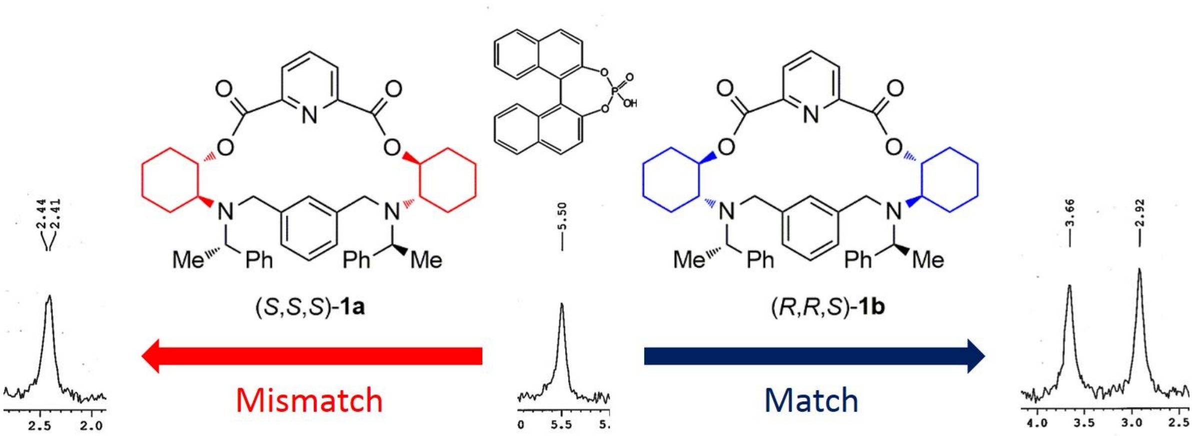
Chapter-2

Synthesis and Application of chiral aza-crown ethers and aza-macrocycles



2.1 Introduction:

Crown ethers and other macrocyclic compounds have a unique place in the field of supramolecular chemistry. These host molecules interact with guest entities by predictable and non-covalent manner. This phenomena has been well studied over the last several decades.[1] Importance of optically active molecules in the field of medicine, fragrance and flavours, material science and supramolecular chemistry has already been well established. The supramolecular interactions in biological systems between the chiral receptors and guest substrates are in general more enantiospecific. Many studies have been conducted on large complex biological assemblies and their interactions based on supramolecular principles.[2]

2.1.1 History of crown ethers:

The field of crown ethers got its impetus since the discovery of dibenzo-18-crown-6 (**1**), by Pedersen in 1967, while trying to prepare a complexing agent for divalent cations.[3] The isolated product showed absence of ionizable hydroxyl groups confirming the cyclic structure. The complexing ability of crown ethers with metals in terms of binding strength and selectivity has since been widely studied. This remarkable selective binding ability of crown ethers has largely contributed to the development of supramolecular chemistry. The chiral recognition ability of crown ethers was studied by Lehn et al in 1975 when they synthesized chiral crown ether (**2**) incorporating L-(+)-Tartaric acid into a macrocyclic system through alkylation of hydroxyl groups. The tetraamide (**2**) derivative was used for complexation with ammonium salt of amino acids.[4] In 1980, Cram and coworkers designed a binol based dilocular crown ether to determine the extent of chiral recognition for amino acid perchlorate salts. The (*RR*)-**3** and (*SS*)-**3** were found to preferentially extract *R* and *S* isomers of amino acids respectively (Figure 2.1).[5]

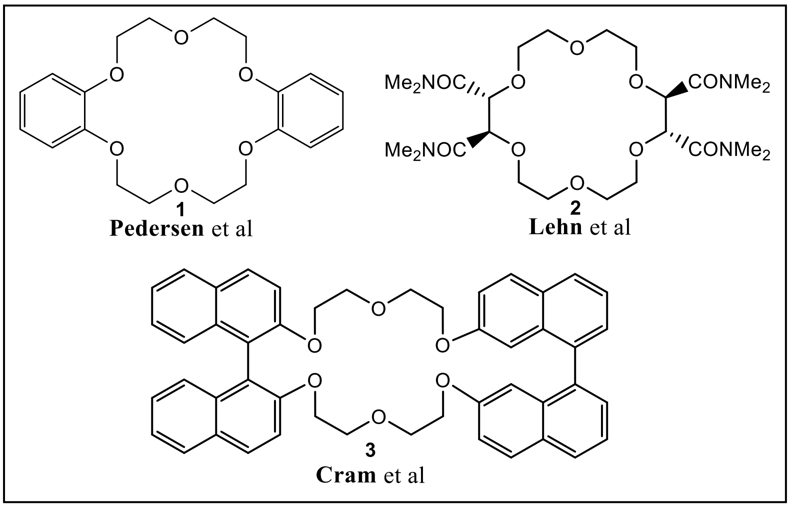


Figure 2.1: Evolution of crown ethers

2.1.2 Aza-crown ethers and aza-macrocycles:

Although crown ethers have been successfully employed for molecular recognition, the application of oxa-crown ethers is limited to ammonium salts. In order to further widen the scope of crown ethers for chiral recognition, aza-crown ethers with nitrogen in the crown ether framework have been introduced. Aza-crown ethers are known to have complexation properties that fall between those of the all-oxygen crowns, which strongly complex alkali and alkaline earth metal ions, and those of the all-nitrogen cyclams, which strongly complex heavy-metal cations. These mixed complexation properties make the aza-crowns interesting to researchers in many areas.[6]

The single and double lariat aza-crown ethers (**4**) and (**5**), by Gokel et al, bearing *N*-pivot dipeptide arms, have been employed in enantioselective transport of benzyloxy-carbonyl-amino acids and dipeptide K^+ carboxylates through a bulky chloroform membrane (Figure 2.2).[7] The aza-crown ethers (**4**) and (**5**) were also known to be efficient carriers with chiral recognition properties. The single-armed (**4**) showed higher transport rates than the double-armed (**5**), but (**5**) exhibited better chiral recognition than the former. The highest enantioselectivity was observed for (**5**) and D,L-Z-α-phenylglycineO^-K^+, giving a ratio of transport rates (L/D) of 1.6. The different transport rates between lariat ethers (**4**) and (**5**) were a result of different numbers of chiral pendant arms. The study indicated that the chiral pendant arm(s) not only participated in interactions with the transported substrates but also resulted in enantiomeric recognition.

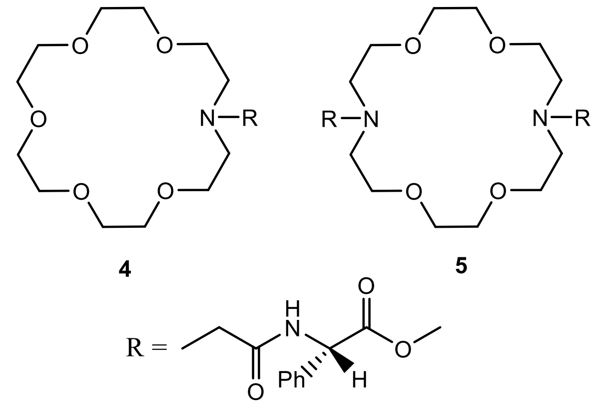


Figure 2.2: Chiral aza-crown ethers for enantioselective ion transport

In 1991, Bradshaw and coworkers synthesized pyridine containing chiral aza-crown ether (**8**) for chiral recognition with organic ammonium salts. These pyridino crowns show appreciable enantiorecognition for ammonium salts on account of stronger complexation and triple hydrogen bond between ammonium cation and pyridine nitrogen atom and alternate oxygen atoms (Figure 2.3).[8]

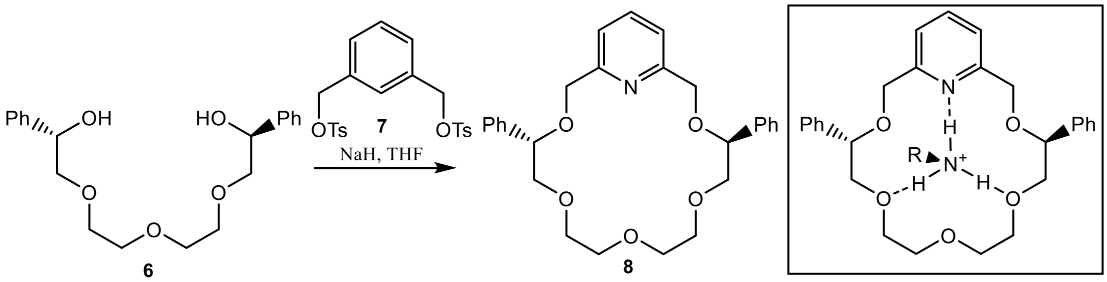


Figure 2.3: Synthesis of pyridine crown ether (**8**) (left); b) probable transition state with triple hydrogen bond with ammonium salt (right).

The synthesis of aza-crown ether have been commonly based on amino acid core attached to glycol subunits. However structural rigidity is an important pre-requisite for molecular recognition. *In general, two factors ensure a fixed conformation of diastereomeric complexes. First, macrocycles should be rather rigid. A rigid macrocycle cannot modify its conformation easily during complexation resulting in a rigid macrocycle complex. Second, a multipoint bonding interaction increases the complex rigidity.*[6b] In order to provide rigidity to macrocyclic system BINOL moiety has been frequently incorporated in crown ethers (Figure 2.4).[5,9]

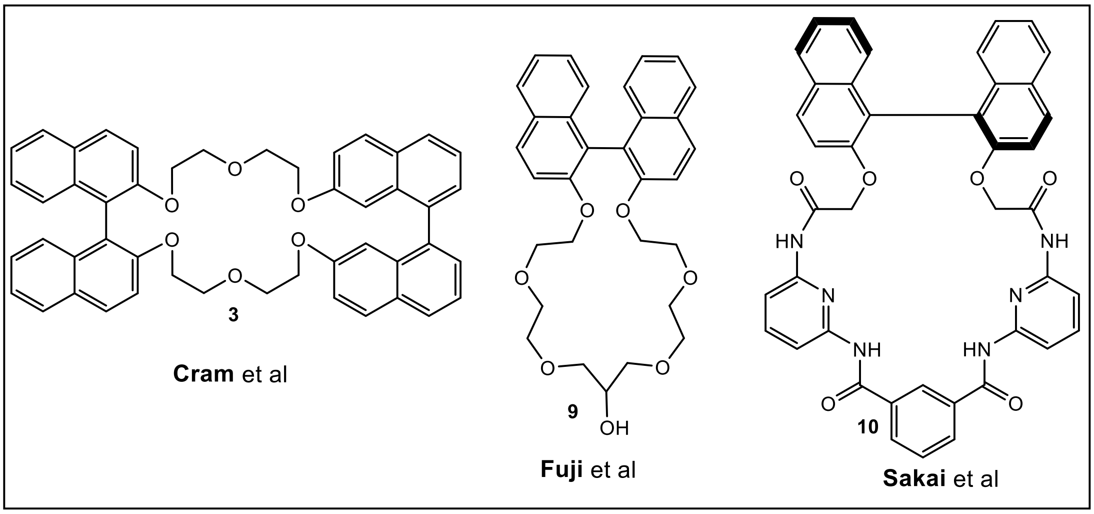


Figure 2.4: BINOL based chiral crown ethers and macrocycle.

2.1.3 Cyclohexane based chiral crown ethers and macrocycles:

Another class of chiral core successfully employed in the synthesis of crown ethers and macrocycles is *trans*-1,2-cyclohexane diamine. The rigidity shown by the crown ether directly bound to a cyclohexyl moiety plays a crucial role in controlling the ability of ligands to complex and transport cations. Some common examples of cyclohexane based chiral crown ethers are listed in Figure 2.5.[10] While most reports of cyclohexane based crown ethers and macrocycles consist of *trans*-1,2-cyclohexane diol and *trans*-1,2-cyclohexane diamine, there are only a few reports of *trans*-2-amino-cyclohexanol.

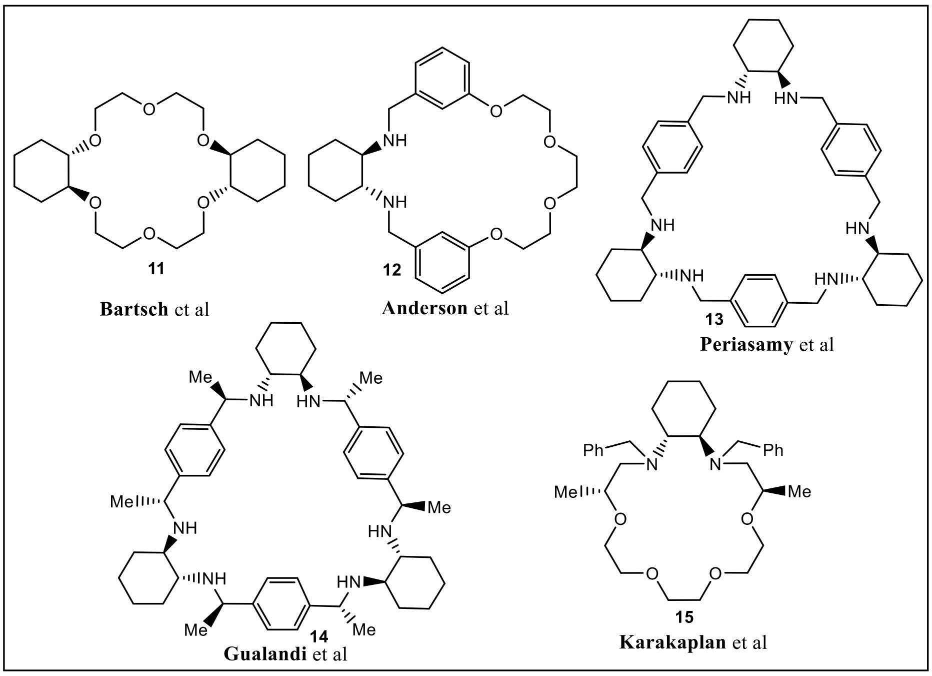


Figure 2.5: Cyclohexane based chiral crown ethers

2.1.4 Concept of Dual Chirality:

Optically active crown ethers and macrocycles can be designed by introducing chirality in the backbone of the ring (Type-A)[4,10b] or by attaching chiral pendent groups (Type-B)[11] to the achiral framework of the crown. The crown ethers and macrocycles can be differentiated based on their chiral core. Additionally some crown ethers have been designed with dual chirality where chiral pendent groups are present along with the chiral backbone (Type-C) (Figure 2.6).[12]

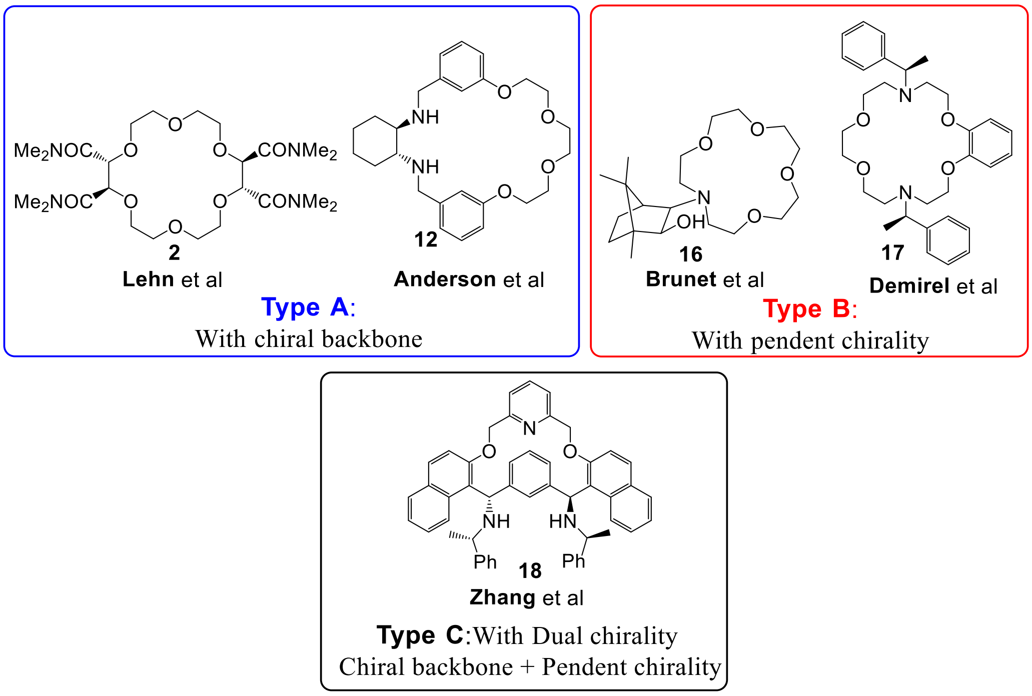


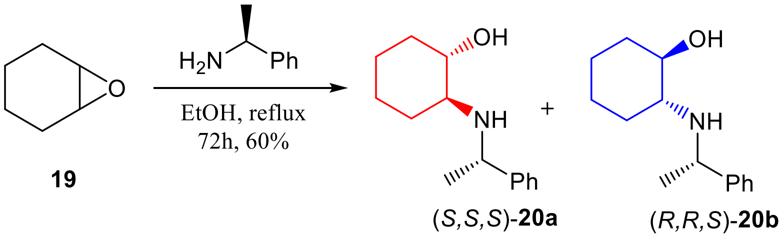
Figure 2.6: Types of Chiral Crown ethers and Macrocycles based on adherent chirality

Here we report synthesis of new chiral aza-crown ethers and aza-macrocycles with chiral backbone along with chiral pendent groups. We propose to evaluate their ability to discriminate chiral organic compounds by NMR and fluorescence spectroscopy. Two chiral elements will allow the study of match - mismatch effect, and further help to fine tune their ability of molecular recognition for suitable applications.

2.2 Result and Discussion:

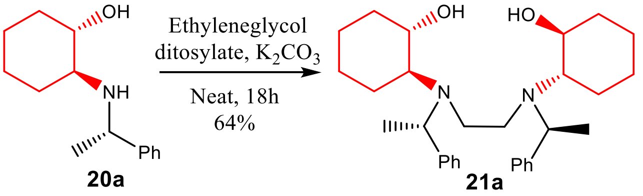
2.2.1 Synthesis of chiral aza-crown ether:

The two diastereomers of the aminocyclohexanol, (**20a**) and (**20b**), were obtained by ring opening reaction of cyclohexene oxide (**19**) with (*S*)-2-phenylethyl amine (Scheme 2.1).[13]



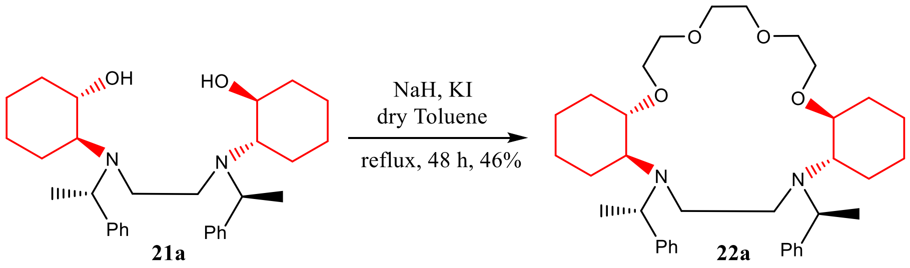
Scheme 2.1: Preparation of amino alcohols from cyclohexeneoxide

The separated diastereomer (**20a**) was converted to building block diamino diol (**21a**) for the synthesis of diaza 18-crown-6 derivative by treatment with ethylene glycol ditosylate and base under neat condition (Scheme 2.2).



Scheme 2.2: Synthesis of diamino diol building block (**21a**).

The diamino diol (**21a**) was treated with triethylene glycol ditosylate in dry toluene in presence of NaH for 48h resulting in formation of diazacrown ethers (**22a**). The reaction was observed to progress upon the addition of KI. The reaction mixture upon column chromatography yielded desired chiral aza-crown ether (Scheme 2.3).



Scheme 2.3: Synthesis of aza-crown ethers (**22a**).

2.2.2 Application of chiral aza-crown ether (22a) as Chiral Solvating Agent:

An important feature of asymmetric synthesis is the determination of enantiomeric purity. α-substituted chiral acids have been frequently utilized in synthesis of various important intermediates and drug molecules. Thus, quick determination of optical purity of these compounds is essential from synthetic point of view. With this aim the synthesized chiral crown ether (**22a**) has been employed as chiral solvating agent for chiral recognition of few representative acid analytes (Figure 2.7).

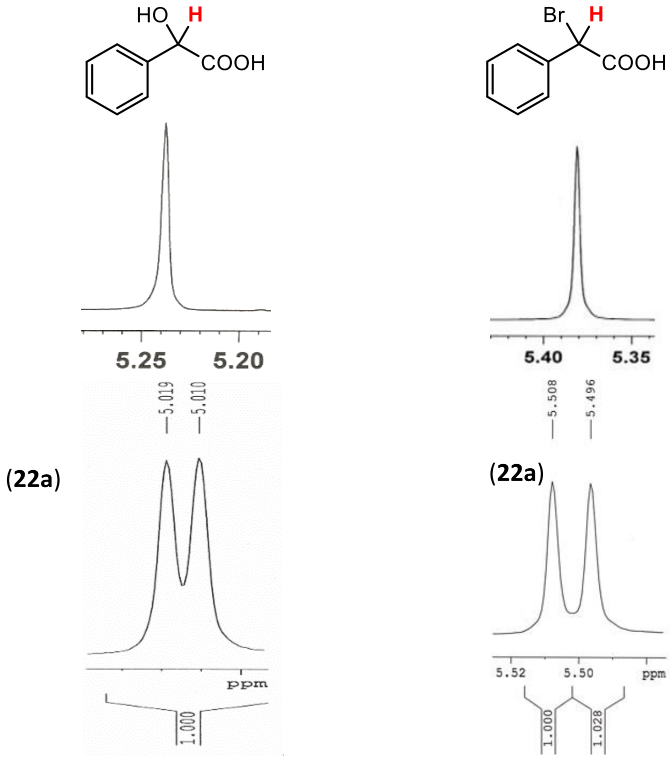
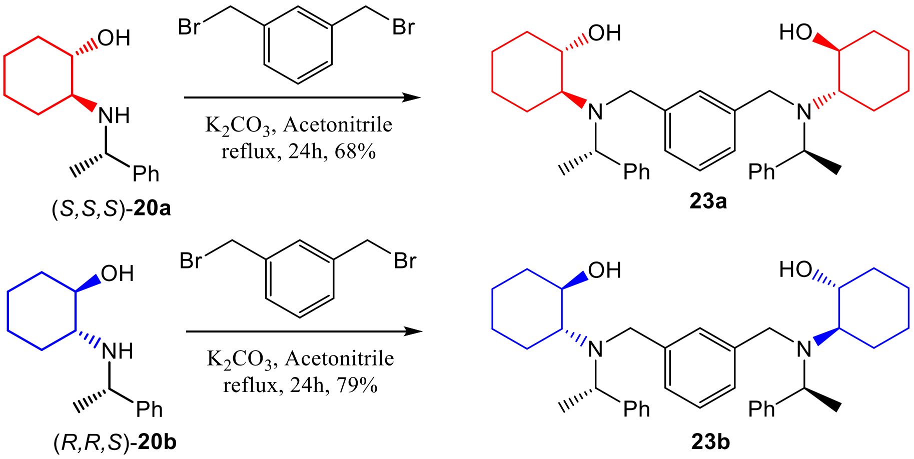


Figure 2.7: Selected ^{1}H NMR region of mandelic acid with (**22a**) left; and α-bromo phenylacetic acid with (**22a**)

2.2.3 Synthesis of chiral aza-crown ethers (24) and (25) with aromatic linkers:

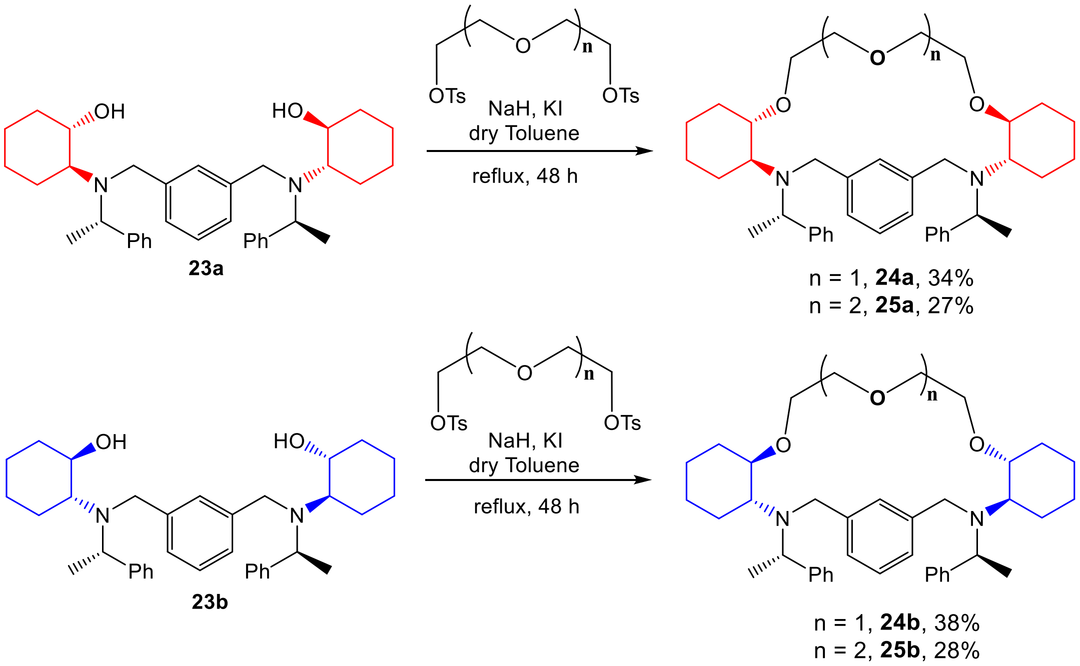
The aza-crown ether (**22a**) exhibited low separation of $C_\alpha H$ signal for mandelic acid while the resolution in case of α-bromo-phenylacetic acid was moderate. This result may be attributed to lack of aromatic ring in the core of crown ether which eliminates the possibility of π-π and C*H*-π interactions. Considering this, a new class of chiral aza-crown ethers (**24**) and (**25**) were designed with aromatic linkers which should enable better enantiomeric recognition on account of favorable non-covalent interactions.

The two separated diastereomers (**20a**) were condensed with *m*-xylene dibromide in presence of K_2CO_3 in acetonitrile resulting in formation of diamino diol (**23a**). The other diastereomer of amino alcohol (**20b**) yielded the diastereomeric diol (**23b**) (Scheme 2.4).



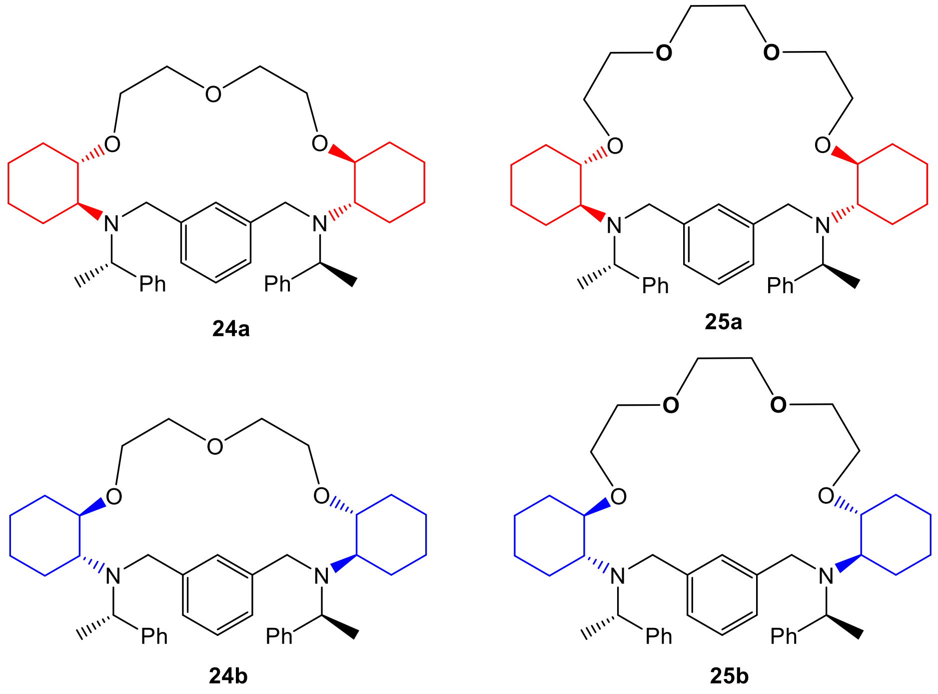
Scheme 2.4: Synthesis of diamino diol (**23a**) and (**23b**).

The synthesized diastereomeric diols were then converted to aza-crown ethers by subsequent cyclization with diethylene glycol ditosylate and triethyleneglycol ditosylate in presence of NaH and KI resulting in formation of aza-crown ethers (**24**) and (**25**) respectively (Scheme 2.5). The structures of crown ethers (**24**) and (**25**) are presented in (Chart 2.1).



Scheme 2.5: Synthesis of diastereomeric aza-crown ethers (**24**) and (**25**).

Chart 2.1: Structures of aza-crown ether (**24**) and (**25**).



2.2.4 Application as Chiral Solvating Agent:

Chiral aza-crown ethers[14] and aza-macrocycles[15] have been prominently explored as CSA for molecular recognition of chiral analytes. The diastereomeric crown ethers (**24**) and (**25**) were screened as chiral solvating agents for mandelic acid and binaphthyl phosphoric acid. The crown ethers (**24a**) and (**25a**) showed separation for mandelic acid while the other diastereomers (**24b**) and (**25b**) showed no separation which indicates the possibility of match-mismatch effect. In case of binaphthyl phosphoric acid, the crown ether (**24a**) showed good baseline separation while the other diastereomer (**24b**) was found to be ineffective. The diastereomeric crown ethers (**25**) showed no separation for binaphthyl phosphoric acid which may be due to increased flexibility caused by triethylene glycol sub-unit or larger cavity (Figure 2.8).

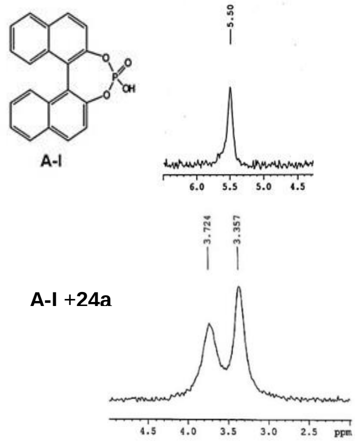
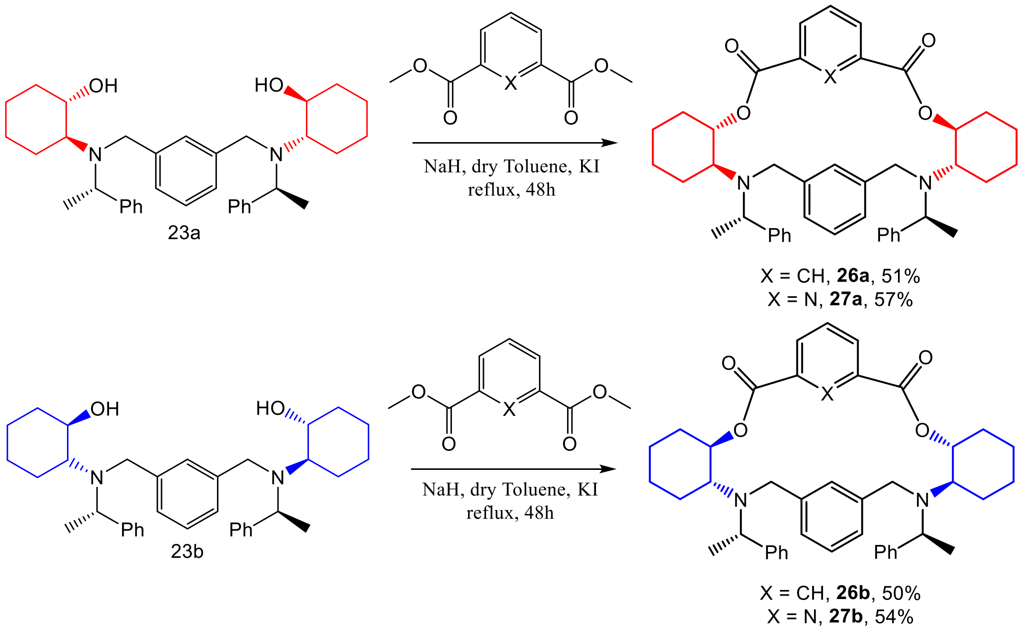


Figure 2.8: ^{31}P NMR Spectra of binaphthyl phosphoric acid with crown ether (**24a**).

2.2.5 Synthesis of Chiral Aza-macrocycles:

The limited conformational flexibility of diastereomeric host-guest complexes is an important factor in obtaining good enantiomeric recognition. If the conformation of the complexes is flexible, both enantiomers can find a proper position to interact with the macrocyclic ligand and avoid the large steric hindrance caused by the chiral centers. Thus for efficient enantiomeric recognition, low flexibility of the diastereomeric complexes would be better.

In order to increase the rigidity of macrocyclic ring the ethylene glycol unit was replaced with aromatic diester system. The diamino diol (**23**) was subjected to transesterification with dimethyl-isophthalate and pyridine-2,6-dimethyl-carboxylate yielding macrocyclic diesters (**26**) and (**27**) (Scheme 2.6).



Scheme 2.6: Synthesis of aza-macrocycles (**26**) and (**27**).

Single crystal X-ray analysis of both the diastereomers of macrocycles revealed interesting features. In case of (*S*,*S*,*S*)-**26a** the phenyl unit of the pendent groups were seen to lie on the top and cover the bottom of the macrocyclic cavity making the cavity less accessible for interaction with guest molecules while in case of (*R*,*R*,*S*)-**26b** they appear to be away which makes the cavity easily available for non-covalent interactions with the chiral guest analytes. (Figure 2.9). Also the crystal structure of macrocycles (**27a**) and (**27b**) exhibit similar structural features as observed in case of macrocycles (**26a**) and (**26b**) respectively (Figure 3.0).

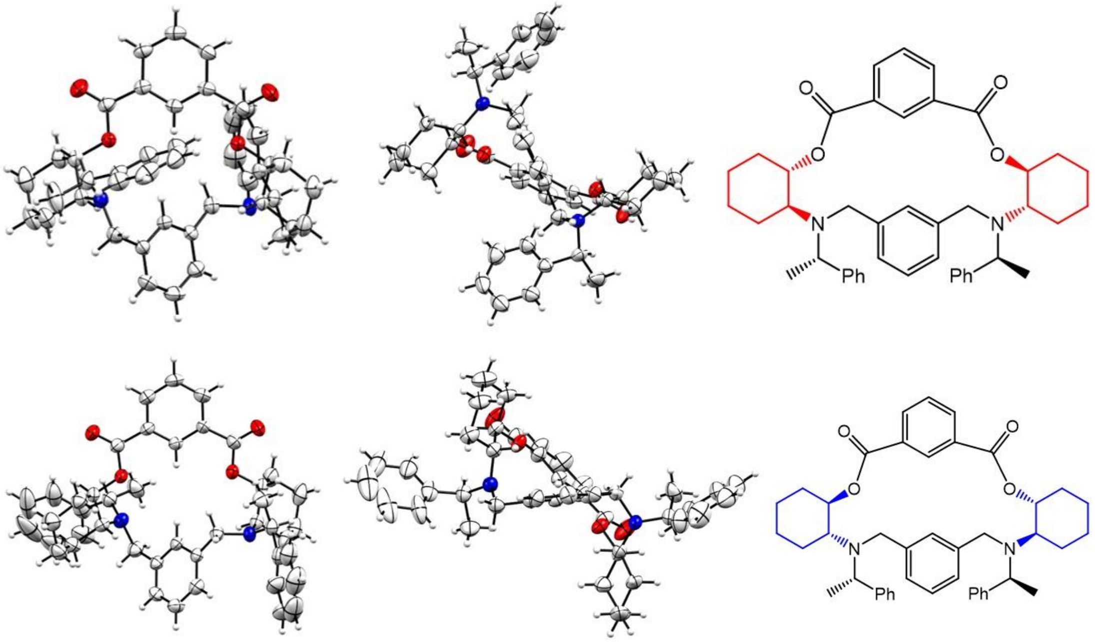


Figure 2.9: a) X-ray structure of macrocycle (**26a**) revealing partially closed cavity (top); b) X-ray structure of macrocycle (**26b**) with open cavity (bottom).

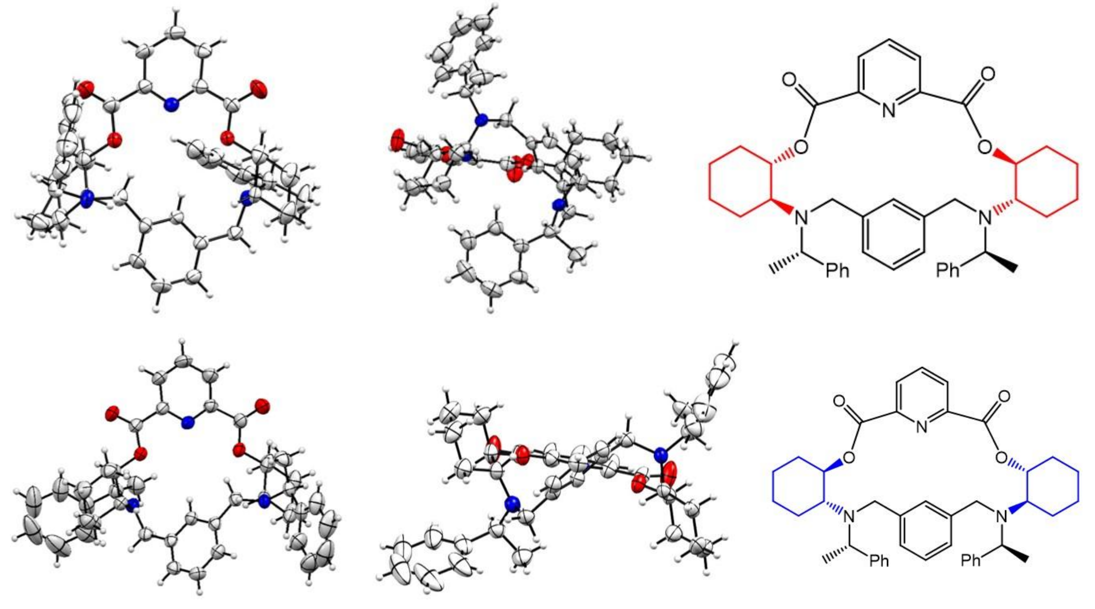


Figure 2.10: a) X-ray structure of macrocycle (**27a**) revealing partially closed cavity (top); b) X-ray structure of macrocycle (**27b**) with open cavity (bottom).

2.2.6 Applications of Chiral Aza-macrocycles (26):

Recently chiral Brønsted acids such as phosphoric acid derivative 1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate **A-I** and its analogues have found wide uses as chiral catalysts.[16] Chiral ligands based on organic phosphoric acids have been synthesized for asymmetric reactions. There can be three different types of chiral organic phosphorous containing acid derivatives (Chart 2.2).

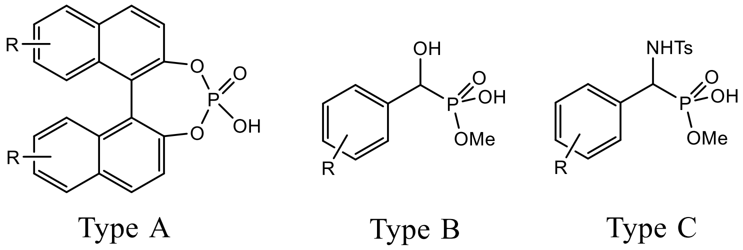


Chart 2.1: Types of phosphorous containing analytes

The chiral diastereomeric macrocycles (**26a**) and (**26b**) have been screened for molecular recognition of **A-I** by UV-Vis spectroscopy. The macrocycle (**26a**) with partially open cavity when treated with the enantiomers of **A-I**, exhibited lesser separation as compared to macrocycle (**26b**) (Figure 2.11).

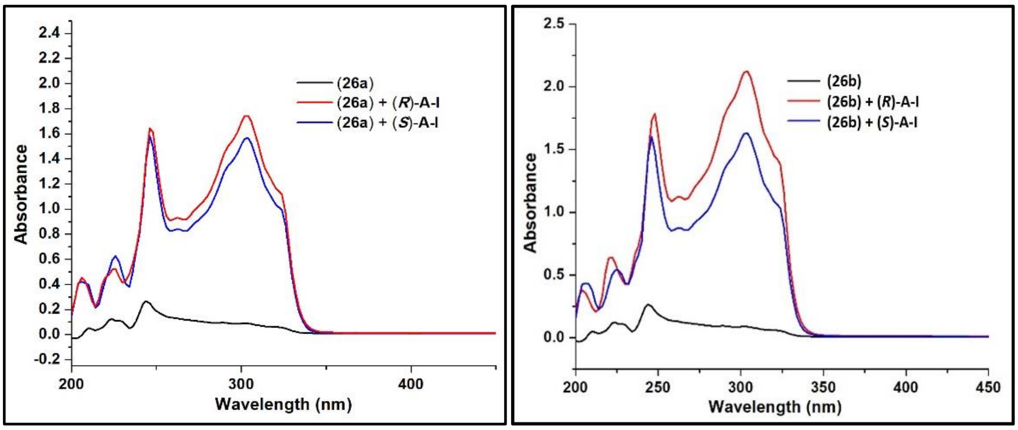


Figure 2.11: a) UV-Vis Spectra of (*R*) and (*S*)-**A-I** with (**26a**) left; UV-Vis Spectra of (*R*) and (*S*)-**A-I** with (**26b**).

Although macrocycle (**26b**) shows better recognition for binaphthyl phosphoric acid **A-I** as compared to macrocycle (**26a**), the extent of recognition is not very high. Considering this aspect, the macrocycles were screened for their ability to distinguish the isomers of **A-I** by fluorescence spectroscopy. In this study the fluorescence property of the analyte **A-I** was utilized to evaluate the interactions with the two isomers of macrocycles (**26**). The isomers of **A-I** were subjected to discrimination using diastereomeric macrocycles (**26a**) and (**26b**) and the relative quenching of fluorescence signal due to **A-I** was observed (Figure 2.12). The fluorescence spectra clearly indicates better recognition with macrocycle (**26b**) with open cavity which enables better interactions between chiral cavity and binaphthyl skeleton.

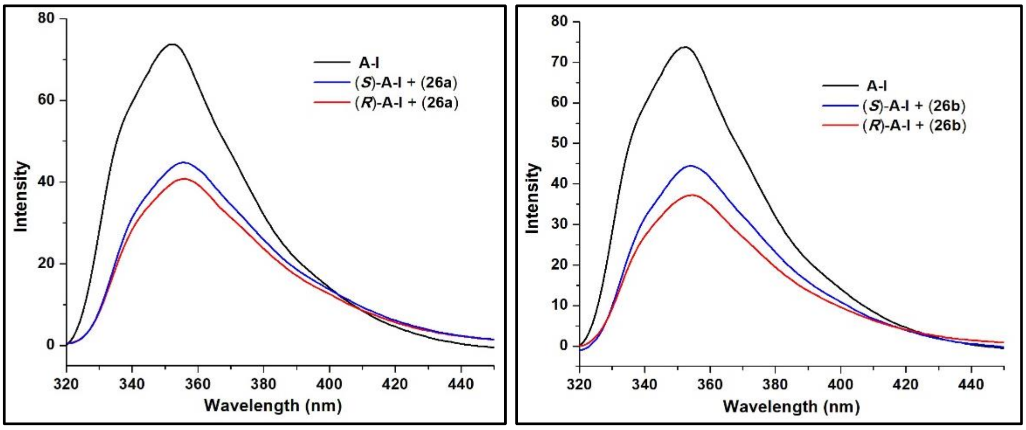
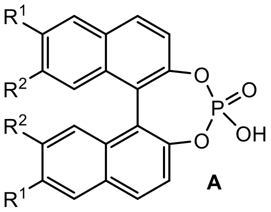


Figure 2.12: a) Fluorescence Spectra of (*R*) and (*S*)-**A-I** with (**26a**) left; Fluorescence Spectra of (*R*) and (*S*)-**A-I** with (**26b**).

In order to further improve the molecular recognition for binaphthyl phosphoric acid **A-I**, the other set of macrocycles with pyridine ring providing additional anchoring site were employed. The quick determination of optical purity of these binaphthyl phosphoric acid analogs is equally important. The two derivatives of (**27**) were screened to study their ability to discriminate the ^{31}P NMR signals[17] of derivatives of **A-I** by measuring the chemical shift non-equivalence (ΔΔδ) (Table 1)



A

Table 2.1: Discrimination of Binaphthyl phosphoric acid[a]

No	Comd. No.	R^1	R^2	(ΔΔδ) ppm	
				(*S,S,S*)-**27a**	(*R,R,S*)-**27b**
1	**A-I**	H	H	0.003	0.74
2	**A-II**	H	OMe	--[b]	0.68
3	**A-III**	H	O^{i}Pr	--[b]	0.76
4	**A-IV**	NO_2	H	--[b]	0.81
5	**A-V**	Br	H	--[b]	0.40

[a]In $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR), ratio of **A:27** (2:1); [b]Not resolved.

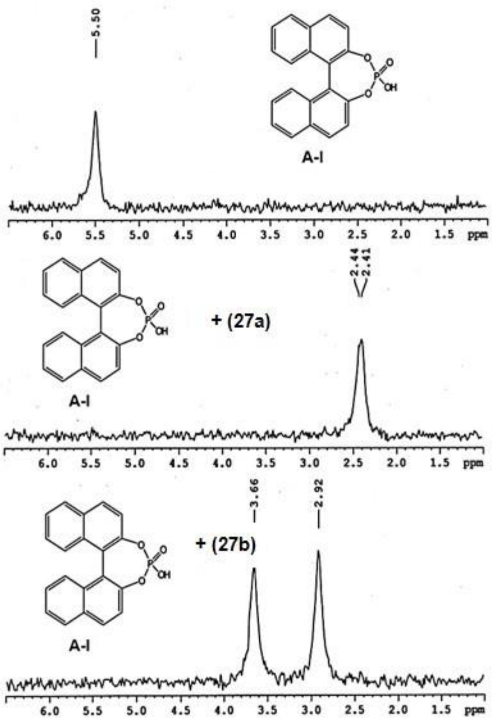


Figure 2.13: Selected region of ^{31}P NMR Spectra of **A-I** blank (top); **A-I** with (**27a**) (middle) and **A-I** with (**27b**) bottom.

A clear pattern of better discrimination for (*R*,*R*,*S*)-**27b** was observed in all the examples, while the other derivative (*S*,*S*,*S*)-**27a**, with closed cavity was found ineffective (Figure 2.13). The separation of signals was further studied to establish linear relationship between experimental and actual values of optical purity for establishing practical utility of CSA (Figure 2.14).

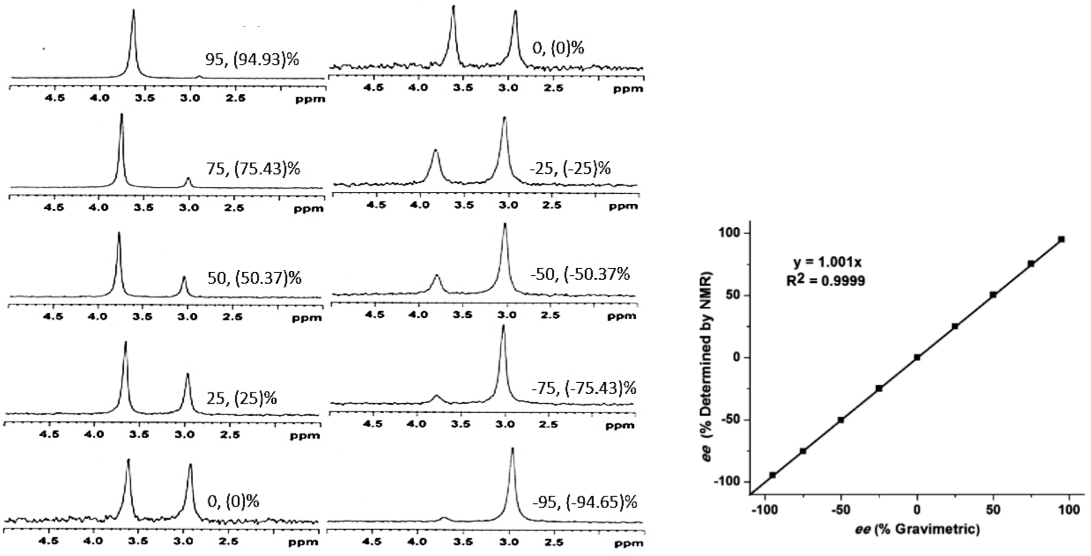


Figure 2.14: Selected region of ^{31}P NMR spectra of scalemic mixture of **A-I** in presence of **27b** (Left) and its correlation between theoretical and observed % *ee* values (Right).

The nature of complex between **A-I** and the isomers of macrocycle was determined by IR spectroscopy. Complex of **A-I** with (**27a**) showed a weak band at 1098 cm-1 for phosphoryl bond stretching,[18] but appears much stronger for (**27b**). This may indicate a better complexation in case of (**27b**) supporting the observation (Figure 2.15).

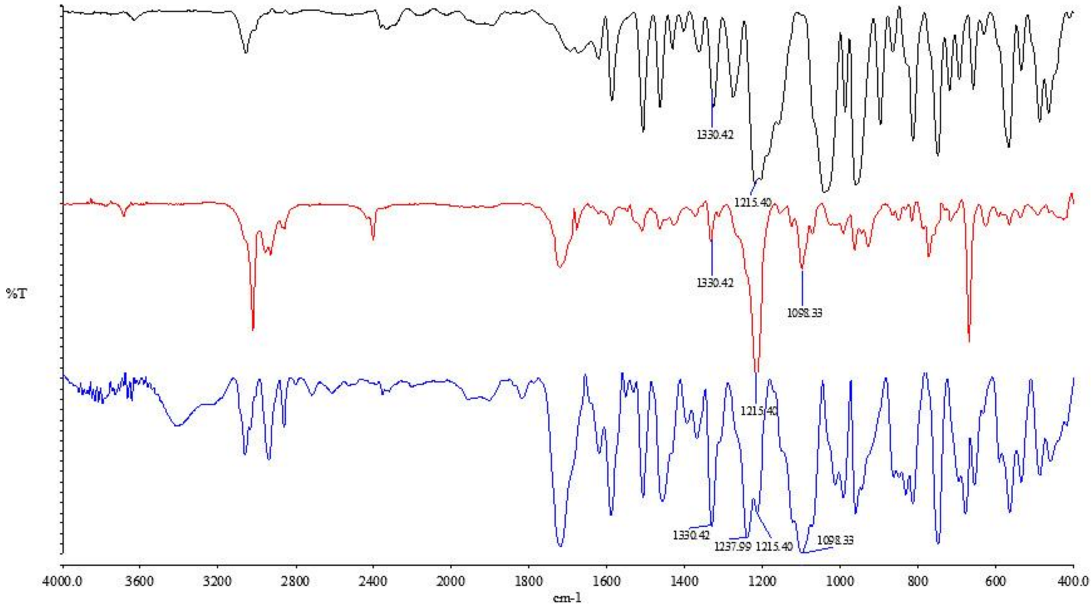


Figure 2.15: IR Spectra of **A-I** blank (top); **A-I** with (**27a**) middle and **A-I** with (**27b**) bottom

Use of fluorescence spectroscopy for understanding the recognition of chiral molecules has received considerable attention.[19] Many chiral fluorescent host molecules have been known to exhibit enantioselective quenching[19c] or enhancement[19g] on interaction with chiral guests. Such chirality dependent quenching of both enantiomers of **A-I** in presence of macrocycles (**27a**) and (**27b**) have been investigated. The recognition ability of macrocycles towards the phosphoric acid was evident from the extent of quenching (Figure 2.16). The macrocycle (**27b**) showed greater extent of fluorescence quenching as compared to macrocycle (**27a**) which is in agreement with the ^{31}P NMR results. The static quenching is probably attributed to the deprotonation of phosphoric acid **A-I**, which is indicated by appearance of new peak in the UV-Vis spectra[19c] (at the higher wavelength at 327 nm).

The response of quenching the emission of enantiomers of **A-I** with (**27**) follows the Stern-Völmer equation. The fluorescence quenching efficiency can be expressed as a ratio of $K_{sv}^{(R)\ \mathbf{A\text{-}I}}/K_{sv}^{(S)\ \mathbf{A\text{-}I}}$ which was observed to be 1.05 (Figure 2.16) for macrocycle (**27a**). On the other hand quenching of enantiomers of **A-I** with the other macrocycle

(**27b**) indicated the ratio $K_{sv}^{(R)\ \mathbf{A\text{-}I}}/K_{sv}^{(S)\ \mathbf{A\text{-}I}}$ to be 1.40 (Figure 2.17), indicating its higher quenching ability.[18] This data confirms the recognition observed in ^{31}P NMR analysis. These observations substantiate the assumption that the relatively open cavity of (**27b**) facilitates efficient complexation between protonated macrocycle and phosphate ion as well as π-π interaction of naphthyl ring of **A-I**.

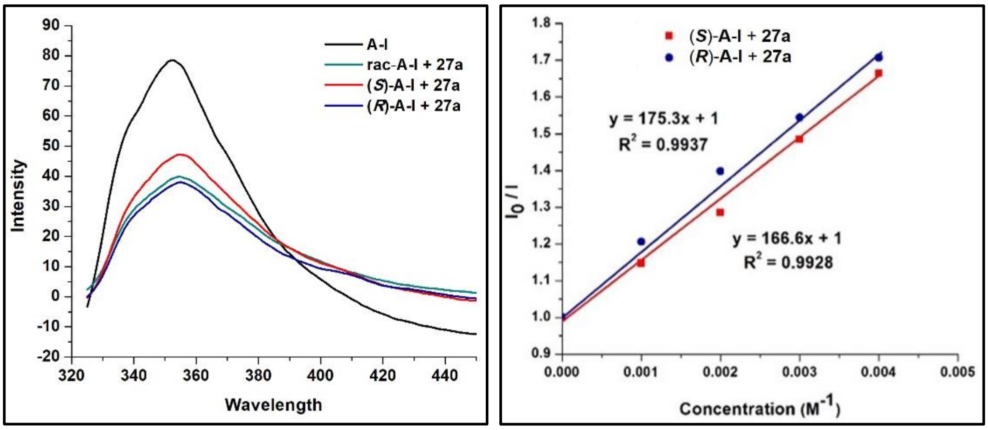


Figure 2.16: Quenching study: Fluorescence spectra of **A-I** (10^{-5} M, $CHCl_3$); (±)-**A-I**, (*S*)-**A-I** and (*R*)-**A-I** in presence of **27a** (λ_{ex} = 305 nm) left; Stern-Völmer plots of (*S*)-**A-I** and (*R*)-**A-I** with **27a** right;

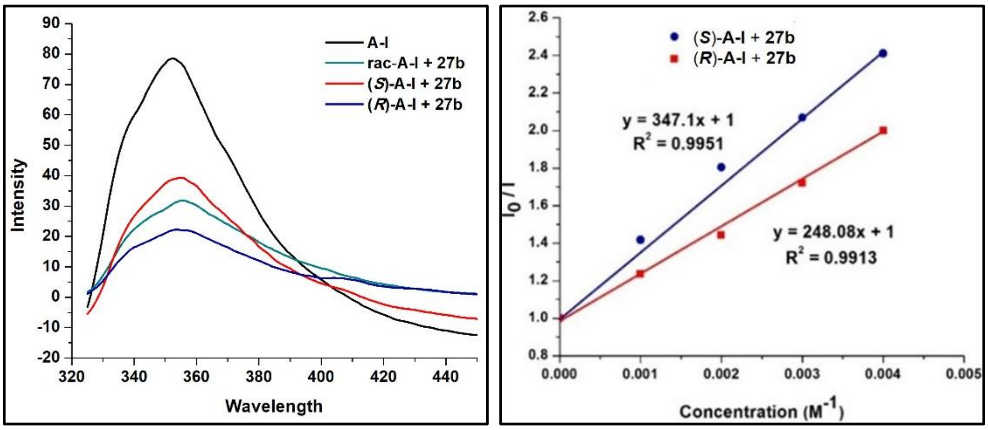


Figure 2.17: Quenching study: Fluorescence spectra of **A-I** (10^{-5} M, $CHCl_3$); (±)-**A-I**, (*S*)-**A-I** and (*R*)-**A-I** in presence of **27b** (λ_{ex} = 305 nm); Stern-Völmer plots of (*S*)-**A-I** and (*R*)-**A-I** with **27b** right.

Preliminary investigation was made to determine effective stoichiometric ratio of host-guest association in the present system (Table 2.2). Although each macrocycle contains three basic sites, out of which the two tertiary nitrogens undergo protonation to generate ion pairs, as evident from entry 2 of Table 2.2. While the third site of pyridine is expected to show C*H*-π interaction with the naphthyl ring of guest molecule. The best stoichiometry for the host-guest complex was determined by determining the ΔΔδ value for separation of signal for **A-I** with macrocycle (**27b**)

Table 2.2: Determination of stoichiometry of host (**27b**) and guest (**A-I**)

No.	Ratio[a] **A-I**:**27b**	(ΔΔδ) ppm
1	1:3	0.58
2	**1:2**	**0.74**
3	1:1	0.66
4	1:0.5	0.63

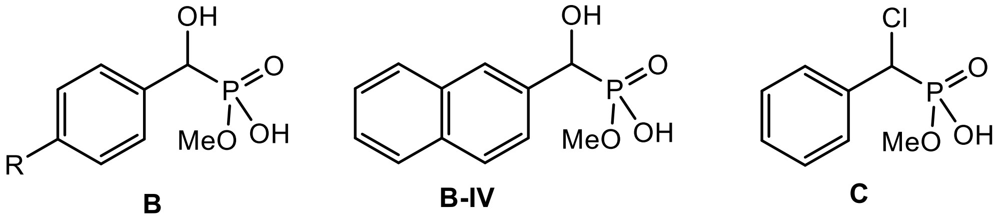
[a] In $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR).

In addition to binaphthyl phosphoric acid **A-I**, its derivatives were also screened with diastereomeric macrocycles (**27**). It was observed that in all the cases macrocycle (**27b**) showed good baseline separation while in case of macrocycle (**27a**) almost negligible separation was seen. Furthermore NO_2 derivative **A-IV**, exhibited best separation of 0.81 ppm.

Chiral phosphonic acid derivatives which resemble closely with amino acids have also been found useful in medicinal chemistry and in asymmetric transformations.[20] It was noteworthy to see a reverse trend for a second group of analytes of α-substituted phosphonic acids (Type **B**) with the same set of macrocyclic CSAs (Table 2.3) (Figure 2.18). These analytes, being smaller in size are better accommodated in the partially closed cavity of macrocycle (**27a**) while poor or no separation was observed with the other diastereomer. The results were consistent with all the derivatives of α-hydroxy phosphonic acid used in the study. However, the naphthyl derivative **B-IV** showed slight decrease in separation which may be due to its poor solubility.

The effect of presence of hydrogen bond donor group at the position of phosphonic acid was also studied. In case of α-chloro derivative **C** both the macrocycles were found to be ineffective in the discrimination which clearly indicates the role of hydrogen bonding in enantiomeric recognition for α-substituted phosphonic acids.

Chart 2.3: List of α-hydroxy phosphonic acids screened with macrocycles



B **B-IV** **C**

Table 2.3: Discrimination of monomethyl esters of substituted phosphonic acids (Type-**B** and Type-**C**)[a]

No.	Comd. No.	R	(ΔΔδ) ppm	
			(*S*,*S*,*S*)-**27a**	(*R*,*R*,*S*)-**27b**
1	**B-I**	H	0.17	0.04
2	**B-II**	Me	0.19	--[b]
3	**B-III**	Cl	0.16	--[b]
4	**B-IV**	--	0.17	--[b]
5	**C**	--	--[b]	--[b]

[a]In CD_3OD (5%) in $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR), ratio of **B** and **C**:**27** (2:1); [b]Not resolved.

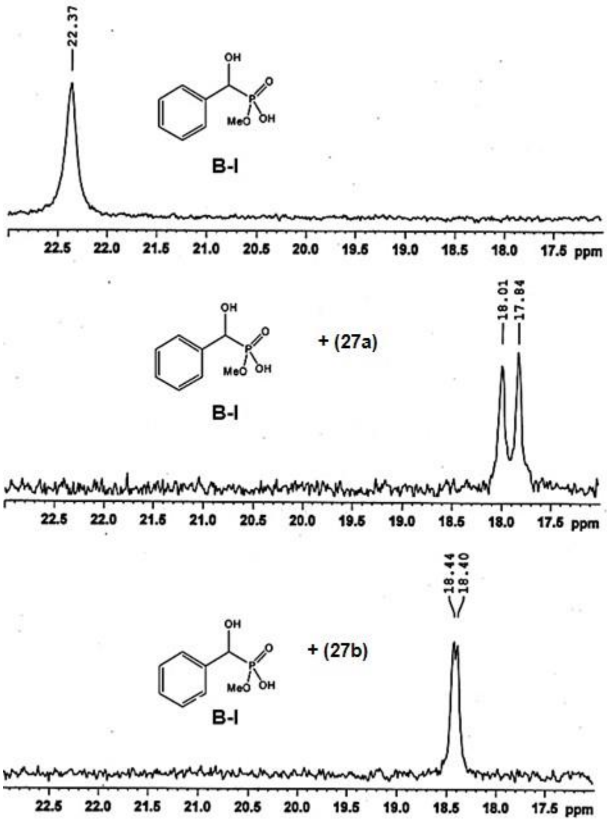
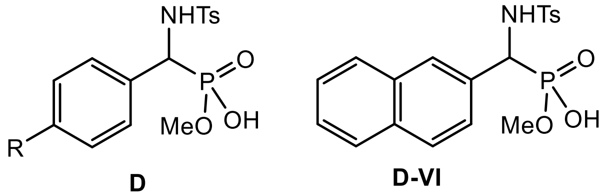


Figure 2.18: ^{31}P NMR Spectra of **B-I** blank (top), **B-I + 27a** (middle) and **B-I + 27b** (bottom)

In both the cases protonation of nitrogen of macrocycles result in electrostatic interactions holding the diastereomers together effecting the chiral discrimination. In the second set of analytes there could be additional H-bonding interaction working in tandem. The formation of H-bond between phosphonic acid analyte and H-bond acceptor sites of macrocyclic CSA are probably favored by partially close cavity of (**27a**).

Along with α-hydroxy phosphonic acids, the diastereomeric macrocycles were also screened for α-amino phosphonic acid derivatives. In case of α-amino phosphonic acids, the macrocycles depicted similar trend as observed for α-hydroxy analogs (Figure 2.19). However the separation of signal in case of α-amino phosphonic acid derivatives was observed to be better than α-hydroxy phosphonic acid analogs. This may be partially attributed to the better solubility of α-amino phosphonic acid derivatives and also due to better hydrogen bonding ability of α-amino analogs (Type **D**).

Chart 2.4: List of α-amino phosphonic acids screened with macrocycles



D **D-VI**

Table 2.4: Discrimination of monomethyl esters of α-aminophosphonic acids (Type-**D**)[a]

No	Comd. No.	R	(ΔΔδ) ppm	
			(*S*,*S*,*S*)-**27a**	(*R*,*R*,*S*)-**27b**
1	D-I	H	0.40	--[b]
2	D-II	Me	0.42	--[b]
3	D-III	Cl	0.45	0.10
4	D-IV	OMe	0.43	--[b]
5	D-V	NO_2	0.40	0.12
6	D-VI	--	0.37	--[b]

[a]In CD_3OD (5%) in $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR), ratio of **D**:**27** (2:1);
[b]Not resolved.

In case of α-amino phosphonic acid, the separation of signal was observed to be better in case of *p*-methyl derivative **D-II** which further improved for methoxy derivative **D-III**. The best result was observed in case of *p*-chloro derivative **D-IV** which showed a separation of about 0.45 ppm. The resolution was slightly reduced for *p*-nitro derivative which showed resolution almost similar to **D-I**. The naphthyl derivative **D-V** also showed significant baseline separation of signal.

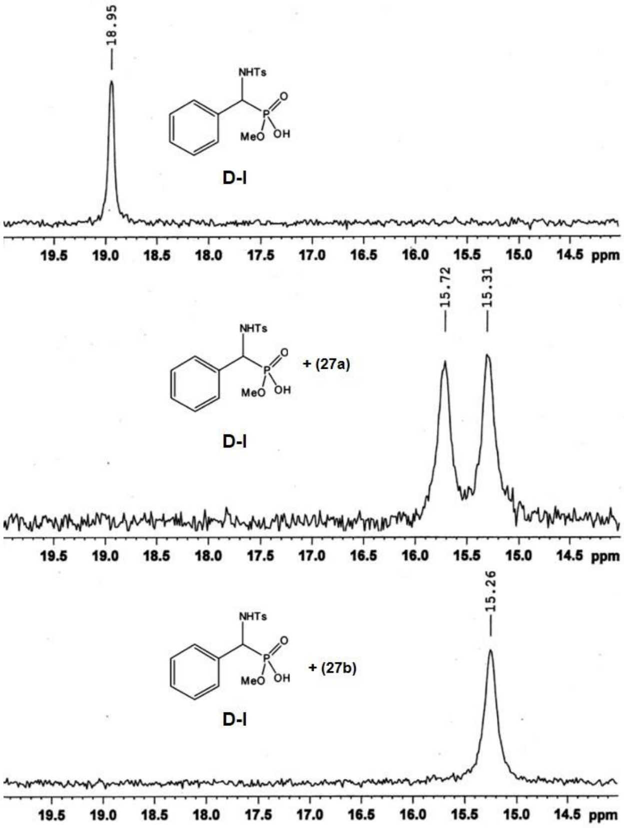


Figure 2.19: ^{31}P NMR Spectra of **D-I** blank (top), **D-I + 27a** (middle) and **D-I + 27b** (bottom)

In summary, two diastereomers of eighteen member N,O-macrocycles are synthesized and evaluated as CSA for effective discrimination of ^{31}P NMR signals and fluorescence quenching of several organo phorphoric and phosphonic acid derivatives. Combination of chirality on the backbone of macrocycle and of the pendant group was explored for molecular recognition of optically active hosts for quantifiable discrimination.

2.3 Conclusion:

In summary synthesis of chiral azacrown ethers was achieved from aminoalcohol, prepared by diastereomeric ring opening of *meso* cyclohexenoxide with chiral amine. These azacrown ethers were screened as CSA for enantiomeric recognition of α-functional carboxylic acids.

The detailed investigation of crown ethers as CSA along with mechanistic study of binding with guest molecules is currently under progress.

Furthermore, two diastereomeric N,O-macrocycles were synthesized and screened for molecular recognition of binpahthyl phosphoric acid by UV-Vis spectroscopy and fluorescence Spectroscopy.

In addition two diastereomeric macrocycles with pyridine moiety were syntheisized for molecular recognition.

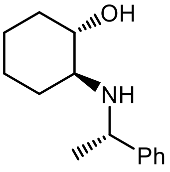
The pyridine based macrocycles have been evaluated as CSA for effective discrimination by ^{31}P NMR signals and fluorescence quenching of several organo phorphoric and phosphonic acid derivatives.

Combination of chirality on the backbone of macrocycle and of the pendant group was explored for molecular recognition of optically active hosts for quantifiable discrimination.

2.4 Experimental Procedure:

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, Sisco, Qualigens, Avara Chemicals Limited etc. All solvents that were used were stored on oven dried molecular sieves (4Å). All commercial products were used without further purification. Toluene was distilled and dried by passing Sodium wire. All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. ^{1}H, ^{13}C and ^{31}P NMR spectra are recorded on a 400 MHz Bruker Avance 400 Spectrometer (100 MHz for ^{13}C and 162 MHz for ^{31}P respectively) spectrometer with $CDCl_3$ as solvent and TMS as internal standard. Signal multiplicity is denoted as singlet (s), doublet (d), doublet of doublet of doublets (ddd), triplet (t), doublet of triplet (dt), quartet (q) and multiplet (m). Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a Perkin-Elmer FTIR RXI spectrometer as KBr pallets or neat in case of liquids. UV-Vis spectra were recorded on Perkin-Elmer λ–35. Fluorescence spectra were recorded on Jasco FP-6300 Spectrofluorometer. The 1,1'-Binaphthyl-2,2'-diylhydrogen phosphate derivatives (**A**) were synthesized by reported procedure.[22] Monomethyl esters of α-hydroxy and α-amino phosphonic acids **B-D** were synthesized by following literature procedure.[22] All ^{31}P CSA NMRs were recorded by mixing 1 equiv (10 mmol) of (**27a**) or (**27b**) and 2 equiv (20mmol) of hosts (**A-D**) in 0.6ml $CDCl_3$ or indicated otherwise.

Synthesis of (1*S*,2*S*)-*trans*-2-(*N*-Benzoyl-*N*-methyl)amino-1-cyclohexanol (20a)



A mixture of (*S*)-phenylethyl amine (1.0 g, 8.3 mmol) and cyclohexenoxide (0.97 g, 9.9 mmol), in 15mL dry ethanol, was refluxed under nitrogen atmosphere for 72 h. The solvent was then evaporated under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 3:7) yielding compound (**20a**) as colourless oil. (0.63 g, 35 %); $[\alpha]_D^{25}$= +11.5 (*c* = 1.0 in MeOH) (Lit[3] +20.9 *c* = 1.64, MeOH)[13]

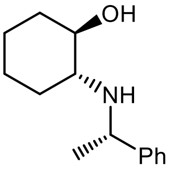
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.32 (m, 4H), 7.28-7.24 (m, 1H), 3.96-3.91 (q, *J* = 6.4 Hz, 1H, $C_\alpha H$), 3.14-3.08 (dt, *J* = 9.2, 4.4 Hz, 1H, -C*H*OH), 2.38-2.32 (ddd, *J* = 13.2, 9.2, 4.0 Hz, 1H, -C*H*NH-), 2.09-2.06 (m, 1H), 1.98-1.94 (m, 1H), 1.73-1.66 (m, 2H), 1.36-1.34 (d, *J* = 6.4 Hz, 3H, CH_3), 1.35-1.15 (m, 3H), 0.91-0.80 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 128.5, 127.1, 126.4, 74.0, 61.5, 55.2, 33.0, 31.3, 25.4, 24.2, 23.5.

IR (neat): *υ* 3412, 2980, 1449, 1370, 1062, 762, 700.

Mass (ESI): *m/z* 242 (30), 221 (50), 220 (94), 158 (30), 116 (99), 106 (24), 105 (100).

Synthesis of (1*R*,2*R*)-*trans*-2-[(*S*)-(α-Methylbenzyl)amino]-1-cyclohexanol (20b)



As described above, the compound (**20b**) was obtained from the later fractions from column chromatography (ethyl acetate/petroleum ether, 2:3) as white solid. (0.54 g, 30%);

Mp: 53-54 °C. $[\boldsymbol{a}]_{D}^{25}$= -99.6 (*c* = 1.0 in MeOH) (Lit$^{3.}$ -100.2 *c* = 1.20, MeOH)[13]

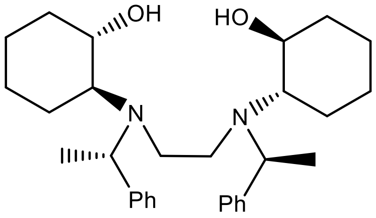
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.35-7.31 (m, 4H), 7.27-7.25 (m, 1H), 4.04-3.99 (q, *J* = 6.4 Hz, 1H, CαH), 3.20-3.14 (m, 1H, -C*H*OH), 2.20-2.14 (m, 1H, -C*H*NH-), 2.05-1.99 (m, 2H), 1.69-1.64 (m, 2H),1.38-1.36 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.30-1.19 (m, 1H), 1.13-1.07 (m, 2H), 1.01-0.88 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$):δ 145.0, 128.6, 127.1, 126.7, 74.0, 60.0, 54.1, 32.9, 30.3, 25.6, 25.0, 24.2.

IR (KBr): *υ* 3480, 2924, 1452, 1368, 1350, 1127, 1064, 762, 698.

Mass (ESI): *m/z* 242 (7), 221 (48), 220 (96), 116 (96), 106 (24), 105 (100).

(1*S*,1'*S*,2*S*,2'*S*)-2,2'-(ethane-1,2-diylbis(((*S*)-1-phenylethyl)azanediyl))bis-(cyclohexan-1-ol) (21a)



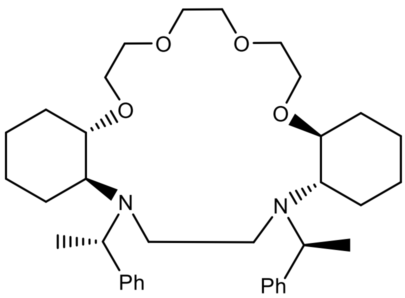
A mixture of amino alcohol (**20a**) (0.5 g, 2.2 mmol), ethylene glycol ditosylate (0.51 g, 1.4 mmol) and K$_2$CO$_3$ (0.69 g, 5.0 mmol) was heated at 100 °C for 12 h. The mixture was then cooled and CHCl$_3$ (8 mL) was added and the mixture was refluxed under nitrogen for 4 h. The solvent was then evaporated under vacuum and the mixture was poured in cold water and extracted from ethyl acetate (3 x 50 mL) and the combined extracts were washed with water (2 x 25mL). The organic layer was dried over anh. Na$_2$SO$_4$, evaporated under vacuum and then subjected to column chromatography on silica gel (ethyl acetate/ petroleum ether, 1:4) to afford compound (**21a**) as white solid.(0.32 g, 62%); Mp**:** 84-86 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.21 (m, 10H), 3.71-3.66 (q, *J* = 6.8 Hz, 2H), 3.06-3.01 (m, 2H), 2.46-2.34 (m, 2H), 2.16-2.09 (m, 4H), 2.07-2.00 (m, 2H), 1.67-1.62 (m, 4H), 1.54-1.53 (m, 2H), 1.23-1.21 (d, *J* = 6.8 Hz, 6H), 1.12-1.06 (m, 8).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 128.4, 127.7, 127.1, 69.6, 64.4, 58.3, 47.0, 33.3, 25.6, 25.0, 24.0, 18.4.

Mass (ESI): *m/z* 464 (M^+), 232, 231 (100), 127.

Synthesis of Aza-crown ether (22a)



In a three neck round bottom flask fitted with septa, a mixture of diamino diol (**21a**) (0.4 g, 0.86 mmol), NaH (0.17 g, 4.3 mmol) and KI (0.14 g, 0.86 mmol) was heated to reflux under nitrogen in 30 mL dry toluene for 0.5 h. To this mixture a solution of triethyleneglycol ditosylate (0.47 g, 1.0 mmol) in 10 mL dry toluene was added dropwise with a syringe over a period of 0.5 h. The mixture was then refluxed for 48 h. After completion of reaction the mixture was poured in cold water and extracted from ethyl acetate (3 x 50 mL) and the combined extracts were washed with water (2 x 25mL). The organic layer was dried over anh. Na_2SO_4, evaporated under vacuum and then subjected to column chromatography on silica gel (ethyl acetate/petroleum ether, 4:6) resulting in colorless oil. (0.23 g, 46%);

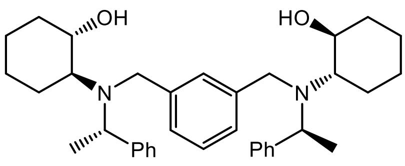
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.44 (m, 4H), 7.30-7.26 (m, 4H), 7.21-7.17 (m, 2H), 4.03-3.98 (q, J = 6.8 Hz, 2H), 3.80-3.63 (m, 12H, glycol unit -O-CH_2-CH_2-O-), 3.36-3.33 (m, 2H), 2.74-2.68 (m, 2H), 2.59-2.50 (m, 2H), 2.50-2.46 (m, 2H), 2.24-2.21 (m, 2H), 2.00-1.98 (m, 2H), 1.62-1.56 (m, 6H), 1.32-1.31 (d, J = 6.8 Hz, 6H), 0.99-0.88 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 128.1, 127.9, 126.1, 70.9, 70.7, 66.6, 62.8, 60.0, 48.2, 30.9, 29.0, 25.5, 24.2, 21.6.

Mass (ESI): *m/z* 578 (M^+), 577, 472 (100), 369, 105.

HRMS: Calculated for $C_{36}H_{55}N_2O_4$ $[M+H]^+$ = 579.4156 Found 579.4157.

(1*S*,1'*S*,2*S*,2'*S*)-2,2'-((*S*)-(1,3-phenylenebis(methylene))bis(((*S*)-1-phenylethyl)azanediyl))-dicyclohexanol (23a)



A solution of amino alcohol (**20a**) (0.5 g, 2.2 mmol) in 10mL acetonitrile was added K_2CO_3 (0.69 g, 5.0 mmol) and α,α'-dibromo-*m*-xylene (0.33 g, 1.3 mmol). The mixture was then refluxed under nitrogen for 24 h. The solvent was then evaporated under vacuum and the mixture was poured in cold water and extracted from ethyl acetate (3 x 50 mL) and the combined extracts were washed with water (2 x 25mL). The organic layer was dried over anh. Na_2SO_4, evaporated under vacuum and then subjected to column chromatography on silica gel (ethyl acetate/ petroleum ether, 1:4) to afford compound (**23a**) as white solid.(0.42 g, 68%); Mp**:** 58-60 °C. $[\alpha]_D^{25}$= +83.9 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 1H), 7.25-7.13 (m, 6H), 4.07-4.02 (q, *J* = 6.8 Hz, 1H, $C_\alpha H$), 3.89-3.86 (d, *J* = 13.6 Hz, 1H, CH_2), 3.67-3.64 (d, *J* = 1.6 Hz, 1H, CH_2), 3.68-3.33 (m, 1H), 2.39-2.34 (m, 1H), 2.03-1.96 (m, 1H), 1.93-1.92 (m, 1H), 1.78-1.76 (m, 1H), 1.66-1.64 (m, 1H), 1.49-1.47 (d, *J* = 6.4 Hz, 3H, CH_3), 1.39-1.27 (m, 1H), 1.28-1.21 (m, 3H).

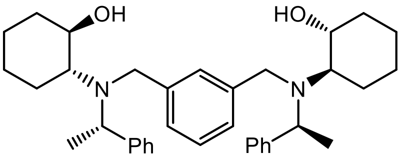
^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 140.7, 130.2, 128.8, 128.4, 128.0, 127.6, 127.1, 69.4, 62.3, 55.9, 49.9, 33.3, 27.7, 25.9, 24.2, 13.9.

IR (KBr): υ 3465, 2934, 1603, 1450, 1374, 1218, 1076, 759, 701.

Mass (ESI): *m/z* 542 (40), 541 (100), 349 (10), 348 (46), 234 (13).

HRMS: Calculated for $C_{36}H_{49}N_2O_2$ $[M+H]^+$ = 541.3788. Found 541.3789.

(1*R*,1'*R*,2*R*,2'*R*)-2,2'-((*S*)-(1,3-phenylenebis(methylene))bis(((*S*)-1-phenylethyl)azanediyl))-dicyclohexanol (23b)



The title compound was obtained by following the same procedure as for compound (**23a**) from the corresponding amino alcohol (**20b**)**.** The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:4) to yield compound (**23b**) as white solid. (0.49 g, 79%); Mp: 111-112 °C. $[\alpha]_D^{25}$= -161.4 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 1H), 7.22-7.19 (m, 2H), 7.17-7.09 (m, 3H), 6.69-6.67 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H, -O*H*), 4.02-3.96 (m, 2H), 3.69-3.67 (d, *J* = 13.2 Hz, 1H, CH_2), 3.47-3.41 (m, 1H), 2.65-2.59 (m, 1H), 2.11-2.09 (m, 1H), 1.98-1.95 (m, 1H), 1.99-1.77 (m, 1H), 1.71-1.70 (m, 1H), 1.47-1.145 (d, *J* = 6.8 Hz, 3H, CH_3), 1.38-1.22 (m, 4H).

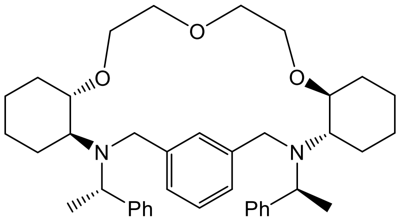
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 140.9, 128.9, 128.7, 128.3, 127.8, 127.3, 127.1, 69.2, 62.8, 57.4, 50.2, 33.4, 25.8, 25.6, 24.2, 20.1.

IR (KBr): υ 3440, 2928, 1603, 1449, 1373, 1349, 1198, 1084, 761, 699.

Mass (ESI): *m/z* 542 (37), 541 (100), 523 (5).

HRMS: Calculated for $C_{36}H_{49}N_2O_2$ $[M+H]^+$ = 541.3788. Found 541.3789.

Synthesis of Aza-crown ether (24a)



The title compound was obtained by following the same procedure as for compound (**22a**) from the corresponding diamino diol (**23a**). The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound (**24a**) as colorless oil. (0.15 g, 34%);

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.57-7.55 (m, 4H), 7.30-7.26 (m, 4H), 7.21-7.17 (m, 5H), 4.30-4.28 (m, 2H), 4.0 (s, 4H), 3.83-3.80 (m, 2H), 3.74-3.68 (m, 2H), 3.66-3.65 (m, 2H), 3.42 (m, br, 2H), 3.32 (m, br, 2H), 2.65-2.60 (m, 2H), 2.15 (m, br, 2H) 1.87-1.84 (m, 2H), 1.35-1.33 (d, J = 6.4 Hz, 6H), 1.31-1.28 (m, 4H), 1.04-0.85 (m, 8H).

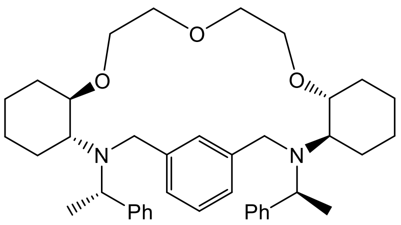
^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 143.4, 128.1, 127.9, 127.7, 127.2, 126.0, 125.2, 80.7, 71.5, 67.3, 62.8, 49.6, 31.2, 30.7, 29.7, 25.7, 24.5, 22.7, 20.3.

IR: υ 3058, 2931, 1603, 1489, 1449, 1361, 1099, 850.

Mass (ESI): *m/z* 611 (M+H).

HRMS: Calculated for $C_{36}H_{55}N_2O_4$ $[M+H]^+$ = 611.4207 Found 611.4207.

Synthesis of Aza-crown ether (24b)



The title compound was obtained by following the same procedure as for compound (**22a**) from the corresponding diamino diol (**23b**). The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound (**24b**) as colorless oil. (0.15 g, 34%);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.45-7.43 (m, 4H), 7.37-7.29 (m, 4H), 7.23-7.19 (m, 5H), 4.11-4.08 (m, 2H), 4.05-3.91 (m, 4H), 3.89-3.81 (m, 3H), 3.78-3.72 (m, 3H), 3.63 (m, br, 2H), 3.29-3.27 (m, 2H), 2.74-2.69 (m, 2H), 2.22-2.19 (m, 2H) 1.63-1.61 (m, 3H), 1.52-1.50 (m, 2H), 1.42-1.41 (m, 9H, -CH_3 signal merged), 1.18-0.89 (m, 10H).

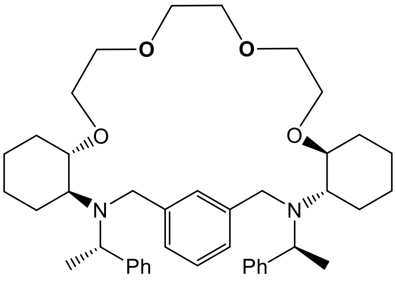
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 142.4, 128.8, 127.9, 127.8, 127.7, 127.7, 126.2, 125.8, 80.1, 71.4, 67.5, 60.1, 56.3, 51.0, 31.2, 30.0, 29.7, 25.6, 25.3, 24.5, 18.3.

IR: υ 3056, 2930, 1603, 1489, 1450, 1369, 1105, 852.

Mass (ESI): *m/z* 611 (M+H).

HRMS: Calculated for $C_{36}H_{55}N_2O_4$ $[M+H]^+$ = 611.4207 Found 611.4207.

Synthesis of Aza-crown ether (25a)



The title compound was obtained by following the same procedure as for compound (**22a**) from the corresponding diamino diol (**23a**). The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound (**25a**) as colorless oil. (0.13 g, 27%);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.51-7.49 (d, J = 7.2 Hz, 4H), 7.33-7.23 (m, 7H), 7.20-7.16 (m, 2H), 4.43-4.38 (q, J = 6.8 Hz, 2H), 3.98 (s, 4H), 3.84-3.80 (m, 4H), 3.79-3.72 (m, 6H), 3.47-3.40 (m, 2H), 3.31-3.27 (m, 2H), 2.67-2.60 (m, 2H), 2.08-2.05 (m, 2H) 1.92-1.89 (m, 2H), 1.59 (m, br, 2H), 1.30-1.28 (d, J = 6.8 Hz, 6H -CH_3 signal + 2H merged), 1.06-0.99 (m, 4H).

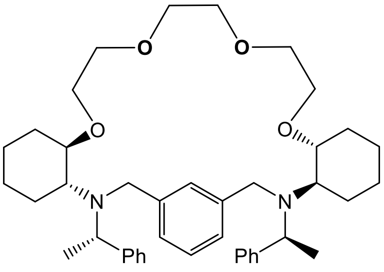
^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 143.6, 127.9, 127.8, 127.5, 126.8, 125.9, 80.8, 71.4, 71.3, 67.8, 62.5, 60.3, 49.9, 32.0, 31.3, 30.8, 29.8, 25.7, 25.5, 24.6, 22.7, 20.9.

IR: υ 3058, 2930, 1579, 1454, 1367, 1095.

Mass (ESI): *m/z* 655 (M+H).

HRMS: Calculated for $C_{42}H_{59}N_2O_4$ $[M+H]^+$ = 655.4469 Found 655.4469.

Synthesis of Aza-crown ether (25b)



The title compound was obtained by following the same procedure as for compound (**22a**) from the corresponding diamino diol (**23b**). The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound (**25b**) as colorless oil. (0.14 g, 28%);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.40-7.39 (m, 4H), 7.29-7.26 (m, 6H), 7.22-7.20 (m, 4H), 7.19-7.17 (m, 1H), 4.04-4.02 (m, 2H), 3.86-3.76 (m, 14H, triethylene-glycol subunit and benzylic protons merged), 3.57-3.56 (m, 2H), 3.26-3.22 (m, 2H), 2.69-2.64 (m, 2H), 2.16-2.13 (m, 2H), 1.66-1.51 (m, 2H), 1.47-1.43 (m, 12H, -CH_3 signal merged) 1.31-1.30 (m, 4H), 1.27-1.20 (m, 2H), 1.08-0.90 (m, 10H).

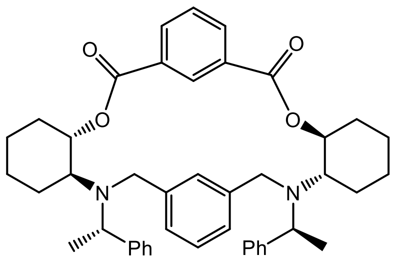
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 142.0, 127.9, 127.7, 126.6, 126.2, 80.6, 71.4, 71.2, 68.1, 60.4, 51.2, 31.4, 31.0, 29.7, 25.7, 24.6, 17.5, 14.2.

IR: υ 3024, 2929, 1603, 1449, 1349, 1106.

Mass (ESI): *m/z* 655 (M+H).

HRMS: Calculated for $C_{42}H_{59}N_2O_4$ $[M+H]^+$ = 655.4469 Found 655.4469.

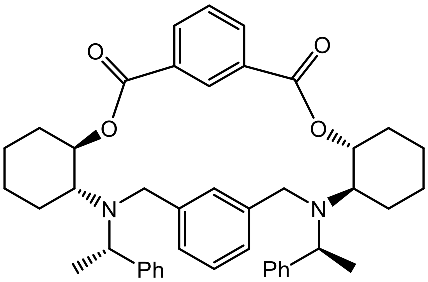
Synthesis of Aza-macrocycle (26a)



In a three neck round bottom flask fitted with septa, a mixture of diamino diol (**23a**) (0.4 g, 0.74 mmol), NaH (0.15 g, 3.7 mmol) and KI (0.13 g, 0.74 mmol) was heated to reflux under nitrogen in 30mL dry toluene for 0.5 h. To this mixture a solution of dimethyl-isophthalate (0.17 g, 0.89 mmol) in 10 mL dry toluene was added dropwise with a syringe over a period of 0.5 h. The mixture was then refluxed for 48 h. After completion of reaction the solvent was removed under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 1:9) resulting in white solid. (0.25 g, 51%); Mp: >200 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -196.1 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.18-8.16 (dd, *J* = 7.6, 1.2 Hz, 2H), 8.11 (s, 1H), 7.51-7.47 (m, 1H), 7.45-7.43 (m, 4H), 7.32-7.29 (m, 1H), 7.24-7.23 (m, 2H), 7.11-6.91 (m, 6H), 5.11-5.05 (dt, *J* = 14.4, 10.4, 4.0 Hz, 2H, -C*H*OCO-), 4.31-4.26 (q, *J* = 6.8 Hz, 2H, $C_\alpha H$), 4.15-4.11(d, *J* = 14.4 Hz, 2H, CH_2), 4.07-4.04 (d, *J* = 14.0 Hz, 2H, CH_2), 3.06-3.00 (m, 2H), 2.33-2.30 (m, 2H), 2.01-1.98 (m, 2H), 1.72-1.65 (m, 4H), 1.57-1.56 (d, *J* = 6.8 Hz, 6H, $-CH_3$), 1.42-1.32 (m, 2H), 1.27-1.18 (m, 2H), 1.07-1.01 (m, 2H).

IR (KBr): υ 3057, 2950, 1711, 1600, 1448, 1366, 1079.



Synthesis of Aza-macrocycle (26b)

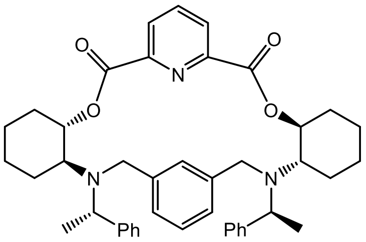
The title compound was obtained by following the same procedure as for compound (**26a**) from the corresponding diamino diol (**23b**). The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound (**26b**) as white solid. (0.16 g, 50%); Mp: >200 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= +34.2 (*c* = 1.0 in $CHCl_3$).

The ^{1}H and ^{13}C NMR spectra of compound (**26b**) exhibit broad signals. This type of observation for macrocyclic system has been reported earlier by Periasamy et al.[10b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (m, 3H), 8.08-8.04 (t, *J* = 8.0 Hz, 1H), 7.54 (s, 3H), 7.30-7.28 (m, 4H), 7.20-7.19 (m, 4H), 7.07 (s, 2H), 5.31 (s, 2H), 4.25 (m, 4H), 3.64-3.61 (d, J = 13.6 Hz, 2H), 3.32-2.97 (m, 2H), 2.23 (s, 2H), 1.69-1.59 (m, 9H), 1.43-1.30 (m, 7H), 1.28-1.26 (m, 4H).

IR (KBr): υ 3056, 2937, 1711, 1601, 1449, 1368, 1137, 1078.

Synthesis of Aza-macrocycle (27a)



In a three neck round bottom flask fitted with septa, a mixture of diamino diol (**23a**) (0.4 g, 0.74 mmol), NaH (0.15 g, 3.7 mmol) and KI (0.13 g, 0.74 mmol) was heated to reflux under nitrogen in 30 mL dry toluene for 0.5 h. To this mixture a solution of dimethyl 2,6-pyridinedicarboxylate (0.17 g, 0.89 mmol) in dry toluene (10 mL) was added dropwise with a syringe over a period of 0.5 h. The mixture was then refluxed for 48 h. After completion of reaction the solvent was removed under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 1:9) resulting in white solid. (0.28 g, 57%); Mp: >200 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$= -162.7 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.24-8.22 (d, *J* = 7.6 Hz, 2H), 7.91-7.87 (t, *J* = 4.0, 1H), 7.64 (s, 4H), 7.26-7.17 (m, 3H), 7.01-6.98 (m, 6H), 5.16-5.12 (dt, *J* = 10.8, 3.6 Hz, 1H, -C*H*OCO-), 4.30-4.28 (q, *J* = 6.4 Hz, 2H, CαH), 4.10-4.07 (d, *J* = 13.6 Hz, 2H, CH_2), 4.04-4.01 (d, *J* = 13.6 Hz, 2H, CH_2), 3.10-3.04 (dt, *J* = 10.8, 3.2 Hz, 2H), 2.31-2.29 (m, 2H), 1.99-1.69 (m, 2H), 1.69-1.59 (m, 5H), 1.59-1.57 (d, *J* = 6.4 Hz, 6H, CH_3), 1.54-1.53 (m, 1H), 1.42-1.26 (m, 4H), 1.10-0.91 (m, 2H).

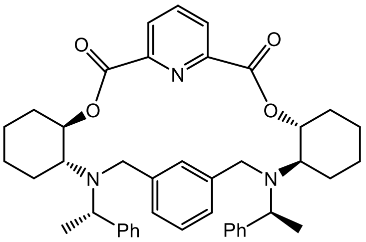
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 148.8, 145.8, 140.6, 136.9, 130.7, 128.5, 127.8, 127.6, 126.5, 125.9, 77.4, 58.7, 53.6, 50.5, 32.0, 29.4, 25.5, 24.6.

IR (KBr): υ 2940, 1704, 1602, 1585, 1448, 1368, 1330, 1243, 1144, 957, 701.

Mass (ESI): *m/z* 672 (100), 568 (60), 464 (70) 462(20), 105(20).

HRMS: Calculated for $C_{43}H_{50}N_3O_4$ $[M+H]^+$ = 672.3790. Found 672.3796.

Synthesis of Aza-macrocycle (27b)



The title compound was obtained by following the same procedure as for compound (**27a**) from the corresponding diamino diol (**23b**). The organic extract was column chromatographed (ethyl acetate/ petroleum ether, 1:9) to yield compound (**27b**) as white solid. (0.27 g, 54%); Mp: >200 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$= +36.8 (*c* = 1.0 in $CHCl_3$).

The ^{1}H and ^{13}C NMR spectra of compound **27b** exhibit broad signals. This type of observation for macrocyclic system has been reported earlier by Periasamy et al.[10b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (m, 3H), 8.08-8.04 (t, *J* = 8.0 Hz, 1H), 7.54 (s, 3H), 7.30-7.28 (m, 4H), 7.20-7.19 (m, 4H), 7.07 (s, 2H), 5.31 (s, 2H), 4.25 (m, 4H), 3.64-3.61

(d, J = 13.6 Hz, 2H), 3.32-2.97 (m, 2H), 2.23 (s, 2H), 1.69-1.59 (m, 9H), 1.43-1.30 (m, 7H), 1.28-1.26 (m, 4H).

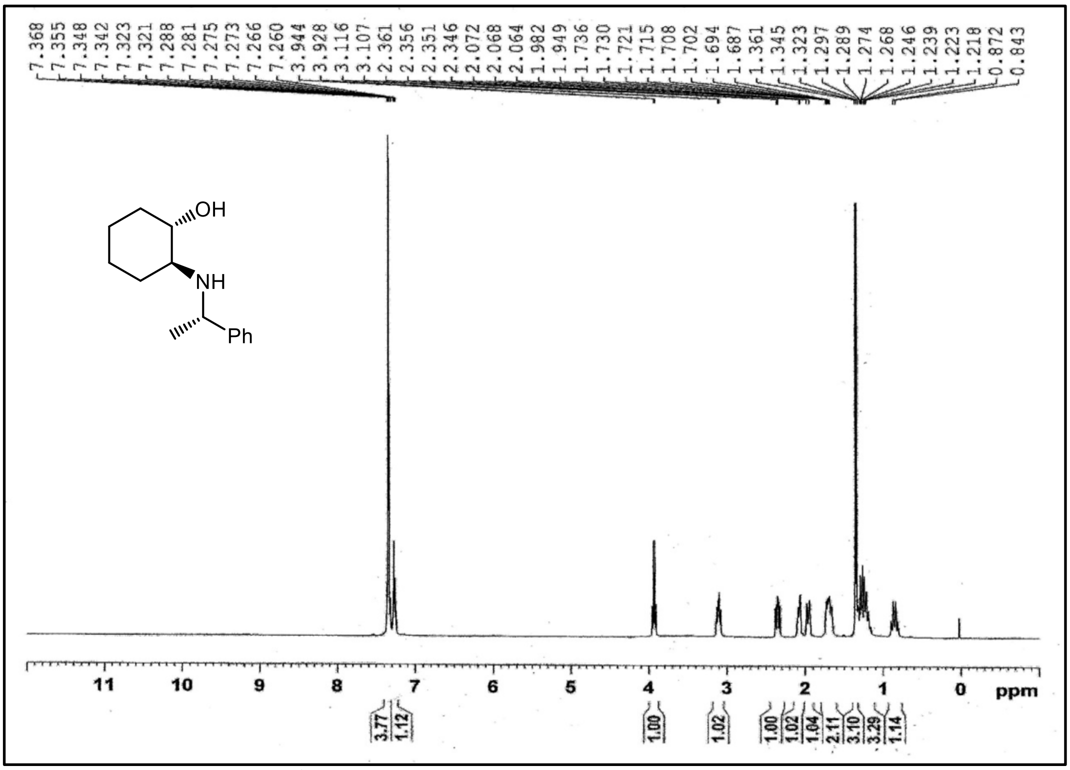
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 149.4, 146.5, 140.1, 137.8, 133.6, 129.2, 127.9, 127.6, 126.8, 126.2, 79.2, 57.8, 53.4, 52.2, 50.7, 31.9, 30.0, 25.4, 24.4, 18.3.

IR (KBr): υ 2941, 1705, 1559, 1449, 1369, 1333, 1245, 1082, 700.

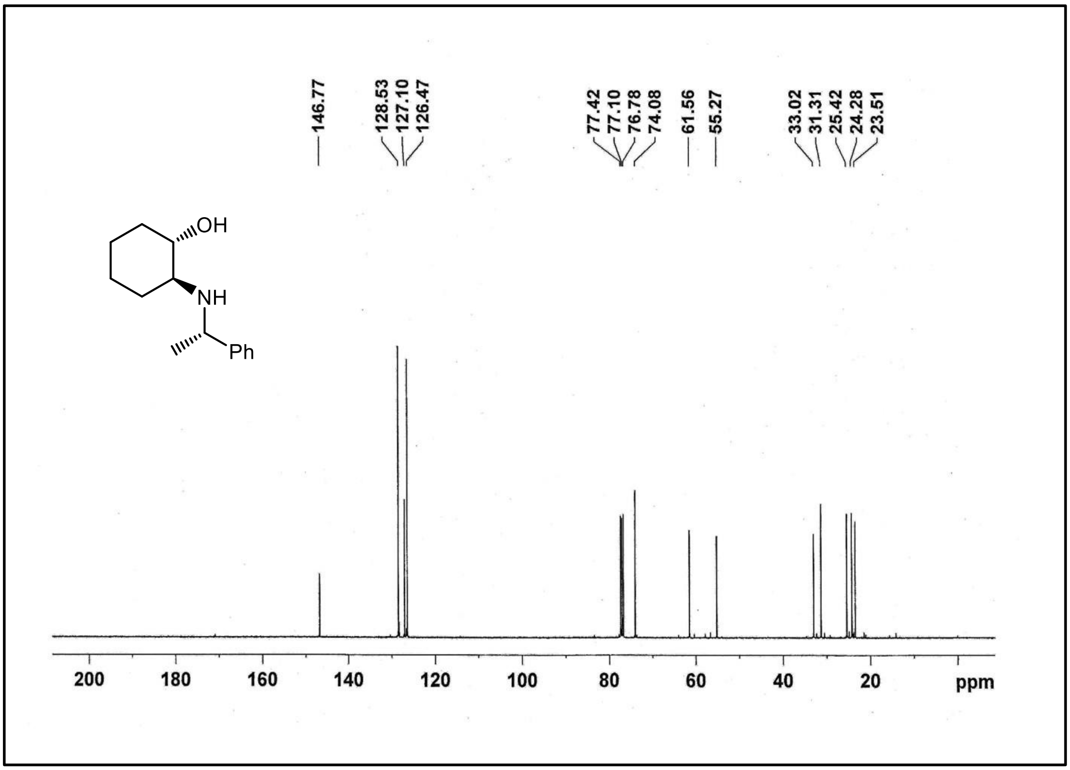
Mass (ESI): *m/z* 695 (45), 694 (80), 672 (M+1, 100), 568 (10).

HRMS: Calculated for $C_{43}H_{50}N_3O_4$ $[M+H]^+$ = 672.3790. Found 672.3797.

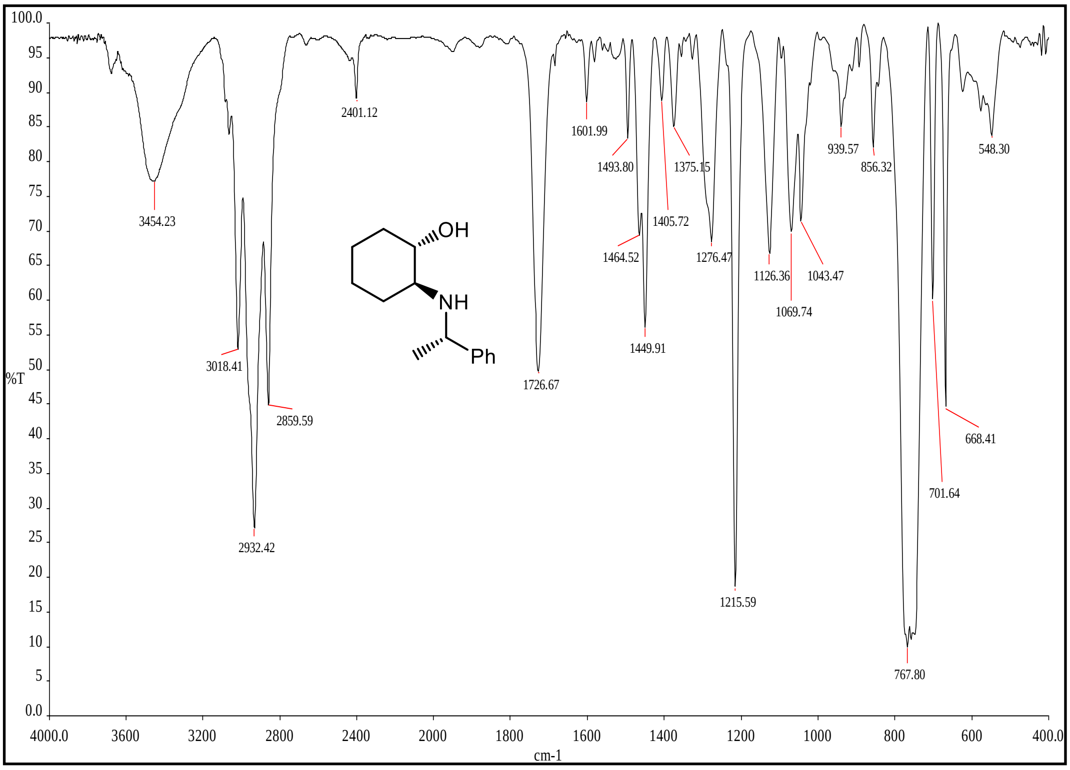
2.5.1 Spectral Data



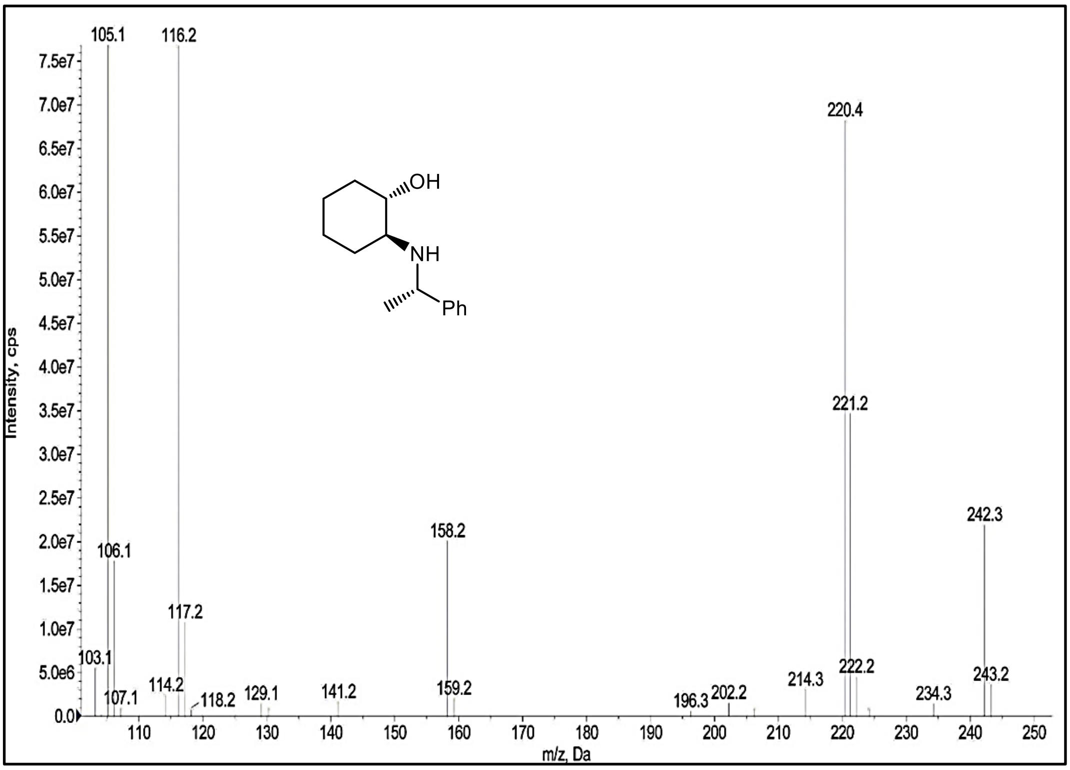
^{1}H NMR Spectra of Compound (**20a**)



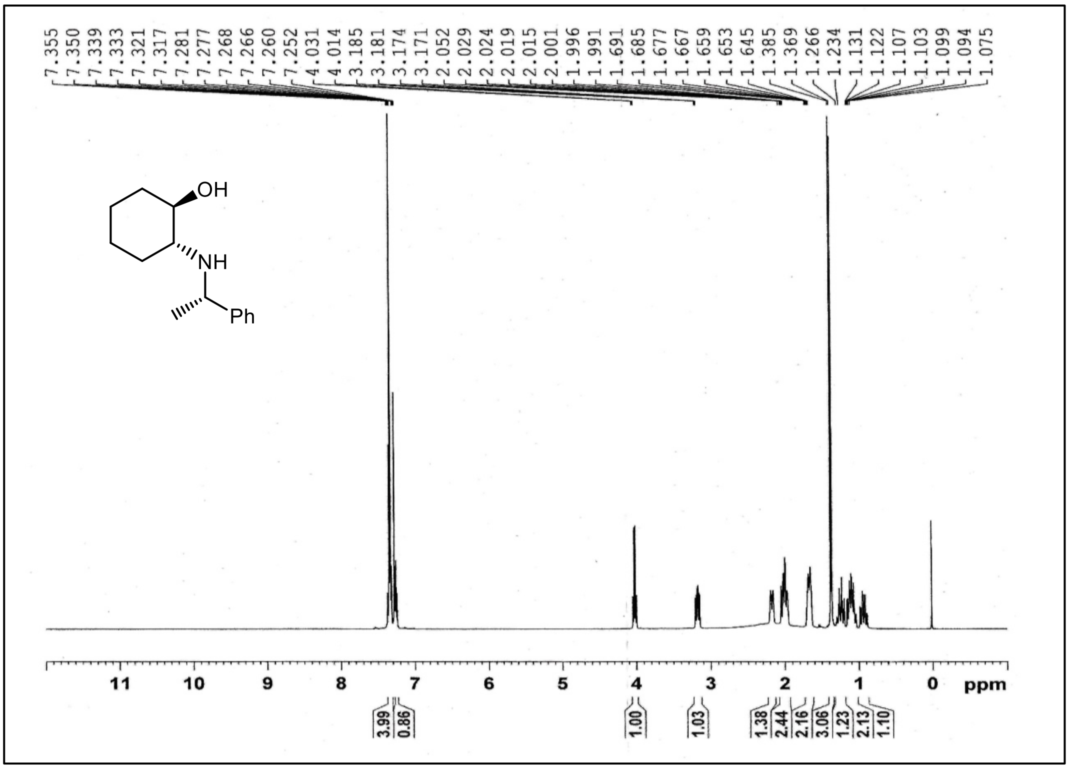
^{13}C NMR Spectra of Compound (**20a**)



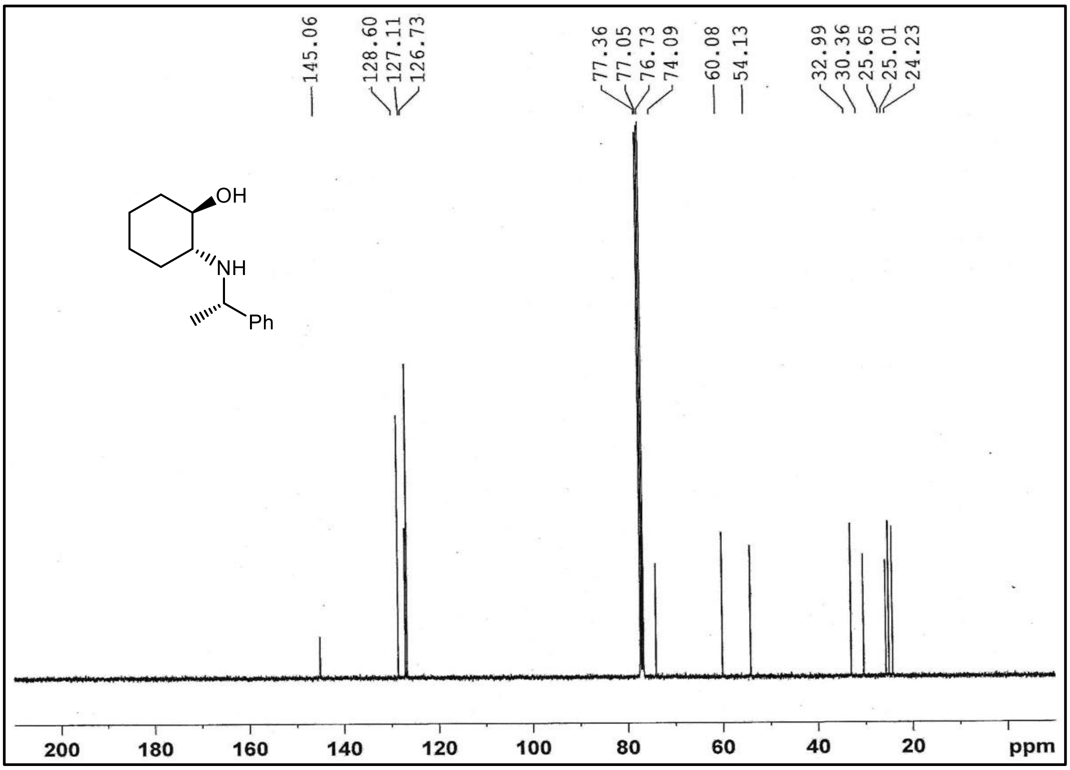
IR Spectra of Compound (**20a**)



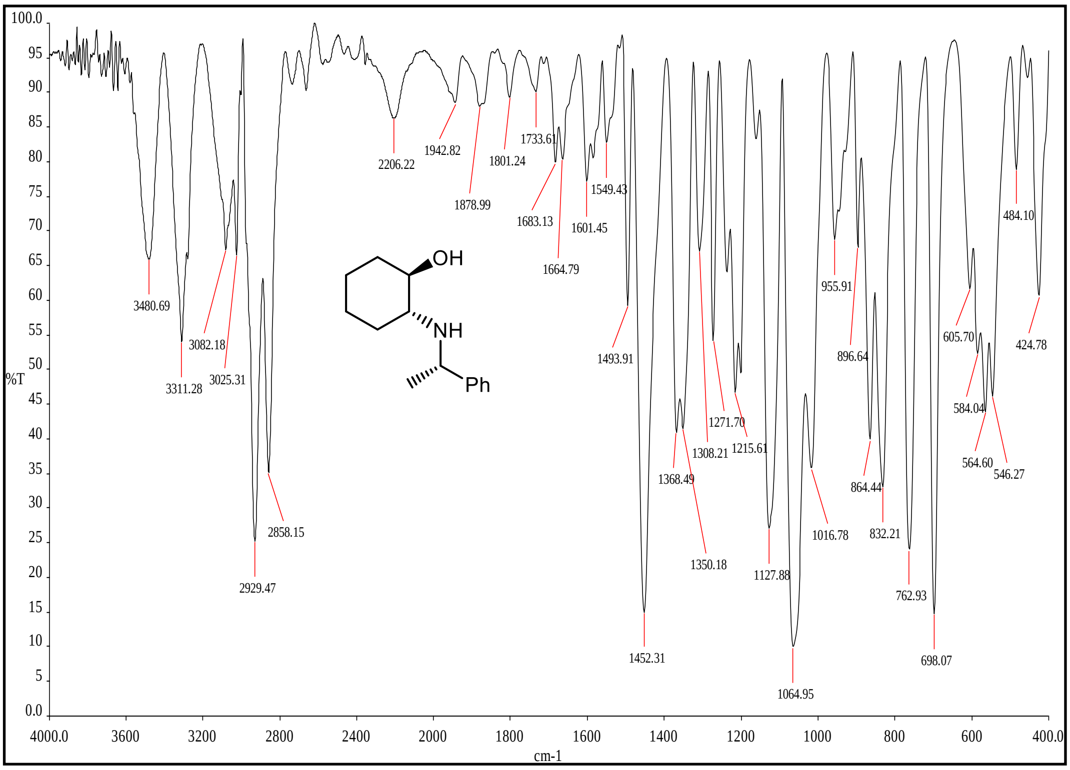
MS Spectra of Compound (**20a**)



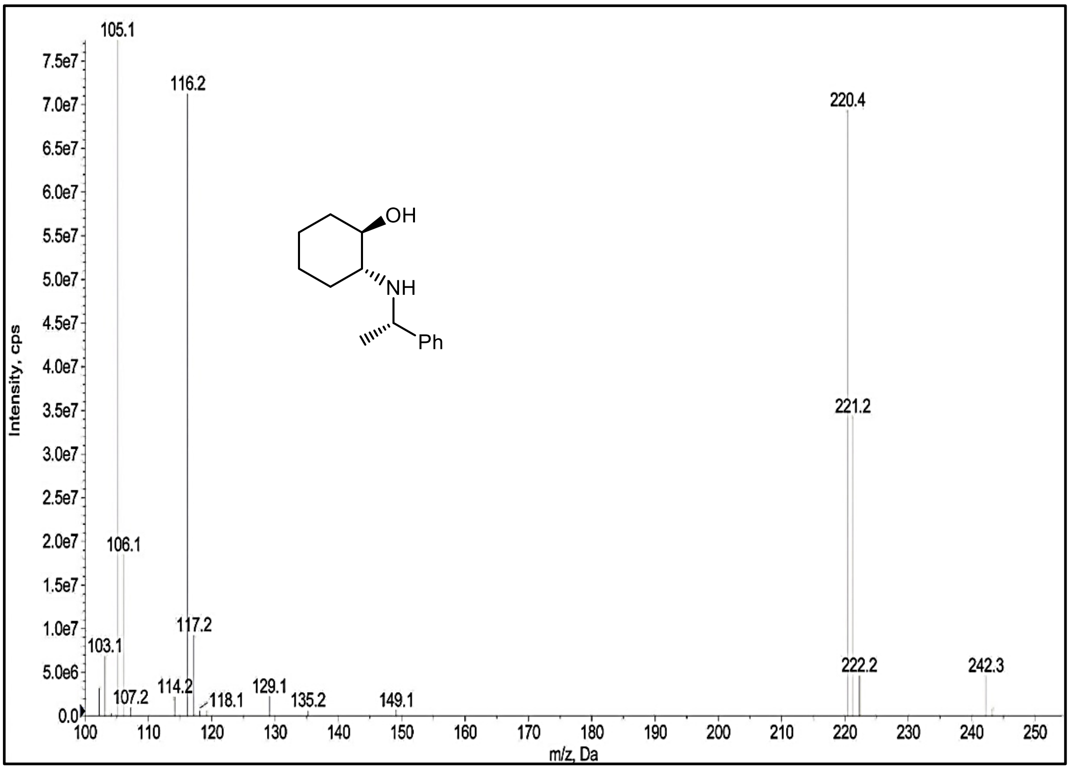
^{1}H NMR Spectra of Compound (**20b**)



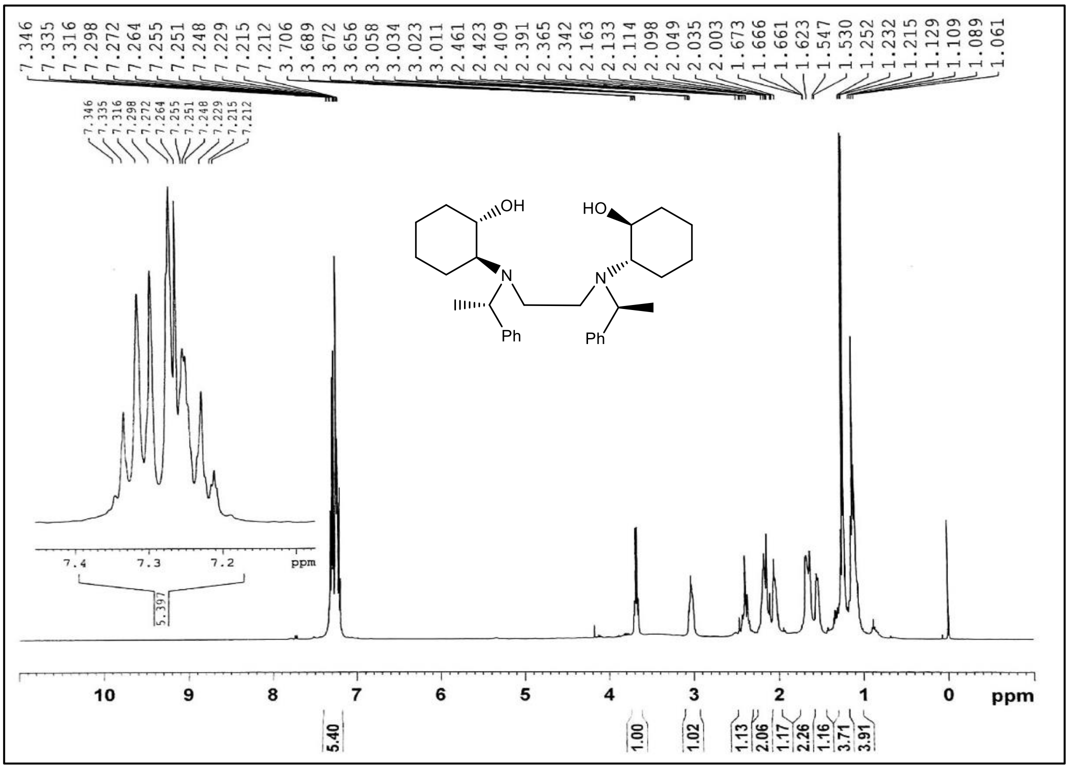
^{13}C NMR Spectra of Compound (**20b**)



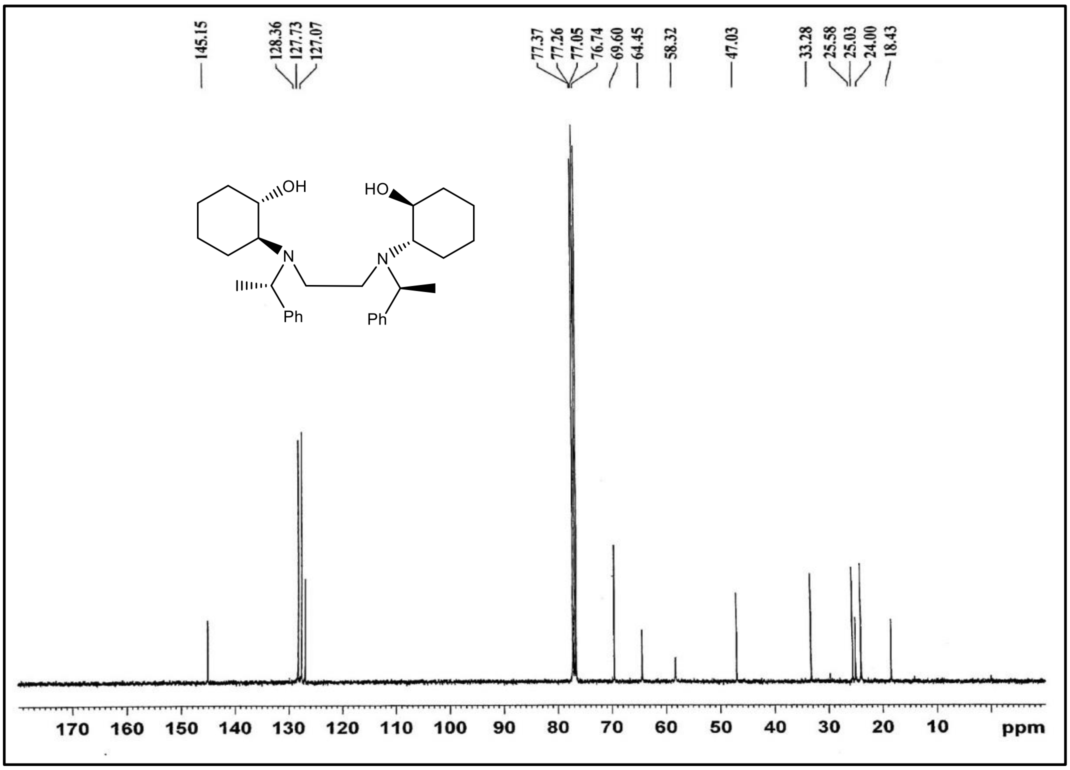
IR Spectra of Compound (**20b**)



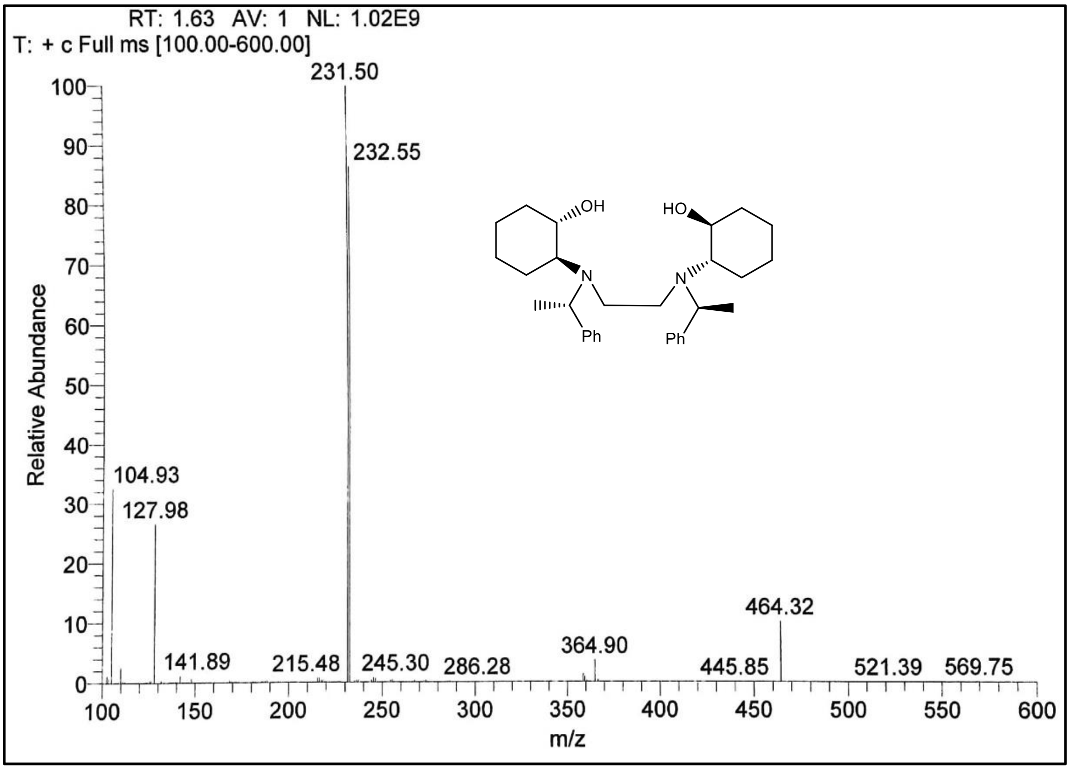
MS Spectra of Compound (**20b**)



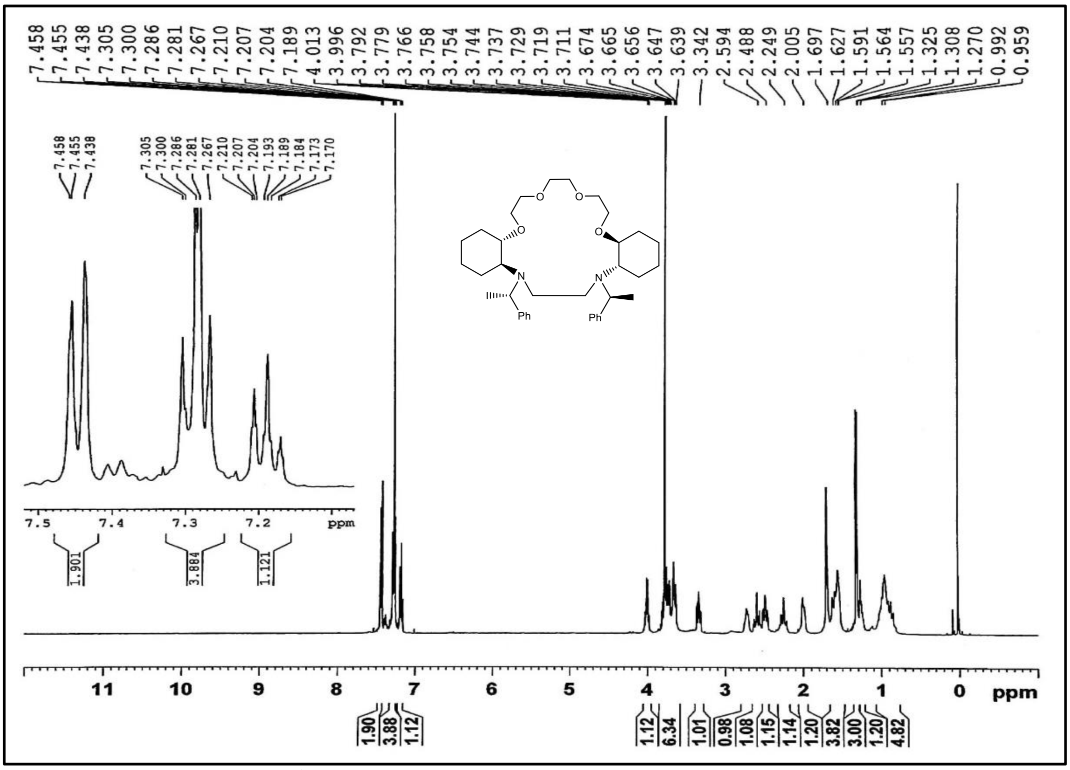
^{1}H NMR Spectra of Compound (**21a**)



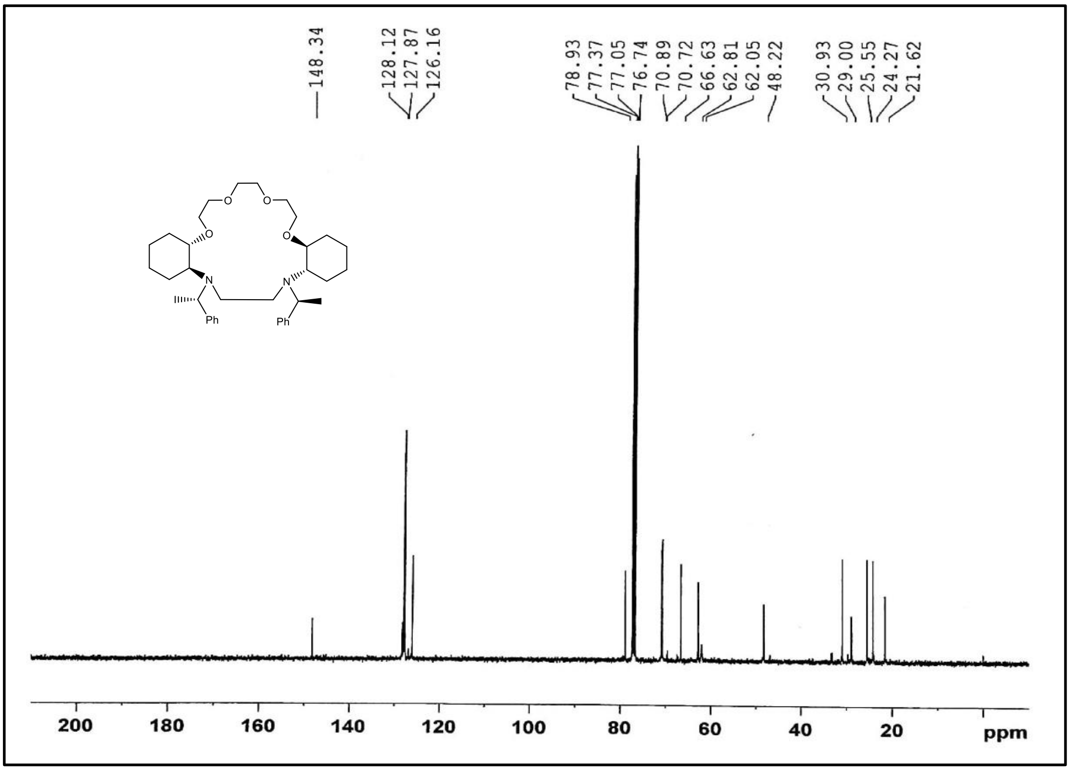
^{13}C NMR Spectra of Compound (**21a**)



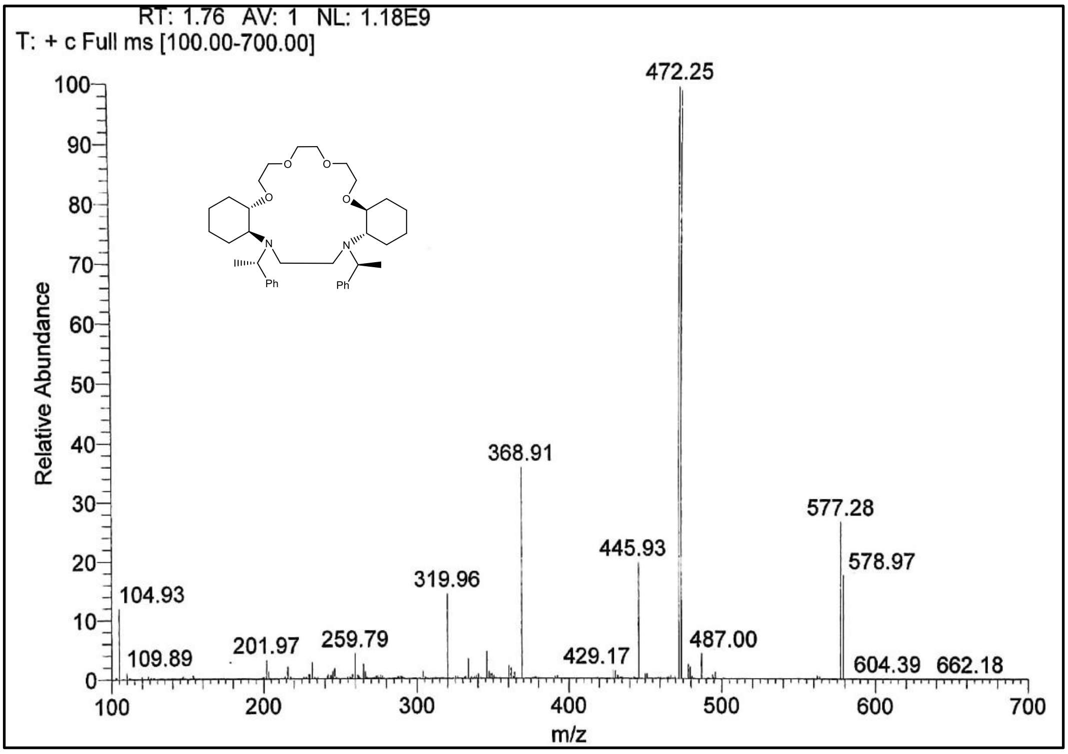
MS Spectra of Compound (**21a**)



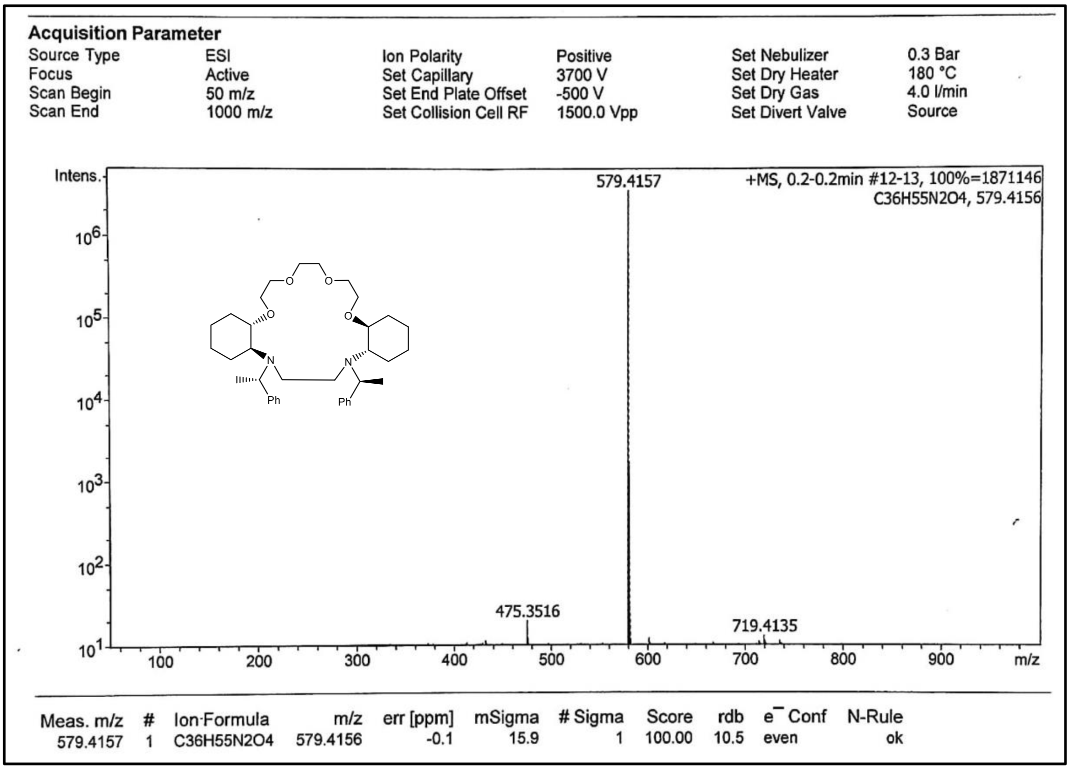
^{1}H NMR Spectra of Compound (**22a**)



^{13}C NMR Spectra of Compound (**22a**)



MS Spectra of Compound (**22a**)



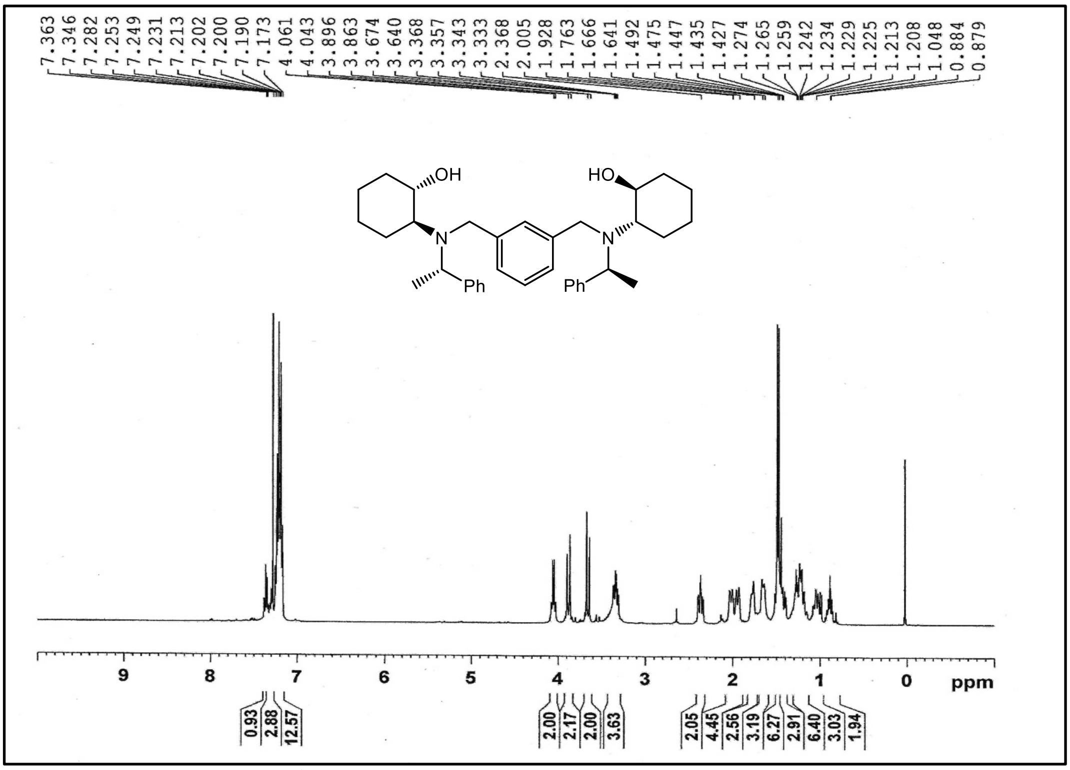
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	3700 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	1500.0 Vpp	Set Divert Valve	Source

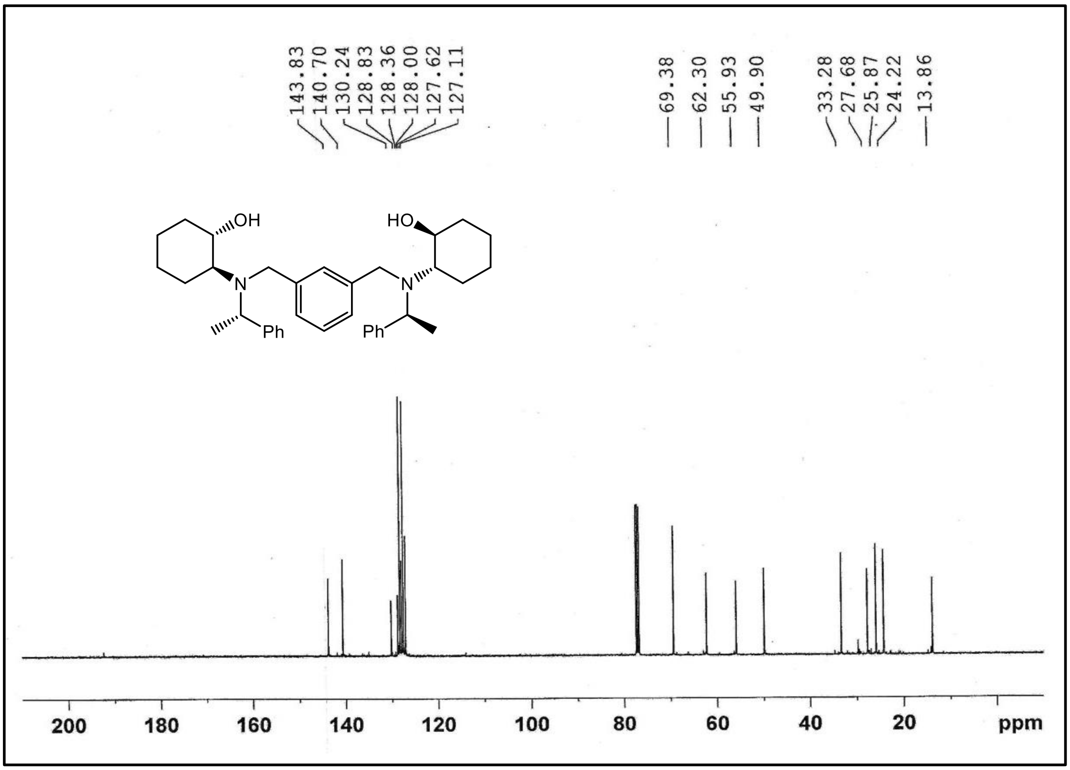
+MS, 0.2-0.2min #12-13, 100%=1871146
C36H55N2O4, 579.4156

Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# Sigma	Score	rdb	e⁻ Conf	N-Rule
579.4157	1	C36H55N2O4	579.4156	-0.1	15.9	1	100.00	10.5	even	ok

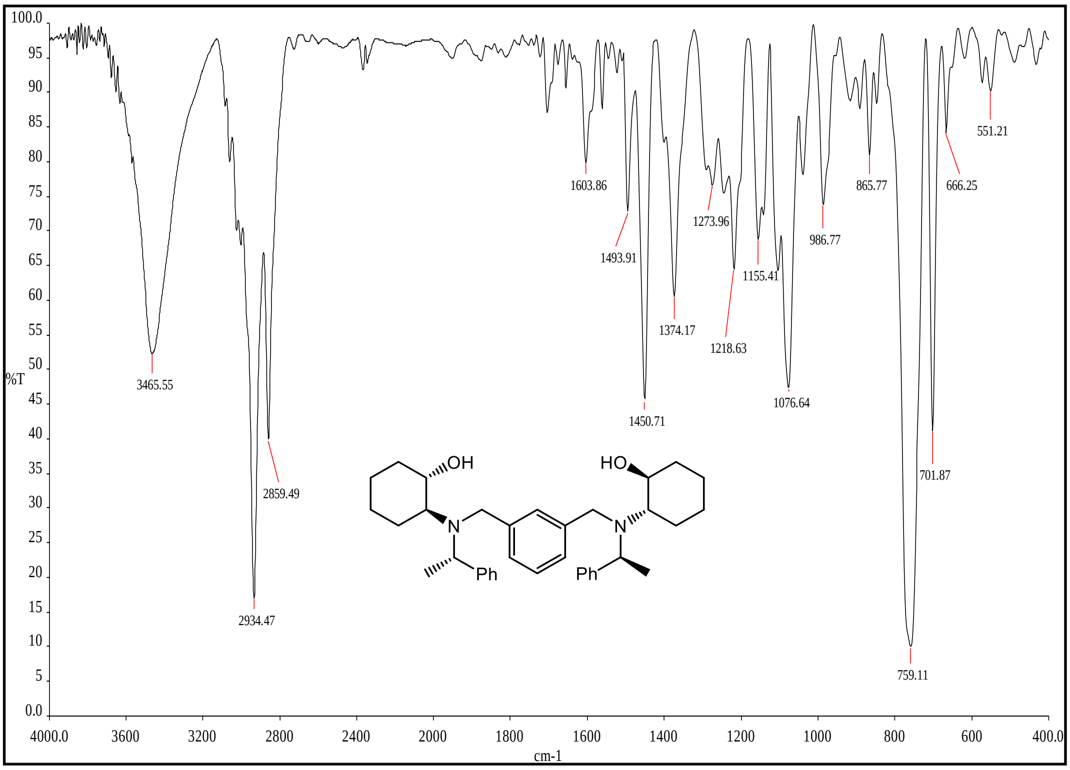
HRMS Spectra of Compound (**22a**)



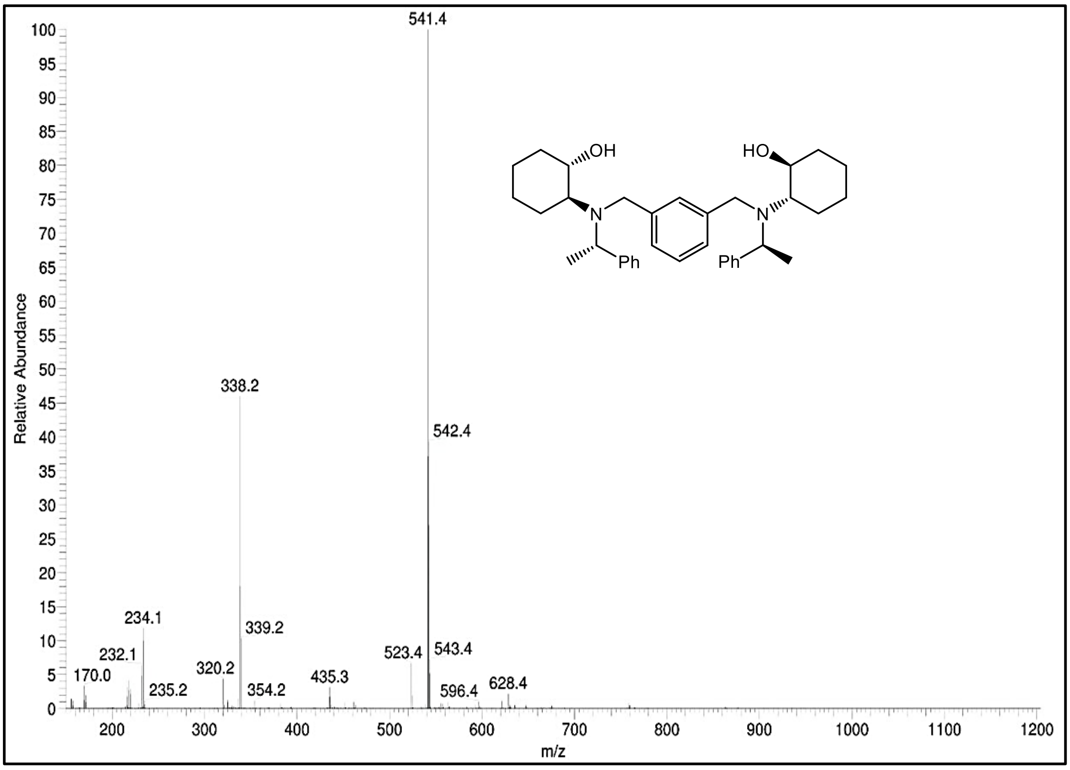
^{1}H NMR Spectra of Compound (**23a**)



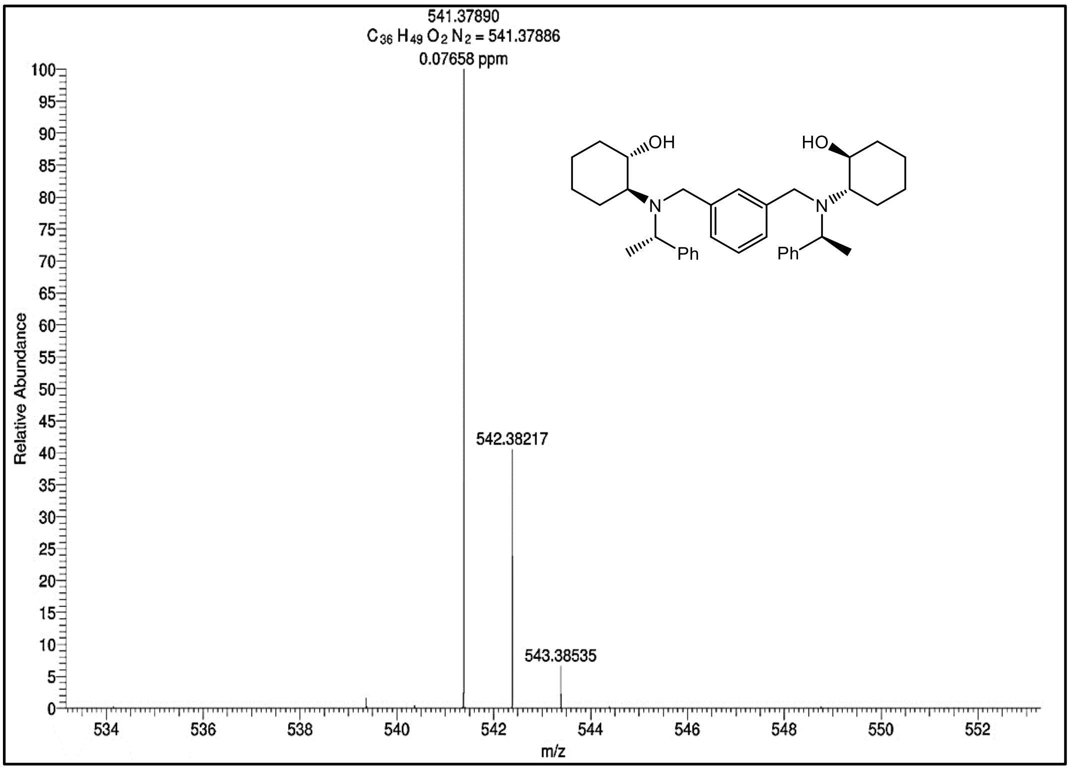
^{13}C NMR Spectra of Compound (**23a**)



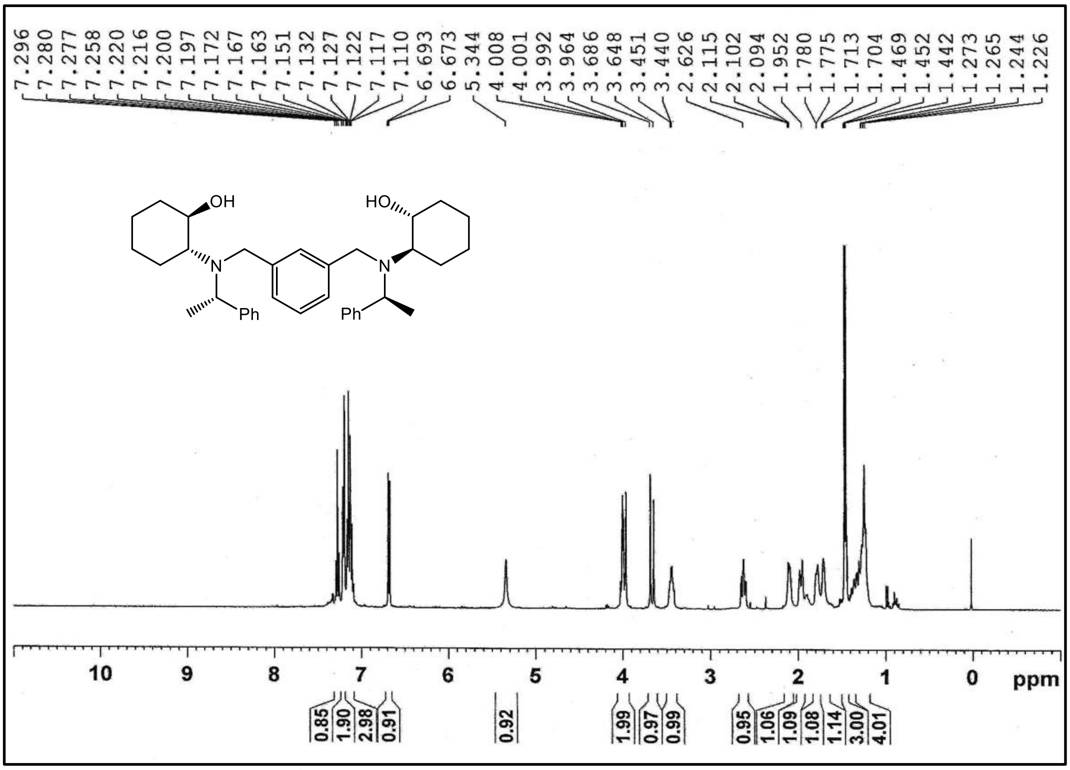
IR Spectra of Compound (**23a**)



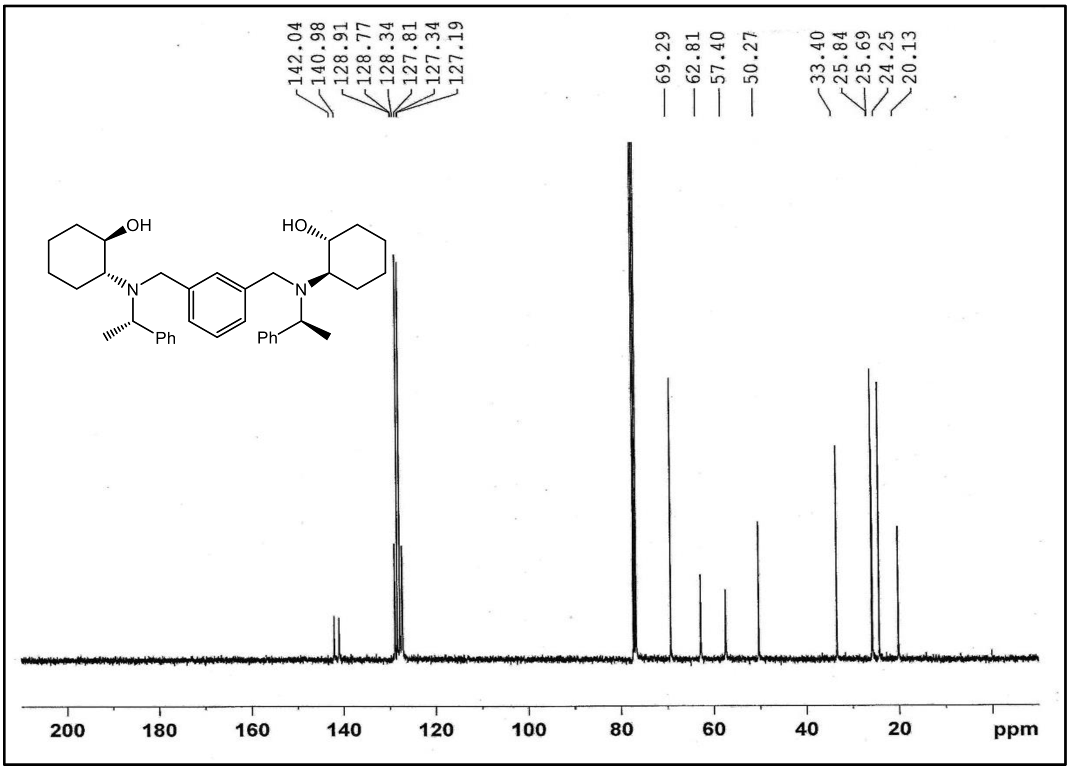
MS Spectra of Compound (**23a**)



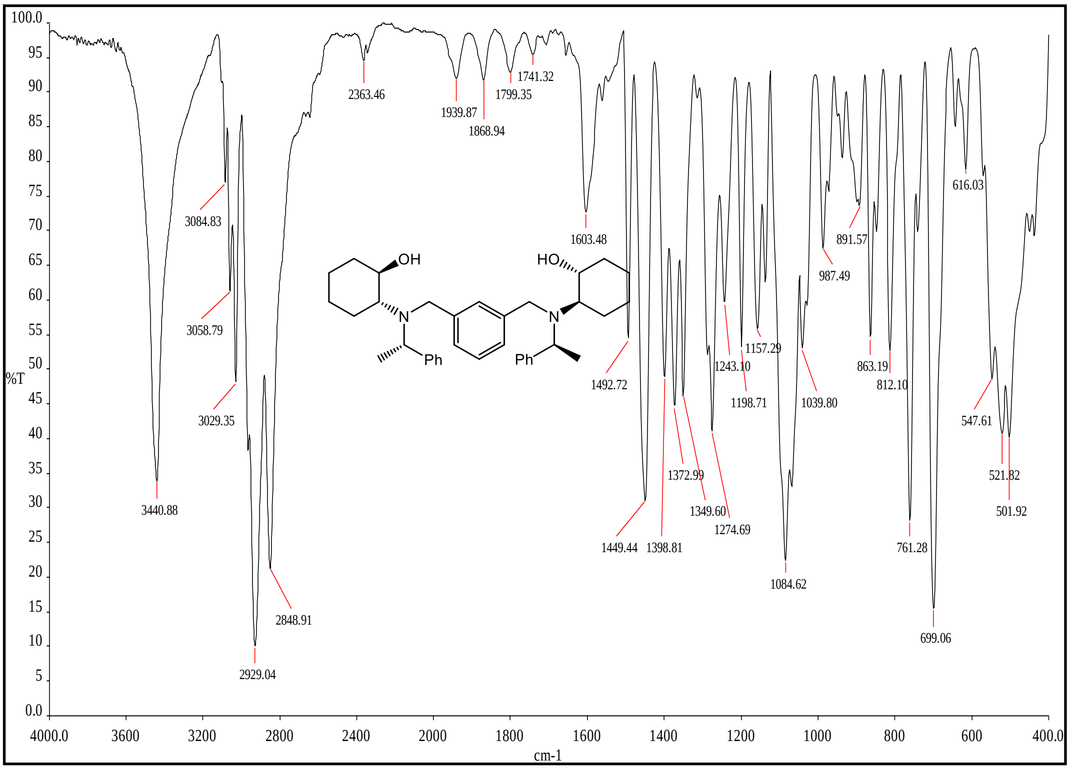
HRMS Spectra of Compound (**23a**)



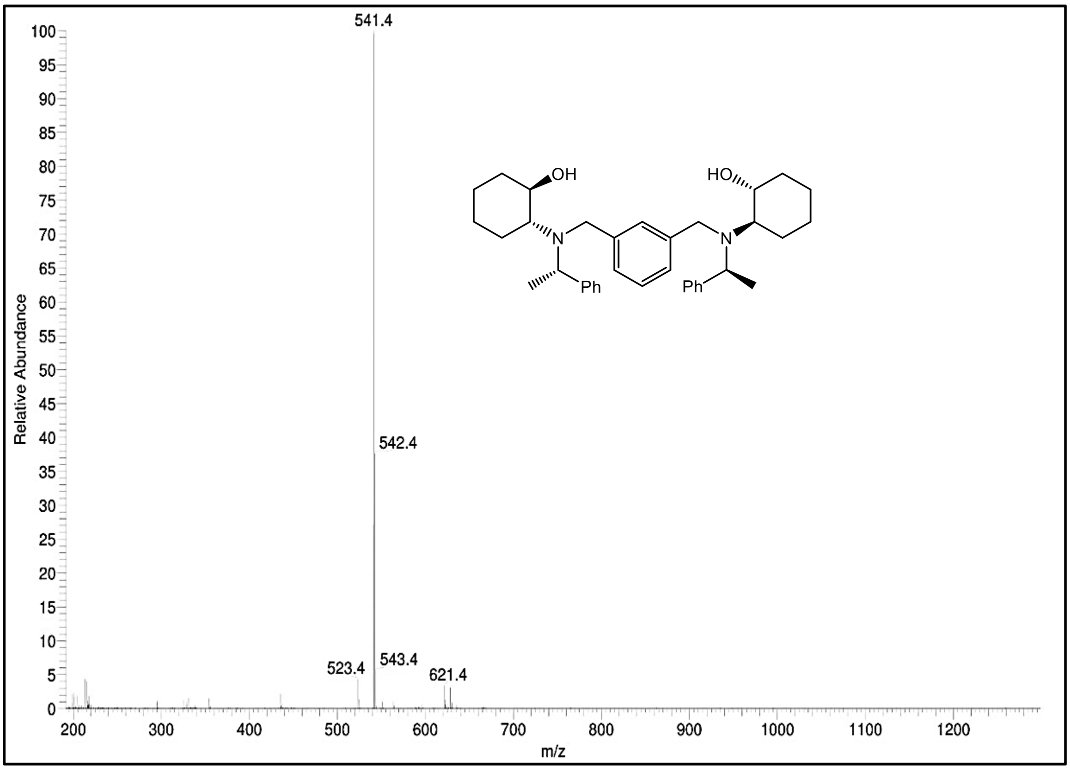
^{1}H NMR Spectra of Compound (**23b**)



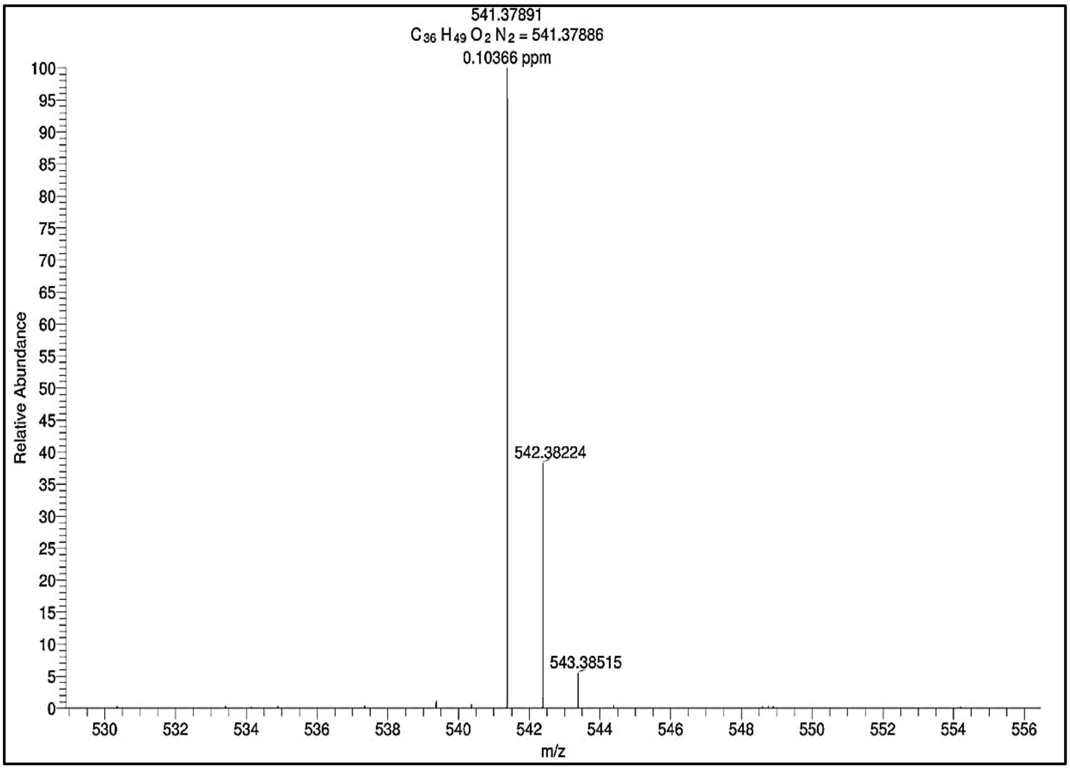
^{13}C NMR Spectra of Compound (**23b**)



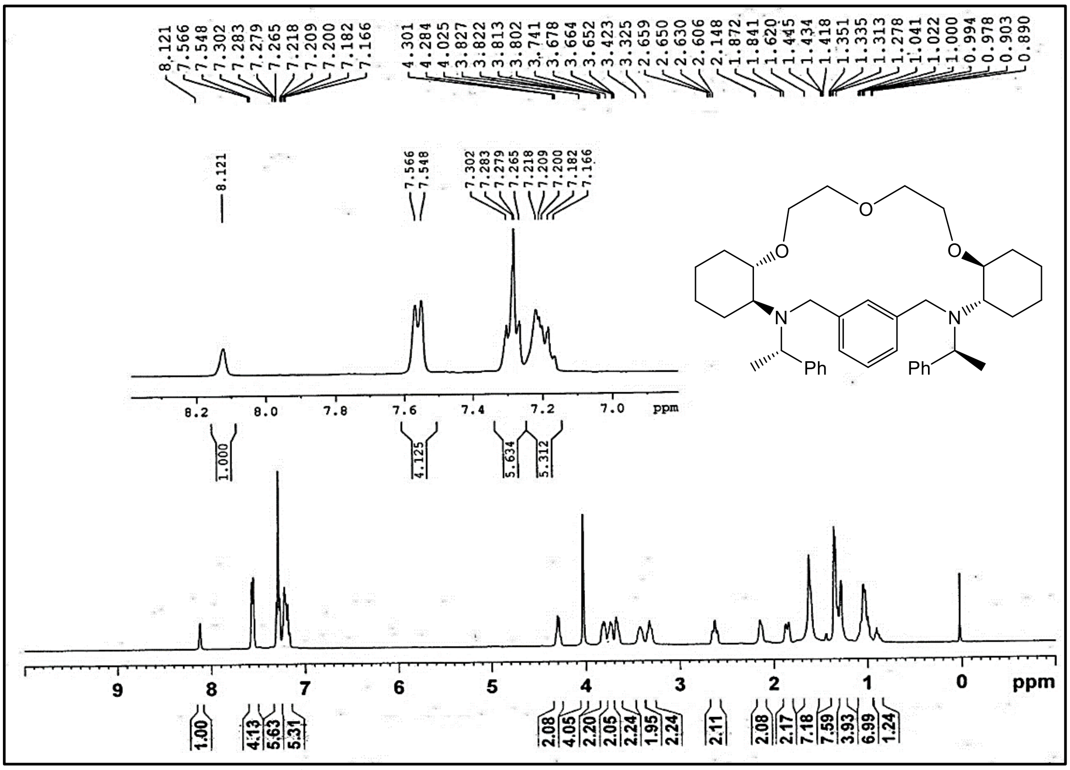
IR Spectra of Compound (**23b**)



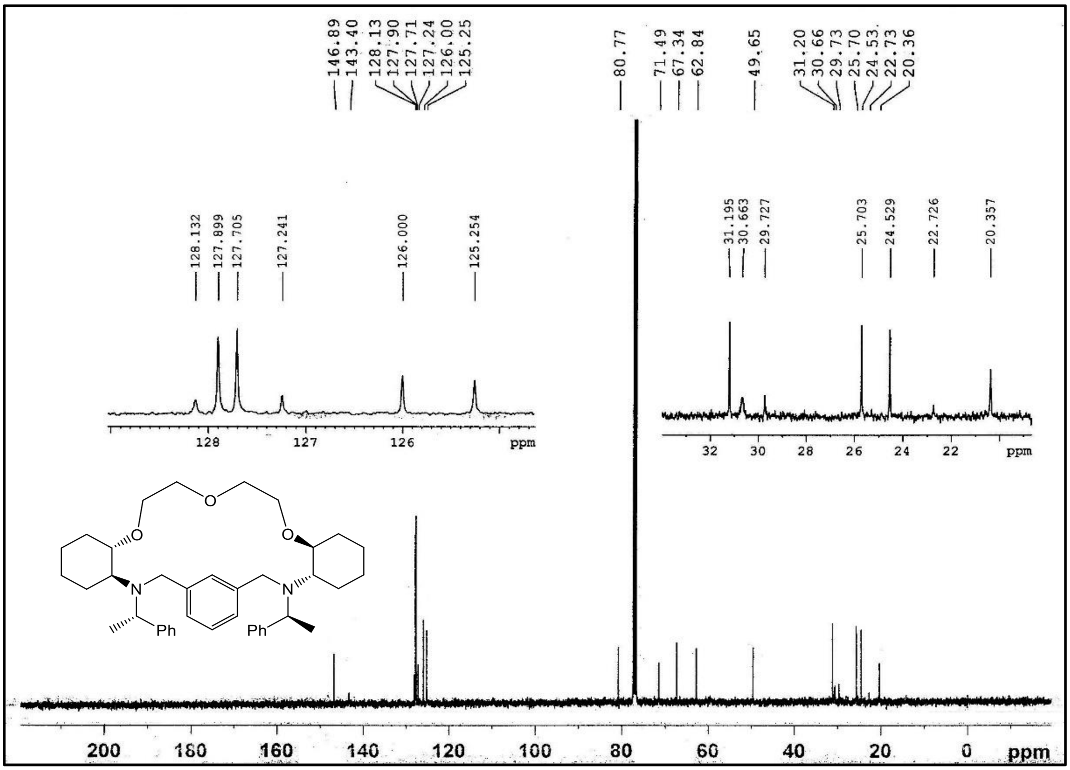
MS Spectra of Compound (**23b**)



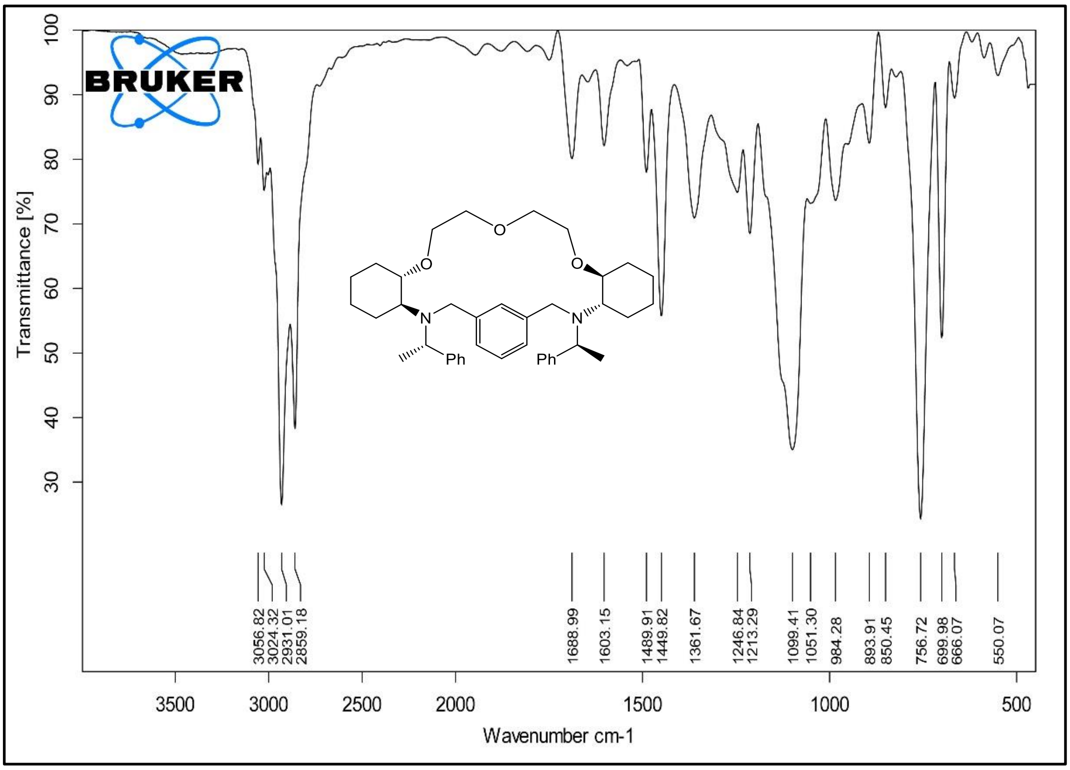
HRMS Spectra of Compound (**23b**)



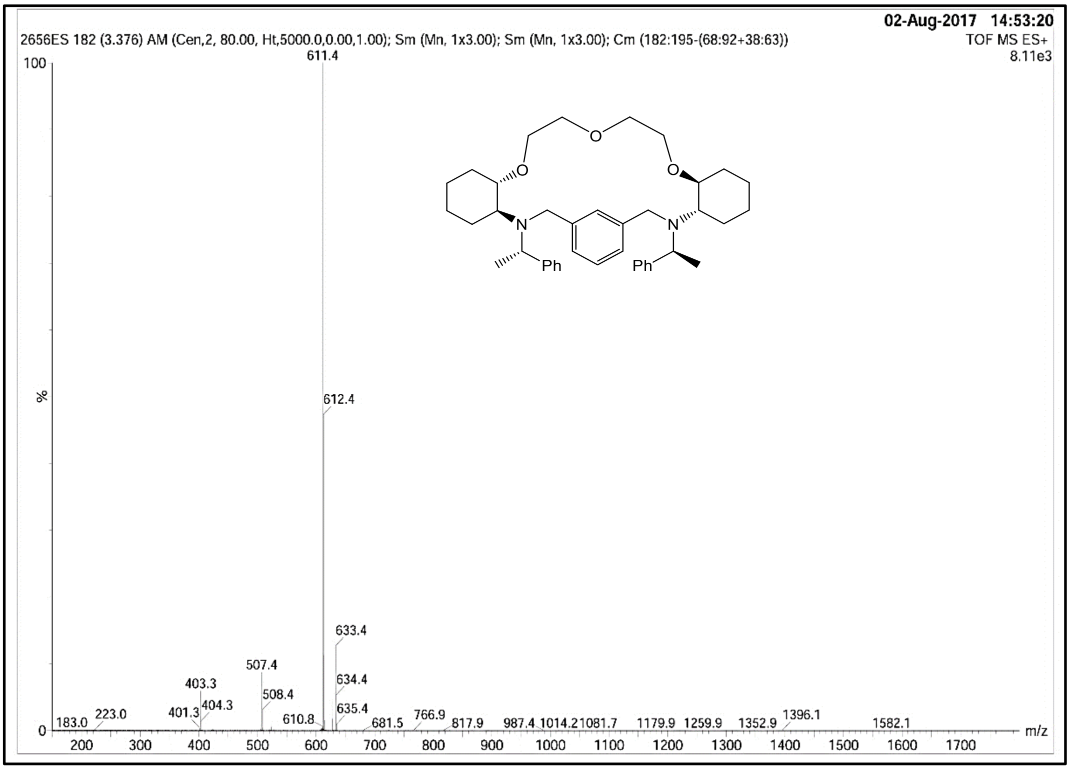
^{1}H NMR Spectra of Compound (**24a**)



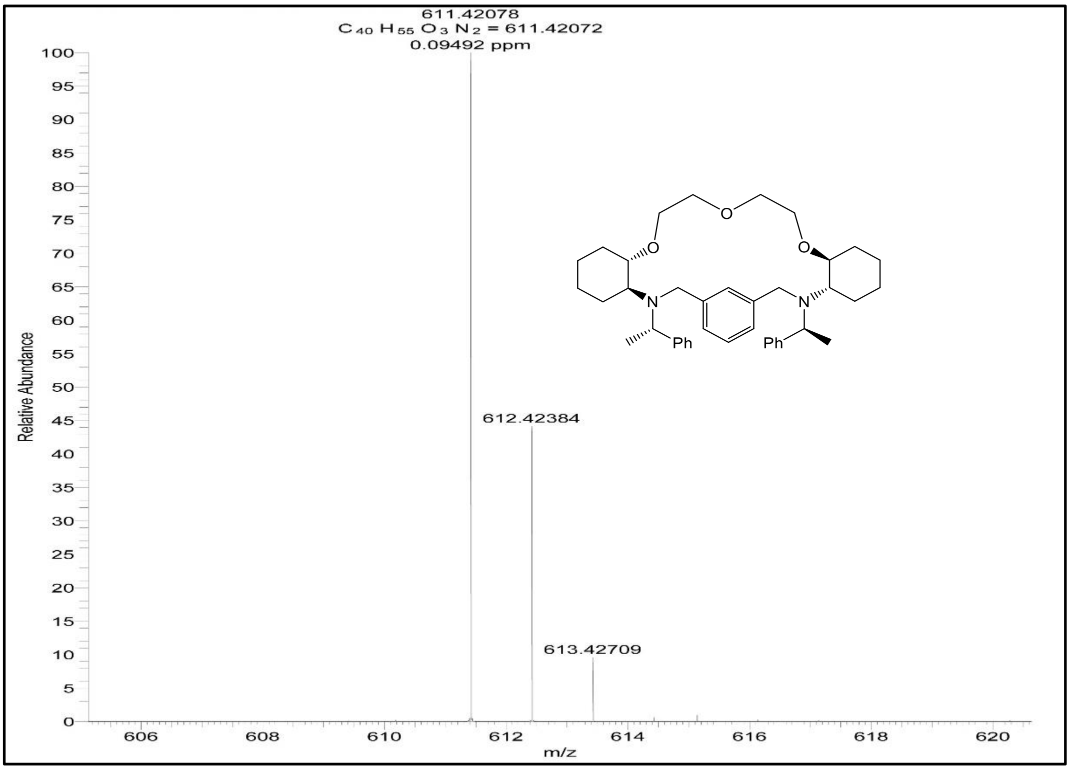
^{13}C NMR Spectra of Compound (**24a**)



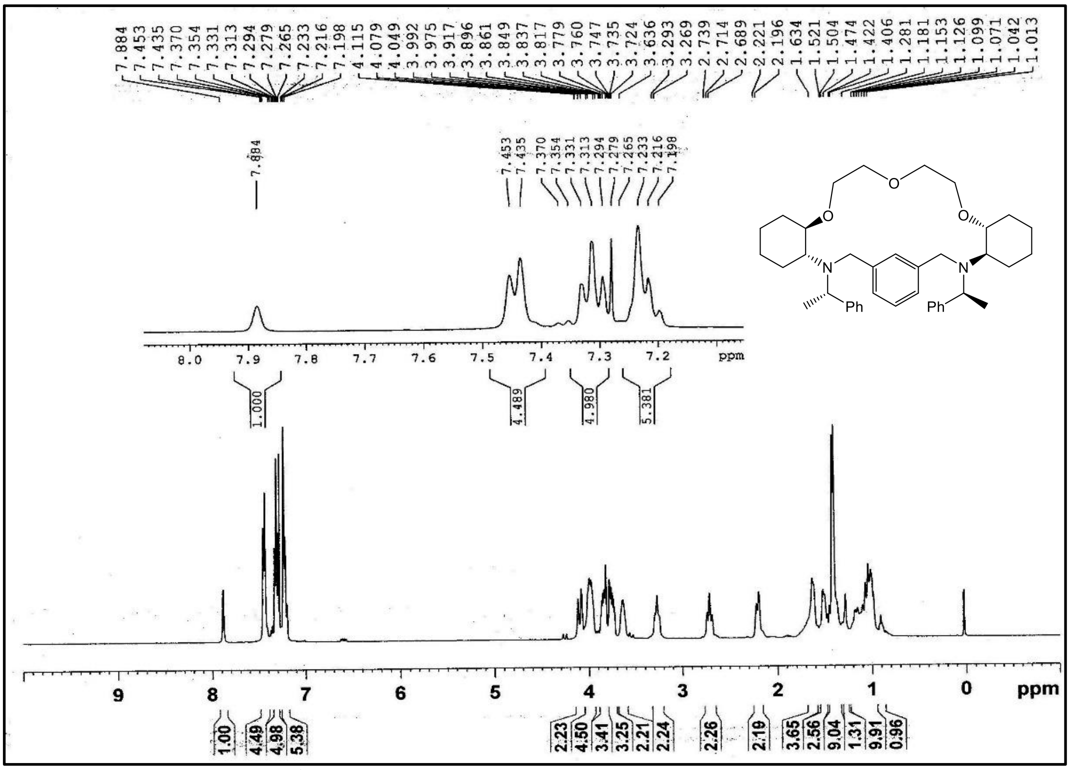
IR Spectra of Compound (**24a**)



MS Spectra of Compound (**24a**)



HRMS Spectra of Compound (**24a**)



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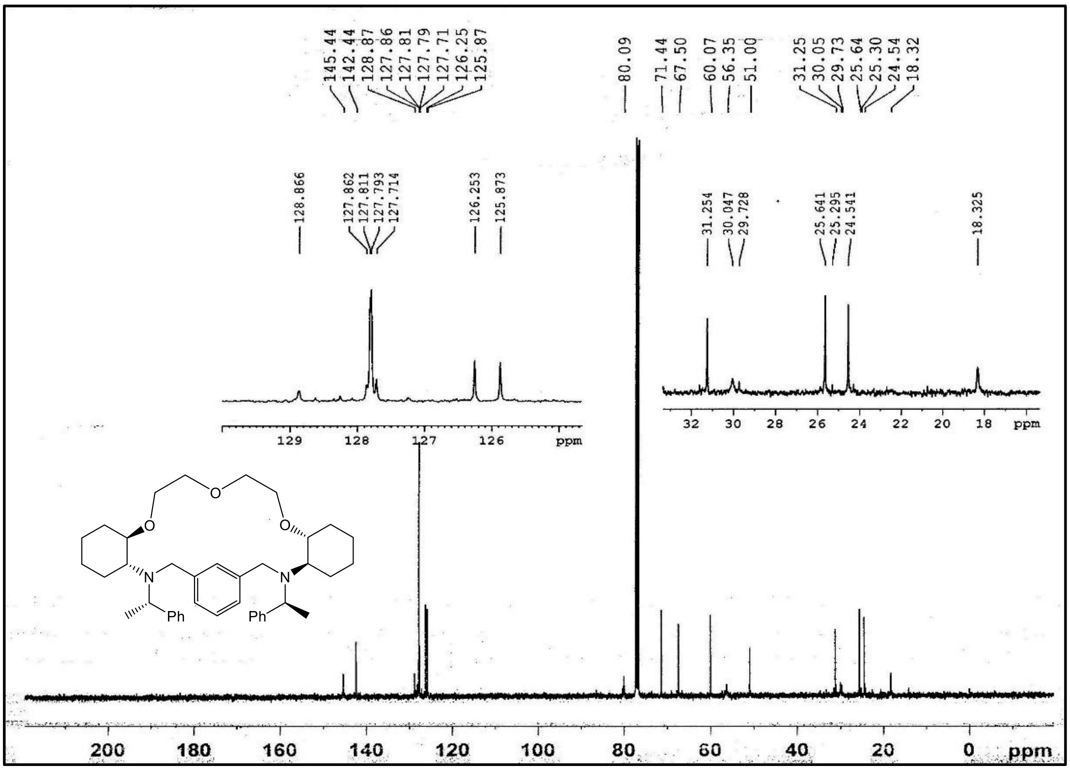
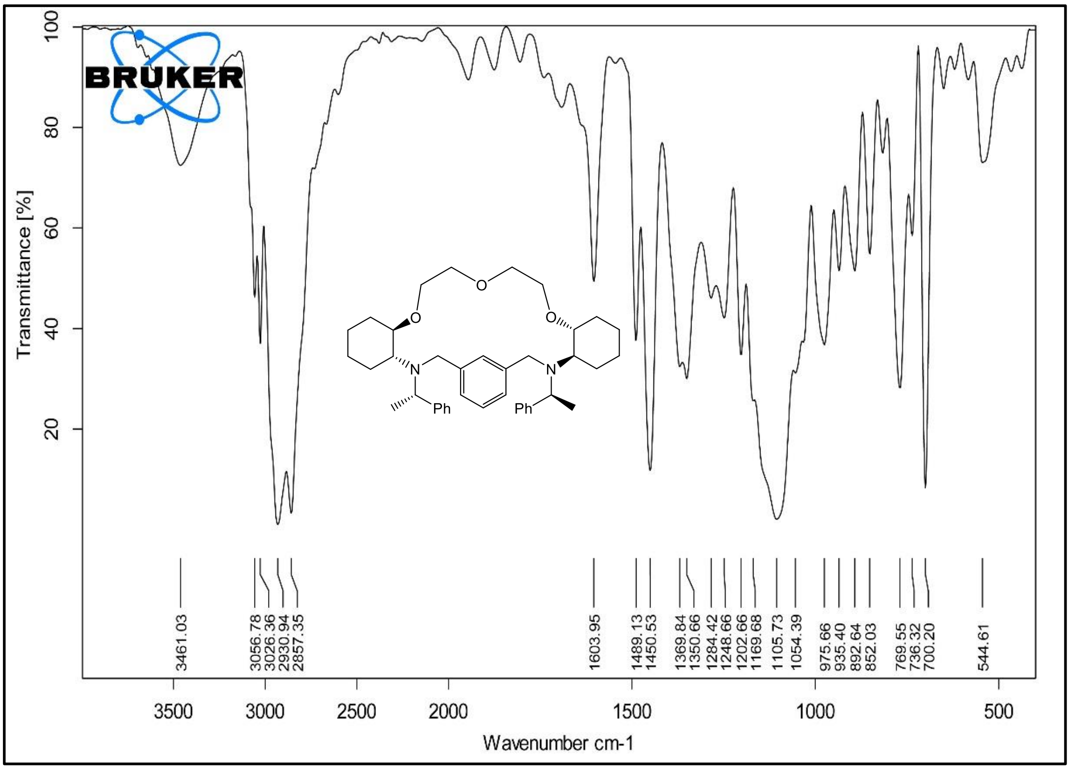
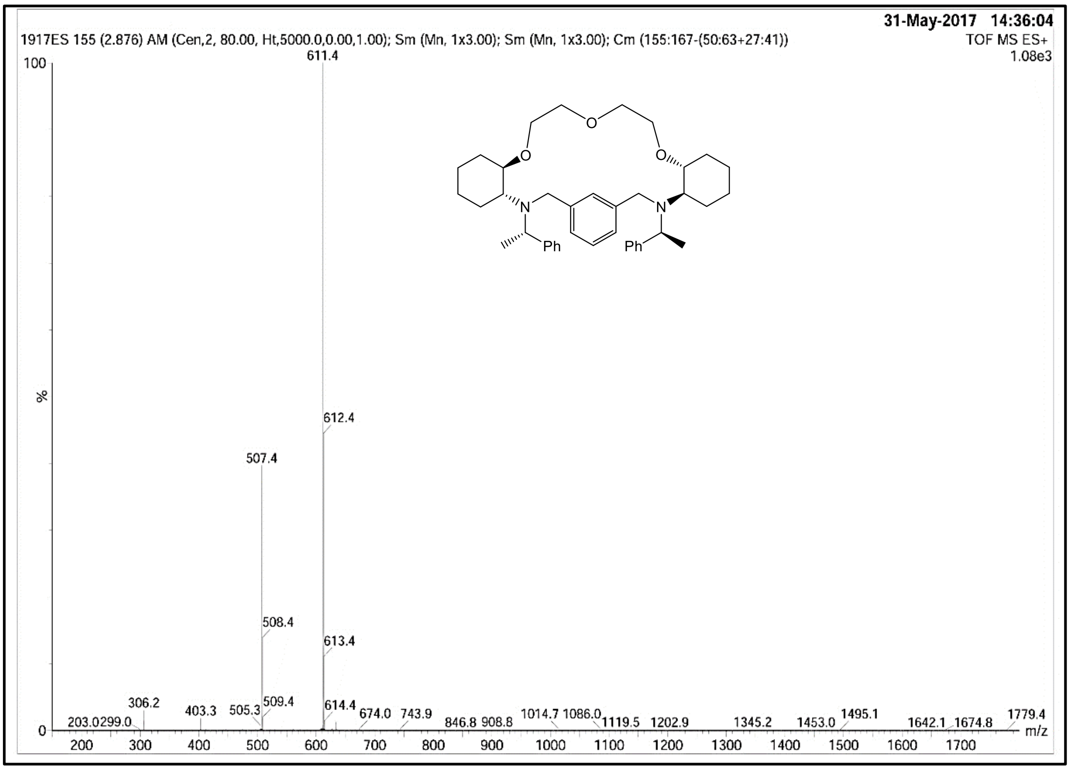


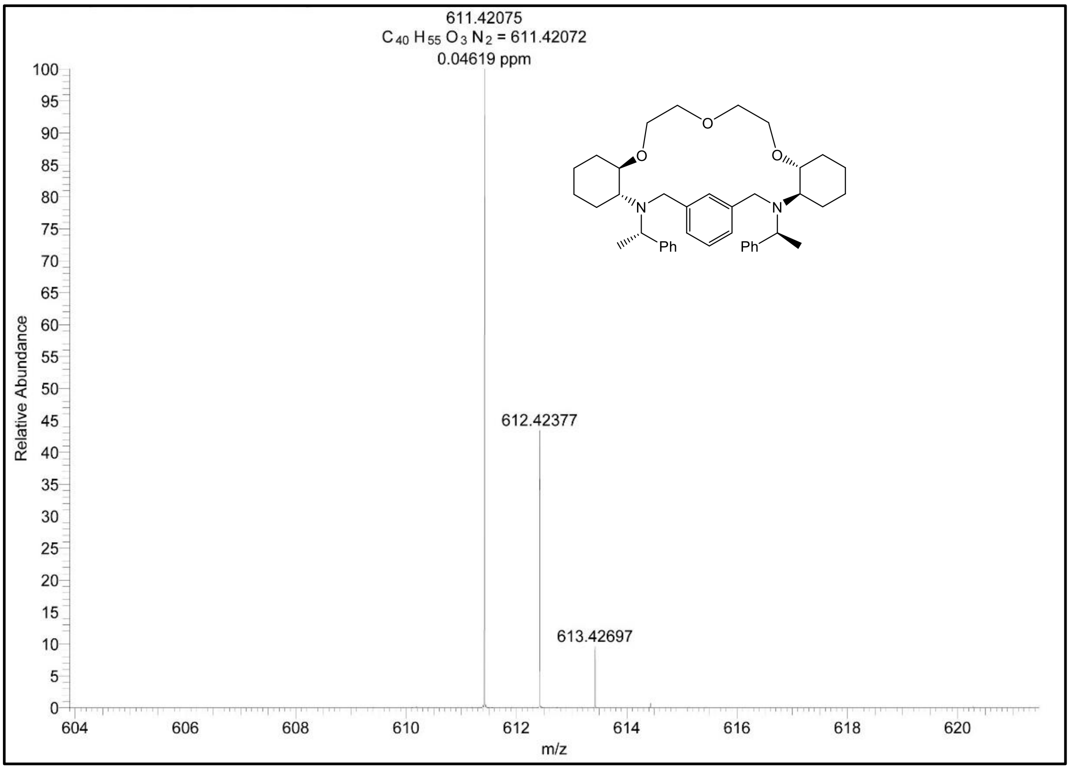
^{13}C NMR Spectra of Compound (**24b**)



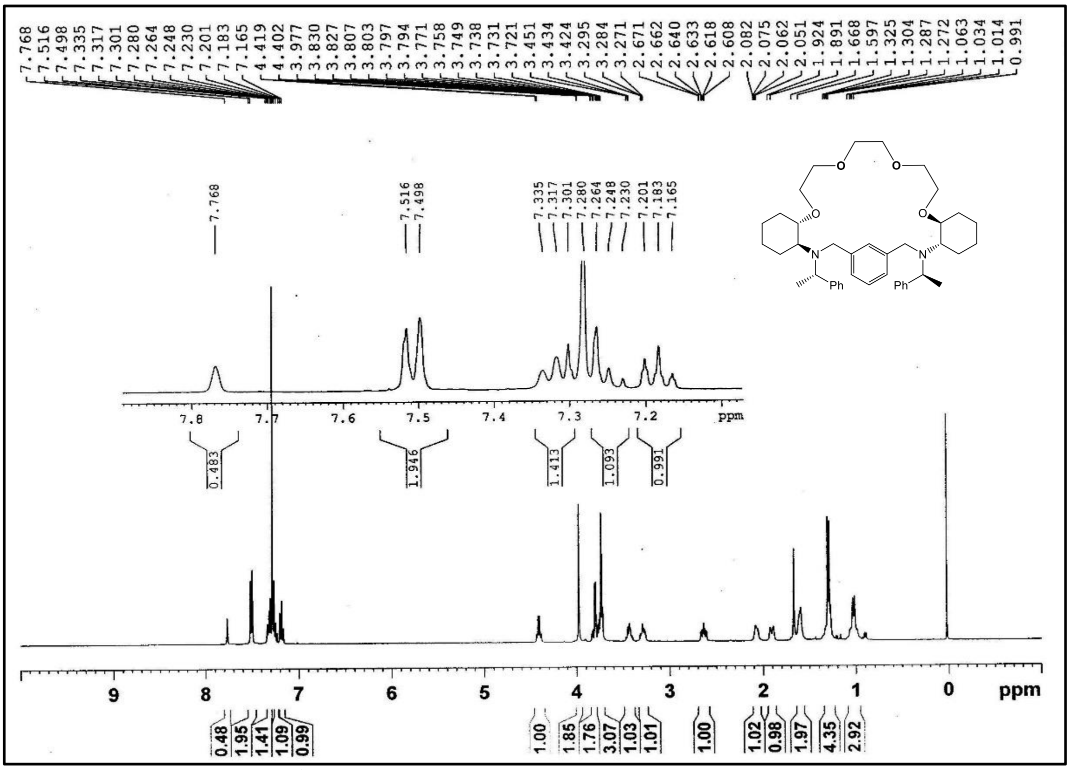
IR Spectra of Compound (**24b**)



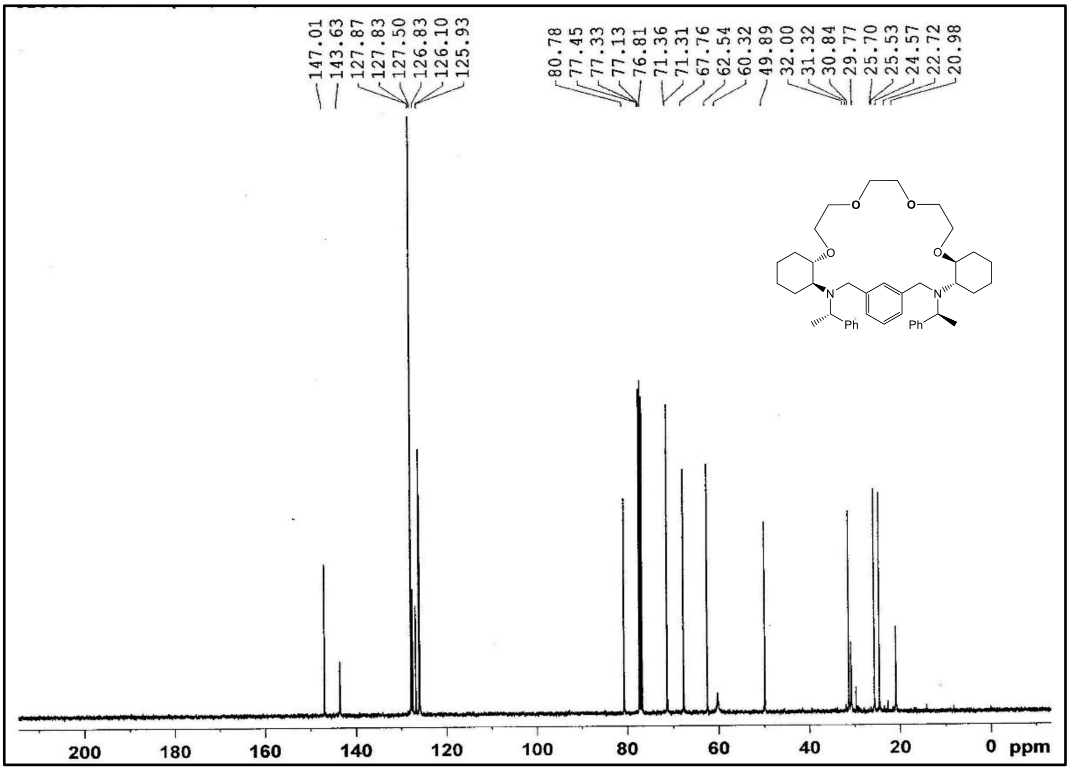
MS Spectra of Compound (**24b**)



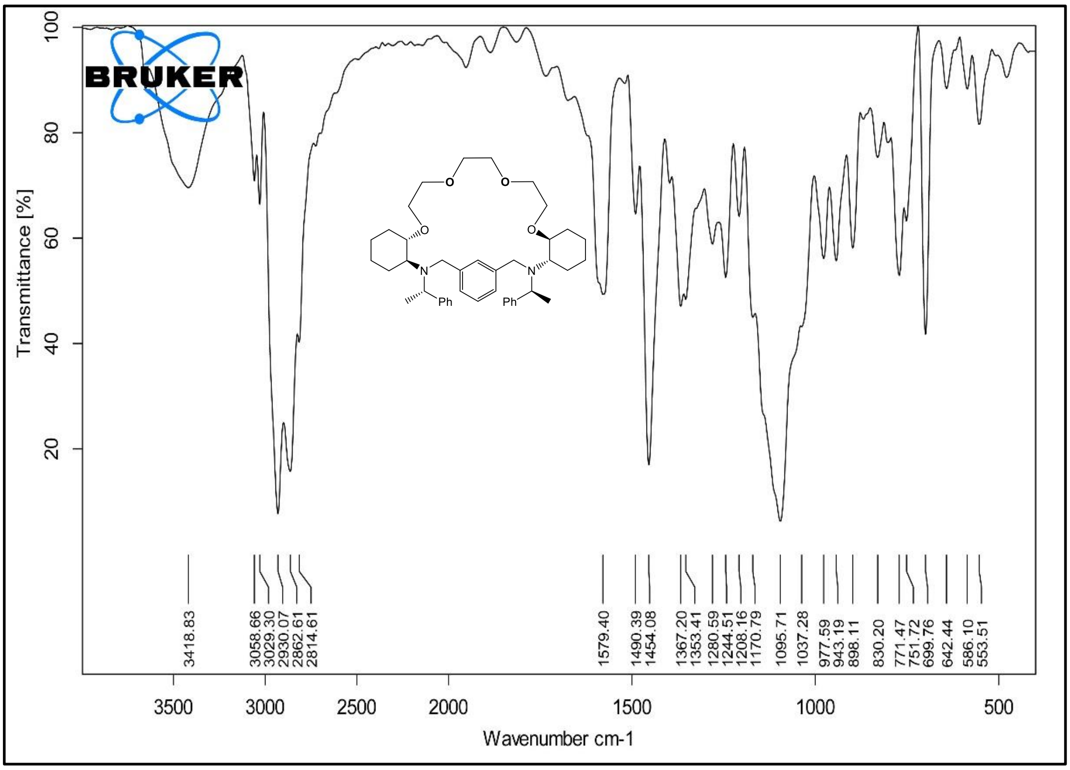
HRMS Spectra of Compound (**24b**)



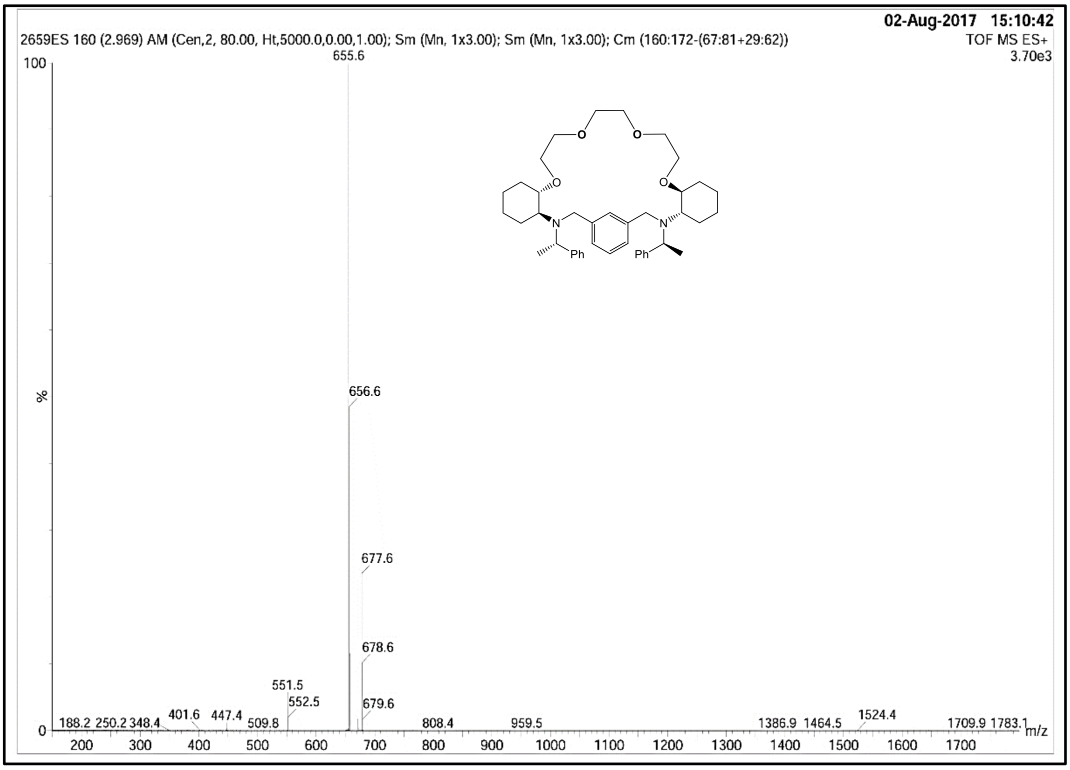
^{1}H NMR Spectra of Compound (**25a**)



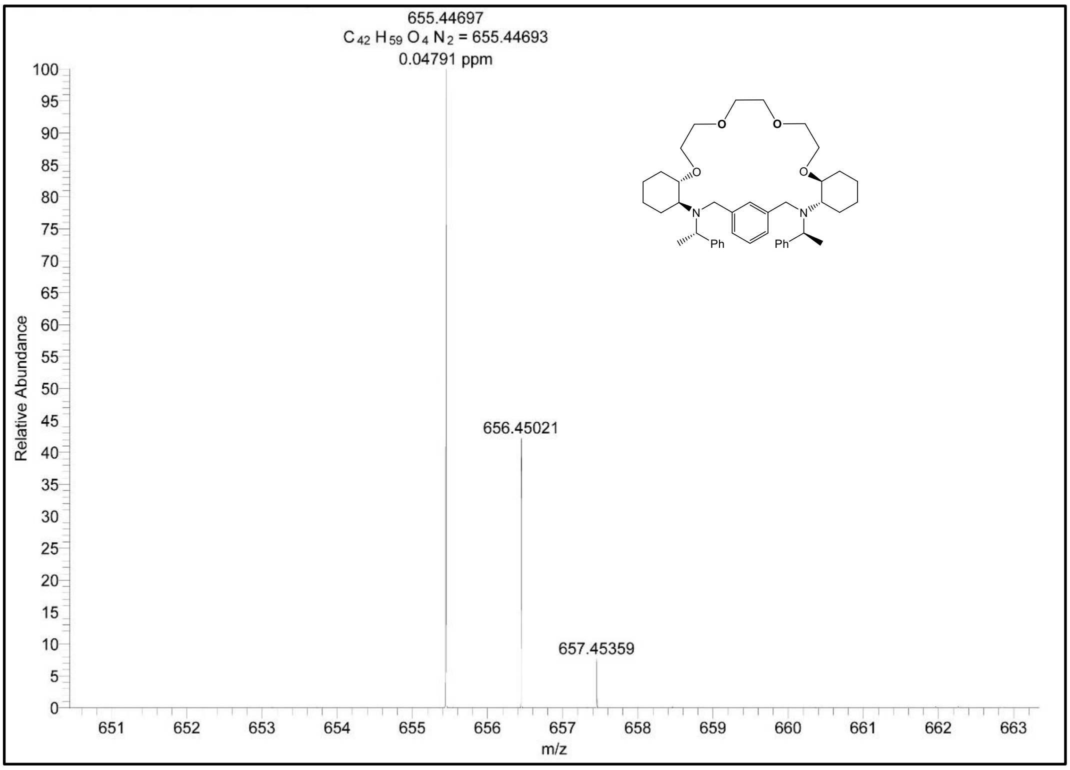
^{13}C NMR Spectra of Compound (**25a**)



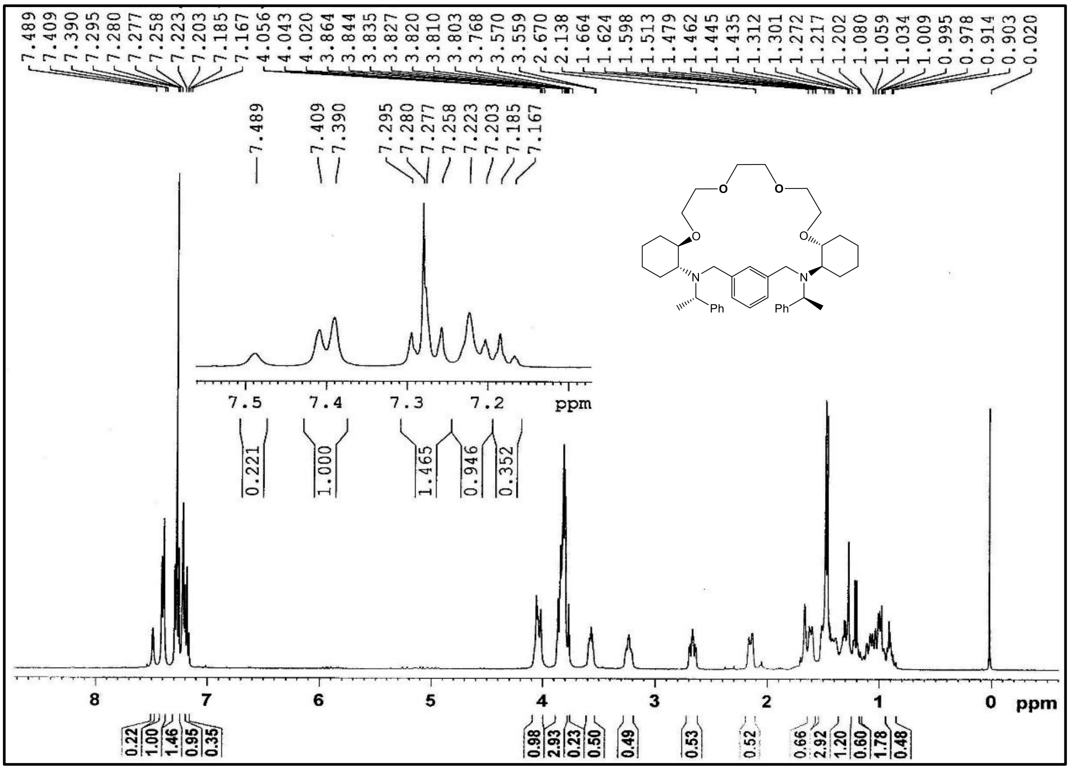
IR Spectra of Compound (**25a**)



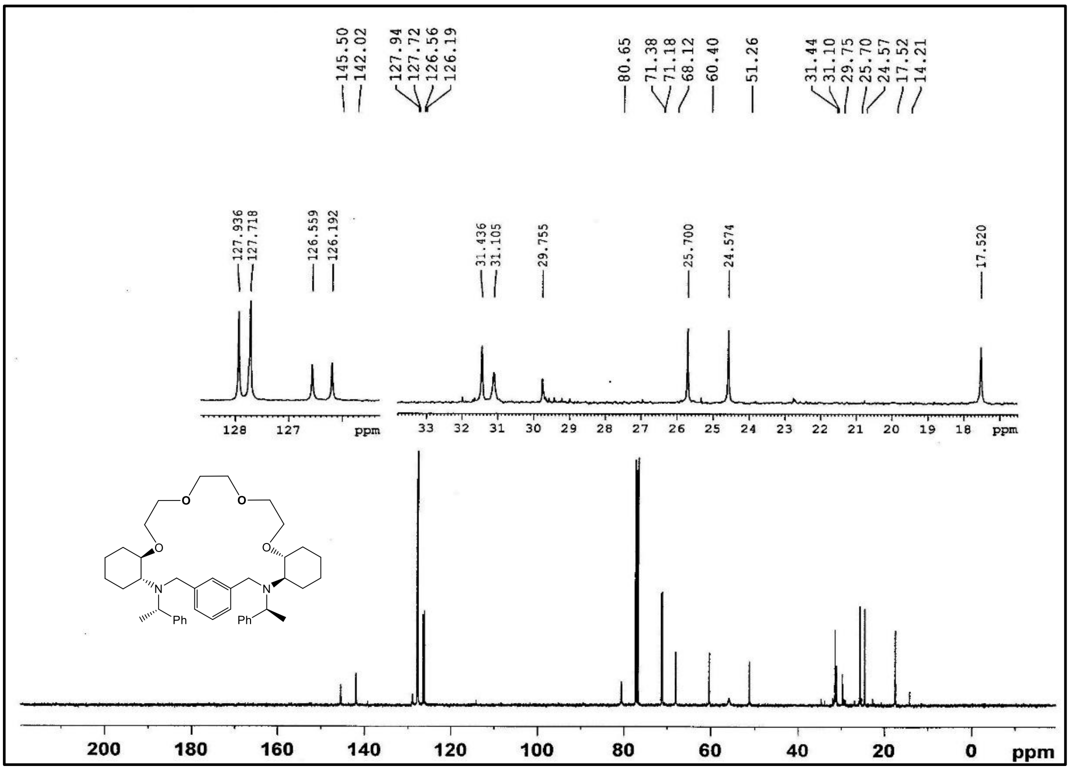
MS Spectra of Compound (**25a**)



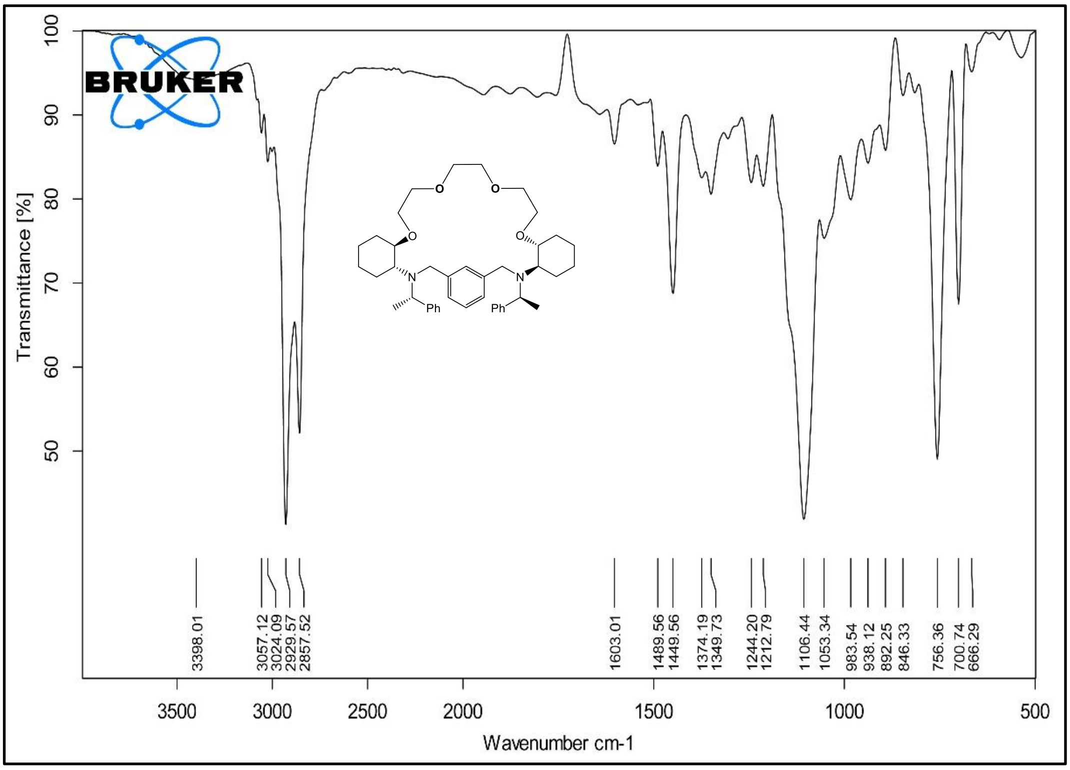
HRMS Spectra of Compound (**25a**)



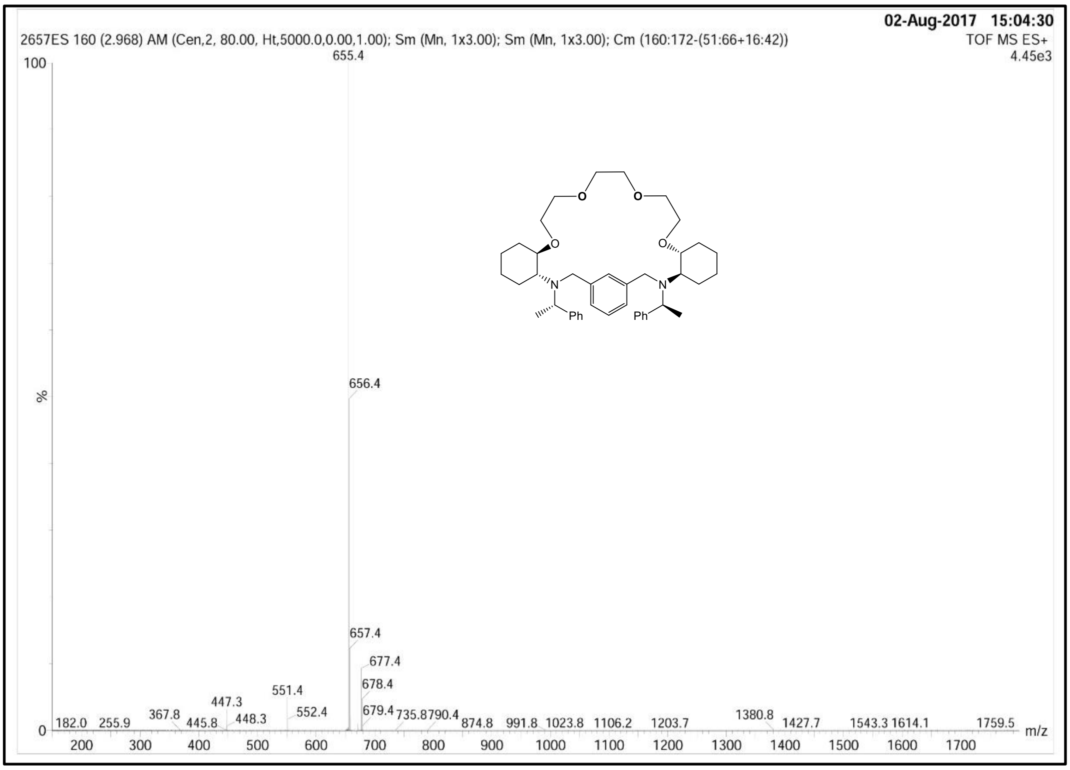
^{1}H NMR Spectra of Compound (**25b**)



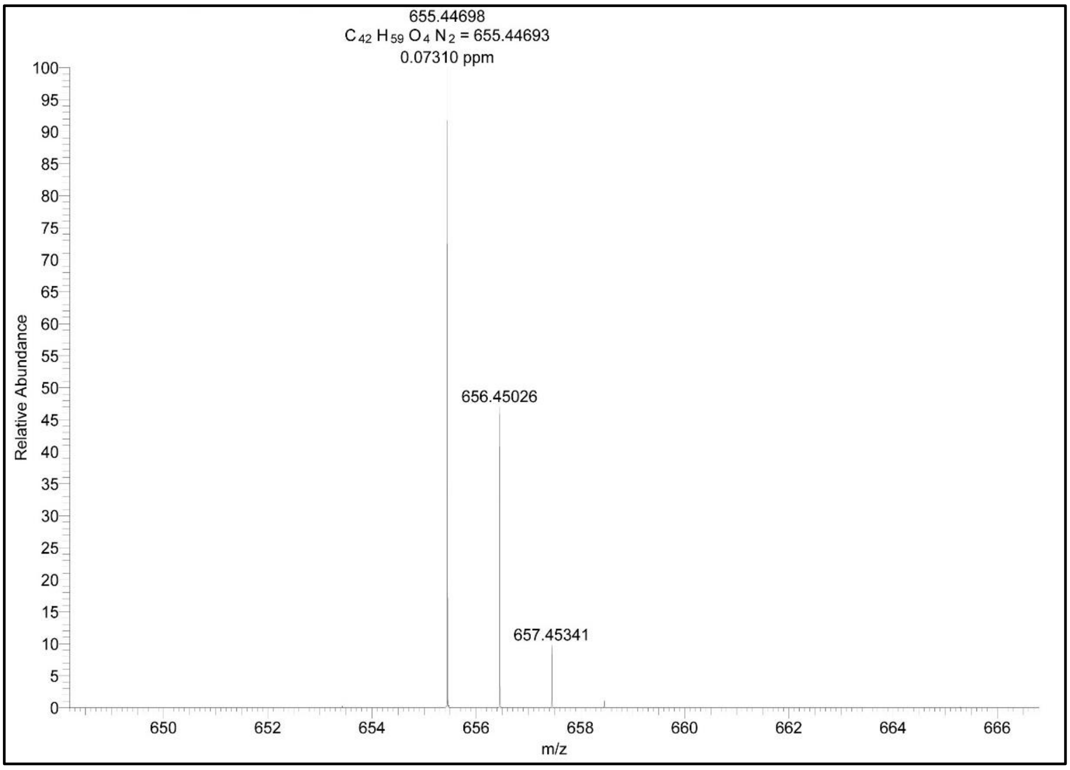
^{13}C NMR Spectra of Compound (**25b**)



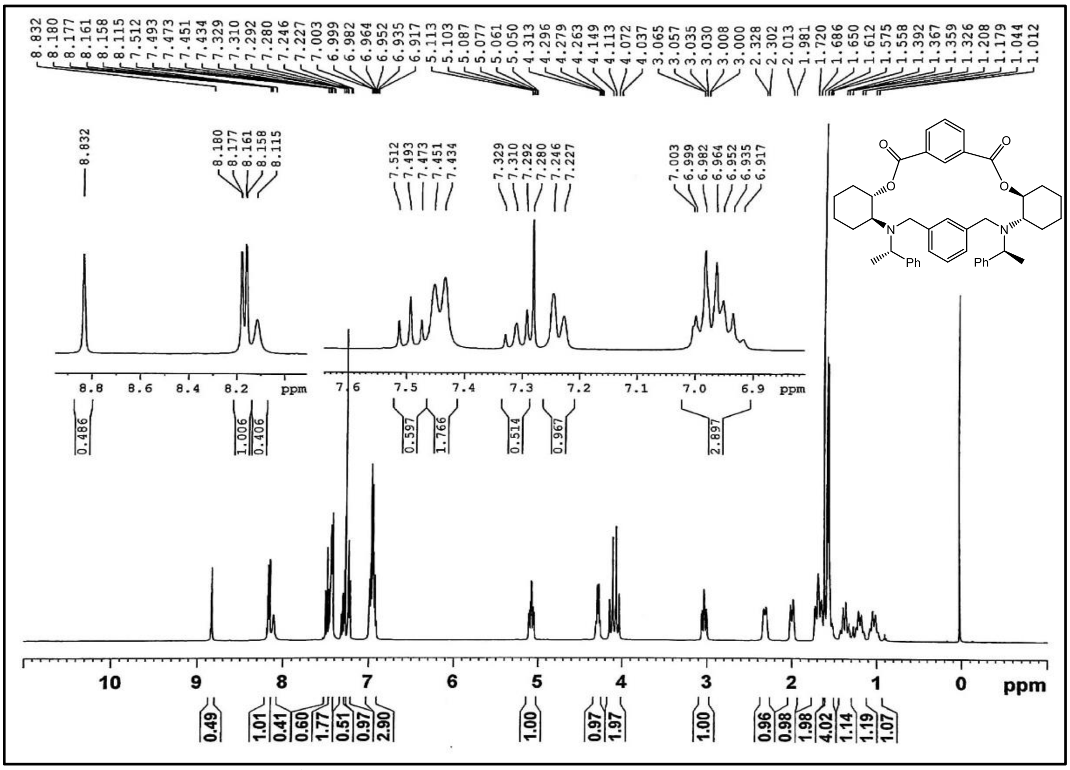
IR Spectra of Compound (**25b**)



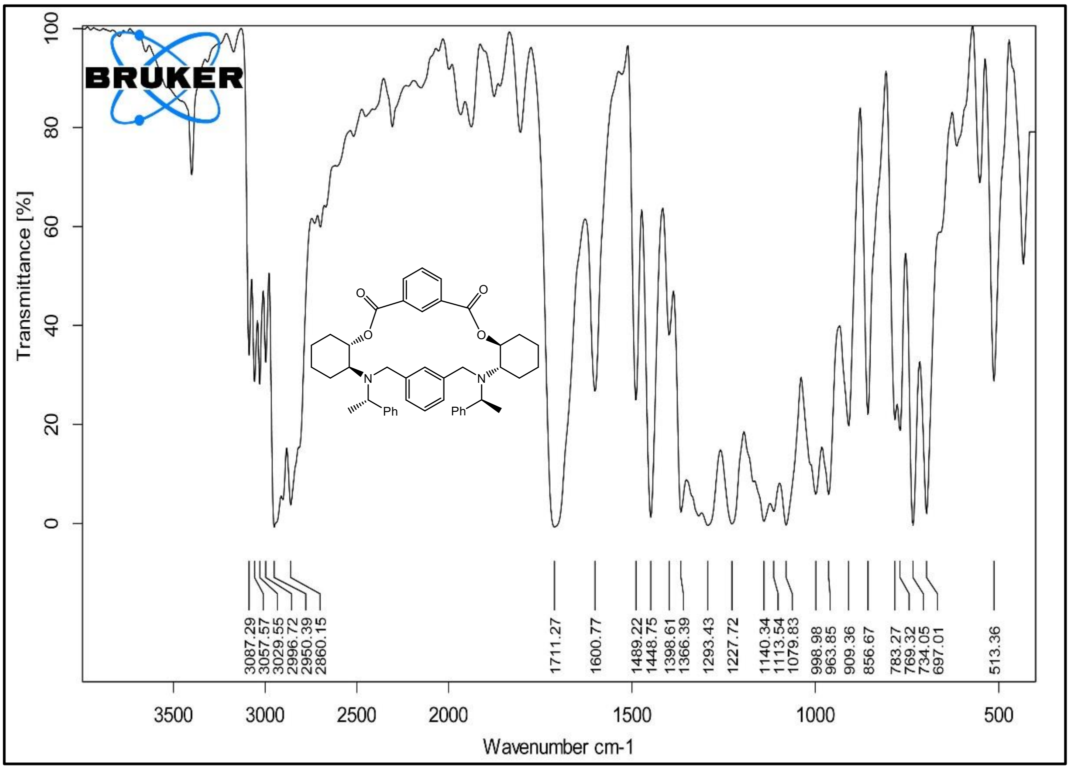
MS Spectra of Compound (**25b**)



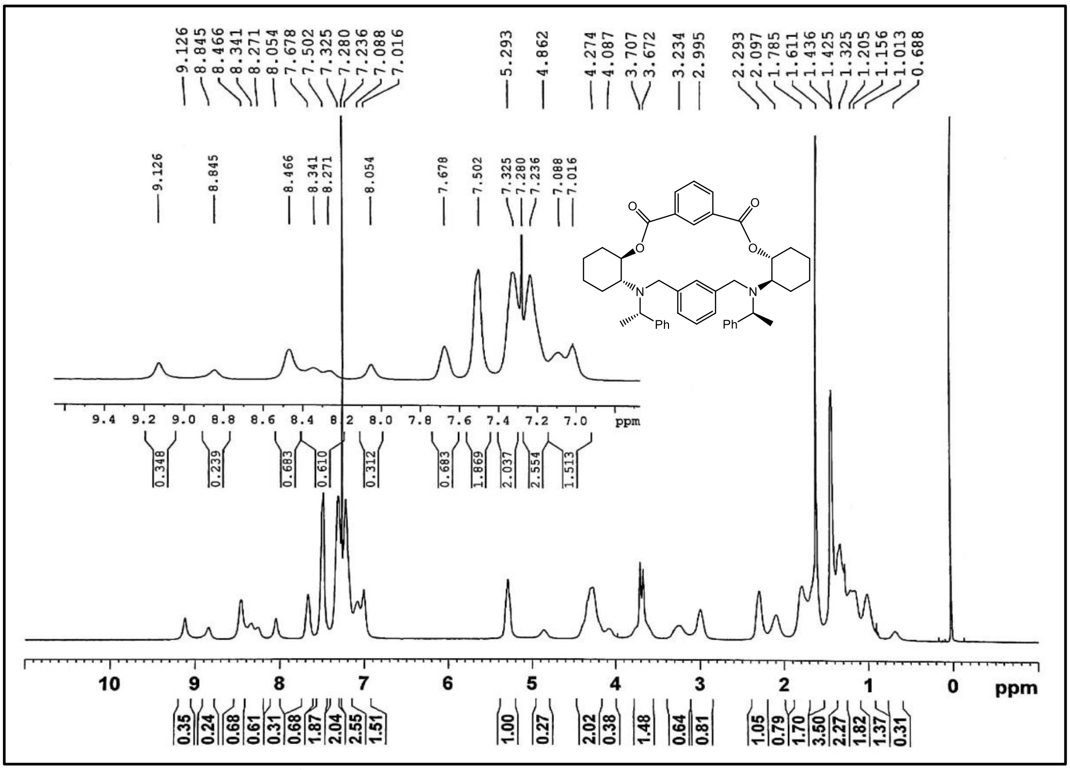
HRMS Spectra of Compound (**25b**)



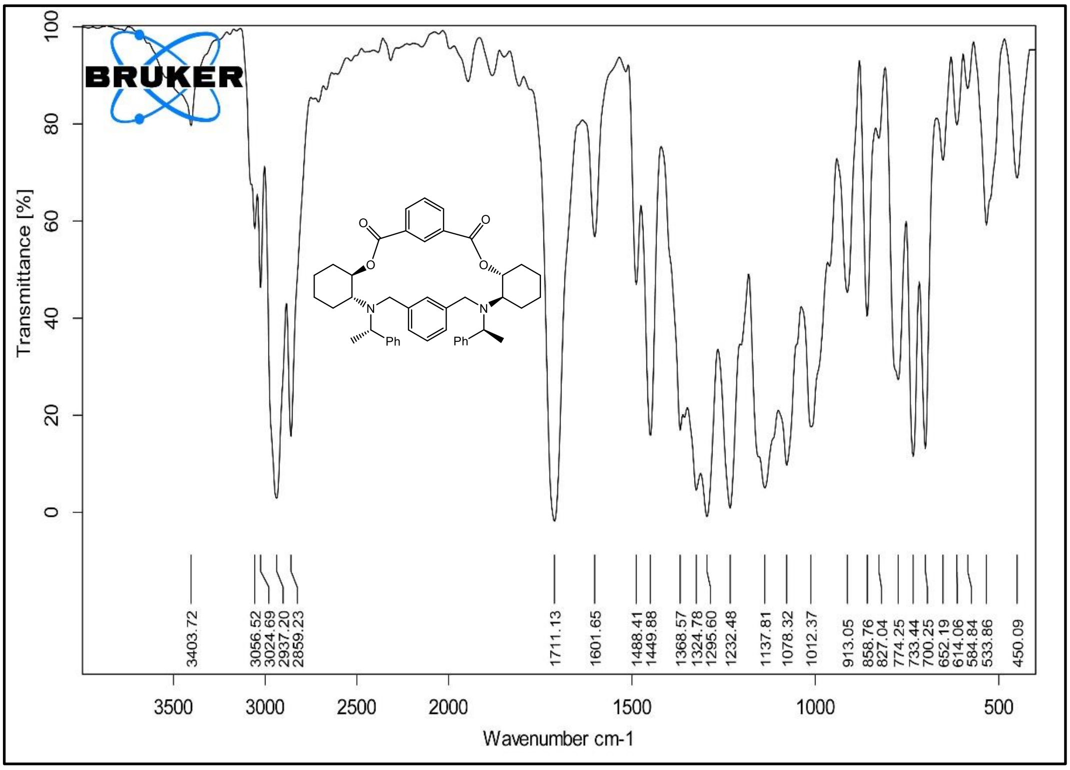
^{1}H NMR Spectra of Compound (**26a**)



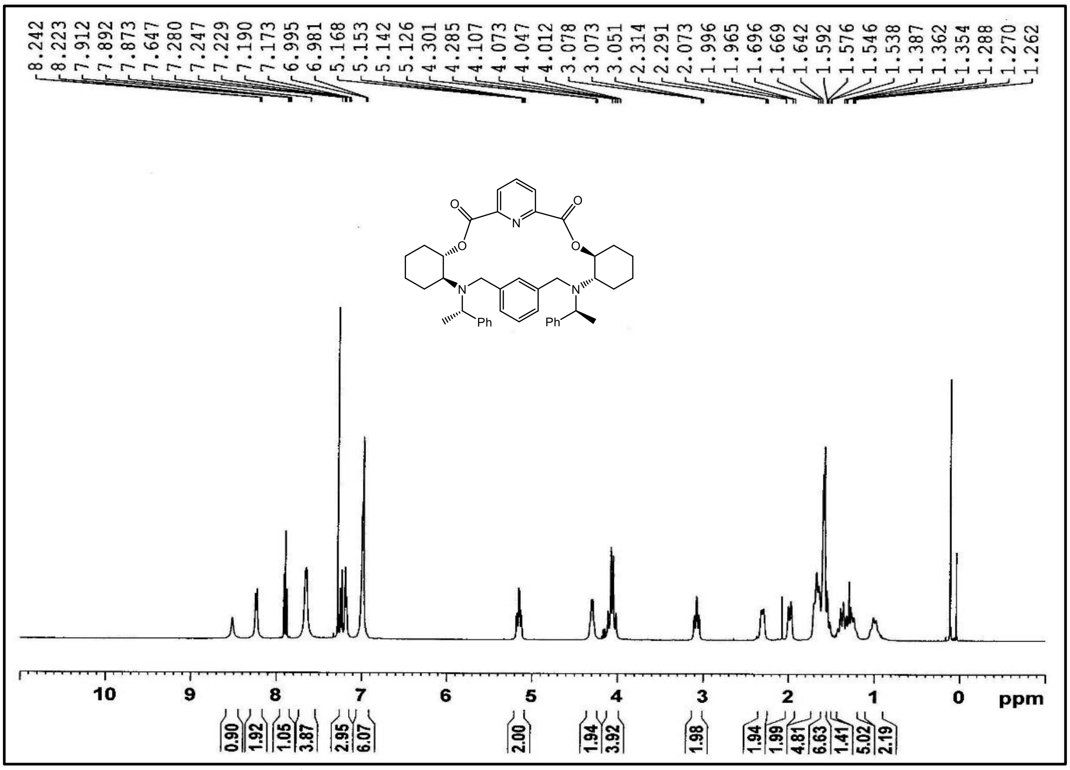
IR Spectra of Compound (**26a**)



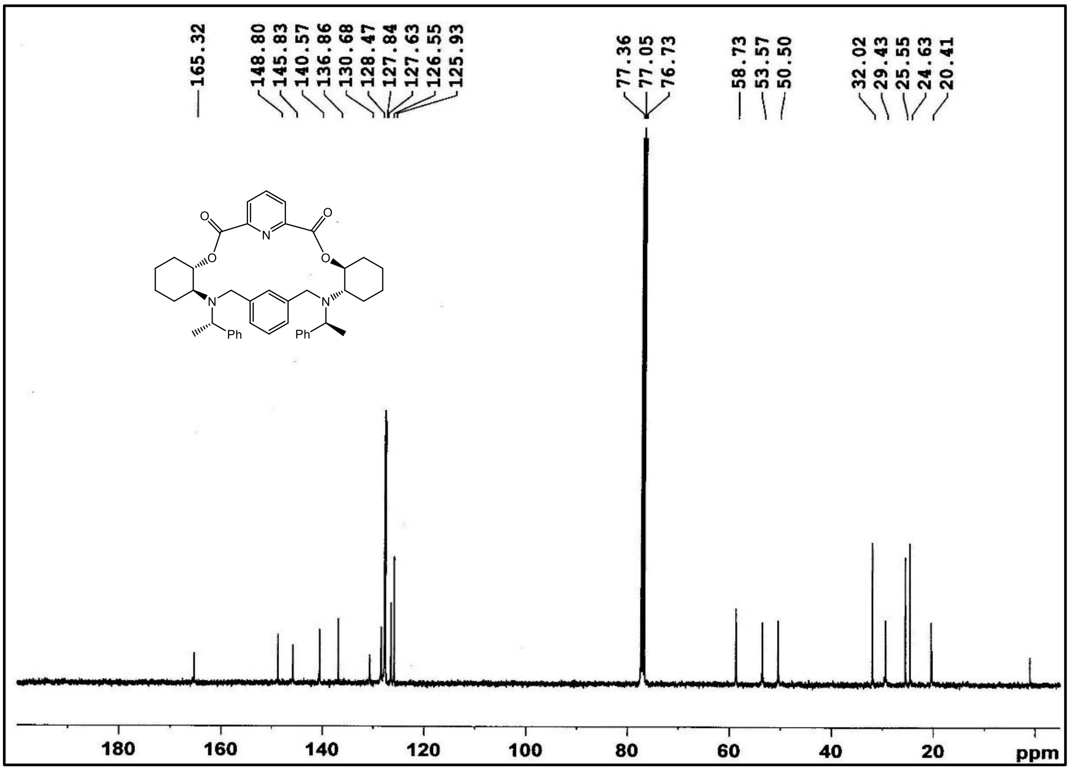
^{1}H NMR Spectra of Compound (**26b**)



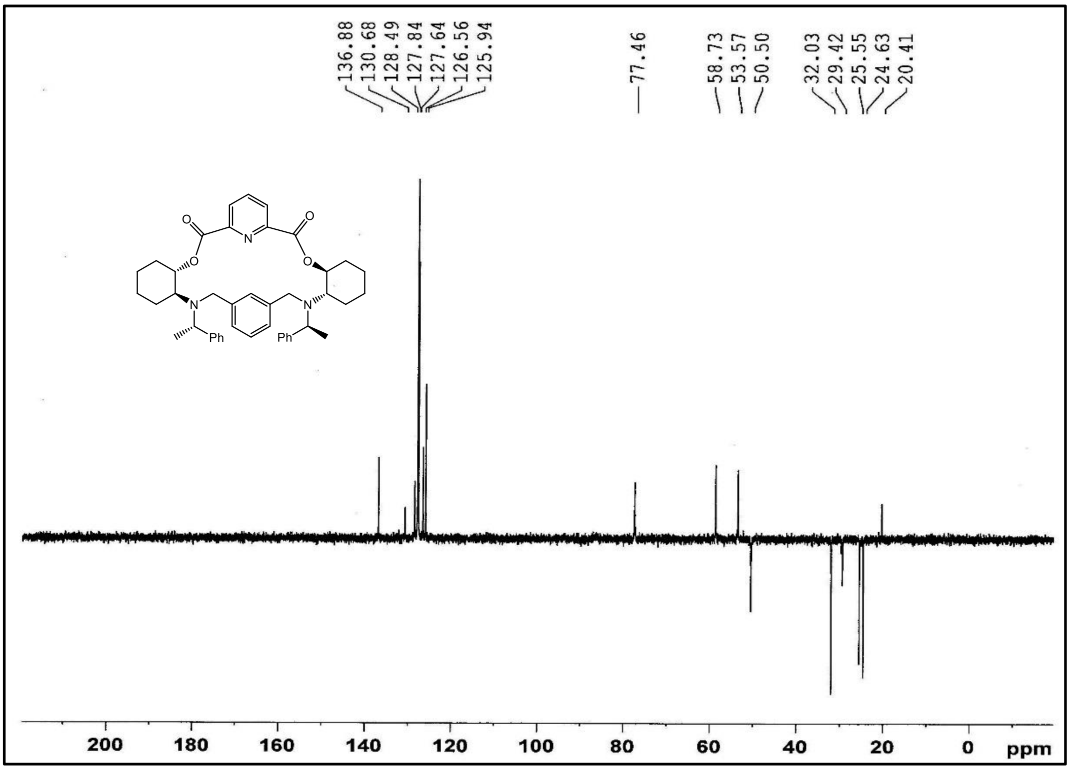
IR Spectra of Compound (**26b**)



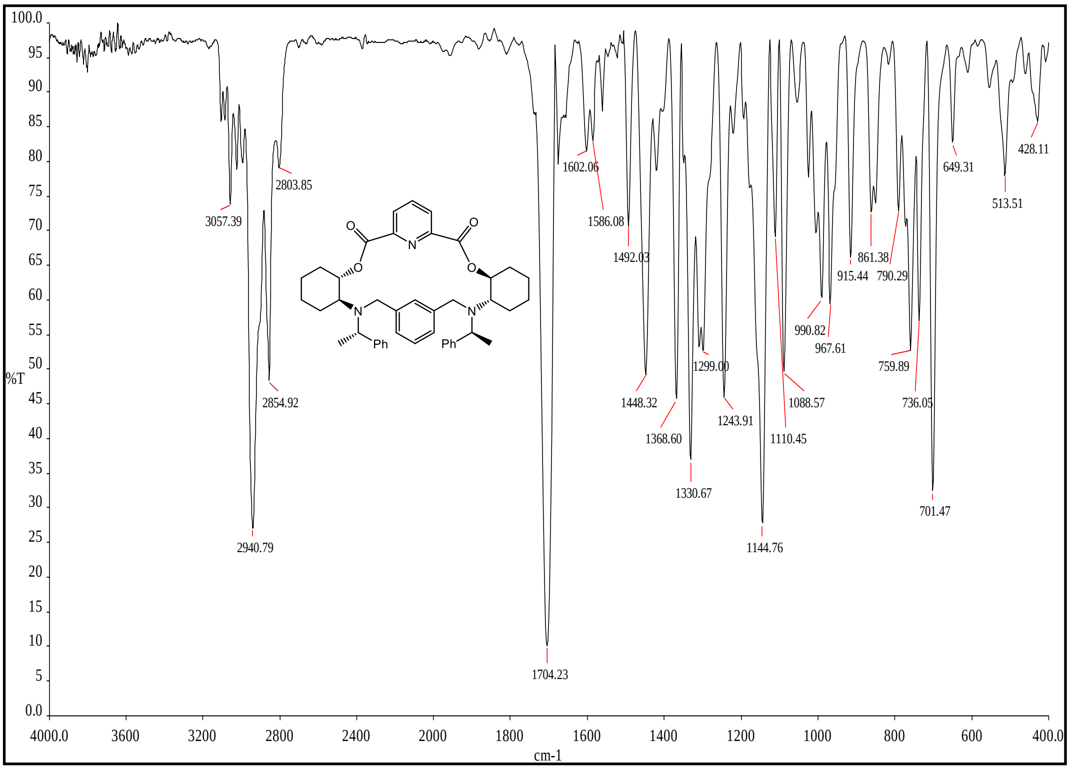
^{1}H NMR Spectra of Compound (**27a**)



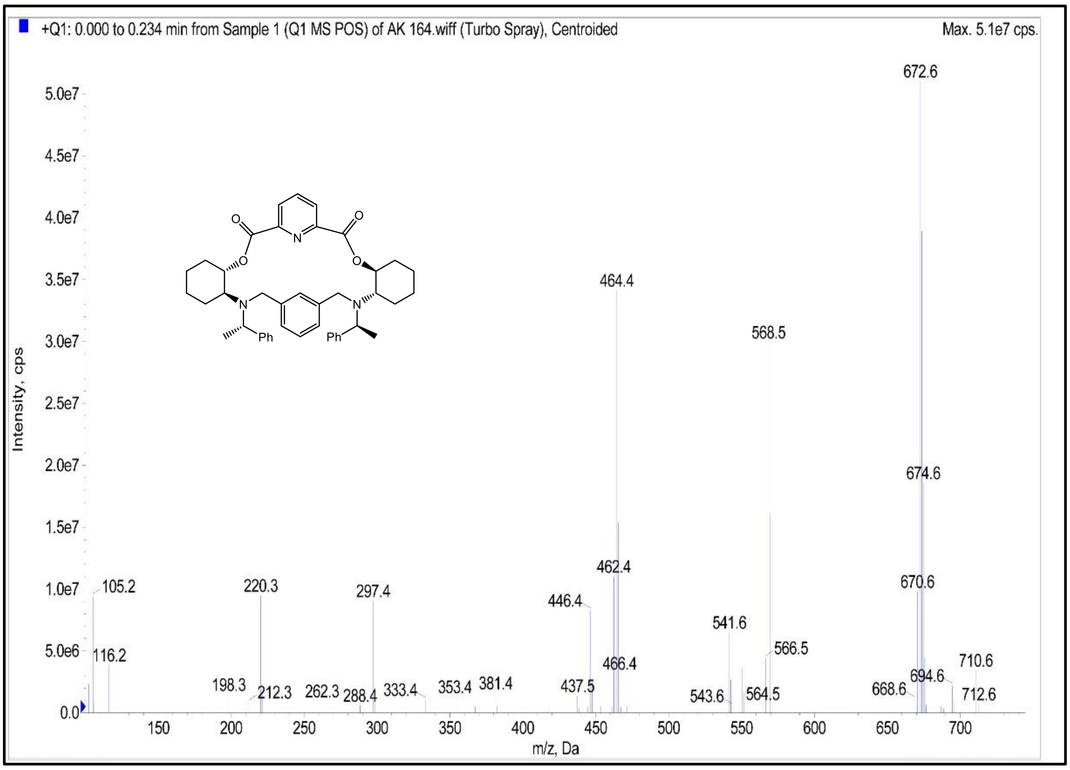
^{13}C NMR Spectra of Compound (**27a**)



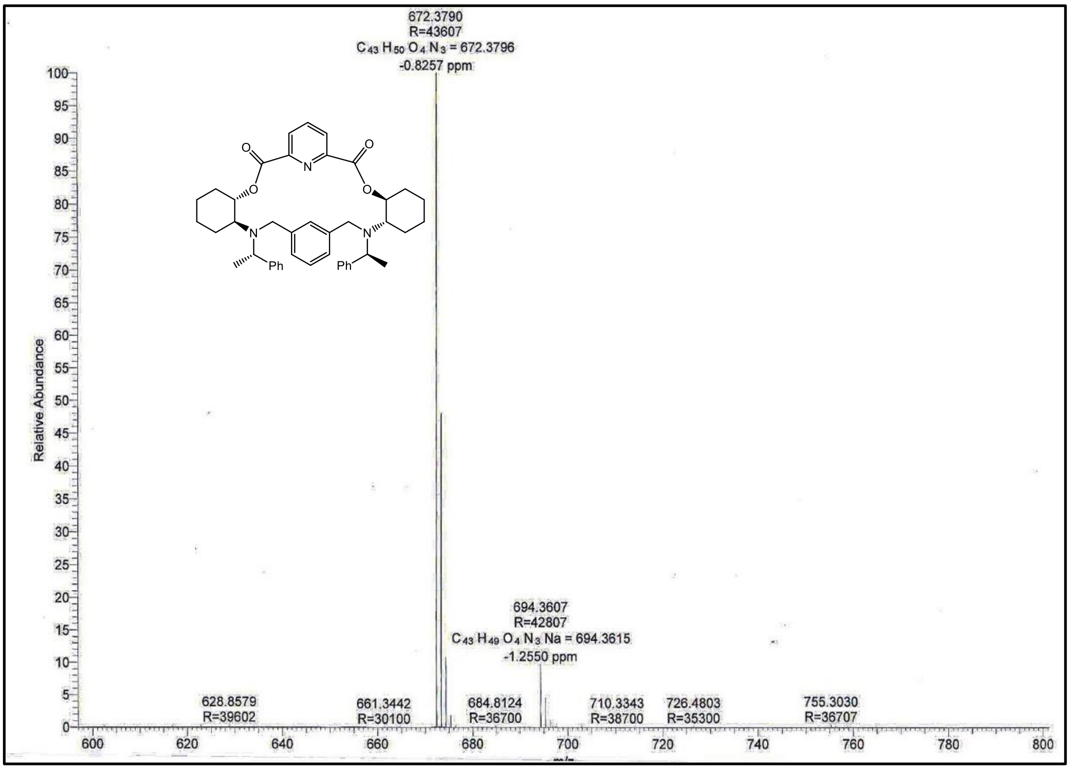
DEPT-135 Spectra of Compound (**27a**)



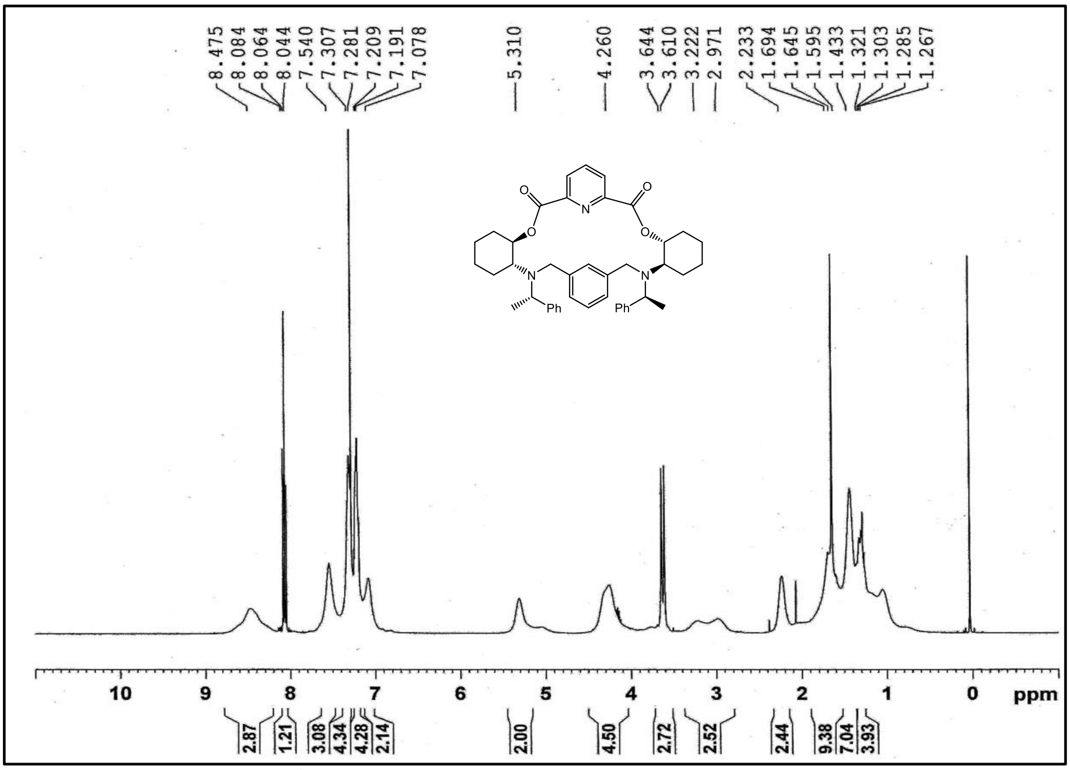
IR Spectra of Compound (**27a**)



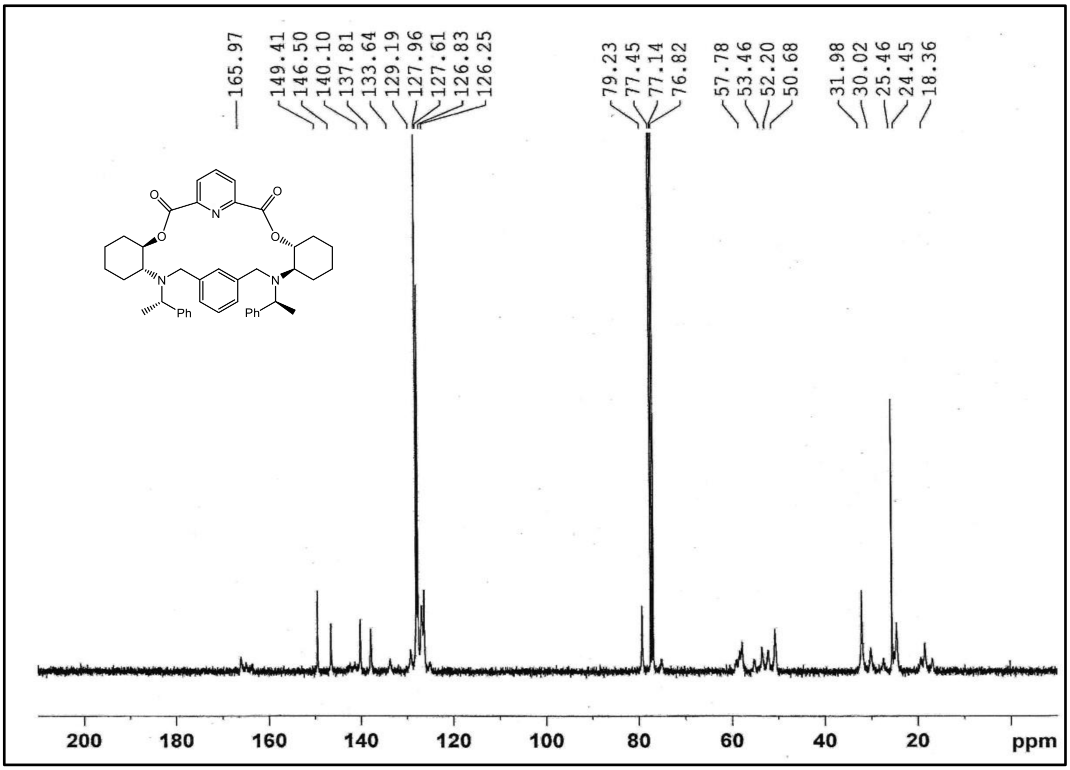
MS Spectra of Compound (**27a**)



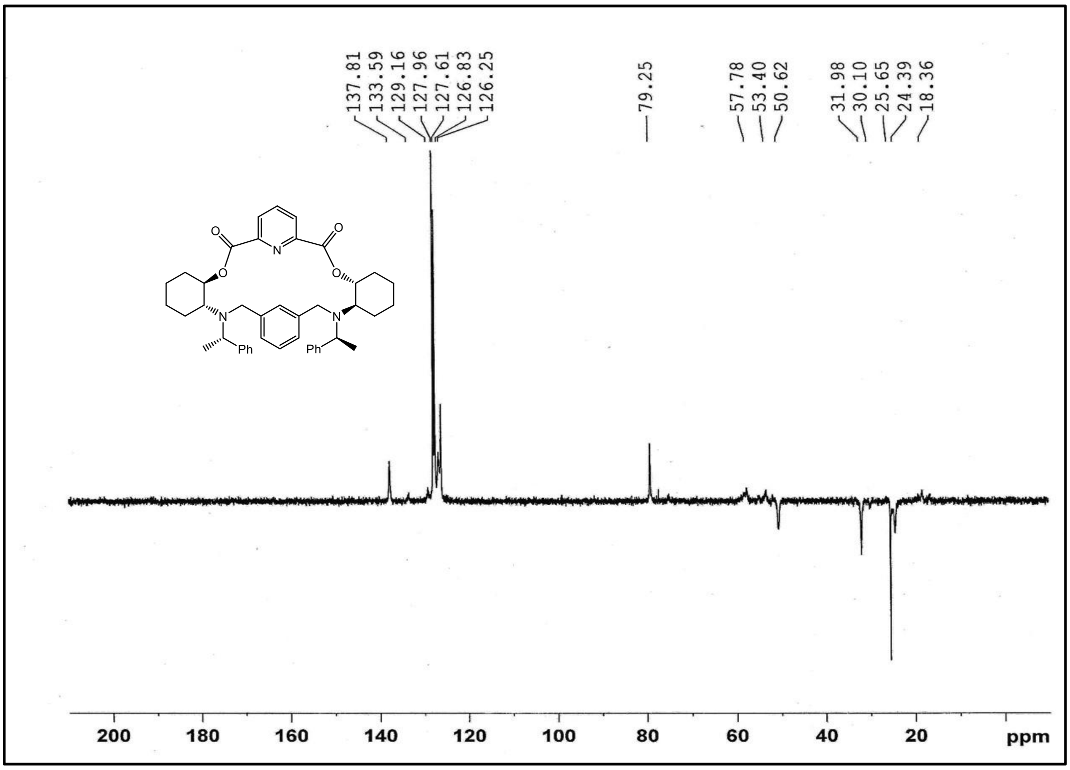
HRMS Spectra of Compound (**27a**)



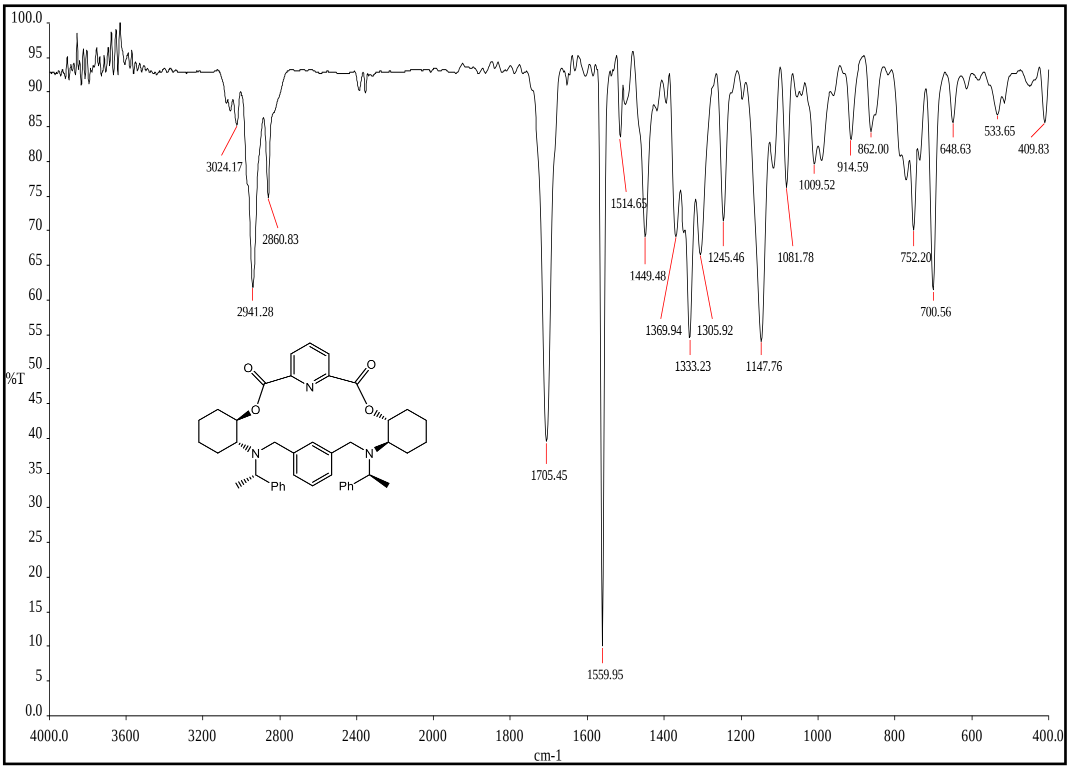
^{1}H NMR Spectra of Compound (**27b**)



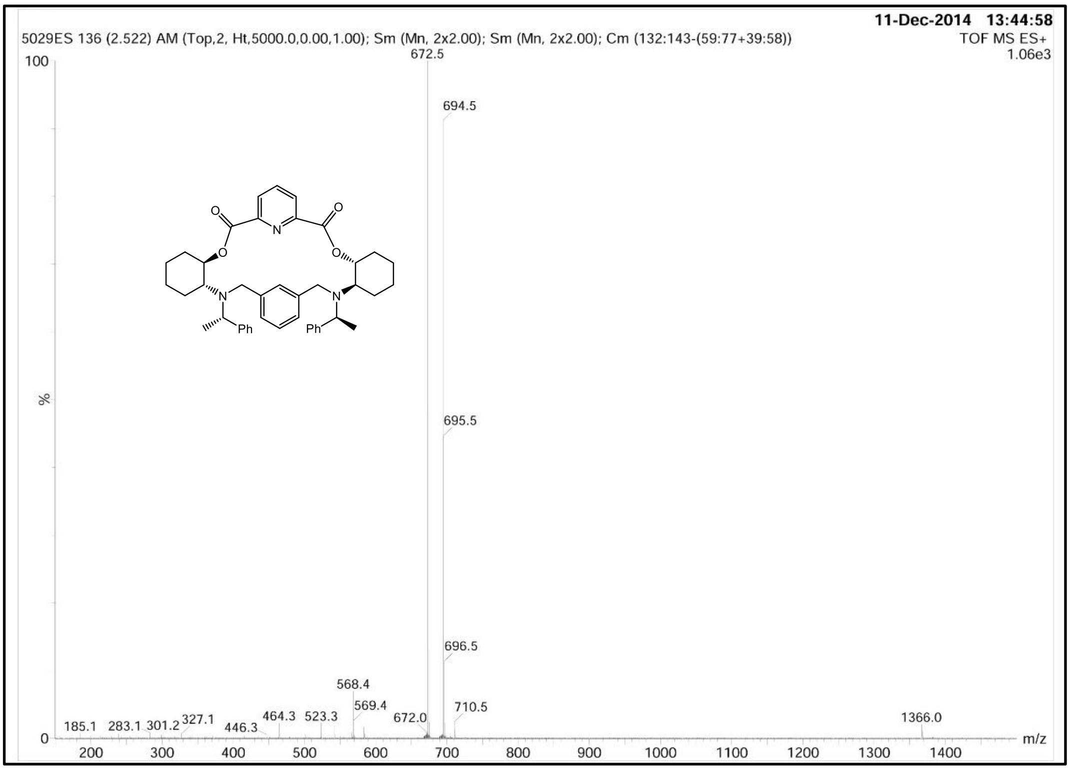
^{13}C NMR Spectra of Compound (**27b**)



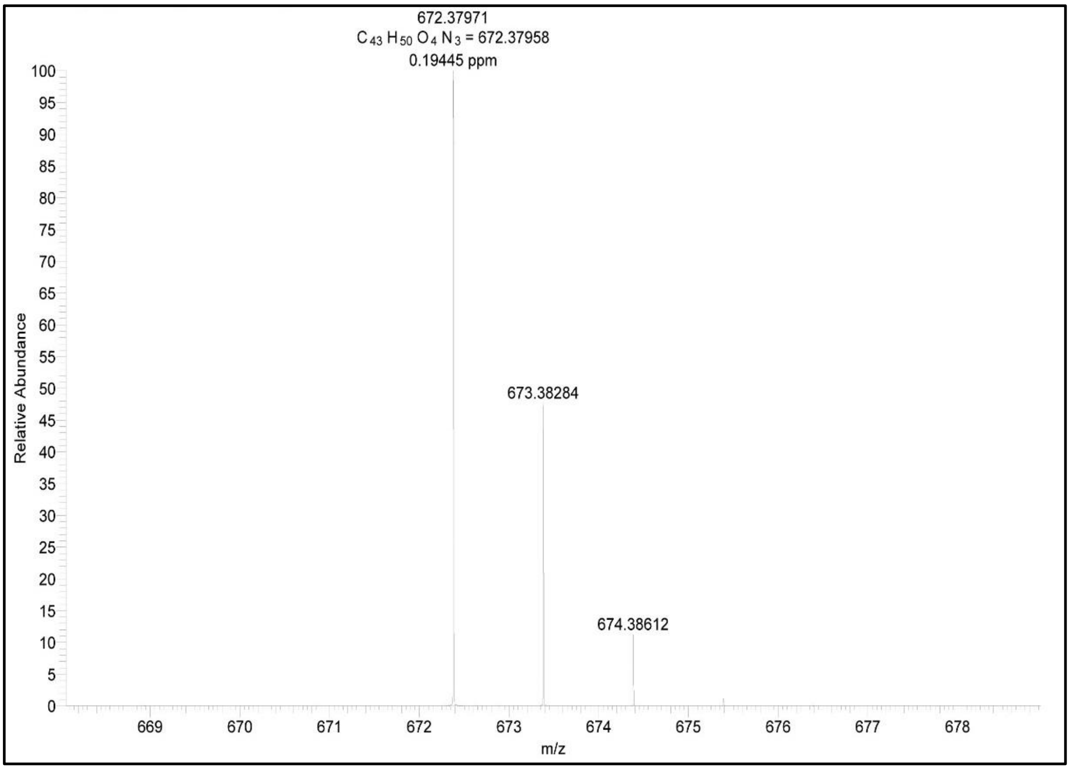
DEPT-135 Spectra of Compound (**27b**)



IR Spectra of Compound (**27b**)



MS Spectra of Compound (**27b**)

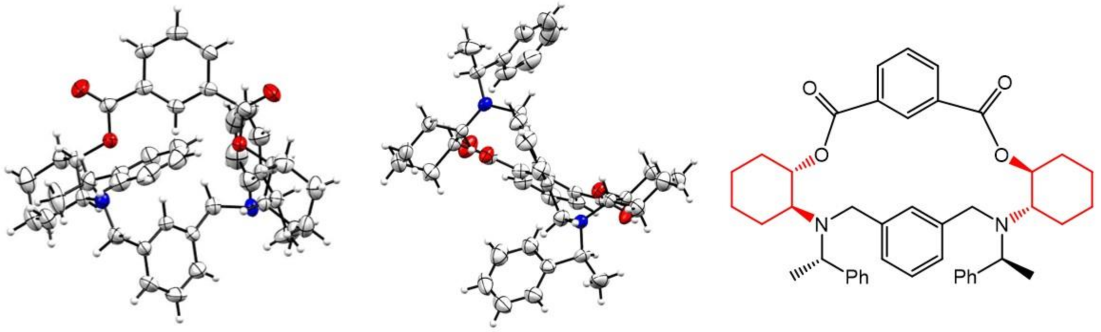


HRMS Spectra of Compound (**27b**)

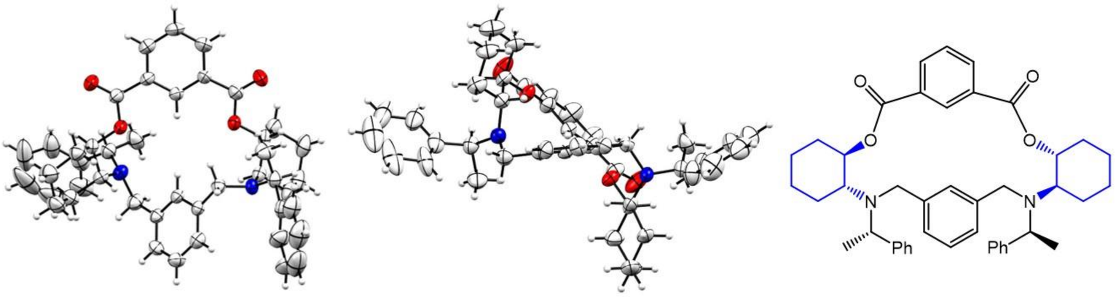
2.5.2 X-Ray Crystal data

X-ray crystal data for CCDC No 1883253 (*S*,*S*,*S*)-**26a** and CCDC No 1883254 (*R*,*R*,*S*)-**26b**

Details	Compound (*S*,*S*,*S*)-**26a** CCDC-1883253	Compound (*R*,*R*,*S*)-**26b** CCDC-1883254
Empirical Formula	$C_{45}H_{50}NO_4$	$C_{45}H_{50}NO_4$
Formula Weight	670.86	670.86
Temperature	293(2)	293(2)
Wavelength	0.71073A	0.71073A
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	a = 12.5528(10) Å b = 16.6022(12) Å c = 17.6393(17) Å α = 90° β = 90° γ = 90°	a = 12.9233(10) Å b = 13.9480(18) Å c = 21.032(13) Å α = 90° β = 90° γ = 90°
Volume	3676.1	3791 (7)
Z	4	4
(Density calculated)	1.2121	1.1754
Absorption coefficient(μ)	0.077	0.075
F(000)	1440.6	1440.6
Crystal size	-	-
2θ range for data collection	6.5 to 58.04°	6.5 to 58.12°
Reflections collected	10721	10742
Independent reflections	7445[R(int) = 0.0337]	7439[R(int) = 0.0477]
Refinement method	Least Squares minimisation	Least Squares minimization
Data / restraints / Parameters	7445/0/453	7439/0/453
Goodness of fit on F2	0.865	0.979
Final R indices [I>2sigma(I)]	R1 =0.0504, wR2 =0.0828	R1 =0.0619, wR2 = 0.0923
R indices (all data)	R1 = 0.1063, wR2 = 0.1031	R1 = 0.1539, wR2 = 0.1267
Largest difference peak and hole	0.23/-0.25	0.32/-0.36
Flack parameter	0.2(18)	-0.9(11)



ORTEP diagram of the compound (*S*,*S*,*S*)-**26a** CCDC No 1883253
(50% probability factor for thermal ellipsoids)

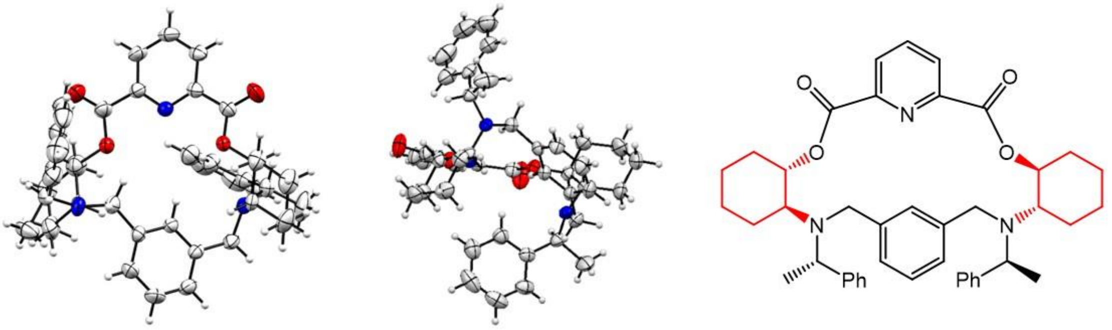


ORTEP diagram of the compound (*R*,*R*,*S*)-**26b** CCDC No 1883254
(50% probability factor for thermal ellipsoids)

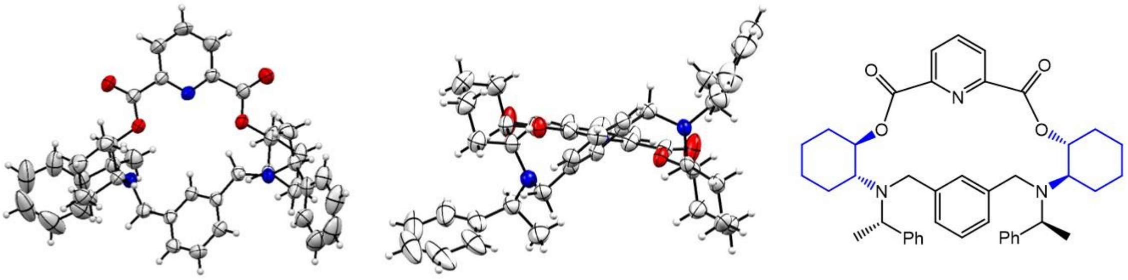
X-ray crystal data for CCDC No 1004162 (*S*,*S*,*S*)-**27a** and CCDC No 1016922 (*R*,*R*,*S*)-**27b**

Details	Compound (*S*,*S*,*S*)-**27a** CCDC-1004162	Compound (*R*,*R*,*S*)-**27b** CCDC-1016922
Empirical Formula	$C_{43}H_{49}N_3O_4$	$C_{43}H_{49}N_3O_4$
Formula Weight	671.85	671.85
Temperature	293(2)	293(2)
Wavelength	0.71073A	1.54184 A
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	a = 12.5755(7)Å b = 16.6410(10) Å c = 17.7068(10) Å α = 90° β = 90° γ = 90°	a = 12.8516(2) Å b = 13.9590(3) Å c = 21.1978(4) Å α = 90° β = 90° γ = 90°
Volume	3705.5(4)	3802.80(14)
Z	4	4
(Density calculated)	1.206	1.170
Absorption coefficient(μ)	0.077	0.570
F(000)	1440.0	1440.0

Crystal size(mm)	0.49x0.28x0.12	7.58 to140.06°
θ range for data collection	6.14 to 58°	8447
Reflections collected	10724	5807[R(int) = 0.0235]
Independent reflections	7779[R(int) = 0.0246]	Least Squares minimization
Refinement method	Least Squares minimization	5807/0/453
Data / restraints / Parameters	7779/0/453	1.054
Goodness of fit on F^2	0.957	R_1 =0.0512, wR_2 = 0.1531
Final R indices [I>2sigma(I)]	R_1 =0.0516, wR_2 = 0.0884	R_1 = 0.0621, wR_2 = 0.1597
R indices (all data)	R_1 = 0.0897, wR_2 = 0.1001	0.33/-0.35
Largest difference peak and hole	0.19/-0.30	7.58 to140.06°

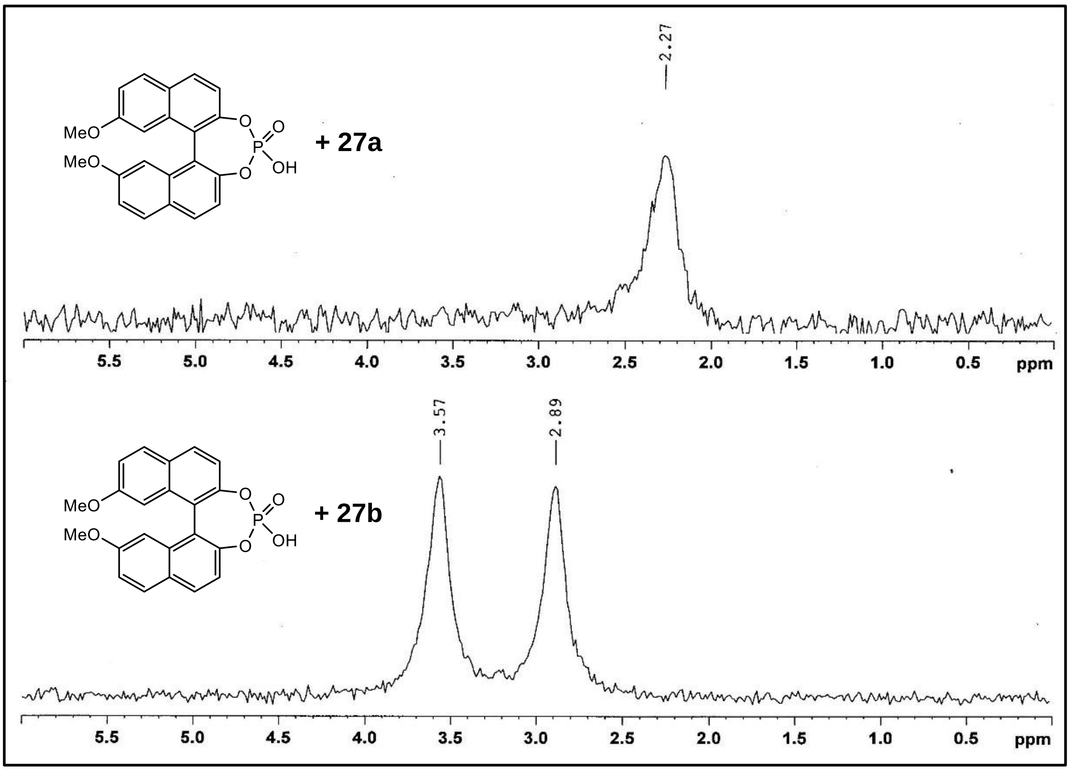


ORTEP diagram of the compound (*S*,*S*,*S*)-**27a** CCDC No 1004162
(50% probability factor for thermal ellipsoids)

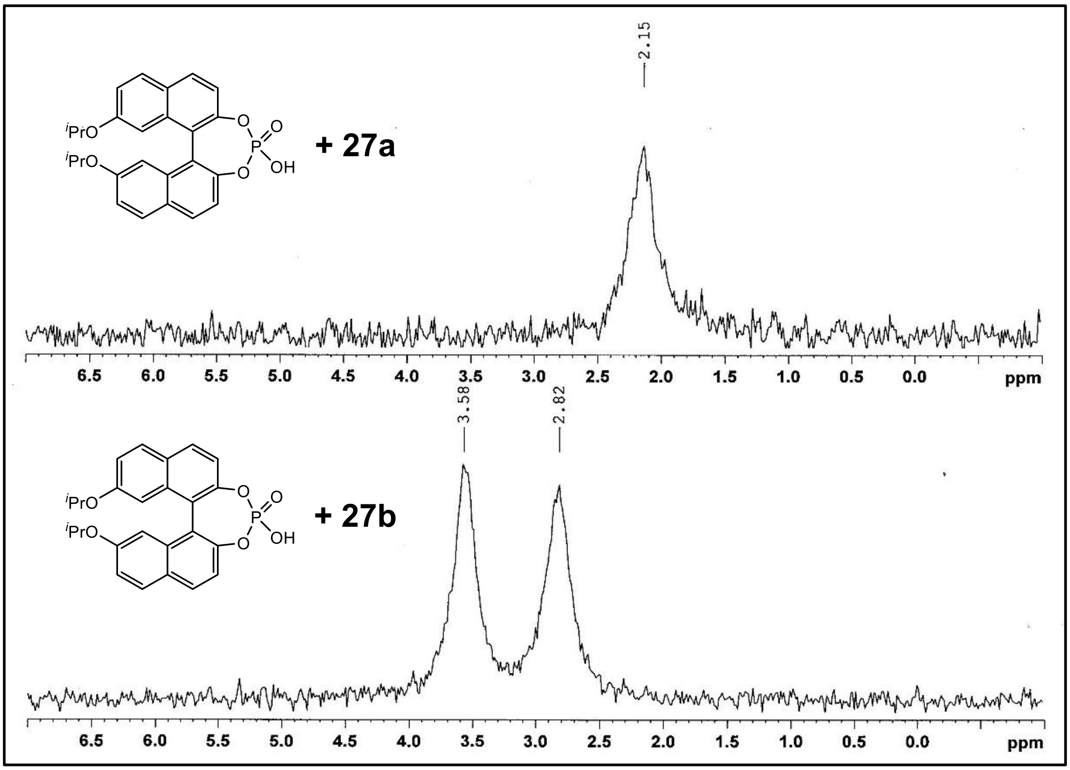


ORTEP diagram of the compound (*R*,*R*,*S*)-**27b** CCDC No 1016922
(50% probability factor for thermal ellipsoids)

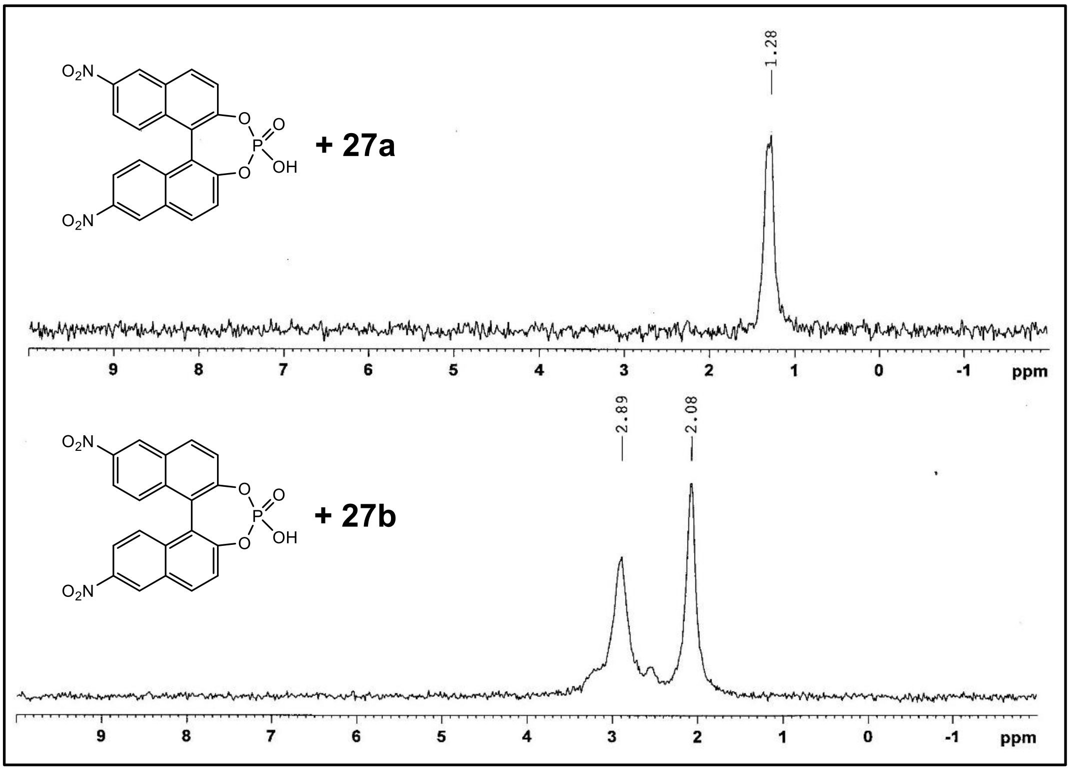
2.5.3 CSA Spectras:



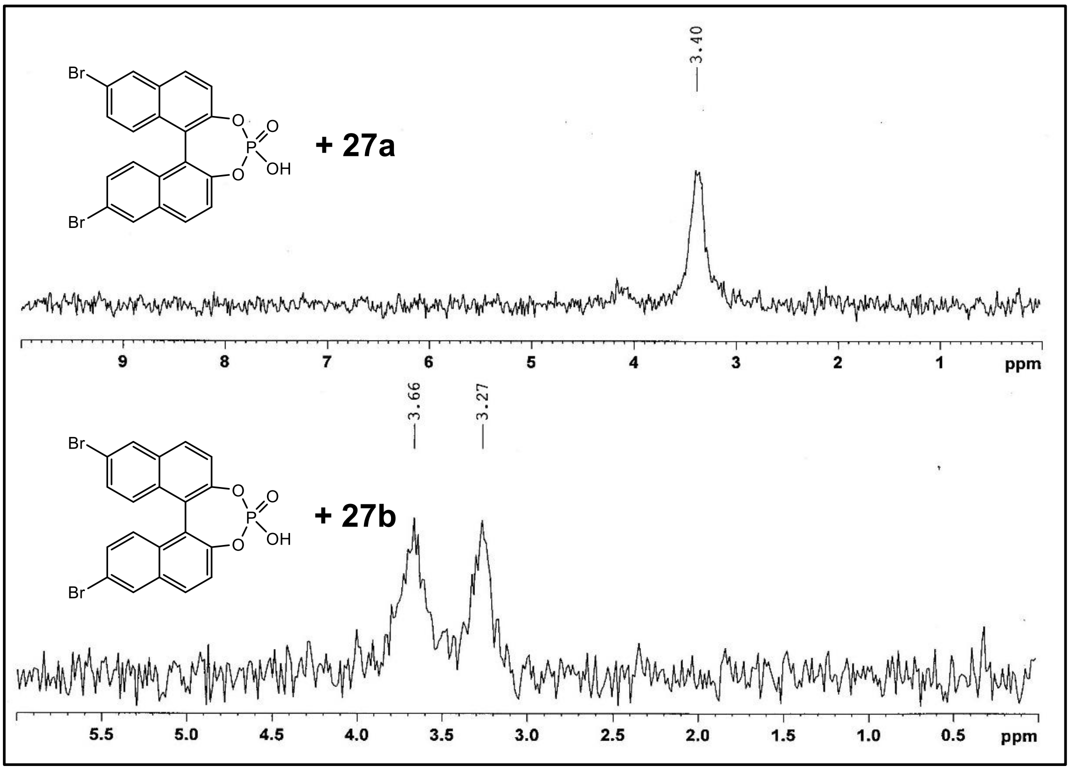
^{31}P NMR Spectra of Compound **A-II** with (**27a**) top; and **A-II** with (**27b**) bottom



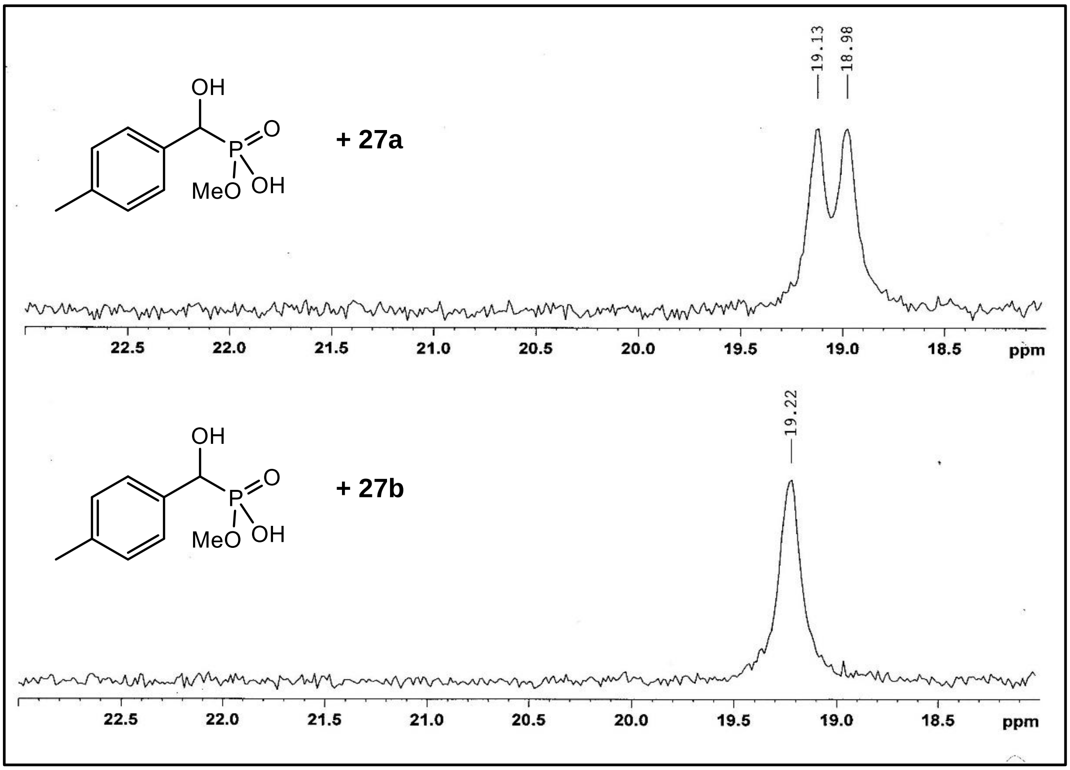
^{31}P NMR Spectra of Compound **A-III** with (**27a**) top; and **A-III** with (**27b**) bottom



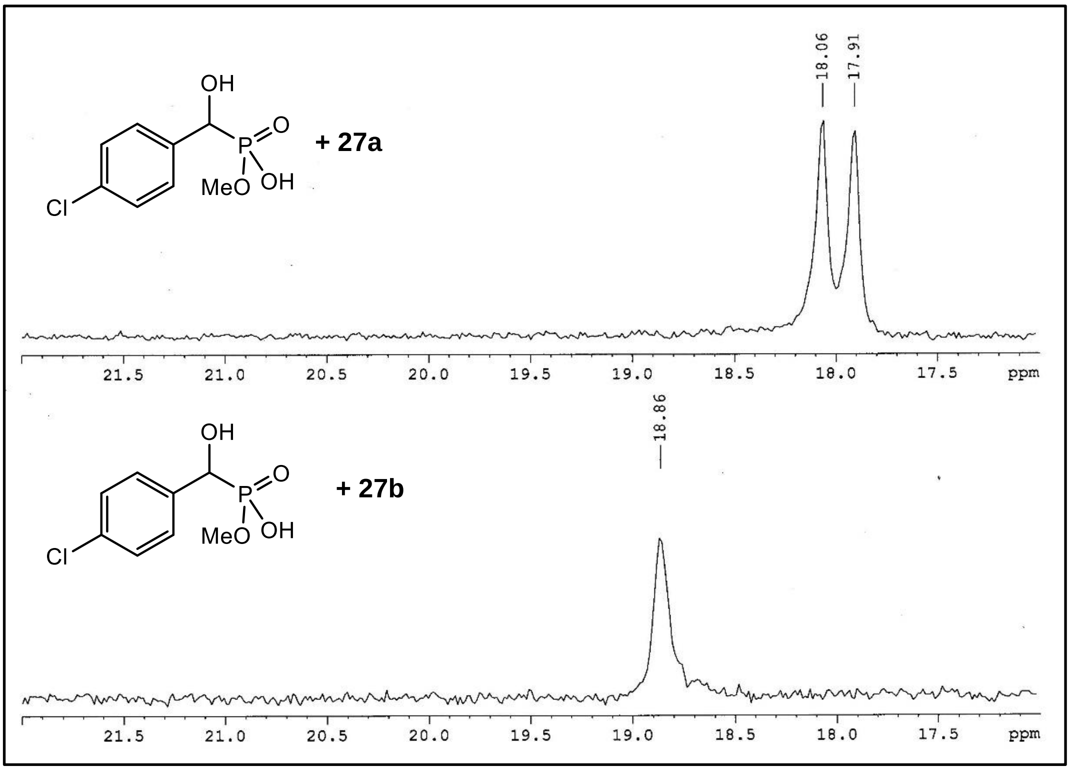
^{31}P NMR Spectra of Compound **A-IV** with (**27a**) top; and **A-IV** with (**27b**) bottom



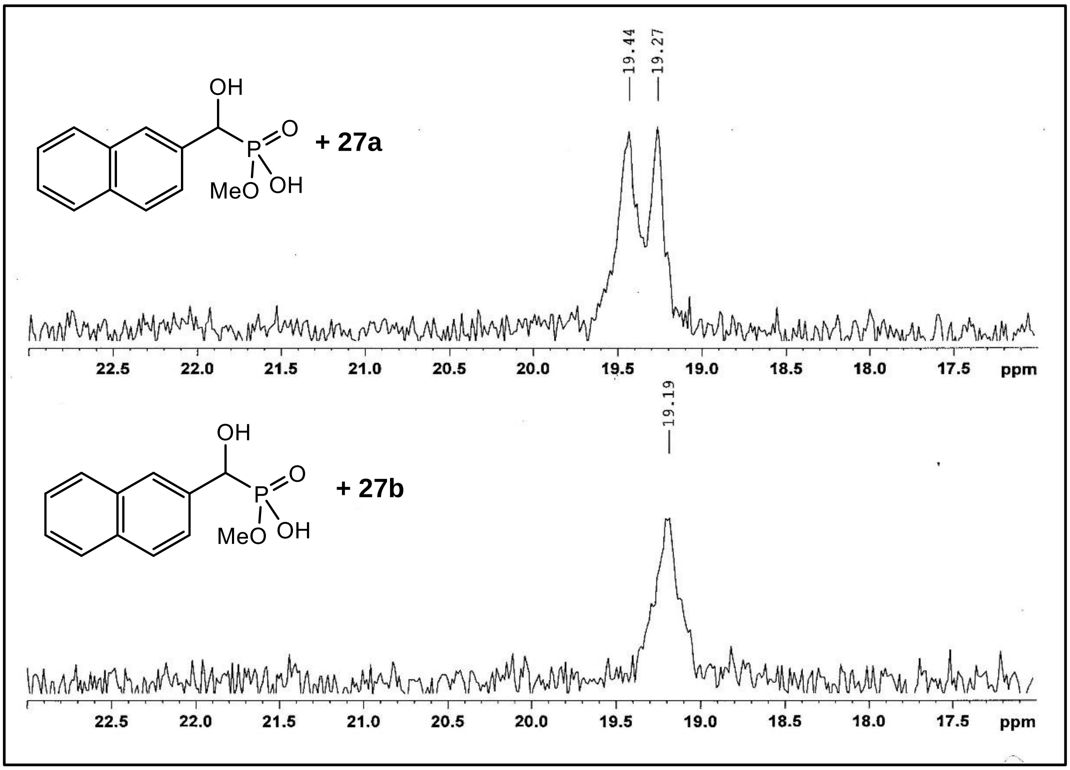
^{31}P NMR Spectra of Compound **A-V** with (**27a**) top; and **A-V** with (**27b**) bottom



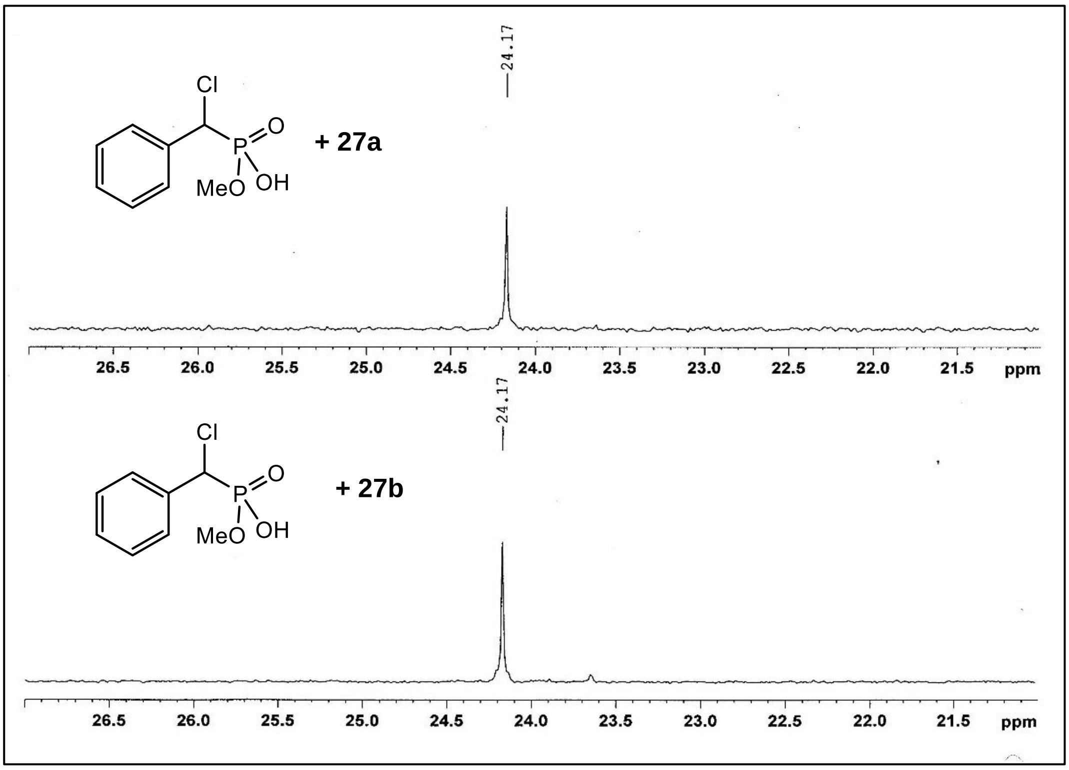
^{31}P NMR Spectra of Compound **B-II** with (**27a**) top; and **B-II** with (**27b**) bottom



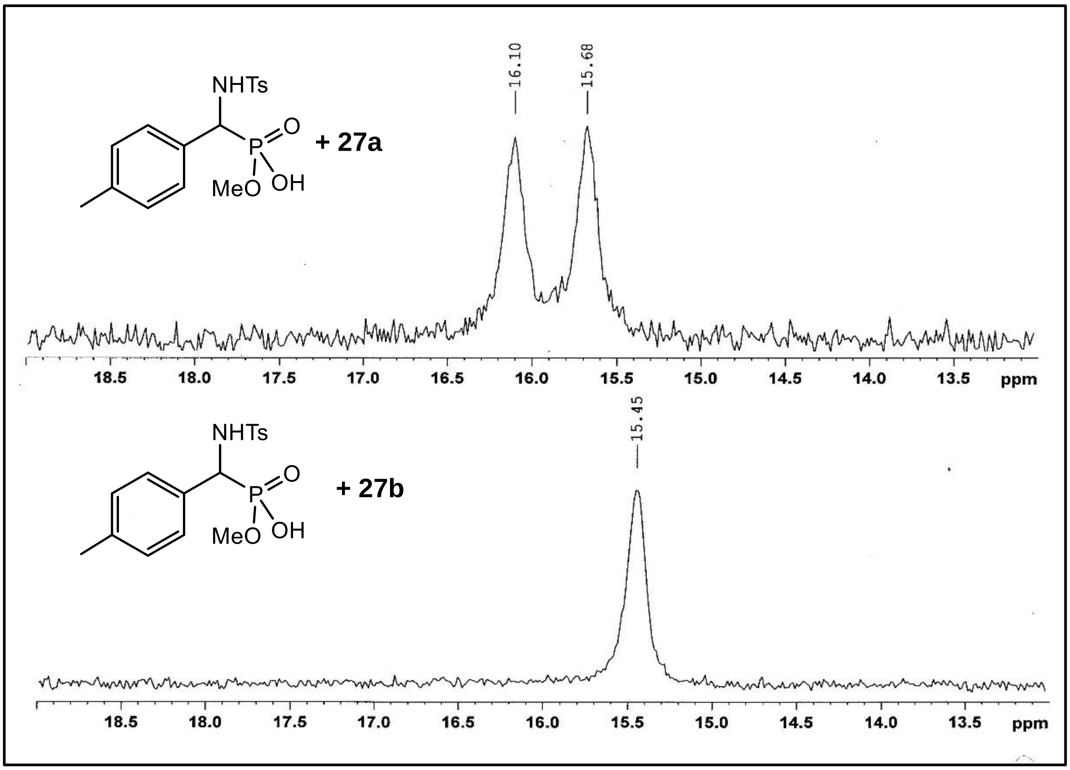
^{31}P NMR Spectra of Compound **B-III** with (**27a**) top; and **B-III** with (**27b**) bottom



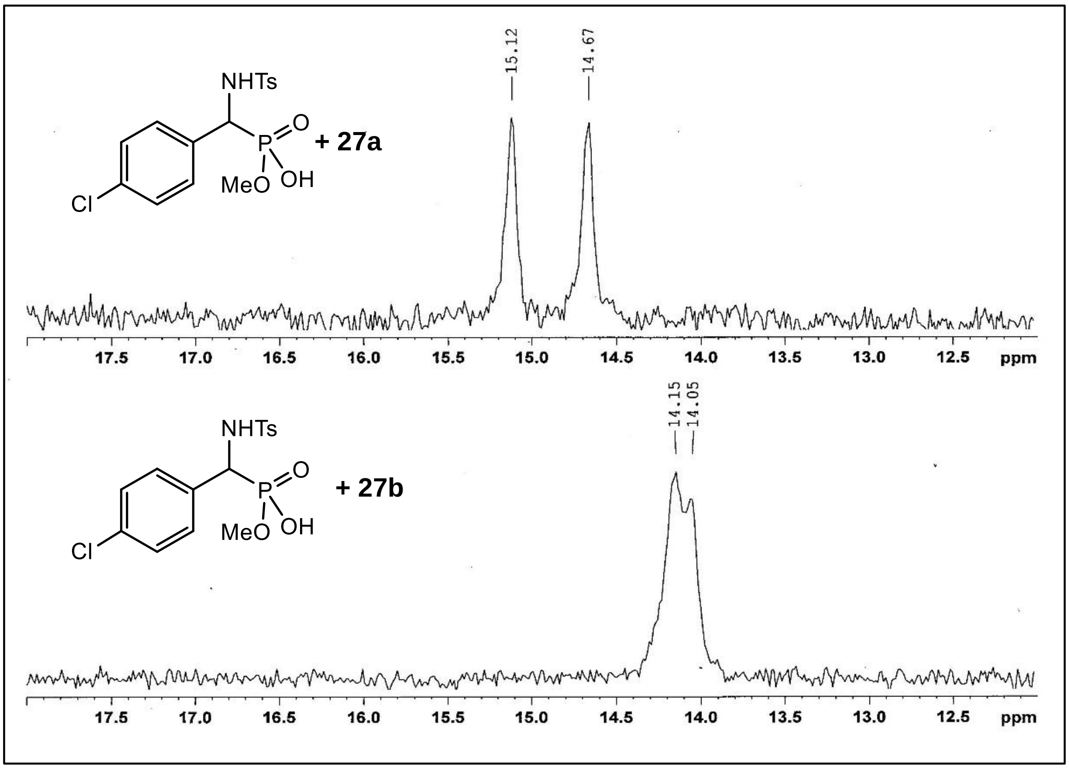
^{31}P NMR Spectra of Compound **B-IV** with (**27a**) top; and **B-IV** with (**27b**) bottom



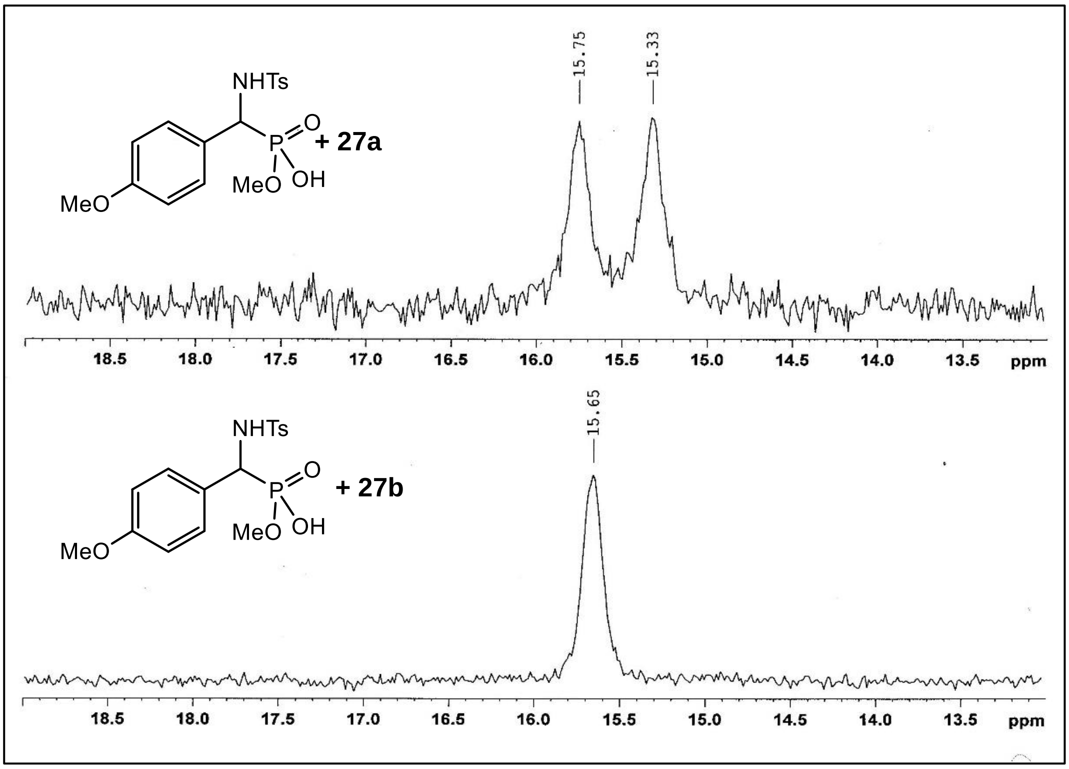
^{31}P NMR Spectra of Compound **C** with (**27a**) top; and **C** with (**27b**) bottom



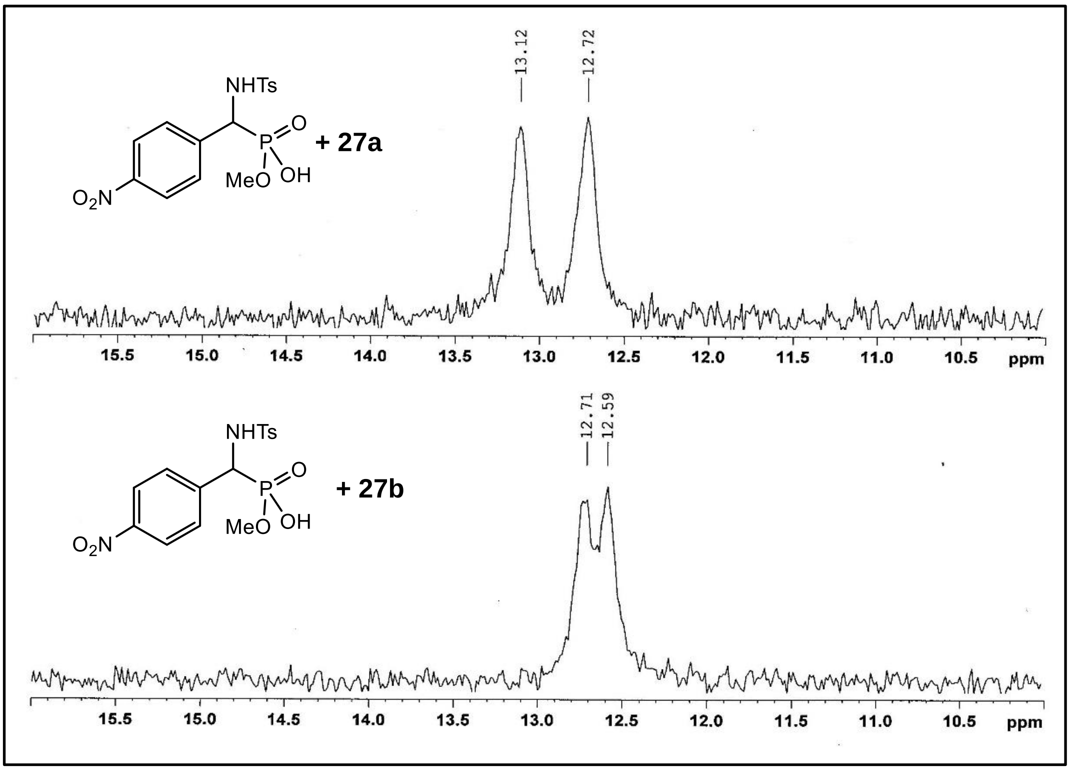
^{31}P NMR Spectra of Compound **D-II** with (**27a**) top; and **D-II** with (**27b**) bottom



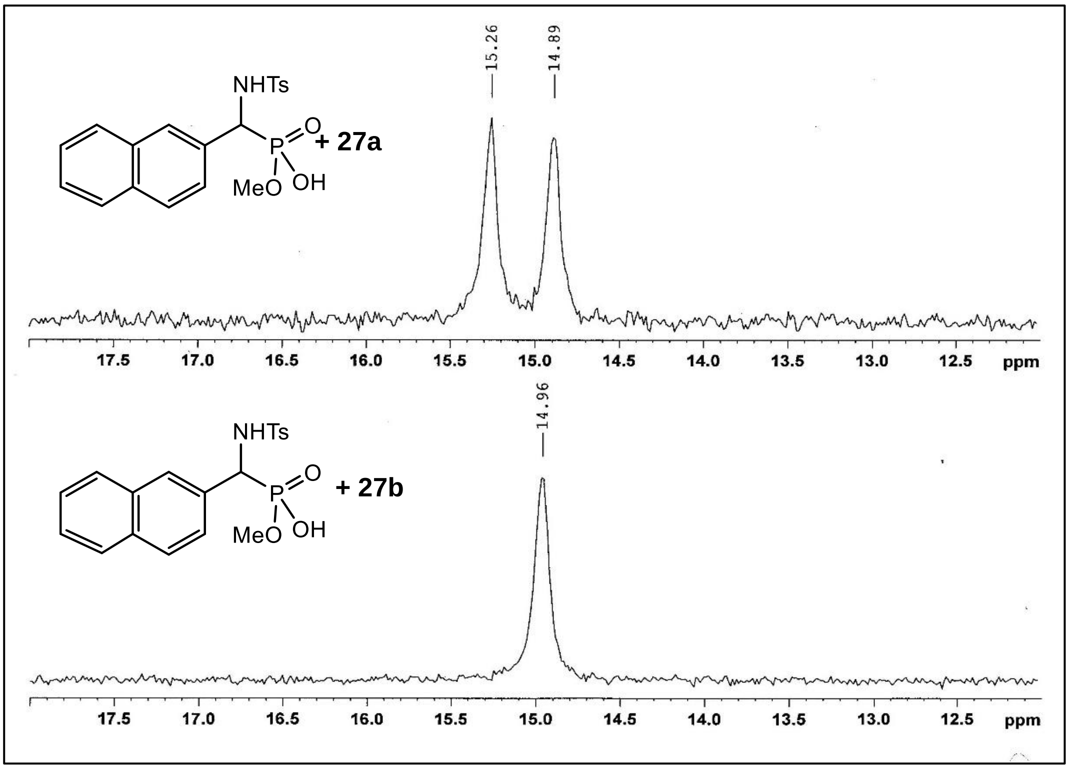
^{31}P NMR Spectra of Compound **D-III** with (**27a**) top; and **D-III** with (**27b**) bottom



^{31}P NMR Spectra of Compound **D-IV** with (**27a**) top; and **D-IV** with (**27b**) bottom

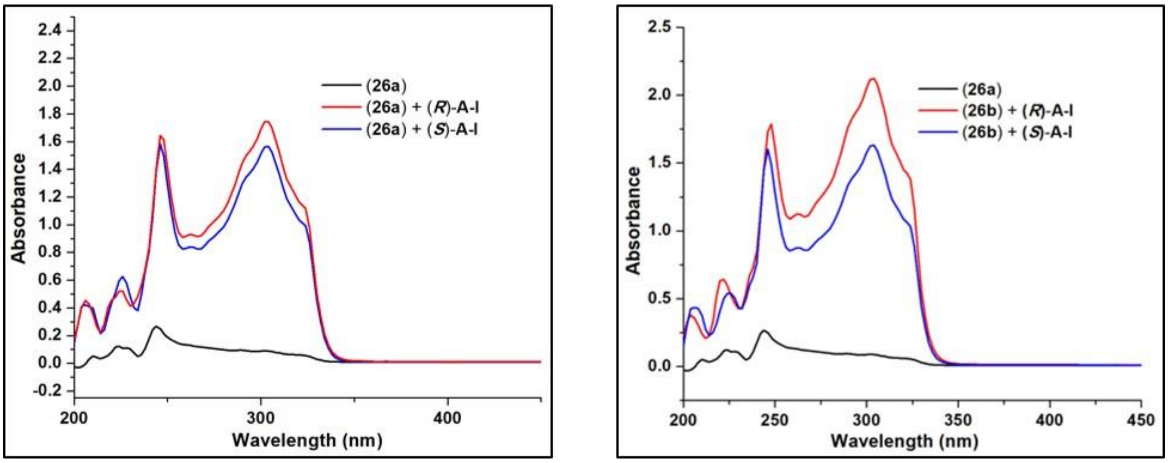


^{31}P NMR Spectra of Compound **D-V** with (**27a**) top; and **D-V** with (**27b**) bottom

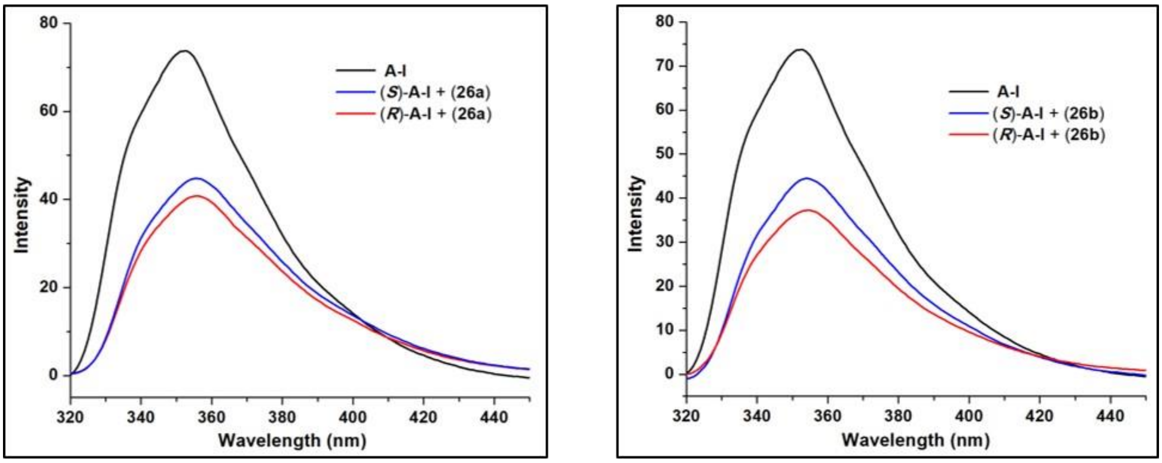


^{31}P NMR Spectra of Compound **D-VI** with (**27a**) top; and **D-VI** with (**27b**) bottom

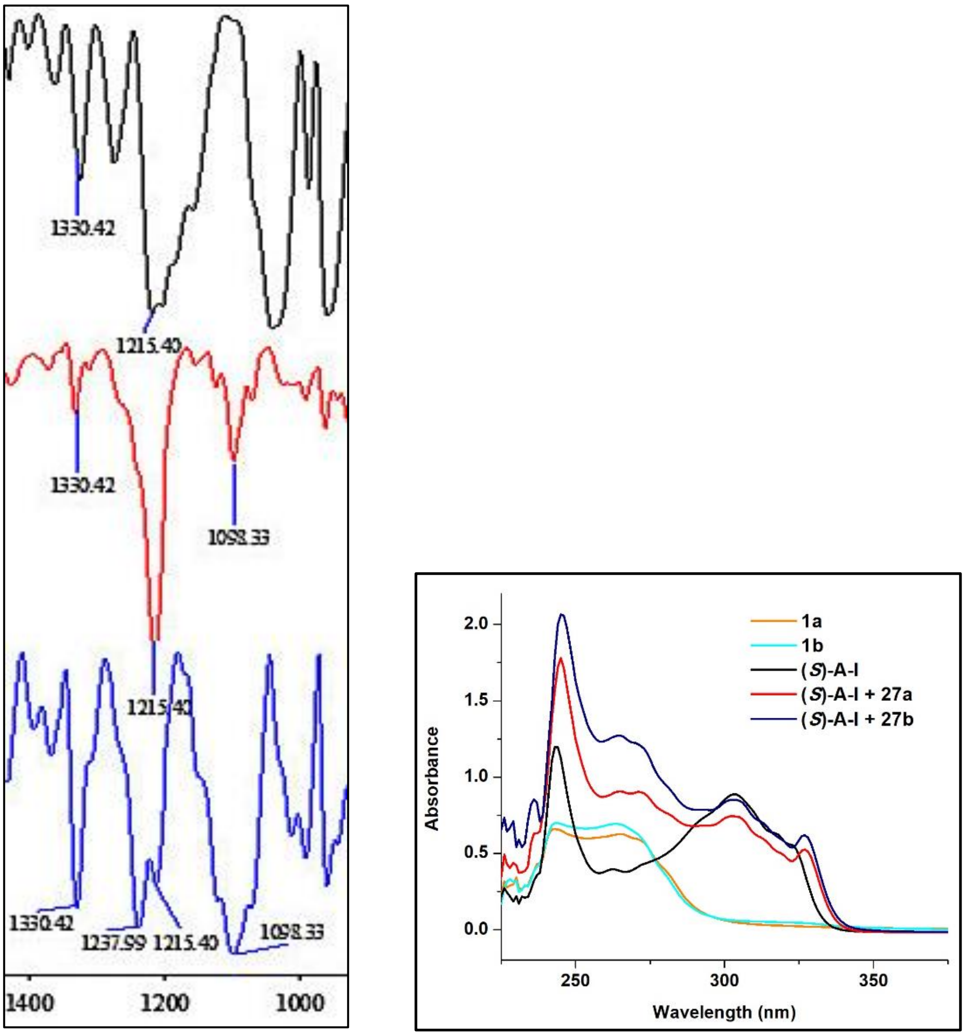
2.5.4 UV and Fluorescence Spectras:



a) UV-Vis Spectra of (*R*) and (*S*)-**A-I** with (**26a**) left; b) UV-Vis Spectra of (*R*) and (*S*)-**A-I** with (**26b**).



a) Fluorescence Spectra of (*R*) and (*S*)-**A-I** with (**26a**) left; b) Fluorescence Spectra of (*R*) and (*S*)-**A-I** with (**26b**).



a) Selected region of IR Spectra of **A-I** (top), **A-I + 27a** (middle) and **A-I + 27b** (bottom) left; b) a) UV-Vis Spectra of (*S*) **A-I**, (*S*)-**A-I** with (**27a**) and (*S*)-**A-I** with (**27b**)

2.6 References:

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