STEREOSELECTIVE OXIDATION OF SULFIDES TO SULFOXIDES BY *N*-CHLORAMINES

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STEREOSELECTIVE OXIDATION OF SULFIDES TO SULFOXIDES BY *N*-CHLORAMINES

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

STEREOSELECTIVE OXIDATION OF SULFIDES TO SULFOXIDES BY *N*-CHLORAMINES

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Chiral sulfoxides are present in many biologically active compounds. Asymmetric synthesis of the sulfoxides has been performed by chiral metal complexes and chiral peroxides. Although the asymmetric organooxidation of sulfides by chiral peroxides proved to be successful, peroxides are difficult to handle and obtain. In this study, a new metal free method has been developed to oxidize sulfides to chiral sulfoxides with easily accessible chiral *N*-chloramines. For this purpose, chiral reagents were synthesized and chlorinated to yield N-chloramines. In oxidation reactions, chiral information has been transferred to sulfides with the transfer of chlorine onto sulfur from nitrogen. With *N*-chloramines, we observed enantioenriched sulfoxide formation. The results were also subjected to computational studies. These studies revealed that the amine-Cl goes through anion pair intermediate while imide-Cl transfers chlorine in an S_N2 fashion. The observed results have been promising, yet the conditions still need to be further optimized.

Key Words: asymmetric oxidation, chiral sulfoxides, N-chloramines

ÖZ

SULFİDLERİN *N*-KLORAMİNLER KULLANILARAK SULFOKSİTLERE STEREOSEÇİCİ OLARAK YÜKSELTGENMESİ

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Kiral sülfoksitler biyolojik aktivite göstermektedir. Kiral sülfoksidlerin asimetrik olarak sentezlenmesi için kiral metal kompleksleri ve kiral peroksitler kullanılmıştır. Kiral peroksitler ile yapılan asimetrk sülfoksidasyon çalışmaları başarılı olmalarına rağmen bu maddelerle çalışmak kolay değildir. Bu çalışmada *N*-kloramin türevleri kullanılarak kükürt içeren maddelerin metal kullanılmadan asimetrik olarak yükseltgenmesi için yeni bir yöntem geliştirilmiştir. Bunun için kiral maddeler sentezlenmiş olup bu maddeler klorlanarak *N*-kloramin türevleri elde edilmiştir. Yükseltgenme tepkimelerinde, kiralite kükürde, azottan kükürde klor transferi ile aktarılmıştır. *N*-kloraminler kullanılarak yapılan çalışmalarda enantiyomerce zenginleşmiş sülfoksitler elde edilmiştir. Bu sonuçlar ayrıca teorik olarak da hesaplanmıştır. Bu hesaplamalar sonucunda amin-Cl ile iyon çifti ara ürün oluştuğu ve imid-Cl üzerinden klor transferinin, S_N2 mekanizmasıyla gerçekleştiği bulunmuştur. Elde edilen sonuçlar olumludur ancak, optimizasyon çalışmaları henüz tamamlanmamıştır.

Anahtar Kelimeler: asimetrik yükseltgeme, kiral sülfoksitler, N-kloraminler

To My Family

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CHAPTER 1

INTRODUCTION

1.1 Chirality

The term chirality, was first mentioned by Lord Kelvin in 1884.[1] Chirality, derived from kheir which means "hand" in Greek, can be simply defined as "handedness". Moreover, Lord Kelvin described the concept of chirality in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light by stating "*I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.*" in 1904.[2]

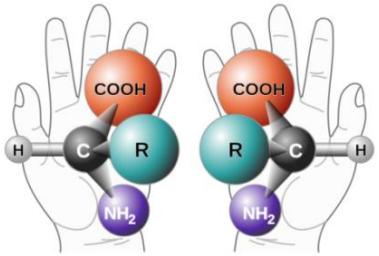


Figure 1-Representation for the enantiomeric forms of the aminoacids (http://en.wikipedia.org/wiki/Chirality, last visited 2014 August)

Louis Pasteur analyzed a mixture of tartaric acid salts and revealed that there were different crystal types in the mixture. These crystals were shown to be with different physical properties. He also stated that two different enantiomers rotates polarized light in opposite directions.[3] In order to differentiate stereoisomers, enantiomers were specified based on the direction that they rotate plane polarized light. The isomers were named as *D*-isomer (dextrotatory) if they rotate plane polarized light clockwise and *L*-isomer (leavorotary) if they rotate plane polarized light counter clockwise. Then, a new system was designed so as to differentiate two different isomers by Cahn, Ingold and Prelog in 1956. This system was based on assigning atoms around the stereogenic center based on decreasing atomic number and by using these order, determining absolute configuration of molecule as *R* (rectus) or *S* (sinister).[4]

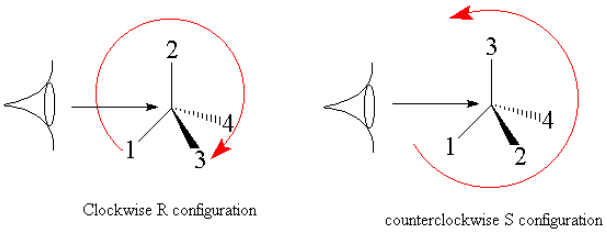


Figure 2-Configurations of the enantiomers
(http://tigger.uic.edu/~kbruzik/text/chapter5.htm, last visited 2014 August)

These concepts are valid for consideration of compounds in 3-dimension. Therefore, one should systematically examine such compounds using group theory.

1.1.1 Chirality and Group Theory

In order to classify molecules as having high symmetry, low symmetry or no symmetry, it was necessary to use a mathematical criterion of symmetry. This rigid criterion was developed by using two factors: symmetry elements molecules have and symmetry operations molecules may undergo. Symmetry operation is the movement of the molecule keeping all the points of molecule at the same point after carried on. Symmetry element is the geometrical point, line or plane that symmetry operations may be undergone with respect to **(Table 1)**. According to the group theory for a molecule to be chiral, molecule should lack a mirror plane (σ), a center of symmetry (i) or an improper axis of rotation (Sn).

Symmetry Elements	Symmetry Operations
1. Mirror Plane (σ)	Reflection in the plane
2. Center of symmetry or inversion (i)	Inversion of all atoms through the center
3. Proper axis of rotation (C_n)	One or more rotations about the axis
4. Improper axis of rotation (S_n)	One or more repetitions of the sequence: rotation followed by reflection in a plane perpendicular to the rotation axis

Table 1-Symmetry elements and symmetry operations

For the molecules which are not superimposable on their mirror images it is better to use dissymmetric instead of asymmetric because asymmetric molecules have no symmetry however dissymmetric molecules may possess some symmetry elements. All asymmetric molecules are dissymmetric, yet all dissymmetric molecules are not asymmetric.[5] For example; 1,3-dimethylallene and binaphtol **(Figure 3)** are not asymmetric compounds however, these compounds have rotational axis of symmetry (C_n), where n>1, therefore they are dissymmetric compounds. For a molecule to be asymmetric, molecule should only have C_1 rotational axis of symmetry.

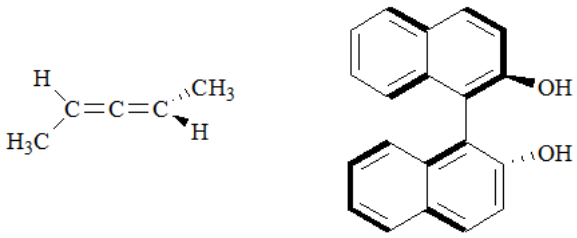


Figure 3-Dissymmetric molecules

There is another special case for chirality: planar chirality. A molecule is said to be planar chiral, does not have an asymmetric carbon atom, but has dissymmetric rings which are not coplanar. For instance, compound shown in Figure 4 is a planar chiral molecule having dissymmetric planar rings non-coplanar to each other.[6]

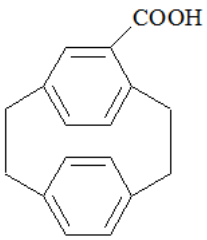


Figure 4-Planar chiral molecule

1.1.2 Chirality and Bioactivity

A compound with one chiral center, can have two isomers called enantiomers which are identical in achiral media. However, these enantiomers (*R* and *S*) will behave differently in chiral media. For instance, carvones interacting with chiral smelling receptors result in different odors depending on configuration. (*4S*)-(+)-carvone has a

odor for distinct caraway while (*4R*)-(-)-carvone has sweet spearmint odor **(Figure 5)**.[7]

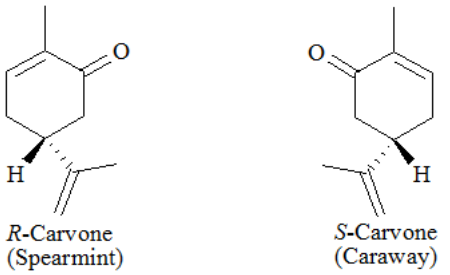


Figure 5-Carvone enantiomers with different smells

1.1.3 Chirality in Pharmacology

Chirality is a very significant factor in pharmacology; it directly affects the drug efficacy. In fact, nearly 60% of currently used drugs are chiral compounds.[8] Omeprazole-Esomeprazole case may be a good example; Omeprazole, which is a racemic compound, is very effective inhibitor for gastric acid secretion and it was marketed with tradenames Losec and Prilosec.[9] Then, Esomeprazole **(Figure 6)** which is the (*S*)-(-)-enantiomer of Omeprazole (chirality center is on sulfur) was developed and higher efficacy of enantiomer when compared to the racemic drug was recorded.[10] This is again due to the fact that receptors are chiral.

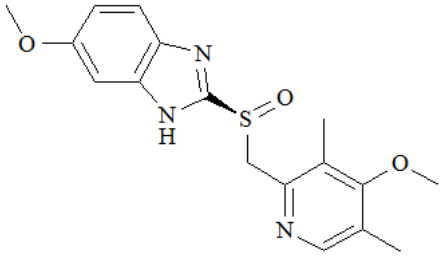


Figure 6- Structure of Esomeprazole

1.1.4 Chirality at Nitrogen Phosphorus and Sulfur

As it is mentioned for Esomeprazole, chiral centers can be on different atoms than carbon. This is obvious from the discussion of chirality from a group theory point of view. The most encountered atom at the stereogenic center of a chiral molecule is a

carbon atom, however nitrogen, phosphorus and sulfur atoms can also be a stereogenic center. For example; trivalent nitrogen compound has tetrahedral electron domain geometry according to valence shell electron pair repulsion (VSEPR) model. Theoretically, trivalent nitrogen with three different substituents is a chiral center. The inversion from one configuration to the other requires low activation energy **(Figure 7)**. This, in turn, makes it difficult to isolate the nitrogen based chiral compounds.

Figure 7-Inversion of configuration for ethylmethylamine enantiomers

Trivalent phosphorus compounds behave similar to nitrogen since phosphorus is in the same group with nitrogen in periodic table. However, phosphorous compounds have larger inversion barrier than nitrogen compounds and hence phosphorous compounds are easier to isolate.

Sulfur can also be a stereogenic center of a chiral compound. For typical sulfoxides, the energy of inversion barrier is in the range of 35–43 kcal/mol depending on substituents **(Figure 8)**. This energy barrier is difficult to be overcome at typical working temperature ranges hence, chiral sulfoxide enantiomers are easy to isolate. [11]

Figure 8-Inversion of configuration for ethylmethyl sulfoxide enantiomers

1.2 Chiral Sulfoxides

Description of the first optically active sulfoxide in 1926 shed light on nature of the bond between sulfur-oxygen atoms and the geometry of sulfur.[12] With this study, tetrahedral electron group geometry of the optically active sulfoxide molecule was proven by mentioning that sulfur atom is linked to three atoms with three covalency and one electrovalancy. This theory was also in consistence with the valance theory

because otherwise leads to the surplus of electrons on the sulfur atom. Lone pair of electrons on the sulfur atom can be counted like the substituent, and sulfoxides become arranged in tetrahedral electron group geometry with four different substituents. As mentioned before, chirality has a close link to biological activity, therefore chiral sulfoxides were also studied in this context. With this in mind, numorous sulfoxides have found use in pharmaceutical industry such as Omeprazole, Lansoprazole, Pantoprazole and Rabeprazole as gastric acid inhibitors **(Figure 9)**.

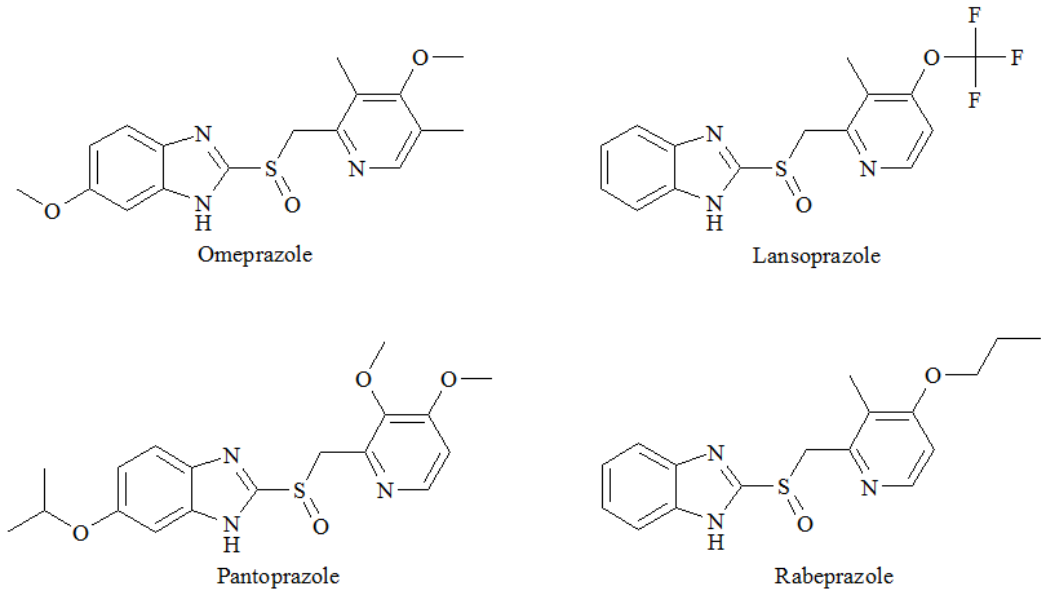
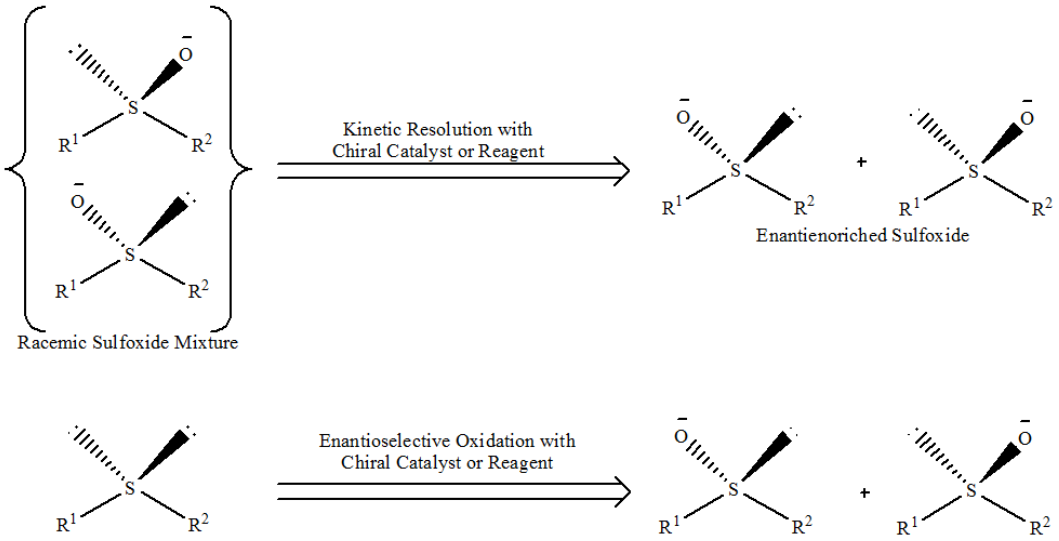


Figure 9- Some sulfoxides used in pharmaceutical industry

After the discovery of use of such compounds in pharmaceutical industry, many methods have been developed to get enantiomerically pure sulfoxides from corresponding sulfides. In literature, there are mainly two methods **(Scheme 1)** used to attain chiral sulfoxides: Kinetic resolution of sulfoxides, stereoselective oxidation of prochiral sulfides.[13]



Scheme 1- Two main methods to attain chiral sulfoxides

1.2.1 Kinetic Resolution of Chiral Sulfoxides

Kinetic resolution is a method used for the seperation of the enantiomers in a racemic mixture. Two enantiomers react with a catalyst or a reagent in different reaction rates. More reactive enantiomer becomes consumed while less reactive does not; this is mainly controlled by steric effects. As a result mixture becomes enantioenriched at the end of process. For sulfoxides, one enantiomer of the sulfoxide in the racemic mixture generally oxidizes to the sulfone during kinetic resolution leading to the enantiomeric excess of the less reactive enantiomer of the sulfoxide.[14]

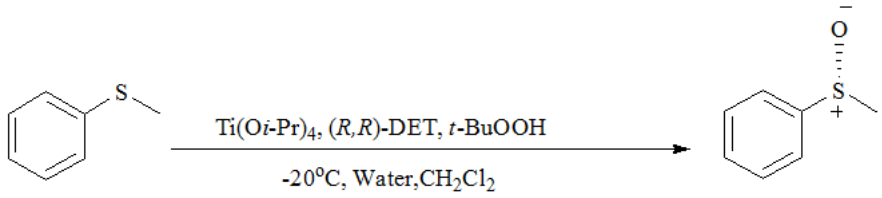
1.2.2 Asymmetric Sulfoxidation with a Chiral Metal Catalysis

Chiral metal complexes were employed to oxidized prochiral sulfides to enantioenriched sulfoxides.[15] These metallic systems were summarized below.

1.2.2.1 Titanium Complexes

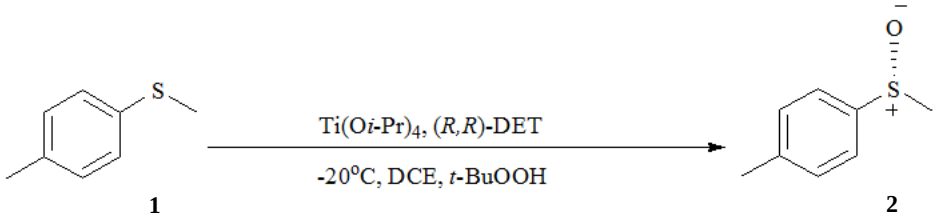
The use of titanium complexes in asymmetric sulfoxidation were firstly reported in 1984 by Kagan's *et al.*[16] In this study, titanium complex prepared from Ti(O*i*-Pr)$_4$, (*R*,*R*)-diethyl tartrate (DET), water were employed in 1:2:1 ratio and *t*-butyl hydroperoxide (TBHP) was employed as oxidant in this reaction. 91% enantiomeric

excess and 90% yield was reported in the oxidation **(Scheme 2)**.[17] With high enantioselective reaction in hand, researcher turned their attention to the catalytic oxidation with the same system. Although the catalytic system functioned as expected, the enantiomeric excesses were relatively low compared to stoichiometric reactions.[18]



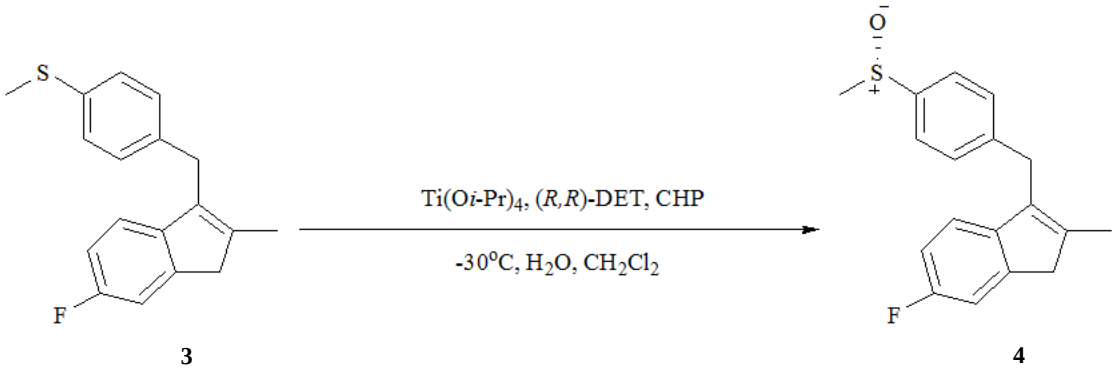
Scheme 2-Kagan's oxidation system

In the same year Modena *et al.* carried out another chiral sulfide oxidation procedure with 88% stereoselectivity by using the same titanium complex with different oxidant **(Scheme 3)**. Cumyl hydroperoxide (CHP) as oxidant, dichloroethane (DCE) as solvent were employed with Ti(O*i*-Pr)$_4$/DET in 1:4 ratio.[19]



Scheme 3-Modena's oxidation

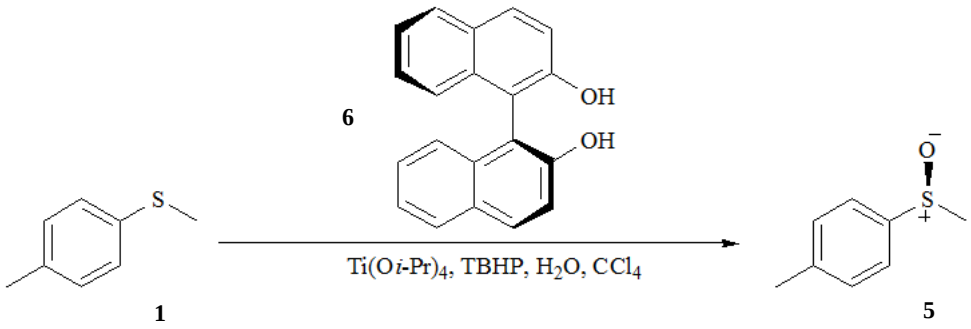
Kagan's system was also used for the enantioselective sulfoxidation for the synthesis of sulindac **(4) (Scheme 4)** by Maguire *et al.* with enantioselectivity up to 90%.[20]



3 **4**

Scheme 4-Synthesis of sulindac

Imamoto reported an enantioselective sulfide oxidation by performing Kagan's method with other chiral diols as ligands and CHP as oxidant.[21] Enantiomeric excess values of oxidation were around 95% with moderate yields. In the reaction, moleculer sieves were employed, high enantiomeric excess values were reported. This led scientists question the necessity of water for high enantioselectivity. Uemura investigated the effect of water on enantioselectivity and stated that excess or lack of water decreases the enantioselectivity. Uemura also reported another chiral sulfoxidation reaction **(Scheme 5)** with titanium complex in which chiral ligand was binaphthol **(6)** and oxidizing agent was TBHP. Enantiomeric excess was 96% and yield was 43%.[22]



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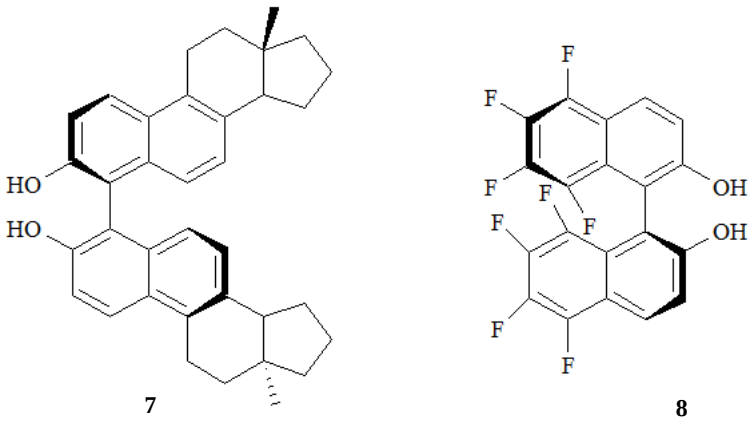
Scheme 5-Oxidation with binaphtol (BINOL)

Binaphtol (BINOL) derivatives were used as chiral ligands for the asymmetric sulfide oxidation by various research groups. Bolm and Dabard facilitated steroid derived BINOL derivative **(7)** with 92% enantioselectivity **(Figure 10)**.[23] Martyn and co-workers substituted BINOL with fluorine **(8)** from different positions to investigate the effect of fluorine. It was revealed that using binaphtol as chiral ligand

leads to "*S*" enantiomer while using fluorine substituted binaphtol leads to "*R*" enantiomer.[24]



7 **8**

Figure 10-Steroid derived BINOL and fluorine substituted BINOL

Complex of titanium metal containing naphtol derivative **(9)** was used for the chiral oxidation of methyl *p*-tolyl sulfide by Yuan and Wang **(Figure 11)**. In this study, 50% yield and 99% enantiomeric excess were reported.[25]

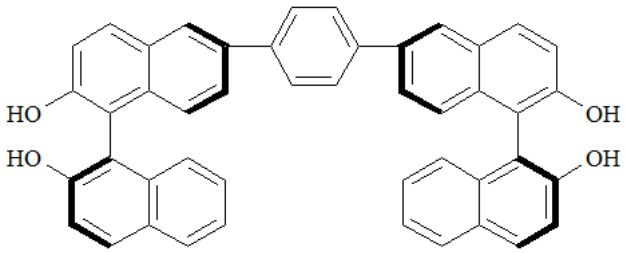


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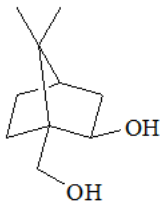
Figure 11-Naphtol derivative chiral reagent

Camphanediols **(10)** were used as chiral ligands in the chiral oxidation of sulfides by Zeng and co-workers. Although yield of the oxidation reaction was poor, up to 99% enantiomeric excess value was reported.[26] Zhu *et al.* reported the asymmetric oxidation of aryl methyl sulfoxides by using 2,5-dialkyl cyclohexane-1,4-diols **(11)** as a chiral ligand with 84% enantioselectivity and 79% yield **(Figure 12)**.[27]



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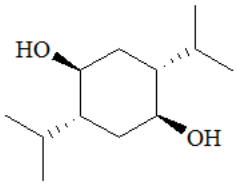

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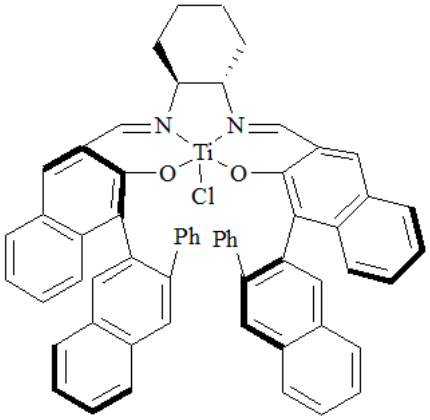
Figure 12- Camphanediol and 2,5-dialkyl cyclohexane-1,4-diol

Salen complexes of titanium metal **(12)** have also been used for enantiopure oxidation of sulfides **(Figure 13)**. Katsuki and co-workers reported excellent enantioselective oxidation (99% ee) of aryl alkyl sulfides by using urea hydrogen peroxide (UHP) as oxidizing agent at 0^{o}C with the yield of 88%.[28]



12

Figure 13-Salen complex of titanium

Bryliakov and Talsi conducted studies on the stereoselective sulfoxidation by using salen complexes of titanium. They used amino alcohol derived Schiff base **(13)** as ligand and hydrogen peroxide as oxidizing agent in their experiment **(Figure 14)**. In this work, up to 60% enantioselectiviy was reported with 96% yield.[29]

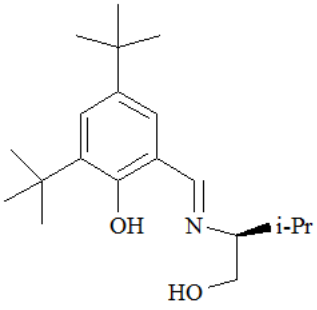


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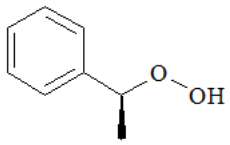
Figure 14-Amino alcohol derived Schiff base

Adam *et al.* used hydroperoxides **(14)** as oxidant with complexes of titanium metal and in that study 75% enantiomeric excess value was reported with 69% yield **(Figure 15)**. Also kinetic resolution was performed with the same conditions where selectivity was increased while yield was decreased.[30]



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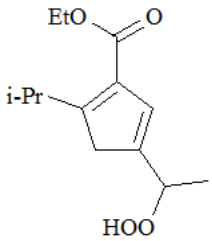

15

Figure 15-Hydroperoxide and furyl hydroperoxide

Furyl hydroperoxides **(15)** were also used for the synthesis of chiral sulfoxides as oxidant. Scettri and co-workers performed enantioriched oxidation reactions with chiral furyl hydroperoxides as oxidant leading to 75% yield and 95% enantioselectivity.[31] Same group also examined norcamphor-derived furyl hydroperoxides and it is proven that with these type of oxidants having steric interactions with sulfide leading to enantioselectivity, it is not necessary to use any chiral ligand.[32]

Another chiral peroxide **(16)** derived form 4-bromoisoquinoline, (R)-menthyl chloroformate and TBHP was used for the stereoselective oxidation of sulfide by Blumenthal and Liebscher **(Figure 16)**. In this work, yield was low (16%) because of full oxidation of sulfide to sulfone, yet 99% enantiomeric excess was recorded for the low yielded sulfoxides.[33]

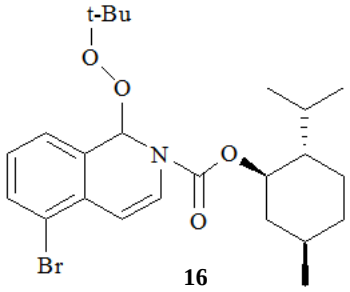

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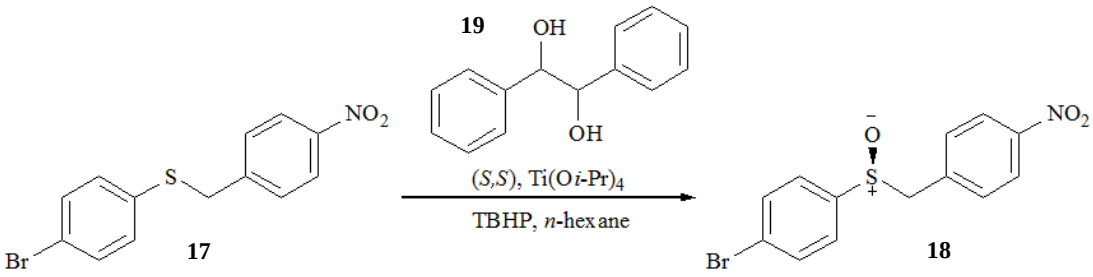
Figure 16- Chiral peroxide derivative

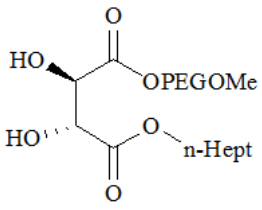
By using a titanium complex including hydrobenzoin **(19)** as the catalyst, Cardellicchio and co-workers reported aryl benzyl sulfides with the good yields and the enantioselectivities **(Scheme 6)**.[34]



17 **18**

Scheme 6-Hyrobenzoin titanium complex catalyzed oxidation

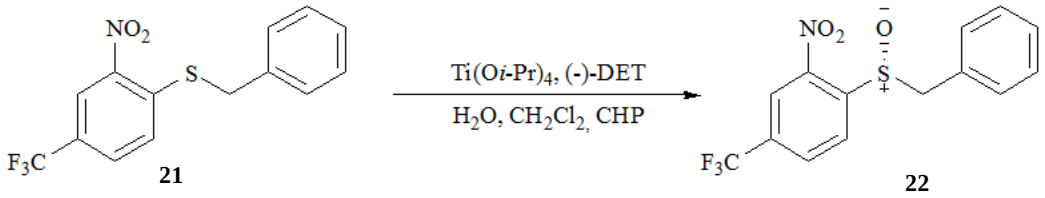
Various research groups examined the use of immobilized catalyst systems. Iwamoto employed complex of titanium immobilized on mesoporous silica, however, low enantiomeric excess value about 30% was recorded.[35] Gao *et al.* used another immobilized catalyst system **(Figure 17)** by using tartrate ligand attached on polyethylene glycol **(20)** and great selectivity (up to 99%) with great yield (91%) was reported.[36]



20

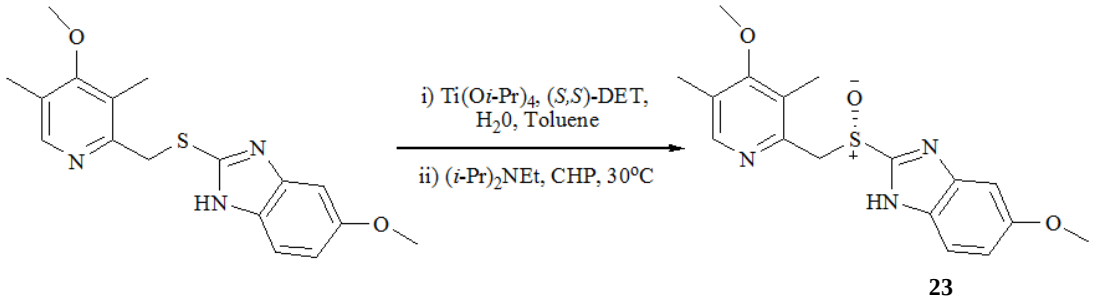
Figure 17-Tartrate ligand attached on polyethylene glycol

Rodygin *et al.* used Kagan's system for asymmetric sulfoxidation for highly electron poor sulfides **(Scheme 7)** and obtained 85% yield and 78% enantiomeric excess.[37]



Scheme 7-Sulfoxidation of electron poor sulfide

In pharmaceutical industry, titanium complexes have also great importance for the synthesis of enantiopure sulfoxides. Esomerprazole **(23)**, the enantiomer of omeprazole, was synthesized **(Scheme 8)** with high stereoselectivity by Von Unge and co-workers.[38]



Scheme 8-Synthesis of Esomeprazole

Enantiopure oxidation of omeprazole was also performed by Volcho and co-workers by using chiral ligand (*R*)-N,N-dimethyl-1-phenylethylamine with titanium catalysis. Yield was 64% and enantioselectivity was 99%.[39] Delamare *et al.* synthesized (*S*)-tenatoprazole **(24)** with titanium-catalyzed asymmetric oxidation with yield 90% and enantiomeric excess 99% by using (+)-(*1R,2S*)-cis-1-amino-2-indanol **(25)** as chiral ligand **(Figure 18)**.

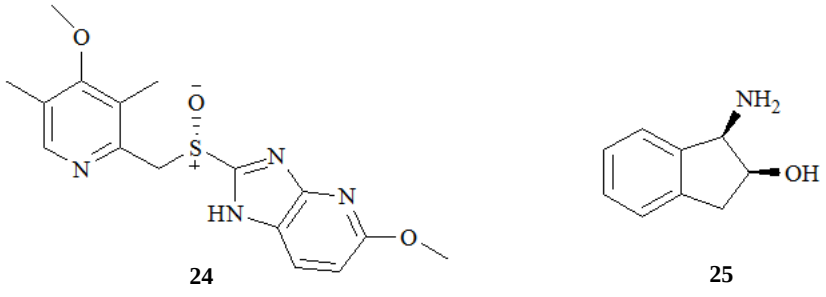
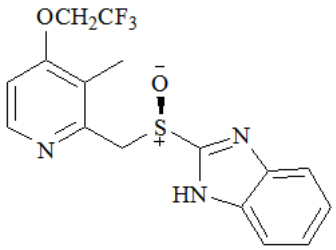


Figure 18- (*S*)-tenatoprazole and (+)-(*1R,2S*)-cis-1-amino-2-indanol

Raju *et al.* performed chiral dexlansoprazole **(26)** synthesis with the high enantioselectivity and yield by using Kagan's system **(Figure 19)**.[40]



26

Figure 19-Structure of dexlanprazole

Caturla synthesized enantioriched sulfoxides as prodrugs **(Figure 20)** by using Modena's system. In this study, excellent enantioselectivities were reported (88-100%) with modereate yield.[41,42]

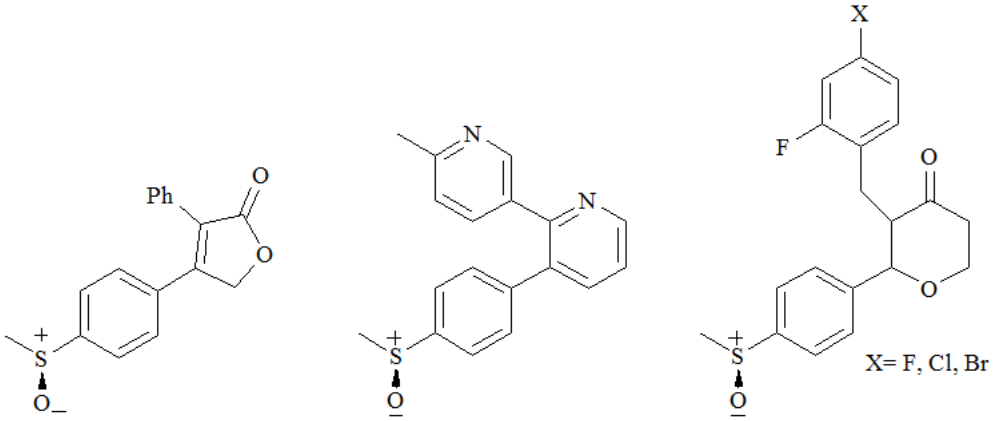


Figure 20-Prodrug sulfoxides

To synthesize (*R*)-modafinil **(27)**, Rebiere *et al.* successfully employed CHP as the oxidant and DET as the chiral ligand with Ti(O*i*-Pr)$_4$ with enantiomeric excess more than 99% **(Figure 21)**. Moreover, a tertiary amine additive seemed to be crucial in order to attain such high enantiomeric excesses. Also increase in enantioselectivity was performed by adding tertiary amine to the reaction.[43]

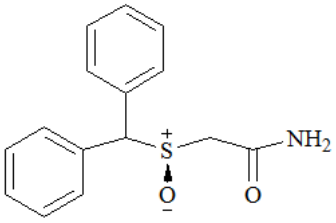


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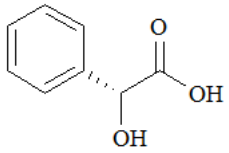
Figure 21- (*R*)-modafinil

It turns out that the titanium based oxidation procedures were settled. The only thing that the researcher changed in the procedure was the ligand. Matsuigi *et al.* used (*S*)-mandelic acid **(28)** to oxidize sulfide to sulfoxide with 89% yield and 76% enantiomeric excess **(Figure 22)**.[44,45]



28

Figure 22- (*S*)-Mandelic acid

1.2.2.2 Vanadium Complexes

Vanadium was facilitated with chiral Schiff bases for the stereoselective oxidation of sulfides to chiral sulfoxides. The structure of the chiral Schiff base is shown in the **Figure 23**. Chiral ligands used in vanadium complexes are modifications of ligand **29**.

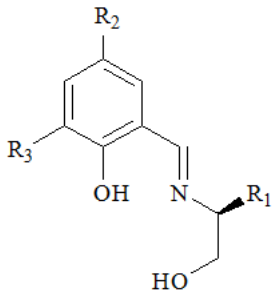


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Figure 23-Structure of Schiff base

Effect of different positions on the Schiff base examined by Ellman and co-workers by performing chiral oxidations **(Figure 24)**. As a result of the study, largest enantiomeric excess value was observed when R_1 was a *tert*-butyl group. It was observed that R_2 group has only electronic effect while R_3 group has both steric and electronic effect on the stereoselectivity of the sulfoxidation reaction.[46]

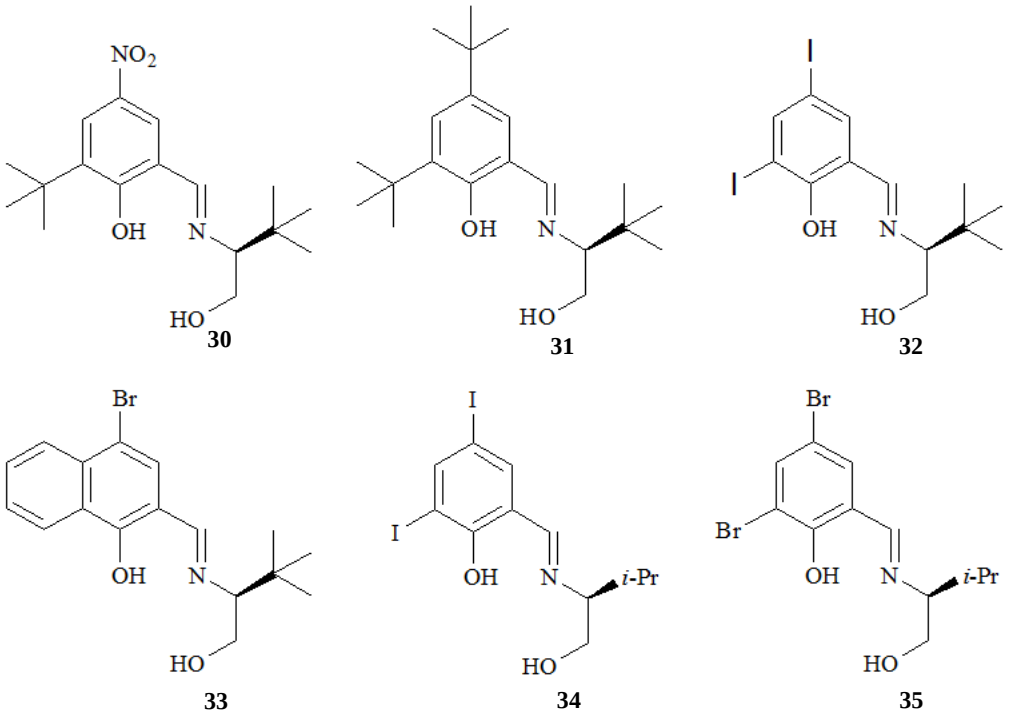


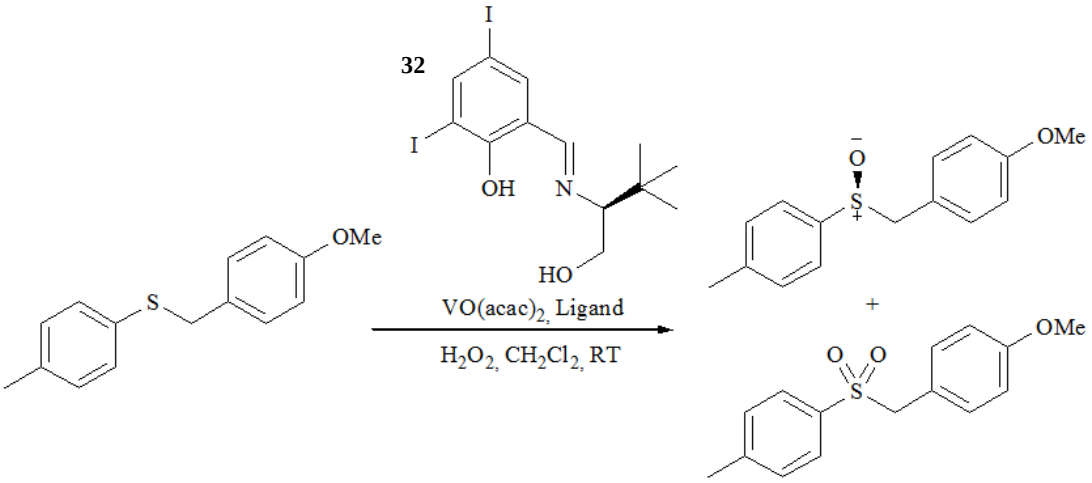
Figure 24-Chiral ligands used in vanadium complexes

Schiff base complexes of vanadium was used as the catalyst by Fujita and co-workers for the thioanisole oxidation with moderate enantioselectivity up to 40%.[47] Bolm and Bienewald employed another vanadium complex of Schiff base in order to perform enantioenriched oxidation of various aryl alkyl sulfides. Sulfoxidation was performed with enantioselectivities 70% with ligand **30** and 59% with ligand **31** were produced with this system. Hydrogen peroxide was used as the oxidizing agent and small amounts of catalyst use became sufficient for the asymmetric sulfoxidation.[48] Various ligands were examined by changing substituents on different positions of Schiff base by Jackson and co-workers. Highest enantioselectivites were reported with the ligands **32** (81%) and ligand **33** (88%).[49]Gao *et al.* used isopropyl substituted Schiff based ligands for the asymmetric sulfoxidation. 88% Enantiomeric excess was reported with ligand **34** and 81% enantiomeric excess was reported with ligand **35 (Table 2)**.[50]

LIGAND	R_1	R_2	R_3	ee (%)
31	*tert*-butyl	NO_2	*tert*-butyl	70
32	*tert*-butyl	*tert*-butyl	*tert*-butyl	59
33	*tert*-butyl	I	I	81
34	*tert*-butyl	Br	-	88
35	*i*-propyl	I	I	88
36	*i*-propyl	Br	Br	81

Table 2-Effect of substituents of the Schiff base on stereoselectivity

Magiure and co-workers used Bolm's system with Schiff base derived ligand **32** for the production of enantioenriched oxidation of aryl benzyl sulfides. Despite observed excellent enantioselectivities, moderate yields were observed with moderate yield due to the over-oxidation to sulfones **(Scheme 9)**.[51]



Scheme 9-Over-oxidation to sulfone with Schiff base ligand

Li and co-workers examined a Schiff base with two stereocenters **(36)** for the asymmetric sulfoxidation **(Figure 25)**. They reported enantiomeric excesses up to 99% in chloroform.[52]

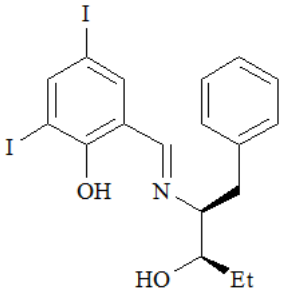


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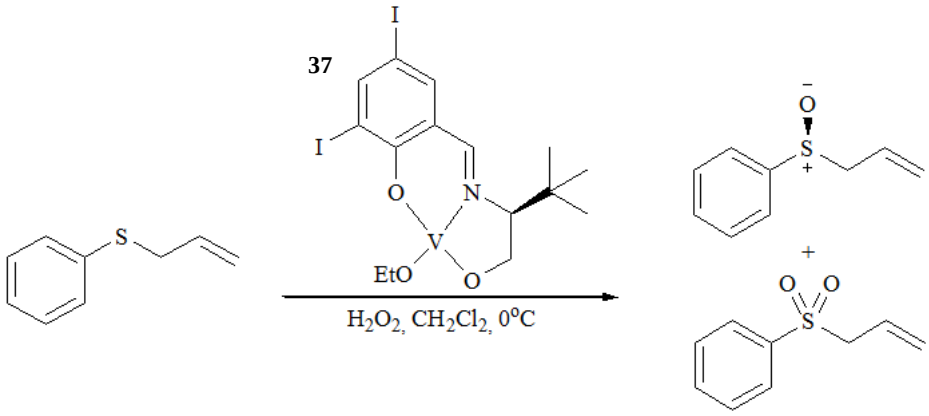
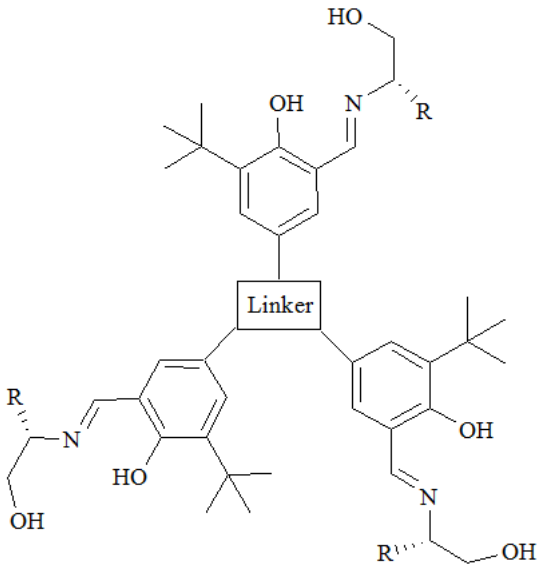
Figure 25-Chiral Schiff base ligand with two chiral centers

Zeng. e*t al.* prepared the complex of vanadium with Schiff base developed by Jackson instead of in situ complex formation. Increasing the equivalence of the hydrogen peroxide resulted in the increase of enantioselectivity. They reported up to 93% enantiomeric excess for allyl phenyl sulfide oxidation **(Scheme 10).**[53]



Scheme 10-Allyl phenyl sulfide oxidation with vanadium Schiff base ligand

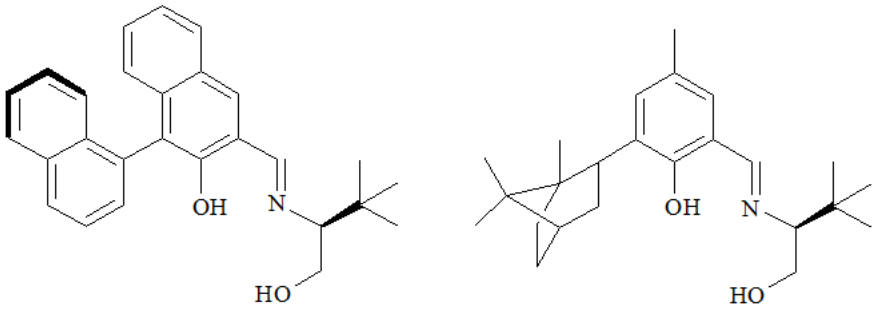
Another study utilized the trimeric form of the Schiff base **(Figure 26)**. In this study, increased enantioselectivity was observed in the asymmetric sulfoxidation reaction with these catalysts. With these catalysts, aryl benzyl sulfides were oxidized with yields up to 92% and enantiomeric excesses up to 92%.[54]



38

Figure 26-Trimeric form a Schiff base

Khiar *et al.* conducted a research on asymmetric sulfoxidation of sterically hindered disulfides and reported high enantioselectivity by using carbohydrate ligand.[55] Effect of vanadium complexes containing sterically bulky ligands **(Figure 27)** on stereoselectivity have been analyzed by various research groups. Vetter and Berksessel reported good enantioselectivities by using these ligand systems.[56]



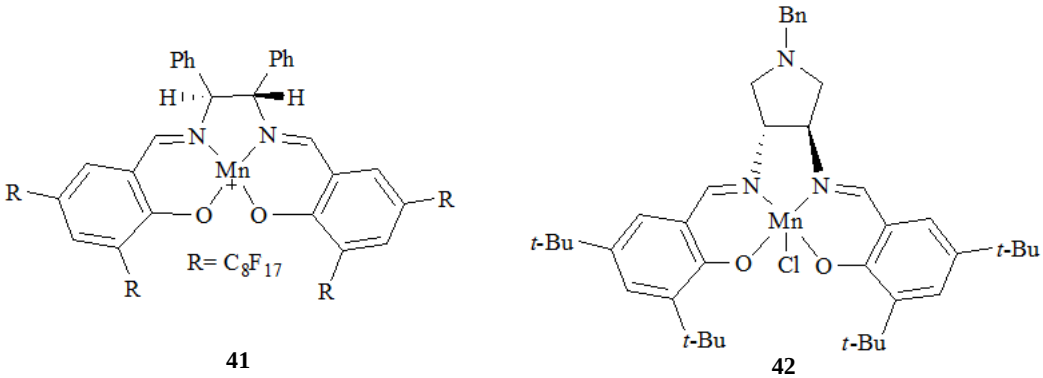
39 **40**

Figure 27-Bulky Schiff base ligands

Bioactive sulfoxides such as (*R*)-Modafinil were synthesized by using vanadium complexes. Aysmmetric oxidation of sulfides to bioactive sulfoxides was performed by using Schiff base containing complexes resulting in high yield production with modest enantioselectivity.[57]

1.2.2.3 Manganese Complexes

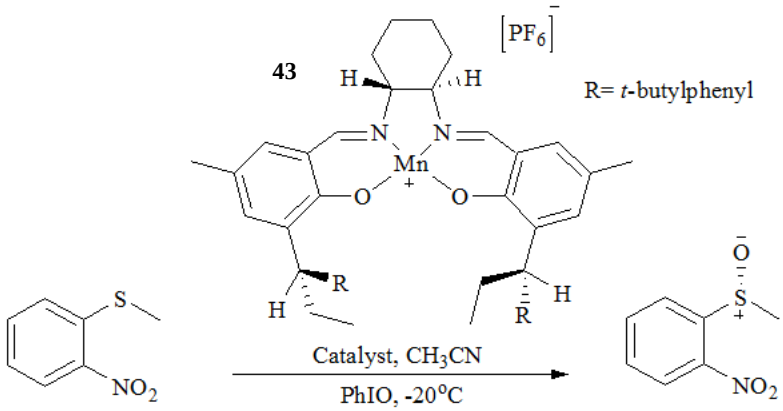
Salen complexes of manganese have been studied by various research groups for the synthesis of stereoselective sulfoxidation **(Figure 28)**. Quici and co-workers reported the use of tetradentate Schiff base ligand with manganese **(41)** for the stereoselective oxidation of methyl aryl sulfides. The stereoselectivity of the oxidation was about 17%.[58] When manganese complexes with pyrolidine backbone **(42)** was employed, enantioselectivity was increased to %42.[59] In this process, iodosylbenzene was used as oxidizing agent, because hydrogen peroxide decomposes the catalyst.



41 **42**

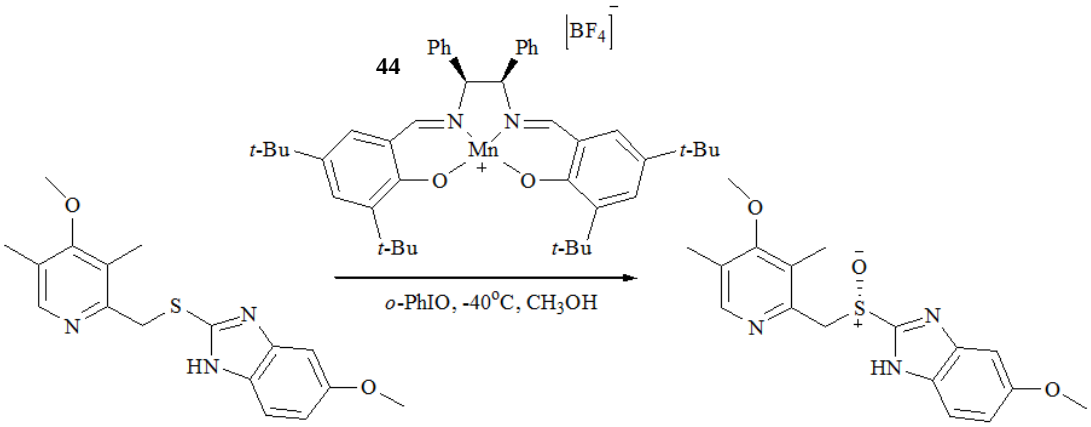
Figure 28-Ligands with manganese

Fontecave and co-workers studied the effect of metal source on the configuration. (*S*)-enantiomer was produced when the $Mn(ClO_4)_2$ was used, while (*R*)-enantiomer was produced when the $Mn(acac)_2$ was used as the metal source.[60] Katsuki oxidation is the most efficient method for the asymmetric sulfoxidation with manganese complex catalysis **(Scheme 11)**. In this study, *ortho*-nitrophenyl methyl sulfide was oxidized to corresponding sulfoxide in great stereoselectivity (90%) with 51% yield.[61]



Scheme 11-Katsuki oxidation

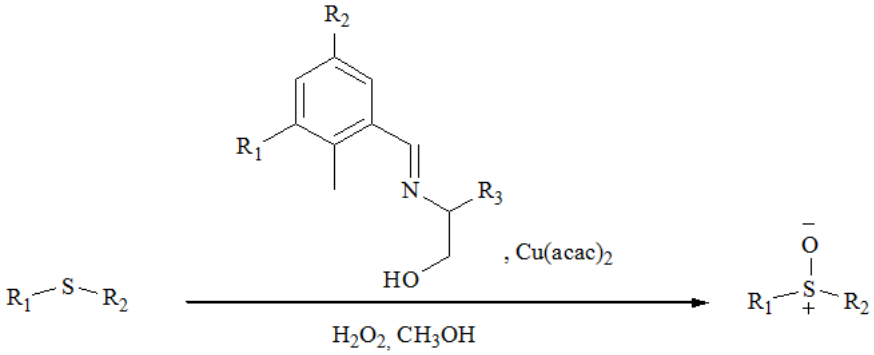
Oxidation to bioactive compound Esomeprazole with the use of manganese complex **(44)** was reported by Ryu and co-workers.[62] High enantioselectivity (70%) was observed with moderate yield.



Scheme 12-Esomeprazole synthesis with manganese complex

1.2.2.4 Copper Complexes

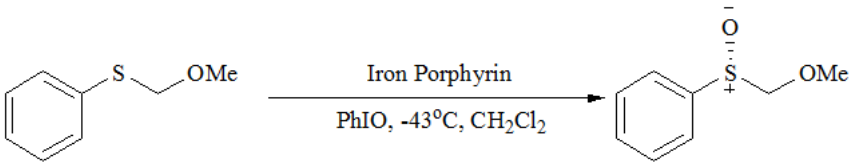
Copper-catalyzed synthesis of chiral sulfoxides have been investigated by Sanchez and co-workers using NaOCl as the oxidant. Altough numerous ligands were utilized, poor enanitoselectivities were observed. Immobilized copper salen type complexes were also investigated and TBHP was used as an oxidant for the chiral oxidation of aryl methyl sulfides, however no significant improvement was reported on the stereoselectivity.[63] Enantioselectivity of 81% was observed in the sulfoxidation by Maguire and co-workers **(Scheme 13)**.[64] Strategy of this work was to use optically active Schiff base complexes of copper metal in mixed solvent systems of low moleculer weight alcohols like methanol and nonpolar alkanes like hexane.



Scheme 13- General strategy of sulfide oxidation with copper Schiff base complexes

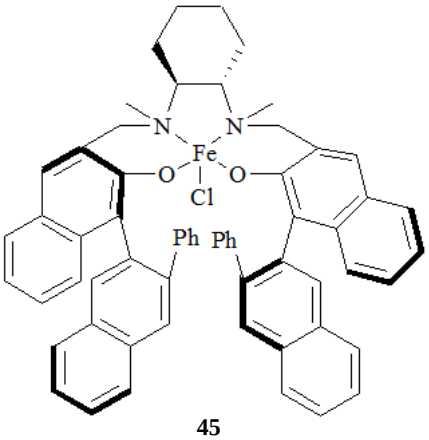
1.2.2.5 Iron Complexes

For iron as well, Schiff base ligands were examined and chiral oxidation of thioanisole was performed with 90% enantioselectivity with moderate yield in the presence of lithium 4-methoxybenzoate by Legros and Bolm.[65] Porphyrin complexes of iron metal were employed by various research groups. Asymmetric sulfoxidation reactions were performed with these complexes with low enantioselectivities, the improved enantioselectivity (71%) was observed in the presence of imidazole **(Scheme 14)**. It was also reported that imidazole enhances enantioselectivity of chiral oxidation of sulfides with iron-porphyrin complexes.[66]



Scheme 14-Oxidation with iron porphyrin complex

Salen complexes of iron **(Figure 29)** have also been used for the production of the oxidation. Egami and Katsuki used salen derivatives **(45)** including optically active binaphtyl components where the oxidizing agent was hydrogen peroxide. By this method enantioselectivities up to 96% were reported with high yield.[67]



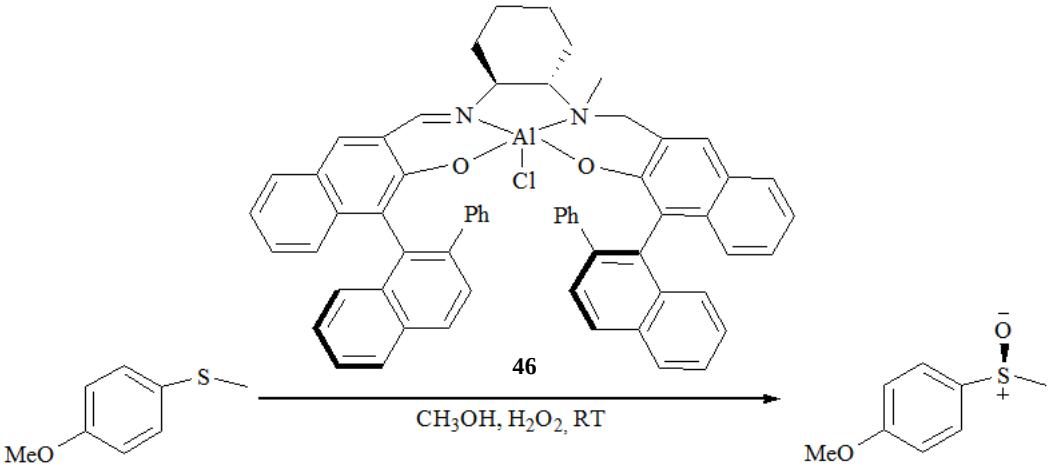
45

Figure 29- Salen complex of iron

By using iron complex systems bioactive enantioriched sulfoxides have also been synthesized. Asymmetric sulfoxidation to bioactive sulfoxides sulindac was reported with 58% eanantioselectivity[68] and another biologically active sulfoxide modafinil was produced with 15% enantioselectivity.[69]

1.2.2.6 Aluminum Complexes

Aluminum complexes have been employed for the stereoselective oxidations. The highest efficiency was reported by Katsuki and co-workers with aluminum salen complexes. Enantioselectivities up to 99% was observed in this study **(Scheme 15)**. Due to the use of methanol as solvent and hydrogen peroxide as oxidizing agent, this procedure can be counted as green. Also, high substrate scope and low catalyst use made this method very efficient.[70]



Scheme 15-Oxidation with aluminium salen complex

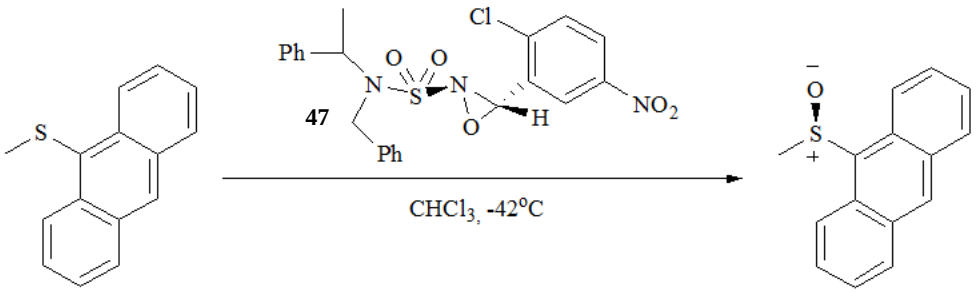
1.2.2.7 Niobium, Tungsten, Osmium and Molybdenum Complexes

Salen complexes of niobium was reported as a good catalyst system by Miyazaki and Katsuki for the stereoselective sulfoxidations.[71] In their procedure, UHP was used as the oxidizing agent and dichloromethane was used as a solvent with moleculer sieves. High enantioselectivities (86% ee) were achieved with moderate (58%) yields. Besides, in order to perform asymmetric sulfoxide production, tungsten complexes (up to 65% ee)[72], osmium complexes (up to 51% ee)[73] and molybdenum complexes (up to 99% ee)[74] were also reported.

1.2.3 Asymmetric Sulfoxidation with Nonmetal Based Systems

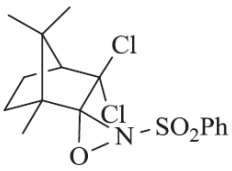
1.2.3.1 Chiral Oxaziridines

Chiral oxaziridines were firstly used by Davis and co-workers for the synthesis of enantioenriched sulfoxides. Despite the low stereoselectivities, this study indicated the importance of relationship among stereogenic center on the reagent, electrophilic oxygen and geometry of the oxidant to have high enantioselectivity.[75] Davis *et al.* used oxaziridines for the asymmetric oxidation of sulfinates and disulfides resulting in enantioselectivities up to 46%. Also, with this study, it was revealed that the configuration and the stereoselectivity depended on the steric factors.[76] Sulfamyloxaziridines **(47)** were facilitated for the enantioriched sulfide oxidation and enantioselectivity of the produced sulfoxide improved up to 68% **(Scheme 16)**.[77]



Scheme 16-Oxidation with sulfamyloxaziridine

By the use of dichlorocamphorylsulfonyloxaziridine **(48)** stereoselectivity of the sulfoxidation reached to 95% with the yield of 95%.[78] Another camphor based oxaziridine **(49)** was examined and enantioselectivity of the sulfoxide was about 80% with 85% yield.[79] Oxaziridine derivatives containing binaphtyl groups **(50)** were employed for the chiral sulfoxidation and stereoselectivities were moderate (20-80%) with good yields **(Figure 30)**.[80]



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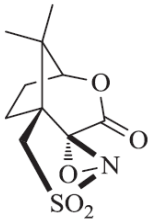

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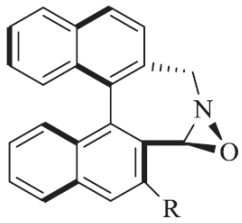

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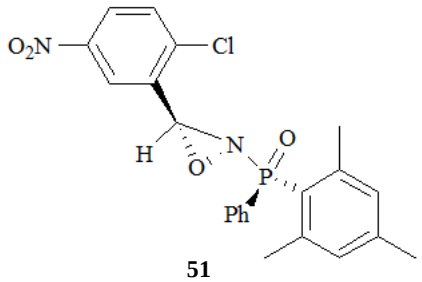
Figure 30-Oxaziridine derivatives

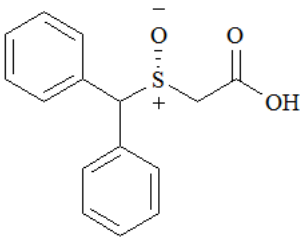
Schwan and Pippert examined the oxidation of numerous aryl and alkyl 2-(trimethylsilyl)ethyl sulfides by using the same optically (*vide supra*) active oxaziridine derivative. The result showed that the more sterically bulky sulfides' oxidation leads to the sulfoxides having higher enantioselectivities when compared to less sterically bulky sulfides.[81] The use of chiral N-phosphinoyloxaziridines **(51)** for the sulfoxidation was performed, it was observed that optically active phosphorus atom induced the stereoselectivity of the reaction **(Figure 31)**.[82]



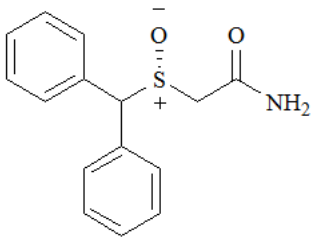
51

Figure 31- N-phosphinoyloxaziridines

In addition to the enantioriched sulfoxides synthesized with the use of oxaziridines above, some of the biologically active sulfoxides were produced with oxaziridines. Asymmetric oxidation of omeprazole to esomeprazole was performed by Von Unge and co-workers with excellent enantioselectivities up to 94%.[83] (*S*)-modafinic acid **(52)** (47% yield and 90% ee) and (*S*)-Modafinil **(53)** (66% yield and 60% ee) were synthesized by the use of chiral oxaziridines **(Figure 32)**.[84] The precursor of a neuroprotective agent, CNS 5788, was synthesized by the asymmetric sulfoxidation reaction using oxaziridine derivative by Padmanabhan et al. with the enantioselectivity of %75 and yield of 95%.[85]



52

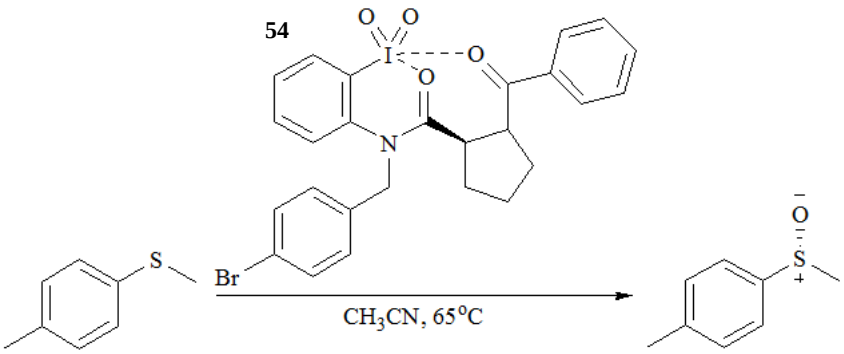


53

Figure 32-(*S*)-Modafinic acid and (*S*)-Modafinil

1.2.3.2 Hypervalent Iodine Complexes

Iodine complex **54** was used as the catalyst in the oxidation of *p*-tolyl sulfide **(Scheme 17)** but enantioselectivity was poor (29%).[86]



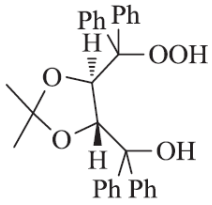
Scheme 17-Sulfoxidaion with iodine complex

1.2.3.3 Bovine Serum Albumin

The enantioriched oxidation of aromatic sulfides were studied in the presence of bovine serum albumin with sodium metaperiodate. Enantioselectiviy of the produced sulfoxide was about 80%.[87]

1.2.3.4 Chiral Hydroperoxides

Chiral hydroperoxides were employed for the asymmetric sulfoxidations. 86% Enantiomeric excess with 73% yield was reported with the use of compound **55**.[88]



55

Figure 33-Chiral Hydroperoxide

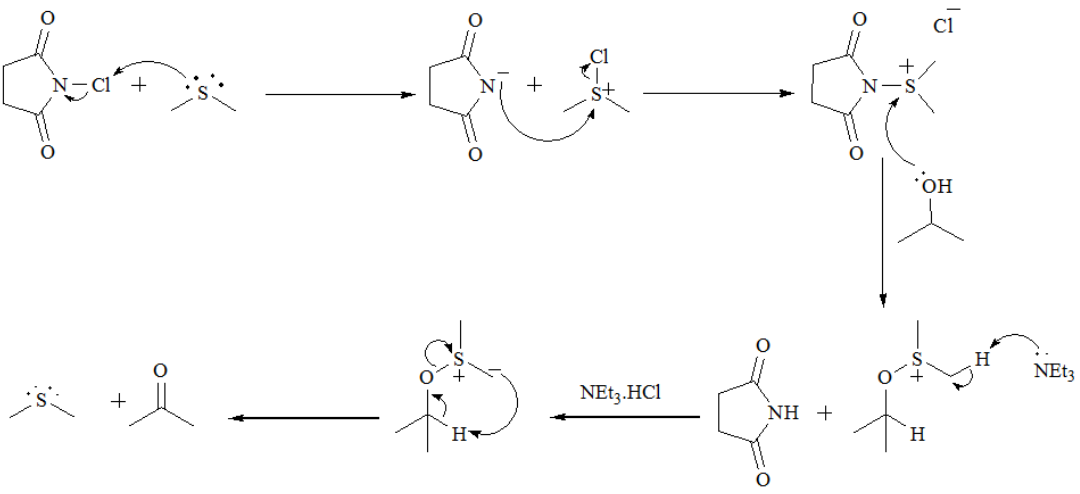
CHAPTER 2

AIM OF THE STUDY

As summarized in the introduction part of this thesis, there are numerous methods available for the asymmetric oxidation of sulfides. The metal based procedures are very sensitive, as the non-metal procedures employ not easy to handle compounds. Therefore, we aim at developing a user-friendly method for such oxidations.

The general goal of the study is to develop a new method for the stereoselective oxidation of sulfides to the corresponding sulfoxides without using metal complexes. In this study, chiral reagents amines, amides and imide derivatives were designed and synthesized. Then, these nitrogen containing materials are chlorinated and used for the enantioselective oxidation of the sulfides.

The basic theory behind this thesis was borrowed from Corey-Kim oxidation **(Scheme 18)**.[89] This oxidation mechanism suggests that chlorine is transferred from N-chlorosuccinimide to sulfur on dimethyl sulfide. We theorized that if the N-chlorosuccinimide is chiral, than a stereodifferentiation should occur while chlorine transfers to the prochiral sulfides. Such a reaction was previously published by the Worley Research Group.[90] for oxidation of sulfides. This study did not deal with symmetric synthesis.



Scheme 18- Mechanism of Corey-Kim reaction as proposed by Corey

CHAPTER 3

RESULTS AND DISCUSSIONS

3.1 General Asymmetric Sulfoxidation Strategy

N-chlorosuccinimide (NCS) and *N*-chloramines[89] in general oxidize sulfides to sulfoxides. This method provides racemic mixture. As mentioned before, we were encouraged by these results to attempt this research. The idea is that a chiral N-chloroamine should transfer chlorine cation to sulfide through a diastereomeric transition state. This was expected to be directed by steric effects. Six chiral reagents were designed and synthesized for the stereoselective sulfoxidation. **(Figure 34)** These chiral reagents contain amine, amide and imide functionalities.

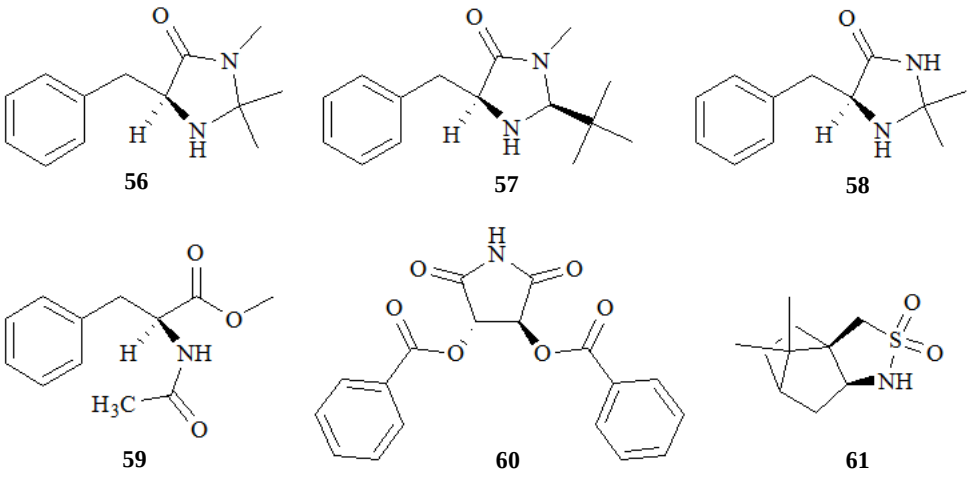
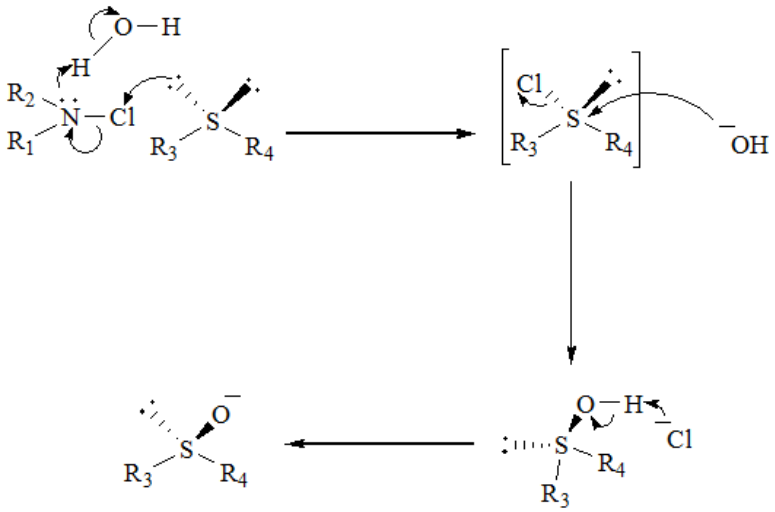


Figure 34-Designed chiral reagents

In this thesis, two main steps are foreseen:

1) Chlorination of the chiral amines, imides, amides
2) Use of these chlorinated chiral reagents in oxidation of sulfides (This step was summarized in **Scheme 19**)



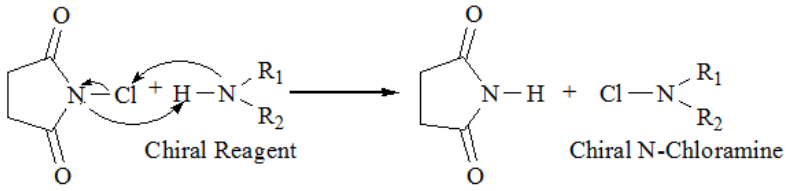
Scheme 19-Predicted mechanism for the asymmetric sulfoxidation

Stability order of N-Cl bonds in amine-Cl, amide-Cl and imide-Cl is determined based on the calculations and the dissociation constants of the bond between nitrogen and chlorine atoms: dissociation constant in water for N-Cl in amine is the smallest dissociation constant and N-Cl in imide is the largest dissociation constant **(Table 3)**.[89]

***N*-Chloramine**	**Dissociation Constant**
Amine-Cl	$<10^{-12}$
Amide-Cl	$<10^{-9}$
Imide-Cl	$<10^{-4}$

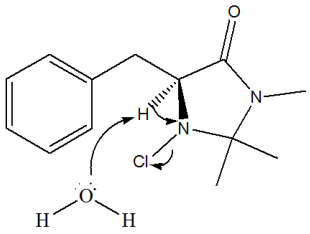
Table 3-Dissociation constants of different N-Cl bonds

This means that chlorine transfer should occur faster on imide-Cl. Thermodynamically, transfer of chlorine from imide to amine and amide found to be spontaneous **(Scheme 20)**. Therefore, we used this strategy to chlorinate chiral amines and imides. Chiral imides were chlorinated with hypochlorous acid.



Scheme 20-Chlorine transfer from *N*-chlorosuccinimide to the chiral reagents

Amines should be chlorinated with care that dehydrochlorination could ocur. With this in mind, chlorination should not be carried out with hypochlorous acid in water. The proposed mechanism for dehydrochlorination is shown in **Scheme 21**.



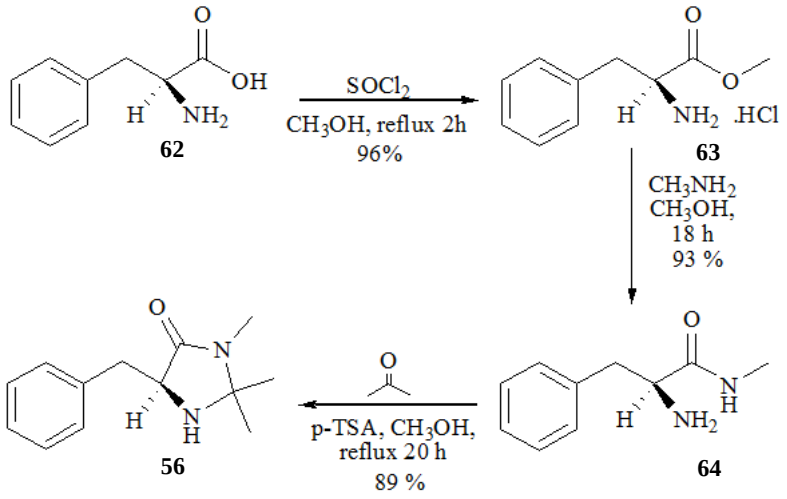
Scheme 21-Dehydrochlorination mechanism

All the compounds but the imide was chlorinated with N-chlorosuccinimide as chlorinating agent. These chiral reagents could also be called catalysts, due to the fact that they only carry chlorine onto sulfur atom.

3.2 Design and Synthesis of the Chiral Reagents

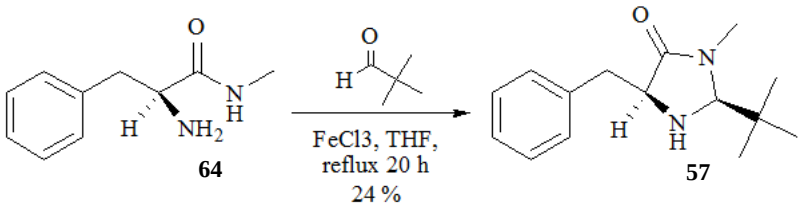
This study is the first to stereoselectively oxidized sulfides by chiral chloroamines to the best of our knowledge. With this in mind, easy to obtain nitrogen containing materials were chosen. The compounds **56, 57, 58** and **59** were synthesized from *L*-phenylalanine while compound **60** was synthesized from *L*-tartaric acid. Compound **61** was commercially available. With all compounds in hand, the study covered amines, amides and imides. Firstly synthesized chiral reagent was (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **(56)**, which was reported as MacMillan imidazolidinone[91] and starting material of this imidazolidinone derivative was *L*-phenylalanine. Esterification of *L*-phenylalanine was performed with methanol in 96% chemical yield.[92] After this step by using methylamine solution, ester **63** was

converted to the corresponding amide **64** with the yield 93%. By the condensation with acetone in the presence of *p*-toluenesulfonic acid resulted the desired compound **56**, in 89% chemical yield **(Scheme 22)**.



Scheme 22-Synthesis of (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one

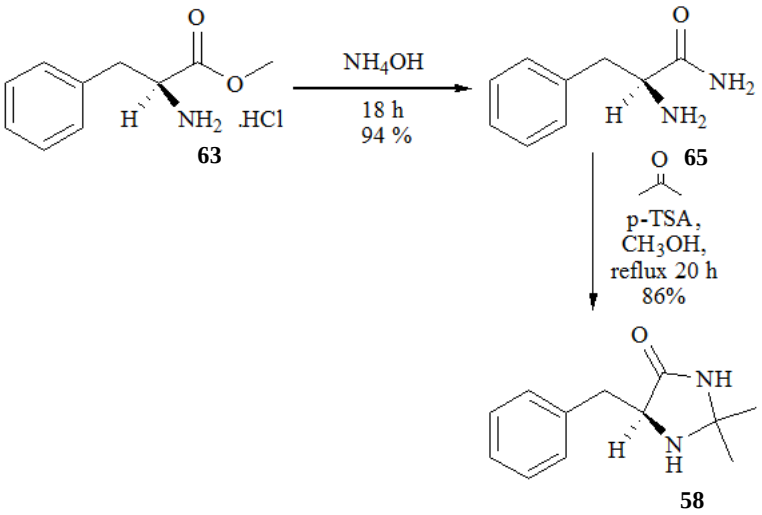
(*2S,5S*)-2-*tert*-Butyl-5-benzyl-3-methylimidazolidin-4-one **(57)** is another MacMillan imidazolidinone derivative.[90] Condensing the amide **64** with trimethylacetaldehyde yielded a mixture of two diastreomers. It is known that physical properties of the diastereomers are different and by using solubility differences of two diastereomers, they were separated from each other. One diastereomer of the imidazolidinone derivative was soluble in saturated solution of hydrochloric acid in diethylether while another diastereomer was not. By filtering insoluble particles from mixture, desired compound **57** was separated and the yield was 34% **(Scheme 23)**.



Scheme 23- Synthesis of (*2S,5S*)-2-tert-Butyl-5-benzyl-3-methylimidazolidin-4-one

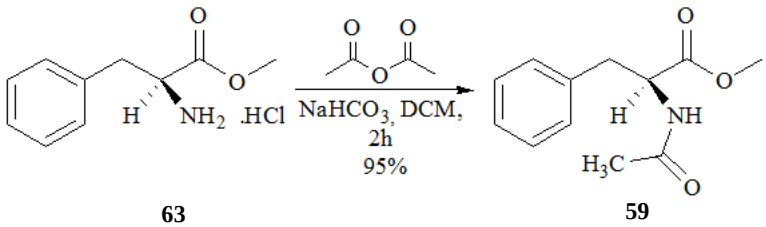
(*S*)-5-Benzyl-2,2-dimethylimidazolidin-4-one **(58)** was synthesized from *L*-phenylalanine. The ester **63** was converted to (*S*)-2-amino-3-phenylpropanamide.

First the ester was treated with NH_3(g) after dissolving the ester in methanol. This reaction was performed at room temperature and in reactor at 80°C. However, according to the ^1H and ^{13}C NMR and IR analysis it was observed that this method did not yield the desired compound, the starting ester was recovered. The ester was dissolved in ammonium hydroxide solution and stirred for 18 hours at room temperature to get the desired amide **65** in 94% chemical yield. Finally by the condensation of the amide with acetone, designed imidazolidinone derivative **58** was obtained in 86% chemical yield **(Scheme 24)**.



Scheme 24- Synthesis of (*S*)-5-benzyl-2,2-dimethylimidazolidin-4-one

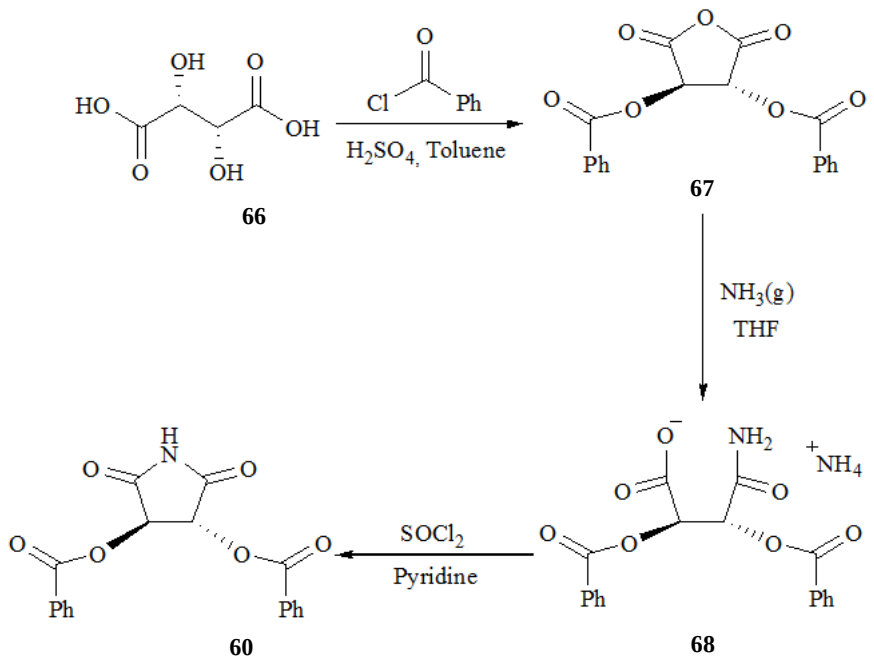
The compound **63** was treated with acetic anhydride to get compound **59** in 95% chemical yield. **(Scheme 25)**.



Scheme 25- Synthesis of (*S*)-methyl-2-acetamido-3-phenylpropanoate

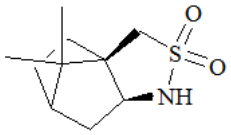
Another chiral reagent (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione **(60)** was synthesized starting from *L*-tartaric acid **(66)** (Scheme 24). *L*-Tartaric acid was treated with benzoyl chloride in toluene in the presence of H_2SO_4 to get (*2R,3R*)-dibenzoyltartaric anhydride **(67)**. Then, the product was dissolved in ammonia

solution in tetrahydrofuran to yield **68**. The compound **68** was dissolved in thionyl chloride and pyridine, and stirred at 60°C. Then concentrated to yield desired imide derivative **60 (Scheme 26)**.



Scheme 26-Synthesis of (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione

(*1R*)-(+)-2,10-Camphorsultam **(61)** which is another amide derivative was commercially available **(Figure 35)**.



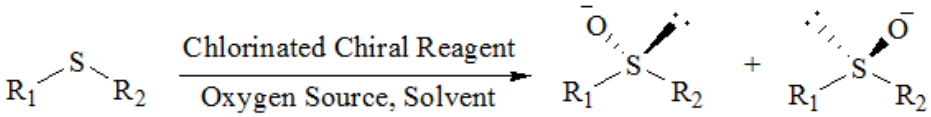
61

Figure 35-Structure of (*1R*)-(+)-2,10-camphorsultam

3.3 Asymmetric Sulfoxidation Studies

In 1968, Harville reported a racemic sulfoxidation study for several sulfides by using N-chlorosuccinimide.[92] In this study, sulfoxidation was performed by using anhydrous methanol both as a solvent and the oxygen source. According to the procedure, sulfide was dissolved in anhydrous methanol and the resulting mixture was cooled to 0°C. At 0°C, *N*-chlorosuccinimide was introduced to the mixture, and the mixture was stirred at room temperature for 2 hours to yield racemic sulfoxide.

Inspired by Harville's study, sulfoxidation studies were performed. In our studies, chlorinating agent NCS and one of the chiral reagents was stirred at room temperature in selected reaction solvent for two hours. Then the reaction temperature was adjusted to different temperatures in order to determine temperature effect on the stereoselectivity. After adjusting the temperature, sulfide was added to the reaction mixture and after stirring mixture for half an hour, oxygen source was then added to the reaction mixture at selected temperature. Then, the mixture was stirred at room temperature and the reaction was ended based on thin layer chromatography results **(Scheme 27)**.



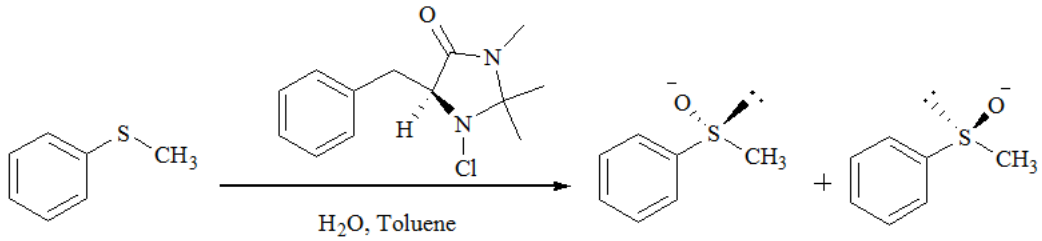
Scheme 27-Asymmetric Sulfoxidation Strategy

At the end of the sulfoxidation reaction, one of the end products was methyl phenyl sulfone. The sulfone formation was due to the overoxidation of the sulfoxide. This occurs after the reaction was ceased: Because, there is, as mentioned before, an equilibrium between *N*-chloramine and amine in water, and as a result, hypochlorous acid is formed. This hypochlorous acid oxidizes sulfoxide to the sulfone. When the reaction work-up is done with sodium sulfite (Na_2SO_3), sulfone formation was not observed. Because, the hypochlorous acid was deactivated with sulfite anion.

In all of sulfoxidation studies, thioanisole was selected as the sulfide to be oxidized due to the fact that methyl phenyl sulfide was used as the model compound in such studies. The first sulfoxidation experiments were performed in toluene; (*S*)-5-benzyl-

2,2,3-trimethylimidazolidin-4-one **(56)** was used as the chiral reagent, *N*-chlorosuccinimide was used as chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78^{o}C. Highest enantiomeric excess was observed at 0^{o}C as 18% **(Table 4)** in 16% chemical yield. With decreasing temperature from 0 to -78^{o}C, a decrease in stereoselectivity was observed. This could be on account of the activation barrier for chlorine transfer.

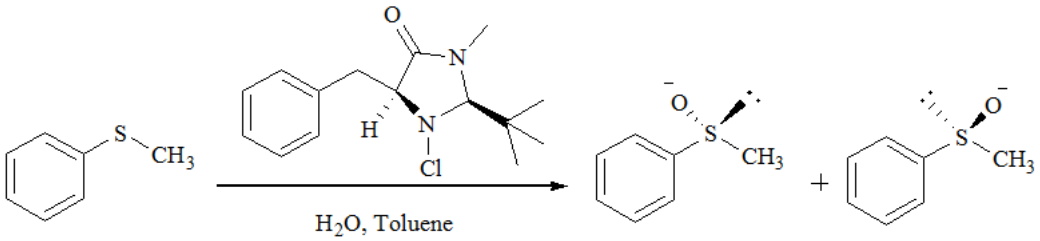
Table 4-Oxidation with chlorinated compound **56** in toluene



Temperature	Stereoselectivity (ee%)
25 ^{o}C	12
0 ^{o}C	18
-10 ^{o}C	16
-78 ^{o}C	10

In the second set of sulfoxidation reactions (*2S,5S*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one **(57)** was used as the chiral reagent, *N*-chlorosuccinimide was used as chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78^{o}C **(Table 5).** Highest enantiomeric excess was observed at 0^{o}C as 6%.

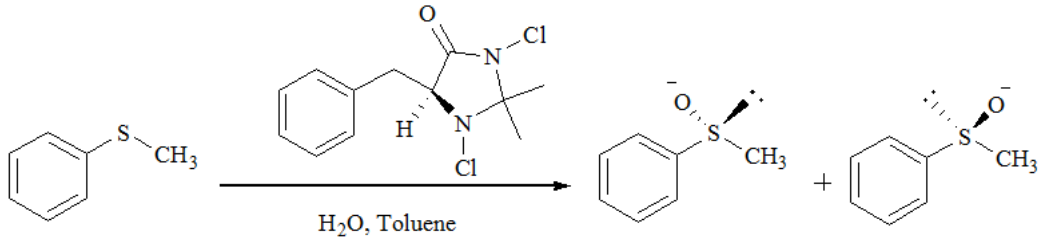
Table 5- Oxidation with chlorinated compound **57** in toluene



Temperature	Stereoselectivity (ee %)
25 °C	2
0 °C	6
-10 °C	4
-78 °C	2

Then, sulfoxidation tests were performed by employing (*S*)-5-benzyl-2,2-dimethylimidazolidin-4-one **(58)** as the chiral reagent**.** *N*-chlorosuccinimide was used as chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78°C **(Table 6)**. In this sulfoxidation set, 2 equivalents of *N*-chlorosuccinimide were used due to the presence of two nitrogen atoms to be chlorinated. First, amine nitrogen is expected to be chlorinated and then, chlorination of amide nitrogen is expected. However, interaction between chlorine and sulfur atom would be performed firstly with the chlorine atom bonded to the amide nitrogen on account of the larger reactivity of amide-Cl than that of amine-Cl. Highest enantiomeric excess was observed at 0°C as 7%.

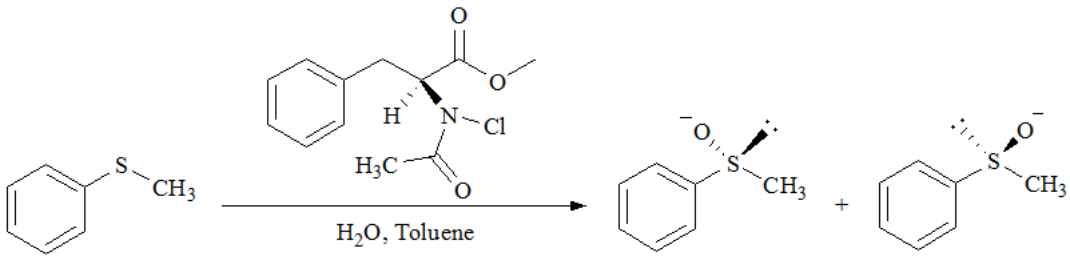
Table 6-Oxidation with chlorinated compound **58** in toluene



Temperature	Stereoselectivity (ee %)
25 °C	2
0 °C	7
-10 °C	2
-78 °C	4

Another set of sulfoxidation reactions was performed by using (*S*)-methyl 2-acetamido-3-phenylpropanoate **(59)** as a chiral reagent, *N*-chlorosuccinimide as the chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78°C **(Table 7)**. Highest enantiomeric excess was observed at 0°C as 22%.

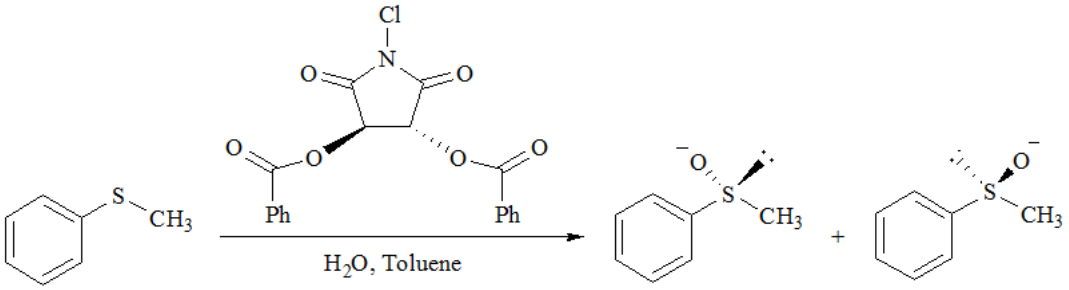
Table 7- Oxidation with chlorinated compound **59** in toluene



Temperature	Stereoselectivity (ee %)
25 °C	6
0 °C	22
-10 °C	19
-78 °C	19

(*3S,4S*)-3,4-Diphenylpyrrolidine-2,5-dione **(60)**, which is an imide derivative was employed for chiral sulfoxidation as the chiral inducer. In this sulfoxidation reaction, sodium hypochlorite was used for the chlorination of (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione, instead of *N*-chlorosuccinimide, because there is no driving force for the chlorine transfer from imide to imide derivative chiral reagent. For this purpose, mixture of sodium hypochlorite and acetic acid was prepared whose pH was about 7. Then, (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione was stirred in prepared mixture in order to be chlorinated. Sulfoxidation reactions were carried out by employing (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione as the chiral reagent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78^{o}C **(Table 8)**. Highest enantiomeric excess was observed at -10^{o}C as 20%.

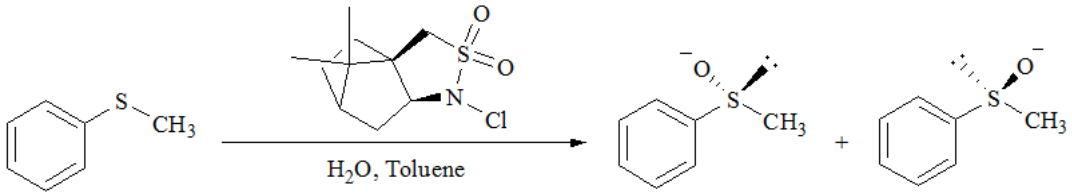
Table 8- Oxidation with chlorinated compound **60** in toluene



Temperature	Stereoselectivity (ee %)
25 ^{o}C	4
0 ^{o}C	4
-10 ^{o}C	20
-78 ^{o}C	8

(*1R*)-(+)-2,10-Camphorsultam **(61)** was another chiral reagent used for chiral sulfoxidation. In these reactions, *N*-chlorosuccinimide was used as chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by the addition of thioanisole at 25, 0, -10 and -78^{o}C **(Table 9)**. Highest enantiomeric excess was observed at 0^{o}C as 7%.

Table 9- Oxidation with chlorinated compound **61** in toluene

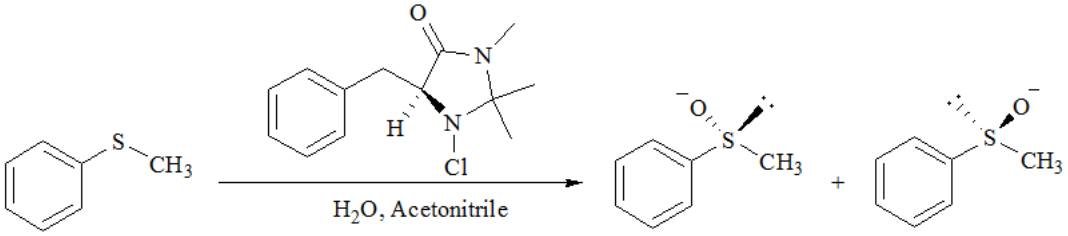


Temperature	Stereoselectivity (ee %)
25 °C	6
0 °C	7
-10 °C	6
-78 °C	4

According to the chiral HPLC analysis performed with the sulfoxides obtained by using designed chiral reagents in toluene, most enantioselective sulfoxidation system was obtained with the reactions in which (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **(56)**, (*S*)-methyl 2-acetamido-3-phenylpropanoate **(59)** and (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione **(60)** were used as the chiral reagents. After selection of these chiral reagents that gave the most stereoselective sulfoxidation system in toluene, next step was to perform sulfoxidation reactions with different solvents. Acetonitrile was selected for this purpose on account of its polarity and it does not include any reactive functional groups that may interact during the oxidation. Before performing sulfoxidation reactions in acetonitrile, acetonitrile was freshly distilled over CaH_2 and stored over 4 Å moleculer sieves.

First set of sulfoxidation reaction in acetonitrile was performed by using (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **(56)** as the chiral reagent, *N*-chlorosuccinimide as the chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78°C **(Table 10)**. Highest enantiomeric excess was observed at 0°C as 23%.

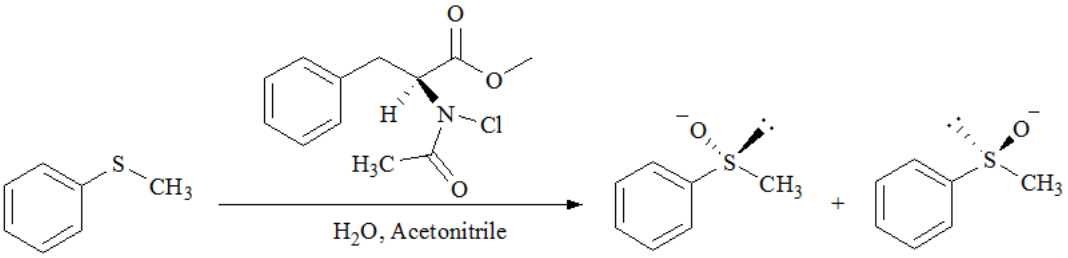
Table 10- Oxidation with chlorinated compound **56** in acetonitrile



Temperature	Stereoselectivity (ee %)
25 °C	2
0 °C	23
-10 °C	6
-78 °C	6

Second set of sulfoxidation reactions in acetonitrile were performed by using (*S*)-methyl-2-acetamido-3-phenylpropanoate **(59)** as a chiral reagent, *N*-chlorosuccinimide as the chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78°C **(Table 11)**. Highest enantiomeric excess was observed at 0°C as 12%.

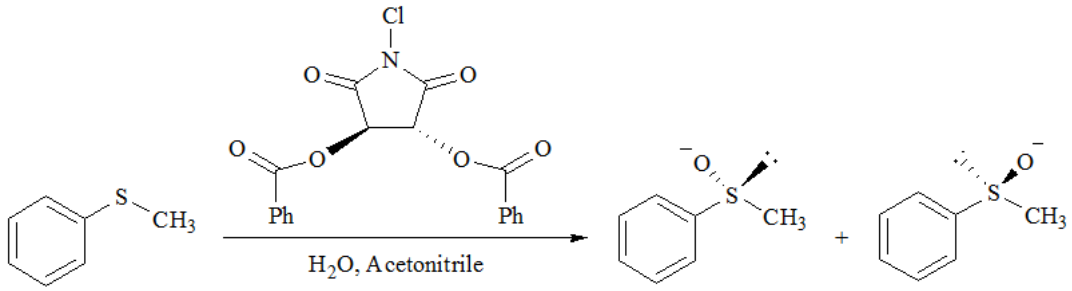
Table 11- Oxidation with chlorinated compound **59** in acetonitrile



Temperature	Stereoselectivity (ee %)
25 °C	10
0 °C	12
-10 °C	8
-78 °C	9

Another sulfoxidation reaction in acetonitrile was performed with (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-dione **(60)** as the chiral reagent. Imide derivative chiral reagent was chlorinated by using sodium hypochlorite as mentioned before and chlorinated imide derivative was used for the sulfoxidation. Thioanisole was used as the sulfide and water as the oxygen source**.** Stereoselectivity of this reaction was examined by addition of thioanisole at 25, 0, -10 and -78^{o}C **(Table 12).** Highest enantiomeric excess was observed at -10^{o}C as 11%.

Table 12- Oxidation with chlorinated compound **60** in acetonitrile



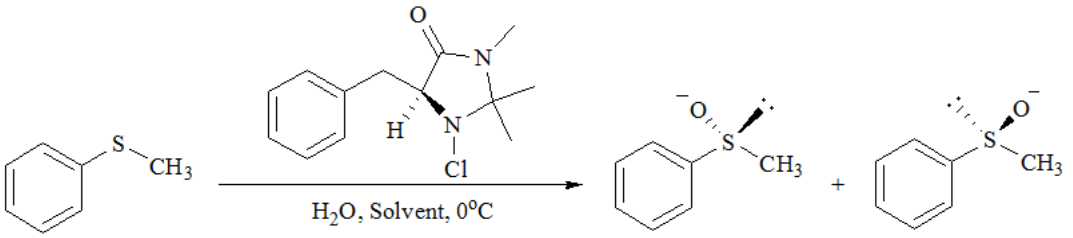
Temperature	Stereoselectivity (ee %)
25 ^{o}C	5
0 ^{o}C	6
-10 ^{o}C	11
-78 ^{o}C	8

Based on the results of the sulfoxidation reactions in both toluene and acetonitrile, the best stereoselectivities were obtained in the set of reactions in which (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **(56)** was used as the chiral reagent. Moreover, according to the all sets of sulfoxidation reactions, it was observed that the most stereoselective sulfoxidation was observed when thioanisole addition was performed at 0^{o}C.

Therefore, it was decided to use (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-on **(56)** as the chiral reagent in the next sulfoxidation reactions and it was decided to perform thioanisole addition to the reaction mixture at 0^{o}C as a conclusion of the sulfoxidation screenings.

After selection of best temperature for thioanisole addition and chiral reagent which leaded to the most stereoselective sulfoxidation reaction, other solvents were examined. For this purpose, dimethylformamide and tert-butanol were employed and water was used as the oxidizing agent in these studies too. In both of reactions, (*S*)-5-benzyl-2,2,3-trimethylimidazolid in-4-one **(56)** was used as the chiral reagent, *N*-chlorosuccinimide was used as chlorinating agent, thioanisole and water was used as the oxygen source. Stereoselectivity of this reaction was examined by addition of thioanisole at 0^{o}C. Then *tert*-butanol was selected as the reaction solvent, and for this reaction, water addition was not performed because *tert*-butanol was also able to act as the oxygen source in the sulfoxidation reaction. (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one was used as the chiral reagent, *N*-chlorosuccinimide was used as the chlorinating agent and thioanisole was used as the sulfide. Stereoselectivity of this reaction was examined by addition of thioanisole at 0^{o}C. However, stereoselectivies obtained with these solvents did not exceed the stereoselectivites of the sulfoxidations with (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one in acetonitrile **(Table 13)**.

Table 13-Oxidation with chlorinated compound **56** in different solvents



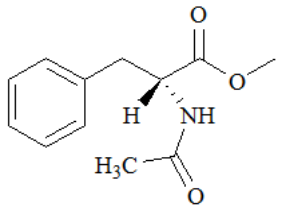
Solvent	Stereoselectivity (ee %)
Dimethylformamide	12
Dichloromethane	10
tert-Butanol	14

After performing asymmetric sulfoxidation reactions in several solvents, the highest steresoelectivity was obtained with the sulfoxidation reaction performed in acetonitrile. As a result, acetonitrile was selected as the best reaction solvent, (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one was selected as the most chirality inducing

reagent among the desired chiral reagents and addition of thioanisole to the reaction mixture at 0^{o}C leaded to the highest stereoselectivity in the sulfoxidation.

Then, concentration screening was performed with the determined reaction conditions. Concentration of the sulfoxidation reaction mixture might have been affecting the stereoselectivity of the sulfoxidation both directly or inversely. Sulfoxidation reaction was performed with four different concentrations and then, stereoselectivity of the resulting sulfoxides were analysed. According to these analysis no change in the stereoselectivity was observed by changing the concentration of reactants.

Up to this step, all the sulfoxidation studies yielded to "*S*" enantiomer of methylphenyl sulfoxide because negative optical rotation values were obtined with the analysis performed with polarimeter. In order to strengthen offered sulfoxidation mechanism and to examine the effect of chiral reagents on the configuration of the sulfoxide, it was decided to synthesize one of the chiral reagents by starting *D*-phenylalanine instead of using *L*-phenylalanine. For this purpose, "*R*" enantiomer of the chiral reagent **59** was synthesized starting from *D*-phenylalanine to yield (*R*)-methyl 2-acetamido-3-phenylpropanoate **(69)**.



69

Figure 36-"*R*" enantiomer of compound **59**

By using (*R*)-methyl 2-acetamido-3-phenylpropanoate **(69)**, another sulfoxidation reaction was performed. As a result of this reaction, it was expected to observe excess of the "R" enantiomer of the phenyl methyl sulfoxide unlike the observed results before. (*R*)-methyl 2-acetamido-3-phenylpropanoate **(69)** was used as the chiral reagent, N-chlorosuccinimide as the chlorinating agent, thioanisole as the sulfide and water as the oxygen source. Stereoselectivity of this reaction was examined by the addition of thioanisole at 0 ^{o}C. According to the analysis performed with polarimeter and the chiral HPLC analysis, it was observed that of (*S*)-methyl 2-

acetamido-3-phenylpropanoate was leaded to the "*S*" enantiomer of methylphenyl sulfoxide while (*R*)-methyl 2-acetamido-3-phenylpropanoate was leaded to the "R" enantiomer of methylphenyl sulfoxide as it was expected. However, enantioselectivity observed in sulfoxidation with (*R*)-methyl 2-acetamido-3-phenylpropanoate was 2% (R configuration) while enantioselectivity observed with of (*S*)-methyl 2-acetamido-3-phenylpropanoate was 12% (*S* configuration).

3.4 Asymmetric Sulfoxidation Strategy and Theoretical Considerations

When compound **56** is considered, there are two possible orientations for the chlorine position. To model this, for the sake of computational time, we used alanine derivative of **56** in the computational studies. Chlorine can be on the same side with the methyl group at the stereogenic center or opposite side of that methyl group **(Figure 37)**. Computational studies at the level of B3LYP/SVP showed that chlorine at the opposite side of the methyl was more stable by 4.40 kcal/mol than the same side. Inversion barrier from one side to another is 5.60 kcal/mol relative to the lowest energy diastereomer. This barrier is higher by 3.60 kcal/mol than the amine itself.

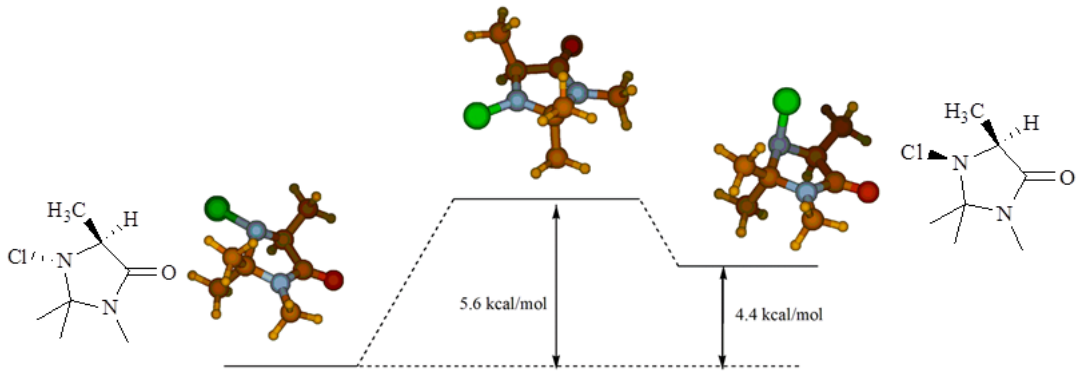
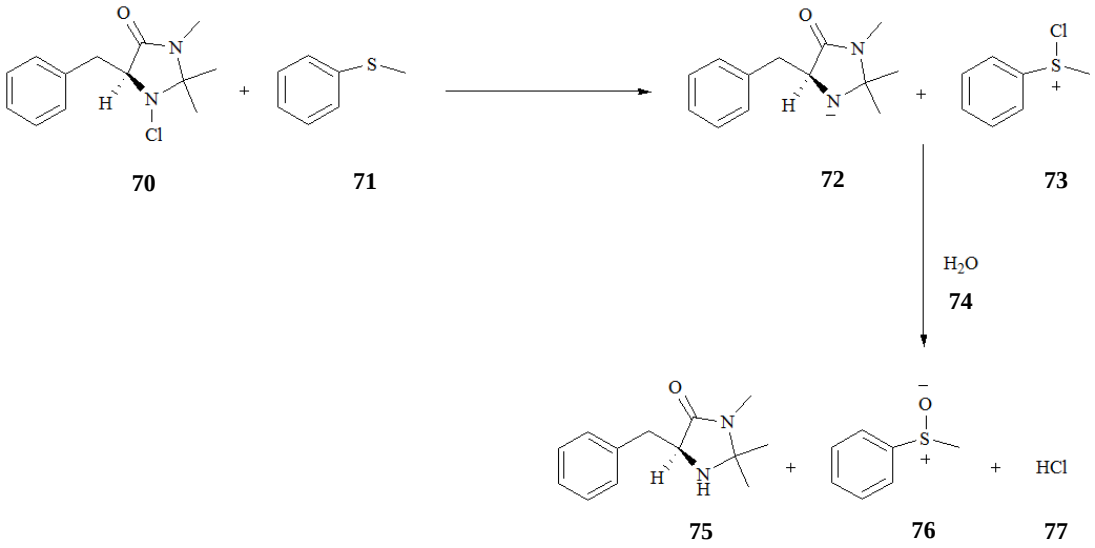


Figure 37- Inversion barrier and stability of chloramine diastereomers

This low inversion barrier could be one reason for observing low enantioselectivities. The other reasons could be due to the mechanism of formation of sulfoxides as discussed below.

There are two mechanistic pathways plausible for the enantioenriched sulfoxidation reaction in this study. Computation studies showed that a chlorine transfer from

amine N-Cl to sulfur thermodynamically was not feasible. That is, chlorine wants to stay on nitrogen rather than on the sulfur. Experimentally, on the contrary, we observed that sulfoxide formation occurred. This contradiction between what we thought and what actually happened can be explained by an S_N1 reaction through ion pair formation. This reaction computationally was proposed as shown in **Scheme 28** according to our initial guesses.



Scheme 28- Sulfoxidation reaction with chlorinated **56**

The Gibbs free energies and enthalpies were calculated using B3LYP/SVP level of theory as implemented into Gaussian 09 electronic structure package program and the results were summarized in the **Table 14.**

Compound	ΔH (Hartree)	ΔG (Hartree)
70	-1149.602238	-1149.664934
71	-669.309908	-669.351158
72	-689.565778	-689.625014
73	--1129.090499	-1129.135903
74	-76.333309	-76.354752
75	-690.164692	-690.224650
76	-744.416280	-744.459677
77	-460.660043	-460.681240

Table 14- Calculated enthalpies and Gibbs free energies

With raw data in hand the reaction given in **Scheme 28** was analysed in the **Table 15**. As seen in the table the reaction is driven forward because of the second step.

Even though we did not model, we think that first chlorine transfer from nitrogen to sulfur goes with the help of some minute amount of water present in the reaction medium. This could probably reduce the values of ΔH and ΔG for the first step. These computations were performed in the gas phase, that is when solvation is included, the reaction would be more exothermic and exoergic. This is still understudy.

Compounds in Interaction	**ΔH (kcal)**	**ΔG (kcal)**
70+71	0	0
72+73	160.56	160.12
72+73+74	0	0
75+76+77	-157.77	-156.81

Table 15-Calculated relative enthalpies and Gibss free energies

Even though for the same catalyzed sulfoxidation reactions we did not observe any transition states, we modelled N-chlorosuccimide (NCS) and dimethyl sulfide (DMS) in which we located a transition state. This modelling studies were performed at the level of B3LYP/SVP as implemented in Gaussian 09. Modelling NCS with DMS, we have observed an imaginary frequency when we visualized it we saw that the chlorine "Cl^+" was going back and forth from nitrogen onto sulfur atom. These observations from the computational studies let us conclude that most probably when imide-Cl catalyzed oxidations occur via S_N2 reactions and amine-Cl reactions goes through S_N1 reactions. The reason that we did not observe high enantiomeric excess for the NCS-derivative **(60)** is that the chiral center was far away from the reactive site.

CHAPTER 4

CONCLUSIONS

In this study, a new method for the enantioenriched oxidation of sulfides to sulfoxides was offered. Unlike the other methods used for the chiral sulfoxidation, this method was metal free and reagents used are easy to handle and obtain. For this purpose, easily accessible chiral reagents **(56, 57, 58, 59, 60** and **61)** were designed and synthesized, and used in the sulfoxidation reactions. In the sulfoxidation reactions, chiral reagents are firstly chlorinated to yield *N*-chloramines and then, sulfide was added to the medium at the adjusted temperature. In these reactions, water was used as the oxygen source.

At the end of the oxidation reactions, besides the sulfoxidation, over-oxidation of sulfide to the sulfone was observed. By performing extraction with saturated sodium sulphite solution and dichloromethane, sulfone formation was not observed. Then with the column chromatography sulfoxide was separated from other compounds in the reaction medium. In this thesis our purpose was to observe if chiral induction occurs on sulfides by oxidation with chiral N-chloramines. With this in mind, we pay more attention to the enantiomeric excesses than the chemical yields. Chemical yields in the reactions are low because the reactions are not optimized to increase the chemical yields. Still, the chemical yields vary between 10-37% though, chemical yields for all reactions were not properly calculated. This remains to be calculated.

According to the HPLC analysis performed with the yielded methylphenyl sulfoxide samples, the highest enantiomeric excess was observed with compound **56** as chiral reagent, at 0^{o}C and in acetonitrile. Enantioselectivity of the sulfoxidation was 23% with 37% chemical yield. After optimization of the reaction conditions, theoretical calculations were performed so as to explain the reaction mechanism.

With these conclusions in mind, we proved that the oxidation of sulfides to sulfoxides with chiral chloramines was possible. This study will provide an important role in designing better *N*-halamines for stereoselective oxidation of prochiral sulfides.

CHAPTER 5

EXPERIMENTAL

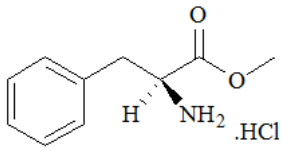
General:

All commercially available chemicals were used as received from Sigma-Aldrich, unless otherwise is stated. All moisture sensitive experiments performed under the nitrogen atmosphere. During reactions, temperature was adjusted to 0^{o}C with ice, -10^{o}C with ice - sodium chloride mixture and -78^{o}C with dry ice-acetone mixture. NMR spectra were was recorded at 400 MHz Bruker Spectrospin Advance DPX NMR spectrometer with using solvents $CDCl_3$, D_2O and d_6-DMSO. NMR solvents were purchased from Merck. Chemical shifts were recorded in parts per million (ppm) relative to the internal standard tetramethylsilane. Coupling constants (*J*) were reported in Hertz (Hz). ^{1}H and ^{13}C NMR spectra of products are given in Appendix A. Polarimetric measurements were recorded at Rudolph Scientific Autopol III polarimeter. IR spectra was recorded with Bruker Platinium ATR-IR spectrometer and IR spectra of the products are given in Appendix B. Melting points were recorded on Stuart SMP11 and uncorrected. HPLC chromatograms (given in Appendix C) were recorded with Agilent 1100 HPLC and analysis were performed with OD-H chiral column with the solvent system of n-Hexane:*i*-propanol (90:10). GC-Mass analysis were recorded with Agilent 7890A GC system. Silica gel 60 (0.040-0.063 mm) purchased from Merck was used for the column chromatography. In thin layer chromatography analysis, UV-lamp and iodine were used for visualization of the spots. All calculations were performed with Gaussian 09, A.02.[93] The level of theory used indicated in the text.

Optimized procedure for the enantioenriched sulfoxidation of thioanisole:

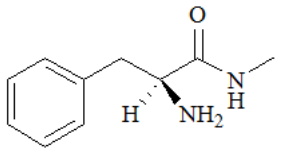
(*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one **(56)** (0.9 g, 4.13 mmol) and *N*-chlorosuccinimide (0.9 g, 6.21 mmol) were stirred in acetonitrile (30 mL) at room temperature for 2 hours. Then, reaction flask was cooled to 0^oC and (thioanisole 0.47 mL, 4.00 mmol) was added to the flask at 0^oC. Mixture was stirred at 0^oC for 30 minutes and water (0.1 mL, 5.55 mmol) was added at this temperature. Then, reaction mixture was stirred at 0^oC for 1 hour and reaction was ended. After ending the reaction, mixture was concentrated *in vacuo*. Then, by performing extraction with dichloromethane and the saturated aqueous sodium sulfite solution, sulfone and *N*-succinimde was separated from the product. Seperated organic layer was dried over $MgSO_4$(s) and concentrated. After concentrating the organic layer, thin layer chromatography (TLC) was performed and it was observed that thioanisole and (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **(56)** were also present in the resulting mixture besides methylphenyl sulfoxide. Presence of these compounds were also proven with the GC-mass spectroscopy (m/z: 140.0). Therefore, column chromatography was performed with the solvent system of hexane:ethyl acetate (50:10) in order to separate methylphenyl sulfoxide in 37% chemical yield (pale yellow liquid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.46 (m,5H), 2.73 (s,1H). ^{13}C NMR (CDCl3, 100 MHz) δ 131.0, 123.4, 123.5, 43.9. According to the chiral HPLC analysis 23% enantiomeric excess was recorded. Optical rotation observed was $[\alpha]^{25}_{589\,(D)}$= -0.066^o. (Several optical rotation values were recorded, this value seemed to be reproducible. Only the sign of the optical rotation value was taken into account to show that "S" configuration of sulfoxides were obtained and enantiomeric excess values were extracted according to the chiral HPLC data.) IR: 1033 cm^{-1} (S=O) stretching.

Synthesis of (S)-methyl 2-amino-3-phenylpropanoate hydrochloride (63)



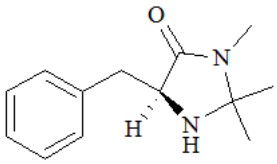
L-Phenylalanine (1.00 g, 6.06 mmol) was dissolved in anhydrous methanol (25.00 mL). Then reaction mixture was cooled to 0^{o}C and thionyl chloride (0.44 mL, 6.06 mmol) was added to reaction mixture dropwise. Mixture was stirred at room temperature for 2 hours and then heated to reflux for 2 hours. After the reaction was completed, mixture was concentrated *in vacuo* to yield (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride (white solid). For purification, product was washed with diethyl ether twice. Melting point: 146-150 ^{o}C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.81 (s, 3H), 7.41-7.23 (m, 5H), 4.27 (bs, 1H), 3.69 (m, 3H), 3.24 (dd, *J*=13.9, 5.7, 1H), 3.15 (dd, *J*=13.9, 7.5, 1H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ 169.3, 134.7, 129.3, 128.5, 127.2, 53.2, 52.5, 35.8. IR: 2835 cm^{-1} (C-H) stretching, 1744 cm^{-1} (C=O) stretching, 1238 cm^{-1} (C-N) stretching.

Synthesis of (S)-2-amino-N-methyl-3-phenylpropanamide (64)



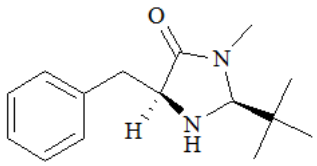
(*S*)-Methyl 2-amino-3-phenylpropanoate hydrochloride (1.00 g, 4.65 mmol) was dissolved in methanol (25.00 mL) and stirred in methanol for an hour. Then 40 wt. % methylamine solution in H_2O (1.00 mL, 29.21 mmol) was added to the reaction mixture and stirred for 18 hours at room temperature. After the reaction was completed mixture was concentrated *in vacuo* to yield (*S*)-2-amino-N-methyl-3-phenylpropanamide (brown vicous liquid). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57-7.33 (m,5H), 3.65 (m, 1H), 3.27 (dd, *J*=3.6, 3.5, 1H), 2.75 (dd, *J*=9.1, 2.1, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7, 137.9, 129.3, 128.7, 126.8, 56.5, 41.0, 25.8. IR: 2945 cm^{-1} (C-H) stretching, 1646 cm^{-1} (C=O) stretching, IR: 1411 cm^{-1} (C-N) stretching.

Synthesis of (S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (56)



(*S*)-2-Amino-N-methyl-3-phenylpropanamide (1.00 g, 5.62 mmol) was dissolved in methanol (25.00 mL). *p*-TSA (20 mg, 0.11 mmol) was added to the reaction mixture as the catalyst. Then, anhydrous acetone (5.00 mL, 68.09 mmol) was added to the mixture and reaction was heated to reflux for 20 hours. After the reaction was completed mixture was concentrated *in vacuo* to yield (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (brown viscous liquid). Then for purification, extraction was performed by using diethyl ether and distilled water. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.23 (m, 5H), 3.83 (m, 1H), 3.17 (dd, *J*=14.2, 4.4 1H), 3.06 (dd, *J*=14.2, 6.8 1H), 2.79 (s, 3H), 1.29 (s, 3H), 1.19 (s,3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 137.2, 129.5, 128.6, 126.8, 125.9, 75.6, 59.3, 37.3, 27.2, 25.3, 25.2. IR: 2974 cm^{-1} (C-H) stretching, 1660 cm^{-1} (C=O) stretching, 1425 cm^{-1} (C-N) stretching.

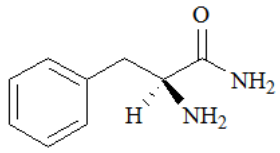
Synthesis of (2S,5S)-2-tert-butyl-5-benzyl-3-methylimidazolidin-4-one (57)



(*S*)-2-Amino-N-methyl-3-phenylpropanamide (1.00 g, 5.62 mmol) was dissolved in freshly distilled dry tetrahydrofuran (25.00 mL). Then moleculer sieves were added to the reaction mixture. Iron(III) chloride (20 mg, 0,12 mmol) was added as the catalyst and trimethylacetaldehyde (0.66 mL, 6.12 mmol) was added to the reaction mixture. Mixture was heated to reflux for 20 hours and concentrated *in vacuo* to yield diastereomeric mixture 2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one. Then; the product was dissolved in saturated HCl solution of diethylether to give the (*2S,5S*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (white solid). Melting point: 182-186 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.21 (m, 5H), 4.08 (s, 1H), 3.72 (m, 1H), 3.16 (dd, *J*=13.8, 3.9 1H), 2.96 (dd, *J*=13.8, 7.6 1H), 2.93 (s, 3H), 0.85

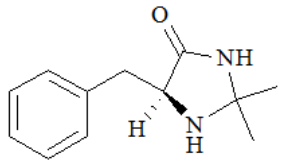
(s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 137.2, 129.4, 129.3, 129.3, 128.4, 128.3, 75.5, 75.4, 59.2, 59.1, 37.3, 29.1, 25.2, 25.1. IR: 2870 cm^{-1} (C-H) stretching, 1702 cm^{-1} (C=O) stretching, 1396 cm^{-1} (C-N) stretching.

Synthesis of (S)-2-amino-3-phenylpropanamide (65)



(*S*)-Methyl 2-amino-3-phenylpropanoate hydrochloride (1.00 g, 4.65 mmol) was dissolved in %28 aqueos ammonium hydroxide solution (25.00 mL) and stirred at room temperature for 18 hours. Then reaction mixture was concentrated *in vacuo* to yield (*S*)-2-amino-3-phenylpropanamide (white solid). Melting point: 212-216 ^oC. ^1H NMR (D_2O, 400 MHz) δ 7.36-7.25 (m, 5H), 7.24-7.18 (m, 2H), 4.04 (m, 1H), 3.10 (dd, *J*=14.1, 6.7 1H), 3.02 (dd, *J*=14.1, 7.5 1H). ^{13}C NMR (D_2O, 100 MHz) δ 175.4, 137.0, 132.0, 131.7, 130.4, 57.1, 39.9. IR: 3179 cm^{-1} (amine N-H) stretching, 1660 cm^{-1} (amide C=O) stretching.

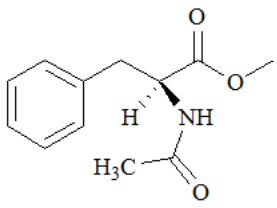
Synthesis of (S)-5-benzyl-2,2-dimethylimidazolidin-4-one (58)



(*S*)-2-Amino-3-phenylpropanamide (1 g, 6.09 mmol) was dissolved in methanol (25.00 mL). *p*-TSA (20 mg, 0.11 mmol) was added to the reaction mixture as the catalyst. Then, anhydrous acetone (5.00 mL, 68.09 mmol) was added to the mixture and reaction was heated to reflux for 20 hours. After the reaction was completed mixture was concentrated *in vacuo* to yield (*S*)-5-benzyl-2,2-dimethylimidazolidin-4-one (brown viscous liquid). Then for purification, extraction was performed by using diethyl ether and distilled water. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (s, 1H), 7.40-7.19 (m, 5H), 3.88 (m, 1H), 3.14 (dd, *J*=14.2, 4.5 1H), 3.03 (dd, *J*=14.2, 6.8 1H),

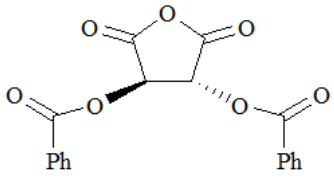
1.38 (s,1H), 1.24 (s,3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.9, 137.1, 129.5, 128.6, 126.8, 72.4, 60.1, 37.1, 29.8, 29.3. IR: 3250 cm^{-1} (amine N-H) stretching, 1691 cm^{-1} (amide C=O) stretching. HRMS: calcd. for $C_{12}H_{17}N_2OH$ 205.1341 $[M-H]^+$; found 205.1332.

Synthesis of (S)-methyl 2-acetamido-3-phenylpropanoate (59)



(*S*)-Methyl 2-amino-3-phenylpropanoate hydrochloride (1.00 g, 4.65 mmol) was neutralized with saturated sodium bicarbonate solution. Then the neutralized ester was extracted with dichloromethane. To the ester dissolved in dichloromethane (25.00 mL), acetic anhydride (0.57 mL, 6.12 mmol) was added and reaction mixture was stirred at room temperature for 2 hours. After the reaction was completed mixture was concentrated in vacuo to yield (*S*)-methyl 2-acetamido-3-phenylpropanoate (white solid). Melting point: 74-78 ^oC. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.06 (m, 5H), 5.9 (d, 1H), 4.91 (m, 1H), 3.74 (s, 3H), 3.09 (dd, *J*=13.8, 5.8 1H), 3.03 (dd, *J*=13.8, 5.7 1H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.4, 137.1, 129.2, 128.6, 127.1, 53.1, 37.9, 23.1, 22.1. IR: 2930 cm^{-1} (C-H) stretching, 1719 cm^{-1} (ester C=O) stretching, 1660 cm^{-1} (amide C=O) stretching.

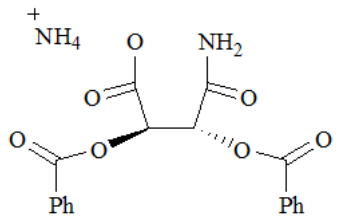
Synthesis of (2R, 3R)-dibenzoyltartaric anhydride (67)



L-Tartaric acid (1g, 6.66 mmol) was dissolved in toluene (25 ml). Then, benzoyl chloride (2.35 mL, 19.98) and sulfuric acid (0.05 ml, 1.02 mmol) was added to the reaction mixture. Mixture was heated to reflux for 3 hours and (*2R,3R*)-

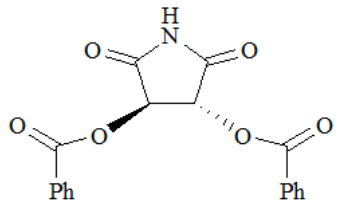
dibenzoyltartaric anhidrid was yielded (white solid). Then, these crystals were filtrated and washed with toluene. Melting point: 188-192 ^{o}C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.02 (m, 4H), 7.75 (m, 2H), 7.61 (m, 4H), 5.88 (s, 2H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ 167.1,164.6, 134.1, 129.4, 129.0, 71.4. IR: 1820 cm^{-1} (O=C-O) stretching, 1736 cm^{-1} (ester C=O) stretching.

Synthesis of (2R, 3R)- 2,3-dibenzoyl-3-carbamoylpropionate (68)



(*2R,3R*)-Dibenzoyltartaric anhydride (1g, 2.7 mmol) was dissolved in ammonia solution in tetrahydrofuran (25ml). Then, mixture was stirred at room temperature in nitrogen atmosphere for 8 hours to yield (*2R-3R*)-2,3-dibenzoyl-3-carbamoylpropionate (white solid). Melting point: 106-110 ^{o}C. This was used without further identification and purification in the next step. IR: 1680 cm^{-1} (amide C=O) stretching, 1239 cm^{-1} (carboxylic acid C-O) stretching.

Synthesis of (3S,4S)-3,4-diphenylpyrrolidine-2,5-dione (60)



(*2R-3R*)-2,3-Dibenzoyl-3-carbamoylpropionate (1g, 2.8 mmol) was dissolved in thionyl chloride and pyridine(0.6 ml, 8.4 mmol) was added to the reaction mixture. Mixture was heated to 60^{o}C for 30 minutes. Then, thionyl chloride was evoparated and dichloromethane was added to the mixture. After addition of dichloromethane precipitation of salt was occurred and the salt was separated by filtration. Then, mixture was concentrated *in vacuo* to yield (*3S,4S*)-3,4-diphenylpyrrolidine-2,5-

dione (white solid). Melting point: 106-110 ^{o}C. ^{1}H NMR (d_6-DMSO, 100 MHz) δ 12.15 (s, 1h), 8.02 (m, 4H), 7.75 (m, 2H), 7.61 (m, 4H), 6.22 (s, 2H). ^{13}C NMR (d_6-DMSO, 400 MHz) δ 176.9,165.6, 134.2, 130.0, 128.6, 74.0, 30.9, 18.42. IR: 3577 cm^{-1} (N-H) stretching, 1720 cm^{-1} (C=O) stretching, 1272 cm^{-1} (amide C-N) stretching. HRMS: calcd. for $C_{18}H_{13}N_1O_6Na$ 362.0641 $[M+Na]^+$; found 362.0649.

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APPENDIX A

NMR DATA

NMR spectra was recorded at 400 MHz Bruker Spectrospin Advance DPX NMR spectrometer with using $CDCl_3$, D_2O and d_6-DMSO.

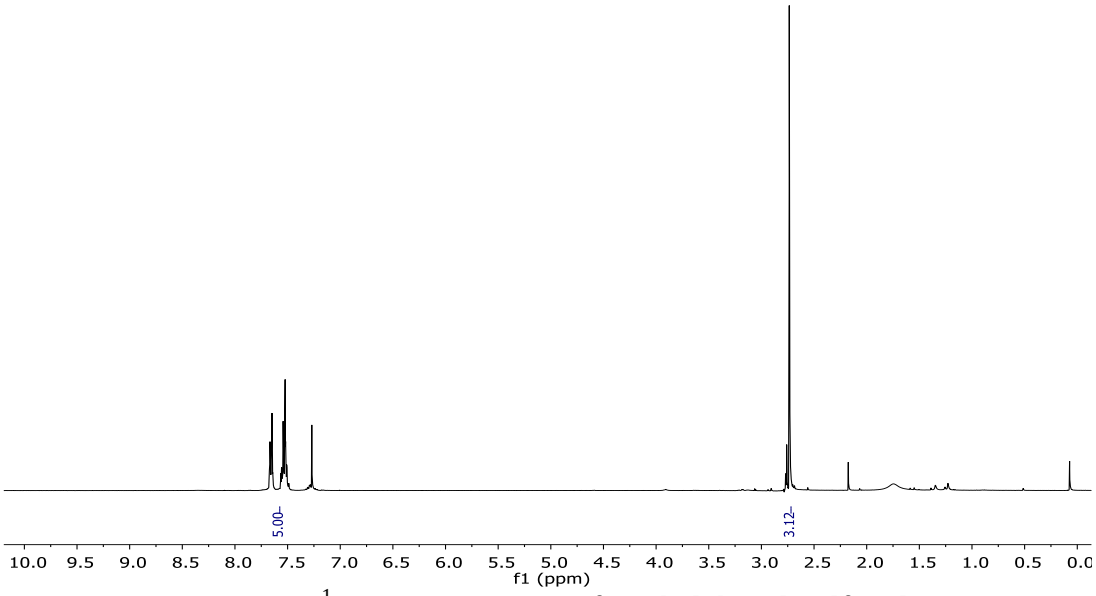


Figure A1-^{1}H NMR Spectrum of Methylphenyl Sulfoxide

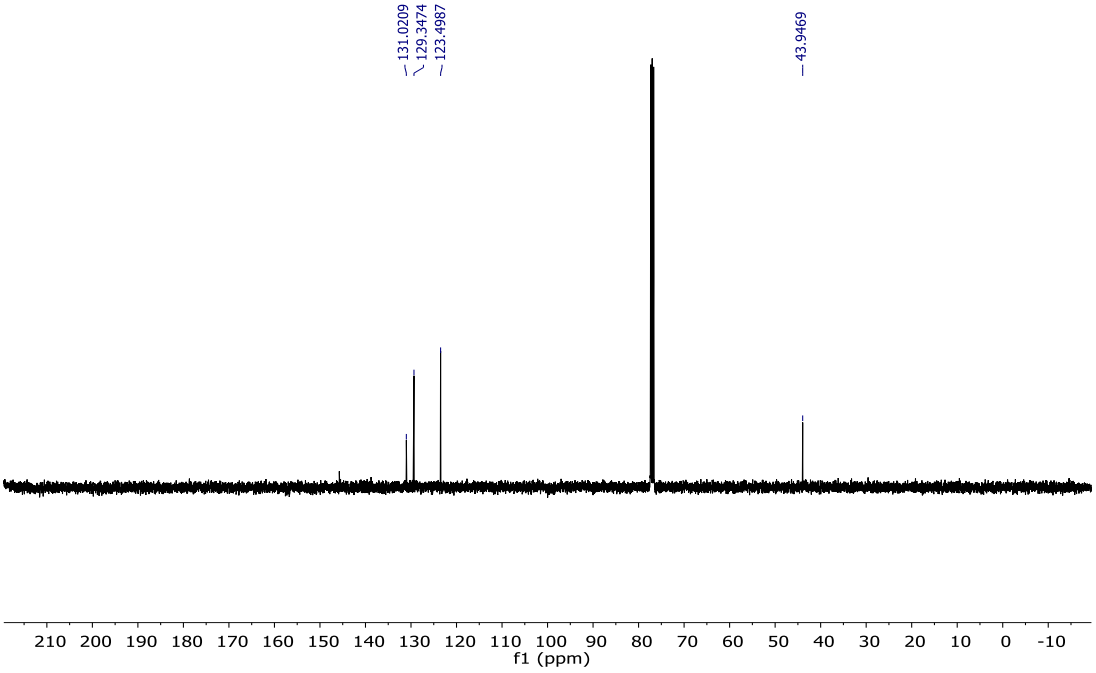


Figure A2-^{13}C NMR Spectrum of Methylphenyl Sulfoxide

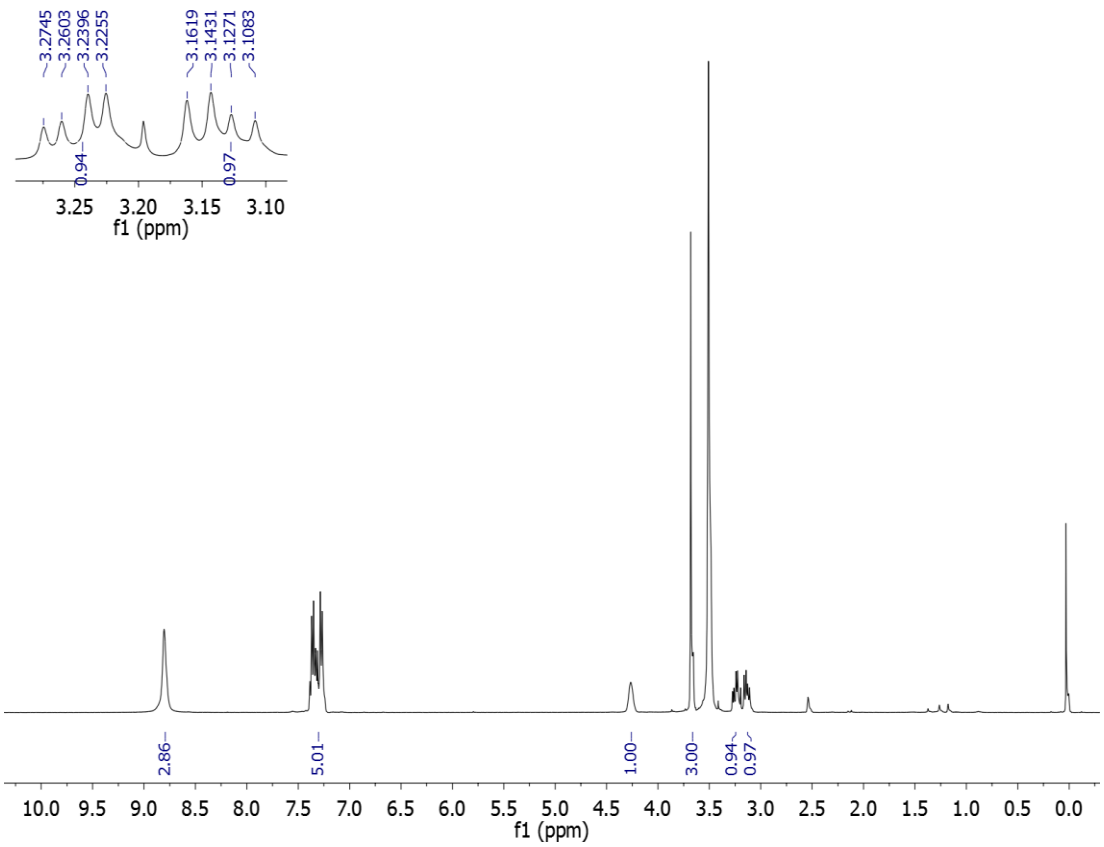


Figure A3-^{1}H NMR Spectrum of **63**

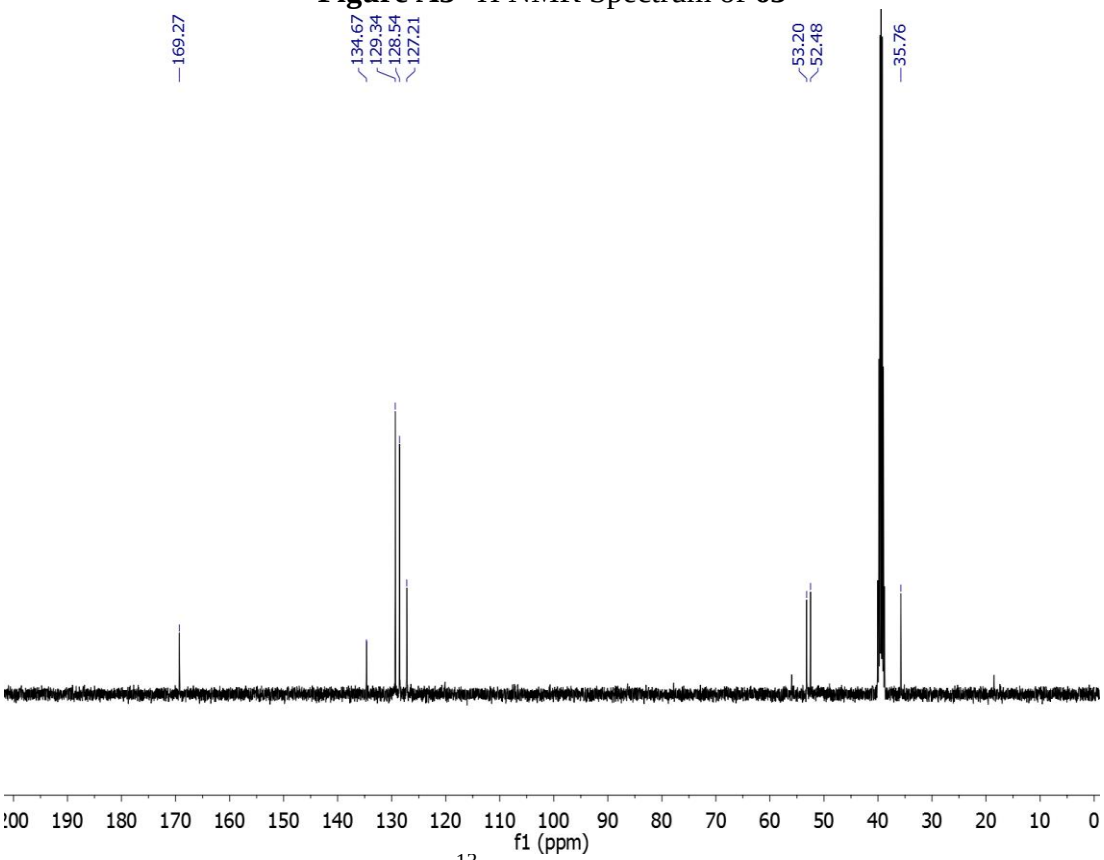


Figure A4^{-13}C NMR Spectrum of **63**

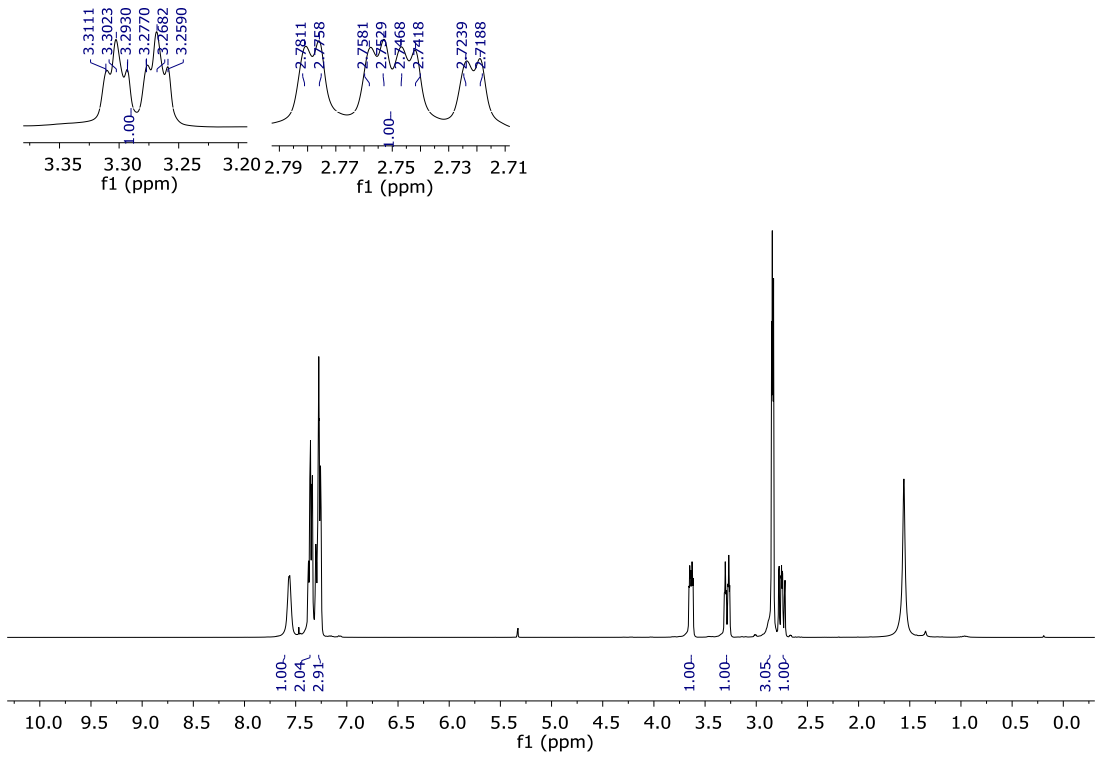


Figure A5-^{1}H NMR Spectrum of **64**

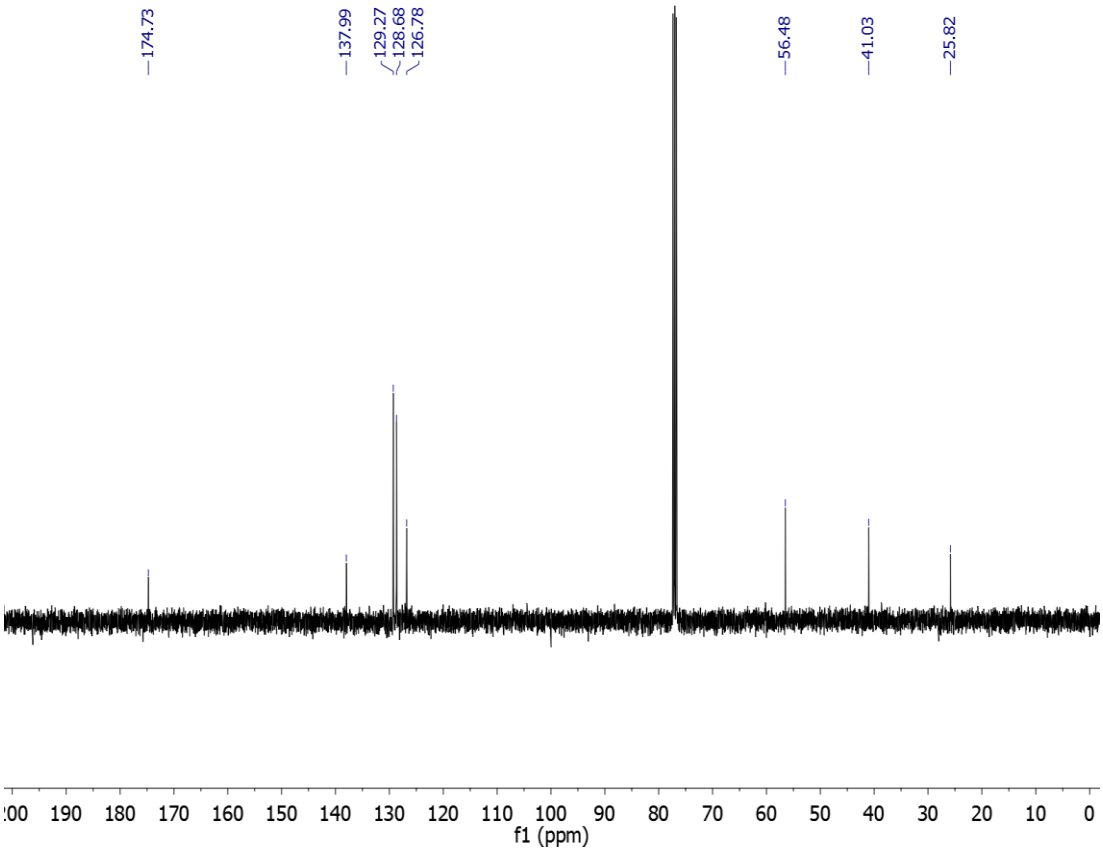


Figure A6-^{13}C NMR Spectrum of **64**

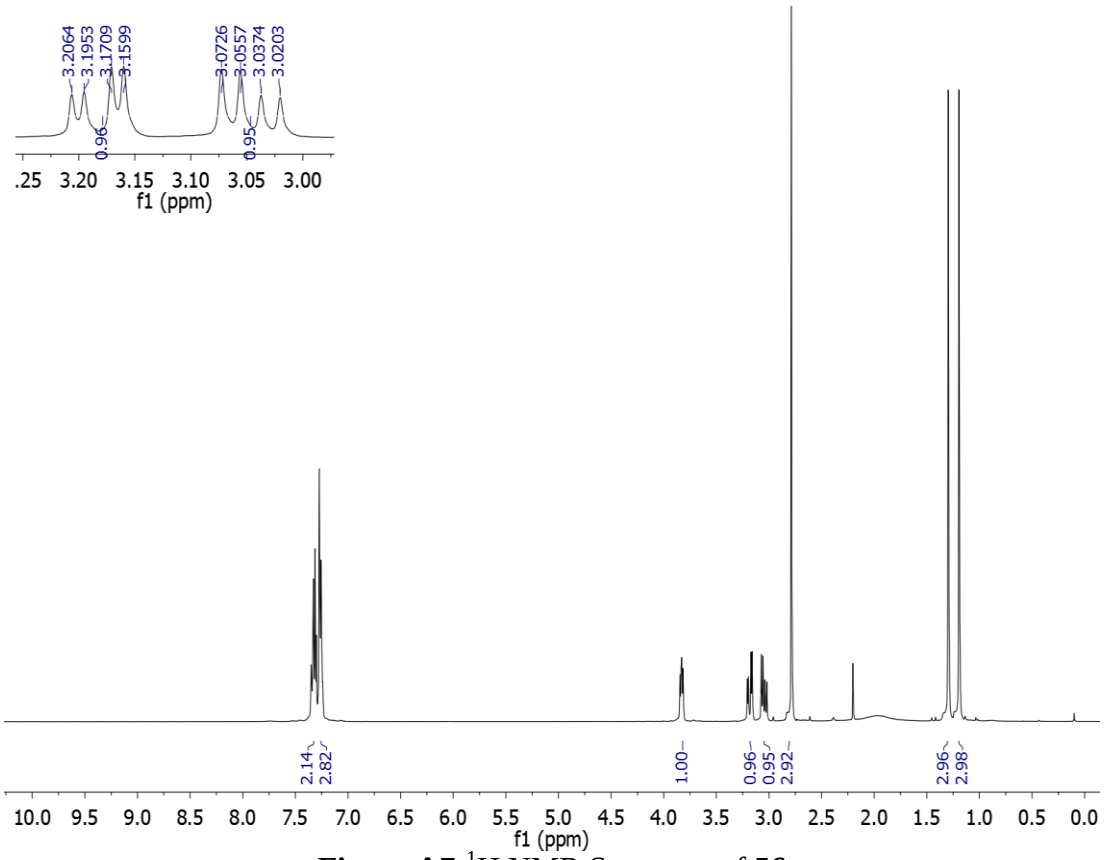


Figure A7-^{1}H NMR Spectrum of **56**

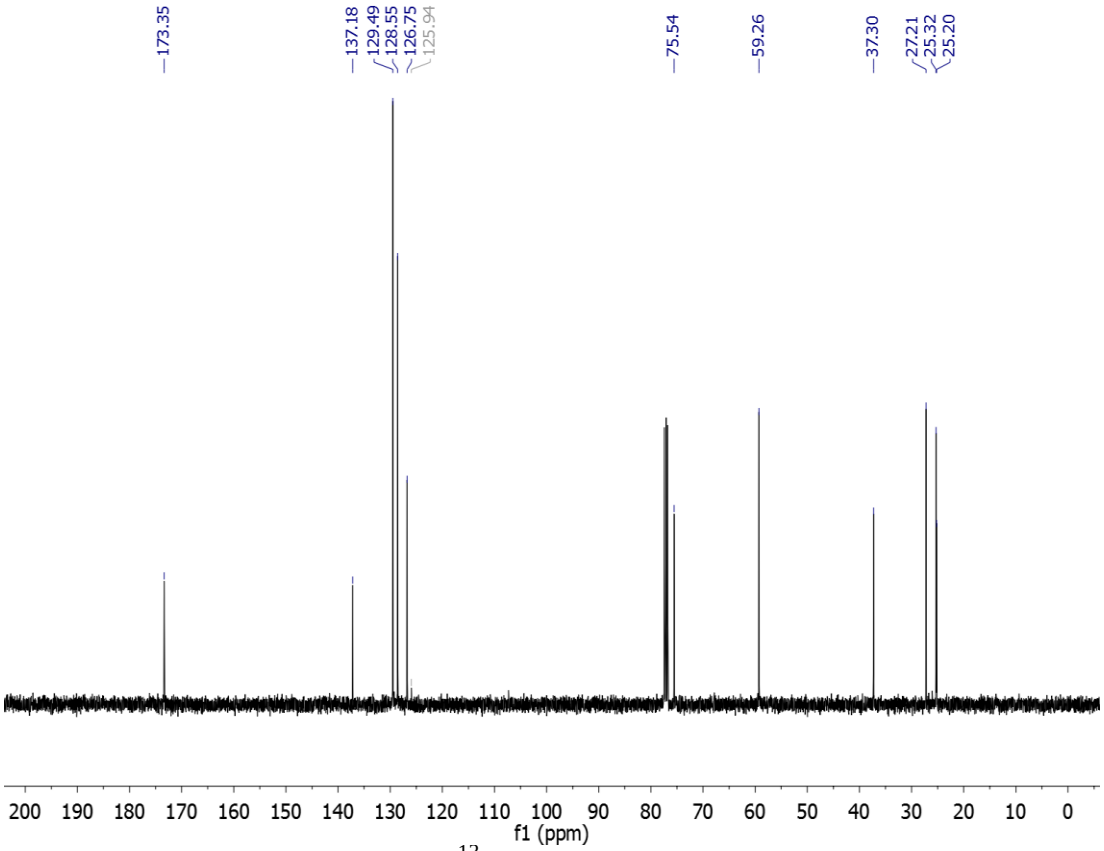


Figure A8-^{13}C NMR Spectrum of **56**

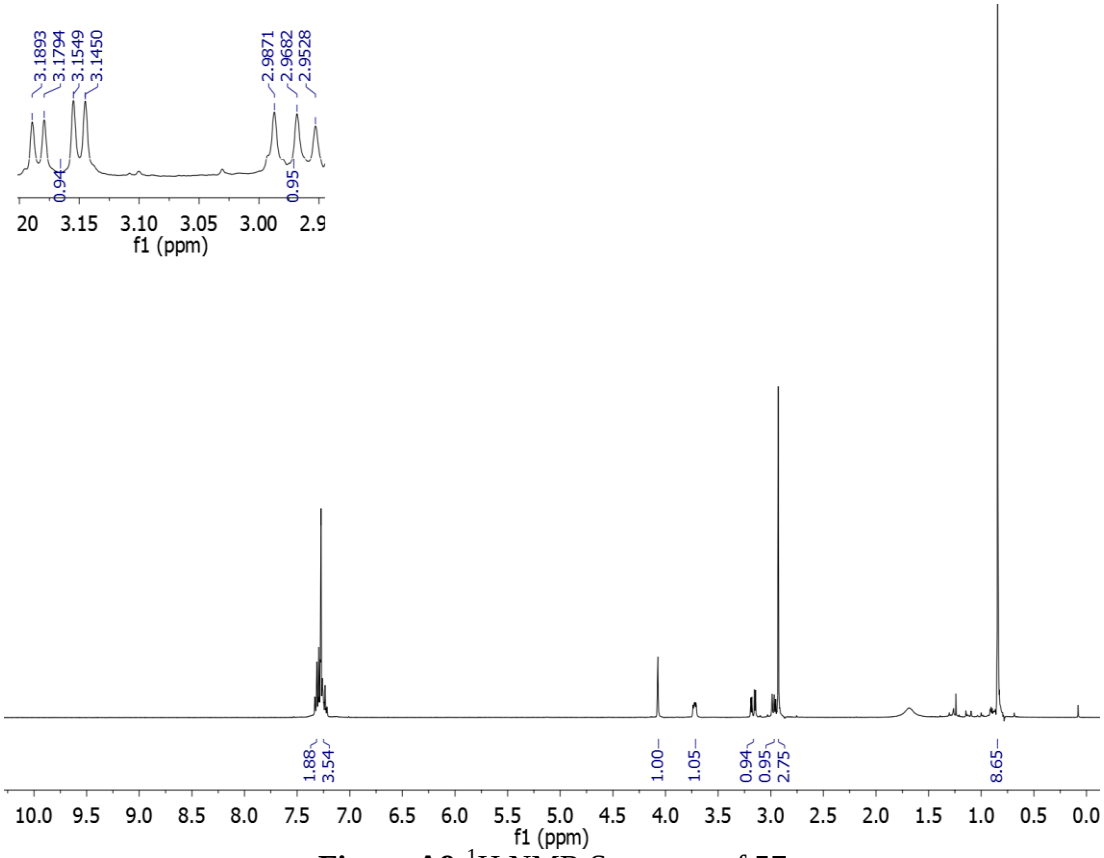


Figure A9-^{1}H NMR Spectrum of **57**

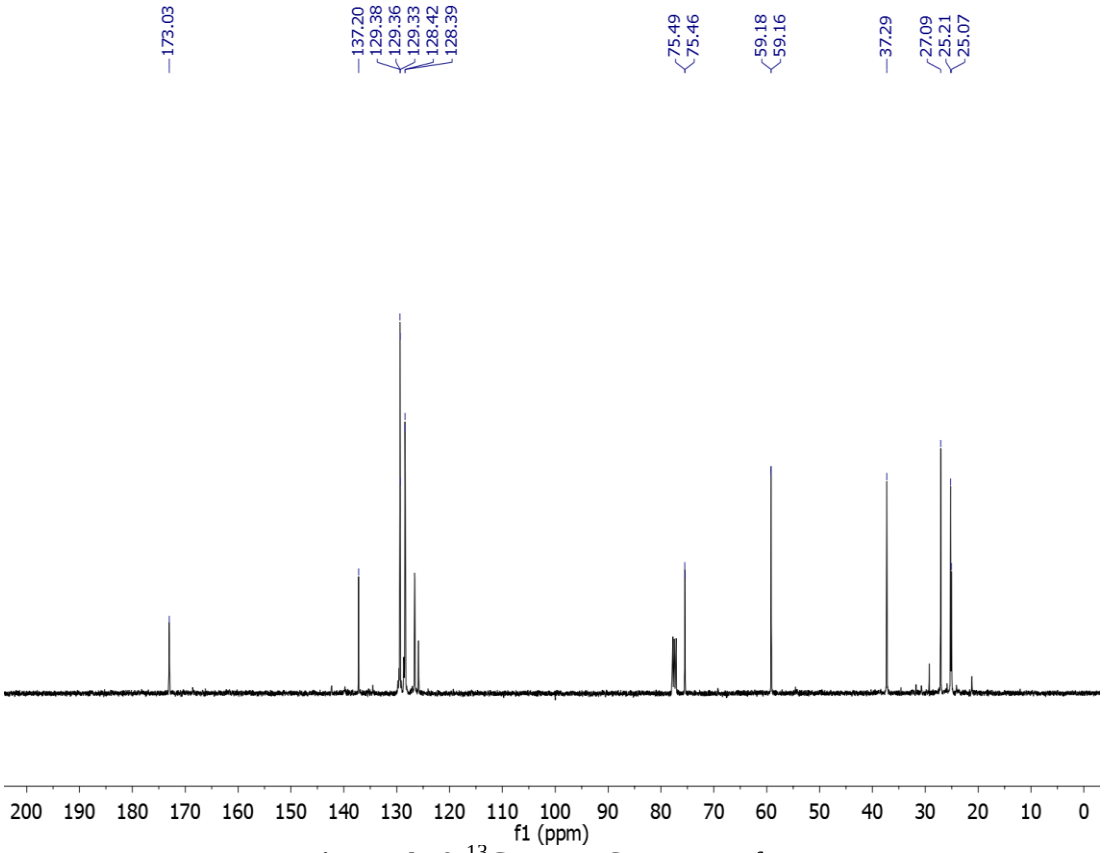


Figure A10-^{13}C NMR Spectrum of **57**

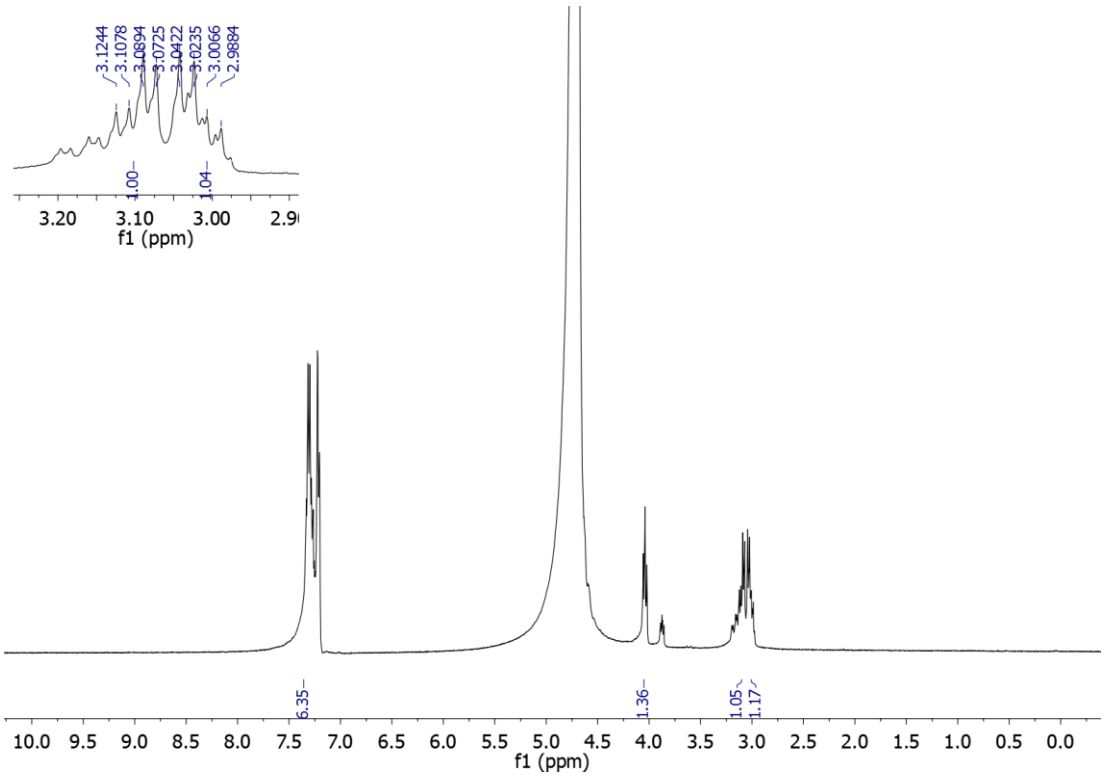


Figure A11-^{1}H NMR Spectrum of **65**

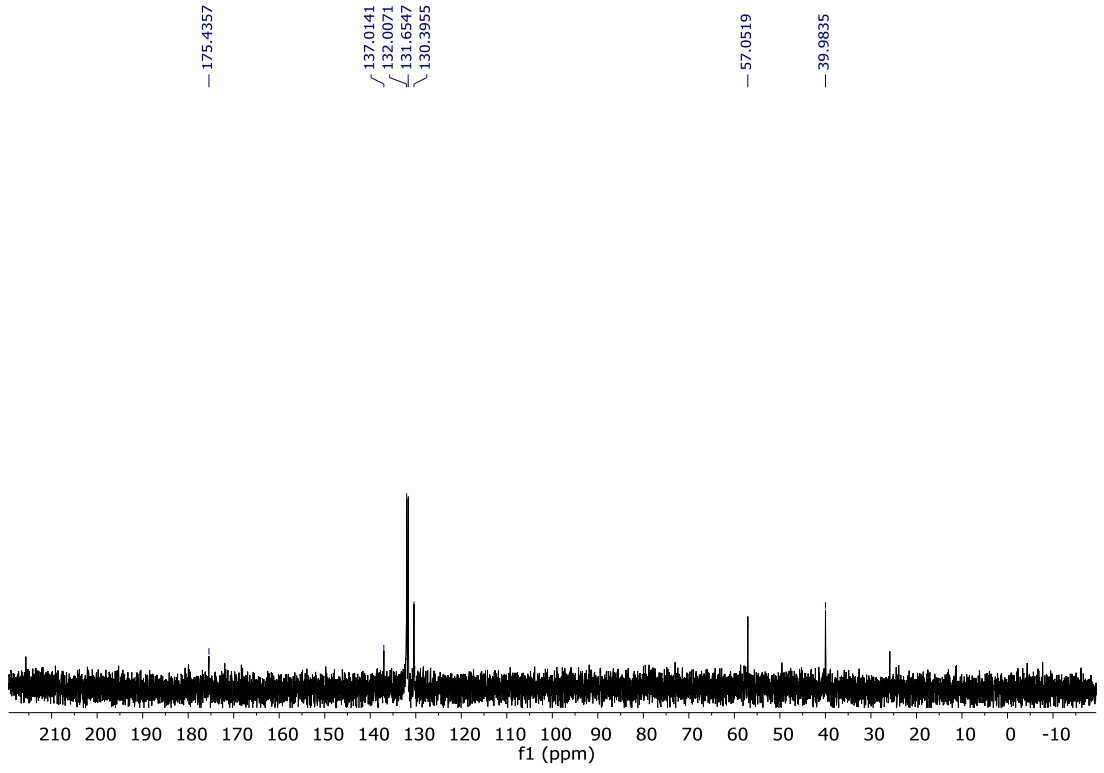


Figure A12-^{13}C NMR Spectrum of **65**

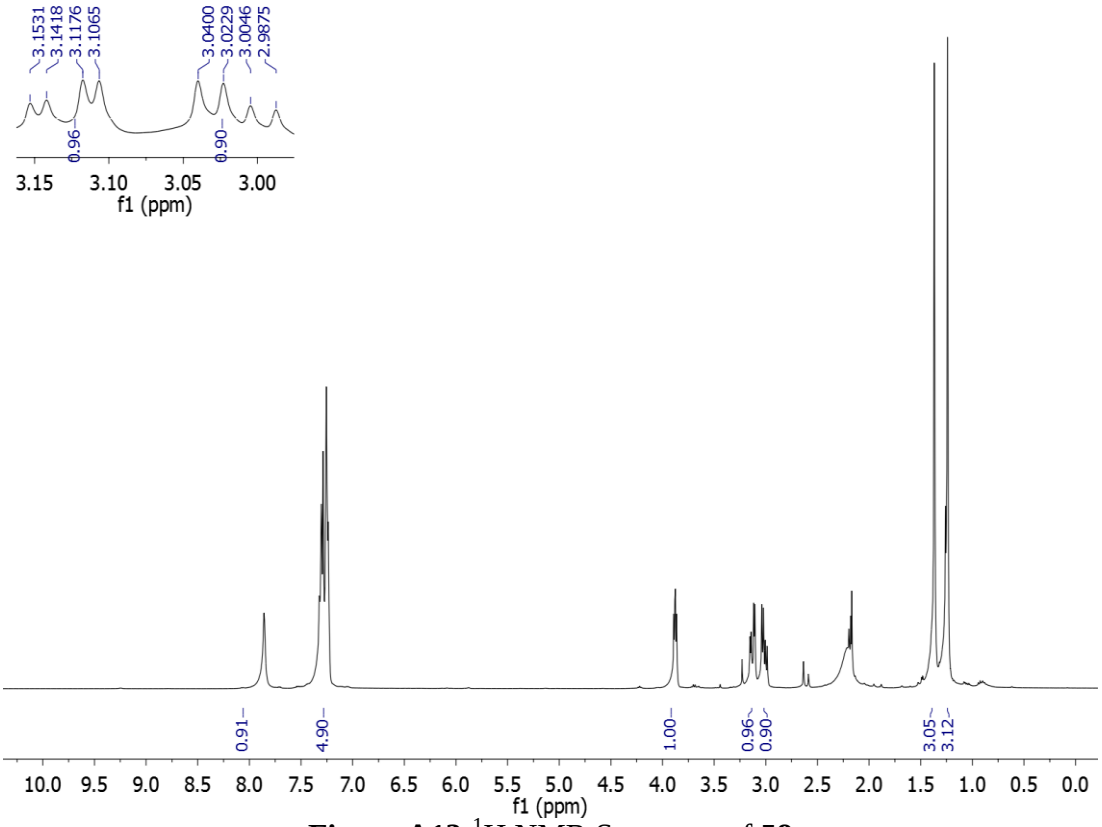


Figure A13-^{1}H NMR Spectrum of **58**

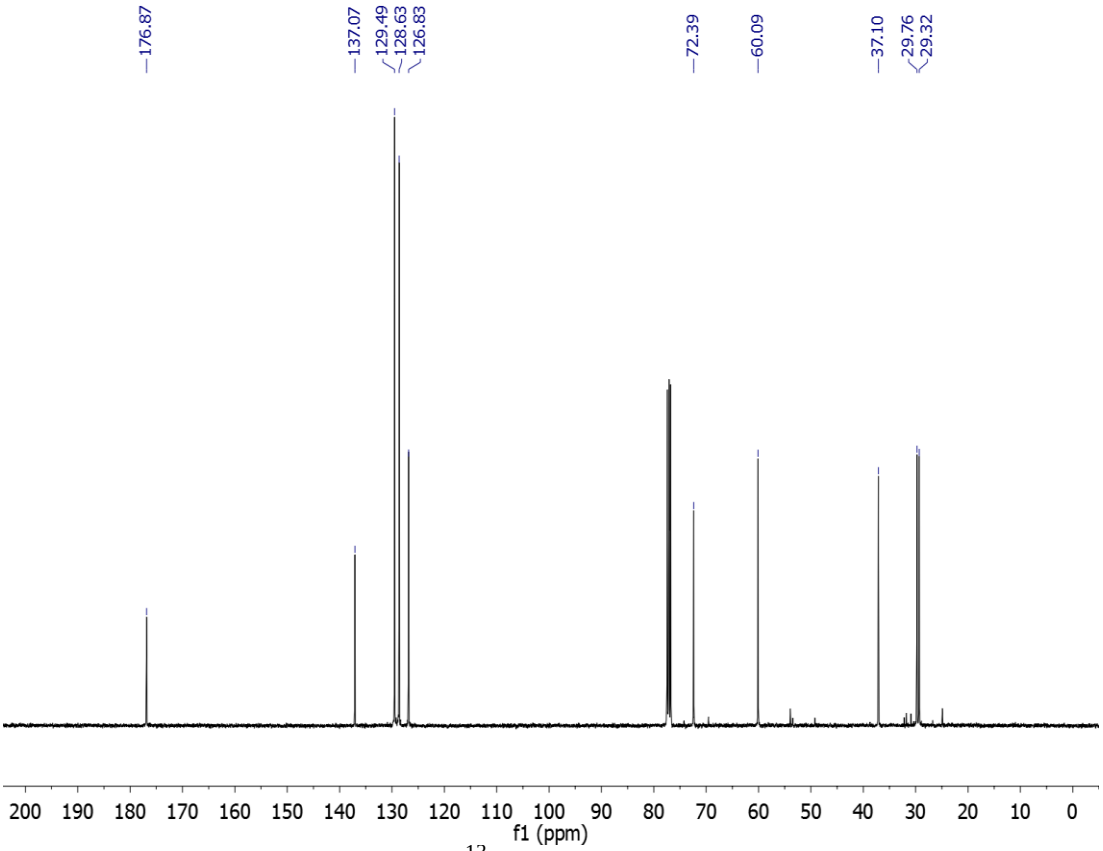


Figure A14-^{13}C NMR Spectrum of **58**

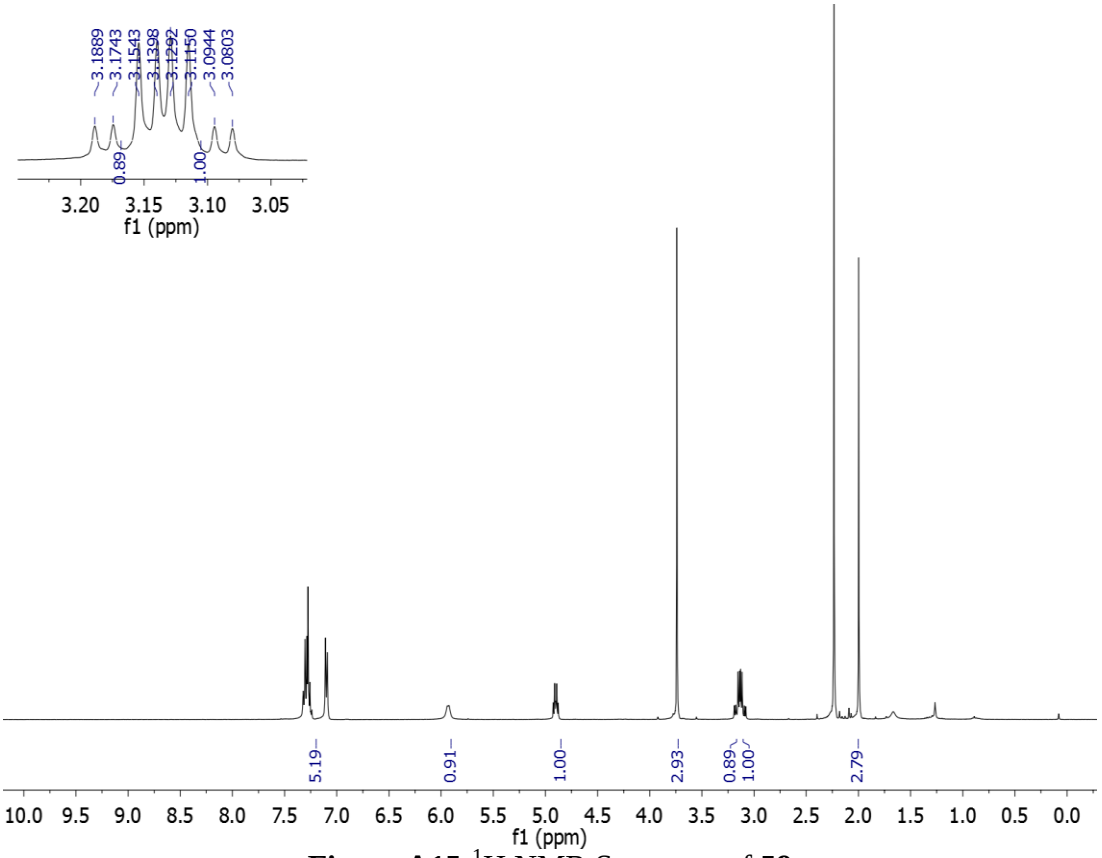


Figure A15-^{1}H NMR Spectrum of **59**

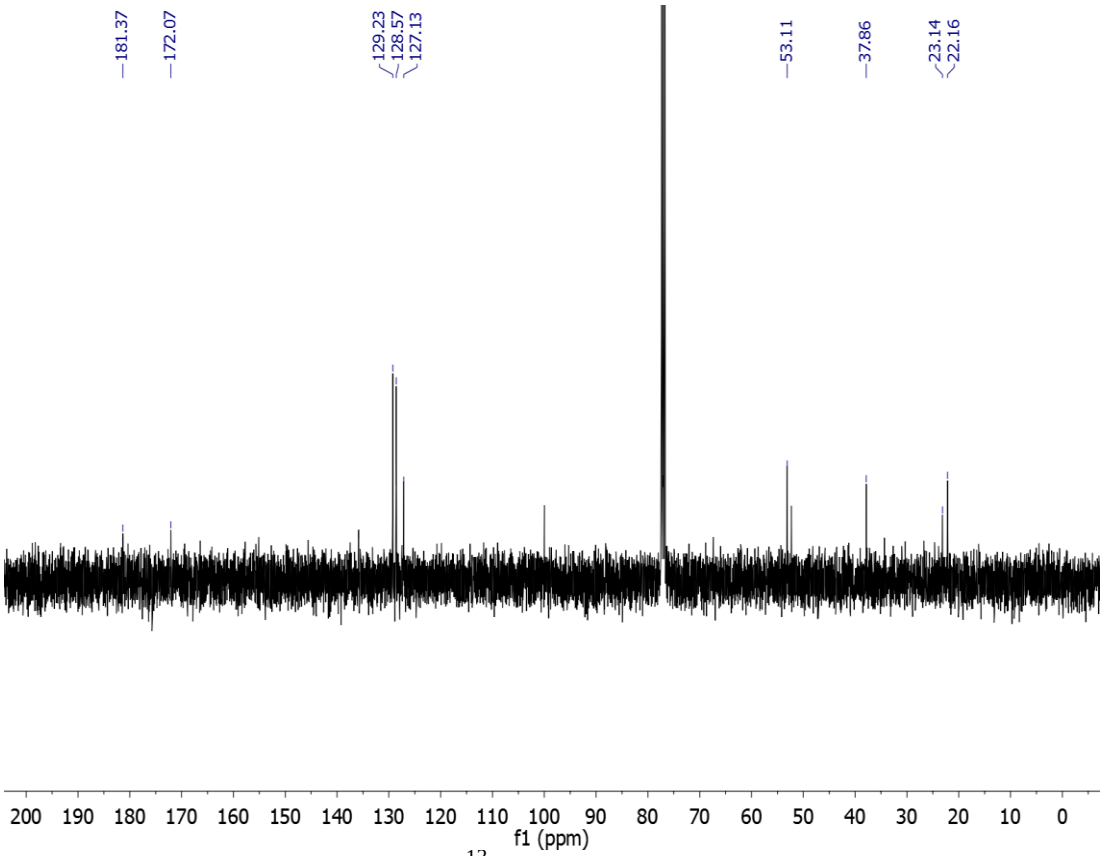


Figure A16-^{13}C NMR Spectrum of **59**

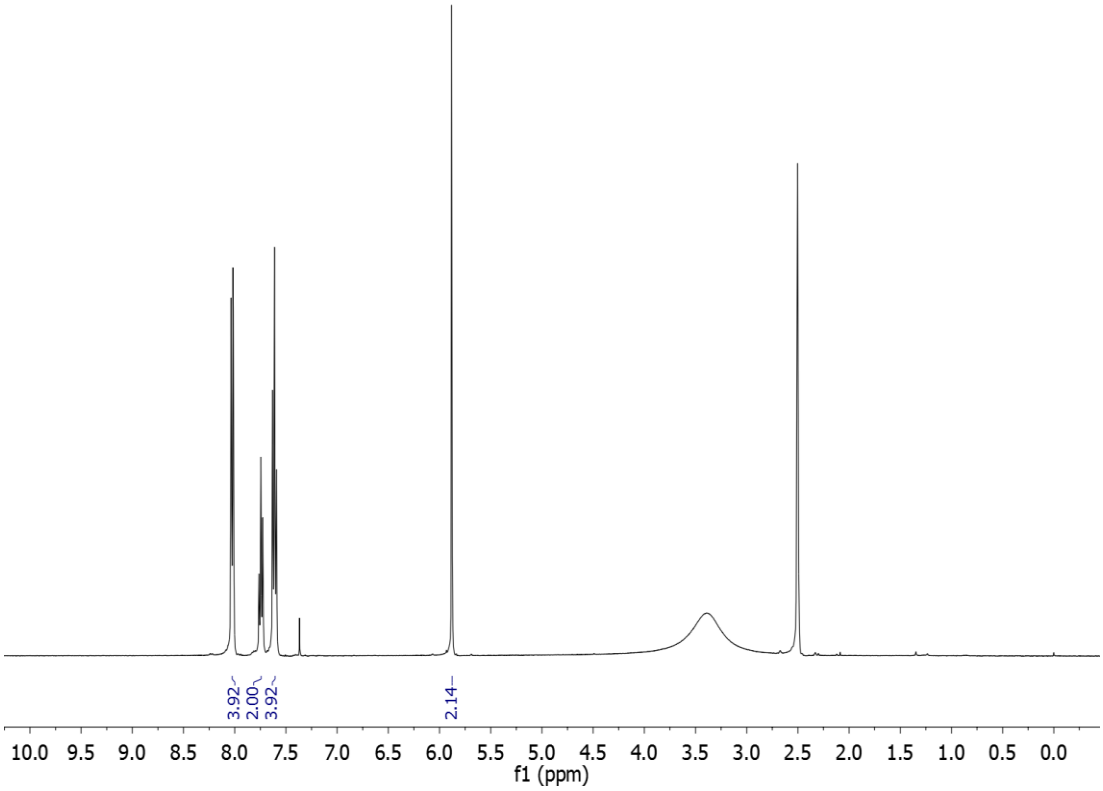


Figure A17-^{1}H NMR Spectrum of **67**

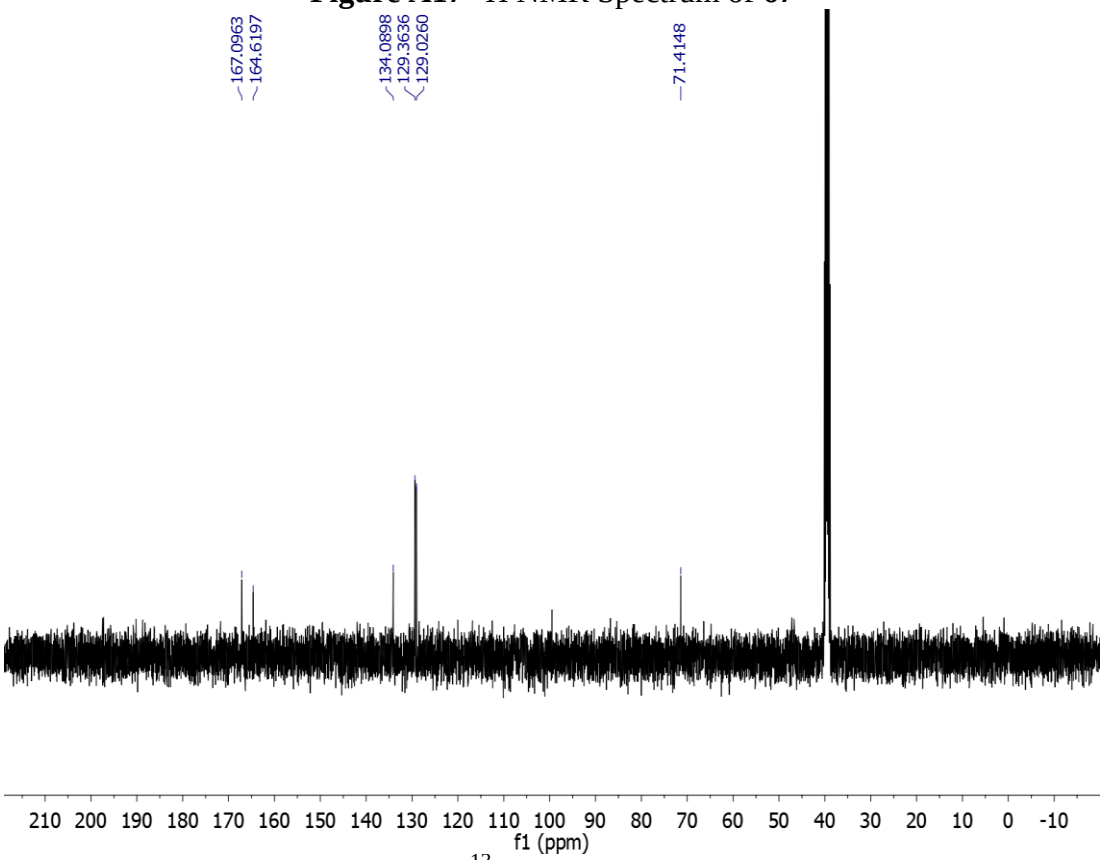


Figure A18-^{13}C NMR Spectrum of **67**

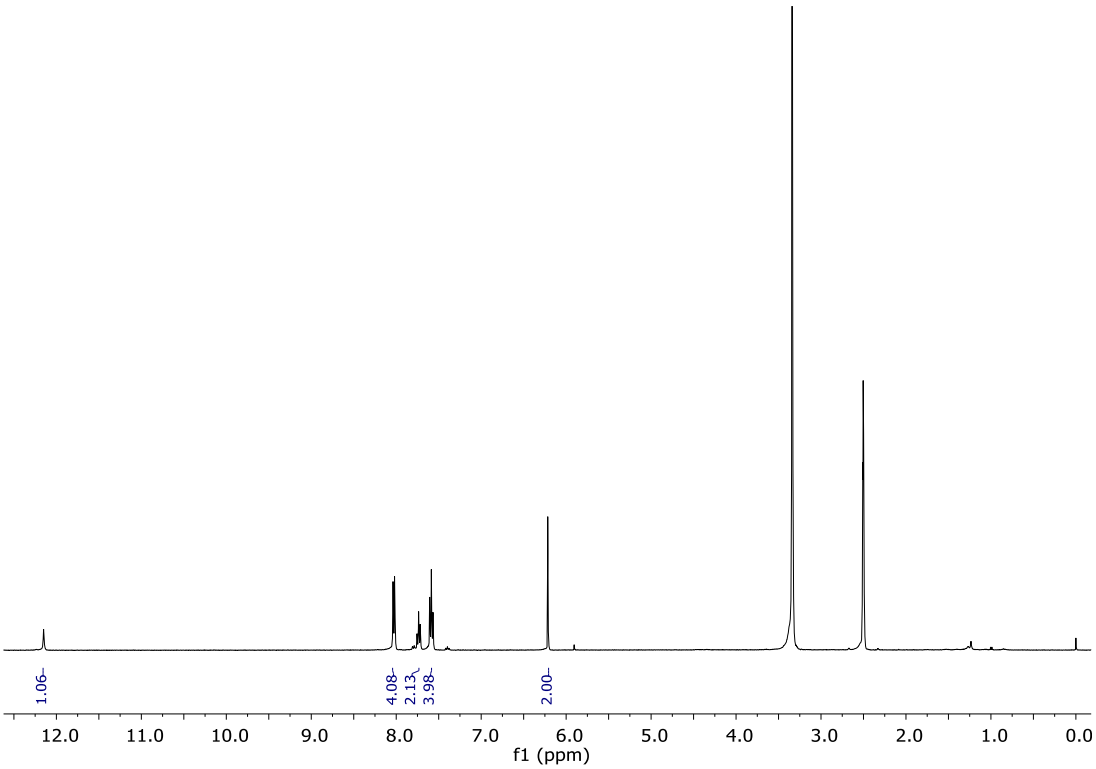


Figure A19-^{1}H NMR Spectrum of **60**

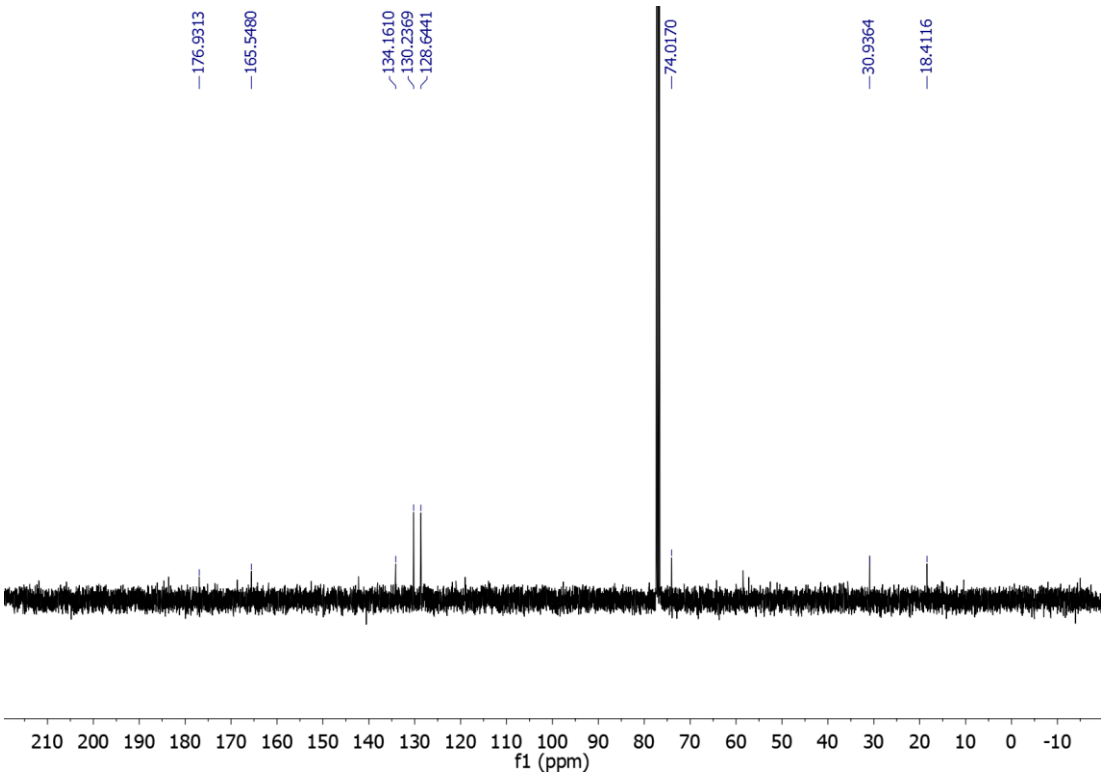


Figure A20- ^{13}C NMR Spectrum of **60**

APPENDIX B

IR DATA

IR spectra were recorded at Bruker Platinium ATR-IR spectrometer.

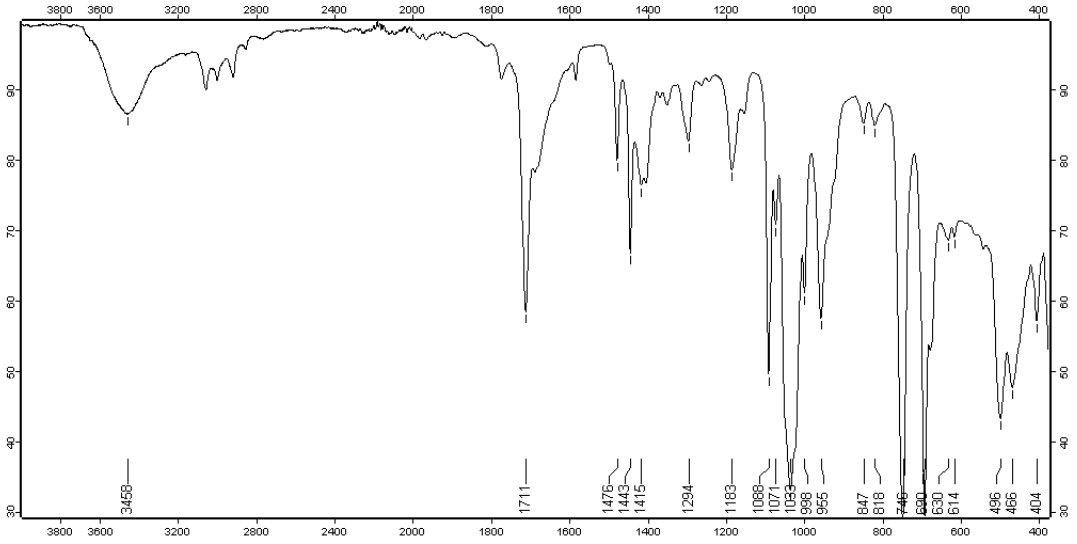


Figure B1- IR data of Methylpheny sulfoxide

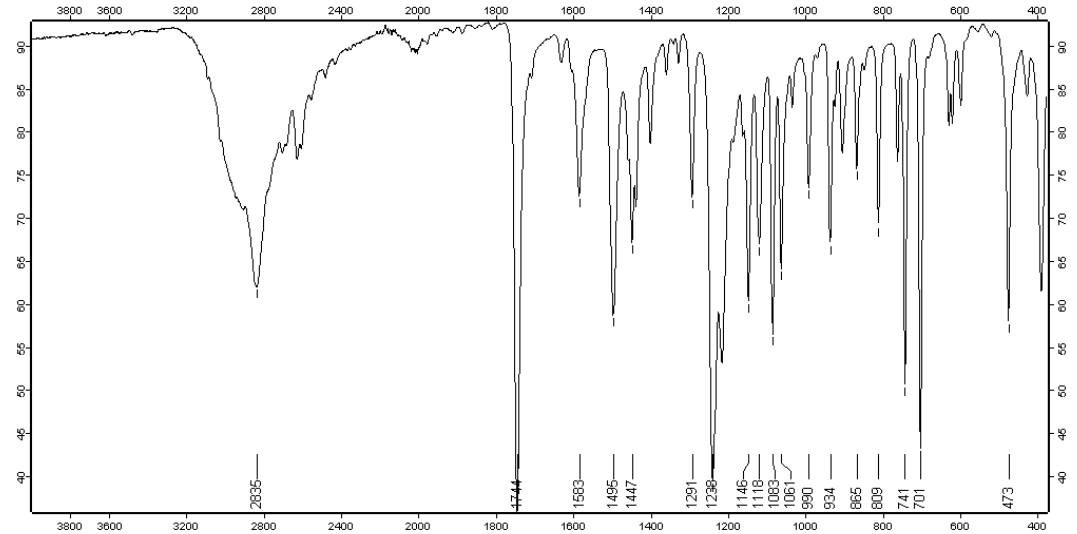


Figure B2- IR data of **63**

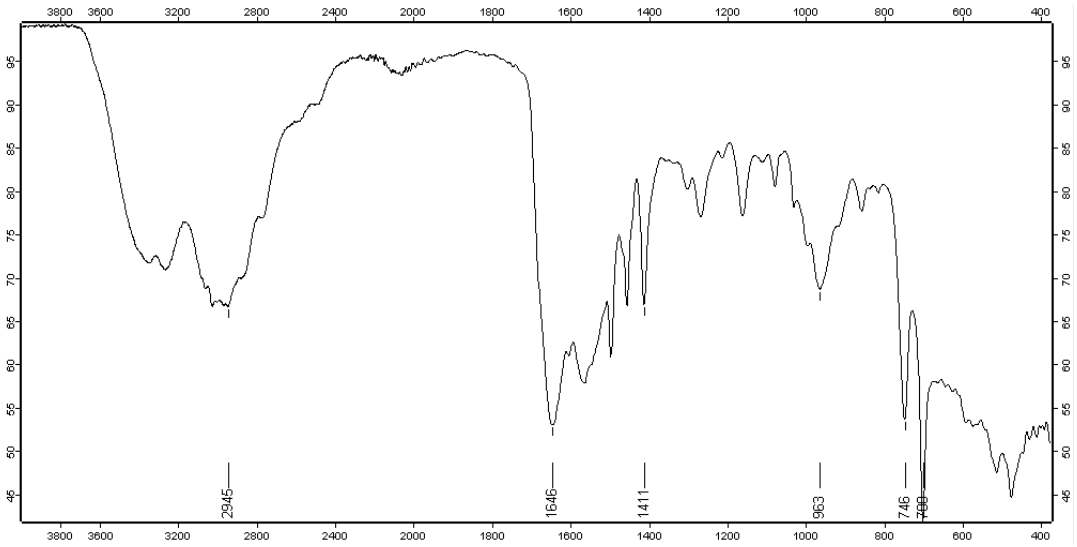


Figure B3- IR data of **64**

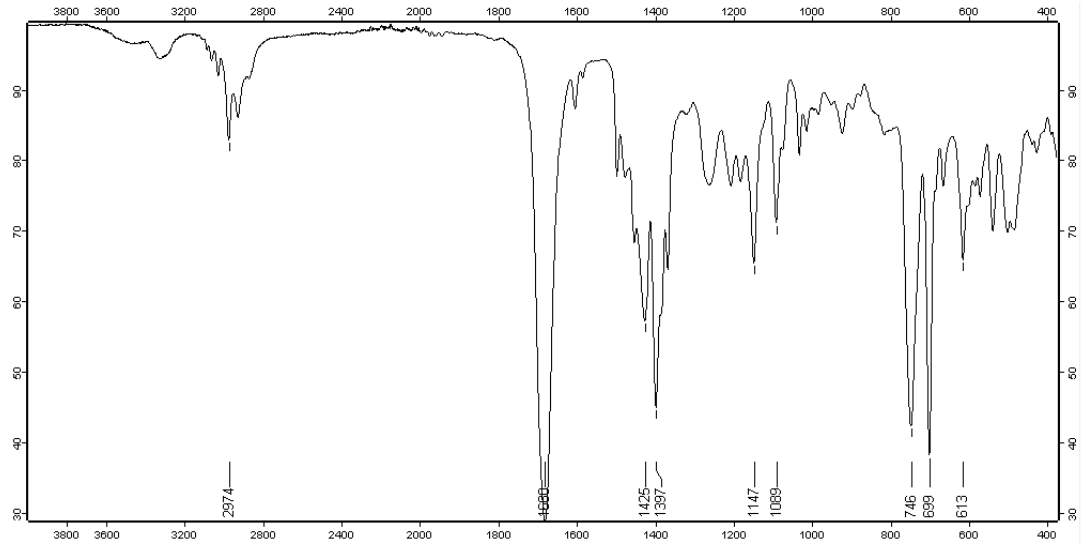


Figure B4- IR data of **56**

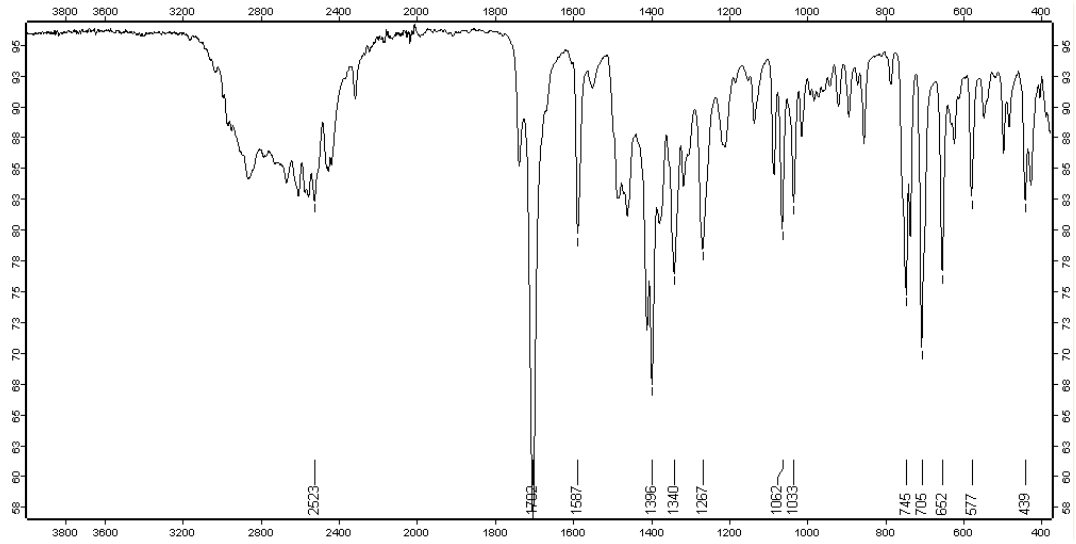


Figure B5- IR data of **57**

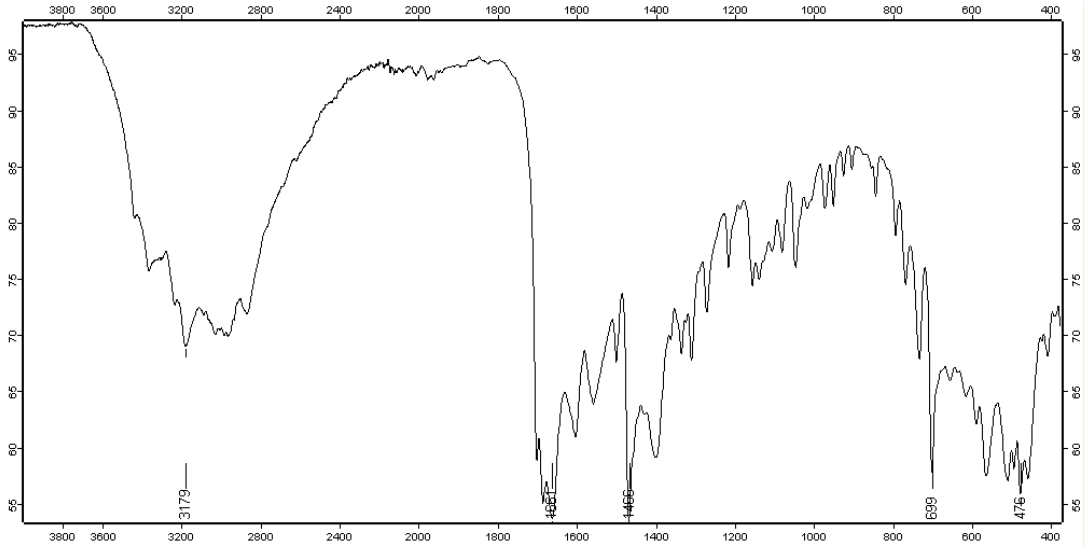


Figure B6- IR data of **65**

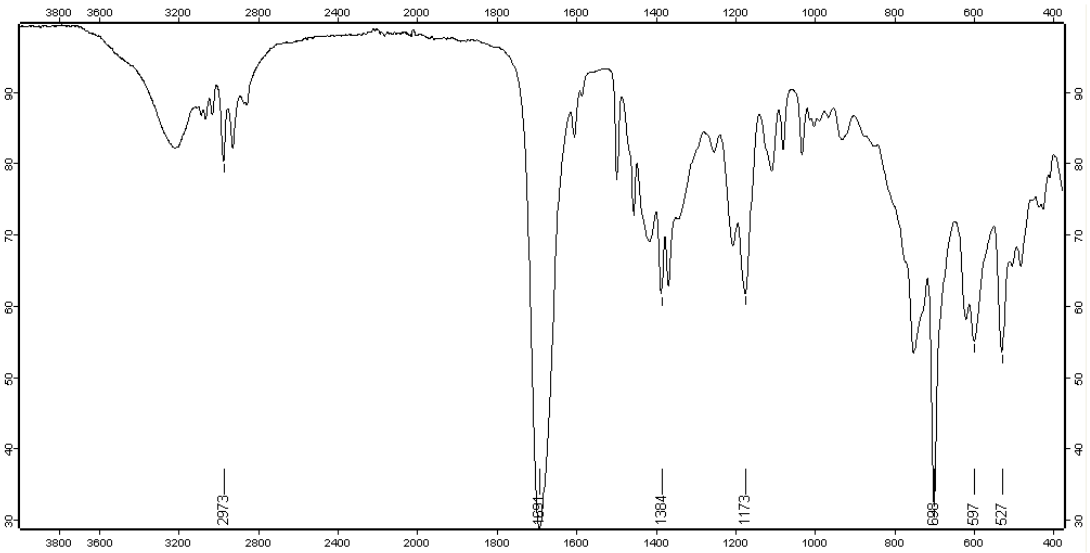


Figure B7- IR data of **58**

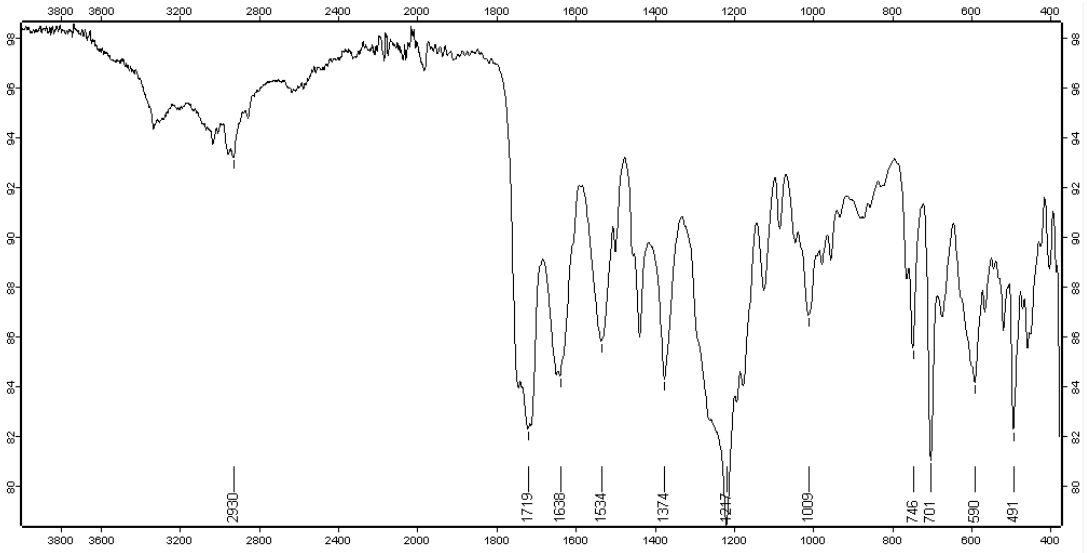


Figure B8- IR data of **59**

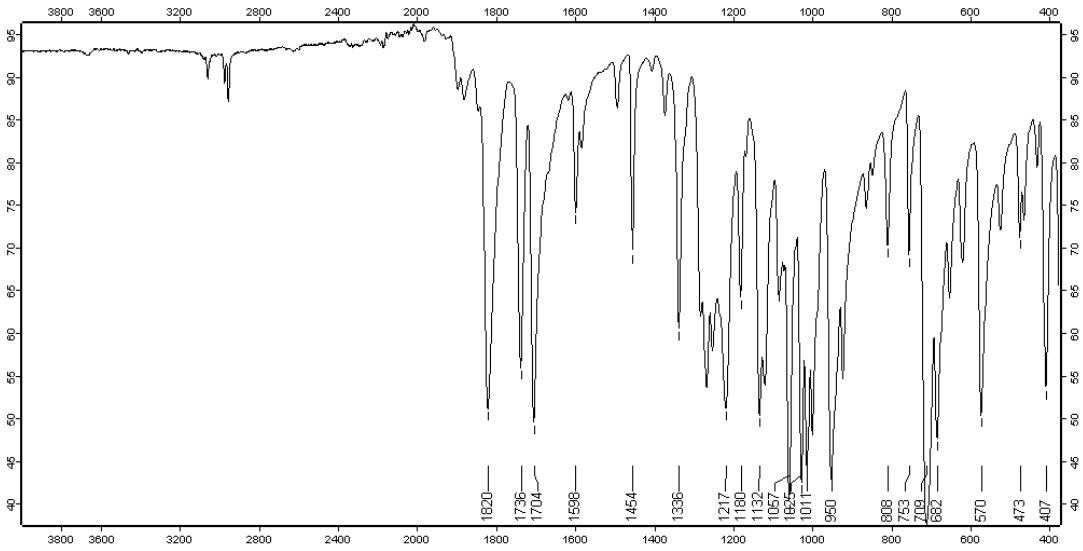


Figure B9- IR data of **67**

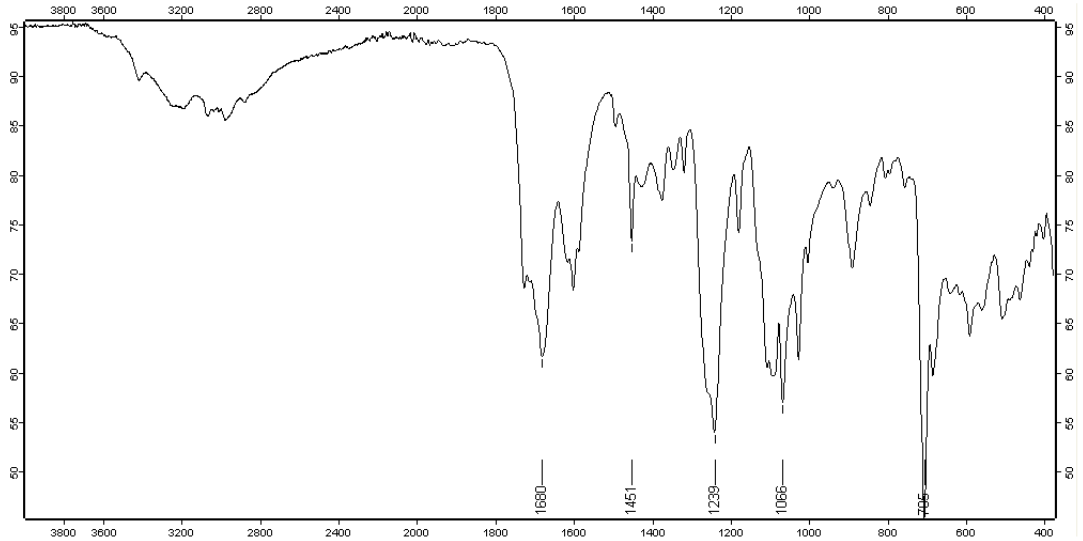


Figure B10-IR data of **68**

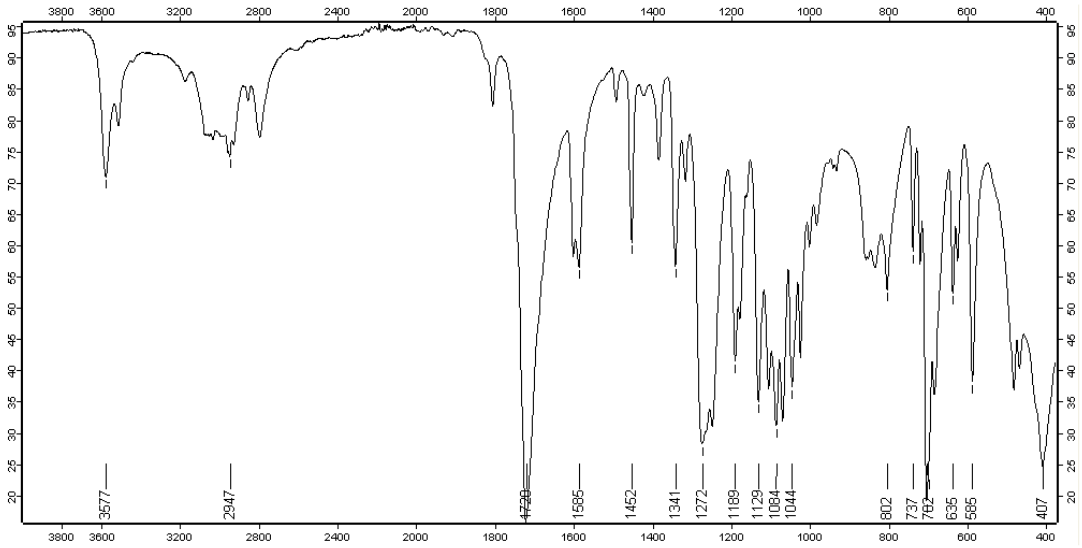
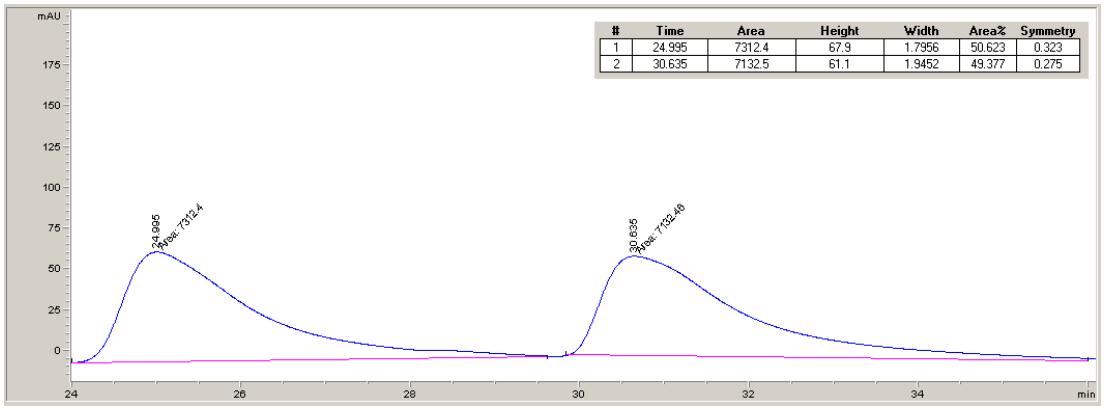


Figure B11-IR data of **60**

APPENDIX C

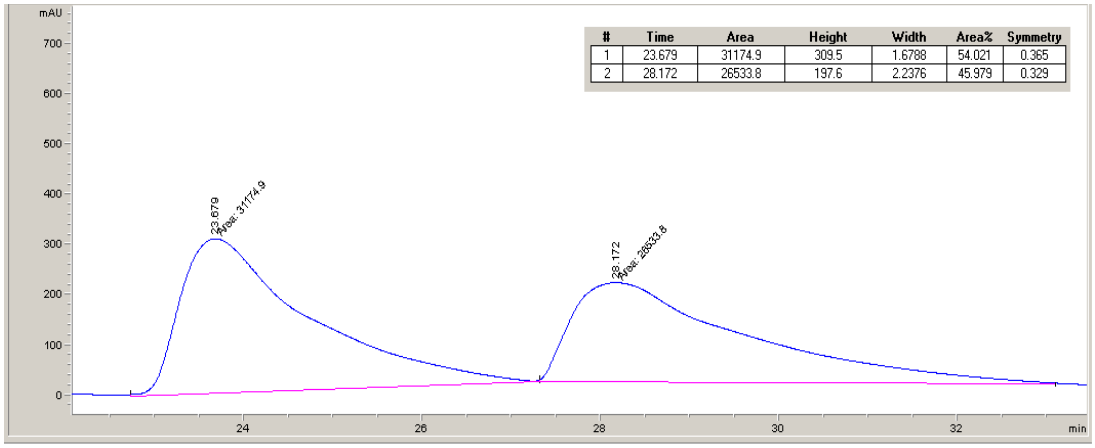
HPLC DATA

All HPLC analysis were performed at Agilent 1100 HPLC and OD-H chiral column with the solvent system of n-Hexane:2-propanol (90:10)



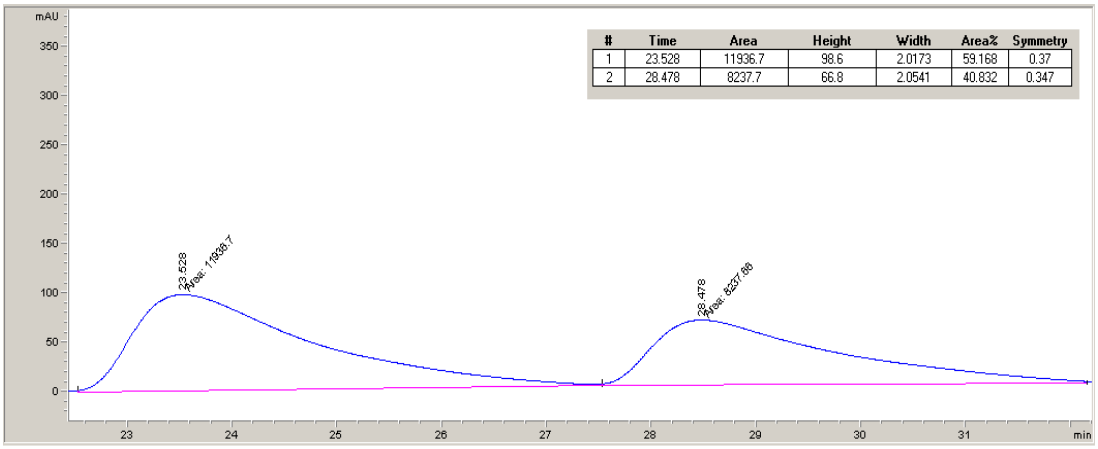
#	Time	Area	Height	Width	Area%	Symmetry
1	24.995	7312.4	67.9	1.7956	50.623	0.323
2	30.635	7132.5	61.1	1.9452	49.377	0.275

Figure C1-HPLC analysis with the racemic mixture of methylphenyl sulfoxide



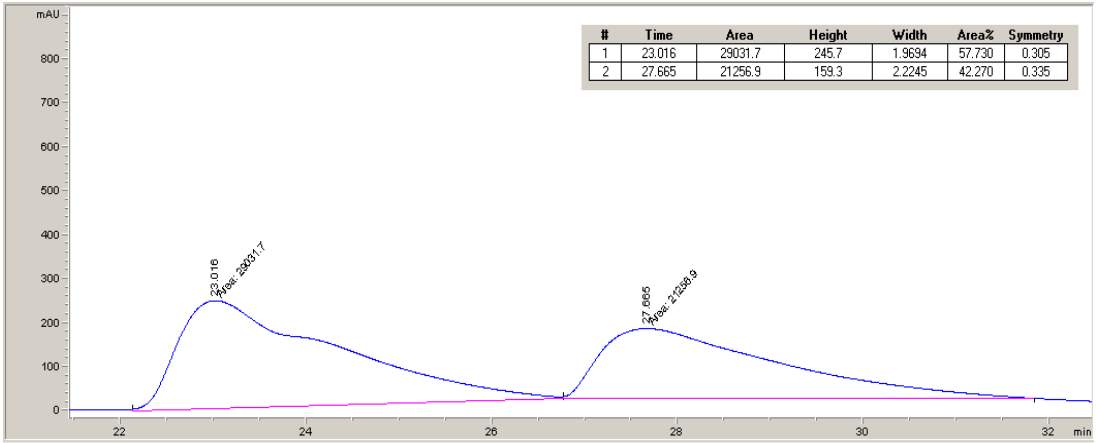
#	Time	Area	Height	Width	Area%	Symmetry
1	23.679	31174.9	309.5	1.6788	54.021	0.365
2	28.172	26533.8	197.6	2.2376	45.979	0.329

Figure C2-HPLC analysis with **(56)** in toluene at 25^{o}C



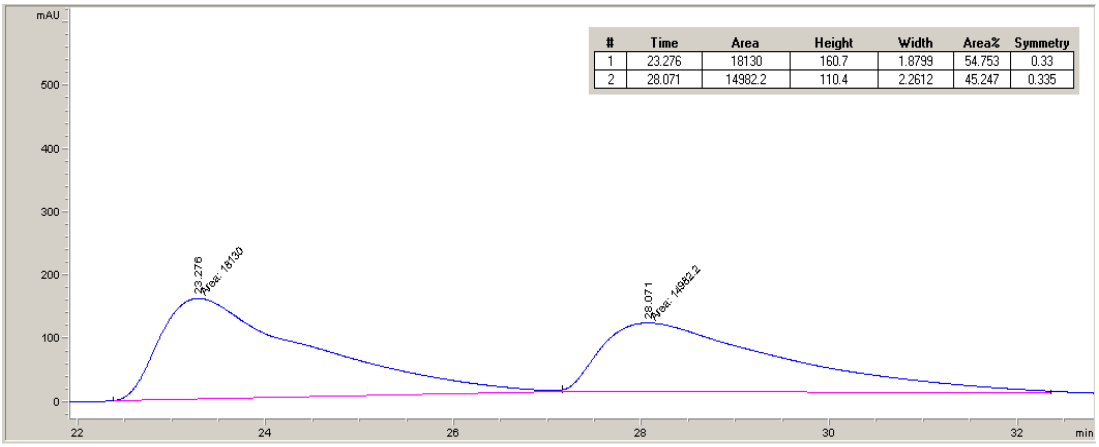
#	Time	Area	Height	Width	Area%	Symmetry
1	23.528	11936.7	98.6	2.0173	59.168	0.37
2	28.478	8237.7	66.8	2.0541	40.832	0.347

Figure C3-HPLC analysis with **(56)** in toluene at 0^{o}C



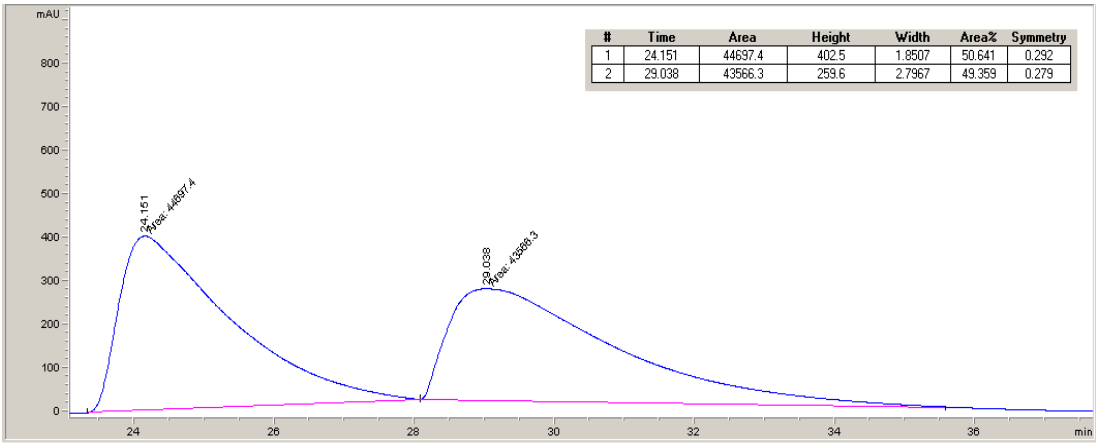
#	Time	Area	Height	Width	Area%	Symmetry
1	23.016	29031.7	245.7	1.9694	57.730	0.305
2	27.665	21256.9	159.3	2.2245	42.270	0.335

Figure C4-HPLC analysis with **(56)** in toluene at -10^{o}C



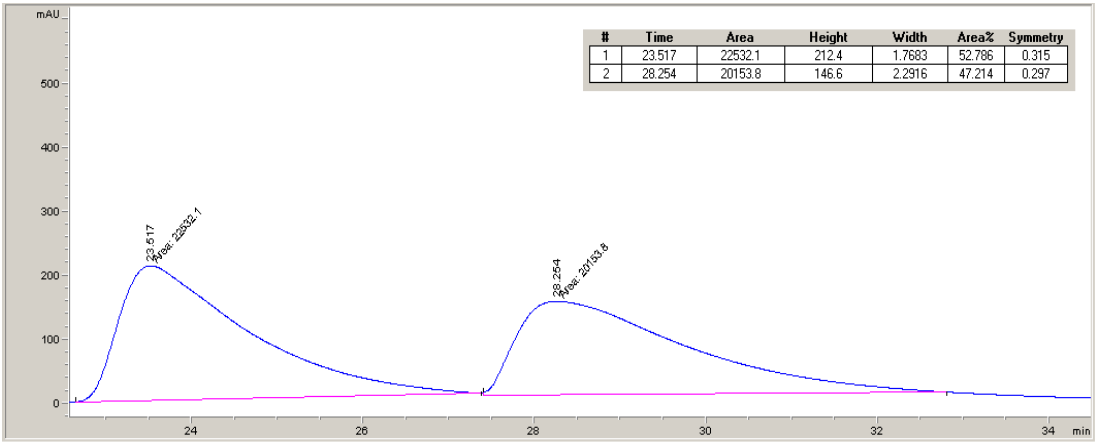
#	Time	Area	Height	Width	Area%	Symmetry
1	23.276	18130	160.7	1.8799	54.753	0.33
2	28.071	14982.2	110.4	2.2612	45.247	0.335

Figure C5-HPLC analysis with **(56)** in toluene at -78^{o}C



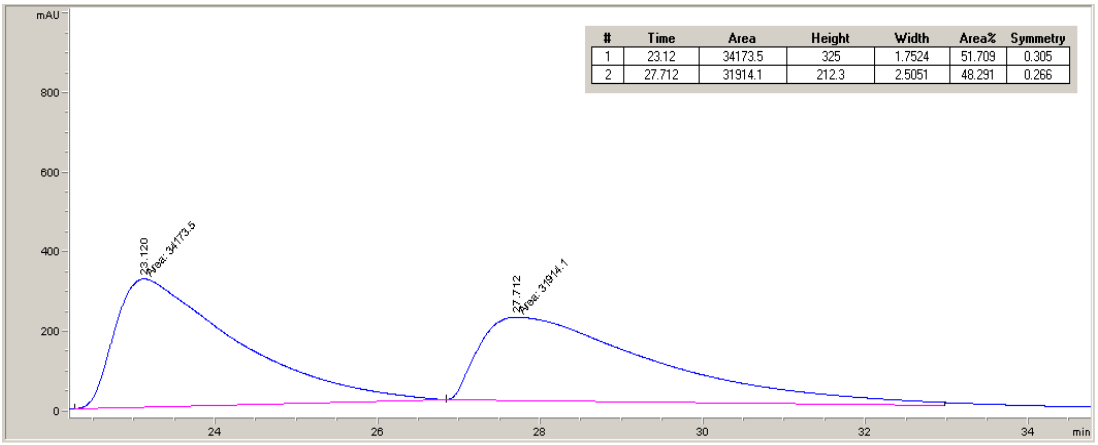
#	Time	Area	Height	Width	Area%	Symmetry
1	24.151	44697.4	402.5	1.8507	50.641	0.292
2	29.038	43566.3	259.6	2.7967	49.359	0.279

Figure C6-HPLC analysis with **(57)** in toluene at 25^{o}C



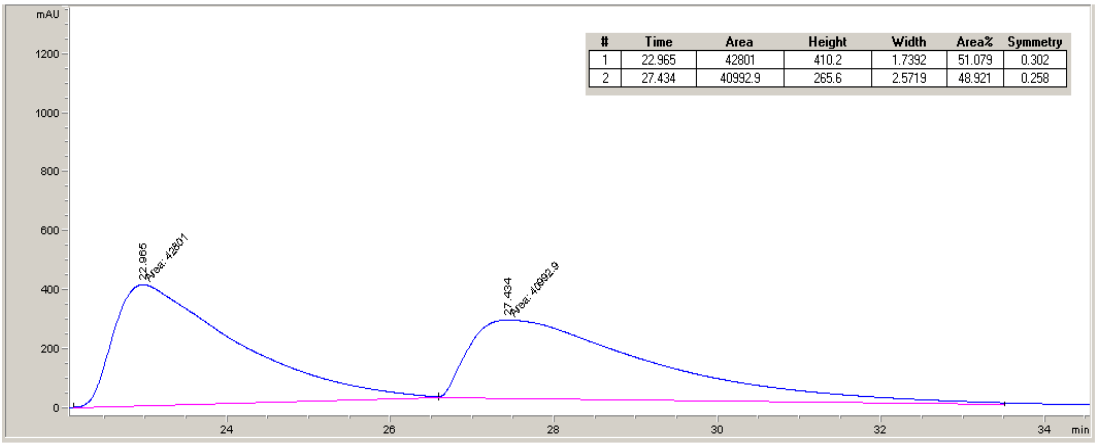
#	Time	Area	Height	Width	Area%	Symmetry
1	23.517	22532.1	212.4	1.7683	52.786	0.315
2	28.254	20153.8	146.6	2.2916	47.214	0.297

Figure C7-HPLC analysis with **(57)** in toluene at 0^{o}C



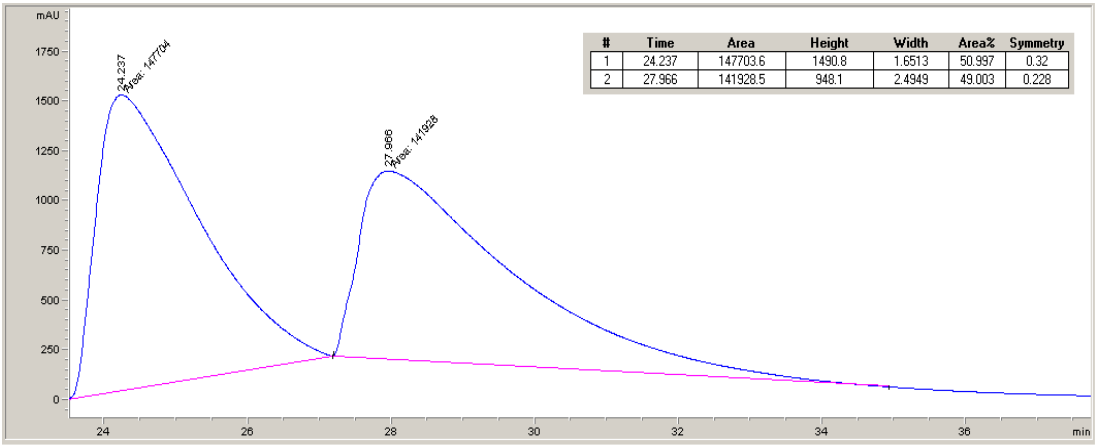
#	Time	Area	Height	Width	Area%	Symmetry
1	23.12	34173.5	325	1.7524	51.709	0.305
2	27.712	31914.1	212.3	2.5051	48.291	0.266

Figure C8-HPLC analysis with **(57)** in toluene at -10^{o}C



#	Time	Area	Height	Width	Area%	Symmetry
1	22.965	42801	410.2	1.7392	51.079	0.302
2	27.434	40992.9	265.6	2.5719	48.921	0.258

Figure C9-HPLC analysis with **(57)** in toluene at -78^{o}C



#	Time	Area	Height	Width	Area%	Symmetry
1	24.237	147703.6	1490.8	1.6513	50.997	0.32
2	27.966	141928.5	948.1	2.4949	49.003	0.228

Figure C10-HPLC analysis with **(58)** in toluene at 25^{o}C

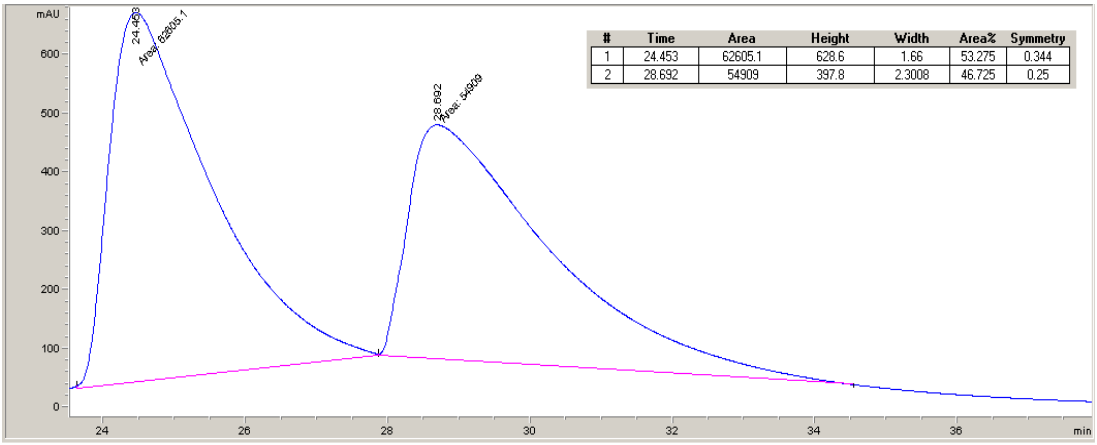


Figure C11-HPLC analysis with **(58)** in toluene at 0^{o}C

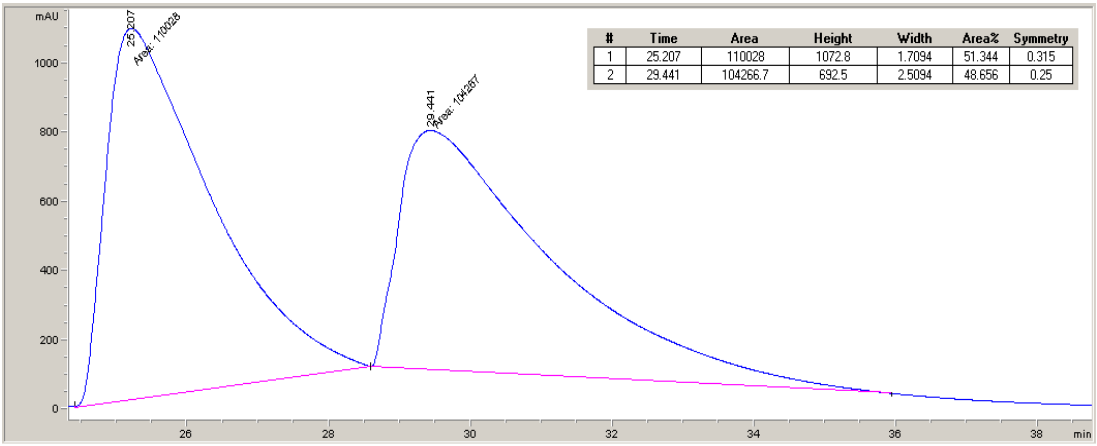


Figure C12-HPLC analysis with **(58)** in toluene at -10^{o}C

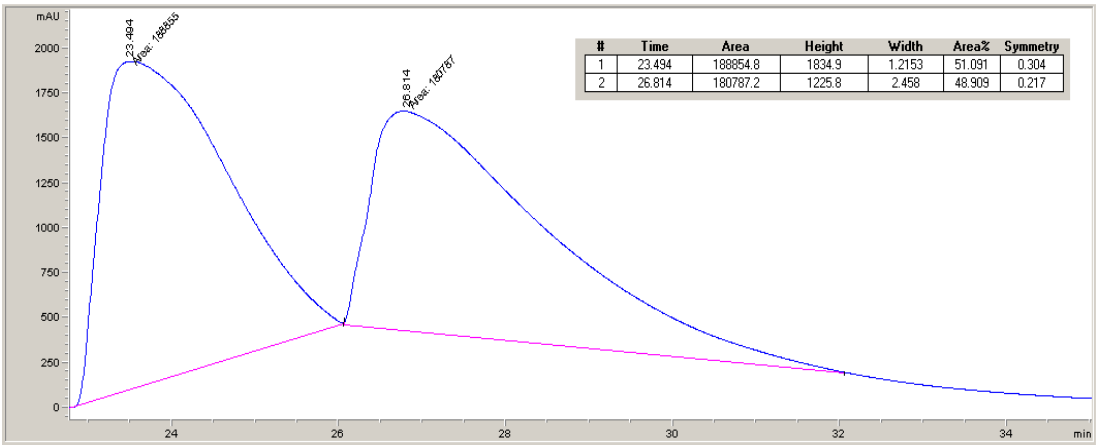
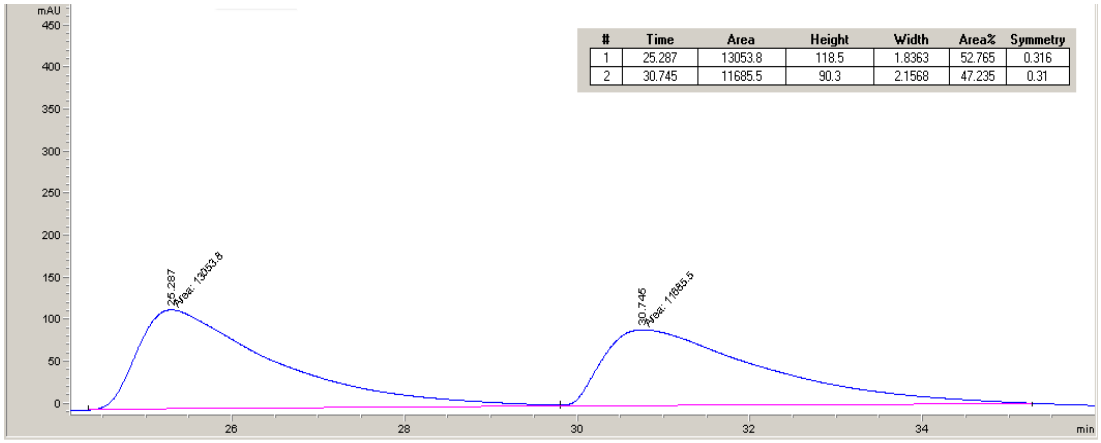
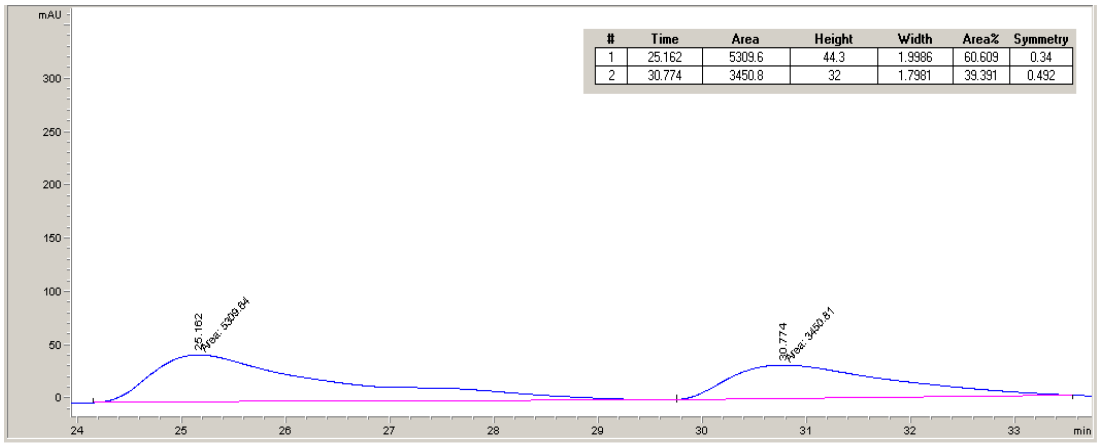


Figure C13-HPLC analysis with **(58)** in toluene at -78^{o}C



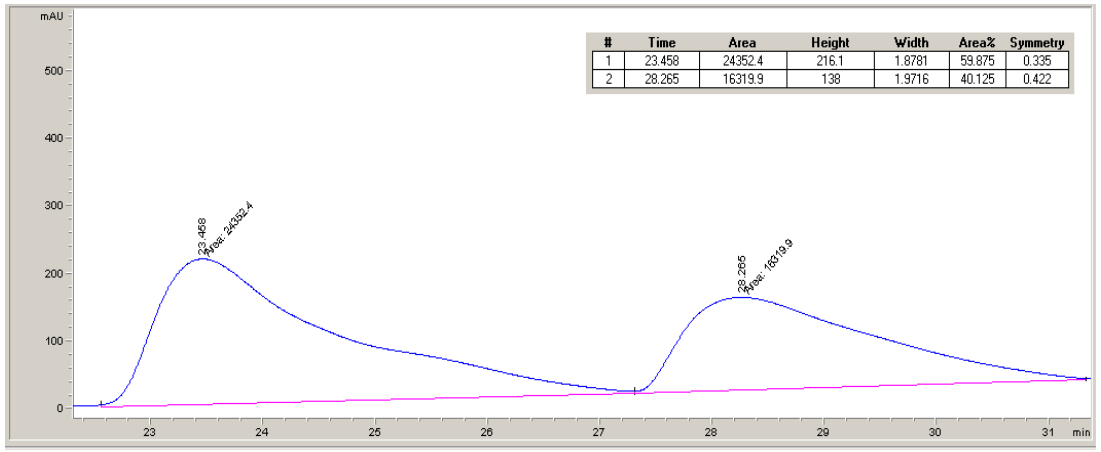
#	Time	Area	Height	Width	Area%	Symmetry
1	25.287	13053.8	118.5	1.8363	52.765	0.316
2	30.745	11685.5	90.3	2.1568	47.235	0.31

Figure C14-HPLC analysis with **(59)** in toluene at 25^{o}C



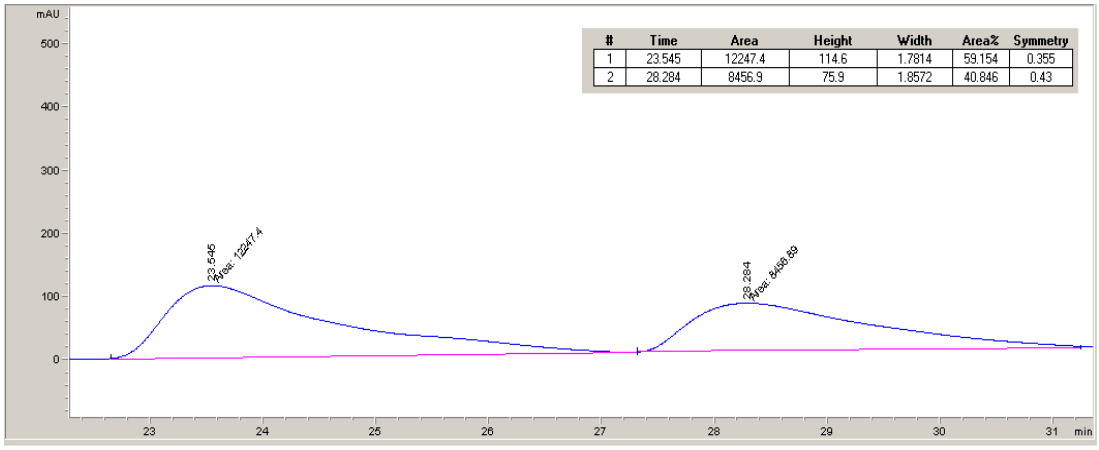
#	Time	Area	Height	Width	Area%	Symmetry
1	25.162	5309.6	44.3	1.9986	60.609	0.34
2	30.774	3450.8	32	1.7981	39.391	0.492

Figure C15-HPLC analysis with **(59)** in toluene at 0^{o}C



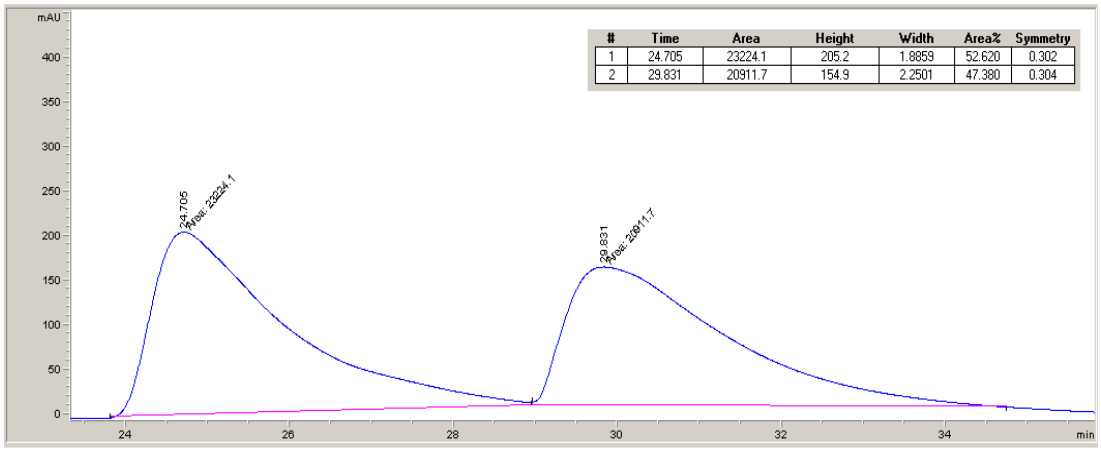
#	Time	Area	Height	Width	Area%	Symmetry
1	23.458	24352.4	216.1	1.8781	59.875	0.335
2	28.265	16319.9	138	1.9716	40.125	0.422

Figure C16-HPLC analysis with **(59)** in toluene at -10^{o}C



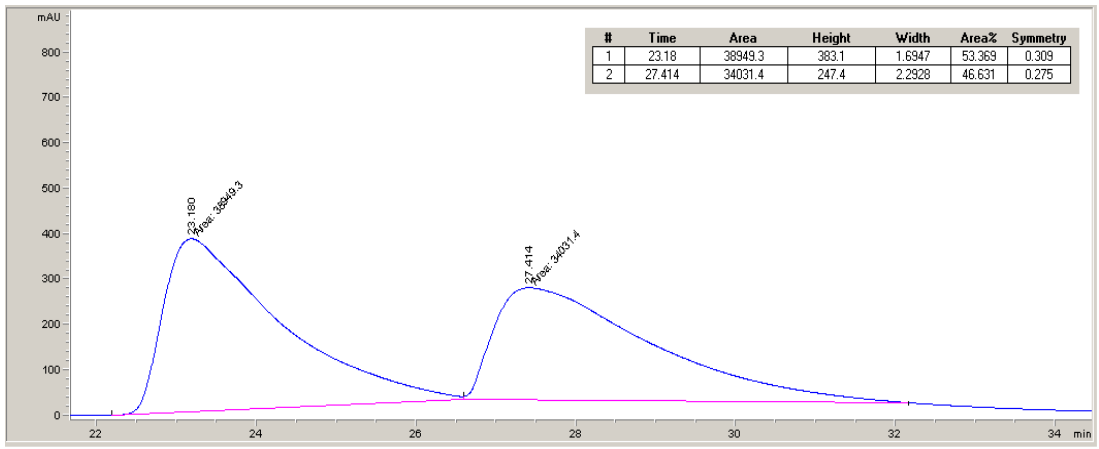
#	Time	Area	Height	Width	Area%	Symmetry
1	23.545	12247.4	114.6	1.7814	59.154	0.355
2	28.284	8456.9	75.9	1.8572	40.846	0.43

Figure C17-HPLC analysis with **(59)** in toluene at -78^{o}C



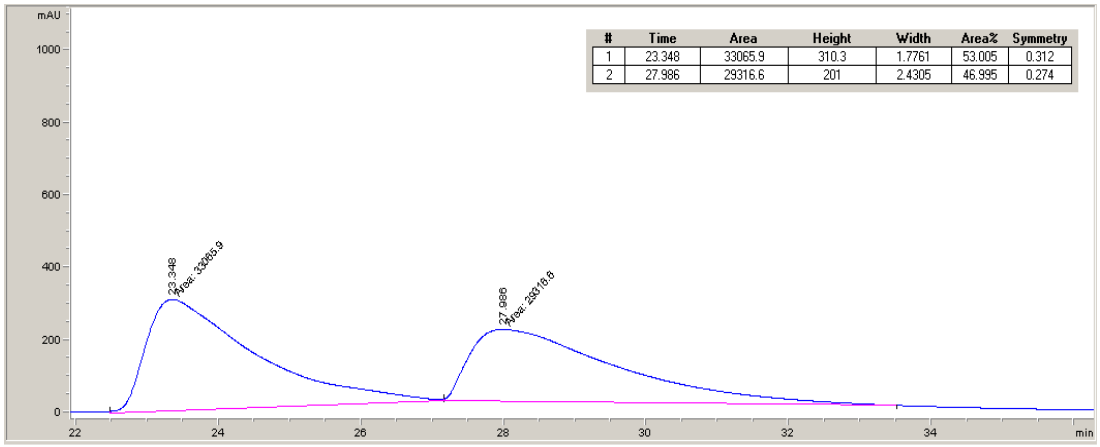
#	Time	Area	Height	Width	Area%	Symmetry
1	24.705	23224.1	205.2	1.8859	52.620	0.302
2	29.831	20911.7	154.9	2.2501	47.380	0.304

Figure C18-HPLC analysis with **(61)** in toluene at 25 ^{o}C



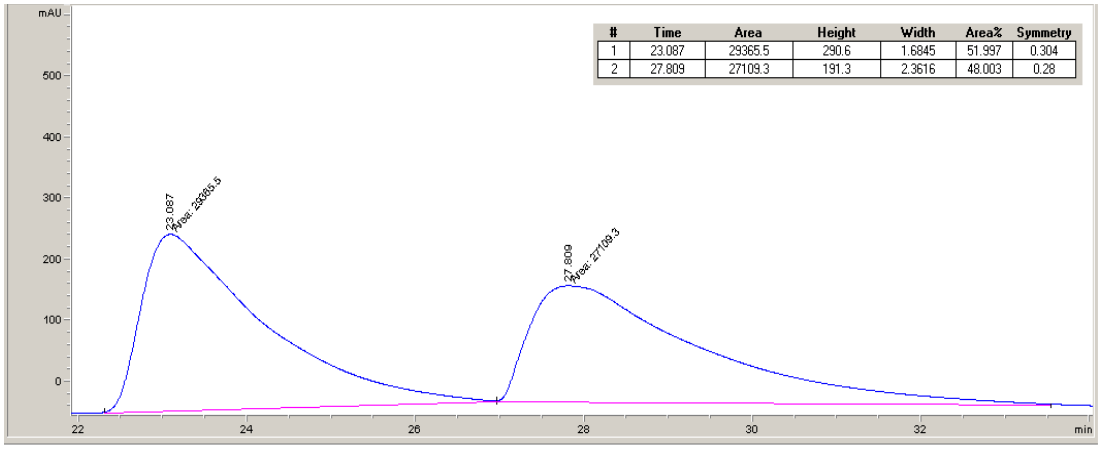
#	Time	Area	Height	Width	Area%	Symmetry
1	23.18	38949.3	383.1	1.6947	53.369	0.309
2	27.414	34031.4	247.4	2.2928	46.631	0.275

Figure C19-HPLC analysis with **(61)** in toluene at 0 ^{o}C



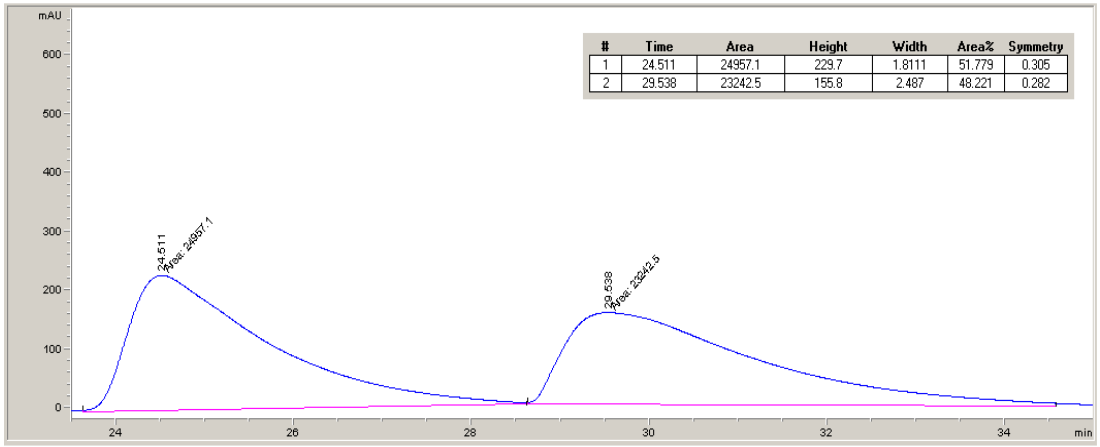
#	Time	Area	Height	Width	Area%	Symmetry
1	23.348	33065.9	310.3	1.7761	53.005	0.312
2	27.986	29316.6	201	2.4305	46.995	0.274

Figure C20-HPLC analysis with **(61)** in toluene at -10 ^{o}C



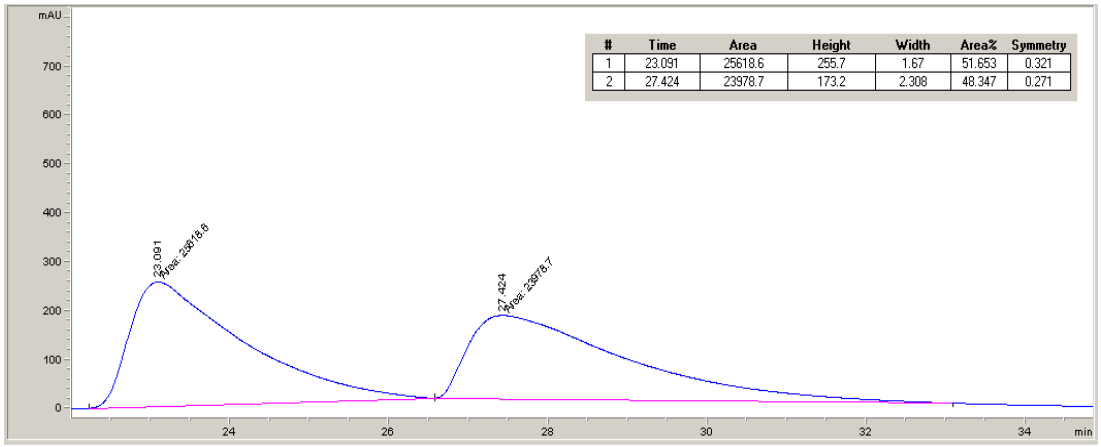
#	Time	Area	Height	Width	Area%	Symmetry
1	23.087	29365.5	290.6	1.6845	51.997	0.304
2	27.809	27109.3	191.3	2.3616	48.003	0.28

Figure C21-HPLC analysis with **(61)** in toluene at -78 ^{o}C



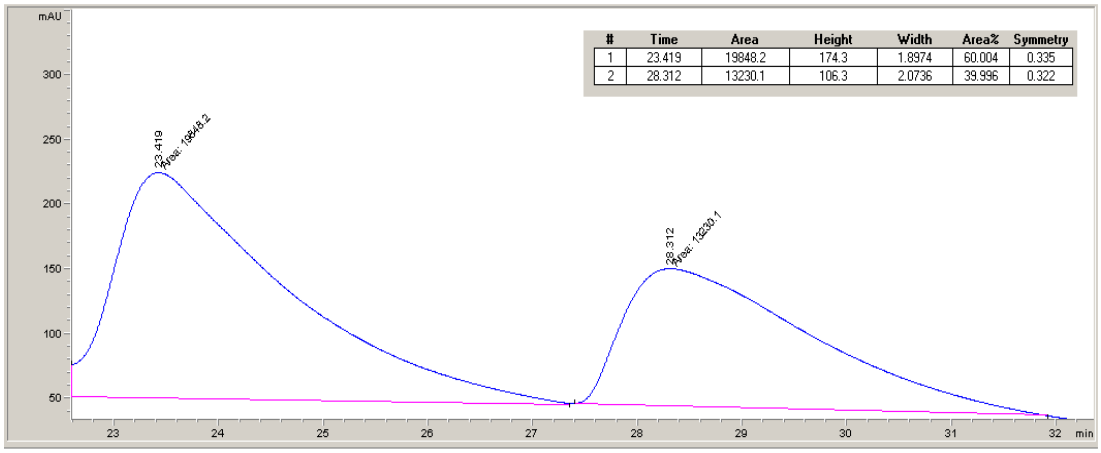
#	Time	Area	Height	Width	Area%	Symmetry
1	24.511	24957.1	229.7	1.8111	51.779	0.305
2	29.538	23242.5	155.8	2.487	48.221	0.282

Figure C22-HPLC analysis with **(60)** in toluene at 25 ^{o}C



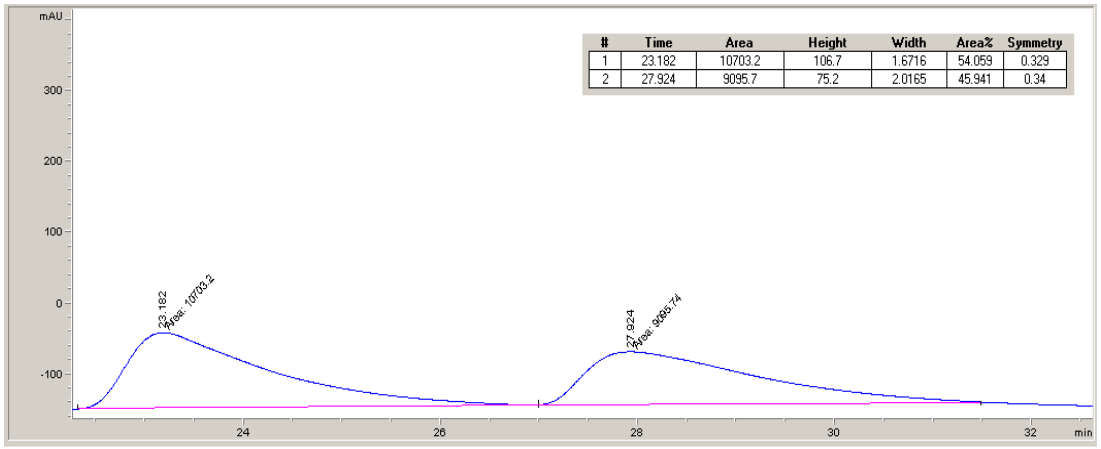
#	Time	Area	Height	Width	Area%	Symmetry
1	23.091	25618.6	255.7	1.67	51.653	0.321
2	27.424	23978.7	173.2	2.308	48.347	0.271

Figure C23-HPLC analysis with **(60)** in toluene at 0 ^{o}C



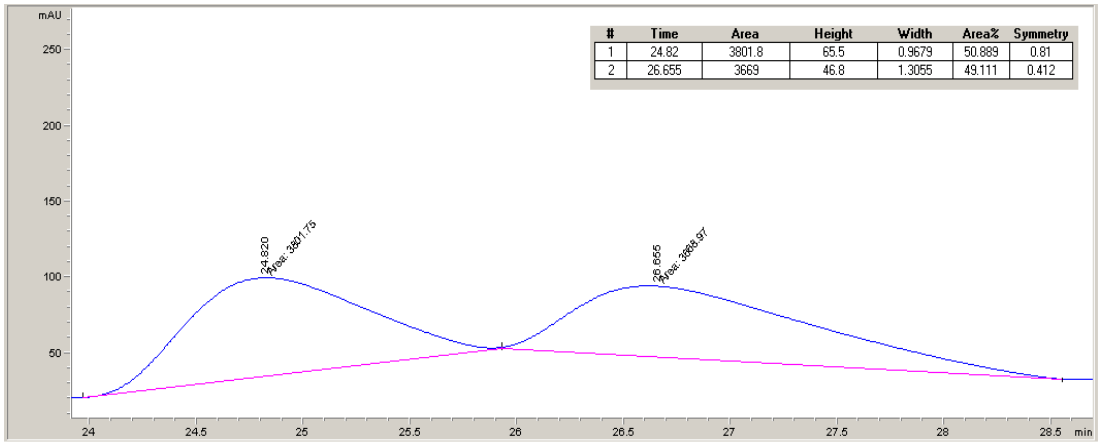
#	Time	Area	Height	Width	Area%	Symmetry
1	23.419	19848.2	174.3	1.8974	60.004	0.335
2	28.312	13230.1	106.3	2.0736	39.996	0.322

Figure C24-HPLC analysis with **(60)** in toluene at -10 ^{o}C



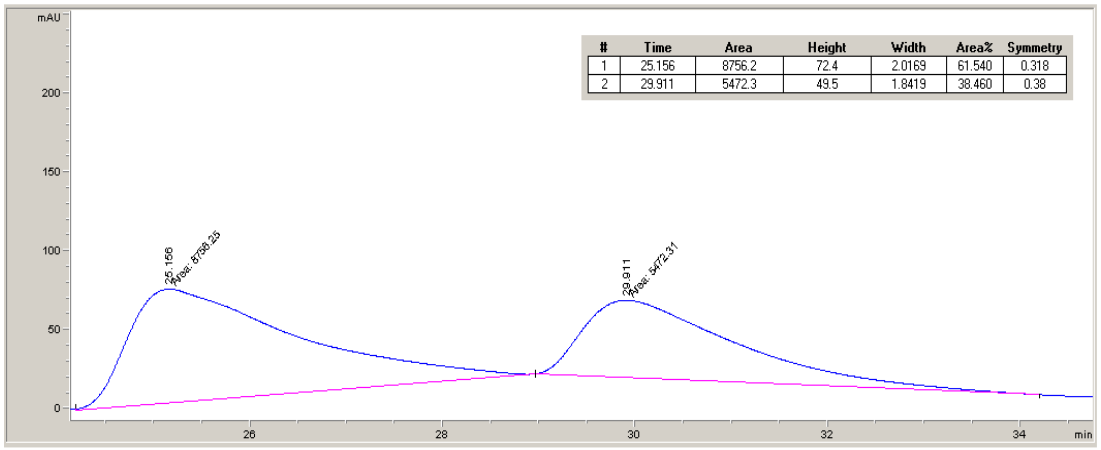
#	Time	Area	Height	Width	Area%	Symmetry
1	23.182	10703.2	106.7	1.6716	54.059	0.329
2	27.924	9095.7	75.2	2.0165	45.941	0.34

Figure C25-HPLC analysis with **(60)** in toluene at -78 ^{o}C



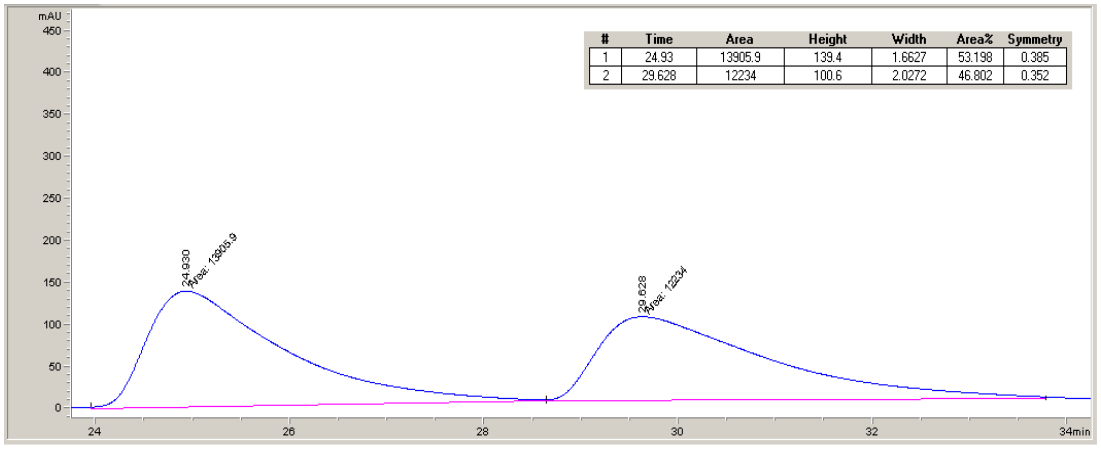
#	Time	Area	Height	Width	Area%	Symmetry
1	24.82	3801.8	65.5	0.9679	50.889	0.81
2	26.655	3669	46.8	1.3055	49.111	0.412

Figure C26-HPLC analysis with **(56)** in acetonitrile at 25 ^{o}C



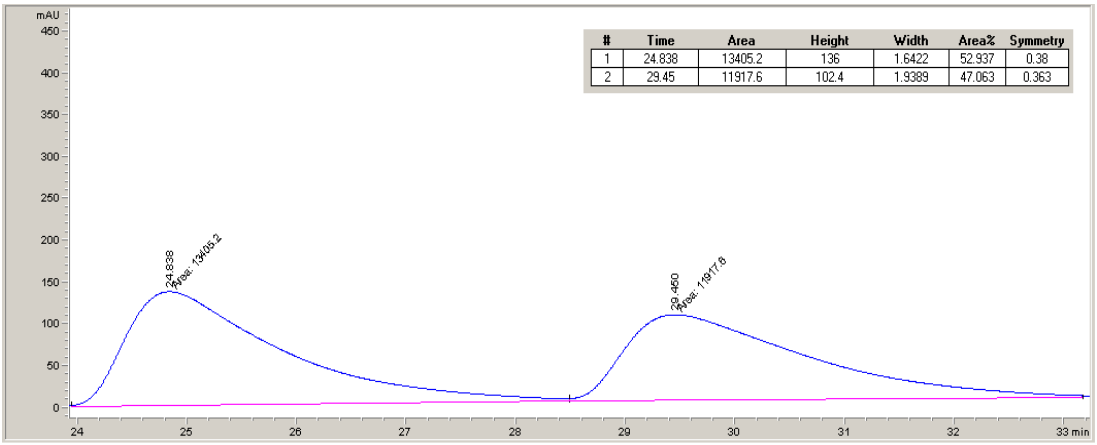
#	Time	Area	Height	Width	Area%	Symmetry
1	25.156	8756.2	72.4	2.0169	61.540	0.318
2	29.911	5472.3	49.5	1.8419	38.460	0.38

Figure C27-HPLC analysis with **(56)** in acetonitrile at 0 ^{o}C



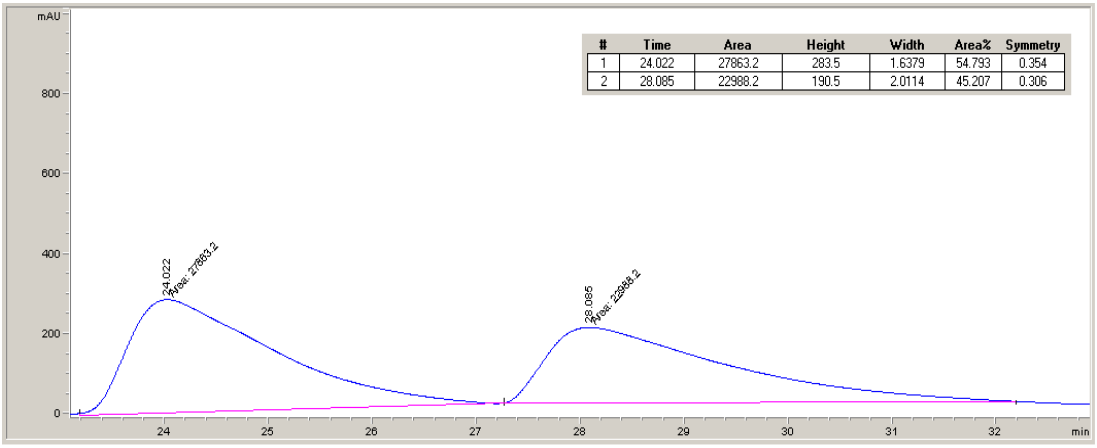
#	Time	Area	Height	Width	Area%	Symmetry
1	24.93	13905.9	139.4	1.6627	53.198	0.385
2	29.628	12234	100.6	2.0272	46.802	0.352

Figure C28-HPLC analysis with **(56)** in acetonitrile at -10 ^{o}C



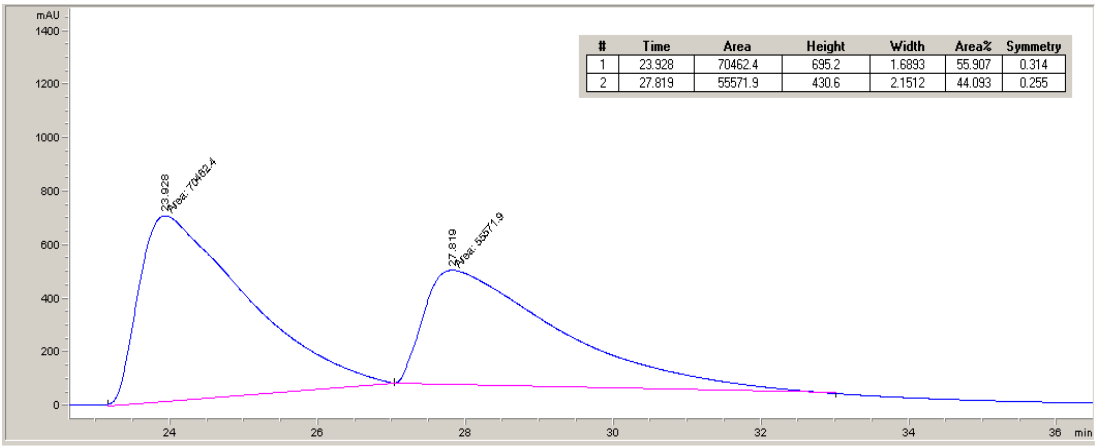
#	Time	Area	Height	Width	Area%	Symmetry
1	24.838	13405.2	136	1.6422	52.937	0.38
2	29.45	11917.6	102.4	1.9389	47.063	0.363

Figure C29-HPLC analysis with **(56)** in acetonitrile at -78 ^{o}C



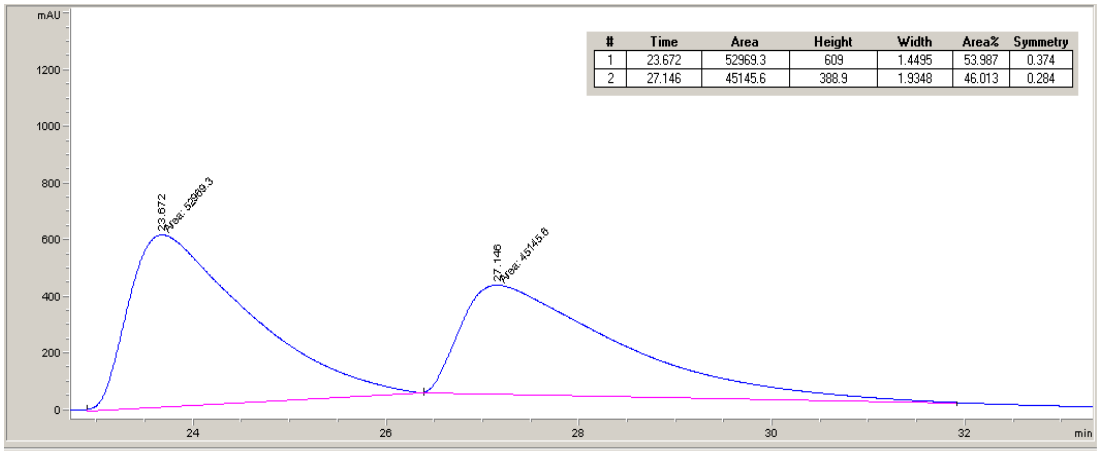
#	Time	Area	Height	Width	Area%	Symmetry
1	24.022	27863.2	283.5	1.6379	54.793	0.354
2	28.085	22988.2	190.5	2.0114	45.207	0.306

Figure C30-HPLC analysis with **(59)** in acetonitrile at 25 ^{o}C



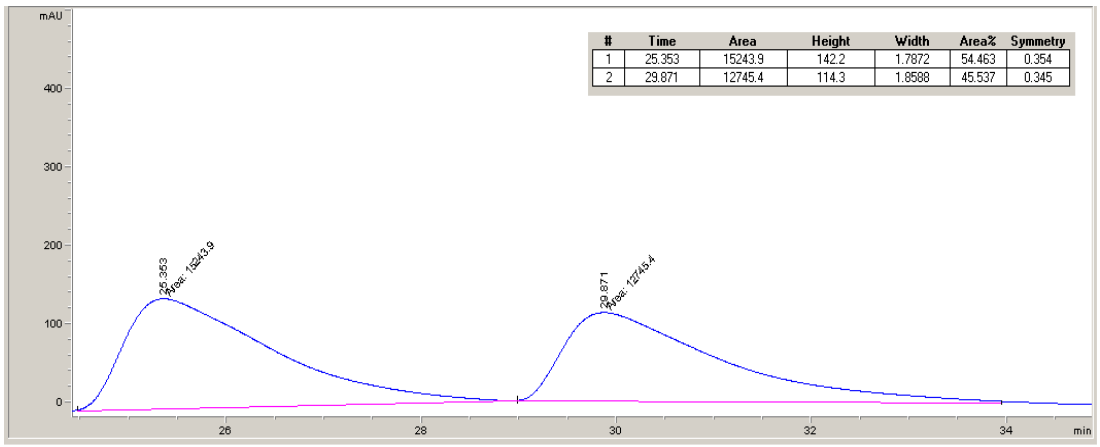
#	Time	Area	Height	Width	Area%	Symmetry
1	23.928	70462.4	695.2	1.6893	55.907	0.314
2	27.819	55571.9	430.6	2.1512	44.093	0.255

Figure C31-HPLC analysis with **(59)** in acetonitrile at 0 ^{o}C



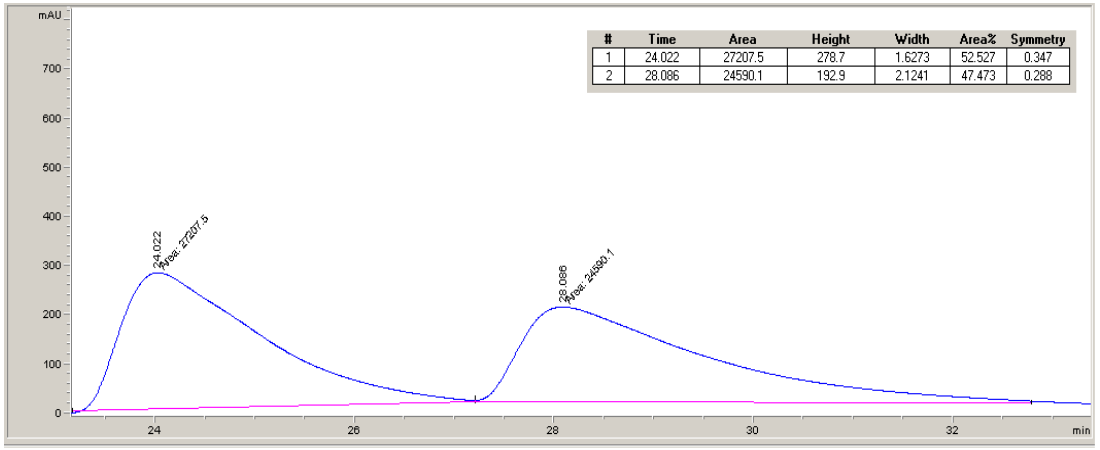
#	Time	Area	Height	Width	Area%	Symmetry
1	23.672	52969.3	609	1.4495	53.987	0.374
2	27.146	45145.6	388.9	1.9348	46.013	0.284

Figure C32-HPLC analysis with **(59)** in acetonitrile at -10 ^{o}C



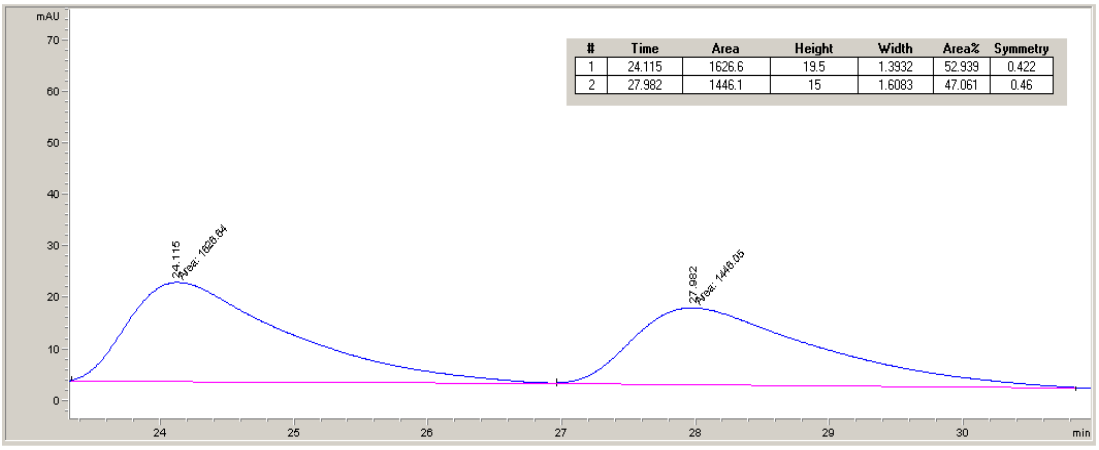
#	Time	Area	Height	Width	Area%	Symmetry
1	25.353	15243.9	142.2	1.7872	54.463	0.354
2	29.871	12745.4	114.3	1.8588	45.537	0.345

Figure C33-HPLC analysis with **(59)** in acetonitrile at -78 ^{o}C



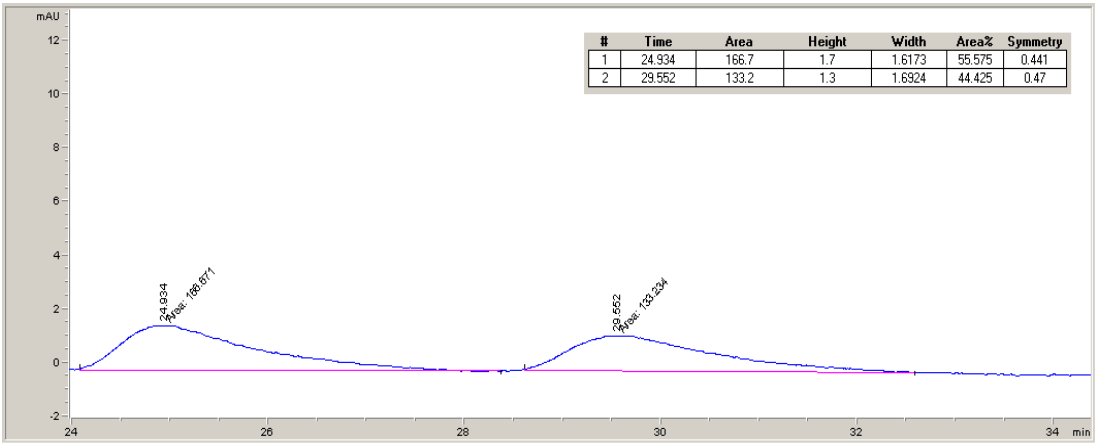
#	Time	Area	Height	Width	Area%	Symmetry
1	24.022	27207.5	278.7	1.6273	52.527	0.347
2	28.086	24590.1	192.9	2.1241	47.473	0.288

Figure C34-HPLC analysis with **(60)** in acetonitrile at 25^{o}C



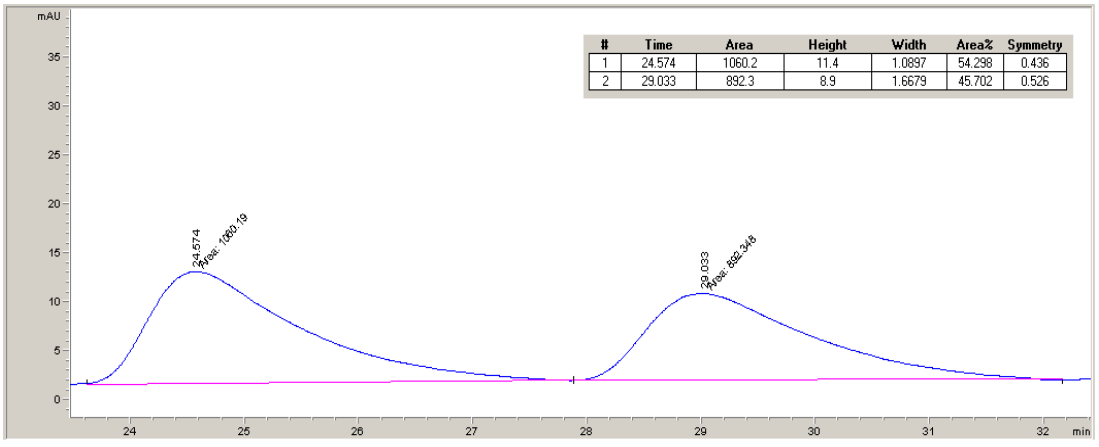
#	Time	Area	Height	Width	Area%	Symmetry
1	24.115	1626.6	19.5	1.3932	52.939	0.422
2	27.982	1446.1	15	1.6083	47.061	0.46

Figure C35-HPLC analysis with **(60)** in acetonitrile at 0^{o}C



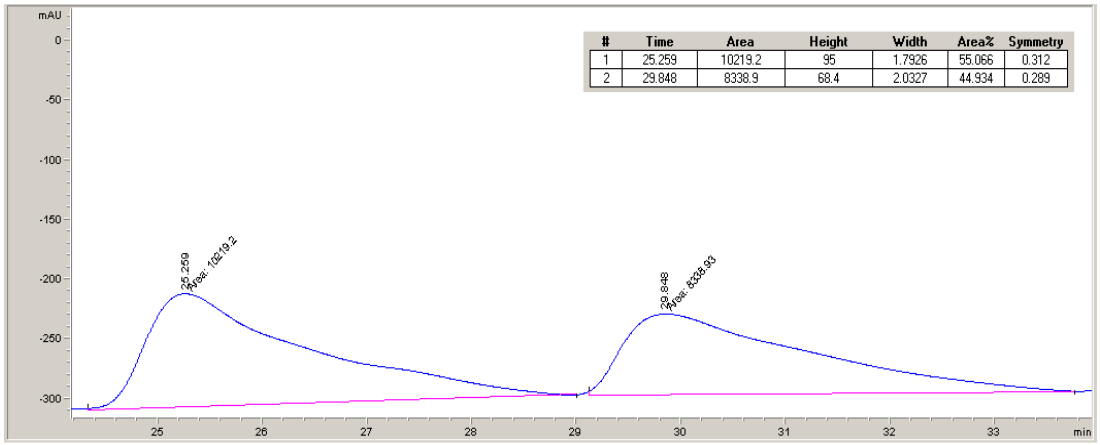
#	Time	Area	Height	Width	Area%	Symmetry
1	24.934	166.7	1.7	1.6173	55.575	0.441
2	29.552	133.2	1.3	1.6924	44.425	0.47

Figure C36-HPLC analysis with **(60)** in acetonitrile at -10^{o}C



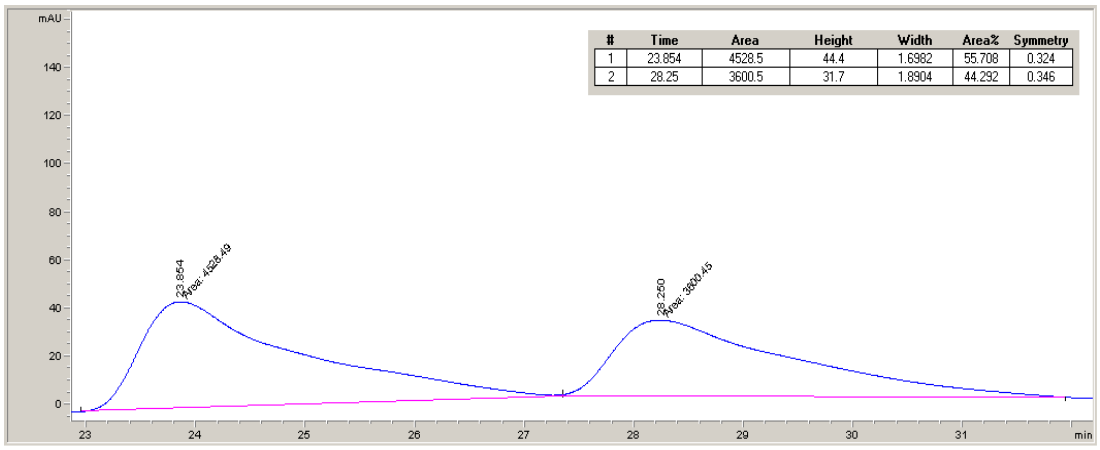
#	Time	Area	Height	Width	Area%	Symmetry
1	24.574	1060.2	11.4	1.0897	54.298	0.436
2	29.033	892.3	8.9	1.6679	45.702	0.526

Figure C37-HPLC analysis with **(60)** in acetonitrile at -78^{o}C



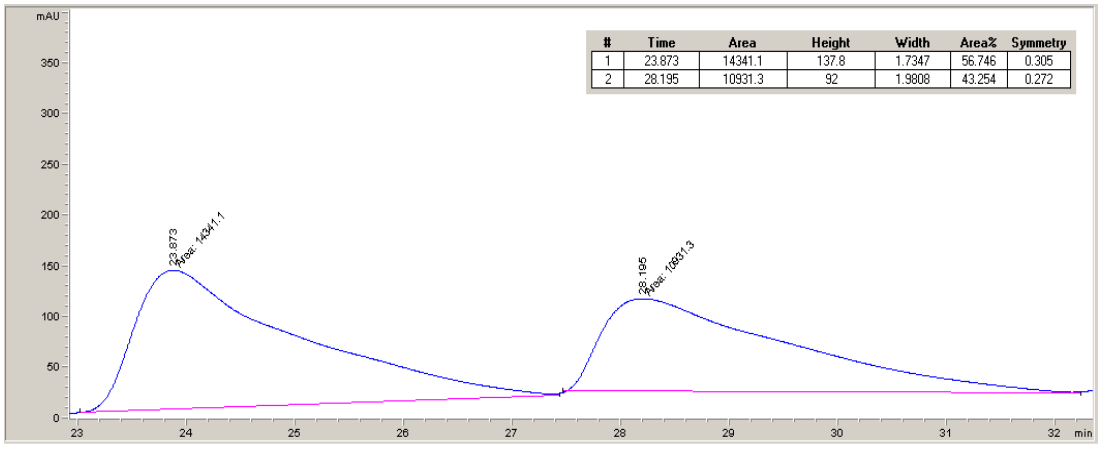
#	Time	Area	Height	Width	Area%	Symmetry
1	25.259	10219.2	95	1.7926	55.066	0.312
2	29.848	8338.9	68.4	2.0327	44.934	0.289

Figure C38-HPLC analysis with **(56)** in dichloromethane at 0^{o}C



#	Time	Area	Height	Width	Area%	Symmetry
1	23.854	4528.5	44.4	1.6982	55.708	0.324
2	28.25	3600.5	31.7	1.8904	44.292	0.346

Figure C39-HPLC analysis with **(56)** in dimethylformamide at 0^{o}C



#	Time	Area	Height	Width	Area%	Symmetry
1	23.873	14341.1	137.8	1.7347	56.746	0.305
2	28.195	10931.3	92	1.9808	43.254	0.272

Figure C40-HPLC analysis with **(56)** in tert-butanol at 0^{o}C