STUDIES TOWARDS SYNTHESIS OF UREA CONTAINING HELICAL POLYMERS

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STUDIES TOWARDS SYNTHESIS OF UREA CONTAINING HELICAL POLYMERS

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ABSTRACT

STUDIES TOWARDS SYNTHESIS OF UREA CONTAINING HELICAL POLYMERS

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This thesis deals with design and synthesis of chiral polyurea type polymers. These polymers were analyzed with molecular mechanics that they could take a helical form. The polymers are polyurea type polymers and ureas are synthesized by treating isocyanates with amines. Starting from tartaric acid, ((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5diyl)dimethaneamine was synthesized. The other diamine was naturally occuring L-lysine. These diamine functionalized compounds were treated with *p*-phenylene diisocyanate synthesized from *p*-phenylene diamine and triphosgene and polymerized with diamines. Similarly, (*S*)-methyl 2,6-diisocyanatohexanoate was synthesized by reacting with triphosgene and L-lysine methyl ester and polymerized with L-lysine. The results toward synthesis of these 'helical' polymers were discussed.

Keywords: Urea, thiourea, tartaric acid, helical polymer

ÖZ

ÜRE İÇEREN HELİKAL POLİMERLERİN SENTEZLERİ ÜZERİNE ÇALIŞMALAR

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Yüksek Lisans, Kimya Bölümü

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Bu tezde kiral poliüre fonksiyonel gruplu helikal polimerlerin sentezi üzerinde çalışılmıştır. Helikal yapılar moleküler mekanik kullanılarak analiz edilmiştir. Üre fonksiyonel gruplu polimerler diisosiyanat ve diamine kullanılarak sentezlenmiştir. Tartarik asitten başlanarak ((4*S*,5*S*)-2,2-dimetil-1,3-dioxolan-4,5diyl)dimetanamin çok basamaklı sentez çalışmaları sonunda elde edilmiştir. Tartarik asit bazlı diamin ve bir diğer diamin olan L-lysin, *p*-fenilen diamine ile trifosgenin reaksiyonu sonucu elde edilen *p*-fenilen diisosiyanat ile polimerleştirilmiştir. Öte yandan L-lysin bazlı (*S*)-metil 2,6-diisosiyanatohekzanoat, trifosgen kullanılarak sentezlenmiş ve L-lysin ile polimerleştirilmiştir. Sentezlenen 'helikal' polimerlerin sonuçları tartışılmıştır.

Anahtar Kelimeler: Üre, tiyoüre, tartarik asit, helikal polimer

To My Dear Family…

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INTRODUCTION

1.1. Optical Activity and Chirality

Optically active (compounds rotates plane polarized light) compounds have been playing an important role in chemistry since the discovery by Pasteur that the tartaric acid stereoisomers were seperated. The field was further exploited by Fischer on sugars. All naturally occuring aminoacids are L (levorotatory) and all naturally occuring sugars are D (dextrotatory). Furthermore, Fischer developed a 2D projection of compounds to help chemists, it is now called Fischer Projection Method. In short, the studies by Fischer concluded that, all essential organic compounds i.e. aminoacids, sugars are optically active in nature.[1]

Morover, it was realized that sugars and aminoacids are not superimposable with their mirror images. Therefore, scientists use the term chirality (comes from Greek word *'kheir'* meaning hand) as stated by Lord Kelvin. From a general point of view molecules which are not superimposable with their mirror images are chiral. The following tartaric acid derivatives are chiral (Figure 1):

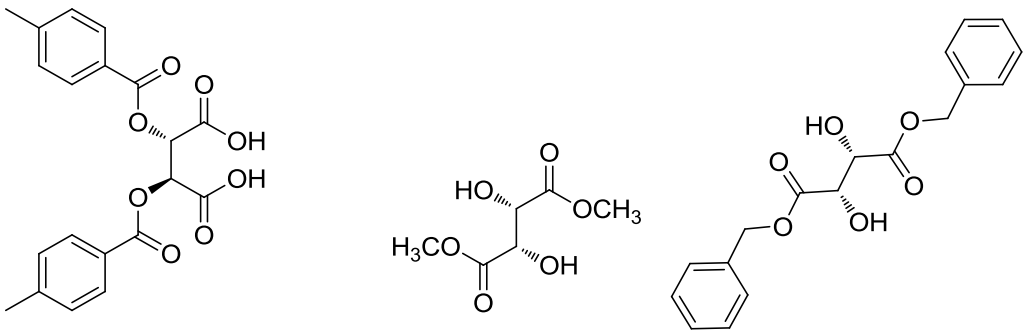


Figure 1. Tartaric acid derivatives

Compounds which are mirror images of each other are called enantiomers. For compounds to be enantiomers in a carbon containing molecules, if the carbon has four different groups on it, carbon center is called stereogenic center (carbon with sp^3 hybridized is tetrahedral). Other than carbon, atoms of all main group elements with four different groups including electron pair are also called chiral. This is concluded from VSEPR model. However nitrogen centers with four different groups, one group being an electron pair goes through rapid inversion which in turn results in racemic mixtures. On the other hand, sulfoxides could be obtained as single enantiomer due to the high inversion barrier[2,3](Figure 2).

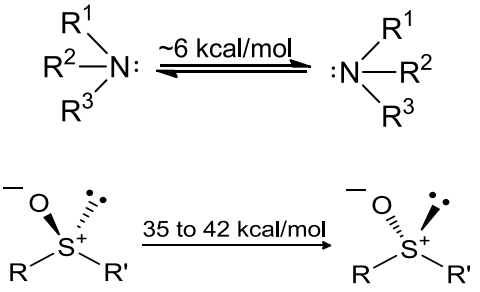


Figure 2. Inversion energy of **a)** amine **b)** sulfoxide

Diastereomers are compounds in which at least two stereocenters exist. Moreover cis and trans are also called diastereomers. The diastereomeric relationship is defined as one stereogenic center retains its absolute configuration, the other one changes.

1.2. Origin of Chirality

With all these information given above in mind, it is still a mystery what the origin of chirality is. In another words, why do we have L aminoacids or D sugars in nature, not the opposite? There are many theories regarding this question. This question was addressed by many researchers.

Both theoretical and experimental results supports the early idea of Terent'ev and

Klabunovskii (1957) which was ‘‘life cannot and could never exist without molecular dissymmetry’’. Later on Avetisov et al. (1985) proved that without high degree of chiral purity, not even the simplest self replicating systems could take place. Finally, Goldanski and Kuzmin (1988) and Ametisov and Goldanski concluded debates by the idea ‘‘Even in principle chiral molecules could not have occured after the appearance of life.’’ Looking these evidences one can easily say the source of life comes from chiral molecules.[4]

From this point of view, abiotic origin of chiral molecules has become more logical. One of the abiotic theory that explain the origin of life is chance mechanism. According to this theory, formation of excess L or D enantiomer have an equal probability in the terrestrial biosphere. In this system one enantiomer catalyzed its further production and inhibited the occurance of its antipode, it eventually resulted in the formation of one enantiomer in excess and vanishing of the other one. Precipitation of randomly preferred enantiomer from racemic solution distrupted thermodynamic equilibrium (kinetic process), since there were no antipode enantiomer in the medium for the establishment of the equilibrium. Once one of the enantiomer became dominant in the primitive Earth with the help of heat, electric field etc. the molecular evolution started and chirality has been integrated to Earth biosphere. Although this method (autocatalytical formation of enantiomers) provides high purity in many experimental systems, its prebiotic success is still debatable. Since no experimental proof is found up to now.[4–6]

Another approach, according to Breslow, is D-sugars and L-aminoacids landed on Earth with meteorites. However they were not in the same form with aminoacids of terrestrial living organisms. Instead, they were in the α-methylated form. Five α-methylated aminoacids were found in Murchison meteorite with the small excess of L-enantiomers (Figure 3).[7]

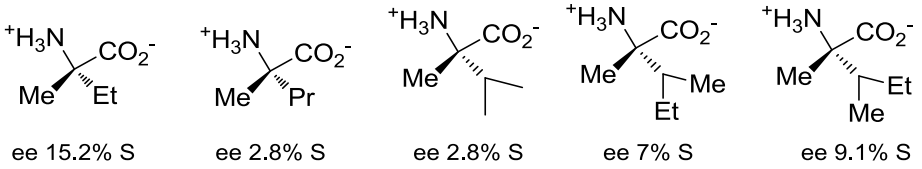


Figure 3. α-methylated aminoacids found in Murchison meteorite.

After this discovery, Breslow believed that aminoacids and sugars that are the basic part of life, first 'seeded' by α-methylated aminoacids arrived to Earth by meteorites. They were in the partially deracemated form. The reason of deracemization is circularly polarized light having short wavelength. It is believed that deracemization occured out of the Earth since light with proper wavelength for the formation of deracemization could not pass through the Earth's atmosphere not now or not in the past.

L-aminoacids were unmethylated in prebiotic conditions of Earth. Enantiomeric excess ratio was amplified by higher solubility, lower melting point and different activation energy of D and L-enantiomers' crystals with respect to racemate crystals. Besides racemic crystals intereact both crystal structure of L and D enantiomers to lower the free energy while L enantiomers interacts only another L enantiomer. All these conditions resulted in the formation of small enantiomeric excess and it was enough to raise the ratio of enantiomeric excess that would be proper for the beginning of primitive biological activities. Furthermore, synthesis of glycolaldehyde on prebiotic Earth triggered the formation of glyceraldehyde. Aldol reaction between glycolaldehyde and formaldehyde without catalyst produced glyceraldehyde racemates the building part of sugars (Figure 4). Under the condition of earth L-aminoacids would catalyze the aldol reaction to give D-glyceraldehyde. As expected all other sugars were derived from it by addition of aldehyde group without changing the stereochemistry of corresponding glyceraldehyde.

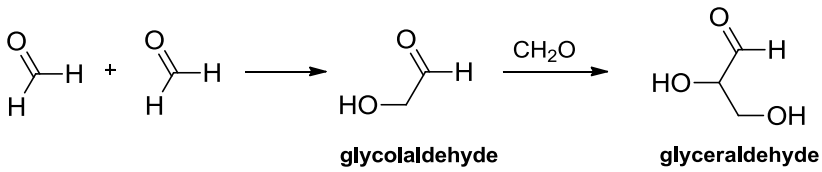


Figure 4. Glycolaldeyde formation by condensation between two formaldehyde molecules followed by aldol reaction of glycol aldehyde with another formaldehyde to form glyceraldehyde.

However, this theory is based on the examples in meteorites that are found by people. Is it possible to find any other meteorites that might contain D-aminoacids?

The reasons behind the arising of asymmetry in nature are still unclear. However use of racemic mixtures in living organisms may result in difficulties in metabolic reactions. All chemical reactions ocur under the control of enzymes which consist of proteins. Each protein has active center and these centers fit with proper substrate. It can be thought as lock-key mechanism. If biological systems were composed of racemic mixtures of proteins, it would cause challanging conditions for persistance of life.[8]

1.3. Supramolecular Chirality

Supramolecule (or supermolecule) is a term proposed by Karl Lothar Wolf et.al. as 'ubermolecule' in 1937. It was used to define acetic acid dimers held together with H-bonding (Figure 5).[9]

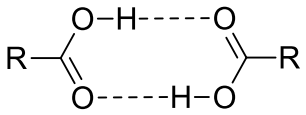


Figure 5. H-bonded carboxylic acid dimers

As it is mentioned before chirality describes the spatial arrangement of molecule that is not superimposable with its mirror image. Similarly, chirality at the supramolecular

level defines the arrangement of molecules in a nonsymmetric way with the help of noncovalent interactions (i.e. hydrogen bonding, dipole-dipole and van-der Waals forces metal coordination, hydrophobic forces). Supramolecular chirality can emerge two different ways:

- Assemble of achiral component in a special pattern to yield chiral association
- Presence of asymmetric component

In the first case achiral components arrange themselves by non-covalent bonding i.e. hydrogen bonding to form supramolecules that have no symmetry element.[10]

Glutaimide compound has symmetry plane perpendicular to molecular plane. Besides aminoadenine also has symmetry plane lie in the molecular plane. Thus both compounds are achiral. Nonsymmetric arrangement between these two compounds with non-covalent H-bonding results in the formation of chiral supramolecule (Figure 6).[10]

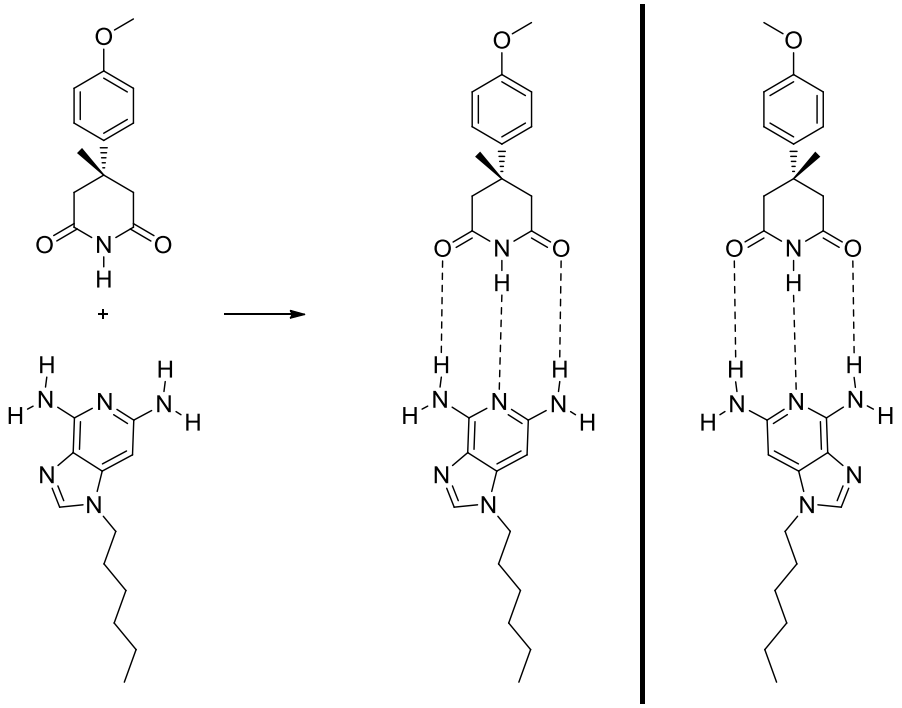


Figure 6. Nonsymmetric arrangement between glutaimide and aminoadenine

In the second case, the presence of chiral component in the reaction medium leads to the formation of chiral supramolecules. As an example, Moran and coworkers used *S* lactic acid derivative as substrate and chromenone-benzoxazole derivative as a receptor. Due to the chiral feature of lactic acid derivative, supramolecular chirality arised on the the chromenone benzoxazole derivative with the help of H-bonding (Figure 7).[11]

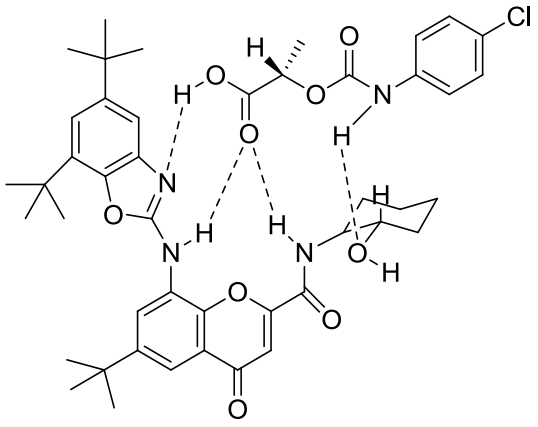


Figure 7. Supramolecular chirality arised on the the chromenone benzoxazole derivative with the help of H-bonding

Chiral supramolecules are plentiful in living systems. Double helix of DNA, the helical structure of protein etc. are the result of induction of chirality to supramolecules. Helical structure of these compounds are stabilized by H-bonding between two strands and handedness is regulated with the help of chiral centers on the backbones.

1.4. Structure of DNA

DNA is one of the most crucial genetic material in living system. It is a long polymeric material made up of monomers namely as ‘nucleotides’. It was first discovered by Friederich Miesher in 1869 and called as ‘nuclein’. He isolated pure sample, now known as DNA, from the sperm of solmon. In 1953 correct structure of DNA was suggested by James Watson and Francis Crick. Before them, double helix

two stranded structure of DNA was proved by X-Ray diffaraction analysis taken by Rosalind

Franklin and Raymond Gosling in 1952 (Figure 8).[12]

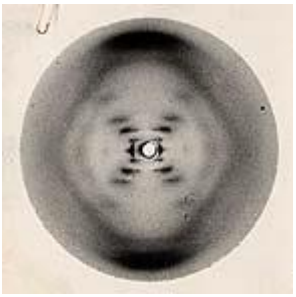


Figure 8. "Photograph 51" X-ray diffraction photo of a DNA, structure B.[13]

In the helical structure of DNA, strands wrap around the other. By this movement 3'-5' phosphate deoxyribose backbone (hydrophobic side) subjected to solvent (water) and corresponding counter ions. At the same time bases (adenine, guanine, cytosine and tymine) stay interior side. Double helical DNA structure is crucial for genetic information storage in stable form.[14] Double stranded structure is stabilized by H-bonding between purines and pyrimidines. It provides constant diameter to long polymeric chain. However helicity is not directly related with H-bonding. Electrostatic interactions between base pairs, conformational structure of deoxyribose sugar, stacking interactions and phosphate backbone are potential suspects for the helical structure of DNA.[14,15]

1.4.1. B-DNA

The structure proposed by Watson and Crick is the most common DNA form in living systems and it is called as 'B-DNA'. Helix of B-DNA is right handed, along the helix axis it turns clockwise direction, with the 36^{o} of rotation. This type of DNA is found in fully hydrated medium.[16] The right handed helix structure is originated

from the D-configuration of deoxyribose sugars in B-DNA. Due to the flexibility it can be bent or coiled (Figure 9).[14]

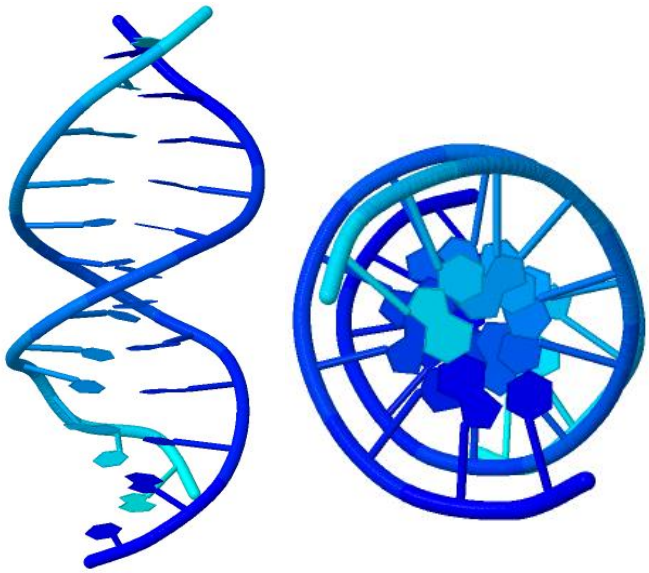


Figure 9. Structure of B-DNA [17]

1.4.2. Z-DNA

Besides the B-DNA, DNA can be found different conformation in biological systems. Z-DNA is one of the most interesting example of them. In contrast to B-DNA, it is left handed helix, with the 30^{o} of rotation. Difference between helix rotation direction of two forms are arose from the different conformation of bases. In B-DNA all bases have *anti* conformation. On the contrary, Z-DNA bases *anti-syn* alternation conformation which causes formation of zig-zag on the backbone (Figure 10).[18]

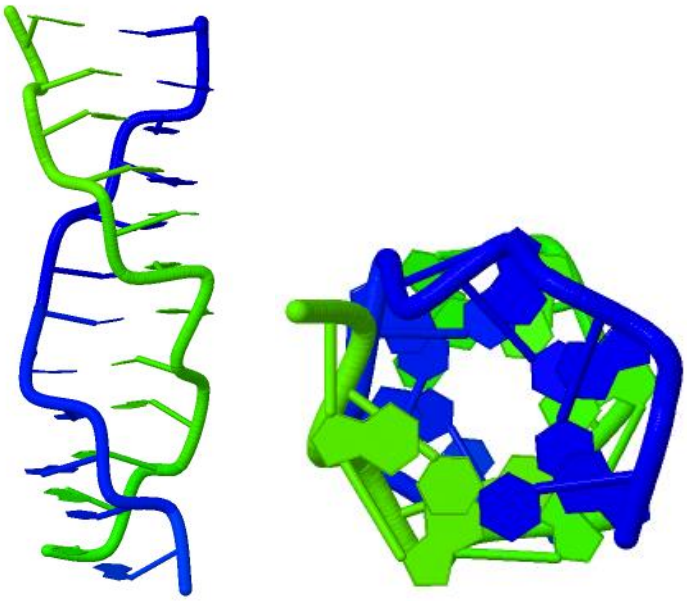


Figure 10. Structure of Z-DNA[19]

1.5. Secondary Structure of Proteins: α-Helices

Proteins are the 'factotum' molecules of living systems. They are building blocks of every cell machinery, such as carrying oxygen and help copying DNA. In other words, they are another important class of compounds for the maintenance of life.

Proteins consist of long aminoacid chains bound together via peptide bonds. Numereous parts of these biomacromolecules adopt helical form as a secondary structure. Helical form of proteins namely 'α-helix' first determined by Pauling et.al.[20] It is the most common form for secondary structure of naturally occuring proteins. As a result of L-configuration of aminoacids α-helices have right handed twist (Figure 11).

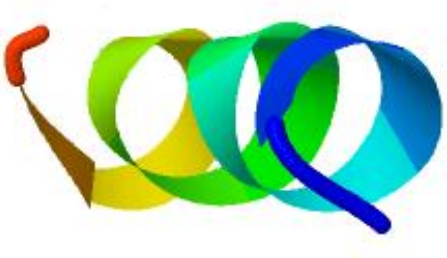


Figure 11. Structure of α-helix of protein [20]

In a polypeptide chain, there are two variables that affect the conformation that determines whether the secondary structure is going to be an α-helix. They can define as 'dihedral angle, Ψ', and 'torsion angle, Φ'. These are first determined by G.N. Ramachandran C. Ramakrishnan and V. Sasisekrahan in 1963 to envisage the stable backbone conformation of polypeptide chain (Figure 12).[21]

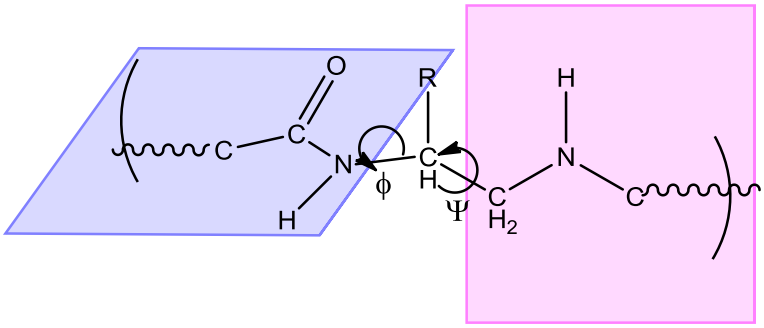


Figure 12. Dihedral angle,Ψ', and 'torsion angle,Φ representation on the backbone of polypeptide chain

Ramachandran used computer model which examine stable structure by varying Ψ and Φ angle. In the diagram white regions show the sterically disallowed combinations. Plot has four regions. The first region shows angles of left handed α-helix conformations. The second region has the most favorable conformations which creates

beta-sheet of proteins. At the third region right handed helices occur (Figure 13).

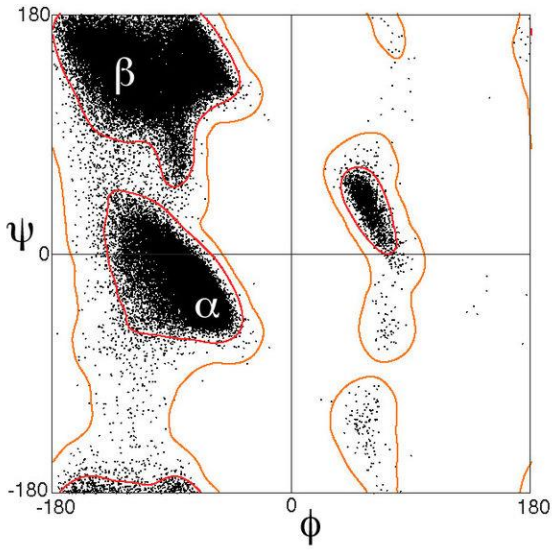


Figure 13. Ramachandran plot [22]

Since peptide bonds behave like double bond, rotation around an amide bond is not allowed. As a result of this, not all Ψ and Φ angles are available due to the steric restrictions. According to Pauling and Corey two structures are possible: α-helix and β-sheet. The form of α-helix has $\Phi = -50^{o}$ and $\Psi = -60^{o}$. Repetition of these angles results in the formation of corresponding α-helix.

Occurance of helical structure decreases the entropy of the molecule and it is thermodynamically compansated with the help of intramolecular H-bonding ($\Delta G = \Delta H - T\Delta S$). To stabilize α-helix structure, hydrogen bond forms between the carbonyl oxygen at *i* position and carboxamide hydrogen at *i+4* position (Figure 14).[23]

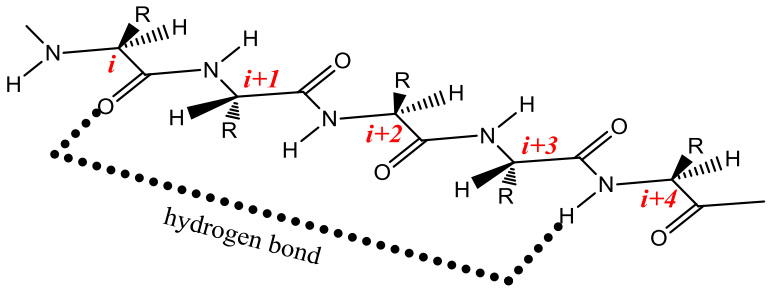


Figure 14. Representation of hydrogen bond formation between the carbonyl oxygen at *i* position and carboxamide hydrogen at *i+4* position

α-Helices are important secondary structure, since they are in the bioactive regions of various proteins and crucial for the proteins and DNA, RNA. For instance, in order to regulate gene expression, 'helix turn helix' motif is necessary. This structure consists of two α-helices held together with a short aminoacid strand and provides protein-DNA binding with the help of hydrogen bonds and Van der Waals interactions. It includes wide range of functions beyond the transcription adjustment, such as DNA repair and replication, RNA metabolism and protein–protein interactions (Figure 15).[24,25]

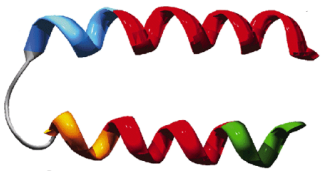


Figure 15. 'helix turn helix' motif [26]

1.6. Helical Polymers

In nature, highly functional macromolecules compose of precisely ordered structures. These ordered structures in nature might give rise to the formation of α-helices of protein, α-helical coiled coils of miyosin and keratin, triple helices of collogen and double helices of DNA on the molecular level.[27]In such systems, helix structure is

critical for biological activities as mentioned *vide supra*.

Inspired by biological helices, scientists have endeavored to synthesize helical polymers since 1950s due to their broad applications and unique features such as seperation of enantiomers, asymmetric catalysis and potential utilization in optical field.[28–30]

Discovery of α-helical structure of protein by Pauling and then double helical structure of DNA by Watson and Crick were the milestones in the field of helical macromolecules. The history of synthetic helical polymers has started with the discovery of Natta in 1950 (Ziegler-Natta catalysis) (Figure 16a), highly stereoregular isotactic polypropylene (Figure 16b). Addition of catalyst provides helical structure in the solid state.[31,32]

Figure 16. a) Ziegler-Natta catalyst **b)** stereoregular isotactic polypropylene

Natta reasoned the formation of helical structure due to steric repulsion. In principle all methyl groups must be in the same plane. However in order to reach ordered crystalline state methyl groups are spiralized.

In 1960, Pino et al. suggested that, besides the spiral (helical) conformation of vinyl polymers in solid state, optically active poly-α-olefins also show helical properties in liquid state and in dilute solutions. Isotactic poly(3-methyl,1-pentene) is the best example for optically active helical poly-α-olefins (Figure 17).[33]

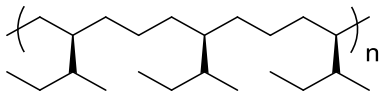


Figure 17. Helical isotactic poly(3-methyl, 1-pentene)

In 1979, by using chiral anionic initiator helical vinyl polymer have been successfully synthesized from achiral monomer, triphenylmethyl methacrylate.[34]This was the first vinyl polymer synthesized from achiral monomer and it has a single handed helicate stable in solution. These types of polymerization is called as the helix sense selective polymerization (Figure 18).

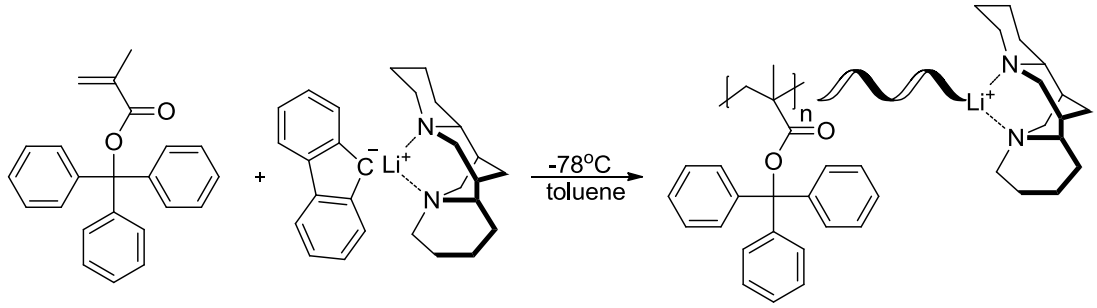


Figure 18. Helix sense selective polymerization of triphenylmethyl methacrylate via chiral anionic initiator

Polymers synthesized with this method have been facilitated as chiral stationary phase (CSP) in **h**igh **p**erformance **l**iquid **c**hromatography (HPLC) to seperate racemic mixtures.[35]

Polymers like poly(triphenylmethyl)methacrylate are stable in solution and called static helical polymers. They have high helix inversion barrier. With this in mind, these polymers are prepared by helix sense selective polymerization method with either right or left handed helical structure under kinetic control.[28]

Besides the static helical polymers, Green et al. has uncovered alternative structure namely dynamic helical polymers in late 1980s. Polyisocyanates such as poly(2-butylhexylisocyanate) and poly(n-hexyl isocyanates) have low helix inversion barriers. These polymers lack stereogenic center and have equal amount of right and left handed helices seperated by a junction called helical reversals (Figure 19).[36]

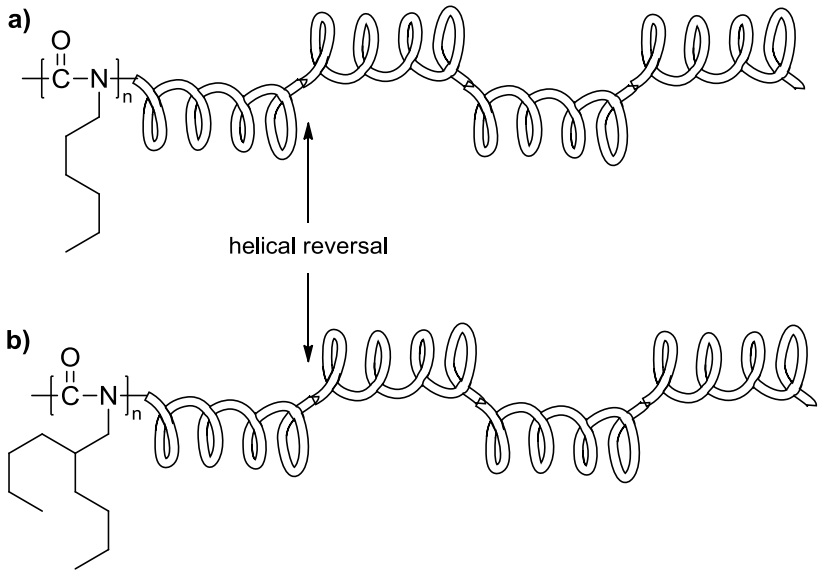


Figure 19. Dynamic helical a) poly(2-butylhexylisocyanate) and b) poly(n-hexyl isocyanates)

Because of low inversion barriers, dynamic helical polyisocyanates can be synthesized with the excess of helix structure by adding small amount of chiral vanguard.

Green et al. showed that copolymerization of optically inactive isocyanates with a small amount of chiral isocyanates or mixture of enantiomers (with small enantiomeric excess (ee)), generate optically active helical polyisocyanates either left or right handed helices. This type of chirality induction was called as 'sergeant and soldier effect' by same research group. Synthesis of dynamic helical polymers occurs under the control of thermodynamic conditions.[28]

To summarize, helical polymers can be divided into two groups due to their helical behaviour; static and dynamic. Besides the difference in helix inverison barrier, in the former case preferred helix structures are fixed during the polymerization, while the latter case dynamic conformations are regulated under the control of chiral pendentgroups covalently bonded to backbone of polymer.[36]

In this thesis (*vide infra*), the polyurea and the polythiourea structures will be studied. Therefore, it is worth mentioning to discuss the structural features of urea and thiourea.

1.7. Urea and Thiourea Functional Groups

Urea is an organic compound with chemical formula of $CO(NH_2)_2$. In 1828, Frederich Wöhler discovered that the urea can be synthesized from inorganic starting materials namely NH_4NCO and NH_3 (Figure 20). It was one of the most important landmark in Chemistry, since it refuted the hypothesis of vitalism. According to this hypothesis organic compounds can be derived from living subjects due to the precence of some special 'vital force'. It was the beginning of the end of the common thought 'only living organisms can produce organic compounds'.[37,38]

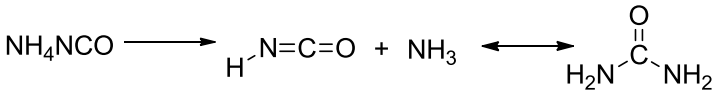


Figure 20. Wöhler urea synthesis

Besides, it is also valuable compound for the medicinal chemistry. For example barbital (Veronal), derivative of urea, has been used as sleeping pill since1903 (Figure 21).[39]

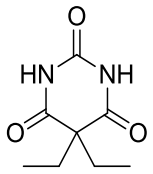


Figure 21. Structure of barbital (Veronal)

Thiourea is an organosulphur compound with the $SC(NH_2)_2$ chemical formula. It is structurally similar to urea compound. Thiourea and its derivatives are used in organic reactions as reagents. For example, thioureas are used in the reduction of peroxides to corresponding diols (Figure 22).[40]

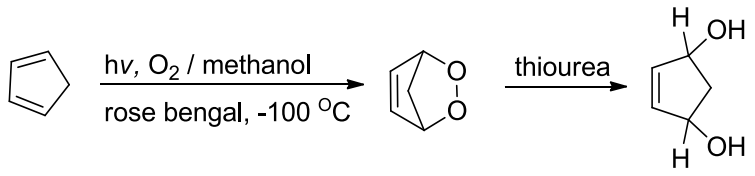


Figure 22. Reduction of peroxides to corresponding diols by thiourea

Furthermore, thiourea functionality is essential in medicinal chemistry. Heterocyclic thioureas help the medication of thyroid. Some thiourea containing compounds can be used as short acting anestesy.[41]In the clinical treatment of tuberculosis thiocarlide was used as a therapatic agent (Figure 23).[42]

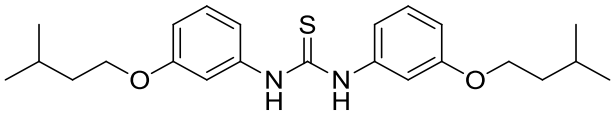


Figure 23. Structure of thiocarlide

From this point of view, additional features of thiourea and urea compounds must be pointed out; urea and thiourea derivatives has the ability as hydrogen bond donor. As mentioned before, the structural architectures of DNA, proteins and other essential biological supramolecules are the result of H-bonding capability of these compounds. In addition to the structural importance, H-bonding has significant functionality as a catalyst. For instance, hydrogen bonding to an electrophile causes the decreasing of electron density, lowering LUMO, by this way it is available for any nucleophilic attack.

Use of hydrogen bonding as a catalyst in chemical reaction opened the new research area: Chiral hydrogen bond donors for enantioselective synthesis.[43]Thiourea and urea derivatives got the attention due to the two hydrogen bonding features.

Chiral thiourea and urea derivatives were used as catalyst first in the asymmetric hydrocyanation reaction. These catalysts were originally designed because of the

potential ligand feature for Lewis acidic metals. It was noticed that they showed enantiomeric selectivity without metals (Figure 24).[44]

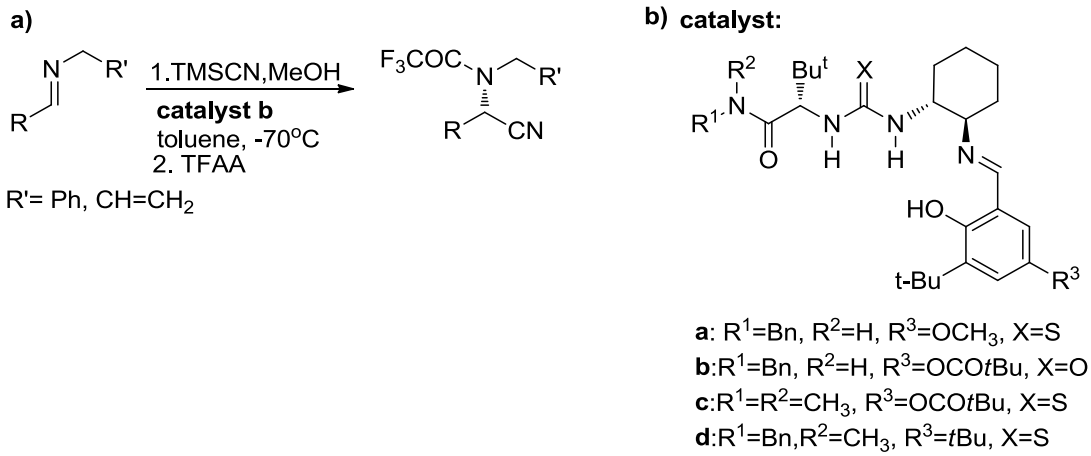


Figure 24. **a)** Asymmetric hydrocyanation reaction **b)** catalysts structure

The next question is which functional group, urea or thiourea showed better hydrogen bonding ability for asymmetric catalysis applications?

According to research conducted by Bordwell et al. illustrated that thiourea is more acidic, which means better hydrogen bond donor than corresponding urea.[45]

Three factors account for the acidity difference:

1. A field/ inductive (F) effect
2. A polarizability (P) effect
3. A resonance (R) effect

For the case of acetamide and thioacetamide (Figure 25) F factor should decrease as the dipole moments decreases. Dipole moment of C=S was calculated as 2,95 D, while

C=O was 2,5 D as it is expected. Besides, thioacetamide has larger P and R factor, due to the relative weakness of C=S bond and higher capability of sulfur to shelter

(stabilize) a negative charge than oxygen. These three factors make thioacetamide more acidic than acetamide.

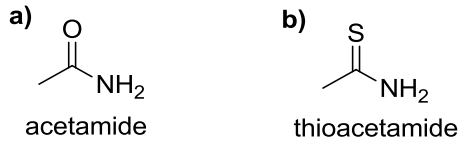


Figure 25. Structure of **a)** acetamide and **b)** thioacetamide

The replacement of methyl group in thioacetamide by amino group produces thiourea functionality and its acidity relatively lower than corresponding thioacetamide. Similarly, replacement of methyl group in acetamide provides the formation of urea compound and again acidity decreases with respect to acetamide. However, the decrease is smaller than the case of thiourea. The reason of that can be explained by lowering the ground state energy of thiourea and urea compounds. More polarizable thiourea exhibits it more effectively. The relationship between ground state energy and acidity can be explained; it is difficult to remove proton from amides that have lower ground state energy (Figure 26).

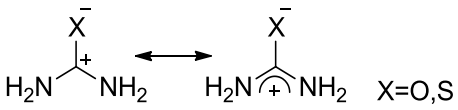


Figure 26. Resonance forms of urea and thiourea

Additionally, substitution of amino hydrogen with different groups affect the acidity of corresponding thiourea and urea compounds. It is related to the electron withdrawing or donating character of substituents (Figure 27).[46] The choice of urea or thiourea as a catalyst provides the change in hydrogen bond strength by changing nitrogen substituents on catalysts.

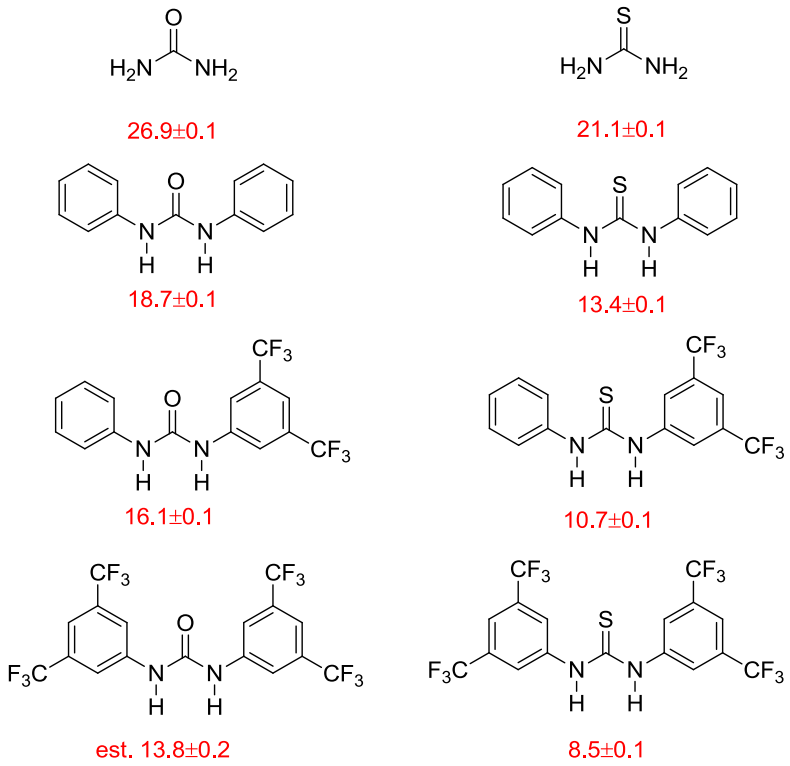
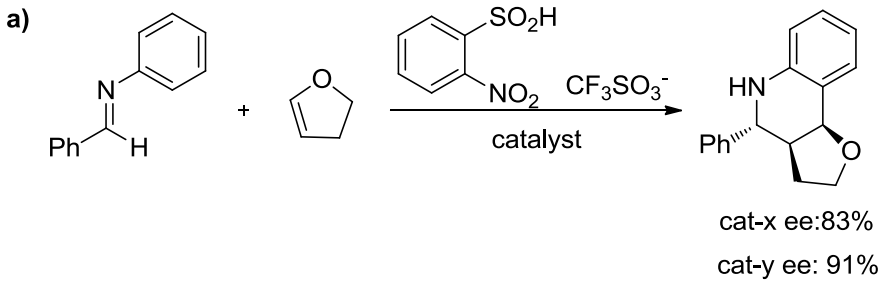


Figure 27. pKa values of urea and thiourea with respect to different substituents

In the recent study of Jacobsen, chiral thiourea and urea derivatives are used as catalyst in the Povarov reaction, cycloaddition between aromatic imine and alkene (Figure 28).[47]



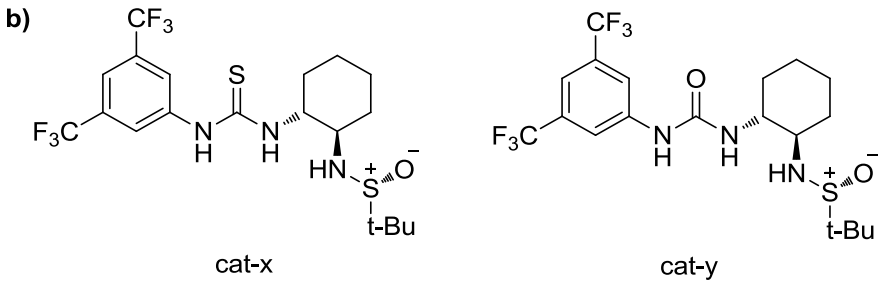


Figure 28. a) Asymmetric Povarov reaction and **b)** Synthesized catalysts structure for this reaction

Urea derivative gives higher *dr* and *ee* value than thiourea catalyst in this study. Conformational positioning of catalyst in the reaction medium is the most crucial case for the observation of enantiomeric excess. Conformation of catalyst bound iminium ions stand as in figure 29 provides transion structure which has minimum energy. The experimental and calculated results are consistent with each other and it proves the conformation of catalyst contribute one sided available intermediate for cycloaddition reaction.

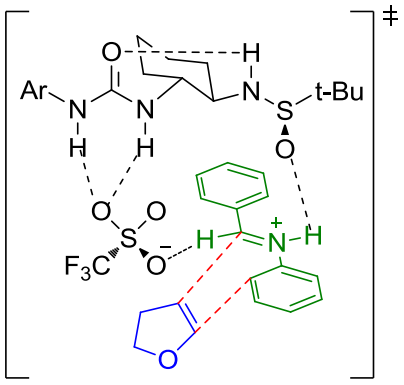
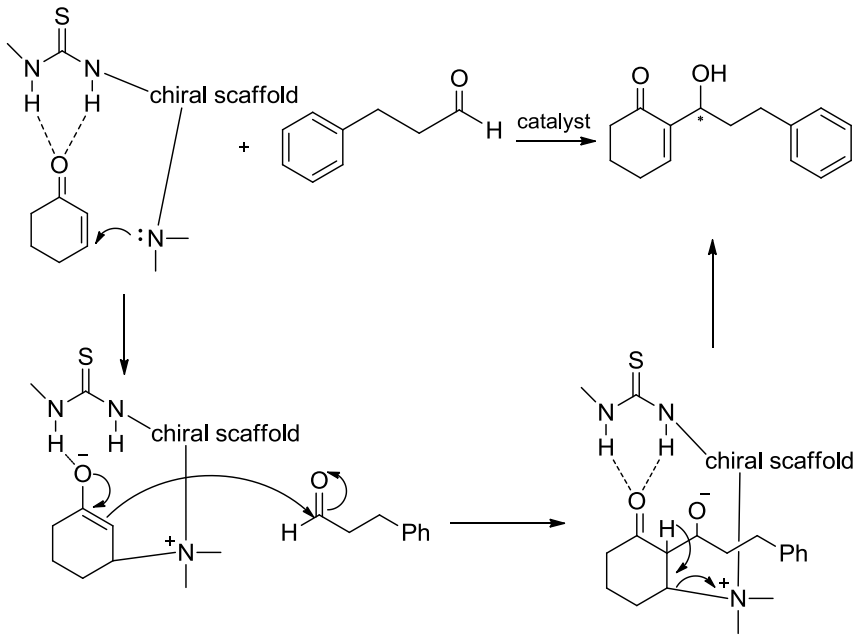


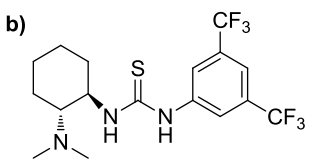
Figure 29. Conformational positioning of catalyst in the reaction medium

Another study, conducted the asymmetric Morita−Baylis−Hillman reaction of cylclohexenone with aldehyde via bifunctional binaphthyl-derived amine thiourea, as

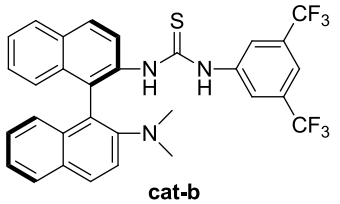
a catalysts. Among of screened organocatalysts, cat-c has better enantioselectivity, respectively (Figure 30).[48]



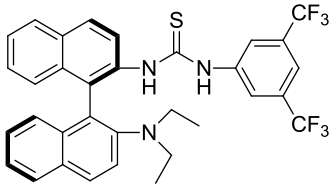
b)



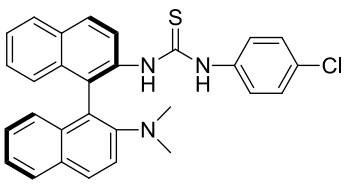
cat-a



cat-b



cat-c



cat-d

c)

catalyst	**ee (%)**
cat-a	39
cat-b	71
cat-c	73
cat-d	Not determined

Figure 30. a) Morita−Baylis−Hillman reaction of cylclohexenone with aldehyde via chiral binapthol derivative **b)** bifunctional binaphthyl-derived amine thiourea, as a catalysts **c)** observed enantiomeric excess with different catalysts

In short, generally thioureas are more versatile than ureas. To incoorparate these structures into polymers is an undiscovered territory. With this thesis, we aimed at incorporating urea and thiourea units into polymers.

CHAPTER 2

AIM OF STUDY

The wonderful opportunities that helical polymers can provide are summarized in the introduction part. These opportunities could be in catalysis and material science. Even though numerous helical polymers are known, they were not designed purposefully. With all these in mind, our goal is to design and synthesize helical polymers. For this, we choose to utilize (thio)urea repating unit containing polymers. Towards this goal chiral diamines will be synthesized and converted to diiso(thio)cyanates. Diamines treated with diiso(thio)cyanates will furnish corresponding polymers. Tartaric acid is a cheap and readily available compound which will be converted to diamines. Furthermore, L-lysine will be converted to diisocyanates. The diamines will be treated with L-lysine based diisocyanates and also *p*-phenylene diisocyanates for the synthesis of helical polymers. The polymers obtained from these reactions will be studied.

CHAPTER 3

RESULTS AND DISCUSSION

2.1 Polymer Design:

As mentioned in the aim of the study part of this thesis, our goal is to synthesize urea and thiourea containing chiral polymers. For this reason, 3 different polymers were designed by using computational methods. These polymers could be synthesized from bifunctional isocyanates and amines and they are novel in structure. Therefore, our strategy was to first optimize a portion of these polymer using molecular mechanics. Molecular mechanics calculations showed that targeted polymers could possibly have a helical conformation. MMFF calculations were performed as implemented in Avogadro molecular modelling program.[49] Figure 31, Figure 32 and Figure 33 show three polymers designed for this thesis:

- Tartaric acid derived diamine with 1,4-phenylene diisocyanate: **POL-A**

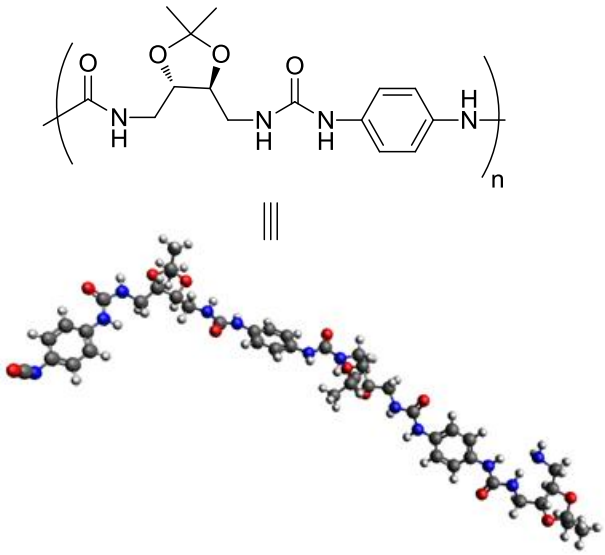


Figure 31. Designed polymer **POL-A**

- L-lysine with 1,4-phenylene diisocyanate: **POL-B**

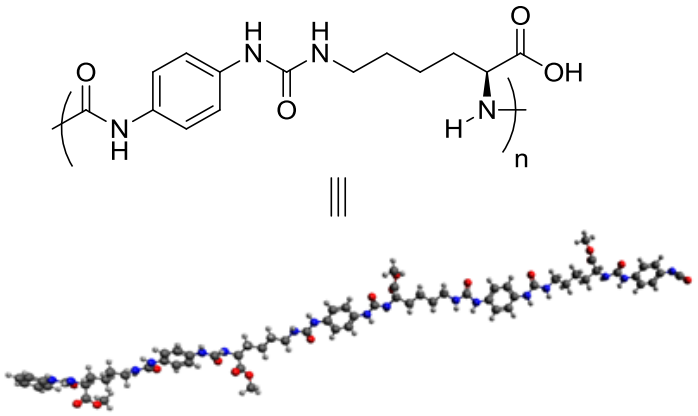


Figure 32. Designed polymer **POL-B**

- L-lysine methyl ester with L-lysine diisocyanate methyl ester: **POL-C**

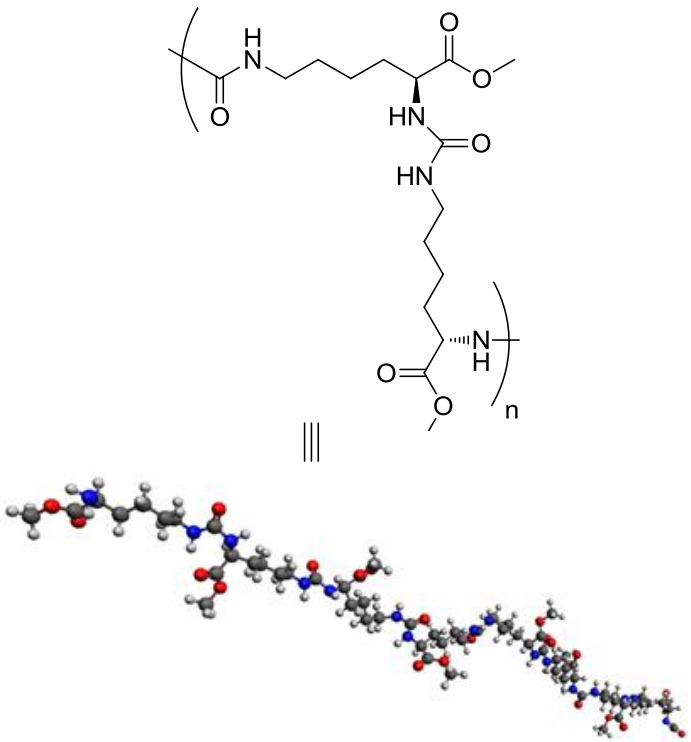
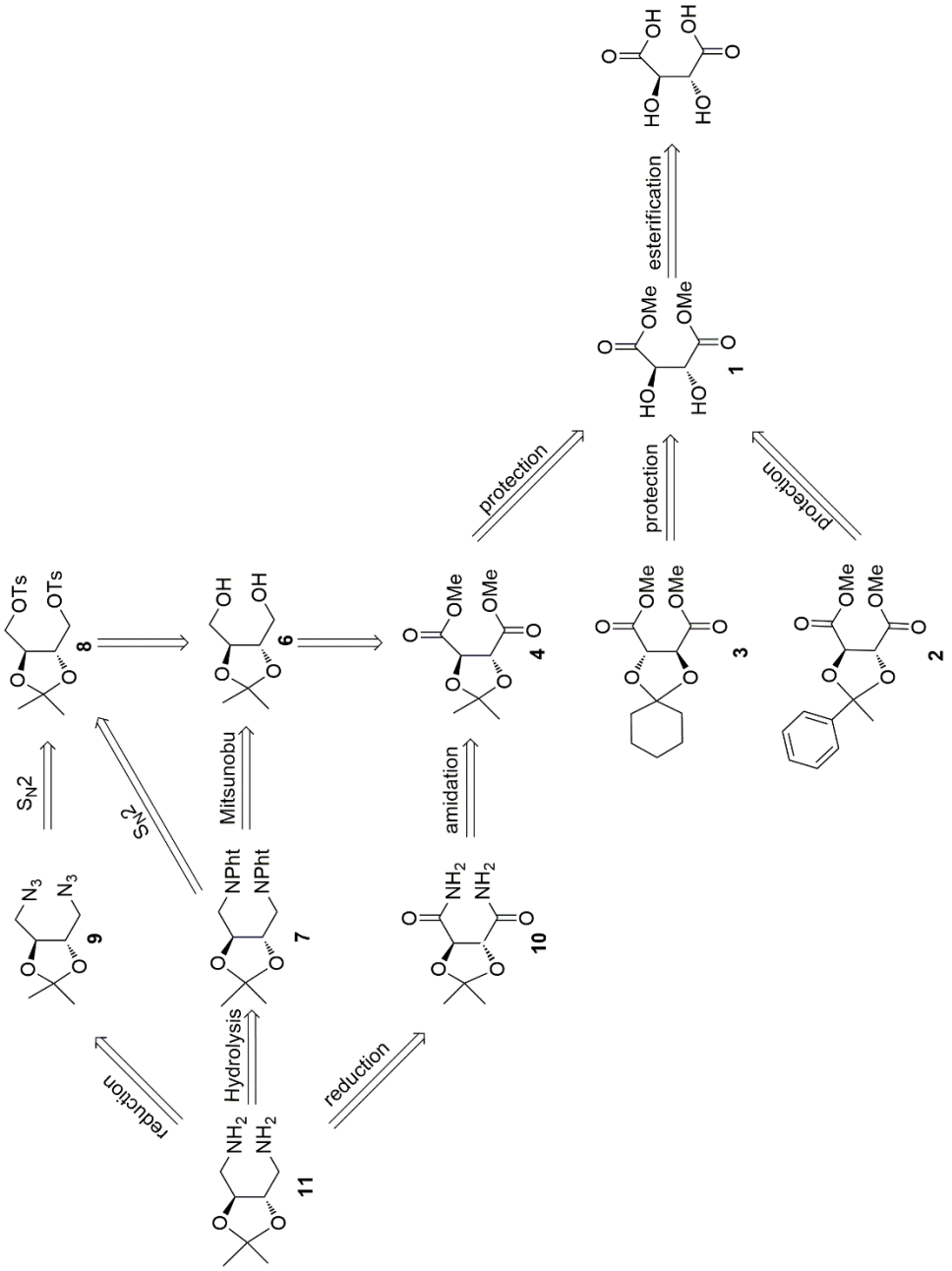


Figure 33. Designed polymer **POL-C**

2.2. Synthesis of monomers:

With designed polymers in mind, the synthesis part of the thesis started with the synthesis of tartaric acid diamine **11**

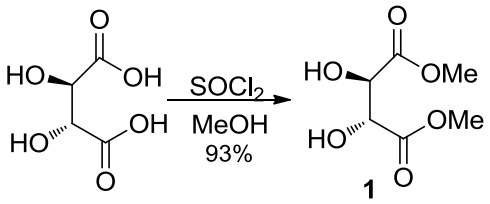


Scheme 1. Retro synthesis of **11**

The retro synthesis for diamine was described in Scheme 1. It was envisioned that the diamine could be synthesized from 3 different compounds which could be obtained from L-tartaric acid.

2.2.1. Esterification

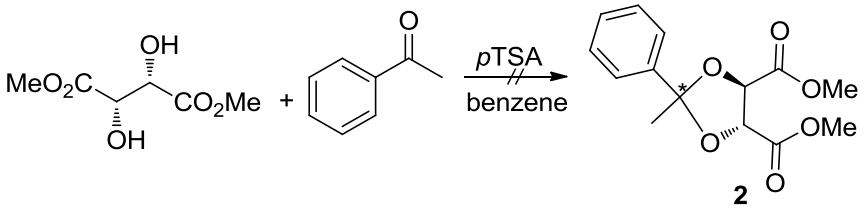
L-tartaric acid was subjected to esterification with methanol in the presence of thionyl chloride. The compound **1** was obtained as desired. Unlike described in literature, synthesized compound **1** was observed in high yield and used in next step without further purification.



Scheme 2. Synthesis of **1**

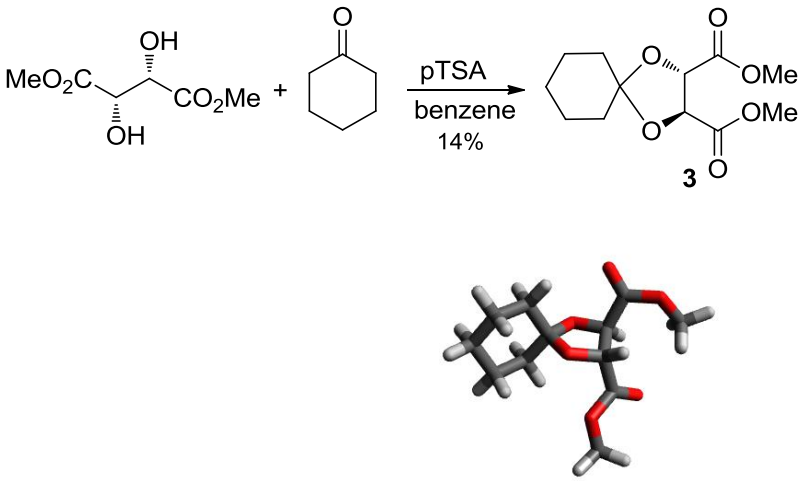
2.2.2. Protection

The diol **1** was treated with acetophenone to get compound **2**. This reaction did not result in the formation of desired product. Nevertheless, product of the reaction could have been a diastereomeric mixture. The reason why we performed this reaction was the availability of the starting materials in our laboratory.



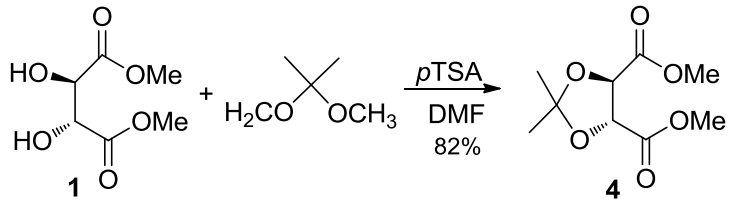
Scheme 3. Synthesis of **2**

From this point, compound **1** was subjected to protection with cyclohexanone. The yield of this reaction was very low due to the formation of spiro compound (strain) and difficulties in purification **3** was also encountered.



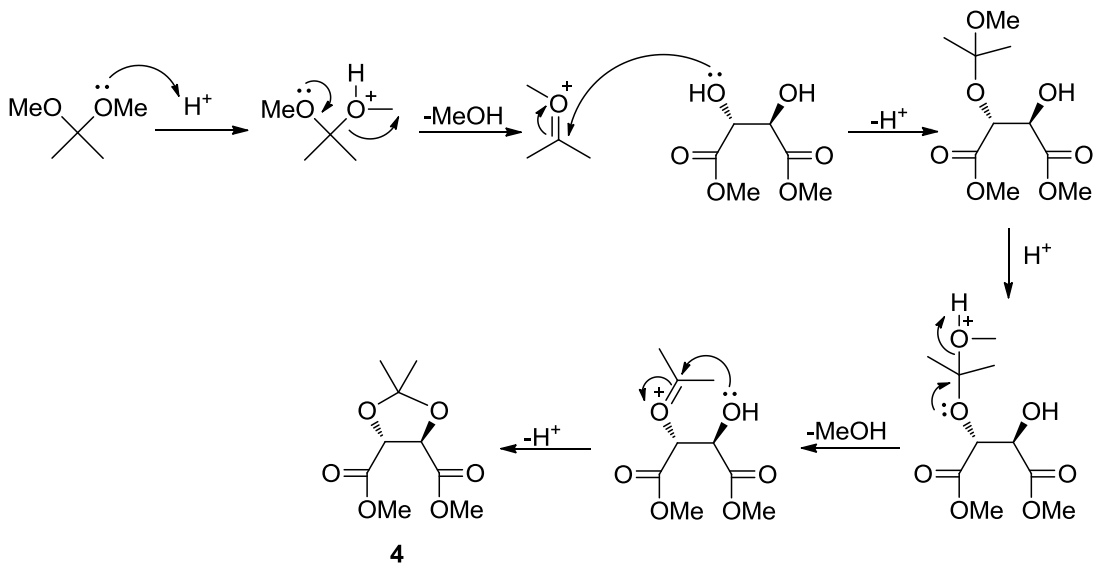
Scheme 4. Synthesis and 3D structure of **3**

There exist numerous methods for protection of diols in literature.[50] Among these, we choose the method which employ acetone protection of diol (Scheme 5). For this purpose, we used 2,2-dimethoxypropane. The yields were sufficient enough and the compound **4** was easily purified. Hence, this was the method of choice throughout this thesis.



Scheme 5. Protection reaction of **4**

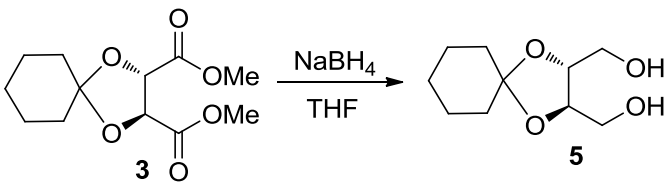
2,2-dimethoxypropane was used as a protecting group due to its efficiency. The mechanism of the reaction in the presence of *p*-toluene sulfonic acid is shown in scheme 6.



Scheme 6. The proposed mechanism of the protection of **4**

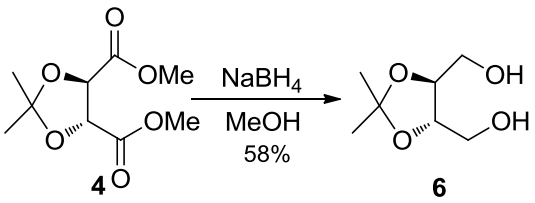
2.2.3. Reduction

Protection of compound **1** with cyclohexanone and 2,2-dimethoxy propane led us to reduction reaction. Firstly, compound **3** was reduced with $NaBH_4$ in methanol. The reduction was successful. However the purification was problematic. Besides, starting material was not in hand in large amounts because of low yield of previous reaction. Therefore, the synthesis of target compound **11** from this route was abandoned.



Scheme 7. Reduction reaction of **3**

Acetonide **4** was reduced with the $NaBH_4$ in methanol to the diol **6**. ^1H NMR spectrum was consistent with the literature.[51]

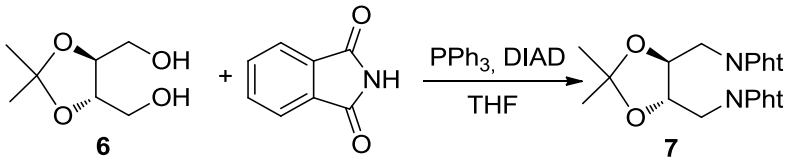


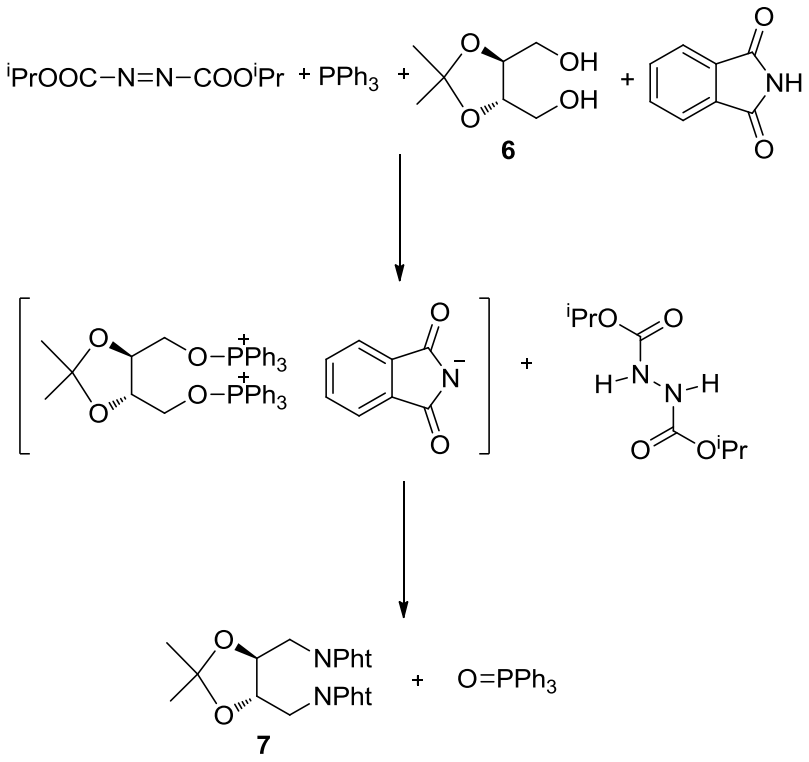
Scheme 8. Reduction reaction of **4**

The remarkable point of this reaction is, $NaBH_4$ was used for the reduction of ester functionality. As it is known, esters are less reactive toward nucleophilic attack than ketones and aldehydes. Thus, strong reducing agents, such as $LiAlH_4$, are needed. In contrast to common knowledge, $NaBH_4$ can reduce ester in the presence of methanol as a solvent. It provides not only milder conditions, but also easier work-up.

2.2.4. Mitsunobu Reaction

Efficiently synthesized diol **6** was used in Mitsunobu reaction. Treatment of diol with phthalimide in the presence of DIAD (Diisopropyl azodicarboxylate) and PPh_3 was yielded compound **7**. Resulted product needed rigorous further purification. Moreover this reaction is not atom economical. General reaction is shown in Scheme 9.

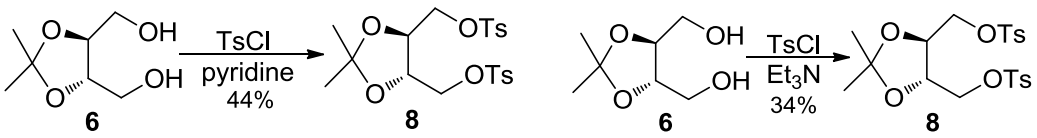




Scheme 9. Formation steps of **7** by Mitsunobu reaction

2.2.5. Reactions with *p*-toluenesulfonyl chloride

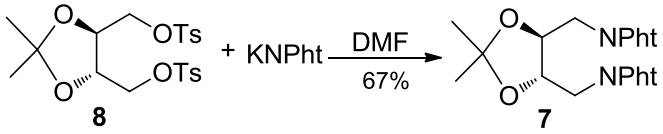
To functionalize alcohol groups, *p*-toluenesulfonyl chloride was used to convert diols into the ditosylates. Two different amines as base were used: Triethylamine and pyridine (Scheme 10). Both reactions were successful, but in the pyridine case, the yield was higher than triethylamine case. The main problem for these reactions is removal of excess base. Since our product is acid sensitive due to protecting group (acetonide), in the work up we could not use acid. The solution is, use of $CuSO_4$, since amine bases are coordinated to copper complex and easily pass to the aqueous phase during extraction.



Scheme 10. Tosylation reaction of **6** with two different bases

With installation of tosyl groups onto compound **6,** we envisioned an S_N2 reaction toward our final compound. Potassium phthalimide was treated with ditosylated compound **8** in the presence of DMF and resulted in the formation of compound **7** with a reasonable yield. Excess potassium phthalimide was needed to be removed from the medium. However, addition of base could have caused the cleavage of phthalimide groups on our compound. Moreover, purification with column chromatography (SiO_2) destroyed protecting group due to the acidic feature of stationary phase. Because of these reasons and remaining phthalimide cannot affect our further reactions, we used compound **7** as it is.

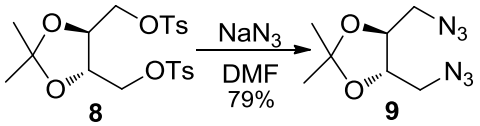
2.2.6. S_N2 Reaction with Potassium Phthalimide



Scheme 11. Reaction of **8** with potassium phthalimide

2.2.7. Reaction with Sodium Azide

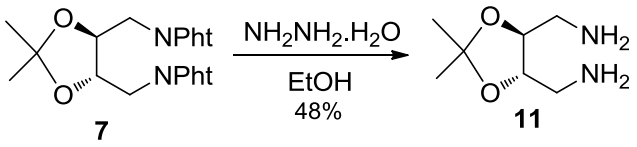
At this point of the synthesis, we tried another method that is alternative to previous reaction; insertion of azide functionality to compound **8**. This method was more versatile, due to the fact that it could be easily purified and gave high yield product.



Scheme 12. Synthesis of **9**

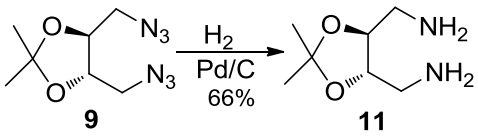
2.2.8. Synthesis of Tartaric Acid Derived Diamine

With the compound **7** and **9** in hand, the diamine **11** was one step away. Hydrazine monohydrate ($NH_2NH_2.H_2O$) was appropriate reagent for the conversion of phthalimide functionality to amine. Yield of this reaction was reasonable and product **11** was obtained successfully.



Scheme 13. Formation reaction of **11** from **7**

Another approach for the synthesis of diamine **11** was the reduction of compound **9**. For this purpose, H_2 atmosphere was created in reaction medium firstly with a balloon. Product was reduced and yield was acceptable. However, use of H-cube instrument for the same purpose did not yield with the formation of diamine **11** due to the partial reduction. The reason can be said as unstable reaction conditions provided by the instrument.

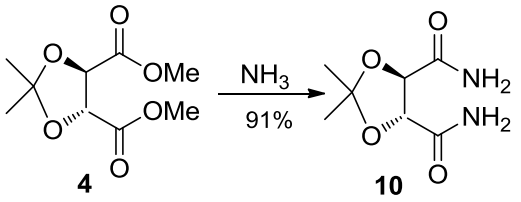


Scheme 14. Formation reaction of **11** from **9**

2.2.9. Further Studies for the Synthesis of Tartaric Acid Derived Diamine

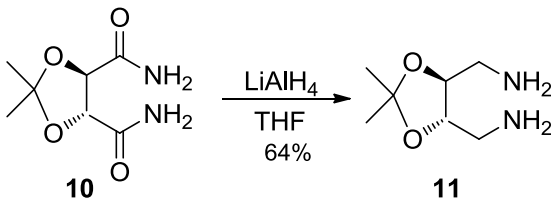
Keeping in mind these reactions and results, we decided to synthesize amide **10**, because reduction of amide usually results in the formation of amine. Furthermore, this method reduced the reaction steps used to access target compound **11** significantly, although we used $LiAlH_4$ which is more difficult to handle than $NaBH_4$. Fortunately, both amidation and reduction reaction worked efficiently.

The difficulty faced amidation reaction was the condensation of ammonia. Since its boiling point was very low, −33.34 °C, to reach this temperature dry ice-acetonitrile system was chosen. To supply proper condition for this reaction, high pressure reactor was used. With this instrument we could obtain both closed system and high pressure reaction condition. The yield of this reaction was very high and product did not require any further purification.



Scheme 15. Synthesis of **10**

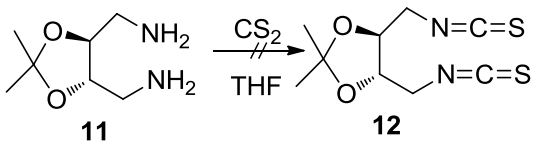
From this point, target diamine **11** was directly synthesized by reducing amide functionality in compound **10**. Although it was hard to handle $LiAlH_4$, product was obtained as it was expected. This reaction gave the highest yield among the other diamine synthesis method mentioned above.



Scheme 16. Formation reaction of **11** from **10**

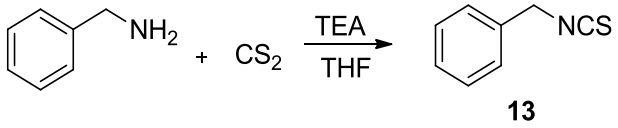
2.2.10. Isothiocyanate Synthesis Studies

With diamine product **11** in hand, we turned our attention to the synthesis of (thio)isocyanate. To do so, compound **11** was reacted with carbondisulfide in the presence of triethylamine. This synthesis was a modification of a literature procedure. The reaction did not yield the desired diisothioocyanate.



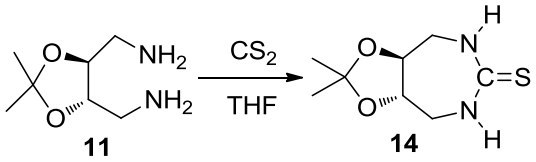
Scheme 17. First route tried for the synthesis of **12**

To check the applicability of the first procedure, same experiment was conducted with benzylamine. The formation of isothiocyanate **13** was observed with no difficulty.



Scheme 18. Synthesis of **13**

With this result, the reaction of diamine **11** with carbondisulfide was checked again, cyclic thiourea **14** formation was observed.

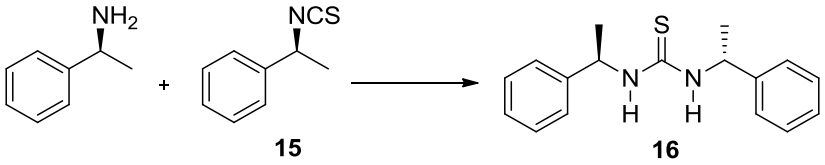


Scheme 19. Formation of cyclic thiourea derivative **14**

The literature also states that, such diamines, with close approximity of amines to each other, give cyclic thiourea species.[52]

We also wanted to check if the isothiocyanate formation affects the stereogenic centers. For the purpose of isothiocyanate synthesis, (*S*)-methylbenzylamine was treated with carbon disulfide with procedure discussed above. It was difficult to judge conclusively from NMR spectra of the compound if the compound is formed

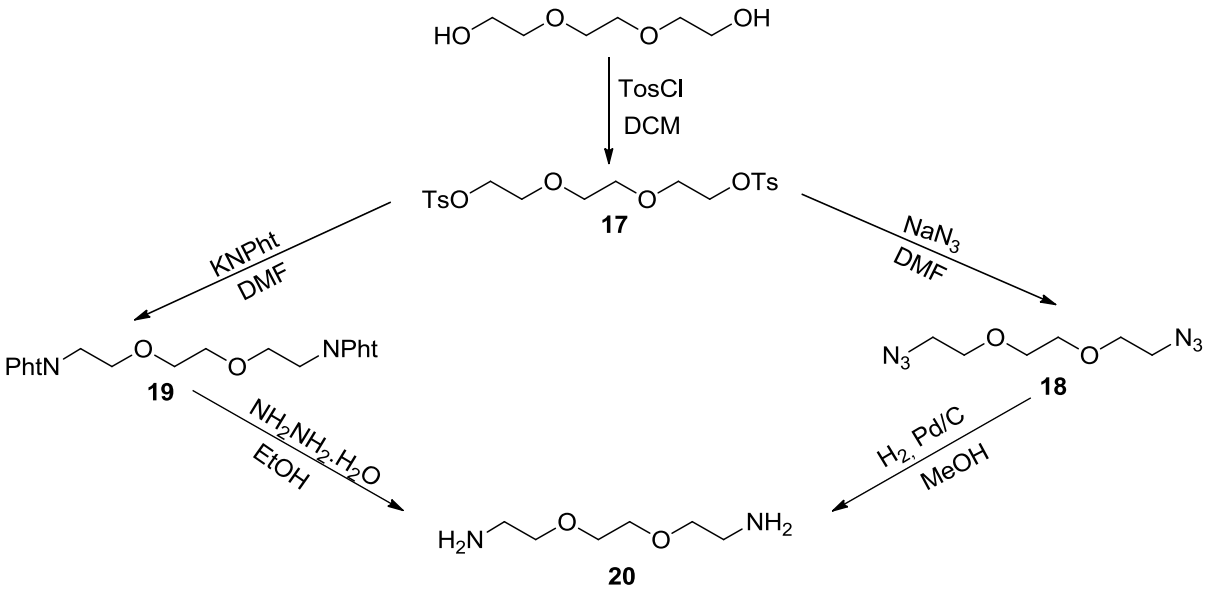
or not. Therefore, chemically we checked whether thiourea formation observed in the action of (*S*)-methylbenzylamine. Thiourea product **16** was achieved successfully.



Scheme 20. Synthesis of **16** from chiral amine and chiral isothiocyanate

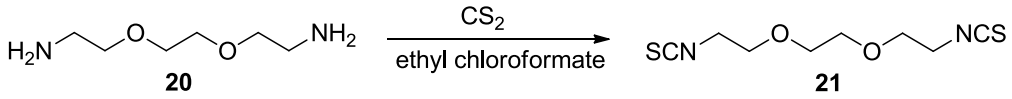
2.2.11. Synthesis of Triethylene Glycol Based Diamine and Isothiocyanate

For diamine **11**, amine functionality closeness resulted in cyclic thiourea derivatives. Taking this into consideration, we revised our route by seperating diamines far away from each other could furnish dithioisocyanates. For that, triethylene glycol was modified to corresponding diamine **20** using the following scheme.



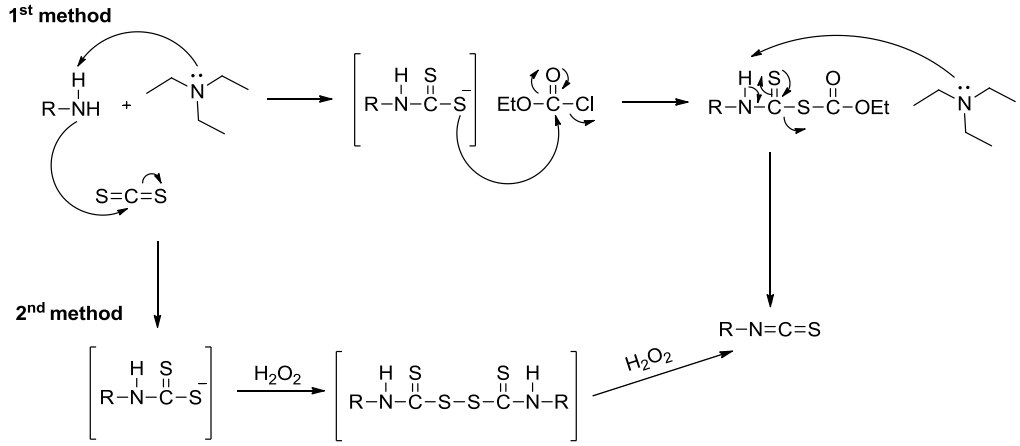
Scheme 21. Reaction pathway for the synthesis of triethylene glycol diamine **20**

Synthesis of triethylene glycol diamine **20** was similar with the case of tartaric acid diamine **11**. In this case potassium phthalimide method gave better yield (pages 28,29,30). After synthesis of diamine **20**, as in the previous experiments, it was treated with carbon disulfide. The reaction did not yield the isothiocyanate product. Thus, a new procedure was executed for synthesis of isothiocayanate, in which ethyl chloroformate was employed.



Scheme 22. Synthesis of **21**

Mechanism of these two methods was summarized in Scheme 23.

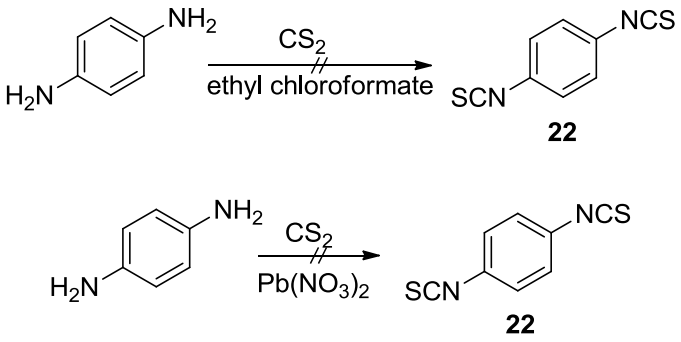


Scheme 23. General formation mechanism of isothiocyanates by different methods

Since there is no dimerization product observed and the good leaving group property of ethyl chloroformate, second method was seen more feasible.

For the synthesis of diisothiocyanates 1,4-phenylenediamine was also treated with CS_2. In addition to ethyl chloroformate method, in this case $Pb(NO_3)_2$ was also

examined in the synthesis reaction of compound **22**. Again, no satisfactory result was observed from both reactions.



Scheme 24. Trial experiments for the synthesis of **22**

2.2.12. Isocyanate Studies

2.2.12.1 Phosgene and Triphosgene

Since reproducibility become a problem in all isothiocyanates formation experiments, we continued our research with isocyanates synthesis.

The challenging point of isocyanate synthesis is the use of phosgene. This chemical is in the gas form above 8 ^{o}C and it is very toxic. Besides it was used as chemical weapon during World War I.[53,54]

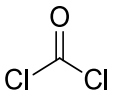


Figure 34. Structure of phosgene

Because of these reasons, instead of phosgene, a safer equivalent triphosgene was used in the synthesis of isocyanates. It is in solid form at room temperature and easy to handle.

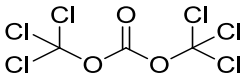
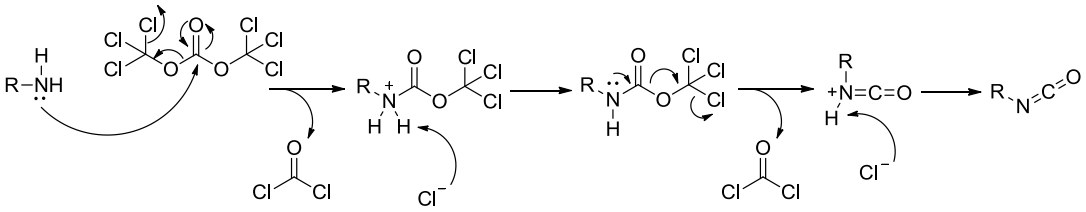


Figure 35. Structure of triphosgene

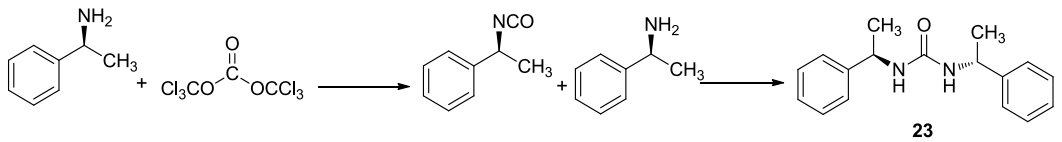
2.2.12.2. Reactions with Triphosgene

In the reaction medium one equivalent triphosgene produces three equivalents of phosgene which react with amine to yield corresponding isocyanate.



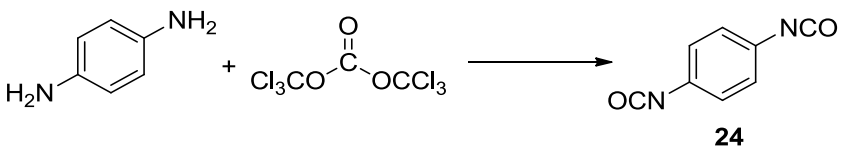
Scheme 25. Formation mechanism of isocyanate with triphosgene

In the light of these information, we firstly examined whether urea functionality could be observed by designed pathway. *S*-Methyl benzyl amine was chosen because of its chiral feature. In addition to pathway analysis, we could also have an idea about the effect of chiral center on the formation of urea compound. Synthesis of urea **23** was done in one pot reaction. Both ^{1}H NMR and IR spectra decisively concluded the formation of corresponding urea **23**



Scheme 26. One pot synthesis of **23**

Then, the synthesis of 1,4-phenylenediisocyanate **24** was carried out from 1,4-phenylenediamine under the action of triphosgene and observed satisfactory yield.



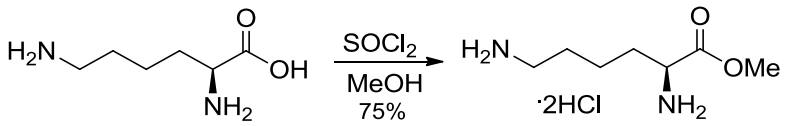
24

Scheme 27. Synthesis of *p*-phenylene diisocyanate **24**

2.2.12.3. Synthesis of L-lysine Based Isocyanate

With this promising result, we resolved to synthesize another diisocyanate having chiral center. For this purpose, L-lysine which is commercially available diamine was reacted in the same manner. Before adding isocyanate functionality to acid group of L-lysine, compound was converted to ester to prevent any possible cyclization reaction after insertion of isocyanate functional group to lysine **25**.

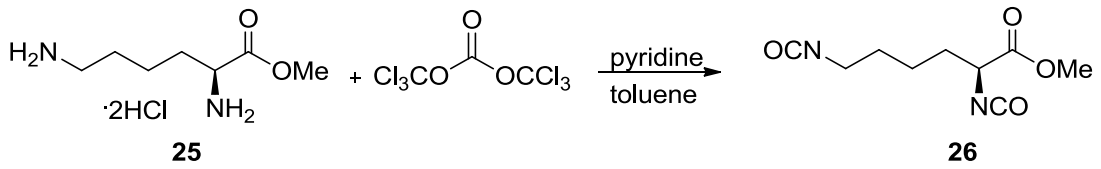
Esterification reaction was performed with thionyl chloride in the presence of methanol. After the synthesis target compound was observed as a salt as expected.



25

Scheme 28. Synthesis of L-lysine methyl ester **25**

The compound **25** was reacted with triphosgene in a similar way with previous case. The difference was, the addition of pyridine as a base to the reaction medium. The reason of that, was to remove HCl from amine functionality and to make them active for nucleophilic attack. Target compound **26** was successfully synthesized.

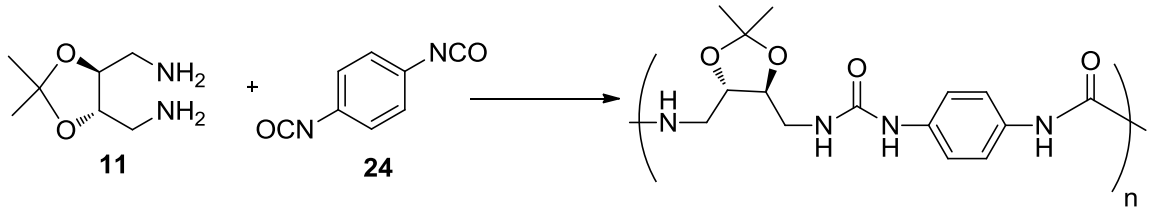


Scheme 29. Synthesis of **26** from **25** and triphosgene

Synthesized diisoyanates and diamines were lead us to focus polymerization reactions. Both diamines and disoyanates was treated with each other to get polyurea type polymers. These were discussed below:

2.2.13. Synthesis of Polymers

2.2.13.1. Synthesis of POL-A



Scheme 30. Synthesis of **POL-A**

The diamine **11** was treated with 1,4-phenylene diisocyanate in DMF to get **POL-A**. This polymer is a solid and do not dissolve in various organic solvents such as $CHCl_3$, CH_2Cl_2, methanol and DMSO. Therefore CP/MAS (Cross Polarization Magic Angle Spinning) ^{13}C-NMR of this polymer was measured. The NMR results showed that in the region between 5-15 ppm $\mathbf{a}^{\mathbf{POL\text{-}A}}$ carbons, 15-75 ppm $\mathbf{c}^{\mathbf{POL\text{-}A}}$, $\mathbf{d}^{\mathbf{POL\text{-}A}}$ 85-95 ppm $\mathbf{b}^{\mathbf{POL\text{-}A}}$ carbons appear Aromatic carbons were in the region between 95-150 ppm. In the region between 200-250 ppm urea carbon peak was observed (Figure 37).

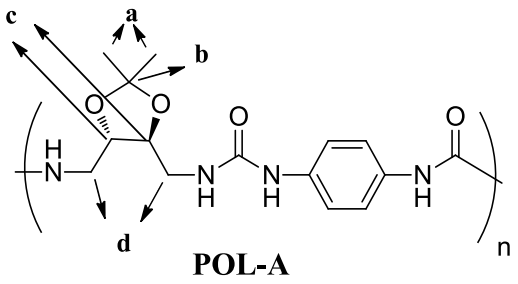


Figure 36. Hydrogen labeling for **POL-A**

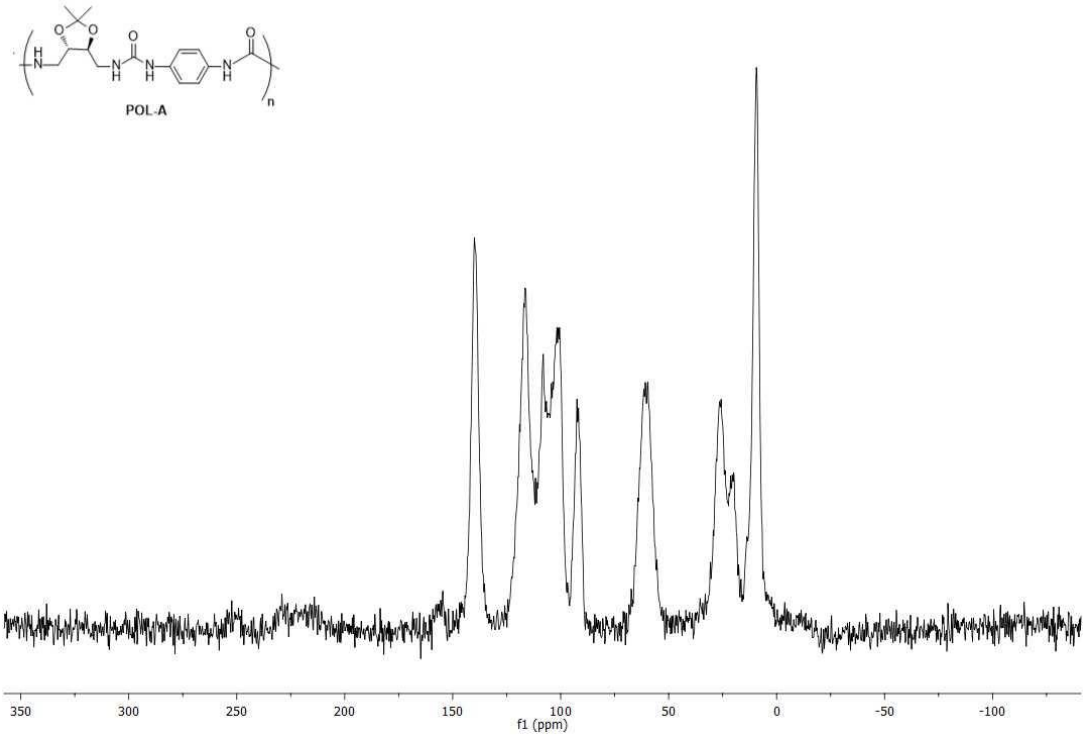
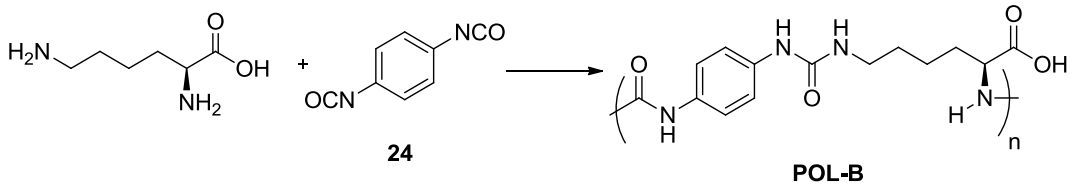


Figure 37. CP/ MASS ^{13}C NMR spectrum of **POL-A**

According to DSC (Differential Scanning Calorimetry) results POL-A has Tg at 24.70 ^{o}C. There was also an endothermic peak at 82.05 ^{o}C, which must be Tm for polymer. However, melting point was measured with melting point apparatus, there was also no melting around this temperature. Therefore, this endothermic peak was probably due to the deformation in between the polymer chains. (For DSC thermogram see

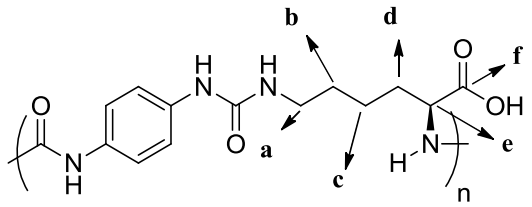
Appendices Part C). Moreover it was observed that the polymer darkens above 250 ^{o}C which indicates that the polymer decompose above this temperature. IR spectrum of the polymer also showed the formation of urea functionality with peaks at 1648 cm^{-1} and 3313 cm^{-1} (Figure 77).

2.2.13.2. Synthesis of POL-B



Scheme 31. Synthesis of **POL-B**

For the synthesis of POL-B, 1,4 phenylene diisocyanate and L-lysine were treated with each other. Again, the resulting polymer can not be dissolved in any solvents. Because of that reason, it was decided to analyze the structure of polymer with CP/MAS ^{13}C-NMR. The NMR results showed that in the region between 10-90 ppm **a**, **b, c**, **d, e, f** carbons appear. Aromatic carbons were in the region between 95-150 ppm. In the region between 200-250 ppm urea carbon peak was arose. Sharp peaks might belong to DMF that can not be separated due to the hydrogen bonding (Figure 39).



POL-B

Figure 38. Hydrogen labeling for **POL-B**

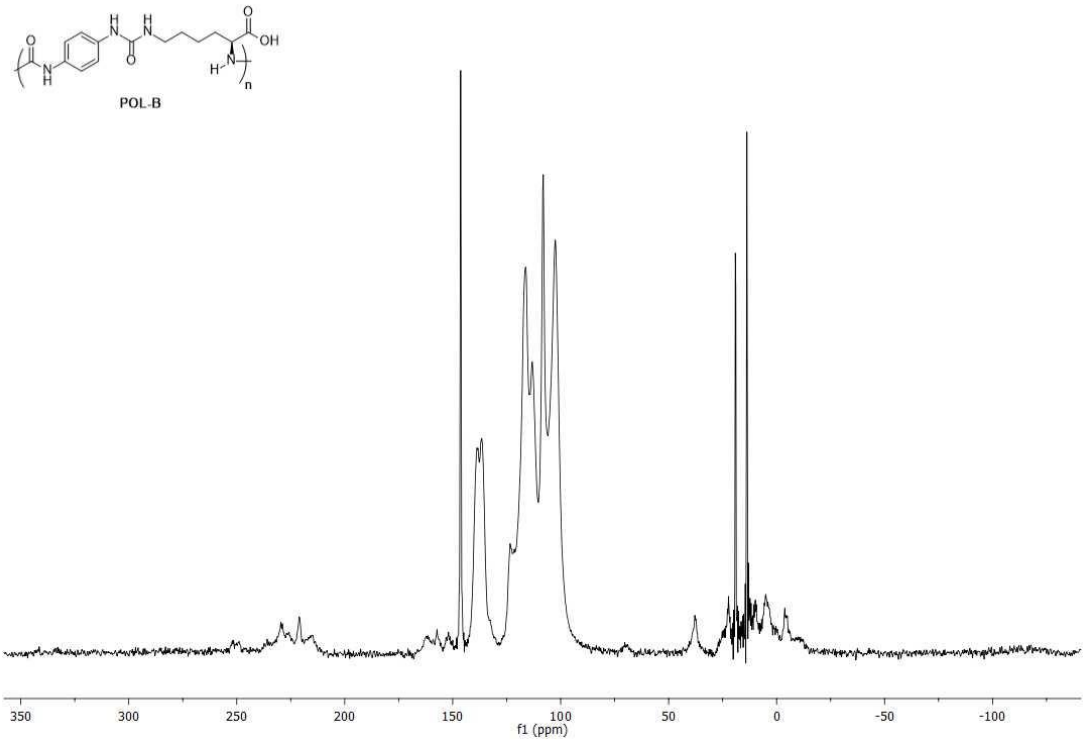
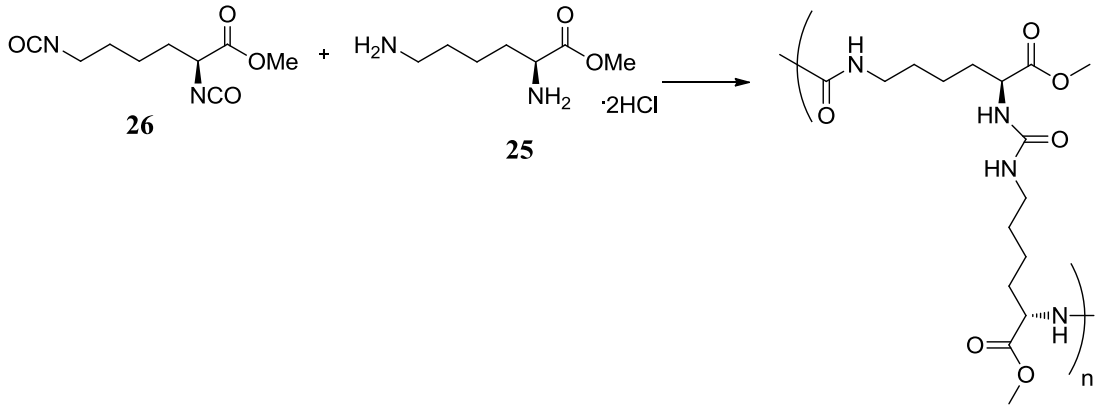


Figure 39. CP/ MASS ^{13}C NMR spectrum of **POL-B**

According to DSC (Differential Scanning Calorimetry) results POL-B has Tg at 35.20 ^{o}C. The endothermic peak around 96.46 ^{o}C was also due to the deformation in between the polymer chains. (For DSC thermogram see Appendices Part C). Moreover it was observed that the polymer darkens above 200 ^{o}C which indicates that the polymer decompose above this temperature. In IR spectrum, peaks at 1650 cm^{-1} and 3290 cm^{-1} indicates the formation of urea (Figure 78).

2.2.13.3. Synthesis of POL-C



Scheme 32. Synthesis of **POL-C**

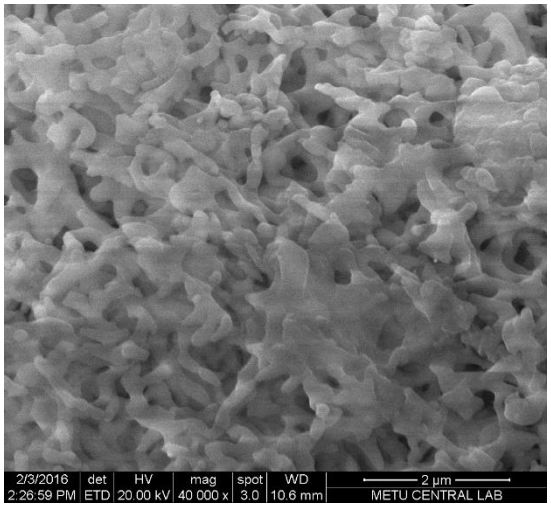
Another polymer of the interest as stated at the beginning of this chapter was lysine bonded to another lysine through the urea linkage, namely as **POL-C**. to accomplish this, amino functionalities on lysine were converted into isocyanates **26**. Then the diisocyanates **26** were treated with lysine methyl ester **25** in the presence of pyridine. The reaction vessel turned cloudy. Solvent was evaporated. The residue was precipitated in methanol. Methanol was removed under vacuum. The remaining part dissolved in DMSO-d_6 and proton NMR could be taken (Figure 68). Lysine peaks were present on the NMR spectrum. In order to remove pyridinium hydrochloride from the medium the polymer was washed with water. White residue was obtained in the flask. This white residue did not dissolve in DMSO-d_6. The residue's IR spectrum showed the urea peaks at 1619 cm^{-1} and 3340 cm^{-1} (Figure 79)

According to DSC (Differential Scanning Calorimetry) results POL-C upon heating up to 250 ^oC absorbs heat. However melting point was not detected. Interestingly, upon cooling from 250 ^oC, at around 97 ^oC an endothermic peak was observed. This peak is probably due to enforced interpolymer chain interaction. Moreover upon heating again up to 240 ^oC. Melting point was observed at 234 ^oC. This implies that heating and cooling cycles provides crystallinity to the polymer.

2.2.13.4. SEM (Scanning Electron Microscopy) Analysis

SEM micrographs show that POL-B are not fibrous. However POL-A micrographs showed fibrous nanostructures with regional helical parts (Figure 40)

a)



b)

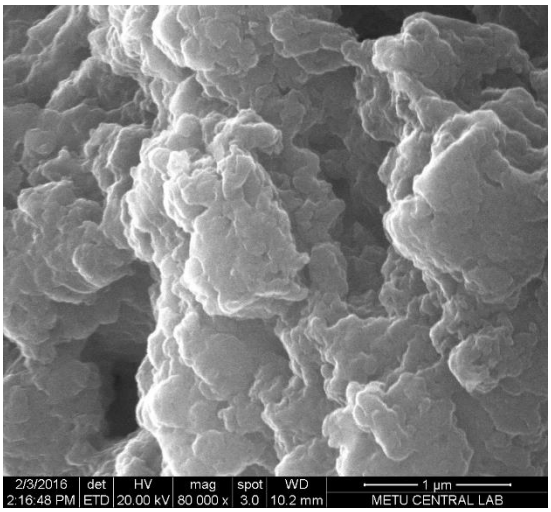


Figure 40. a) SEM image of **POL-A b)** SEM image of **POL-B**

CHAPTER 4

CONCLUSIONS

Due to the synthetic utility of ureas and polymers, these two concepts were merged in this thesis. Helical polymers carry high potential in material science with synthetic biomedical applications. Toward this goal, synthetic strategies with the aid of computational methods were developed.

Ureas are synthesized by treating amines with isocyanates. To get a urea containing polymer, orthogonal functionalities (diamines and diisocyanates) were treated with each other. A successful conversion of tartaric acid to (4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-dimethamine through a multistep synthesis was accomplished. Moreover, many synthetic methods were applied throughout this synthesis.

Diamines, phenlylene diamine and L-lysine, were successfully converted into diisocyanates. However, diisothiocyanates synthesis were not as smooth as the synthesis of diisocyanates. Nevertheless, several synthetic methods were attempted to convert diamines into diisothiocyanates.

Diamines and diisocyanates in hand were treated with each other to get urea containing chiral polymers. Among these three polymers, polymer obtained from 1,4-phenylenediisocyanates with (4*S*, 5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dimethamine provided helical nanostructures regionally as judged from SEM micrographs

In order to utilize these polymers in above mentioned areas of research we need to synthesize easily processable (soluble) polymer. With the current study, a gate was opened toward functional helical polymers.

CHAPTER 5

EXPERIMENTALS

Methods and Materials: Structural determinations of compounds were done with the instruments as written below.

^{1}H and ^{13}C nuclear resonance spectra of compounds were recorded in $CDCl_3$ and DMSO-d_6 with Bruker Avance III Ultrashield 400 Hz NMR spectrometer. Chemical shifts were given in parts per million (ppm) with TMS as internal reference. Spin multiplicities were specified as a s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) and coupling constants (*J*) were reported as in Hz (Hertz). ^{1}H and ^{13}C NMR spectra of products were given in Appendix A. NMR spectrums were processed with MestReNova processor.

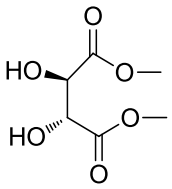
Infrared Spectra were recorded with Bruker Alpha Platinum ATR. Peak positions were reported in reciprocal centimeter (cm^{-1}). IR spectra of products are given in Appendix B.

All DSC termograms were recorded with Scinco DSC N-650 Differential Scanning Calorimetry.

All reactions were monitored by TLC (Merck Silica Gel 60 F254), visualized by UV light.

All starting materials and solvents were purschased from Sigma Aldrich and were used without further purifications.

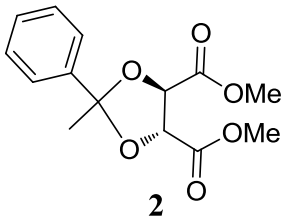
(2R, 3R)-dimethyl 2,3-dihydroxysuccinate (1)[51]



1

To L-tartaric acid (5.00 g, 33.31 mmol) solution in 16.00 ml methanol, $SOCl_2$ (20.74 g, 174.33 mmol) was added (Addition must be done slowly in water-ice bath, since reaction is exothermic). After an hour with stirring, mixture was heated to reflux temperature for 3 hours to give pale yellow solution. After cooling down, solvent and excess thionyl chloride were removed under vacuo to yield oily product (5.45 g 93%). ^{1}H NMR ($CDCl_3$): δ 4.50 (s, 2H), 3.80 (s, 6H), 3.11-3.10 (b, 2OH)

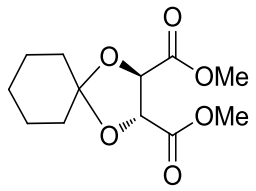
(4R, 5R)-dimethyl 2-methyl-2-phenyl-1,3 dioxolane-4,5-dicarboxylate (2)[55]



2

L-dimethyl tartarate (5.87 g, 33 mmol), acetophenone (3.85 ml, 33 mmol), a crystal of *p*TSA and benzene were placed in a round bottomed flask fitted with Dean-Stark apparatus. Reaction was over after all water was collected. Benzene was removed under reduced pressure and extraction was done with diethyl ether, $NaHCO_3$ solution followed by water. Organic part is was dried and ether was removed. Crude NMR showed no product peaks.

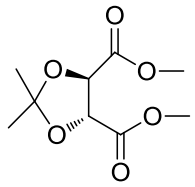
(2S,3S)-dimethyl 1,4-dioxaspiro [4.5]decane-2,3-dicarboxylate (3)[55]



3

L-dimethyl tartarate **(1)** (0.86 g, 4.82 mmol), cyclohexanone (0.47 g, 4.82 mmol), a crystal of *p*TSA and benzene were placed in a round bottomed flask fitted with Dean-Stark apparatus. Reaction was finished after all water was collected. Benzene was removed under reduced pressure and extraction was done with diethyl ether, $NaHCO_3$ solution followed by water. Organic part is was dried and ether was removed (0.17 g, 14%). ^{1}H NMR ($CDCl_3$): δ 4.83 (s,2H), 3.83 (s, 6H), 1.73-1.56 (m, 10H)

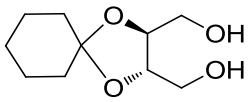
4R, 5R-dimethyl 2,2 dimethyl-1,3-dioxolane-4,5-dicarboxylate (4)[56]



4

To a solution of dimethyl tartrate (8.00 g, 44.91 mmol) in 20.00 ml DMF, 2-2 dimethoxy propane (28.71 g, 275.75 mmol) and 0.4 g *p*TSA were added. The mixture was refluxed overnight and then concentrated under decreased pressure. It was treated with a 2% aqueous solution of $NaHCO_3$ and extracted with $CHCl_3$. Organic layer was washed with water, dried with Na_2SO_4, filtered and $CHCl_3$ was evaporated. The product is oily dark brown residue (8.01 g, 82%). ^{1}H NMR ($CDCl_3$): δ 4.75 (s, 2H), 3.76 (s, 6H), 1.43 (s, 6H)

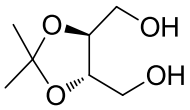
(2R, 3R)-1,4-dioxaspiro [4.5]decane-2,3-diyldimethanol (5)[57]



5

Solution of sodium borohydride (0.149 g, 3.95 mmol) in THF (2.00 ml) was added to **5** (0.17 g, 0.65 mmol) in THF (1.50 ml) during 15 minutes under reflux (70 ^{o}C) and stirring. With the addition of MeOH (1.00 ml) gas was evolved. Stirring and reflux were continued about 60 minutes. Reaction mixture was cooled to room temperature and quenched with the saturated solution of NH_4Cl with stirring 1.5 hours. Water was added and extracted with ethyl acetate. Combined organic parts dried with Na_2SO_4 and concentrated under low pressure for purification column chromatography was used. According to NMR results, no pure product was observed.

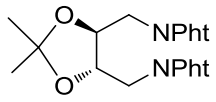
((4S, 5S)-2,2-dimethyl-1,3-dioxalane-4,5-diyl)dimethanol (6)[51]



6

To a solution of **7** (5.96 g, 27.33mmol) in 100.00 ml anhydrous methanol was added $NaBH_4$ (5.08 g, 136.10 mmol) at 0 ^{o}C slowly. After the addition is completed reaction mixture was allowed to reach room temperature and it was stirred overnight. Methanol was removed under reduced pressure and then remaining part was extracted with NH_4Cl solution and ethyl acetate. Organic phase was washed with water and dried over anhydrous $MgSO_4$, filtered and concentrated to give pale yellow oil (2.58 g, 58%). ^{1}H NMR ($CDCl_3$): δ 3.97-3.91 (m, 2H), 3.77-3.72 (m, 2H), 3.66-3.62 (m, 2H), 1.37 (s, 6H)

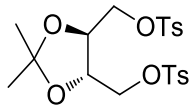
2,2'-((2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(isoindoline-1,3-dione) (7)[58]



7

DIAD (Diisopropyl azodicarboxylate) (8.83 g, 36.8 mmol) was added to a solution of diol **(9)**, PPh_3 (triphenylphoshine) (11.48 g, 36.8 mmole) and phthalimide (6.44 g, 36.8 mmol) in 100.00 ml anhydrous THF at 0 ^oC. The mixture was allowed to stirred at room temperature 24 hours. Then it was refluxed 2 hours and continued stirring overnight. THF was removed then methanol was added to resulting residue for crystallization.

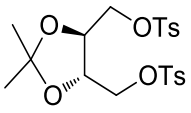
((4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (methylene) bis (4-methyl benzene sulfonate) (8)



8

A solution of **9** (3.00 g, 18.49 mmol) in 15 ml pyridine was cooled to 0 ^oC and tosyl chloride (7.37 g, 38.7 mmol) was added. The mixture was remained at fridge 3 days. 17 ml of water was added and the resulting mixture was kept in refrigerator about 2 hours. The reaction mixture was washed with water, 5% $CuSO_4$ solution, saturated $NaHCO_3$ and brine consecutively. The organic phase was dried with $MgSO_4$, and concentrated to yield white precipitate. (3.83 g, 44%)

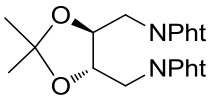
((4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (methylene) bis (4-methyl benzene sulfonate) (8)[59]



8

To a solution of **9** (1.5 g, 9.25 mmol) in 50 ml CH_2Cl_2 at 0 ^oC was added Et_3N (1.92 g, 19.33 mmol) and TsCl (3.69 g, 19.33 mmole) then it was stirred overnight. The reaction mixture was washed with water, 5% $CuSO_4$ solution, saturated $NaHCO_3$ and brine consecutively. The organic phase was dried with $MgSO_4$, and concentrated. Excess tosyl chloride and target compound were separated with column chromatography (EtOAc: Hexane, 1:5) to observed white precipitate (1.48 g, 34%). ^1H NMR ($CDCl_3$): δ 7.71 (d, *J*= 8.28, 4H), 7.29 (d, *J*= 8.02, 4H), 4.04 (m,4H), 3.94 (m, 2H), 2.39 (s, 6H), 1.23 (s, 6H)

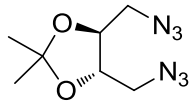
2,2'-((2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(isoindoline-1,3-dione) (7)[60]



7

Tosylated compound **(10)** (0.25 g, 0.53 mmol) was dissolved in 20 ml DMF and potassium phthalimide salt (0.39 g, 2.09 mmol) was added to the solution. Reaction mixture was heated 95 ^oC and stirred overnight. Mixture was diluted with dichloromethane and extracted with first brine followed by water, dried over $MgSO_4$. Solvent was removed under reduced pressure to observe **13** (0.15g, 68%). ^1H NMR ($CDCl_3$): δ 7.76-7.73 (m, 4H), 7.64-7.61 (m, 4H), 4.16-4.12 (m, 2H), 3.94-3.88 (m, 2H), 1.29 (s, 6H)

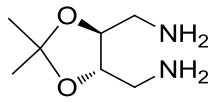
(4S, 5S)-2,2-dimethyl, 4,5-bis (azidomethyl) 1,3-dioxolane (9)[59]



9

Tosylated compound **(10)** (1.40 g, 2.98 mmol) was dissolved in 20 ml DMF, NaN_3 (0.68 g, 10.41 mmol) was added and the mixture was stirred at 80 ^oC overnight. After cooling to room temperature the suspension was diluted with water and diethyl ether. The organic part was separated and washed with water several times to remove DMF. The organic layer was then washed with brine, dried with $MgSO_4$ and concentrated under vacuo to afford the corresponding diazide **(11)**, (0.50 g, 79%) as a pale yellow oil. ^1H NMR ($CDCl_3$): δ 3.90-3.82 (m,2H), 3.37-3.31 (m, 2H), 3.15-3.11 (m,2H), 1.26 (s,6H)

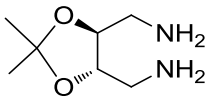
(4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-dimethamine (11)



11

Compound **11** was dissolved in 20 ml methanol. 0,01 g of Pd/C was added to mixture very carefully. Reduction was performed by using H_2 in balloon and stirred overnight. After reaction completed, catalyst was filtered off and filtrate was concentrated under reduced pressure to yield **12** (0.5 g, 67%)

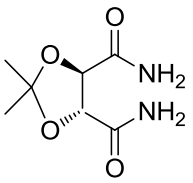
(4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-dimethamine (11)[58]



11

13 (2.81g, 6.68 mmol) was dissolved in 25 ml ethanol and hydrazine monohydrate (10.03 g, 200.4 mmol) was added and the resulting mixture was refluxed 4 hours. Solvent was removed under reduced pressure, residue was dissolved in 20% NaOH solution and extracted with dichloromethane (x3) and dried with Na_2SO_4. Remaining solvent was removed under reduced pressure to get **12** (0.50 g, 48%)

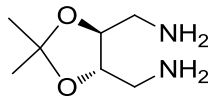
(4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide (10)[61]



10

High pressure reactor was charged with dimethyl tartrate **(4)** (5.00 g, 28.06 mmol) in 35 ml of methanol. The reactor was cooled to -40 ^oC and ammonia gas was bubbled to solution until it was saturated. Reactor was closed tightly and kept at 50 ^oC for 6 hours. Resulting reaction mixture was cooled to 0 ^oC, reactor was opened and allowed to reach room temperature. Excess ammonia and methanol was removed under reduced pressure to obtain white to yellowish crystals (3.9 g, 91 %). ^1H NMR (DMSO-d_6): δ 7.49 (s, -NH_2), 7.42 (s, -NH_2), 4.43 (s, 2H), 1.39 (s, 6H)

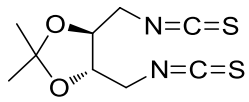
(4S, 5S)-2,2-dimethyl-1,3-dioxolane-4,5-dimethamine (11)[61]



11

Compound **14** (6 gr, 31.88 mmol) was placed in a soxhlet thimble and by refluxing into a suspension of $LiAlH_4$ (3.02 g, 79.57 mmol) in 200 ml THF, it was extracted to reaction medium. After 6 hours reflux, the suspension stirred at room temperature overnight. Minimum amount of water and then 15% NaOH solution was added to resulting mixture to quench reaction. The mixture was filtered and precipitates were washed with THF. Filtrates were combined and solvent was removed to yield corresponding diamine **11** (3.25 g, 64%). ^{1}H NMR (DMSO-d_6): δ 3.69-3.63 (m,2H), 2.75-2.65 (m, 4H), 1.29 (s, 6H)

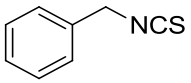
(4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbonyl isothiocyanate (12)[62]



12

Carbon disulfide was added dropwise to a mixture of diamine **(12)** and trimethylamine in THF at 2-5 ^oC. Stirring was continued about half an hour, followed by slow addition of H_2O_2 (50%). The mixture was evaporated under reduced pressure and extracted with ethyl acetate. The remaining residue was yellowish brown oily product. However observed oily product was not target compound.

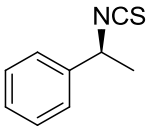
(isothiocyanatomethyl)benzene (13)[62]



13

Carbon disulfide was added dropwise to a stirred mixture of benzylamine and THF solution at 2-5 ^{o}C slowly. Agitation was continued about half an hour, followed by slow addition of H_2O_2 (50%). The mixture was evaporated under reduced pressure and extracted with ethyl acetate. The remaining residue was **16** as yellowish oily liquid (1.10 g, 74%). ^{1}H NMR ($CDCl_3$): δ 7.33-7.20 (m, 5H), 4.60 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 134.2, 129.0, 128.4, 127.9, 126.6, 48.7

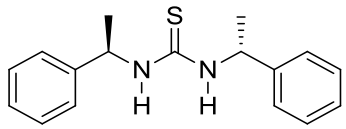
(S)-(1-isothiocyanatoethyl)benzene (15)[62]



15

Carbon disulfide (0.62 g, 8.25 mmol) was added dropwise to a stirred mixture of S-methyl benzylamine (1.00 g, 8.25 mmol) and THF (50 ml) at 2-5 ^{o}C slowly. Agitation was continued about half an hour, followed by slow addition of H_2O_2 (50%). The mixture was evaporated under reduced pressure and extracted with ethyl acetate. The remaining residue **15** was obtained as white solid (1.19 g, 88%). ^{1}H NMR ($CDCl_3$): δ 7.44-7.33 (m, 5H), 4.97-4.91 (q, *J*=6.8 1H), 1.70 (d, *J*=6.8, 3H). ^{13}C NMR ($CDCl_3$): δ 140.2, 132.2, 128.9, 128.3, 125.5, 57.08, 25.02

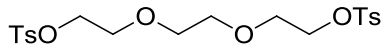
1,3-bis((R)-1-phenylethyl)thiourea (16)



16

A solution of of S-methyl benzylamine (0.88 g, 7.29 mmol) in 10 ml diethylether was added to the solution of **15** (1.19 g, 7.29 mmol) in ml diethylether.the reaction mixture was stirred overnight. Precipitated product was filtered off and washed with diethylether to yield compound **16** (1.82 g, 88 %). ^{1}H NMR (DMSO d6): δ 7.74 (b, 2-NH), 7.31-7.22 (m, 10H), 5.42 (b, 2H), 1.39 (s, 6H). ^{13}C NMR (DMSO d6): δ 180.8, 144.2, 128.2, 126.6, 126.0, 52.2, 22.4

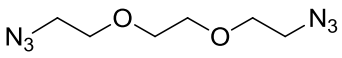
(Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl)bis(4-methylbenzenesulfonate) (17)[63]



17

Triethylene glycol (5.00 g, 33.29 mmol) was dissolved in 33 ml DCM (dichloromethane). Tosyl chloride (12.69 g, 66.59 mmol) was added and the mixture was cooled to 0 ^{o}C in water-ice bath. In order to keep temperature below 5 ^{o}C potassium hydroxide was added slowly. After stirring 3 hours at 0 ^{o}C, DCM and ice water were added. The organic part separated and extraction was done with DCM. The combined organic parts were concentrated under reduced pressure to yield white solids as a product (12.22 g, 85%). ^{1}H NMR ($CDCl_3$): δ 7.81 (d, *J*= 8.3, 4H), 7.36 (d, *J*= 7.9, 4H), 4.17-4.14 (t, *J*=4.7, 4H), 3.68-3.66 (t, *J*= 4.8, 4H)

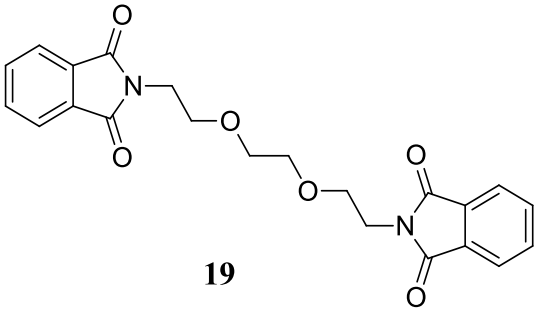
1,2-bis(2-azidoethoxy)ethane (18)[59]



18

Ditosylated triethyleneglycol **17** (3.00 g, 6.54 mmol) and sodium azide (1.48 g, 22.89 mmol) were mixed in 50 ml DMF and stirred at 80 ^{o}C overnight. The mixture was diluted with water and extracted with diethylether. Combined organic layers were washed with water repeatedly and then brine. After drying with $MgSO_4$, solvent was removed under reduced pressure (0.59 g, 45%). ^{1}H NMR ($CDCl_3$): δ 3.69-3.65 (m, 8H), 3.39-3.36 (t, *J*=5.1, 4H)

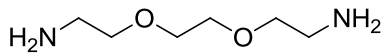
2,2'-((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(isoindoline-1,3-dione) (19)[60]



19

Ditosylated triethyleneglycol **17** (4.56 g, 24.63 mmol) was dissolved in 120 ml DMF and potassium phthalimide was added. After the addition of a pinch of potassium iodide reaction mixture was refluxed overnight. DMF was removed under reduced pressure and remaining part diluted with dichloromethane. Extraction was done with first brine and followed by water. Product was observed after removal of dichloromethane as a white solid (6.1 g, 61%). ^{1}H NMR ($CDCl_3$): δ 7.89-7.83 (m, 4H), 7.76-7.71 (m, 4H), 3.88-3.82 (t, *J*=5.8 4H) 3.71-3.68 (t, *J*=5.8 4H), 3.61 (s, 4H)

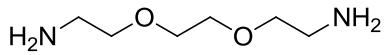
2,2'-(ethane-1,2-diylbis(oxy))diethanamine (20)



20

Triethyleneglycol diazide **18** (0.59 g, 2.95 mmol) was dissolved in methanol and 0,01 g of Pd/C was added to mixture very carefully. Reduction was performed by using H_2 in balloon. After reaction completed, catalyst was filtered off and filtrate was concentrated under reduced pressure to yield **20** (0.21 g, 48%)

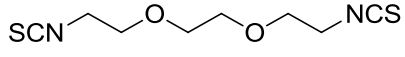
2,2'-(ethane-1,2-diylbis(oxy))diethanamine (20)



20

To a solution of **19** (5.80 g, 14.20 mmol) in 75 ml, hydrazine monohydrate (2.84 g, 56.81 mmol) was added. The resulting mixture was refluxed. First all solids were dissolved and after a while white precipitation was formed. Precipitates were filtered off and washed with EtOH, resulting filtrates were evaporated under reduced pressure. To the remaining solids dichloromethane was added and solids were filtered again. Remaining organic solution was concentrated under vacuo to afford diamine as a pale yellow liquid (1.34g, 65%). ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 4H), 3.56-3.53 (m, 4H), 3.14 (b, 4 -NH), 2.92-2.98 (m, 4H)

1,2-bis(2-isothiocyanatoethoxy)ethane (21)[64]

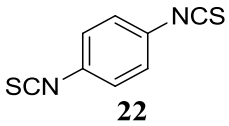


21

To a solution of diamine **20** (1.34 g, 9.04 mmol) and triethylamine (1.83 g, 18.08

mmol) in 14.00 ml chloroform was added CS_2 (1.38 g, 18.08 mmole). At room temperature, reaction mixture was stirred for 2 hour then cooled to 0 ^oC. To the mixture ethylchloroformate (1.96 g, 18.08 mmole) was added slowly and stirred at this temperate half an hour and continued to stirring at room temperature for 2 hours. Resulting solution was washed with water (x3), dried over Na_2SO_4 and solvent was evaporated under reduced pressure. After getting crude material it was purified by vacuum distillation to give desired isothiocyanate. However product was not observed.

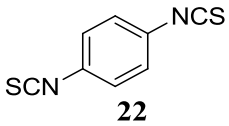
1,4-diisothiocyanatobenzene (22)[64]



22

To a solution of 1,4 phenylene diamine (2.50 g, 23.00 mmol) and trimethylamine (4.65 g, 46.00 mmol) in 30.00 ml chloroform was added CS_2 (3.50 g, 46.00 mmol). At room temperature, reaction mixture was stirred for 2 hour then cooled to 0 ^oC. To the mixture ethylchloroformate (4.99 g, 46.00 mmol) was added slowly and stirred at this temperate half an hour and continued to stirring at room temperature for 2 hours. Resulting solution was washed with water (x3), dried over Na_2SO_4 and solvent was evaporated under reduced pressure. After getting crude material it was purified by vacuum distillation to give desired isothiocyanate. No product was obtained.

1,4-diisothiocyanatobenzene (22)[65]

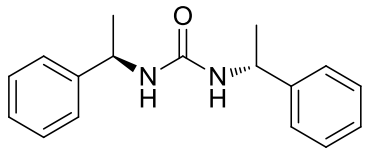


22

To a round bottomed flask, CS_2 (8.29 g, 0.11 mmol) and concentrated aqueous ammonia (6.99 g, 200.24 mmol) was added and striired in ice-salt bath.

Phenylenediamine (5.00 g, 46.24 mmol) was added to that solution with dropping funnel. After all amine was added the reaction mixture was allowed to stir thirty minutes. During the stirring ammonium phenyldithiocarbamate was precipitated. It was dissolved in water and to the solution lead nitrate (15.24 g, 46.24 mmol) in water was added. Lead sulfide was seen as brown-black precipitate. Remaining part was separated from the precipitate and concentrated under reduced pressure. No product was obtained.

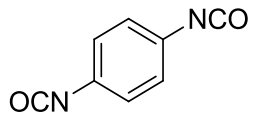
1,3-bis((R)-1-phenylethyl)urea (23)



23

To the solution of triphosgene (4.89 g, 17 mmole) and 120 ml of toluene in 2-necked round bottomed flask, (S)-methylbenzylamine (2.00 g, 16.50 mmole) in 50 ml toluene was added slowly in water-ice bath. After addition is completed, reaction mixture was refluxed until all of the HCl gas was released. When the reaction completed, (S)-methylbenzylamine was added to yield corresponding urea as a white precipitate. Solids were filtered off and dried (3.08 g, 67%). ^{1}H NMR (DMSO d6): δ 7.33-7.19 (m, 10H), 6.32 (d, *J*= 8.1, 2-NH), 4.74-4.66 (m, 2H), 1.28 (d, 6H)

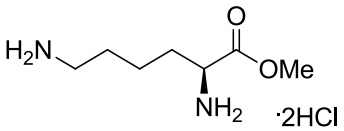
1,4-diisocyanatobenzene (24)



To a solution of triphosgene (27.44 g, 92.47 mmol) in 450 ml toluene was added p-phenylenediamine (5.00 g, 46.23 mmol) in water ice bath slowly.After addition is completed, reaction mixture was refluxed until all of the HCl gas was released

(reaction was refluxed overnight). Reaction mixture was cooled down and filtered. Remaining filtrates was concentrated under reduced pressure to obtain corresponding diisocyanate as a white-yellowish solid. (6.22 g, 84 %). ^{1}H NMR ($CDCl_3$): δ 7.06 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 131.1, 125.8, 125.0

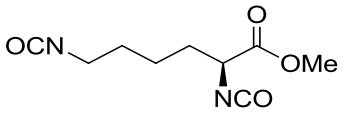
L-lysine methyl ester (25)[51]



25

L-Lysine (5.00 g, 34.20 mmol) was put in a round bottomed flask and dissolved in 40 ml methanol. Thionyl chloride (8.13 g, 68.40 mmol) was added to the solution in a water-ice bath very slowly. After an hour stirring, the reaction mixture was heated to reflux for three hours. The solvent and if any remaining thionyl chloride was removed under reduced pressure to give white solid. (5.98 g, 75%). ^{1}H NMR (DMSO d6): δ 8.76 (s, -NH_3), 8.22 (s, -NH_3), 3.99-3.96 (t, *J*= 6.3), 1.90-1.78 (m, 2H), 1.63-1.55 (m, 2H), 1.50-1.36 (m, 2H)

(S)-methyl 2,6-diisocyanatohexanoate (26)



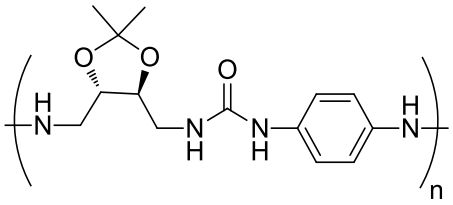
26

To a solution of triphosgene (9.72 g, 37.77 mmol) in 150 ml toluene, pyridine (7.40 g, 93.6 mmol) was added slowly in water-ice bath. After stirring 10 minutes, compound **25** (2.50 g, 15.60 mmol) added slowly, then mixture was refluxed until no more HCl gas was evolved. The resulting reaction mixture was filtered off and

filtrate was concentrated under reduced pressure. Residue was dissolved in chloroform and

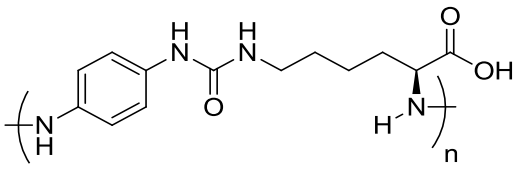
extracted with 0.1 M HCl aqueous solution. Organic part was washed with water and chloroform was removed under reduced pressure to obtain brownish liquid (1.40 g, 42%). ^{1}H NMR ($CDCl_3$): δ 4.05 (dd, *J*= 7.9, 4.5, 2H), 3.79 (s, 3H), 3.31 (t, *J*=6.5, 2H), 2.00-1.42 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 171.9, 126.8, 121.7, 57.2, 53.1, 42.6, 33.2, 30.9, 22.4

Synthesis of POL-A



Diamine **11** (1.00 g, 6.24 mmol) was dissolved in 20 ml DMF. To this solution phenylene diisocyanate **24** was added slowly and stirred at room temperature overnight. Resulting mixture was poured into distilled water and white precipitate was filtered off.

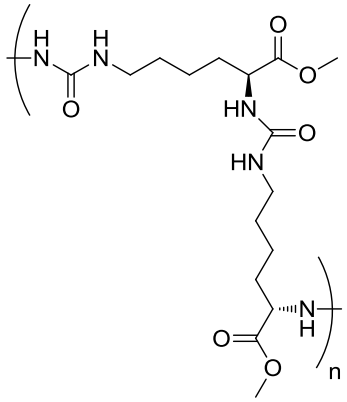
Synthesis of POL-B



L-lysine (0.73 g, 5.00 mmol) and triethylamine (2.02 g, 20.00 mmole) was dissolved in 45 ml DMF. To the mixture phenylene diisocyanate **24** was added and stirred about 60 hours at room temperature. The reaction mixture was poured into distilled

water and yellow precipitate was obtained. Precipitate was filtered out and washed with chloroform.

Synthesis of POL-C



L-lysine methyl ester **25** (1.00 g, 4.71 mmol) and pyridine (1.49 g, 18.84 mmol) was dissolved in 45 ml DMF. To the mixture L-lysine (0.76 g, 4.71 mmol) was added and stirred overnight at room temperature. The reaction mixture was poured into distilled water and yellow precipitate was obtained. Precipitate was washed with ethanol-methanol mixtıre and dried.

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APPENDICES

PART A: NMR SPECTRA

NMR spectra was recorded at Bruker Avance III Ultrashield 400 Hz using $CDCl_3$, and d_6-DMSO as solvents.

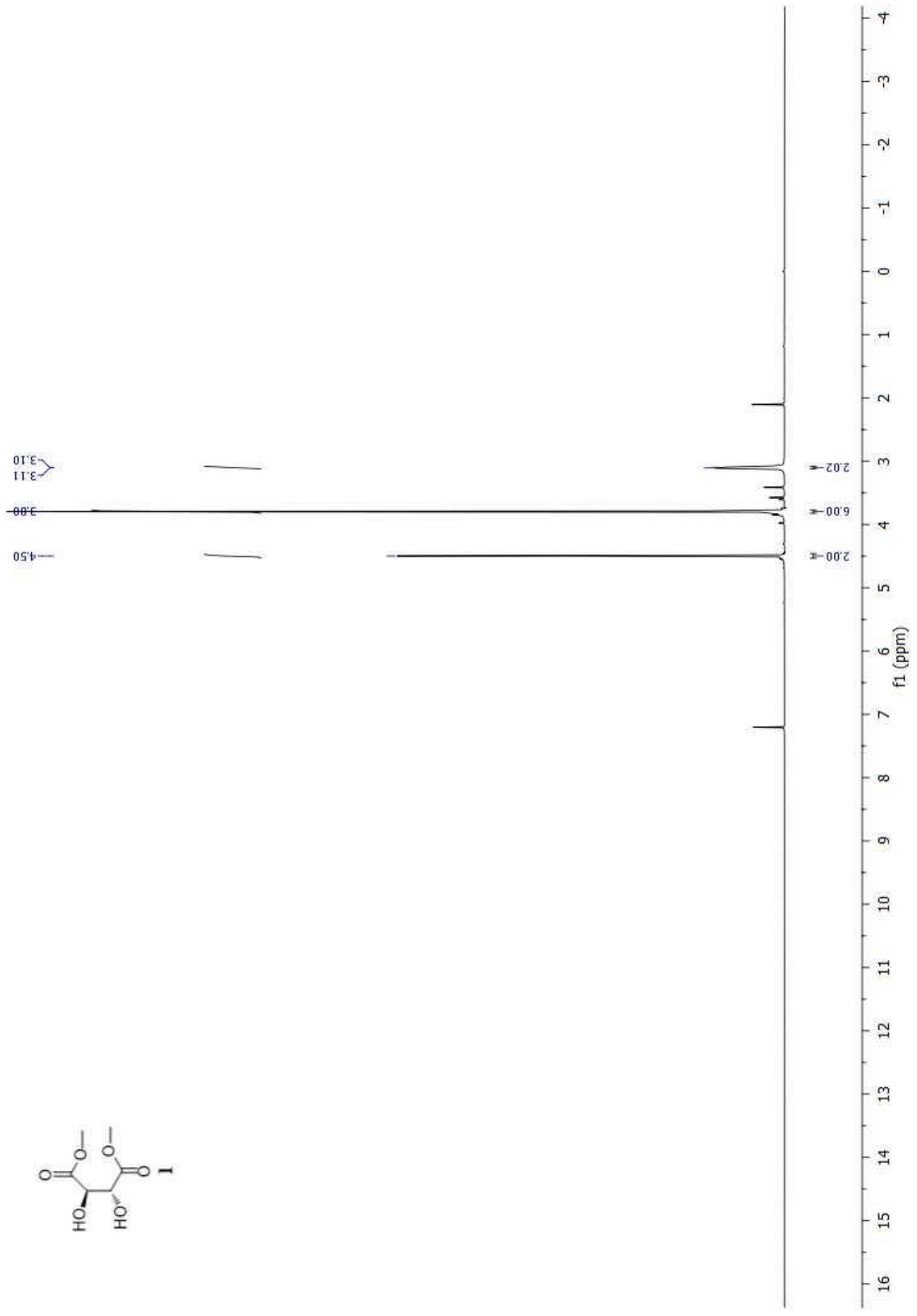

Figure 41. ^{1}H NMR spectrum of **1**

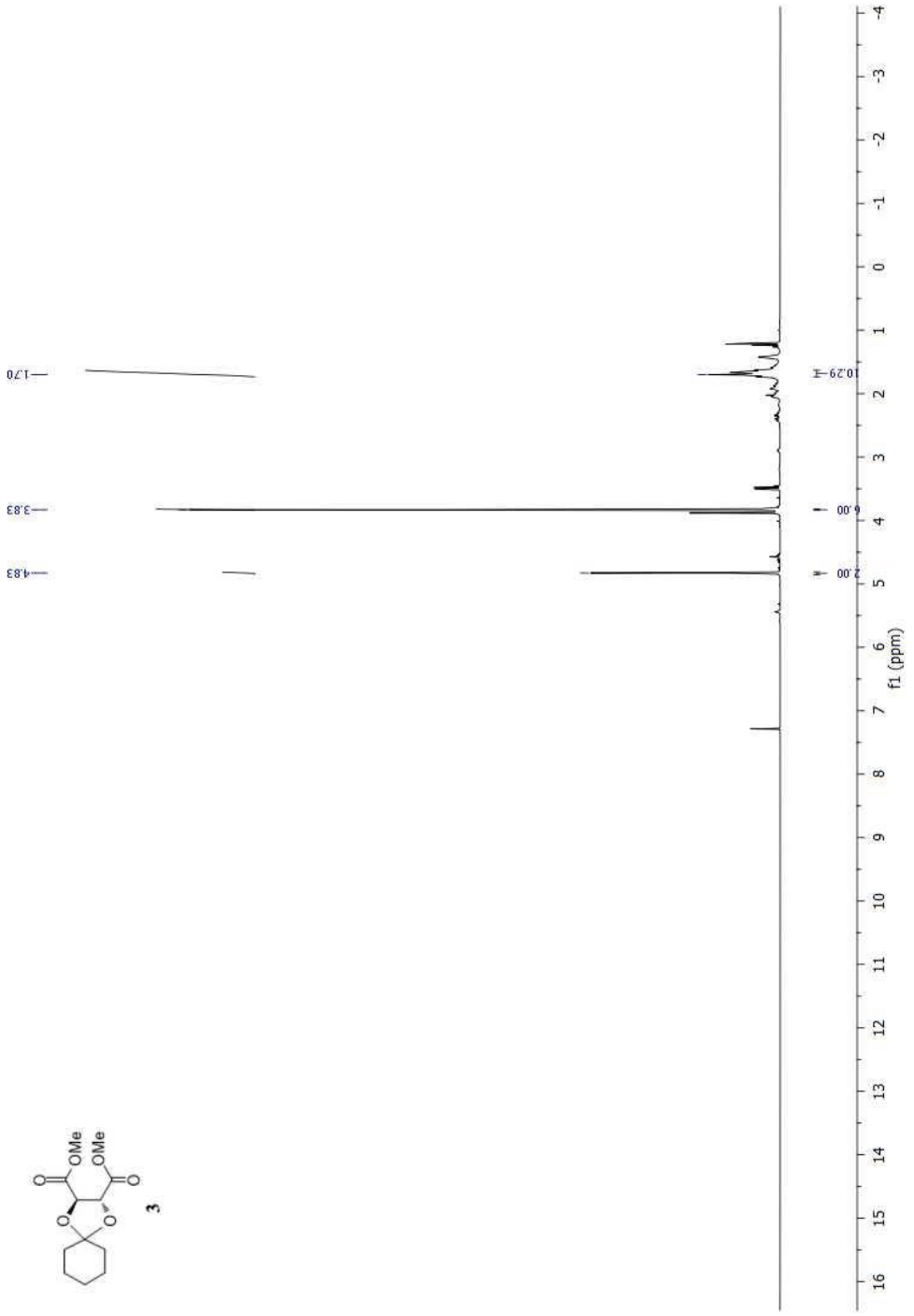

Figure 42. ^{1}H NMR spectrum of **3**

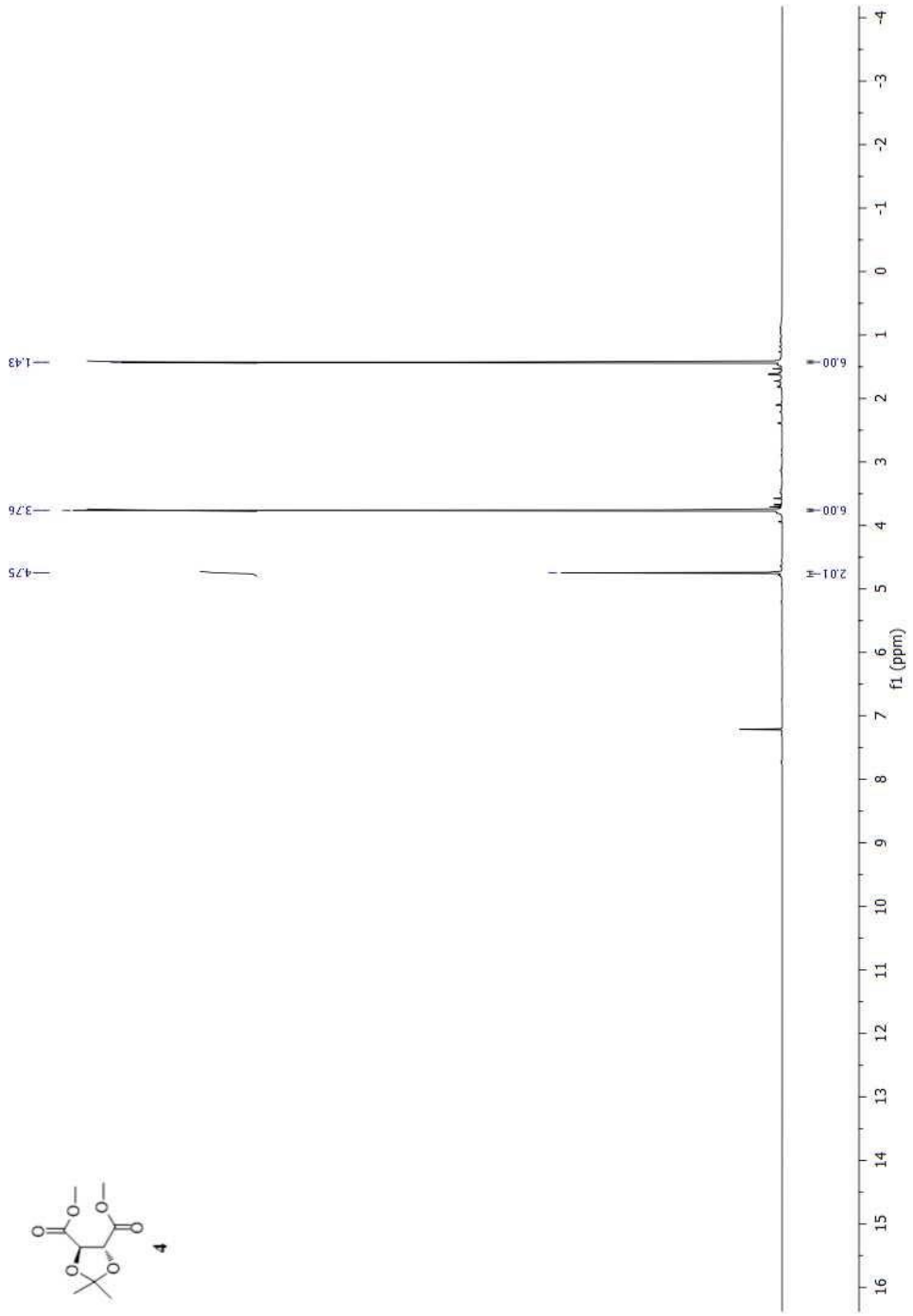

Figure 43. ^{1}H NMR spectrum of **4**

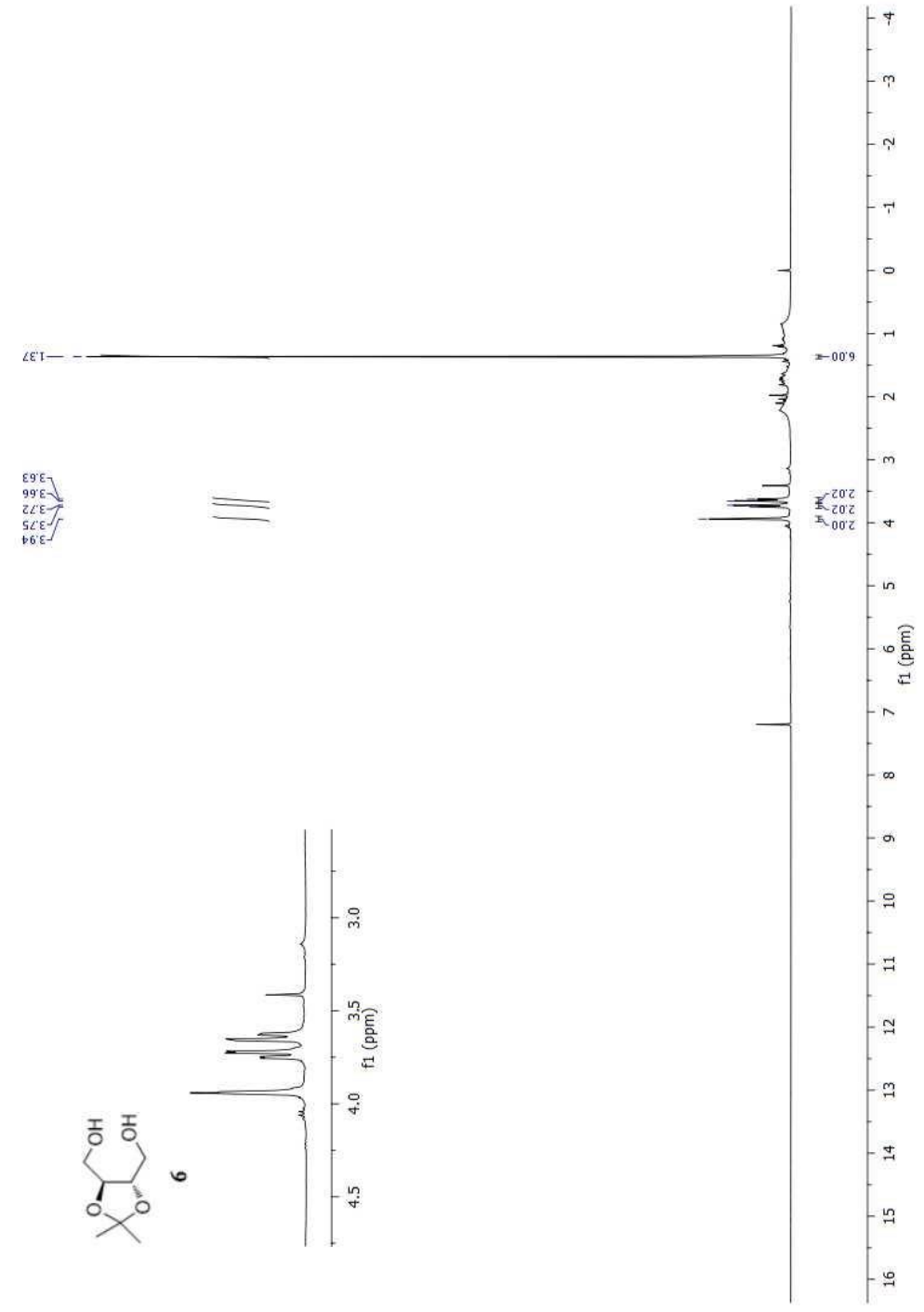

Figure 44. ^{1}H NMR spectrum of **6**

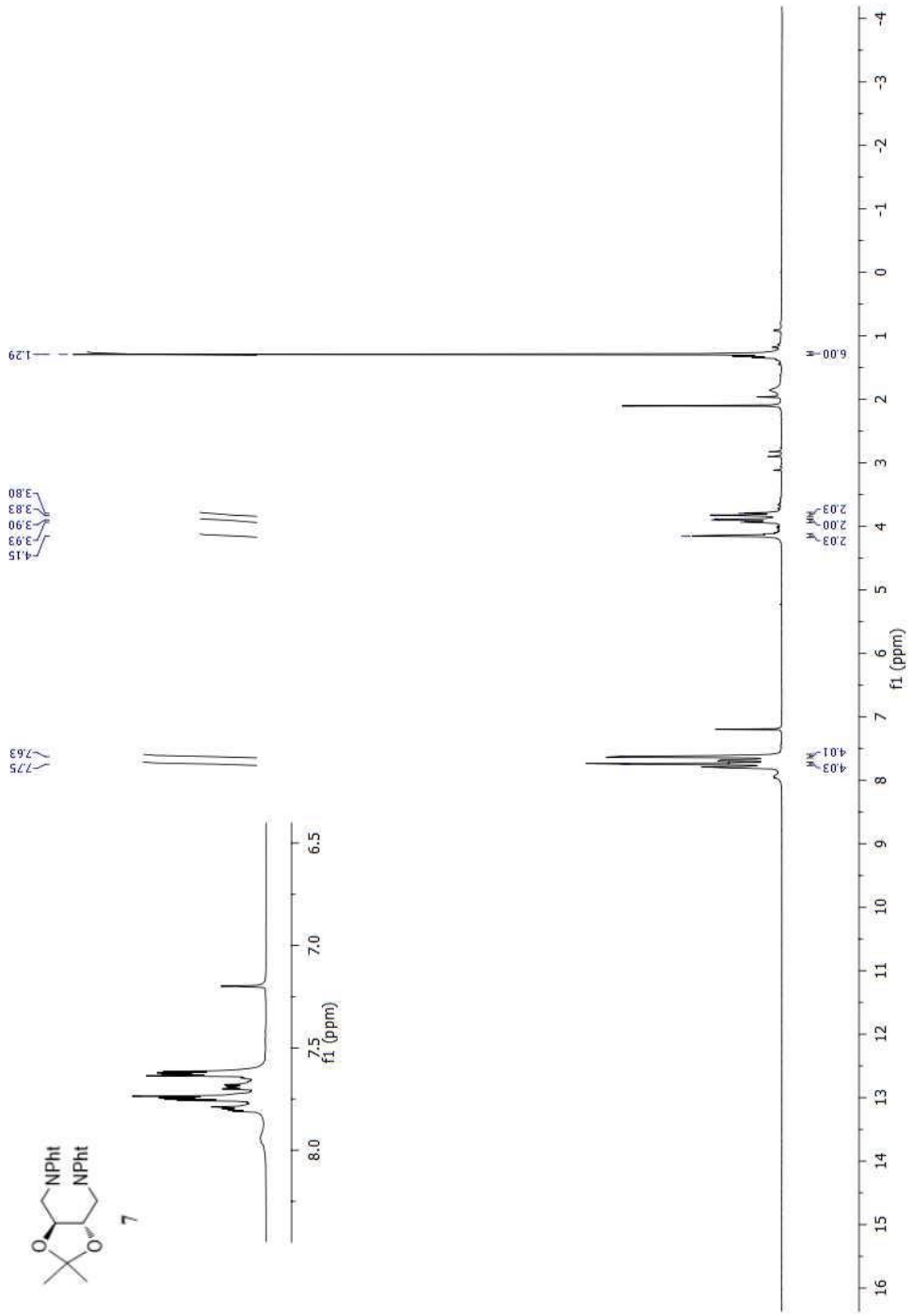

Figure 45. ^{1}H NMR spectrum of **7**

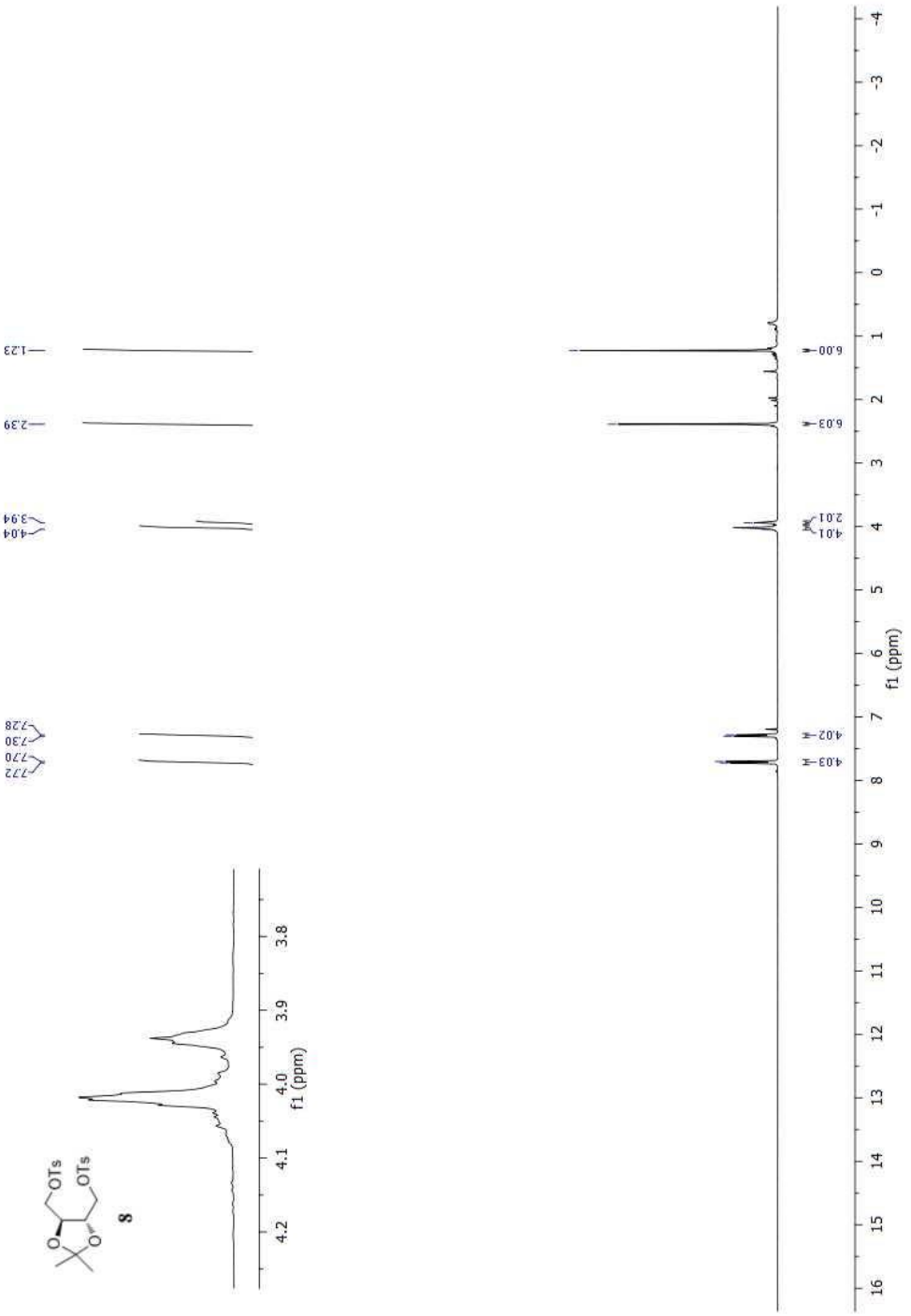

Figure 46. ^{1}H NMR spectrum of **8**

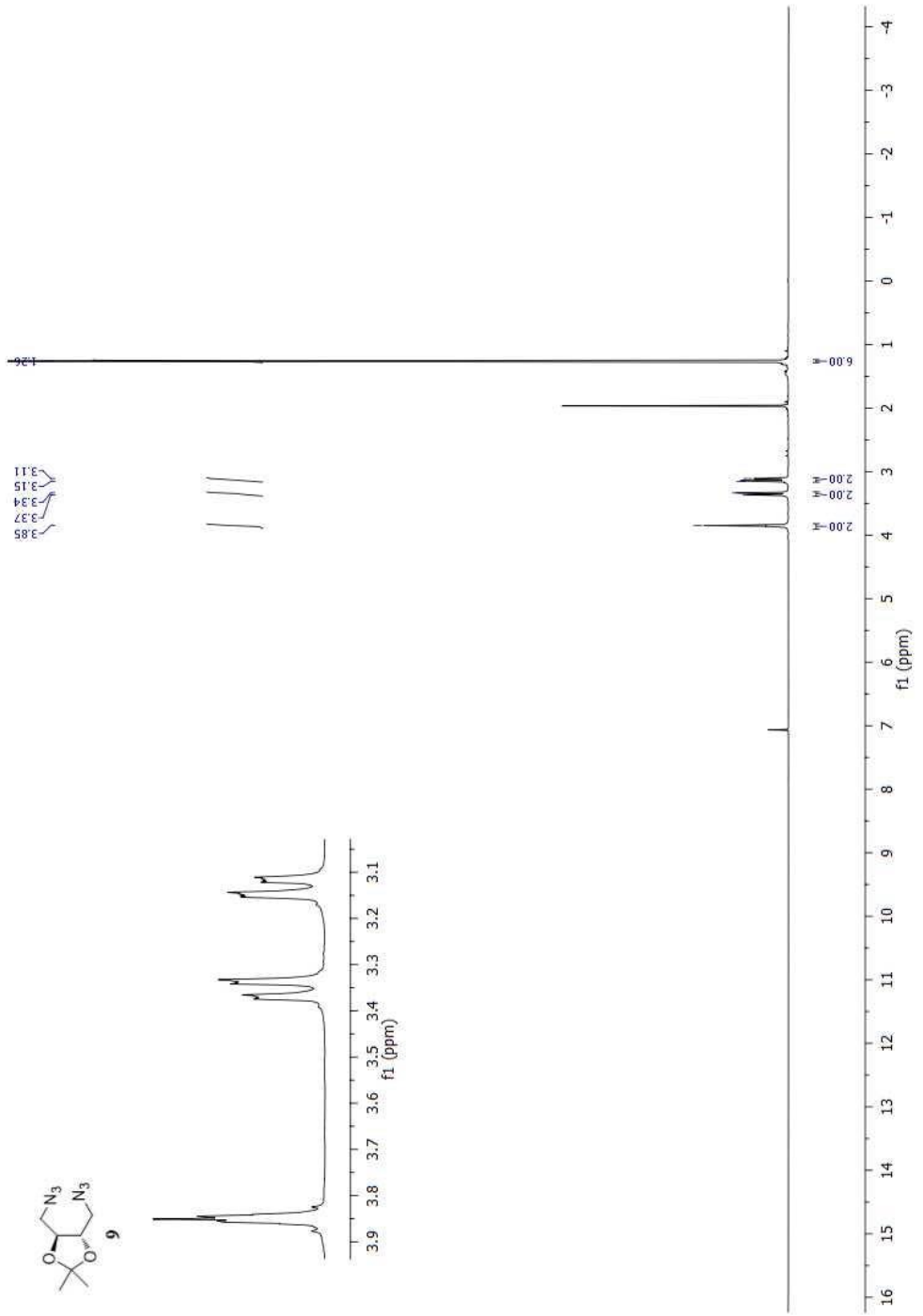

Figure 47. ^{1}H NMR spectrum of **9**

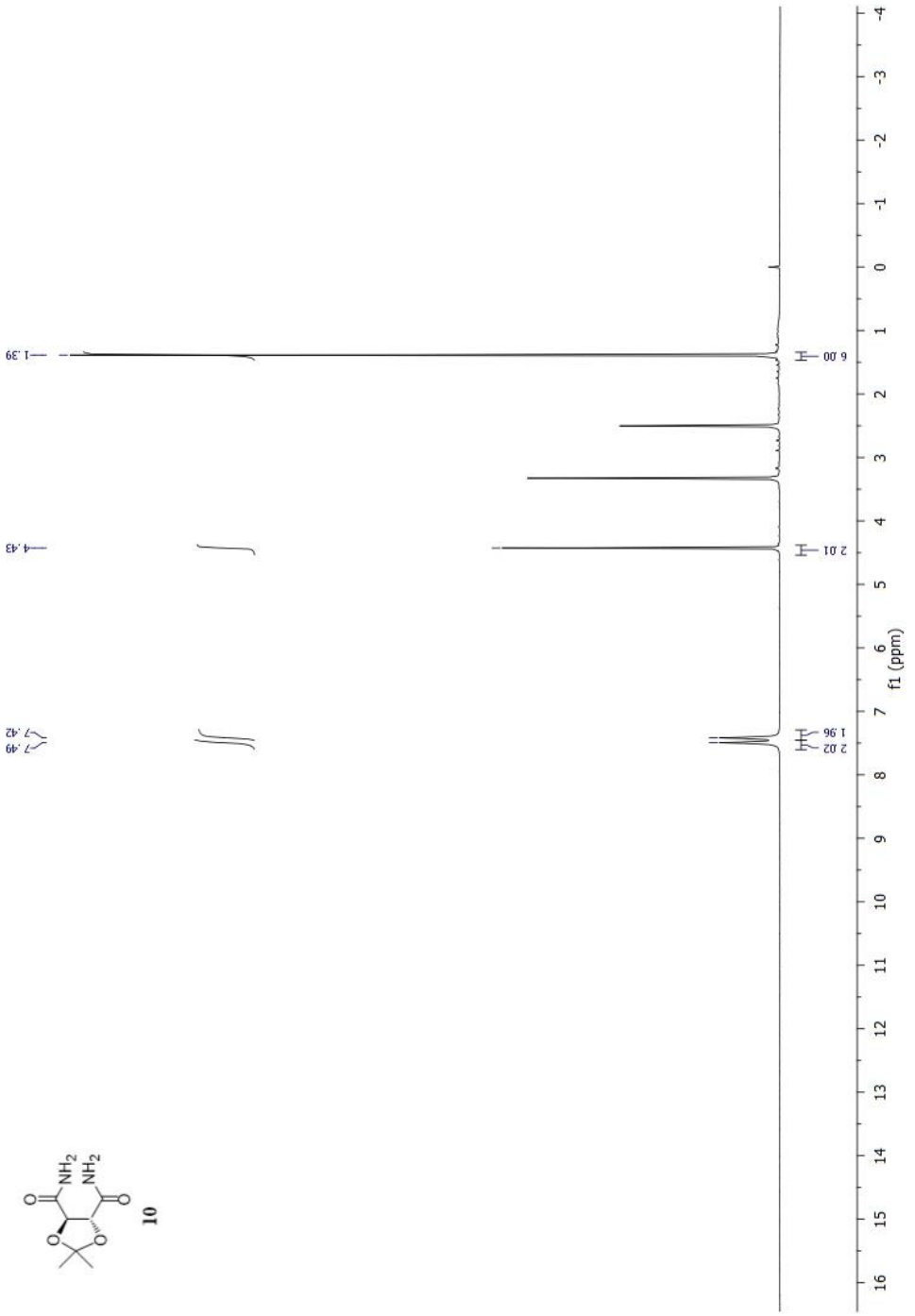

Figure 48. ^{1}H NMR spectrum of **10**

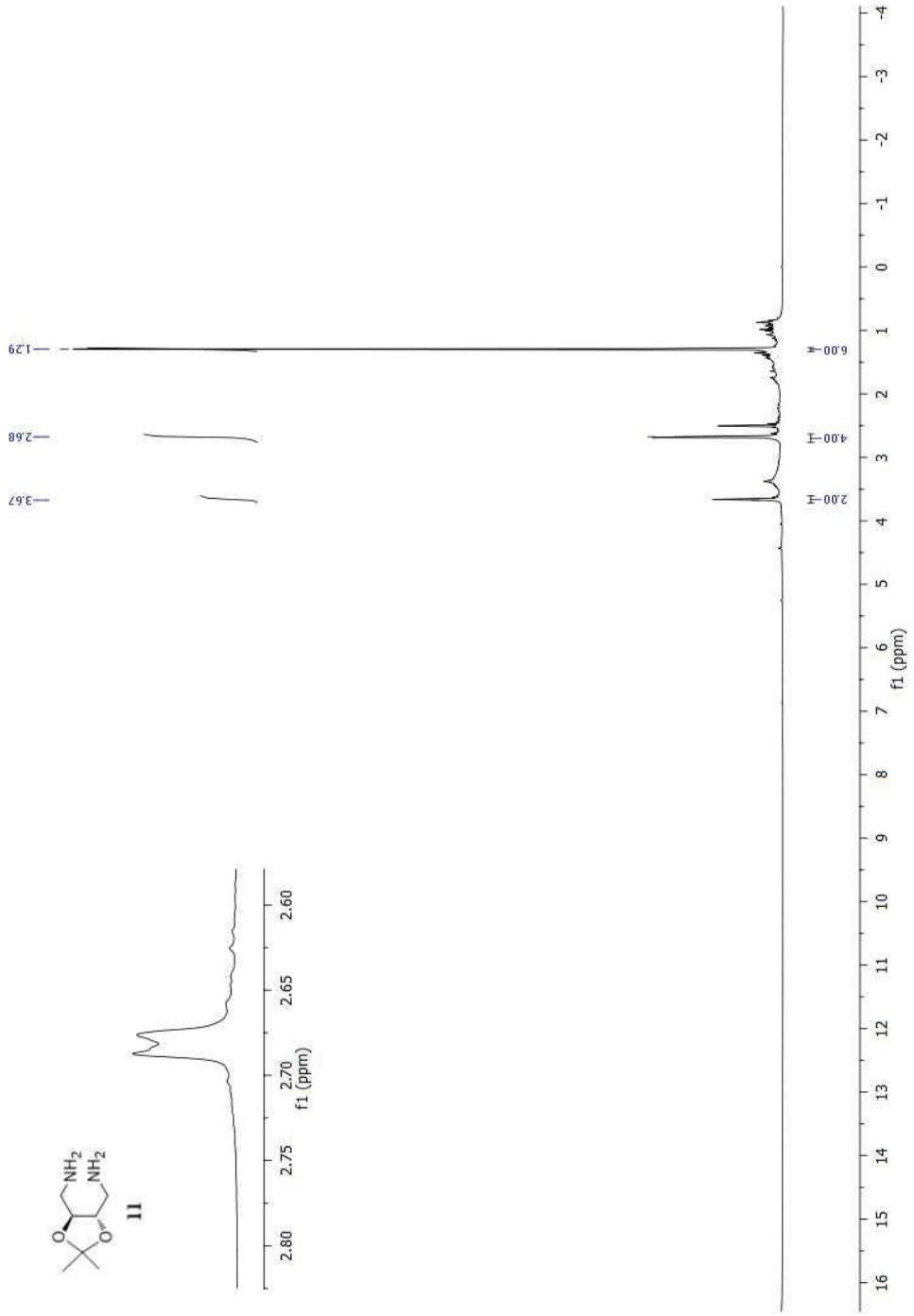

Figure 49. ^{1}H NMR spectrum of **11**

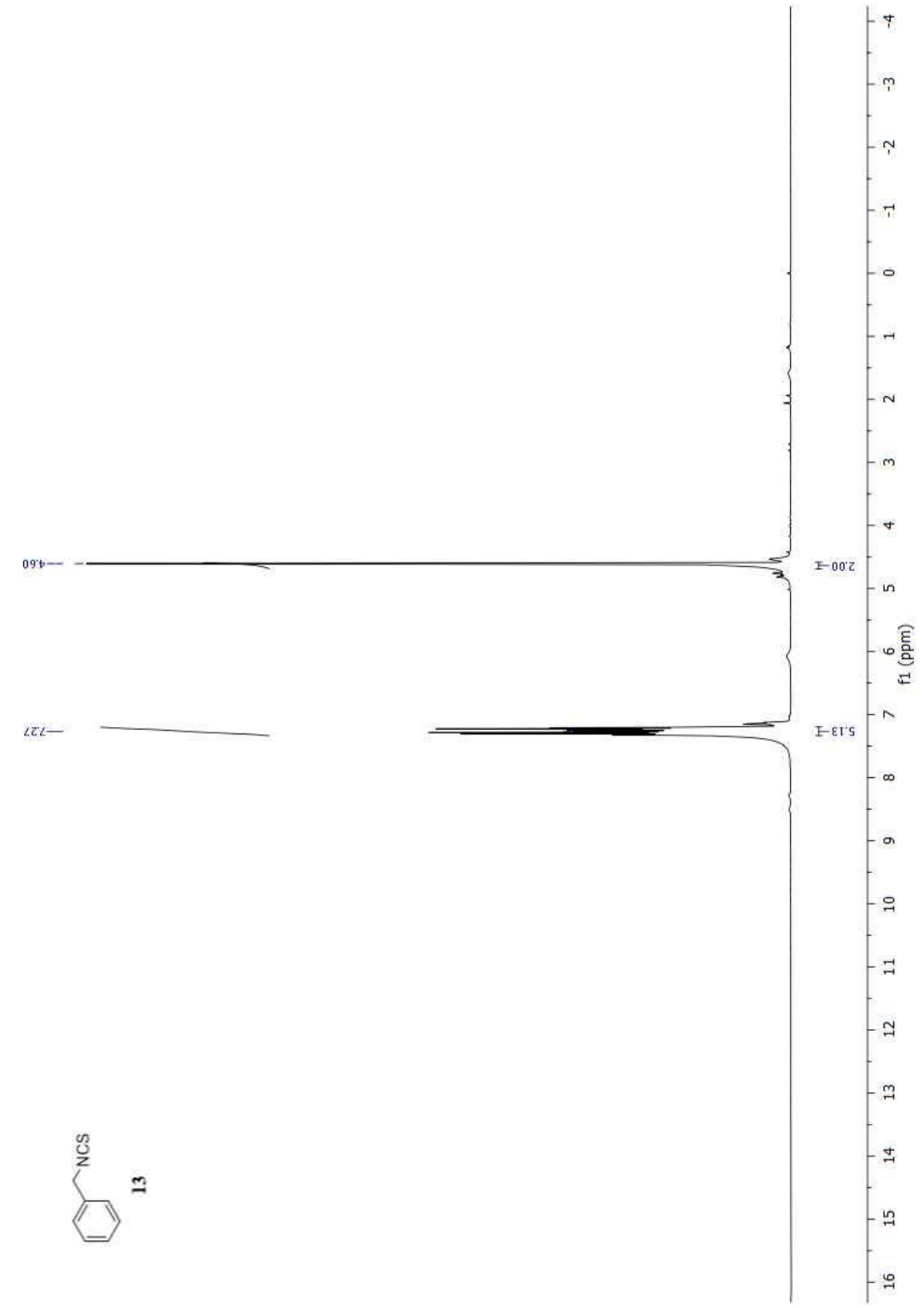

Figure 50. ^{1}H NMR spectrum of **13**

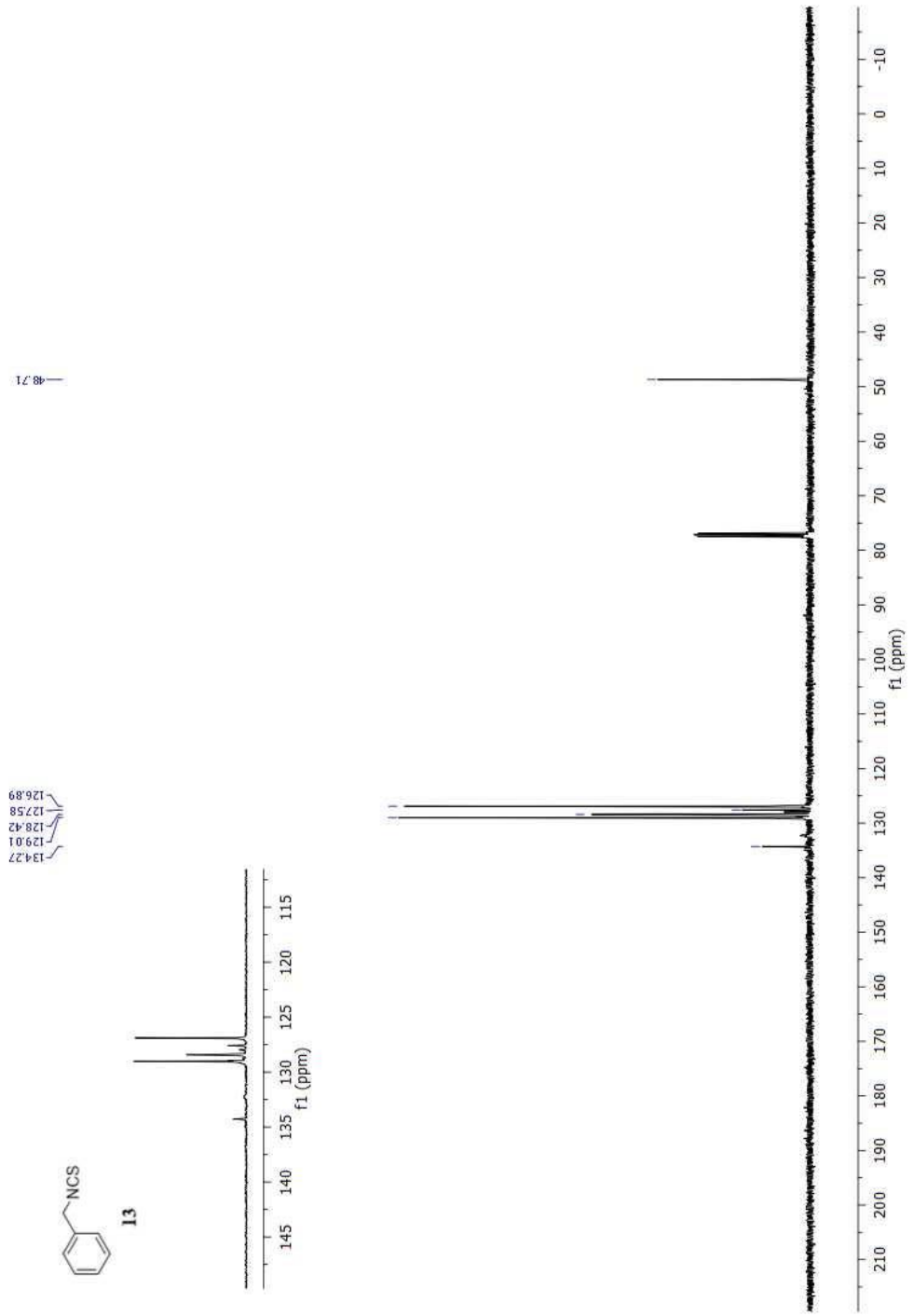

Figure 51. ^{13}C NMR spectrum of **13**

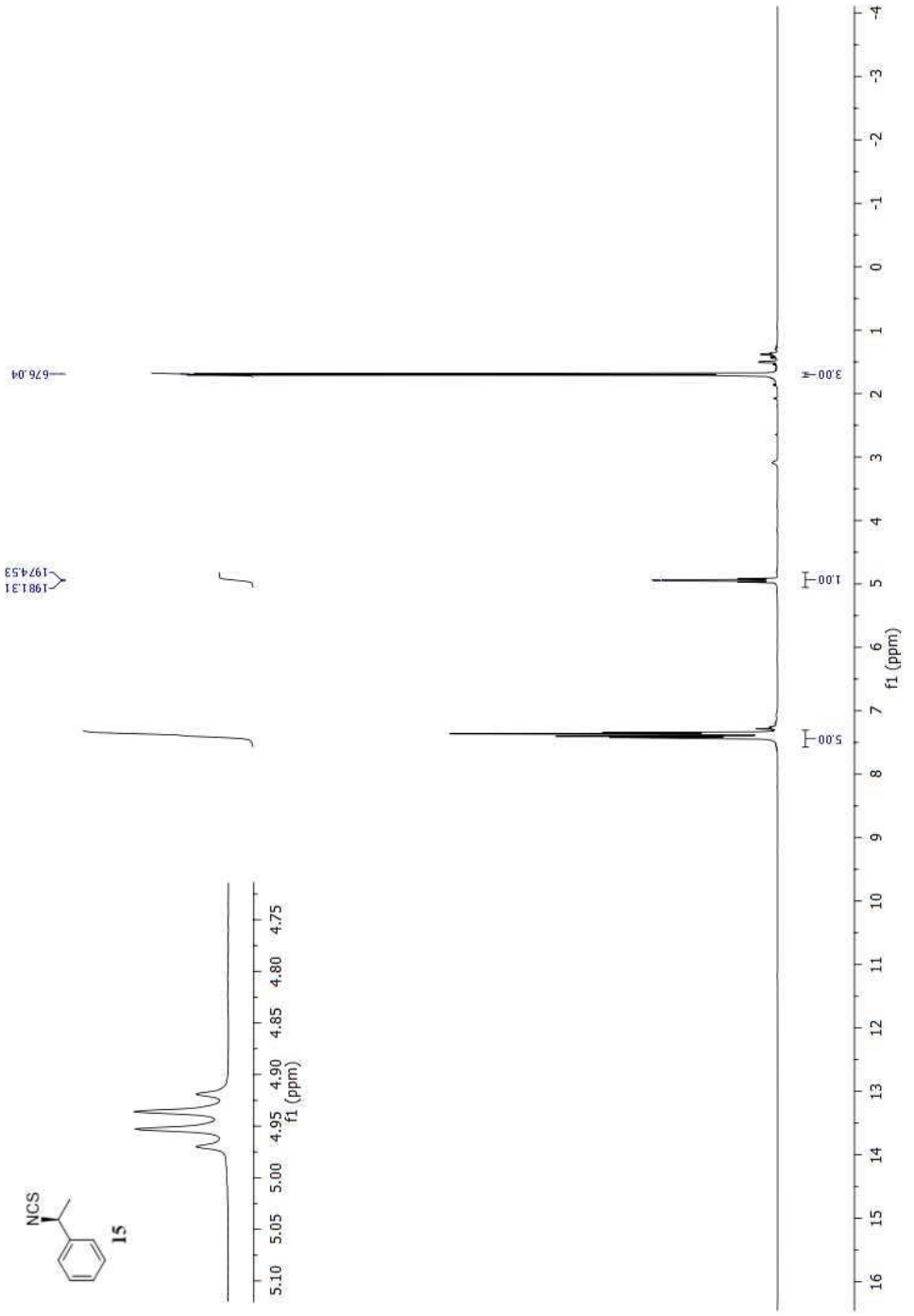

Figure 52. ^{1}H NMR spectrum of **15**

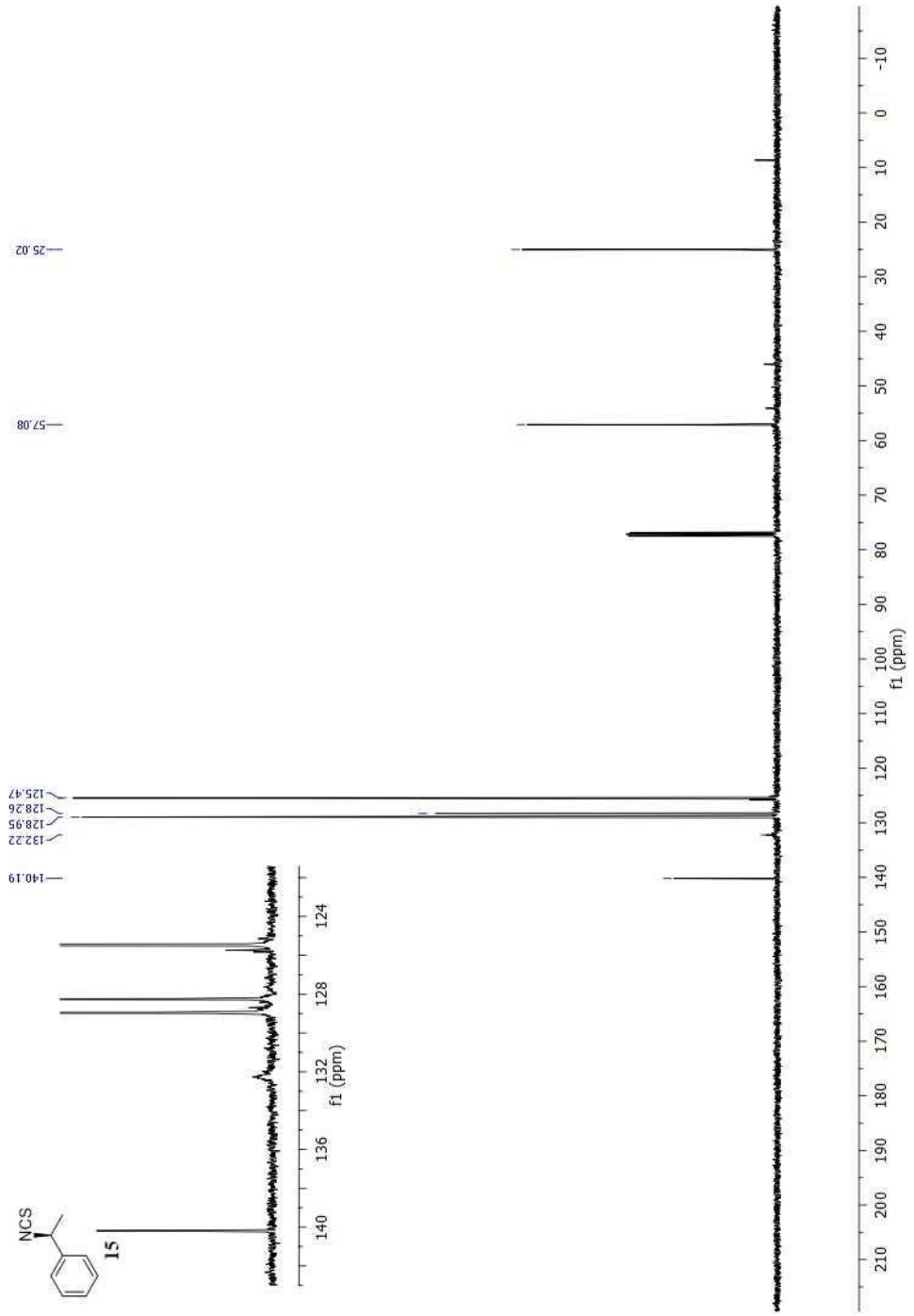

Figure 53. ^{13}C NMR spectrum of **15**

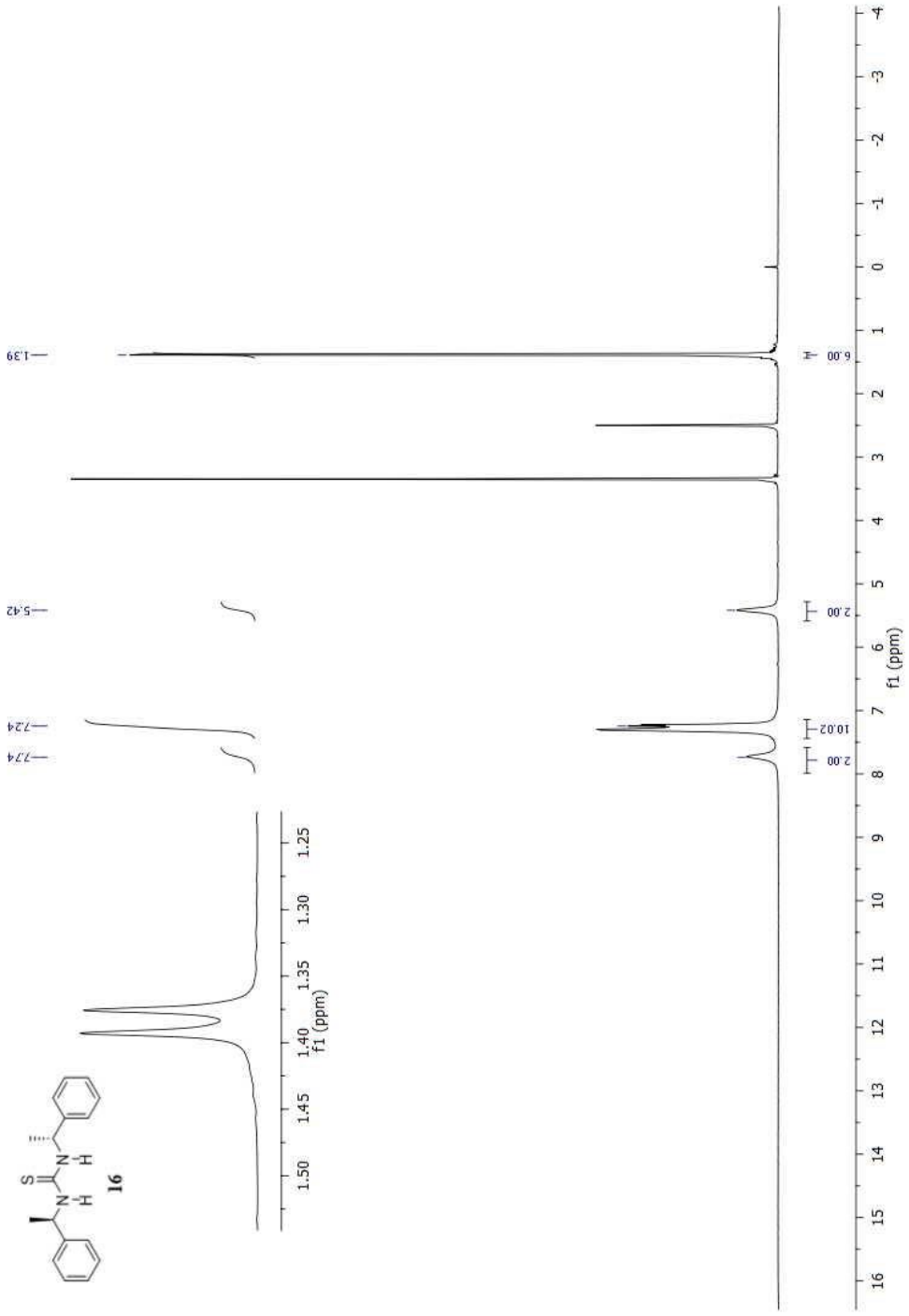

Figure 54. ^{1}H NMR spectrum of **16**

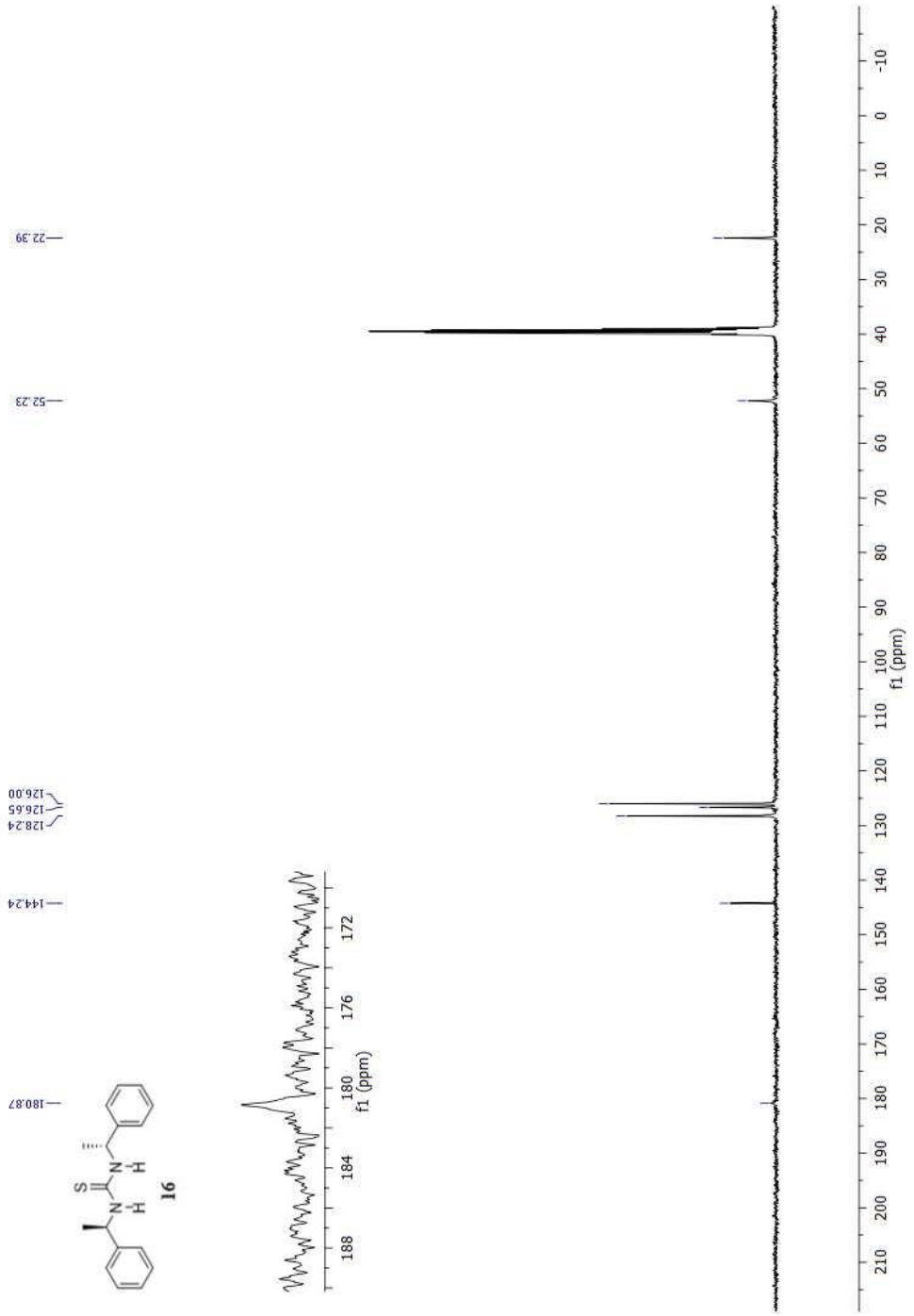

Figure 55. ^{13}C NMR spectrum of **16**

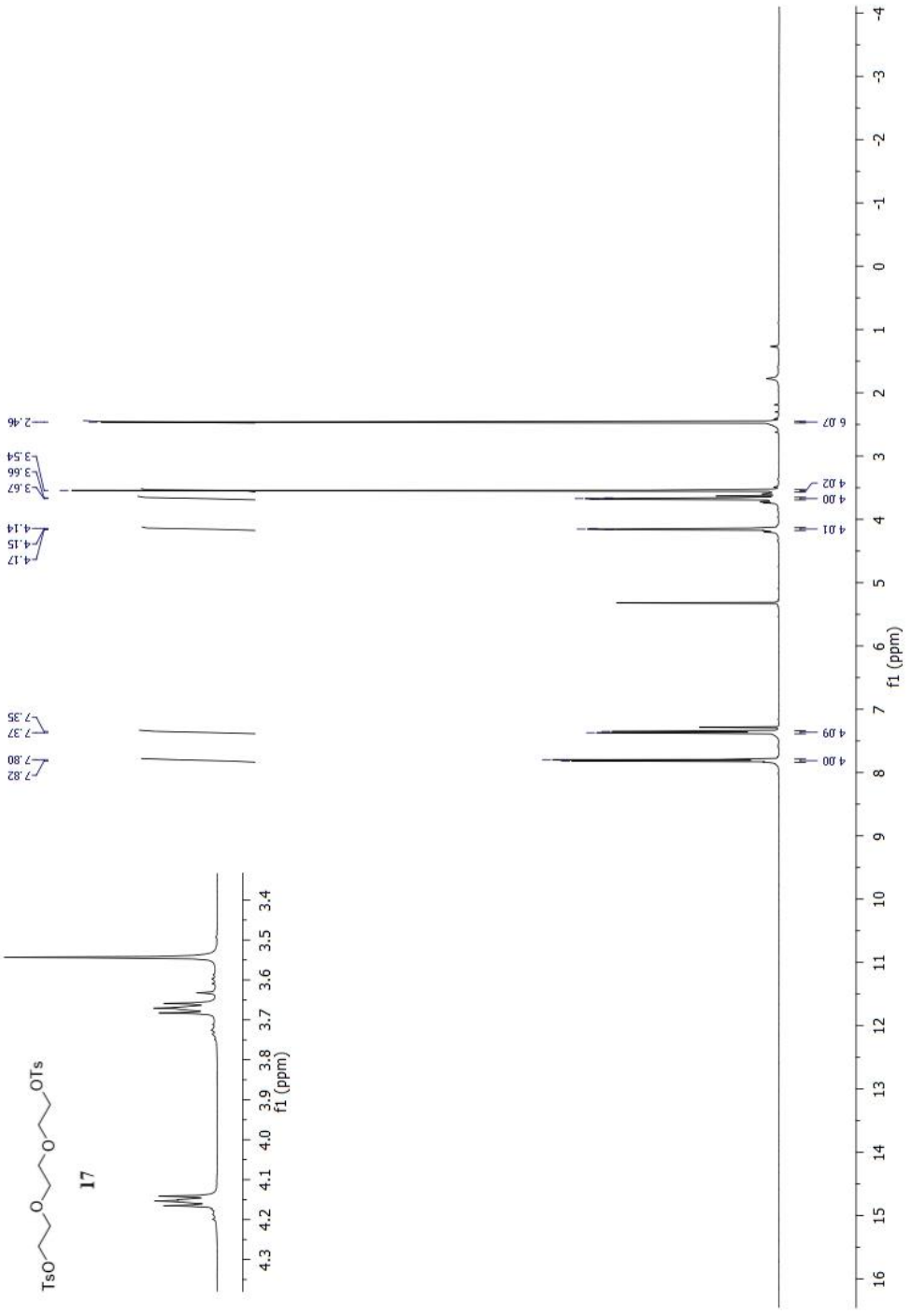

Figure 56. ^{1}H NMR spectrum of **17**

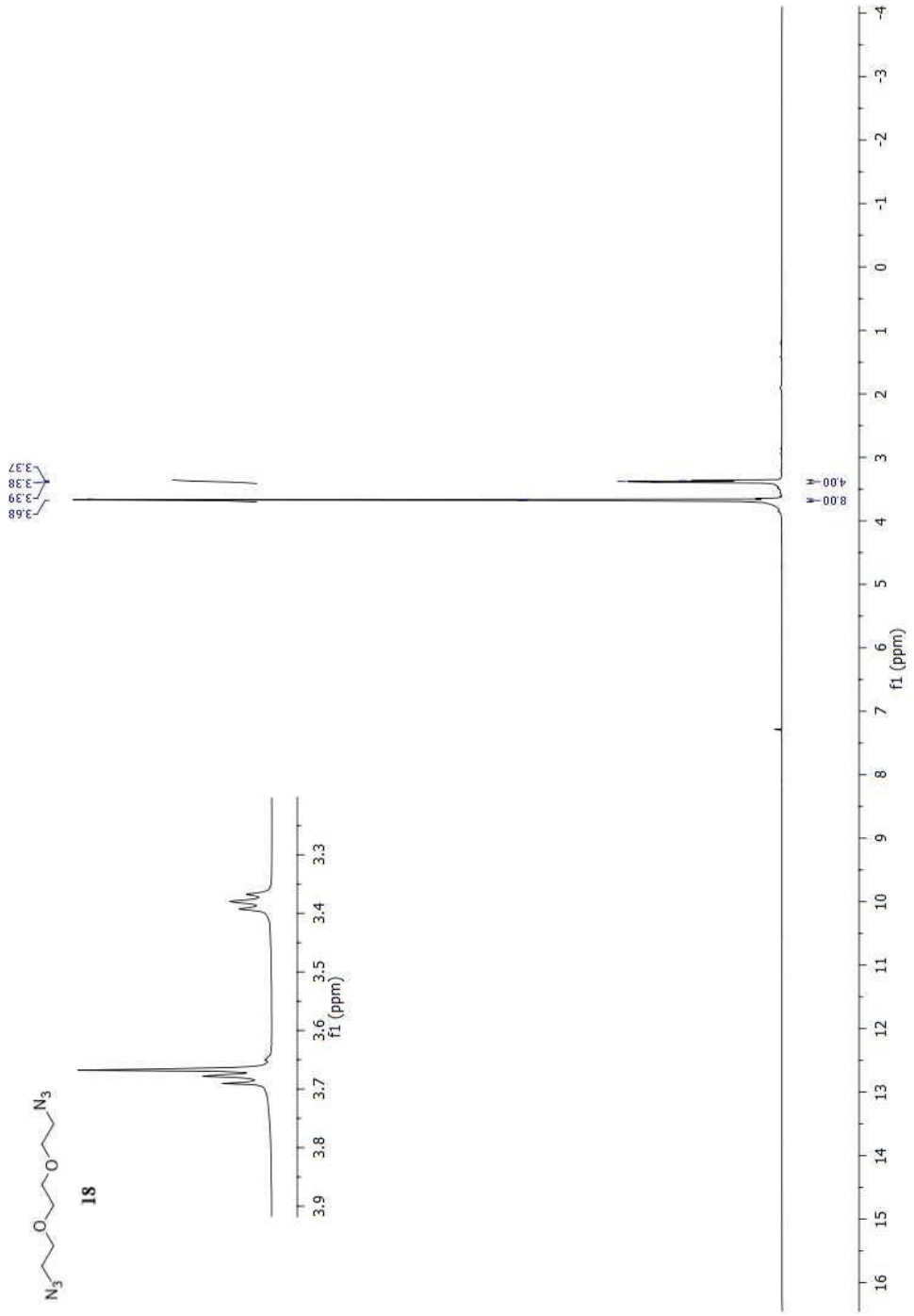

Figure 57. ^{1}H NMR spectrum of **18**

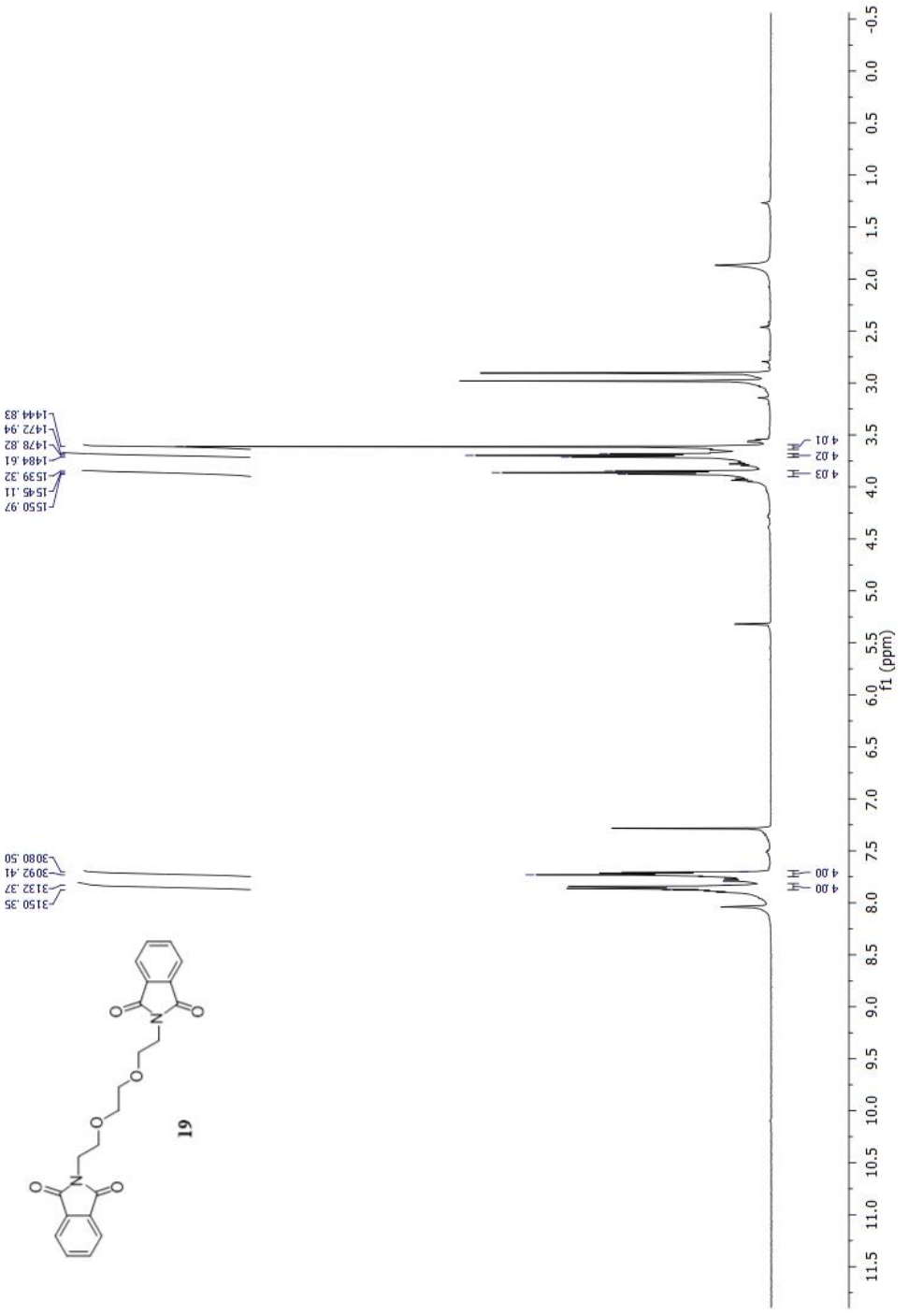

Figure 58. ^{1}H NMR spectrum of **19**

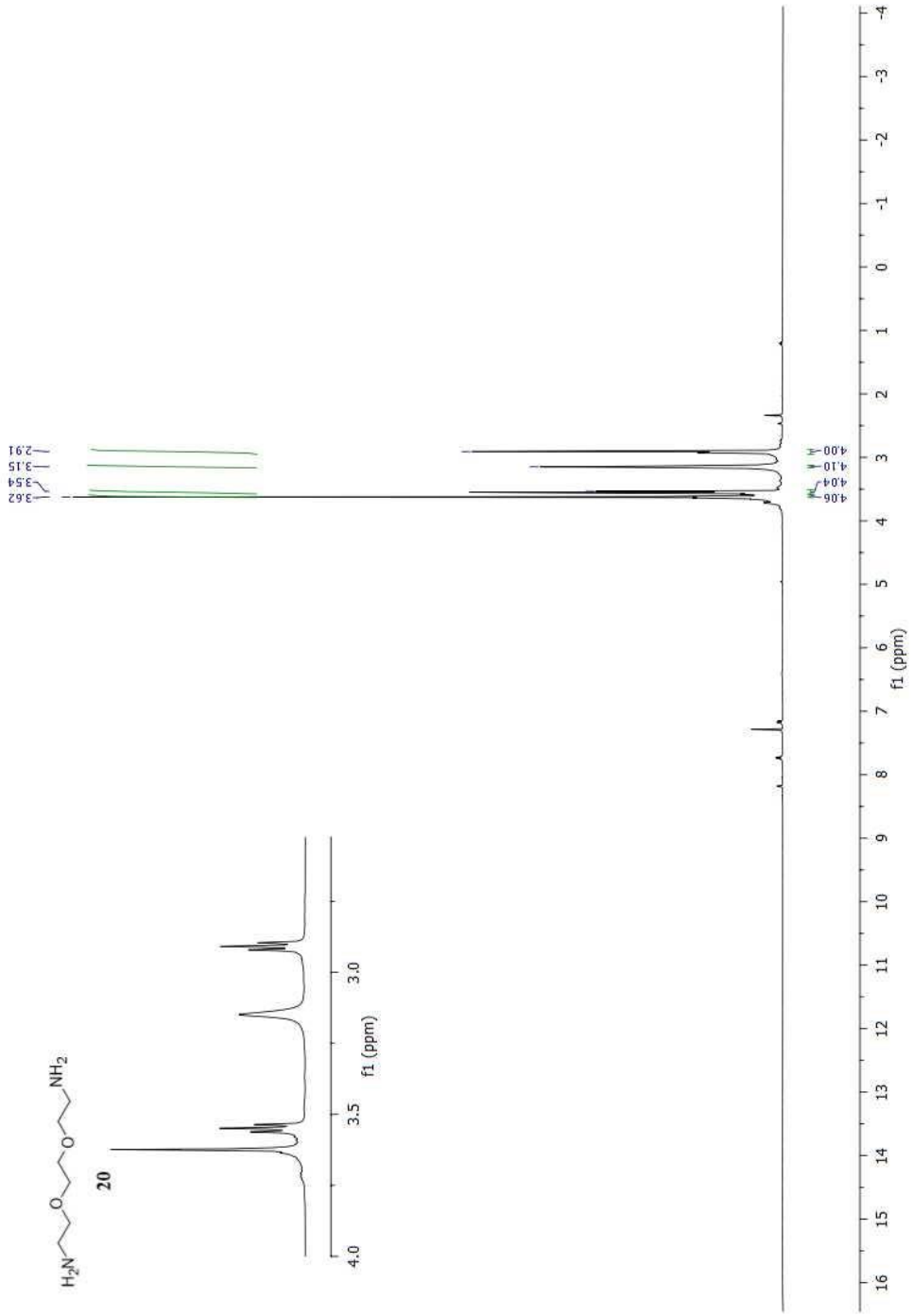

Figure 59. ^{1}H NMR spectrum of **20**

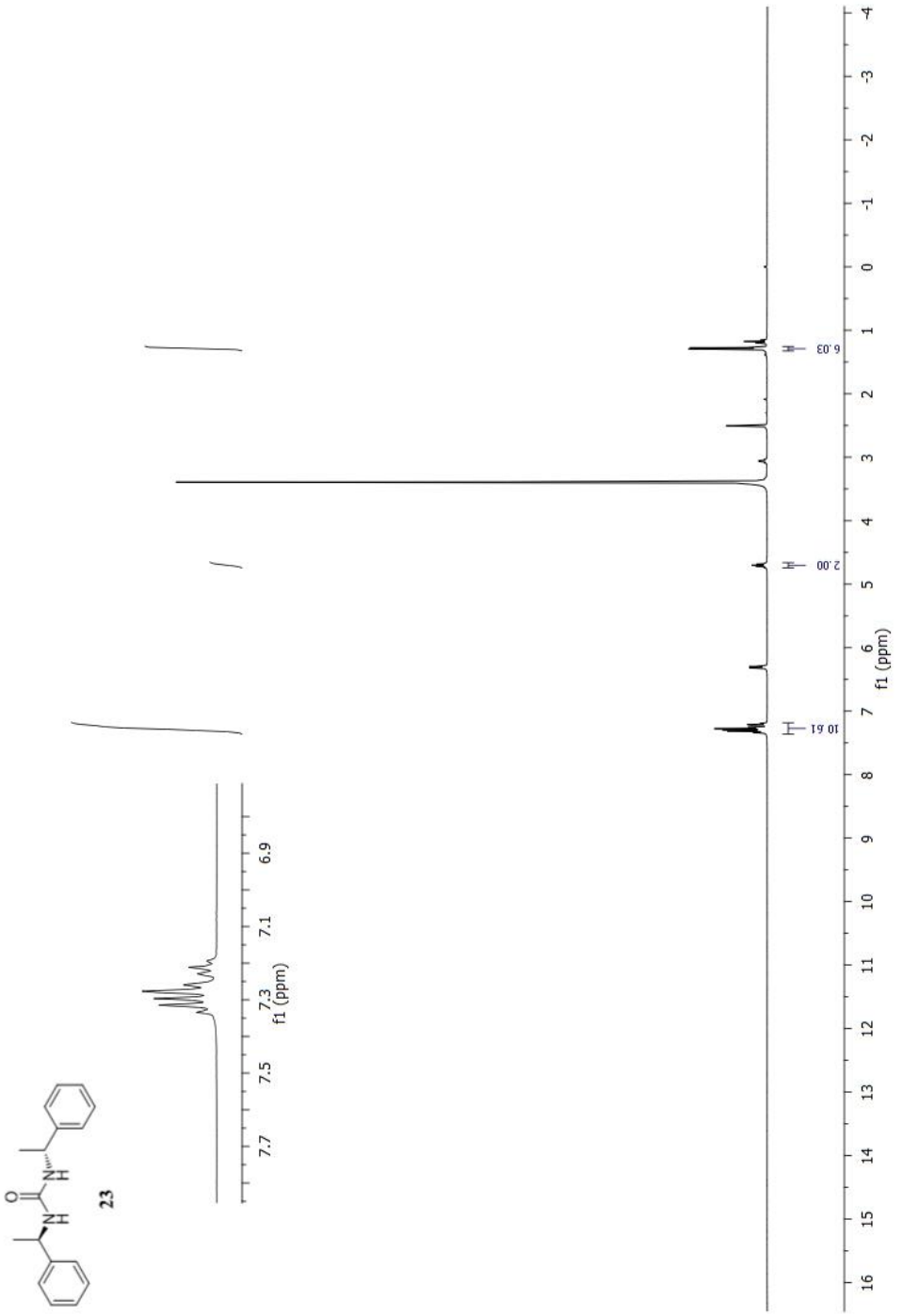

Figure 60. ^{1}H NMR spectrum of **23**

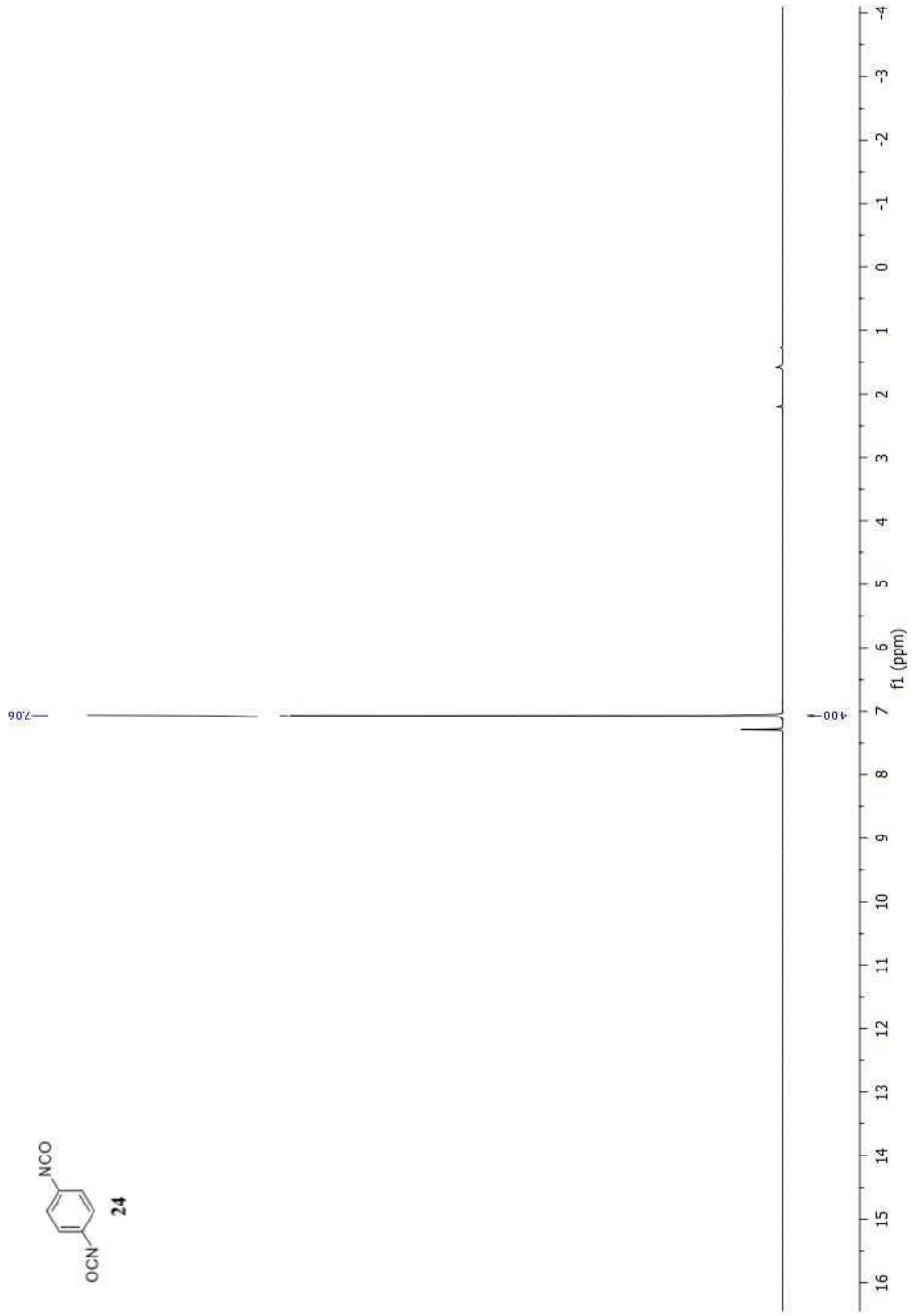

Figure 61. ^{1}H NMR spectrum of **24**

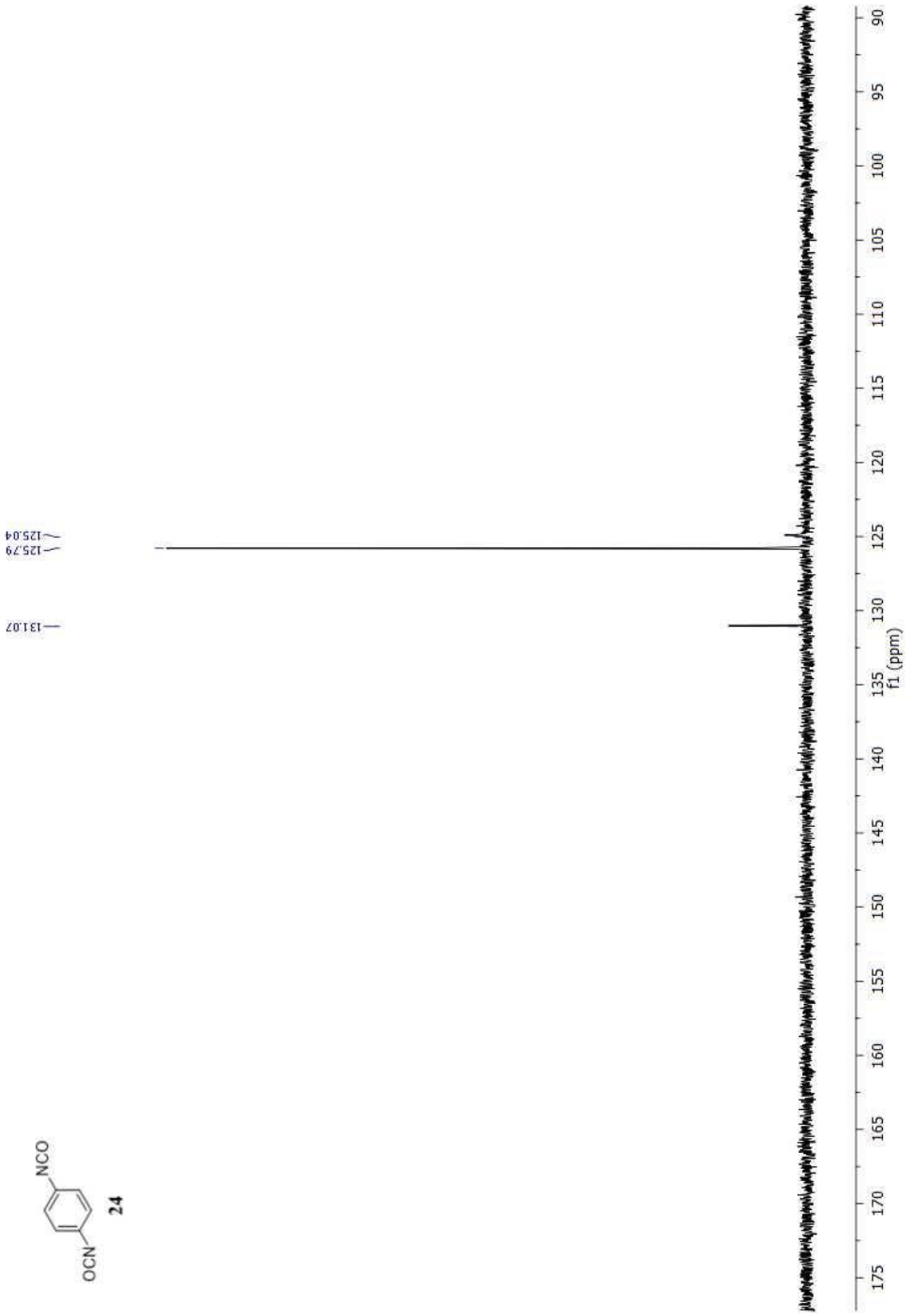

Figure 62. ^{13}C NMR spectrum of **24**

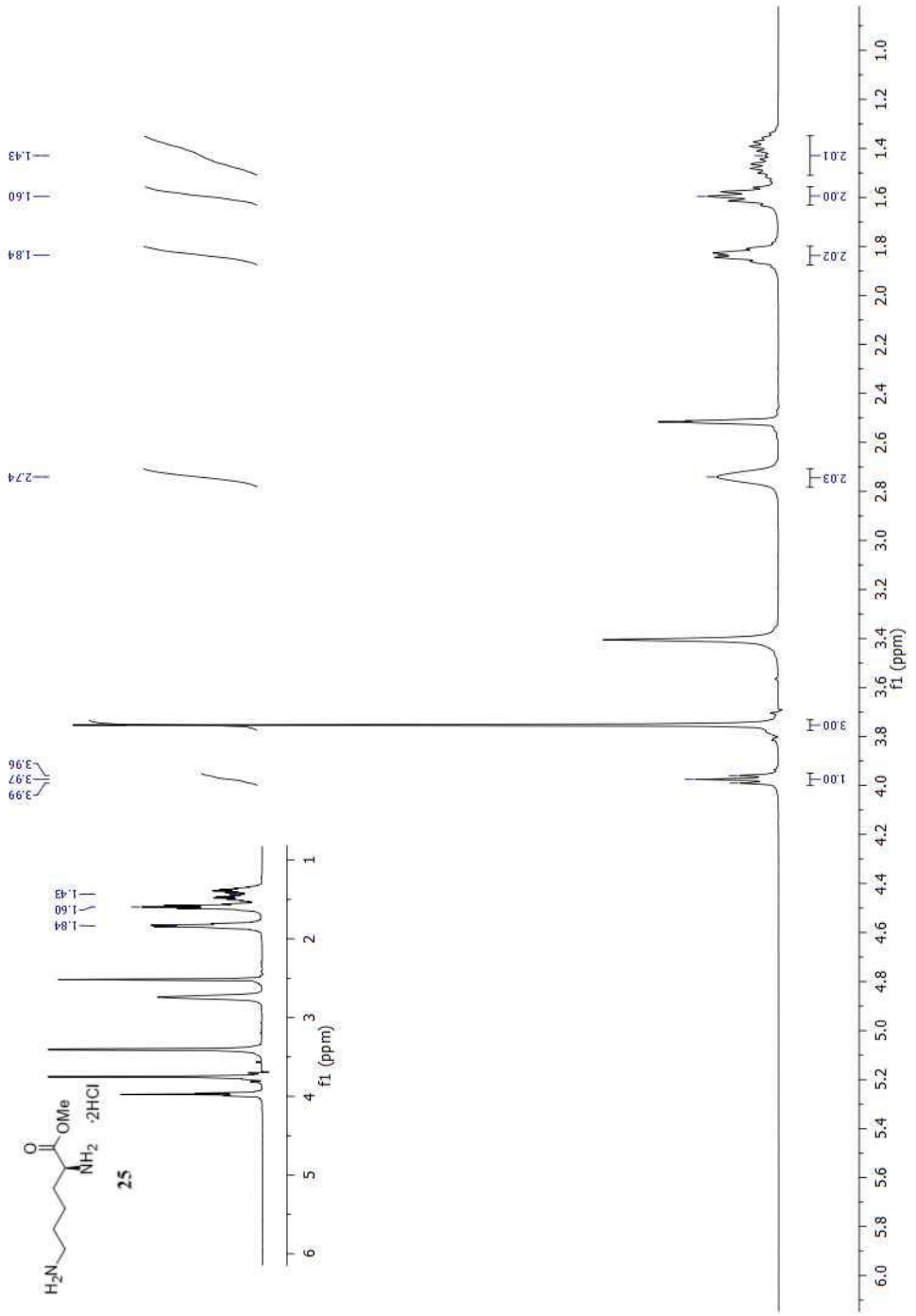

Figure 63. ^{1}H NMR spectrum of **25**

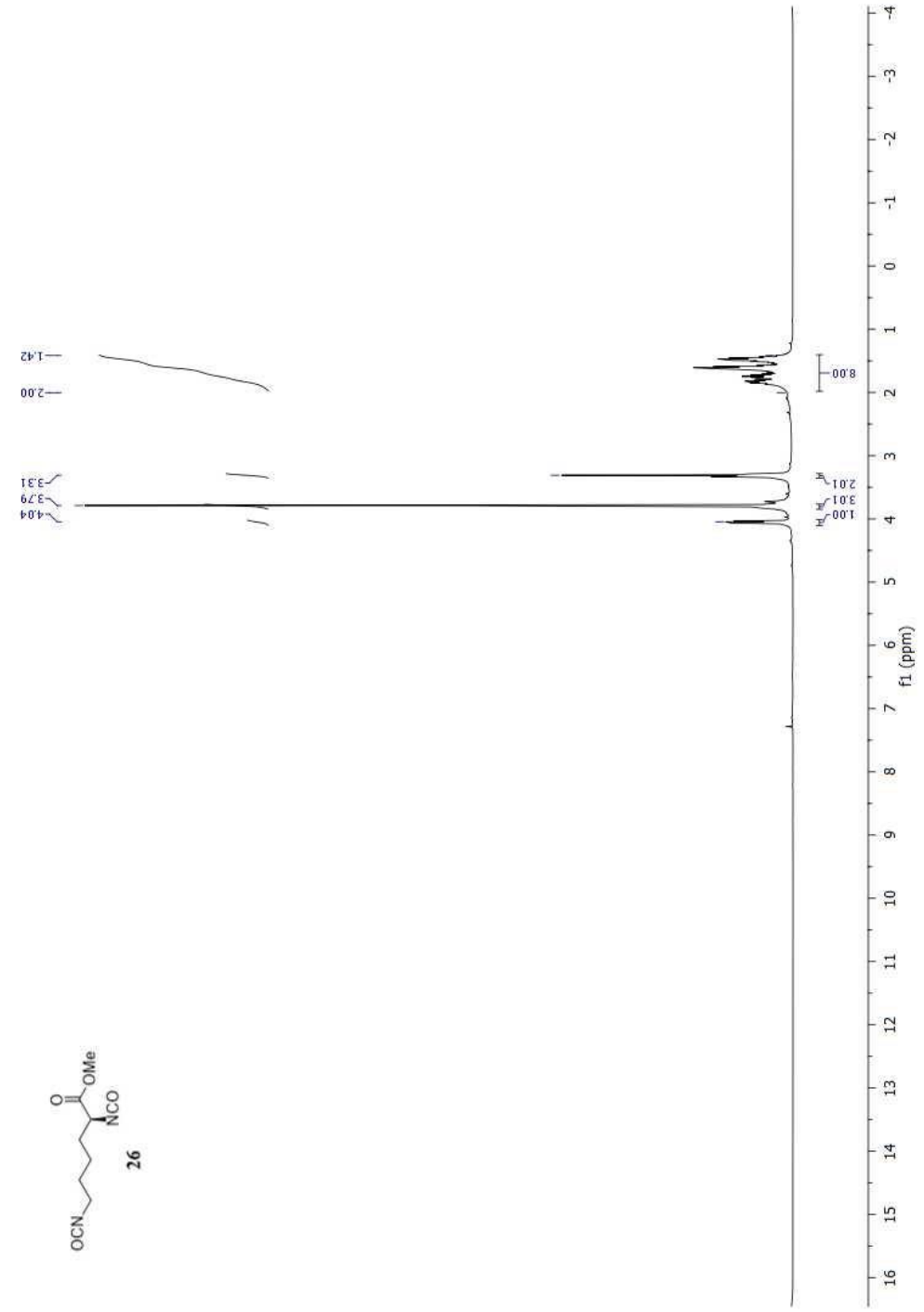

Figure 64. ^{1}H NMR spectrum of **26**

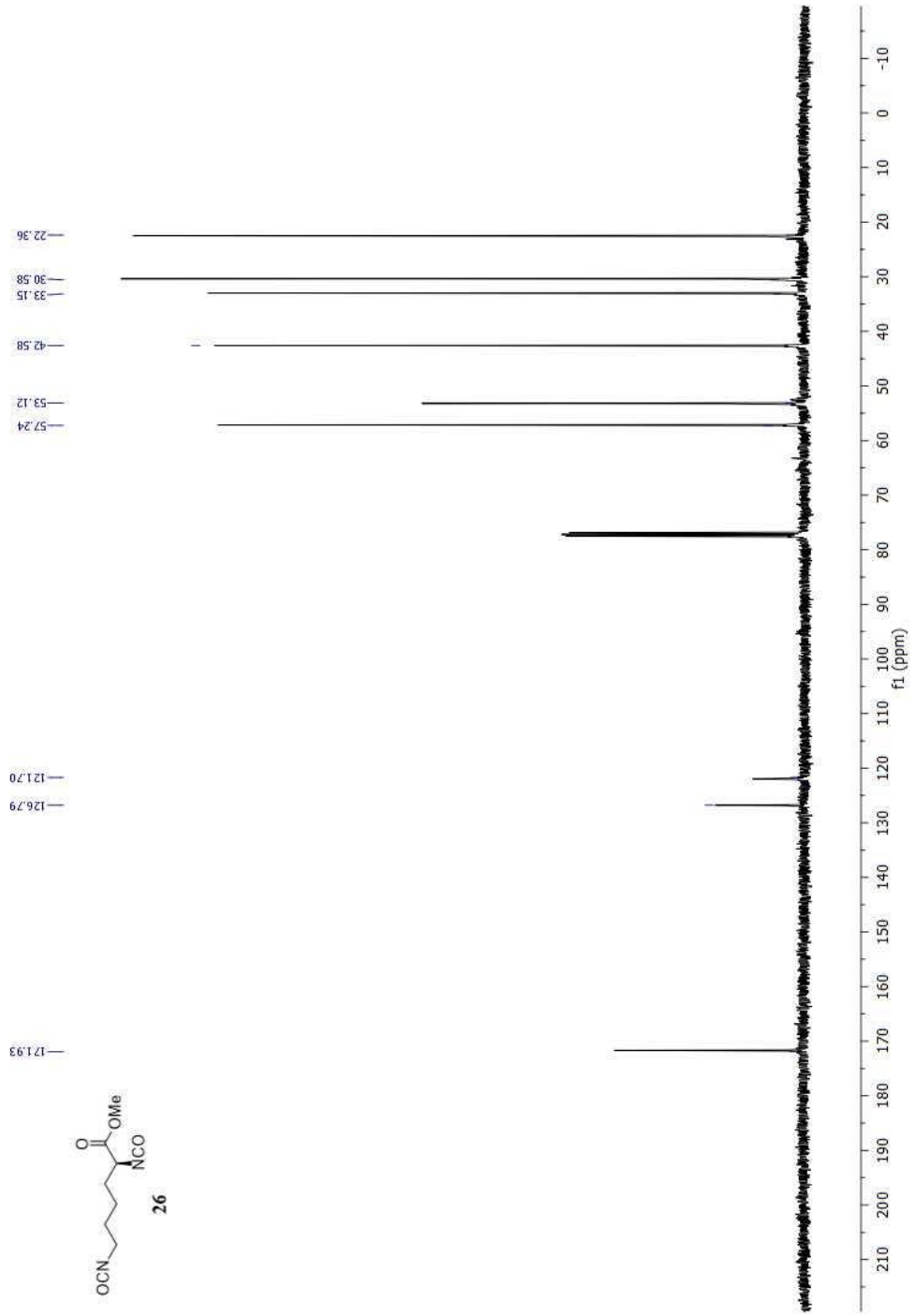

Figure 65. ^{13}C NMR spectrum of **26**

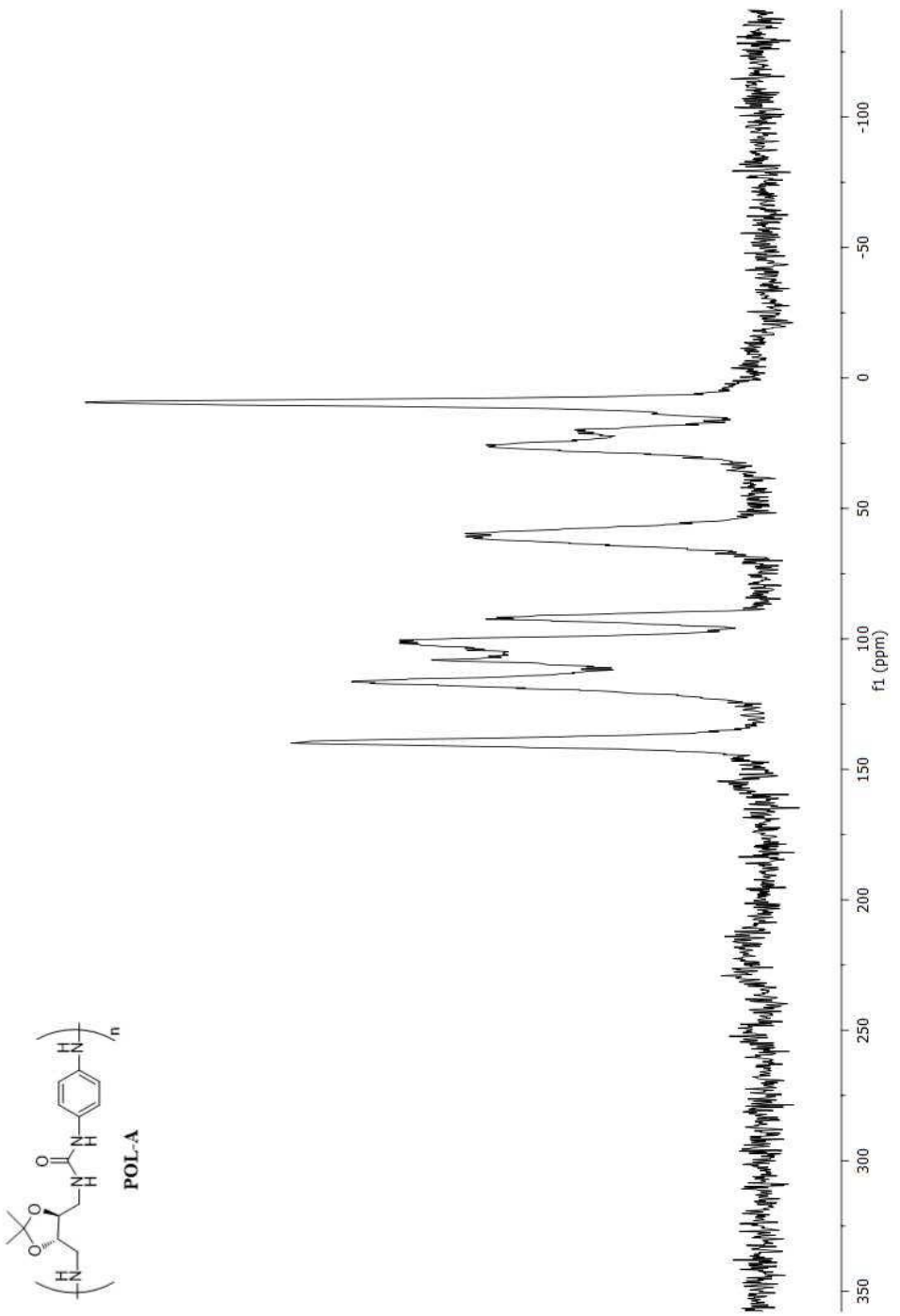

Figure 66. ^{13}C Solid State NMR spectrum of **POL-A**

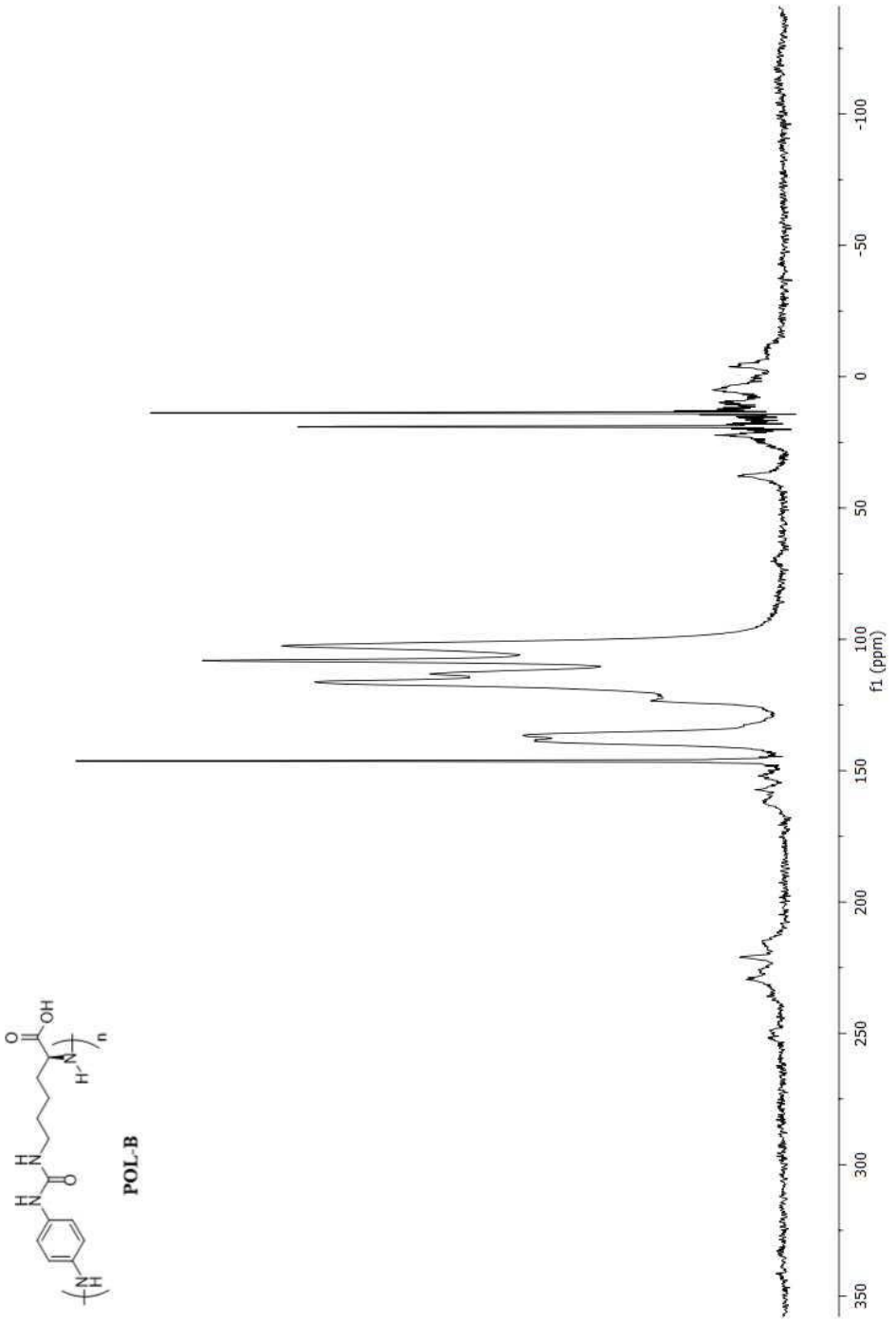

Figure 67. ^{13}C Solid State NMR spectrum of **POL-B**

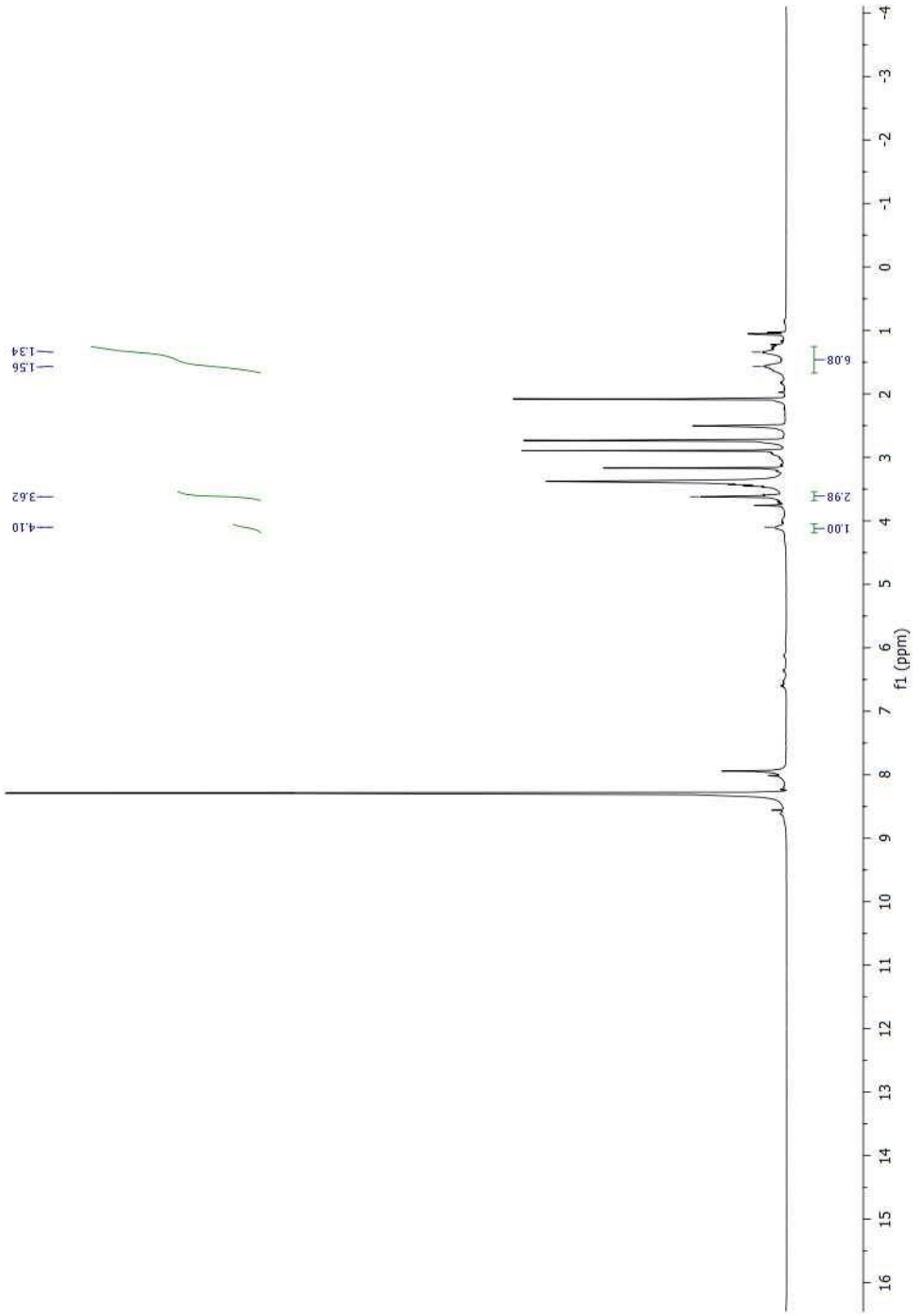

Figure 68. ^{1}H NMR spectrum of **POL-C**

PART B: IR SPECTRA

IR spectra were recorded at Bruker Platinium ATR-IR spectrometer and BRUKER IFS 66/S spectrometer.

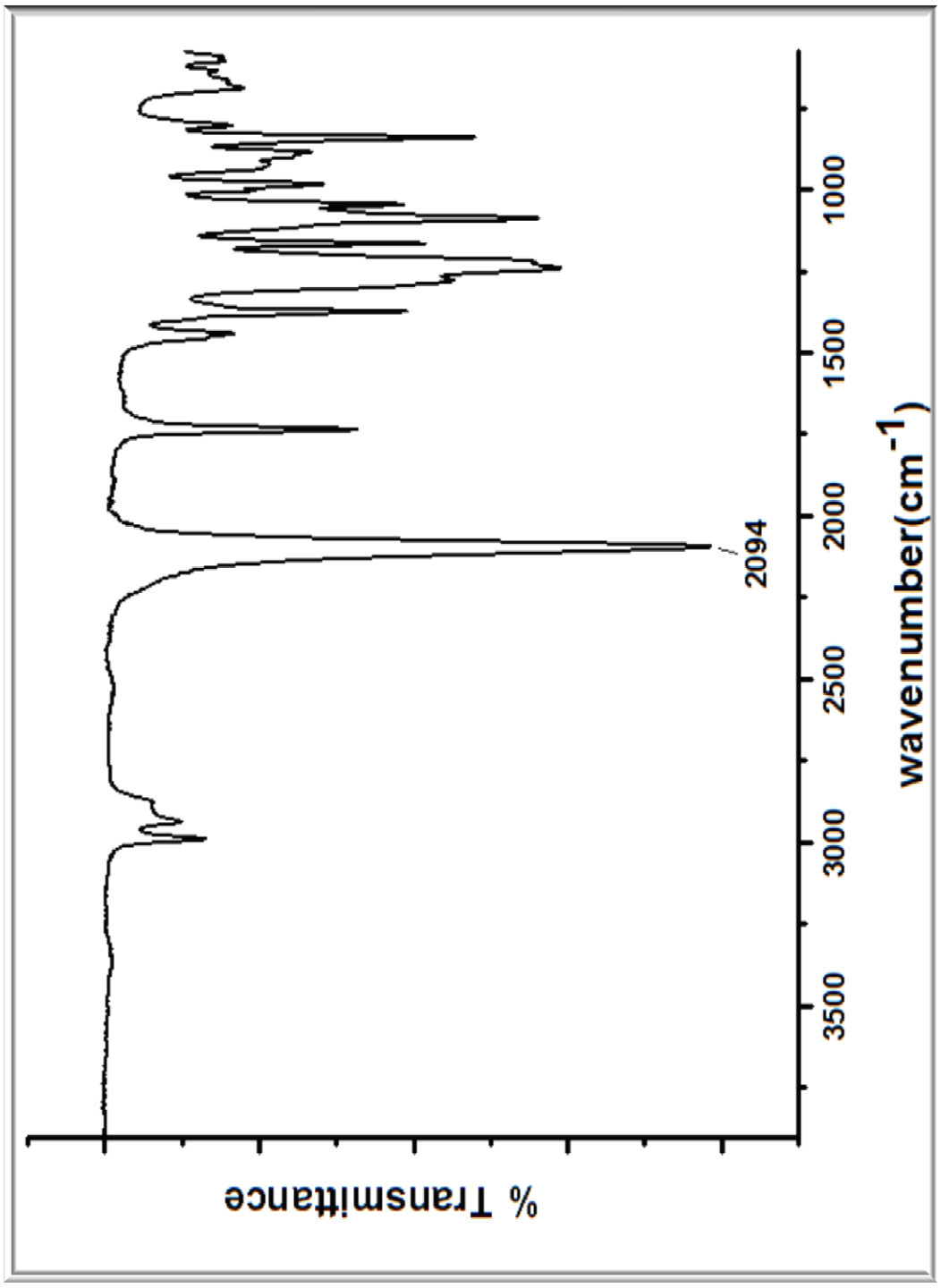

Figure 69. IR spectrum of **9**

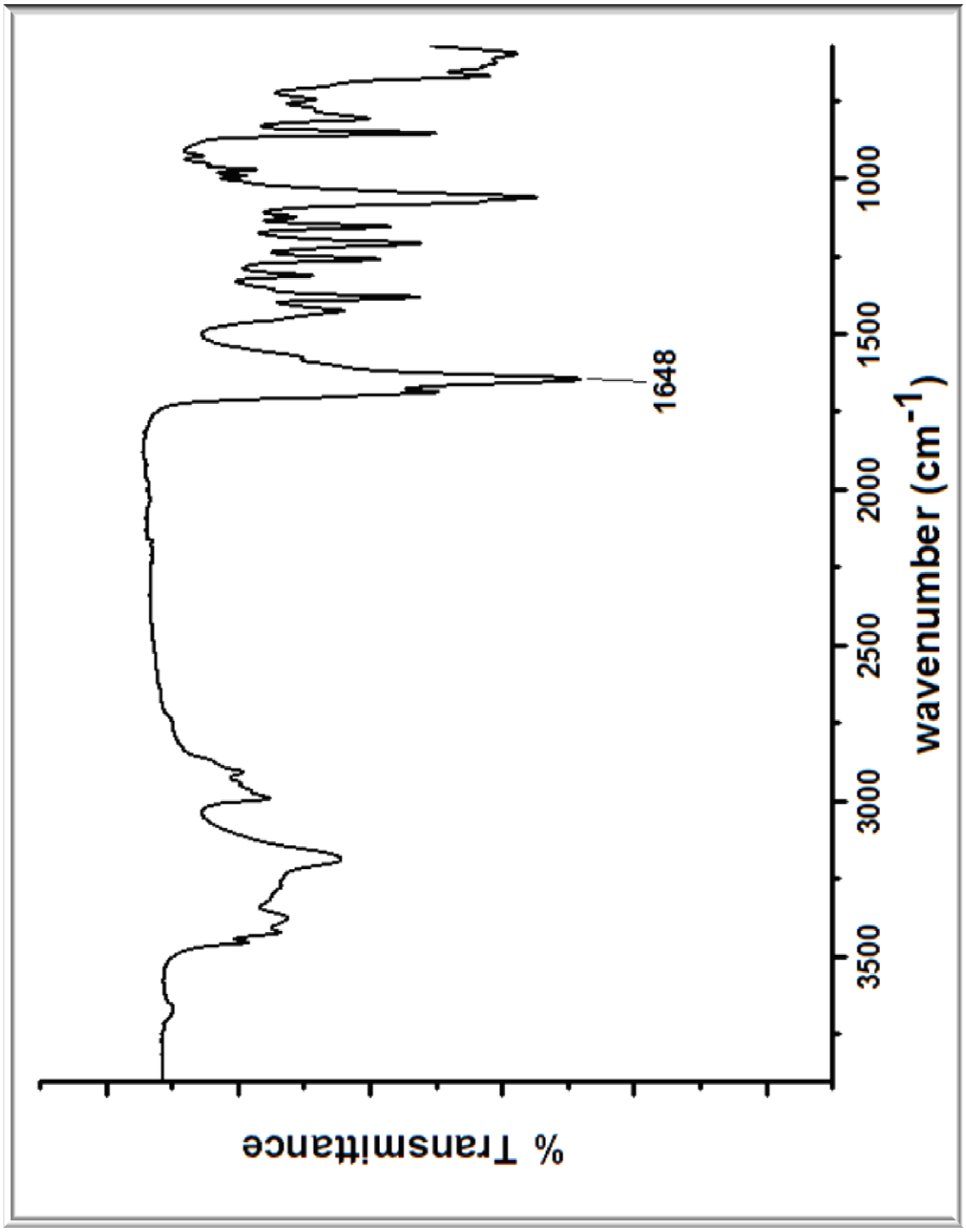

Figure 70. IR spectrum of **10**

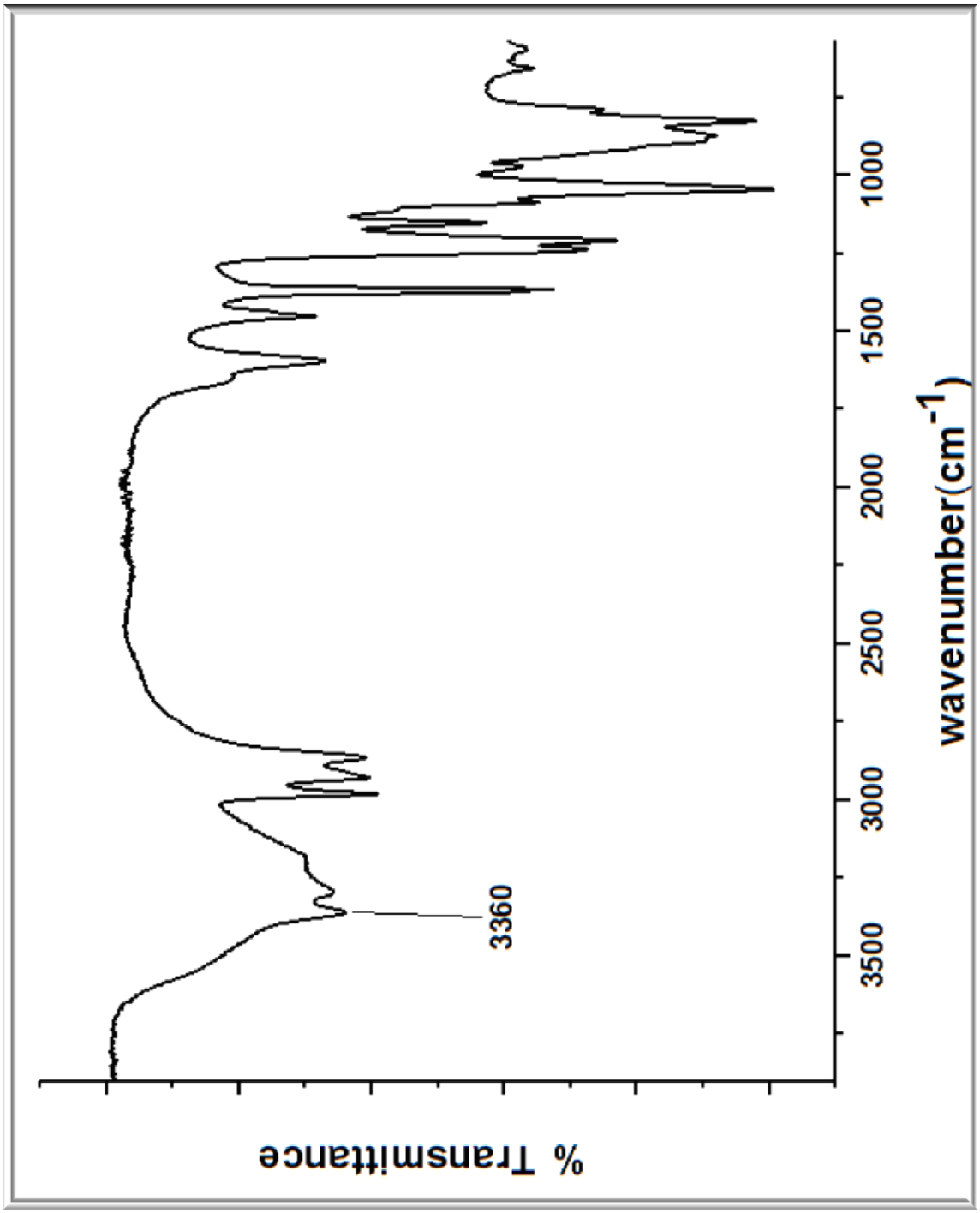

Figure 71. IR spectrum of **11**

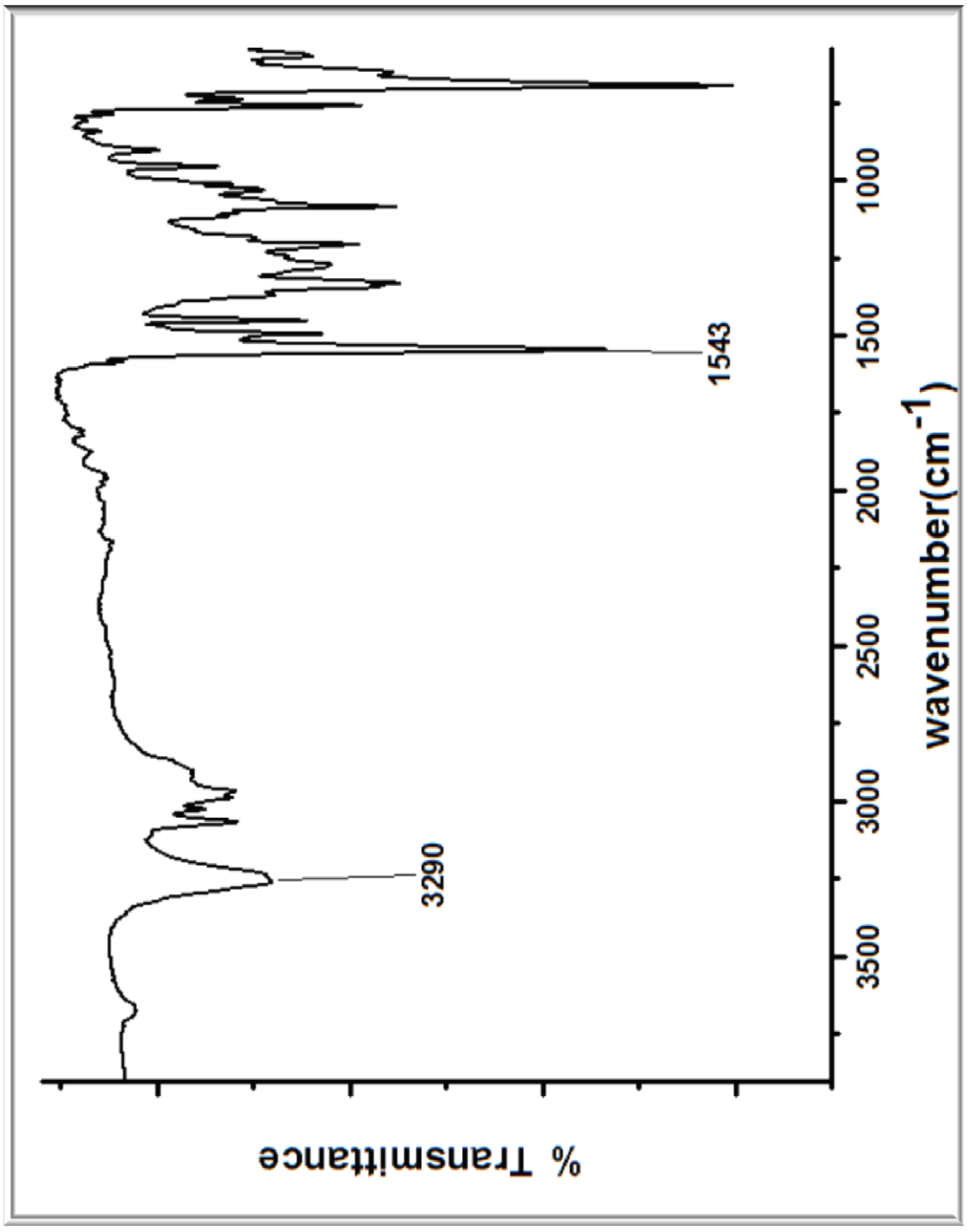

Figure 72. IR spectrum of **16**

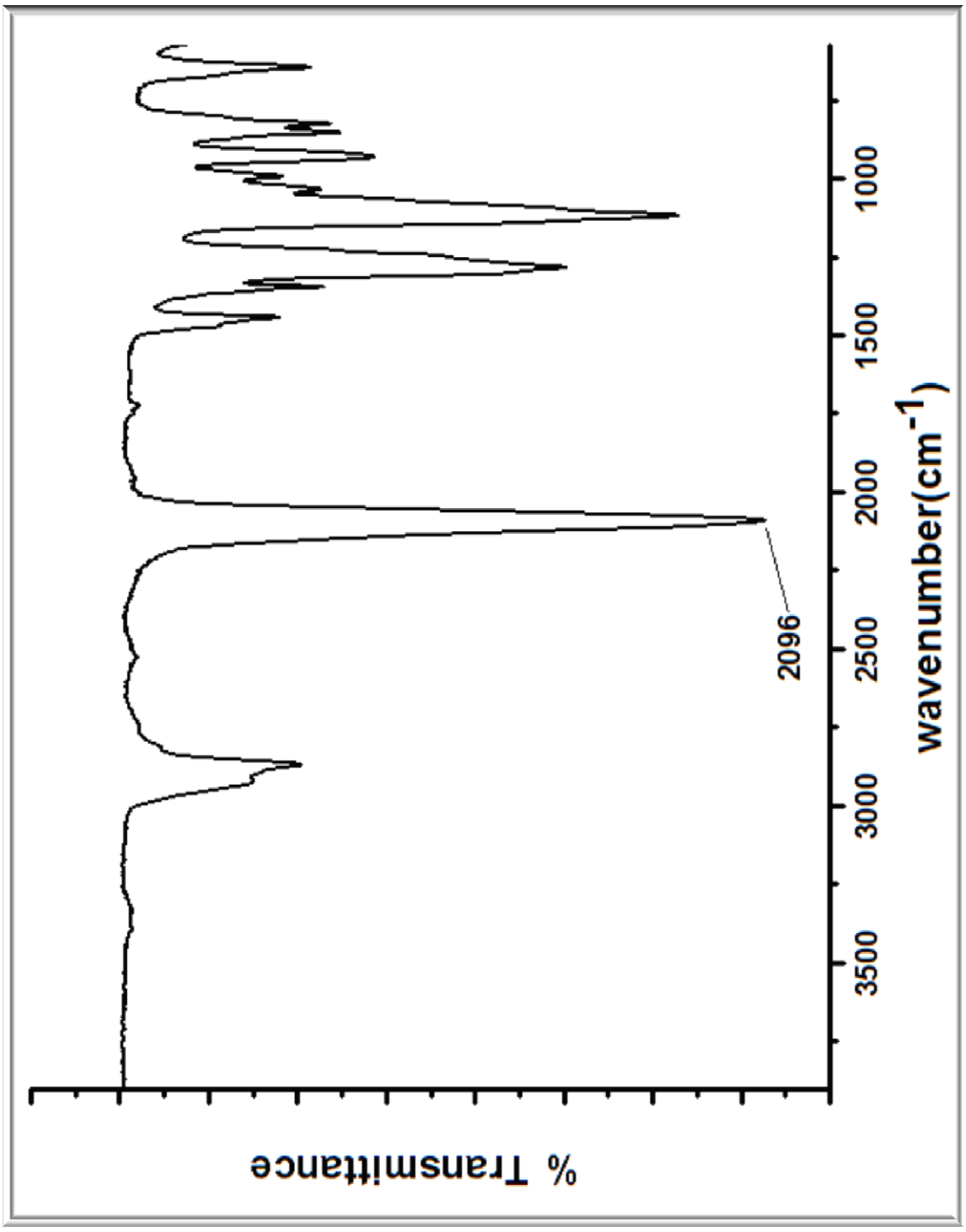

Figure 73. IR spectrum of **18**

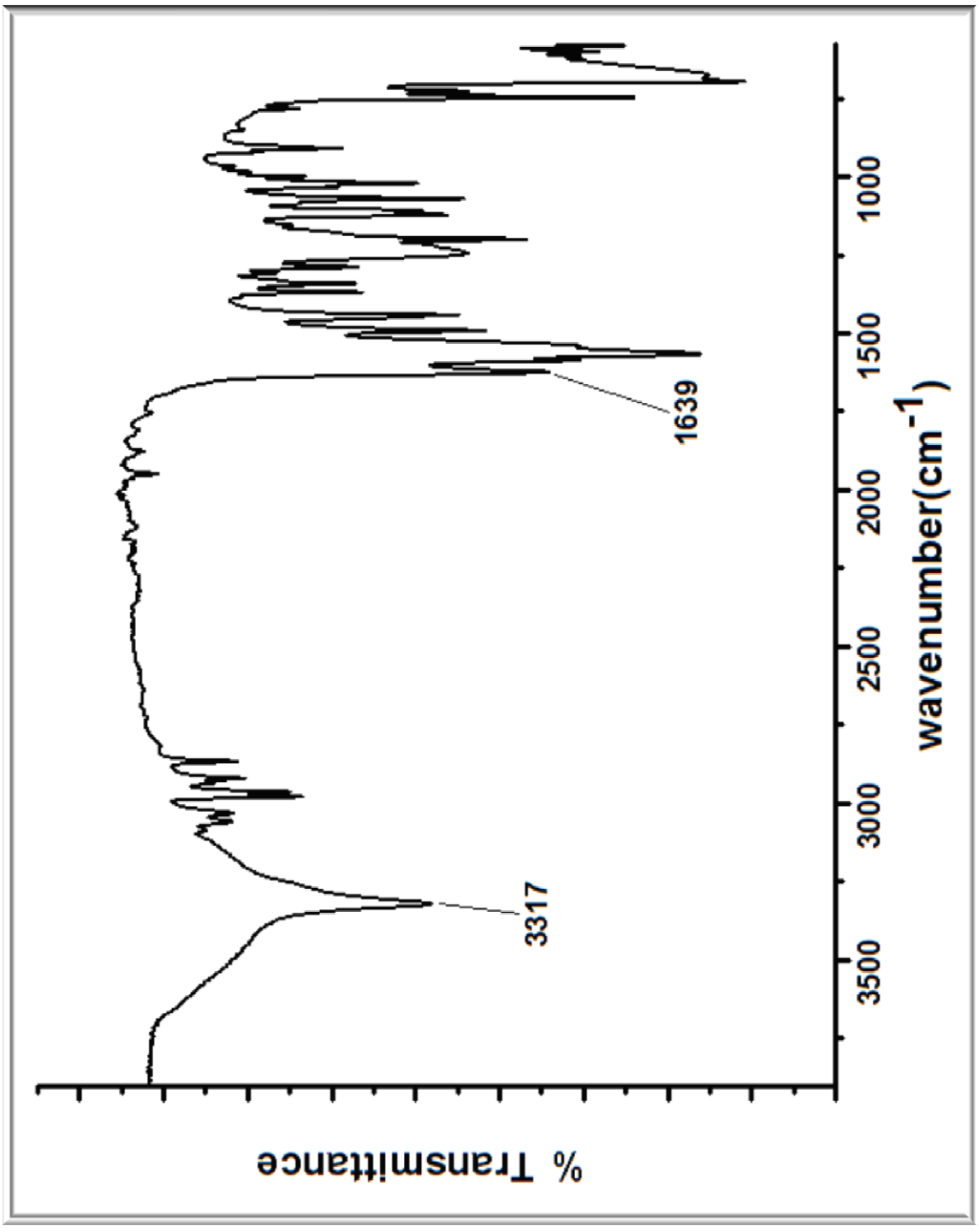

Figure 74. IR spectrum of **23**

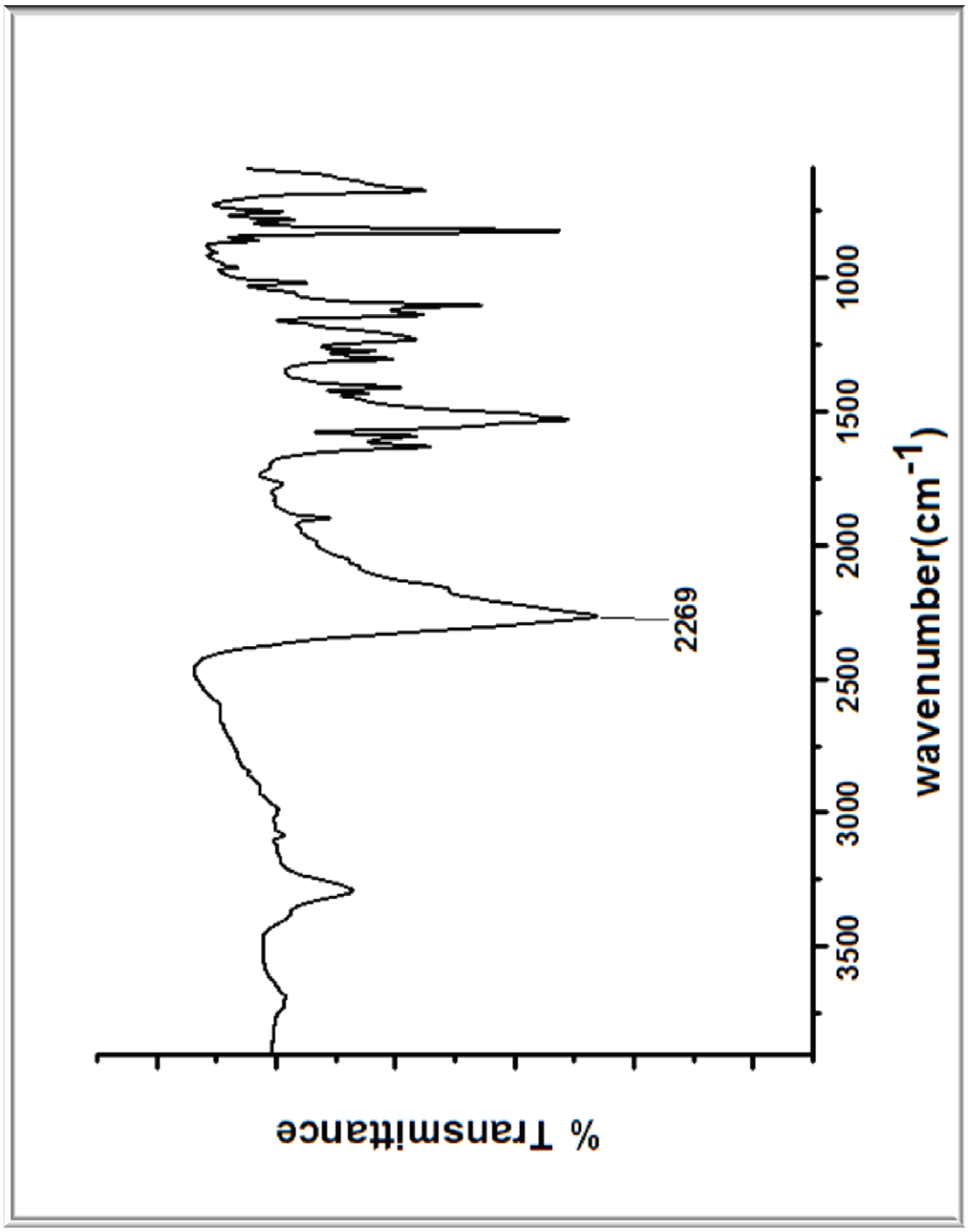

Figure 75. IR spectrum of **24**

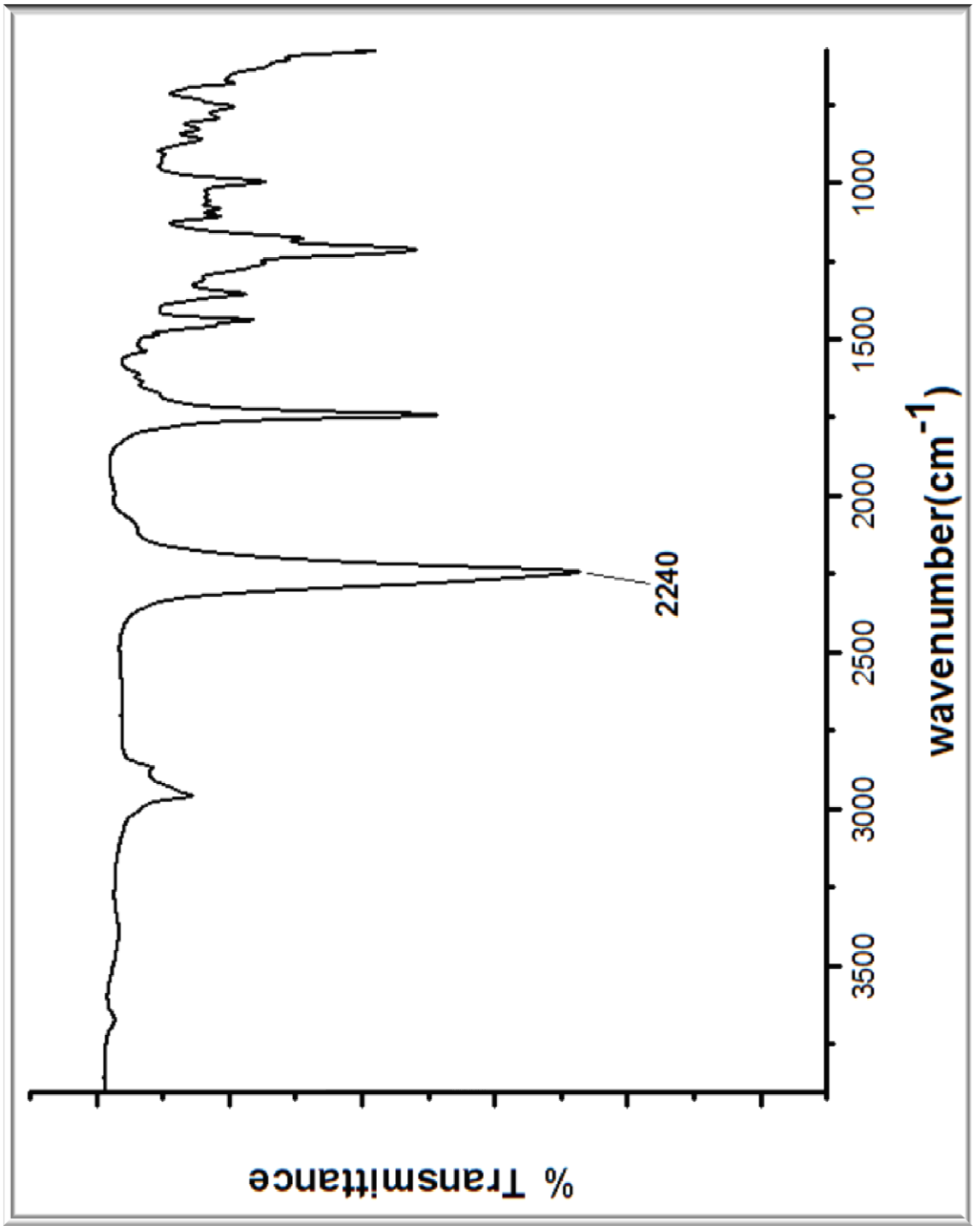

Figure 76. IR spectrum of **26**

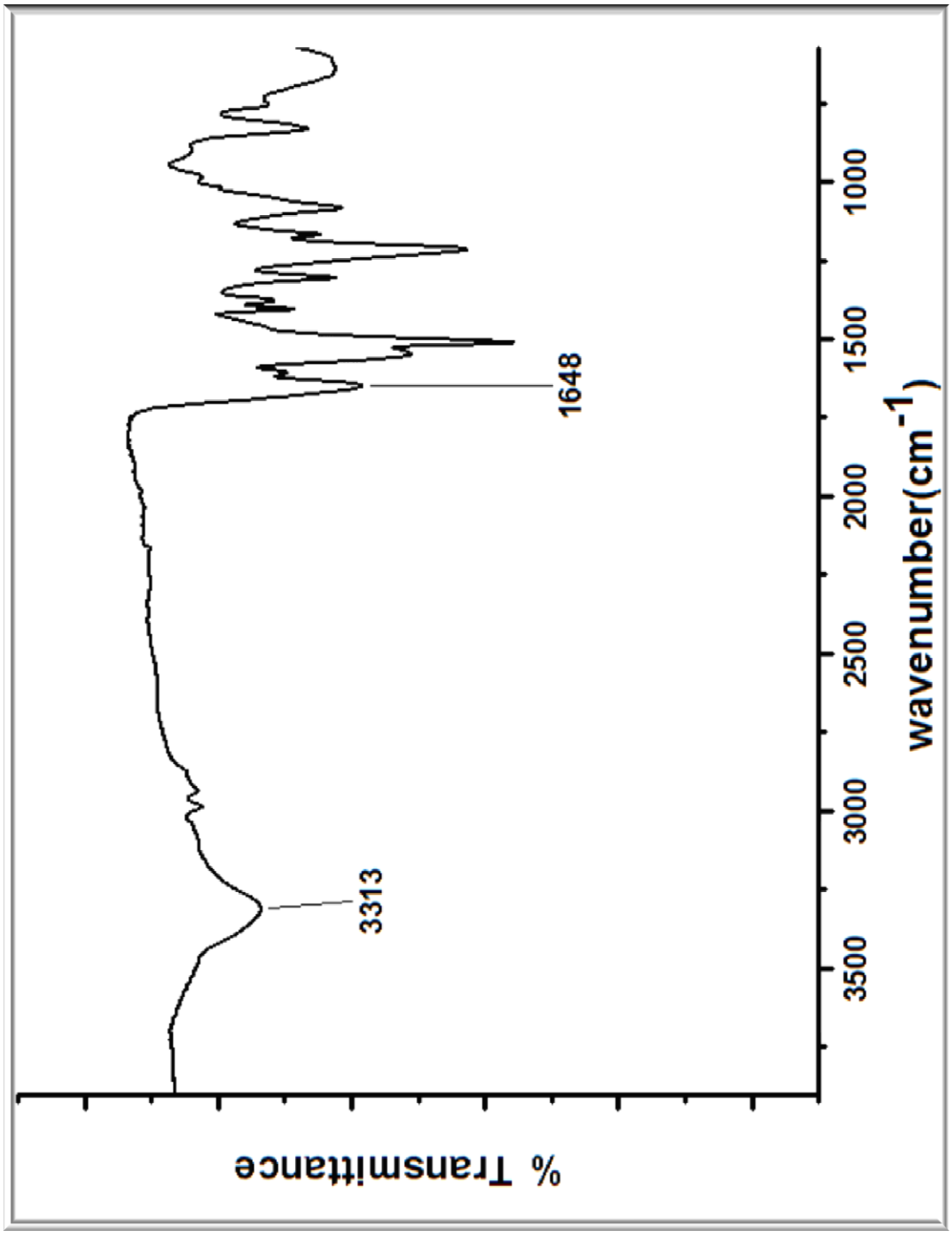

Figure 77. IR spectrum of **POL-A**

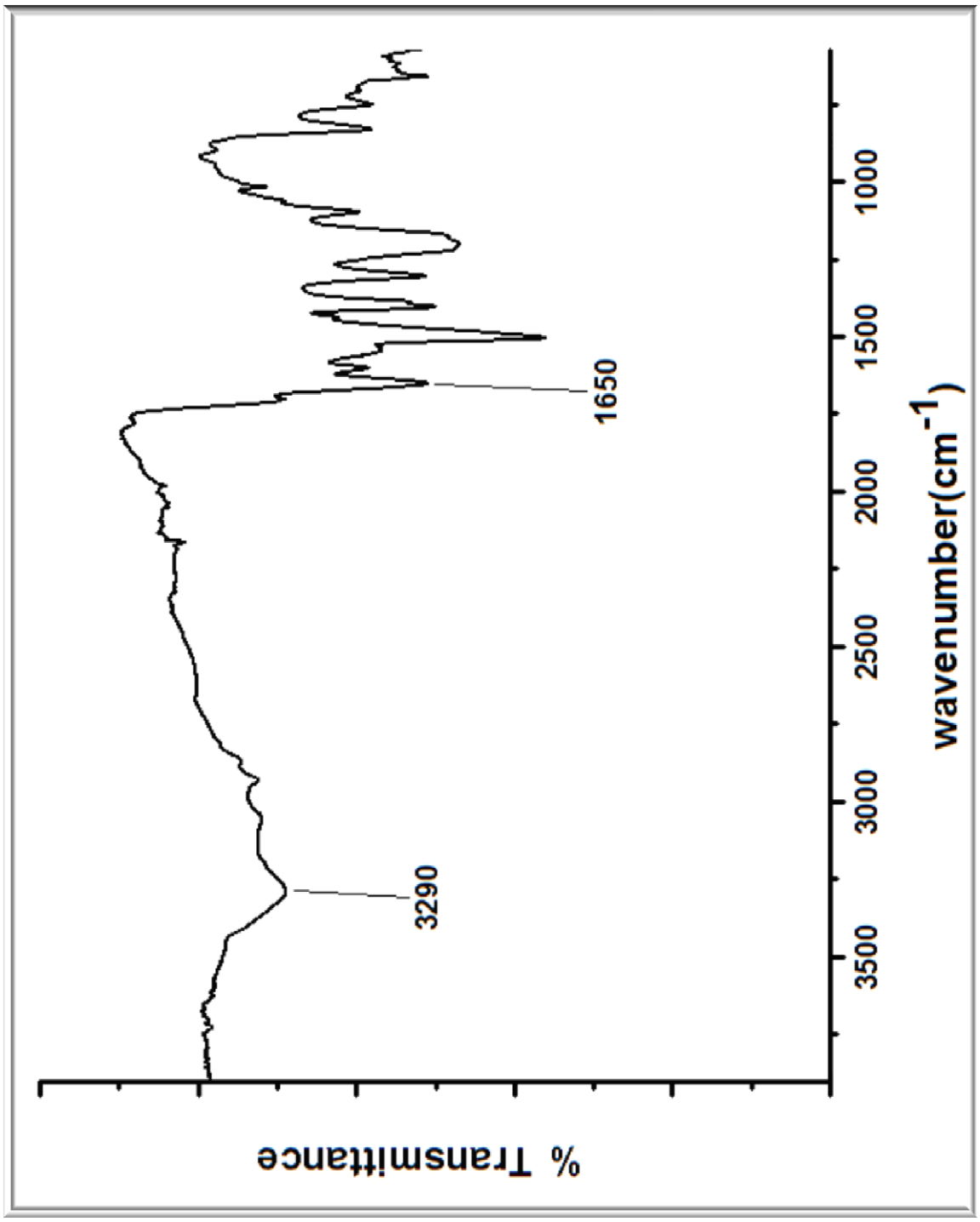

Figure 78. IR spectrum of **POL-B**

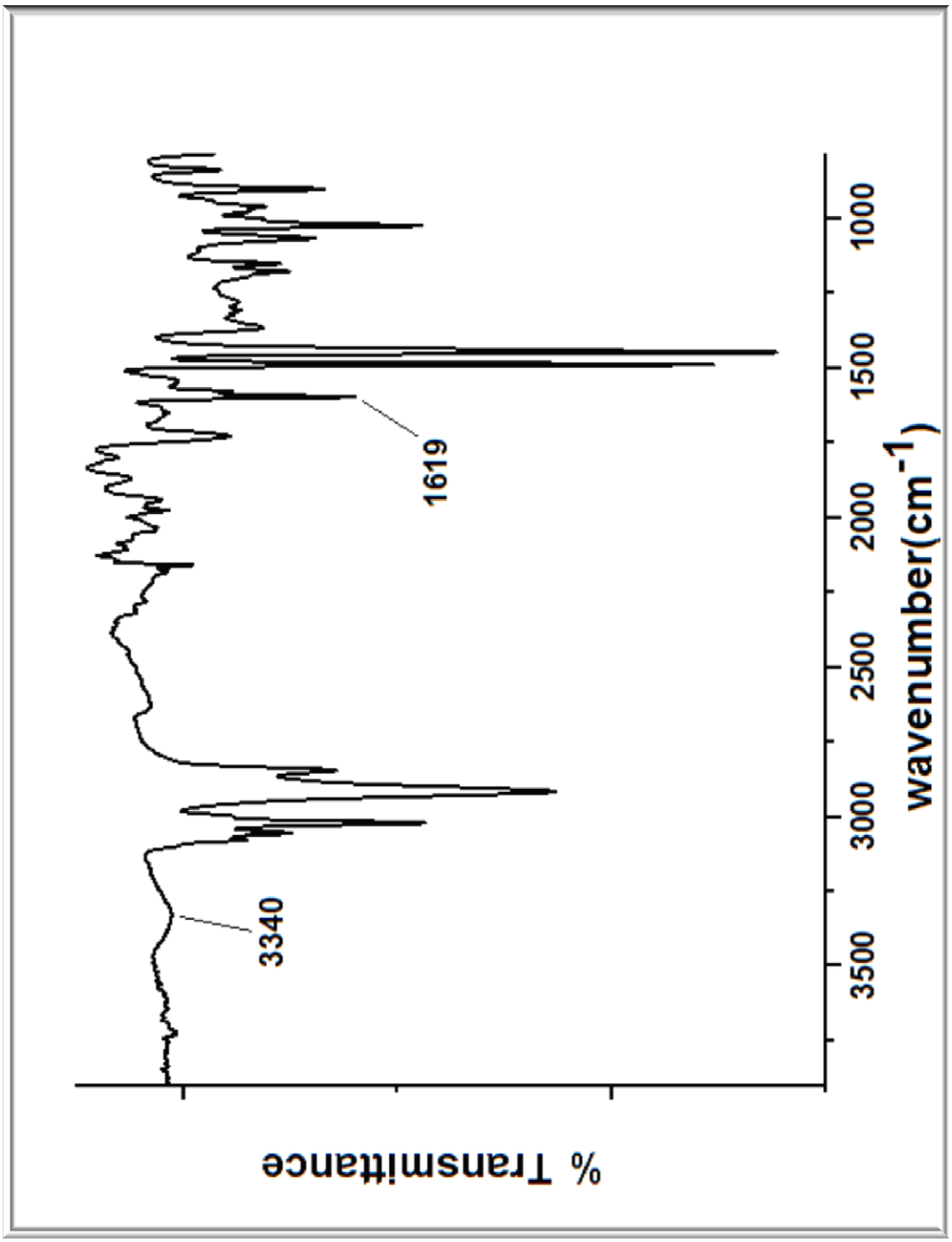

Figure 79. IR spectrum of **POL-C**

PART C: DSC SPECTRA

All DSC termograms were recorded with Scinco DSC N-650 Differential Scanning Calorimetry.

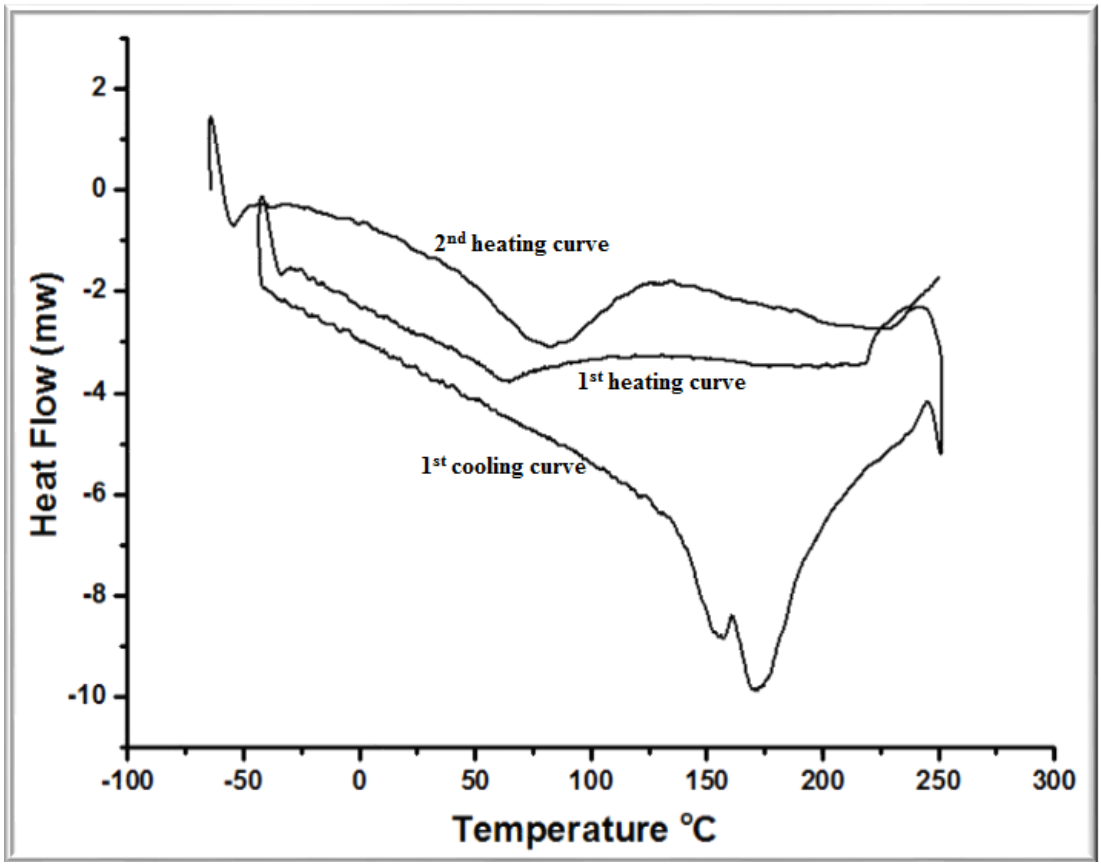

Figure 80. DSC spectrum of **POL-A**

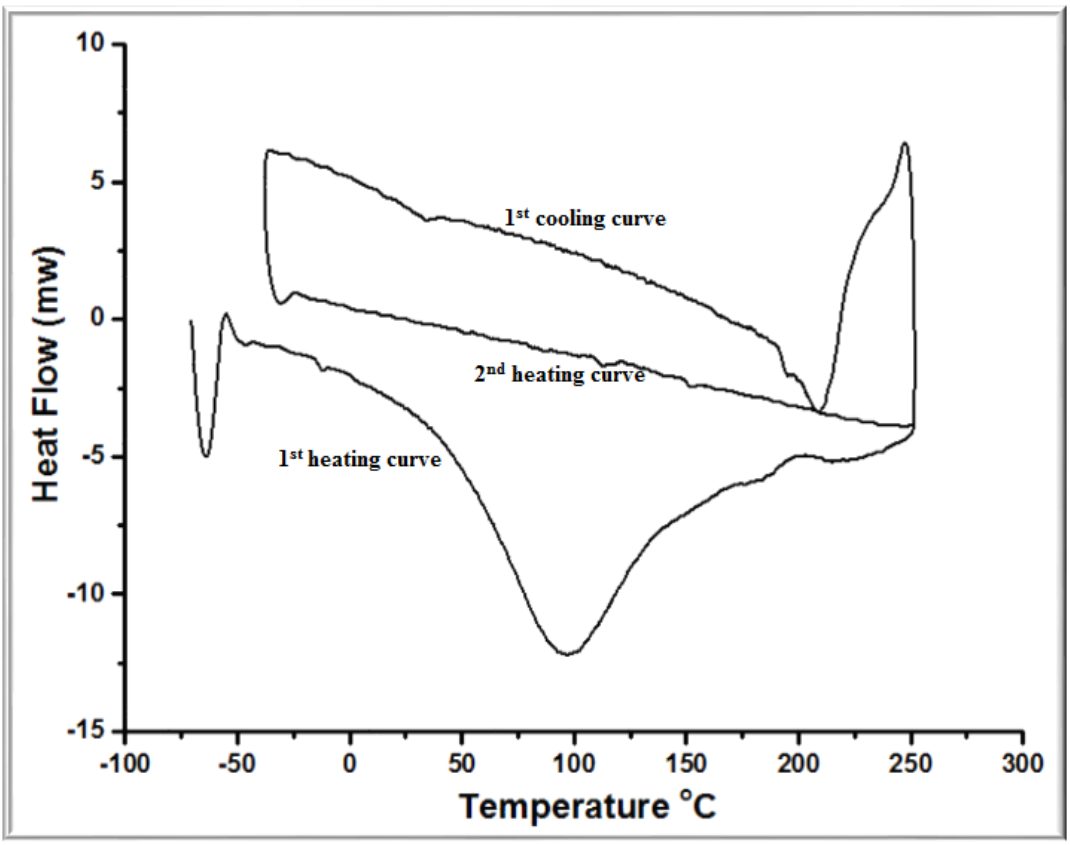

Figure 81. DSC spectrum of **POL-B**

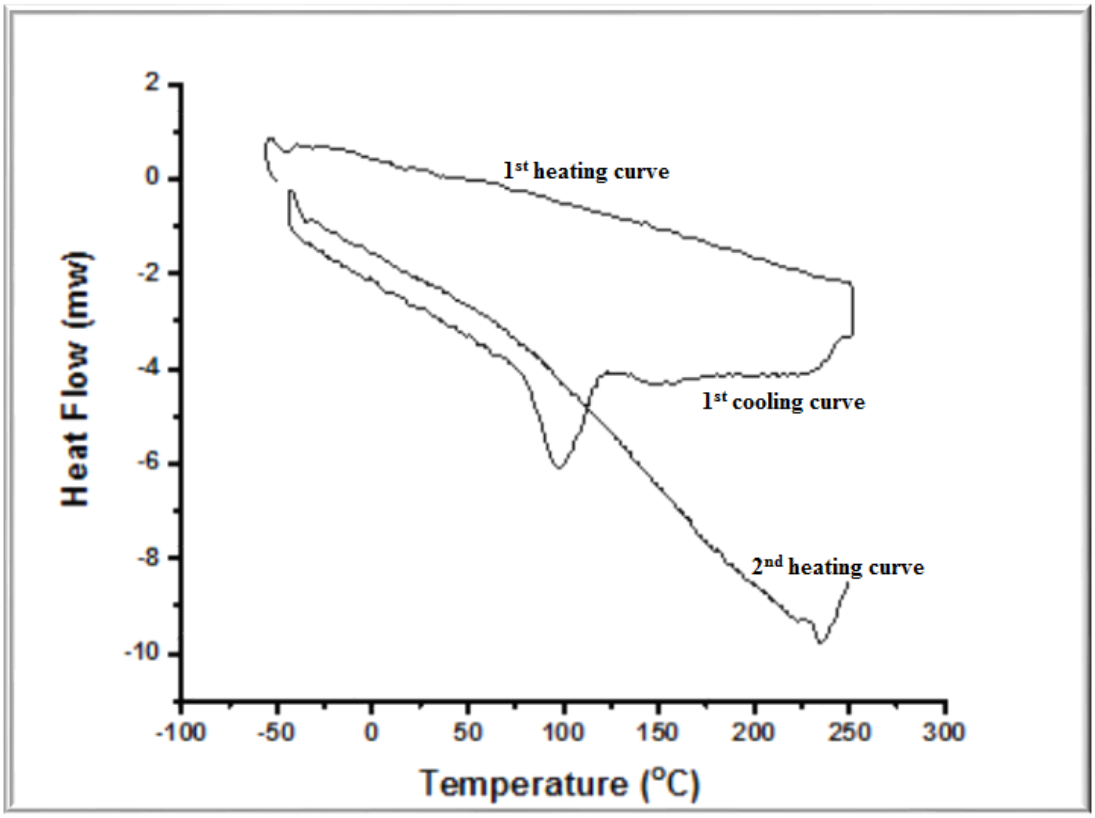

Figure 82. DSC spectrum of **POL-C**