl chloroformate
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	-	Diisopropyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
DPPA	-	Diphenylphosphoryl azide
DTTP	-	Deoxythymidine Triphosphate
ee	-	Enantiomeric excess
eq. or equiv	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl

Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
h	-	Hours
HKR	-	Hydrolytic kinetic resolution
Hz	-	Hertz
IBS	-	Iodoxybenzoic Acid
Im	-	Imidazole
i-Pr	-	Isopropyl
LDA	-	Lithium diisopropylamide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
p-TSA	-	*para*-Toluenesulfonic acid
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TMSCN	-	Trimethylsilyl cyanide
TPP	-	Triphenylphosphine
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on LC-ESI-MS by injecting the sample in Waters aquity ultra performance LC system equipped with a PDA and SQ detector.
- HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, Q Exactive).
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Enantiomeric excesses were determined by chiral HPLC, performed on 'SHIMADZU SCL-10A unit' system controller and UV monitor as detector.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 ºC.
- Silica gel (60–120) used for column chromatography was purchased from Spectrochem Pvt. Limited, Mumbai, India.

ABSTRACT

The thesis entitled "**Asymmetric syntheses of pharmaceutically important compounds employing hydrolytic kinetic resolution strategy and development of novel chromone based derivatives as potent antitubercular agents**" has been divided into four chapters.

Chapter 1: A Brief account on impact of chirality in pharmaceuticals & application of Jacobsen's Hydrolytic Kinetic Resolution (HKR) in asymmetric syntheses and enantioselective synthesis of Pregabalin.

Chapter 2: Asymmetric syntheses of antiepileptic drugs Lacosamide, Levetiracetam and antiparkinson's agent Safinamide.

Chapter 3: Asymmetric syntheses of EEHP, (*R*)-Phenampromide and (*R)*-Bepridil.

Chapter 4: Development of novel chromone based derivatives as potent antitubercular agents.

C H A P T E R – 1

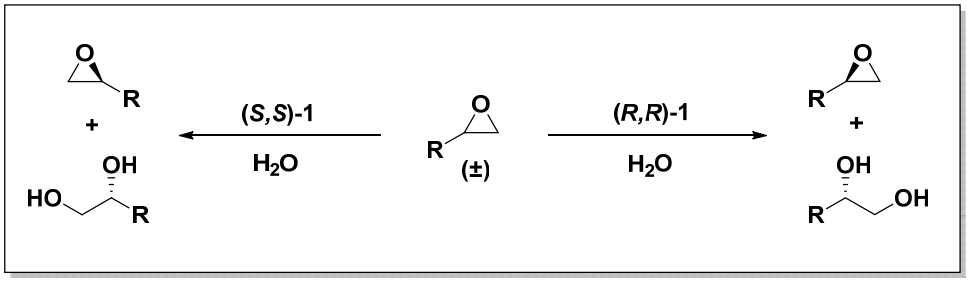
A Brief account on impact of chirality in pharmaceuticals & application of Jacobsen's Hydrolytic Kinetic Resolution (HKR) in asymmetric syntheses and enantioselective synthesis of Pregabalin.

This chapter is divided into 2 sections

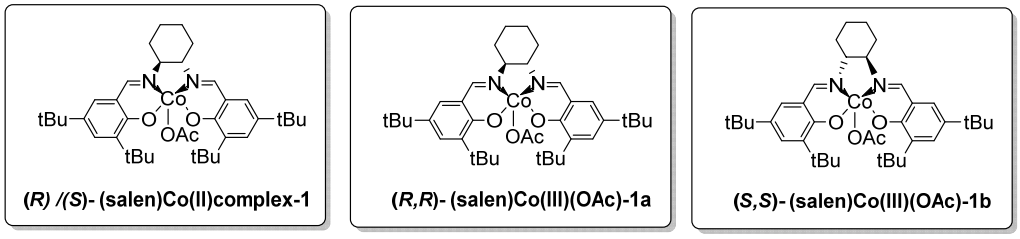
Section A: A Brief account on impact of chirality in pharmaceuticals and application of Jacobsen's Hydrolytic Kinetic Resolution (HKR) in asymmetric syntheses.

This chapter gives a brief introduction to importance of chirality and its impact in the pharma industry for the production of chiral pharmaceuticals. Further, application of Jacobsen's Hydrolytic Kinetic Resolution (HKR) in asymmetric syntheses is also detailed in this chapter.

In recent years, asymmetric syntheses of optically pure compounds are gaining great momentum mainly because of the increase in number of chiral, non-racemic pharmaceuticals on the market place. The importance of optically pure drugs is widely recognized mainly because only one enantiomers accounts for the drug activity whereas, the other form is either inactive or responsible for side effects. Because of tragedies such as thalidomide one, finding a way of making only one chiral form of a drug or drug intermediate is now most important, challenging and competitive area for research in chemistry.[1] Further in recent years, there is an unprecedented growth in the area of enantioselective processes; many new and versatile reactions and reagents are being introduced regularly, which can be used conveniently for the synthesis of many pharmaceutically important compounds with high enantiopurity.



Hydrolytic kinetic resolution (HKR) reaction



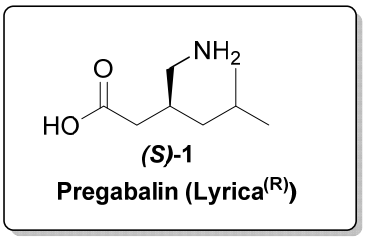
Commercially available Jacobsen's catalyst

Hydrolytic kinetic resolution (HKR) strategy is one such, which was developed by Jacobsen *et al* using chiral (salen) Co complex catalyst which allows the preparation of terminal epoxides and vicinal diols in high enantiomeric purity. Due to easy access of terminal epoxides, high level of selectivity, low catalyst loading and easy recyclability of the catalyst made this method extremely useful for the synthesis of many biologically active compounds.[2] Considering the significance of "*Chiral*

drugs", in this research proposal it has been decided to utilize the elegant HKR strategy for the preparation of pharmaceutically important compounds.

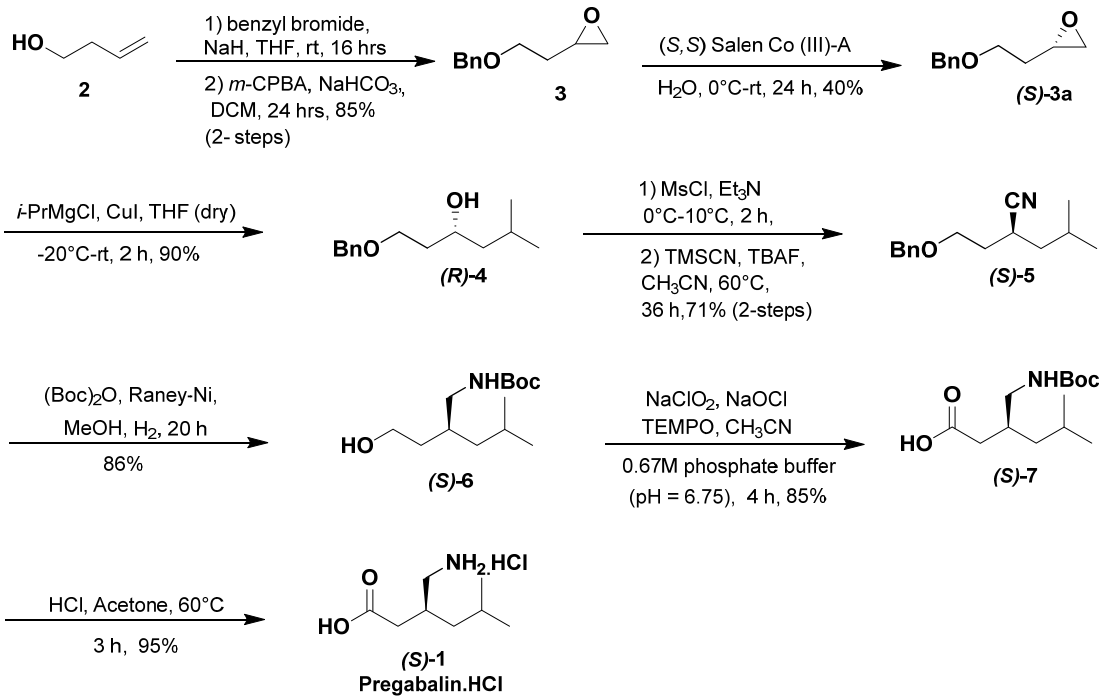
<u>Section B</u>: Asymmetric synthesis of Pregabalin via hydrolytic kinetic resolution

Pregabalin (Lyrica®) is the (*S)* enantiomer of 3-(aminoethyl)-5-methylhexanoic acid, structurally similar to the neurotransmitter γ-aminobutyric acid (GABA) and a successor to Gabapentin which is a neurontin drug. It is found to be potent for the treatment of neurological related disorders, epilepsy, anxiety and social phobia.[3] Pharmacological studies show that only (*S*)-enantiomer is responsible for the drug activity, whereas (*R*)-enantiomer is inactive.[4] Due to its unique mode of action it became Pfizer's second best selling drug, with worldwide sale of $998 million in 2011 showing 22 % increase from previous year. Numerous methods describing the synthesis of pregabalin have been reported. Although most of the methods have their own advantages, some of them suffer have their intrinsic disadvantages such as low optical purity, less yield, use of expensive reagents and starting materials, etc.[5] Therefore developing a new and practical method for the synthesis of pregabalin is highly desirable.



***(S)*-1**
Pregabalin (Lyrica$^{(R)}$)

In this section, we describe an enantioselective synthesis of pregabalin starting from commercially available 3-buten-1-ol using HKR as a key step and source of chirality. (Scheme 1). The required *rac*-epoxide **3** was prepared from 3-buten-1-ol. The *rac*-epoxide **3** was subjected to Jacobsen's hydrolytic kinetic resolution conditions to give enantiomerically pure epoxide (*S*)-**3a** from the racemic mixture in 40% yield and >99% ee. The epoxide (*S*)-**3a** was subjected to regioselective ring opening with isopropyl magnesium chloride in presence of CuI to afford the key intermediate secondary alcohol (*R*)-**4** in 90% yield. The secondary alcohol (*R*)-**4** was converted to its corresponding mesylate and the crude mesylate was displaced using TMSCN in presence of TBAF to furnish the cyano derivative (*S*)-**5** in 71% yield (2-steps). Further, compound (*S*)-**5** on simple hydrogenation/hydrogenolysis and concomitant Boc-protection using $(Boc)_2O$ and raney-Ni as a catalyst in methanol furnished amino alcohol (*S*)-**6**.



Scheme 1

Oxidation of compound (*S*)-**6** went smoothly using sodium chlorite catalyzed by TEMPO & bleach in acetonitrile-phosphate buffer (pH 6.8) condition and afforded the corresponding acid (*S*)-**7** in 86 % yield. Finally, Boc-deprotection of (*S*)-**7** derivative furnished pregabalin (*S*)-**1** in excellent enantioselectivity (*ee* >99 %).

C H A P T E R – II

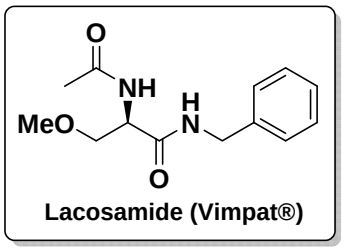
Asymmetric syntheses of antiepileptic drugs Lacosamide, Levetiracetam and antiparkinson's agent Safinamide

This chapter is divided further into 3 sections

Section-A: First asymmetric synthesis of antiepileptic drug, Lacosamide

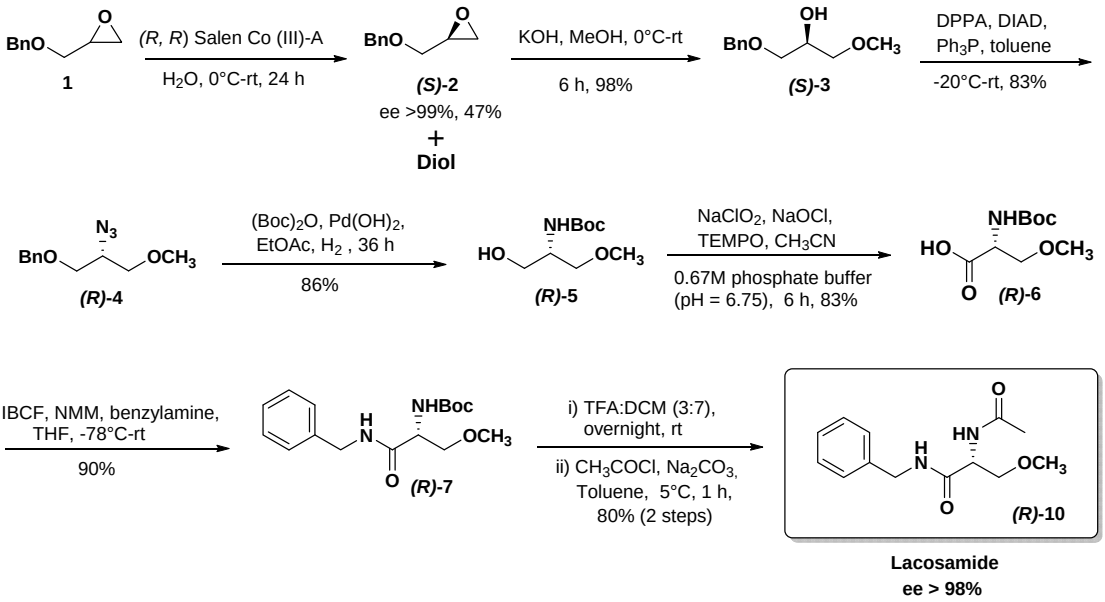
Epilepsy is a complex neurological disorder characterized by recurrent spontaneous seizures and it affects almost 50 million people worldwide. The life time prevalence of this disease is 1% and it affects individuals of all ages regardless of gender or socio-economic status. Further, epilepsy requires prolonged and sometimes lifelong drug therapy.[6] Lacosamide is the (*R*)-enantiomer of *N*-benzyl-2-acetamido-3-methoxypropionamide, recently approved by FDA (Oct, 2008) as an add-on therapy

for partial-onset seizures in adults with epilepsy (Trade Name: Vimpat® owned by UCB Pharma). Although the mechanisms of action of lacosamide is not yet clearly understood, but it is believed that it enhances slow inactivation of voltage-gated Na^+ channels and binds to dihydropyrimidinase-related protein 2 (CRMP 2), there as to control the seizures. Due to this unique mode of action, it differs from other antiepileptic drugs (AEDs) and it is expected to be a potential blockbuster of annual sales ~1 billion dollars-in epilepsy. Commercially, lacosamide is prepared using chiral pool approach starting from unnatural amino acid *D*-Serine and its derivatives.[7]



Lacosamide (Vimpat®)

In this section, we describe first asymmetric synthesis of lacosamide starting from commercially available benzyl glycidyl ether using HKR as a key step and source of chirality (Scheme 2).



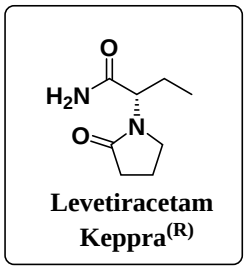
Scheme 2

The synthesis started from readily available racemic benzyl glycidyl ether 1. The glycidyl ether 1 was subjected to Jacobsen's HKR conditions with 0.55 eq water, using the catalyst *(R,R)*-Salen Co(III)OAc (0.5 mol%) at ambedient temperature for 24 h to provide enantiomerically pure glycidyl ether *(S)*-**2** (47% yield) and (*R*)-diol (43% yield). The epoxide (*S*)-**2** was converted into the desired *β*-hydroxy ether *(S)*-**3** via regioselective ring opening using methanol under basic condition. *β*-hydroxy ether *(S)*-**3** was readily transformed into a *N*-Boc protected *β*-amino alcohol *(R)*-**5** by stereospecific substitution of the hydroxyl group with azido group employing a

typical Mitsunobu procedure with DPPA followed by hydrogenation using $Pd(OH)_2$ in the presence of $(Boc)_2O$. Subsequently the alcohol was oxidized to acid under NaOCl/ $NaClO_2$, cat TEMPO condition followed by coupling reaction with benzylamine using mixed anhydride procedure to afford compound (*R)*-**7**. Finally, Boc deprotection followed by *N*-acetylation of compound (*R)*-**7** completes the synthesis of lacosamide in high enantiopurity (ee >98%).

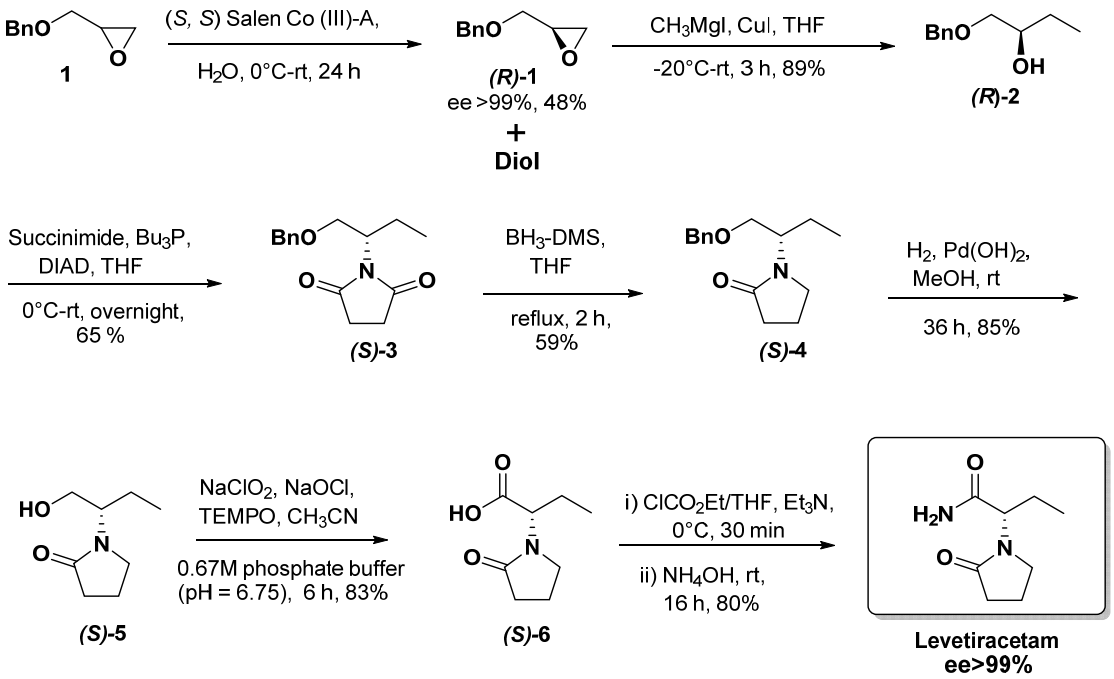
<u>Section-B</u>: Asymmetric synthesis of antiepileptic drug, Levetiracetam

Levetiracetam ((*S*)-α-ethyl-2-oxo-pyrrolidine acetamide, *Keppra*®)[8] is a novel antiepileptic drug with a unique antiepileptic mechanism.[9] Further, its beneficial effects of levetiracetam in patients with bipolar disorders, migraine, chronic or neuropathic pain, diabetic complications are also reported.[10] Hence it has attracted a great deal of attentions of synthetic chemists and different methods of preparation of levetiracetam has been extensively investigated. The reported methods of preparation involves classical resolution processes,[11] asymmetric synthesis[12] and some of these methods have their own intrinsic disadvantages such as expensive chiral starting materials and catalysts, problems associated with the installation of 2-pyrrolidone moiety with harsh reaction conditions which often leads to the loss of optical purity, usage of hazardous alkylating agents, tedious and time consuming experiments, and so on. Hence, to overcome these disadvantages, development of newer methods in the preparation of levetiracetam is highly desirable.



Levetiracetam
Keppra(R)

In this section, we describe an efficient synthesis of levetiracetam starting from commercially available benzyl glycidyl ether using HKR (Scheme 3). The synthesis began with the commercially available benzyl glycidyl ether 1 which was subjected to Jacobsen's HKR conditions as described earlier to provide chiral epoxide (*R*)-**1**. Firstly, the regioselective ring opening of epoxide (*R*)-**1** was carried out with MeMgI and catalytic amount of CuI in anhydrous THF at -20 ºC to provide secondary alcohol (*R*)-**2** in 93 % yield. Further (*R*)-**2** was readily transformed into a succinimido ether (*S*)-**3** by stereospecific substitution of the hydroxyl group with succinimide using Bu_3P and DIAD in THF under Mitsunobu condition followed by mono reduction with one equiv. of BH_3-DMS complex in dry THF to afford compound (*S*)-**4** in 66% yield.

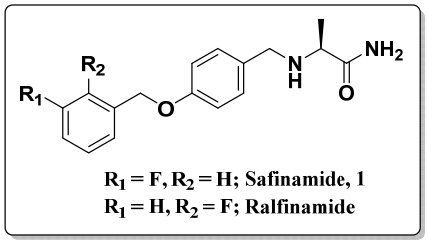


Scheme 3

Subsequently, the compound (*S*)-**4** was subjected to $Pd(OH)_2$ catalyzed hydrogenolysis, followed by oxidation with sodium chlorite catalyzed by TEMPO and bleach in an acetonitrile-phosphate buffer (pH 6.8) and afforded the acid (*S*)-**6** in 80% yield (two steps). Finally, the acid (*S*)-**6** was transformed into the corresponding amide by consecutive reaction with ethyl chloroformate and aq. ammonia completed the synthesis of levetiracetam in excellent enantioselectivity (>99% ee).

Section-C: Asymmetric synthesis of antiparkinson's agent Safinamide

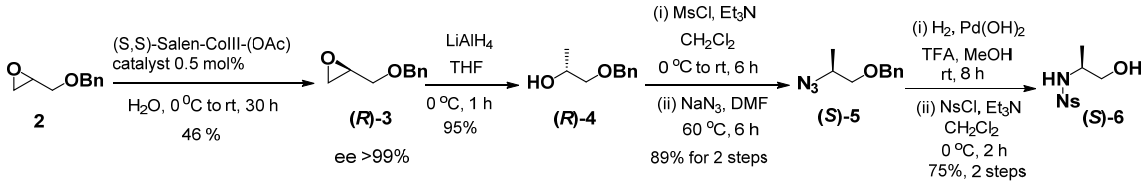
Benzyloxy-benzylamine class of derivatives are important structural class, they have prevalent use in treating many neurological disorders including PD. Among them, safinamide ((*S*)-N^2-{4-[3-fluorobenzyl)oxy]benzyl}-alaninamide methanesulfonate) is an noted example which is progressing phase III clinical trials as an add-on therapy to dopamine agonists and L-dopa in patients with Parkinson's disease.[13] The strategy employed to prepare this compound is chiral pool approach starting from L-alaninamide and reductive condensation with 4-(3-fluorobenzyloxy)benzaldehyde.[14] Although this method is very simple and



straightforward, however it suffers from the formation of toxic impurities in large scale production.

In this section, we describe first asymmetric synthesis of safinamide starting from commercially available benzyl glycidyl using hydrolytic kinetic resolution. Accordingly, the synthesis began with benzyl glycidyl ether which was subjected to Jacobsen's HKR as described earlier to provide chiral epoxide (*R*)-**3**. The epoxide (*R*)-**3** was converted into the desired secondary alcohol (*R*)-**4** using lithium aluminium hydride in anhydrous THF at 0 °C (Scheme 4). The secondary alcohol (*R*)-**4** was converted into the azido derivative (*S*)-**5** in 89 % yield (two steps) employing mesylation followed by displacement with NaN_3. Next, the azido compound (*S*)-**5** was subjected to $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis followed by *N*-nosylation to give the compound (*S*)-**6** in 75% yield.

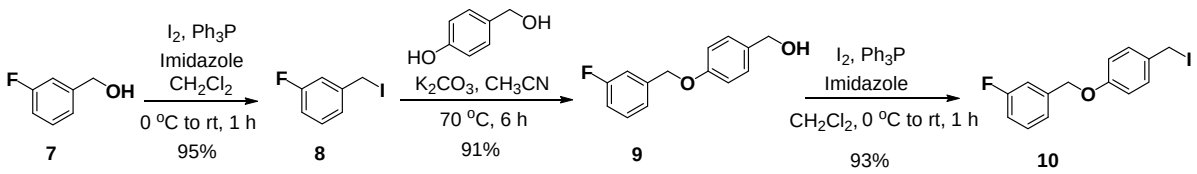
Fragment 1



Scheme 4

The synthesis of iodo fragment **10** was started from commercially available 3-fluoro benzyl alcohol **7** (Scheme 5). Thus, iodination of compound **7** using triphenylphosphine, iodine and imidazole afforded compound **8** in 95 % yield. Subsequently, compound **8** upon treatment with 4-(hydroxymethyl)phenol under basic condition afforded *O*-alkylated product **9** in 91 % yield. Iodination of **9** under the condition mentioned above to afford the required iodo fragment **10**.

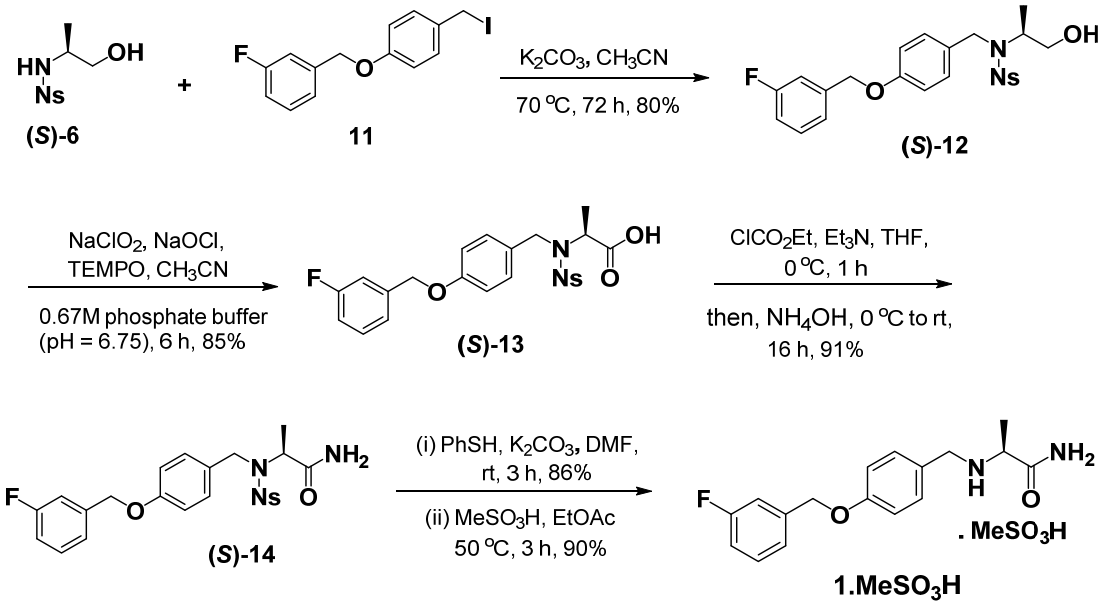
Fragment 2



Scheme 5

With amino alcohol (*S*)-**6** and alkyl iodide **10** in hand, the coupling of these two fragments (*S*)-**6** and **10** was conducted in the presence of potassium carbonate in acetonitrile at 70 ^{0}C to give the corresponding coupled product in 80% yield (Scheme

6). Next, oxidation of the coupled product (*S*)-**12** give the acid (*S*)-**13** in 85% yield. Subsequently, the acid (*S*)-**13** was converted into the amide (*S*)-**14** using mixed anhydride procedure. Finally, cleavage of the nosyl group followed by treatment with methane sulphonic acid complete the synthesis of safinamide in high enantiopurity ee>99%.



Scheme 6

C H A P T E R – III

Asymmetric syntheses of EEHP, (*R*)-Phenampromide and (*R)*-Bepridil

This chapter is divided further into 3 sections

Section-A: Asymmetric synthesis of ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP), a key intermediate of PPAR agonists

Ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP), is an essential component present in many PPAR agonists such Ragaglitazar, Tesaglitazar, etc (Fig 1).[15] Different methods for the preparation of EEHP have been extensively studied.[16] Some of these methods have their own intrinsic disadvantages such as expensive chiral starting materials or catalysts, low enantioselectivity, less yield, problems associated with the *O*-alkylation step which often leads to the loss of optical purity,

etc. So, in this section we describe an efficient and straightforward synthesis of EEHP starting from commercially available benzyl glycidyl using HKR as a key step.

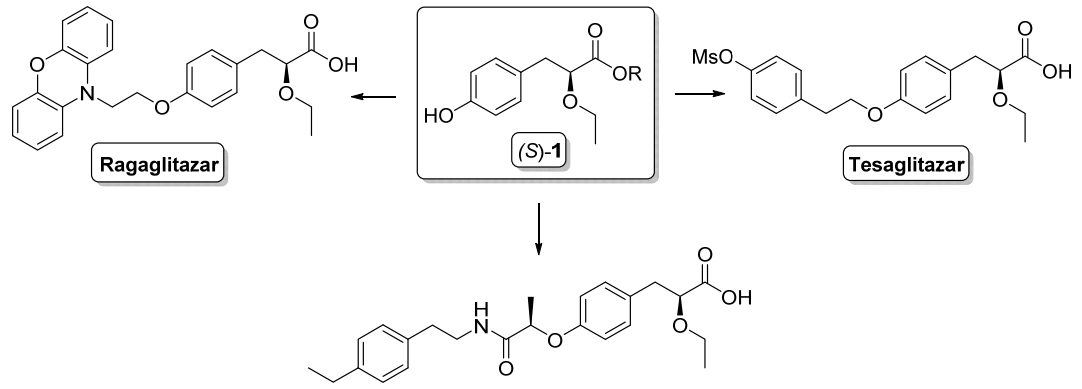
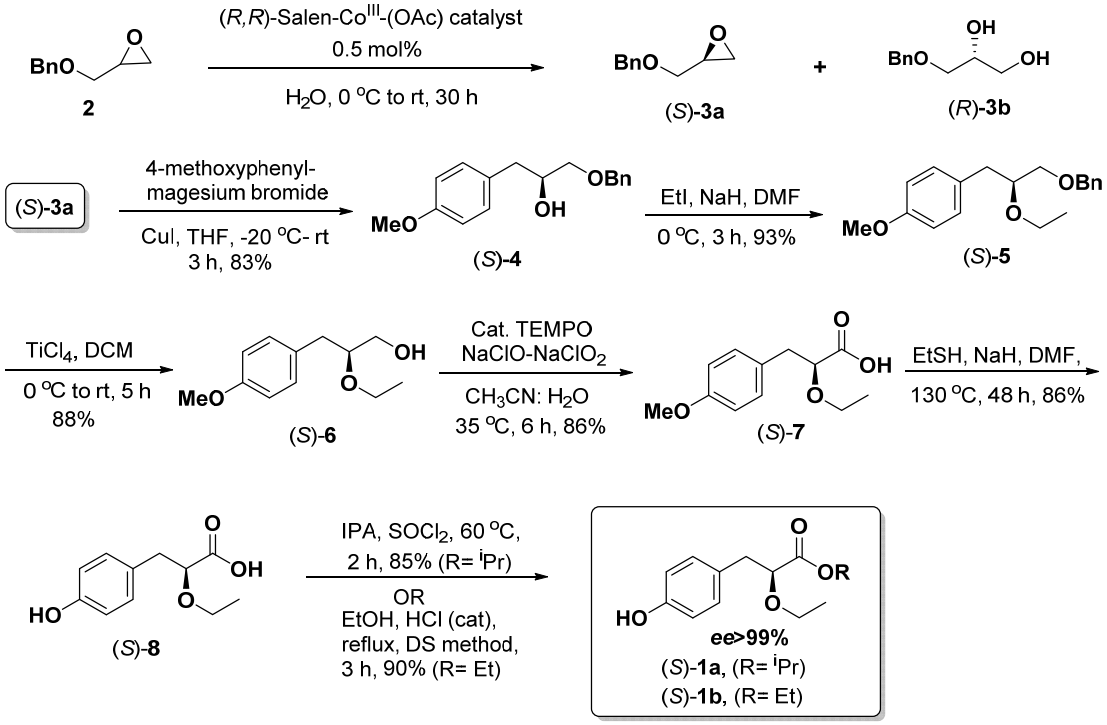


Figure 1. Examples of PPAR agonists based on EEHP intermediate

Commercially available *rac*-benzyl glycidyl ether was subjected to hydrolytic kinetic resolution conditions to give enantiomerically pure epoxide (*S*)-**3a** (Scheme 7).



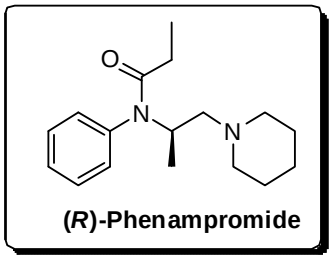
Scheme 7

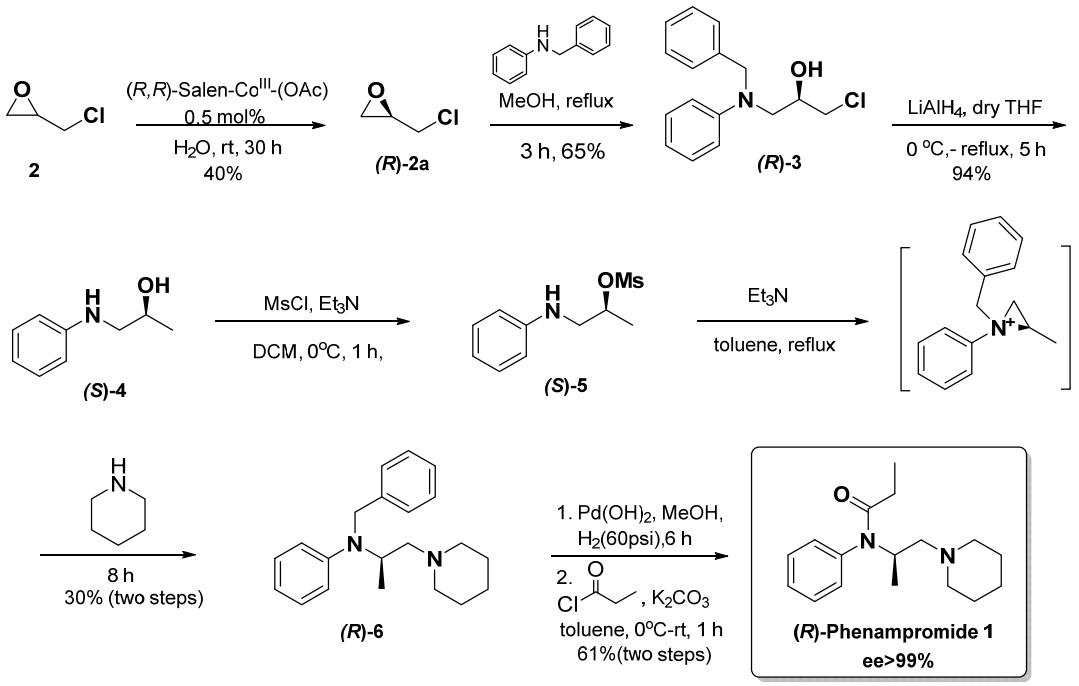
Subsequently, the regioselective ring opening of (*S*)-epoxide (*S*)-**3a** was carried out with 4-methoxyphenylmagnesium bromide in presence of catalytic amount of CuI in anhydrous THF at -20 °C to provide secondary alcohol (*S*)-**4** in 83 % yield. *O*-alkylation of (*S*)-**4** went smoothly using simple conditions such as ethyl iodide and sodium hydride in anhydrous DMF at 0 ºC to give ethylated derivative (*S*)-**5** in 93%

yield**.** Further, debenzylation of compound (*S*)-**5** followed by oxidation with sodium chlorite catalyzed by TEMPO and bleach afforded the acid (*S*)-**7** in 76% yield (two steps). Lastly, demethylation followed by esterification was performed using reported procedures to afford final molecules (*S*)-**1a** & (*S*)-**1b** in excellent enantioselectivity (>99% ee) without any additional crystallization.

Section-B: Asymmetric synthesis of (*R*)-Phenampromide via aziridine ring formation

Phenampromide is an opioid analgesic drug and it was invented in the 1960s by American Cyanamid Co.[17] Pharmacological studies show that only (*R*)-enantiomer is more active than (*S*)-enantiomer.[18] Previous synthesis of (*R*)-phenampromide was carried out using chiral pool approach starting from (+)-*N*-phenylalanine.[19] No asymmetric synthesis of this molecule is reported yet.





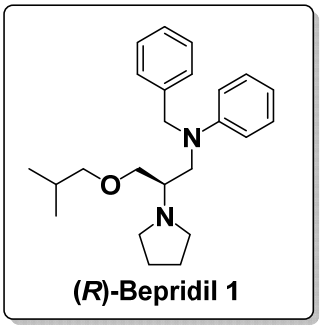
Scheme 8

So, in this section we describe first asymmetric synthesis of (*R*)-phenampromide starting from *rac*-epichlorohydrin which was subjected to Jacobsen's HKR conditions to get enantiopure (*R*)-epichlorohydrin (Scheme 8). Further regioselective ring

opening of the chiral epoxide *(R)*-**2a** was performed using *N*-benzylaniline in methanol under reflux conditions to get the required chlorohydrin derivative (*R*)-**3**. Now the (*R*)-**3** derivative was reduced using lithium aluminium hydride to give hydroxy derivative (*S*)-**4**. Mesylation of (*S*)-**4** compound using methane sulfonyl chloride provided mesylated derivative (*S*)-**5** which on treatment with Et_3N and piperidine in refluxing toluene furnished (*R*)-**6** derivative via formation of aziridinium ion. Further, *N*-debenzylation of (*R*)-**6** compound using catalytic $Pd(OH)_2$ under H_2 pressure, followed by treatment with propionyl chloride in presence of base afforded the targeted compound (*R*)-phenampromide **1** in high enantiopurity (ee>99%).

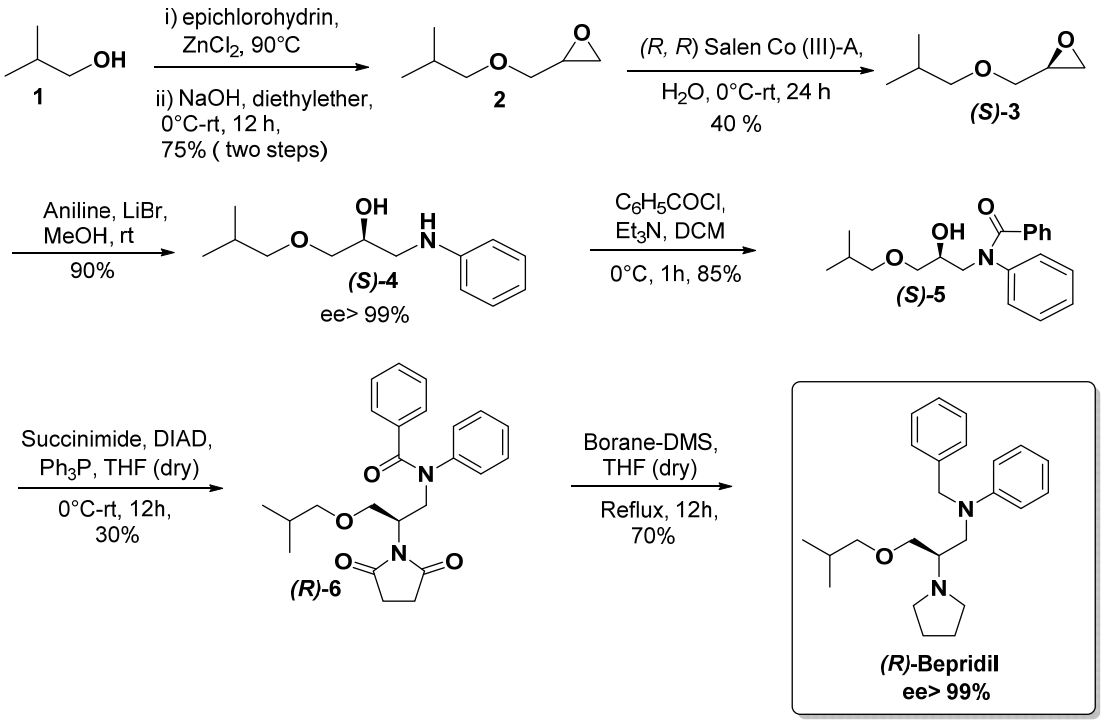
<u>Section C</u>: Asymmetric synthesis of calcium channel blocker (*R*)-Bepridil

Bepridil (Vascor) is long-acting calcium-blocking agent with significant anti-anginal activity. The drug produces significant coronary vasodilation and modest peripheral effects. It has antihypertensive and selective anti-arrhythmia activities and acts as a calmodulin antagonist.[20] Literature studies shows that *(R)* isomer of bepridil is more active than *(S)*-isomer.[21] However, there is no effort has been made so far to synthesize this compound enantioselectively. Hence, in this section we describe first asymmetric synthesis of (*R*)-bepridil starting from commercially available epichlorohydrin using HKR as a key step and source of chirality (Scheme 9). The required *rac*-epoxide **2** was prepared using standard protocol starting from commercially available epichlorohydrin and *iso*-butanol**.** Next, the *rac*-epoxide **2** was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equivalents of water using the catalyst *(R,R)*-Salen Co(III)OAc (0.5 mol %) at ambient temperature for 24 hours to afford enantiopure epoxide *(S)*-**3.** The epoxide *(S)*-**3** was subjected to regioselective ring opening with aniline in presence of catalytic LiBr using methanol as a solvent to furnish key intermediate amino alcohol *(S)*-**4** in 90% yield. Further, the compound *(S)*-**4**, was converted into hydroxy phenylbenzamide *(S)*-**5** using benzoyl chloride and triethylamine in 85% yield. Now, the *N*-benzoylated derivative *(S)*-**5** was exposed to typical Mitsunobu conditions to furnish succinimide derivative *(R)*-**6** in 40% yield. Finally, amide reduction was performed using borane-



(*R*)-Bepridil 1

DMS under reflux condition to achieve the target molecule *(R)*-bepridil **1** with ee> 99%.



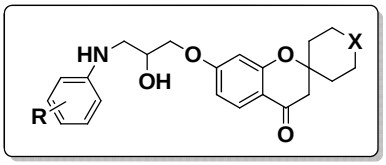
Scheme 9

C H A P T E R – IV

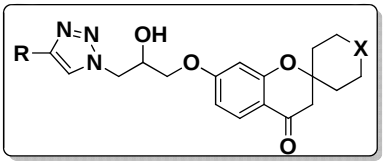
Development of novel chromone based derivatives as potent antitubercular agents.

This chapter deals with the synthesis of different novel spirochromone conjugates and evaluation of their antimycobacterial properties. Three different series of compounds were prepared like aminoalcohol spirochromone conjugates, triazole fused spirochromone derivatives and chalcone-spirochromone conjugates. All the compounds were assayed for their inhibitory activity against *Mycobacterium tuberculosis* H37Rv (ATCC27294). The minimum inhibitory concentration (µg/mL) was determined for each compound. Isoniazid, Rifampicin and ethambutol were used as a reference compounds. In case of aminoalcohol spirochromone conjugates six compounds showed moderate inhibition, MIC in the range of 6.25 µg/mL, whereas one compound showed good activity with MIC value of 3.13 µg/mL, among triazole - spirochromone conjugates most of the compound possess good activity and one of the

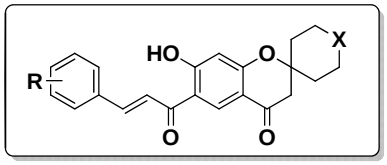
compound showed excellent activity with MIC value of 0.78 µg/mL which is better than anti-TB drug Ethambutol (MIC- 1.56 µg/mL), whereas in chalcone-spirochromone conjugates only one compound showed better activity with MIC value of 3.25 µg/mL. From the above discussion, as triazole- spirochromone conjugates showed excellent results, we envisage that this new class of compounds may open new doors in tuberculosis research.



Chromone aminoalcohol conjugates
21 examples
MIC- 3.25- 25 µg/mL



Chromone triazole conjugates
10 examples
MIC- 0.78- 25 µg/mL



Chromone chalcone conjugates
17 examples
MIC- 3.25- 25 µg/mL

References

1. Kotha, S. *Tetrahedron* **1994**, 50, 3639 and references cited therein.
2. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307; (c) Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745.
3. (a) Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 823; (b) Bryans, J. S.; Wustrow, D. *J. Med. Res. Rev*.**1999**, *19*, 149; (c) Belliotti, T.; Capiris, T.; Ekhato, V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Meltzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Zhi-Su, T.; Weber, M.; Wustrow, D. J. *J. Med. Chem*. **2005**, *48*, 2294 and references therein.
4. Taylor. C. P.; Vartanian, M. G.; Yuen, P.W.; Bigge, C.; Suman-Chauhan, N.; Hill, D. R. *Epilepsy Res*. **1993**, *14*, 11.
5. (a) Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org.Process Res. Dev*. **1997**, *1*, 26; (b) Grote, T. M.; Huckabee, B. K.; Mulhern, T. A.; Sobieray, D. M.; Titus, R. D. WO 9640617, 1996.

6. (a) Duncan, J.S., Sander, J. W., Sisodia, S. M., Walker, M. C., *Lancet*, **2006**, *367*, 1087; (b) 'Epilepsy' World Health Organization:http://www.who.int/mediacentre/factsheets/fs999/en/index.html

7. (a) Bialer, M.; White H. S., *Nat. Rev. Drug. Disc*. **2010**, *9*, 68; (b) Pandey, B.; Shah, K., PCT Int. Appl., WO 2011039781A1, 2011; *Chem. Abstr*. **2011**, *154*, 410331; (c) Vrbanec, G.; Harca, M.; Sucec, A.; Sahnic, D.; Avdagic, A., PCT Int. Appl., WO 2010107993A2, 2010; *Chem. Abstr*. **2010**, *153*, 431066; (d) Morieux, P.; Salome, C.; Park, K. D.; Stables, J. P.; Kohn, H. *J. Med. Chem*., **2010**, *53*, 5716; (e) Park, K. D.; Stables, J. P.; Liu, R.; Kohn, H. *Org. Biomol. Chem*., **2010**, *8*, 2803.

8. (a) Prous, J.; Mealy, N.; Castaner, J. *Drugs future*, **1994**, *19*, 111; (b) Shorvon, S. D.; Rijckevorsel, K. V., *J. Neurol. Neurosurg. Psychiatry*, **2002**, *72*, 426; (c) Williamson, L.; Katherine, A., *Drugs*, **2011**, *71*, 489; (d) Crepeau, A. Z.; Treiman, D. M., *Expert rev. Neurotherapeutics*, **2010**, *10*, 159.

9. (a) Bialer, M.; White, H. S., *Nat. Rev. Drug discovery*, **2010**, *9*, 68; (b) Lynch, B. A.; Lambeng, N.; Nocka, K.; Hammes, P. K.; Bajjalieh, S. M.; Matagne, A.; Fuks, B., *Proc. Nat. Acad. Sci. U.S. A.,* **2004**, *101*, 9861.

10. (a) Tucker, J. L.; Xu, L.; Yu, W.; Scott, R. W.; Zhao, L.; Ran, N.; PCT Int. Appl, WO 2009009117, 2009; *Chem. Abstr.* **2009**, *150*, 119828; (b) Olszanecki, R.; Bujak, G. B.; Korbut, R.; Gajda, M., PCT Int. Appl, WO 2011/049475, 2011; *Chem. Abstr.* **2011**, *154*, 477389.

11. (a) Futagava, T.; Canvat, J.P.; Cavoy, E.; Deleers, M.; Hamende, M.; Zimmermann, V.; US patent 6107492, 2000; *Chem. Abstr.* **2000**, 133, 183002; (b) Cavoy, E.; Hamende, M.; Deleers, M.; Canvat, J.P.; Zimmermann, V.; US patent 6124473, 2000; *Chem. Abstr.* **2000**, *133*, 268549; (c) Li, Y.Q.; Wang, Z.X.; Guntoori, B.R.; PCT Int. Appl, WO 2006/053441, 2006; *Chem. Abstr.* **2006**, *144*, 488939; (d) Artús Surroca, J. J.; Rafecas Jané, L.; PCT Int. Appl, WO 2004/076416, 2004; *Chem. Abstr.* **2004**, *141*, 260546; (e) Mandal, A.K.; Mahajan, S.W.; Ganguly, P.; Chetia, A.; Chauhan, N.D.; Bhatt, N.D.; Baria, R.R.; PCT Int. Appl, WO 2006/103696, 2006; *Chem. Abstr.* **2006**, 145, 397360; (f) Boschi, F.; Camps, P.; Franchini, M, C.; Torrero, D. M.; Ricci, A.; Sanchez, L.; *Tetrahedron: Asymmetry*, **2005**, 16, 3739.

12. (a) Mylavarapu, R.; Anand, V. R.; Kondaiah, G.C.M.; Reddy, L.A.; Reddy, G.S.; Roy, A.; Bhattacharya, A.; Mukkanti, K.; Bandichhor, R.; *Green Chem.*

Lett. and Rev., **2010**, *3*, 225. (b) Imahori, T.; Omoto, K.; Hirose Y.; Takahata, H.; *Heterocycles*, **2008**, *76*, 1627; (d) Kotkar, S. P.; Sudalai, A.; *Tetrahedron Lett.* **2006**, 47, 6813; (e) Sarma, K. D.; Zhang, J.; Huang, Y.; Davidson, J. G.; *Eur. J. Org. Chem.* **2006,** 16, 3730.

13. (a) Chazot, P. L. *Curr. Opin. Invest. Drugs* **2001**, *2*, 809; (b) Marzo, A.; Dal Bo, L.; Ceppi Monti, N.; Crivelli, F.; Ismaili, S.; Caccia, C.; Cattaneo, C.; Fardello, R. G. *Pharmacol. Res.* **2004**, *50*, 77; (c) Stocchi, F.; Arnold, G.; Onofrj, M.; Kwiecinski, H.; Szczudlik, A.; Thomas, A.; Bonuccelli, U.; Van Dijk, A.; Cattaneo, C.; Sala, P.; Fariello, R. G. *Neurology* **2004**, *63*, 746.
14. Pevarello, P.; Bonsignori, A.; Dostert, P.; Heidempergher, F.; Pinciroli, V.; Colombo, M.; McArthur, R. A.; Salvati, P.; Post, C.; Fariello, R. G.; Varasi, M. *J. Med. Chem.* **1998**, *41*, 579.
15. Balakumar, P.; Rose, M.; Ganti, S. S.; Krishan, P.; Singh, M. *Pharm. Res*. **2007**, *56*, 91.
16. (a) Potlapally, R. K.; Siripragada, M. R.; Kotra, N. M.; Sirisilla, R.; Mamillapalli, R. S.; PCT Appl. WO 02/24625.; (b) Potlapally, R. K.; Siripragada, M. R.; Mamillapalli, R. S.; Gaddam, O. R.; Jangaigar, T. R.; Velagala, V. R. M. K. R.; PCT Appl. WO 03/027084; (c) Woltering, M.; Bunlakasnanusorn, T.; Gerlach, A. PCT Appl. US 2007/0149804.; (d) Houpis, I. N.; Patterson, L. E.; Alt, C. A.; Zhang, T. Y.; Haurez, M. *Org. Lett*. **2005**, *7*, 1947.
17. Portoghese, P. S.; *J Med Chem*, **1965**, 8, 147.
18. Wright, W. B.; Brabander, H. J.; Hardy, R.A.; *J Org Chem*, **1961**, 26, 476.
19. Wright, W. B.; Woodcliff Lake, N. J.; Brabander, H. J.; River, P.; U.S. 3,016,382 Jan. 9, 1962.
20. (a) Y. Li, T. Sato, M. Arita, *J. Pharmacol. Exp. Ther*. **1999**, *291*, 562-568; (b) E. N. Prystowsky, *Am J Cardiol*. **1985**, *55*, 59C-62C; (c) L. M. Hollingshead, D. Faulds, A. Fitton, *Drugs*. **1992**, *44*, 835-857; (d) R. A. Janis, D. J. Triggle, *J. Med. Chem.* **1983,** *26,* **775-**785 and references cited therein; (e) P. C. Deedwania, *West. J. Med.* **1982,** 137, 24-31; (f) A. Fleckenstein, *Ann. Rev. Pharmacol. Toxicol.* **1977,** *17,* 149.
21. F. T. van Amsterdam. J. Zaagsma, *Naunyn Schmiedebergs Arch Pharmacol*, **1988**, 337, 213.

Chapter-1

A Brief account on impact of chirality in pharmaceuticals & application of Jacobsen's Hydrolytic Kinetic Resolution (HKR) in asymmetric syntheses and enantioselective synthesis of Pregabalin

1.1. SECTION A

A Brief account on impact of chirality in pharmaceuticals and application of Jacobsen's Hydrolytic Kinetic Resolution (HKR) in asymmetric syntheses

1.1.1. Chirality

In 1815, the first report on chirality was presented by French physicist Jean-Baptiste Biot. He observed that α-quartz rotated the plane polarized light[1] but, the first chiral separation was performed in 1848 by Louis Pasteur in which he separated enantiomers of racemic sodium ammonium tartrate by the use of magnifying glass and tweezers thereby postulating different three- dimensional arrangement of enantiomers.[2]

Figure 1. Pioneer's of asymmetric synthesis

But the actual breakthrough in stereochemical research was made by Jacobus H van't Hoff and Joseph Achille Le Bel in 1874. They independently proposed that the four bonds attached to carbon atom have tetrahedral orientation and there was a correlation between spatial arrangement of the four bonds and property of molecule. They further assumed that dissymmetry and optical rotation of a molecule is due to tetrahedral geometry of carbon.[3]

Today we know that chirality is a property of matter found in all living systems present in nature. Chirality is formally defined as geometric property of a molecule which is not superimposable on their mirror images. Chirality can be easily understood with the fact of right and left handedness means a right hand and the left hand are mirror images of each other but are not superimposable. Similarly, the two non superimposable mirror images of a molecule are called as enantiomers. In achiral or symmetric environment, enantiomers exhibit similar physical and chemical properties except for their ability to rotate plane-polarized light in which they differ from each other and from achiral molecule.

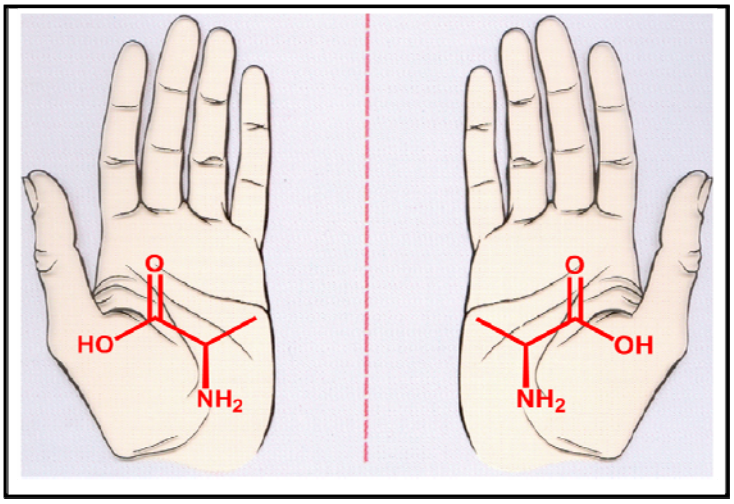


Figure 2. Molecules or objects that are non-identical with their mirror image are said to be chiral.

The two enantiomers of a particular molecule can be identified on their absolute configuration or optical rotation. The enantiomer which rotates the plane-polarized light to clockwise direction is described as *(R)* or (+) enantiomer and the other enantiomer of same molecule which has opposite and equal rotation under same conditions is described as (*S*) or (-) enantiomer. Cahn-Ingold-Prelog nomenclature[4] which is related to R/S notation (latin; *rectus* "right" and *sinister* "left") has largely replaced D/L notation and now they are used to assign absolute configuration of the molecular structure of chiral tetrahedral molecules.[5]

1.1.2. Importance of chirality in pharmaceuticals

Most of the macromolecules present in the living systems are chiral because they are made of chiral building blocks such as amino acids, sugars, protein and nucleic acids. In nature these molecules exist in single enantiomeric form for e.g. natural amino acids exists in L-form while natural sugars exist in D-form. Therefore in an environment of a living organism which itself is chiral each of the enantiomers of a chiral drug can behave very differently *in vivo*. In simple words, (*R*)-enantiomer of a particular drug may behave differently than the (*S*)-enantiomer when consumed by a patient. There are mainly four different possibilities for biologically active chiral compounds; i) both enantiomers have equal or nearly equal biological activity; ii) only one enantiomer have the required activity whereas the other isomer may be inactive; iii) quantitatively both enantiomers have different activity; iv) both enantiomers have different kind of biological activities.

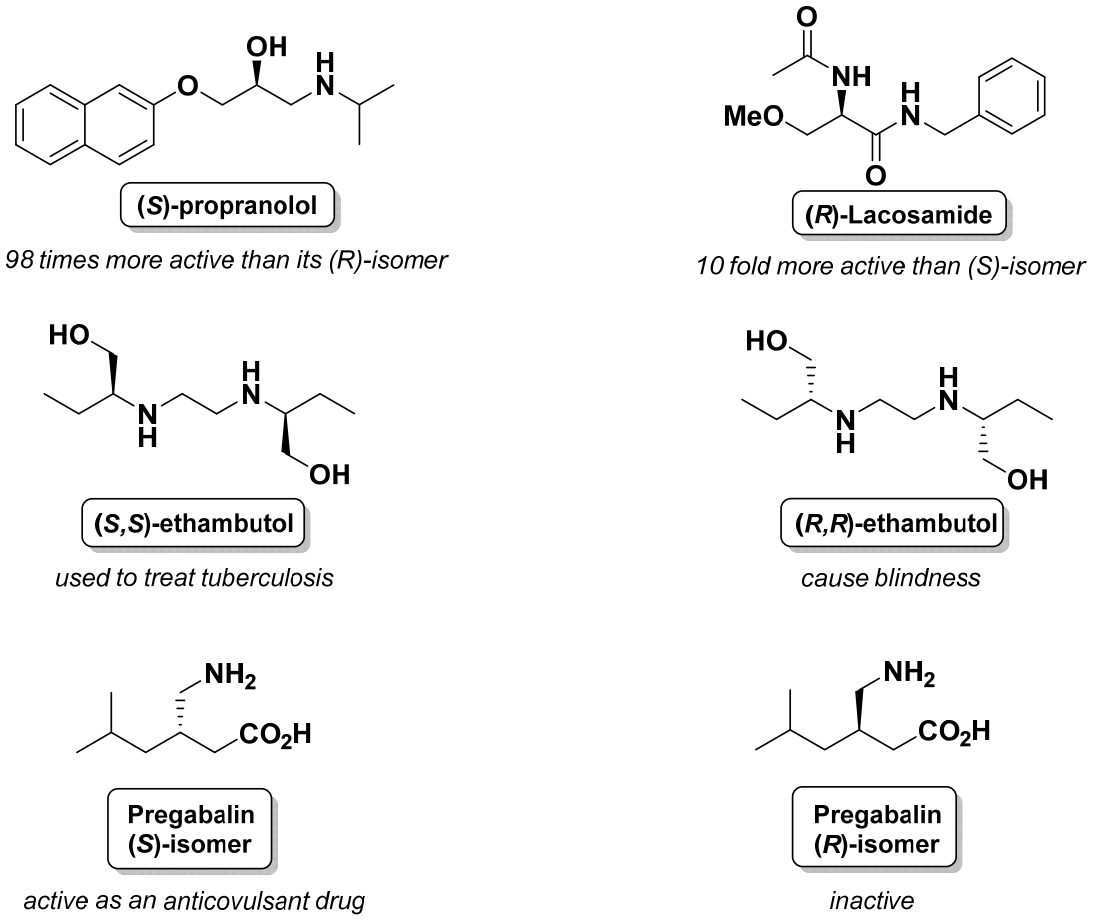


Figure 3. Chiral Compounds showing different biological activities

The two enantiomers of a particular molecule may have different taste, or smell and most importantly they may show different pharmacological properties.[6] For example (*R*)-limonene has an orange smell whereas (*S*)-limonene has an odor of lemons similarly natural L-asparagine has a bitter taste whereas D-asparagine is sweet. In case of drug molecules, β-blocker (*S*)-propranolol is 98 times more active than (*R*)-isomer. Lacosamide the (*R*)-enantiomer of *N*-benzyl-2-acetamido-3-methoxypropionamide, recently approved by FDA (Oct, 2008) as an add-on therapy for partial-onset seizures in adults with epilepsy is at least 10 fold more active than the (*S*)-isomer. (*S,S*)-ethambutol is an antitubercular drug, while (*R,R*)-ethambutol causes blindness. Thus it is essential to administer the (*S,S*) form to the patient and not the mixture of enantiomers. In case of Pregabalin which is an anticonvulsant agent, the (*S*)-enantiomer is responsible for the drug activity, whereas (*R*)-enantiomer is inactive. Thus it would be appropriate to consider two enantiomers of a particular drug molecule as two different drugs with different properties unless proven otherwise.

1.1.3. Market of chiral pharmaceuticals

A large fraction of the many thousand drugs on the market are chiral compounds (Fig. 4)[7].

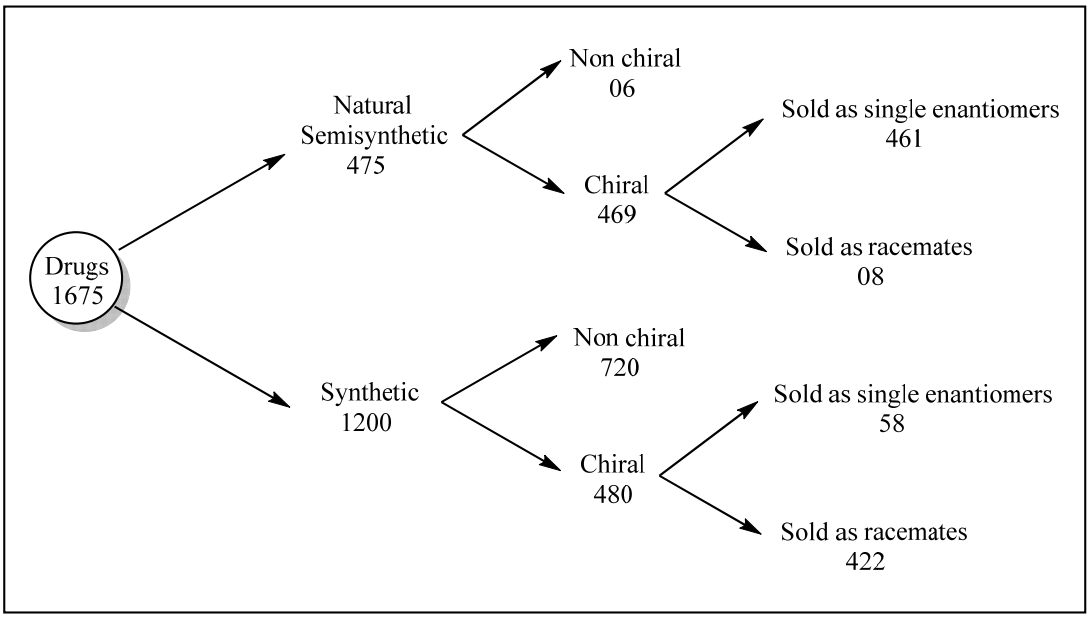


Figure 4. Chiral drugs: applications as single enantiomers or as racemic mixtures.

The concept of chirality has been known over many decades but the complete understanding of how this affects the pharmacological activity of drugs in pharmaceutical applications is very recent. Previously, synthetic chiral drugs were sold as racemates. Nowadays complete investigation of the pharmacological properties of the individual enantiomers became the rule for all new racemic drugs and chiral considerations are an integral part of drug research and development. In 1987, the U.S. Food and Drug Administration issued a guideline that pharmaceutical companies should investigate individual enantiomers in racemic mixtures preclinically and clinically, and for chiral drugs only its therapeutically useful enantiomer should be brought to market.[8] For the approval of a racemate of chiral drugs proper justifications are required from the market. However, many chiral drugs are still sold as racemic mixtures.[9] Beside ethical and economical reasons, the therapeutic benefits like efficiency, safety and in several cases, extension of the life cycle of the drug attracts the pharmaceutical industry for the development of single enantiomers of a particular drug. Hence in the past two decades rapid development of enantioselective processes has been observed which have reached a high degree of diversity and complexity. Some important chiral drugs from various therapeutic classes are presented in Table 1.[10]

Table 1. Examples of chiral drugs from various therapeutic classes

Antiarrhythmics	Propafenone, tocainide
Antibiotics	Ofloxacin, moxalactam
Anticoagulants	Warfarin, acenocoumarol
Anesthetics	Prilocaine, ketamine,
Antiemetics	Ondansetron
Antihistamine	Terfenadine, loratadine
Antihyperlipidemic	Atorvastatin
Antineoplastics	Cyclophosphamide,
Antimalarials	Chloroquine, halofantrine, mefloquine
Muscle relaxants	Methocarbamol, baclofen
NSAIDS	Ibuprofen, ketorolac

β -blockers	Propranolol, metoprolol
β -adrenergics	Salbutamol, terbutaline
Calcium channel blockers	Verapamil, nimodipine
Opiate analgesics	Methadone, pentazocine
Proton pump inhibitors	Omeprazole, pantoprazole, lansoprazole

1.2. Methods for the preparation of enantiopure compounds

Among several different approaches for the preparation of enantiopure compounds, the three main strategies are:

1. Chiral pool approach

2. Resolution of racemates

3. Asymmetric synthesis

1.2.1. Chiral pool approach

This method is based on the transformation of enantiomerically pure starting material derived from natural resources such as amino acids, carbohydrates, terpenes and hydroxy acids (Fig. 5).[11]

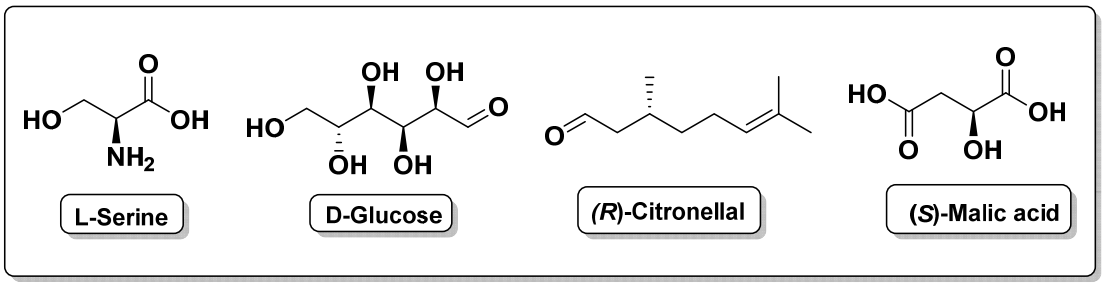
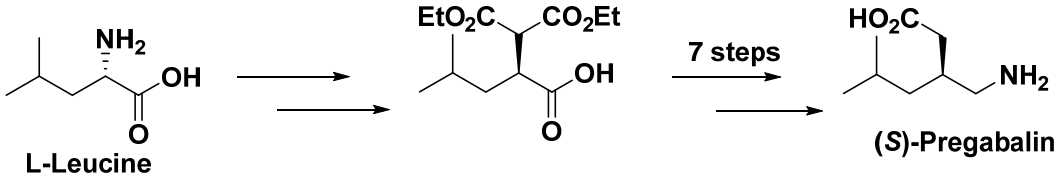


Figure 5. Examples of naturally occurring chiral starting materials

If the right source of starting material is available from chiral pool, then this approach often becomes the most cost effective way of introducing chirality. But, the main drawback of the chiral pool approach is the availability of limited numbers of starting material, sometimes which can be expensive or difficult to obtain thus limiting its

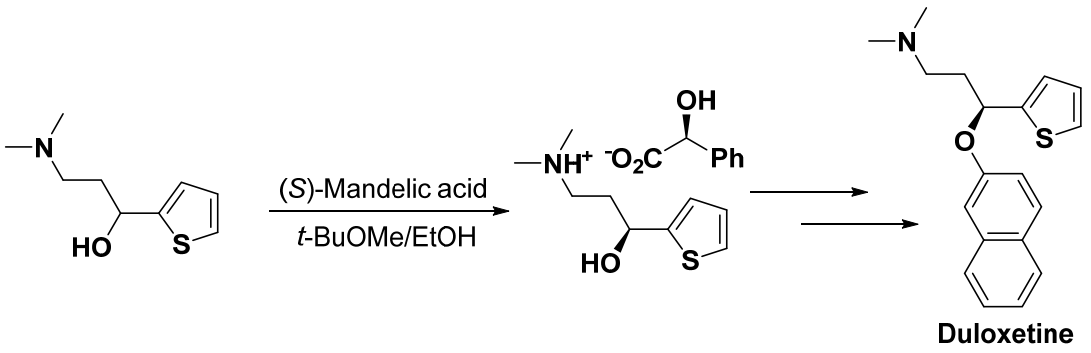
synthetic utility. The synthesis of Pregabalin, an anticonvulsant agent starting from L-leucine[12] is a typical example of the Chiron approach (Scheme 1).



Scheme 1. Chiral pool approach for the synthesis of (*S*)-Pregabalin

1.2.2. Resolution of racemates

For the preparation of enantiopure compounds, one of the oldest and widely used protocols is the resolution of racemates in which resolution is performed at the end of a racemic reaction sequence with the help of a chiral compound. As, in most of the cases only one enantiomer is useful, half of the synthetic product is often discarded. Further, this method requires equimolar amount of an enantiomerically pure compound which cannot be reused or recycled. But, still this method is widely used in industries. For example synthesis of antidepressant drug Duloxetine was carried out via resolution method using (*S*)-Mandelic acid.[13]



Scheme 2. Synthesis of duloxetine via resolution method

1.2.3. Asymmetric synthesis

Asymmetric synthesis deals with the formation of a new stereogenic centre under the influence of a chiral group. In recent years, asymmetric synthesis has gained much importance due to introduction of advanced separation techniques and development of

novel and exciting chiral auxiliaries. However this method is divided into four major categories, depending on how the stereo-centre is formed:

a) Substrate-controlled methods.

b) Auxiliary-controlled methods.

c) Reagent-controlled methods.

d) Catalyst-controlled methods.

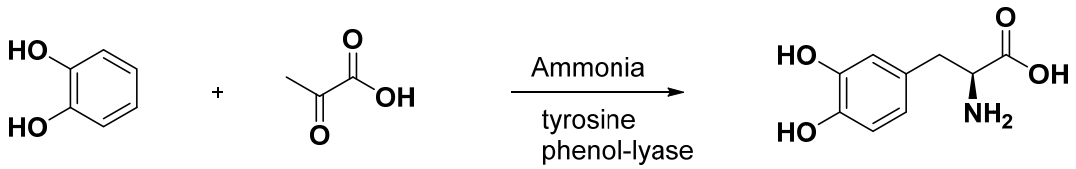
In the case of the substrate-controlled method, a chiral substrate is reacted with an achiral reagent so that the reaction is directed intramolecularly by a stereogenic unit already present in the substrate. The auxiliary-controlled method consists of attaching chiral auxiliary to an achiral substrate in order to direct the reaction of an incoming group. The chiral auxiliary can be removed once the purpose is served and often reused. This method usually offers high level of selectivity and has proven to be extremely versatile as it can be used to make large variety of target molecules in enantiomerically pure form. However, this methodology suffers from the drawback that it requires two extra steps to attach and remove the chiral auxiliary. Reagent-controlled methods involve a direct transformation of an achiral substrate to the chiral product by use of a chiral reagent in which the control of the reaction is intermolecular. However, the range of reactions for which effective chiral reagents are available is somewhat limited. All three previously described methods have a common disadvantage in which atleast one equivalent of an enantiomerically pure compound is required which is not suitable from the economical as well as environmental perspective. Thus to overcome this problem, the most significant advancement in asymmetric synthesis during the past few decades was the development and application of chiral catalysts to induce the transformation of an achiral molecule to an enantiomerically pure chiral product. Due to its importance this method will be discussed in detail in the following section.

1.2.4. Asymmetric Catalysis

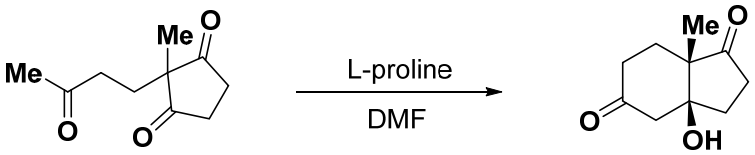
Catalysis is the change in rate of a chemical reaction due to the involvement of a substance called a catalyst without itself being consumed or transformed. Catalysis can be divided into homogeneous catalysis (catalyst exists in the same phase as the reaction mixture) and heterogeneous catalysis (catalyst act in different phase than the

reaction mixture). In asymmetric catalysis, small amounts of a chiral catalyst is needed to synthesize large amounts of enantiomerically pure molecules.[14]

There are different kinds of asymmetric catalysis including; (a) biocatalysis: involving the use of an enzyme (Scheme 3)[15] (b) organocatalysis: involving the use of small organic molecules (Scheme 4)[16] (c) organometallic catalysis: involving the use of metal complexes. All these asymmetric catalysis are widely used in small as well as large scale synthesis to form the chiral product in high enantiopurity, as they have significant advantages over other methods which involve chiral resolution or synthesis from enantiomerically pure starting compounds.

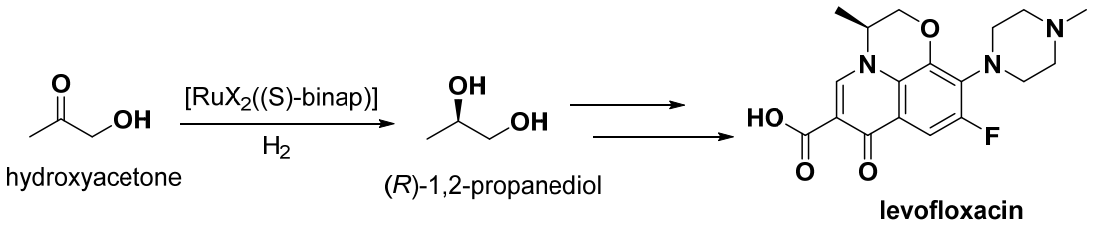


Scheme 3. Industrial production of L-Dopa using enzyme

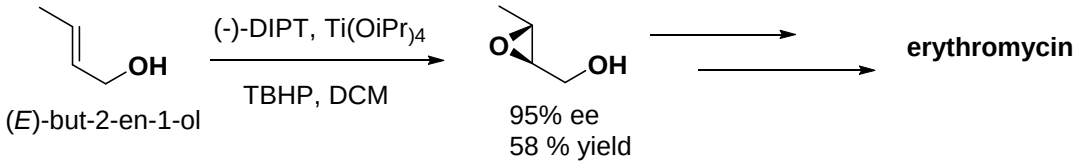


Scheme 4. Organocatalyzed asymmetric Robinson annulations

The main revolution in asymmetric catalysis was the development of chiral transition metal complexes and this was made possible principally by the work of Ryoji Noyori (who developed the ruthenium and rhodium catalyzed reductions) and K. Barry Sharpless (who developed the osmium and titanium catalyzed oxidations). This work won Noyori and Sharpless the Nobel Prize for chemistry in 2001, along with William Knowles (who first applied metal-catalyzed asymmetric reactions to industrial targets). The Sharpless epoxidation reaction has the great impact for asymmetric catalytic reaction, providing easy access to highly enantio-enriched epoxy alcohols but it is limited only for allylic alcohol systems (Scheme 6).



Scheme 5. Example of Noyori asymmetric hydrogenation[17]



Scheme 6. Example of Sharpless asymmetric epoxidation[18]

1.3. Hydroltic Kinetic Resolution (HKR)

Despite the considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched terminal epoxides, arguably the most valuable class of epoxides for organic synthesis. The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[19] but also the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with various nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have been very well documented.[20] For the synthesis of enantiopure epoxides nature's chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, chiral epoxides have been prepared indirectly from the chiral pool via multistep procedures.[21] Recently Jacobsen discovered the (salen)Co complex **1** (Fig. 6) catalyzed efficient hydrolytic kinetic resolution (HKR) for preparation of enantiopure terminal epoxides (Scheme 7).[22,23] The key features of HKR strategy are: firstly, cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** are commercially available, easily accessible and easy to handle with very low catalytic loading.

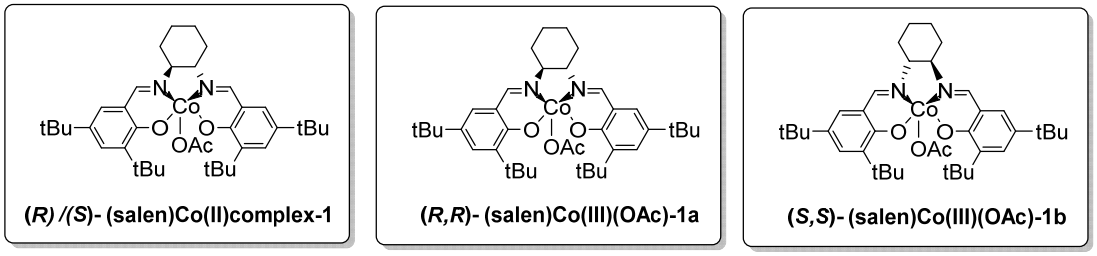
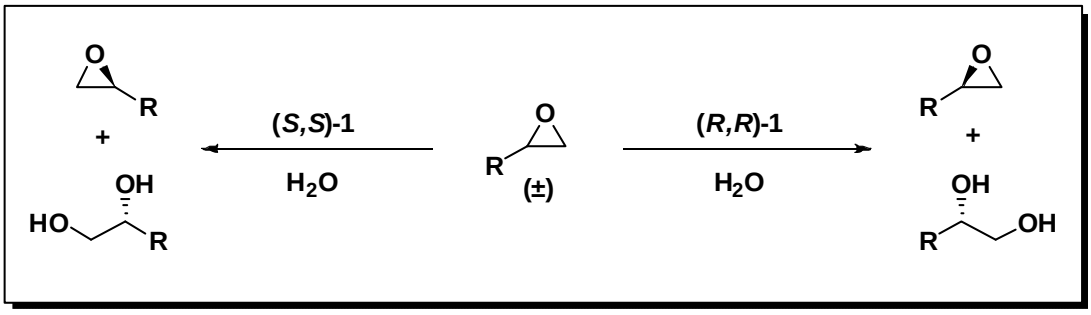


Figure 6. Jacobsen's Catalyst



Scheme 7. General reaction of hydrolytic kinetic resolution for synthesis of chiral epoxides

Secondly, water is used as a reactant and nucleophile for effecting the resolution reaction; water is safe and inexpensive, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture.

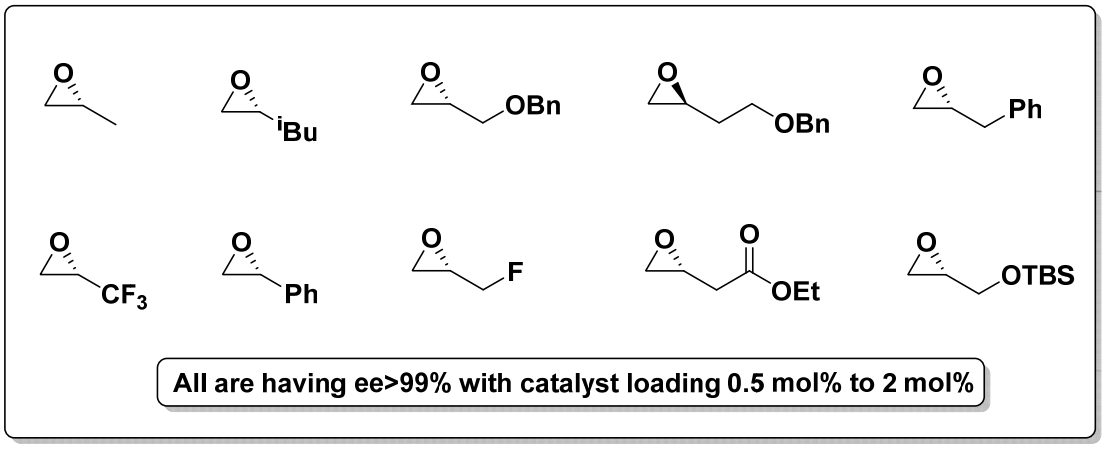


Figure 7. Few examples of terminal epoxides prepared employing HKR method

Thirdly, extraordinary substrate generality in high enantiopurity (Fig. 7), solvent-free reaction conditions which make this protocol environment friendly and easy separation of products often by simple distillation or by column chromatography are the added advantages.[24] Finally, this method provides useful enantio-enriched 1,2-

diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[25]

Since its discovery in the year 1996, HKR has been successfully utilized for the synthesis of wide range of bioactive natural products (Fig. 8).[26] Racemic 1,2-epoxides are often commercially available at low cost or they can be prepared in a single step either from aldehydes or olefins.

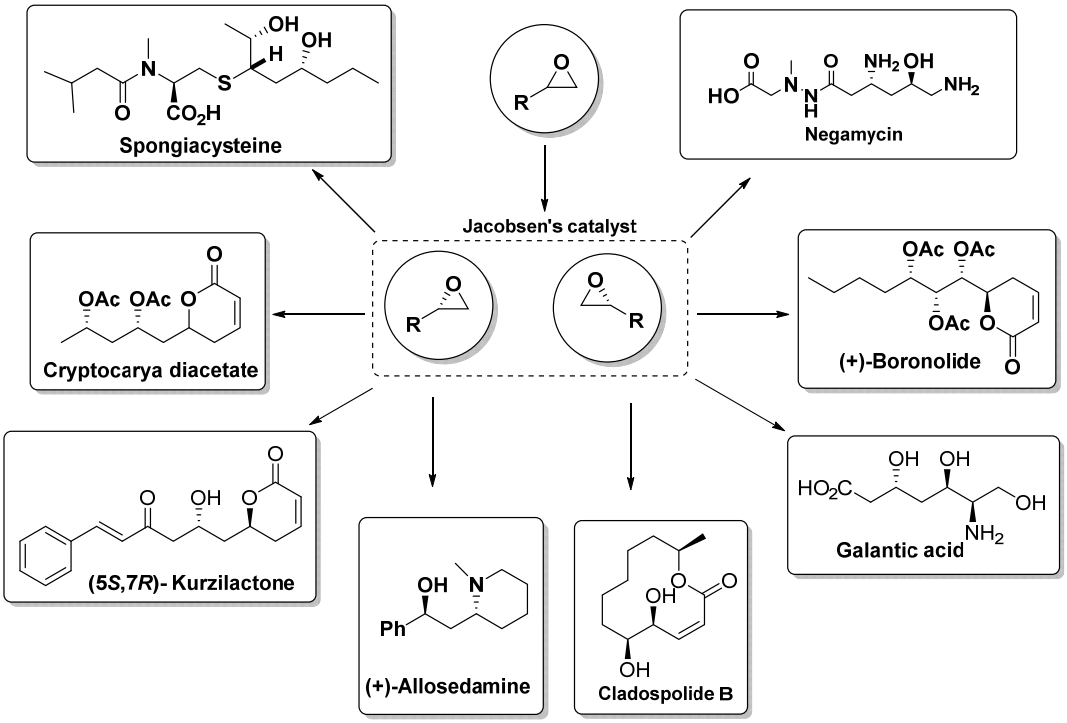


Figure 8. Some examples of application of Jacobsen's HKR for the synthesis of bioactive natural products

1.3.1. Industrial perspective of HKR[27]

Recently, 'Rhodia ChiRex', a chemical company successfully developed kinetic resolution technology of terminal epoxides on ton scale. Further this technology was transferred to a company 'Diaso', a bulk producer of enantiopure epoxides using microbial resolution and they recently switched over to Jacobsen's technology with production capacity of 50 ton/annum. Researchers at Synetix are developing immobilized Jacobsen catalyst on zeolites for easy separation and reuse of the spent catalyst.

1.4. References

1. Loudon, G. M. Addison-Wesley Publishing Co., Massachusetts, **1984**.
2. Pasteur, L. *Am. Chim., Phys.* **1848**, *24*, 442.
3. Le Bel, J. A. *Bull. Soc. Chim. France.* **1874**, *22*, 337; (b) J. H. van't Hoff, *Bull. Soc. Chim. France* **1875**, *23*, 295.
4. Cahn R, S; Ingold C, K; Prelog V. The specification of asymmetric configuration in organic chemistry. *Experientia.* **1956**, *12*, 81..
5. Mislow, K. Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.
6. (a) Frank, H. Holmstedt, B. Testa, B. *Chirality and Biological Activity*, Liss, H. R. Inc, New York, **1990**; (b) Ahuja, S. *Chiral Separation by Liquid Chromatography*, ed. Ahuja, S. Washington D.C., **1991**.(c) Welch, C. J. *Advances in Chromatography*, Vol. 35, Marcel Dekker, NewYork, **1995**, p. 171.(d). Drayer, D. E. *Clin. Pharmacol. Ther.* **1986**, *40*, 125.
7. Ariens, E., J. *Clin. Pharmacal. Ther*. **1987**, *42*, 361.
8. (a) Strong, M. *Food and Drug L. J.* **1999**, *54*, 463. (b) Branch, S. K. in: *Chiral Separation* Stinson, S. *Chem. Eng. News* **1995**, *73*, 49.
9. Lin, B. C; Zhu, X. F. Koppenhoefer, B. Epperlein, U. *LC GC-Mag. Sep. Sci.* **1997**, *15*, 40.
10. Davies, N. M; Teng, X. W. *Advances in Pharmacy*. **2003**, *vol I* (3), 242.
11. Hanessian, S. *Total synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, U. K., **1983**.
12. Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org.Process Res. Dev*. **1997**, *1*, 26.
13. Fujima, Y.; Ikunaka, I.; Inoue, T.; Matsumoto, J. *Org Process Res Dev.* **2006**, *10*, 905.
14. Walsh, P. J. Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*, University Science Books, **2009**.
15. Industrial production of L-Dopa using enzyme: Blaser, H.-U. Schmidt, E. *Asymmetric Catalysis on Industrial Scale - Challenges, Approaches and Solutions*, Wiley, New York, **2004**.
16. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

17. Nyori, R. *Angew. Chem. Int. Ed.* **2002**, *48*, 2008.

18. Rossiter, B. E; Katsuki, T; Sharpless, K. B. *J. Am. Chem. Soc.* **1981,** *103*, 465.

19. (a) Epothilones: Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325; (b) FR901464: Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96.

20. (a) Winstein, S.; Henderson, R. B. In*Heterocyclic Compounds*, Vol. 1; Elderfield, R. C., Ed.; Wiley: New York, 1950; Chapter 1; (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737; (c) Barto´k, M.; La´ng, K. L. Small Ring Heterocycles. In *The Chemistry of Heterocyclic Compounds*, Vol. 42, Part 3; Hassner, A., Ed.; Wiley: New York, 1985; Chapter 1; (d) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323; (e) Smith, J. G. *Synthesis,* **1984**, 629.

21. (a) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993; (b) Larchevêque, M.; Henrot, S. *Tetrahedron* **1990**, *46*, 4277; (c) de March, P.; Figueredo, M.; Font, J.; Monsalvatje, M. *Synth. Commun.* **1995**, *25*, 331; (d) Adiyaman, M.; Khanapure, S. P.; Hwang, S. W.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 7367.

22. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org.Chem*. **1998**, *63*, 6776.

23. (a) Tekeichi, T.; Arihara, M.; Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391. (b) Maruyama, K.; Nakamura, T.; Nakamura, S.; Ogino, A.; Nishinaga, A. *React. Kinet. Catal. Lett.* **1991**, *45*, 165. (c) Larrow, J. F., Schaus, S. E., Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.

24. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen. E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307.

25. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448.

26. Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron.* **2007**, *63,* 2745.

27. Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Sturmer, R.; Zelinski, T.; *Angew. Chem. Int. Ed*. **2004**, 43, 788.

1.2. SECTION B

Asymmetric synthesis of Pregabalin via hydrolytic kinetic resolution

1.2.1. Introduction

γ-Aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the mammalian central nervous system (CNS). It is estimated that depending on the brain region about 20 to 50% of all central synapses use GABA as their transmitter.[1] It is well known that GABA deficiency is associated with several important neurological disorders such as Parkinson's and Alzheimer's disease, Huntington's chorea, and other psychiatric disorders such as depression, anxiety, pain, panic or mania.[2] Although, it is a known fact that increasing the brain concentration of GABA prevent convulsions, unfortunately GABA does not enter the central nervous system by systematic administration. It is due to the highly polar and flexible nature of this compound, hence make it inefficient as an anticonvulsant agent when administered orally or intravenously.[3] To circumvent this problem, many GABA analogues were designed and synthesized. Few examples of GABA analogues (gabapentin, baclofen and pregabalin) are represented in Fig. 1.[4]

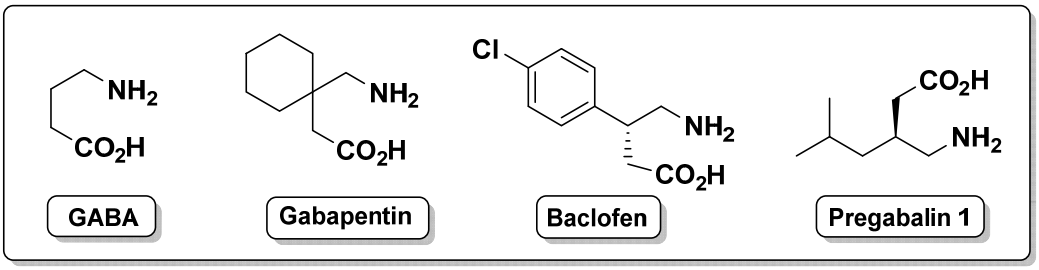


Figure 1. Pregabalin and GABA analogues

In 1991, Silverman and co-workers synthesized a series of GABA analogues possessing substitution at *C*-3 carbon. These compounds were studied for their anticonvulsant properties and found that 3- isobutyl analogue of GABA was more active.[5] Further, the anticonvulsant activity of racemic 3-isobutyl GABA resides only in the (*S)* enantiomer called pregabalin (PGB) (Fig. 1).[6] Gabapentin and pregabalin **1** are the 3-alkylated GABA analogues which are structurally similar, but differs in the

oral absorption profile. In fact, pregabalin can achieve therapeutically efficacious blood levels at lower doses than those required with gabapentin. Pregabalin underwent extensive clinical studies and proved to be successful in completing double-blind clinical studies which includes partial seizures (add-on treatment), diabetic neuropathy, post-herpetic neuralgia, generalized anxiety disorder, social anxiety disorder, fibromyalgia pain (and sleep), and tooth extraction pain.[7]

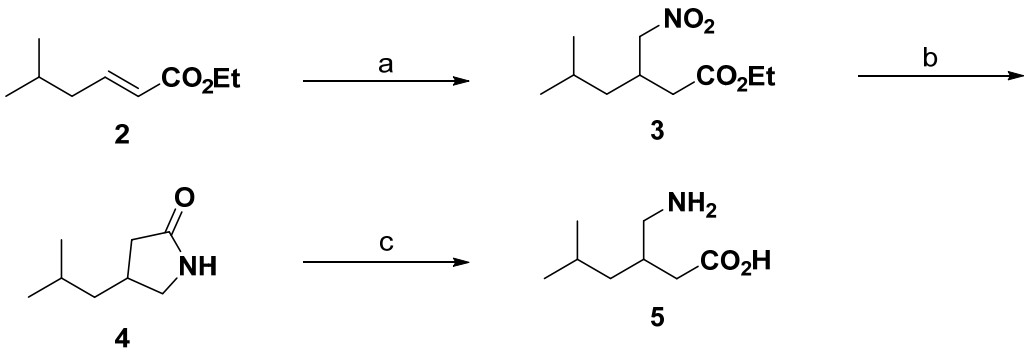
In 2005, pregabalin received FDA approval for the treatment of diabetic neuropathy, post-herpetic neuralgia, and as an add-on treatment for partial seizures under the trade name of Lyrica®. Pregabalin displays a new mechanism of action and acts as a voltage-dependent calcium channel α_2-δ subunit ligand. Due to its unique mode of action it became Pfizer's second best selling drug, with worldwide sale of $998 million in 2011 showing 22 % increase from previous year.[8]

1.2.2. Review of Literature

Several approaches have been reported in the literature for the synthesis of racemic as well as optically active pregabalin **1**. A few significant syntheses of pregabalin **1** are described below.

Silverman *et al.* synthesis of *rac*-pregabalin (1989)[9]

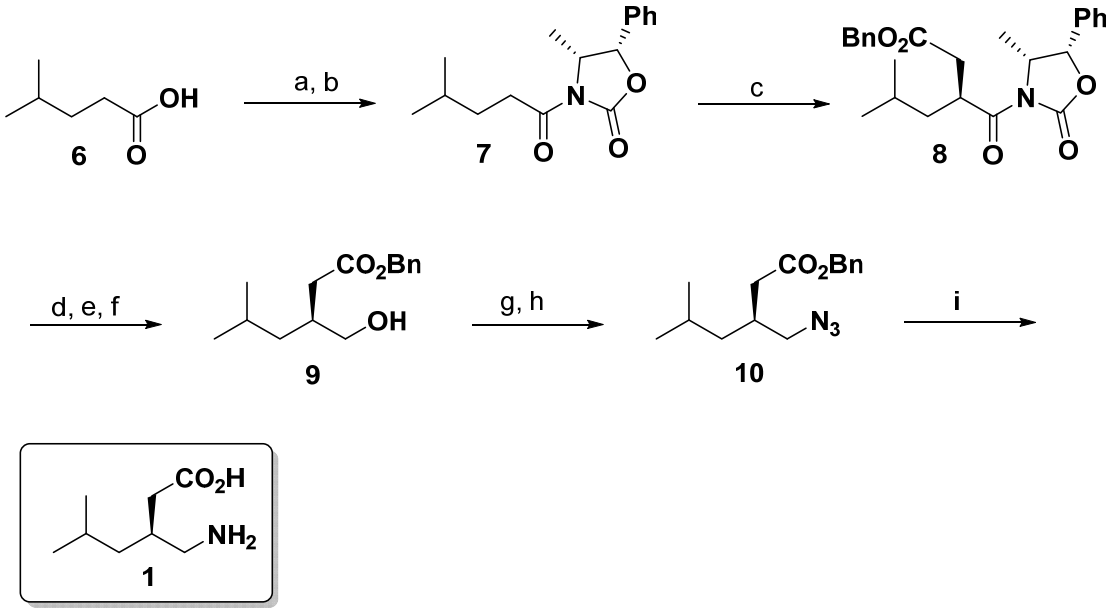
Silverman *et al.* reported the first racemic synthesis of pregabalin via conjugate addition of nitromethane to ethyl 5-methyl-hexenoate **2** to give nitroester **3**. Nitroester **3** was hydrogenated to produce lactam **4** followed by hydrolysis under acidic conditions to furnish *rac*- pregabalin **5** in 58% overall yield (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) TMG, $MeNO_2$, 66%; (b) H_2, Pd/C, AcOH; (c) 6N HCl then ion exchange, 88%.

Yeun *et al.* (The original Pfizer synthesis- 1994)[10]

Yeun *et al.* presented the first enantioselective synthesis of pregabalin using Evan's chiral auxiliary (Scheme 2). Thus, 4-Methylpentanoic acid was converted into the corresponding acid chloride followed by treating with (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone to give acyloxazolidinone derivative **7**. The resulting acyloxazolidinone **7** was alkylated with benzyl bromoacetate to give the benzyl ester intermediate **8**. The removal of chiral auxiliary followed by a modified bisulfite work-up at pH 7 gave the corresponding acid. Borane reduction of the acid intermediate and the resulting alcohol **9** was then converted to the corresponding azide **10** via tosylation. Finally, debenzylation and azide reduction under catalytic hydrogenation condition gave pregabalin **1**.

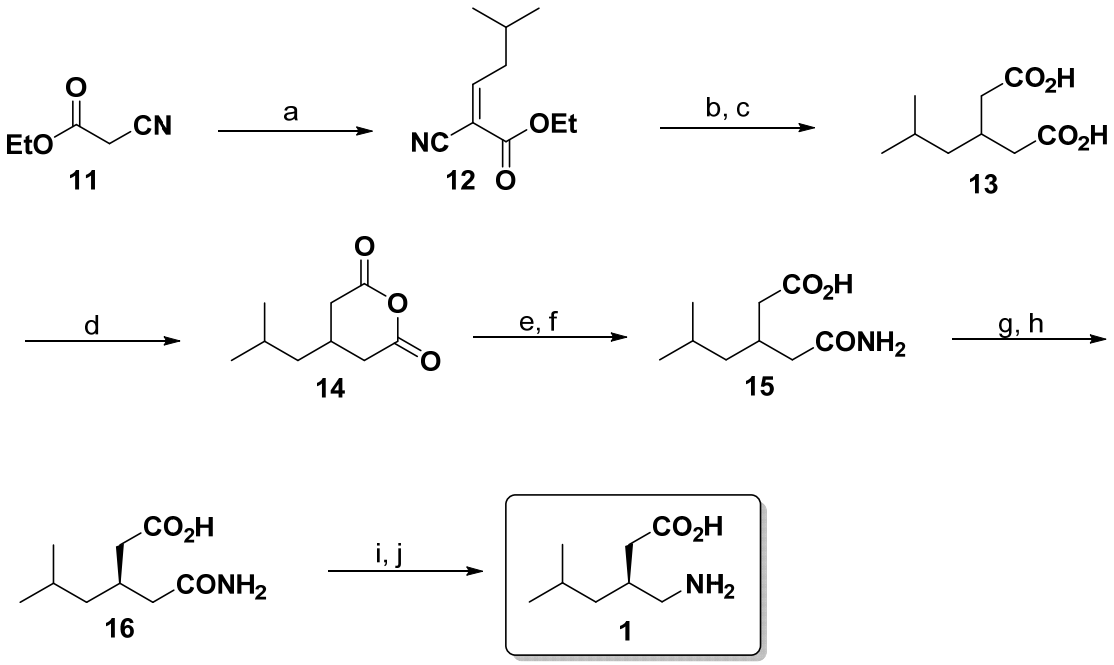


Scheme 2. *Reagents and conditions***:** (a) $SOCl_2$, $CHCl_3$; (b) (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone, THF, 64%; (c) benzyl bromoacetate, LDA, THF, 53%; (d) LiOH, H_2O_2; THF, H_2O; (e) Na_2SO_3, $NaHSO_3$, pH 7; (f) $BH_3.SMe_2$, THF, 73% (3 steps); (g) TsCl, pyridine; (h) NaN_3, DMSO, 76% (2 steps); (i) H_2, Pd/C, HCl, THF 65%.

Huckabee *et al.* (1996)[11]

Huckabee *et al.* started with ethyl cyanoacetate **11** which on condensation with isovaleraldehyde gave unsaturated ester **12**. Michael addition followed by acid-

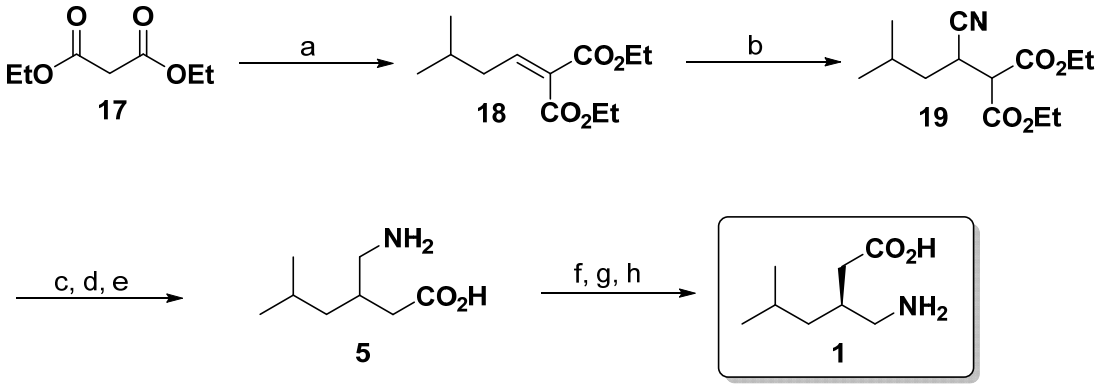
induced decarboxylation gave glutaric acid **13**. Acid **13** was then converted to the acid amide derivative **15** via the anhydride **14**. Acid amide **15** was further resolved using (*R*)-methylbenzylamine to give the chiral acid amide **16** in 98% ee. Hofmann rearrangement of amide **16** gave pregabalin **1** (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) isovaleraldehyde, *n*-dipropylamine, heptane, 98%; (b) diethyl malonate, *n*-dipropylamine; (c) HCl, H_2O, 82% (2 steps); (d) Ac_2O, 92%; (e) NH_3 (aq), MTBE; (f) HCl, 95% (2 steps); (g) (*R*)-methylbenzylamine, EtOH, $CHCl_3$; (h) HCl, H_2O, 75% (2 steps); (i) NaOH, Br_2; (j) HCl, 59% (2 steps).

Grote *et al.* (1996)[12]

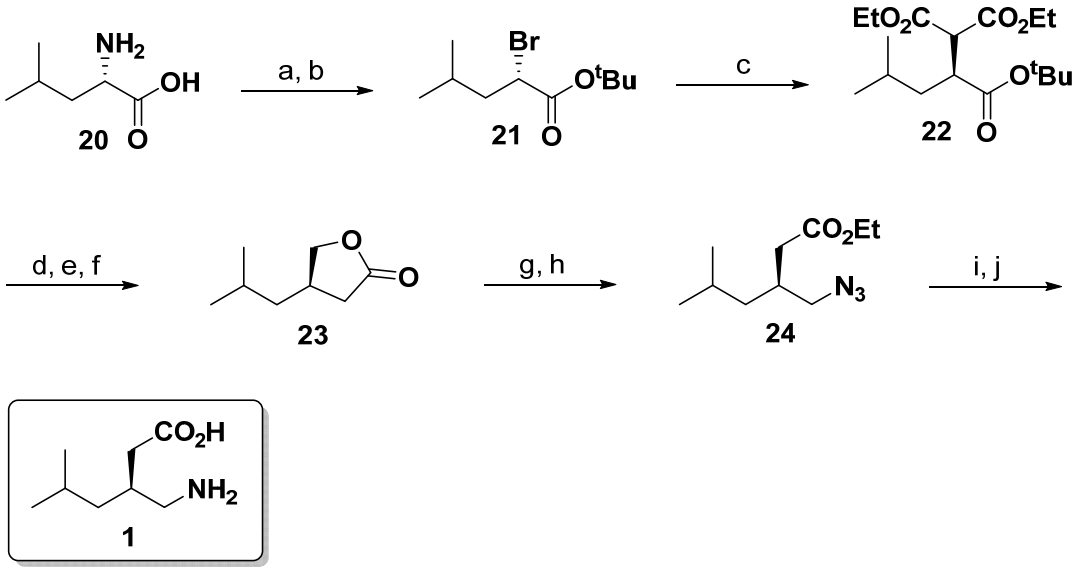
Grote *et al.* synthesized pregabalin 1 starting from diethyl malonate **17** which was condensed with isovaleraldehyde to give unsaturated diester **18**. Michael addition of potassium cyanide to the unsaturated diester **18** gives cyanodiester **19**. The cyano derivative was then saponified; the resulting malonic acid was decarboxylated and the cyano acid hydrogenated using a nickel catalyst to give *rac*- pregabalin **5**. Resolution of *rac*-pregabalin **5** using mandelic acid afforded pregabalin **1** (Scheme 4).



Scheme 4. *Reagents and conditions***:** (a) isovaleraldehyde, *n*-dipropylamine, HOAc, hexane, 89%; (b) KCN, EtOH, 94%; (c) KOH, H_2O, MeOH; (d) H_2, Ni, H_2O, EtOH; (e) HOAc, EtOH, H_2O, 73% (3 steps); (f) (*S*)-(+)-Mandelic acid, *i*-PrOH, H_2O; (g) THF, H_2O; (h) recrystallization in *i*-PrOH/H_2O, 56% (3 steps).

Hoekstra *et al.* (1997)[13]

Hoekstra *et al.* reported a chiral pool approach starting with L-leucine **20** (Scheme 5). Thus, L-leucine **20** was converted to the bromoester **21** followed by treating with excess sodium salt of diethyl malonate to give ester derivative **22**.

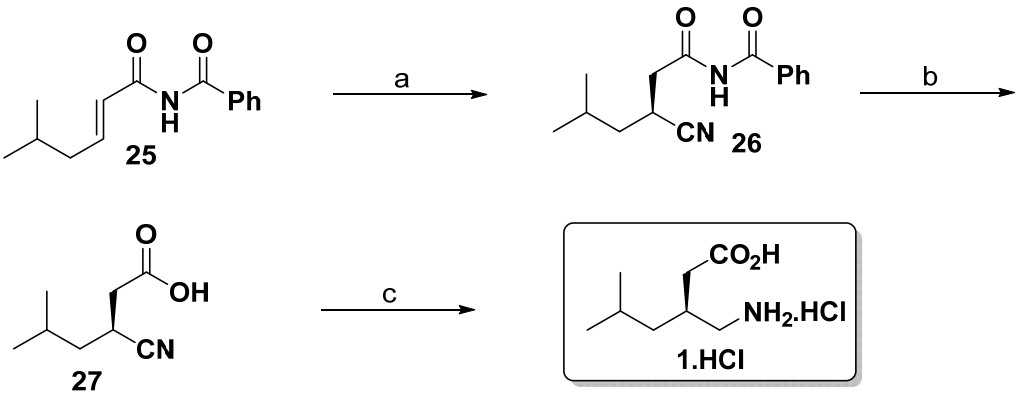


Scheme 5. *Reagents and conditions*: (a) $NaNO_2$, NaBr, H_2SO_4, 76%; (b) *t*-BuOAc, BF_3.HOAc, 83%; (c) $NaCH(CO_2Et)_2$, THF, 93%; (d) HCO_2H; (e) $BH_3.SMe_2$; (f) HCl, H_2O, 87% (3 steps); (g) TMSI, EtOH, 94%; (h) NaN_3, DMSO, 94%; (i) KOH, EtOH, H_2O, 86%; (j) H_2, Pd/C, 76%.

The *t*-butyl ester was deprotected using formic acid and the resulting acid was reduced with borane to the corresponding alcohol. The alcohol was treated with aqueous hydrochloric acid to effect hydrolysis of the esters followed by decarboxylation and lactone formation to give intermediate **23**. Lactone **23** was treated with trimethylsilyl iodide to give the iodoester and the iodide was further converted to azidoester **24** using sodium azide. Saponification followed by catalytic hydrogenation of the azidoester **24** gave pregabalin **1**.

Jacobsen *et al.* (2003)[14]

Jacobsen *et al.* utilized their excellent methodology of conjugate addition of hydrogen cyanide into the unsaturated imide **25** using 10 mol% of the (*R,R*)-aluminum salen catalyst to give the cyano derivative **26** in 96% ee. Cyano intermediate was then hydrolyzed to give acid **27** followed by hydrogenation in the presence of platinum oxide to give pregabalin hydrochloride (Scheme 6).

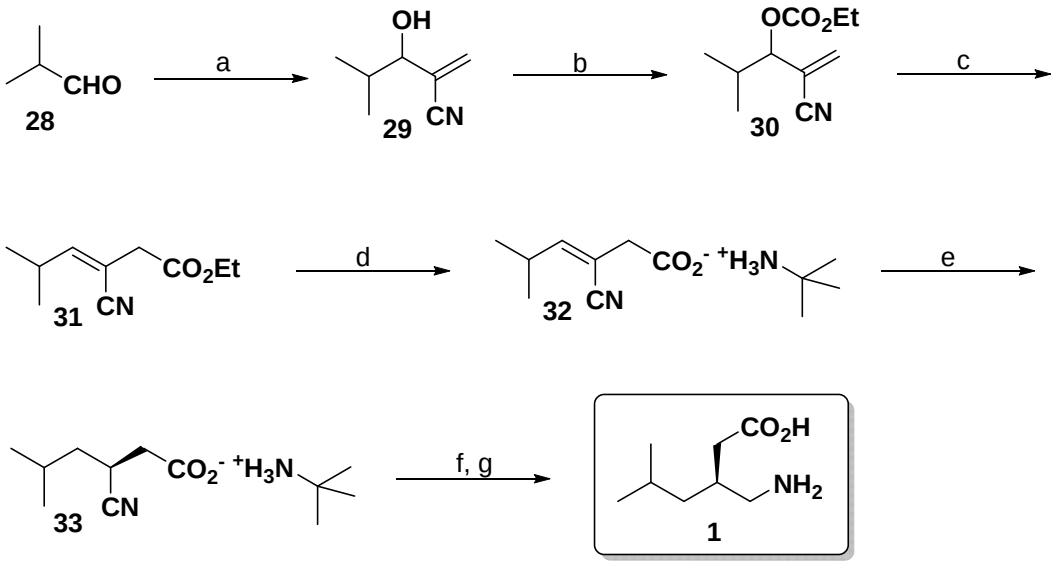


Scheme 6. *Reagents and conditions*: (a) chiral aluminium salen complex, TMSCN, *i*-PrOH, PhMe, 93%; (b) 1N NaOH, THF, 94%; (c) H_2 (500 psi), PtO_2, HCl, H_2O, 92%.

Burk *et al.* (2003)[15]

Burk *et al.* started their synthesis with the condensation of isobutyraldehyde **28** with acrylonitrile under Baylis–Hillman conditions to give allylic alcohol **29**. This alcohol was activated as the carbonate **30** and subjected to palladium-catalyzed carbonylation conditions to give unsaturated cyanoester **31**. The ester was hydrolyzed and converted to its corresponding *t*-butyl ammonium salt **32**, which on catalytic asymmetric hydrogenation using (*R,R*)-methylDuPHOS rhodium give the cyanoacid ammonium

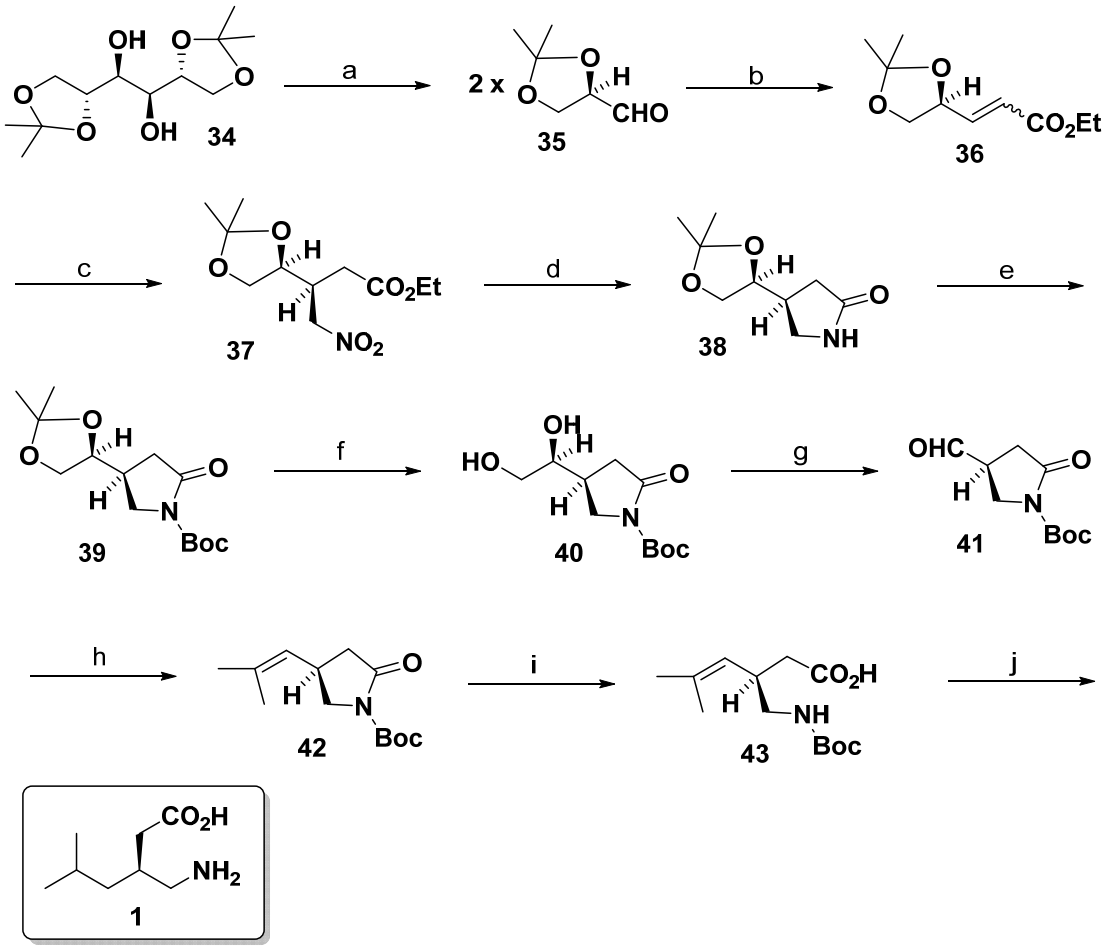
salt **33** in 98% ee. Hydrogenation of cyanoacid **33** over nickel gave pregabalin **1** in high enantiopurity (Scheme 7).



Scheme 7. *Reagents and conditions*: (a) acrylonitrile, DABCO, H_2O, 2, 6-di-*tert*-butyl-4-methylphenol, 97%; (b) $EtCO_2Cl$, pyridine, 95%; (c) $Pd(OAc)_2$, PPh_3, EtOH, CO, 83%; (d) LiOH, H_2O, *tert*-$BuNH_2$; (e) [(*R,R*)-(MeDuPHOS)Rh(COD)]-BF_4, H_2, MeOH, 100%; (f) H_2(50 psi), Ni, KOH, H_2O, EtOH; (g) HOAc, 61% (2 steps).

Izquierdo *et al.* (2008)[16]

In 2008, Izquierdo *et al.* reported synthesis of pregabalin starting from D-mannitol bisacetonide **34** which on oxidative cleavage gave aldehyde **35** (Scheme 8). Using Wadsworth–Emmons olefinization aldehyde **35** was transformed to unsaturated ester intermediate **36**. Further, 1,4-addition of nitromethane to unsaturated ester **36** produced nitroester derivative **37** followed by reduction of the nitro group and in situ cyclization to give lactam derivative **38**. *N*-Boc protection of lactam **38** followed by chemoselective ketal deprotection provided diol **40**. Oxidative cleavage of diol gave aldehyde **41** followed by incorporation of the isopropyl group through a Wittig condensation of **41** with isopropylidenetriphenyl phosphorane leading to isobutenyl oxazolidin-2-one **42**. The lactam ring was then opened by the reaction between **42** and 1 M LiOH in THF at room temperature to afford acid **43**. The reduction of the C–C double bond and the hydrolysis of the *N*-Boc carbamate was carried out using hydrogenation of acid **43** over 20% $Pd(OH)_2/C$ in ethanol, in the presence of aqueous HCl, under 6 atmosphere pressure at room temperature to furnish pregabalin **1**.



Scheme 8. *Reagents and conditions*: (a) $NaIO_4$, THF-H_2O, 93%; (b) $(EtO)_2POCHCO_2Et$, *t*-BuOK, DCM, 80%; (c) CH_3NO_2/TBAF, THF, 75%; (d) NH_4HCO_2, $Pd(OH)_2$/C, MeOH; (e) $(Boc)_2O$, TEA, DMAP, 100%; (f) 90% AcOH, 100%; (g) $NaIO_4$, MeOH-H_2O, 100%; (h) $Ph_3PC(CH_3)_2$, THF, 60%; (i) 1M LiOH, THF, 100%; (j) H_2, $Pd(OH)_2$/C, HCl, MeOH, 100%.

1.2.3. Present Work

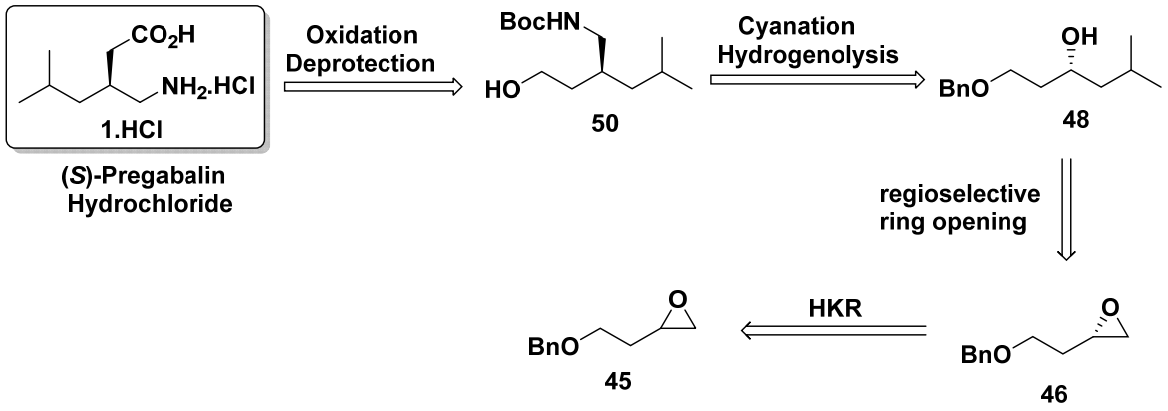
Objective

As pregabalin possess interesting medicinal properties, interest in the synthesis of this class of compounds continues unabated. Although a few syntheses are reviewed in foregoing section, several more are documented in the literature. There has been surprisingly no report on the synthesis of this molecule using Jacobsen's HKR

method. We thought it would be worthwhile to design a synthetic route for this molecule using Jacobsen's HKR method as a key step.

1.2.4. Results and Discussion

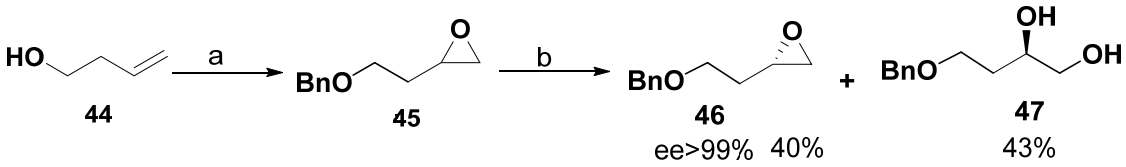
A retrosynthetic analysis of pregabalin **1** is outlined in Scheme 9. It is envisaged that the secondary alcohol **48** would serve as a key intermediate for the synthesis which can be extended to the *Boc*-protected amino alcohol **50** via cyanation and hydrogenolysis. Simple oxidation and deprotection of compound **50** can lead to pregabalin **1**. Further, the key intermediate **48** in turn can be accessed from the enantiopure epoxide **46** by regioselective ring opening using Grignard reagent. The enantiopure epoxide **46** can be easily obtained with high enantiopurity from its racemic epoxide **45** employing Jacobsen's hydrolytic kinetic resolution strategy.



Scheme 9. Retrosynthetic analysis of pregabalin **1**

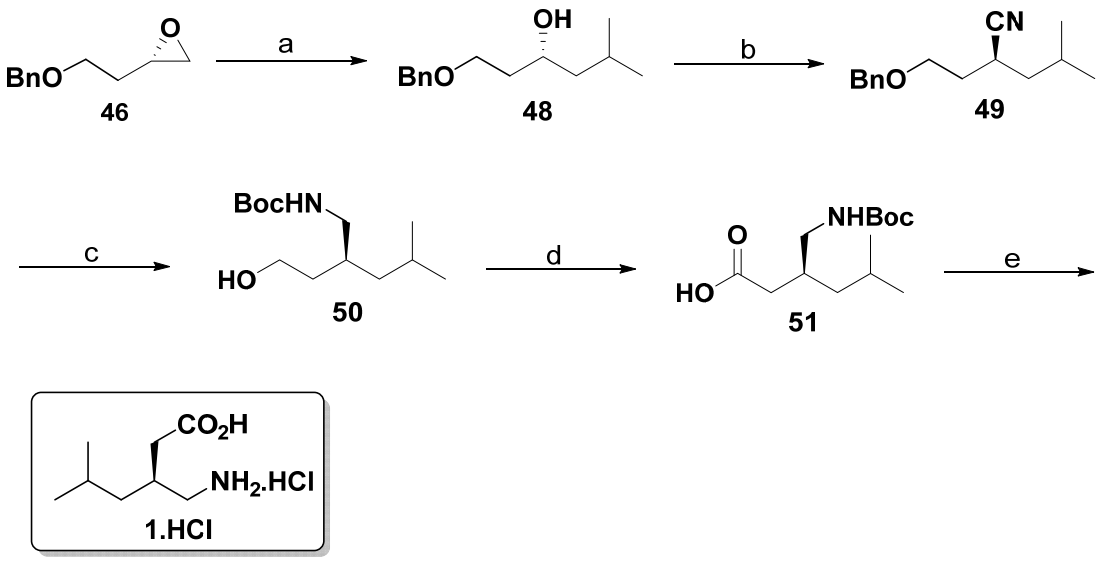
The synthesis commences from readily available starting material 3-buten-1-ol **44 (**Scheme 10). Thus, 3-buten-1-ol on *O*-benzylation using benzyl bromide and NaH followed by epoxidation reaction using *m*-CPBA gave the required epoxide **45**. Appearance of multiplets in the range of δ 1.69-2.04 (2H) & 3.03-3.12 (1H) and peaks at δ 2.51 (1H) & 2.76 (1H) in ^{1}H NMR and m/z peak at 201 $(M+Na)^{+}$ in mass spectrum indicated the formation of epoxide **45**. The *rac*-epoxide **45** was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equivalent of water using, the catalyst (*S,S*)-Salen Co(III)OAc (0.5 mol%) at ambient temperature for 30 h. After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give enantiomerically pure epoxide **46** from the racemic mixture

in 40% yield and >99% ee {$[\alpha]_D$ = -15.2 (c = 2.5, $CHCl_3$) Lit[17]: -15.7 (c = 4.06, $CHCl_3$)} along with its diol **47** in 43% yield.



Scheme 10. *Reagents and conditions*: (a) (i) benzyl bromide, NaH, THF, rt, 16 h; (ii) *m*-CPBA, $NaHCO_3$, DCM, 24 h, 75% (2- steps); (b) (*S, S*) Salen Co (III)-A, 0˚C-rt, 30 h.

The epoxide **46** was subjected to regioselective ring opening with isopropyl magnesium chloride in presence of CuI at -20 ºC to provide the key intermediate secondary alcohol **48** in 90% yield (Scheme 11). Appearance of a doublet at δ 0.91 (6H) and multiplets in the range of δ 1.12-1.29 (1H) & 1.38-1.58 (1H) in ^{1}H NMR and peaks at δ 23.4 (CH_3) & 22.2 (CH_3) in ^{13}C NMR confirmed the formation of alcohol **48**. The compound **48** was readily transformed into a cyano derivative **49** with an overall yield of 71% in two steps: (i) mesylation of the secondary alcohol (MsCl, Et_3N, DCM, 0 $^\circ$C) to afford mesylate and (ii) cyanation (TMSCN, TBAF, CH_3CN, 60 $^\circ$C) to obtain cyano derivative **49**. Performing cyanation reaction using NaCN/DMF condition did not enhance the yield of the cyano product **49**. Appearance of a multiplet in the range of δ 2.79-2.94 (1H) in ^{1}H NMR and a characteristic cyanide absorption band at 2236 cm^{-1} in IR spectrum showed the formation of compound **49**. Further, compound **49** on simple hydrogenation/hydrogenolysis and concomitant Boc-protection using $(Boc)_2O$ and Raney-Ni as a catalyst in methanol furnished amino alcohol **50**. Disappearance of a doublet at δ 4.53 (2H) and multiplet at 7.26-7.41 (5H) in ^{1}H NMR showed the removal of benzyl group. Appearance of a singlet at δ 1.44 (9H) ascribable to Boc group and a peak at δ 3.10 (2H) in ^{1}H NMR and m/z peak at 268 $(M+Na)^+$ in mass spectrum showed the formation of amino alcohol **50**. Further, oxidation of compound **50** went smoothly using sodium chlorite catalyzed by TEMPO & bleach in acetonitrile-phosphate buffer (pH 6.8) condition and afforded the corresponding acid **51** in 80% yield.



Scheme 11. *Reagents and conditions*: (a) *i*-PrMgCl, CuI, THF, -20 ºC-rt, 2 h, 90%; (b) (i) MsCl, Et_3N, 0 ºC- 10 ºC, 2 h; (ii) TMSCN, TBAF, CH_3CN, 60 °C, 36 h,71% (2-steps); (c) $(Boc)_2O$, Raney-Ni, H_2 (60 psi), MeOH, 20 h, 86%; (d) $NaClO_2$, NaOCl, TEMPO (cat), phosphate buffer, CH_3CN, 35 °C, 6 h, 85%; (e) conc HCl, acetone, 60 ºC, 3 h, 95%.

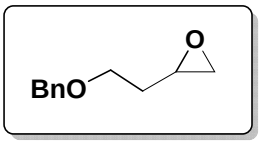
Finally, Boc-deprotection of **51** was carried out using conc HCl/acetone to complete the synthesis of Pregabalin hydrochloride **1.HCl** in excellent enantioselectivity (>99 % ee) {$[\alpha]_D$ = +7.8 (c 1.1, H_2O); lit[14] $[\alpha]_D$ = +7.0 (*c* 1.1, H_2O)}. The structure of Pregabalin **1** was confirmed by its IR, ^1H NMR, ^{13}C NMR and mass spectral analysis.

1.2.5. Conclusion

In conclusion, a practical and highly enantioselective synthesis of pregabalin **1** was achieved using Jacobsen's hydrolytic kinetic resolution method as the key step and source of chirality. This strategy simple protocol may find a viable alternative for the large scale production of pregabalin in the pharmaceutical industry. Further, this approach can easily be applied to prepare other GABA analogues.

1.2.6. Experimental

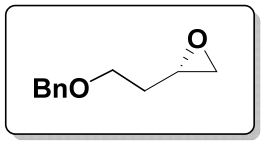
1) 2-(2-(benzyloxy)ethyl)oxirane 45



3-Buten-l-ol **44** (10 g. 139 mmol) was added dropwise to a suspension of sodium hydride (7.4 g of 50% dispersion in oil. washed twice with dry petroleum ether, 154 mmol) in dry THF (150 ml) at 0 ºC under argon. After stirring at room temperature for l h, benzyl bromide (18 ml. 152 mmol) was added dropwise and the resulting mixture left overnight. Saturated aqueous sodium chloride (150 ml) was added. and the mixture extracted with diethyl ether (3 x 75 ml). The organic extracts were dried over magnesium sulphate, and the solvent removed under reduced pressure, to give crude 1-benzyloxy but-3-ene. Crude benzyl was dissolved in dichloromethane (250 ml) and the solution cooled to 0 ºC. Sodium hydrogen carbonate (15 g) was added, followed by 80% *m*-CPBA (44 g, 210 mmol, added in batches). The mixture was stirred at 0 ºC for l h, and then at room temperature overnight. Solid sodium thiosulphate (5 g) was added, the mixture stirred for 15 min. filtered, and concentrated under reduced pressure. The resulting solid was dissolved in water (100 ml) and extracted with diethyl ether (3 x 75ml). The organic layers were dried over magnesium sulphate, and the solvent removed under reduced pressure, to give the crude epoxide. The residue was purified by column chromatography (silica gel, petroleum ether/acetone (95:5) to afford racemic epoxide (18.5 g, 75 %).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3013, 2923, 2861, 1720, 1495, 1453, 1411, 1362, 1102; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.69-2.04 (m, 2H), 2.51 (dd, J = 5.1, 2.7 Hz, 1H), 2.76 (dd, J = 5.2, 4.0 Hz, 1H), 3.03-3.12 (m, 1H), 3.60-3.66 (ddd, J = 7.0, 5.6, 1.0 Hz, 2H), 4.53 (s, 2H), 7.27-7.37 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 138.3 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.1 (CH_2), 67.1 (CH_2), 50.1 (CH), 47.2 (CH_2), 33.0 (CH_2); MS: *m/z* 201 $[M+Na]^+$.

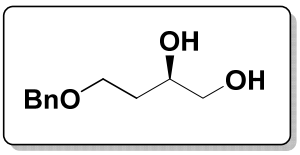
2) (*S*)-2-(2-(benzyloxy)ethyl)oxirane 46



A mixture of 2-(2-(benzyloxy)ethyl)oxirane **45** (10 g, 56.1 mmol) and (*S,S*) salen Co(III)OAc complex-A (0.1 g, 0. 14 mmol) were vigorously stirred for 15 min, then cooled to 0 °C, and water added (0.56 mL, 30.8 mmol) over a period of 15 min, through a micro-syringe. The reaction mixture was stirred at room temperature for 15 h, and additional (*S,S*) salen Co(III)OAc complex-A (0.09 g, 0.13 mmol) was added and stirring was continued for additional 15 h. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/acetone (95:5). The less polar epoxide **46** eluted first as a colorless oil (4.0 g, 40%), followed by diol **47** as a colorless oil (4.7 g, 43%).

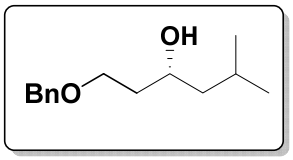
$[\alpha]^{25}_D$ = -15.2 (*c* 2.5, $CHCl_3$) {lit.[17] $[\alpha]^{25}_D$ = -15.7 (c = 4.06, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 3013, 2923, 2861, 1720, 1495, 1453, 1411, 1362, 1102; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.69-2.04 (m, 2H), 2.51 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.76 (dd, *J* = 5.2, 4.0 Hz, 1H), 3.03-3.12 (m, 1H), 3.60-3.66 (ddd, *J* = 7.0, 5.6, 1.0 Hz, 2H), 4.53 (s, 2H), 7.27-7.37 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 138.3 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.1 (CH_2), 67.1 (CH_2), 50.1 (CH), 47.2 (CH_2), 33.0 (CH_2); MS: *m/z* 201 $[M+Na]^+$.

3) (*R*)-4-(benzyloxy)butane-1,2-diol 47



$[\alpha]^{25}_D$ = +18.0 (*c* 2.0, EtOH) {lit.[18] $[\alpha]^{25}_D$ = +22.7 (c = 5.16, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3600, 3435, 3013, 2923, 2861, 1495, 1453, 1411, 1362, 1102; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.70-1.79 (m, 2H), 3.47-3.67 (m, 5H), 3.88 (m, 1H), 4.50 (s, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.7 (C), 128.3 (CH, 2 carbons), 127.6 (CH, 3 carbons), 73.0 (CH_2), 70.6 (CH), 67.7 (CH_2), 66.2 (CH_2), 32.9 (CH_2); MS: *m/z* 219 $[M+Na]^+$.

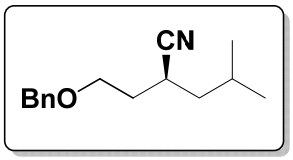
4) (*R*)-1-(benzyloxy)-5-methylhexan-3-ol 48



To a pre cooled (-20 ºC) solution of epoxide **46** (3.8 g, 21.2 mmol) and CuI (0.1 g) in dry THF (30 mL) was added isopropyl magnesium chloride (15.8 mL, 31.8 mmol) in THF for about 15 mins. Subsequently, the reaction mixture was allowed to attain ambient temperature and continued the stirring for additional 2 h. After completion of the reaction (indicated by TLC), aqueous NH_4Cl was added, after which the reaction mixture was filtered, and washed with ethyl acetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/ethylacetate, 85:15) to yield **48** as a colorless oil. (4.2 g; 90%).

$[\alpha]^{25}_D$ = +17.5 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3502, 3018, 2957, 1603, 1454, 1366, 1307, 1092; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.91 (d, *J* = 6.6 Hz, 6H), 1.12-1.29 (m, 1H), 1.38-1.58 (m, 1H), 1.73 (dd, *J* = 11.7, 5.6 Hz, 2H), 1.74-1.85 (m, 1H), 2.84 (bd, *J* = 2.6 Hz, 1H), 3.60-3.78 (m, 2H), 3.82-3.96 (m, 1H), 4.53 (s, 2H), 7.27-7.37 (m, 5H); ^{l3}C NMR(50 MHz, $CDCl_3$): δ_C 138.0 (C), 128.5 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.4 (CH_2), 69.4 (CH), 69.3 (CH_2), 46.7 (CH_2), 36.9 (CH_2), 24.5 (CH), 23.4 (CH_3), 22.2 (CH_3); MS: *m/z* 245 $[M+Na]^+$; HRMS: calc for $C_{14}H_{22}O_2Na$ $[M+Na]^+$ 245.1512; found $[M+Na]^+$ 245.1513.

5) (*S*)-2-(2-(benzyloxy)ethyl)-4- methylpentanenitrile 49

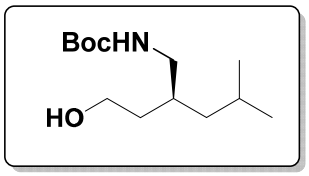


To a pre cooled (0 °C) solution of alcohol **48** (4.0 g, 17.9 mmol) in dry DCM (50 mL) was added triethylamine (5.4 mL, 39.3 mmol) followed by slow addition of methanesulfonyl chloride (1.5 mL, 19.6 mmol) dropwise. The reaction mixture was stirred at 10 °C for 1.5 hours before quenching with water, more DCM was added and extracted with water, washed with brine and evaporated under reduced pressure. The crude product was used for next step without purification.

Trimethylsilyl cyanide (3.3 mL, 26.8 mmol) and TBAF (26.7 mL, 26.8 mmol) were added to a stirring solution of crude mesylated product as obtained above in acetonitrile under an atmosphere of nitrogen at room temperature. The reaction mixture was stirred at 60 °C for 24 hours. After completion of the reaction (indicated by TLC), solvent was removed and the crude product was subjected to column chromatography (silica gel, petroleum ether/ ethylacetate, 92:8) to yield **49** as a colorless oil. (2.9 g; 71%, 2 steps)

$[\alpha]^{25}_{D}$ = + 17.9 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3421, 2958, 2871, 2236, 1603, 1496, 1455, 1368, 1116; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.92 (d, *J* = 5.2 Hz, 3H), 0.95 (d, *J* = 5.4 Hz, 3H), 1.23-1.37 (m, 1H), 1.53-1.67 (m, 1H), 1.76-1.97 (m, 3H), 2.79-2.94 (m, 1H), 3.63 (apparent t, *J* = 6.1 Hz, 2H), 4.53 (d, *J* = 11.8 Hz, 2H), 7.26-7.41 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 138.0 (C), 128.5 (CH, 2 carbons), 127.7 (CH, 3 carbons), 122.1 (C), 73.3 (CH_2), 66.9 (CH_2), 41.2 (CH_2), 33.0 (CH_2), 26.7 (CH), 26.2 (CH), 23.0 (CH_3), 21.5 (CH_3); MS: *m/z* 254 $[M+Na]^+$; HRMS: calc for $C_{15}H_{21}NONa$ $[M+Na]^+$ 254.1515; found $[M+Na]^+$ 254.1514.

6) (*S*)-tert-butyl (2-(2-hydroxyethyl)-4-methylpentyl)carbamate 50

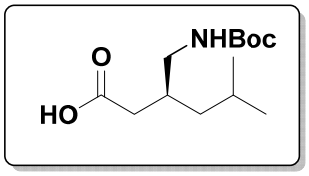


To a solution of **49** (2.0 g, 8.6 mmol) and Boc_2O (2.0 g, 9.5 mmol) in methanol (30 mL) was added activated Raney-nickel catalyst (200 mg) and the reaction mixture was stirred under hydrogen (60 psi) for 20 h. After completion of the reaction (indicated by TLC), filtered the catalyst over a plug of celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/ ethylacetate, 70:30) to yield **50** as colorless oil (1.8 g, 86%);

$[\alpha]^{25}_{D}$ = +1.8 (c = 1.4,$CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3457, 3019, 2959, 2931, 1698, 1513, 1393, 1367, 1168; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.88 (apparent t, *J* = 6.2 Hz, 6H), 1.06-1.18 (m, 2H), 1.44 (s, 9H), 1.47-1.74 (m, 4H), 2.25 (bs, 1H), 3.10 (apparent t, *J* = 5.6 Hz, 2H), 3.65-3.79 (m, 2H), 4.80 (bs, 1H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 156.5 (CO), 79.5 (C), 60.7 (CH_2), 44.0 (CH_2), 42.0 (CH_2), 34.7 (CH_2), 33.6 (CH),

28.4 (CH_3, 3 carbons), 25.2 (CH), 22.8 (CH_3), 22.7 (CH_3); MS: *m/z* 268 $[M+Na]^+$; HRMS: calc for $C_{13}H_{27}NO_3Na$ $[M+Na]^+$ 268.1883; found $[M+Na]^+$ 268.1883.

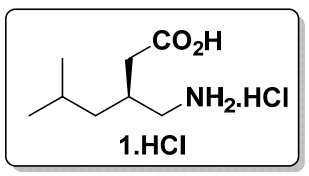
7) (*S*)-3-(((tert-butoxycarbonyl)amino)methyl)-5-methylhexanoic acid 51



A mixture of **50** (1 g, 4.0 mmol), TEMPO (0.05 g, 0.32 mmol), acetonitrile (20 mL), and sodium phosphate buffer (16 mL, 0.67 M, pH 6.7) was heated to 35 °C. Then sodium chlorite (1.32 g dissolved in 2 mL water, 14.6 mmol) and dilute bleach (4-6 %, 1 mL diluted in 2 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at 35 °C until the reaction is complete (6 h, TLC), then cooled to room temperature. Water (30 mL) was added and the pH is adjusted to 8 with 2 N NaOH. The reaction is quenched by pouring into ice cold Na_2SO_3 solution maintained at <20 °C. After stirring for 30 min at room temperature, ethylacetate (30 mL) was added and continued the stirring for additional 15 min. The organic layer was separated and discarded. More ethylacetate (30 mL) was added, and the aqueous layer was acidified with 2N HCl to pH 3-4. The organic layer was separated, washed with water (2 x 15 mL), brine (20 mL) and concentrated under reduced pressure to afford the carboxylic acid **51** (0.88 g, 85%)

$[\alpha]^{25}_D$ = - 8.6 (*c* 1.1, $CHCl_3$) {lit.[12] $[\alpha]^{25}_D$ = - 1.4 (*c* 3.3, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3450, 3020, 2927, 1646, 1521, 1423; NMR (200 MHz, $CDCl_3$): δ_H 0.90 (apparent t, *J* = 6.8 Hz, 6H), 1.16-1.19 (m, 2H), 1.45 (s, 9H), 1.62-1.69 (m, 1H), 2.10-2.35 (m, 3H), 3.05-3.09 (m, 1H), 3.21-3.25 (m, 1H), 4.78 (bs, 1H); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 177.8 (CO), 156.5 (CO), 79.7 (C), 43.8 (CH_2), 41.4 (CH_2), 37.1 (CH_2), 33.8 (CH), 28.4 (CH_3, 3 carbons), 25.2 (CH), 22.7 (CH_3, 2 carbons); MS: *m/z* 282 $[M+Na]^+$

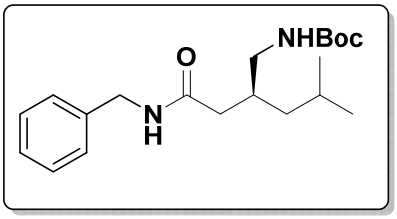
8) (*S*)-3-(aminomethyl)-5-methylhexanoic acid hydrochloride 1.HCl



To a solution of compound **51** (0.25 g, 1 mmol) in acetone (10 mL) was added HCl (1 mL) and the reaction mixture was stirred at 60 °C for 3 hours, after which the solvent was evaporated under reduced pressure. Water (10 mL) was added and extracted with DCM. Aqueous layer was heated followed by filtration through Celite bed and concentrated under reduced pressure furnished a residue, which was dried at 50 °C for more than 48 hours to afford pregabalin hydrochloride **1.HCl** (0.18 g, 95%).
$[\alpha]^{25}_{D}$ = + 7.8 (*c* 1.1, H_2O) {lit.[14] $[\alpha]^{25}_{D}$ = + 7.0 (*c* 1.03, H_2O)}; IR (Neat, cm^{-1}): ν_{max} 3448, 3211, 3130, 1720, 1431, 1215; NMR (200 MHz, D_2O): δ_H 0.87 (d, *J* = 4.7 Hz, 3H), 0.90 (d, *J* = 4.6 Hz, 3H), 1.25 (apparent t, *J* = 6.7 Hz, 2H), 1.58-1.75 (m, 1H), 2.22-2.28 (m, 1H), 2.50 (m, 2H), 3.02 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR(50 MHz, CD_3OD): δ_C 175.7 (CO), 44.2 (CH_2), 41.7 (CH_2), 37.0 (CH_2), 32.3 (CH), 25.8 (CH), 22.9 (CH_3), 22.2 (CH_3); MS: *m/z* 160 $[M+H]^+$; HRMS: calc for $C_8H_{18}NO_2$ $[M+H]^+$ 160.1332; found $[M+H]^+$ 160.1333.

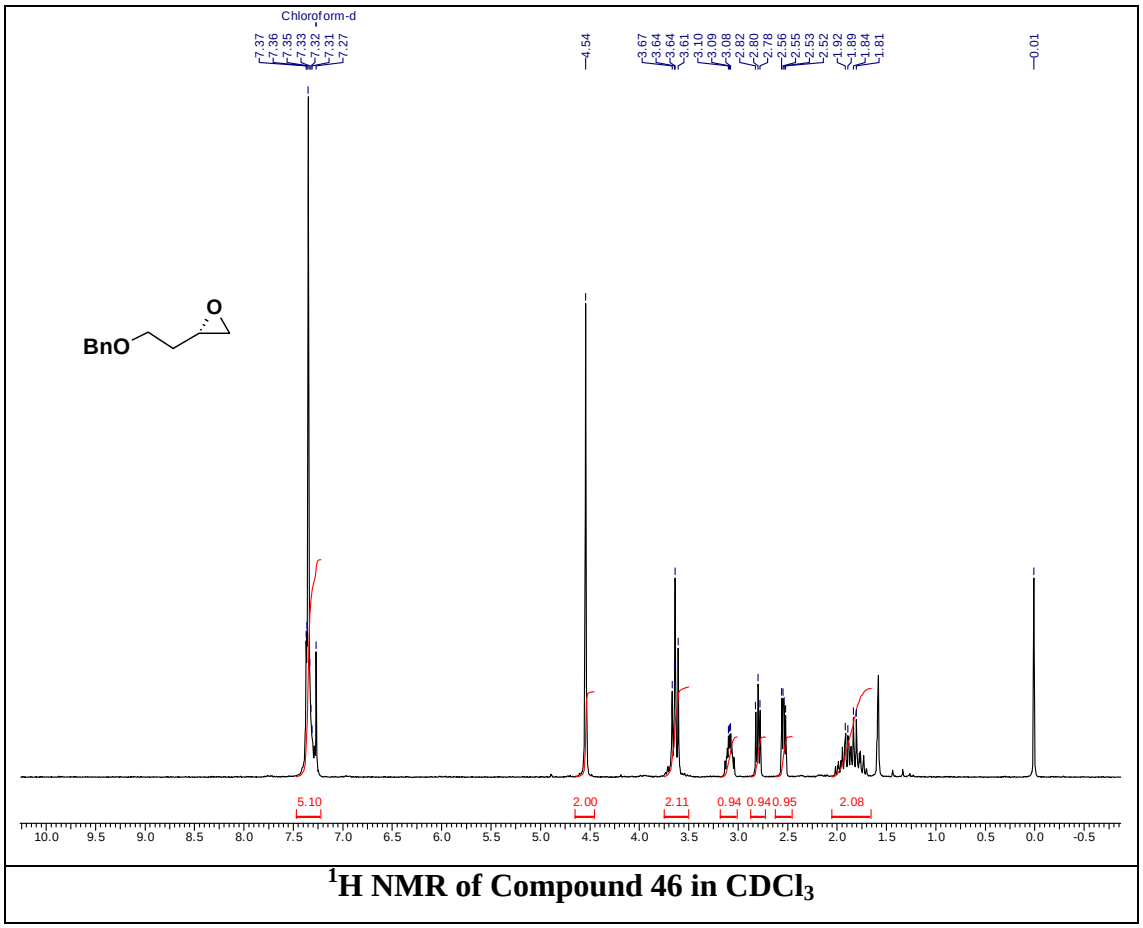
For purpose of *ee* determination Boc-protected acid was converted to *N*-benzyl amide.

9) (*S*)-*tert*-butyl(2-(2-(benzylamino)-2-oxoethyl)-4- methylpentyl)carbamate 52

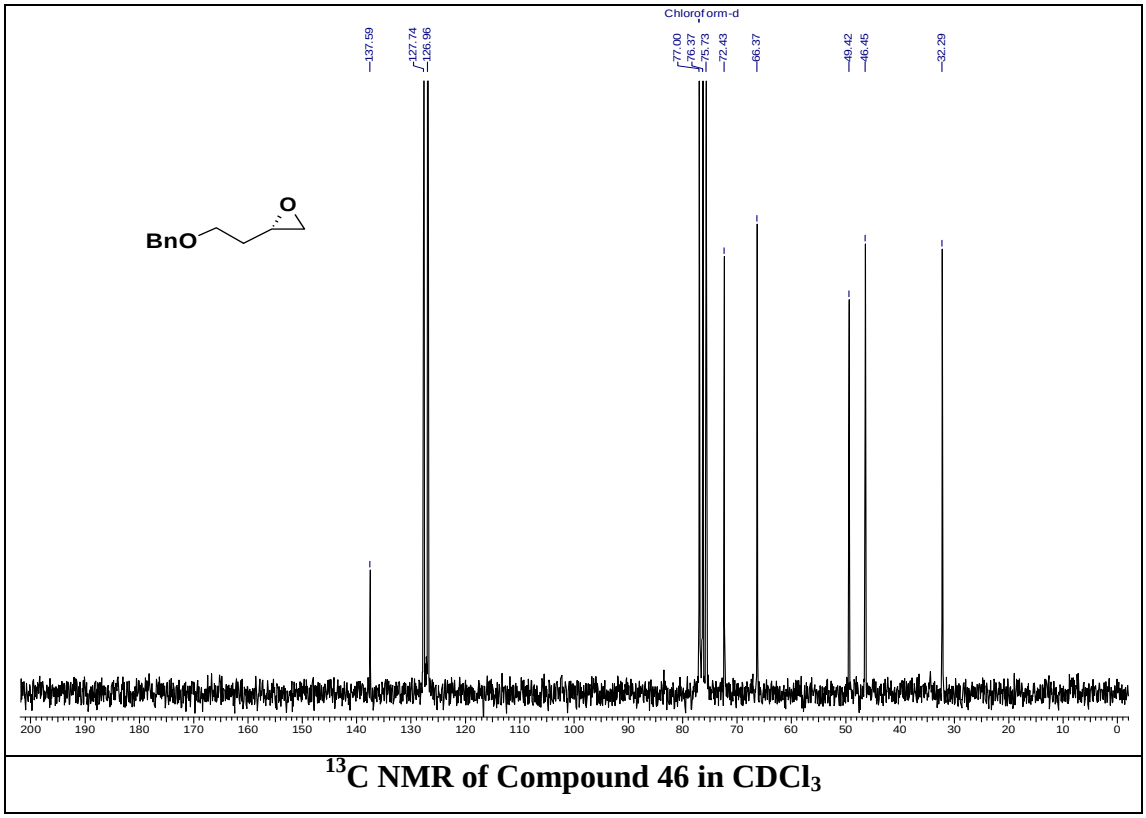


To a solution of acid **51** (0.11 g, 0.42 mmol) in dry THF was added *N*-methylmorpholine (0.05 mL, 0.46 mmol) at -78 °C under argon atmosphere. After 5 min, isobutyl chloroformate (0.06 mL, 0.46 mmol) was added and stirred the content for another 5 min. To this reaction mixture benzylamine (0.05 mL, 0.46 mmol) was added at -78 °C and allowed the reaction mixture to stir at room temperature for 2 h. After completion of the reaction, reaction mixture was filtered, washed with ethylacetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/ ethylacetate, 65:35) to yield *N*-benzyl amide **52** (0.12 g, 85%) $[\alpha]^{25}_{D}$ = - 3.5 (*c* 0.8, $CHCl_3$) The enantiomeric ratio was determined by chiral HPLC: Chiralcel OJ-H (250 x 4.6 mm), pet ether: ethanol (90:10), Wavelength- 220 nm, Flow- 0.5 mL/min (37 kgf). (*R)*-isomer- Retention time: 8.208 min & peak area: 0.347 %. (*S)*-isomer-Retention time: 8.808 min & peak area: 99.653%.

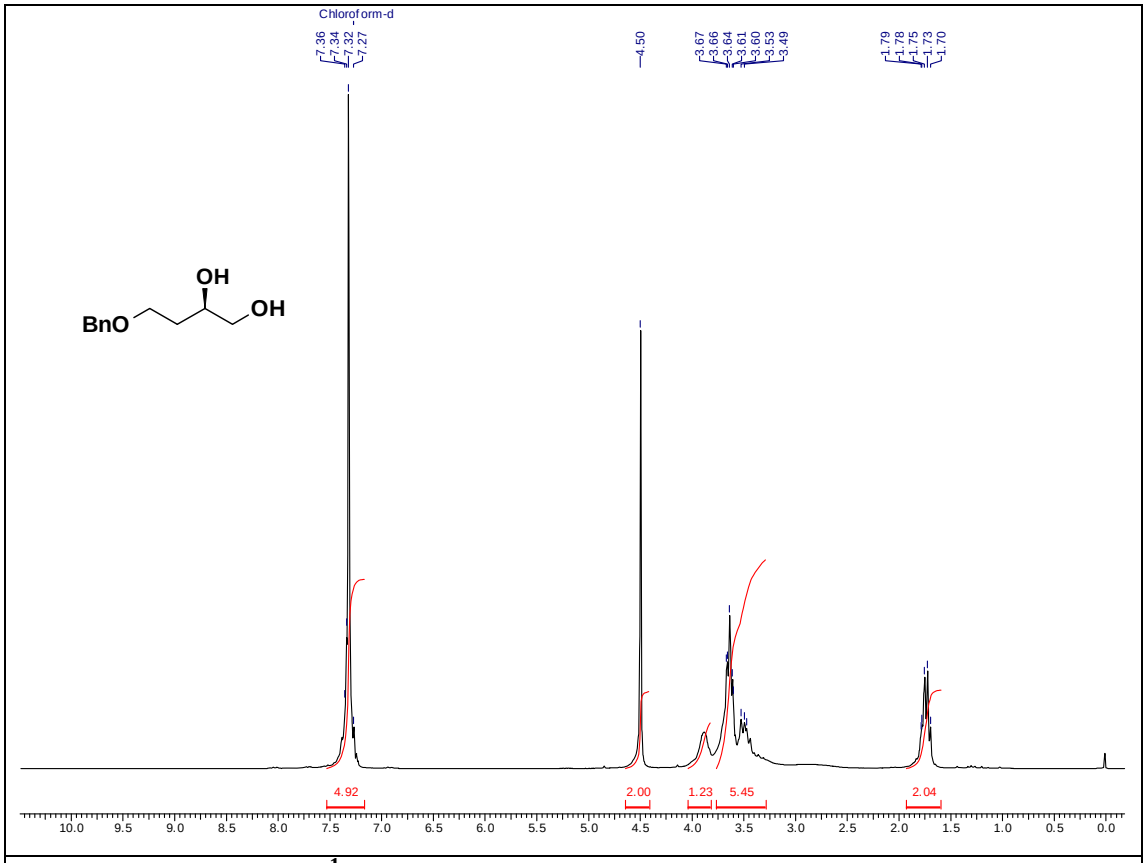
1.2.7. Analytical Data



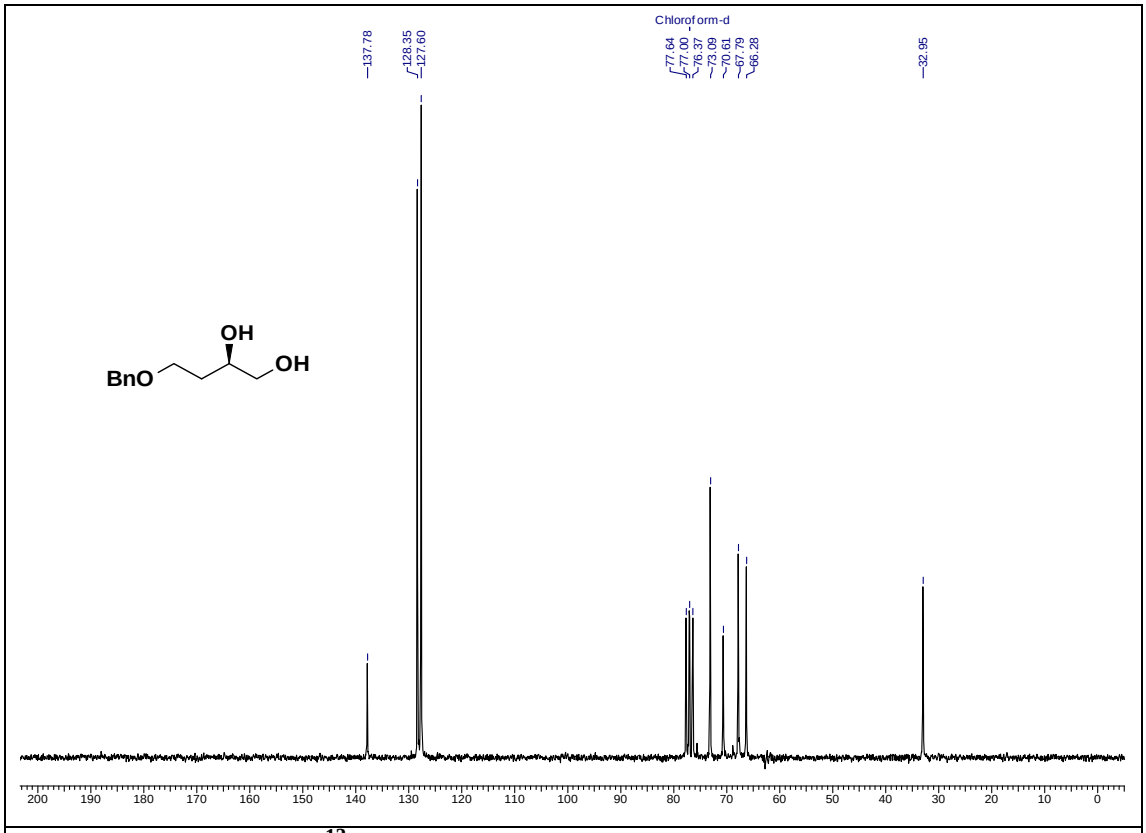
^{1}H NMR of Compound 46 in $CDCl_3$



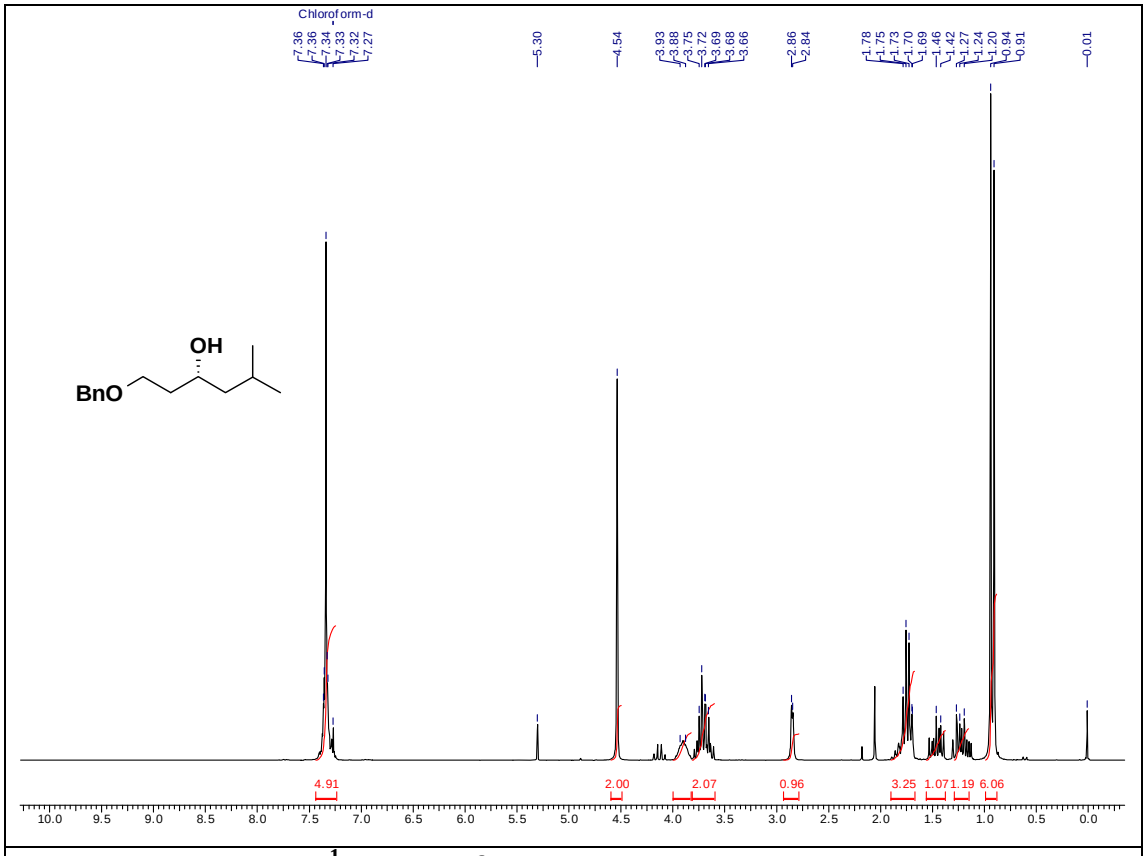
^{13}C NMR of Compound 46 in $CDCl_3$



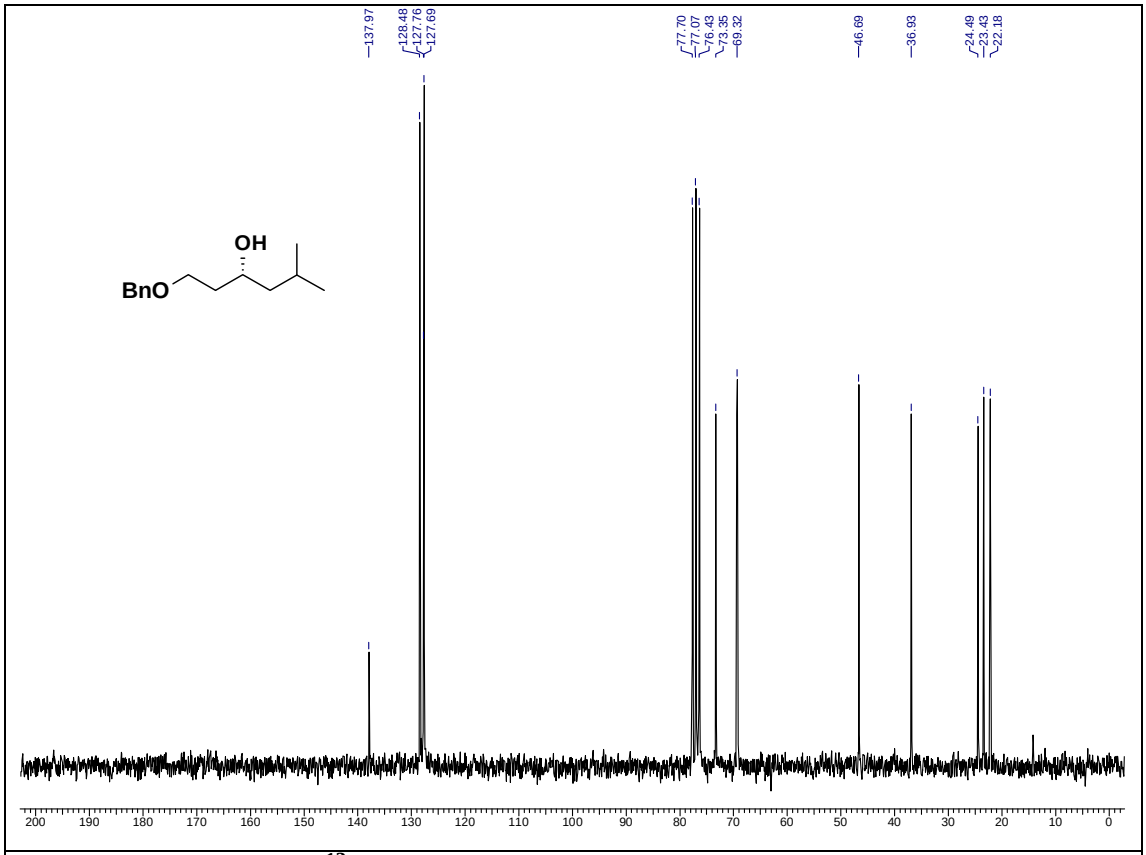
^{1}H NMR of Compound 47 in $CDCl_3$



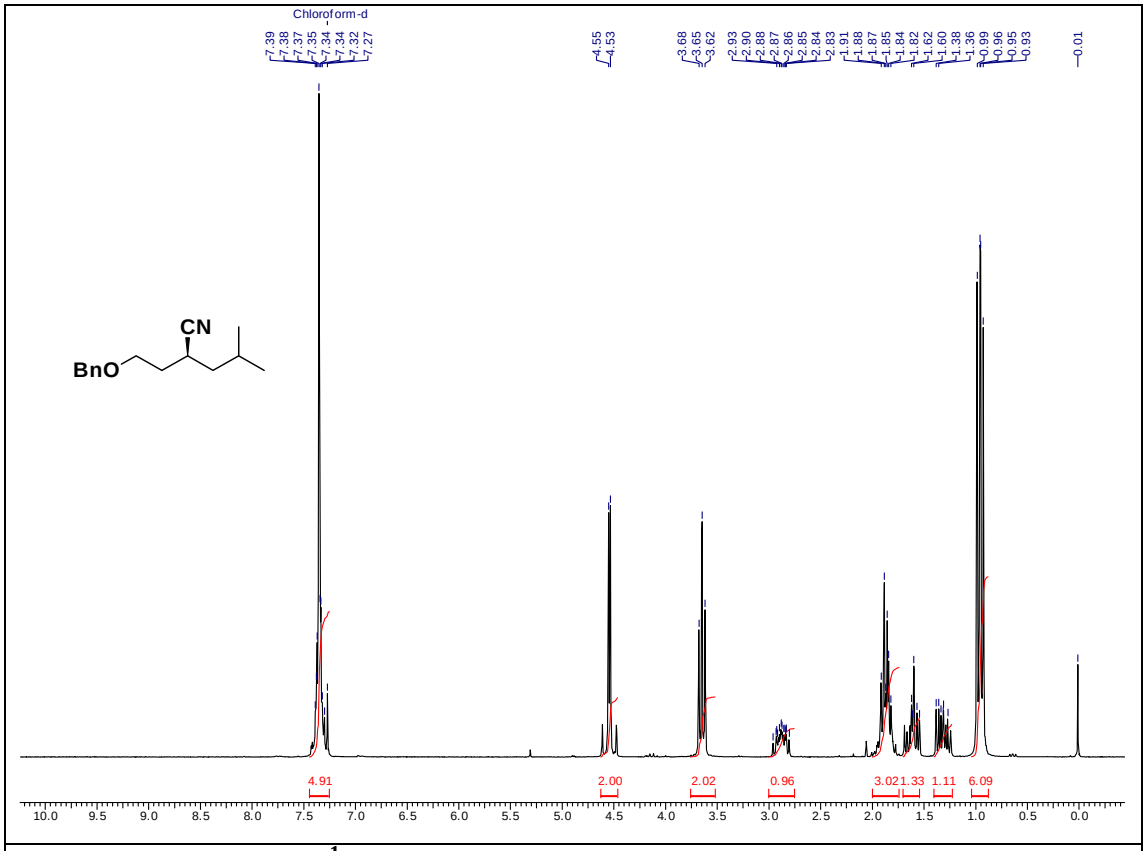
^{13}C NMR of Compound 47 in $CDCl_3$



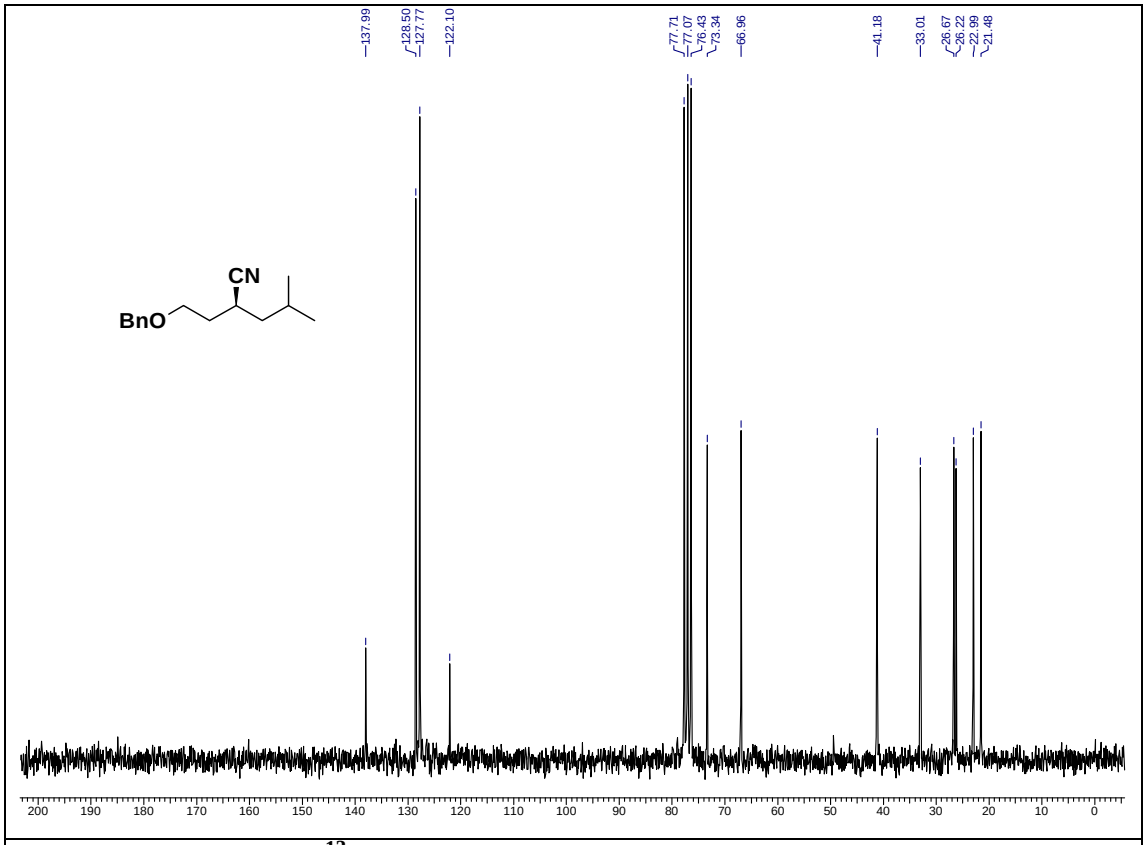
^{1}H NMR of Compound 48 in $CDCl_3$



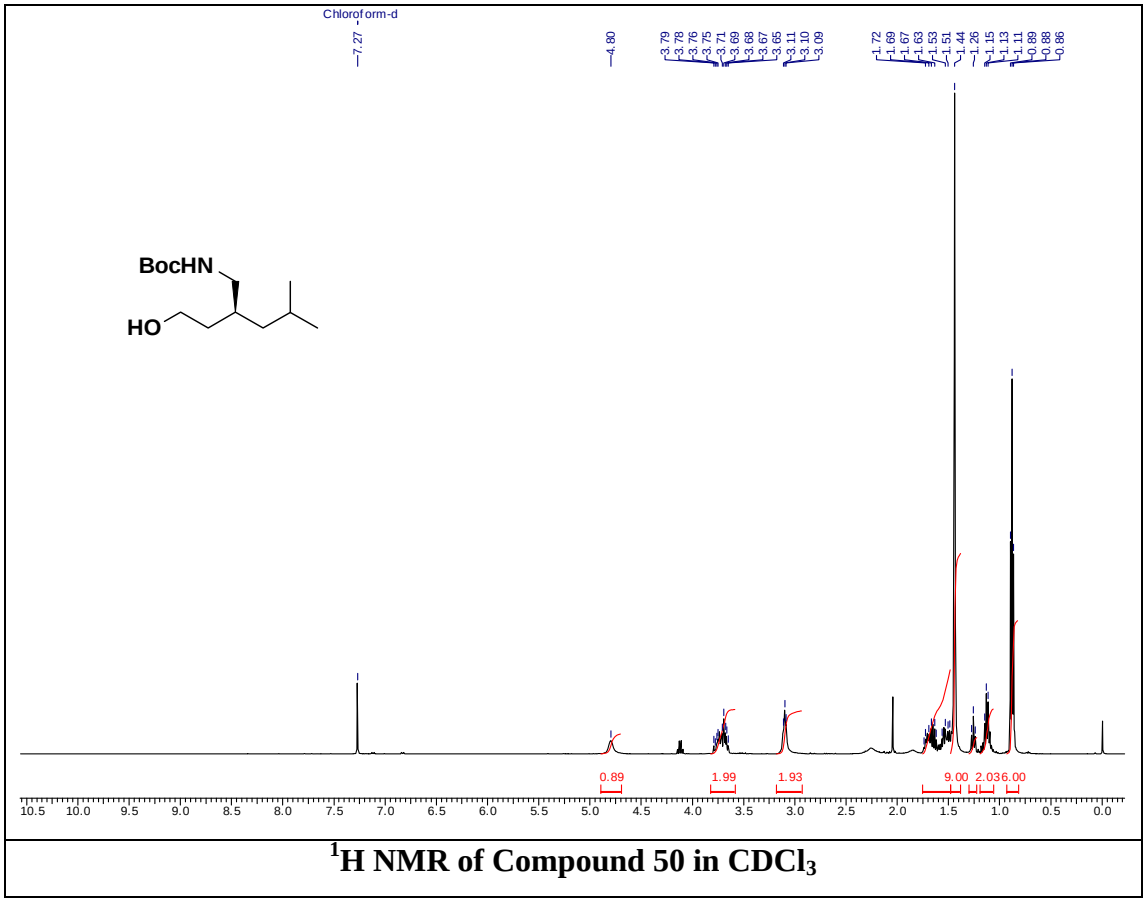
^{13}C NMR of Compound 48 in $CDCl_3$



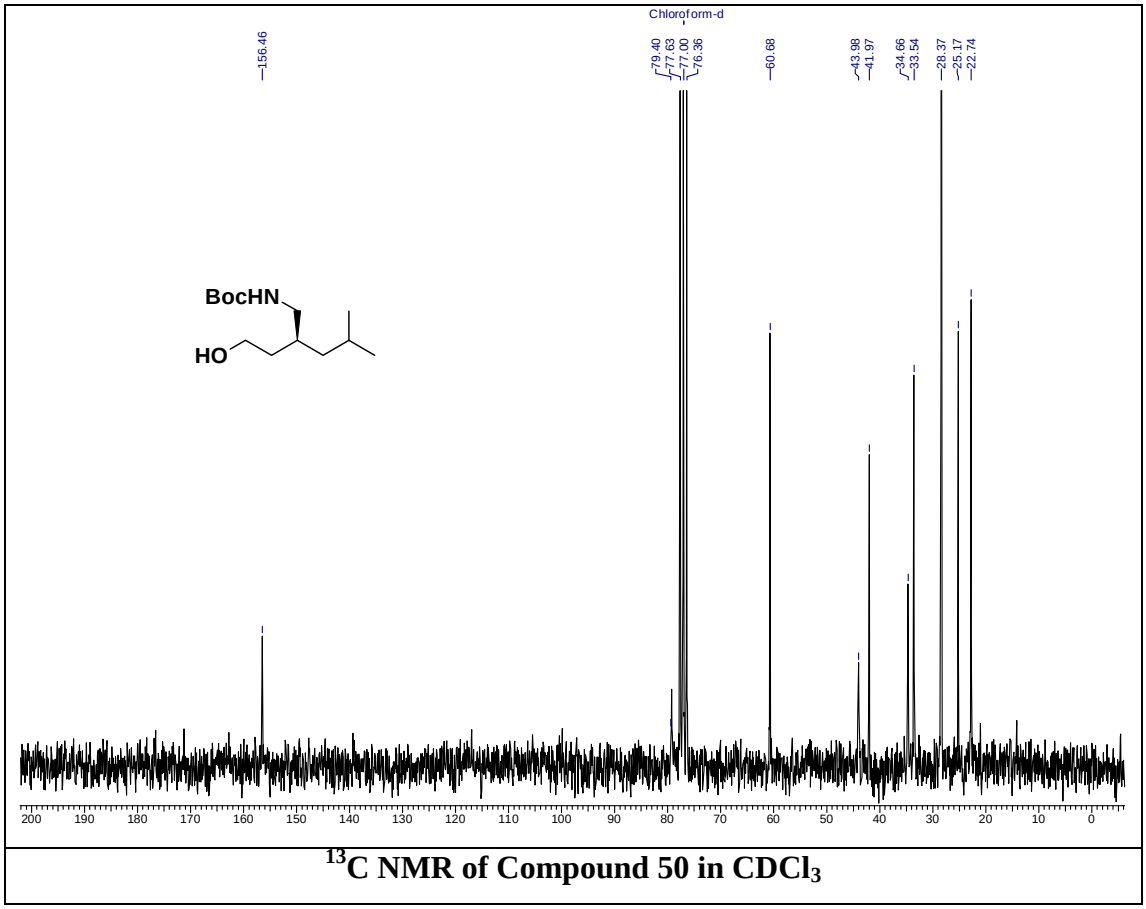
^{1}H NMR of Compound 49 in $CDCl_3$



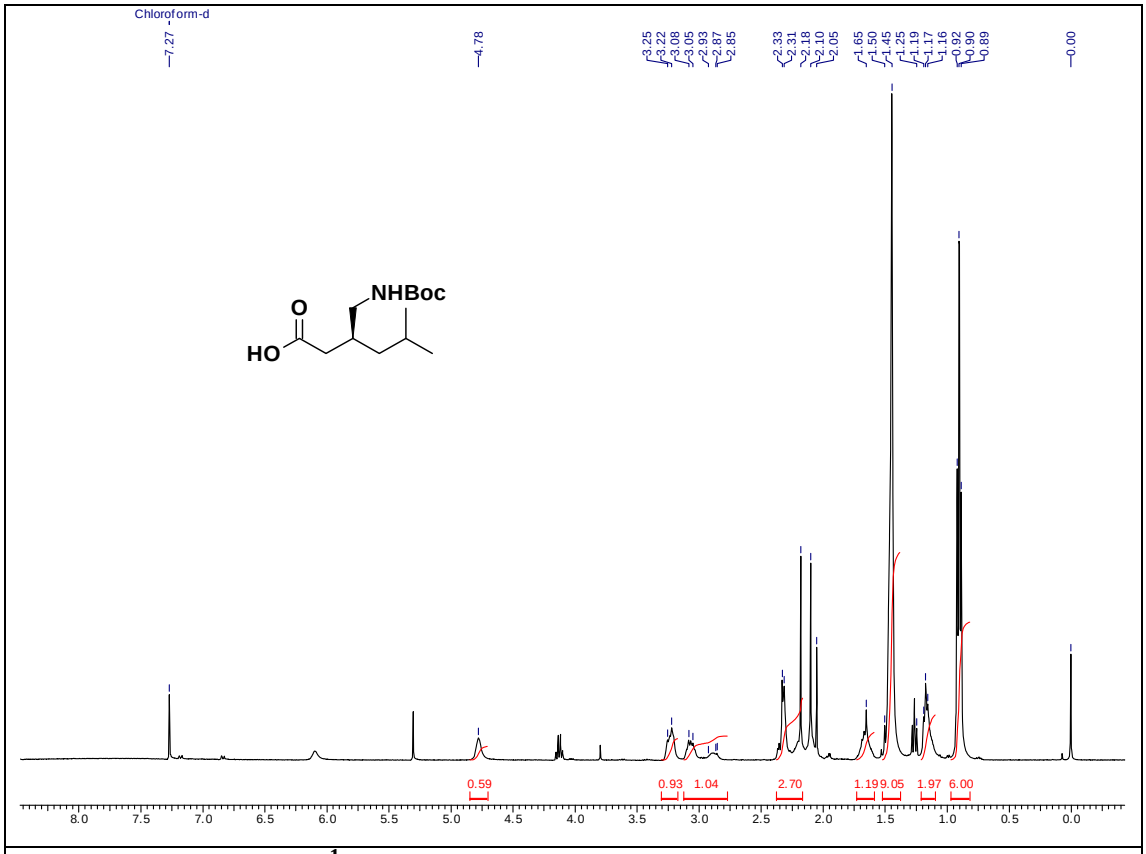
^{13}C NMR of Compound 49 in $CDCl_3$



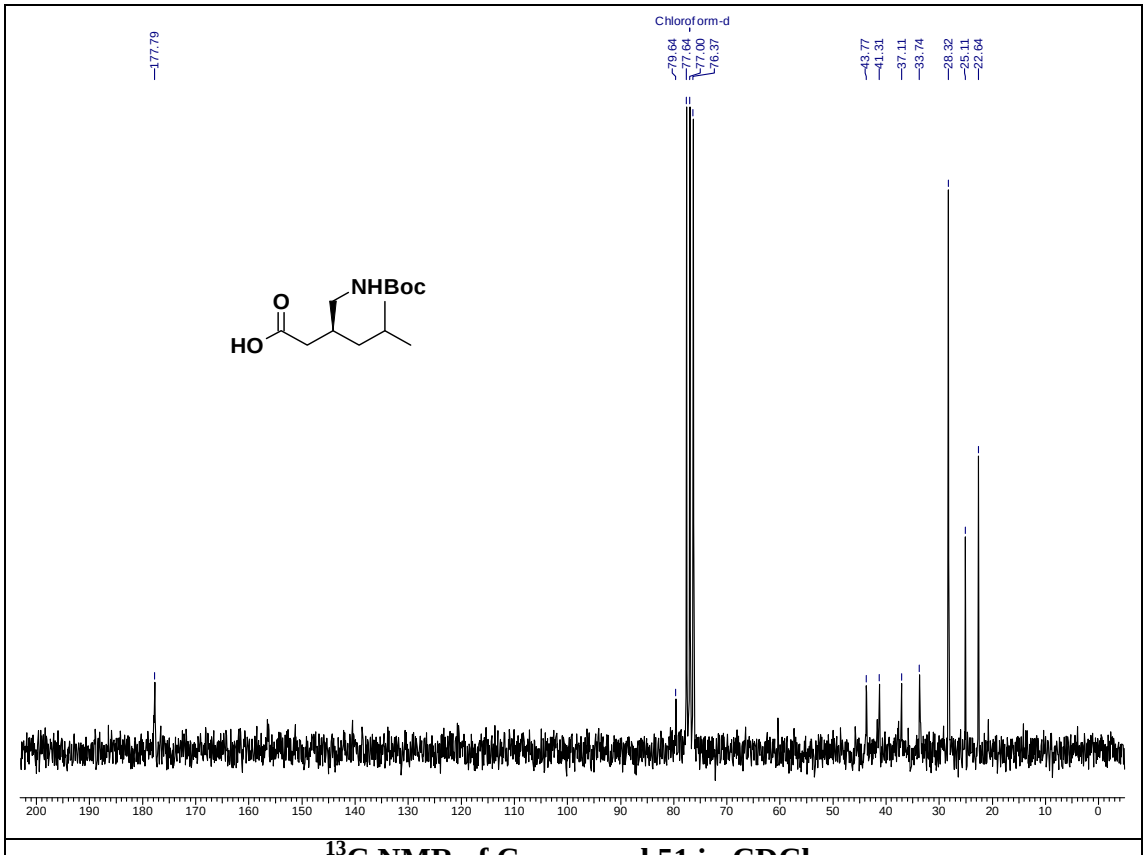
^{1}H NMR of Compound 50 in $CDCl_3$



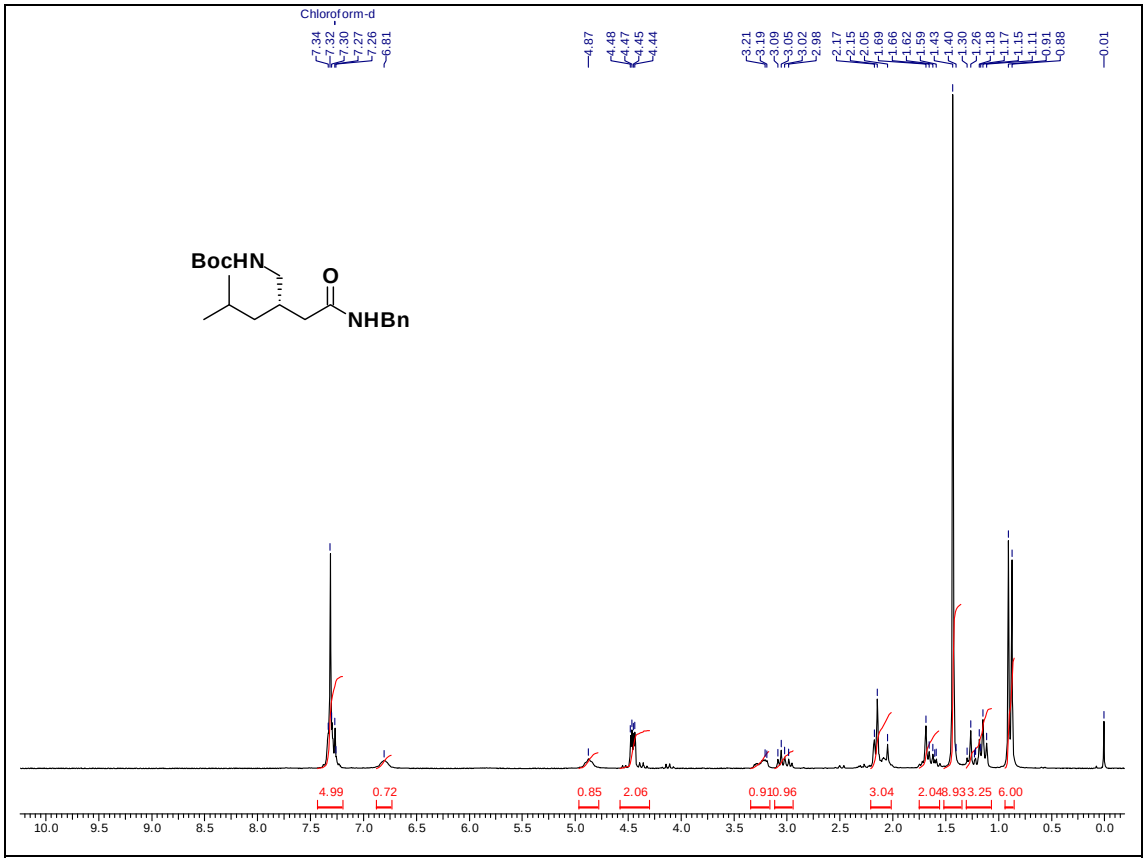
^{13}C NMR of Compound 50 in $CDCl_3$



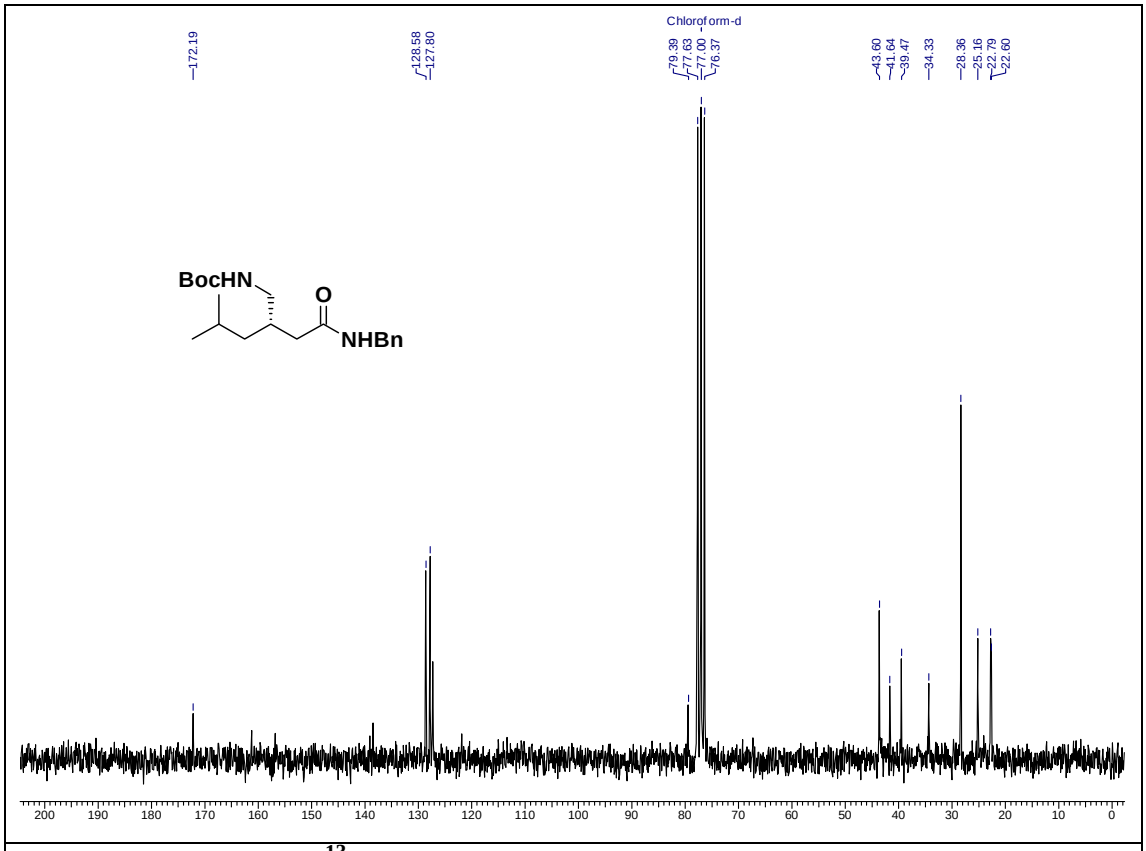
^{1}H NMR of Compound 51 in $CDCl_3$



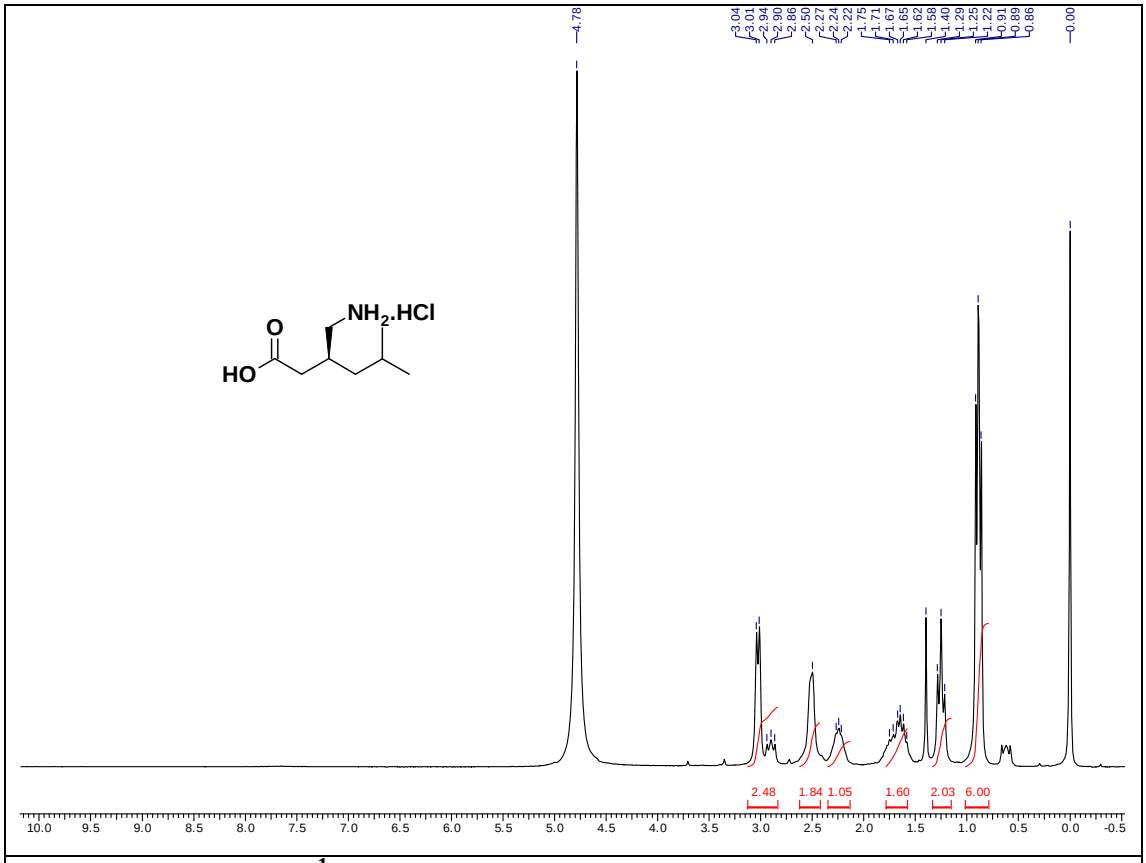
^{13}C NMR of Compound 51 in $CDCl_3$



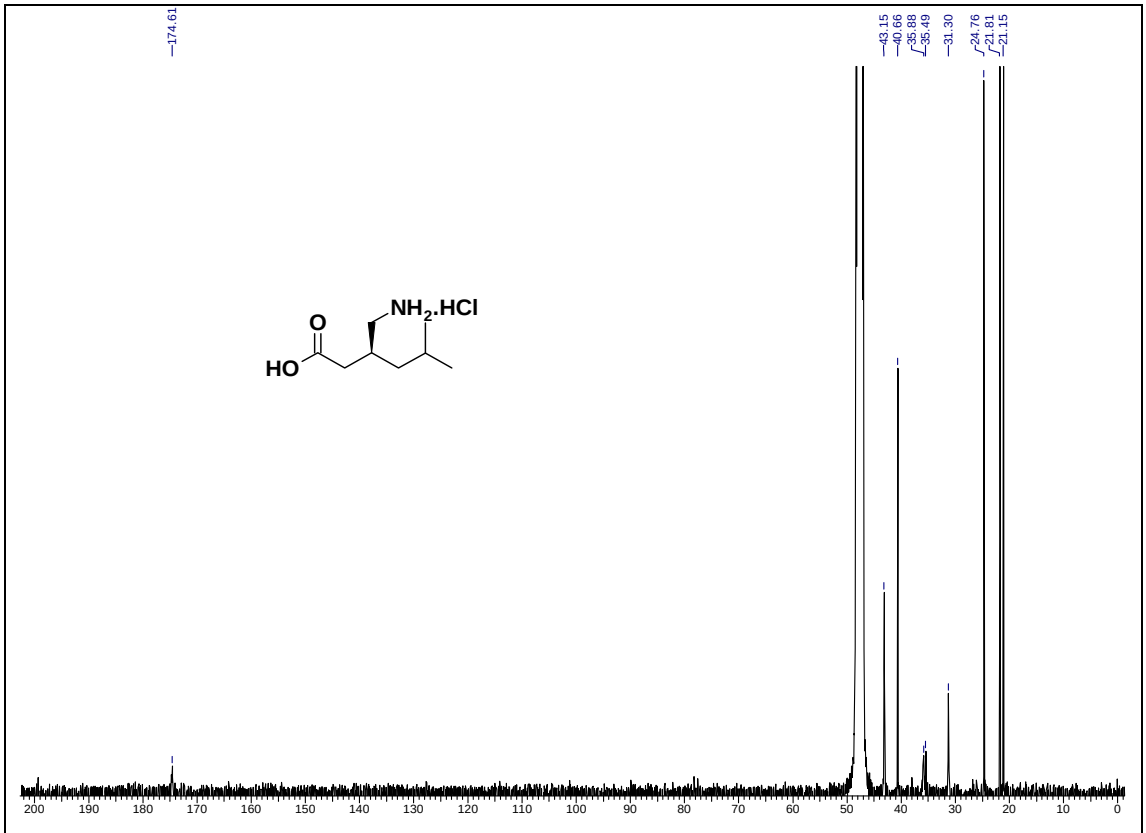
^{1}H NMR of Compound 52 in $CDCl_3$



^{13}C NMR of Compound 52 in $CDCl_3$

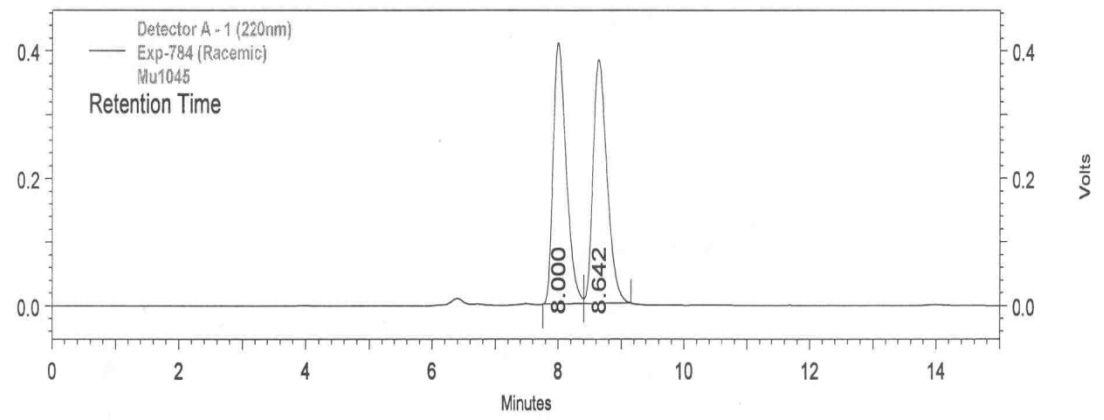


^{1}H NMR of Compound 1.HCl in D_2O



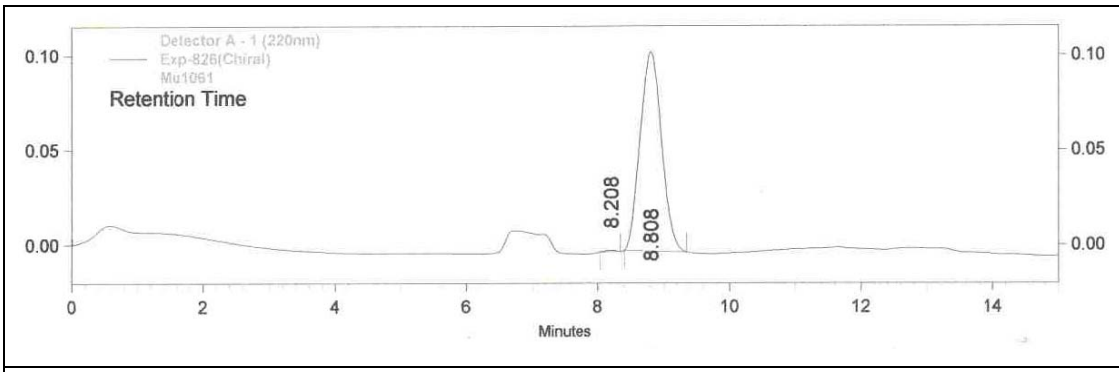
^{13}C NMR of Compound 1.HCl in CD_3OD

Chiral HPLC Analysis of Compound 52



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	8.000	5856642	49.146
2	8.642	5867259	50.854
Totals		11723901	100.000



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	8.208	8210	0.347
2	8.808	2360582	99.653
Totals		2368792	100.000

1.2.8. References

1. (a) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed.; Hardman, J. G., Limbird, L. E., Goodman, G. A., Eds.; McGraw Hill: New York, 2001; (b) Roberts, E. *Biochem. Pharmacol*. **1974**, *23*, 2637.
2. (a) Anderssen, K.; Braestrup, C.; Groenwald, F. C.; Jorgensen, A. S.; Nielsen, E. B.; Sonnewald, U.; Sorensen, P. O.; Suzdak, P. D.; Knutsen, L. J. S. *J. Med. Chem*. **1993**, *36*, 1716; (b) Krogsgaard-Larsen, P., Scheel-Krueger, J., Kofod, H., Eds. GABA-Neurotransmitters. Pharmacochemical, Biochemical and Pharmacological Aspects; Munksgaard: Copenhagen, 1979.
3. (a) Andus, K. L.; Chikale, P. J.; Miller, D. W.; Thomson, S. E.; Borcardt, R. T. *Adv. Drug Res*. **1992**, *23*, 1; (b) Madrid, Y.; Langer, L. F.; Breue, H.; Langer, R. Adv. Pharmacol. **1991**, *22*, 299; (c) Pardridge, W. M. *Ann. Rep. Med. Chem*. **1985**, *20*, 305.
4. Gajcy, K.; Lochynski, S.; Librowski, T. *Curr. Med. Chem*, **2010**, *17*, 2345 and references cited therein.
5. Silverman, R. B.; Andruszkiewicz, R.; Nanavati, S. M.; Taylor, C. P.; Vartanian, M. G. *J. Med. Chem.* **1991**, *34*, 2295.
6. Taylor. C. P.; Vartanian, M. G.; Yuen, P.W.; Bigge, C.; Suman-Chauhan, N.; Hill, D. R. *Epilepsy Res*. **1993**, *14*, 11.
7. The Art of Drug Synthesis; Johnson, D. S.; Li, J. J., Eds.; Wiley & Sons, Inc. Hoboken (NJ), 2007.
8. (a) Lauria-Horner, B. A.; Pohl, R. B. *Expert Opin. Investig. Drugs* **2003**, *12*, 663; (b) Selak, I. *Curr. Opin. Investig. Drugs*. **2003**, *2,* 828.
9. Silverman, R. B.; Andruszkiewicz, R. *Synthesis*, **1989**, 953.
10. Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 823.
11. Huckabee, B. K. and Sobieray, D. M. **1996**. WO 96/38405.
12. Grote, T. M.; Huckabee, B. K.; Mulhern, T. A.; Sobieray, D. M.; Titus, R. D. **1996**. WO 96/40617.
13. Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org.Process Res. Dev*. **1997**, *1*, 26.
14. Sammis, G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2003**, *125*, 4442.

15. Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem*. **2003**, *68*, 5731.

16. Izquierdo, S.; Aguilera, J.; Buschmann, H. H.; Garcia, M.; Torrens, A.; Ortuno, R. M. *Tetrahedron: Asymmetry* **2008**, *19*, 651.

17. Schaus, S. E.; Brandes, B.D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A.E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307.

18. Jakob, B.; Voss, G.; Gerlach, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3255.

Chapter-2

Asymmetric syntheses of antiepileptic drugs Lacosamide, Levetiracetam and antiparkinson's agent Safinamide

2.1. SECTION A

First asymmetric synthesis of antiepileptic drug, Lacosamide

2.1.1. Introduction

Epilepsy is one of the complex neurological disorders characterized by recurrent spontaneous seizures and is a global health problem that affects almost 50 million people worldwide.[1] The word epilepsy is derived from Greek language "epilepsia" or "epilamvanein" which means to be seized or attacked.[2] Earlier medical documents reveal that epilepsy is one of the oldest recorded diseases that were linked to certain misconceptions such as possession of evil spirits. One of the oldest records of epilepsy is present in ancient Indian medicine 4500-1500 B.C. According to Ayurvedic literature of Charaka Samhita epilepsy was named as "Apasmara" which means loss of consciousness.[3]

Today advancement on scientific discoveries related to epilepsy enabled a better understanding of this disease. There are many possible causes for epilepsy as anything that injures the brain can lead to seizures. Broadly epileptic seizures are divided into three categories such as partial seizures, generalized seizures and unclassified seizures.[4]

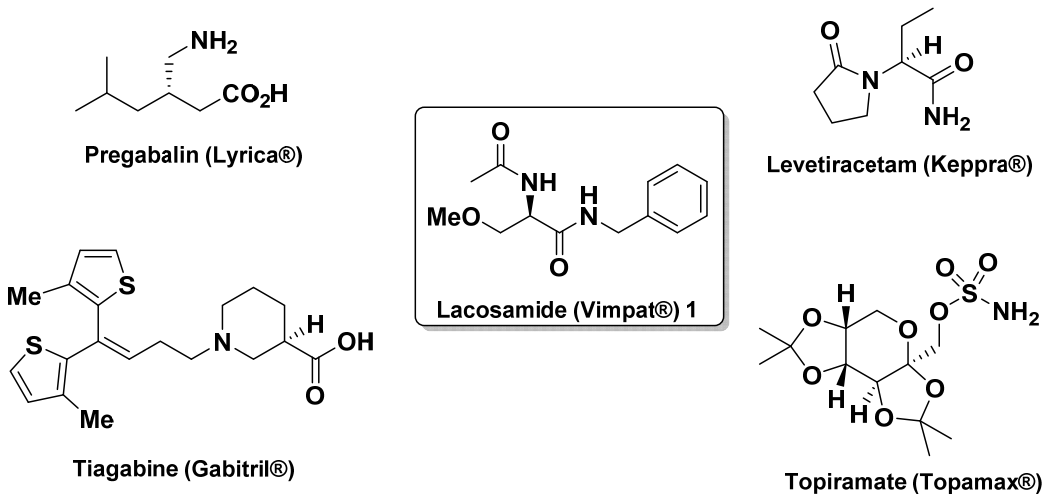


Figure 1. Examples of few chiral antiepileptic drugs

Treatment of epilepsy requires constant administration of anticonvulsants also named as antiepileptic drugs (AEDs). In 1857, Sir Charles Locock introduced potassium

bromide as the first antiepileptic drug but due to the side effects associated with bromide has limited its efficacy. The new beginning of modern pharmacotherapy of epilepsy came into light in 1912 due to accidental discovery of phenobarbital as an anticonvulsant agent. Phenobarbital was synthesized in 1904 by German chemist Fischer and it showed sedative and hypnotic properties, but in 1912 Hauptmann accidentally discovered its anticonvulsant effects. Further, new AEDs such as phenytoin, carbamazepine and sodium valproate were discovered and termed as "first generation" drugs. Modern or "second generation" were introduced on or after year 1989 which include vigabatrin followed by lamotrigine, gabapentin, felbanate, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin and zonisamide. Despite the availability of wide range of AEDs nowadays, still newer agents are required with unique mode of action because current medications are not useful for approximately one-third of the patients with epilepsy as most of them continue to have seizures while others suffers from one or more side effects such as nausea, dizziness, liver damage, etc.[5]

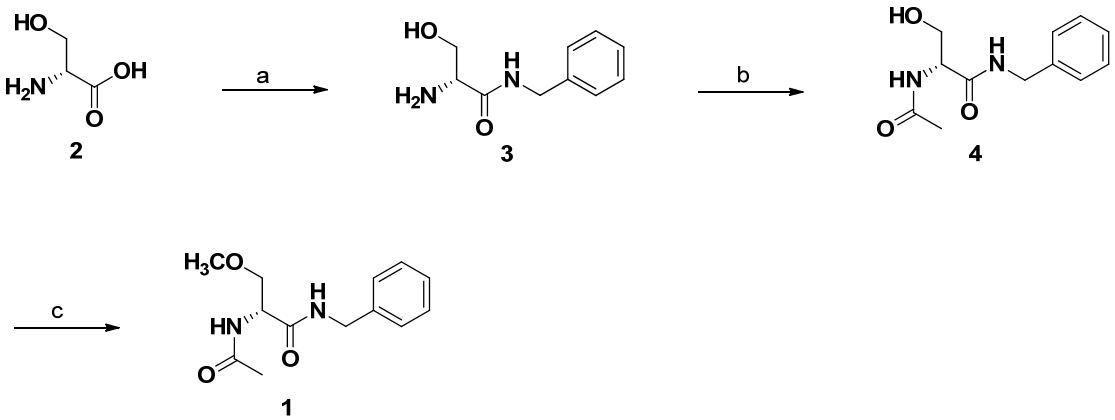
Very recently lacosamide **1** (Fig. 1) has been approved by FDA (Oct 2008) as a new AED for adjuvant treatment of partial-onset seizures in adults with epilepsy.[6] Lacosamide is the (*R*)-enantiomer of *N*-benzyl-2-acetamido-3-methoxypropionamide which is marketed under the trade name Vimpat® owned by UCB Pharma.[6,7] Clinical trial studies shows that lacosamide was effective in controlling seizure frequency when provided as adjunctive treatment in refractory partial-onset seizures. Nearly 40% patients showed a >50% reduction in seizures at the highest recommended dose of 400 mg/day.[7b] The exact mechanism of action of lacosamide is not yet clearly understood, but it is believed that it enhances slow inactivation of voltage-gated Na^+ channels and binds to dihydropyrimidinase-related protein 2 (CRMP 2), there as to control the seizures.[7d] Due to this unique mode of action, it differs from other antiepileptic drugs (AEDs) and it is expected to be a potential blockbuster drug in epilepsy.

2.1.2. Review of Literature

Generally, lacosamide is prepared using chiral pool approach starting from expensive unnatural amino acid *D*-Serine and its derivatives.[6,7] To the best of our knowledge, there is no asymmetric synthesis of this molecule is reported yet.

Kohn *et al.* (1996)[7e]

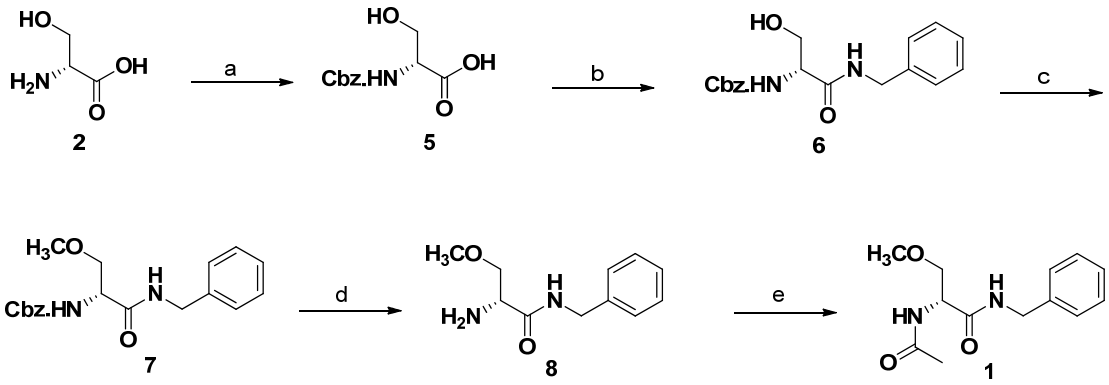
Harold Kohn *et al.* have reported the synthesis of lacosamide using chiral pool approach starting from unnatural amino acid D-Serine **2** (Scheme 1). Esterification of D-Serine **2** using methanol in presence of HCl gave serine methyl ester followed by treatment with benzylamine provided benzylamide **3.** *N*-acetylation of benzylamide **3** followed by *O*-alkylation with MeI and Ag_2O furnished lacosamide **1.** Although this route is short, but the main drawback is usage of expensive silver (I) oxide with prolonged reaction period *i.e.* 4 days for *O*-alkylation.



Scheme 1. *Reagents and conditions***:** (a) HCl, MeOH then benzylamine, 27%; (b) Ac_2O, DCM, 62% then recrystallized 29%; (c) MeI, Ag_2O, CH_3CN, 80 %.

Kohn *et al* (1998)[8]

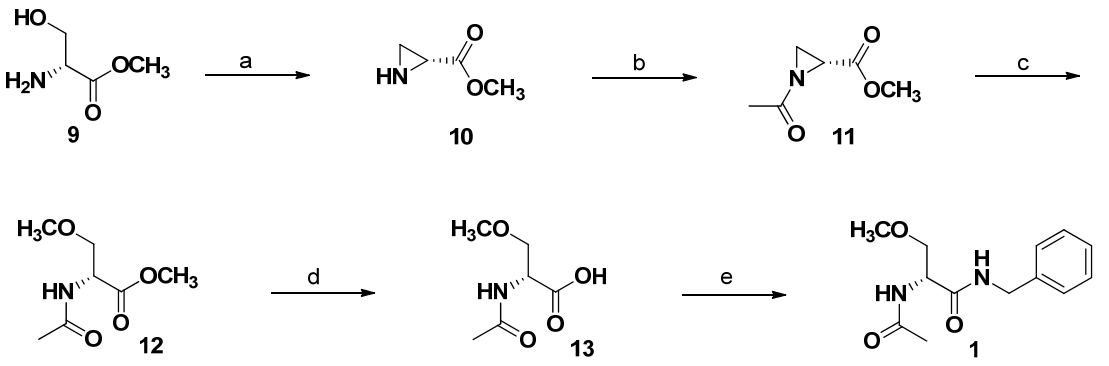
In 1998, Kohn *et al.* modified their earlier synthesis of lacosamide **1** using the same starting material and by changing the protecting groups and reaction sequences. Thus, Cbz protection of D-serine **2** followed by coupling with benzylamine using mixed anhydride procedure (MAC) to benzylamide derivative **6**. Methylation of benzylamide **6** with MeI and Ag_2O gave ester **7**. Cbz deprotection followed by *N*-acetylation furnished lacosamide **1** (Scheme 2).



Scheme 2. *Reagents and conditions***:** (a) Cbz-Cl, MgO, Et_2O, H_2O, 80%; (b) *N*-Methyl morpholine, isobutyl chloroformate, benzylamine, THF, 84%; (c) MeI, Ag_2O, CH_3CN, 84%; (d) H_2, Pd/c, MeOH, 100%; (e) Ac_2O, pyridine, DMAP (cat), THF, 90%.

Kohn *et al* (2008)[7f]

Another approach was reported by Kohn *et al.* for the synthesis of lacosamide **1** via aziridine ring formation. Utilizing Evan's one-step cyclodehydration procedure, serine methyl ester **9** was converted to the desired methyl (2*R*)-aziridinium-2-carboxylate **10** using DTTP.



Scheme 3. *Reagents and conditions***:** (a) DTPP, CH_3CN; 69% (b) Ac_2O, Et_3N, DMAP (cat), DCM, 94%; (c) $BF_3.Et_2O$, MeOH, DCM, 56%; (d) LiOH, H_2O, THF, recrystallization, 38%; (e) DMTMM, benzylamine, THF, 61%.

Subsequently, N-acetylation followed by ring opening of aziridine furnished the product **12**. Ester hydrolysis followed by coupling with benzylamine furnished lacosamide **1** (Scheme 3).

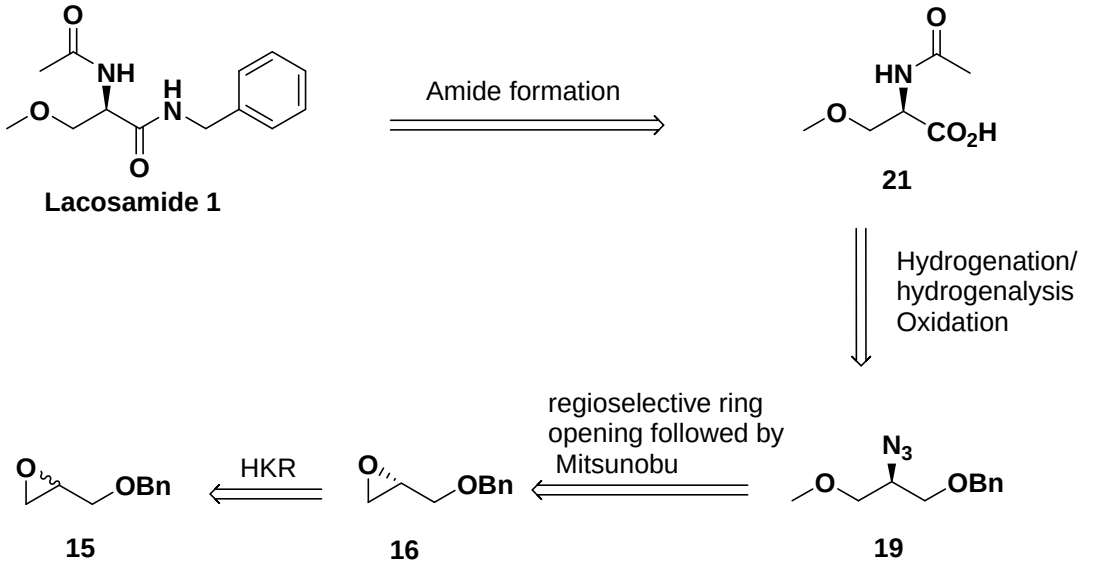
2.1.3. Present Work

Objective

The existing methods for the synthesis of lacosamide utilize unnatural amino acid *D*-serine or its derivatives as starting material which is expensive. Secondly, most of the methods employ excess of silver (I) oxide for *O*-methylation. Further, prolonged reaction time *i.e.* about 3-4 days is required for *O*-methylation. There has been surprisingly no report on the asymmetric synthesis of this molecule. We thought it would be worthwhile to design a synthetic route for this molecule using Jacobsen's HKR method as a key step.[9] Jacobsen's HKR method uses readily available catalyst and water as the only reagent to resolve racemic epoxide into enantiopure epoxide and diol in high enantiomeric excess. These advantages have made it a very attractive asymmetric synthetic tool.

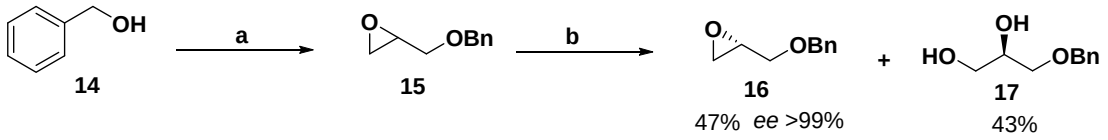
2.1.4. Results and Discussion

A retrosynthetic analysis of lacosamide is outlined in Scheme 4. As shown in Scheme 4, we envisaged that the azido compound **19** would serve as a key intermediate for the synthesis and it can be elaborated to the advanced acid precursor **21** by simple hydrogenation, hydrogenolysis and oxidation sequences followed by amidation can lead to the target molecule **1**. Compound **19** in turn can be accessed from (*S*)-benzyl glycidyl ether **16** employing regioselective ring opening as well as Mitsunobu reaction protocols. (*S*)-benzyl glycidyl ether **16** can be easily obtained with high enantiopurity from its racemic benzyl glycidyl ether **15** using Jacobsen's hydrolytic kinetic resolution strategy.



Scheme 4. Retrosynthetic analysis of Lacosamide **1**

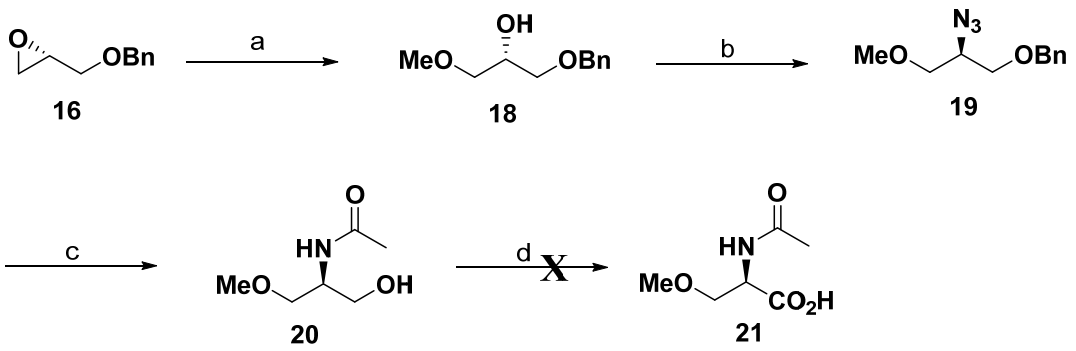
The synthesis commenced with the readily available starting material benzyl alcohol **14** as depicted in Scheme 5. Thus, the reaction of benzyl alcohol **14** with *rac*-epichlorohydrin in the presence of NaOH as a base gave *rac*- benzyl glycidyl ether **15** in 90% yield. Appearance of signals at δ 3.39-3.48 (m, 1H) and 3.73-3.81 (m, 1H) in ^{1}H NMR and m/z peak at 187 $(M+Na)^+$ in mass spectrum showed the formation of epoxide **15**. The *rac*- benzyl glycidyl ether **15** was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equivalent of water using, the catalyst (*R,R*)-Salen Co(III)OAc (0.5 mol%) at ambient temperature for 30 h. After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give enantiomerically pure epoxide **16** from the racemic mixture in 47% yield and >99% ee {$[\alpha]_D$ = +8.1 (*c* 0.4, EtOH); lit.[10] $[\alpha]_D$ = +7.8 (*c* 0.4, EtOH)} along with its diol **17** in 43% yield.



Scheme 5. *Reagents and conditions***:** (a) epichlorohydrin, aq NaOH, TBAI, rt, 24 h, 90%; (b) (*R, R*) Salen Co (III)-A, 0˚C-rt, 24 h, 47%.

The epoxide **16** was subjected to regioselective ring opening with methanol in the presence of KOH as a base to give the corresponding secondary alcohol **18** in 98%

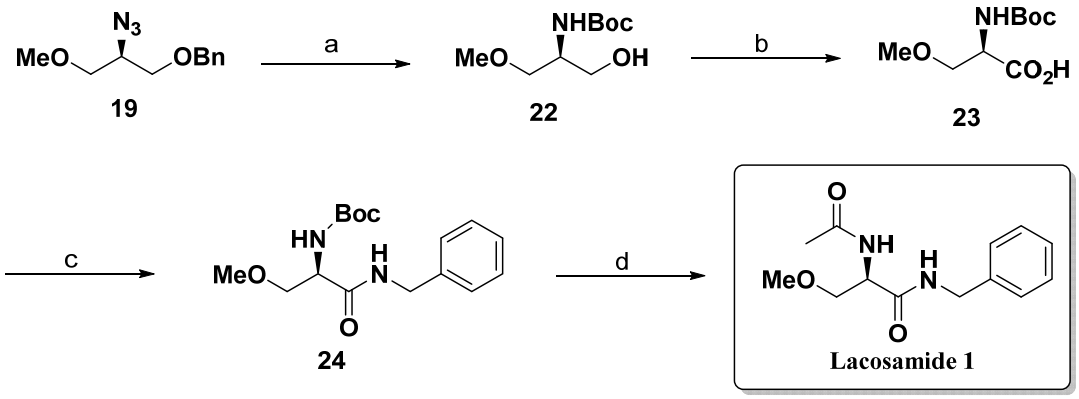
yield. Appearance of a singlet at δ 3.38 (3H) and multiplet in the range of δ 3.94-4.04 (1H) in ^{1}H NMR and a peak at δ 59.2 (OCH_3) in ^{13}C NMR confirmed the formation of compound **18**. The secondary alcohol **18** was converted to the desired azido derivative **19** in 83% yield using DPPA under Mitsunobu condition. Subsequently, the azido compound **19** was subjected to $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis followed by *N*-acetylation using acetyl chloride under basic condition afforded the compound **20** in 85% yield (two steps). Having successfully synthesized the precursor **20**, our next aim was to convert the compound **20** into an acid **21**, followed by coupling with benzylamine to complete the synthesis of lacosamide **1**. However, oxidation of compound **20** to acid **21** posed a problem. Oxidative conditions viz sodium chlorite catalyzed by TEMPO & bleach and Jones oxidative conditions did not provide the desired acid **21** (Scheme 6).



Scheme 6. *Reagents and conditions***:** (a) MeOH, KOH, Et_2O, 0 °C- rt, 6 h, 98%; (b) DPPA, DIAD, PPh_3, toluene, -20 °C- rt, 10 h, 83%; (c) (i) $Pd(OH)_2$ (cat), H_2, MeOH, rt, 24 h; (ii) CH_3COCl, Na_2CO_3, toluene, 5 °C, 1 h, 85% (two steps); (d) $NaClO_2$, NaOCl, TEMPO (cat), phosphate buffer, CH_3CN, 35 °C, 10 h, 0%; or Jones reagent, acetone, 5 h, 0%.

To circumvent this problem, we planned to change the strategy slightly by converting the azido compound **19** into *N*-Boc protected aminoalcohol **22** and attempting an oxidation. Accordingly, the azido compound **19** was subjected to $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis and concomitant protection with $(Boc)_2O$ afforded the *N*-Boc protected aminoalcohol **22** in 86 % yield (Scheme 7). Disappearance of a singlet at δ 4.52 (2H) and multiplet at δ 7.28-7.37 (5H) in ^{1}H NMR showed the removal of benzyl group. Appearance of a singlet at δ 1.45 (9H) showed the presence of Boc group and multiplet in the range of δ 3.61-3.80 (2H) in ^{1}H NMR confirmed the

formation of aminoalcohol **22.** Gratifyingly, the compound **22** underwent oxidation very smoothly under sodium chlorite catalyzed by TEMPO & bleach in acetonitrile-phosphate buffer (pH 6.8) condition and afforded the corresponding acid **23** in 83 % yield. Subsequently, the acid **23** was converted to the amide **24** by coupling with benzylamine using mixed anhydride procedure. Appearance of multiplet in the range of δ 7.22-7.37 (5H) in ^{1}H NMR and a peak at δ 170.3 (CO) in ^{13}C NMR indicated the formation of compound **24**.



Scheme 7. *Reagents and conditions***:** (a) $(Boc)_2O$, $Pd(OH)_2$ (cat), H_2, EtOAc, rt, 36 h, 86%; (b) $NaClO_2$, NaOCl, TEMPO (cat), phosphate buffer, CH_3CN, 35 °C, 6 h, 83%; (c) isobutyl chloroformate , NMM, benzylamine, THF, -78 °C- rt, 1 h, 90 %; (d) (i) CF_3CO_2H, DCM, 0 °C- rt, overnight; (ii) CH_3COCl, Na_2CO_3, toluene, 5 °C, 1 h, 80% (two steps).

Finally, subjection of compound **24** to Boc-deprotection followed by *N*-acetylation using acetyl chloride in the presence of Na_2CO_3 as a base, complete the synthesis of lacosamide **1** in good overall yield of 20.3% and excellent enantioselectivity (>98 % ee) {$[\alpha]_D$ = +16.1 (c 1, MeOH); lit[7e] $[\alpha]_D$ = +16.4 (*c* 1, MeOH)}. The structure of lacosamide **1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

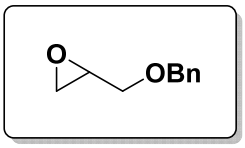
2.1.5. Conclusion

In summary, a practical and highly enantioselective synthesis of lacosamide **1** has been achieved using Jacobsen's hydrolytic kinetic resolution method as the key step and source of chirality. The main advantages of the present method being high enantioselectivity, the ready availability of the starting material & the catalyst and use

of water (0.55 equiv) as the medium and reactant at the key step. Moreover, the Jacobsen catalyst can be regenerated by treating with acetic acid and recycled.

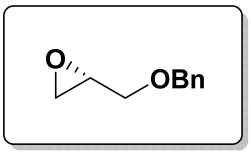
2.1.6. Experimental

1) 4.2 2-(benzyloxymethyl) oxirane (racemic) 15



To a stirred solution of aqueous sodium hydroxide (125 mL, 50% w/w), epichlorohydrin (54 mL, 925 mmol) and tetrabutylammonium iodide (3.4 g, 9.4 mmol) was added benzyl alcohol **14** (20 g, 185 mmol) at temperature below 25 ºC and the resulting mixture was stirred at room temperature for 24 h. After completion of the reaction cold water (250 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/acetone, 95:5) to afford 2-(benzyloxymethyl) oxirane **15** as a colorless oil (27.6 g, 91%); IR ($CHCl_3$, cm^{-1}): ν_{max} 3418, 3020, 2401, 1719, 1603, 1523, 1495, 1421, 1216, 1094, 929, 669; ^1H NMR (200 MHz, $CDCl_3$): δ_H 2.60-2.64 (dd, J = 5.1, 2.7 Hz, 1H), 2.78-2.82 (dd, J = 5.3, 4.2 Hz, 1H), 3.15-3.23 (m, 1H), 3.39-3.48 (dd, J = 11.3, 5.8 Hz, 1H), 3.73-3.81 (dd, J = 11.4, 3.0 Hz, 1H), 4.60 (s, 2H), 7.28-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.8 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.3 (CH_2), 70.7 (CH_2), 50.8 (CH), 44.2 (CH_2); MS: *m/z* 187 $[M+Na]^+$.

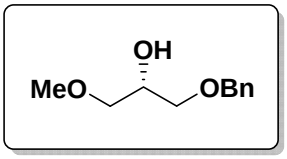
2) (*S*)-2-(benzyloxymethyl) oxirane 16



A mixture of 2-(benzyloxymethyl)-oxirane **15** (10 g, 61 mmol) and (*R,R*) salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) were vigorously stirred for 15 min, then cooled to 0 ^oC, and water added (0.6 mL, 34 mmol) over a period of 15 min, through a micro-syringe. The reaction mixture was stirred at room temperature for 20 h, and additional (*R,R*) salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) was added and

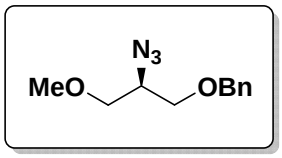
stirring was continued for additional 10 h. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/acetone (95:5). The less polar epoxide **16** eluted first as a colorless oil (4.7 g, 47%), $[\alpha]^{25}_D$ = + 8.1 (*c* 0.4, EtOH) {lit.[10] $[\alpha]^{23}_D$ = + 7.8 (*c* 0.4, EtOH)}; ee > 99% [chiral HPLC analysis; CHIRALCEL OD-H (250 x 4.6 mm) column; eluent: n-hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector: 220 nm [(*S*)-isomer t_R=15.25 min; (*R*)-isomer t_R=16.46 min], followed by diol **17** as a colorless oil (4.8 g, 43%); $[\alpha]^{25}_D$ = - 1.6 (*c* 3.1, EtOH) {lit.[9b] $[\alpha]^{25}_D$ = - 1.4 (*c* 3.3, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3020, 1600, 1495, 1215, 1045, 1029, 929, 697; NMR (200 MHz, $CDCl_3$): δ_H 2.73 (t, *J* = 5.8 Hz, 1H, OH), 3.13 (d, *J* = 5 Hz, 1H, OH), 3.51-3.54 (dd, *J* = 5.4, 2.6 Hz, 2H), 3.57-3.68 (m, 2H), 3.82-3.92 (m, 1H), 4.54 (s, 2H), 7.28-7.39 (m, 5H, Ph); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 137.6 (C), 128.4 (CH, 2 carbons), 127.8 (CH, 3 carbons), 73.5 (CH_2), 71.6 (CH_2), 70.7 (CH), 63.9 (CH_2).

3) (*S*)-1-(benzyloxy)-3-methoxypropan-2-ol 18



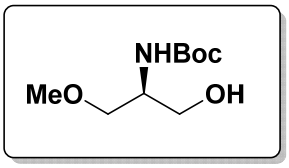
To a stirred solution of epoxide **16** (4 g, 24.3 mmol) in methanol (40 mL) was added slowly a powdered KOH (4 g; 70 mmol) at 10°C and the reaction mixture was stirred at ambient temperature for 8 h, after which the solvent was evaporated under reduced pressure. The residue was dissolved in ethylacetate (50 mL), washed with water, dried over Na2SO4, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 90:10) to afford (*S*)-1-(benzyloxy)-3-methoxypropan-2-ol **18** as a colorless oil (4.6 g, 98 %); $[\alpha]^{25}_D$ = - 1.97 (*c* 1.55, EtOH) {lit.[11] $[\alpha]^{25}_D$ = - 1.3 (*c* 1.54, EtOH)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3686, 3444, 3020, 2401, 1603, 1523, 1473, 1422, 1120, 1045, 758, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.38 (s, 3H), 3.43-3.47 (dd, *J* = 5.3, 3.4 Hz, 2H), 3.50-3.55 (dd, *J* = 5.8, 3.1 Hz, 2H), 3.94-4.04 (m, 1H), 4.56 (s, 2H), 7.29-7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.9 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 73.8 (CH_2), 73.4 (CH_2), 71.3 (CH_2), 69.4 (CH), 59.2 (CH_3); Analysis: $C_{11}H_{16}O_3$; Calcd: C, 67.32; H, 8.22; Found: C, 66.77; H, 7.89; MS: *m/z* 219 $[M+Na]^+$.

4) (*R*)-((2-azido-3-methoxypropoxy)methyl)benzene 19



A solution of DIAD (3.1mL, 15.9 mmol) in dry toluene (5 mL) was added dropwise to a solution of **18** (2.5 g, 13.2 mmol) and triphenylphosphine (4.1 g, 15.9 mmol) in dry toluene (50 mL) under N_2 atmosphere at 0 °C. After 15 min, diphenylphosphoryl azide (3.6 mL, 15.9 mmol) was added drop wise and the reaction mixture was stirred at ambient temperature for 10 h. Solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 95:05) to yield **19** as colorless oil (2.4 g, 83%); $[\alpha]^{25}_{D}$ = + 8.3 (*c* 2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3392, 2969, 2878,1661, 1542, 1463, 1441, 1384, 1289, 1073, 1017, 988, 930, 756, 667; ^{l}H NMR (200 MHz, $CDCl_3$): δ_H 3.37 (s, 3H), 3.46-3.52 (dd, *J* = 5.4, 3.7 Hz, 2H), 3.54-3.61 (m, 2H), 3.68-3.79 (m, 1H), 4.56 (s, 2H), 7.28-7.37 (m, 5H); ^{l3}C NMR (50 MHz, $CDCl_3$): δ_C 137.7 (C), 128.5 (CH, 2 carbons), 127.8 (CH), 127.7 (CH, 2 carbons), 73.5 (CH_2), 72.2 (CH_2), 69.8 (CH_2), 60.6 (CH), 59.2 (CH_3); MS: *m/z* 244 [M+Na].

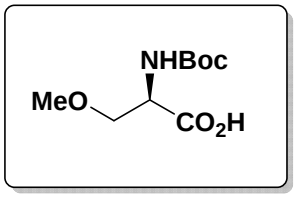
5) (*S*)-*tert*-butyl 1-hydroxy-3-methoxypropan-2-ylcarbamate 22



To a solution of **19** (2.0 g, 9 mmol) and Boc_2O (2.1 g, 10 mmol) in ethyl acetate (30 mL) was added palladium hydroxide on activated charcoal (200 mg, 10-20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 36 h. After completion of the reaction (indicated by TLC), filtered the catalyst over a plug of celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 80:20) to yield **22** as colorless oil (1.6 g, 86%); $[\alpha]^{25}_{D}$ = +3.8 (*c* 0.95, $CHCl_3$) {lit.[12] $[\alpha]^{25}_{D}$ = +26.4 (*c* 0.995, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3683, 3443, 3018, 2981, 2898, 1703, 1504, 1393, 1368, 1169, 1092, 928, 848, 669; ^{l}H NMR (200 MHz, $CDCl_3$): δ_H 1.45 (s, 9H), 2.94 (bs, 1H), 3.37 (s, 3H), 3.52-3.56 (apparent t, *J* = 3.7 Hz, 2H), 3.61-3.80 (m,

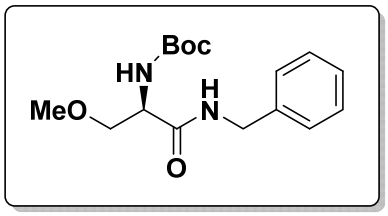
2H), 5.20 (m, 1H); ^{l3}C NMR (50 MHz, $CDCl_3$): δ_C 156.1 (CO), 79.2 (C), 73.1 (CH_2), 63.8 (CH_2), 59.2 (CH), 51.4 (CH_3), 28.3 (CH_3, 3 carbons); MS: *m/z* 228 $[M+Na]^+$.

6) (*R*)-2-(*tert*-butoxycarbonylamino)-3-methoxypropanoic acid 23



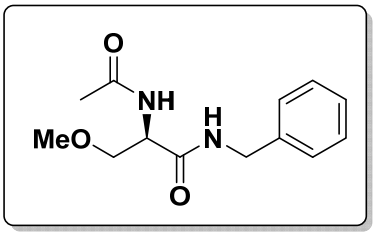
A mixture of **22** (1 g, 4.9 mmol), TEMPO (0.05 g, 0.32 mmol), acetonitrile (20 mL), and sodium phosphate buffer (16 mL, 0.67 M, pH 6.7) was heated to 35 ^{0}C. Then sodium chlorite (1.32 g dissolved in 2 mL water, 14.6 mmol) and dilute bleach (4-6 %, 1 mL diluted in 2 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at 35 ^{o}C until the reaction is complete (6 h, TLC), then cooled to room temperature. Water (30 mL) was added and the pH is adjusted to 8 with 2 N NaOH. The reaction is quenched by pouring into ice cold Na_2SO_3 solution maintained at <20 ^{o}C. After stirring for 30 min at room temperature, ethylacetate (30 mL) was added and continued the stirring for additional 15 min. The organic layer was separated and discarded. More ethylacetate (30 mL) was added, and the aqueous layer was acidified with 2N HCl to pH 3-4. The organic layer was separated, washed with water (2 x 15 mL), brine (20 mL) and concentrated under reduced pressure to afford the carboxylic acid **23** (0.88 g, 83%); $[\alpha]^{25}_D$ = -19.2 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3443, 3019, 2982, 2932, 1708, 1501, 1393, 1369, 1216, 1164, 1119, 1064, 927, 757, 669; ^{l}H NMR (200 MHz, $CDCl_3$): δ_H 1.46 (s, 9H), 3.38 (s, 3H), 3.59-3.66 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.84-3.90 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.41-4.47 (m, 1H), 5.42 (d, *J* = 8.2 Hz, 1H) 8.16 (bs, 1H); ^{l3}C NMR (50 MHz, $CDCl_3$): δ_C 175.4 (CO), 155.8 (CO), 80.3 (C), 72.1 (CH_2), 59.3 (CH), 53.7 (CH_3), 28.3 (CH_3, 3 carbons); Analysis: $C_9H_{17}NO_5$; Calcd: C, 49.31; H, 7.82; N, 6.39; Found: C, 48.97; H, 8.08; N, 6.01; MS: *m/z* 242 $[M+Na]^+$.

7) (*R*)-*tert*-butyl 1-(benzylamino)-3-methoxy-1-oxopropan-2-ylcarbamate 24



To a solution of acid **23** (0.7 g, 3.2 mmol) in dry THF was added *N*-methylmorpholine (0.43 mL, 3.8 mmol) at -78 °C under argon atmosphere. After 5 min, isobutyl chloroformate (0.5 mL, 3.8 mmol) was added and stirred the content for another 5 min. To this reaction mixture benzylamine (0.4 mL, 3.8 mmol) was added at -78 °C and allowed the reaction mixture to stir at room temperature for 1 h. After completion of the reaction, reaction mixture was filtered, washed with ethylacetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/acetone, 85:15) to yield **24** as colorless solid (0.9 g, 90%); m.p 63-64 ^{o}C; $[\alpha]^{25}_{D}$ = -20.5 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3683, 3431, 3020, 2931, 2401, 1714, 1523, 1496, 1368, 1165, 1119, 928, 758, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.43 (s, 9H), 3.37 (s, 3H), 3.47-3.54 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.82 (dd, *J* = 9.3, 3.7 Hz, 1H), 4.27 (m, 1H), 4.47 (d, *J* = 5.1 Hz, 1H), 5.41 (bs, 1H), 6.77 (m, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 170.3 (CO), 155.5 (CO), 137.9 (C), 128.7 (CH, 2 carbons), 127.5 (CH, 3 carbons), 80.4 (C), 72.1 (CH_2), 59.1 (CH_3), 54.0 (CH), 43.5 (CH_2), 28.3 (CH_3, 3 carbons); MS: *m/z* 331 $[M+Na]^+$.

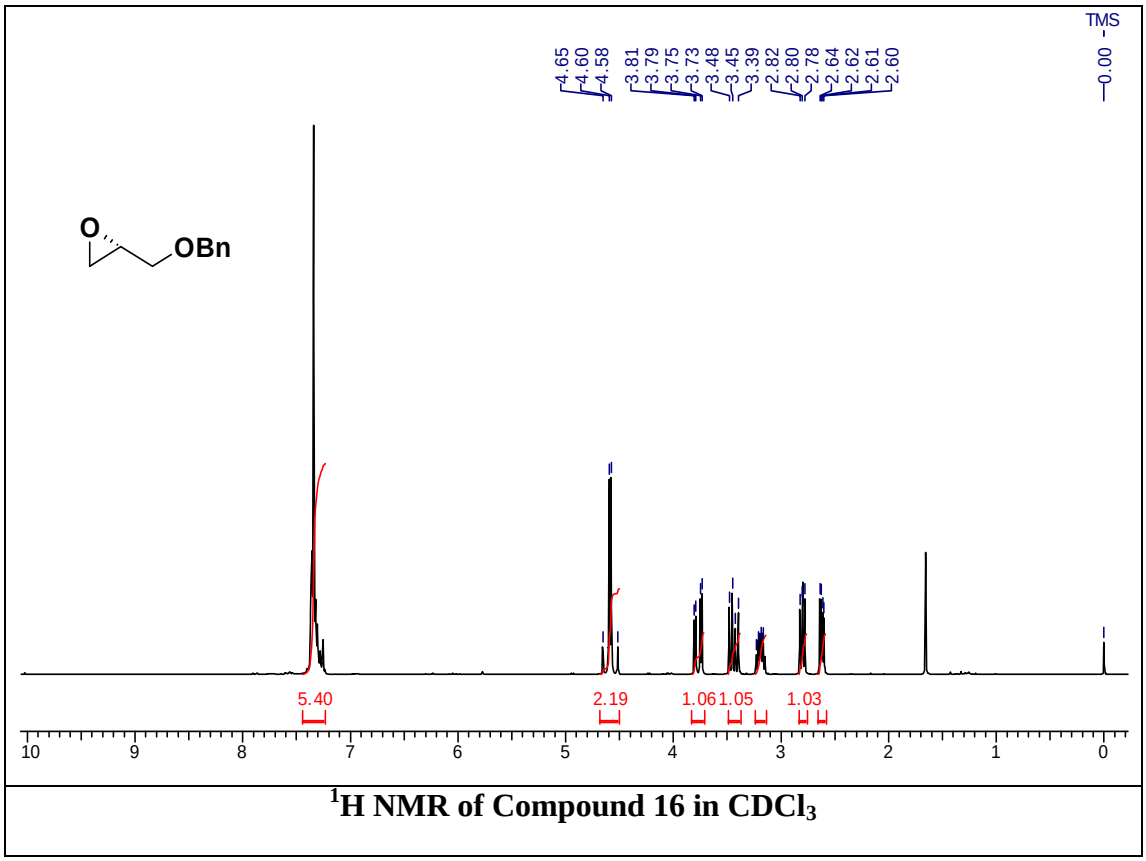
8) (*R*)-2-acetamido-N-benzyl-3-methoxypropanamide 1 (Lacosamide)



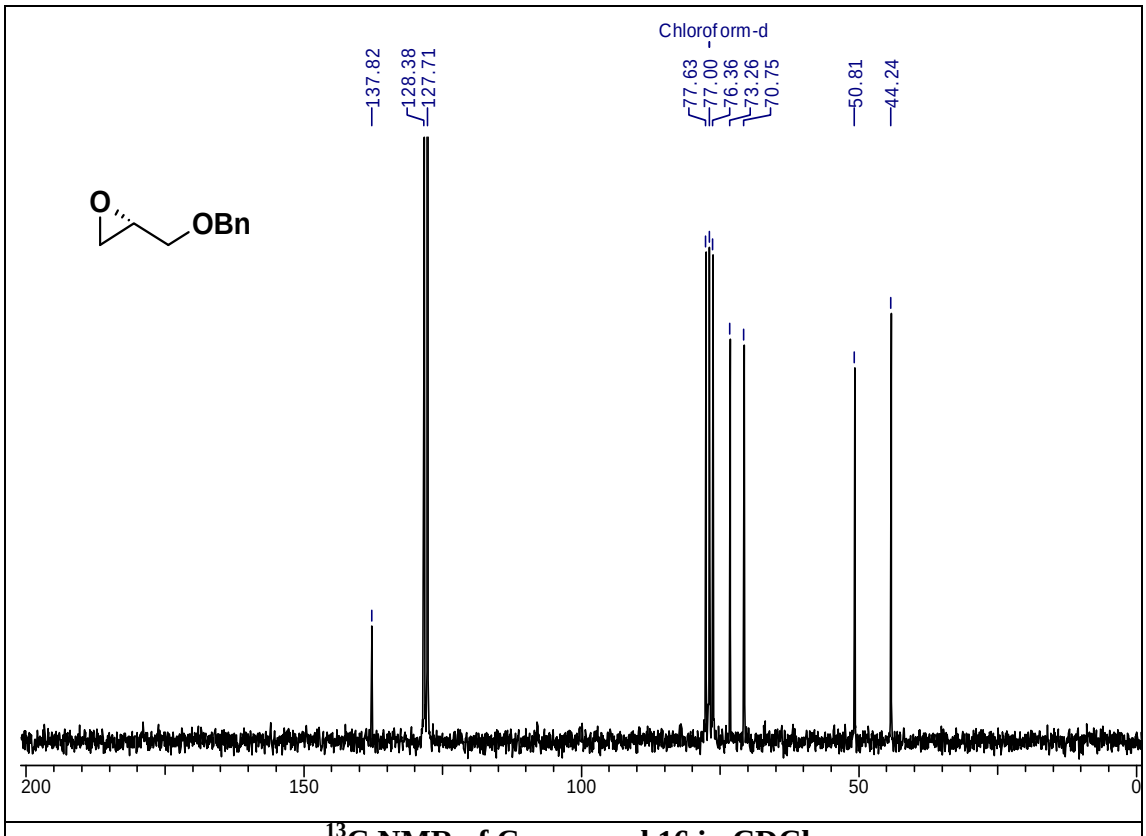
To a solution of compound **24** (0.6 g, 1.9 mmol) in dichloromethane (7 mL) was added trifluoroacetic acid (3 mL) and the reaction mixture was stirred at room temperature overnight, after which the solvent was evaporated under reduced pressure. Subsequently, the residue was dissolved in dry toluene and added Na_2CO_3 (0.6 g, 5.7 mmol). The reaction mixture was cooled to 0 °C and acetyl chloride (0.14

mL, 2.0 mmol) was added slowly and stirred the content at 5°C for 1 h. After completion of the reaction, filtered the solid and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, dichloromethane/ methanol, 95:05) to afford **1** (Lacosamide) as a colorless solid (0.38 g, 80%); Colorless solid; m.p 139-40 °C (Lit[7e] 143-44 °C); $[\alpha]_D$: +16.1 (*c* 1, MeOH) {Lit.[7e] +16.4 (*c* 1, MeOH)}; IR ($CHCl_3$): γ 3685, 3421, 3020, 1663, 1523, 1426, 1118, 1030, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 3.40 (s, 3H, OCH_3), 3.45 (apparent t, *J* = 9.7, 8.0 Hz, 1H, OCH_2), 3.83 (dd, *J* = 9.4, 3.4 Hz, 1H, OCH_2), 4.50 (d, *J* = 4.5 Hz, 2H, CH_2Ph), 4.52-4.58 (m, 1H), 6.48 (bs, 1H, NH), 6.78 (bs, 1H, NH), 7.26-7.38 (m, 5H, Ph);^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7 (CO), 170.0 (CO), 137.7 (C), 128.6 (CH, 2 carbons), 127.4 (CH, 3 carbons), 71.8 (CH_2), 59.1 (CH_3), 52.6 (CH), 43.6 (CH_2), 23.2 (CH_3); MS: m/z 273 $[M+Na]^+$; ee >98% [The *ee* of **1** was determined by chiral HPLC analysis; Chiralcel OD-H (250 x 4.6 mm) column ; eluent : pet.ether/isopropanol/trifluoroacetic acid (60 : 40 : 0.1) ; flow rate 0.5 mL/min ; detector : 220 nm [(*R*)-isomer t_R = 10.43 min; (*S*)-isomer t_R = 11.8 min].

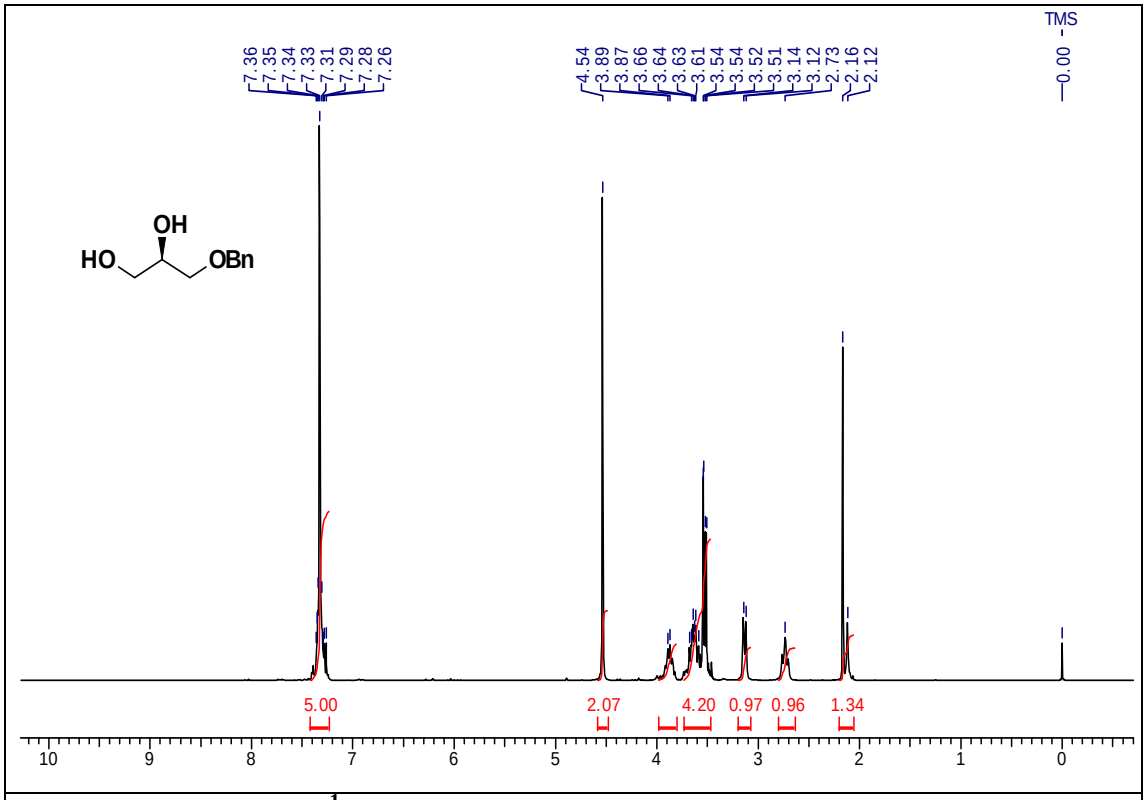
2.1.7. Analytical Data



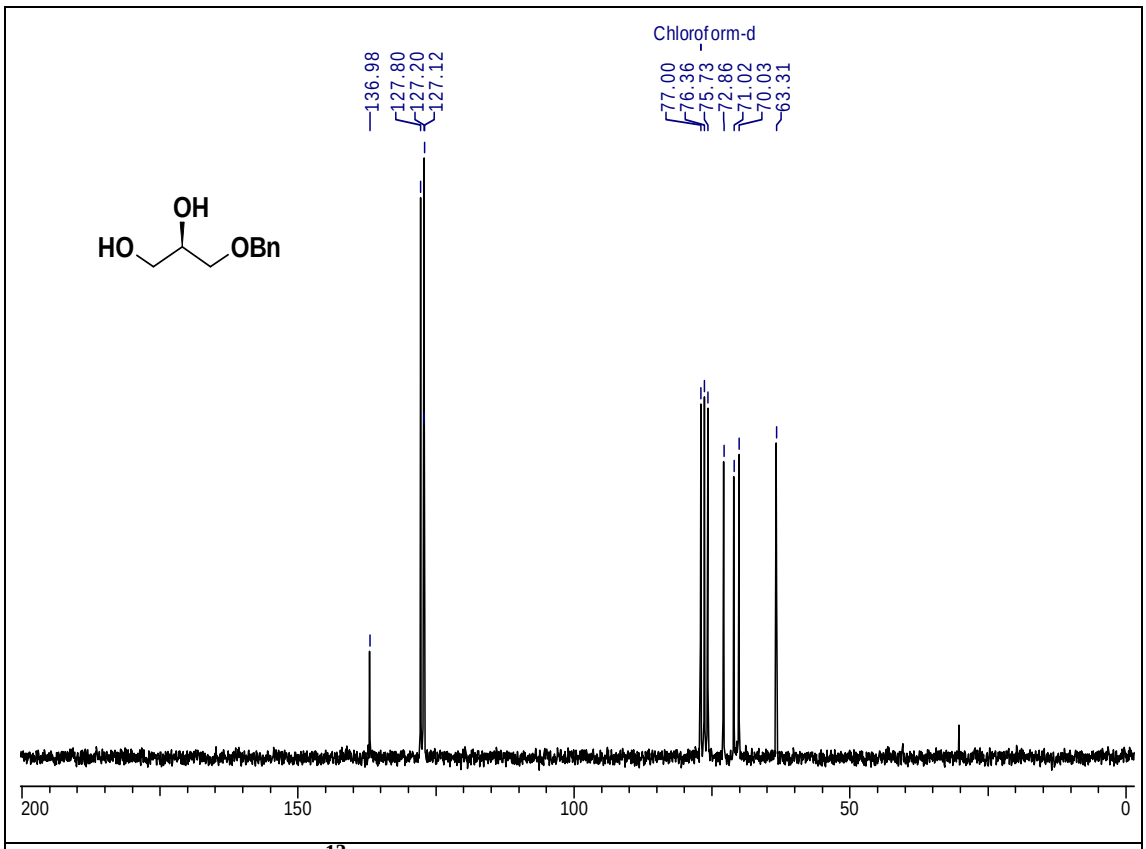
^{1}H NMR of Compound 16 in $CDCl_3$



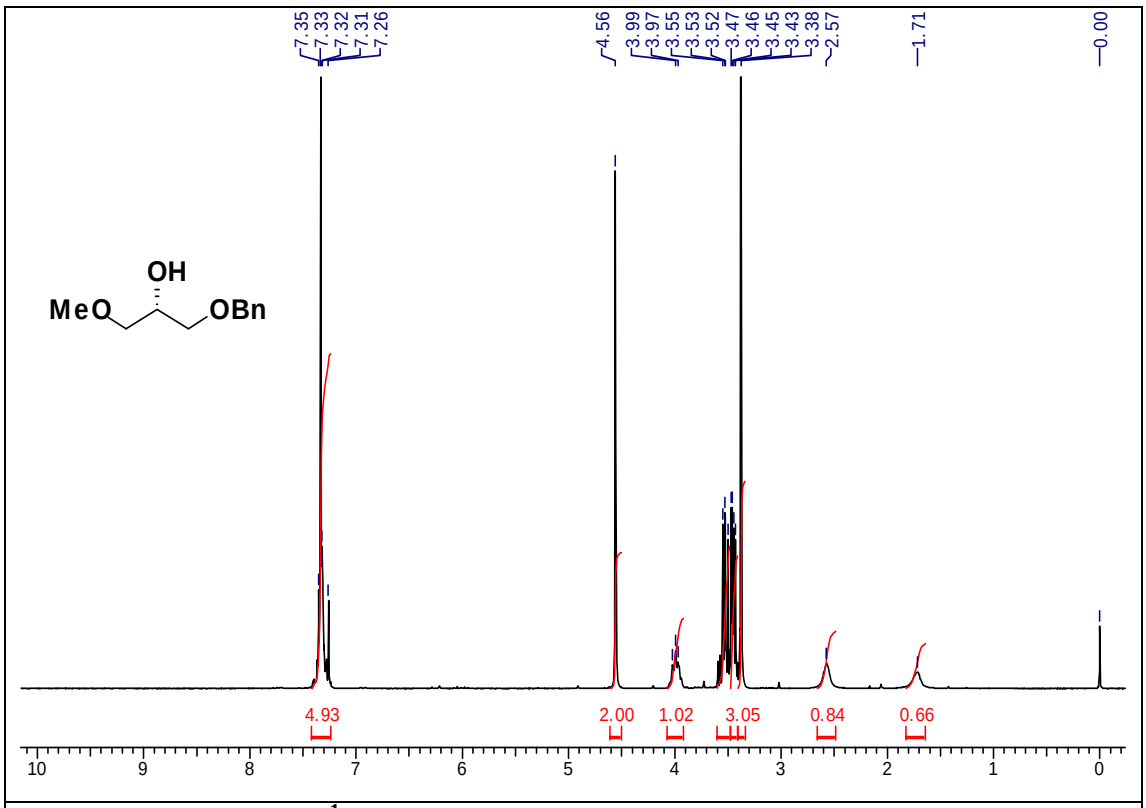
^{13}C NMR of Compound 16 in $CDCl_3$



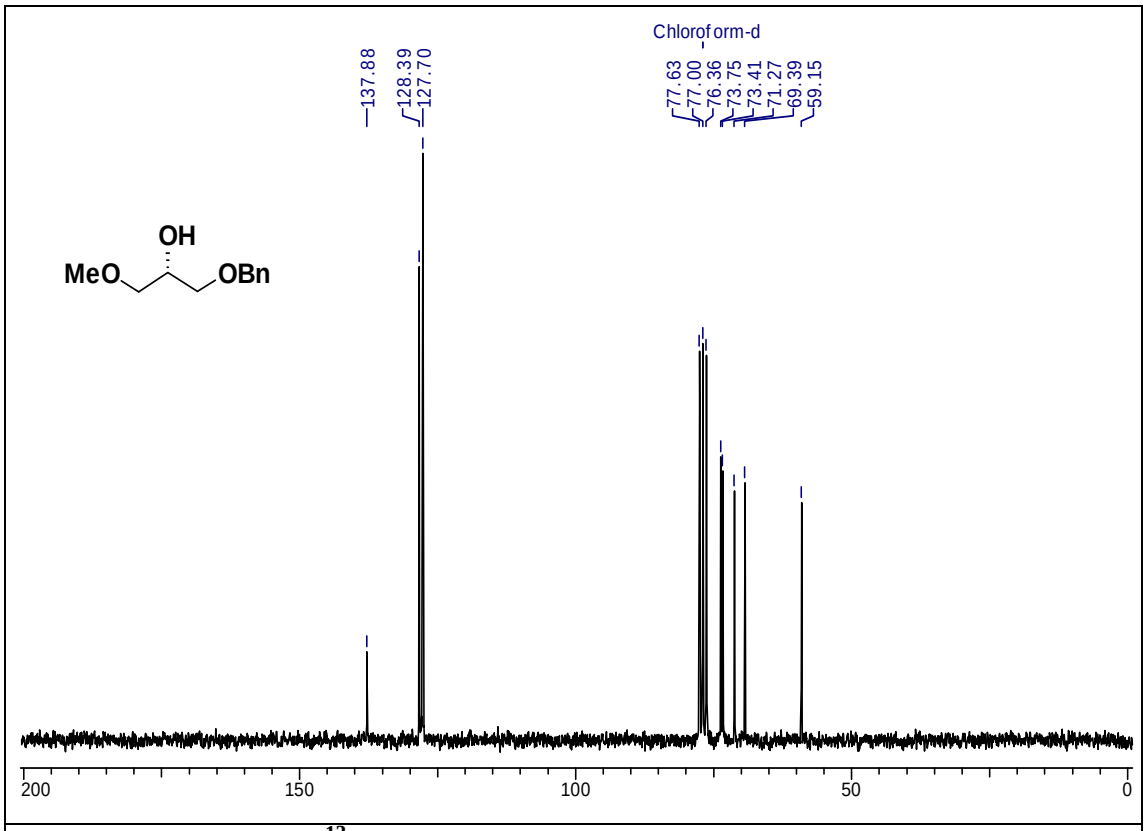
^{1}H NMR of Compound 17 in $CDCl_3$



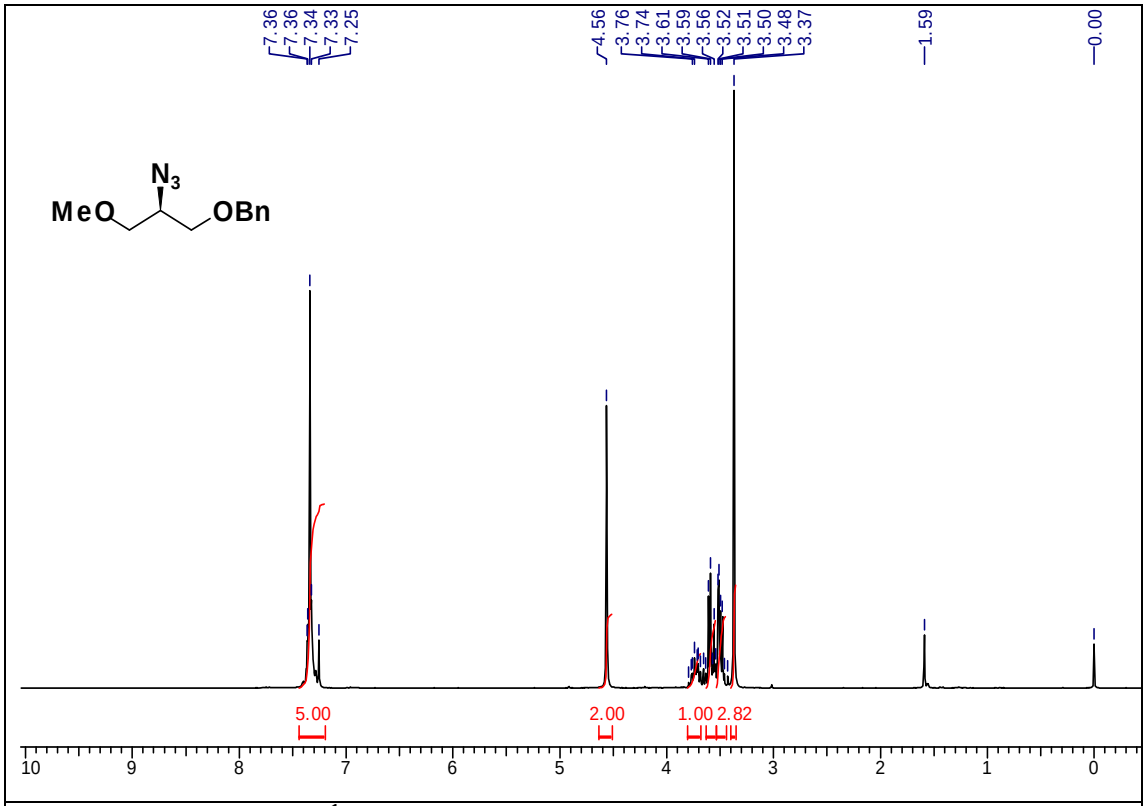
^{13}C NMR of Compound 17 in $CDCl_3$



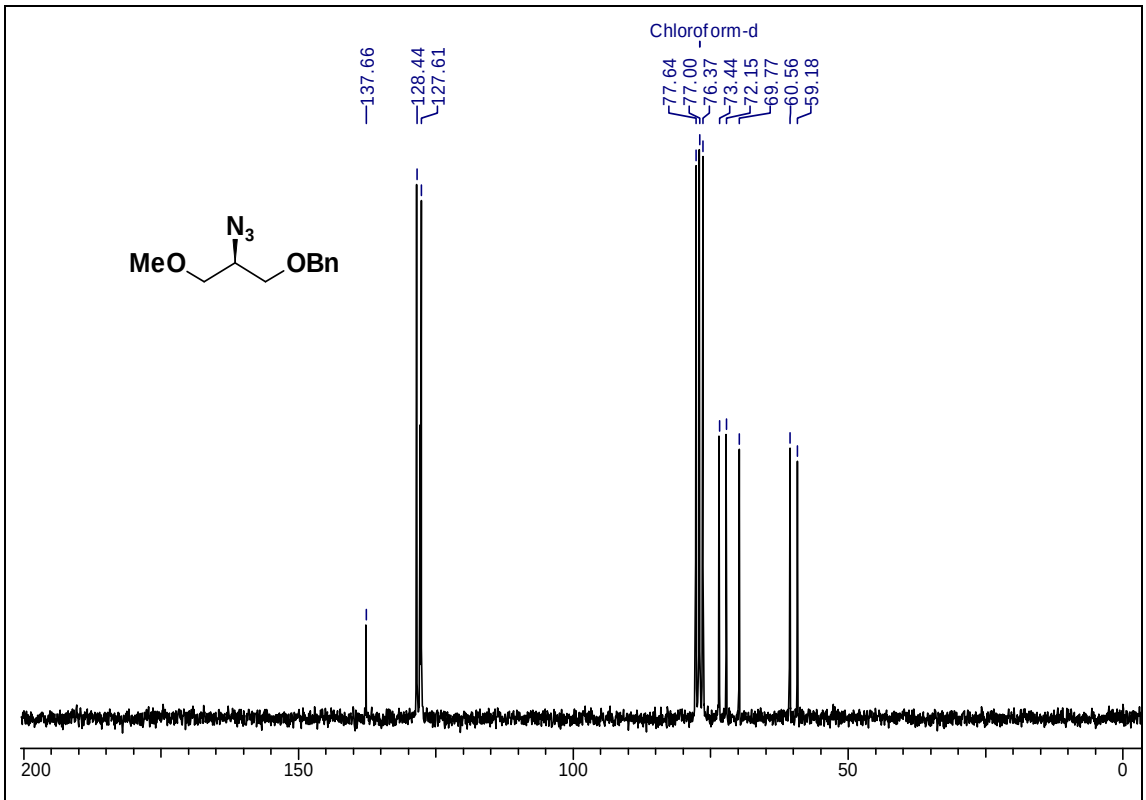
^{1}H NMR of Compound 18 in $CDCl_3$



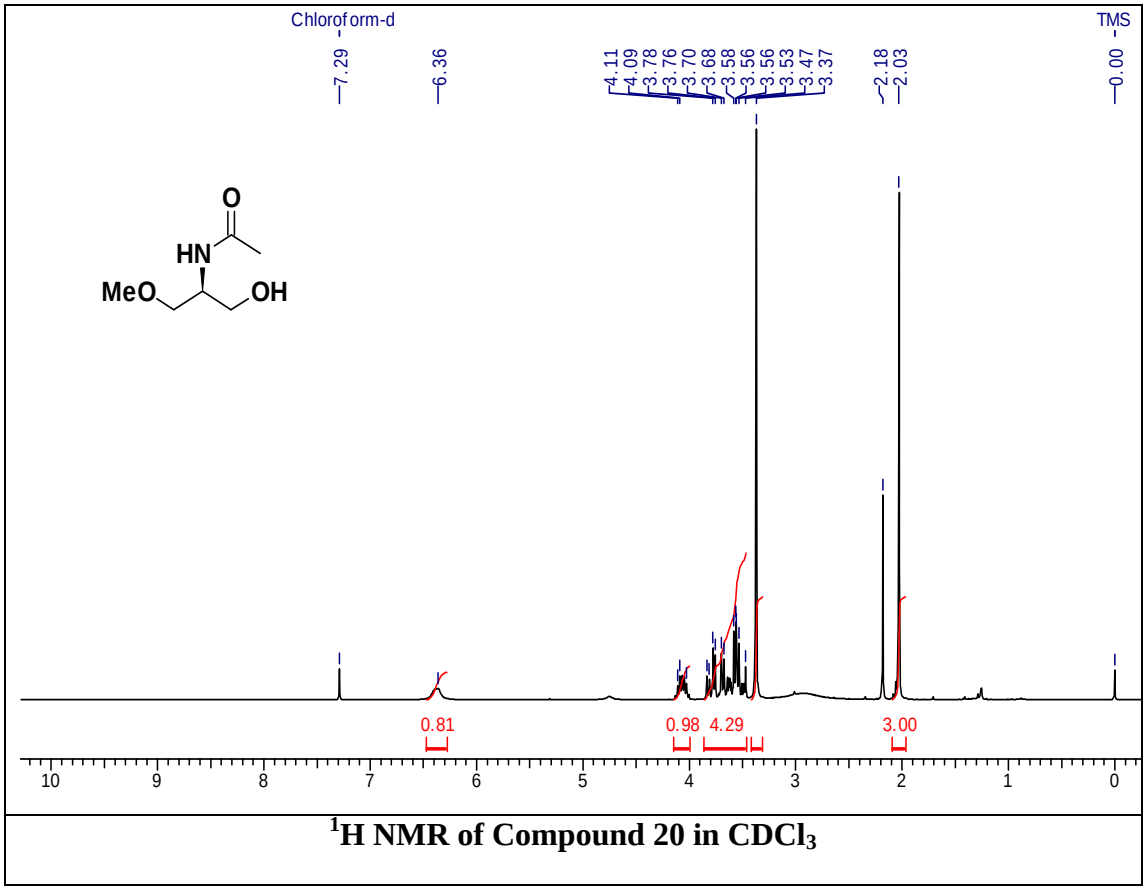
^{13}C NMR of Compound 18 in $CDCl_3$



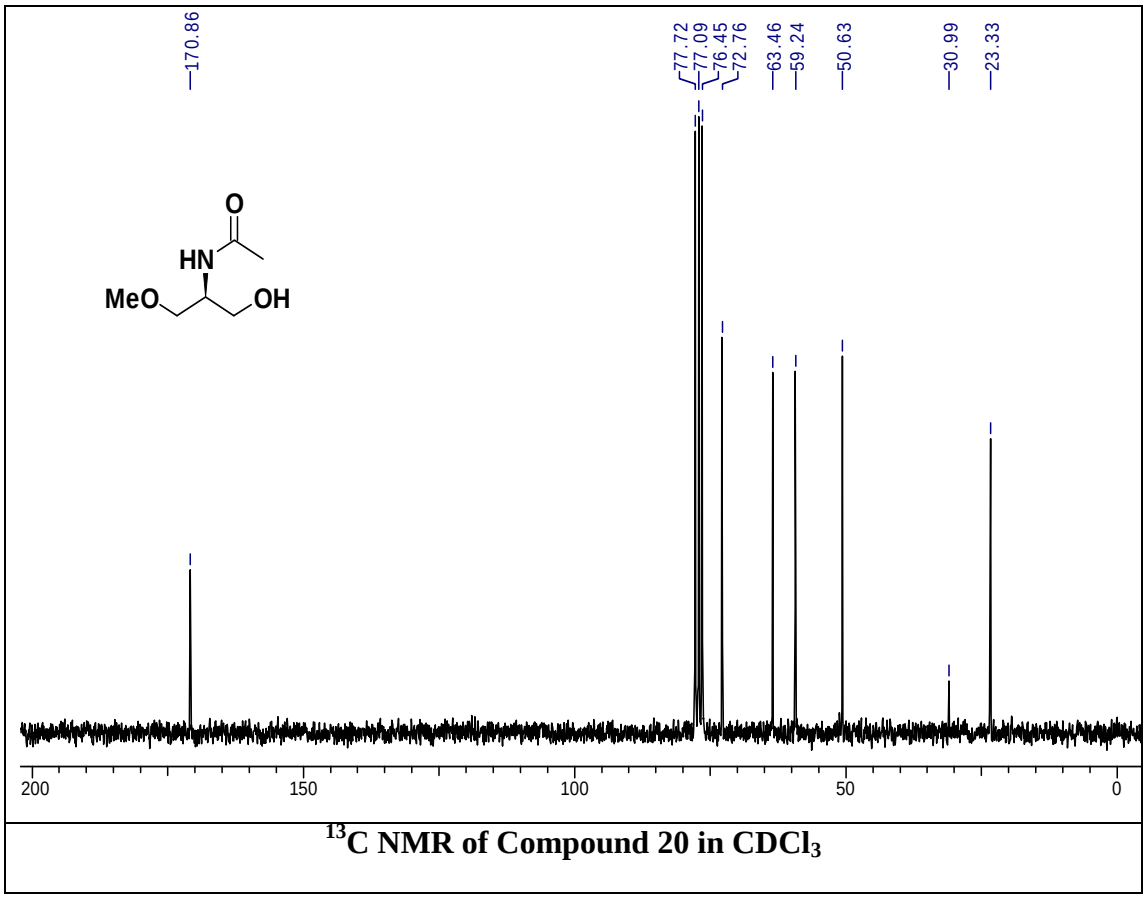
^{1}H NMR of Compound 19 in $CDCl_3$



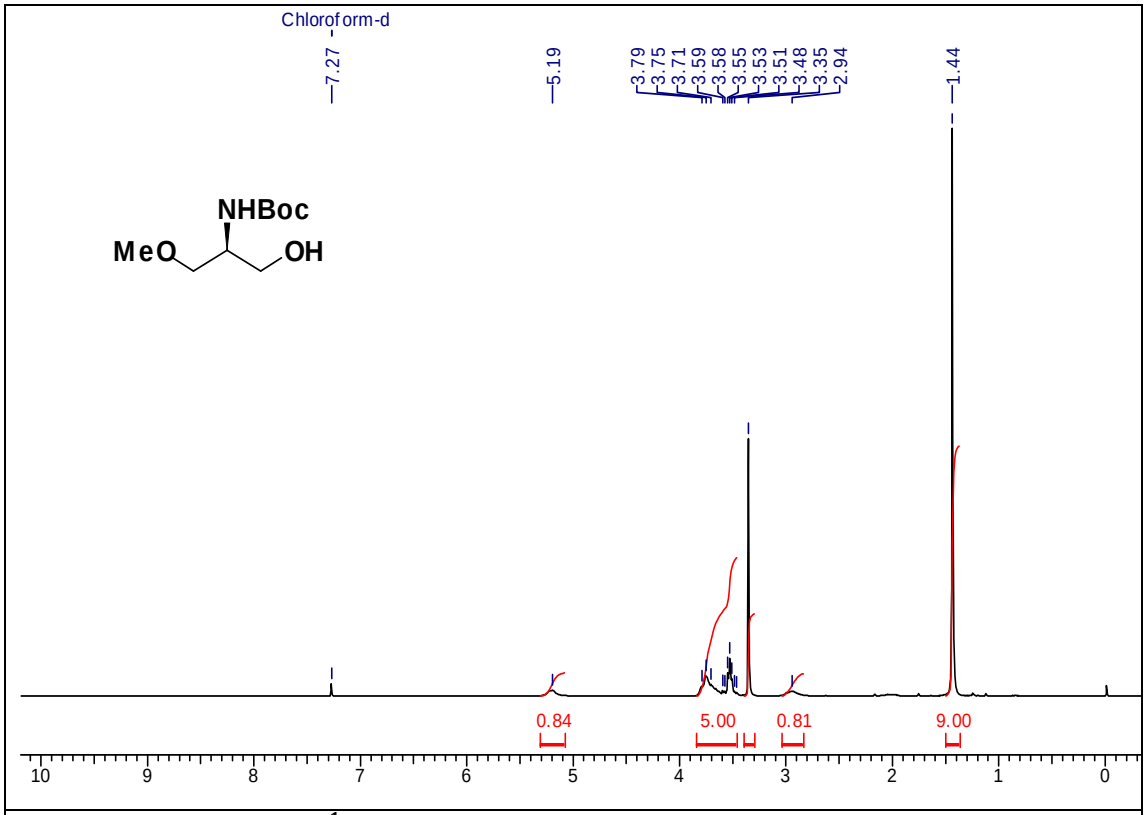
^{13}C NMR of Compound 19 in $CDCl_3$



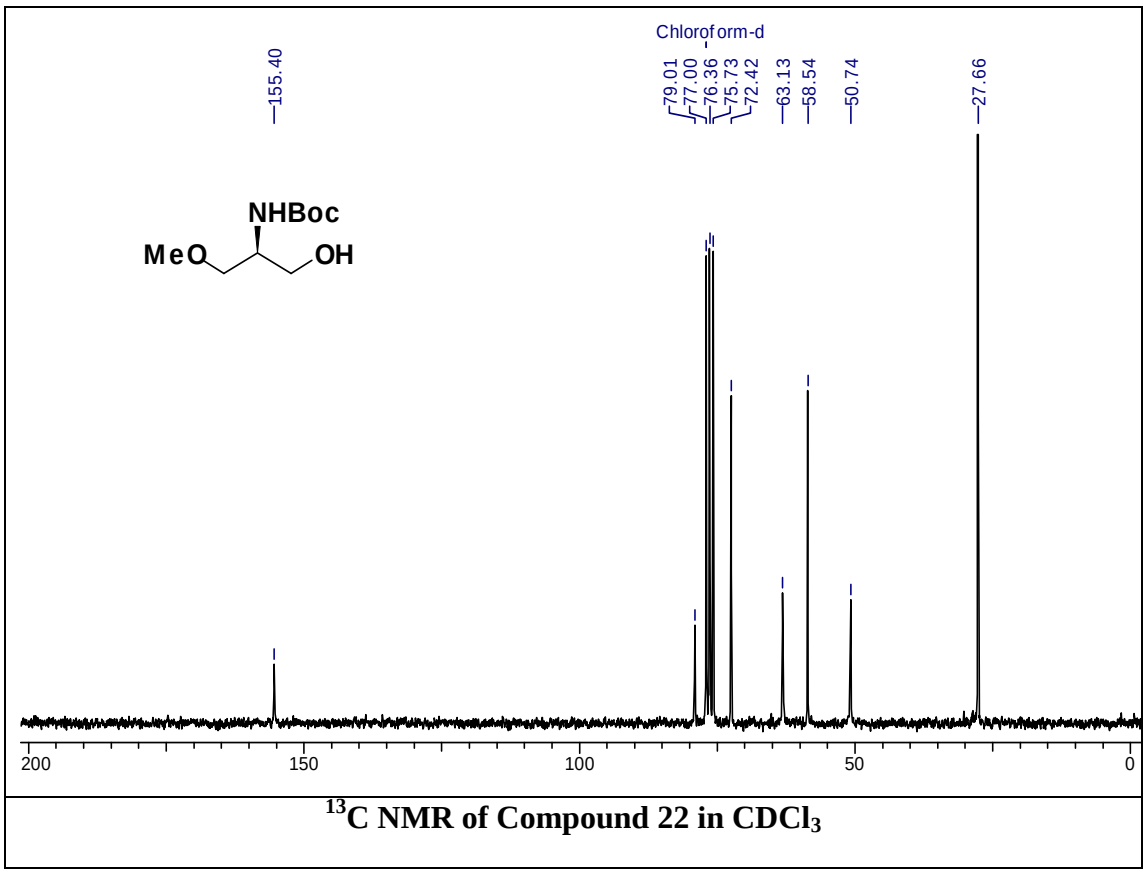
^{1}H NMR of Compound 20 in $CDCl_3$



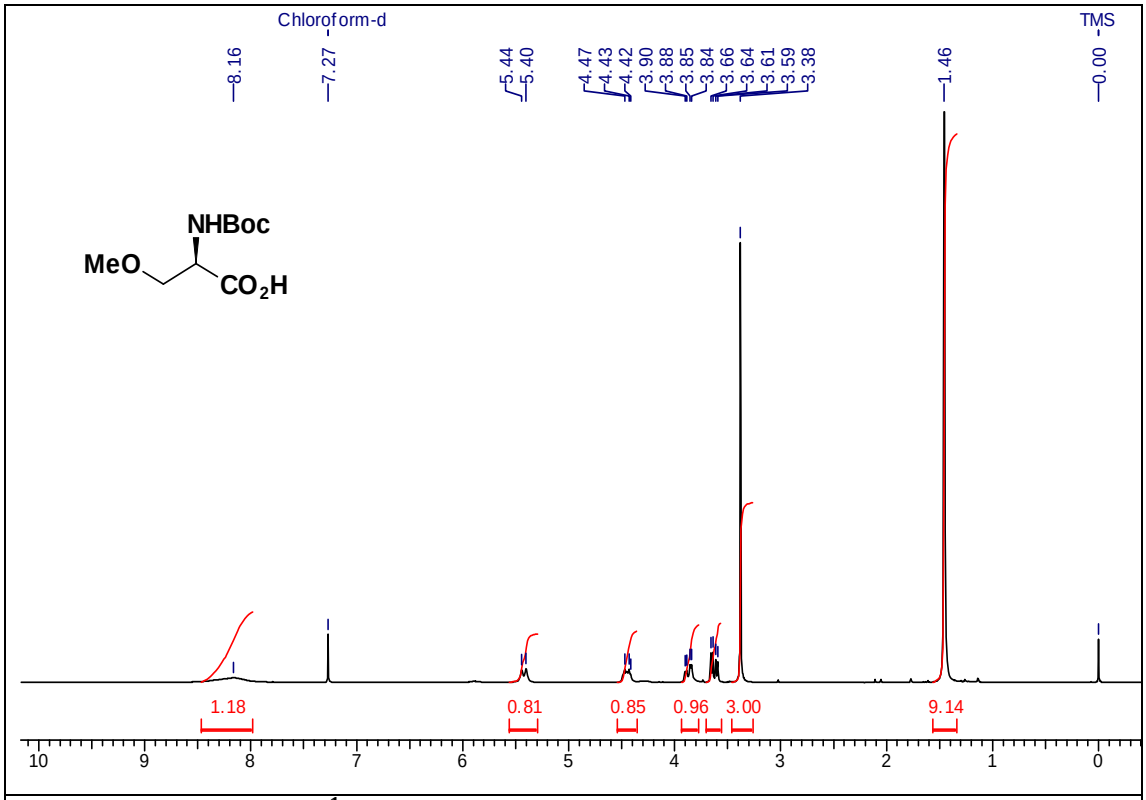
^{13}C NMR of Compound 20 in $CDCl_3$



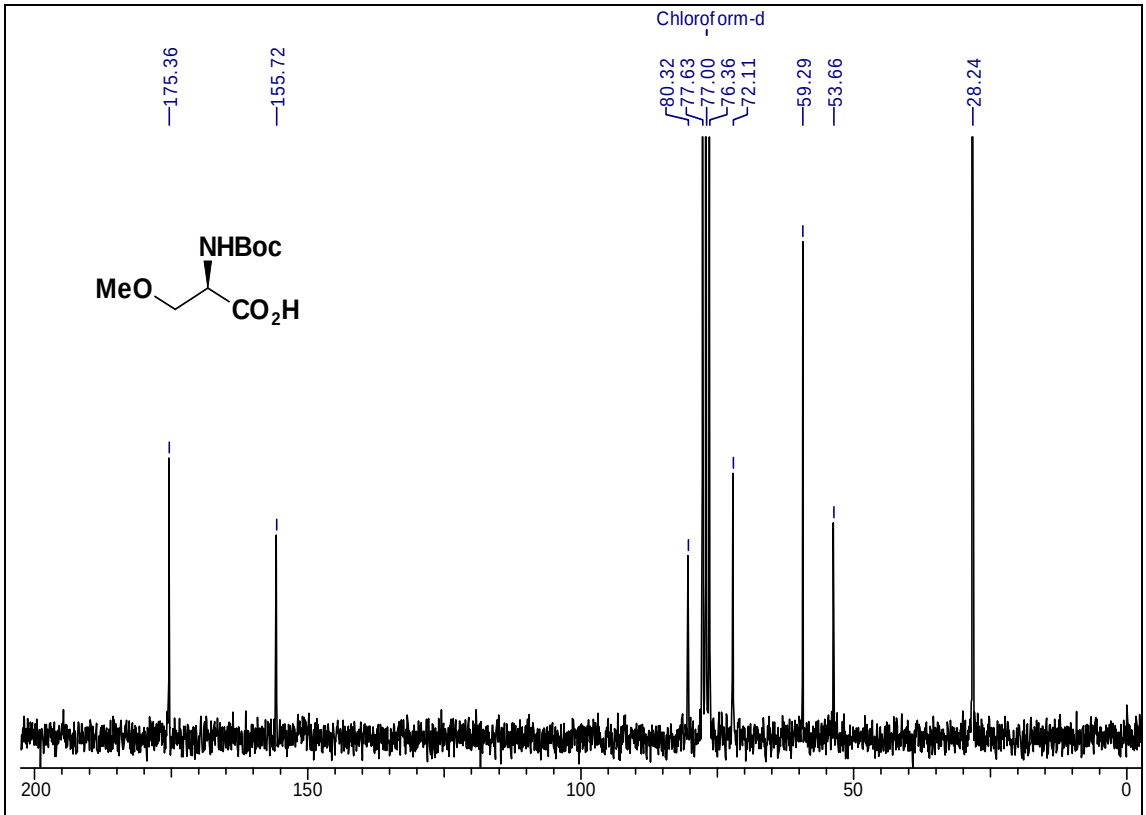
^{1}H NMR of Compound 22 in $CDCl_3$



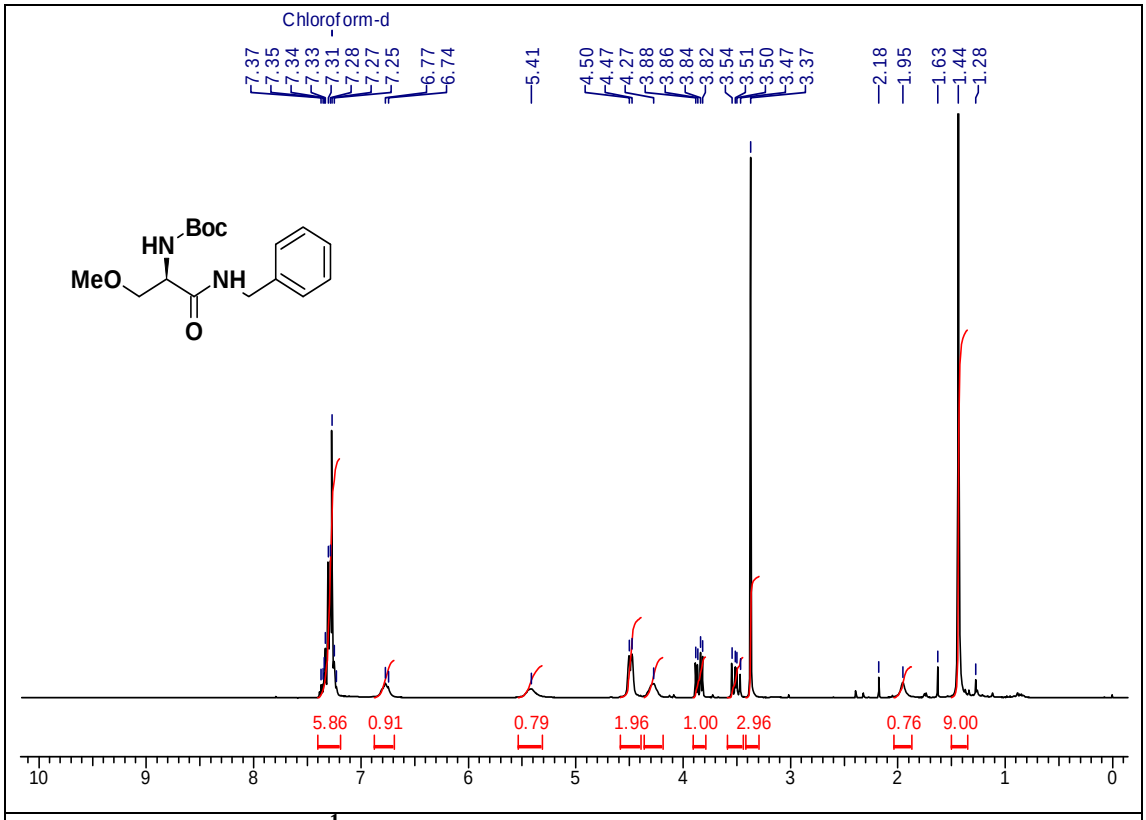
^{13}C NMR of Compound 22 in $CDCl_3$



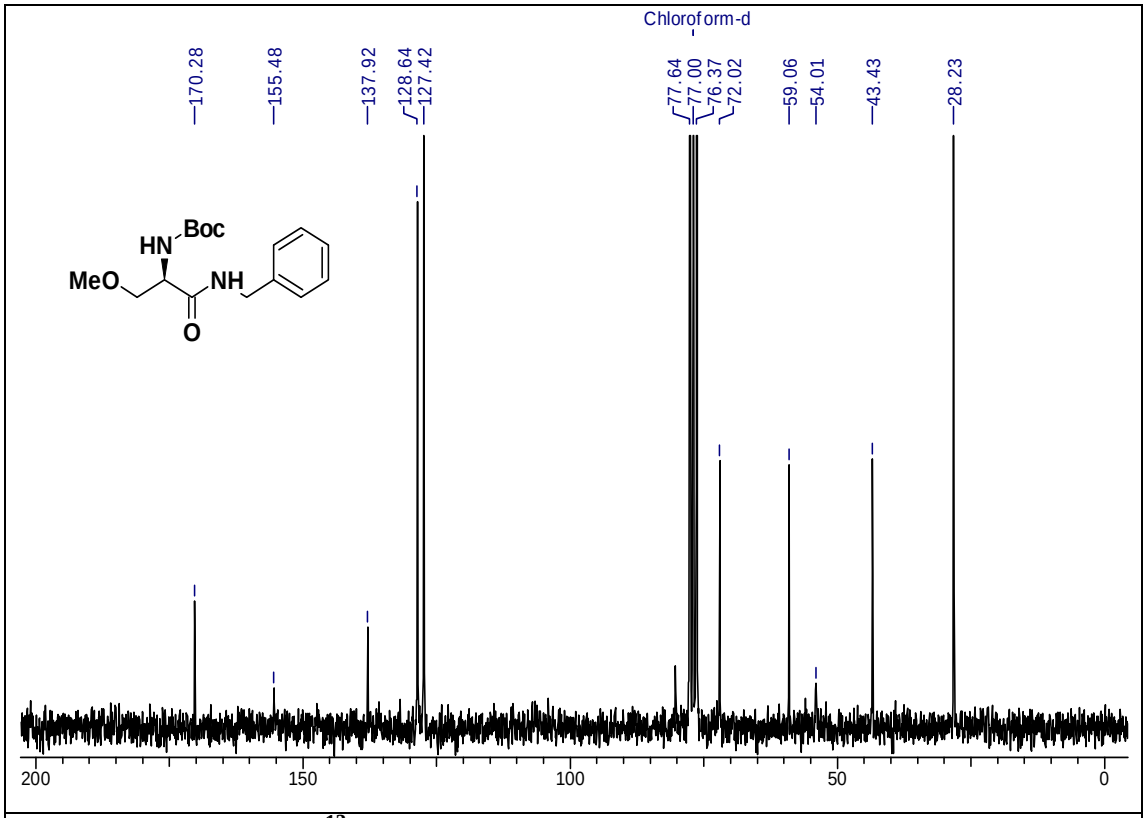
^{1}H NMR of Compound 23 in $CDCl_3$



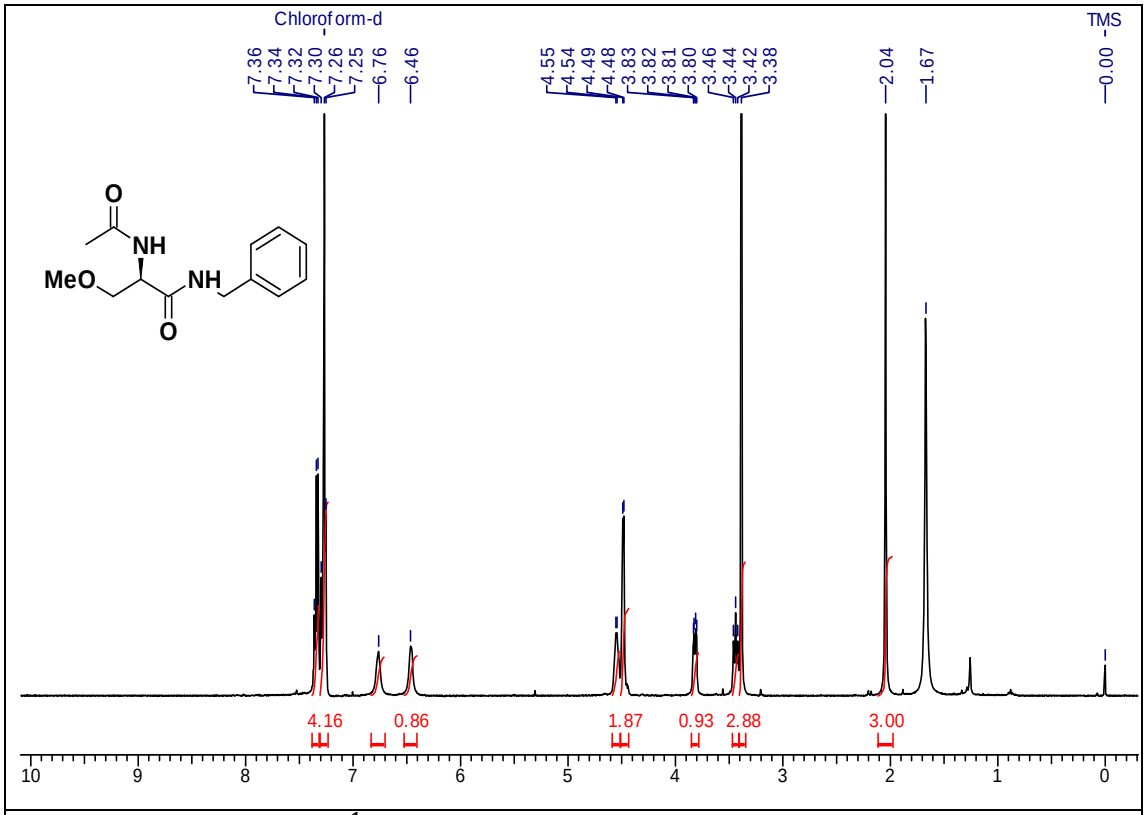
^{13}C NMR of Compound 23 in $CDCl_3$



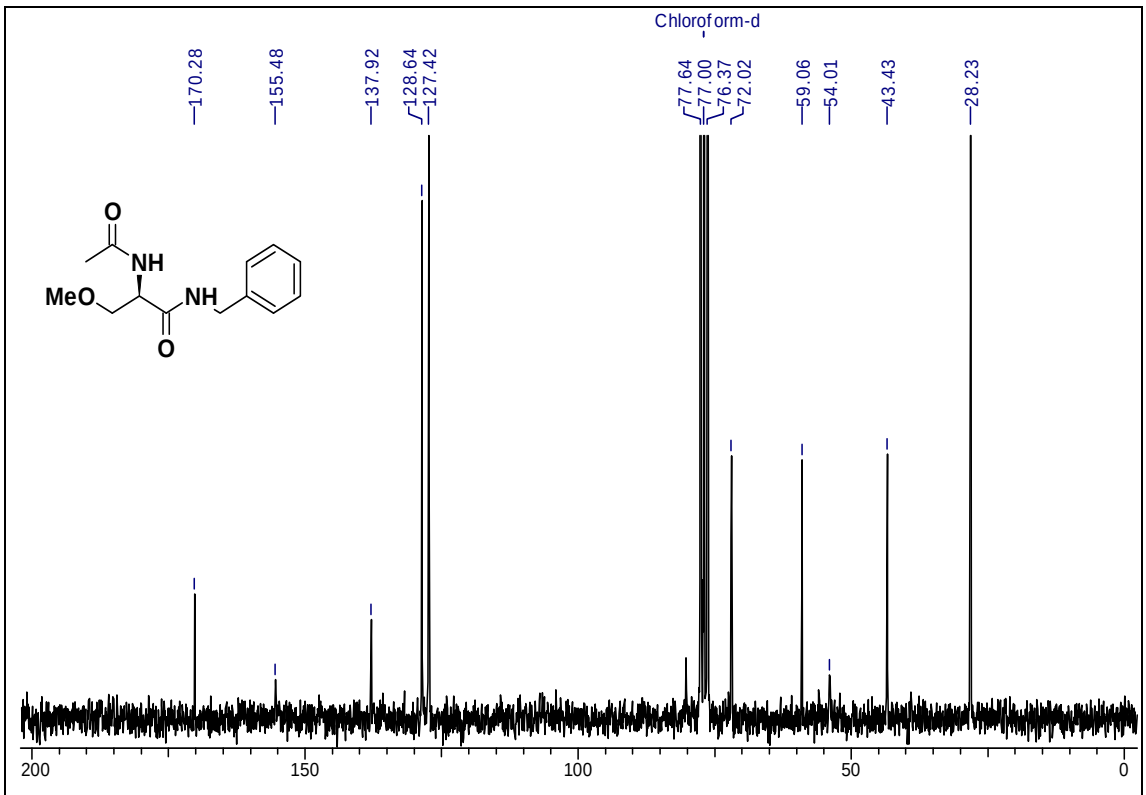
^{1}H NMR of Compound 24 in $CDCl_3$



^{13}C NMR of Compound 24 in $CDCl_3$

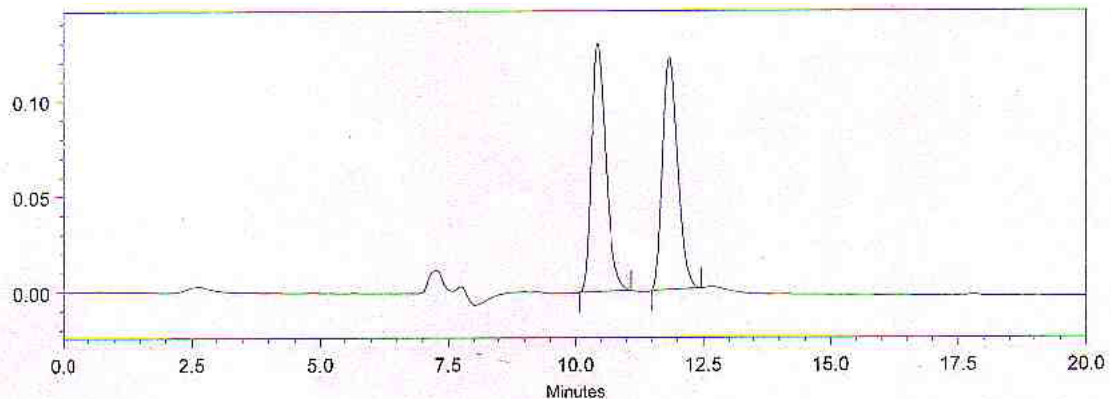


^{1}H NMR of lacosamide in $CDCl_3$



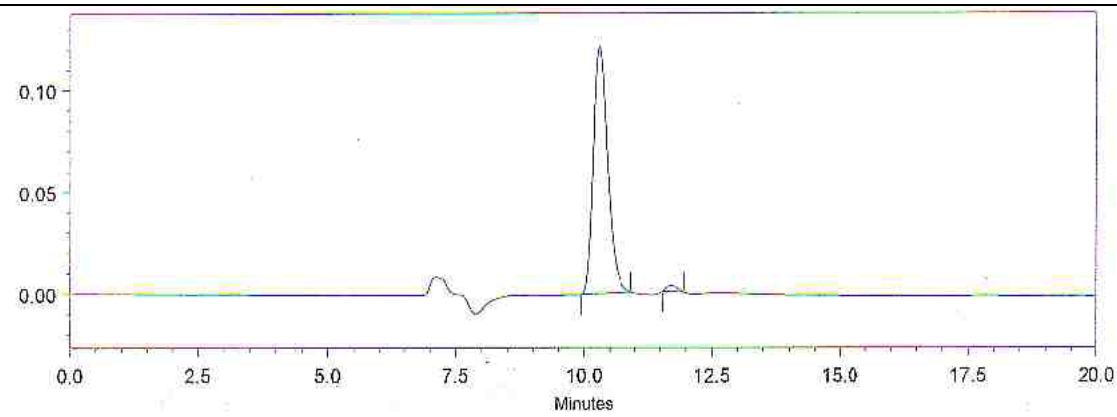
^{13}C NMR of lacosamide in $CDCl_3$

Chiral HPLC Analysis of Lacosamide 1



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	10.433	2563261	50.854
2	11.850	2477131	49.146
Totals		5040392	100.000



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	10.292	2379890	99.107
2	11.708	31011	0.893
Totals		2410901	100.000

2.1.8. References

1. (a) Duncan, J.S., Sander, J. W., Sisodia, S. M., Walker, M. C. *Lancet* **2006**, *367*, 1087; (b) 'Epilepsy' World Health Organization:http://www.who.int/mediacentre/factsheets/fs999/en/index.html; (c) Shorvon, S., Epilepsy, 2009, Oxford University Press Inc., Newyork.
2. Fong, G. G., Fong, J. K. *Hong Kong Medical Journal* **2001**, *7*, 73.
3. Pierce, J. M. *Brain* **2002**, *125*, 441.
4. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*, **1981**, *22*, 489.
5. Brodie, M. J. *Seizure*, **2010**, *19*, 650.
6. (a) Bialer, M.; White H. S., *Nat. Rev. Drug. Disc*. **2010**, *9*, 68; (b) Pandey, B.; Shah, K., PCT Int. Appl., WO 2011039781A1, 2011; *Chem. Abstr*. **2011**, *154*, 410331; (c) Vrbanec, G.; Harca, M.; Sucec, A.; Sahnic, D.; Avdagic, A., PCT Int. Appl., WO 2010107993A2, 2010; *Chem. Abstr*. **2010**, *153*, 431066; (c) Bouvy, D.; Merschaert, A.; Pinilla, V.; Hamann, J.; Kanzler, R.; Thomas, A., PCT Int. Appl., WO 2010052011A1, 2010; *Chem. Abstr*. **2010**, *152*, 526141; (d) Madhra, M. K.; Singh, P. K.; Khanduri, C. H., US patent 0143472A1, 2009; *Chem. Abstr*. **2009**, *151*, 8933; (e) Riedner, J., European Patent EP 1642889A1, 2006; *Chem. Abstr*. **2006**, *144*, 331695.
7. (a) Mcintyre, J. A.; Castaner, J.; Martin, L., *Drugs Fut*. **2004**, *29*, 992; (b) Perucca, E.; Yasothan, U.; Clincke, G.; Kirkpatrick, P. *Nat. Rev. Drug. Disc*. **2008**, *7*, 973; (c) Salome, C. ; Grosjean, E. S. ; Park, K. D.; Morieux, P.; Swendiman, R. ; DeMarco, E.; Stables, J. P.; Kohn, H. *J. Med. Chem*., **2010**, *53*, 1288; (d) Morieux, P.; Salome, C.; Park, K. D.; Stables, J. P.; Kohn, H. *J. Med. Chem*., **2010**, *53*, 5716; (e) Choi, D.; Stables, J. P.; Kohn, H. *J. Med. Chem*., **1996**, *39*, 1907; (f) Morieux, P.; Stables, J. P.; Kohn, H. *Bioorg Med Chem*., **2008**, *16*, 8968.
8. Andurkar, S, V.; Stables, J. P.; Kohn, H. *Tetrahedron: Asymmetry*, **1998**, *9*, 3841.
9. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E.N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Brandes, B.D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A.E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307; (c) Larrow, J. F.; Hemberger, K. E.; Jasmin, S.; Kabir, H.;

Morel, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3589; (d) Kumar, P.; Naidu, V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745.

10. Hansen, T. V.; Vaagen, V.; Partali, V.; Anthonsen, H. W.; Anthonsen, T. *Tetrahedron: Asymmetry* **1995**, *6*, 499.
11. Waagen, V.; Partali, V.; Hollingsaeter, I.; Huang, M. S. S.; Anthonsen, T. *Acta Chem. Scand*. **1994**, *48*, 506.
12. Ojika, M.; Kigoshi, H.; Yoshida, Y.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Arakawa, M.; Ekimoto, H.; Yamada, K. *Tetrahedron* **2007**, *63*, 3138.

2.2. SECTION B

Asymmetric synthesis of antiepileptic drug, Levetiracetam

2.2.1. Introduction

γ-Butyrolactam (pyrrolidinone) framework is ubiquitous in a wide variety of naturally occurring and synthetic compounds that exhibit wide range of biological activities.[1] Further, their utility as anticonvulsants came into light when they were studied for the development of sedative agents. Around 1960s there was increased interest to develop sedatives that were supposed to act via the inhibitory effect of GABAergic system. For this reason several pyrrolidinone derivatives were prepared with the rationale to design cyclic derivatives of γ-aminobutyric acid (GABA). However, instead of possessing sedative properties, some of these compounds showed cognitive enhancing effects in the animal model studies. In this context piracetam was discovered, which represents the first nootropic drug that was applied in clinical therapy.[2] In 1992, potent effect of (*S*)-enantiomer of ethylated derivative of piracetam *i.e.* levetiracetam was discovered.

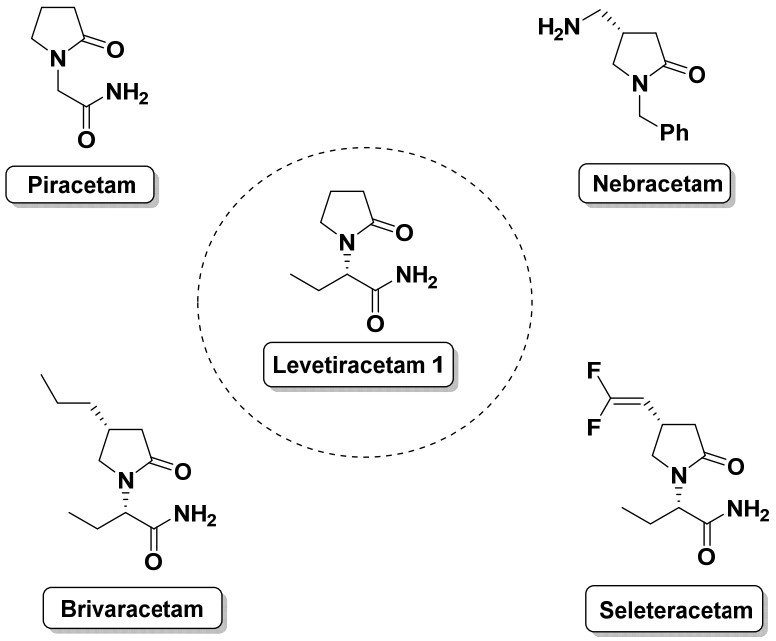


Figure 1. Examples of γ-butyrolactam based drugs used in epilepsy and related disorders

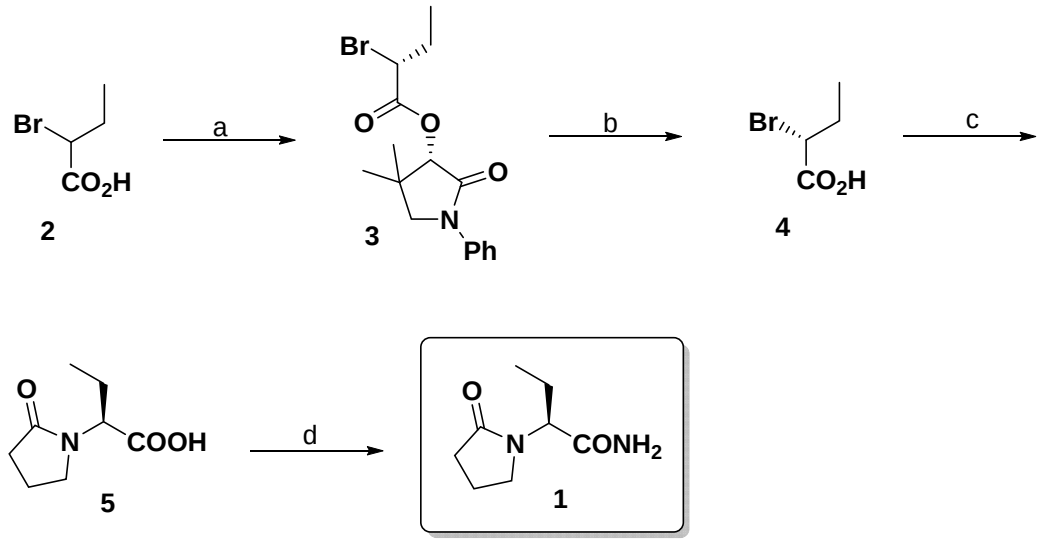
Levetiracetam **1** ((*S*)-α-ethyl-2-oxo-pyrrolidine acetamide, *Keppra*®)[3] showed excellent pharmacokinetic and pharmacological activity which has led to the rapid approval of this antiepileptic drug by the FDA. Further, levetiracetam **1** offers several advantages over traditional therapy, including twice daily dosing, a wide margin of safety with no requirements for serum drug concentration monitoring, no interactions with other anticonvulsants and has less adverse effects than traditional treatments.[4] Although the exact mechanism of action has not been fully established, levetiracetam is known to bind to synaptic vesicle protein 2A (SV2A) in the central nervous system and does not appear to directly affect the traditional excitatory and inhibitory neurotransmitter systems.[5] Further, the beneficial effects of levetiracetam **1** in patients with bipolar disorders, migraine, chronic or neuropathic pain, diabetic complications are also reported.[6] Therefore, since its launch in the USA in April 2000, levetiracetam has become one of the leading adjunctive antiepileptic drugs prescribed in neurology clinics around the world.

2.2.2. Review of Literature

Due to its importance, several approaches for the synthesis of levetiracetam **1** have been reported in the literature. Recent and significant approaches for the syntheses of levetiracetam **1** are described below.

Camps *et al.* (2005)[7]

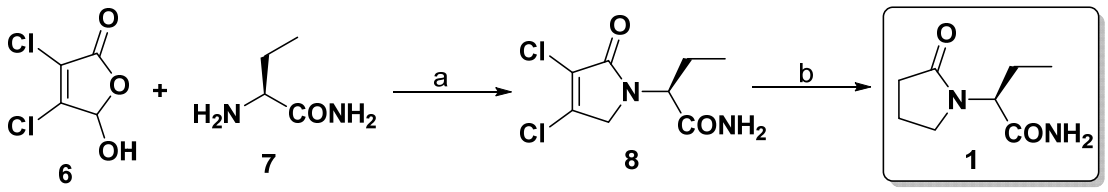
Camps *et al.* have reported the synthesis of levetiracetam **1** based on deracemization of (±)-2-bromobutyric acid **2** using (*S*)-N-phenylpantolactam as a chiral auxiliary. Accordingly, 2-bromobutyric acid **2** was converted to its acid chloride followed by treating with (*S*)-*N*-phenylpantolactam to give ester derivative **3**. Hydrolysis of intermediate **3** using $LiOH/H_2O_2$ in THF afforded (*R*)-2-bromobutyric acid **4** which on treatment with the sodium salt of 2- pyrrolidinone to afford the product **5**. Finally, compound **5** was transformed into the final product **1** (levetiracetam) by amidation reaction (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) (i) $SOCl_2$; (ii) (*S*)-*N*-phenylpantolactam, CH_2Cl_2, Et_3N, 67%; (b) LiOH, H_2O_2, THF, 96%; (c) NaH, 2- pyrrolidinone, THF, 55%; (d) $ClCO_2Et$, CH_2Cl_2, Et_3N then NH_4OH, 65%.

Zhang *et al.* (2006)[8]

Zhang *et al.* reported a synthesis of levetiracetam **1** starting from mucochloric acid **6** and chiral amino acid amide **7** which on reductive amination provided amide intermediate **8**. Further, dehalogenation and hydrogenation furnished levetiracetam **1** in 56% overall yield (Scheme 2).

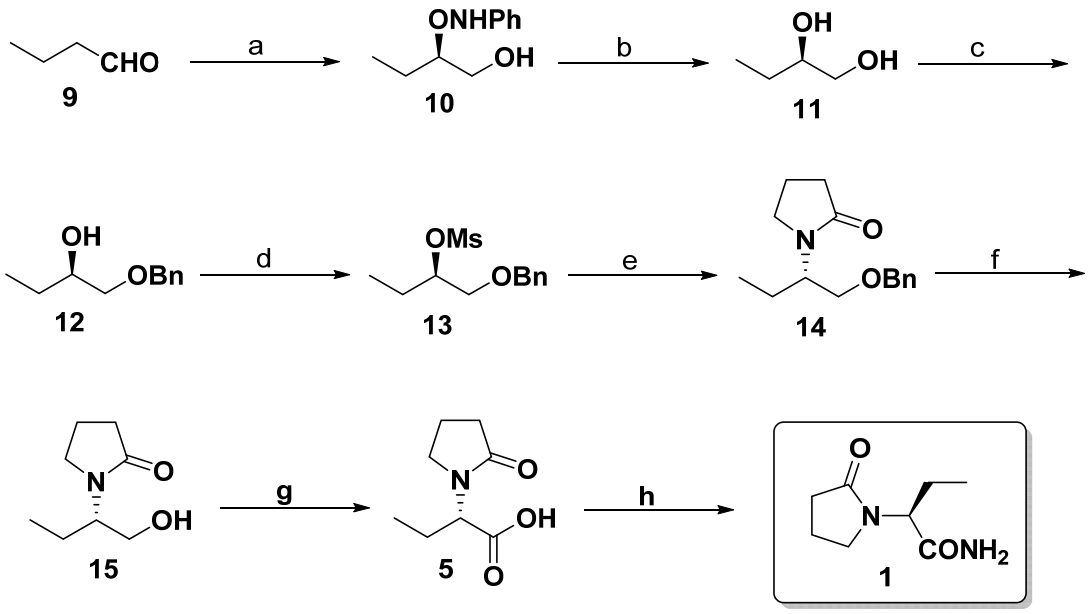


Scheme 2. *Reagents and conditions*: (a) $NaBH(OAc)_3$, $CHCl_3$, HOAc, 62%; (b) Pd/C, EtOH, Et_3N, H_2, 91%.

Sudalai *et al.* (2006)[9]

Sudalai *et al.* utilized proline catalyzed α-aminooxylation strategy for the synthesis of levetiracetam **1**. Thus, α-aminooxylation of *n*-butyraldehyde **9** using nitrosobenzene and L-proline (25 mol%) to furnish the aminooxy aldehyde which was reduced *in situ*, with sodium borohydride to afford (*R*)-α-aminooxy alcohol **10**. The alcohol **10** was

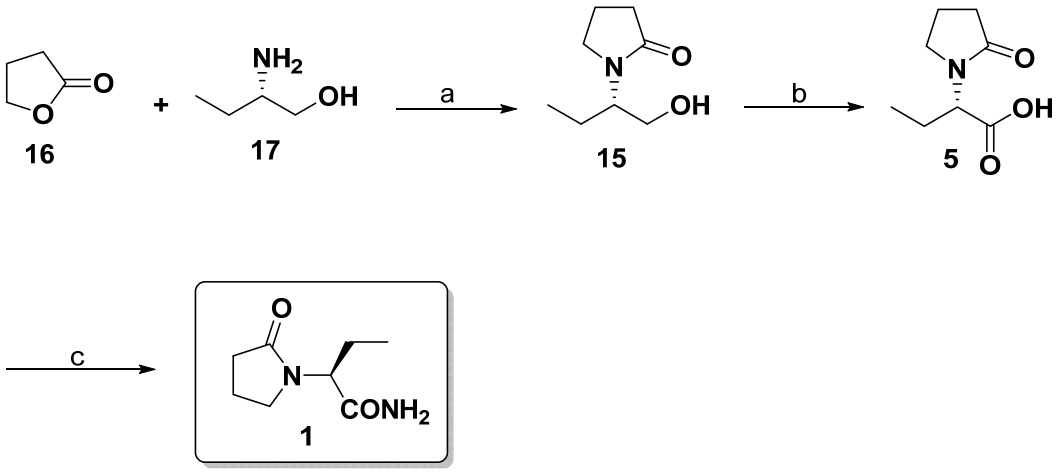
then hydrogenated, followed by selective monobenzylation to give compound **12**. Subsequently 2- pyrrolidone moiety was installed via mesylation followed by displacement with 2- pyrrolidone to afford intermediate **14**. Debenzylation of compound **14** followed by oxidation and amidation reaction sequences provided levetiracetam **1** (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) PhNO, L-proline (25 mol%), then MeOH, $NaBH_4$, 85%; (b) H_2 (1 atm.), Pd/C (10%), MeOH, 90%; (c) Bu_2SnO, toluene, then Bu_4NBr, BnBr, 95%; (d) MsCl, Et_3N, CH_2Cl_2, 92%; (e) 2-pyrrolidone, NaH, DMF, 62%; (f) H_2 (1 atm.), Pd/C (10%), MeOH, 97%; (g) TEMPO (7 mol%), NaClO-$NaClO_2$, acetonitrile, phosphate buffer (pH 6.8), 90%; (h) $ClCO_2Et$, CH_2Cl_2, Et_3N then NH_4OH, 75%.

Bandichhor *et al.* (2010)[10]

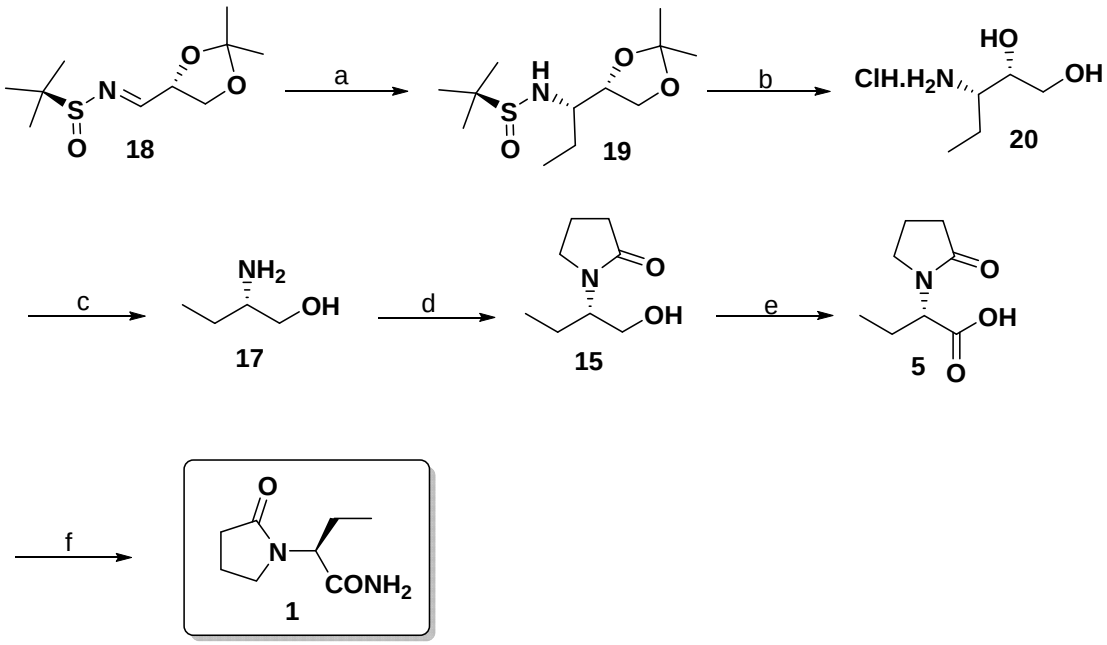
Bandichhor *et al.* reported the synthesis of levetiracetam **1** employing solvent-free condensation of (*S*)-aminobutanol **17** and γ-butyrolactone **16**. The alcohol **15** obtained was oxidized using Cat. RuO_2/NaOCl to acid **5** which was transformed to the final product **1** via known reaction sequence (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) Thermal (93%), Microwave (82%); (b) Cat. RuO_2/NaOCl, H_2O, 65%; (c) $ClCO_2Et$, CH_2Cl_2, Et_3N then NH_4OH, 65%.

Madhusudhan *et al.* (2012)[11]

Very recently, Madhusudhan *et al.* reported the synthesis of levetiracetam **1** via stereoselective 1,2-addition of ethylmagnesium bromide to *N*-sulfinimine. Sulfinimine **18** on treatment with Grignard reagent provided single diastereomer **19** (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) EtMgBr, TMDEA, Et_2O, 80%; (b) HCl, MeOH, 75%; (c) $NaIO_4$, $NaBH_4$, acetone, 75%; (d) 4-CBC, KOH, toluene, 80%; (e) TBAB, KOH, CH_2Cl_2, $KMnO_4$, HCl, 76%; (f) $ClCO_2Et$, CH_2Cl_2, Et_3N then NH_4OH, 65%.

Deprotection of the *t*-butylsulfinyl group and 1,3-dimethyl acetal gave corresponding amino diol **20**. Oxidation followed by reduction of amino diol **20** using $NaIO_4/NaBH_4$ provided β-amino alcohol **17**. Compound **17** on treatment with 4- chlorobutyryl chloride provided pyrrolidino alcohol **15** in good yield. Further, oxidation of intermediate **15** followed by amidation afforded levetiracetam **1**.

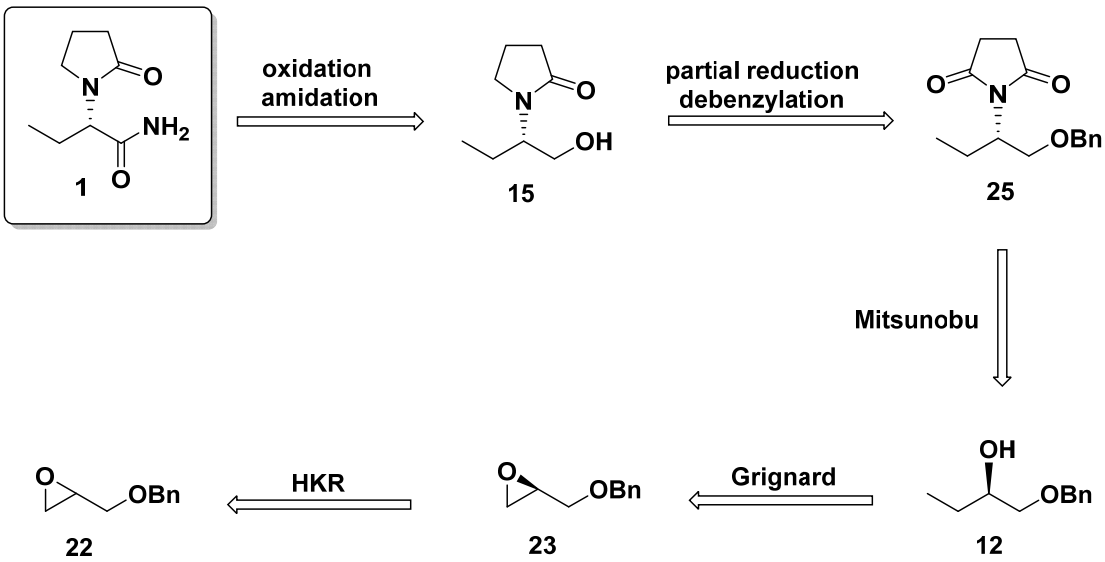
2.2.3. Present Work

Objective

Some of these methods have their own intrinsic disadvantages such as expensive chiral starting materials and catalysts, problems associated with the installation of 2-pyrrolidone moiety with harsh reaction conditions which often leads to the loss of optical purity, usage of hazardous alkylating agents, tedious and time consuming experiments, and so on. In this context, we envisage that it would be worthwhile to design a new route for the synthesis of levetiracetam **1** employing Jacobsen's hydrolytic kinetic resolution strategy.

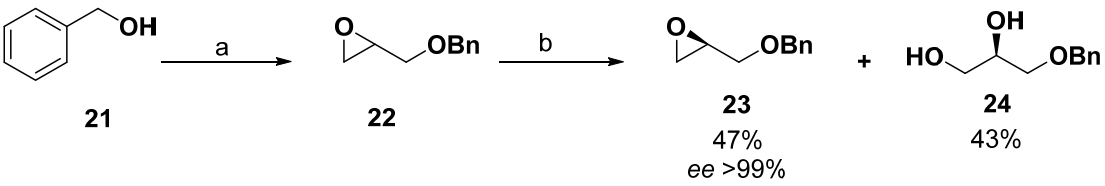
2.2.4. Results and Discussion

A retrosynthetic analysis of levetiracetam **1** is outlined in Scheme 6. As shown in Scheme 6, we envisaged that the secondary alcohol **12** would be an ideal key intermediate for the synthesis of levetiracetam **1** which can be easily obtained from (*R*)-benzyl glycidyl ether **23**. The chiral epoxide **23** can be achieved with high enantiopurity from racemic benzyl glycidyl ether **22** using Jacobsen's hydrolytic kinetic resolution strategy. Further, the key intermediate **12** can be elaborated to the advanced amide precursor **15** via Mitsunobu followed by partial reduction protocols. The intermediate **15** can be transformed to the target molecule **1** by simple oxidation, amidation reactions.



Scheme 6. Retrosynthetic analysis of levetiracetam **1**

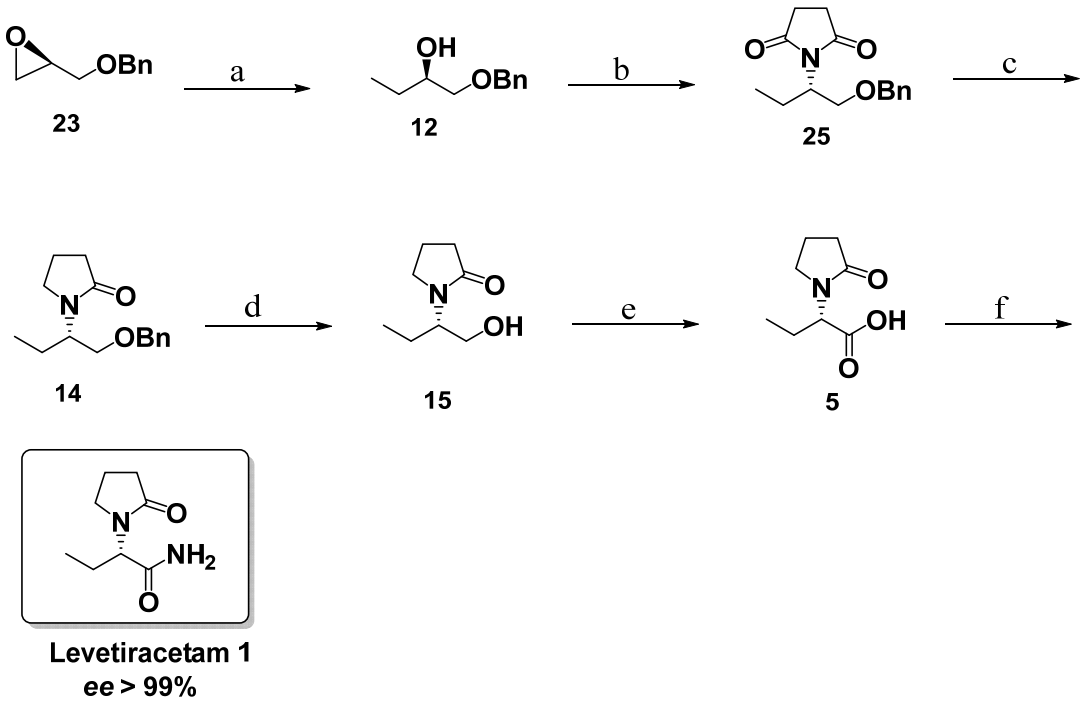
The synthesis commenced with the readily available starting material benzyl alcohol **21** as depicted in Scheme 7. Thus, the reaction of benzyl alcohol **21** with *rac*-epichlorohydrin in the presence of NaOH as a base gave *rac*- benzyl glycidyl ether **22** in 90% yield. The *rac*- benzyl glycidyl ether **22** was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equivalent of water using, the catalyst (*S,S*)-Salen Co(III)OAc (0.5 mol%) at ambient temperature for 24 h. After completion of the reaction, the reaction mixture was chromatographed over silica gel column to give enantiomerically pure epoxide **23** from the racemic mixture in 47% yield and >99% ee {$[\alpha]_D$ = -7.9 (*c* 0.4, EtOH); lit.[12] $[\alpha]_D$ = -5.8 (*c* 0.4, EtOH)} along with its diol **24** in 43% yield.



Scheme 7. *Reagents and conditions***:** (a) epichlorohydrin, aq NaOH, TBAI, rt, 24 h, 90%; (b) (*S, S*) Salen Co (III)-A, 0˚C-rt, 24 h.

Next, the regioselective ring opening of (*R*)-epoxide **23** was carried out with MeMgI and catalytic amount of CuI in anhydrous THF at -20 ºC to provide secondary alcohol **12** in 93 % yield (Scheme 8). Appearance of a triplet at δ 0.96 (3H) and multiplet in

the range of δ 3.68-3.81 (1H) in ^{1}H NMR and a peak at δ 9.3 (CH_3) in ^{13}C NMR showed the formation of compound **12**. Further, installation of 2-pyrrolidone moiety on secondary alcohol **12** was planned in two step sequence via Mitsunobu followed by partial reduction. Accordingly, the secondary alcohol **12** was readily transformed into a succinimido ether **25** by stereospecific substitution of the hydroxyl group with succinimide using Bu_3P and DIAD in THF under Mitsunobu condition. It is also observed that the yield of compound **25** was very low when Ph_3P is used as a reagent. Appearance of peaks at δ 2.65 (4H) and 4.25-4.37 (1H) in ^{1}H NMR and m/z peak at 284 $(M+Na)^+$ in mass spectrum indicated the formation of compound **25**. Several reaction conditions were tried for the mono reduction of succinimido ether **25** to get the compound **14**. Gratifyingly, the mono reduction of succinimido ether **25** employing a dropwise addition of one equiv. of BH_3-DMS complex in anhydrous THF, the condition recently reported by Ortiz-Marciales *et al.*[13] worked well at our hand and afforded the compound **14** in 66% yield.



Scheme 8. *Reagents and conditions*: (a) CH_3MgI, CuI, THF, -20ºC, 4 h, 93%; (b) pyrrolidone, Bu_3P, DIAD, THF, 0 ºC-rt, 8 h, 82%; (c) BH_3SMe_2, THF, reflux, 3 h, 66%; (d) $Pd(OH)_2$, H_2, MeOH, rt, 24 h, 92%; (e) NaOCl-$NaClO_2$, cat TEMPO, CH_3CN:H_2O, 87%; (f) $ClCO_2Et$, Et_3N, THF, -20 ºC, 1 h then aq NH_3, rt, 16 h, 80%.

Disappearance of a signal corresponding to carbonyl carbon at δ 177.7 in the ^{13}C NMR and m/z peak at 270 $(M+Na)^+$ in mass spectrum showed the formation of compound **14**. It is noteworthy to mention here that, the installation of 2-pyrrolidone moiety employing Mitsunobu followed by mono reduction using BH_3-DMS is straightforward and mild protocol as compared to the harsh reaction conditions reported earlier. Subsequently, the compound **14** was subjected to $Pd(OH)_2$ catalyzed hydrogenolysis, followed by oxidation with sodium chlorite catalyzed by TEMPO and bleach in an acetonitrile-phosphate buffer (pH 6.8) and afforded the acid **5** in 80% yield (two steps). Finally, the acid **5** was transformed into the corresponding amide by consecutive reaction with ethyl chloroformate and aq. ammonia completed the synthesis of levetiracetam **1** in excellent enantioselectivity (>99% ee) without any additional crystallization (which is often require to get high ee in many reported methods) {$[\alpha]_D^{25}$= -91.5 (*c* 1, acetone) {lit.[7] $[\alpha]_D^{25}$= -90.5 (*c* 0.99, acetone)}. The structure of levetiracetam **1** was confirmed by its IR, ^1H NMR, ^{13}C NMR, and mass spectroscopic analysis. The enantiomeric purity of levetiracetam 1 was determined by chiral HPLC analysis.

2.2.5. Conclusion

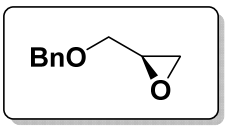
In conclusion, developed a concise and efficient new route for the synthesis of antiepileptic drug levetiracetam **1**, using Jacobsen's hydrolytic kinetic resolution method as a key step and source of chirality. High enantiopurity (>99%) has been achieved without any recrystallization of the final product. Further, the required 2-pyrrolidone moiety was conveniently introduced through Mitsunobu and mono-reduction protocols. This simple protocol may find a viable alternate in the pharmaceutical industry for the large scale production of levetiracetam **1** and the strategy could be exploited further for the preparation of other pharmaceutically important γ-butyrolactam analogues.

2.2.6. Experimental

1) 2-(benzyloxymethyl) oxirane (racemic) 22

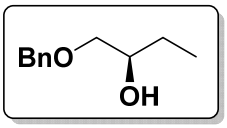
The preparation and characterization of racemic epoxide **22** is depicted in Chapter 2 section A.

2) (*R*)-2-(benzyloxymethyl) oxirane 23



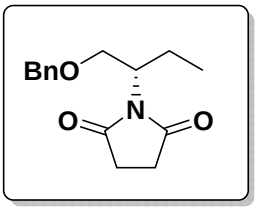
A mixture of 2-(benzyloxymethyl)-oxirane **22** (10 g, 61 mmol) and (*S,S*) salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) were vigorously stirred for 15 min, then cooled to 0 ^{o}C, and water added (0.6 mL, 34 mmol) over a period of 15 min, through a micro-syringe. The reaction mixture was stirred at room temperature for 20 h, and additional (*S,S*) salen Co(III)OAc complex-A (0.09 g, 0.14 mmol) was added and stirring was continued for additional 10 h. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/acetone (95:5). The less polar epoxide **23** eluted first as a colorless oil (4.8 g, 48%), $[\alpha]^{25}_{D}$ = -7.9 (*c* 0.4, MeOH) {lit.[12] $[\alpha]^{20}_{D}$ = -5.8 (*c* 0.4, EtOH)}; ee > 99% [chiral HPLC analysis; CHIRALCEL OD-H (250 x 4.6 mm) column; eluent: n-hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector: 220 nm [(*S*)-isomer t_R=15.25 min; (*R*)-isomer t_R=16.46 min], followed by diol **24** as a colorless oil (4.7 g, 43%); $[\alpha]^{25}_{D}$ = -2.3 (*c* 6.5, $CHCl_3$) {lit.[14] $[\alpha]^{25}_{D}$ = -3.64 (*c* 6.6, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3020, 1600, 1495, 1215, 1045, 1029, 929, 697; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.73 (t, *J* = 5.8 Hz, 1H, OH), 3.13 (d, *J* = 5 Hz, 1H, OH), 3.51-3.54 (dd, *J* = 5.4, 2.6 Hz, 2H), 3.57-3.68 (m, 2H), 3.82-3.92 (m, 1H), 4.54 (s, 2H), 7.28-7.39 (m, 5H, Ph); ^{13}C NMR(50 MHz, $CDCl_3$): δ_C 137.6 (C), 128.4 (CH, 2 carbons), 127.8 (CH, 3 carbons), 73.5 (CH_2), 71.6 (CH_2), 70.7 (CH), 63.9 (CH_2).

3) (*R*)-1-(Benzyloxy)butan-2-ol 12



To a pre cooled (-20 °C) solution of epoxide **23** (4.5 g, 27.4 mmol) and CuI (0.1 g) in dry THF (30 mL) was added methyl magnesium iodide (7.5 mL, 54.8 mmol) in diethyl ether dropwise for about one hour. Subsequently, the reaction mixture was allowed to attain ambient temperature and continued the stirring for additional 4 h. After completion of the reaction (indicated by TLC), aqueous NH_4Cl was added, after which the reaction mixture was filtered, and washed with ethylacetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, petroleum ether/acetone, 93:7) to yield **12** as colorless oil. (4.6 g; 93%); $[\alpha]_D^{25}$= -9.5 (*c* 0.8, $CHCl_3$) {lit.[9] $[\alpha]_D^{25}$= -10.0 (*c* 1, $CHCl_3$)}; IR ($CHCl_3$): 3435, 3020, 1601, 1422, 1118 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 0.96 (t, *J* =7.4 Hz, 3H), 1.42-1.56 (m, 2H), 2.35 (d, *J* = 3.4 Hz, 1H), 3.28-3.38 (m, 1H), 3.49-3.60 (m, 1H), 3.68-3.81 (m, 1H), 4.56 (s, 2H), 7.31-7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 138.0 (C), 128.5 (CH, 2 carbons), 127.9 (CH), 127.8 (CH, 2 carbons), 73.5 (CH), 72.6 (CH_2), 69.9 (CH_2), 26.1 (CH_2), 9.3 (CH_3); MS: *m/z* 180 $[M]^+$.

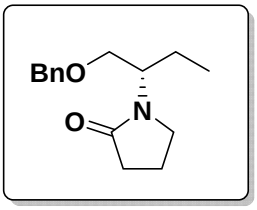
4) (*S*)-1-(1-(Benzyloxy)butan-2-yl)pyrrolidine-2,5-dione 25



A solution of DIAD (5.3 mL, 26.6 mmol) in dry THF (5 mL) was added dropwise to a solution of **12** (4 g, 22.2 mmol), succinimide (2.64 g, 26.6 mmol) and tributylphosphine (50% ethyl acetate solution; 19.1 mL, 53.2 mmol) in dry THF (50 mL) under N_2 atmosphere at 0 ºC. The reaction mixture was stirred at ambient temperature for 10 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 80:20) to yield **25** as a colorless oil. (4.4 g; 75 %); $[\alpha]_D^{25}$= +31.5 (*c* 3.1, $CHCl_3$); IR ($CHCl_3$): 3458, 3020, 2970, 2938, 2877, 1773, 1699, 1496, 1455, 1377, 1296, 1216, 1199, 1124, 1028, 952, 907, 820; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 0.85

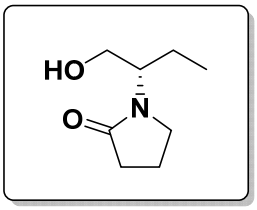
(t, *J* = 7.4 Hz, 3H), 1.60-1.99 (m, 2H), 2.65 (s, 4H), 3.55-3.63 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.98 (apparent t, *J* = 9.8 Hz, 1H), 4.25-4.37 (m, 1H), 4.41-4.51 (m, 2H), 7.23-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.7 (CO, 2 carbons), 138.0 (C), 128.3 (CH, 2 carbons), 127.6 (CH), 127.5 (CH, 2 carbons), 72.6 (CH_2), 68.7 (CH_2), 53.4 (CH), 27.9 (CH_2, 2 carbons), 21.1(CH_2), 10.7 (CH_3); Analysis: $C_{15}H_{19}NO_3$; Calcd: C, 68.94; H, 7.33; N, 5.36; Found: C, 68.75; H, 7.78; N, 6.01; MS: *m/z* 284 $[M+Na]^+$.

5) (*S*)-1-(1-(Benzyloxy)butan-2-yl)pyrrolidin-2-one 14



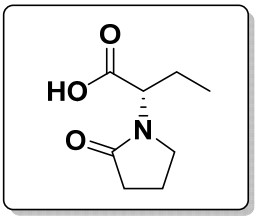
To a solution of compound **25** (4 g, 15.3 mmol) in dry THF (20 mL) at 0 ºC was added dropwise BH_3-DMS (1.4 mL, 15.3 mmol) under N_2 atmosphere. Subsequently, the reaction mixture was refluxed for 2h. After completion of the reaction, methanol (5 mL) was added carefully at 0 ºC and stirred the content for 20 min. The solvent was removed under reduced pressure and the residue was dissolved in ethylacetate (40 mL). After an aqueous workup the residue was purified by column chromatography (silica gel, petroleum ether/acetone, 70:30) to yield **14** as a colorless oil. (2.3 g; 61 %); $[\alpha]_D^{25}$ = -30.5 (*c* 1, $CHCl_3$) {lit.[9] $[\alpha]_D^{25}$ = -35.0 (*c* 1, $CHCl_3$)}; IR ($CHCl_3$): 3421, 3019, 1670, 1461, 1425, 1288, 1216, 1093, 928 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 7.5 Hz, 3H), 1.43-1.64 (m, 2H), 1.90-2.05 (m, 2H), 2.41 (apparent t, *J* = 8 Hz 2H), 3.23-3.39 (m, 2H), 3.44-3.58 (m, 2H), 4.17-4.30 (m, 1H), 4.40-4.50 (m, 2H), 7.24-7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 175.5 (CO), 138.2 (C), 128.3 (CH, 2 carbons), 127.6 (CH, 3 carbons), 72.7 (CH_2), 70.4 (CH_2), 52.1 (CH), 43.3 (CH_2), 31.4 (CH_2), 21.5 (CH_2), 18.3 (CH_2), 10.6 (CH_3); MS: *m/z* 270 $[M+Na]^+$.

6) (*S*)-1-(1-Hydroxybutan-2-yl)pyrrolidin-2-one 15



To a solution of **14** (2 g, 8.1 mmol) in methanol (10 mL) was added palladium hydroxide (0.2 g, 10-20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 24 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of celite bed and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethylacetate/methanol, 95:5) to yield **15** as a colorless oil. (1.1 g; 92 %); $[\alpha]_D^{25}$ = -20.1 (*c* 1.1, $CHCl_3$) {lit.[15] $[\alpha]_D^{25}$ = -11.8 (*c* 0.9, $CHCl_3$)} IR ($CHCl_3$): 3434, 3019, 1661, 1524, 1474, 1424, 1215, 1045, 928 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 0.87 (t, *J* = 7.4 Hz, 3H), 1.36-1.62 (m, 2H), 1.93-2.1 (m, 2H), 2.39-2.47 (m, 2H), 3.24-3.50 (m, 2H), 3.54-3.72 (m, 3H), 3.87-4.01 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 176.8 (CO), 62.8 (CH_2), 55.8 (CH), 43.7 (CH_2), 31.5 (CH_2), 21.1 (CH_2), 18.2 (CH_2), 10.6 (CH_3); MS: *m/z* 157 $[M]^+$, 158 $[M+1]^+$, 180 $[M+Na]^+$.

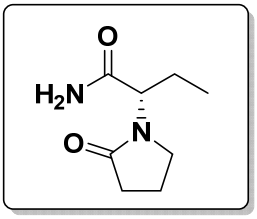
7) (*S*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid 5



A mixture of **15** (1 g, 6.3 mmol), TEMPO (0.04 g, 0.31 mmol), acetonitrile (20 mL), and sodium phosphate buffer (9 mL, 0.67 M, pH 6.7) was heated to 35 ºC. Then sodium chlorite (0.6 g dissolved in 2 mL water, 6.4 mmol) and dilute bleach (4-6 %, 2 mL diluted in 4 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at 35 ^oC until the reaction is complete (6 h, TLC), then cooled to room temperature. Water (20 mL) was added and the pH is adjusted to 8 with 2 N NaOH. The reaction is quenched by pouring into ice cold Na_2SO_3 solution maintained at <20 ^oC. After stirring for 30 min at room temperature, ethylacetate (20 mL) was added and continued the stirring for additional 15 min. The organic layer was separated and discarded. More ethylacetate (20 mL) was added, and the aqueous layer was acidified

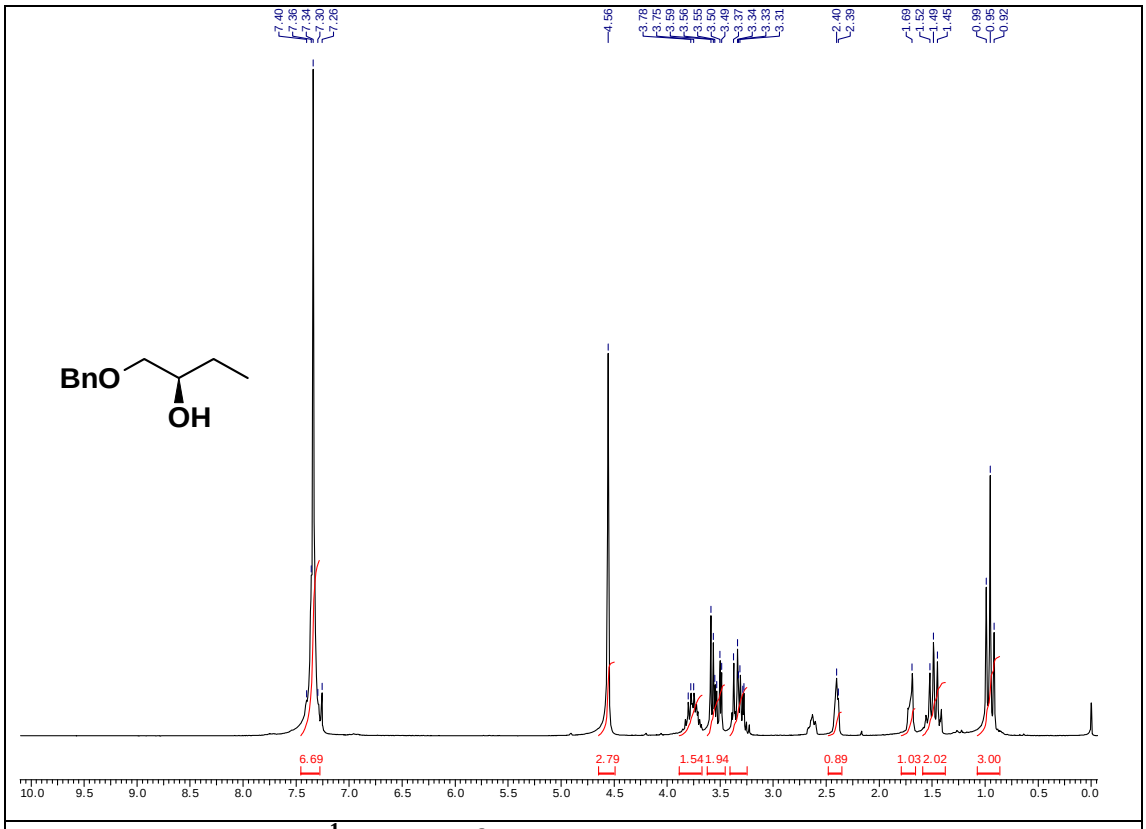
with 2N HCl to pH 3-4. The organic layer was separated, washed with water (2 x 15 mL), brine (20 mL) and concentrated under reduced pressure to afford the carboxylic acid **5** (0.85 g, 78 %); $[\alpha]_D^{25}$: -27.1 (*c* 1.1, $CHCl_3$) {lit.[10] $[\alpha]_D^{25}$= -23.6 (*c* 0.97, $CHCl_3$)}; IR ($CHCl_3$): 3444, 3020, 1646, 1422, 1215, 1122, 1043, 929, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 0.94 (t, *J* = 7.3 Hz, 3H), 1.64- 1.81 (m, 2H), 2.01-2.18 (m, 2H), 2.50 (t, *J* = 7.7 Hz, 2H), 3.31-3.42 (m, 1H), 3.50-3.62 (m, 1H), 4.61-4.69 (dd, *J* = 10.7, 5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 177.1 (CO), 174.4 (CO), 55.5 (CH), 43.9 (CH_2), 30.8 (CH_2), 21.9 (CH_2), 18.2 (CH_2), 10.8 (CH_3); MS: *m/z* 171 $[M]^+$, 194 $[M+Na]^+$.

8) (*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide (levetiracetam) 1

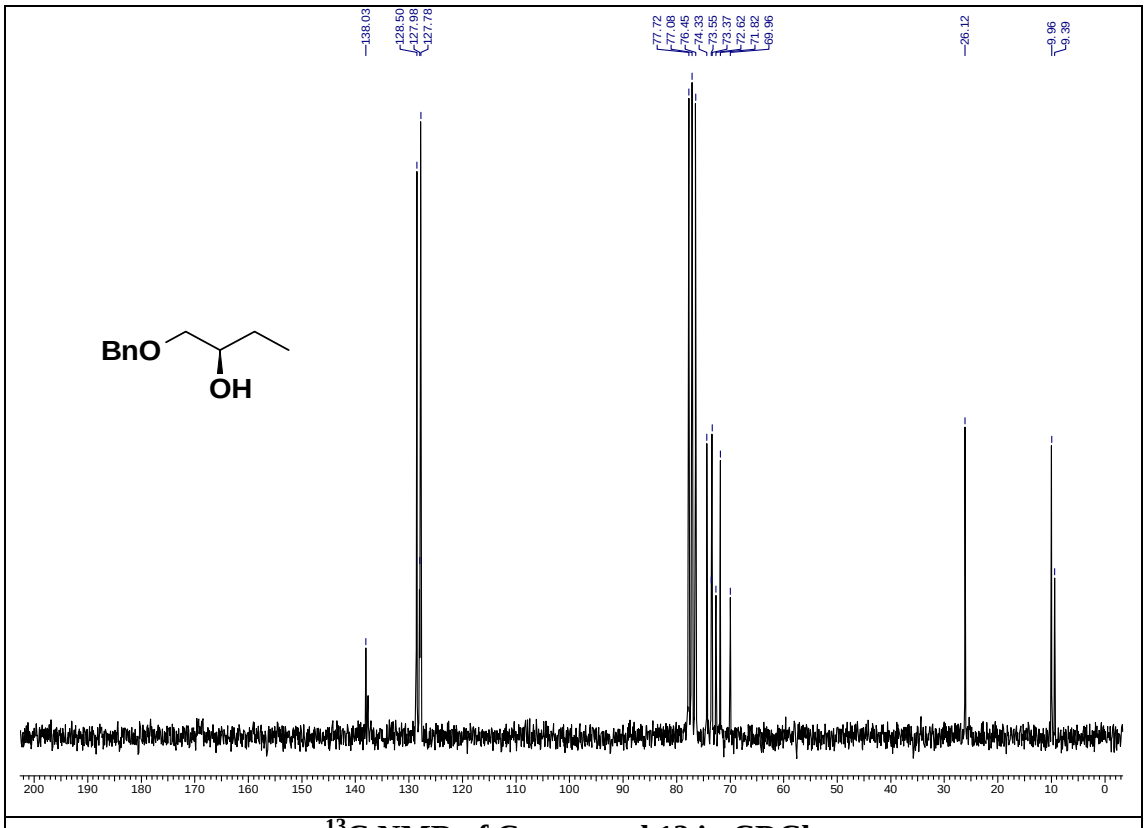


To a solution of acid **5** (0.7 g, 4.1 mmol) and triethylamine (0.7 mL, 4.9 mmol) in dry THF (10 mL) was added ethyl chloroformate (0.4 mL, 4.5 mmol) at 0 °C under an argon atmosphere. After 30 min, ammonium hydroxide (25% w/v aqueous solution, 2.8 mL, 20.4 mmol) was added and stirred the content at ambient temperature for another 16 h. After completion of the reaction, potassium carbonate (0.8 g, 6 mmol) was added and the reaction mixture was filtered, washed with ethyl acetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography (silica gel, dichloromethane/methanol, 95:5) to yield **1** as a pale yellow solid (0.56 g, 80 %); ee > 99% [The ee was determined by chiral HPLC analysis: DAICEL CHIRALCEL OD-H (250x4.6 mm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector 210 nm [(*R*) isomer t_R = 33.30 min; (*S*) isomer t_R = 46.71 min]; M.p = 116-17 ºC {lit.[7] m.p = 115-117 °C}; $[\alpha]_D^{25}$: -91.5 (*c* 1, acetone) {lit.[7] $[\alpha]_D^{25}$= -90.5 (*c* 0.99, acetone)}; IR ($CHCl_3$): 3409, 3019, 1670, 1523, 1422, 1215, 1045, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 0.90 (t, *J* = 7.4 Hz, 3H), 1.60-1.79 (m, 1H), 1.85-2.14 (m, 3H), 2.38-2.47 (m, 2H), 3.33-3.52 (m, 2H), 4.42-4.50 (dd, *J* = 8.9, 6.7 Hz, 1H), 5.77 (brs, 1H), 6.47 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 176.0 (CO), 172.5 (CO), 55.9 (CH), 43.7 (CH_2), 30.9 (CH_2), 21.1 (CH_2), 18.0 (CH_2), 10.4 (CH_3); MS: *m/z* 171 $[M+1]^+$, 193 $[M+Na]^+$.

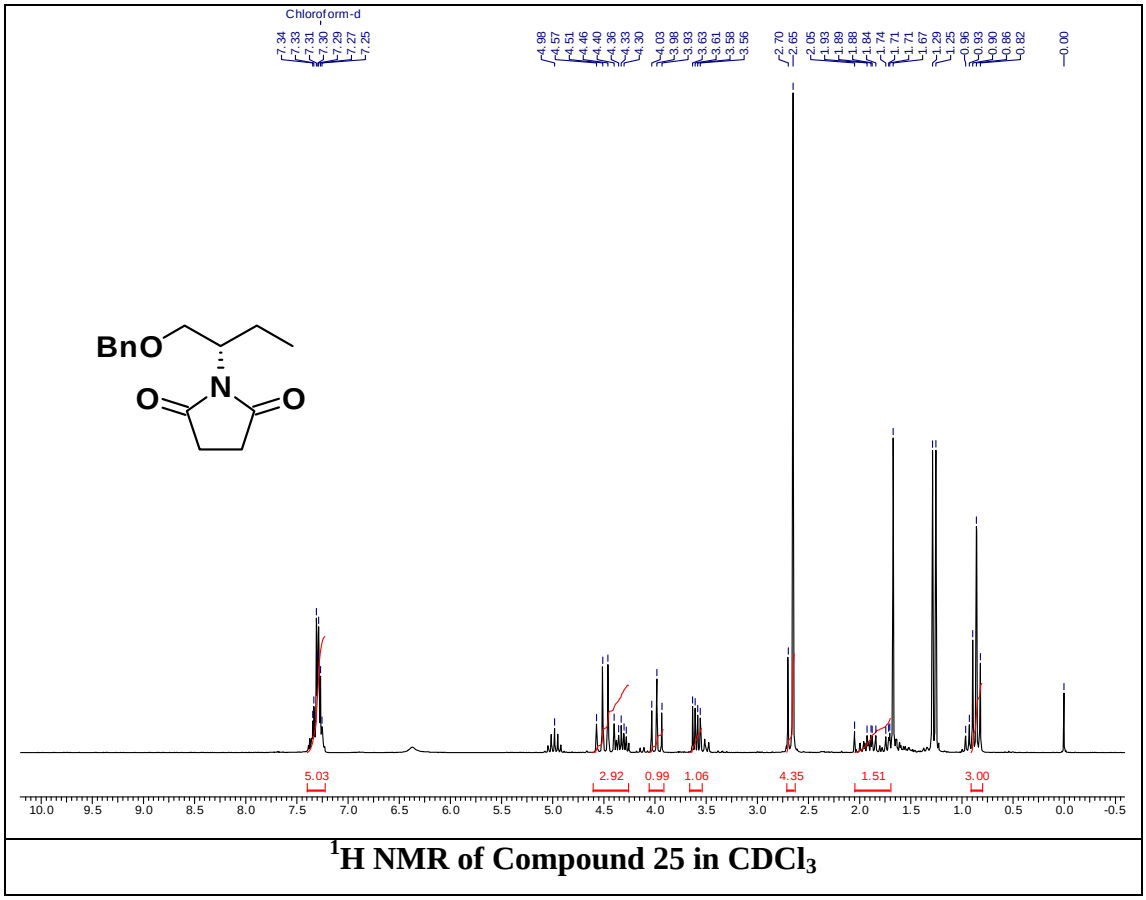
2.2.7. Analytical Data



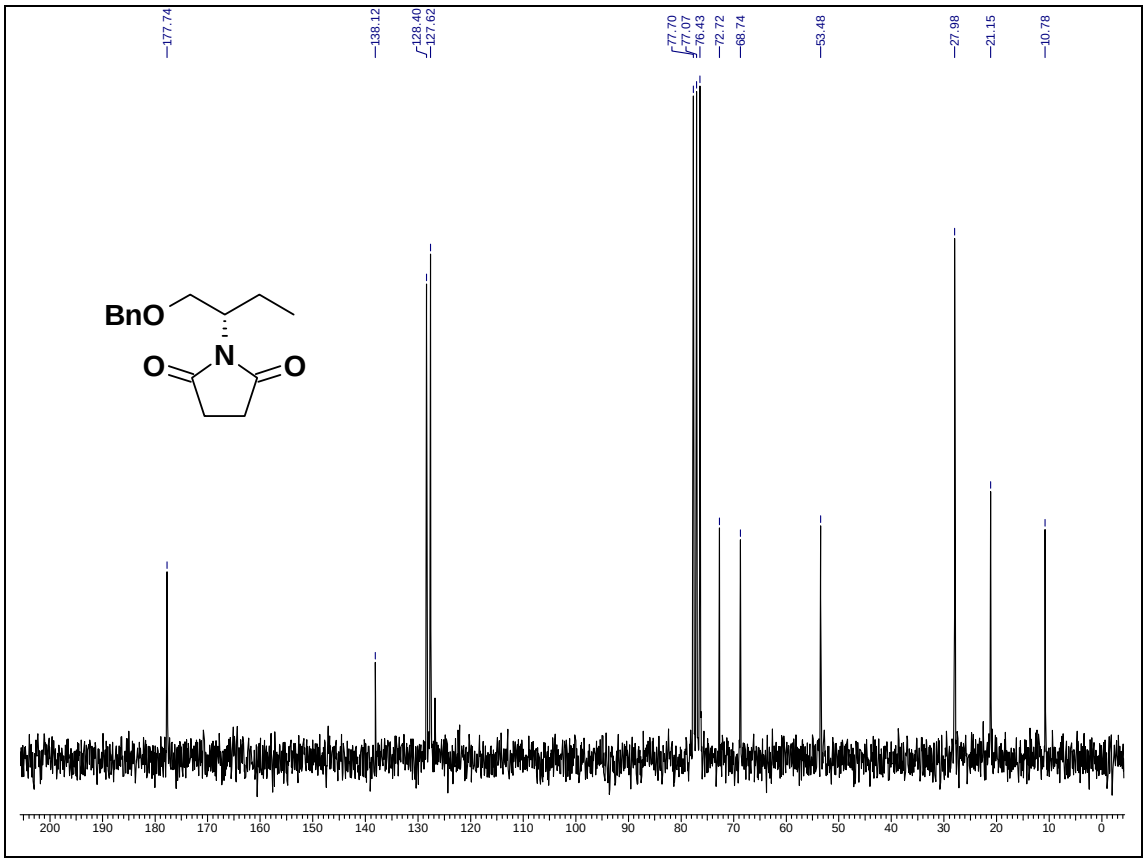
^{1}H NMR of Compound 12 in $CDCl_3$



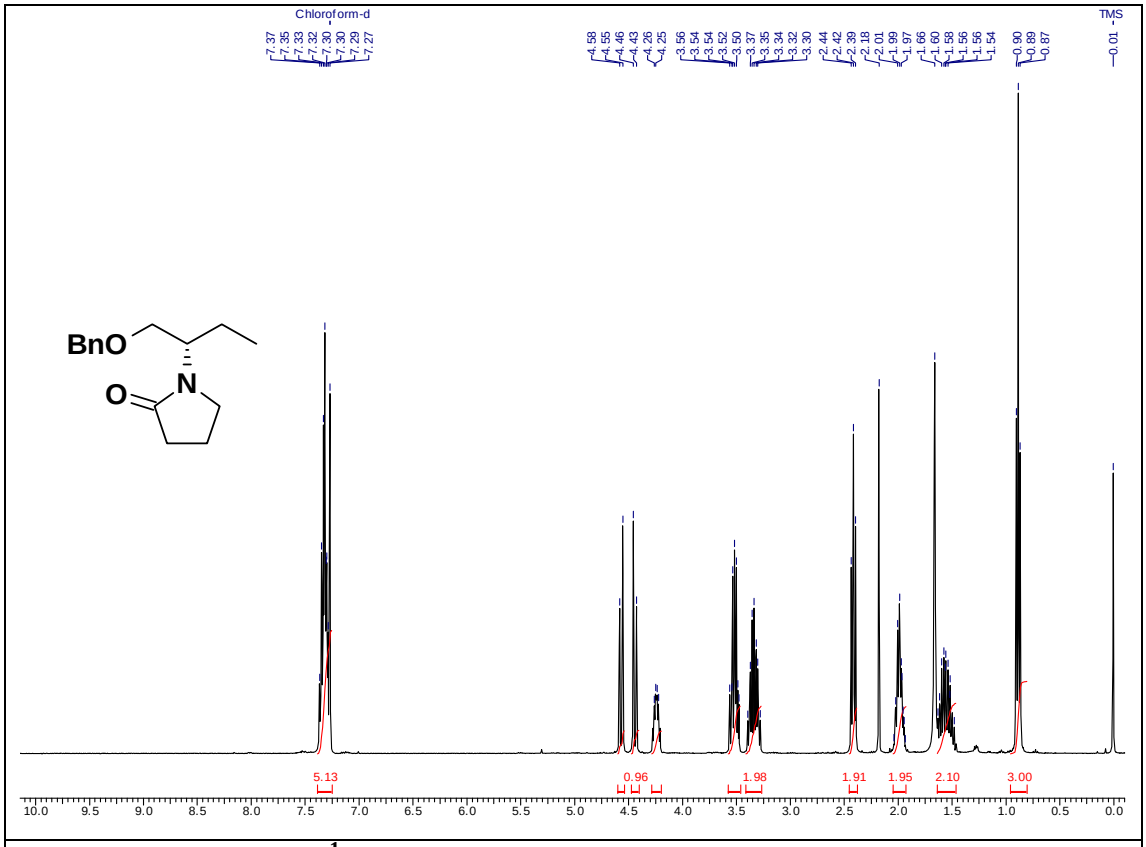
^{13}C NMR of Compound 12 in $CDCl_3$



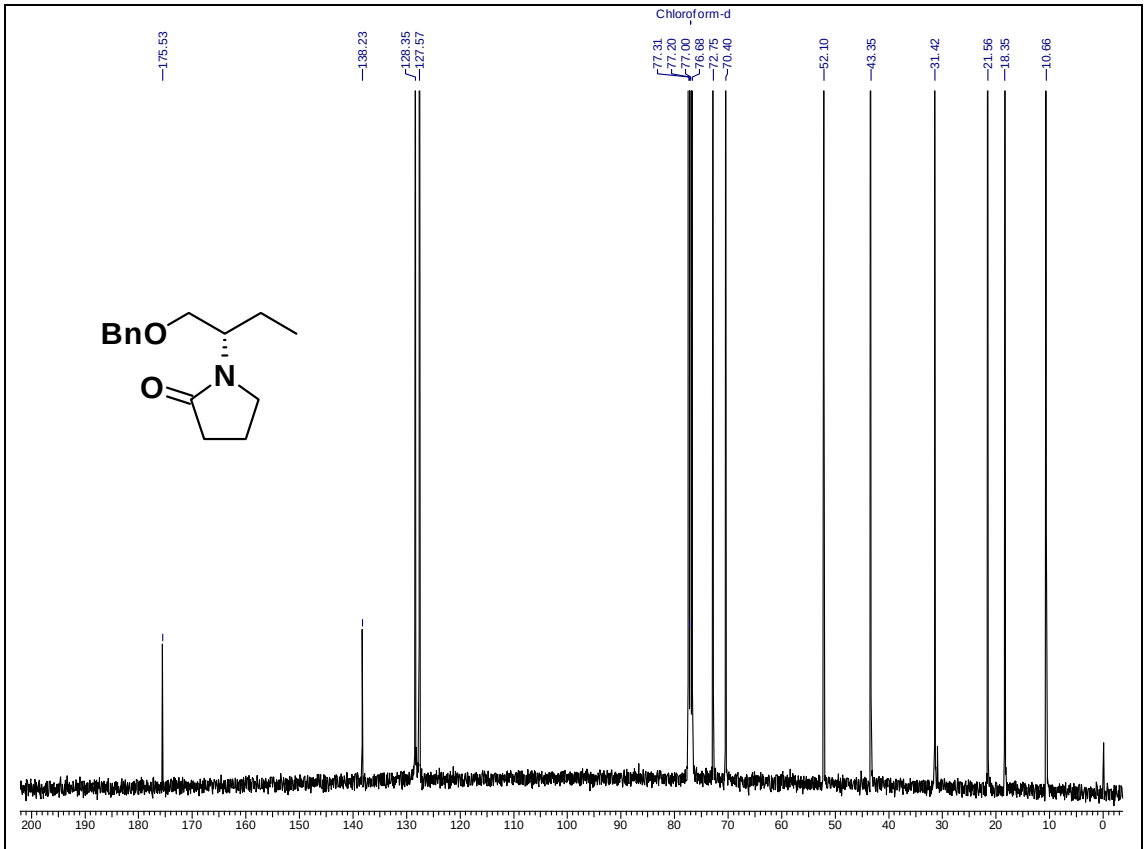
^{1}H NMR of Compound 25 in $CDCl_3$



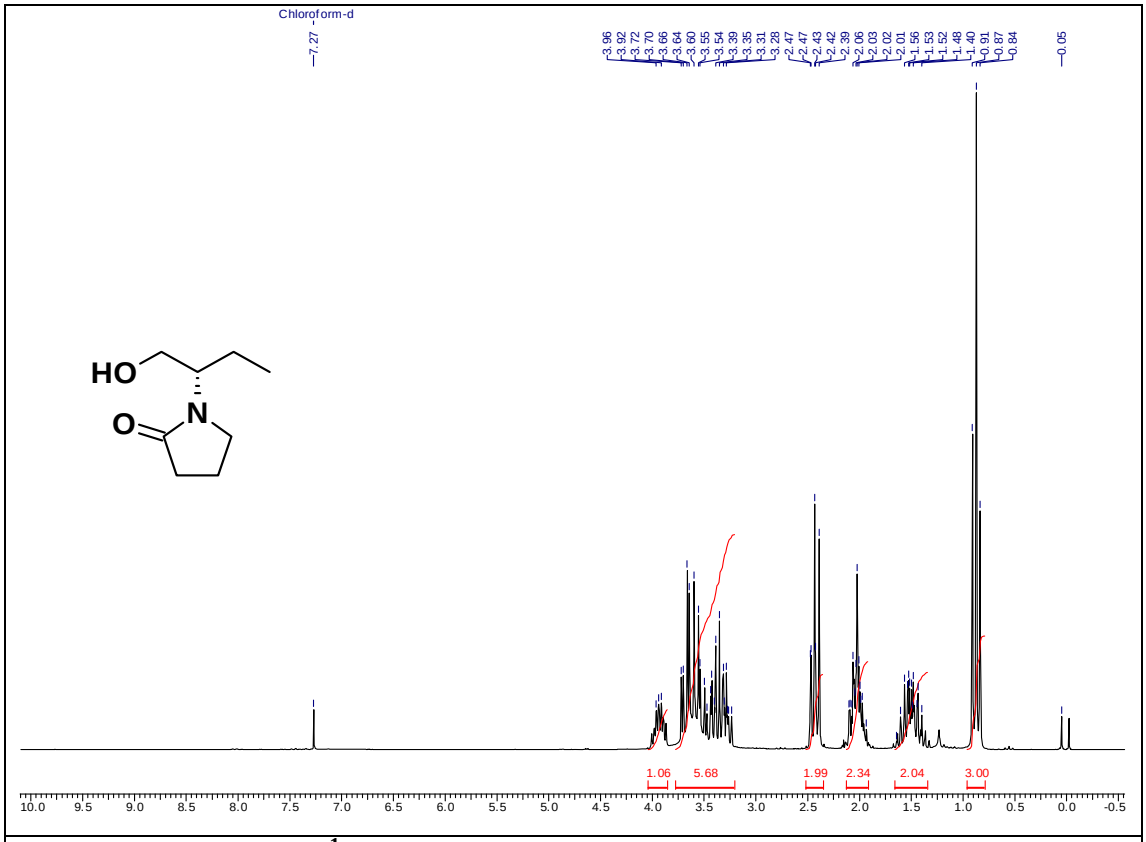
^{13}C NMR of Compound 25 in $CDCl_3$



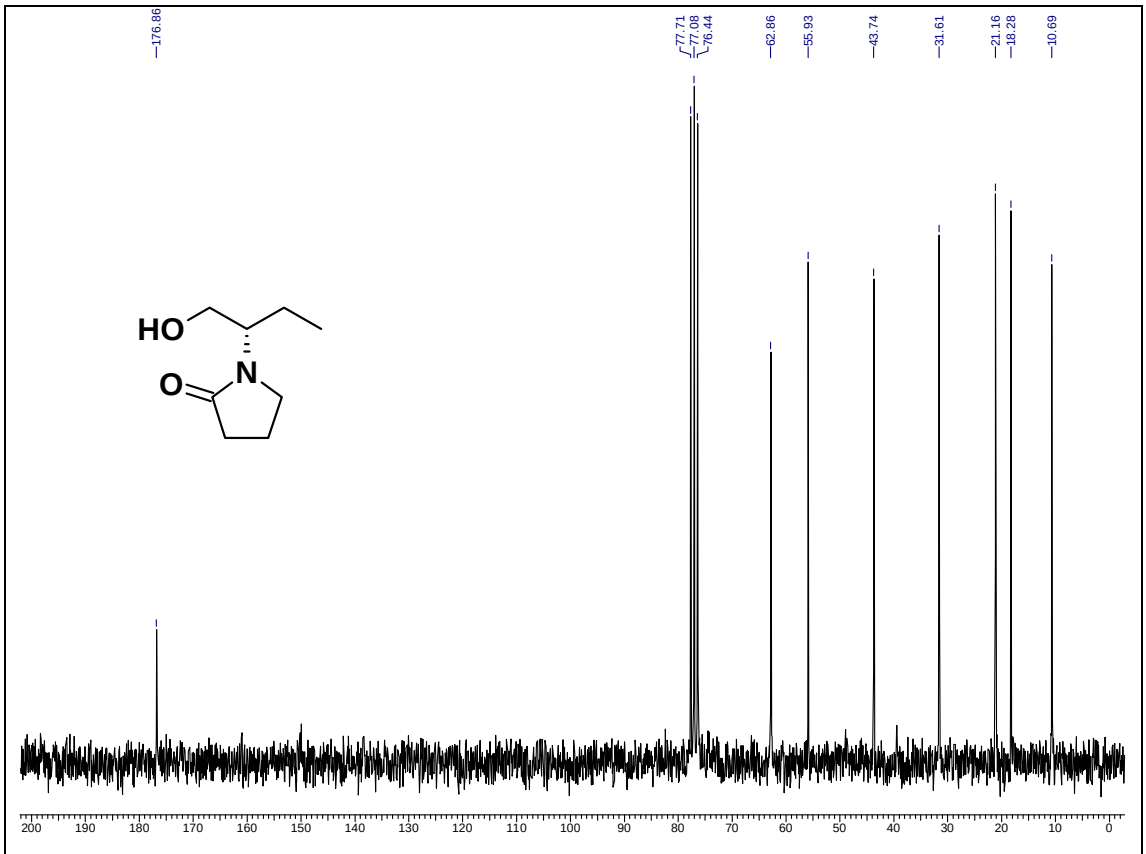
^{1}H NMR of Compound 14 in $CDCl_3$



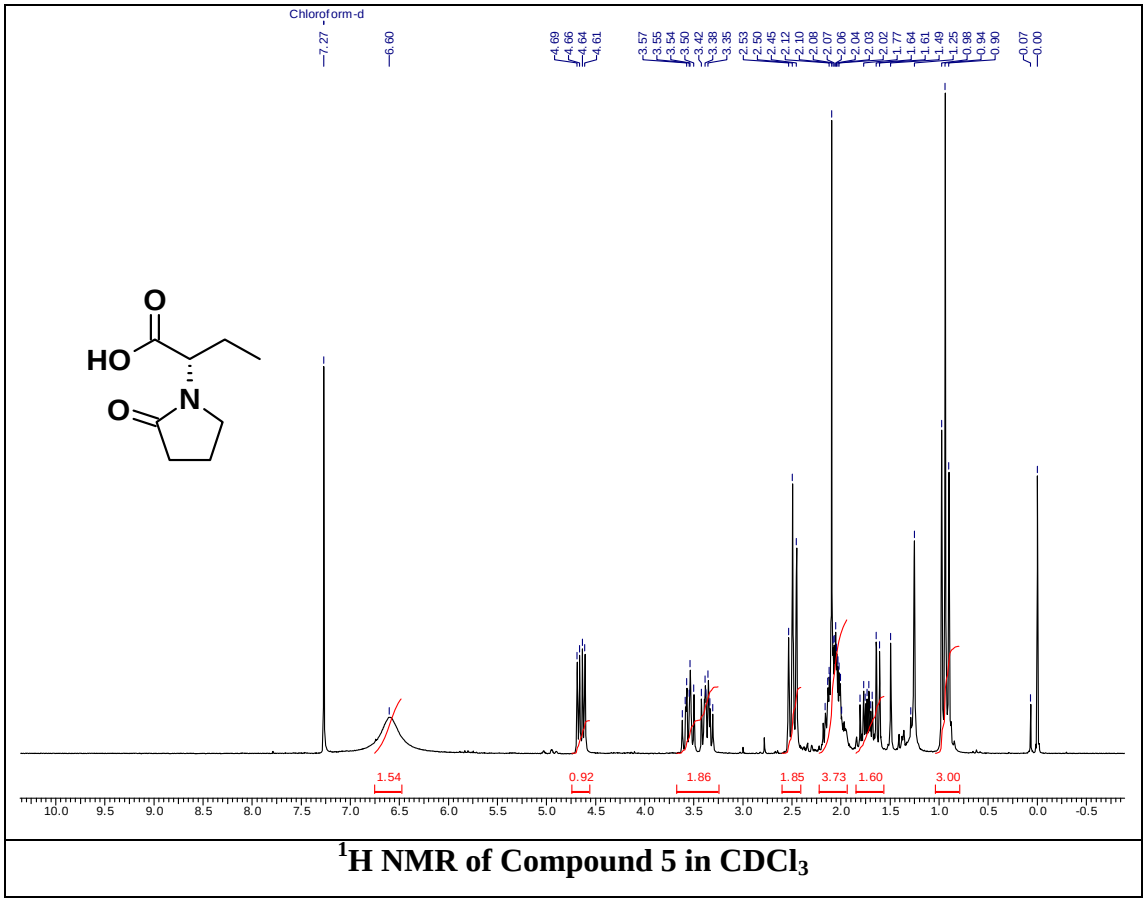
^{13}C NMR of Compound 14 in $CDCl_3$



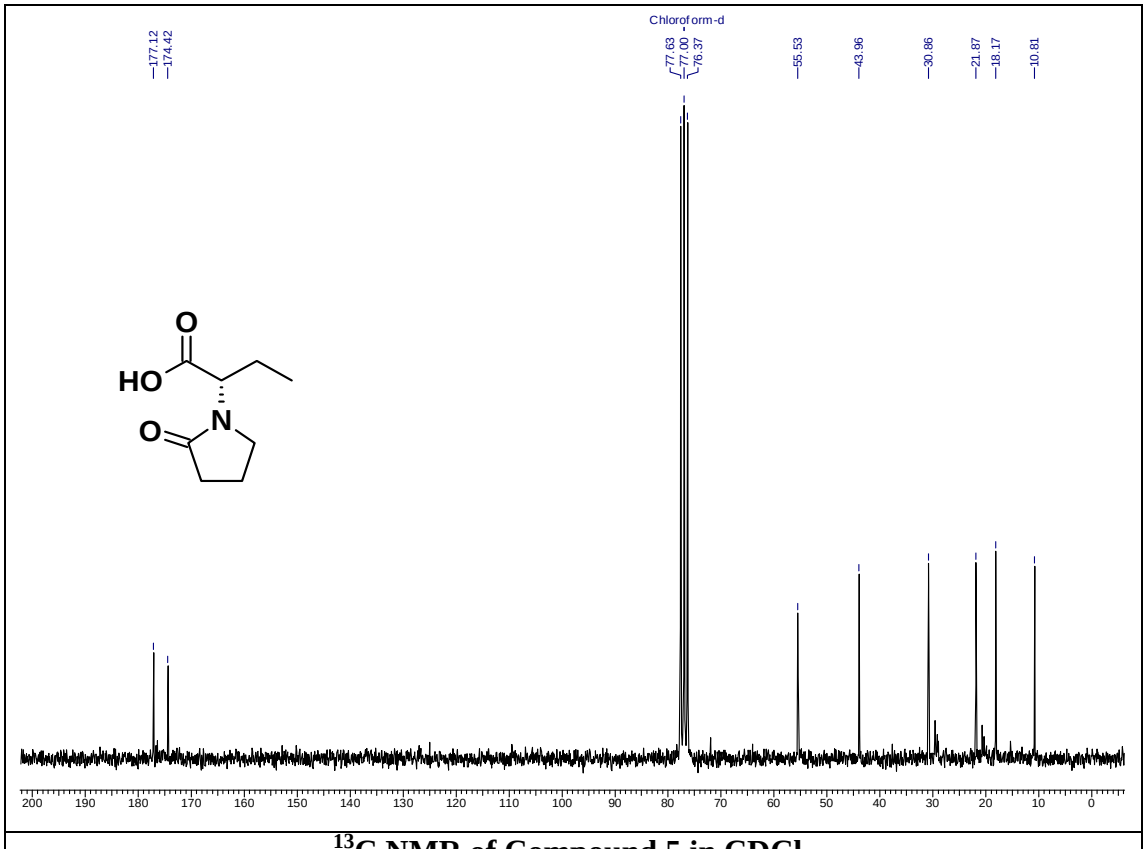
^{1}H NMR of Compound 15 in $CDCl_3$



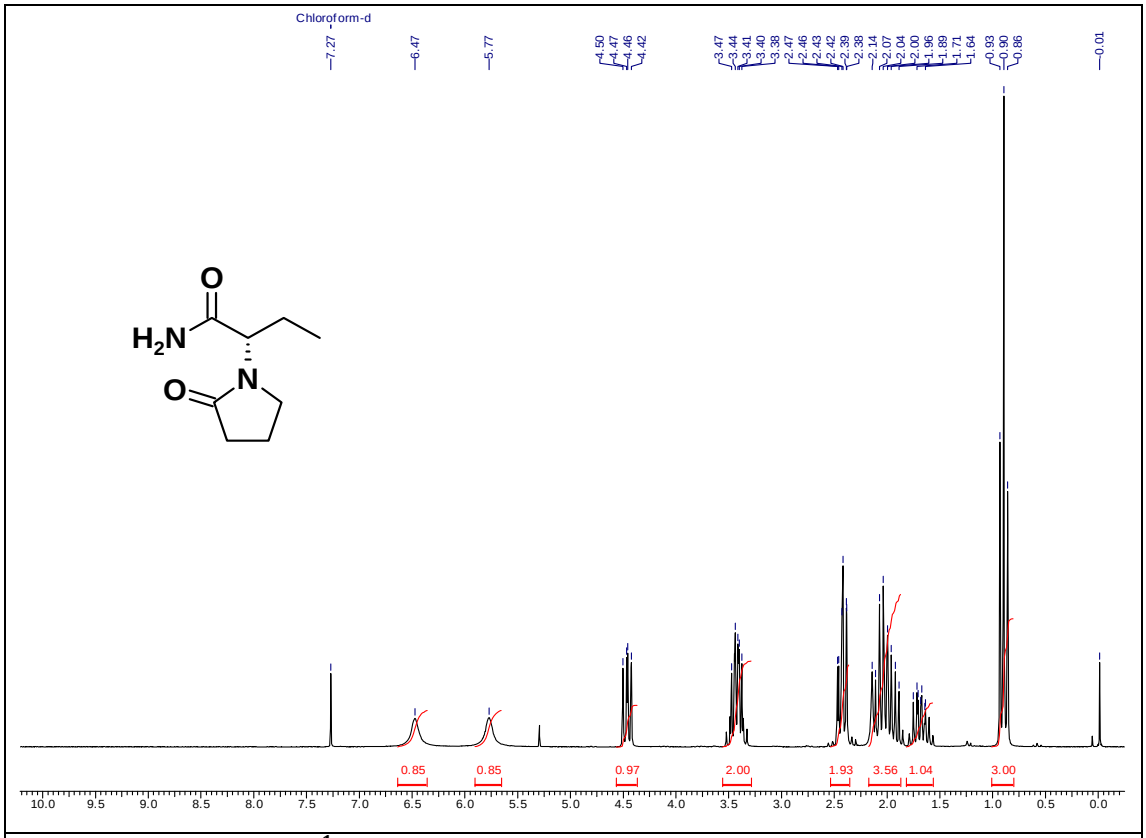
^{13}C NMR of Compound 15 in $CDCl_3$



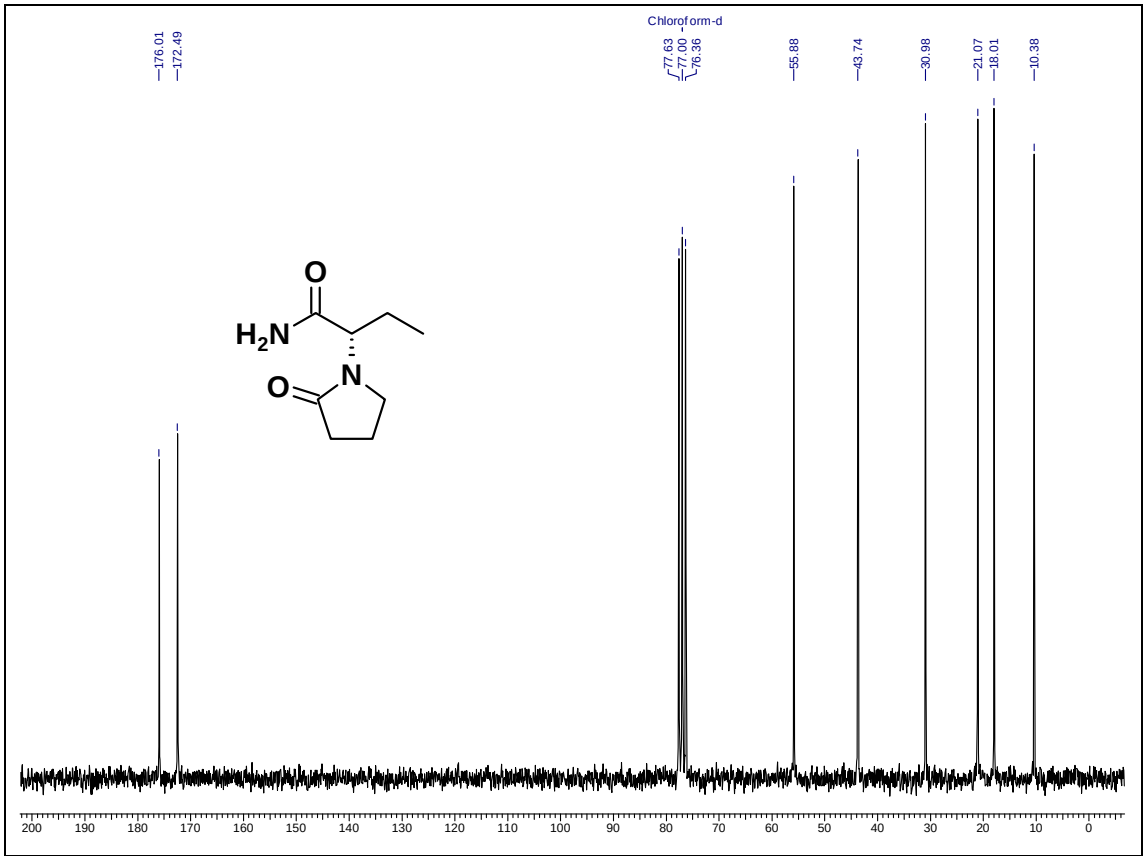
^{1}H NMR of Compound 5 in $CDCl_3$



^{13}C NMR of Compound 5 in $CDCl_3$

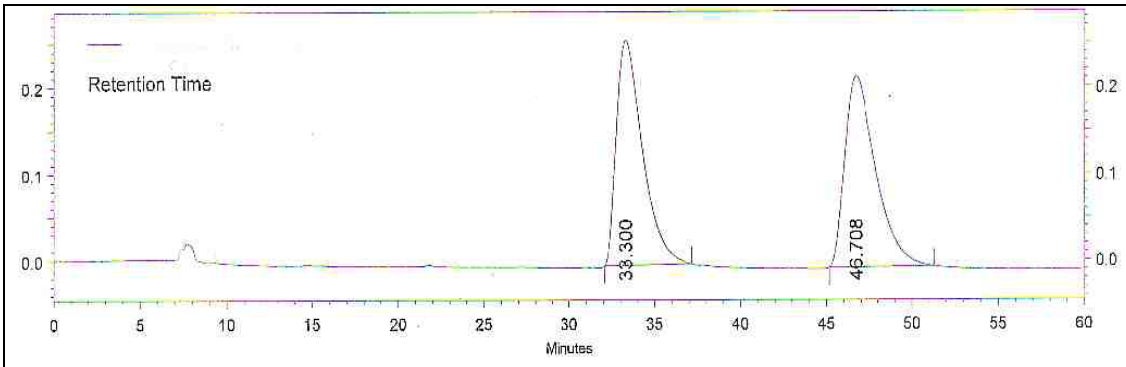


^{1}H NMR of levetiracetam 1 in $CDCl_3$



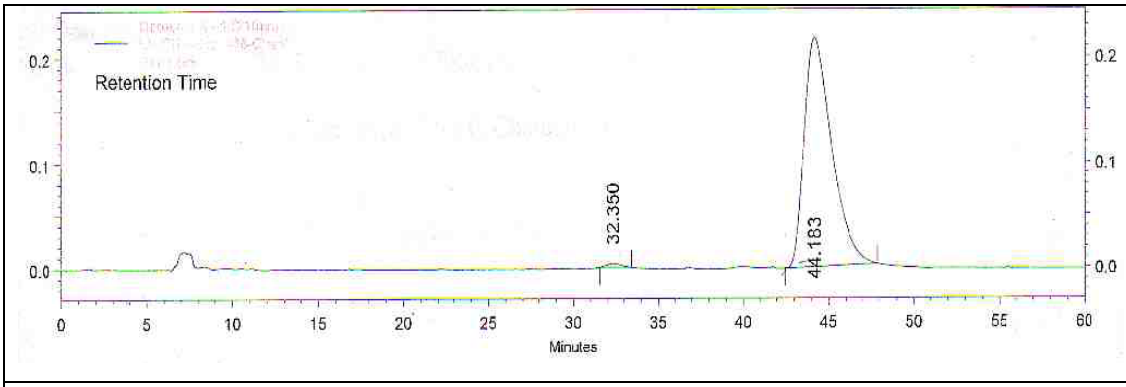
^{13}C NMR of levetiracetam 1 in $CDCl_3$

Chiral HPLC Analysis of Levetiracetam 1



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	**33.300**	**27589368**	**49.749**
2	**46.708**	**27867405**	**50.251**
Total		**55456773**	**100.000**



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	**32.350**	**109026**	**0.401**
2	**44.183**	**24273808**	**99.599**
Total		**24382834**	**100.000**

2.2.8. References

1. (a) Corey, E. J.; Li, W.-D. *Chem. Pharm. Bull.* **1999**, *47*, 1. (b) Baldwin, J. E.; Lynch, G. P.; Pitlik, J. *J. Antibiot.* **1991**, *44*, 1; (c) Yee, N. K.; Dong, Y.; Kapadia, S. R.; Song, J. J. *J. Org. Chem.* **2002**, *67*, 8688. (d) Xie, X.; Lu, X.; Liu, Y.; Xu, W. *J. Org. Chem.* **2001**, *66*, 6545.
2. Giurgea, C.; Lefevre, D.; Lescrenier, C.; David-Remacle, M. *Psychopharmacologia* **1971**, *20*, 160-168.
3. (a) Prous, J.; Mealy, N.; Castaner, J. *Drugs of the future*, **1994**, *19*, 111; (b) Shorvon, S. D.; Rijckevorsel, K. V. *J. Neurol. Neurosurg. Psychiatry*, **2002**, *72*, 426; (c) Williamson, L.; Katherine, A. *Drugs*, **2011**, *71*, 489; (d) Crepeau, A. Z.; Treiman, D. M. *Expert rev. Neurotherapeutics*, **2010**, *10*, 159.
4. (a) Dooley, M.; Plosker, G. L. *Drugs* **2000**, *60*, 871; (b) Hovinga, C. A. Pharmacotherapy, **2001**, *21*, 1375; (c) Shorvon S. D.; van Rijckevorsel K. J. *Neurol. Neurosurg. Psychiatry,* **2002**, *72*, 426.
5. (a) UCB Pharma. Product information: Keppra (TM) levetiracetam. 2008, http://www.ucb.com/products/product-list/cns/keppra; (b) Lynch, B. A.; Lambeng, N.; Nocka, K.; Hammes, P. K.; Bajjalieh, S. M.; Matagne, A.; Fuks, B., *Proc. Nat. Acad. Sci. U.S. A.,* **2004**, *101*, 9861.
6. (a) Tucker, J. L.; Xu, L.; Yu, W.; Scott, R. W.; Zhao, L.; Ran, N.; PCT Int. Appl, WO 2009009117, 2009; *Chem. Abstr.* **2009**, *150*, 119828; (b) Olszanecki, R.; Bujak, G. B.; Korbut, R.; Gajda, M., PCT Int. Appl, WO 2011/049475, 2011; *Chem. Abstr.* **2011**, *154*, 477389.
7. Boschi, F.; Camps, P.; Franchini, M, C.; Torrero, D. M.; Ricci, A.; Sanchez, L.; *Tetrahedron: Asymmetry*, **2005**, *16*, 3739.
8. Sarma, K. D.; Zhang, J.; Huang, Y.; Davidson, J. G.; *Eur. J. Org. Chem.* **2006,** *16*, 3730.
9. Kotkar, S. P.; Sudalai, A.; *Tetrahedron Lett.* **2006**, *47*, 6813.
10. Mylavarapu, R.; Anand, V. R.; Kondaiah, G.C.M.; Reddy, L.A.; Reddy, G.S.; Roy, A.; Bhattacharya, A.; Mukkanti, K.; Bandichhor, R.; *Green Chem. Lett. and Rev.*, **2010**, *3*, 225.
11. Babu, K. C.; Reddy, R. B.; Naresh, E.; Mohan, K. R.; Madhusudhan, G.; Mukkanti, K. *Journal of Chemistry*. **2013**, vol 2013, Article ID 176512, 5 pages.

12. Hansen, T. V.; Vaagen, V.; Partali, V.; Anthonsen, H. W.; Anthonsen, T. *Tetrahedron: Asymmetry*, **1995**, *6*, 499.
13. Huang, K.; Ortiz-Marciales, M.; Correa, W.; Pomales, E.; Lopez, X.Y. *J. Org. Chem*., **2009**, *74*, 4195.
14. Thompson, A. M.; Sutherland, H. S.; Palmer, B. D.; Kmentova, I.; Blaser, A.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W. A. *J. Med. Chem*., **2011**, *54*, 6563.
15. Imahori, T.; Omoto, K.; Hirose Y.; Takahata, H.; *Heterocycles*, **2008**, *76*, 1627.

2.3. SECTION C

Asymmetric synthesis of antiparkinson's agent Safinamide

2.3.1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity, resting tremor, and ataxia. These symptoms are caused by decreased dopamine release in the striatum. Clinically, PD is defined by the presence of Lewy bodies, intracellular neuronal inclusions in the substantia nigra and at other sites in the brain.[1] Estimated prevalence of this disease is 100 to 200 per 100 000 population including males and females across the entire age group.[2] Current treatment for PD comprises dopaminergic medications that include levodopa, dopamine agonists (DAs), monoamine oxidase-B (MAO-B) inhibitors.[3]

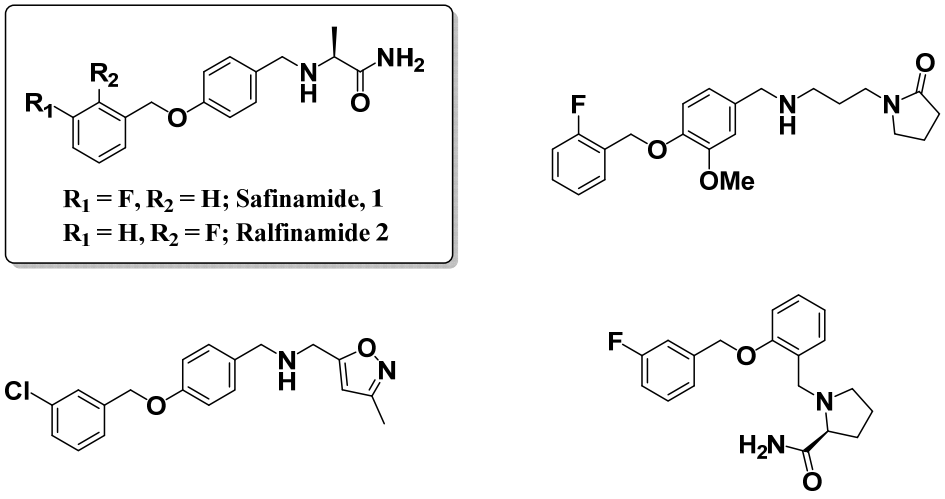


Figure 1. Few examples of pharmaceutically important benzyloxy-benzylamine derivatives.

In this context, recently many benzyloxy-benzylamine derivatives were synthesized and their utility in treating various CNS related disorders are documented.[4] Among them safinamide ((*S*)-N^2-{4-[3-fluorobenzyl)oxy]benzyl}-alaninamide methanesulfonate) is an noted example which is under phase III clinical trials against Parkinson's disease.[5] Its mechanism of action is manifold which comprise MAO-B and dopamine uptake inhibition. Further, safinamide is believed to block voltage-dependent sodium channels, modulates calcium channels and reduction of glutamate

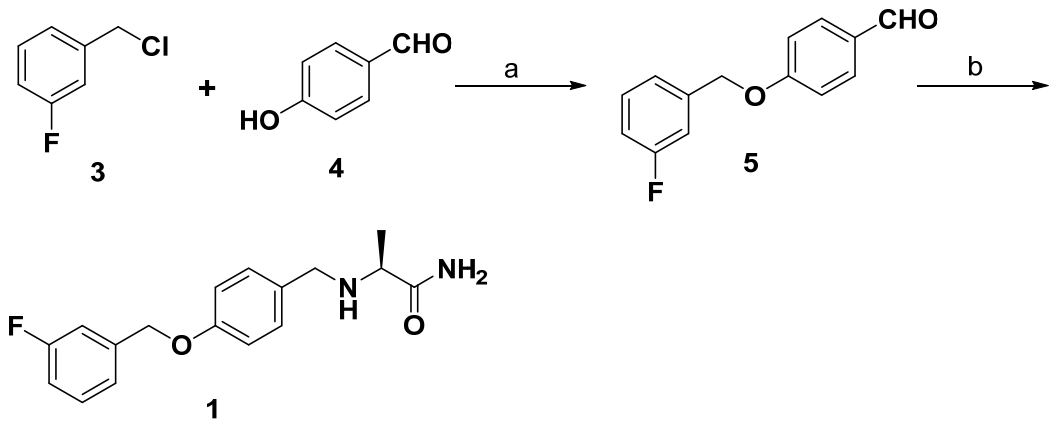
release in the central nervous system.[6]

2.3.2. Review of Literature

The only available method for the synthesis of safinamide employs chiral pool approach which is described below.

Pevarello *et al.* (1998)[7]

Pevarello *et al.* reported the synthesis of safinamide **1** starting from 3-fluorobenzyl chloride **3**. *O*-alkylation of 4-hydroxybenzaldehyde **4** using 3-fluorobenzyl chloride **3** afforded ether intermediate **5**, which on reductive condensation with L-alaninamide to give safinamide **1** (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) K_2CO_3, cat. tetradecyl triethylammonium bromide, reflux, 6 h, 85%; (b) L-alaninamide, $NaBH_3CN$, MeOH, 3-Aº molecular sieves, rt, 3 h, 45%.

This method is simple and straightforward. However, during large scale production of safinamide **1** and ralfinamide **2**, two toxic impurities were identified (Fig. 2).

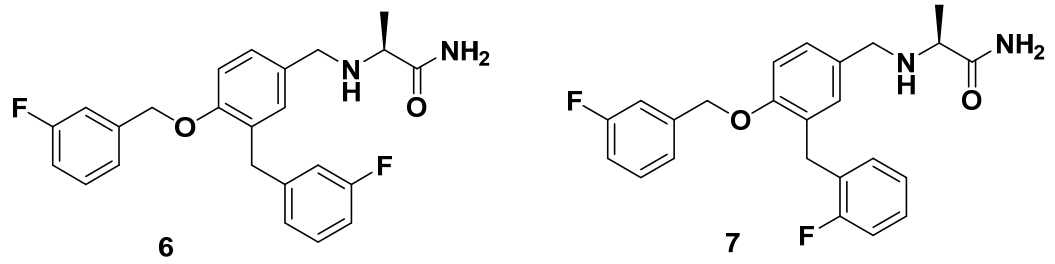
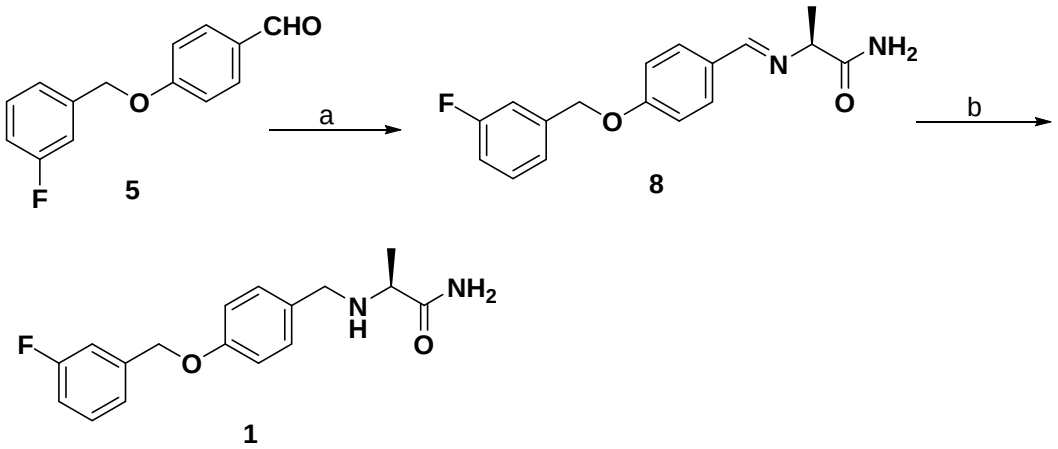


Figure 2. Toxic impurities identified in Pevarello's approach.

Further, in the above reaction sodium cyanoborohydride is used for reductive alkylation which produces highly toxic sodium cyanide as a by-product.

Barbanti *et al* (2007)[8]

Barbanti *et al* modified the previous route via formation of Schiff's base intermediate. Thus, L-alaninamide hydrochloride was treated with 4-(3-fluorobenzyloxy)benzaldehyde **5** under basic conditions to give Schiff's base intermediate **8** which on hydrogenation provided safinamide **1** (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) L-alaninamide hydrochloride, Et_3N, MeOH, 1 h, 73%; (b) cat Pt/C, MeOH, H_2 (5 bar), 1 h, 94%.

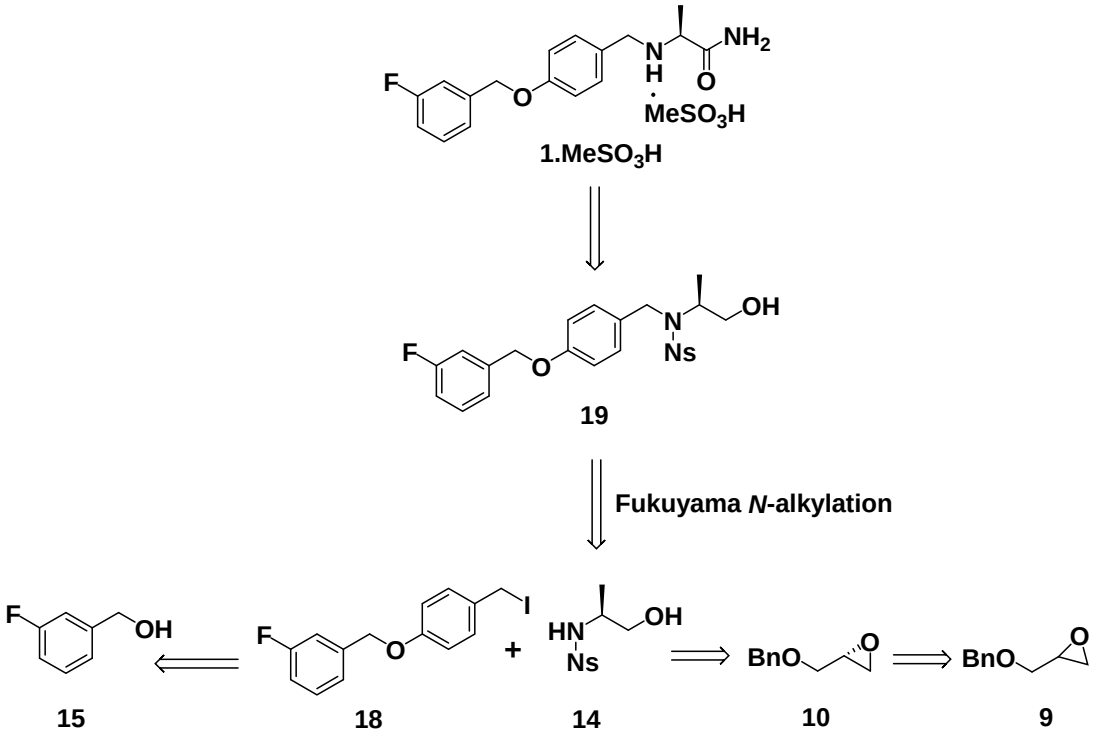
2.3.3. Present Work

Objective

The existing method for the synthesis of safinamide utilizes only chiral pool approach starting from L-alaninamide. In this approach unwanted toxic impurities were identified. Further, generation of safinamide analogues, especially the variation at the chiral carbon is limited in this approach. In this context, we felt that it would be worthwhile to develop a new route for safinamide by taking the advantage of Jacobsen's HKR strategy.

2.3.4. Results and Discussion

A retrosynthetic analysis of the target compound **1** is based on a convergent approach as depicted in Scheme 3. We envisioned that the *N*-protected aminoalcohol **19** can serve as a key intermediate for the synthesis and it can be elaborated to the final product via oxidation and amidation reaction sequences. Further, the key intermediate **19** can be accessed via the coupling reaction between amino alcohol **14** and alkyl iodide **18** employing Fukuyama *N*-alkylation strategy. The amino alcohol **14** in turn could be prepared from (*R*)-benzyl glycidyl ether **10.** The chiral epoxide **10** can be easily obtained with high enantiopurity from its racemic benzyl glycidyl ether **9** using Jacobsen's hydrolytic kinetic resolution method. The iodo fragment **18** could be easily obtained from commercially available 3-fluorobenzyl alcohol **15**.

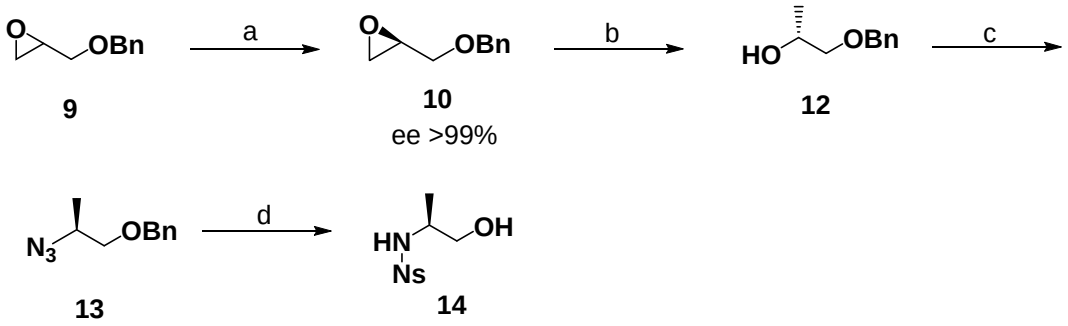


Scheme 3. Retrosynthetic analysis of safinamide **1**

Synthesis of amino alcohol fragment 14

Accordingly, the synthesis commences with the preparation of amino alcohol fragment **14.** Thus, the readily available benzyl glycidyl ether **9** was subjected to hydrolytic kinetic resolution (HKR) in the presence of Jacobsen's (*S,S*)-(salen)Co III

catalyst to afford enantiomerically enriched epoxide **10** in 46 % yield (> 99% *ee*) and its corresponding diol **11**. (Scheme 4). The epoxide **10** was converted into the desired secondary alcohol **12** via regioselective reductive ring opening using lithium aluminium hydride in anhydrous THF at 0 ºC. Appearance of a doublet at δ 1.15 (3H) and multiplet in the range of δ 3.91-4.13 (1H) in ^{1}H NMR and a peak at δ 18.6 (CH_3) in ^{13}C NMR indicates the formation of compound **12**.



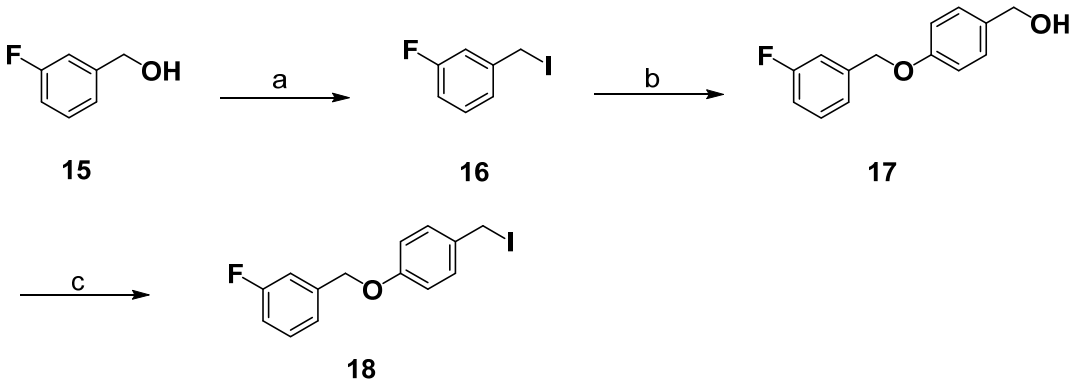
Scheme 4. *Reagents and conditions***:** (a) (*S, S*) Salen Co (III)-A, 0˚C- rt, 24 h, 46%; (b) $LiAlH_4$, THF, 0 ºC, 1 h, 95%; (c) (i) MsCl, DCM, 0 ºC- rt, 6 h; (ii) NaN_3, DMF, 60 ºC, 6 h, 89% (2 steps); (d) (i) $Pd(OH)_2$, TFA, MeOH, H_2 (60 psi), 8 h; (ii) NsCl, Et_3N, DCM, 0 ºC, 2 h, 75% (2 steps).

The secondary alcohol **12** was converted into its azido derivative **13** in 89 % yield (two steps) via mesylation followed by displacement with sodium azide. Next, the azido compound **13** was subjected to $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis followed by *N*-nosylation using nosyl chloride under basic conditions to give the amino alcohol fragment **14** in 75% yield. Disappearance of a singlet at δ 4.57 (2H) and multiplet at δ 7.25-7.39 (5H) in ^{1}H NMR showed the removal of benzyl group. Appearance of the aromatic protons at δ 7.73-7.80 (2H), 7.86-7.91 (1H), 8.13-8.22 (1H) showed the presence of nosyl group and a peak in the range of δ 5.61 (1H) in ^{1}H NMR confirmed the formation of aminoalcohol **14.**

Synthesis of iodo fragment 18

Subsequently the iodo fragment **18** was prepared from commercially available 3-fluorobenzyl alcohol **15**. Thus, iodination of compound **15** using triphenylphosphine and iodoimidazole generated in situ by iodine and imidazole to give compound **16** in 95% yield. Subsequently, compound **16** upon treatment with 4-

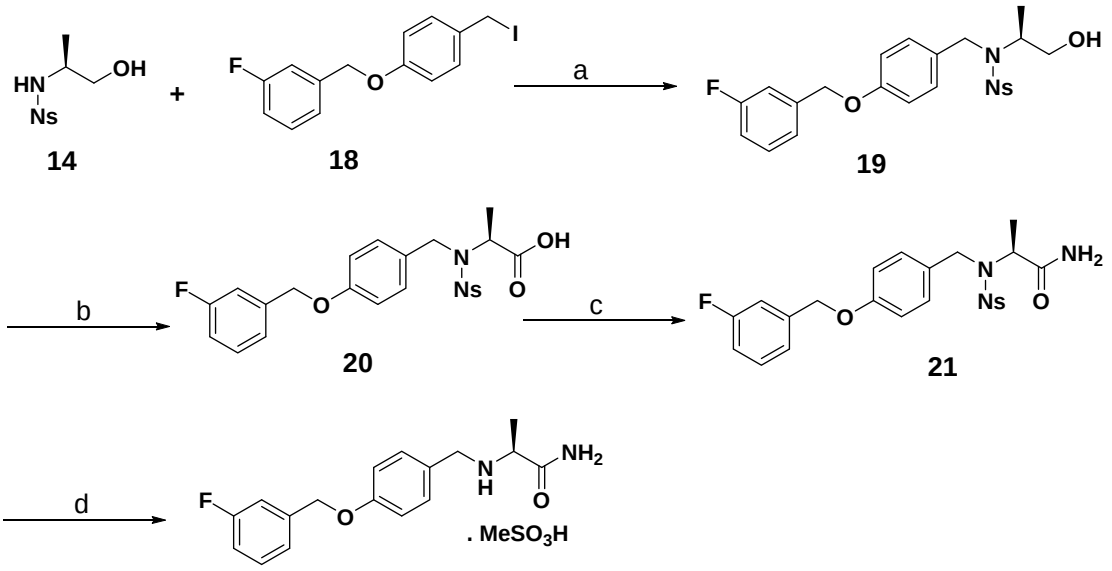
(hydroxymethyl)phenol under basic condition afforded *O*-alkylated product **17** in 91 % yield. Iodination of **17** under the condition mentioned above afforded the required iodo fragment **18** (Scheme 5).



Scheme 5. *Reagents and conditions***:** (a) I_2, Ph_3P, imidazole, DCM, 0 ºC- rt, 1 h, 95%; (b) 4-hydroxy benzylalcohol, K_2CO_3, CH_3CN, 70 ºC, 6 h, 91%; (c) I_2, Ph_3P, imidazole, DCM, 0 ºC- rt, 1 h, 93%.

Coupling of fragments 14 and 18

Having prepared coupling partners amino alcohol **14** and alkyl iodide **18** successfully, next plan was to couple these two fragments suitably. As shown in scheme 6, coupling of **14** and **18** was carried out in the presence of potassium carbonate in acetonitrile at 70 ºC to give the corresponding coupled product **19** in 80% yield. Appearance of characteristic peak at δ 4.37-3.57 (2H) in ^{1}H NMR and m/z peak at 497 $(M+Na)^+$ in mass spectrum showed the formation of 19. Next, oxidation of the coupled product **19** was performed using TEMPO/bleach condition to give the acid **20** in 85% yield. Subsequently, the acid **20** was converted into the amide **21** by consecutive reaction with ethyl chloroformate and aq. ammonia. Appearance of peak at δ 178.3 ($CONH_2$) in ^{13}C NMR and m/z peak at 510 $(M+Na)^+$ in mass spectrum confirmed the formation of 21. Finally, cleavage of the nosyl group with thiophenol and potassium carbonate, followed by salt formation with methane sulphonic acid complete the synthesis of safinamide **1**.



Scheme 6. *Reagents and conditions***:** (a) K_2CO_3, CH_3CN, 70 ºC, 6 h, 80%; (b) $NaClO_2$, NaOCl, TEMPO (cat), phosphate buffer, CH_3CN, 35 °C, 3 h, 85%; (c) $ClCO_2Et$, Et_3N, THF, -20 ºC, 1 h then aq NH_3, rt, 16 h, 91%; (d) (i) PhSH, K_2CO_3, DMF, rt, 6 h, 86%; (ii) $MeSO_3H$, EtOAc, 70 ºC, 3 h, 90%.

The structure of safinamide **1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis. The enantiomeric purity of safinamide was determined by chiral HPLC analysis.

2.3.5. Conclusion

In conclusion, a new enantioselective synthesis of anti Parkinson agent safinamide **1** has been developed employing Jacobsen's hydrolytic kinetic resolution method as a key step and source of chirality. High enantiopurity (>99%) of the final product has been achieved. Further, the synthesis depicted here could be utilized for the preparation of safinamide analogues especially variation at the chiral carbon.

2.3.6. Experimental

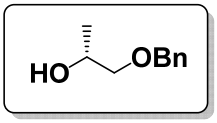
1) 2-(benzyloxymethyl) oxirane (racemic) 9

The preparation and characterization of racemic epoxide **9** is depicted in Chapter 2 section A.

2) (*R*)-2-(benzyloxymethyl) oxirane 10

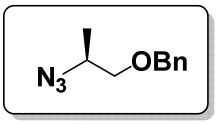
The preparation and characterization of chiral epoxide **10** is depicted in Chapter 2 section B.

3) *(R)*-1-(benzyloxy)propan-2-ol 12



To a pre cooled (0 ºC) mixture of lithium aluminium hydride (1.39 g, 36.54 mmol) in dry THF (20 mL) was added *(R)*-benzyl glycidyl ether **10**, (4 g, 24.3 mmol) dropwise under argon atmosphere and allowed to stir for 1 h at the room temperature. After completion of the reaction (indicated by TLC) the reaction mixture was quenched at 0°C with portion wise addition of KOH pellets (0.5 g) followed by slow addition of ice flakes. The resulting mixture was stirred for 30 min at 0°C, then at room temperature for 30 min. The reaction mixture was filtered through celite bed using ethyl acetate as a washing solvent. Filtrate was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude alcohol thus obtained was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 90:10) to yield **12** as an oil (3.85 g, 95%); $[\alpha]^{22}_D$ = -14.6 (*c* 2, $CHCl_3$) {Lit.[9] $[\alpha]^{22}_D$ = -10.8 (*c* 2.6, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3418, 3087, 3063, 3030, 2963, 2924, 1952, 1873, 1600, 1495, 1454, 1363, 1244, 1099, 1028, 918, 808, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.15 (d, *J* = 6.3 Hz, 3H), 2.50 (bs, 1H), 3.23-3.32 (dd, *J* = 9.34, 8.09 Hz, 1H), 3.43-3.49 (dd, *J* = 9.45, 3.12 Hz, 1H), 3.91-4.13 (m, 1H), 4.55 (s, 2H), 7.25-7.37 (m, 5H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.8 (C), 128.3 (CH, 2 carbons), 127.7 (CH, 3 carbons), 75.7 (CH_2), 73.2 (CH_2), 66.4 (CH), 18.6 (CH_3); MS: m/z 189 $[M+Na]^+$.

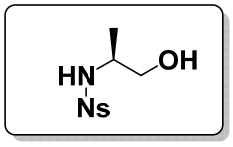
4) *(S)*-((2-azidopropoxy)methyl)benzene 13



To a pre cooled (0 ºC) solution of alcohol **12** (3 g, 18.04 mmol) in dry DCM (30 mL) was added triethylamine (5.4 mL, 39.3 mmol) followed by slow addition of methanesulfonyl chloride (1.68 mL, 21.65 mmol) dropwise. The reaction mixture was stirred at 0 ºC for 3 h then, at room temperature for another 3 h before quenching with water, more DCM was added and extracted with water, washed with brine and evaporated under reduced pressure. The crude product was used for next step without purification.

To a solution of crude mesylate as obtained above in dry DMF (20 mL) was added sodium azide (1.59 g, 24.55 mmol) under argon atmosphere. The reaction mixture was heated to 60 ºC with vigorous stirring over 6 h. After completion of reaction (indicated by TLC), water (15 mL) was added to the reaction mixture and product was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude residue by silica gel column chromatography with petroleum ether/EtOAc (95:5) gave **13** (2.85 g, 91% yield over two steps) as an oil. $[\alpha]^{22}_D$ = +6.16 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3394, 3032, 2977, 2864, 2500, 2104, 1724, 1641, 1496, 1454, 1363, 1269, 1101, 913, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.22 (d, *J* = 6.72 Hz, 3H), 3.39-3.47 (dd, *J* = 8.86, 6.09 Hz, 1H), 3.48-3.54 (dd, *J* = 3.26, 8.82 Hz, 1H), 3.61-3.77 (m, 1H), 4.57 (s, 2H), 7.25-7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 137.8 (C), 128.4 (CH, 2 carbons), 127.7 (CH), 127.5 (CH, 2 carbons), 73.7 (CH_2), 73.2 (CH_2), 56.9 (CH), 16.1 (CH_3); MS: m/z 214 $[M+Na]^+$.

5) *(S)*-N-(1-hydroxypropan-2-yl)-2-nitrobenzenesulfonamide 14

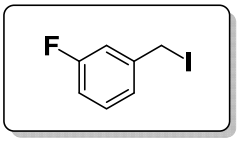


To a solution of azide **13** (2.5 g, 13.0 mmol) in methanol (20 mL) and trifluoroacetic acid (TFA, 2 mL) was added palladium hydroxide (0.05 g, 10-20 wt %). The reaction mixture was stirred for 8 h under hydrogen atmosphere (60 psi) at the same temperature. After completion of the reaction (indicated by TLC), the mixture was

filtered through a plug of celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure. The residue was basified with 2.5 M methanolic NaOH (till pH became 10-12). Evaporation of methanol under reduced pressure followed by filtration of the resulting residue through short bed of basic alumina (eluent: MeOH) provided amino alcohol (0.94 g, 95%) as light brown oil which was subjected to the next reaction without further purification.

To a pre cooled (0 ºC) solution of the amino alcohol (0.9 g, 12.0 mmol) as obtained above was added nosyl chloride (3.18 g, 14.4 mmol) in dry dichloromethane (10 mL) followed by addition of triethylamine (4.18 mL, 29.95 mmol) under argon atmosphere. The reaction mixture was allowed to stirr at 0 ºC for 2 h. After completion of reaction, water (10 mL) was added to the reaction mixture and extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography with petroleum ether/EtOAc (60:40) gave **14** (1.24 g, 67% yield over two steps) as light yellow oil. $[\alpha]^{22}_D$ = +80.2 (*c* 2.14, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3546, 3367, 3022, 2883, 2401, 1594, 1542, 1412, 1362, 1216, 1170, 1125, 1059, 971, 854, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.15 (d, *J* = 6.48 Hz, 3H), 2.16 (bs, 1H), 3.45-3.70 (m, 3H), 5.61 (d, *J* = 6.56 Hz, 1H), 7.73-7.80 (m, 2H), 7.86-7.91 (m, 1H), 8.13-8.22 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 147.8 (C), 134.4 (C), 133.7 (CH), 133.0 (CH), 130.9 (CH), 125.5 (CH), 66.2 (CH_2), 52.5 (CH), 17.8 (CH_3); MS: m/z 283 $[M+Na]^+$.

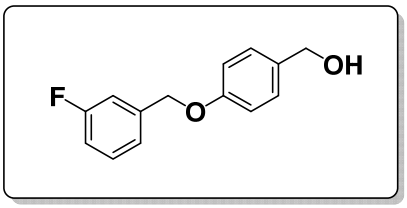
6) 1-fluoro-3-(iodomethyl)benzene 16



To a stirred solution of the triphenyl phosphine (4.15 g, 15.85 mmol), imidazole (1.07 g, 15.85 mmol) and iodine (4.8 g, 19.02 mmol) in dry dichloromethane (20 mL) at 0 ºC was added 3-fluoro benzyl alcohol **15** (2 g, 15.85 mmol) dropwise over 10 min, under argon atmosphere. The reaction mixture was stirred at the same temperature for 1 h. After completion of reaction (indicated by TLC) the reaction mixture was poured into saturated solution of sodium thiosulfate (15 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (15 mL) and were dried over Na_2SO_4. The residue obtained after

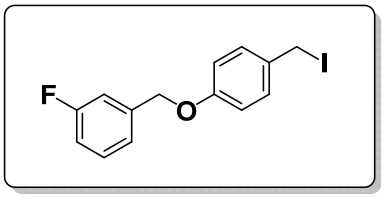
removal of the solvent was purified by silica gel column chromatography using petroleum ether/EtOAc (95:5) to yield **16** (3.62 g, 95%) as oil. IR ($CHCl_3$): ν_{max} 3460, 3060, 2965, 1695, 1613, 1593, 1482, 1446, 1259, 1156, 1068, 944, 871, 782, 736, 686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 4.42 (s, 2H), 6.89-6.99 (m, 1H), 7.05-7.17 (m, 2H), 7.21-7.29 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.0 (C), 141.6 (C), 130.2 (CH), 124.4 (CH), 115.9 (CH), 114.7 (CH), 3.9 (CH_2).

7) (4-((3-flurobenzyl)oxy)phenyl)methanol 17



To the solution of 4-(hydroxymethyl)phenol (1.53 g, 12.71 mmol) in dry acetonitrile (20 mL) was added K_2CO_3 (8.8 g, 63.5 mmol) followed by addition of **16** (3 g, 12.71 mmol) in dry acetonitrile (5 mL) over 10 min under argon atmosphere. The reaction mixture was stirred at 70°C for 6 h. After completion of the reaction (indicated by TLC), the reaction mixture was filtered and the solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography using petroleum ether/EtOAc (70:30) gave **17** (2.7 g, 91%) as a solid; mp 63-65 °C; IR ($CHCl_3$): ν_{max} 3422, 3017, 1612, 1512, 1489, 1381, 1216, 1174, 1020, 829, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 4.61 (s, 2H), 5.06 (s, 2H), 6.91-6.98 (m, 2H), 7.00-7.06 (m, 1H), 7.12-7.20 (m, 2H), 7.25-7.37 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.4 (C), 160.5 (C), 158.0 (C), 139.6 (C), 133.5 (CH), 130.2 (CH), 128.7 (CH, 2 carbons), 122.7 (CH), 114.8 (CH, 2 carbons), 113.9 (CH), 69.1 (CH_2), 64.9 (CH_2); MS: m/z 255 $[M+Na]^+$.

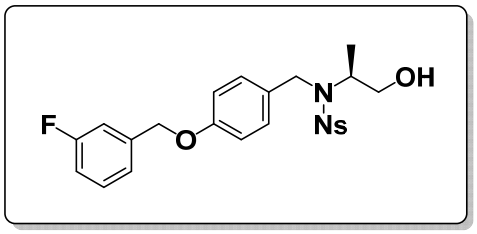
8) 1-fluoro-3-((4-(iodomethyl)phenoxy)methyl)benzene 18



To a stirred solution of the triphenyl phosphine (2.82 g, 10.7 mmol), imidazole (0.73 g, 10.7 mmol) and iodine (3.27 g, 12.9 mmol) in dry dichloromethane (20 mL) at 0°C was added compound **17** (2.5 g, 10.7 mmol) dropwise over 10 min, under argon

atmosphere. The reaction mixture was stirred at the same temperature for 1 h. After completion of reaction (indicated by TLC) the reaction mixture was poured into saturated solution of sodium thiosulfate (15 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified by silica gel column chromatography using petroleum ether/EtOAc (95:5) to yield **18** (3.52 g, 93%) as oil. IR ($CHCl_3$): ν_{max} 3503, 3033, 2925, 2089, 1607, 1509, 1488, 1381, 1301, 1250, 1155, 1079, 944, 869, 776, 684 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 4.47 (s, 2H), 5.04 (s, 2H), 6.85-6.91 (m, 2H), 6.96-7.02 (m, 1H), 7.05-7.12 (m, 1H), 7.16-7.20 (m, 1H), 7.29-7.40 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.4 (C), 160.5 (C), 158.1 (C), 131.9 (C), 130.2 (CH), 130.1 (CH, 2 carbons), 122.7 (CH), 115.1 (CH, 2 carbons), 114.7 (CH), 113.9 (CH), 69.2 (CH_2), 6.33 (CH_2).

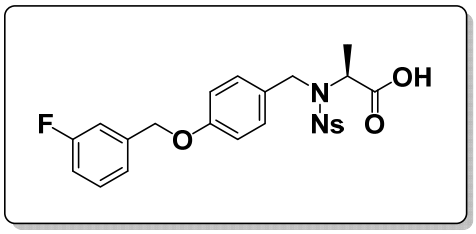
9) *(S)*-N-(4-((3-flurobenzyl)oxy)benzyl)-N-(1-hydroxypropan-2-yl)-2-nitrobenzenesulfonamide 19



To the solution of **14** (1 g, 3.84 mmol) in dry acetonitrile (20 mL) was added K_2CO_3 (2.65 g, 19.21 mmol) followed by addition of **18** (1.84 g, 5.37 mmol) under argon atmosphere. The reaction mixture was stirred for 72 h at 70°C. After completion of the reaction (indicated by TLC), the reaction mixture was filtered and the solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography with petroleum ether/EtOAc (80:20) gave **19** (1.46 g, 80%) as oil. $[\alpha]^{22}_D$ = +5.43 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3445, 3020, 2928, 2400, 1613, 1544, 1512, 1453, 1371, 1216, 1162, 1029, 852, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.09 (d, *J* = 6.95 Hz, 3H), 1.91 (t, *J* = 5.04 Hz, 1H), 3.41-3.53 (m, 2H), 4.05-4.22 (m, 1H), 4.37-4.57 (m, 2H), 5.02 (m, 2H), 6.87 (d, *J* = 8.53 Hz, 2H), 6.97-7.12 (m, 2H), 7.20 (d, J = 7.2 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.47-7.67 (m, 3H), 7.89 (d, *J* = 8.09 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.5 (C), 160.6 (C), 158.4 (C), 147.7 (C), 139.6 (C), 134.1 (C), 133.4 (CH), 131.6 (CH), 131.4 (CH), 130.3 (CH), 129.7 (CH, 2 carbons), 124.1 (CH), 122.8 (CH), 115.1 (CH), 114. 9 (CH, 2

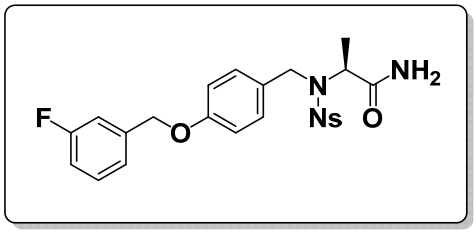
carbons), 114.0 (CH), 69.2 (CH_2), 64.3 (CH_2), 56.2 (CH), 46.9 (CH_2), 15.4 (CH_3); Analysis: $C_{23}H_{23}FN_2O_6S$; Calcd: C, 58.22; H, 4.89; F, 4.00; N, 5.90; S, 6.76; Found: C, 57.94; H, 4.54; F, 3.77; N, 5.57; S, 6.34 MS: m/z 497 $[M+Na]^+$.

10) *(S)*-2-(N-(4-((3-flurobenzyl)oxy)benzyl)-2-nitrophenylsulfonamido)propanoic acid 20



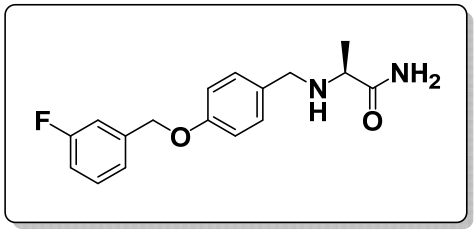
A mixture of primary alcohol **19** (1.25 g, 2.63 mmol), TEMPO (0.026 g, 0.17 mmol), acetonitrile (20 mL), and sodium phosphate buffer (16 mL, 0.67 M, pH 6.7) was heated to 35°C. Next, sodium chlorite (0.71 g dissolved in 2 mL water, 7.9 mmol) and diluted bleach (4–6%, 0.09 mL diluted in 1 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at 35 ºC until the reaction was complete (3 h, TLC), then cooled to room temperature. Water (30 mL) was added and the pH adjusted to 8 with 2 M NaOH. The reaction was quenched by pouring it into an ice cold Na_2SO_3 solution maintained at <20°C. After stirring for 30 min at room temperature, ethyl acetate (20 mL) was added and the stirring continued for an additional 15 min. The organic layer was separated and discarded. More ethyl acetate (20 mL) was added, and the aqueous layer was acidified with M HCl to pH 3–4. The organic layer was separated, washed with water (2 x 15 mL), brine (15 mL) and concentrated under reduced pressure to afford acid **20** (1.13 g, 85%). $[\alpha]^{22}_D$ = -20.42 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3398, 3095, 1718, 1612, 1591, 1543, 1512, 1489, 1457, 1371, 1303, 1251, 1163, 1059, 900, 852, 831, 778, 684 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.46 (d, *J* = 7.34 Hz, 3H), 4.27 (d, *J* = 15.65 Hz, 1H), 4.68 (d, *J* = 15.65 Hz, 1H), 4.82-4.90 (q, *J* = 7.2 Hz, 1H), 4.92 (s, 2H), 6.68 (d, *J* = 8.57 Hz, 2H), 6.89-7.01 (m, 2H), 7.07-7.13 (m, 3H), 7.18-7.33 (m, 2H), 7.43-7.55 (m, 3H), 8.81 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 176.5 (C), 165. 0 (C), 158.0 (C), 147.4 (C), 139.4 (C), 134.1 (C), 133.2 (CH), 131.4 (CH), 130.3 (CH), 129.9 (CH, 2 carbons), 128.4 (C), 124.1 (CH), 122.6 (CH), 115.0 (CH), 114.6 (CH, 2 carbons), 114.3 (CH), 113.8 (CH) 69.1 (CH_2), 56.1 (CH), 49.0 (CH_2), 16.8 (CH_3); MS: m/z 511 $[M+Na]^+$.

11) *(S)*-2-(N-(4-((3-fluorobenzyl)oxy)benzyl)-2-nitrophenylsulfonamido)propanamide 21



To a solution of acid **20** (1 g, 2.04 mmol) and triethylamine (0.3 mL, 2.14 mmol) in dry THF (20 mL) was added ethyl chloroformate (0.2 mL, 2.12 mmol) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 30 min. Ammonium hydroxide (25% w/v aqueous solution, 0.36 mL, 9.41 mmol) was added and the resulting reaction mixture was stirred at room temperature for 16 h. After the addition of K_2CO_3 (0.29 g, 2.1 mmol), the reaction mixture was filtered, washed with ethyl acetate. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography using petroleum ether/EtOAc (50:50) gave **21** (0.91 g, 91%) as an oil. $[\alpha]^{22}_D$ = -32.13 (*c* 1.23, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3472, 1961, 1611, 1592, 1542, 1511, 1449, 1371, 1304, 1243, 1163, 1060, 1029, 895, 852, 684 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.44 (d, *J* = 7.08 Hz, 3H), 4.40-4.59 (q, *J* = 29.5, 14.11 Hz, 2H), 4.60-4.71 (q, J = 14.2, 7.06 Hz, 1H), 5.01 (s, 2H), 5.50 (bs, 1H), 6.31 (bs, 1H), 6.78 (d, J = 8.71 Hz, 2H), 6.98-7.11 (m, 2H), 7.15-7.22 (m, 3H), 7.31-7.45 (m, 2H), 7.59-7.64 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 172.3 (C), 165.5 (C), 158.2 (C), 147.5 (C), 139.6 (C), 139.4 (C), 133.6 (CH), 131.7 (CH), 130.5 (CH, 2 carbons), 130.3 (CH), 128.1 (C), 124.2 (CH), 122.7 (CH), 115.1 (CH), 114.7 (CH, 2 carbons), 114.4 (CH), 113.9 (CH), 69.0 (CH_2), 55.7 (CH), 48.3 (CH_2), 14.9 (CH_3); Analysis: $C_{23}H_{22}FN_3O_6S$; Calcd: C, 56.67; H, 4.55; F, 3.90; N, 8.62; S, 6.58; Found: C, 56.44; H, 414; F, 3.65; N, 8.44; S, 6.42; MS: m/z 510 $[M+Na]^+$.

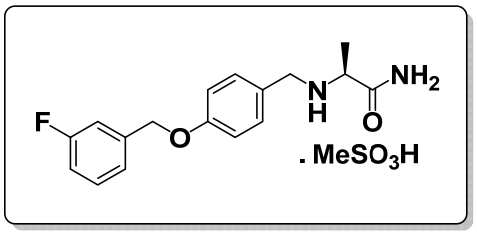
12) *(S)*-2-((4-((3-fluorobenzyl)oxy)benzyl)amino)propanamide 1



To a solution of amide **21** (0.8 g, 1.64 mmol) and activated K_2CO_3 (1.13 g, 8.20 mmol) in dry DMF (15 mL) under argon atmosphere was added thiophenol (0.2 mL,

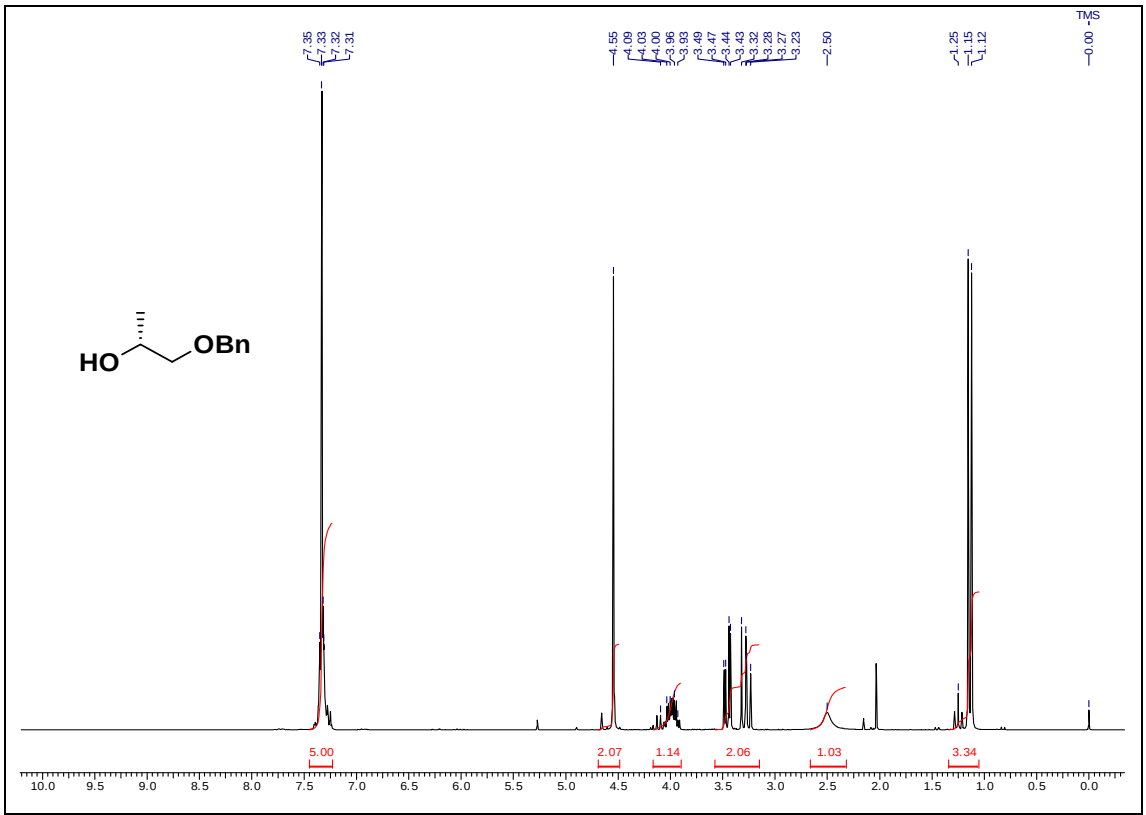
1.96 mmol) over 10 min at room temperature. The resulting reaction mixture was stirred at the same temperature for 6 h. After the completion of reaction (TLC), water (15 mL) was added and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (2 x 15 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography with petroleum ether/EtOAc (60:40) gave **1** (0.45 g, 86%) as solid; mp 207-209°C; $[\alpha]^{22}_D$ = +3.89 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3341, 2970, 2927, 2853, 1648, 1592, 1512, 1489, 1445, 1406, 1384, 1254, 1176, 1137, 1030, 953, 928, 829, 680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.36 (d, *J* = 6.96 Hz, 3H), 2.01 (bs, 2H), 3.19-3.30 (q, *J* = 14.03, 7.02 Hz, 1H), 3.72 (d, *J* = 3.91 Hz, 2H), 5.05 (s, 2H), 5.85 (bs, 1H), 6.95 (d, *J* = 8.72 Hz, 2H), 7.00-7.06 (m, 1H), 7.13-7.24 (m, 4H), 7.29-7.40 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 178.3 (C), 165.4 (C), 157.7 (C), 139.6 (C), 132.1 (C), 130.2 (CH), 129.3 (CH, 2 carbons), 122.7 (CH), 114.9 (CH, 2 carbons), 114.6 (CH), 113.9 (CH), 69.2 (CH_2), 57.3 (CH), 51.9 (CH_2), 19.6 (CH_3); MS: m/z 325 $[M+Na]^+$.

13) Preparation of *(S)*-Safinamide mesylate 1.MeSO$_3$H

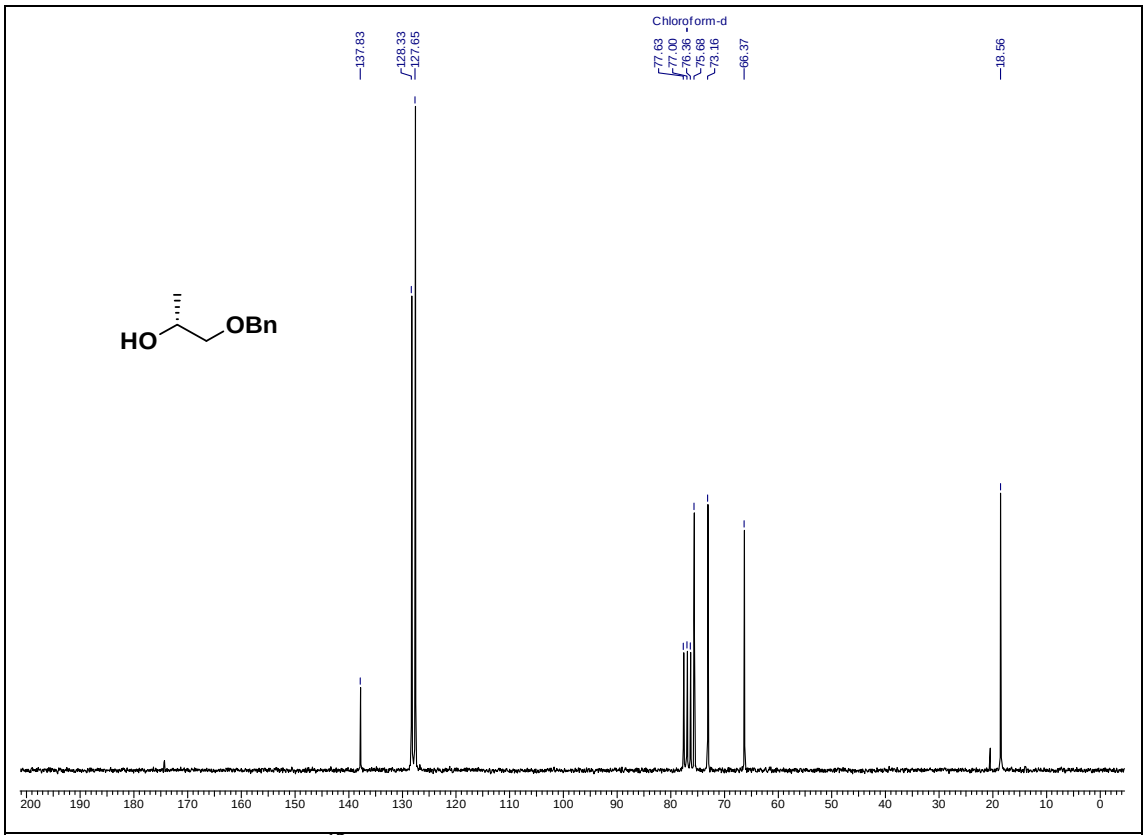


To a solution of **1** (0.1 g, 0.33 mmol) in EtOAc (2 mL) was added methanesulfonic acid (0.02 mL, 0.33 mmol) and the reaction mixture was heated to 70 °C and stirred for 2 h. The reaction mixture was allowed to attain room temperature and stirred for another 1 h. The residue obtained after evaporation of solvent under reduced pressure was filtered through short bed of basic alumina [eluent MeOH/EtOAc; (10:90)] in order to furnish safinamide mesylate (0.118 g, 90%) **1.MeSO$_3$H** as white solid; mp 209-211°C; $[\alpha]^{22}_D$ = +9.6 (*c* 1.1, AcOH); ee >99% [The ee of **1.MeSO$_3$H** was determined by chiral HPLC analysis; Chiralcel OD-RH (150 x 4.6 mm) column; eluent: Methanol/Acetonitrile/Buffer-TEAP, pH 3 (20:10:70); flow rate 0.5 mL/min (780 psi); detector: 224 nm] [*(R)*-isomer t_R = 11.55 min, *(S)*-isomer t_R = 12.94 min]

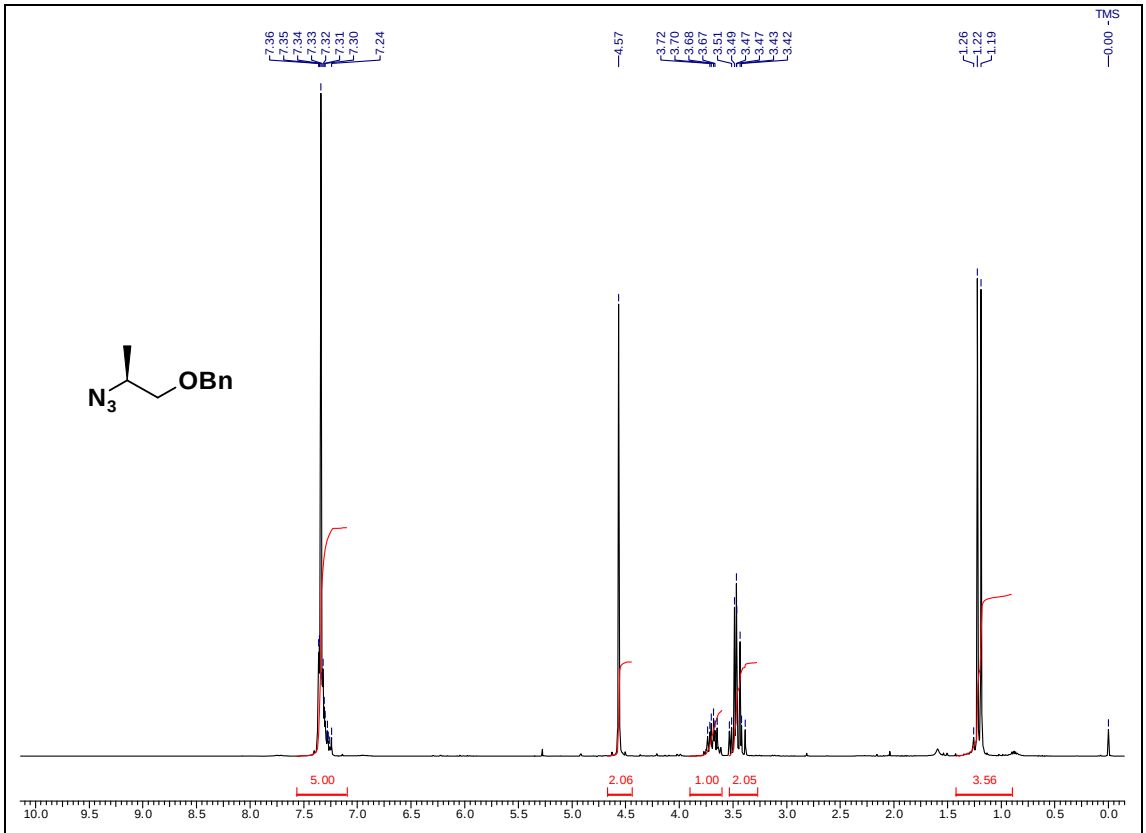
2.3.7. Analytical Data



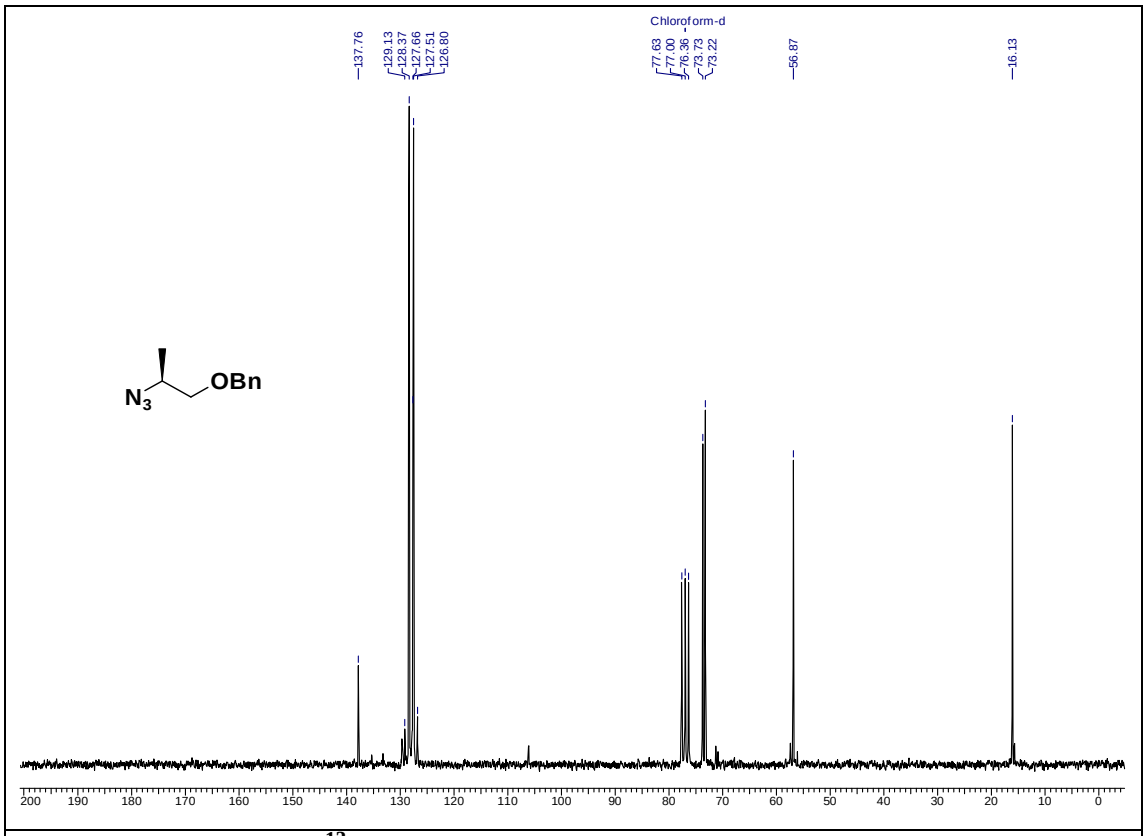
^{1}H NMR of Compound 12 in $CDCl_3$



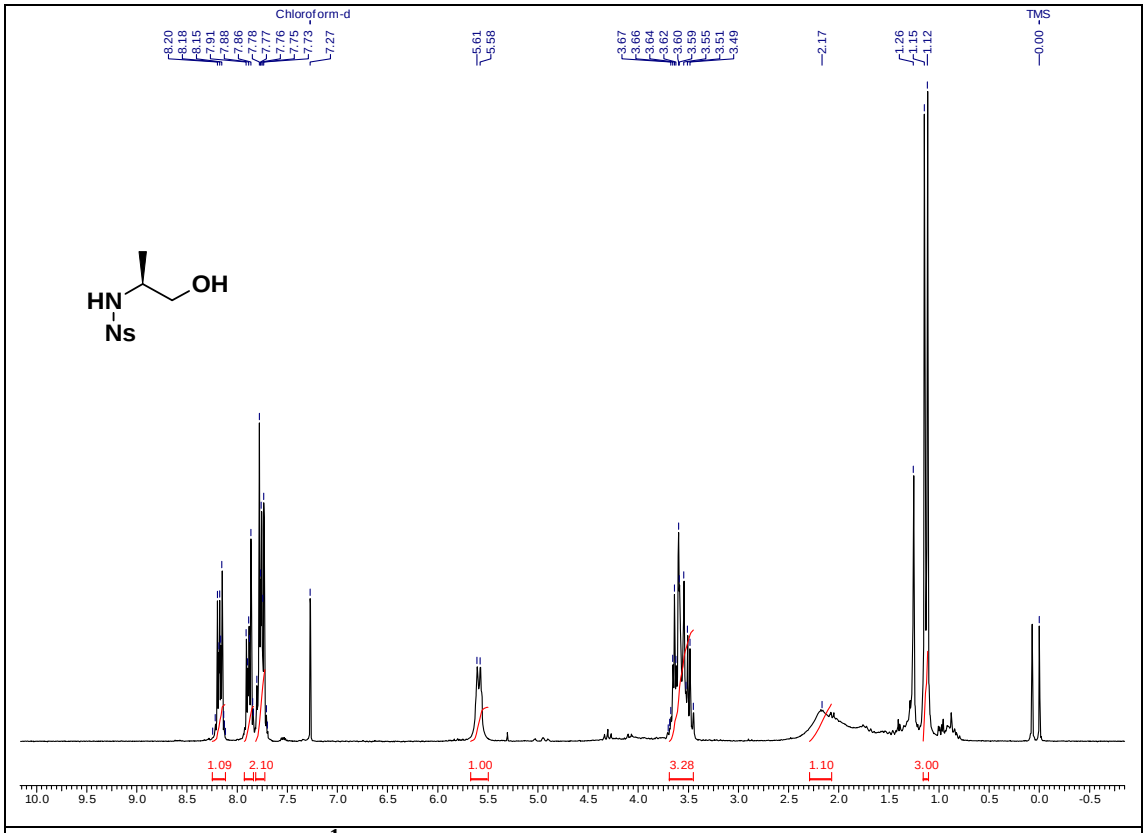
^{13}C NMR of Compound 12 in $CDCl_3$



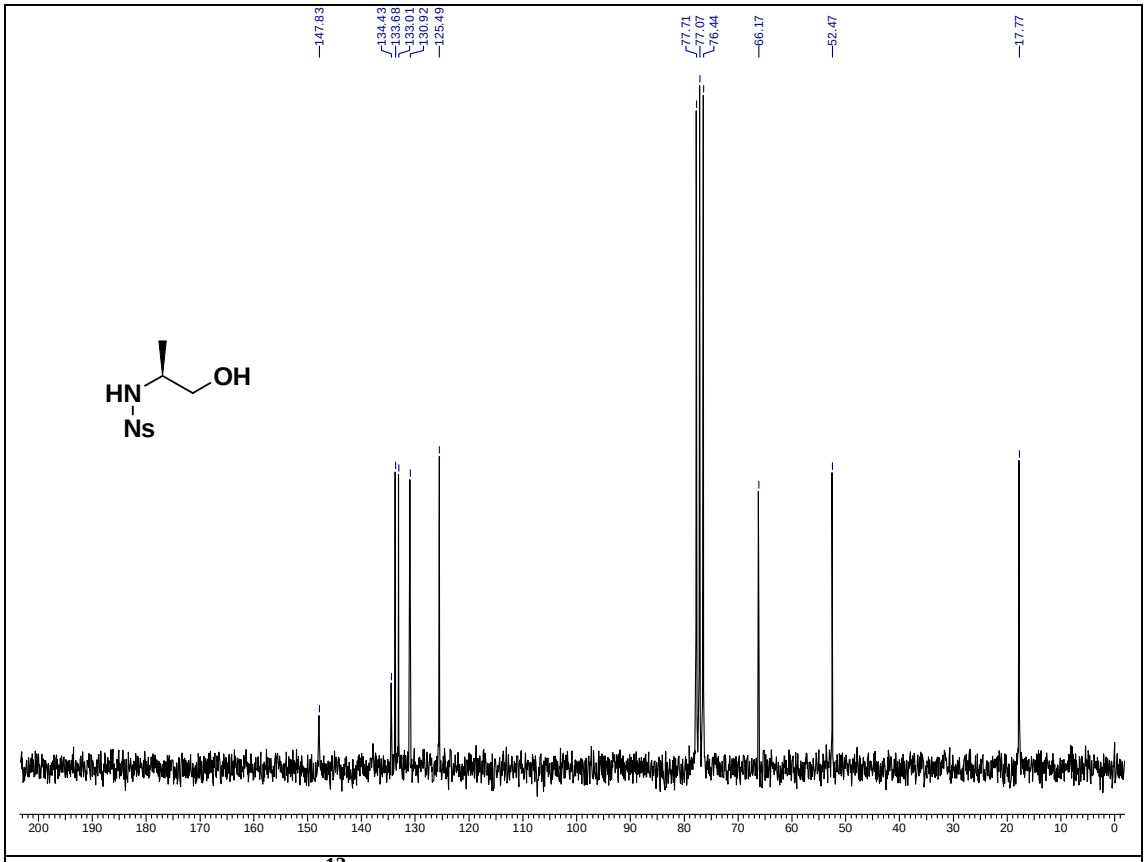
^{1}H NMR of Compound 13 in $CDCl_3$



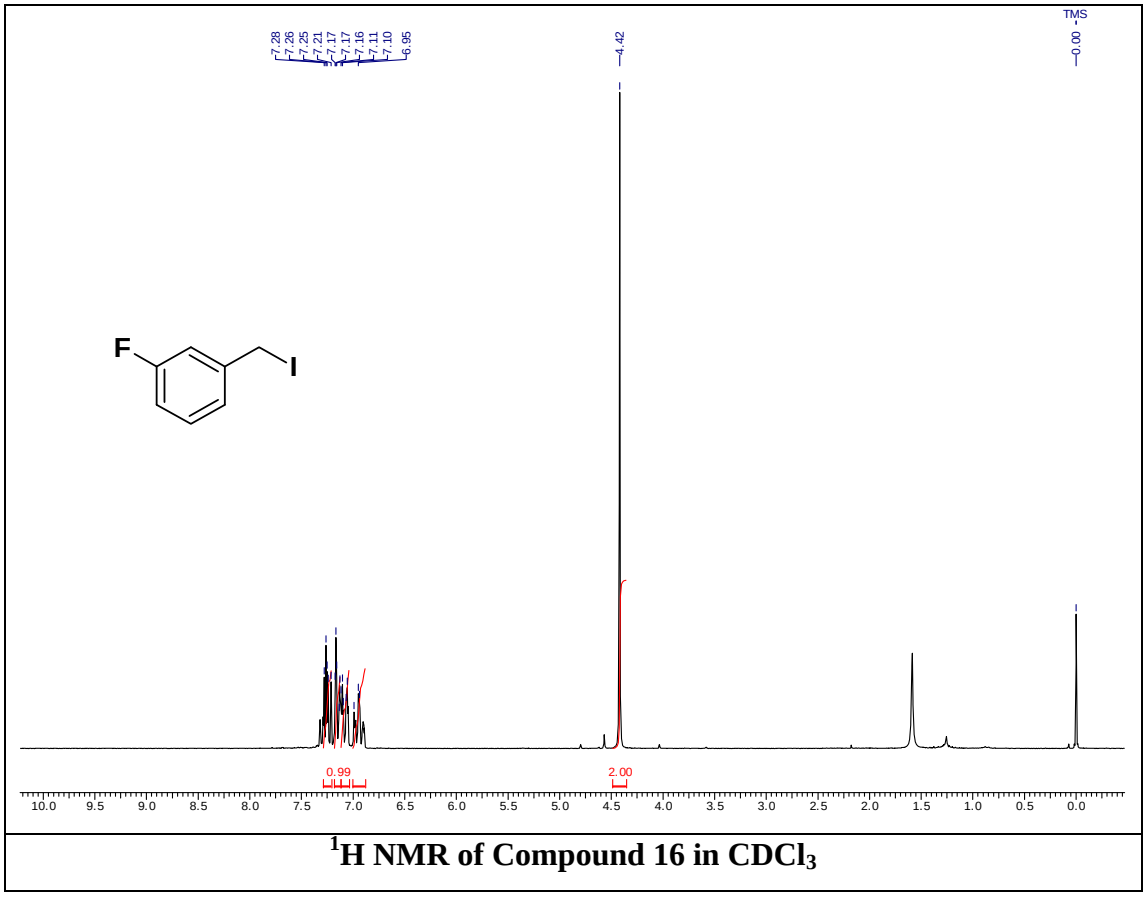
^{13}C NMR of Compound 13 in $CDCl_3$



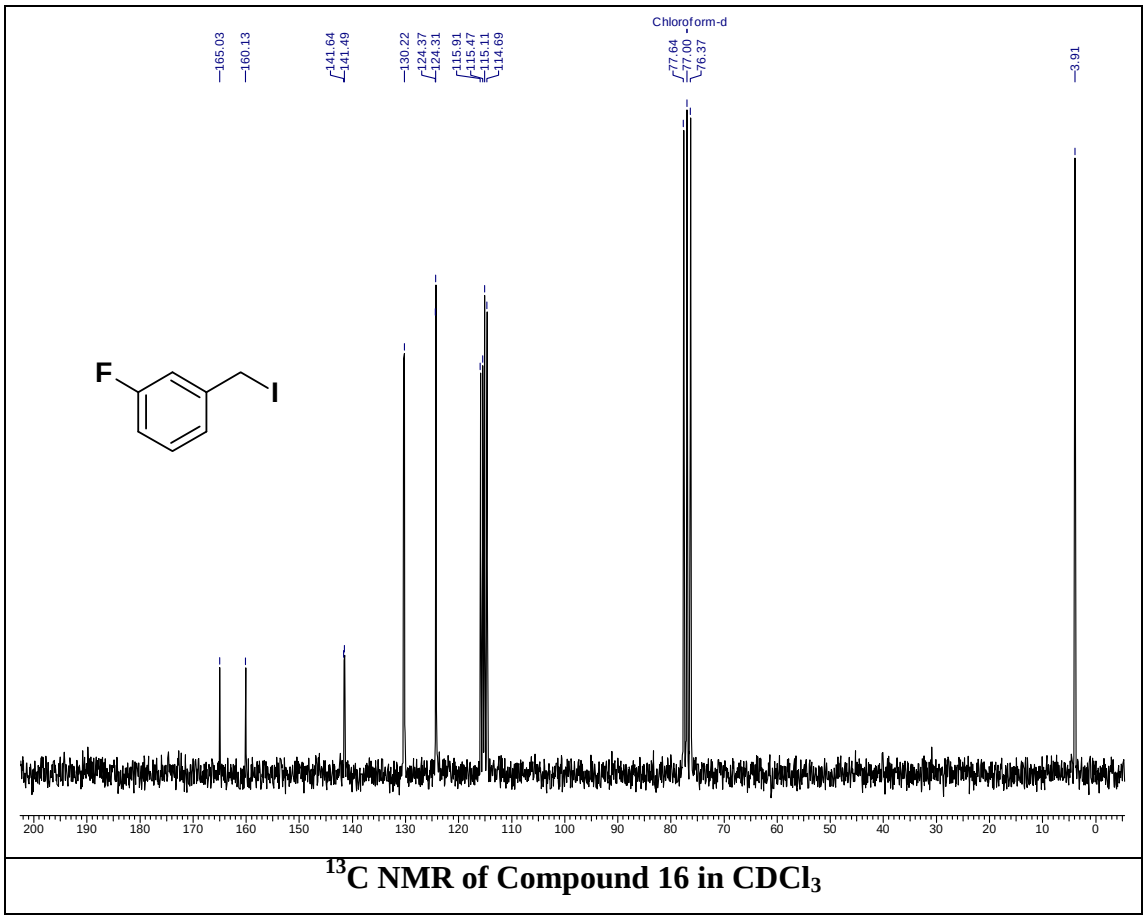
^{1}H NMR of Compound 14 in $CDCl_3$



^{13}C NMR of Compound 14 in $CDCl_3$



^{1}H NMR of Compound 16 in $CDCl_3$



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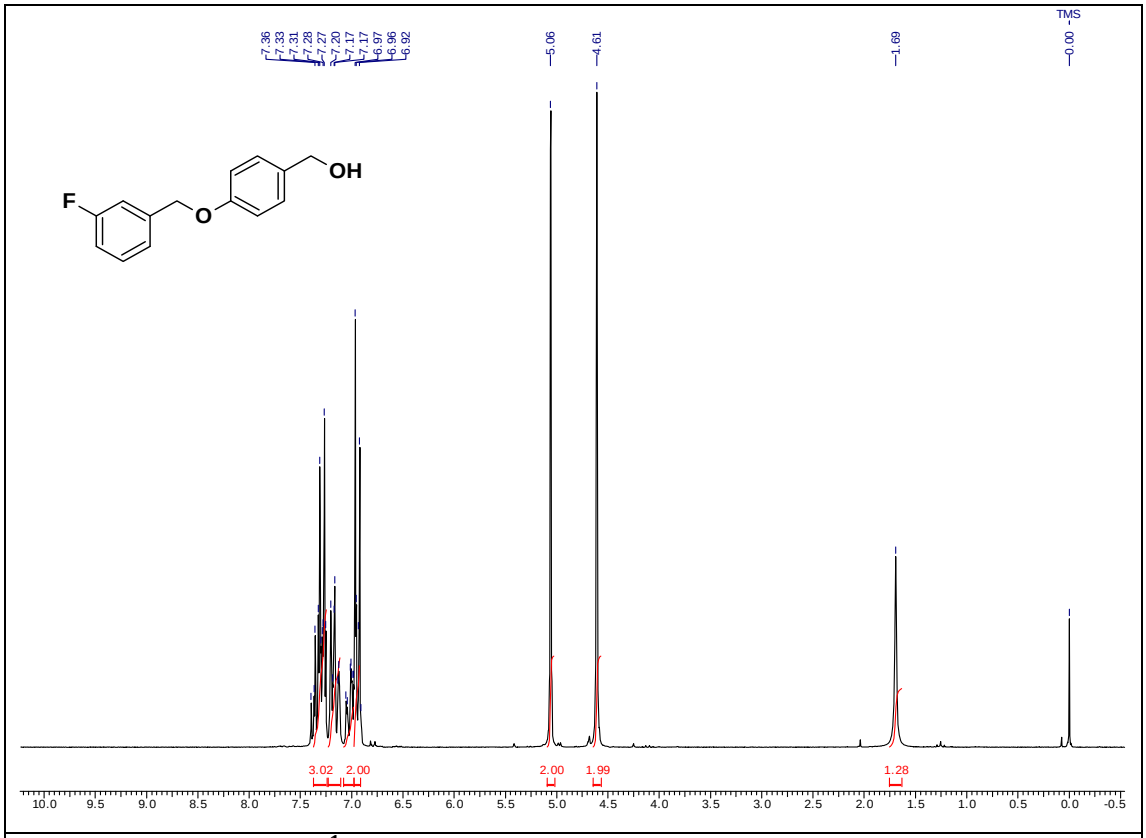
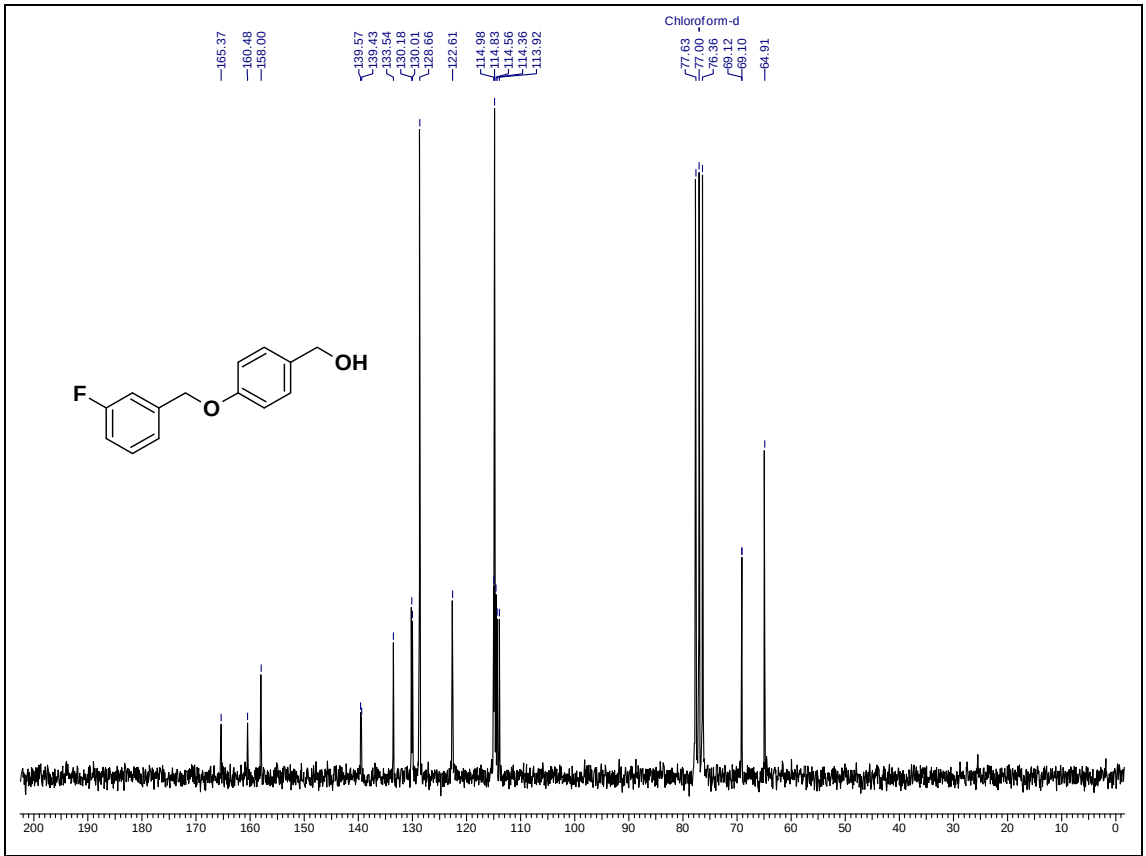
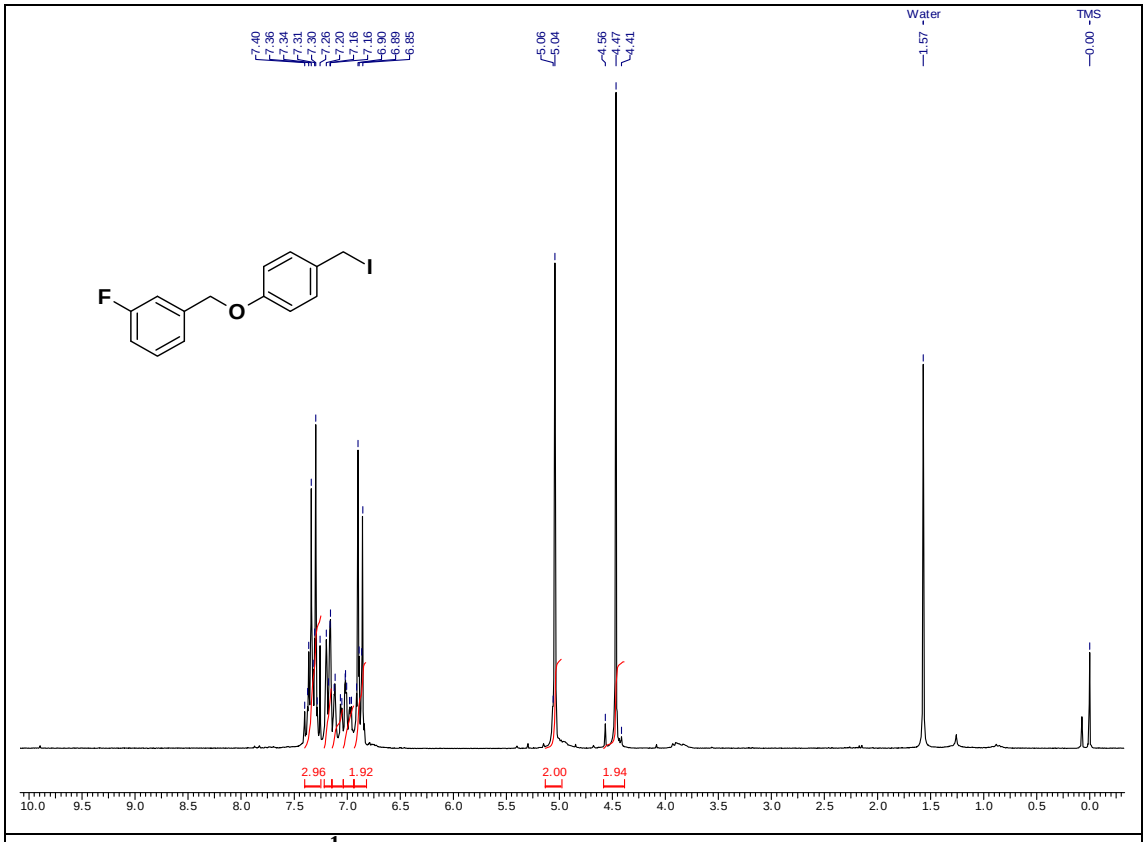


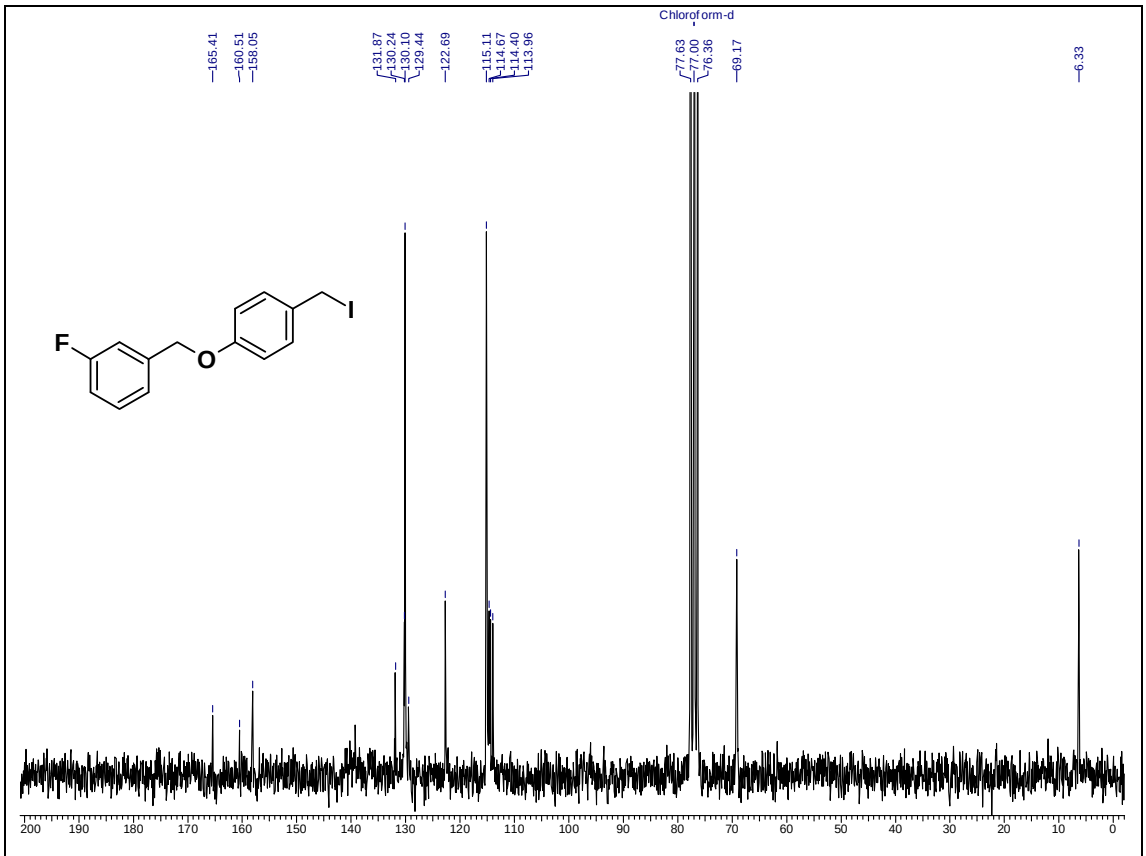
^{1}H NMR of Compound 17 in $CDCl_3$



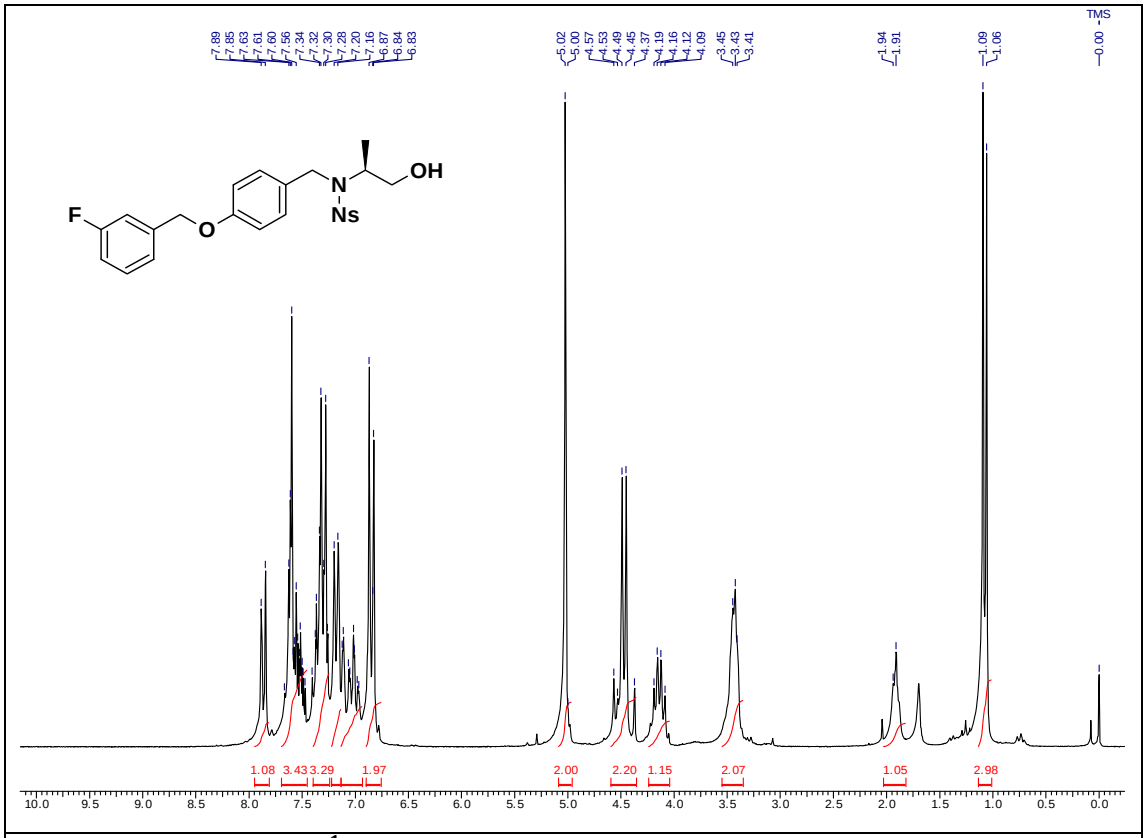
^{13}C NMR of Compound 17 in $CDCl_3$



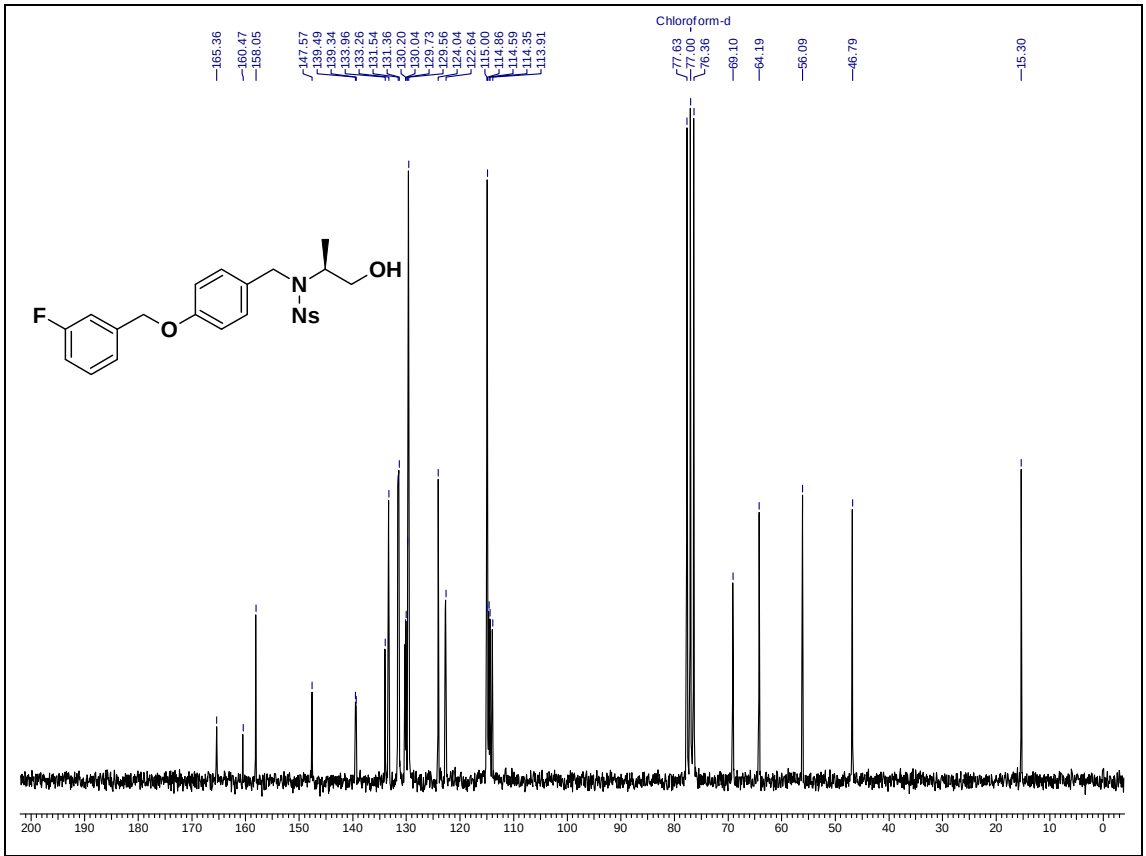
^{1}H NMR of Compound 18 in $CDCl_3$



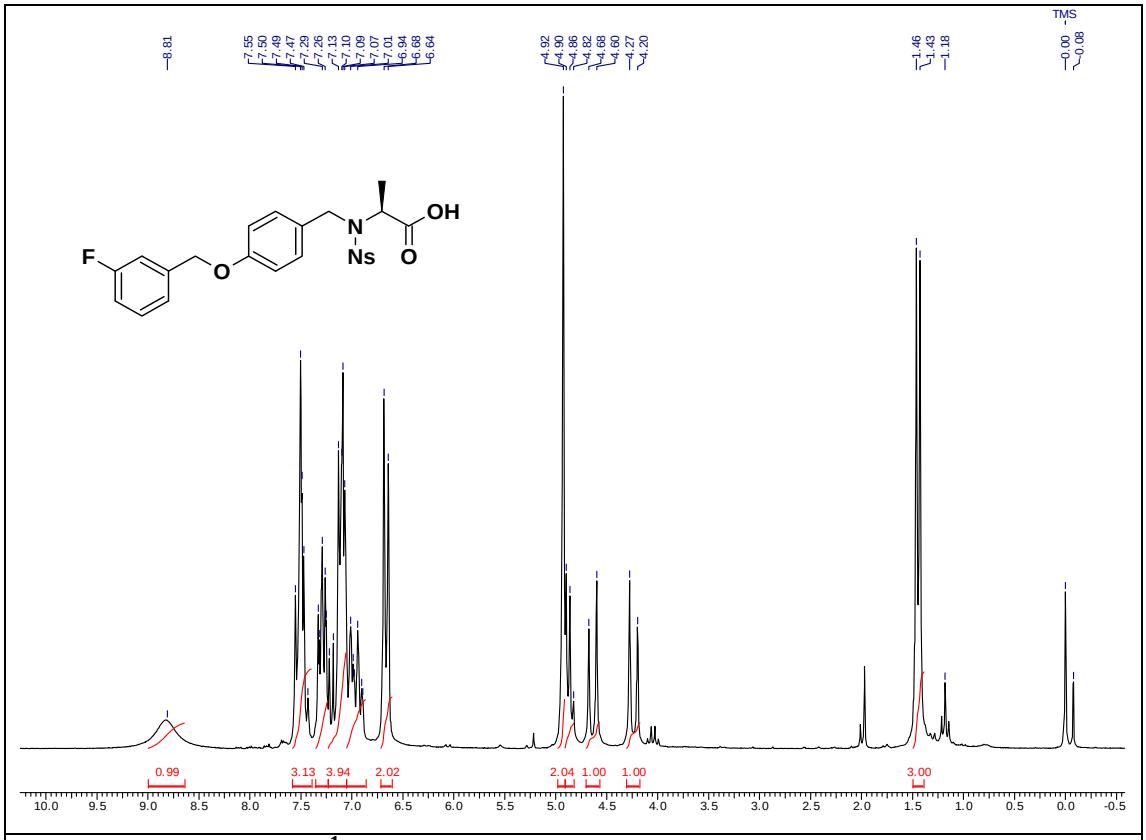
^{13}C NMR of Compound 18 in $CDCl_3$



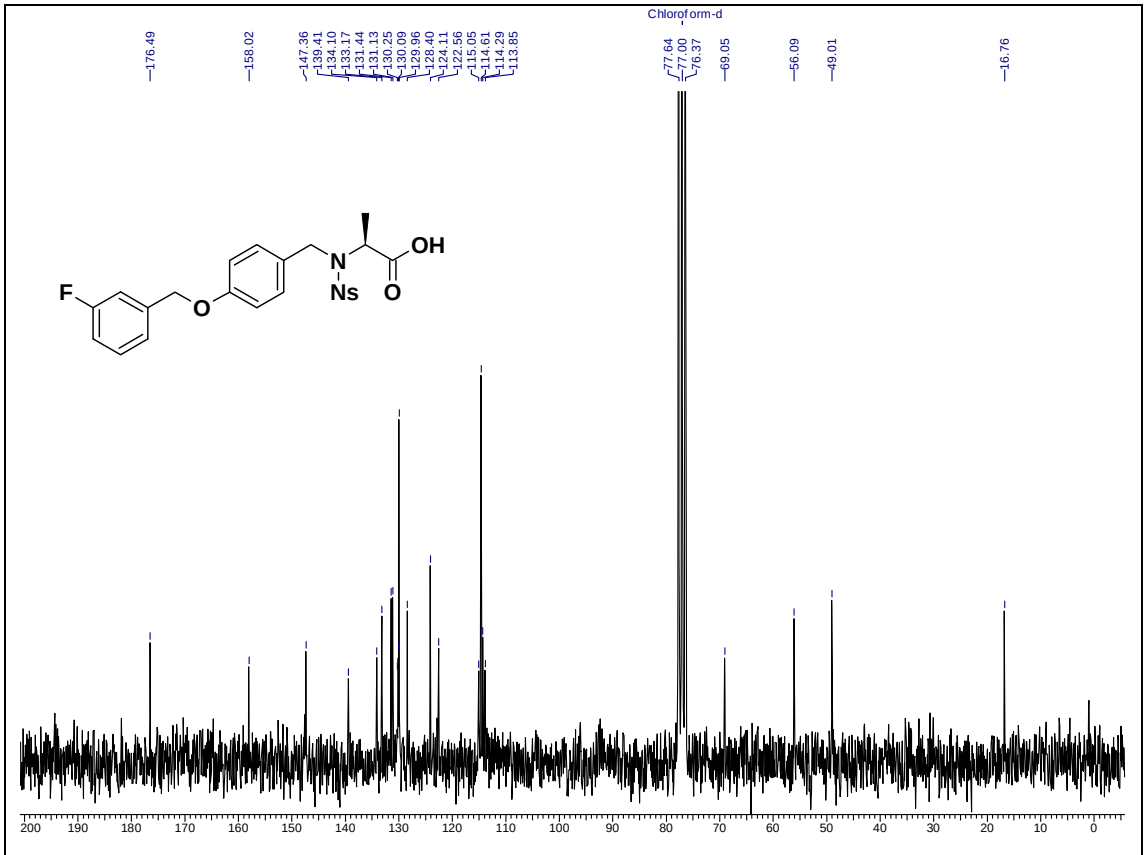
^{1}H NMR of Compound 19 in $CDCl_3$



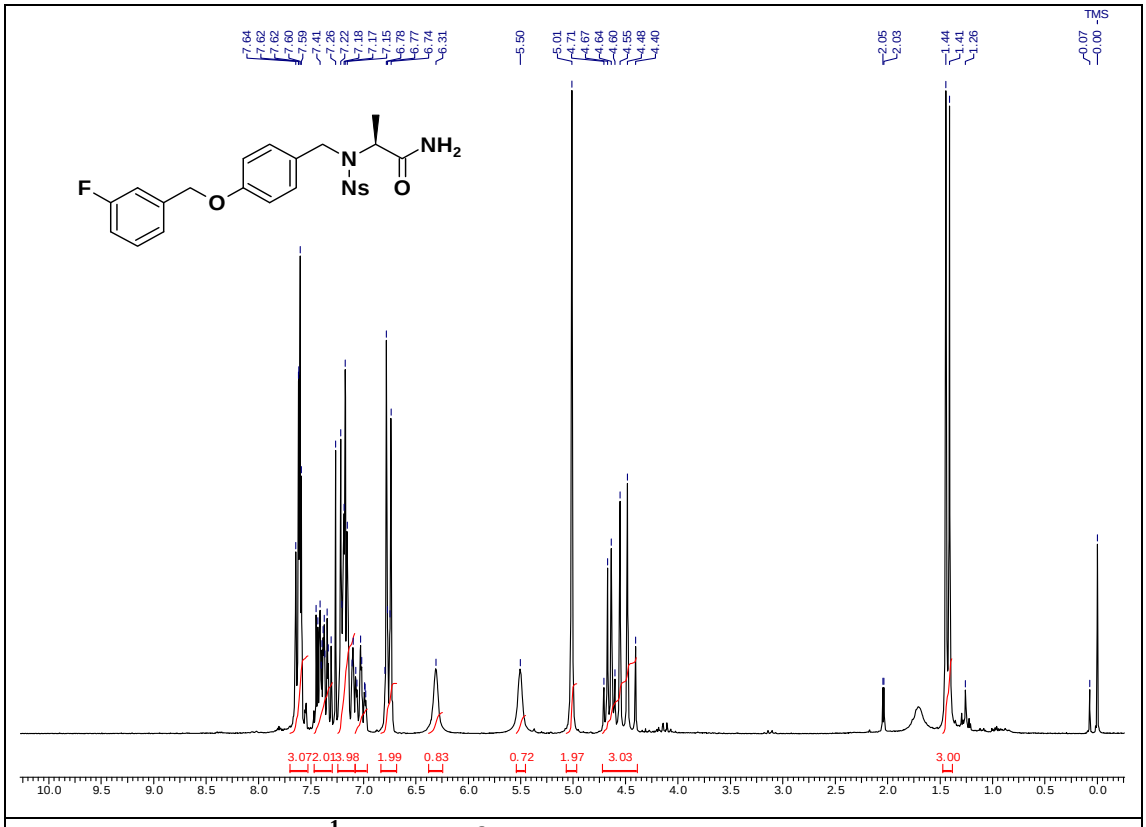
^{13}C NMR of Compound 19 in $CDCl_3$



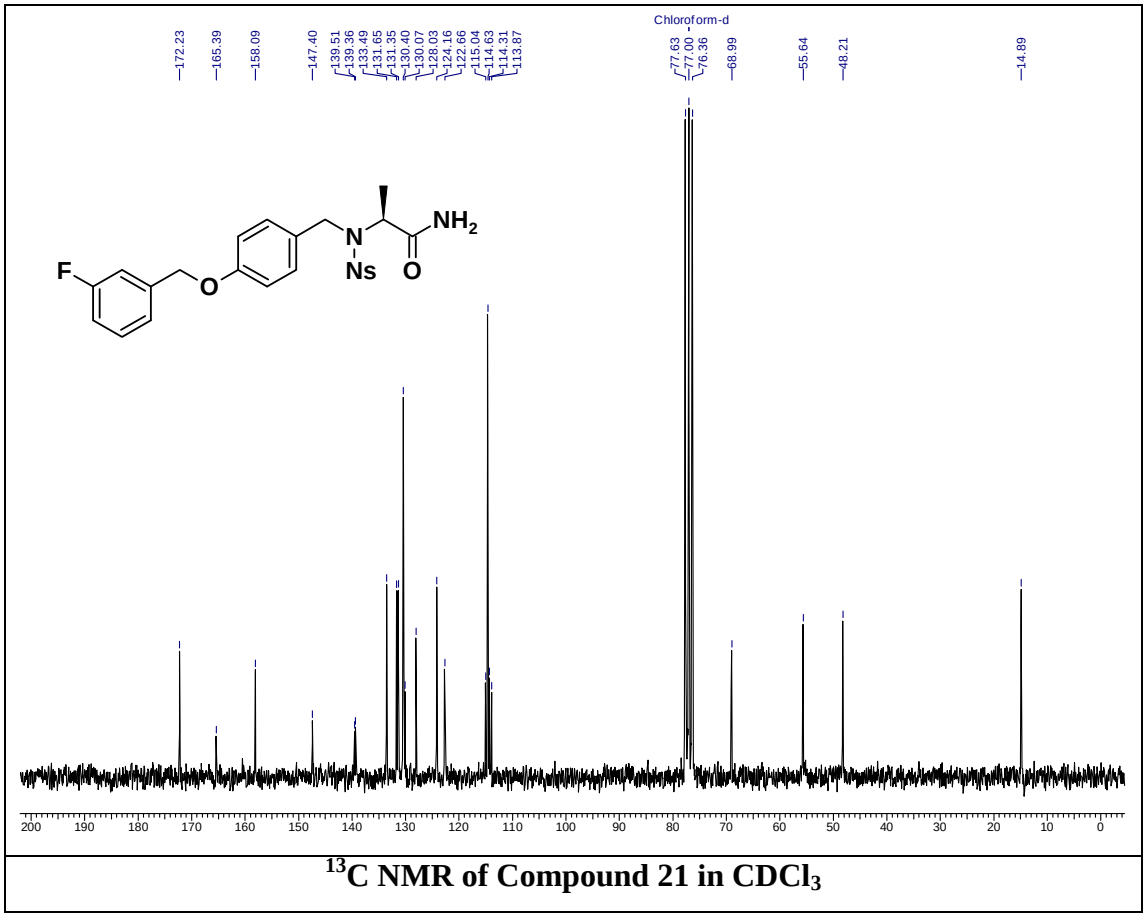
^{1}H NMR of Compound 20 in $CDCl_3$



^{13}C NMR of Compound 20 in $CDCl_3$



^{1}H NMR of Compound 21 in $CDCl_3$



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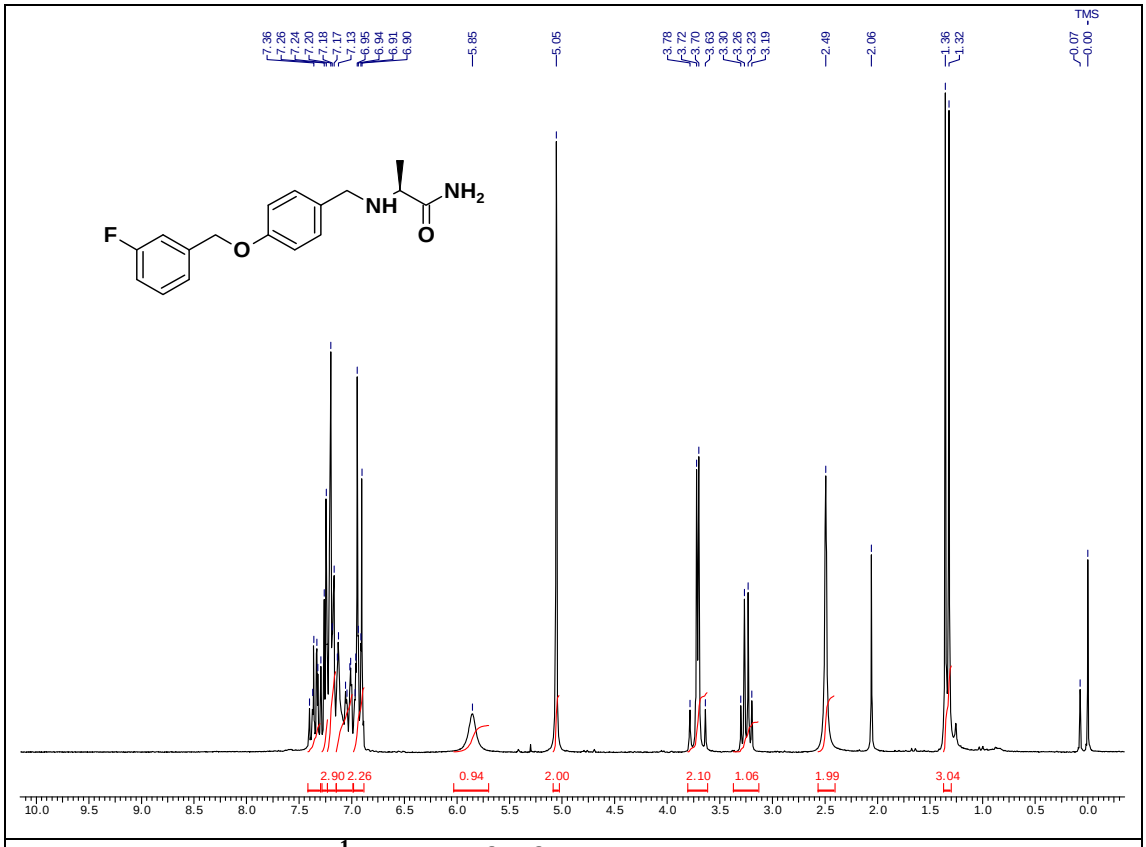
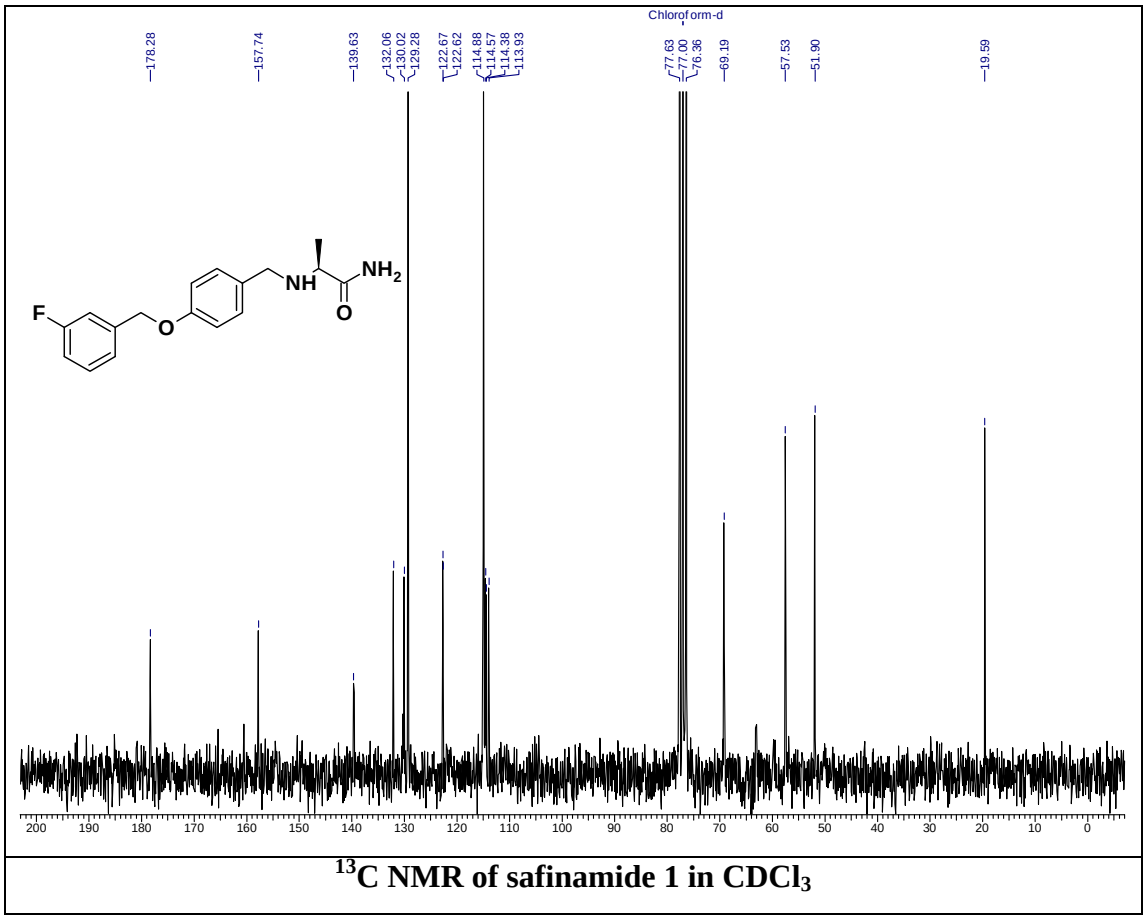
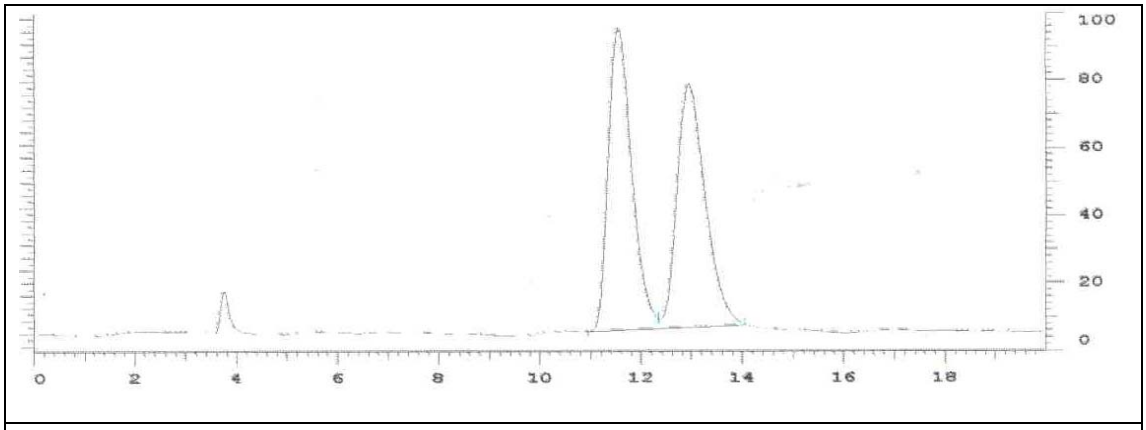


^{1}H NMR of safinamide 1 in $CDCl_3$



^{13}C NMR of safinamide 1 in $CDCl_3$

Chiral HPLC Analysis of Safinamide 1



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
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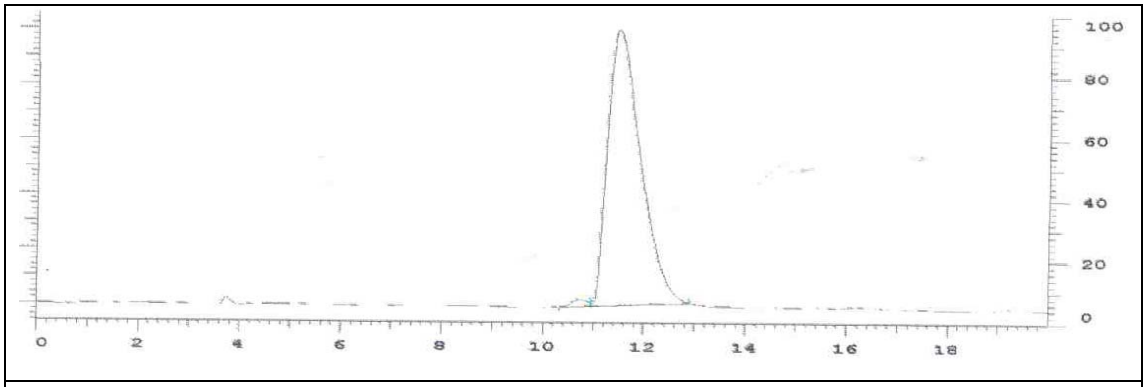
2	12.94	768228	49.822
Total		1541930	100.000



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	10.75	52607	1.147
2	11.49	4534575	98.853
Total		4587182	100.000

2.3.8. References

1. Neurological disorders: public health challenges, World Health Organization, Geneva, **2006**, pp 140.
2. Miyasaki, J. M.; Martin, W.; Suchowersky, O.; Weiner, W. J.; Lang, A. E. *Neurology* **2002**, 58, 11.
3. Schapira, A. H. V.; Stocchi, F.; Borgohain, R.; Onofrj, M.; Bhatt, M.; Lorenzana, P.; Lucini, V.; Giuliani, R.; Anand, R. *Eur. J. Neurol*. **2013**, *20*, 271.
4. (a) Salvati, P.; Caccia, C.; Melloni, P.; Restivo, A.; Sabido, DC.; Vallese, S. EP1524267, 2005; (b) Caccia, C.; La Porta, E.; Maestroni, S.; Melloni, P.; Sabido, DC.; Salvati, P. EP1534265, 2005; (c) Thaler, F.; Sabido, DC.; Farvelli, L.; Gagliardi, S.; Colombo, E.; Salvati, P. EP1535908, 2005.
5. (a) Chazot, P. L. *Curr. Opin. Invest. Drugs* **2001**, *2*, 809; (b) Marzo, A.; Dal Bo, L.; Ceppi Monti, N.; Crivelli, F.; Ismaili, S.; Caccia, C.; Cattaneo, C.; Fardello, R. G. *Pharmacol. Res.* **2004**, *50*, 77; (c) Stocchi, F.; Arnold, G.; Onofrj, M.; Kwiecinski, H.; Szczudlik, A.; Thomas, A.; Bonuccelli, U.; Van Dijk, A.; Cattaneo, C.; Sala, P.; Fariello, R. G. *Neurology* **2004**, *63*, 746.
6. Caccia, C.; Maj, R.; Calabresi, M.; Maestroni, S.; Faravelli, L.; Curatolo, L.; Salvati, P.; Fariello, R. G. *Neurology* **2006**, *67*, 18.
7. Pevarello, P.; Bonsignori, A.; Dostert, P.; Heidempergher, F.; Pinciroli, V.; Colombo, M.; McArthur, R. A.; Salvati, P.; Post, C.; Fariello, R. G.; Varasi, M. *J. Med. Chem.* **1998**, *41*, 579.
8. Barbanti, E.; Caccia, C.; Salvati, P.; Velardi, F.; Rufilli, T.; Bogogna, L. PCT Int. Appl., WO 2007147491A1, 2007.
9. Hoff, B. H.; Waagen, V.; Anthonsen, T. *Tetrahedron: Asymmetry* **1996**, 7, 3181.

Chapter-3

Asymmetric syntheses of EEHP, (*R*)-Phenampromide and (*R*)-Bepridil

3.1. SECTION A

Asymmetric synthesis of ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP), a key intermediate of PPAR agonists

3.1.1. Introduction

Peroxime proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily. They are lipid sensors activated by specific ligands which are mostly lipophilic small molecules.[1] There are three distinct subtypes PPARα, PPARγ and PPARδ which are encoded by different genes. PPARα and PPARγ are important regulators of lipid and carbohydrate metabolism and their agonists have shown therapeutic application for the treatment of diabetes and dyslipidemia.[2] As combined treatment with PPARγ and PPARα agonists has been identified to improve insulin resistance and lower triglyceride levels. Several companies have been actively pursuing research on PPAR α/γ dual-acting compounds.[3] Some of the representative PPAR α/γ dual agonists reported so far include ragaglitazar[4], tesaglitazar[5], muraglitazar[6] and naveglitazar[7] (Fig.1).

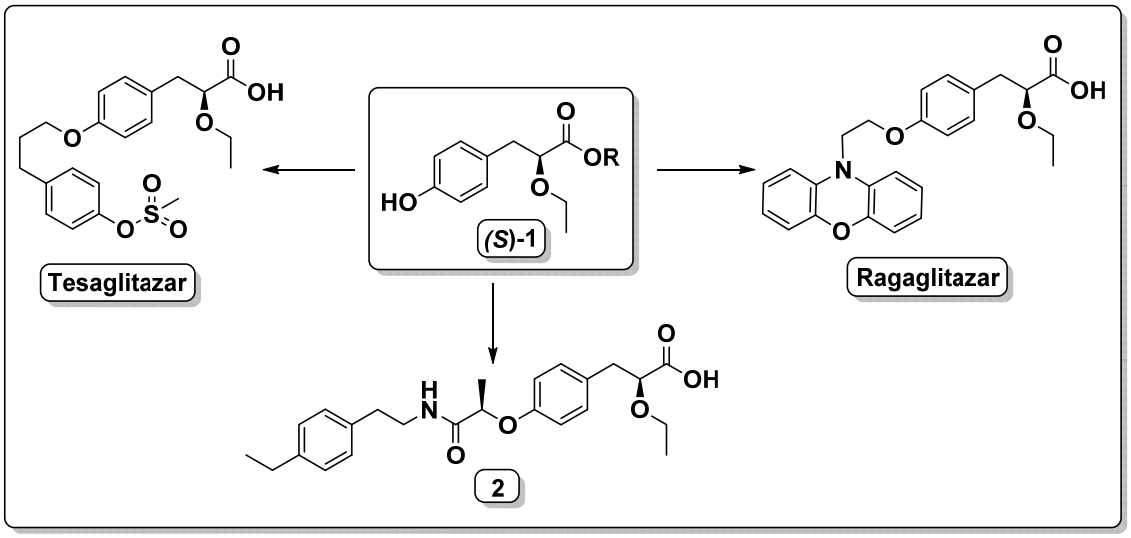


Figure 1. Examples of PPAR agonists based on EEHP intermediate

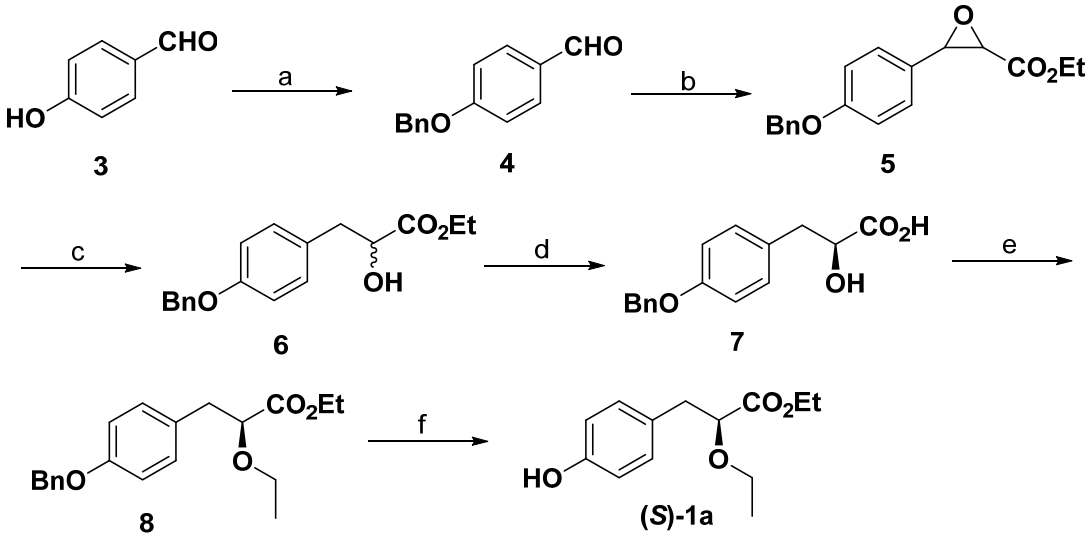
Ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP),[8] is an important pharmaceutical intermediate, which is an integral part of many of these PPAR α/γ dual agonists. Although, ragaglitazar and tesaglitazar were discontinued in their late clinical trials due to the side effects such as rodent bladder tumors and decreased glomerular filtration respectively, but still EEHP has been serving as a useful pharmaceutical intermediate for the development of more reliable and safer generation of PPAR agonist. In addition these derivatives found application in photosensitive materials, sweetening agents, treatment of certain eating disorders, etc.

3.1.2. Review of Literature

Due to its significant application in the pharmaceutical industries, several approaches have been reported in the literature for the synthesis of EEHP **(*S*)-1**. A few interesting and recent syntheses of EEHP **(*S*)-1** are described below.

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

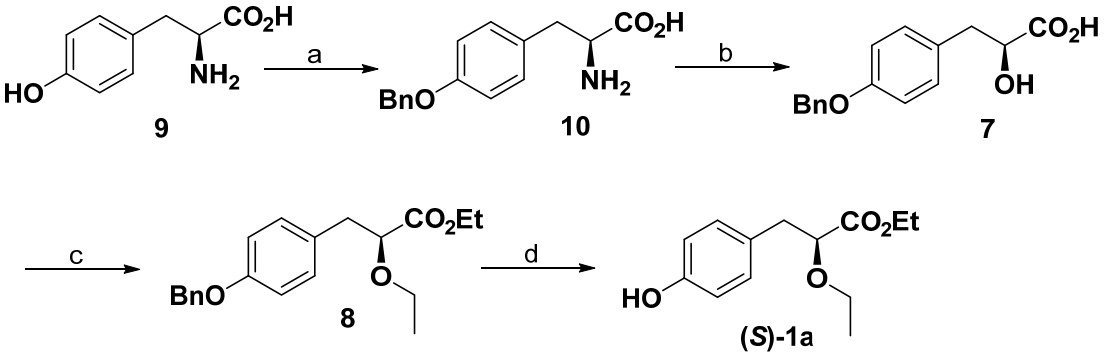
Siripragada *et al.* have reported different methods for the synthesis of **(*S*)-1**. The first approach was based on resolution using chiral amines (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) benzyl bromide, K_2CO_3, acetone, 93%; (b) methylchloroacetate, sodium methoxide, MeOH, 90%; (c) Ni (cat), H_2 (30-40 psi), 1,4-dioxane, 80%; (d) NaOH then (*S*)-phenylglycinol, 90%; (e) diethylsulfate, KOH, 1,4-dioxane, H_2O, 80%; (f) Pd/C (cat), H_2 (50-60 psi), 1,4-dioxane, 97%.

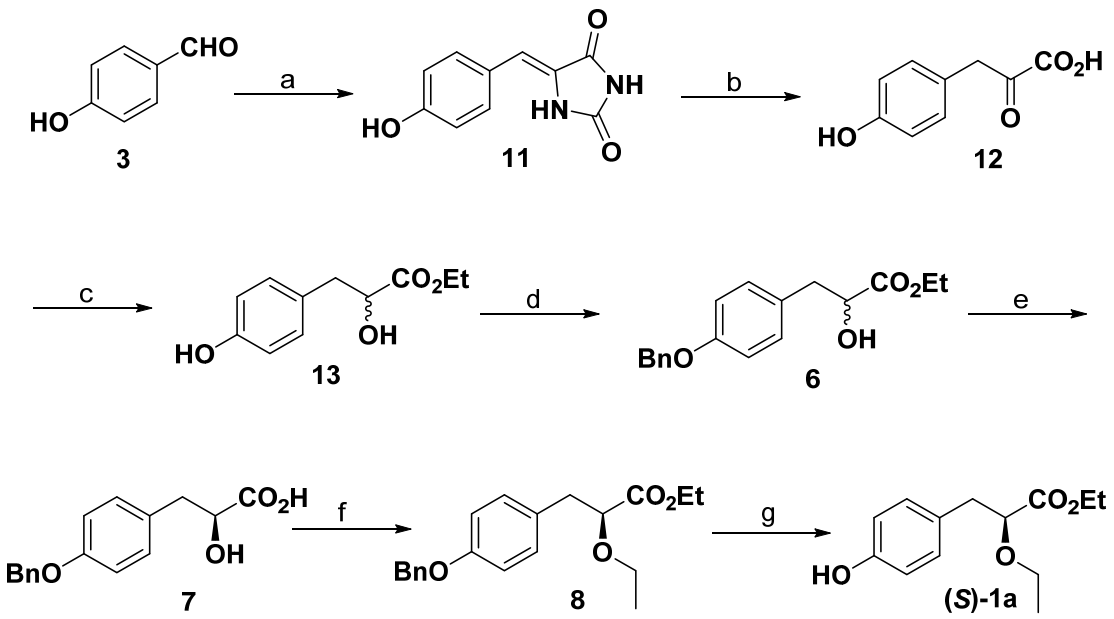
Reaction between protected aldehyde **4** with methylchloroacetate, in the presence of a base gave glycedic ester **5**. The glycedic ester **5** was opened up with Raney-Ni to give the racemic hydroxy ester **6**. Hydrolysis of the ester **6** followed by resolution using (*S*)-phenylglycinol afforded the optically active hydroxy acid **7**, which on alkylation using diethylsuphate afforded the compound **8**. Finally, debenzylation of the compound **8** furnished the targeted compound **(*S*)-1a**.

The same group has developed another approach (chiral pool) starting from L-tyrosine **9** (Scheme 2). L-tyrosine **9** on selective benzylation followed by diazotization under acidic condition provided hydroxy acid **7**. Alkylation of acid **7** using diethylsulphate followed by debenzylation afforded the final product **(*S*)-1a**.



Scheme 2. *Reagents and conditions*: (a) benzyl bromide, 2N NaOH, $CuSO_4$, MeOH, H_2O, 66%; (b) $NaNO_2$, dil H_2SO_4, THF, H_2O, 48%; (c) diethylsulfate, K_2CO_3, toluene, 65%; (d) Pd/C (cat), H_2 (50-60 psi), ethyl acetate, 95%.

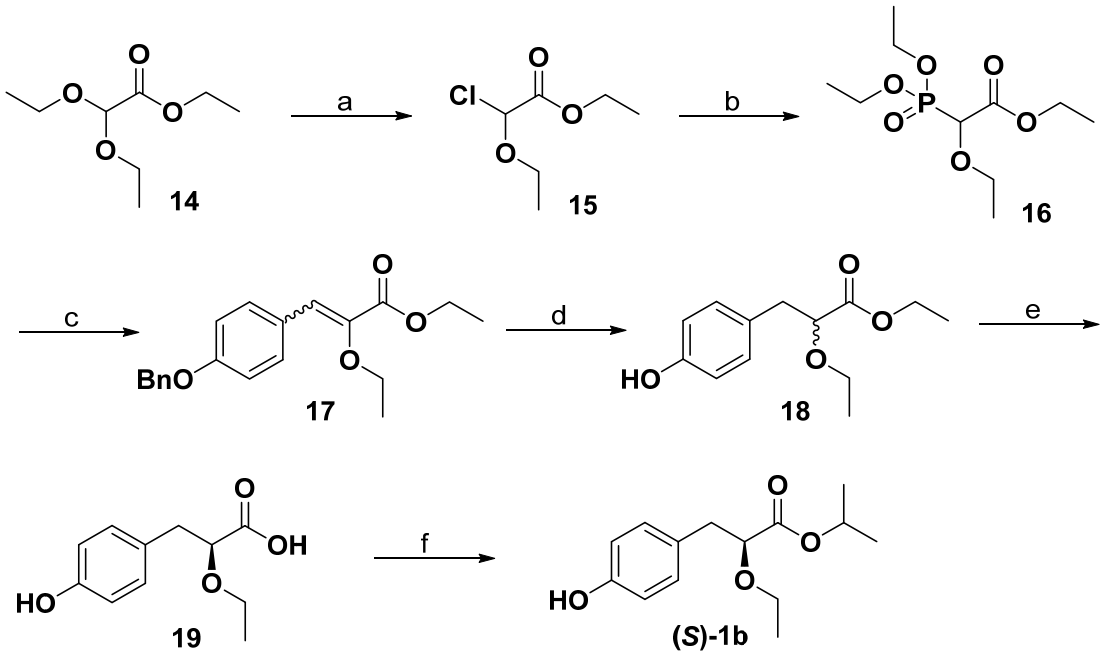
In another approach, 4-hydroxybenzaldehyde was used as a starting material. 4-Hydroxybenzaldehyde on treatment with hydantoin afforded the unsaturated intermediate **11**, which on hydrolysis gave the pyruvic acid derivative **12**. The acid derivative **12** on reduction followed by treatment with ethanolic H_2SO_4 provided racemic hydroxy ester **13**. Selective benzylation of ester **13** followed by resolution with chiral amine such as (*R*)-methylbenzylamine furnished optically pure hydroxy acid **7**. Esterification of acid **7** followed by debenzylation gave the required **(*S*)-1a** derivative (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) hydantoin, piperidine, 88%; (b) 20% NaOH, 65%; (c) Pd/C (cat), H_2 (60 psi), ethyl acetate then 5% ethanolic H_2SO_4, 69%; (d) benzyl chloride, K_2CO_3, DMF, 76%; (e) 10% NaOH then (*R*)-methylbenzylamine, ethyl acetate, 72%; (f) ethyl iodide, NaH, DMF, 98%; (g) Pd/C (cat), H_2 (50-60 psi), THF, 97%.

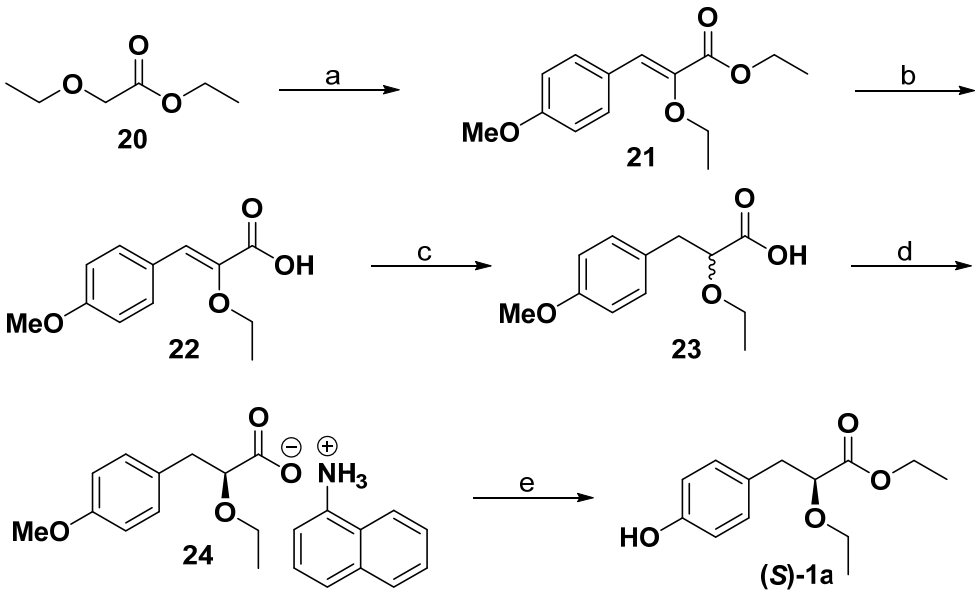
Deussen *et al.* (2003)[10]

Deussen *et al.* reported a biocatalytic approach for the synthesis of **(*S*)-1**, starting from commercially available 2,2-diethoxyacetate **14** (Scheme 4). Compound **14** on chlorination followed by heating with triethylphosphite gave triethyl 2-ethoxyphosphonoacetate **16.** Compound **16** was reacted with 4-benzyloxybenzaldehyde under Horner-Emmons-Wadsworth reaction condition to give unsaturated derivative **17**. Hydrogenation of **17** followed by enantioselective hydrolysis using an enzyme *Aspergillus oryzae* leads to the required product **(*S*)-1b**.



Scheme 4. *Reagents and conditions*: (a) acetyl chloride, I_2 (cat); (b) triethylphosphite, 96%; (c) 4-benzyloxybenzaldehyde, *t*-BuOK, toluene 84%; (d) Pd/C (cat), H_2 (2-6 bar), EtOH, AcOH, 96%; (e) *Aspergillus oryzae*, 44%; (f) IPA, $SOCl_2$, 88%.

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

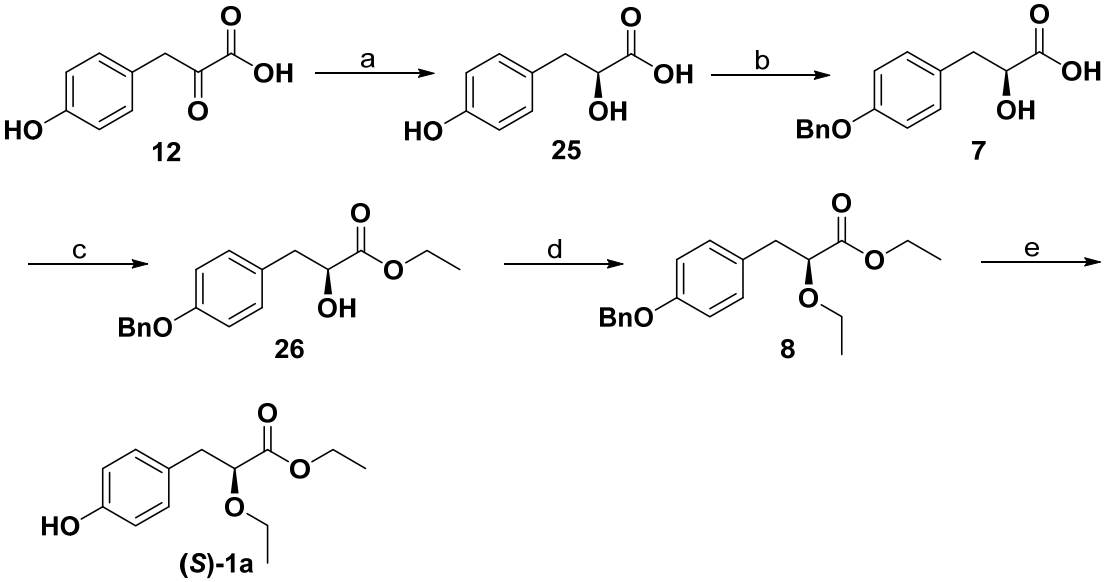


Scheme 5. *Reagents and conditions*: (a) 4-methoxybenzaldehyde, NaOEt, $(EtO)_2CO$, EtOH, 80%; (b) NaOH then HCl, 81%; (c) Pd/C (cat), H_2 (4 bar), isopropyl acetate, 85%; (d) (*S*)-1-(1-napthyl)ethylamine, isopropyl acetate, 38%; (e) (i) NaOH, OctSH, NMP; (ii) 12M HCl, EtOH, 66%.

Linderberg *et al.* started their synthesis with ethyl ethoxyacetate (EEA) **20**. Condensation between EEA **20** and anisaldehyde in THF at -10 °C using *t*-BuOK as a base gave unsaturated ester **21**. Ester hydrolysis followed by hydrogenation using H_2/Pd-C furnished the racemic acid intermediate **23**. Further, resolution of racemic acid **23** with (*S*)-1-(1-napthyl)ethylamine followed by demethylation and esterification afforded the target molecule **(*S*)-1a** (Scheme 5).

Aikins *et al.* (2005)[12]

Aikins *et al.* reported an asymmetric route towards the synthesis of **(*S*)-1**. Thus, *p*-hydroxyphenyl pyruvic acid was reduced with (+)-DIP-Cl to afford **25**. Benzylation of phenolic-OH followed by esterification of compound **7** gave ester **26**. Alkylation of ester **26**, followed by debenzylation provided the target compound **(*S*)-1a** (Scheme 6).

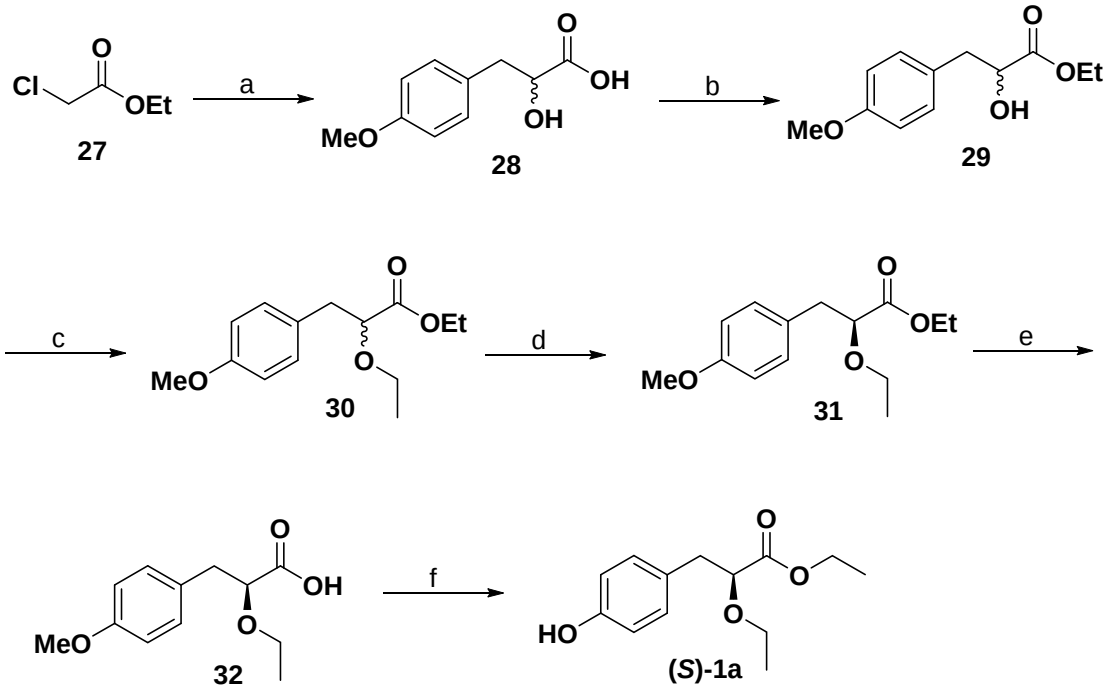


Scheme 6. *Reagents and conditions*: (a) (+)-DIP-Cl, THF/Et_3N, 92%; (b) (i) benzyl chloride, K_2CO_3, EtOH; (ii) NaOH (iii) isopropanol, crystallization, 76%; (c) H_2SO_4 (cat), EtOH; (d) ethyl iodide, sodium *tert*-amylate, $PhCH_3$/DMF, 99%; (e) Pd/C (cat), H_2 (50 psi), EtOH, quant.

Brenna *et al.* (2009)[13]

Another approach for the synthesis of **(*S*)-1** using biocatalysis was reported by Brenna *et al* (Scheme 7). Darzens condensation of anisaldehyde with ethyl chloroacetate **27** gave the crude glycidic ester which on catalytic hydrogenolysis followed by

hydrolysis afforded acid **28**. Esterification of acid **28** followed by *O*-alkylation provided racemic intermediate **30**. Further, enzyme mediated resolution of **30** was performed using α-chymotrypsin to afford compound **31**. Ester hydrolysis of **31** followed by demethylation and esterification protocols provided the required product **(*S*)-1a**.



Scheme 7. *Reagents and conditions*: (a) (i) 4-methoxybenzaldehyde, *t*-BuOK, toluene; (ii) Pd/C, H_2 (70 psi), EtOH then NaOH, EtOH/H_2O 65%; (b) H_2SO_4 (cat), EtOH, 96%; (c) Ethyl bromide, NaH, THF, 78%; (d) α-chymotrypsin, H_2O/CH_3CN (95:5), buffer pH 7.8, 39%; (e) NaOH, MeOH/H_2O, 96%; (f) (i) EtSNa, DMF; (ii) HCl (cat), EtOH, 91%.

3.1.3. Present Work

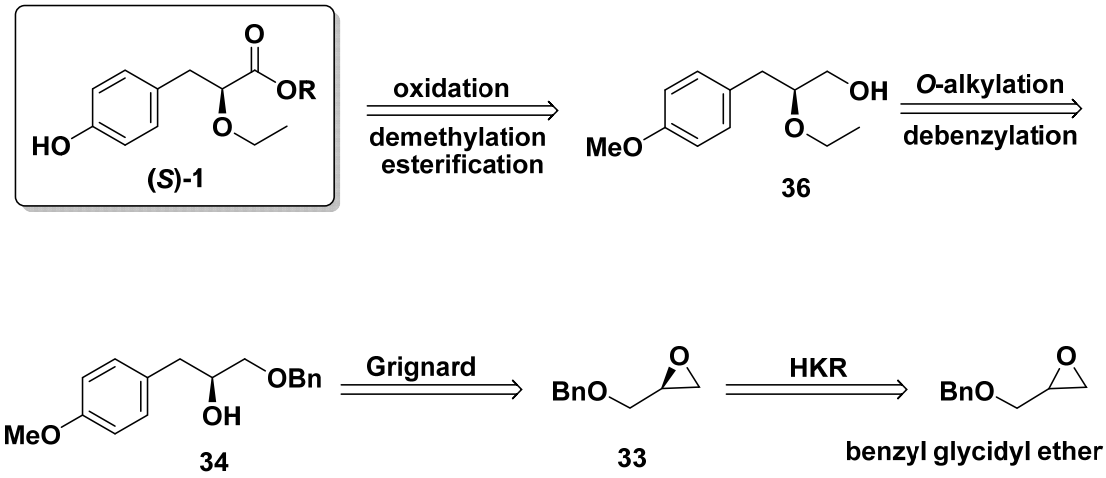
Objective

As EEHP **(*S*)-1** is an essential component in many drugs, it has attracted a great deal of interest among synthetic organic chemists. As part of our research programme aimed at developing enantioselective syntheses of bioactive molecules[14] we became interested in devising an efficient route to ***(S)*-1** and the present study describes our

endeavors towards the synthesis of ***(S)*-1** from commercially available benzyl glycidyl ether employing Jacobsen's hydrolytic kinetic resolution as a key step and source of chirality.

3.1.4. Results and Discussion

Our approach for the synthesis of compound **(*S*)-1** was envisioned via the retrosynthetic route as outlined in Scheme 8. As shown in Scheme 8, we envisaged that the secondary alcohol **34** can be visualized as a key intermediate for the synthesis which can be elaborated to primary hydroxy derivative **36** using simple *O*-alkylation and debenzylation reactions.

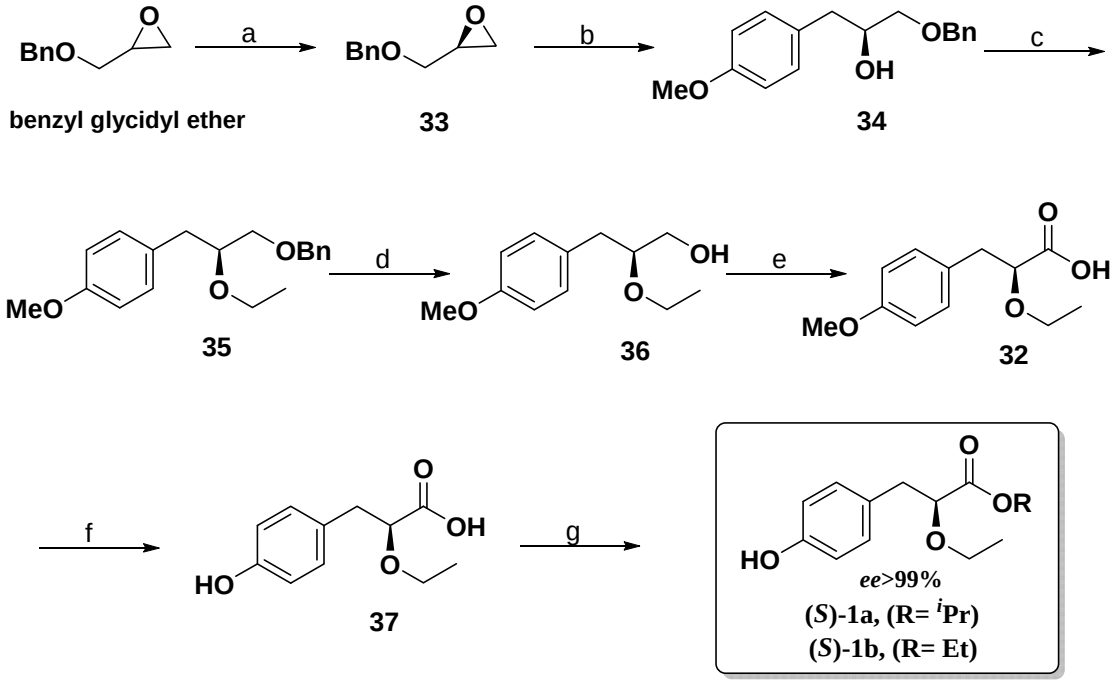


Scheme 8. Retrosynthetic analysis of (*S*)-**1**

Further, compound **36** can be transformed into the target molecule **(*S*)-1** *via* oxidation followed by demethylation and esterification protocols. The key intermediate **34** in turn can be obtained from the (*S*)-epoxide **33**. The chiral epoxide **33** in turn can be easily obtained from benzyl glycidyl ether with high enantiopurity using Jacobsen's HKR method.

Accordingly, our synthesis began with the commercially available *rac*-benzyl glycidyl ether. Firstly, *rac*-benzyl glycidyl ether was subjected to hydrolytic kinetic resolution conditions as described in foregoing chapters to get enantiomerically pure epoxide **33** in 47% yield and >99% ee (Scheme 9). Subsequently, the regioselective ring opening of (*S*)-epoxide **33** was carried out with 4-methoxyphenylmagnesium bromide in presence of catalytic amount of CuI in anhydrous THF at -20 ºC to provide secondary

alcohol **34** in 83 % yield. Appearance of characteristic peaks (doublets) at δ 2.76 (2H), 6.86 (2H), 7.10 (2H) and a singlet at δ 3.79 in ^{1}H NMR and a peak at δ 55.32 (OCH_3) in ^{13}C NMR indicated the formation of compound **34**.



Scheme 9. *Reagents and conditions*: (a) (*R, R*) Salen Co (III)-A, 0 ºC-rt, 24 h; (b) 4-methoxyphenylmagnesium bromide, CuI, THF, -20 ºC-rt, 3 h, 83%; (c) ethyl iodide, NaH, DMF, 0 ºC, 1 h, 93%; (d) $TiCl_4$, DCM, 0 ºC-rt, 5 h, 88%; (e) $NaClO_2$, NaOCl, TEMPO (cat), phosphate buffer, CH_3CN, 35 ºC, 6 h, 86%; (f) EtSH, NaH, DMF, 130 ºC, 48 h; (g) HCl (cat), EtOH, reflux, DS method, 3 h, 90% (R= Et) or IPA, $SOCl_2$, 60 ºC, 2 h, 85% (R= ^{i}Pr).

The *O*-alkylation of compound **34** was considered to be important in this sequence, because racemization occurred at this stage in reported methods and expensive alkylating reagents were used to avoid racemization. However, *O*-alkylation on our substrate went smoothly using simple condition employing ethyl iodide and sodium hydride in anhydrous DMF at 0 ºC to give ethylated derivative **35** in 93% yield without any racemization. Appearance of a triplet at δ 1.14 (3H) in ^{1}H NMR and a peak at δ 14.9 (CH_3) in ^{13}C NMR showed the formation of compound **35**. Further, debenzylation of compound **35**, followed by oxidation with sodium chlorite catalyzed by TEMPO and bleach in an acetonitrile-phosphate buffer (pH 6.8) afforded the acid **32** in 76% yield (two steps). Appearance of characteristic peak at δ 176.3 (CO) in ^{13}C

NMR and m/z peak at 247 $(M+Na)^+$ in mass spectrum confirmed the formation of acid **32**. Finally, demethylation followed by esterification using standard protocols afforded the target compounds **(*S*)-1a** & **(*S*)-1b** in excellent enantioselectivity (>99% ee) without any additional crystallization (which is often require to get high ee in many reported methods). The structure of **(*S*)-1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic analysis. The enantiomeric purity of the final product was determined by chiral HPLC analysis.

3.1.5. Conclusion

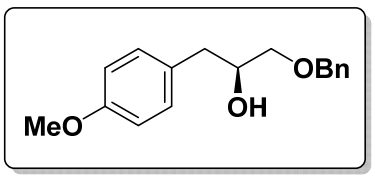
In conclusion, we have developed a concise and highly enantioselective synthesis of Ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP) starting from commercially available benzyl glycidyl ether. High enantiopurity (>99%) has been achieved without any racemization in the *O*-alkylation step. This simple protocol may find application in the generation of valuable PPAR agonists.

3.1.6. Experimental

1) (*S*)-2-(benzyloxymethyl) oxirane 33

The preparation and characterization of chiral epoxide **33** is depicted in Chapter 2 section A.

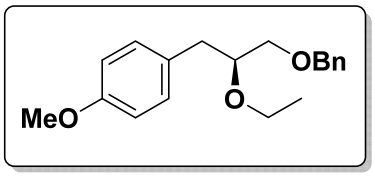
2) (*S*)-1-(benzyloxy)-3-(4-methoxyphenyl)propan-2-ol 34



To a pre cooled (-20 ºC) solution of epoxide **33** (4.5 g, 27.4 mmol) and CuI (0.1 g) in dry THF (30 mL) was added 4-methoxyphenylmagnesium bromide (12 mL, 54.8 mmol) in THF dropwise for about one hour. Subsequently, the reaction mixture was allowed to attain ambient temperature and continued the stirring for additional 3 h. After completion of the reaction (indicated by TLC), aqueous NH_4Cl was added, after which the reaction mixture was filtered, and washed with ethyl acetate. The solvent was removed under reduced pressure and the crude product was subjected to column

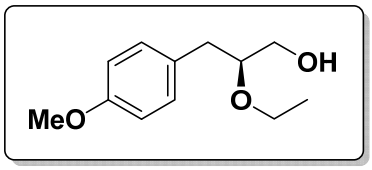
chromatography (silica gel, petroleum ether/acetone, 95:5) to yield **34** as colorless oil. (6.1g; 83%); $[\alpha]_D^{25}$ = +11.3 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 3387, 3019, 2977, 2933,1612, 1496, 1454, 1370, 1296, 1216, 1104, 929, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 2.76 (d, *J* = 6.5 Hz, 2H), 3.43 (dd, *J* = 9.5, 6.8 Hz, 1H), 3.54 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.79 (s, 3H), 3.95-4.07 (m, 1H), 4.54 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.31-7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 158.2 (C), 138.0 (C), 138.2 (CH, 2 carbons), 129.8 (C), 128.4 (CH, 2 carbons), 127.7 (CH, 3 carbons), 113.9 (CH, 2 carbons), 73.5 (CH_2), 73.3 (CH_2), 71.5 (CH), 55.3 (CH_3), 38.9 (CH_2); Analysis: $C_{17}H_{20}NO_3$; Calcd: C, 74.97; H, 7.40; Found: C, 74.45; H, 7.78; MS: *m/z* 295 $[M+Na]^+$.

3) (*S*)-1-(3-(benzyloxy)-2-ethoxypropyl)-4-methoxybenzene 35



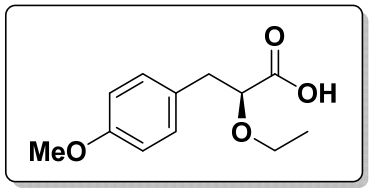
In a 50 mL two-necked round bottomed flask sodium hydride (0.9 g, 36.5 mmol) was taken under N_2 atmosphere, and washed with pet ether followed by addition of dry DMF (15 mL). It was cooled to 0 ºC, then compound **34** (4 g, 14.6 mmol) in dry DMF (3 mL) was added slowly. After stirring for 10 minutes, ethyl iodide (2.4 mL, 29.2 mmol) in 2 mL dry DMF was added slowly to the reaction mixture and again stirred at 0 ºC for 1 h. After completion of the reaction (indicated by TLC), reaction was quenched with ice-cold water, extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried, concentrated under reduced pressure and purified using column chromatography (silica gel, petroleum ether/acetone, 97:3) to yield **35** as colorless oil. (4.2 g; 93%); $[\alpha]_D^{25}$ = -3.9 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 3387, 3019, 2977, 2933,1612, 1496, 1454, 1370, 1296, 1216, 1104, 929, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.14 (t, *J* = 6.7 Hz, 3H), 2.76-2.81 (m, 2H), 3.42-3.50 (m, 3H), 3.55-3.63 (m, 2H), 3.79 (s, 3H), 4.54 (s, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.31-7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 157.3 (C), 137.7 (C), 130.1 (C), 129.7 (CH, 2 carbons), 127.6 (CH, 2 carbons), 127.0 (CH, 2 carbons), 126.8 (CH), 112.9 (CH, 2 carbons), 79.2 (CH), 72.6 (CH_2), 70.9 (CH_2), 64.8 (CH_2), 54.8 (CH_3), 36.6 (CH_2), 14.9 (CH_3); MS: *m/z* 323 $[M+Na]^+$.

4) (*S*)-2-ethoxy-3-(4-methoxyphenyl)propan-1-ol 36



To a solution of compound **35** (4 g, 15.3 mmol) in dry DCM (10 mL) at 0 ºC was added slowly $TiCl_4$ (2.5 mL, 23.0 mmol) under N_2 atmosphere. Subsequently, the reaction mixture was allowed to stir for 4 h at room temperature. The reaction was quenched with saturated NH_4Cl solution and the mixture was allowed to stand for 1 h. The organic layer was separated and washed with 0.1 N HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried, concentrated under reduced pressure and purified using column chromatography (silica gel, petroleum ether/acetone, 80:20) to yield **36** as colorless oil. (2.8 g; 88%); $[\alpha]_D^{25}$= +2.8 (*c* 1.8 $CHCl_3$); IR ($CHCl_3$): 3420, 3019, 1635, 1514, 1215, 1113, 928, 770, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.23 (t, *J* = 6.9 Hz, 3H), 2.64-2.82 (m, 2H), 3.47-3.61 (m, 5H), 3.80 (s, 3H), 3.91-3.95 (m, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, CDCl3): δ_C = 157.0 (C), 130.3 (CH, 2 carbons), 130.3 (C), 113.8 (CH, 2 carbons), 81.1 (CH), 65.2 (CH_2), 63.2 (CH_2), 55.2 (CH_3), 36.4 (CH_2), 15.5 (CH_3); MS: *m/z* 211 $[M+H]^+$.

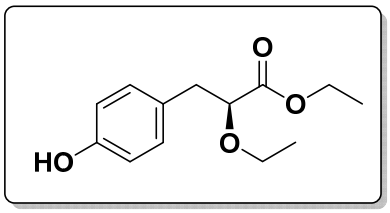
5) (*S*)-2-ethoxy-3-(4-methoxyphenyl)propanoic acid 32



A mixture of **36** (1 g, 4.4 mmol), TEMPO (0.034 g, 0.22 mmol), acetonitrile (20 mL), and sodium phosphate buffer (16 mL, 0.67 M, pH 6.7) was heated to 35 ºC. Then sodium chlorite (0.6 g dissolved in 2 mL water, 6.4 mmol) and dilute bleach (4-6 %, 2 mL diluted in 4 mL water) were added simultaneously over 1 h. The reaction mixture was stirred at 35 ºC until the reaction is complete (6 h, TLC), then cooled to room temperature. Water (20 mL) was added and the pH is adjusted to 8 with 2 N NaOH. The reaction is quenched by pouring into ice cold Na_2SO_3 solution maintained at <20 ºC. After stirring for 30 min at room temperature, ethyl acetate (20 mL) was added and continued the stirring for additional 15 min. The organic layer was separated and discarded. More ethyl acetate (20 mL) was added, and the aqueous layer was acidified

with 2N HCl to pH 3-4. The organic layer was separated, washed with water (2 x 15 mL), brine (20 mL) and concentrated under reduced pressure to afford the carboxylic acid **32** (0.85 g, 86%); $[\alpha]_D^{25}$= -15.3 (*c* 2.7 $CHCl_3$); IR ($CHCl_3$): 3412, 3020, 1614, 1425, 1216, 1110, 1031, 928, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.19 (t, *J* = 7.0 Hz 3H), 2.90-3.15 (m, 2H), 3.39-3.65 (m, 2H), 3.80 (s, 3H), 4.03-4.16 (m,1H), 6.87 (d, *J* = 8.5 Hz 2H), 7.20 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, CDCl3): δ_C = 176.3 (CO), 158.5 (C), 130.4 (CH, 2 carbons), 128.6 (C), 113.7 (CH, 2 carbons), 79.7 (CH), 66.7 (CH_2), 55.1 (CH_3), 37.8 (CH_2), 14.9 (CH_3); MS: *m/z* 247 $[M+Na]^+$

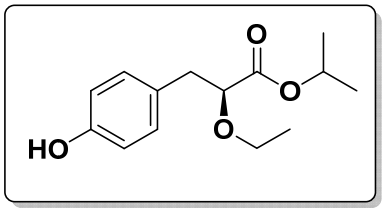
6) Ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (*S*)-1a



To a suspension of NaH (0.4 g, 60% disp. in min oil, 10 mmol) in DMF (5 mL) was added EtSH (0.75 g, 12.0 mmol) under N_2 atmosphere. After 30 min, a solution of acid **32** (0.44 g, 2.0 mmol) in DMF (5 mL) was added. After 48 h at 130 ºC, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (40 mL) and washed with CH_2Cl_2 (3 x 20 mL). The aqueous phase was acidified with HCl (1 M) and extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford demethylated product **37**. To a stirred solution of **37** in EtOH was added conc. HCl and the resulting mixture was heated to reflux for 3 h in a vessel well equipped with dean stark assembly for azeotropic removal of water formed in the reaction restoring the volume of ethanol. After completion of the reaction (Indicated by TLC), reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried, concentrated under reduced pressure and purified using column chromatography (silica gel, petroleum ether/ethyl acetate, 95:05) to afford **(*S*)-1a** (0.43 g; 90%); $[\alpha]_D^{25}$= -26.9 (*c* 0.4, $CHCl_3$), [lit.[13] $[\alpha]_D^{25}$= -21.3 (*c* 1.45, $CHCl_3$) for 93% ee]; ^1H NMR(200 MHz, $CDCl_3$): δ_H = 1.17 (t, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 2.90 (d, *J* = 7.0 Hz, 2H), 3.32- 3.44 (m, 1H), 3.53- 3.65 (m, 1H), 3.98 (t, *J* = 6.6 Hz, 1H), 4.15 (dd, *J* = 14.2, 7.0 Hz, 2H), 5.09 (bs, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, CDCl3): δ_C = 172.6 (CO), 154.3

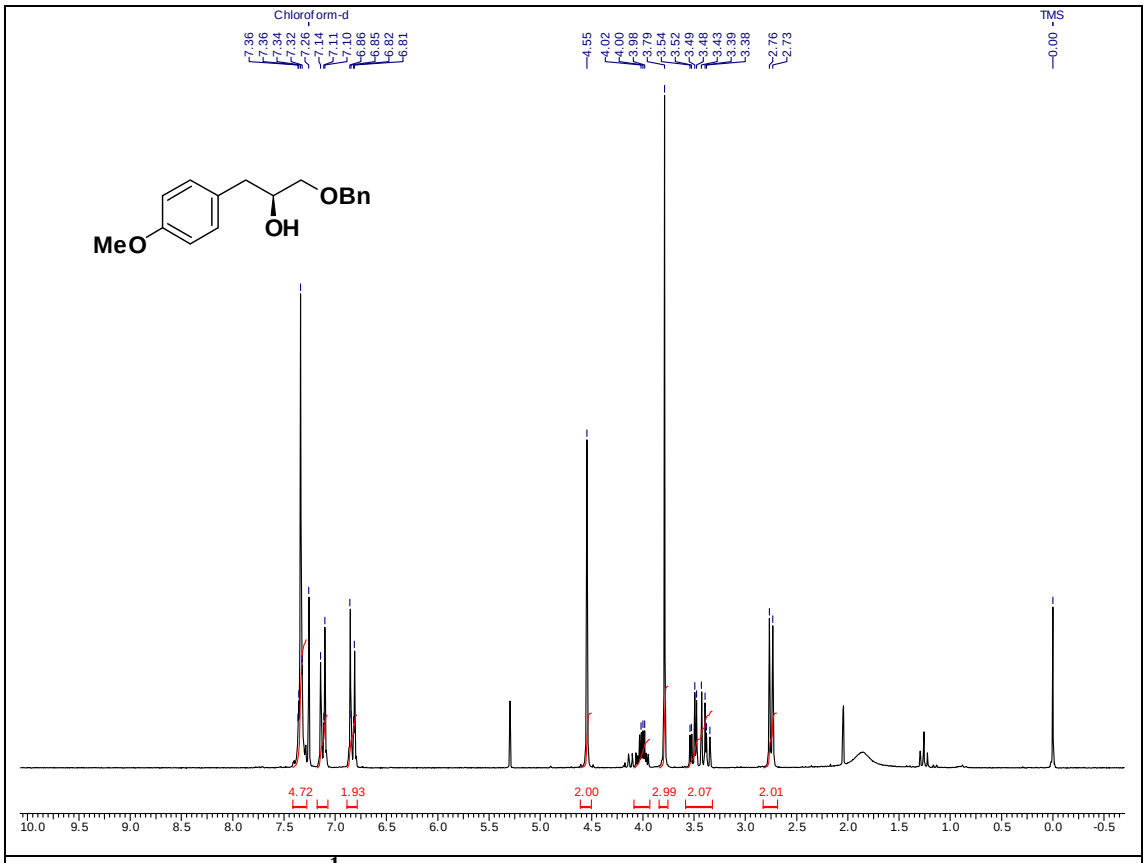
(C), 130.5 (CH, 2 carbons), 129.2 (C), 115.1 (CH, 2 carbons), 80.4 (CH), 66.2 (CH), 60.8 (CH_2), 38.4 (CH_2), 15.0 (CH_3), 14.2 (CH_3); MS: *m/z* 239 $[M+H]^+$ 261 $[M+Na]^+$.

7) Isopropyl (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (*S*)-1b

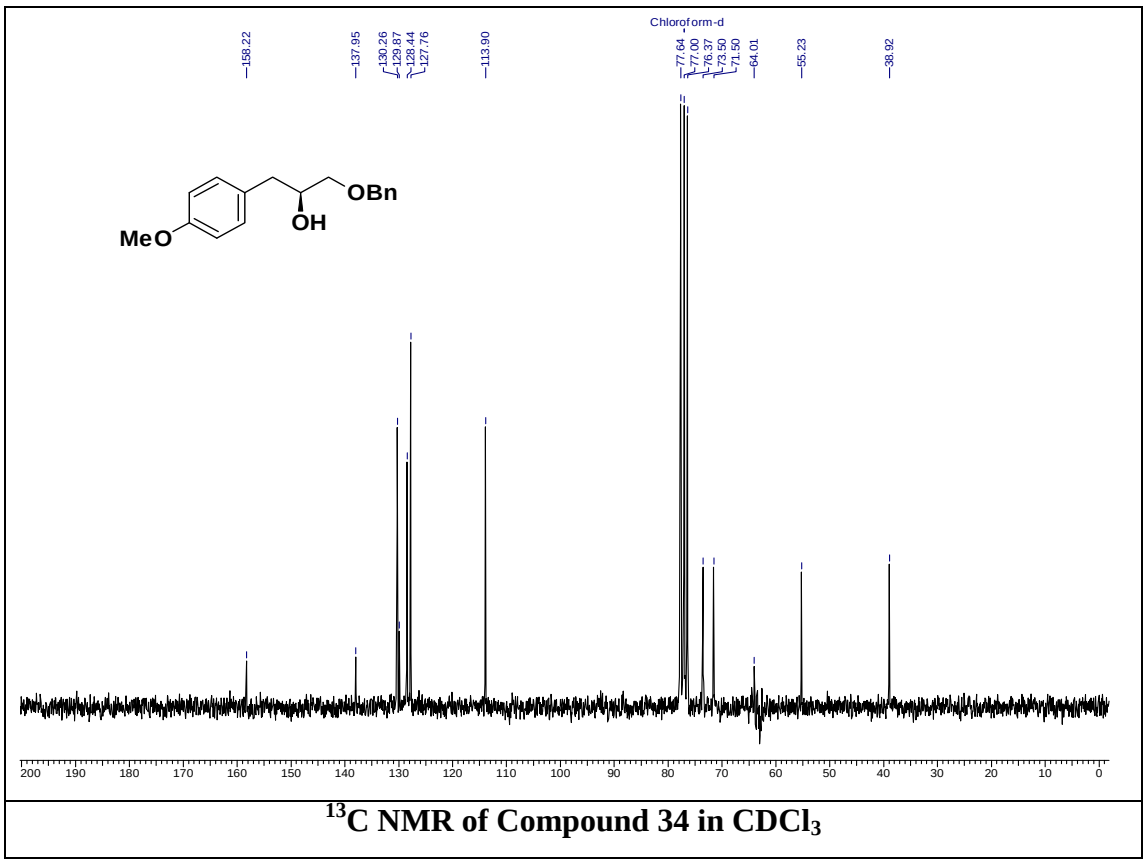


To a stirred solution of **37** in anhydrous 2-propanol (5 mL) was added thionyl chloride (0.2 mL, 2.6mmol) slowly at room temperature. The mixture was stirred for 2 h at 60 ºC and solvent was removed under reduced pressure. Ethyl acetate was added and the organic layer was washed with 10% $NaHCO_3$ solution (2 x 15 mL), dried, concentrated under vacou and purified using column chromatography (silica gel, petroleum ether/ethyl acetate, 95:05). to furnish (*S*)-**1b** as oil (0.42 g; 85%); $[\alpha]_D^{25}$ = -19.4 (*c* 1.02 $CHCl_3$); IR ($CHCl_3$): 3392, 3019, 2400, 1601, 1216, 1116, 928, 757cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$): δ_H = 1.14- 1.26 (m, 9H), 2.96 (d, *J* = 6.6 Hz, 2H), 3.31-3.46 (m, 1H), 3.53- 3.68 (m, 1H), 3.96 (t, *J* = 6.6 Hz, 1H), 4.95- 5.13 (m, 1H), 5.74 (bs, 1H), 6.75 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, CDCl3): δ_C = 172.3 (CO), 154.5 (C), 130.5 (CH, 2 carbons), 128.8 (C), 115.1 (CH, 2 carbons), 80.4 (CH), 68.5 (CH), 66.0 (CH_2), 38.3 (CH_2), 21.7 (CH_3), 21.6 (CH_3), 15.0 (CH_3); MS: *m/z* 275 $[M+Na]^+$. [The ee was determined by chiral HPLC analysis: Kromasil 5-Amycoat (250 x 4.6 mm) column; eluent: pet ether/ethanol = 95/05; flow rate: 0.5 mL/min; detector 220 nm [(*R*) isomer t_R = 16.53 min; (*S*) isomer t_R = 19.01 min].

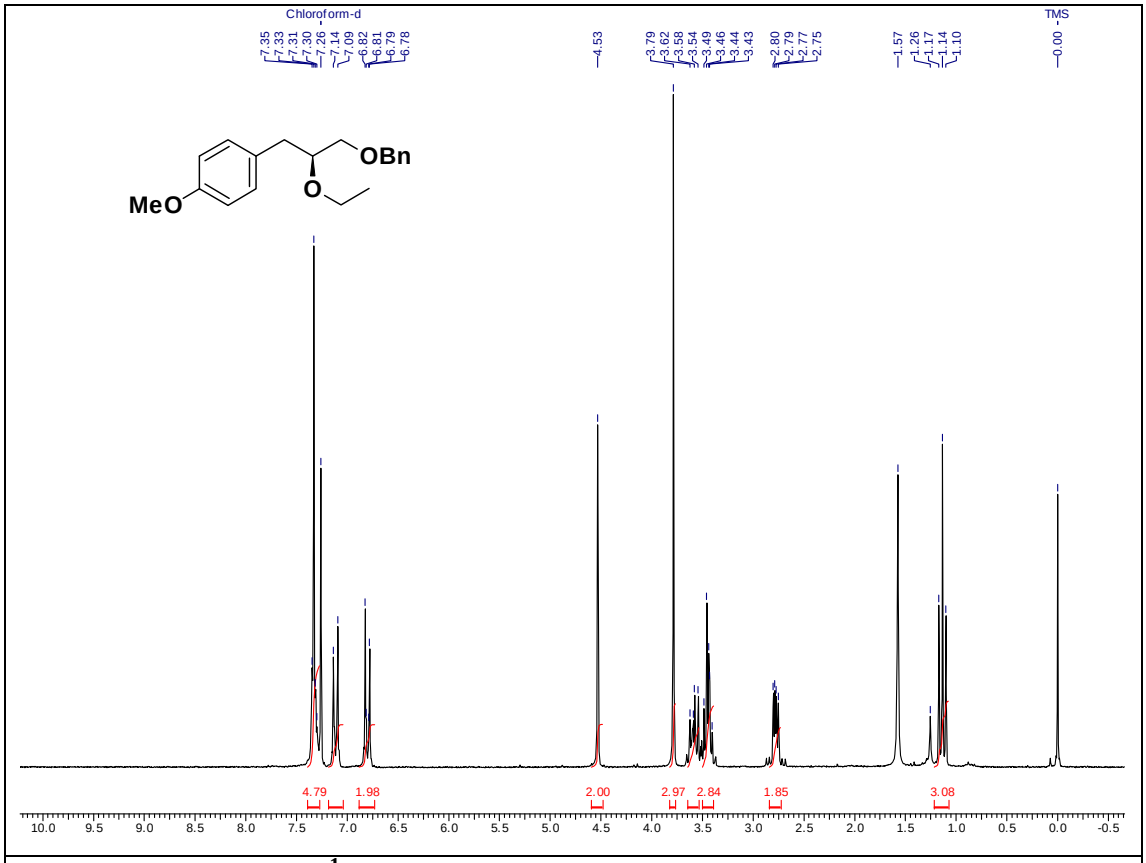
3.1.7. Analytical data



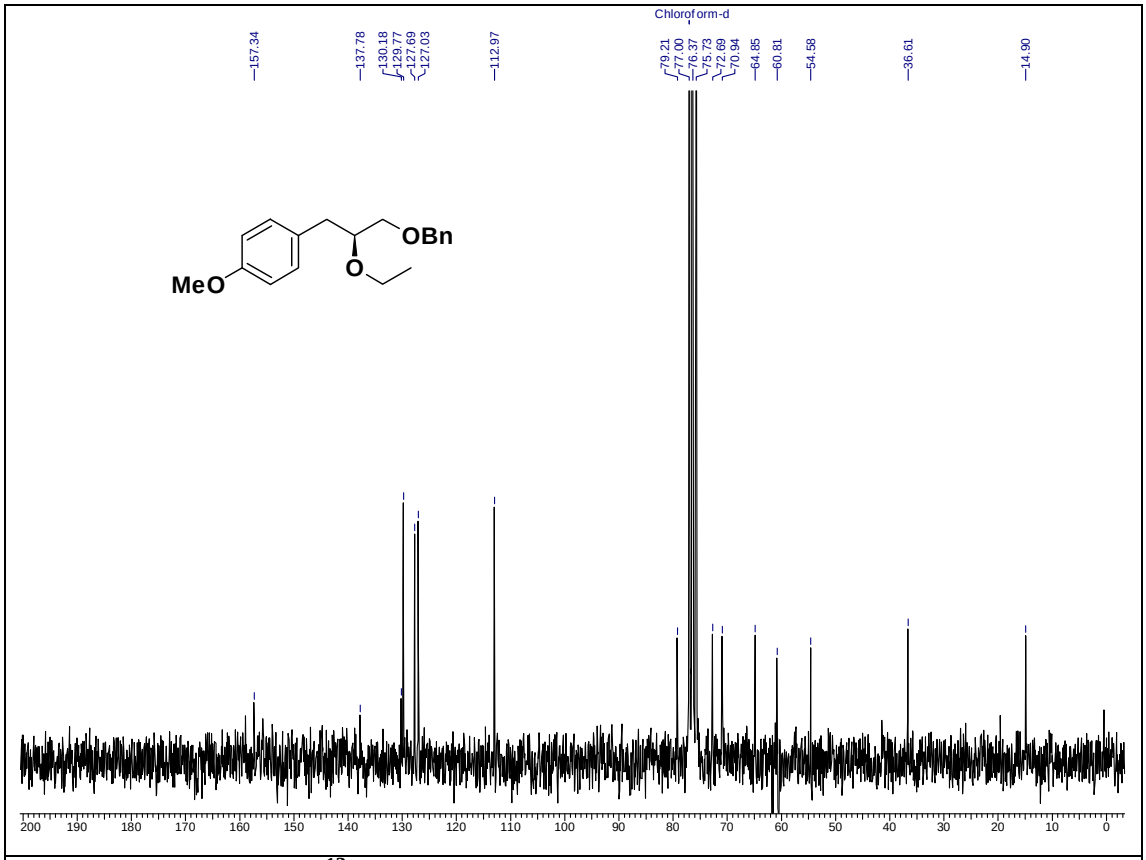
^{1}H NMR of Compound 34 in $CDCl_3$



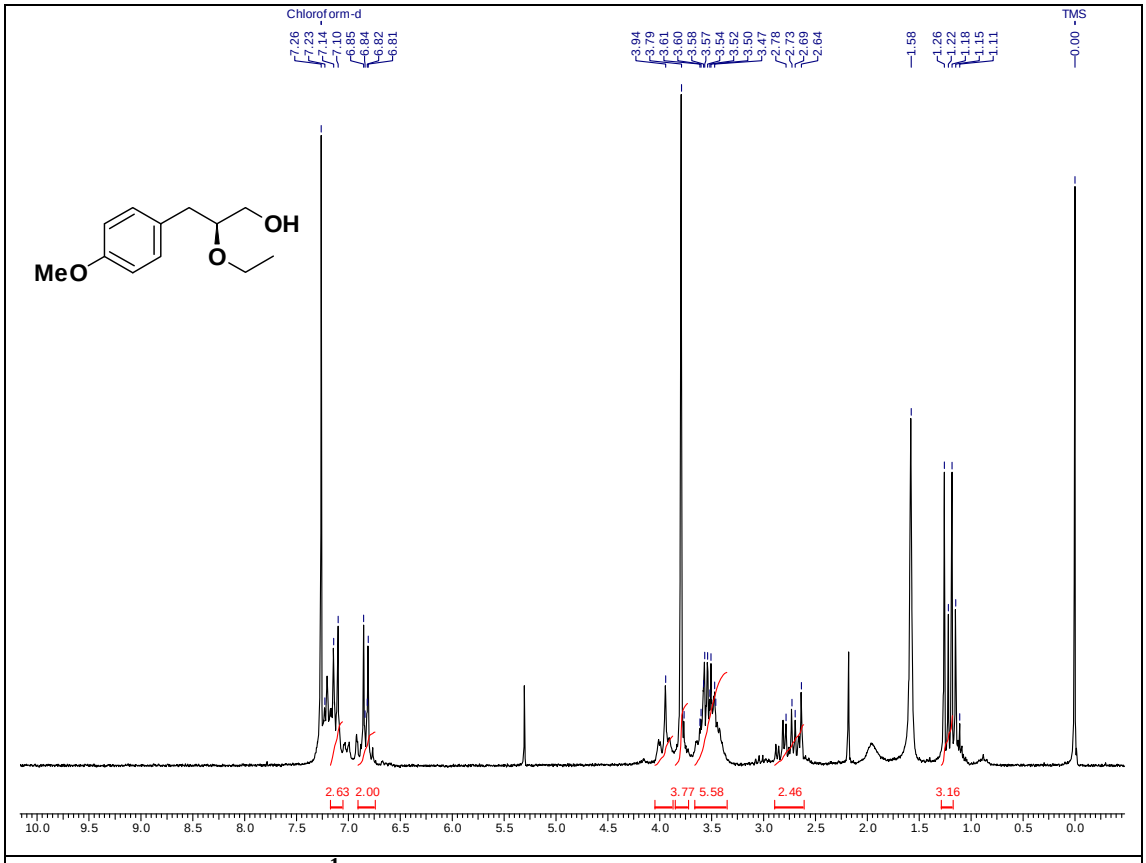
^{13}C NMR of Compound 34 in $CDCl_3$



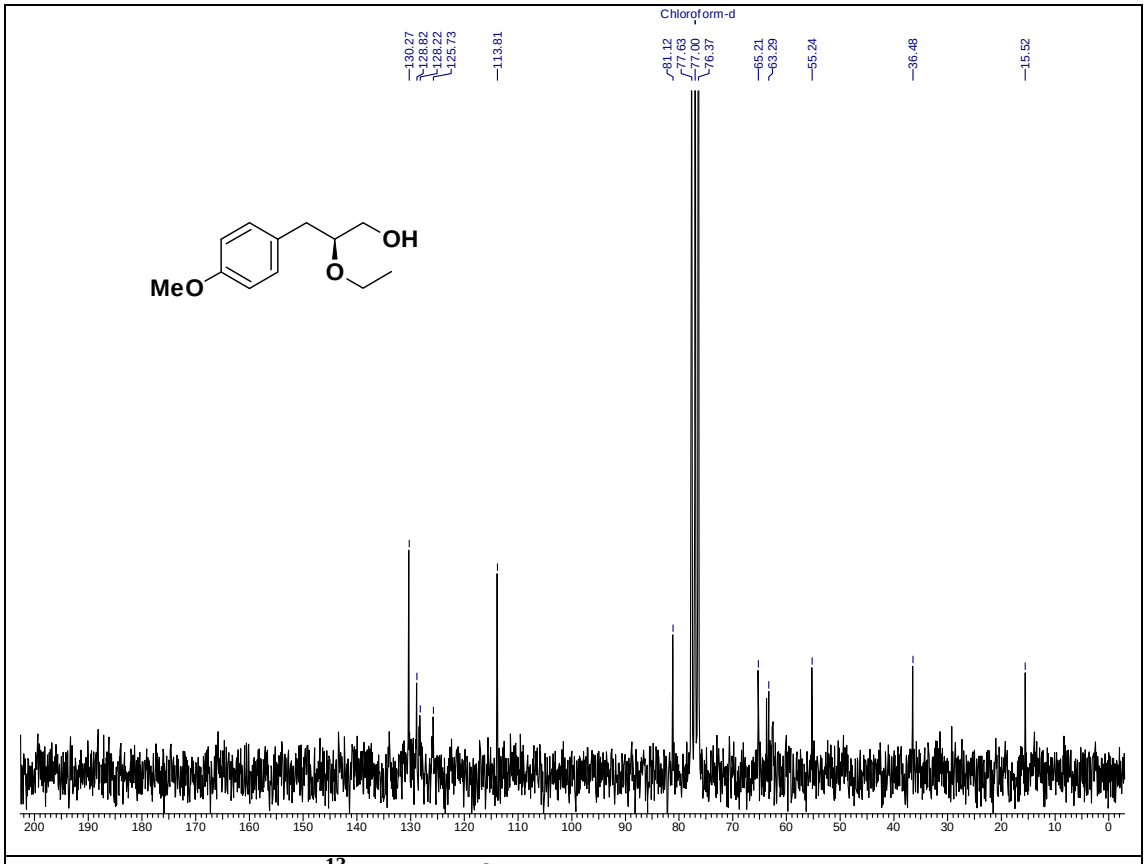
^{1}H NMR of Compound 35 in $CDCl_3$



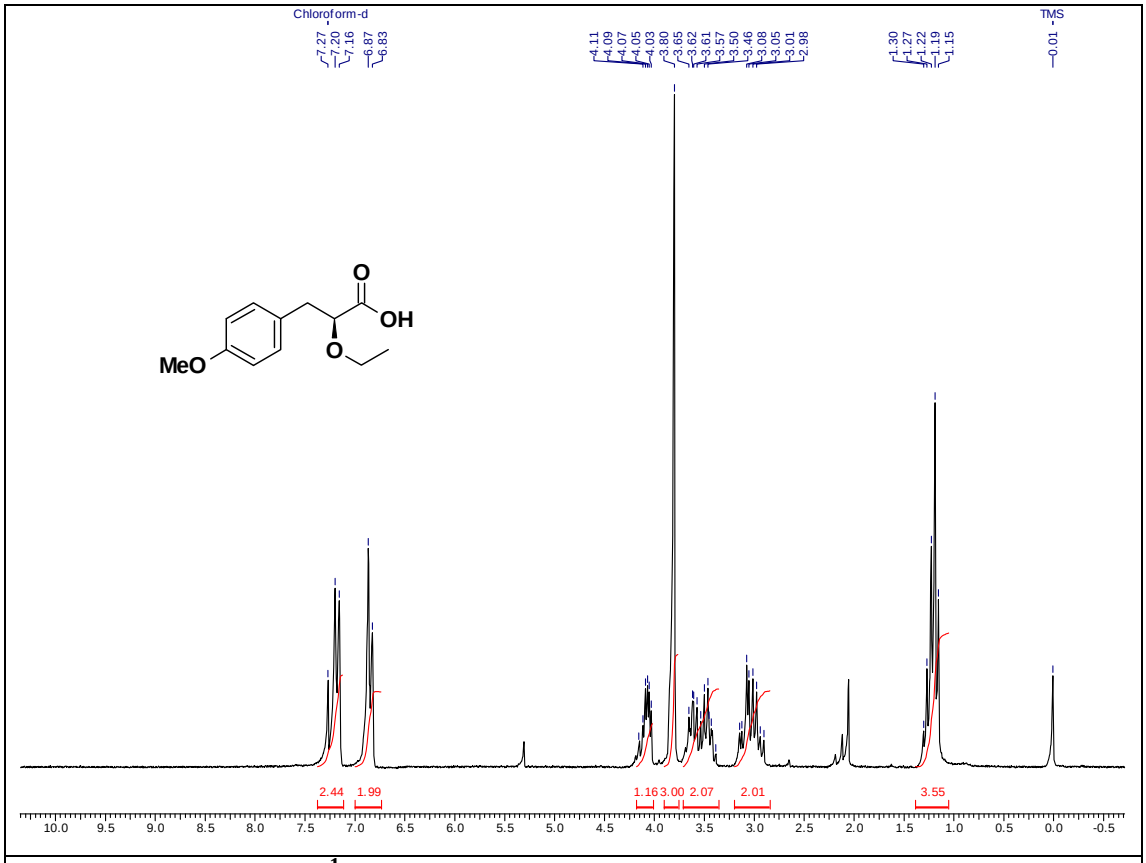
^{13}C NMR of Compound 35 in $CDCl_3$



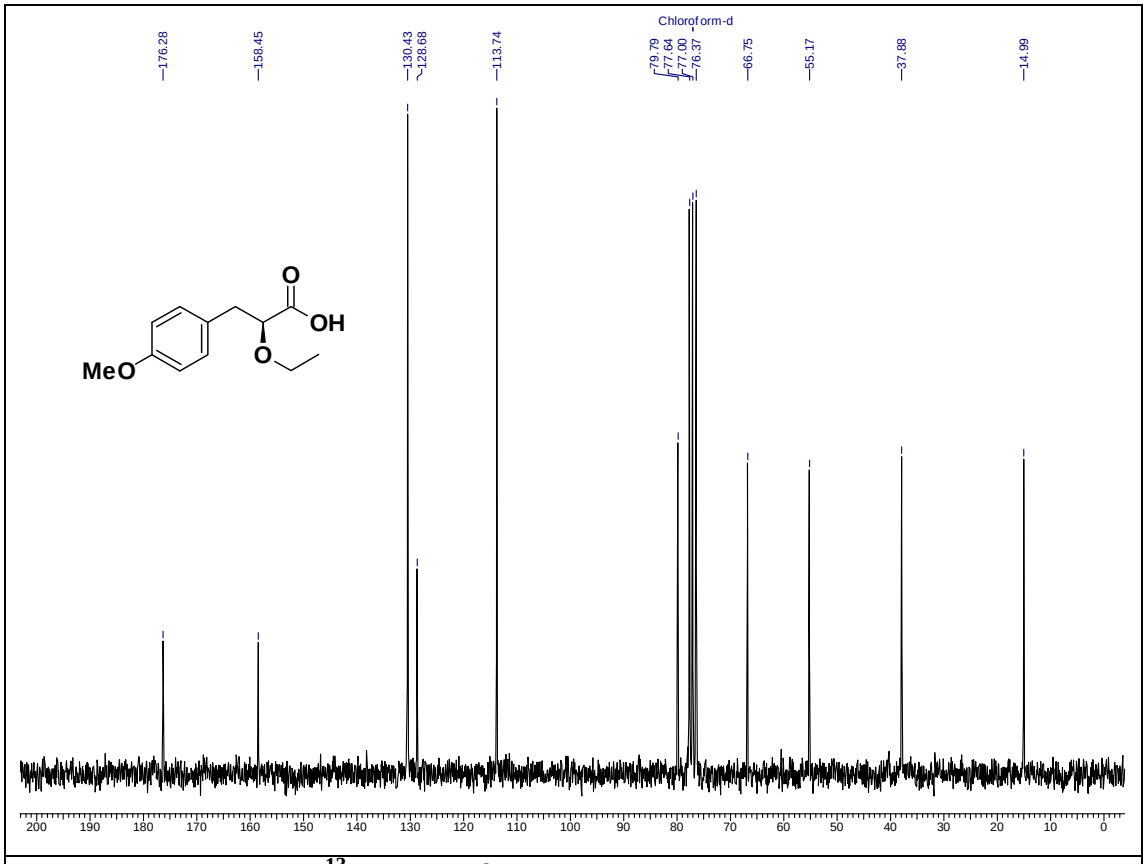
^{1}H NMR of Compound 36 in $CDCl_3$



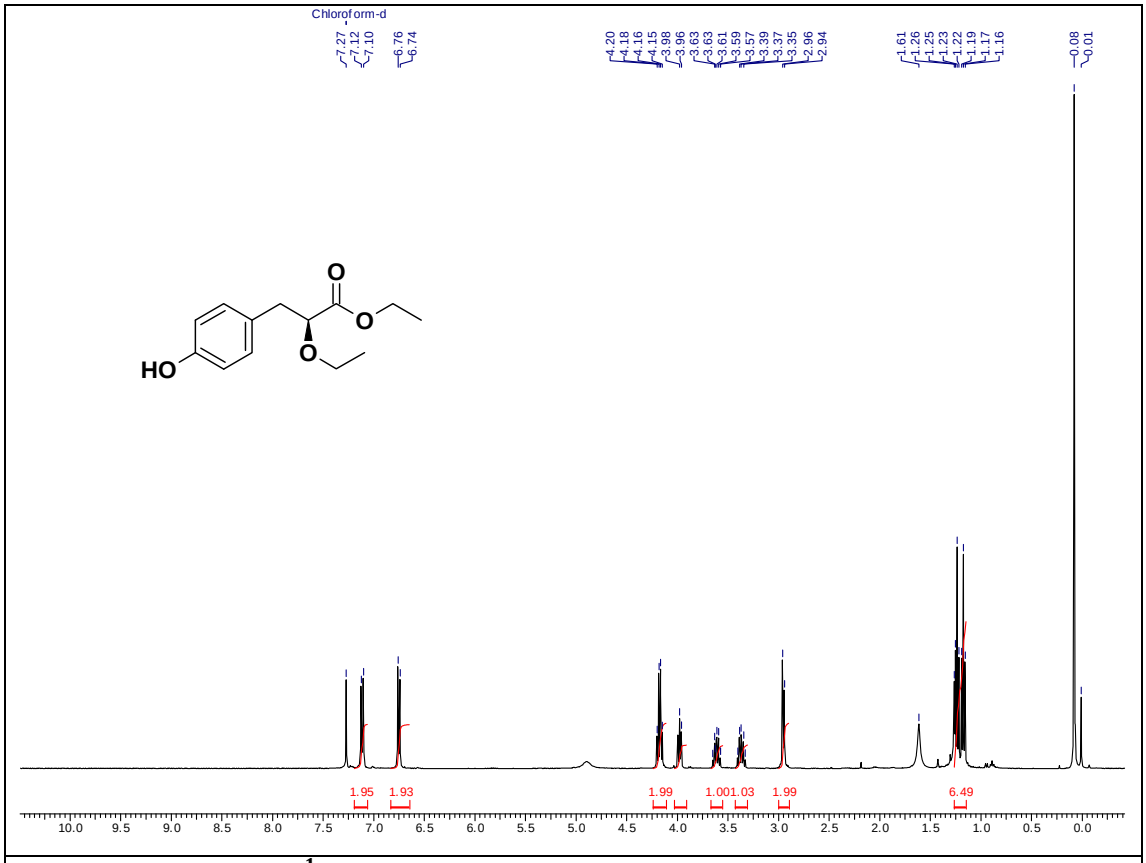
^{13}C NMR of Compound 36 in $CDCl_3$



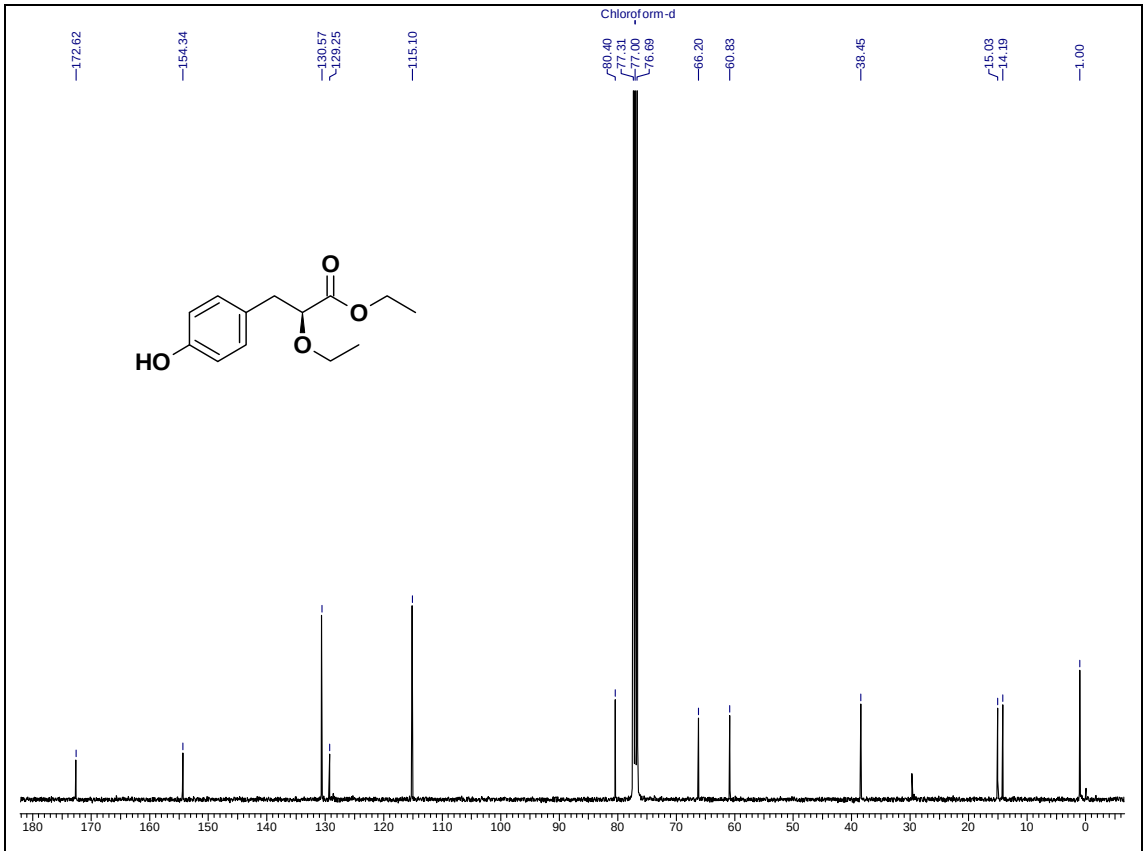
^{1}H NMR of Compound 32 in $CDCl_3$



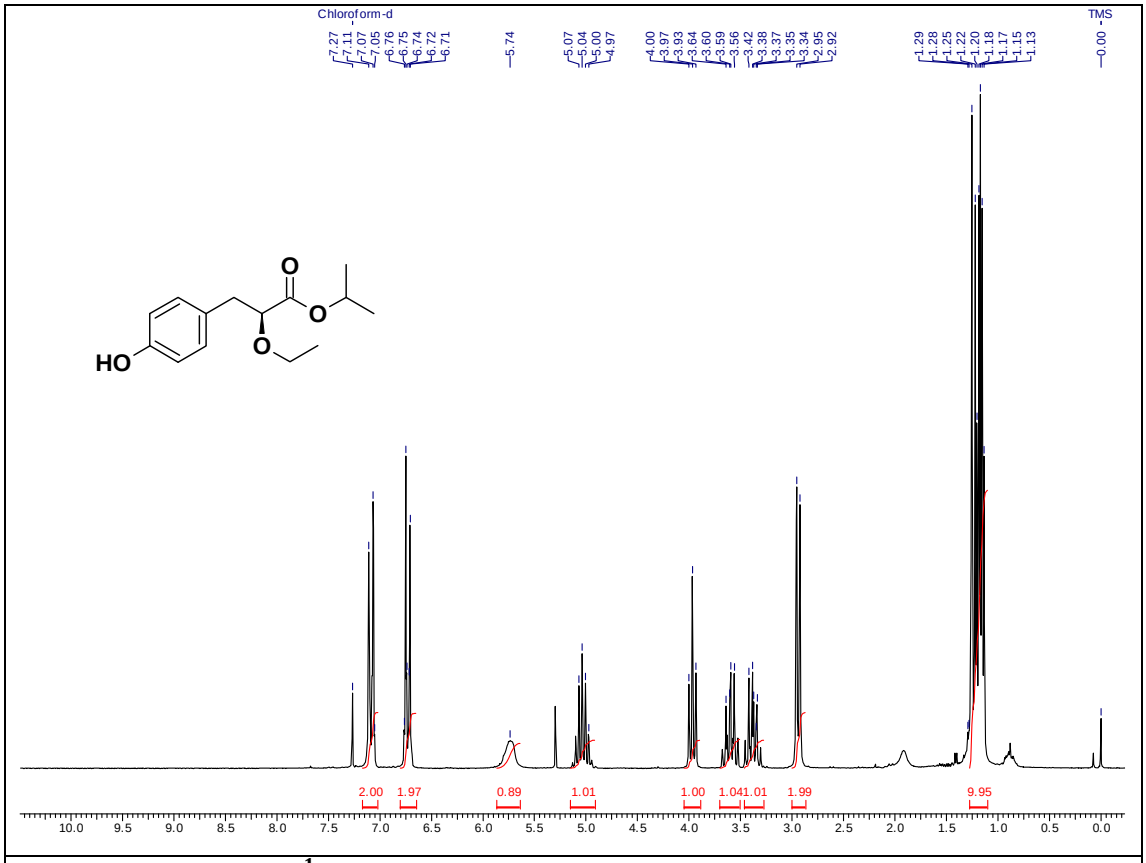
^{13}C NMR of Compound 32 in $CDCl_3$



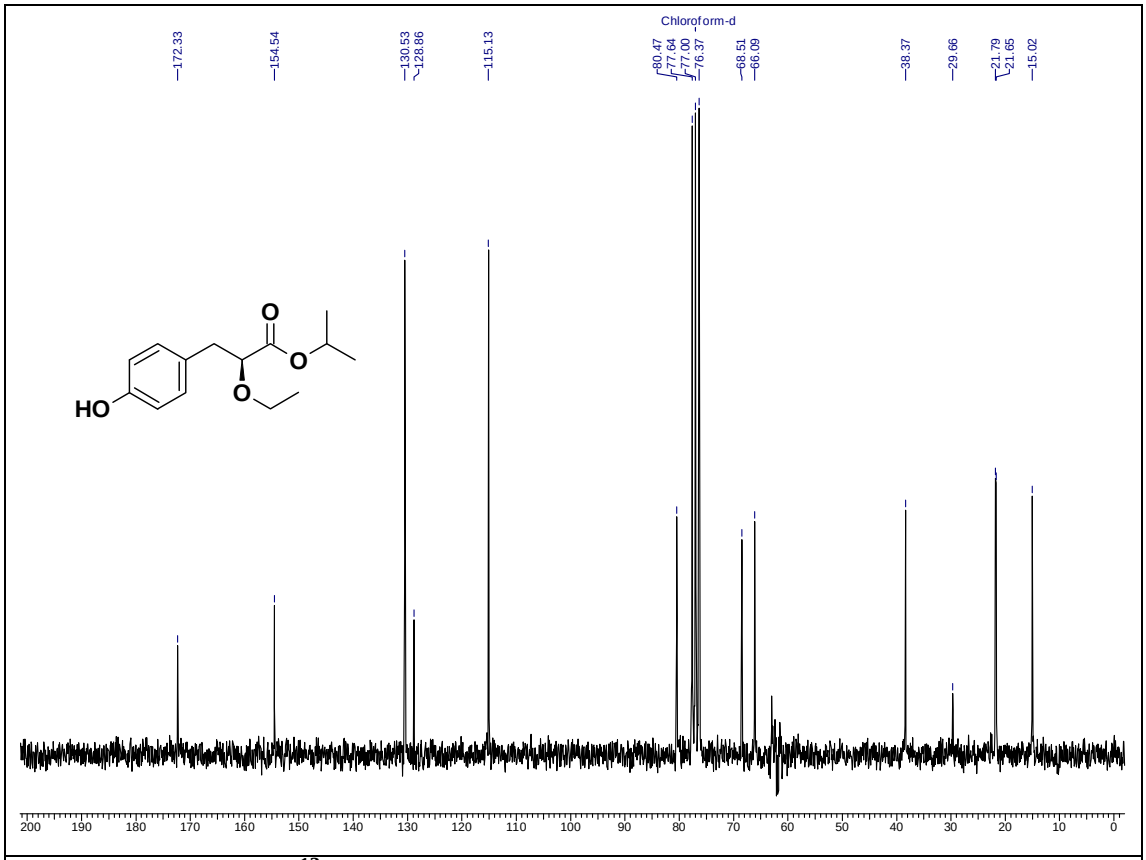
^{1}H NMR of Compound (*S*)-1a in $CDCl_3$



^{13}C NMR of Compound (*S*)-1a in $CDCl_3$

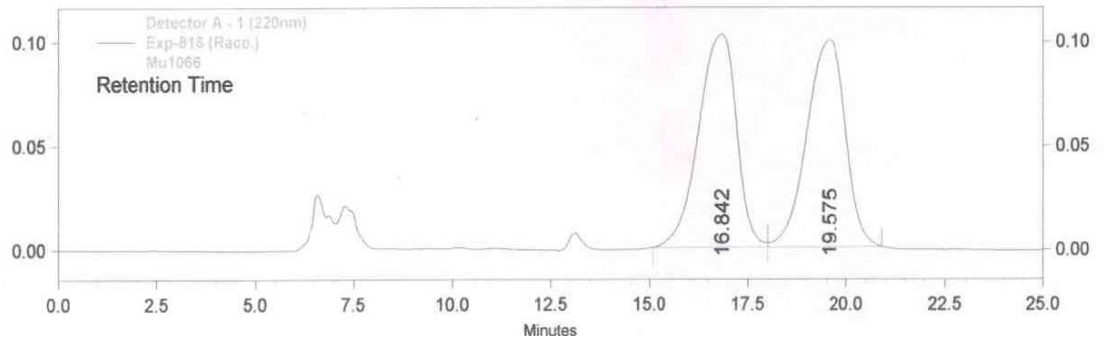


^{1}H NMR of Compound (*S*)-1b in $CDCl_3$



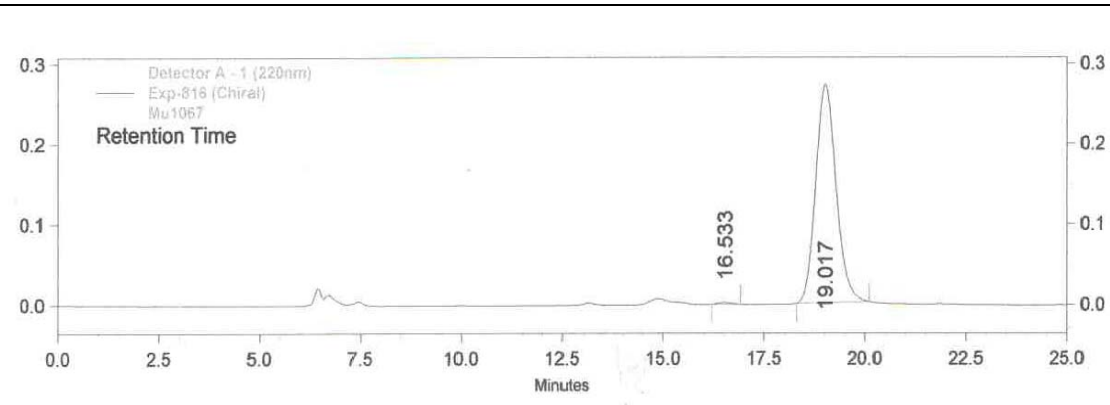
^{13}C NMR of Compound (*S*)-1b in $CDCl_3$

Chiral HPLC Analysis of Compound (*S*)-1b



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	**16.842**	**6842611**	**50.022**
2	**19.575**	**6836618**	**49.978**
Totals		**13679229**	**100.000**



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	**16.533**	**47643**	**0.492**
2	**19.017**	**9629629**	**99.508**
Totals		**9677272**	**100.000**

3.1.8. References

1. Kliewer, S. A.; Sundseth, S. S.; Jones, S. A.; Brown, P. J.; Wisely, G. B.; Kolbe, C. S.; Devchand, P.; Wahli, W.; Willson, T. M.; Leenhard, J. M.; Lehmann, J. M. *Proc. Natl. Acad. Sci. U.S.A* **1997**, *94*, 4318.
2. (a) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem*. **2000**, *43*, 527; (b) Verges, B. *Diabetes Metab*. **2004**, *30*, 7; (c) Akiyama, T. E.; Meinke, P. T.; Berger, J. P. *Curr. Diabetes Rep* **2005**, *5*, 45.
3. (a) Henke, B. R. *J. Med. Chem.* **2004**, *47*, 4118; (b) Gervois, P.; Fruchart, J. C.; Staels, B. *Int. J. Clin. Pract.; Suppl.* **2004**, *143*, 22.
4. Ebdrup, S.; Pettersson, I.; Rasmussen, H. B.; Deussen, H-J.; Jensen, A. F.; Mortensen, S. B.; Fleckner, J.; Pridal, L.; Nygaard, L.; Sauerberg, P. *J. Med. Chem.* **2003**, *46*, 1306.
5. Anderson, K. PCT Appl. WO 99/62872 (1999 to Astra).
6. Devasthale, P. V.; Chen, S.; Jeon, Y.; Qu, F.; Shao, C.; Wang, W.; Zhang, H.; Cap, M.; Farrelly, D.; Golla, R.; Grover, G.; Harrity, T.; Ma, Z.; Moore, L.; Ren, J.; Seethala, R.; Cheng, L.; Sleph, P.; Sun, W.; Tieman, A.; Wetterau, J. R.; Doweyko, A.; Chandrasena, G.; Chang, S. Y.; Humphreys, W. G.; Sasseville, V. G.; Biller, S. A.; Ryono, D. E.; Selan, F.; Hariharan, N.; Cheng, P. T. *J. Med. Chem.* **2005**, *48*, 2248.
7. Martín, J. A.; Brooks, D. A.; Prieto, L.; Gonzalez, R.; Torrado, A.; Rojo, I.; Lopez de Uralde, B.; Lamas, C.; Ferritto, R.; Dolores Martín-Ortega, M.; Agejas, J.; Parra, F.; Rizzo, J. R.; Rhodes, G. A.; Robey, R. L.; Alt, C. A.; Wendel, S. R.; Zhang, T. Y.; Reifel-Miller, A.; Montrose-Rafizadeh, C.; Brozinick, J. T.; Hawkins, E.; Misener, E. A.; Briere, D. A.; Ardecky, R.; Fraser, J. D.; Warshawsky, A. M. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 51.
8. Balakumar, P.; Rose, M.; Ganti, S. S.; Krishan, P.; Singh, M. *Pharm. Res*. **200**7, 56, 91.
9. Siripragada, M. R.; Chebiyyam, P.; Potlapally, R. K.; Batchu, C. S.; Mamillapally, R. S. PCT Appl. WO 00/26200.
10. Deussen, H.-J.; Zundel, M.; Valdois, M.; Lehmann, S. V.; Weil, V.; Hjort, C. M.; Østergaard, P. R.; Marcussen, E.; Ebdrup, S. *Org. Process Res. Dev*. **2003**, *7,* 82.

11. Linderberg, M. T.; Moge, M.; Sivadasan, S. *Org. Process Res. Dev*. **2004**, *8*, 838.

12. Aikins, J. A.; Haurez, M.; Rizzo, J. R.; Van Hoeck, J.-P.; Brione, W.; Kestemont, J.-P.; Stevens, C.; Lemair, X.; Stephenson, G. A.; Marlot, E.; Forst, M.; Houpis, I. N. *J. Org. Chem*. **2005**, *70*, 4695.

13. Brenna, E.; Fuganti, C.; Gatti, F. G, Parmeggiani, F. *Tetrahedron: Asymmetry* **2009**, *20*, 2594.

14. (a) Nikalje, M. D.; Sasikumar, M.; Muthukrishnan, M. *Tetrahedron: Asymmetry* **2010**, *21*, 2825; (b) Sasikumar, M.; Nikalje, M. D.; Muthukrishnan, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2814; (c) Muthukrishnan, M.; Garud, D. R.; Joshi, R. R.; Joshi, R. A. *Tetrahedron*, **2007**, *63*, 1872. (d) Joshi, R.A.; Garud, D.R.; Muthukrishnan, M.; Joshi, R.R.; Gurjar, M.K. *Tetrahedron: Asymmetry* **2005**, *16*, 3802; (e) Muthukrishnan, M.; Mujahid, M.; Sasikumar, M.; Mujumdar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1353; (f) Mujahid, M.; Mujumdar, P.; Sasikumar, M.; Kunte, S. S.; Muthukrishnan, M. *Tetrahedron: Asymmetry*, **2012**, *23*, 1512.

3.2. SECTION B

Asymmetric synthesis of (*R*)-Phenampromide via aziridine ring formation

3.2.1. Introduction

Commonly known as *painkillers*, analgesic drugs act in various ways on the peripheral and central nervous system. They are different from anesthetics, which reversibly eliminate sensation, and these drugs include paracetamol, the non-steroidal anti-inflammory agents such as salicylates, and opioid drugs such as morphine and opium.[1]

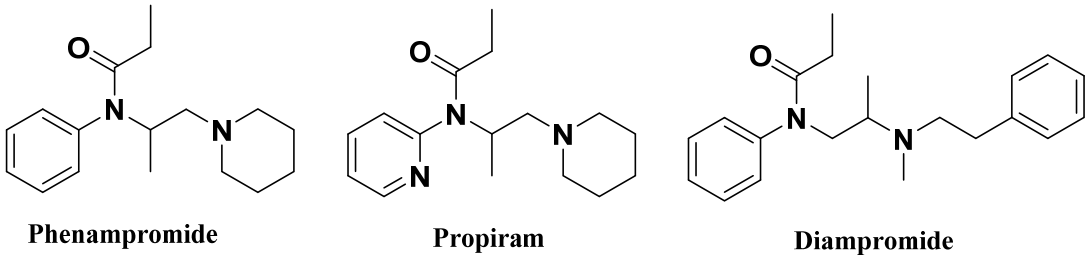


Figure 1. Examples of few opioid analgesic

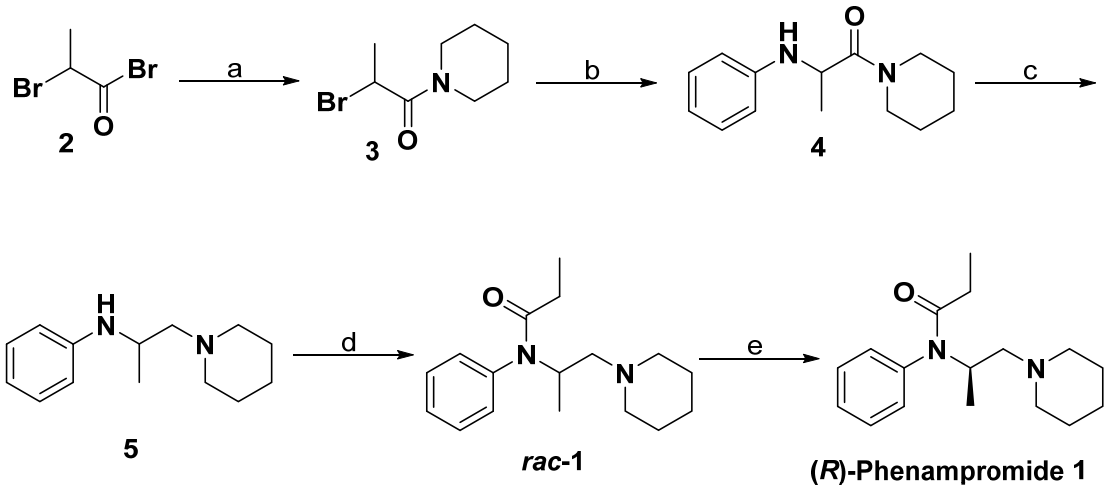
Phenampromide **1** is an opioid analgesic drug which was introduced in the 1960s by American Cyanamid Company. It produces similar effects to other opioids, including analgesia, sedation, dizziness and nausea. Phenampromide belongs to the ampromide family of drugs and the structure is very similar to other opioids diampromide and propiram (Fig. 1). Literature study reveals that (*R*)-enantiomer of phenampromide possess greater analgetic potency than its (*S*)-enantiomer.[2]

3.2.2. Review of Literature

There are few reports available in the literature for the synthesis of *(R)*-enantiomer of phenampromide. These are mainly based on resolution processes which are described below.

Wright *et al.* (1961)[2]

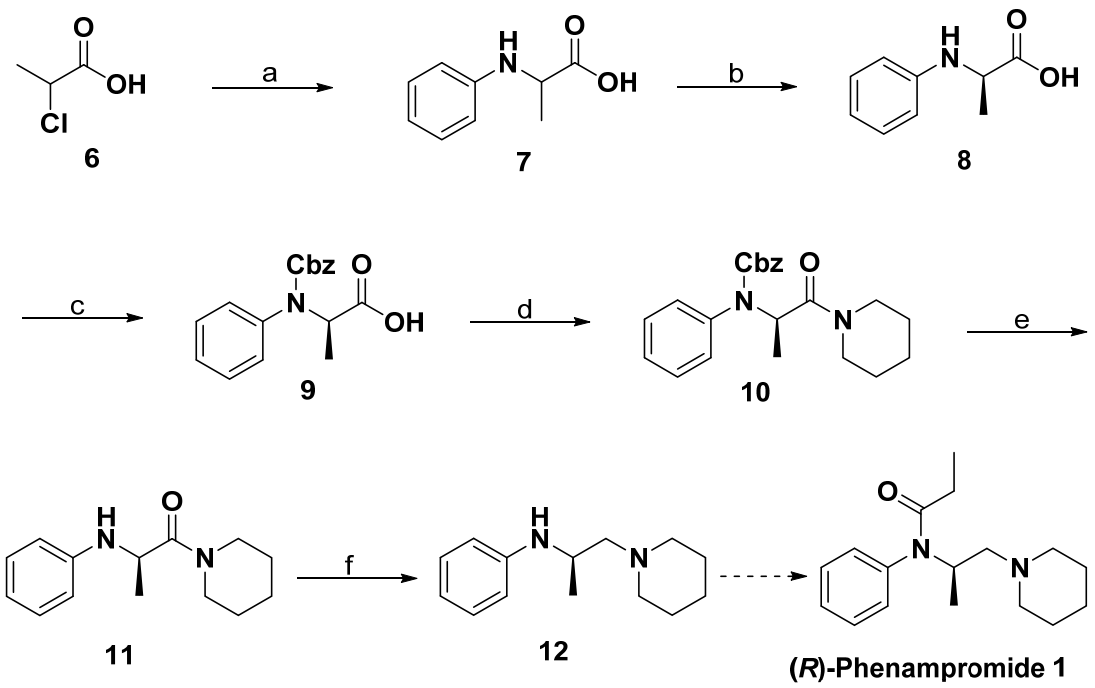
Wright *et al.* reported the resolution method for the synthesis of *(R)*-phenampromide **1** (Scheme 1). The synthesis started with 2-bromo-propionyl bromide **2** which on treatment with piperidine to give amide derivative **3**. Amination of intermediate **3** followed by reduction of amido group provided diamine **5**. *N*-acylation of **5** using propanoic anhydride afforded *rac*-phenampromide. Finally, *rac*-phenampromide was resolved with L-malic acid.



Scheme 1. *Reagents and conditions*: (a) piperidine, ether; (b) aniline, benzene; (c) $LiAlH_4$, THF; (d) propanoic anhydride; (e) L-malic acid, EtOH then 1N NaOH.

Portoghese (1964)[3]

Portoghese reported another method for the synthesis of *(R)*-phenampromide **1** starting with 2- chloropropionic acid. The acid **6** which on treatment with aniline under basic condition provided *rac*-*N*-phenylalanine **7** which was resolved using quinine to afford (*R*)-*N*-phenylalanine **8**. Cbz protection of **8** followed by reaction with piperidine afforded amide derivative **10**. Deprotection of Cbz group followed by reduction provided compound **12** which could be transformed to *(R)*-phenampromide **1** by *N*-acylation (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) aniline, NaOH, EtOH, 67%; (b) quinine, acetone, MeOH, 18%; (c) benzyl chloroformate, $NaHCO_3$, H_2O, 27%; (d) piperidine, 11%; (e) Pd/C, H_2 (25 psi), MeOH, 87%; (f) $LiAlH_4$, THF.

3.2.3. Present Work

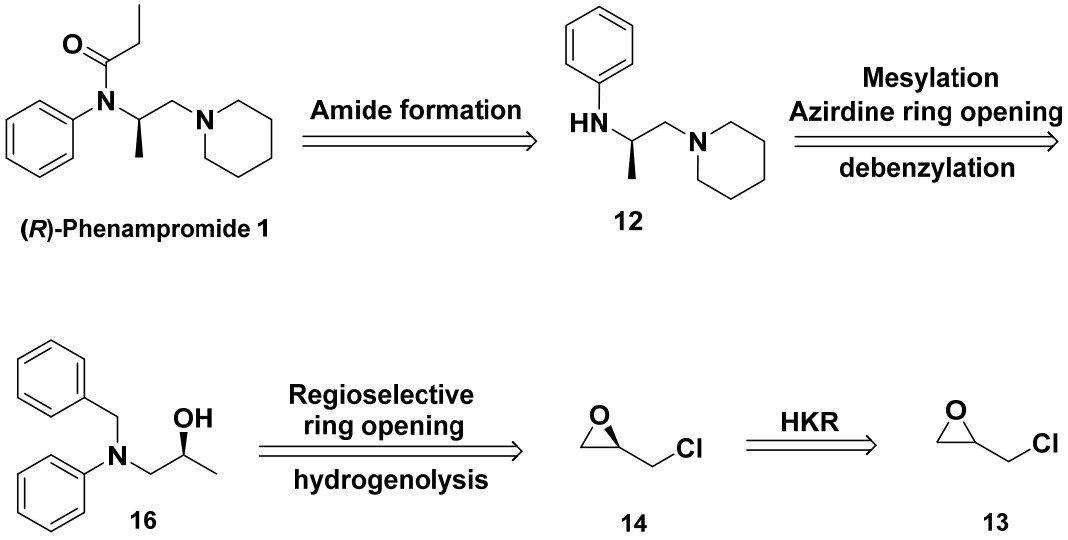
Objective

Despite the importance of *(R)*-phenampromide **1** and related drugs, only few methods are available for its preparation. Further, the available methods are only resolution processes, hence the development of asymmetric synthetic route to these kinds of molecules are highly desirable. As part of our research programme, we became interested to develop a new and highly enantioselective synthesis of *(R)*-phenampromide **1** employing hydrolytic kinetic resolution.

3.2.4. Results and Discussion

A retrosynthetic analysis of *(R)*-phenampromide **1** is depicted in Scheme 3. We envisaged that the secondary hydroxy compound **16** would serve as a key

intermediate for the synthesis which can be extended to the final molecule **(*R*)-1** *via* formation of aziridinium ion and amide.

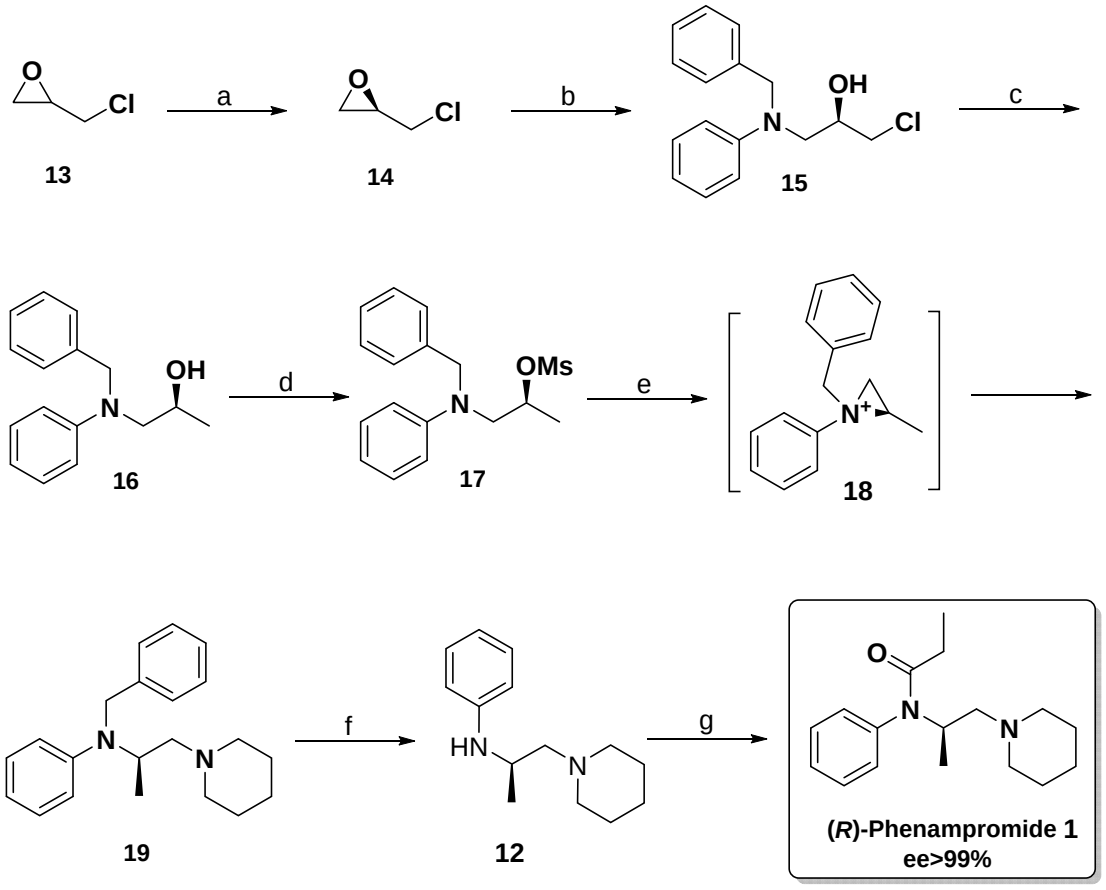


Scheme 3. Retrosynthetic analysis of *(R)*-phenampromide **1**

The key intermediate **16** in turn can be obtained from (*R*)-epichlorohydrin **14** employing regioselective ring opening using *N*-benzyl aniline. (*R*)-epichlorohydrin can be easily obtained with high enantiopurity from its racemic epichlorohydrin using Jacobsen's hydrolytic kinetic resolution strategy.

Accordingly, (*R*)-epichlorohydrin **14** was prepared using reported procedure.[4] Regioselective ring opening of the chiral epoxide **14** was performed using *N*-benzylaniline in methanol under reflux conditions to get the required chlorohydrin derivative **15** in 65% yield (Scheme 4). Now the derivative **15** was reduced using lithium aluminium hydride to give secondary hydroxy compound **16** in 94% yield. Appearance of a doublet at δ 1.16 (3H) and multiplet in the range of δ 3.99-4.13 (1H) in ^{1}H NMR and a signal at δ 20.2 (CH_3) in ^{13}C NMR indicated the formation of compound **16**. Mesylation of compound **16** using methane sulfonyl chloride provided mesylated derivative **17** which on treatment with Et_3N and piperidine in refluxing toluene furnished derivative **19** via aziridinium ion.[5] Multiplets in the range of 1.39-1.58 (m, 6H) & 2.23-2.54 (m, 6H) in ^{1}H NMR and peaks at δ 55.2 (CH_2, 2 carbons), 26.0 (CH_2, 2 carbons) & 24.3 (CH_2) in ^{13}C NMR corresponds to piperidine ring of compound **19**. Further, *N*-debenzylation of compound **19** using catalytic $Pd(OH)_2$ under H_2 pressure, followed by treatment with propionyl chloride in presence of base afforded the target compound (*R*)-phenampromide **1** in high enantiopurity (ee>99%).

The structure of phenampromide **1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis.



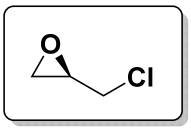
Scheme 4. *Reagents and conditions*: (a) (*S,S*) Salen Co (OAc) (0.5 mol %), H_2O (0.55 equiv.), 0 ºC to rt, 24 h, 40 %; (b) *N*-benzyl aniline, MeOH, reflux, 24 h, 65%; (c) $LiAlH_4$, THF (dry), 0 ºC to reflux, 6 h, 94%; (d) MsCl, Et_3N, DCM, 0 ºC, 2 h; (e) piperidine, Et_3N, toluene, reflux, 8 h, 30% (two steps); (f) $Pd(OH)_2$, H_2 (60 psi), MeOH, 6 h 91%; (g) propionyl chloride, K_2CO_3, toluene, 0 ºC to rt, 4 h, 69%.

3.2.5. Conclusion

In conclusion, a practical and enantioselective synthesis of (*R*)-phenampromide **1** has been achieved using Jacobsen's HKR strategy and aziridine ring formation as key steps. The synthetic strategy described has significant potential for further extension to other isomer and related analogues.

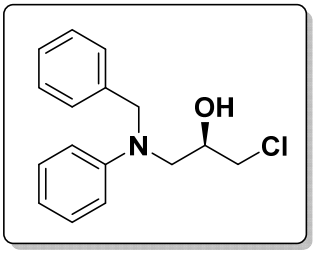
3.2.6. Experimental

1) (*R*)-epichlorohydrin 14



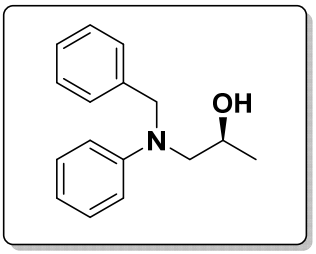
A mixture of epichlorohydrin **13** (5.6 g, 61 mmol) and (*S*,*S*) salen Co(III)OAc complex-A (0.18 g, 0.28 mmol) in THF (0.6 mL) were cooled to 0 ^{o}C and vigorously stirred for 15 min then, water (0.6 mL, 34 mmol) was added over a period of 15 min, through a micro-syringe. The reaction mixture was stirred at 4 ^{o}C for 24 h. (*R*)-epichlorohydrin (2.3 g, 41%) was isolated by vacuum distillation (25 ^{o}C, 0.25 torr) from the reaction mixture into a cold (-78 ^{o}C) receiving flask. $[\alpha]^{25}_{D}$ = -33.4 (*c* 1.4, MeOH) {lit.[4] $[\alpha]^{23}_{D}$ = -32.8 (*c* 1.27, MeOH)}

2) (*R*)-1-(benzyl (phenyl) amino)-3-chloropropan-2-ol 15



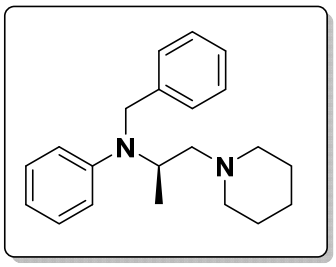
To a stirred solution of (*R*)-epichlorohydrin **14** (0.98 g, 10.6 mmol) and methanol (8 ml) at room temperature was added *N*-benzyl aniline (1.94 g, 10.6 mmol) dissolved in methanol (10 ml) for 5 minutes. Then the reaction mixture was refluxed for 24 h. After completion of the reaction methanol was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 85:15) so as to afford **15** as an oil (1.9 g, 65%); $[\alpha]_{D}^{25}$ = -10.8 (*c* 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.26 (brs, 1H), 3.55-3.71 (m, 4H), 4.16-4.22 (m, 1H), 4.64 (s, 2H), 6.73-6.84 (m, 3H), 7.17-7.35 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 148.1 (C), 137.8 (C), 129.3 (CH, 3 carbons), 128.6 (CH, 3 carbons), 127.0 (CH), 126.8 (CH), 117.9 (CH), 113.4 (CH), 69.0 (CH), 55.7 (CH_2), 54.8 (CH_2), 47.7 (CH_2); MS: *m/z* 275 $[M]^{+}$.

3) (*S*)-1-(benzyl(phenyl)amino)propan-2-ol 16



A solution of **15** (1.4 g, 5.0 mmol) in dry THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (0.2 g, 5.7 mmol) in dry THF (15 mL) at 0 ºC. After being stirred at room temperature for 30 min, the mixture was refluxed for 6 h. After completion of the reaction, the mixture was allowed to cool to 0 ºC and aq. KOH (5 mL) was added slowly followed by addition of ethyl acetate (25 mL). The residue was filtered over celite and the filtrate was washed with water, brine and dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified over column chromatography (silica gel, petroleum ether/EtOAc, 80:20) so as to afford **16** as an oil (1.13 g, 94%); $[\alpha]_D^{25}$ = +8.3 (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.16 (d, *J* = 6.5 Hz, 3H), 3.20-3.43 (m, 2H), 3.99-4.13 (m, 1H), 4.57 (s, 2H), 6.65-6.76 (m, 3H), 7.09-7.27 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 156.3 (C), 140.0 (C), 129.2 (CH, 3 carbons), 128.6 (CH, 3 carbons), 126.9 (CH), 126.7 (CH), 113.4 (CH), 113.2 (CH), 65.5 (CH), 59.6 (CH_2), 55.3 (CH_2), 20.2 (CH_3); MS: *m/z* 242 $[M+H]^+$.

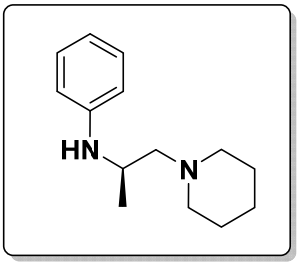
4) (*R*)-*N*-benzyl-*N*-(1-(piperidin-1-yl)propan-2-yl)aniline 19



To a pre cooled (0 °C) solution of alcohol **16** (1.1 g, 4.5 mmol) in dry DCM (50 mL) was added triethylamine (1.9 mL, 13.6 mmol) followed by slow addition of methanesulfonyl chloride (0.4 mL, 5.9 mmol) dropwise. The reaction mixture was stirred at 10°C for 2 h before quenching with water, more DCM was added and extracted with water, washed with brine and evaporated under reduced pressure. The crude product **17** was used for next step without purification.

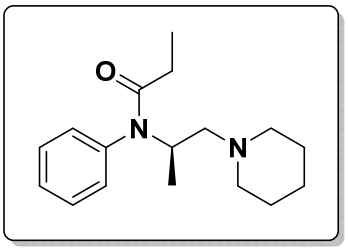
To a stirred solution of the crude product **17** in dry toluene was added triethylamine (0.6 mL, 4.9 mmol) followed by addition of piperidine (0.8 mL, 8.1 mmol). The reaction mixture was refluxed for 8 h and the solvent was evaporated under vacou. DCM (25 mL) was added and the organic layer was washed with water (2 x 15 mL), brine and dried over Na_2SO_4 and evaporated under reduced pressure. The crude oil obtained was purified over column chromatography (silica gel, petroleum ether/EtOAc, 80:20) so as to afford **19** as oil (0.4 g, 30%); $[\alpha]_D^{25}$ = +26.5 (c 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.25 (d, *J* = 6.5 Hz, 3H), 1.39-1.58 (m, 6H), 2.23-2.54 (m, 6H), 4.20-4.30 (m, 1H), 4.42 (s, 2H), 6.61-6.73 (m, 3H), 7.10-7.34 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 149.2 (C), 140.4 (C), 128.9 (CH, 2 carbons), 128.2 (CH, 2 carbons), 126.4 (CH, 2 carbons), 126.3 (CH), 116.3 (CH), 113.4 (CH, 2 carbons), 62.6 (CH_2), 55.2 (CH_2, 2 carbons), 50.9 (CH), 48.8 (CH_2), 26.0 (CH_2, 2 carbons), 24.3 (CH_2), 16.6 (CH_3); Analysis: $C_{21}H_{28}N_2$; Calcd: C, 81.77; H, 9.15; N, 9.08; Found: C, 81.43, H, 8.88; N, 9.41; MS: *m/z* 331 $[M+Na]^+$.

5) (*R*)-*N*-(1-(piperidin-1-yl)propan-2-yl)aniline 12



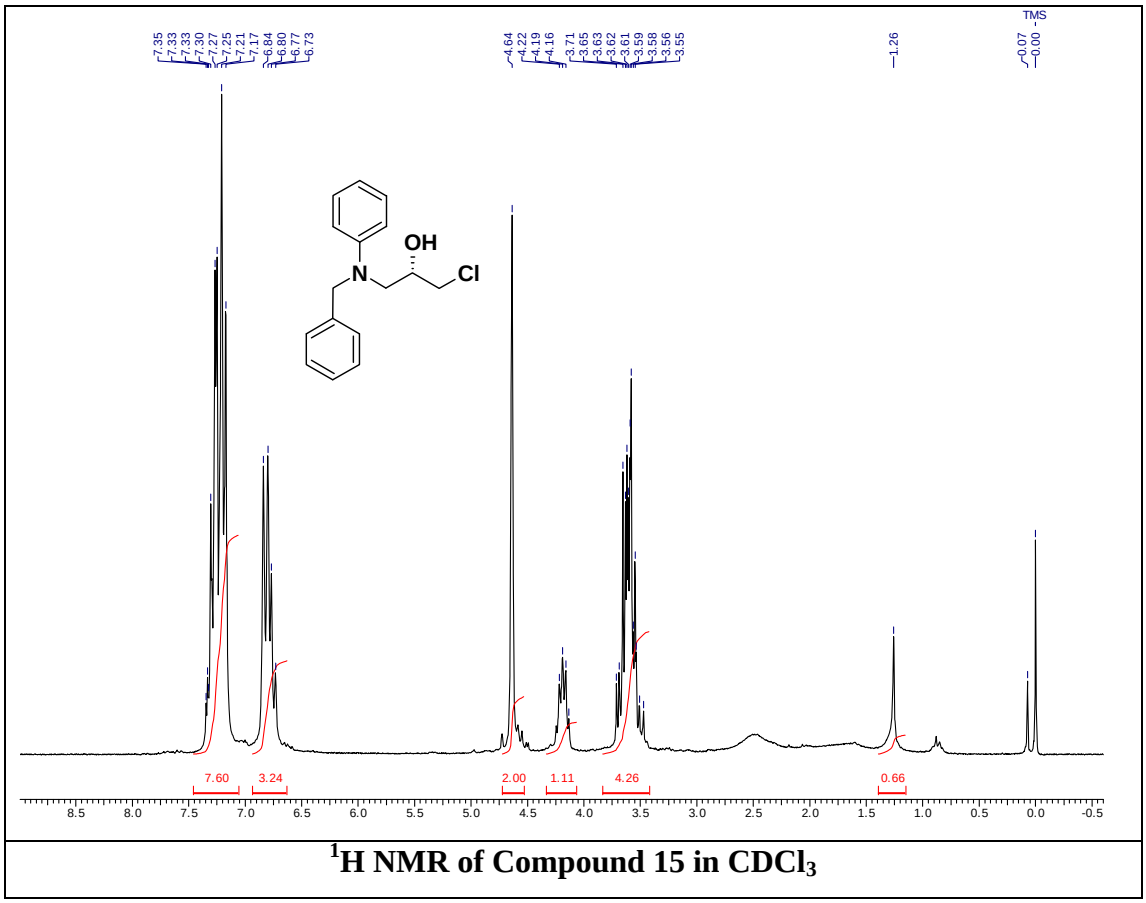
To a solution of **19** (0.2 g, 0.6 mmol) in methanol (10 mL) was added palladium hydroxide (0.02 g, 10-20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 6 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of celite bed and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 80:20) so as to afford **12** as a colorless oil (0.12 g, 91%); $[\alpha]_D^{25}$ = -22.3 (*c* 1.28, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.20 (d, *J* = 6.0 Hz, 3H), 1.47-1.59 (m, 6H), 2.23-2.47 (m, 6H), 3.38-3.54 (m, 1H), 6.64-6.73 (m, 3H), 7.13-7.21 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 148.5 (C), 129.1 (CH, 2 carbons), 117.1 (CH), 113.6 (CH, 2 carbons), 64.5 (CH_2), 54.5 (CH_2, 2 carbons), 45.6 (CH), 26.0 (CH_2, 2 carbons), 24.3 (CH_2), 19.8 (CH_3); MS: *m/z* 219 $[M+H]^+$.

6) (*R*)-*N*-phenyl-*N*-(1-(piperidin-1-yl)propan-2-yl)propionamide 1

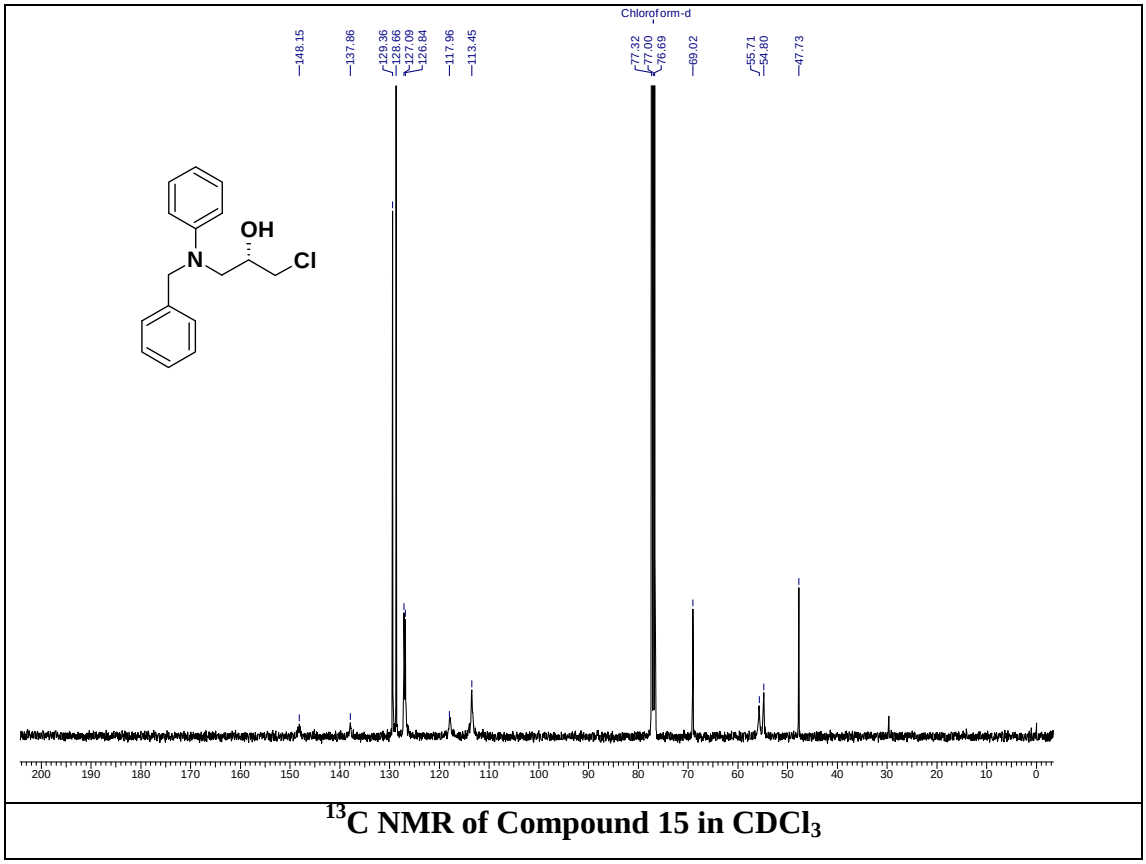


To a solution of compound **12** (0.1 g, 0.45 mmol) in dry toluene (2 ml) was added K_2CO_3 (0.13 g, 0.9 mmol). The reaction mixture was cooled to 0 °C and propionyl chloride (0.045 ml, 0.5 mmol) was added slowly and stirred the content at 10 ºC for 4 h. After completion of the reaction, filtered the solid and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 95:5) to afford **1** as colorless oil (0.08 g, 69%); $[\alpha]_D^{25}$ = -28.4 (c 1.05, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$= -16.3 (*c* 2, H_2O)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.00-1.04 (m, 6H), 1.40-1.43 (m, 2H), 1.52-1.59 (m, 4H), 1.89-1.97 (m, 3H), 2.12-2.24 (m, 3H), 2.49-2.50 (m, 2H), 5.16-5.18 (m, 1H), 7.08-7.09 (m, 1H), 7.38-7.41 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 173.7 (CO), 138.8 (C), 130.6 (CH, 2 carbons), 128.9 (CH), 128.0 (CH, 2 carbons), 62.2 (CH_2), 54.5 (CH_2, 2 carbons), 46.5 (CH), 28.4 (CH_2), 26.2 (CH_2, 2 carbons), 24.5 (CH_2), 17.4 (CH_3), 9.7 (CH_3); MS: *m/z* 297 $[M+Na]^+$.

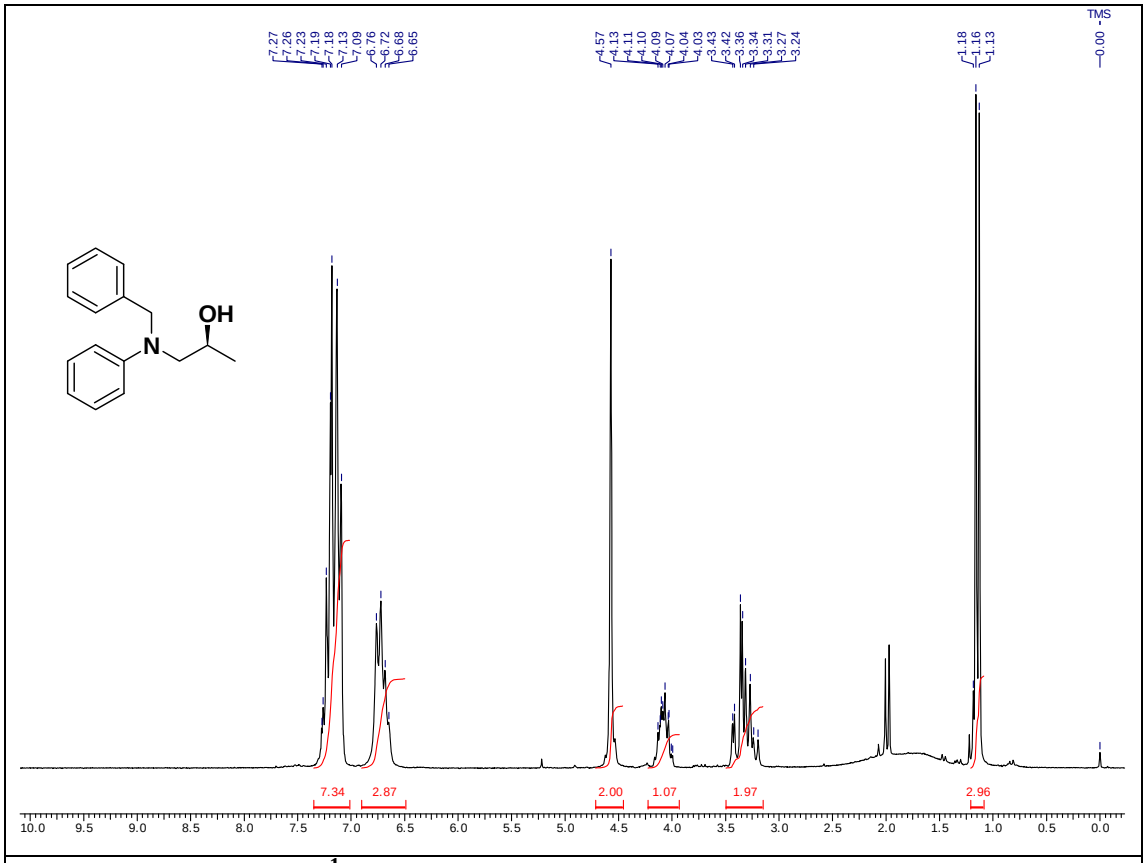
3.2.7. Analytical data



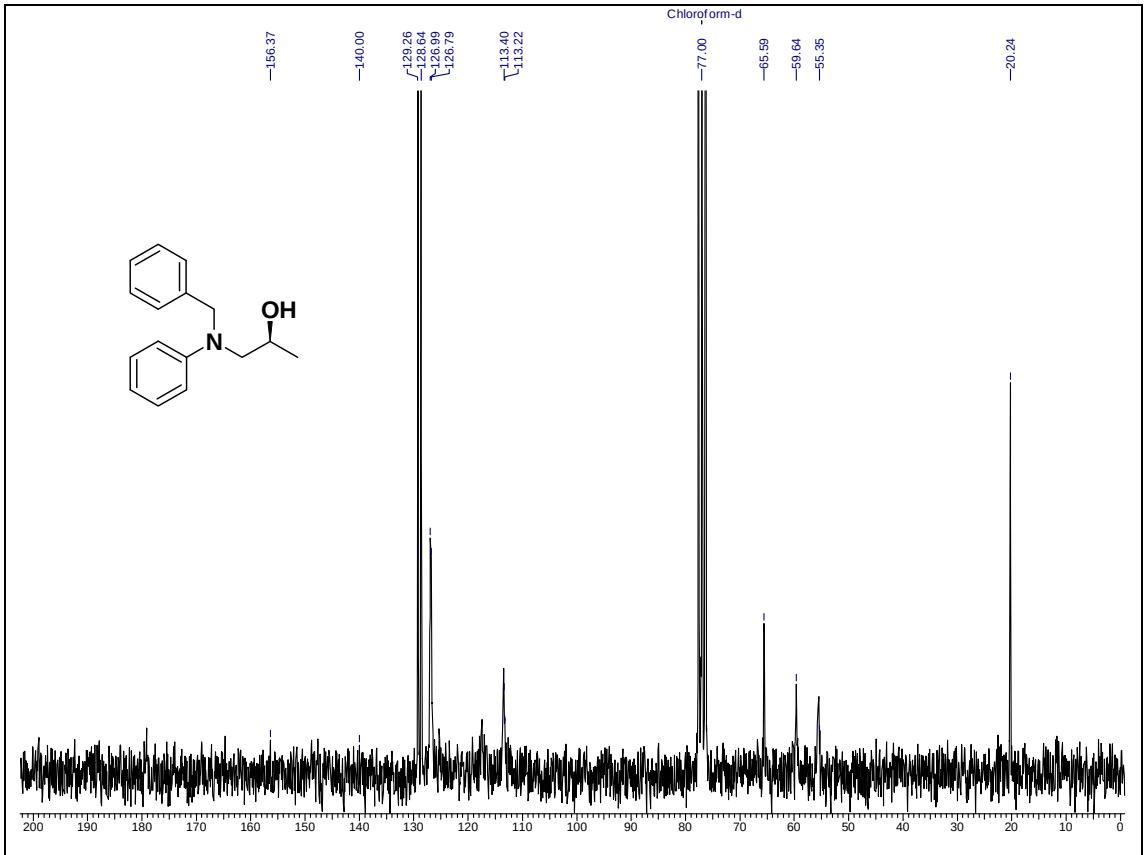
^{1}H NMR of Compound 15 in $CDCl_3$



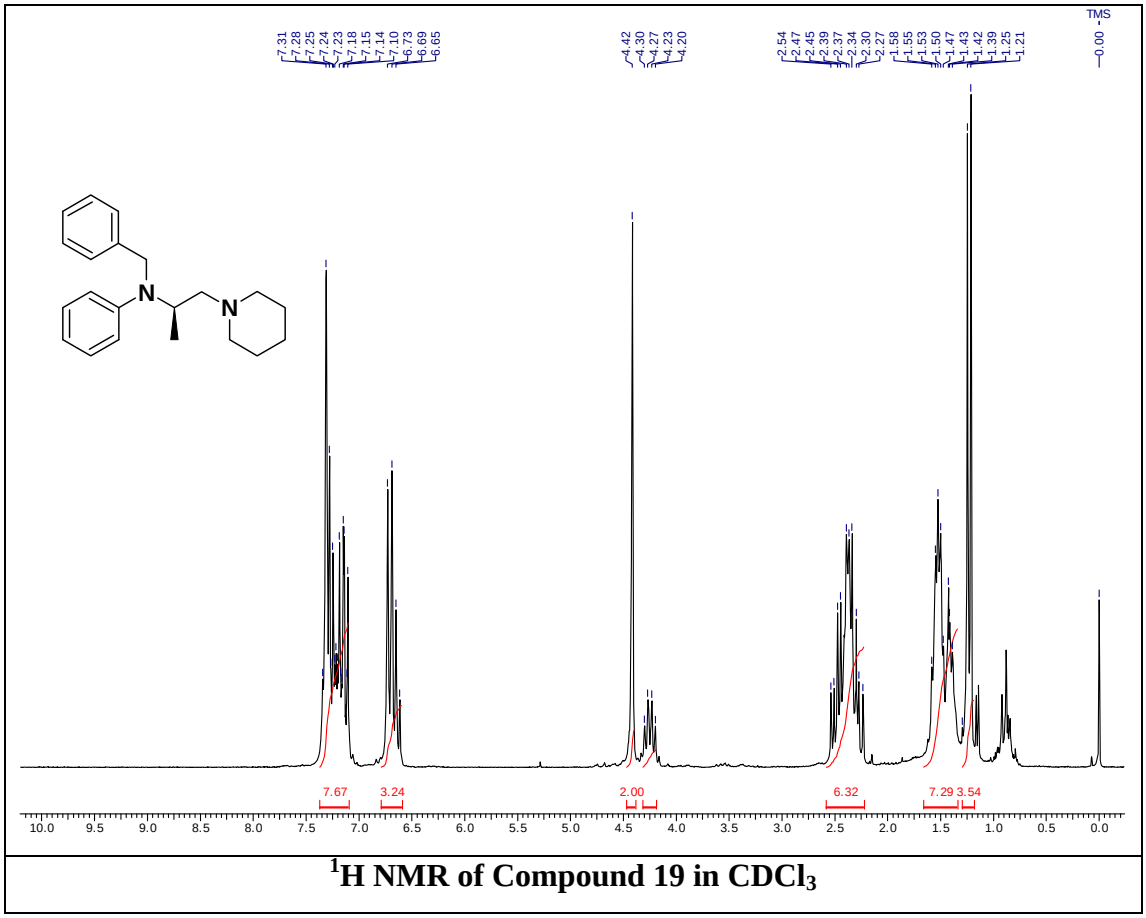
^{13}C NMR of Compound 15 in $CDCl_3$



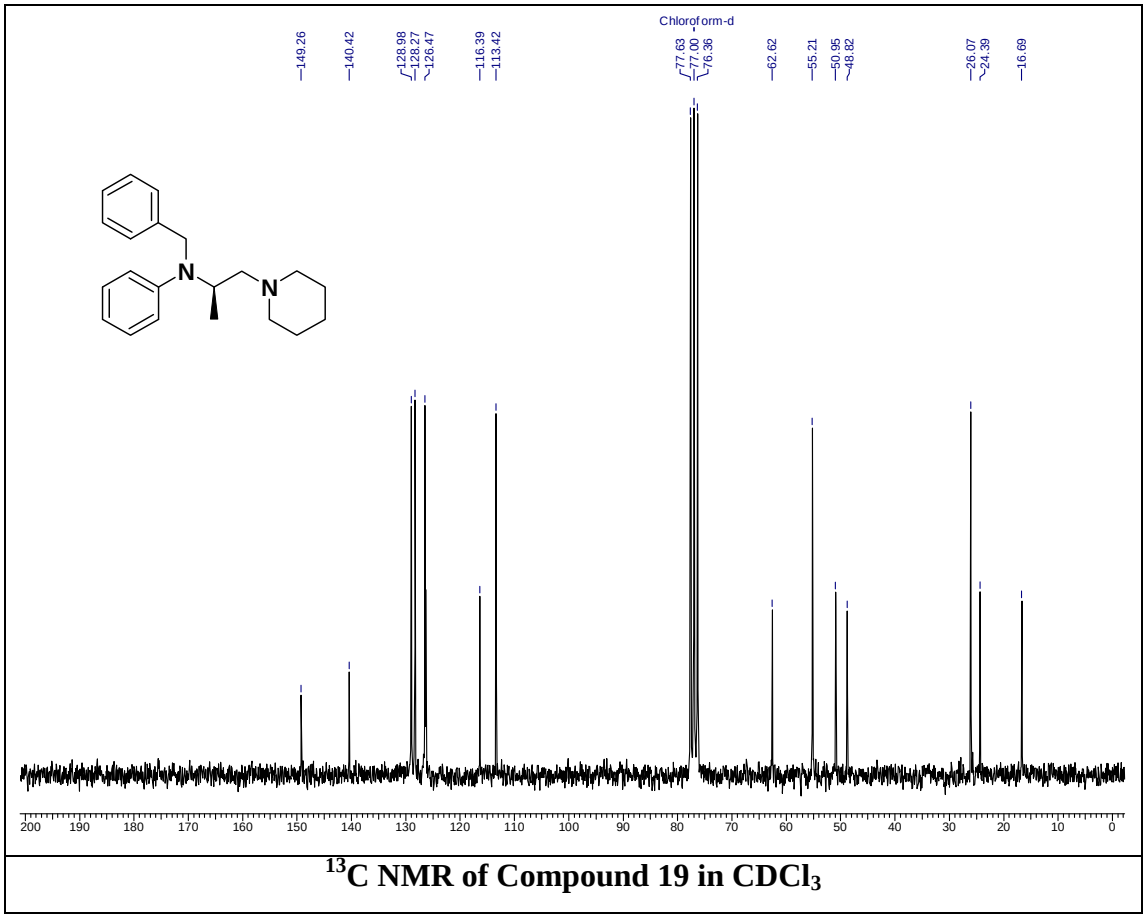
^{1}H NMR of Compound 16 in $CDCl_3$



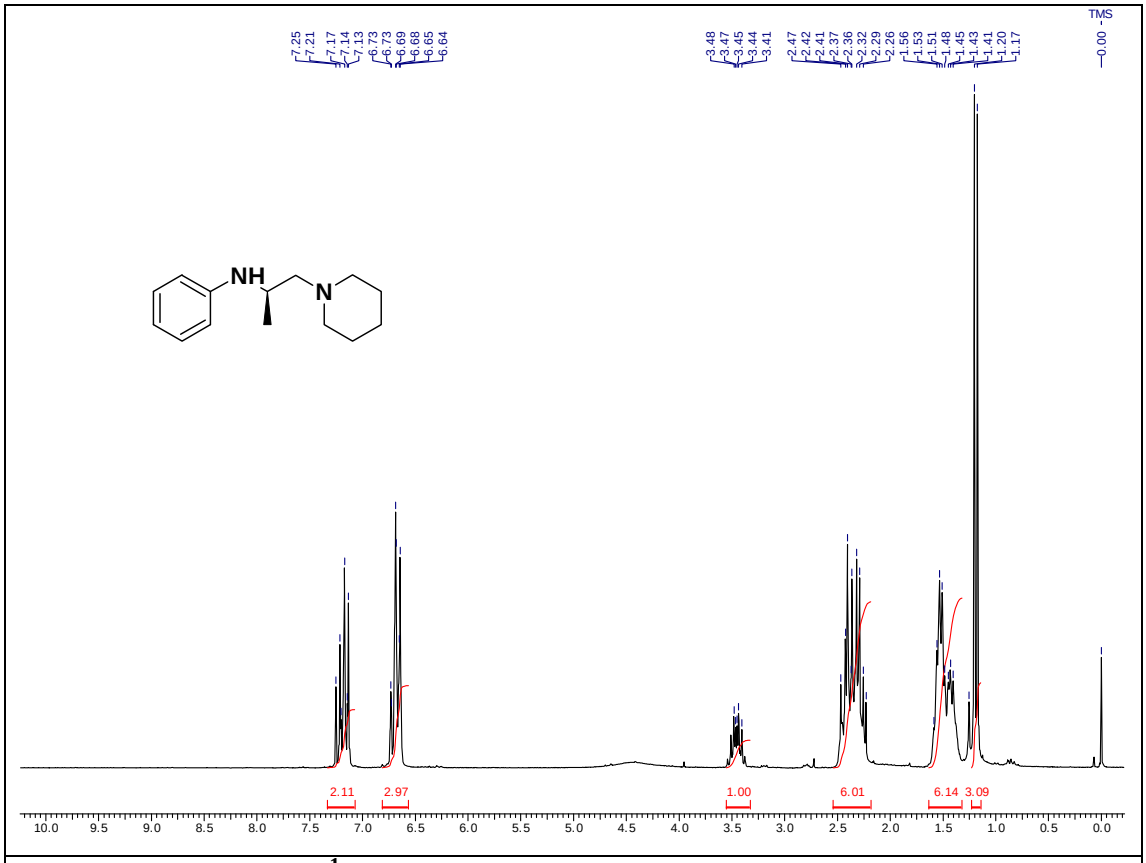
^{13}C NMR of Compound 16 in $CDCl_3$



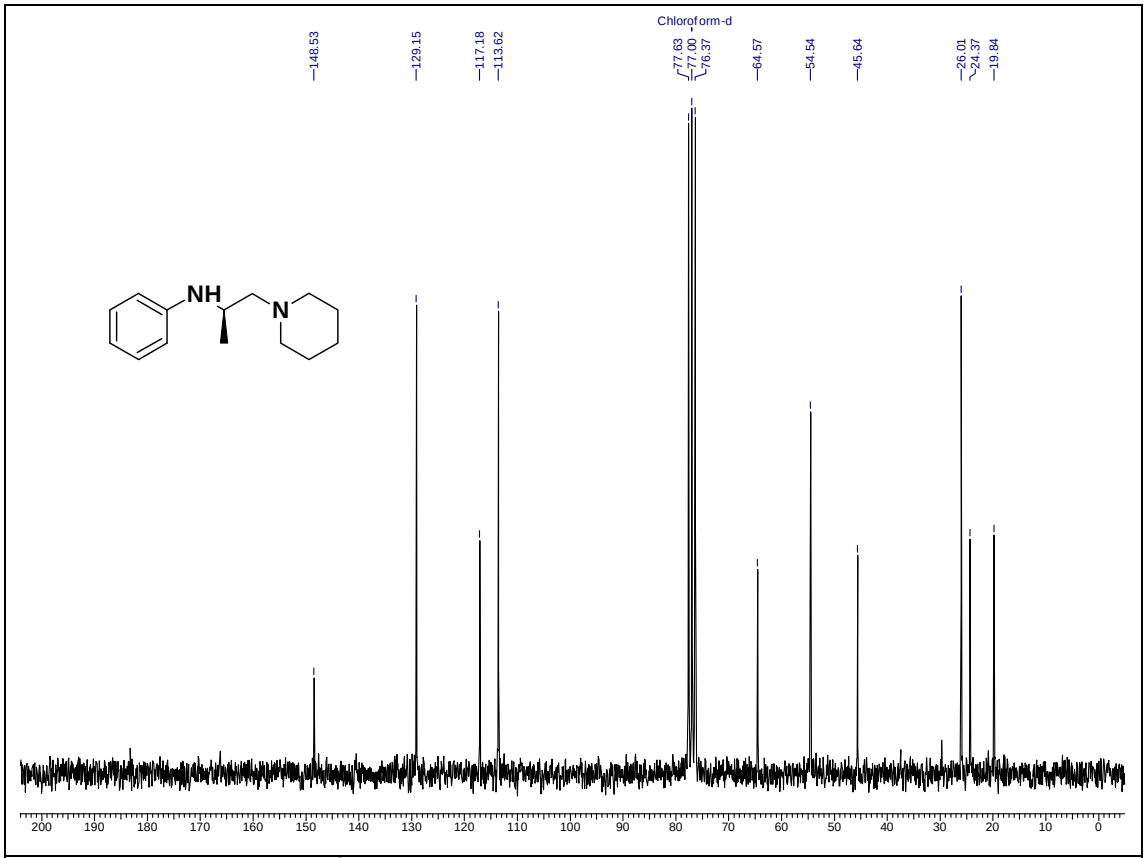
^{1}H NMR of Compound 19 in $CDCl_3$



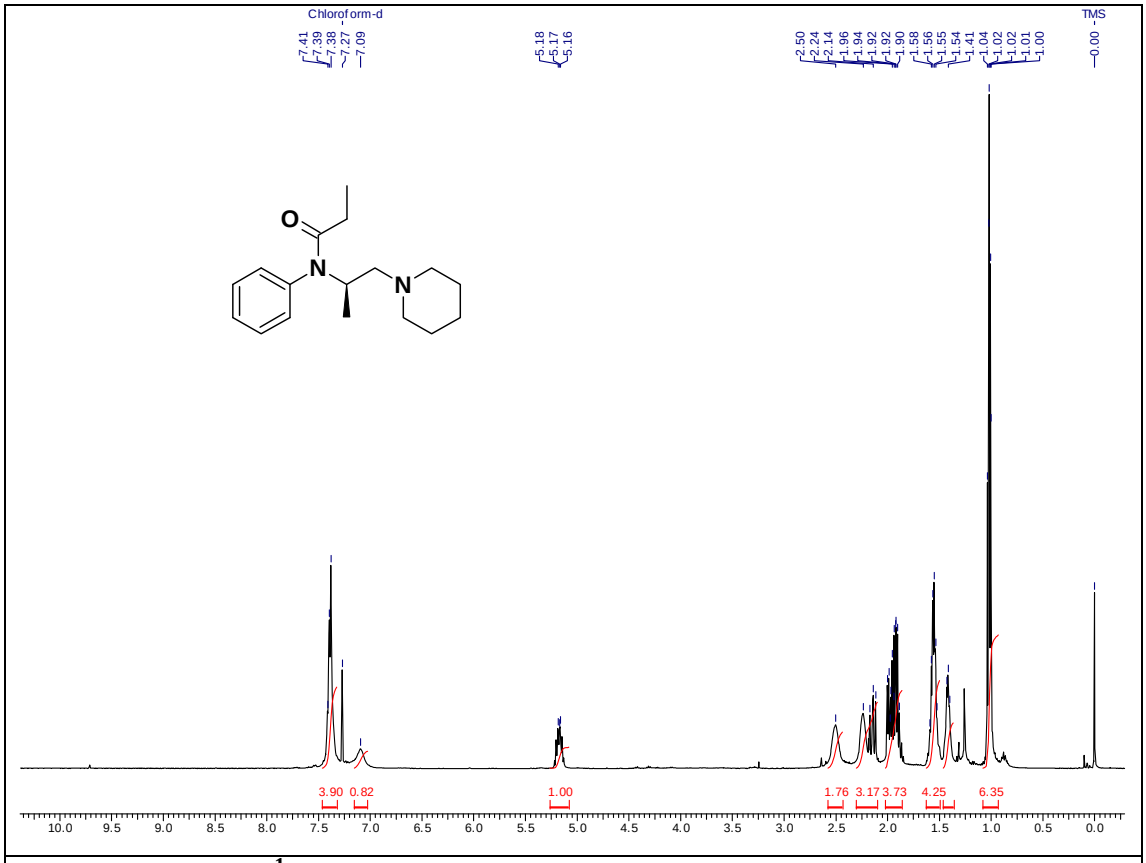
^{13}C NMR of Compound 19 in $CDCl_3$



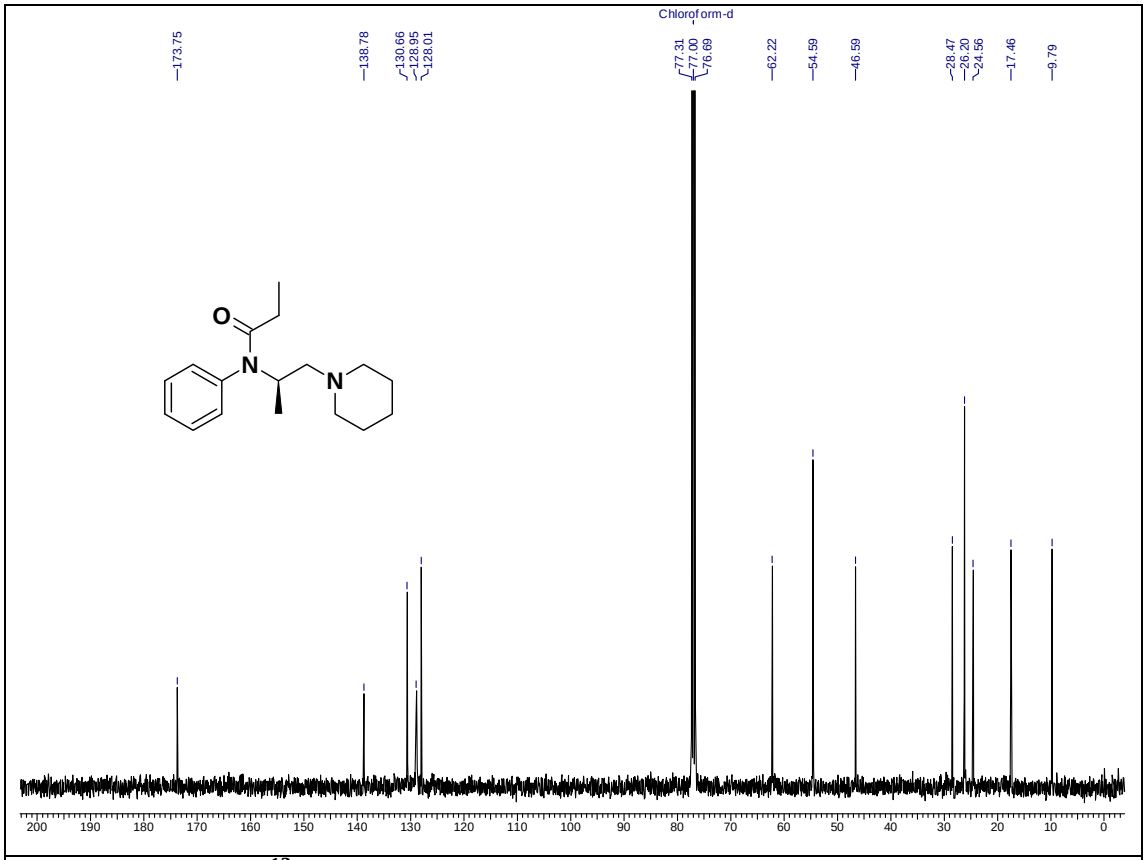
^{1}H NMR of Compound 12 in $CDCl_3$



^{13}C NMR of Compound 12 in $CDCl_3$

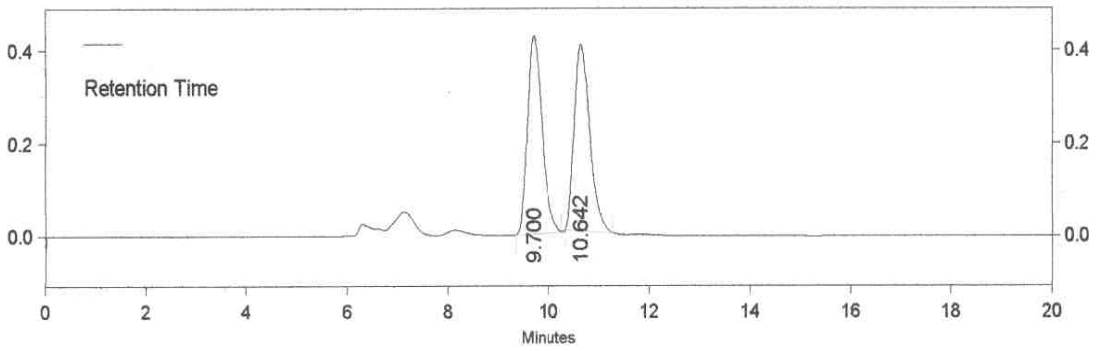


^{1}H NMR of (*R*)-phenampromide 1 in $CDCl_3$



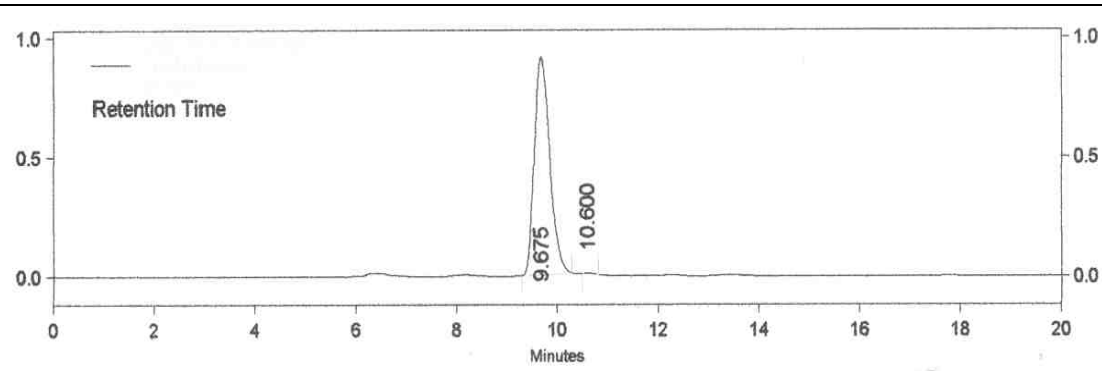
^{13}C NMR of (*R*)-phenampromide 1 in $CDCl_3$

Chiral HPLC Analysis of (*R*)-Phenampromide



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	**9.700**	**8711218**	**50.100**
2	**10.642**	**8507408**	**49.900**
Totals		**17218626**	**100.000**



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
1	**9.675**	**19600245**	**99.800**
2	**10.600**	**39187**	**0.200**
Totals		**9677272**	**100.000**

3.2.8. References

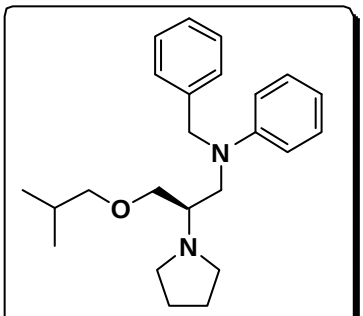
1. Harper, D. *Online Entymology Dictionary: Analgesia* **(2001)**
2. Wright, W. B.; Brabander, H. J.; Hardy, R. A. *J. Org. Chem.*, **1961**, *26*, 476.
3. Portoghese, P. S.; *J. Med. Chem*., **1965**, *8*, 147.
4. Schaus, S. E.; Brandes, B.D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A.E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307.
5. Metro, T-X.; Duthion, B.; Pardo D. G.; Cossy, J. *Chem. Soc. Rev*. **2010**, *39*, 89.

3.3. SECTION C

Asymmetric synthesis of calcium channel blocker (*R*)-Bepridil

3.3.1. Introduction

Calcium channel blockers are chemical compounds that disrupt the movement of calcium (Ca^{2+}) through calcium channels. Calcium channel blockers interfere with the inward movement of calcium ions through the slow channels in heart and vascular smooth muscle cell membranes, leading to relaxation of vascular smooth muscle.[1] The most widespread clinical usage of calcium channel blockers is to decrease blood pressure in patients with hypertension. They are particularly efficacious in treating elderly patients. Calcium channel blockers are also frequently used to alter heart rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris.



(R)-Bepridil
***(R)*-1**

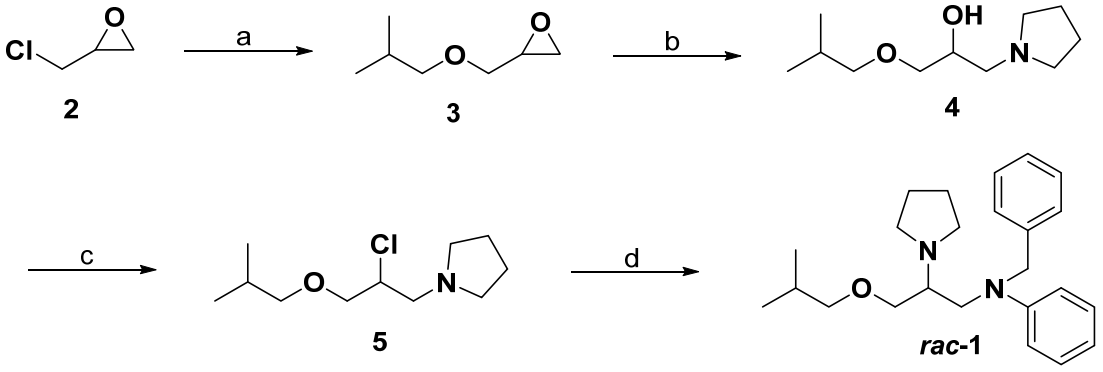
Bepridil **1** is an important calcium channel blocker, highly effective anti-arrhythmic agent with anti-anginal properties.[2] Further, bepridil along with another calcium channel blocker verapamil are used as an alternative to a β-blocker to treat stable angina. However, pharmacological studies on the effect of the stereoisomers of bepridil on the coronary flow and the maximum systolic left ventricular pressure (MSLVP) of heart shows that *(R)*-enantiomer of bepridil was found to be more potent than its *(S)*-enatiomer.[3] Further, recent investigations reveals the potential utility of bepridil as an antiviral agent[4] as well as treating against neurological disorders.[5]

3.3.2. Review of Literature

Only few reports are available in the literature for the synthesis of racemic as well as optically active *(R)*-bepridil **(*R*)-1** which are described below.

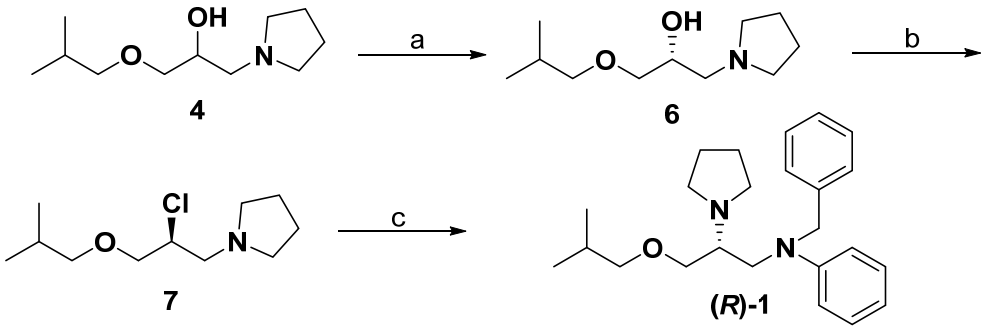
Mauvernay *et al.* (1976)[6]

Mauvernay *et al.* reported the racemic synthesis of bepridil (Scheme 1). The synthesis started with epichlorohydrin **2** which on treatment with isobutanol under basic conditions provided epoxide **3**. Further, the epoxide **3** was regioselectively opened with pyrrolidine followed by treatment with thionyl chloride afforded the intermediate **5**. The intermediate **5** on treatment with *N*-benzylaniline afforded bepridil **1** via formation of aziridinium ion.



Scheme 1. *Reagents and conditions*: (a) isobutanol, NaOH; (b) pyrrolidine; (c) $SOCl_2$, $CHCl_3$; (d) *N*-benzylaniline, $NaNH_2$, xylene.

Winslow *et al.* (1985)[7]



Scheme 2. *Reagents and conditions*: (a) D-(+) dibenzoyl tartaric acid monohydrate, EtOH then NaOH, 27%; (b) $SOCl_2$, toluene, 75%; (c) *N*-benzylaniline, toluene, 74%.

Winslow *et al.* reported the synthesis of *(R)*-bepridil **(*R*)-1** using resolution method (Scheme 2). Thus, compound **4** was resolved using D-(+) dibenzoyl tartaric acid monohydrate to provide optically active compound **6** in 27% yield. Compound **6** on treatment with thionyl chloride followed by reaction with *N*-benzylaniline afforded (*R*)-bepridil **(*R*)-1** via formation of aziridinium ion.

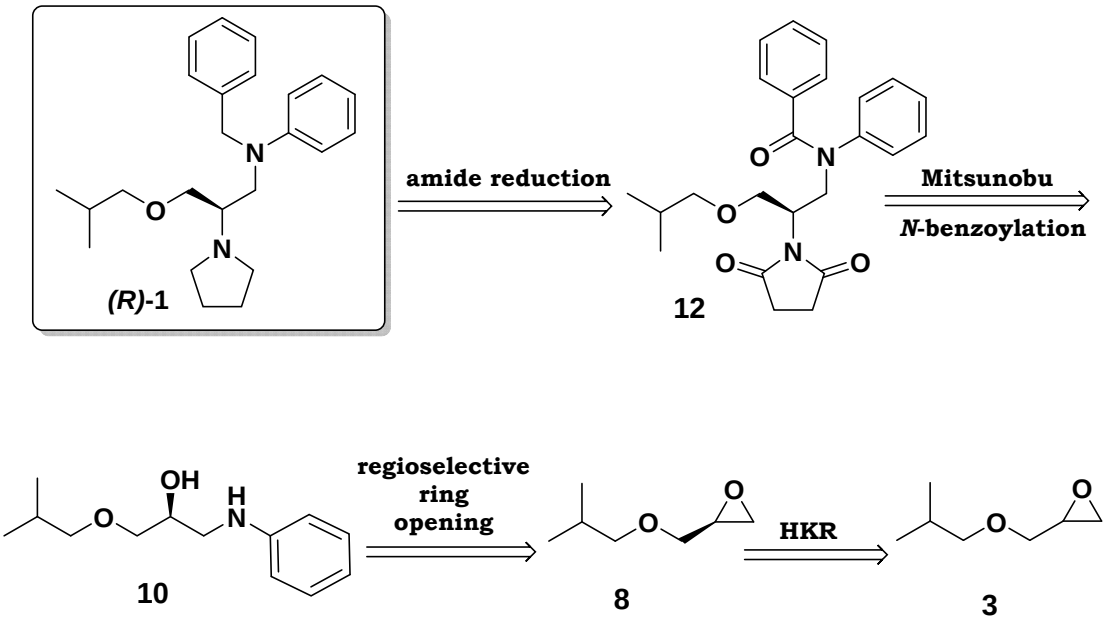
3.3.3. Present Work

Objective

The existing methods for the synthesis of *(R)*-bepridil **(*R*)-1** comprises only resolution processes and there is no asymmetric synthetic route to this potential molecule till date. Therefore, there is a need for practical and highly enantioselective synthesis of *(R)*-bepridil **(*R*)-1**. We thought it would be worthwhile to design a synthetic route for this molecule using Jacobsen's HKR method as a key step.

3.3.4. Results and Discussion

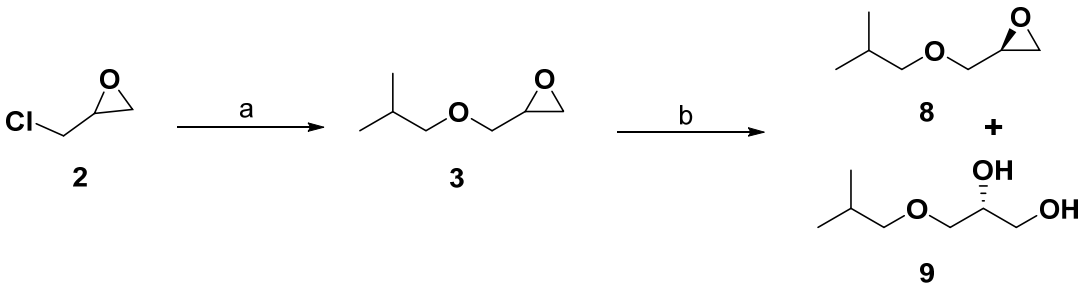
A retrosynthetic analysis of *(R)*-bepridil **(*R*)-1** is outlined in Scheme 3.



Scheme 3. Retrosynthetic analysis of *(R)*-Bepridil

We envisaged that the amino alcohol precursor **10** can be visualized as a key intermediate for the synthesis. Further, amino alcohol **10** can be transformed to succinimido derivative **12** via Mitsunobu and *N*-benzoylation. Compound **12** can be elaborated to the target molecule employing amide reduction. The key intermediate amino alcohol derivative **10** can be accessed from enantiopure epoxide **8** via regioselective ring opening. The optically pure epoxide **8** can be obtained from its racemic form using Jacobsen's hydrolytic kinetic resolution technique.

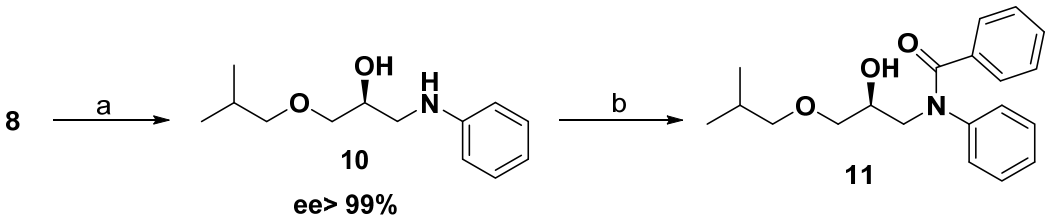
Accordingly, our synthesis commenced with readily available starting material epichlorohydrin (Scheme 4) which on treatment with isobutanol under basic conditions using catalytic amount of phase transfer catalyst provided epoxide **3.** Appearance of a doublet at δ 0.89 (6H) and a multiplet at δ 3.12-3.18 (1H) in ^{1}H NMR and m/z peak at 153 $(M+Na)^{+}$ in mass spectrum confirmed the formation of epoxide **3**. The *rac*-epoxide **3** was subjected to Jacobsen's hydrolytic kinetic resolution conditions with 0.55 equivalents of water using the catalyst (*R,R)* Salen Co (III)-OAc (0.5 mol %) at ambient temperature for 24 h. After completion of the reaction, enantiopure (*S*)-epoxide **8** was isolated using vacuum distillation (75 ºC, 8 mbar) in 40% yield $\{[\alpha]^{21}_{D} = +3.4$ (*c* 1.99, $CHCl_3)\}$ followed by diol **9** in 42% yield $\{[\alpha]^{22}_{D} = -2.0$ (*c* 2.11, $CHCl_3)\}$. As the HKR on epoxide **3** is new, we liked to determine its enantiopurity using chiral HPLC analysis. However, attempts to resolve this compound in HPLC were unsuccessful and decided to check enantiopurity at next stage.



Scheme 4. *Reagents and conditions*: (a) isobutanol, aq. KOH (50 % w/w), TBAI (cat), room temp., 24 h, 62 % (b) (*R,R*) Salen Co (OAc) (0.5 mol %), H_2O (0.55 equiv.) 0 ºC to room temp., 24 h, [40 % for **8,** 42% for **9]**

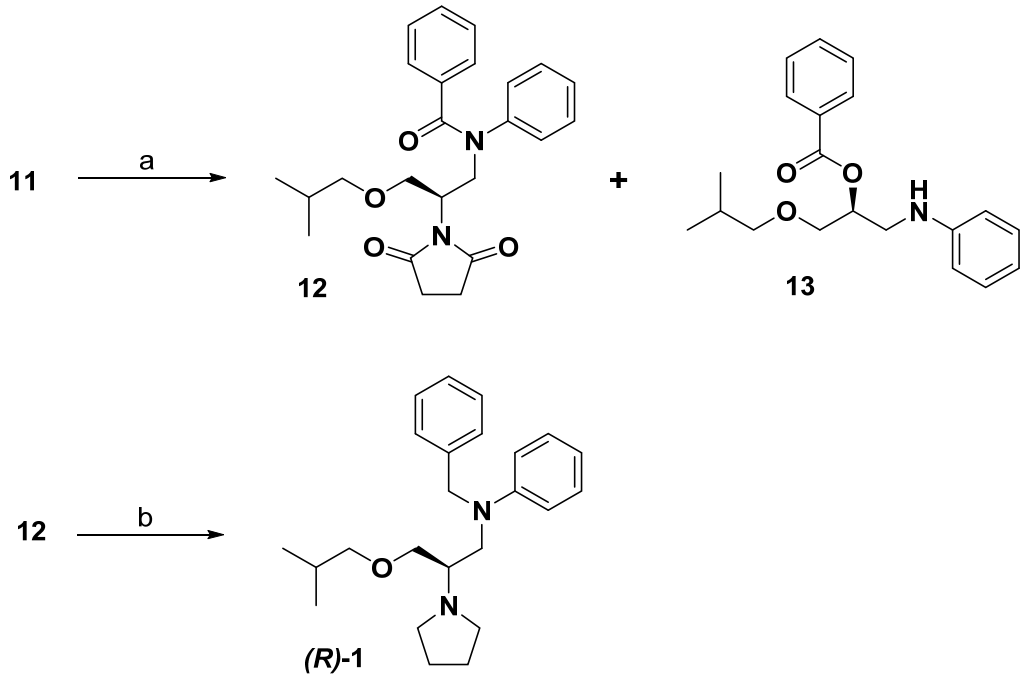
Accordingly, the epoxide **8** was subjected to regioselective ring opening with aniline in presence of catalytic LiBr using methanol as a solvent afforded the amino alcohol

10 in 90% yield. At this stage, we could resolve the amino alcohol **10** through chiral HPLC and the optical purity was found to be >99%. Appearance of aromatic protons at δ 6.62-6.75 (m, 3H) and 7.11-7.25 (m, 2H) in ^{1}H NMR and m/z peak at 246 $(M+Na)^+$ in the mass spectrum supports the formation of amino alcohol **10**. Subsequently, the compound **10** was *N*-benzolyated using benzoyl chloride to get hydroxy phenylbenzamide **11** in 85% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) aniline, LiBr, MeOH, room temp.,12 h, 90%; (b) C_6H_5COCl, Et_3N, DCM, 0 ºC, 1h, 85%.

Compound **11** upon treatment with succinimide under Mitsunobu condition using PPh_3 and DIAD provided succinimide derivative **12** in 40% yield.

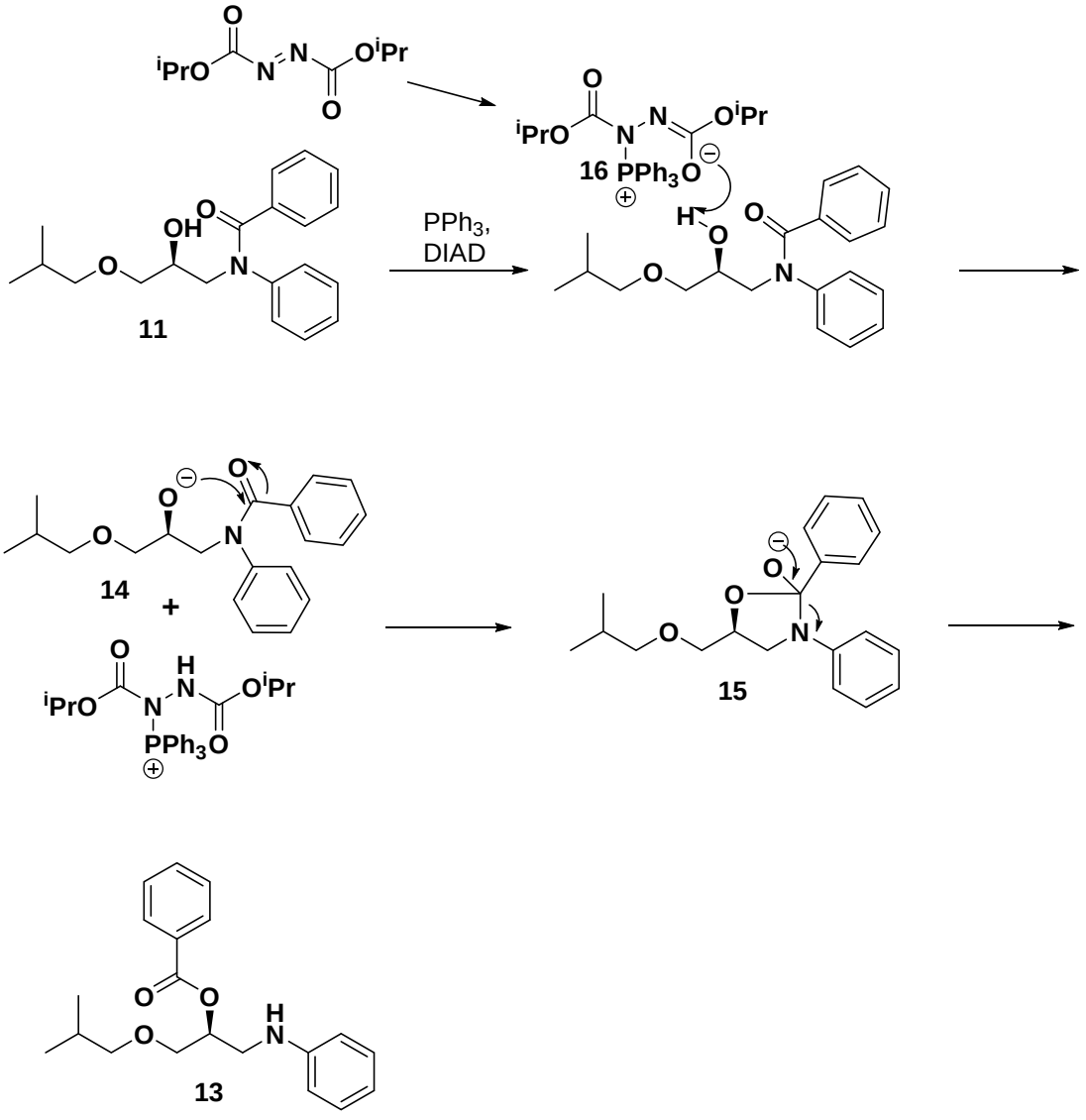


Scheme 6. *Reagents and conditions*: (a) succinimide, DIAD, Ph_3P, THF (dry), 0 ºC-rt, 12 h, [40% for **12**, 25% for **13]**; (b) Borane-DMS, THF (dry), reflux, 12 h, 70%.

Interestingly, in addition to the desired compound **12**, we isolated less polar N→O benzoyl migrated product **13** in 25% yield (Scheme 6). To improve the yield of **12**,

Mitsunobu reaction was repeated with DIAD and Bu_3P instead of PPh_3. Although the yield has been improved to 52%, complete racemization of the final product ***(R)*-1** was observed. Finally, the reduction of all the amide bonds were carried out using borane-DMS under reflux condition to achieve the target molecule *(R)*-bepridil (*R*)-**1** $\{[\alpha]^{21}_D = -19.9$ (*c* 1.23, MeOH)$\}$. The structure of ***(R)*-1** was confirmed by its IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis.

The formation of N→O benzoyl migration product **13** during Mitsunobu reaction can be explained through the mechanism which is depicted in Scheme 7.[8]



Scheme 7. Proposed mechanism for the formation of N→O migrated product **13**.

Firstly, betaine **16** abstracts a proton of the *C*-2 hydroxyl group of **11** derivative to produce alkoxy anion **14** which on intramolecular nucleophilic addition to the

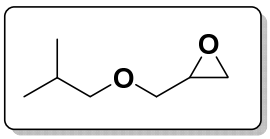
carbonyl carbon of the benzoyl group would result in the formation of five-membered cyclic intermediate **15**. Ring opening of the intermediate **15** would result in the migration of the benzoyl group to adjacent *C*-2 position to provide compound **13**.

3.3.5. Conclusion

In conclusion, a new, practical and highly enantioselective synthesis of (*R*)-bepridil **(*R*)-1** was achieved employing HKR as a key step. High enantiopurity (ee >99%) of *(R)*-bepridil **(*R*)-1** has been obtained. This strategy is well amenable to prepare the other isomer of bepridil **1** and its analogues.

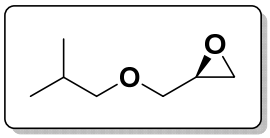
3.3.6. Experimental

1) 2-(isobutoxymethyl)oxirane 3



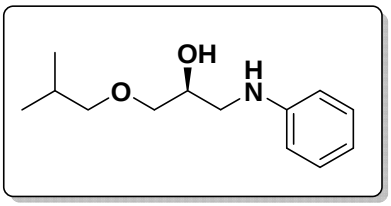
To a stirred solution of aqueous potassium hydroxide (30 mL, 50% w/w), epichlorohydrin **2** (36 mL, 461.5 mmol) and tetrabutylammonium iodide (1.7 g, 4.6 mmol) was added isobutanol (15 mL, 92.3 mmol) at temperature below 25 ºC and the resulting mixture was stirred at room temperature for 24 h. After completion of the reaction cold water (60 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (60 mL), dried over Na_2SO4, and evaporated under reduced pressure. residue was purified by vacuum distillation (75 ºC, 8 mbar) as colorless oil (7.4 g, 62%); IR ($CHCl_3$): ν_{max} 2960, 2873, 1522, 1474, 1421, 1097 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.89 (d, *J* = 6.7 Hz, 6H), 1.81- 1.94 (m, 1H), 2.59- 2.63 (dd, *J* = 4.9, 2.6 Hz, 1H), 2.77- 2.82 (dd, *J* = 4.9, 4.1 Hz, 1H), 3.12-3.18 (m, 1H), 3.23 (d, *J* = 3.4 Hz, 1H), 3.28 (d, J = 3.5 Hz, 1H), 3.33-3.42 (dd, *J* = 11.5, 5.7 Hz, 1H), 3.67-3.74 (dd, *J* = 11.5, 3.0 Hz, 1H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 78.4 (CH_2), 71.5 (CH_2), 50.9 (CH), 44.2 (CH_2), 28.4 (CH), 19.2 (CH_3, 2 carbons); MS: m/z 153 $[M+Na]^+$.

2) *(S)*-2-(isobutoxymethyl)oxirane 8



A mixture of 2-(isobutoxymethyl)oxirane **3** (5 g, 38.4 mmol) and *(R,R)* Salen Co(III)-OAc complex (0.055 g, 0.0812 mmol) was vigorously stirred for 15 min at room temperature, then cooled to 0 ºC and water was added (0.380 mL, 21.12 mmol) over a period of 15 min, through a microsyringe. The reaction mixture was stirred at room temperature for 12 h, followed by addition of *(R,R)* Salen Co(III)-OAc complex (0.055 g, 0.0812 mmol) and stirring was continued for additional 12 h. The reaction mixture was diluted with ethyl acetate, dried over Na_2SO_4, and evaporated under reduced pressure. The (*S*)-epoxide **8** from residual liquid was purified by vacuum distillation (75 ºC, 8 mbar) as colorless oil (2.0 g, 40%), $[\alpha]^{21}_D$ = +3.4 (*c* 1.99, $CHCl_3$) followed by the diol **9** (150 ºC, 8 mbar) as light yellow oil (2.4 g, 42%), $[\alpha]^{22}_D$ = -2.0 (*c* 2.11, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3751, 3574, 2961, 2875, 1524, 1477, 1400, 1031, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.93 (d, *J* = 6.7 Hz, 6H), 1.78- 1.98 (m, 1H), 2.60- 2.64 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.78- 2.82 (dd, *J* = 5.0, 4.1 Hz, 1H), 3.15- 3.25 (m, 2H), 3.48- 3.51 (m, 2H), 3.68- 3.75 (m, 2H), 3.82- 3.92 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 78.4 (CH_2), 72.5 (CH_2), 70.6 (CH), 64.2 (CH_2), 28.3 (CH), 19.2 (CH_3, 2 carbons); MS: m/z 171 $[M+Na]^+$.

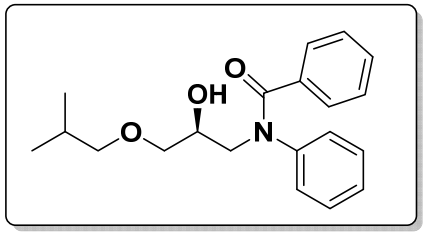
3) *(S)*-1-isobutoxy-3-(phenylamino)propan-2-ol 10



To a stirred solution of epoxide **8** (1 g, 7.68 mmol) and aniline (0.858 g, 9.21 mmol) in methanol (20 mL) under N_2 atmosphere was added lithium bromide (0.13 g, 1.5 mmol) and the resulting mixture was stirred for 12 hours at room temperature. After completion of the reaction, (indicated by TLC) methanol was evaporated under reduced pressure. Water (15 mL) was added and extracted with ethyl acetate (15 mL x 3). The organic phase was washed by brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified using column chromatography (silica gel, petroleum ether/ethyl acetate, 85:15) to yield **10** as an oil (1.54 g, 90%), $[\alpha]^{22}_D$ = +2.5

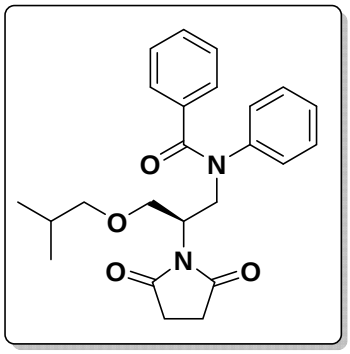
(*c* 2.5, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3751, 3682, 3660, 3573, 3020, 2400, 1699, 1603, 1511, 1419, 1215, 1017, 929, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.94 (d, *J* = 6.7 Hz, 6H), 1.79-1.99 (m, 1H), 3.10-3.35 (m, 5H), 3.42-3.57 (m, 2H), 3.96-4.07 (m, 1H), 6.62-6.75 (m, 3H), 7.11-7.25 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 148.3 (C), 129.2 (CH, 2 carbons), 117.7 (CH), 113.1(CH, 2 carbons), 78.4 (CH_2), 73.0 (CH_2), 69.0 (CH), 46.7 (CH_2), 28.4 (CH), 19.2 (CH_3, 2 carbons); MS: m/z 224 $[M+H]^+$, 246 $[M+Na]^+$; ee >99% [Chiralcel OD-H (250 x 4.6 mm) column; eluent: pet ether/ethanol/trifluoroacetic acid (85:15:0.1); flow rate 0.5 mL/min; detector: 254 nm] [*(S)*-isomer t_R = 11.10 min, *(R)*-isomer t_R = 12.17 min].

4) *(S)*-*N*-(2-hydroxy-3-isobutoxypropyl)-*N*-phenylbenzamide 11



To a stirred solution of **10** (1.2 g, 5.37 mmol) in dry DCM at 0 °C, under N_2 atmosphere was slowly added benzoyl chloride (0.68 mL, 5.91 mmol) followed by triethyl amine (1.49 mL, 10.75 mmol) dropwise over 15 minutes. The resulting mixture was stirred for 1 hour at 0 ºC. After completion of reaction (indicated by TLC) cold water (15 mL) was added and the crude mixture was extracted with DCM (3 x 15 mL). The organic layer was washed with 1N HCl (15 mL), sat $NaHCO_3$ solution (15 mL), and dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified using column chromatography (silica gel, petroleum ether/acetone, 90:10) to yield **11** as an oil (1.5 g, 85%), $[\alpha]^{22}_D$ = +67.3 (*c* 2.32, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3683, 3020, 1578, 1521, 1401, 1017, 928 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.85 (d, *J* = 6.7 Hz, 6H), 1.68-1.85 (m, 2H), 3.16 (d, *J* = 6.6 Hz, 2H), 3.47 (d, *J* = 5.3 Hz, 2H), 3.94- 4.02 (m, 1H), 4.06-4.13 (m, 1H), 4.24 (dd, *J* = 13.2, 7.4 Hz, 1H), 7.09-7.33(m, 10 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 172.5 (CO), 143.9 (C), 135.4 (C), 129.9 (CH), 129.1 (CH, 2 carbons), 128.9 (CH, 2 carbons), 127.7 (CH, 2 carbons), 127.6 (CH, 2 carbons), 126.7 (CH), 78.3 (CH_2), 72.7 (CH_2), 69.7 (CH), 55.0 (CH_2), 28.3 (CH), 19.2 (CH_3, 2 carbons); MS: m/z 328 $[M+H]^+$, 350 $[M+Na]^+$.

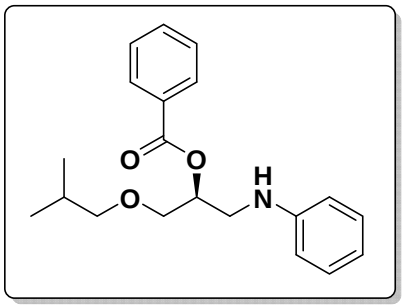
5) *(R)*-*N*-(2-(2,5-dioxopyrrolidin-1-yl)-3-isobutoxypropyl)-*N*-phenylbenzamide 12



A solution of DIAD (0.52 mL, 2.68 mmol) in dry THF (5 mL) was added dropwise to a solution of **11** (0.8 g, 2.44 mmol), succinimide (0.266 g, 2.68 mmol) and triphenyl phosphine (0.7 g, 2.68 mmol) in dry THF (20 mL) under N_2 atmosphere at 0 ºC. The reaction mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 65:35) to yield **12** as an oil (0.4 g, 40%), $[\alpha]^{22}_D$ = +106.8 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3682, 1704, 1524, 1398, 1018 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.81 (d, *J* = 6.5 Hz, 6H), 1.65-1.85 (m, 1H), 2.39 (s, 4H), 3.05-3.21 (m, 2H), 3.78 (d, *J* = 1.7 Hz, 1H), 3.81 (d, *J* = 2.3 Hz, 1H), 4.05 (d, *J* = 11.6 Hz, 1H), 4.64- 4. 82 (m, 2H), 7.02-7.26 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 177.8 (CO, 2 carbons), 171.1 (CO), 143.3 (C), 135.5 (C), 129.7 (CH), 129.0 (CH, 2 carbons), 128.5 (CH, 2 carbons), 127.7 (CH, 2 carbons), 127.3 (CH, 2 carbons), 126.6 (CH), 77.6 (CH_2), 67.3 (CH_2), 51.0 (CH), 47.3 (CH_2), 28.3 (CH), 27.9 (CH_2, 2 carbons), 19.1 (CH_3, 2 carbons); Analysis: $C_{24}H_{28}N_2O_4$; Calcd: C, 70.57; H, 6.91; N, 6.86; Found: C, 70.43, H, 6.88; N, 6.41; MS: m/z 409 $[M+H]^+$, 431 $[M+Na]^+$.

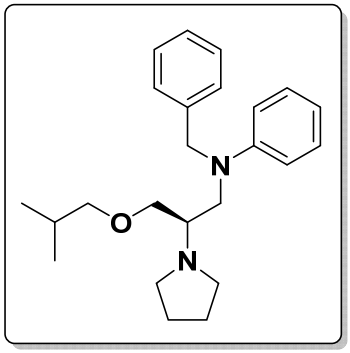
In addition to the above product **12** we have isolated the less polar rearranged product **13**.

(*S*)-1-isobutoxy-3-(phenylamino)propan-2-yl benzoate 13



Colorless oil (0.2 g, 25%); $(\alpha)^{25}_D$ +34.5 (1.18, $CHCl_3$);); IR ($CHCl_3$): ν_{max} 3633, 3020, 2963, 2873, 1716, 1603, 1510, 1423, 1272 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.91 (d, *J* = 6.7 Hz, 6H), 1.61 (brs, 1H), 1.80-2.00 (septet, 1H), 3.27 (dd, *J* = 6.5, 1.3 Hz, 2H), 3.58 (dd, *J* = 5.8, 2.0 Hz, 2H), 3.66- 3.82 (m, 2H), 5.36-5.47 (m, 1H), 6,67-6.75 (m, 3H), 7.15-7.23 (m, 2H), 7.41-7.49 (m, 2H), 7.54-7.63 (m, 1H), 8.03-8.08 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 166.2 (CO), 147.9 (C), 133.4 (CH), 130.0 (C), 129.7 (CH, 2 carbons), 129.2 (CH, 2 carbons), 128.3 (CH, 2 carbons), 117.6 (CH), 112.8 (CH, 2 carbons), 78.5 (CH_2), 72.2 (CH), 70.2 (CH_2), 44.7 (CH_2), 28.4 (CH), 19.2 (CH_3, 2 carbons); MS: 350 $[M+Na]^+$.

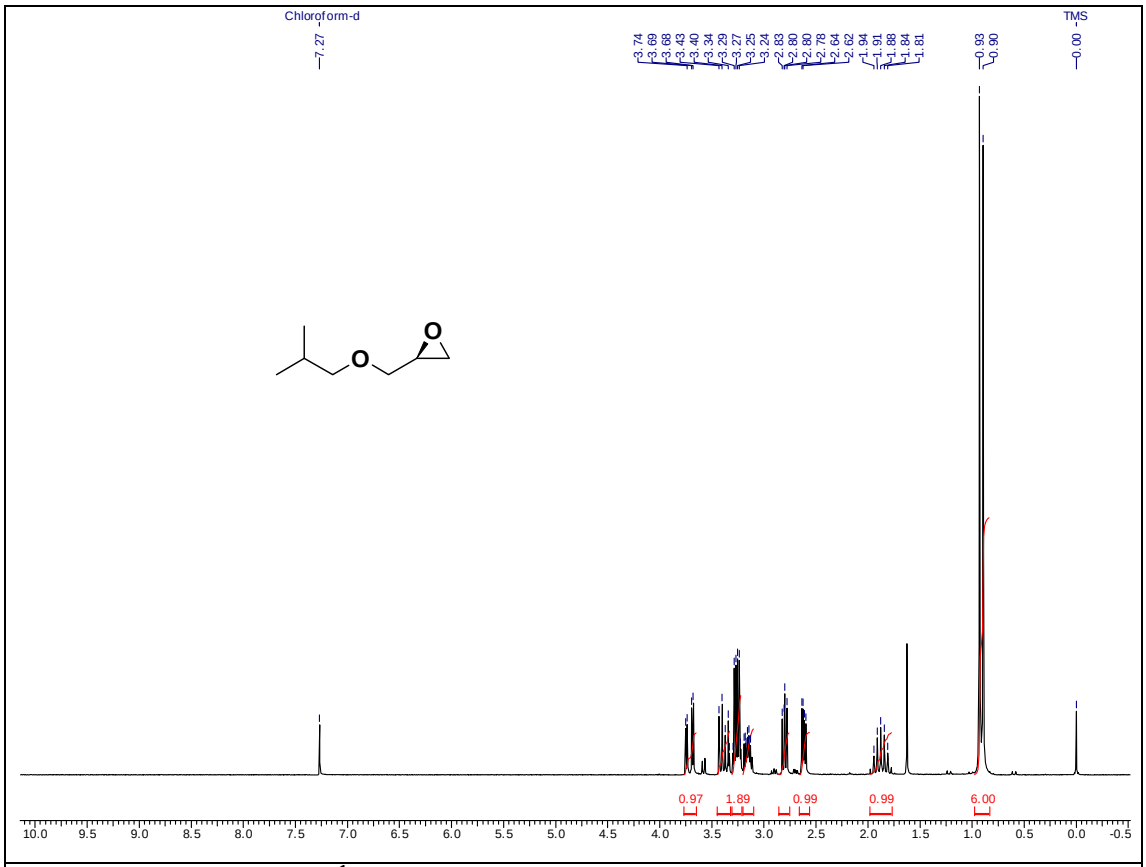
6) *(R)*-*N*-benzyl-*N*-(3-isobutoxy-2-(pyrrolidin-1-yl)propyl)aniline *(R)*-1



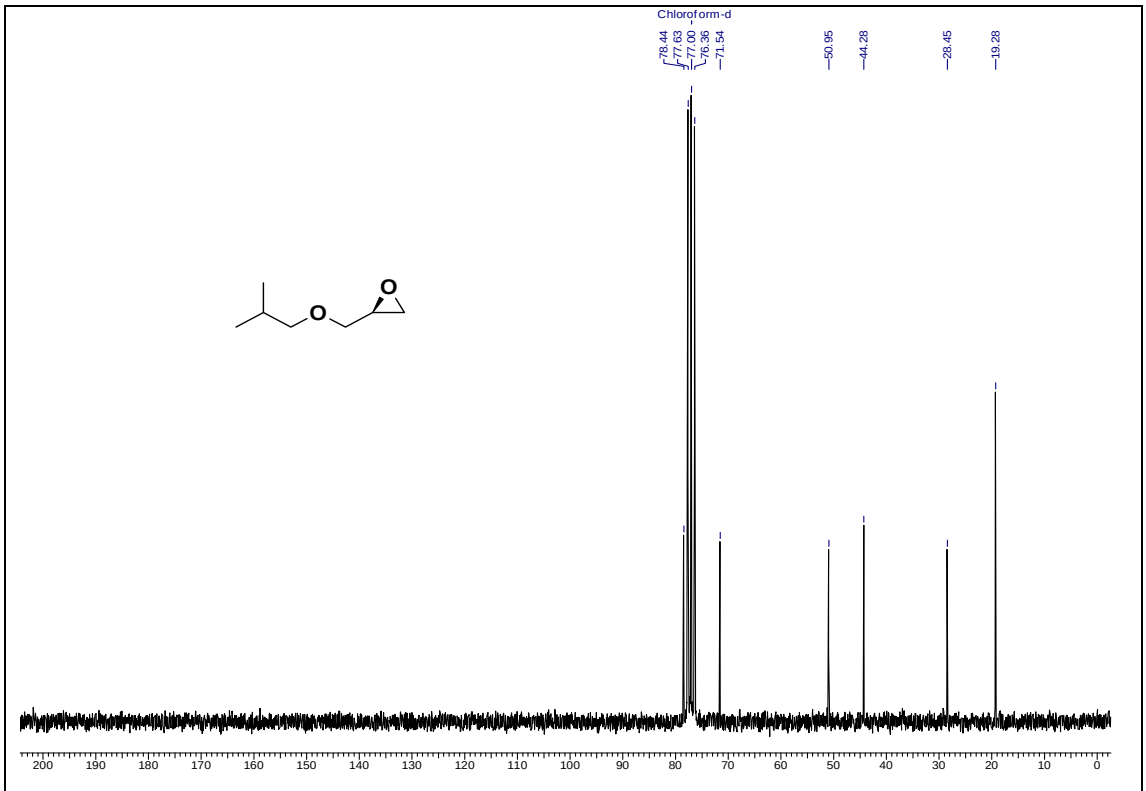
To a solution of compound **12** (0.180 g, 0.44 mmol) in dry THF (5 mL) at 0 ºC was slowly added BH_3-DMS complex (0.2 mL, 2.20 mmol) under N_2 atmosphere. Subsequently, the reaction mixture was refluxed for 12 h. After completion of the reaction, methanol (5 mL) was added carefully at 0 ºC and stirred the content for 20 min. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (40 mL). After an aqueous workup the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 70:30) to yield ***(R)*-1** as an oil (0.113 g, 70%), $[\alpha]^{22}_D$ = -19.9 (*c* 1.23, MeOH); IR ($CHCl_3$): ν_{max} 3061, 3026, 2957, 2799, 1943, 1806, 1735, 1682, 1598, 1505, 1452, 1354, 1294, 1224, 1112, 987, 873,

746, 694 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$): δ_H 0.95 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.77-1.82 (m, 4H), 1.83-185 (m, 1H), 2.78-2.92 (m, 5H), 3.05 (d, *J* = 6.4Hz, 2H), 3.44-3.53 (m, 2H), 3.58-3.70 (m, 2H), 4.61-4.72 (quartet, *J* = 17.3 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 2H), 7.18-7.24 (m, 5H), 7.29-7.32 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 148.5 (C), 138.7 (C), 129.1 (CH, 2 carbons), 128.5 (CH, 2 carbons), 128.2 (CH), 126.6 (CH, 2 carbons), 116.2 (CH), 112.3 (CH, 2 carbons), 78.4 (CH_2), 73.4 (CH_2), 68.9 (CH_2), 60.9 (CH), 54.7 (CH_2), 51.2 (CH_2, 2 carbons), 27.2 (CH), 23.4 (CH_2, 2 carbons), 19.6 (CH_3, 2 carbons); MS: m/z 367 $[M+H]^+$; ee >99% [Chiralcel OD-H (250 x 4.6 mm) column; eluent: n-hexane/ethanol (96:4); flow rate 0.5 mL/min; detector: 254 nm] [*(R)*-isomer t_R = 13.05 min, *(S)*-isomer t_R = 15.01 min].

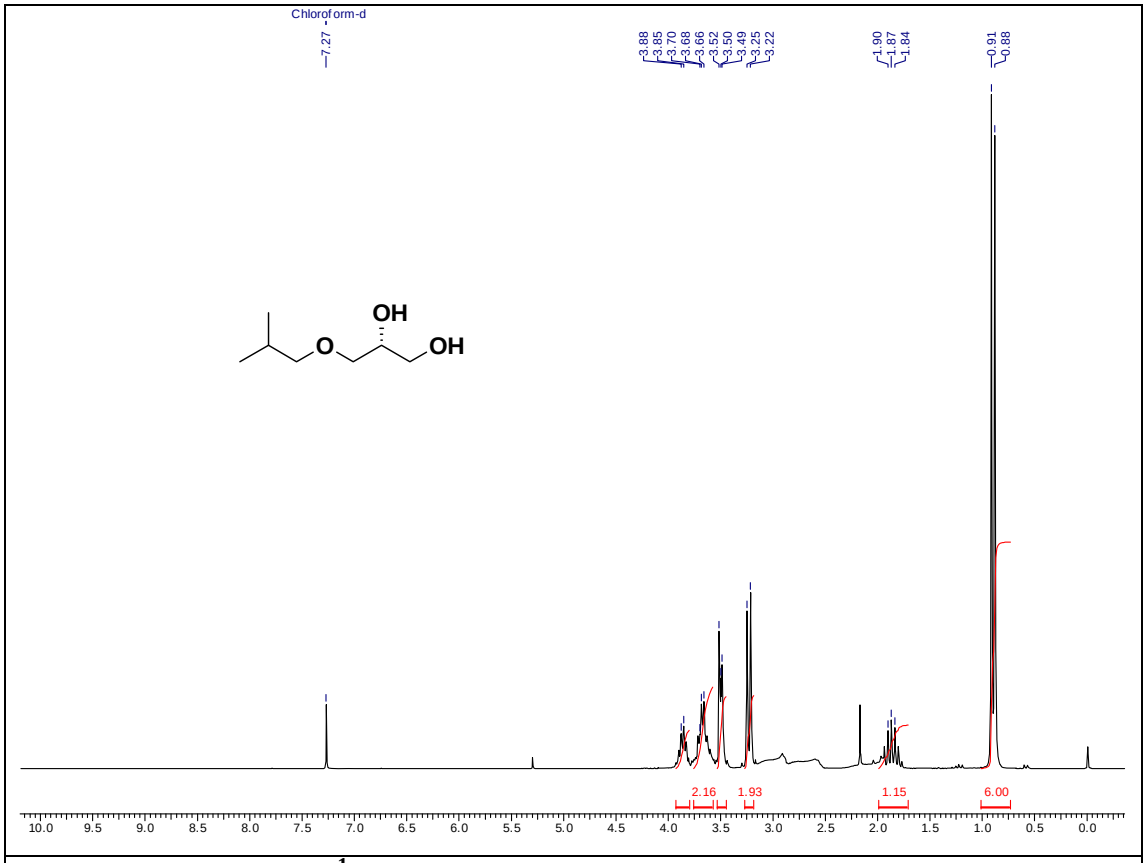
3.3.7. Analytical data



^{1}H NMR of Compound 8 in $CDCl_3$



^{13}C NMR of Compound 8 in $CDCl_3$



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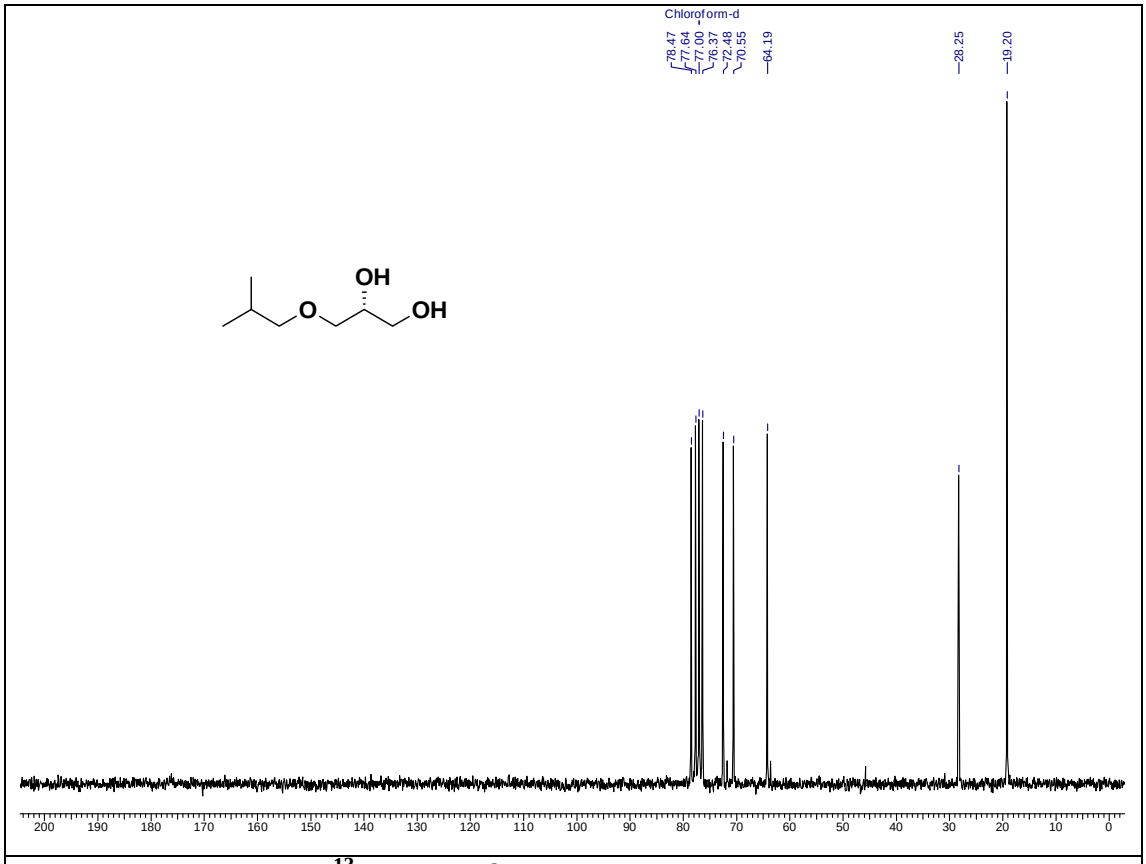

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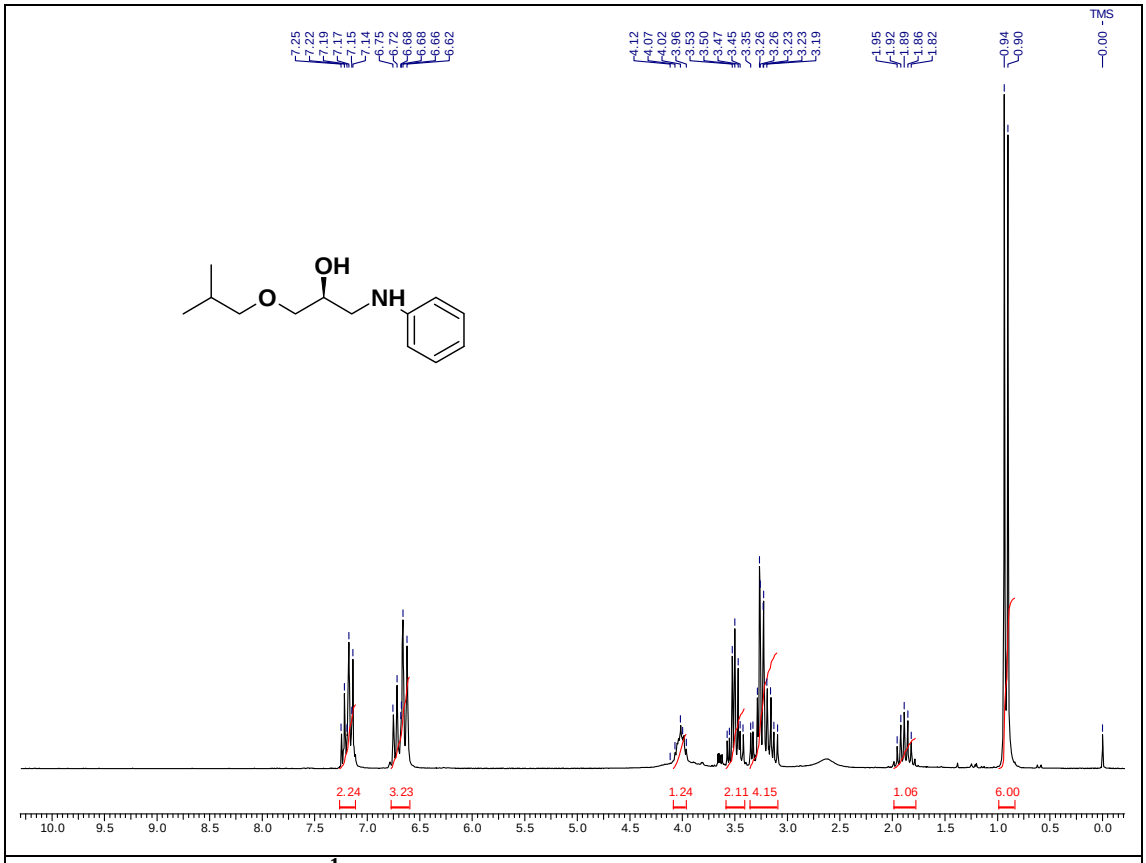

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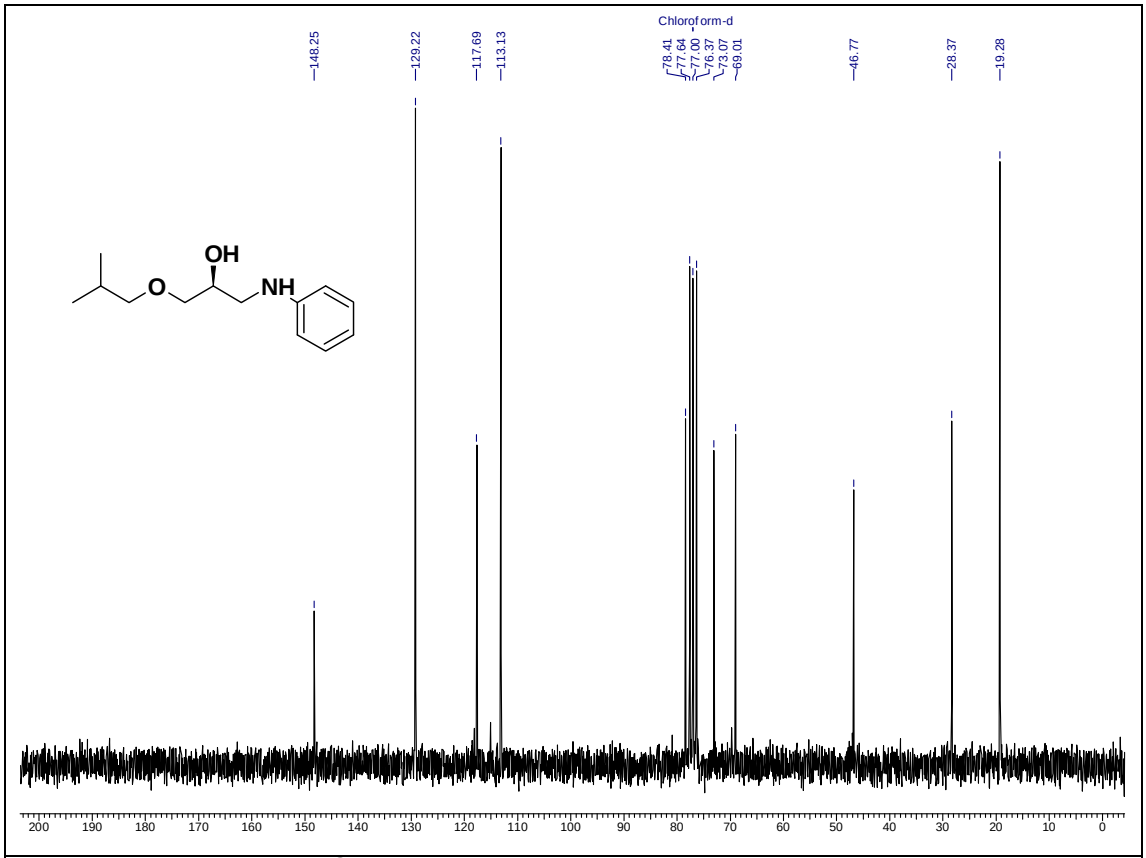

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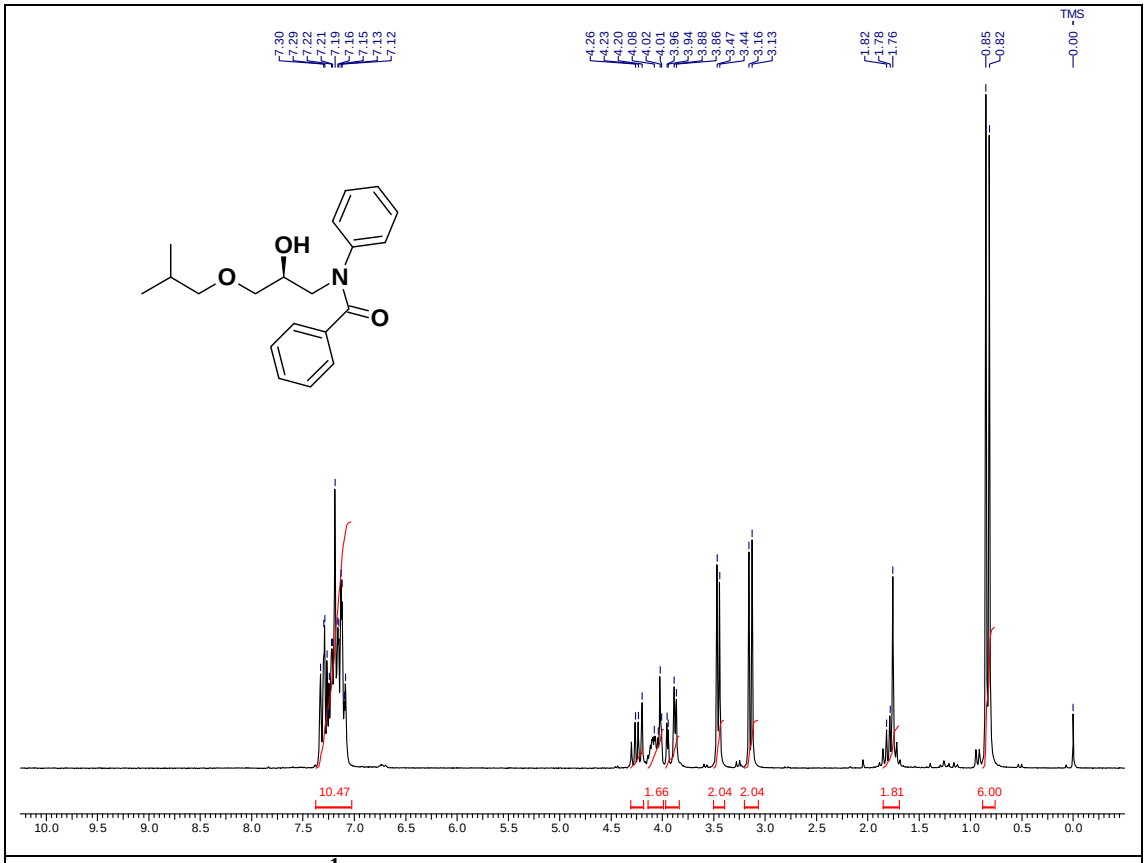

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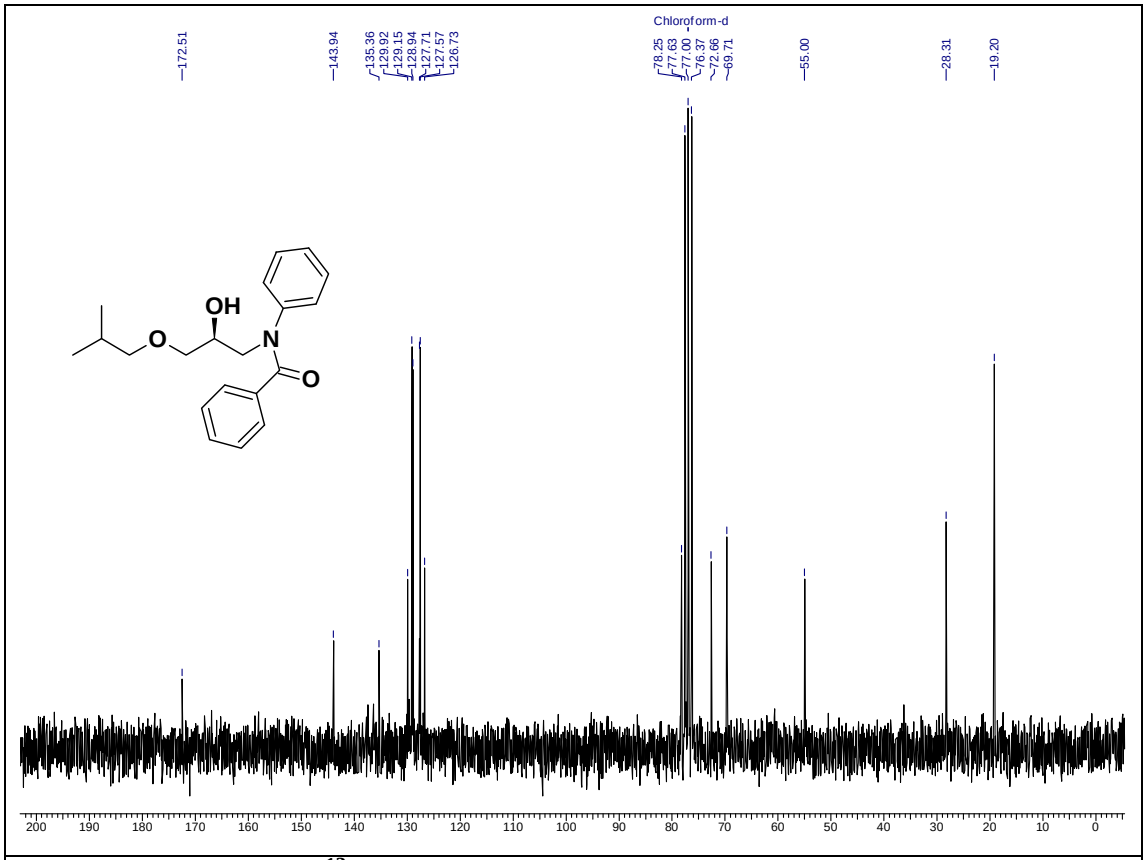

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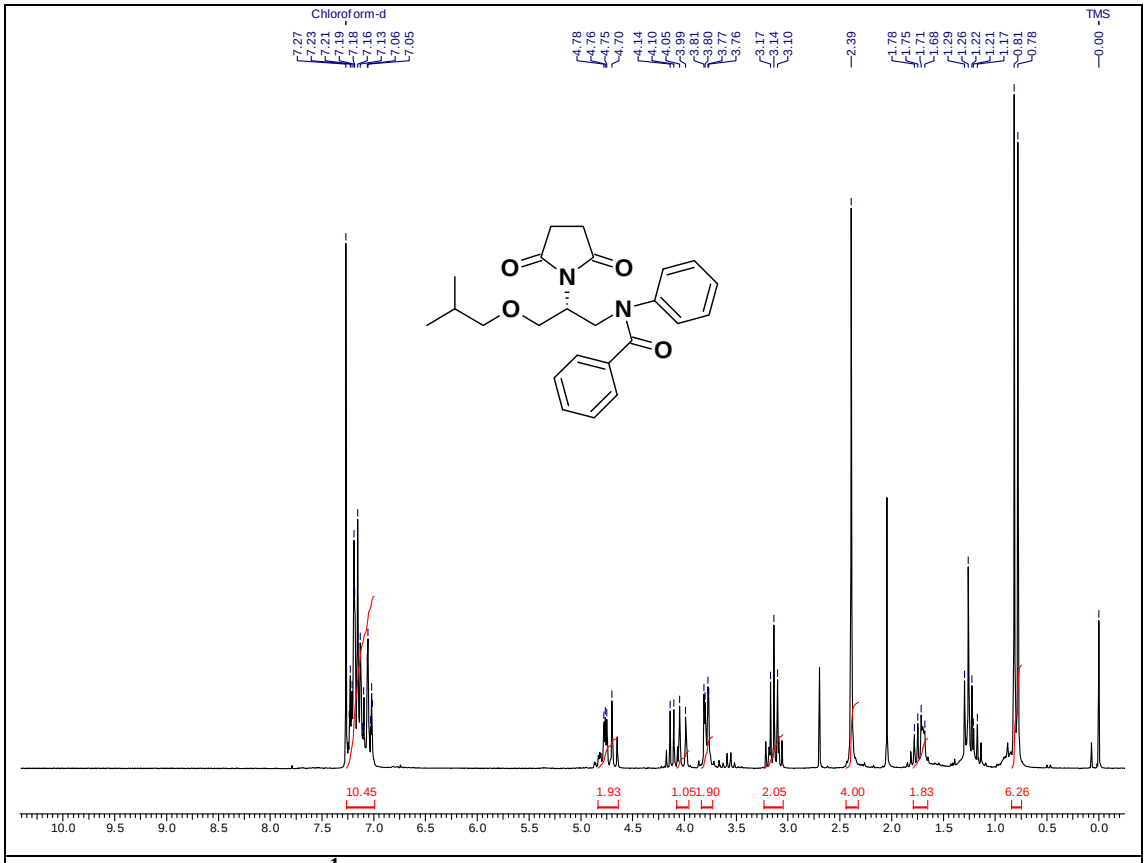

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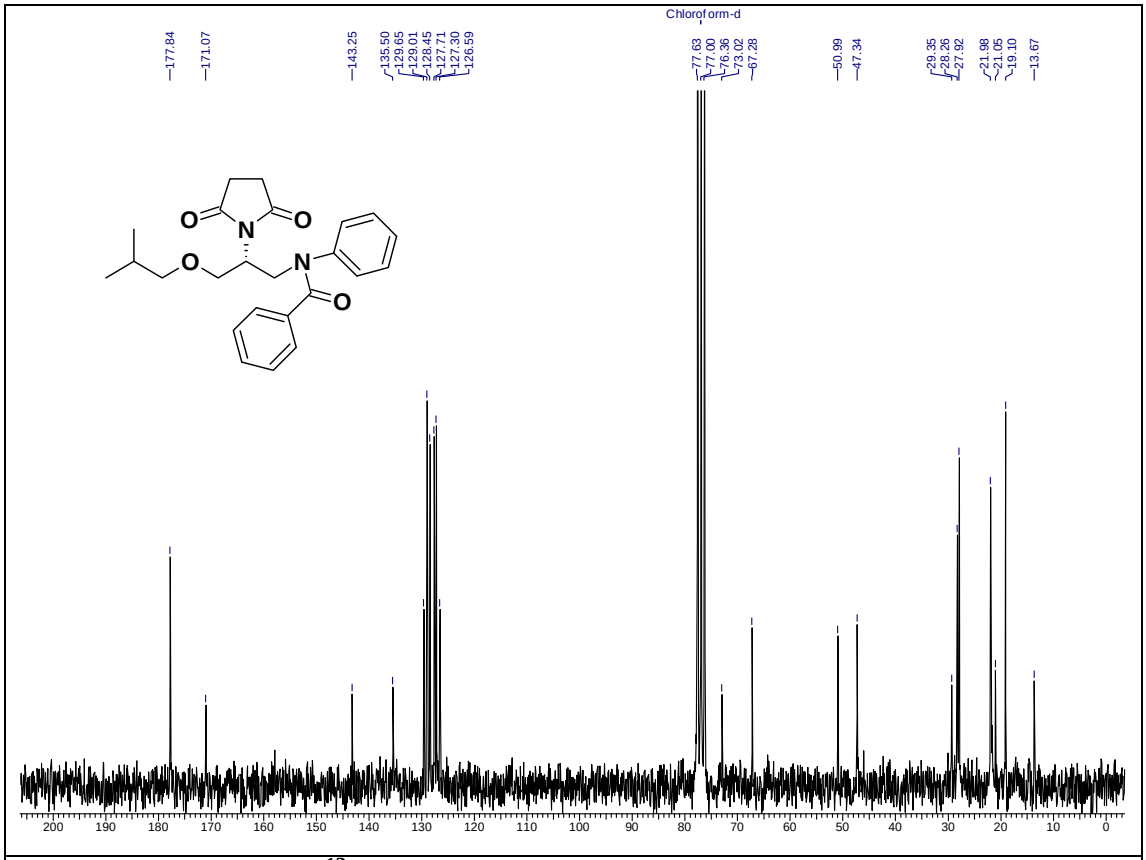

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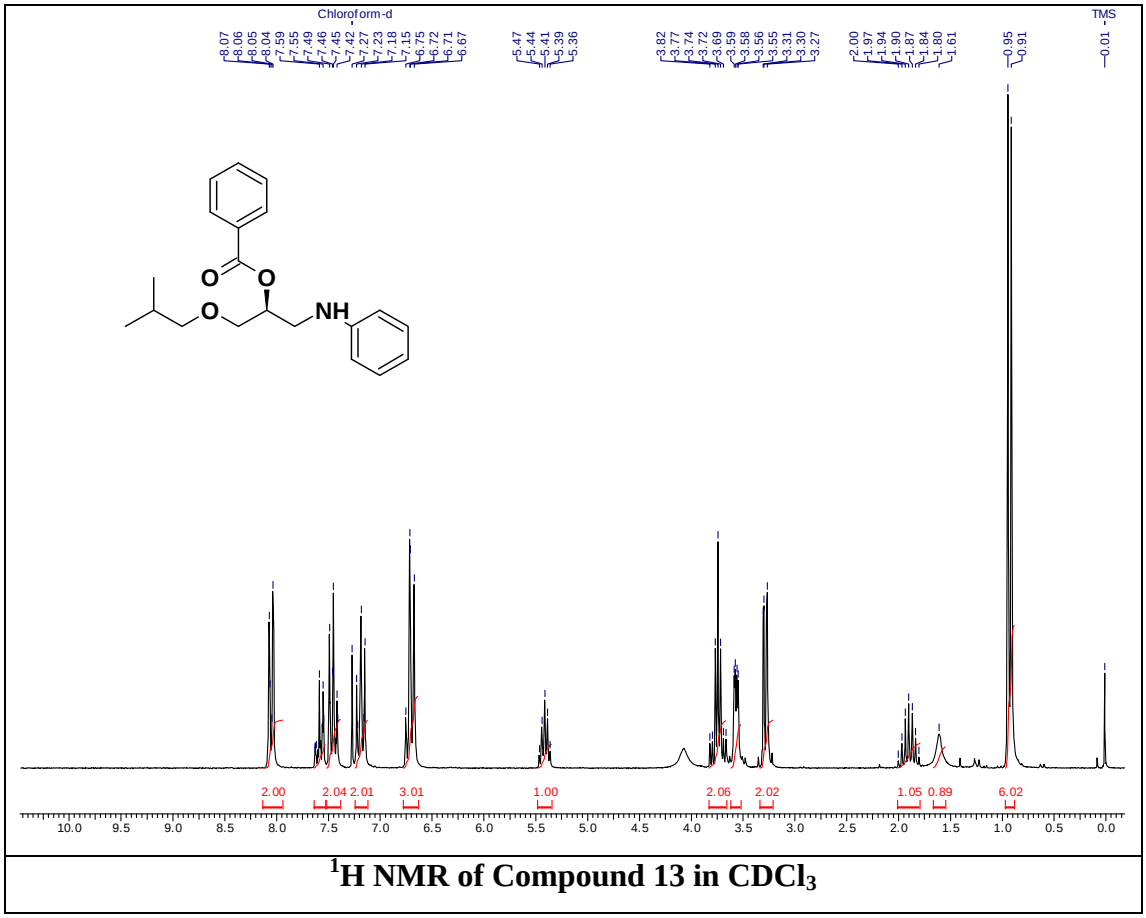

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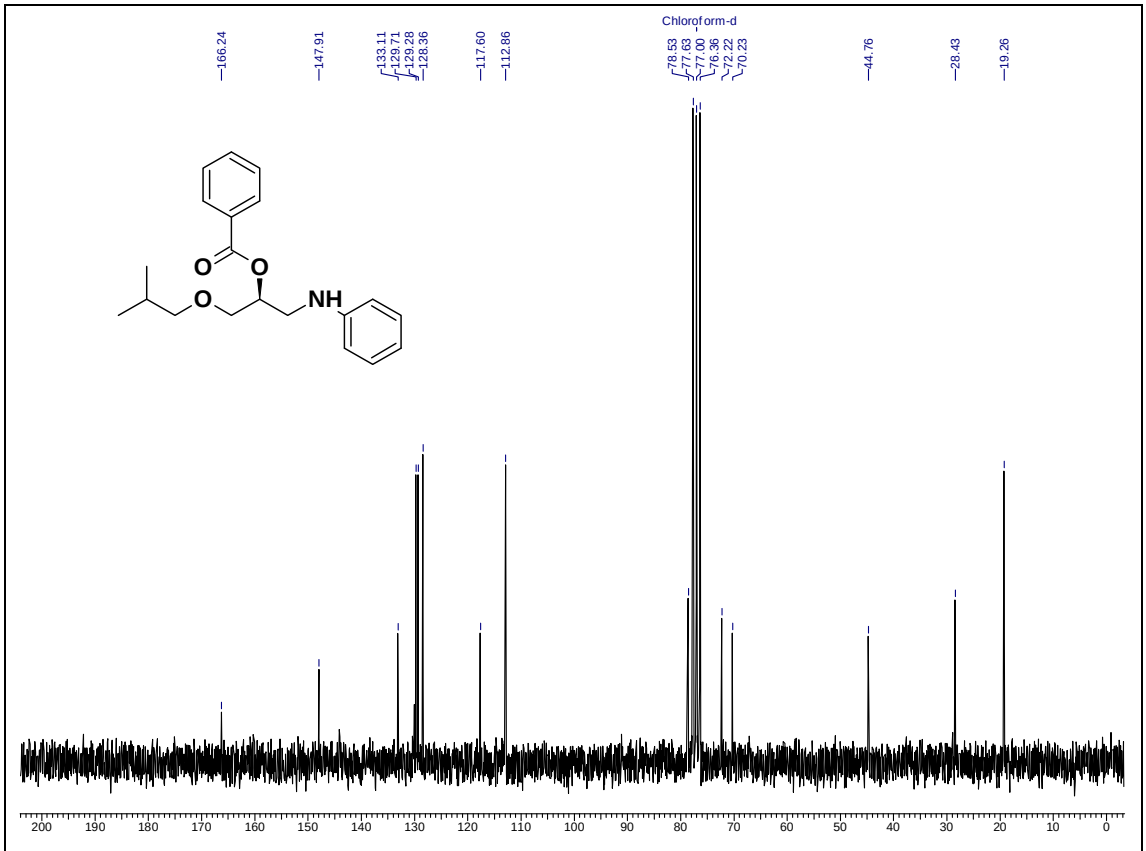

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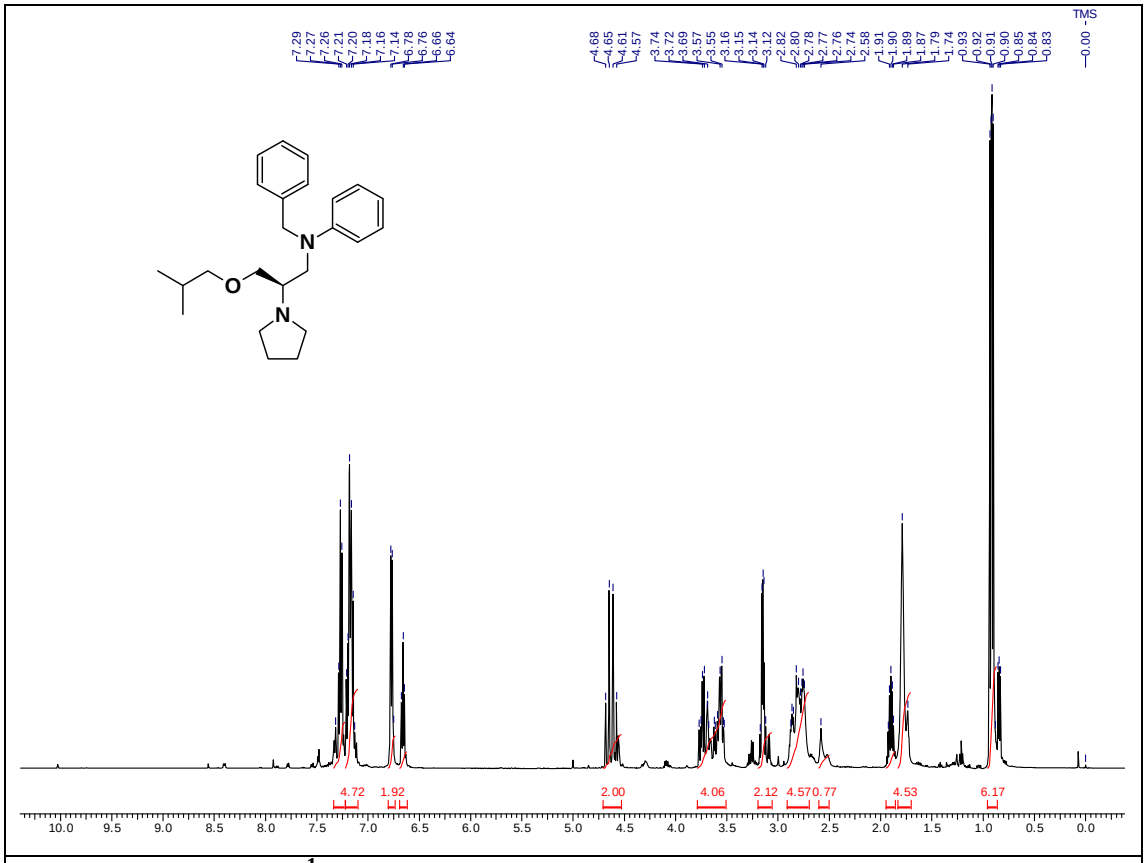

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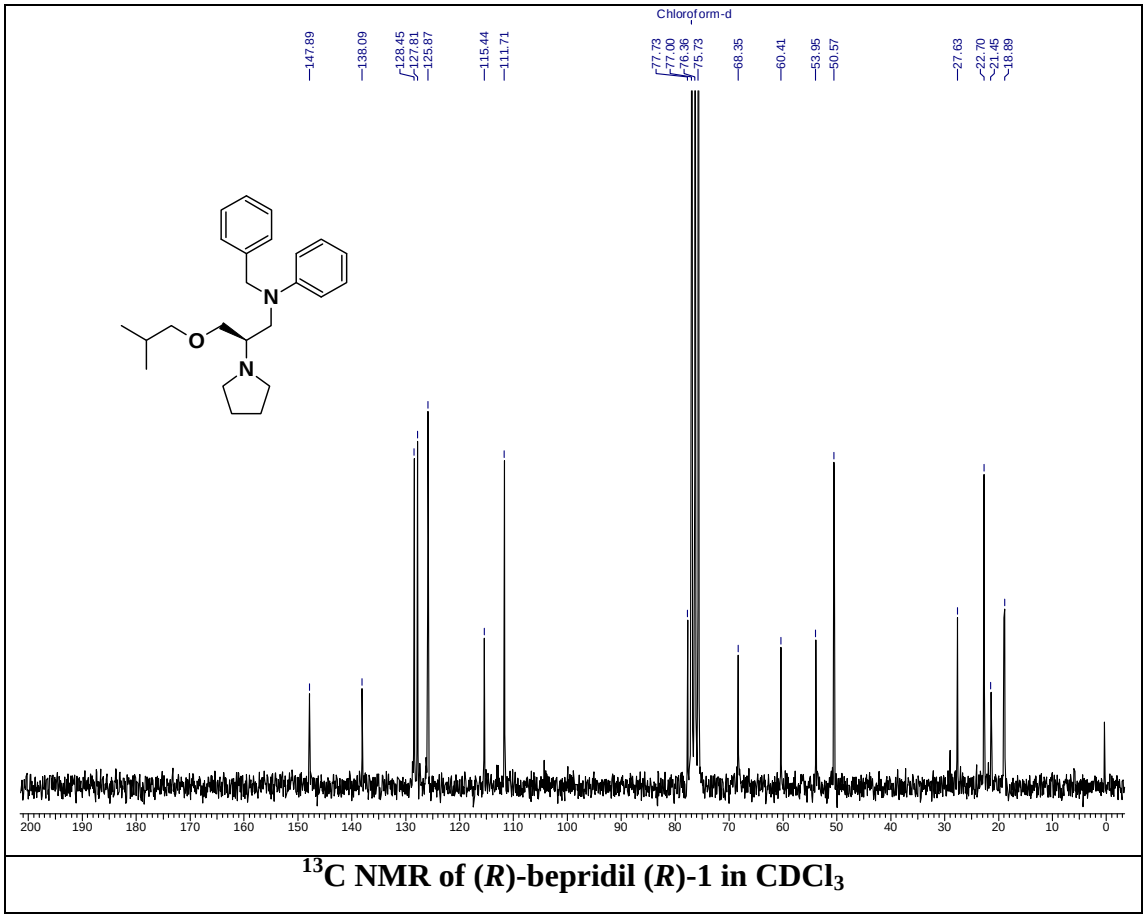
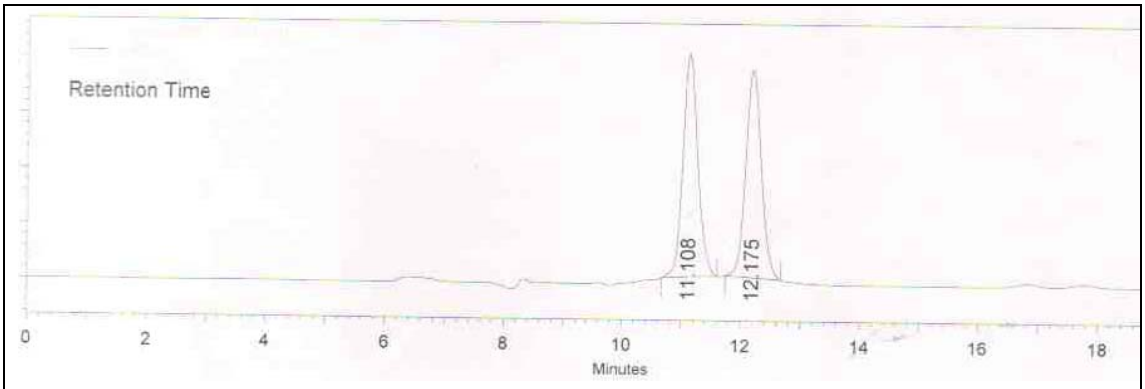


^{13}C NMR of (*R*)-bepridil (*R*)-1 in $CDCl_3$

Chiral HPLC Analysis of Compound 10



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
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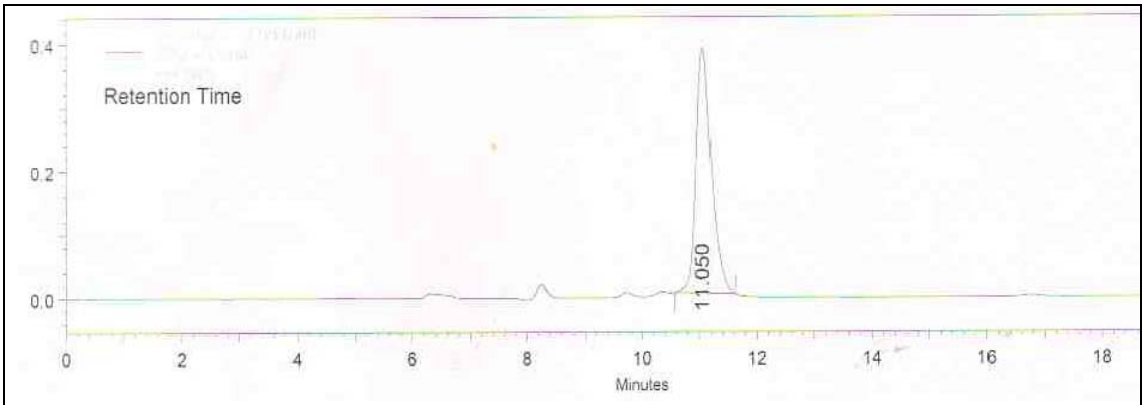
2	12.175	683422	49.207
Totals		13826030	100.000



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
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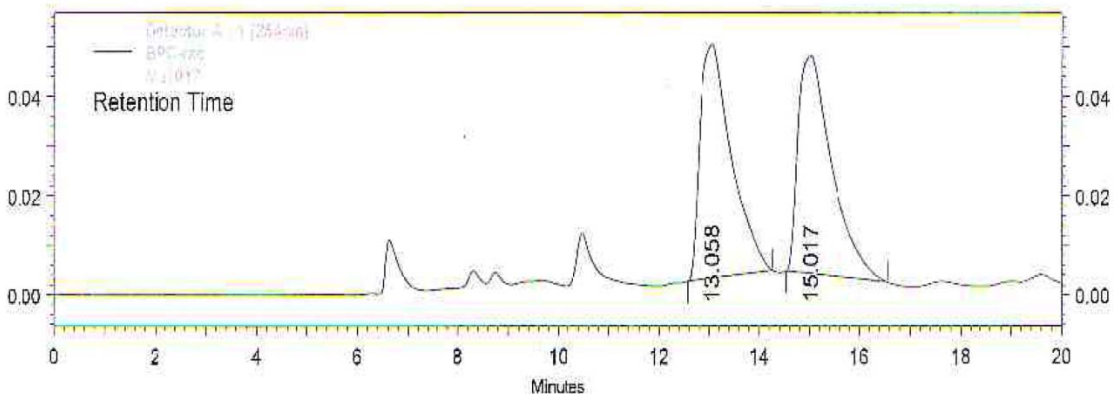
Chiral HPLC Analysis of (*R*)-Bepridil (*R*)-1



Racemic Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
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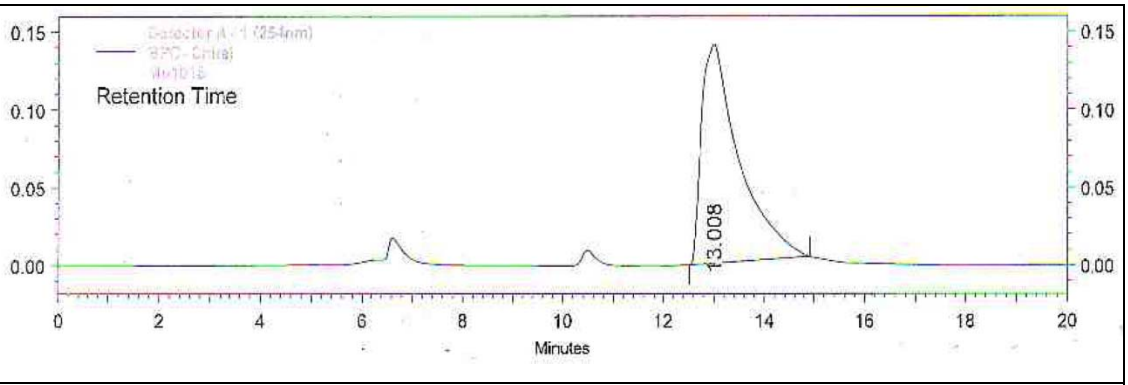
2	**15.017**	**2060176**	**49.732**
Totals		**4142596**	**100.000**



Chiral Sample Chromatograph

Pk #	Retention Time (mins)	Area	Area %
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Totals		**7265488**	**100.000**

3.3.8. References

1. (a) Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983,** *26,* **775** and references cited therein; (b) Deedwania, P. C. *West. J. Med.* **1982,** *137*, 24; (d) Fleckenstein, A. *Ann. Rev. Pharmacol. Toxicol.* **1977,** *17*, 149.
2. (a) Li, Y.; Sato, T.; Arita, M.; *J. Pharmacol. Exp. Ther*. **1999**, *291*, 562; (b) Prystowsky, E. N.; *Am J Cardiol*. **1985**, *55*, 59C; (c) Hollingshead, L. M.; Faulds, D.; Fitton, A.; *Drugs*. **1992**, *44*, 835.
3. van Amsterdam, F. T.; Zaagsma, J. *Naunyn Schmiedeberg's Arch Pharmacol*, **1988**, *337*, 213.
4. Mcdonald, N.; Hodge, T. PCT Int. Appl, WO 2011/008230, 2011.
5. Lichten, T.; Mitter, R. PCT Int. Appl, WO 2007/062862, 2007.
6. Mauvernay, R. Y.; Busch, N.; Moleyre, J.; Monteil, A.; Simond, J. US patent 3962238, **1976**.
7. Winslow, E.; Johannes, E. M.; EP 0146155 A1, **1985**.
8. Ganesan, M.; Salunke, R. V.; Singh, M.; Ramesh, N. G. *Org. Biomol. Chem.* **2013**, *11*, 599.

Chapter-4

Development of novel chromone based derivatives as potent antitubercular agents

4.1. SECTION A

Introduction

4.1.1. Introduction

Tuberculosis is an infectious pulmonary disease caused by the pathogenic species Mycobacterium tuberculosis (Mtb) which is responsible for almost 8.7 million new infections and 1.4 million casualties in 2011 alone.[1] This is the alarming situation for a disease in which both vaccine and chemotherapeutic treatments are available. Further, the emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) Mtb strains coupled with HIV co-infection making the disease even more challenging.[2] The highest incidences of TB are observed in Africa and Asia, however the incidence in industrialized countries has risen in recent years.[3]

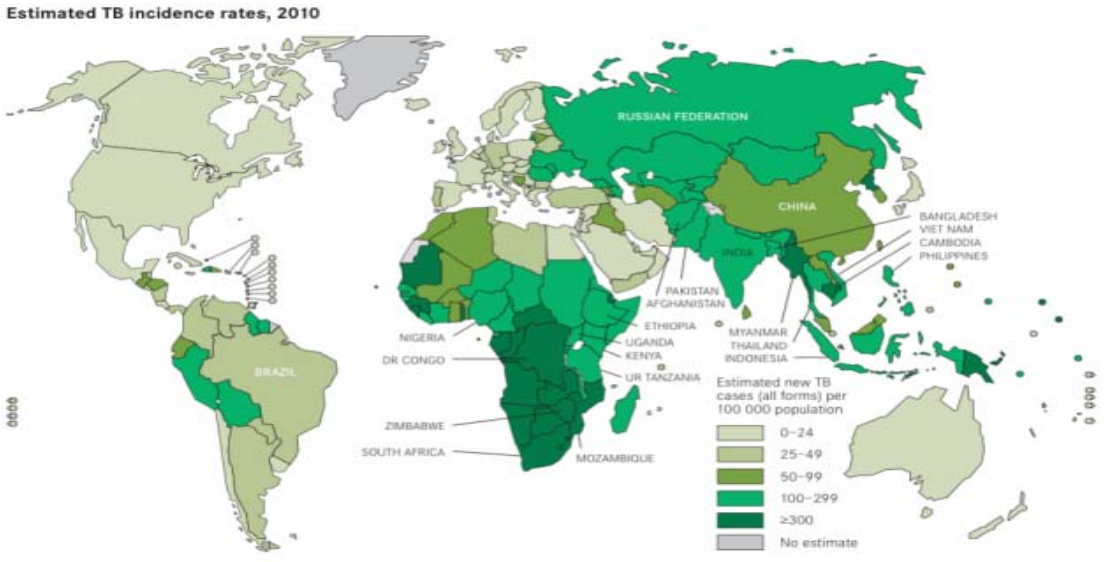


Figure 1. Estimated number of TB cases in the year 2010 (WHO, 2011)

Tuberculosis is a disease primarily affecting the lungs, but can attack any organ of the body. When people with active pulmonary TB cough, sneeze, speak or spit, they expel infectious aerosol droplets 0.5 to 5.0 μm in diameter. A single sneeze can release up to 40,000 droplets.[4] Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low (the inhalation of fewer than 10

bacteria may cause an infection).[5] People nearby may become infected, however not everyone who is infected will show clinical signs. As a result, two types of TB exist *i.e.* latent TB infection and active TB disease. In most cases, the body's immune system is able to fight the bacteria and stop them from growing. The bacteria are inactive, but remain alive in the body and can become active later.[6] People with latent TB cannot spread the disease to others, and a simple skin test can diagnose the infection so that treatment can be administered before it has the chance to become active. People with active TB disease may experience symptoms such as fever, loss of appetite, weight loss, and a cough that lasts for more than 2 weeks. Treatment of TB requires antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which hinders the entry of drugs and makes many antibiotics ineffective.[7] Some common drugs used to treat TB are shown in Figure 2.

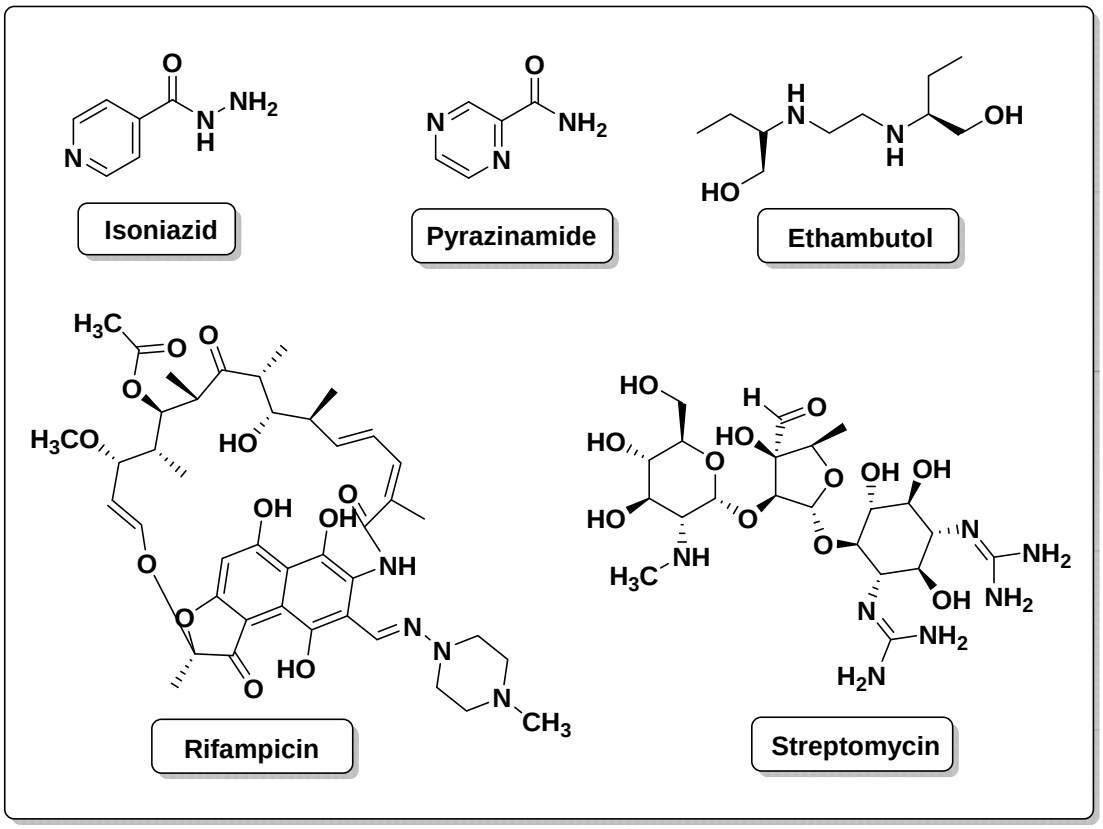


Figure 2. Structures of some commonly used antitubercular drugs

The drug usually used for treatment of latent TB infection is isoniazid. The usual drugs to treat active TB disease are isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. The two antibiotics most commonly used

are isoniazid and rifampicin, and treatments can be prolonged, taking several months. Active TB disease is best treated with combinations of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance.

Although, several compounds are currently in advanced phases of clinical trials, for the last 40 years there is no new compounds have been brought to the market for TB treatment but the new strains of *Mycobacterium tuberculosis* resistant to many currently effective antibiotics are constantly emerging.[8] Considering the global impact of this devastating disease, the discovery and development of new types of chemical entities endowed with promising antimycobacterial activities is urgently needed.

There are two basic approaches to develop a new drug for tuberculosis: (a) synthesis of analogues, modifications or derivatives of existing compounds for shortening and improving TB treatment and (b) searching for novel structures that TB organism has never been presented with before, for the treatment of MDRTB.[9]

Role of Natural Products as Privileged Structures in Drug Discovery

Nature has always been proved to be an important source for providing lead molecules. Many marketed drugs are either natural products or inspired by natural products.[10] Additionally, natural products have been extensively utilized to elucidate complex cellular mechanisms, including signal transduction and cell cycle regulation leading to the identification of important targets for therapeutic intervention.[11] As a result of recent advances in biology, there is now an increased demand for new natural product-like small molecules.

Despite the increased need for new natural products, their isolation and structure elucidation still remain a highly laborious and time consuming process.[12] To circumvent this problem one such alternative is development of small molecule libraries based upon a natural product template. One of the best example of this approach is Nicolaou and co-workers[13] synthesis of a 10,000 membered library of 2, 2-dimethylbenzopyran, a structural motif found in numerous natural products with diverse activities. Subsequent screening of this library for antibacterials identified several cyanostilbenes with micromolar activity against methicillin-resistant staphylococcus aureus (MRSA) strains. After SAR studies, they identified compound

1, which had a 5 μM MIC against six different MRSA strains and is essentially equipotent to vancomycin (Fig. 3).

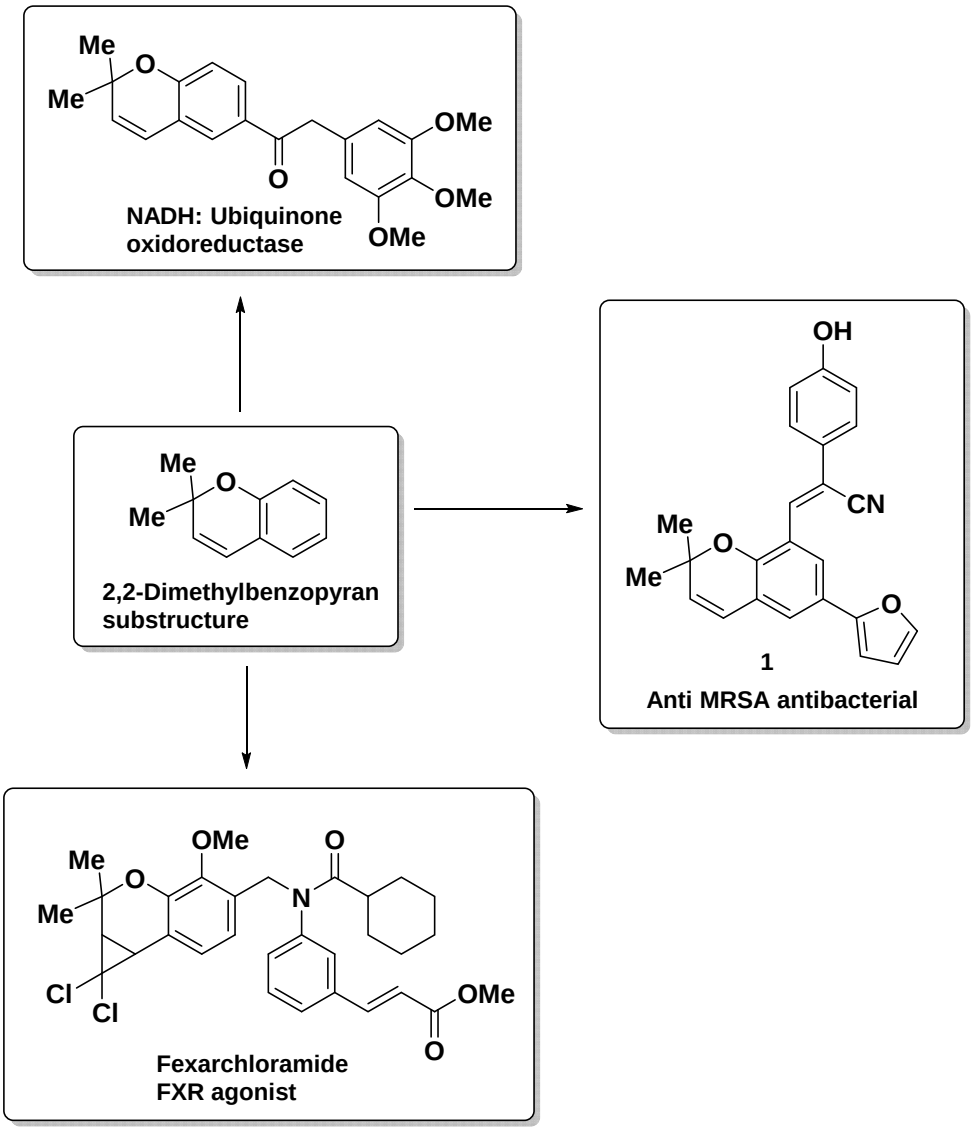


Figure 3. Nicolaou's synthesis of 2, 2-dimethylbenzopyran library

Another important demonstration was Shair and co-workers discovery of secramine, a novel secretory pathway inhibitor (effective at 2 μM), from a 2527 membered library based on the enantiomer scaffold of galanthamine, a known acetylcholinesterase inhibitor.[14] Notably, galanthamine had no effect upon the secretory pathway at up to 100 μM (Fig. 4).

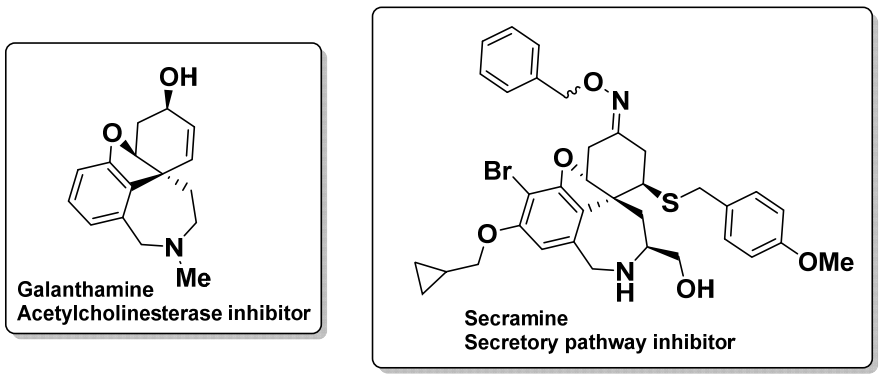


Figure 4. Shair's synthesis of Galanthamine based library

Another interesting example is the development of 1,3-dioxane based libraries by Schreiber and co-workers that provided novel pharmacophores having diversified activities (Fig. 5).[15]

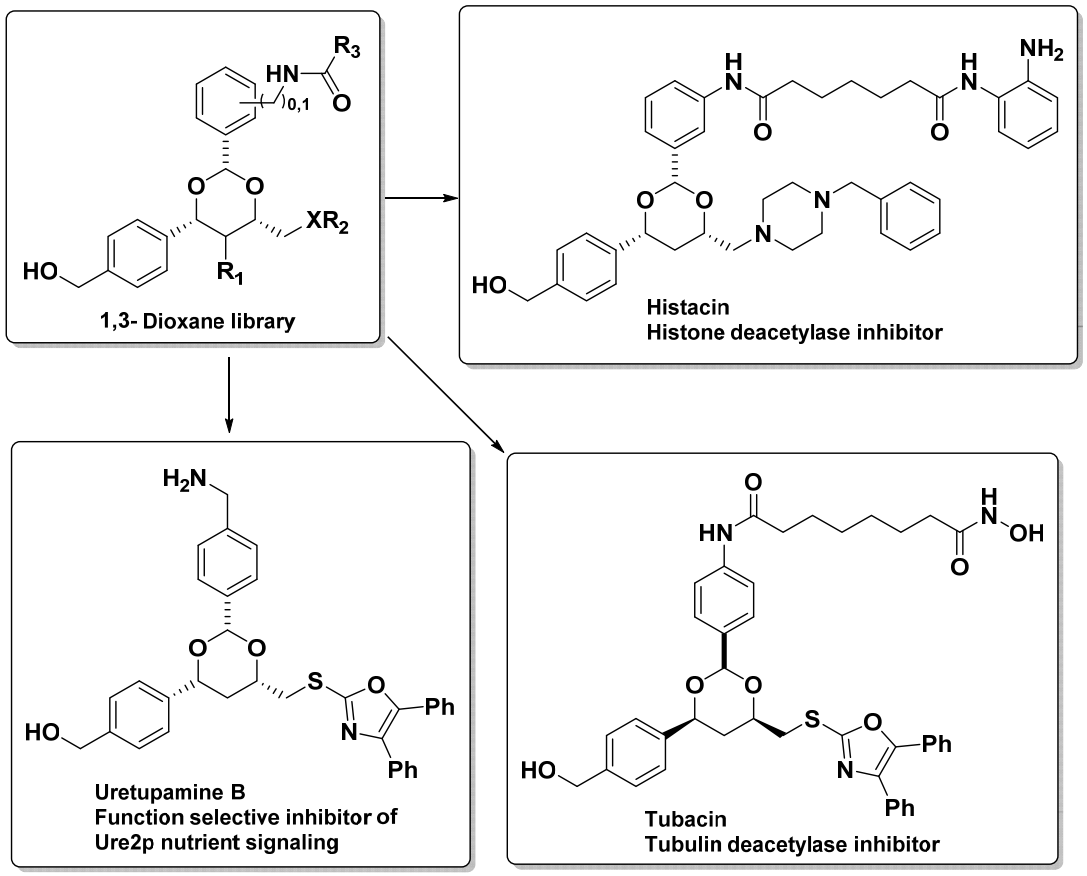


Figure 5. Schreiber's synthesis of 1,3-dioxane based library

Similarly, many groups have synthesized several other natural product libraries based upon the concept of "Privileged structures".[16] Importantly, despite their smaller size, the latest generation of these libraries has been a rich source of new biologically active molecules.

From the above discussion, it is clear that selecting the appropriate privileged structure from biologically active molecules for use in library development is very crucial and this step determines the success of the library. In deliberating, we require a structure that is a subunit in a large number of natural products with diverse biological activities, and this template need to accommodate the installation of a maximum degree of diversity. Importantly, the template should be sufficiently lipophilic to ensure good cell membrane penetration, and that the majority of final library members be of molecular weight less than 500.[17]

Therefore after careful examination, we have chosen chromone scaffold as a privileged structural unit for our library generation. As a Privileged structure in drug discovery, the chromone framework is ubiquitous in a wide variety of naturally occurring and synthetic compounds that exhibit wide range of biological activities.[18] Some pharmaceutically active compounds possessing chromone framework are presented in Fig. 6.

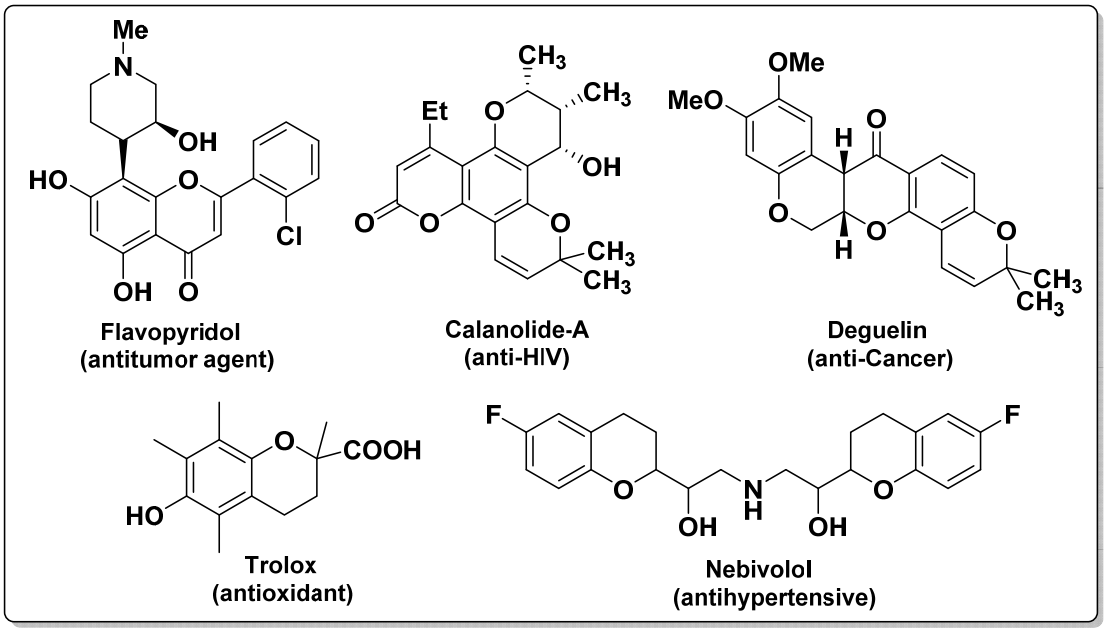


Figure 6. Some pharmaceutically important compounds containing chromone scaffold

Interestingly, many naturally occurring chromones exhibits anti-TB property as well (Fig. 7).[19] However no systematic investigation has been carried out to exploit its anti-TB potential. Hence, in the present study we aimed to explore privileged chromone scaffold, in particular spirochromone moiety for detail investigation and study their anti-TB potential.

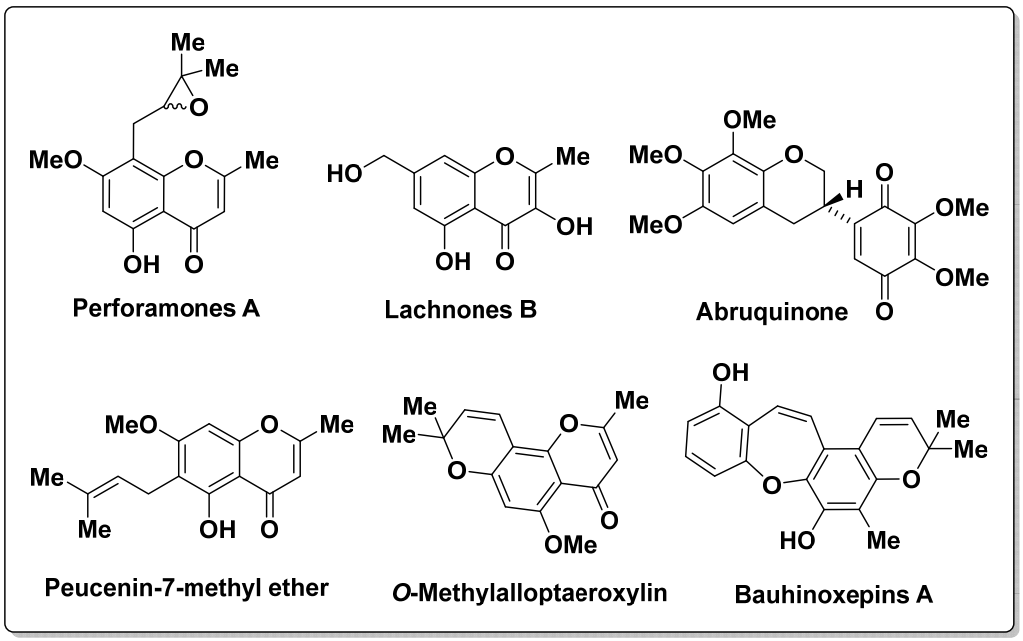


Figure 7. Some naturally occurring chromone scaffolds possessing antimycobacterial activity

4.1.2. References

1. Global Tuberculosis Report 2012, World Health Organization, Geneva, 2012.
2. (a) Corbett, E. L.; Watt, C. J.; Walker, N.; Maher, D.; Williams, B. G.; Raviglione, M. C.; Dye, C. Arch. Intern. Med. **2003**, *163*, 1009; (b) Long, R. Can. Med. Assoc. J. **2000**, *163*, 425; (c) Pozniak, A. J. Tuberc. Lung Dis. **2000**, *4*, 993.
3. McKenna, M. T.; McCray, E.; Onorato, I. N. Engl. J. Med. **1995**, 332, 1071.
4. Cole, E, C.; Cook, C. E.; *Am J Infect Control* **1998**, *26,* 453.
5. Nicas, M.; Nazaroff, W, W.; Hubbard, A. *J Occup Environ Hyg* **2005** *2,* 143.
6. Centers for Disease Control and Prevention - Division of Tuberculosis Elimination (DTBE) Internet site: http://www.cdc.gov/nchstp/tb/.
7. Brennan, P. J.; Nikaido, H. *Annu. Rev. Biochem.* **1995**, *64*, 29.
8. Pablos-Mendez, A.; Raviglione, M. C.; Laszlo, A.; Binkin, N.; Rieder, H. L.; Bustreo, F.; Cohn, D. L.; Lambregts van Weezenbeek, C. S.; Kim, S. J.; Chaulet, P.; Nunn, P. N. Engl. J. Med. **1998**, *338*, 1641.
9. Sriram, D.; Yogeswari, P.; Devakaram, R. V. *Bioorg. Med. Chem.* **2006**, *14*, 3113.

10. (a) Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52. (b) Shu, Y.-Z. *J. Nat. Prod.* **1998**, *61*, 1053.

11. (a) Hinterding, K.; Alonso-Diaz, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 688. (b) Hung, D. T.; Jamison, T. F.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 623.

12. (a) Cordell, G. A.; Shin, Y. G. *Pure Appl. Chem.* **1999**, *71*, 1089. (b) Corley, D. G.; Durley, R. C. *J. Nat. Prod.* **1994**, *57*, 1484-1490. (c) Cordell, G. A. *Phytochemistry* **1995**, *40*, 1585.

13. a) Nicolaou, K. C.;Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc*. **2000**,122, 9939; b) Nicolaou, K. C.;Pfefferkorn, J. A.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc*. **2000**,122, 9954; c) Nicolaou, K. C.;Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.;Roecker, A. J.; Cao, G. Q. *J. Am. Chem. Soc*. **2000**,122, 9968.

14. Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D., *J. Am. Chem. Soc*., **2001**,123, 6740.

15. Wong, J. C.; Sternson, S. M.; Louca, J. B.; Hong, R.; Schreiber, S. L. *Chem. Biol*., **2004**, 11, 1279.

16. a) Kissau, L.; Stahl, P.; Mazitscheak, R.; Giannis, A.; Waldmann, H, *J. Med. Chem*, **2003**, 46, 2917; b) Su, Q.; Beeler, A. B.; Lobkovsky, E.; Porco, J. A.; Penek, J. S. *Org. Lett.*, **2003**, 5, 2149; c) Boger, D. L., *Bioorg Med Chem*., **2003,** 11, 1607.

17. (a) Martin, E. J.; Critchlow, R. E. *J. Comb. Chem.* **1999**, *1*, 32-45. (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeneyt, P. J. *Adv.Drug Deliv. Rev.* **1997**, *23*, 3 and references therein. (c) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3743.

18. (a) Ellis, G. P. Chromenes, Chromanones and Chromones In The Chemistry of Heterocyclic Compounds; Wiley: New York, 1977; Vol. 31, pp 11–139; (b) Hepworth, J. In Comprehensive Heterocyclic Chemistry; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford UK, 1984; Vol. 3, pp 737–883; (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893; (d) Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481.

19. Gale, G. A.; Kirtikara, K.; Pittayakhajonwut, P.; Sivichai, S.; Thebtaranonth, Y.; Thongpanchang, C.; Vichai, V. *Pharmacol Ther* **2007**, *115*, 307.

4.2. SECTION B

Synthesis and antimycobacterial activity of novel amino alcohol fused spirochromone conjugates

4.2.1. Introduction

In the foregoing section, we have discussed about the importance of privileged chromone framework that exhibits wide range of biological activities. Understanding the significance of chromone framework, in this section we planned to develop a small library around chromone framework, incorporating amino alcohol moiety. Amino alcohol moiety is present in a wide variety of biologically active natural products and different compounds possessing this unit have significant pharmaceutical value as antihypertensives, antimalarials, anti-HIV agents etc.[1,2,3] Importantly, the commercially available anti-TB drug ethambutol (EMB) possess amino alcohol moiety. Despite its modest anti-tubercular activity, EMB is used in combination with other front-line antitubercular agents mainly owing to its synergy with the other drugs and also to its low toxicity.[4] Few important drugs possessing amino alcohol unit is represented in Figure 1.

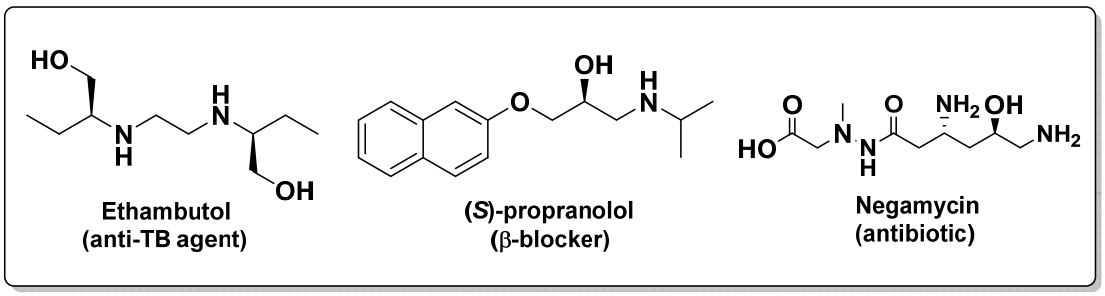


Figure 1. Examples of few important amino alcohol derivatives

So in the present study we have designed and synthesized a series of novel amino alcohol annulated spirochromone conjugates (Fig. 2) by introduction of amino alcohol unit to the phenolic –OH on the C-7 chromone ring and evaluated their anti TB properties. Further, to the best of our knowledge, synthesis and antimycobacterial activities of these amino alcohol annulated spirochromone conjugates is unprecedented.

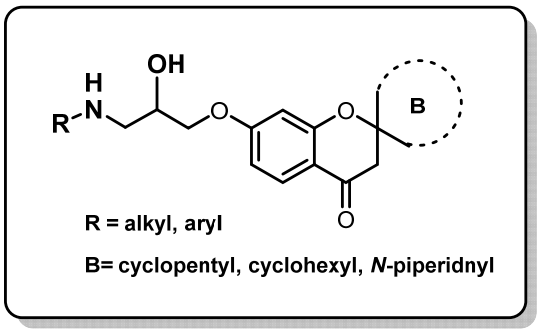


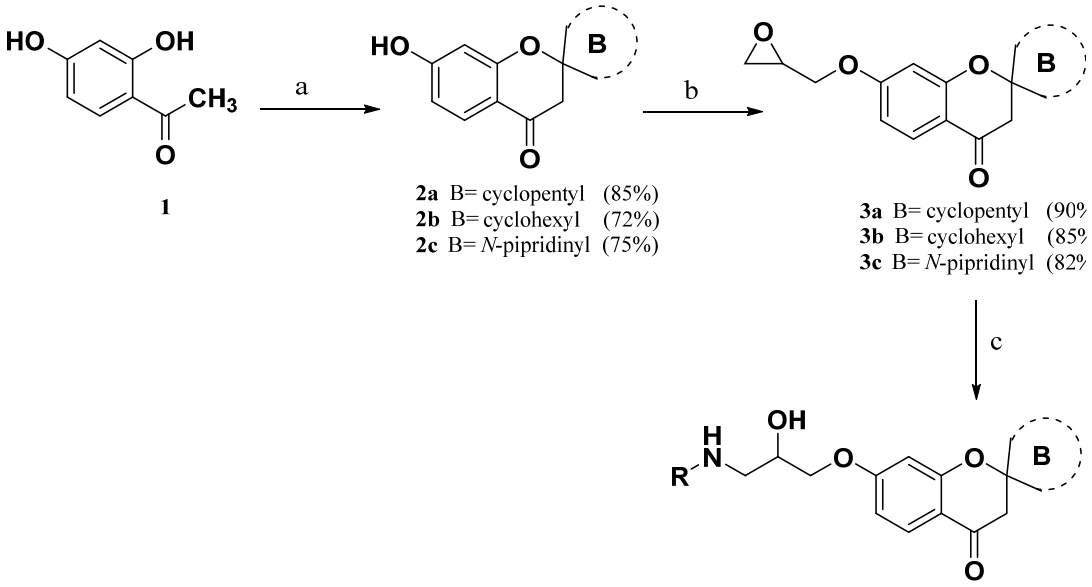
Figure 2. Design of amino alcohol annulated spirochromone conjugates

4.2.2. Results and Discussions

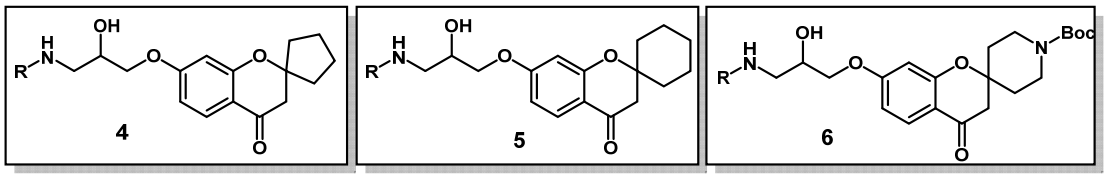
Chemistry

The synthetic strategy followed for the preparation of amino alcohol fused spirochromone conjugates is given in scheme 1. Firstly, for the preparation of precursor spirochromanone moiety **2a-c** a Kabbe condensation[5] between various cycloalkanones and 2,4-dihydroxy acetophenone was employed. In the Kabbe condensation, the use of acetonitrile as solvent and carrying out the reaction at 50 ºC for 24 h in the presence of pyrrolidine as a base is optimum in order to obtain spirochromanone **2a-c** in 72 to 80% yields.[6] On the other hand, refluxing with toluene or ethanol as a solvent using DS apparatus, the condition generally used in Kabbe condensation did not produce the required products in good yield. Subsequently, the spirochromanone **2a-c** were *O*-alkylated with epichlorohydrin in the presence of K_2CO_3 in refluxing acetone gave epoxides **3a-c** in 82 to 90% yields. Finally, the amino alcohol moiety was incorporated through nucleophilic ring opening of this spirochromone epoxides **3a-c** with various aromatic/aliphatic amines to afford amino alcohol fused spirochromone conjugates **4-6,** in moderate to good yields. The structure of all the new products **4-6** (21 compounds) were confirmed by the IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. In the IR spectrum (compound **4h** as a representative example), a signal corresponding to the chromanone carbonyl was observed at 1640 cm^{-1}. The signal corresponding to the *C*-3 protons of chromanone

skeleton was observed as a singlet at δ 2.77 ppm in the ^{1}H NMR spectrum



Scheme 1. Reagents and conditions: (a) Cylopentanone/ Cyclohexanone/N-Boc-piperidone, pyrrolidine, acetonitrile, 50°C, 24 h; (b) epichlorohydrin, K_2CO_3, acetone, reflux, 12 h; (c) alkyl/aryl amine, LiBr, MeOH, rt, 12 h.



	R	
4a	C_6H_5	(85%)
4b	(2-CH_3) C_6H_4	(72%)
4c	(2-Cl) C_6H_4	(35%)
4d	(2-iPr) C_6H_4	(67%)
4e	(2-OMe) C_6H_4	(79%)
4f	(3-F) C_6H_4	(56%)
4g	(4-OMe) C_6H_4	(76%)
4h	(4-^{i}Pr) C_6H_4	(90%)
4i	(2-OH, 4-NO_2) C_6H_3	(55%)
4j	-CH_2(4-OMe) C_6H_4	(38%)
4k	morpholinyl	(81%)

	R	
5a	C_6H_5	(88%)
5b	(2-CH_3) C_6H_4	(80%)
5c	(2-OMe) C_6H_4	(82%)
5d	(4-OMe) C_6H_4	(84%)
5e	(4-^{i}Pr) C_6H_4	(85%)

	R	
6a	C_6H_5	(75%)
6b	(2-CH_3) C_6H_4	(73%)
6c	(2-OMe) C_6H_4	(80%)
6d	(4-OMe) C_6H_4	(84%)
6e	(4-^{i}Pr) C_6H_4	(80%)

and the corresponding ^{13}C resonance signal was observed at δ 47 ppm. In the ^{13}C NMR spectrum, the spirocarbon was discernible at δ 90.5 ppm. Similarly, the characteristic signal appeared as a multiplet at δ 4.26-4.33 ppm was ascribable to the methine proton attached to secondary –OH. Conclusive evidence for its structure was obtained from single-crystal X-ray analysis (Fig. 3).[7,8]

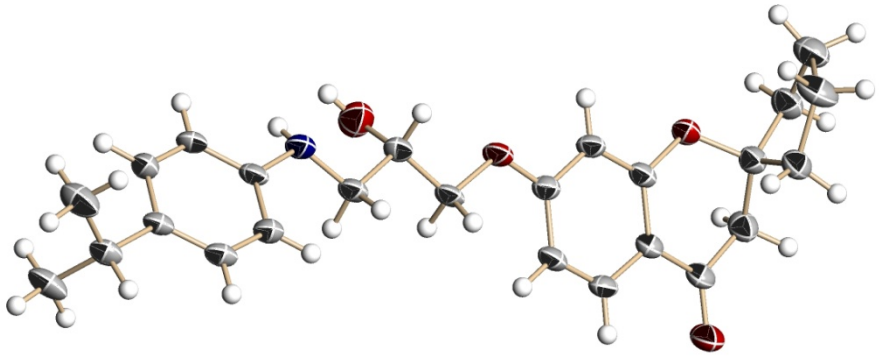
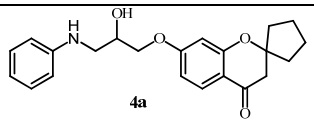
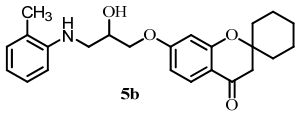
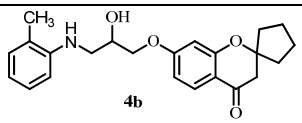
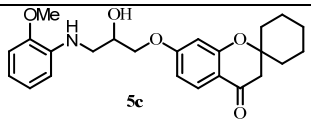
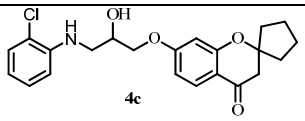
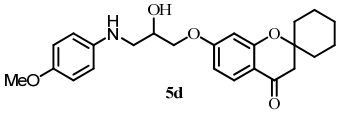
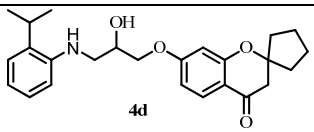
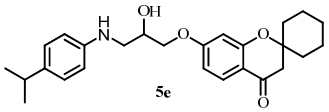
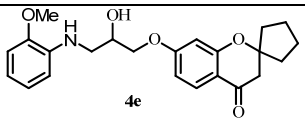
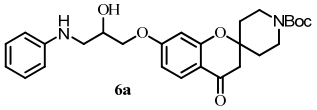
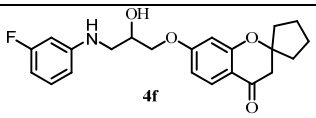
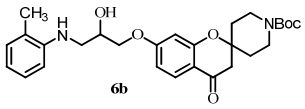
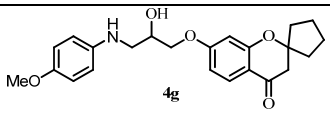
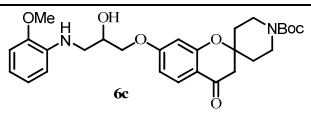
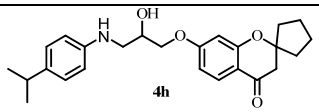
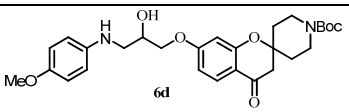
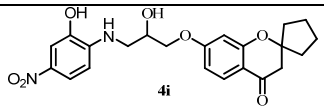
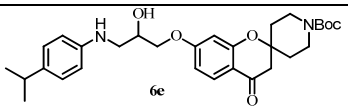
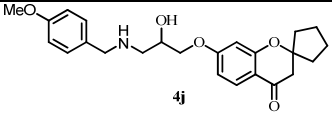
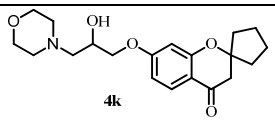
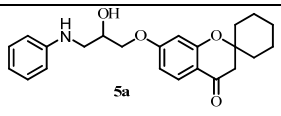


Figure 3. ORTEP diagram of the compound **4h** (thermal ellipsoids are drawn at 50% probability level)

Anti-mycobacterial activity

All the new amino alcohol fused spirochromone conjugates were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (ATCC27294) using an agar dilution method.[9] The minimum inhibitory concentration (MIC; µg/mL) was determined for each compound. The MIC is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. Rifampicin and Ethambutol were used as reference compounds. The MIC values of the synthesized compounds along with the standard drugs for comparison were reported in Table 1. Among the 21 synthesized compounds, seven compounds (**4c, 4d, 4f, 4h, 4i, 5b, 5e)** were found to be active with MIC in the range of 3.13-6.25 µg/mL. The compound **4f**, is found to be more active having MIC 3.13 µg/mL among all the compounds screened. Importantly, compound **4f** represents a novel structural chemotype for which antitubercular properties have not been previously noted. Preliminary structure activity relationship of the amino alcohol fused spirochromone conjugates reveals that compounds possessing cycloalkyl group at 2nd position of the chromone ring favors better activity than piperidinyl moiety. Among cycloalkyl groups, compounds possessing cyclopentyl group (**4c, 4d, 4f, 4h, 4i**) exhibits better activity than cyclohexyl counterpart. Furthermore, halide substitution at aromatic ring of amino alcohol favors better activity (**4c, 4f**). Further it is also observed that, isopropyl group in the aromatic ring is very favorable in enhancing the activity (**4d, 4h, 5e**).

Table 1. *In vitro* antimycobacterial activity of the amino alcohol fused spirochromone conjugates

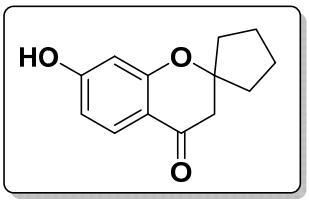
Sr. No	Compound	MIC (µg/mL)	Sr. No	Compound	MIC (µg/mL)
1	 **4a**	25	13	 **5b**	6.25
2	 **4b**	12.5	14	 **5c**	12.5
3	 **4c**	6.25	15	 **5d**	12.5
4	 **4d**	6.25	16	 **5e**	6.25
5	 **4e**	12.5	17	 **6a**	>25
6	 **4f**	**3.13**	18	 **6b**	25
7	 **4g**	25	19	 **6c**	25
8	 **4h**	6.25	20	 **6d**	>25
9	 **4i**	6.25	21	 **6e**	12.5
10	 **4j**	12.5	22	Rifampicin	0.2
11	 **4k**	>25	23	Ethambutol	1.56
12	 **5a**	12.5			

4.2.3. Conclusion

In conclusion, a series of amino alcohol fused spirochromone conjugates were synthesized for the first time via an easy and convenient synthetic procedure starting from 2,4-dihydroxy acetophenone and all these new compounds were confirmed by ^{1}H NMR, ^{13}C NMR and MS spectra. The single X-ray diffraction study was used to confirm the molecular structure of a representative compound **4f** unambiguously. The in vitro antimycobacterial evaluation showed that most of the synthesized amino alcohol fused spirochromone conjugates exhibited moderate to good antimycobacterial activity. Noticeably, compound **4h** is most potent compound in vitro with MIC of 3.13 mg/mL, against MTB.

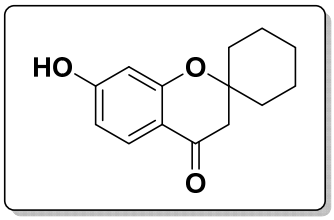
4.2.4. Experimental

1) 7-hydroxyspiro[chroman-2,1'-cyclopentan]-4-one (2a)



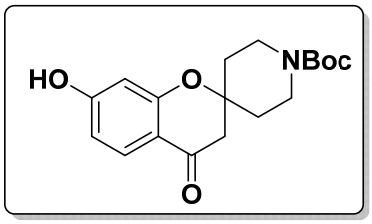
Cyclopentanone (3.5 mL, 39.4 mmol) was added to a solution of 2,4-dihydroxy acetophenone (3 g, 19.7 mmol) and pyrrolidine (3.3 mL, 39.4 mmol) in acetonitrile (25 mL). The resulting solution was stirred for 24 h at 50 ^{o}C, before being concentrated invacuo. The residue was taken in ethylacetate, washed with 1N HCl, saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (12% ethyl acetate in petroleum ether) afforded **2a** as a colorless solid (3.4 g, 78%); mp 182-83 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3413, 1614, 1522, 1426, 850; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.60-1.78 (m, 6H), 2.03-2.12 (m, 2H), 2.79 (s, 2H), 6.37 (d, *J*= 2.2 Hz, 1H) 6.52 (dd, *J*= 8.7, 2.2 Hz, 1H), 7.76 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 192.3 (CO), 163.5 (C), 162.7 (C), 129.1 (CH), 109.9 (CH), 103.9 (CH), 90.3 (C), 46.8 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); ESI-MS: *m/z* 219 $[M+ H]^{+}$.

2) 7-hydroxyspiro[chroman-2,1'-cyclohexan]-4-one (2b)



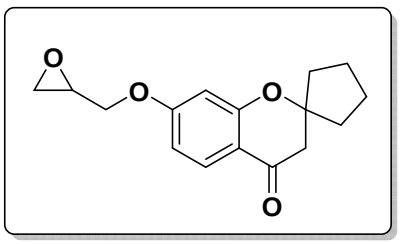
The same procedure as in the preparation of **2a** was used with the cyclohexanone (4 mL, 39.4 mmol) affording spirocompound **2b** as a colorless solid (3.3 g, 72 %); mp 171-72 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3411, 1616, 1426, 850; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.43-1.73 (m, 8H), 1.95-2.01 (m, 2H), 2.66 (s, 2H), 6.43 (d, *J* = 2.1 Hz, 1H), 6.53 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 192.3 (CO), 163.7 (C), 162.0 (C), 128.8 (C), 114.5 (C), 109.9 (C), 103.7 (C), 80.3 (C), 47.7 (CH_2), 34.8 (CH_2. 2 carbons), 25.2 (CH_2), 21.4 (CH_2, 2 carbons); ESI-MS: *m/z* 233 $[M+ H]^+$.

3) *ter*-butyl 7-hydroxy-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (2c)



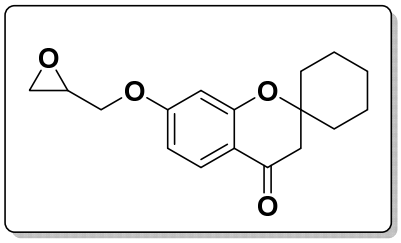
The same procedure as in the preparation of **2a** was used with the *N*-Boc piperidone (5.9 g, 29.5 mmol) affording spirocompound **2c** as a colorless solid (4.9 g, 75 %); mp 173-74 °C**;** IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 1668, 1616, 1524, 1427, 1368, 1289, 850; ^1H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.52-1.79 (m, 4H), 2.01-2.07 (m, 2H), 2.66 (s, 2H), 3.86-3.93 (m, 2H), 6.37 (d, *J*= 2.3 Hz, 1H) 6.52 (dd, *J*= 8.8, 2.3 Hz, 1H), 7.78 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 190.8, 164.8, 161.1, 155.1, 128.9, 113.9, 110.7, 103.5, 80.6, 77.7, 47.6, 39.2, 34.0, 28.4; ESI-MS: *m/z* 356 $[M+ Na]^+$.

4) 7-(oxiran-2-ylmethoxy)spiro[chroman-2,1'-cyclopentan]-4-one (3a)



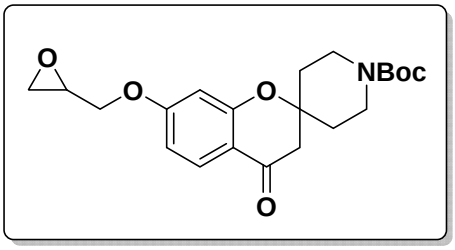
A mixture of compound **2a** (2.8 g; 12.9 mmol), epichlorohydrin (3 mL; 38.7 mmol) and K_2CO_3 (9 g; 64.5 mmol) in anhydrous acetone (50 mL) was heated under reflux for 12 h with vigorous stirring. The reaction mixture was filtered and evaporated. Purification of the crude by column chromatography (18 % ethyl acetate in petroleum ether) afforded **3a** as colorless oil (3.1 g; 88%); IR ($CHCl_3$, cm^{-1}): ν_{max} 2968, 2877, 1676, 1609, 1577, 1495, 1442, 1262, 1177, 1094, 849; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.69-1.90 (m, 6H), 2.02-2.12 (m, 2H), 2.74-2.78 (m, 3H), 2.91-2.95 (apparent t, *J*= 4.6 Hz, 1H), 3.33-3.41 (m, 1H), 3.96 (dd, *J*= 11.0, 5.7 Hz, 1H), 4.29 (dd, *J*= 11.2, 3.1 Hz, 1H), 6.39 (d, *J*= 2.3 Hz, 1H), 6.58 (dd, *J*= 8.7, 2.4 Hz, 1H), 7.78 (d, *J*= 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.3 (CO), 164.8 (C), 162.2 (C), 128.5 (CH), 115.2 (C), 109.4 (CH), 102.2 (CH), 90.4 (C), 68.9 (CH_2), 46.7 (CH), 46.7 (CH_2), 44.2 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 275 $[M+H]^+$, 297 $[M+Na]^+$.

5) 7-(oxiran-2-ylmethoxy)spiro[chroman-2,1'-cyclohexan]-4-one (3b)



The same procedure as in the preparation of **3a** was used with the spiro compound **2b** (3.0 g, 12.9 mmol) affording the epoxide **3b** as a colorless oil (3.2 g; 85%); IR ($CHCl_3$, cm^{-1}): ν_{max} 2936, 2877, 1678, 1607, 1517, 1442, 1262, 1094, 849; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.43-1.74 (m, 8H), 1.94-2.01 (m, 2H), 2.65 (s, 2H), 2.77 (dd, *J*= 4.9, 2.6 Hz, 1H), 2.91-2.98 (apparent t, *J*= 4.7 Hz, 1H), 3.33-3.41 (m, 1H), 3.98 (dd, *J*= 11.1, 5.7 Hz, 1H), 4.26 (dd, *J*= 11.1, 3.0 Hz, 1H), 6.44 (d, *J*= 2.4 Hz, 1H), 6.58 (dd, *J*= 8.6, 2.3 Hz, 1H), 7.77 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.2 (CO), 164.9 (C), 161.5 (C), 128.3 (CH), 115.1 (C), 109.3 (CH), 102.0 (CH), 80.5 (C), 68.9 (CH_2), 49.8 (CH), 47.8 (CH_2), 44.6 (CH_2), 34.8 (CH_2, 2 carbons), 25.2 (CH_3), 21.5 (CH_2, 2 carbons); MS: *m/z* 288 $[M+H]^+$, 289 $[M+Na]^+$.

6) *ter*-butyl 7-(oxiran-2-ylmethoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (3c)



The same procedure as in the preparation of **3a** was used with the spiro compound **2c** (4.3 g, 12.9 mmol) affording the epoxide **3c** as a colorless solid (4.1 g, 82 %); mp 101-102 ^{0}C**;** IR ($CHCl_3$, cm^{-1}): ν_{max} 1681, 1610, 1425, 1368, 1177, 1094, 849; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.52-1.66 (m, 4H), 1.99-2.05 (m, 2H), 2.67 (s, 2H), 2.75-2.79 (dd, *J*= 4.8, 2.6 Hz, 1H), 2.92-2.96 (apparent t, *J*= 4.5 Hz, 1H), 3.15-3.27 (m, 2H), 3.33-3.41 (m, 1H), 3.92-4.00 (dd, *J*= 10.6, 5.9 Hz, 1H), 4.26-4.33 (dd, *J*= 11.2, 2.9 Hz, 1H), 6.45 (d, *J*= 2.2 Hz, 1H), 6.59 (dd, *J*= 8.6, 2.3 Hz, 1H), 7.81 (d, *J*= 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 190.1,165.1, 160.9, 154.7, 128.5, 114.9, 109.8, 102.1, 79.8, 78.2, 69.0, 49.7, 47.7, 44.5, 39.2, 34.0, 28.4; ESI-MS: *m/z* 390 $[M+ H]^+$, 412 $[M+ Na]^+$.

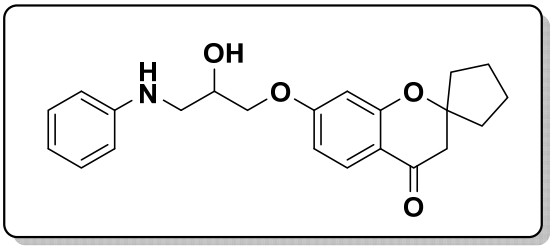
7) Synthesis of amino alcohol fused spirochromone conjugates (4-6)

General procedure:

To a stirred solution of epoxide **3a/3b/3c** (0.5 mmol) and LiBr (0.1 mmol) in methanol (3 mL) was added an appropriate amine (0.55 mmol) and the resulting reaction mixture was stirred at rt for 12 h. After completion of the reaction (monitored by TLC), solvent was removed in vacuo and the reaction mixture was diluted with ethyl acetate (20 mL) and then washed with water (2 X 5 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (ethyl acetate/ petroleum ether 3:7 (v/v)) afforded pure product **4-6**.

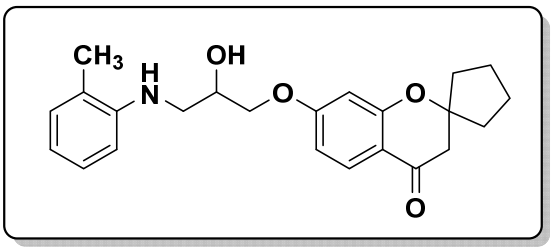
Spectroscopic data for all the compounds are given below.

7-(2-hydroxy-3-(phenylamino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4a)



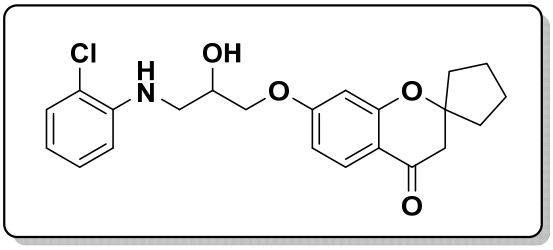
Yellow oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 2970, 2083, 1610, 1505, 1442, 1261; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.63-1.83 (m, 6H), 2.02-2.09 (m, 2H), 2.77 (s, 2H), 3.33 (dd, *J* = 12.9, 6.9 Hz, 1H), 3.41 (dd, *J* = 12.9, 4.1, 1H), 4.07-4.14 (m, 2H), 4.22-4.32 (m, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 7.23 Hz, 1H), 7.19 (dd, *J* = 15.3, 5.9 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.0 (CO), 164.8 (C), 162.3 (C), 147.1 (C), 129.4 (CH, 2 carbons), 128.6 (CH), 118.2 (CH), 115.2 (C), 113.3 (CH, 2 carbons), 109.4 (CH), 102.2 (CH), 90.5 (C), 70.3 (CH_2), 68.5 (CH), 46.7 (CH_2), 46.5 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 368 $[M+H]^+$, 390 $[M+Na]^+$.

7-(2-hydroxy-3-(o-tolylamino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4b)



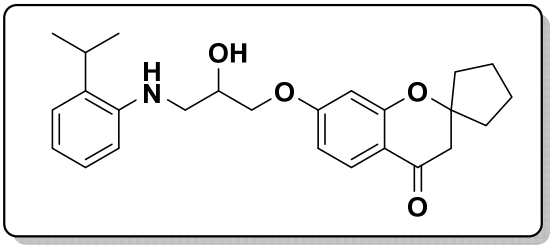
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3431, 2967, 2877, 1673, 1607, 1514, 1443 ; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.63-1.89 (m, 6H), 2.02-2.10 (m, 2H), 2.18 (s, 3H), 2.77 (s, 2H), 3.34 (dd, *J* = 12.7, 6.9 Hz, 1H), 3.46 (dd, *J* = 13.0, 4.4 Hz, 1H), 4.09-4.12 (m, 2H), 4.27-4.37 (m, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.58 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.68 (m, 2H), 7.10 (m, 2H), 7.78 (d, *J* = 8.7 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.5 (CO), 164.8 (C), 162.3 (C), 145.8 (C), 130.3(CH), 128.6 (CH), 127.2 (CH), 122.7 (C), 117.8 (CH), 115.3 (C), 110.1 (CH), 109.4 (CH), 102.2 (CH), 90.5 (C), 70.5 (CH_2), 68.4 (CH), 46.7 (CH_2), 46.5 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons), 17.5 (CH_3); MS: *m/z* 382 $[M+H]^+$, 404 $[M+Na]^+$.

7-(3-((2-chlorophenyl)amino)-2-hydroxypropoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4c)



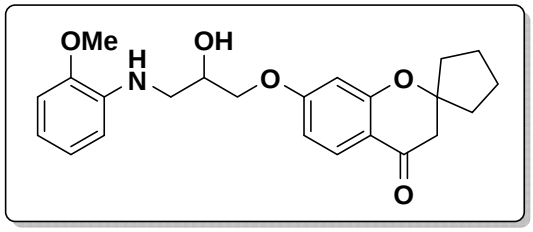
Colorless oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3433, 2087, 1642, 1510, 1422; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.53-1.79 (m, 6H), 1.95-2.10 (m, 2H), 2.71 (s, 2H), 3.25-3.58 (m, 2H), 4.03-4.07 (m, 2H), 4.17-4.30 (m, 1H), 4.65 (br s, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 6.51 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.56-6.67 (m, 2H), 7.03-7.22(m, 2H), 7.76 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.4 (CO), 164.7 (C), 162.3 (C), 143.8 (C), 129.3(CH), 128.6 (CH), 127.8 (CH), 119.7 (C), 117.9 (CH), 115.3 (C), 111.5 (CH), 109.4 (CH), 102.2 (CH), 90.5 (C), 70.2 (CH_2), 68.4 (CH), 46.7 (CH_2), 46.2 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 402 $[M+H]^+$, 424 $[M+Na]^+$.

7-(2-hydroxy-3-((2-isopropylphenyl)amino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4d)



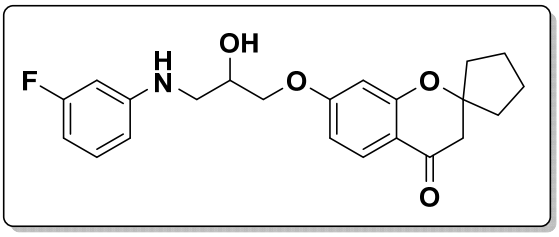
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3444, 2966, 1673, 1608, 1508, 1443, 1162; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.16 (d, *J* = 6.6 Hz, 6H), 1.51-1.77 (m, 6H), 1.93-2.01 (m, 2H), 2.68 (s, 2H), 2.78-2.91 (m, 1H), 3.28 (dd, *J* = 12.5, 6.9 Hz, 1H), 3.37 (dd, *J* = 12.8, 4.1, 1H), 4.01-4.03 (m, 2H), 4.20-4.29 (m, 1H), 6.32 (d, *J* = 1.8 Hz, 1H), 6.48 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.70 (apparent triplet, *J* = 7.4 Hz, 1H), 7.07 (dd, *J* = 13.2, 7.7 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 190.2 (CO), 163.5 (C), 161.0 (C), 143.3 (C), 131.7 (C), 127.2 (CH), 125.4 (CH), 123.8 (CH), 116.8 (CH), 113.8 (C), 109.8 (CH), 108.1(CH), 100.9 (CH), 89.1 (C), 69.2 (CH_2), 67.0(CH), 45.4 (CH_2), 45.3 (CH_2), 36.1 (CH_2, 2 carbons), 25.8 (CH), 22.5 (CH_2, 2 carbons), 21.0 (CH_2, 2 carbons); MS: *m/z* 410 $[M+H]^+$, 432 $[M+Na]^+$.

7-(2-hydroxy-3-((2-methoxyphenyl)amino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4e)



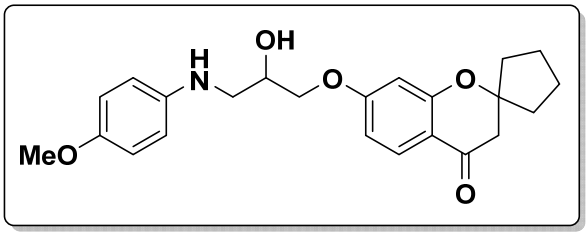
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 2083, 1642, 1512, 1442 ; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.57-1.78 (m, 6H), 2.02-2.11 (m, 2H), 2.78 (s, 2H), 3.38 (dd, *J* = 13.2, 6.9 Hz, 1H), 3.44 (dd, *J* = 13.2, 4.6 Hz, 1H), 3.86 (s, 3H), 4.07-4.14 (m, 2H), 4.25-4.35 (m, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.56 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.66-6.92 (m, 4H), 7.79 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.4 (CO), 164.9 (C), 162.3 (C), 147.1 (C), 137.8 (C), 128.5 (CH), 121.2 (CH), 117.3 (CH), 115.2 (C), 110.2 (CH), 109.6 (CH), 109.4 (CH), 102.2 (CH), 90.9 (C), 70.4 (CH_2), 68.5 (CH), 55.4 (CH_3), 46.7 (CH_2), 46.4 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 398 $[M+H]^+$, 420 $[M+Na]^+$.

7-(3-((3-fluorophenyl)amino)-2-hydroxypropoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4f)



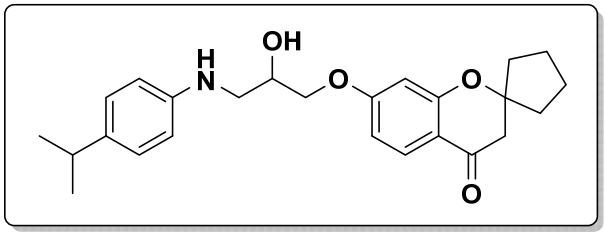
Colorless oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 2970, 2090, 1625, 1511, 1443, 1263 ; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.61-1.78 (m, 6H), 1.95-2.03 (m, 2H), 2.70 (s, 2H), 3.25-3.57 (m, 2H), 4.00-4.07 (m, 2H), 4.22-4.32 (m, 1H), 4.65 (br s, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 6.48 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.60 (dd, *J* = 13.6, 6.8 Hz, 2H), 7.11 (m, 2H), 7.76 (d, *J* = 8.7 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.7 (CO), 166.5 (C), 164.8 (C), 162.4 (C), 149.9 (C), 130.3 (CH), 128.5 (CH), 115.2 (C), 109.4 (CH), 109.1 (CH), 104.5 (CH), 102.2 (CH), 100.1 (CH), 90.5 (C), 70.2 (CH_2), 68.3 (CH), 46.6 (CH_2, 2 carbons), 37.5 (CH_2. 2 carbons), 23.8 (CH_2. 2 carbons); MS: *m/z* 385 $[M+H]^+$, 408 $[M+Na]^+$.

7-(2-hydroxy-3-((4-methoxyphenyl)amino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4g)



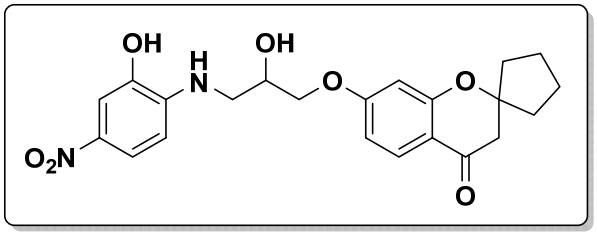
Colorless oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3448, 1674, 1609, 1513, 1441; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.60-1.90 (m, 6H), 2.01-2.11 (m, 2H), 2.77 (s, 2H), 3.24 (dd, *J* = 12.8, 6.9 Hz, 1H), 3.36 (dd, *J* = 12.8, 4.2 Hz, 1H), 3.75 (s, 3H), 4.06-4.10 (m, 2H), 4.22-4.28 (m, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.4 Hz, 2H), 6.82 (dd, *J* = 9.0, 2.2 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.4 (CO), 164.8 (C), 162.3 (C), 152.7 (C), 142.0 (C), 128.5 (CH), 115.2 (C), 114.9 (CH), 114.8 (CH, 2 carbons), 109.4 (CH), 102.2 (CH, 2 carbons), 90.5 (C), 70.4 (CH_2), 68.5 (CH), 55.8 (CH_3), 47.8 (CH_2), 46.7 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 398 $[M+H]^+$, 420 $[M+Na]^+$.

7-(2-hydroxy-3-((4-isopropylphenyl)amino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4h)



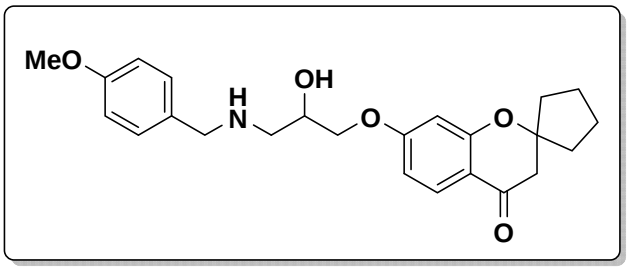
Colorless solid; mp 117-18 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3414, 2935, 1608, 1441; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.22 (d, *J* = 6.7 Hz, 6H), 1.60-1.83 (m, 6H), 2.02-2.10 (m, 2H), 2.77 (s, 2H), 2.81-2.88 (m, 1H), 3.32 (dd, *J* = 12.8, 6.9 Hz, 1H), 3.39 (dd, *J* = 12.8, 4.0 Hz, 1H), 4.06-4.14 (m, 2H), 4.25-4.30 (m, 1H), 6.30 (d, *J* = 1.3 Hz, 1H), 6.52-6.65 (m, 3H), 7.08 (d, *J* = 8.0, 2H), 7.82 (d, *J* = 8.9 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.4 (CO), 164.9 (C), 162.3 (C), 145.9 (C), 138.8 (C), 128.5 (CH), 127.2 (CH, 2 carbons), 115.2 (C), 113.4 (CH, 2 carbons), 109.4 (CH), 102.2 (CH), 90.5 (C), 70.4 (CH_2), 68.5 (CH), 46.9 (CH_2), 46.7 (CH_2), 37.5 (CH_2, 2 carbons), 33.1 (CH), 24.2 (CH_3, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 410 $[M+H]^+$, 432 $[M+Na]^+$.

7-(2-hydroxy-3-((2-hydroxy-4-nitrophenyl)amino) propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4i)



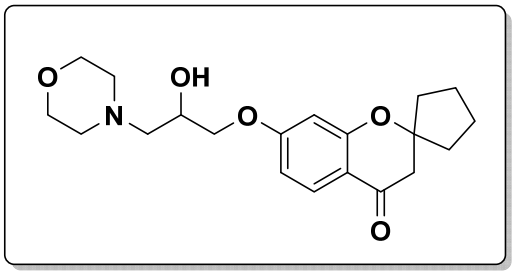
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3418, 1609, 1519, 1442, 1314; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.54-1.81 (m, 6H), 1.97-2.04 (m, 2H), 2.78 (s, 2H), 3.42-3.62 (m, 2H), 4.20-4.31 (m, 2H), 4.47-4.51 (m, 1H), 6.36 (dd, *J* = 7.4, 2.1 Hz, 1H), 6.42-6.54 (m, 2H), 7.58-7.78 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.3 (CO), 164.8 (C), 162.5 (C), 144.1 (C), 142.3 (C), 138.1 (C), 128.6 (CH), 119.9 (CH), 115.2 (C), 112.2 (CH), 109.4 (CH), 107.3 (CH), 102.2 (CH), 90.5 (C), 69.8 (CH_2), 68.3 (CH), 60.5 (CH_2), 46.5 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons); MS: *m/z* 451 $[M+Na]^+$.

7-(2-hydroxy-3-((4-methoxybenzyl)amino)propoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4j)



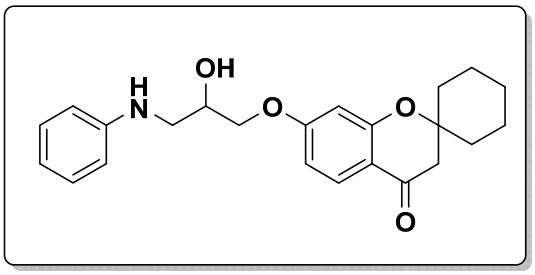
Colorless oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3444, 1643, 1515, 1476, 1423; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.52-1.78 (m, 6H), 1.94-2.01 (m, 2H), 2.69-2.82 (m, 6H), 3.71 (s, 3H), 3.82-3.84 (m, 2H), 3.99-4.06 (m, 1H), 6.26 (d, *J* = 1.7 Hz, 1H), 6.40 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.5 Hz, 2H), 7.16 (dd, *J* = 8.7, 3.1 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.4 (CO), 164.9 (C), 162.3 (C), 159.0 (C), 130.3 (CH, 2 carbons), 129.9 (C), 128.4 (CH), 115.1 (C), 113.9 (CH, 2 carbons), 109.4 (CH), 102.1 (CH), 90.4 (C), 70.3 (CH_2), 67.8 (CH), 59.5 (CH_2), 57.6 (CH_2), 55.2 (CH_3), 46.7 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons). MS: *m/z* 412 $[M+H]^+$, 426 $[M+Na]^+$.

7-(2-hydroxy-3-morpholinopropoxy)spiro[chroman-2,1'-cyclopentan]-4-one (4k)



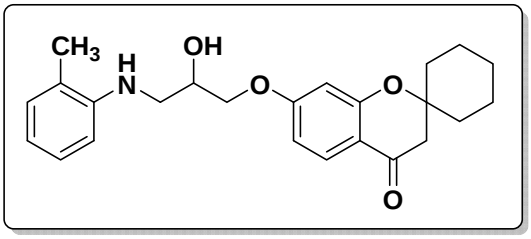
Yellow oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3435, 2090, 1638, 1497, 1442, 1264, 1117; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.59-1.89 (m, 6H), 2.01-2.10 (m, 2H), 2.44-2.59 (m, 4H), 2.64-2.74 (m, 2H), 2.76 (s, 2H), 3.74 (apparent triplet, *J* = 4.7 Hz, 4H), 3.98-4.01 (m, 2H), 4.07-4.19 (m, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 6.54 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 191.4 (CO), 165.0 (C), 162.3 (C), 128.5 (CH), 115.1 (C), 109.5 (CH), 102.1 (CH), 90.4 (C), 70.3 (CH_2), 66.8 (CH_2, 2 carbons), 65.1 (CH), 60.8 (CH_2), 53.7 (CH_2, 2 carbons), 46.7 (CH_2), 37.5 (CH_2, 2 carbons), 23.8 (CH_2, 2 carbons) MS: *m/z* 362 $[M+H]^+$, 384 $[M+Na]^+$.

7-(2-hydroxy-3-(phenylamino)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5a)



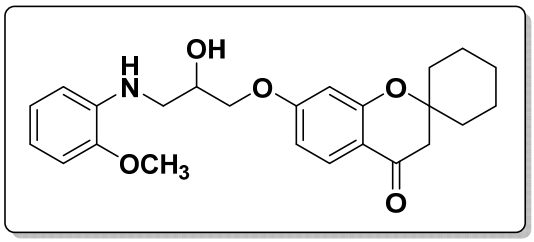
Yellow oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 2935, 1605, 1505, 1443, 1271; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.33-1.72 (m, 8H), 1.94-2.00 (m, 2H), 2.64 (s, 2H), 3.30 (dd, *J* = 13.1, 7.0 Hz, 1H), 3.42 (dd, *J* = 13.1, 4.2 Hz, 1H), 4.07-4.13 (m, 2H), 4.22-4.33 (m, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 6.56 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.65-6.78 (m, 3H), 7.15-7.26 (m, 2H), 7.80 (d, *J* = 8.6 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 191.4 (CO), 165.0 (C), 161.6 (C), 147.9 (C), 129.3 (CH, 2 carbons), 128.3 (CH), 118.1 (CH), 115.0 (C), 113.3 (CH, 2 carbons), 109.3 (CH), 102.0 (CH), 80.5 (C), 70.3 (CH_2), 68.5 (CH), 47.8 (CH_2), 46.5 (CH_2), 34.8 (CH_2. 2 carbons), 25.1 (CH_2), 21.5 (CH_2. 2 carbons); MS: *m/z* 382 $[M+H]^+$, 404 $[M+Na]^+$.

7-(2-hydroxy-3-(o-tolylamino)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5b)



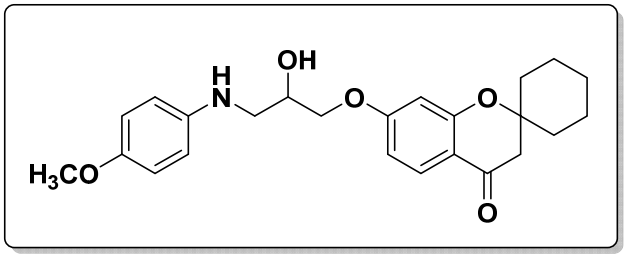
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 2089, 1844, 1640, 1541, 1456; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.25-1.73 (m, 8H), 1.94-2.04 (m, 2H), 2.17 (s, 3H), 2.64 (s, 2H), 3.30 (dd, *J* = 12.8, 7.1 Hz, 1H), 3.44 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.07-4.13 (m, 2H), 4.26-4.37 (m, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.64-6.74 (m, 2H), 7.09 (dd, *J* = 15.0, 7.5 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 191.4 (CO), 165.0 (C), 161.6 (C), 145.8 (C), 130.3 (CH), 128.3 (CH), 127.2 (CH), 122.7 (C), 117.7 (CH), 115.0 (C), 110.1 (CH), 109.3 (CH), 102.0 (CH), 80.5 (C), 70.5 (CH_2), 68.4 (CH), 47.8 (CH_2), 46.5 (CH_2), 34.8 (CH_2, 2 carbons), 25.1 (CH_2), 21.5 (CH_2, 2 carbons), 17.5 (CH_3); MS: *m/z* 396 $[M+H]^+$, 418 $[M+Na]^+$.

7-(2-hydroxy-3-((2-methoxyphenyl)amino)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5c)



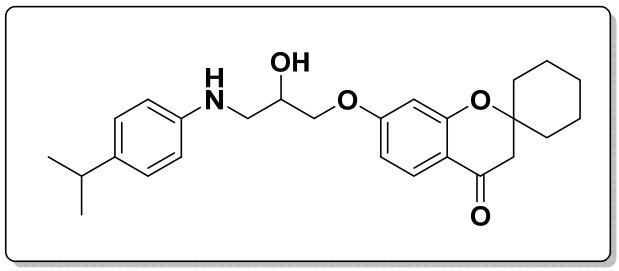
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3422, 2089, 1844, 1640, 1541, 1456; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.21-1.79 (m, 8H), 1.94-2.01 (m, 2H), 2.64 (s, 2H), 3.33 (dd, *J* = 13.1, 6.7 Hz, 1H), 3.43 (dd, *J* = 13.1, 4.6 Hz, 1H), 3.84 (s, 3H), 4.09-4.11 (m, 2H), 4.24-4.35 (m, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 6.56 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.66-6.92 (m, 4H), 7.76 (d, *J* = 8.7 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 191.4 (CO), 165.1 (C), 161.6 (C), 147.1 (C), 137.8 (CH), 128.3 (CH), 121.3 (CH), 117.3 (CH), 115.0 (C), 110.3 (CH), 109.6 (CH), 109.4 (CH), 102.1 (CH), 80.4 (C), 70.4 (CH_2), 68.5 (CH), 55.4 (CH_3), 47.8 (CH_2), 46.5 (CH_2), 34.8 (CH_2, 2 carbons), 25.1 (CH_2), 21.5 (CH_2, 2 carbons); MS: *m/z* 412 $[M+H]^+$, 434 $[M+Na]^+$.

7-(2-hydroxy-3-((4-methoxyphenyl)amino)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5d)



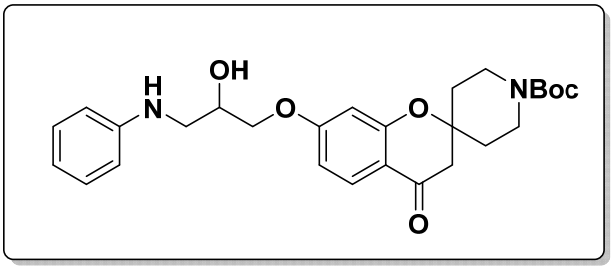
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3421, 2937, 2253, 1674, 1607, 1513, 1442 ; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.27-1.77 (m, 8H), 1.93-1.99 (m, 2H), 2.63 (s, 2H), 3.26 (dd, *J* = 12.8, 7.3 Hz, 1H), 3.36 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.74 (s, 3H), 3.77-3.81 (m, 2H), 4.05-4.07 (m, 2H), 4.23-4.34 (m, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.69-6.81 (m, 4H), 7.78 (d, *J* = 8.8 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 191.4 (CO), 165.0 (C), 161.6 (C), 153.3 (C), 140.9 (C), 128.3 (CH), 115.6 (CH, 2 carbons), 115.5 (C), 114.9 (CH, 2 carbons), 109.3 (CH), 102.0 (CH), 80.5 (C), 70.4 (CH_2), 68.2 (CH), 55.7 (CH_3), 48.5 (CH_2), 47.8 (CH_2), 34.8 (CH_2, 2 carbons), 25.1 (CH_2), 21.5 (CH_2, 2 carbons) MS: *m/z* 412 $[M+H]^+$.

7-(2-hydroxy-3-((4-isopropylphenyl)amino)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5e)



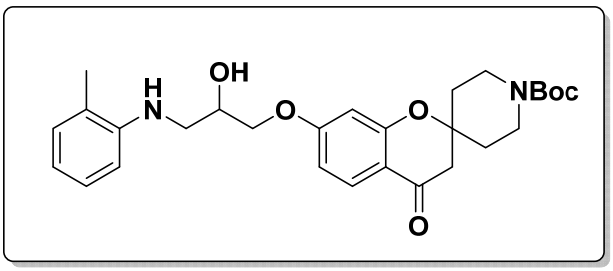
Brown oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3420, 2935, 1608, 1441; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.23 (d, *J* = 6.8 Hz, 6H), 1.41-1.74 (m, 8H), 1.95-2.02 (m, 2H), 2.65 (s, 2H), 2.75-2.89 (m, 2H), 3.30 (dd, *J* = 13.0, 6.9 Hz, 1H), 3.41 (dd, *J* = 13.0, 4.3 Hz, 1H), 3.74 (s, 3H), 3.77- 3.81 (m, 2H), 4.05-4.07 (m, 2H), 4.23-4.34 (m, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.10 (m, 2H), 7.77 (d, *J* = 8.6 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 191.3 (CO), 165.0 (C), 161.6 (C), 145.9 (C), 138.8 (C), 128.3 (CH), 127.2 (CH, 2 carbons), 115.0 (C), 113.4 (CH, 2 carbons), 109.3 (CH), 102.0 (CH), 80.5 (C), 70.3 (CH_2), 68.5 (CH), 47.9 (CH_2), 46.9 (CH_2), 34.8 (CH_2, 2 carbons), 33.7 (CH), 25.2 (CH_2), 24.2 (CH_3, 2 carbons), 21.5 (CH_2, 2 carbons); MS: *m/z* 424 $[M+H]^+$, 446 $[M+Na]^+$.

***tert*-butyl 7-(2-hydroxy-3-(phenylamino)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6a)**



Colorless solid; mp 143-44 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 2345, 1682, 1606, 1508, 1425 ; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.46 (s, 9H), 1.50-1.66 (m, 2H), 1.97-2.05 (m, 2H), 2.65 (s, 2H), 3.13-3.24 (m, 2H), 3.31 (dd, *J* = 13.2, 7.0 Hz, 1H), 3.42 (dd, *J* = 13.0, 4.2 Hz, 1H), 3.83-3.90 (m, 2H), 4.08-4.11 (m, 2H), 4.23-4.34 (m, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.65-6.71 (m, 2H), 6.78 (d, *J* = 7.3 Hz, 1H), 7.15-7.23 (m, 2H), 7.78 (d, *J* = 8.9 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 190.2 (CO), 165.2 (C), 160.9 (C), 154.7 (C), 147.9 (C), 129.3 (CH, 2 carbons), 128.5 (CH), 118.2 (CH), 114.9 (C), 113.3 (CH, 2 carbons), 109.8 (CH), 102.1 (CH), 79.9 (C), 78.3 (C), 70.4 (CH_2), 68.4 (CH), 47.7 (CH_2, 2 carbons), 46.5 (CH_2, 2 carbons), 34.0 (CH_2, 2 carbons), 28.4 (CH_3, 3 carbons); MS: *m/z* 483 $[M+H]^+$, 505 $[M+Na]^+$.

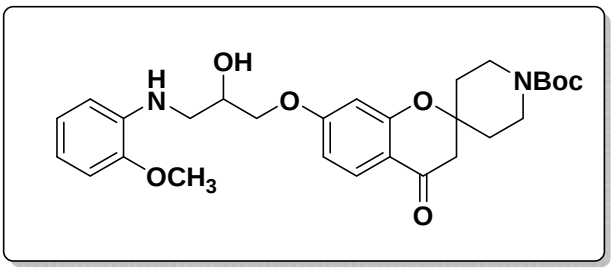
***tert*-butyl 7-(2-hydroxy-3-(o-tolylamino)propoxy)- 4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6b)**



Colorless oil; IR ($CHCl_3$, cm^{-1}): ν_{max} 3447, 1674, 1607, 1541 1522, 1426; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.46 (s, 9H), 1.59-1.67 (m, 2H), 1.98-2.05 (m, 2H), 2.18 (s, 3H), 2.66 (s, 2H), 3.14-3.26 (m, 2H), 3.35 (dd, *J* = 13.0, 6.9 Hz, 1H), 3.47 (dd, *J* = 13.0, 4.2 Hz, 1H), 3.83-3.90 (m, 2H), 4.11-4.14 (m, 2H), 4.28-4.38 (m, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.65-6.74 (m, 2H), 7.06-7.17 (m, 2H), 7.84 (d, *J* = 8.9 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 190.1 (CO), 165.1 (C), 160.9 (C), 154.7 (C), 145.8 (C), 130.3 (CH), 128.5 (CH), 127.2 (CH), 122.7 (C), 117.8 (CH), 115.0 (C), 110.1 (CH), 109.8 (CH), 102.1 (CH), 79.9 (C), 78.3 (C), 70.6

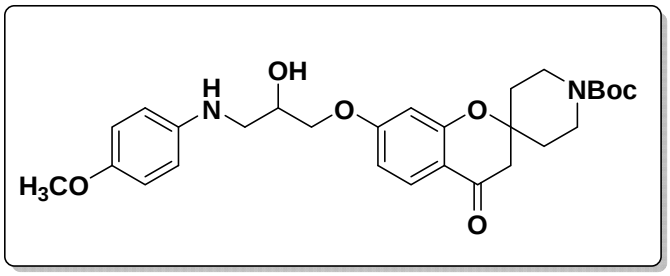
(CH_2), 68.4 (CH), 47.7 (CH_2, 2 carbons), 46.4 (CH_2, 2 carbons), 34.0 (CH_2, 2 carbons), 28.4 (CH_3, 3 carbons), 17.5 (CH_3) ; MS: *m/z* 497 $[M+H]^+$, 519 $[M+Na]^+$.

tert-butyl 7-(2-hydroxy-3-((2-methoxyphenyl)amino)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6c)



Colorless solid; mp 114-15 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3448, 1672, 1609, 1514, 1426, 1136; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.45 (s, 9H), 1.55-1.63 (m, 2H), 1.95-2.03 (m, 2H), 2.63 (s, 2H), 3.17-3.25 (m, 4H), 3.31 (dd, *J* = 13.0, 6.6 Hz, 1H), 3.41 (dd, *J* = 13.0, 4.6 Hz, 1H), 3.82 (s, 3H), 4.05-4.10 (m, 2H), 4.25-4.31 (m, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 6.55 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.62-6.89 (m, 4H), 7.76 (d, *J* = 8.7 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 190.2 (CO), 165.3 (C), 160.9 (C), 154.7 (C), 147.1 (C), 137.8 (C), 128.4 (CH), 121.2 (CH), 117.2 (CH), 114.8 (C), 110.2 (CH), 109.8 (CH), 109.6 (CH), 102.1 (CH), 79.6 (C), 78.2 (C), 70.5 (CH_2), 68.4 (CH), 55.4 (CH_3), 47.6 (CH_2, 2 carbons), 46.4 (CH_2, 2 carbons), 34.0 (CH_2, 2 carbons), 28.4 (CH_3, 3 carbons); MS: *m/z* 535 $[M+Na]^+$.

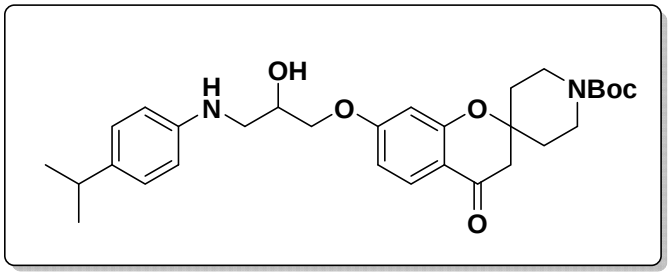
tert-butyl 7-(2-hydroxy-3-((4-methoxyphenyl)amino)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6d)



Colorless solid; mp 123-24 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 1678, 1609, 1514, 1427, 1237; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.46 (s, 9H), 1.52-1.67 (m, 2H), 1.98-2.05 (m, 2H), 2.67 (s, 2H), 3.14-3.43 (m, 4H), 3.75 (s, 3H), 3.84-3.89 (m, 2H), 4.08-4.11 (m, 2H), 4.22-4.32 (m, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 6.61 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.68 (dd, *J* = 9.0, 2.4 Hz, 2H), 6.78 (dd, *J* = 9.0, 2.4 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 190.2 (CO), 165.2 (C), 160.9 (C), 154.7 (C),

152.7 (C), 142.0 (C), 128.5 (CH), 114.9 (C), 114.9 (CH, 2 carbons), 114.8 (CH, 2 carbons), 109.8 (CH), 102.0 (CH), 79.9 (C), 78.3 (C), 70.5 (CH_2), 68.5 (CH), 55.8 (CH_3), 47.7 (CH_2, 2 carbons), 47.6 (CH_2, 2 carbons), 34.0 (CH_2. 2 carbons), 28.4 (CH_3. 3 carbons); MS: *m/z* 513 $[M+H]^+$, 535 $[M+Na]^+$.

tert-butyl 7-(2-hydroxy-3-((4-isopropylphenyl)amino)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6e)



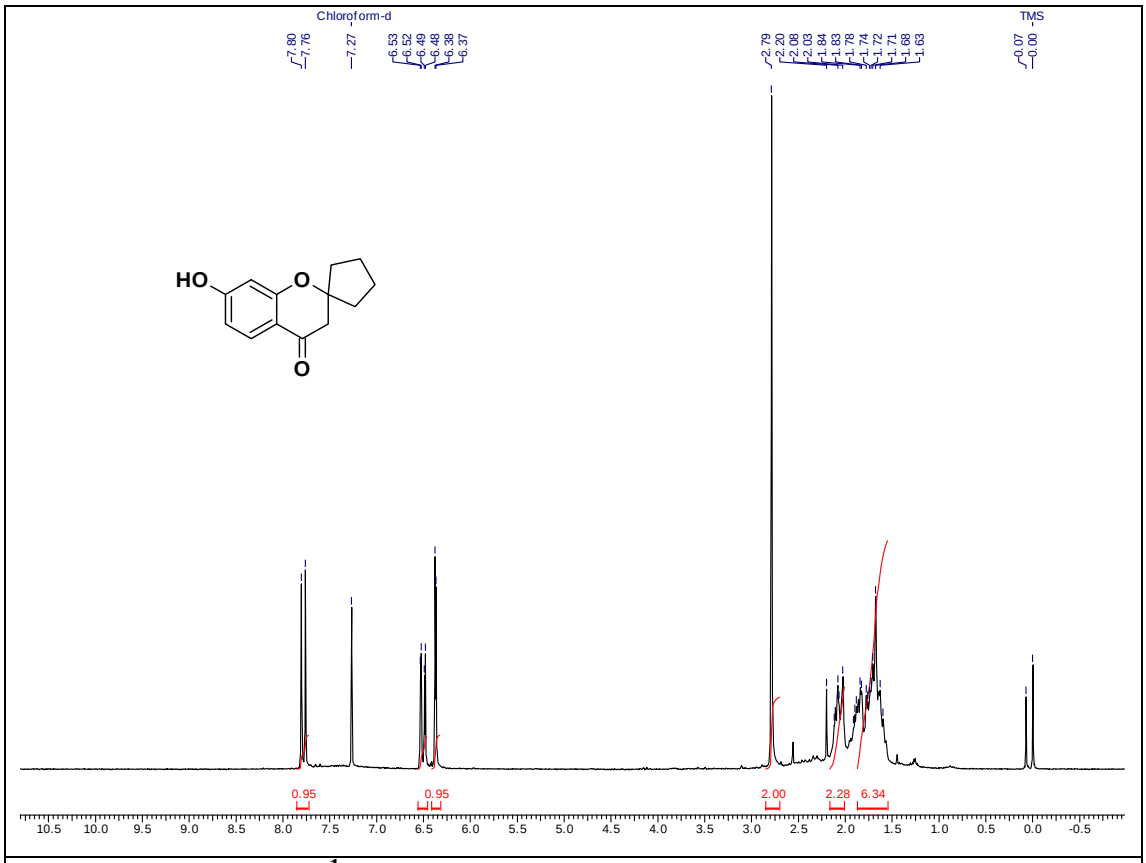
Yellow solid; mp 100-01 °C; IR ($CHCl_3$, cm^{-1}): ν_{max} 3448, 2091, 1638, 1519, 1475, 1424; ^1H NMR (200 MHz, $CDCl_3$): δ_H = 1.21 (d, *J* = 6.8 Hz, 6H), 1.46 (s, 9H), 1.51-1.64 (m, 2H), 1.95-2.03 (m, 2H), 2.63 (s, 2H), 2.73-2.87 (m, 1H), 3.12-3.45 (m, 4H), 3.82-3.88 (m, 2H), 4.06-4.09 (m, 2H), 4.21-4.31 (m, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.53-6.63 (m, 3 H), 7.02-7.06 (m, 2H), 7.76 (d, *J* = 8.8 Hz, 1H)); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 190.3 (CO), 165.3 (C), 160.9 (C), 154.7 (C), 146.0 (C), 138.6 (C), 128.4 (CH), 127.2 (CH, 2 carbons), 114.8 (C), 113.4 (CH, 2 carbons), 109.8 (CH), 102.1 (CH), 79.9 (C), 78.2 (C), 70.5 (CH_2), 68.4 (CH), 47.6 (CH_2, 2 carbons), 46.9 (CH_2, 2 carbons), 34.0 (CH_2. 2 carbons), 33.1 (CH), 28.4 (CH_3. 3 carbons), 24.2 (CH_3. 2 carbons); MS: *m/z* 525 $[M+H]^+$, 547 $[M+Na]^+$.

Single crystal X-ray data of compound 4h:

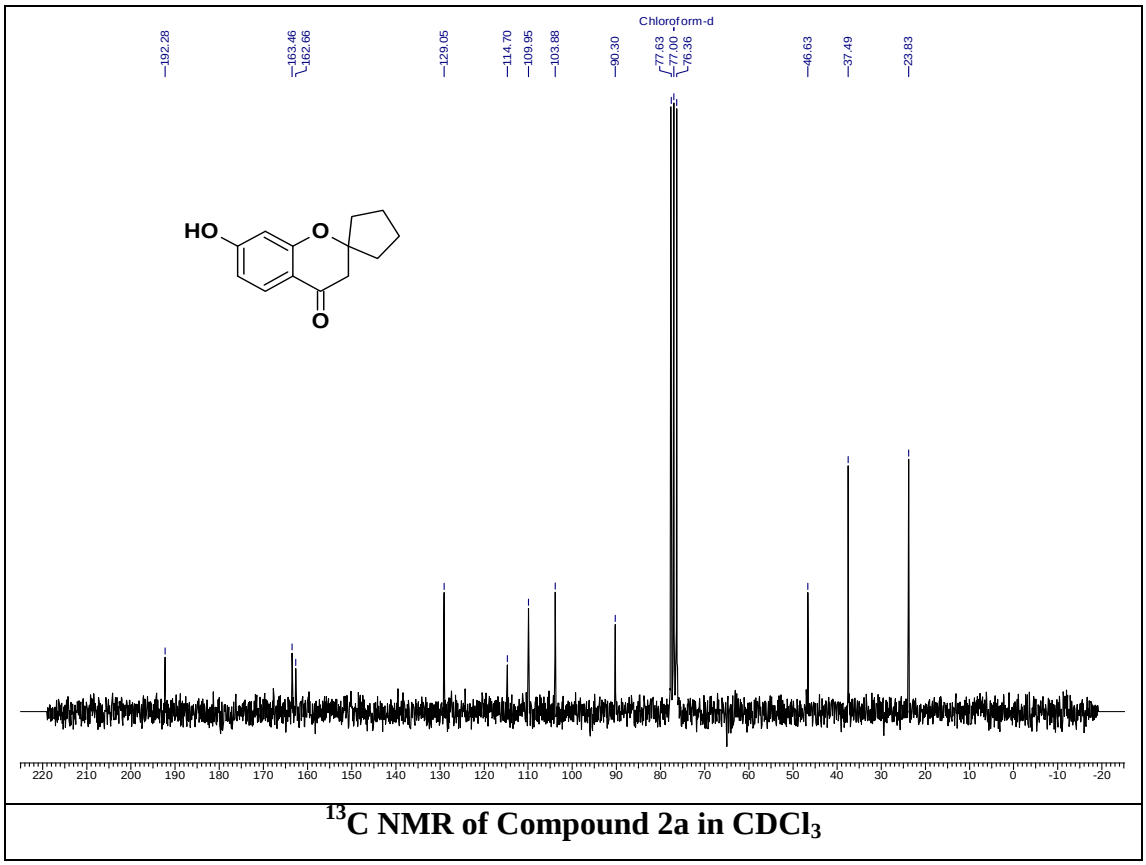
X-ray intensity data measurements of compound **4h** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at 100 (2) K. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from 277 reflections harvested from three sets of 36 frames. Data were collected with ω scan width of 0.5° at eight different settings of φ and 2θ with a frame time of 15 sec keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006). Crystal data of **4h.** $C_{25}H_{31}NO_4$, M=409.51, colorless plate, 0.27 x 0.18 x 0.09 mm^3, monoclinic, space

group $P2_1/n$, a =17.2460(10), b=6.3452(3), c=20.4880(11)Å, β =104.277(4)°, V = 2172.7(2) Å^3, Z = 4, T = 100(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.252, $F(000)$ = 880, μ (mm^{-1}) = 0.084, 28261 reflections collected, 3838 unique reflections (R_{int}=0.0812), 2420 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.978, T_{max} = 0.992, 278 refined parameters, S=1.061, $R1$=0.0646, $wR2$=0.1588 (all data R = 0.1100, $wR2$ = 0.1883), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 1.027, $\Delta\rho_{min}$ = -0.502 (eÅ^{-3}). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[2] Hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms.

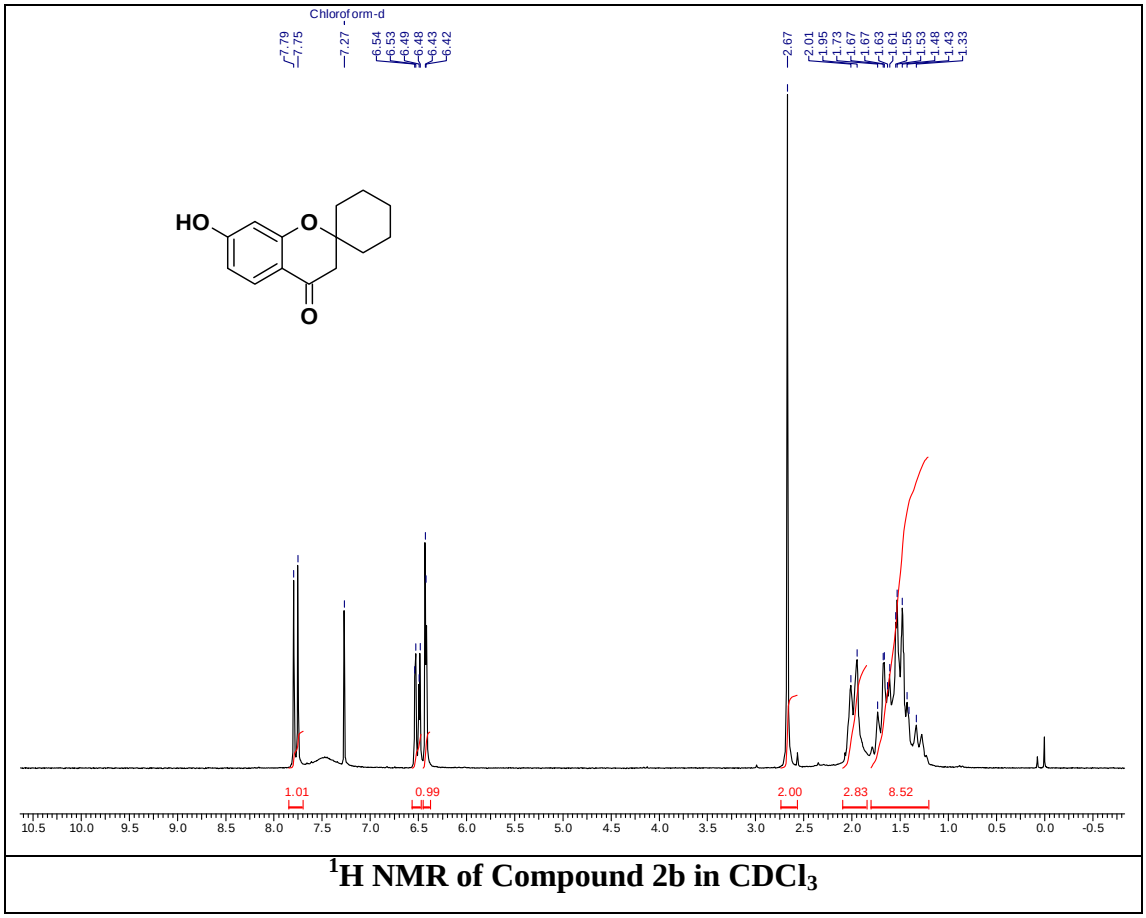
4.2.5. Analytical data



^{1}H NMR of Compound 2a in $CDCl_3$



^{13}C NMR of Compound 2a in $CDCl_3$



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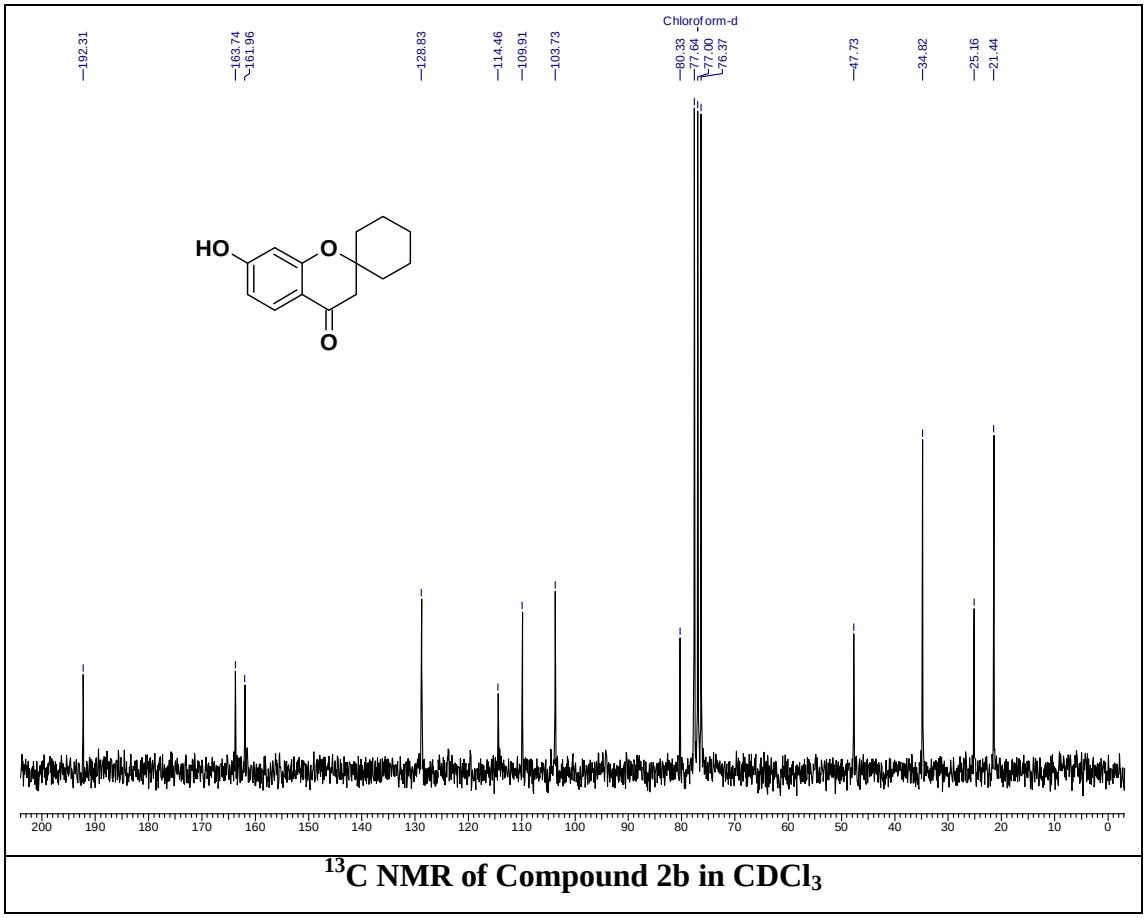

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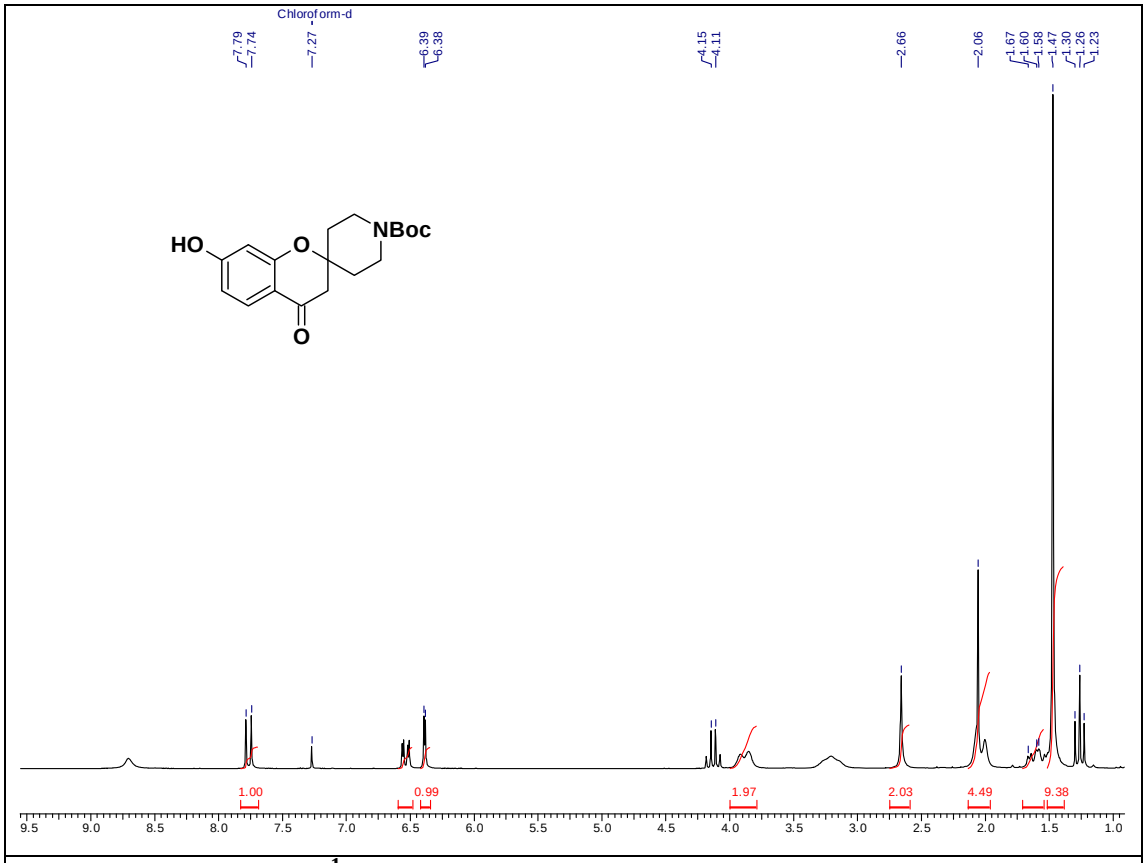

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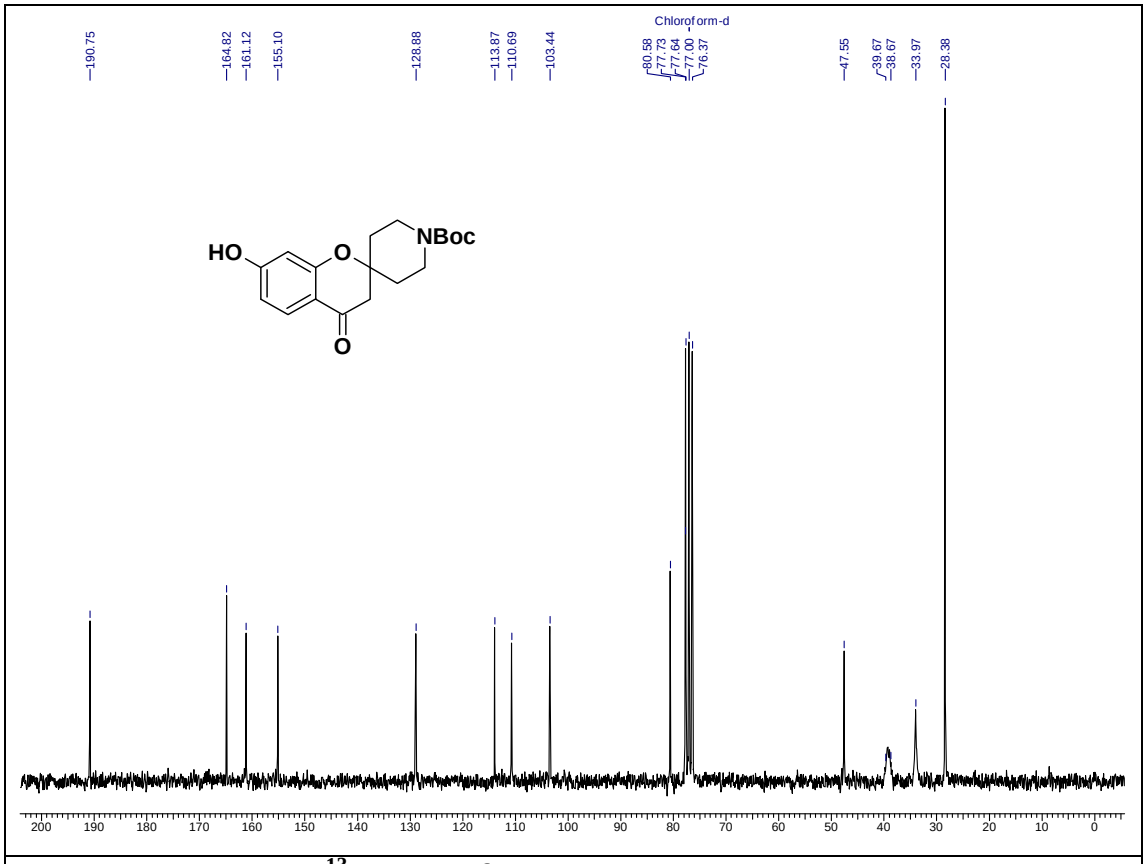

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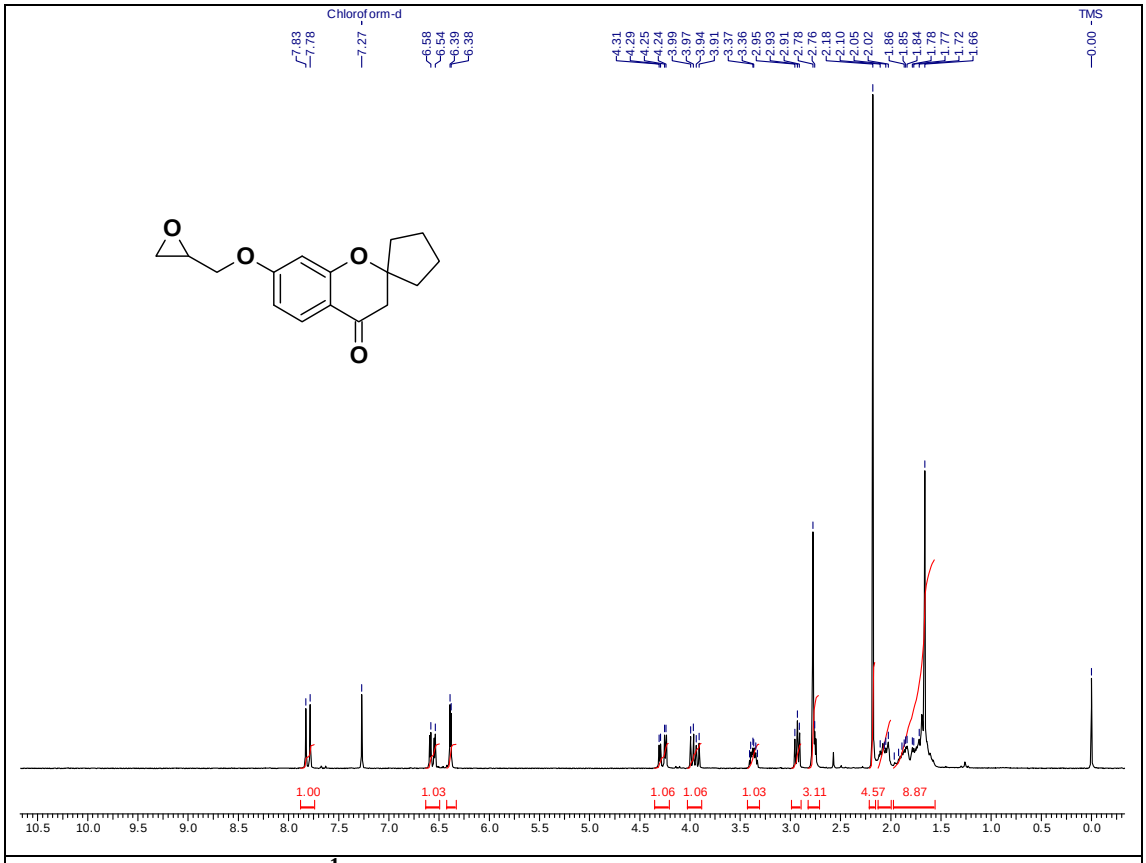
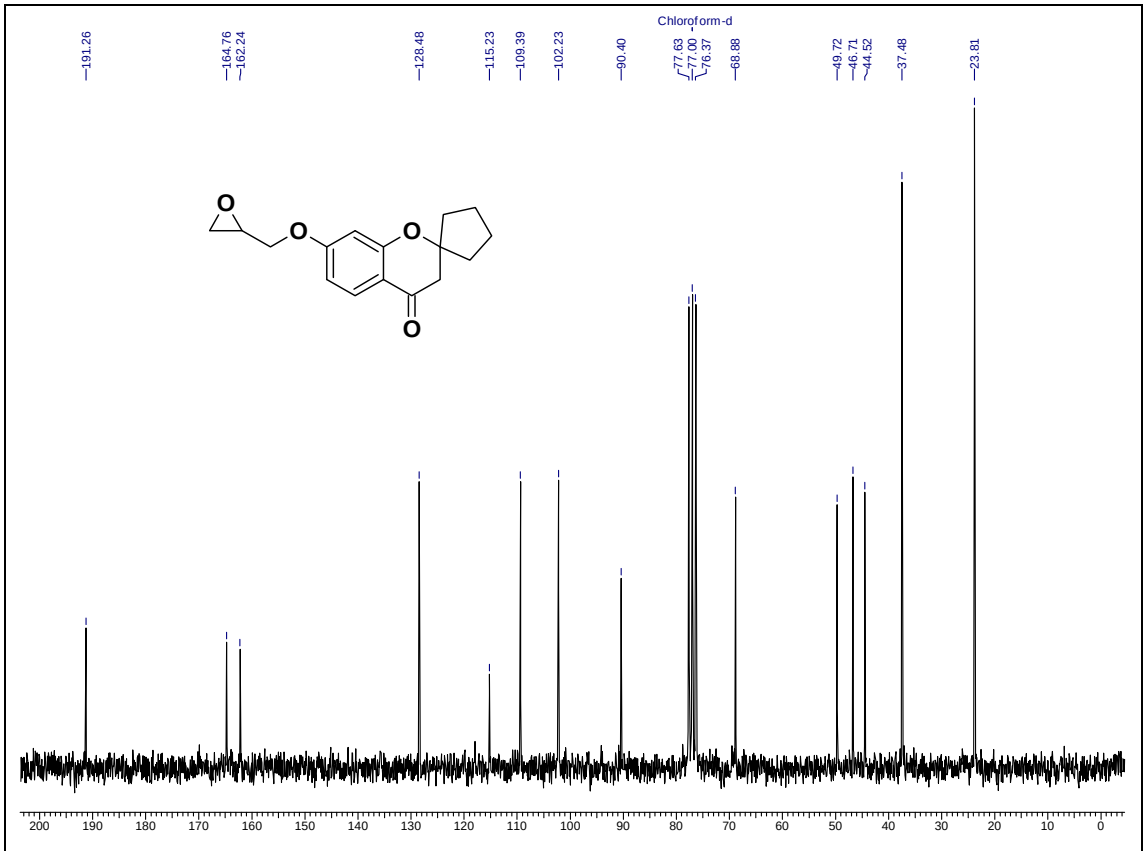
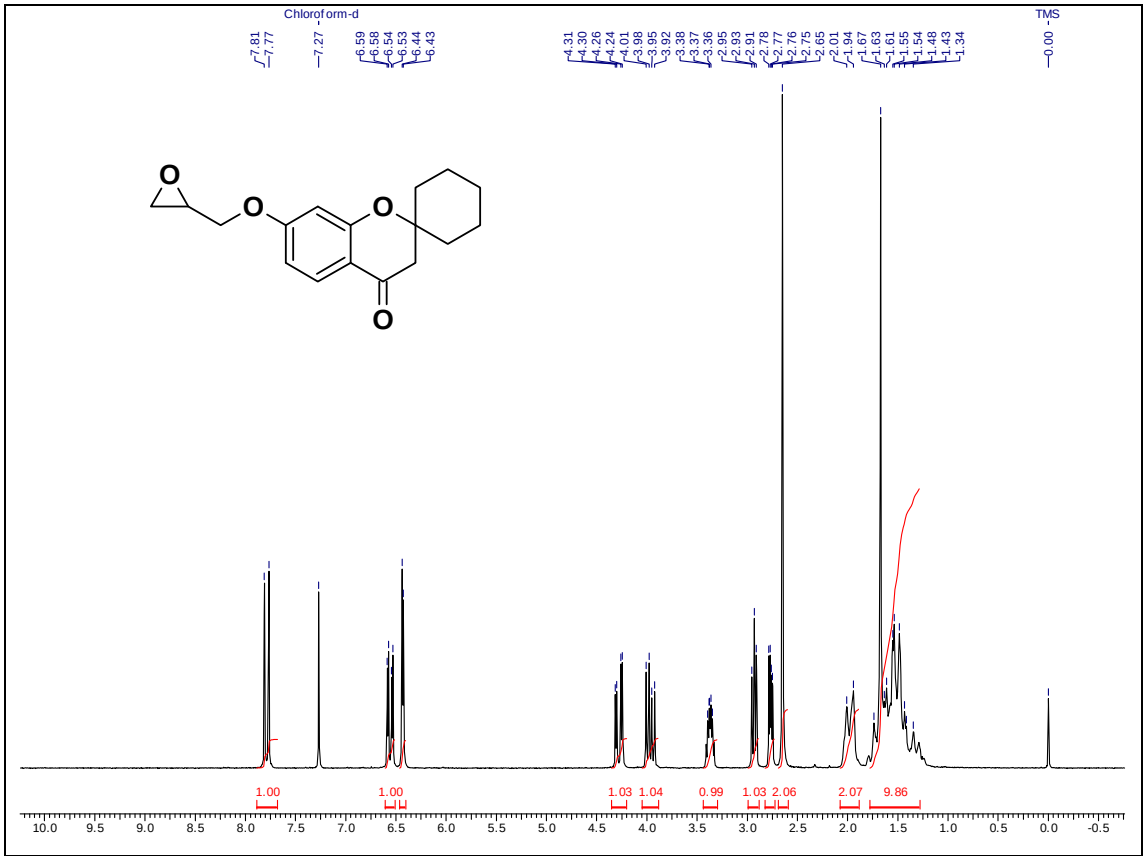


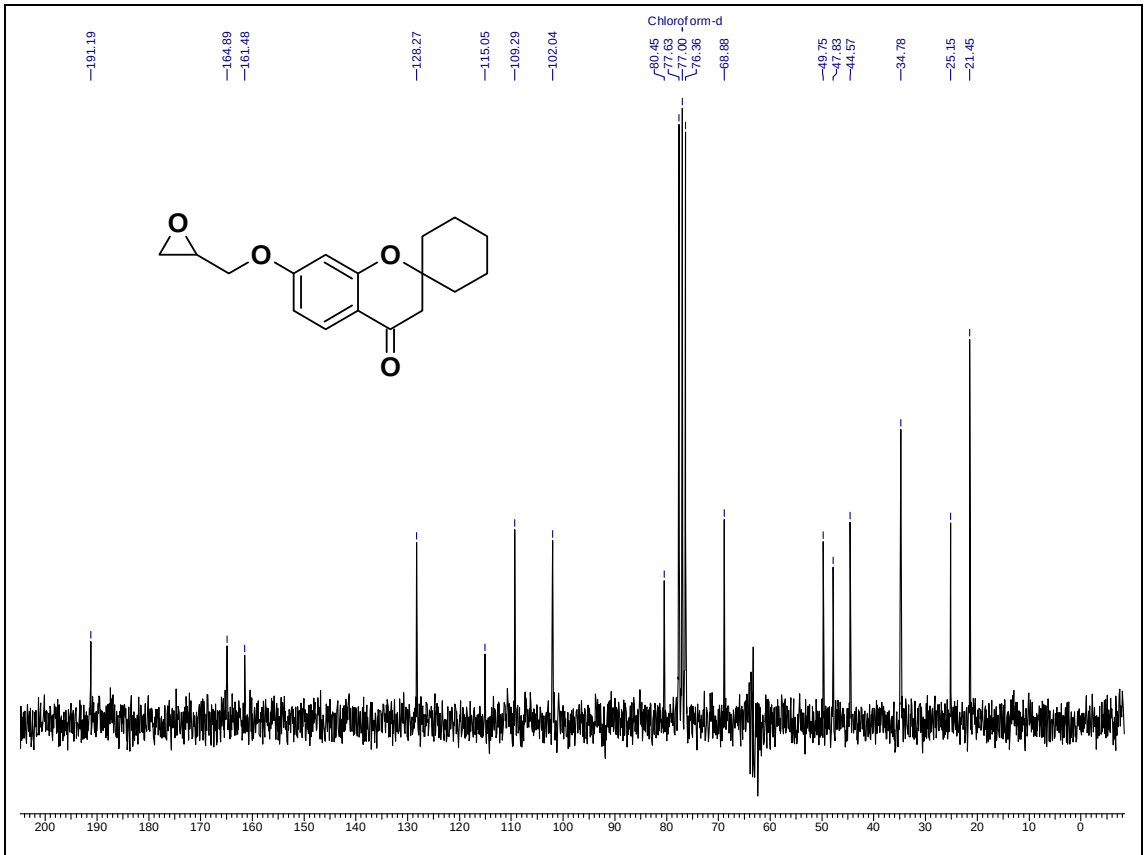
^{1}H NMR of Compound 3a in $CDCl_3$



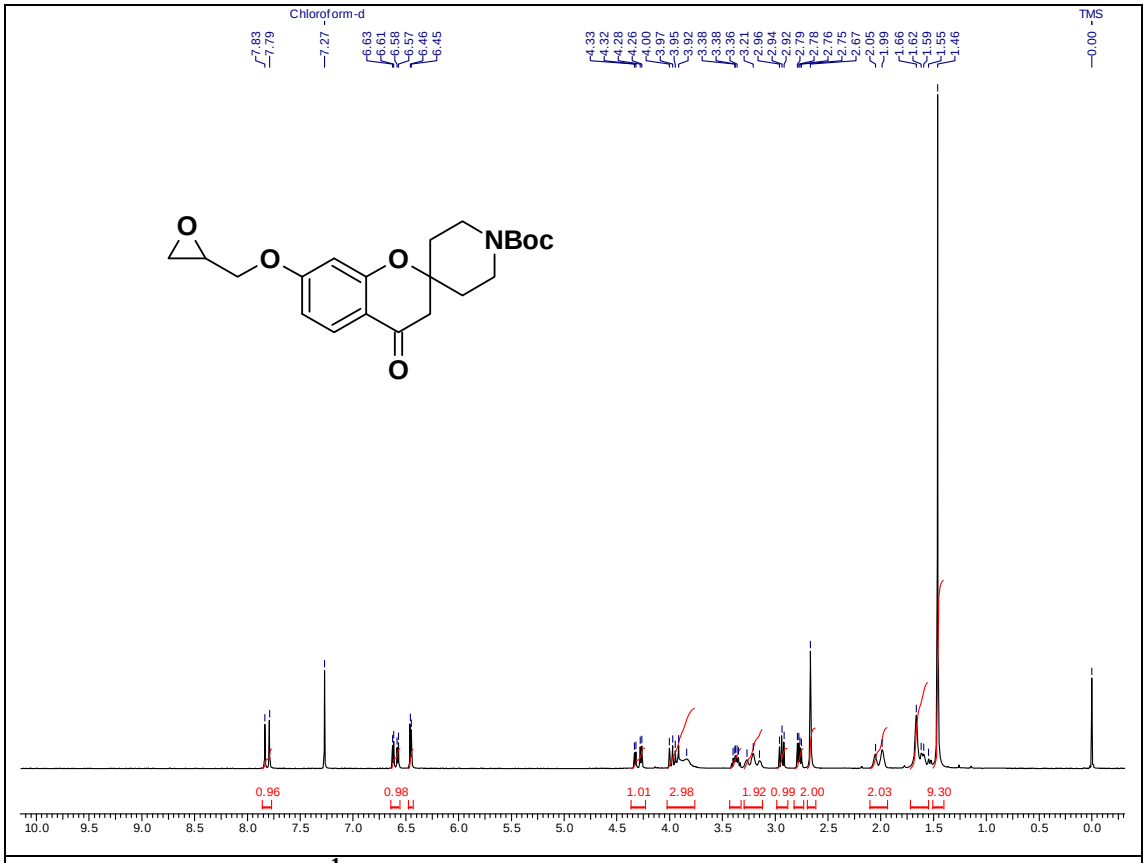
^{13}C NMR of Compound 3a in $CDCl_3$



^{1}H NMR of Compound 3b in $CDCl_3$



^{13}C NMR of Compound 3b in $CDCl_3$



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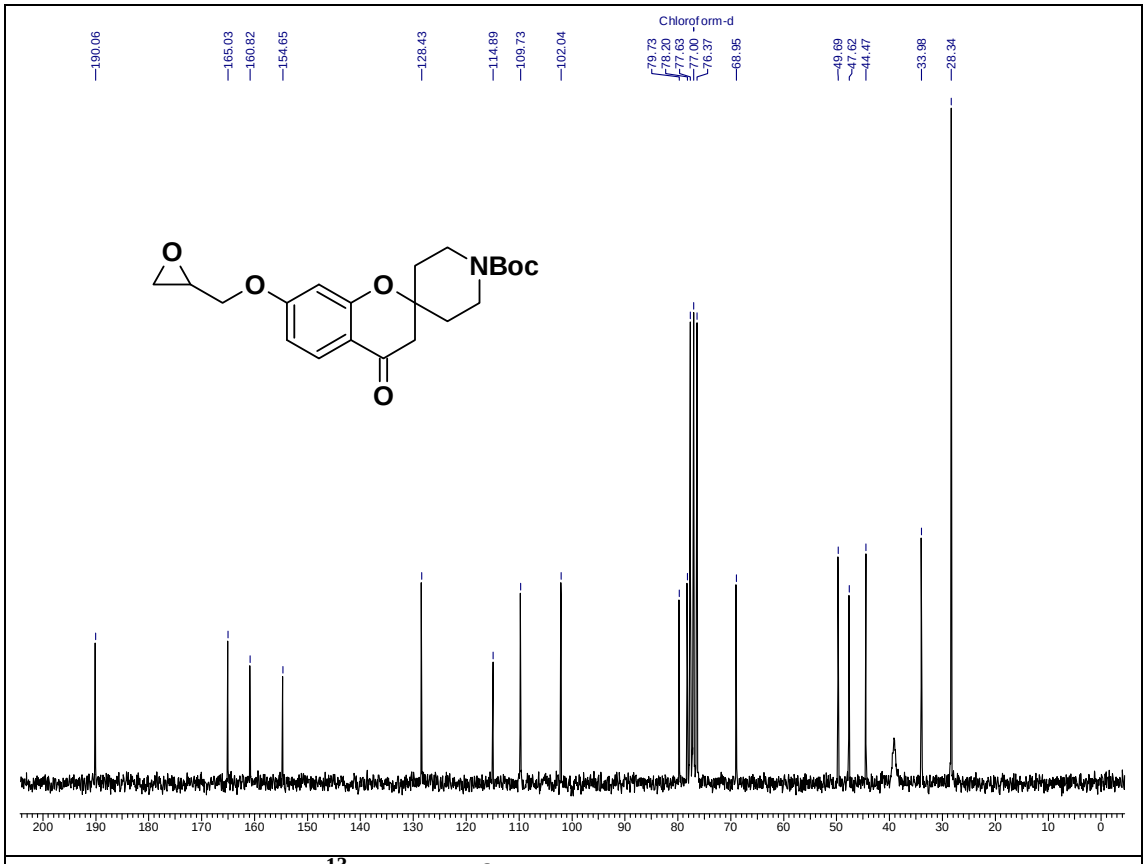
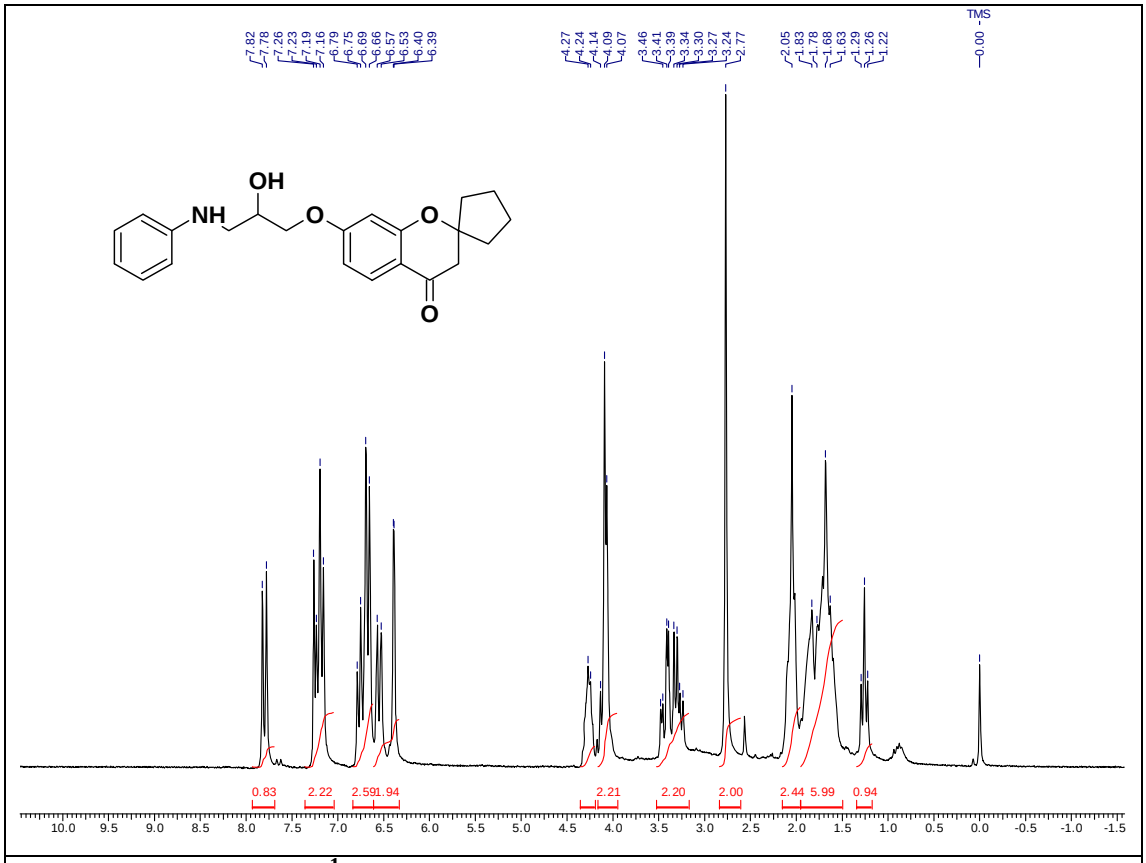


^{13}C NMR of Compound 3c in $CDCl_3$



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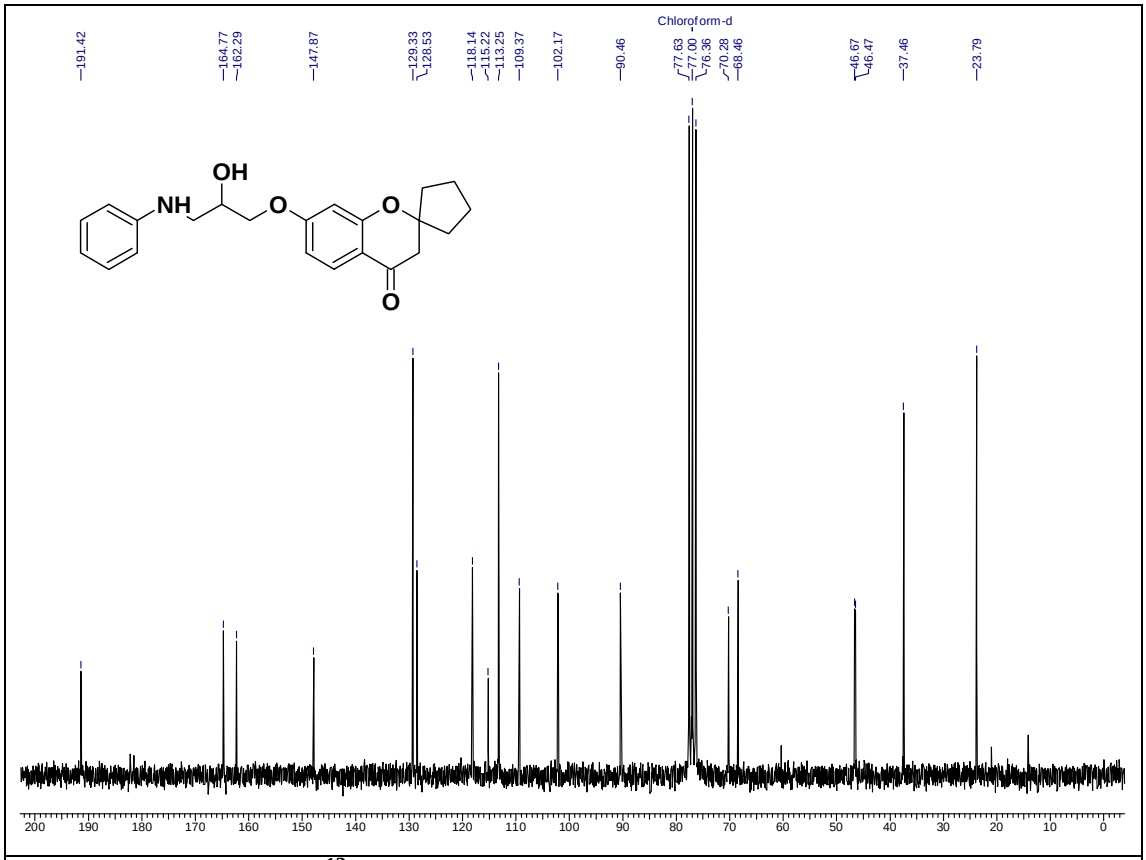

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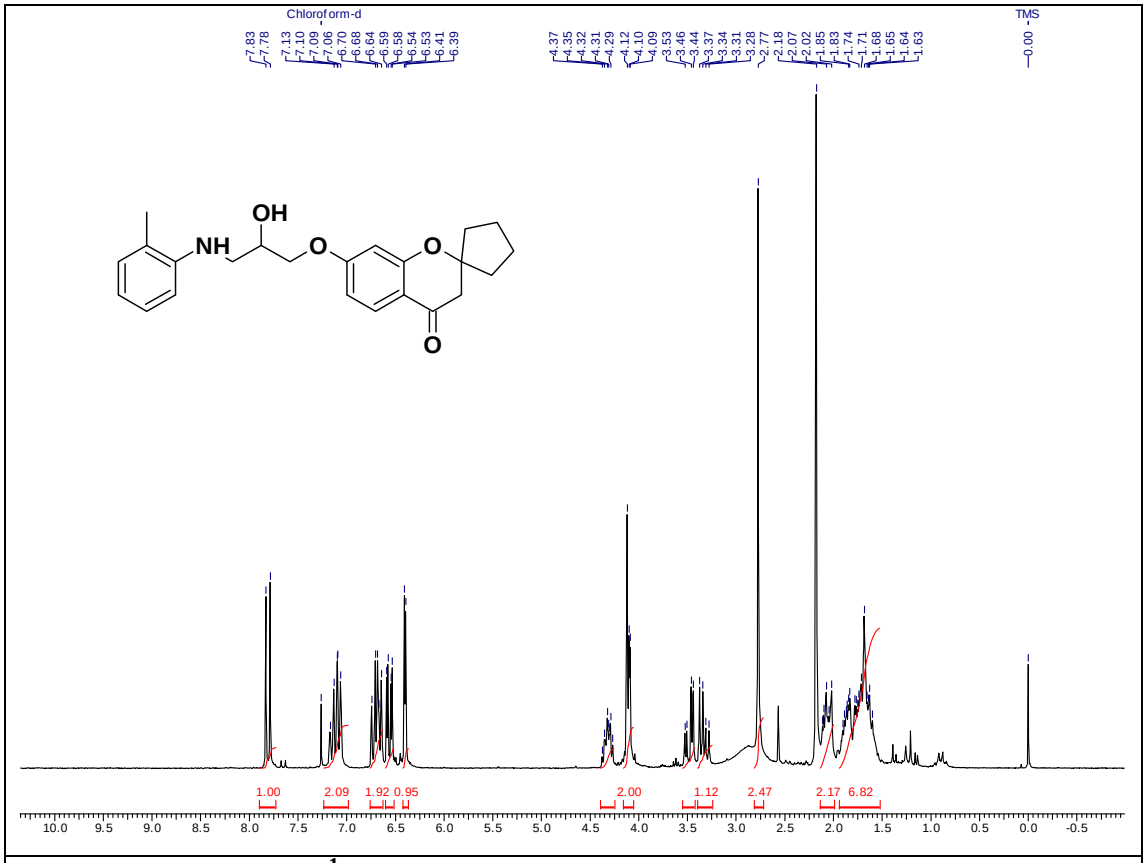

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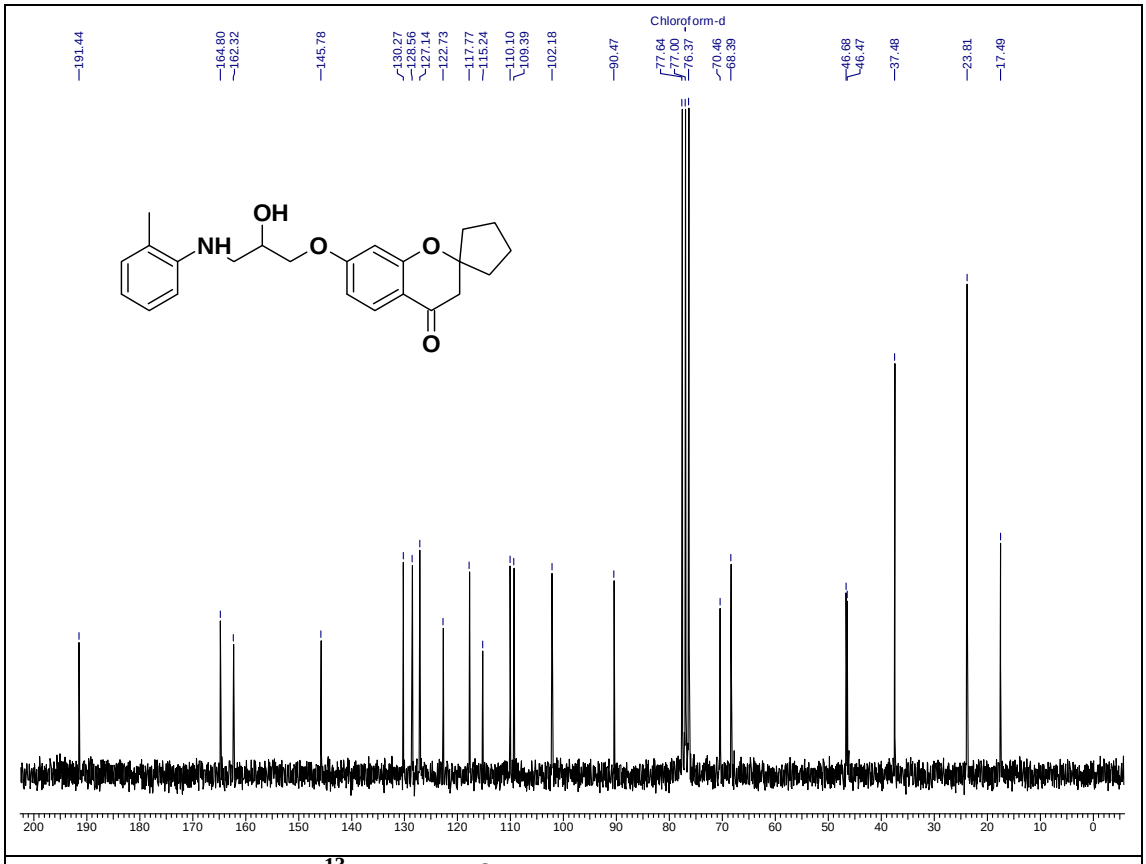

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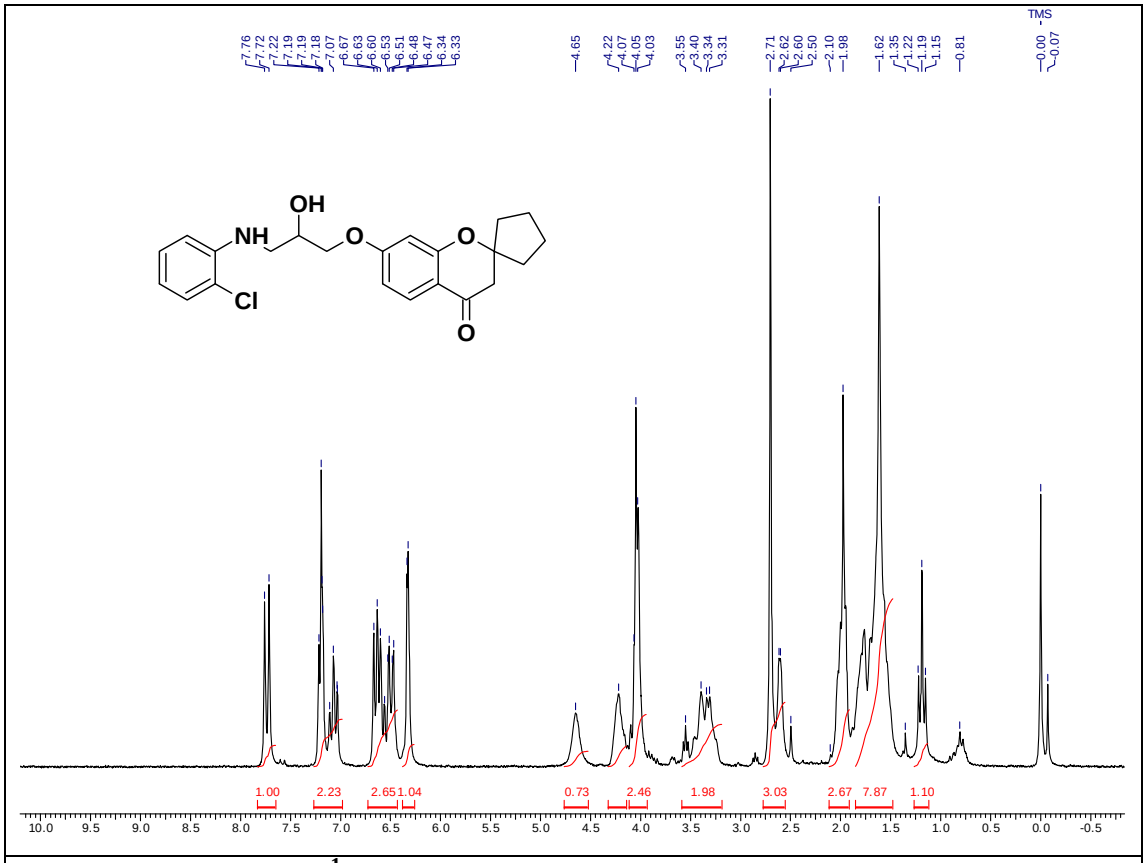

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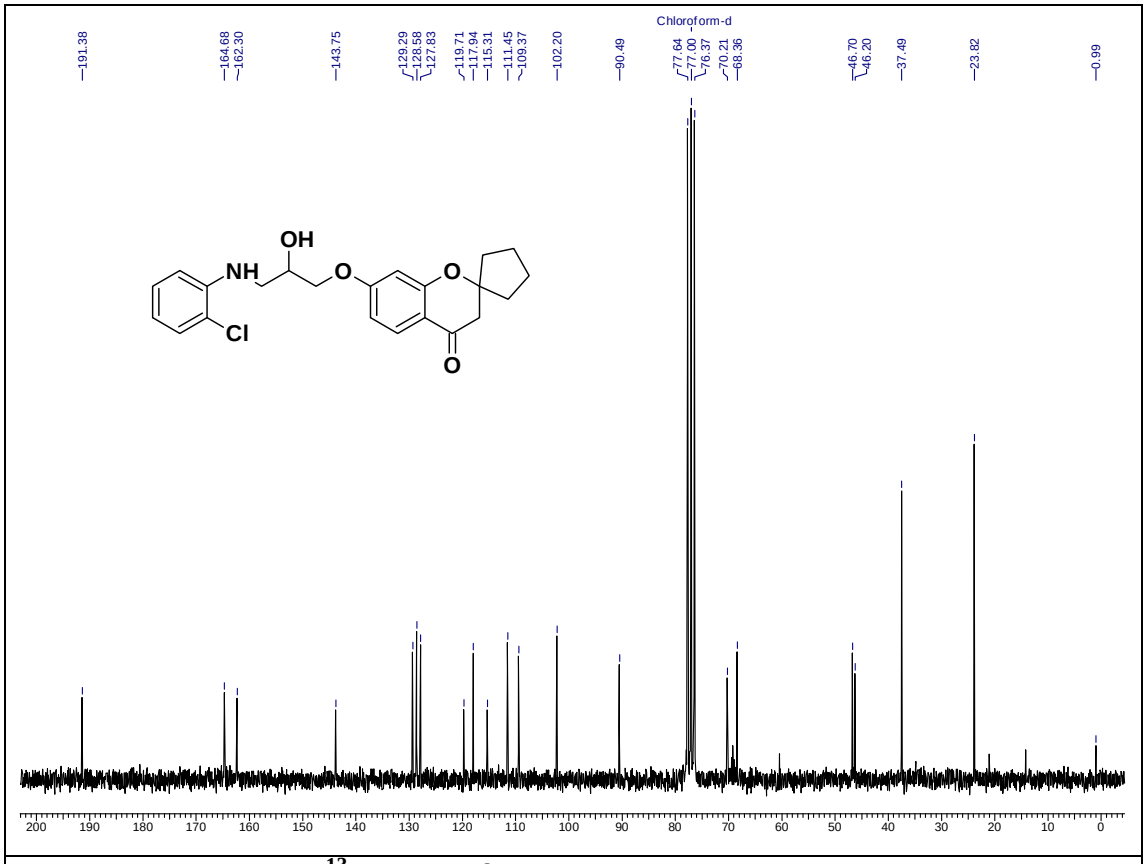

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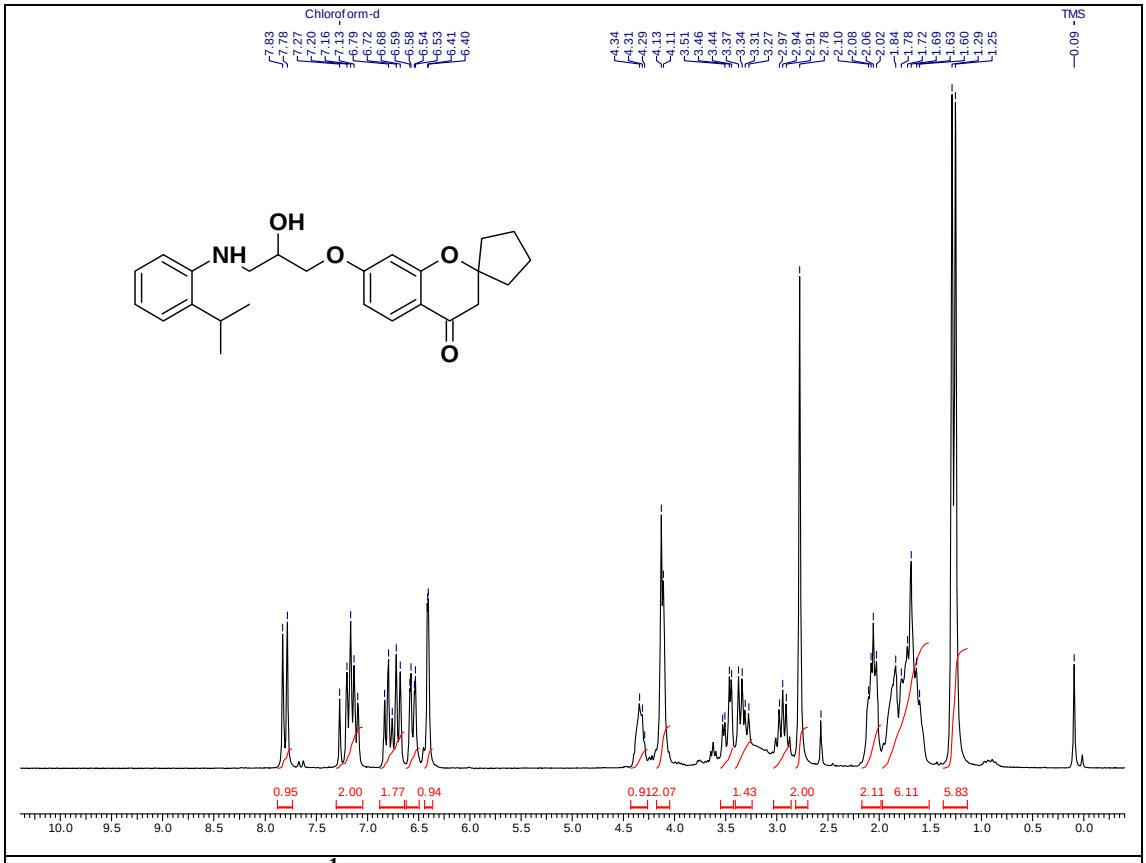

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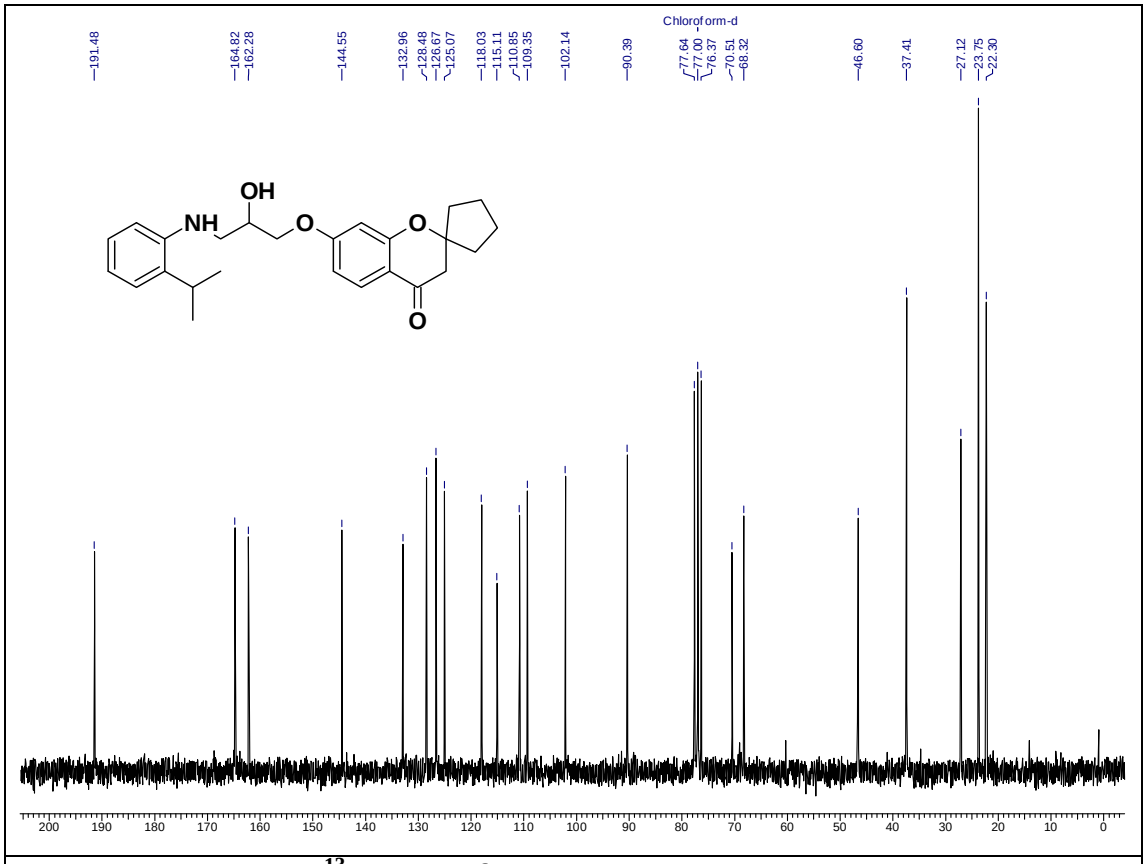

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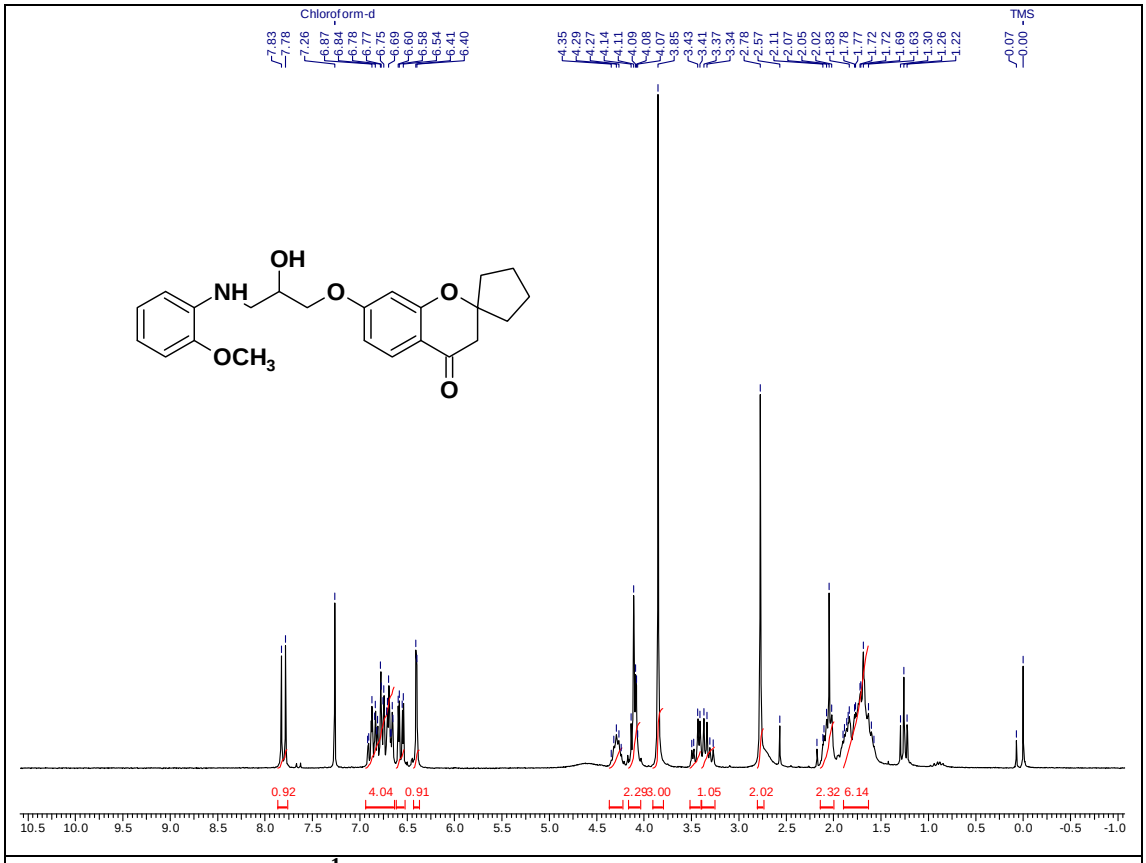

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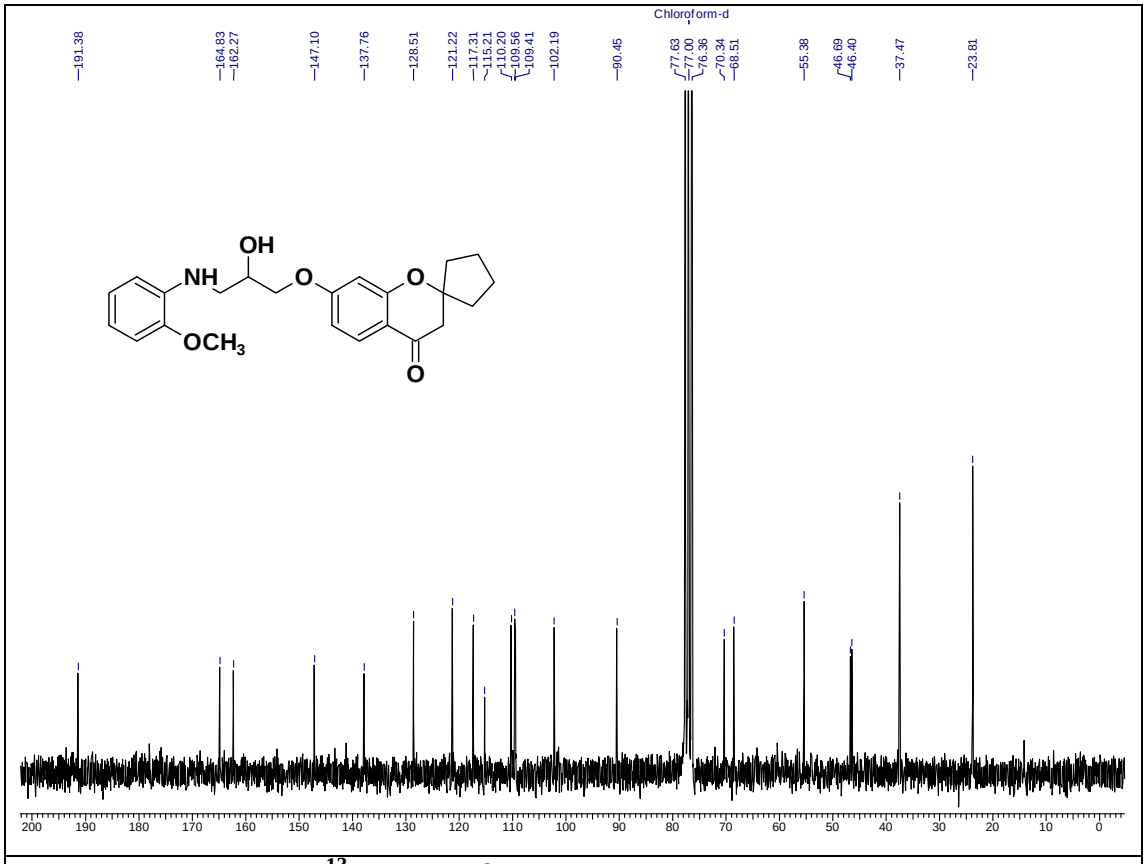

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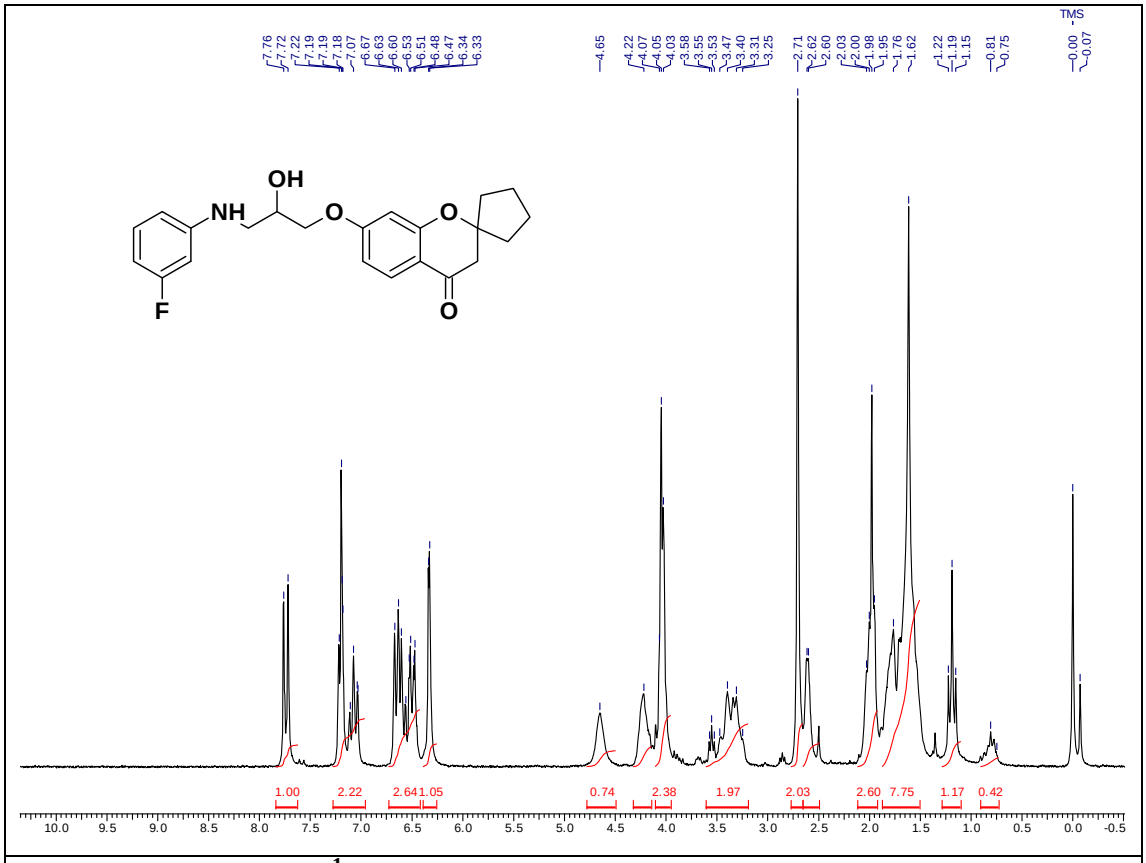

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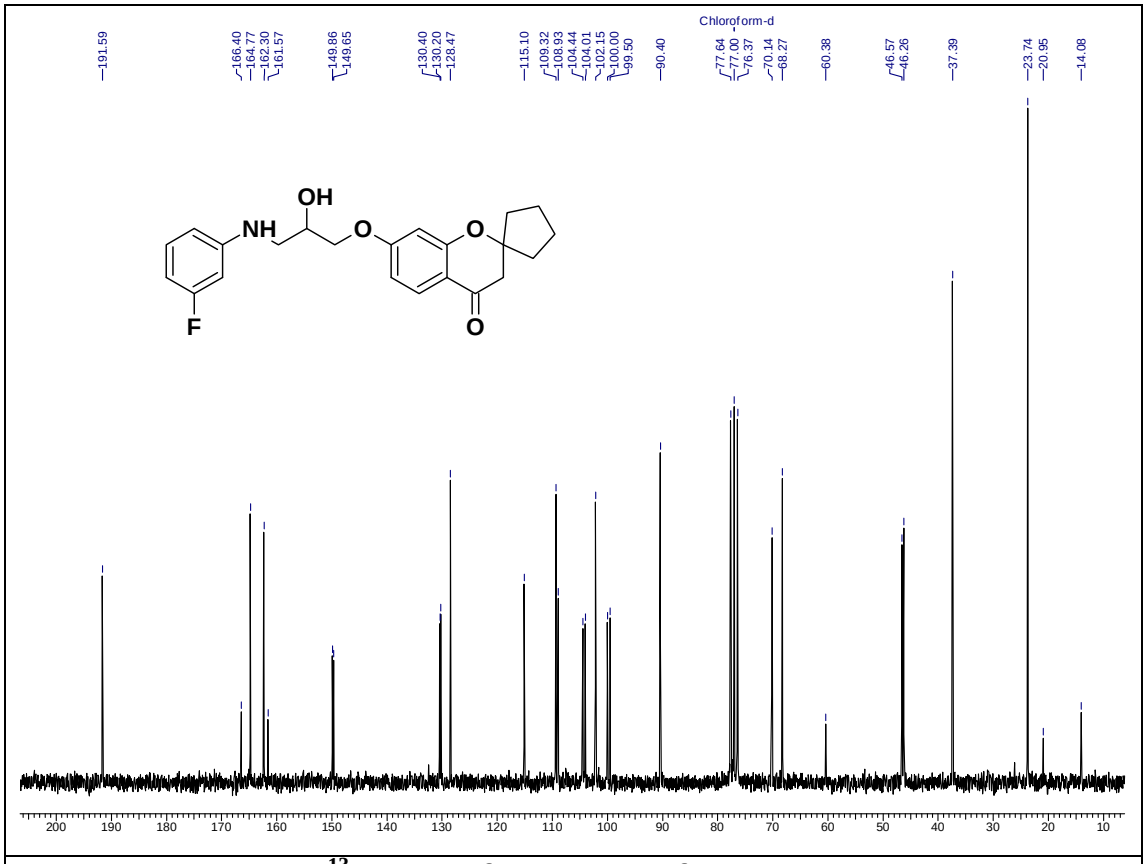

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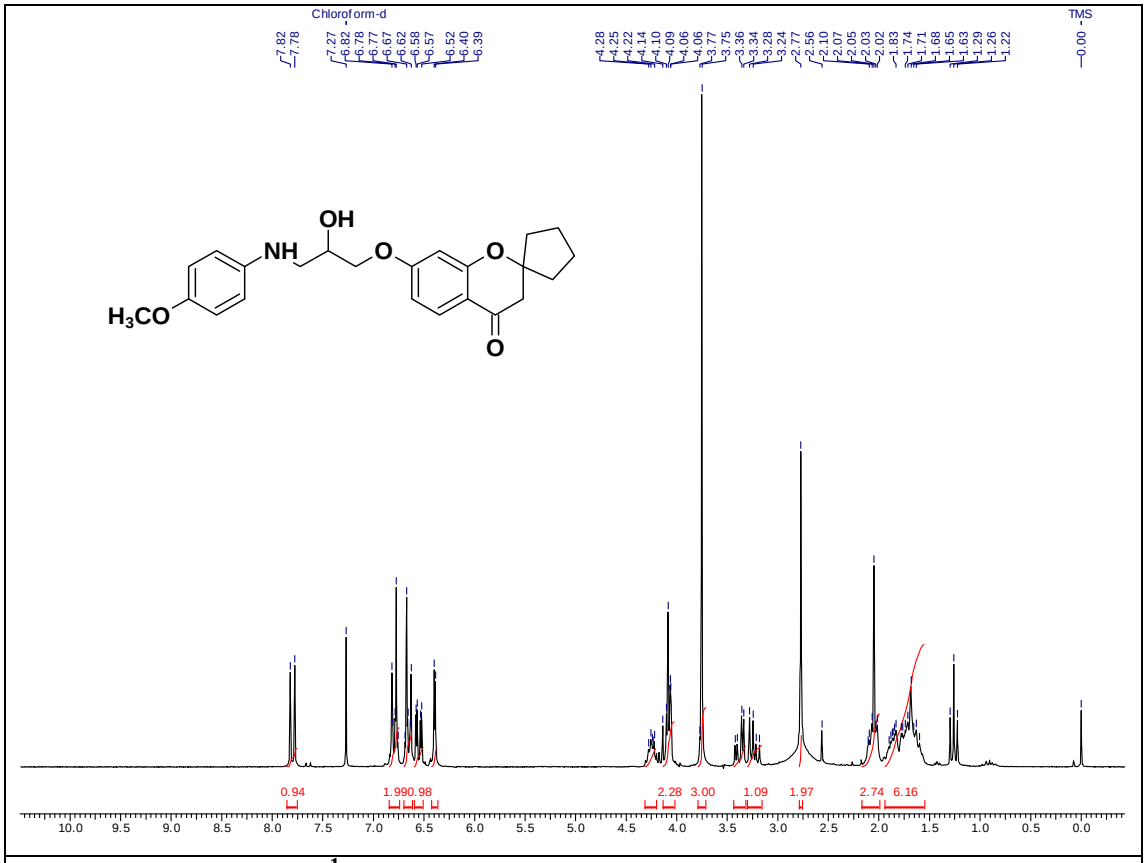

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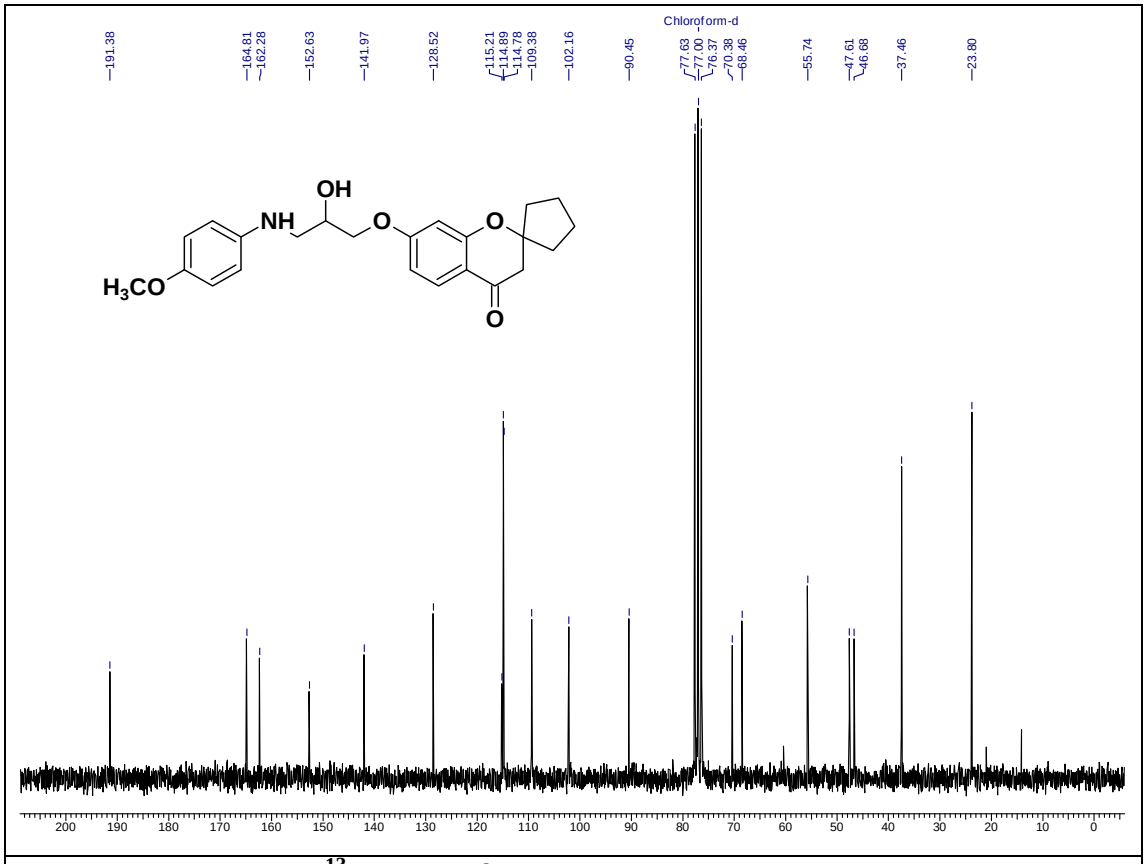

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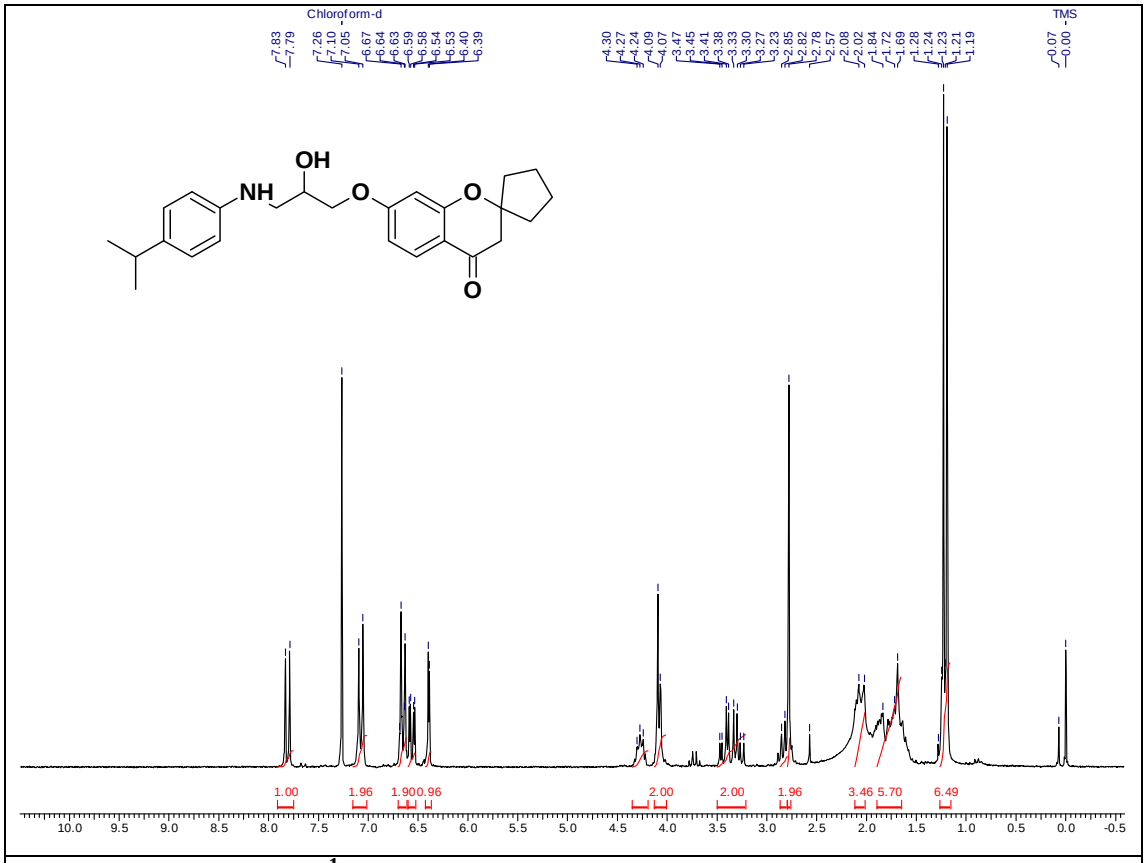
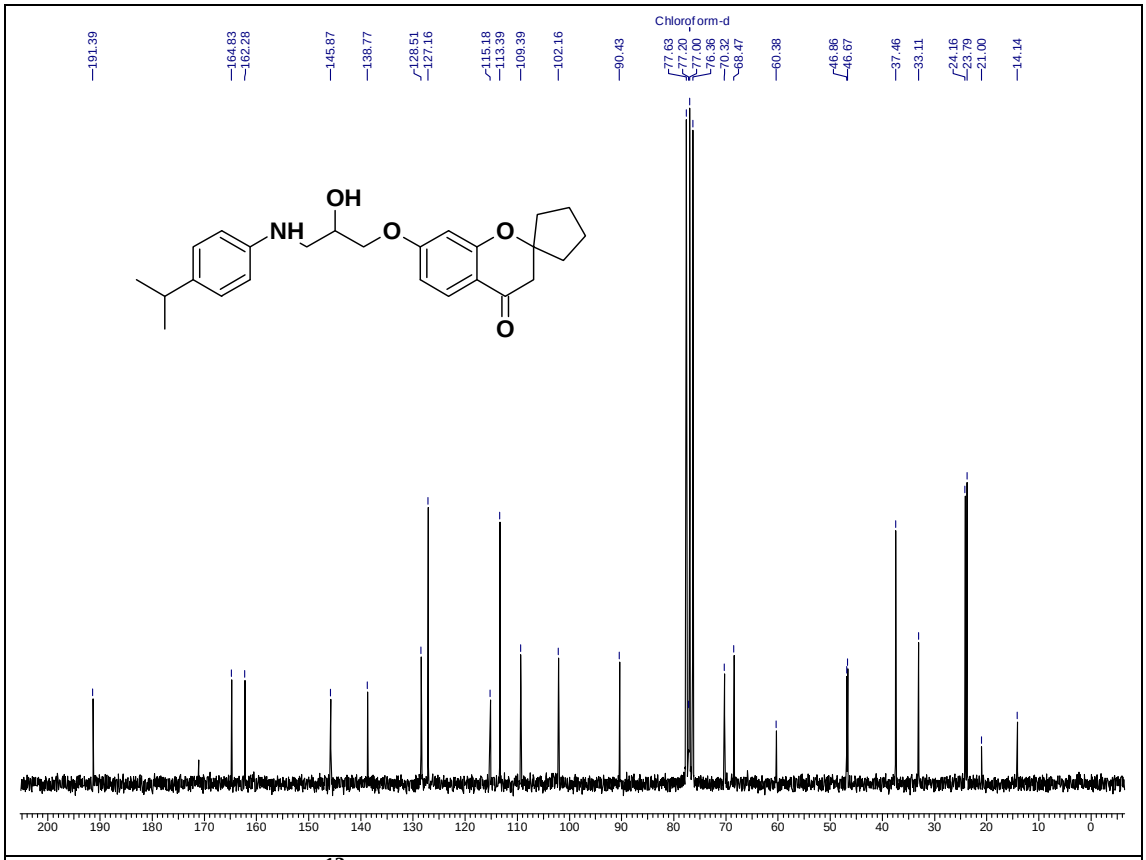


^{1}H NMR of Compound 4h in $CDCl_3$



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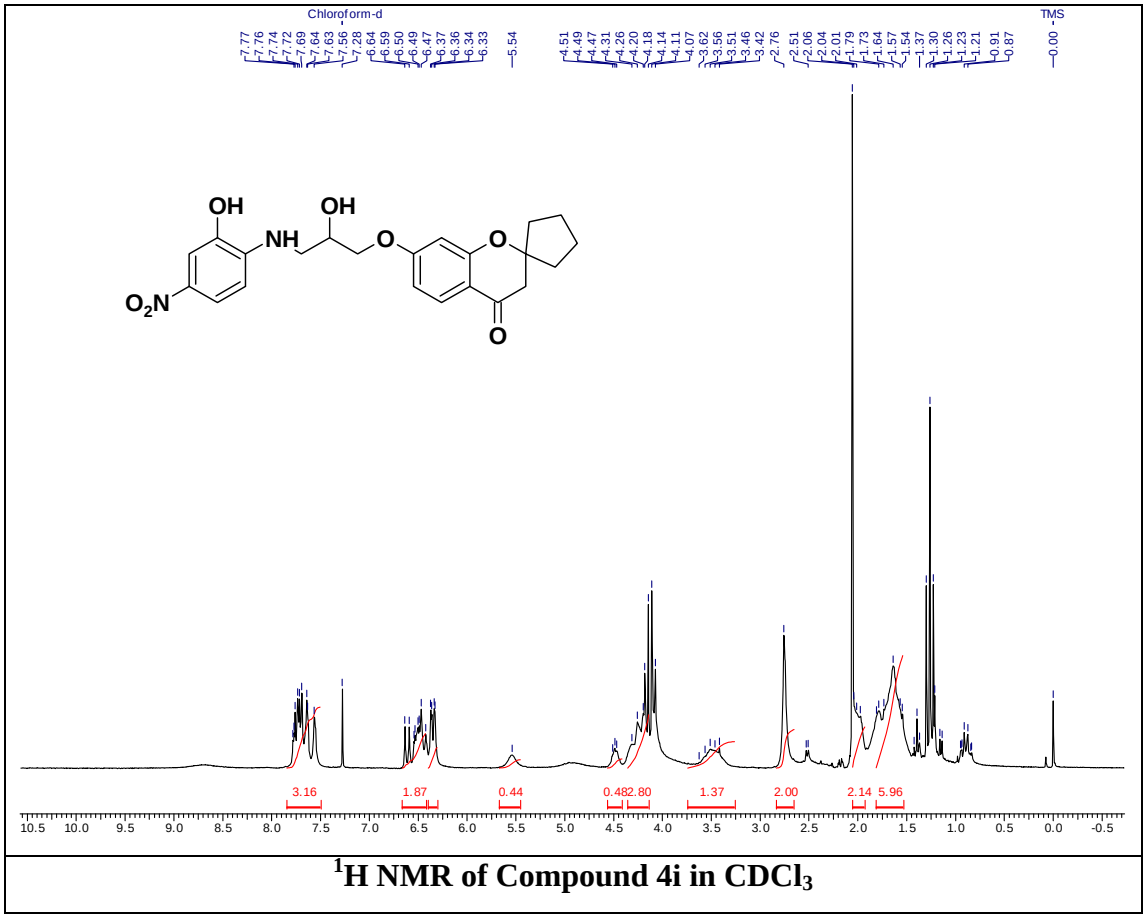

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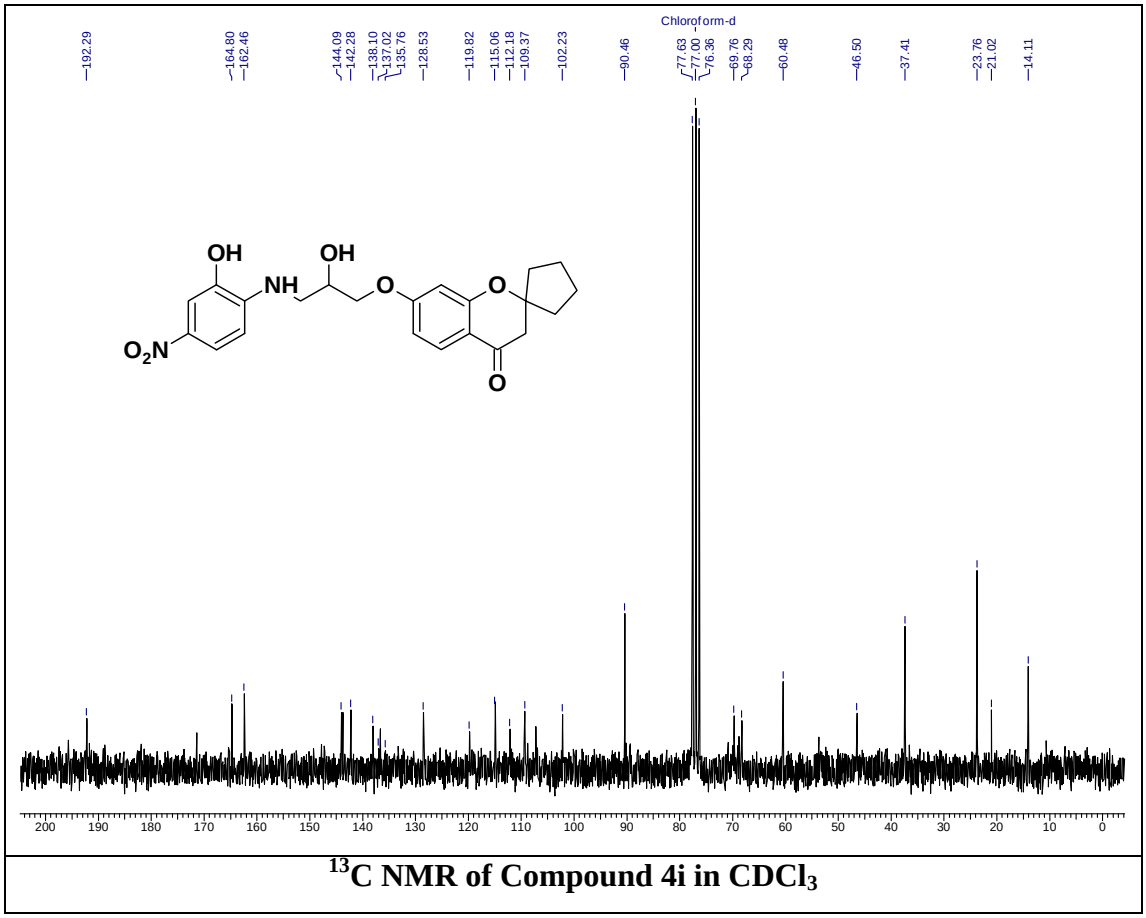

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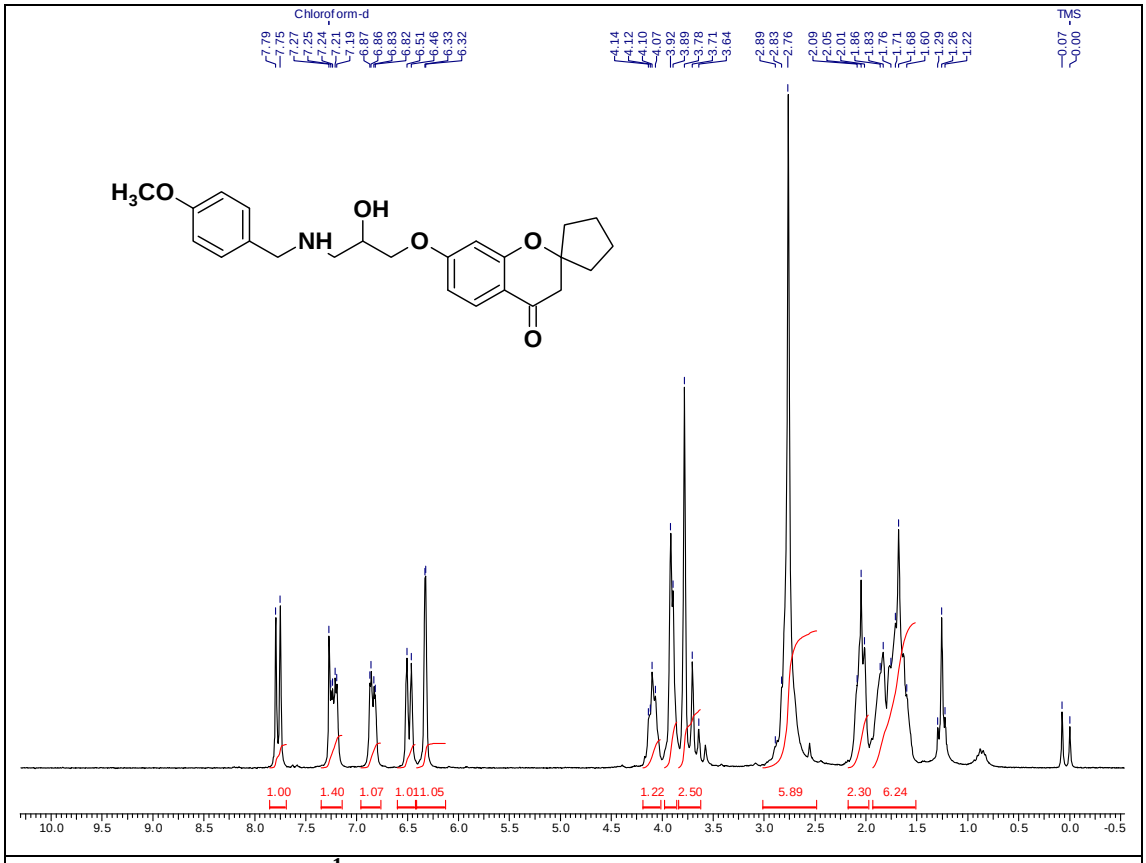

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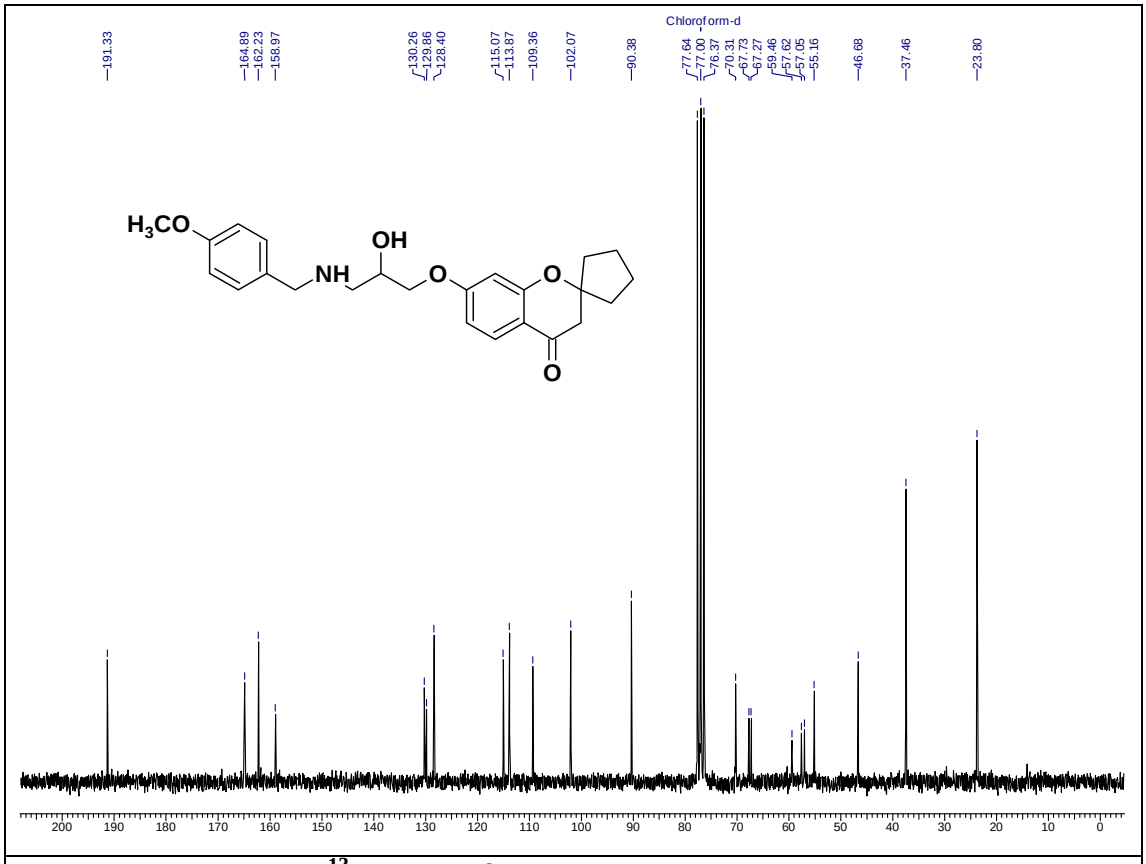

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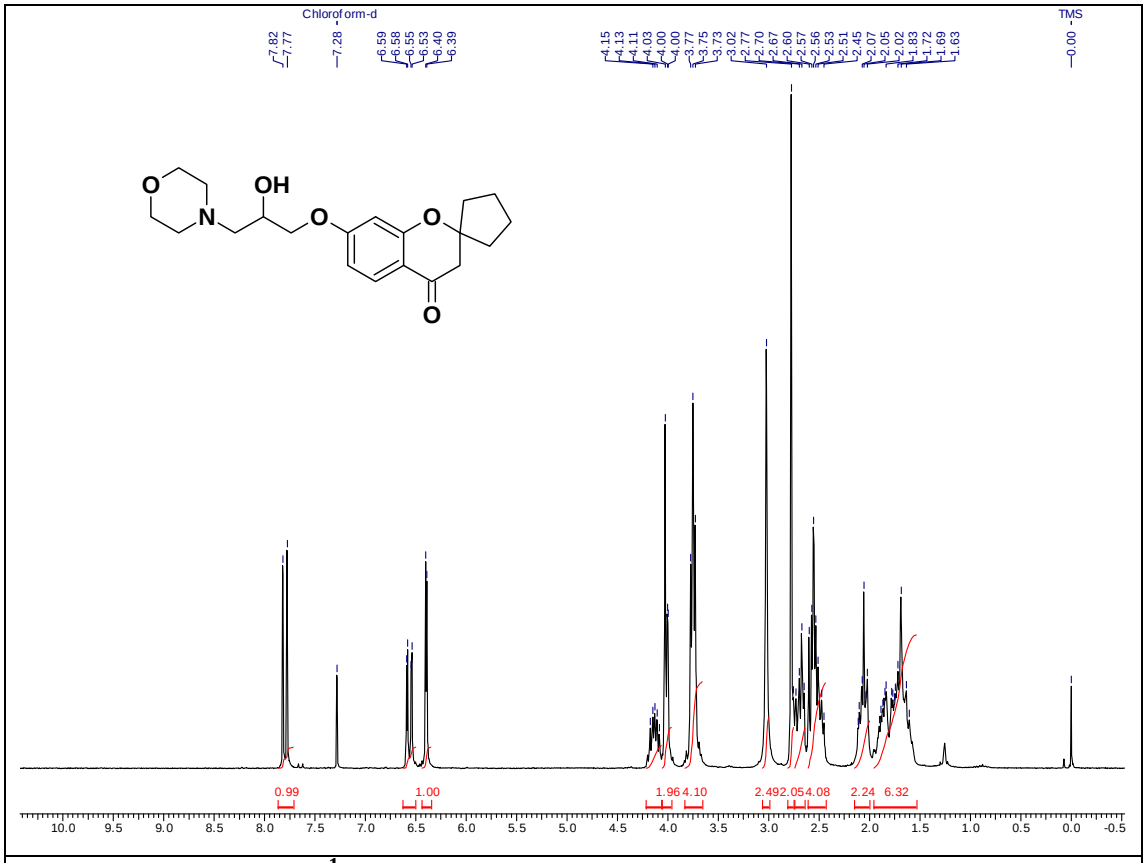

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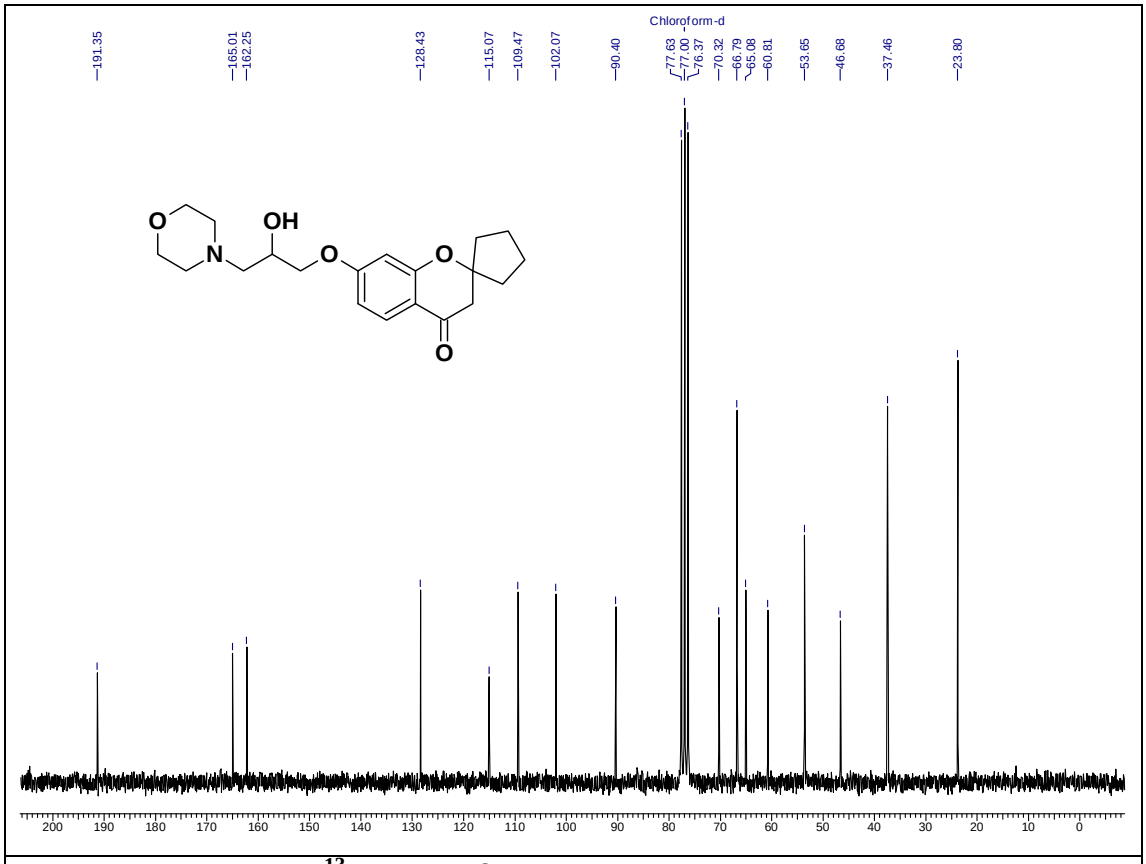

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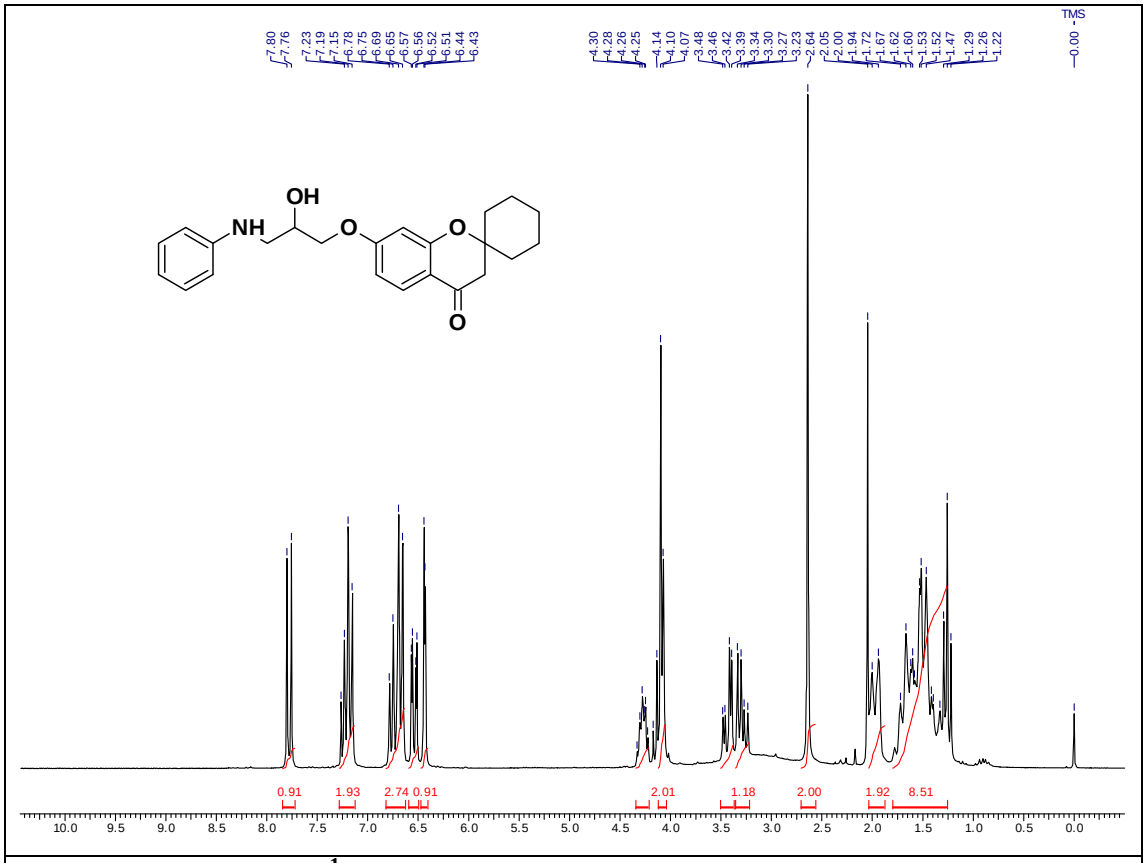

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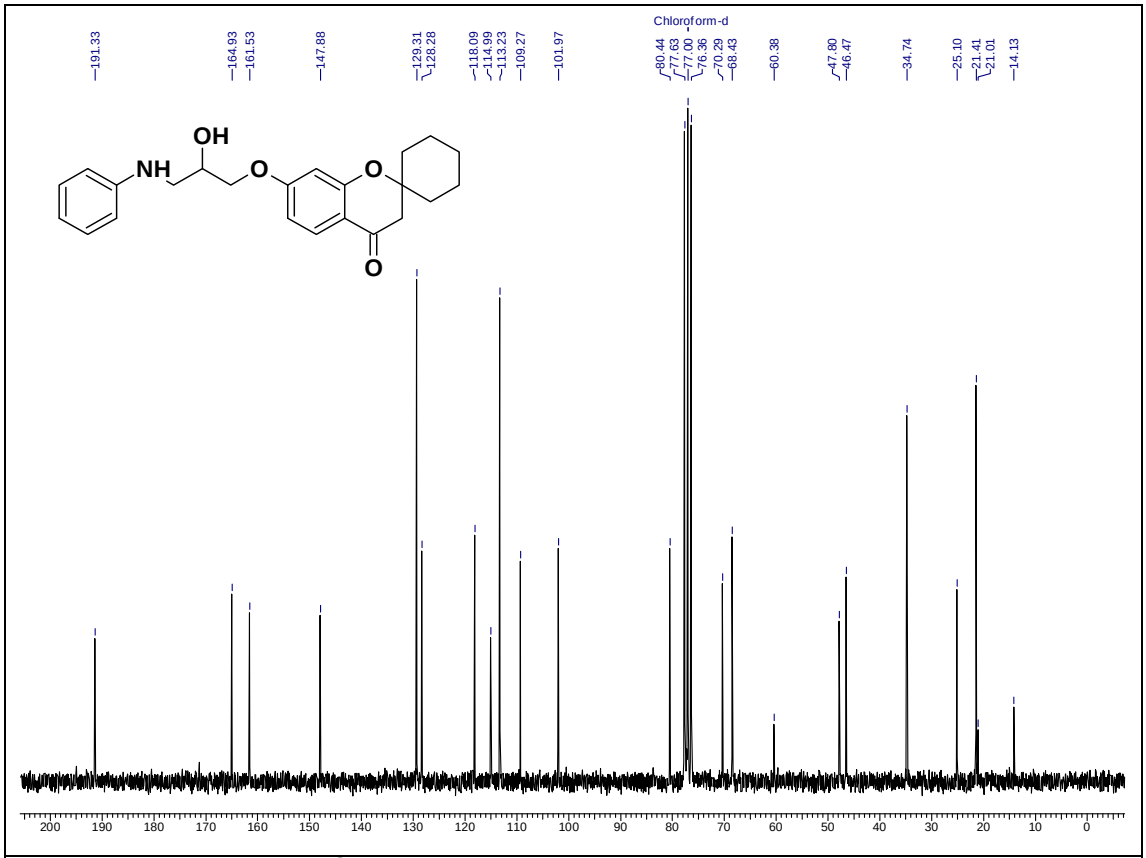

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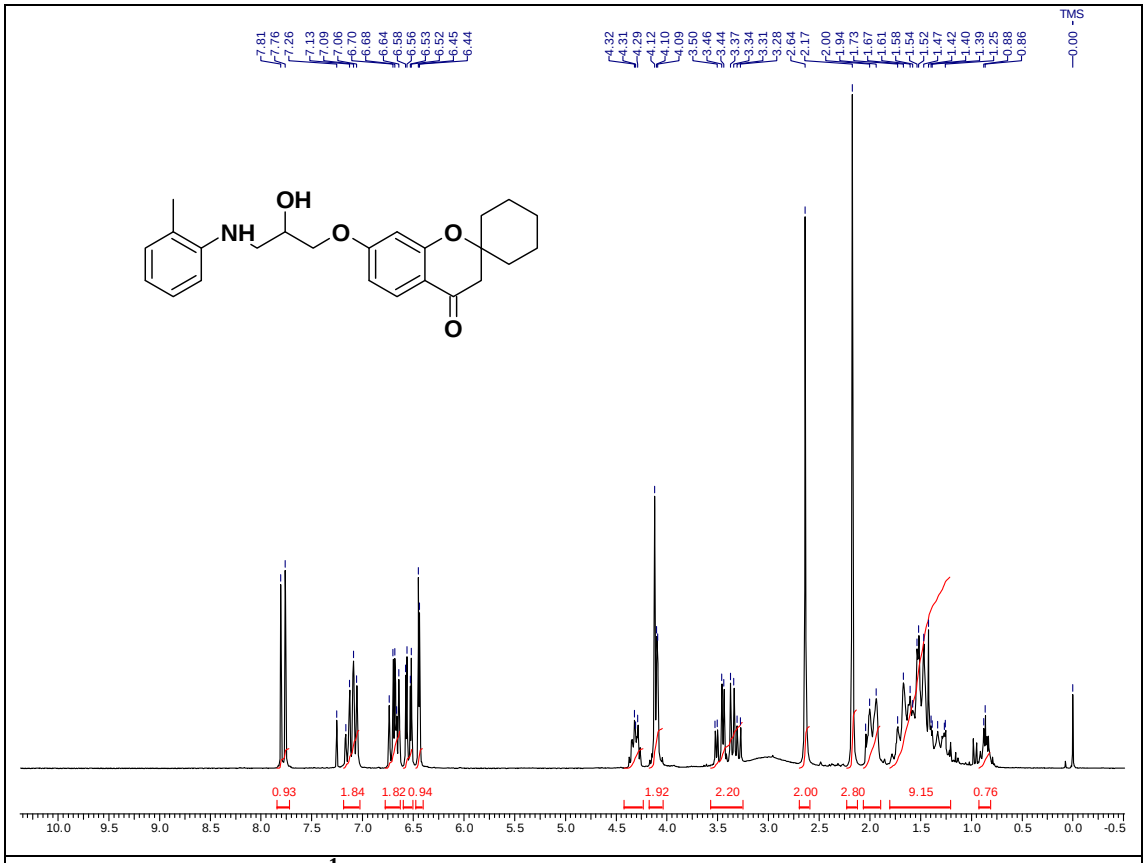

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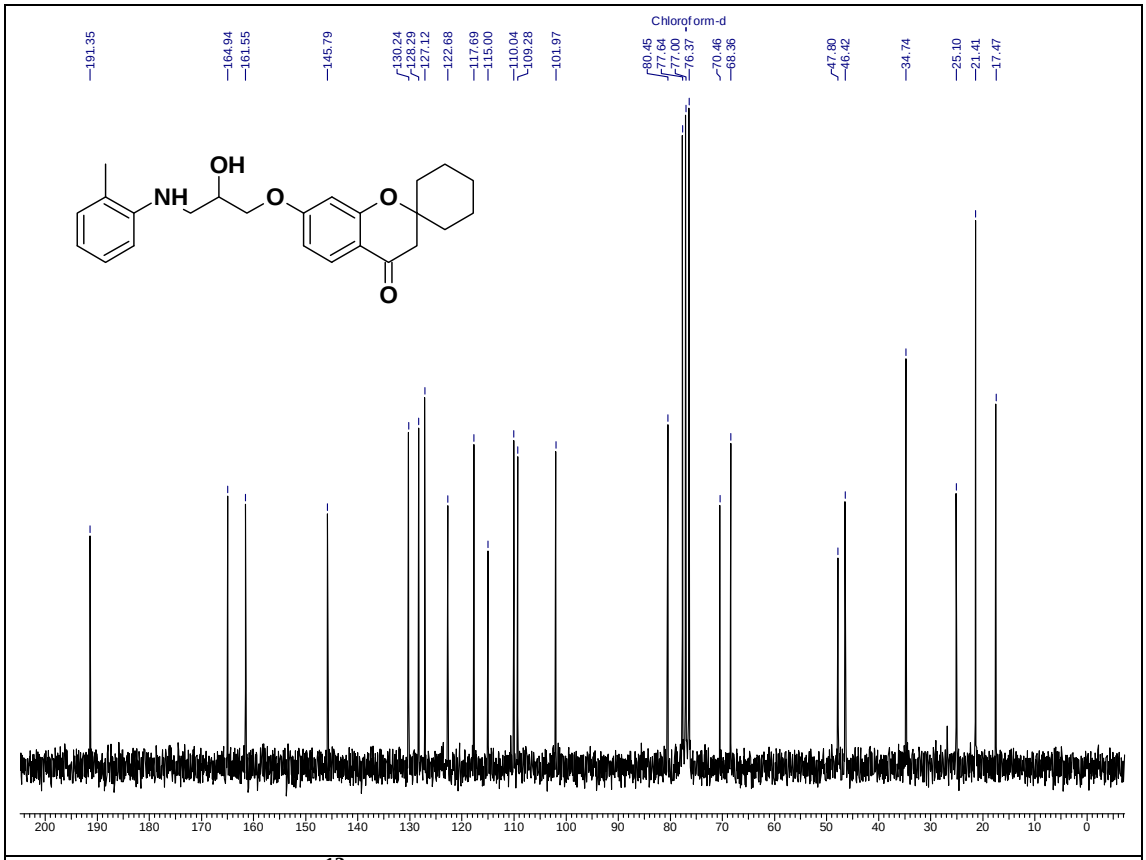

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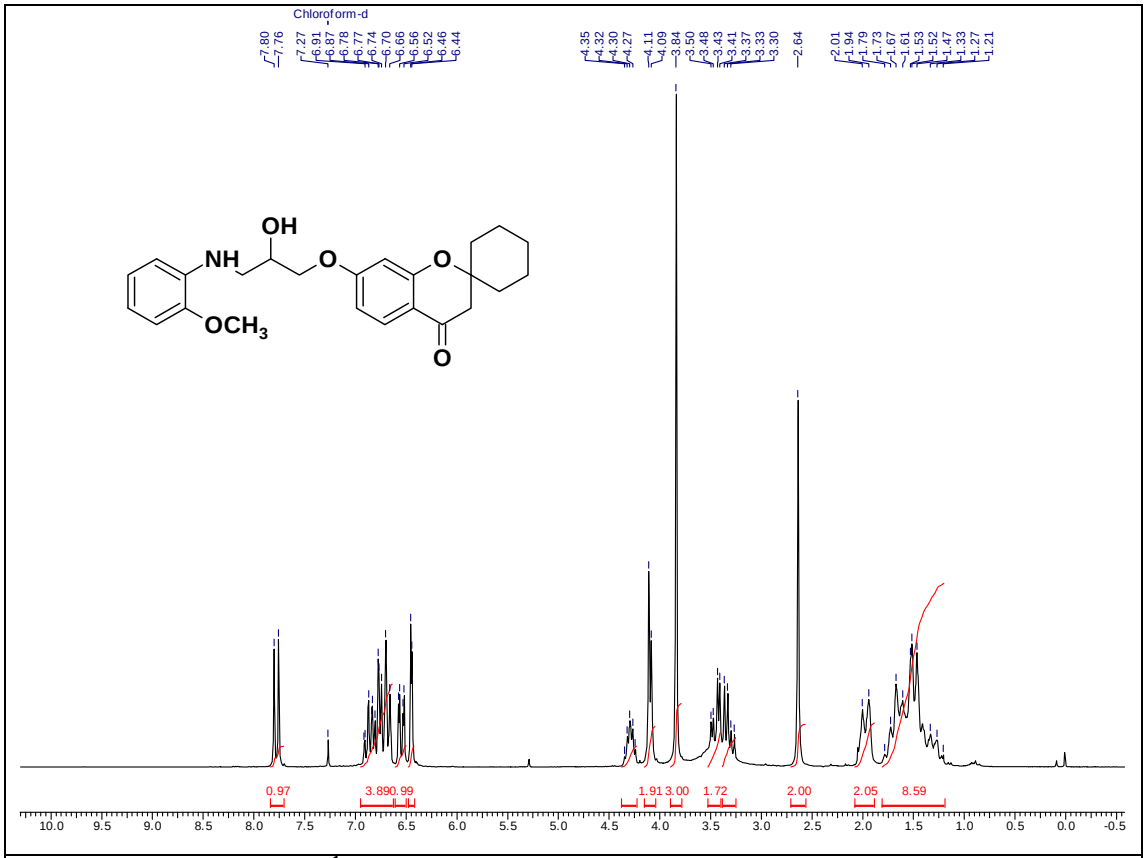
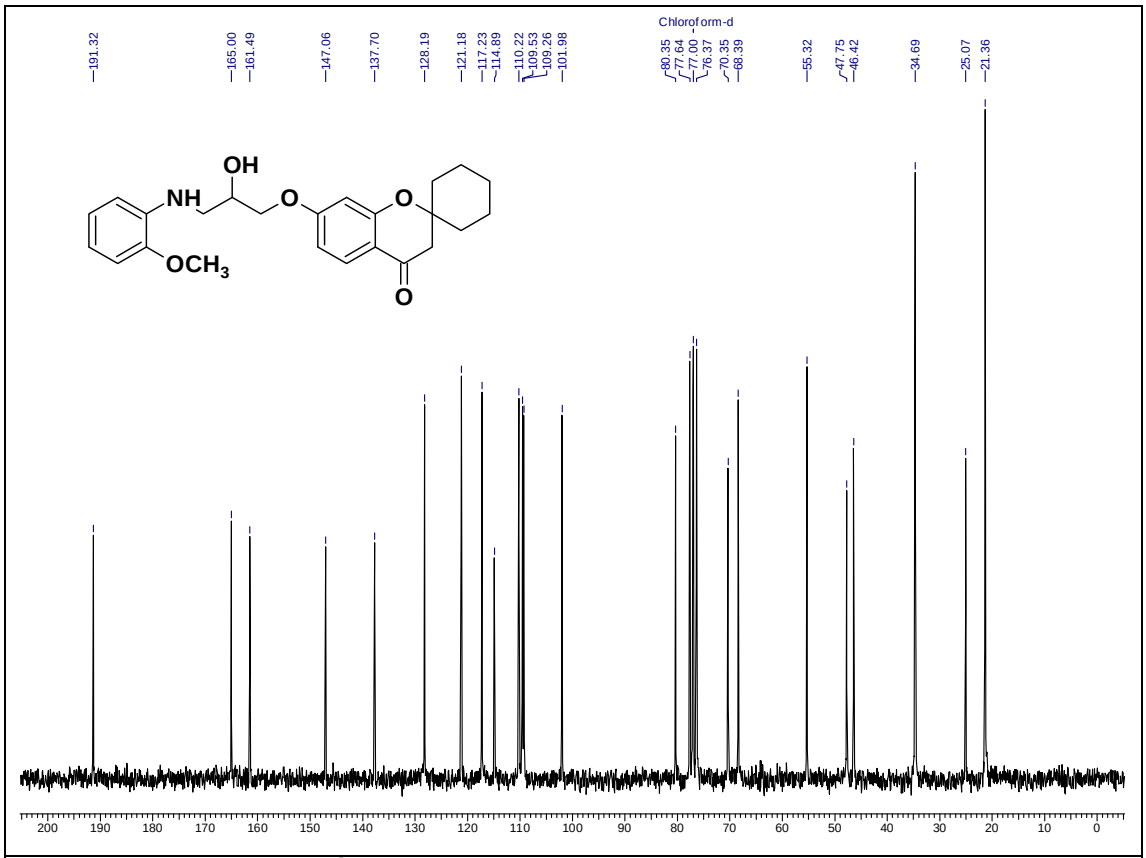


^{1}H NMR of Compound 5c in $CDCl_3$



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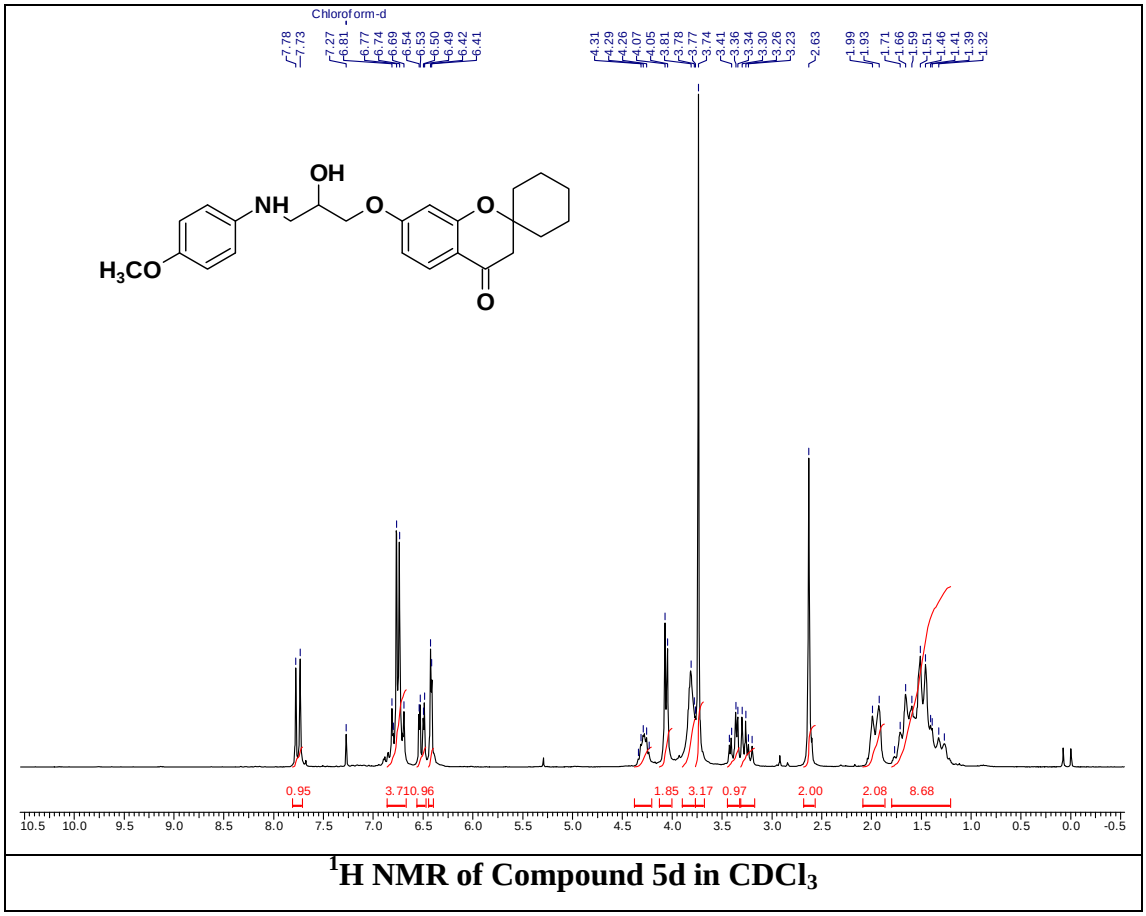

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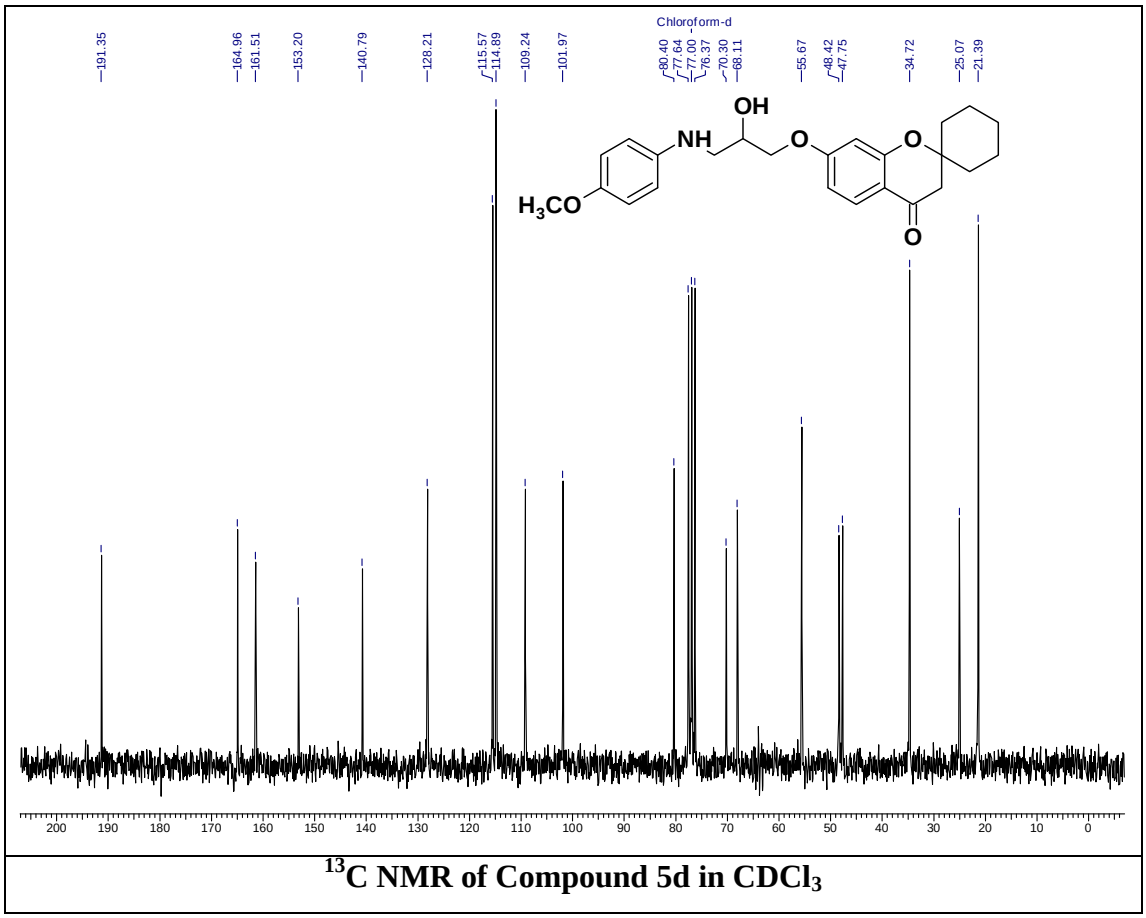

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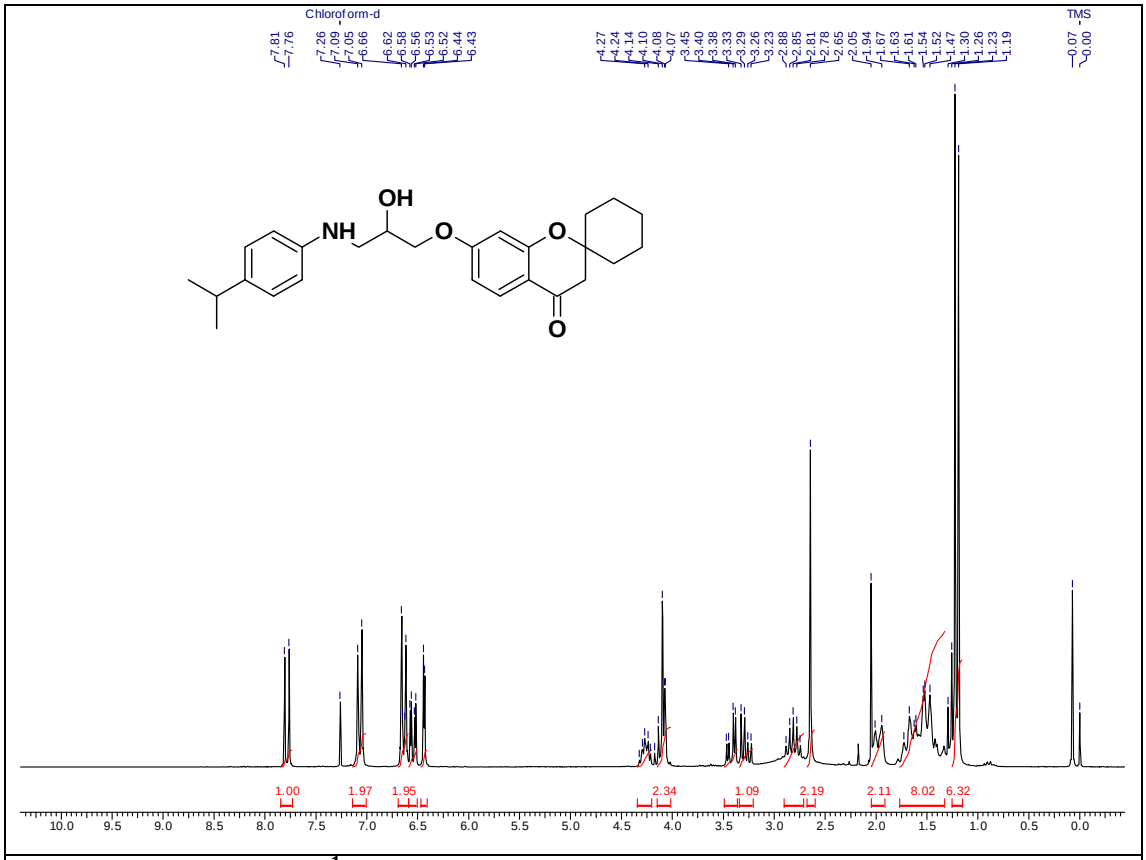
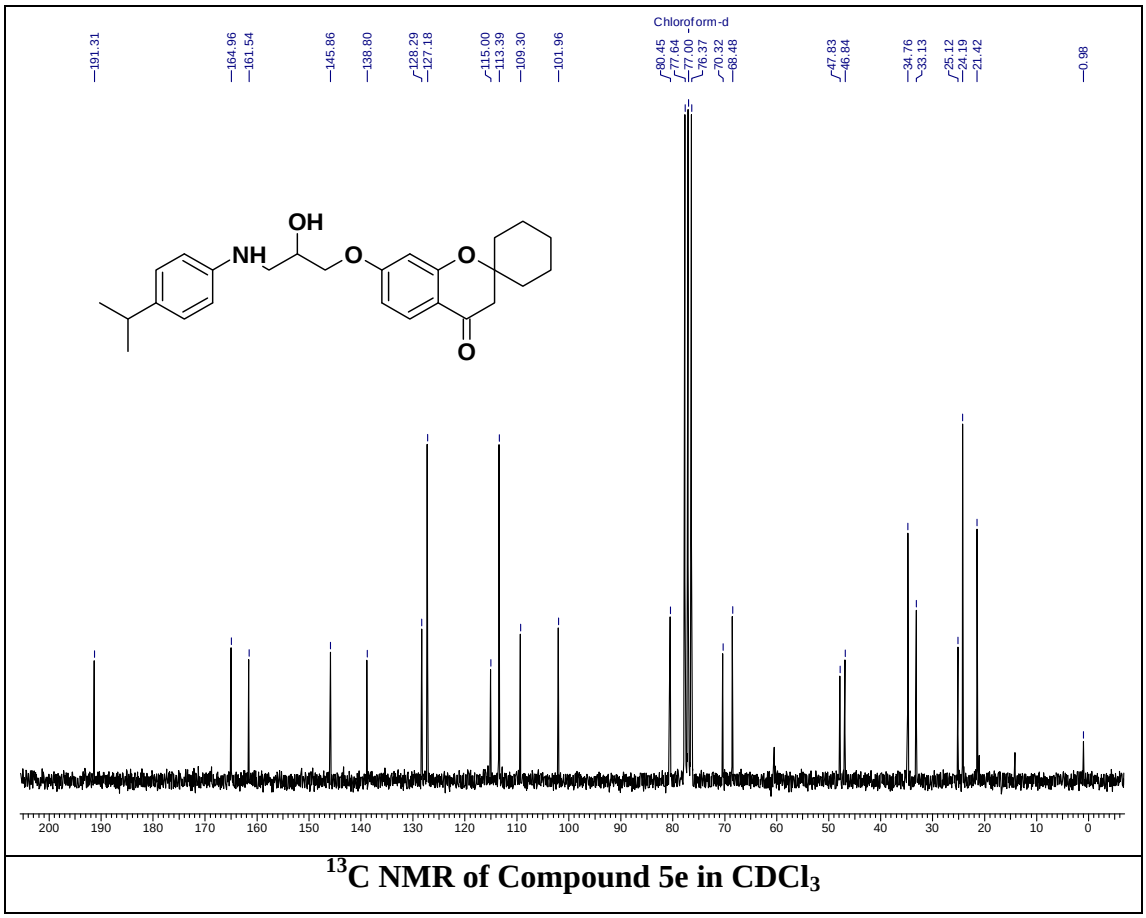
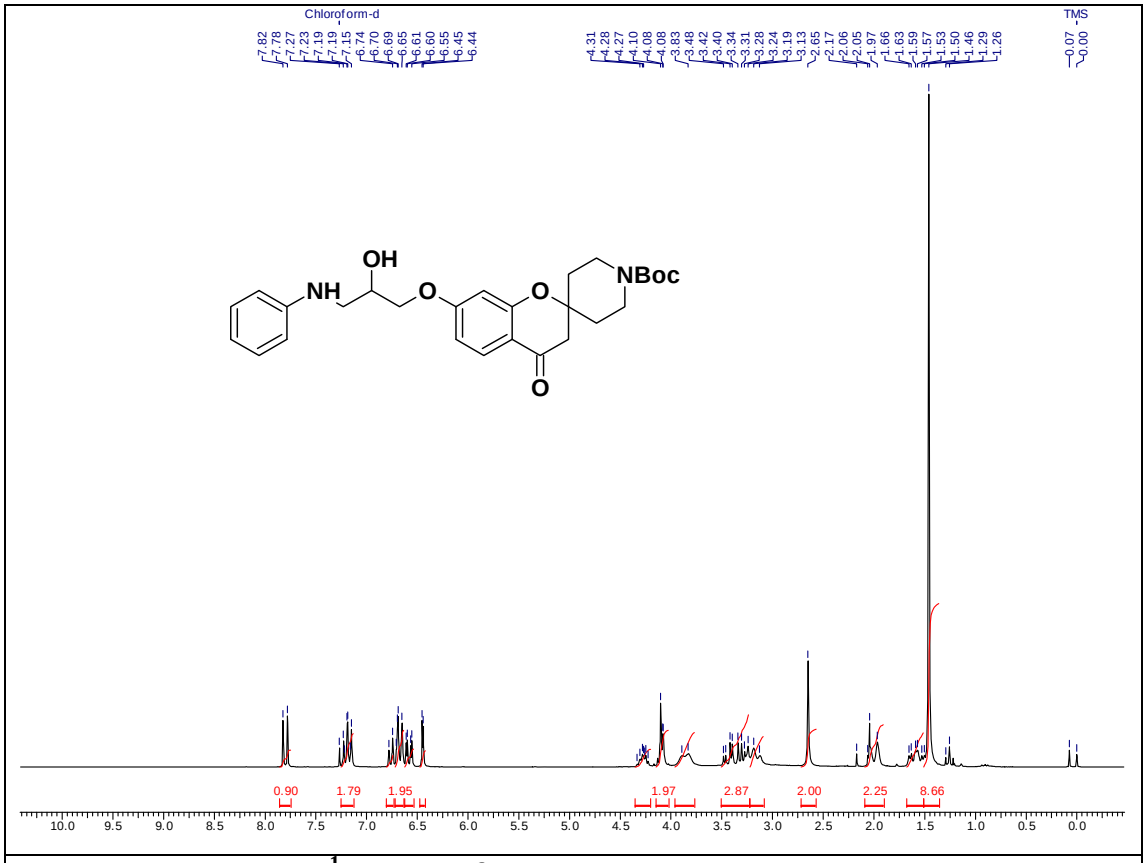


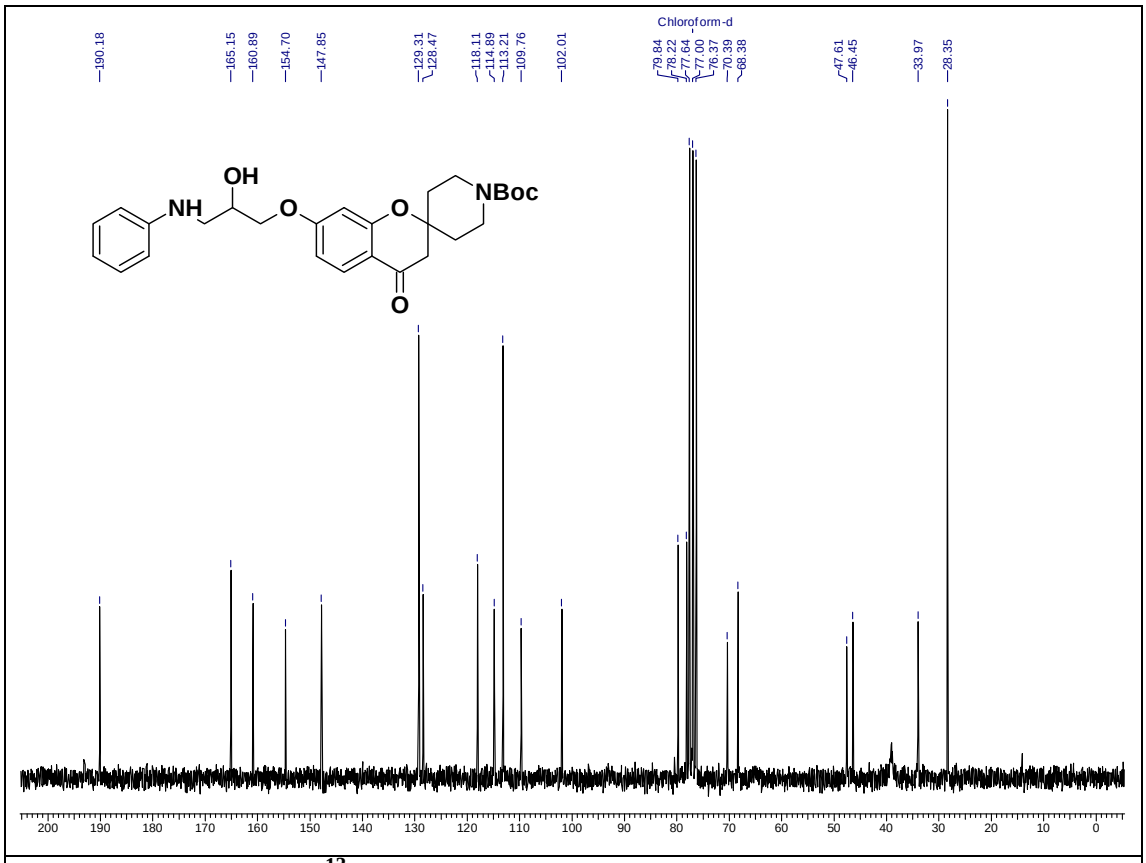
^{1}H NMR of Compound 5e in $CDCl_3$



^{13}C NMR of Compound 5e in $CDCl_3$



^{1}H NMR of Compound 6a in $CDCl_3$



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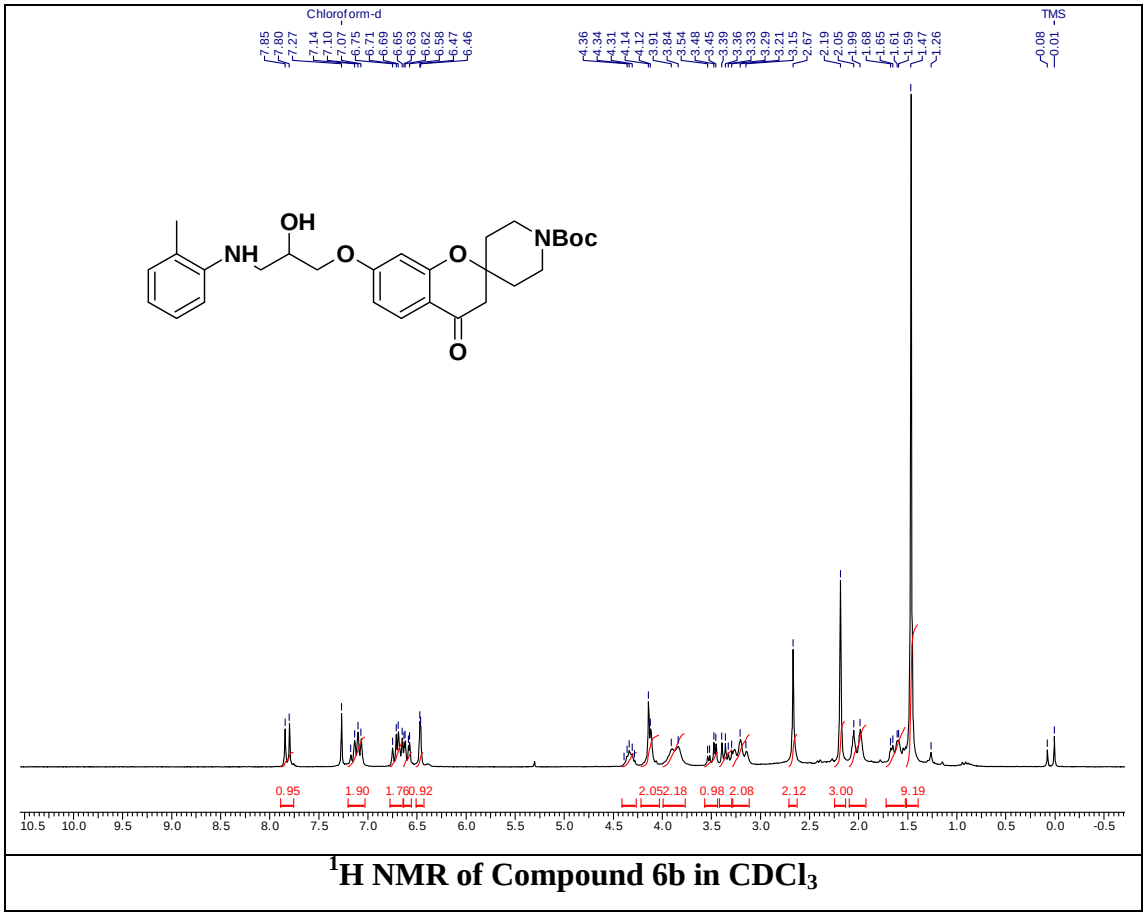

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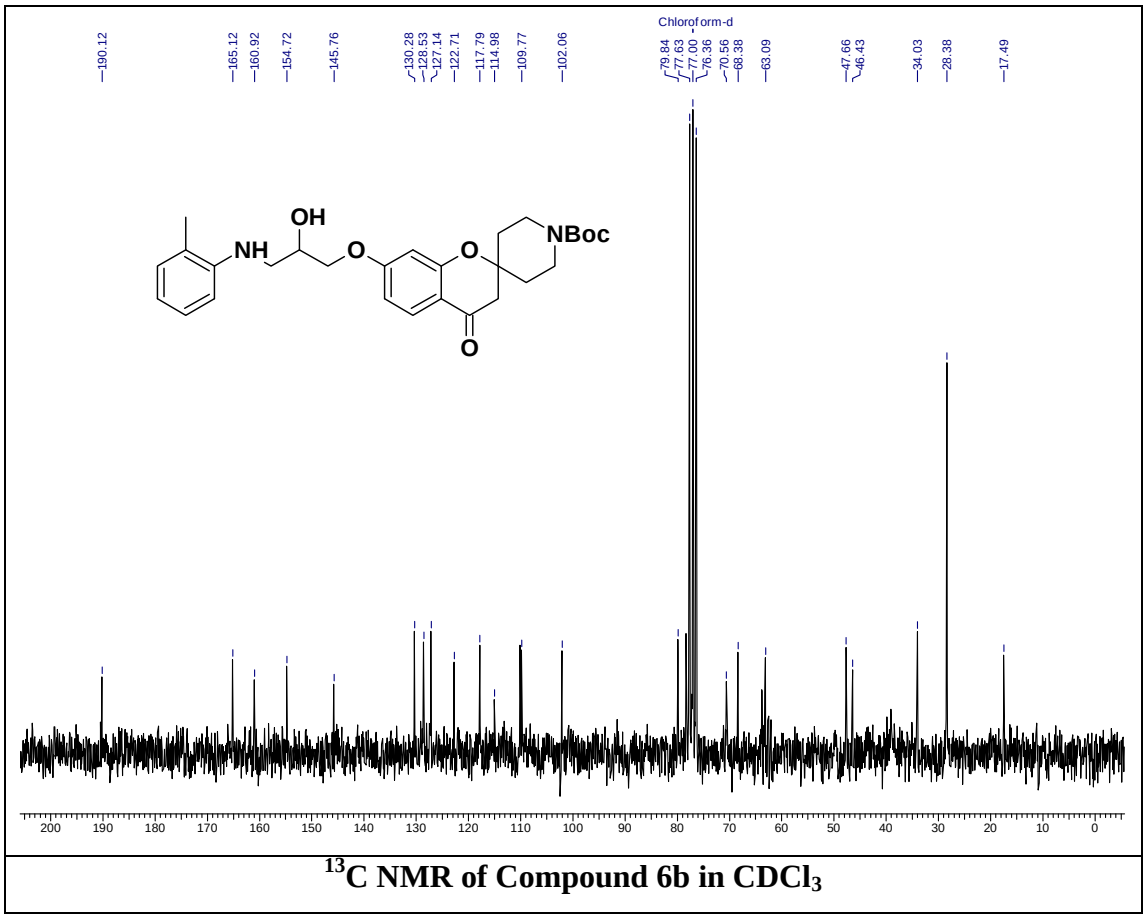

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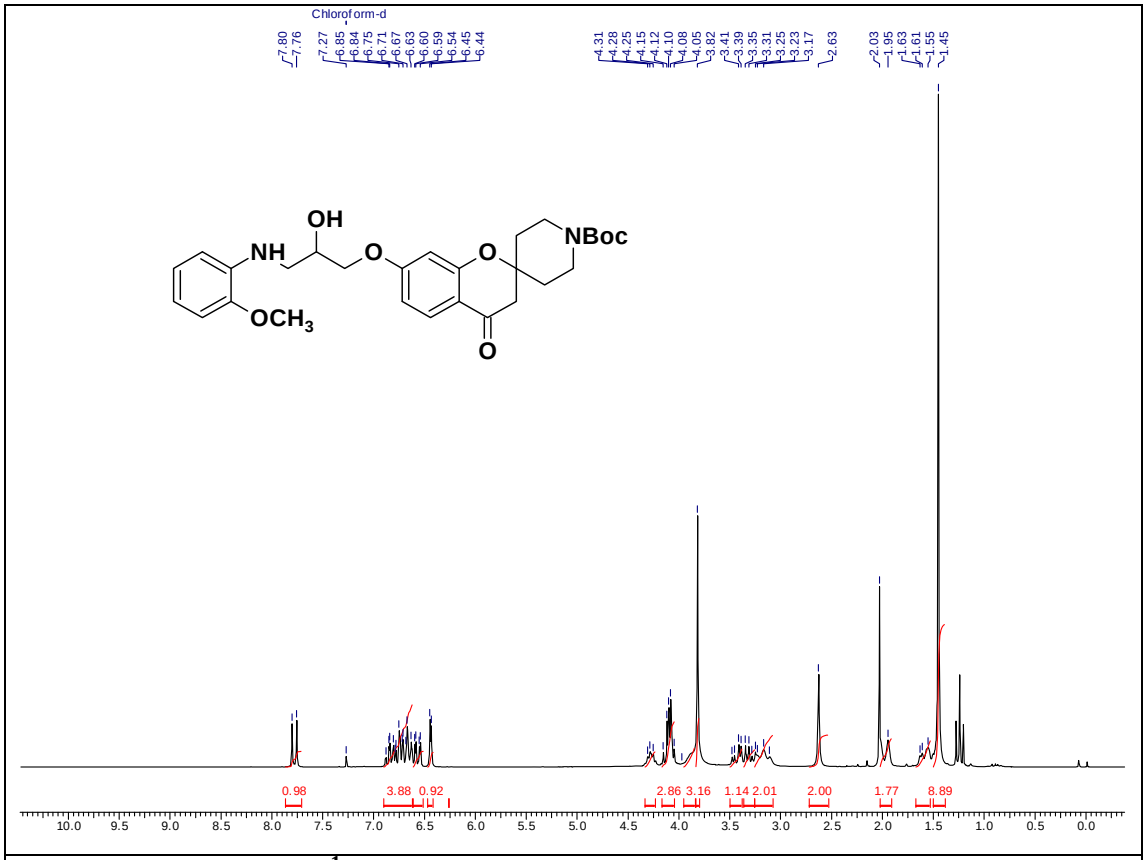

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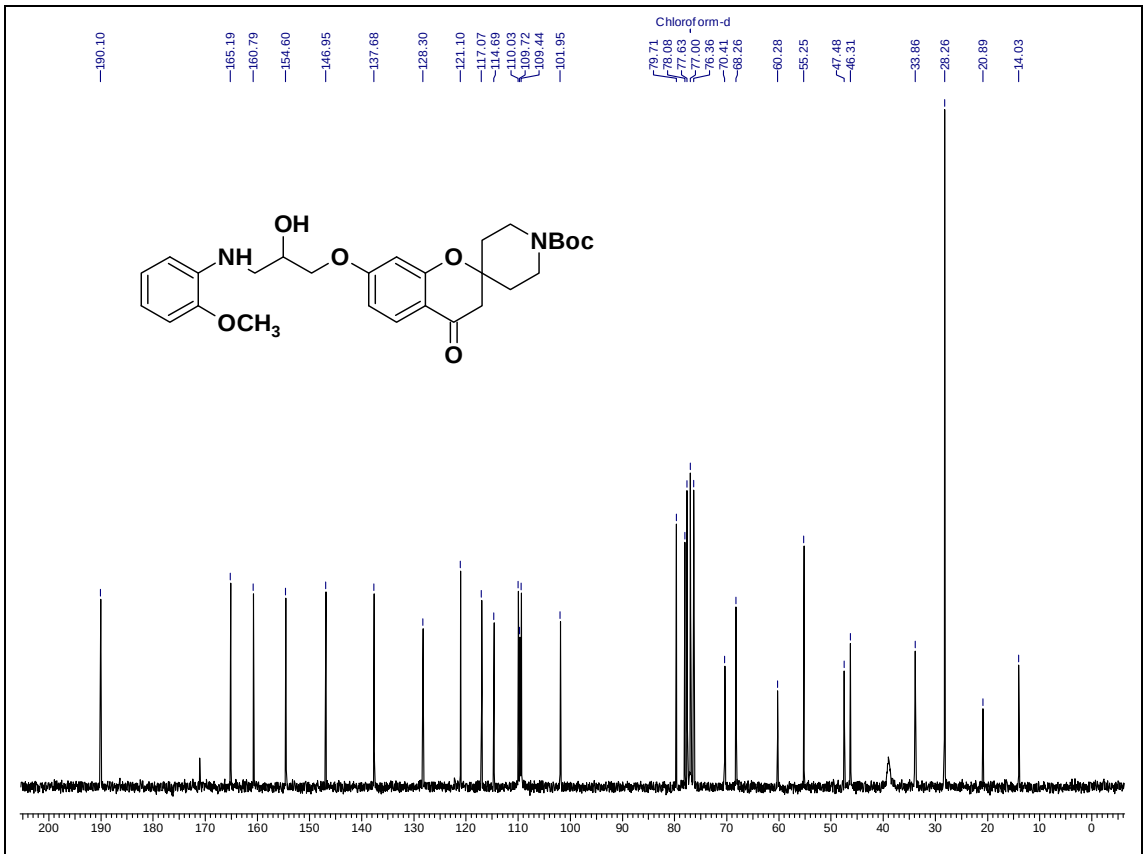

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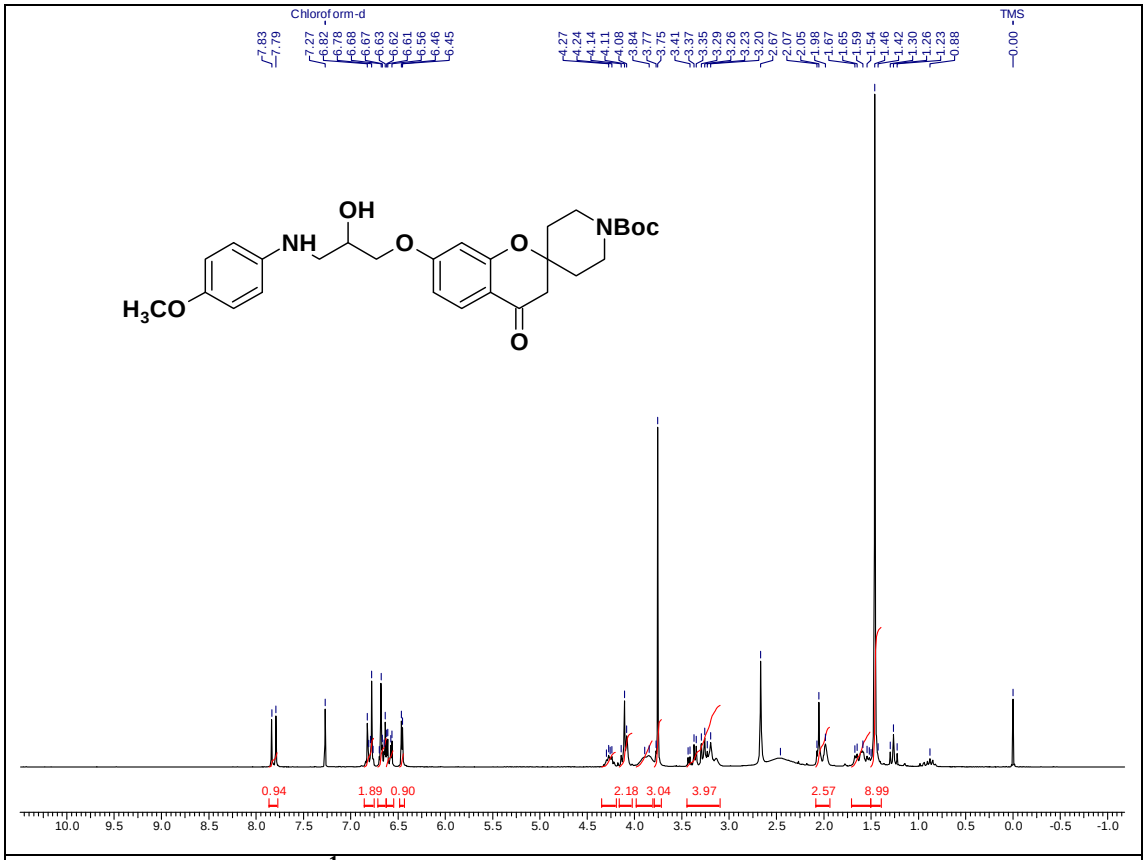

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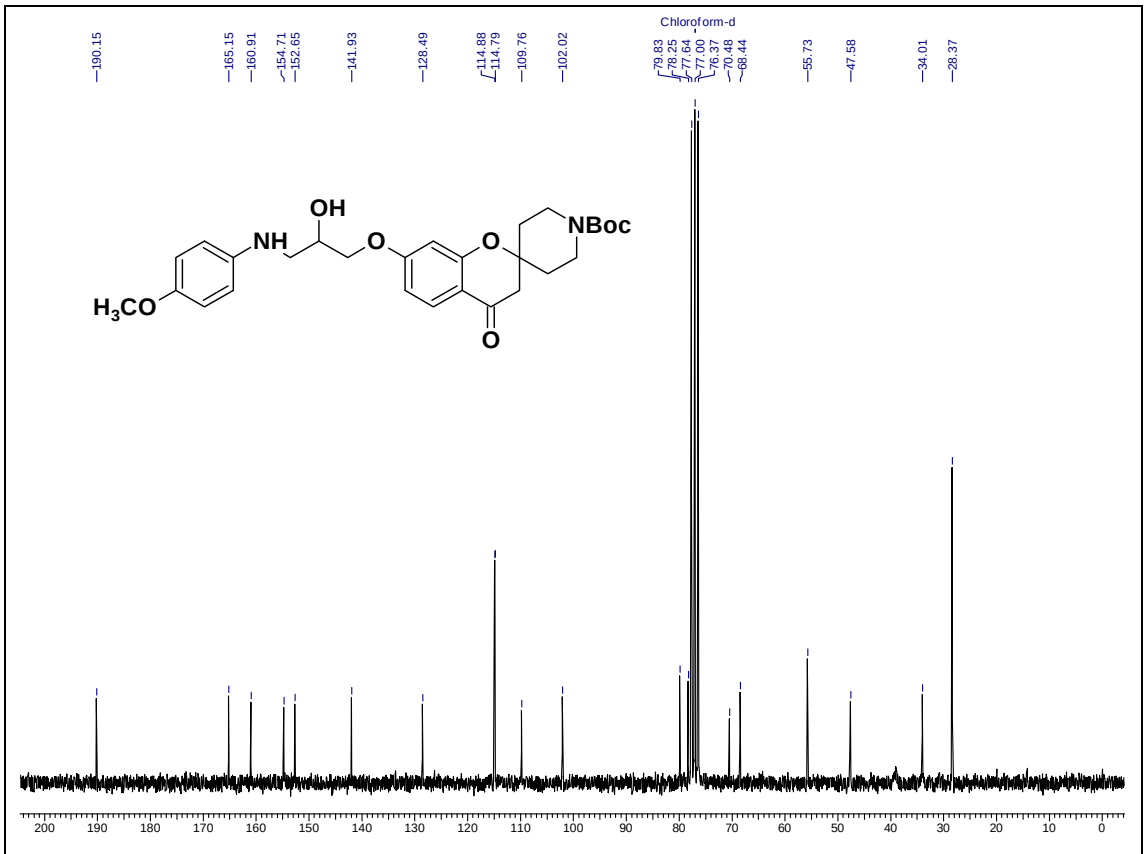
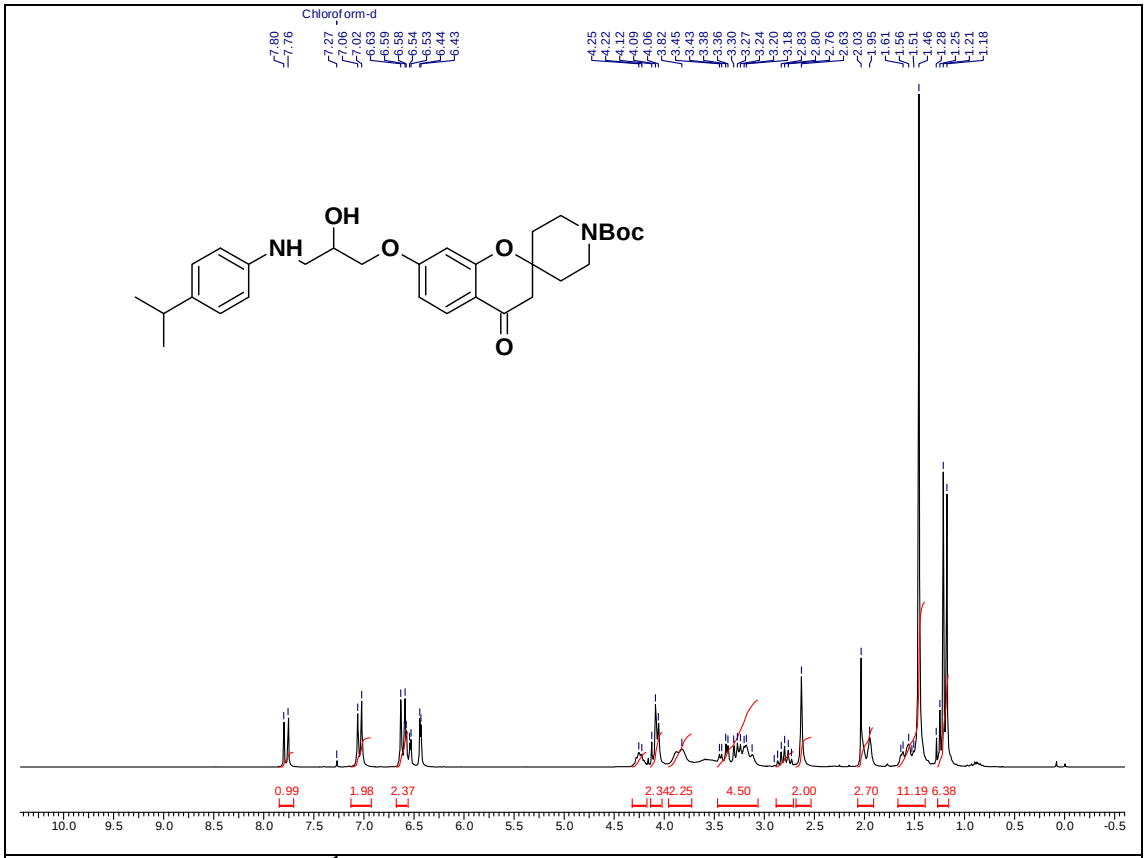


^{13}C NMR of Compound 6d in $CDCl_3$



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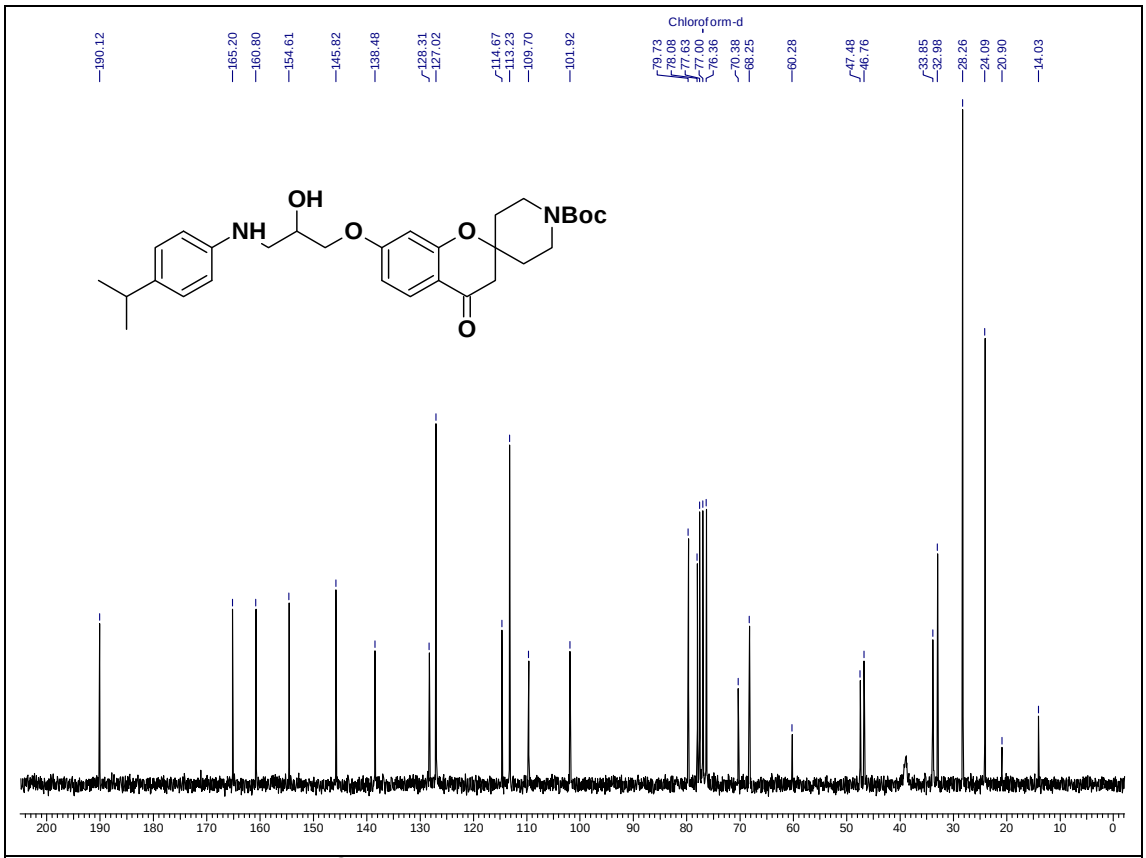


^{13}C NMR of Compound 6e in $CDCl_3$

3.2.6. References

1. (a) Ferreira, M. L.; Vasconcelos, T. R. A.; de Carvalho, E. M.; Lourenco, M. C. S.; Wardell, S. M. S. V.; Wardell, J. L.; Ferreira, V. F.; de Souza, M. V. N. *Carbohydr. Res*. **2009**, *344*, 2042.
2. (a) Parikh, S.; Gut, J.; Istvan, E.; Goldberg, D. E.; Havlir, D. V.; Rosenthal, P. J. **2005**, *49,* 2983; (b) Andrews, K. T.; Fairlie, D. P.; Madala, P. K.; Ray, J.; Wyatt, D.M.; Hilton, P. M.; Melville, L. A.; Beattie, L.; Gardioner, D. L.; Reid, R. C.; Stoermer, M. J.; Skinner-Adams, T.; Berry, C.; McCarthy, J. S. *Antimicrob. Agents Chemother.* **2006**, *50,* 639; (c) Noteberg, D.; Hamelink, E.; Hulten, J.; Wahlgren, M.; Vrang, L.; Samuelsson, B.; Hallberg, A. *J. Med. Chem*. **2003**, *46*, 734.
3. (a) Brik, A.; Wong, C.-H. *Org. Biomol. Chem*. **2003**, *1*, 5; (b) Ghosh, A.K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203.
4. Yendapally, R.; Lee, R. E. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1607.
5. Kabbe, H. J. *Synthesis* **1978**, 886.
6. Moskvina, V. S.; Garazd, Y. L.; Garazd, M. M.; Turov, A. V.; Khilya, V. P. *Chem. Heterocycl. Compd.* **2007**, *43*, 421.
7. (a) The data on X-ray intensity of compound **4h** were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, k (Mo Ka) = 0.71073 Å at T= 293 (2) K. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least squares of F2 using SHELXL-97. Hydrogen atoms were included in the refinement as per the riding model; (b) Sheldrick, G. M. SHELX-97 Program for Crystal Structure Solution and Refinement; University of Göttingen: Germany, 1997.
8. The crystallographic data of compound **4h** has been deposited with the Cambridge Crystallographic Data Center as deposition No. CCDC 895296. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

9. NCCLS-National Committee for clinical Laboratory Standards, Antimycobacterial susceptibility testing for Mycobacterium tuberculosis. Proposed standard M24-T; Villanova, PA, 1995.

4.3. SECTION C

Synthesis and biological evaluation of novel 1,2,3-triazole based spirochromone conjugates as inhibitors of *Mycobacterium tuberculosis*

4.3.1. Introduction

Most of the nitrogen-containing molecules are biologically very important which can be attributed to the fact that nitrogenous compounds are the integral part of the biomolecular diversity.[1-4] Amongst the pharmacologically active nitrogenous compounds, a large number of 1,2,3-triazoles and their derivatives attracted considerable attention for the past few decades due to their significant medicinal properties. Generally, 1,2,3-triazoles known to possess anti-bactericidal,[5] anti-HIV,[6,7] antitumor properties.[8] Further, they can also act as GABA[9] and glycosidase inhibitors[10] as well. This heterocycle has been compared to amide bonds and serve as bioisosters of peptide bonds due its electronic features.[11,12] Some pharmaceutically important 1,2,3-triazoles derivatives are presented in Figure 1.

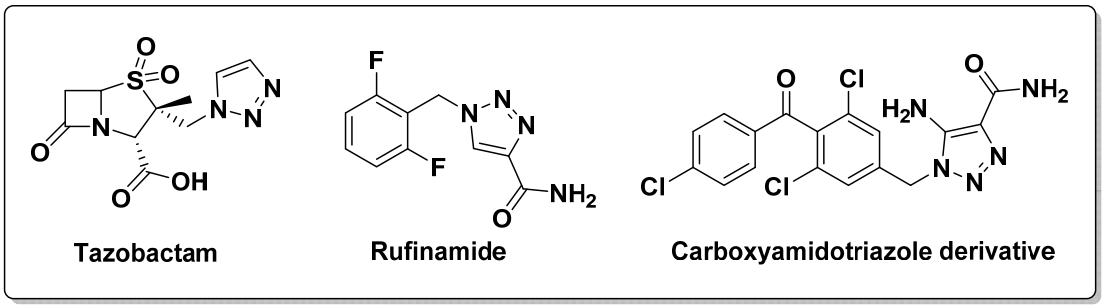


Figure 1. Examples of few important 1,2,3-triazoles derivatives

For example, the 1,2,3-triazole compound tazobactam **1a** is a β-lactamase inhibitor used in combination with the β-lactam antibiotic piperacillin.[13,14] The 1,4-disubstituted 1,2,3-triazoles rufinamide **1b** exhibits anticonvulsant activity and has been used to treat childhood mental impairment of the Lennox-syndrome.[15] The

triazole derivative of carboxyamidotriazole **1c** is an angiogenesis inhibitor useful in cancer therapy.[16]

In the previous section, we synthesized various spirochromone analogues possessing amino alcohol moiety and evaluated their anti-TB properties. Interestingly, few compounds showed significant inhibition against *Mycobacterium tuberculosis* H37Rv. Encouraged by these results we wanted to take-up this spirochromone motif as an active pharmacophore for further diversification to exploit its anti TB potential. Towards this goal, it was decided to design and synthesize, a series of novel 1,2,3-triazoles fused spirochromone conjugates and study their anti-TB properties. Further, 1,2,3-triazole ring system can be easily incorporated using click chemistry protocol which is finding wide applications in drug discovery process and chemical biology due to its high yield, high selectivity, wide scope, atom economy and simple purification procedure.[17]

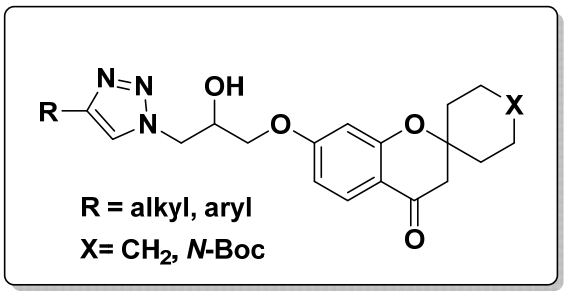


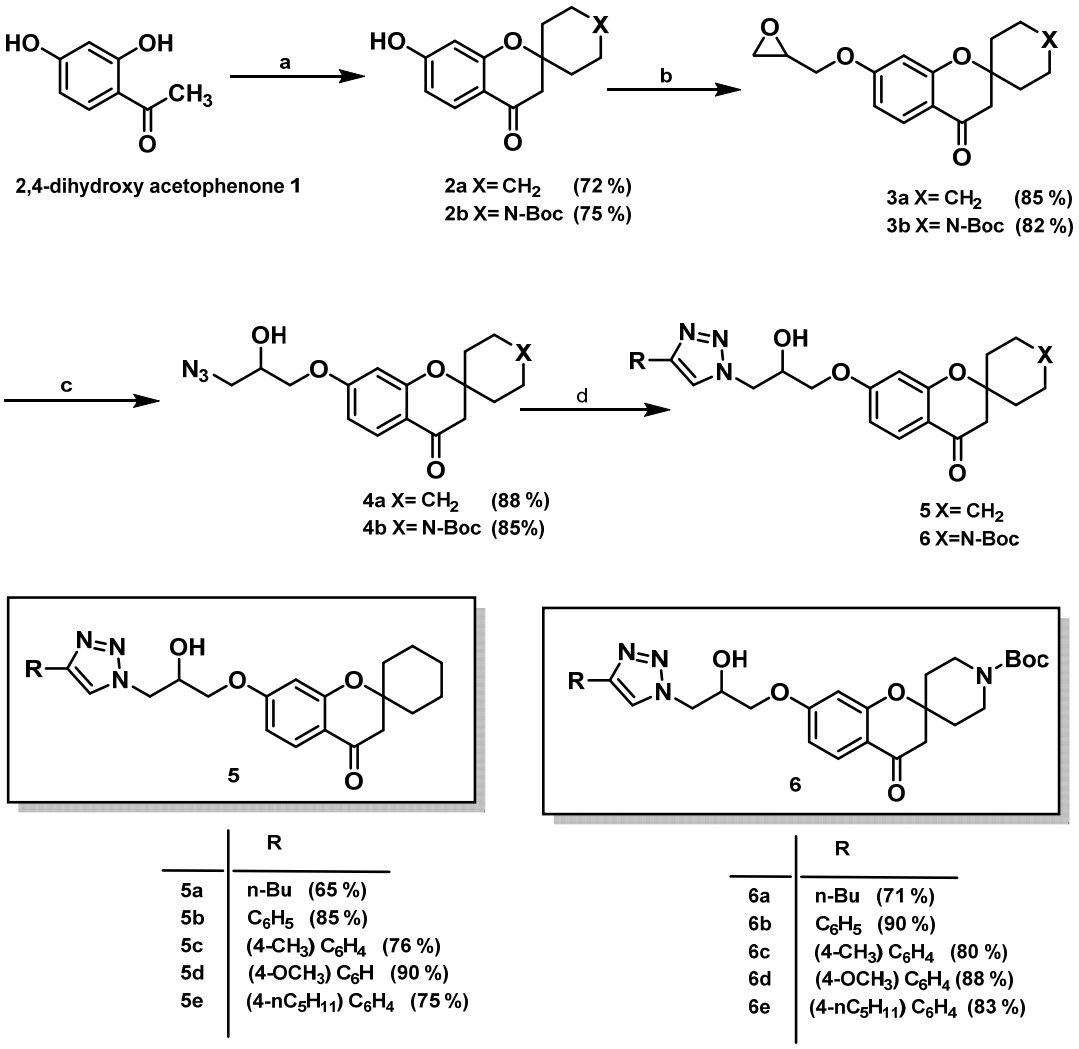
Figure 2. Design of 1,2,3- triazole annulated spirochromone conjugates

4.3.2. Results and Discussions

Chemistry

The synthetic strategy followed for the preparation of 1,2,3-triazole fused spirochromone conjugates is given in Scheme 1. Firstly, for the preparation of precursor spirochromanone moiety **2a,b** a Kabbe condensation between the cyclohexanone or *N*-Boc piperidone and 2,4-dihydroxy acetophenone was employed. In the Kabbe condensation, the use of acetonitrile as solvent and carrying out the reaction at 50 ºC for 24 h in the presence of pyrrolidone as a base is optimum in order to obtain spirochromanone **2a,b** in 72% and 75% yields. On the other hand, refluxing with toluene or ethanol as a solvent using Dean–Stark apparatus, the condition

generally used in Kabbe condensation did not produce the required products in good yield.



	R
5a	n-Bu (65 %)
5b	C_6H_5 (85 %)
5c	(4-CH_3) C_6H_4 (76 %)
5d	(4-OCH_3) C_6H (90 %)
5e	(4-nC_5H_{11}) C_6H_4 (75 %)

	R
6a	n-Bu (71 %)
6b	C_6H_5 (90 %)
6c	(4-CH_3) C_6H_4 (80 %)
6d	(4-OCH_3) C_6H_4 (88 %)
6e	(4-nC_5H_{11}) C_6H_4 (83 %)

Scheme 1. *Reagents and conditions*: (a) Cyclohexanone/N-Boc piperidone, pyrrolidine, acetonitrile, 50 ºC, 24 h; (b) epichlorohydrin, potassium carbonate, acetone, reflux, 12 h; (c) sodium azide, ammonium chloride, methanol, reflux, 5 h; (d) alkyne, $CuSO_4$, *ter*-butanol: water(1:1), 60 ºC, 12 h.

Subsequently, the spirochromanone **2a,b** were O-alkylated with epichlorohydrin in the presence of K_2CO_3 in refluxing acetone gave epoxides **3a,b** in 85% and 82% yields. These epoxides **3a,b** that were subjected to ring opening with sodium azide in the presence of ammonium chloride afforded the corresponding azides **4a,b** in 88% and 85% yields. Finally, 1,2,3- triazole moiety was incorporated through the 1,3-dipolar cycloaddition of these azides **4a,b** with various terminal alkynes to afford 1,2,3-triazole fused spirochromone conjugates **5a–e**, **6a–e** in 65–90% yields with high

purity. In this reaction, the copper(I) catalyst was generated in situ by the reduction of copper(II)sulfate with sodium ascorbate, as described by Sharpless.[18] The structure of all the new compounds **5a–e**, **6a–e** were confirmed by the 1H NMR, ^{13}C NMR and mass spectral data.

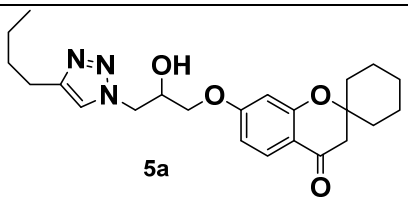
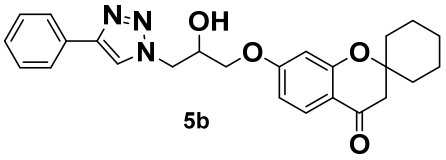
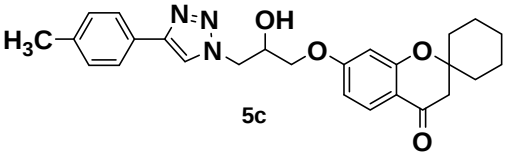
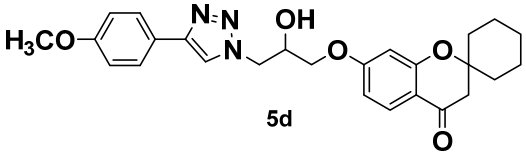
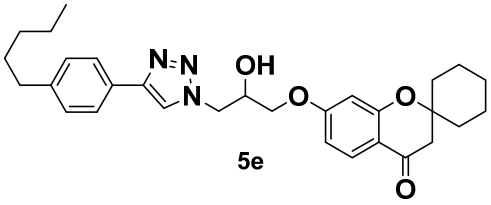
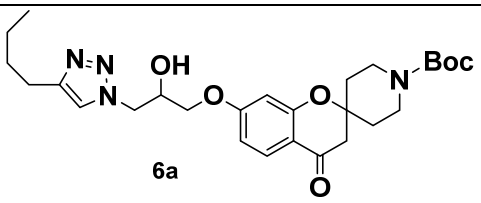
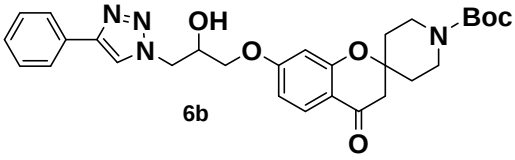
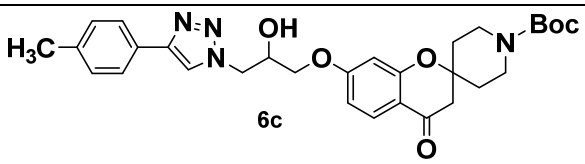
Anti-mycobacterial activity

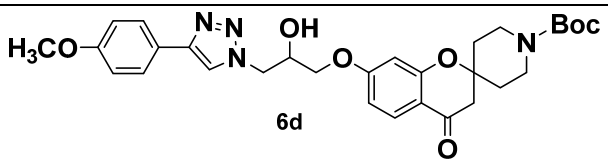
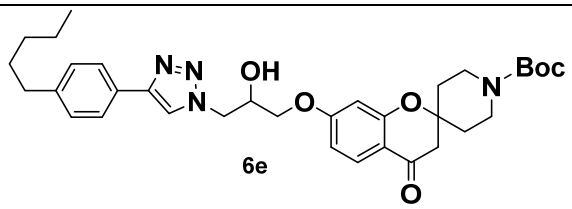
All the new triazole fused spirochromone conjugates were screened for their in vitro antimycobacterial activity against M. tuberculosis H37Rv (ATCC27294) using an agar dilution method. The minimum inhibitory concentration (MIC; μg/mL) was determined for each compound. The MIC is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. Rifampicin and ethambutol were used as reference compounds. The MIC values of the synthesized compounds along with the standard drugs for comparison were reported in Table 1. Most of the compounds (**5b–c**, **5e**, **6c**, **6e**) showed a significant in vitro activity against M. tuberculosis, MIC in the range of 0.78– 6.25 μg/mL. Among them, compound **5e** is found to be more active having MIC 0.78 μg/mL among all the compounds screened and the potency is better than first line antibacterial drug ethambutol. Importantly, compound **5e** represents a novel structural chemotype for which antitubercular properties have not been previously noted. Preliminary structure–activity relationship of the triazole fused spirochromone conjugates reveals that compounds possessing cyclohexyl group at 2nd position of the chromone ring favor better activity than piperidinyl moiety. Furthermore, aromatic substitution at 4th position of the triazole is favorable than alkyl substitution.

4.3.3. Conclusion

In conclusion, a new class of 1,2,3-triazole fused spirochromone conjugates has been synthesized using click chemistry protocol. All the compounds were obtained in good yield and were tested as new potential antitubercular agents. The in vitro antimycobacterial evaluation showed that most of the synthesized 1,2,3-triazole fused spirochromone conjugates exhibited significant antimycobacterial activity. One of those compounds, **5e** showed excellent results with MIC value of 0.78 μg/mL, which is better than anti-TB drug ethambutol (MIC-1.56 μg/mL).

Table 1. *In vitro* antimycobacterial activity of the triazole fused spirochromone conjugates

Entry	Compound	MIC (µg/mL)
1	 **5a**	12.5
2	 **5b**	6.25
3	 **5c**	3.13
4	 **5d**	12.5
5	 **5e**	**0.78**
6	 **6a**	25.0
7	 **6b**	12.5
8	 **6c**	6.25

9	 6d	25.0
10	 6e	3.13
11	**Rifampicin**	0.2
12	**Ethambutol**	1.56

4.3.4. Experimental

1) 7-hydroxyspiro[chroman-2,1'-cyclohexan]-4-one (2a)

The preparation and characterization of compound **2a** is depicted in Chapter 4; Section B.

2) *ter*-butyl 7-hydroxy-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (2b)

The preparation and characterization of compound **2b** is depicted in Chapter 4; Section B.

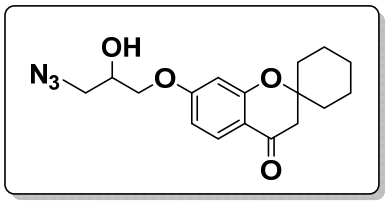
3) 7-(oxiran-2-ylmethoxy)spiro[chroman-2,1'-cyclohexan]-4-one (3a)

The preparation and characterization of compound **3a** is depicted in Chapter 4; Section B.

4) *ter*-butyl 7-(oxiran-2-ylmethoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (3b)

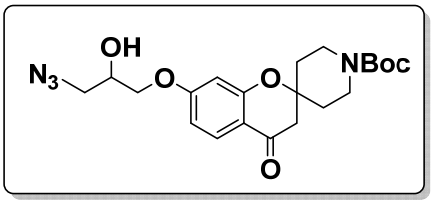
The preparation and characterization of compound **3b** is depicted in Chapter 4; Section B.

5) 7-(3-azido-2-hydroxypropoxy)spiro[chroman-2,1'-cyclohexan]-4-one (4a)



To a solution of compound **3a** (2 g, 6.9 mmol) in methanol (10 mL) was added sodium azide (0.9 g, 14 mmol) and ammonium chloride (0.75 g, 14 mmol). The resulting solution was refluxed for 5 h before concentrated invacuo. The residue was taken in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. Purification of the crude by column chromatography (20 % ethyl acetate in petroleum ether) afforded **4a** as a colorless oil (2 g, 88%).

6) *ter*-butyl 7-(3-azido-2-hydroxypropoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (4b)



The same procedure as in the preparation of **4a** was used with the epoxide **3b** (3g, 7.7 mmol) affording the azide compound **4b** as a colorless oil (2.8 g, 85%)

Representative physical data of *ter*-butyl 7-(3-azido-2-hydroxypropoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (4b): Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.52-1.67 (m, 2H), 1.98-2.04 (m, 2H), 2.66 (s, 2H), 3.20 (bt, *J*= 11.8 Hz, 1H), 3.42-3.62 (m, 2H), 3.76-3.89 (m, 2H), 4.04 (d, *J*= 5.4 Hz, 2H), 4.11-4.27 (m, 1H), 6.45 (d, *J*= 2.3 Hz, 1H), 6.58 (dd, *J*= 8.9, 2.3 Hz, 1H), 7.80 (d, *J*= 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 190.2, 164.9, 160.9, 154.7, 128.5, 115.0, 109.7, 102.1, 79.9, 78.3, 69.3, 68.9, 53.2, 47.6, 38.7, 34.0, 28.4; ESI-MS: *m/z* 455 $[M+ Na]^+$.

7) Synthesis of 1,2,3-triazole fused spirochromone derivatives (5-6):

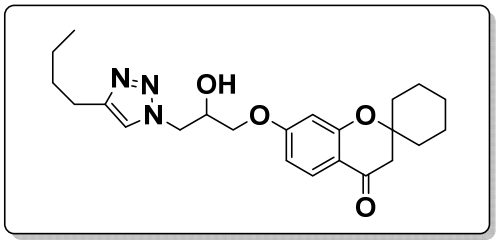
General procedure:

To a solution of azide (**4a** or **4b**) (0.7 mmol) and aliphatic/aromatic alkyne (0.77 mmol) in *tert*. butanol (3 mL) was added sequentially copper sulphate pentahydrate (0.035 g; 0.14 mmol), sodium ascorbate (0.028 g; 0.14 mmol) and distilled water (3

mL). The resulting reaction mixture was stirred for 12 h at 60 ^{0}C. After completion of the reaction (by TLC), the reaction mixture was diluted with CH_2Cl_2 (10 mL) and then washed with water (2 x 5 mL). The organic layer was dried (Na_2SO_4) and concentrated invacuo. Purification via column chromatography (Ethyl acetate, petroleum ether 1:1 (v/v)) afforded pure product **5-6**.

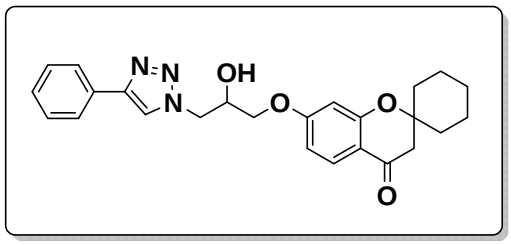
Spectroscopic data for all the compounds are given below.

7-(3-(4-butyl-1*H*-1,2,3-triazol-1-yl)-2-hydroxypropoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5a)



Pale yellow solid; yield 65%; mp 97-98 ºC**;** ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J*= 7.1 Hz, 3H),1.15-1.72 (m, 12H), 1.93-1.99 (m, 2H), 2.63-2.70 (m, 4H), 4.00-4.02 (bd, *J*= 4.7 Hz, 2H), 4.42-4.69 (m, 3H), 6.40 (d, *J*= 2.4 Hz,1H), 6.49-6.55 (dd, *J*= 8.6, 2.3 Hz, 1H), 7.42 (s, 1H), 7.76 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 191.3, 164.6, 161.5, 148.2, 128.3, 128.3, 122.4, 115.1, 109.2, 101.9, 80.5, 69.1, 68.5, 52.7, 47.8, 34.7, 31.3, 25.1, 25.0, 22.2, 21.4, 13.7; ESI-MS: *m/z* 436 $[M+ Na]^+$.

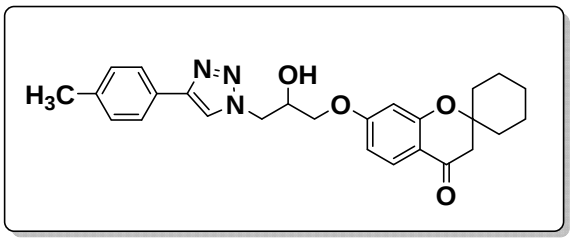
7-(2-hydroxy-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5b)



Colourless solid; yield 85%; mp 154-55 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40-1.73 (m, 8H), 1.93-2.00 (m, 2H), 2.64 (s, 2H), 4.07-4.10 (bd, *J*= 4.8 Hz, 2H), 4.35 (s, 1H), 4.47-4.78 (m, 3H), 6.43 (d, *J*= 2.4 Hz 1H), 6.52-6.57 (dd, *J*= 8.7, 2.4 Hz, 1H), 7.30-7.41 (m, 3H), 7.65-7.70 (dd, *J*= 7.9, 1.5 Hz , 2H), 7.78 (d, *J*= 8.7 Hz 1H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 191.3, 164.6, 161.5, 147.4, 129.9, 128.8, 128.3, 128.2,

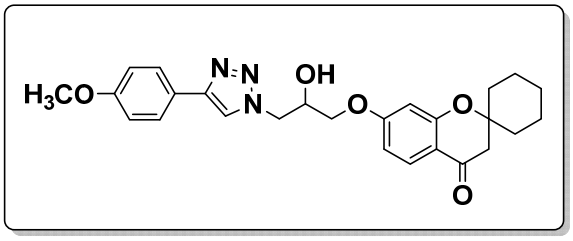
125.5, 121.4, 115.2, 109.2, 102.0, 80.5, 69.2, 68.5, 53.2, 47.9, 34.8, 25.1, 21.4; ESI-MS: *m/z* 456 $[M+ Na]^+$.

7-(2-hydroxy-3-(4-*p*-tolyl-1*H*-1,2,3-triazol-1-yl)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5c)



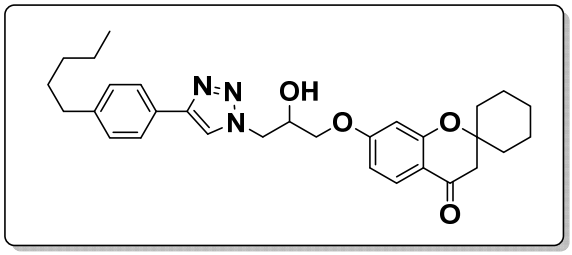
Colourless solid; yield 76%; mp 128-29 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33-1.72 (m, 8H), 1.93-1.99 (m, 2H), 2.35 (s, 3H), 2.64 (s, 2H), 4.07-4.09 (bd, *J*= 4.7 Hz, 2H), 4.44-4.73 (m, 4H), 6.43 (d, *J*= 2.3 Hz 1H), 6.51-6.56 (dd, *J*= 8.8, 2.4 Hz, 1H), 7.15 (d, *J*= 8.0 Hz, 2H), 7.54 (d, *J*= 8.0 Hz, 2H), 7.77 (d, *J*= 8.0 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 191.3, 164.6, 161.5, 147.4, 138.0, 129.4, 128.3, 127.1, 125.4, 121.1, 115.1, 109.2, 102.0, 80.5, 69.2, 68.4, 53.2, 47.8, 34.7, 25.1, 21.4, 21.2; ESI-MS: *m/z* 470 $[M+ Na]^+$.

7-(2-hydroxy-3-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5d)



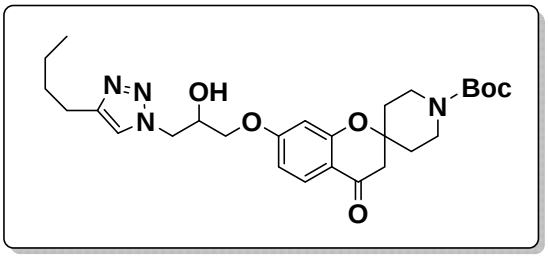
Colourless solid; yield 90%; mp 109-10 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40-1.81 (m, 8H), 1.93-2.00 (m, 2H), 2.64 (s, 2H), 3.83 (s, 3H), 4.08-4.10 (bd, *J*= 4.6 Hz, 2H), 4.45-4.73 (m, 4H), 6.43 (d, *J*= 2.4 Hz 1H), 6.52-6.57 (dd, *J*= 8.7, 2.4 Hz, 1H), 6.89 (d, *J*= 8.8 Hz, 2H), 7.59 (d, *J*= 8.9 Hz, 2H), 7.76 (s, 1H), 7.78 (d, *J*= 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 191.3, 164.6, 161.5, 159.6, 128.3, 126.8, 122.7, 115.2, 114.2, 109.2, 102.0, 80.5, 69.2, 68.5, 55.3, 53.1, 47.8, 34.8, 25.1, 21.4; ESI-MS: *m/z* 486 $[M+ Na]^+$.

7-(2-hydroxy-3-(4-(4-pentylphenyl)-1*H*-1,2,3-triazol-1-yl)propoxy)spiro[chroman-2,1'-cyclohexan]-4-one (5e)



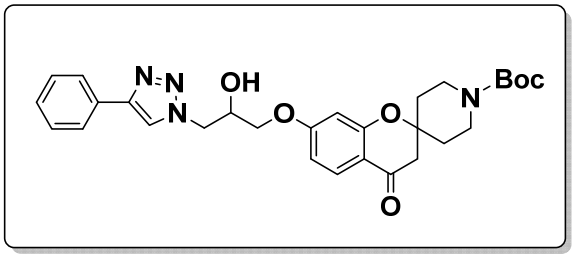
Colourless solid; yield 75%; mp 156-57 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J*= 6.4 Hz, 3H),1.22-1.72 (m, 14H), 1.93-2.0 (m, 2H), 2.56-2.60 (m, 2H), 2.63 (s, 2H), 4.08-4.11 (bd, *J*= 4.6 Hz, 2H), 4.43-4.74 (m, 3H), 4.96 (d, *J*= 4.2 Hz, 1H), 6.43 (d, *J*= 2.3 Hz 1H), 6.52-6.57 (dd, *J*= 8.6, 2.4 Hz, 1H), 7.14 (d, *J*= 8.4 Hz, 2H), 7.52 (d, *J*= 8.1 Hz, 2H), 7,77 (d, *J*= 9.0 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 191.3, 164.7, 161.5, 147.4, 143.1, 128.8, 128.3, 127.3, 125.4, 121.1, 115.1, 109.2, 102.0, 80.5, 69.3, 68.4, 53.2, 47.8, 35.6, 34.7, 31.4, 31.0, 25.1, 22.5, 21.4, 14.0; ESI-MS: *m/z* 526 [M+ Na]$^{+}$.

***ter*-butyl 7-(3-(4-butyl-1*H*-1,2,3-triazol-1-yl)-2-hydroxypropoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6a)**



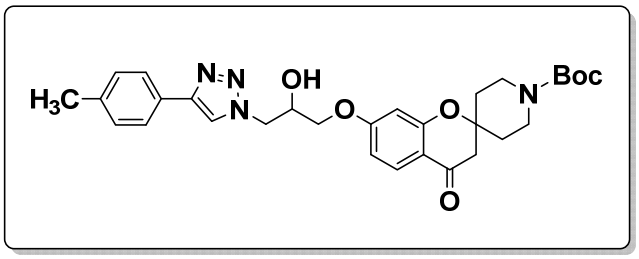
Colourless solid; yield 71%; mp 122-23 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, *J*= 7.2 Hz, 3H), 1.25-1.69 (m, 6H), 1.45 (s, 9H), 1.97-2.04 (m, 2H), 2.63-2.70 (m, 2H), 2.65 (s, 2H), 3.13-3.25 (m, 2H), 3.83-3.89 (m, 2H), 4.00-4.03 (bd, *J*= 4.7 Hz, 2H), 4.42-4.69 (m, 3H), 6.42 (d, *J*= 2.3 Hz, 1H), 6.54-6.59 (dd, *J*= 8.5, 2.2 Hz, 1H), 7.41 (s, 1H), 7.79 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 190.1, 164.8, 160.9, 154.7, 148.2, 128.5, 122.4, 115.0, 109.7, 102.0, 79.8, 78.3, 69.2, 68.4, 52.6, 47.6, 38.9, 33.9, 31.4, 28.4, 25.2, 22.2, 13.7; ESI-MS: *m/z* 537 [M+ Na]$^{+}$.

ter-butyl 7-(2-hydroxy-3-(4-phenyl-1_H_-1,2,3-triazol-1-yl)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6b)



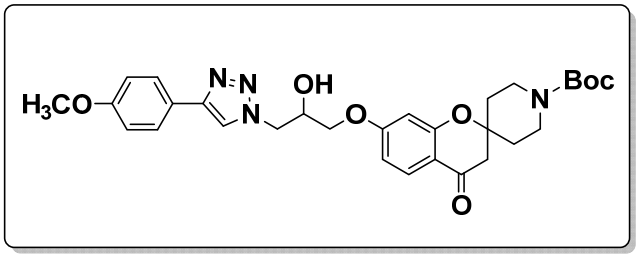
Colourless solid; yield 90%; mp 167-68 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.50-1.65 (m, 2H), 1.90-2.02 (m, 2H), 2.64 (s, 2H), 3.13-3.24 (m, 2H), 3.82-3.88 (m, 2H), 4.10 (bs, 2H), 4.47-4.75 (m, 4H), 6.44 (d, *J*= 2.3 Hz, 1H), 6.55-6.61 (dd, *J*= 8.5, 2.2 Hz, 1H), 7.26-7.41 (m, 3H), 7.66 (dd, *J*= 7.9, 1.9 Hz, 2H), 7.80 (d, *J*= 8.7 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 190.1, 164.8, 161.0, 154.7, 147.5, 129.9, 128.8, 128.5, 128.3, 125.5, 121.4, 115.1, 109.7, 102.1, 79.8, 78.3, 69.3, 68.5, 53.1, 47.6, 39.2, 33.9, 28.4; ESI-MS: *m/z* 557 $[M+ Na]^+$.

ter-butyl 7-(2-hydroxy-3-(4-p-tolyl-1_H_-1,2,3-triazol-1-yl)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6c)



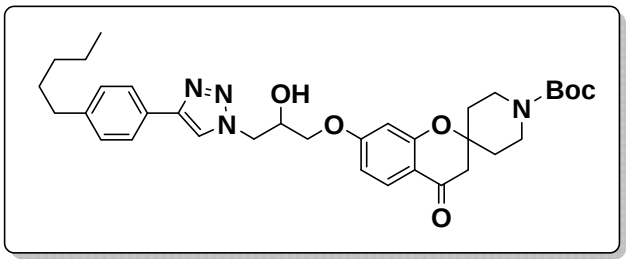
Colourless solid; yield 80%; mp 128-29 ºC**;** ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.50-1.66 (m, 2H), 1.90-1.96 (m, 2H), 2.36 (s, 3H), 2.65 (s, 2H), 3.13-3.25 (m, 2H), 3.82-3.88 (m, 2H), 4.07-4.10 (bd, *J*= 4.9 Hz, 2H), 4.45-4.73 (m, 4H), 6.44 (d, *J*= 2.3 Hz, 1H), 6.55-6.61 (dd, *J*= 8.9, 2.4 Hz, 1H), 7.16 (d, *J*= 8.2 Hz, 2H), 7.55 (d, *J*= 7.6 Hz, 2H), 7.79(d, *J*= 7.6 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 190.2, 164.8, 160.9, 154.7, 147.5, 138.1, 129.5, 128.5, 127.2, 125.4, 121.1, 115.0, 109.7, 102.1, 79.8, 78.3, 69.4, 68.4, 60.4, 53.2, 47.6, 39.1, 34.0, 28.4, 21.3; ESI-MS: *m/z* 571 $[M+ Na]^+$.

ter-butyl 7-(2-hydroxy-3-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6d)



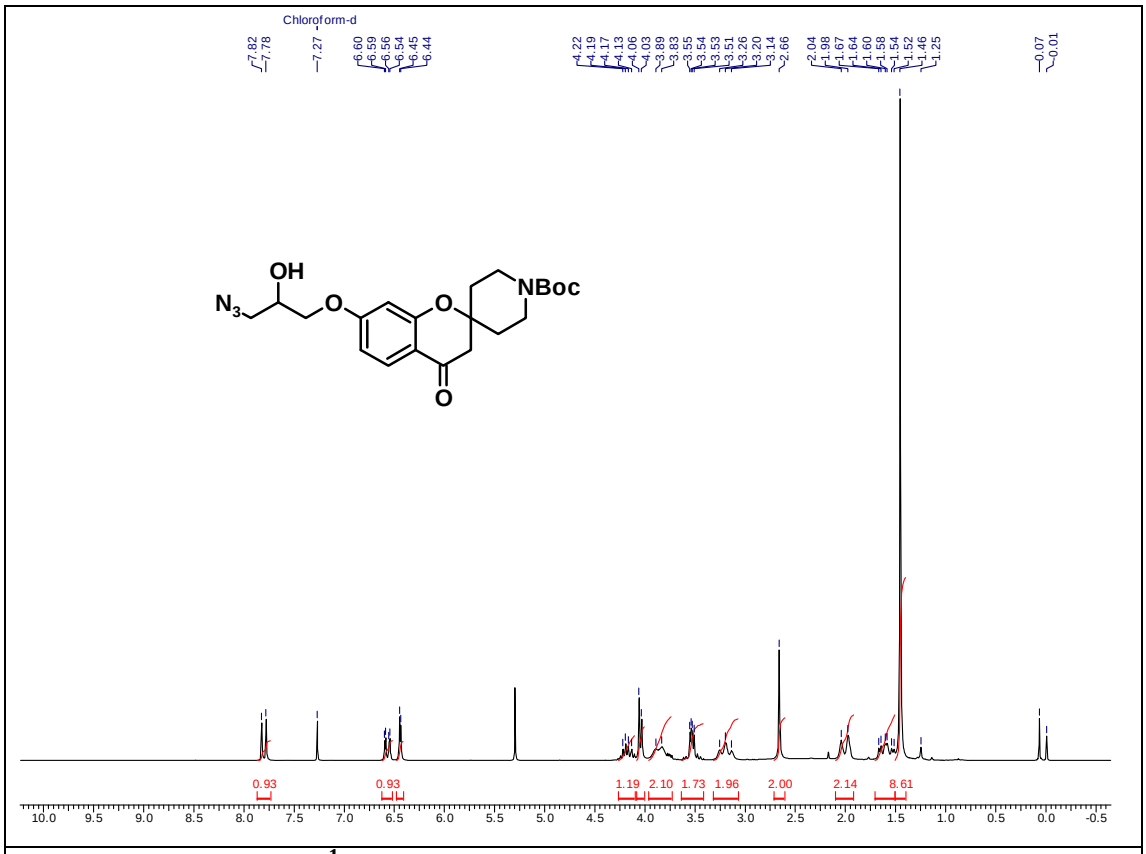
Colourless oil; yield 88%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.51-1.66 (m, 2H), 1.85-2.04 (m, 2H), 2.65 (s, 2H), 3.13-3.25 (m, 2H), 3.83 (s, 3H), 3.84-3.89 (m, 2H), 4.08-4.10 (bd, *J*= 4.2 Hz, 2H), 4.45-4.73 (m, 4H), 6.43 (d, *J*= 2.3 Hz, 1H), 6.56-6.61 (dd, *J*= 8.7, 2.2 Hz, 1H), 6.89 (d, *J*= 9.3 Hz, 2H), 7.59 (d, *J*= 9.3 Hz, 2H), 7.76 (s, 1H), 7.80 (d, *J*= 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 190.1, 164.8, 160.9, 159.6, 154.7, 147.3, 128.5, 126.8, 122.7, 120.6, 115.1, 114.2, 109.7, 102.1, 79.8, 78.3, 69.3, 68.5, 55.3, 53.1, 47.6, 39.0, 34.0, 28.4; ESI-MS: *m/z* 587 $[M+ Na]^{+}$.

ter-butyl 7-(2-hydroxy-3-(4-(4-pentylphenyl)-1*H*-1,2,3-triazol-1-yl)propoxy)-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6e)

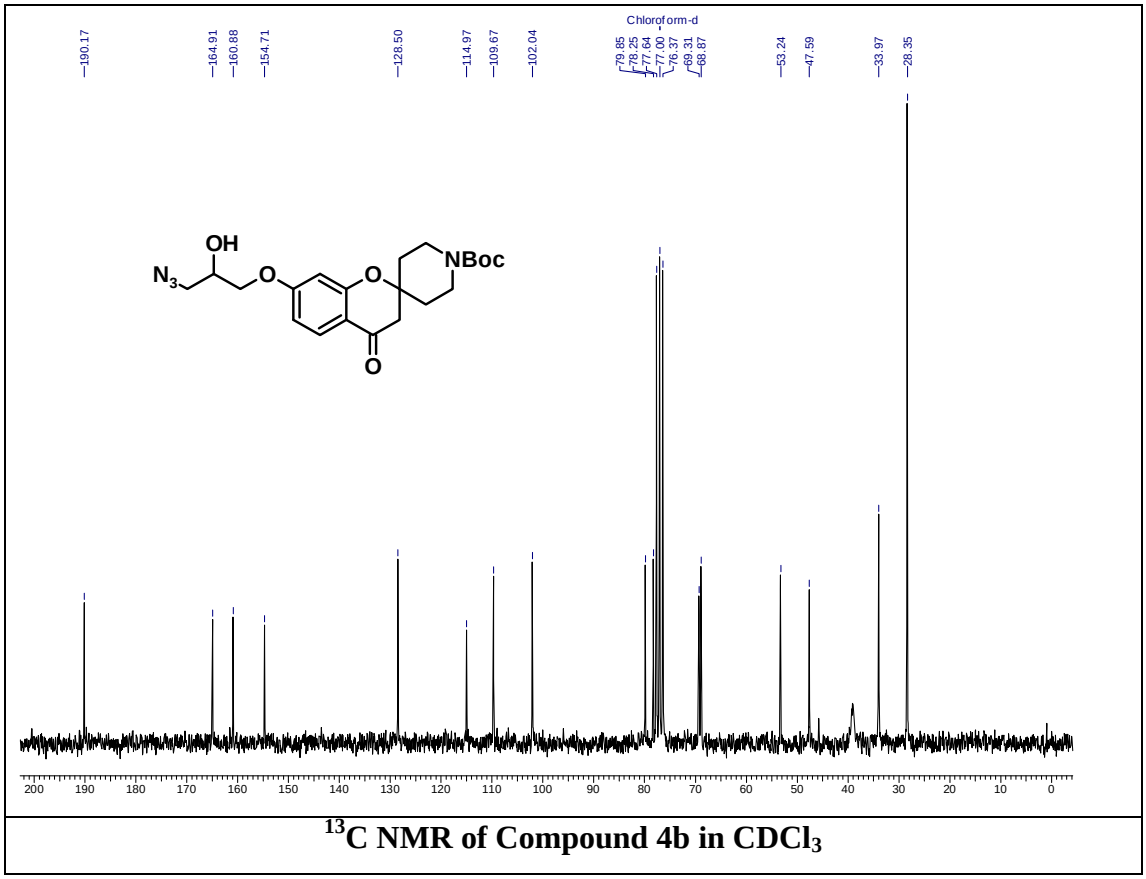


Colourless solid; yield 83%; mp 62-63 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J*= 6.6 Hz, 3H), 1.26-1.36 (m, 4H), 1.46 (s, 9H), 1.54-1.66 (m, 4H), 1.97-2.05 (m, 2H), 2.57-2.66 (m, 2H), 2.66 (s, 2H), 3.14-3.26 (m, 2H), 3.84-3.90 (m, 2H), 4.09 (bd, *J*= 4.4 Hz, 2H), 4.46-4.74 (m, 4H), 6.46 (d, *J*= 2.3 Hz, 1H), 6.59 (dd, *J*= 8.7, 2.4 Hz, 1H), 7.17 (d, *J*= 8.0 Hz, 2H), 7.57 (d, *J*= 8.2 Hz, 2H), 7.79-7.83 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 190.1, 164.8, 160.9, 154.7, 147.6, 143.2, 128.8, 128.5, 127.3, 125.4, 121.1, 115.1, 109.7, 102.1, 79.8, 78.3, 69.3, 68.5, 66.5, 53.1, 47.6, 39.3, 35.7, 34.0, 31.4, 31.0, 28.4, 22.5, 14.0; ESI-MS: *m/z* 627 $[M+ Na]^{+}$.

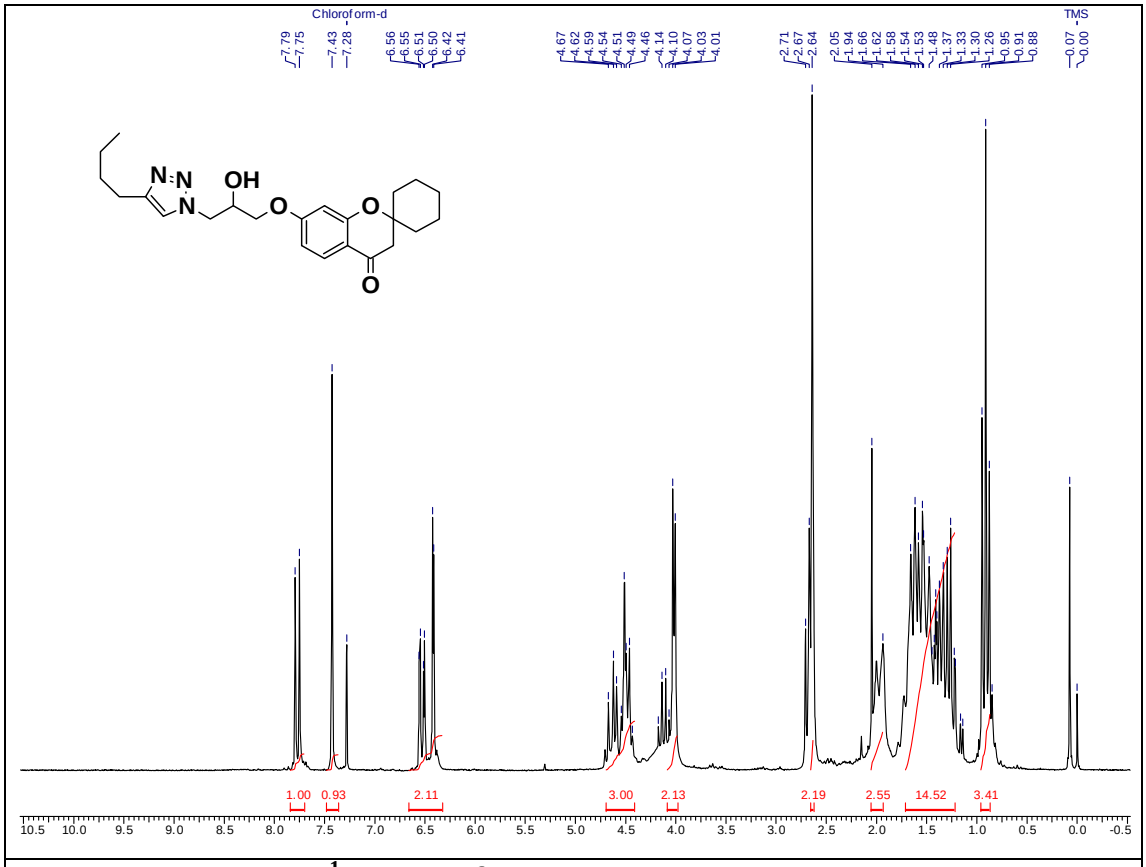
4.3.5. Analytical data



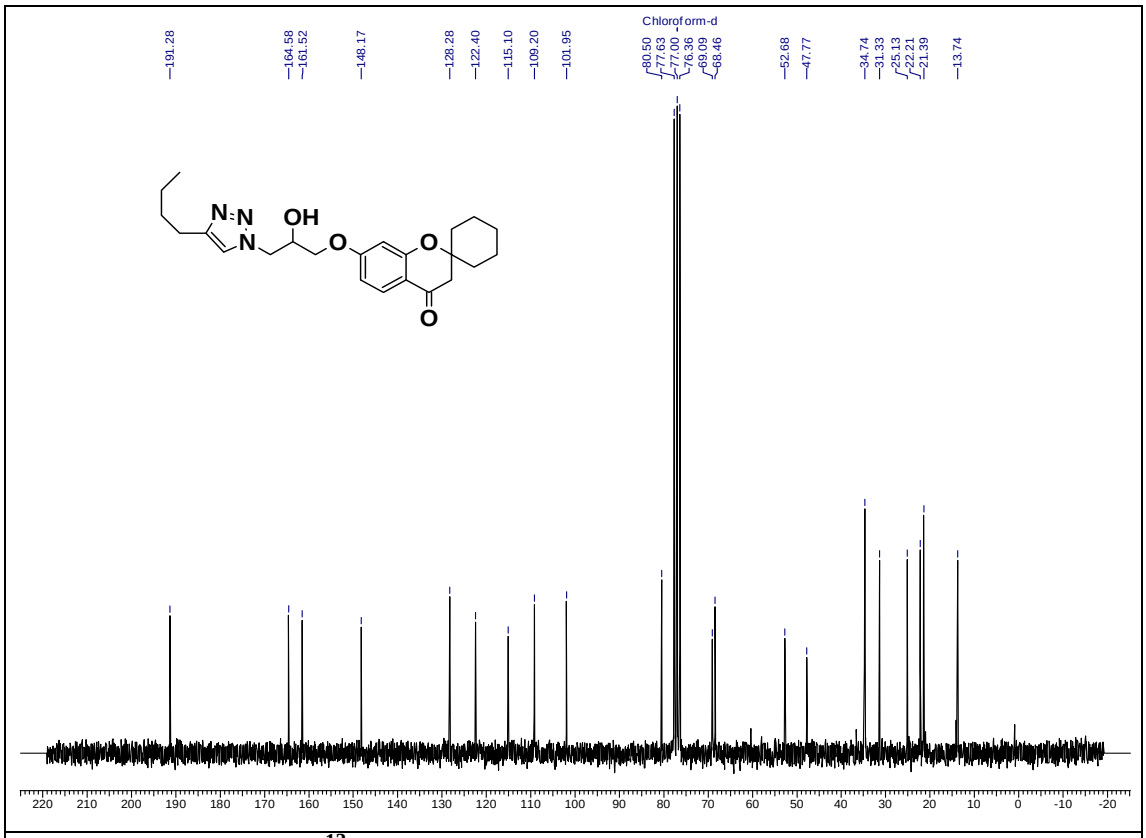
^{1}H NMR of Compound 4b in $CDCl_3$



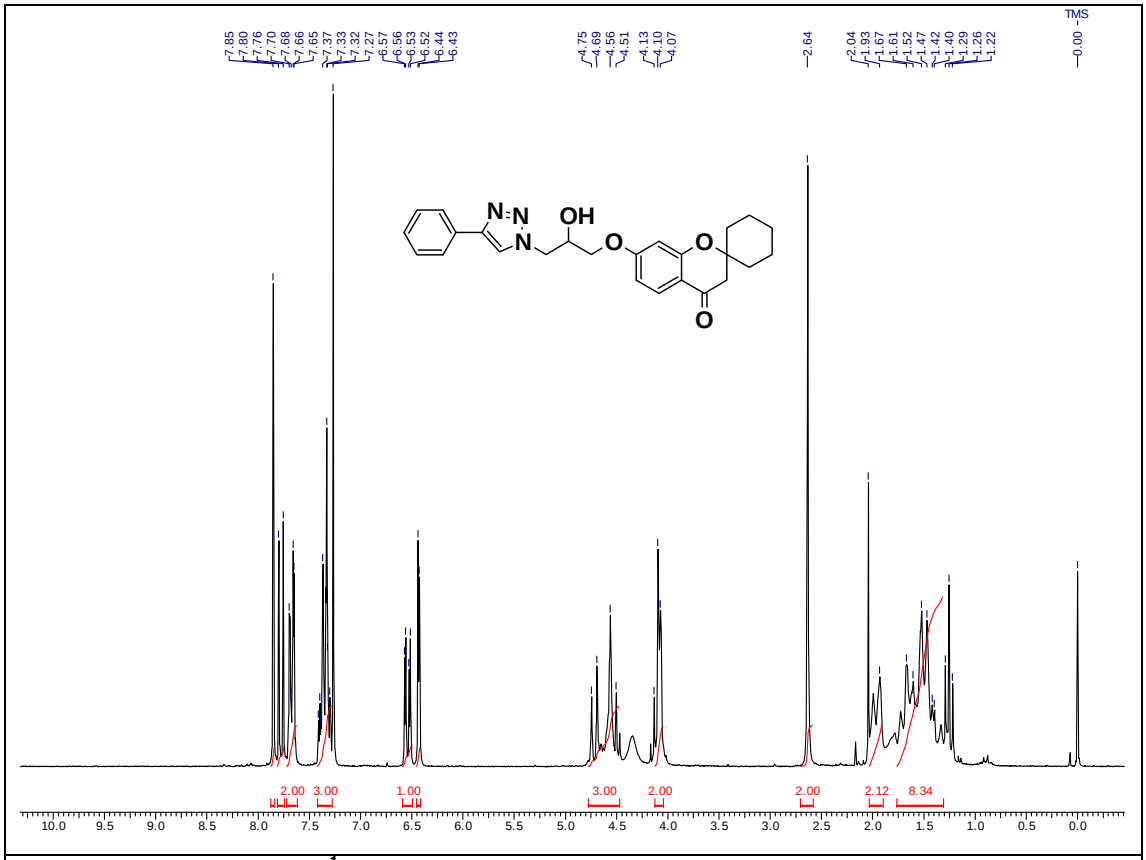
^{13}C NMR of Compound 4b in $CDCl_3$



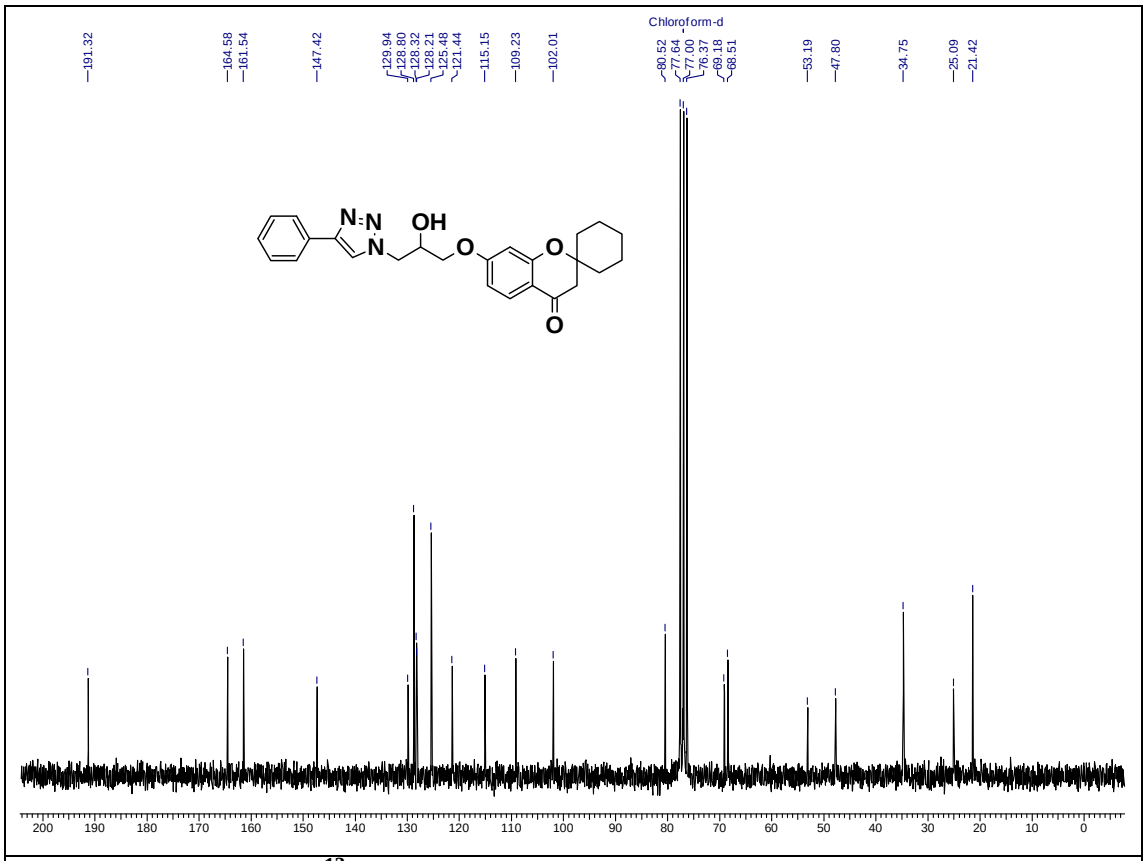
^{1}H NMR of Compound 5a in $CDCl_3$



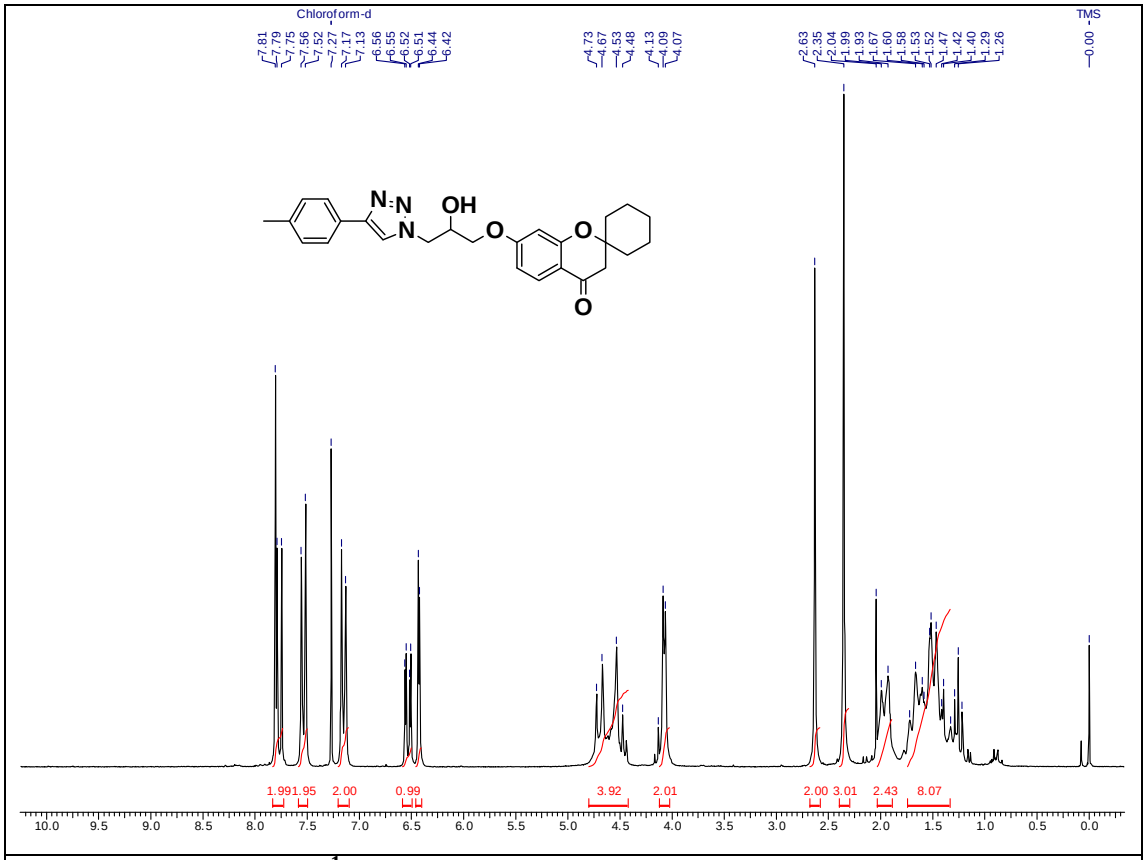
^{13}C NMR of Compound 5a in $CDCl_3$



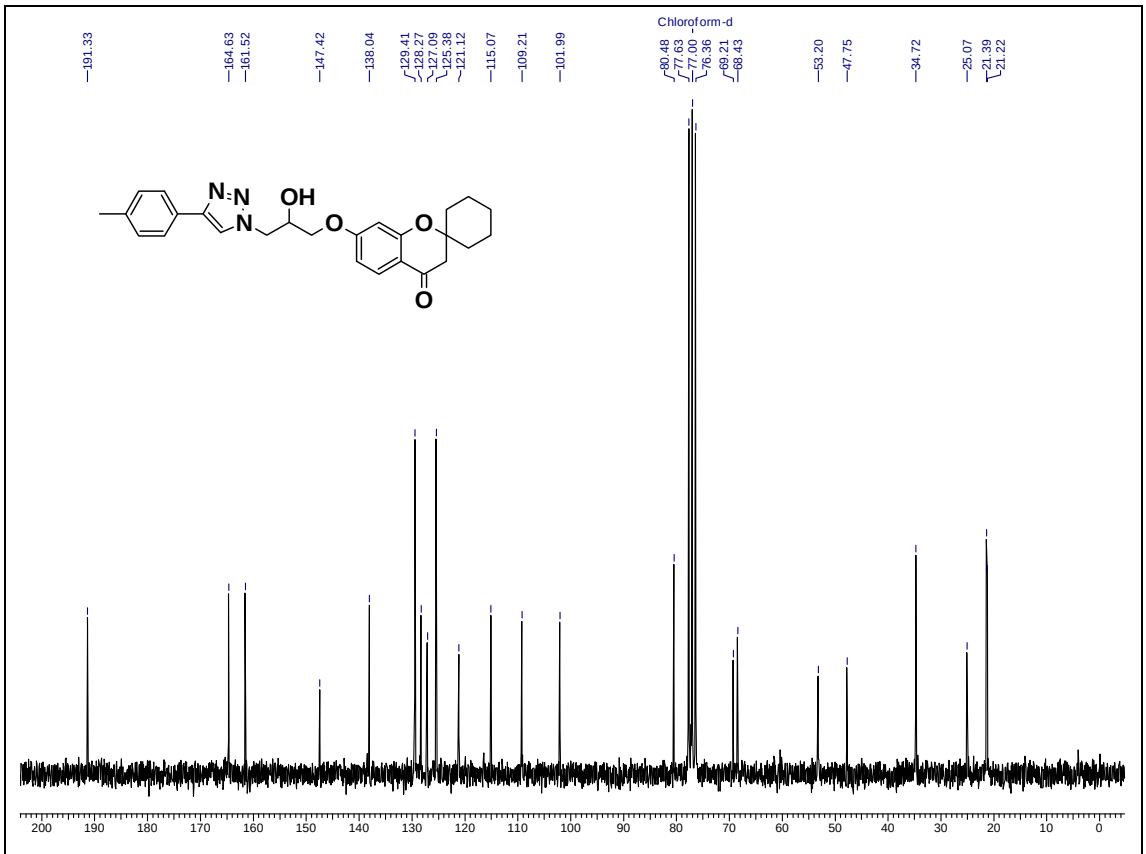
^{1}H NMR of Compound 5b in $CDCl_3$



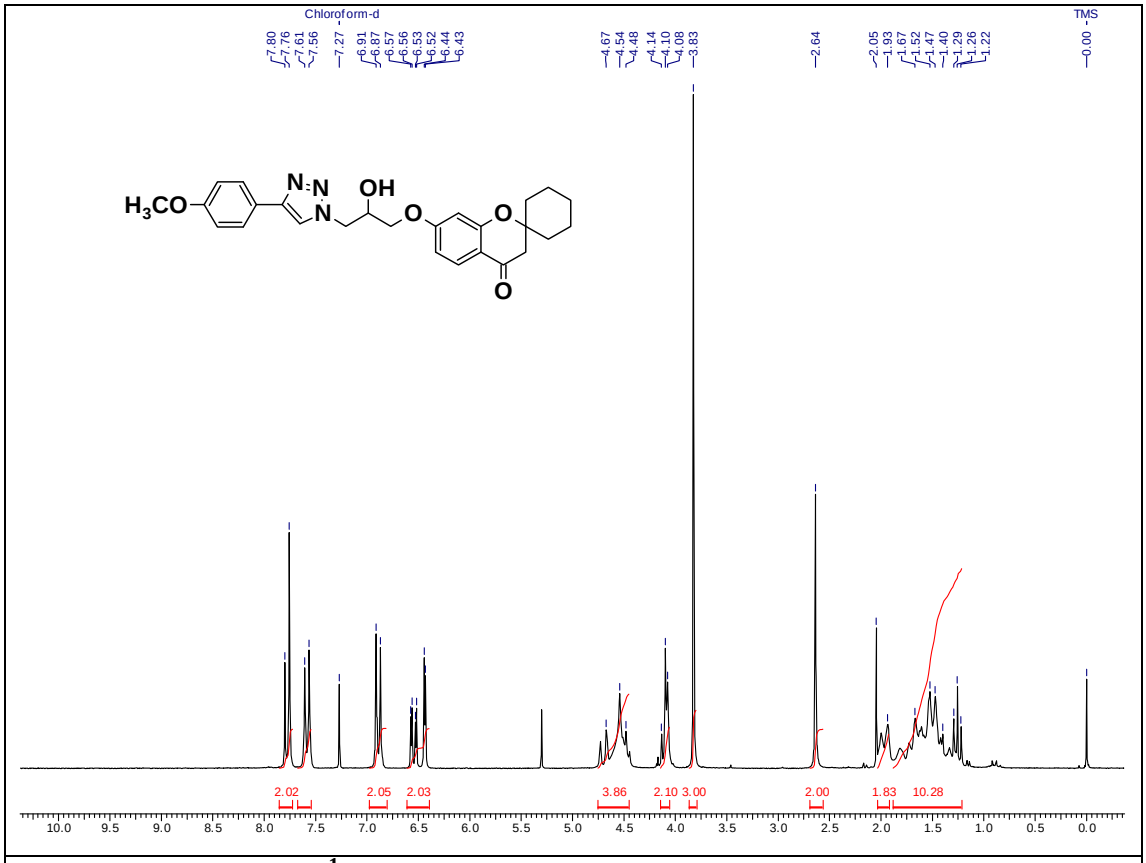
^{13}C NMR of Compound 5b in $CDCl_3$



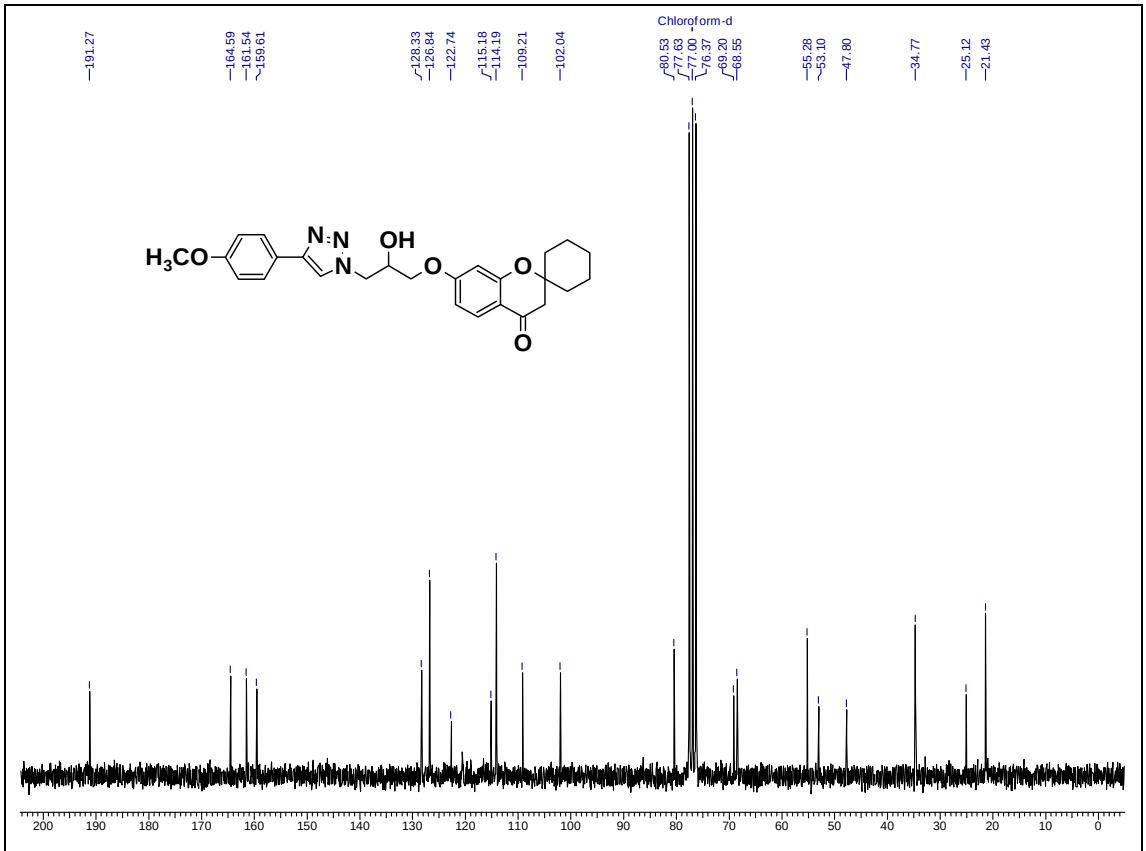
^{1}H NMR of Compound 5c in $CDCl_3$



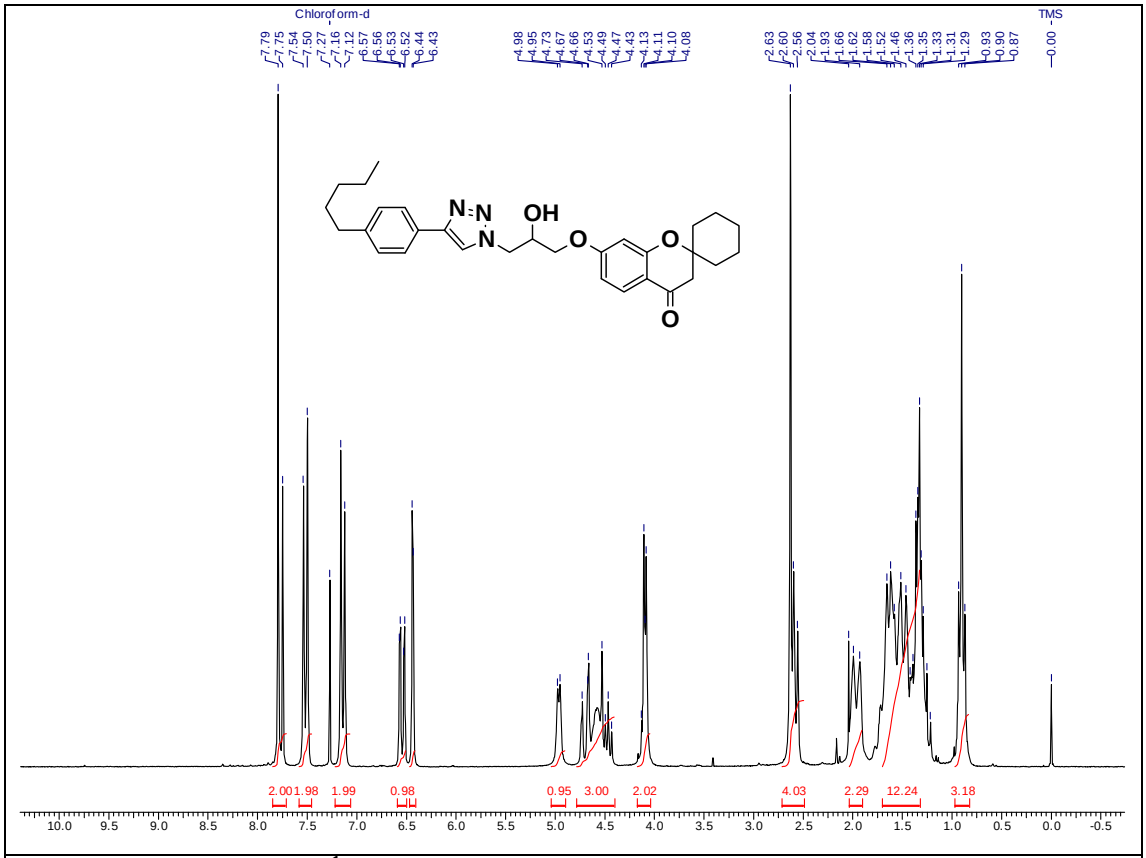
^{13}C NMR of Compound 5c in $CDCl_3$



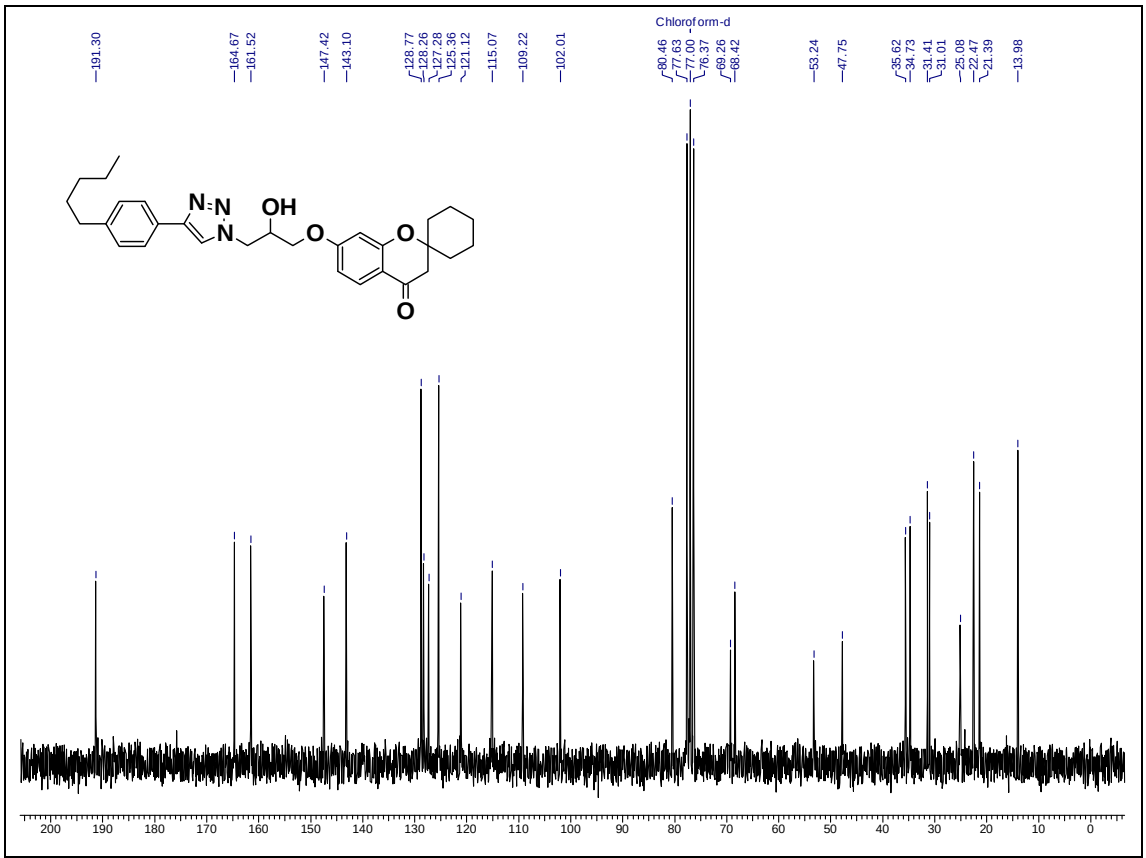
^{1}H NMR of Compound 5d in $CDCl_3$



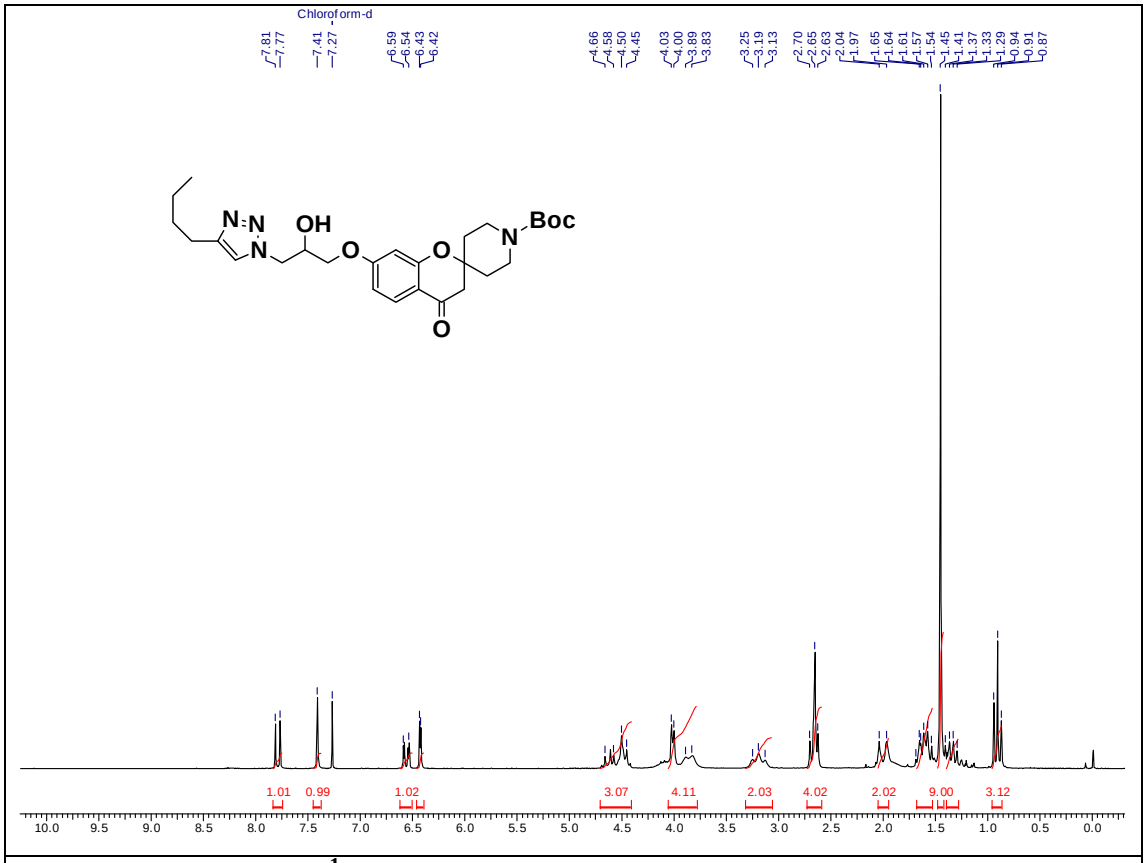
^{13}C NMR of Compound 5d in $CDCl_3$



^{1}H NMR of Compound 5e in $CDCl_3$



^{13}C NMR of Compound 5e in $CDCl_3$



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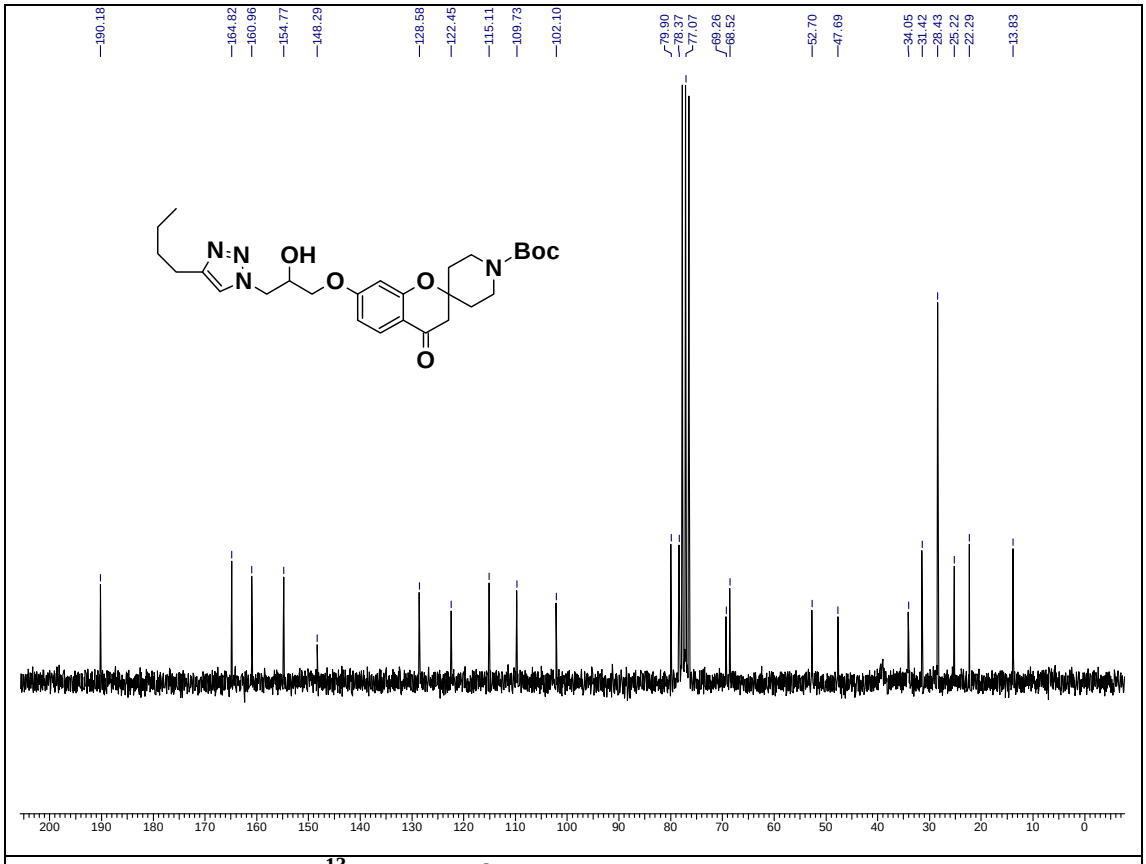

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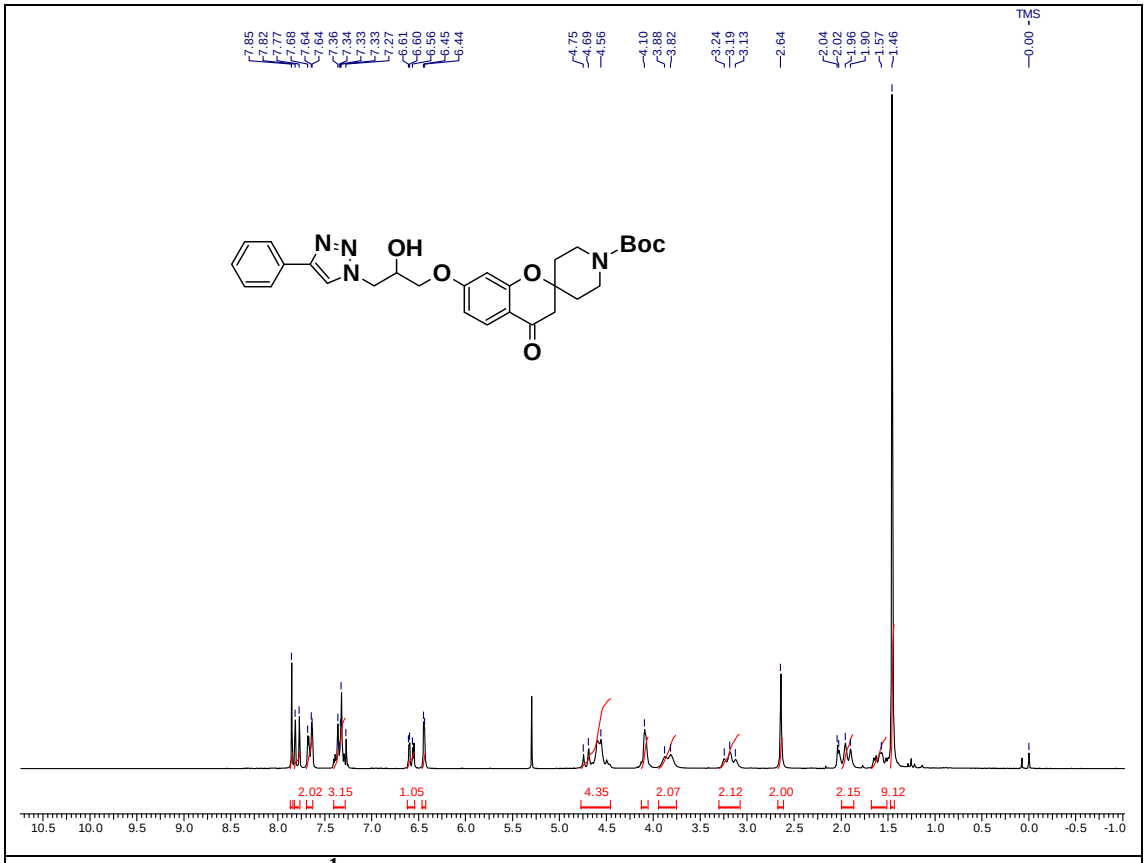

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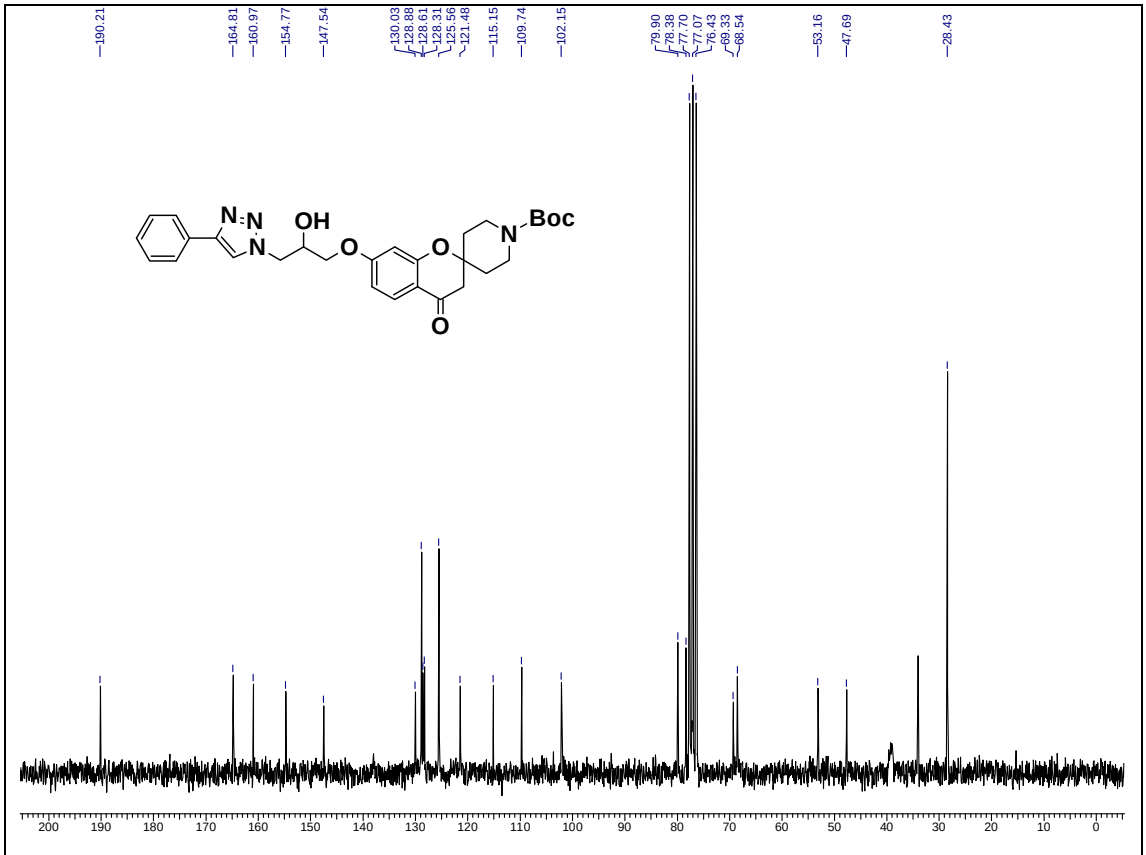

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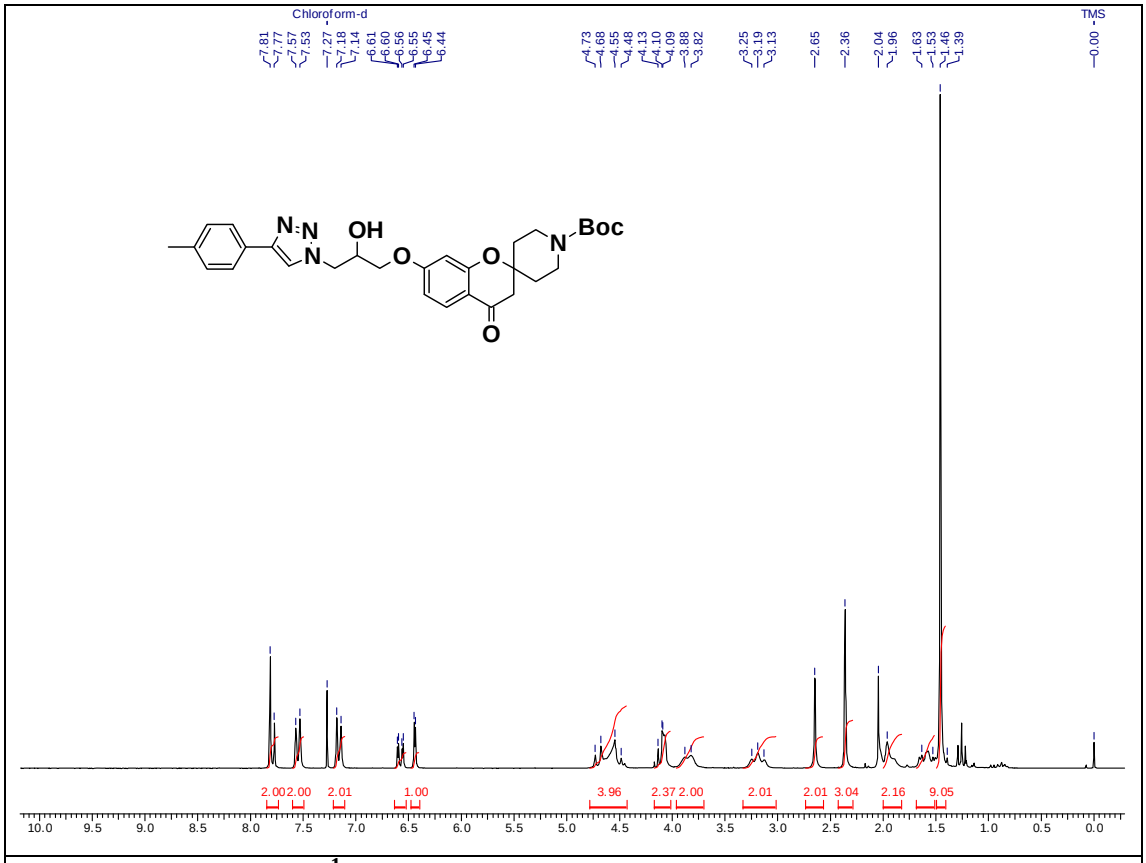

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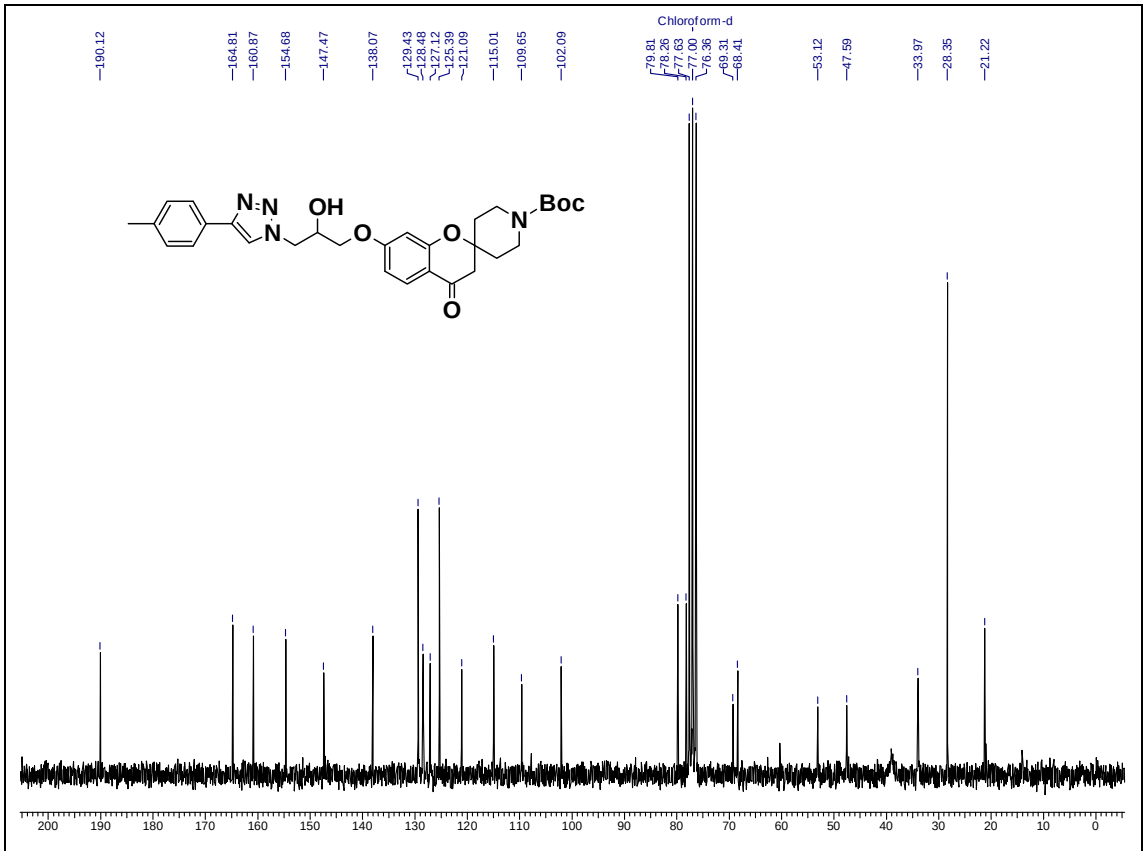

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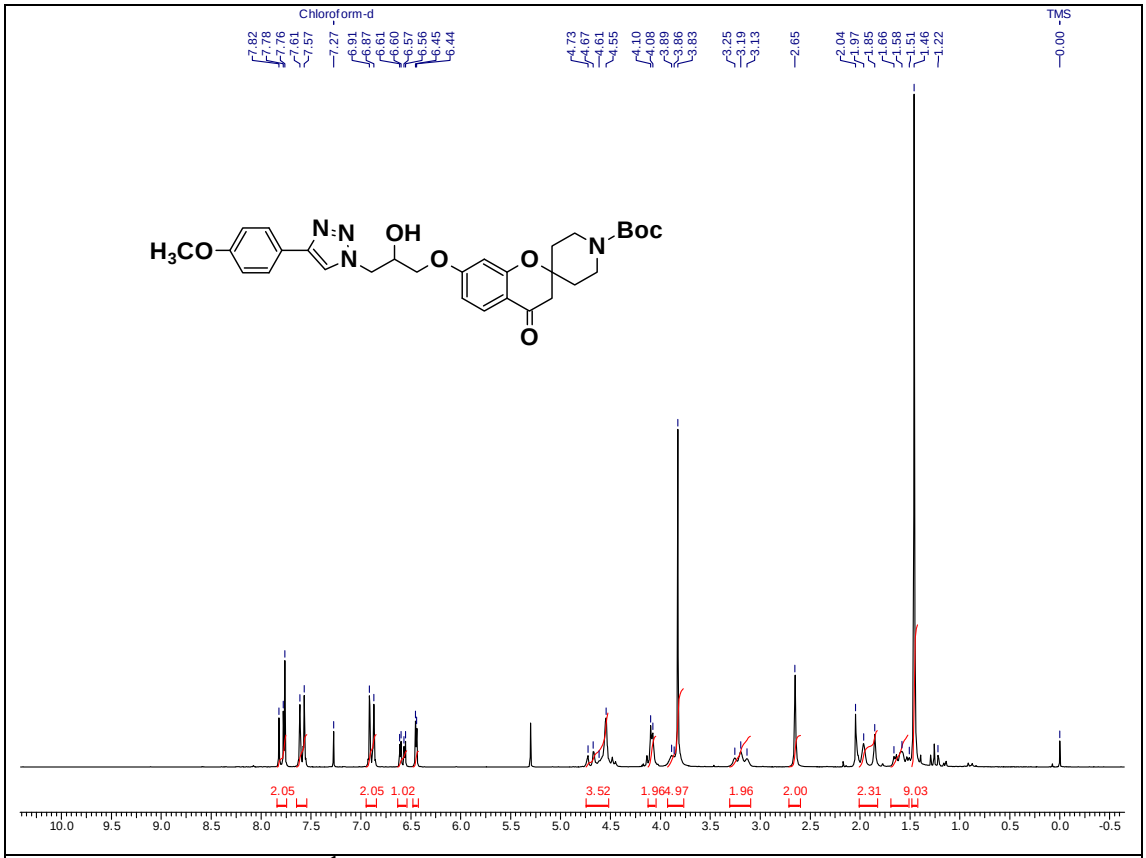

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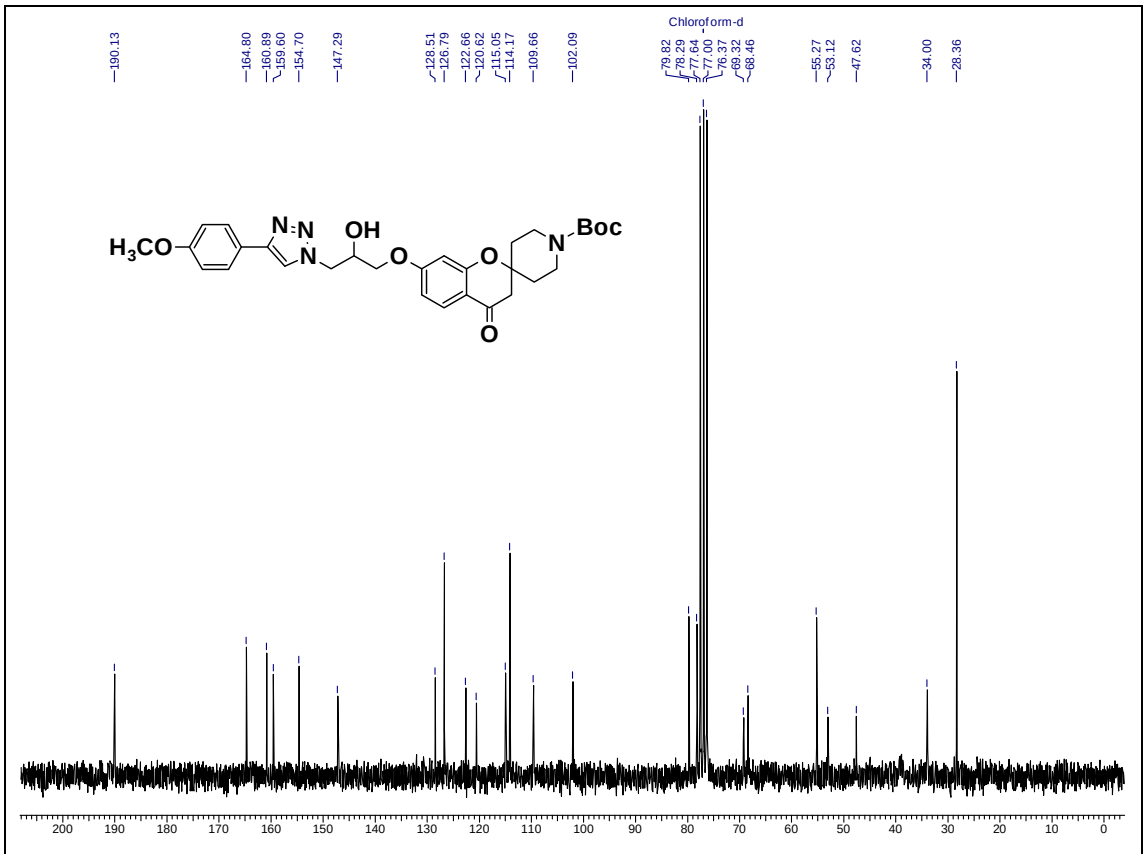
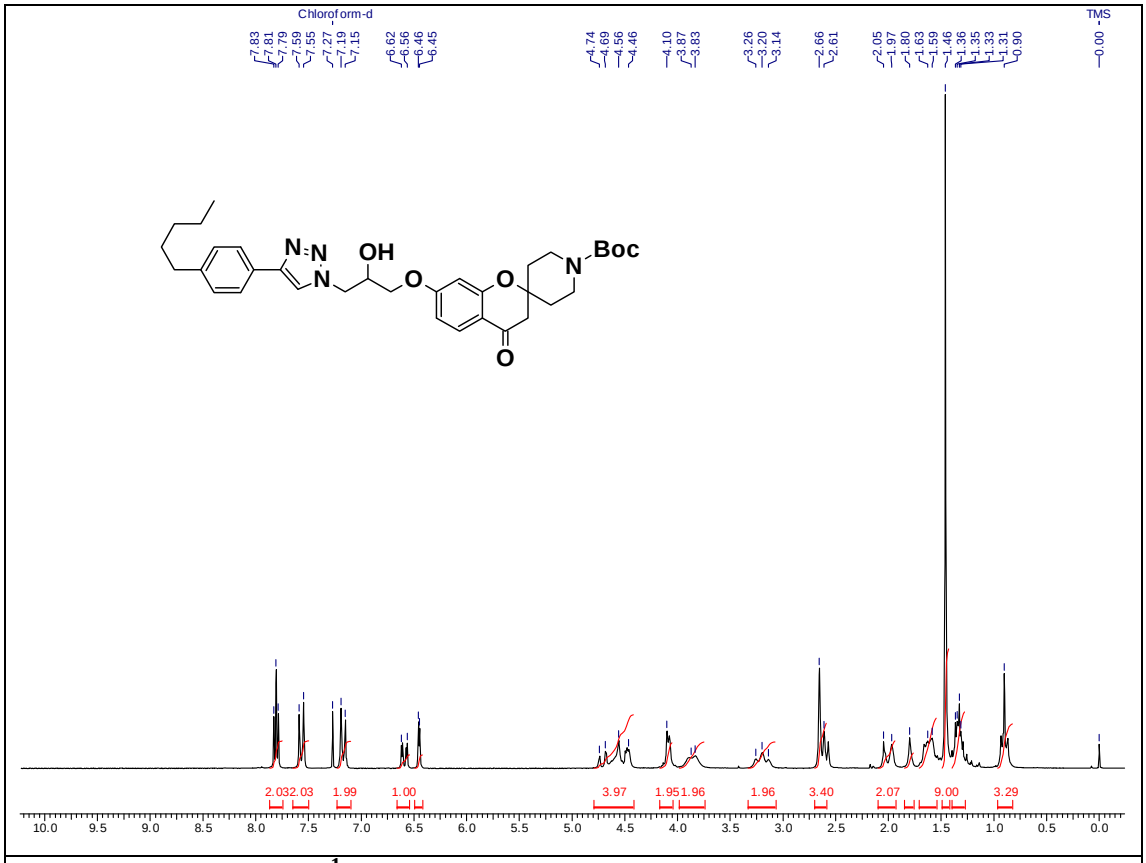
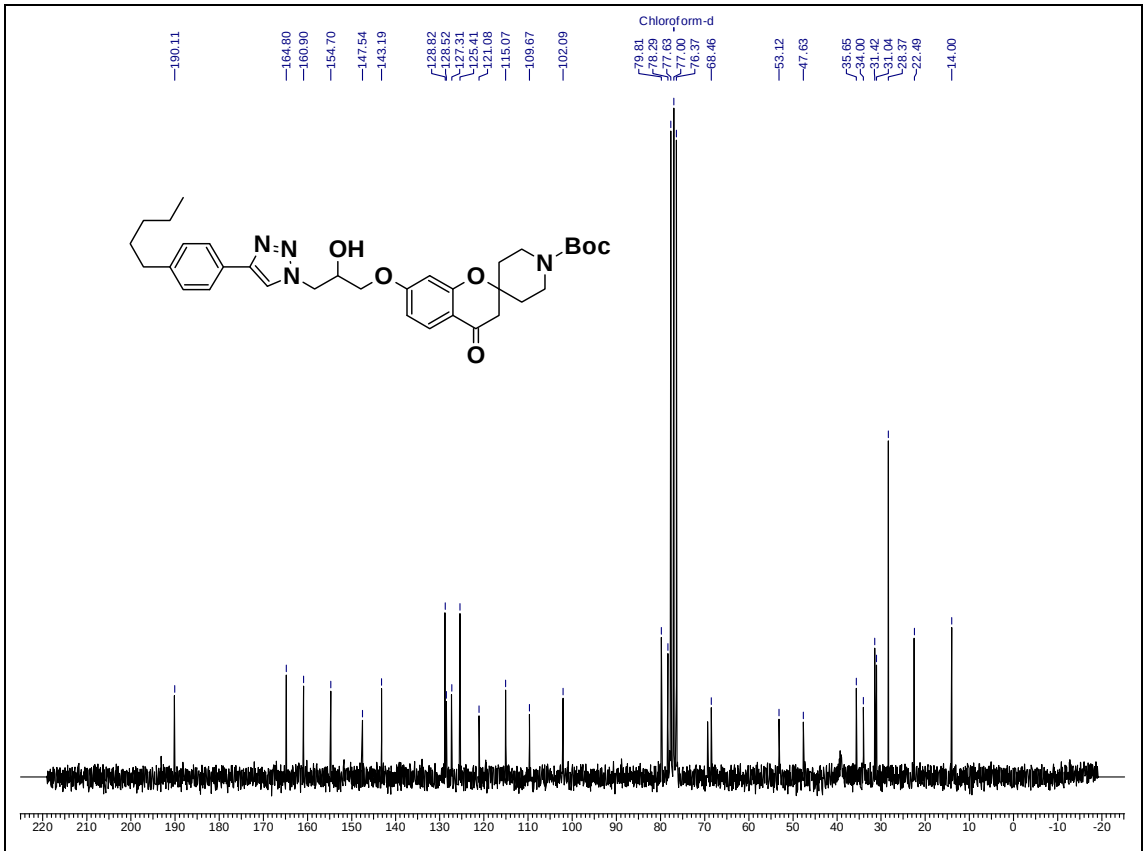


^{13}C NMR of Compound 6d in $CDCl_3$



^{1}H NMR of Compound 6e in $CDCl_3$



^{13}C NMR of Compound 6e in $CDCl_3$

4.3.6. References

1. Larock, R. C.; Babu, S. *Tetrahedron Lett* **1987**, *28*, 5291.
2. Chauhan, P. M.; Srivastava, S. K. Comb Chem High Throughput Screen. **2001**, *4*, 35.
3. Butler, M. S. *J Nat Prod*, **2004**, *67,* 2141.
4. Banday, A. H.; Bhupinder, S. A.; Alam, M. S.; Kumar, H. M. S. *Helv Chem Acta*, **2007**, *90*, 2368.
5. Gallardo, H.; Conte, G.; Bryk, F.; Lourenço, M. C. S.; Costa, M.S.; Ferreira, V.F.; *J. Braz. Chem. Soc.* **2007**, *18*, 1285.
6. Lenda, F.; Guenoun, F.; Martinez, J.; Lamaty, F. *Tetrahedron Lett.* **2007**, 48, 805.
7. Whiting, M.; Tripp, J. C.; Lin, Y.-C.; Lindstrom, W.; Olson, A. J.; Elder, J. H. Sharpless, K. B.; Fokin, V. V. *J. Med. Chem*. **2006**, *49*, 7697.
8. Cafici, L.; Pirali, T.; Condorelli, F.; Del Grosso, E.; Massarotti, A.; Sorba, G.; Canonico, P. L.; Tron, G. C.; Genazzani, A. A. *J. Comb. Chem.* **2008**, *10*, 732.
9. Alam, M. S.; Huang, J.; Ozoe, F.; Matsumura, F.; Ozoe, Y. *Bioorg. Med. Chem.* **2007**, *15*, 5090.
10. Perion, R.; Ferrieres, V.; Garcia-Moreno, M. I.; Mellet, C.O.; Duval, R.; Fernandez, J. M. G.; Plusquellec, D. *Tetrahedron* **2005**, *61*, 9118.
11. Kolb, H. C.; Sharpless, K. B. *Drug Disc. Today* **2003**, 8, 1128.
12. Bock, V. D.; Speijer, D.; Hiemstra, H.; van Maarseveen, J. H. *Org. Biomol. Chem*. **2007**, *5*, 971.
13. Bennet, I. S.; Brooks, G.; Broom, N. J. P.; Calvert, S. H.; Coleman, K.; Francois, I. *J. Antibiotic*, **1991**, *4*. 969.
14. Bennett, I.; Broom, N. J. P.; Bruton, G.; Calvert, S.; Clarke, B. P.; Coleman, K.; Edmondson, R.; Edwards, P.; Jones, D.; Osborne, N. F.; Walker, G. *J. Antibiotics* **1991**, *44*, 331.
15. Hakimian, S, Cheng-Hakimian, A.; Anderson, G. D.; Miller, J. W. *Expert. Opin. Pharmacother.* **2007**, *12*, 1931.
16. Luzzi, J. K.; Varghese, J. H.; MacDonald, C. I.; Schmidt, E. E.; Kohn, C. Morris, L. V.; Marshall, E. K.; Chamber, F. A.; Groom, C. A. *Angiogenesis* **1999**, *2*, 373.

17. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2001**, *40*, 2004; (b) Meldel, M.; Tornoe, C. W. *Chem. Rev*., **2008**, *108*, 2952; (c) Tron, G. C.; Pirali, T. ; Billington, R. A. ; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev*., **2008**, *28*, 278; (d) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org Chem*., **2002**, *67*, 3057; (e) Yoon, J., Ryu, J. S. *Bioorg. Med. Chem. Lett*., **2010**, *20*, 3930.

18. Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc*., **2005**, *127*, 210.

4.4. SECTION D

Synthesis and antimycobacterial activity of new chalcone-spirochromone conjugates

4.4.1. Introduction

The concept of "molecular hybridization" usually involves the combination of two or more pharmacophores or structural units either linked with one another or fused together to create a new chemical entity.[1] The selection of pharmacophores is based upon their known bioprofiles, as the resulting hybrid structures are expected to possess superior pharmacological properties.[2] Hence, the development of strategies that can provide easy access to hybrid structures are very important. In this context, we planned a strategy to generate a library based on chromone motif by incorporating chalcone moiety with the privileged spirochromone scaffold. The selection of chalcone nucleus stems from the fact that this chalcone moiety is present in plethora of natural and synthetic compounds which possessing wide range of biological activities such as anti-inflammatory,[3] antifungal,[4] antibacterial,[5] antimalarial,[6] antitumor[7] and antitubercular[8] activities. Further, relatively simple structure, good safety profile, possibility of oral administration,[9] and easy synthesis are the major factors for the interest in exploring this scaffold. Importantly, many of the naturally occurring chalcones possess anti-TB property (Fig. 1).

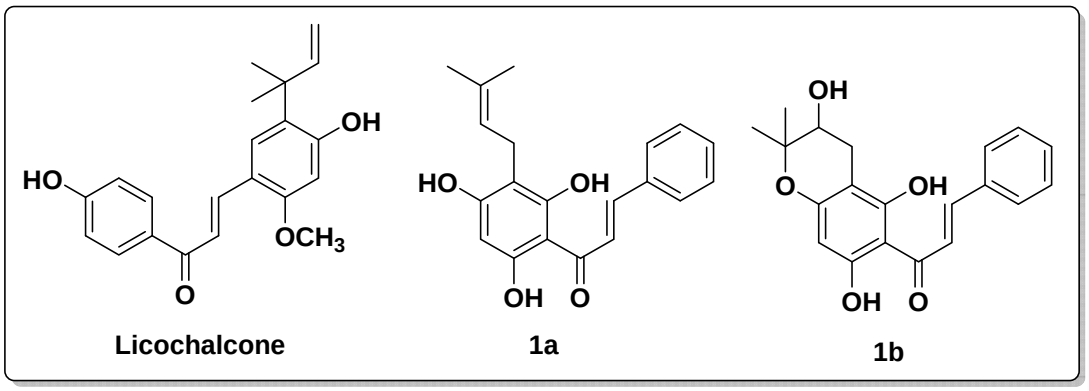


Figure 1. Few naturally occurring chalcones possessing anti-TB activity

So, in the present study we have designed and synthesized a series of novel spirochromone based chalcone conjugates and evaluated their anti-TB potential.

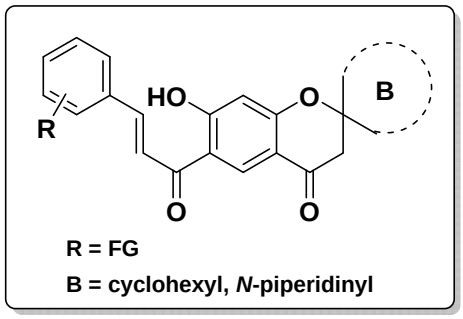
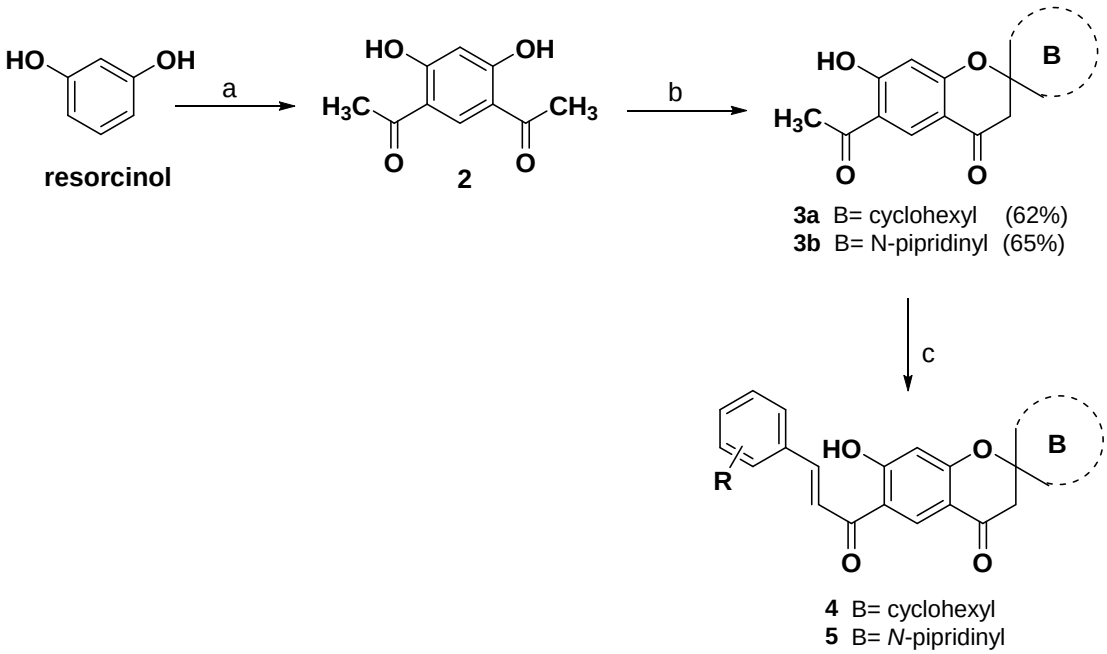


Figure 2. Design of spirochromone annulated chalcone conjugates

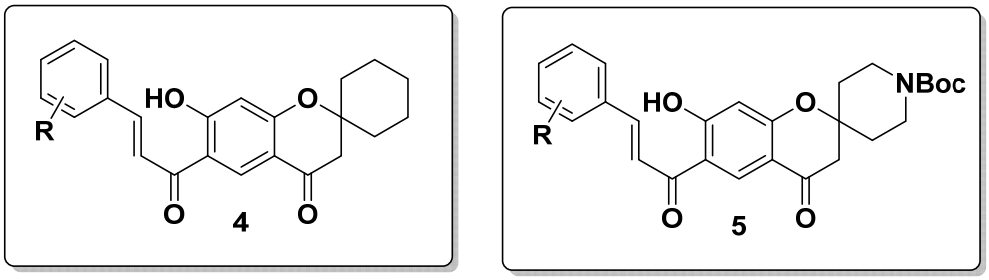
4.4.2. Results and Discussions

Chemistry

The synthetic strategy followed for the preparation of chalcone fused spirochromone conjugates is depicted in Scheme 1. Readily available resorcinol on heating with acetic anhydride in the presence of anhydrous zinc chloride provided 4,6-diacetyl resorcinol intermediate **2** in 75% yield.[10] The diacetyl compound **2** on Kabbe condensation with cyclohexanone/*N*-Boc piperidone using pyrrolidine as a base under Dean-Stark condition provided spirochromone derivative **3a,b** in good yields. Finally, spirochromone derivatives **3a,b** on treatment with various aromatic aldehydes using 50% aq. KOH provided chalcone fused spirochromone conjugates **4a-g** & **5a-i** in moderate to good yields. The structure of all the new compounds (14 compounds) were confirmed by the IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. In the Nuclear Magnetic Resonance (^{1}H NMR) spectra (compound **4h** as a representative example), a signal corresponding to the *C*-3 protons of chromanone skeleton was observed as a singlet at δ 2.73 ppm and the corresponding ^{13}C resonance signal was observed at 47.8 ppm. In the ^{13}C NMR spectrum, the spirocarbon was discernible at δ 81.4 ppm. Further, the appearance of signals corresponds to two sets of protons at δ 7.61 & 7.87 with coupling constant 15.4 Hz, confirms the formation of *trans*-chalcone nucleus.



Scheme 1. *Reagents and conditions*: (a) Ac_2O, $ZnCl_2$, 140ºC, 30 min, 75%; (b) Cyclohexanone/N-Boc-piperidone, pyrrolidine, toluene, reflux, 12 h; (c) aromatic aldehyde, 50 % KOH, MeOH.



	R	
4a	4-F	(68%)
4b	2-F	(72%)
4c	2-Cl	(65%)
4d	4-OMe	(65%)
4e	2, 4-dimethoxy	(78%)
4f	3-methoxy	(75%)
4g	3,4-methylenedioxy	(76%)

	R	
5a	C_6H_5	(80%)
5b	2-F	(74%)
5c	2-Cl	(70%)
5d	3-OMe	(64%)
5e	4-OMe	(65%)
5f	2, 4-dimethoxy	(71%)
5g	2,5-dimethoxy	(72%)

The appearance of a sharp signal (1H) at δ 13.50 ppm in ^{1}H NMR suggesting the presence of one chelated hydroxy group. This assignment was further confirmed by carbon resonance at δ 190.6 in the ^{13}C NMR spectrum. In addition, two sharp singlets at δ 6.52 & 8.57 and four multiplets around δ 6.98, 7.19 & 7.28 corresponds to aromatic protons. Conclusive evidence for its structure was obtained from single-crystal X-ray analysis (Compound **4f**: Fig. 3).

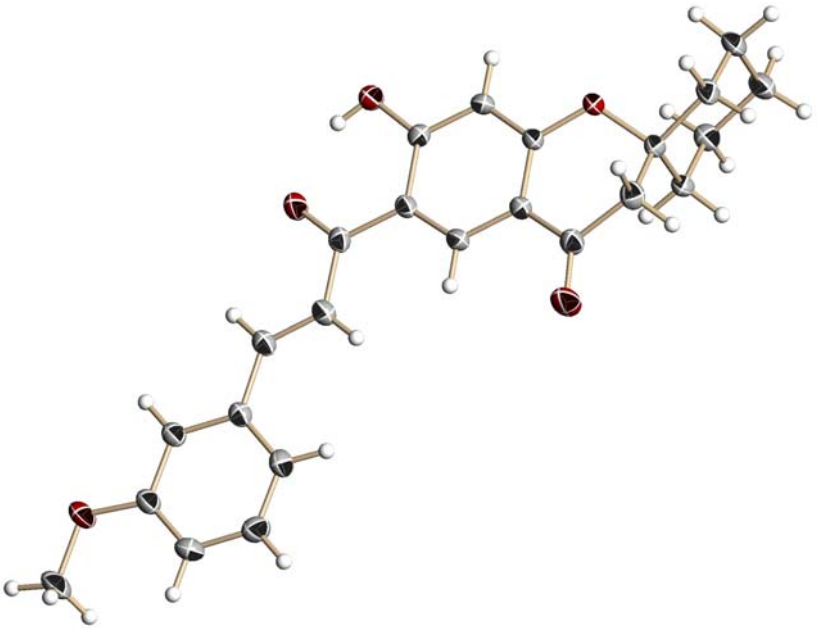
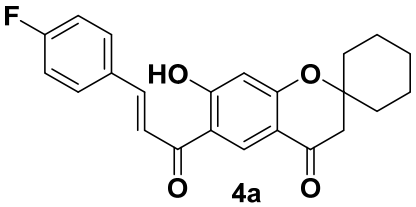
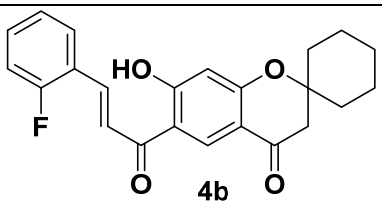
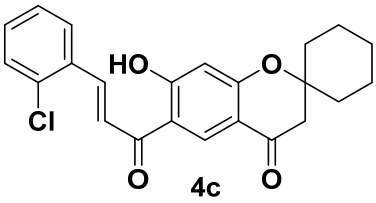
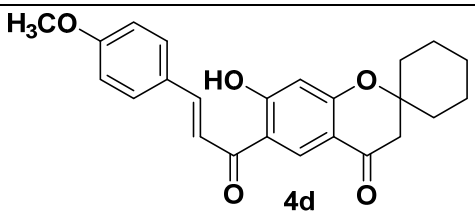
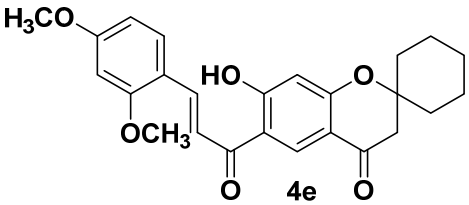
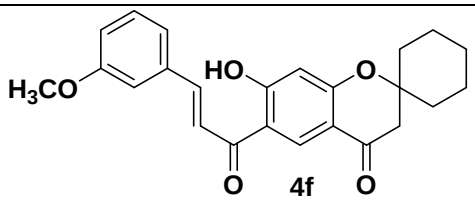
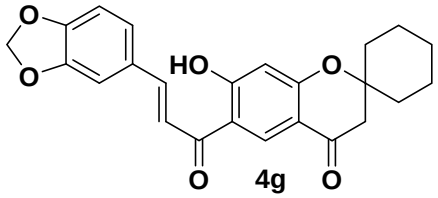
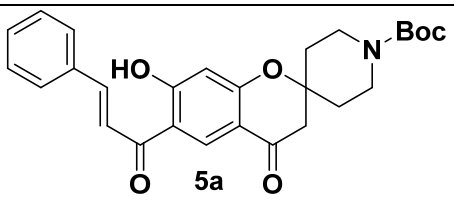


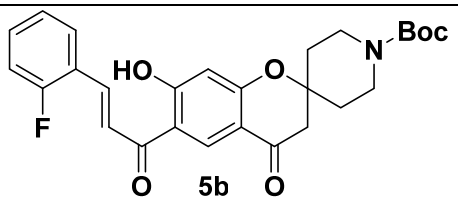
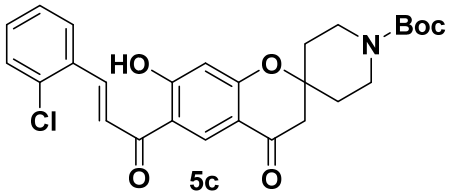
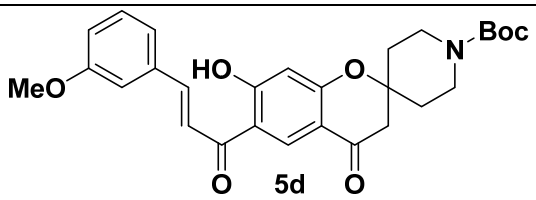
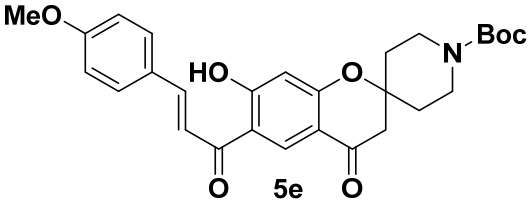
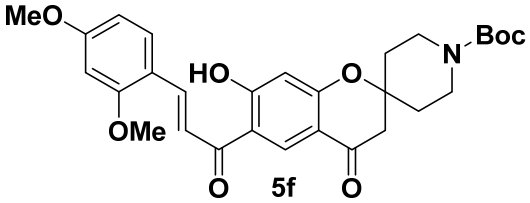
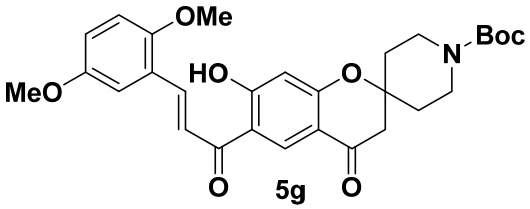
Figure 3. ORTEP diagram of the compound **4f** (thermal ellipsoids are drawn at 50% probability level)

Anti-mycobacterial activity

All the new chalcone fused spirochromone conjugates were screened for their in vitro antimycobacterial activity against M. tuberculosis H37Rv (ATCC27294) using an agar dilution method. The minimum inhibitory concentration (MIC; µg/mL) was determined for each compound. The MIC is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. Rifampicin and ethambutol were used as reference compounds. The MIC values of the synthesized compounds along with the standard drugs for comparison were reported in Table 1. Among the 14 synthesized compounds, the compound **5b**, is found to be more active having MIC 3.13 µg/mL among all the compounds screened. Preliminary structure activity relationship of the chalcone fused spirochromone conjugates reveals that compounds possessing piperidinyl moiety at 2nd position of the chromone ring favors better activity than cycloalkyl group. Furthermore, halide substitution at aromatic ring, especially fluoro substitution at aromatic ring showed better activity. It is also observed that the presence of methoxy substitution at aromatic ring does not favor the activity.

Table 1. *In vitro* antimycobacterial activity of the chalcone fused spirochromone conjugates

Sr.No	Compound	MIC (μg/mL)
1		12.5
2		12.5
3		25
4		>25
5		>25
6		>25
7		>25
8		>25

9	 5b	**3.13**
10	 5c	12.5
11	 5d	25
12	 5e	25
13	 5f	25
14	 5g	>25
15	**Rifampicin**	0.2
16	**Ethambutol**	1.56

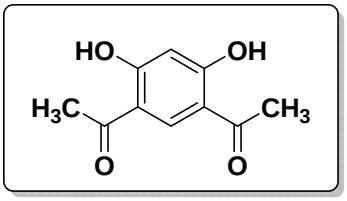
4.4.3. Conclusion

In conclusion, a series of chalcone fused spirochromone conjugates were synthesized for the first time using a simple protocol starting from resorcinol. All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR and MS spectra analysis. In vitro antimycobacterial evaluation of these compounds exhibited moderate to good

antimycobacterial activity. Noticeably, compound **5b** is most potent compound *in vitro* with MIC of 3.13 µg/mL, against MTB. SAR studies as well as attempts to expand the library of compounds to get more potent analogues is in progress.

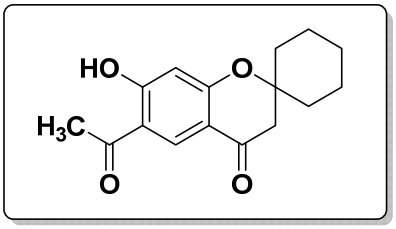
4.4.4. Experimental

1) 1,1'-(4,6-dihydroxy-1,3-phenylene)bis(ethan-1-one) (2)



To a mixture of resorcinol (5.00 g, 45.5 mmol) and acetic anhydride (9.28 g, 91.0 mmol) was added zinc chloride (10.0 g, 73.4 mmol) and the resulting mixture was heated at 140 ºC for 30 minutes. The hot mixture was allowed to attain ambient temperature followed by addition of 50% dilute HCl (140 mL) and the solution was allowed to stand for 1 h. The orange crude product was obtained by filtration with suction, washed with distilled water till the color of the filtrate is nearly colorless. The crude product was crystallized using ethanol to yield 4,6-diacetylresorcinol **2** (6.6 g, 75%), m.p. 178-79 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 2.64 (s, 6H), 6.42 (s, 1H), 8.21 (s, 1H), 12.93 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 202.4 (CO, 2 carbons), 168.8 (C, 2 carbons), 136.2 (CH), 113.5 (C, carbons), 104.9 (CH), 26.0 (CH_3, 2 carbons).

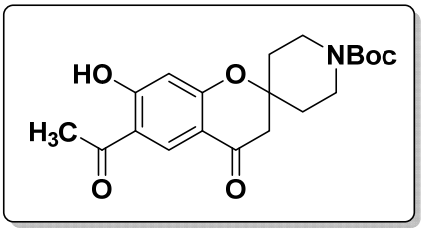
2) 6-acetyl-7-hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (3a)



To a solution of **2** (5 g, 24.7 mmol) in ethanol (20 mL) was added cyclohexanone (6 mL, 49.0 mmol) followed by addition of pyrollidine (5.7 mL, 49.0 mmol) and the resulting mixture was refluxed using Dean-Stark apparatus for 12 h. After completion of the reaction solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 1N HCl followed by dilute $NaHCO_3$, brine and concentrated. The crude product was purified using column

chromatography (silica gel, pet ether/ ethyl acetate, 95:5) to yield **3a** (4.2 g, 62%) as a colorless solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.44-1.75 (m, 8H), 1.94-2.03 (m, 2H), 2.63 (s, 3H), 2.70 (s, 2H), 6.48 (s, 1H), 8.36 (s, 1H), 12.82 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 203.3 (CO), 190.5 (CO), 168.6 (C), 165.1 (C), 131.8 (CH), 115.0 (C), 113.9 (C), 105.1 (CH), 81.3 (C), 47.7 (CH_2), 34.9 (CH_2, 2 carbons), 26.4 (CH_3), 24.9 (CH_2), 21.3, (CH_2, 2 carbons); 297 $(M+Na)^+$.

3) *tert*-butyl 6-acetyl-7-hydroxy-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (3b)



The same procedure as in the preparation of **3a** was used with the *N*-Boc piperidone (5.9 g, 29.5 mmol) affording spirocompound **3b** as a colorless solid (7.1 g, 65%); m.p. 181-82 ºC. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.46 (s, 9H), 1.56-1.71 (m, 2H), 1.97-2.04 (m, 2H), 2.64 (s, 3H), 2.72 (s, 2H), 3.16-3.27 (m, 2H), 3.88-3.92 (m, 2H), 6.48 (s, 1H), 8.38 (s, 1H), 12.85 (s, 1H);^{13}C NMR ($CDCl_3$): δ 203.6(CO), 189.4 (CO), 168.8 (C), 164.4 (C), 154.5 (C), 131.9 (CH), 115.3 (C), 113.7 (C), 105.2 (CH), 79.8 (C), 79.1 (C), 47.6 (CH_2), 34.2 (CH_2), 28.3 (CH_3, 3 carbons), 26.4 (CH_3).

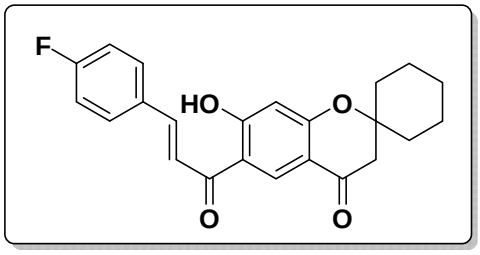
4) Synthesis of chalcone fused spirochromone derivatives (4-5):

General procedure:

To a well-stirred mixture of (**3a** or **3b**) (0.7 mmol) and substituted aldehydes (0.77 mmol) in methanol (3 mL) at room temperature was slowly added 50% KOH solution (5 mL) dropwise. The resulting reaction mixture was stirred for 12 h at 60 ºC. After completion of the reaction (by TLC), solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with 5% HCl followed by brine, dried and concentrated. The residue was purified by column chromatography (silica gel, pet ether/ ethyl acetate, 75:25) to yield pure product **4-5**.

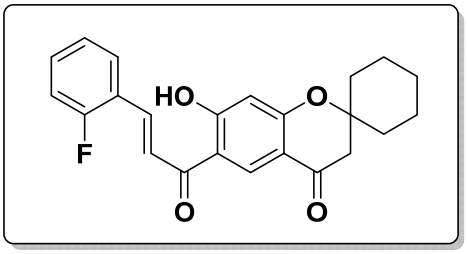
Spectroscopic data for all the compounds are given below.

(*E*)-6-(3-(4-fluorophenyl)acryloyl)-7-hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (4a)



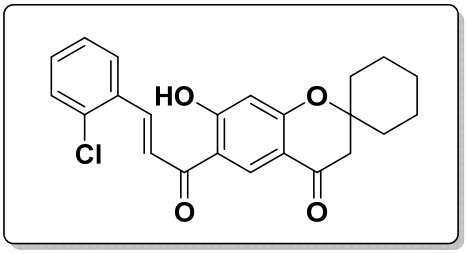
Yellow solid; m.p. 156-57 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.46-1.77 (m, 8H), 1.97-2.05 (m, 2H), 2.73 (s, 2H), 6.50 (s, 1H), 6.95-7.19 (m, 2H), 7.51 (dd, *J* = 15.4, 9.3 Hz, 1H), 7.65-7.74 (m, 2H), 7.86 (dd, 15.4, 3.1Hz, 1H), 13.5 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.3, 190.6 (CO), 169.9 (C), 165.2 (C), 161.8 (C), 144.4 (CH), 130.9 (CH, 2 carbons), 130.7 (CH), 130.6 (C), 119.2 (CH), 116.4 (CH, 2 carbons), 115.2 (C), 113.9 (C), 105.4 (CH), 81.4 (C), 47.8 (CH_2), 35.0 (CH_2, 2 carbons), 24.9 (CH_2), 21.3 (CH_2, 2 carbons); MS: *m/z* 380 (M^+), 393 $(M+Na)^+$.

(*E*)-6-(3-(2-fluorophenyl)acryloyl)-7-hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (4b)



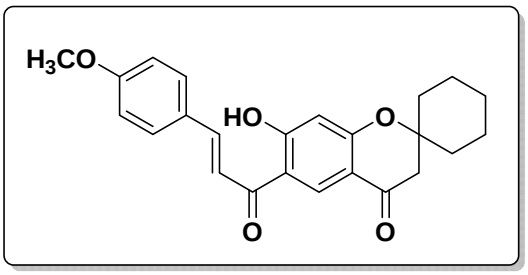
Yellow solid; m.p. 188-89 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.46-1.77 (m, 8H), 1.97-2.03 (m, 2H), 2.73 (s, 2H), 6.50 (s, 1H), 6.95-7.24 (m, 2H), 7.38-7.49 (m, IH), 7.69-7.82 (m, 2H), 8.03 (d, 15.4, 1H), 8.55 (s, 1H), 13.49 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.6, 190.6 (CO), 170.0 (C), 165.3 (C), 159.3 (C), 138.2 (CH), 132.4 (CH), 130.8 (CH), 129.5(CH), 124.6 (CH), 122.0 (CH), 121.9 (C), 116.1 (CH), 115.3 (C), 114.0 (C), 105.4 (CH), 81.5 (C), 47.8 (CH_2), 35.1 (CH_2, 2 carbons), 25.0 (CH_2), 21.4 (CH_2, 2 carbons); MS: *m/z* 381 $(M+H)^+$.

(*E*)-6-(3-(2-chlorophenyl)acryloyl)-7-hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (4c)



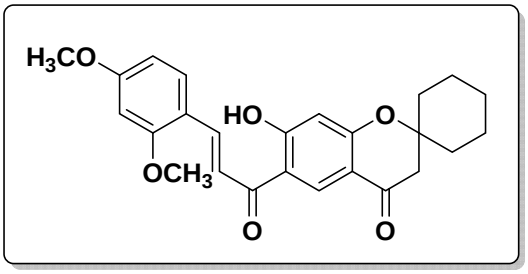
Yellow solid; m.p. 162-63 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.52-1.70 (m, 8H), 1.97-2.03 (m, 2H), 2.73 (s, 2H), 6.52 (s, 1H), 7.34-7.39 (m, 2H), 7.43-7.48 (m, 1H), 7.62 (d, *J* = 15.5 Hz, 1H), 7.82-7.86 (m, 1H), 8.30 (d, *J* = 15.5 Hz, 1H), 8.55 (s, 1H), 13.45 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.2 (CO), 190.6 (CO), 170.0 (C), 165.3 (C), 144.4 (CH), 135.8 (C), 132.7 (C), 131.6 (CH), 130.7 (CH), 130.3 (CH), 128.0 (CH), 127.1(CH), 122.0 (CH), 115.2 (C), 113.9 (C), 105.4 (CH), 81.4 (C), 47.8 (CH_2), 35.0 (CH_2, 2 carbons), 24.9 (CH_2), 21.3 (CH_2, 2 carbons); MS: *m/z* 396 (M^+).

(*E*)-7-hydroxy-6-(3-(4-methoxyphenyl)acryloyl)spiro[chromane-2,1'-cyclohexan]-4-one (4d)



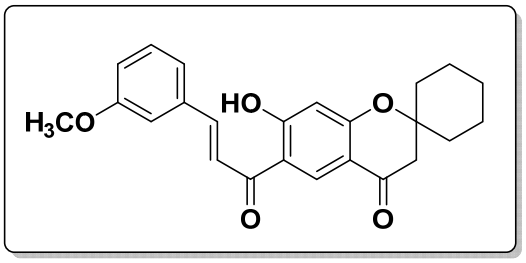
Yellow solid; m.p. 164-65 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47-1.67 (m, 8H), 1.96-2.03 (m, 2H), 2.72 (s, 2H), 3.87 (s, 3H), 6.50 (s, 1H), 6.94 (dd, *J* = 8.8, 2.8 Hz, 2H), 7.50 (d, *J* = 15.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.87 (dd, *J* = 15.2, 8.0 Hz, 1H), 8.55 (s, 1H), 13.73 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.5 (CO), 190.7 (CO), 170.0 (C), 165.0 (C), 162.1 (C), 145.7 (CH), 130.8 (CH, 2 carbons), 130.7 (CH), 127.1 (C), 116.8 (CH), 115.3 (C), 114.5 (CH, 2 carbons), 113.8 (C), 105.3 (CH), 81.3 (C), 55.4 (CH_3), 47.8 (CH_2), 35.0 (CH_2, 2 carbons), 24.9 (CH_2), 21.3 (CH_2, 2 carbons); MS: *m/z* 393 $(M+H)^+$.

(*E*)-6-(3-(2,4-dimethoxyphenyl)acryloyl)-7-hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (4e)



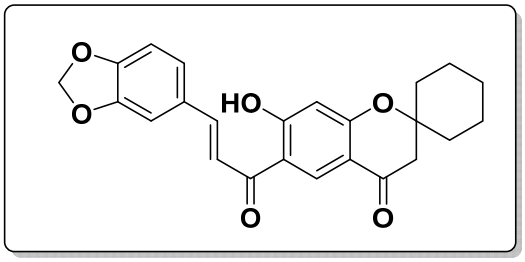
Yellow solid; m.p. 215-16 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.51-1.77 (m, 8H), 1.97-2.03 (m, 2H), 2.71 (s, 2H), 3.88 (s, 3H), 3.93 (s, 3H), 6.48-6.49 (m, 2H), 6.54 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 15.6 Hz, 1H), 8.56 (s, 1H), 13.88 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 193.1 (CO), 190.7 (CO), 170.1 (C), 164.9 (C), 163.6 (C), 160.7 (C), 141.4 (CH), 131.3 (CH), 130.5 (CH), 117.3 (CH), 116.7 (C), 115.6 (C), 113.7 (C), 105.6 (CH), 105.2 (CH), 98.4 (CH), 81.2 (C), 55.6 (CH_3), 55.5 (CH_3), 47.9 (CH_2), 35.1 (CH_2, 2 carbons), 25.0 (CH_2), 21.4 (CH_2, 2 carbons); MS: *m/z* 423 $(M+H)^+$.

(*E*)-7-hydroxy-6-(3-(3-methoxyphenyl)acryloyl)spiro[chromane-2,1'-cyclohexan]-4-one (4f)



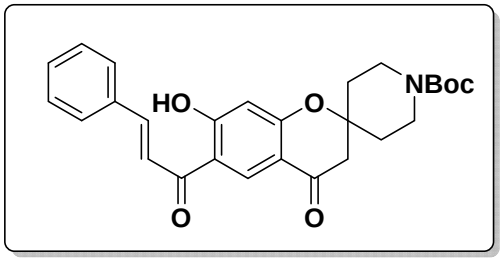
Yellow solid; m.p. 140-41 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.48-1.70 (m, 8H), 1.97-2.04 (m, 2H), 2.73 (s, 2H), 3.90 (s, 3H), 6.52 (s, 1H), 6.98-7.04 (m, 1H), 7.19-7.20 (m, 1H), 7.28-7.42 (m, 2H), 7.61 (d, *J* = 15.4 Hz, 1H), 7.87 (d, *J* = 15.4 Hz, 1H), 8.57 (s, 1H), 13.50 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.6 (CO), 190.6 (CO), 170.0 (C), 165.2 (C), 160.0 (C), 145.8 (CH), 130.7 (CH), 130.0 (CH), 121.5 (CH), 121.4 (C), 119.8 (CH), 117.1 (C), 117.0 (CH), 113.9 (C), 113.6 (CH), 105.4 (CH), 81.4 (C), 55.4 (CH_3), 47.8 (CH_2), 35.0 (CH_2, 2 carbons), 25.0 (CH_2), 21.3 (CH_2, 2 carbons); MS: *m/z* 393 $(M+H)^+$.

(*E*)-6-(3-(benzo[d][1,3]dioxol-5-yl)acryloyl)-7-hydroxyspiro[chromane-2,1'-cyclohexan]-4-one (4g)



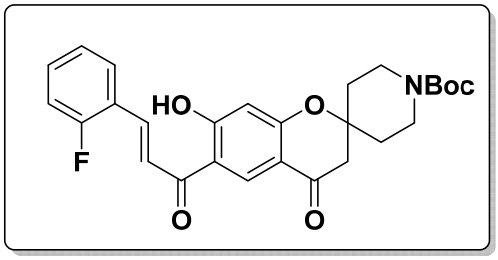
Yellow solid; m.p. 207-08 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.52-1.77 (m, 8H), 1.97-2.03 (m, 2H), 2.73 (s, 2H), 6.06 (m, 2H), 6.51 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.23-7.24 (m, 1H), 7.46 (d, *J* = 15.5 Hz, 1H), 7.82 (d, *J* = 15.5 Hz, 1H), 8.54 (s, 1H), 13.66 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.4 (CO), 190.6 (CO), 170.0 (C), 165.1 (C), 150.4 (C), 148.5 (C), 145.6 (CH), 130.5 (CH), 128.8 (C), 125.8 (CH), 117.4 (CH), 115.3 (C), 113.8 (C), 108.7 (CH), 107.0 (CH), 105.3 (CH), 101.7 (CH_2), 81.3 (C), 47.8 (CH_2), 35.0 (CH_2, 2 carbons), 24.9 (CH_2), 21.3 (CH_2, 2 carbons); MS: *m/z* 407 $(M+H)^+$.

***tert*-butyl 6-cinnamoyl-7-hydroxy-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5a)**



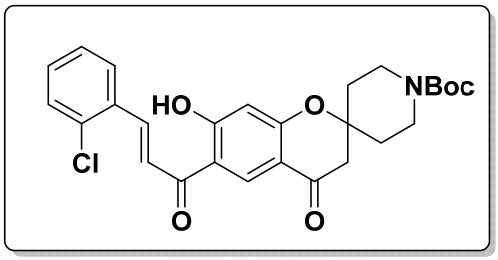
Yellow solid; m.p. 165-66 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.61-1.69 (m, 2H), 1.99-2.04 (m, 2H), 2.75 (s, 2H), 3.22-3.24 (m, 2H), 3.87-3.96 (m, 2H), 6.54 (s, 1H), 7.46-7.47 (m, 3H), 7.66-7.72 (m, 3H), 7.94 (d, *J* = 15.5 Hz, 1H), 8.59 (s, 1H), 13.58 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.6 (CO), 189.6 (CO), 170.2 (C), 164.4 (C),154.6 (CO), 148.1 (CH), 134.3 (C), 131.2 (CH), 130.8 (CH), 129.0 (CH, 2 carbons), 128.9 (CH, 2 carbons), 119.3 (CH), 115.7 (C), 113.7 (C), 105.5 (CH), 79.9 (C), 79.2 (C), 47.7 (CH_2, 2 carbons), 47.6 (CH_2), 34.2 (CH_2, 2 carbons), 28.3 (CH_3, 3 carbons); MS: *m/z* 464 $(M+H)^+$.

***tert*-butyl (*E*)-6-(3-(2-fluorophenyl)acryloyl)-7-hydroxy-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5b)**



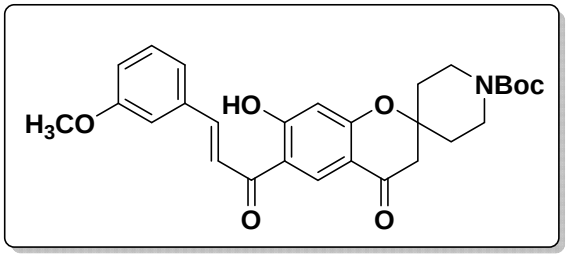
Yellow solid; m.p. 174-75 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.63-1.69 (m, 2H), 2.01-2.05 (m, 2H), 2.75 (s, 2H), 3.21-3.24 (m, 2H), 3.89-3.90 (m, 2H), 6.54 (s, 1H), 7.14-7.25 (m, 2H), 7.42-7.47 (m, 1H), 7.71-7.78 (m, 2H), 8.06 (d, *J* = 15.4 Hz, 1H), 8.57 (s, 1H), 13.50 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.6 (CO), 189.5 (CO), 170.1 (C), 164.5 (C), 160.5 (C), 154.6 (CO), 138.5 (CH), 130.9 (C), 129.6 (CH), 124.6 (CH), 122.4 (C), 121.8 (CH), 116.4 (CH), 116.2 (CH) 115.6 (C), 113.7 (C), 105.5 (CH), 79.9 (C), 79.2 (C), 47.7 (CH_2, 3 carbons), 34.3 (CH_2, 2 carbons), 28.3 (CH_3, 3 carbons); MS: *m/z* 481 (M^+).

***tert*-butyl (*E*)-6-(3-(2-chlorophenyl)acryloyl)-7-hydroxy-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5c)**



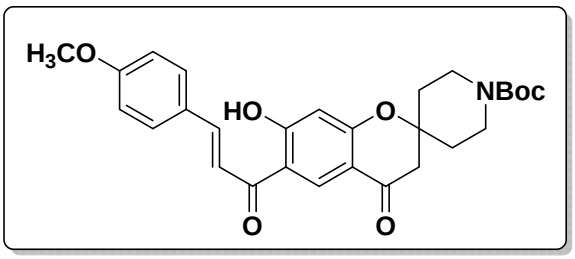
Yellow solid; m.p. 183-84 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.58-1.73 (m, 2H), 2.00-2.05 (m, 2H), 2.75 (s, 2H), 3.17-3.29 (m, 2H), 3.88-3.93 (m, 2H), 6.55 (s, 1H), 7.36-7.50 (m, 3H), 7.61 (d, *J* = 15.5 Hz, 1H), 7.82-7.87 (m, 1H), 8.33 (d, *J* = 15.5 Hz, 1H), 8.57 (s, 1H), 13.49 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.3 (CO), 189.5 (CO), 170.1 (C), 164.5 (C), 159.3 (C), 154.6 (CO), 141.7 (CH), 135.8 (C), 132.6 (C), 131.8 (CH), 130.9 (CH), 130.4 (CH), 128.0 (CH), 127.2 (CH), 121.9 (CH), 113.7 (C), 105.5 (CH), 79.9 (C), 79.2 (C), 47.7 (CH_2, 3 carbons), 34.3 (CH_2, 2 carbons), 28.3 (CH_3, 3 carbons); MS: *m/z* 498 $(M+H)^+$.

***tert*-butyl (*E*)-7-hydroxy-6-(3-(3-methoxyphenyl)acryloyl)-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5d)**



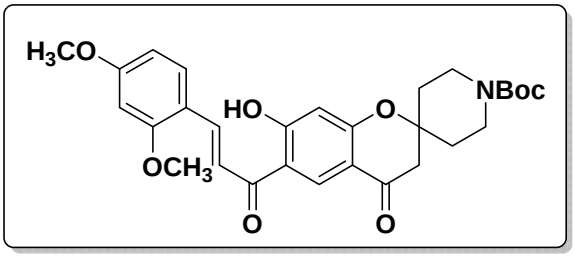
Yellow solid; m.p. 162-63 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.61-1.67 (m, 2H), 2.00-2.07 (m, 2H), 2.73 (s, 2H), 3.16-3.29 (m, 2H), 3.84-3.89 (m, 5H), 6.52 (s, 1H), 6.96-7.02 (m, 1H), 7.17-7.20 (m, 1H), 7.31-7.41 (m, 2H), 7.59 (d, *J* = 15.2 Hz, 1H), 7.87 (d, *J* = 15.2 Hz, 1H), 8.56 (s, 1H), 13.56 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.6 (CO), 189.5 (CO), 170.2 (C), 164.5 (C), 160.3 (C), 154.6 (CO), 146.2 (CH), 135.6 (CH), 130.8 (CH), 130.0 (CH), 121.5 (CH), 119.6 (C), 117.1 (CH), 115.7 (C), 113.7 (CH), 113.7 (C), 105.5 (CH), 79.9 (C), 79.2 (C), 55.4 (CH_3), 47.7 (CH_2, 3 carbons), 34.3 (CH_2, 2 carbons), 28.3 (CH_3, 3 carbons); MS: *m/z* 494 $(M+H)^+$.

***tert*-butyl (*E*)-7-hydroxy-6-(3-(4-methoxyphenyl)acryloyl)-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5e)**



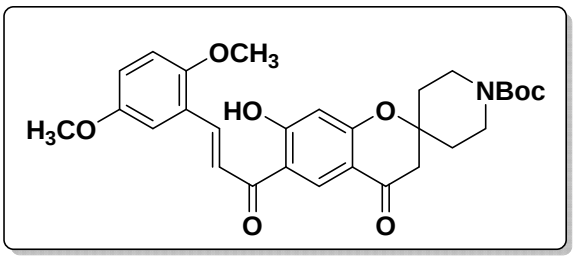
Yellow solid; m.p. 176-77 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.60-1.73 (m, 2H), 2.00-2.06 (m, 2H), 2.74 (s, 2H), 3.18-3.29 (m, 2H), 3.89-3.90 (m, 5H), 6.53 (s, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 15.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 15.7 Hz, 1H), 8.58 (s, 1H), 13.76 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 192.5 (CO), 189.7 (CO), 170.2 (C), 164.2 (C), 162.2 (C), 154.6 (CO), 146.0 (CH), 130.8 (CH, 2 carbons), 130.6 (CH), 127.0 (C), 116.7 (CH), 115.7 (C), 114.4 (CH, 2 carbons), 113.5 (C), 105.3 (CH), 79.9 (C), 79.0 (C), 55.4 (CH_3), 47.6 (CH_2, 3 carbons), 34.3 (CH_2, 2 carbons), 28.4 (CH_3, 3 carbons); MS: *m/z* 494 $(M+H)^+$.

tert-butyl (_E_)-6-(3-(2,4-dimethoxyphenyl)acryloyl)-7-hydroxy-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5f)



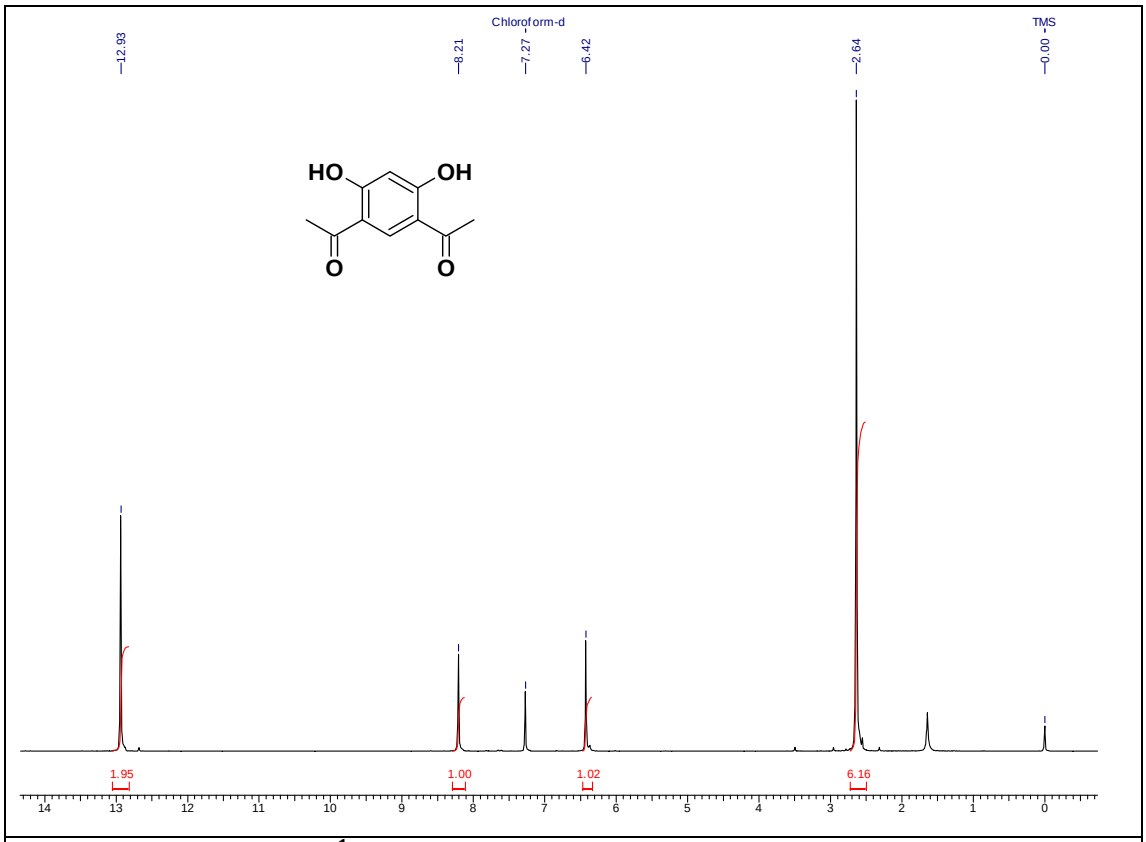
Yellow solid; m.p. 160-61 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.66-1.72 (m, 2H), 1.99-2.05 (m, 2H), 2.73 (s, 2H), 3.16-3.31 (m, 2H), 3.88-3.89 (m, 5H), 3.93 (s, 3H), 6.48-6.49 (m, 1H), 6.51 (s, 1H), 6.54-6.60 (m, 1H), 7.62-7.63 (m, 1H), 7.67 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 15.4 Hz, 1H), 8.57 (s, 1H), 13.93 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 193.0 (CO), 189.7 (CO), 170.3 (C), 164.1 (C), 163.7 (C), 160.7 (C), 154.6 (CO), 141.7 (CH), 131.3 (CH), 130.6 (CH), 116.9 (CH), 116.5 (C), 115.9 (C), 113.5 (C), 105.5 (CH), 105.3 (CH), 98.3 (CH), 79.8 (C), 78.9 (C), 55.6 (CH_3), 55.5 (CH_3), 47.7 (CH_2, 3 carbons), 34.2 (CH_2, 2 carbons), 28.3 (CH_3, 3 carbons); MS: *m/z* 546 $(M+Na)^+$.

tert-butyl (_E_)-6-(3-(2,5-dimethoxyphenyl)acryloyl)-7-hydroxy-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (5g)

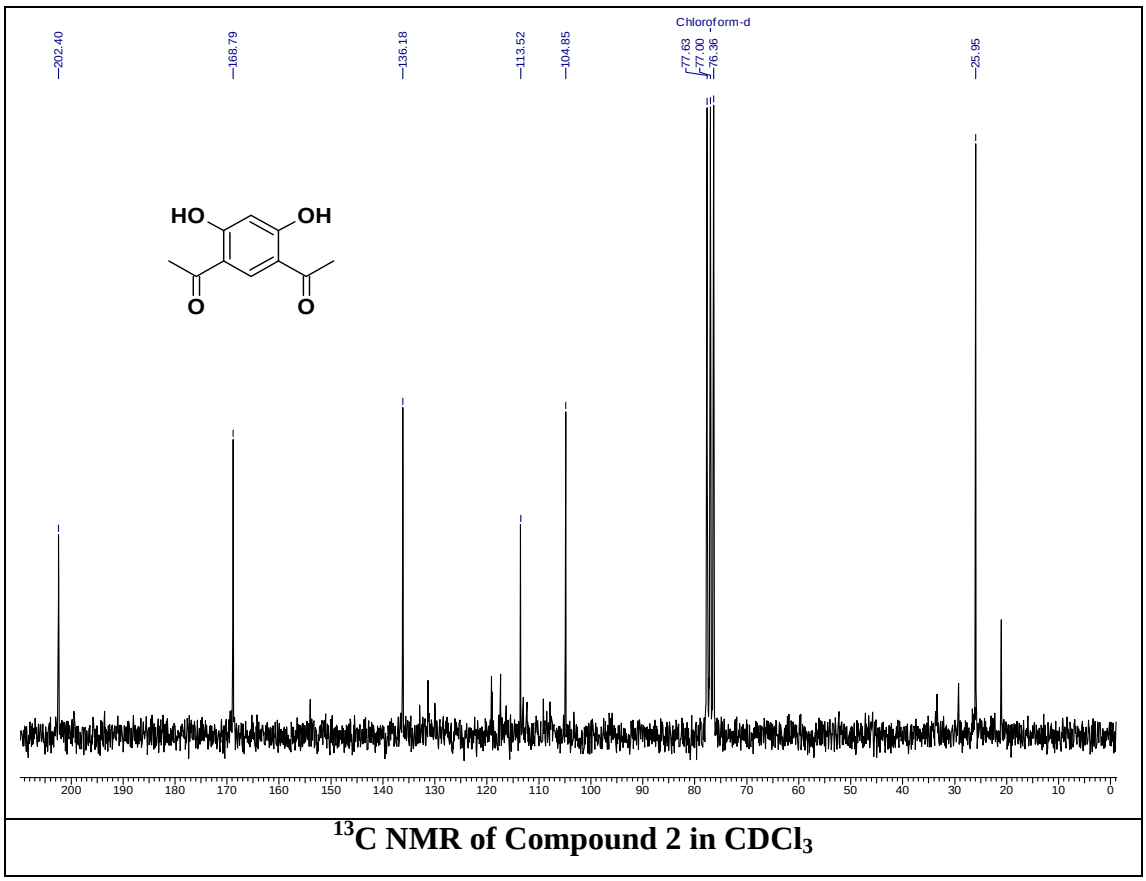


Yellow solid; m.p. 150-51 ºC; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 1.47 (s, 9H), 1.70-1.72 (m, 2H), 2.00-2.07 (m, 2H), 2.74 (s, 2H), 3.16-3.29 (m, 2H), 3.84-3.86 (m, 5H), 3.91 (s, 3H), 6.53 (s, 1H), 6.88-7.03 (m, 3H), 7.19 (d, J = 3.0 Hz, 1H), 7.70 (d, J = 15.4 Hz, 1H), 8.21 (d, J = 15.4 Hz, 1H), 8.59 (s, 1H), 13.72 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 190.0 (CO), 189.5 (CO), 170.1 (C), 164.3 (C), 154.5 (CO), 153.6 (C), 153.4 (C), 141.4 (CH), 130.8 (CH), 123.7 (C), 120.0 (CH), 118.2 (CH), 115.8 (C), 113.7 (CH), 113.6 (C), 112.4 (CH), 105.3 (CH), 79.8 (C), 79.0 (C), 56.0 (CH_3), 55.9 (CH_3), 47.7 (CH_2), 47.6 (CH_2, 2 carbons), 34.2 (CH_2, 2 carbons), 28.3 (CH_3, 3 carbons); MS: *m/z* 546 $(M+Na)^+$.

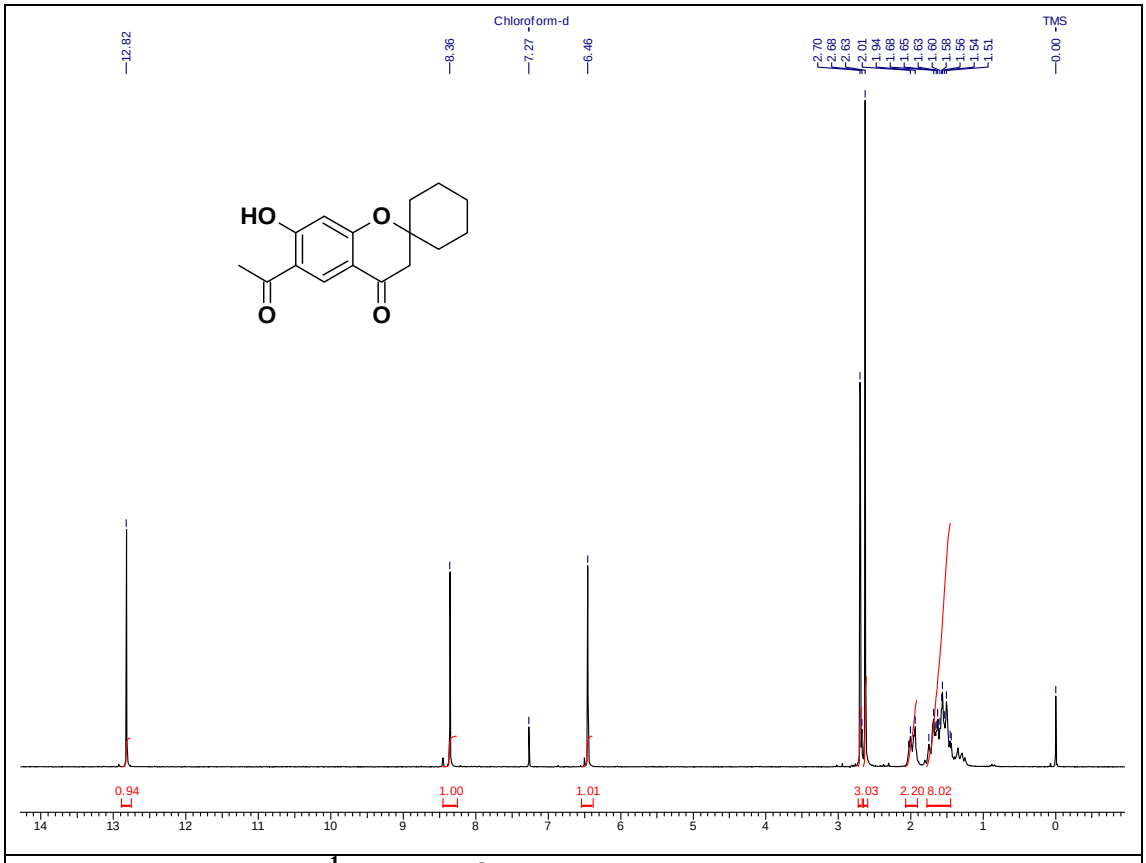
4.2.5. Analytical data



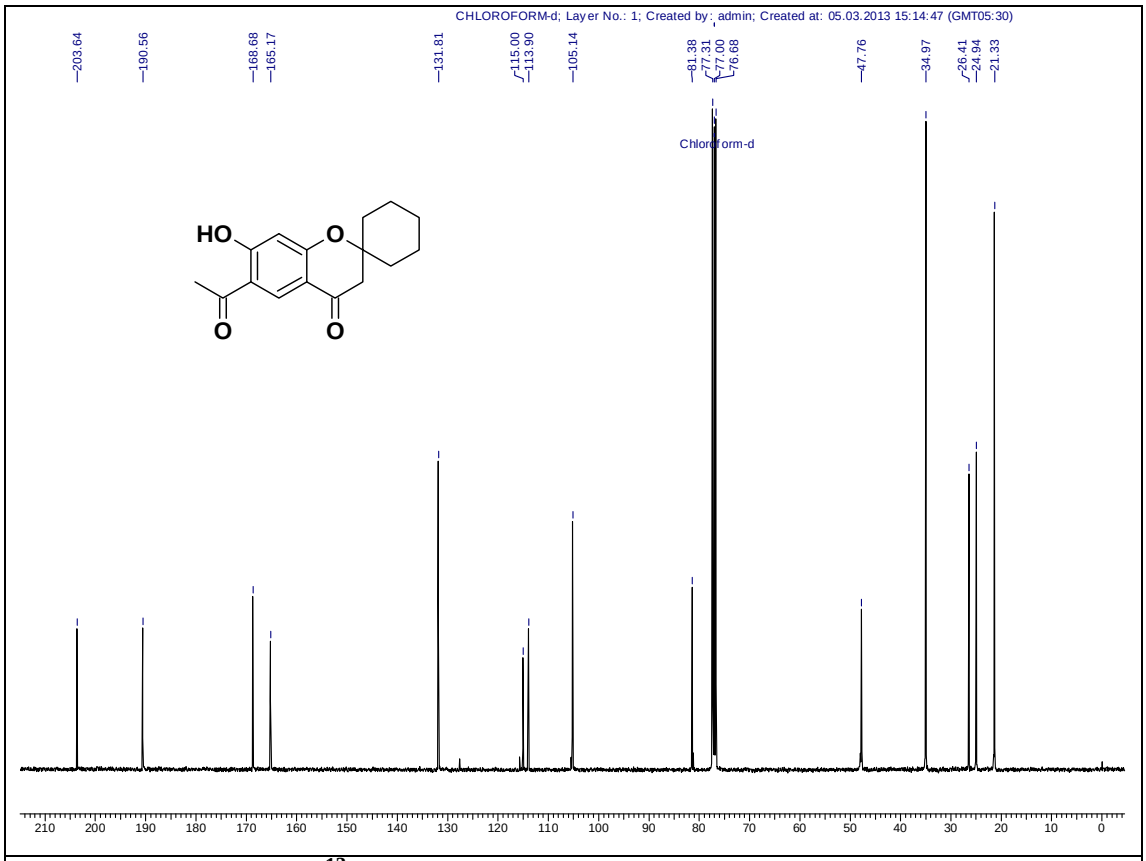
^{1}H NMR of Compound 2 in $CDCl_3$



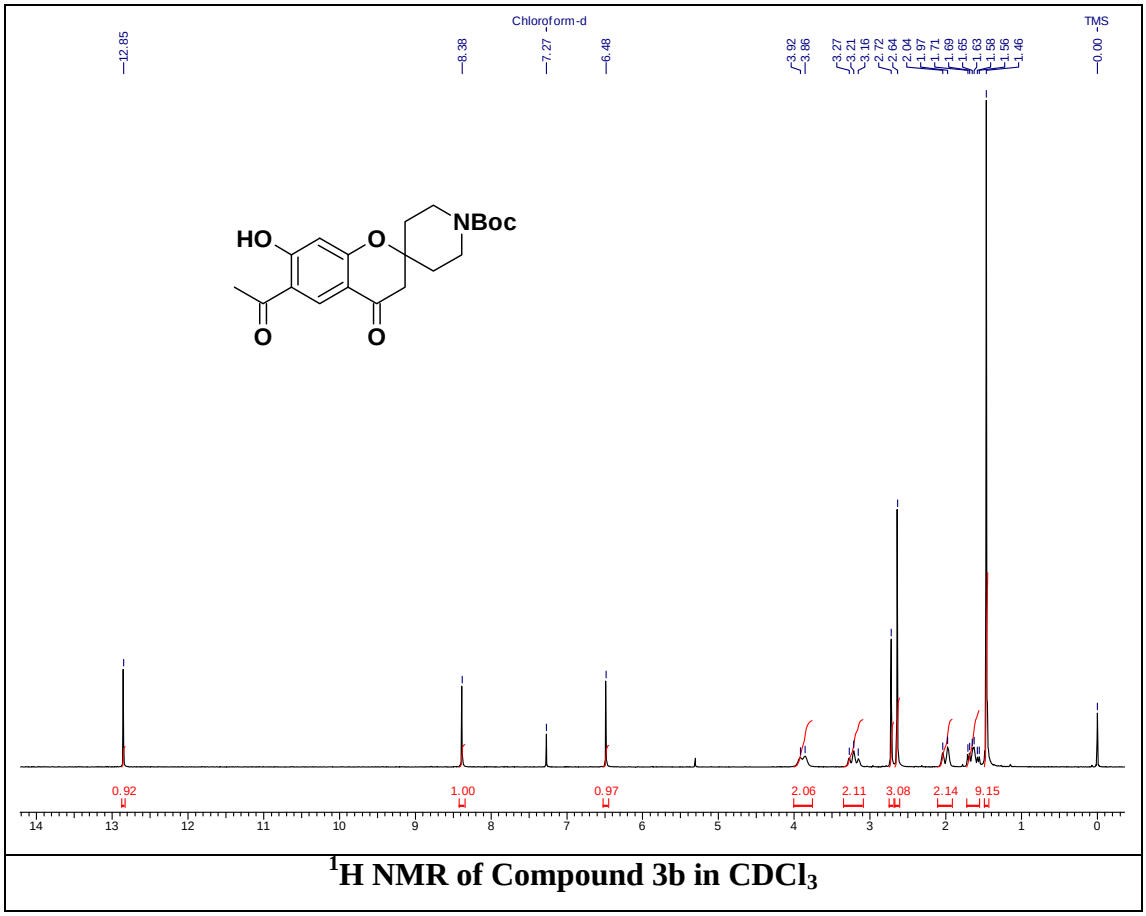
^{13}C NMR of Compound 2 in $CDCl_3$



^{1}H NMR of Compound 3a in $CDCl_3$



^{13}C NMR of Compound 3a in $CDCl_3$



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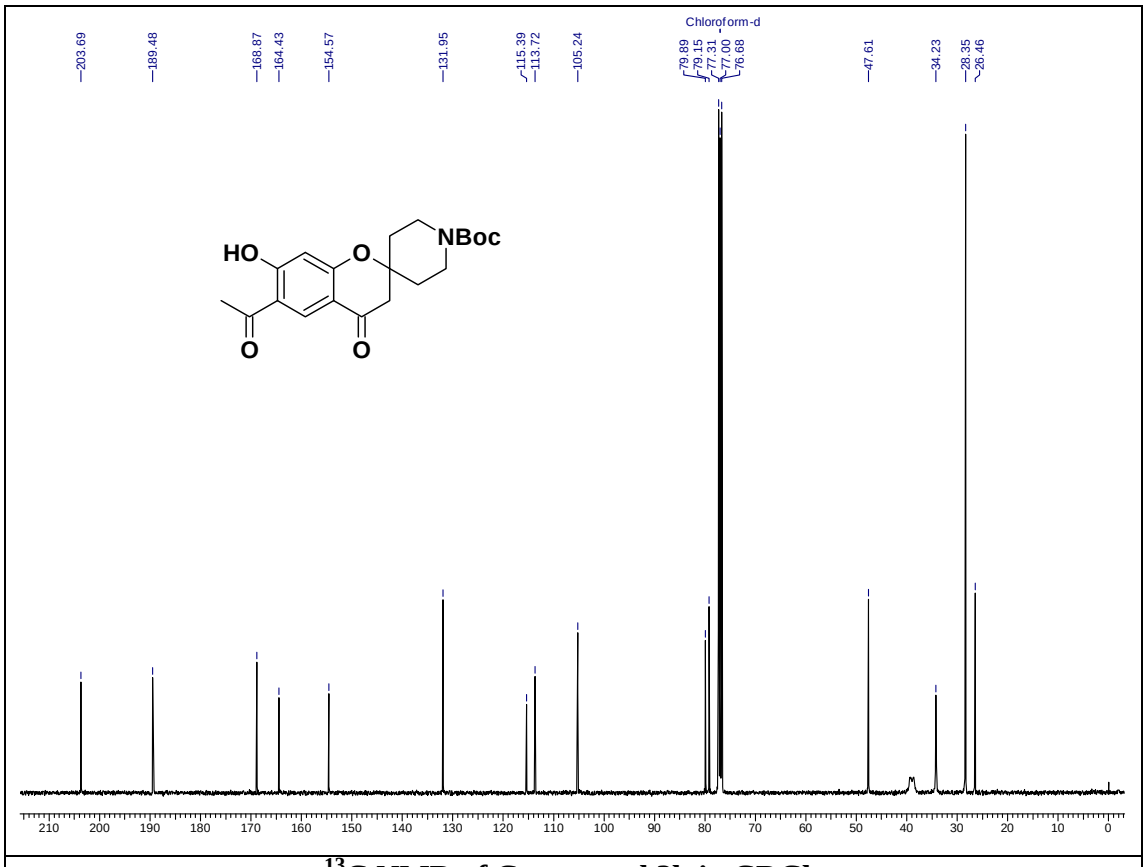
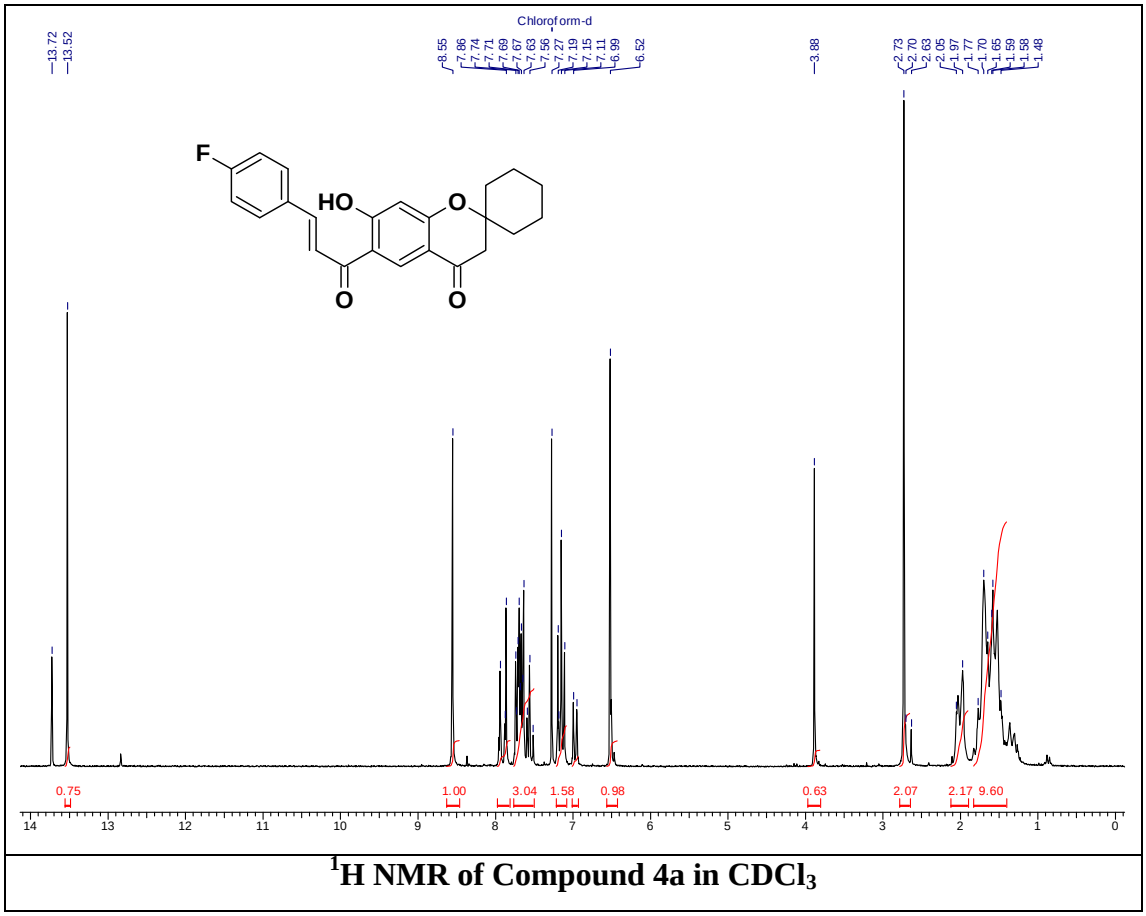
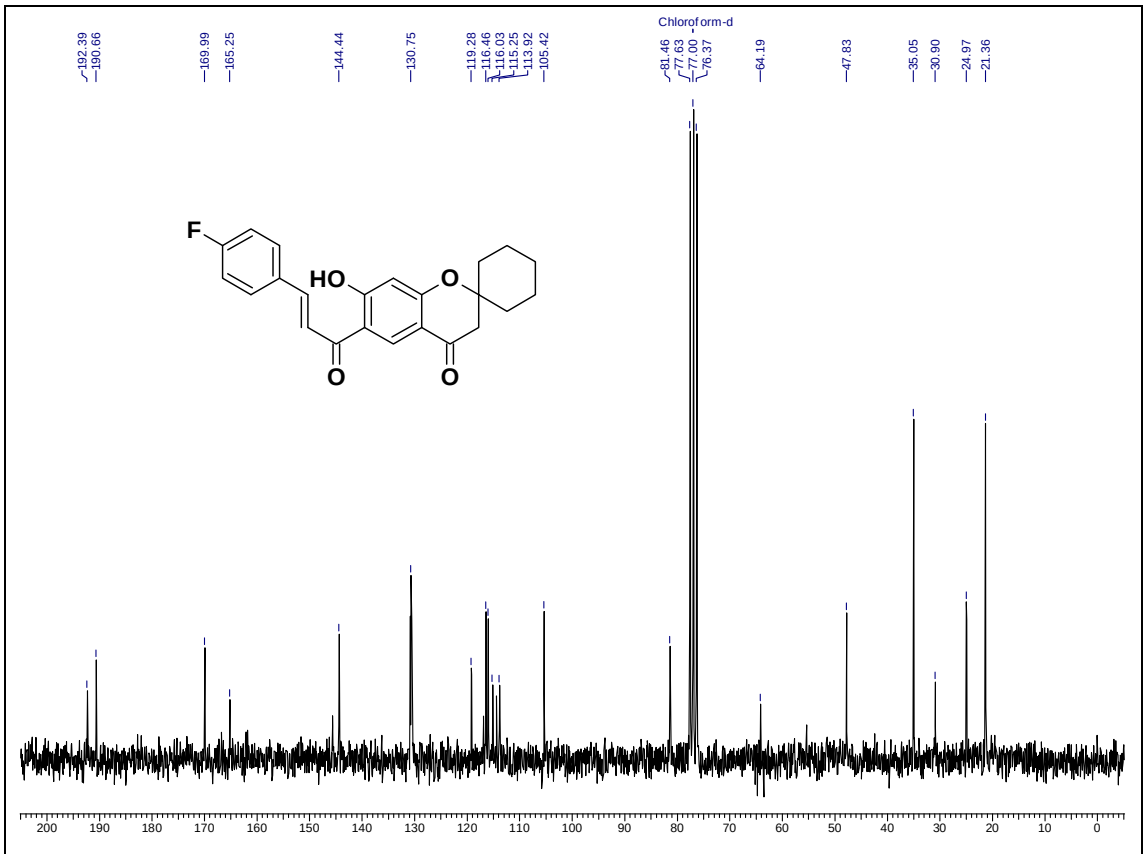


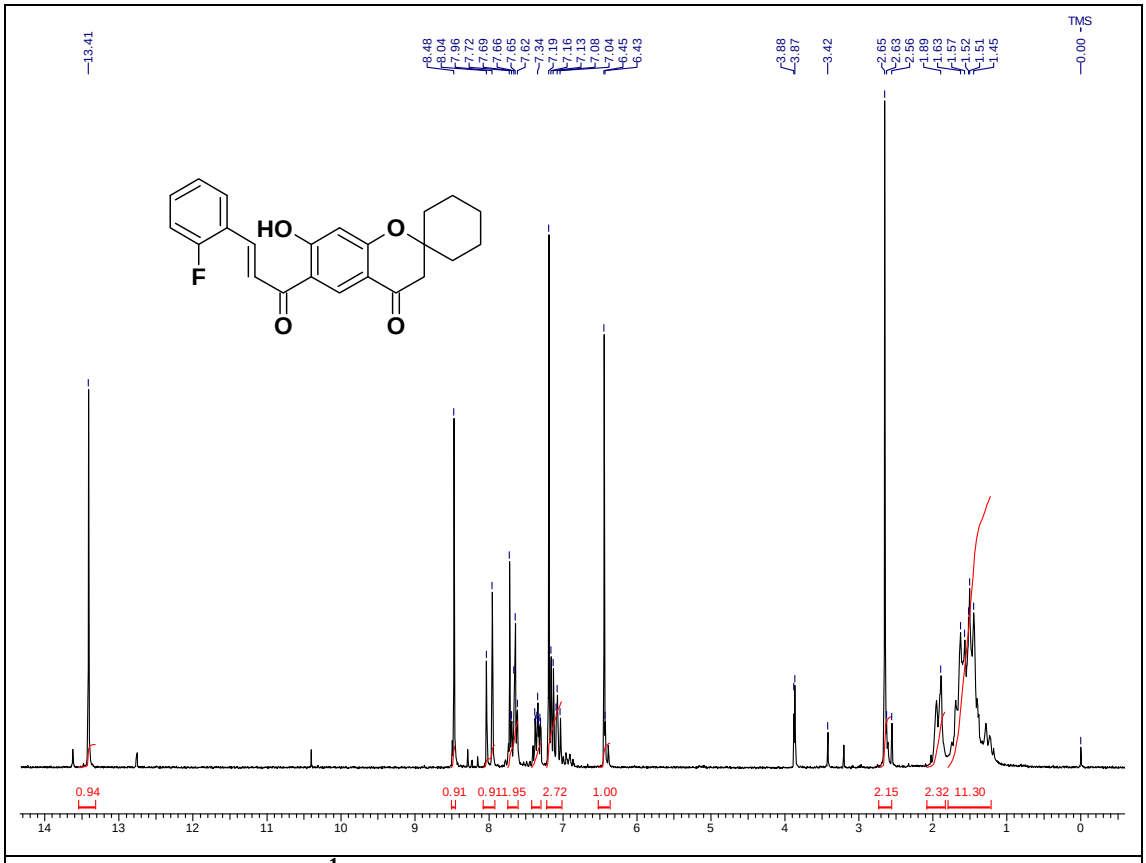
^{13}C NMR of Compound 3b in $CDCl_3$



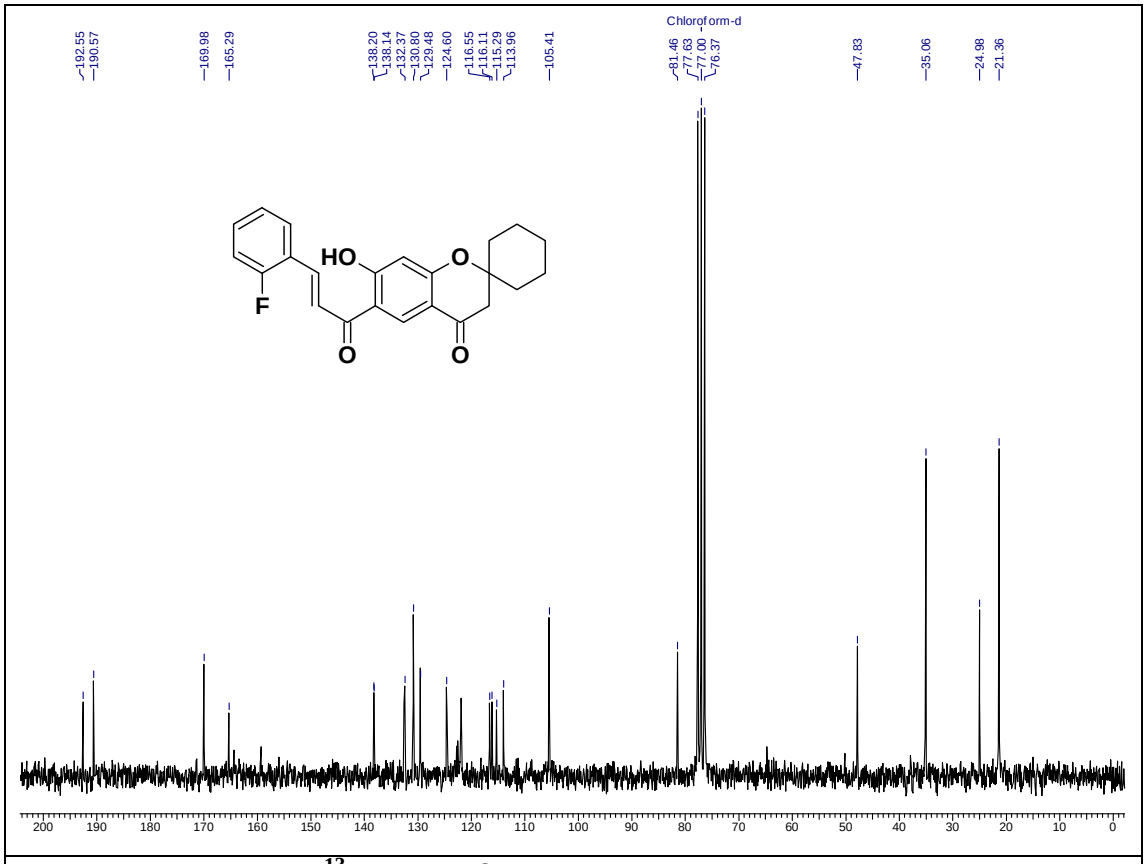
^{1}H NMR of Compound 4a in $CDCl_3$



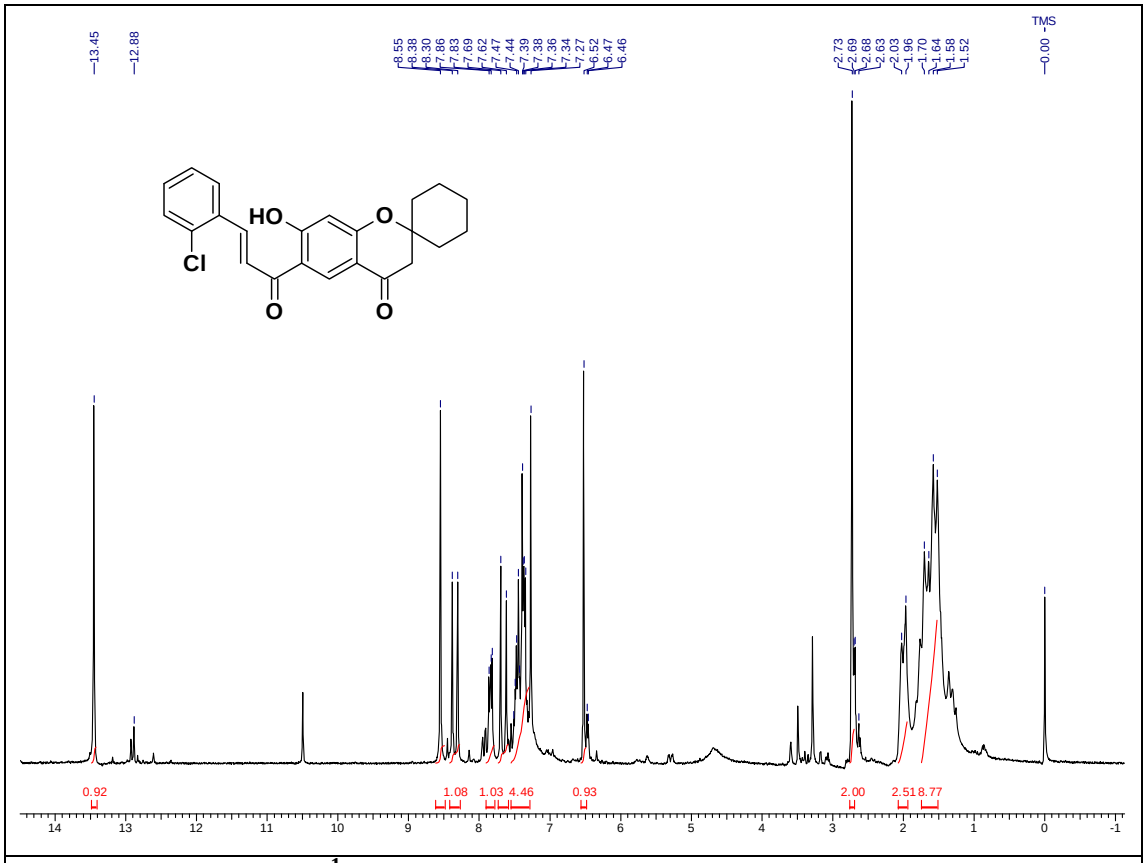
^{13}C NMR of Compound 4a in $CDCl_3$



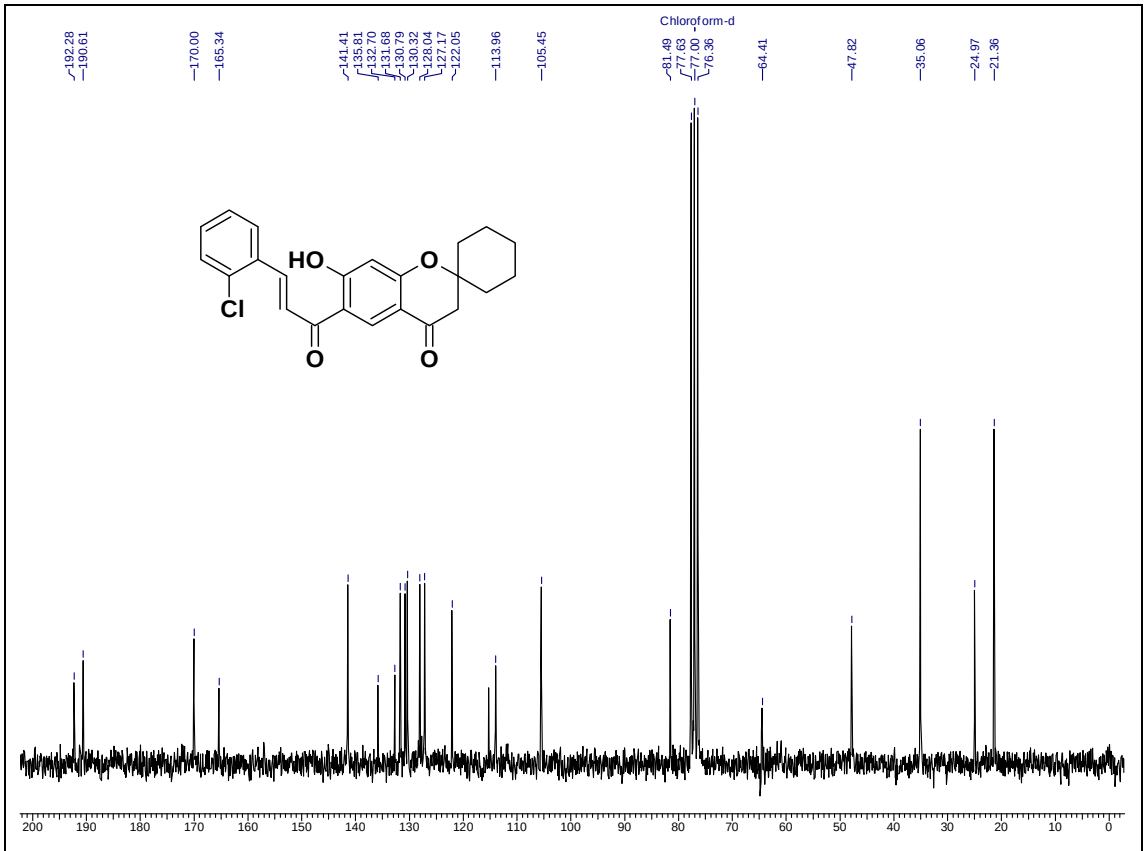
^{1}H NMR of Compound 4b in $CDCl_3$



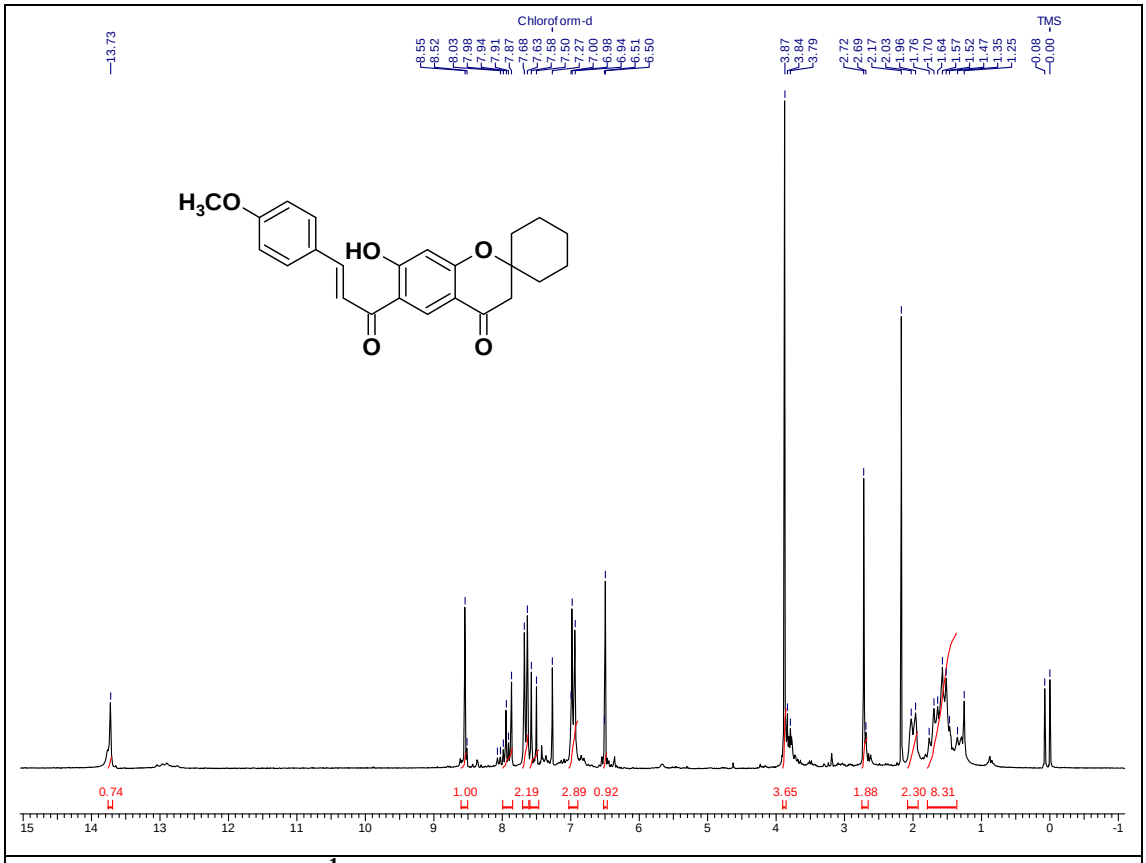
^{13}C NMR of Compound 4b in $CDCl_3$



^{1}H NMR of Compound 4c in $CDCl_3$



^{13}C NMR of Compound 4c in $CDCl_3$



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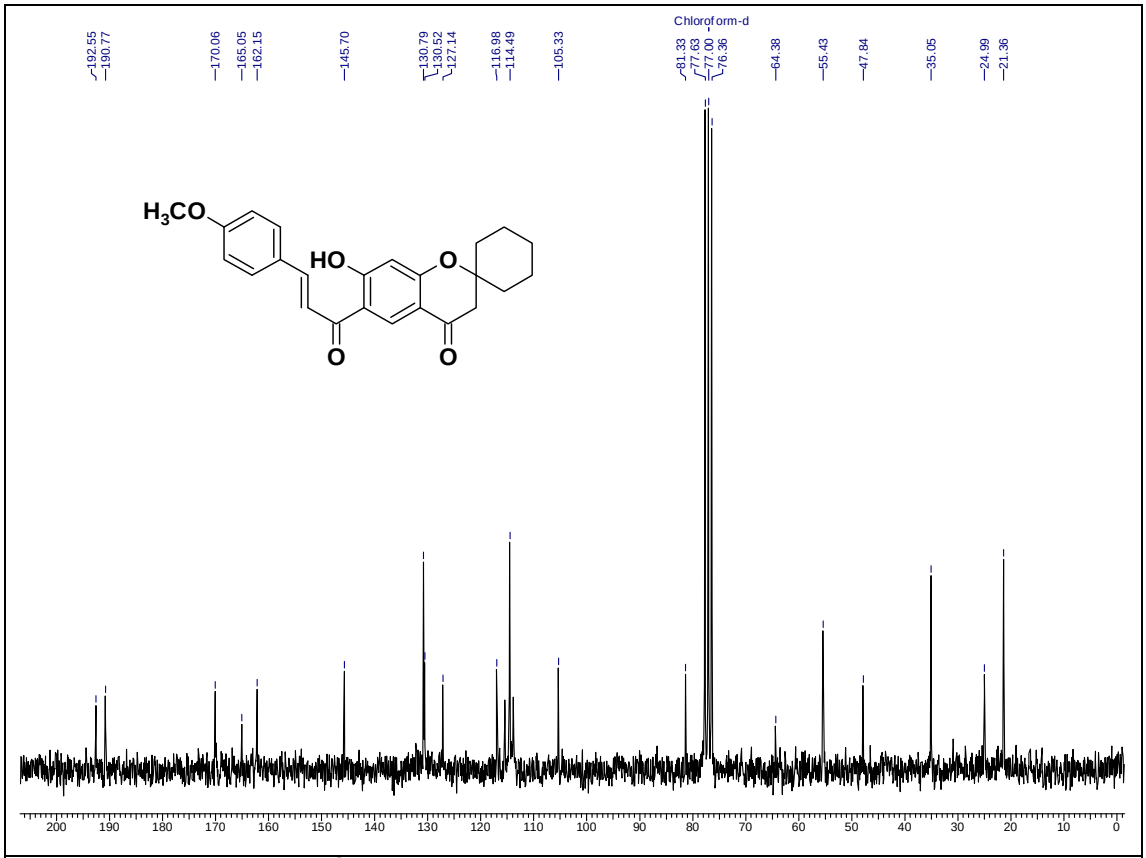
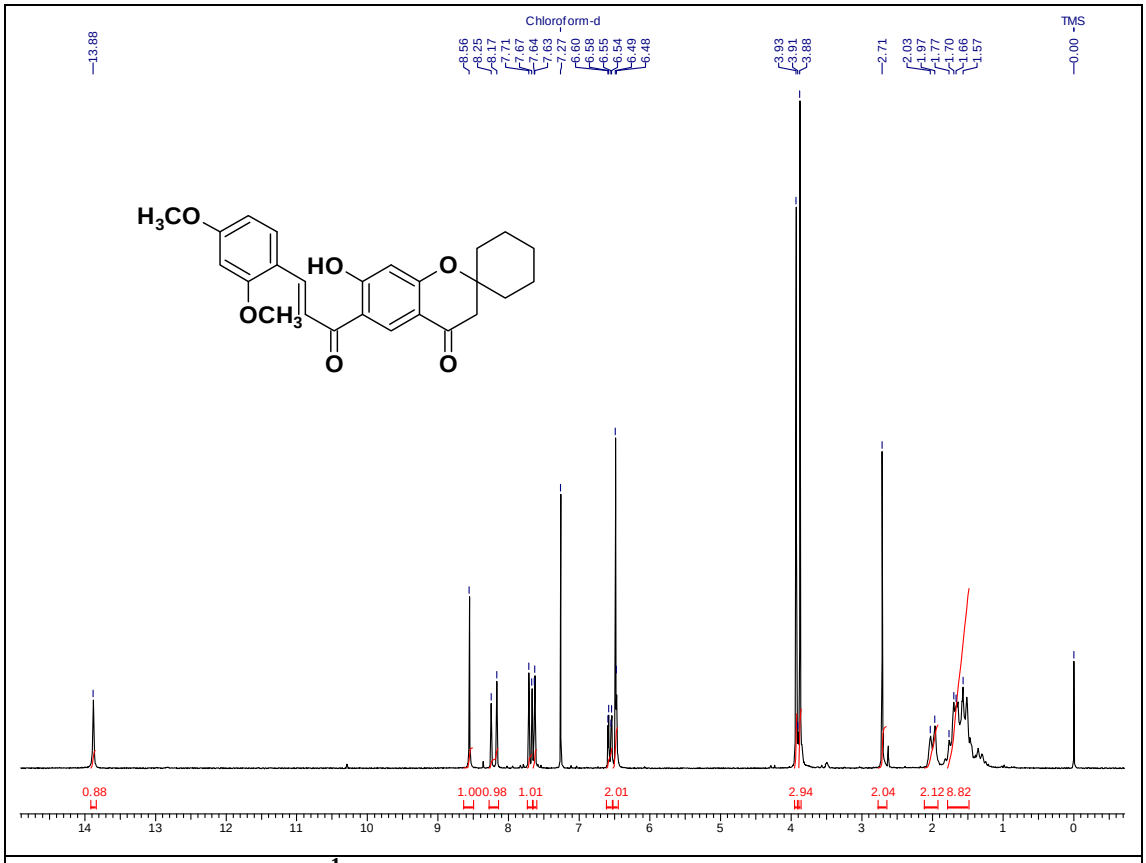
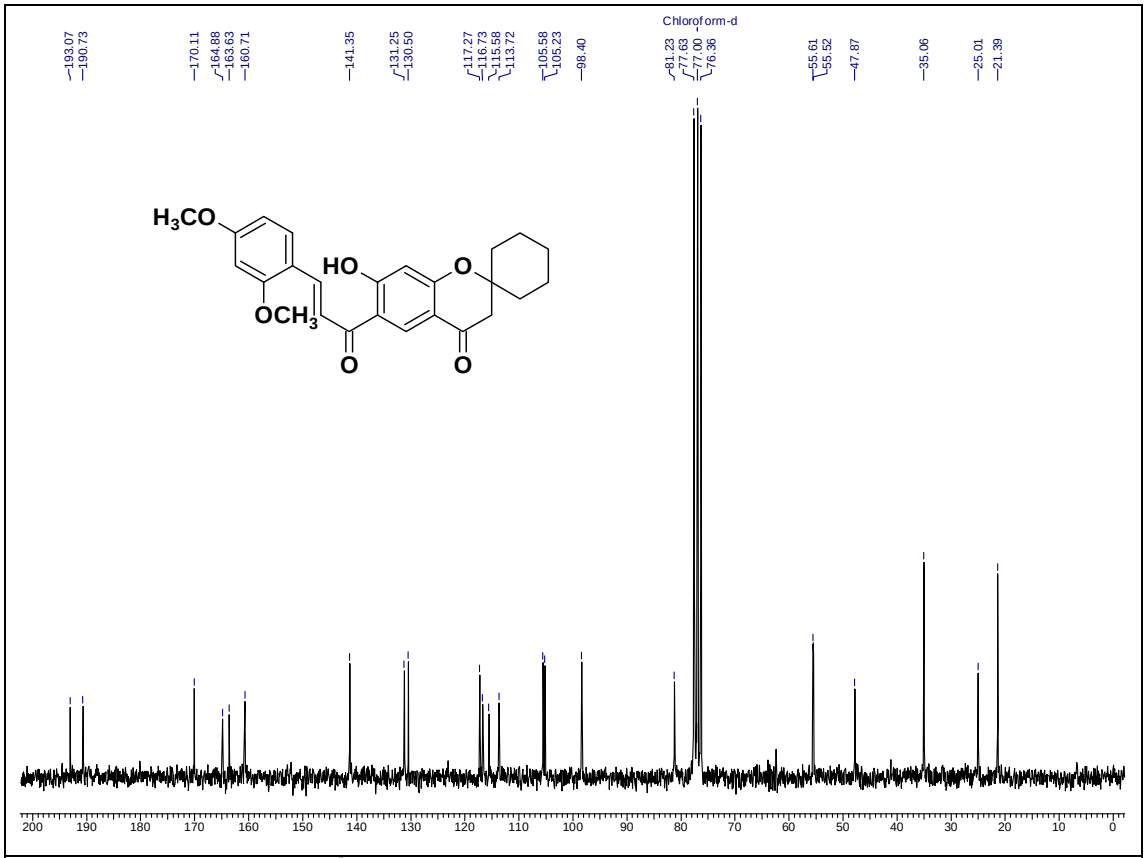


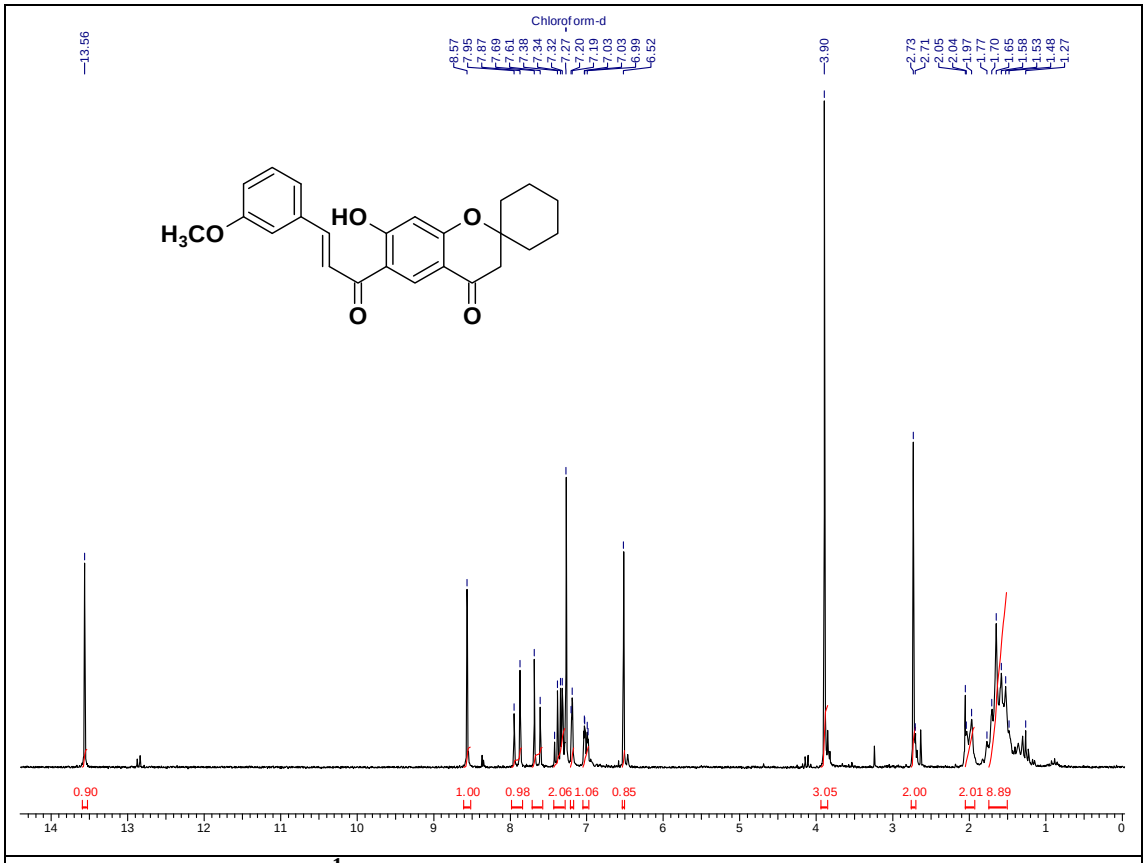
^{13}C NMR of Compound 4d in $CDCl_3$



^{1}H NMR of Compound 4e in $CDCl_3$



^{13}C NMR of Compound 4e in $CDCl_3$



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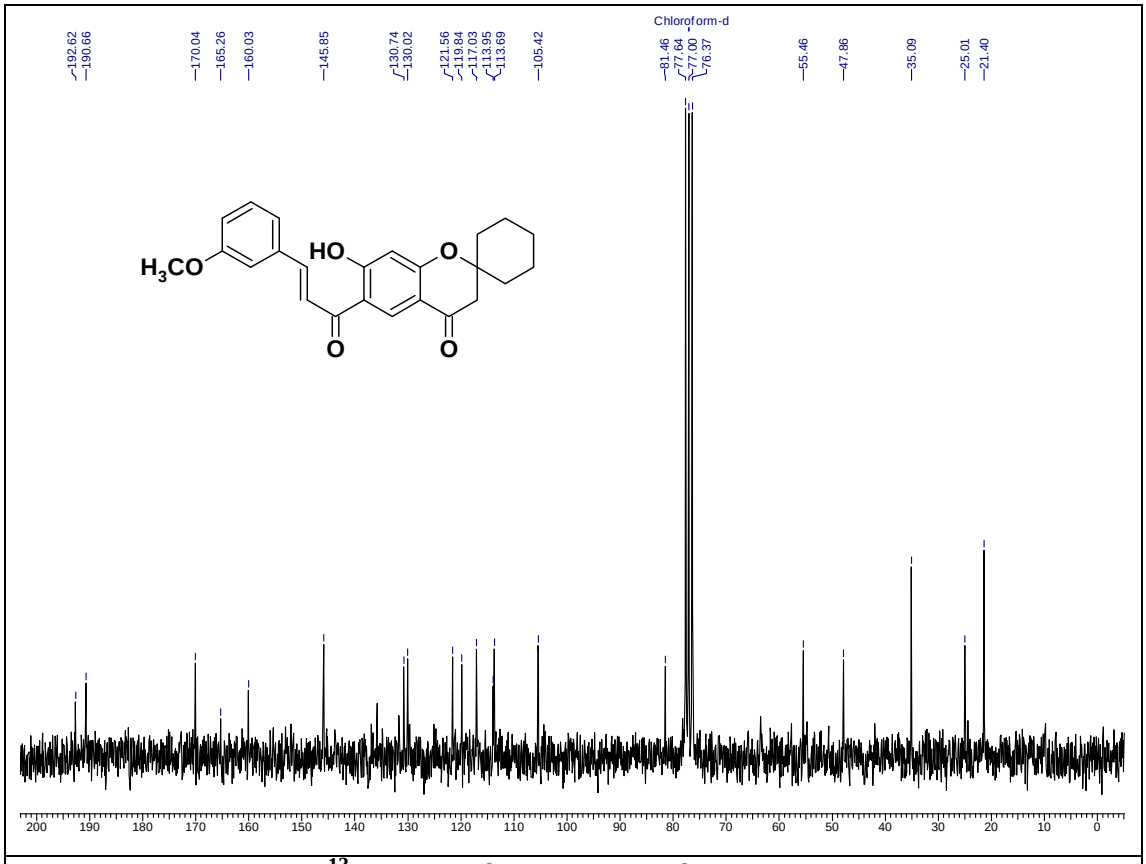
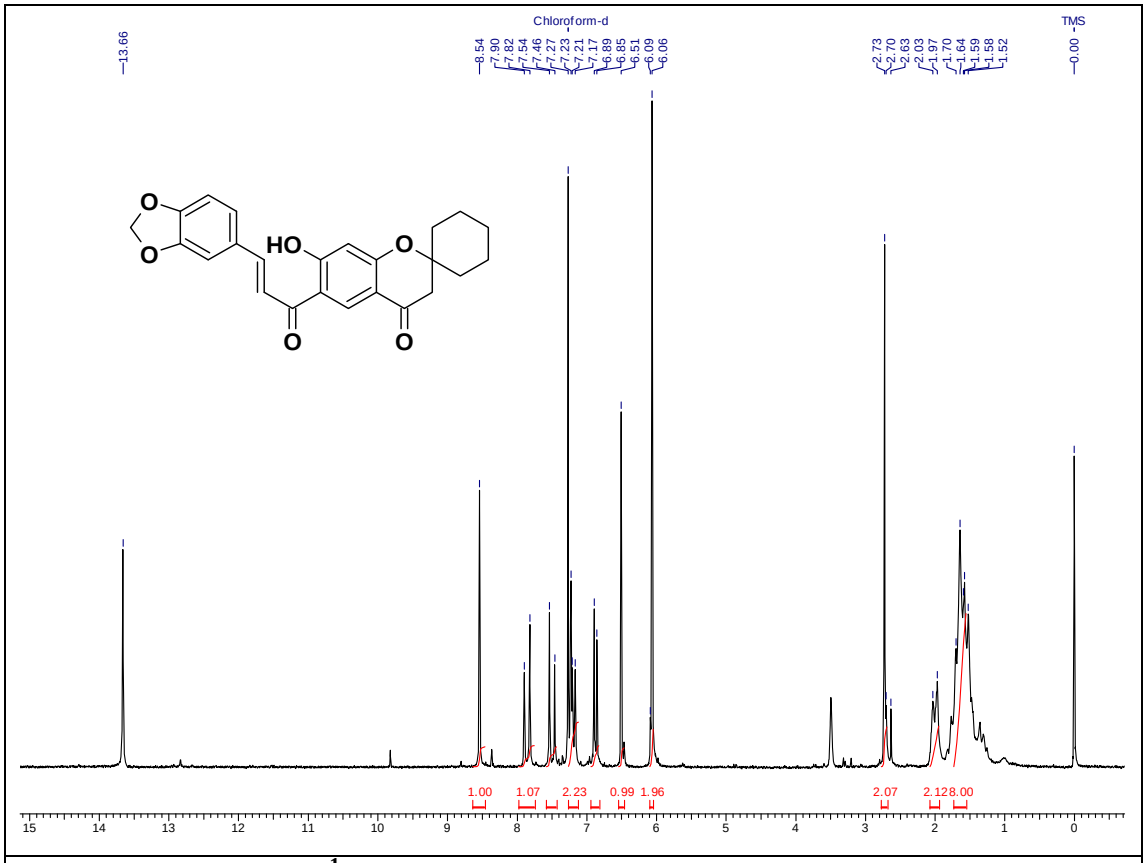
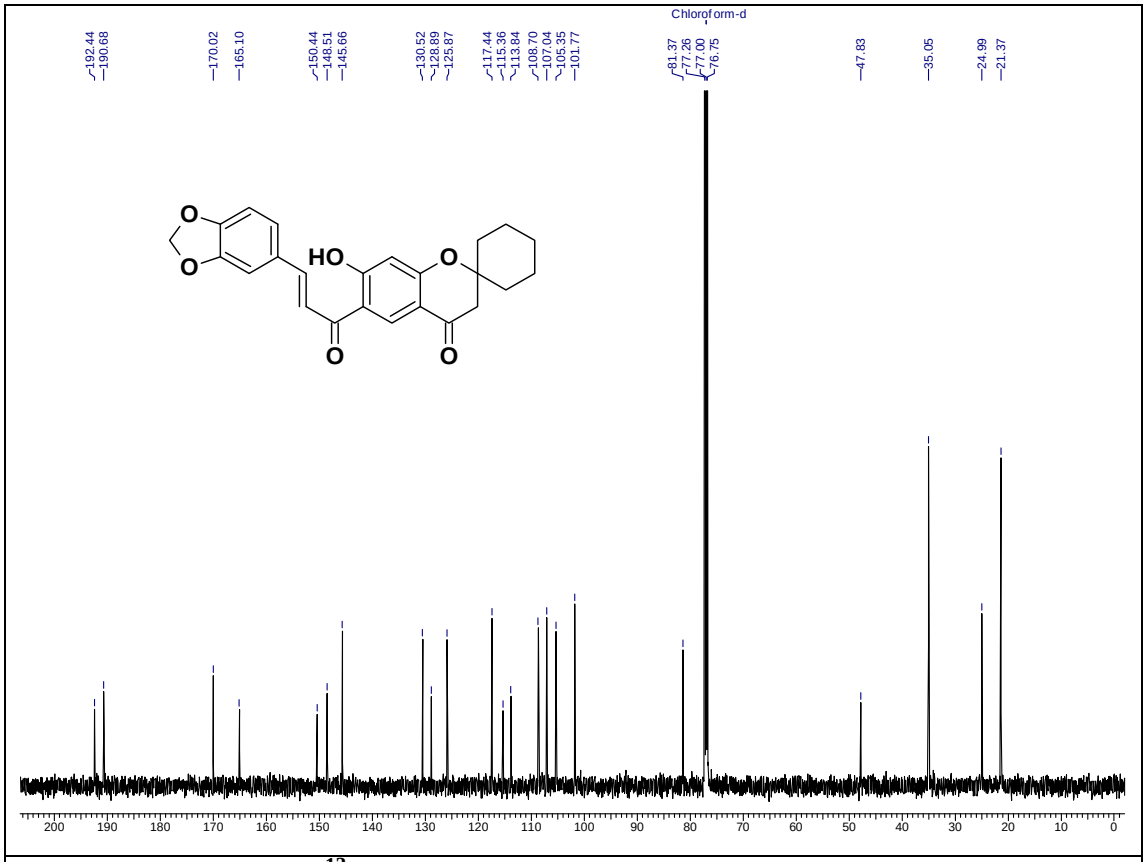


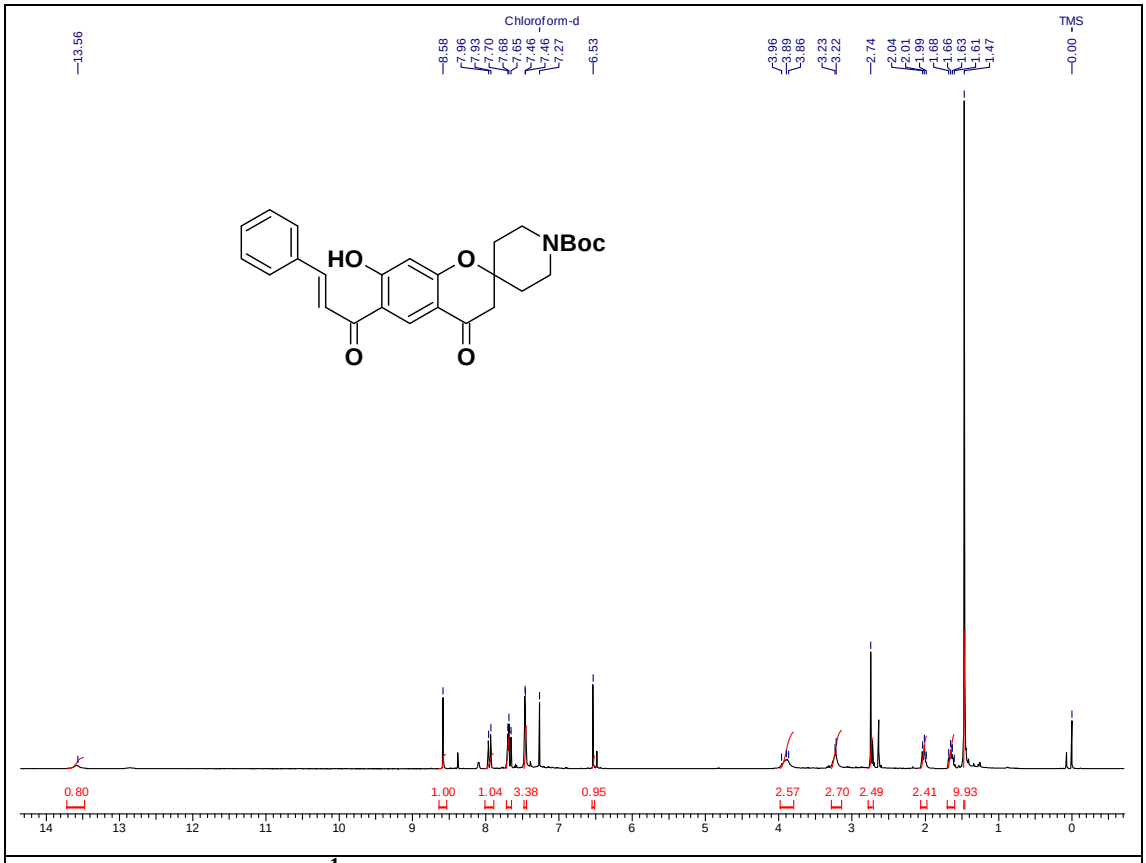
^{13}C NMR of Compound 4f in $CDCl_3$



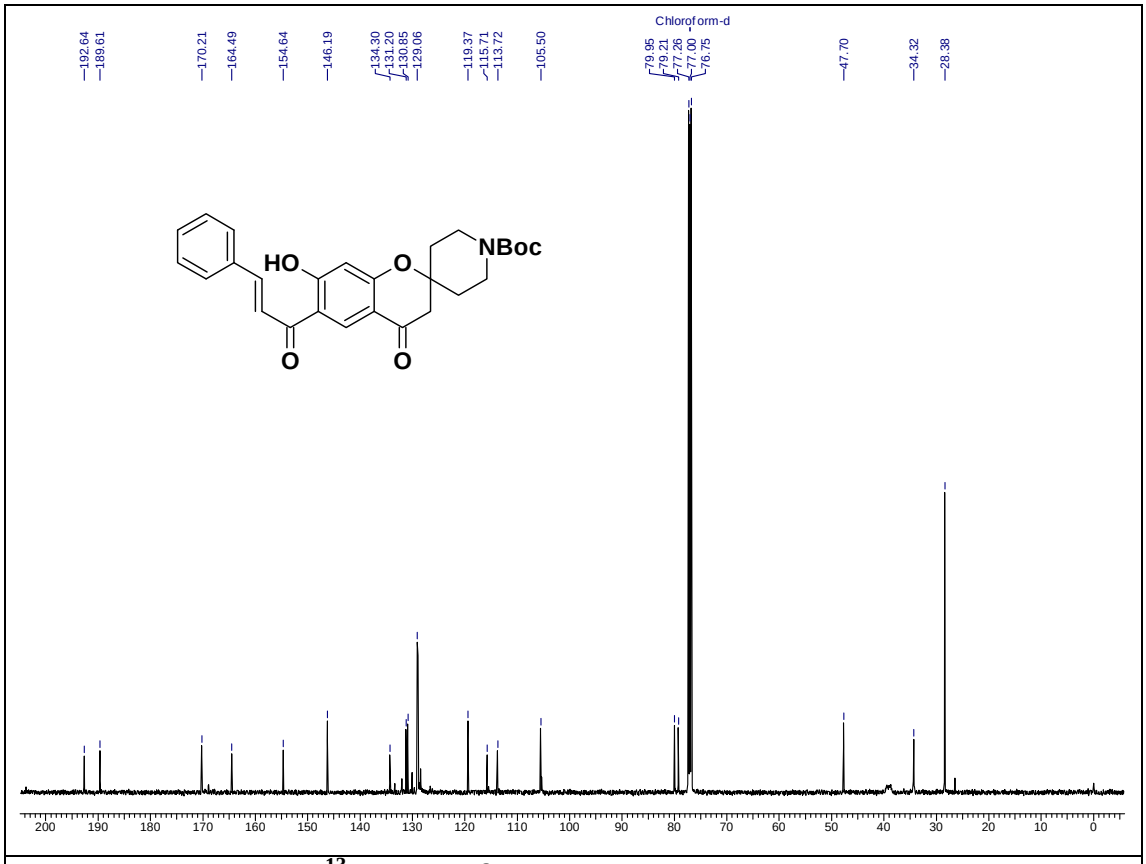
^{1}H NMR of Compound 4g in $CDCl_3$



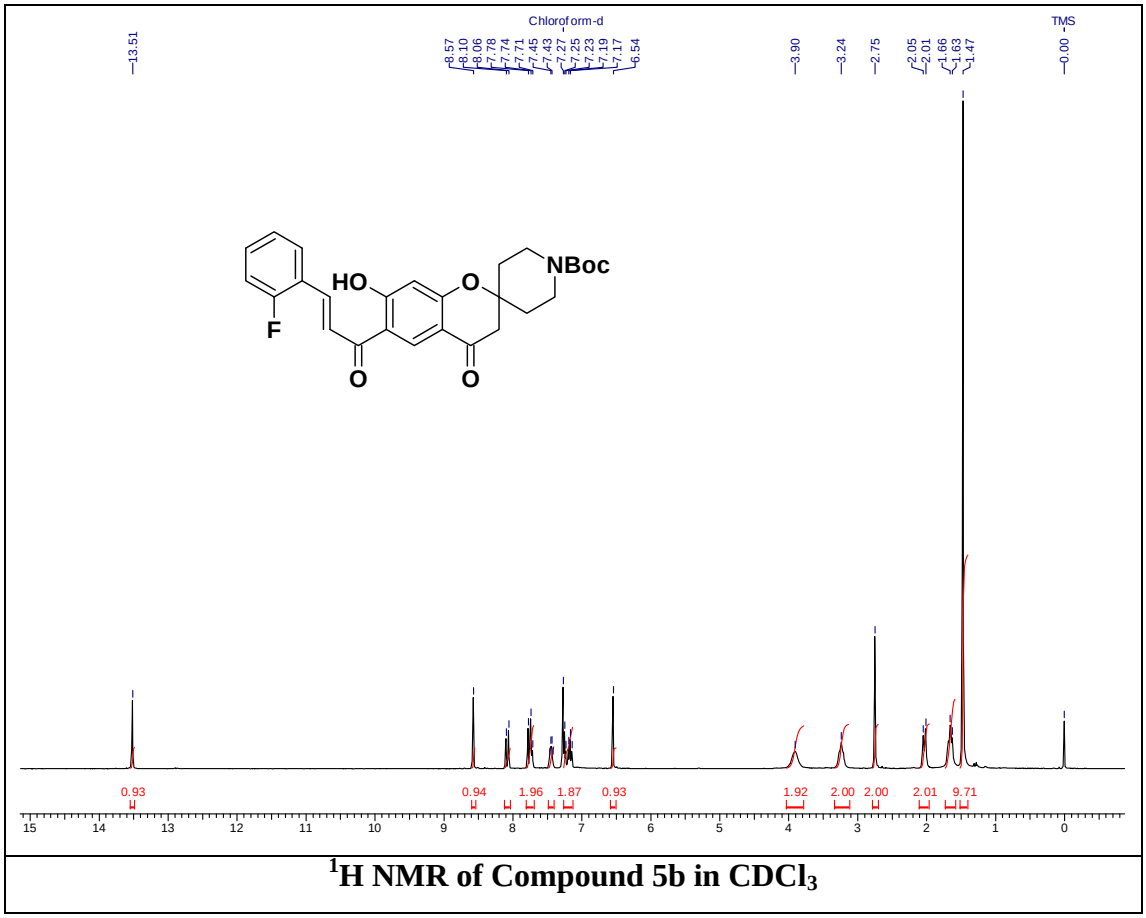
^{13}C NMR of Compound 4g in $CDCl_3$



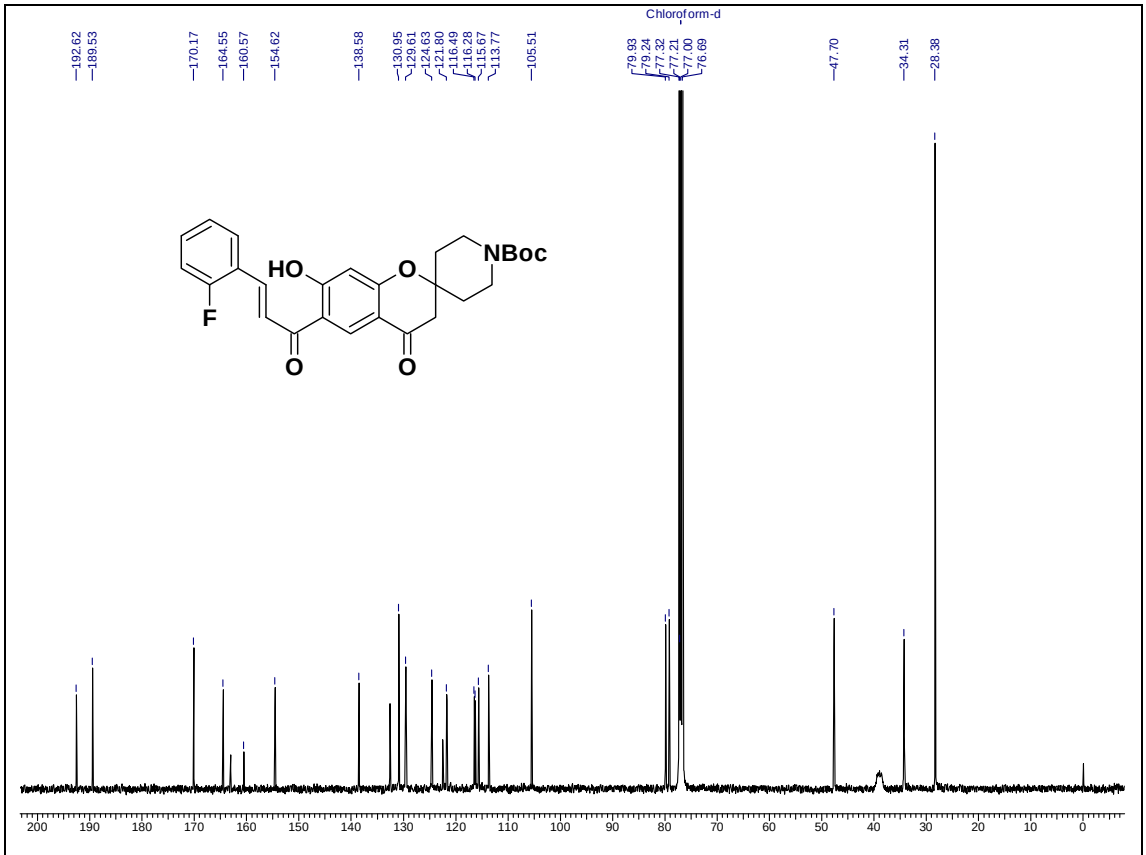
^{1}H NMR of Compound 5a in $CDCl_3$



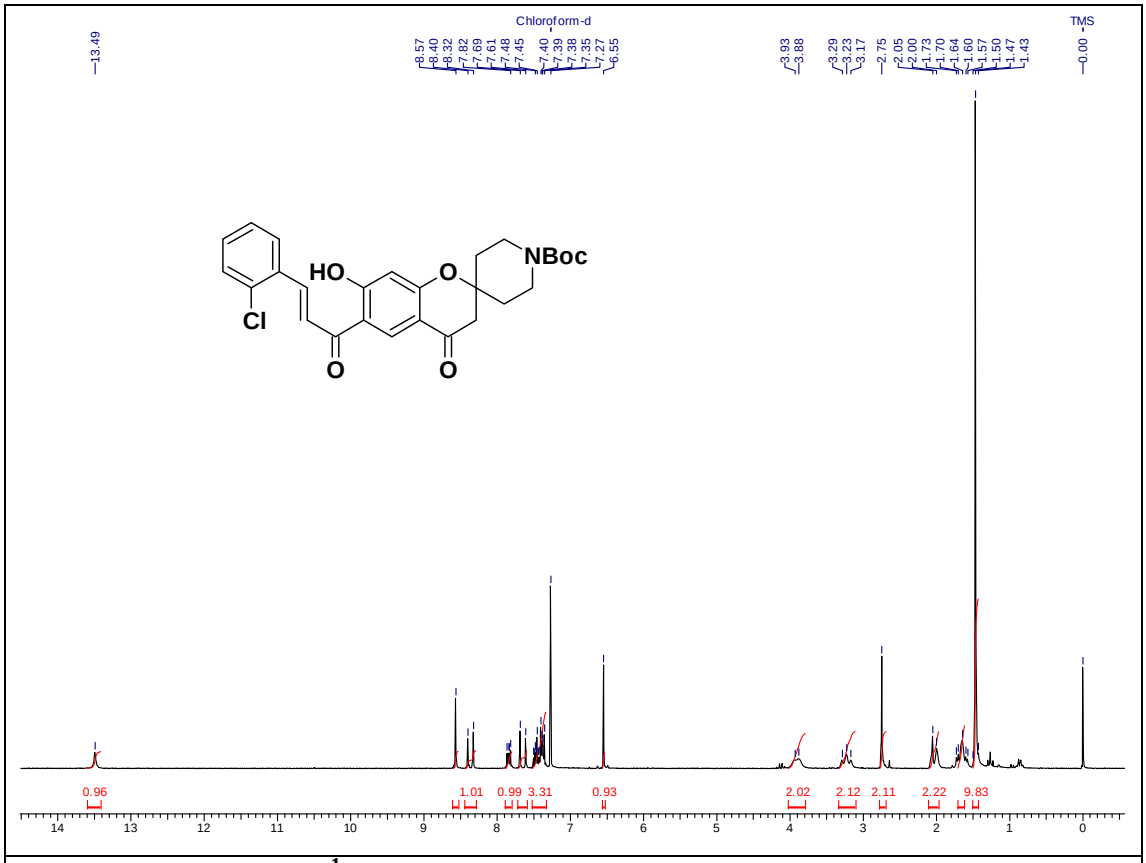
^{13}C NMR of Compound 5a in $CDCl_3$



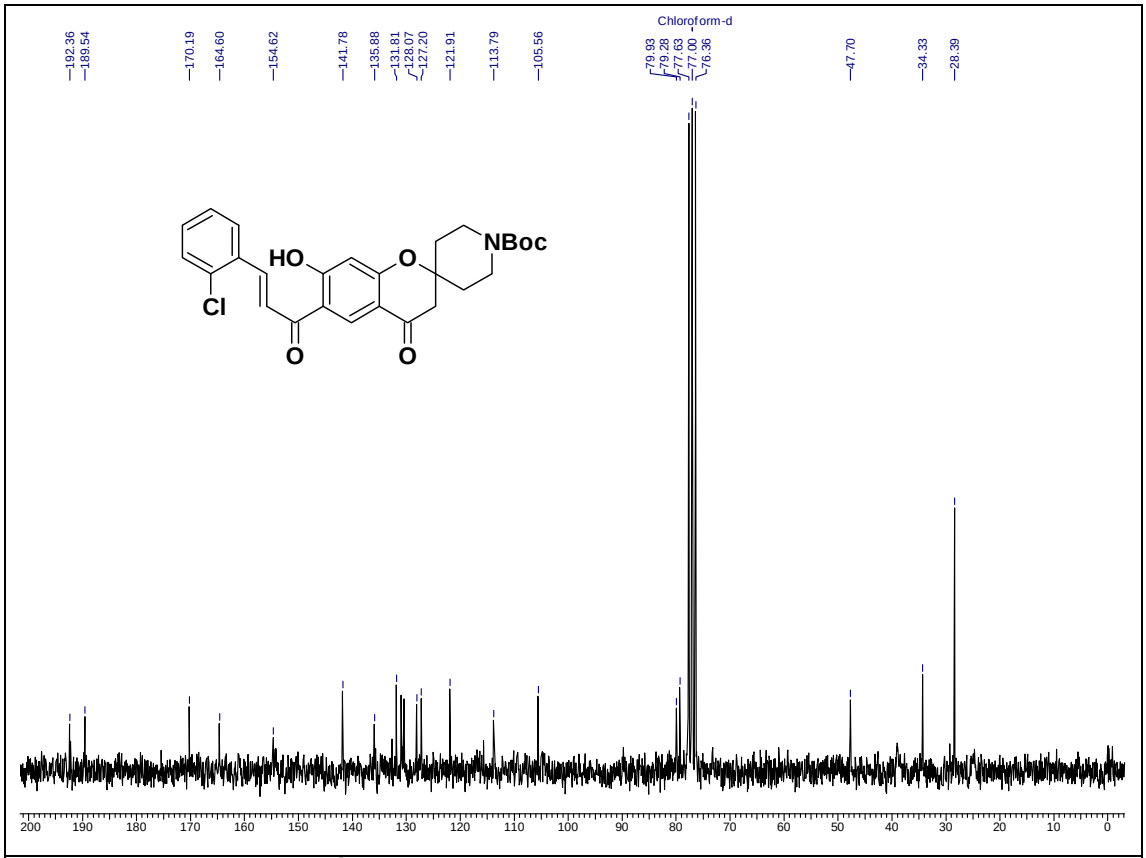
^{1}H NMR of Compound 5b in $CDCl_3$



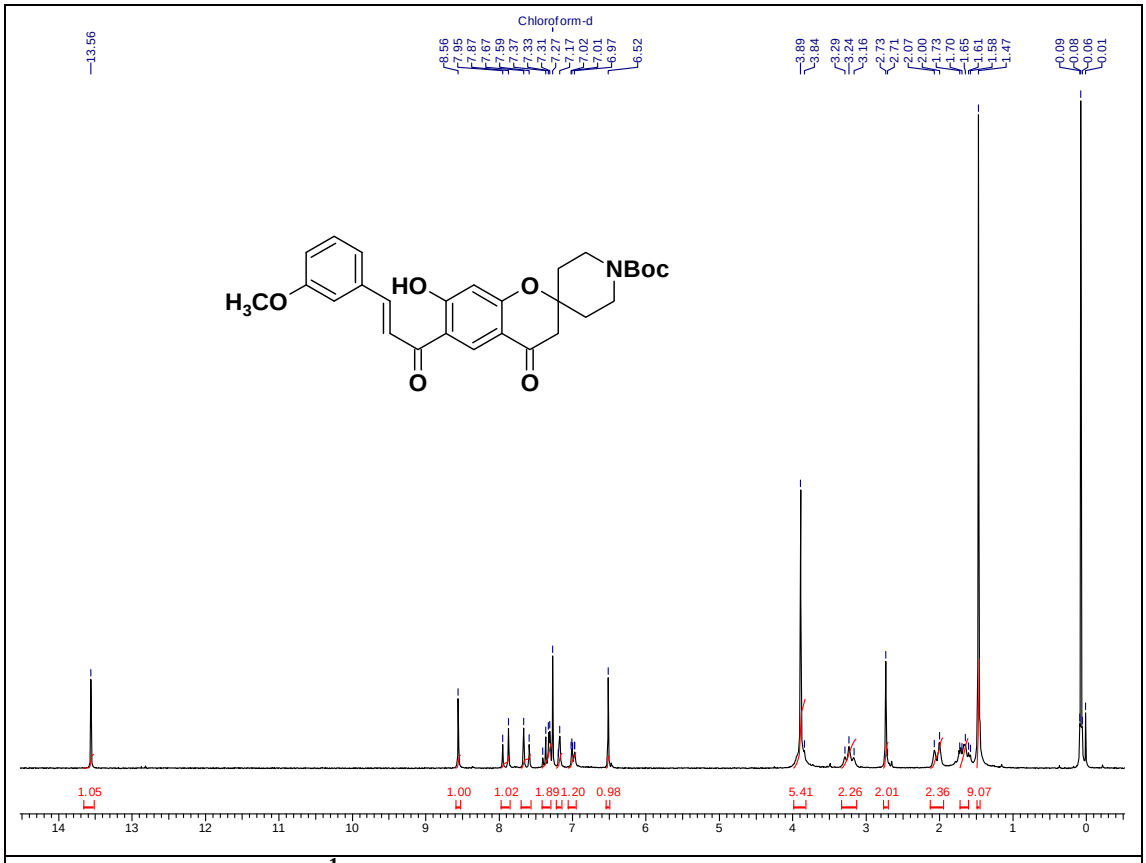
^{13}C NMR of Compound 5b in $CDCl_3$



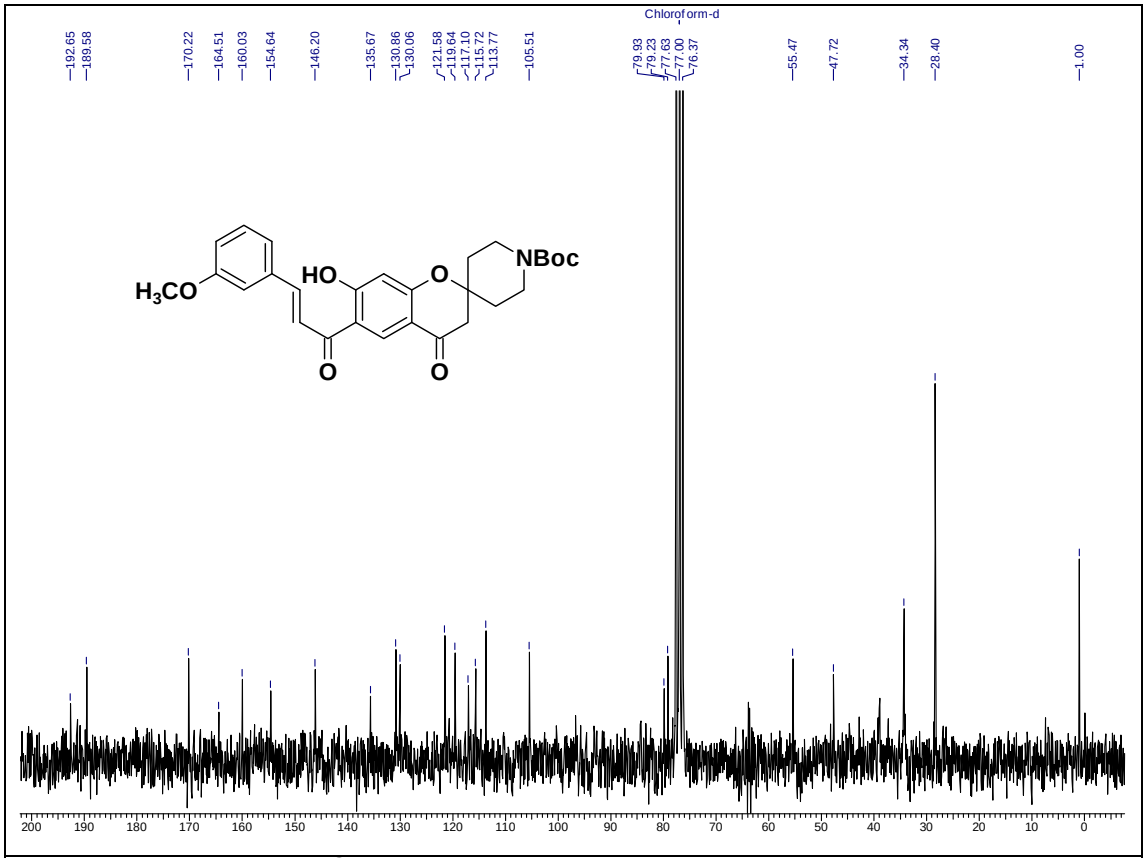
^{1}H NMR of Compound 5c in $CDCl_3$



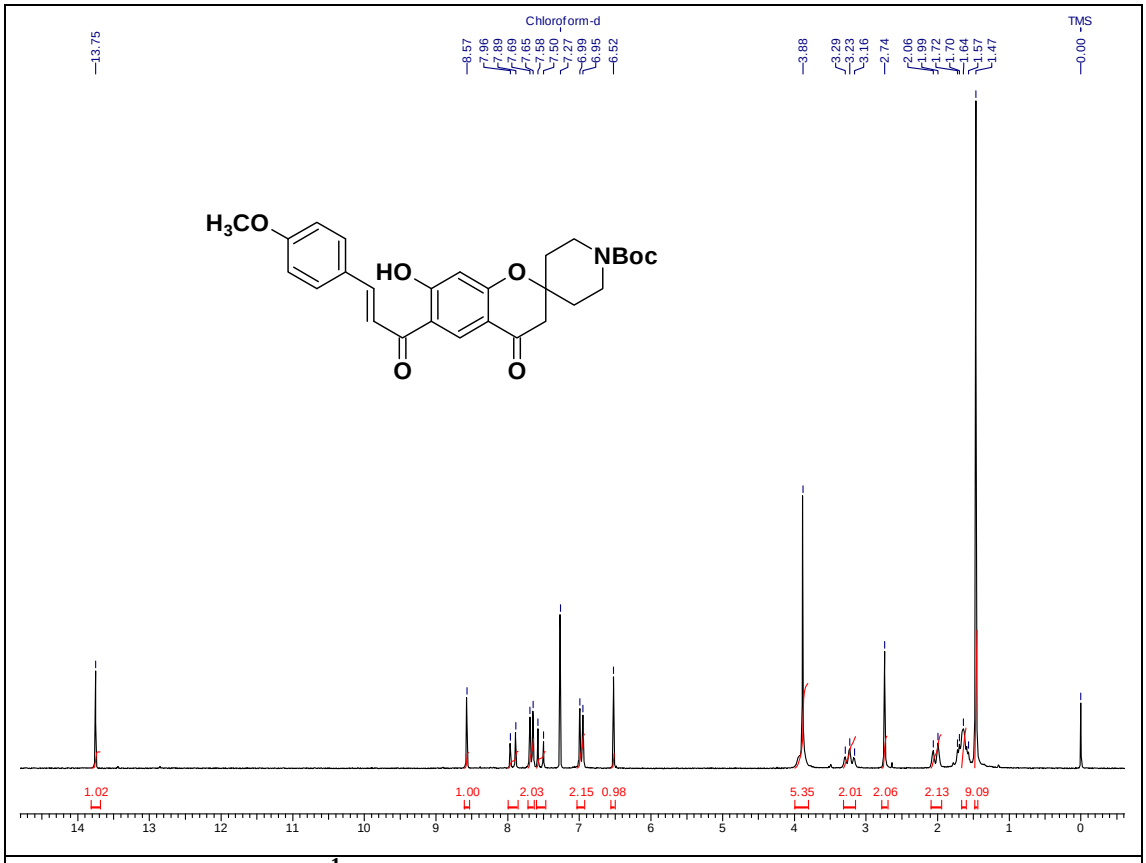
^{13}C NMR of Compound 5c in $CDCl_3$



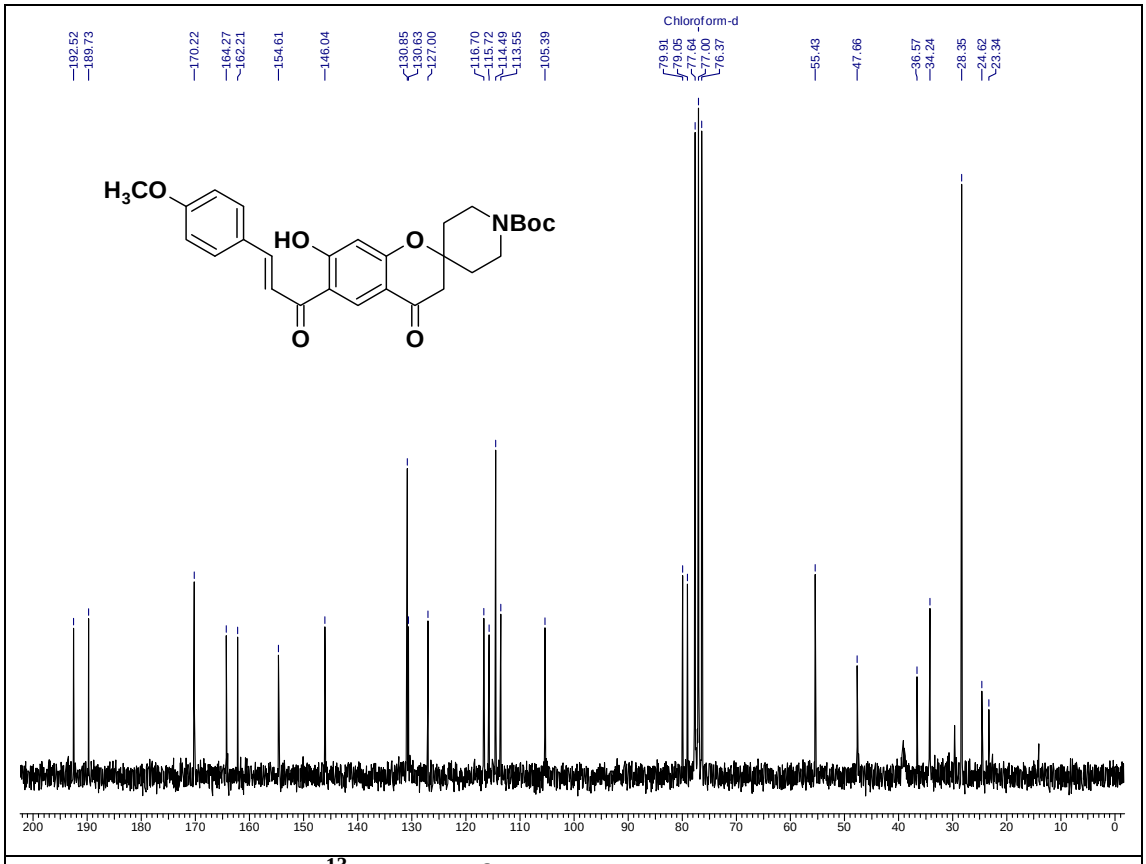
^{1}H NMR of Compound 5d in $CDCl_3$



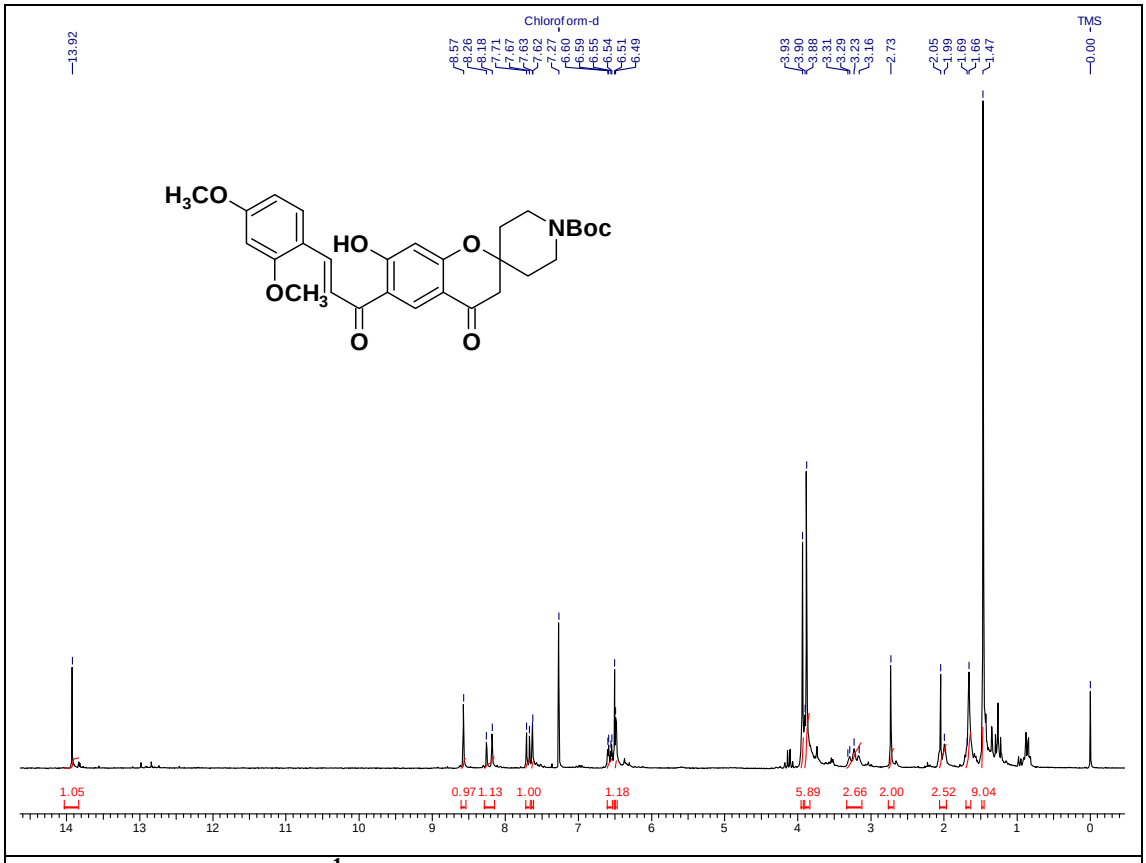
^{13}C NMR of Compound 5d in $CDCl_3$



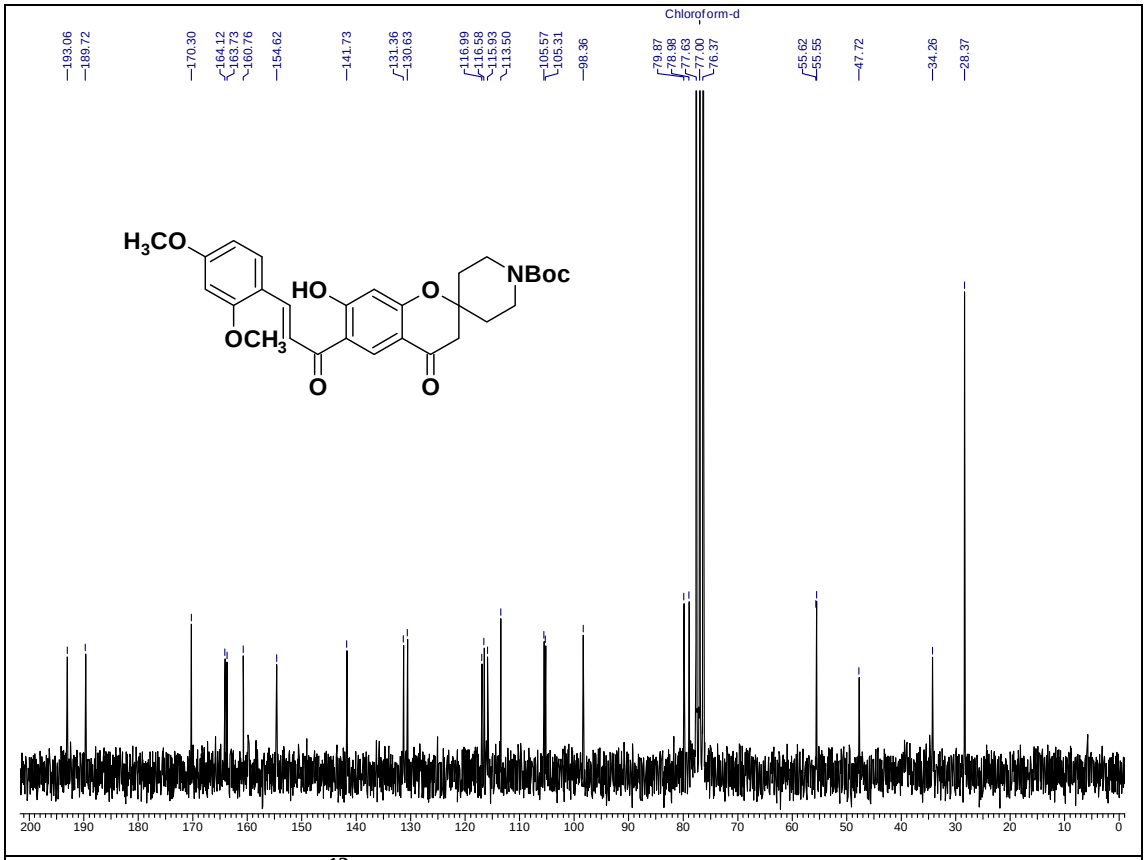
^{1}H NMR of Compound 5e in $CDCl_3$



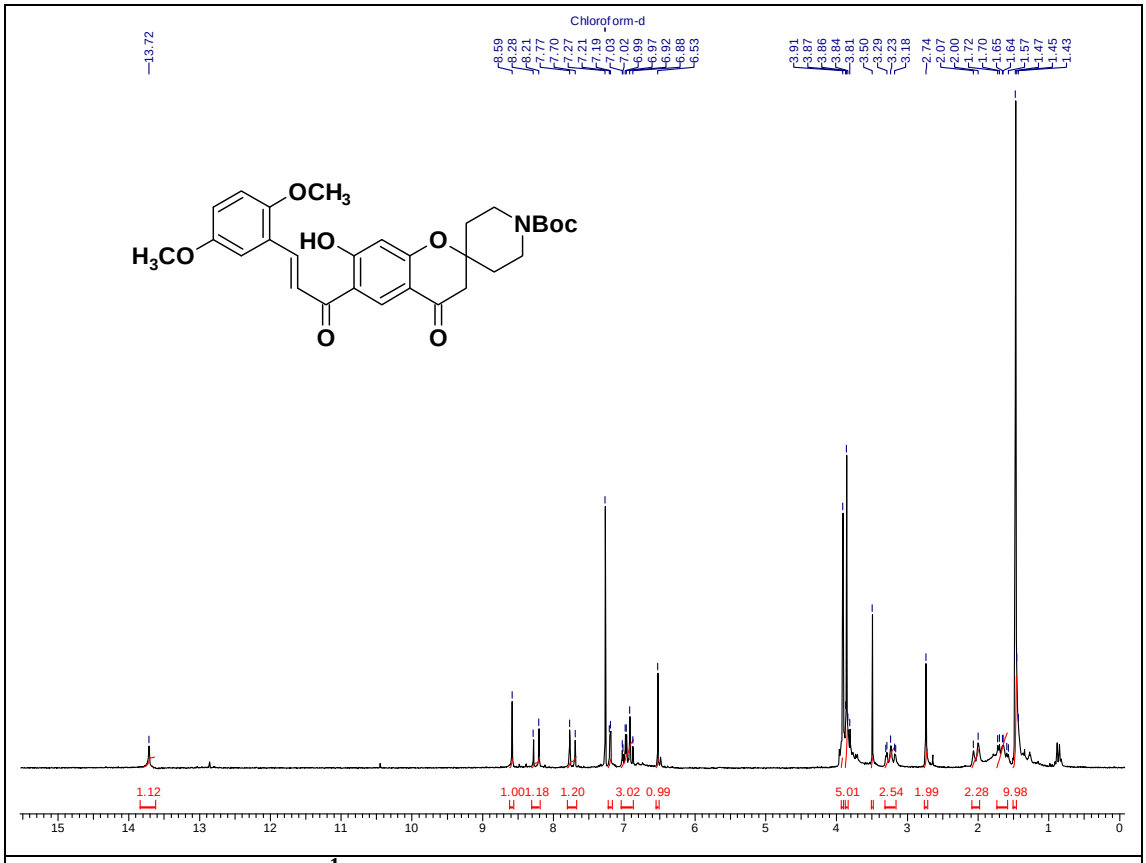
^{13}C NMR of Compound 5e in $CDCl_3$



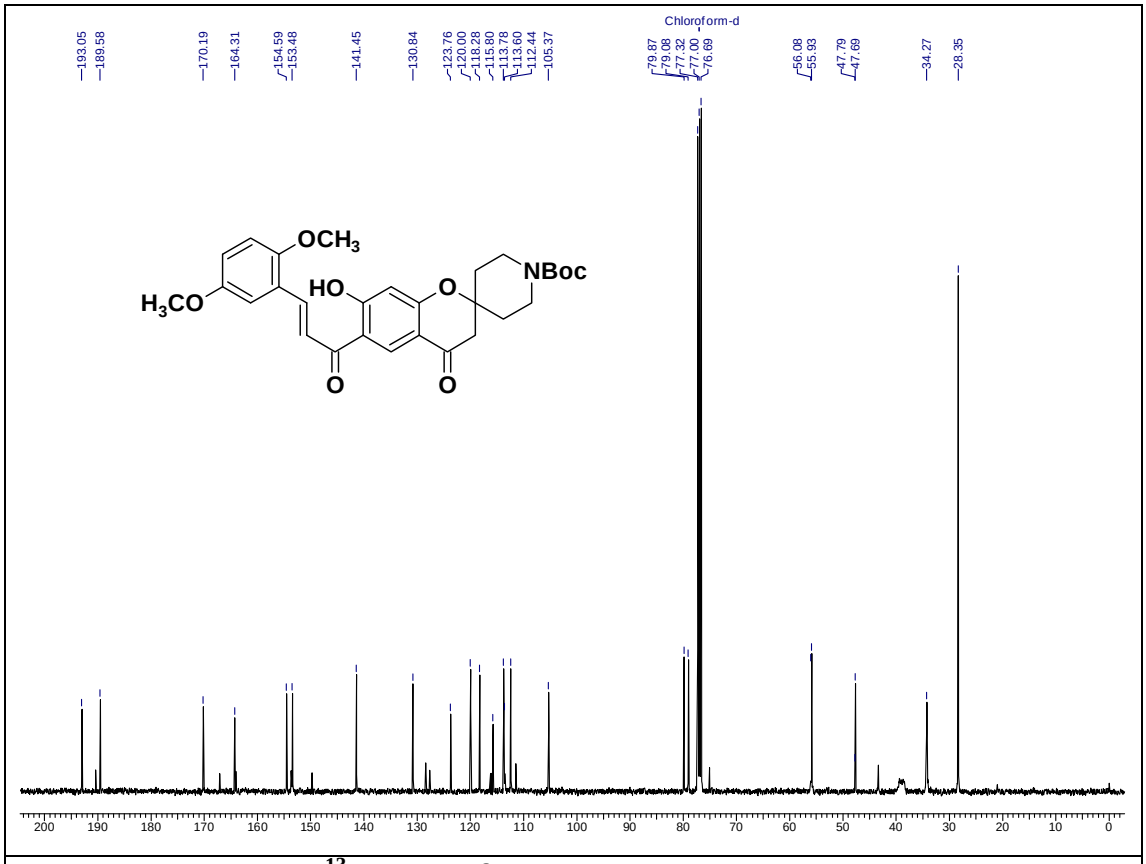
^{1}H NMR of Compound 5f in $CDCl_3$



^{13}C NMR of Compound 5f in $CDCl_3$



^{1}H NMR of Compound 5g in $CDCl_3$



^{13}C NMR of Compound 5g in $CDCl_3$

4.4.6. References

1. Walsh, J. J.; Bell, A. *Curr. Pharm. Des*. **2009**, *15*, 2970.
2. (a) Guantai, E. M.; Ncokazi, K.; Egan, T. J.; Gut, J.; Rosenthal, P. J.; Smith, P. J.; Chibale, K. *Bioorg. Med. Chem*. **2010**, *18*, 8243; (b) Alberto, C.; Fraga, M. *Expert Opin. Drug Discov*. **2009**, *4*, 605.
3. Yang, H. M.; Shin, H. R.; Cho, S. H.; Bang, S. C.; Song, G. Y.; Ju, J. H. *Bioorg. Med. Chem*. **2007**, *15*, 104.
4. (a) Bag, S.; Ramar, S.; Degani, M. S. *Med Chem Res*. **2009**, *18*, 309; (b) Lahtchev, K. L.; Batovska, D. I.; Parushev, S. P.; Ubiyvovk, V. M.; Sibirny, A. A. *Eur. J. Med. Chem.* **2008**, *43*, 2220.
5. (a) Nielsen, S. F.; Bosen, T.; Larsen, M.; Schonning, K.; Kromann, H. *Bioorg Med Chem*. **2004**, *12*, 3047; (b) Nielsen, S. F.; Larsen, M.; Bosen, T.; Schonning, K.; Kromann, H. *J. Med. Chem.* **2005**, *48*, 2667.
6. Li, R.; Kenyon, G. L.; Cohen, F. E.; Chen, X.; Gong, B.; Dominguez, J. N.; Davidson, E.; Kurzban, G.; Miller, R. E.; Nuzum, E. O.; Rosenthal, P. J.; McKerrow, J. H. *J. Med. Chem*. **1995**, *38*, 5031.
7. Seo, W. D.; Ryu, Y. B.; Curtis-Long, M. J.; Lee, C. W.; Ryu, H. W.; Jang, K. C. *Eur. J. Med. Chem*. **2010**, *45*, 2010.
8. Lin, Y. M.; Zhou, Y.; Flavin, M. T.; Zhou, L. M.; Nie, W.; Chen, F. C. *Bioorg. Med. Chem*. **2002**, *10*, 2795.
9. Vanhoecke, B. W.; Delporte, F.; Van Braeckel, E.; Heyerick, A.; Depypere, H. T.; Nuytinck, M.; De Keukeleire, D.; Bracke, M. E. *In Vivo.* **2005**, *19*, 103.
10. Emara, A. A. A.; Abou-Hussen, A. A. A. *Spectrochim Acta A.* **2006**, *64*, 1010.

Publications

Thesis

1. Synthesis and antitubercular activity of amino alcohol fused spirochromone conjugates.
   M. Mujahid, R. G. Gonnade, P. Yogeeswari, D. Sriram, M. Muthukrishnan. ***Biorg. Med Chem Lett,*** **2013**, *23*, 1416.

2. A new enantioselective synthesis of anticonvulsant drug Pregabalin (Lyrica®) based on hydrolytic kinetic resolution method.
   M. Mujahid, M. Muthukrishnan.
   Chirality **2013** (accepted manuscript).

3. An alternate synthesis of enantiomerically pure levetiracetam (Keppra)®.
   M. Mujahid, P. Mujumdar, M. Sasikumar, S. S. Kunte, M. Muthukrishnan. ***Tetrahedron: Asymmetry***, **2012**, *23*, 1512.
   This is one of the most downloaded articles (January to March 2013) http://www.journals.elsevier.com/tetrahedron-asymmetry/most-downloaded-articles/
   This is among top 25 articles (October to December 2012) http://top25.sciencedirect.com/subject/chemistry/6/journal/tetrahedron-asymmetry/09574166/archive/41/

4. First asymmetric synthesis of the antiepileptic drug Lacosamide (Vimpat®) based on a hydrolytic kinetic resolution strategy.
   M. Muthukrishnan, **M. Mujahid**, M. Sasikumar, P. Mujumdar.
   Tetrahedron: Asymmetry, **2011**, *22*, 1353.
   This is among top 25 articles (July to September 2011)
   http://top25.sciencedirect.com/subject/chemistry/6/journal/tetrahedron-asymmetry/09574166/archive/34

5. Syntheses and biological evaluation of new triazole-spirochromone conjugates as inhibitors of Mycobacterium tuberculosis.
   M. Muthukrishnan, **M. Mujahid**, P. Yogeeswari, D. Sriram.
   Tetrahedron Letters, **2011**, *52*, 2387.

Highlighted in weekly newsletter from USA *Tuberculosis week* http://www.newsrx.com/newsletters/Tuberculosis-Week/2011-06-27/41062720115TB.html

6. An efficient synthesis of ethyl-(*S*)-2-ethoxy-3-(4-hydroxyphenyl) propanoate (EEHP), a key intermediate for PPAR agonists.
M. Mujahid, M. Muthukrishnan. (To be communicated).

7. Asymmetric synthesis of calcium channel blocker (*R*)-Bepridil using hydrolytic kinetic resolution.
M. Mujahid, M. Sasikumar, M. Muthukrishnan. (To be communicated).

Patents

1. New process for the preparation of an antiepileptic drug levetiracetam in high optical purity. M. Muthukrishnan, **M. Mujahid**, P. Mujumdar. Indian Patent (2012, Provisional application no. 2652/DEL/2012, Filing date: 27/08/2012).

2. New process for the preparation of an antiepileptic drug lacosamide. M. Muthukrishnan, **M. Mujahid**, P. Mujumdar. US patent (2012, Provisional application no. 13/589923, Filing date: 20/08/2012).

3. New process for the preparation of the anticonvulsant agent pregabalin. M. Muthukrishnan, **M. Mujahid**. Indian Patent (2013, Provisional application no. 1391/DEL/2013, Filing date: 15/04/2013).

4. New process of preparation of anti-Parkinson agent safinamide. M. Muthukrishnan, **M. Mujahid**. Indian Patent (2013, Provisional application no. 1307/DEL/2013, Filing date: 05/03/2013).

5. New process for the preparation of 3-aryl-2-hydroxy propanoic acid derivatives, useful pharmaceutical intermediates of PPAR agonists.
M. Muthukrishnan, **M. Mujahid**. Indian Patent (2013, Provisional application no. 1388/DEL/2013, Filing date: 09/05/2013).

Publications (Others)

1. An efficient Bakers' yeast catalyzed multicomponent synthesis of α-aminophosphonates in one-Pot.
   A. K. Bhattacharya, **M. Mujahid**.
   Synthetic Communications, **2013**, *43*, 2583.

2. Simple and efficient synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones using silica chloride as a new catalyst under solvent-free conditions.
   M. Muthukrishnan, **M. Mujahid**, V. Punitharasu, D. A. Dnyaneshwar.
   Synthetic Communications, **2010,** *40*, 1391.

3. Synthesis and in vitro study of 14-aryl-14H-dibenzo[a.j]xanthenes as cytotoxic agents.
   A. K. Bhattacharya, K. C. Rana, **M. Mujahid**, I. Sehar, A. K. Saxena.
   Biorg. Med Chem Lett, **2009**, *19*, 5590.

4. Antimony trichloride as a highly efficient and versatile catalyst for synthesis of acylals from aldehydes under solvent-free conditions.
   A. K. Bhattacharya, **M. Mujahid** and A. A. Natu.
   Synthetic Communications, **2008,** *38*, 128.

Bio-data

Educational Qualification

MSc **Organic chemistry** (2005),
Sant Gadge Baba Amravati University,
Amravati.

BSc Chemistry, Mathematics and Industrial Chemistry,
Sant Gadge Baba Amravati University,
Amravati.

Award / Fellowship

2010-2013: **Senior Research Fellowship** awarded by Council of Science and Industrial Research (CSIR) India.

Research Experience

April 2010- till date: Working as ***CSIR-Senior Research Fellow*** at Division of Organic Chemistry.

January 2009- March 2010: Worked as **Project Assistant II** on the project entitled **"Diversity Oriented Synthesis of Natural Product like small molecules"** a DST sponsored project.

September 2005 – December 2007: Worked as **Project Assistant II** on the project entitled **"Fractionation of Natural Products & High Throughput Screening of Botanicals in Skin Care"**, a P&G, USA Sponsored project.

Research Interest

Synthesis of biologically active compounds, asymmetric synthesis and development of new synthetically important methodologies.