SYNTHESIS AND REACTIONS OF THIOUREAS, THEIR CYCLIZED DERIVATIVES AND OXAZOLIDINDIONES

by

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ABSTRACT

SYNTHESIS AND REACTIONS OF THIOUREAS, THEIR CYCLIZED DERIVATIVES AND OXAZOLIDINDIONES

In this study, several single enantiomer thioureas were synthesized and converted to their cyclic derivatives: 2-imino-thiazolidin-4-ones and 5-benzylidene derivatives. The conformations of the thioureas were determined in solution and in the solid state. In solution; an interconversion between the *E,Z* and *Z,E* conformations was observed with $\Delta G^{\neq}$ values of around 50 kJ/mole. However in the solid state X-Ray crystal structure analyses revealed that they possess a *Z,Z* conformation. The thiazolidin-4-ones were found to be present only in the *anti*-conformation. Chiral hemiaminals were synthesized from the corresponding 2-iminothiazolidine-4-ones by $LiAlH_4$ reductions stereoselectively and were converted to single enantiomer thiazol-2-imines by a water elimination reaction. The optical purities of thiazol-2-imines were proven by polarimetric measurements. The kinetics of the dehydration reactions which occured spontenaously both in the solid state and in solution were followed by time dependent ^1H NMR spectroscopy. The corresponding first order rate constants and free energies of activation for the conversions were reported. It was found that the N-naphthalen-1-yl)ethyl derivatized hemiaminals were the most stable of all, the half-lives amounting to 267 days in the solid state and 96 hours in soluton. A series of axially chiral pyridine compounds carrying 2-iminothiazolidin-4-one core were also reduced to their hemiaminal derivatives using $LiAlH_4$. Due to the restricted rotation around the N_3-aryl single bond, the *M/P* isomerization was observed. Single enantiomers of the new 5-methyl-3-aryloxazolidine-2,4-diones were synthesized by an asymmetric synthesis using chiral pool strategy and their optical purities were proven. Enantiomerically pure 5-methyl-3-aryloxazolidine-2,4-diones were reduced to their hemiaminal derivatives and ring opening products in the presence of $LiAlH_4$ and $NaBH_4$, respetively. Partial racemization was observed due to enolization of the molecules because of the acidic α-hydrogen at C-5 of the ring during these reactions.

ÖZET

TİYOÜRELER, HALKALAŞMIŞ TÜREVLERİ VE OKSAZOLİDİNDİONLARIN SENTEZİ VE REAKSİYONLARI

Bu çalışmada, çeşitli tiyoüre türevleri tek enantiyomer olarak sentezlendi ve halkalı türevleri olan 2-imino-tiyoazolidin-4-on ve 5-benzilidenlere dönüştürüldü. Tiyoürelerin konformasyonları çözeltide ve katı halde saptantı. Çözeltide , *E*,*Z* ve *Z*,*E* konformasyonları arasında bir denge olduğu 50 kJ/mol civarında $\Delta G^{\neq}$ değeriyle gözlemlendi. Ancak katı halde X-Ray kristal yapı analizi, bileşiklerin *Z*,*Z* konformasyonuna sahip olduğunu gösterdi. Tiyoazolidin-4-onların sadece *anti*-konformasyonda mevcut oldukları bulundu. Kiral hemiaminaller $LiAlH_4$ indirgemesiyle 2-imino-tiyoazolidin-4-onlardan stereoseçimli olarak sentezlendi ve tek enantiyomer tiyoazol-2-iminlere su eliminasyonu reaksiyonu ile dönüştürüldü. Tiyoazol-2-iminlerin optik saflıkları polarimetrik ölçümlerle kanıtlandı. Hem katı halde hem de çözeltide kendiliğinden oluşan dehidrasyon reaksiyonlarının kinetikleri zamana bağlı ^{1}H NMR spektroskopisiyle takip edildi. Dönüşümler için birinci derece hız sabitleri ve serbest aktivasyon enerjisi değerleri tayin edildi. N-naftil-1-il)etil türevli hemiaminallerin hepsinin en kararlısı olduğu, yarı ömürlerinin katı halde 267 gün çözeltide 96 saat kadar olduğu bulundu. 2-İmino-tiyoazolidin-4-on halkası taşıyan aksiyel olarak kiral bir seri piridin bileşiği de $LiAlH_4$ kullanılılarak hemiaminal türevlerine indirgendi. N_3-aril tek bağı çevresindeki dönmeden dolayı *M*/*P* izomerlerinin oluştuğu gözlemlendi. Yeni 5-metil-3-ariloksazolidin-2,4-dionlar kiral havuz yaklaşımı kullanılarak tek enantiyomer olarak elde edildi ve optik saflıkları kanıtlandı. Enantiyomerik olarak saf 5-metil-3-ariloksazolidin-2,4-dionlar hemiaminal ve halka açılma ürünlerine sırasıyla $LiAlH_4$ ve $NaBH_4$ kullanılılarak indirgendi. Bu reaksiyonlar sırasında halkanın C-5 karbonundaki asidik α-hidrojenden dolayı molekülün enolizasyonu sebebiyle kısmi rasemizasyon gözlemlendi.

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LIST OF SYMBOLS

[α]	Specific Rotation
dr	Diastereomeric ratio
h	Hour
h	Planck's constant
H	Hertz
J	Joule
K	Kelvin
k_b	Boltzman constant
s	Second
t	Time
T	Temperature
$t_{1/2}$	Half-life
t_R	Retention time
δ	Chemical shift
$\Delta G^{\neq}$	Free energy of activation

LIST OF ACRONYMS/ABBREVIATIONS

CH_3COOH	Acetic acid
$CDCl_3$	Deuterated chloroform
C_6D_6	Deuterated benzene
CS_2	Carbon Disulfide
COX	Cyclooxygenase
CSA	Chiral solvating agent
CSP	Chiral stationary phase
EtOH	Ethanol
$GABA_A$	γ-Aminobutyric acid type A
HPLC	High-Performance Liquid Chromatography
HIV	Human Immunodeficiency Virus
IC_{50}	The Half Maximal Inhibitory Concentration
$LiAlH_4$	Lithium aluminium hydride
LOX	Lipooxygenase
S-TFAE	S-(+)-1-(9-antryl)-2,2,2-trifluoro ethanol
S1P	Sphingosine-1-phosphate
MAO	Monoamineoxidase
$NaBH_4$	Sodium borohydride
NaOAc	Sodium acetate
R-TFAE	R-(-)-1-(9-antryl)-2,2,2-trifluoro ethanol
THF	Tetrahydrofuran
$VOSO_4$	Vanadium(IV) oxide

1. INTRODUCTION

1.1. Chirality

Chirality stems from different orientations of the groups attached to the three-dimensional objects. If a molecule is chiral, it can not be superimposed on its mirror image. A chiral molecule and its non-superimposible mirror image reflection are enantiomers of each other. The existence of enantiomers is generally associated with the presence of a chiral center or a chiral axis. On the other hand, diastereomers contain more than one of these elements.

A great deal of chiral molecules exist in central chirality (Figure 1.1) where four different groups are attached to a tetrahedral central atom (C, N, P, S). The transformation of one enantiomer of a centrally chiral molecule to other one requires bond-breakage and this process is called as racemization.

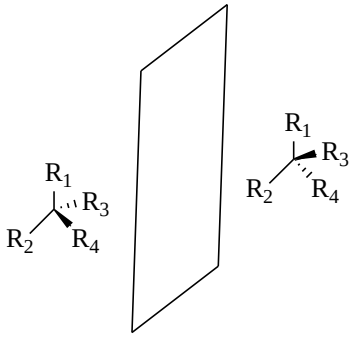
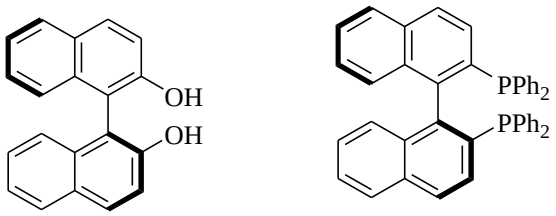


Figure 1.1. ***R*** and ***S*** enantiomers derived from central chirality.

Axial chirality results from restricted rotation about a single bond. The typical and well-known examples of this type of chirality are BINOL and BINAP derivatives (Figure 1.2) [1].



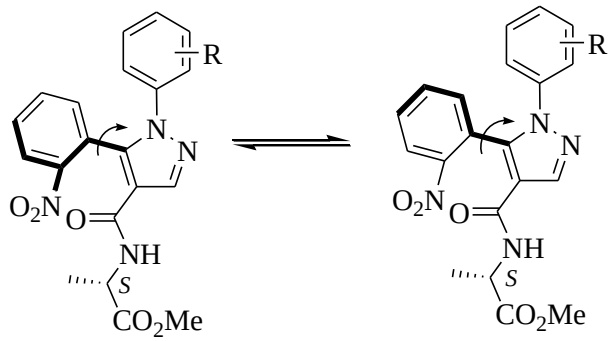
(*S*)-BINOL **(*S*)-BINAP**

Figure 1.2. The structures of axially chiral biaryl atropisomers.

The 180^{o} rotation about the chiral axis gives rise to the formation of interconvertible stereoisomers. The interconvertable stereoisomers are defined as atropisomers if they have life-times greater than 1000 seconds at a given temperature [2]. The atropisomers are usually nomenclatured according to their helicities *P* (positive helix) and *M* (negative helix) or *R* (or R_a) and *S* (or S_a), (Cahn−Ingold−Prelog rules) [3].

Although the interconversion of the classical stereoisomers requires a bond-breakage, axially chiral compounds resulting from an intramolecular restricted rotation can interconvert to one another with time through slow bond rotation. The rate of rotation depends on the steric hindrance to rotation and on the temperature of the medium [4]. The rotational barier ($\Delta G^{\neq}$) value is an important parameter for the evaluation of the stability of the axially chiral compounds. LaPlante *et al*. (2011) divided the axially chiral compounds into three classes. Class 1: Compounds with rotational barrier less than 20 kcal/mol have fast axial rotation rates on the order of seconds or faster, show no axial chirality at room temperature (25 ^{o}C). Class 2: Compounds with rotational barrier greater than 20 kcal/mol are atropisomeric at ambient temperature. Class 3: Compounds with rotational barrier greater than 30 kcal/mol have very small axial rotation rates and their racemizations take years [5].

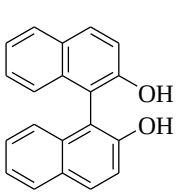
Šenica *et al.* (2016) synthesized a series of 1‑substituted methyl (*S*)‑[5-(2-nitrophenyl)‑1H‑pyrazole-4-carbonyl]alaninates (**I**) (Figure 1.3) and determined the free energy barriers of rotation, ($\Delta G^{\neq}$) using temperature-dependant ^{1}H NMR spectroscopy. However, they could not succeed to isolate the isomers due to the low rotational bariers $\Delta G^{\neq}_{298}$ values of 19.5-20.5 kcal/mol at [6].



I-*M* **I-*P***

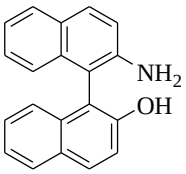
Figure 1.3. Fast interconversion between the atropisomers of 1‑substituted methyl (*S*)‑[5-(2-nitrophenyl)‑1H‑pyrazole-4-carbonyl]alaninates.

Patel *et al*. (2017) investigated thermal racemization of BINOL (**II**), BINAM (**III**), NOBIN (**IV**) , Phenap (**V**) and TriChlophbin (**VI**) and they found that the compounds were atropisomeric. They reported that the free energy barrier of rotation ($\Delta G^{\neq}$) about the $C_{aryl} - C_{aryl}$ single bond changed in the range of 26-43 kcal/mol [7] (Figure 1.4).



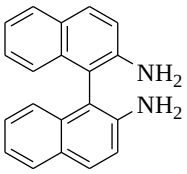
II

$\Delta G^{\#}_{463}$= 39.5 kcal/mol,



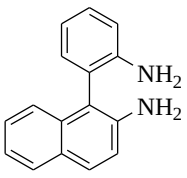
III

$\Delta G^{\#}_{473}$= 40.8 kcal/mol



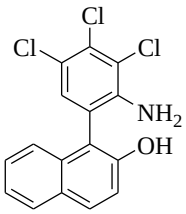
IV

$\Delta G^{\#}_{483}$= 42.6 kcal/mol



V

$\Delta G^{\#}_{333}$= 29.9 kcal/mol,



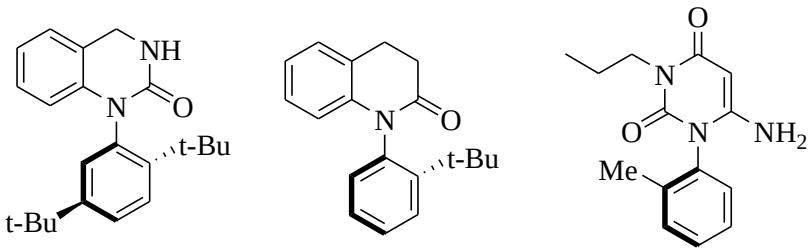
VI

$\Delta G^{\#}_{298}$= 26.3 kcal/mol

Figure 1.4. Structures of biaryls showing $\Delta G^{\neq}$ values needed for slow interconversion between the atropisomers.

The hindered rotation about C-N single bond may also result in the formation of axial chirality. There are extended studies in the literature about such type of axial chirality and rotational barier studies over the years [8-13]. Suzumura *et al*. (2012) reported the activation barier ($\Delta G^{\neq}$) value of a highly rotationally stable C-N axially chiral compound 1-(2,5-di-tert-buthyphenyl)-dihydroquinazolin-2-one (**VII**) as 30 kcal/mol (Figure 1.5) [14]. Suzuki *et al*. (2015) reported a rotational barier ($\Delta G^{\neq}$) of 32 kcal/mol for *N*-(2-*tert*-butylphenyl)-3,4-dihydroquinolin-2-one (**VIII**) (Figure 1.5) [15].

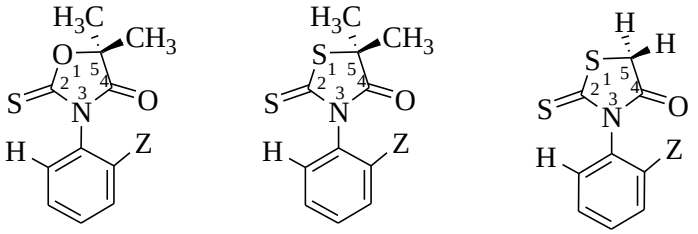
Hagesawa *et al*. (2017) compared the rotational bariers ($\Delta G^{\neq}$) of axially chiral 1-phenyl-6-aminouracil derivatives (**IX**) and the corresponding biaryl compounds and reported that shorter C–N bond length than the C–C bond in the biaryl systems contributes to the stability of the molecules via hindering the rotation around the chiral axis with a high rotational barier value. They found a $\Delta G^{\neq}$ value for 1-phenyl-6-aminouracil derivatives (**IX**) as 30.5 kcal/mol with a racemization half-life 81.2 years (Figure 1.5) [16].



VII **VIII** **IX**

Figure 1.5. Selected examples of axial chirality about C-N single bond.

Another factor affecting the rotational barier $\Delta G^{\neq}$ value of axially chiral compounds is a bulky group attached at *ortho*-posititon. Yılmaz *et al.* (2008) synthesized a series of axially chiral 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-oxazolidinones (**X**), 5,5-dimethyl-3-(*o*-aryl)-2-thioxo-4-thiazolidinones (**XI**), and 3-(*o*-aryl)-2-thioxo-4-thiazolidinones (**XII**). They found the barriers to rotation about the N_{sp2}–C_{aryl} single bond ($\Delta G^{\neq}$) in the range of 19.6-30.8 kcal/mol depending on the the size of the substituents at *ortho*-position (Figure 1.6) [17].



X **XI** **XII**

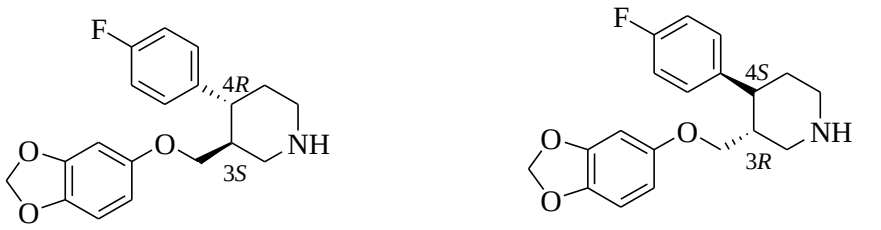
Z=F, Cl, Br, I

Figure 1.6. Structure of axially chiral N-(o-aryl)-2-thioxo-oxazolidine-4-one and rhodanine derivatives.

1.2. Biological Importance of Chirality

Chirality posseses a crucial importance for living organisms due to the fact that the components of a living organism such as proteins, peptides, most amino acids, saccharides, enzymes and many metabolites are chiral [18] and only one form of these molecules is selected by the organism while the other is eliminated [19]. Enantiomers have the same physical and chemical properties in achiral media but they have different properties if the medium is chiral. Therefore, they cause different effects on a living organism due to the fact that living systems are stereoselective against an enantiomeric pair of a chiral molecule. In other words, although one enantiomer of a chiral drug has the positive influence (eutomer) and the other may not have (distomer) [20]. The cases experienced with the racemic drugs thalidomide and perhexiline underline the importance of the stereochemistry in medicinal chemistry. Due to the rapid interconvertion between the thalidomide enantiomers *in vivo*, the drug caused catastrophic effects in 1960s [21]. Also, perhexiline was used as an antianginal agent in its racemic form and it was withdrawn from the markets in 1980s because of serious hepatic and neurological toxic effects of its (+) enantiomer. The studies revealed that the drug underwent a series of oxidative reactions to form the active metabolite *cis*-4-monohydroxyperhexiline. (−)-Perhexiline was more quickly transformed into this metabolite than its (+) enantiomer and in this way the concentration of the toxic (+)-perhexiline in the body was found to increase [22].

Paroxetine which is used as an antidepressant drug contains two stereogenic centers and has four stereoisomers two in *cisoid* and two in *transoid* configurations. However, just the (-)-*transoid* configuration, (-)-*trans*-4-(4-fluorophenyl)-3-(3,4-ethylenedioxyphenoxymethyl)piperidine is the active stereoisomer (Figure 1.7) [23].



transoid-(-)-paroxetine *transoid*-(+)-paroxetine

Figure 1.7. The chemical structures of *transoid* -(−)-and *transoid*-(+)-paroxetine.

L-Histidine (*L*-His) is one of the essential amino acids which is important for human health and participates in many biological activities in the human body. *L*-His is converted into histamine which is a neurotransmitter in the brain however its *D*-form is not active (Figure 1.8) [24].

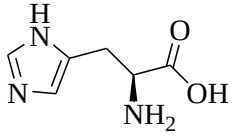
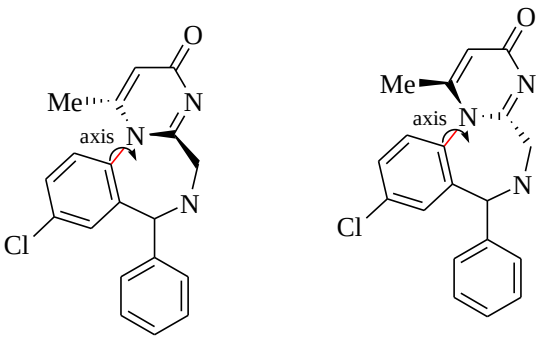


Figure 1.8. The chemical structure of *L*-Histidine.

Atropisomers act in the same way as stereoisomers with classical chiral centers, however the presence of atropoisomeric forms increase the complexity of drug molecules due to their isomerization rates [25]. In recent years there have been extended studies demonstrating different biological activities of atropisomers. Lee *et al*. (2008) investigated selectivity of 1,4-benzodiazepines at the $GABA_A$ receptor and they found that the atropisomers of pyrimido[1,2-*a*][1,4]benzodiazepines derivatives had different selectivities at the receptor; the *R* atropisomer had 50 fold stronger potency than its *S* one. (Figure 1.9) [26].



R-form

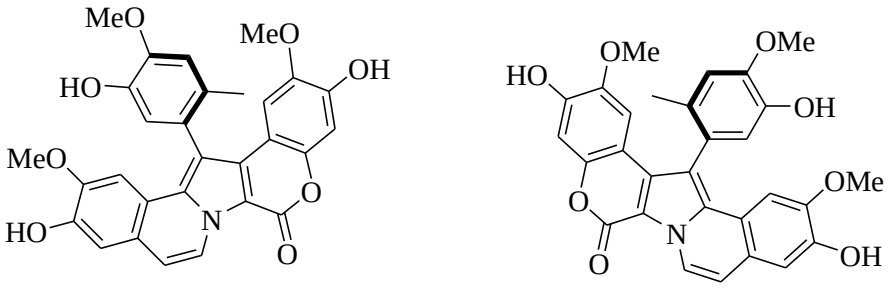
IC_{50} =46 nM

S-form

IC_{50} =2320 nM

Figure 1.9. Atropoisomers of Pyrimido[1,2-*a*][1,4]benzodiazepine.

Yoshida *et al*. (2013) synthesized axially chiral lamellarin *N* derivates and seperated the atropisomers. They found that each atropisomer had different selectivity in terms of their protein kinase inhibitory activity (Figure 1.10) [27].



S-form

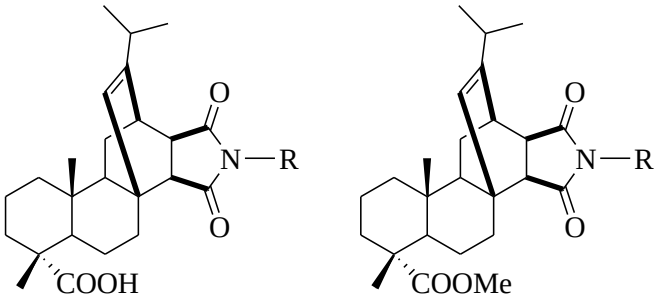
Selective inhibitor activity

R-form

Non-selective inhibitor activity

Figure 1.10. Enantiomers of axially chiral lamellarin *N* derivates.

Yao *et al.* (2013) synthesized maleopimaric acid N-aryl imides and methyl maleopimaric acid N-aryl imides and seperated the enantiomerically pure forms of atropisomers (*R* and *S*) (Figure 1.11). They investigated the cytotoxicity of atropisomers against several cancer cell lines. They found that the *R* atropisomer had stronger cytotoxicity than the *S* one [28].

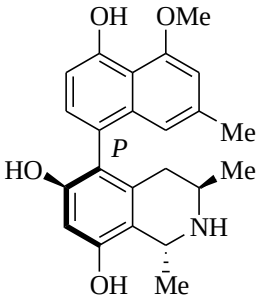


Maleopimaric acid N-aryl imide Methyl maleopimaric acid N-aryl imide

R Configuration ***S*** Configuration

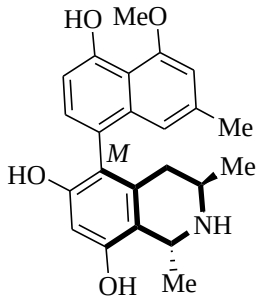
Figure 1.11. Chemical structures of maleopimaric acid N-aryl imides.

The axial chirality also exist in the natural products having important biological activities. Hallock *et al*. (1994) isolated atropisomers of korupensamines from the Cameroonian tropical liana *Ancistrocladus korupensis* and found that these axially chiral alkaloids have different antiviral activities against HIV-1, HIV-2 and antimalarial activity (Figure 1.12) [29].



IC_{50} =0.31 µg/mL aganist *P. falciparum*
IC_{50} =0.56 µg/mL aganist *P. berghei*

Korupensamine A



IC_{50} =0.18 µg/mL aganist *P. falciparum*
IC_{50} =0.41 µg/mL aganist *P. berghei*

Korupensamine B

Figure 1.12. Structures of biologically active axially chiral natural products.

1.3. Methods Used for the Evaluation of Enantiomeric Purity and Assigment of Absolute Chemistry of Chiral Molecules

1.3.1. HPLC with a Chiral Stationary Phase

Seperation of enantiomers has a crucial importance in drug chemistry and the HPLC on a chiral stationary phase method is the most efficient and reliable technique. The ordinary stationary phases cannot work to seperate the enantiomeric pair because of the same retention times. Therefore a chiral medium is needed. Commercially available chiral stationary phases (CSP) are successfully used to resolve the chiral compounds. One enantiomer of a chiral compound binds strictly to the stationary phase to form a transient diastereomeric complex and a result of this binding they retain at different retention times. The factors affecting the binding to CSP are hydrogen bonding, π-π interactions and dipole-dipole interactions. The advantage of this technique is the fact that even a small amount of sample is enough to take measurement.

1.3.2. ^{1}H-NMR in the presence of a Chiral Auxilary Compound

Enantiomers exhibit identical NMR spectra in an achiral medium. However, absolute configuration (AC) of a chiral compound can be assigned *via* creating a chiral environment. There are two approaches for qualitative enantioseperation by NMR: The first approach comprises the addition of an enantiomerically pure chiral solveting agent (CSA) or a chiral solvent into the mixture of the sample and an achiral NMR solvent and so that they form transient association complexes through non-covalent interactions. Thus the two enantiomers of the sample become distinguishable by differences (may be very small) in chemical shifts. At the second approach, an enantiopure sample is reacted with the two enantiomers of a chiral derivatizing agent (CDA) to produce two diasteromeric derivatives. As a result of covalent binding between the auxiliary reagent and the substrate, much larger differences in chemical shifts can be observed than the CSAs method [30].

Demir-Ordu *et al*. (2004) proposed an association complex model between (*S*)-TFAE and 5,5-dimethyl-3-(o-aryl)-2,4-oxazolidinedione derivatives. According to their model, the formation of the association complex is related with hydrogen bonding between

the hydroxyl group of chiral auxiliary (*S*)-TFAE and oxygen atoms of the heterocyclic ring and also π-π interaction between anthryl group and benzene ring [31] (Figure 1.13).

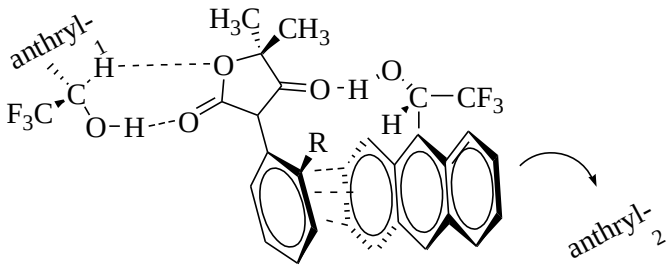


Figure 1.13. The proposed solvation model.

1.3.3. By X-Ray Crystallography

X-ray crystolography which is the most reliable method provides two types of stereochemical information: relative configration of chiral centers can be determined and absolute configuration can be established [32].

1.4. Determination of Rotational Barrier by Low Temperature NMR

Nuclear Magnetic Resonance (NMR) at ambient temperature cannot detect the conformational exchanges or transitions and shows only an ensemble of all conformations undergoing rapid interconversions. However, if the exchange is slowed down, the NMR signals of exchanging conformations become distinguishable [33]. Dynamic Nuclear Magnetic Resonance (DNMR) is a process used to detect rapid interconversions of stereoisomers at variable temperature. In DNMR spectroscopy; if $k<<\Delta v$, the exchange is slow, the two signals having different chemical environment are merged into one signal by increasing the temperature. However; if $k>>\Delta v$, the exchange is fast, one signal undergoes exchanging by decreasing the temperature and the stereoisomers become distinguishable. In this process the temperature at which the peaks coalesce is called the coalescence temperature, T_c.

For the coalescence temperature, T_c , the *pseudo* first order rate constant k_c was determined using the equation (1.1):

$$k_c = \pi\Delta v/2^{1/2} \quad (1.1)$$

Δv: the chemical shift difference between ^1H NMR signals of certain protons in Hz at low temperature.

This rate constant is substituted into the appropriately modified Eyring equation (1.2) to find free enegy of activation values ($\Delta G^{\neq}$):

$$k_c = [(k_b.T_c)/h]e^{-\Delta G\neq/RT} \quad (1.2)$$

R: the gas constant (=8.3143 J/mol.K)

T: temperature (K)

k_b: the boltzman constant(=$1.3805x10^{-23}$ J/K)

h: the planck's constant (=$6.625x10^{-34}$ J.s)

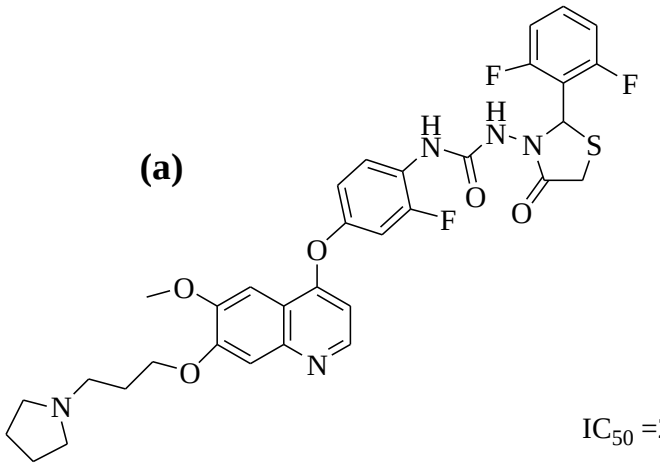
1.5. Thioureas

Thioureas have long been attracting considerable attention due to their biological importance and versatile usage in organic chemistry. The facile synthesis of thioureas enabled the preparation of their numerous derivatives, most of which have been evaluated for their biological activities [34]. In the last years, several optically active thioureas and their thiazole derivatives were shown to posses antitumor activites and therefore have been proposed as a novel class of anticancer agents [35]. Indolyl and acridine conjugated thiourea analogues were found to be monoamine oxidase and cholinesterase inhibitors respectively, were proposed for the Alzheimer's disease treatment [36, 37]. Recently an iridium complex of a thiourea derivative has been shown to have a good antimicrobial activity against the Gram-positive bacteria [38].

The ***E*** and ***Z*** conformations of thioureas have been shown to influence the binding and biological properties of the compounds [39, 40]. Chiral thioureas, in addition to their bioactivities are also highly effective organocatalysts used in asymmetric syntheses [41-45].

1.6. 2-Imino-Thiazolidin-4-ones and Their 5-Benzylidene Derivatives

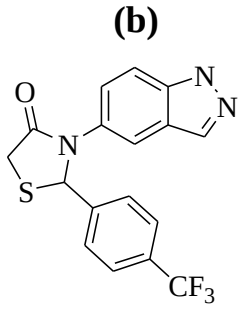
There have been an increasing interest for 1,3-thiazolidin-4-ones over the years in organic and medicinal chemistry since this heterocyclic core display diverse biological activities [46]. Qi *et al*. (2018) synthesized N^1-(2-aryl-1, 3-thiazolidin-4-one)-N^3-aryl urea derivatives which have potent multi-tyrosine kinase inhibitory activities [47] (Figure 1.14 (**a**)). Angapelly *et al*. (2017) developed a simple method using $VOSO_4$ as a catalyst under ultrasonic irradiation for the synthesis of indazole-4-thiazolidinone derivatives which have encouraging antimicrobial activity [48] (Figure 1.14 (**b**)). Filho *et al*. (2015) examined the chemistry and pharmacology of thiazolidinones derived from a thiosemicarbazone which is a highly potent cruzain inhibitor [49] (Figure 1.14 (**c**)). Ruiz *et al*. (2011) found that N-(aminoalkyl)thiazolidin-4-one derivatives had best *in vitro* and *in vivo* antimalarial activity and low cytotoxicity compared to the reference drug chloroquine [50] (Figure 1.14 (**d**)).



(a)

c-Met IC_{50} =0.021 µM
c-Kit IC_{50} =0.029 µM
c-Ron IC_{50} =0.00031 µM
Src IC_{50}=0.061µM

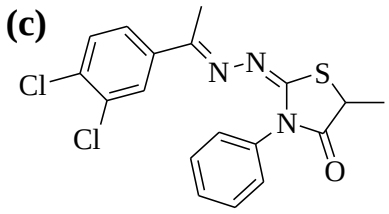
Multi-tyrosine kinase inhibitor



(b)

IC_{50} =20.28 µM aganist *K. planticola*

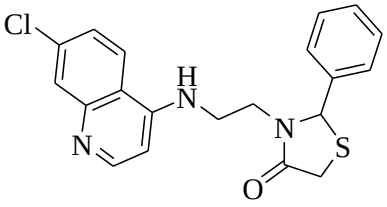
Antimicrobial activity



(c)

IC_{50} =5.9 µM aganist *T. cruzi*

Trypanocidal activity



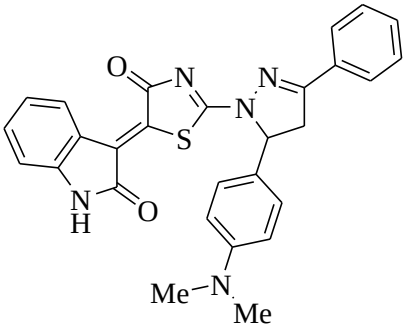
(d)

IC_{50} =0.44 µM

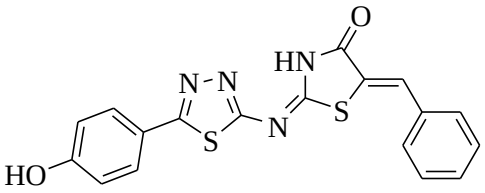
Antimalarial activity

Figure 1.14. Biologically active 1,3-Thiazolidin-4-ones described in the literature.

5-Ene derivatives of thiazolidin-4-ones are also among the most promising molecules as drug candidates due to their wide range biological activities such as anticancer [51], antiamoebic [52] HCV NS5B polymerase inhibitor [53] activities as well dual cyclooxygenase (COX-2) and 15-lipooxygenase (15-LOX) inhibitor activity in the treatmet of inflammatory disorders [54], sphingosine-1-phosphate (S1P) receptor agonist for autoimmune disorders [55] (Figure 1.15),

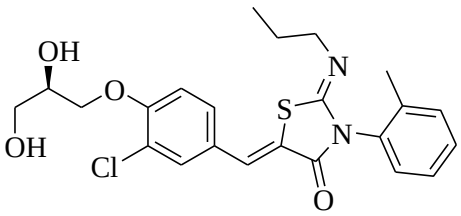


Anticancer agent

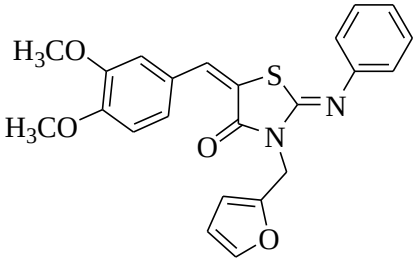


COX-2 IC_{50}=0.085 µM
15-LOX IC_{50}=5.74 µM

Anti-inflammatory

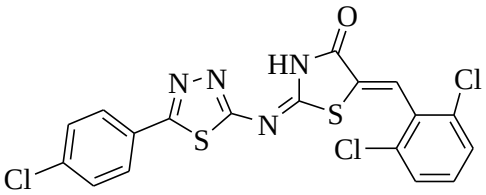


Sphingosine-1-phosphate (S1P) receptor agonist



IC_{50}=0.47 µM

Antiamobeic activity



IC_{50}=5.6µM

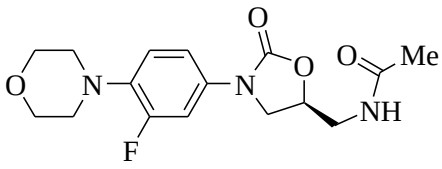
HCV NS5B polymerase inhibitor

Figure 1.15**.** Biologically active 5-ene- thiazolidin-4-ones described in the literature.

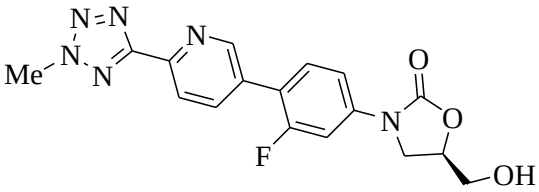
1.7. Oxazolidindiones

Compounds carrying oxazolidinone skeleton attract considerable interest in synthetic and medicinal chemistry due to the fact that this skeleton exists in the structure of many biologically active drugs [56]. Linezolid which is an antibiotic drug belonging to the class of marketed chiral drugs containg oxazolidinone moeity is highly effective molecule against serious Gram-positive bacteria strains [57] (Figure 1.16). Tedizolid is used in the treatment of acute bacterial skin and skin-structure infections [58] (Figure 1.16).

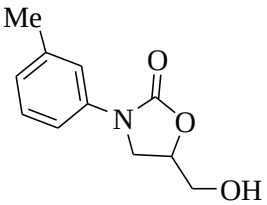
Toloxatone (5-(hydroxymethyl)-3-(3-methylphenyl)-1,3-oxazo lidin-2-one) is used as a selective monoamine oxidase inhibitor MAO-A [59] (Figure 1.16).



Linezolid (antibiotic)



Tedizolid (antibacterial)



Toloxatone (antidepressant)

Figure 1.16. Commercial drugs containing oxazolidinone structure.

The importance of this hetereocyclic core prompted the researchers to develope new synthetic routes. Demir *et al*. (2003) synthesized 5-methyl-3-(o-aryl)-2,4-oxazolidinediones from the reaction of (*S*)-(-)-ethyl lactate and *o*-aryl isocyanates in the presence of sodium metal [60]. Farsbhaf *et al*. (2018) synthesized various 2-oxazolidinones through dehydrative condensation of β-amino alcohols with carbon dioxide [61]. Zhang *et al*. (2015) synthesized chiral oxazolidinone derivatives enantioselectively through enzyme-catalyzed reaction of 1,2 aminoalchols with diphenyl carbonate [62].

1.8. Hemiaminals

Hemiaminals (carbinolamines) are unstable intermediates containing a hydroxyl group and a nitrogen atom attached to tetrahedral carbon atom. The characterizations and isolations of these unstable intermediates are almost impossible [63] and they are easily

subject to dehydration to give the imine or the related compond [64]. Theoretical studies showed that H-bonding had an important role in the stabilization of hemiaminals [65]. Suni *et al*. (2005) obtained a stable hemiaminal as single crystal from the condensation reaction of di-2-pyridyl ketone with 4-cyclohexyl-3-thiosemicarbazide and X-ray diffraction result showed that the intermolecular hydrogen bonding interactions affect the stability of the molecule [66]. A recent study about the X-ray-diffractions of hemiaminals obtained from 4-amino-3,5-dipyridyn-2-yl-1,2,4- triazole revealed that the crystals are stabilized by strong hydrogen bonds between hydroxyl group and the nitrogen atom of the triazole ring [67].

In 2016, our research group synthesized stable hemiaminals in the solute state but, undergoing elimination of water in solution to give the thiazol-2-imines. We found that the half-life of the *o*-methoxyphenyl derivative of the hemiaminals in the solution was longer than the others due to the intramolecular H-bonding and even the amidine conjugation of the hemiaminal nitrogen contributed to the stabilities of all hemiaminals in the solid state [68] (Figure 1.17).

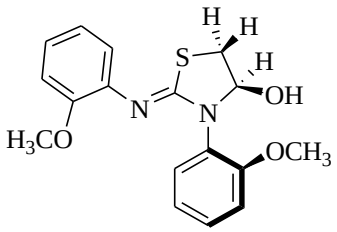
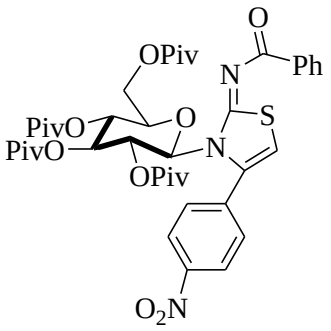


Figure 1.17. Stabilization of hemiaminals through the H-bonding and amidine conjugation.

Hemiaminals were also proposed as intermediates during enzymatic Schiff base forming processes by the reaction of the amino acid lycine and the ring opened form of fructose 1,6-bisphosphate [69].

Thiazol-2-imines which are the dehydration products of hemiaminals are biologically active compounds whose synthesis by various different methods have received considerable attention [70-76]. Murru *et. al*. (2008) succeeded the one-pot synthesis of substituted thiazol-2-imines by the condensation reaction of carbonyl compounds with thioureas and 1,3-disubstituted thioureas [70]. Zhao *et. al*. (2010) synthesized glycosyl thiazol-2-imines from the hydrolysis of thiazol-2(3H)-imine-linked glycoconjugates and

found that 1-benzoyl-4-(4-nitrophenyl)-3-b-D-glucopyranosyl-thiazol-2(3H)-imine derivative of the series was the most potent antitumor agent (Figure 1.18) [71].



IC_{50}= 34.02 µM aganist HCT-8

Figure 1.18. Chemical structure of 1-benzoyl-4-(4-nitrophenyl)-3-b-D-glucopyranosyl-thiazol-2(3H)-imine.

The single enantiomer thiazol-2-imines can be used in asymmetric chemistry as chiral substrates, such as in the preparation of chiral α-aminonitriles [77], in asymmetric hydrogenations [78] or as catalysts in converting olefins to primary amides [79].

2. AIM OF THE STUDY

In this study, we aimed to synthesize *N*,*N*'-bis thiourea, chiral thiazolidine-4-one, and their corresponding 5-benzylidene derivatives as single enantiomers and investigate their antimicrobial activity. We also aimed to obtain oxazolidine-2,4-dione derivatives by an asymmetric synthesis using chiral pool strategy to investigate their *in vitro* monoamine oxidase (hMAO) inhibitory activities In addition, we aimed to synthesize the hemiaminal derivatives of thiazolidine-4-ones and oxazolidine-2,4-diones. Therefore, we planned to carry out the followings:

- To synthesize *N*,*N*'-bis thioureas as single enantiomer from the reaction of chiral amines with carbon disulfide and to determine the conformations of *N*,*N*'-bis thioureas in solution and solid state.

- To synthesize chiral 2-imino-thiazolidine-4-ones from the cyclization of *N*,*N*'-bis thioureas with α-bromo acetic acids in the presence of sodium acetate. To synthesize 5-benzylidene derivatives of the corresponding chiral 2-imino-thiazolidine-4-ones by the reaction of benzaldehyde and prove their enantiomeric purities by chiral HPLC.

- To synthesize single enantiomer oxazolidine-2,4-diones from the reaction of enantiomerically pure *R*- and *S*- ethyl lactate with the aryl isocyanates and prove their enantiomeric purities by HPLC on chiral stationary phase and by ^{1}H NMR spectroscopy using optically active chiral auxiliary (*R*)-(-)-1-(9-antryl)-2,2,2-trifluoro ethanol ((*R*)-TFAE).

- To reduce the on C-4 carbonyl group of chiral 2-imino-thiazolidine-4-ones distereoselectively and to determine their elimination kinetics to the corresponding single enantiomer thiazol-2-imines in solution and in solvent free media.

- To reduce axially chiral pyridine compounds to their hemiaminal derivatives and examine their stabilities.

- To reduce the single enantiomer oxazolidine-2,4-diones regioselectively from the carbonyl group at the C-4 instead of C-2 with $LiAlH_4$ and $NaBH_4$ and determine the racemization ratio by HPLC on chiral stationary phase.

3. RESULTS AND DISCUSSION

3.1. Chiral Thioureas and Their Cyclized Derivatives [80]

3.1.1. Synthesis of Chiral Thioureas, 2-Imino-Thiazoidin-4-ones and 5-Benzylidenes

Chiral amines were reacted with carbon disufide (CS_2) under N_2 atmosphere in proper solvent to obtain the single enantiomer *N*,*N*'-bis-thioureas. The reaction of the thioureas with α-bromoacetic acid yielded 2-imino-thiazolidin-4-ones which were converted to their benzylidene derivatives in the presence of benzaldehyde and sodium acetate (Figure 3.1) [10].

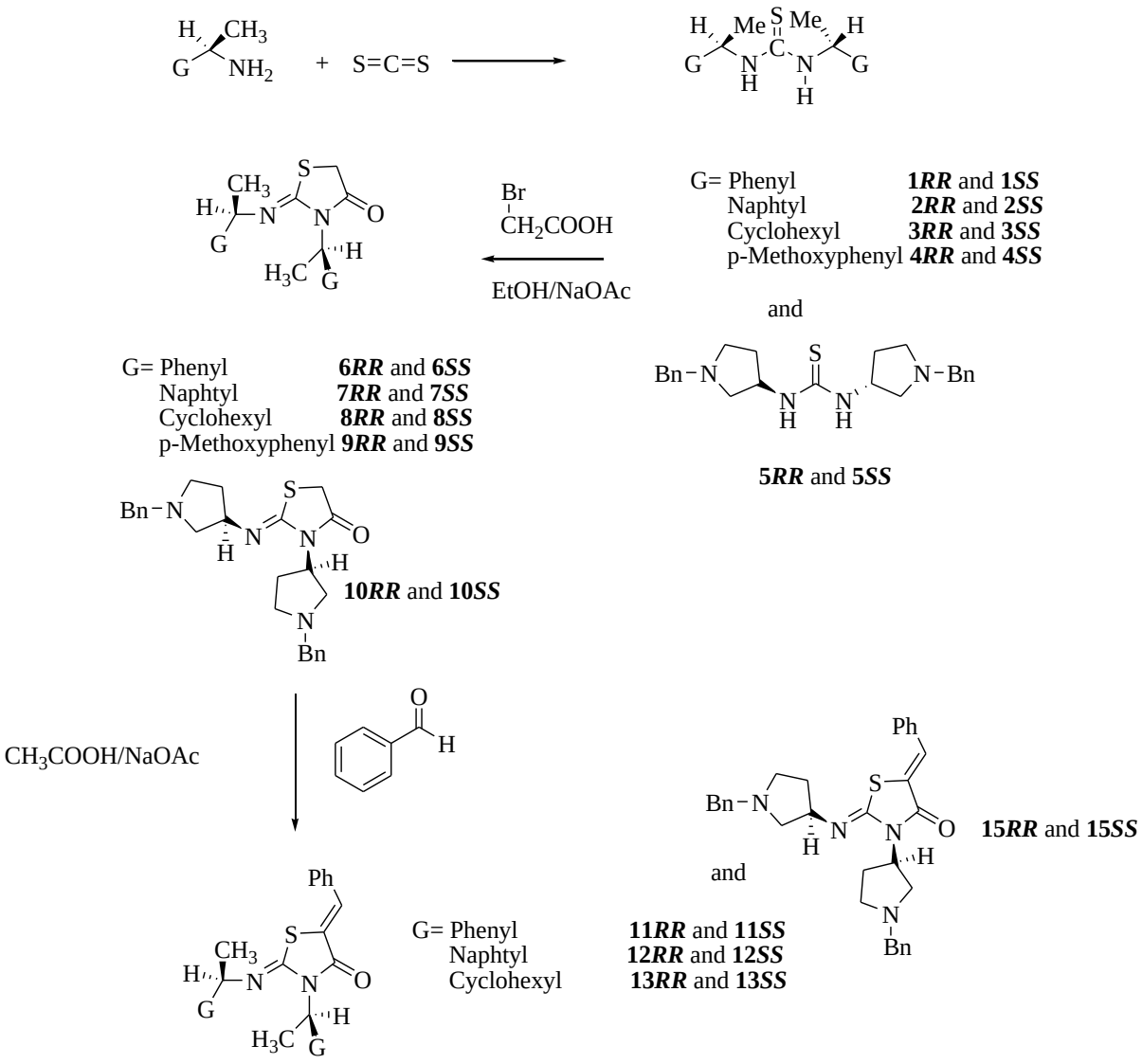


Figure 3.1. Synthesis of *N*,*N*'-bis-thioureas **1**-**5**, the axially chiral 2-iminothiazolidin-4-ones **6**-**10** and the corresponding 5-benzylidene-2-imino-thiazolidine-4ones **11**-**13** and **15**.

3.1.2. Conformational Analysis of Thioureas

Thioureas can in principle exist in four different conformations: ***EE***, ***EZ***, ***ZE*** and ***ZZ*** due to the partial double bond character of the C-N bond resulting from the thiourea resonance (Figure 3. **2**).

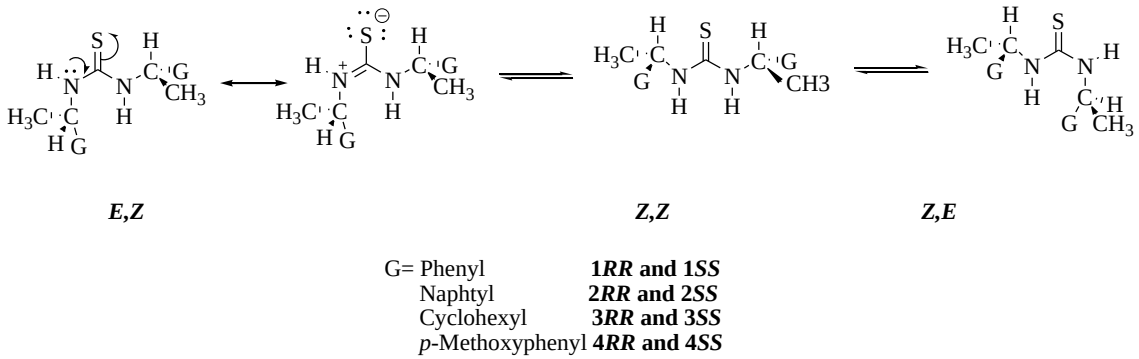


Figure 3. 2. Interconverting conformers of *N*,*N*-bis-thioureas.

X-ray analyses of the thioureas **2*RR***, **2*SS*, 4*RR*** and **4*SS*** showed that the molecules prefer to stay at ***Z*,*Z*** conformation in the solid state (Figure 3.3). The data obtained from crystal structures of compounds **2*RR***, **2*SS***, **4*RR*** and **4*SS*** are summarized in Table 3.1 and

Table 3.2. Room temperature (298 K) ^{1}H NMR of the thioureas on the other hand showed a broadening in all of their proton signals (Figure 3.4) in $CDCl_3$ solution. When ^{1}H NMR spectra were taken at 233 K, two different set of signals for each proton of the molecule were observed with equal intensities (Figure 3.4, Figure 3.5, Figure 3.6, Figure 3.7, Figure 3.8, Figure 3.9). This result indicated the presence of two different conformations of the molecule at low temperature and a rapid interconversion between them at room temperature. Variable temperature analyses of the spectra enabled us to determine the free energy of activation, $\Delta G^{\neq}$ values for the interconversions (Figure 3.4, Table 3.3). The results revealed a $\Delta G^{\neq}$ value of about 50 kJ/mole independent from the size of the G group in the molecule (Figure 3. **2Hata! Başvuru kaynağı bulunamadı.**, Table 3.3). A $\Delta G^{\neq}$ value of 53.5 kJ/mol (12.8 kcal/mol) has been determined previously by Rang *et. al.* for the compound **1*SS*** [81] where G=phenyl.

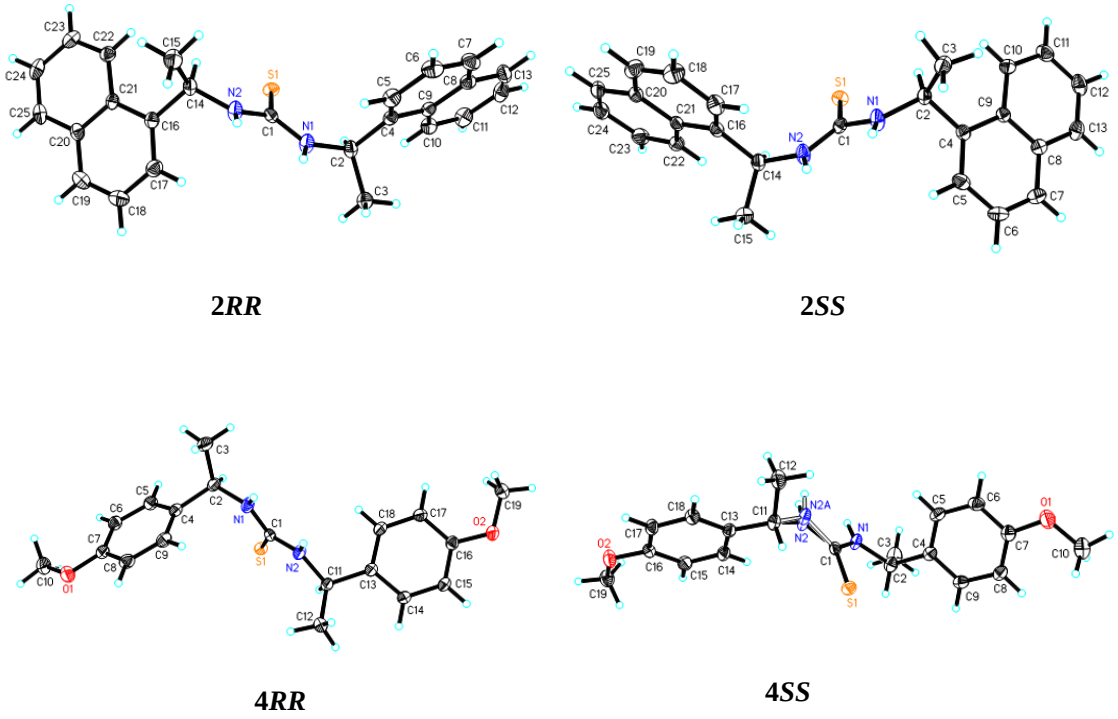


Figure 3.3. Crystal structures of compounds **2*RR***, **2*SS***, **4*RR*** and **4*SS*.**

Table 3.1. Data from cyrstal structures of compounds **2*RR*** and **2*SS*.**

	2RR	**2SS**
	Bond Distances (Å)	
S(1)-C(1)	1.7056	1.6998
C(1)-N(1)	1.3470	1.3450
C(1)-N(2)	1.3420	1.3388
N(1)-C(2)	1.4623	1.4574
N(2)-C(14)	1.4643	1.4586
C(2)-C(3)	1.5386	1.5348
C(14)-C(15)	1.5330	1.5259
C(2)-C(4)	1.5328	1.5257
C(14)-C(16)	1.5309	1.5255
	Bond Angles (^{o})	
S(1)-C(1)-N(1)	121.87	121.88
S(1)-C(1)-N(2)	123.33	123.55
N(1)-C(1)-N(2)	114.79	114.55
C(1)-N(1)-C(2)	126.45	126.31
C(1)-N(2)-C(14)	126.82	126.48
N(1)-C(2)-C(3)	108.13	108.05
N(2)-C(14)-C(15)	108.07	107.93
N(1)-C(2)-C(4)	112.90	112.92
N(2)-C(14)-C(16)	112.29	112.26
C(3)-C(2)-C(4)	110.45	110.60
C(15)-C(14)-C(16)	111.06	110.99
	Dihedral Angles (^{o})	
S(1)-C(1)-N(1)-C(2)	9.50	-9.69
S(1)- C(1)-N(2)-C(14)	4.70	-4.78
C(1)-N(1)-C(2)-C(3)	-142.56	142.63
C(1)-N(2)-C(14)-C(15)	-141.88	141.94
C(1)-N(1)-C(2)-C(4)	94.94	-94.72
C(1)-N(2)-C(14)-C(16)	95.29	-95.43
N(1)-C(2)-C(4)-C(5)	21.01	-21.09
N(2)-C(14)-C(16)-C(17)	19.51	-19.33

Table 3.2.Data from cyrstal structures of compounds ***4RR*** and ***4SS***.

	4RR	**4SS**
	Bond Distances (Å)	
S(1)-C(1)	1.6973	1.6955
C(1)-N(1)	1.3605	1.3839
C(1)-N(2)	1.3458	1.3430
N(1)-C(2)	1.4660	1.4667
N(2)-C(11)	1.4664	1.4760
C(2)-C(3)	1.5277	1.5290
C(11)-C(12)	1.5272	1.5280
C(2)-C(4)	1.5195	1.5170
C(11)-C(13)	1.5240	1.5210
C(7)-O(1)	1.3737	1.3708
C(16)-O(2)	1.3702	1.3669
O(1)-C(10)	1.4173	1.4170
O(2)-C(19)	1.4239	1.4246
	Bond Angles (^{o})	
S(1)-C(1)-N(1)	121.45	121.78
S(1)-C(1)-N(2)	123.89	123.96
N(1)-C(1)-N(2)	114.65	114.26
C(1)-N(1)-C(2)	124.14	122.99
C(1)-N(2)-C(11)	125.22	125.18
N(1)-C(2)-C(3)	107.11	106.23
N(2)-C(11)-C(12)	109.74	110.21
N(1)-C(2)-C(4)	113.44	113.83
N(2)-C(11)-C(13)	110.58	110.13
C(3)-C(2)-C(4)	110.42	110.70
C(12)-C(11)-C(13)	113.73	113.75
C(7)-O(1)-C(10)	117.77	117.73
C(16)-O(2)-C(19)	117.65	117.65
	Dihedral Angles (^{o})	
S(1)-C(1)-N(1)-C(2)	2.96	-2.92
S(1)- C(1)-N(2)-C(11)	0.70	1.3
C(1)-N(1)-C(2)-C(3)	-162.02	162.60
C(1)-N(2)-C(11)-C(12)	-116.02	114.30
C(1)-N(1)-C(2)-C(4)	75.10	-75.32
C(1)-N(2)-C(11)-C(13)	117.7	-119.4
N(1)-C(2)-C(4)-C(5)	-153.75	154.51
N(2)-C(11)-C(13)-C(18)	-28.40	28.2

Table 3.3. Selected Thermodynamic and Kinetic Parameters for Compounds **2*SS***, **3*SS*** and **4*SS*** Determined by ^{1}HNMR in $CDCI_3$ (* at 233 K and **at 243 K).

Compd.	**Type of proton**	**Δv_0**	**T_c (K)**	**k_c (s^{-1})**	**$\Delta G^{\neq}_c$ (kJ/mol)**
2*SS*	CH	60.0*	258	131.0	52.4
	CH_3	80.0*	258	177.6	52.0
3*SS*	CH	479.2**	273	1064	50.8
	NH	201.6**	263	447.6	50.7
4*SS*	CH	87.6*	273	194.5	52.6
	OCH_3	26.0*	253	58.6	53.0
	CH_3	27.6*	253	61.3	52.9

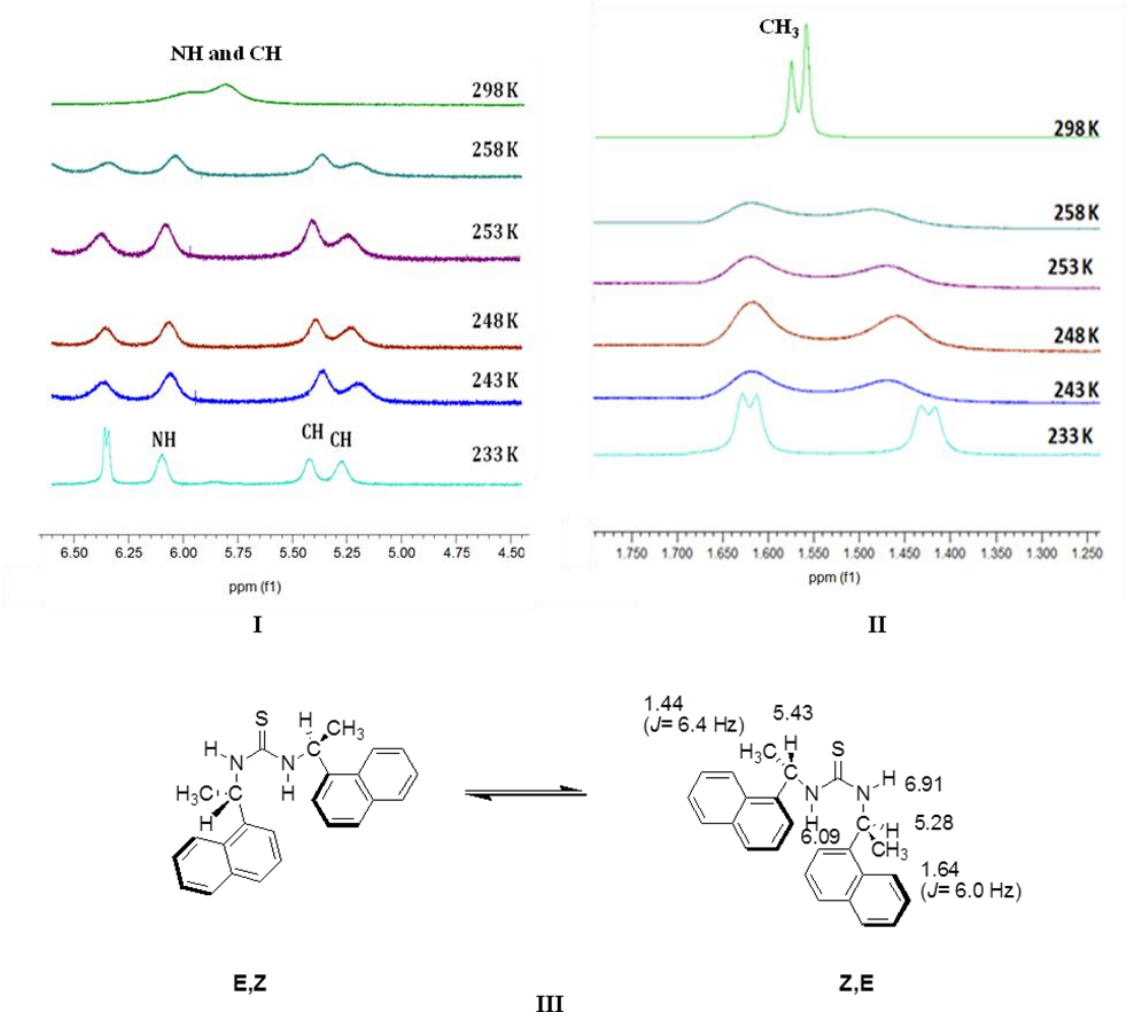


Figure 3.4. Partial ^{1}H NMR spectra of compound **2*SS*** ($CDCl_3$,400 MHz) showing the temperature dependance of the NH, CH **(I)** and the CH_3 **(II)** proton signals**.** Assignment of ^{1}H NMR shifts of compound **2*SS*** at 233 K are given with the coupling constants (Hz) in parenthesis **(III).**

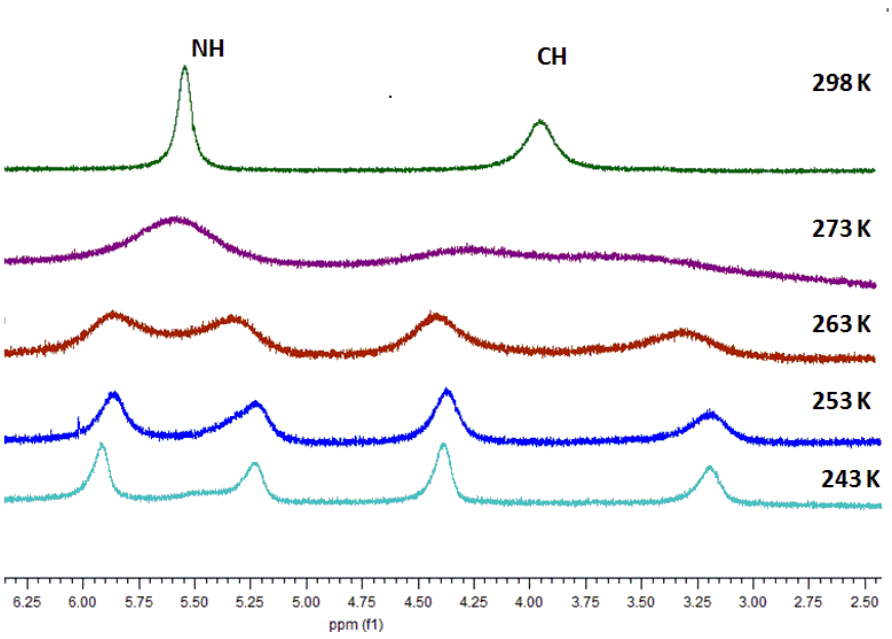


Figure 3.5. Partial ^{1}H NMR spectrum of compound **3*SS*** ($CDCl_3$) showing the temperature dependance of the NH and CH protons.

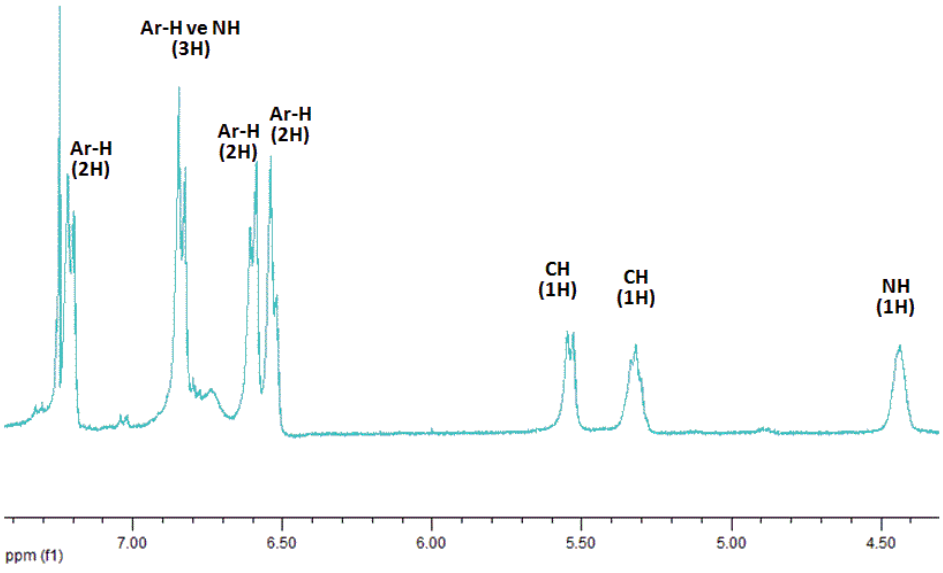


Figure 3.6. Partial ^{1}H NMR spectrum of compound **4*SS*** ($CDCl_3$) showing the aromatic, NH and CH protons.

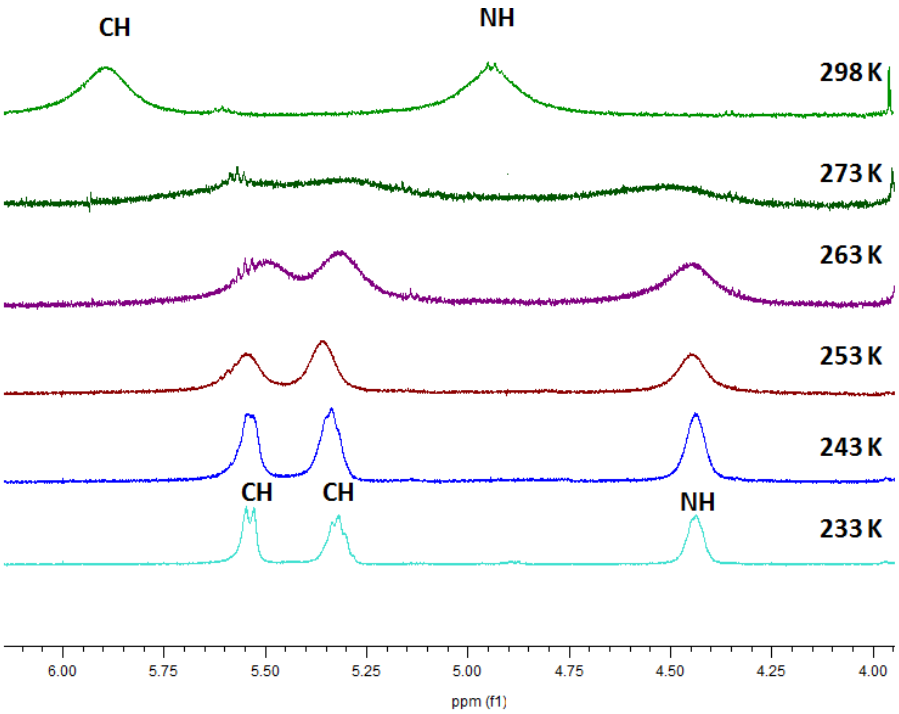


Figure 3.7. Partial ^{1}H NMR spectrum of compound ***4SS*** ($CDCl_3$) showing the temperature dependance of the NH and CH protons.

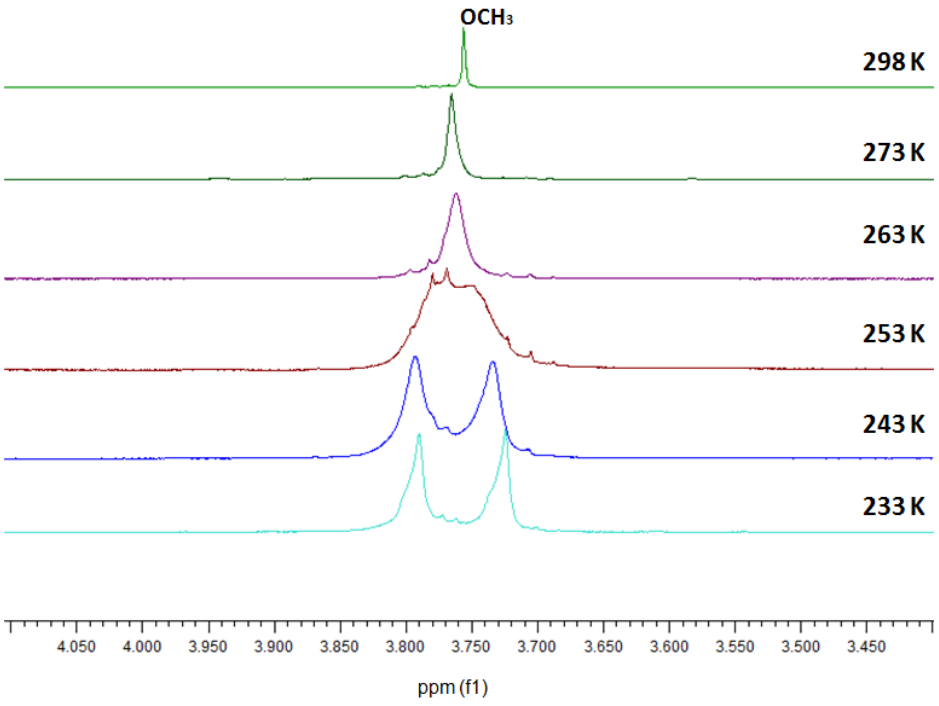


Figure 3.8. Partial ^{1}H NMR spectrum of compound ***4SS*** ($CDCl_3$) showing the temperature dependance of the OCH_3 protons.

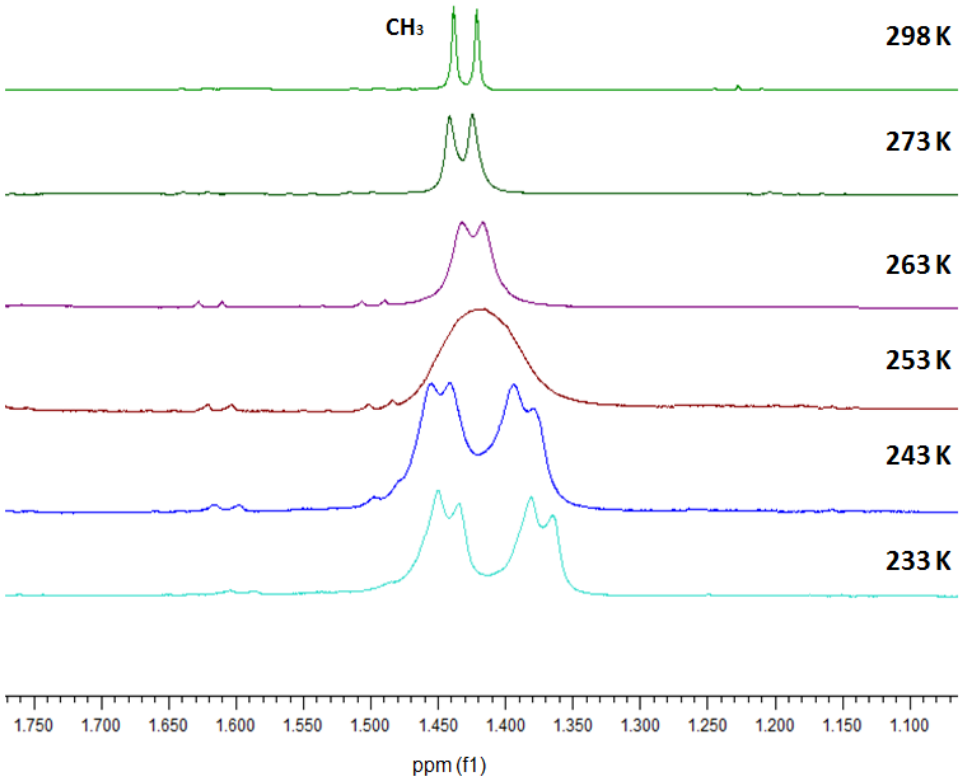


Figure 3.9. Partial ^{1}H NMR spectrum of compound **4*SS*** ($CDCl_3$) showing the temperature dependance of the CH_3 protons.

3.1.3. 2-Imino-Thiazolidine-4-ones and Their 5-Benzylidene Derivatives

There are only few atropisomeric axially chiral molecules resulting from rotations around Csp^2-Csp^3 single bonds in literature [82]. Among compounds showing restricted rotations about a Csp^2-Csp^3 single bond, conformational analysis of N-phenylethyl substituted thiazoline-2-thiones [83] and rhodanines [84] showed that the molecules are axially chiral, however only with small barriers to rotation. In addition, the molecules were found to be oriented such that N_3–methine proton (the proton on the methine carbon which is bonded to N_3 of the heterocylic ring) was pointing towards the larger exocylic group of the heterocyclic ring. The corresponding conformation has been called as the *anti* conformation [84]. The ^{1}H NMR of 6-10*RR* and *SS* studied in this work showed the presence of only one rotamer at ambient temperature and based on the earlier work done on structurally similar compounds [84], we assigned an *anti* confirmation to 6-10. This assignment has been supported by the NOESY experiments as will be explained further in the text.

Compounds 6-10 have an amidine linkage in their structures. For this reason there exists a resonance structure (Figure 3.10) whose contribution increases the electron density in the vicinity of the group bonded to the imino nitrogen ($C=N_b$). Accordingly in NMR, these groups are expected to appear more shielded with respect to the groups attached to the amido nitrogen (N_a). ^{1}H NMR of the compounds supports this expectation (Figure 3.11).

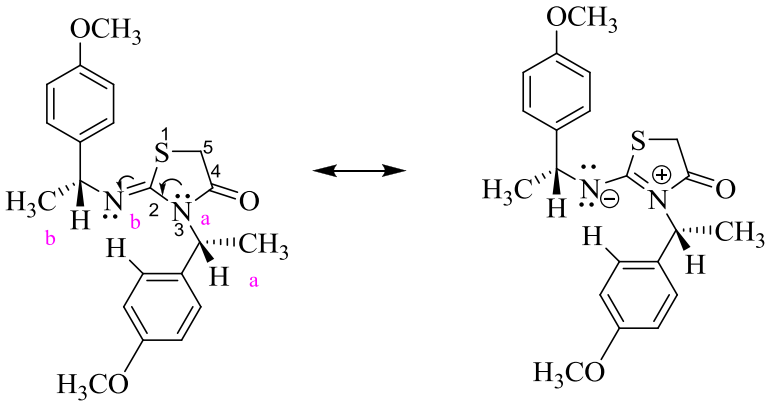


Figure 3.10. Resonance structures of **9*RR*** showing a higher electron density on the imino nitrogen.

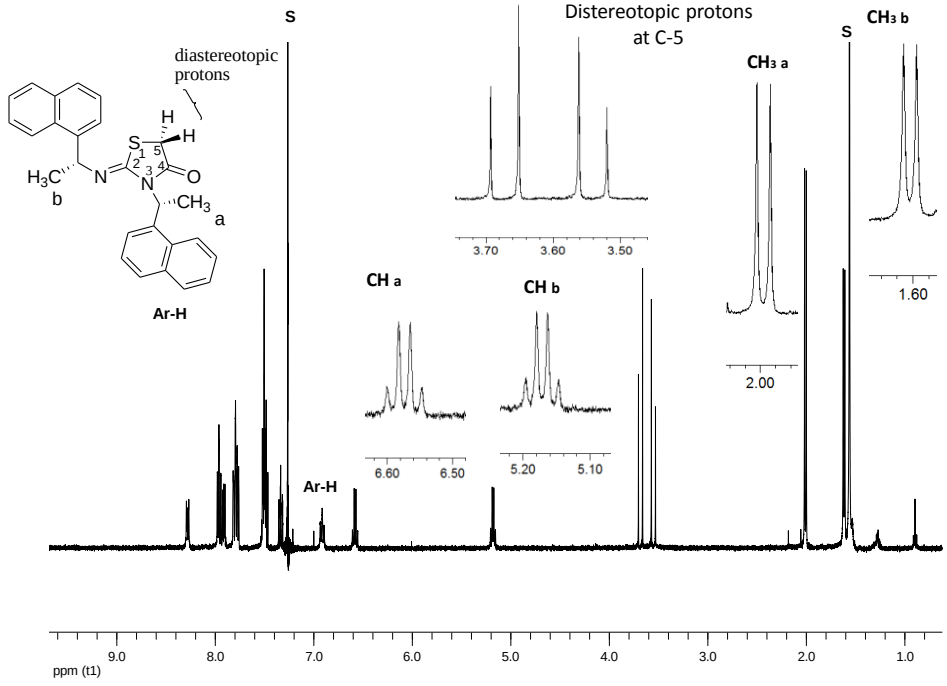


Figure 3.11. The 400 MHz ^{1}H NMR spectrum of compound **7*RR*** in $CDCl_3$ showing AB type splitting for diastereotopic methylene protons at C-5.

The NOESY spectrum taken for **9*RR*,** did not show any cross peak between the protons of the two methoxyphenyl rings of the molecule but did show a cross peak between the methine proton bonded to the imino nitrogen (H_b) and a hydrogen phenyl

bonded to N_3 through a methine linkage (Figure 3.12). This observation enabled us to draw the conformation shown in Figure 3.12.

Additionally, the ^{1}H NMR spectra of the compounds **6*RR***, **6*SS***, **7*RR***, **7*SS***, and **9*RR***, **9*SS*** have shown that the diastereotopic protons at C-5 gave AB type splitting at around 3.60 ppm with coupling constants of 16.8 Hz (J_{AB} =16.8 Hz) regardless of the attached group G (Figure 3.1). On the other hand, the compounds **8*RR***, **8*SS***, **10*RR*** and **10*SS*** gave a singlet for these C-5 protons. The HPLC and the polarimetric results are summarized in Table 3.4.

Table 3.4. The polarimetric and the HPLC data for compounds **6-10** and **11-15**.

Compd.	**$[\alpha]^{26}_{360}$**	**Stationary phase**	**Mobile phase**	**Flow rate (ml/min)**	**Retetion time (min.)**
6*RR*	(+) 2597.5^o	Chiralpak	Hexane:Ethanol	0.6	20.14
6*SS*	(-) 2597.5^o	IC	(99:1)		16.51
7*RR*	(+)6050.9^o	Chiralpak	Hexane:Ethanol	0.6	14.82
7*SS*	(-)6050.9^o	IC	(95:5)		12.66
8*RR*	(-)744.9^o	Chiralpak	Hexane:Ethanol	0.6	6.48
8*SS*	(+)744.9^o	IB	(99:1)		6.30
9*RR*	(+)1180.6^o	Chiralpak	Hexane:Ethanol	0.6	34.91
9*SS*	(-)1180.6^o	IC	(95:5)		23.72
10*RR*	-*	Chiralpak	Hexane:Ethanol	0.6	25.09
10*SS*		IC	(95:5)		22.99
11*RR*	(+)444.4^o	Chiralpak	Hexane:Ethanol	0.8	12.76
11*SS*	(-)488.9 ^{o}	IA	(99:1)		9.94
12*RR*	(-)177.8^o	Chiralpak	Hexane:Ethanol	0.8	19.35
12*SS*	(+)133.3^o	AD-H	(90:10)		39.08
13*RR*	(+)88.9 ^{o}	Chiralpak	Hexane:Ethanol	0.8	8.33
13*SS*	(-)88.9 ^{o}	IB	(99:1)		7.98

Table 3.4. The polarimetric and the HPLC data for compounds **6-10** and **11-15**.

14*R*	(+)222.2^{o}	Chiralpak	Hexane:Ethanol	1.0	40.21
14*S*	(-)222.2^{o}	IC	(90:10)		55.50
15*RR*	-*	Chiralpak	Hexane:Ethanol	0.6	12.33
15*SS*		IC	(95:5)		14.42

*measurements could not be performed due to the color of the compound (even in lower concentration).

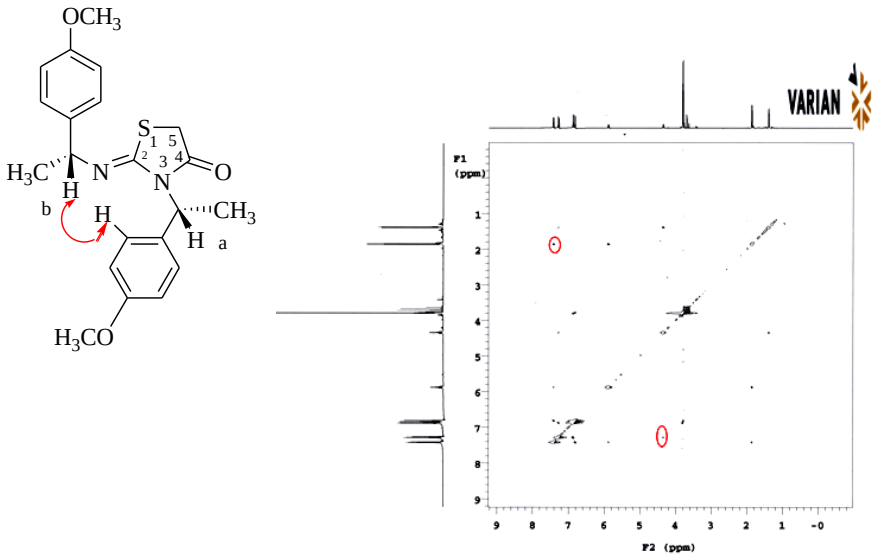
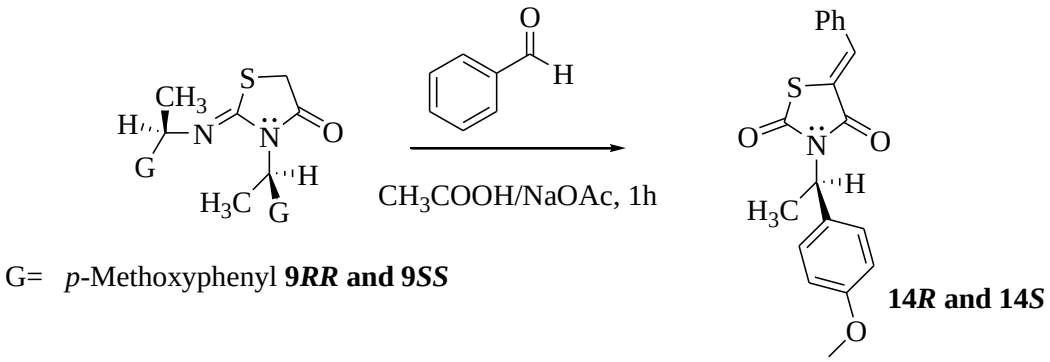


Figure 3.12. The NOESY spectrum of **9*RR*** in $CDCl_3$ showed a crosspeak between the methine proton bonded to the imino nitrogen (H_b) and the phenyl hydrogen bonded to N_3 through a methine linkage.

The 5-benzylidene derivatives **11-15** were synthesized from 2-imino thiazolidine-4-ones by reaction with benzaldehyde in the presence of sodium acetate [10]. The disapperance of CH_2 protons at C-5 of starting compounds (**6-10**) and the appearance of =C**H**Ph proton as a singlet at about δ 7.70 ppm in the ^{1}H NMR spectra of compounds **11-15** proved the formation of the benzylidene bond on the fifth position of the heterocyclic ring. All the 2-imino thiazolidine-4-ones except the 4-methoxyphenyl derivative of the

series have been found to give the corresponding 2-imino-5-benzylidene derivatives. The 4-methoxyphenyl derivatives **9*RR*** and **9*SS*** were found to give the 5-benzylidene-thiazolidine-2,4-diones **14*R*** and **14*S*** (Figure 3.13). For compounds **11-15** ***E*** or ***Z*** conformation steaming from the C-C double bond at C-5 is possible. But the literature ^{1}H NMR and X-ray studies have revealed that these compounds have preferred to be on ***Z*** configuration [85, 86].



G= *p*-Methoxyphenyl **9*RR* and 9*SS***

14*R* and 14*S*

Figure 3.13. Synthesis of 5-benzylidene-thiazolidine-2,4-diones **14*R*** and **14*S*** starting from the 2-imino-thiazolidine-4-ones **9*RR*** and **9*SS*.**

3.2. 2,4-Oxazolidinediones [87]

3.2.1. Asymmetric Synthesis of 5-Methyl-3-aryloxazolidine-2,4-diones

The synthesis of 5-methyl-3-aryloxazolidine-2,4-diones starting with *S*-ethyl lactate were carried out by our research group before. However we found out that the chiral center at C5 of the oxazolidinone ring coming from the lactate has been racemized during the synthesis in the presence of sodium metal [88]. Therefore enantiomerically pure *R*- and *S*-ethyl lactate was reacted with the aryl isocyanates under reflux conditions in xylene without any sodium metal, and then acid catalyzed cyclization of the formed carbamate yielded the enantiomerically pure oxazolidindiones (Figure 3.14).

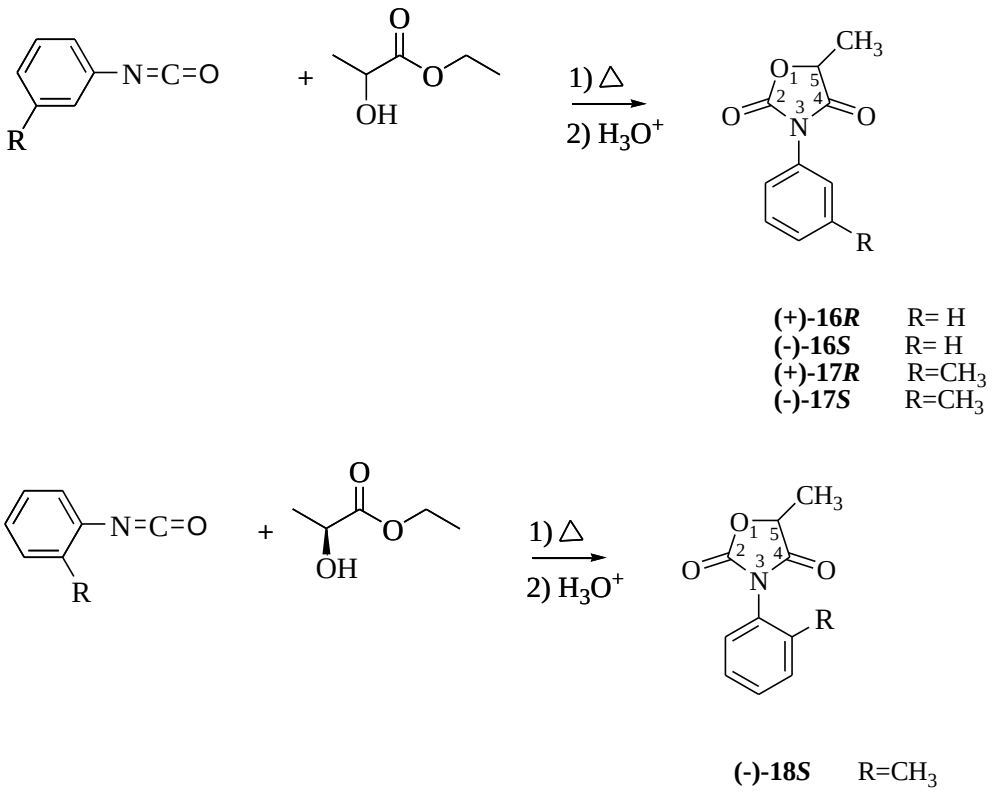


Figure 3.14. Synthesis of 5-Methyl-3-aryloxazolidine-2,4-diones.

In order to determine the enantiomeric purities of chiral compounds, optically active auxiliary compounds were used. In this method, the single enantiomer auxiliary is expected to associate with each enantiomer and form two ^{1}H NMR distinguishable complexes [89]. Thus if the oxazolidinedione is racemic, the doubled signals will be observed as at the ^{1}H NMR spectrum. On the other hand if it is enantiomerically pure, only one set of signals will be observed. The optical purities of the synthesized oxazolidinediones were proved by ^{1}H NMR in the presence of the optically active auxiliary compound (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*R*)-TFAE) and by HPLC on an optically active stationary phase (Figure 3.15). The observation of only one set of signals in NMR in the presence of (*R*)-TFAE and one chromatographic peak in the HPLC chromatogram (Figure 3.15) have been taken as proofs for the existence of **16** and **17** as single enantiomers. The enantiomeric purity of axially chiral compound **18*S*** was proved on Chiralpak IB by HPLC (Eluting solvent: Hexane:Ethanol (99:1), flow rate: 0.7 mL/min, Retention time: 67.22 min.).

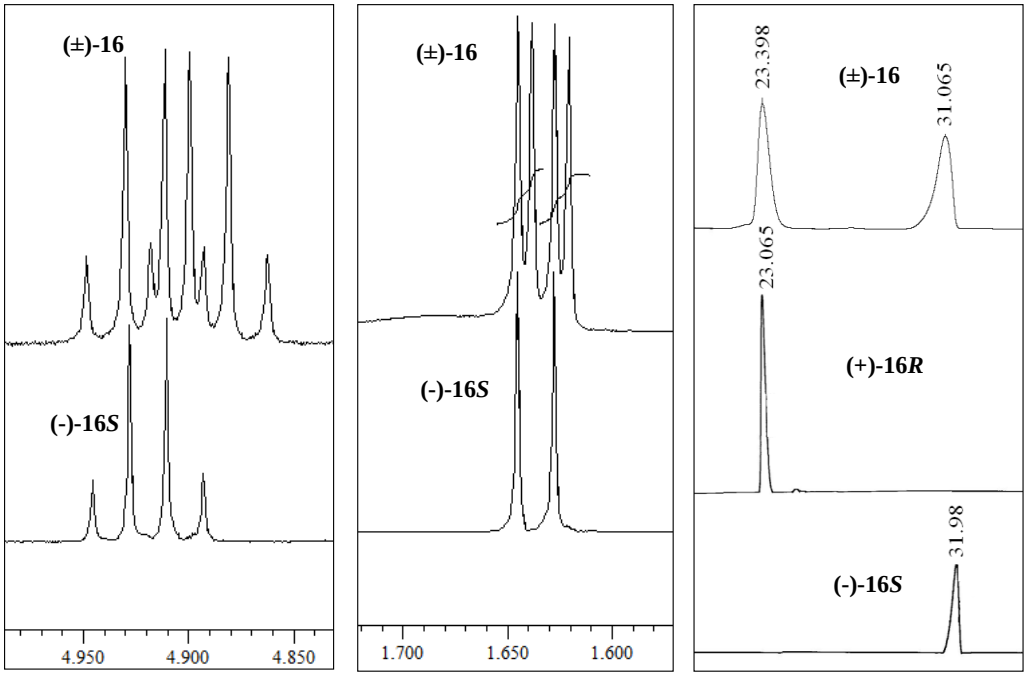


Figure 3.15. Partial ^{1}H NMR spectrum of compounds **(±) 16** and **(-)-16*S*** showing quartets for CH protons at C-5 **(I)** and the doublets for methyl groups at C-5 **(II)** in the presence of six equivalent of chiral auxiliary (*R*)-TFAE in $CDCl_3$. **(III)** The HPLC chromotograms of compounds **(±)-16, (+)-16*R*** and **(-)-16*S*** on Chiralpak IC. Retetion times (min) are writen the on top of the chromatographic peaks. Eluting solvent: Hexane:Ethanol (95:5), flow rate: 0.8 mL/min.

3.3. Chiral Hemiaminals from Chiral 2-imino-thiazolidine-4-ones

3.3.1. Synthesis of Chiral Hemiaminals

Chiral hemiaminals **19-22** were synthesized from the corresponding chiral 2-iminothiazolidine-4-ones **6-9** by $LiAlH_4$ reductions diastereoselectively in THF at room temperature and they were found to convert to chiral thiazol-2-imines **23-26** with time (Figure 3.16).

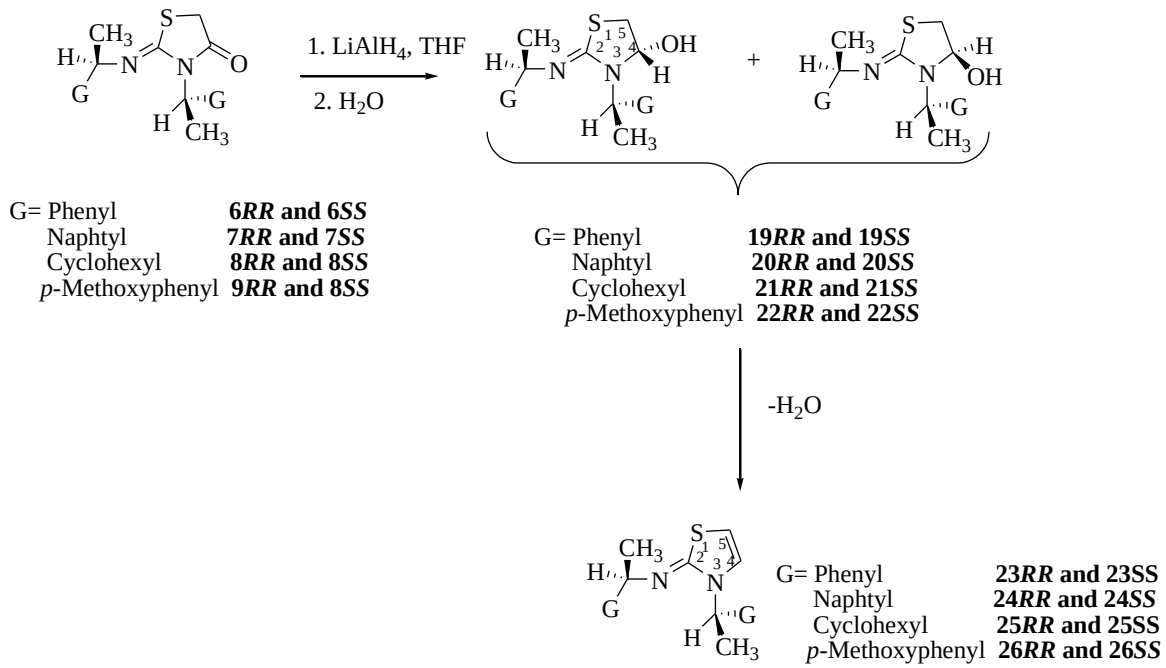


Figure 3.16. Synthesis of chiral hemiaminal derivatives and their elimination products.

The ^{1}H NMR spectra of hemiaminals **19-22** showed the formation of major and minor isomers with a 3:1 ratio. The isomers of the hemiaminal **19*RR*** have been identified based on the observation of a doublet for H_e proton at C-4 (at 5.03 and 5.50 ppm for the major and the minor isomers respectively) coupling with H_c at C-5 ($^3J_{HcHe}$= 4.8 Hz) which is *cis* to it however not coupling with H_d which is *trans* to it. ($^3J_{HdHe}$=~0 Hz) (Figure 3.17). The *cis-trans* assignment has been done based on the ^{1}H NMR spectra of the *trans* vicinal dibromides obtained from **23*SS***, as will be explained further in the text. The methylene protons at C-5 H_c and H_d gave an AB type splitting (at δ_A=3.17 and δ_B=3.01 ppm for the major and at δ_A=3.32 and δ_B=3.03 ppm for the minor isomers respectively) having a geminal coupling between H_c and H_d ($^2J_{HcHd}$=11.2 Hz) and a vicinal coupling between H_c and H_e ($^3J_{HcHe}$=4.8 Hz) (Figure 3.17).

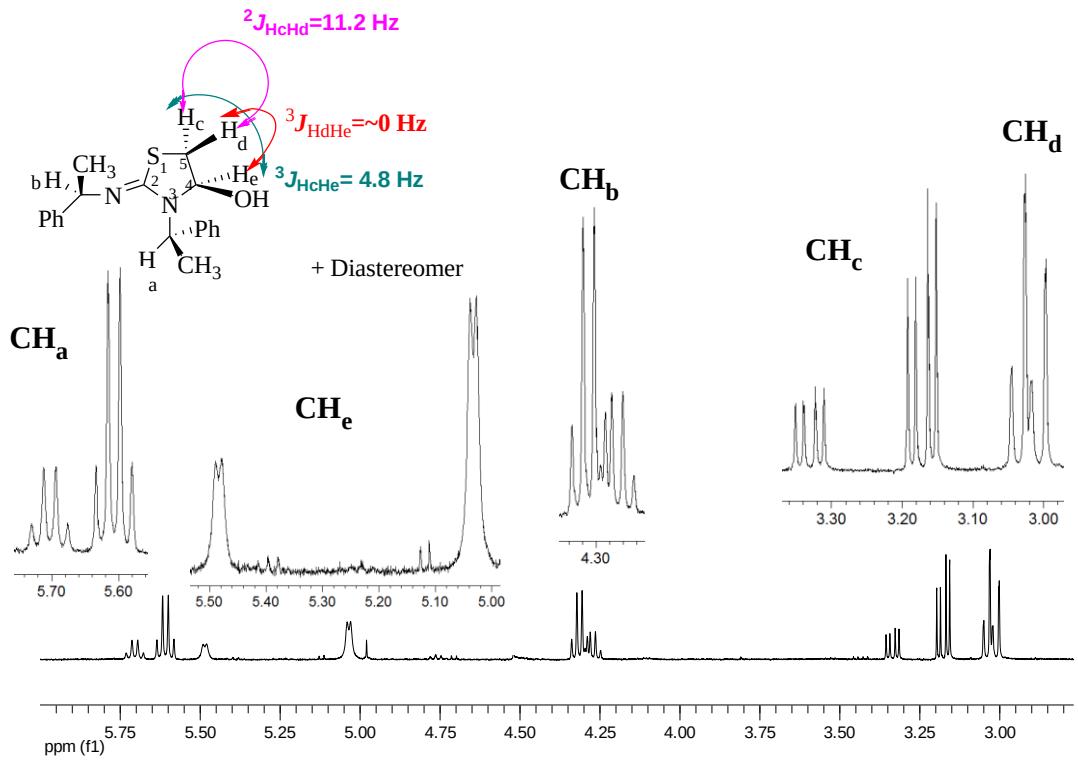


Figure 3.17. Partial ^{1}H NMR spectrum of hemiaminal **19*RR***.

A new chiral center on C-4 is formed from the reaction of 2-imino-thiazolidine-4-ones with $LiAlH_4$. The ^{1}H NMR signal of H_e bonded to C-4 of the major diastereomers were found to appear more shielded than their minor counterparts for **19*RR***, **20*RR***, and **22*RR*** but not for **21*RR***. The former three compounds carry an aromatic group G, bonded to the methine carbon, whereas the latter has a cyclohexyl group on CH (Figure 3.18). The aromatic groups apparently have a shielding effect on the H_e proton signal. This in turn gave a clue about the configuration of the C4 carbon atom. Previously, the X-ray analysis of 3-(S)-(1-Phenylethyl)-5-methylrhodanines revealed that the 1-phenylethyl group is oriented so that the Ph-C-Me angle is approximately bisected by the rhodanine plane with the methine proton pointing towards the more bulky exocyclic group [84]. Therefore for the hemiaminal obtained from the compound **19*RR***, the major isomer's C-4 configuration was assigned as ***R*** and that of the minor one as ***S*** (Figure 3.19). The diastereomeric ratios of the hemiaminals **19*RR*-22*RR*** and **19*SS*-22*SS*** were all found as 3:1 (Figure 3.18).

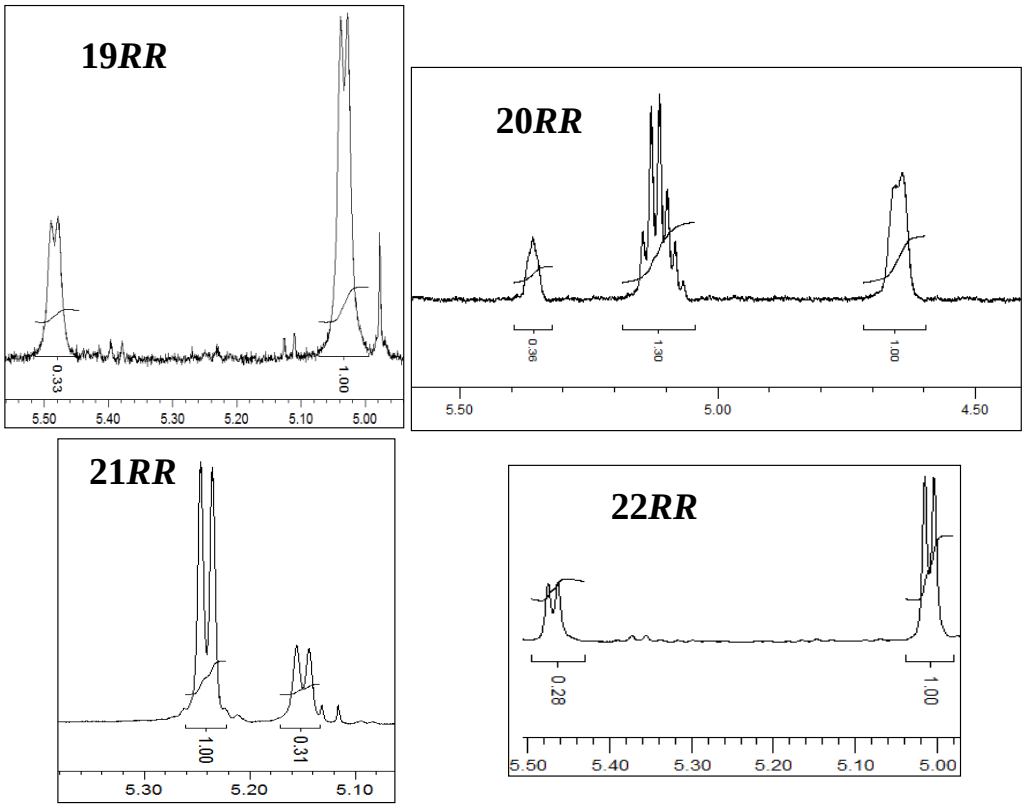


Figure 3.18. ^{1}H NMR signals of the H_e protons on C4 for the major and the minor diastereomers of the hemiaminals **19*RR***, **20*RR***, **21*RR*** and **22*RR*** (dr=3:1).

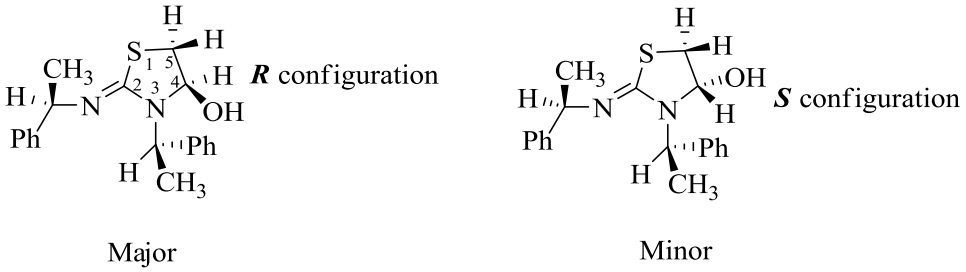


Figure 3.19. The major and the minor diastereomers of the compound **19*RR***.

3.3.2. Transformation of the Chiral Hemiaminals to Single Enantiomer Thiazol-2-Imine Derivatives

The chiral hemiaminal derivatives can be transformed into thiazol-2-imine *via* an elimination of a water molecule (Figure 3.16). It was observed that chiral hemiaminals **19-**

22 underwent elimination of water even in solvent free media. First, the formation of the elimination product **23*RR*** of chiral hemiaminal **19*RR*** was examined by ^{1}H NMR analysis. The peaks of H_e on C-4 at 5.48-5.03 ppm and those of H_c and H_d on the C-5H at 3.33-3.01 ppm of the major and minor isomers of **19*RR*** disappered, whereas the peaks of the proton on C-4 at 6.46 ppm and of proton on C-5 at 5.76 ppm of **23*RR*** appeared as doublets with time (Figure 3.20). For the transformation of compound **19*RR*** to **23*RR***, the rate constant was found as $6x10^{-5}$ s^{-1}, $\Delta G^{\neq}$ as 97.1 kJ/mol and the half life as 3.20 h in $CDCl_3$ (Figure 3.21). The kinetics of the process was found to be solvent dependent. The rate constant was found as $2x10^{-5}$ s^{-1}, $\Delta G^{\neq}$ as 99.8 kJ/mol and the half life as 9.63 h in C_6D_6. The transformation of compound **19*RR*** to **23*RR*** has been shown in Figure 3.20. The elimination kinetics for compounds **19*RR***, **20*RR***, **21*RR***, **22*SS*** followed similarly by ^{1}H NMR with time. The results for the transformation kinetics of compounds **19-22** to their elimination products are summarized in Table 3.5.

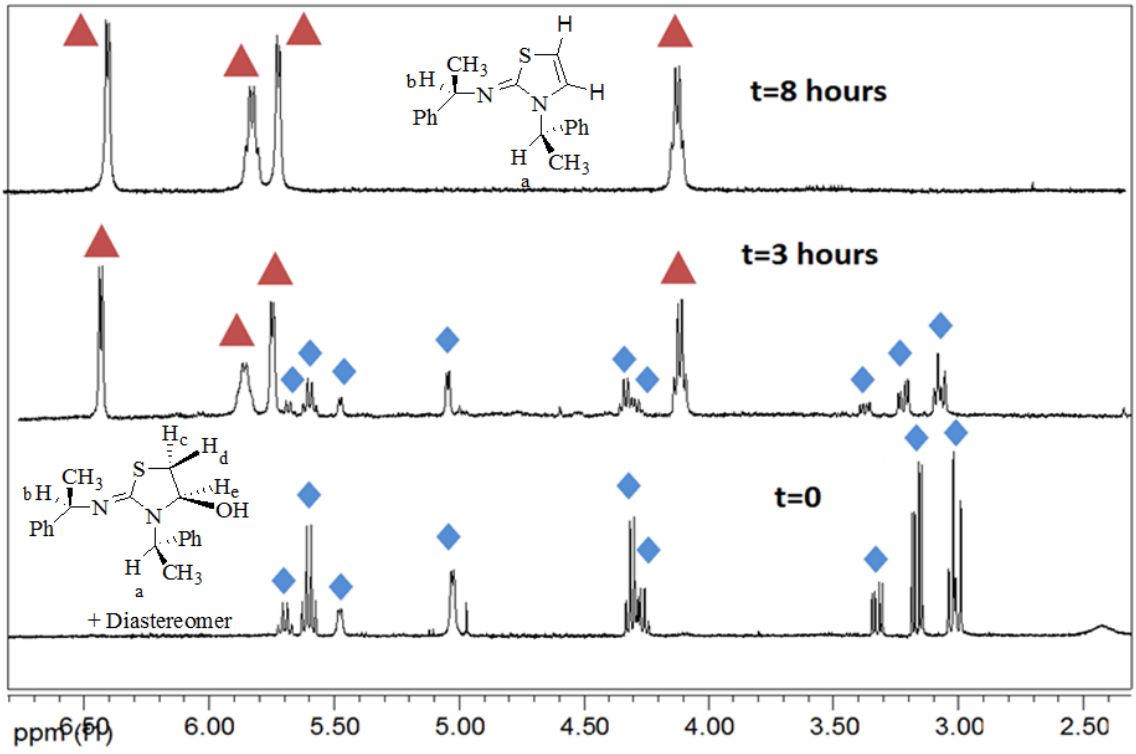


Figure 3.20. Partial ^{1}H NMR spectrum of hemiaminal **19*RR*** showing its transformation to thiazol-2-imine **23*RR*** in $CDCl_3$ with time. (♦) = hemiaminal and (▲) = thiazol-2-imine.

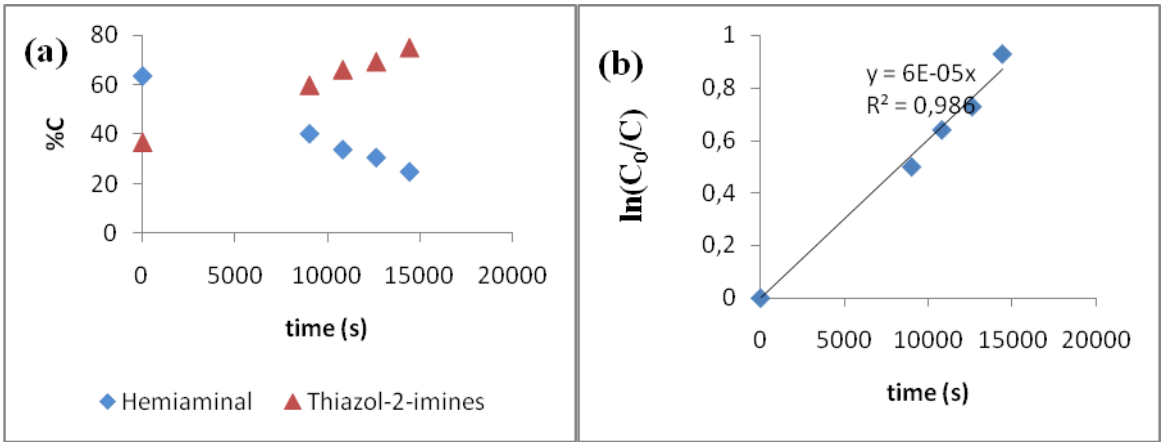


Figure 3.21. **(a)** The % consumption of compound **19*RR*** and the formation of compound **23*RR*** in $CDCl_3$. **(b)** the plot of ln (C_0/C) versus time. C_0/C the ratio of the initial amount of hemiaminal consumption to the elimination product.

Table 3.5. Experimental first order rate constants (k), $\Delta G^{\neq}$ and $t_{1/2}$ for the transformation of chiral hemiaminals to chiral thiazol-2-imines.

Compounds	**Solvent**	**k (s^{-1})**	**$\Delta G^{\neq}$ (kJ/mol)**	**$t_{1/2}$ (hour)**
19*RR*	$CDCl_3$	$6x10^{-5}$	97.1	3.20
	C_6D_6	$2x10^{-5}$	99.8	9.63
20*RR*	$CDCl_3$	$6x10^{-6}$	102.8	32.10
	C_6D_6	$2x10^{-6}$	105.5	96.27
21*RR*	$CDCl_3$	$5x10^{-5}$	97.5	3.85
	C_6D_6	$2x10^{-5}$	99.8	9.63
22*SS*	$CDCl_3$	$5x10^{-5}$	97.5	3.85
	C_6D_6	$3x10^{-5}$	99.1	6.42

The stabilities of compounds **19*RR*** and **20*RR*** in solvent free media were also investigated. The solid state samples taken at time intervals have been dissolved in the NMR solvent and the spectrum was taken immediatelly. The rate constants were found as

$2x10^{-7}$ s^{-1} for **19*RR*** and $3x10^{-8}$ s^{-1} for **20*RR*** (Figure 3.22). The results are summarized in Table 3.6.

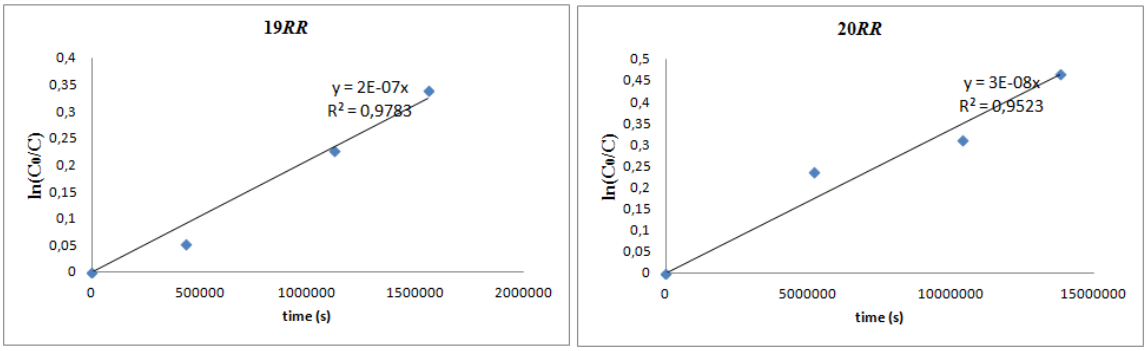


Figure 3.22. The plot of ln (C_0/C) versus time for compound **19*RR*** and **20*RR*** in solvent free media.

Table 3.6. Experimental first order rate constants (k), $\Delta G^{\neq}$ and $t_{1/2}$ for chiral hemiaminals **19*RR*** and **20*RR*** during their transformation to chiral thiazol-2-imines in solvent free media.

Compounds	**Solvent**	**k (s^{-1})**	**$\Delta G^{\neq}$ (kJ/mol)**	**$t_{1/2}$ (day)**
19*RR*	$CDCl_3$	$2x10^{-7}$	111.2	40.1
20*RR*	$CDCl_3$	$3x10^{-8}$	115.9	267.4

The polarimetric measurments done for compounds **23-26** are shown in Table 3.7.

Table 3.7. The polarimetric data for compounds **23-26**.

Compound	$[\alpha]^{26}_{360}$
23*RR*	+1111.11
23*SS*	-1200.00
24*RR*	+1555.56
24*SS*	-1644.44

Table 3.7. The polarimetric data for compounds **23-26**.

25*RR*	+88.89
25*SS*	-88.89
26*RR*	+666.67
26*SS*	-755.56

3.4. Bromination of Compound 23*SS*

3.4.1. Synthesis of Compound 27

The double bond of the chiral compound thiazol-2-imine **23*SS*** was brominated as shown in Figure 3.23.

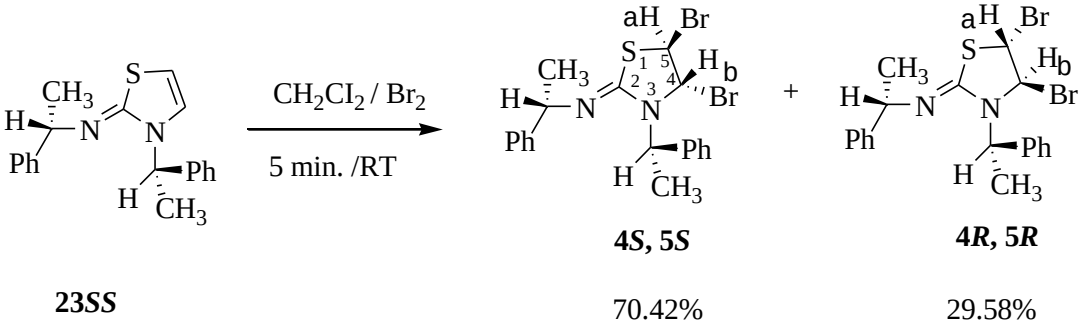


Figure 3.23. Bromination of compound **23*SS***.

The addition mechanism of bromine to alkene is essentially related with the formation of a bromonium ion and the formation of a *trans*-addition product by *anti*-attack of bromide to a cyclic ion [90]. From the reaction of compound **23*SS*** with Br_2, compound **27** was obtained as a diastereomeric pair as expected (Figure 3.23). The ratio of diastereomers for compound **27** was found as 2.4:1 (Figure 3.24). Due to the presence of $PhCHCH_3$ group on N_3 of the thiazol ring, the bromide ion is tought to prefer to attack from the opposite site of CH_3 group to form the major product and the minor has been

formed by the attack from the same site as CH_3. The vicinal protons on the newly forming chiral centers on C-4 and C-5 appeared as singlets and the protons did not couple with each other. According to Karplus if the dihedral angle is about 90°, ^3J coupling is in the range of 0-2 Hz. This points to the fact that dihedral angle between the H_a and H_b (Figure 3.23) is close to 90° which points to a *trans* orientation. In this way, it was shown that there exists no coupling between the *trans* protons of the 5-membered heterocyclic ring. Also, due to the shielding effect of the phenyl group, the C-4 proton of the major isomer (which is on the same site with the phenyl group) appeared at a higher field than the C4-H of the minor isomer (Figure 3.24).

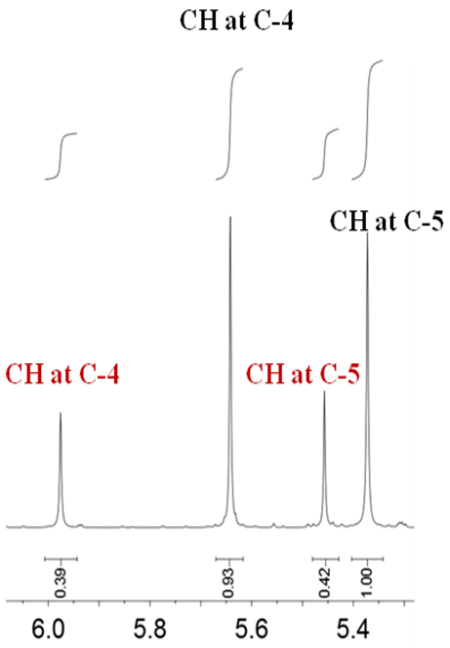
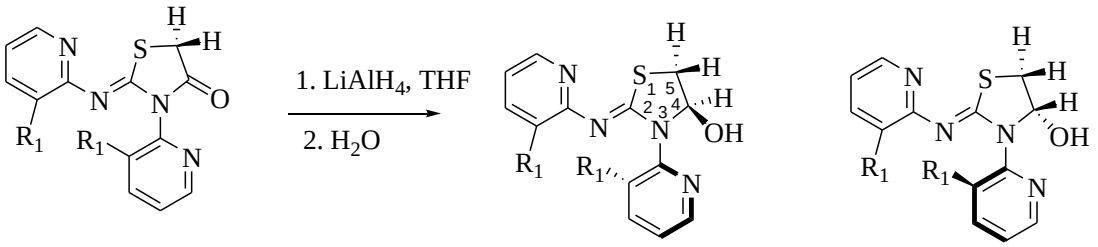


Figure 3.24. Partial ^{1}H NMR spectrum of the compound **27** showing the diastereoselectivity on C-4 and C-5 protons.

3.5. Stable Hemiaminals from Axially Chiral Pyridine Compounds

3.5.1. Synthesis of Stable Hemiaminals from Axially Chiral Pyridine Compounds

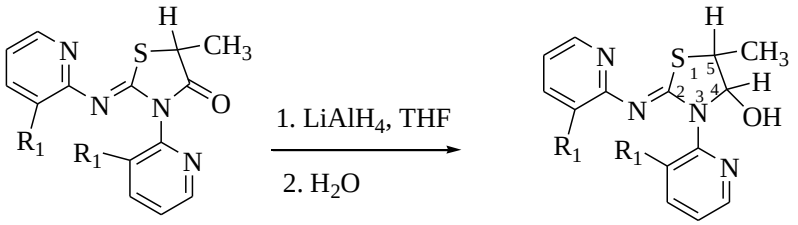
As a part of this study, we synthesized a series of stable 3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (**32-33**) and 5-methyl-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (**34-35**) derivatives (hemiaminals) regioselectively from 2-iminothiazolidin-4-one derivatives using $LiAlH_4$ (Figure 3.25).



Compound **28**: R_1=H
Compound **29**: R_1=CH_3

Compound **32**: R_1=H
Compound **33**: R_1=CH_3

and



Compound **30**: R_1=H
Compound **31**: R_1=CH_3

Compound **34**: R_1=H
Compound **35**: R_1=CH_3

Figure 3.25. Synthesis of stable hemiaminals from pyridine compounds.

The hemiaminals **32-35** obtained from axially chiral pyridine compounds [11] did not undergo an elimination reaction to form the corresponding thiazole-2-imines. The formation of an intramolecular hydrogen bond between the N_3 pyridine nitrogen and the hemiaminal OH (Figure 3.26) has been deduced from ^{1}H NMR where the OH signal was observed to shift to more down field (from 2.43 ppm to 6.22 ppm). The *RM* and *SP*

enantiomeric pair of compound **33** has been isolated by crystallization and the enantiomeric ratio has been determined as 1:1 by ^{1}H NMR for in the presence of chiral auxiliary (*R*)-TFAE (Figure 3.27). By the 2D-NOESY experiment (Figure 3.26), the OH group was found to prefer to be on the same side with the N_3 pyridine nitrogen probably because of the possibility for an intramolecular H-bond formation. As a matter of fact, the OH signal was shifted towards more down field in ^{1}HNMR taken in $CDCl_3$ (Figure 3.27).

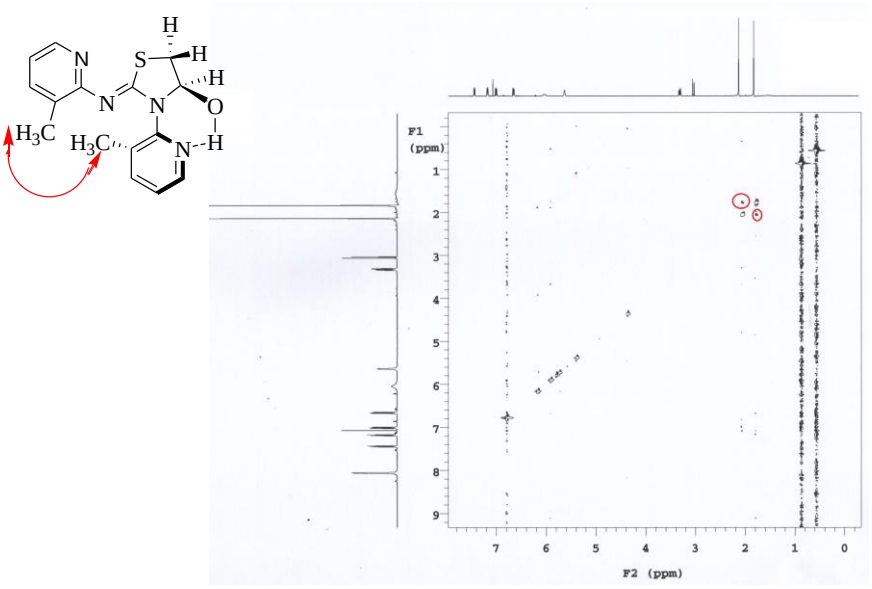


Figure 3.26. The NOESY spectrum of **33**.

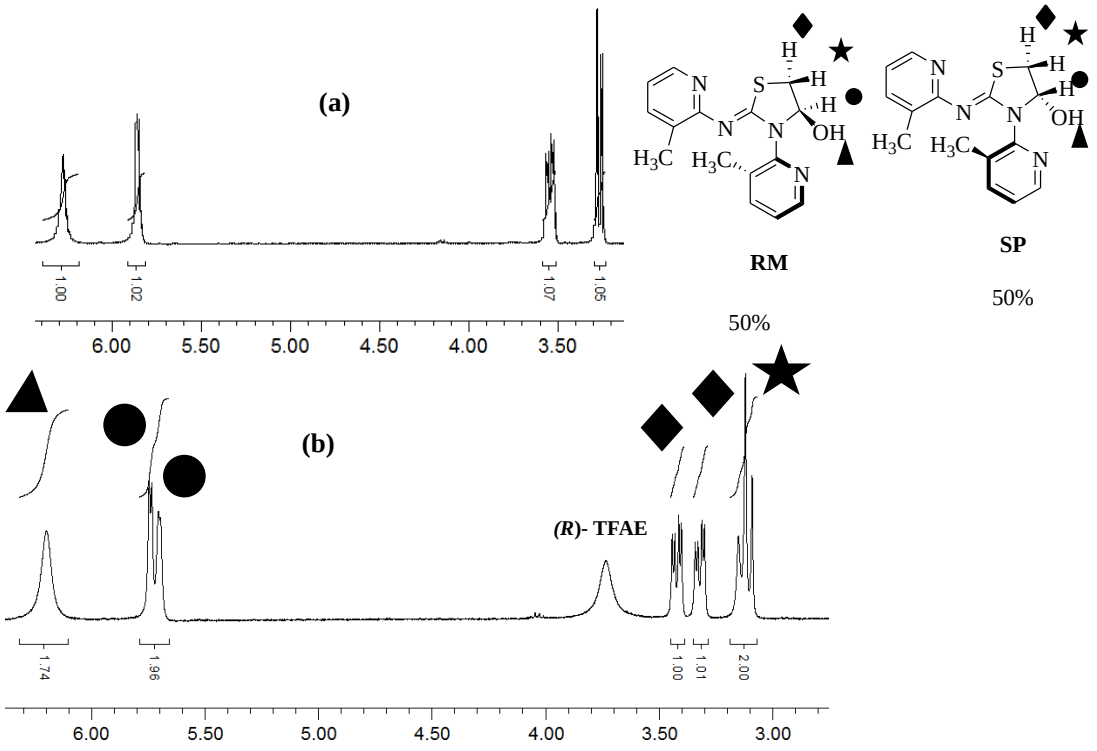


Figure 3.27. The partial ^{1}H NMR spectra of compound **33** in the absence of chiral auxiliary (**a**) and showing the enantiomer ratio in the presence of chiral auxiliary (*R*)- TFAE showing the enantiomer ratio (**b**).

When an 87.2:12.8 isomeric mixture (*SP*/*RM*: *SM*/*RP*) of compound **31** was reduced to its hemiaminal derivative, the formation of eight isomers were expected due to the presence of the chiral center at C-5, the N_3-$C_{(aryl)}$ chiral axis and the newly formed chiral center at C-4. (Figure 3.28). However, the ^{1}H NMR spectrum of compound **35** showed three sets of peaks for three enantiomeric pairs (Figure 3.29). The larger groups OH at C-4 and CH_3 group at C-5 stay *anti* to each other and OH group prefered to make an H-bond with the nitrogen atom of the pyridine at N_3. Consequently, 4*R,5R,P/4S,5S,M* enantiomeric pair became the major and the *4R,5S,P/4S,5RM* enantiomeric pair, the minor products. The ratio of the isomers (major:minor:trace) was determined as 69.9:26.4:3.7.

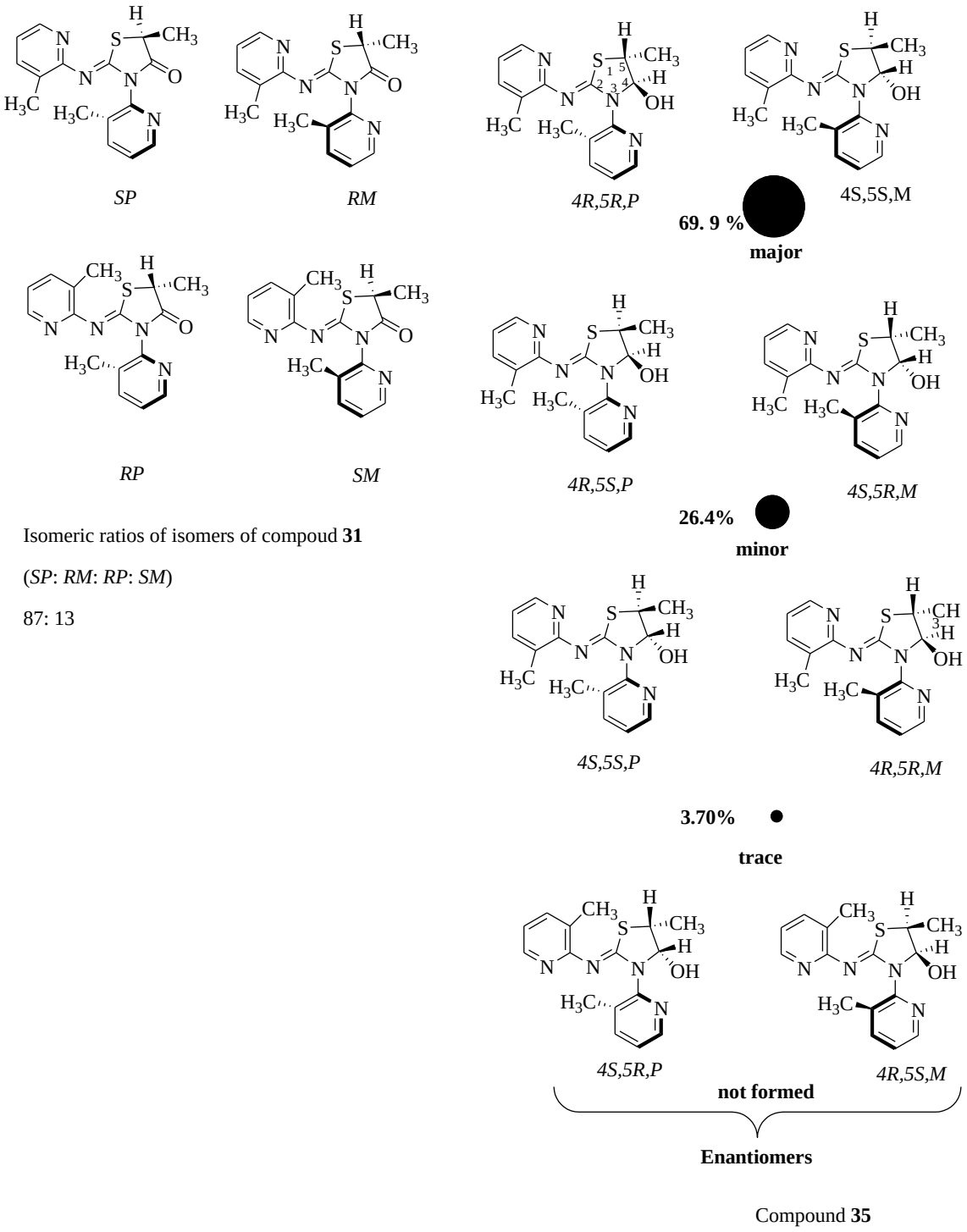


Figure 3.28. The expected eight isomers for compound **35** (the different sized balls under the molecules represent the enantiomeric pairs on the partial ^{1}H NMR in Figure 3.29).

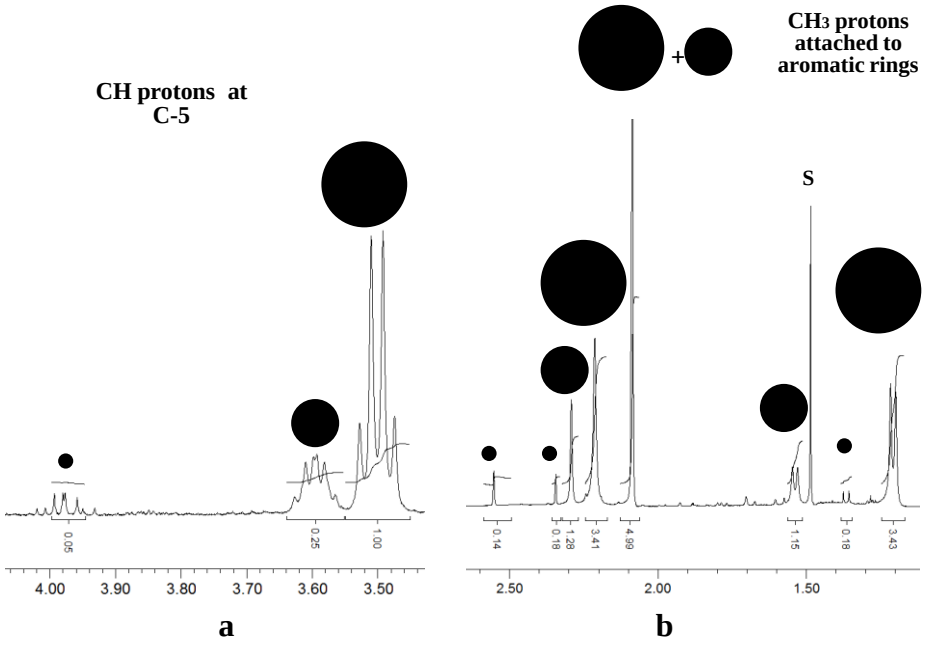
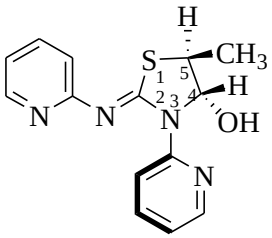


Figure 3.29. Partial ^{1}H NMR spectra of compound **35** showing the quartet for CH proton at C-5 (**a**) and the CH_3 groups at C-5 and attached to pyridine rings (**b**).

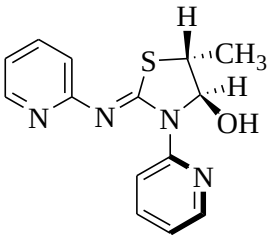
Two sets of peaks were observed from the ^{1}H NMR spectrum of compound **34** belonging to 4*S*,5*S*,*M*/ 4*R*,5*R*,*P* enantiomeric pair as the major isomer and 4*S*,5*R*,*M*/ 4*R*,5*S*,*P* enantiomeric pair as the minor one. The diastereomeric ratio of the major to minor isomers were determined as 77:23 (Figure 3.30).



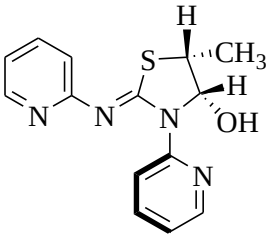
4*S*,5*S*,*M*

76.6%

major



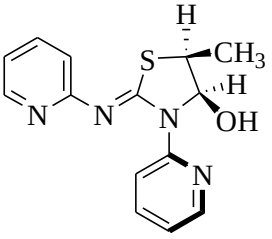
4*R*,5*R*,*P*



4*S*,5*R*,*M*

23.4%

minor



4*R*,5*S*,*P*

Figure 3.30. The chemical structures of the major and the minor isomers of compound 34.

3.6. Reduction of 5-Methyl-3-aryloxazolidine-2,4-diones with $LiAlH_4$

3.6.1. Synthesis of Hemiaminals from Single Enantiomer 5-Methyl-3-aryloxazolidine-2,4-diones

The single enantiomers of 5-Methyl-3-aryloxazolidine-2,4-diones **16*S*** and **17*S*** were reduced to their hemiaminal derivatives **36** and **37** regioselectively from the carbonyl group at the C-4 instead of C-2 in the presence of $LiAlH_4$ (Figure 3.31).

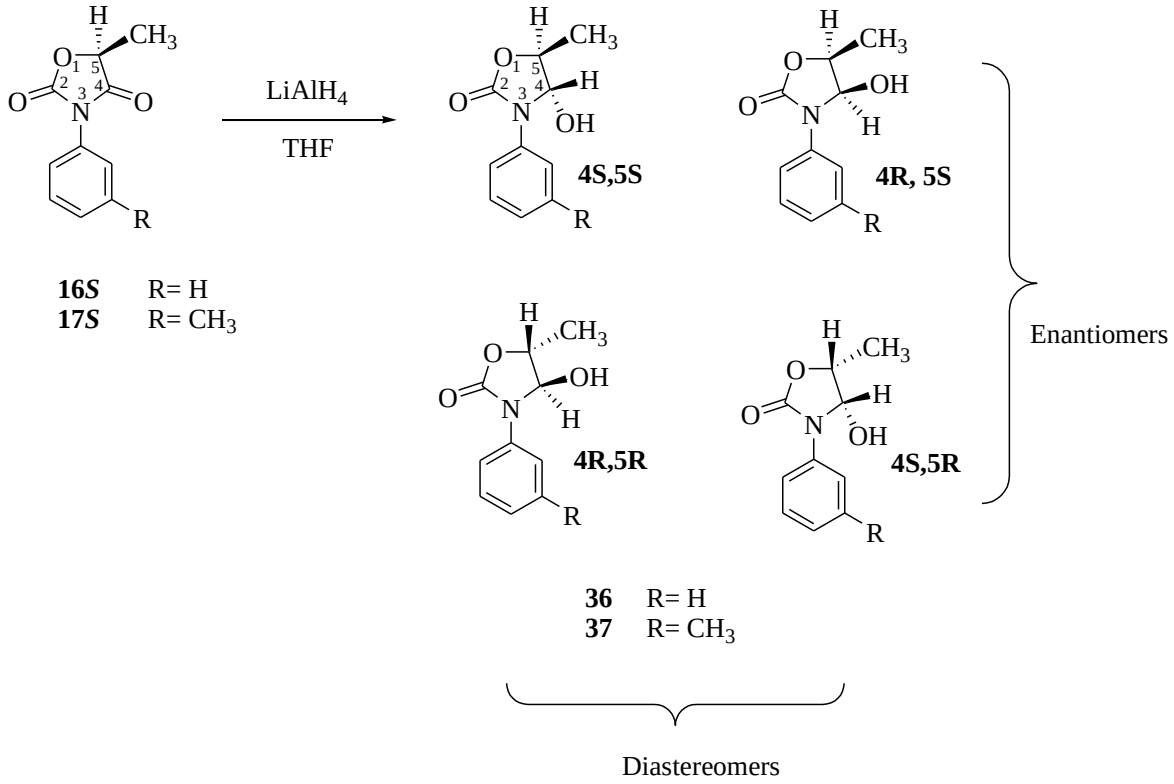


Figure 3.31. Reduction of 5-Methyl-3-aryloxazolidine-2,4-diones.

3.6.2. Diastereoselectivity in Reduction of 5-Methyl-3-aryloxazolidine-2,4-dione Derivatives with $LiAlH_4$

From the reductions of oxazolidin-2,4-dione derivatives **16*S*** and **17*S*** with $LiAlH_4$, the formation of a diastereomeric pair was expected by the attack of hydride ion. The ^1H NMR spectra showed the formation of the diasteromers with a ratio of 2:1 as shown in Figure 3.32 and Figure 3.33 for hemiaminal **36** and **37** respectively. In addition, the HPLC chromatogram revealed that although the starting oxazolidin-2,4-diones **16*S*** and **17*S*** were enantiomerically pure, the obtained hemiaminals **36** and **37** were found to partially racemize at C-5 (Figure 3.34 and Figure 3.35, racemization ratio 90:10). This result can be explained by the enolization of the molecule due to the presence of the acidic α-hydrogen at C-5 of the ring. Thus, the configuration of oxazolidin-2,4-dione derivatives at C-5 could not be retained completely.

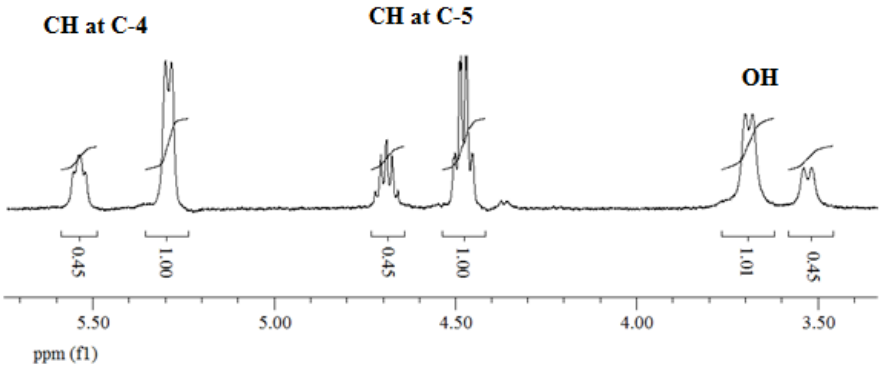


Figure 3.32. Partial ^{1}H NMR spectrum of compound **36** showing the diastereoselectivity for C-4, C-5 and OH protons (dr=2:1).

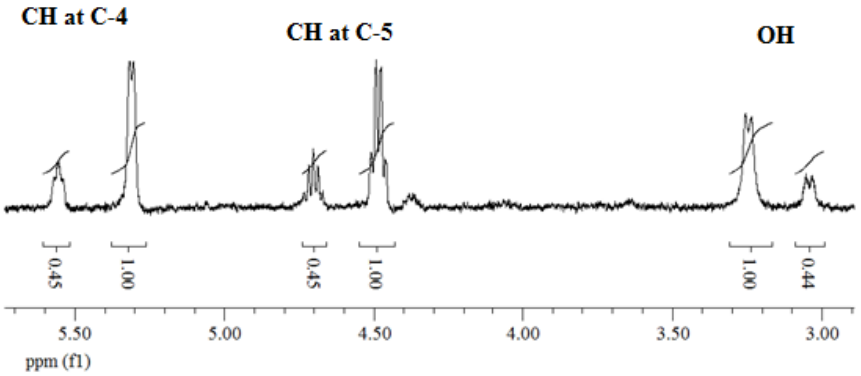


Figure 3.33. Partial ^{1}H NMR spectrum of compound **37** showing the diastereoselectivity for C-4, C-5 and OH protons (dr=2:1).

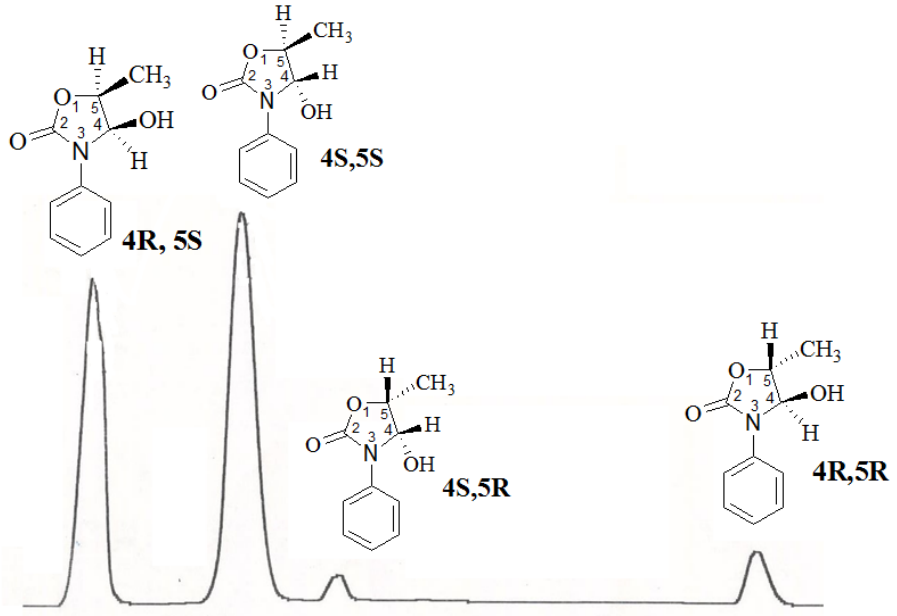


Figure 3.34. The HPLC chromatogram showing the diastreomeric pairs for compound **36** **(**Chiralpak IC, mobile phase: Hexane:Ethanol (95:5), flow rate: 0.8 mL/min, retention times: t_1: 11.028 min, t_2: 17.07 min, t_3: 21.06 min, t_4: 38.432 min) (dr=2:1 and racemization ratio= 90:10).

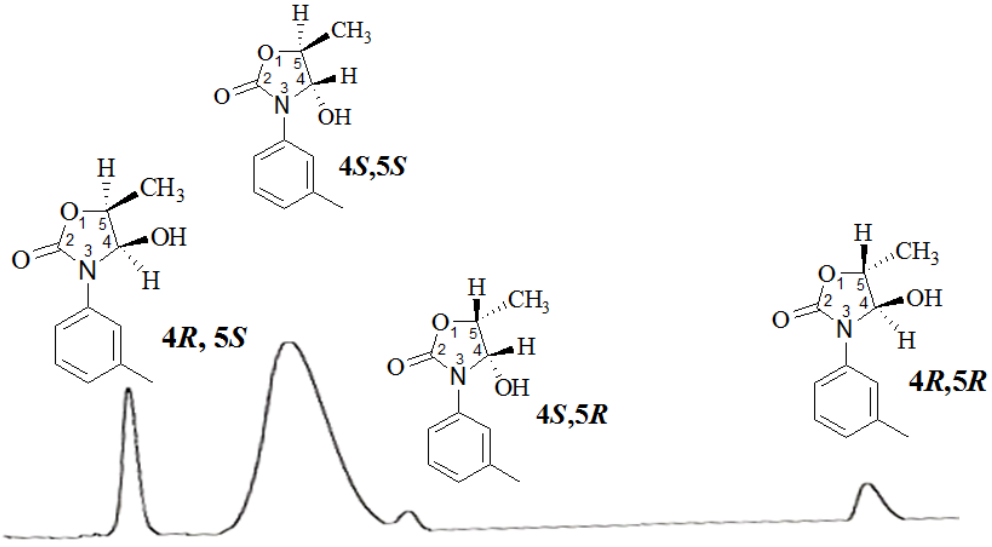


Figure 3.35. The HPLC chromatogram showing the diastreomeric pairs for compound **37** **(**Chiralpak IC, mobile phase: Hexane:Ethanol (95:5), flow rate: 0.8 mL/min, retention times: t_1: 11.073 min, t_2: 17.833 min, t_3: 22.5 min, t_4: 41.848 min) (dr=2:1 and racemization ratio= 90:10).

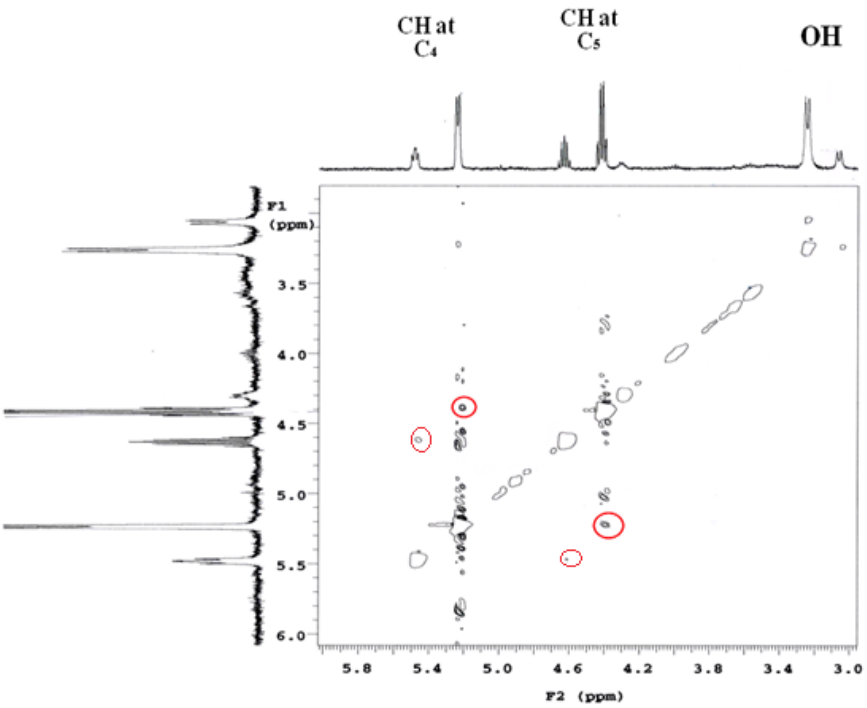


Figure 3.36. 2D-NOESY spectrum of compound **37**.

To clarify the stereochemistry of the compound **37**, a 2D-NOESY spectrum was taken in $CDCl_3$ (Figure 3.36). A crosspeak between the CH proton at C-4 and CH proton at C-5 was observed not only for the major isomer but also for the minor one due to being adjacent to one another. This result did not give a satisfactory information about the stereochemistry. However when the 1D ^1H NMR result was examined, CH proton at C-4 of the minor isomer was found to couple with both OH and CH at C-5 protons (which is *cis* to CH at C-4) and splitted into a doublet of a doublet which appeared as a triplet. However, the CH proton at C-4 of major isomer just coupled with the OH proton and splitted into a doublet (protons at C-4 and C-5 are *trans* to each other). In the light of all these results it was concluded that the hyride ion prefered to attack from the same side of the directing methyl group at C-5 so that the configuration where the larger groups (CH_3 and OH) are *trans* to each other was favored and formed as the major product.

3.7. Reduction of 5-Methyl-3-Aryloxazolidine-2,4-Diones with $NaBH_4$

3.7.1. Synthesis of the Ring Opening Products from 5-Methyl-3-Aryloxazolidine-2,4-Diones

The reduction of compounds **16*S***, **17*S*** and **18*S*** were also carried out using 4 equivalents $NaBH_4$ in THF at room temperature. The reaction was found to produce a reductive ring opened product. The reduction proceeded regioselectively where only the carbonyl group at C-4 was reduced (Figure 3.37). The racemization ratio of compound **40** was found to be less than the other ring opened products **38** and **39** because of the steric hindrance of *ortho* methyl group that hindered the approach of the hydride ion.

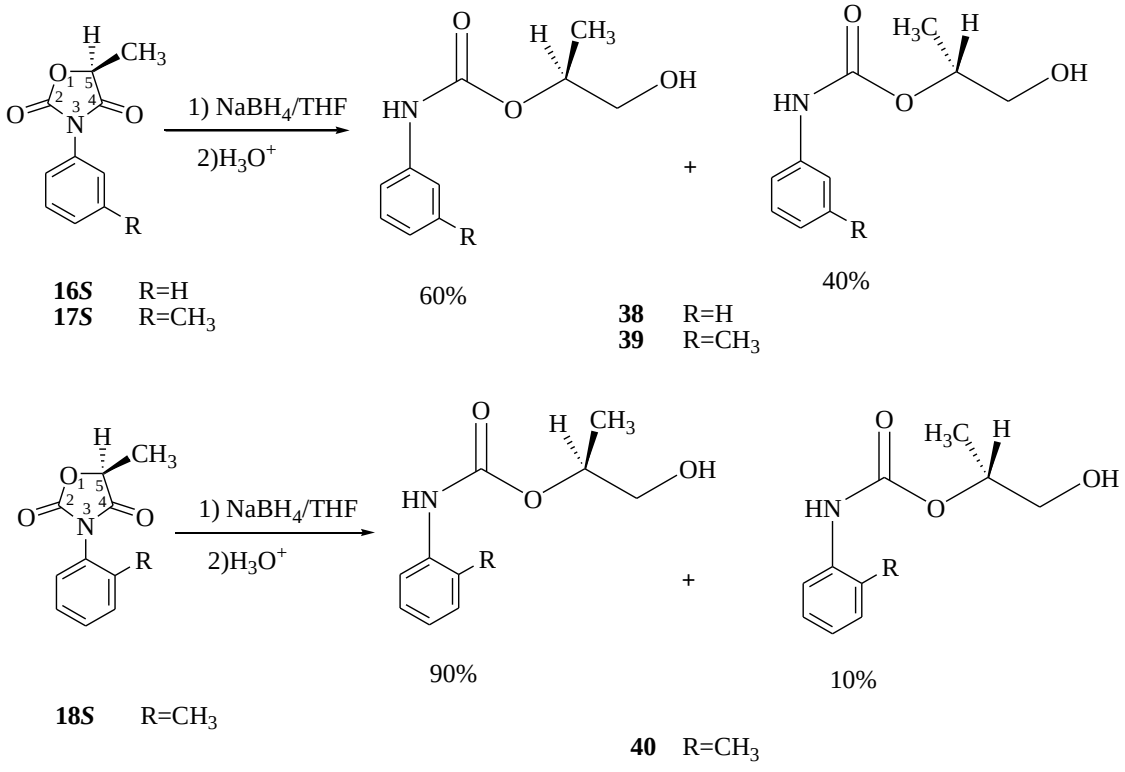


Figure 3.37. Ring-opening reaction of oxazolidin-2,4-diones **16*S***, **17*S*** and **18*S***.

The apperance of two peaks on the HPLC chromatograms of compounds **38**, **39**, **40** on chiralpak AD-H showed that a partial racemization at C-5 also took place during the reduction with $NaBH_4$ (Table 3.8, Figure 3.38).

Table 3.8. Racemization ratios of compounds (obtained from the integration of the HPLC peaks) **38**, **39** and **40** during the ring opening reaction with $NaBH_4$ on Chiralpak AD-H, mobile phase: Hexane:Ethanol (95:5).

Compd.	**Racemization ratio**
38	60:40
39	60:40
40	90:10

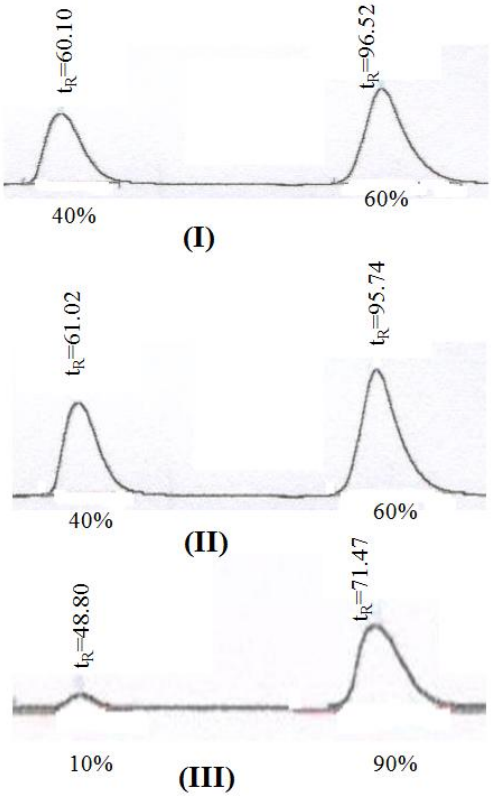


Figure 3.38. The HPLC chromatograms of compounds **38 (I)**, **39 (II)**, **40 (III)** showing the racemization ratios on Chiralpak AD-H, mobile phase: Hexane:Ethanol (95:5).

It was interfered from the ^{1}H NMR spectrum of compound **38** that, during the reduction with $NaBH_4$ the ring opening process occured through the formation of hemiaminal as an intermediate product and then the hemiaminal went to ring opening (Figure 3.39).

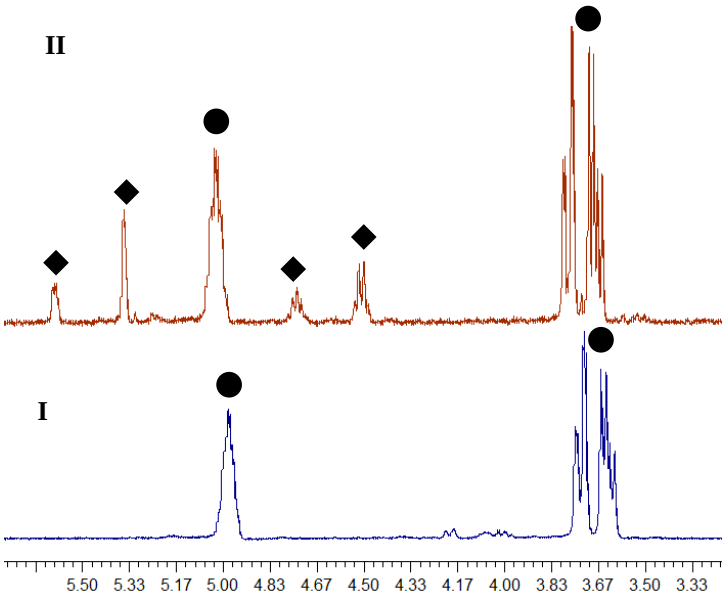


Figure 3.39. Partial ^{1}H NMR spectra of compound **38** containing just the ring opening product (**I**) and the progression of the reaction through hemiaminal formation **(II)** (● = ring opening product and ♦ = hemiaminal).

4. EXPERIMENTAL

4.1. Synthesis of *N,N'*–Bis-Thioureas

4.1.1. General procedure

The appropriate amine derivative was dissolved in the appropriate solvent (ethanol or pyridine) after which CS_2 was added. The mixture was refluxed overnight under N_2. Next, the solution was concentrated by evaporating the solvent and then cooled to give a precipitate. The precipitated product was isolated by vacuum filtration. The crude *N,N'*–bis-thiourea was purified by recrystallization from ethanol.

4.1.1.1. *N,N'*-bis((*R*)-1-phenylethyl)thiourea (1*RR*). The compound was synthesized according to the general procedure using (*R*)-(+)-1-Phenylethylamine 10.91 g (90 mmol), carbon disulfide 13.71 g (180 mmol) and ethanol (50 mL). Yield: 12.13 g (95%), mp: 186-188 ^{0}C, (white coloured crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.01 (m, 10H, Ar-H), 6.01 (br, 2H, NH), 5.04 (br, 2H, CH), 1.47 (d, 6H, *J* = 6.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 142.4, 129.1, 127.8, 125.8, 54.3, 23.4 ppm. ATR-FTIR: 3240, 1541 cm$^-$1. Calculated for: $C_{17}H_{20}N_2S$: C: 71.79; H: 7.09; N: 9.85. Found: C: 71.84; H: 7.03; N: 9.05. $[\alpha]^{26}_{360}$ = (+) 163.4^o.

4.1.1.2. *N,N'*-bis((*S*)-1-phenylethyl)thiourea (1*SS*). The compound was synthesized according to the general procedure using (*S*)-(-)-1-Phenylethylamine 10.91 g (90 mmol), carbon disulfide 13.71 g (180 mmol) and ethanol (50 mL). Yield: 12.8 (100%), mp: 186-188 ^{0}C, (white coloured crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.01 (m, 10H, Ar-H), 6.01 (br, 2H, NH), 5.04 (br, 2H, CH), 1.47 (d, 6H, *J* = 6.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 142.4, 129.1, 127.8, 125.8, 54.3, 23.4 ppm. ATR-FTIR: 3237, 1542 cm^{-1}. Calculated for: $C_{17}H_{20}N_2S$: C: 71.79; H: 7.09; N: 9.85. Found: C: 72.19; H: 6.88; N: 9.58. $[\alpha]^{26}_{360}$ = (-) 163.4^o.

4.1.1.3. *N,N'*-bis(1-phenylethyl)thiourea (1*DL*). The compound was synthesized according to the general procedure using *DL*-1-Phenylethylamine 10.91 g (90 mmol), carbon disulfide 13.71 g (180 mmol) and ethanol (50 mL). Yield: 11.72 (92%), mp: 120-122 ^{0}C, (white coloured crystal).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.01 (m, 10H, Ar-H), 6.01

(br, 2H, NH), 5.04 (br, 2H, CH), 1.47 (d, 6H, *J* = 6.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 142.4, 129.1, 127.8, 125.8, 54.3, 23.4 ppm. ATR-FTIR: 3257, 1544 cm^{-1}. Calculated for: $C_{17}H_{20}N_2S$: C: 71.79; H: 7.09; N: 9.85. Found: C: 72.18; H: 7.14; N: 9.16 .

4.1.1.4. *N,N'*-bis((R)-1-(naphtalen-1-yl)ethyl)-thiourea (2*RR*). The compound was synthesized according to the general procedure using (*R*)-(+)-1-(1-Naphtyl)ethylamine 5 g (30 mmol), carbon disulfide 4.42 g (60 mmol) and ethanol (30 mL). Yield: 4.8 g (83.2%), mp: 178-180 ^{0}C, (white coloured crystal).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.02 (m, 14H, Ar-H), 5.79 (br, 4H, CH and NH) 1.58 (d, 6H, *J* = 6.4 Hz,CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 137.1, 133.9, 130.3, 129.1, 128.5, 126.8, 125.9, 125.3, 122.8, 50.6, 31.1, 21.8 ppm. ATR-FTIR: 3251, 1540 cm^{-1}. Calculated for $C_{25}H_{24}N_2S$: C: 78.09; H: 6.29; N: 7.28. Found: C: 78.32; H: 6.49; N: 6.85. $[\alpha]^{26}_{360}$ = (-) 1535.0^o.

4.1.1.5. *N,N'*-bis((*S*)-1-(naphtalen-1-yl)ethyl)-thiourea (2*SS*). The compound was synthesized according to the general procedure using (*S*)-(-)-1-(1-Naphtyl)ethylamine 5 g (30 mmol), carbon disulfide 4.42 g (60 mmol) and ethanol (30 mL).Yield: 4.97 g (86.3%), mp: 178-180 ^{0}C, (white coloured crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.02 (m, 14H, Ar-H), 5.79 (br, 4H, CH and NH) 1.58 (d, 6H, *J* = 6.4 Hz,CH_3) ppm. ^{1}H NMR (400 MHz, Pyridine-d_5): δ 8.60 (2H, br, NH), 7.92-7.32 (m, 14H, Ar-H), 6.79 (br, 2H, CH), 1.72 (d, 6H, *J* = 6.8 Hz, CH_3) ppm. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.12-7.38 (m, 14H, Ar-H), 7.29 (br, 2H, NH), 6.18 (br, 2H, CH), 1.53 (d, 6H, *J* = 6.64 Hz, CH_3) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17-7.47 (m, 14H, Ar-H), 6.20 (br, 2H, CH) 1.50 (d, 6H, *J* = 6.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 137.1, 133.9, 130.3, 129.1, 128.5, 126.8, 125.9, 125.3, 122.8, 50.6, 31.1, 21.8 ppm. ATR-FTIR: 3254, 1541 cm^{-1}. Calculated for: $C_{25}H_{24}N_2S$: C: 78.21; H: 6.29; N: 6.87. Found: C: 78.09; H: 6.29; N: 7.28. $[\alpha]^{26}_{360}$ = (+) 1534.9^o.

4.1.1.6. *N,N'*-bis(1-(Naphtalen-1-yl)ethyl)thiourea (2*DL*). The compound was synthesized according to the general procedure using *DL*-1-(1-Naphtyl)ethylamine 5 g (30 mmol), carbon disulfide 4.42 g (60 mmol) and ethanol (30 mL). Yield: 5.03 (87.3%), mp: 156-160 ^{0}C, (white coloured solid).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.02 (m, 14H, Ar-H), 5.79 (br, 4H, CH and NH) 1.58 (d, 6H, *J* = 6.8 Hz,CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 137.1, 133.9, 130.3, 129.1, 128.5, 126.8, 125.9, 125.3, 122.8, 50.6, 31.1, 21.8 ppm.

ATR-FTIR: 3252, 1540 cm^{-1}. Calculated for: $C_{25}H_{24}N_2S$; C: 78.09; H: 6.29; N: 7.28. Found: C: 78.43; H: 6.29; N: 6.72.

4.1.1.7. *N,N'*-bis((*R*)-1-cyclohexylethyl)thiourea (3*RR*). The compound was synthesized according to the general procedure using (*R*)-(-)-1-cyclohexylethylamine 7.62 g (60 mmol), carbon disulfide 9.12 g (120 mmol) and pyridine (20 mL). Yield: 2.70 g (27%), mp : 178-180 ^{0}C, (white coloured crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (br, 2H, NH), 3.91 (br, 2H, CH), 1.78-0.94 (m, 22H, cyclohexyl protons) 1.15 (d, 6H, *J* = 6.8 Hz CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 54.6, 43.2, 29.4, 28.8, 26.3, 26.2, 26.1, 17.5 ppm. ATR-FTIR: 3225, 1538 cm^{-1}. Calculated for: $C_{17}H_{32}N_2S$: C: 68.86; H: 10.88; N: 9.45. Found: C: 68.83; H: 11.31; N: 8.74. $[\alpha]^{26}_{360}$ = (+) 163.5^o.

4.1.1.8. *N,N'*-bis((*S*)-1-cyclohexylethyl)thiourea (3*SS*). The compound was synthesized according to the general procedure using (*S*)-(+)-1-cyclohexylethylamine 7.62 g (60 mmol), carbon disulfide 9.12 g (120 mmol) and pyridine (20 mL). Yield: 2.70 (27%), mp : 178-180 ^{0}C, (white coloured crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (br, 2H, NH), 3.91 (br, 2H, CH), 1.78-0.94 (m, 22H, cyclohexyl protons) 1.15 (d, 6H, *J* = 6.8 Hz CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 54.6, 43.2, 29.4, 28.8, 26.3, 26.2, 26.1, 17.5 ppm. ATR-FTIR: 3223, 1536cm^{-1}. Calculated for: $C_{17}H_{32}N_2S$: C: 68.86; H: 10.88; N: 9.45. Found: C: 68.72; H: 10.47; N: 8.02. $[\alpha]^{26}_{360}$ = (-) 163.5^o.

4.1.1.9. *N,N'*-bis((*R*)-1-(4-methoxyphenyl)ethyl)thiourea (4*RR*). The compound was synthesized according to the general procedure using (*R*)-(+)-1-(4-Methoxyphenyl)ethylamine 7.56 g (50 mmol), carbon disulfide 7.61 g (100 mmol) and ethanol (30 mL). Yield: 4.00 g (46.5%), mp: 136-140 ^{0}C, (white coloured crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94- 6.73 (m, 8H, Ar-H), 5.93 (br, 2H, CH), 4.96 (br, 2H, NH), 3.72 (s, 6H, OCH_3), 1.44 (d, 6H, *J* = 6.8 Hz CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 159.2, 134.3, 127.1, 114.4, 110.2, 55.4, 53.8, 23.2 ppm. ATR-FTIR: 3269, 3232, 1533cm^{-1}. Calculated for: $C_{19}H_{24}N_2O_2S$: C: 66.25; H: 7.02; N: 8.13. Found: C: 65.29; H: 6.83; N: 7.69. $[\alpha]^{26}_{360}$ = (+) 1108.0^o.

4.1.1.10. *N,N'*-bis((*S*)-1-(4-methoxyphenyl)ethyl)thiourea (4*SS*). The compound was synthesized according to the general procedure using (*S*)-(-)1-(4-Methoxyphenyl)ethylamine 7.56 g (50 mmol), carbon disulfide 7.61 g (100 mmol) and ethanol (30 mL). Yield: 5.57 g (64.7%), m.p: 136-140 ^{0}C, (white coloured crystal). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 6.94- 6.73 (m, 8H, Ar-H protons), 5.93 (br, 2H, CH), 4.96 (br, 2H, NH), 3.72 (s, 6H, OCH_3), 1.44 (d, 6H, J = 6.8 Hz CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 159.2, 134.3, 127.1, 114.4, 110.2, 55.4, 53.8, 23.2 ppm. ATR-FTIR: 3269, 3233, 1537cm^{-1}. Calculated for: $C_{19}H_{24}N_2O_2S$: C: 66.25; H: 7.02; N: 8.13. Found: C: 66.12; H: 7.10; N: 7.92. $[\alpha]^{26}_{360}$ = (-) 1108.0^o.

4.1.1.11. *N,N'*-bis((*R*)-1-benzylpyrrolidine-3-yl)thiourea (5*RR*). The compound was synthesized according to the general procedure using 5.28 g (30 mmol) (3*R*)-(-)-1-Benzyl-3-aminopyrrolidine, carbon disulfide 4.42 g (60 mmol) and ethanol (30 mL). Yield: 6.40 (98%), mp :124-126 ^{0}C, (yellow coloured solid).^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (br, 2H, NH), 7.49-7.30 (m, 10H, Ar-H), 4.89 (m, 2H at C-3 pyrrolidine ring), 4.27 (m, 4H, benzyl –CH_2 protons), 3.43-1.97 (m, 12H, pyrrolidine protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 198.5, 181.5, 139.0-127.4, 62.4-49.5 ppm. ATR-FTIR: 3213, 1541cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{23}H_{30}N_4SH^+$: 394,22 Found: 395,2268. $[\alpha]^{26}_{360}$ = (-) 36.3^o.

4.1.1.12. *N,N'*-bis((*S*)-1-benzylpyrrrolidine-3-yl)thiourea (5*SS*): The compound was synthesized according to the general procedure using 5.28 g (30 mmol) (3*S*)-(+)-1-Benzyl-3-aminopyrrolidine, carbon disulfide 4.42 g (60 mmol), ethanol (30 mL). Yield: 6.43 (98%), mp:124-126 ^{0}C, (yellow coloured solid): ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (br, 2H, NH), 7.49-7.30 (m, 10H, Ar-H), 4.89 (m, 2H at C-3 pyrrolidine ring), 4.27 (m, 4H, benzyl –CH_2 protons), 3.43-1.97 (m, 12H, pyrrolidine protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 198.5, 181.5, 139.0-127.4, 62.4-49.5 ppm. ATR-FTIR: 3208, 1541cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{23}H_{30}N_4SH^+$: 394,22 Found: 395,2374. $[\alpha]^{26}_{360}$ = (+) 36.3^o.

4.2. Synthesis of 2-Imino-Thiazolidine-4-ones

4.2.1. General procedure

The appropriate *N,N'*-diarylthiourea and α-bromoacetic acid were refluxed for 7/12 h in absolute ethanol in the presence of sodium acetate. At the end of this period, the excess of ethanol was evoporated. The compounds were purified from a mixture of ethyl

acetate and hexane (a minimum amount of ethyl acetate was used to dissolve the crude product and then hexane was added until the precipitation was observed).

4.2.1.1. 3-((*R*)-1-phenylethyl)-2-((*R*)-1-phenylethylimino)thiazolidine-4-one (6*RR*) The compound was synthesized according to the general procedure using 1.42 g (5 mmol) 1*RR*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.94 g (58 %), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.20 (m, 10H, Ar-H), 5.94 (q, 1H, CH_a, J = 6.8 Hz), 4.38 (q, 1H, CH_b, J= 6.4 Hz), 3.77, 3.69 (AB quartet, 1H for each, J_{AB} =16.8 Hz), 1.88 (d, 3H, CH_{3a}, J = 7.2 Hz), 1.37 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 145.2, 139.9, 128.5, 128.1, 127.9, 127.5, 127.0, 126.5, 61.9, 53.3, 32.6, 25.0, 16.1 ppm. ATR-FTIR: 1716,1633 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{19}H_{20}N_2OSH^+$: 325,1375 ; Found: 325,1368.$[\alpha]^{26}_{360}$ = (+) 2597.5^{o}.

4.2.1.2. 3-((*S*)-1-phenylethyl)-2-((*S*)-1-phenylethylimino)thiazolidine-4-one (6*SS*). The compound was synthesized according to the general procedure using 1.42 g (5 mmol) 1*SS*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.88 g (54%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.20 (m, 10H, Ar-H), 5.94 (q, 1H, CH_a, J = 6.8 Hz), 4.38 (q, 1H, CH_b, J= 6.4 Hz), 3.77, 3.69 (AB quartet, 1H for each, J_{AB} =16.8 Hz), 1.88 (d, 3H, CH_{3a}, J = 7.2 Hz), 1.37 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 145.2, 139.9, 128.5, 128.1, 127.9, 127.5, 127.0, 126.5, 61.9, 53.3, 32.6, 25.0, 16.1 ppm. ATR-FTIR: 1716,1633 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{19}H_{20}N_2OSH^+$: 325,1375 ; Found:325,1361. $[\alpha]^{26}_{360}$ = (-) 2597.5^{o}.

4.2.1.3. 3-(1-phenylethyl)-2-(1-phenylethylimino)thiazolidine-4-one (6*DL*). The compound was synthesized according to the general procedure using 1.42 g (5 mmol) 1*DL*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and 30 ml ethanol. Yield: 1.2 g (76%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-6.96 (m, 20H, Ar-H), 5.94 (q, 1H, CH_a, J = 7.2 Hz), 5.50 (q, 1H, CH_a, J = 7.2 Hz), 4.38 (q, 1H, CH_b, J= 6.4 Hz), 4.30 (q, 1H, CH_b, J= 6.4 Hz), 3.68 (s, 2H, CH_2 C-5), 3.69, 3.62 (AB quartet, 1H for each, J_{AB} =16.8 Hz), 1.81 (d, 6H, CH_{3a}, J = 7.2 Hz), 1.40 (d, 3H, CH_{3b}, J = 6.4 Hz), 1.37 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 145.2, 139.9, 128.5, 128.1, 127.9, 127.5, 127.0, 126.5, 61.9, 53.3, 32.6, 25.0, 16.1 ppm. ATR-FTIR: 1716,1633 cm^{-1}. HRMS (TOF

MS ES+): Calculated for: $C_{19}H_{20}N_2OSH+$: 325,1375 ; Found:325,1388.

4.2.1.4. 3-((*R*)-1-(naphthalen-1-yl)ethyl)-2-((*R*)-1-naphthalen-1-yl)ethylimino) thiazolidine-4-one (7*RR*). The compound was synthesized according to the general procedure using 1.92 g (5 mmol) 2*RR*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.58 g (27%), mp : 72-74 ^{0}C (white coloured solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-6.89 (m, 14 H, Ar-H), 6.57 (q, 1H, CH_a, *J* = 7.2 Hz), 5.17 (q, 1H, CH_b, *J*= 6.4 Hz), 3.67, 3.54 (AB quartet, 1H for each, J_{AB} =16.8 Hz), 1.99 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.60 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4,150.9, 141.0, 134.3, 134.2, 133.7, 131.8, 130.8, 129.2, 128.9, 128.6, 127.8, 127.6, 126.4, 126.1, 125.8, 125.6, 125.4, 124.8, 124.4, 123.9, 123.7, 59.2, 50.4, 32.4, 24.3, 16.4ppm. ATR-FTIR: 1708,1620 cm^{-1}.HRMS (TOF MS ES+): Calculated for: $C_{27}H_{24}N_2OSH+$: 425,1688 ; Found: 425,1686. $[\alpha]^{26}_{360}$ = (+) 6050.9^o.

4.2.1.5. 3-((*S*)-1-(naphthalen-1-yl)ethyl)-2-((*S*)-1-naphthalen-1-yl)ethylimino) thiazolidine-4-one (7*SS*). The compound was synthesized according to the general procedure using 1.92 g (5 mmol) 2*SS*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.69 g (32.5%), mp : 72-74 ^{0}C (white coloured solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-6.89 (m, 14 H, Ar-H), 6.57 (q, 1H, CH_a, *J* = 7.2 Hz), 5.17 (q, 1H, CH_b, *J*= 6.4 Hz), 3.67, 3.54 (AB quartet, 1H for each, J_{AB} =16.8 Hz), 1.99 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.60 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 150.9, 141.0, 134.3, 134.2, 133.7, 131.8, 130.8, 129.2, 128.9, 128.6, 127.8, 127.6, 126.4, 126.1, 125.8, 125.6, 125.4, 124.8, 124.4, 123.9, 123.7, 59.2, 50.4, 32.4, 24.3, 16.4ppm. ATR-FTIR: 1708, 16189 cm^{-1}. HRMS (TOF MS ES+):Calculated for: $C_{27}H_{24}N_2OSH+$: 425,1688 ; Found: 425,1671. $[\alpha]^{26}_{360}$ = (-) 6050.9^o.

4.2.1.6. 3-(1-(naphthalen-1-yl)ethyl)-2-(1-naphthalen-1-yl)ethylimino)thiazolidine-4-one (7*DL*). The compound was synthesized according to the general procedure using 1.92 g (5 mmol) 2DL, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate and ethanol (30 mL). Yield: 0.82 g (37%), mp: 172-178 ^{0}C (white coloured solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-6.89 (m, 28 H, Ar-H), 6.63 (q, 1H, CH_a, *J* = 6.8 Hz), 6,57 (q, 1H, CH_a, *J* = 6.8 Hz), 5.17 (q, 1H, CH_b, *J*= 6.4 Hz), 3.67, 3.54 (AB quartet, 1H for each, J_{AB} =16.8 Hz), 3.62 (s, 2H, CH_2 C-5), 2.00 (d, 3H, CH_{3a}, *J* = 6.8 Hz), 1.99 (d, 3H, CH_{3a}, *J* = 6.8 Hz) 1.76 (d, 3H, CH_{3b}, *J* = 6.4 Hz), 1.60 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$): δ 171.4,150.9, 141.0, 134.3, 134.2, 133.7, 131.8, 130.8, 129.2, 128.9, 128.6, 127.8, 127.6, 126.4, 126.1, 125.8, 125.6, 125.4, 124.8, 124.4, 123.9, 123.7, 59.2, 50.4, 32.4, 24.3, 16.4ppm. ATR-FTIR: 1709, 1619 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{27}H_{24}N_2OSH+$: 425,1688 ; Found:425.1678.

4.2.1.7. 3-((*R*)-1-cyclohexylethyl)-2-((*R*)-1-cyclohexylethylimino)thiazolidine-4-one (8*RR*). The compound was synthesized according to the general procedure using 1.48 g (5 mmol) 3*RR*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.83 g (49%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (br, 1H, CH_a), 3.67 (s, 2H, CH_2 at C-5), 2.88 (m, 1H, CH_b), 2.15-0.74 (m, 22H cyclohexyl protons), 1.31 (d, 3H, CH_{3a}, J = 6.8 Hz), 1.00 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172. 8, 148.4 44.7, 38.7, 32.4, 30.8, 30.1, 29.2, 26.8, 26.6, 26.5, 24.4, 26.1, 26.0, 18.7, 15.6ppm. ATR-FTIR: 1715, 1635 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{19}H_{32}N_2OSH+$: 337,2314 ; Found: 337,2317. $[\alpha]^{26}_{360}$ = (-) 744.9^o.

4.2.1.8. 3-((*S*)-1-cyclohexylethyl)-2-((*S*)-1-cyclohexylethylimino)thiazolidine-4-one (8*SS*). The compound was synthesized according to the general procedure using 1.48 g (5 mmol) 3*SS*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.74 g (44%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (br, 1H, CH_a), 3.67 (s, 2H, CH_2 at C-5), 2.89 (m, 1H, CH_b), 2.15-0.74 (m, 22H cyclohexyl protons), 1.31 (d, 3H, CH_{3a}, J = 6.8 Hz), 1.00 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172.8, 148.4 63.8, 44.7, 38.7, 32.4, 30.8, 30.1, 29.2, 26.8, 26.6, 26.5, 24.4, 26.1, 26.0, 18.7, 15.6 ppm. ATR-FTIR: 1716, 1636 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{19}H_{32}N_2OSH+$: 337,2314 ; Found:337,2313. $[\alpha]^{26}_{360}$ = (+)744.9^o.

4.2.1.9. 3-((*R*)-1-(4-methoxyphenylethyl)-2-((*R*)-1-(4-methoxyphenylethylimino) thiazolidin-4-one (9*RR*). The compound was synthesized according to the general procedure using 1.72 g (5 mmol) 4*RR*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 1.33 g (69.3%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-6.76 (m, 8H, Ar-H), 5.87 (q, 1H, CHa, J = 7.2 Hz), 4.33 (q, 1H, CH_b, J= 6.4 Hz), 3.80 (s, 3H, OCH_{3b}), 3.79 (s, 3H, OCH_{3a}), 3.73, 3.65 (AB quartet , 1H for each, J_{AB} =16.8 Hz), 1.85 (d, 3H, CH_{3a}, J = 7.2 Hz), 1.38 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ171.6, 159.0, 158.4, 137.5, 133.6, 132.1, 129.4, 127.8, 127.5, 114.4, 113.9, 113.4, 110.2, 61.3, 55.9, 55.4, 52.9, 32.6, 25.2, 16.3ppm. ATR-FTIR: 1714,

1633 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{21}H_{24}N_2O_3SH^+$: 385,1586 ; Found: 385,1642. $[\alpha]^{26}_{360}$ = (+) 1180.6°.

4.2.1.10. 3-((*S*)-1-(4-methoxyphenylethyl)-2-((*S*)-1-(4- methoxyphenylethylimino) thiazolidin-4-one (9*SS*). The compound was synthesized according to the general procedure using 1.72 g (5 mmol) 4*SS*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.78 g (40.6%) , oily.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-6.76 (m, 8H, Ar-H), 5.87 (q, 1H, CHa, *J* = 7.2 Hz), 4.33 (q, 1H, CH_b, *J*= 6.4 Hz), 3.80 (s, 3H, OCH_{3b}), 3.79 (s, 3H, OCH_{3a}), 3.73, 3.65 (AB quartet , 1H for each, J_{AB} =16.8 Hz), 1.85 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.38 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ171.6, 159.0, 158.4, 137.5, 133.6, 132.1, 129.4, 127.8, 127.5, 114.4, 113.9, 113.4, 110.2, 61.3, 55.9, 55.4, 52.9, 32.6, 25.2, 16.3ppm. ATR-FTIR:1714, 1632 cm^{-1}.HRMS (TOF MS ES+):Calculated for: $C_{21}H_{24}N_2O_3SH^+$: 385,1586 ; Found: 385,1591. $[\alpha]^{26}_{360}$ = (-) 1180.6°.

4.2.1.11. 3-((*R*)-1-benzylpyrrolidin-3-yl)-2-((*R*)-1-benzylpyrrolidine-3-ylimino) thiazolidine-4-one (10*RR*). The compound was synthesized according to the general procedure using 1.97 g (5 mmol) 5*RR*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.87 g (40%), mp: 78-80 ^{0}C (red coloured solid). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48-7.20 (m, 10H, Ar-H), 4.77 (br, 1H, pyrrolidine CH_a proton at C-3), 4.63 (br, 1H, pyrrolidine CH_b proton at C-3), 4.00 (s, 2H, CH_2 protons at C-5), 4.04 (b, 2H, benzyl CH_{2a} protons), 4.04 (br, 2H, benzyl CH_{2b} protons), 3.89-0.82 (m, 12H, pyrrolidine protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 170.5, 134.1, 130.5, 130.3, 130.0, 129.9, 129.1, 129.0, 128.9, 128.7, 128.6, 79.6, 58.9, 58.5, 58.2 58.1, 55.8, 52.6, 52.5, 41.3, 37.8, 30.2, 29.6, 21.5 ppm. ATR-FTIR:1727, 1616 cm^{-1}.HRMS (TOF MS ES+): Calculated for: $C_{25}H_{30}N_4OSH^+$: 435,2219 ;Found: 435,2218.

4.2.1.12. 3-((*S*)-1-benzylpyrrolidine-3-yl)-2-((*S*)-1-benzylpyrrolidine-3-ylimino) thiazolidine-4-one (10*SS*). The compound was synthesized according to the general procedure using 1.97 g (5 mmol) 5*SS*, 0.84 g (6 mmol) α-bromoacetic acid, 0.49 g (6 mmol) sodium acetate, and ethanol (30 mL). Yield: 0.93 g (43%), mp: 78-80 ^{0}C (red coloured solid). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48-7.20 (m, 10H, Ar-H), 4.77 (br, 1H, pyrrolidine CH_a proton at C-3), 4.63 (br, 1H, pyrrolidine CH_b proton at C-3), 4.00 (s,

2H, CH_2 protons at C-5), 4.04 (br, 2H, benzyl CH_{2a} protons), 4.04 (b, 2H, benzyl CH_{2b} protons), 3.89-0.82 (m, 12H, pyrrolidine protons) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 170.5, 134.1, 130.5, 130.3, 130.0, 129.9, 129.1, 129.0, 128.9, 128.7, 128.6, 79.6, 58.9, 58.5, 58.2 58.1, 55.8, 52.6, 52.5, 41.3, 37.8, 30.2, 29.6, 21.5 ppm. ATR-FTIR: 1727, 1616 cm^{-1}. HRMS (TOF MS ES+): Calculated for: $C_{25}H_{30}N_4OSH^+$:435,2219 ; Found: 435,2213.

4.3. Synhesis of 5-Benzylidene-2-Imino thiazolidine-4-ones and 5-Benzylidene-thiazolidine-2,4-diones

4.3.1. General procedure

The appropriate 2-imino thiazolidine-4-one derivatives and benzaldehyde were refluxed for 7/12 h in acetic acid in the presence of sodium acetate. At the end of this period, the excess of acetic acid was evoporated. The compounds were washed with water and purified from a mixture of ethyl acetate and hexane (a minimum amount of ethyl acetate was used to dissolved the crude product and then hexane was added until the precipitation was observed).

4.3.1.1. 5-Benzylidene-3-((*R*)-1-phenylethyl)-2-((*R*)-1-phenylethylimino)thiazolidin-4-one (11*RR*). The compound was synthesized according to the general procedure using 0.81 g (2.5 mmol) 6*RR*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.42 g (41%), oily.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H, =CHPh), 7.51-7.24 (m, 15H Ar-H), 6.08 (q, 1H, CH_a, J = 7.2 Hz), 4.48 (q, 1H, CH_b, J = 6.4 Hz), 1.96 (d, 3H, CH_{3a}, J = 7.2 Hz), 1.39 (d, 3H, CH_{3b}, J = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 146.2, 145.1, 140.1, 134.3, 130.1-126.5, 121.9, 62.9, 53.4, 29.9, 25.2, 16.4 ppm.HRMS (TOF MS ES+): Calculated: $C_{26}H_{24}N_2OSH^+$: 413.1688 ; Found:413.1670.ATR-FTIR: 1705, 1638 cm^{-1}. $[\alpha]^{26}_{360}$ = (+) 444.4^o.

4.3.1.2. 5-Benzylidene-3-((S)-1-phenylethyl)-2-((*S*)-1-phenylethylimino)thiazolidin-4-one (11*SS*). The compound was synthesized according to the general procedure using 0.81 g (2.5 mmol) 6*SS*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.39 g (38%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.68 (s, 1H, =CHPh), 7.51-7.24 (m, 15H Ar-H), 6.08 (q, 1H, CH_a, *J* = 7.2 Hz), 4.48 (q, 1H, CH_b, *J* = 6.4 Hz), 1.96 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.39 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ166.8, 146.2, 145.1, 140.1, 134.3, 130.1-126.5, 121.9, 62.9, 53.4, 29.9, 25.2, 16.4 ppm. HRMS (TOF MS ES+): Calculated: $C_{26}H_{24}N_2OSH^+$: 413.1688 ;Found:413.1696. ATR-FTIR:1705, 1638 cm^{-1}. $[\alpha]^{26}_{360}$ = (-) 488.9^o.

4.3.1.3. 5-Benzylidene-3-((*R*)-1-(naphthalen-1-yl)ethyl)-2-((*R*)-1-naphthalen -1-yl)ethylimino)thiazolidine-4-one (12*RR*). The compound was synthesized according to the general procedure using 1.06 g (2.5 mmol) 7*RR*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.31 g (24%), m.p: 228-230 ^{o}C, white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H, =CHPh), 8.15-6.15 (m, 19H Ar-H), 6.35 (m, 1H, CH_a, *J* = 7.2 Hz), 5.59 (q, 1H, CH_b, *J* = 6.4 Hz), 2.00 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.87 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ181.5, 174.0, 137.7-122.5, 110.2, 53.2, 51.1, 29.9, 22.9, 20.1 ppm. HRMS (TOF MS ES+): Calculated: $C_{34}H_{28}N_2OSH^+$: 513.2001 ;Found:513.2052.ATR-FTIR: 1674, 1616 cm^{-1}. $[\alpha]^{26}_{360}$ = (-) 177.8^o.

4.3.1.4. 5-Benzylidene-3-((*S*)-1-(naphthalen-1-yl)ethyl)-2-((*S*)-1-naphthalen -1-yl)ethylimino)thiazolidine-4-one (12*SS*). The compound was synthesized according to the general procedure using 1.06 g (2.5 mmol) 7*SS*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.40 g (31%). m.p: 228-230 ^{o}C, white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H, =CHPh), 8.15-6.15 (m, 19H Ar-H), 6.35 (m, 1H, CH_a, *J* = 7.2 Hz), 5.59 (q, 1H, CH_b, *J* = 6.4 Hz), 2.00 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.87 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ181.5, 174.0, 137.7-122.5, 110.2, 53.2, 51.1, 29.9, 22.9, 20.1 ppm. HRMS (TOF MS ES+): Calculated: $C_{34}H_{28}N_2OSH^+$: 513.2001 ; Found: 513.2052. ATR-FTIR: 1674, 1616 cm^{-1}. $[\alpha]^{26}_{360}$ = (+) 133.3.

4.3.1.5. 5-Benzylidene-3-((*R*)-1-cyclohexylethyl)-2-((*R*)-1-cyclohexylethylimino) thiazolidine-4-one (13*RR*). The compound was synthesized according to the general procedure using 0.95 g (2.8 mmol) 8*RR*, 0.33 g (3.1 mmol) benzaldehyde, 0.25 g (3.1 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.50 g (40%), oily.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H, =CHPh), 7.54-7.34 (m, 5H Ar-H), 4.39 (br, 1H, CH_a,), 3.08 (m, 1H, CH_b,), 1.92-0.89 (m, 22H cyclohexyl protons), 1.46 (d, 3H, CH_{3a}, *J* = 6.4 Hz), 1.15

(d, 3H, CH_{3b}, *J* = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 134.4, 129.9, 129.1, 128.9, 128.5, 122.3, 64.8, 60.4, 56.8, 44.5, 38.9, 31.6, 30.7, 30.0, 29.1, 26.6, 26.4, 26.3, 25.9, 25.8, 22.6, 18.9, 15.7, 14.1 ppm. HRMS (TOF MS ES+): Calculated: $C_{26}H_{36}N_2OSH^+$: 425.2627 ; Found: 425.2629. ATR-FTIR: 1705, 1642 cm^{-1}. $[\alpha]^{26}_{360}$ = (+) 88.9^o.

4.3.1.6. 5-Benzylidene-3-((*S*)-1-cyclohexylethyl)-2-((*S*)-1-cyclohexylethylimino) thiazolidine-4-one (13*SS*). The compound was synthesized according to the general procedure using 0.95 g (2.8 mmol) 8*SS*, 0.33 g (3.1 mmol) benzaldehyde, 0.25 g (3.1 mmol) sodium acetate, and 10 ml acetic acid. Yield 0,56 g (47%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H, =CHPh), 7.54-7.34 (m, 5H Ar-H), 4.39 (br, 1H, CH_a,), 3.08 (m, 1H, CH_b,), 1.92-0.89 (m, 22H cyclohexyl protons), 1.46 (d, 3H, CH_{3a}, *J* = 6.4 Hz), 1.15 (d, 3H, CH_{3b}, *J* = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ166.9, 134.4, 129.9, 129.1, 128.9, 128.5, 122.3, 64.8, 60.4, 56.8, 44.5, 38.9, 31.6, 30.7, 30.0, 29.1, 26.6, 26.4, 26.3, 25.9, 25.8, 22.6, 18.9, 15.7, 14.1 ppm.HRMS (TOF MS ES+): Calculated: $C_{26}H_{36}N_2OSH^+$: 425.2627; Found: 425.2627.ATR-FTIR: 1705, 1642 cm^{-1}. $[\alpha]^{26}_{360}$ = (-) 88.9^o.

4.3.1.7. 5-Benzylidene-3-((*R*)-1-(4-methoxyphenylethyl)-thiazolidine-2,4-dione (14*R*). The compound was synthesized according to the general procedure using 0.85 g (2.5 mmol) 9*RR*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid and refluxed for 1.5 hours. The reaction was followed by TLC Yield: 0.67 g (79%), m.p : 182-184 ^{o}C, yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.78 (s, 1H, =CHPh), 7.55-6.88 (m, 9H, Ar-H), 4.72 (q, 1H, CH, *J* = 6.8 Hz), 1.89 (d, 3H, CH_3, *J* = 6.8 Hz) ppm. For minor isomer δ 7.82 (s, 1H, =CHPh), 7.55-6.88 (m, 9H, Ar-H), 5.34 (q, 1H, CH, *J* = 6.8 Hz), 1.67 (d, 3H, CH_3, *J* = 6.8 Hz) ppm (Major/minor : 4.54). ^{13}C NMR (100 MHz, $CDCl_3$):δ179.2, 176.0, 159.2, 134.1-126.5, 114.2, 56.6, 55.2, 22.5 ppm. HRMS (TOF MS ES+): Calculated: $C_{19}H_{17}NO_3SH^+$: 339.0929 ; Found:339.1150.ATR-FTIR: 1667 cm^{-1}. $[\alpha]^{26}_{360}$ = (+) 222.2^o.

4.3.1.8. 5-Benzylidene-3-((*S*)-1-(4-methoxyphenylethyl)-thiazolidine-2,4-dione (14*S*). The compound was synthesized according to the general procedure using 0.85 g (2.5 mmol) 9*SS*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid and refluxed for 1.5 hours. The reaction was followed by TLC Yield: 0.54 g (63%), m.p : 182-184 ^{o}C, yellow powder.^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.78 (s,

1H, =CHPh), 7.55-6.88 (m, 9H, Ar-H), 4.72 (q, 1H, CH, *J* = 6.8 Hz), 1.89 (d, 3H, CH_3, *J* = 6.8 Hz) ppm. For minor isomer δ 7.82 (s, 1H, =CHPh), 7.55-6.88 (m, 9H, Ar-H), 5.34 (q, 1H, CH, *J* = 6.8 Hz), 1.67 (d, 3H, CH_3, *J* = 6.8 Hz) ppm (Major/minor : 4.54). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 176.0, 159.2, 134.1-126.5, 114.2, 56.6, 55.2, 22.5 ppm. HRMS (TOF MS ES+): Calculated: $C_{19}H_{17}NO_3SH^+$: 339.0929 ;Found:339.1148.ATR-FTIR: 1667 cm^{-1}. $[\alpha]^{26}_{360}$ = (-) 222.2^o.

4.3.1.9. 5-Benzylidene-3-((*R*)-1-benzylpyrrolidine-3-yl)-2-((*R*)-1-benzylpyrrolidine -3-ylimino)thiazolidine-4-one (15*RR*): The compound was synthesized according to the general procedure using 1.09 g (2.5 mmol) 10*RR*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.48 g (37%), m.p: 70-72 ^{o}C, brown colored solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.17 (m, 15H, Ar-H), 7.46 (s, 1H, =CHPh), 4.62-1.52 (br, 18H benzyl $CH_{2\,a}$ and $CH_{2\,b}$ protons and pyrrolidine protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 168.8, 166.6, 151.6, 138.8,-121.8, 60.0, 59.3, 59.2, 58.7, 54.2, 53.6, 53.1, 52.4, 52.1, 47.9, 30.9, 26.4, 22.5,21.1 ppm. HRMS (TOF MS ES+): Calculated: $C_{32}H_{34}N_4OSH^+$: 523.2532 ;Found:523.2547.ATR-FTIR: 1708, 1599 cm^{-1}.

4.3.1.10. 5-Benzylidene-3-((*S*)-1-benzylpyrrolidine-3-yl)-2-((*S*)-1-benzylpyrrolidine -3-ylimino)thiazolidine-4-one (15*SS*). The compound was synthesized according to the general procedure using 1.09 g (2.5 mmol) 10*SS*, 0.30 g (2.8 mmol) benzaldehyde, 0.23 g (2.8 mmol) sodium acetate, and 10 ml acetic acid. Yield: 0.39 g (30%), m.p: 70-72 ^{o}C, brown colored solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.17 (m, 15H, Ar-H), 7.46 (s, 1H, =CHPh), 4.62-1.52 (br, 18H benzyl $CH_{2\,a}$ and $CH_{2\,b}$ protons and pyrrolidine protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172.1, 168.8, 166.6, 151.6, 138.8,-121.8, 60.0, 59.3, 59.2, 58.7, 54.2, 53.6, 53.1, 52.4, 52.1, 47.9, 30.9, 26.4, 22.5,21.1 ppm. HRMS (TOF MS ES+): Calculated: $C_{32}H_{34}N_4OSH^+$: 523.2532 ;Found:523.2526. ATR-FTIR: 1708, 1599 cm^{-1}.

4.4. Synthesis of 5-Methyl-3-aryloxazolidine-2,4-diones

4.4.1. General procedure

The compounds 16*R*, 16*S*, 17*R*, 17*S* and 18*S* were synthesized by the reaction of corresponding aryl isocyanates and ethyl lactate. The appropriate aryl isocyanates and

ethyl lactate were refluxed for 7 h in xylene. At the end of the reflux period, the obtained oily compound was heated in 6N HCl and then cooled to give precipitate. The precipitated product was isolated by vacuum filtration, washed with water, and dried in vacuo.

4.4.1.1. (5*R*)-Methyl-3-phenyloxazolidine-2,4-dione (+16*R*). The compound was synthesized according to the general procedure using phenyl isocyanate (1.39 g, 0.012 mol), (R)- ethyl lactate (1.42 g, 0.012 mol) and 25 mL xylene. Yield: 0.60 g (26 %), mp: 76-78 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.40 (m, 5H), 5.03 (q, 1H, *J*=7.0 Hz), 1.72 (d, 3H, *J*=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172.6, 154.1, 130.9-110.2, 76.1, 17.0 ppm. ATR-FTIR: 1728.3 cm^{-1}. HRMS (TOF MS ES+): Calculated for $C_{10}H_9NO_3$: 191.0582; Found:191.0554. $[\alpha]^{26}_{360}$ = (+)111.1^{o}.

4.4.1.2. (5*S*)-Methyl-3-phenyloxazolidine-2,4-dione (-16*S*). The compound was synthesized according to the general procedure using phenyl isocyanate (1.39 g, 0.012 mol), (S)- ethyl lactate (1.42 g, 0.012 mol) and 25 mL xylene. Yield: 0.25 g (11 %), mp: 76-78 °C. ^{1}H NMR (400 MHz, CDCl3): δ 7.52-7.40 (m, 5H), 5.03 (q, 1H, *J*=7.0 Hz), 1.72 (d, 3H, *J*=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172.6, 154.1, 130.9-110.2, 76.1, 17.0 ppm. ATR-FTIR: 1733.6 cm^{-1}.HRMS (TOF MS ES+): Calculated for $C_{10}H_9NO_3H^{+}$: 192.0616; Found:192.0600. $[\alpha]^{26}_{360}$ =(-)114.3^{o}.

4.4.1.3. (5*R*)-Methyl-3-(*m*-tolyl)oxazolidine-2,4-dione (+17*R*). The compound was synthesized according to the general procedure using *m*-tolyl isocyanate (1.60 g, 0.012 mol), (R)- ethyl lactate (1.42 g, 0.012 mol) and 25 mL xylene. Yield: 0.2 g (8 %), mp: 56-58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.20 (m, 4H), 5.02 (q, 1H, *J*=7.0 Hz), 2.41 (s, 3H), 1.73 (d, 3H, *J*=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 172.7, 154.2, 140.6-120.5, 76.1, 21.5, 17.0 ppm. ATR-FTIR:1727.9 cm^{-1}.HRMS (TOF MS ES+): Calculated for $C_{11}H_{11}NO_3NaH^{+}$: 229.0715 ; Found: 229.0736. $[\alpha]^{26}_{360}$ = (+)116.3^{o}.

4.4.1.4 (5*S*)-Methyl-3-(*m*-tolyl)oxazolidine-2,4-dione (-17*S*). The compound was synthesized according to the general procedure using *m*-tolyl isocyanate (1.60 g, 0.012 mol), (S)- ethyl lactate (1.42 g, 0.012 mol) and 25 mL xylene. mp.: 56-58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.20 (m, 4H), 5.02 (q, 1H, *J*=7.0 Hz), 2.41 (s, 3H), 1.73 (d, 3H, *J*=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172.7, 154.2, 140.6-120.5, 76.1, 21.5, 17.0 ppm. ATR-FTIR: 1727.9 cm^{-1}. HRMS (TOF MS ES+): Calculated for $C_{11}H_{11}NO_3NaH^{+}$: 229.0715; Found: 229.0742. $[\alpha]^{26}_{360}$ = (-)119.1^{o}.

4.4.1.5. (5*S*)-Methyl-3-(*o*-tolyl)oxazolidine-2,4-dione (-18*S*). The compound was synthesized according to the general procedure using *o*-tolyl isocyanate (1.60 g, 0.012 mol), (S)- ethyl lactate (1.42 g, 0.012 mol) and 25 mL xylene. mp.: 56-58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.20 (m, 4H), 5.02 (q, 1H, *J*=7.0 Hz), 2.41 (s, 3H), 1.73 (d, 3H, *J*=7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ172.7, 154.2, 140.6-120.5, 76.1, 21.5, 17.0 ppm. ATR-FTIR: 1727.9 cm^{-1}. HRMS (TOF MS ES+): Calculated for $C_{11}H_{11}NO_3NaH^+$: 229.0715; Found: 229.0742. $[\alpha]^{26}_{360}$ = (-)96.8^{o}.

4.5. Reduction of 2-Imino-Thiazolidine-4-ones with $LiAlH_4$.

4.5.1. General Procedure

The appropriate amount of 2-imino-thiazolidine-4-one was dissolved in THF and appropriate equiv. $LiAlH_4$ was added to the mixture. The reaction mixture was stirred at room temperature for 5 minutes. At the end of the this period water was added to quench the reaction mixture. And the mixture was extracted with ethyl acetate and dried with $CaCl_2$. And the solvent was evoporated.

4.5.1.1. 3-((*R*)-1-phenylethyl)-2-((*R*)-1-phenylethylimino)thiazolidine-4-ol (19*RR*). This compound was synthesized according to the general procedure using 0.2 g 6*RR* (0.62 mmol), 0.035 g $LiAlH_4$ (0.93 mmol) and 10 mL THF. Yield: 0.06 g (29%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.55-7.17 (m, 10H, Ar-H), 5.61 (q, 1H, CH_a, *J* =7.2 Hz), 5.03 (d, 1H, *J*=4.8 Hz), 4.31 (q, 1H, CH_b, *J*=6.4 Hz), 3.17, 3.01 (AB quartet , 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.74 (d, 3H, CH_{3a}, *J* =7.2 Hz), 1.47 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm and for minor isomer δ 7.55-7.17 (m, 10H, Ar-H), 5.70 (q, 1H, CH_a, *J* = 7.2 Hz), 5.48 (d, 1H, *J*=4.8 Hz,), 4.27 (q, 1H, CH_b, *J*=6.4 Hz,), 3.32, 3.03 (AB quartet, 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.67 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.46 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. (major/minor: 3.2). ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 153.8, 146.8, 142.0, 129.0-125.6, 82.0, 64.2, 53.3, 36.9, 25.7, 18.3 ppm and for minor isomer δ 154.1, 146.8, 142.5, 129.0-125.6, 81.4, 64.4, 52.6, 36.4, 25.8, 18.0 ppm. ATR-FTIR: 3340, 1626 cm^{-1}.

4.5.1.2. 3-((*S*)-1-phenylethyl)-2-((*S*)-1-phenylethylimino)thiazolidine-4-ol (19*SS*). This compound was synthesized according to the general procedure using 0.2 g 6*SS* (0.62 mmol), 0.035 g $LiAlH_4$ (0.93 mmol) and 10 mL THF. Yield: 0.06 g (29%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.55-7.17 (m, 10H, Ar-H), 5.61 (q, 1H, CH_a, *J* =7.2 Hz), 5.03 (d, 1H, *J*=4.8 Hz), 4.31 (q, 1H, CH_b, *J*=6.4 Hz), 3.17, 3.01 (AB quartet , 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.74 (d, 3H, CH_{3a}, *J* =7.2 Hz), 1.47 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm and for minor isomer δ 7.55-7.17 (m, 10H, Ar-H), 5.70 (q, 1H, CH_a, *J* = 7.2 Hz), 5.48 (d, 1H, *J*=4.8 Hz,), 4.27 (q, 1H, CH_b, *J*=6.4 Hz,), 3.32, 3.03 (AB quartet, 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.67 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.46 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. (major/minor: 3.2). ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 153.8, 146.8, 142.0, 129.0-125.6, 82.0, 64.2, 53.3, 36.9, 25.7, 18.3 ppm and for minor isomer δ 154.1, 146.8, 142.5, 129.0-125.6, 81.4, 64.4, 52.6, 36.4, 25.8, 18.0 ppm. ATR-FTIR: 3338, 1625 cm^{-1}.

4.5.1.3. 3-((*R*)-1-(naphthalen-1-yl)ethyl)-2-((*R*)-1-(naphthalen-1-yl)ethylimino) thiazolidin-4-ol (20*RR*). This compound was synthesized according to the general procedure using 0.2 g 7*RR* (0.47 mmol), 0.027 g $LiAlH_4$ (0.71 mmol) and 10 mL THF. Yield: 0.09 g (45%), white solid, mp: 48-50 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 8.42-6.30 (m, 14H, Ar-H), 6.30 (q, 1H, CH_a, *J*=6.8 Hz), 5.12 (q, 1H, CH_b, *J*=6.4 Hz), 4.65 (d, 1H, CH, *J*=6.4 Hz), 2.84, (d, 2H, CH_2 at C-5, *J*=2,4 Hz), 2.43 (d, 1H, OH, *J*=8.0 Hz), 1.93 (d, 3H, CH_{3a}, *J*=6.8 Hz,), 1.74 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. for minor isomer δ 8.49-7.34 (m, 14H, Ar-H), 6.54 (q, 1H, CH_a, *J*=6.8 Hz), 5.36 (br, 1H, CH), 5.09 (q, 1H, CH_b, *J*=6.4 Hz), 3.27, 2.93 (AB quartet, 1H for each, J_{AB}=11.6 Hz and *J*=4.8 Hz), 2.43 (d, 1H, OH, *J*=8.0 Hz), 1.76 (d, 3H, CH_{3a}, *J* = 6.8 Hz), 1.74 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. (major/minor: 3.2). ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 152.9, 142.9, 136.4-123.9, 82.0, 61.6, 49.7, 36.9, 24.9, 17.6 ppm and for minor isomer δ 156.5, 142.6, 137.1, 134.1-123.9, 80.6, 60.5, 48.4, 36.5, 25.0, 17.5 ppm. ATR-FTIR: 3379, 1614 cm^{-1}.

4.5.1.4. 3-((*S*)-1-(naphthalen-1-yl)ethyl)-2-((*S*)-1-(naphthalen-1-yl)ethylimino) thiazolidin-4-ol (20*SS*). This compound was synthesized according to the general procedure using 0.2 g 7*SS* (0.47 mmol), 0.027 g $LiAlH_4$ (0.71 mmol) and 10 mL THF. Yield:0.12 g (60%), white solid, mp: 48-50 ^{o}C . ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 8.42-6.30 (m, 14H, Ar-H), 6.30 (q, 1H, CH_a, *J*=6.8 Hz), 5.12 (q, 1H, CH_b, *J*=6.4

Hz), 4.65 (d, 1H, CH, *J*=6.4 Hz), 2.84, (d, 2H, CH_2 at C-5, *J*=2,4 Hz), 2.43 (d, 1H, OH, *J*=8.0 Hz), 1.93 (d, 3H, CH_{3a}, *J*=6.8 Hz,), 1.74 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. for minor isomer δ 8.49-7.34 (m, 14H, Ar-H), 6.54 (q, 1H, CH_a, *J*=6.8 Hz), 5.36 (br, 1H, CH), 5.09 (q, 1H, CH_b, *J*=6.4 Hz), 3. 3.27, 2.93 (AB quartet, 1H for each, J_{AB}=11.6 Hz and *J*=4.8 Hz), 2.43 (d, 1H, OH, *J*=8.0 Hz), 1.76 (d, 3H, CH_{3a}, *J* = 6.8 Hz), 1.74 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. (major/minor: 3.2). ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 152.9, 142.9, 136.4-123.9, 82.0, 61.6, 49.7, 36.9, 24.9, 17.6 ppm and for minor isomer δ 156.5, 142.6, 137.1, 134.1-123.9, 80.6, 60.5, 48.4, 36.5, 25.0, 17.5 ppm. ATR-FTIR: 3379, 1614 cm^{-1}.

4.5.1.5. 3-((*R*)-1-cyclohexylethyl)-2-((*R*)-1-cyclohexylethylimino) thiazolidine-4-ol (21*RR*). This compound was synthesized according to the general procedure using 0.2 g 8*RR* (0.60 mmol), 0.034 g $LiAlH_4$ (0.89 mmol) and 10 mL THF. Yield: 0.07 g (36%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 5.29 (d, 1H, CH, *J*=4.8 Hz), 4.01 (qd, 1H, CH_a, *J*=7.2 Hz and *J*=6.8 Hz), 3.29, 3.07 (AB quartet, 1H for each, J_{AB}=11.6 Hz and *J*=4.8 Hz), 2.81 (qd, 1H, CH_b *J*=5.2 Hz and *J*=6.4 Hz), 1.78-0.80 (m, 22H cyclohexyl protons), 1.26 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.06 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm and for minor isomer δ 5.21 (d, 1H, CH, *J*=4.8 Hz), 3.71 (qd, 1H, CH_a, *J*=7.2 Hz and *J*=6.8 Hz), 3.31, 3.05 (AB quartet, 1H for each, J_{AB}=11.6 Hz and *J*=4.8 Hz), 2.71 (qd, 1H, CH_b, *J*=5.2 Hz and *J*=6.4 Hz), 1.78-0.80 (m, 22H cyclohexyl protons), 1.28 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.03 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 152.9, 83.9, 66.9, 55.0, 45.1, 41.6, 36.6, 31.1-26.1, 19.6, 17.5 ppm and for minor isomer δ 152.9, 81.9, 66.2, 57.1, 45.0, 41.8, 36.8, 31.1-26.1, 19.5, 17.4 ppm. ATR-FTIR: 3338, 1638 cm^{-1}.

4.5.1.6. 3-((*S*)-1-cyclohexylethyl)-2-((*S*)-1-cyclohexylethylimino) thiazolidine-4-ol (21*SS*). This compound was synthesized according to the general procedure using 0.2 g 8*SS* (0.60 mmol), 0.034 g $LiAlH_4$ (0.89 mmol) and 10 mL THF . Yield:0.09 g (46%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 5.29 (d, 1H, CH, *J*=4.8 Hz), 4.01 (qd, 1H, CH_a, *J*=7.2 Hz and *J*=6.8 Hz), 3.29, 3.07 (AB quartet, 1H for each, J_{AB}=11.6 Hz and *J*=4.8 Hz), 2.81 (qd, 1H, CH_b *J*=5.2 Hz and *J*=6.4 Hz), 1.78-0.80 (m, 22H cyclohexyl protons), 1.26 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.06 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm and for minor isomer δ 5.21 (d, 1H, CH, *J*=4.8 Hz), 3.71 (qd, 1H, CH_a, *J*=7.2 Hz and

J=6.8 Hz), 3.31, 3.05 (AB quartet, 1H for each, J_{AB}=11.6 Hz and *J*=4.8 Hz), 2.71 (qd, 1H, CH_b, *J*=5.2 Hz and *J*=6.4 Hz), 1.78-0.80 (m, 22H cyclohexyl protons), 1.28 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.03 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 152.9, 83.9, 66.9, 55.0, 45.1, 41.6, 36.6, 31.1-26.1, 19.6, 17.5 ppm and for minor isomer δ 152.9, 81.9, 66.2, 57.1, 45.0, 41.8, 36.8, 31.1-26.1, 19.5, 17.4 ppm. ATR-FTIR: 3338, 1638 cm^{-1}.

4.5.1.7. 3-((*R*)-1-(4-methoxyphenyl)ethyl)-2-((*R*)-1-(4-methoxyphenyl) ethylimino) thiazolidin-4-ol (22*RR*). This compound was synthesized according to the general procedure using 0.2 g 9*RR* (0.52 mmol), 0.059 g $LiAlH_4$ (1.56 mmol) and 10 mL THF. Yield: 0,071 (35%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.29-6.83 (m, 8H, Ar-H), 5.54 (q, 1H, CH_a, *J* = 6.8 Hz), 4.99 (d, 1H, *J*=4.8 Hz), 4.27 (q, 1H, CH_b, *J*=6.4 Hz), 3.76 (s, 6H, OCH_3), 3.14, 2.99 (AB quartet, 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.71 (d, 3H, CH_{3a}, *J*=6.8 Hz), 1.45 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. for minor isomer δ 7.47-6.88 (m, 8H, Ar-H), 5.66 (q, 1H, CH_a, *J*=7.2 Hz,), 4.47 (d, 1H, *J*=4.8 Hz), 4.23 (q, 1H, CH_b, *J*=6.8 Hz), 3.76 (s, 6H, OCH_3), 3.30, 3.02 (AB quartet, 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.71 (d, 3H, CH_{3a}, *J* = 6.8 Hz), 1.45 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. (major/minor: 3.2). ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ158.0, 139.0-126.9, 82.1, 63.5, 55.2, 36.8, 25.6, 18.2 ppm and for minor isomer δ 158.8, 136.2-126.9, 81.4, 61.2, 55.8, 52.8, 36.2, 24.9, 18.0 ppm. ATR-FTIR: 3349, 1610 cm^{-1}.

4.5.1.8. 3-((*S*)-1-(4-methoxyphenyl)ethyl)-2-((*S*)-1-(4-methoxypheyl) ethylimino) thiazolidin-4-ol (22*SS*). This compound was synthesized according to the general procedure using 0.2 g 9*SS* (0.52 mmol), 0.059 g $LiAlH_4$ (1.56 mmol) and 10 mL THF. Yield: 0,086 (43%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.29-6.83 (m, 8H, Ar-H), 5.54 (q, 1H, CH_a, *J*=6.8 Hz), 4.99 (d, 1H, *J*=4.8 Hz), 4.27 (q, 1H, CH_b, *J*=6.4 Hz), 3.76 (s, 6H, OCH_3), 3.14, 2.99 (AB quartet, 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.71 (d, 3H, CH_{3a}, *J*=6.8 Hz), 1.45 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. for minor isomer δ 7.47-6.88 (m, 8H, Ar-H), 5.66 (q, 1H, CH_a, *J*=7.2 Hz,), 4.47 (d, 1H, *J*=4.8 Hz), 4.23 (q, 1H, CH_b, *J*=6.8 Hz), 3.76 (s, 6H, OCH_3), 3.30, 3.02 (AB quartet, 1H for each, J_{AB}=11.2 Hz and *J*=4.8 Hz), 1.71 (d, 3H, CH_{3a}, *J*=6.8 Hz), 1.45 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. (major/minor: 3.2). ATR-FTIR: 3328, 1609 cm^{-1}.

4.6. Transformation of Chiral Hemiaminals to Thiazol-2-imines

4.6.1. General Procedure

Transformations of the chiral hemiaminals **19-22** to thiazol-2-imine **23-26** were followed by taking ^{1}H NMR spectra periodically. The solvent effect for the transformation was investigated by following the kinetics in $CDCl_3$ and in C_6D_6.

4.6.1.1. 3-((*R*)-1-phenylethyl)-2-((*R*)-1-phenylethylimino)thiazoline (23*RR*). Oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.14 (m, 10H), 6.46 (d, 1H, CH(C-4), *J*=4.8 Hz), 5.86 (q, 1H, CH_a, *J*=7.2 Hz), 5.76 (d, 1H, CH(C-5), *J*=4.8 Hz), 4.09 (q, 1H, CH_b, *J*=6.4 Hz), 1.72 (d, 3H, CH_{3a}, *J* = 7.2 Hz), 1.50 (d, 3H, CH_{3b}, *J*=6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 128.8, 128.7, 128.6, 125.5, 127.9, 127.3, 126.9, 126.5, 126.2, 124.3, 96.6, 63.6, 53.1, 25.2, 19.4 ppm.

4.6.1.2. 3-((*S*)-1-phenylethyl)-2-((*S*)-1-phenylethylimino)thiazoline (23*SS*). Oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.14 (m, 10H), 6.46 (d, 1H, CH(C-4), *J*=4.8 Hz), 5.86 (q, 1H, CH_a, *J*=7.2 Hz), 5.76 (d, 1H, CH(C-5), *J*=4.8 Hz), 4.09 (q, 1H, CH_b, *J*=6.4 Hz), 1.72 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.50 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 128.8, 128.7, 128.6, 125.5, 127.9, 127.3, 126.9, 126.5, 126.2, 124.3, 96.6, 63.6, 53.1, 25.2, 19.4 ppm.

4.6.1.3. 3-((*R*)-1-(naphthalen-1-yl)ethyl)-2-((*R*)-1-(naphthalen-1-yl) ethylimino)thiazoline (24*RR*). Oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-6.99 (m, 14H, ArH), 6.55 (q, 1H, *J*=6.8 Hz), 6.14 (d, 1H, CH(C-4), *J*=5.2 Hz), 5.58 (d, 1H, CH(C-5), *J*=5.2 Hz), 4.88 (q, 1H, *J*=6.4 Hz), 1.85 (d, 3H, CH_{3a}, *J* = 6.8 Hz), 1.79 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 142.2, 136.8, 134.0, 133.8, 131.6, 131.3, 128.8, 128.4, 127.1, 126.7, 125.9, 125.5, 124.9, 124.4, 124.2, 124.1, 123.6, 9, 96.8, 61.6, 49.7, 24.3, 18.2 ppm.

4.6.1.4. 3-((*S*)-1-(naphthalen-1-yl)ethyl)-2-((*S*)-1-(naphthalen-1-yl) ethylimino)thiazoline (24*SS*). Oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-6.99 (m, 14H, ArH), 6.55 (q, 1H, *J*=6.8 Hz), 6.14 (d, 1H, CH(C-4), *J*=5.2 Hz), 5.58 (d, 1H, CH(C-5), *J*=5.2 Hz), 4.88 (q, 1H, *J*=6.4 Hz), 1.85 (d, 3H, CH_{3a}, *J* = 6.8 Hz), 1.79 (d, 3H, CH_{3b}, *J* = 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 142.2, 136.8, 134.0, 133.8, 131.6, 131.3, 128.8, 128.4, 127.1, 126.7, 125.9, 125.5, 124.9, 124.4, 124.2, 124.1, 123.6, 9, 96.8, 61.6, 49.7, 24.3, 18.2 ppm.

4.6.1.5. 3-((*R*)-1-cyclohexylethyl)-2-((*R*)-1-cyclohexylethylimino) thiazoline (25*RR*). Oily.^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, 1H, CH(C-4), *J*=5.2 Hz), 5.95 (d, 1H, CH(C-5), *J*=5.2 Hz), 4.20 (qd, *J*=7.2 Hz and *J*=6.8 Hz, 1H, CH_a), 2.56 (qd, *J*=6.4 Hz, 1H, CH_b), 1.77-0.87 (m, 22H cyclohexyl protons), 1.18 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.01 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 127.1, 105.9, 63.9, 60.1, 43.6, 42.3, 30.3-25.7, 18.1, 16.8 ppm.

4.6.1.6. 3-((*S*)-1-cyclohexylethyl)-2-((*S*)-1-cyclohexylethylimino) thiazoline (25*SS*). Oily.^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, 1H, CH(C-4), *J*=5.2 Hz), 5.95 (d, 1H, CH(C-5), *J*=5.2 Hz), 4.20 (qd, *J*=7.2 Hz and *J*=6.8 Hz, 1H, CH_a), 2.56 (qd, *J*=6.4 Hz, 1H, CH_b),1.77-0.87 (m, 22H cyclohexyl protons), 1.18 (d, 3H, CH_{3a}, *J*=7.2 Hz), 1.01 (d, 3H, CH_{3b}, *J*=6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 127.1, 105.9, 63.9, 60.1, 43.6, 42.3, 30.3-25.7, 18.1, 16.8 ppm.

4.6.1.7. 3-((*R*)-1-(4-methoxyphenyl)ethyl)-2-((*R*)-1-(4-methoxyphenyl) ethylimino) thiazoline (26*RR*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-6.70 (m, 8H, ArH), 6.34 (d, 1H, CH(C-4), *J*=4.8 Hz), 5.76 (q, 1H, *J*=6.8 Hz), 5.66 (d, 1H, CH(C-5), *J*=4.8 Hz), 3.98 (q, 1H, *J*=6.4 Hz), 3.70 (s, 3H, OCH_{3a}), 3.70 (s, 3H, OCH_{3b}), 1.60 (d, 3H, CH_{3a}, *J*=6.8 Hz), 1.42 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 159.9, 159.5 128.4, 127.9, 114.5, 111.4, 106.6, 59.7, 55.3, 55.2, 23.1, 19.5 ppm.

4.6.1.8. 3-((*S*)-1-(4-methoxyphenyl)ethyl)-2-((*S*)-1-(4-methoxyphenyl) ethylimino) thiazoline (26*SS*). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-6.70 (m, 8H, ArH), 6.34 (d, 1H, CH(C-4), *J*=4.8 Hz), 5.76 (q, 1H, *J*=6.8 Hz), 5.66 (d, 1H, CH(C-5), *J*=4.8 Hz), 3.98 (q, 1H, *J*=6.4 Hz), 3.70 (s, 3H, OCH_{3a}), 3.70 (s, 3H, OCH_{3b}), 1.60 (d, 3H, CH_{3a}, *J*=6.8 Hz), 1.42 (d, 3H, CH_{3b}, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 159.9, 159.5 128.4, 127.9, 114.5, 111.4, 106.6, 59.7, 55.3, 55.2, 23.1, 19.5 ppm.

4.7. Bromination of Compound 23*SS*

4.7.1. General Procedure

The starting compound was dissolved in CH_2Cl_2 and excess Br_2 was added to the solution. The mixture was stirred at room temperature for 5 minutes. At the end of the this period, the solvent was evaporeted and the crude product was purified from a mixture of ethyl acetate-hexane.

4.7.1.1. (*S*)-*N*-(4,5-dibromo-3-((*S*)-1-phenylethyl)thiazolidin-2-ylidene) -1-phenylethanamine (27). This compound was synthesized using 0.08 g (0.26 mmol) 23*SS* and excess Br_2 in CH_2Cl_2. Yield: 0,048 g (39%), purified from ethyl acetate/hexane mixture. Pale yellow solid, mp: 144.8-146.2 ^{0}C.^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.63-7.04 (m, 10H, ArH), 6.24 (q, 1H, CH, *J*=6.8 Hz), 5.64(s, 1H, CH at C-4), 5.37 (s, 1H, CH at C-5), 4.56 (q, 1H, CH, *J*=6.8 Hz), 1.81 (d, 3H CH_3, *J*=6.8 Hz), 1.77 (d, 3H CH_3, *J*=6.8 Hz) ppm, for minor isomer δ 7.63-7.04 (m, 10H, ArH), 6.28 (q, 1H, CH, *J*=6.8 Hz), 5.96(s, 1H, CH at C-4), 5.45 (s, 1H, CH at C-5), 4.59 (q, 1H, CH, *J*=6.8 Hz), 1.58 (d, 3H CH_3, *J*=6.8 Hz), 1.33 (d, 3H CH_3, *J*=6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 139.6, 137.4, 129.6, 129.4, 129.3, 128.4, 127.6, 126.4, 125.7, 94.2, 60.9, 57.7, 51.3, 22.5, 19.1 ppm.

4.8. Reduction of Axially Chiral Pyridine Compounds with $LiAlH_4$

4.8.1. General Procedure

The reduction of axially chiral pyridine compounds **28**-**31** were carried out according to general procedure 4.5.1.

4.8.1.1. (±)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (32). This compound was synthesized according to the general procedure using 0.1 g (28) (0.37 mmol), 0.021 g $LiAlH_4$ (0.56 mmol) and 10 mL THF. Yield: 0,065 g (65%), oily. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, 1H, ArH, *J*=4.0 Hz), 8.34 (m, 2H, ArH), 7.80 (m, 1H, ArH), 7.71 (m, 1H, ArH), 7.11 (m, 2H, ArH), 7.05 (m, 1H, ArH), 6.24 (d, 1H, *J*=5.6 Hz), 5.52 (br, s, 1H,

OH), 3.52, 3.27 (AB quartet, 1H for each, J_{AB}=12.0 Hz and J=5.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 156.1, 150.3, 148.1, 138.6, 125.6, 122.4, 119.5, 117.3, 104.8, 85.4, 34.0 ppm. ATR-FTIR: 3331, 1654 cm^{-1}.

4.8.1.2. (±)-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino)thiazolidin-4-ol (33). This compound was synthesized according to the general procedure using 0.1 g (29) (0.34 mmol), 0.019 g $LiAlH_4$ (0.50 mmol) and 10 mL THF. Yield: 0,052 g (51%), pale yellow cyristal, mp: 168-170 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (d, 2H, ArH, J = 2.8 Hz), 7.61 (d, 1H, ArH, J = 7.2 Hz), 7.35 (d, 1H, ArH, J=6.8 Hz), 7.18 (dd, 1H, ArH, J=4.8 Hz and J=7.2 Hz), 6.83 (dd, 1H, ArH, J= 4.8 Hz and J=7.2 Hz), 6.22 (br, s, 1H, OH), 5.80 (d, 1H, J=4.8 Hz), 3.49, 3.21 (AB quartet, 1H for each, J_{AB}=11.6 Hz and J=4.8 Hz), 2.30 (s, 3H, CH_3), 2.00 (d, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 154.1, 145.0, 144.2, 139.9, 138.3, 131.6, 128.3, 122.5, 119.1, 83.9, 36.1, 18.8, 17.4 ppm. ATR-FTIR: 1575 cm^{-1}.

4.8.1.3. (±)-5-methyl-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-ol (34). This compound was synthesized according to the general procedure using 0.1 g (30) (0.35 mmol), 0.020 g $LiAlH_4$ (0.53 mmol) and 10 mL THF. Yield: 0,043 g (43%), yellow colored solid, mp: 64-66 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 8.42-6.34 (m, 8H, ArH), 5.82 (d, 1H, CH at C_4, J=0.8 Hz), 5.12 (br, 1H, OH), 3.56 (qd, 1H, CH at C_5, J=0.8 Hz and J=7.2 Hz), 1.48 (d, 3H, CH_3, J=7.2 Hz) ppm. for minor isomer δ 8.43-6.72 (m, 8H, ArH), 5.96 (d, 1H, CH at C_4, J=5.2 Hz), 5.29 (br, 1H, OH), 3.86 (qd, 1H, CH at C_5, J=5.2 Hz and J=7.2 Hz), 1.54 (d, 3H, CH_3, J=6.8 Hz ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 159.3, 157.7, 153.2, 153.0, 147.3, 137.6, 137.6, 137.5, 137.4, 119.6, 119.5, 118.9, 118.8, 113.4, 109.4, 89.7, 85.1, 43.3, 41.9, 21.2, 13.0 ppm. ATR-FTIR: 3342, 1589 cm^{-1}.

4.8.1.4. (±)-5-methyl-3-(3-methylpyridin-2-yl)-2-(3-methylpyridin-2-ylimino) thiazolidin-4-ol (35). This compound was synthesized according to the general procedure using 0.1 g (31) (0.32 mmol), 0.018 g $LiAlH_4$ (0.48 mmol) and 10 mL THF. Yield: 0,038 g (38%), yellow colored solid, mp:112-115 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 8.06-6.60 (m, 6H, ArH), 6.27 (br s, 1H, OH), 5.26 (s, 1H, CH at C_4), 3.50 (q, 1H, CH at C_5, J=7.2 Hz), 2.21 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.21 (d, 3H, CH_3 at C-5, J=7.2 Hz) ppm. for minor isomer δ 8.06-6.60 (m, 6H, ArH), 6.27 (br s, 1H, OH), 5.26 (s, 1H, CH

at C_4), 3.60 (dq, 1H, CH at C_5, *J*=6.8 Hz and *J*=11.2 Hz), 2.29 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.54 (d, 3H, CH_3 at C-5, *J*=6.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 156.8, 146.4, 144.9, 143.8, 139.6, 138.1, 131.3, 128.0, 123.5, 122.2, 120.4, 118.7, 117.2, 116.4, 113.3, 89.7, 85.7, 45.2, 44.0, 20.9, 18.4, 18.2, 17.2 ppm. ATR-FTIR: 3358, 1599 cm^{-1}.

4.9. Reduction of 5-Methyl-3-aryloxazolidine-2,4-diones with $LiAlH_4$.

4.9.1. General Procedure

The appropriate amount of enantiomericaly pure 5-methyl-3-aryloxazolidine-2,4-dione was dissolved in THF and appropriate equiv. $LiAlH_4$ was added to the mixture. The reaction mixture was stirred at room temperature for 5 minutes. At the end of the this period water was added to quench the reaction mixture. And the mixture was extracted with ethyl acetate and dried with $CaCl_2$. And the solvent was evoporated.

4.9.1.1. (±)-4-hydroxy-5-methyl-3-phenyloxazolidin-2-one (36). This compound was synthesized according to the general procedure using 0.115 g 16*S* (0.60 mmol), .034 g $LiAlH_4$ (0.89 mmol) and 10 mL THF. Oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.61-7. 22 (m, 5H, Ar-H), 5.29 (d, 1H, CH at C-4, *J* = 6.4 Hz), 4.48 (dq, 1H, CH at C-5, *J*=1.6 Hz and *J*=6.4 Hz), 3.69 (d, 1H, OH, *J* = 8.4 Hz), 1.50 (d, 3H, CH_3, *J*=6.8 Hz) ppm and for minor isomer δ 8.66-7. 05 (m, 5H, Ar-H), 5.54 (t, 1H, CH at C-4, *J* = 5.6 Hz), 4.69 (dq, 1H, CH at C-5, *J*=6.4 Hz and *J*=6.8 Hz), 3.53 (d, 1H, OH, *J* = 8.4 Hz), 1.45 (d, 3H, CH_3, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 155.0, 136.3, 129.8, 125.8, 121.8, 121.6, 86.7, 78.8, 18.8, 13.1 ppm and for minor isomer δ 159.3, 129.7, 125.6, 124.9, 120.0, 116.9, 83.0, 75.5, 18.8, 13.1 ppm. ATR-FTIR: 3306, 1725 cm^{-1}.

4.9.1.2. (±)-4-hydroxy-5-methyl-3-*m*-tolyloxazolidin-2-one (37). This compound was synthesized according to the general procedure using 0.123 g 17*S* (0.60 mmol), .034 g $LiAlH_4$ (0.89 mmol) and 10 mL THF. Oily. ^{1}H NMR (400 MHz, $CDCl_3$): for major isomer δ 7.42-6.81 (m, 5H, Ar-H), 5.31 (d, 1H, CH at C-4, *J* = 5.6 Hz), 4.49 (dq, 1H, CH at C-5, *J*=1.6 Hz and *J*=7.6 Hz), 3.25 (d, 1H, OH, *J* = 8.4 Hz), 1.48 (d, 3H, CH_3, *J*=6.4 Hz) ppm and for minor isomer δ 8.66-6.81 (m, 5H, Ar-H), 5.56 (t, 1H, CH at C-4, *J* = 4.8 Hz), 4.70 (dq, 1H, CH at C-5, *J*=6.0 Hz and *J*=6.4 Hz), 3.53 (d, 1H, OH, *J* = 8.4 Hz), 1.49 (d,

3H, CH_3, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): for major isomer δ 172.0, 129.3, 127.1, 122.8, 119.2, 86.8, 82.9, 21.7, 19.1 ppm and for minor isomer δ 170.6, 126.4, 125.9, 117.2, 116.2, 78.5, 75.5, 21.7, 19.1 ppm. ATR-FTIR: 3302, 1730 cm^{-1}.

4.10. Ring Opening Reaction of 5-Methyl-3-aryloxazolidine-2,4-diones with $NaBH_4$

4.10.1. General Procedure

To a mixture of 5-methyl-3-aryloxazolidine-2,4-dione (1 eq.) in THF was added a solution of sodium borohydride (4 eq.) in water maintaing the reaction mixture temperature at 24-25 ^oC. The mixure was stirred at room temperature until the completion of the reaction. As soon as the disappearance of stating compound, 2 M HCl (5 eq.) was added to the reaction mixture. And the mixture was extracted with ethyl acetate and dried with $CaCl_2$. And the solvent was evaporated.

4.10.1.1. (±)1-hydroxypropan-2-yl phenylcarbamate (38). This compound was prepared according to the general procedure using 0.1 g (0.52 mmol) compound 16*S* in 0.63 ml THF (0,33 M), 0.08 g (2.09 mmol) sodium borohydride in 0,51 ml water (4,05 M). Yield: 0.056 (55%). Oily. ^1H NMR (400 MHz, $CDCl_3$): δ7.38-7.07 (m, 5H, Ar-H), 6.69 (br s, 1H, NH), 5.03-4.99 (m, 1H, CH), 3.73 and 3.69, 3.71 and 3.70 (2 AB quartets, 1 H each, CH_2, *J*= 12.00 Hz), 2.20 (s,br, 1H, OH), 1.31 (d, 3H, CH_3, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 137.7, 129.0, 123.6, 120.5, 118.8, 72.9, 66.4, 16.4 ppm. ATR-FTIR: 3303, 1700 cm^{-1}.

4.10.1.2. (±)1-hydroxypropan-2-yl *m*-tolylcarbamate (39). This compound was prepared according to the general procedure using 0.1 g (0.49 mmol) compound 17*S* in 0.60 ml THF (0,33 M), 0.075 g (1.97 mmol) sodium borohydride in 0,48 ml water (4,05 M). Yield: 0.043 (42%). ^1H NMR (400 MHz, $CDCl_3$): δ7.78-7.05 (m, 4H, Ar-H), 6.48 (br s, 1H, NH), 5.05-4.97 (m, 1H, CH), 3.76 and 3.66, 3.73 and 3.71 (2 AB quartets, 1 H each, CH_2, *J*= 12.00 Hz), 1.85 (br, 1H, OH), 2.26 (s, 3H, CH_3) ppm 1.31 (d, 3H, CH_3, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 130.5, 130.4, 126.9, 124.5, 124.3, 73.2, 66.2, 17.7, 16.5 ppm. ATR-FTIR: 3287, 1689 cm^{-1}.

4.10.1.3. (±)1-hydroxypropan-2-yl *o*-tolylcarbamate (40). This compound was prepared according to the general procedure using 0.1 g (0.49 mmol) compound 18*S* in 0.60 ml THF (0,33 M), 0.075 g (1.97 mmol) sodium borohydride in 0,51 ml water (4,05 M). Yield: 0.085 (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.76-7.04 (m, 4H, Ar-H), 6.48 (br s, 1H, NH), 5.05-4.97 (m, 1H, CH), 3.76 and 3.66, 3.73 and 3.71 (2 AB quartets, 1 H each, CH_2, *J*= 12.00 Hz), 2.26 (s, 3H, CH_3) ppm 1.31 (d, 3H, CH_3, *J*=6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 130.5, 130.4, 126.9, 124.5, 124.3, 73.2, 66.2, 17.7, 16.5 ppm. ATR-FTIR: 3274, 1688 cm^{-1}.

5. CONCLUSION

N,N'-bis-thioureas and their cyclized derivatives were synthesized as single enantiomers and their optical purities were proven by polarimetric measurements and HPLC analyses on optically active stationary phases. Conformational structures steming from the rotation about C-N partial double bond of the thioureas were studied experimentally. The variable NMR revealed that there is a rapid equilibrium between the *E,Z/Z,E* conformations in the solution but X-Ray analyses showed that the thioureas prefer to stay on the *Z,Z* conformation in the crystalline state.

Single enantiomers of the new 5-methyl-3-aryloxazolidine-2,4-diones were obtained by an asymmetric synthesis and their optical purities were proven by polarimetric measurements, HPLC analyses on optically active stationary phases and optically active auxiliary compound (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((*R*)-TFAE).

Chiral hemiaminals were synthesized from the corresponding 2-iminothiazolidine-4-ones by $LiAlH_4$ reductions stereoselectively. The hemiaminals were converted to single enantiomer thiazol-2-imines and their conversion kinetics have been followed by time dependent ^1H NMR spectroscopy. One of the thiazol-2-imine derivative was brominated stereoselectively and a diastereomeric pair was obtained from the *trans*-addition of bromine to the double bond of the alkene. The *trans* hydrogens of the dibrominated products present on adjacent carbons of the thiazolidine-4-one ring, did not couple with each other. This fact was exploited to differentiate the *cis* oriented hydrogens of the hemiaminals and from the *trans* oriented ones based on their observed coupling constants.

Another series of hemiaminals were synthesized from the axially chiral pyridine compounds carrying 2-iminothiazolidin-4-one core from the reduction with $LiAlH_4$. For these compounds because of the restricted rotation around the N_3-aryl single bond, the *M/P* isomerization was observed. The 2D-NOESY ^1H NMR experiments revealed that the OH prefer to be on the same side with the N_3 pyridine nitrogen because of the possibility for an intramolecular H-bond formation.

The single enantiomers of 5-methyl-3-aryloxazolidine-2,4-diones were reduced to their hemiaminal derivatives *via* $LiAlH_4$ reductions. Additionally their ring opening

reactions were carried out in the presence of $NaBH_4$. During these reactions, it was investigated that whether the configuration at C-5 is retained or not. It was revealed that compounds partially racemize under basic conditions because of the enolization of the molecule due to the presence of the acidic α-hydrogen at C-5 of the ring. The *ortho* tolyl derivative of 5-methyl-3-aryloxazolidine-2,4-diones was found to have less racemization ratio than the others during the ring opening reaction with $NaBH_4$. This can be explained by the steric hindrance of *ortho* methyl group that hindered the approach of the hydride ion. Furthermore, during the ring opening reactions of 5-methyl-3-aryloxazolidine-2,4-diones, the corresponding hemiaminals were found as intermediates.

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APPENDIX A: SPECTROSCOPIC DATA

^{1}H and ^{13}C NMR data for the synthesized compounds are given.

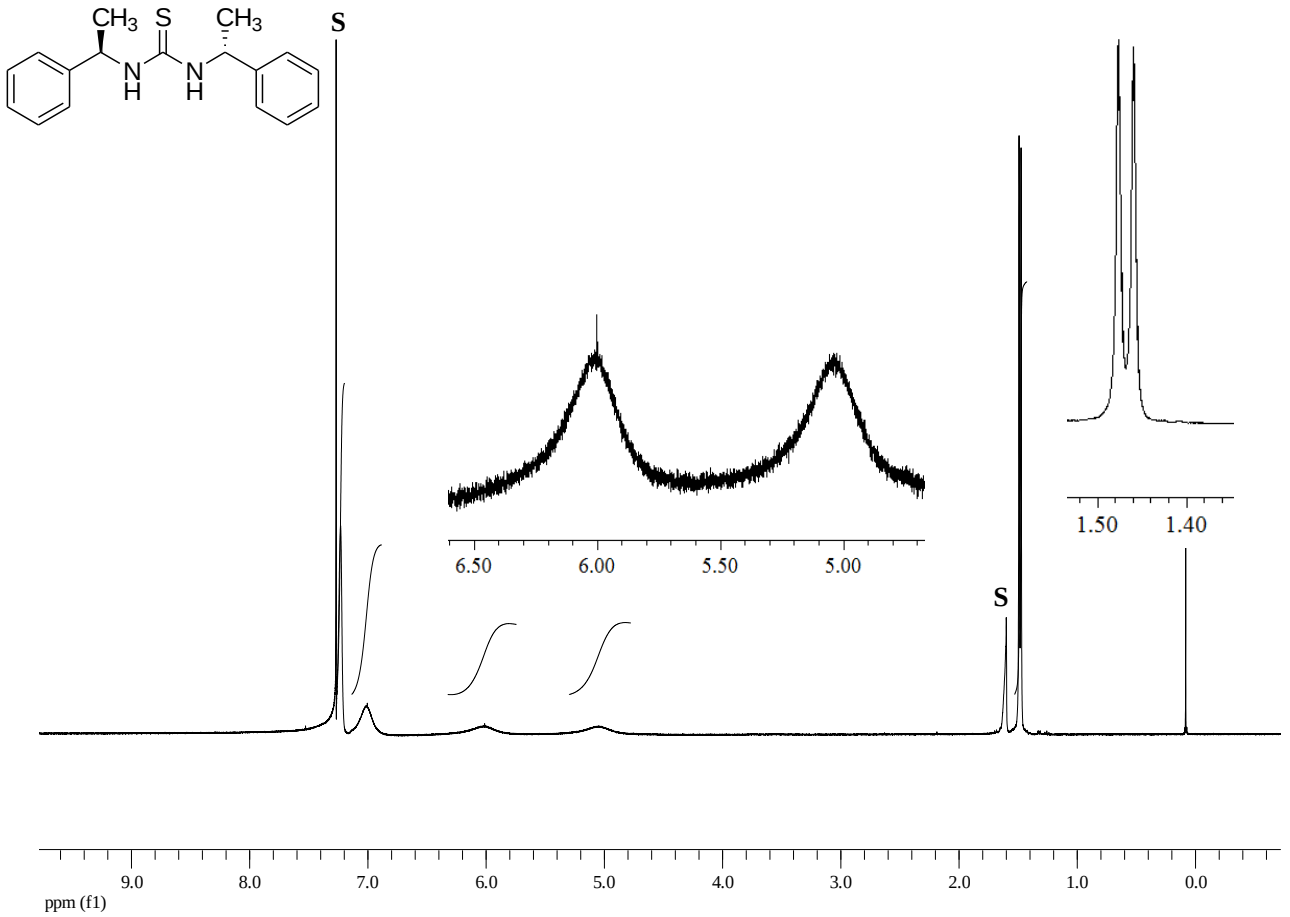

Figure A.1 ^{1}H NMR of compounds **1*RR*, 1*SS*** and **1*DL*** ($CDCl_3$).

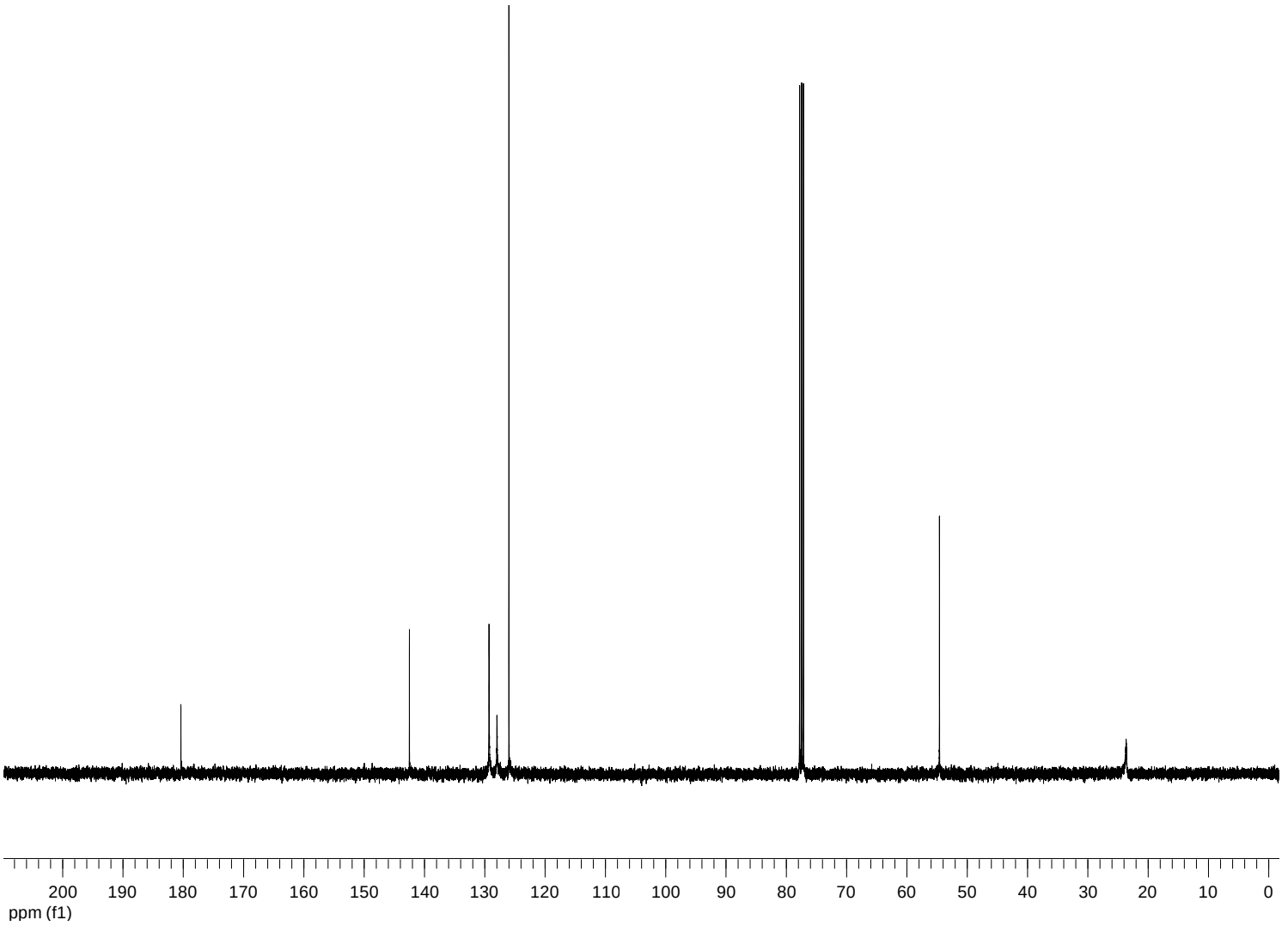

Figure A.2. ^{13}C NMR of compounds **1*RR***, **1*SS*** and **1*DL*** ($CDCl_3$).

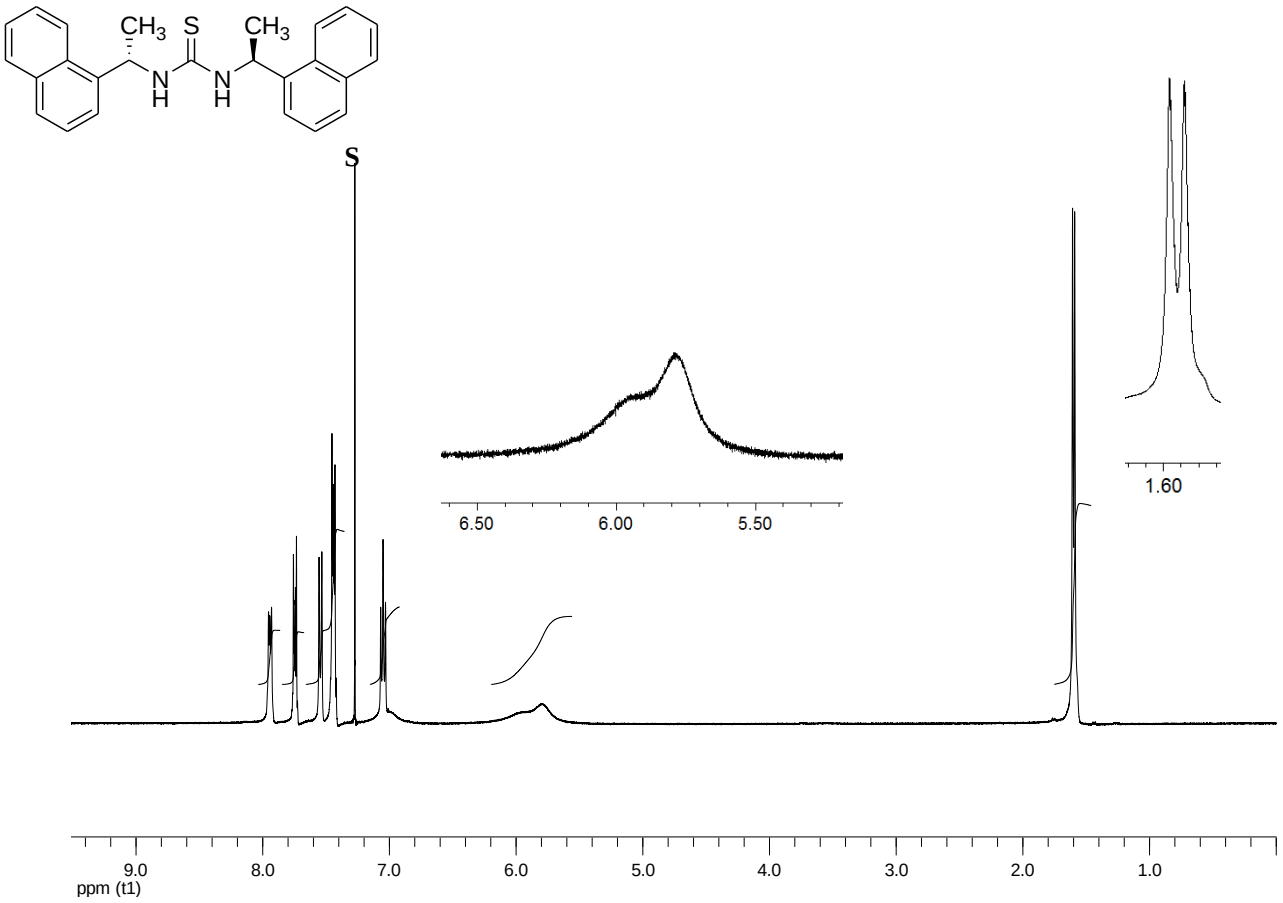

Figure A.3. ^{1}H NMR of compounds **2*RR*, 2*SS*** and **2*DL*** ($CDCl_3$).

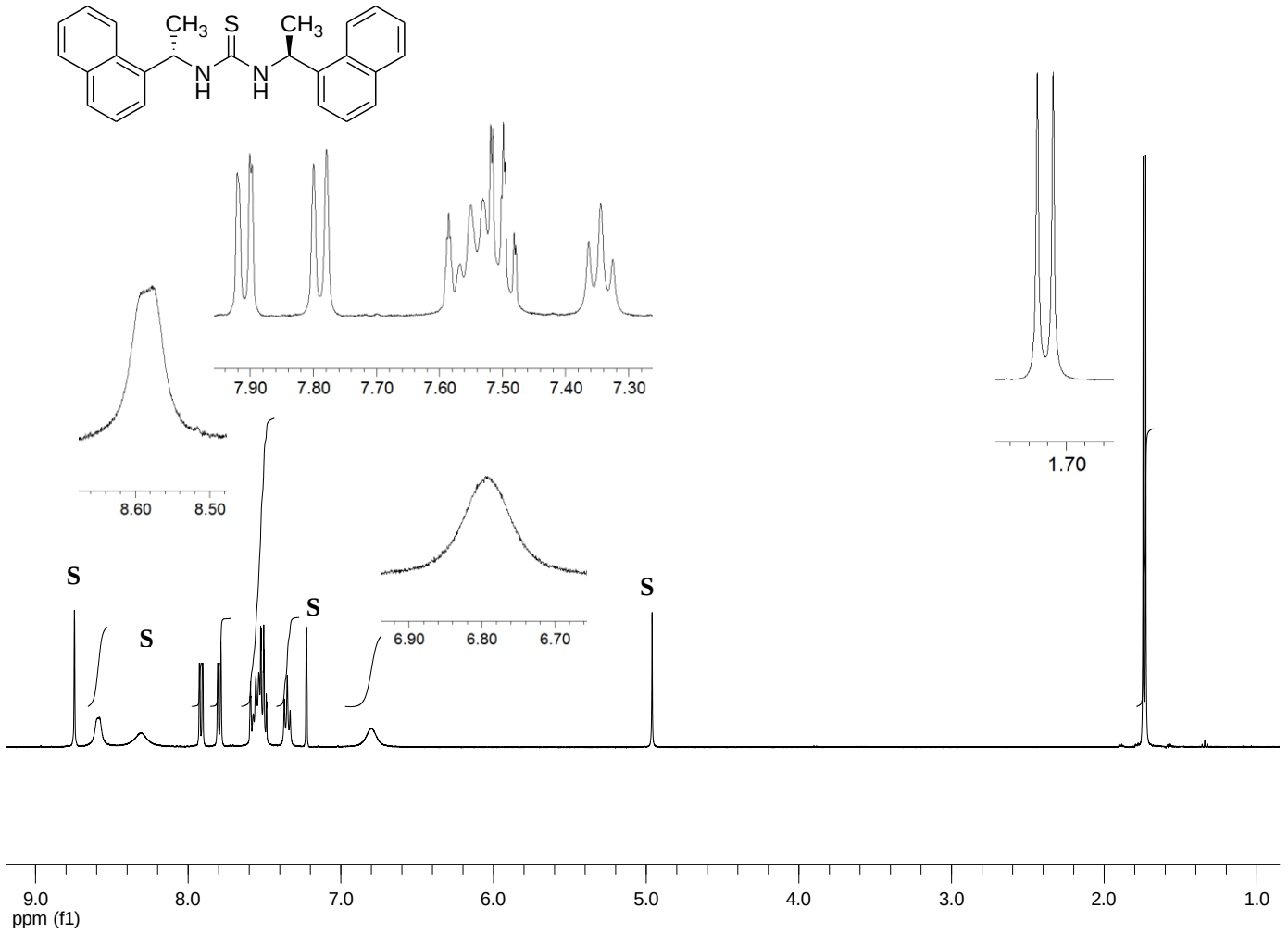

Figure A.4. ^{1}H NMR of compound **2*SS*** in Pyridine-d_5

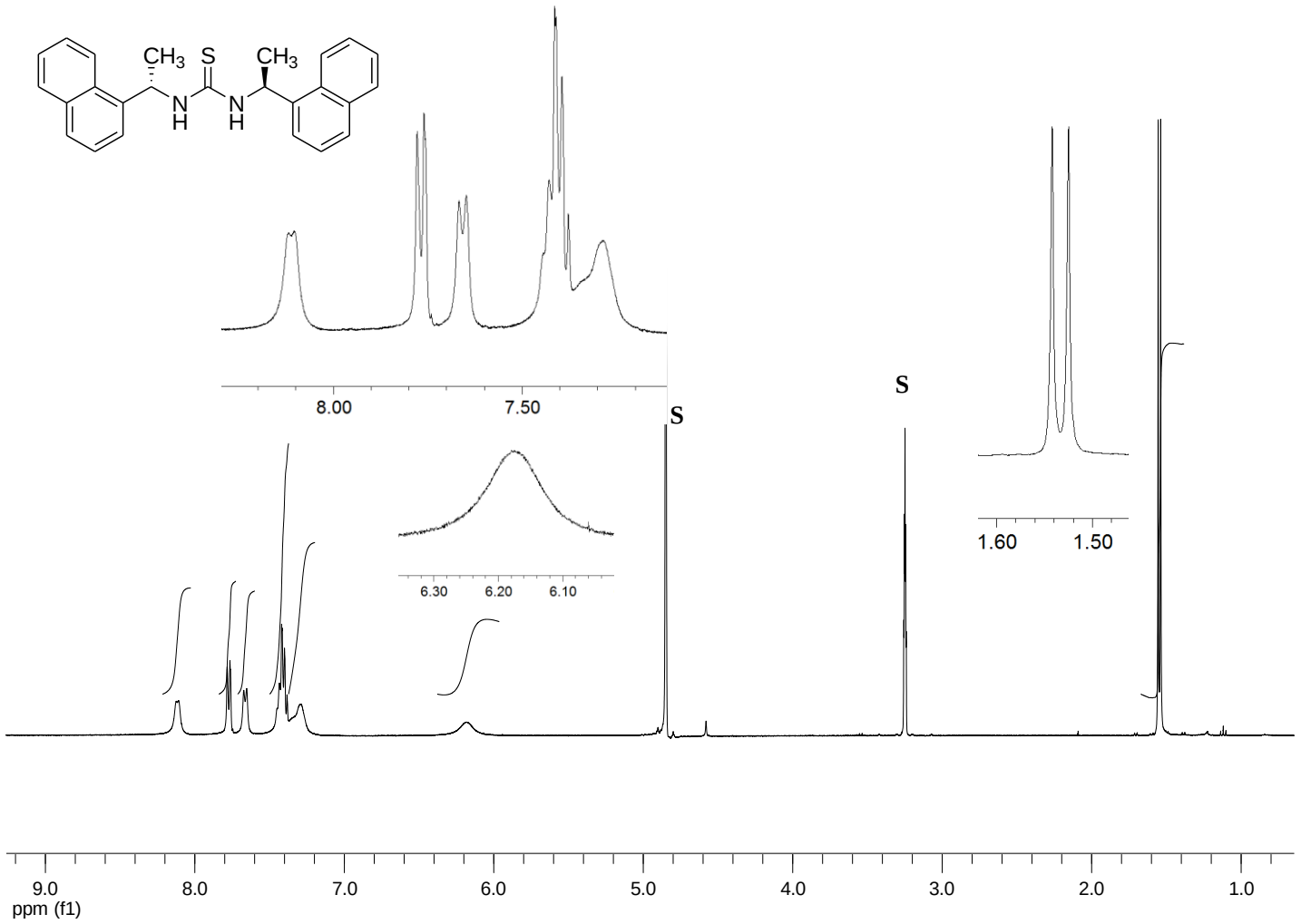

Figure A.5. ^{1}H NMR of compound **2*SS*** in Methanol-d_4.

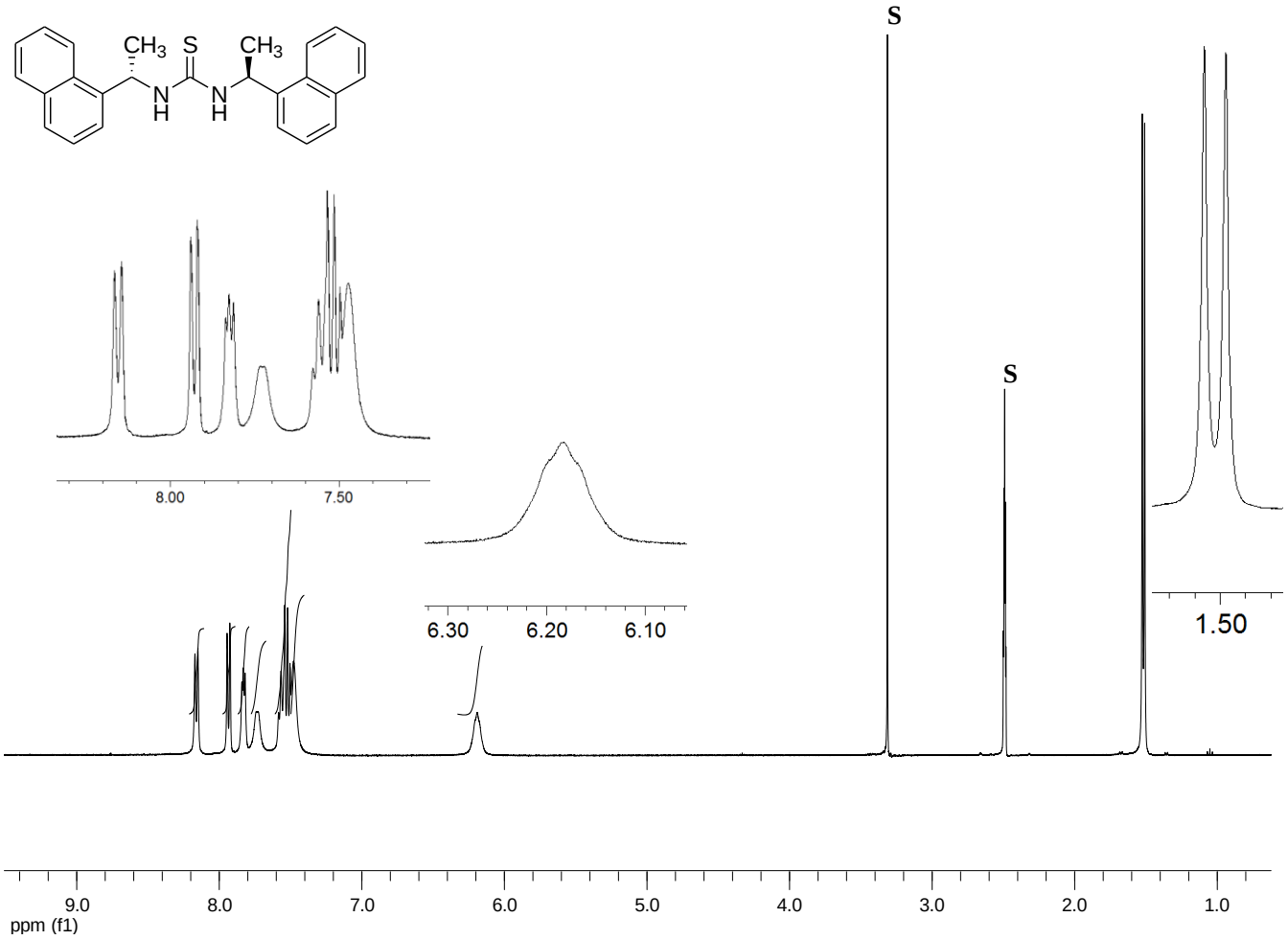

Figure A.6. ^{1}H NMR of compound **2*SS*** in DMSO-$d_{6.}$

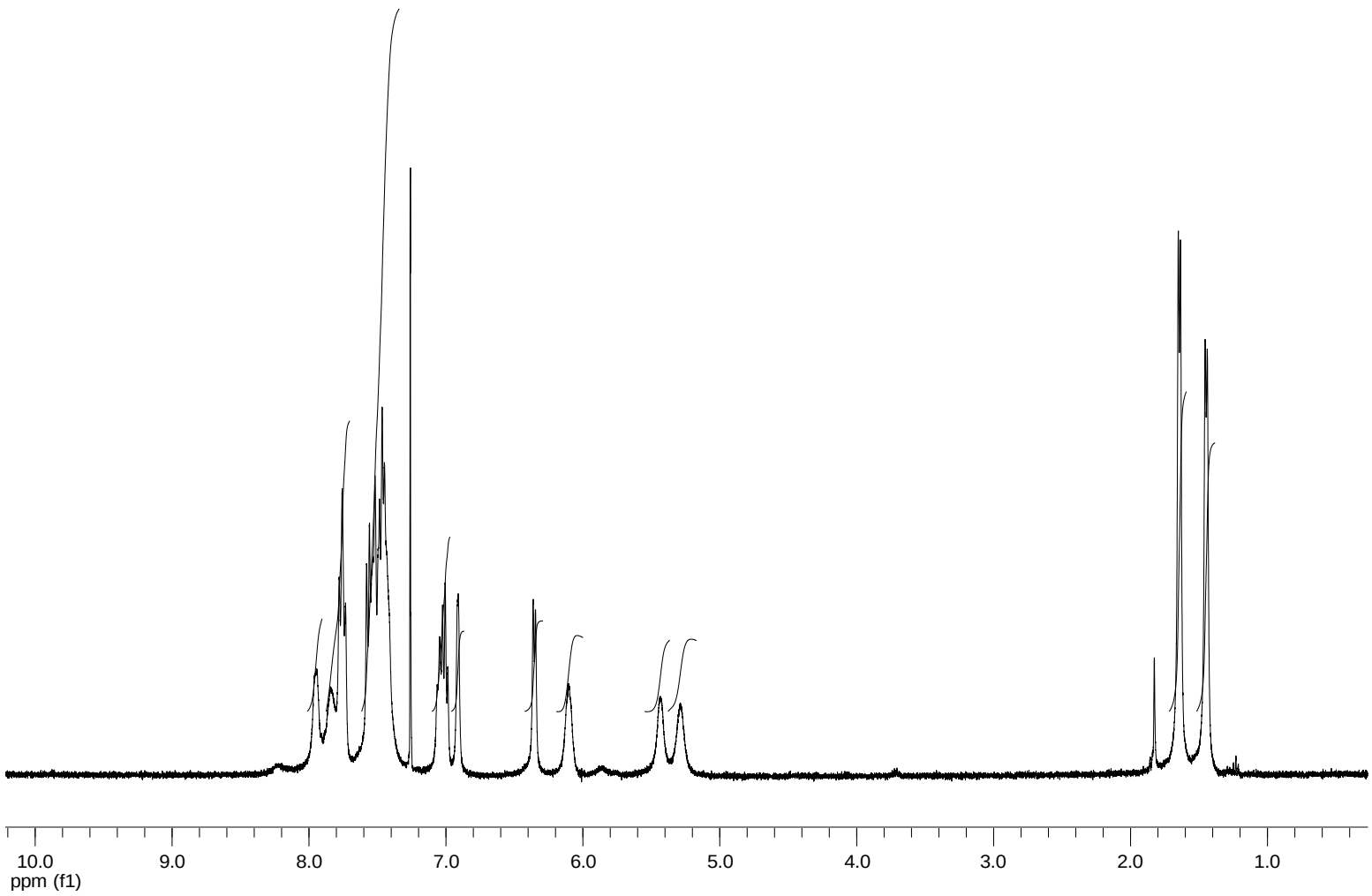

Figure A.7. ^{1}H NMR of compound **2*SS*** at 233 K in $CDCl_3$.

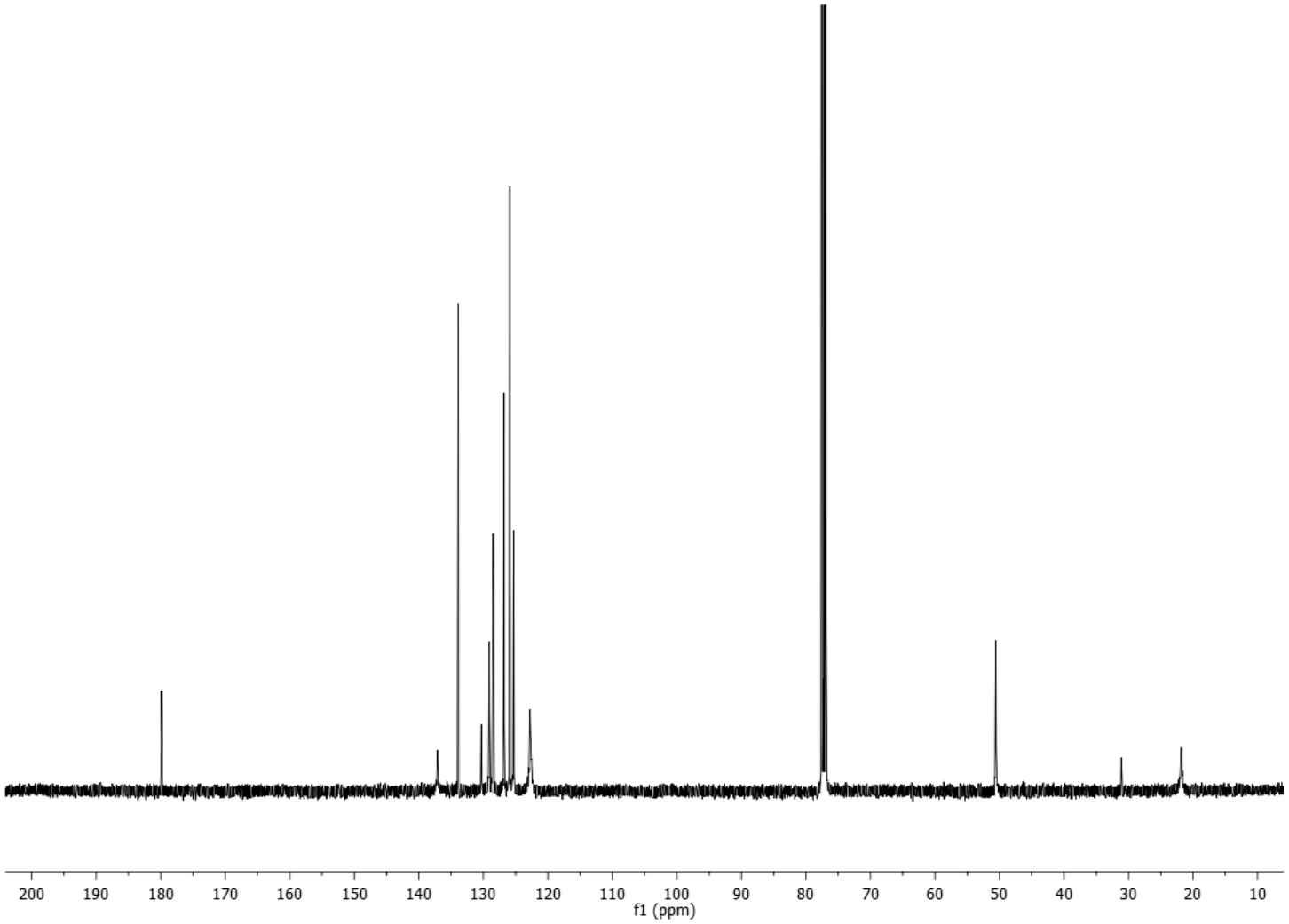

Figure A.8. ^{13}C NMR of compounds **2*RR*, 2*SS*** and **2*DL*** ($CDCl_3$).

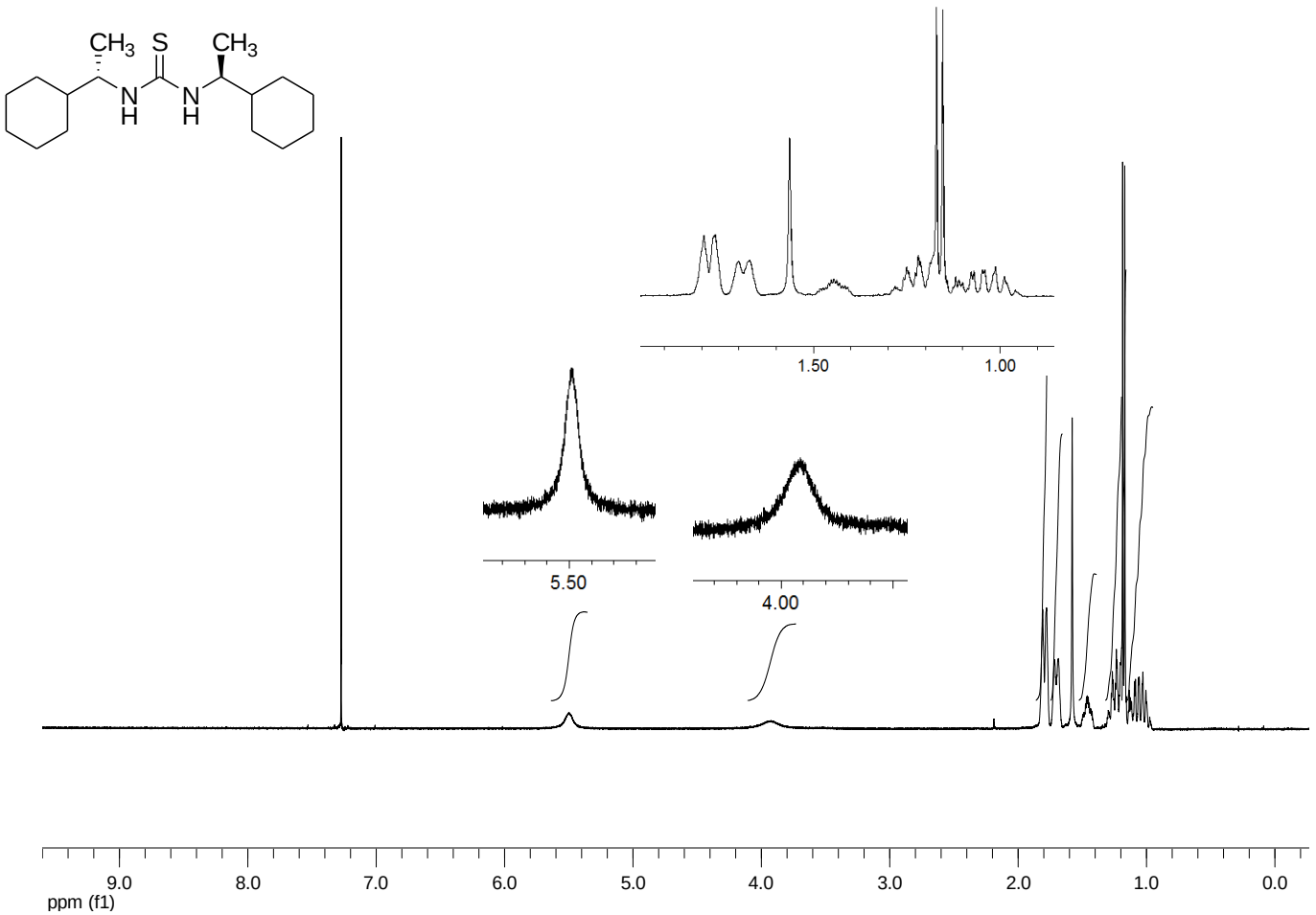

Figure A.9. ^{1}H NMR of compounds **3*RR*** and **3*SS*** ($CDCl_3$).

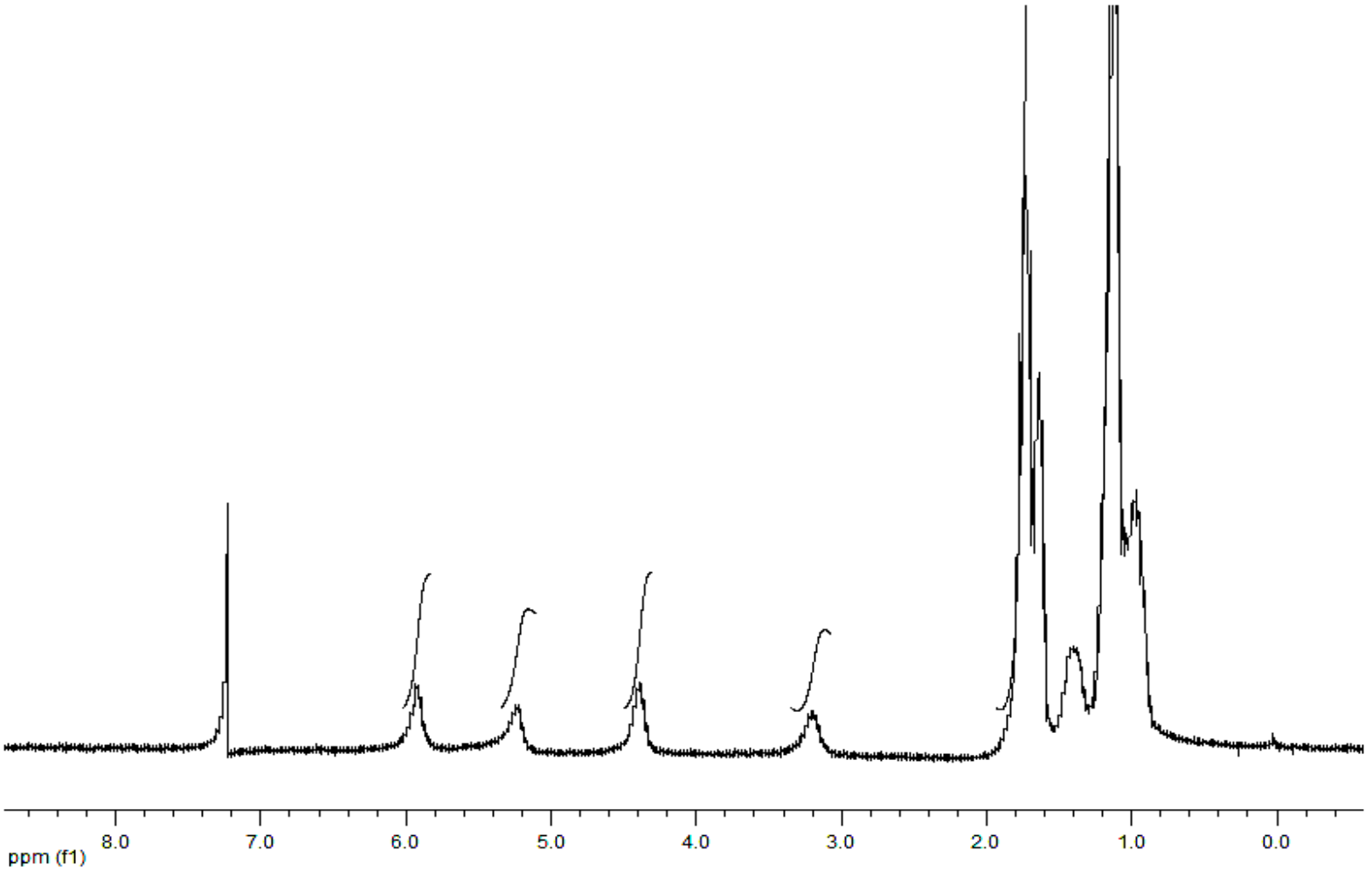

Figure A.10. ^{1}H NMR of compound **3*SS*** at 243 K in $CDCl_3$.

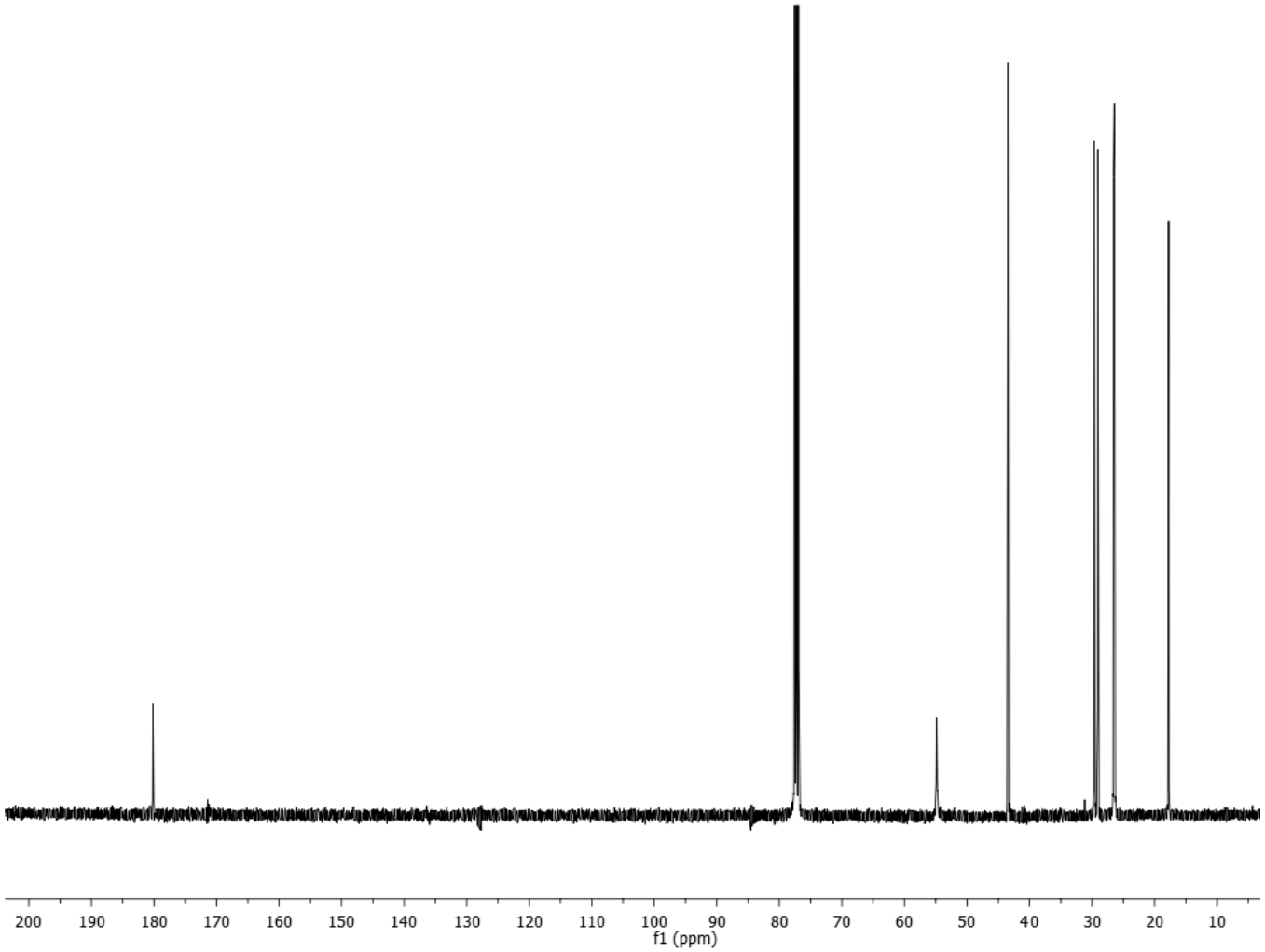

Figure A.11. ^{1}H NMR of compounds **3*RR*** and **3*SS*** ($CDCl_3$).

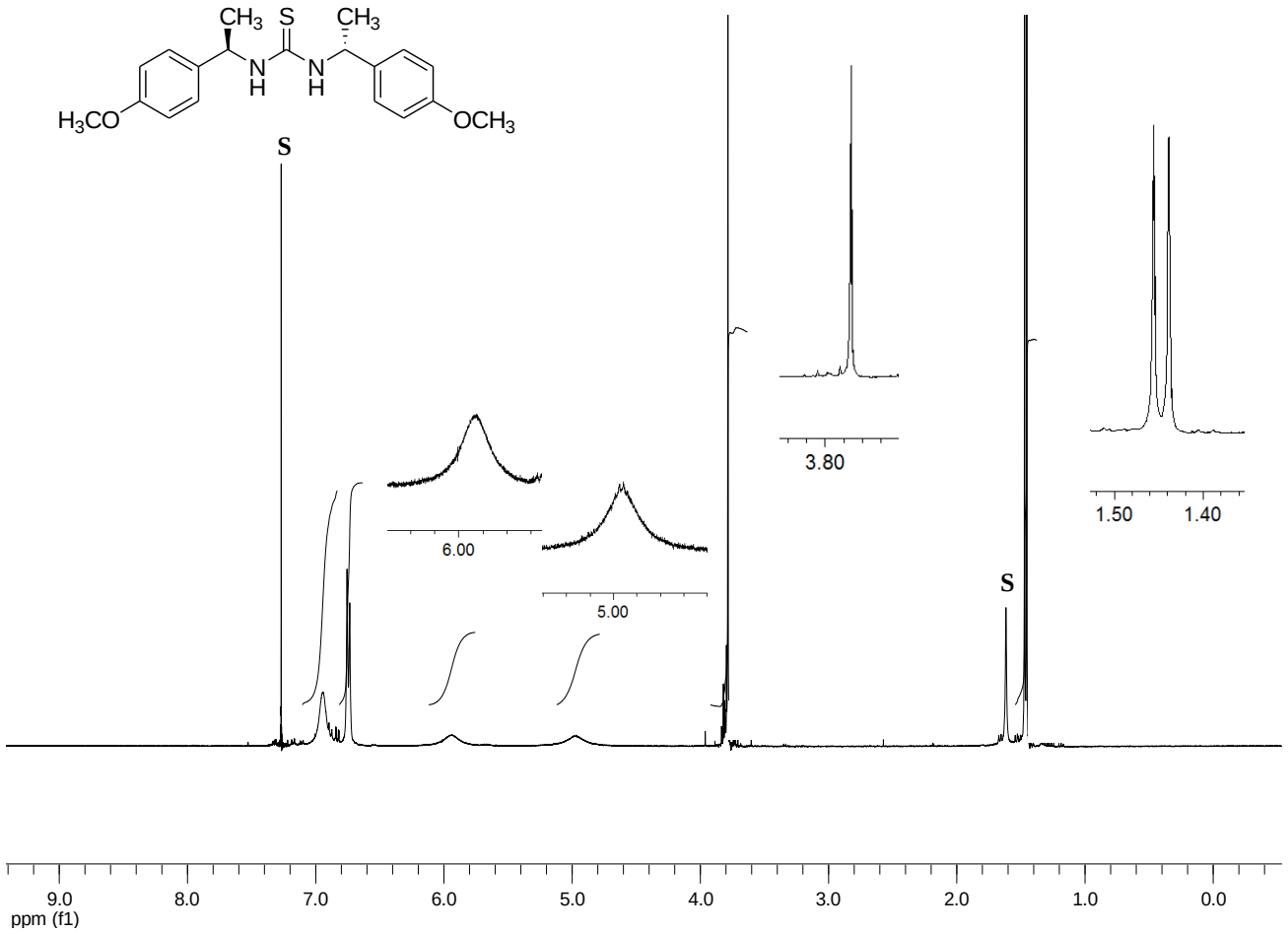

Figure A.12. ^{1}H NMR of compounds **4*RR*** and **4*SS*** ($CDCl_3$).

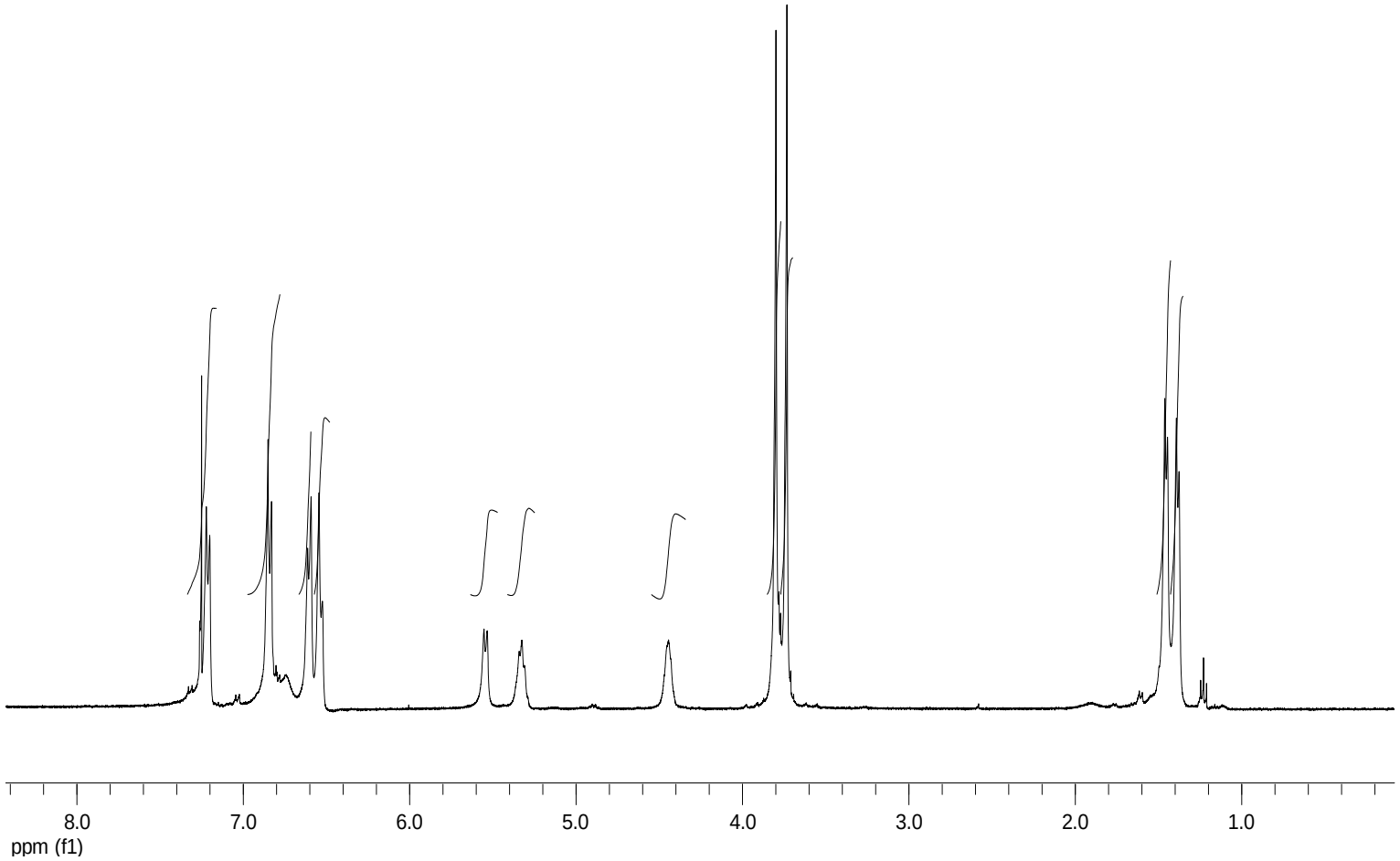

Figure A.13. ^{1}H NMR of compound **4*SS*** at 233 K in $CDCl_3$.

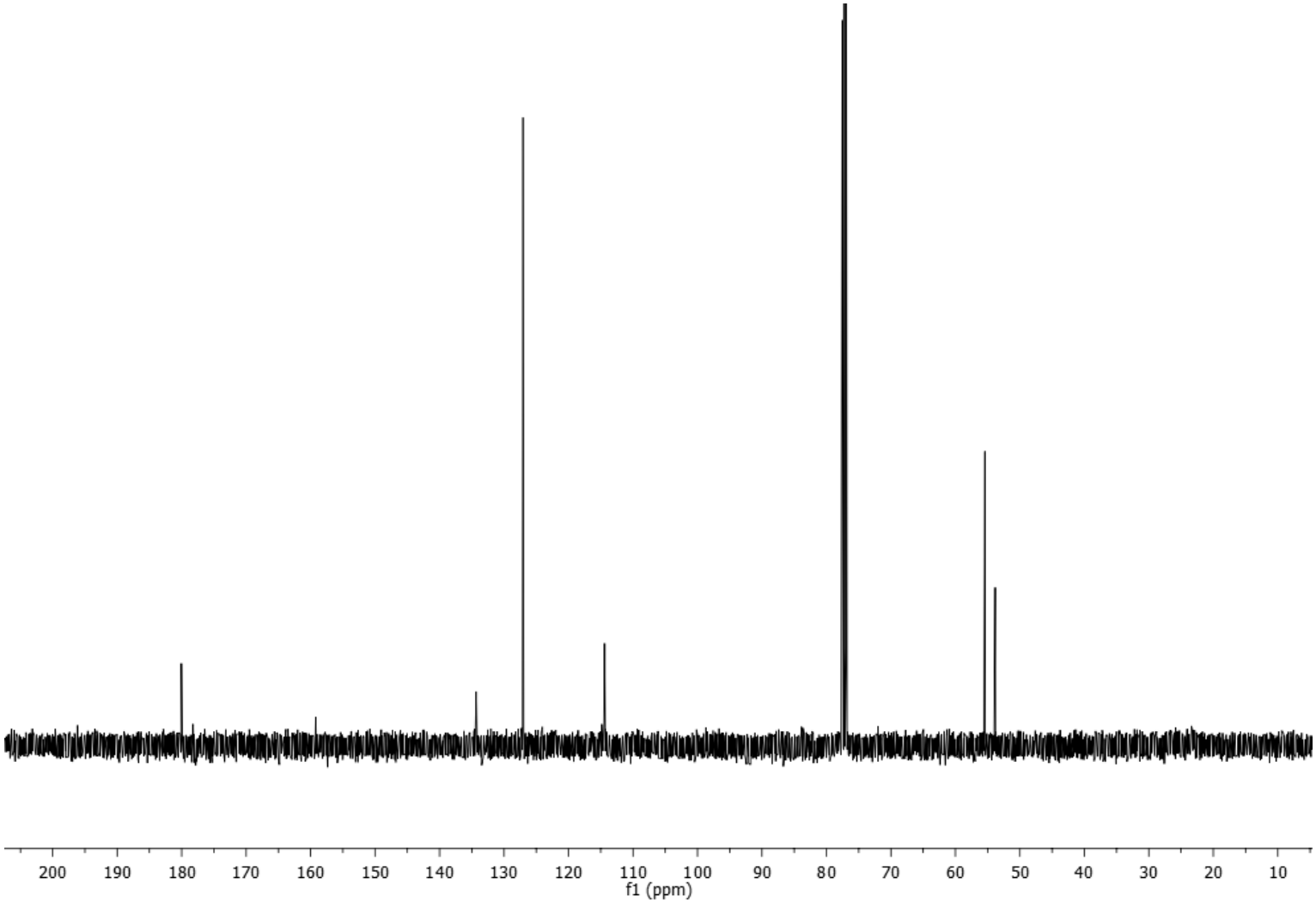

Figure A.14. ^{13}C NMR of compounds **4*SS*** and **4*RR*** ($CDCl_3$).

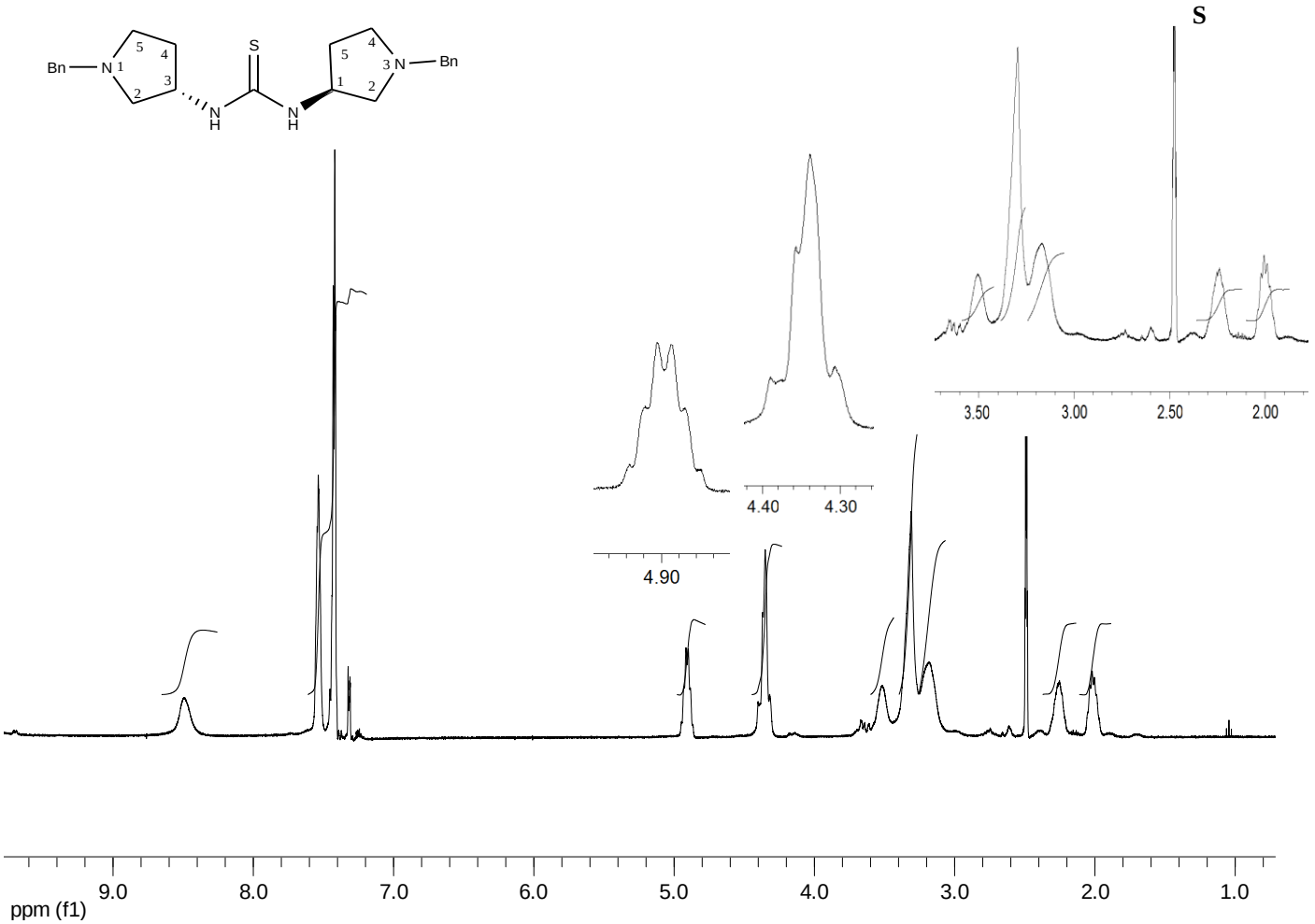

Figure A.15. ^{1}H NMR of compounds **5*SS*** and **5*RR*** (DMSO-d_6).

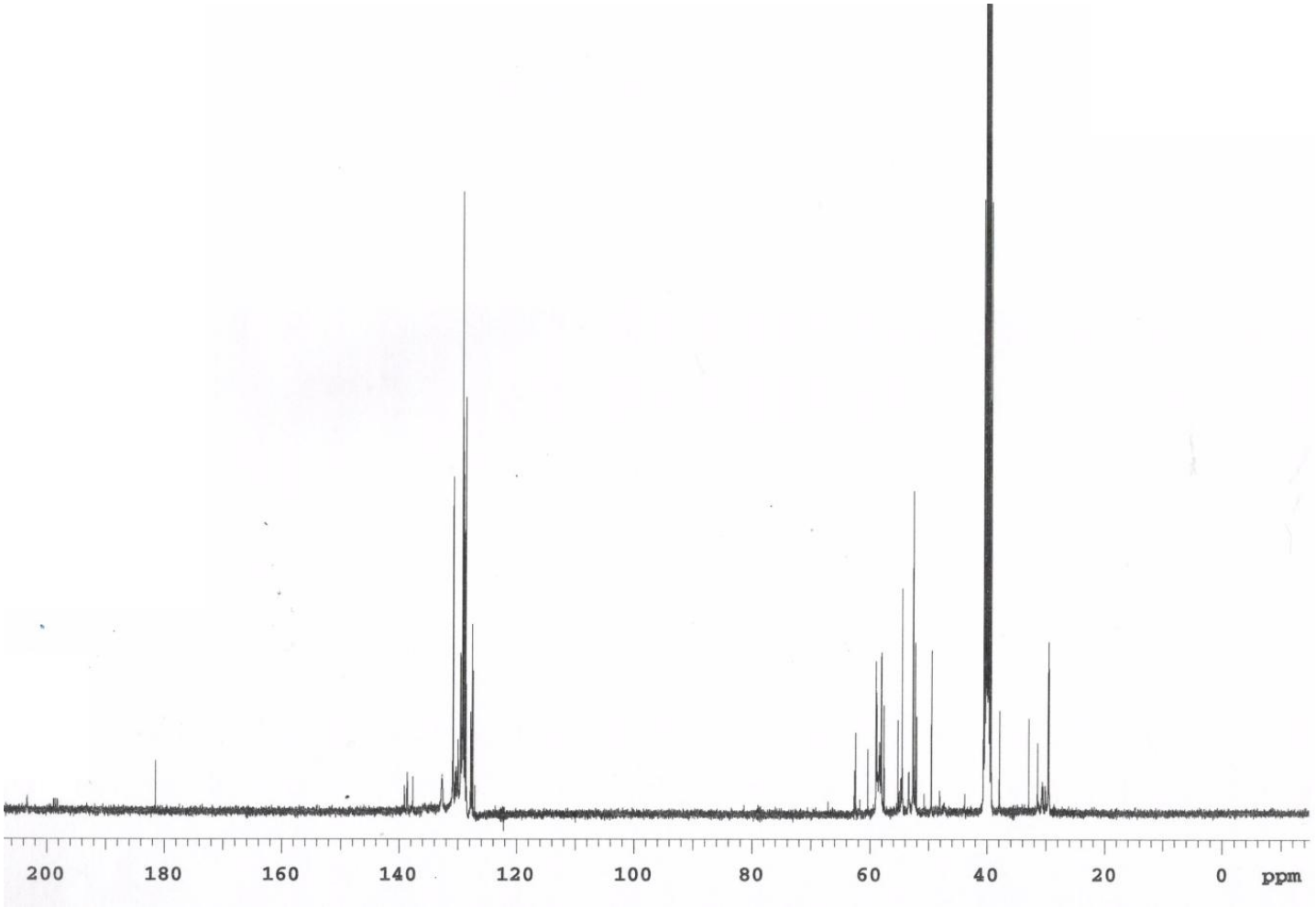

Figure A.16. ^{1}H NMR of compounds **5*RR*** and **5*SS*** (DMSO-d_6).

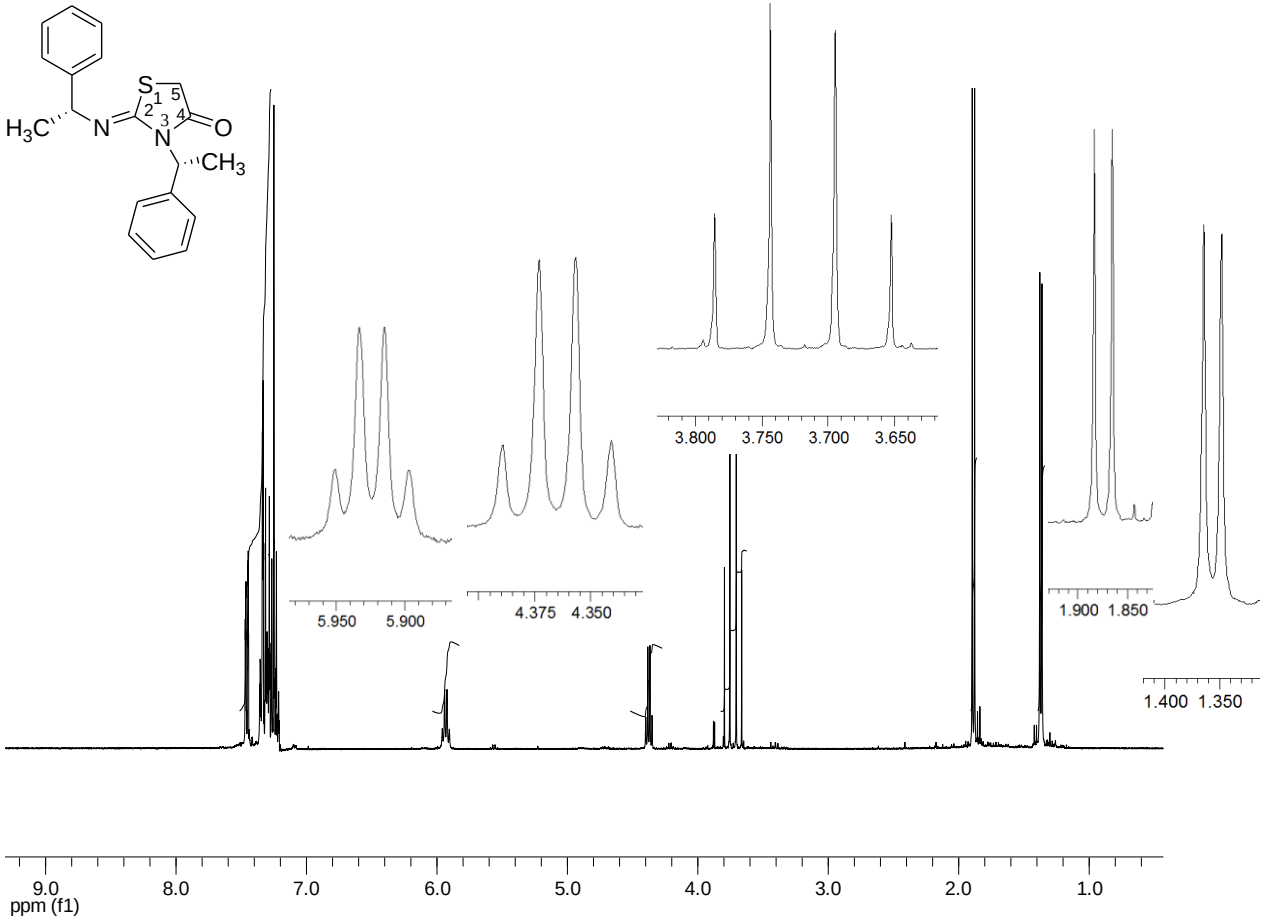

Figure A.17. ^{1}H NMR of compounds **6*RR*** and **6*SS*** ($CDCl_3$).

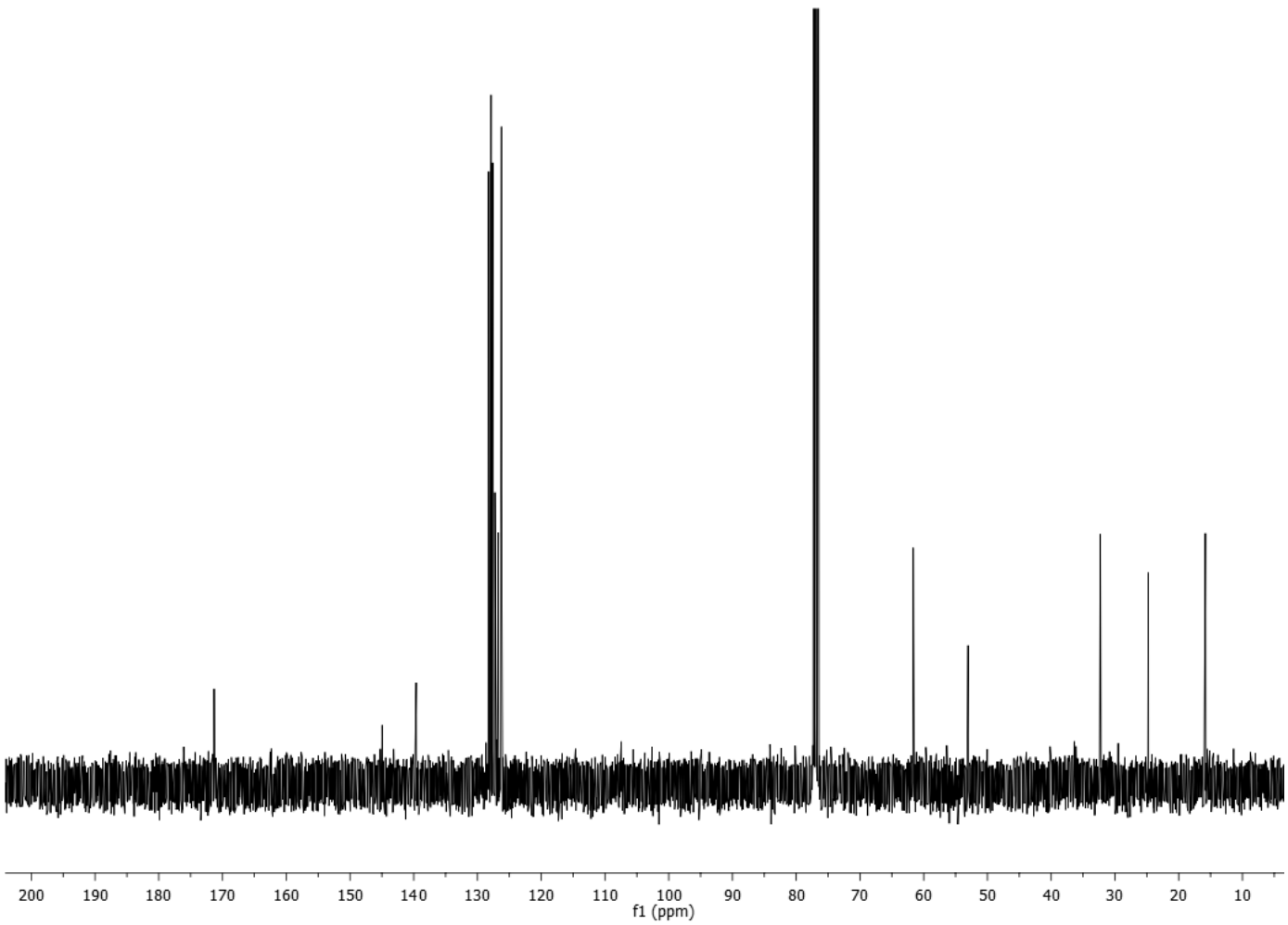

Figure A.18. ^{13}C NMR of compounds **6*RR*** and **6*SS*** ($CDCl_3$).

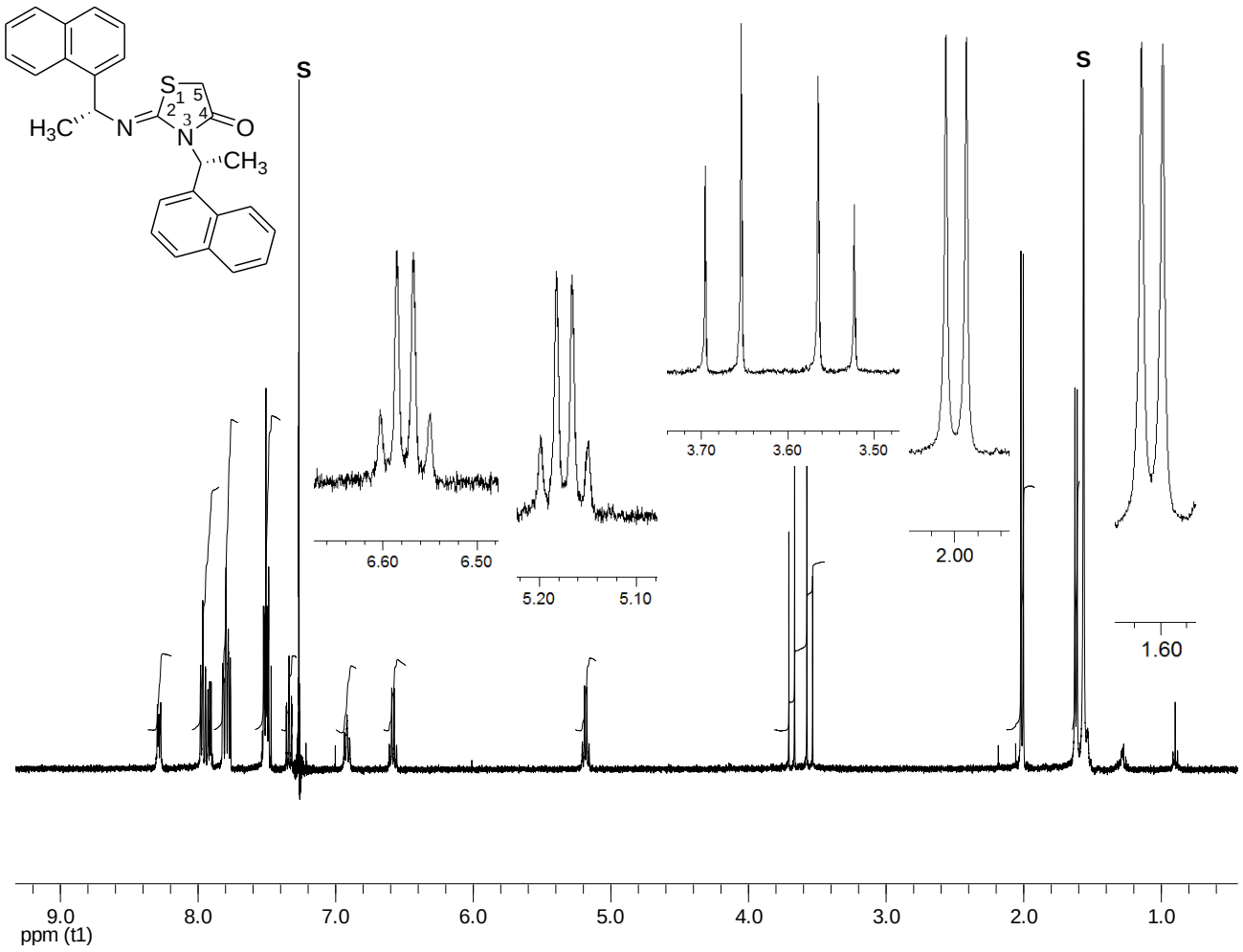

Figure A.19. ^{1}H NMR of compounds **7*RR*** and **7*SS*** ($CDCl_3$).

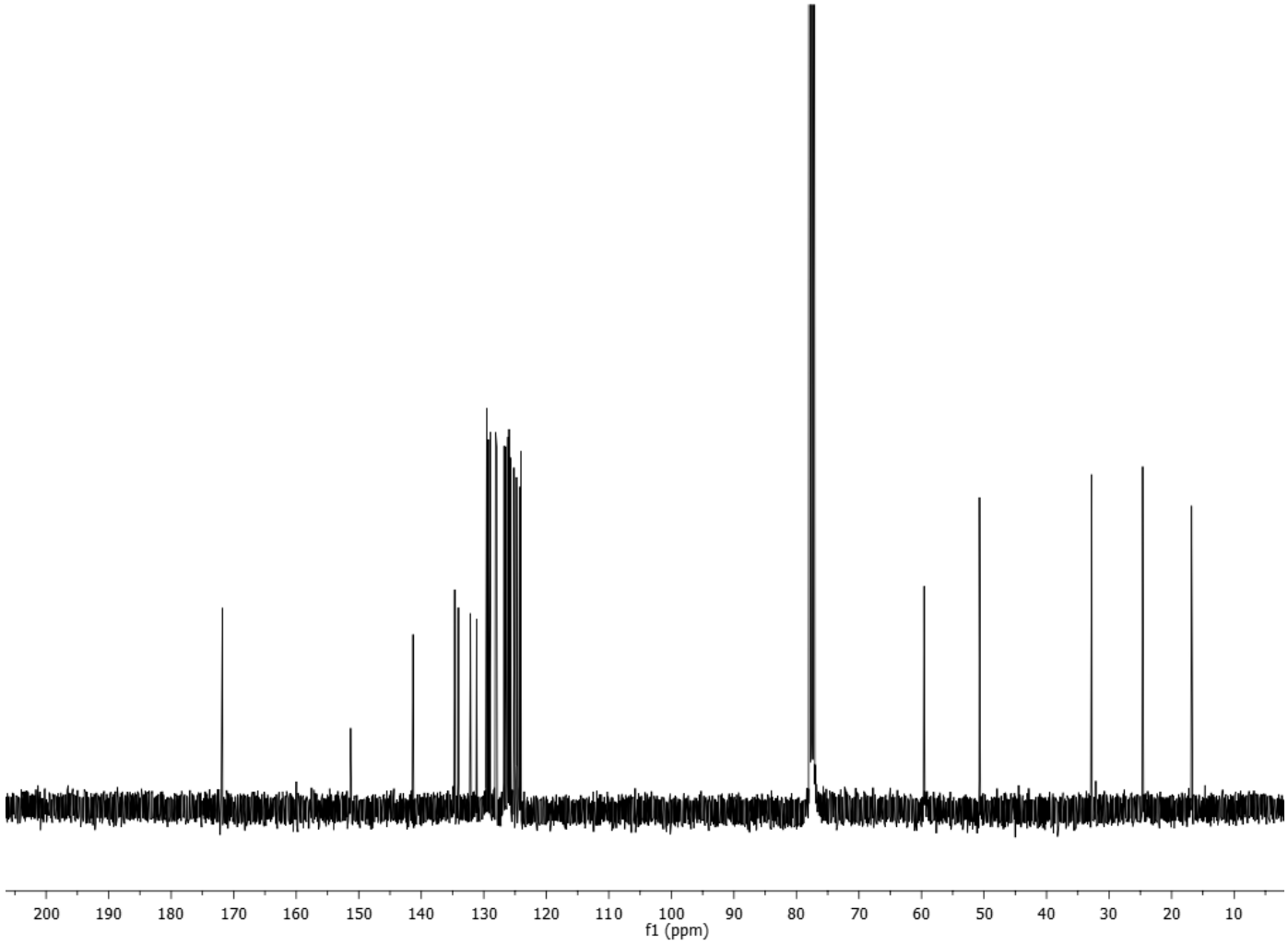

Figure A.20. ^{13}C NMR of compounds **7*RR*** and **7*SS*** ($CDCl_3$).

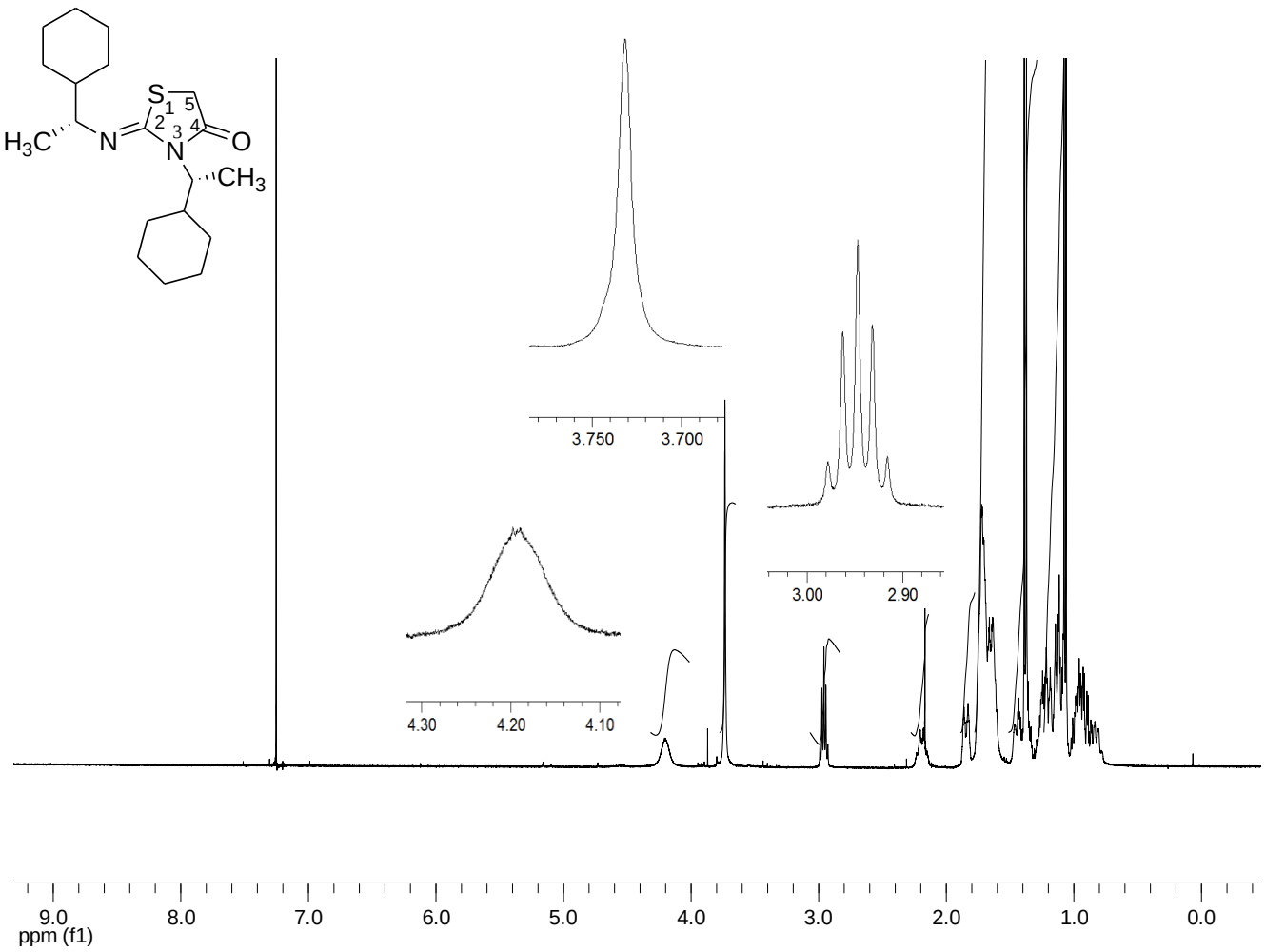

Figure A.21. ^{1}H NMR of compounds **8*RR*** and **8*SS*** ($CDCl_3$).

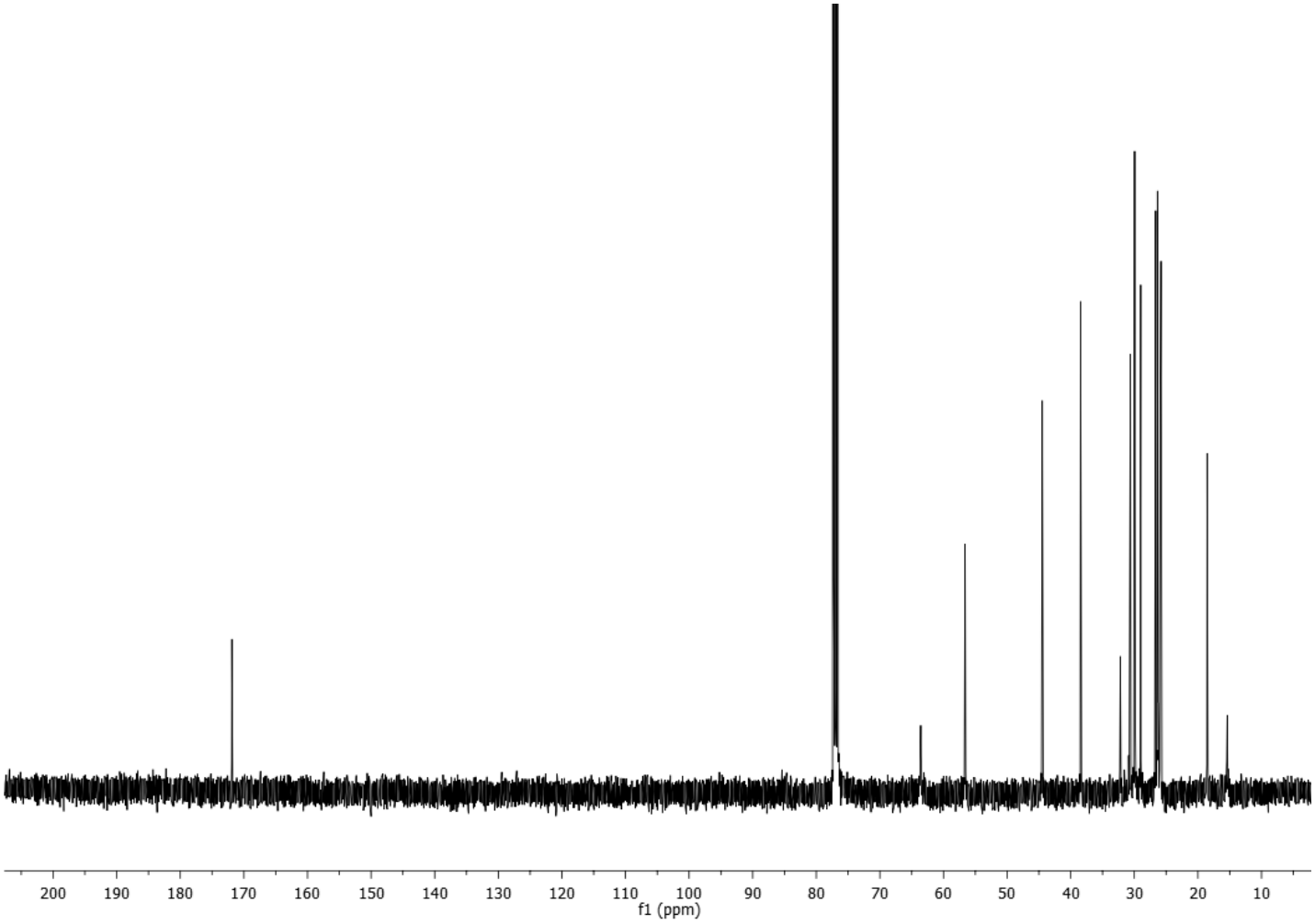

Figure A.22. ^{13}C NMR of compounds **8*RR*** and **8*SS*** ($CDCl_3$).

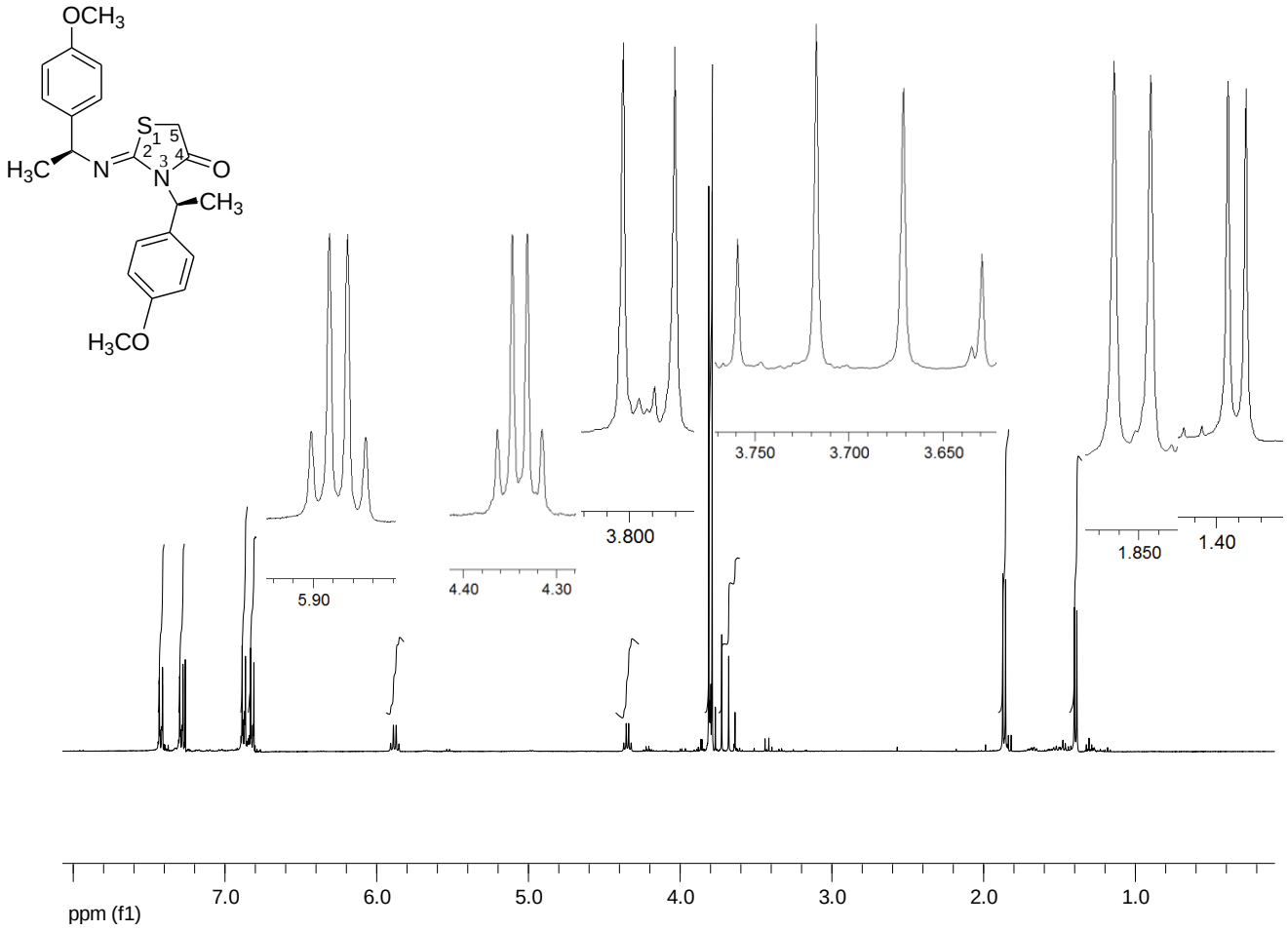

Figure A.23. ^{1}H NMR of compounds **9*RR*** and **9*SS*** ($CDCl_3$).

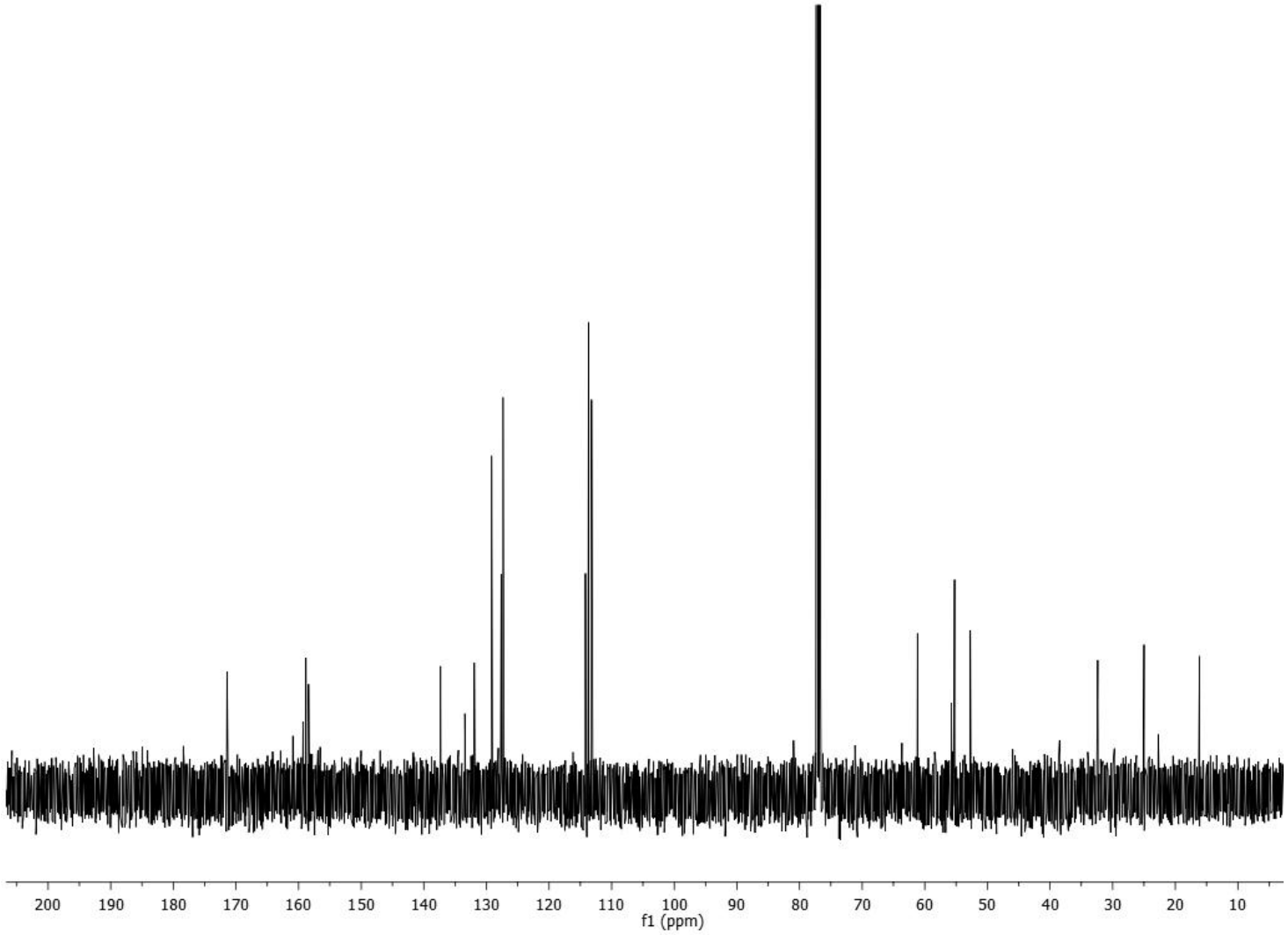

Figure A.24. ^{13}C NMR of compounds **9*RR*** and **9*SS*** ($CDCl_3$).

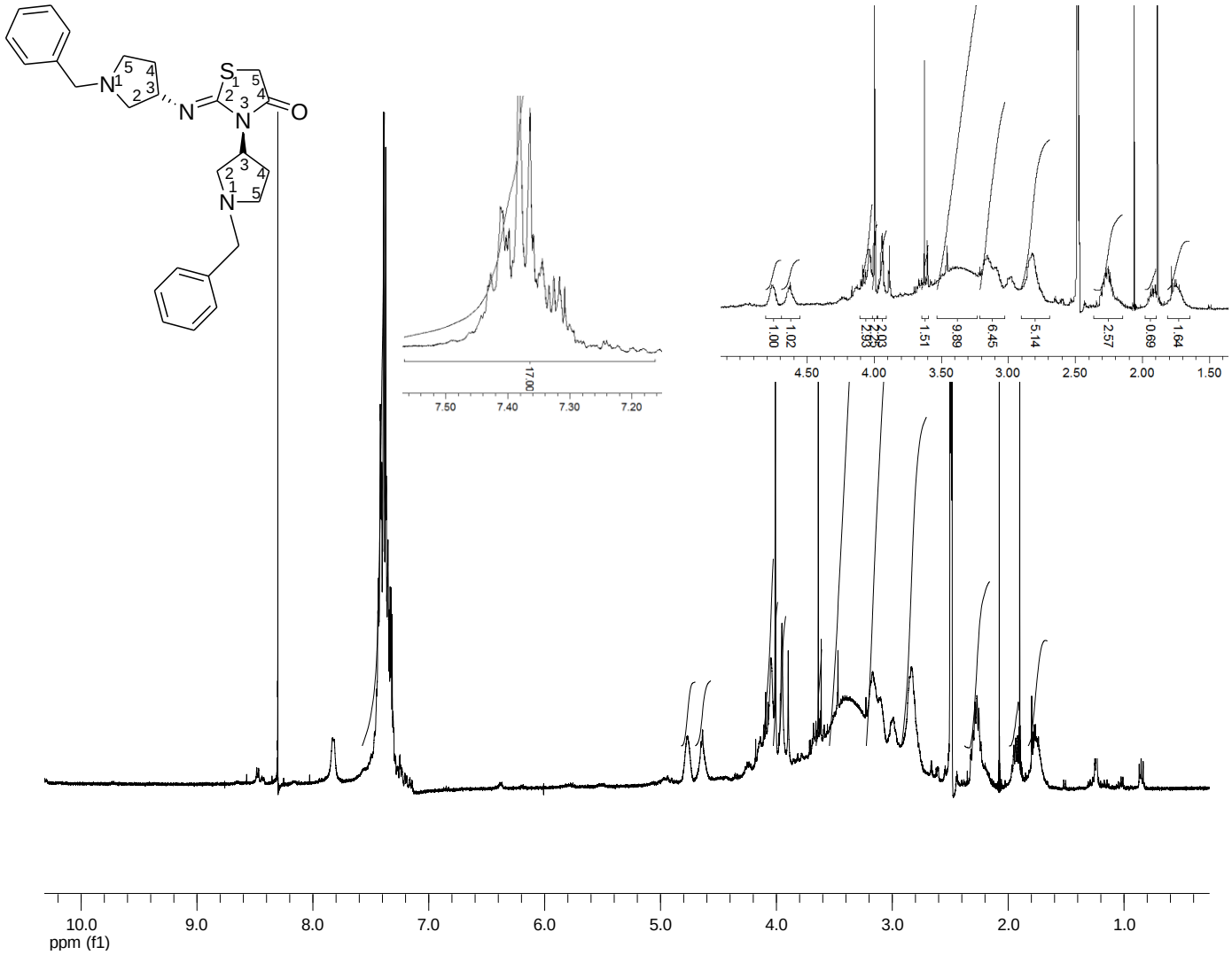

Figure A.25. ^{1}H NMR of compounds **10*RR*** and **10*SS*** (DMSO-d_6).

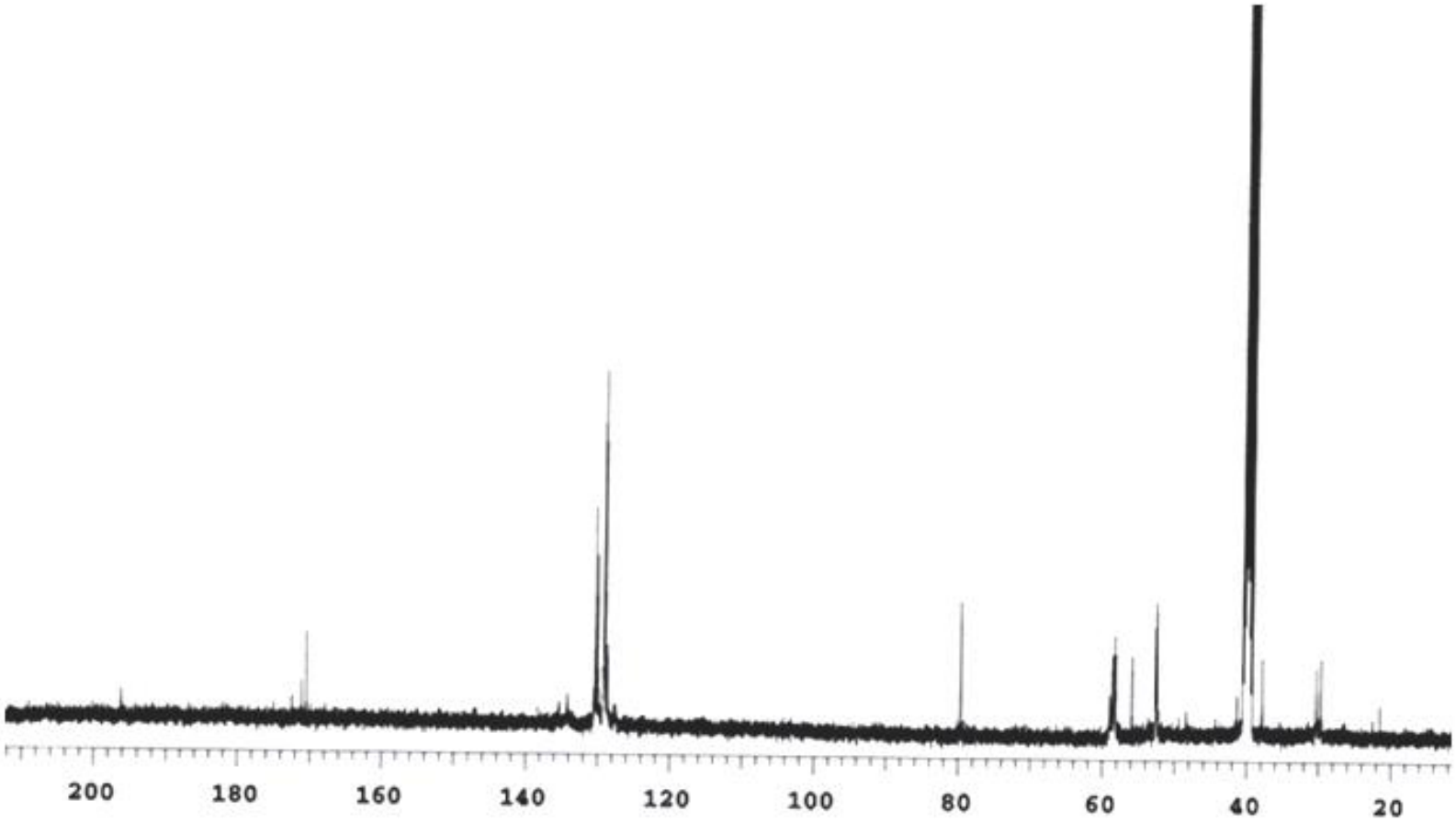

Figure A.26. ^{13}C NMR of compounds **10*RR*** and **10*SS*** (DMSO-d_6).

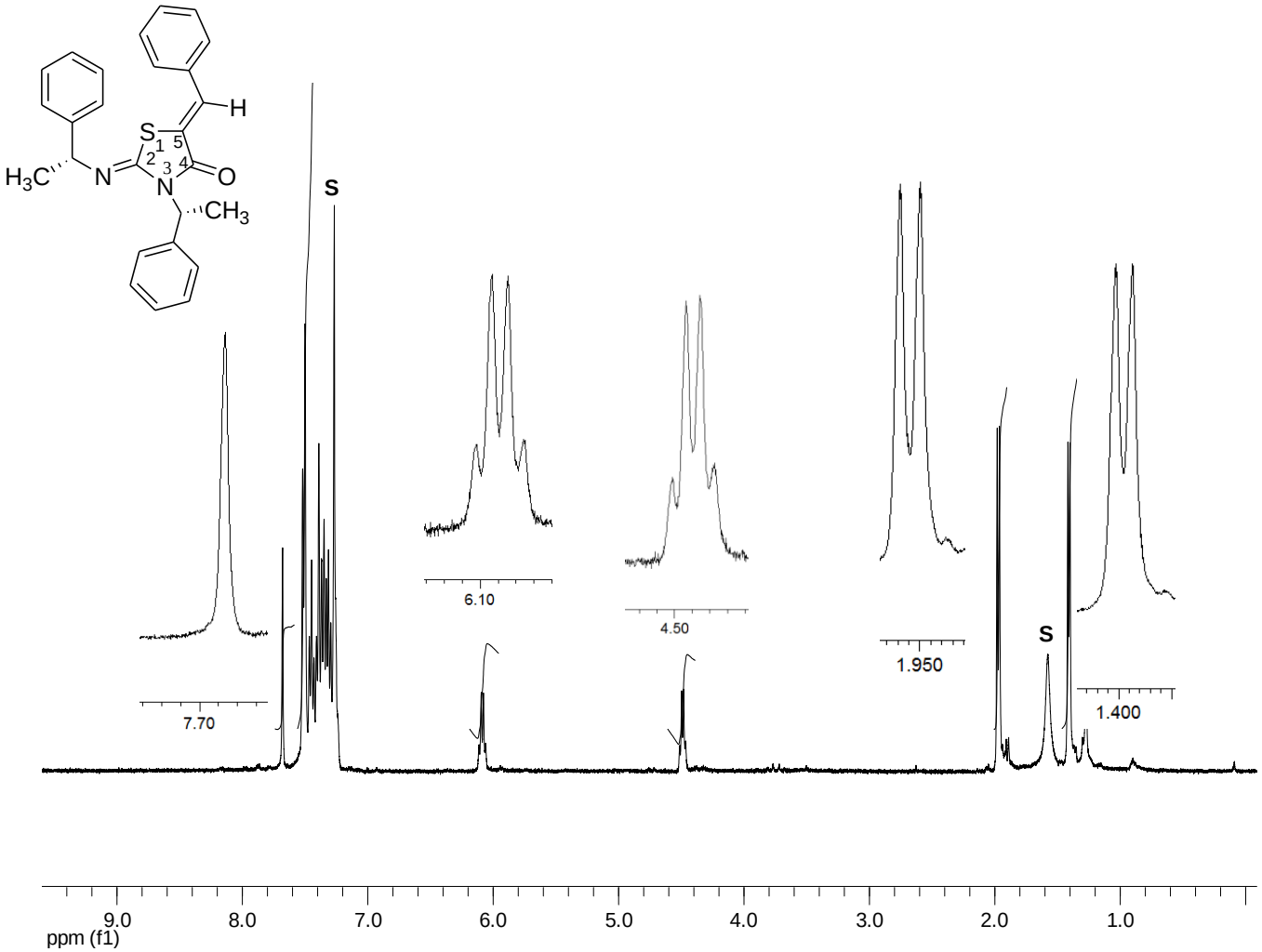

Figure A.27. ^{1}H NMR of compounds **11*RR*** and **11*SS*** ($CDCl_3$).

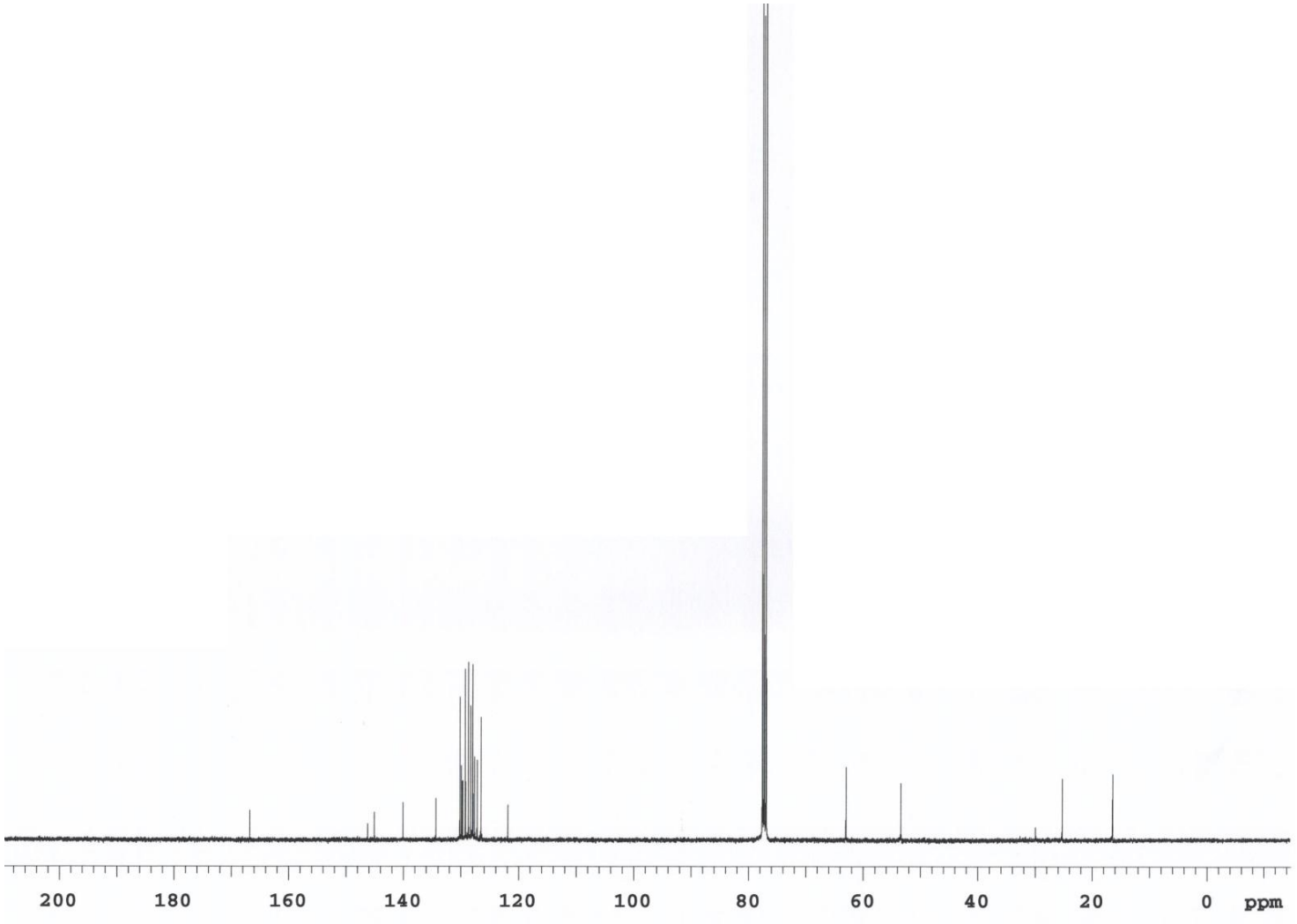

Figure A.28. ^{13}C NMR of compounds **11*RR*** and **11*SS*** ($CDCl_3$).

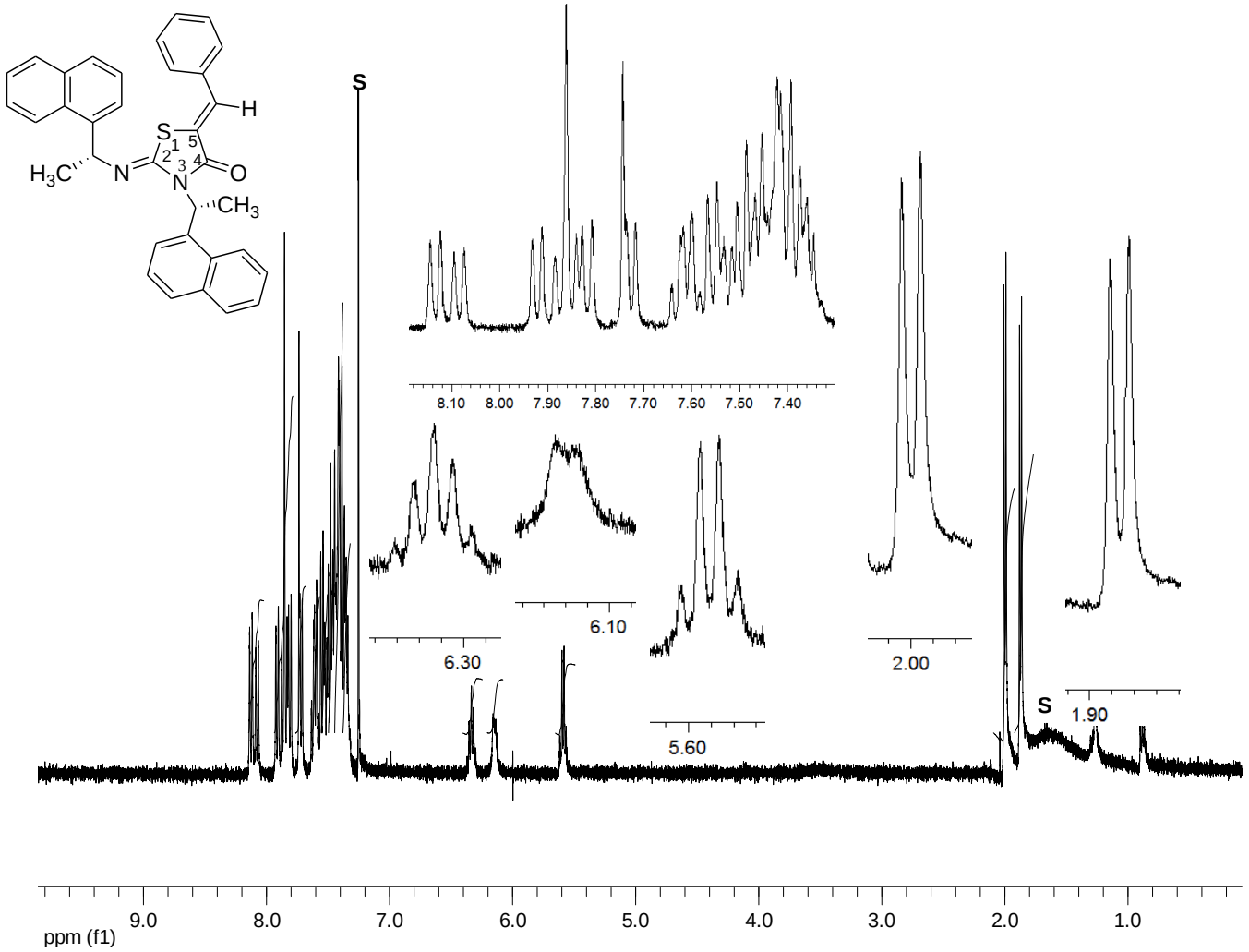

Figure A.29. ^{1}H NMR of compounds **12*RR*** and **12*SS*** ($CDCl_3$).

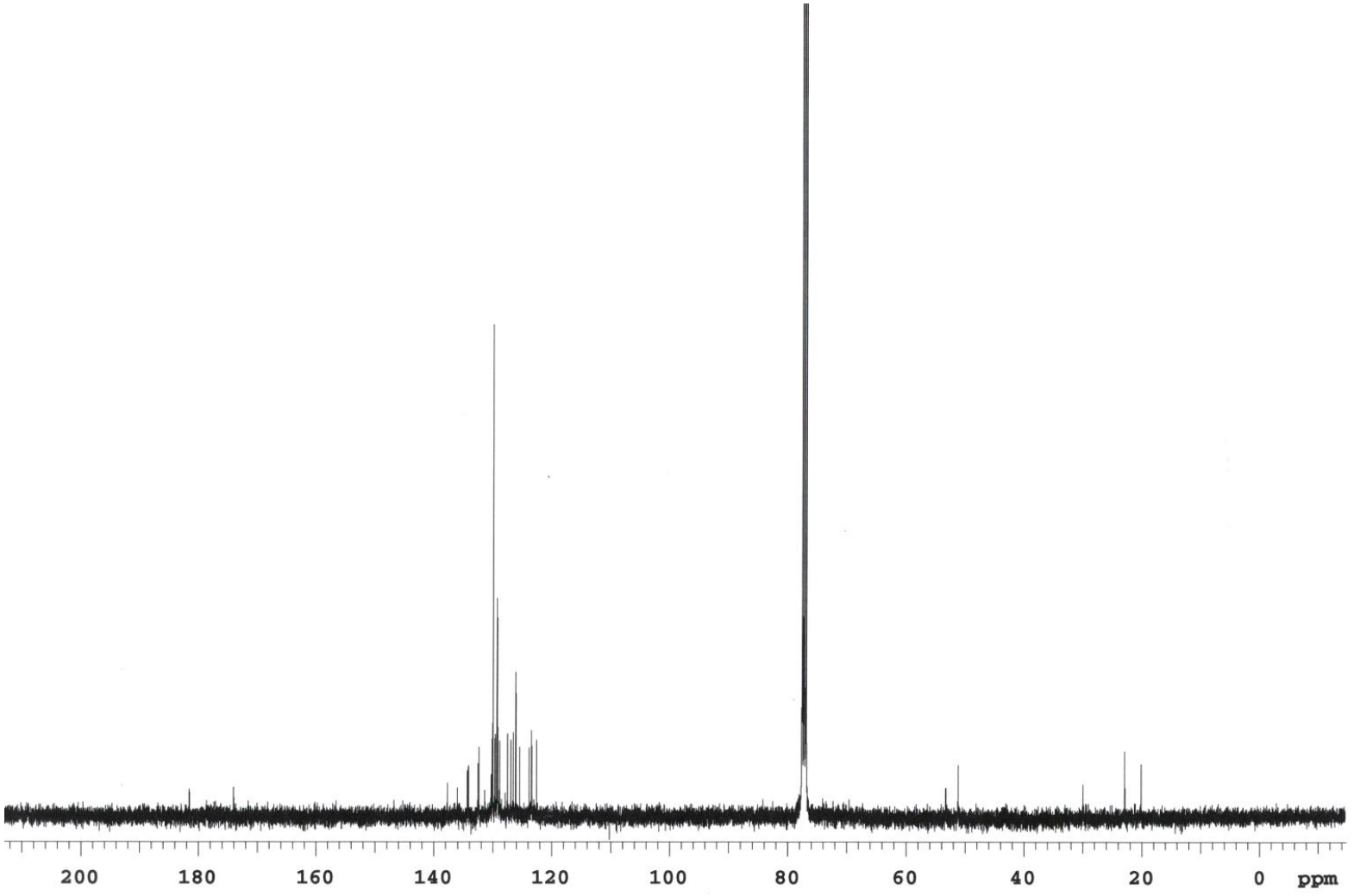

Figure A.30. ^{13}C NMR of compounds **12*RR*** and **12*SS*** ($CDCl_3$).

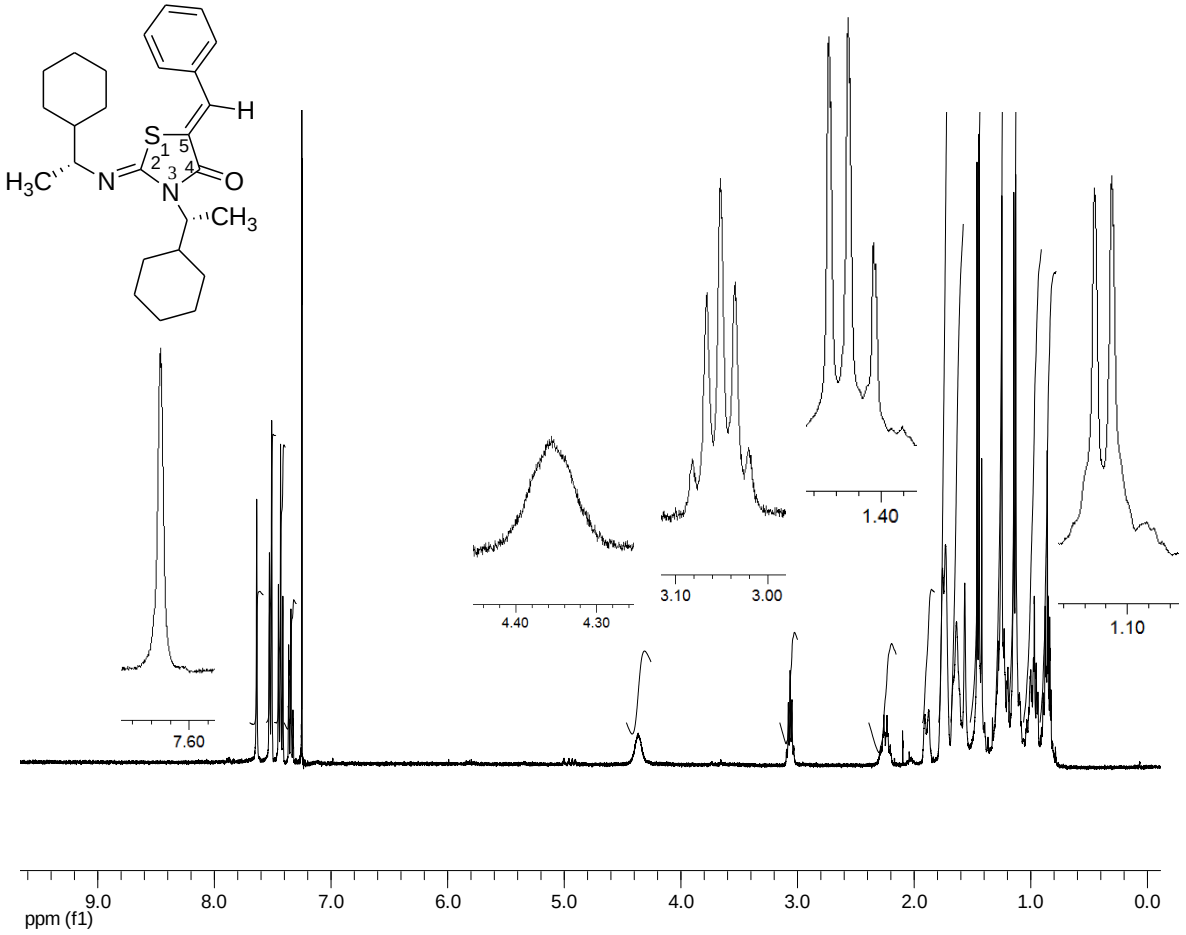

Figure A.31. ^{1}H NMR of compounds **13*RR*** and **13*SS*** ($CDCl_3$).

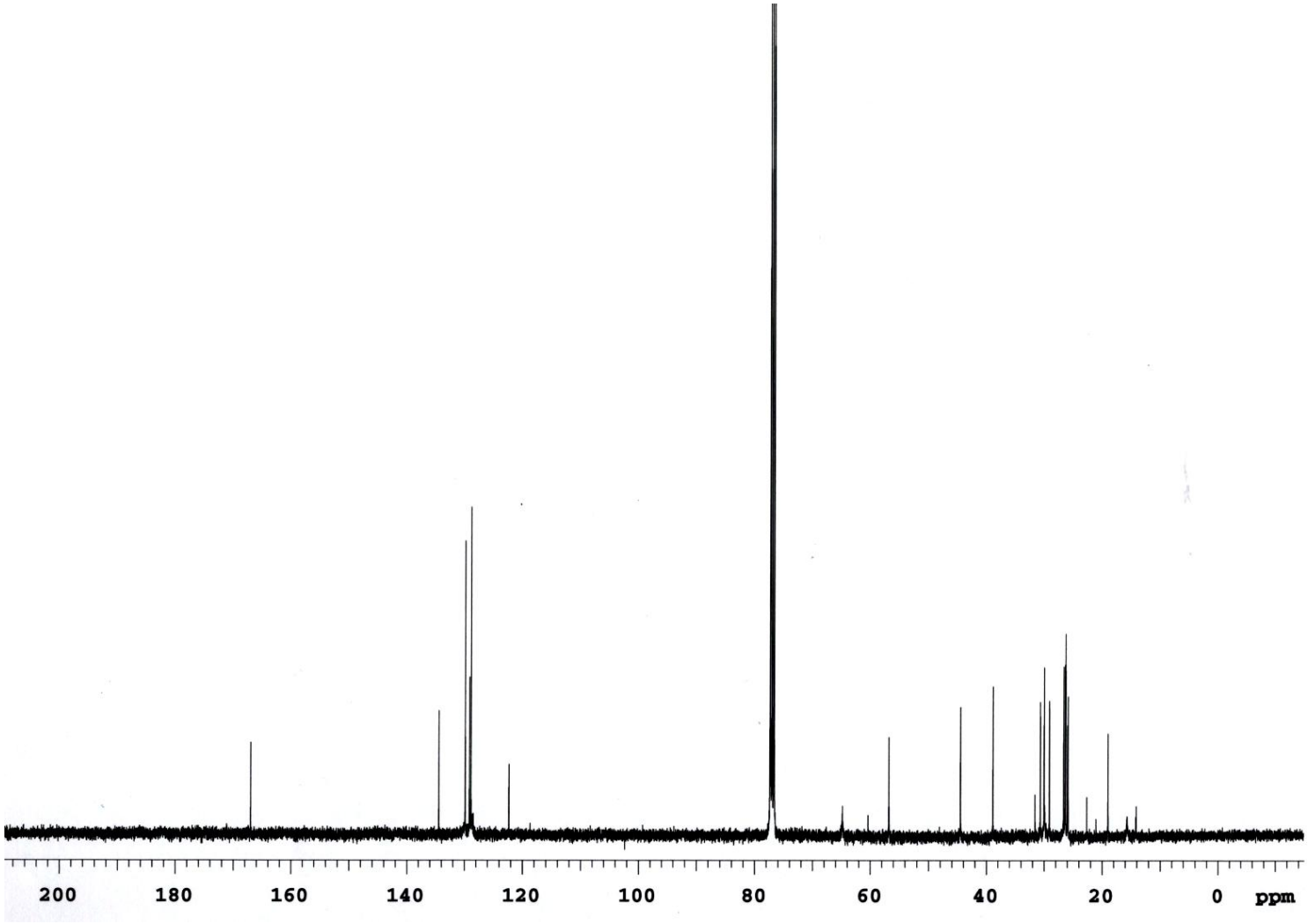

Figure A.32. ^{13}C NMR of compounds **13*RR*** and **13*SS*** ($CDCl_3$).

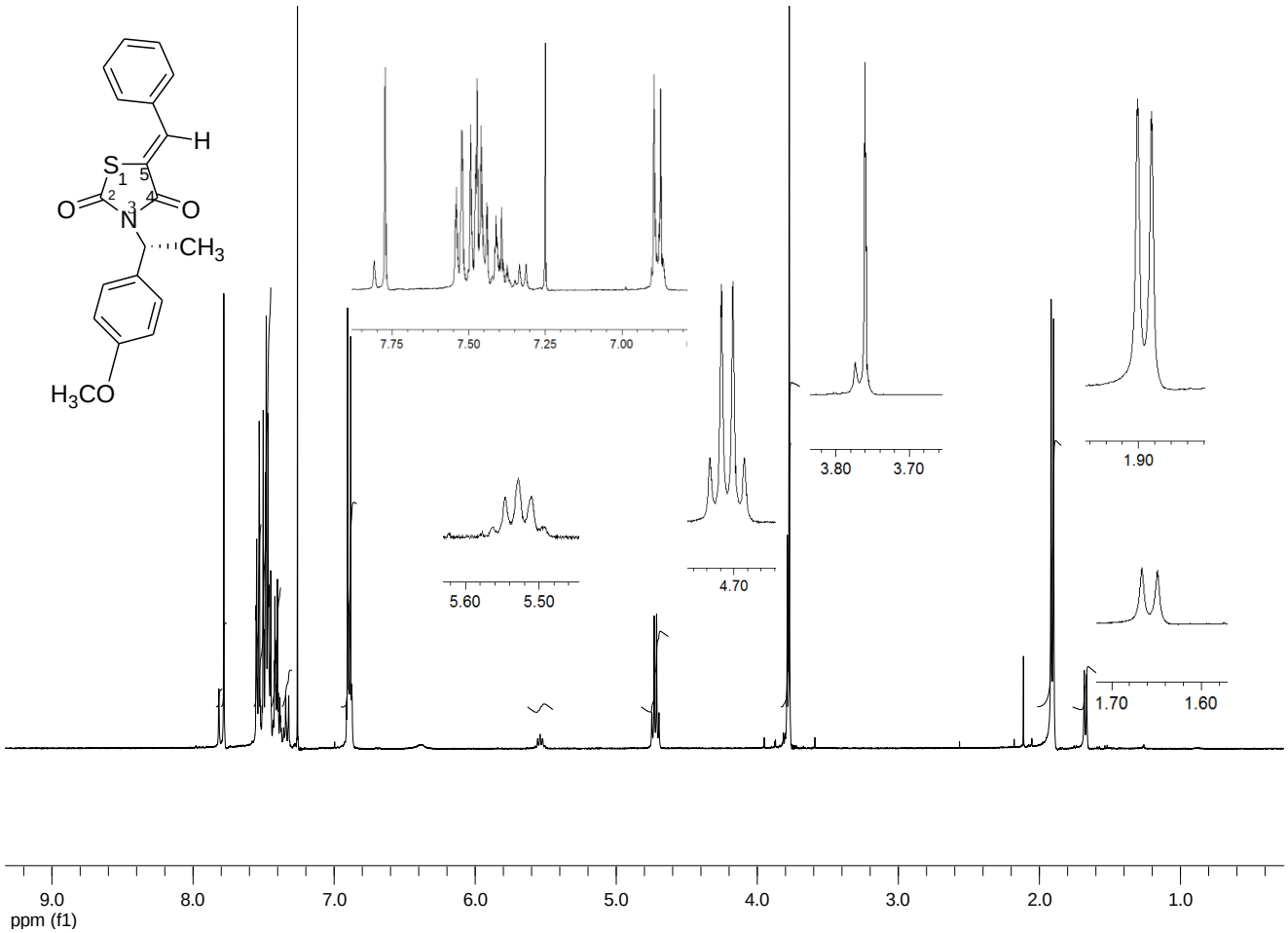

Figure A.33. ^{1}H NMR of compounds **14*R*** and **14*S***($CDCl_3$). (major/minor=4.54)

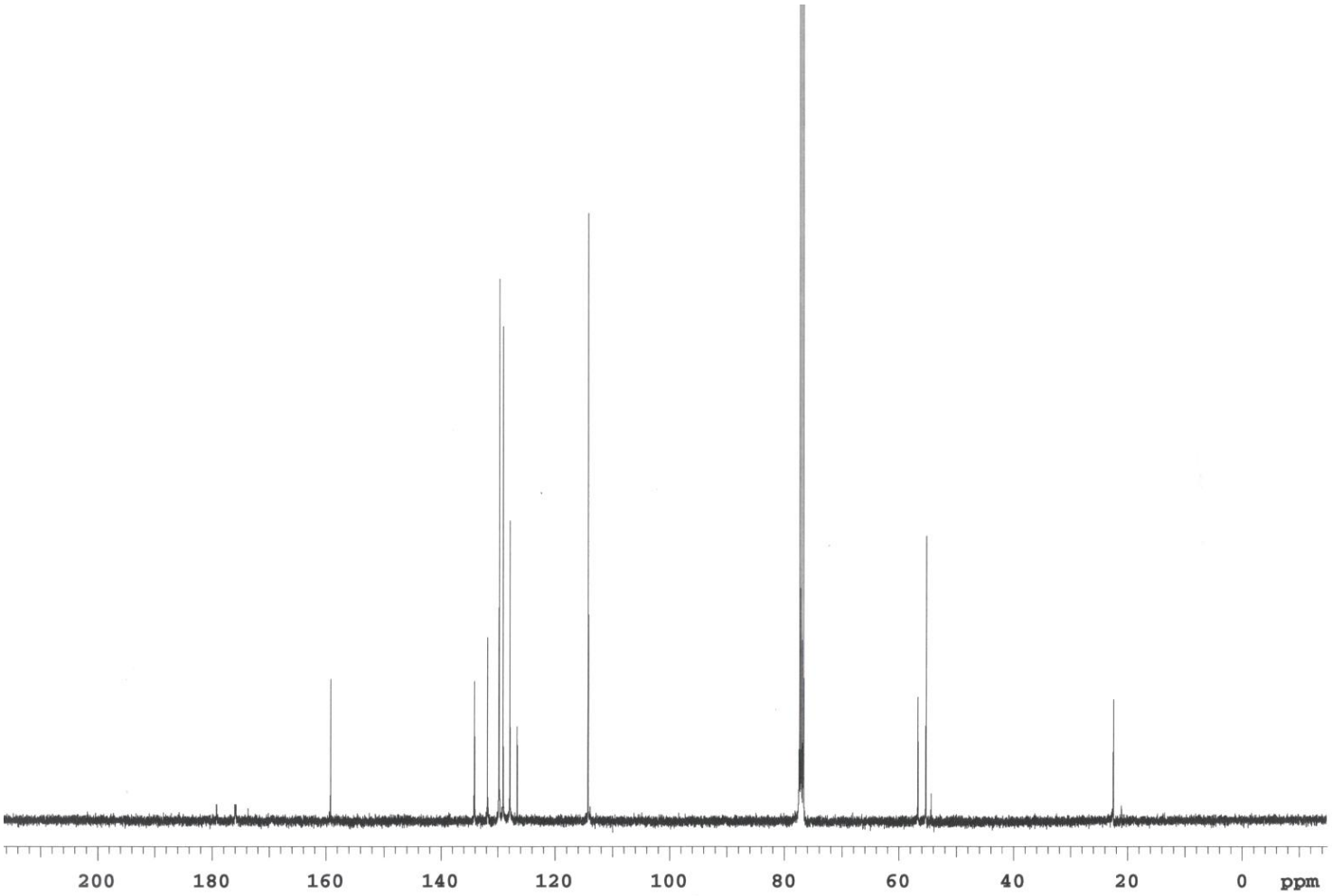

Figure A.34. ^{13}C NMR of compounds **14*R*** and **14*S*** ($CDCl_3$).

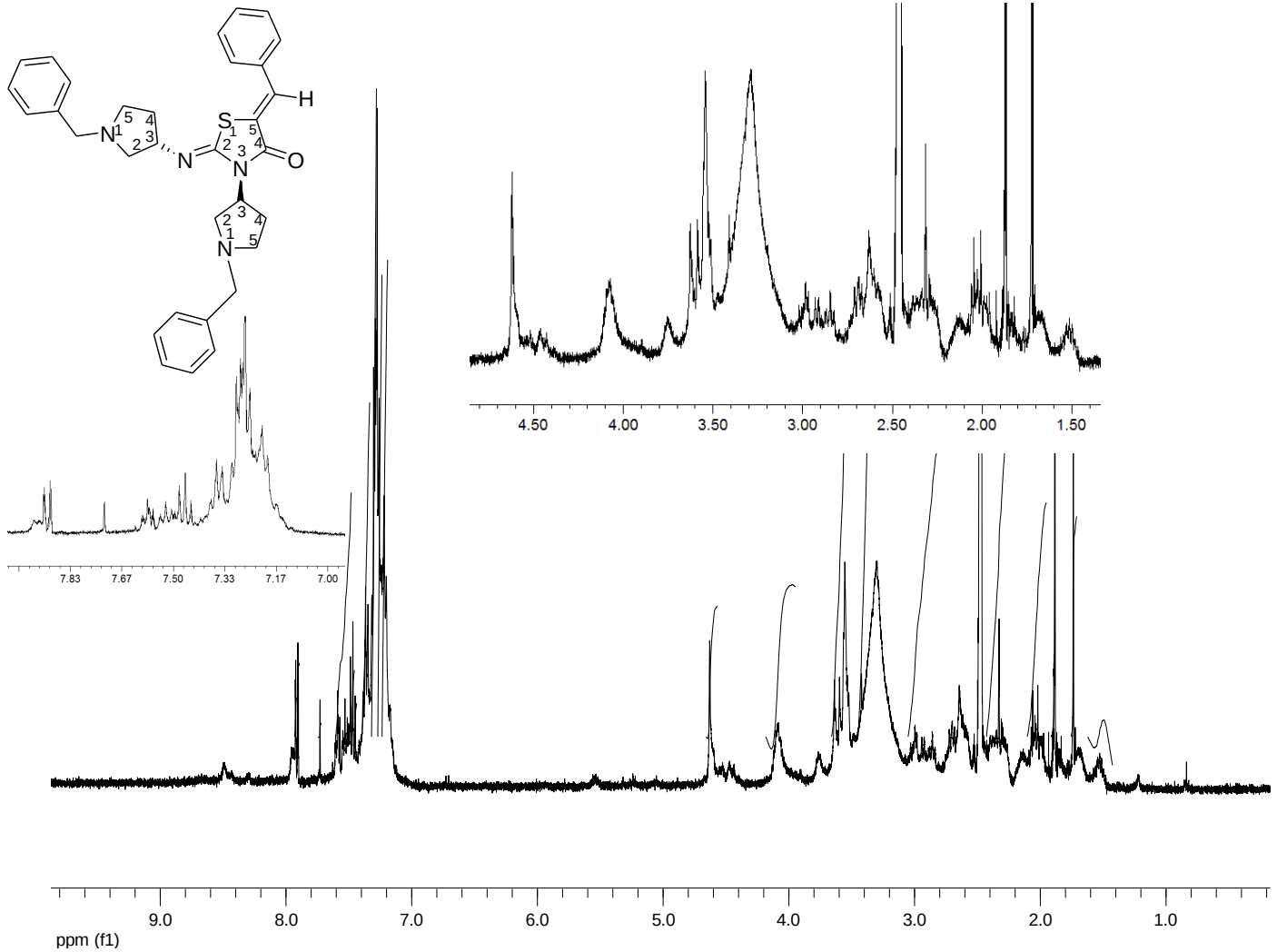

Figure A.35. ^{1}H NMR of compounds ***15RR*** and ***15SS*** (DMSO-d_6).

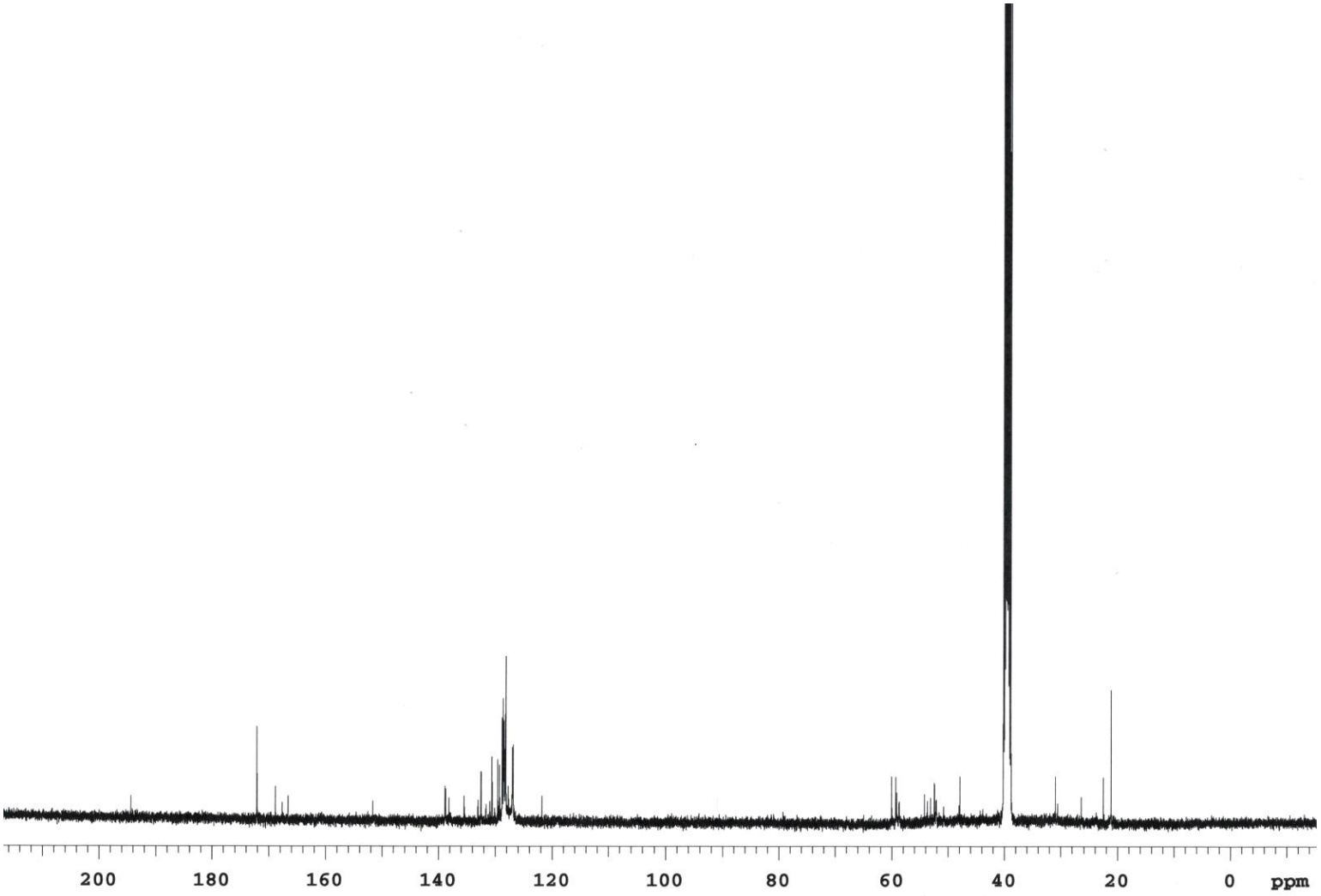

Figure A.36. ^{13}C NMR of compounds ***15RR*** and ***15SS*** (DMSO-d_6).

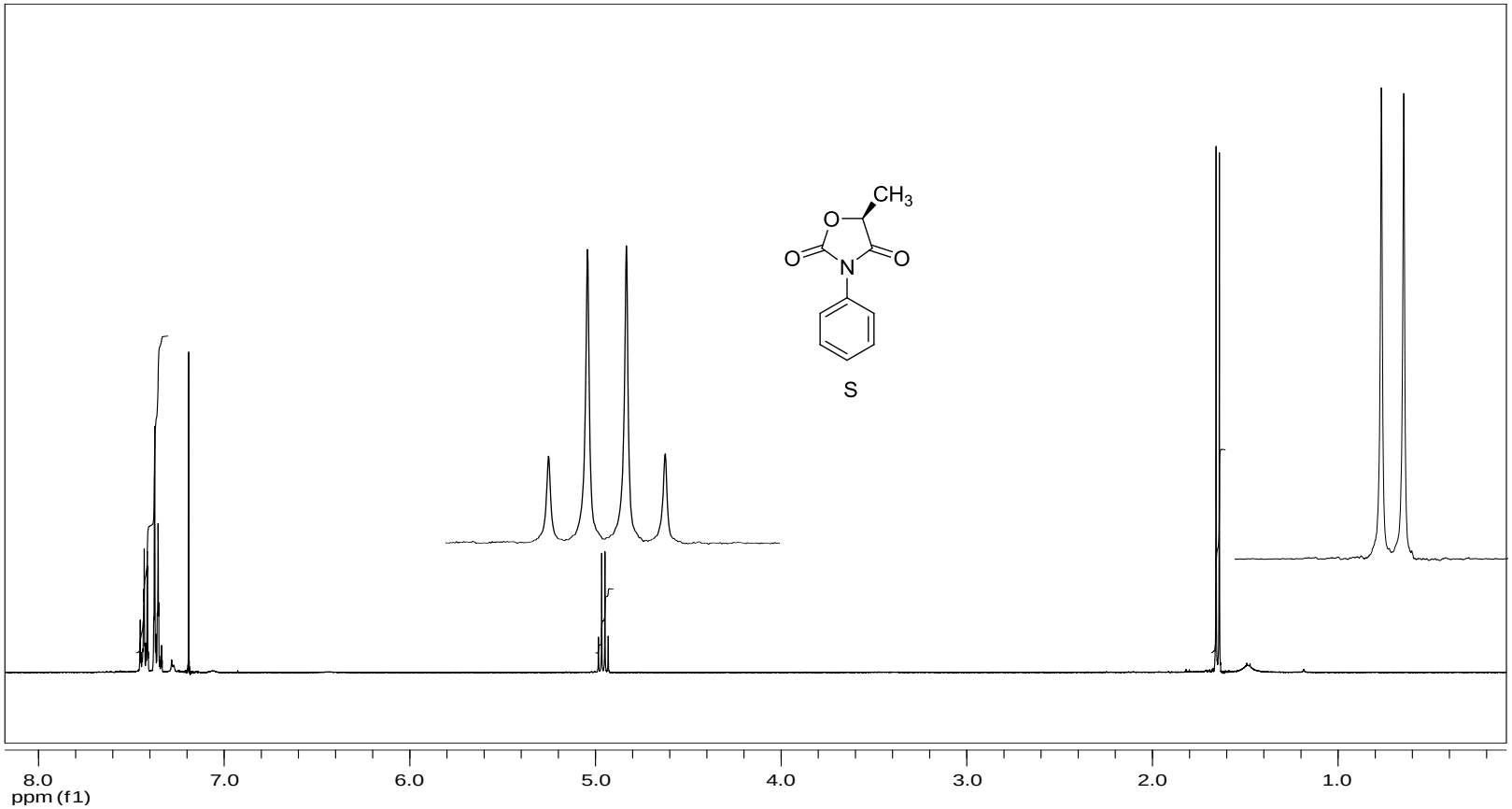

Figure A.37. ^{1}H NMR of compounds ***16S*** and ***16R*** ($CDCl_3$).

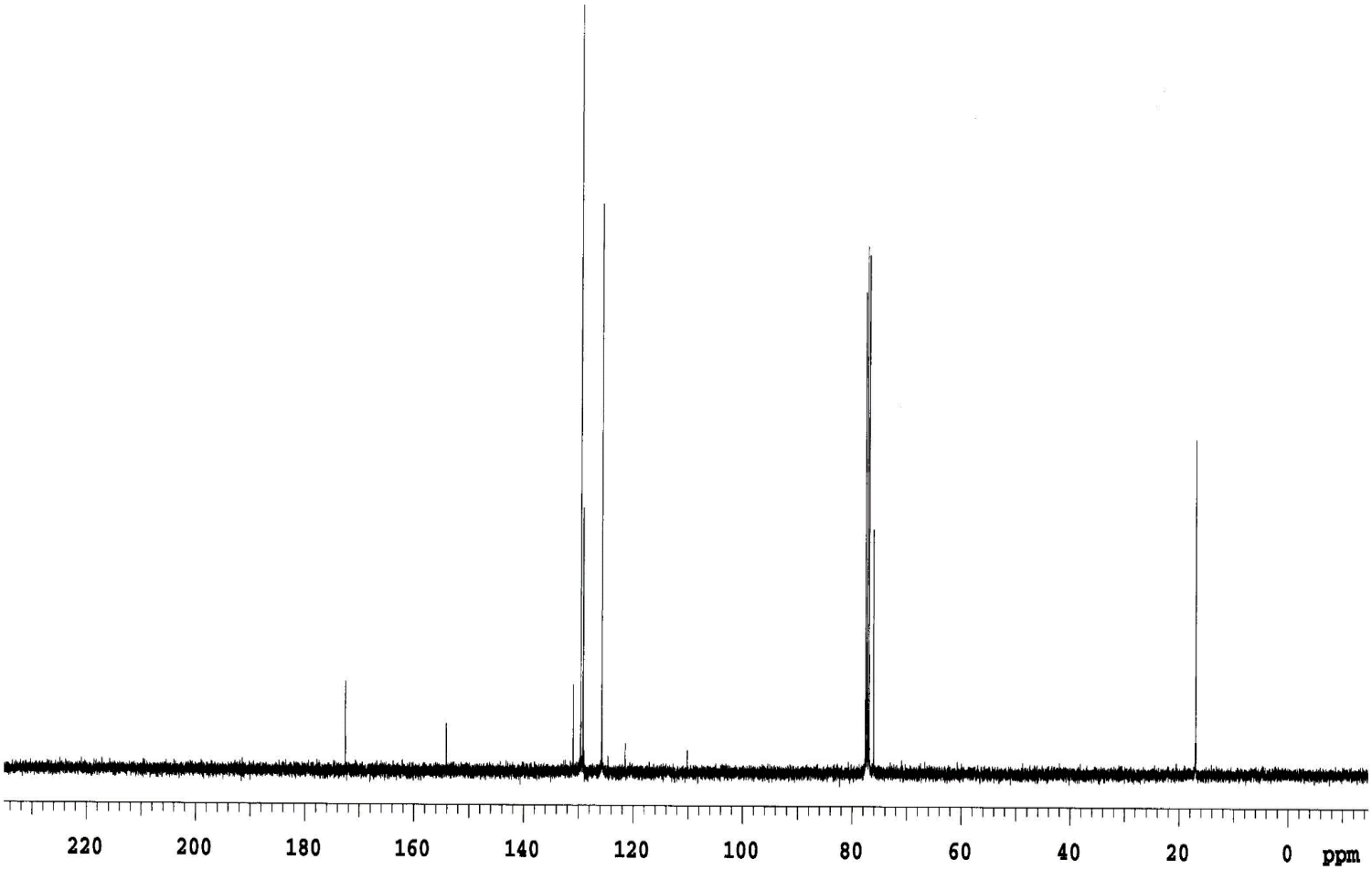

Figure A.38. ^{13}C NMR of compounds ***16S*** and ***16R*** ($CDCl_3$).

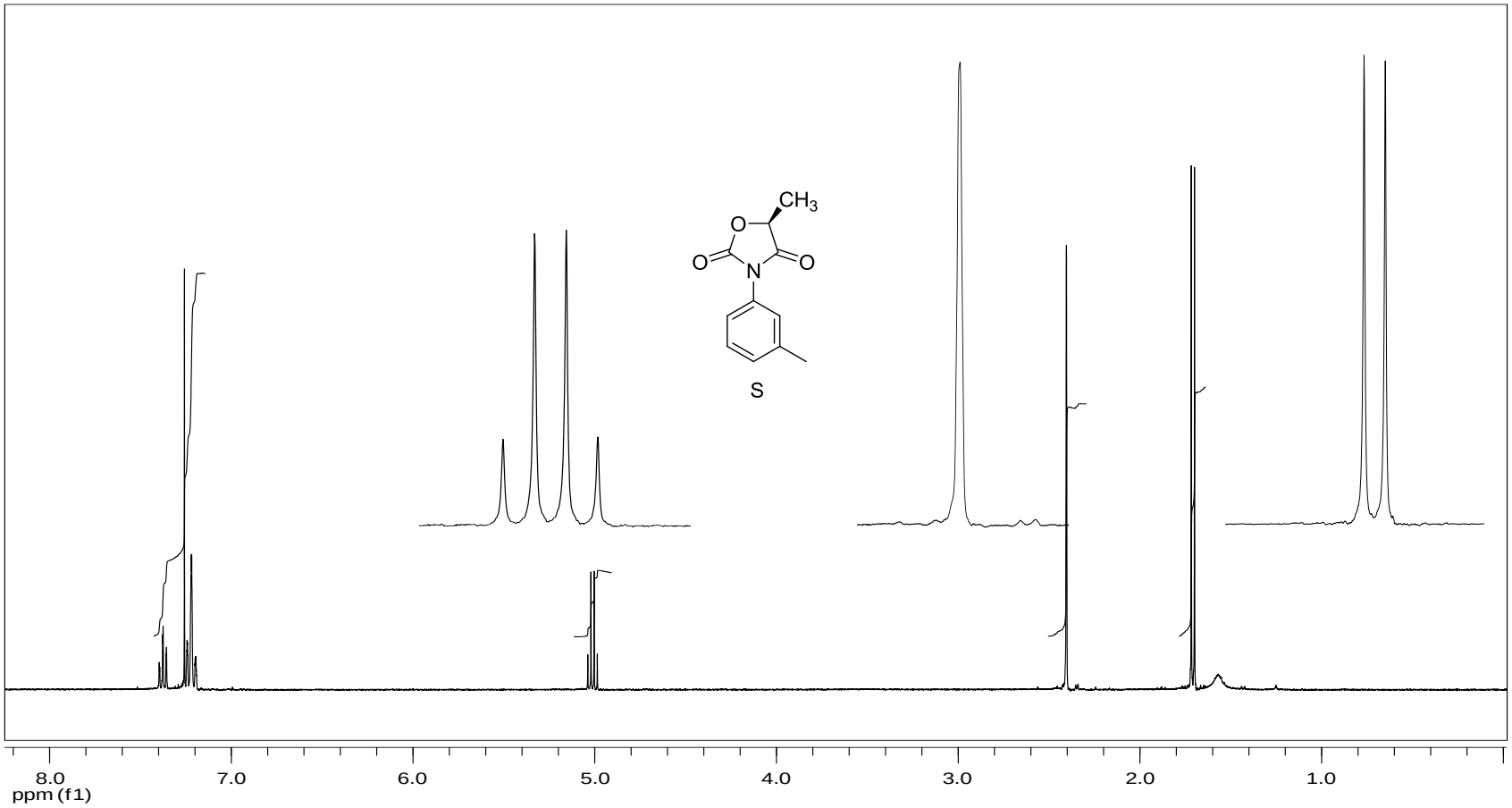

Figure A.39. ^{1}H NMR of compounds ***17S*** and ***17R*** ($CDCl_3$).

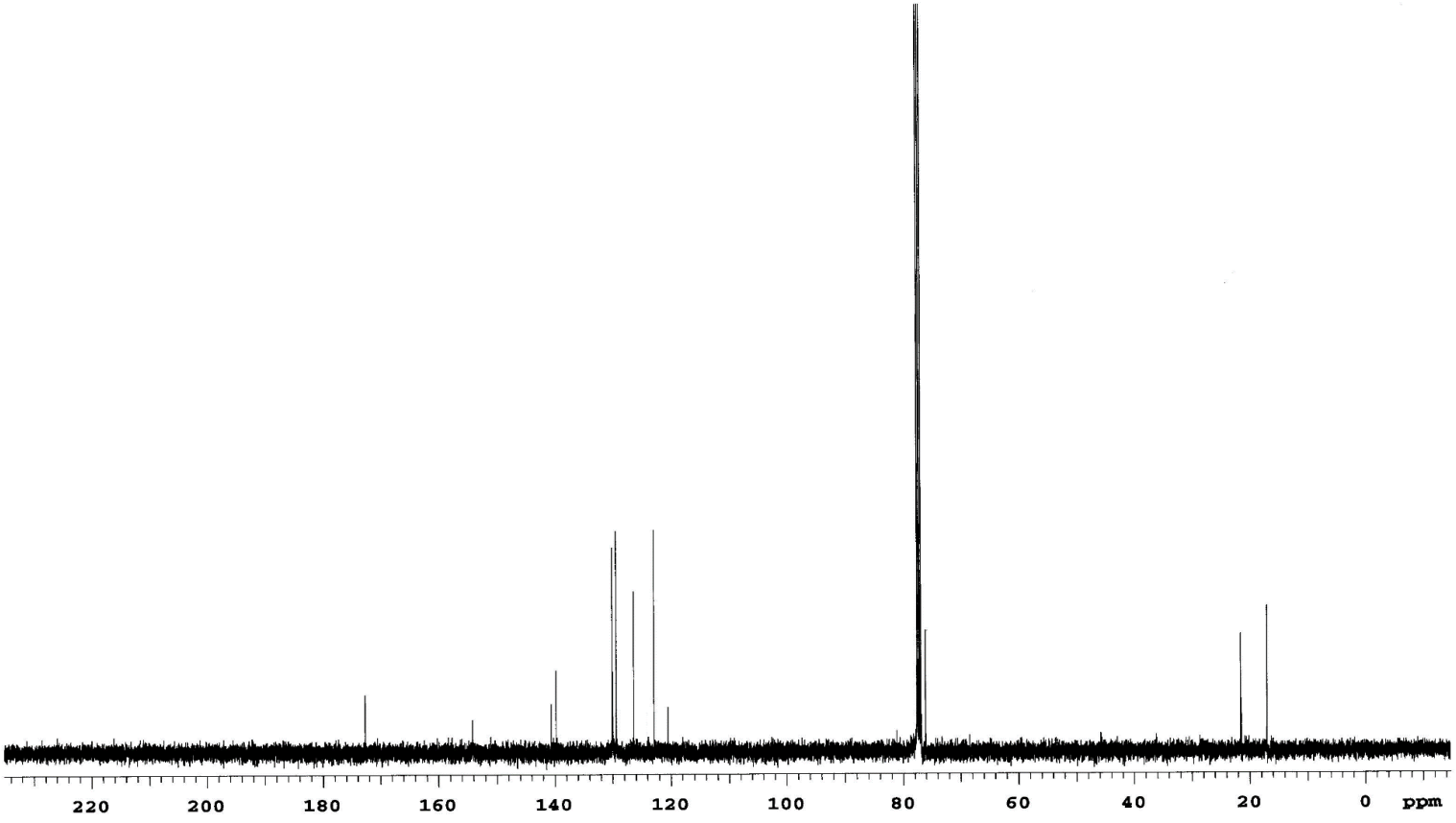

Figure A.40. ^{13}C NMR of compounds ***17S*** and ***17R*** ($CDCl_3$).

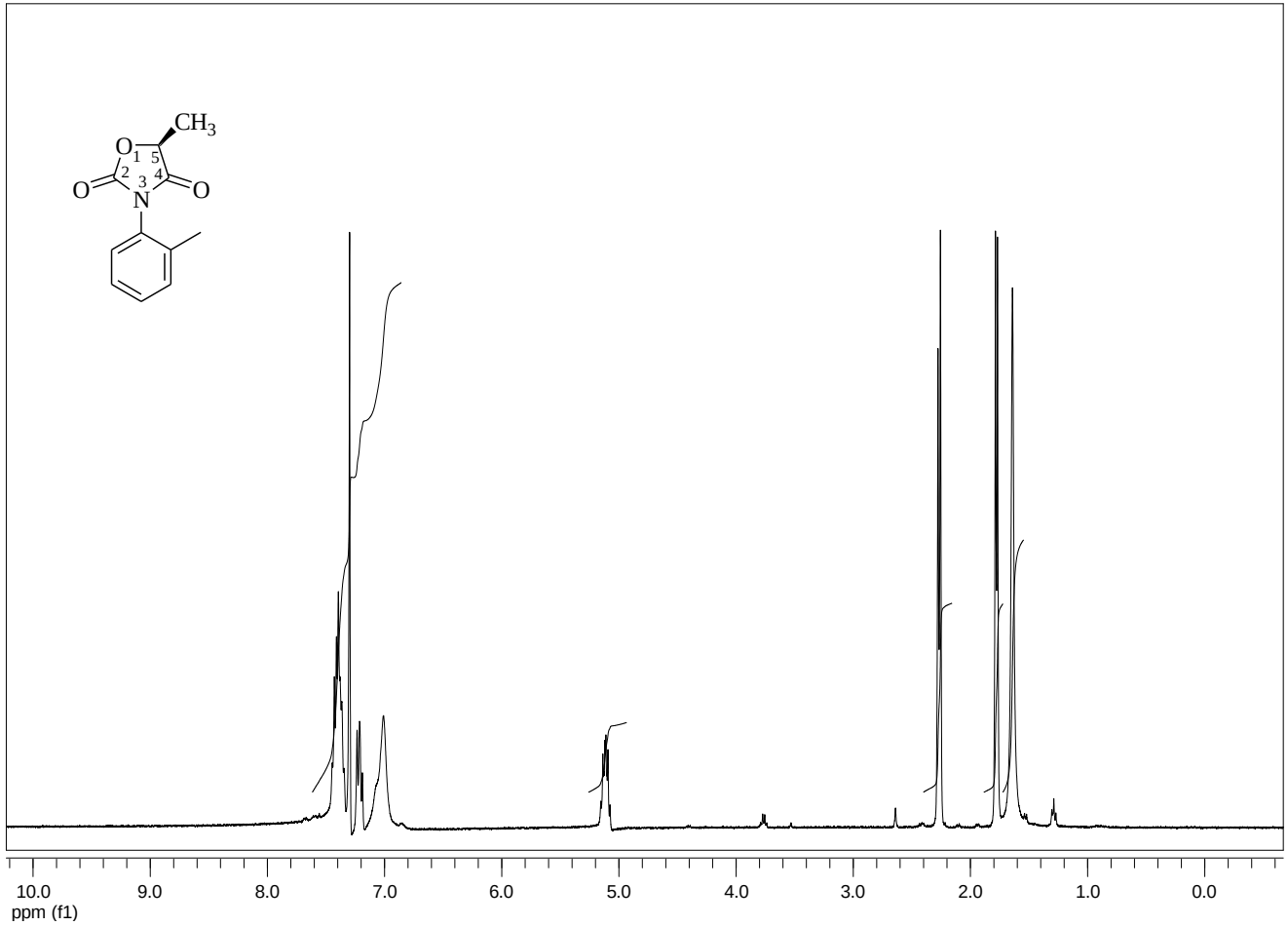

Figure A.41. ^{1}H NMR of compound ***18S*** ($CDCl_3$).

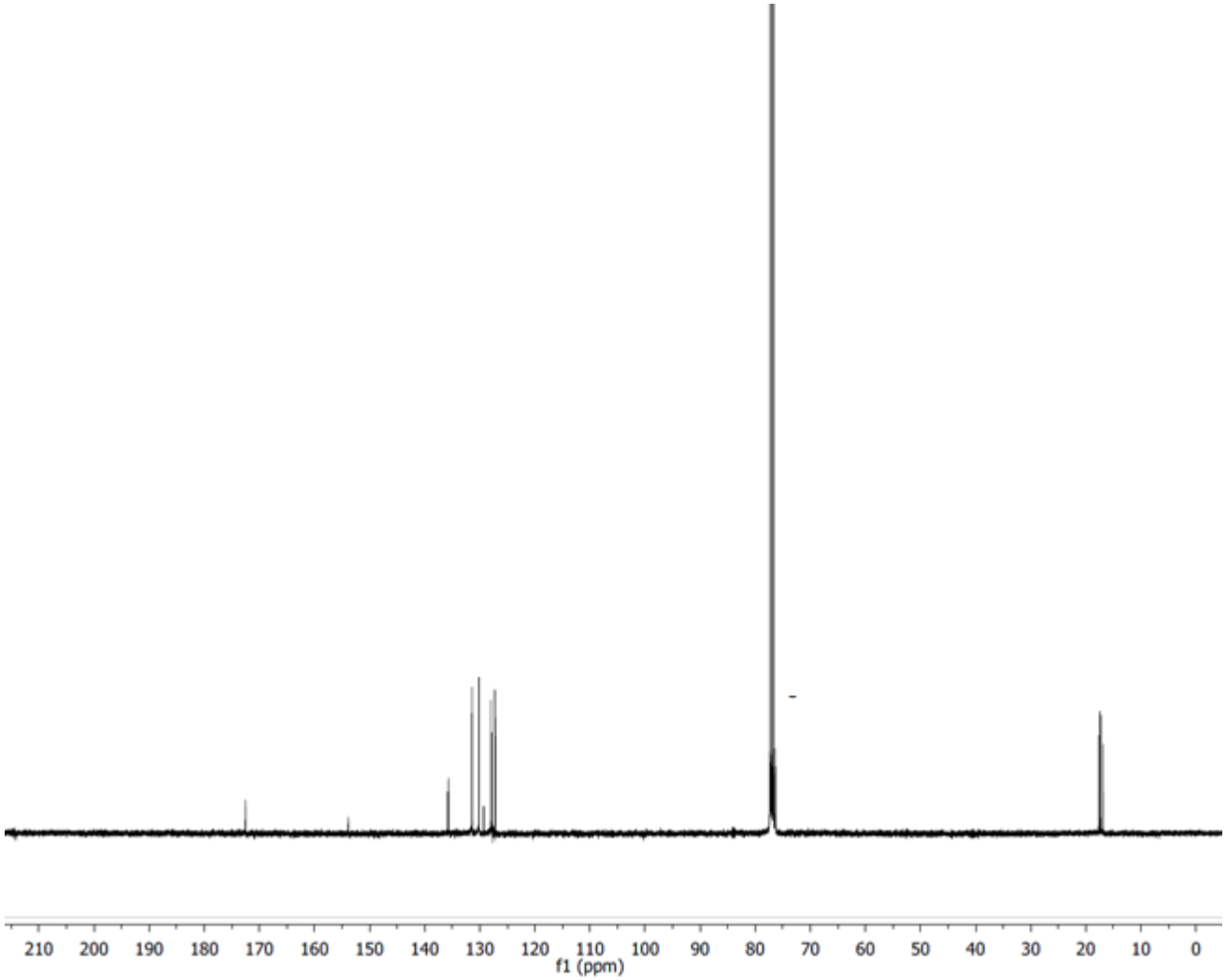

Figure A.42. . ^{13}C NMR of compound ***18S*** ($CDCl_3$).

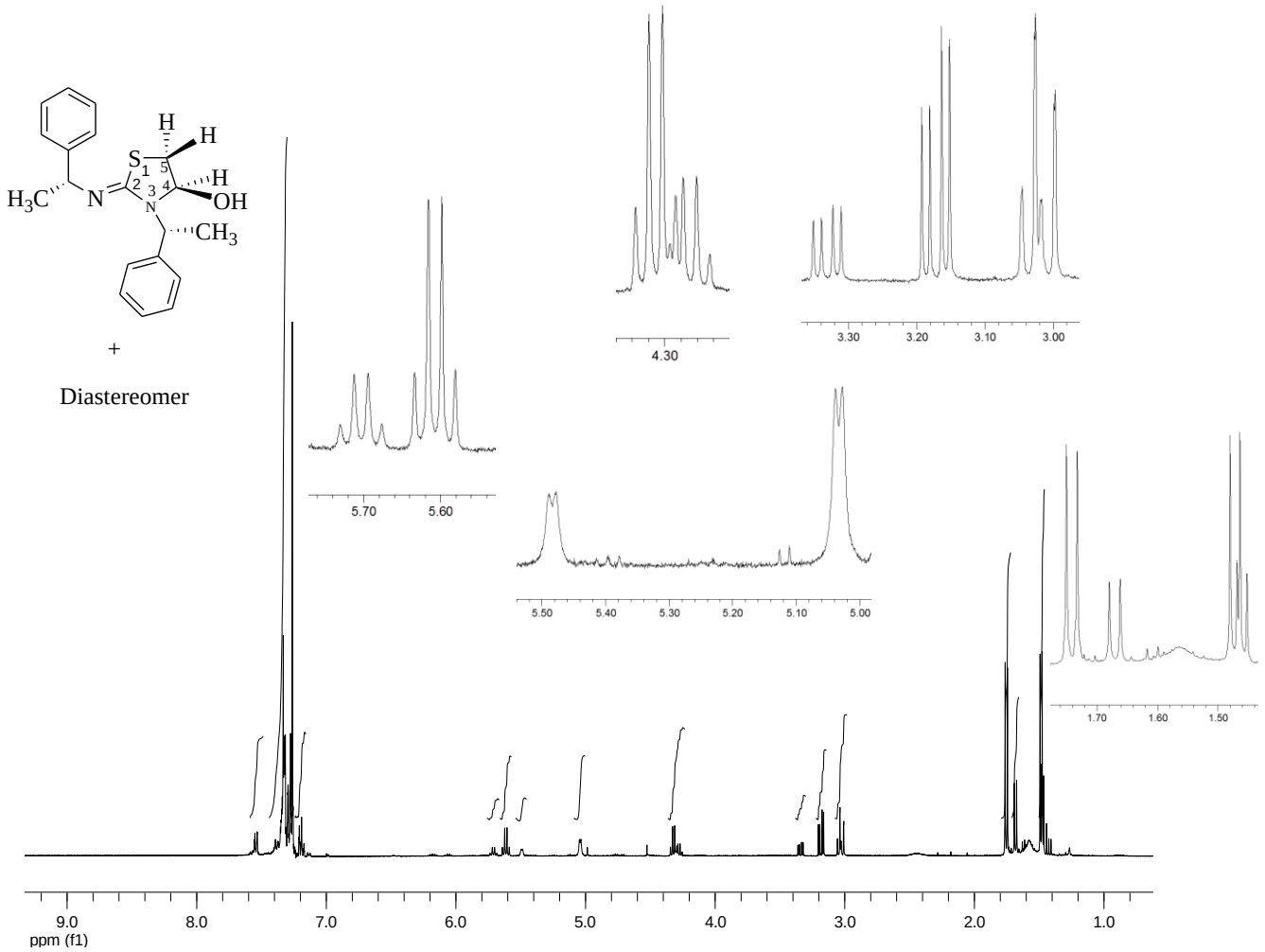

Figure A.43. ^{1}H NMR of compounds **19*RR*** and **19*SS*** ($CDCl_3$).

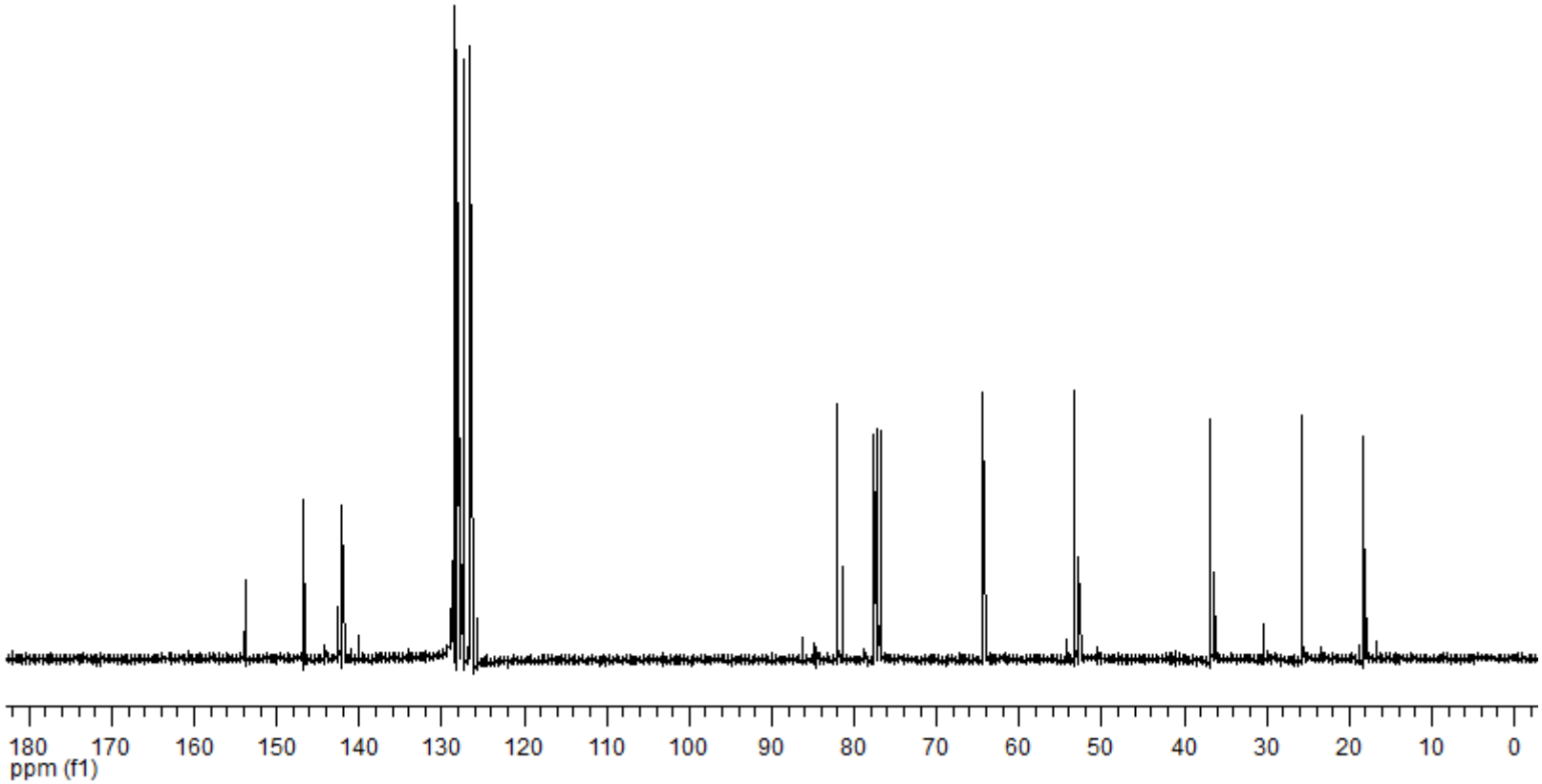

Figure A.44. ^{13}C NMR of compounds **19*RR*** and **19*SS*** ($CDCl_3$).

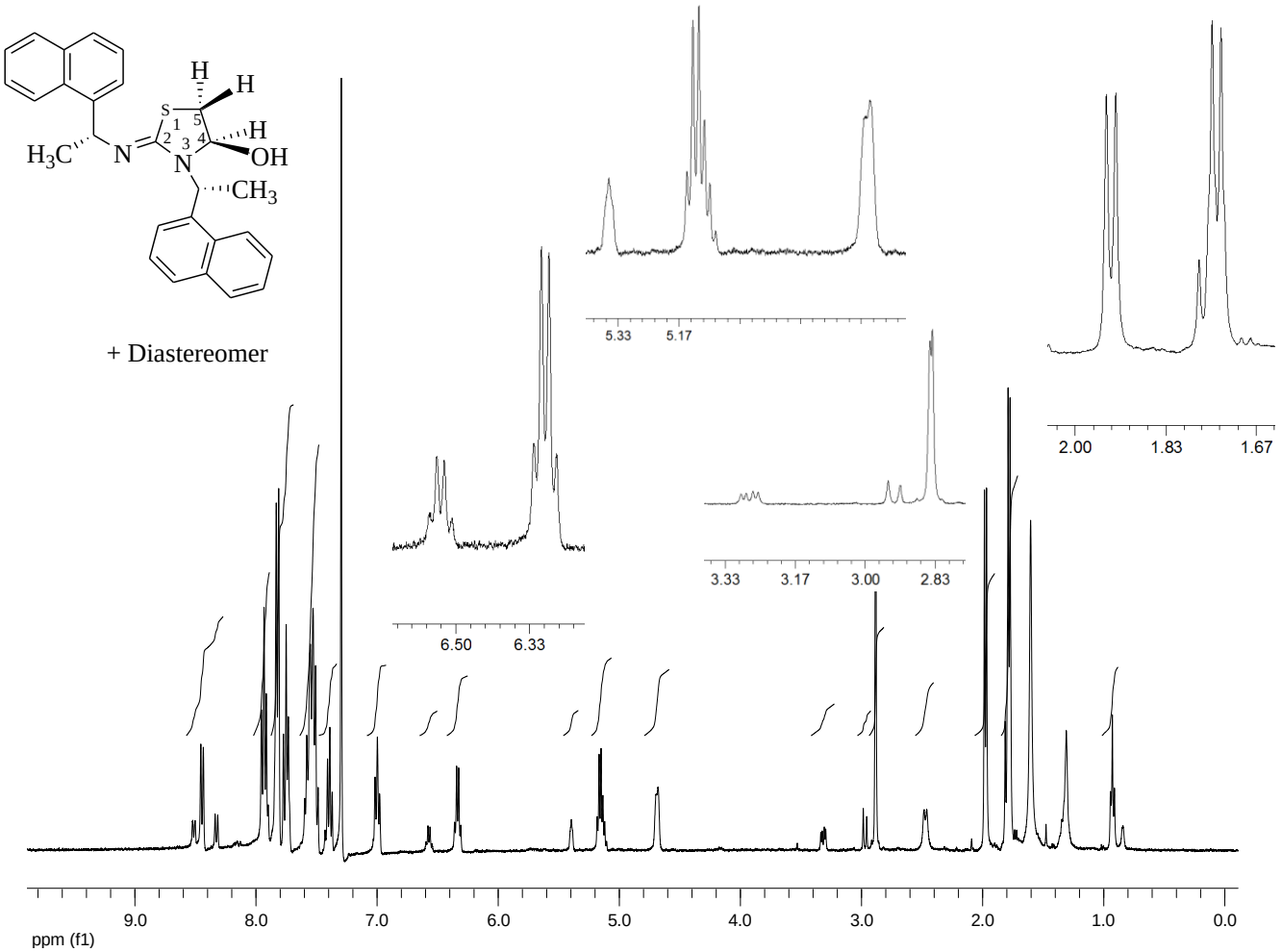

Figure A.45. ^{1}H NMR of compounds **20*RR*** and **20*SS*** ($CDCl_3$).

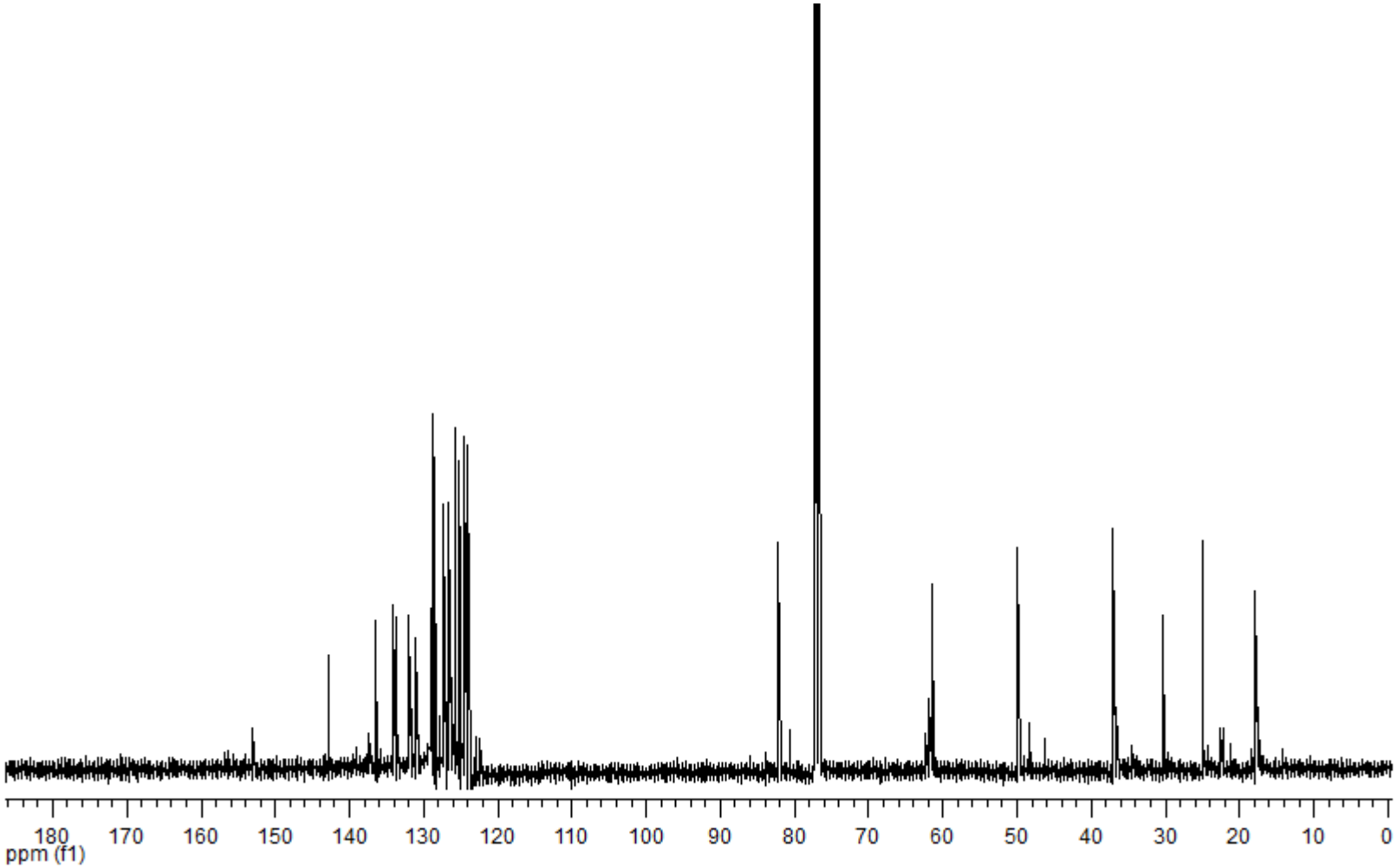

Figure A.46. ^{13}C NMR of compounds **20*RR*** and **20*SS*** ($CDCl_3$).

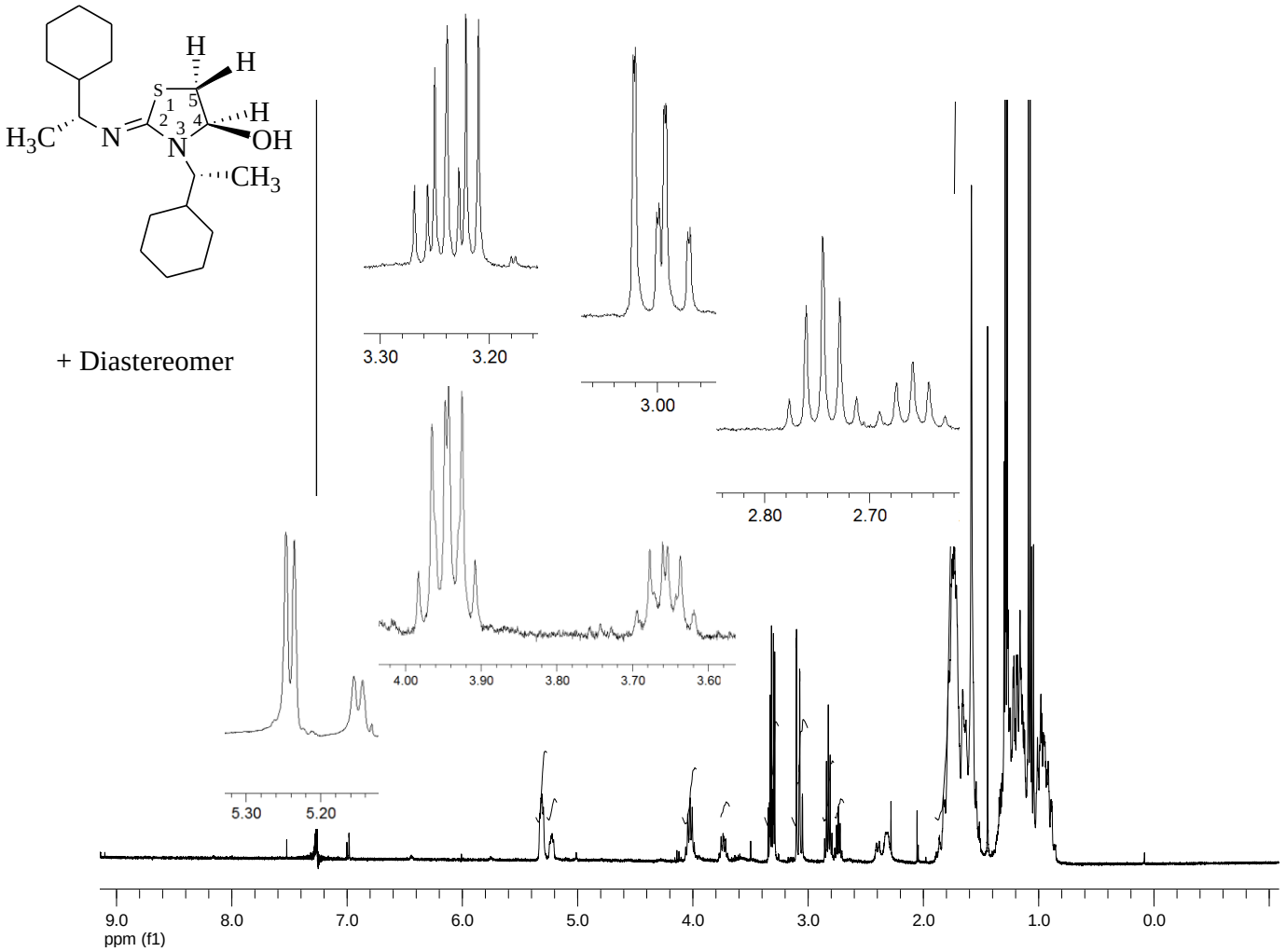

Figure A.47. ^{1}H NMR of compounds **21*RR*** and **21*SS*** ($CDCl_3$).

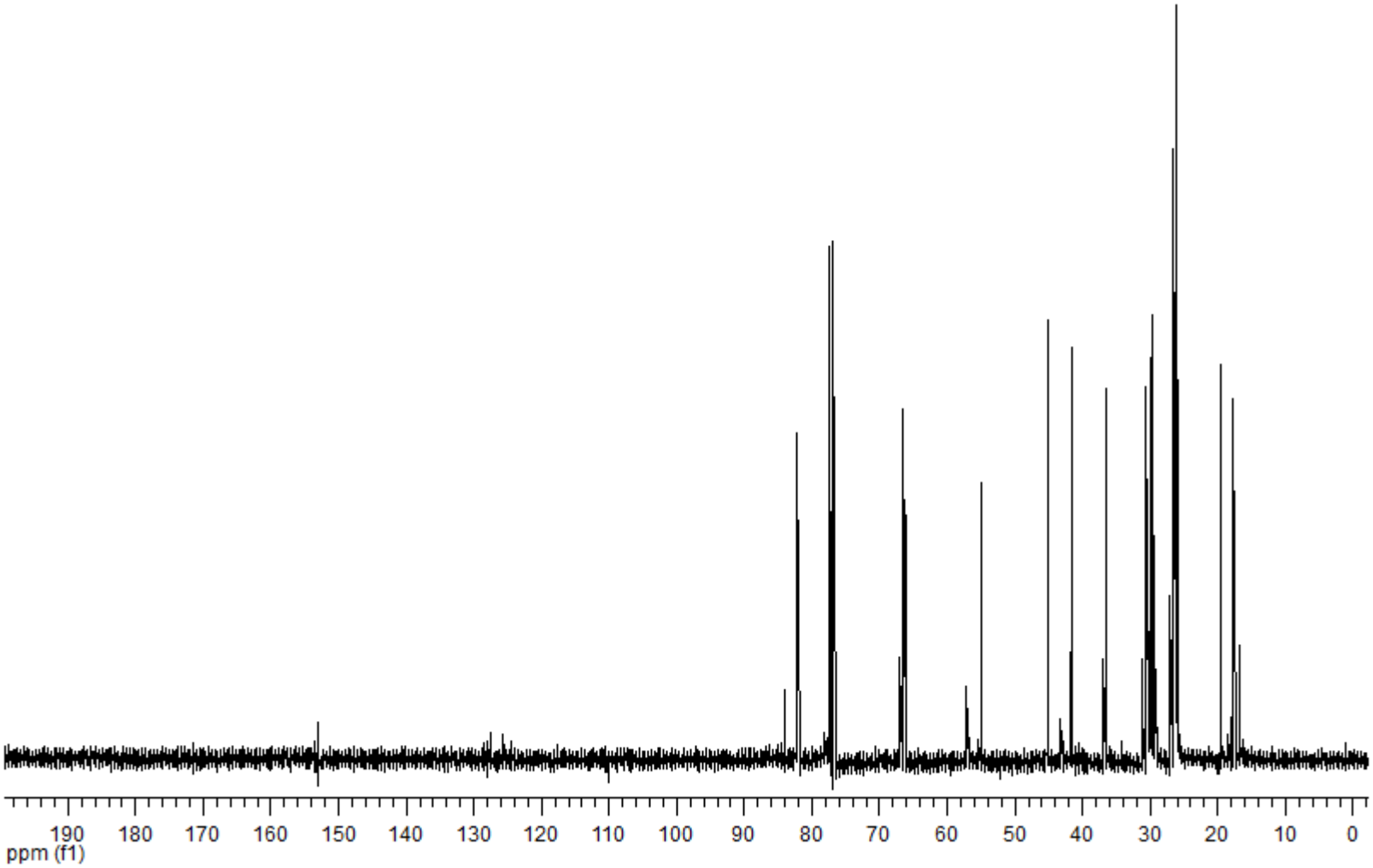

Figure A.48. ^{13}C NMR of compounds **21*RR*** and **21*SS*** ($CDCl_3$).

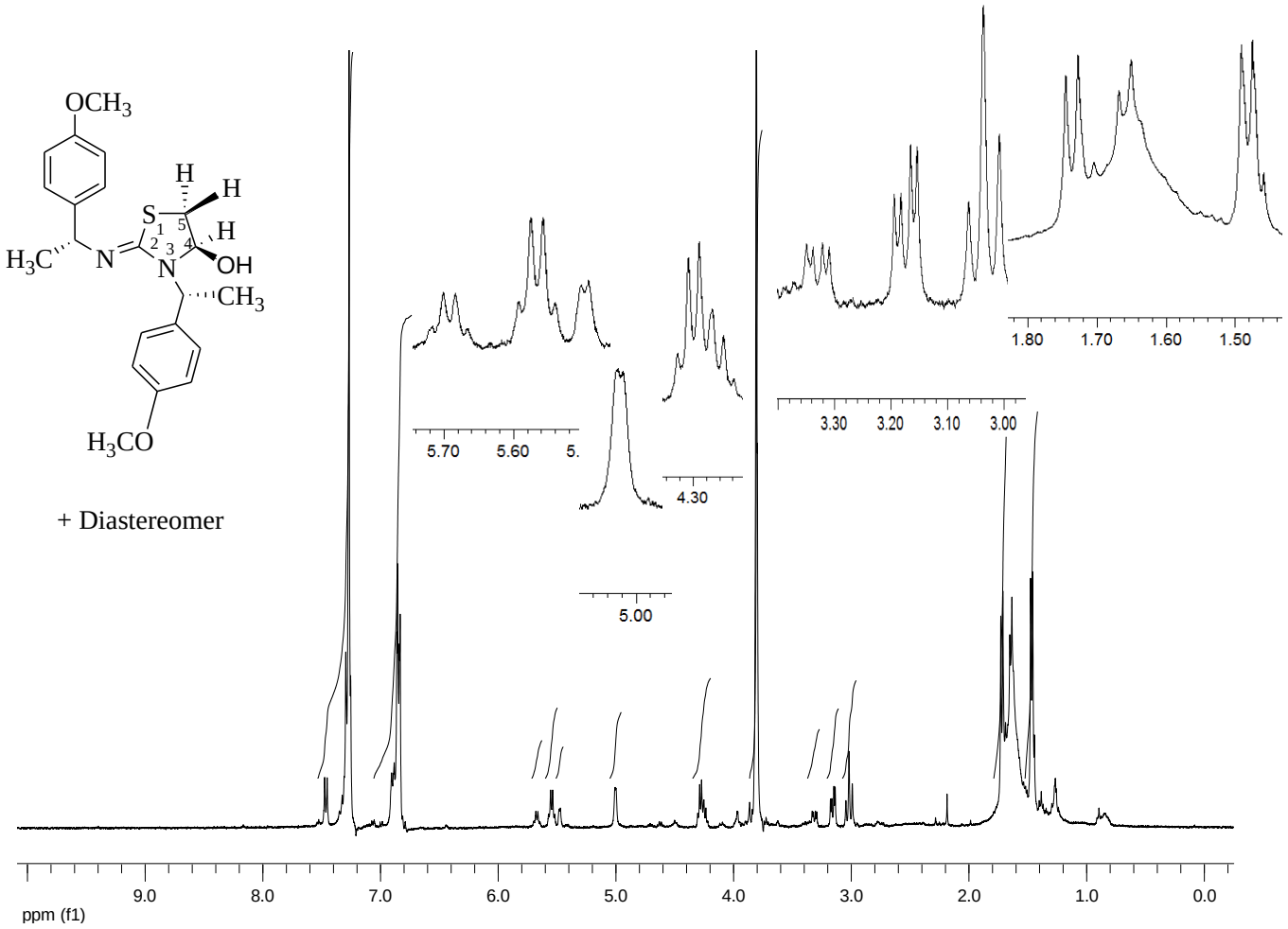

Figure A.49. ^{1}H NMR of compounds **22*RR*** and **22*SS*** ($CDCl_3$).

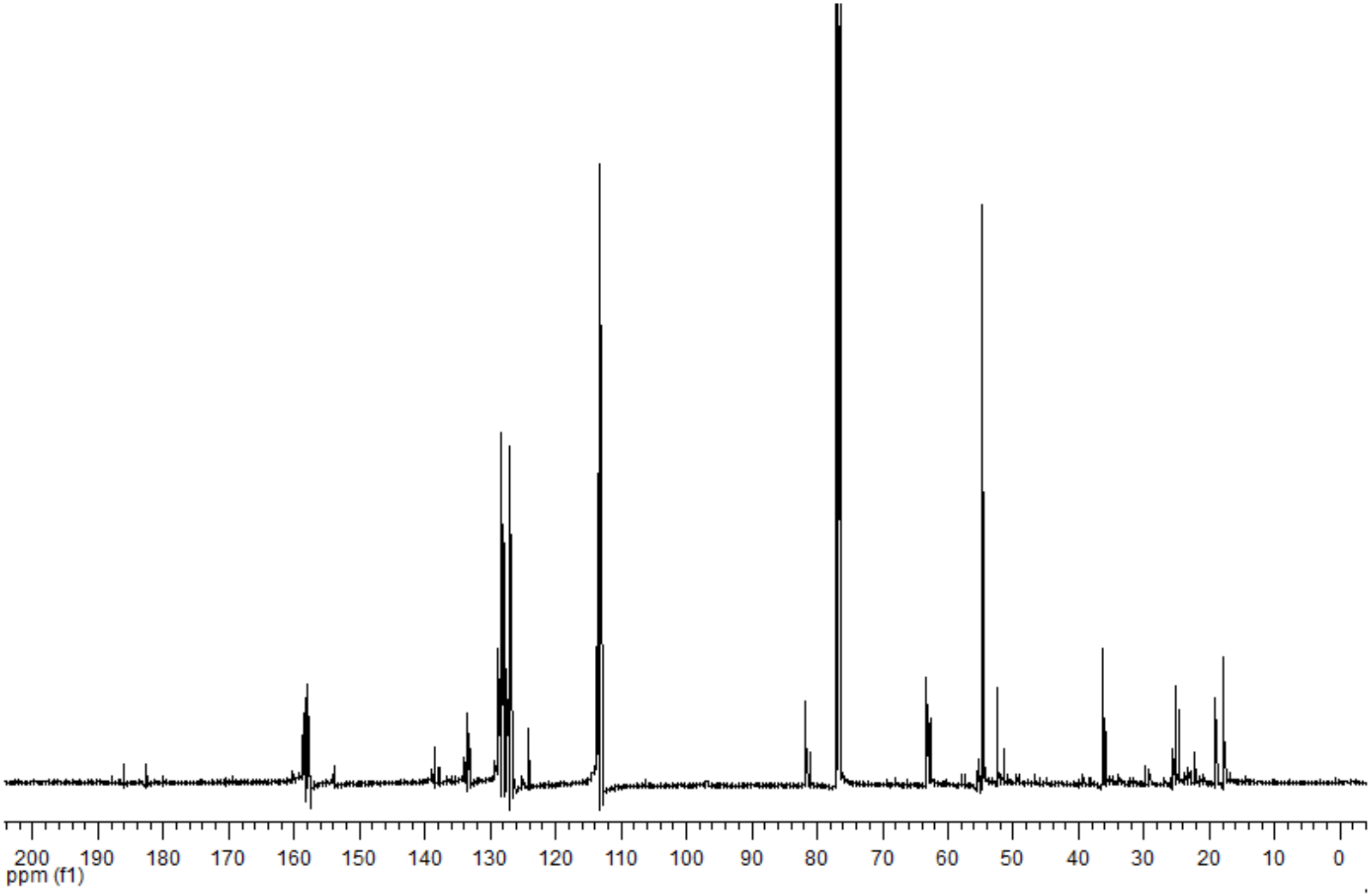

Figure A.50. ^{13}C NMR of compounds **22*RR*** and **22*SS*** ($CDCl_3$).

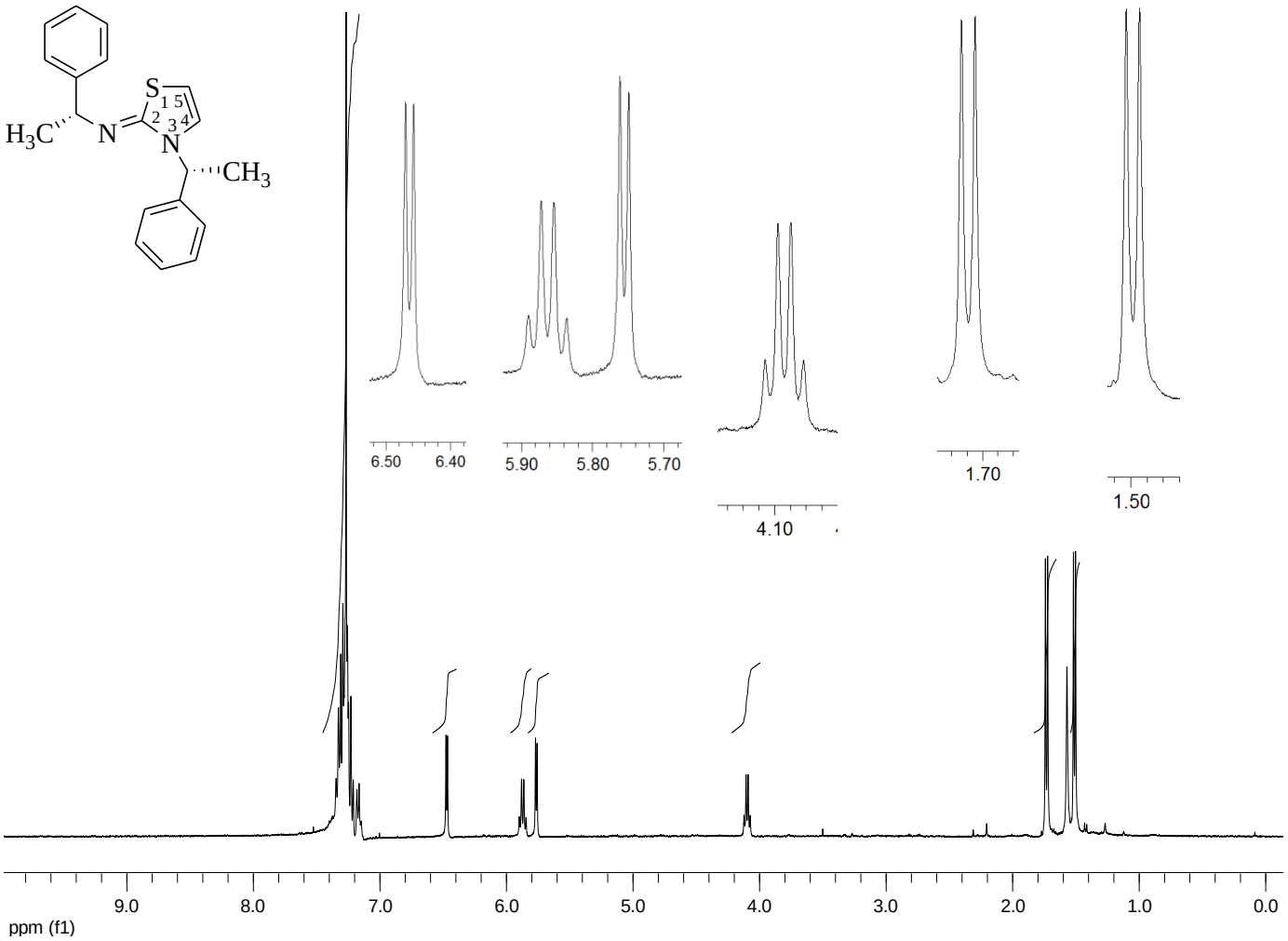

Figure A.51. ^{1}H NMR of compounds **23*RR*** and **23*SS*** ($CDCl_3$).

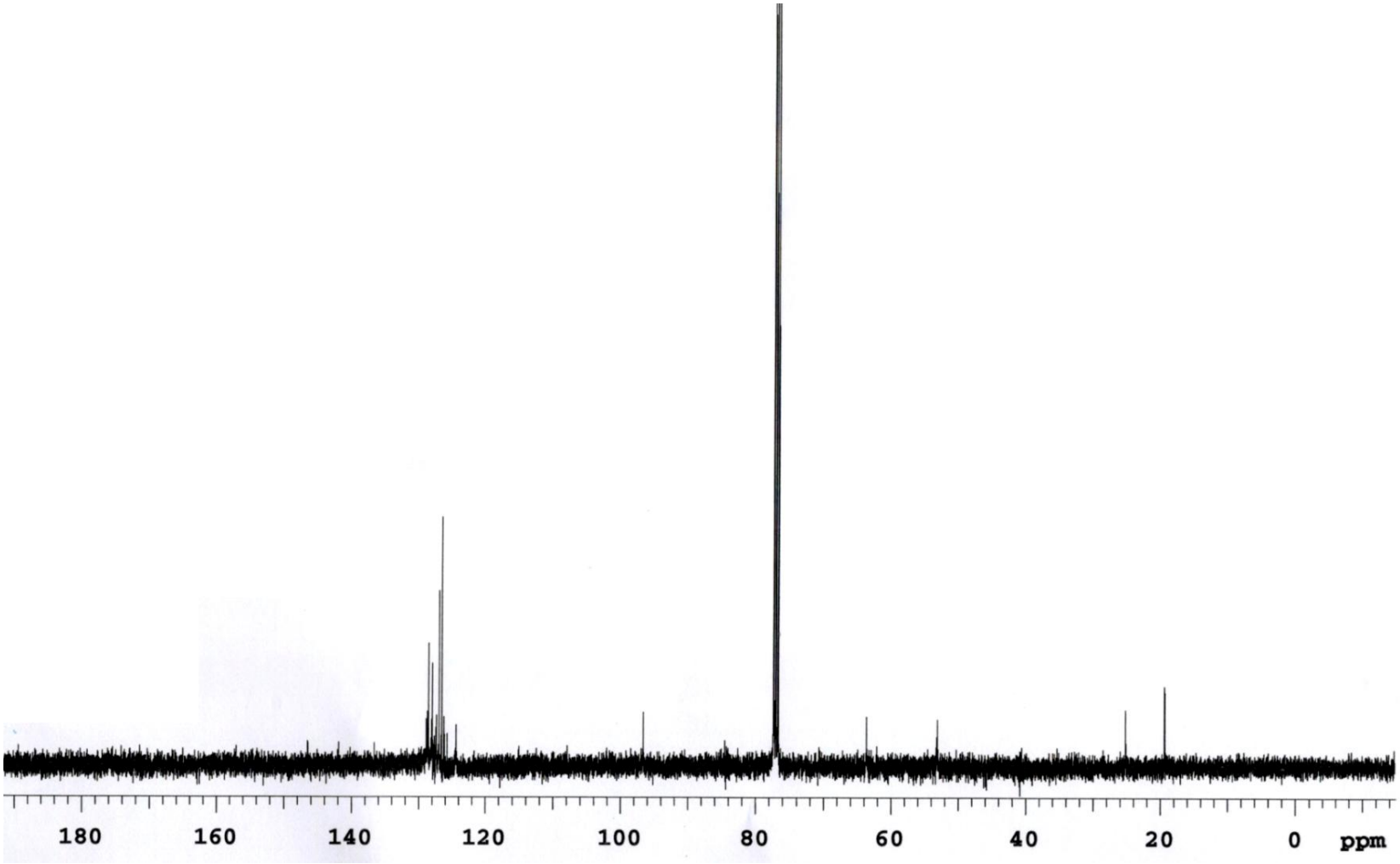

Figure A.52. ^{13}C NMR of compounds **23*RR*** and **23*SS*** ($CDCl_3$).

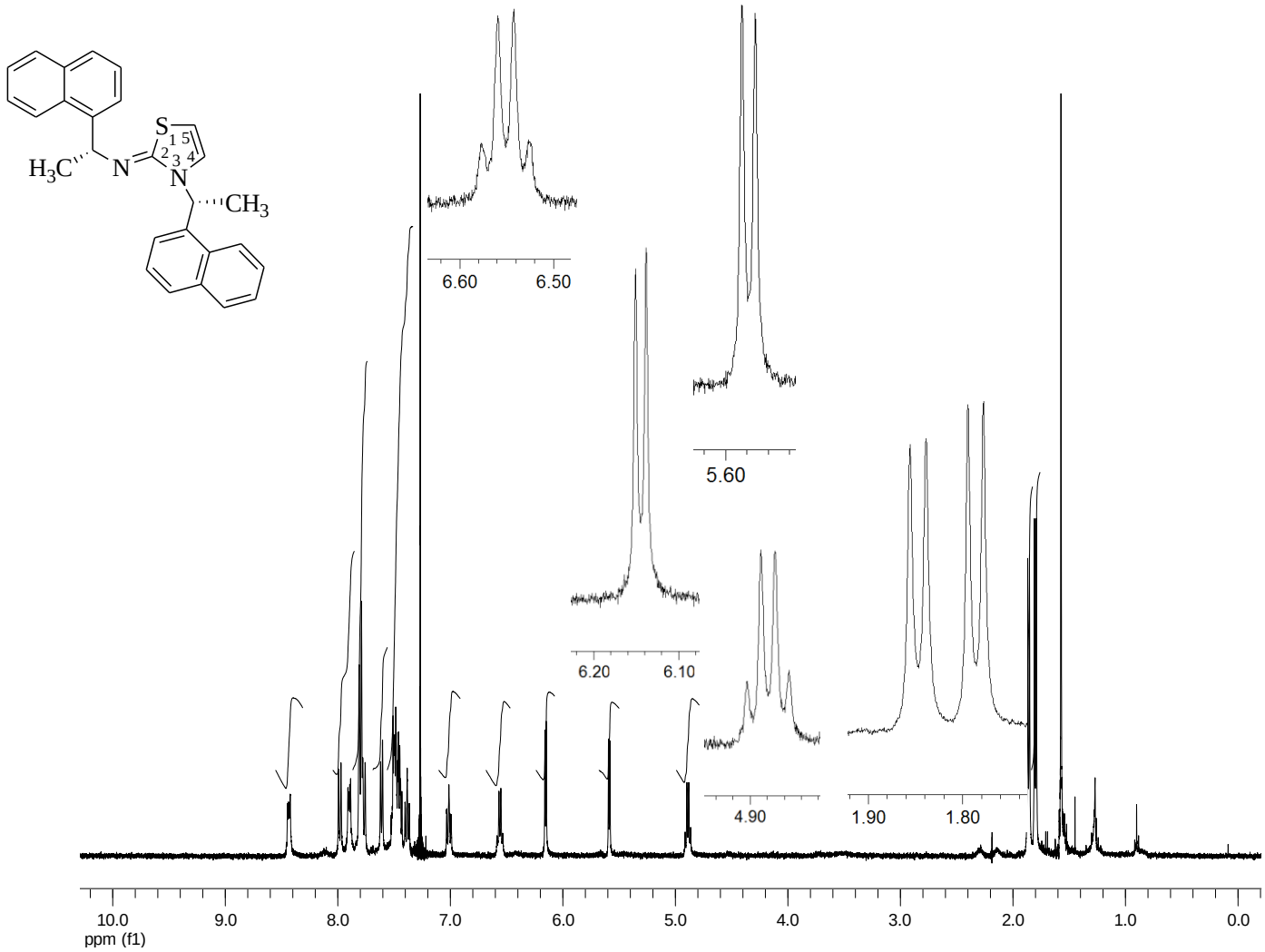

Figure A.53. ^{1}H NMR of compounds **24*RR*** and **24*SS*** ($CDCl_3$).

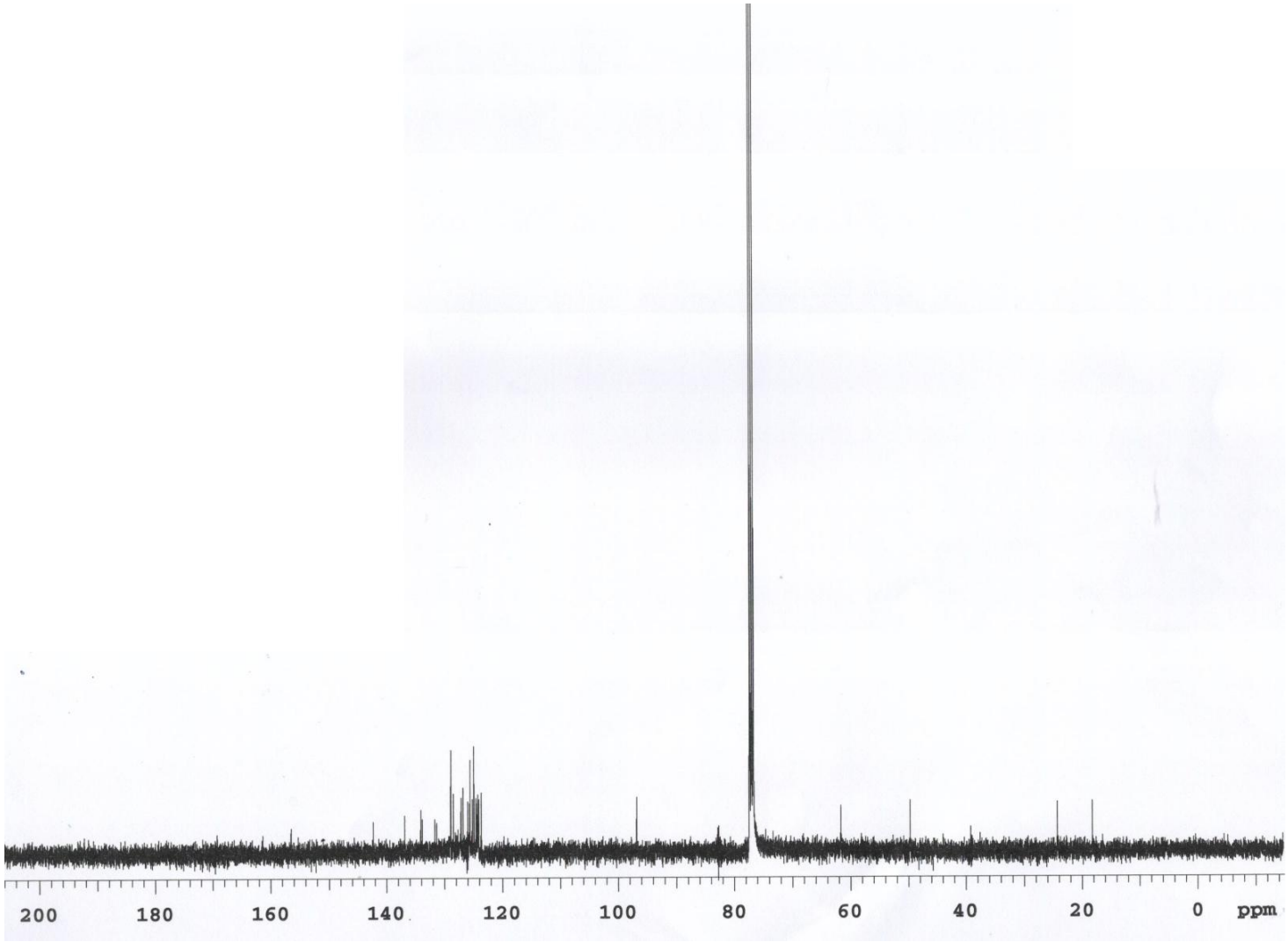

Figure A.54. ^{13}C NMR of compounds **24*RR*** and **24*SS*** ($CDCl_3$).

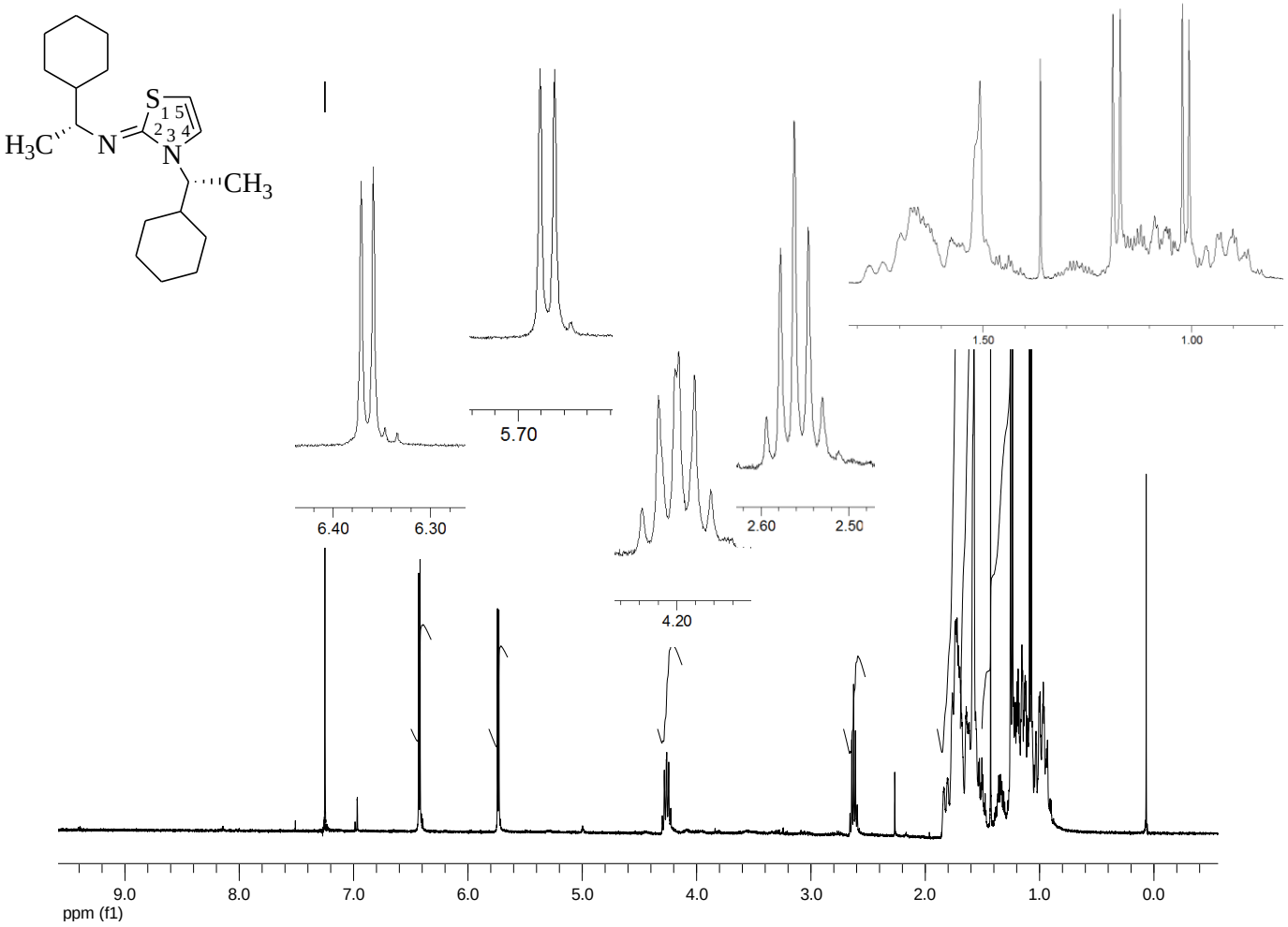

Figure A.55. ^{1}H NMR of compounds **25*RR*** and **25*SS*** ($CDCl_3$).

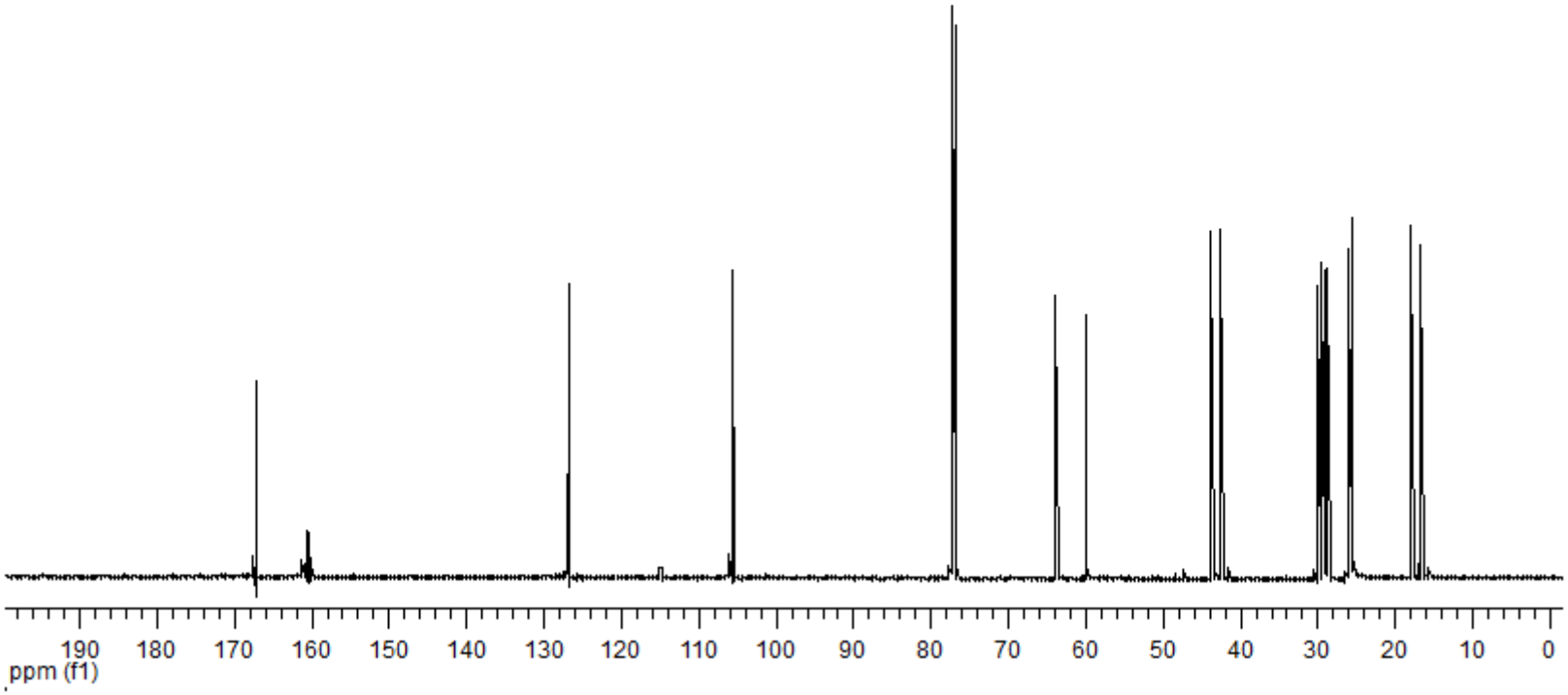

Figure A.56. ^{13}C NMR of compounds **25*RR*** and **25*SS*** ($CDCl_3$).

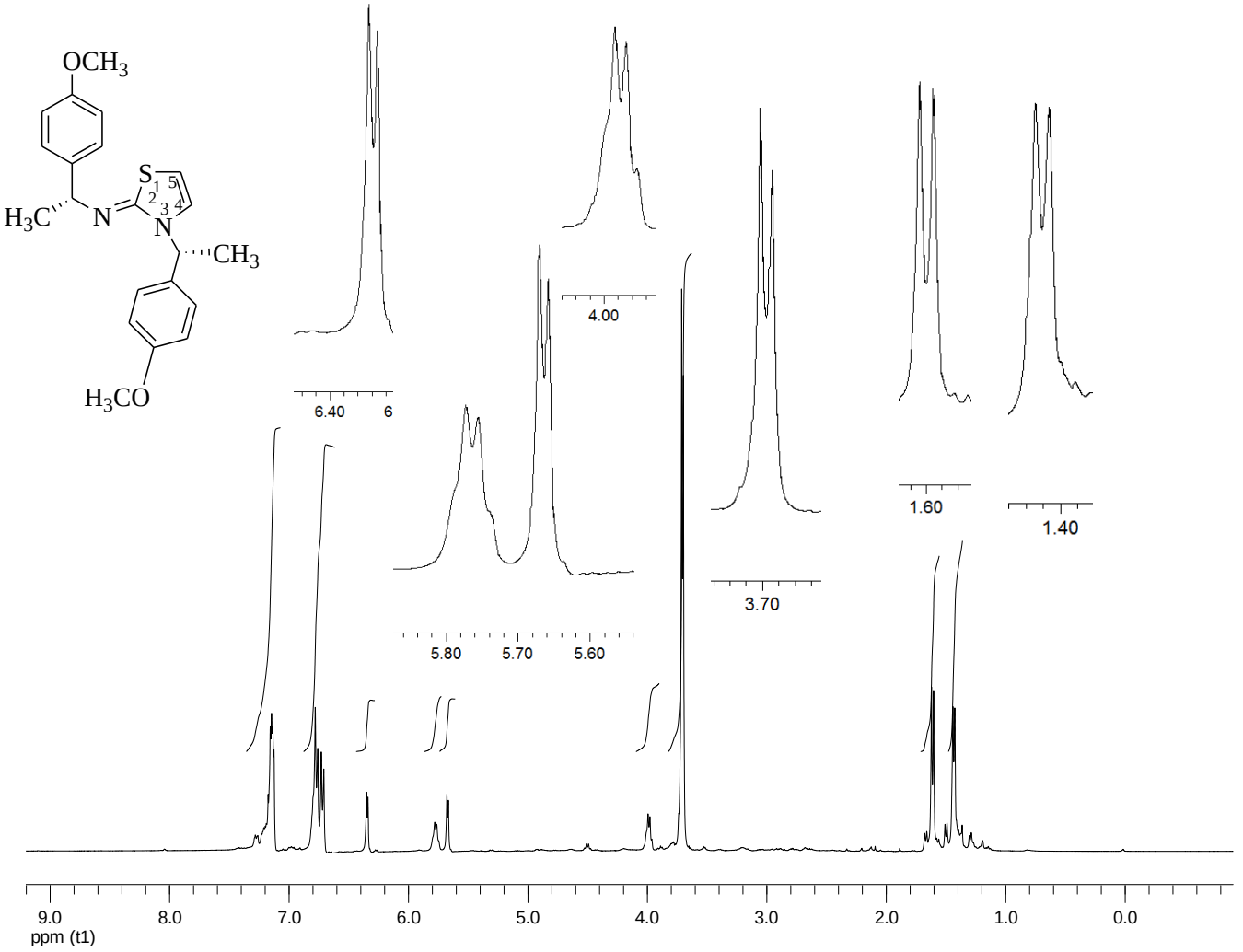

Figure A.57. ^{1}H NMR of compounds **26*RR*** and **26*SS*** ($CDCl_3$).

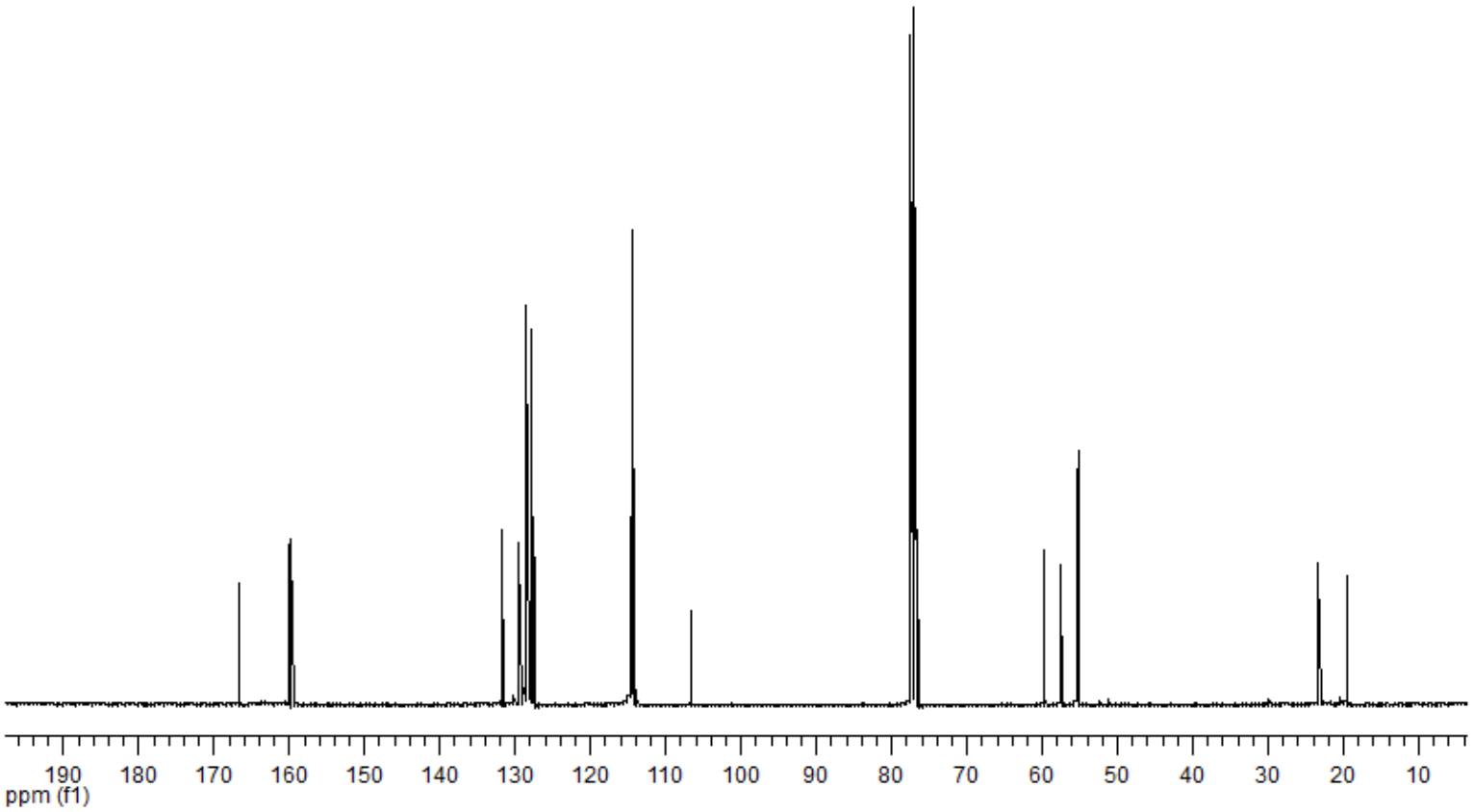

Figure A.58. ^{13}C NMR of compounds **26*RR*** and **26*SS*** ($CDCl_3$).

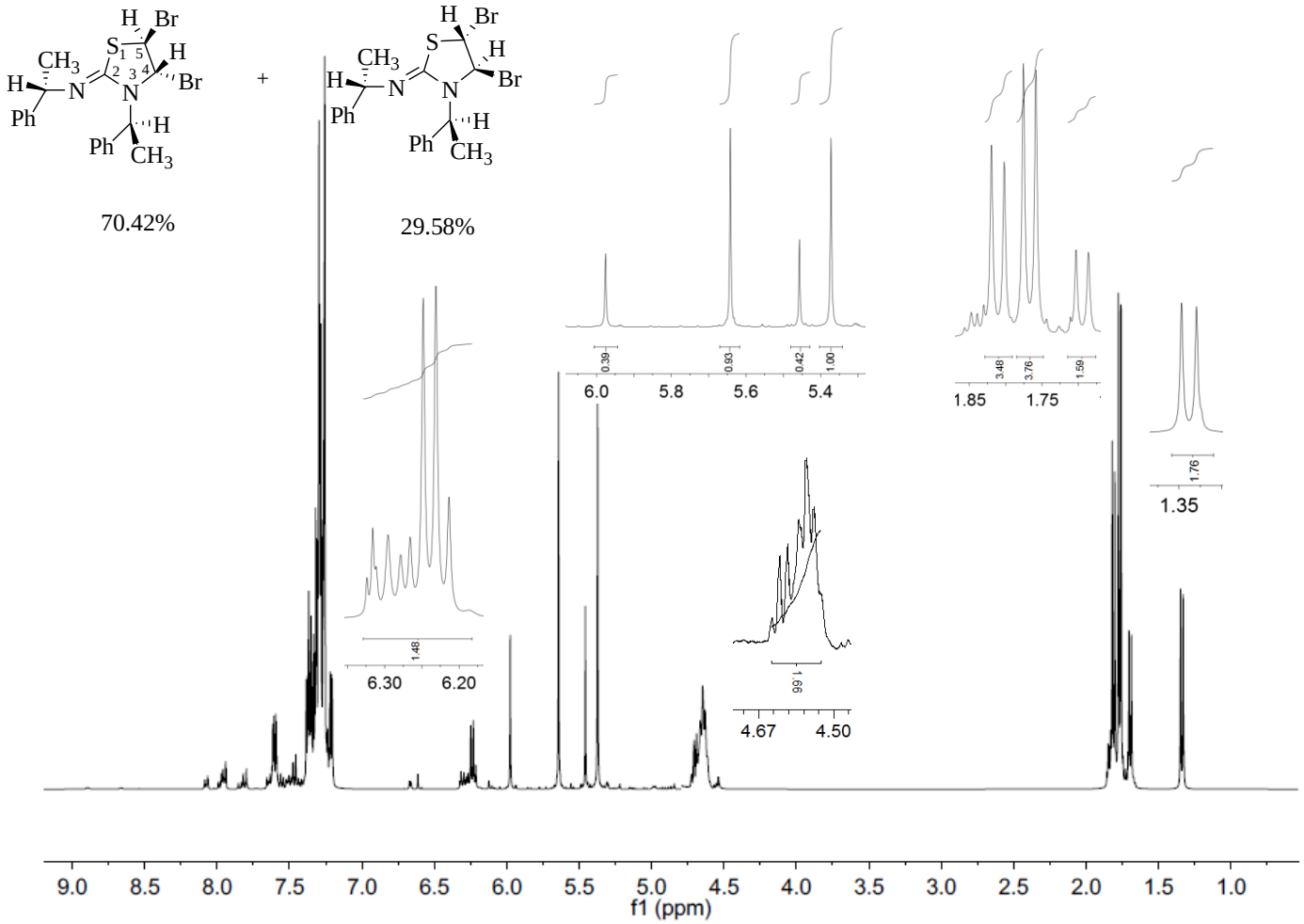

Figure A.59. ^{1}H NMR of compound **27** ($CDCl_3$).

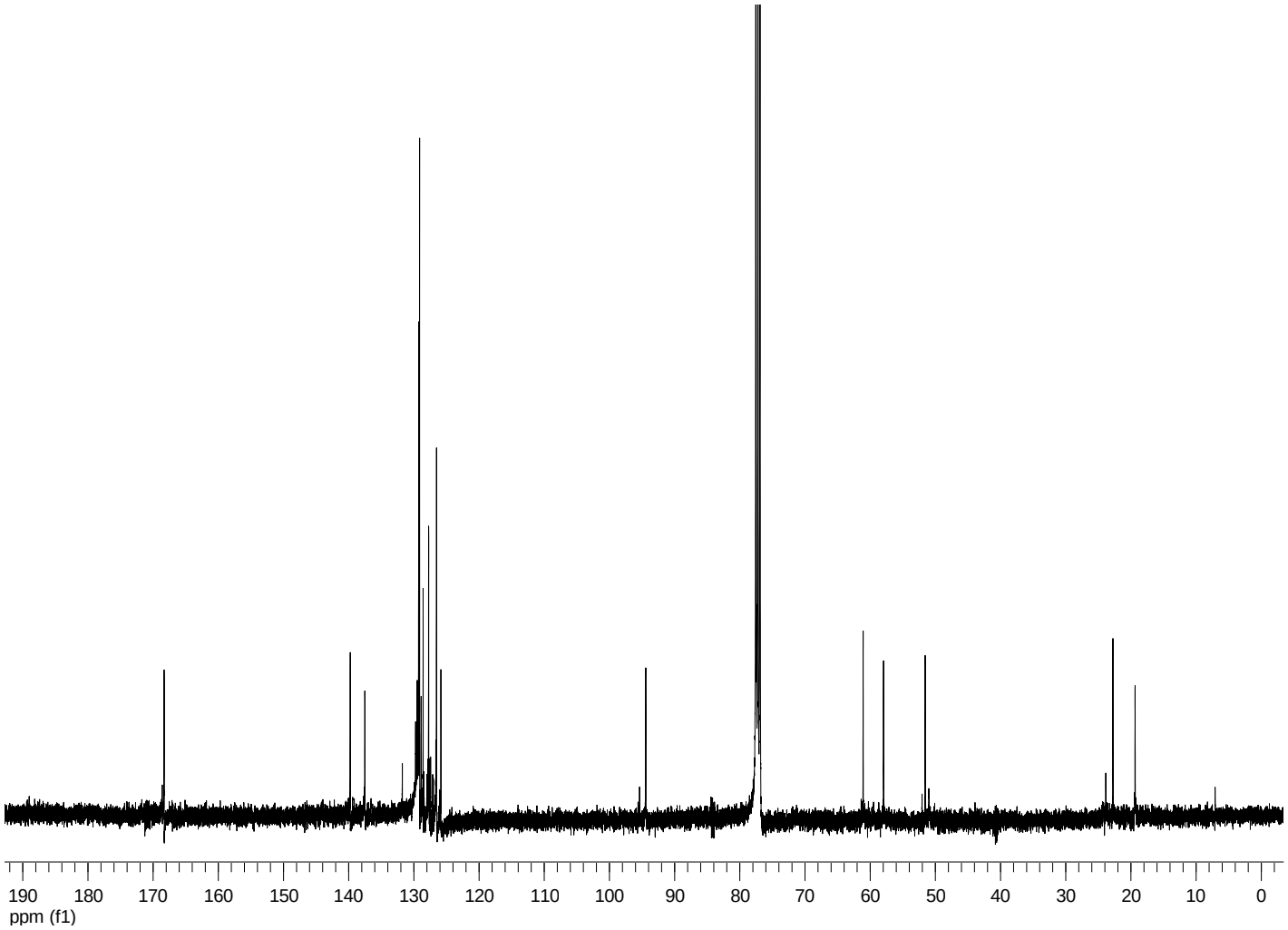

Figure A.60. ^{13}C NMR of compound **27** ($CDCl_3$).

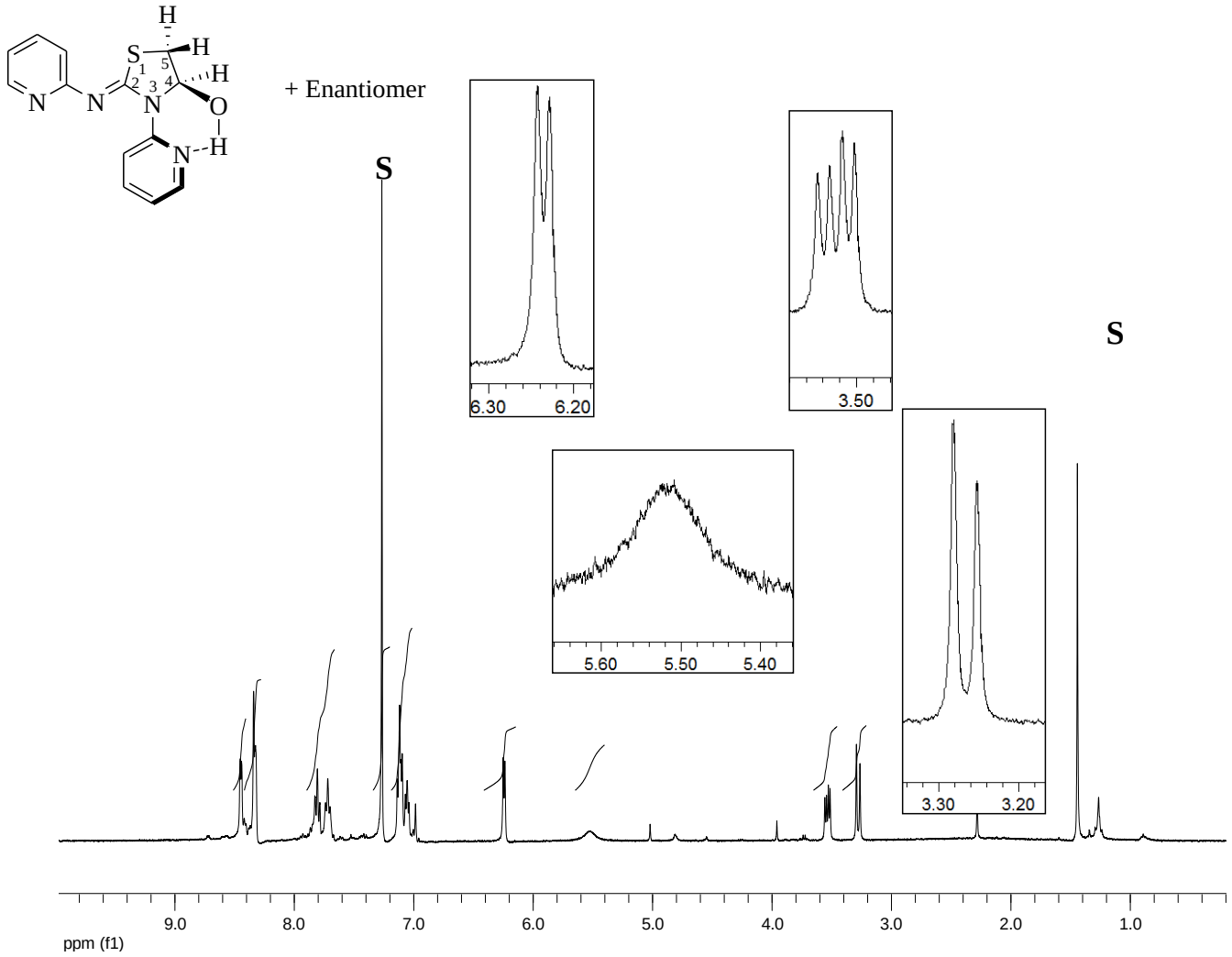

Figure A.61. ^{1}H NMR of compound **32** ($CDCl_3$).

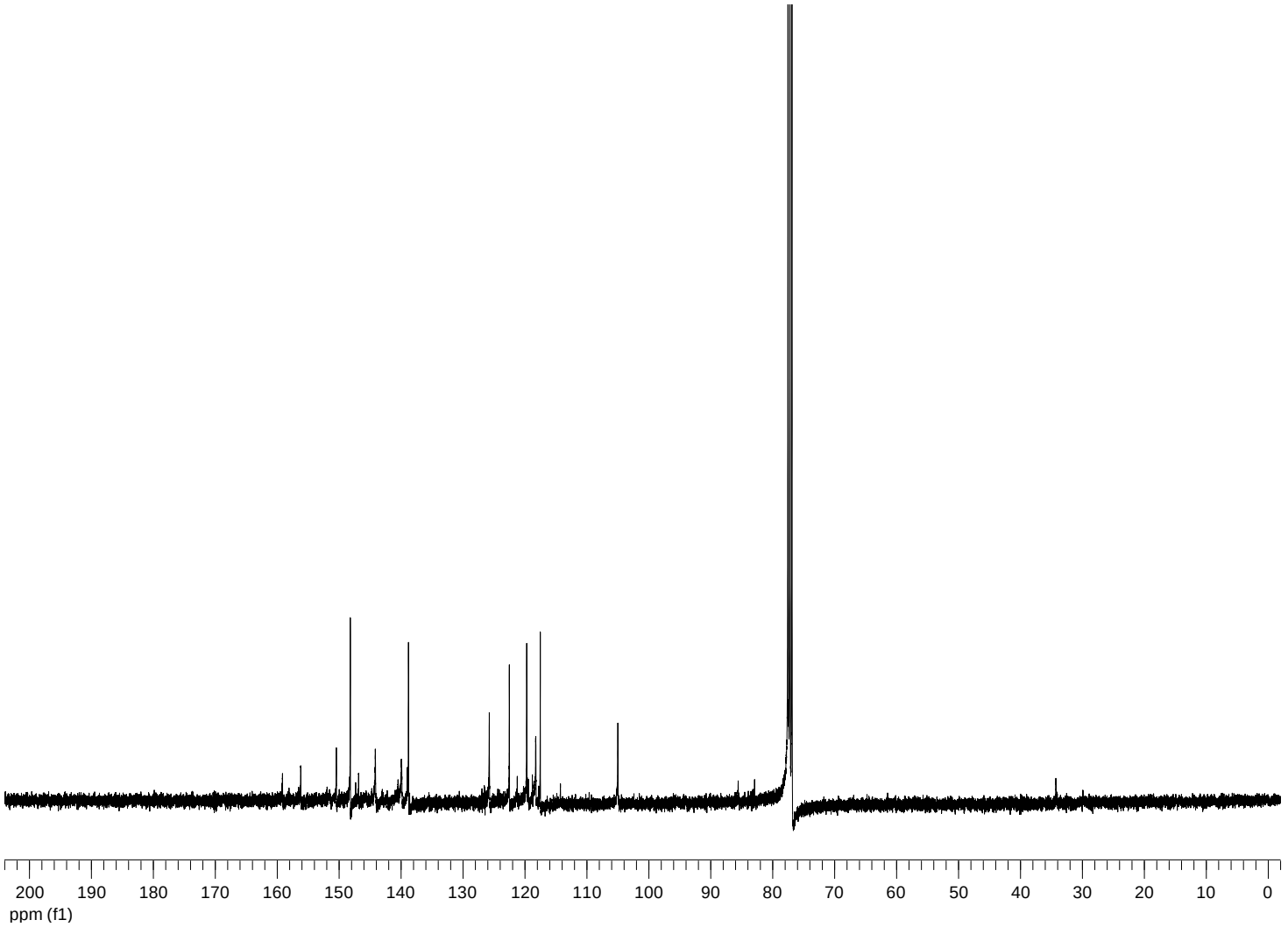

Figure A.62. ^{13}C NMR of compound **32** ($CDCl_3$).

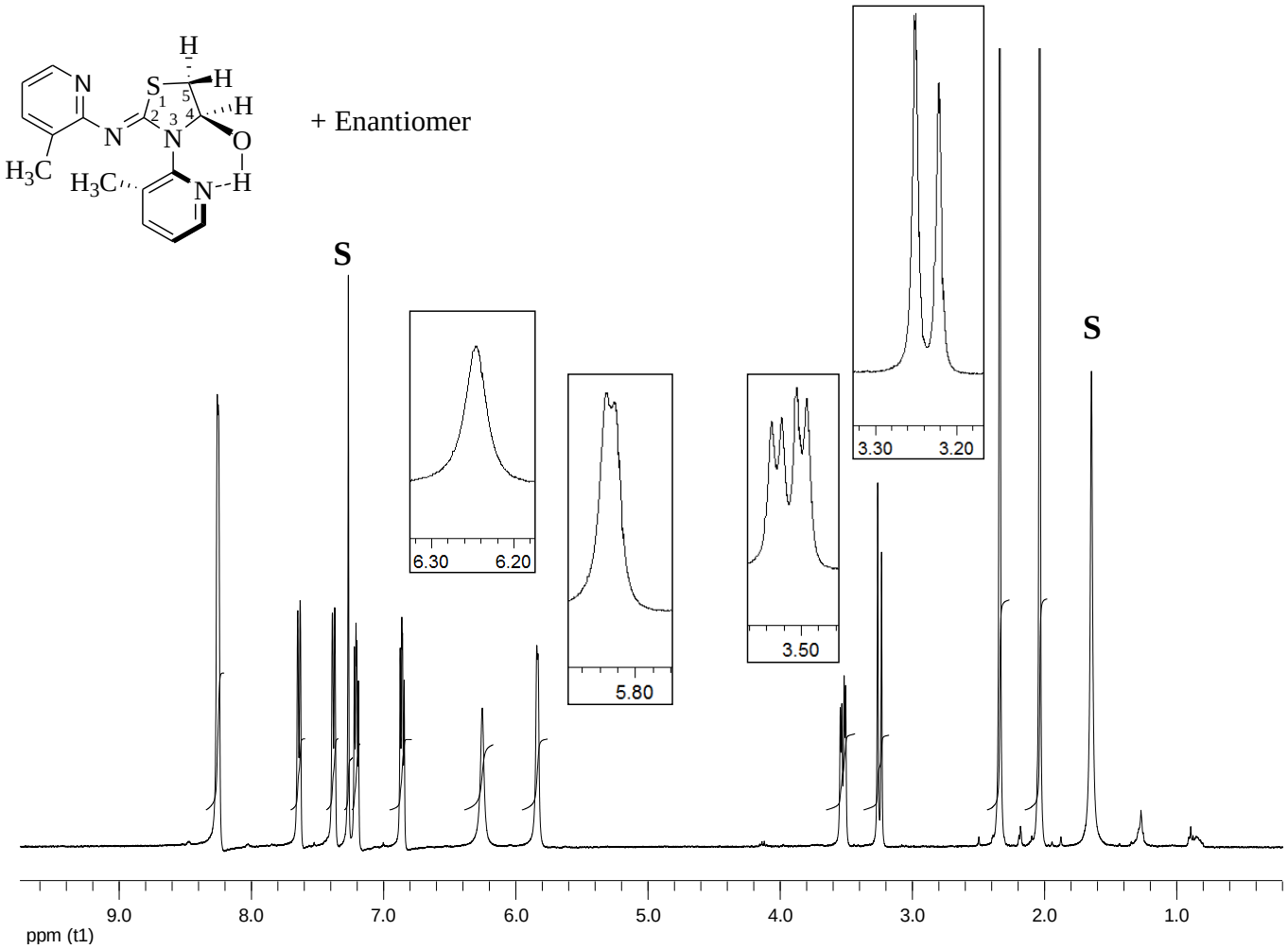

Figure A.63. ^{1}H NMR of compound **33** ($CDCl_3$).

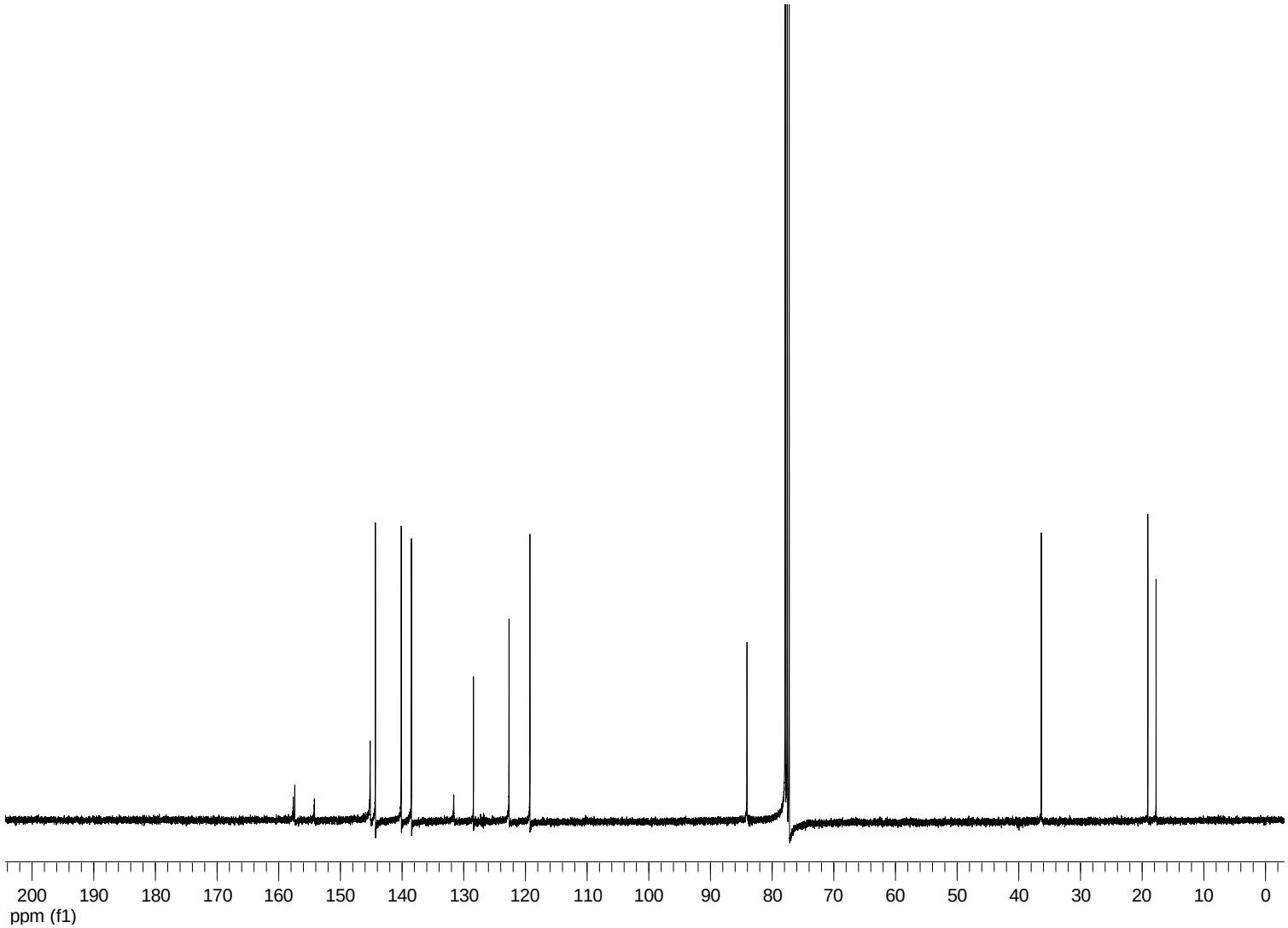

Figure A.64. ^{13}C NMR of compound **33** ($CDCl_3$).

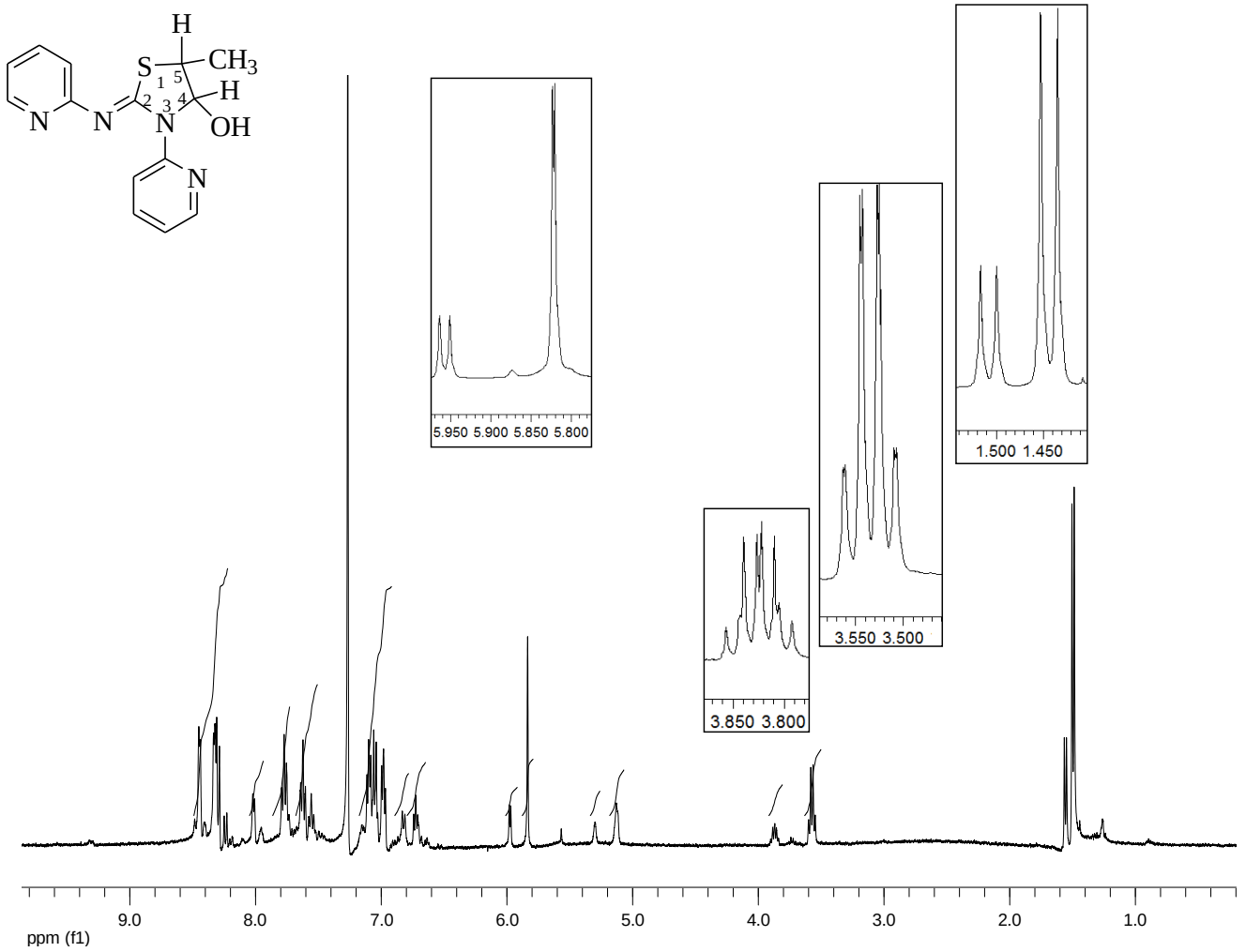

Figure A.65. ^{1}H NMR of compound **34** ($CDCl_3$).

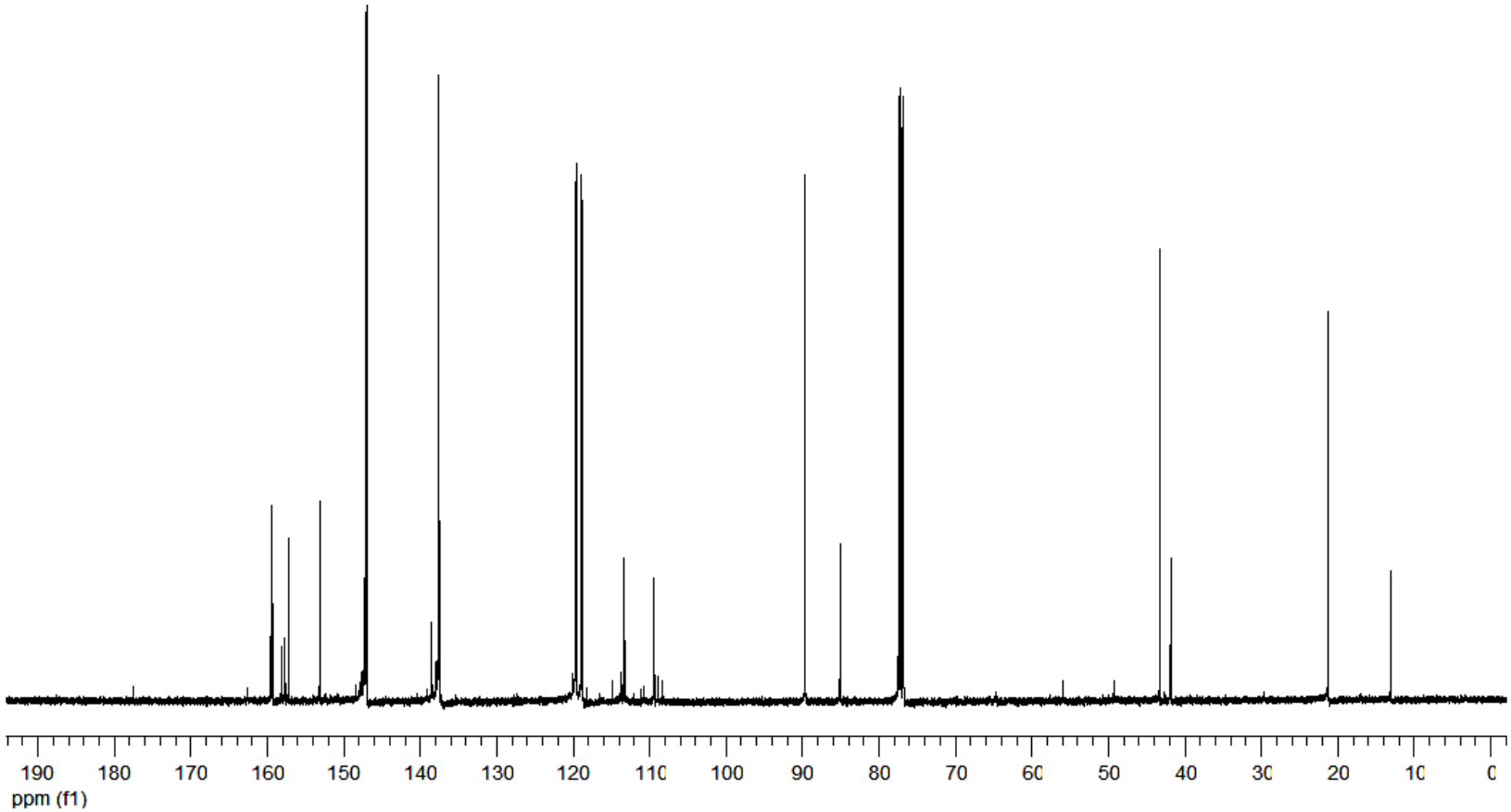

Figure A.66. ^{13}C NMR of compound **34** ($CDCl_3$).

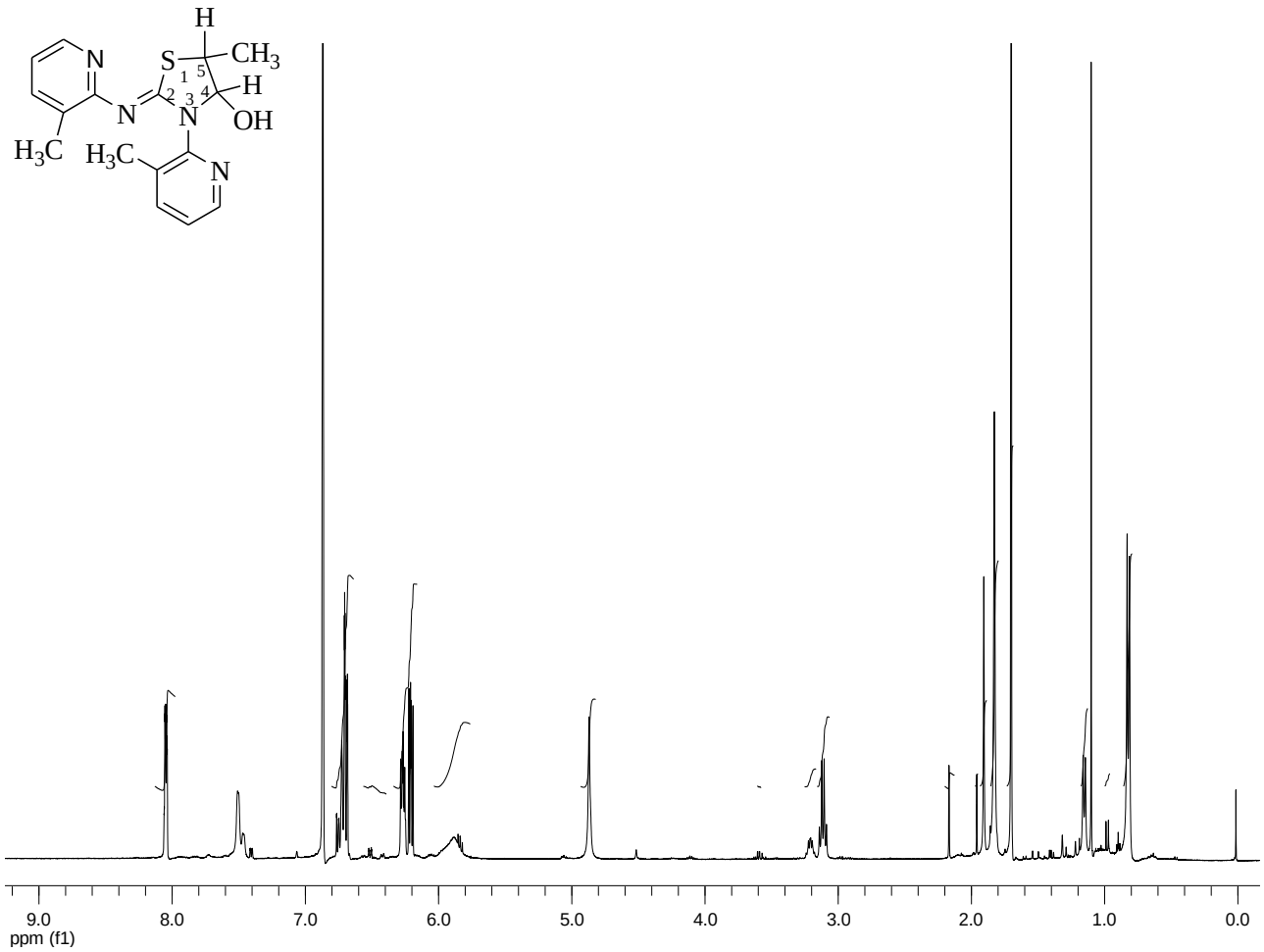

Figure A.67. ^{1}H NMR of compound **35** ($CDCl_3$).

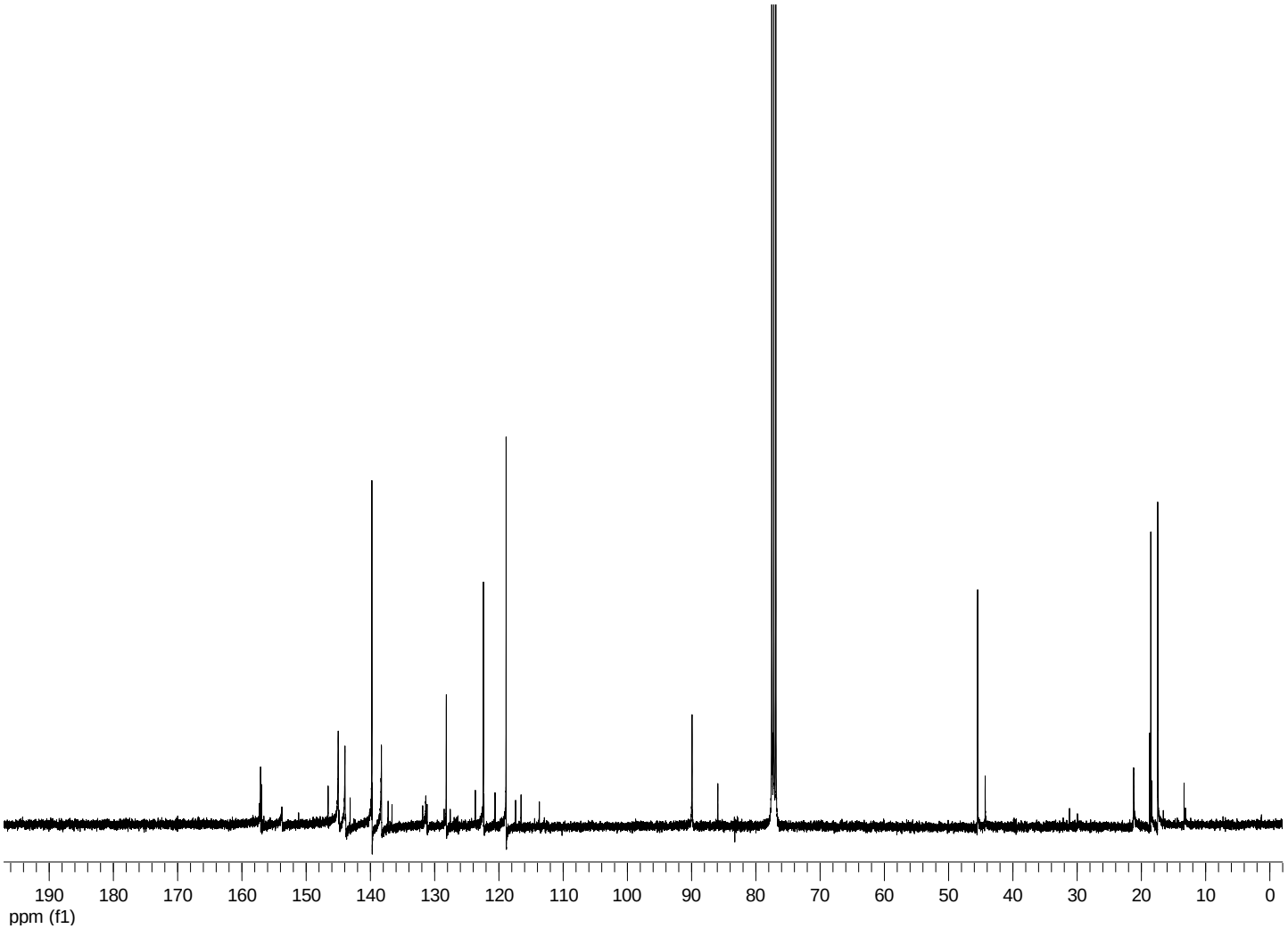

Figure A.68. ^{13}C NMR of compound **35** ($CDCl_3$).

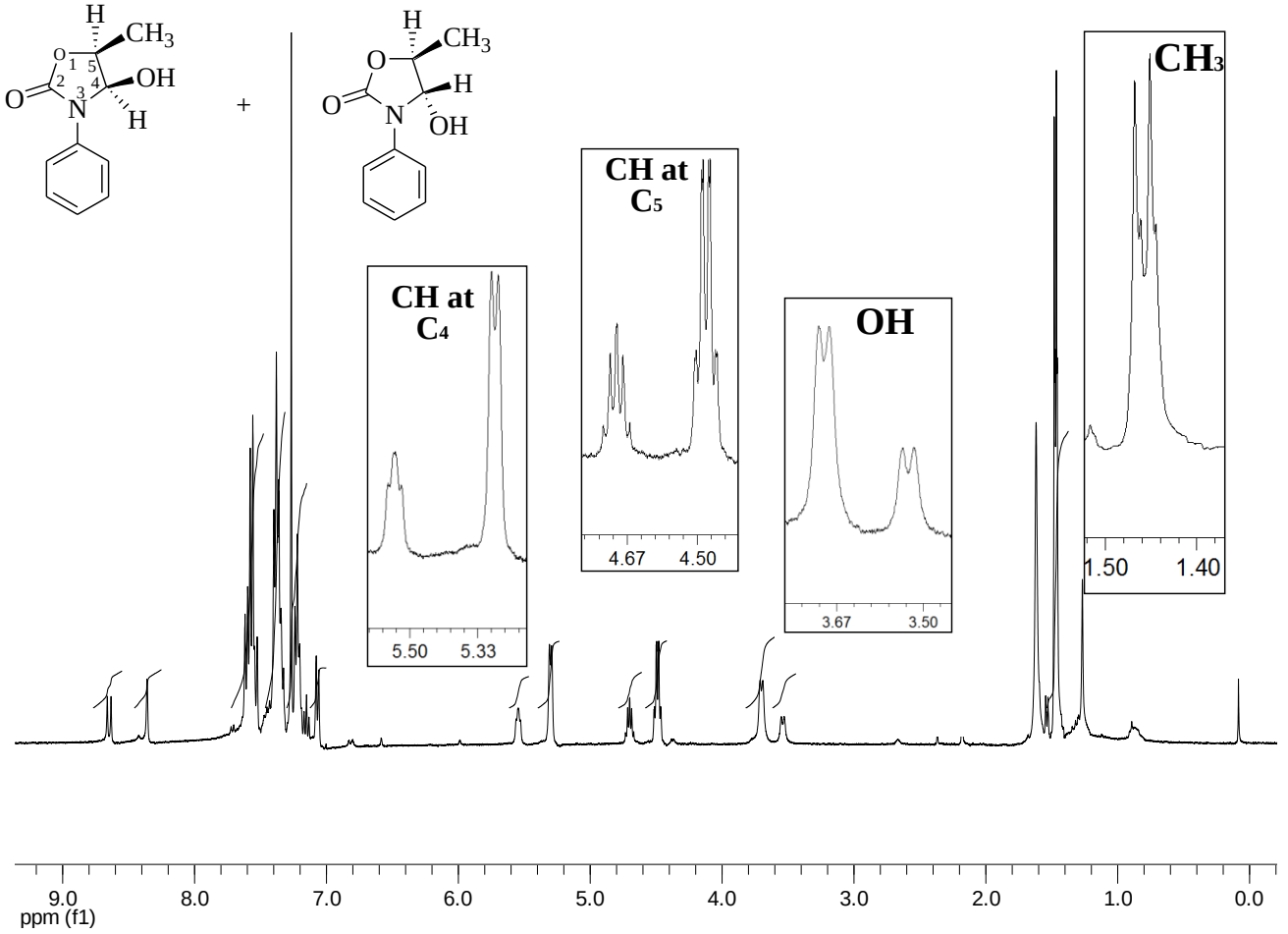

Figure A.69. ^{1}H NMR of compound **36** ($CDCl_3$).

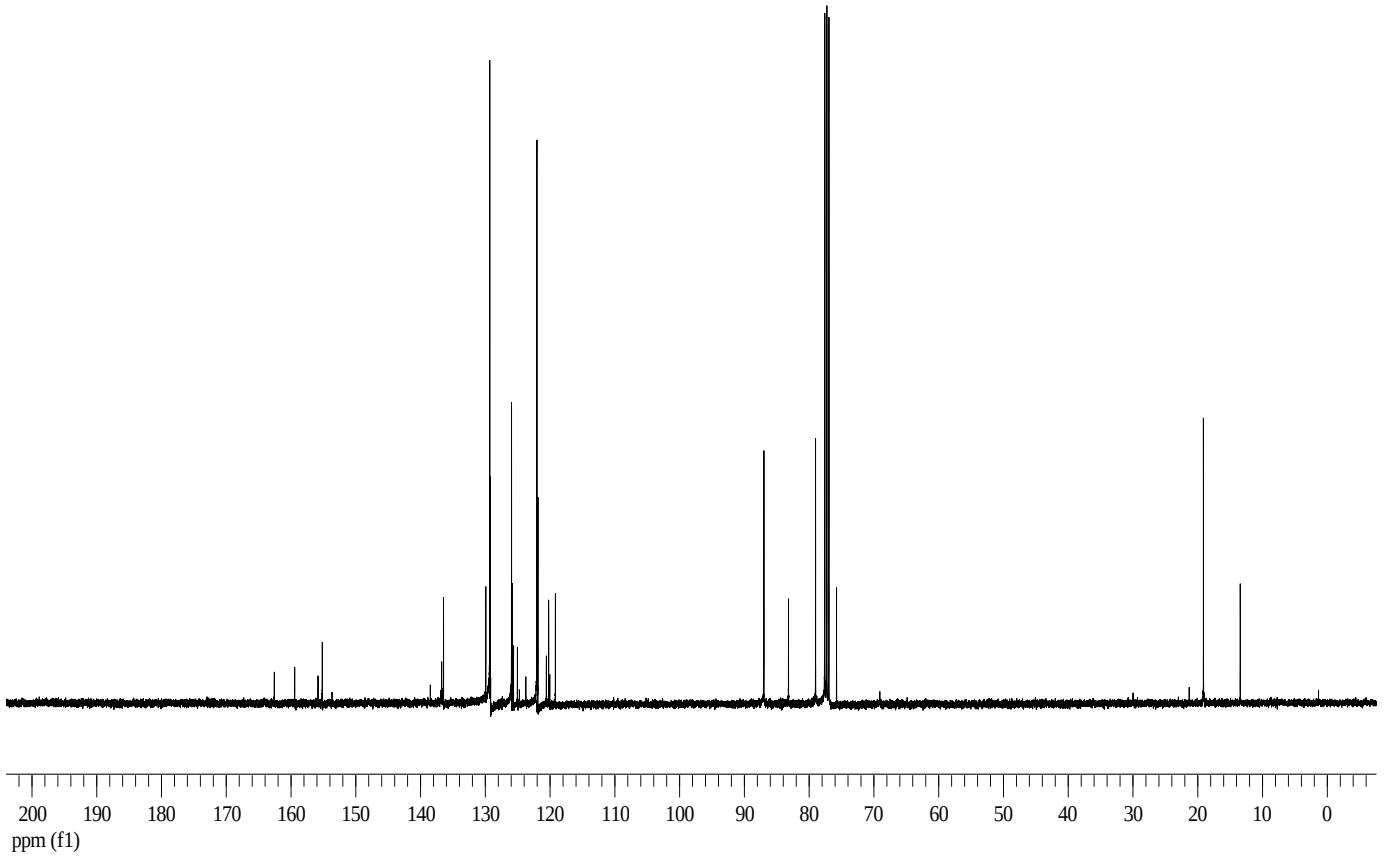

Figure A.70. ^{13}C NMR of compound **36** ($CDCl_3$).

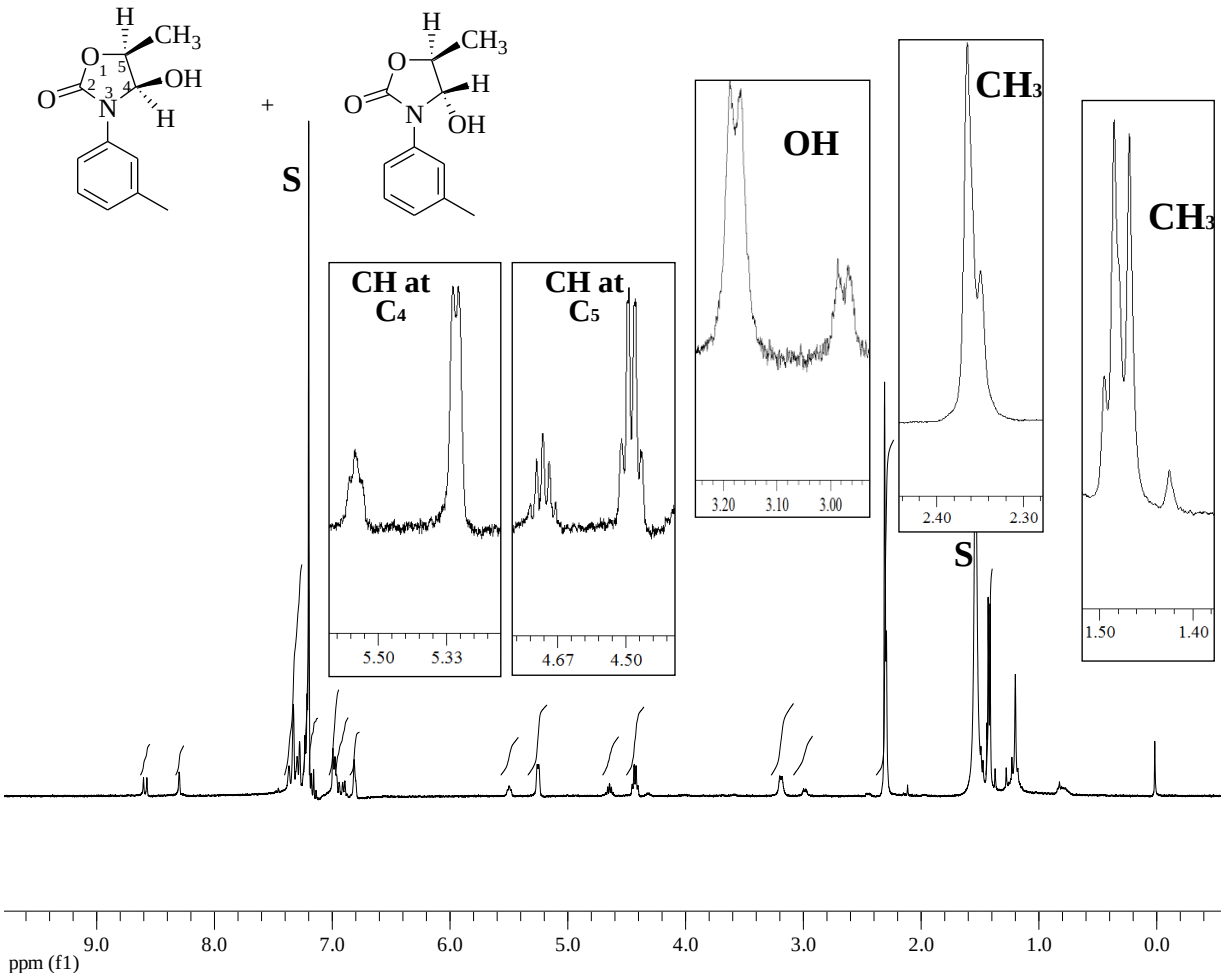

Figure A.71. ^{1}H NMR of compound **37** ($CDCl_3$).

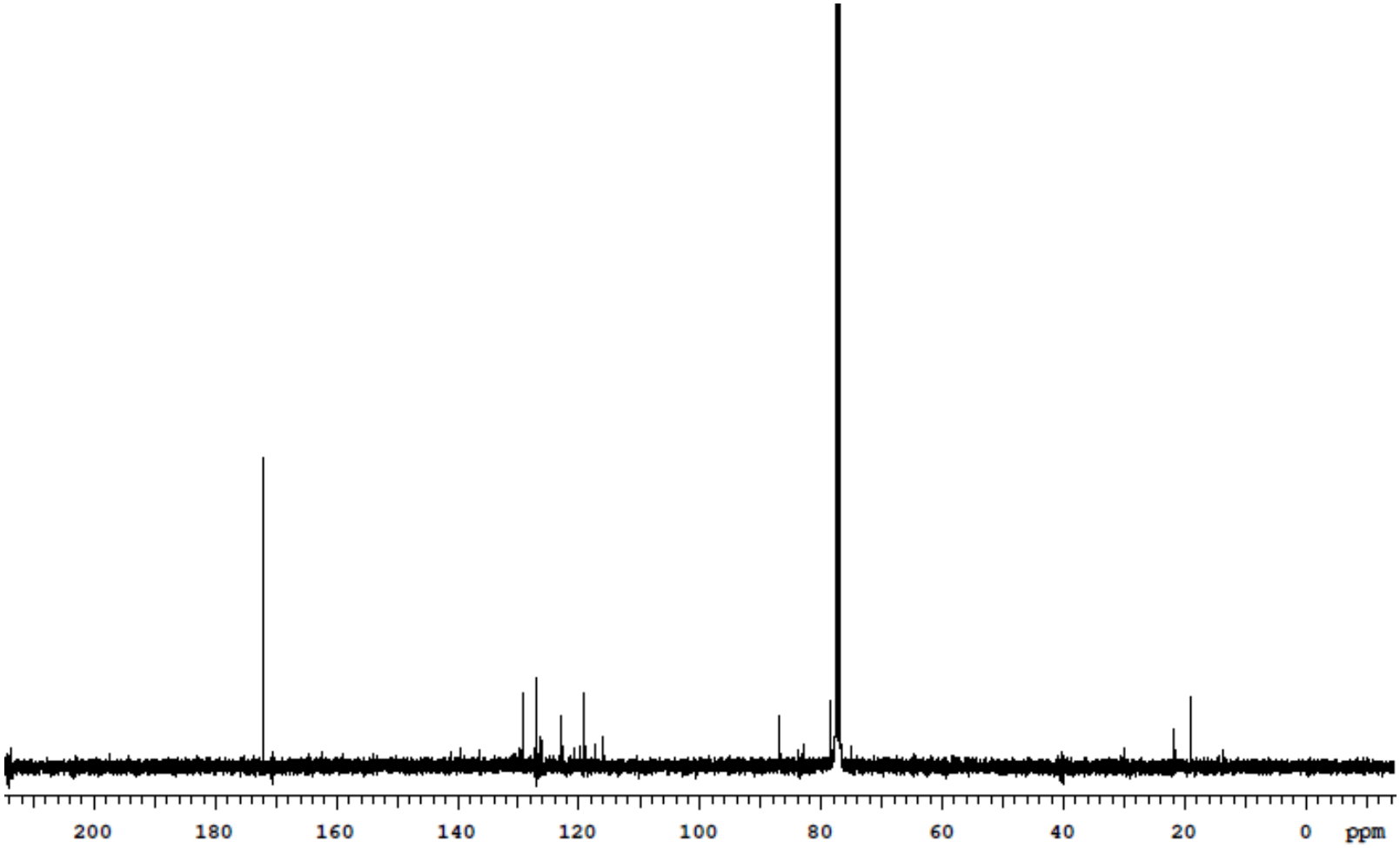

Figure A.72. ^{13}C NMR of compound **37** ($CDCl_3$).

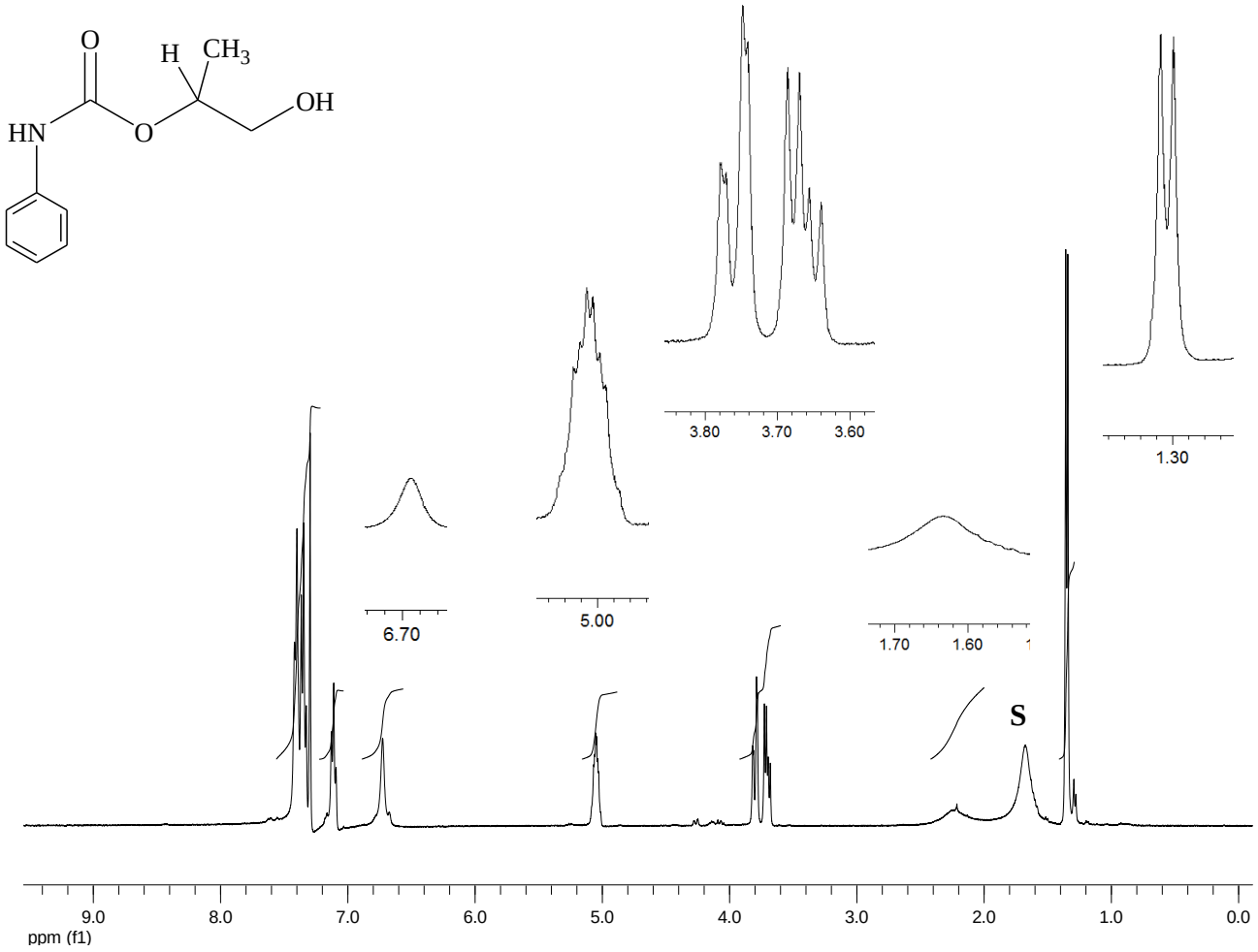

Figure A.73. ^{1}H NMR of compound **38** ($CDCl_3$).

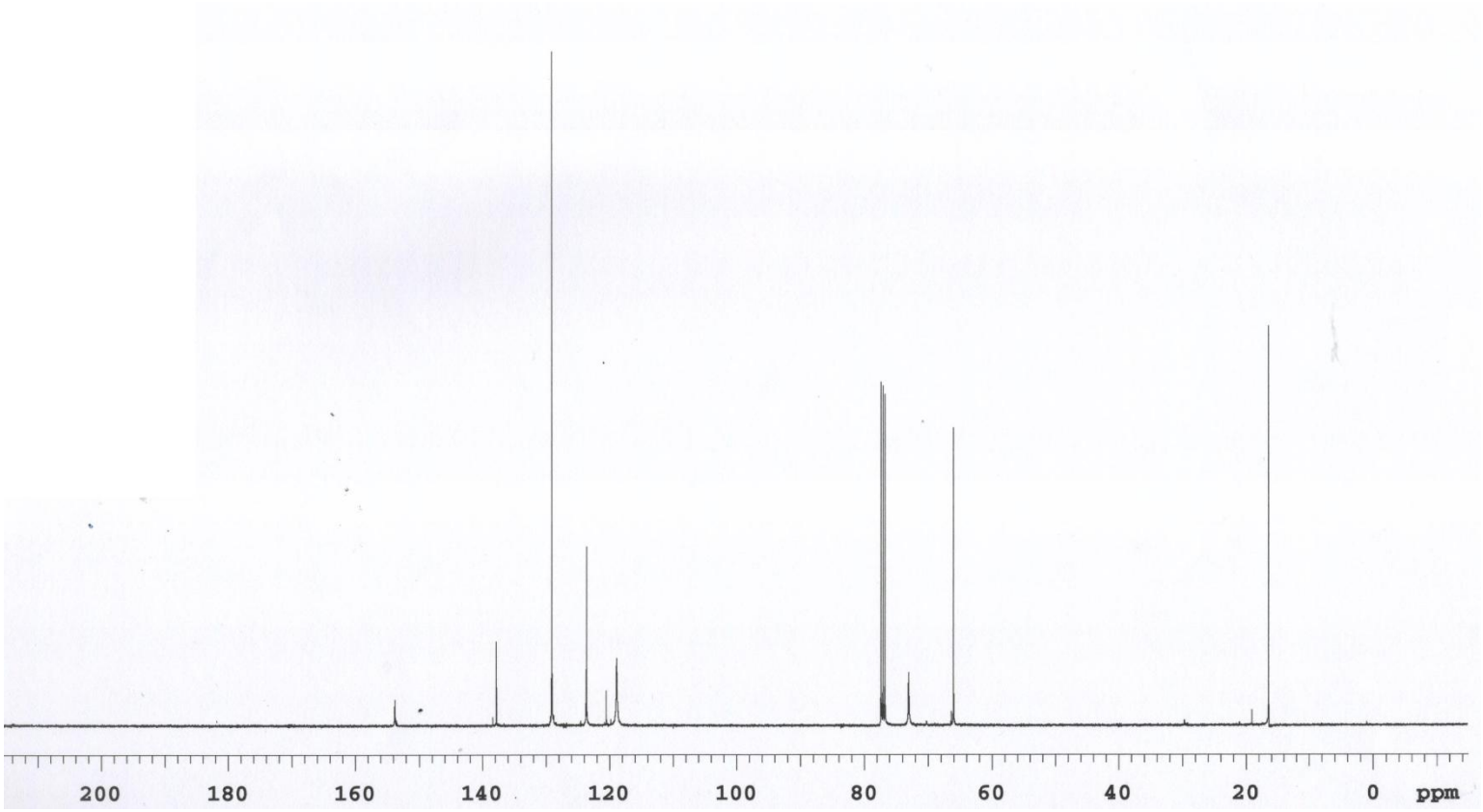

Figure A.74. ^{13}C NMR of compound **38** ($CDCl_3$).

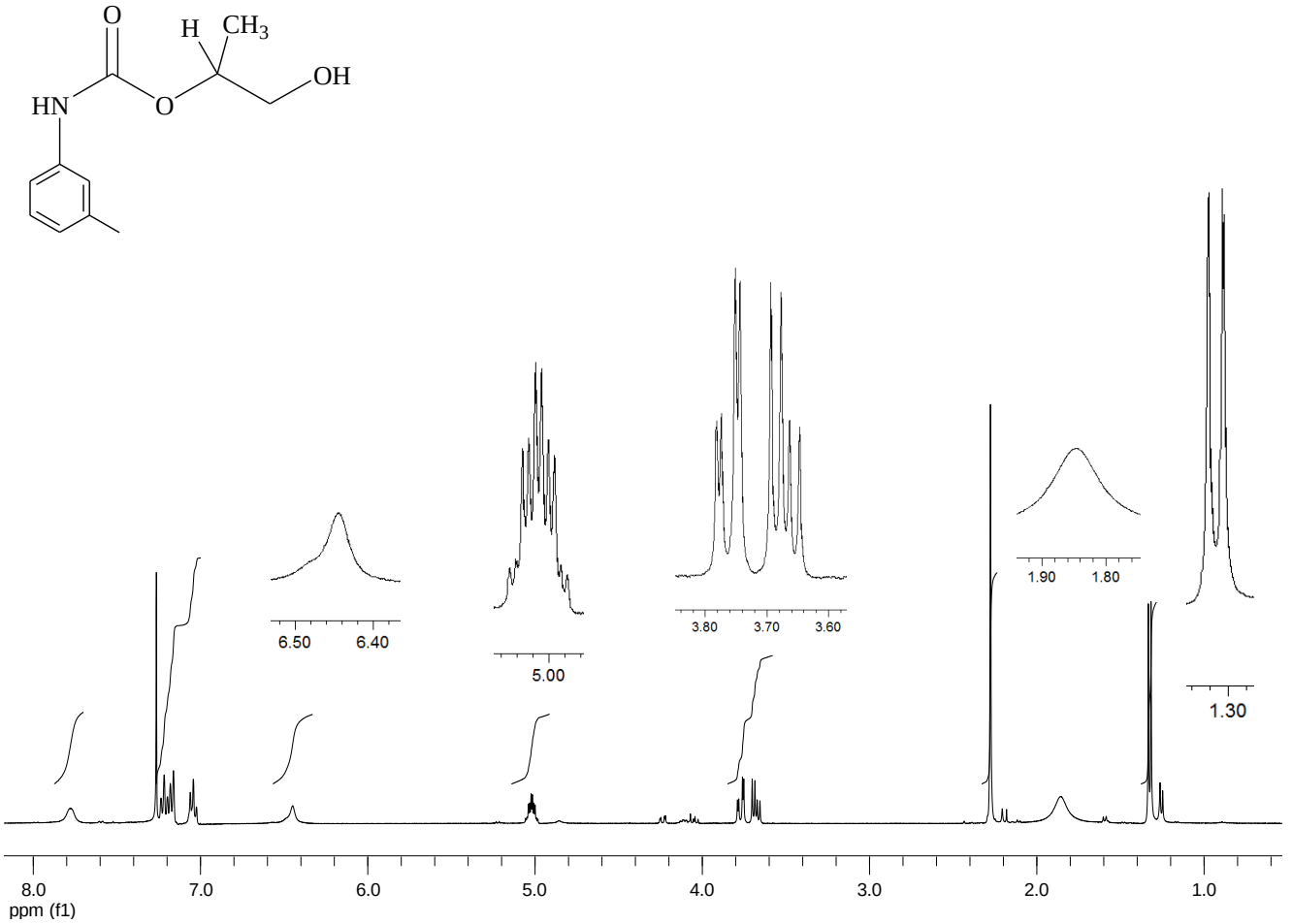

Figure A.75. ^{1}H NMR of compound **39** ($CDCl_3$).

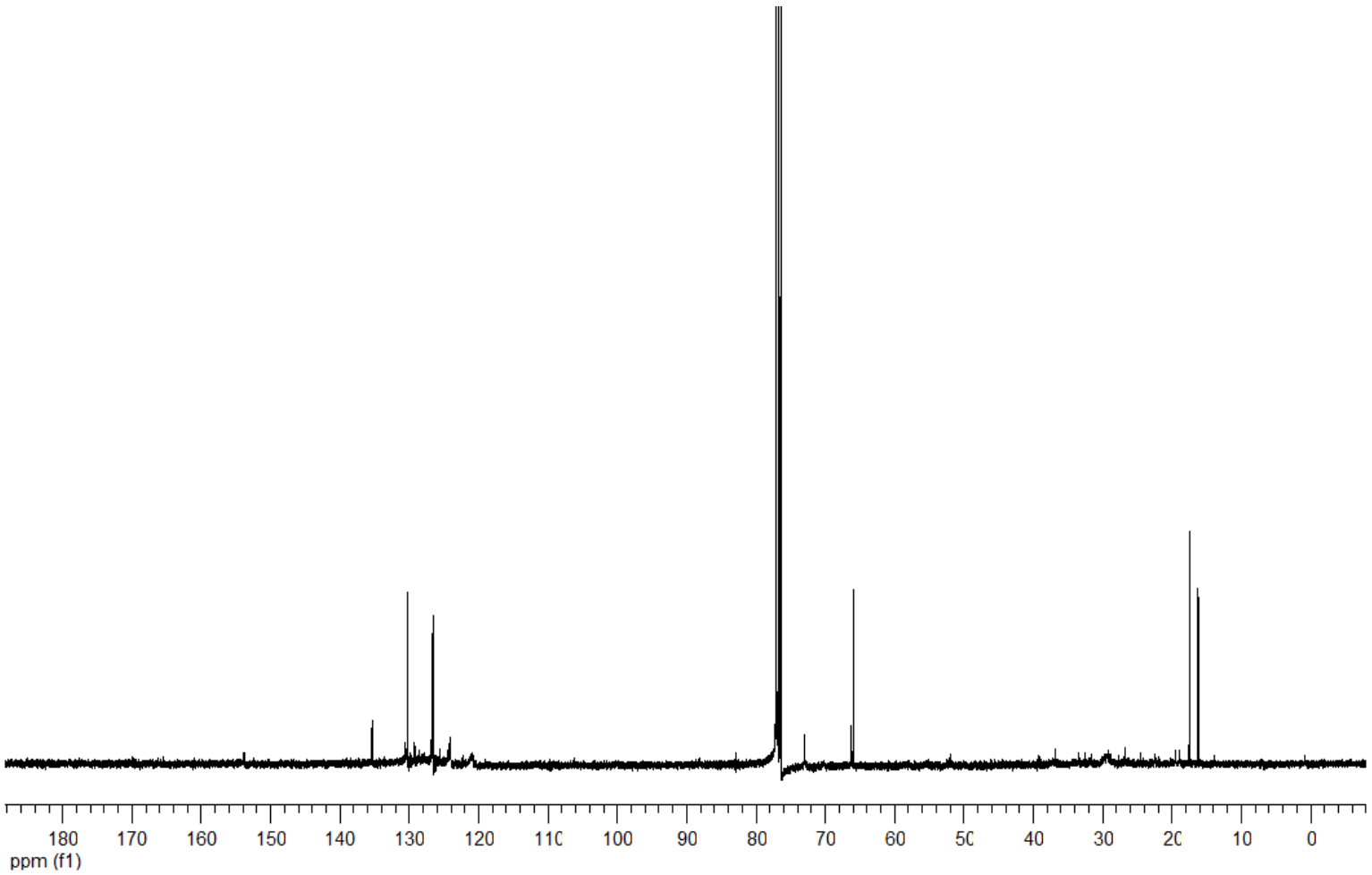

Figure A.76. ^{13}C NMR of compound **39** ($CDCl_3$).

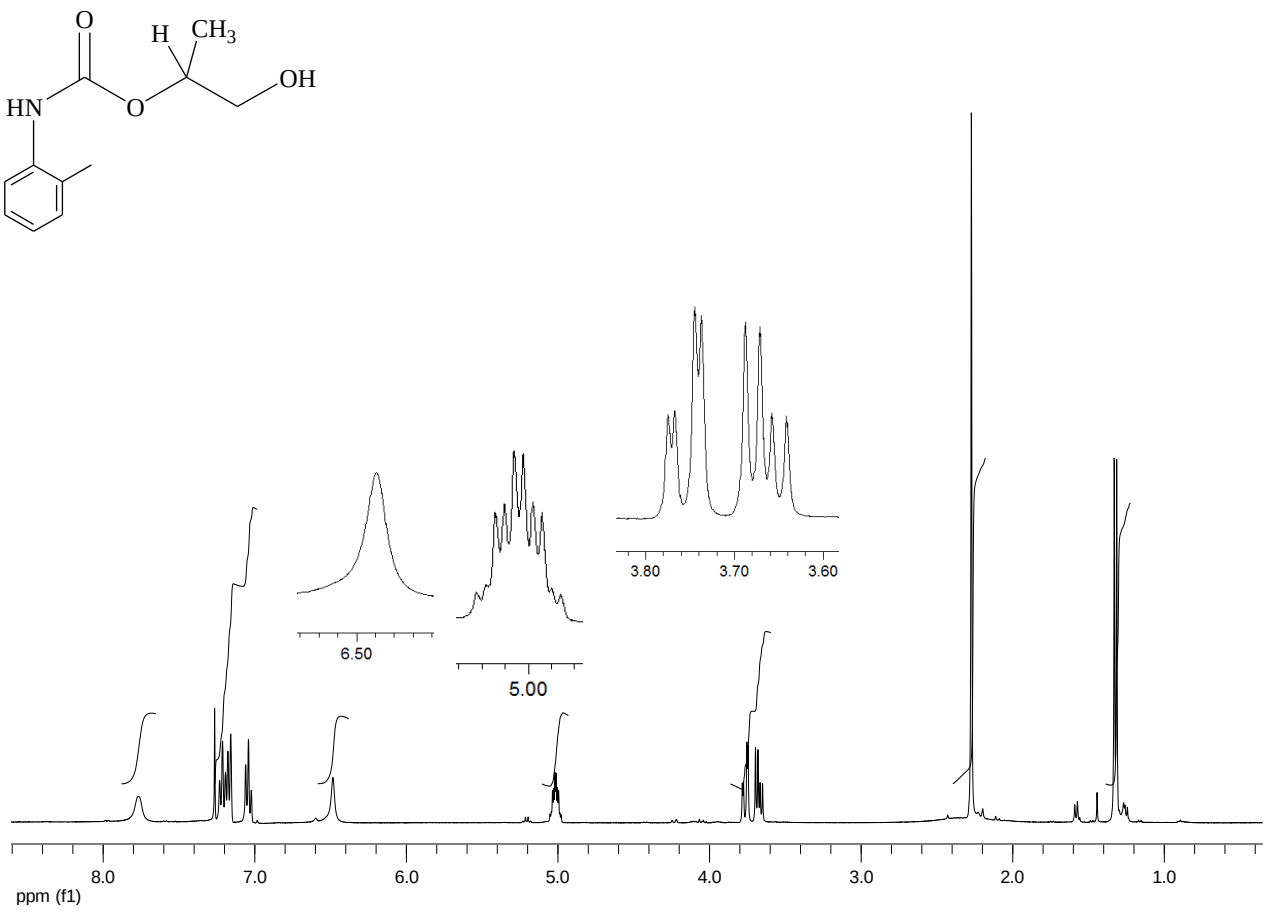

Figure A.77. ^{1}H NMR of compound **40** ($CDCl_3$).

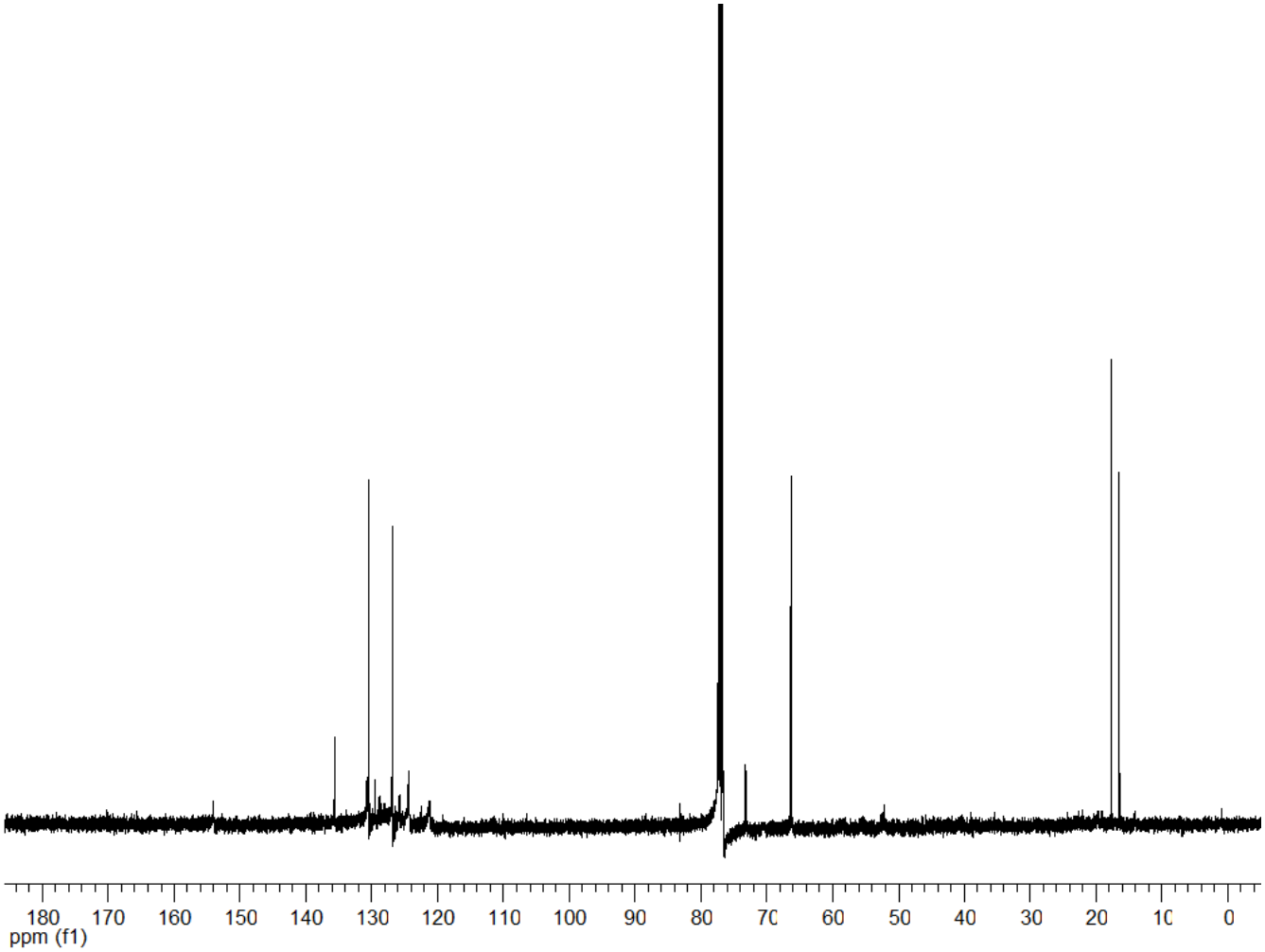

Figure A.78. ^{13}C NMR of compound **40** ($CDCl_3$).