Section-I

2.I.1 Introduction

The design and synthesis of chiral compounds is one of the most important fields in organic chemistry. The connection of structural features of chiral molecules and their specific properties is now a well-established field [1]. It is well accepted concept that shape of a molecule, a molecule's arrangement or a molecule's spatial structure, plays a key role in determining its properties. The search for new chiral molecules with different shape, size and functional group is a crucial aspect of modern chemistry.

The nature of the functionality and the shape of chiral molecules are important considerations for the design of optically active compounds. These play significant role in the field of molecular recognition, medicinal chemistry and asymmetric synthesis. Hence, it is a matter of interest for the contemporary organic chemists to design and synthesize structurally diverse novel chiral molecules.

2.I.2 Molecules with different shape & size

Structurally diverse molecules have attracted considerable attention in different areas. Depending upon the uses, researchers have designed molecules with different shapes and with varied substitutions to provide the particular desired characteristics.

In literature there are different types of molecules which show different characteristic due to their shape and size.

2.I.3 Cleft like Molecules

Molecules with rigid cleft-like structure have attracted considerable attention. One of the most prominent molecules is Troger's base (Figure 2.1), which was first synthesized more than one hundred and twenty years ago [3]. The molecule has a dihedral angle of around 90° and the two phenyl rings are fused to the bicyclic[3.3.1] framework to form a rigid V-shaped scaffold [3b]. Troger's base contains two chiral centers at the nitrogen and it was resolved by an optically active chiral acid [4].

Studies were also carried out on a series of related systems, including Kagan's ether (Figure 2.1) [5].

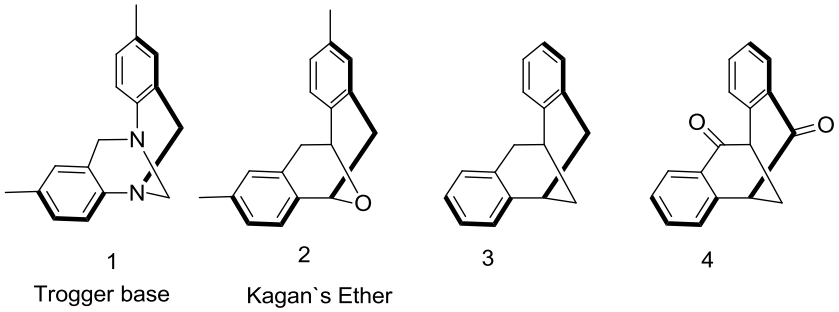


Figure 2.1: Structure of cleft like molecule

Such types of molecules possess chirality and are shaped appropriately for incorporation into tweezers like molecules. The utility of different cleft like molecules are well defined in the diverse fields of molecular recognition, studies on self-assembly and also their potential applications in organic synthesis [6].

2.I.4 Butterfly shape molecules

Dimerization reaction involving 2,3-dihydroxynaphthalene yields a dinaphthofuran framework which has structural similarity to a butterfly (Figure 2.2). This method was used to synthesize a variety of butterfly-shaped naphthofuran [7].

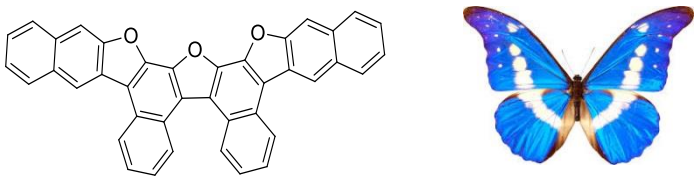


Figure 2.2: Structure of Butterfly shape molecule

The λ_{max} of such molecules for the absorbance and emission spectra varied with the dihedral angle formed between adjacent aryl groups and/or with electron delocalization across the aromatic ring systems.

Application of such molecules particularly, oxygen-containing polycyclic aromatic compounds, especially furan-containing polycyclic aromatics, are expected to provide relatively high HOMO levels and offer utility in electronic devices, such as light-emitting diodes (LEDs) and organic light-emitting diodes (OLEDs). Many furan containing compounds, for example, higher order oligonapthofurans such as hexafuranylbenzenes and oxahelicenes have been synthesized, and their properties have been examined as OFETs and p-type semiconductors [8].

2.I.5 Molecules with Buky ball [Fullerene]

Unusual topologies of polycyclic hydrocarbons have been the subject of continuous and considerable attention. Within this large family of chemical compounds, architectures based on a central ring surrounded by several cyclic subunits are of particular interest mainly because such molecules display various shapes such as planar (*PL*), bowl-shaped (*BS*), or saddle-shaped (*SS*).

2.I.5.1 Fullerene

The discovery of fullerenes greatly expanded the number of known carbon allotropes, which until recently were limited to graphite, diamond, and amorphous carbon such as soot and charcoal. Buckyballs and Buckytubes have been the subject of intense research, both for their unique property and for their technological applications, especially in materials science, electronics, and nanotechnology. Spherical fullerenes are also called bucky-balls, and they resemble the balls used in football (soccer) (Figure 2.3) [9].

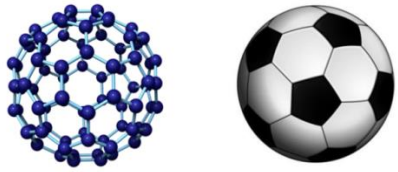


Figure 2.3: Structure of Fullerene, football like molecule

Fullerenes have been extensively used for several biomedical applications including the design of high-performance MRI contrast agents, X-Ray imaging contrast agents, photodynamic therapy and drug delivery.

2.I.6 Bowl shaped Molecules

Sumanene is a polycyclic aromatic hydrocarbon and of scientific interest because the molecule can be considered a fragment of buckminsterfullerene.

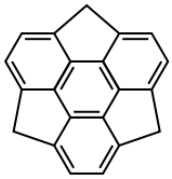


Figure 2.3a: Structure of Sunamene

The core of the arene is a benzene ring and the periphery consists of alternating benzene rings and cyclopentadiene rings [10].

2.I.7 Roof shaped Molecules

In 1987 Weber introduced the concept of geometrically designed roof shaped molecules with applications as clathrate hosts and has studied their inclusion properties [11]. The roof shaped molecule consists of two components of functional groups and a bulky skeleton or base, as presented in Figure 2.4. The Diels-Alder adducts are easily prepared by the cycloaddition reaction of anthracene as diene and with different dienophile, resemble the shape of a roof [12].

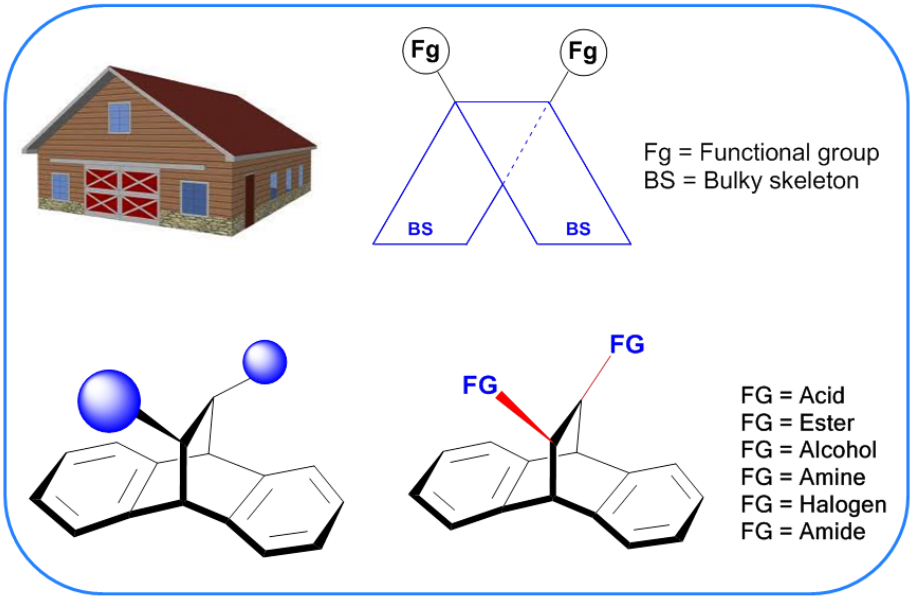
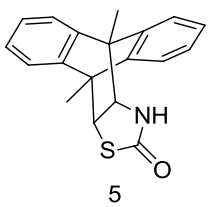


Figure 2.4: Concept of roof-shaped molecules

Some other molecules like iptacene [13] triptacene [14] and molecular tweezers [15] are structurally similar to the above roof shaped compounds and have found several useful applications.

Some of this molecule and their derivative **5** (Figure 2.5) serve as excellent chiral auxiliaries in enatiocontrolled transformation ranging from alkylation to Michael type addition as well as Diels-Alder reaction [16] due to their conformational rigidity and steric reason.

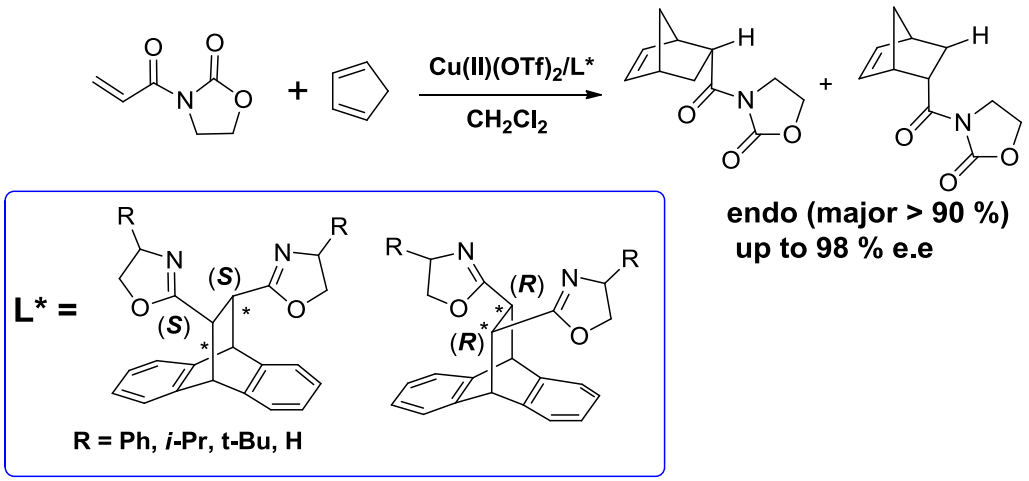


5

Figure 2.5: Structure of Roof shaped chiral auxiliary

The Roof shape molecules in optically pure form are the subject of various studies [17]. These basic roof shaped molecules are precursors of a number of entities with wide applications, such as in medicinal chemistry [18], as ligands in catalytic transformations [19], as mediator for organocatalytic reaction [20], for preparation of chiral selectors [21] and in preparation of functional polymers [22].

Simonneaux and co-worker reported synthesis of 1,4-bis(oxazoline) ligands which were derived from L- or D-amino alcohols and either (*S*,*S*) or (*R*,R) dihydroethano *trans*-dicarboxylic acid, a complete series of ligands was evaluated in the asymmetric Diels-Alder reaction [19i].

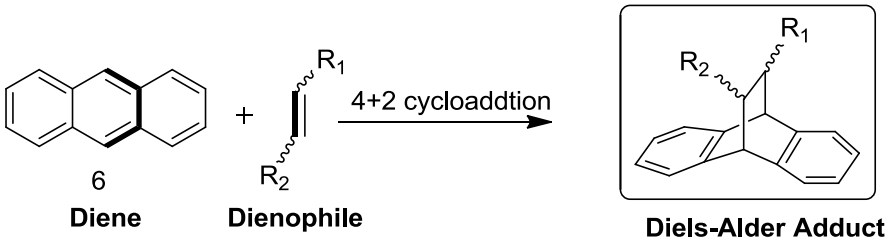


The copper-catalyzed asymmetric Diels-Alder reaction between N-acryloyloxazolidinone and N-crotonyloxazolidinone with cyclopentadiene was carried out with these chiral ligands. The most efficient ligands with a phenyl substituent on the oxazoline ring afforded enantiomeric excess up to 98%.

2.I.8 Synthesis of Roof shape molecules

It is well known that a molecule of anthracene undergoes Diels- Alder reaction with electron deficient dienophile (Scheme 2.1). Weber had explored this reaction to build roof shape molecules and converted them to their functionalized derivatives to study their inclusion property [11].

Scheme 2.1: Common strategy for synthesis of Roof shape molecules

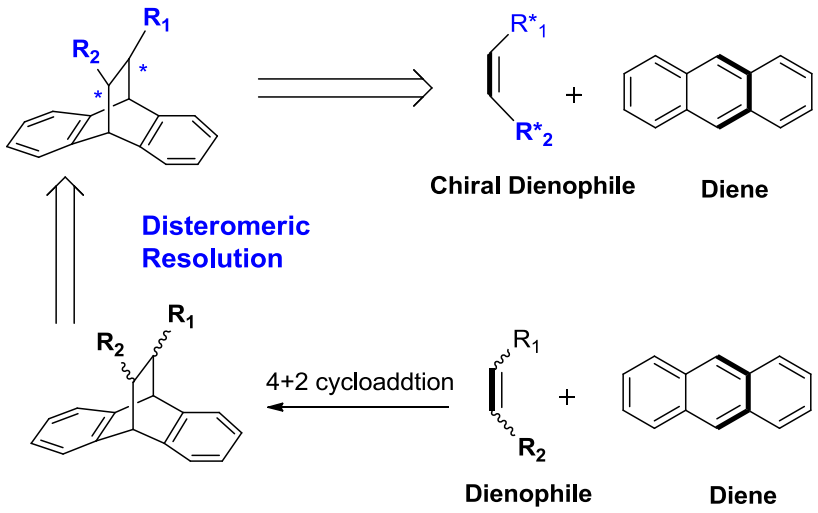


2.I.9 Synthesis of Chiral Roof Shape Molecules

The optically pure analogues were obtained by Diels-Alder cycloaddition reaction of anthracene (**6**) with chiral derivatives of dienophiles [23] (Scheme 2.2).

The other method of accessing the pure enantiomers of Diels-alder adduct is by fractional separation of racemic mixture using chiral resolving agent such as (*S*)-proline [24].

Scheme 2.2: Common strategy for synthesis of chiral Roof shape molecules



2.I.10 Limitation

1. The use of chiral material in stoichiometric amount as auxiliary or resolving agent is expensive and cumbersome as it needs extra efforts for detachment for reuse.
2. Its availability in both enantiomeric forms is not always feasible.

Hence, we have undertaken the present study to resolve different type of roof shape compounds (Figure 2.6) such as alcohol and diol by kinetic separation using bio-catalysis.

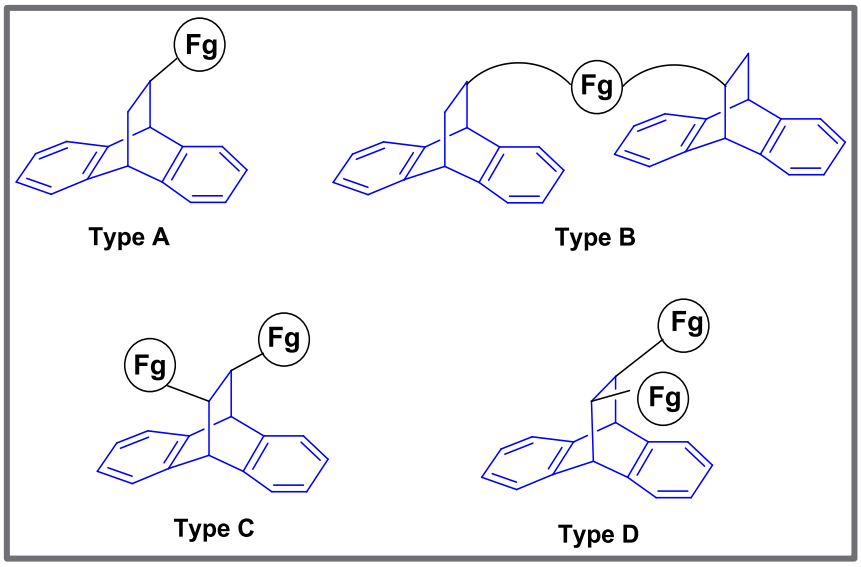


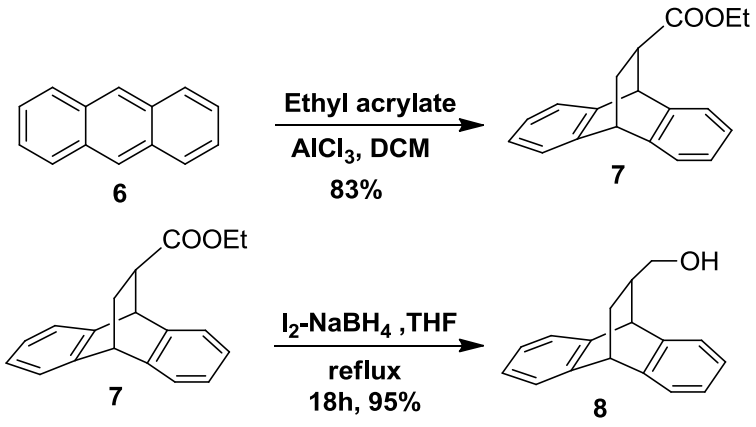
Figure 2.6: Basic skeleton of different roof shape moieties (Type A to D)

In the present chapter such roof shape molecules with ester or alcohol as functional groups are synthesized and investigated. These roof shape esters, acids and its reduced alcohols were prepared by the cycloaddition reaction of anthracene as diene and ester or acid as dienophile.

2.I.11 Synthesis and Enzymatic resolution of Type A

Our efforts to obtain Type A compounds begin with the synthesis of the ester **7** by the established Diels-Alder reaction of anthracene **6** and ethyl acrylate. The ester **7** was efficiently converted to the alcohol **8** by a mild reduction using $NaBH_4$-I_2 [25] (Scheme 2.3).

Scheme 2.3: Synthesis of roof shape alcohol (±)-**8**



2.I.11.1 Resolution of Roof shape alcohol

Bio-catalytic and enzyme assisted organic transformations are fast becoming attractive and efficient methods. Besides the mild nature of the bio-catalyst the additional advantage of being highly selective in their actions has established them as important tools in modern synthesis [26a]. Separation of enantiomers of alcohols by selective acetylation of one isomer while not affecting the other, kinetic resolution is one of the widely studied biocatalyzed reactions. Hence, in this study we have screened commercially available immobilized lipase as biocatalyst for enantioselective acetylation of racemic alcohol **8**. The alcohol (±)-**8** was treated with appropriate acetylating reagent in the presence of a commercial sample of immobilized lipase. We commenced our studies with steapsin lipase under different conditions and data are summarised in Table 2.1.

Table 2.1: Optimization of conditions for resolution of (±)-**8**.

No	Conditions	ee (%) of **8**	ee (%) of **9**	Conversion	E value
	(Steapsin Lipase)				
1	VA (1.5 eq.), THF 30 ^{o}C, 48 h	77	60	56	10
2	VA (1.5 eq.), THF 8-10 ^{o}C, 48 h	59	78	43	14
3	IPA (1.5 eq.), THF 30 ^{o}C, 48 h	5	55	6	11
4	IPA (3.0 eq.), THF 30 ^{o}C, 100 h	29	61	32	6
5	VA (1.5 eq.), Dioxane 30 ^{o}C, 48 h	16	80	16	11
6	EA (3.0 eq.), THF, RT, 48 h	-	-	-	-

VA = vinyl acetate; IPA = *iso*-propenyl acetate; EA = ethyl acetate; [a]Ratio of (±)-**8** to enzyme: 1.0:1.3 (W/W); ee was measured on Chiral HPLC Column. Reaction for entry 2 was performed in Refrigerator.
$C = ee_s/(ee_s+ee_p)$; $E = \{In[ee_p(1-ee_s)]/(ee_p+ee_s)\}/\{In[ee_p(1+ee_s)]/(ee_p+ee_s)\}$

Reactions in dioxane and THF gave comparatively better results for % ee of acetate however the ee of alcohol observed were low. (Table 2.1, entry 4 & 5)

To improve selectivity reaction was performed in THF with the three different acyl donors vinyl acetate (VA), isopropenyl acetate (IPA) and ethyl acetate (EA). The *E*-value was dependent of the use of different acyl donors in the acetylation of the alcohols. Ethyl acetate proved to be poor acyl donor and reaction did not progress (entry 6). On the other hand *iso*-propenyl acetate gave better selectivity for the acetate **9** as compared to unreacted alcohol **8** (entry 3 & 4). Efforts to obtain high optical activity were not successful beyond this level. This steapsin lipase (SL) might not be

suitable catalyst for resolution of alcohol **8**. Hence some other commercially available lipases were investigated.

Hence *Candida rugosa* lipase (CRL) was screened for acetylation of alcohol **8** under different conditions (Table 2.2)

Table 2.2: Optimization of conditions for resolution of (±)-**8**.

No	Conditions	e.e. (%) of **8**	e.e. (%) of **9**	Conversion	E value
	(Candidia Rugasa Lipase)				
1	VA (3.0 eq.), THF, 96 h	4	26	1.8	13
2	IpA (3.0 eq.), THF, 96 h	6	19	1.6	23

vinyl acetate; IPA = *iso*-propenyl acetate; ee was measured on Chiral HPLC colum

It was clear from Table 2.2 that CRL gave very poor results in the few experiments; no further standardization was taken up with this enzyme (Table 2.2, entry 1 & 2).

One of the most popular lipase used in the organic synthesis is lipase *Candida anractica* lipase B (CAL-B) obtained from Novozyme, called as Novozyme-435 [26b]. Next we treated the alcohol with appropriate acetylating reagent in the presence of a commercial sample of immobilized Novozyme-435 lipase under various conditions (Table 2.3).

Table 2.3: Optimization of conditions for resolution of (±)-**8**.

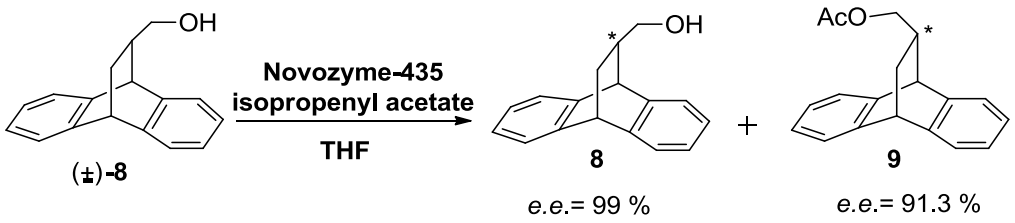
No	Conditions	e.e. (%) of **8**	e.e. (%) of **9**	Conversion	E value
	(Novozyme-435 lipase)				
1	VA (1.0 eq.), DIPE, 2 h	65	95	41	77
2	EA (5.0 eq.), DIPE,15 h	21	59	26	5
3	VA (1.0 eq.), THF, 4 h	63	89	42	36
4	IPA (1.0 eq.), THF, 3 h	99	91	52	125
5	IPA (1.0 eq.), THF 8-10 ^{o}C, 6 h	85	74	53	17

For entry 1 to 4 reactions were performed on room temp.ee was measured on Chiral HPLC column.

For the solvent studies we chose diisopropyl ether (DIPE) and dry THF. In DIPE even though we observed good % ee for the acetate but % ee for alcohol was poor (Table 2.3, entry 1 & 2). THF gave comparatively better enantiopurity for both the compounds. Thus better results were obtained with *Candida Antarctica* lipase (commercially available as Novozyme 435), iso-propenyl acetate as the acyl donor, and THF as the solvent (Table 2.3, entry 4).

After the completion of reaction two spots were observed on TLC which indicated that under present condition one of the isomers remained unchanged while the other isomer underwent acetylation to give ester. Both the products were carefully separated by silica gel column chromatography.

Scheme 2.4: Optimizes condition for kinetic resolution of (±)-**8**

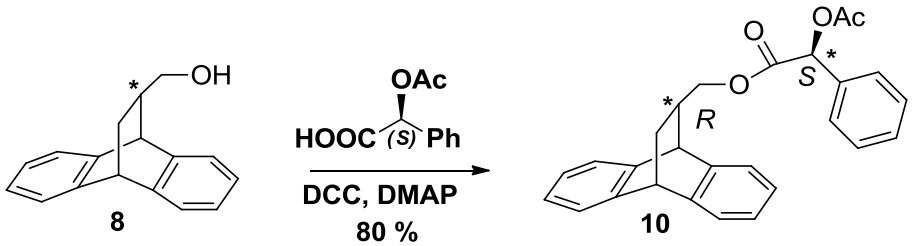


2.I.12 Determination of absolute configuration

For known chiral products the absolute configuration can be established by comparison of the specific rotation with the known data. For unknown compound it can be established by some other technique, such as single crystal analysis of a derivative prepared with another chiral molecule with known chiral center.

The absolute configuration of enantiomerically pure **8** was established by preparing its ester with optically pure (*S*) *O*-acetyl mandelic acid, standard protocol [27]. The optically pure alcohol **8** was converted to the diastereomerically pure ester **10** by its reaction with (*S*)-*O*-acetyl mandelic acid (Scheme 2.5).

Scheme 2.5: Formation of diastereomeric ester



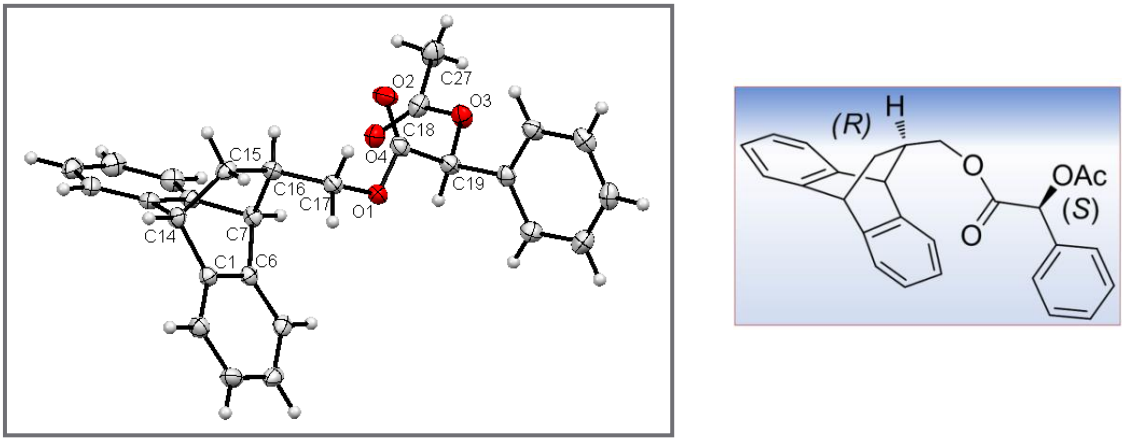
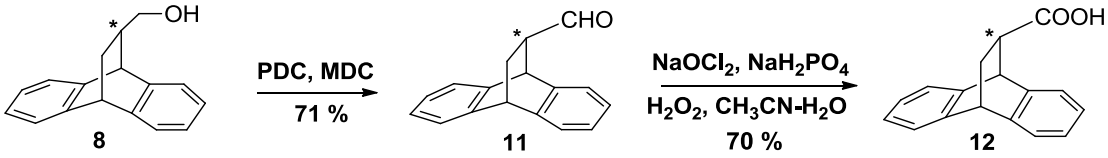


Figure 2.7: ORTEP diagram of compound **10**

Single crystals of compounds **10** were obtained by recrystallization from hexane-dichloromethane (~95:5) (Figure 2.7). The single crystal X-ray diffraction analysis of **10** clearly established the absolute configuration of the stereogenic carbon to be '*R*' [28].

The alcohol **8** was also converted to the corresponding acid **12**, *via* the aldehyde **11** using mild oxidation conditions [29]. The absolute configuration was further confirmed by comparison of the sign of its specific rotation with the known data [30].

Scheme 2.6: Determination of absolute configuration

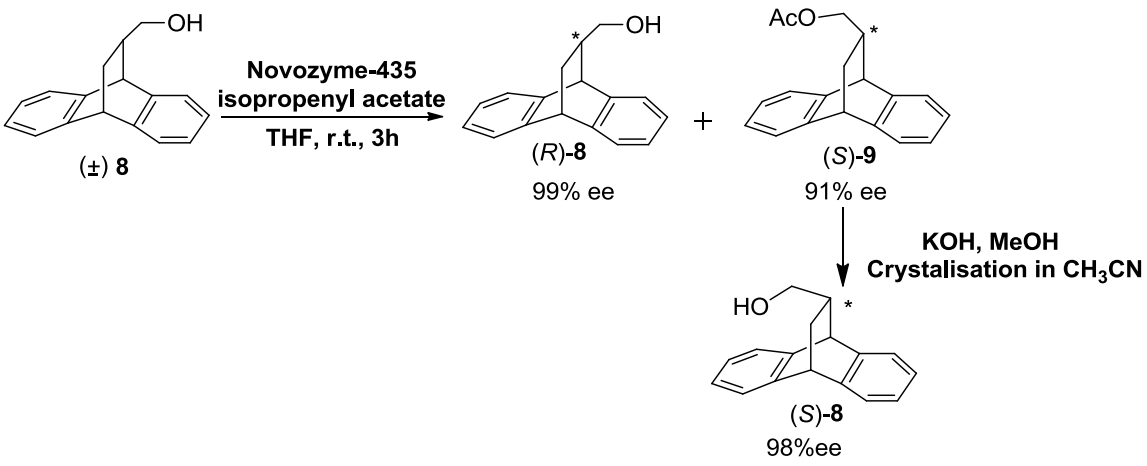


The specific rotation of the reported acid **12** was (+) 7.2 for ***S*** isomer and we observed similar value at same concentration with opposite sign which further confirmed that the absolute configuration of stereogenic carbon to be '*R*'.

After establishment of absolute configuration of unreacted alcohol, the OAc derivative **8** was further hydrolysed in presence of sodium hydroxide in methanol.

The (*S*)-isomer of alcohol **8** obtained after hydrolysis was further crystallised in acetonitrile to improve it's optically purity **(**Scheme 2.7). The optical purity of *S* isomer after crystallisation was found to be 98%.

Scheme 2.7: Hydrolysis of ester (*S*)-**9**



2.I.13 CD spectra

Circular dichroism (CD) analysis of both the isomer show similar pattern but opposite in nature due to the reverse cotton effect **(**Figure: 2.8).

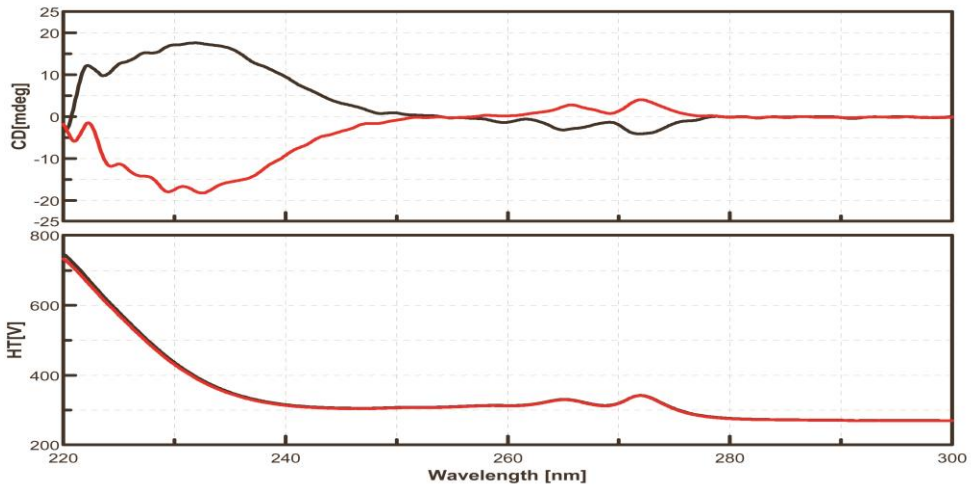
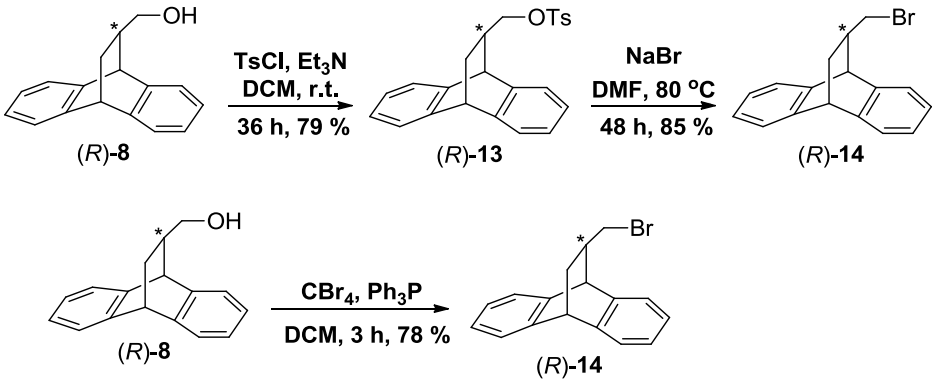


Figure: 2.8 CD Spectra of *R* (Red line) and *S* (Black line) isomer of in CH_3CN (c =1.5 x10^{-3} M)

2.I.14 Synthesis of amino ligand

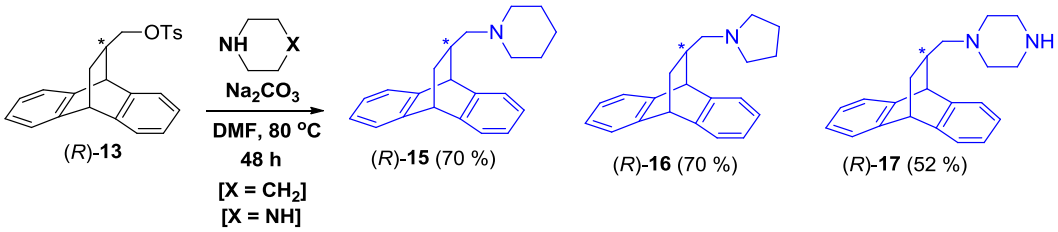
The optically pure isomers of the alcohol **8** were converted to the corresponding tosylate **13** by treatment with freshly crystallized *p*-toluene sulfonyl chloride in presence of triethyl amine (Scheme 2.8). The chiral alcohol was also converted into bromo analogue via appel reaction [31] using carbon tetrabromide in presence of triphenyl phosphine.

Scheme 2.8: Conversion of alcohol **8** into -OTs & bromo analogue



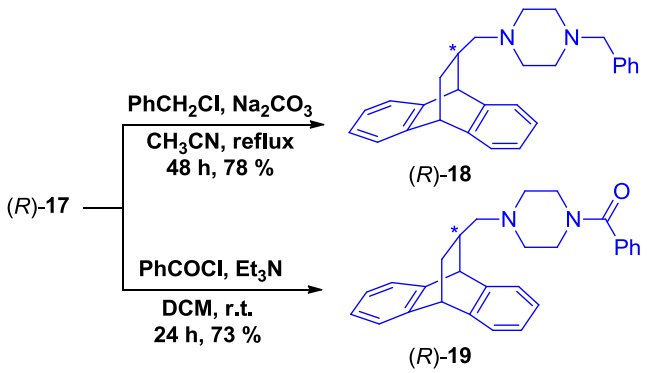
The tosylate (*R*)-**13** was converted to three roof shape amines (*R*)-**15,** (*R*)-**16** and (*R*)-**17** by treatment with piperidine, pyrrolidine and piperazine respectively (Scheme 2.9). The reaction was carried out in DMF at 70 ^{o}C with sodium carbonate and the corresponding products were isolated by column chromatography over neutral alumina with moderate yield.

Scheme 2.9: Synthesis of amine derivative



The piperazine derivative (*R*)-**17** with a free *NH* group was further condensed with benzyl chloride to give *N*-benzyl derivative (*R*)-**18** and with benzoyl chloride to give *N*-benzoyl derivative (*R*)-**19** in straightforward manner.

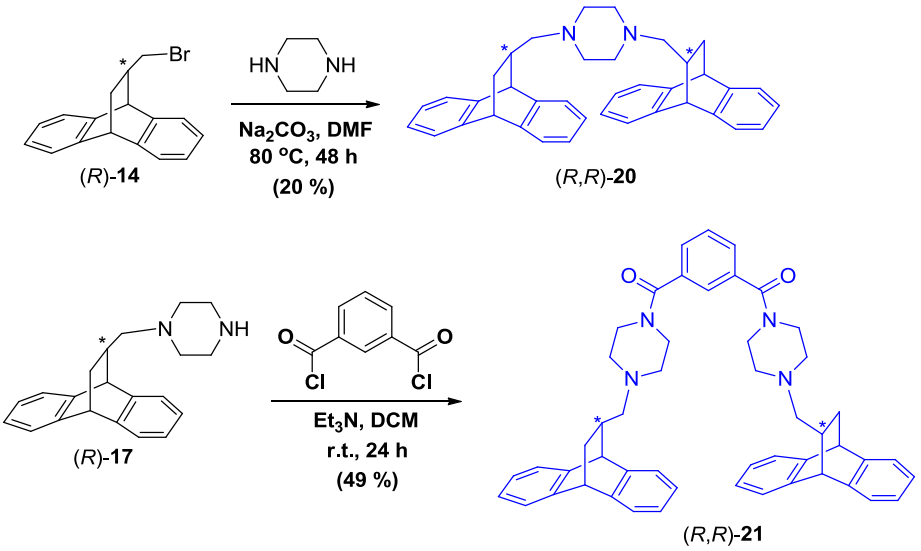
Scheme 2.10: Synthesis of amino derivative



2.I.15 Synthesis of Type B ligand

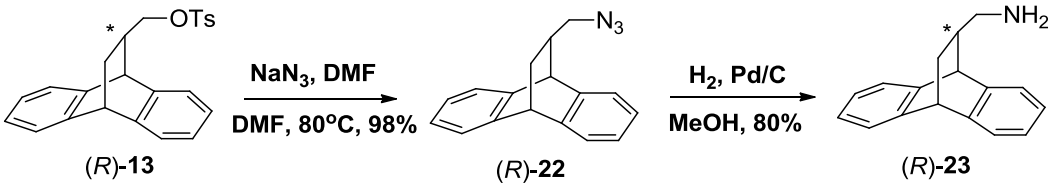
In order to study the effect of the rigid bicyclic frame with the two aromatic rings and the chiral centre, two more molecules were designed and synthesized. The earlier synthesized mono bromo analogue (*R*)-**14** was treated with piperazine to obtain double *N*-alkylated derivative (*R,R*)-**20**. Further structurally rigid unit, di-amino di-amide (*R,R*)-**21** was prepared when the mono amine (*R*)-**17** was condensed with isophthaloyl chloride.

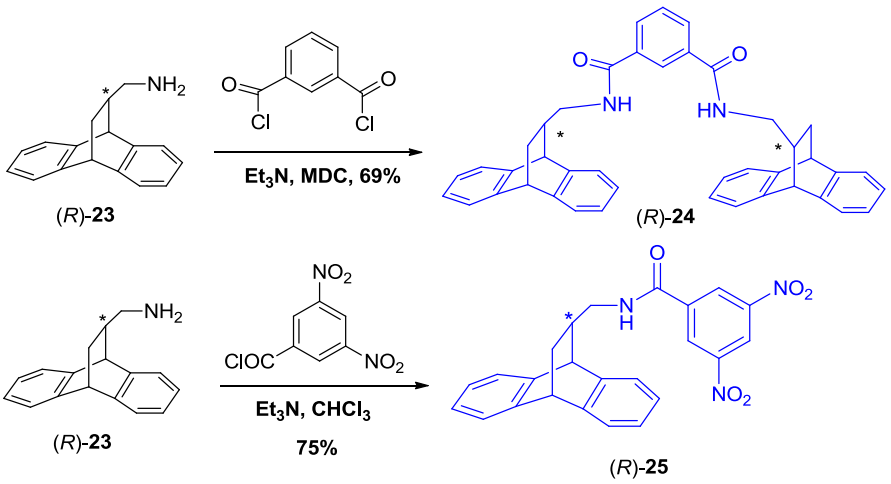
Scheme 2.11: Synthesis of Type B ligand



In another way, tosyl derivative **13** was converted into azide **22** which was further reduced to amine in positive pressure of hydrogen (Scheme 2.12). Roof shape amine was further condensed with isophthaloyl chloride & 3, 5-dinitrobenzyol chloride to obtain rigid amide **24** & diamide **25** molecules.

Scheme 2.12: Synthesis of rigid diamide ligand





All the roof shape chiral amines and amides were characterized by usual spectroscopic and analytical techniques.

2.I.16 Synthesis of Type C & D Molecules.

After the resolution and preparation of roof shape molecule of Type A, next we focussed on the preparation of roof shape *trans* and *cis* diol.

This section deals with the design and synthesis of C_2 symmetric diols which were directly derived from the anthracene as diene and fumaric acid and maleic anhydride as dienophile.

(a) Kinetic resolution of *trans*-diol and preparation of various diamine ligands.

(b) Enzymatic desymmetrisation of *cis*-diol.

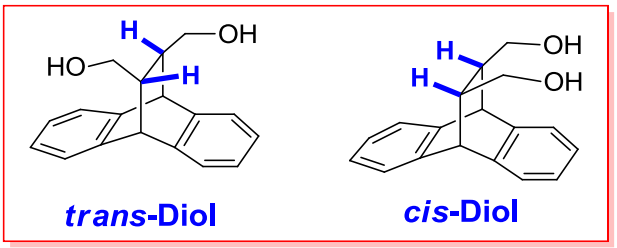
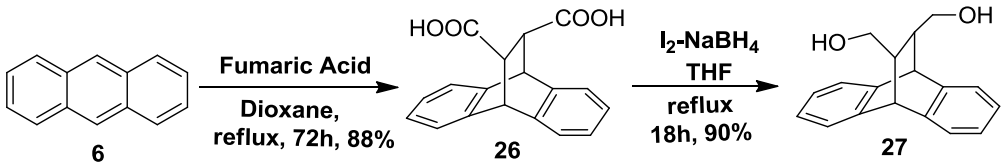


Figure 2.9: Structure of anthracene derived diols

2.I.17 Synthesis of roof shape *trans*-diol

Our efforts to obtain optically pure diol began with the synthesis of the required diacid by the established Diels-Alder reaction of anthracene **6** and fumaric acid [32]. The Diels Alder adduct **26** was reduced to the diol **27** by reduction using $NaBH_4$-I_2 [25] (Scheme 2.13).

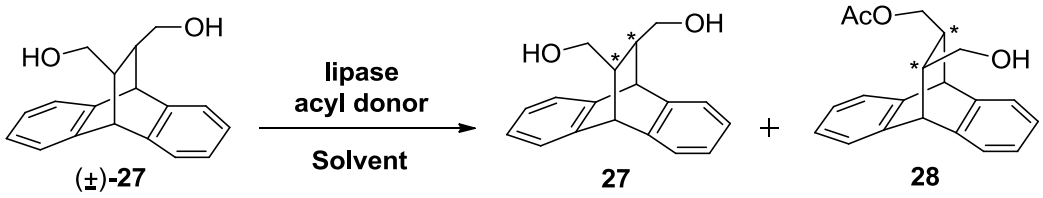
Scheme 2.13 Synthesis of *trans*-Diol (±)-**27**



2.I.18 Kinetic Resolution of *trans*-Diol (±)-27

Separation of enantiomers of alcohols by selective acetylation of one isomer while not affecting the other, kinetic resolution is one of the more studied biocatalyzed reactions. In this study we have screened commercially available immobilized lipase as biocatalyst for enantioselective acetylation of racemic *trans*-diol **27**. The diol (±)-**27** was treated with appropriate acetylating reagent in the presence of a commercial sample of immobilized steapsin lipase (Scheme 2.14, Table 2.4).

Scheme 2.14 Condition for kinetic resolution of *trans*-Diol (±)-**27**



Under the present conditions one of the isomer of **27** remained unchanged while the other isomer underwent mono acetylation to give monoester **28**. Ether solvents were found to be compatible to get better conversion and selectivity. Effect of low temperature on the action of biocatalysts was well documented [33]. The reaction in THF, or dioxane, was performed at 8-9 ^{o}C with vinyl acetate in tetrahydrofuran to observe improvement in the selectivity and conversion (entry 3 to 5, Table 2.4).

Different acetylating reagents were screened and vinyl acetate was found to give satisfactory conversion and selectivity. Although other reagents were quite selective the conversions were poor even if used in excess (entry 8-10, Table 2.4).

Table 2.4: Conditions for kinetic resolution of diol **(±)-27**

Entry	Conditions				% e.e. of acetate **28**[a]	% e.e. of diol **27**[a]	C[b]	E[c]
	acyl donor	solvent	temp ^oC	time h				
1	vinyl acetate[d]	DME	r.t.	48	93.2	57.1	38	49
2	vinyl acetate[d]	Et_2O	r.t.	48	64.1	90.0	58	13
3	vinyl acetate[d]	THF	r.t.	48	94.1	37.6	28	46
4	vinyl acetate[d]	THF	8-9	48	96.6	99.6	51	>200
5	vinyl acetate[d]	dioxane	8-9	60	97.8	56.5	37	176
6	ethyl acetate[d]	THF	r.t.	120		No reaction		
7	ethyl acetate[e]	THF	r.t.	96	78.2	39.8	34	12
8	ethyl acetate[e]	THF	8-9	96	>99	15.3	14	>200
9	butyl acetate[d]	THF	r.t.	96	>99	10.9	20	>200
10	isopropyl acetate[d]	THF	r.t.	96	99	16.7	15	>200

[a]Optical purity was determined by chiral phase HPLC analysis using Chiralcel-OD and OD-H columns; [b]Conversion, $C = ee_s/(ee_s+ee_p)$; $E = \{In[ee_p(1-ee_s)]/(ee_p+ee_s)\}/\{In[ee_p(1+ee_s)]/(ee_p+ee_s)\}$
[d]1.5 eq.; [e]6.0 eq.

In the next study the ratio of lipase to substrate was investigated (Table 2.5). Reaction with the ratio of diol **27** to the granular, immobilized sample of lipase (1:1.33 w/w) was most effective (entry 5 & 6, Table 2.5).

Table 2.5: Effect of substrate to enzyme ratio on kinetic resolution of (±)-**27**.

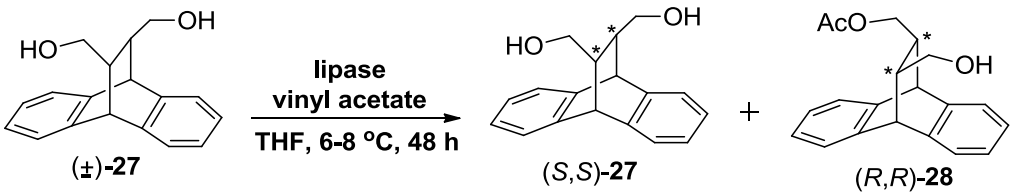
Entry	Conditions with vinyl acetate (1.5 eq.) in THF			% e.e. of acetate **28**[a]	% e.e. of diol **27**[a]	C[b]	E[c]
	Ratio (W/W) **27**: Lipase	temp ^oC	time h				
1	1 : 0.33	r.t.	36	58.5	55.1	49	6
2	1 : 0.33	40	48	53.8	30.2	36	4
3	1 : 0.6	8-9	48	62.8	43.1	41	6
4	1 : 1.0	8-9	48	72.8	39.6	35	9
5	1 : 1.3	r.t.	48	94.1	37.6	28	46
6	1 : 1.3	8-9	48	96.5	>99	50	>200

[a, b & c]same as Table 2.4

2.I.19 Determination of absolute configuration

For this compound S.O.R data was documented in the literature and by comparison of that data with the observed data, it was found that under the present conditions the (*S*,*S*) isomer of **27** [$[\alpha]_D$ = +11.3 (c = 1, MeOH (Reported) for (*S*, *S*)-isomer $[\alpha]_D$ = +11.1(c = 1, MeOH (Observed)] remained unchanged while the (*R*,*R*) isomer underwent mono acetylation to give monoester (*R*,*R*) **28**. (Scheme 2.15).

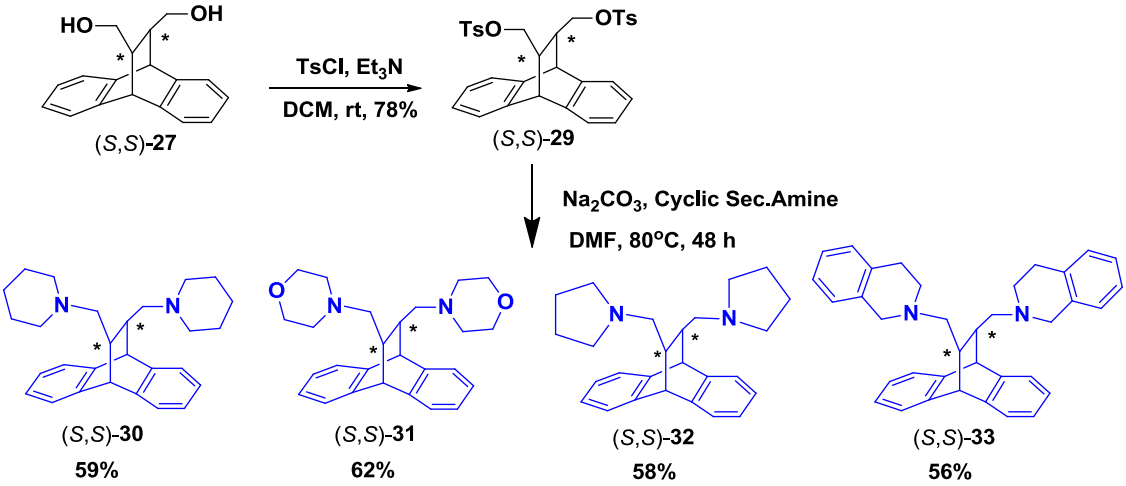
Scheme 2.15: Assignment of absolute configuration



2.I.20 Synthesis of Type C ligand

Similar strategy was also followed for the preparation of Type C diamine ligand where diol was first transformed into ditosylate derivative which was further replaced by different type of cyclic secondary amines to gave another Type C_2 symmetrical diamines (Scheme 2.16). The reaction is carried out in DMF at 70 ^oC with sodium carbonate and the corresponding products were isolated by column chromatography over neutral alumina.

Scheme 2.16: Conversion of diol into diamine ligand



The applications of these roof shape amines will be discussed in subsequent sections of the thesis.

2.I.21 Enzymatic desymmetrisation

During the recent years, tremendous efforts have been made to establish selective routes for the preparation of enantiomerically pure compounds due to their importance in various fields [34].

Enzymatic desymmetrisation of prochiral or *meso* compounds to yield enantiomerically enriched products has proved to be valuable tool in asymmetric synthesis [35].

Applications of chiral molecules, natural and unnatural, are found in wide range of areas covering medicinal, supramolecular, material, analytical chemistry, agro and food industry and in asymmetric synthesis of other chiral compounds. The strategy of chiral pool synthesis is widely explored to access chiral starting materials for useful synthesis but it has its limitations [36]. Scope and applications of unnatural chiral compounds is widely being recognized. Recent focus is on the use of efficient synthetic methodologies to access such chiral molecules from achiral or prochiral materials. Along with several elegant methods of generation of chiral elements by synthetic operations, it is also possible to separate enantiomers of the chiral compounds. Separation of isomers of chiral compounds can be achieved by metal based catalytic reactions or by non-metal based organocatalytic and enzymatic reactions. Enzymes are generally recognized as effective, mild, selective, environment friendly catalysts for accessing optically active compounds, mostly by separating the isomers [37]. The development is also helped by availability of immobilized enzymes which can tolerate non-aqueous reaction conditions for practical applications. Although biocatalysts can target several functional groups like esters, acids, amines they are often studied for effecting conversion of alcohols to esters by suitable transesterification reactions. Racemic alcohols can be selectively converted to the esters of one enantiomer while not affecting the other, based on the process of kinetic resolution (KR) [38]. The drawback of this process involves limited yield of maximum 50 %, of the product and unchanged starting material. This may be overcome by dynamic kinetic resolution (DKR) which consists of carrying out continuous interconversion or racemization of the substrate molecule. At the same time the process of desymmetrization which effectively removes the element of symmetry from suitable molecules is an attractive option to access chiral molecules. Basically a molecule with two identical functional groups is subjected to selective

conversion of one of them to different functionality, theoretically giving quantitative yield of the product. Such desymmetrization has been known to be achieved by metal catalytic or non-enzymatic reactions [39] or by biocatalyzed conversions [40]. The protocol of enzymatic enantiomer desymmetrization (EED) has been applied on *meso*-diols for the preparation of chiral molecules [41] and for the synthesis of complex natural products [42]. The 1,4 arrangement of *meso*-diol which is subjected for enzymatic desymmetrization are presented in Figure 2.10.

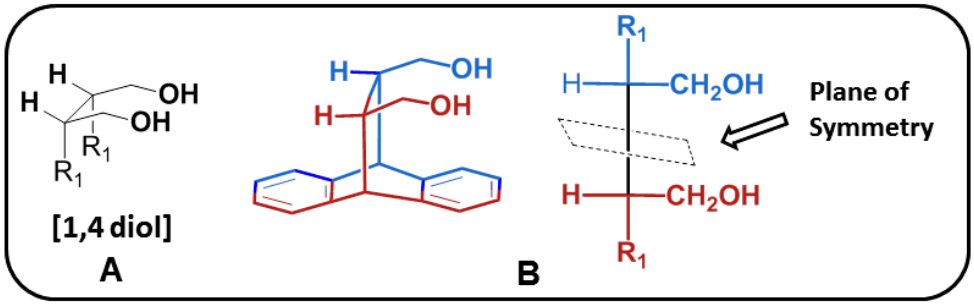


Figure 2.10: (A) *meso* 1,4-diols (B) Roof shape *meso* diol and presence of plane of symmetry.

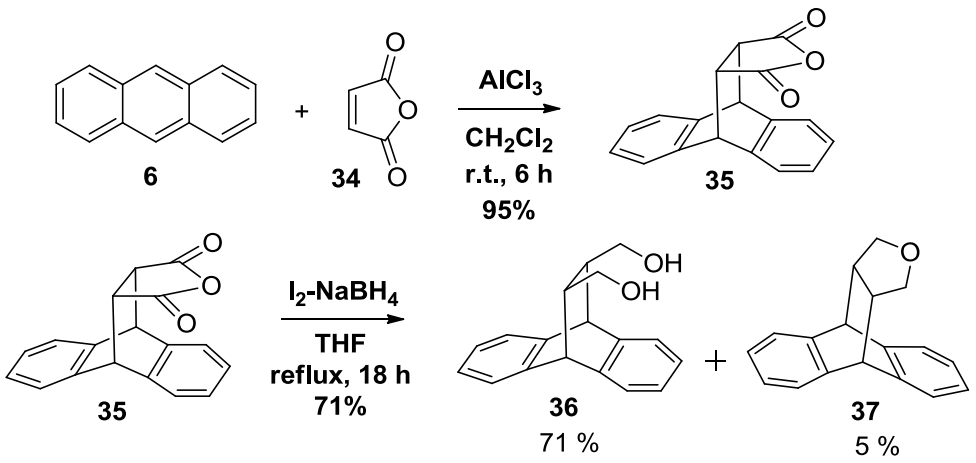
In desymmetrisation process the important parameters to which attention has been paid are enantioselectivity and the yield of the EED, which should be higher than 50% so that the desymmetrisation implies a clear advantage over KRs.

In the present study we extend the scope of such molecules by studying the *meso* isomer of *cis*-diol, which was synthesized and resolved using biocatalytic approach. The separation of *cis*-diol involving enantioselective acylation and hence may give theoretically up to quantitative yield as against the case of *trans*-diol (±) **27**.

2.I.22 Synthesis of *cis* diol

The synthesis of *cis*-diol **36** is outlined in Scheme 2.17. The roof shape framework is constructed by Lewis acid catalyzed Diels-Alder cycloaddition of anthracene **6** and maleic anhydride **34** at ambient conditions. The adduct anhydride **35** separated as crystals was then subjected to reduction under mild conditions of I_2-$NaBH_4$ to afford *cis*-diol **3** in good yield, Along with 5% of *cis* ether **37** was also formed. Both the products were separated with column chromatography on silica gel.

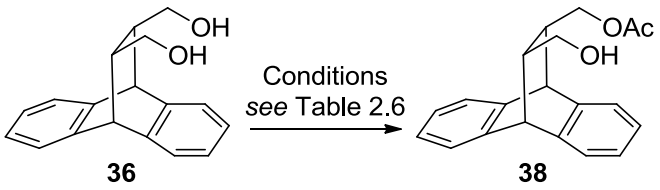
Scheme 2.17: Synthesis of *cis*-diol **36**



2.I.23 Enzymatic Desymmetrisation

The *cis*-diol **36** was then subjected to desymmetrization reaction involving enzyme mediated transesterification reaction (Scheme 2.18). In our earlier study on resolution of roof shape alcohols we had successfully screened Novozyme-435 for alcohol **8**, while Steapsin lipase was effective for *trans*-diol **27**. For both the reactions THF was found to be a good solvent. The optically pure materials were obtained in high purity and efficiency, particularly at low temperature. Our observation of higher selectivity at lower temperature is consistent with the literature reports. Hence, we started our initial screening with these conditions for the desymmetrization of diol **36** (Table 2.6).

Scheme 2.18: Resolution of *cis* diol **36**



The reaction of diol **36** with vinyl acetate as acyl donor in presence of Steapsin lipase (SL) in THF was clean and only one product of mono acylation **38** was detected in the reaction mixture. The product could be easily separated and analysed. The optical purity of the product **38** was established by HPLC analysis on Chiralpak OD-H column. As can be observed acylation was more effective with higher amount of acylating reagent (entry 4). The other enzymes Novozyme-435 and *Candida rugasa*

were ineffective in chiral discrimination (Table 2.6, entry 5 to 7). We scanned two more solvents, DME and Toluene, although conversion was notable the selectivity was not high (Table 2.6, entry 8 & 9). We also scanned different acyl donors, where ethyl acetate was found effective when used as solvent. Although the selectivity was good the conversion was quite poor (Table 2.6, entry 10).

Table 2.6: Condition for Enzymatic desymmetrization of **36**.[a]

No	Enzyme[a]	Solvent	Time (h)	Acyl donor[b] (eq.)	Yield[c] (%) [ee[d] (%)] of **38**
1	SL	THF	72	VA (3)	35 [13]
2	SL	THF	72	VA (15)	71 [48]
3	SL	THF	60	VA (30)	93 [72]
4	**SL**	**THF**	**30**	**VA (60)**	**90 [79]**
5	N-435	THF	60	VA (7)	29 [0]
6	N-435	THF	60	VA (7)	35 [0]
7	CR	THF	60	VA (7)	12 [0]
8	SL	DME	60	VA (30)	75 [55]
9	SL	Toluene	60	VA (30)	53 [55]
10	SL	THF	120	EA[e]	27 [71]
11	SL	THF	60	IPA (30)	35 [52]
12	SL	THF	60	BA (30)	-- [--][f]

[a]All reaction run at 8-9 ^{o}C; [a]SL = Steapsin lipase; N-435 = Novozyme-435; CR = Candida rugasa. [b]VA = vinyl acetate; IPA = isopropenyl acetate; . EA = ethyl acetate; BA = butyl acetate. [c]Isolated. [d]Determined by HPLC on Chiralcel OD-H. [e]As solvent. [f]No reaction.

The enzyme mediated reactions on structurally demanding substrates are often found difficult and challenging [43]. The present *cis*-diol **36** in comparison with the other two roof shape substrates **8** and **27** may also pose difficulty due to the similar considerations. This was addressed by studying the improved ratio of enzyme to substrate (Table 2.7). Although there was not much improvement in the conversion, the selectivity was drastically improved when high amounts were used with excess of acyl donor. Significantly no product of diacetylation was observed in any of the experiments investigated in the present study.

Table 2.7: Effect of substrate:enzyme (Steapsin lipase) ratio.

No	Substrate: Enzyme	Time (h)	Yield[a] (%) [ee[b] (%)] of **4**
1	1 : 1	72	90 [48]
2	1 : 2	60	93 [72]
3	1 : 3	60	95 [73]

[a]Isolated. [b]Determined by HPLC on Chiralcel OD-H.

2.I.24 Racemisation study

Molecules where the two groups capable of chemically undergoing acylation reactions are juxtaposed in the manner where the internal acyl transfer reactions are feasible pose some additional issues. When the two alcohol groups were placed close to each other the acyl group may migrate from each other leading to the interconversion of the mono acyl derivative. Such problem leads to low selectivity as discussed by Fadel and Arzel [41b, 41c] and others [44]. In the course of our present study we envisaged similar possibility as the two hydroxymethyl arms in *cis*-diol **36** were protruding in the same direction and were placed close to each other.

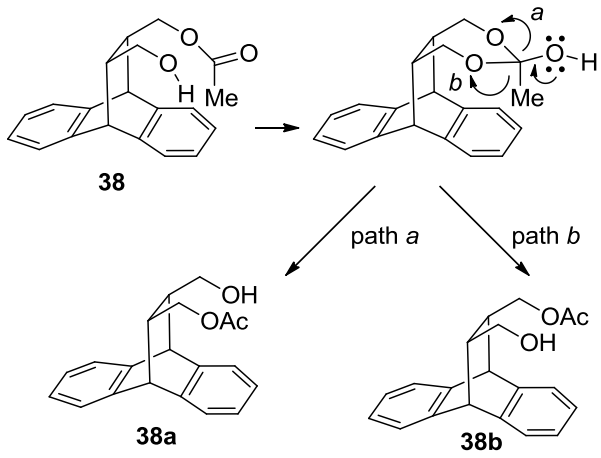
The possibility may attribute to the observed low selectivity in some of the experiments we had studied. To confirm this possibility a sample of optically pure mono acetate **38** was refluxed in isopropanol and its purity was checked periodically (Table 2.8). Within a relatively short time the product lost its optical purity to a considerable extent confirming the isomerization of mono acetate **38**. The possible mode of internal transfer of acyl unit in **38** may be explained in Scheme 2.19. Attach of free hydroxyl group on the acetate can give a *meso* intermediate 1,3-dioxolan-2-ol derivative (hemiacetal), which can open from two sides, 'path-a' giving one isomer **38a**, while 'path-b' will lead to the other isomer **38b**, both the steps will be equally promoted at higher temperature.

Table 2.8: Racemization study.[a]

No	Time (h)	Ee[b] (%)
1	2	83
2	6	81
3	12	72
4	15	52
5	18	33
6	24	30
7	30	29
8	48	22

[a]The sample was heated in reflux IpA

Scheme 2.19: Mechanism of racemization **4**.



2.I.25 Enrichment in optically purity via crystallization

Optically active compounds, particularly with more than one chiral center, are often subjected to enrichment by crystallization under proper conditions. Right from the pioneering work of Louis Pasteur such observations are well studied [45]. The process of enrichment of chiral isomers during procedure of crystallization appears to be more of an art than science and success depends on certain structural arrangement responsible for definite supramolecular interactions. There were frequent reports in the literature where the technique of recrystallization has been utilized to improve the optically pure compounds [46]. The isolated optically enriched sample of the product **38** was crystallized from different solvents in order to purify as well as to further improve the ratio of its diastereomers.

Different solvents were investigated to recrystallize optically pure samples of **38** (~72 % ee). In dichoromethane -hexane mixture (~10:90) we observed formation of crystals of two distinct shapes. Careful observation indicated that few crystals were of plate like shape and more transparent in nature. These crystals, though seen in very few numbers, were physically separated and characterized by single crystal X-ray diffraction analysis and their optical purity was established by chiral phase HPLC analysis (Chiralpak ODH). The optical purity was observed to be enriched and on average seen to be in the rage of 93-95 % ee. The X-ray analysis of these crystals showed unique features (Figure 2.11A) [47]. The crystal showed packing of only one

stereoisomer with a chiral space group of $P2_12_12_1$. Moreover intermolecular hydrogen bonding between the carbonyl oxygen of [-OC(*O*)CH_3] of one molecule and the hydroxyl group [-CH_2O*H*] of the other was observed. The hydrogen bond distance was found to be 2.138 Å, typical of such cases. [CCDC no. of chiral crystal =1020854, CCDC no of racemic crystal = 1020855]

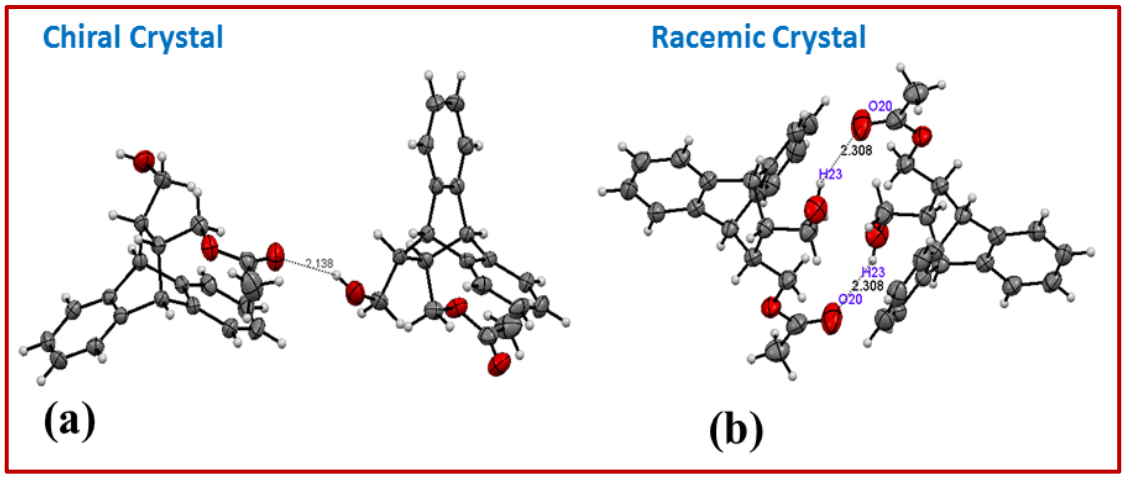


Figure 2.11: (a) ORTEP Diagram of optically pure mono acetate **38**. (b) ORTEP Diagram of racemic mono acetate **38** showing dimmer formation.

The intermolecular hydrogen bonding in the optically pure crystal of **38** was observed in an extended linear way between the series of molecules (Figure 2.12a). Moreover it is noteworthy to see a *P*-helical motif along with the *a* axis marked as green line in Figure 2.12b & marked by yellow rod in Figure 2.12b) with a helical pitch of 15.782 Å. Such molecular assembly arranged due to the weak hydrogen bond network to form a helix with particular stereoisomer is known in the literature [48].

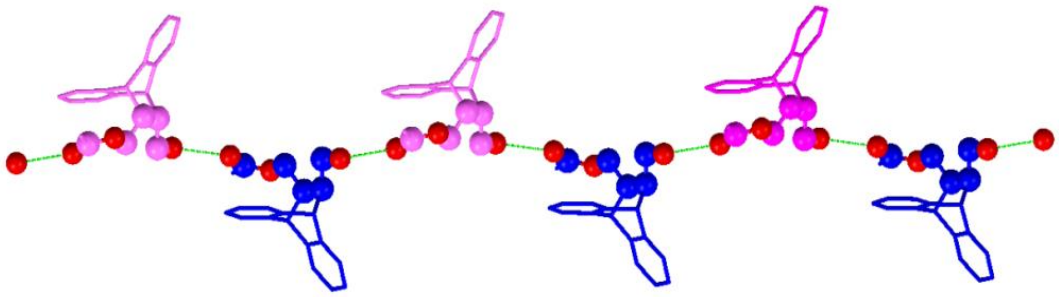


Figure 2.12a: ORTEP Diagram showing H-bond network [**In Green Line]** for optically pure mono acetate **38**.

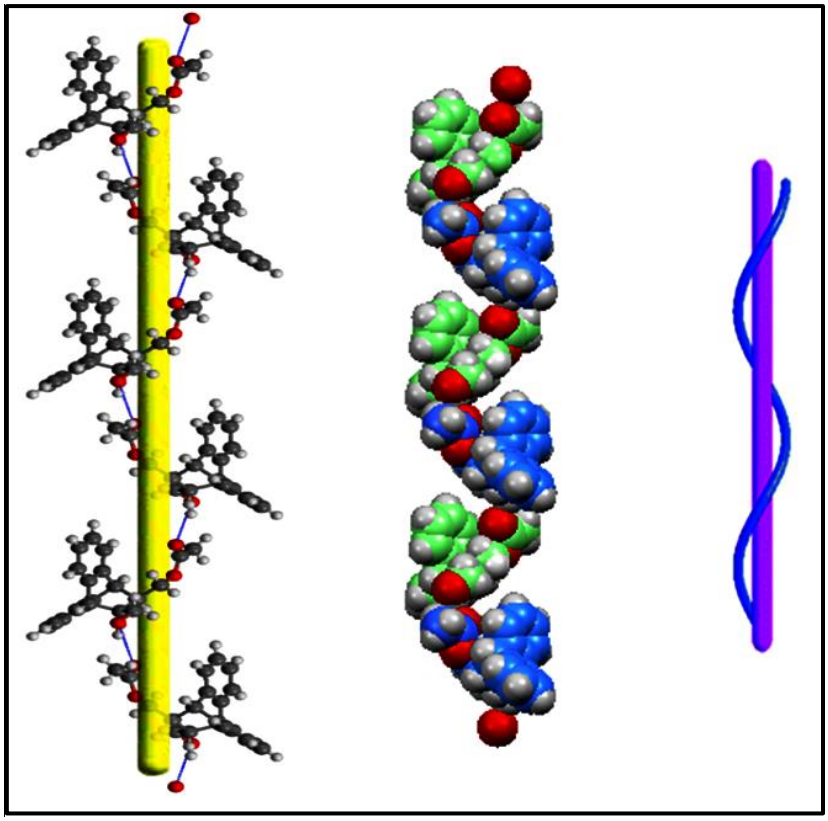


Figure 2.12b: ORTEP Diagram showing H-bond network for optically pure mono acetate **38**

However, the majority of crystals of **38** were colourless and more like cube shape. These crystals were racemic in nature, established by specific optical rotation as well as by HPLC analysis. The single crystal analysis indicated a completely different arrangement (Figure 2.11b) [47]. The analysis revealed the unit cell was consisting of two molecules of opposite stereochemistry held together by two sets of intermolecular hydrogen bonding between the same functionality. The hydrogen bond distance was seen to be 2.308 Å in the case of racemic sample. Slightly weaker hydrogen bond in racemic sample may be attributed to quite a large eighteen member macrocyclic arrangement. The space group of the racemic crystal was observed to be P-1 and a well-organized dimmeric arrangement was detected. No extended hydrogen bond network was observed in the crystal of racemic mono acetate **38**. Such contrasting crystal behaviour between the optically pure and racemic sample of same molecule is a rare phenomena. However, the recrystallization of initial racemic sample of **38** in various solvents under different conditions yielded racemic crystals; hence the possibility of spontaneous resolution may be low [49].

2.I.26 TG-DTA analysis

It was also observed that the melting points of the chiral and racemic samples of **38** differ, as also observed earlier for similar roof shape *trans*-diol [23a] (Figure 2.13). The thermal analysis TG-DTA indicated the M.p. of chiral **38** (sample of ~95 % ee) to be 104.5 ^{o}C while the racemic sample melted at higher temperature of 119.3 ^{o}C.

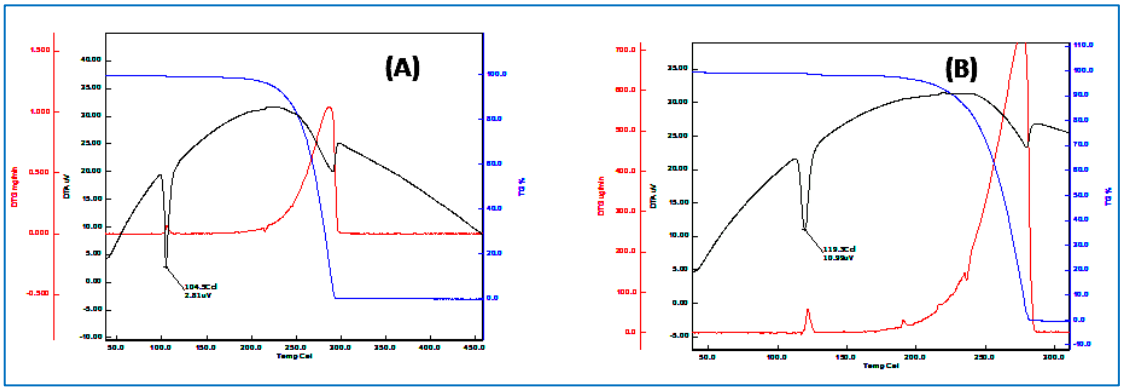
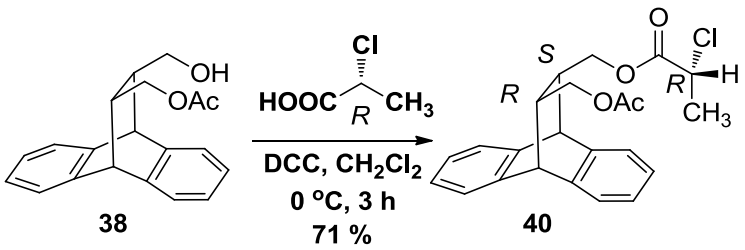


Figure 2.13: TG-DTA analysis of chiral and racemic crystal

2.I.27 Determination of absolute configuration

The absolute configuration of enantiomerically enriched sample of **38** was established by preparing its ester with (*R*)-2-chloropropionic acid [47]. The chiral pure mono acetate **38** obtained during the resolution was converted to the diastereomerically pure ester **40** (Scheme 2.20). The single crystal X-ray diffraction analysis of **40** clearly established the absolute configuration of the stereogenic carbons of the original sample of **38** (Figure 2.14)

Scheme 2.20: Conversion of **38** to ester of known absolute configuration.



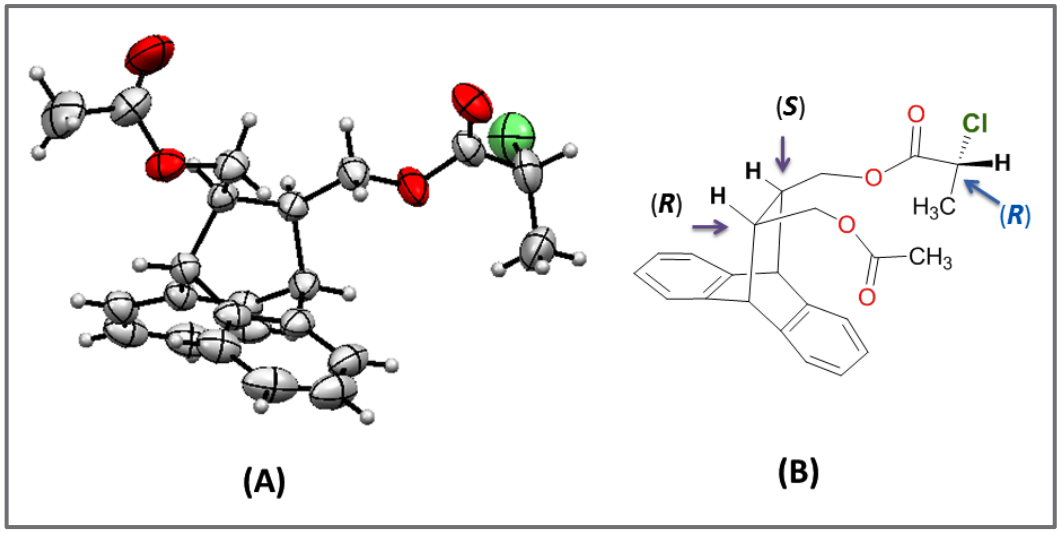
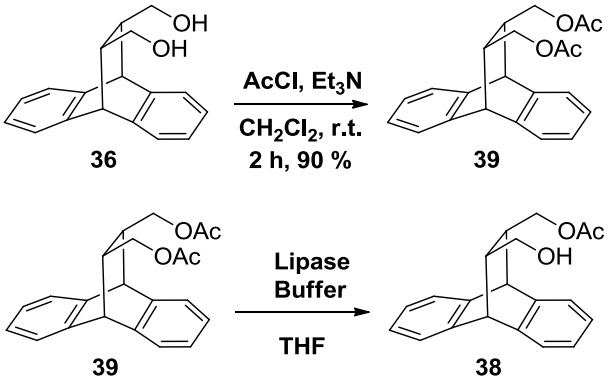


Figure 2.14: ORTEP Diagram of **40**

2.I.28 Enzymatic Hydrolysis

In enzymatic desymmetrisation of *cis* diol we were able to get selectivity of 79%. Optically pure crystal of **38** (11*R*, 12*S*) showed P helical in crystal packing. In next stage the diol was converted to diacetate **39** using standard protocol [scheme 2.21]. Suitable crystal of this compound **39** was also developed and analysed by single crystal X-ray analysis [47]. In literature, it was reported that transestefication and hydrolysis process are in several cases complementary reactions for access of both enantiomers of a compound. [50]. In order to get better selectivity and other isomer, we further attempted enzymatic hydrolysis reaction of diacetate **39**. Some initial experiment of this reaction didn`t proceed well in aqueous media, so no further optimisation was done.

Scheme 2.21: Synthesis of *meso* diacetate **7** and its attempted Hydrolysis



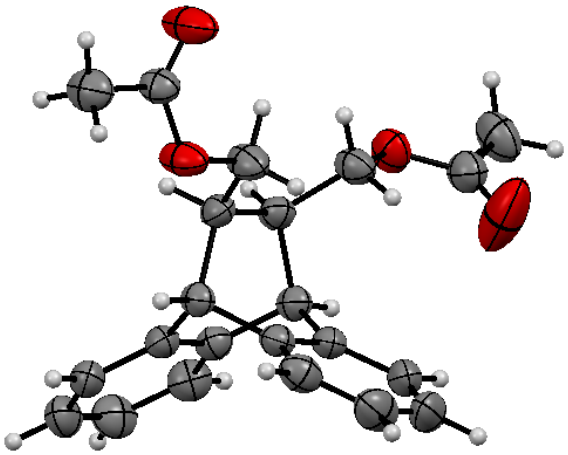
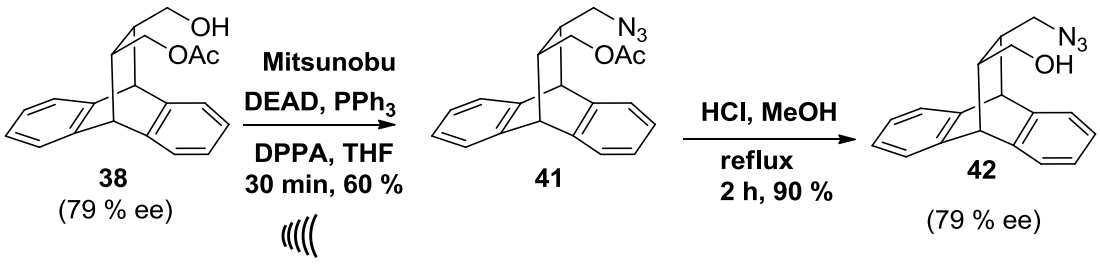


Figure 2.15: ORTEP Diagram of *meso* diacetate **39**.

2.I.29 Synthesis of azido alcohol

The present roof shape chiral molecules are good candidates to be studied in asymmetric synthesis, catalysis and in molecular recognition studies. To increase their utility we need to develop their conversion to other functional groups. Our studies have also established the *cis*-isomers undergo loss of its optical purity due to the internal acyl transfer process. In order to address these issues we consider conversion of the free hydroxyl group of optically pure sample of mono acetate **38** to its azide by Mitsunobu reaction [51] with DPPA.

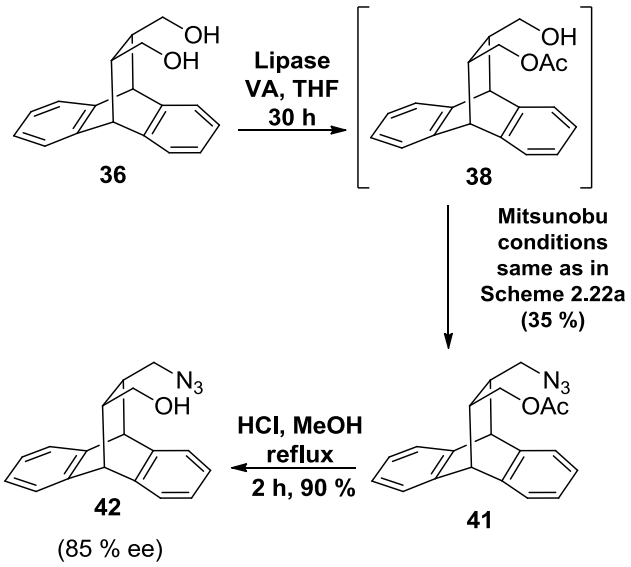
Scheme 2.22a: Synthesis of azido-acetate **41** and azido-alcohol **42**.



The standard procedure [52] was followed to convert sample of **38** with optical purity of 79 % ee under ultrasonic irradiation to afford azido-acetate **41**, which was converted to azido-alcohol **42** by acid catalyzed hydrolysis. The optical purity of **42** remained unchanged during the procedure as both the products were stable and indicating absence of any isomerisation (Scheme 2.21a).

In the earlier part of the study we have established the thermal isomerisation of optically pure sample of mono-acetate **38a** (Table 2.6). During the course of work-up and purification by column chromatography, concentration of the fractions etc. there was a chance of isomerisation of the compound and may contribute in the lowering of optical purity. In order to ascertain this aspect we performed a separate fresh set of lipase mediated resolution of *cis*-diol **36**, where the crude sample, after just filtration of the immobilized enzyme, was subjected to the above sequence of Mitsunobu reaction and hydrolysis (Scheme 2.22).

Scheme 2.22b: One step synthesis of azido-alcohol **42**.

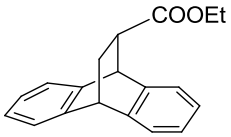


The final product **42** was purified by column chromatography and analysed for its optical purity. The product **42** obtained here showed higher optical purity (85% ee) and the process can be extended for practical applications.

2.I.30 Experimental data

Thin Layer Chromatography was performed on silica gel plates coated on aluminium sheets. The spots were visualized under UV light or with iodine vapour. All the compounds were purified by column chromatography on silica gel (60-120 mesh) and neutral alumina. All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. NMR Spectra were recorded on 400 MHz Spectrometer (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR, 376 MHz for ^{19}F-NMR with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on GCMS instrument. IR Spectra were recorded as KBr pallets. Melting points were recorded in Thiele's tube using paraffin oil and are uncorrected. Specific optical rotations were measured on JACSO P-2000 Polarimeter. For the HPLC analysis Chiralpak OD-H Chiralpak OD and Chiralpak IC column were used.

11-ethyl 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate: **7**



To a suspension of anthracene (**6**) (10.0 g, 56.2 mmol) in dry dichloromethane (100 mL) under nitrogen atmosphere kept in ice bath (0^{o}C), aluminium chloride (7.47 g, 56.2 mmol) was added portion wise. After stirring for 15 min, a solution of ethyl acrylate (5.62 g, 56.2 mmol) in dichloromethane (50 mL) was added drop wise to the reaction mixture. The resulting mixture was stirred at room temperature for 36 h, and poured in ice water (200 mL), the separated organic layer was collected and the aqueous layer was extracted with dichloromethane (3X150 mL). The combined organic extracts were washed with water (2X50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by crystallization with dichloromethane in petroleum ether (10 %). (13.0 g, 83 %).

M.p. = 100-101 ºC (lit.[53] 98-99 ºC).

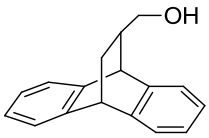
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21-1.61 (t, *J* = 7.2 Hz, 3H), 1.98-2.05 (m, 1H), 2.18-2.23 (m, 1H), 2.88-2.92 (m, 1H), 4.02-4.14 (m, 2H), 4.37-4.38 (t, *J* = 2.8 Hz, 1H), 4.71- 4.72 (d, *J* = 2.8 Hz, 1H), 7.10-7.17 (m, 4H), 7.25-7.37 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.4, 30.7, 43.8, 44.1, 46.9, 60.7, 123.3, 123.5, 123.8, 124.8, 125.7, 125.8, 126.2, 126.3, 140.0, 142.5, 143.7, 144.1, 173.6.

Mass (EI): 278 (3), 202 (4), 201 (1), 178 (100).

IR (KBr): υ 3051, 2962, 1727, 1460, 1370, 1302, 1190, 1097, 1019, 859, 753 cm.$^{-1}$.

9, 10-dihydro 9, 10- ethanoanthracene 11- methanol: **8**



An assembly of three necked round bottom 500 mL flask with magnetic stirbar, a reflux condenser and an addition funnel is prepared. The flask was charged with sodium borohydride (1.64 g, 43.2 moles) and THF (50 mL, predried over sodium). Ester (**6**) (5.0 g, 17.9 mmol) was added in one portion and flask was cooled to 0 ^{o}C in an ice bath. A solution of iodine (4.56 g (17.9 moles dissolved in THF 50 mL), in addition funnel was added drop wise over 30 min resulting in vigorous evolution of hydrogen. After addition of iodine was complete the flask was heated to reflux for 18 h and then cooled to room temperature. Methanol was added cautiously, until the mixture became clear. After stirring for 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of aqueous KOH solution (20 %, 150 mL) was stirred for 12 h and extracted with ethyl acetate (3X150 mL). The organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuum, affording white solid which was further crystallized in acetonitrile. (4.02 g, 95%).

M.p.: 111-112 °C (lit.[53] = 112-113 ^{o}C).

General procedure for resolution of alcohol: **8**

To a solution of racemic alcohol (**3**) (0.30 g, 1.27 mmol) in dry THF (5 mL) lipase (0.1 g, 33% w/w, Novozyme-435) and *iso*-propenyl acetate (0.13 mL, 1.27 mmol) were added and reaction mixture was stirred for 3h at room temperature. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over silica gel using ethyl acetate and petroleum ether as the eluent. The acetate (**9**) was eluted with 10 % ethyl acetate- petroleum ether and alcohol (**8**) with 20 % ethyl acetate- petroleum ether.

(0.131 g, 43.5%) $[\alpha]_D^{28}$ = 3.6 (*c* = 0.7 MeOH). HPLC Condition: Chirapak OD-H column, 10% *Iso*-propanol in hexane, Flow = 0.7 mL/min, UV = 215 nm, Retention time = 14.28 min for (*R*)-isomer, 17.64 min for (*S*)-isomer.

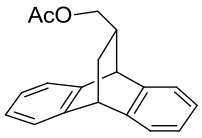
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.04-1.09 (ddd, *J* = 12.0, 4.8, 2.8 Hz, 1H), 1.90-1.96 (m, 1H), 2.12-2.19 (m, 1H), 2.94-2.99 (dd, *J* =10.4, 9.6 Hz, 1H), 3.32- 3.36 (dd, *J* = 10.4, 5.6 Hz, 1H), 4.25-4.27 (t, *J* = 2.8 Hz, 1H), 4.41-4.42 (d, *J* = 2.0 Hz, 1H), 7.03-7.13 (m, 4H), 7.22-7.30 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.0, 40.9, 44.0, 45.5, 66.1, 123.2, 123.5, 123.6, 125.4, 125.6, 125.7 (2C), 126.0, 140.5, 143.8 (2C), 143.9.

Mass (EI): 236 (28), 202 (26), 179 (56), 178 (100), 176(8).

IR (KBr): υ 3433, 3069, 2945, 1637, 1461, 1370, 1333, 1166, 1026, 935, 750, 554 cm.$^{-1}$

9, 10-Dihydro 9, 10-ethanoanthracene -11-acetate: (*S*)-**9**



HPLC condition: Diacel IC column, 1% *Iso-propanol* in Hexane Flow = 0.5 mL/min, UV = 210 nm Retention time 19.4 min (*R*), min, 19.5min (*S*). (0.185 g, 52 %)**.**

M.p**.** = 119-120°C, (lit.[54] = 119 °C) $[\alpha]_D^{28}$ = - 4.3 (*c* = 0.7, MeOH).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13-1.18 (ddd, *J* = 12.4, 4.8, 2.4 Hz, 1H), 1.9-2.03 (m, 1H), 2.11 (s, 3H), 2.26-2.32 (m, 1H), 3.40- 3.45 (dd, *J* = 10.8, 9.8 Hz, 1H), 3.79-3.83 (dd, *J* = 11.2, 6.4 Hz, 1H), 4.29-4.30 (t, *J* = 2.4 Hz, 1H), 4.32-4.33 (d, *J* = 2.0 Hz, 1H), 7.09-7.16 (m, 4H), 7.25-7.34 (m, 4H).

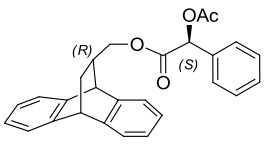
^{13}C-NMR (100 MHz, $CDCl_3$): 21.0, 31.2, 37.4, 43.8, 45.8, 67.3, 123.2, 123.5, 123.6, 125.5, 125.7, 125.8, 125.9, 126.2, 139.4, 143.4, 143.5, 143.6, 171.0.

Mass (EI): 278 (1), 202 (2), 179 (15), 178 (100).

IR (KBr): υ 3068, 3022 2920, 1737, 1461, 1362, 1236, 1035, 951,754 cm.$^{-1}$

Anal. Calcd for $C_{19}H_{18}O_2$: C 81.99, H 6.52 found C 81.83, H 6.57.

(*S*)-((11*R*)-9,10-Dihydro-9,10ethanoanthracene-11-yl)methyl 2-acetoxy-phenylacetate: (**10)**



To a 50 mL r. b. flask alcohol (*R*)-**3** (0.40 g, 1.7 mmol), DCC (0.350 g, 1.7 mmol) and DMAP (0.020 g 0.17 mmol) was added under nitrogen atmosphere, dissolved dry dichloromethane (10 mL) and cooled to 0 °C. A solution of (+)-O-acyl mandelic acid (*S*-**6**) (0.33 g, 1.7 mmol) in dichloromethane (~5 mL) was then added drop wise. The reaction mixture was stirred at 0 ^{o}C for 1 h after which it was allowed to warm to room temperature and stirred (14 h). Then whole reaction mixture was passed through celite bed, washed with dichloromethane and purified by column chromatography over silica gel (10% ethyl acetate- Petroleum ether) affording white foamy solid (0.56 g, 80%) M.p. = 97-98 °C $[\alpha]_D^{28}$ = 63.2 (*c* = 0.5 $CHCl_3$). Suitable crystal for X-ray

analysis was obtained from slow evaporation of **10** in Pet Ether- ethyl acetate (~95:5)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.01-1.06 (ddd, *J* = 12.4, 4.8, 2.4 Hz, 1H), 1.84-1.90 (m, 1H), 2.22 (m, 4H), 3.39-3.45 (t, *J* = 10.4 Hz, 1H), 3.75-3.79 (dd, *J* = 6.0, 5.6 Hz, 1H), 3.95-3.96 (d, *J* = 2.4 Hz, 1H), 4.19-4.21 (t, *J* = 2.4 Hz, 1H), 5.96 (s, 1H), 6.73-6.75 (d, *J* = 7.2 Hz, 1H), 6.95-6.99 (td, *J* = 7.6, 1.2 Hz) 7.03-7.09 (m, 3H), 7.15-7.22 (m, 3H), 7.44-7.50 (m, 3H), 7.54-7.56 (m, 2H).

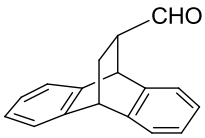
^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.8, 30.7, 37.2, 43.7, 45.3, 68.0, 74.4, 123.1, 123.5, 123.6, 125.3, 125.7, 125.8, 125.9, 126.1, 127.8 (2C), 128.9 (2C), 129.5, 134.1, 139.5, 143.1, 143.3, 143.5, 168.6, 170.4.

Mass (EI): 412(4), 219(4), 203(7), 202(4), 179(94) 178(100).

IR(KBr): υ 3067, 3020, 2951, 1744, 1461, 1373, 1334, 1245, 1048, 971, 746, 699 cm.$^{-1}$

Anal. Calcd for $C_{27}H_{24}O_4$ C 78.62, H 5.86 found C 78.35, H 6.22

9,10-Dihydro-9,10-ethanoanthracene-11-carbhaldehyde: (*R*)-**11**



To a solution of alcohol (*R*)-**3** (0.30 g, 1.27 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere was added PDC (2.4 g, 6.35 mmol) and mixture was stirred vigorously at room temperature (6 h). The reaction mixture was diluted with diethyl ether (30 mL) and passed through celite. The solvent was removed under reduced pressure and the crude product was purified by short column chromatography over silica gel (5% Ethyl acetate- Petroleum ether) affording white solid. (0.225 g, 75 %)

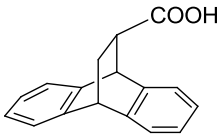
M.p. = 112 °C (lit.[55] = 112-113 °C) $[\alpha]_D^{28}$= -13.4 (c = 1 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.96-2.02 (m, 1H), 2.08-2.13 (m, 1H), 2.75-2.80 (m, 1H), 4.39-4.41 (t, *J* = 2.4 Hz, 1H), 4.68-4.69 (d, *J* = 2.0 Hz ,1H) 7.08-7.14 (m, 4H), 7.25-7.33 (m, 4H), 9.41-9.42 (d, *J* = 1.6 Hz, 1H).

Mass (EI): 233(9), 202(12), 178(72), 177(100).

IR (KBr): υ 3069, 3021, 2949, 2813, 2710, 1714, 1457, 1390, 1234, 1023, 758 cm.$^{-1}$

9, 10-Dihydroethanoanthracene-11-carboxylic acid: (*R*)-**12**



A solution of $NaClO_2$ (0.23g, 2.05 mmol, 80% purity) in water (3 mL) was added drop wise to a stirred solution of aldehyde (*R*)-**8** (0.400 g, 1.7 mmol) in acetonitrile (3 mL), NaH_2PO_4 (0.07 g 0.59 mmol) in water (3 mL) and H_2O_2, (30%, 11.8 mmol, 0.21 mL,) kept in ice bath (5-10 ^oC), and stirred for 3 h. A small amount of Na_2SO_3 (about 0.025 g) was added to destroy the unused HOCl and H_2O_2. Acidification with aqueous HCl (10 %) afforded off white solid (0.30 g, 70%). M.p. = 188 ºC (lit.[11] = 189 ºC) $[\alpha]_D^{28}$ = -7.3 (*c* = 2, $CHCl_3$) lit.[30] $[\alpha]_D$ = +7.2 (*c* = 2, $CHCl_3$).

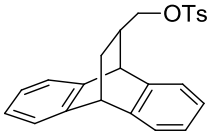
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.98-2.04 (m, 1H), 2.09-2.14 (ddd, *J* = 12.8, 5.2, 2.8 Hz, 1H), 2.88-2.93 (dd, *J* = 10.4, 4.8 Hz, 1H) 4.34-4.35 (t, *J* = 6.4 Hz, 1H), 4.76-4.68 (d, *J* = 2.4 Hz), 7.08-7.24 (m, 4H), 7.26-7.32 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 30.5, 43.7, 43.9, 46.5, 123.3, 123.5, 123.7, 125.0, 125.8(2C), 126.2, 126.3, 139.6, 142.3, 143.8, 143.7, 179.0.

Mass (EI): 250 (4), 202 (6), 179 (91), 178 (100).

IR (KBr): υ 3311, 3024, 2972, 1706, 1459, 1403, 1230, 1124, 936, 761, 599 $cm.^{-1}$

Synthesis of 9,10-Dihydro 9,10-ethanoanthracene -11(4-methylbenzenesulfonate): (*R*)-**13**



To a solution of (*R*)-**7** (1.0 g, 4.24 mmol) in dry dichloromethane (10 mL), triethyl amine (1.71 g, 16.94 mmol) was added under nitrogen atmosphere at 0 °C. Then *p*-toluenesulfonyl chloride (1.0 g, 5.29 mmol) was added in portion wise to the reaction. The solution was stirred for 24 h at room temperature. The reaction mixture was poured into cold water (50 mL) and extracted with dichloromethane (2 X 50 mL). The organic phase was concentrated under vacuum which was purified by column chromatography over silica gel (10% Ethyl acetate- Petroleum ether) affording white solid (1.3 g, 79%). M.p. = 146-147°C (lit.[56] = 148-150°C) $[\alpha]_D^{28}$ = 5.8 (*c* = 1, $CHCl_3$).

^{1}H-NMR (400 MHz, CDCl3): δ 0.94-0.99 (ddd, *J* = 12.8, 4.8, 2.4 Hz, 1H), 1.90-1.97 (m, 1H), 2.30-2.33 (m, 1H), 2.49 (s, 3H), 3.22-3.27 (dd, *J* = 10.4, 9.6 Hz, 1H) , 3.74 - 3.78 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.23-4.24 (t, *J* = 2.8 Hz, 1H), 4.32- 4.33 (d, *J* = 2.4 Hz, 1H), 6.96-6.97 (m, 2H), 7.10-7.12 (m, 2H), 7.19-7.28 (m, 4H), 7.37-7.37 (d, *J* = 1.2

Hz, 2H), 7.79-7.98 (d, *J* = 1.2 Hz, 2H).

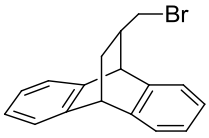
^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7, 30.6, 37.5, 43.5, 44.9, 72.5, 123.1, 123.5, 123.8, 125.6, 125.7, 125.9, 126.0, 126.2, 128.0 (2C), 129.9 (2C), 132.9, 139.2, 142.9, 143.3, 143.4, 144.9.

Mass (EI): 390(1), 202(2), 180(1), 178(100), 176(4), 152(1).

IR (KBr): υ 3070, 2953, 2917, 2862, 2359, 1364, 1177, 713 cm.$^{-1}$

Anal. Calcd for $C_{24}H_{22}O_3S$: C 73.82, H 5.68 found C 73.66, H 5.62.

Synthesis of 9,10-Dihydro-9,10-ethanoanthracene, 11-(bromomethyl): (*R*)-**14**



To a solution of alcohol (*R*)-**8** (0.40 g, 1.70 mmol) in) in dichloromethane (5 mL) under nitrogen atmosphere, was added CBr_4 (0.71 g, 2.13 mmol) and the mixture was stirred vigorously at room temperature for 15 min. The mixture was cooled down to 0 °C and Ph_3P (0.67 g, 2.56 mmol) was added. Then reaction mixture was stirred for 3 h at room temperature. The solvent was distilled off under reduced pressure and material was further purified by column chromatography over silica gel (100% Petroleum ether) affording white solid (0.38 g, 73%). M.p. = 136 °C (lit.[57] = 138 °C), $[\alpha]_D^{28}$ = 27.7 (*c* = 1, $CHCl_3$).

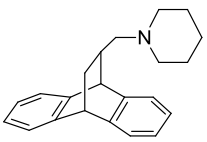
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18-1.23 (ddd, *J* = 12.8, 3.6, 2.8 Hz, 1H), 2.06-2.13 (m, 1H), 2.33-2.41 (m, 1H), 2.80-2.85 (t, *J* = 10 Hz, 1H), 3.09-3.13 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.29-4.30 (t, *J* = 2.8 Hz, 1H), 4.50-4.51 (d, *J* = 2.4 Hz, 1H), 7.11-7.19 (m, 4H), 7.27-7.37 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 34.8, 38.0, 41.0, 41.1, 47.1, 123.3, 123.4, 123.8, 125.6, 125.8, 126.0, 126.3, 139.5, 143.3, 143.5.

Mass (EI): 299 (1), 218 (5), 178 (100).

IR (KBr)υ: 3036, 2938, 1456, 1286, 1228, 1022, 758, 643, 551 cm.$^{-1}$

Synthesis of 9,10-Dihydro-9,10-ethanoanthracen-11-yl)methyl]piperidine: (*R*)-**15**



A mixture of (*R*)-**13** (0.40 g, 1.02 mmol), piperidine (0.43 g, 5.2 mmol) and Na_2CO_3 (0.54 g, 5.12 mmol) was heated at 80°C in dry DMF (5 mL) under nitrogen atmosphere for 48 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 X 75 mL). The organic extract was washed with water and dried over anhydrous sodium sulphate.

The crude product was purified by column chromatography over neutral alumina (2% Ethyl acetate- Petroleum ether) affording white solid. (0.22 g, 70%) M.p. = 145 ºC, $[\alpha]_D^{28}$= -3.7 (c = 0.5 $CHCl_3$**)**

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14-1.43 (br signal, 2H), 1.55-1.60 (m, 4H), 1.80-1.87 (m, 4H), 1.92-1.95 (m, 1H), 2.12-2.32 (br signal, 5H), 4.25-4.26 (t, J = 2.4 Hz,1H), 4.36-4.37 (d, J = 2.4 Hz ,1H), 7.07-7.14 (m, 4H), 7.23-7.32 (m, 4H).

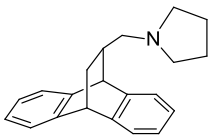
^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.6, 26.1, 33.4, 35.8**,** 44.3, 47.2, 54.9, 64.6, 122.9, 122.9, 123.3, 123.4, 125.3, 125.5, 125.6, 125.6, 141.1, 143.9, 144.0, 145.5.

Mass (EI): 303(3), 203(3), 202 (3), 178(15).

IR (KBr): υ 3066, 3020, 2932, 2800, 1454, 1377, 1330, 1214, 1154, 1125, 1095, 1005, 755 cm.$^{-1}$

Anal. Calcd for $C_{22}H_{25}N$: C 87.08, H 8.30, N 4.62 found C 87.0, H 8.15, N 5.10.

1-[(9,10-Dihydro-9,10-ethanoanthracen-11-yl)methyl]pyrrolidine: (*R*)-**16**



Prepared by the method similar to the one described above. White solid (0.218 g, 74%): M.p. = 121-122 ºC, $[\alpha]_D^{28}$= -5.6 (c = 1 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22-1.26 (m, 1H) ,1.76-1.79 (m, 4H), 1.92-2.04 (m, 3H), 2.11-2.17 (m, 2H), 2.40-2.47 (m, 4H), 4.26-4.28 (t, J = 2.4 Hz, 1H), 4.36-4.37 (d, J = 1.2 Hz ,1H), 7.10-7.14 (m, 4H), 7.25-7.32 (m, 4H).

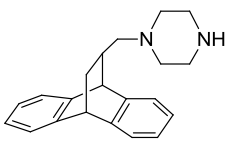
^{13}C-NMR (100MHz, $CDCl_3$): δ 23.5, 33.4, 37.6, 44.3, 47.3, 54.5, 62.1, 122.9, 123.4(2C), 125.4, 125.5, 125.6, 125.7, 140.9, 143.8, 143.9, 144.0, 144.5.

Mass (EI): 289(27), 288(36), 256(22), 178(14).

IR (KBr)υ: 3002, 2974, 2935, 2974, 2785, 1458, 1234, 758 cm.$^{-1}$

Anal. Calcd for $C_{22}H_{25}N$ C 87.15, H 8.04, N 4.84 found C 87.18, H 8.15, N 4.82.

1-[(9, 10-Dihydro-9, 10-ethanoanthracen-11-yl)methyl]piperazine: (*R*)-**17**



Prepared by the method similar to the one described above. Off white solid: 0.162 g, (52%) M.p. = 181-182 ºC, $[\alpha]_D^{28}$= 8.4 (c = 1 $CHCl_3$**).**

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14-1.16 (m, 1H), 1.89-2.01 (m, 3H), 2.10 (br signal, 1H), 2.56-2.72 (br signal, 4H), 3.30-3.31 (t, J = 4.8 Hz, 4H), 4.27-4.28 (t, J =

2.4 Hz, 1H), 4.30-4.31 (d, *J* = 2.4 Hz, 1H), 7.10-7.26 (m, 4H), 7.27-7.29 (m, 4H) **.**

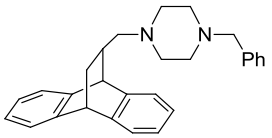
^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.7, 35.8, 44.0, 44.1, 46.5, 49.9, 123.2, 123.4, 125.3, 125.5, 125.6, 125.8, 125.9, 140.5, 143.7, 143.7, 143.8.

Mass (EI): 304(100), 261(10), 219(5), 202(11), 178(40).

IR (KBr): υ 3021, 2950, 2816, 1605, 1457, 1288, 1174, 1094, 1044, 933, 753 cm.$^{-1}$

Anal. Calcd for $C_{21}H_{24}N_2$ C 82.85, H 7.95, N, 9.20 found C 82.65, H 7.67, N 9.45.

1-[(9,10-Dihydro-9,10-ethanoanthracen-11-yl)methyl]-4 (phenylmethyl)piperazine: (*R*)-**18**



A mixture of amine (*R*)-**17** (0.15 g, 4.93 mmol), benzyl chloride (0.078 g, 6.16 mmol) and K_2CO_3 (0.21 g, 14.8 mmol) was reflux in acetonitrile (5 mL) for 24 h. Then the reaction mixture was quenched with water and extracted with ethyl acetate (2X50 mL). The organic extract was washed with water and dried over anhydrous sodium sulphate. The crude product was purified by column chromatography on neutral alumina (5% Ethyl acetate-Petroleum ether) affording white solid (0.152 g 78 %). M.p. = 154-155 ºC, $[\alpha]_D^{28}$ = 12.6 (*c* = 0.5 $CHCl_3$**).**

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14-1.88 (ddd, *J* = 12.4, 4.4, 2.4 Hz, 1H) 1.96-1.97 (d, *J* = 1.2 Hz, 2H), 2.10-2.32 (m, 1H), 2.32-2.49 (br signal, 8H), 3.54 (s, 2H), 4.25-4.26 (t, *J* = 2.4 Hz, 1H), 4.35-4.36 (d, *J* = 2.4 Hz, 1H), 7.07-7.13 (m, 4H), 7.24-7.32 (m, 6H), 7.33-7.34 (d, *J* = 2.4 Hz, 2H).

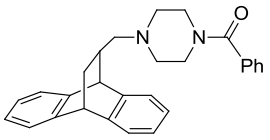
^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.1, 35.7, 44.3, 46.9, 53.3, 53.4, 63.2, 63.6, 122.9, 123.4, 123.4, 125.4, 125.5, 125.8, 127.0, 128.2, 129.3, 138.2, 141.0, 143.9, 144.0, 144.4.

Mass (EI): 394(82), 302(1), 217(5), 202(6), 190(100), 178(58).

IR (KBr): υ 3067, 3020, 2936, 2803, 1455, 1382, 1284, 1165, 1146, 1009, 760, 555 cm.$^{-1}$

Anal. Calcd for $C_{28}H_{30}N_2$: C 85.24, H 7.66, N 7.10 found C 85.67, H 7.56, N 7.05.

(4-(((11*R*)-9,10-Dihydro-9,10-ethanoanthracene-11-y)methyl)piperazin-1-yl) (phenyl)methanone : (*R*)-**19**



A solution of benzoyl chloride (0.07 g, 0.493 mmol) in dry dichloromethane (2 mL) was added drop wise to stirred solution of amine (*R*)-**17** (0.150 g, 0.493 mmol) and triethylamine (0.149 g, 1.48 mmol) in dry dichloromethane (~5 mL) under nitrogen atmosphere and stirred for 24 h. Then the reaction mixture was quenched with water and extracted with ethyl acetate (2X50 mL). The organic extract was washed with water and dried over anhydrous sodium sulphate. The crude product was purified by column chromatography on neutral alumina (20% Ethyl acetate-Petroleum ether) affording white solid (0.165 g, 82.1 %). M.p. = 199-201 ºC, $[\alpha]_D^{28}$= 15.3 (c = 0.5 $CHCl_3$**)**.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14-1.90 (ddd, *J* = 12.4, 8.8, 2.8 Hz, 1H), 1.92-1.98 (m, 3H), 2.14-2.16 (m, 2H), 2.37-2.52 (br signal, 4H), 3.45 (s, 2H), 3.82 (s, 2H), 4.26-4.27 (t, *J* = 2.4 Hz, 1H), 4.36-4.37 (d, *J* = 2.4 Hz, 1H), 7.09-7.13 (m, 4H), 7.25-7.30 (m, 5H), 7.41-7.42 (m, 4H)**.**

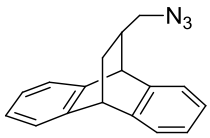
^{13}C-NMR (100 MHz, $CDCl_3$): δ 33.0, 35.5, 44.1, 46.9, 53.0, 53.7, 63.3, 123.1, 123.4 (2C), 125.4, 125.5, 125.6, 125.7 (2C), 125.8 (2C), 127.0, 128.5, 129.7, 135.8, 140.7, 143.8, 143.8, 144.1, 170.3.

Mass (EI): 408(6), 274(54), 229(15), 203(100), 178(43).

IR (KBr): υ 3065, 3018, 2803, 1634, 1422, 1273, 1161, 1009, 760, 555 cm.$^{-1}$

Anal. Calcd for $C_{28}H_{38}N_2O$ C 82.32, H 6.91, N 6.86 found C 81.78, H 6.63, N 6.56.

Synthesis of 9,10-Dihydro-9,10-ethanoanthracene, 11-(azidomethyl): (*R*)-**22**



A mixture of (*R*)-**14** (0.40 g, 1.33 mmol), Sodium azide (0.87 g, 13.2 mmol, 10 eq) was heated at 80°C in dry DMF (~5 mL) under nitrogen atmosphere for 36 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3X75 mL). The organic extract was washed with water and dried over anhydrous sodium sulphate. The crude product was purified by column chromatography over neutral alumina (1% Ethyl acetate-Petroleum ether) affording greasy material which is solidify upon cooling. (0.34 g, 98%) $[\alpha]_D^{28}$ = +10.44 (c = 1, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.10-1.35 (m, 1H), 1.93-2.05 (m, 2H), 2.21-2.25 (m, 1H), 2.27-2.76 (m, 1H), 3.01- 3.05 (dd, *J* = 8. 6.4 Hz, 1H), 4.28-4.29 (t, *J* = 2.8 Hz,

1H), 4.35 (d, *J* = 2.4 Hz, 1H), 7.11-7.17 (m, 4H), 7.27-7.36 (m, 4H), 7.31-7.36 (m, 4H).

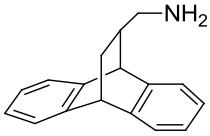
^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.3, 38.4, 43.9, 46.9, 55.6, 123.3, 123.5, 123.70, 123.71, 125.5, 125.8, 125.9, 126.2, 139.7, 143.2, 143.4, 143.6.

Mass (EI): 261(5), 260(13) 202(10), 177(100).

IR (KBr): υ 3017, 2943, 2017, 2925, 2095, 1459, 1279, 1022, 902, 753 cm.$^{-1}$

Anal. Calcd for C 78.13, H 5.79, 16.08. Found C 77.73, H 5.13, 15.91

9,10-Dihydro-9,10-ethanoanthracen-11-yl)methanamine: (*R*)-**23**



A mixture azide (*R*)-**22** (0.365 g, 1.4 mmol) and Pd/C (0.027g, 10% w/w) in methanol (~50 mL) were placed under H_2 atmosphere, and the reaction mixture was vigorously stirred at 0-5^{0}C temperature for 6 h. The mixture was filtered through pad of celite. The solvent was removed under reduced pressure and the residue was purified by neutral alumina chromatography giving product.(0.29 g, 90 %) M.p. = 190-192 ^{o}C

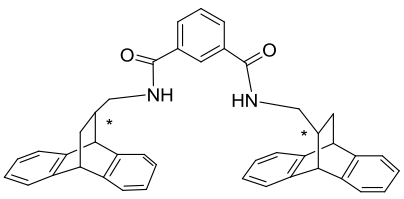
^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.18-1.22 (m, 2H), 1.93-1.98 (m, 1H), 2.11-2.56 (m, 2H), 4.42 (s, 1H), 4.47-4.48 (d, *J* = 2 Hz, 1H), 7.15-7.20 (m, 4H), 7.34-7.46 (m, 4H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ 32.5, 37.7, 43.1, 44.3, 45.3, 123.5, 123.8, 124.1, 125.8, 125.9, 126.2, 140.2, 143.7, 143.8, 144.3.

Mass (EI): 235(80), 202(50), 177(100), 178(90).

IR (KBr): υ 3434, 2946, 1536, 1456, 1170, 1040, 753 cm.$^{-1}$

N, N-bis (((11R)-9,10-dihydro-9,10-ethanoanthracene-11-yl)methyl)isopthalamide : (*R*)-**24**



In a r.b flask amine *R*-**23** (0.1g, 0.42 mmol) and Triethyl amine (0.12 ml,.85mmol) in DCM (40 mL) were slowly added to solution of isopthayol chloride (0.044 g, 0.21 mmol) under N_2 atmosphere at 0^{o}C. The reaction mixture was stirred at a room temperature for 6 h. The solvent was evaporated and residue was washed with sodium bicarbonate and extracted with dichloromethane (2X75 mL). The organic layer were

dried over sodium sulphate and concentrated in reduce pressure. The crude product was purified by column chromatography over silica gel (50% ethyl acetate- petroleum ether) affording white solid. (0.165 g, 64%)

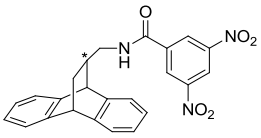
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.31-1.36 (m, 1H), 2.03-2.1 (m, 2H), 2.31-2.39 (m, 2H), 3.12-3.34 (m, 4H), 4.27 (d, *J* = 2 Hz, 2H), 4.31-4.33 (t, *J* = 3.9 Hz, 2H), 6.12 (s, 1H). 7.11-7.17 (m, 8H), 7.26-7.36 (m, 9H), 7.46-7.50 (t, J = 8.4 Hz, 1H), 7.73-7.71 (dd, J = 8.0, 2.0 Hz, 2H), 8.02 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.1, 38.3, 47.0, 44.7, 47.4, 123.4, 123.5, 123.6, 125.1, 125.2, 125.7, 125.8, 126.9, 126.3, 128.8, 129.7, 134.8, 141.3, 143.3, 143.5, 143.6, 144.0, 166.5.

Mass (LC-MS): 602(55%), 601(100%), 429(10%), 320(10%), 219(15%)

IR (KBr): υ 3259. 2940, 1636, 1533, 1270, 1024, 724 cm.$^{-1}$

N-(((11R)-9,10-dihydro-9,10-ethanoanthracen-11-yl)methyl)-3,5-dinitrobenzamide: (*R*)-**25**



Prepared by the method similar to the one described above (Instead of Isopthayol chloride 3, 5 dinitro benzyol chloride (1.1 eq) was used. Yellow solid: (79 %) M.p. = 197 ºC,

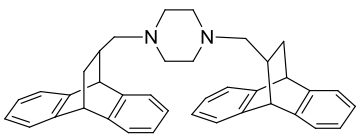
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39-1.44 (m, 1H), 2.2-2.3 (m, 1H), 3.23-3.29 (m, 1H), 2.37-2.42 (m, 1H), 3.60-3.67 (m, 1H), 4.28-4.29 (d, *J* = 2.4 Hz), 4.34-4.36 (t, *J* = 4.8 Hz, 1H) 5.94 (s, 1H), 7.12-722 (m, 4H), 7.29-7.39 (m, 4H), 8.69-8.99 (d, *J* = 2.0 Hz, 2H), 9.15-9.16 (t, *J* = 4 Hz, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.5, 37.8, 43.9, 44.9, 48.1, 121.1, 123.4,123.7, 124.8, 125.9, 126.1, 126.7,127.0, 137.7, 140.5, 143.0, 143.3, 144.2, 148.5, 162.7

IR (KBr): υ 3310, 3099, 1640, 1537, 1343, 1077, 918, 759 cm.$^{-1}$

Experimental Data of Type-B

1,4-Bis (11*R*)-9,10-dihydro-9,10-ethanoanthracene-11-yl)methyl)piperazine : (*R*,*R*)-**20**



A mixture of (*R*)-**14** (0.25 g, 0.836 mmol), (*R*)-**17** (0.38 g, 1.25 mmol) and Na_2CO_3 (0.58 g, 4.18 mmol) was heated at 80°C in DMF (5 mL) under nitrogen atmosphere for 48 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3X75 ml). The organic extract was washed with water and dried

over anhydrous sodium sulphate. The crude product was purified by column chromatography over neutral alumina (10% Ethyl acetate- Petroleum ether) affording white solid (0.09 g, 20%). M.p. = 160-162 ºC, $[\alpha]_D^{28}$= 10.8 (c = 0.5 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.15-1.19 (ddd, *J* = 12.4, 4.4, 2.4 Hz ,1H), 1.87-1.97 (m, 3H), 2.13 (s, 1H), 2.14-2.31 (br signal, 4H), 4.25-4.26 (t, *J* = 2.4 Hz, 1H), 4.34-4.35 (d, *J* = 1.2 Hz, 1H), 7.07-7.13 (m, 4H), 7.26-7.29 (m, 4H).

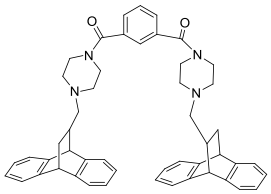
^{13}C-NMR (100 MHz, $CDCl_3$): δ 33.2, 35.6, 44.2, 46.2, 53.4, 63.7, 123.0, 123.3, 123.4, 125.4, 125.5, 125.5 (2C), 125.7, 140.9, 143.9 (2C), 144.4.

Mass (EI): 522(12), 423(10), 345(10), 343(43), 204(13), 178(100).

IR (KBr): υ 3007, 3022, 2931, 1468, 1332, 1240, 1138, 1010, 819, 752 cm.$^{-1}$

Anal. Calcd for $C_{38}H_{38}N_2$ C 87.31, H 7.33, N 5.36 Found C 87.21, H 7.46, N 5.55.

(9,10-Dihydro-9,10-ethanoanthracene-11-yl)methyl)piperazine-1-yl)(3-(4-(((11*R*)-9,10-dihydro-9,10-ethanoanthrcene-11yl)methyl)piperazine-1carbonyl)phenyl)methanone:(*R,R*)-**21**



A solution of isophtaloyl chloride (0.075 g, 0.37 mmol) in dry dichloromethane was added drop wise to stirred solution of amine (*R*)-**17** (0.225 g, 0.740 mmol), and triethylamine (0.373 g, 3.70 mmol) in dry dichloromethane (20 mL) under nitrogen atmosphere and stirred for 24 hours. Then the reaction mixture was quenched with water and extracted with ethyl acetate (2X50 mL). The organic extract was washed with water and (25 mL) dried over sodium sulphate. The crude product was purified by column chromatography on neutral alumina (50% Ethyl acetate- Petroleum ether) to afford thick liquid, which gave white solid on treatment of diethyl ether (0.180 g, 48 %). M.p. = 118-119 ºC, $[\alpha]_D^{28}$ = 8.7 (c = 0.5 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13-1.18 (m, 1H), 1.89-1.99 (m, 3H), 2.14-2.85 (br signal, 5H), 3.43-3.81(s, 2H), 3.81 (s, 2H), 4.26 (s, 1H), 4.35 (d, *J* = 1.6 Hz, 1H), 7.08-7.14 (m, 4H), 7.23-7.30 (m, 5H), 7.42-7.45 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 33.0, 36.0, 42.3, 44.1, 46.8, 47.9, 53.1, 63.3, 53.6, 123.1, 124.4, 125.40, 125.5(2C), 125.6, 125.6, 125.8, 128.2, 136.3, 140.7, 143.8, 143.9, 144.1, 169.3.

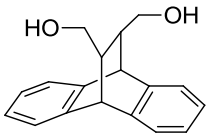
Mass (LC-MS): 741 (25, M+2), 740 (50, M+1), 739 (100), 581 (15), 343 (45).

IR (KBr): υ 3018, 2937, 2862, 1634, 1461, 1331, 1281, 1159, 1004, 816 cm.$^{-1}$

HRMS: 739.4007 (calculated, M+H) Found: 739.4021.

Experimental Data of Type-C

trans-11,12-Bis(hydroxymethyl)-9,10-dihydro-9,10-ethanoanthracene: (*S,S*)-**27**



Racemic Diol was prepared using same procedure as for compound (2). In this case $NaBH_4$ was taken 4.8 eq and I_2 was taken 2 eq. Yield (87 % corresponding to diacid).

General procedure for enzymatic resolution of *trans*-diol (±)-**27**

To a solution of racemic-diol (±)-**27** (0.30 g, 1.12 mmol) in dry THF (10 mL) steapsin lipase enzyme (0.40 g, 1.3 w/w) and vinyl acetate (0.15 g, 1.69 mmol) were added and reaction mixture was stirred for 48 hours at 8-9 ^{o}C. Reaction was followed by TLC, after 48 h the material was filtered and the filtrate was concentrated in vacuum, separation was done by column chromatography over silica gel using light petroleum ether and ethyl acetate as the eluent, the mono acetate **28** was isolated with the ratio of 4:1 (0.15 g, 43.1 %) and the diol **27** with the ratio of 3:2 (0.14 g, 46.7 %).

White solid, m. p. = 125-7 ^{o}C (lit.[23a] 131-2 ^{o}C for *S,S* isomer); $[\alpha]_D$ = + 11.01 (c = 0.9, MeOH). (lit.[231] $[\alpha]_D$ = + 11.1 (c = 0.9, MeOH), HPLC conditions: Chiracel OD column; 5% IPA in hexane, flow = 0.3 mL/min; 22.2 min (*R,R*) and 26.1 min (*S,S*).

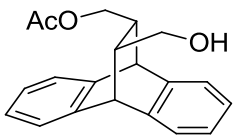
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.65-1.69 (m, 2H), 2.96-3.02 (dd, *J* = 8 Hz, 1.2 Hz, 2H), 3.14 (s, 2H (OH), 3.43-3.47 (dd, *J* = 8 Hz, 1.2 Hz, 2H), 4.20 (s, 1H), 7.09-7.16 (m, 4H), 7.24-7.29 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 46.2, 46.3, 66.1, 123.3, 125.1, 125.8, 126.9, 140.6, 143.5.

Mass (DIP-EI) 266 (2), 202 (4), 179 (15), 178 (100), 177(6).

IR (KBr): υ 3289, 3070, 2951, 2896, 1610, 1464, 1385, 1211, 1167, 1076, 998 cm.$^{-1}$

trans-9,10-Dihydro-9,10-ethanoanthracene-11-acetoxymethyl-12-methanol: (*R,R*)-**28**



White solid, M.p = 113–4 ^{0}C; $[a]_D$ = -14.1 (c 0.9, MeOH). HPLC conditions: Chiracel OD-H column; 5% IPA in hexane, 0.3 mL/ min; 32.6 min (*R*, *R*) and 37.3 min (*S,S*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.72 (m, 2H), 2.01 (s, 3H), 3.14–3.19 (dd, *J* = 10.4 Hz, 8.8 Hz, 1H), 3.36–3.40 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.58–3.63 (dd, *J* = 10.4 Hz, 8.8 Hz, 1H), 3.80–3.85 (dd, *J* =10.8 Hz, 6.0 Hz, 1H), 4.25 (d, *J* = 2.0 Hz, 1H),

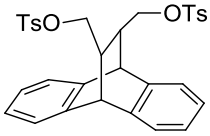
4.36 (d, *J* = 2.4 Hz, 1H), 7.12–7.16 (m, 4H),7.26–7.32 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 42.1, 45.6, 45.7, 45.9, 65.6, 67.1, 123.48, 123.49, 125.3, 125.4, 125.90, 125.93, 126.1, 126.3, 140.2, 140.6, 143.0, 143.3, 171.

Mass (DIP-EI): 308(1), 215(2), 203(2), 202(3), 179(19), 178(100).

IR (KBr): υ 3561, 3066, 3022, 2962, 2881, 1735, 1458, 1363, 1239, 1045, 1022, 969, 755, 556 cm.$^{-1}$

trans-9,10-dihydro-9,10-ethanoanthracene- 11,12-bis-p-toluenesulfonate: (*S*,*S*)-**29**



To a stirred solution of diol (S,S)-**27** (0.30 g, 1.12 mmol) in dry pyridine (5 ml), freshly crystallized p-toluenesulfonyl chloride (0.52 g, 2.70 mmol) was added at 0^{o}C under an N_2 atmosphere. After stirring for 36 h, the reaction mixture was poured into ice cold water and extracted with ethyl acetate and washed with dilute HCl. The organic phase was concentrated under vacuum. The solid was further purified by column chromatography over silica-gel to give a white material (0.480 g, 74.15% yield). M.p. 143–145 ^{o}C, $[\alpha]_D$ = + 28.1 (c =1.0, $CHCl_3$).

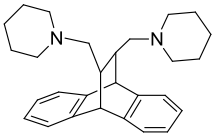
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.57–1.60 (m, 1H), 2.49 (s, 3H), 3.32–3.37 (m, 1H), 3.68–3.72 (m, 1H), 4.23 (s, 1H), 6.96–7.02 (m, 2H), 7.07–7.11 (m, 1H), 7.20–7.22 (d, *J* = 7.2 Hz, 1H), 7.35–7.37 (d, *J* = 8.0 Hz, 2H), 7.75–7.77 (d, *J* = 8.0 Hz, 2H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 21.7, 42.9, 44.7, 71.3, 123.7, 125.6, 126.1, 126.5, 128.0, 130.0, 132.5, 139.1, 142.1, 145.1.

Mass (DIP-EI): 574 (3), 402 (2), 368 (2), 230 (3), 202 (4), 178 (100).

IR (KBr): υ 3069, 2955, 1627, 1596, 1360, 1176, 1095, 949, 857,750, 662 cm.$^{-1}$

trans-11,12-bis(piperdine)-9,10-dihydro-9,10-ethanoanthracene: (*S*,*S*)-**30**



A mixture of ditosylate (*S*,*S*)-**29** (0.30 g, 0.52 mmol) and cyclic sec. amine (5.2 mmol) and Na_2CO_3 (0.28 g, 2.6 mmol) was heated at 70^{o}C in dry DMF (5 mL) under N_2 atmosphere. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulphate. The crude product was purified by column chromatography over neutral alumina by eluting with petroleum ether-ethyl acetate. Yield (59 %) M.p = 102-103 ºC $[\alpha]_D^{28}$ = 20.6 (c = 1 $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43-1.54 (m, 6H), 1.55-1.62 (m, 8H), 1.77-1.82 (m, 2H), 1.86-1.91 (dd, *J* = 12.4 Hz, 5.6 Hz, 2H,), 2.22 (br signal, 4H), 2.36 (br signal, 4H), 4.34 (s, 2H), 7.06-7.13 (m, 4H), 7.26-7.29 (m, 4H).

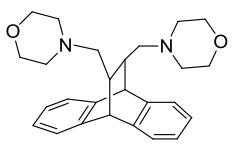
^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.3, 26.2, 42.3, 46.9, 55.1, 63.8, 123.1, 125.2, 125.5(2C), 141.4, 141.9.

Mass (EI): 400 (1), 215 (6), 202 (2), 178 (8), 137 (100).

IR (KBr): υ 3020, 2930, 1456, 1377, 1152, 1152, 1108, 1040, 861, 759 cm.$^{-1}$

Analysis: found C 84.05, H 9.46, N 7.21; required $C_{28}H_{36}N_2$ C 83.95, H 9.06, N 6.99.

trans-11,12-Bis(morpholine)-9,10-dihydro-9,10-ethanoanthracene: (*S*,*S*)-**31**



White solid, Yield (62%) M.p =182-184 ºC, $[\alpha]_D^{28}$= 6.8 (*c* = 0.9 $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.51-1.53 (m, 2H), 1.88-1.96 (m, 4H), 2.29-2.32 (br signal, 4H), 2.43-2.46 (br signal, 4H), 3.71-3.79 (br signal, 8H), 4.34 (s, 2H), 7.08-7.15 (m, 4H), 7.26-7.30 (m, 4H).

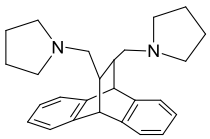
^{13}C-NMR (100 MHz, $CDCl_3$): δ 41.7, 46.6, 54.0, 63.4, 67.2, 123.3, 125.4, 125.5, 125.7, 141.6, 144.0.

Mass (EI): 404(4), 386(12), 215(2), 203(2), 202(2), 178(8), 138 (100), 100 (37).

IR (KBr): υ 3014, 2952, 2918, 2845, 1647, 1454, 1278, 1138, 998, 864, 758, 632 cm.$^{-1}$

Analysis found C 76.75, H 7.87, N 6.65; required $C_{26}H_{32}N_2O_2$ C 77.19, H 7.97, N 6.92.

trans-11,12-Bis(pyrolidine)-9,10-dihydro-9,10-ethanoanthracene: (*S*,*S*)-**32**



The title compound was prepared similary.Yield (58%) M.p = 122 ºC, $[\alpha]_D^{28}$ = 41.9 (c = 0.5 $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44-1.50 (m, 2H), 1.78 (s, 8H), 1.98-2.00 (d, *J* = 9.2 Hz, 2H), 2.09-2.12 (d, *J* = 9.2 Hz, 2H), 2.41-2.51 (br signal, 4H), 4.34 (s, 2H), 7.09-7.13 (m, 4H), 7.29-7.32 (m, 4H).

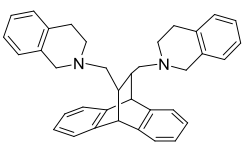
^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.6, 44.6, 46.7, 54.5, 61.1, 123.1, 125.3, 125.5, 125.7, 141.6, 144.5.

Mass (EI): 373 (1), 215 (3), 202 (4), 178 (6), 123 (100).

IR (KBr): υ 3019, 2952, 2918, 1457, 1339, 1155, 1138, 755 cm^{-1}.

Analysis: found C 83.99, H 8.46, N 7.60; required $C_{26}H_{32}N_2$ C 83.82, H 8.66, N 7.52.

trans-11,12-Bis((3,4-dihydroisoquinoline)-9,10-dihydro-9,10-ethanoanthracene: (*S*,*S*)-**33**



Prepared by the similar procedure. (56%) M.p = 123 ºC, $[\alpha]_D^{28}$= 22.4 (c = 1, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.06-2.19 (m, 4H), 2.58-2.64 (m,2H), 2.67-2.73 (m, 2H), 2.82-2.95 (m, 4H), 3.46-3.50 (m, 2H), 3.65-3.69 (m, 2H), 4.28 (s, 2H), 6.98-7.00 (m, 2H), 7.09-7.15 (m, 10H), 7.27-7.30 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 29.2, 42.5, 46.7, 51.2, 56.4, 62.7, 123.3, 125.4, 125.5, 125.6, 125.7, 126.0, 126.6, 128.7, 134.6, 135.2, 141.7, 144.2.

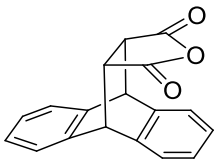
Mass (EI): 496 (5), 495 (1), 202 (5), 186 (11), 178 (5).

IR (KBr): υ 3063, 3019, 2915, 1495, 1461, 1240, 1131, 932, 740 cm.$^{-1}$

Analysis: found C 86.99, H 7.46, N 5.60; required $C_{36}H_{36}N_2$: C 87.05, H 7.31, N, 5.64.

Experimental Data of Type-D

9,10-Dihydroanthracene-9,10- α,β-succinic acid anhydride: **35**



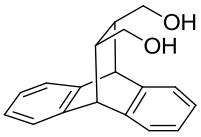
To a suspension of anthracene **6** (10.0 g, 56.2 mmol) in dry DCM (100 mL) under nitrogen atmosphere kept in ice bath (0 to 3^{o}C), aluminium chloride (7.47 g, 56.2 mmol) was added portion wise. After stirring for 15 min, maleic anhydride (5.5 g, 56.2 mmol) was added. The resulting mixture was stirred at room temperature (6 h), and poured into ice-water (200 mL), the separated organic layer was collected and the aqueous layer was extracted with dichloromethane (3X150 mL). The combined organic extracts were washed with water (2X50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by crystallization with ethyl acetate (14.2 g, 91 %). M.p. = 255 ºC (lit.[58] 257-258 ºC).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.55 (s, 2H) 4.85 (s, 2H), 7.21-7.24 (m, 4H), 7.34-7.42 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 47.4, 47.9, 124.4, 125.2, 127.2, 127.7, 138.1, 140.6, 170.5.

IR (KBr): υ 2977, 1783, 1706, 1463, 1258, 1065, 751 cm.$^{-1}$

cis-11,12-bis(hydroxymethyl)-9,10-dihydro-9,10-ethanoanthracene: **36**



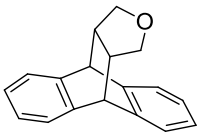
An assembly of three necked round bottom 500 mL flask with magnetic stir bar, a reflux condenser and an addition funnel is prepared. The flask was charged with sodium borohydride (2.7 g, 72.4 mmol) and dry THF (50 mL). To this mixture kept at 0 ^{o}C, the above anhydride (**4**) (5.0 g, 18.1 mmol) was added in one portion. A solution of iodine (9.2 g, 36.2 mmol dissolved in 50 mL THF), was added drop wise over 30 min resulting in vigorous evolution of hydrogen. After addition of iodine was complete the flask was heated to reflux (18 h) and then cooled to room temperature. Dry methanol was added cautiously, until the mixture became clear. After stirring for 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of aqueous KOH solution (5 %, 150 mL) was stirred (1 h) and extracted with ethyl acetate (3X250 mL). The organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuum, which was further purified by column chromatography on silica gel (CH_2Cl_2/ MeOH, gradient elution: 95/5). R_f = 0.4 (CH_2Cl_2-MeOH, 4:1) (3.81 g, 71 %). M.p. 224 °C (lit.[59] = 222-225 ^{o}C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35-2.42 (m, 2H), 2.67 (br signal, 2H), 3.28-3.36 (dd, 11.2, 4.0 Hz, 2H), 3.55-3.58 (dd, *J* = 12.2, 4.0 Hz, 2H), 4.21 (s, 2H), 7.01-7.13 (m, 4H), 7.20-7.31 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 43.5, 47.9, 64.4, 123.3, 124.7, 125.8, 125.9, 140.8, 143.4.

IR (KBr): υ 3325, 3235, 3017, 1466, 1359, 1040, 1022, 749 cm.$^{-1}$

9,10,11,12,13,14-hexahydro-9,10-[3,4]furanoanthracene: **37**



Along with compound **36,** compound **37** (0.223 g) 5 % of [ether] was isolated.

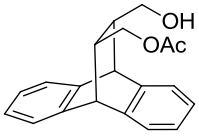
M.p.180 °C (lit[59] = 178-179^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79-2.81 (m, 1H), 3.25-3.28 (m, 1H), 3.72-3.77 (m, 1H), 4.19-4.20 (d, *J* = 2 Hz, 1H), 7.11 (m, 2H), 7.27-7.30 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 46.6, 47.4, 70.8, 123.7, 125.3, 125.9, 126.1, 141.0, 144.0

IR (KBr): υ 3041, 2947, 1459, 1280, 1090, 916, 742 cm.$^{-1}$

cis-9,10-Dihydro-9,10-ethanoanthracene-11-acetoxymethyl-12-methanol: **38**



The lipase (0.30 g) was added to a solution of **36** (0.150 g, 0.56 mmol) in dry THF (10 mL) and vinyl acetate (1.55 mL, 16.9 mmol) and the mixture was stirred at 8-9 ^{o}C. The course of reaction was monitored by TLC. After the period indicated in Table 1, the reaction mixture was filtered through a pad of celite and washed with THF. The filtrate was concentrated in vacuum and purified by short column chromatography. (light petroleum ether (PE)/EtOAc, gradient elution: 80/20. R_f 0.45 (PE/EtOAc, 1:1), M.p. =119.3 ºC for racemic, 104.5 ºC for (11*R*, 12*S*)

$[\alpha]_D^{28}$ = 30.4 (*c* = 0.5, MeOH for 95% *ee*)

HPLC condition Chiralpak OD-H column: 10 % IPA-Hexane, UV = 254 nm, Flow = 0.8 mL/min R_t = 15.8 min (1st Peak) [11*R*, 12*S*-isomer] and R_t – 18.1 min (2nd peak) [11*S*, 12*R* isomer].

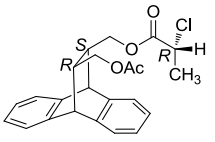
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.31-2.44 (m, 2H), 3.13-3.17 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.49-3.60 (m, 2H), 3.93-3.97 (dd, *J* = 10.8, 5.6 Hz), 4.32 (d, *J* = 2 Hz, 1H), 4.45 (d, *J* = 1.8 Hz, 1H), 7.13-7.27 (m, 4H), 7.28-7.33 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 39.6, 43.1, 46.2, 46.7, 62.3, 64.3, 123.5(2C), 125.2, 125.3, 125.8, 126.0, 126.1(2C), 140.5, 140.8, 143.1, 143.5, 170.9.

IR (KBr): υ 3356, 3021, 2957, 1724, 1468, 1368, 1233, 1020, 746 cm.$^{-1}$

HRMS (ESI+) m/z calculated for $C_{20}H_{20}O_3$ $[M+Na]^+$ 331.1304; found 331.1305.

cis-9,10-Dihydro-9,10-ethanoanthracene-11-yl)methyl 2-chloropropanoate acetoxymethyl-12-acetoxymethyl: **40**.



Alcohol-(**36**) (0.1 g, 0.32 mmol), DCC (0.066 g, 0.32 mmol) was placed in two necked flask under N_2 atmosphere, dissolved in 5 mL of dichloromethane and cooled (0 °C). A solution of (*R*)-2-chloro propionic acid (0.027 mL, 0.32 mmol) in dichloromethane (2 mL) was added drop wise. The reaction mixture was stirred (0^{o}C, 3h). After the reaction was over the reaction mixture was passed through celite, washed with dichloromethane and purified by column chromatography on silica gel. (PE/EtOAc, gradient elution: 90/10. R_f = 0.7 (PE/EtOAc, 3:1). White solid (0.09 g, 71 %). M.p. = 126^{o}C $[\alpha]_D^{28}$ = 19.7 (*c* =1.0, $CHCl_3$).

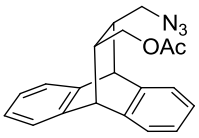
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (d, *J* = 6.8 Hz, 3H), 2.10 (s, 3H), 2.42-2.53 (m, 2H), 3.61-3.75 (m, 2H), 3.88-3.97 (dd, *J* = 11.2, 5.6 Hz, 1H), 4.02-4.05 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.32 (d, *J* = 2 Hz, 1H), 4.37 (d, *J* = 2 Hz, 1H), 4.43-4.49 (q, *J* = 6.8 Hz, 1H), 7.14-7.17 (m, 4H), 7.26-7.33 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.3, 39.6, 39.7, 46.3, 46.6, 52.4, 64.0, 65.5, 123.6, 123.7, 125.4, 125.8, 126.1(2C), 126.3(2C), 140.1, 140.2, 142.8, 143.0, 169.7, 170.7.

IR (KBr): υ 2964, 1740, 1696, 1468, 1274, 1234, 1061, 757, 550 cm.$^{-1}$

HRMS (ESI+) m/z calculated for $C_{23}H_{23}ClO_4$ $[M+Na]^+$ 421.1183; found 421.1177.

cis-9,10-Dihydro-9,10-ethanoanthracene-11-(azidomethyl)-12-yl)methy acetate: **41**



A solution of PPh_3 (0.236 g, 0.90 mmol) in dry THF (1.5 mL) was cooled (0^{o}C) under N_2 atmosphere. To the mixture deithylazodicarboxlate (0.14 mL, 0.90 mmol) was slowly added. Then solution of monoacetate (**5**) (0.16 g, 0.60 mmol) in dry THF (2 mL) was added to the reaction mixture, which was stirred (10 min. at 0^{o}C). To this DPPA (0.16 mL, 0.75 mmol) was added drop wise. The reaction mixture was then exposed to ultrasonic irradiation (30 min.). The solvent was removed under reduced pressure and the crude material was purified silica gel column chromatography on silica gel (PE/EtOAc, gradient elution: 95/5). R_f = 0.78 (Pet Ether/EtOAc, 4:1).

White solid (0.103 g, 60 %). M.p. = 110-111^{o}C $[\alpha]_D^{28}$ = 11.01 (*c* = 1.0, $CHCl_3$)

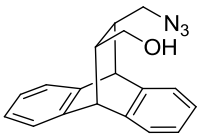
^{1}H-NMR(400 MHz, $CDCl_3$): δ 2.11 (s, 3H), 2.32-2.42 (m, 2H), 2.68-2.72 (dd, *J* = 10.8, 4.8 Hz, 1H) 3.29-3.34 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.60-3.3.65 (dd, 9.6, 8.4 Hz, 1H), 3.78-3.83 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.29 (d, *J* = 2 Hz, 1H), 4.41 (d, *J* = 2 Hz, 1H), 7.14-7.28 (m, 2H), 7.30-7.35 (m, 4H).

^{13}C-NMR: **(100 MHz, $CDCl_3$):** 21.0, 39.8, 40.3, 46.5, 46.7, 51.5, 64.1, 123.5, 123.8, 125.4, 125.6, 126.1, 126.2, 126.3 (2C), 140.1, 140.3, 142.7, 142.9, 170.7.

IR (KBr): υ 3024, 2099, 1734, 1468, 1235, 1035, 755 cm.$^{-1}$.

HRMS (ESI+) m/z calculated for $C_{20}H_{19}N_3O_2$ $[M+Na]^+$ 356.1375 found 356. 1370

cis-9,10-Dihydro-9,10-ethanoanthracene-11-(azidomethyl)-12-yl)methanol : **42**



To a solution of **41** (0.1 g, 0.3 mmol) in methanol (5 mL), HCl (0.04 mL, 0.5 mmol, 36 %) was added. The reaction mixture was refluxed (2h). After completion of reaction (TLC), MeOH was evaporated under reduce pressure. The residue was taken in ethyl acetate (25 mL) and washed with water (2X15 mL). The organic layer was dried with sodium sulphate and concentrated to afford **42** as white solid 0.079 g (90 %). M.p. = 135 ^{o}C $[\alpha]_D^{28}$ = 29.0 (c = 0.5, $CHCl_3$ for 85 % ee)

HPLC Condition Chiralpak OD-H column: 20% IPA-hexane, UV= 215 nm, Flow= 0.75 mL/min R_t –8.7 min (1st Peak) and R_t – 15.7 min (2nd peak).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31-2.35 (m, 2H), 2.75-2.80 (m, 1H), 3.20-3.24 (m, 1H), 3.33-3.41 (m, 2H), 4.39 (s, 2H) 77.14-7.34 (m, 4H), 7.29-7.34 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 40.4, 43.3, 46.6, 46.9, 51.2, 62.7, 123.5, 123.7, 125.1, 125.5, 125.9, 126.1, 140.3, 140.8, 142.8, 143.4.

IR (KBr): υ 3370, 3041, 2933, 2099, 1468, 1273, 1002, 750 cm.$^{-1}$.

HRMS (ESI+) m/z calculated for $C_{18}H_{17}N_3O$ $[M+]^+$ 314.1264 found 314.1264 .

Section II

2.II.1 Introduction of fluorine containing molecules

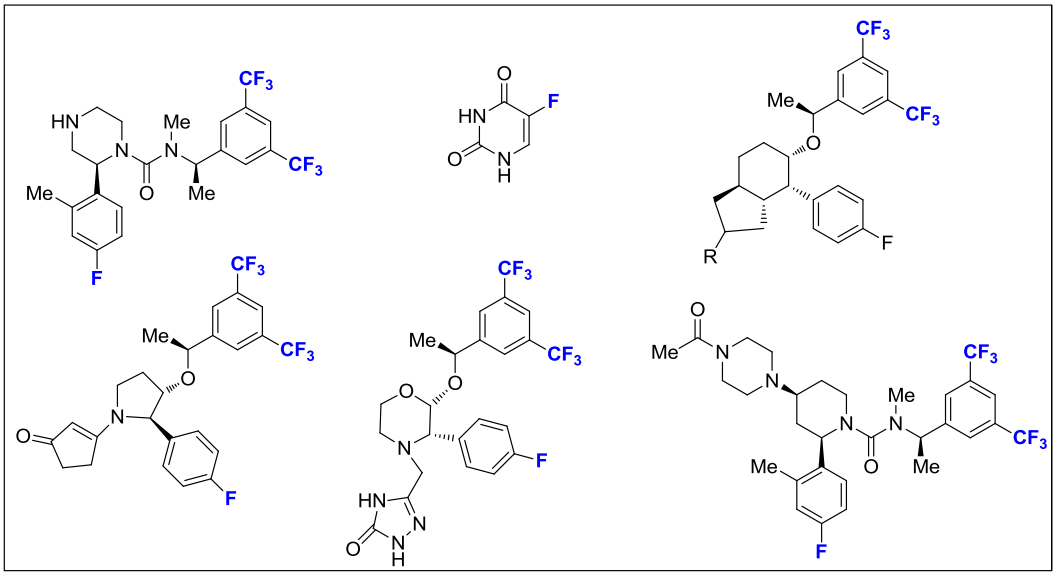
Fluorine has a unique position in the periodic table of elements; it possesses some extreme properties, in particular, very high electronegativity and oxidation potential. Many natural and artificial molecules of important properties and applications contain fluorine atom, and it is believed that the properties are associated with its presence. Introduction of fluorine into natural products can result in beneficial biological properties [60].

It is well known that fluorine's electronegativity, size, lipophilicity and electrostatic interactions can influence chemical reactivity. It is noteworthy that the atom of hydrogen and fluorine are quite close in size but have drastically different electronegativity. Scientists have utilized this significant aspect to prepare and study fluorine derivatives, by replacing H with F, and investigated their effects of the biological properties. Similarly the difference between $–CH_3$ and CF_3 has also been investigated for many cases. Moreover, these special features of the fluorine atom make it attractive for the design of structurally diverse molecules. It is well known that the introduction of fluorine atom strongly modifies the biological and pharmacological activity of a molecule [61].

2.II.2 Fluorine containing Drugs

Today, it is estimated that about 20–25% of drugs contain at least one fluorine atom. There is a constant need for developing new and efficient synthetic methods as well as expanding the availability of versatile fluorine-containing synthetic building blocks and intermediates to promote applications in medicinal chemistry, biology and molecular imaging [62]. Some of the fluorine containing molecules are also used for other applications like the heat and scratch resistant polymers, (e.g. Teflon) and some molecules used in material chemistry [63].

Scheme 2.23: Some representative drug molecules which contains fluorine element



As mentioned in previous chapter, enzymes are present in all biological systems. They are obtained from natural systems, and when they are degraded into amino acids of which they are made can be readily absorbed back into nature. In this way they are **"Green reagents"** in nature.

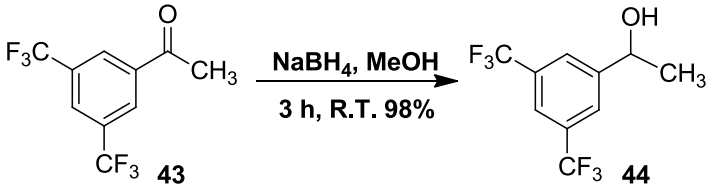
The demand for compounds of high enantiopurity in pharmaceutical industry is increasing since the two enantiomers of a chiral compound may have different physiological properties. To develop methods for preparing compounds in highly selective and in environmentally benign ways is of high priority. One of the effective strategies is to use enzymes in organic synthesis. This is, perhaps one of the most important application of enzymes.

As mentioned earlier, fluorinated molecules are the part of a group of drug intermediates, one such example is aprepritant. The synthesis of aprepritant in optically pure form relies on its starting material. Hence we were attracted to resolve 1-[3,5-bis(trifluoromethyl)phenyl]ethanol (±)-**44**. The improved and standardized parameters of the enantiomer separation study have been summarized in Table 2.7.

2.II.2 Preparation of racemic alcohol

The efforts to obtain enantiomerically pure alcohol **44** began with the reduction of the 1-[3,5-bis(trifluoromethyl)phenyl]ethanone. The fluorinated acetophenone derivative **43** was efficiently reduced to alcohol **44** by using $NaBH_4$ in methanol (scheme 2.24).

Scheme 2.24: Reduction of 1-[3,5-bis(trifluoromethyl)phenyl]ethanone



2.II.4 Resolution of racemic alcohol 44

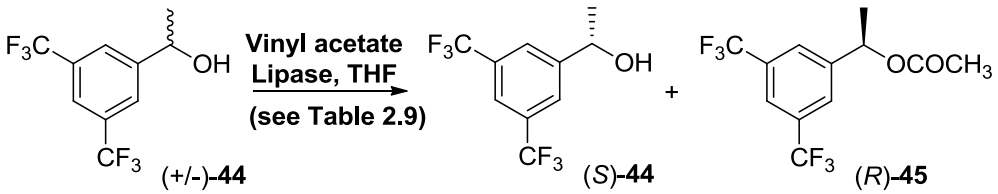
For synthetic purposes, the enantioselectivity of the products should be as high as possible in order to give the best optical purity and yield. Reactions catalyzed by various types of lipase are predominant in biotransformations.

Literature survey revealed that for resolution of secondary alcohol is often achieved by *Candida antarctica Lipase-B* (CAL-B) [64], hence in our study we have screened its commercially available immobilized enzyme CAL-B (Commercial name is Novozyme-435) as biocatalyst for the resolution of secondary alcohol.

Selection of a suitable reaction medium or solvent is critical because some organic solvents can inactivate the enzyme. In literature, generally resolution of various type of alcohol was achieved either in tetrahydrofuran, diisopropyl ether and dioxane.

The optically pure **44**, which is an intermediate of aprepitant, a potent and orally active antagonist of human neurokinin receptor, has also been accessed by similar process [65]. The improved and standardized parameters of the enantiomer separation study have been summarized in Table 2.9.

Scheme 2.25: Enzymatic resolution of (+/-)-**44**



We commence our studies for resolution of alcohol with THF as solvent and Novozyme-435 as enzyme with different acetylating agents (Table-2.9, entry 1 to 3). Ethyl acetate and Butyl acetate proved to be poor acyl donor and reaction did not proceed, on the other hand vinyl acetate gave the better results (Table-2.9, entry-2). Best value of enantiomeric excess were achieved by increasing the time to 84 h and obtaining both ester and alcohol in almost enantiomerically pure form (entry-7).

Table 2.9: Select conditions for resolution of (+/-)-**44**

No	Conditions			% ee of **45**[a] (% Yield)	% ee of **44**[b] (% Yield)	C	E
	Acyl donor	Solvent	Time (h)				
1	IPA	THF	72	>99 (38)	86 (37)	46	>200
2	VA	THF	72	>99 (40)	89 (45)	47	>200
3	EA	THF	72	--[c]	--	--	--
4	--	EA	72	94 (16)	32 (75)	25	44
5	BA	THF	72	--[d]	--	--	--
6	IPA	THF	84	>99 (40)	92 (35)	48	>200
7	VA	THF	84	>99 (43)	>99 (41)	50	>200

All the reactions were run at r.t.; [a]Determined by HPLC by converting to alcohol **44**; [b]Determined by HPLC; [c]Trace reaction, not isolated; [d]No reaction. IPA= *iso*-propenyl acetate, VA = vinyl acetate, EA = ethyl acetate, BA = butyl acetate

After the completion of reaction, two spots were observed on TLC which indicated that under present condition one of the isomers remained unchanged while the other isomer underwent acetylation to give ester. Both the products were then separated by column chromatography. Although we were able to develop good HPLC conditions for separations of isomers of **44**, we were not able to find suitable conditions for separations of isomers of **45**. Hence, the column purified samples of **45** was converted to the corresponding alcohol **44** under acidic hydrolysis condition, for further HPLC analysis. We have confirmed that no racemization occurred during acid catalysed hydrolysis step.

2.II.5 Determination of Absolute Configuration

Since both the compounds were known in the literature its absolute configuration was determined by comparing the sign of optical rotation values. By optical rotation data it was confirmed that (*R*)-isomer underwent acetylation and (*S*) isomer remain unchanged. The optical rotation of both the isomers were recorded in the same solvent with the concentration that was reported in the literature. The S.O.R. data of unreacted alcohol have same sign of optical rotation ($[\alpha]_D$ = -24.8, c = 1.0, $CHCl_3$) that was reported of in literature with similar values (lit.$[\alpha]_D$ = -24.1, c = 1.0, $CHCl_3$) [66].

2.II.5.1 CD spectra

The circular dichroism (CD) spectra of these compounds were run in acetonitrile. The CD spectrum showed similar pattern but opposite cotton effect.

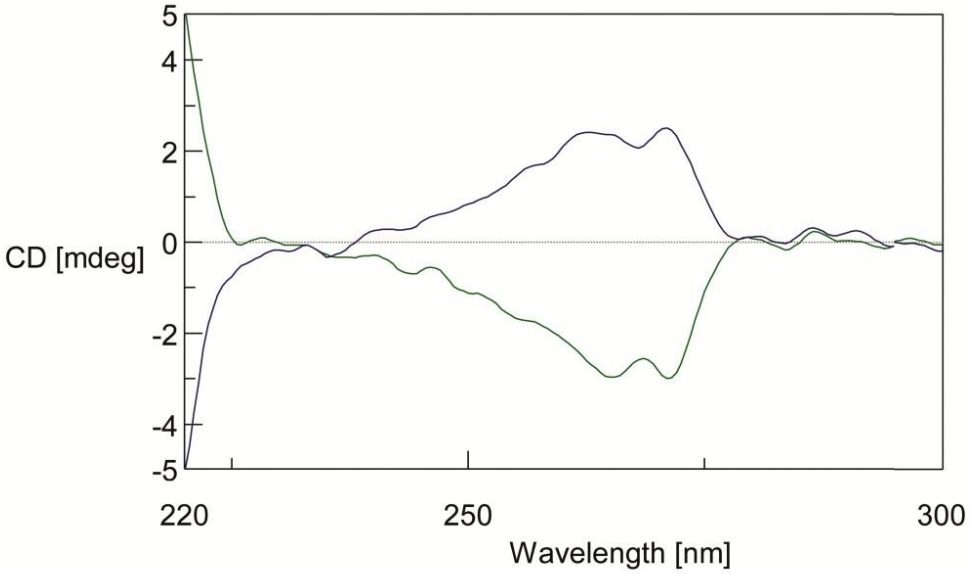


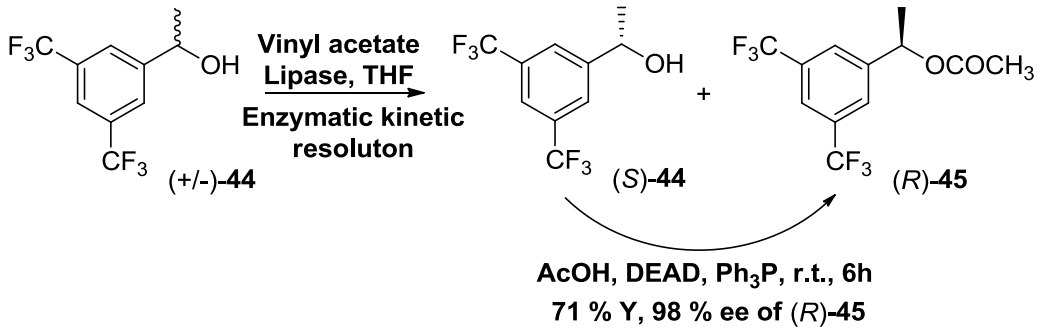
Figure 2.16: CD spectra of (*R*)-**44** and (*S*)-**44** isomer in acetonitrile [c = $1x10^{-3}$] Green line (*R*-isomer) Blue line (*S*-isomer).

However, the kinetic resolution of chiral alcohols cannot furnish either compound in more than 50% chemical yield in optically pure form. To overcome this difficulty a strategy of combination of enzymatic resolution and Mitsunobu reaction [50] has been developed by few groups [67].

2.II.5 Kinetic Resolution followed by Mitsunobu protocol

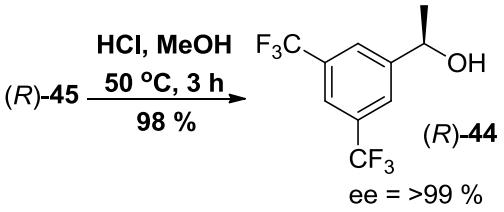
The Mitsunobu reaction involves direct substitution of alcohols with new nucleophiles in presence of triphenyl phosphine and diethyl azodicarboxylate (DEAD) with complete inversion of configuration. In the above reaction (Scheme 2.26) the alcohol (*S*)-**44** was selectively converted to its acetate (*R*)-**45** with excellent selectivity and moderate yield. The unaffected alcohol (*S*)-**44** is also left in high optical purity. In the present effort the same reaction is conducted in acetic acid under mitsunobu conditions, where the acetate ion acts as new nucleophile and the unreacted alcohol (*S*)-**44** was converted selectively to (*R*)-**45** with complete inversion in overall good chemical yield (Scheme 2.26).

Scheme 2.26: Combination of lipase mediated resolution and Mitsunobu reaction



Thus a practical process was developed to access optically pure (*R*)-**45**, which was converted to chiral alcohol (*R*)-**44** under the acidic hydrolysis conditions (Scheme 2.27).

Scheme 2.27: Synthesis of (*R*)-**3**

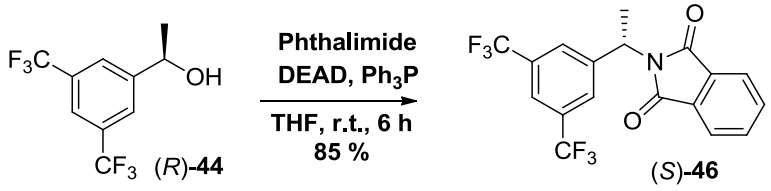


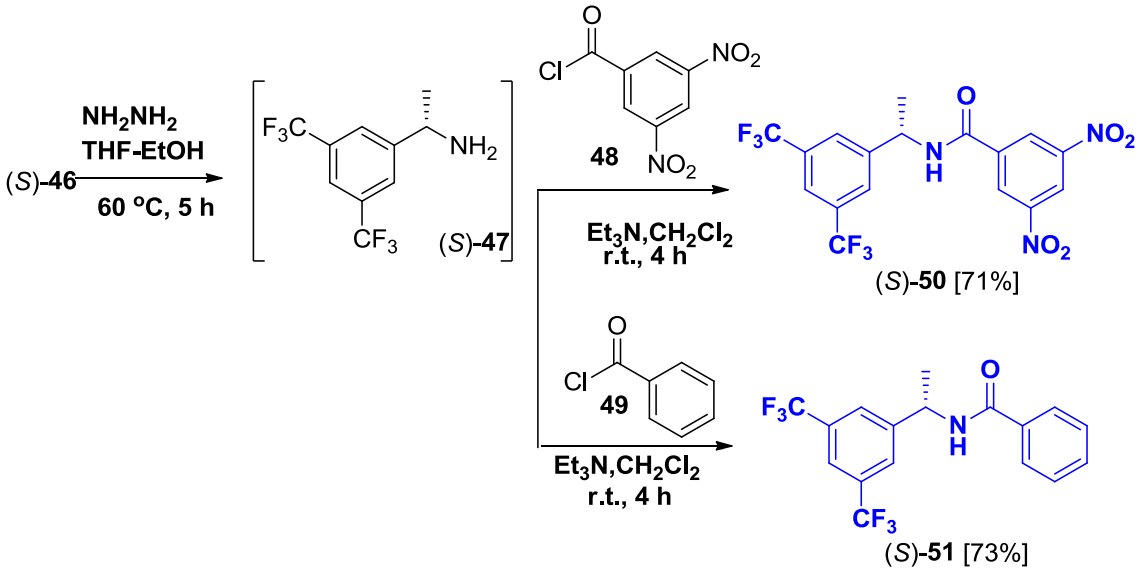
2.II.6 Synthesis of Chiral Amide ligands

Optically pure alcohol (*R*)-**44** was then converted to corresponding amine (*S*)-**47** (Scheme 2.28). This operation involved inversion of configuration by its reaction with phthalimide, Ph_3P and DEAD in dry tetrahydrofuran, furnishing the corresponding phthalimide (*S*)-**46**, which was subsequently deprotected with hydrazine [68].

The amine (*S*)-**47** was not isolated but converted directly to the desired amide (*S*)-**50** by treatment with 3,5-dinitrobenzoyl chloride **48**. Similarly (*S*)-**47** was also converted to (*S*)-**51** by treatment with benzoyl chloride **49**.

Scheme 2.28: Synthesis of (*S*)-**50** and (*S*)-**51**





We could also grow a single crystal of (*S*)-**50** in Toluene and its X-ray diffraction analysis performed (Figure 2.17) [69]. The single crystal analysis of **50** indicated a cleft-like arrangement caused by having the 3,5-dinitrobenzoyl group placed orthogonal to the trifluoro phenyl ring plane. The detail of analysis is further discussed in chapter 3. Amide (*S*)-**50**, and (*S*)-**51** were evaluated in some molecular recognition experiments, discussed in chapter 3.

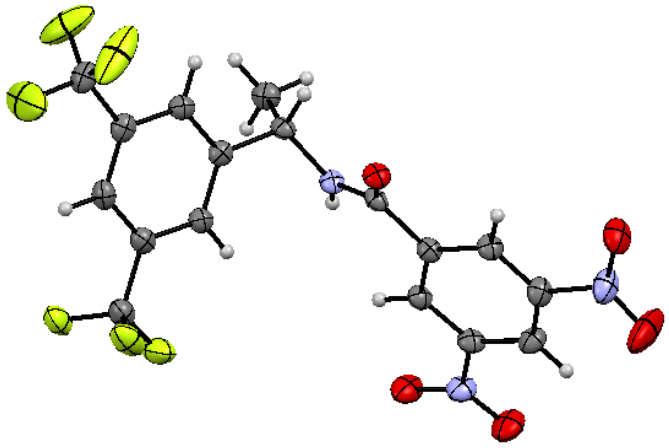


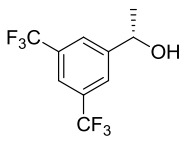
Figure 2.17 ORTEP diagram of (*S*)-**50**

Experimental Section

General procedure for the enzymatic resolution.

To oven dried flask racemic alcohol (±)-**44** (1.0 g, 3.87 mmol) was dissolved in dry THF (10 mL) and lipase (Novozyme-435) (0.3 g, 30% w/w), vinyl acetate (0.36 mL, 3.87 mmol) were added and stirred at room temperature. The reaction was followed by TLC. The material was filtered and the filtrate was concentrated in vacuo. Separation was carried out by column chromatography over silica gel using petroleum ether and ethyl acetate as the eluent. The acetate (*R*)-**45** was isolated with 2 % ethyl acetate in petroleum ether and alcohol (*S*)-**44** 5 % ethyl acetate in petroleum ether.

1-[3,5-bis(trifluoromethyl)phenyl] ethanol: (*S*)-**44**



M.p. = 86-87 ºC (lit.[65] 88 ºC). $[\alpha]_D$ = -24.8 (c = 1.0 $CHCl_3$) (lit.[66] $[\alpha]_D$ = -24.1 (c = 1.0 $CHCl_3$) HPLC condition for alcohol (*S*)-**44** Chiralpak OD-H column: 5% IpA-Hexane, UV= 254 nm, Flow = 0.5 mL/min R_t – 9.5 min (1st Peak) - [*S*-isomer] and R_t – 10.5 min (2nd peak)-[*R*-isomer]

^{1}H-NMR (400MHz, $CDCl_3$): δ 1.53-1.55 (d, *J* = 6.4 Hz, 3H), 2.24 (s, 1H), 5.01-5.10 (q, *J* = 6.4 Hz, 1H), 7.78 (s, 1H), 7.84 (s, 2H).

^{19}F-NMR (376 MHz, $CDCl_3$): δ -62.88

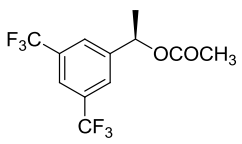
^{13}C-NMR (100 MHz, $CDCl_3$): 25.5, 69.3, 121.3 (sep, J_{C-F} = 4.4 Hz), 123.3 (q, J_{C-F} = 271.0 Hz), 125.6, 131.9 (q, J_{C-F} = 33.0 Hz), 148.2.

Mass (EI): 258(10), 242(100), 243(96), 240(20), 195(74), 194(87), 69(50).

IR (KBr): υ 3257-3159, 2980, 1625, 1467, 1280, 1024, 924, 896, 842, 705, 683 cm.$^{-1}$

1-[3,5-bis(trifluoromethyl)phenyl]ethylacetate: (*R*)-**45**

Procedure for enzymatic reaction followed by Mitsunobu reaction.



After enzymatic resolution enzyme was filtered off. To filtrate AcOH (0.11 mL, 1.93 mmol) and triphenyl phosphine (0.51 g, 1.93 mmol) were added under nitrogen atmosphere followed by the slow addtion of solution of DEAD (0.38 mL, 2.42 mmol) in dry THF (~2 mL) at 0^{o}C. The reaction mixture was stirred for 6h. The solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography (2% Ethyl acetate- Petroleum ether). Colourless liquid which was solidify after cooling. 0.82 g (70.7% Yield) M.p. = 59-60 ^{o}C.

$[\alpha]_D$ = +55.2 (c = 1.0 methanol) lit.[65] $[\alpha]_D$ = +57 (c = 1.MeOH) for (*R*)-isomer.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.58-1.60 (d, *J* = 6.8 Hz, 3H), 2.24 (s, 3H), 5.94-5.99 (q, *J* = 6.8Hz, 1H), 7.81(s, 1H), 7.83(s, 2H).

^{19}F-NMR (376 MHz, $CDCl_3$): δ -62.90.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.1, 22.3, 70.9, 121.9 (sep, J_{C-F} = 4.4 Hz), 123.2, (q, J_{C-F} = 271.0 Hz), 126.2, 131.4 (q, J_{C-F} = 33.0 Hz), 144.3, 170.1.

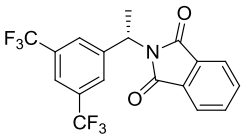
Mass (EI): 299(18), 281(10), 258(100), 257(89), 239(91), 238(56), 200(47), 150(21), 71(18).

IR (KBr): υ 3007, 2941.61, 1732, 1456, 1285, 1173, 1021, 898, 706, 684 cm.$^{-1}$

General procedure for hydrolysis of: (*R*)-**44**

To a solution of (*R*)-**45** (0.82 g, 3.18 mmol) in methanol (15 mL), HCl (0.5 mL, 4.76 mmol, 36 %) was added. The reaction mixture was refluxed (3 h). After completion of reaction, as indicated by TLC, MeOH was evaporated under reduce pressure. The residue was taken in ethyl acetate, and washed with water. The organic layer was dried with sodium sulphate and concentrated to afford (*R*)-**44** in 0.80 g (98%).

Synthesis of 1-[3,5-bis(trifluoromethyl)phenyl]ethylphthalimide: (*S*)-**46**



In two necked round. bottom flask alcohol (*R*)-**44** (1.0 g, 3.86 mmol) was dissolved in dry THF (10 mL) was kept in ice bath at 0 ^oC under nitrogen atmosphere. To this solution PPh_3 (1.01 g, 3.86 mmol) and pthalimide (0.57 g, 3.86 mmol) were added. A solution of diethylazodicarboxylate (DEAD) (0.77 mL, 4.24 mmol) in THF (3 mL) was added drop wise, and the reaction was stirred (6 h). The reaction was followed by TLC. The product was purified by column chromatography over silica gel (10% Ethyl acetate-Petroleum ether) affording white solid (1.2 g, 80 %) M.p = 124-126^0 C

$[\alpha]_D$ = (-) 59.8 (c = 0.5 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.57-1.55 (d, *J* = 7.2 Hz, 3H), 5.79-5.86 (q, *J* = 7.2Hz, 1H), 6.15-6.17 (d, *J* = 7.2 Hz, 1H), 7.28.-7.23 (m, 2H), 7.40-7.36 (m, 1H), 7.47-7.51 (m, 2H), 7.74-7.78 (m, 2H), 8.04 (s, 2H).

^{19}F-NMR (376 MHz, $CDCl_3$): δ -62.76

^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.4, 48.7, 121.9 (sep, J_{C-F} = 4.4 Hz), 123.2 (q, J_{C-F} = 271.0 Hz), 127.9 131.6, 131.7, 132.3 (q, J_{C-F} = 33.0 Hz), 134.3, 142.6, 167.8

Mass (EI): 387(89), 386(53), 372(100), 371(84), 368(89), 343(42), 239(25), 159(45)

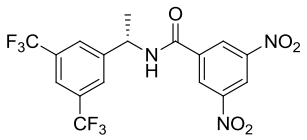
IR (KBr): υ 2999, 2923, 1780, 1705, 1467, 1284, 1126, 1060, 895, 712, 528 cm^{-1}

HRMS (TOF-MS) m/z calculated for $C_{18}H_{11}F_6NO_2$ $[M+H]^+$ 388.0772, found 388.0773

General Procedure for synthesis of amide ligand.

In a dry r.b. flask phthalimide (*S*)-**46** (0.50 g, 1.29 mmol) was dissolved in a mixture of THF (40 mL) & ethanol (10 mL) and treated with drop wise addition of hydrazine hydrate (0.63 mL, 12.9 mmol, 99%). The reaction mixture was stirred at 60 ^oC (5 h). The white suspension formed was filtered, washed with THF (2X20 mL) and then organic solvent was evaporated under reduced pressure. To this residue water (50 mL) was added and extracted with dichloromethane (2X50 mL). The organic layer was concerted in vacuum to furnish viscous liquid. The oil was dissolved in dry chloroform (5 mL) and treated with triethyl amine (0.18 mL, 1.28 mmol). The mixture was allowed to cool (0 ^oC) and a solution of 3,5-dinitrobenzoyol chloride (0.30 g, 1.28 mmol) **48** in chloroform (5 mL) was slowly added (in 30 min.). The mixture was stirred at room temperature (4 h). The solvent was evaporated and the residue was washed with sodium bicarbonate (saturated solution) and extracted with dichloromethane (2X75 mL). The organic layer were dried over anhydrous sodium sulphate and concentrated at reduce pressure. The crude product was purified by column chromatography over silica gel (30% ethyl acetate- Petroleum ether).

N-(1-(3,5-bis(triflouromethyl)phenyl)ethyl)-3,5-dinitrobenzamide: (*S*)-**50**



White solid (0.415 g; 71%). M.p = 196-97 ^oC $[\alpha]_D$ = 37.2 (c = 0.5 $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.75-1.76 (d, *J* = 7.2 Hz, 3H), 5.43-5.50 (m, 1H), 6.89-6.91 (d, *J* = 6.8 Hz, 1H), 7.85 (s, 1H), 7.87 (s, 2H), 9.00-9.01 (d, *J* = 2.0 Hz, 2H), 9.20-9.211 (t, *J* = 2.0 Hz, 1H).

^{19}F-NMR (376 MHz, $CDCl_3$): δ -62.78.

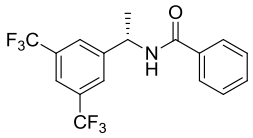
^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6, 49.8, 121.5, 121.9 (sep J_{C-F} = 4.4 Hz), 127.3. 125.8 (q, J_{C-F} = 271.0 Hz), 126.6, 132.3 (q, J_{C-F} = 33.0 Hz), 136.9, 144.8, 148.7, 162.1

Mass (EI): δ 451(29), 450(11), 240(44), 195(100).

IR (KBr): υ 3343, 3088, 1647, 1544, 1348, 1278, 897, 731 $cm.^{-1}$

HRMS (TOF-MS) m/z calculated for $C_{17}H_{11}F_6N_3O_5$ $[M-H]^-$ 450.0530; found: 450.0527.

(*S*)-N-(1-(3,5-bis(triflouromethyl)phenyl)ethyl)benzamide: (*S*)-**51**



The amide was (*S*)-**51** was prepared similarly in 73 % yield starting from (*S*)-**46** and **49** as described above. White Solid, Yield = 73 % M.p = 156 ^oC $[\alpha]_D$ = 22.4 (c= 1, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.65-1.67 (d, *J* = 7.2 Hz, 3H), 5.38-5.45 (m, 1H), 6.43-6.45 (d, *J* = 6.8 Hz), 7.46-7.58 (m, 3H), 7.79-7.781 (m, 3H), 7.84 (s, 2H).

^{19}F-NMR (376 MHz, $CDCl_3$): δ -62.77.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.9, 48.9, 121.4 (sep J_{C-F} = 4.4 Hz), 123.3 (q, J_{C-F} = 271.0 Hz), 126.4, 126.9,128.7, 131.9,132.4 (q, J_{C-F} = 33.0 Hz), 133.7, 146.2, 166.9

Mass (EI): δ 361(100), 360(58), 240(19), 105(90), 104(71).

IR (KBr): υ 3340, 3087, 1639, 1530, 1382, 1124, 920, 895, 845, 703 $cm.^{-1}$

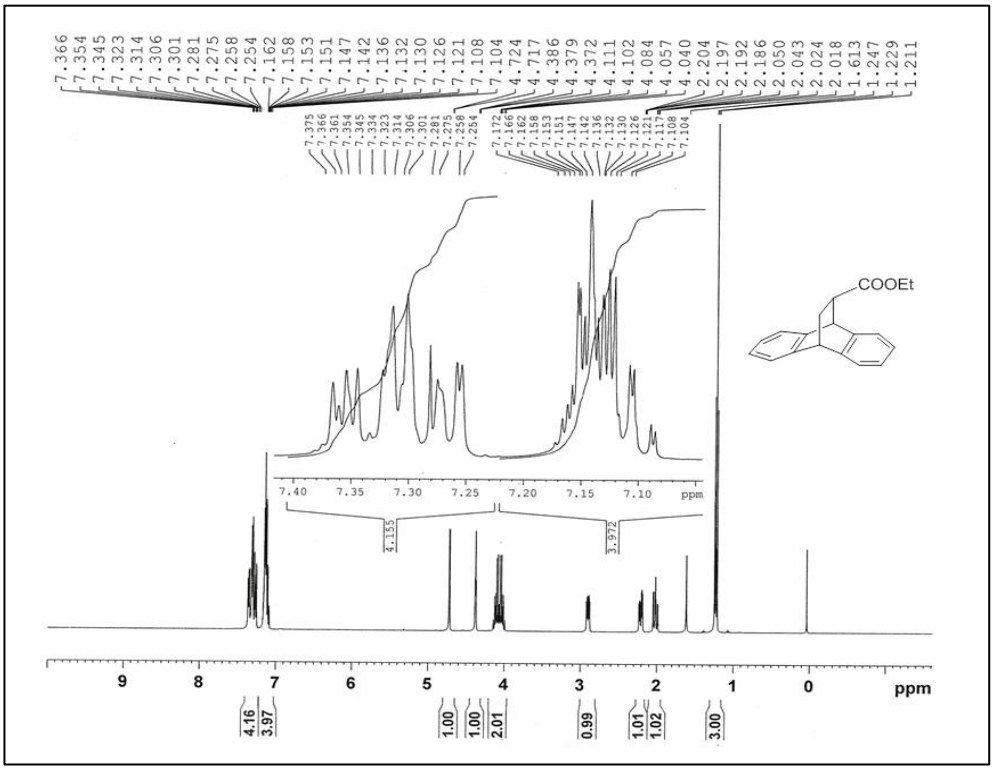
HRMS (ESI+) m/z calculated for $C_{17}H_{13}F_6NO$ $[M+Na]^+$ 384.0799, found :384.0794.

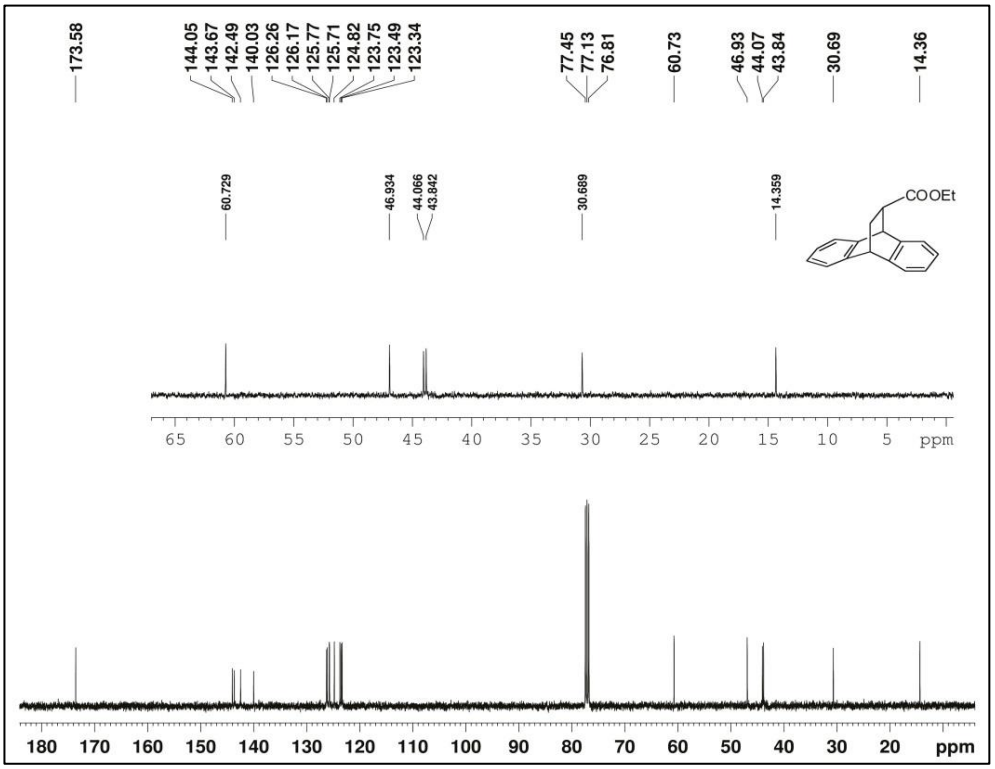
Conclusion

- The resolution of 9, 10-dihydro 9, 10- ethanoanthracene 11- methanol and *trans*-11,12-bis(hydroxymethyl)-9,10-dihydro-9,10-ethanoanthracene was achieved as one isomer of the alcohol is selectively acetylated in presence of suitable acyl donor and lipase as bio-catalyst.
- The acetate obtained in optically pure form is converted to the other isomer of alcohol and diol by simple alkaline hydrolysis. The easily accessible two isomers of alcohol and diol are converted to chiral diamines and mono amine.
- Enzymatic desymmetrisation of *meso* diol was achieved although selectivity was moderate.
- The conversion of *meso cis*-diol **36** to optically pure azido-alcohol **42** will open further possibilities to study applications of functionalized roof shape chiral compounds.
- The fluorine containing compound 1-[3,5 bis(trifluoromethyl)phenyl] ethanol **44** was successfully resolved. With the aid of Mitsunobu protocol yield was achieved up to 71%.

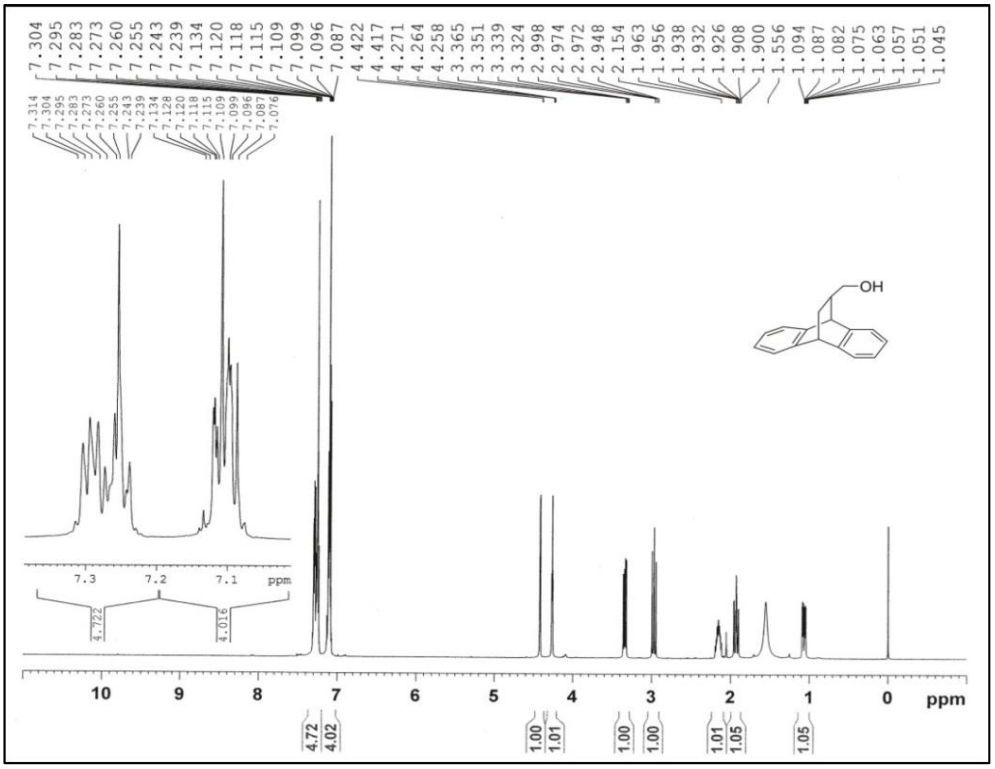
Spectral chart

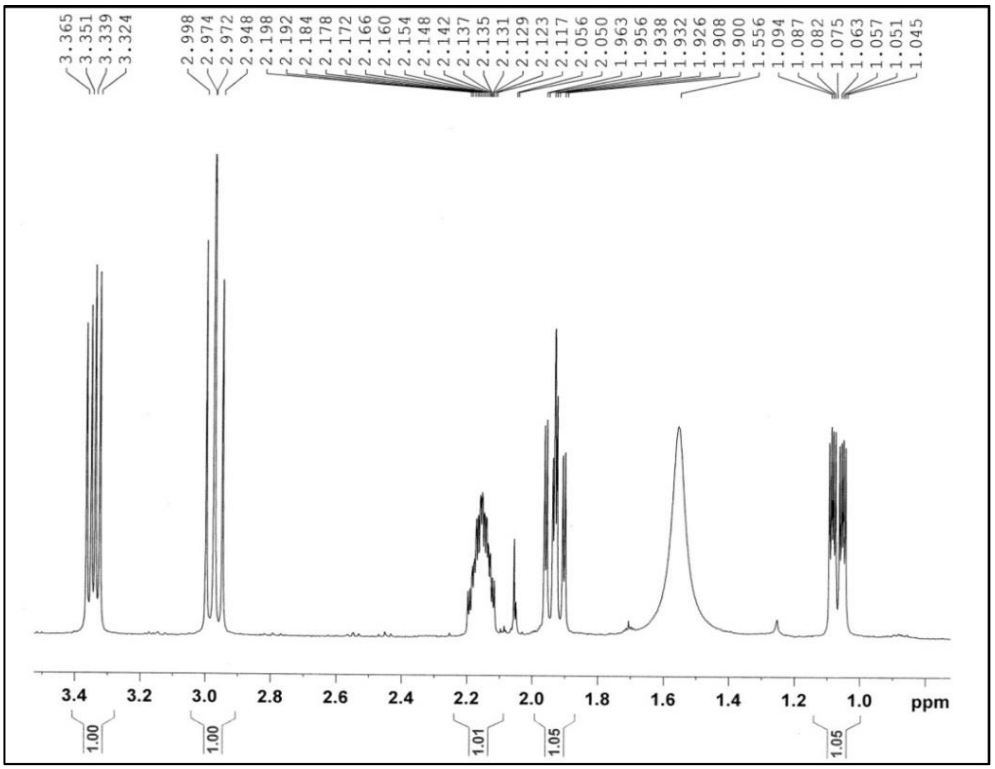
Spectral chart of Type A



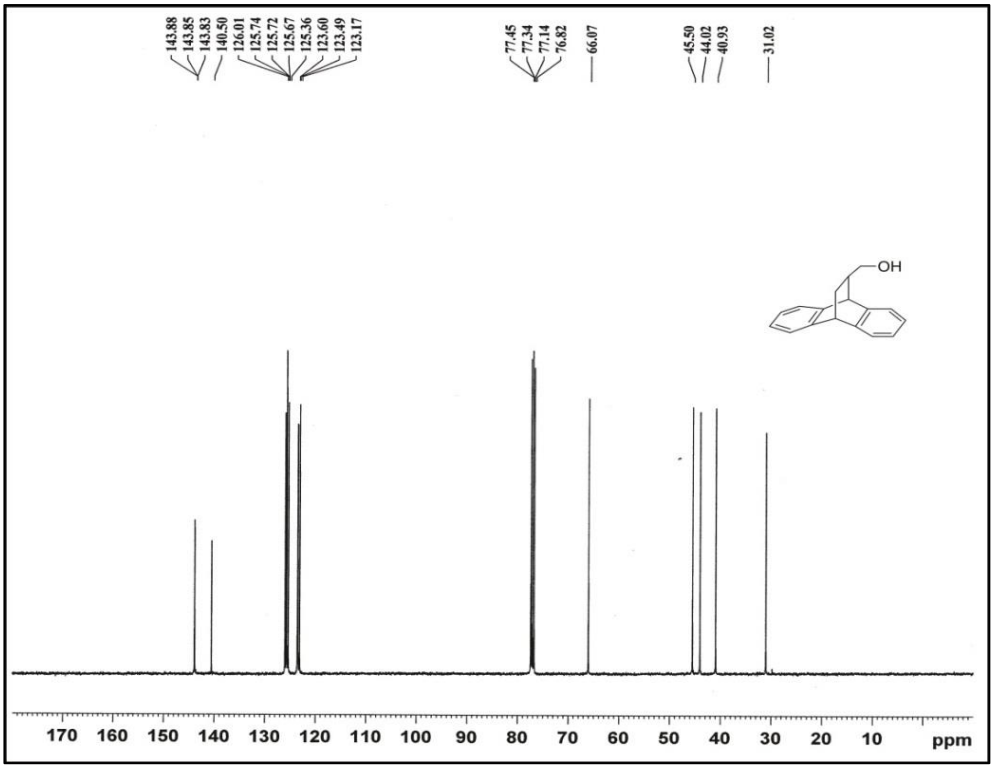


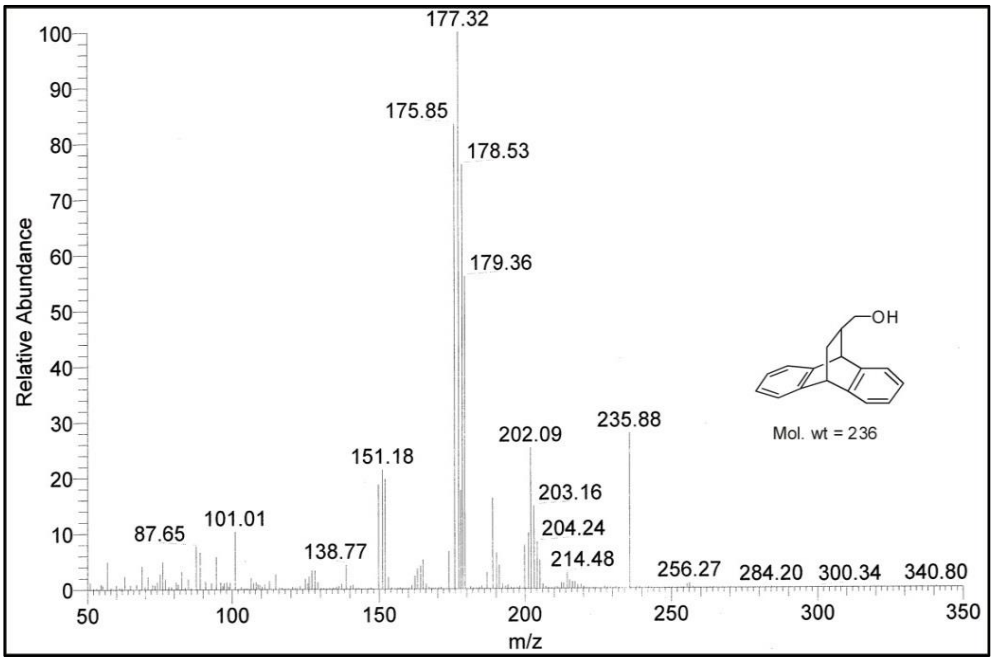
^{1}H NMR & ^{13}CNMR Spectra of compound 7





^{1}H NMR Spectra of compound 8

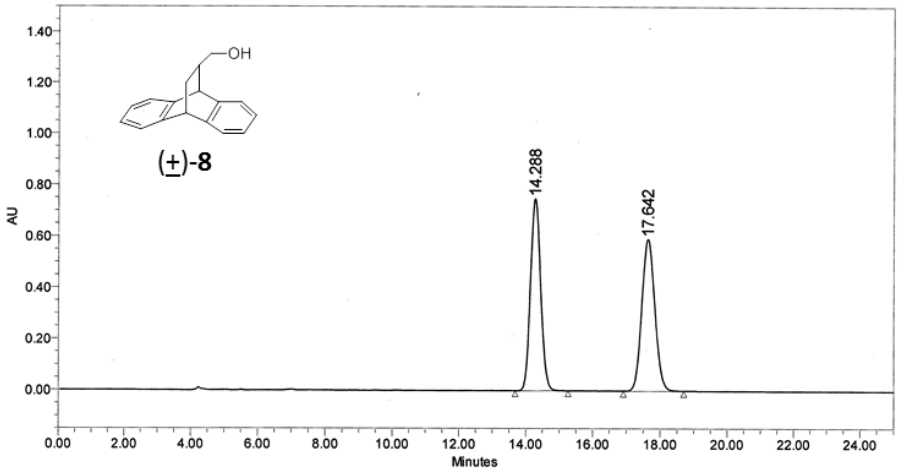




^{13}C NMR & Mass Spectra of compound 8

HPLC chart

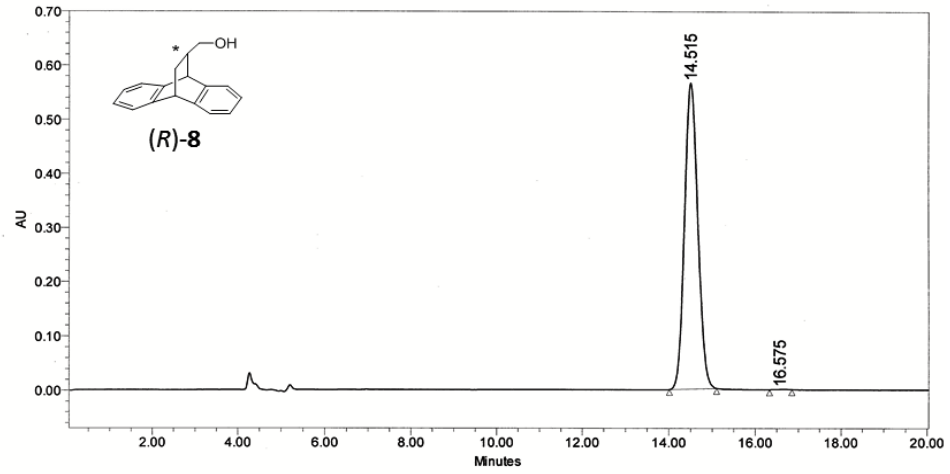
HPLC Condition: Observed two peaks of seperated enantiomers at 1) R_t – 14.29 min and 2) R_t – 17.64 min. Solvent System: hexane: *iso*-propanol (90:10), Flow rate: 0.7 mL/min. Chiral Column: Daicel Chiral OD-H. UV: 215nm.



Peak Table

	RT	Area	% Area	USP Resolution
1	14.29	15923539	49.85	
2	17.64	16020116	50.15	5.17
Sum		31943655	100.00	

Chromatogram

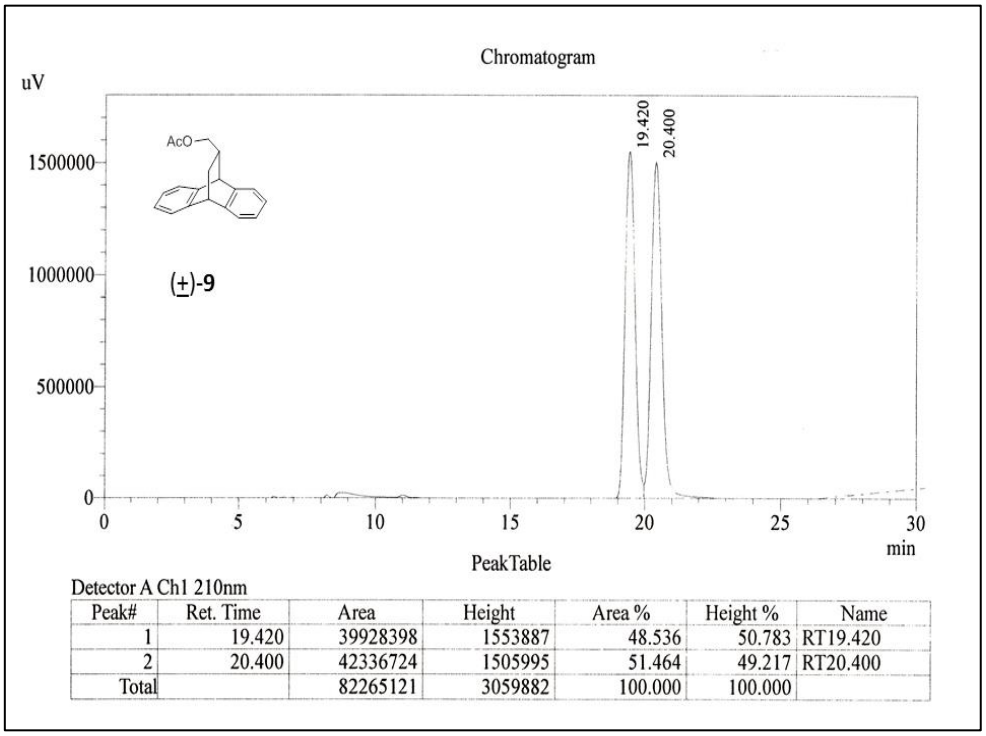


Peak Table

	RT	Area	% Area	USP Resolution
1	14.52	12068504	99.93	
2	16.57	8331	0.07	4.26
Sum		12076835	100.00	

HPLC graph of compound 8

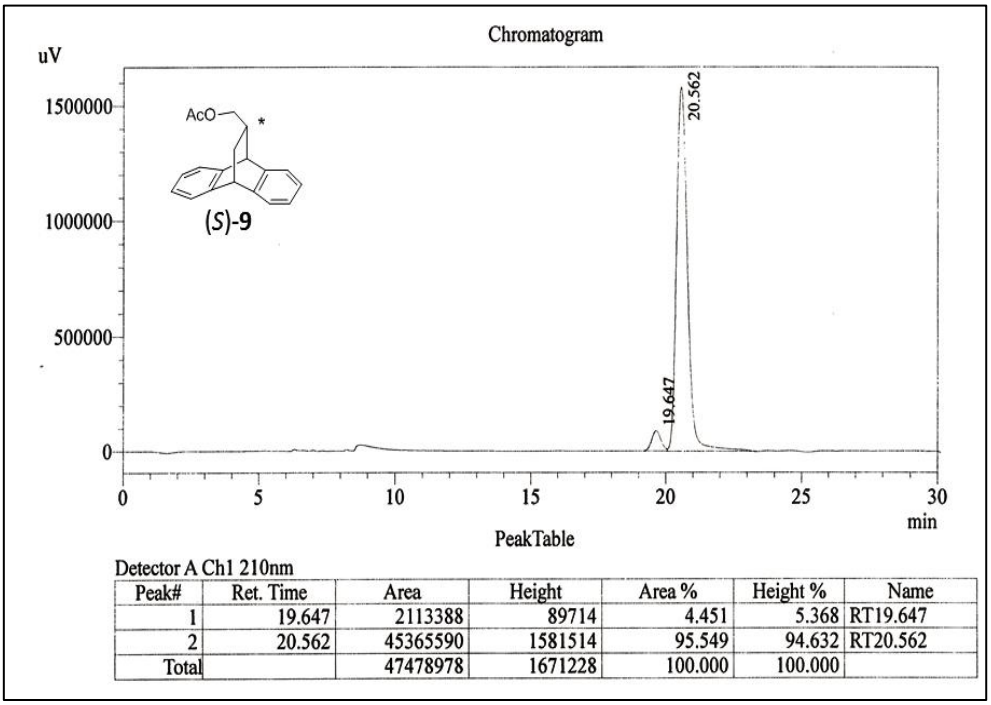
HPLC Condition: (1) R_t – 19.42 min and 2) R_t – 20.40 min. Solvent System: hexane: *iso*-propanol (99:1), Flow rate: 0.5 mL/min. Chiral Column: Diacel-IC Column UV: 210nm



PeakTable

Detector A Ch1 210nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Name
1	19.420	39928398	1553887	48.536	50.783	RT19.420
2	20.400	42336724	1505995	51.464	49.217	RT20.400
Total		82265121	3059882	100.000	100.000	

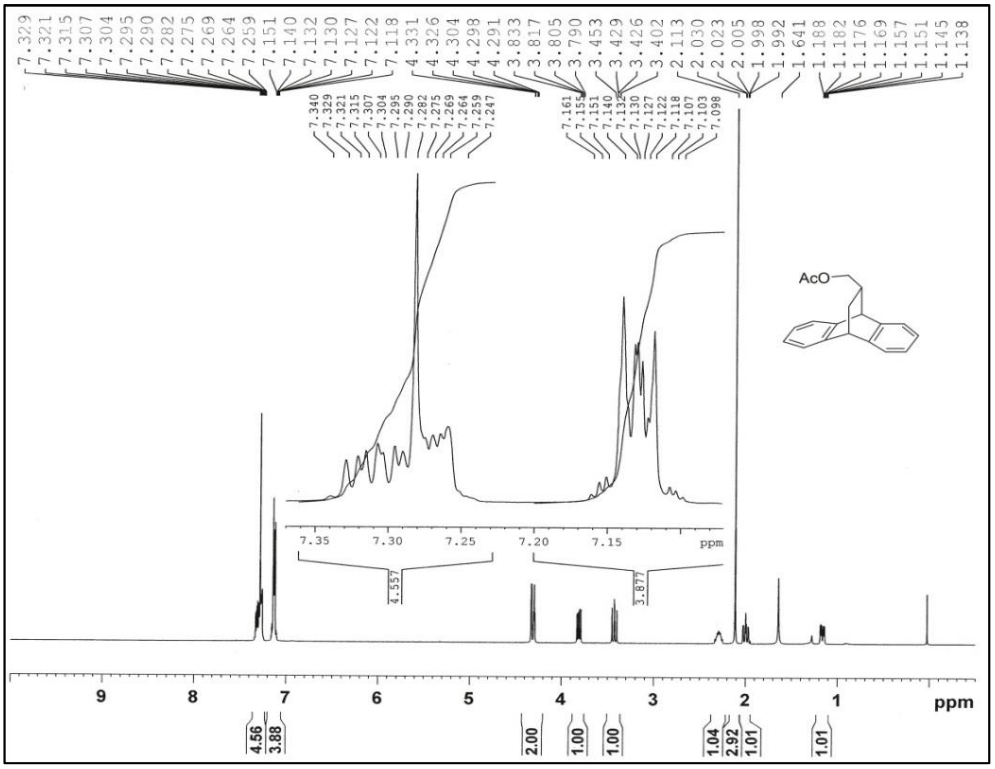


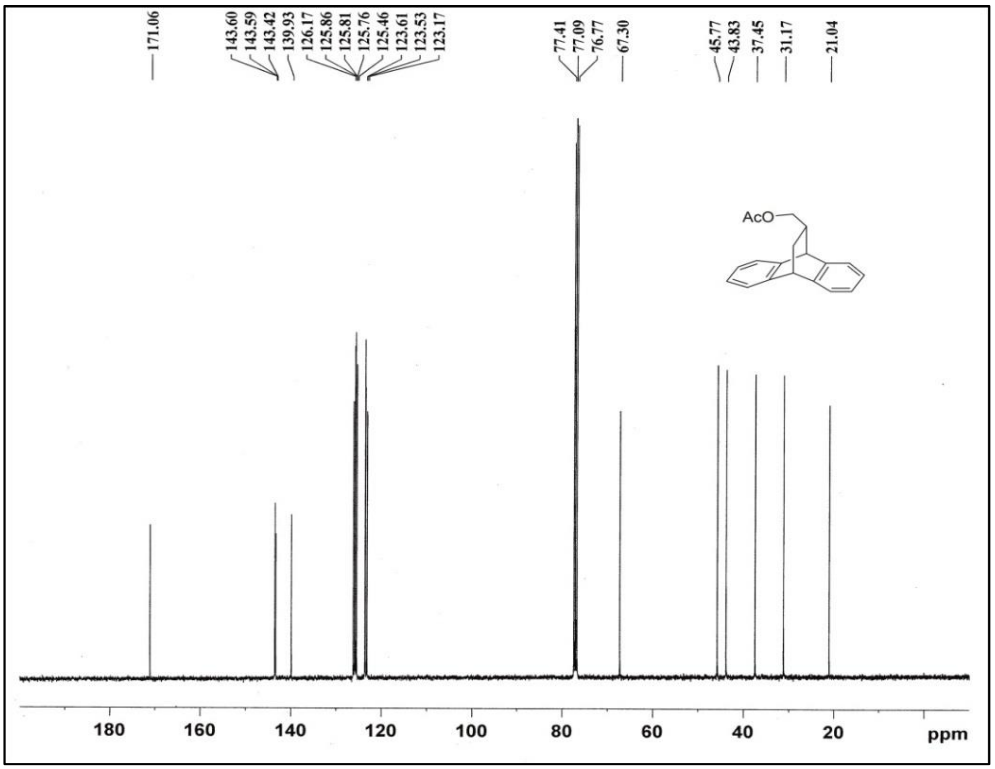
PeakTable

Detector A Ch1 210nm

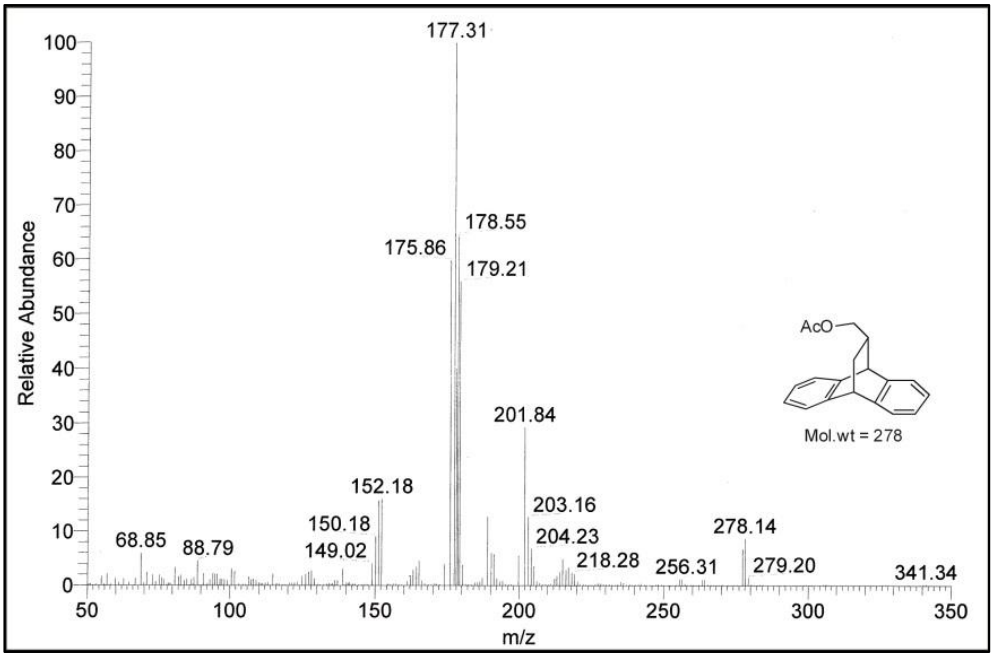
Peak#	Ret. Time	Area	Height	Area %	Height %	Name
1	19.647	2113388	89714	4.451	5.368	RT19.647
2	20.562	45365590	1581514	95.549	94.632	RT20.562
Total		47478978	1671228	100.000	100.000	

HPLC condition for 9

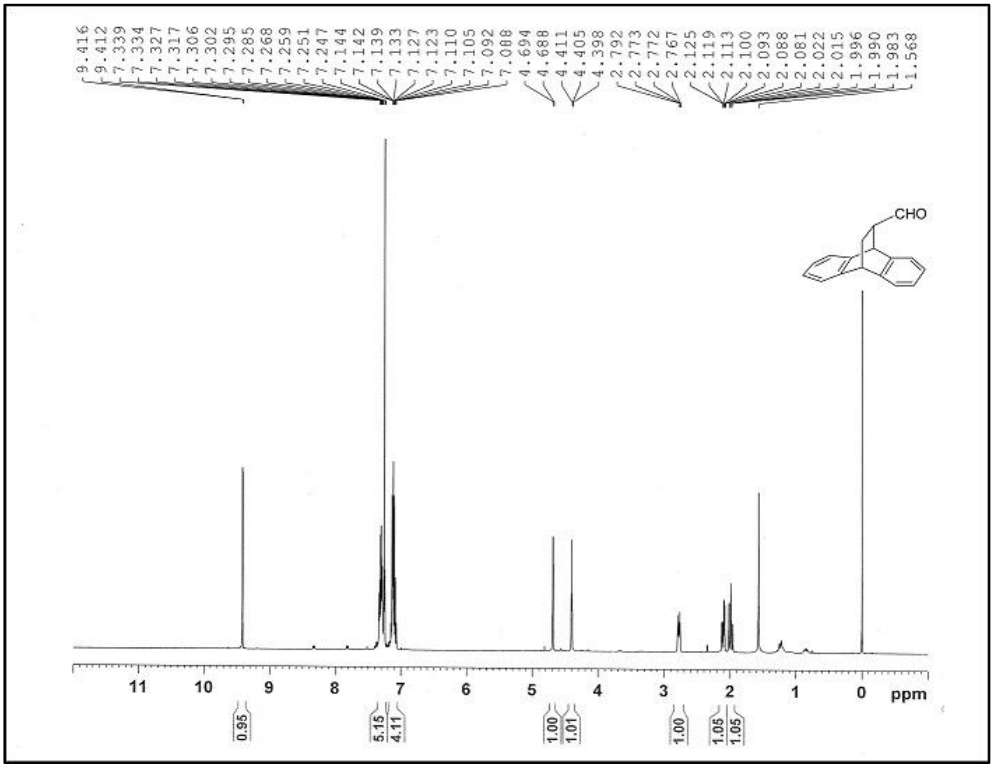




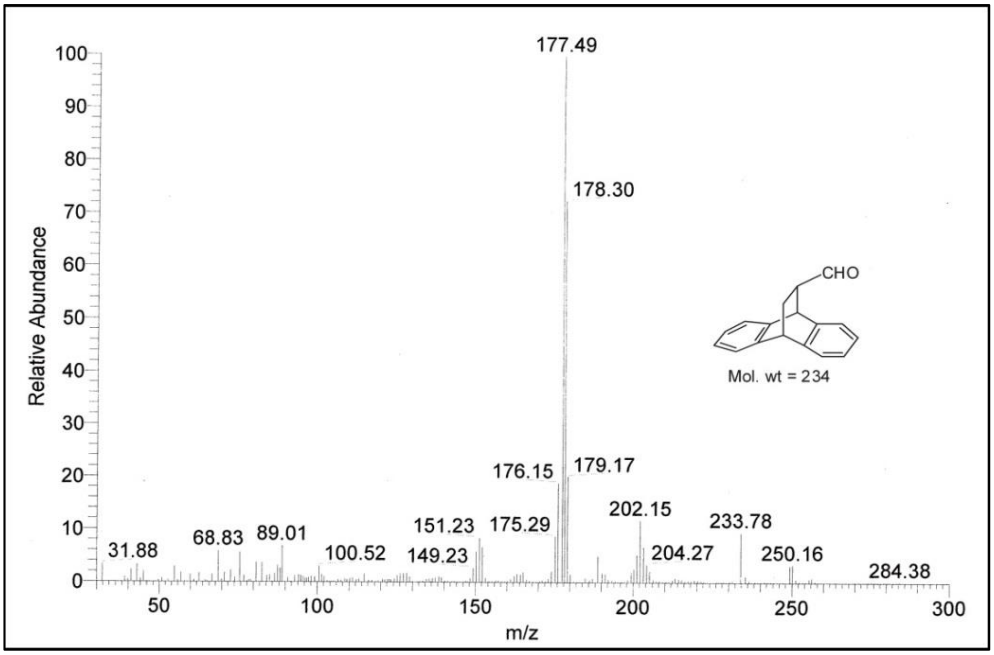
^{1}H NMR & ^{13}C NMR Spectra of compound 9



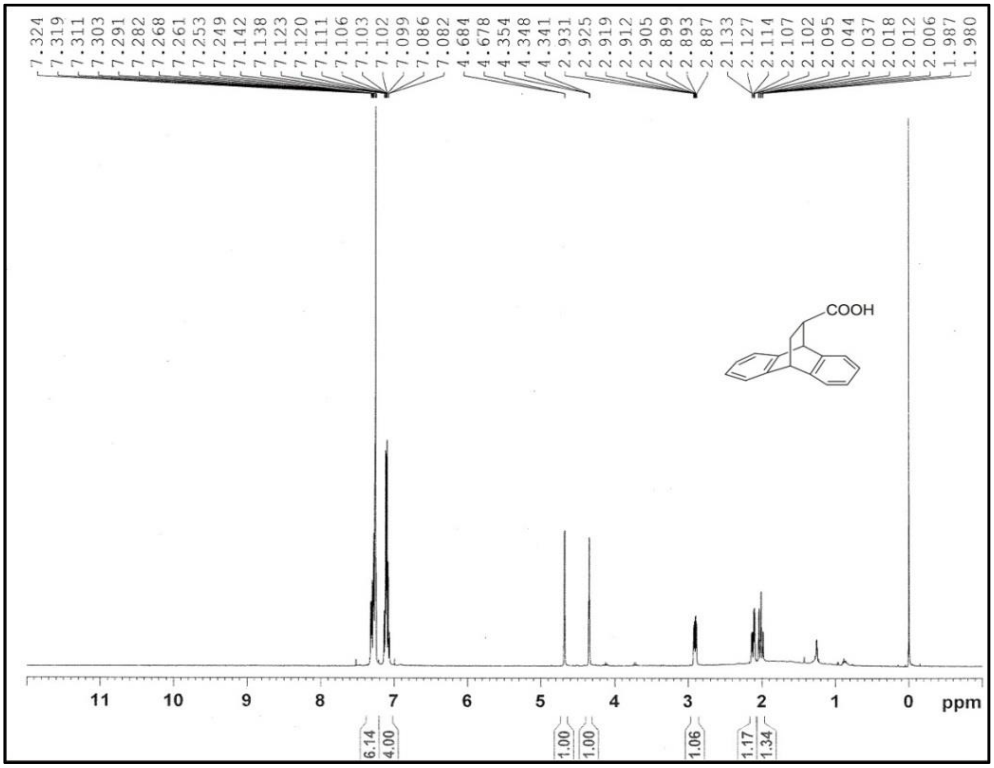
Mass spectra of compound 9



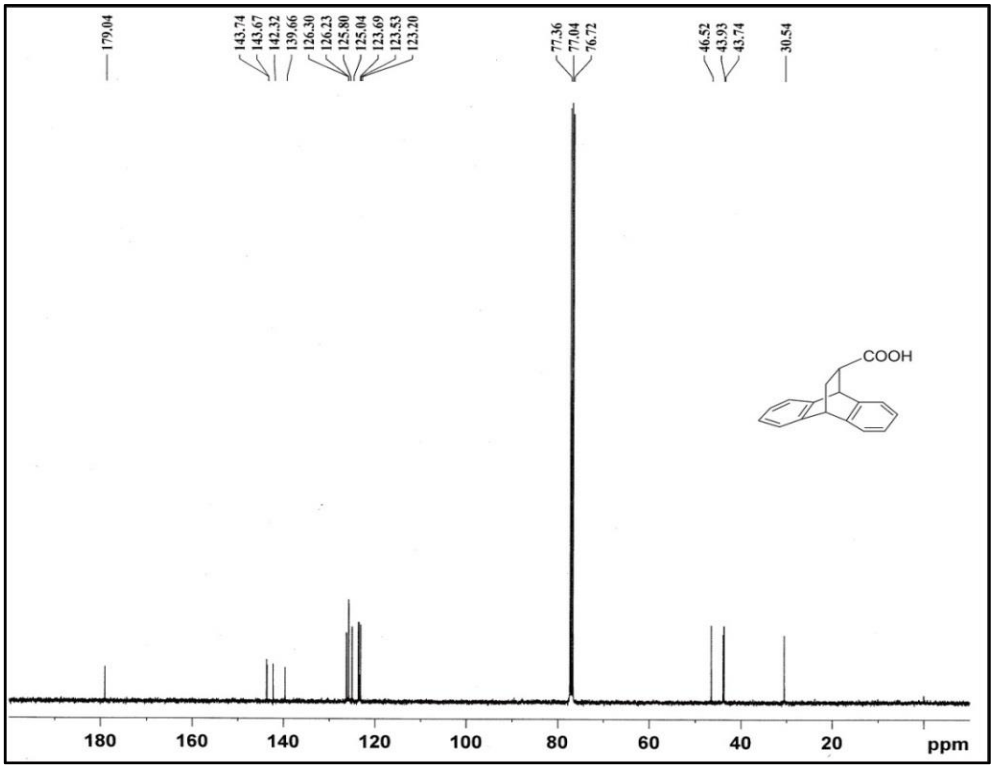
^{1}H NMR of compound 11

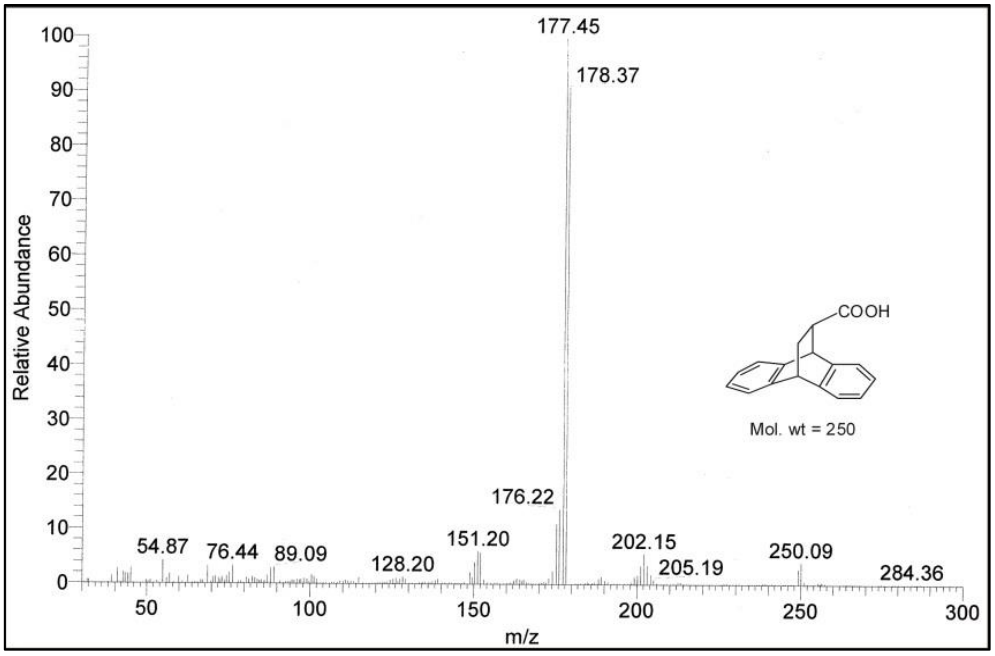


Mass spectra of compound 11

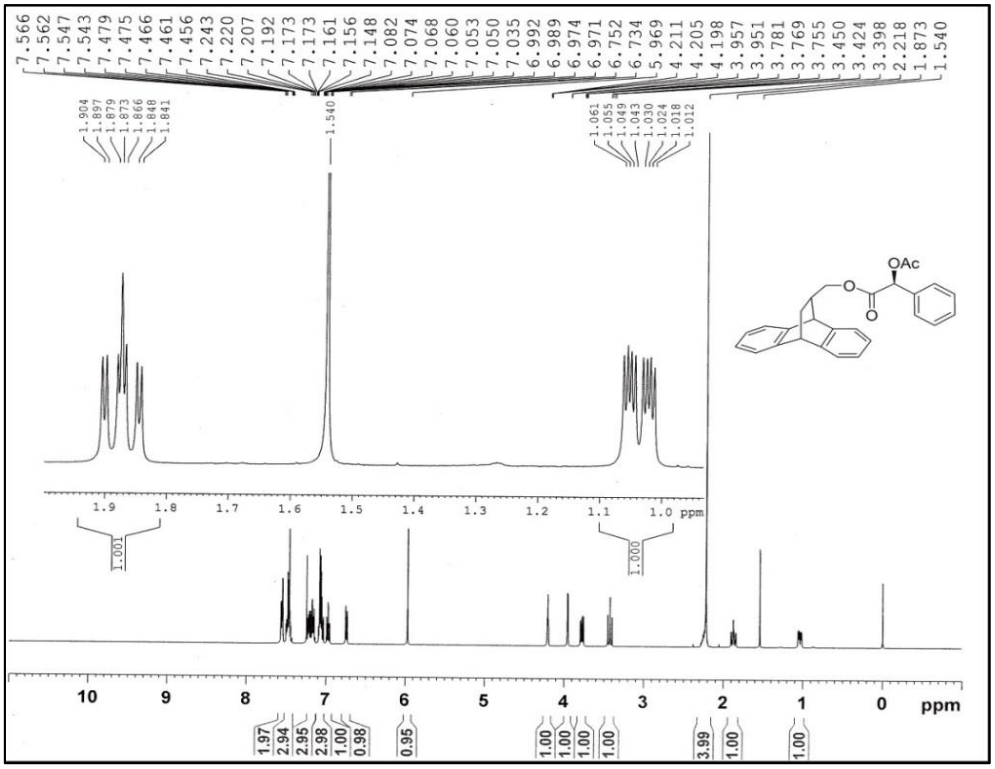


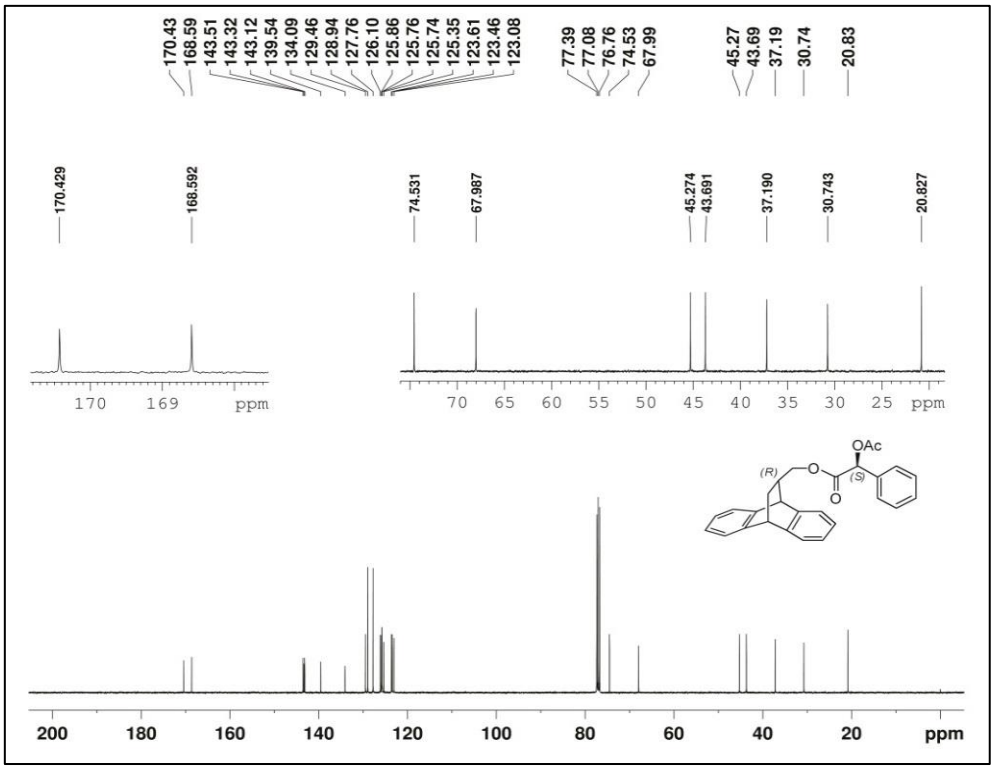
^{1}H NMR Spectra of compound 12



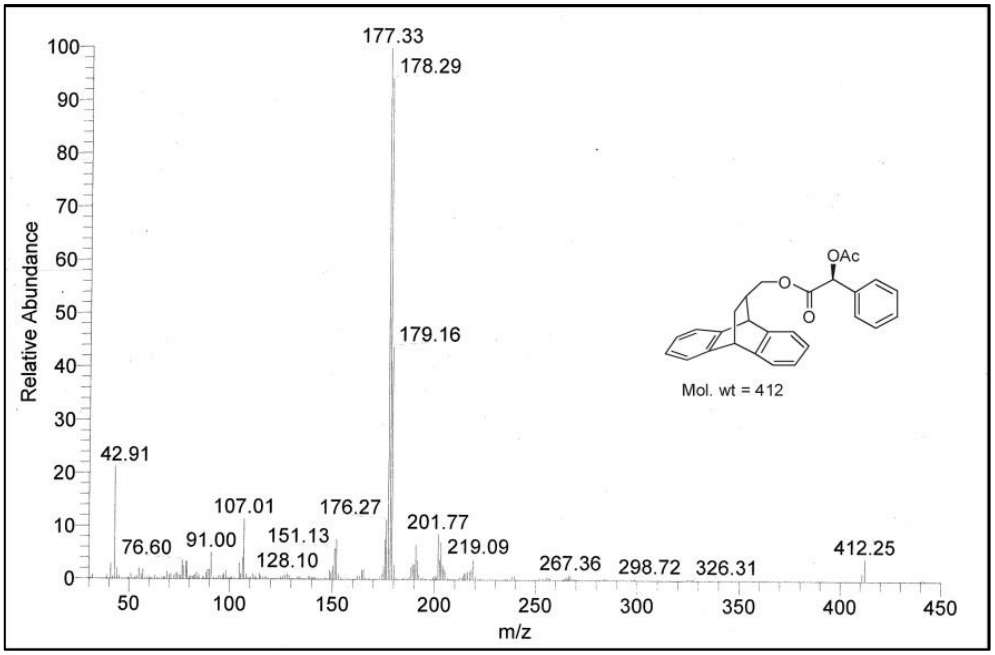


^{13}C NMR & Mass spectra of compound 12

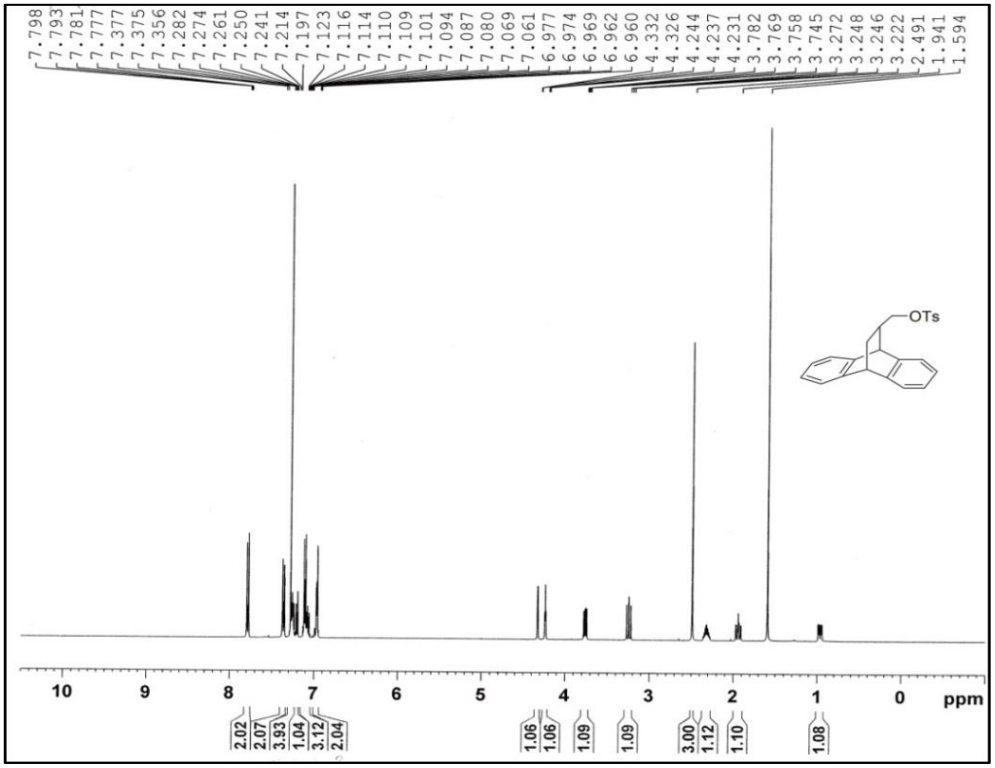




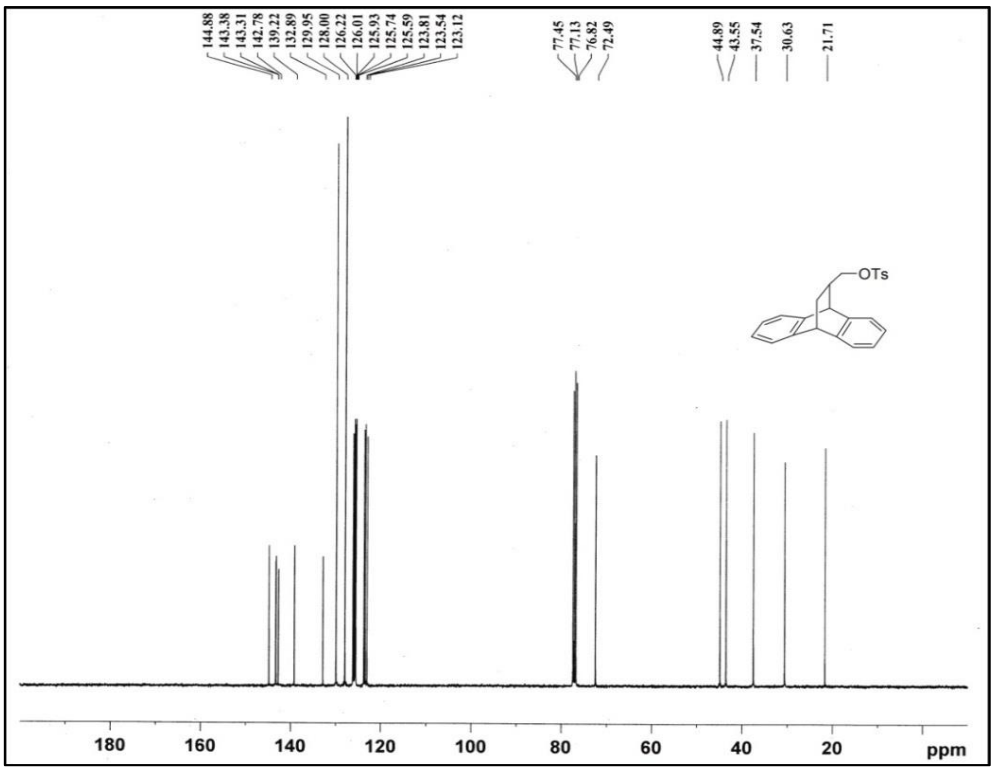
^{1}H NMR & ^{13}C NMR Spectra of compound 10

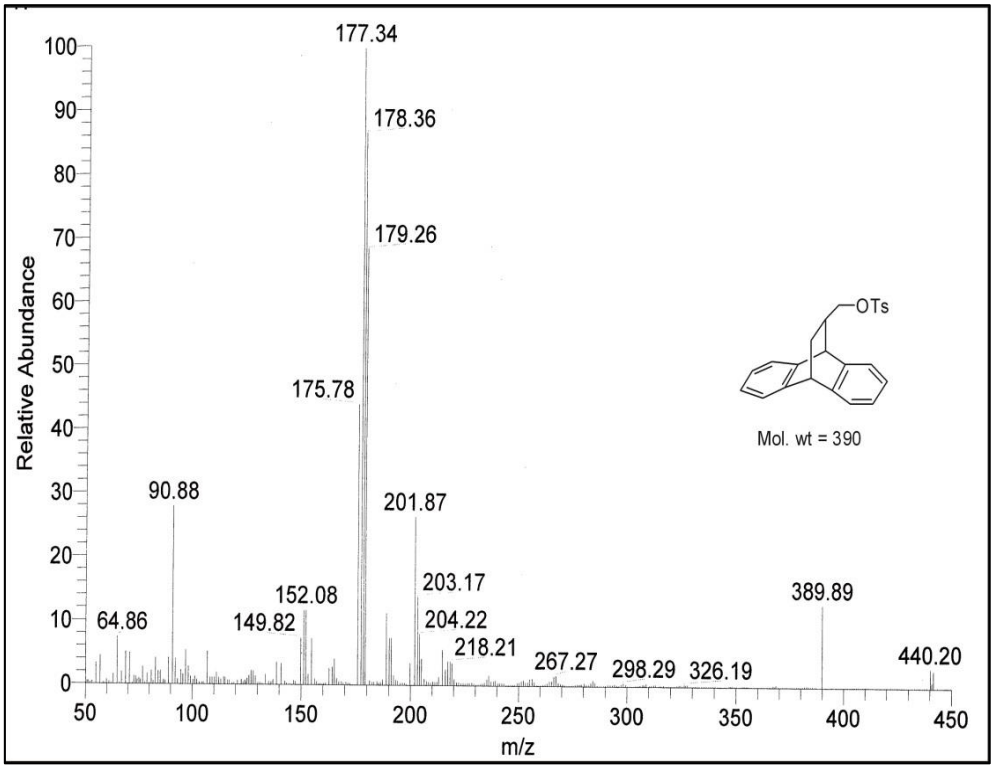


Mass spectra of compound 10

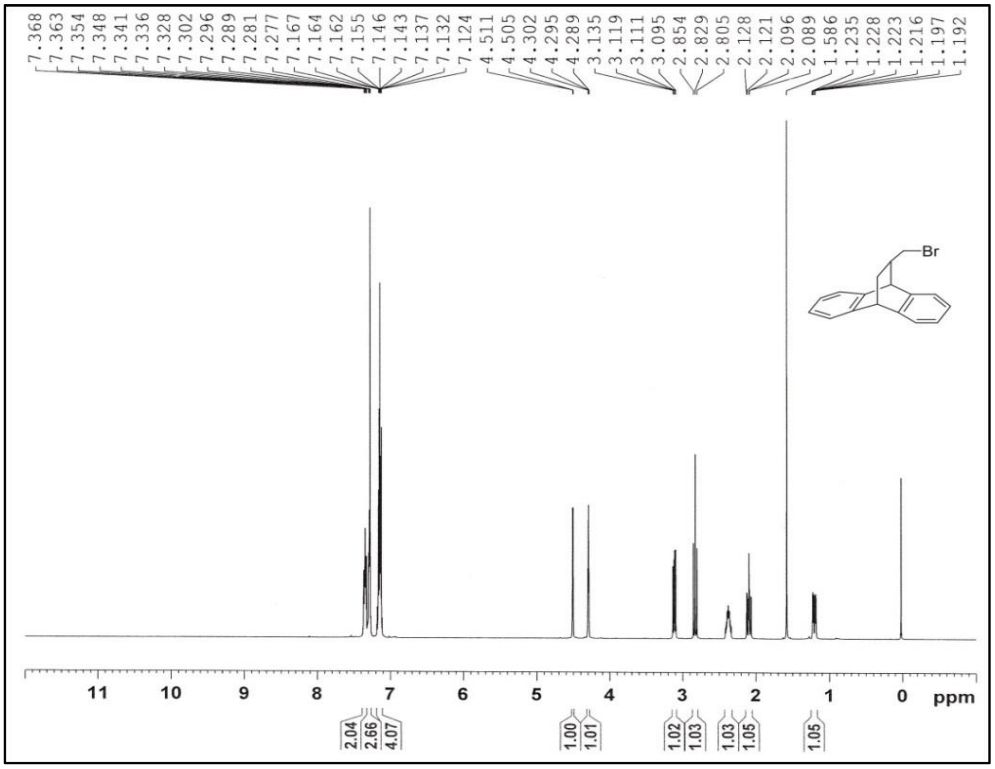


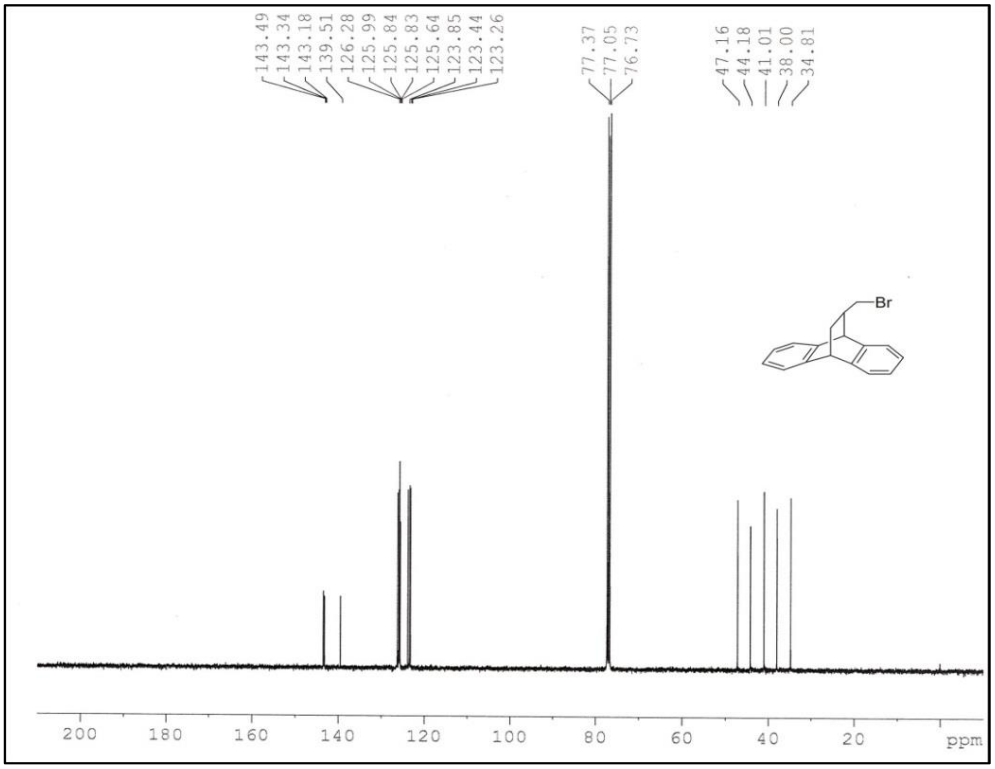
^{1}H NMR Spectra of compound 13



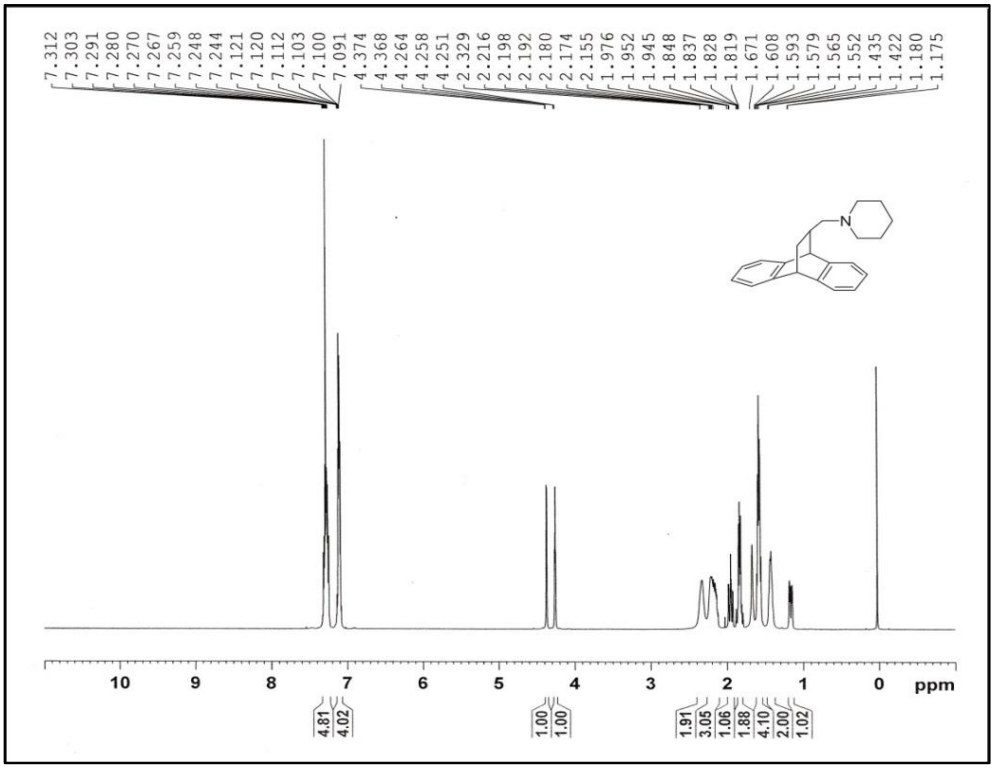


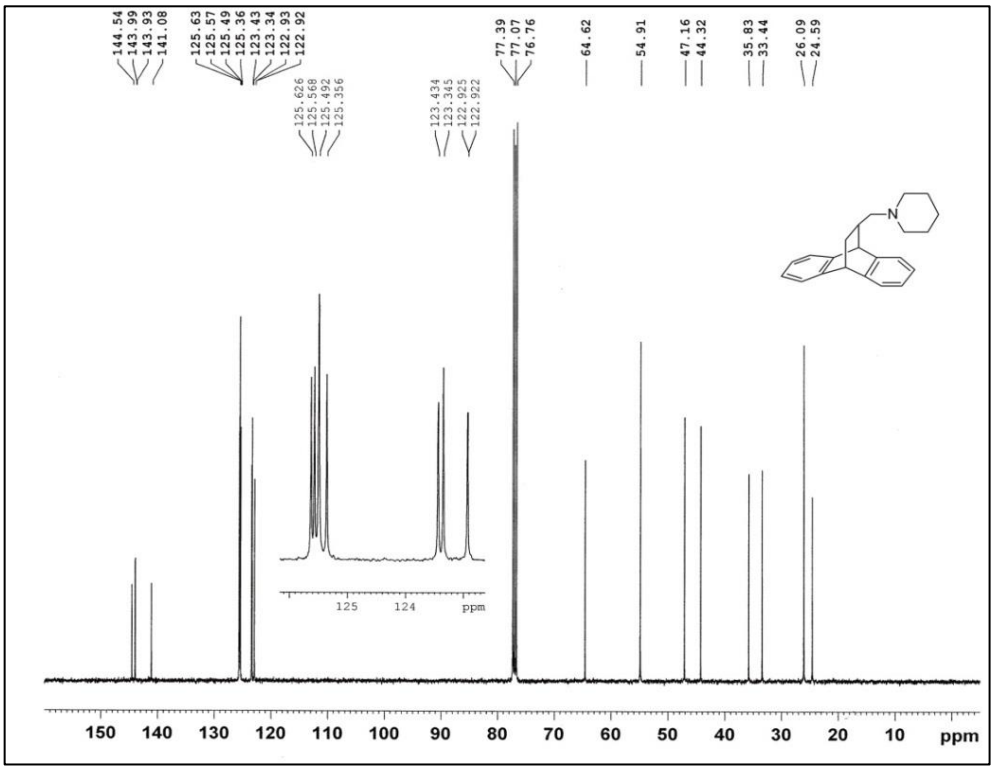
^{13}C NMR spectra Mass spectra of compound 13



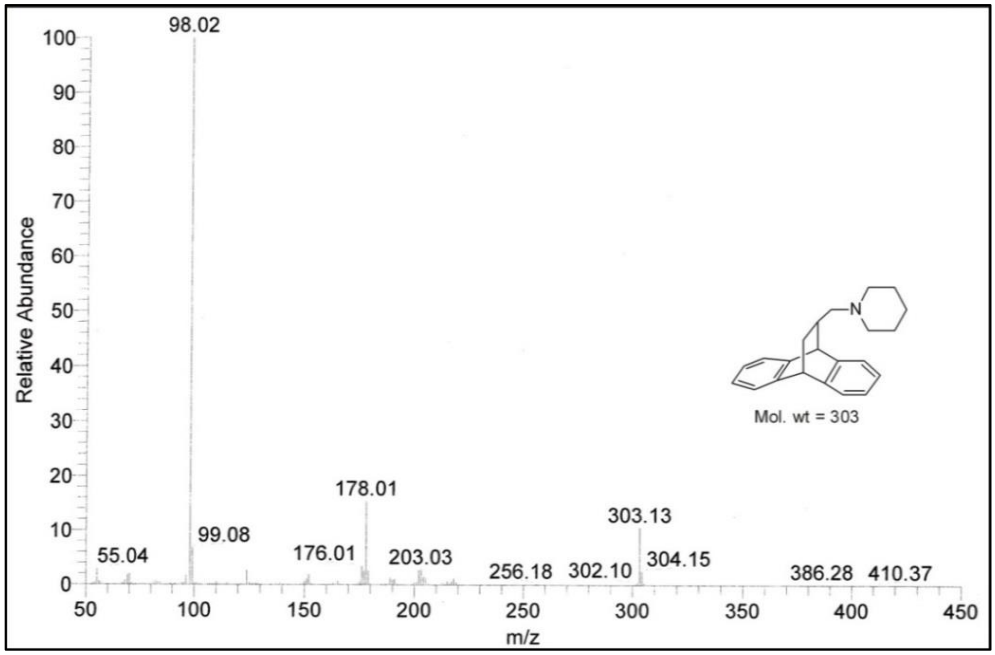


^{1}H NMR & ^{13}C NMR Spectra of compund 14

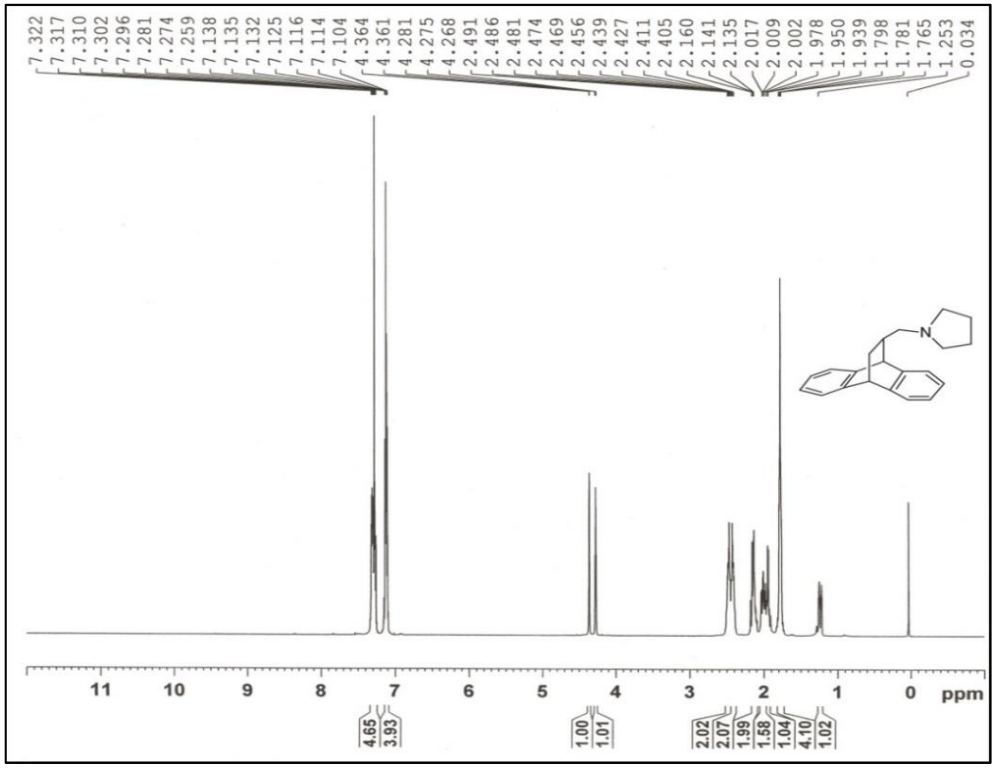




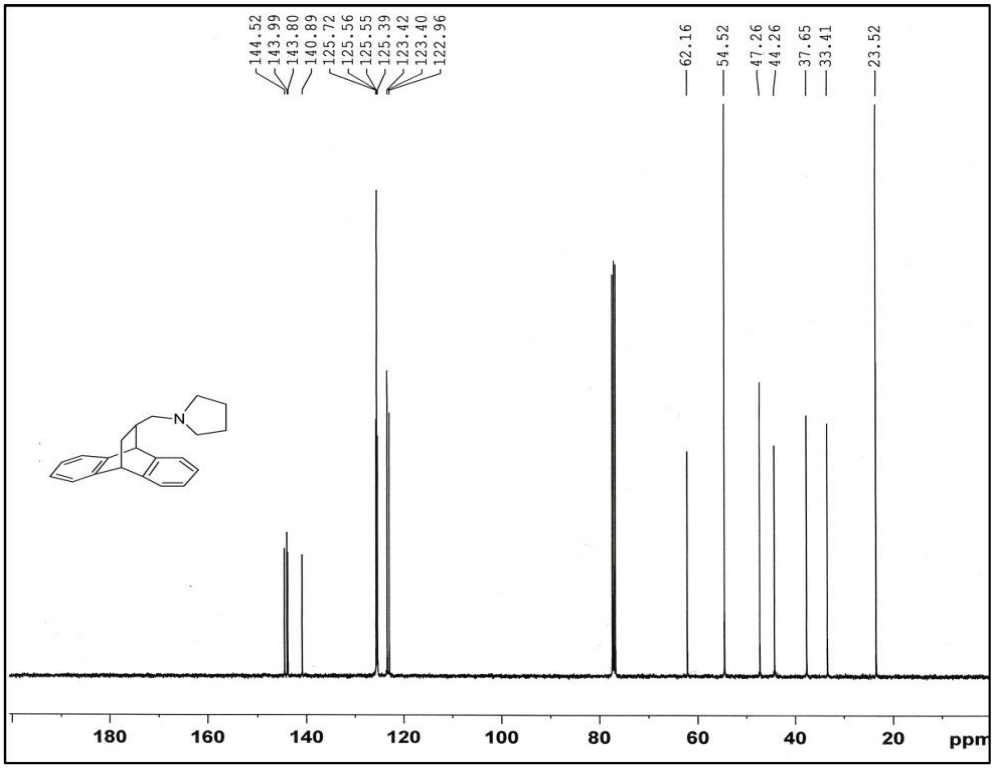
^{1}H NMR & ^{13}C NMR Spectra of compund 15

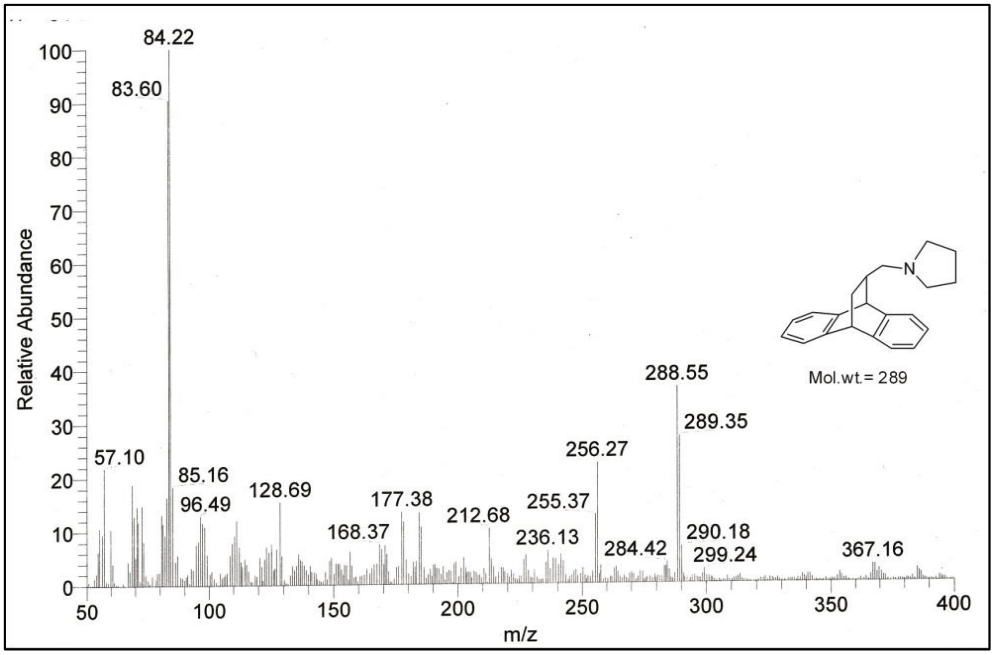


Mass spectra of compound 15

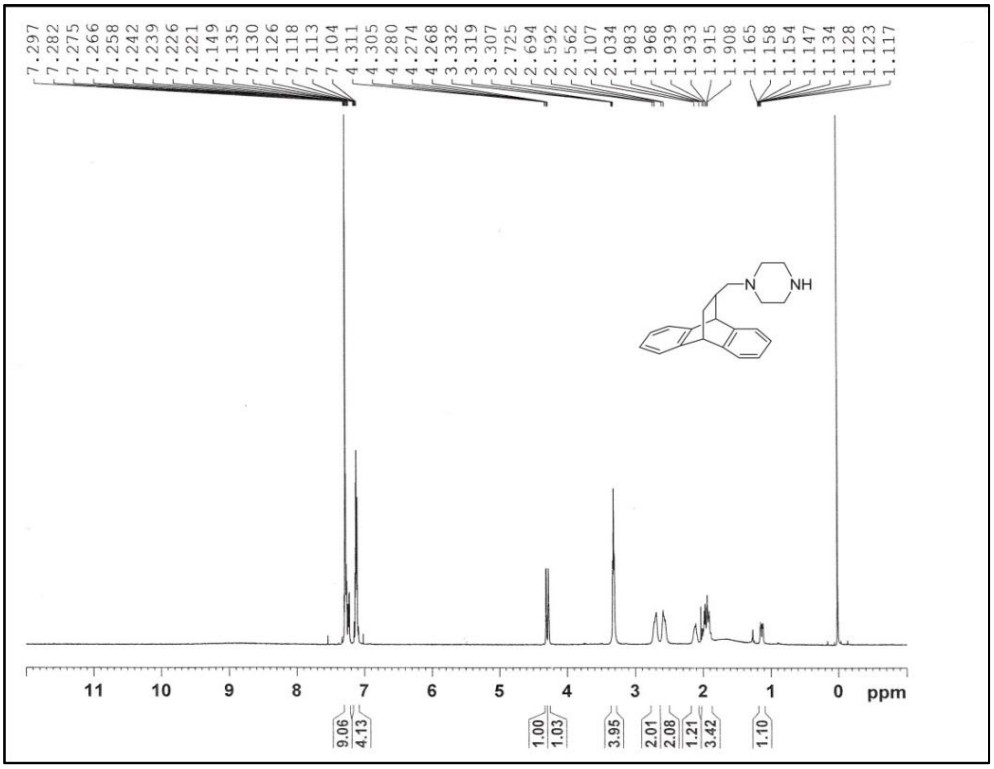


^{1}H NMR spectra of compound 16

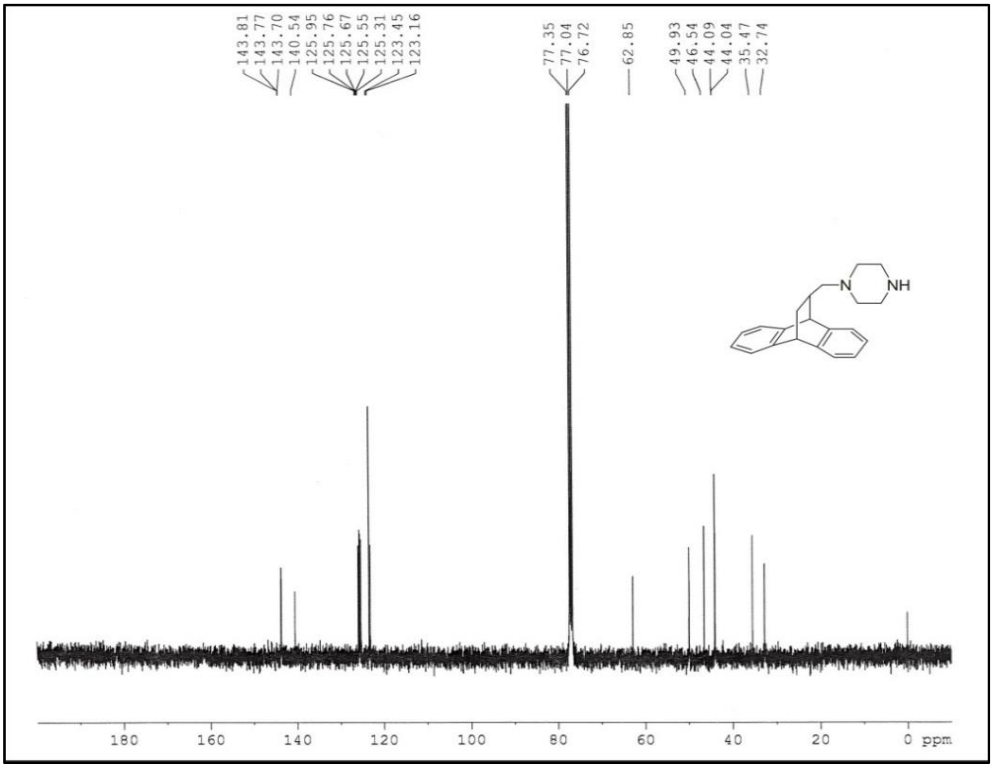




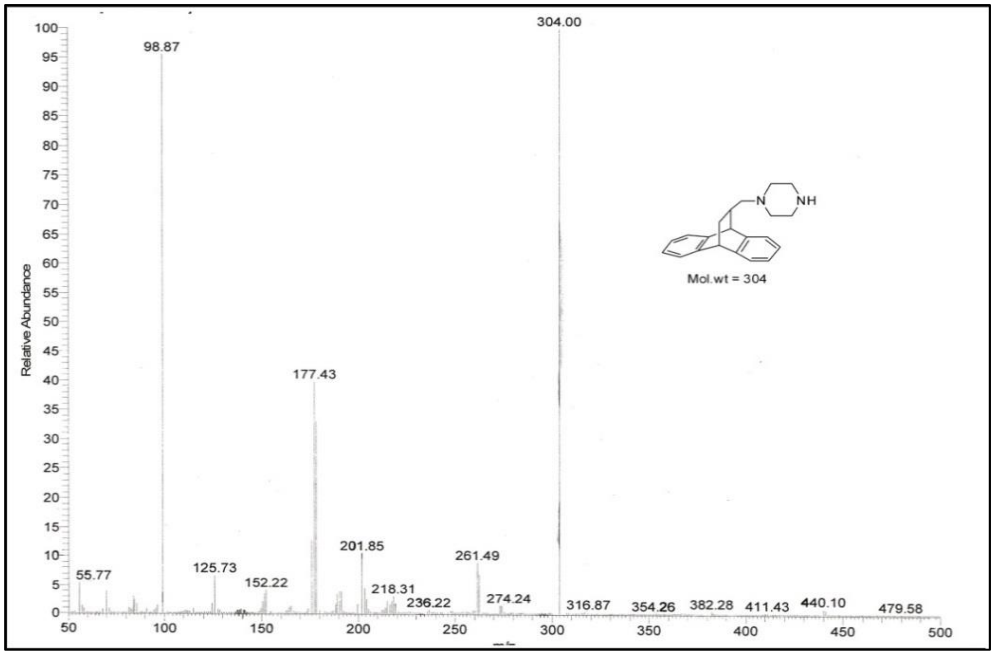
^{13}C NMR Spectra & Mass spectra of compound 16



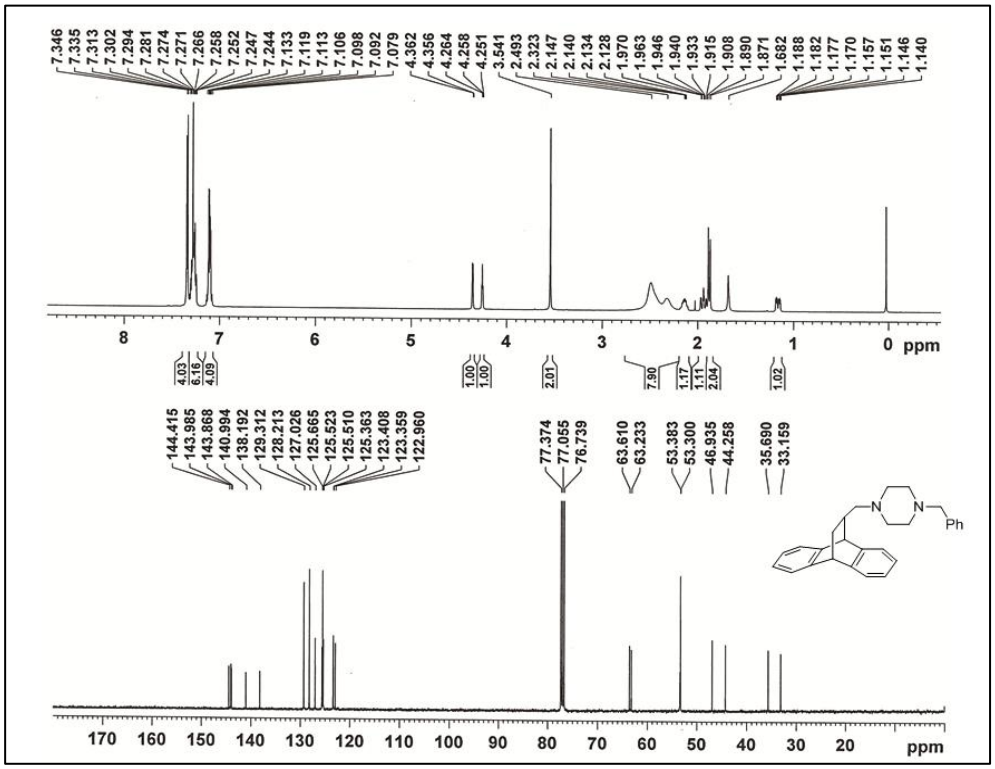
^{1}H NMR spectra of compound 17



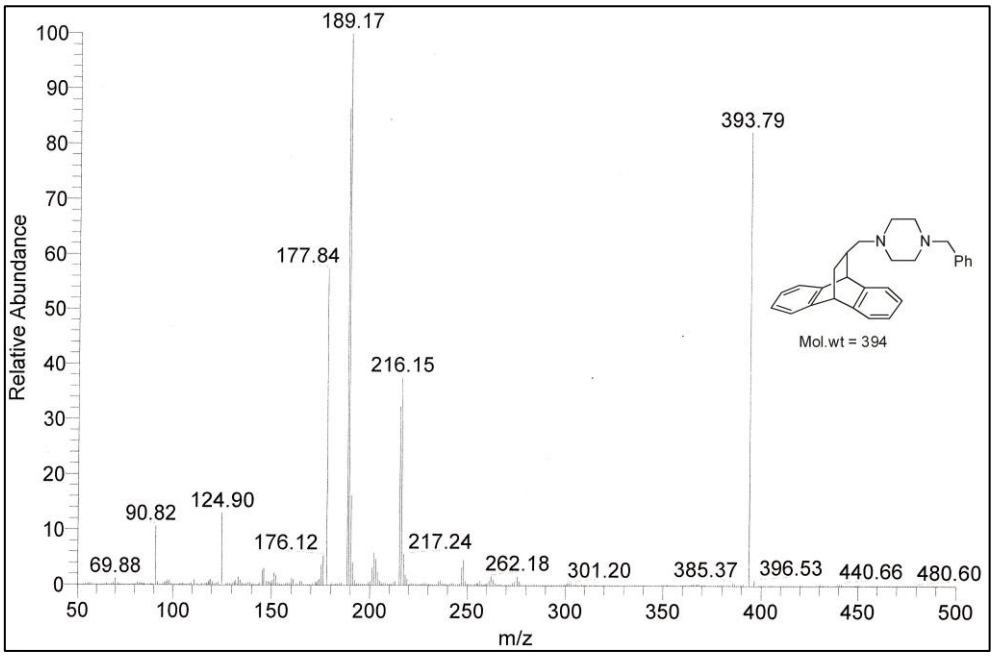
^{1}H NMR spectra of compound 17



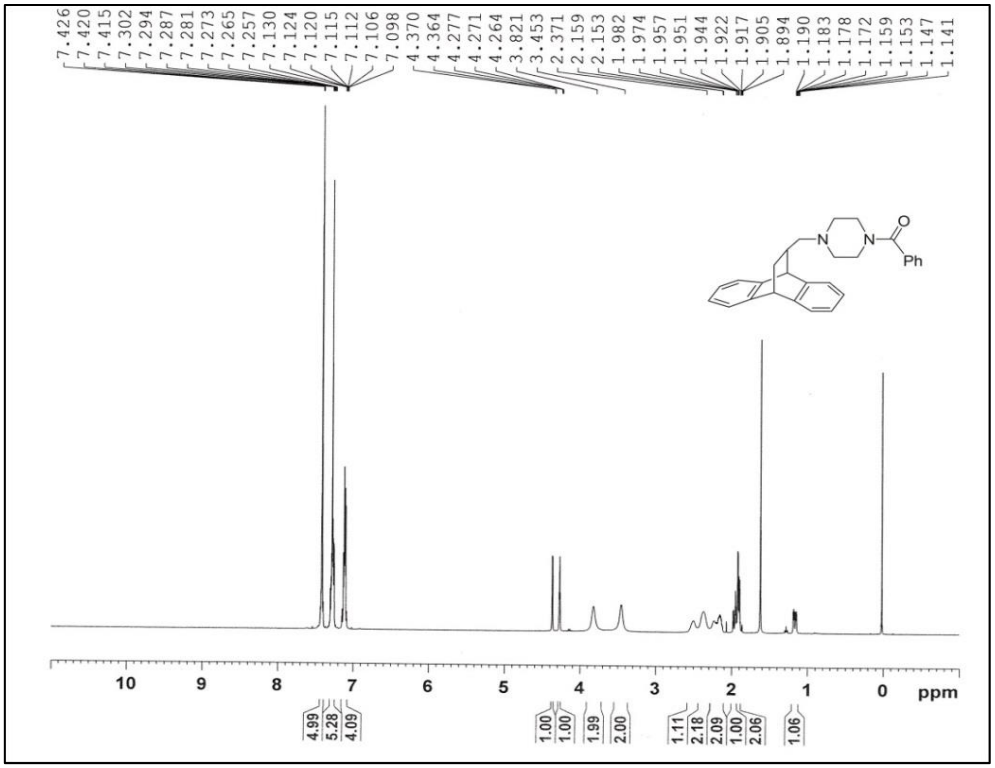
Mass spectra of compound 17



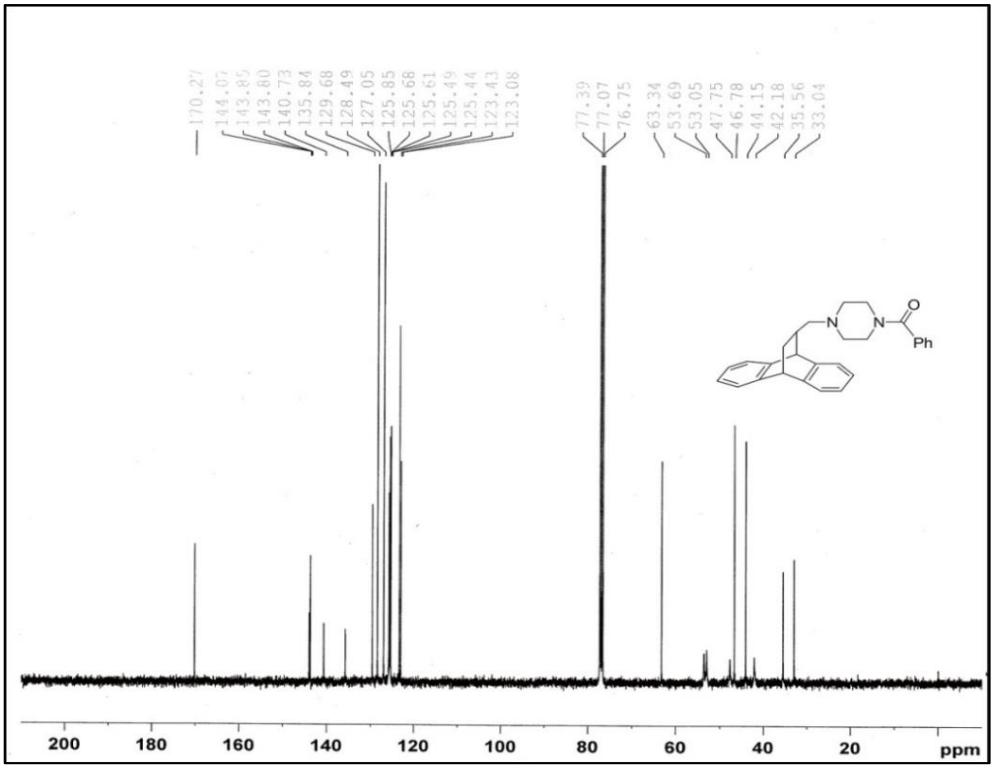
^{1}H NMR & ^{13}C NMR spectra of compound 18

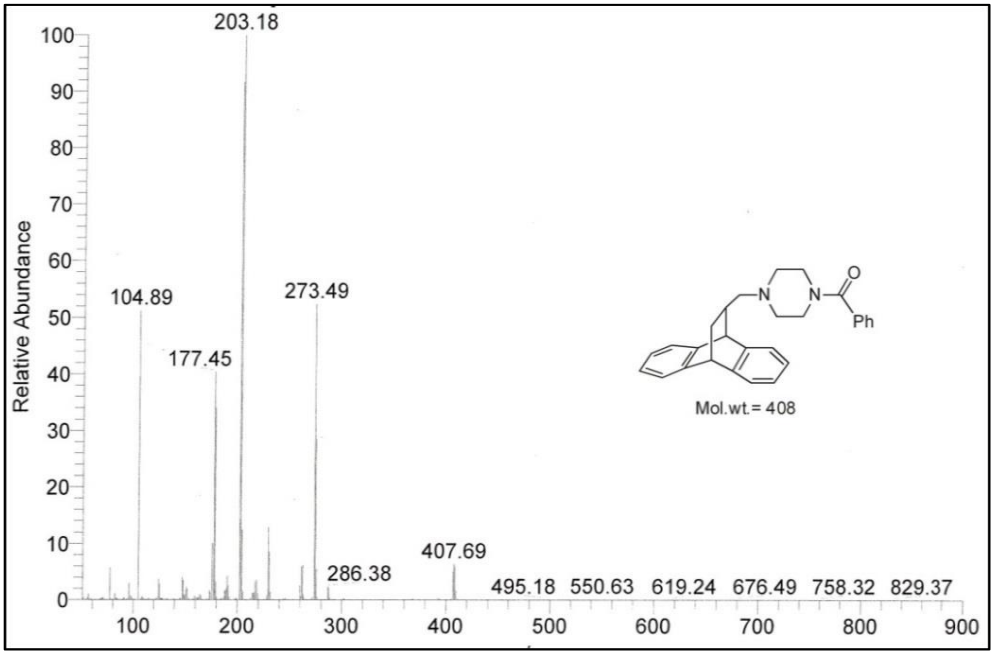


Mass spectra of compound 18

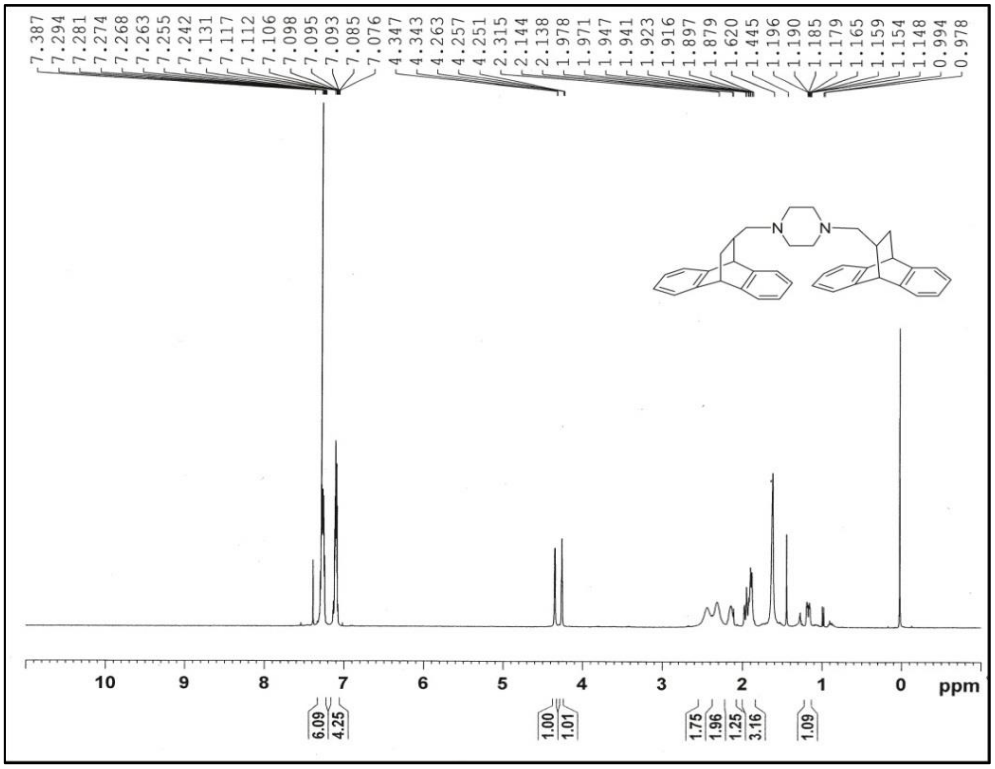


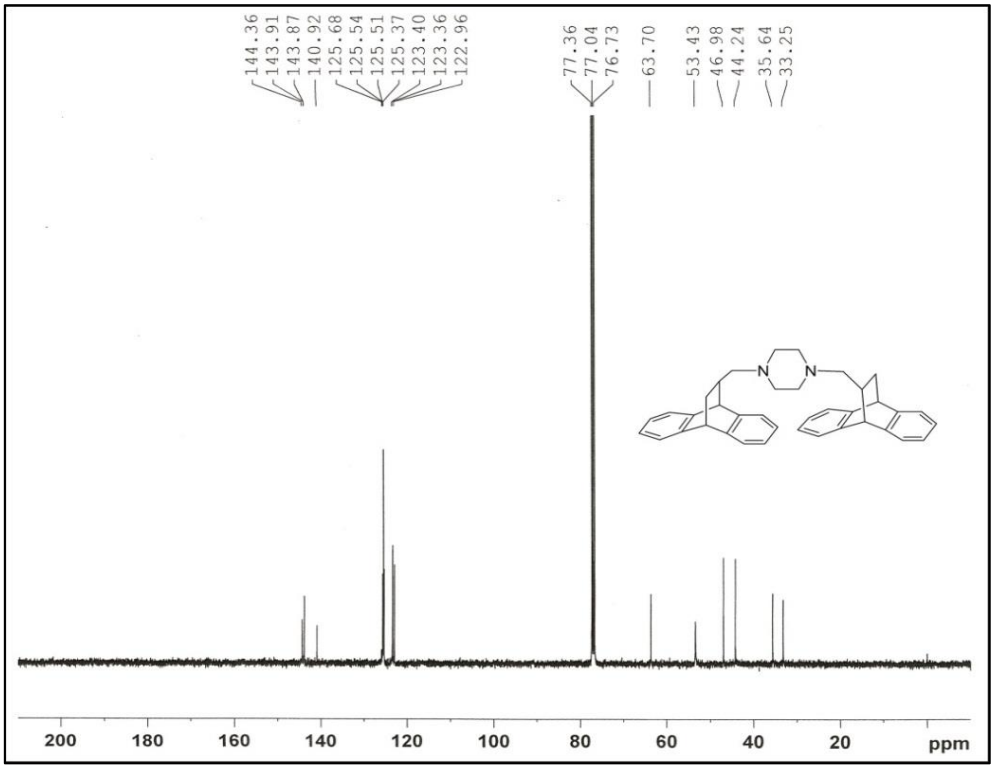
^{1}H NMR spectra of compound 19



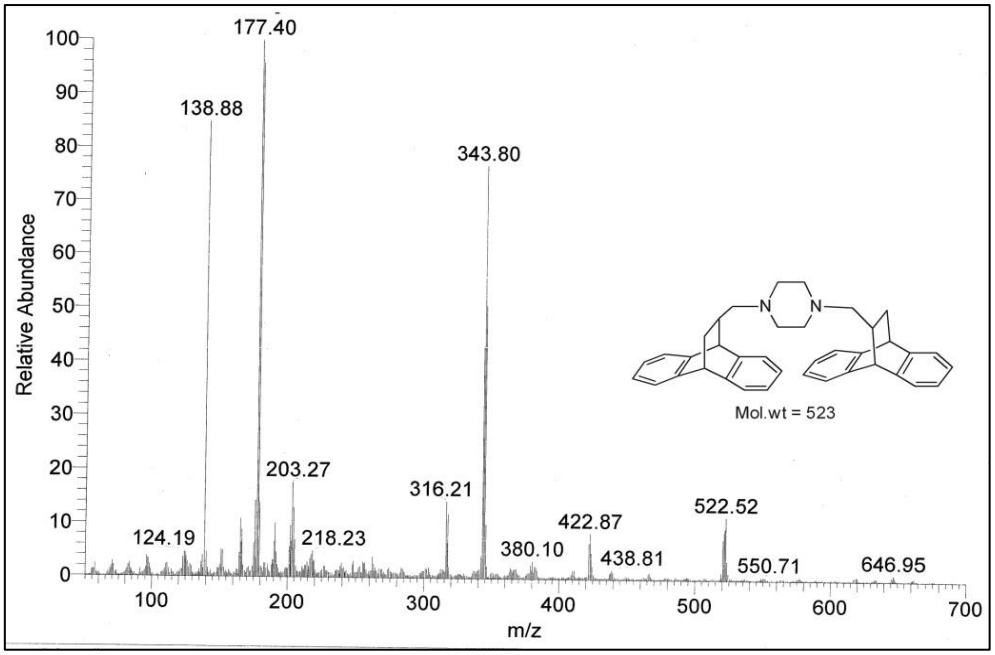


^{13}C NMR & Mass spectra of compound 19

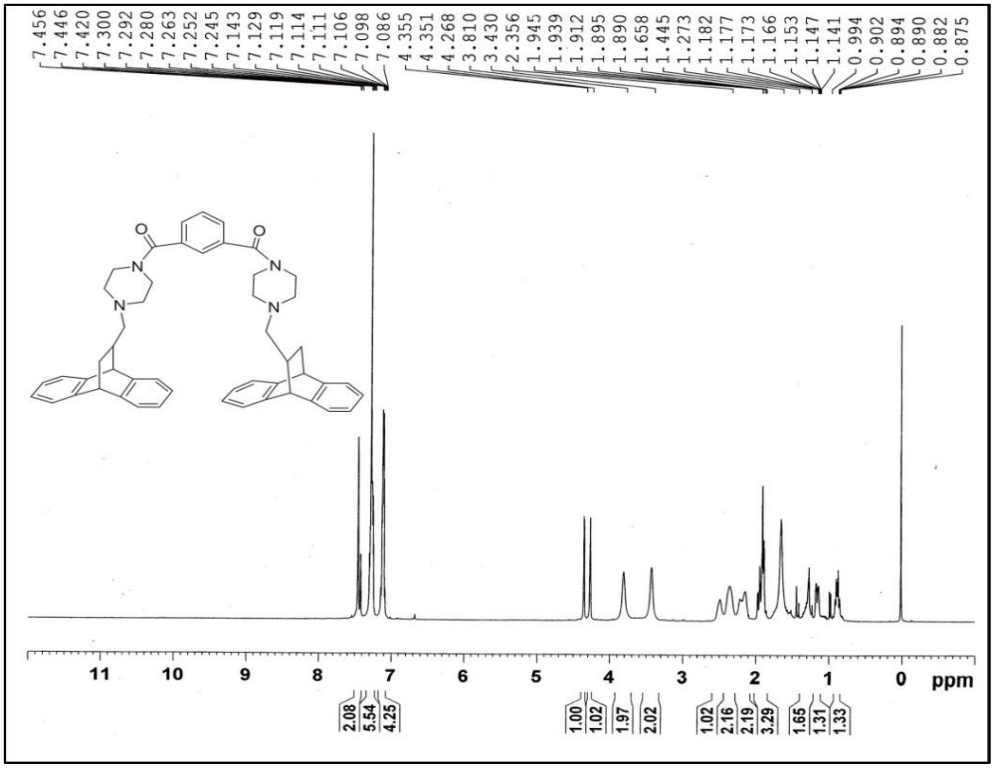




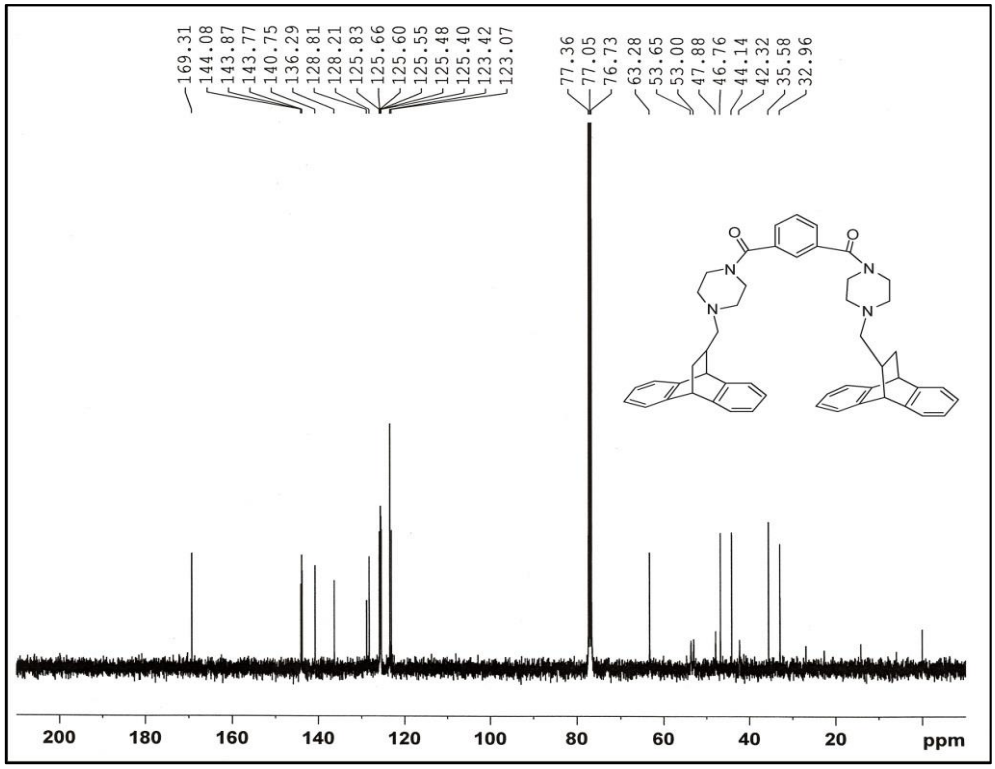
^{1}H NMR & ^{13}C NMR spectra of compound 20

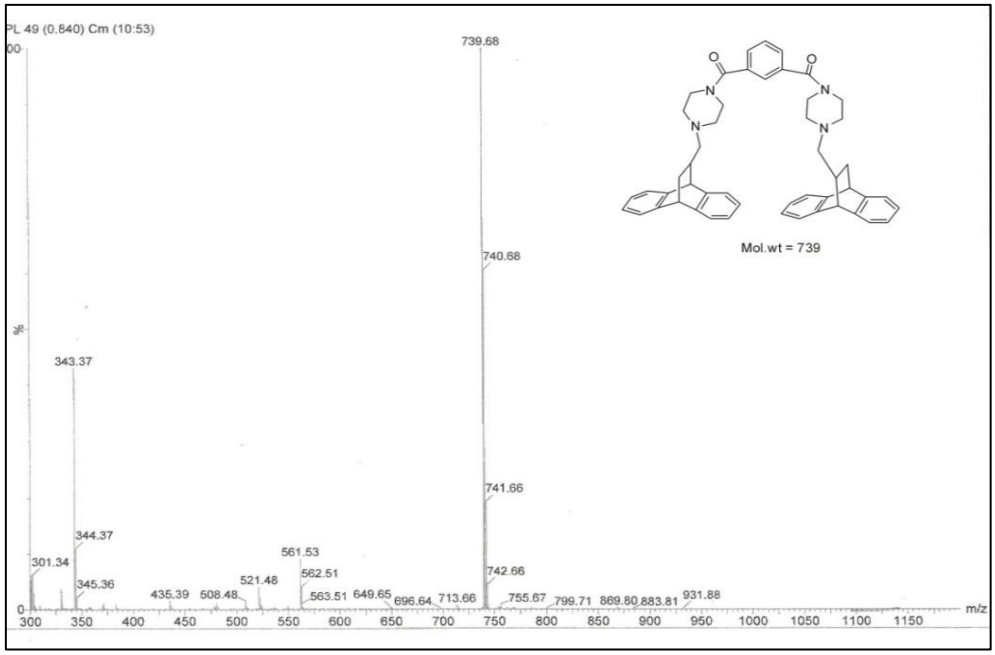


Mass spectra of compound 20

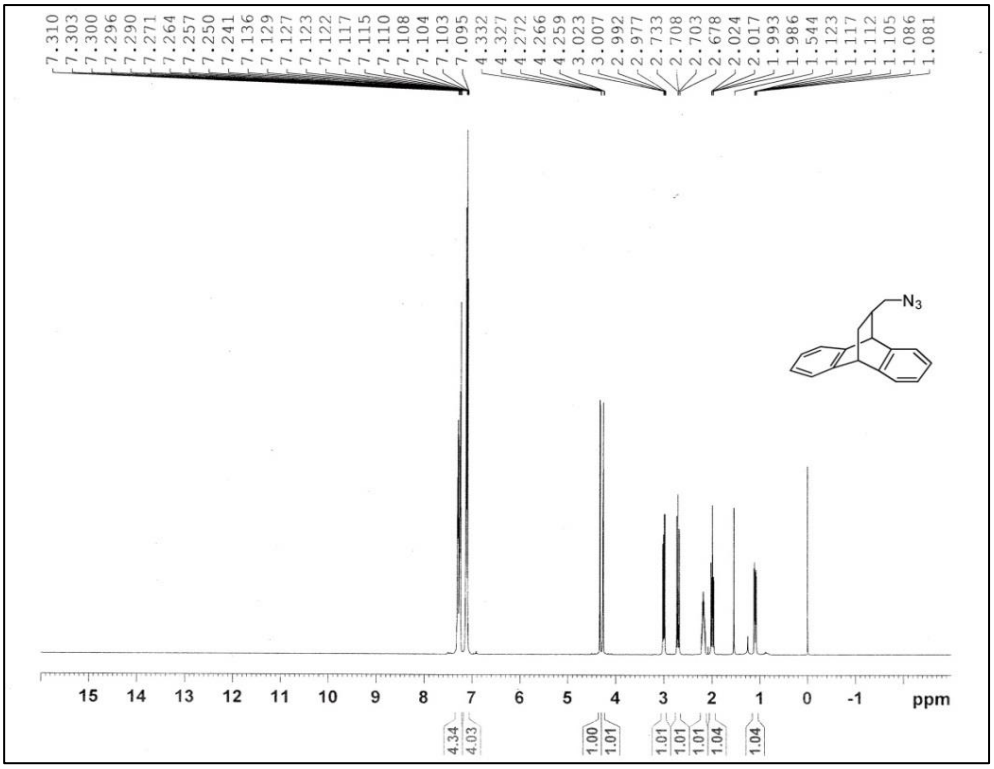


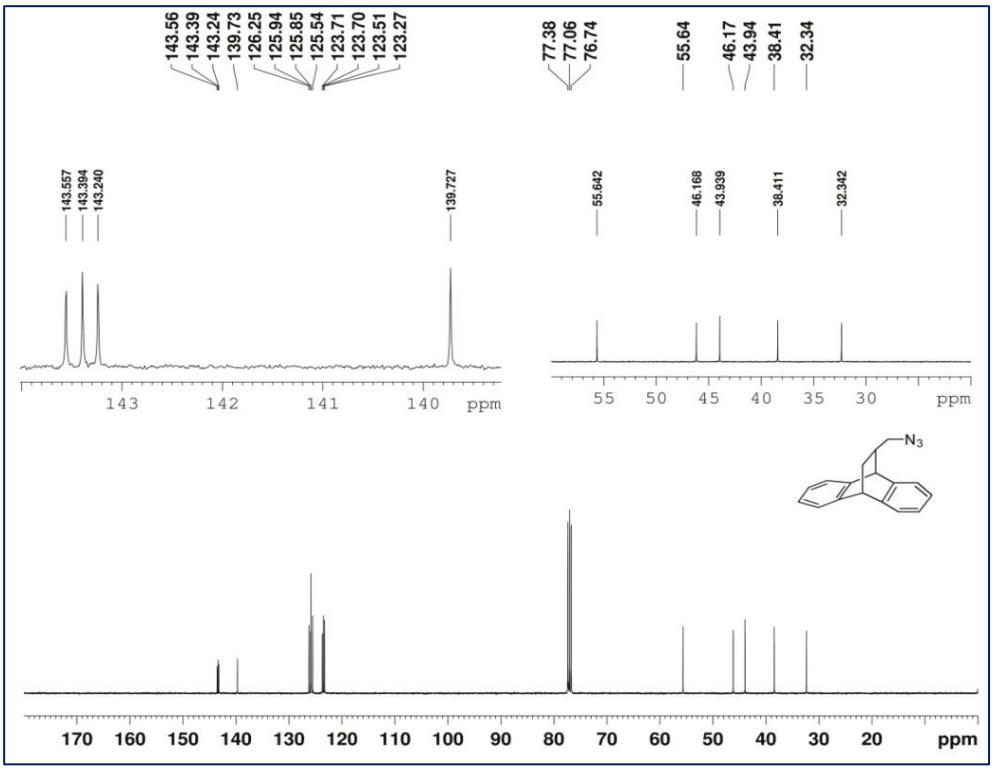
^{1}H NMR spectra of compound 21



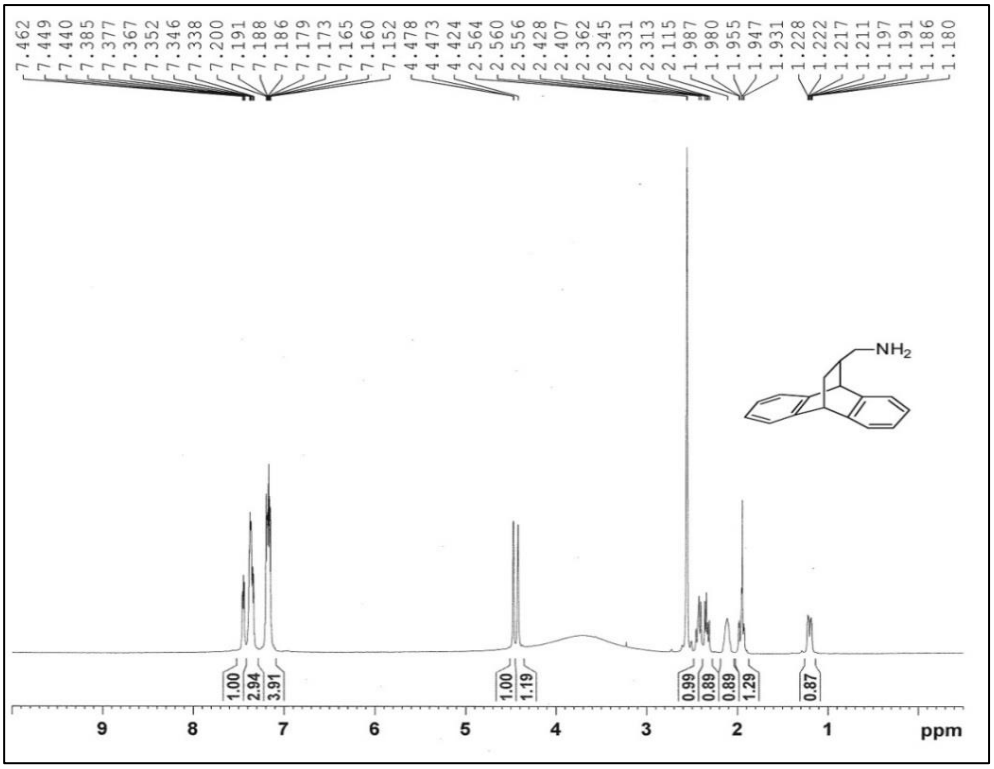


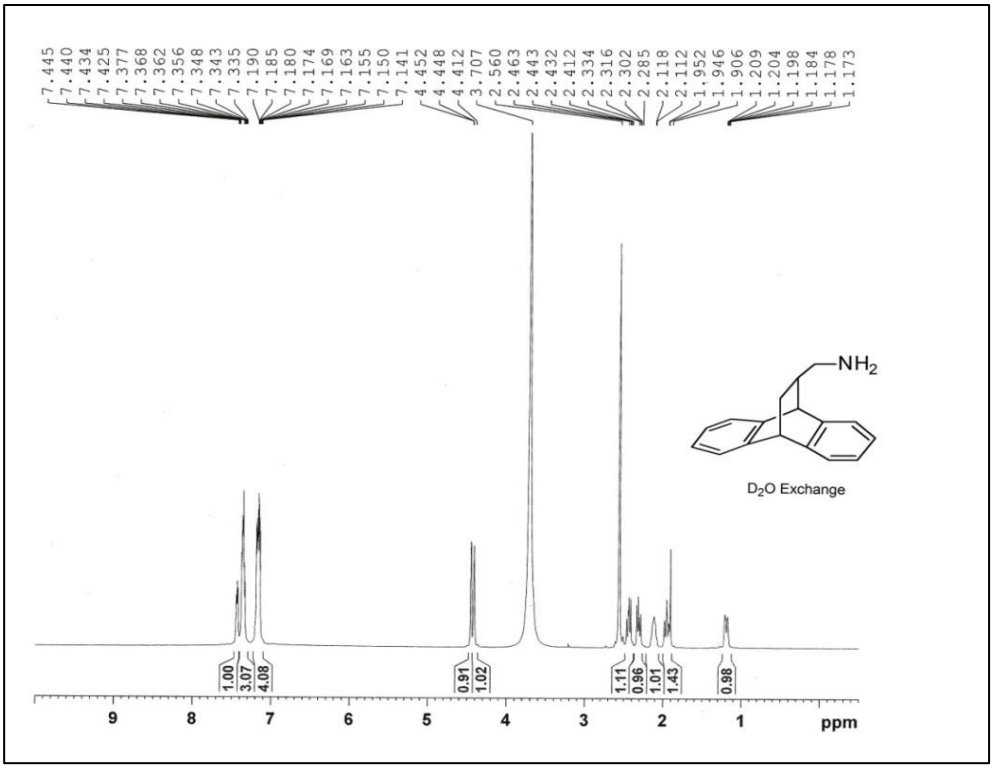
^{13}C NMR & Mass spectra of compound 21



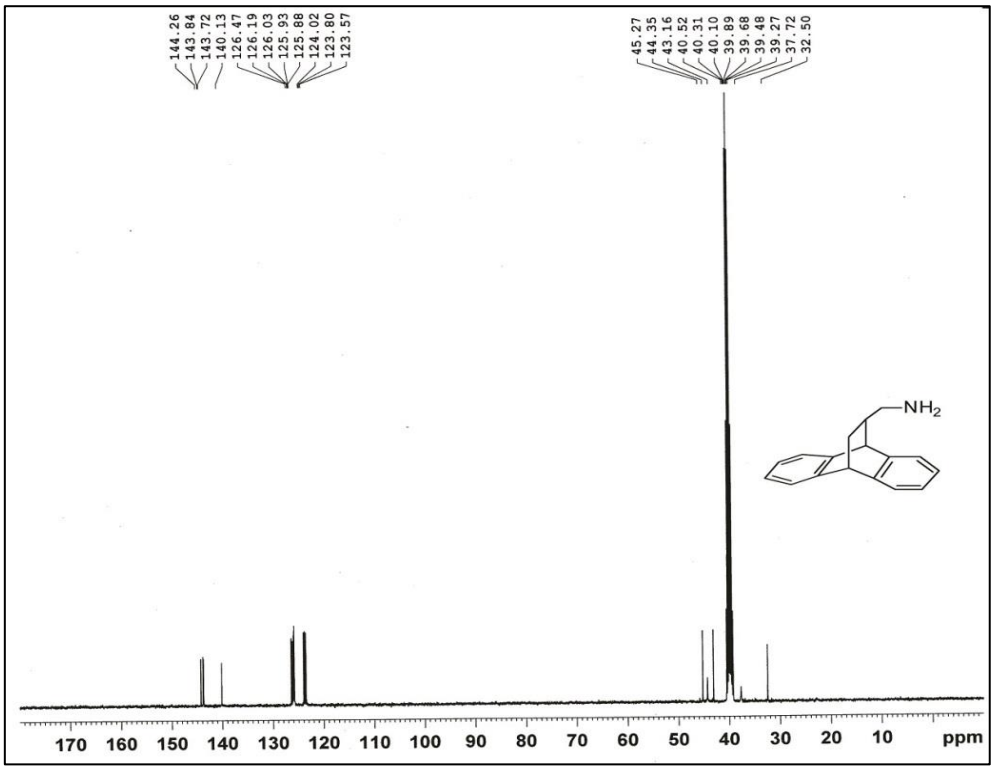


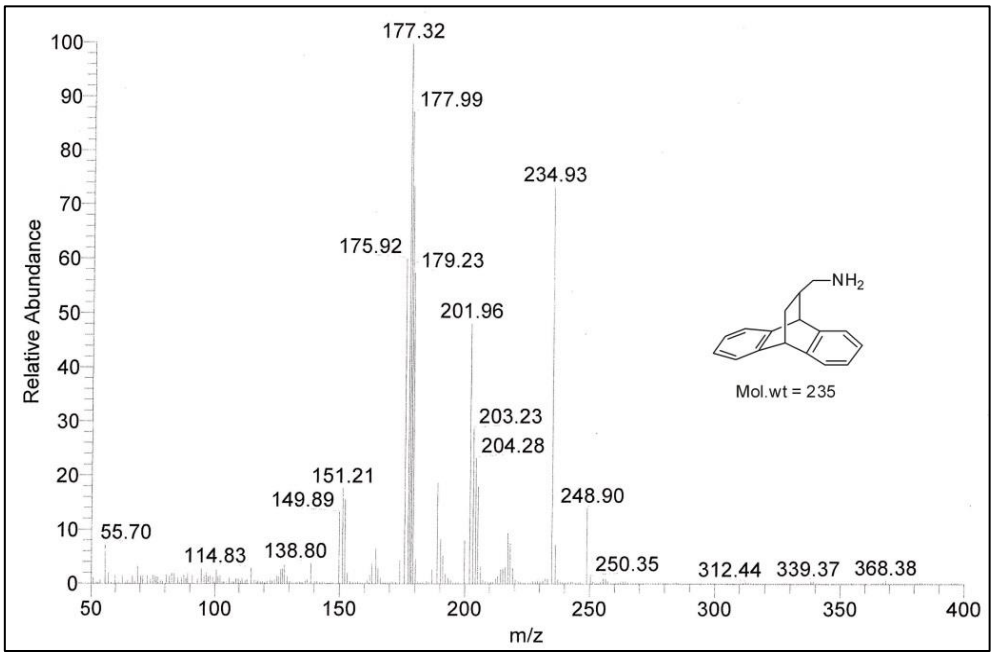
^{1}H NMR & ^{13}C NMR spectra of compound 22



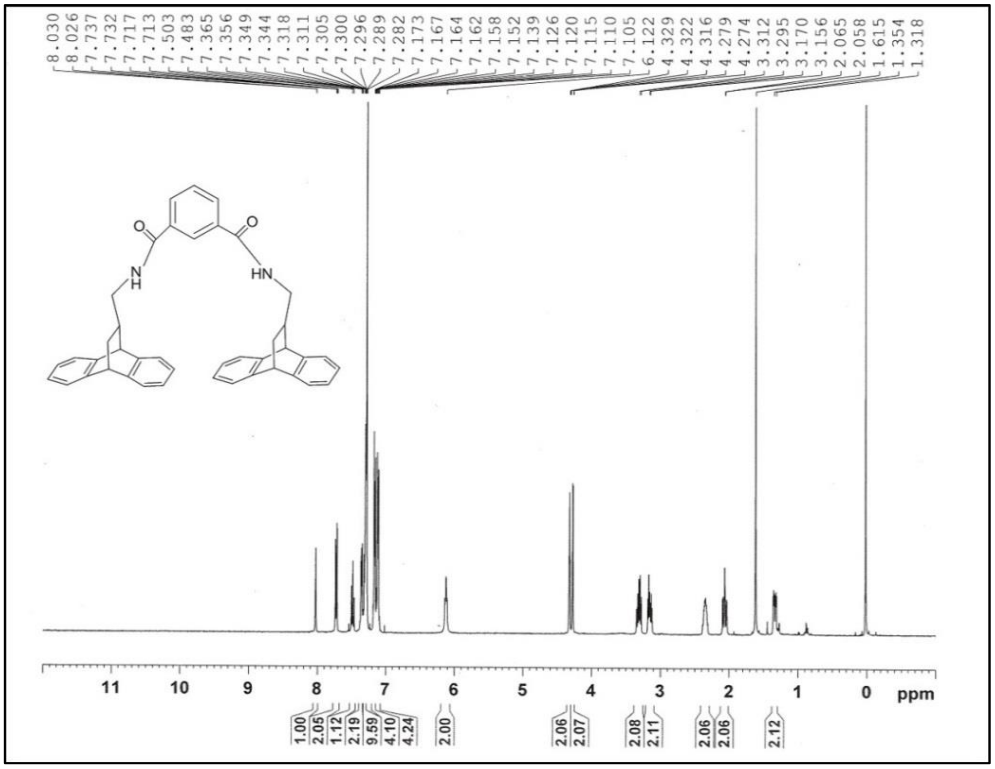


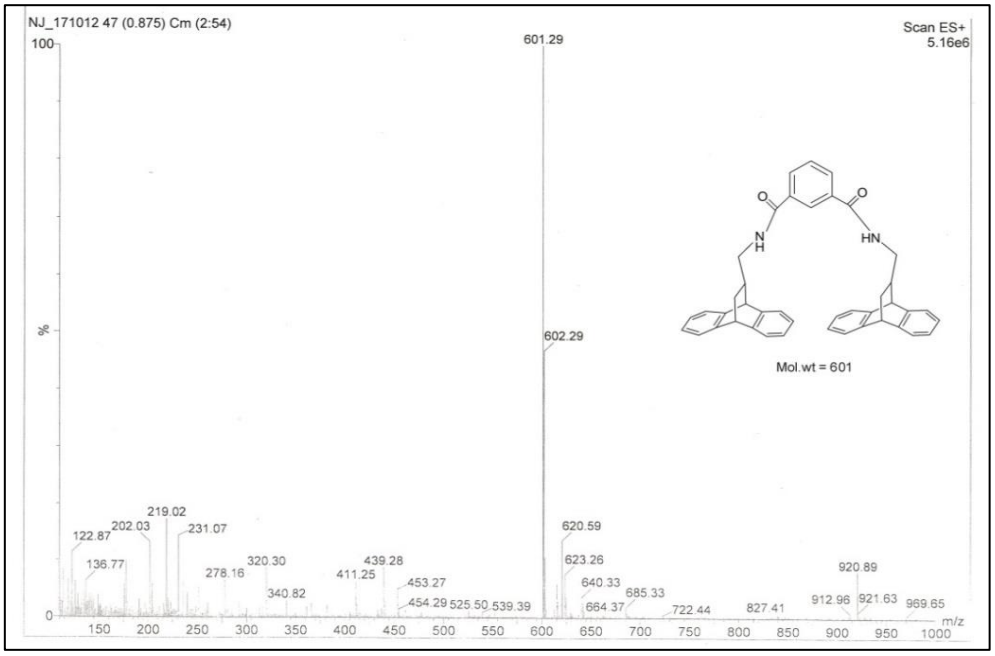
^{1}H NMR & D_2O exchange Spectra of compound 23





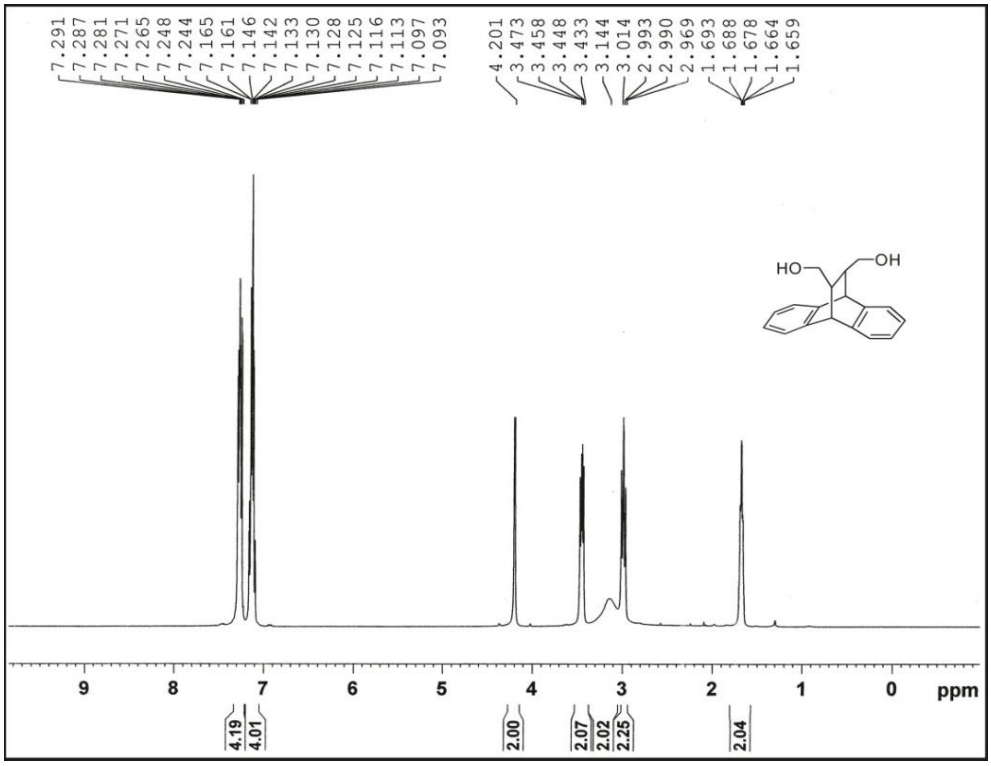
^{13}C NMR & Mass spectra of Compound 23

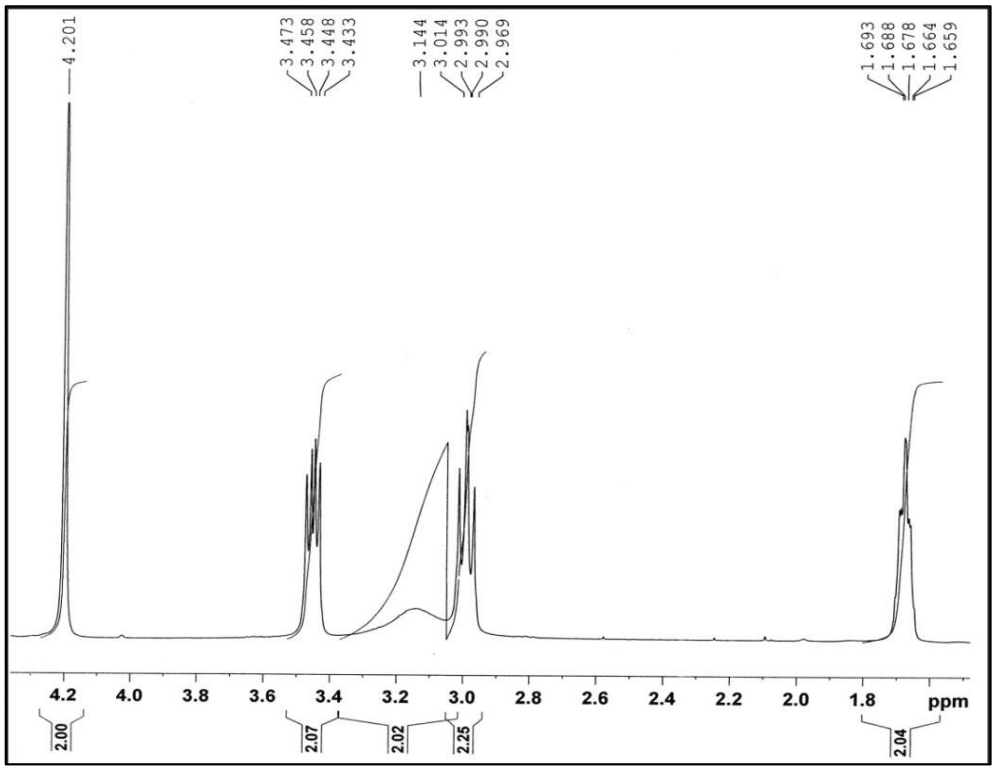




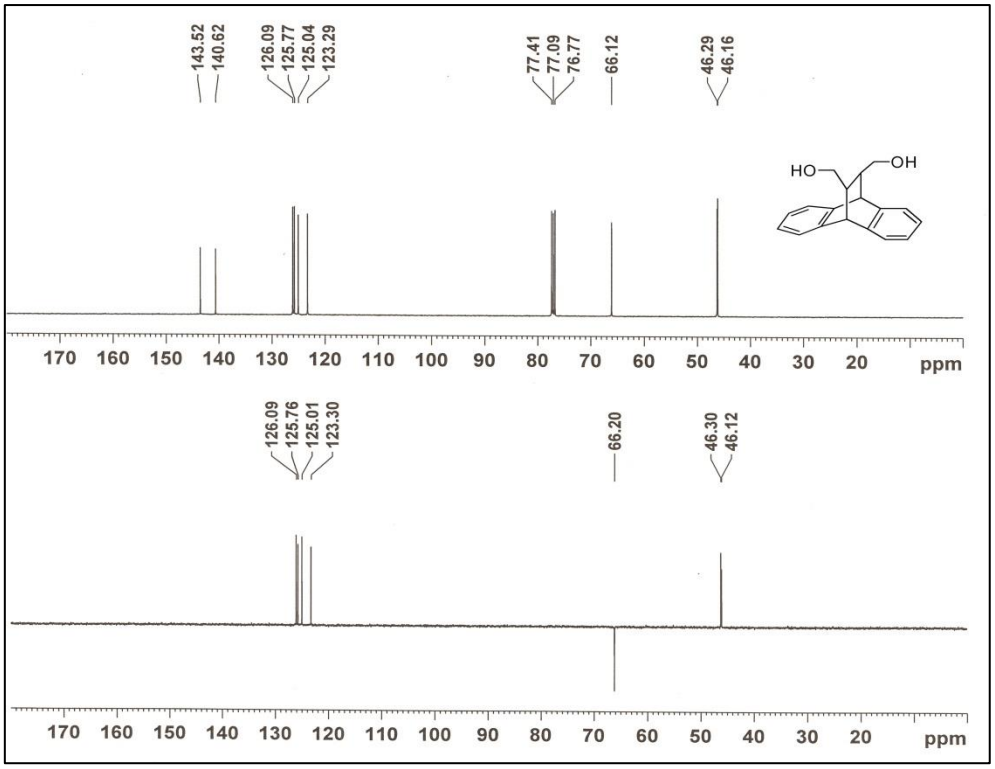
^{1}H NMR & Mass spectra of compound 24

Spectral chart of *trans*-roof shape molecules (Type C)

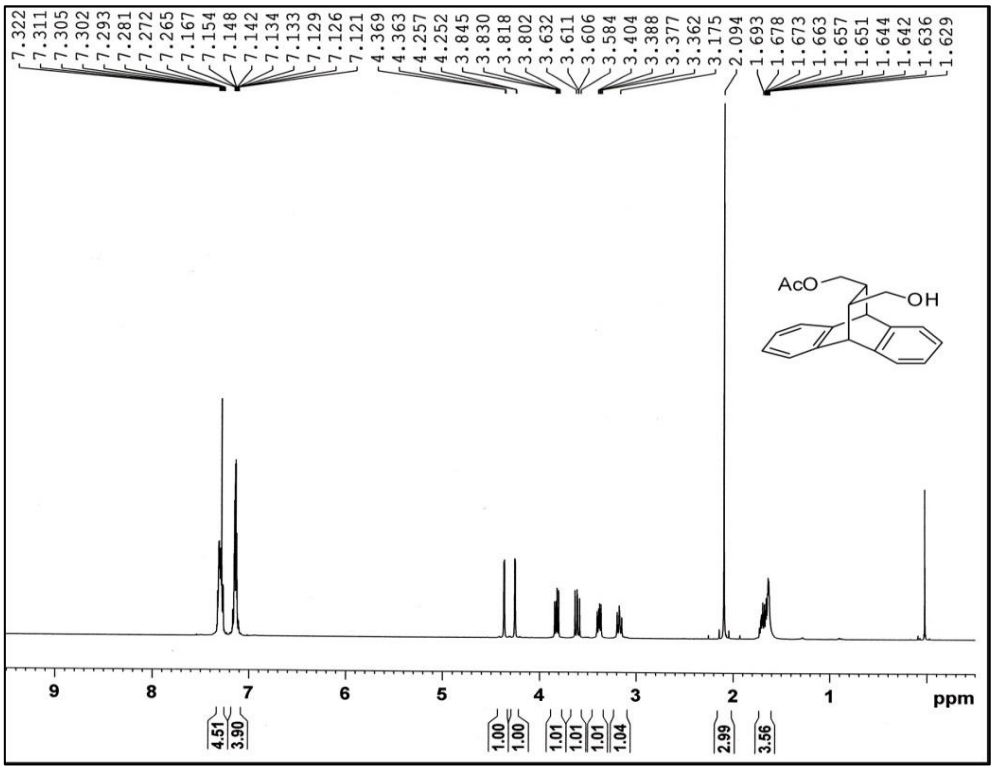




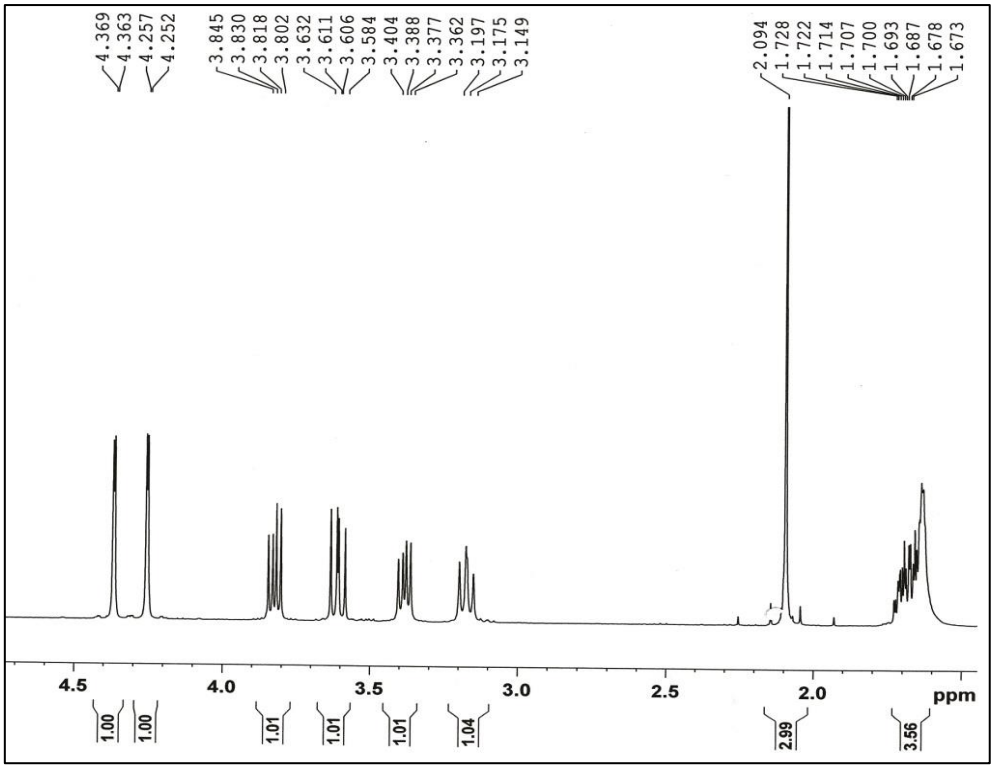
^{1}H NMR Spectra of compound 27 (Top = full spectra; Bottom = Enlarge spectra)



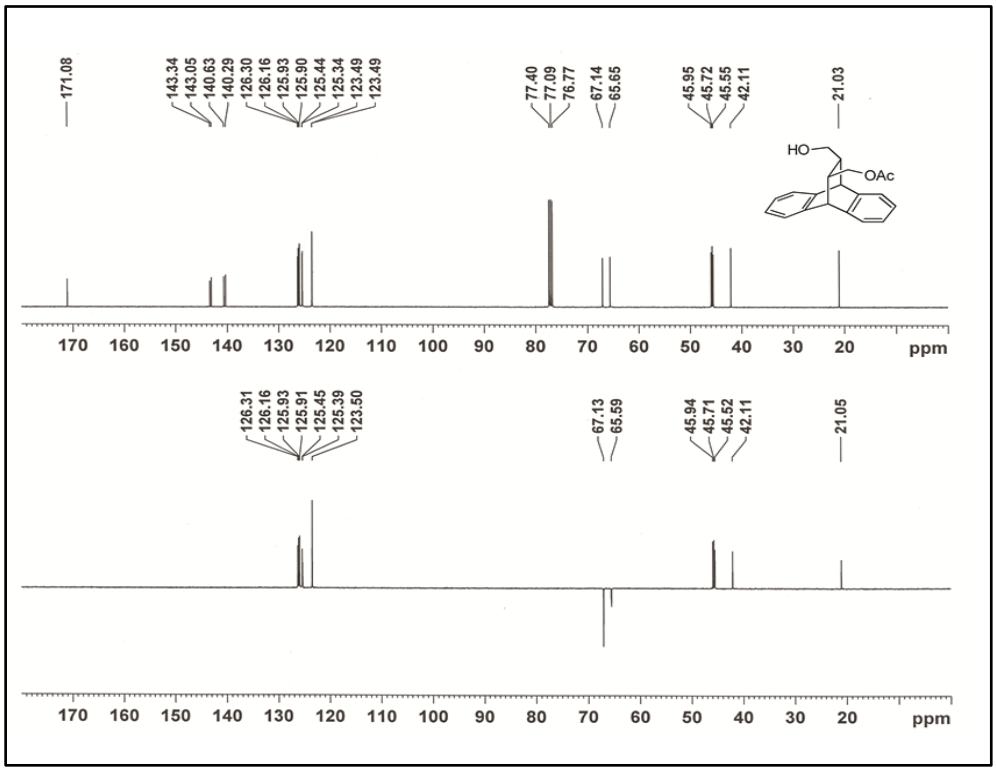
^{13}C NMR & DEPT spectra compound 28



^{1}H NMR Spectra of compound 28

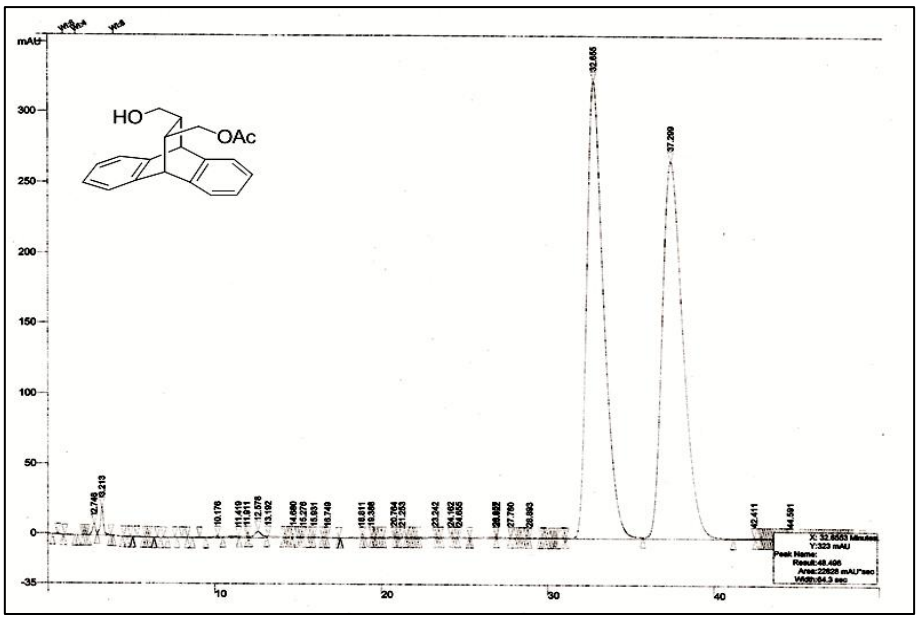


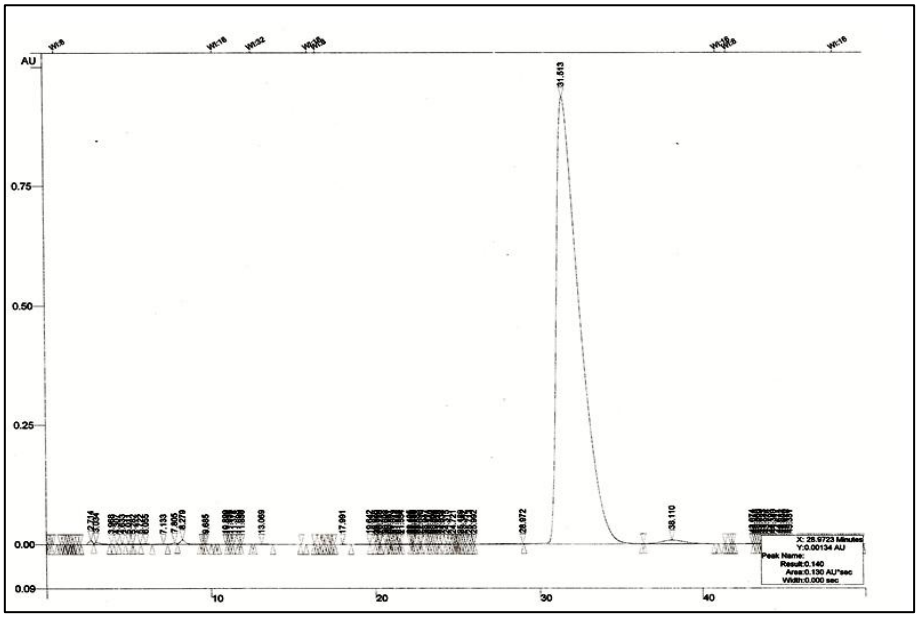
^{1}H NMR spectra compound 28



^{13}C NMR & DEPT 135 Spectra of compound 28

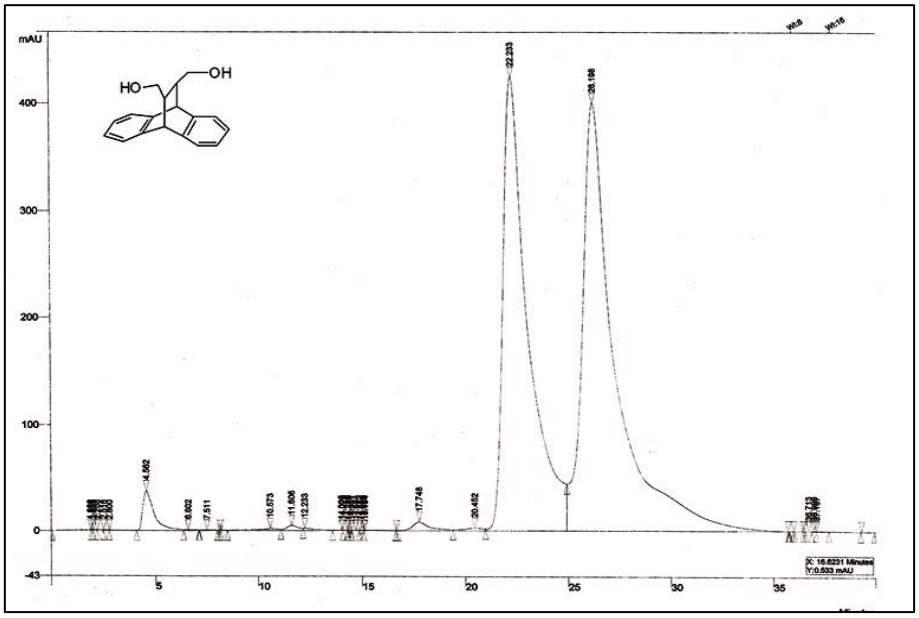
HPLC chart of 28

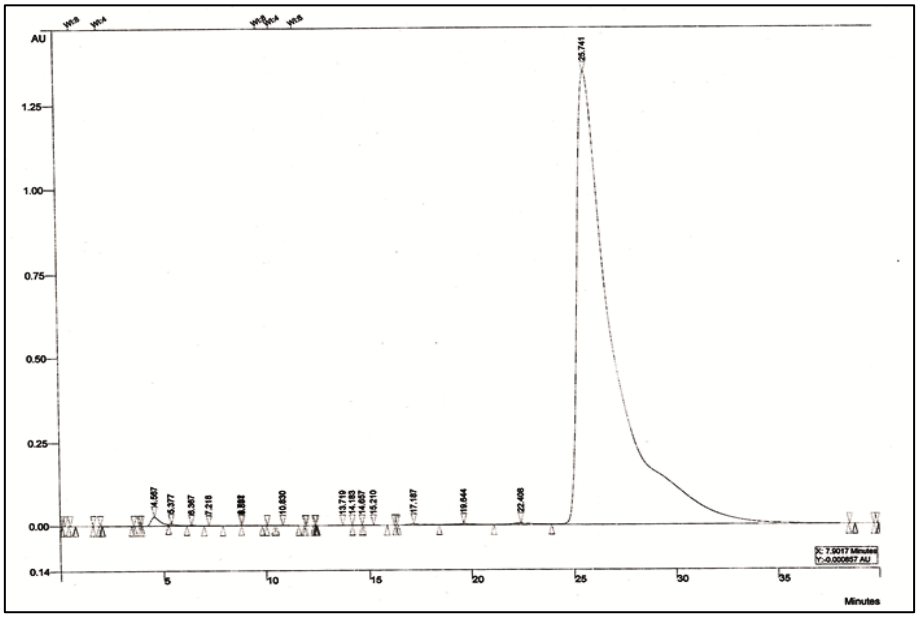




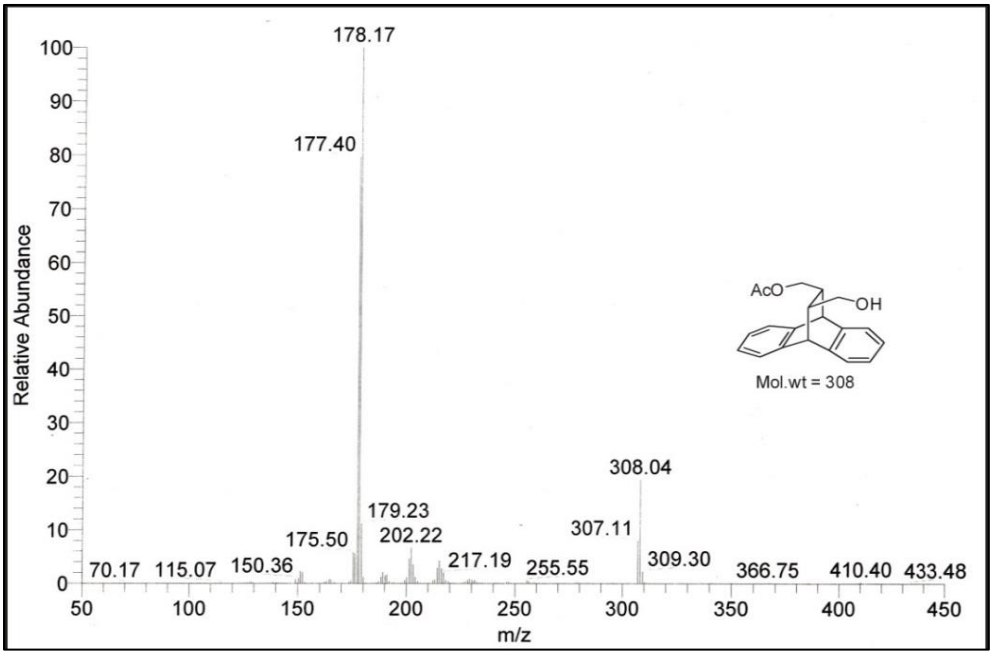
HPLC Chart of compound 28

HPLC chart 0f 27

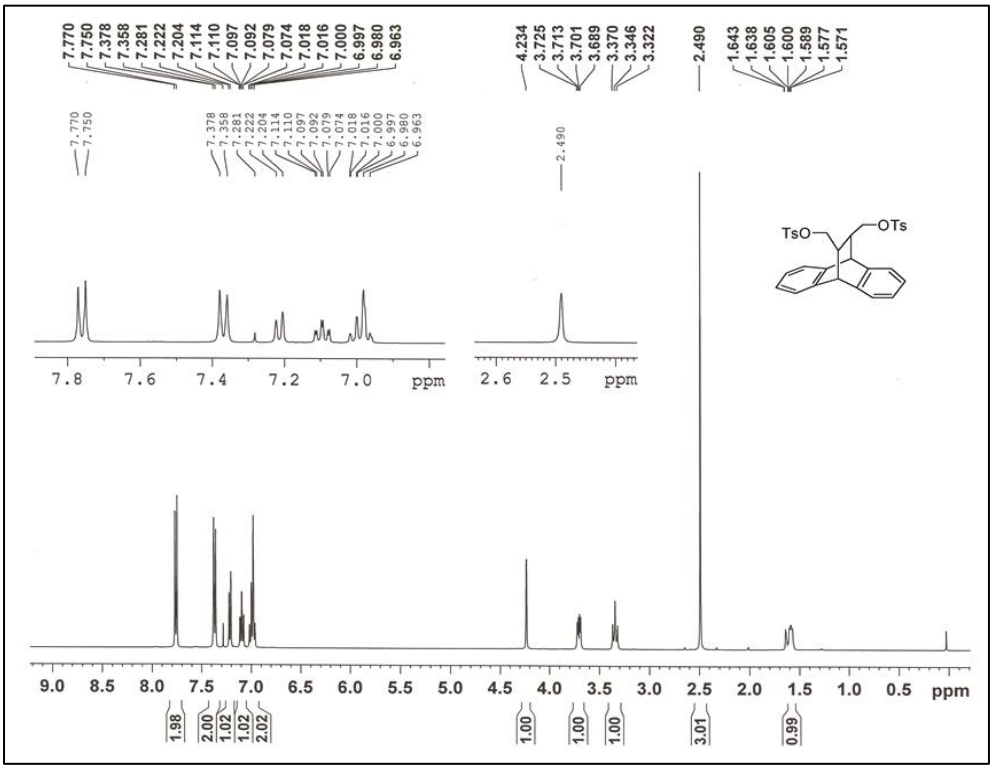




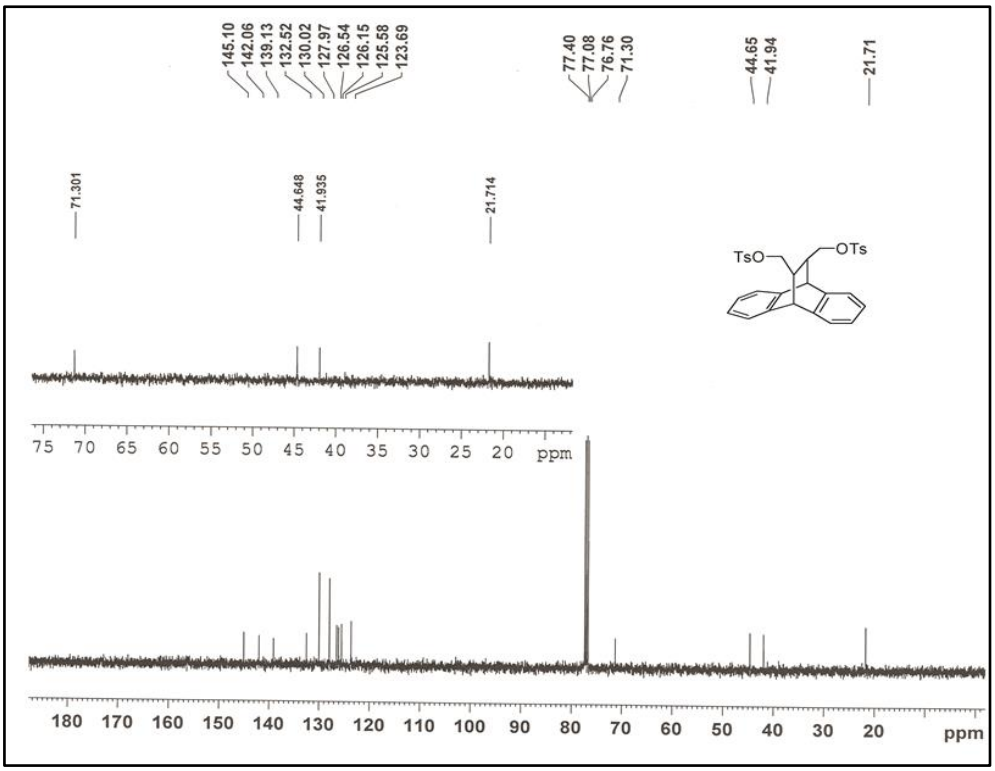
HPLC chart of compound 27

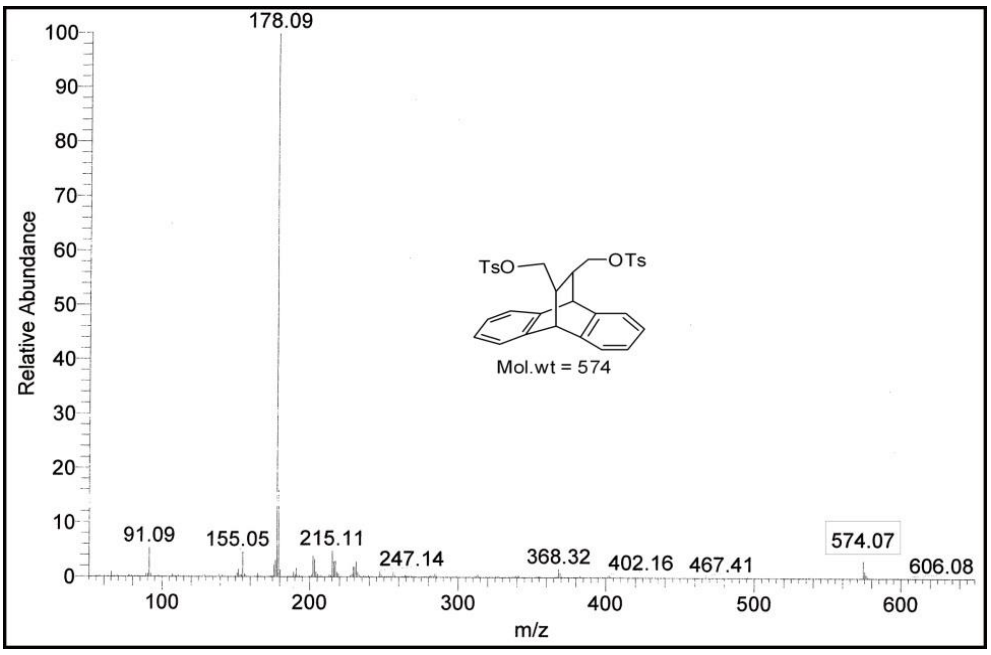


Mass spectra of compound 28

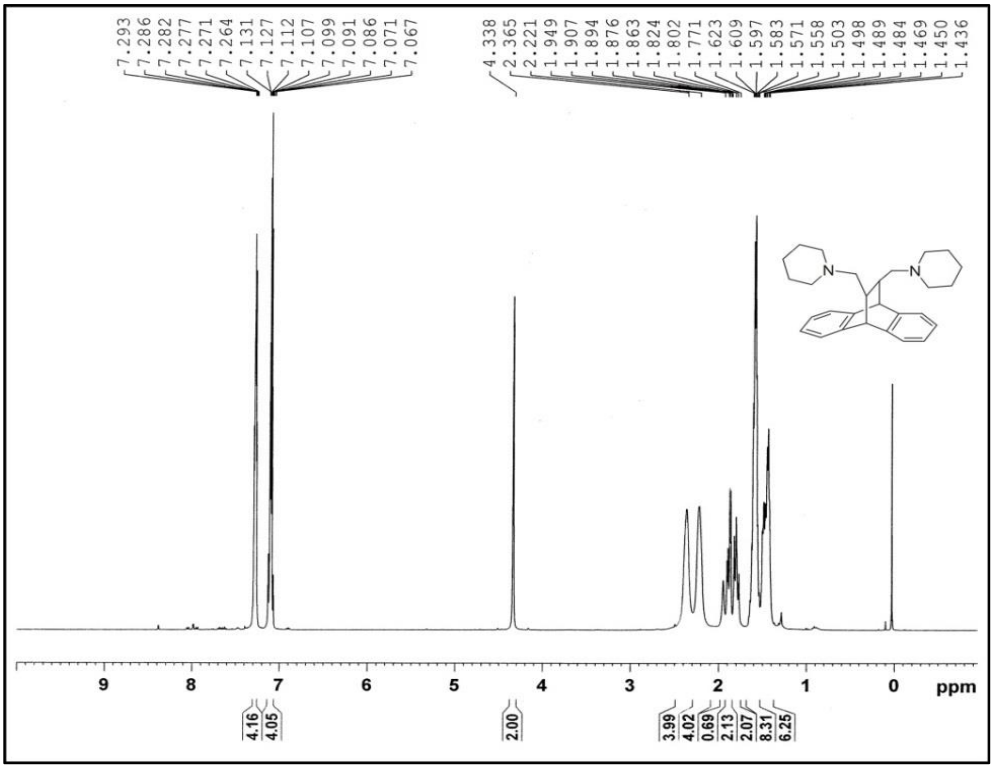


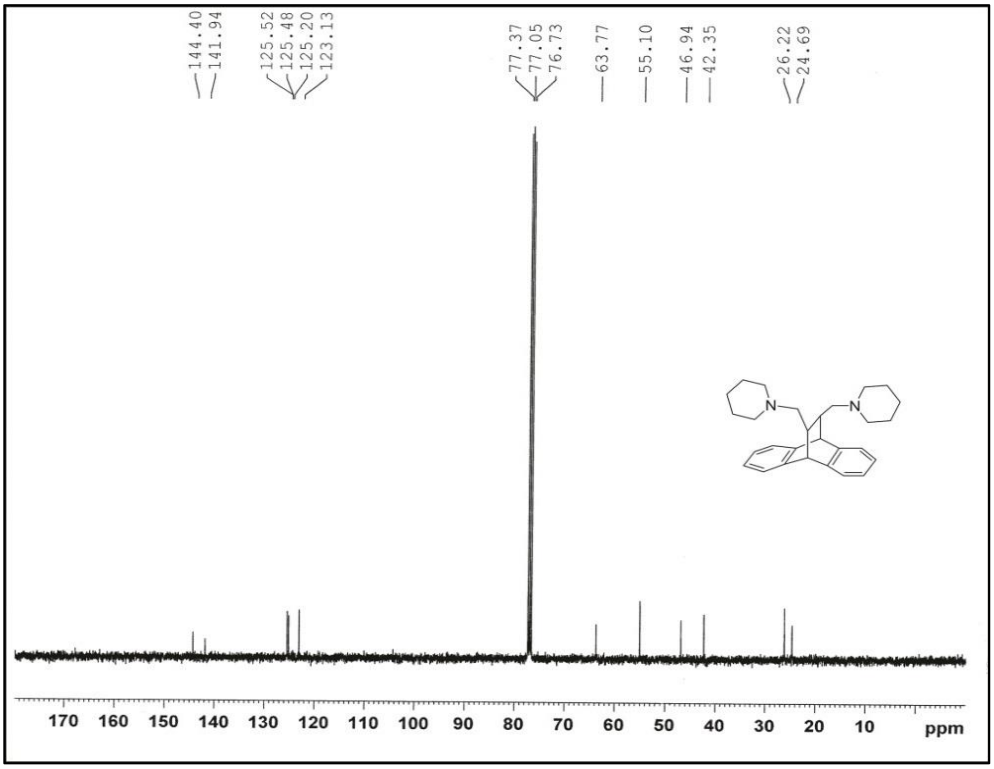
^{1}H NMR spectra of compound 29



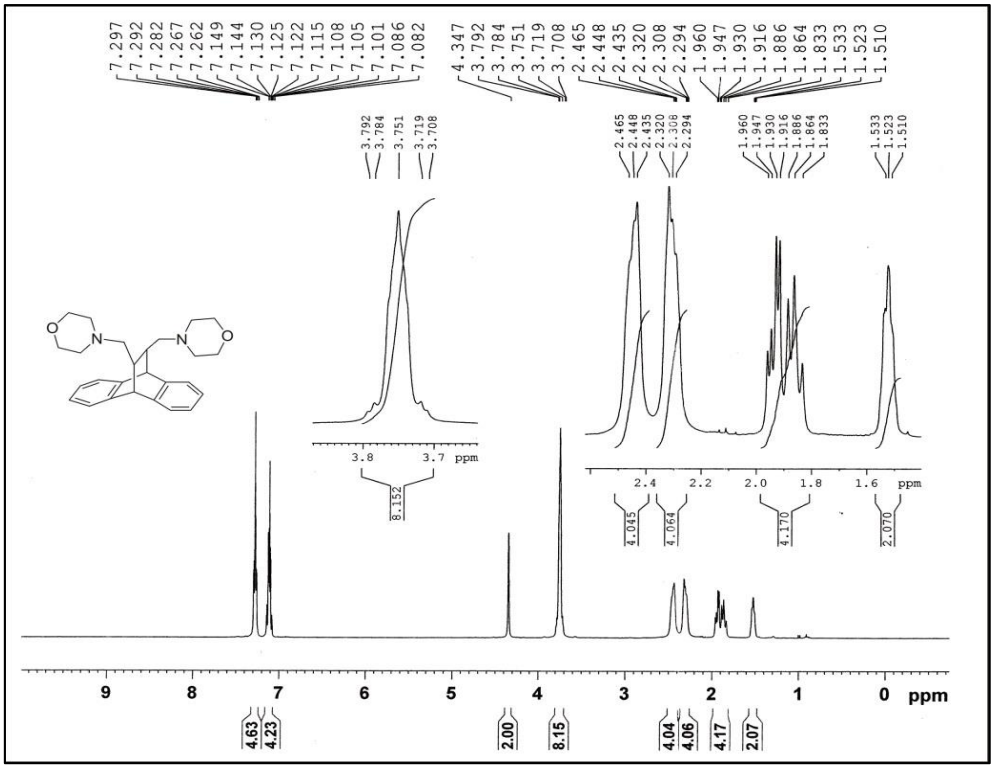


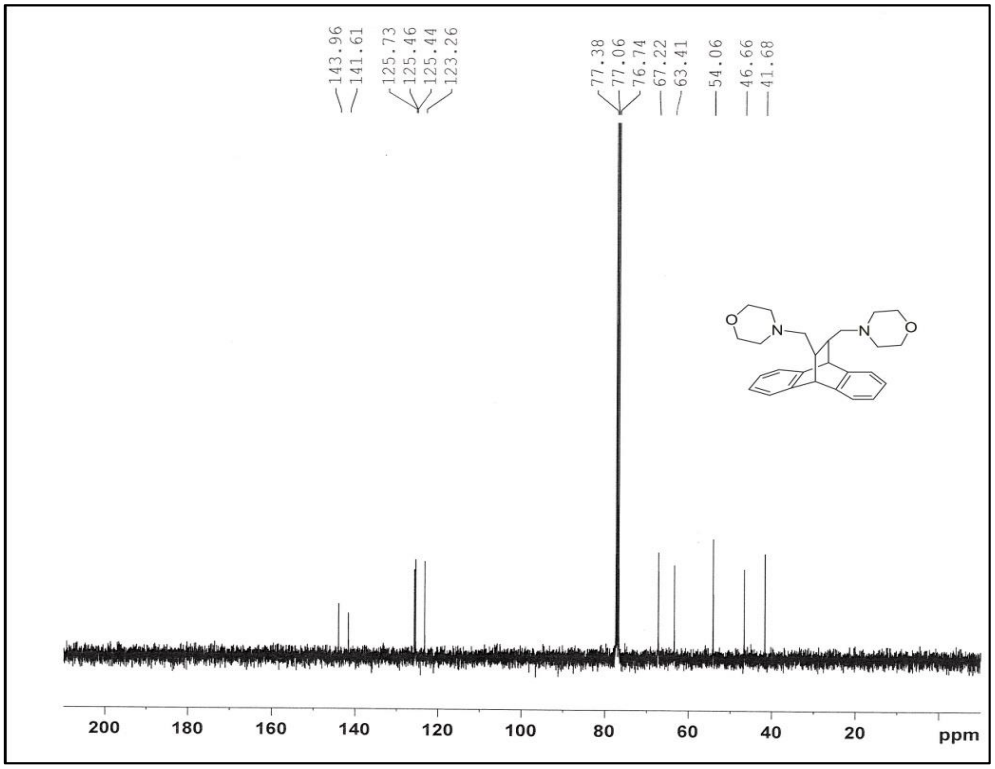
^{13}C NMR & Mass spectra of compound 29



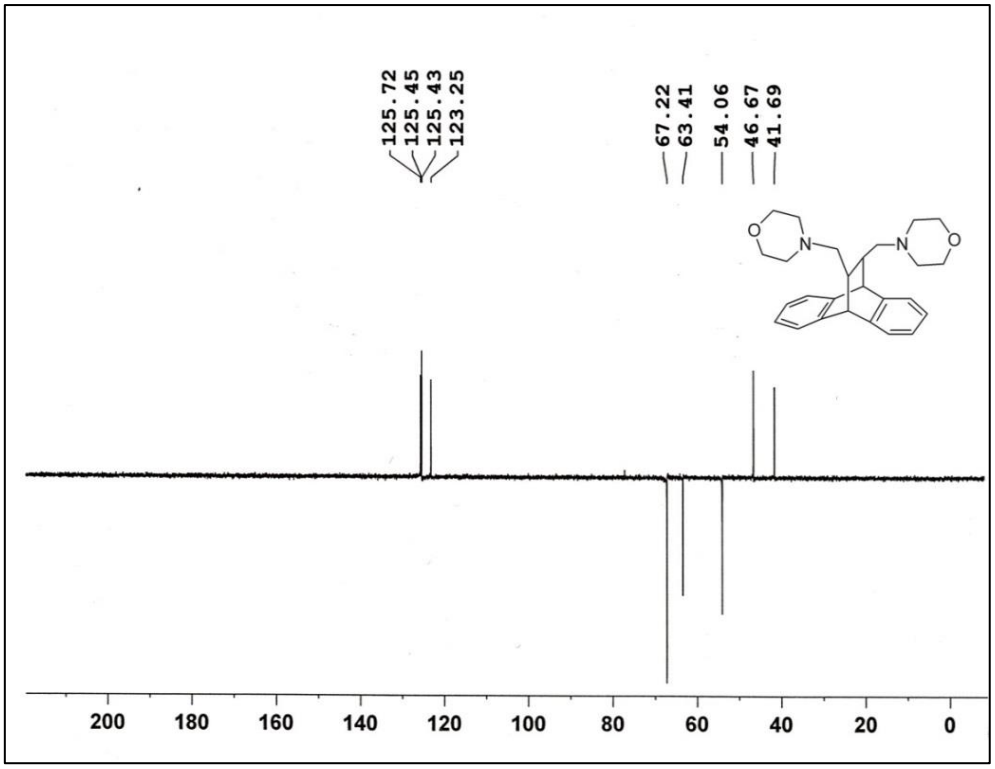


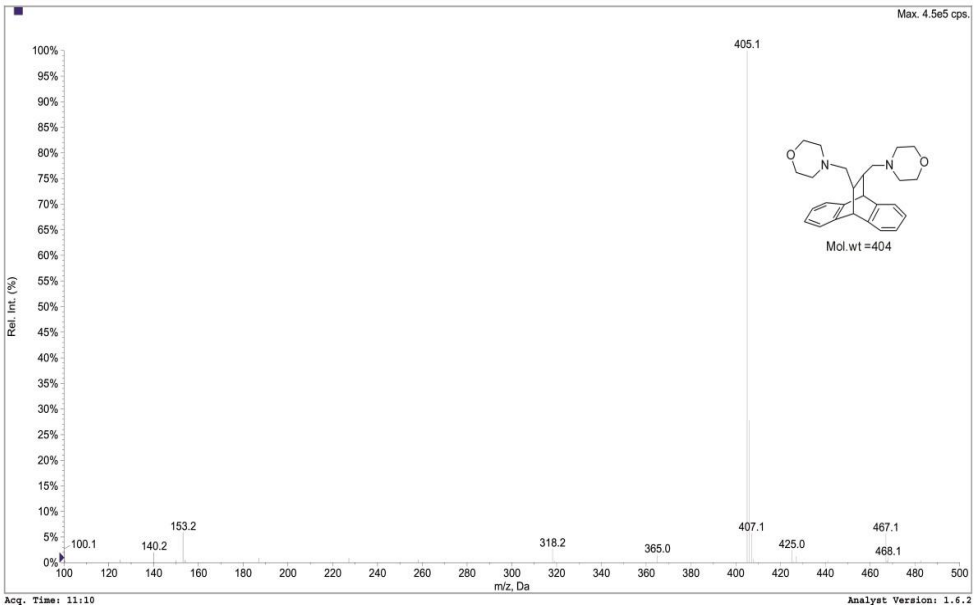
^{1}H NMR & ^{13}C spectra of compound 30



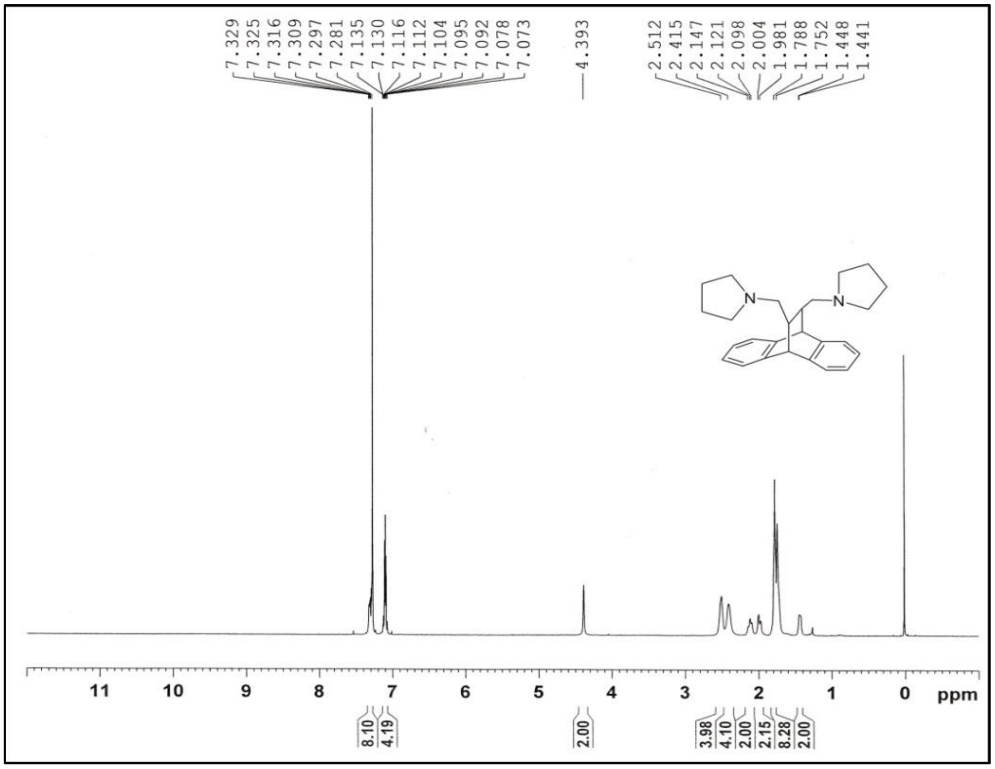


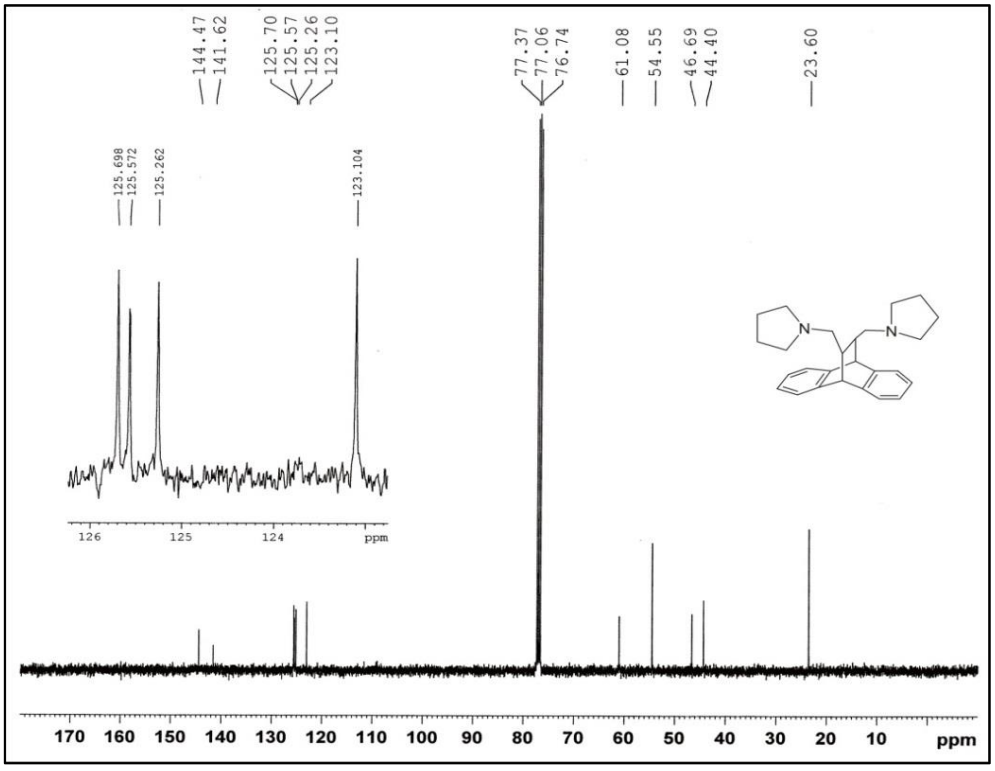
^{1}H NMR & ^{13}C spectra of compound 31



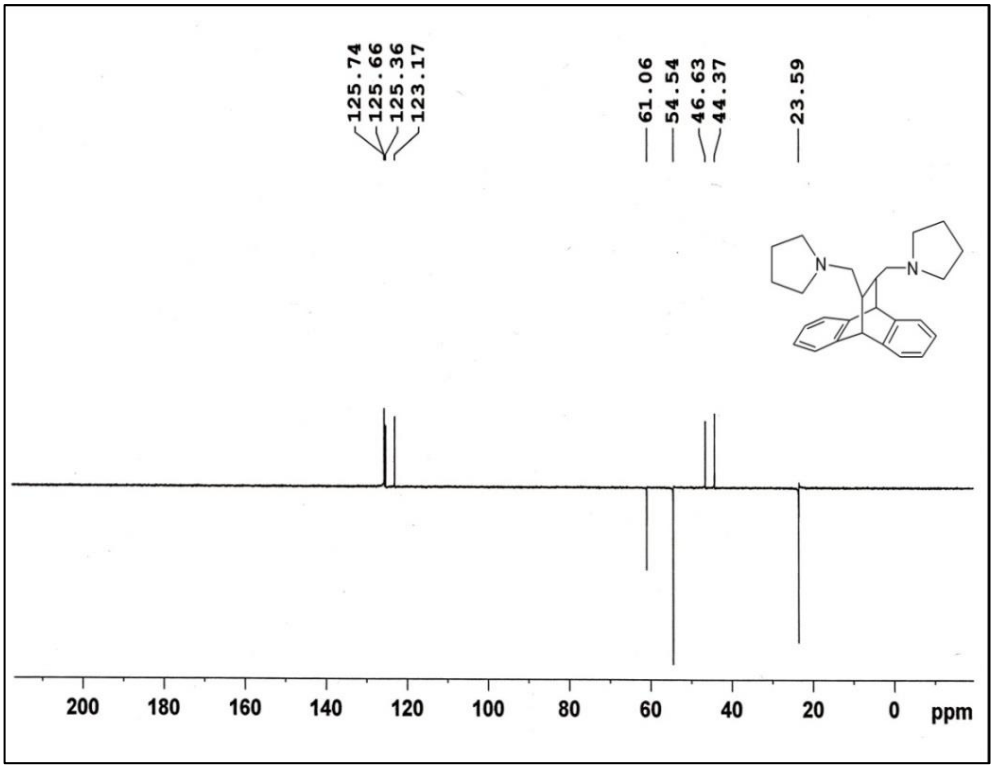


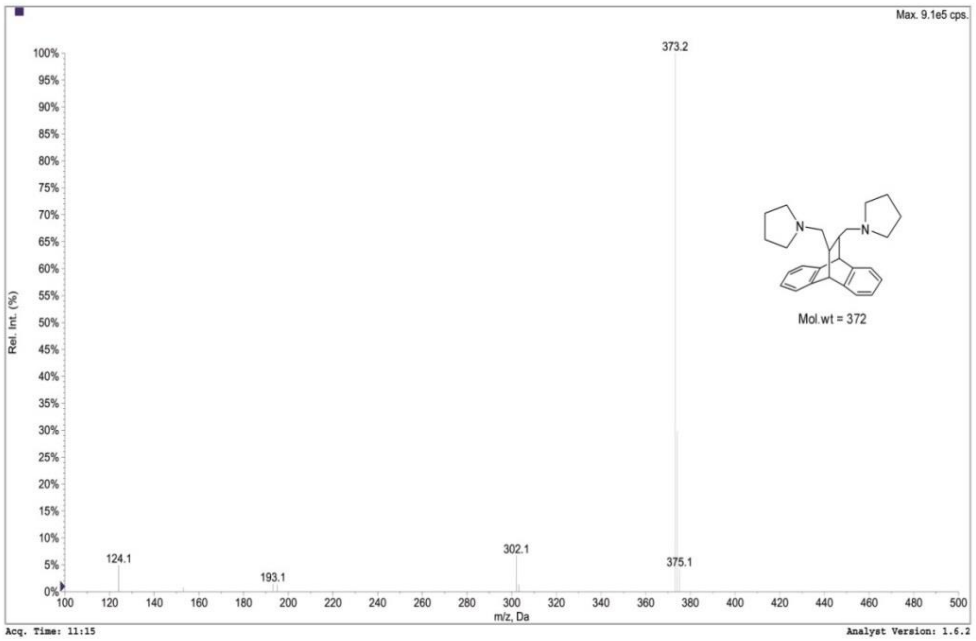
DEPT 135 & Mass spectra of compound 31



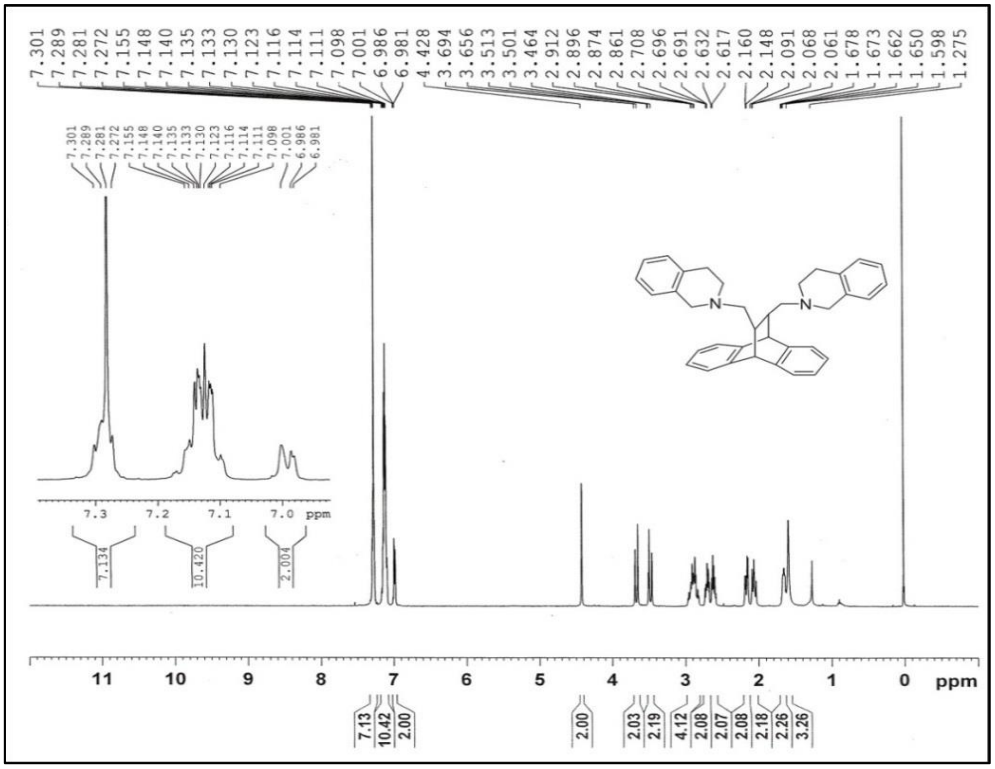


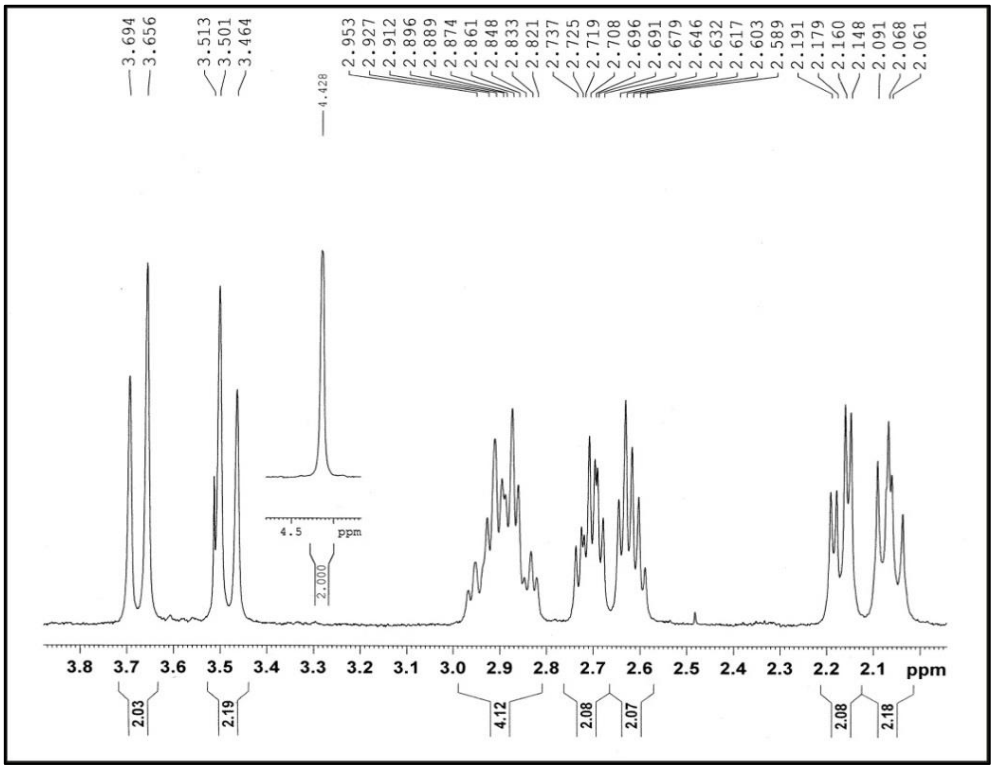
^{1}H NMR & ^{13}C spectra of compound 32



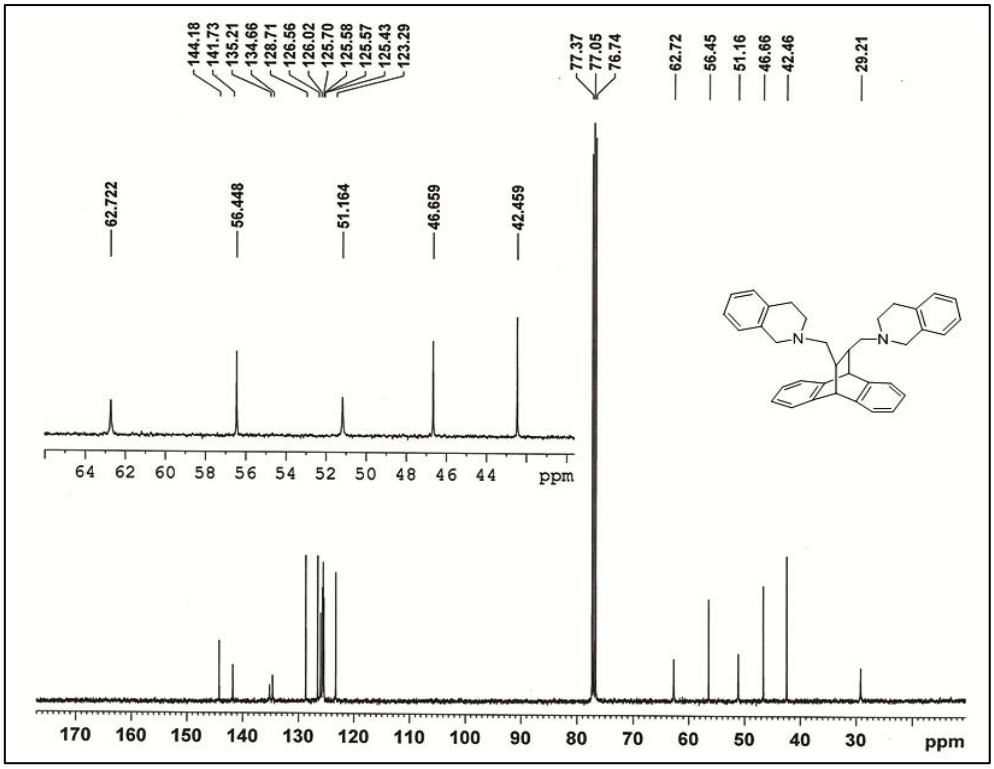


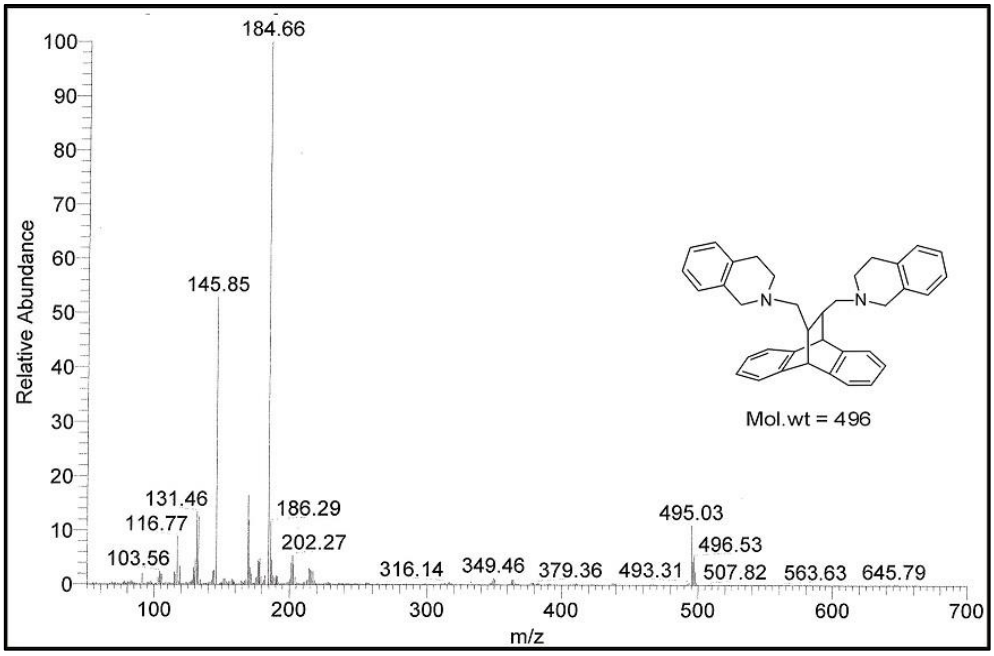
DEPT 135 & Mass spectra of compound 32





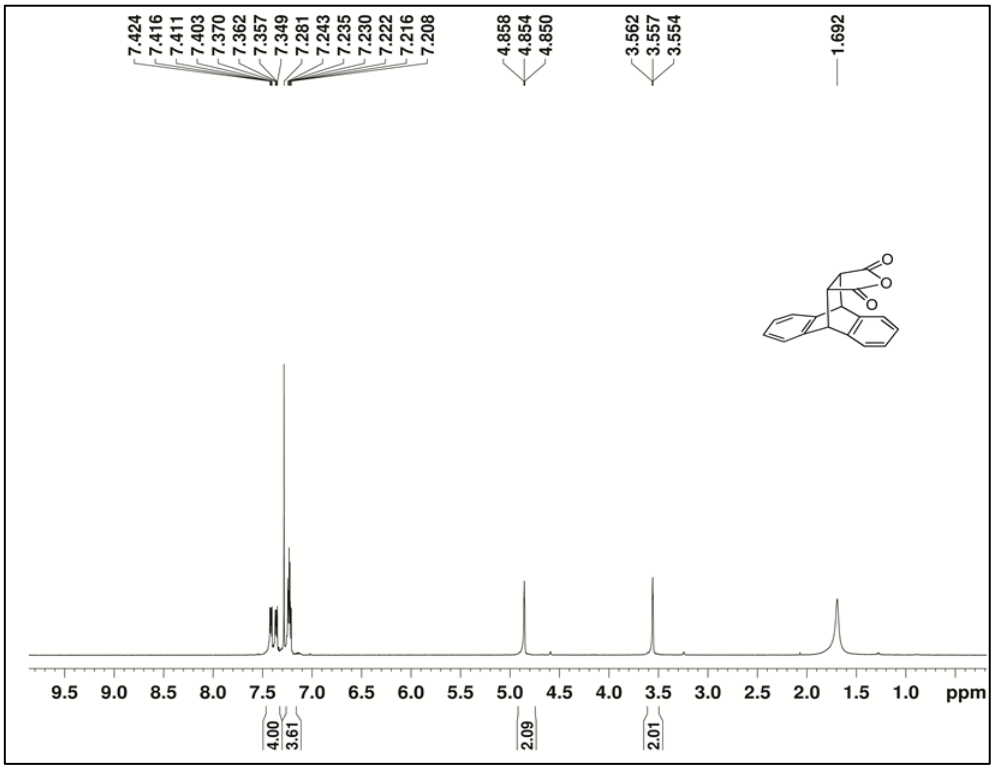
^{1}H NMR spectra of compound 33



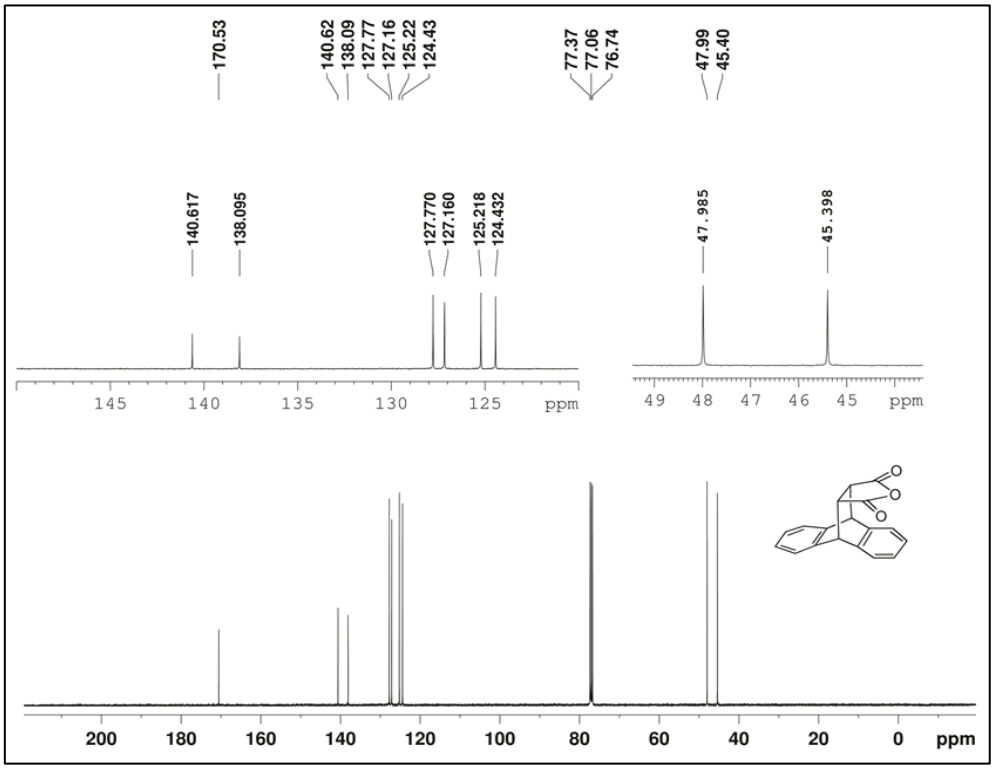


[13] C NMR & Mass spectra of compound 33

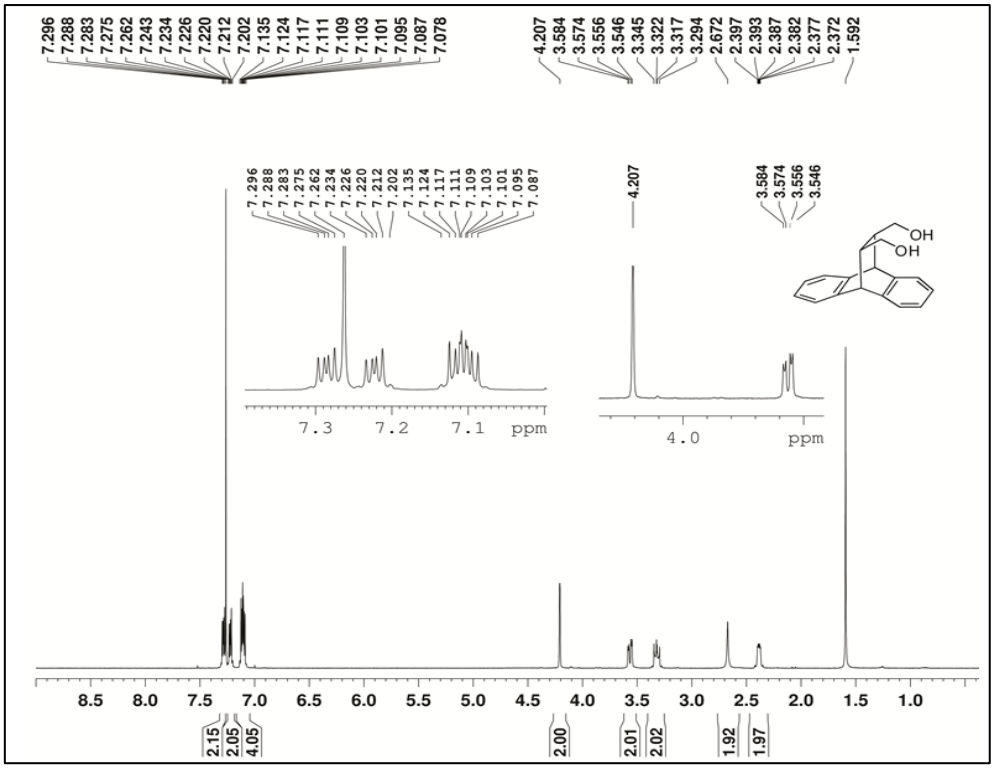
Spectral chart of Enzymatic Desymmetrisation



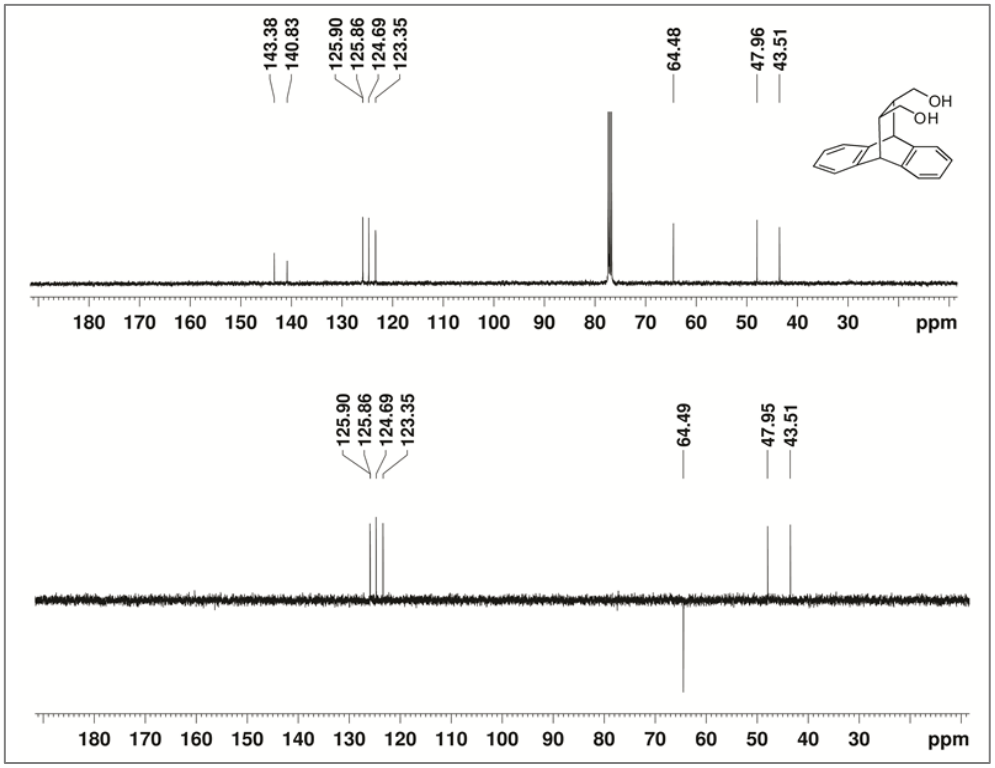
^{1}H NMR spectra compound 34



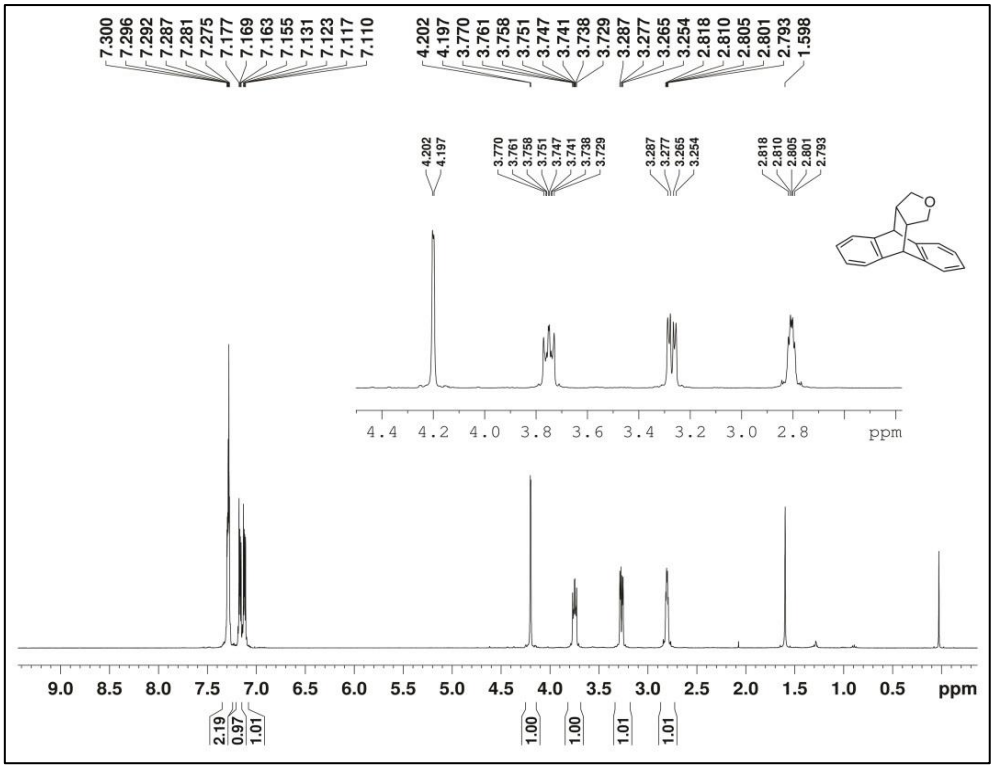
^{13} C NMR spectra of compound 34



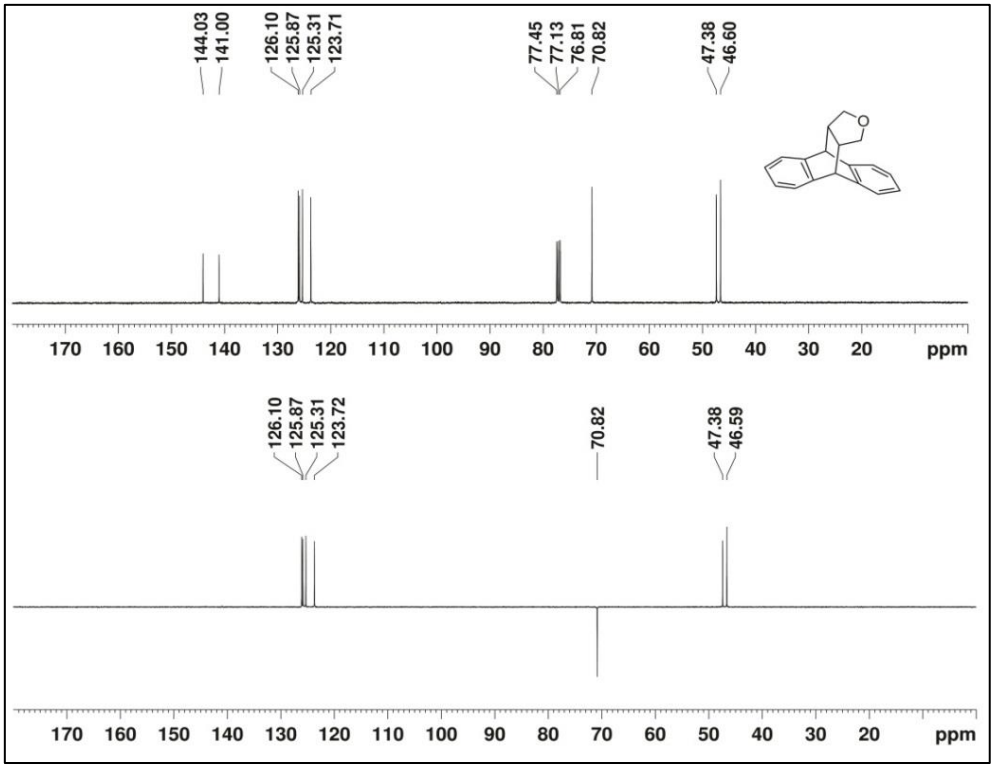
[1]H NMR spectra of compound 36



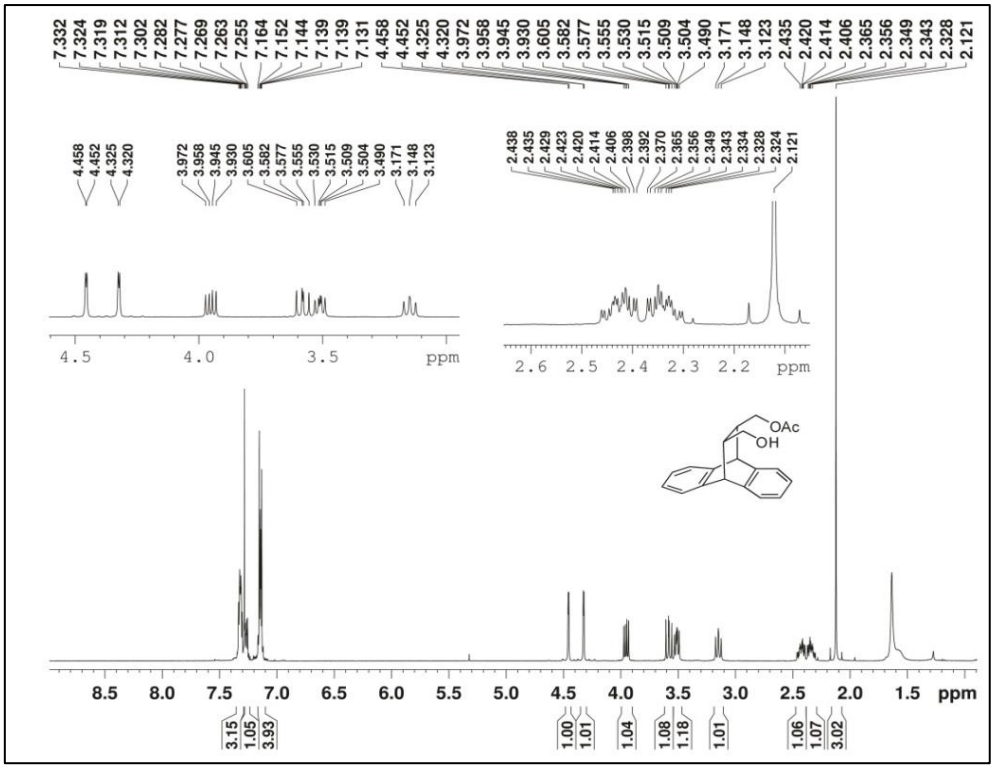
[13]C NMR spectra of compound 36



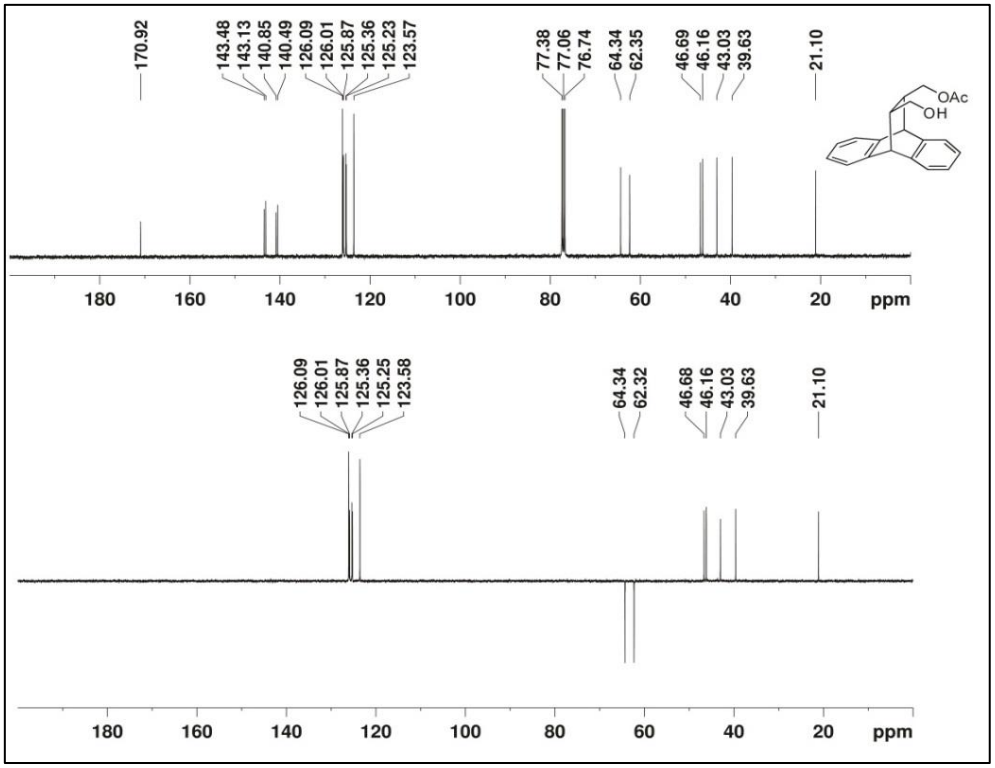
[1]H NMR spectra of compound 37



[13]C NMR & DEPT 135 spectra of compound 37



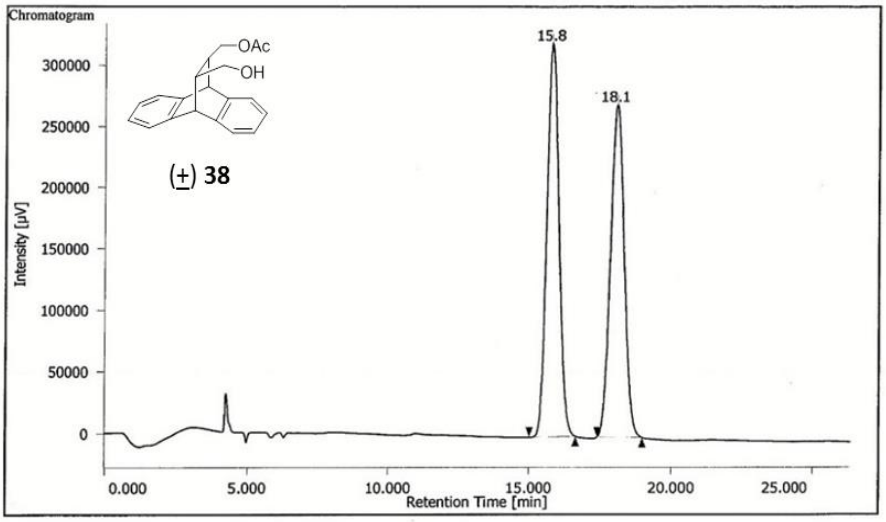
^{1}H NMR spectra of compound 38



^{13}C NMR & DEPT 135 spectra of compound 38

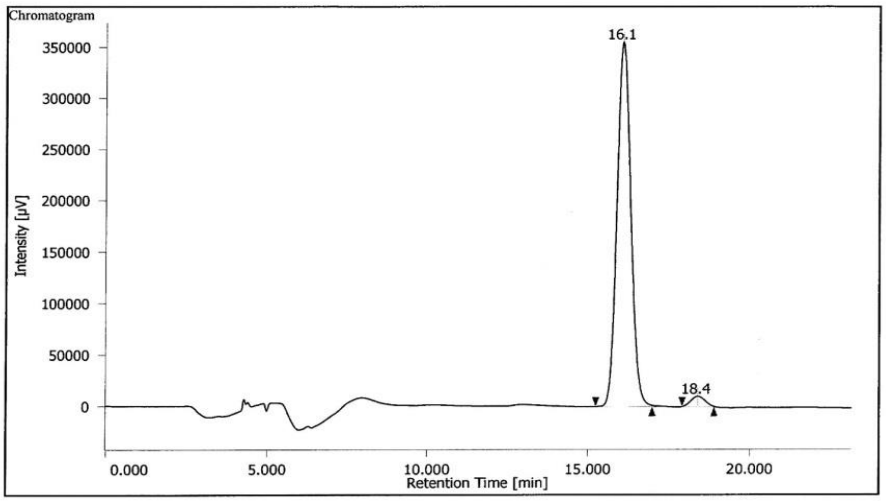
HPLC chart

HPLC condition Chiralpak OD-H column: 10% IPA-Hexane, UV = 254nm, Flow= 0.8 mL/min R_t = 15.8 min (1st Peak) [11*R*, 12*S* isomer] and R_t – 18.1 min (2nd peak) [11*S*, 12*R* isomer].



Peak Information

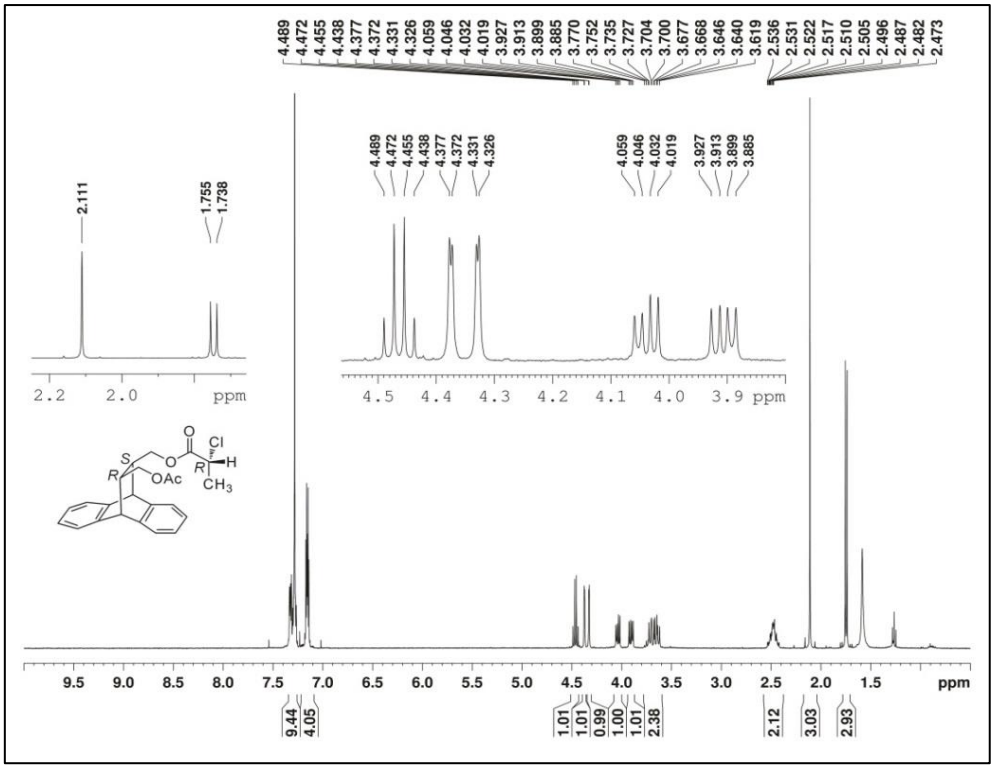
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	15.800	9488023	320759	51.179	6482	2.704	1.123
2	Unknown	1	18.058	9050729	270924	48.821	6588	N/A	1.105



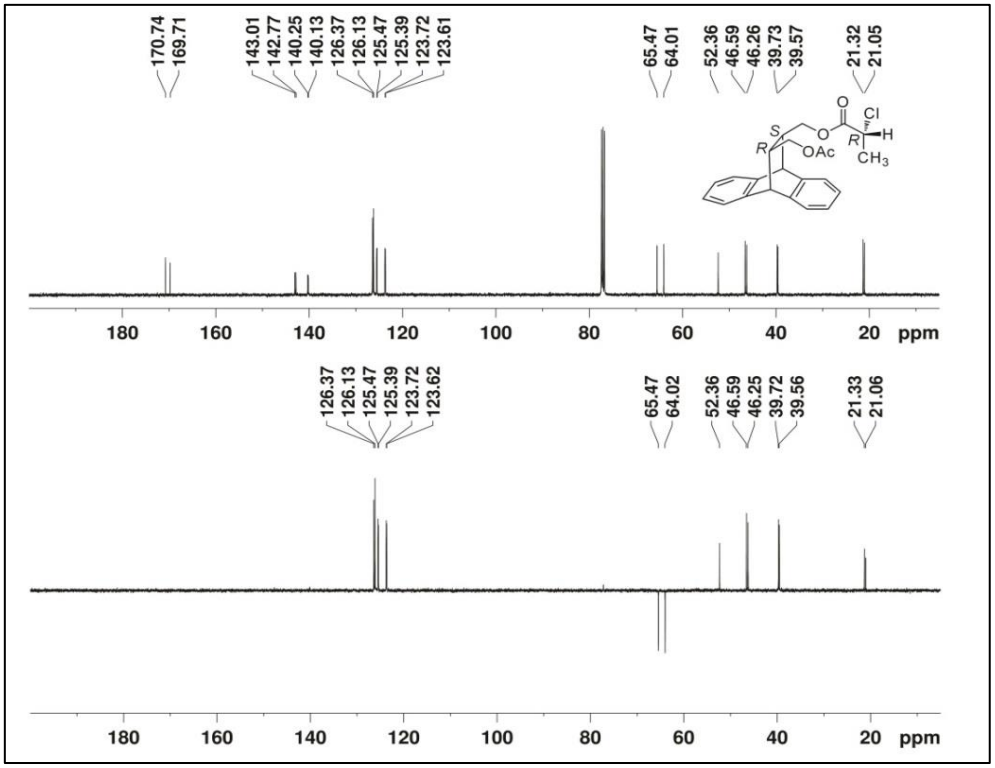
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	16.075	10709431	355340	97.325	6528	2.882	1.131
2	Unknown	1	18.400	294359	9934	2.675	8014	N/A	1.011

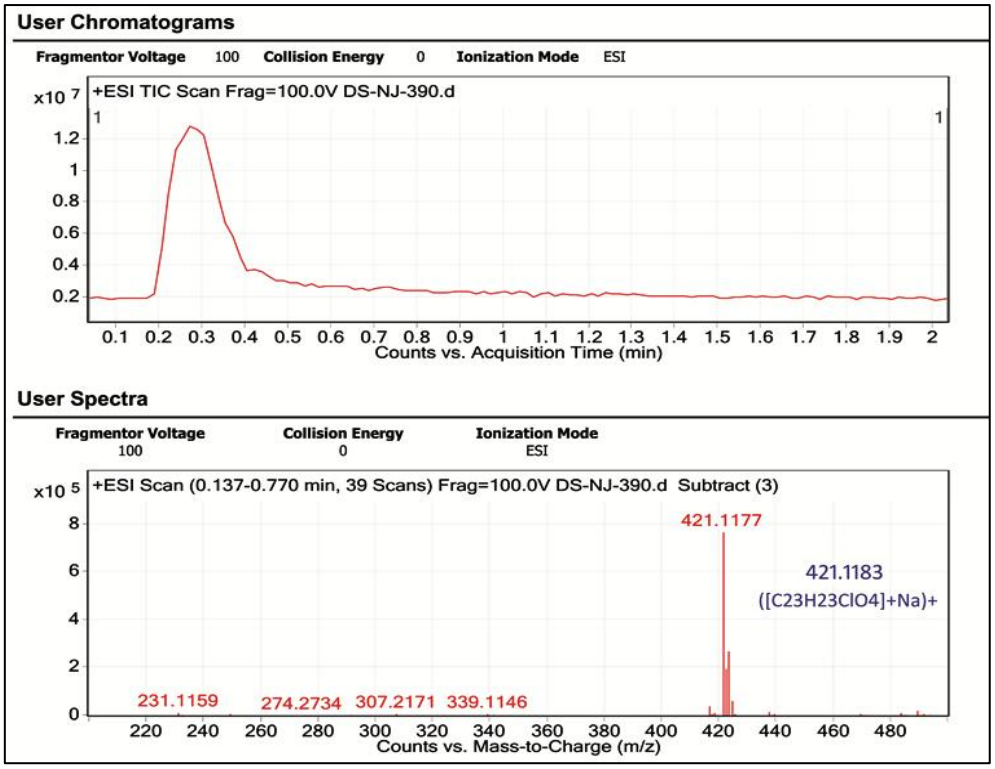
HPLC chart of compound 38



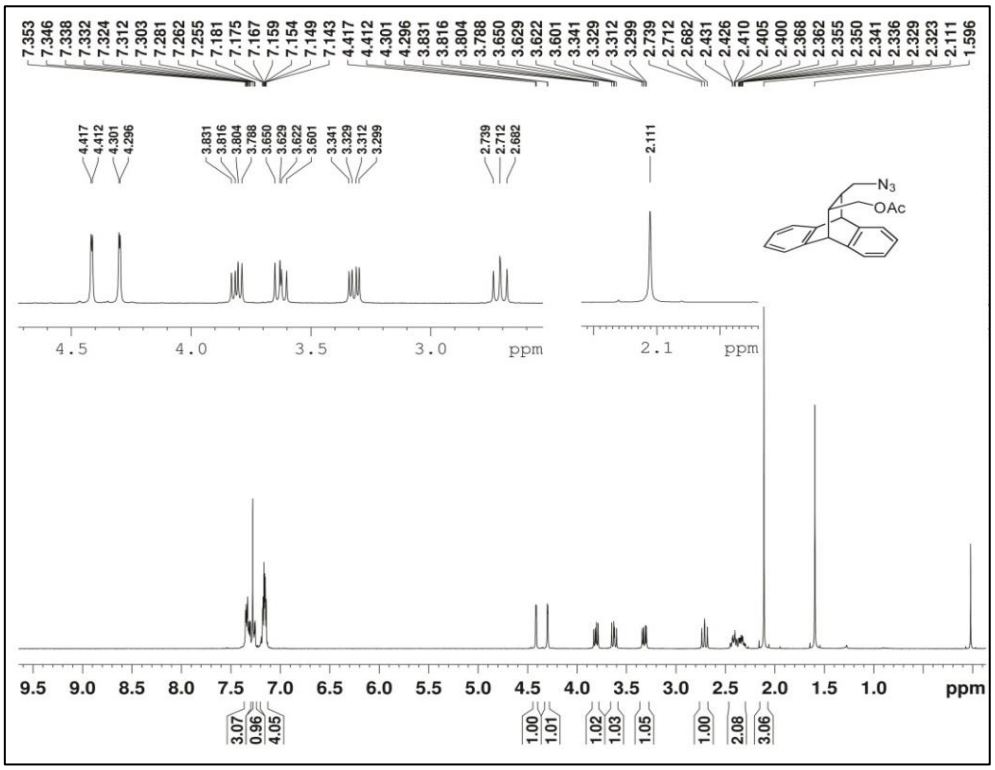
^{1}H NMR spectra of compound 40



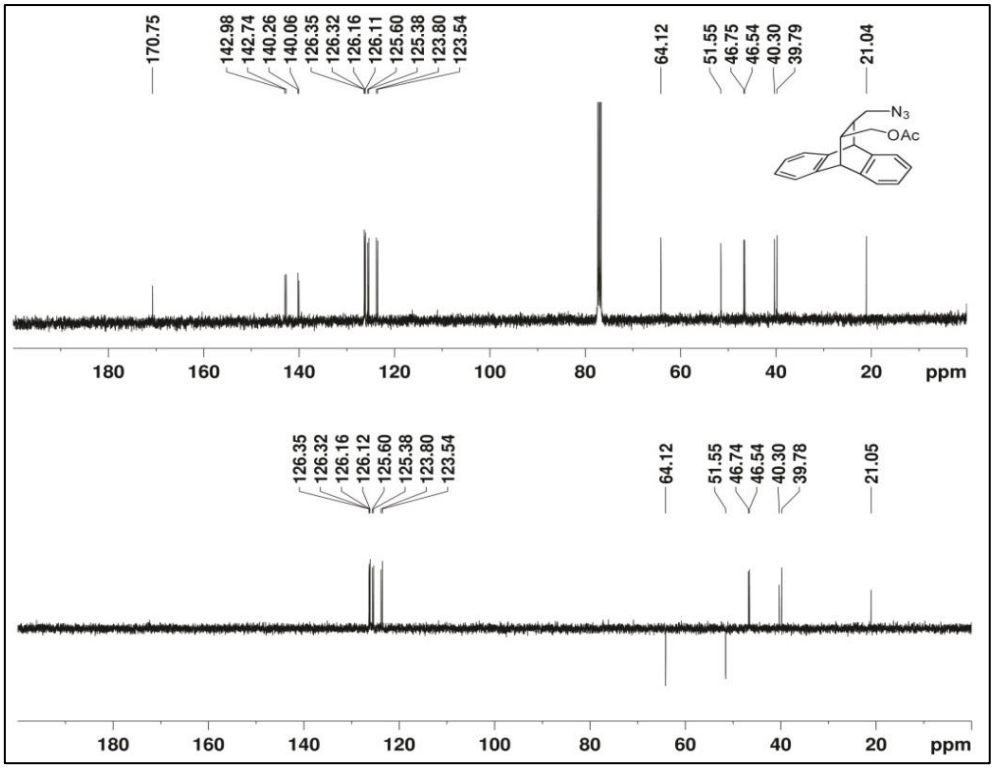
^{13}C NMR spectra of compound 40



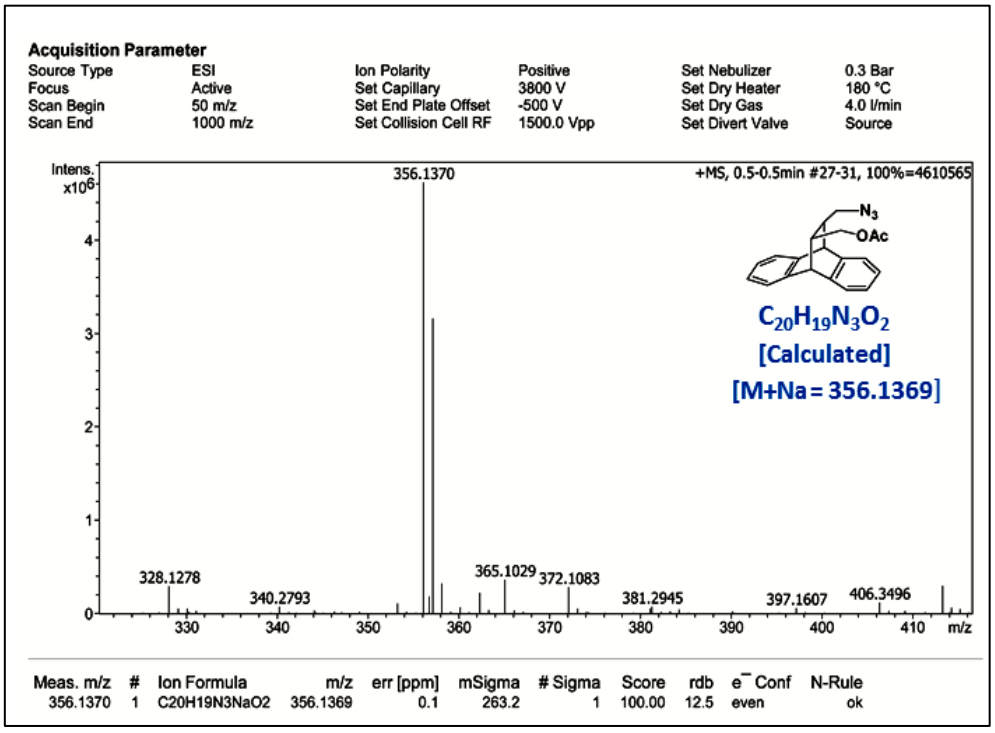
HRMS spectra of compound 40



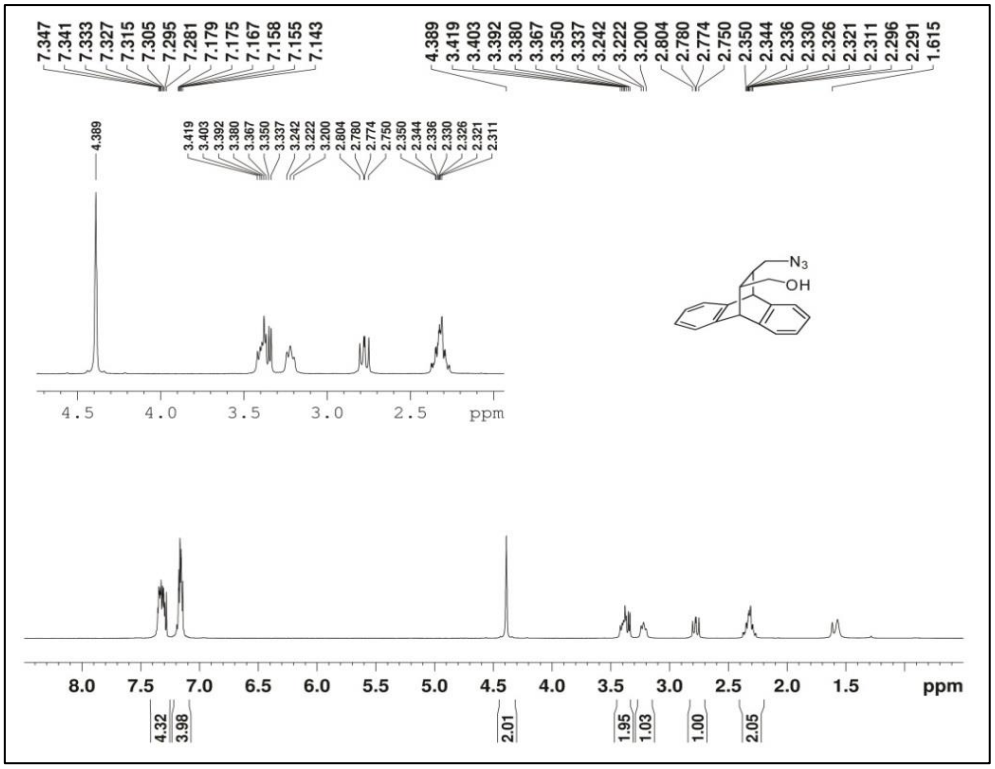
^{1}H NMR spectra of compound 41



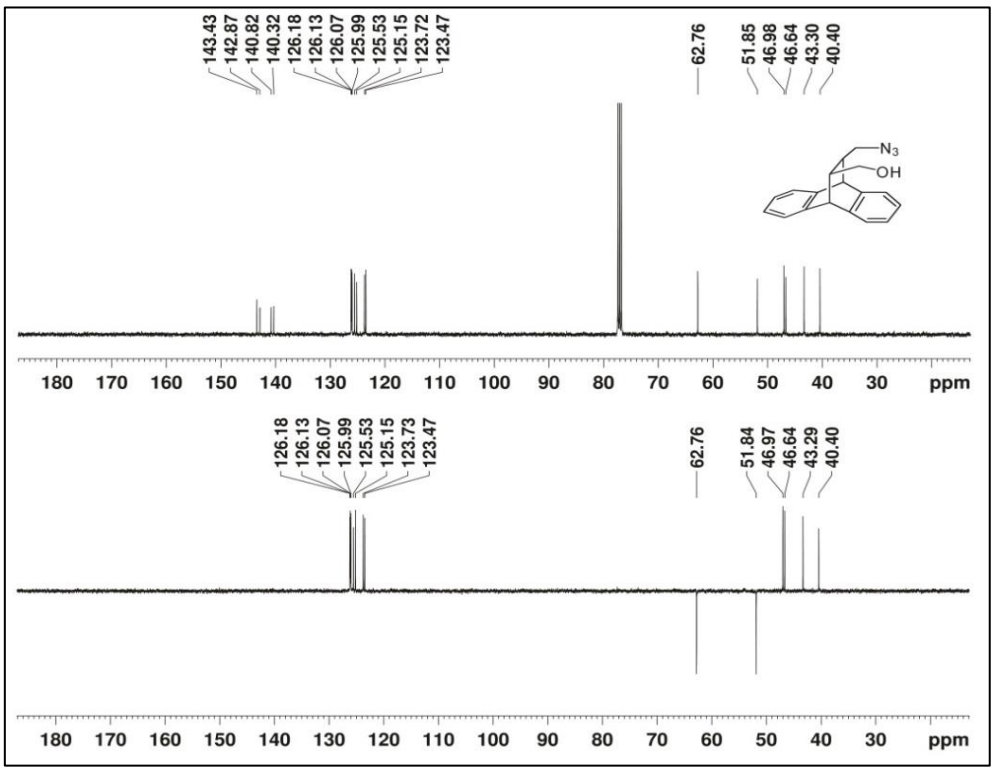
^{13}C NMR spectra of compound 41



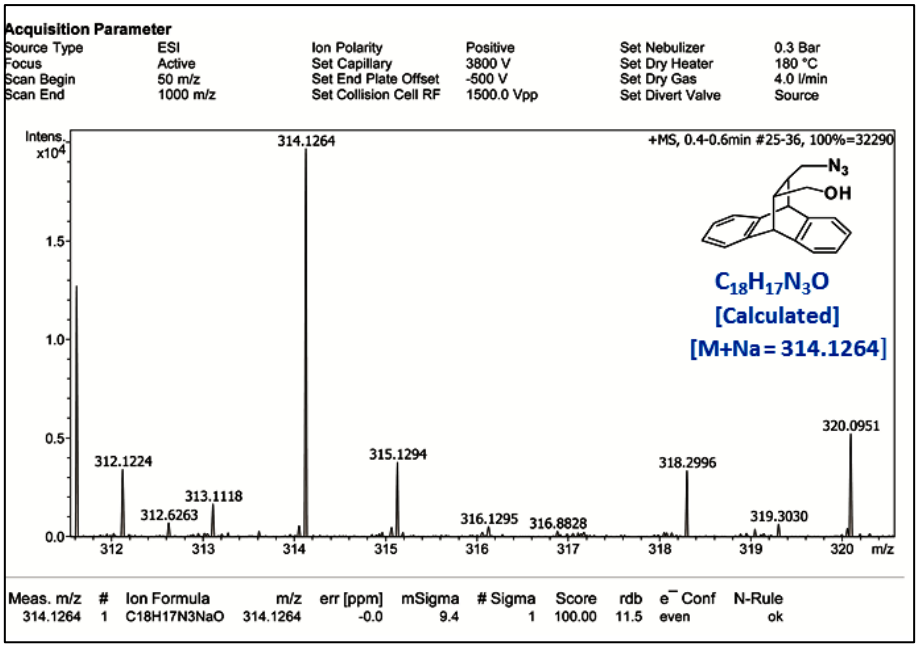
HRMS of compound 41



^{1}H NMR spectra of compound 42



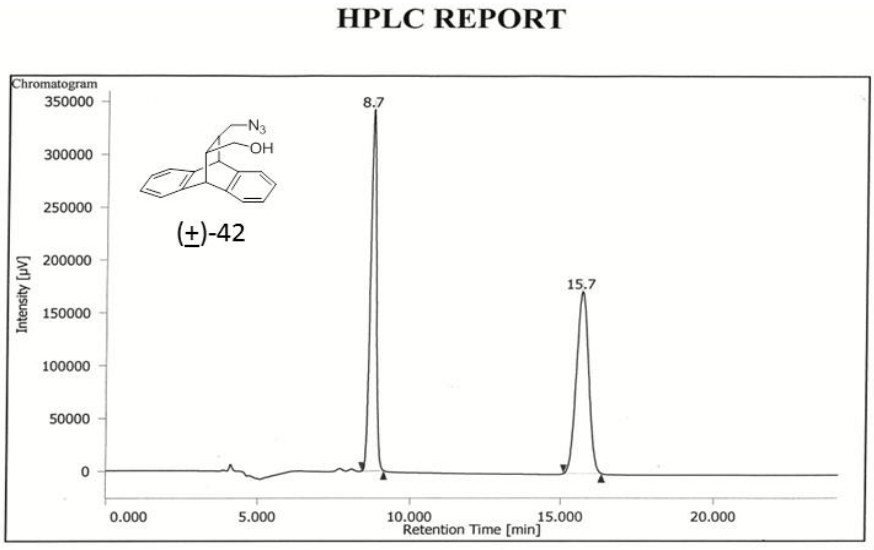
^{13}C NMR spectra of compound 42



HRMS of compound 42

HPLC Chart

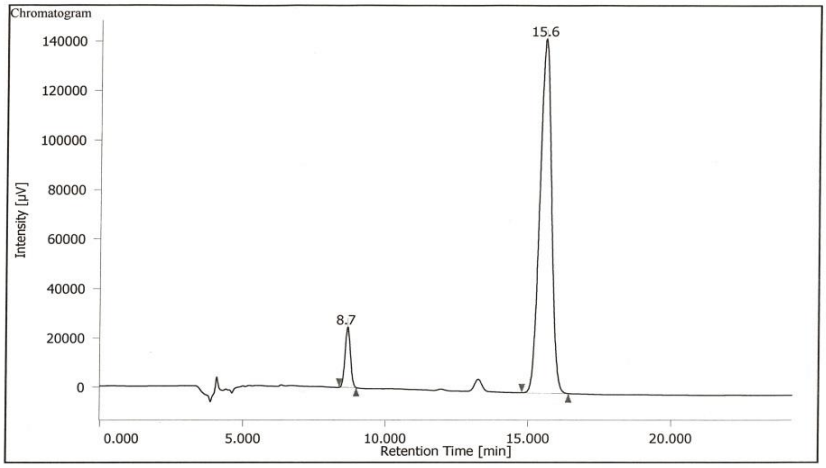
HPLC Condition Chiralpak OD-H column: 20% IPA-hexane, UV= 215 nm, Flow= 0.75 mL/min R_t –8.7 min (1st Peak) and R_t – 15.7 min (2nd peak).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	8.742	4698441	341851	49.370	9203	12.533	1.063
2	Unknown	1	15.683	4818351	172688	50.630	7067	N/A	1.063

HPLC REPORT

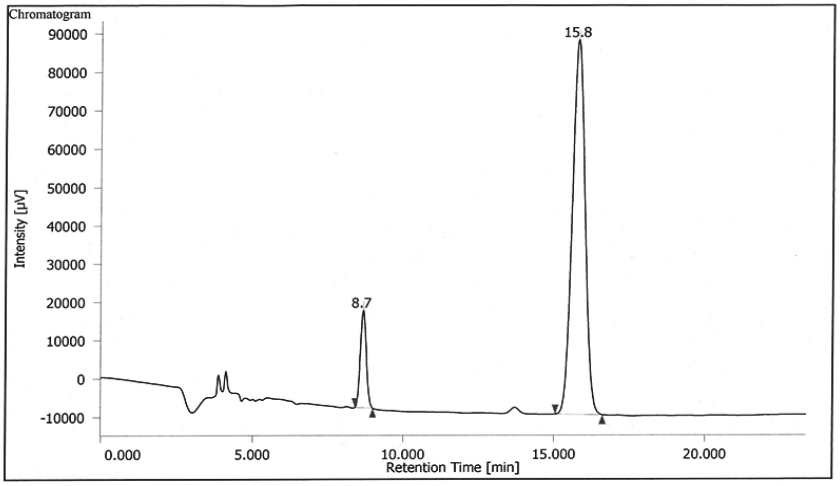


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	8.650	326690	24528	7.502	9502	12.560	1.040
2	Unknown	1	15.550	4027862	143439	92.498	6939	N/A	1.047

HPLC chart of compound 42 [*in*situ conversion]

HPLC REPORT

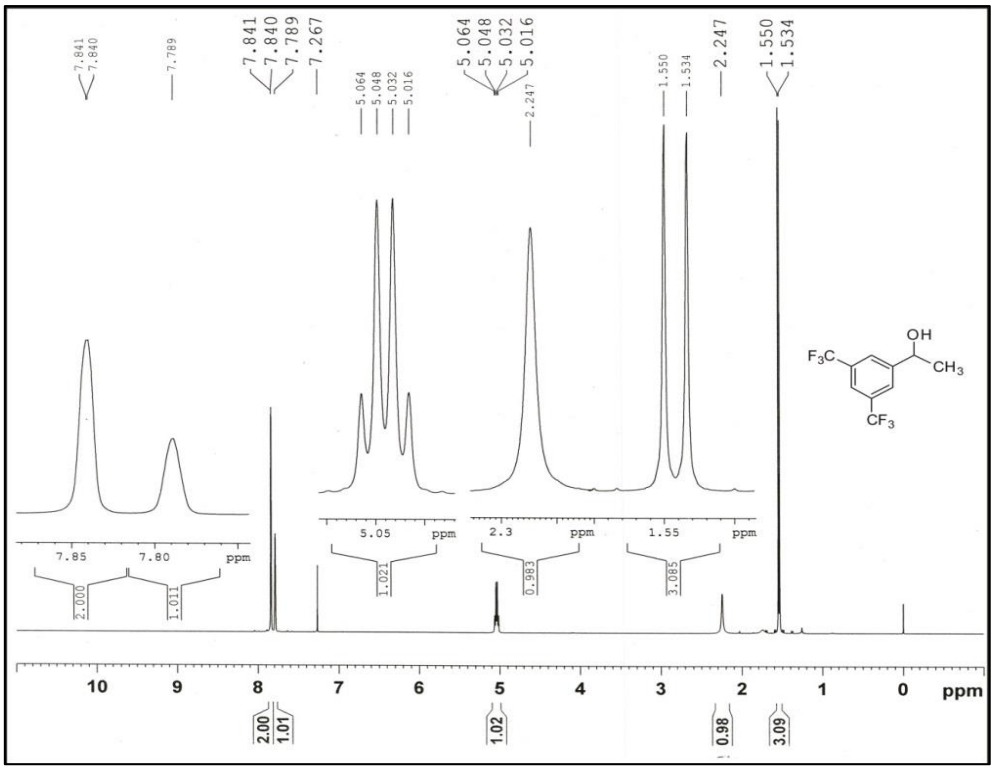


Peak Information

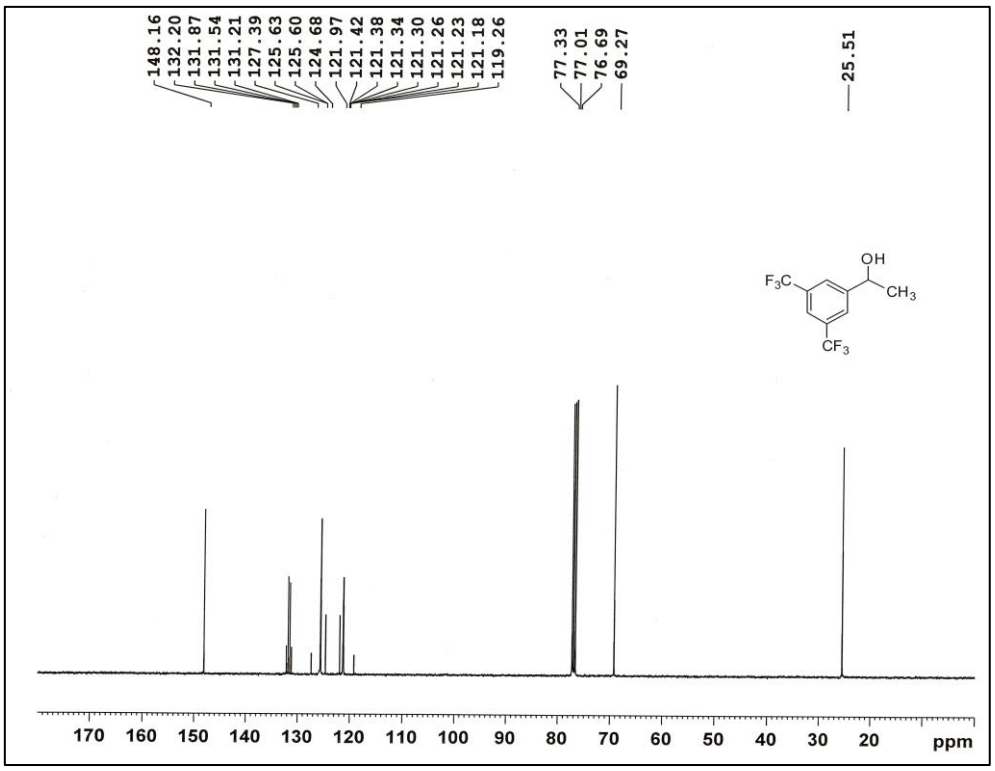
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	NTP	Resolution	Symmetry Factor
1	Unknown	1	8.683	350900	25363	10.909	8885	12.386	1.048
2	Unknown	1	15.775	2865860	97690	89.091	6549	N/A	1.052

HPLC chart of compound 42 [Stepwise conversion]

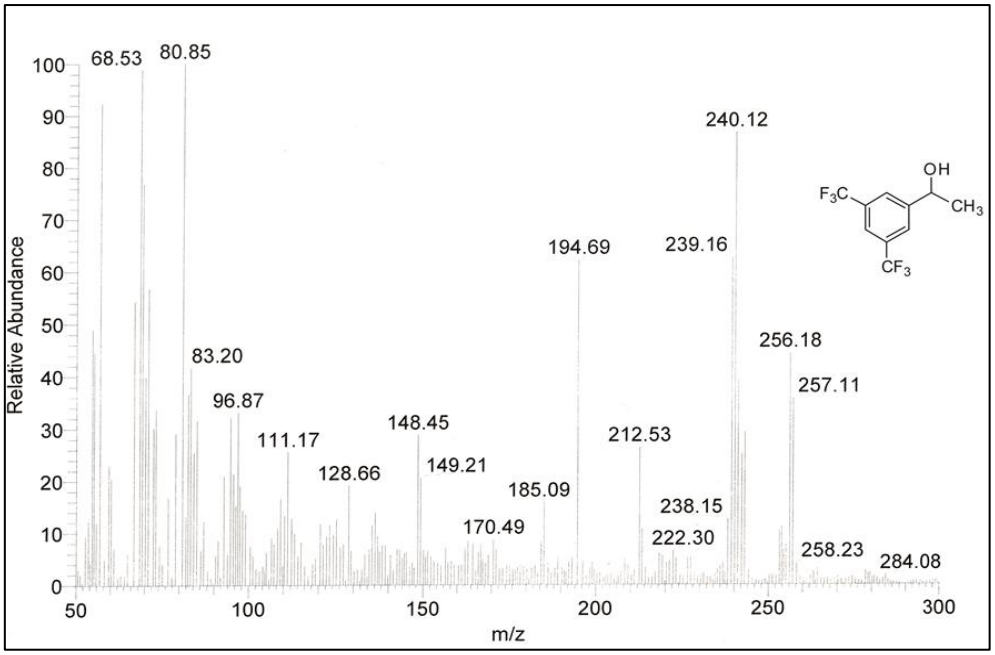
Spectral chart of Fluorinated compound



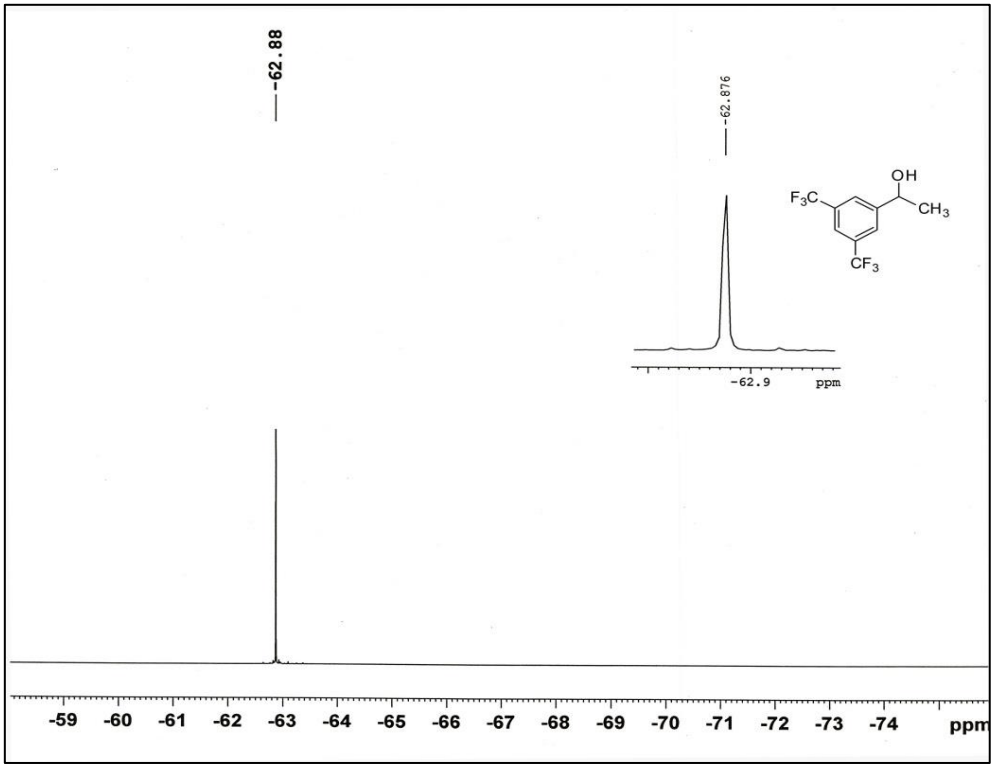
^{1}H NMR spectra of compound 44



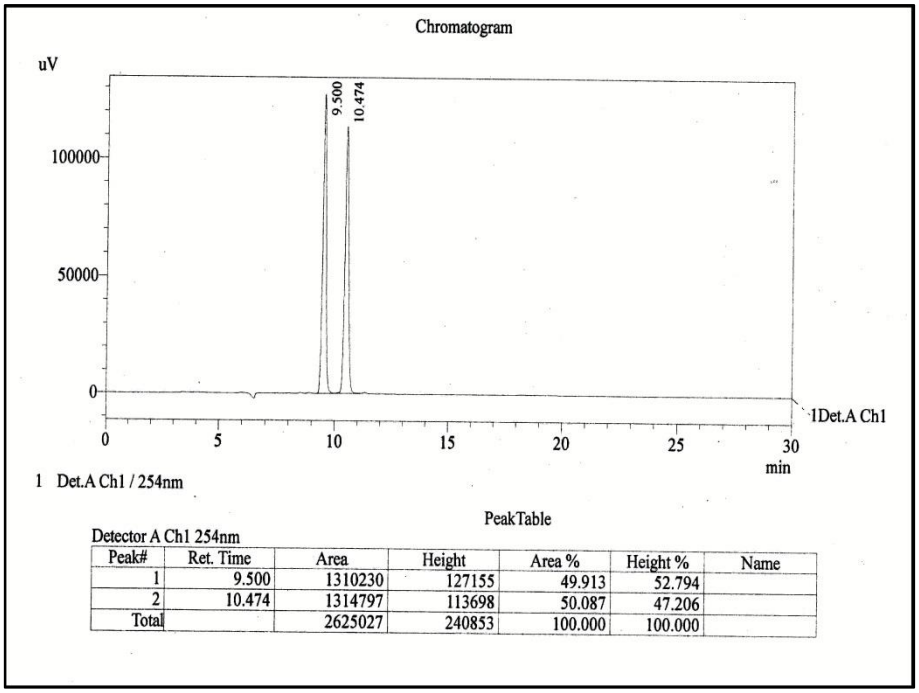
^{1}H NMR spectra of compound 44



Mass Spectra of compound 44



^{19}F NMR spectra of compound 44

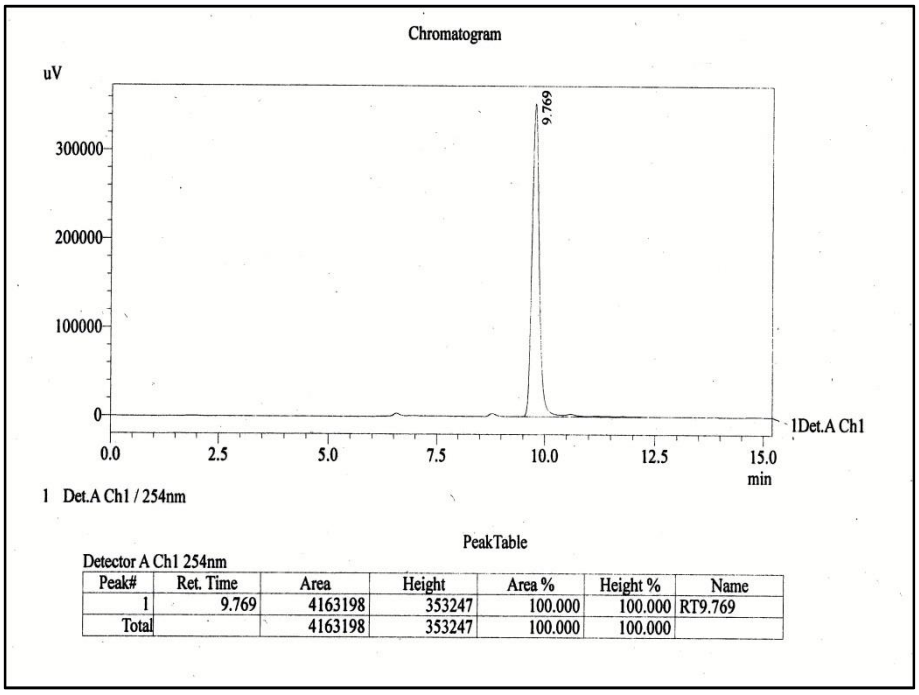


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Name
1	9.500	1310230	127155	49.913	52.794	
2	10.474	1314797	113698	50.087	47.206	
Total		2625027	240853	100.000	100.000	

HPLC graph of Racemic 44

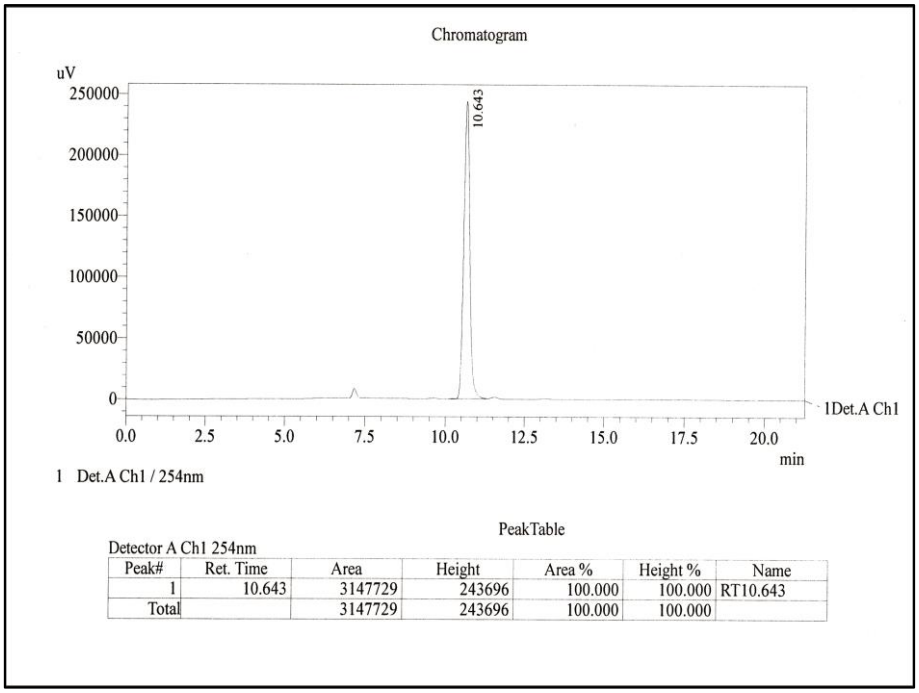


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Name
1	9.769	4163198	353247	100.000	100.000	RT9.769
Total		4163198	353247	100.000	100.000	

HPLC graph of *S* isomer (*S*)-44

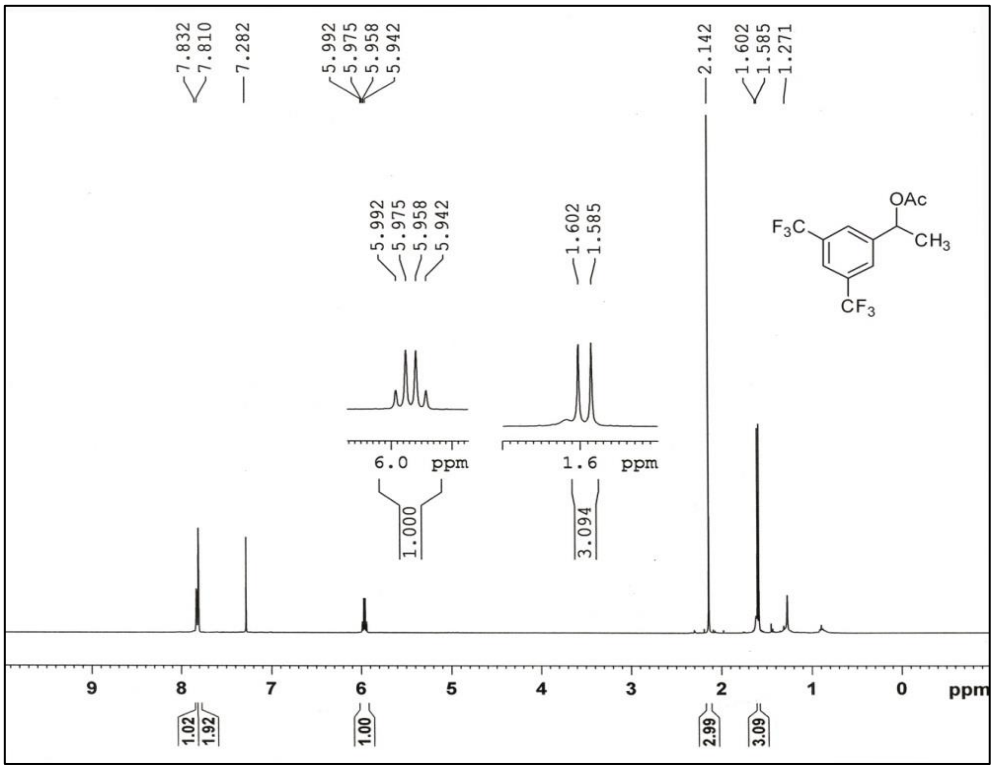


PeakTable

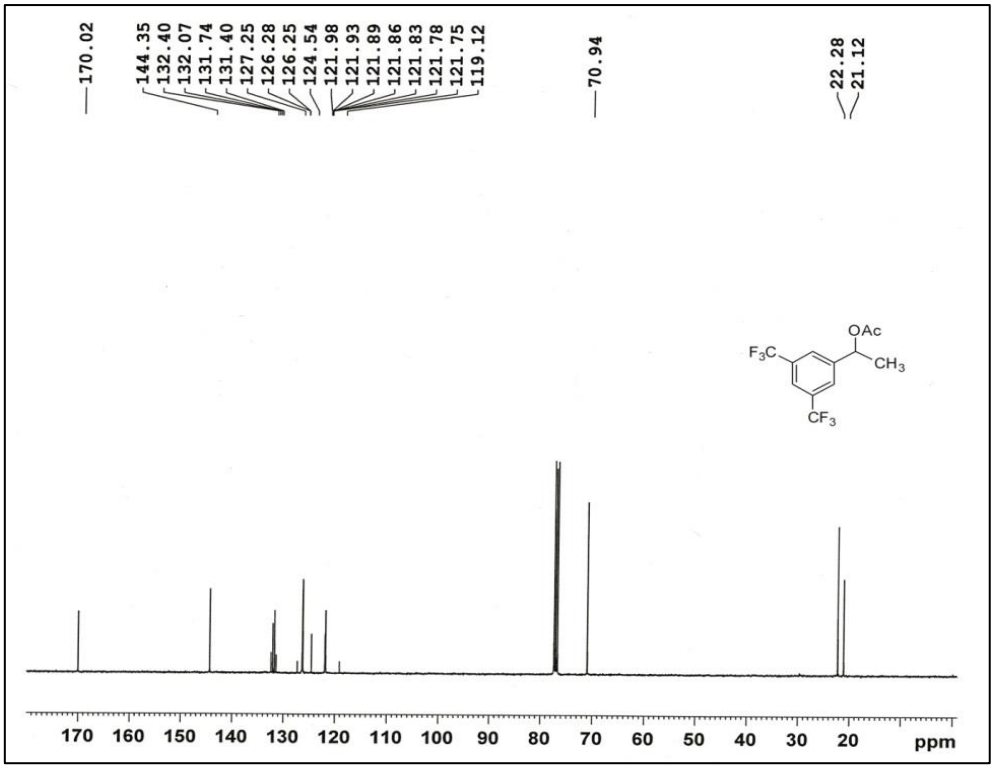
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %	Name
1	10.643	3147729	243696	100.000	100.000	RT10.643
Total		3147729	243696	100.000	100.000	

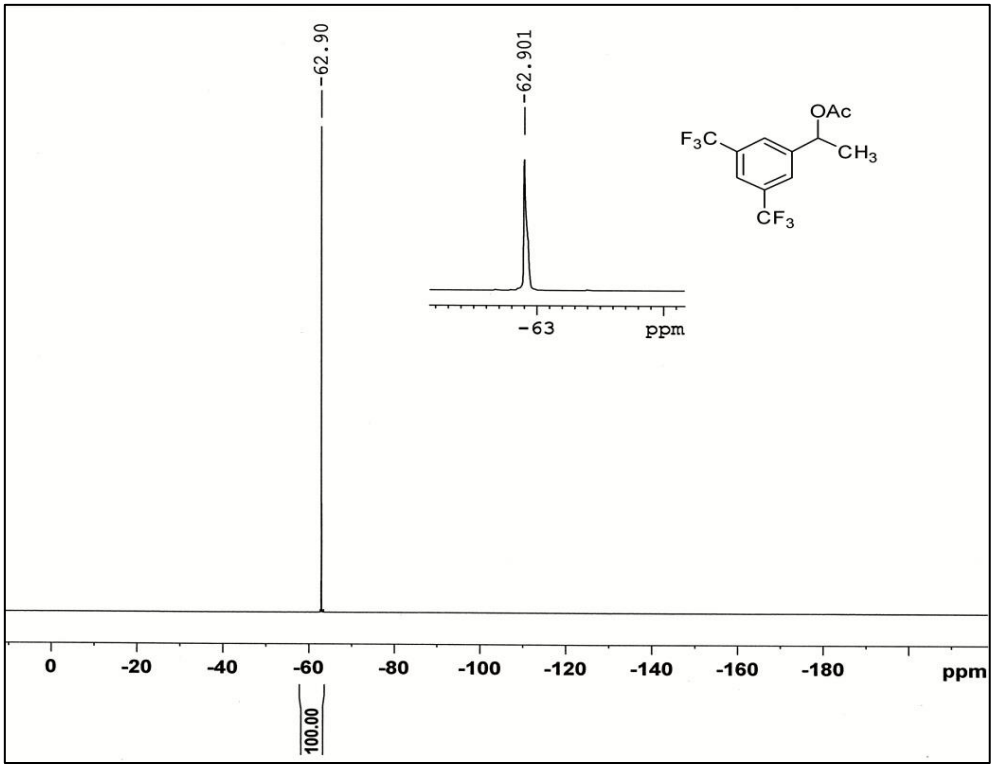
HPLC graph of (*R*)-44



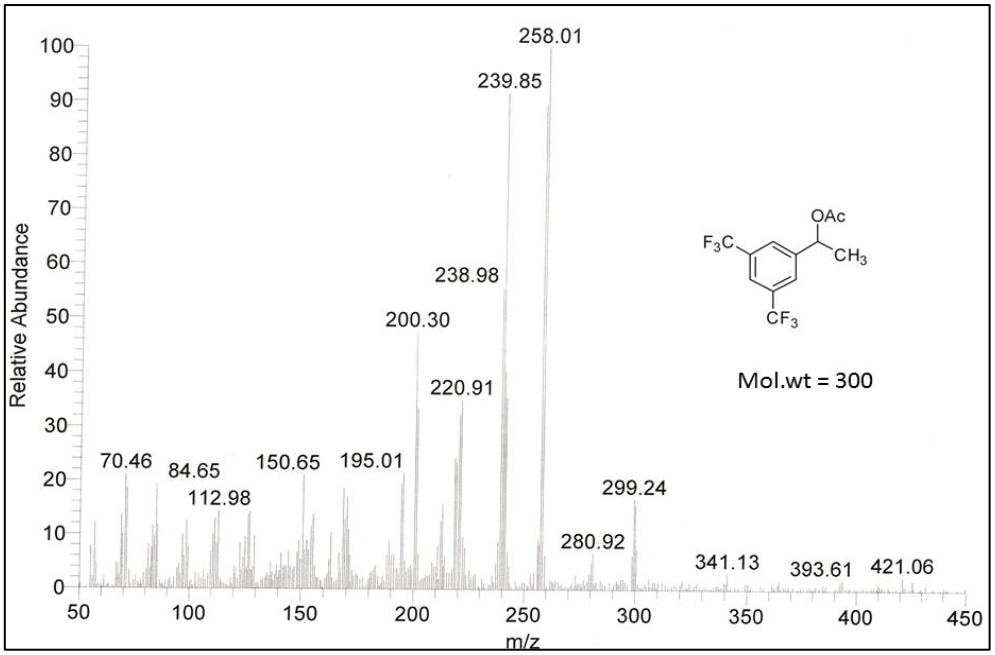
^{1}H NMR spectra of compound 45



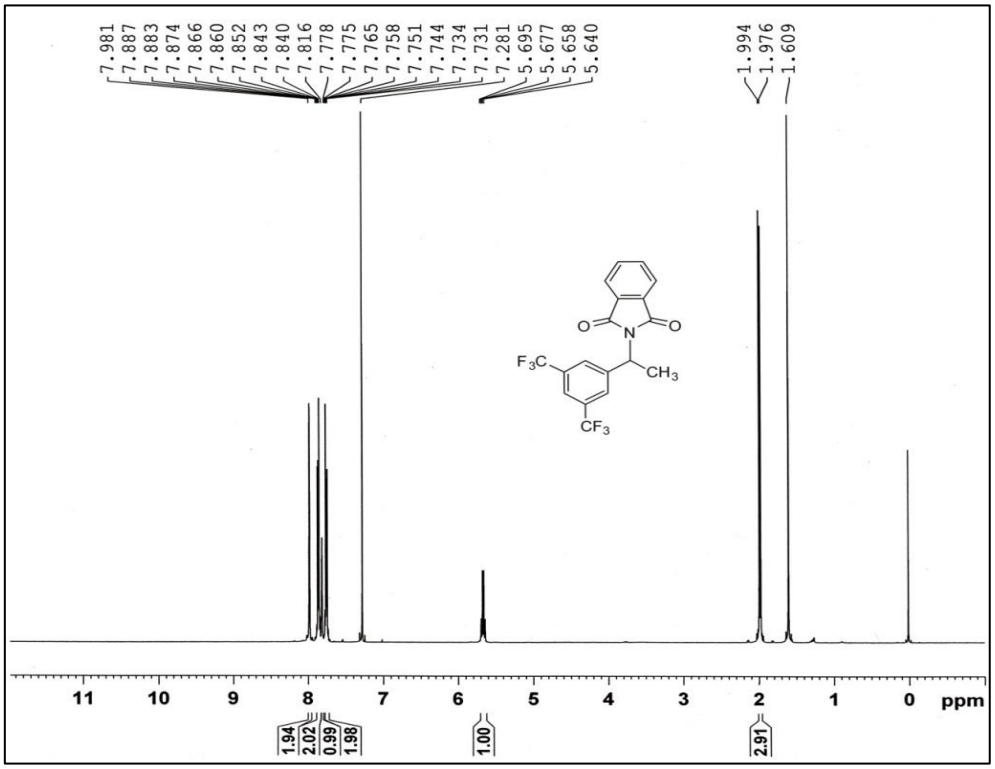
^{13}C NMR spectra of compound 45



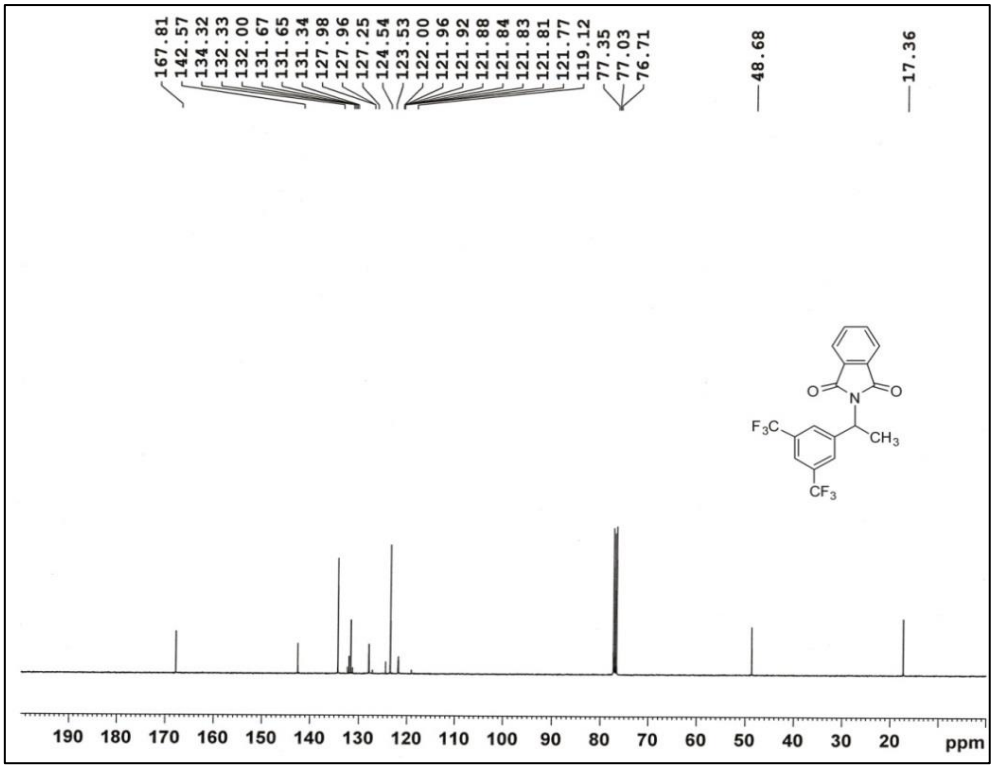
^{19}F NMR spectra of compound 45



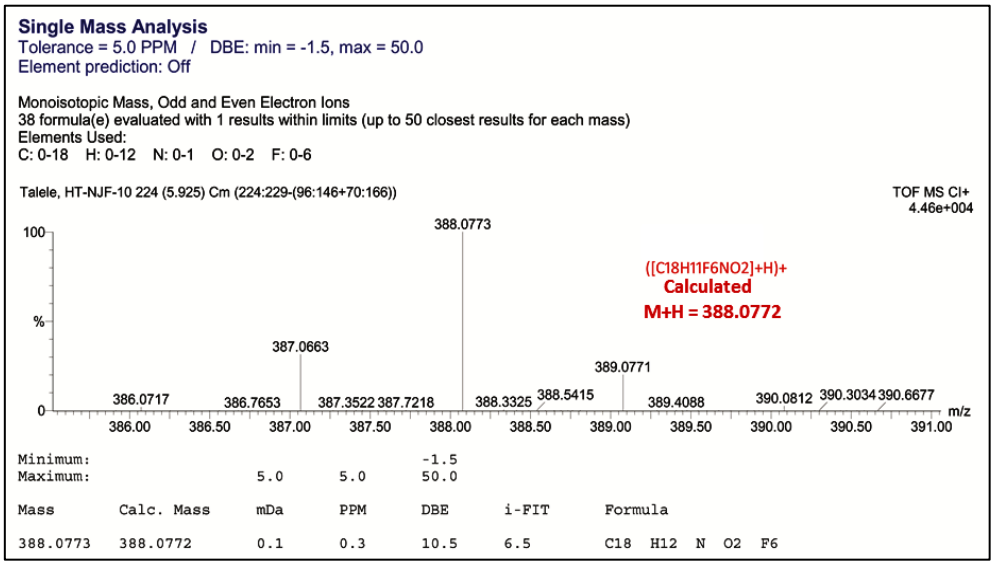
Mass spectra of compound 45



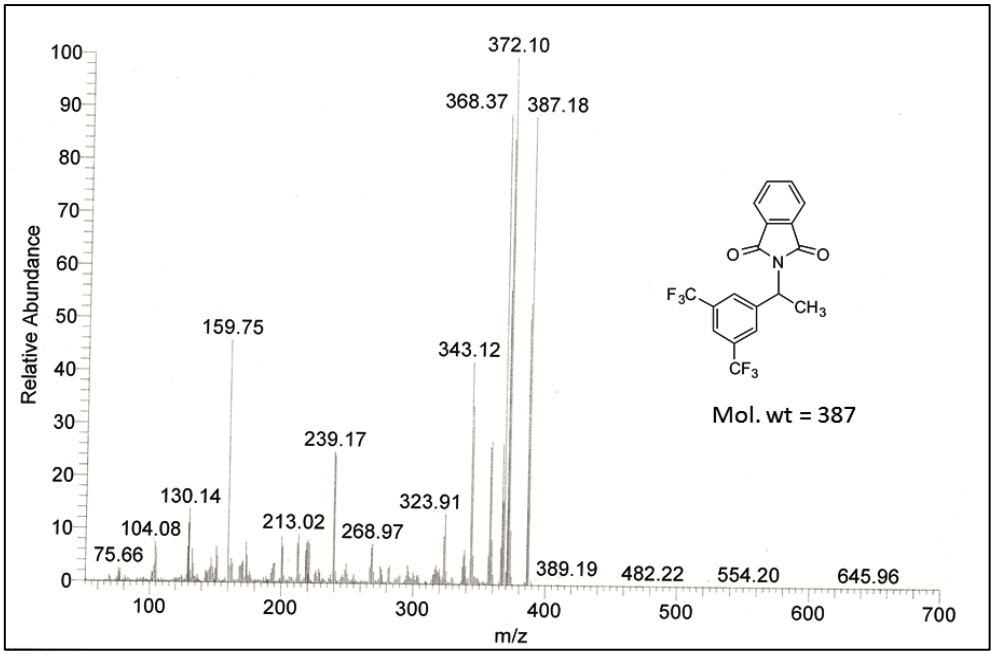
^{1}H NMR spectra of compound 46



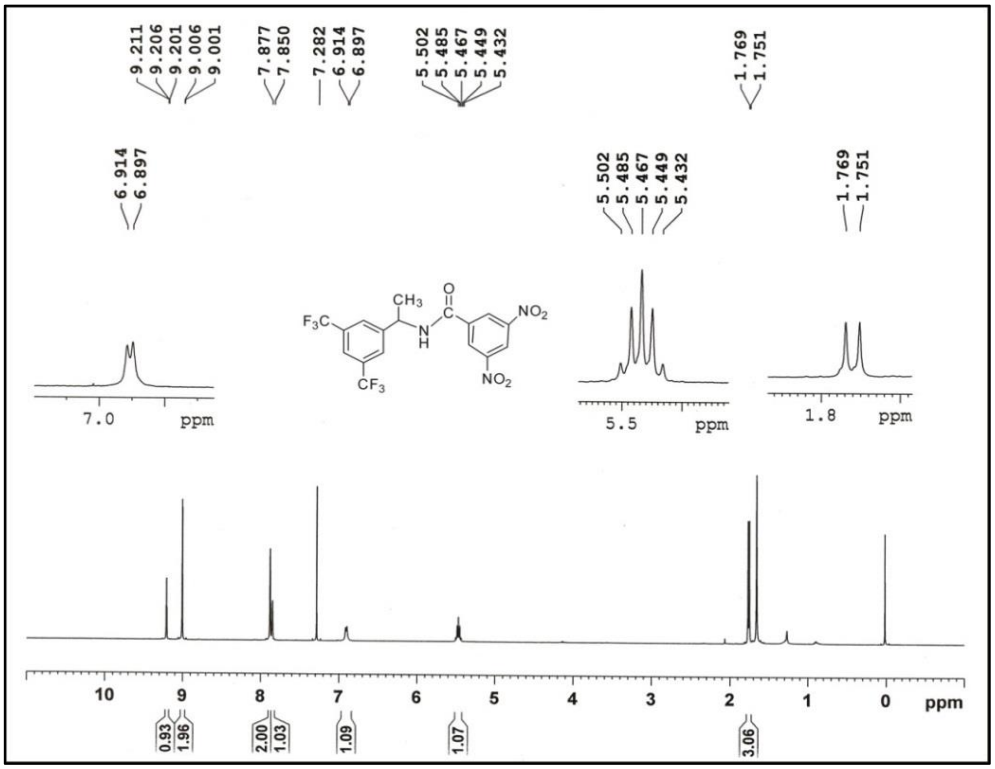
^{13} C NMR spectra of compound 46



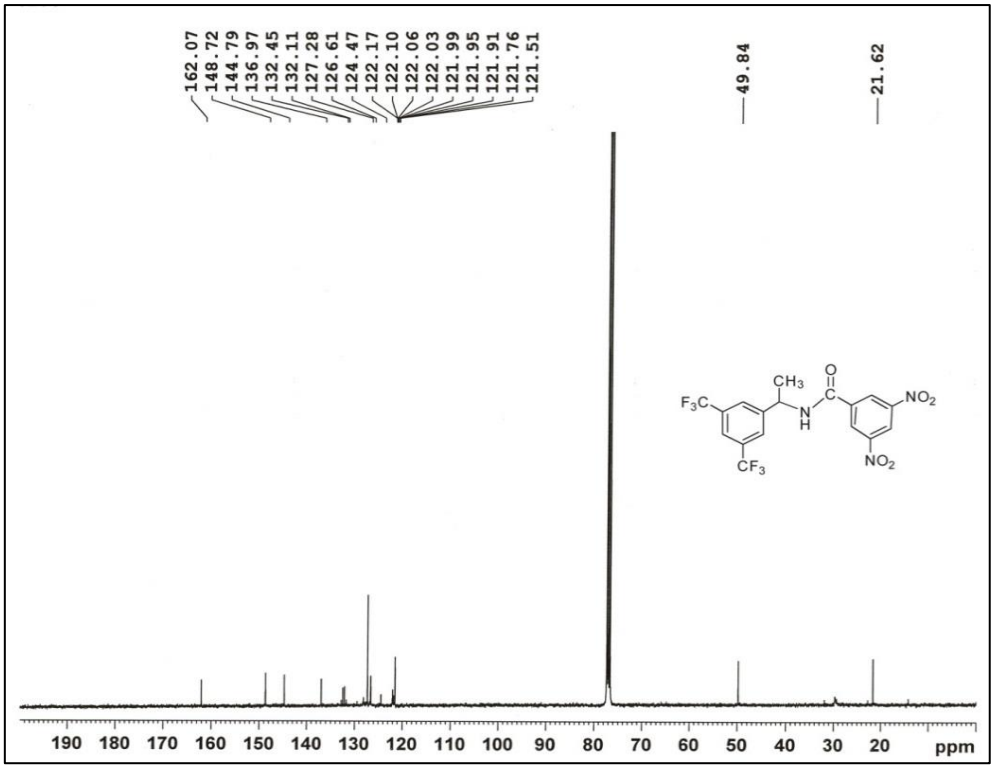
HRMS spectra of compound 46



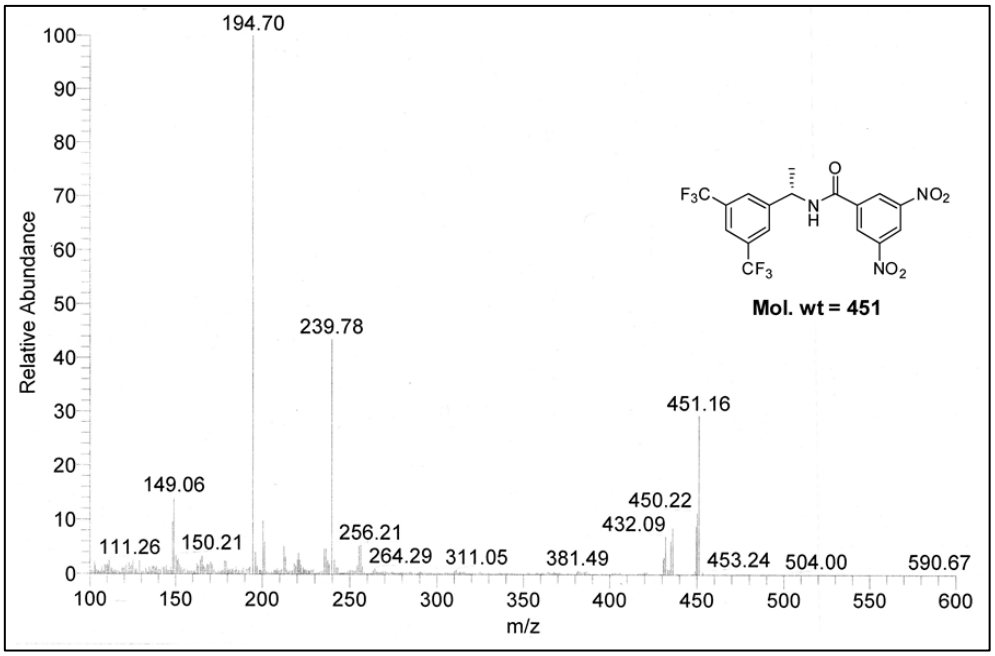
Mass spectra of compound 46



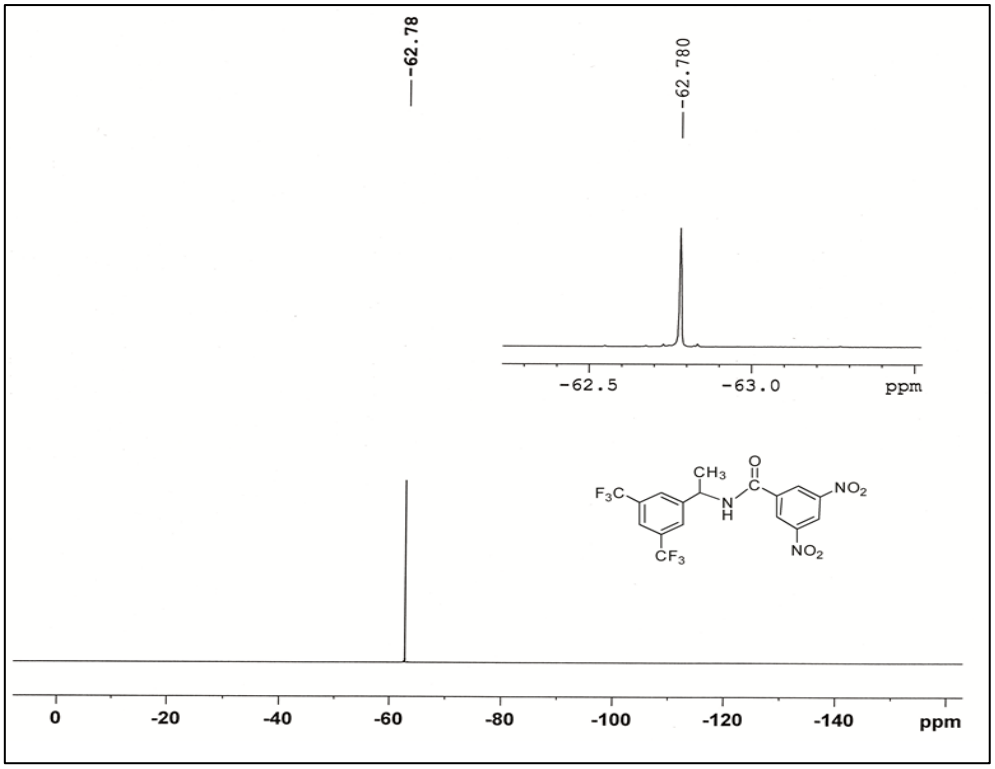
^{1}H NMR spectra of compound 50



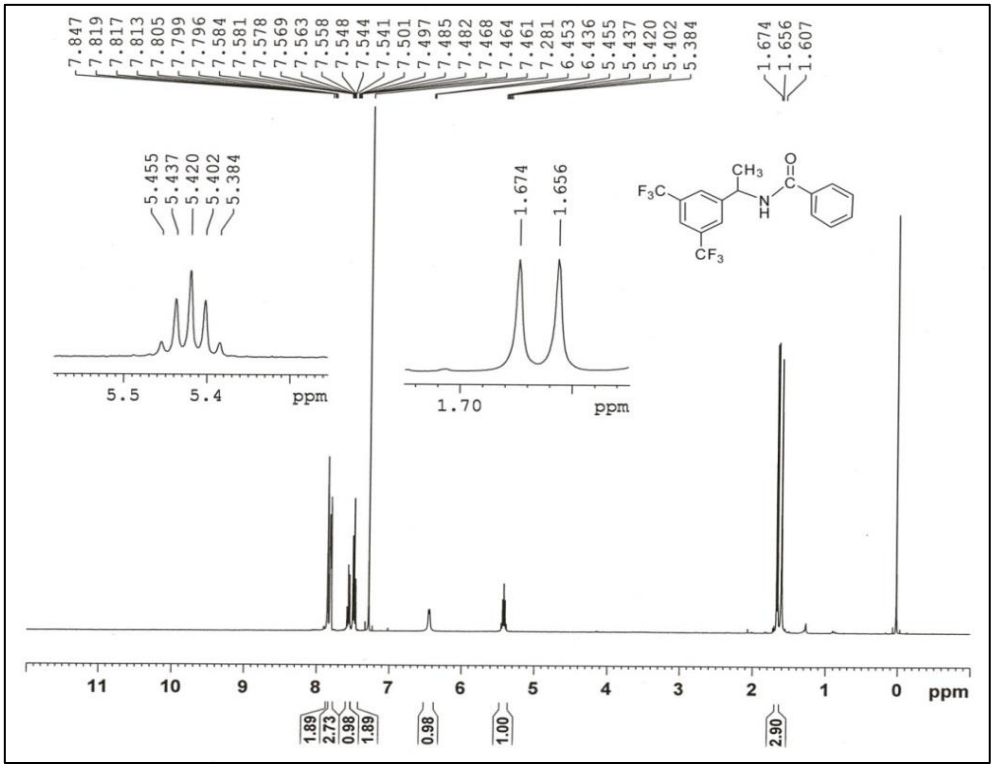
^{13} C NMR spectra of compound 50



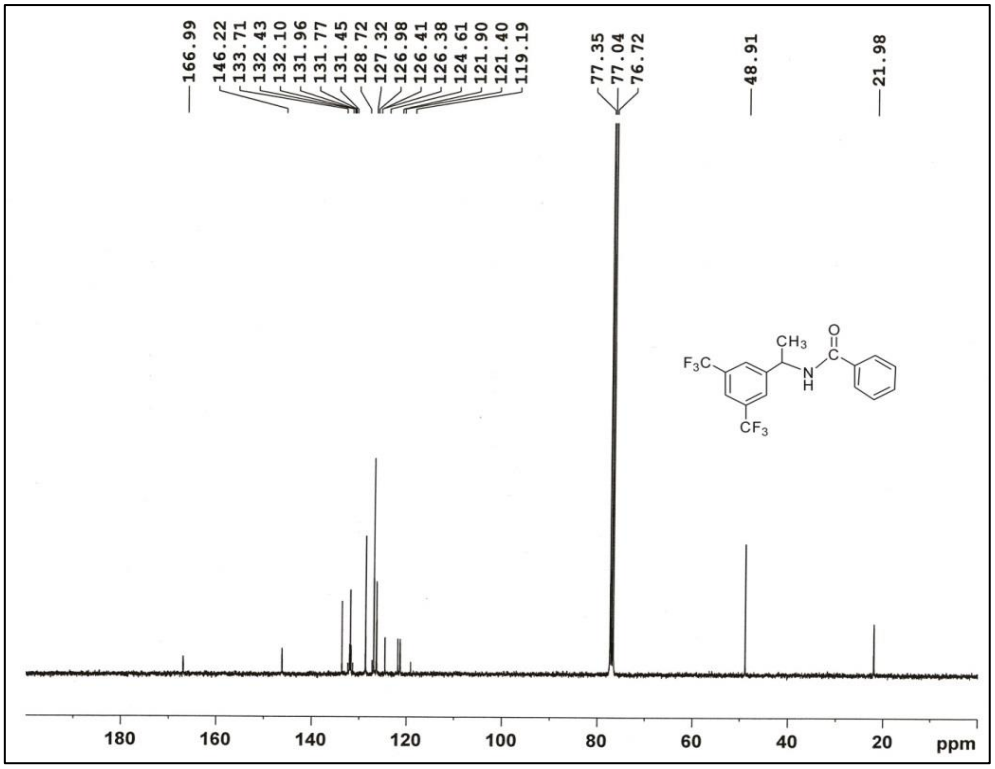
Mass spectra of compound 50



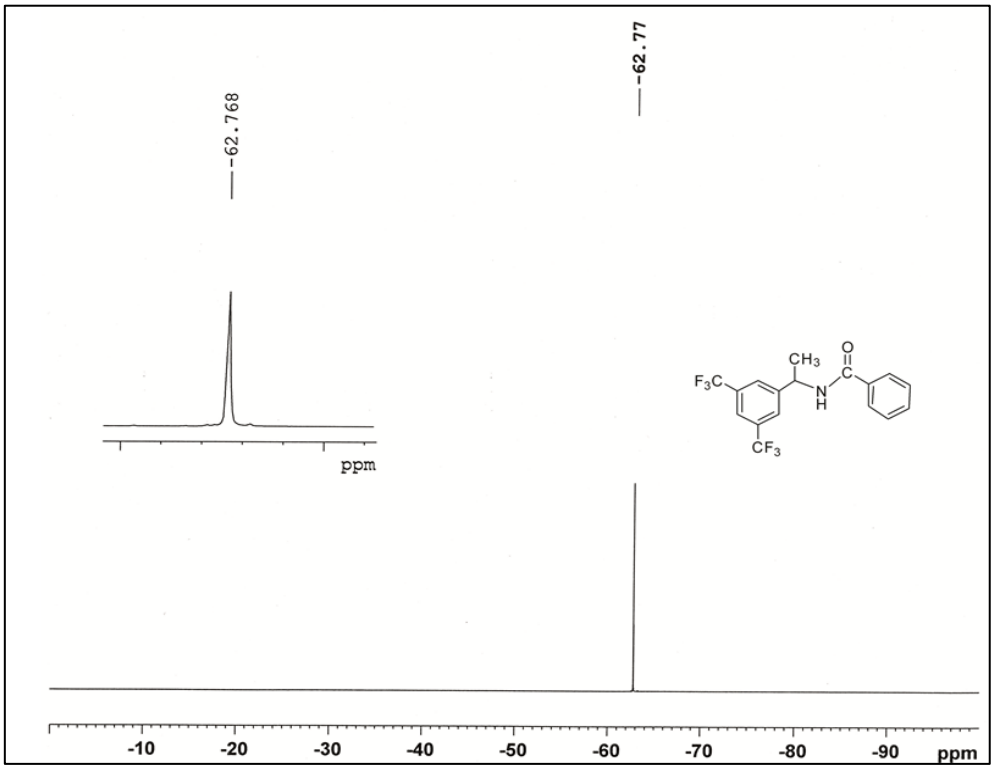
^{19}F NMR spectra of compound 50



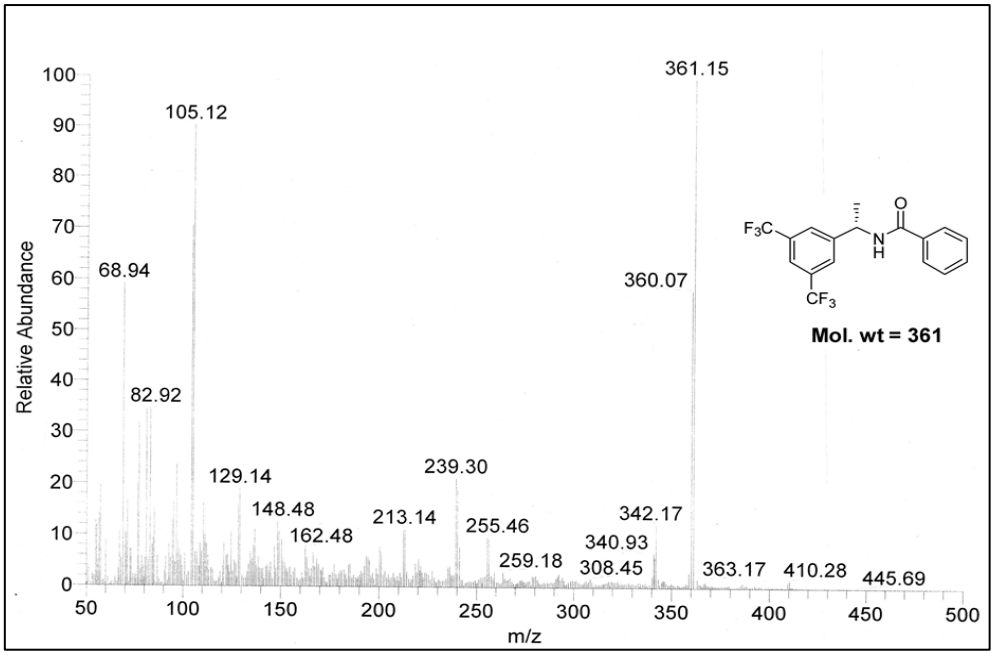
^{1}H NMR analysis of compound 51



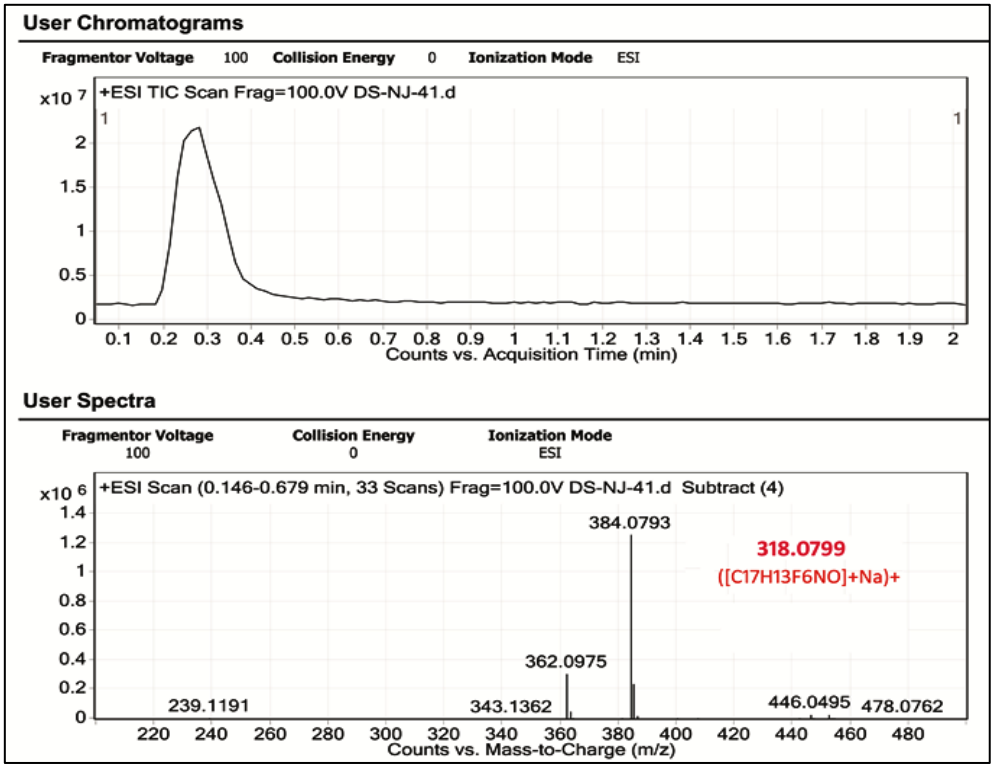
^{13} C NMR analysis of compound 51



^{19}F NMR Spectra of compound 51



Mass spectra of compound 51



HRMS spectra of compound 51

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69. Crystallographic data for the structures of compound (*S*)-**50** have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 1042105). Copies of the data can be obtained from http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CD21EZ, UK (fax: +44-1223-336-033; e-mail: eposit@ccdc.cam.ac.uk