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THE SYNTHESIS OF THIOUREA DERIVATIVE OF BENZIMIDAZOLE COMPOUNDS AND THE INVESTIGATION OF THEIR CATALYTIC AND BIOLOGICAL ACTIVITIES

ODAY OBAIDI

Supervisor: Prof. Dr. Demet ASTLEY

Chemistry Department

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Jüri başkanı	:	**Prof. Dr. Demet ASTLEY**	.....
Raportör Üye	:	**Prof. Dr. Serap ALP**	.....
Üye	:	**Yrd. Doç. Dr. Yeşim Gül SALMAN**	.....

ÖZET

BENZİMİDAZOL TÜREVİ TİYOÜRE BİLEŞİKLERİN SENTEZİ VE KATALİTİK/BİYOLOJİK AKTİVİTELERİNİN İNCELENMESİ

OBAIDI, Oday

Yüksek Lisans Tezi, Kimya Anabilim Dalı
Tez yöneticisi: Prof. Dr. Demet Astlety
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Bu çalışmada L-metiyonin, L-izolösin, D-fenilglisin ve L-fenilalanin başlangıç amino asitleri olarak kullanıldı. Deneysel çalışmalar, bu basit amino asitlerin benzimidazol türevi tiyoüre bileşiklerin sentezleri üzerinde oluşturuldu.

L-metiyonin'in koruyucu ditersiyer bütil dikarbonat tepkimesi sonucu sırasıylaN-Boc-L-metiyonin hazırlandı. N-Boc-L-metiyonin ile o-fenilendiamin DCC (N,N'-disikloheksilkarbodiimit) varlığında tepkimeye sokulmasıyla N-Boc-kiral amit türevi elde edildi. N-Boc-kiral amit türevi asidik ortamda halkalaşma reaksiyonuna sokularak N-Boc-kiral benzimidazol türevi sentezlenmiş oldu.

Elde edilen N-Boc-kiral benzimidazol türevi amin gurubuna bağlı olan koruyucu grup ditersiyer bütil dikarbonat'ı düşürülerek kiral benzimidazol türevi elde edildi. Son aşama olarak da kiral benzimidazol türevi ile 3,5-bis (triflorometil) fenil izotiyosiyanat tepkimeye sokularak istenen tiyoüre bileşiği hazırlandı.

Benzer bir şekilde, aynı sentez zincirinin kullanılmasıyla L-izolösin, D-fenilglisin ve L-fenilalanin'nin amino asitler türevi tiyoüre bileşikleri de elde edildi. Ürünlerin yapıları spektroskopik analizler (IR, ^{1}H-NMR, ^{13}C-NMR) ve elementel analiz sonuçları ile karakterize edildi.

Anahtar Kelimeler: Amino asit, O-fenilendiamin, Bezimidazol, 3,5-bis (triflorometil) fenil izotiyosiyanatve Tiyoüre.

ABSTRACT

THE SYNTHESIS OF THIOUREA DERIVATIVE OF BENZIMIDAZOLE COMPOUNDS AND THE INVESTIGATION OF THEIR CATALYTIC AND BIOLOGICAL ACTIVITIES

OBAIDI, Oday

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In this study, L-methionine, L-isoleucine, D-phenylglycine and L-phenylalanine were used as starting amino acids. The experimental works were constituted on the synthesis of thiourea derivative of benzimidazole compounds of these simple amino acids.

N-Boc-L-methionine was prepared from the reaction of L-methionine and the protective di-tert-butyl dicarbonate. N-Boc-chiral amide derivative was obtained by the reaction of N-Boc-L-methionine with o-phenylenediamine in the presence of DCC (N,N'-Dicyclohexylcarbodiimide). N-Boc-chiral derivative of benzimidazole was synthesized by inserting N-Boc-chiral amide derivative into cyclization reaction in an acidic environment. The synthesized N-Boc-chiral derivative of benzimidazole was deprotected by reducing the protective group which was connected to amine group for obtaining chiral derivative of deprotected benzimidazole. Finally, the desired thiourea derivative was obtained by the reaction of the deprotected benzimidazole derivative with 3,5-bis(trifluromethyl)phenylisothiocyanate.

Similarly, thiourea derivatives of the rest amino acids such as L-isoleucine, D-phenylglycine and L-phenylalanine were also obtained by using the same synthetic pathway. The products were characterized by spectroscopic methods (IR, ^{1}H-NMR, ^{13}C-NMR) and elemental analysis.

Keywords: Amino acid, O-phenylenediamine, Bezimidazole, 3,5-bis(trifluromethyl)phenylisothiocyanate and Thiourea.

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ODAY OBAIDI

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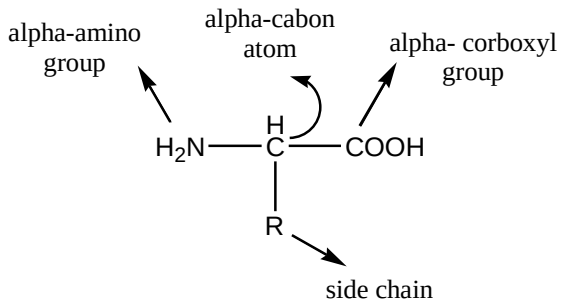
SYMBOLS AND ABBREVIATIONS

NMR	Nuclear Magnetic Resonance
IR	Infrared
$CDCl_3$	Deuteriochloroform
DMSO	Dimethylsulfoxide
FT-IR	Fourier Transformation Infrared
UV	Ultraviolet
T.L.C	Thin Layer Chromatography
rt	room temperature
EtOAc	Ethyl acetate
MeOH	Methanol
Hz	Hertz
AcOH	Acetic acid
H_3PO_4	Phosphoric acid
NaOH	Sodium hydroxide
KBr	potassium hydroxide
Boc	t-butoxycarbonyl
$NaHCO_3$	Sodium bicarbonate
m.p	melting point
THF	Tetrahydrofuran
DCC	Dicyclohexylcarbodiimide
S	Singlet
m	multiplet
b	broad
d	doublet
t	triplet

1. Introduction

1.1 Amino acids

Proteins are the most abundant organic molecules in animals, playing important rules in all aspects of cell structure and function. Proteins are biopolymers of α-amino acids, and the physical and chemical properties of a protein are determined by its constituent amino acids (Wade, 1987). The term amino acids might mean any molecule both an amino group and any type of acid group. However, the term is almost used to refer α-amino acetic acid. Each amino acid consists of α-carbon atom which is connected to a hydrogen atom, α-amino group, a carboxyl group, an R (side chain) group. The various alpha amino acids differ in which side chain (R group) is attached to their alpha carbon. They can vary in size from just a hydrogen atom in glycine through a methyl group in alanine to a large heterocyclic group in tryptophan.



Scheme 1.1 An amino acid

The 20 amino acids that are major components of peptides and proteins are often called standard amino acids (Weininger and Stermitz, 1984). Humans can produce 10 of 20 amino acids. The others must be supplied in the food. Failure to obtain enough of even 1 of the 10 essential amino acids, those that we cannot make, result in degradation of the body's proteins to obtain the one amino acid that is needed. Unlike fat and starch, the human body does not store excess amino acids for later use. The amino acids must be in the food every day. The 10 amino acids that we can produce are; alanine, asparagines, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, serine and tyrosine. The essential amino acids are arginine (required for young but not adults), histidine, isoleucine, phenylalanine, leucine, lysine, methionine, threonine, tryptophan, and valine. These amino acids are

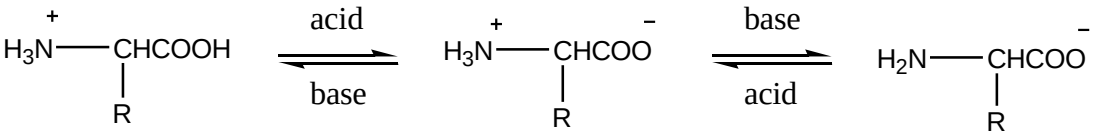
required for the diet. Plants must be able to make all of amino acids. Humans do not have all the enzymes required for the biosynthesis of all of the amino acid.

1.1.1 Properties of amino acids

Amino acids have high melting points, usually decomposing above 200 ^{0}C. They have good solubility in water and low solubility in nonpolar solvents (Ege, 1984). Amino acids have much larger dipole moments (μ) than simple amines or simple acids. Amino acids are less acidic than most carboxylic acids and less basic than most amines. In fact, the acidic part of amino acid molecule is the NH_3^+ group, not a COOH group. The basic part is the COO^- group, and not a free NH_2 group.

Amino acids contain both an acidic carboxyl (-COOH) and a basic amino (-NH_2) group. Carboxylic acids are strong enough to protonate most amines, and the amino acid undergoes an internal acid-base reaction. The carboxyl group loses a proton to become a carboxylate ion, and the amino group is protonated to give an ammonium ion. The overall structure has a net charge of zero, but there is positive charge on nitrogen and negative charge spread over the oxygen of carboxylate group. This structure is called a dipolar ion or zwitterion.

We have seen that an amino acids bears a negative charge in basic solution (high pH), and a positive charge in acidic solution (low pH). There must be an intermediate pH where the amino acid evenly balanced between the two forms, as the dipolar zwitterion with a net charge of zero. This pH is called the isoelectric point or isoelectronic pH (Wade, 1987).



cation predominant form in acid

zwitterion predominant form at the isoelectric point

anion predominant form in base

Scheme 1.2 Dipolar ion or zwitterion of an amino acid

A tetrahedral carbon atom with 4 distinct constituent is said to be chiral. The one amino acid not exhibiting chirality is glycine since its R-group is a hydrogen atom. Chirality describes the handedness of a molecule that is observable by the ability of a molecule to rotate the plane of polarized light either to right (dextrorotatory) or to the left (levorotatory). All of amino acids in proteins exhibit the same absolute steric configuration as L-glyceraldehyde. Therefore, they are all L-α-amino acids. D-amino acids are often found in polypeptide antibiotics.

1.1.2 Essential amino acids

Histidine:

Histidine, an essential amino acid, has as a positively charged imidazole functional group. The imidazole makes it a common participant in enzyme catalyzed reactions. The unprotonated imidazole is nucleophilic and can serve as a general base, while the protonated form can serve as a general acid. The residue can also serve a role in stabilizing the folded structures of proteins. Histidine is given in scheme 1.3

Arginine:

Arginine, an essential amino acid, has a positively charged guanidino group. Arginine is well designed to bind the phosphate anion, and is often found in the active centers of proteins that bind phosphorylated substrates. As a cation, arginine as well as lysine plays a role in maintaining the overall charge balance of a protein. Arginine also plays an important role in nitrogen metabolism. In the urea cycle, the enzyme arginase cleaves (hydrolyzes) the guanidinium group to yield urea and the L-amino acid ornithine. Ornithine is lysine with one fewer methylene groups in the side chain. L-ornithine is not normally found in proteins. Arginine is given in scheme 1.3

Isoleucine:

Isoleucine, an essential amino acid, is one of the three amino acids having branched hydrocarbon side chains. It is usually interchangeable with leucine and

occasionally with valine in proteins. The side chains of these amino acids are not reactive and therefore not involved in any covalent chemistry in enzyme active centers. However, these residues are critically important for ligand binding to proteins, and play central roles in protein stability. Note also that the β carbon of isoleucine is optically active, just as the β carbon of threonine. These two amino acids, isoleucine and threonine, have in common the fact that they have two chiral centers. Isoleucine is given in scheme 1.3

Lysine:

Lysine an essential amino acid has a positively charged α-amino group (a primary amine) Lysine is basically alanine with a propylamine substituent on the β-carbon. Lysine is given in scheme 1.3

The ε-amino group has a significantly higher pKa (about 10.5 in polypeptides) than does the α-amino group. The amino group is highly reactive and often participates in reactions at the active centers of enzymes.

Proteins only have one α-amino group, but numerous α-amino groups. However, the higher pKa renders the lysyl side chains effectively less nucleophilic. Specific environmental effects in enzyme active centers can lower the pKa of the lysyl side chain such that it becomes reactive.

Note that the side chain has three methylene groups, so that even though the terminal amino group will be charged under physiological conditions, the side chain does have significant hydrophobic character. Lysines are often found buried with only the α-amino group exposed to solvent.

Methionine:

Methionine, an essential amino acid, is one of the two sulfur-containing amino acids. The side chain is quite hydrophobic and methionine is usually found buried within proteins. Unlike cysteine, the sulfur of methionine is not highly nucleophilic, although it will react with some electrophilic centers.

It is generally not a participant in the covalent chemistry that occurs in the active centers of enzymes. Methionine is given in scheme 1.3

Threonine:

Threonine, an essential amino acid, is a hydrophilic molecule. Threonine is another hydroxyl-containing amino acid. It differs from serine by having a methyl substituent in place of one of the hydrogens on the β carbon and it differs from valine.

By replacement of a methyl substituent with a hydroxyl group, note that both of α and β carbons of threonine are optically active. Threonine is given in scheme 1.3

Valine:

Valine, an essential amino acid, is hydrophobic, and as expected, is usually found in the interior of proteins. Valine differs from threonine by replacement of the hydroxyl group with a methyl substituent.

Valine is often referred to as one of the amino acids with hydrocarbon side chains, or as a branched chain amino acid. Valine is given in scheme 1.3

Leucine:

Leucine, an essential amino acid and one of the three amino acids with a branched hydrocarbon side chain. It has one additional methylene group in its side chain compared with valine. Like valine, leucine is hydrophobic and generally buried in folded proteins. Leucine is given in scheme 1.3

Phenylalanine:

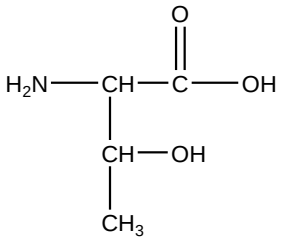
As the name suggests, phenylalanine, an essential amino acid, is a derivative of alanine with a phenyl substituent on the β carbon. Phenylalanine is quite hydrophobic and even the free amino acid is not very soluble in water.

Due to its hydrophobicity, phenylalanine is nearly always found buried within a protein. The π electrons of the phenyl ring can stack with other aromatic systems and

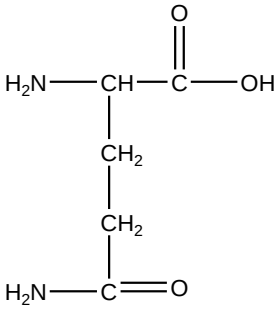
often do within folded proteins, adding to the stability of the structure. Phenylalanine is given in scheme 1.3

Tryptophan:

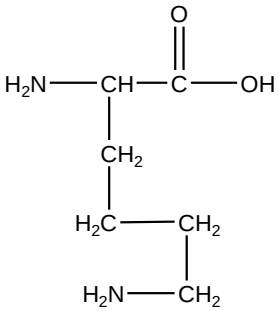
Tryptophan, an essential amino acid, is the largest of the amino acids. It is also a derivative of alanine, having an indole substituent on the β carbon. The indole functional group absorbs strongly in the near ultraviolet part of the spectrum. The indole nitrogen can hydrogen bonds donate, and as a result, tryptophan, or at least the nitrogen, is often in contact with solvent in folded proteins. Tryptophan is given in scheme 1.3



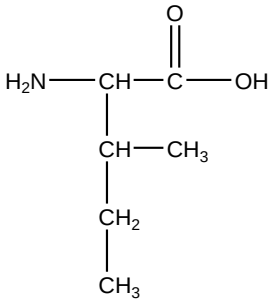
threonine



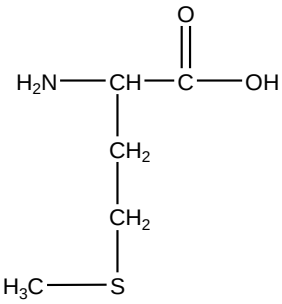
glutamine



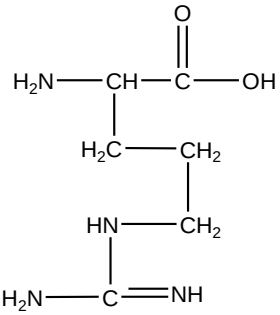
lycine



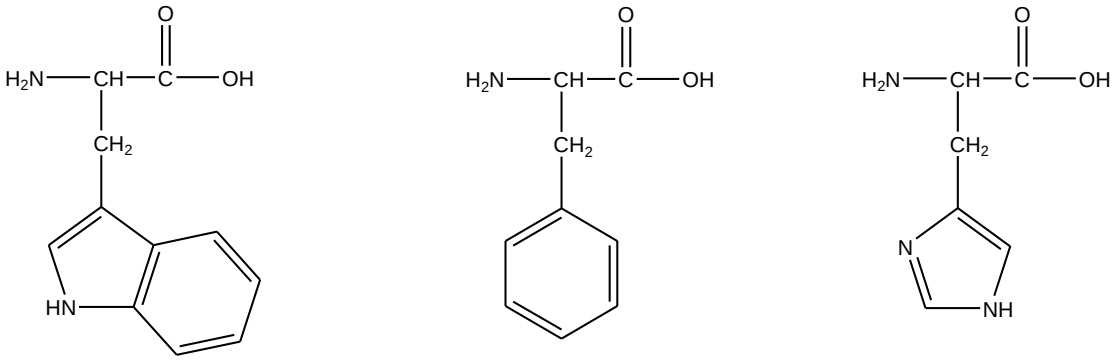
isoleucine



methionine



arginine



tryptophan phenylalanine histidine

Scheme 1.3 Some of amino acids

1.1.3 Protection for the Amino Group

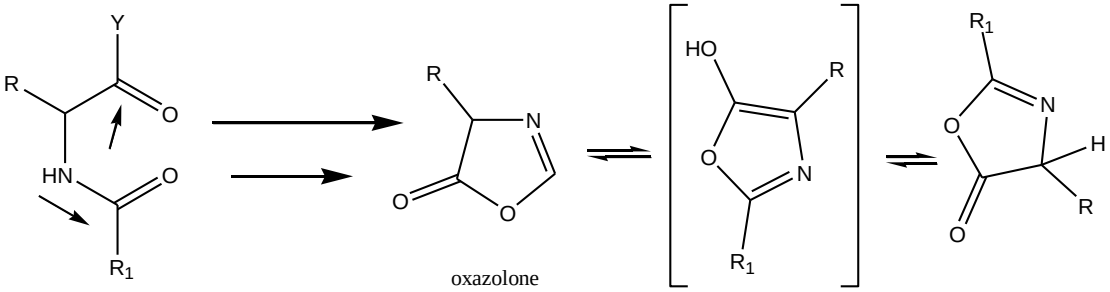
A great many protective groups have been developed for the amino group, including carbamates (NCO_2R), used for the protection of amino acids in peptide and protein syntheses, and amides (NCOR), used more widely in syntheses of alkaloids and for the protection of the nitrogen bases adenine, cytosine and guanine in nucleotide syntheses.

Carbamates are formed from an amine with a wide variety of reagents, the chloroformate being the most common; amides are formed from the acid chloride. N-alkyl carbamates are cleaved by acid-catalyzed hydrolysis; N-alkylamides are cleaved under forcing conditions by acidic or basic hydrolysis at reflux, as well as by ammonolysis in cases where the amine is not very basic such as in heterocyclic amine derivatives (Greene and Wuts, 2007).

Carbamates

Carbamates can be used as protective groups for amino acids to minimize racemization in peptide synthesis. Racemization occurs during the base-catalyzed coupling reaction of N-protected carboxyl-activated amino acid and it takes place in

the intermediate oxazolone that forms readily from N-acyl protected amino acid. (Scheme 1.4)



R=alkyl, aryl, R_1=O-alkyl-aryl

Scheme 1.4 Coupling reaction of N-protected carboxyl-activated amino

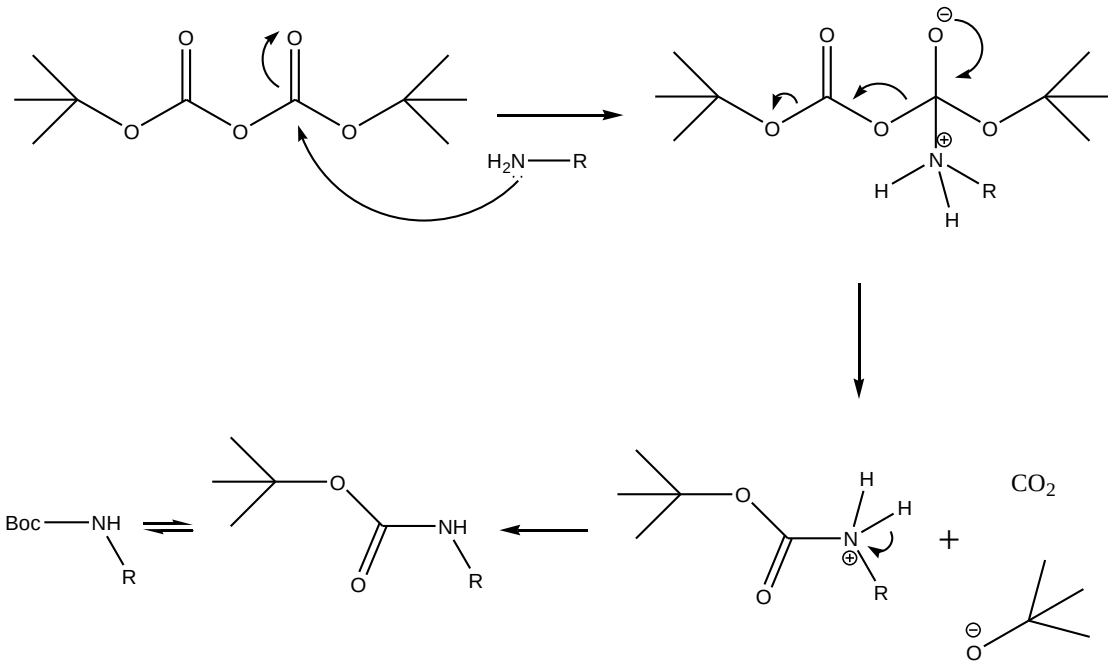
To minimize racemization, the use of nonpolar solvents a minimum of base, low reaction temperatures and carbamate protective groups is effective (Greene and Wuts, 2007).

Many carbamates have been used as protective groups. The most useful compounds are: t-butyl (BOC), readily cleaved by acidic hydrolysis benzyl (Cbz or Z) cleaved by catalytic hydrogenolsis.

Tert- butoxycarbonyl (Boc group):

The Boc group is used extensively in peptide and heterocyclic synthesis for amine protection. It is not readily hydrolyzed under basic condition and is inert to many other nucleophilic reagents. It is usually cleaved with strong acid, giving only t-BuOH or isobutylene and CO_2 as by-products.

As a result, it is one of the most commonly used protective groups for amines. In general, it is considered nonreactive, but there are many cases in which the Boc group participates in reactions-anticipated and unanticipated (Agami and Couty, 2002). The mechanism of Boc group protection is shown on Scheme 1.5



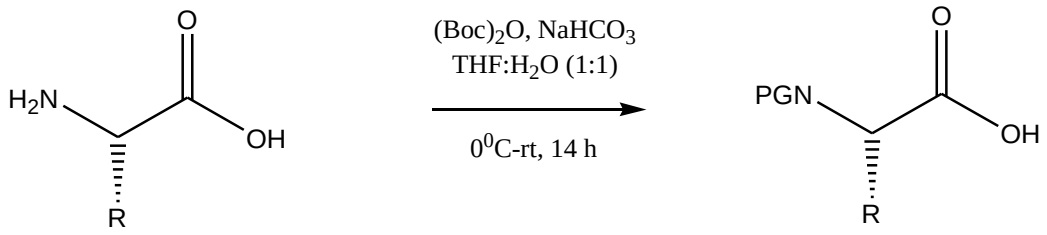
Scheme 1.5 The mechanism of Boc group (protection)

Formation:

1. For simple amines, mixing $(Boc)_2O$ and the amine THF with gentle heating (-40 ˚C) to drive off CO_2 is often the simplest method for preparing Boc derivatives. If at least 2 equivalents of $(Boc)_2O$ are used, primary amines can be converted to the bis-BOC derivative $(Boc)_2O$, THF, reflux, 92% yield (Haug and Rich, 2004).

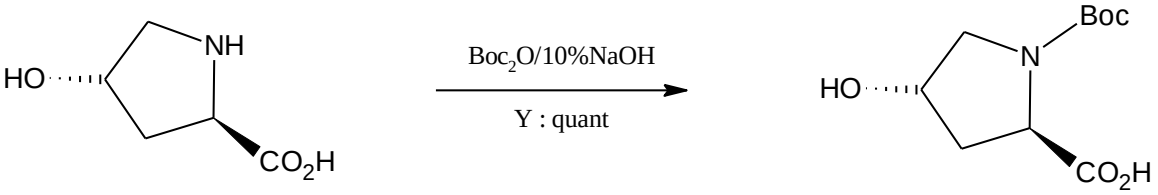
2. $(Boc)_2O$, NaOH, H_2O, 25 ˚C, 10-30 min, 75-95% yield. This one of the more common methods for introduction of the Boc group onto amino acids, but does not work efficiently for hundred amines because of reagent destruction. It has the advantage that the by-products are innocuous and are easily removed (Tarbell et al., 1972).

3. Several amino acids have been N-protected by tert-butoxycarbonyl (Boc) Protecting group (PG) using $(Boc)_2O/NaHCO_3$/ THF-H_2O in nearly quantitative yields (Shendage et al., 2004).



Scheme 1.6 **N**-protection of amino acids

4. Treatment of L-hydroxyproline with di-tert-butyl dicarbonate in the presence of 10% aqueous NaOH provided N-tert-butoxycarbonyl-trans-4-hydroxy-L- proline (Qiu and Qing, 2002).

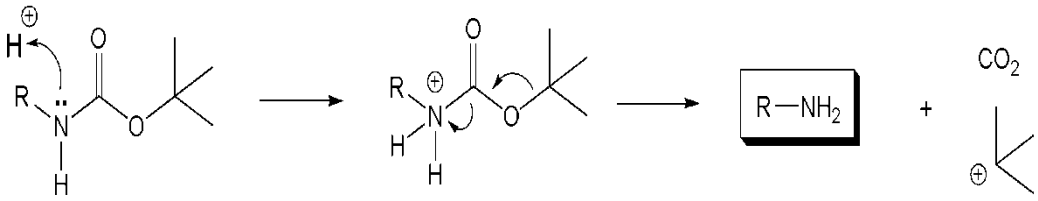


Scheme 1.7 Syntheses of N-tert-butoxycarbonyl-trans-4-hyrdoxy-L-proline

Cleavage:

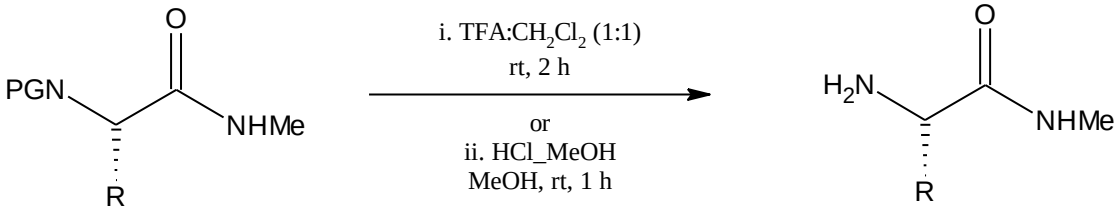
1. Aqueous HCl, toluene, 65 ^{0}C, 93% yield. This method is a commercially convenient method and has been used on a multi kilogram scale (Prashad et al, 2004).

The mechanism of Boc group deprotection is shown on scheme 1.8



Scheme 1.8 Mechanism of Boc group Deprotection

2. The N-protected amides were subsequently hydrolyzed to free amides (peptide building blocks) using TFA/CH_2Cl_2 or to the corresponding HCl-salts by HCl- MeOH in anhydrous MeOH with high yields (Shendage et al, 2004).



Scheme 1.9 N-Deprotection of Amides

3. The environmentally benign aqueous phosphoric acid (85 %) can be used as an alternate reagent for the deprotection of N-Boc groups. The reaction conditions are mild and offer good selectivity among other acid sensitive groups including Cbz, Benzyl and methyl esters, TBDMS and isopropylidene groups. The reaction preserves stereochemical integrity of N-Boc amino acids (Li et al., 2003).

Benzyl Carbamate (Cbz group):

The benzyl carbamate is one of the most popular protective groups that results largely from its facile hydrogenolysis and its orthogonality to numerous other protective groups.

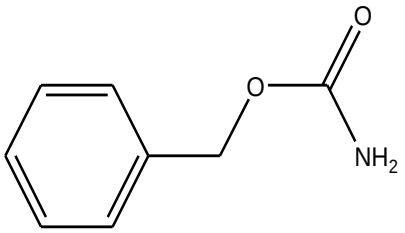


Figure1.1 Benzyl Carbamate

Formation:

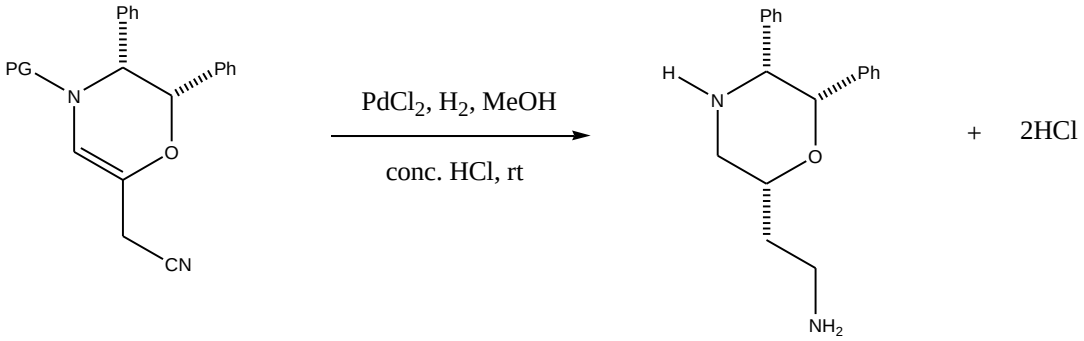
1. $PhCH_2OCOCl$, MgO, EtOAc, 3 h, 70°C to reflux, 60% yield. Zinc metal can be used to scavenge the HCl produced in the protection process. $ZnCl_2$ is formed in the reaction (Dymicky, 1989; Yadav et al., 1998).

2. β-aminopropionic acid was protected by $PhCH_2OCOCl$ with 1 N NaOH from 0°C to ambient temperature overnight (Garcia et al., 2001).

Cleavage:

1. Raney Ni (W-2), MeOH, reflux, 65% yield. (Tamura et al., 2001)

2. $PdCl_2$, MeOH, H_2, conc. HCl, rt, 100% yield. These conditions also reduce olefins, but benzylic ether remained intact. At 80–85°C these conditions will cleave the benzylic amine and ether (Jain et al., 2001).



Scheme 1.10 Formation of desired all syn-substituted oxazine in essentially quantitative yield

1.2 Amide Bond Formation

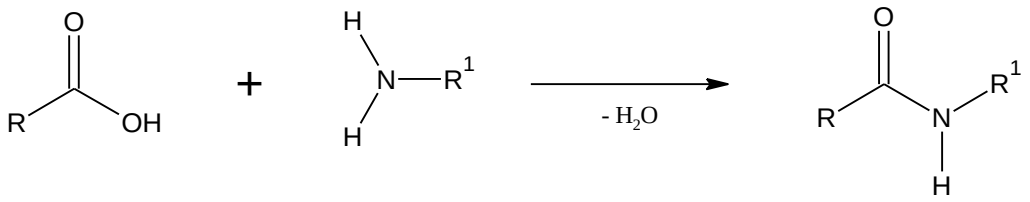
Amide bonds play a major role in the elaboration and composition of biological systems, representing for example the main chemical bonds that link amino acid building blocks together to give proteins.

Amide bonds are not limited to biological systems and are indeed present in a huge array of molecules, including major marketed drugs.

Amide bonds are typically synthesized from the union of carboxylic acids and amines. However, unification of these two functional groups does not occur spontaneously at ambient temperature, with the necessary elimination of water only taking place at high temperatures (e.g. > 200 °C), conditions typically detrimental to the integrity of the substrates.

For this reason, it is usually necessary to first activate the carboxylic acid, a process that usually takes place by converting the –OH of the acid into a good leaving group prior to treatment with the amine.

Enzymatic catalysis has also been investigated for the mild synthesis of amides and the organic chemist may find some of these methods useful as an alternative to traditional methods (Gotor, 1999; Rantwijk et al., 2000).



Scheme 1.11 Principle of the activation process for amide –bond formation

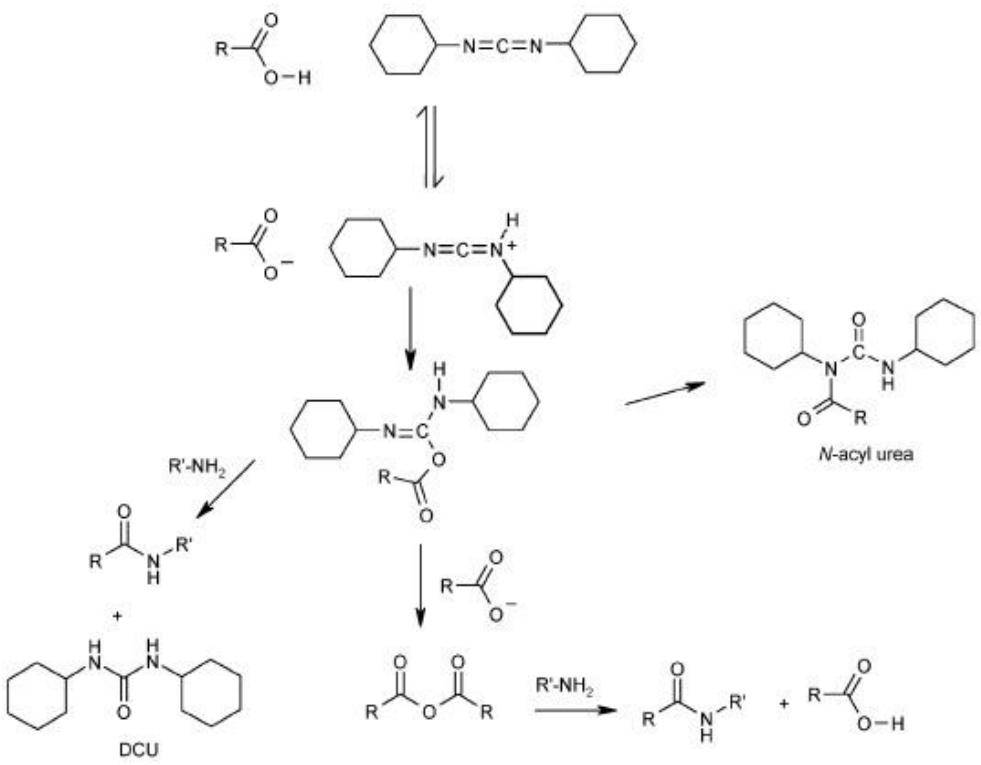
In order to activate carboxylic acids, one can use so-called coupling reagents, which act as stand-alone reagents to generate compounds such as acid chlorides, (mixed) anhydrides, carbonic anhydrides or active esters.

1.2.1 Coupling using carbodiimides

Dicyclohexylcarbodiimides

Carbodiimides were the first coupling reagents to be synthesized. (DCC) Dicyclohexylcarbodiimides has been used for coupling since 1955. The mechanism for coupling carboxylic acids to amines is shown on Scheme 1.12 (Valeur and Bredley, 2009). The first step involves the reaction of the carboxylic acid with DCC to form the O-acylurea. This intermediate can then yield a number of different products. The amide via direct coupling with the amine (the by-product formed), (DCU) dicyclohexylurea, is usually insoluble in the reaction solvent and can be removed via filtration.

Formation of the carboxylic acid anhydride which subsequently yields the amide by reaction with the amine (needs 2 equiv. of acid). When using DCC, oxazolone formation can take place after generation of the o- acylurea leading to epimerization, especially important when activating acid groups in the α position of an amide bond (Valeur and Bradley, 2009) and (Paul, S., Basu B.,2012).

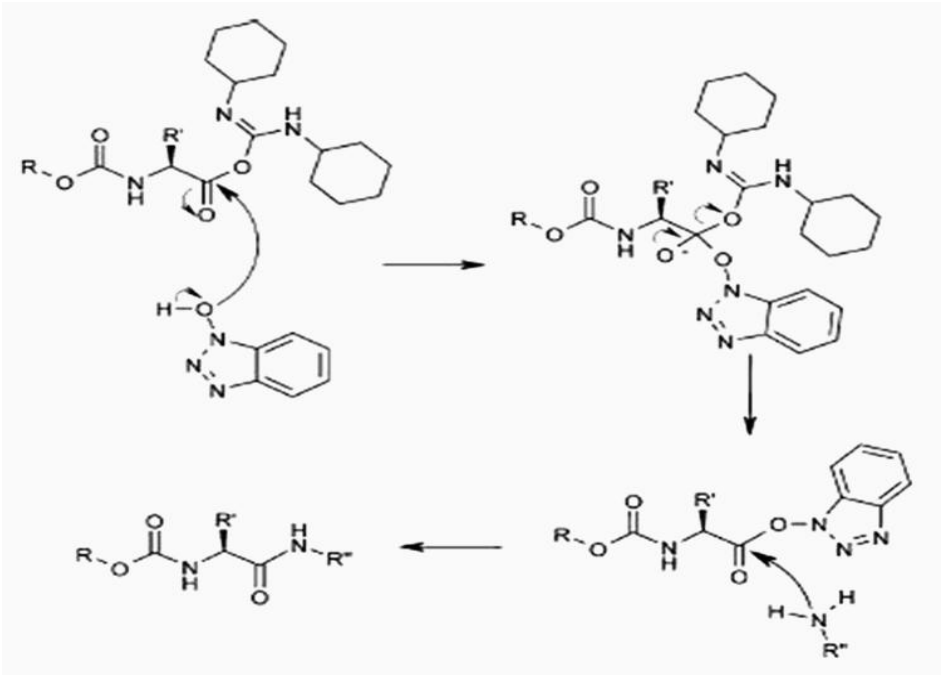


Scheme 1.12 Coupling using DCC

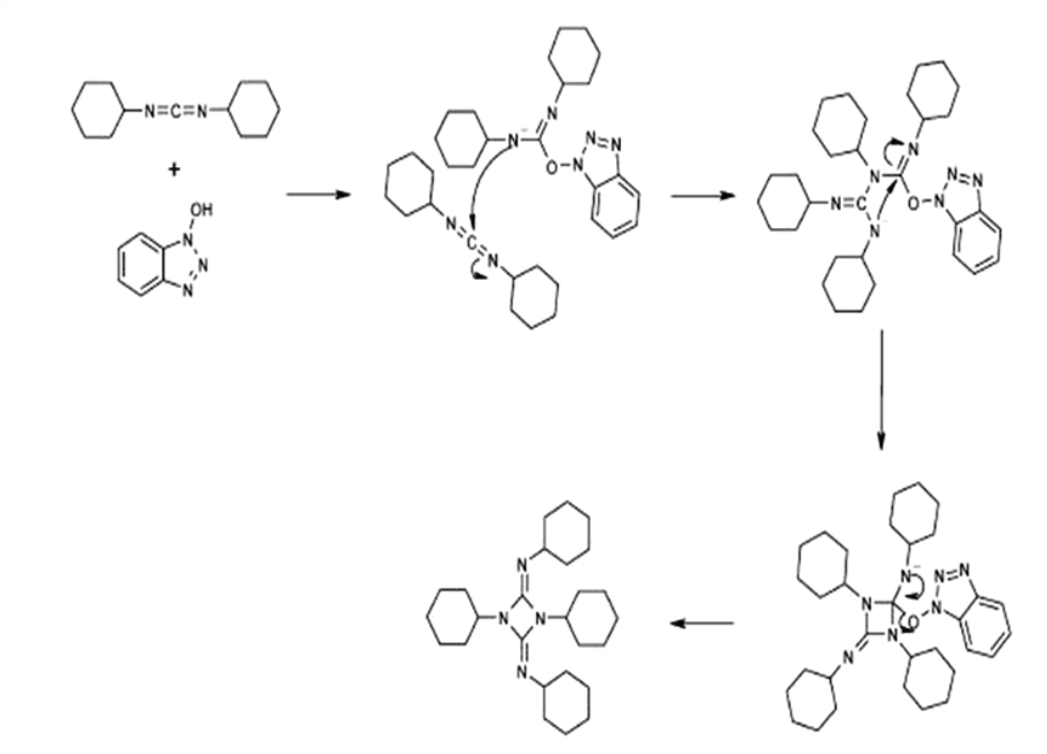
Use of additives in amide formation

In order to reduce the epimerization level when using carbodiimides as coupling reagents, Koenig and Geiger introduced 1-hydroxy-1H-benzotriazole (HOBt) as an additive, showing that, when using this additive, yields were higher and epimerization levels lower. For example, when coupling Z-Gly-Phe-OH to H-Val-OMe, the epimerization levels dropped from 35% to 1.5%.

HOBt is believed to work by initially reacting with the O-acylurea to give the OBt active ester, which enhances the reactivity of the ‘‘activated ester‘‘ by encouraging/stabilizing the approach of the amine via hydrogen bonding (Scheme 1.13). However, HOBt can yield by-products, thus it catalyses the formation of diazetidine (Scheme 1.14). (Valeur and Bradley, 2009)



Scheme 1.13 Mechanism of activation by 1-hydroxy-1H-benzotriazole when used as an additive with DCC



Scheme 1.14 Formation of the diazetidine by-product when using DCC/HOBt

In 1994, Carpino reported a related additive, 1-hydroxy-7-azabenzotriazole (HOAt) (Figure 1.2), which was even more efficient than HOBt in terms of yield, kinetics and reduced epimerization levels. For example epimerization during coupling of Z-Val-OH and H-Val-OMe using DCC dropped from 41,9% with HOBt to 14,9% with HOAt, while during the coupling of Z-PheVal-OH to H-Ala- OMe using EDC, it dropped from 4,1% with HOBt to under 2% with HOAt.

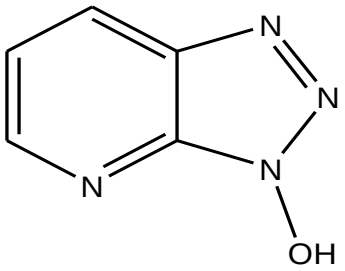


Figure 1.2 Structure of 1-hydroxy-7-azabenzotriazole

Other carbodiimides

Since the application of DCC to amide bond formation, many carbodiimides, including DIC (diisopropylcarbodiimide) have been reported and this field has been reviewed. In particular, attention has focused on so-called water-soluble carbodiimides, as the ureas formed when using DCC or the popular DIC can sometimes be difficult to remove (Williams and Ibrahim, 1981).

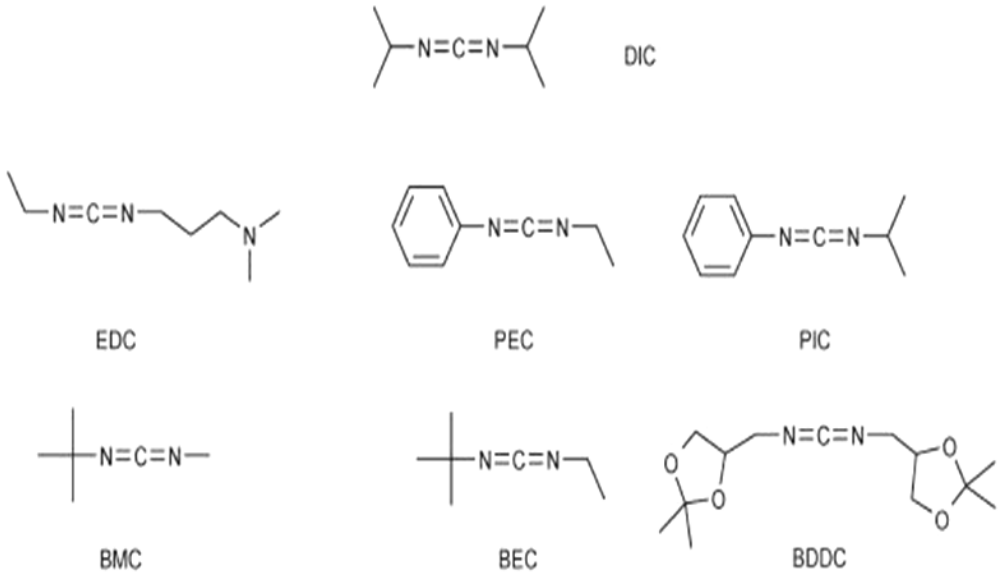
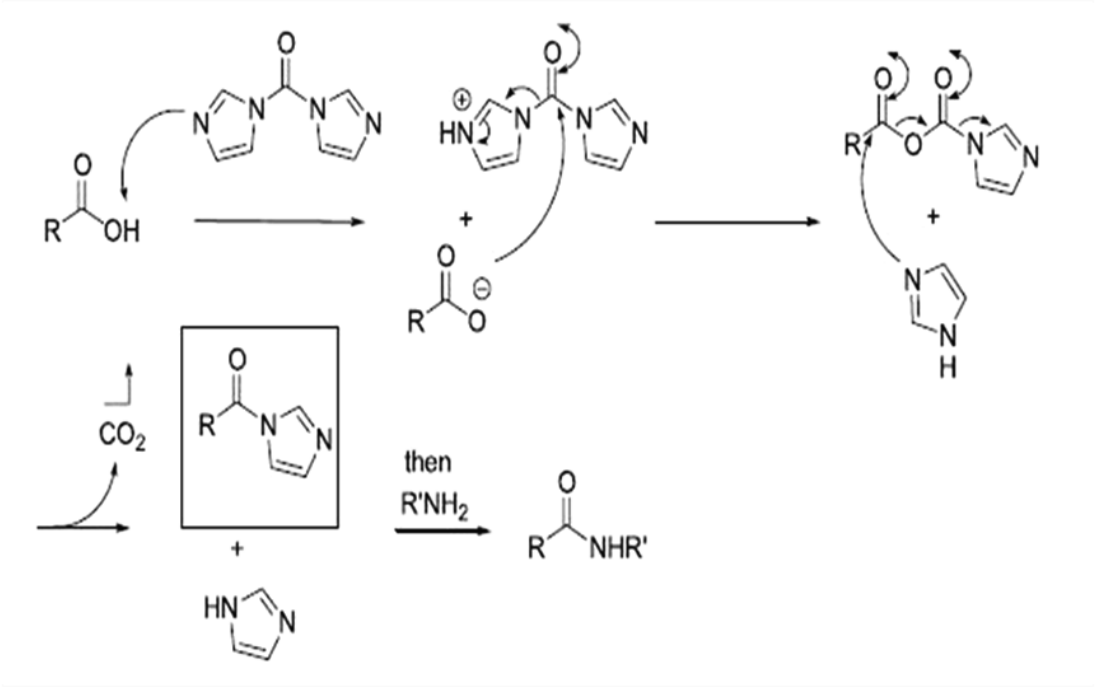


Figure 1.3 Structures of some common carbodiimides

Acylimidazoles using CDI

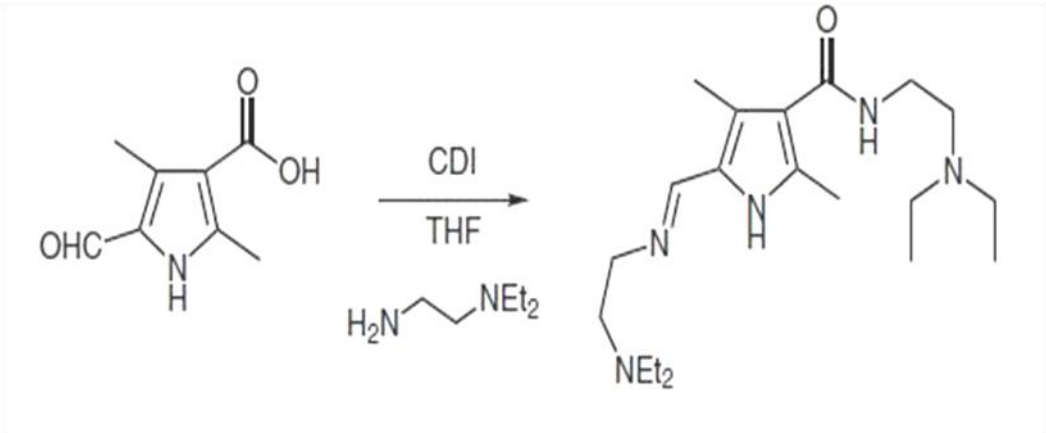
Carbonyl diimidazole (CDI) is a useful coupling reagent that allows one-pot amide formation. Acyl carboxyl imidazole and imidazole are initially formed but readily react together to yield the activated species as the acylimidazole. Practically, the acylimidazole is preformed for 1 h and then the amine is added.

This reaction, which generates imidazole in situ, does not need an additional base and is even compatible with HCl salts of the amine. This reagent is commonly used on a large scale in peptide chemistry and its use can be extended to the formation of esters and thioesters (Montalbetti and Falque, 2005).



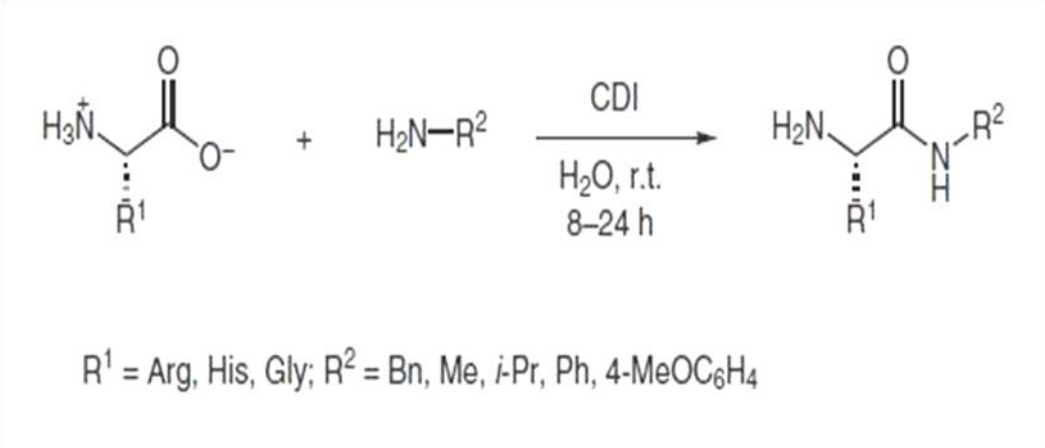
Scheme 1.15 One-pot amide preparation using CDI

Amidation reactions between different sterically hindered acid aldehydes and amines have been reported to be efficiently catalyzed by CDI. First, compound is activated with CDI, then, addition of N,N-diethylethylenediamine to the reaction mixture leads to the imine amide product. Remarkable rate enhancement was observed in the reaction due to catalysis by the released carbon dioxide (Vaidyanathan et al., 2004).



Scheme 1.16 Amidations Using N,N‘-Carbonyldiimidazole

Recently, the first amidation reaction of unprotected α-amino acids in water under neutral conditions with various aliphatic, aromatic, and heteroaromatic primary amines in the presence of CDI at ambient temperature was reported. Zwitterionic amino acids first react with CDI leading to the formation of the intermediate mixed anhydride, followed by nucleophilic attack of amines facilitating the formation of amides in moderate yields (Sharma and Jain, 2007).



Scheme 1.17Amidation of unprotected a-amino acids in water

1.3 Benzimidazole

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12}.1 (Figure 1.4)(Patil A, Ganguly and Surana, 2008).

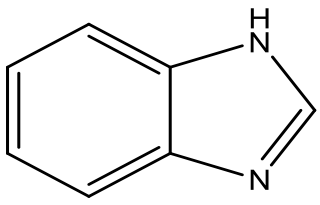


Figure 1.4 1H-benzimidazole

The use of Benzimidazole dates many years back (Cook GC. 1990). In 1990 various benzimidazole derivatives were synthesized with substitution of fluorine, propylene, tetrahydroquinoline and cyclised compound which resulted in compounds with increased stability, bioavailability and significant biological activity. It was also showed that substitution on pyridine by electron donating group increases activity.

In 1991 benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity.

Nowadays infectious microbial diseases are causing problems world-wide, because of resistance to number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin). A variety of clinically significant species of microorganisms has become an important health problem globally. One way to fight with this challenge is the appropriate usage of the available marketed antibiotics the other is the development of novel anti-microbial agents (Metwally KA, Abdel-Aziz. 2006). Hence, there will always be a vital need to discover new chemotherapeutic agents to overcome the emergence of resistance and ideally shorten the duration of therapy.

Due to the structural similarity to purine, antibacterial ability of benzimidazoles is explained by their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins.

Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize. This may be depicted as follows:

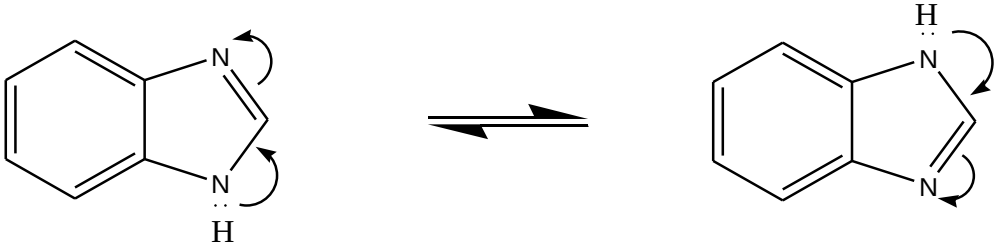


Figure 1.5 Tautomerism of 1H-benzimidazole

1.3.1 Synthesis of Benzimidazoles

Practically all syntheses of benzimidazoles start with benzene derivatives possessing nitrogen-containing functions ortho to each other; that is, the starting material possesses the function designated by formula:

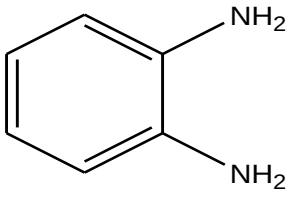


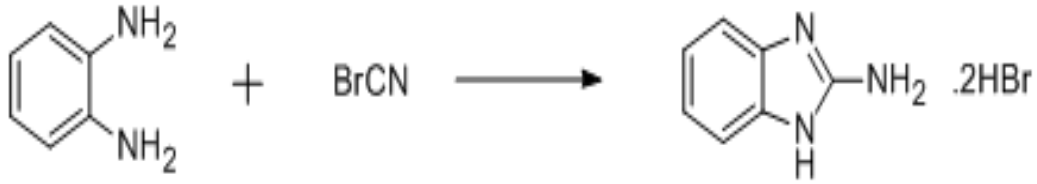
Figure 1.6 Benzene 1, 2 diamine

In the following discussion the synthetic methods have been grouped in the main according to the starting material used (BLATTA. H. 1946).

By reaction of carboxylic acid and carboxylic acid derivatives, o-phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles:

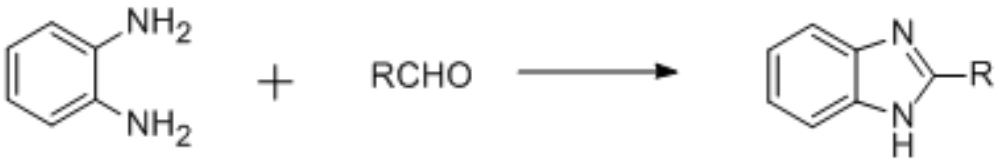
Scheme 1.18 Synthesis of 2-substituted benzimidazoles

By reaction with nitriles, cyanogen bromide reacts with o-phenylenediamine to give 2-aminobenzimidazoles:



Scheme 1.19 Synthesis of 2-amino benzimidazoles

By reaction with aldehydes, under the correct conditions aldehydes may react with o-phenylenediamine to yield 2-substituted benzimidazoles:



Scheme 1.20 Reaction of aldehydes with o-phenylenediamine

1.3.3 Natural Products Containing Benzimidazole Nucleus

The benzimidazole nucleus does not appear to occur very widespread in nature. However, very recently the 5, 6-dimethylbenzimidazole moieties have been shown to be part of the structure of vitamin B_{12}.

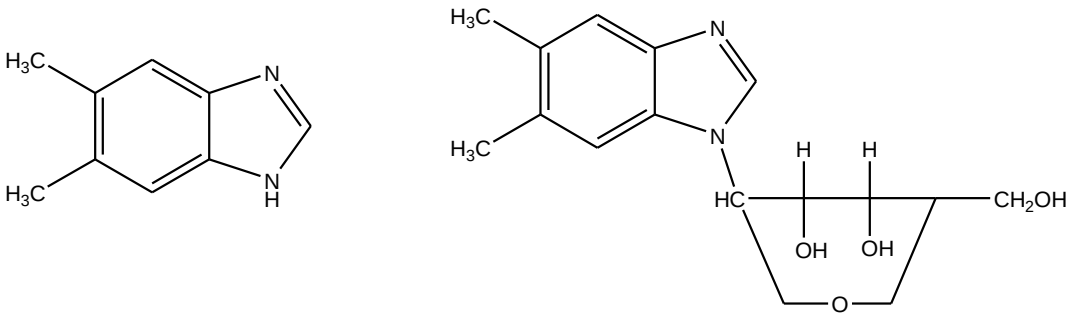


Figure 1.7 Natural Products Containing Benzimidazole Nucleus

Vitamin B_{12} contains one cyano group bound coordinatively to the cobalt atom present. Some of vitamin B_{12} does not contain this cyano group (Kaczka, E. A. 1951).

However, addition of cyanide ions to a solution of them yields vitamin B_{12}. The basis of available evidence is the partial formula:

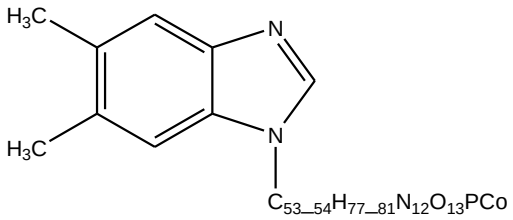


Figure 1.8 Benzimidazole derivative

1.3.4 Biological Action of Benzimidazole

Benzimidazole and a number of derivatives of benzimidazole possess a variety of biological actions. Benzimidazole, 2-methylbenzimidazole and 2-phenylbenzimidazole have been studied pharmacologically by Auverman (Kacakn, E. A.1951).

Benzimidazole is relatively nontoxic and has little effect on the blood pressure. Because of their relation to histamine, a number of 8-aminoethyl derivatives of benzimidazole have been studied. (5or 6)-B-Aminoethylbenzimidazole and 2-methyl-(5or 6)-B-aminoethylbenzimidazole are said to cause a rise in blood pressure.

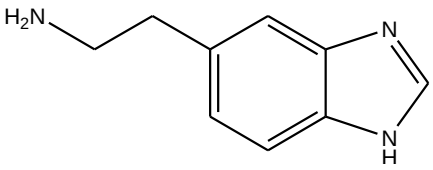
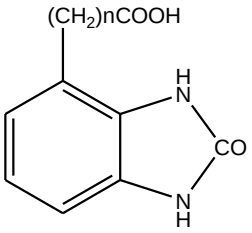


Figure 1.9 (5or 6)-B-Aminoethylbenzimidazole

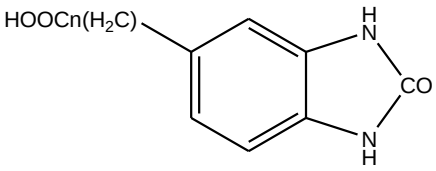
A large number of benzimidazole derivatives is reported to possess trypanosomicidal and spirocheticidal action and is active against diseases caused by protozoa. These compounds in most cases are derivatives of 2(3H)-benzimidazolethione or 2(3H)-benzimidazolone containing an arseno, arsonic acid or arsine oxide grouping on the benzene portion of the benzimidazole ring.

A number of benzimidazoles have been tested for goitrogenic activity (Bywater and Jenesel. 1945). In the main, these compounds are derivatives of 2(3H)-benzimidazolethione.

2(3H)-Benzimidazolethione itself is markedly goitrogenic. 2(3H)-Benzimidazolonecarboxylic acids of the type of CVIII and CIX, (where n = 0, 3, 4).



CVIII



CIX

Figure 1.10 Another Benzimidazole derivatives

1.3.5 Uses of Benzimidazole

A large number of patents describe benzimidazole derivatives of use in the textile industry as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing. In the main, these compounds are sulfonated benzimidazoles. Another use is in the treatment of fibers to improve whiteness of the undyed material or as optical bleach. A number of aminobenzimidazoles have been used for preparation of sulfur and azo dyes of use in the textile industry.

Another use has been in the preparation of fluorescent dyes for use in such preparations as inks for marking clothes to be dry-cleaned. The mark becomes visible under ultraviolet light (John B. Wright. 1951). Several benzimidazole derivatives have found use in the preparation of sun burn preventatives. These compounds protect the skin by absorbing ultraviolet rays.

5-Methylbenzimidazole has been used as a camphor substitute. 2-Methylbenzimidazole is said to be as value of a polymerization inhibitor and initiator in isoprene. 1-Piperidinomethylbenzimidazole has been claimed to be of value as a booster compound for use with antioxidants in rubber. A number of salts of benzimidazolesulfonic acid are said to be of value in preparations for the care of the mouth and teeth.

1.4 Thiourea

Thiourea is an organosulfur compound with the formula $SC(NH_2)_2$. It is structurally similar to urea, except that the oxygen atom is replaced by a sulfur atom, but the properties of urea and thiourea differ significantly. Thiourea is a reagent in organic synthesis. "Thiourea" refers to a broad class of compounds with the general structure (R^1R^2N) (R^3R^4N) C=S. Figure 1.11

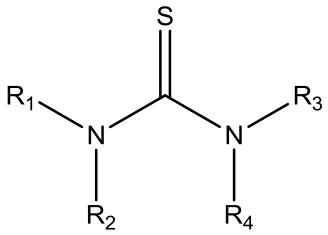
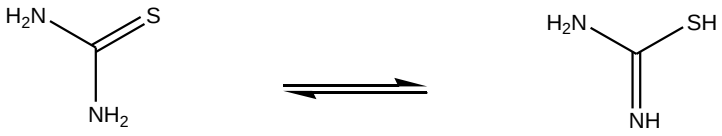


Figure 1.11 General chemical structure of a thiourea

Thiourea is a planar molecule. The C=S bond distance is 1.60±0.1 Å for thiourea (as well as many of its derivatives). The material has the unusual property of changing to ammonium thiocyanate upon heating above 130 °C. Upon cooling, the ammonium salt converts back to thiourea.

Thiourea occurs in two tautomeric forms. In aqueous solution, the thione shown on the left below predominates:



Thione form Thiol form

Figure 1.12 Tautomeric forms of thiourea

1.4.1 Properties of Thiourea

Thiourea is a diamide of thiocarbonic acid and occurs as white or almost colorless crystals at room temperature (Akron 2013). It is soluble in cold water, alcohol, and ammonium thiocyanate, and sparingly soluble in ether. It is stable under normal temperatures and pressures.

1.4.2 Uses of Thiourea

The most common uses for thiourea have been for the production of thiourea dioxide (30%), in leaching of gold and silver ores (25%), in diazo papers (15%), and as a catalyst in the synthesis of fumaric acid (10%). It has also been used in the production and modification of synthetic resins.

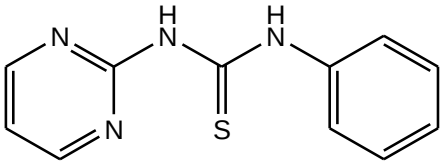
Other uses of thiourea are as a photographic toning agent, in hair preparations, as a dry cleaning agent, in the synthesis of pharmaceuticals and pesticides, in boiler-water treatment, and as a reagent for bismuth and selenite ions.

It has also been used in textile and dyeing auxiliaries, in the production of industrial cleaning agents (e.g., for photographic tanks and metal surfaces in general), for engraving metal surfaces, as an isomerization catalyst in the conversion of maleic to fumaric acid, in copper-refining electrolysis, in electroplating, and as an antioxidant.

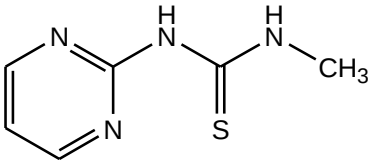
Other uses have included as a vulcanization accelerator, an additive for slurry explosives, as a viscosity stabilizer for polymer solutions, and as a mobility buffer in petroleum extraction.

It is also used as an ingredient of consumer silver polishes and has been used in the removal of mercury from wastewater by chlorine-alkali electrolysis.

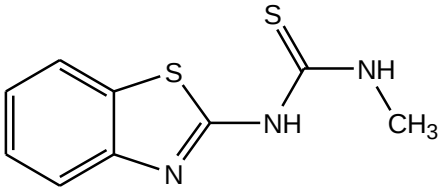
1.4.3 Some Thiourea Structures



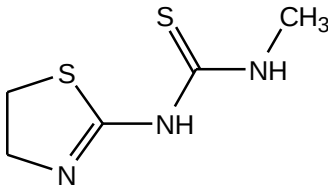
2-Pyrimidylphenylthiourea
(2-Pym TuPh)



2-Pyrimidylmethylthiourea
(2-Pym TuMe)



Benzothiazolemethylthiourea
(Bzt TuMe)



Thiazolemethylthiourea
(Thz TuMe)

Figure 1.13 Some Thiourea Structures

1.4.4 Carcinogenicity of Thiourea

Thiourea is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Thiourea caused tumors in rats at several different tissue sites and by two different routes of exposure. Administration of thiourea in the drinking water caused

benign and malignant thyroid-gland tumors (adenoma and carcinoma) in both sexes and cancer of the Zymbal gland (squamous-cell carcinoma) in males.

Dietary administration caused benign liver tumors (hepatocellular adenoma) in rats of unspecified sex, and intraperitoneal injection followed by administration in the drinking water caused cancer of the Zymbal gland (squamous-cell carcinoma or mixed-cell sarcoma) in rats of both sexes.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to thiourea (Akron. 2013).

2. Materials and Methods

2.1. General techniques and materials

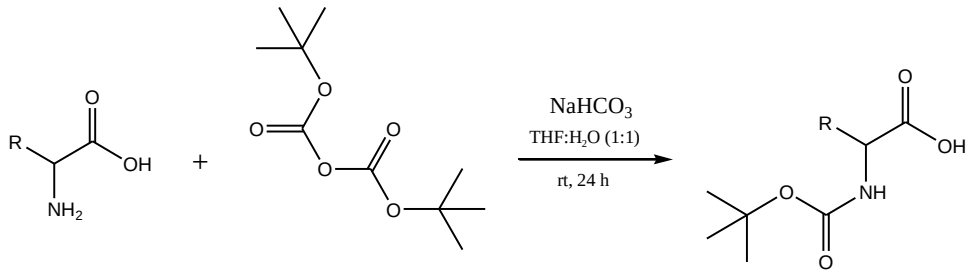
In spectroscopic studies IR spectra were obtained by Perkin Elmer Spectrum 100 FTIR Spectrometer.^{13}C-NMR and ^{1}H-NMR (400MHz) spectra were recorded on an Oxford NMR 400 MHz spectrometer using TMS as the internal standard d-values (in ppm) and coupling constants (in Hz). Melting points were recorded with an electro thermal digital melting points apparatus. All solvents were distilled before use. They also were evaporated under reduced pressure with rotary evaporator after finishing reactions.

For TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silica gel G-60 (Merck 7734), respectively. For UV active components, the spots were observed under the UV lamp for TLC.

L-methionine (Alfa Aesar), L-isoleucine (Alfa Aesar), L-phenylalanine (Alfa Aesar), D-phenylglycine (Alfa Aesar), Orthophenylenediamine (Alfa Aesar), (DCC) N,N'-Dicyclohexylcarbodiimide (Aldrich), Di-tert-butyl dicarbonate (Aldrich), Sodium bicarbonate (Carlo-Erba), 85% Phosphoric acid (Carlo-Erba) and 3,5-Bis (trifluoromethyl) phenyl isothiocyanate (Aldrich), were used as received.

2.2 Experiments

2.2.1 Preparation of N-(tert-butoxycarbonyl)-Amino acid (general procedure)

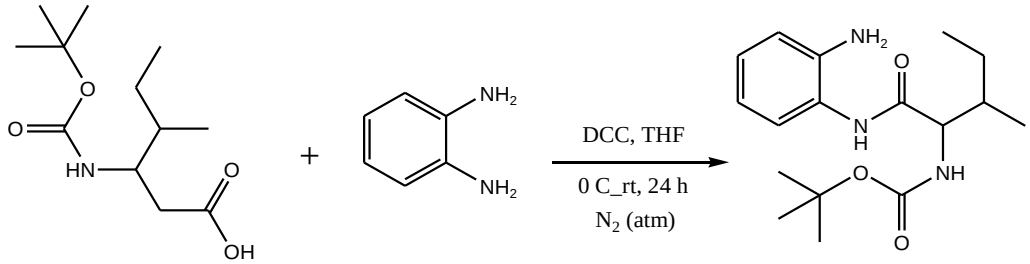


R= $CH(C_2H_5)(CH_3)$, C_6H_6, $CH_2CH_2SCH_3$ or $CH_2(C_6H_6)$

To a mixture of (1 equiv) an amino acid (L-isoleucine, D-Phenylglycine, L-methionine or L-phenylalanine) and (4 equiv) of sodium bicarbonate in 30 ml of water, (1.1 equiv) of di-tert-butyl dicarbonate which dissolved in 30 ml of THF was added to the solution mixture. The reaction mixture was stirred at room temperature for approximately two days until reaction was complete. The reaction was monitored by TLC (MeOH/ EtOAc, 1:1 by volume). THF was removed in vacuo. The residue was adjusting the pH 3 by the addition of 6N HCl. The acidic solution was then extracted with EtOAc (2x20 ml). The combinated ethyl acetate phase was dried over Na_2SO_4, concentrated in vacuo to give the desired product (viscous transparent Colour).

L-isoleucine, D-Phenylglycine, L-methionine and L-phenylalanine was obtained in %90, %92, %89 and %87 yields

2.2.2 Preparation of N-(tert-butoxycarbonyl)-L-isoleucine- benzene-1, 2-diamine (general procedure)



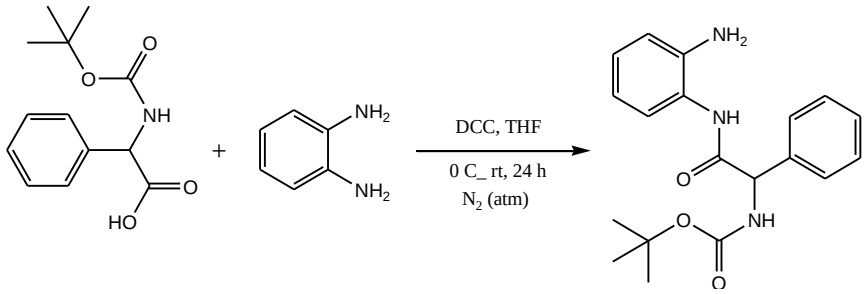
Orthophenylenediamine (0.66 g, 6.13 mmol) and N-(tert-butoxycarbonyl)-L-isoleucine (1.42 g, 6.13 mmol) were dissolved in 30 ml of THF and cooled to 0 °C. Into the above solution was added N, N'-dicyclohexylcarbodiimide (1.53 g, 7.35 mmol) in batches and the mixture was stirred at 0 °C for half an hour and then at

room temperature overnight. The reaction was monitored by TLC with the eluting solvent (3:2, Hexane/EtOAc). The reaction mixture was filtrated and evaporated to afford brown oil.

The product was purified by a silica-gel column chromatography (Hexane / EtOAc, 3:2 by volume) to get a yellow solid yielding (**Compound 1**) (72%) as a white solid and m.p was (156-158) °C.

The IR spectrum, ^{1}H-NMR and ^{13}C-NMR spectrum of N-(tert-butoxycarbonyl)-L-isoleucine-benzene-1,2-diamine (**Compound 1**) are shown in appendix 1 on pages 99, 100, 101 and the result of the elemental analysis is given in table 3.4

2.2.3 Preparation of N-(tert-butoxycarbonyl)-D-phenylglycine - benzene-1,2-diamine



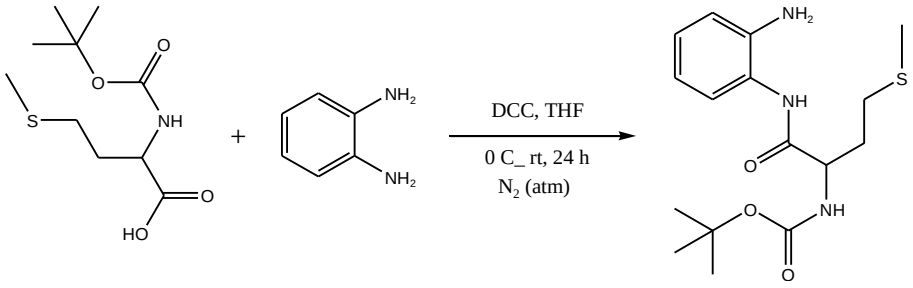
Compound 2 was synthesized according to the same procedure as described above.

Orthophenylenediamine (1.25 g, 11.6 mmol), N-(tert-butoxycarbonyl)-D-phenylglycine (2.91 g, 11.6 mmol), N,N'-dicyclohexylcarbodiimide (2.87 g, 13.9 mmol) and 30 ml THF were used.

Compound 2 was obtained in % 69 yield and m.p was (131-133) °C.

The IR spectrum, ^{1}H-NMR and ^{13}C-NMR spectrums of N-(tert-butoxycarbonyl)-D-phenylglycine-benzene-1,2-diamine (**Compound 2**) are shown in appendix 2 on pages 102, 103, 104 and the result of the elemental analysis is given in table 3.4

2.2.4 Preparation of N-(tert-butoxycarbonyl)-L-methionine - benzene-1, 2-diamine



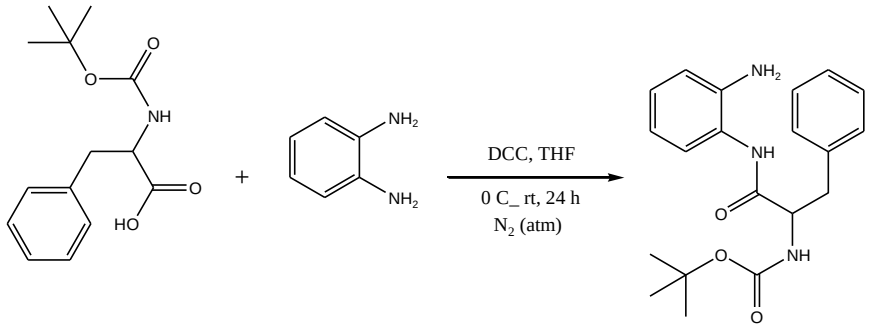
Compound 3 was synthesized according to the same procedure as described above.

Orthophenylenediamine (0.84 g, 7.8 mmol), N-(tert-butoxycarbonyl)-L-methionine (1.94 g, 7.8 mmol), N,N'-dicyclohexylcarbodiimide(1.93 g, 9.3 mmol) and 30 ml THF were used.

Compound 3 was obtained in % 71 yield and m.p was (142-144) °C.

The IR spectrum, ^{1}H-NMR and ^{13}C-NMR spectrum of N-(tert-butoxycarbonyl)-L-methionine-benzene-1,2-diamine (**Compound 3**) are shown in appendix 3 on pages 105, 106, 107and the result of the elemental analysis is given in table 3.4

2.2.5 Preparation of N-(tert-butoxycarbonyl)-L-phenylalanine-benzene-1, 2-diamine



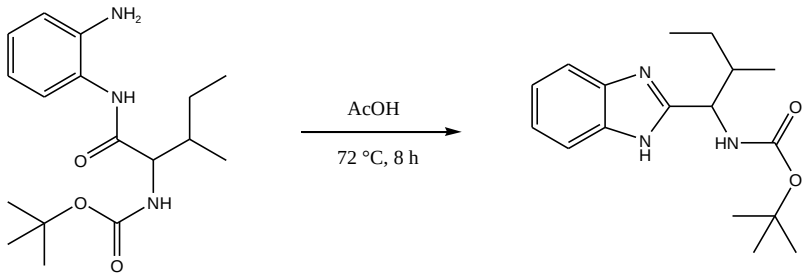
Compound 4 was synthesized according to the same procedure as described above.

Orthophenylenediamine (0.57 g, 5.36 mmol), N-(tert-butoxycarbonyl)-L-phenylalanine (1.42 g, 5.36 mmol), N,N'-dicyclohexylcarbodiimide(1.32 g, 6.3 mmol) and 30 ml THF were used.

Compound 4 was obtained in % 66 yield and m.p was (147-149) °C.

The IR spectrum, ^{1}H-NMR and ^{13}C-NMR spectrum of N-(tert-butoxycarbonyl)-L-phenylalanine-benzene-1,2-diamine (**Compound 4**) are shown in appendix 4 on pages 108, 109, 110 and the result of the elemental analysis is given in table 3.4

2.2.6 Preparation of N-(tert-butoxycarbonyl)-L-isoleucine Derivative of Benzimidazole Compound (general procedure)

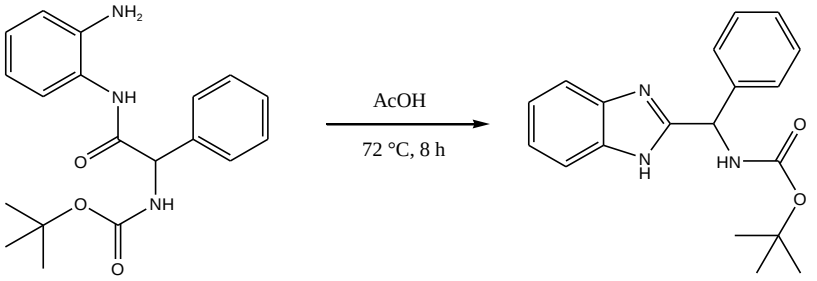


N-(tert-butoxycarbonyl)-L-isoleucine-benzene-1,2-diamine (1 g, 3.17 mmol), was dissolved in 20 ml of acetic acid and the solution was stirred at 72 °C for 8 h. The reaction was monitored by TLC with the eluting solvent (2:1, Hexane/EtOAc). The acetic acid was removed under reduced pressure and the crude compound was purified by a silica-gel column chromatography (Hexane / EtOAc, 3:2 by volume) to afford a white solid.

Compound 5 was obtained in % 75 yield and m.p was (226-228) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-(tert-butoxycarbonyl)-L-isoleucine Derivative of Benzimidazole Compound (**Compound 5**) are shown in appendix 5 on pages 111, 112, 113 and the result of the elemental analysis is given in table 3.4

2.2.7 Preparation of N-(tert-butoxycarbonyl)-D-phenylglycine Derivative of Benzimidazole Compound



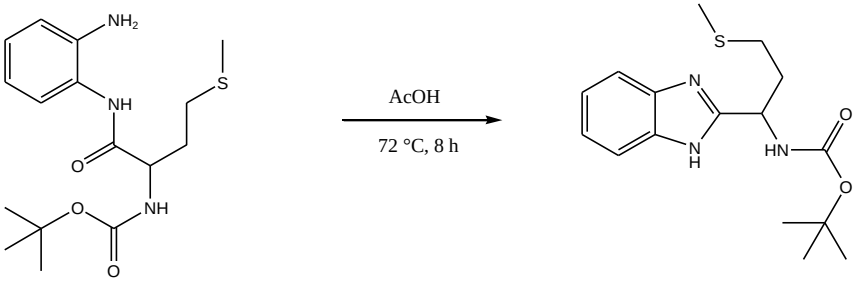
Compound 6 was synthesized according to the same procedure as described above.

N-(tert-butoxycarbonyl)-D-phenylglycine-benzene-1,2-diamine (0.82 g, 2.41 mmol) and 20 ml of Acetic acid were used.

Compound 6 was obtained in % 76 yield and m.p was (195-198) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-(tert-butoxycarbonyl)-D-phenylglycine Derivative of Benzimidazole Compound (**Compound 6**) are shown in appendix 6 on pages 114, 115, 116 and the result of the elemental analysis is given in table 3.4

2.2.8 Preparation of N-(tert-butoxycarbonyl)-L-methionine Derivative of Benzimidazole Compound



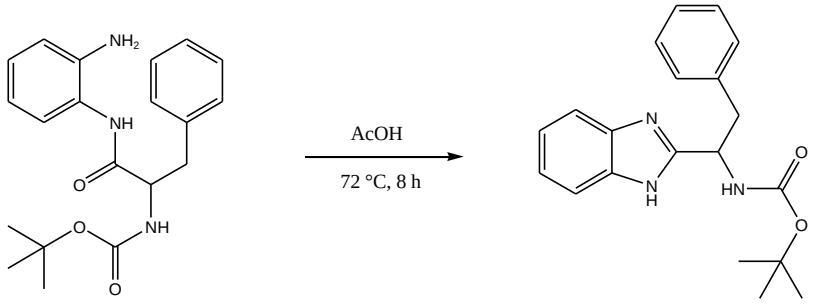
Compound 7 was synthesized according to the same procedure as described above.

N-(tert-butoxycarbonyl)-L-methionine-benzene-1,2-diamine (1.76 g, 5.2 mmol)and 20 ml of acetic acid were used.

Compound 7 was obtained in % 82.5 yield and m.p was (161-163) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-(tert-butoxycarbonyl)-L-methionine Derivative of Benzimidazole Compound (**Compound 7**) are shown in appendix 7 on pages 117, 118, 129 and the result of the elemental analysis is given in table 3.4

2.2.9 Preparation of N-(tert-butoxycarbonyl)-L-Phenylalanine Derivative of Benzimidazole Compound



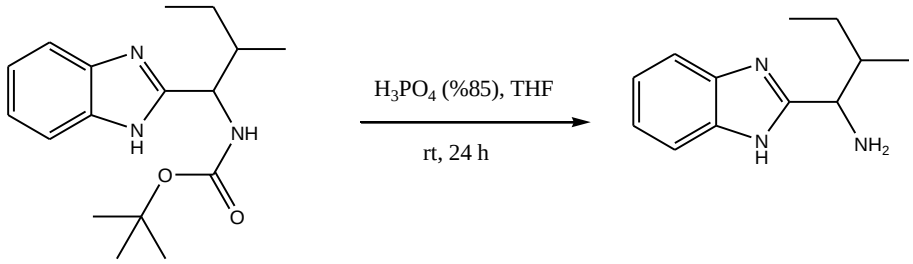
Compound 8 was synthesized according to the same procedure as described above.

N-(tert-butoxycarbonyl)-L-phenylalanine-benzene-1, 2-diamine (1.18 g, 3.3 mmol) and 20 ml of Acetic acid were used.

Compound 8 was obtained in % 68 yield and m.p was (206-208) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-(tert-butoxycarbonyl)-L-phenylalanine Derivative of benzimidazole Compound (**Compound 8**) are shown in appendix 8 on pages 120, 121, 122 and the result of the elemental analysis is given in table 3.4

2.2.10 Preparation of L-isoleucine Derivative of Benzimidazole Compound (general procedure)

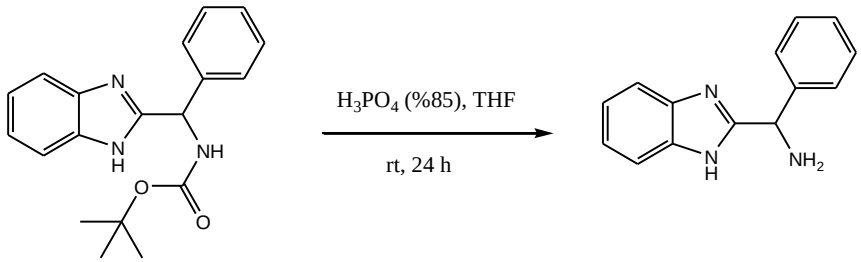


N-(tert-butoxycarbonyl)-L-isoleucine Derivative of Benzimidazole Compound (0.36 g, 1.2 mmol) was dissolved in 5 ml of THF. Aqueous phosphoric acid (85 wt %) was added to a solution. The mixture was stirred at room temperature until reaction was complete (typically 12–24 h). The reaction was monitored by TLC with the eluting solvent (3:2, Hexane/EtOAc). Water was added to dilute the reaction mixture, and sodium hydroxide solution was added to adjust the pH to 7–8. The mixture was then extracted with EtOAc (2x20 ml). The combinated ethyl acetate phase was dried over Na_2SO_4, concentrated in vacuo to give the desired product.

Compound 9 was obtained in % 70 yield and m.p was (162-164) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of L-isoleucine derivative of benzimidazole compound (**Compound 9**) are shown in appendix 9 on pages 123, 124, 125 and the result of the elemental analysis is given in table 3.4

2.2.11 Preparation of D-phenylglycine Derivative of Benzimidazole Compound



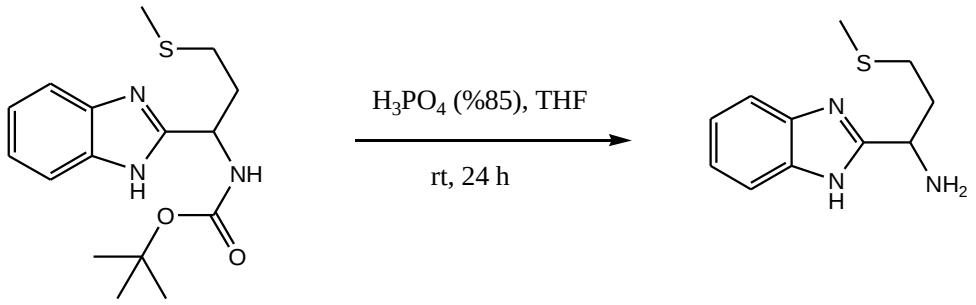
Compound 10 was synthesized according to the same procedure as described above.

N-(tert-butoxycarbonyl)-D-phenylglycine Derivative of Benzimidazole Compound (0.53 g, 1.6 mmol) and aqueous phosphoric acid were used.

Compound 10 was obtained in % 65 yield and m.p was (201-203) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of D-phenylglycine Derivative of Benzimidazole Compound (**Compound 10**) are shown in appendix 10 on pages 126, 127, 128 and the result of the elemental analysis is given in table 3.4

2.2.12 Preparation of L-methionine Derivative of Benzimidazole Compound



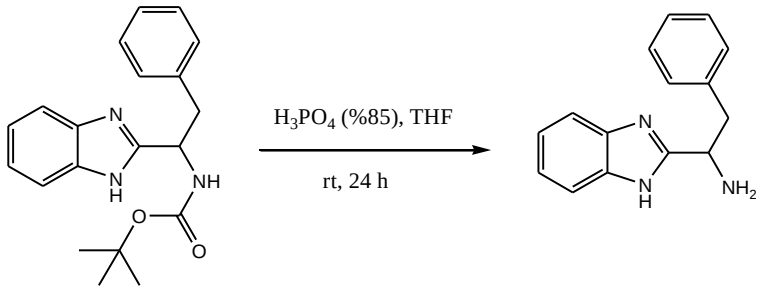
Compound 11 was synthesized according to the same procedure as described above.

N-(tert-butoxycarbonyl)-L-methionine Derivative of Benzimidazole Compound (0.88 g, 2.7 mmol) and aqueous phosphoric acid were used.

Compound 11 was obtained in % 66 yield

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of L-methionine Derivative of Benzimidazole Compound (**Compound 11**) are shown in appendix 11 on pages 129, 130, 131 and the result of the elemental analysis is given in table 3.4

2.2.13 Preparation of L-phenylalanine Derivative of Benzimidazole Compound



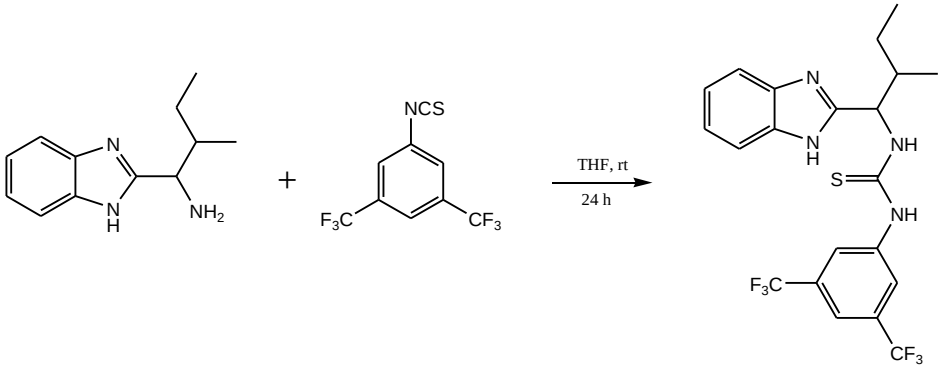
Compound 12 was synthesized according to the same procedure as described above.

N-(tert-butoxycarbonyl)-L-phenylalanine Derivative of Benzimidazole Compound (0.88 g, 2.7 mmol) and aqueous phosphoric acid were used.

Compound 12 was obtained in %88 yield and m.p was (169-172) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of L-phenylalanine Derivative of Benzimidazole Compound (**Compound 12**) are shown in appendix 12 on pages 132, 133, 134 and the result of the elemental analysis is given in table 3.4

2.2.14 Preparation of N-[1-(1H-benzimidazol-2-yl)-2-methylbutyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (General Procedure)

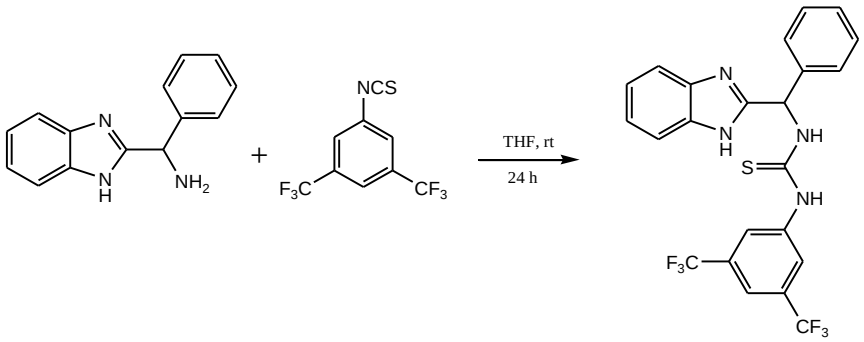


L-isoleucine Derivative of Benzimidazole Compound (0.14 g, 0.68 mmol) was dissolved in 5 ml of dry THF. Then1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.18 g, 0.68 mmol) was added at 0 °C to the solution. The mixture was stirred for 10 min at 0 °C, allowed to reach room temperature, and stirred for a further 24 h. The reaction was monitored by TLC with the eluting solvent (3:2, Hexane/EtOAc). The solvent was removed in vacuum and the resulting material was purified by column chromatography (Hexane/Ethyl acetate, 3:2 by volume) to get a yellow viscous product.

Compound 13 was obtained in % 65 yield and m.p was (175-177) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-[1-(1H-benzimidazol-2-yl)-2-methylbutyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (**Compound 13**) are shown in appendix 13 on pages 135, 136, 137 and the result of the elemental analysis is given in table 3.4

2.2.15 Preparation of N-[1H-benzimidazol-2-yl(phenyl)methyl]-N'-[3,5-bis(trifluoromethyl)phenyl]thiourea



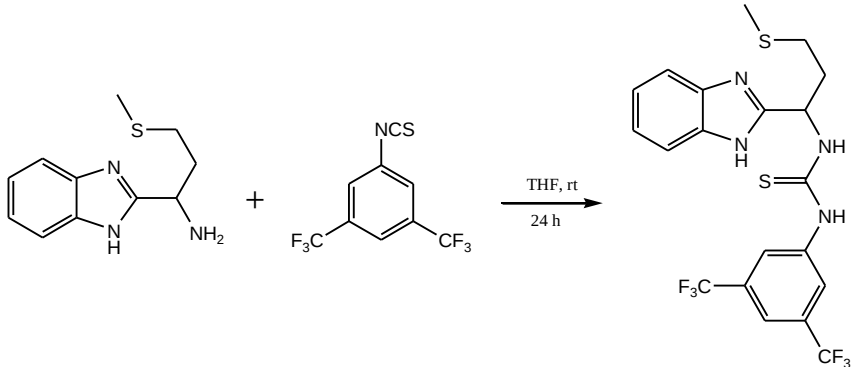
Compound 14 was synthesized according to the same procedure as described above.

D-phenylglycine Derivative of Benzimidazole Compound (0.18 g, 0.83 mmol), 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.22 g, 0.83 mmol) and 5 ml THF were used.

Compound 14 was obtained in % 66 yield and m.p was (104-106) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-[1H-benzimidazol-2-yl(phenyl)methyl]-N'-[3,5-bis(trifluoromethyl)phenyl]thiourea (**Compound** 1**4**) are shown in appendix 14 on pages 138, 139, 140 and the result of the elemental analysis is given in table 3.4

2.2.16 Preparation of 1-[1-(1H-benzimidazol-2-yl)-3-(methylsulfanyl) propyl]-3-[3, 5-bis (trifluoromethyl) phenyl] thiourea



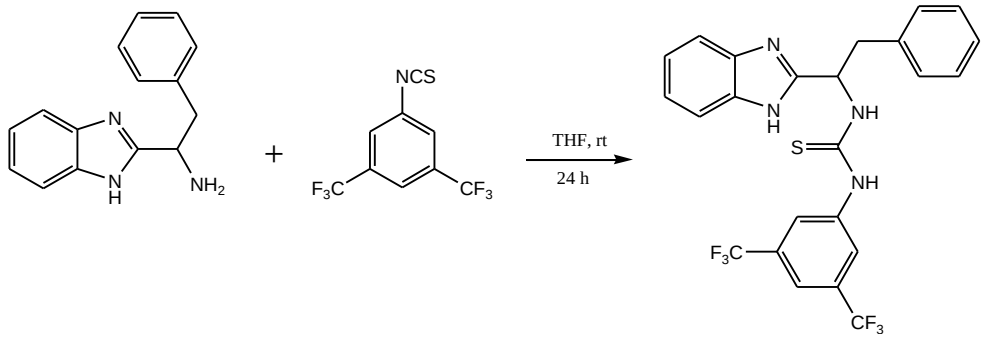
Compound 15 was synthesized according to the same procedure as described above.

L-methionine Derivative of Benzimidazole Compound (0.39 g, 1.7 mmol), 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.48 g, 1.7 mmol) and 5 ml THF were used.

Compound 15 was obtained in % 69 yield and m.p was (105-108) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of 1-[1-(1H-benzimidazol-2-yl)-3-(methylsulfanyl)propyl]-3-[3,5-bis(trifluoromethyl)phenyl]thiourea(**Compound** 1**5**) are shown in appendix 15 on pages 141, 142, 143 and the result of the elemental analysis is given in table 3.4

2.2.17 Preparation of N-[1-(1H-benzimidazol-2-yl)-2-phenylethyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea



Compound 16 was synthesized according to the same procedure as described above.

L-phenylalanine Derivative of Benzimidazole Compound (0.34 g, 1.44 mmol), 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.39 g, 1.44 mmol) and 5 ml THF were used.

Compound 16 was obtained in %65 yield and m.p was (195-197) °C.

The IR, ^{1}H-NMR and ^{13}C-NMR spectrums of N-[1H-benzimidazol-2-yl(phenyl)methyl]-N'-[3,5-bis(trifluoromethyl)phenyl]thiourea (**Compound 16**) are shown in appendix 16 on pages 144, 145, 146 and the result of the elemental analysis is given in table 3.4

3. SPECTROSCOPIC DATA

3.1 IR Spectra and Mode of Bonding

3.1.1 N-(tert-butoxycarbonyl)-L-isoleucine-benzene-1,2-diamine (compound 1)

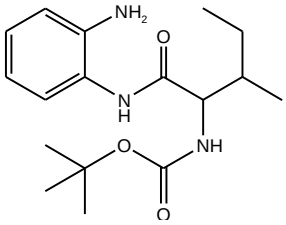


Table 3.1.1 IR Spectral Data (cm^{-1}) of Compound 1

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1673
N-H	3460-3050	3354
C-O	1330-1050	1242
Aromatic C=C	1600-1500	1525
Aliphatic $-CH_3$	2960-2850	1878
Aromatic =C-H	3080-3040	3050

3.1.2 N-(tert-butoxycarbonyl)-D-phenylglycine-benzene-1,2-diamine (compound 2)

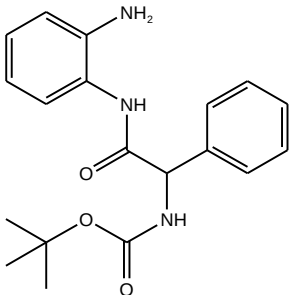


Table 3.1.2 IR Spectral Data (cm^{-1}) of Compound 2

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1685
N-H	3460-3050	3324
C-O	1330-1050	1167
Aromatic C=C	1600-1500	1500
Aliphatic $-CH_3$	2960-2850	2930

3.1.3 N-(tert-butoxycarbonyl)-L-methionine-benzene-1,2-diamine (compound 3)

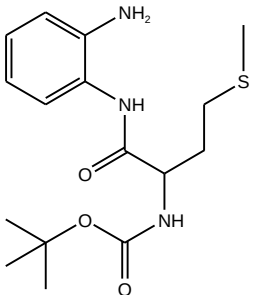


Table 3.1.3 IR Spectral Data (cm^{-1}) of Compound 3

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1664
N-H	3460-3050	3285
C-O	1330-1050	1250
Aromatic C=C	1600-1500	1500
Aliphatic $-CH_3$	2960-2850	2928

3.1.4 N-(tert-butoxycarbonyl)-L-phenylalanine-benzene-1,2-diamine (Compound 4)

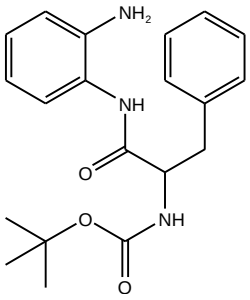


Table 3.1.4 IR Spectral Data (cm^{-1}) of Compound 4

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1663
N-H	3460-3050	3283
C-O	1330-1050	1167
Aromatic C=C	1600-1500	1503
Aliphatic $-CH_3$	2960-2850	2950

3.1.5 N-(tert-butoxycarbonyl)-L-isoleucine Derivative of Benzimidazole Compound (Compound 5)

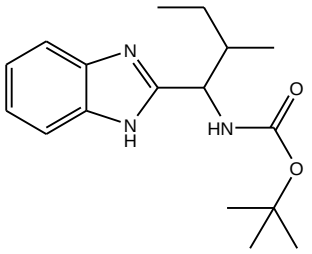


Table 3.1.5 IR Spectral Data (cm^{-1}) of Compound 5

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1674
N-H	3460-3050	3202

C-O	1330-1050	1318-1113
Aromatic C=C	1600-1500	1548
Aliphatic $-CH_3$	2960-2850	2877

3.1.6 N-(tert-butoxycarbonyl)-D-phenylglycine Derivative of Benzimidazole Compound (Compound 6)

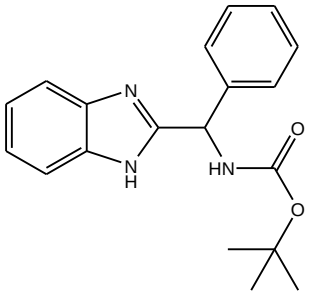


Table 3.1.6 IR Spectral Data (cm^{-1}) of Compound 6

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1671
N-H	3460-3050	3408
C-O	1330-1050	1274-1163
Aromatic C=C	1600-1500	1439
Aliphatic $-CH_3$	2960-2850	2900

3.1.7 N-(tert-butoxycarbonyl)-L-methionine Derivative of Benzimidazole Compound (Compound 7)

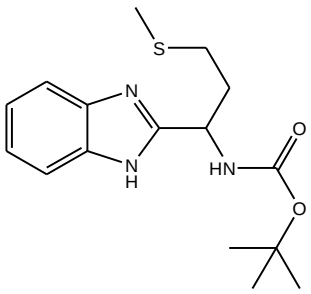


Table 3.1.7 IR Spectral Data (cm^{-1}) of Compound 7

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1680
N-H	3460-3050	3298
C-O	1330-1050	1171
Aromatic C=C	1600-1500	1527
Aliphatic $-CH_3$	2960-2850	2916

3.1.8 N-(tert-butoxycarbonyl)-L-Phenylalanine Derivative of Benzimidazole Compound (Compound 8)

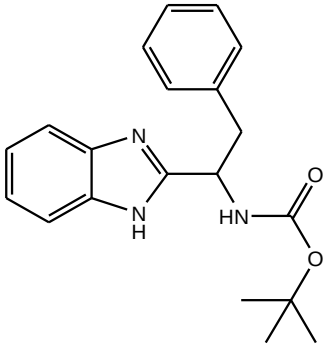


Table 3.1.8 IR Spectral Data (cm^{-1}) of Compound 8

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
C=O	1800-1650	1677
N-H	3460-3050	3315
C-O	1330-1050	1273-1169
Aromatic C=C	1600-1500	1530
Aliphatic $-CH_3$	2960-2850	2930

3.1.9 L-isoleucine Derivative of Benzimidazole Compound (Compound 9)

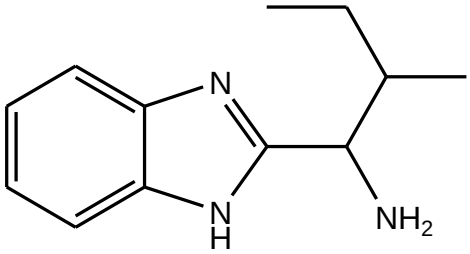


Table 3.1.9 IR Spectral Data (cm^{-1}) of Compound 9

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	2963
Aromatic C=C	1600-1500	1592-1519
Aliphatic $-CH_3$	2960-2850	2928

3.1.10 D-phenylglycine Derivative of Benzimidazole Compound (Compound 10)

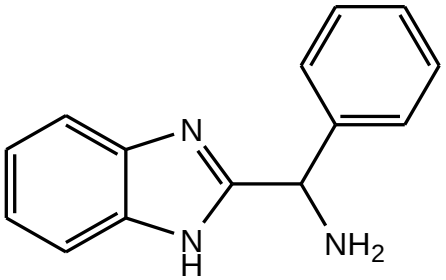


Table 3.1.10 IR Spectral Data (cm^{-1}) of Compound 10

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3380
Aromatic C=C	1600-1500	1564

3.1.11 L-methionine Derivative of Benzimidazole Compound (Compound 11)

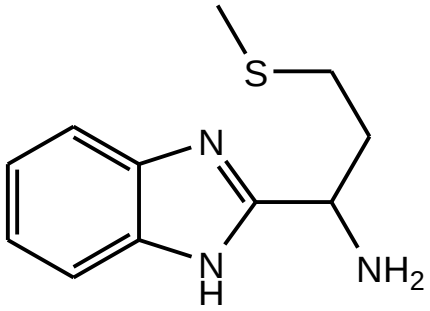


Table 3.1.11 IR Spectral Data (cm^{-1}) of Compound 11

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3056
Aromatic C=C	1600-1500	1575
Aliphatic -CH3	2960-2850	2922

3.1.12 L-phenylalanine Derivative of Benzimidazole Compound (Compound 12)

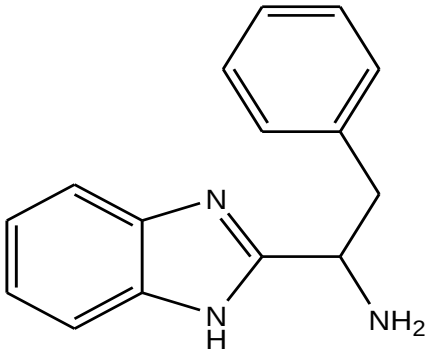


Table 3.1.12 IR Spectral Data (cm^{-1}) of Compound 12

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3056
Aromatic C=C	1600-1500	1575
Aliphatic -CH3	2960-2850	2922

3.1.13 N-[1-(1H-benzimidazol-2-yl)-2-methylbutyl]-N'-[3,5-bis (trifluoromethyl) phenyl] thiourea (Compound 13)

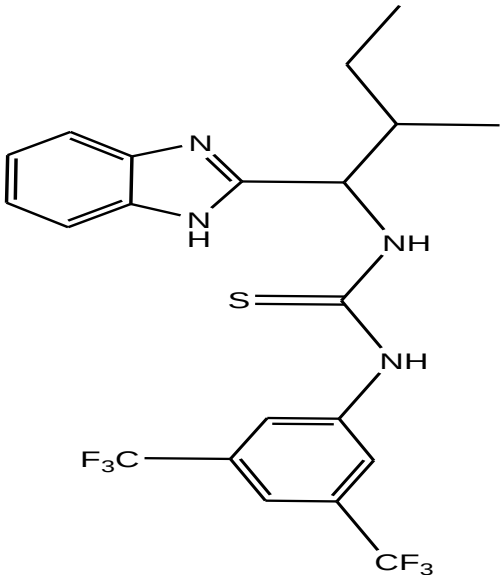


Table 3.1.13 IR Spectral Data (cm^{-1}) of Compound 13

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3267
Aromatic C=C	1600-1500	1542
C=S	1800-1600	1663
Aliphatic -CH3	2960-2850	2957
C-F	1400-1000	1382-1113

3.1.14 N-[1H-benzimidazol-2-yl (phenyl)methyl]-N'-[3,5-bis(trifluoromethyl)phenyl]thiourea (Compound 14)

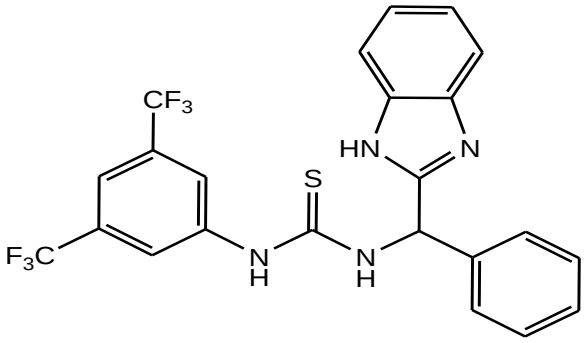


Table 3.1.14 IR Spectral Data (cm^{-1}) of Compound 14

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3052
Aromatic C=C	1600-1500	1541
C=S	1800-1600	1704
C-F	1400-1000	1382-1132

3.1.15 1-[1-(1H-benzimidazol-2-yl)-3-(methylsulfanyl) propyl]-3-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 15)

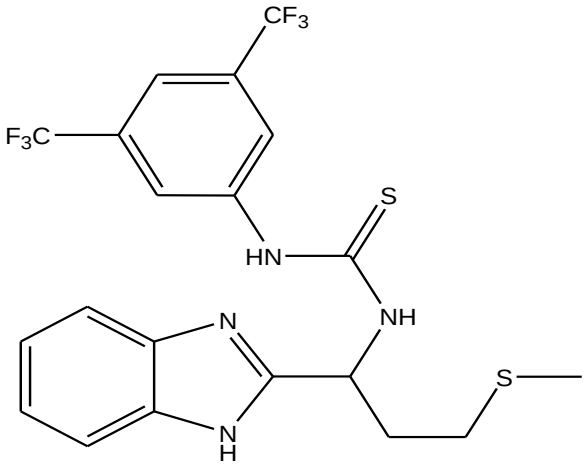


Table 3.1.15 IR Spectral Data (cm^{-1}) of Compound 15

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3247
Aromatic C=C	1600-1500	1542
C=S	1800-1600	1738
C-F	1400-1000	1381-1130

3.1.16 N-[1-(1H-benzimidazol-2-yl)-2-phenylethyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 16)

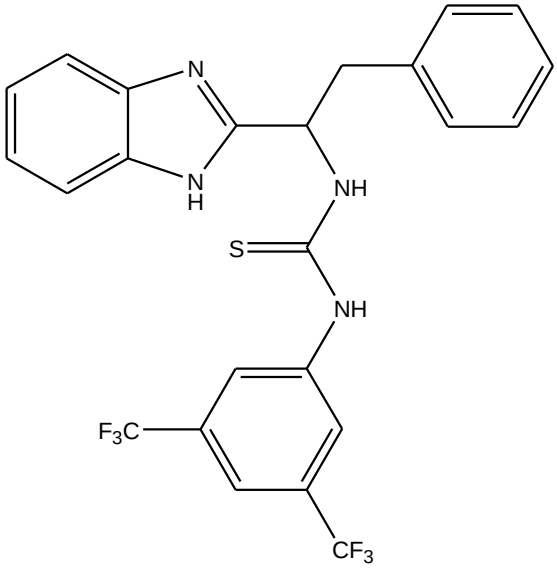


Table 3.1.16 IR Spectral Data (cm^{-1}) of Compound 16

Functional Groups	Expected cm^{-1}	Observed cm^{-1}
N-H	3460-3050	3050
Aromatic C=C	1600-1500	1541
C=S	1800-1600	1738
C-F	1400-1000	1381-1131

3.2 ^{1}H NMR Spectroscopic Data

3.2.1 N-(tert-butoxycarbonyl)-L-isoleucine-benzene-1, 2-diamine (compound 1)

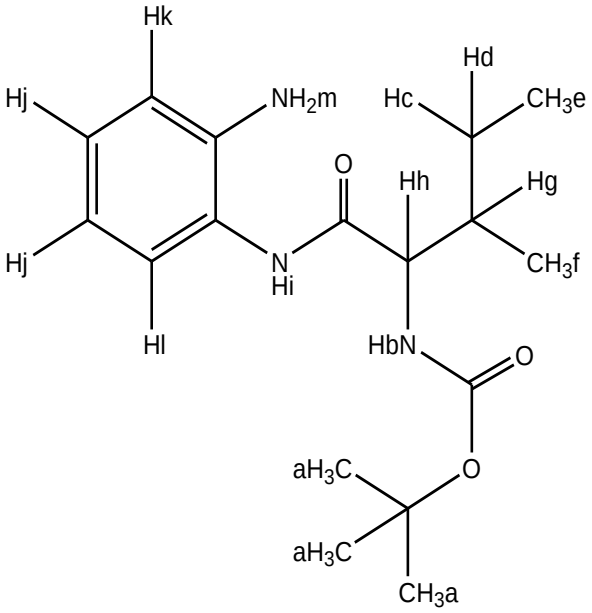


Table 3.2.1 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 1

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.44(s)	9H
Hb	5.21(d)	1H, J =7.6
Hc	1.99(m)	1H, J =6.4, 3.6
Hd	4.79(m)	1H, J =9.6, 7.6
He	0.94(t)	3H, J =14.8, J =7.6
Hf	1.03(d)	3H, J =6.8
Hg	1.36(m)	1H, J =7.6, J =4
Hh	4.06(t)	1H, J =15.2, J =7.2
Hi	7.85(b)	1H
Hj	6.75(dd)	2H, J =12, J =7.6
Hk	7.03(d)	1H, J =16, J =7.6
Hl	7.20(d)	1H, J =7.2
NH_2	3.85(S)	2H

3.2.2 N-(tert-butoxycarbonyl)-D-phenylglycine - benzene-1,2-diamine (compound 2)

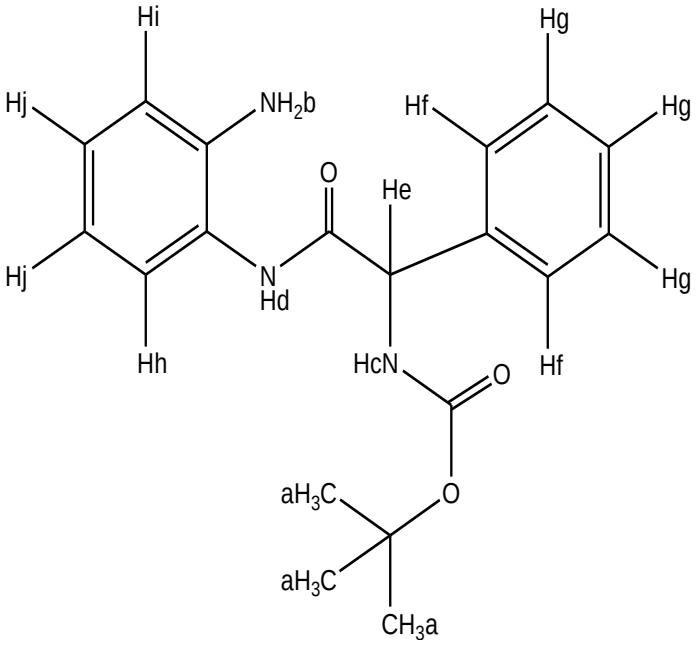


Table 3.2.2 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 2

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.41(s)	9H
Hb	3.66(b)	2H
Hc	5.37(b)	1H
Hd	8.04(s)	1H
He	5.94(d)	1H, J =6.4
Hf	7.42(d)	2H, J =7.6
Hg	7.32(d)	3H, J =5.6
Hh	7.09(d)	1H, J =7.6
Hi	6.98(t)	1H, J =15.6, J =7.6
Hj	6.68(dd)	2H, J =14, J =7.6

3.2.3 N-(tert-butoxycarbonyl)-L-methionine - benzene-1, 2-diamine (compound 3)

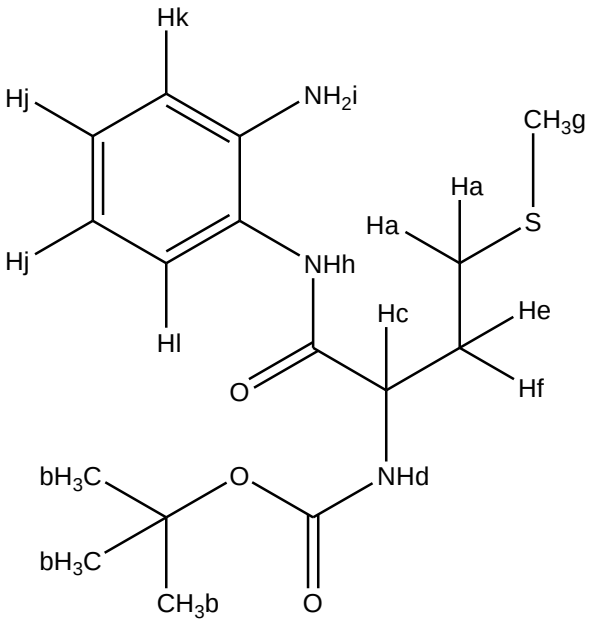


Table 3.2.3 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 3

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	2.59(t)	2H, J =14.4, J =7.2
Hb	1.44(s)	9H
Hc	4.41(d)	1H, J =6.8
Hd	5.53(b)	1H
He	2.16(t.d)	1H, J =14, J =6.8, J =7.2
Hf	2.00(t.d)	1H, J =13.6, J =6.8, J =3.6
Hg	2.09(s)	3H
Hh	8.19(b)	1H
Hi	3.86(b)	2H
Hj	6.72(t)	2H, J =8, J =6.8
Hk	7.01(t)	1H, J =8, J =3.6
Hl	7.17(d)	1H, J =8

3.2.4 N-(tert-butoxycarbonyl)-L-phenylalanine- benzene-1, 2-diamine (Compound 4)

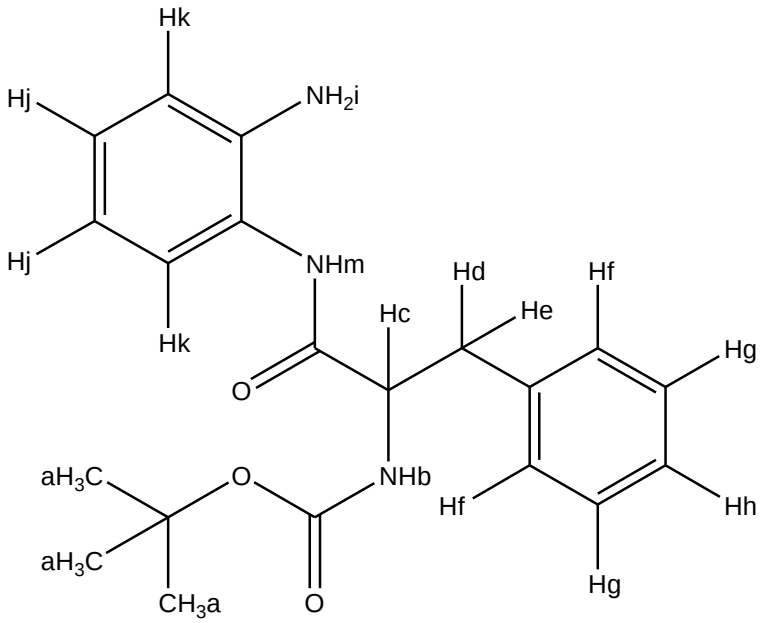


Table 3.2.4 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 4

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.34(s)	9H
Hb	3.31(b)	1H
Hc	4.34(d)	1H, J =5.6
Hd	3.03(dd)	1H, J =13.6, J =5.2
He	2.88(t)	1H, J =22.4, J =9.2
Hf	6.89(dd)	2H, J =15.2, J = 7.6
Hg	7.29(dd)	3H, J =15.2, J =7.6
Hh	7.20(t)	1H, J =13.2, J = 6
Hi	4.77(b)	2H
Hj	7.03(dd)	2H, J =22, J = 8
Hk	6.52(dd)	2H, J =14.8, J = 7.2
Hm	9.19(b)	1H

3.2.5 N-(tert-butoxycarbonyl)-L-isoleucine Derivative of Benzimidazole Compound (Compound 5)

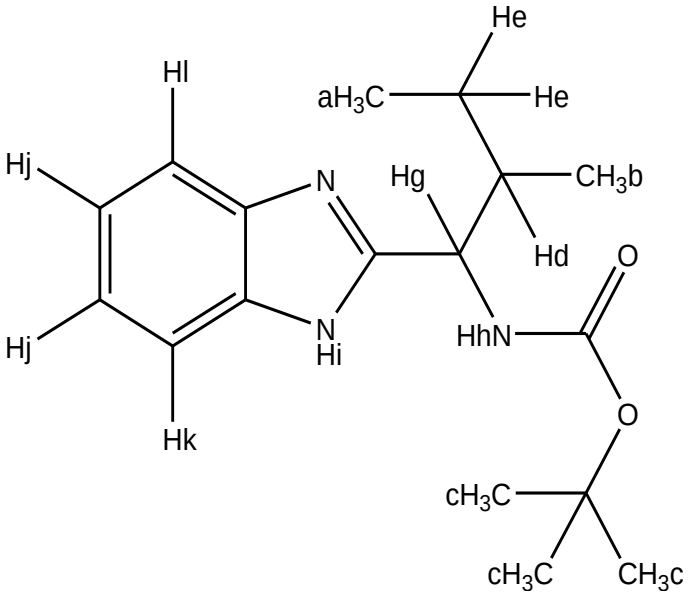


Table 3.2.5 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 5

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	0.74(d)	3H, J =6.8
Hb	0.85(t)	3H, J =14.8, J =7.6
Hc	1.37(s)	9H
Hd	1.48(m)	1H, J =13.6, J =6.8, J =4
He	1.19(m)	2H, J =19.2, J =12, J =7.2
Hg	4.63(t)	1H, J =16.4, J =8
Hh	1.95(s)	1H
Hi	12.10(b)	1H
Hj	7.13(dd)	2H, J =12, J =5.6
Hk	7.55(d)	1H, J =6.8
Hl	7.45(d)	1H, J =7.2

3.2.6 N-(tert-butoxycarbonyl)-D-phenylglycine Derivative of Benzimidazole Compound (Compound 6)

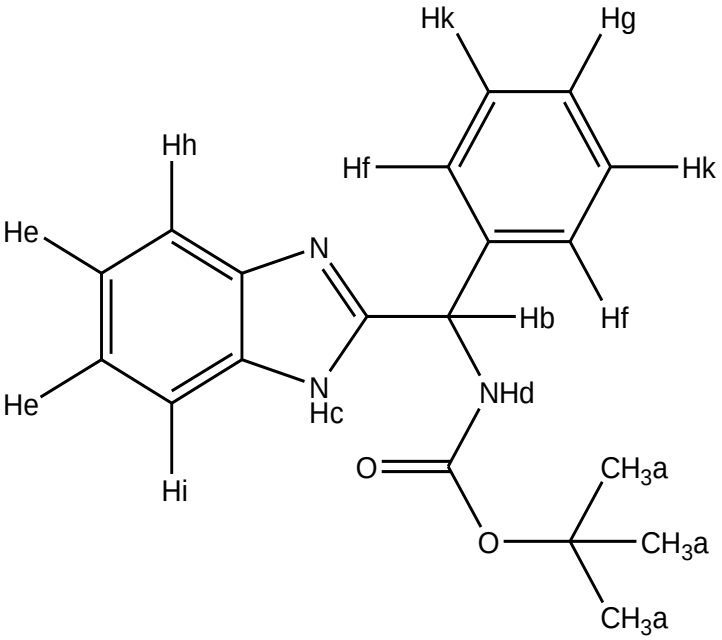


Table 3.2.6 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 6

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.37(s)	9H
Hb	5.99(d)	1H, J =3.6
Hc	7.76(s)	1H
Hd	12.22(b)	1H
He	7.37(dd)	2H, J =19.2, J =8.4
Hh	7.54(d)	1H, J =6.8
Hi	7.41(d)	1H, J =6.4
Hf	7.12(d)	2H, J =0.8
Hk	7.23(dd)	2H, J =12.8, J =6
Hg	7.25(t.d)	1H, J =8.4, J =7.2, J =6.4

3.2.7 N-(tert-butoxycarbonyl)-L-methionine Derivative of Benzimidazole Compound (Compound 7)

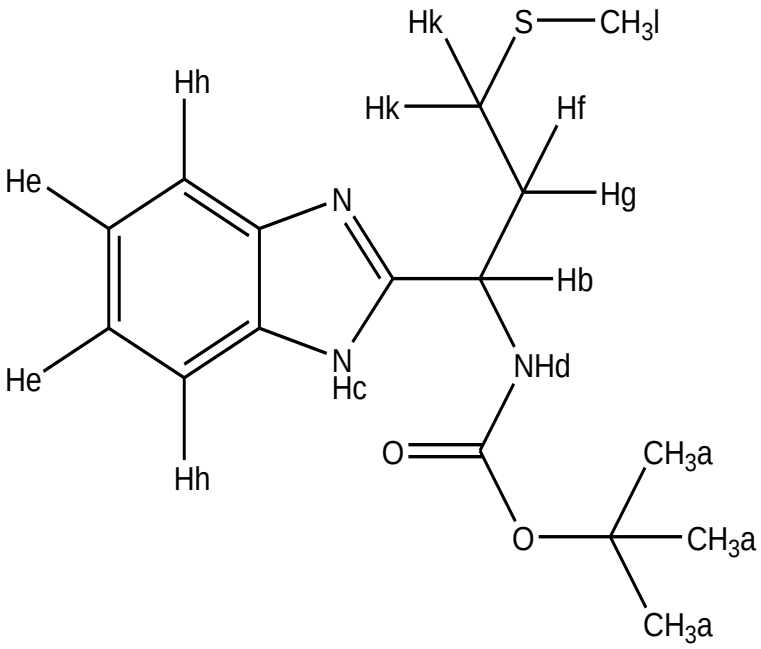


Table 3.2.7 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 7

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.21(s)	9H
Hb	4.90(d)	1H, J = 6.4
Hc	12.15(b)	1H
Hd	3.32(s)	1H
He	7.33(d)	2H, J =8
Hh	7.12(d)	2H, J = 3.6
Hf	2.19(td)	1H, J =14, J =6.4, J =6.8
Hk	2.50(t)	2H, J =14.4, J =6.8
Hg	2.07(t)	1H, J = 15.2, J =7.6
Hl	1.37(s)	3H

3.2.8 N-(tert-butoxycarbonyl)-L-Phnylalanine Derivative of Benzimidazole Compound (Compound 8)

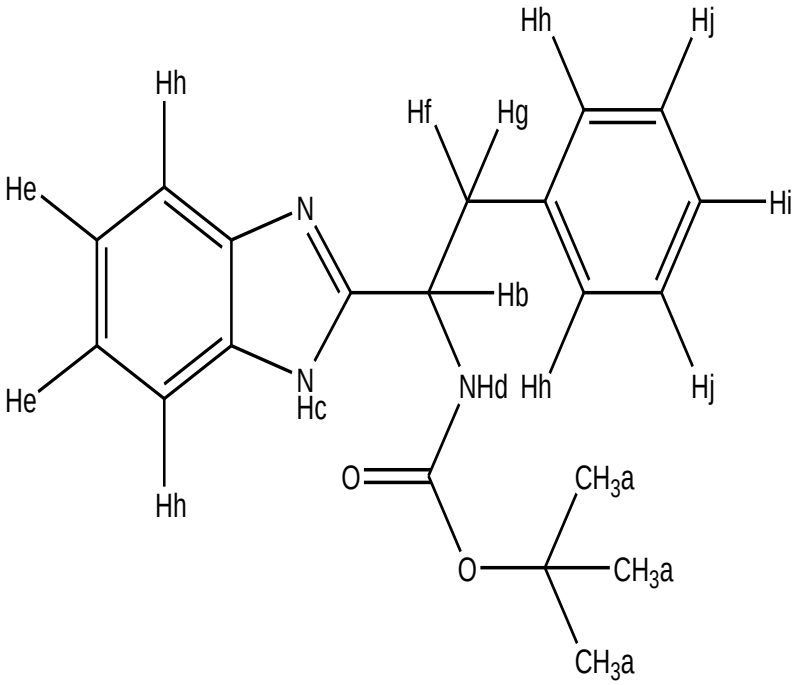


Table 3.2.8 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 8

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.28(s)	9H
Hb	4.99(d)	1H, J =5.6
Hc	8.19(b)	1H
Hd	1.71(s)	1H
He	7.49(dd)	2H, J =6, J =3.6
Hf	3.08(dd)	1H, J = 9.6
Hg	3.34(dd)	1H, J =14, J =5.2
Hh	7.23(d)	4H, J = 4
Hi	7.32(d)	1H, J =4
Hj	7.12(dd)	2H, J =3.6, J = 1.2

3.2.9 L-isoleucine Derivative of Benzimidazole Compound (Compound 9)

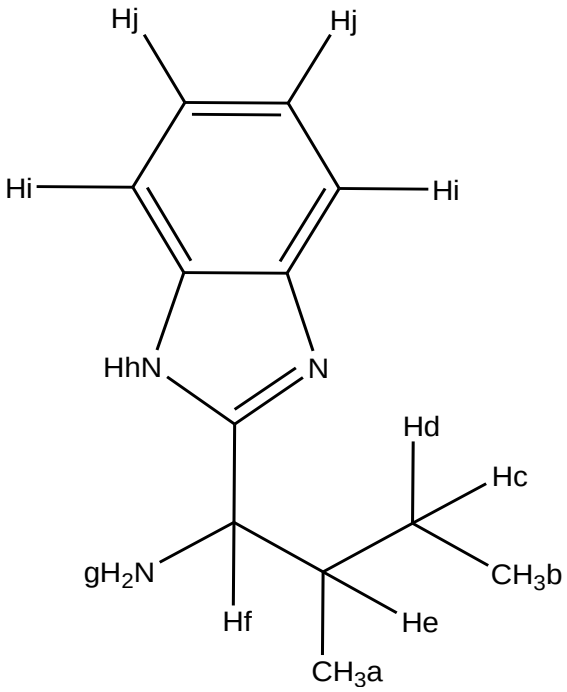


Table 3.2.9 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 9

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	0.83(d)	3H, J =6.8
Hb	0.89(t)	3H
Hc	1.54(m)	1H
Hd	1.14(m)	1H
He	2.01(m)	1H
Hf	4.21(d)	1H, J =6
Hg	5.75(b)	2H
Hh	1.24(s)	1H
Hi	7.54(d)	2H, J =5.2, J =2.8
Hj	7.16(dd)	2H, J =7.2, J =4

3.2.10 D-phenylglycine Derivative of Benzimidazole Compound (Compound 10)

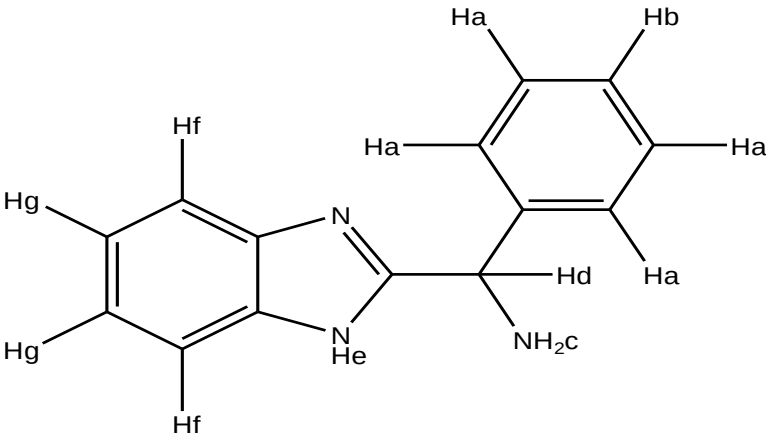


Table 3.2.10 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 10

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	7.84(dd)	4H, J =6.8,J =3.2, J =3.6
Hb	7.20(m)	1H, J =6.8,J =2, J =1.2
Hc	5.29(s)	2H
Hd	2.48(t)	1H, J =4.4,J =2
He	5.74(s)	1H
Hf	7.30(dd)	2H, J =7.6,J =2, J =1.2
Hg	7.11(dd)	2H, J =6.8,J =4, J =3.2

3.2.11 L-methionine Derivative of Benzimidazole Compound (Compound 11)

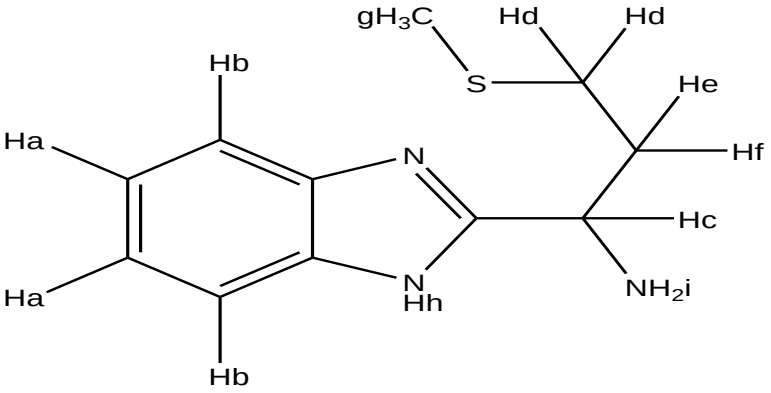


Table 3.2.11 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 11

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	7.21(dd)	2H, J =7.2, J =2.8
Hb	7.55(dd)	2H, J =6, J =3.2
Hc	4.42(t)	1H, J =13.6, J =6.8
Hd	2.56(t)	2H, J =7.2, J =2.8
He	2.30(t.d)	1H, J =13.2, J =6.8
Hf	2.80(t.d)	1H, J =14.8, J =2.8
Hg	2.03(s)	3H
Hh	2.16(s)	1H
Hi	4.99(s)	2H

3.2.12 L-phenylalanine Derivative of Benzimidazole Compound (Compound 12)

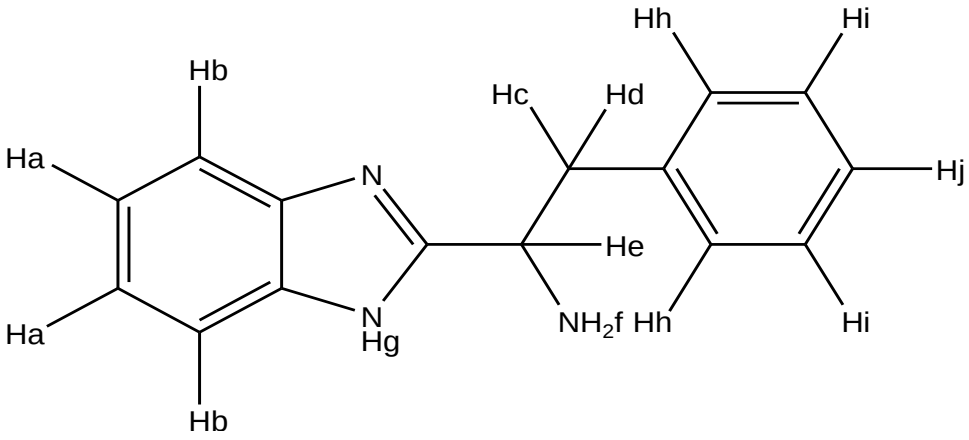


Table 3.2.12 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 12

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	7.10(dd)	2H, J =3.2, J = 1.2
Hb	7.22(d)	2H, J = 7.2
Hc	2.96(dd)	1H, J =13.2, J = 7.6
Hd	3.25(dd)	1H, J =13.2, J = 6
He	4.27(t)	1H, J = 7.6, J = 5,6

Hf	7.48(s)	2H
Hg	8.20(bs)	1H
Hh	7.12(dd)	5H, J = 18.4, J = 6.8

3.2.13 N-[1-(1H-benzimidazol-2-yl)-2-methylbutyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 13)

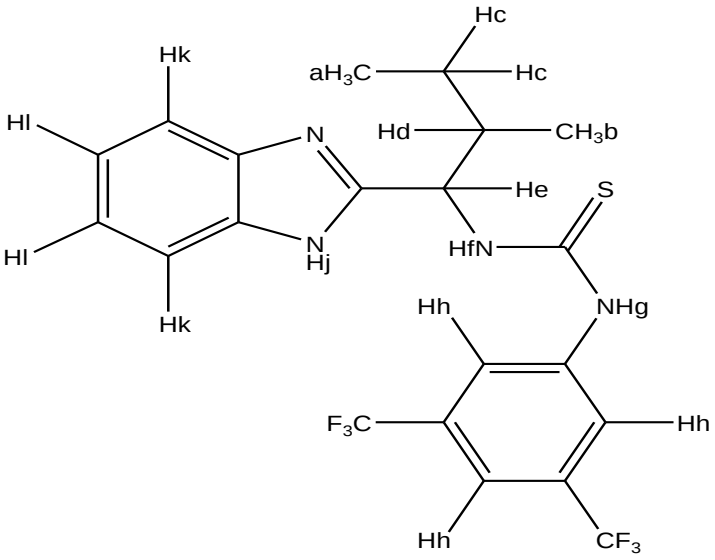


Table 3.2.13 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 13

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	0.94(t)	3H, J =14.4, J =6.8
Hb	1.12(d)	3H, J =6
Hc	1.44(m)	1H, J =10.8, J =6.8, J =3.2
Hd	1.75(t)	1H, J =13.6, J =5.6
He	2.05(s)	1H
Hf, Hg	2.65, 5.80(s)	2H
Hh	7.43(s)	3H
Hj	8.92(bs)	1H
Hk, Hl	7.16, 7.73(d)	2H, 2H, J= 9.6

3.2.14 N-[1H-benzimidazol-2-yl (phenyl) methyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 14)

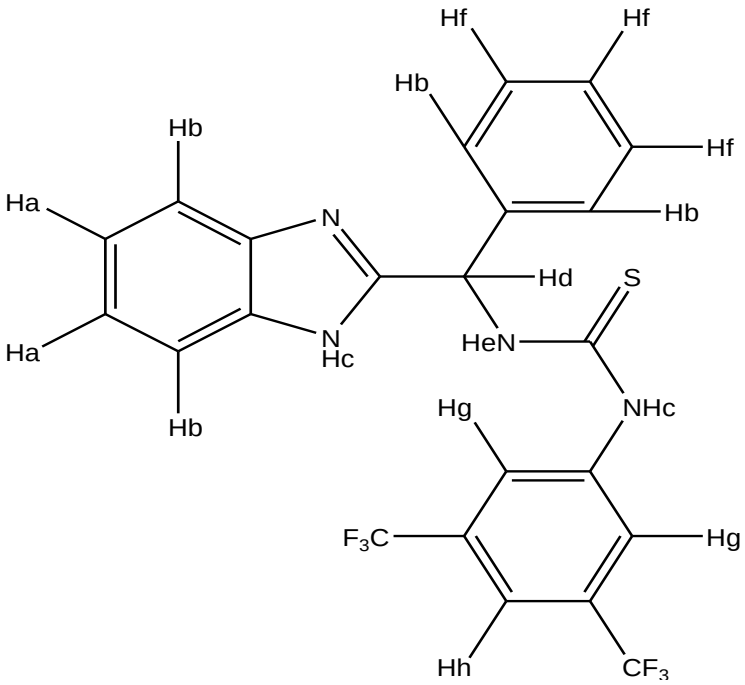


Table 3.2.14 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 14

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	7.22(dd)	2H, J = 6.8, J = 4.2
Hb	7.19(dd)	4H, J = 8.4, J = 2.8
Hc	9.69(s)	2H
Hd	4.10(d)	1H, J =6.4
He	10.18(bs)	1H
Hf	7.32(dd)	3H, J =8.8, J =5.6
Hg	7.75(s)	2H
Hh	7.40(s)	1H

3.2.15 1-[1-(1H-benzimidazol-2-yl)-3-(methylsulfanyl) propyl]-3-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 15)

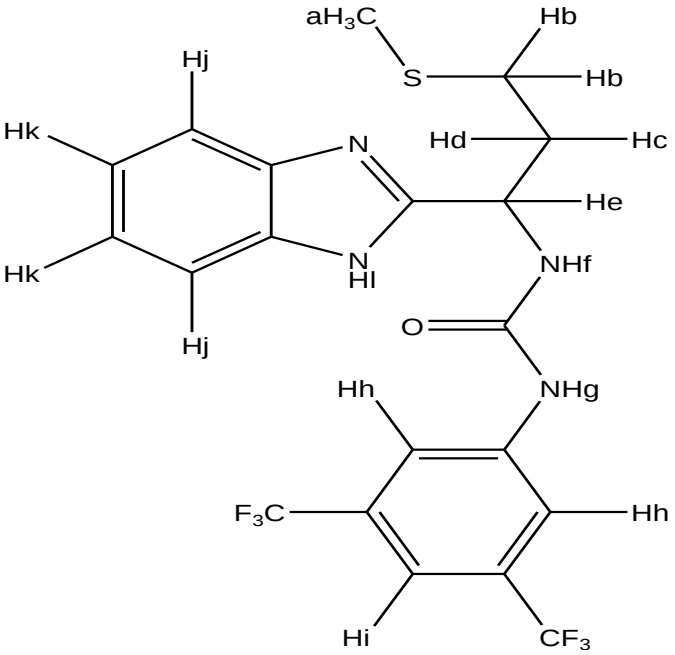


Table 3.2.15 ^{1}H-NMR Spectral Data ($CDCl_3$, 400MHz) of Compound 15

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	1.95(s)	3H
Hb	2.47(d)	2H, J =6.8
Hc	2.65(t.d)	1H, J =12.8, J =6.4
Hd	2.76(t.d)	1H, J =13.2, J =5.6
He	6.14(s)	1H
Hf	7.99(s)	1H
Hg	9.10(s)	1H
Hh	7.63(s)	3H
Hi	7.47(s)	1H
Hj	7.34(s)	1H
Hk	7.20(dd)	2H, J =5.6, J =3.6

3.2.16 N-[1-(1H-benzimidazol-2-yl)-2-phenylethyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 16)

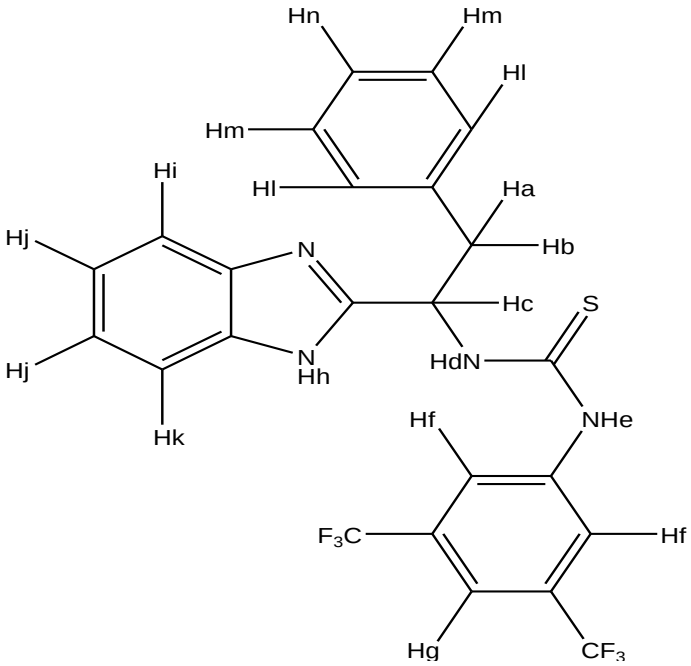


Table 3.2.16 ^{1}H-NMR Spectral Data (DMSO-D_6, 400MHz) of Compound 16

Location of Atoms	^{1}HNMR (δ)	H and Coupling Constants (Hz)
Ha	3.34(dd)	1H, J =13.6, J =6.8
Hb	3.45(dd)	1H, J =14, J =6.8
Hc	4.04(t)	1H, J =7.6, J =6.8
Hd	8.76(d)	1H, J =7.6
He	10.32(s)	1H
Hf	8.29(s)	2H
Hg	7.75(s)	1H
Hh	12.42(bs)	1H
Hi	7.59(d)	1H, J =6.8
Hj	7.19(dd)	2H, J =8, J =6.8
Hk	7.47(d)	1H, J =6.8
Hl, Hm, Hn	7.21(dd)	5H, J =8, J =7.6

3.3 ^{13}C NMR Spectroscopic Data

3.3.1 N-(tert-butoxycarbonyl)-L-isoleucine-benzene-1, 2-diamine (compound 1)

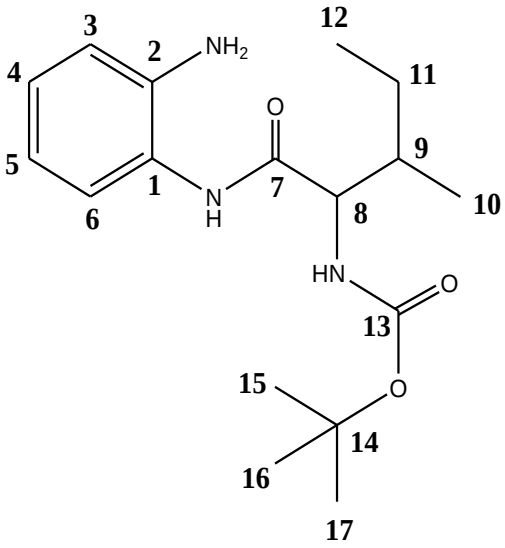


Table 3.3.1 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 1

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	141.45
C_3, C_4, C_5	117.30, 127.32, 118.76
C_6	126.19
C_7	171.57
C_8, C_9	60.08, 37.27
C_{10}, C_{11}, C_{12}	15.79, 25.20, 11.38
C_{13}	156.63
C_{14}	80.16
C_{15}, C_{16}, C_{17}	28.57

3.3.2 N-(tert-butoxycarbonyl)-D-phenylglycine - benzene-1,2-diamine (compound 2)

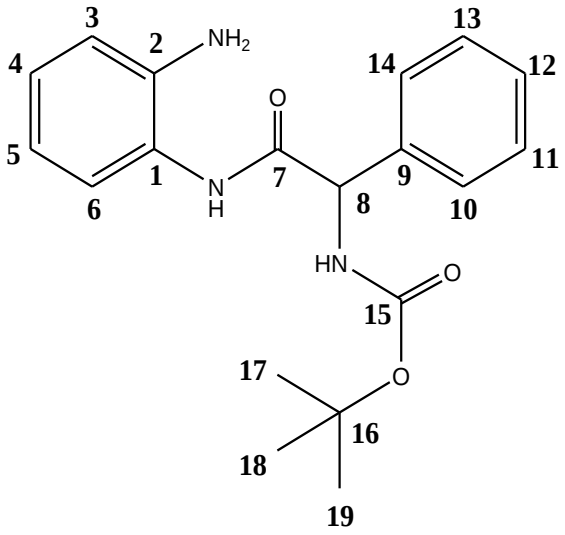


Table 3.3.2 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 2

Location of atoms	^{13}C-NMR (δ in ppm)
$C_{1,}C_2$	138.14, 141.24
$C_{3,}$ $C_{4,}$ C_5	128.71, 127.48, 117.65
C_6	126.09
$C_{7,}$ C_8	169.61, 59.28
C_9	137.35
$C_{10,}$ C_{14}	123.40
$C_{11,}$ $C_{12,}$ C_{13}	127.65, 129.30, 128.71
$C_{15,}$ C_{16}	155.70, 80.64
C_{17},C_{18},C_{18}	28.56

3.3.3 N-(tert-butoxycarbonyl)-L-methionine - benzene-1, 2-diamine (compound 3)

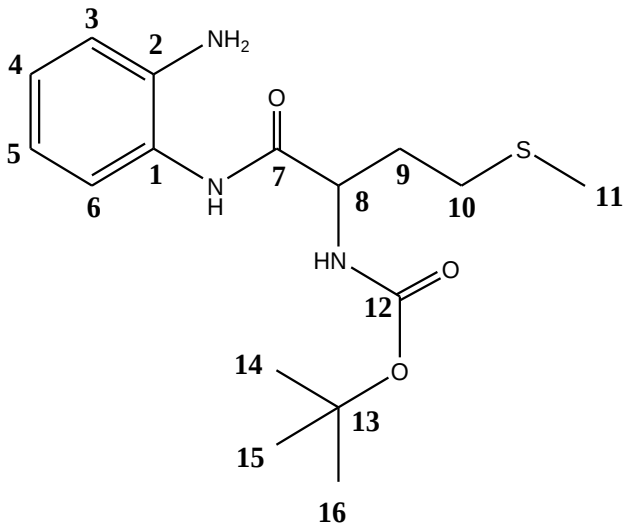


Table 3.3.3 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 3

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2, C_3	123.52, 141.10, 117.58
C_4, C_5	127.50, 119.18
C_6	125.82
C_7	170.79
C_8, C_9	54.41, 30.54
C_{10}, C_{11}	31.59, 15.59
C_{12}	156.29
C_{13}	80.76
C_{14}, C_{15}, C_{16}	28.57

3.3.4 N-(tert-butoxycarbonyl)-L-phenylalanine- benzene-1, 2-diamine (Compound 4)

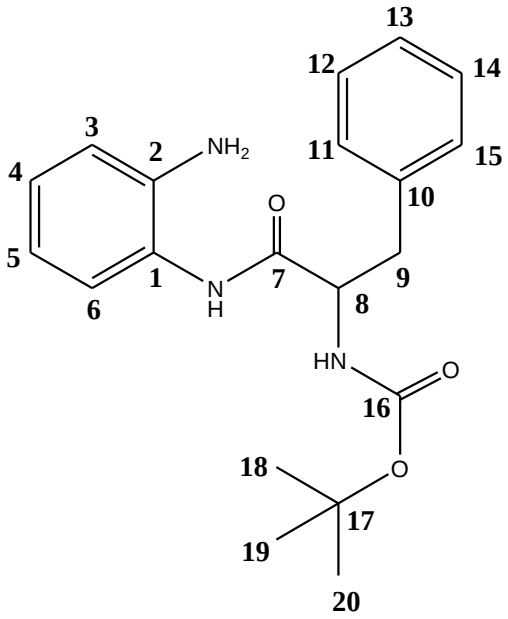


Table 3.3.4 ^{13}C-NMR Spectral Data (DMSO-D_6, 100MHz) of the Compound 4

Location of atoms	^{13}C-NMR (δ in ppm)
C_1	116.65
C_2	143.34
C_3, C_5	116.22
C_4, C_6	126.97, 123.35
C_7, C_8	171.35, 56.94
C_9, C_{10}	38.14, 138.65
C_{11}, C_{15}	130.01
C_{12}, C_{14}	128.75
C_{13}, C_{16}, C_{17}	126.63, 156.21, 78.87
C_{18},C_{19},C_{20}	28.86

3.3.5 N-(tert-butoxycarbonyl)-L-isoleucine Derivative of Benzimidazole Compound (Compound 5)

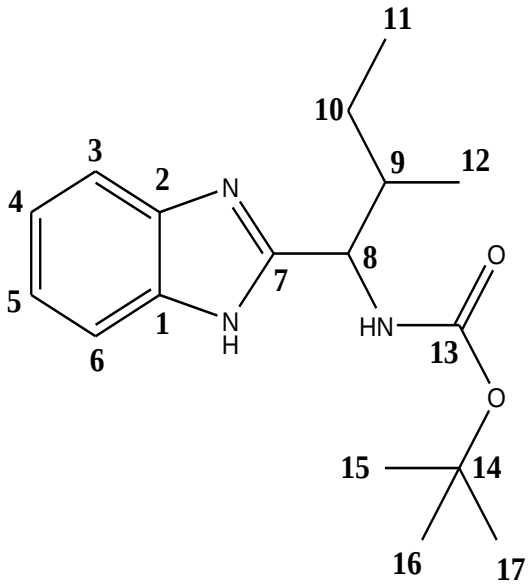


Table 3.3.5 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 5

Location of atoms	^{13}C-NMR (δ in ppm)
C_4, C_5	122.51
C_1, C_2	137.52
C_7, C_{13}	156.70, 155.32
C_3, C_6	117.25
C_8, C_9, C_{10}	54.88, 38.83, 25.82
C_{11}, C_{12}	11.19, 15.86
C_{14}	80.22
C_{15},C_{16}, C_{17}	28.54

3.3.6 N-(tert-butoxycarbonyl)-D-phenylglycineDerivative of Benzimidazole Compound (Compound 6)

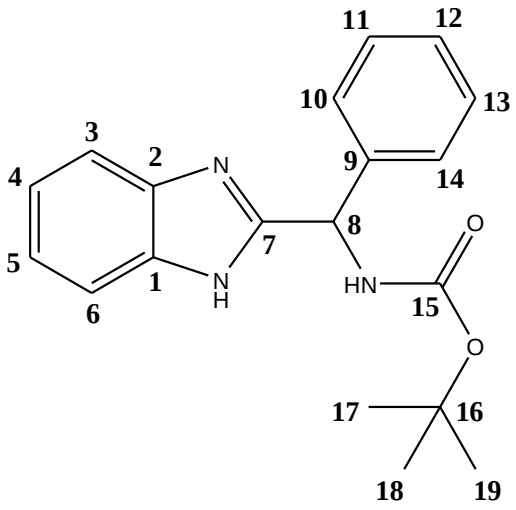


Table 3.3.6 ^{13}C-NMR Spectral Data (DMSO-D_6, 100MHz) of the Compound 6

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	140.86
C_3, C_6	122.36
C_4, C_5	127.96
C_7	157.34
C_8	53.95
C_9, C_{11}, C_{13}	129.04
C_{10}, C_{12}, C_{14}	128.16
C_{15}	154.97
C_{16}	79.27
C_{17}, C_{18}, C_{19}	28.84

3.3.7 N-(tert-butoxycarbonyl)-L-methionine Derivative of Benzimidazole Compound (Compound 7)

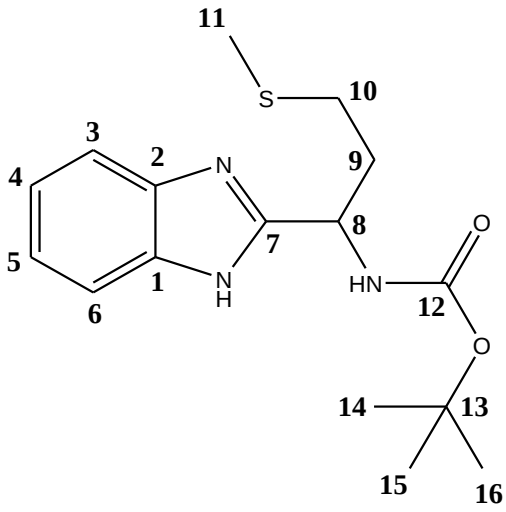


Table 3.3.7 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 7

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	134.87
C_3, C_6	112.00
C_4	122.43
C_5	121.67
C_7	156.05
C_8	49.17
C_9, C_{10}, C_{11}	30.50, 34.13, 15.38
C_{12}	143.69
C_{13}	78.89
C_{14},C_{15},C_{16}	28.88

3.3.8 N-(tert-butoxycarbonyl)-L-phnylalanine Derivative of Benzimidazole Compound (Compound 8)

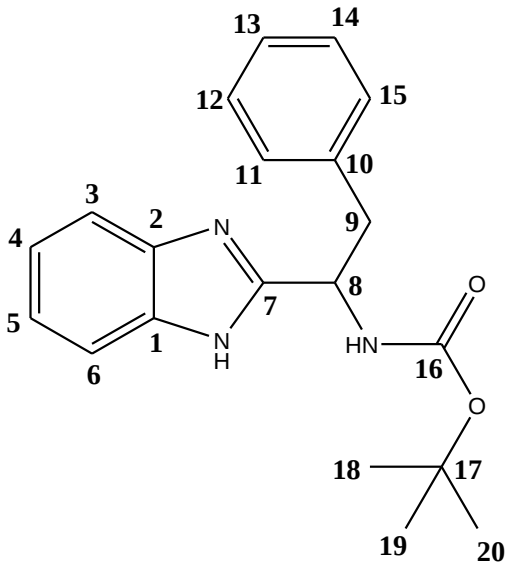


Table 3.3.8 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 8

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	129.89
C_3, C_6, C_{11}, C_{15}	122.13
C_4, C_5	126.86
C_7	155.93
C_8	51.53
C_9	34.04
C_{10}	138.81
C_{12}, C_{13}, C_{14}	128.72
C_{16}	155.83
C_{17}	78.76
C_{18}, C_{19}, C_{20}	28.84

3.3.9 L-isoleucine Derivative of Benzimidazole Compound (Compound 9)

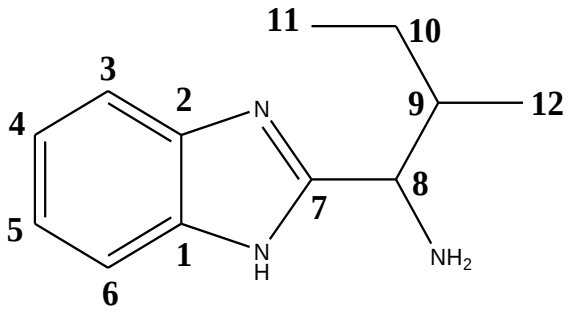


Table 3.3.9 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 9

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	138.49
C_3, C_6	115.19
C_4, C_5	122.42
C_7	157.35
C_8, C_9	55.67, 40.82
C_{10}	24.82
C_{11}, C_{12}	11.69, 15.76

3.3.10 D-phenylglycine Derivative of Benzimidazole Compound (Compound 10)

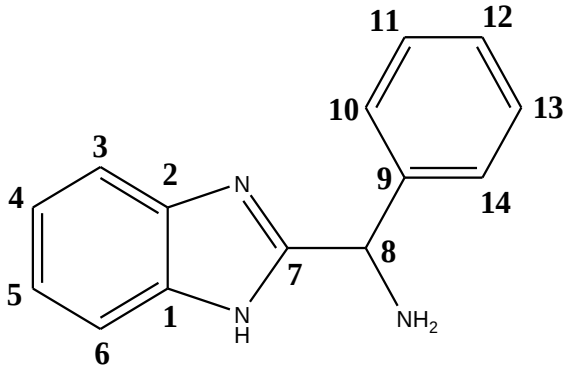


Table 3.3.10 ^{13}C-NMR Spectral Data (DMSO-D_6, 100MHz) of the Compound 10

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2, C_9	144.59
C_3, C_6, C_{13}	121.91
C_4, C_5, C_{11}	127.60
C_7	158.99
C_8	55.36
C_{10}, C_{12}, C_{14}	128.86

3.3.11 L-methionine Derivative of Benzimidazole Compound (Compound 11)

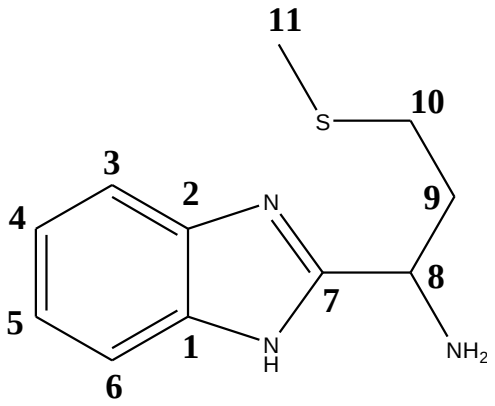


Table 3.3.11 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 11

Location of atoms	^{13}C-NMR (δ in ppm)
C_4, C_5	122.70
C_3, C_6	115.27
C_1, C_2	138.47
C_7	157.27
C_8	49.92

C_9	36.27
C_{10}	30.73
C_{11}	15.61

3.3.12 L-phenylalanine Derivative of Benzimidazole Compound (Compound 12)

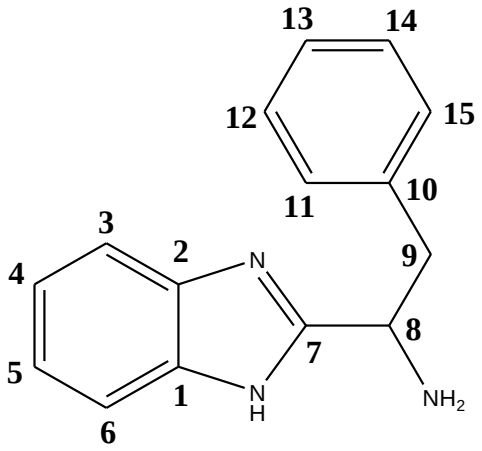


Table 3.3.12 ^{13}C-NMR Spectral Data (DMSO-D_6, 100MHz) of the Compound 12

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	129.94
C_3, C_6	121.83
C_4, C_5, C_{13}	126.74
C_7	159.32
C_8, C_9	52.67, 43.81
C_{10}	139.45
C_{11}, C_{12}, C_{14},C_{15}	128.80

3.3.13 N-[1-(1H-benzimidazol-2-yl)-2-methylbutyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 13)

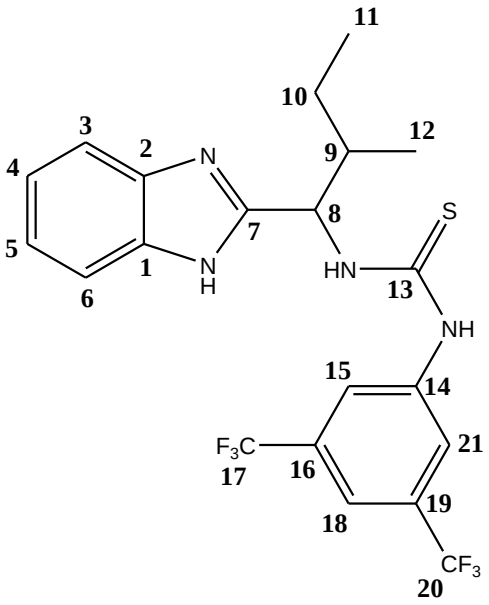


Table 3.3.13 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 13

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	131.52
C_3, C_6	121.60
C_4, C_5	123.83
C_7, C_8	156.33, 59.32
C_9, C_{10}, C_{11}	40.13, 26.66, 11.26
C_{12}	14.38
C_{13}, C_{14}	182.22, 139.49
C_{15}, C_{21}	124.32
C_{16}, C_{19}	131.19
C_{17}, C_{20}	118.52
C_{18}	124.10

3.3.14 N-[1H-benzimidazol-2-yl (phenyl) methyl]-N'-[3, 5-bis(trifluoromethyl)phenyl]thiourea (Compound 14)

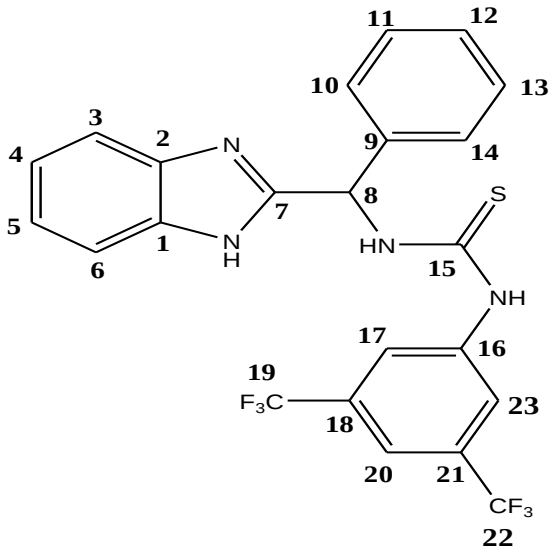


Table 3.3.14 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 14

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	136.94
C_3, C_6	118.32
C_4, C_5	123.94
C_7	155.07
C_8	57.05
C_9	129.19
C_{10}, C_{14}	131.31
C_{11}, C_{13}	131.65
C_{12}, C_{15}, C_{16}	130.97, 181.89, 140.03
C_{17}, C_{23}	124.48
C_{18}, C_{21}	129.47
C_{19}, C_{22}, C_{20}	131.98, 123.65, 121.78

3.3.15 1-[1-(1H-benzimidazol-2-yl)-3-(methylsulfanyl) propyl]-3-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 15)

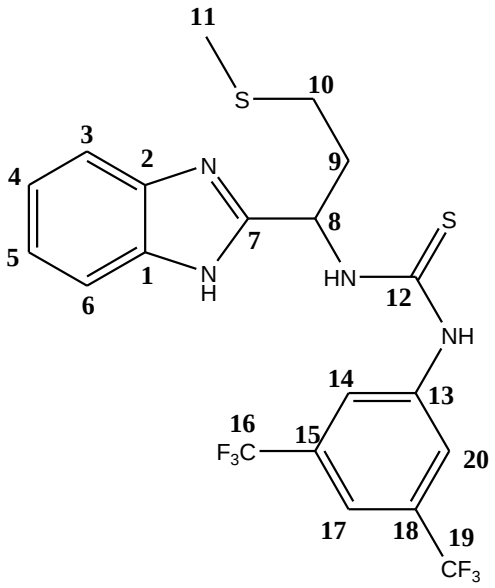


Table 3.3.15 ^{13}C-NMR Spectral Data ($CDCl_3$, 100MHz) of the Compound 15

Location of atoms	^{13}C-NMR (δ in ppm)
$C_{1,}$ C_2	139.46
$C_{3,}$ C_6	121.61
$C_{4,}$ C_5	123.60
C_7	156.46
$C_{8,}$ $C_{9,}$	52.79, 30.93
$C_{10,}$ C_{11}	34.43, 15.50
C_{12}	182.23
C_{13}	131.64
$C_{14,}$ C_{20}	123.99
C_{15}, C_{18}	131.30
$C_{16,}C_{19}$	118.54

3.3.16 N-[1-(1H-benzimidazol-2-yl)-2-phenylethyl]-N'-[3, 5-bis (trifluoromethyl) phenyl] thiourea (Compound 16)

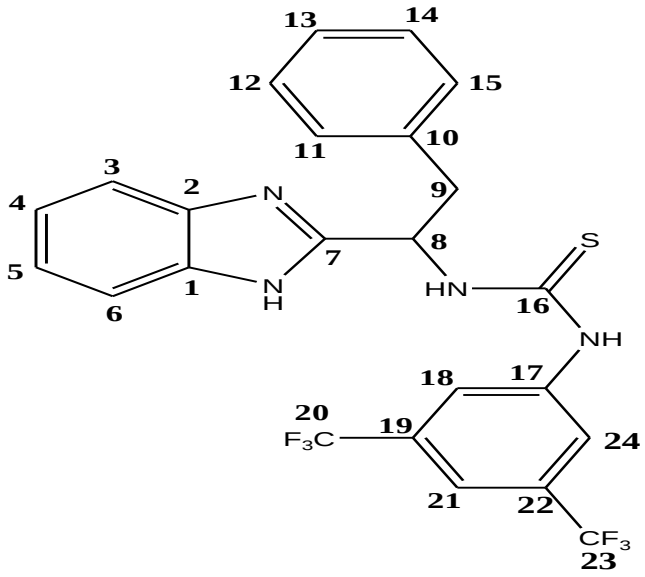


Table 3.3.16 ^{13}C-NMR Spectral Data (DMSO-D_6, 100MHz) of the Compound 16

Location of atoms	^{13}C-NMR (δ in ppm)
C_1, C_2	131.10
C_3, C_6	112.12
C_4, C_5	122.71
C_7	154.38
C_8, C_9	54.52, 39.86
C_{10}, C_{13}	137.80
C_{11}, C_{15}	128.88
C_{12}, C_{14}	130.78
C_{16}	180.88
C_{17}	142.34
C_{18},C_{24}	122.55
C_{19},C_{22} and C_{20},C_{23}	125.26 and 129.84

3.4 The Elemental Analyses Results

Table 3.4 The Elemental Analyses of obtained compounds

Compounds	Calculated			Found		
	%C	%H	%N	%C	%H	%N
Compound 1	63,53	8,47	13,07	62,22	8,358	12,93
Compound 2	66.84	6.79	12.31	66.52	6.86	12.14
Compound 3	56.61	7.42	12.38	56.19	7.22	12.04
Compound 4	67.58	7.09	11.82	66.23	6.81	11.53
Compound 5	67,30	8,31	13,85	66,73	8,103	13,51
Compound 6	70.57	6.55	12.99	69.25	6.70	12.74
Compound 7	59.78	7.21	13.07	58.95	7.08	12.53
Compound 8	71.19	6.87	12.45	70.08	7.04	12.15
Compound 9	70.90	8.43	20.67	69.12	8.57	19.10
Compound 10	75.31	5.87	18.82	69.77	6.07	15.90
Compound 11	59.69	6.83	18.99	57.57	7.21	13.70
Compound 12	75.92	6.34	17.71	74.31	7.09	16.44
Compound 13	53,16	4,25	11,81	52,34	4,351	11,01
Compound 14	55.87	3.26	11.33	55.15	3.82	10.45
Compound 15	48.77	3.68	11.38	48.58	4.05	10.70
Compound 16	56.69	3.57	11.02	56.77	3.86	10.78

4. RESULTS AND DISCUSSION

The main aim of this project was to synthesize thiourea derivative of benzimidazole compounds which are shown below on Figure 1.14. Also, investigate their catalytic and biological activities.

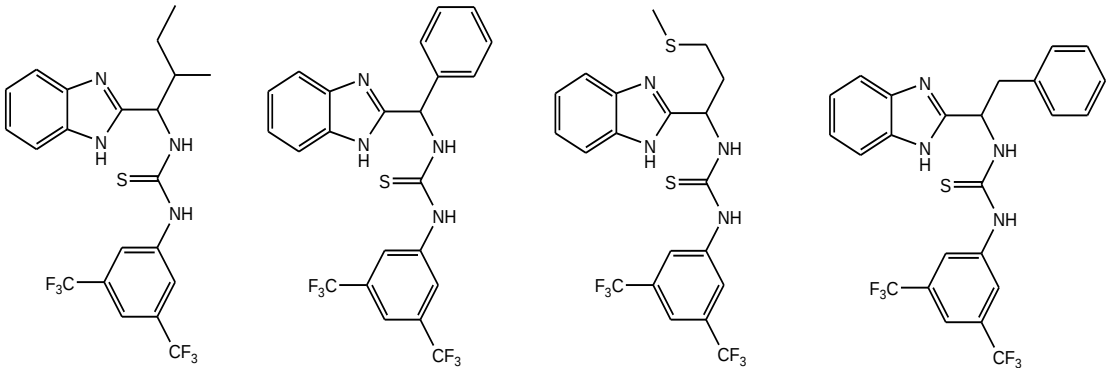


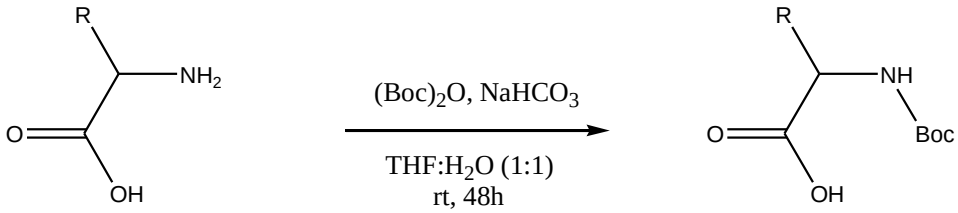
Figure 1.14 Novel synthesized compounds

In the literatures, there are compounds which were synthesized and their catalytic activities were investigated in asymmetric reactions. Our synthesized compounds might have the same capacity as catalyst in asymmetric reactions such as Biginelli, Morita-Bayliss-Hillman, Henry and Michael reactions because they have a chiral centre and hydrogen bonding capacity.

In this study, we tried to synthesize benzimidazole derivatives from different amino acids. We also used them to prepare novel thiourea compounds which have been expected to show high biological activity.

L-Isoleucine, L-phenylalanine, L-methionine and D-phenylglycine were used as simple amino acids. Orthophenylenediamine and 3,5-bis(trifluromethyl)phenylisothiocyanate were used as reactants.

As can be seen below, our strategy involved initial protection of the NH_2 group of the amino acids (a-d) by tert-butyloxycarbonyl $(Boc)_2O$ for obtaining N-Boc-amino acids (1a-d). The protection reactions were occurred at room temperature and the products were obtained in high yields.

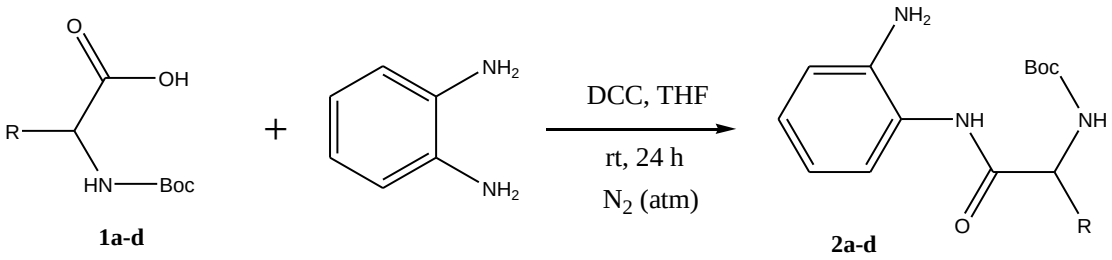


a-d **1a-d**

R = a: $-CH_2CH_2SCH_3$
b: $-CH_2C_6H_5$
c: $-CH(C_2H_5)(CH_3)$
d: $-C_6H_5$

Scheme 1.21 Synthesis of Protection Amino acids

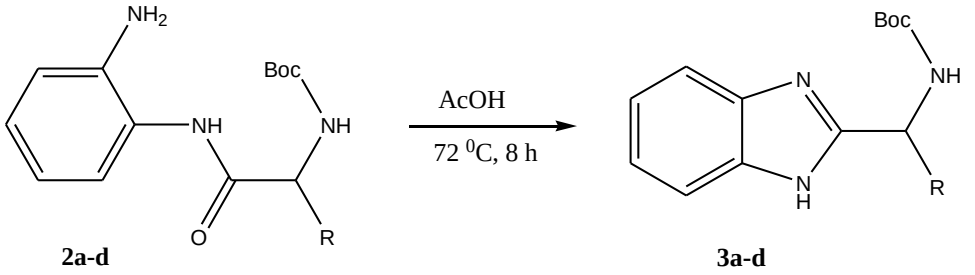
N-Boc-amino acids (1a-d) were reacted with o-phenylenediamine to obtain N-Boc-chiral amide derivatives (2a-d) in the presence of DCC (N,N'-Dicyclohexylcarbodiimide). These reactions were carried out at room temperature and the products were obtained in good yields.



1a-d **2a-d**

Scheme 1.22 Synthesis of N-Boc-Amide Derivatives

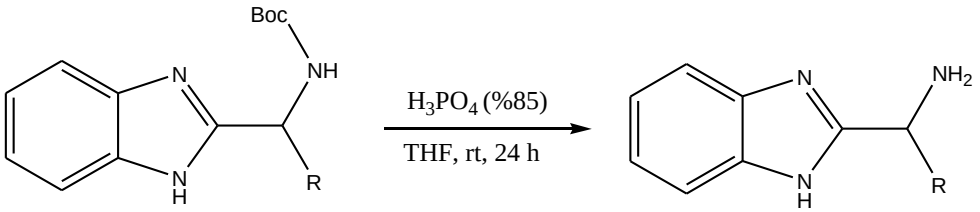
In the next step, acetic acid (AcOH) was used as solvent for ring closure in order to obtain benzimidazole derivatives (3a-d). These reactions were carried out at 72 °C and the products were obtained in good yields.



2a-d **3a-d**

Scheme 1.23 Synthesis of N-Boc-Benzimidazole Derivatives

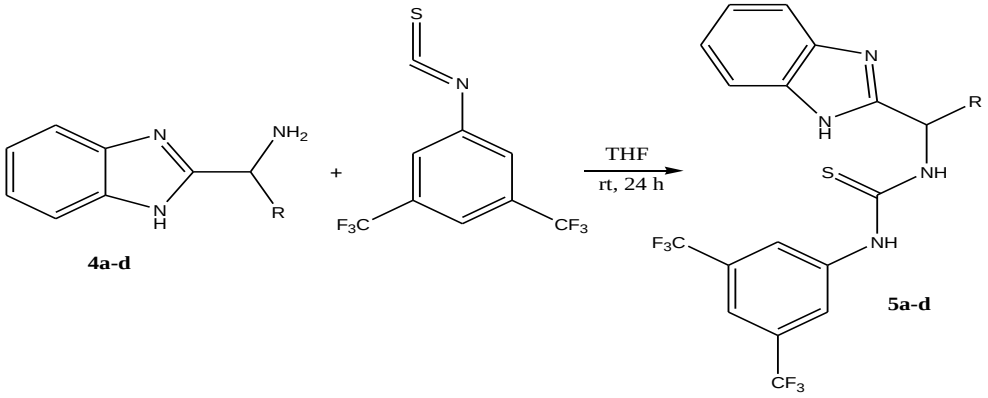
After this reaction, deprotection occurred with H_3PO_4 (85%) and reactions were carried out at room temperature and deprotected amides of benzimidazoles (4a-d) were obtained in good yields.



3a-d **4a-d**

Scheme 1.24 Deprotection of N-Boc-Benzimidazole Derivatives

The deprotected amides of benzimidazoles (4a-d) were reacted with 3,5 bis(trifluromethyl)phenylisothiocyanates. In this reaction, amine groups act as nucleophiles and attack the thiocarbonyl side of the 3,5-bis(trifluromethyl)phenylisothiocyanate. Subsequent rearrangement leads to the desired thiourea derivatives (5a-d) which were obtained in good yields.

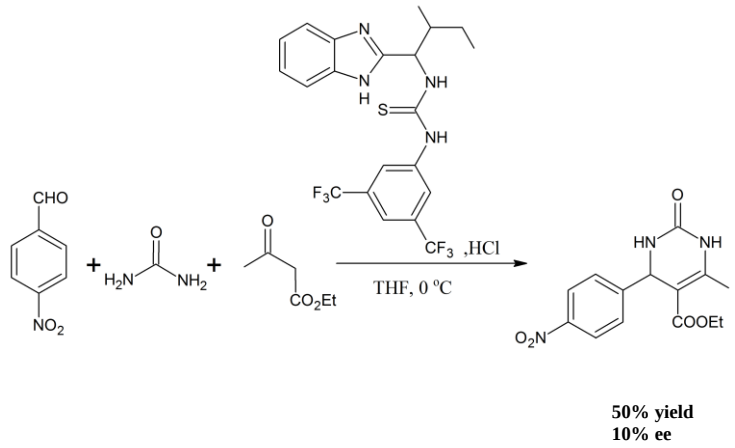


Scheme 1.25 Synthesis of Chiral Thiourea Derivative

Since these products have active functional groups such as benzimidazole and thiourea, they are important and also might be converted to other functional groups. Furthermore, thiourea derivative of benzimidazole compounds can be prepared for ligand synthesis to be used in asymmetric reactions. The most important feature of the products is that they contain a chiral centre. The chirality of the compounds gives them a potential role as key synthetic intermediates for a variety of pharmaceutically important compounds.

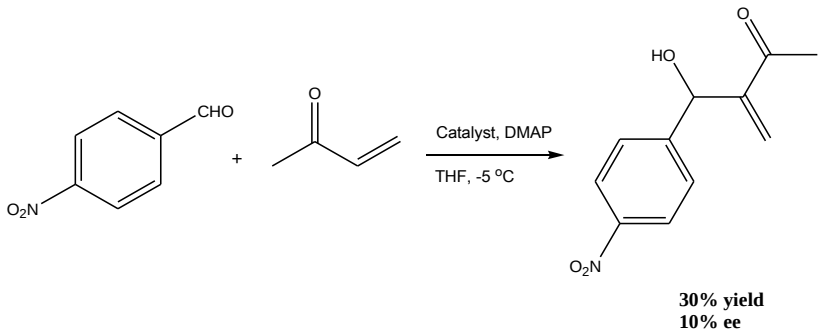
Our synthesized thiourea derivative of benzimidazole compounds were used as catalyst in asymmetric reactions such as Biginelli, Morita-Bayliss-Hillman, Henry and Michael reactions. However, as the determination of model thiourea derivative had shown low enantioselectivity, other thiourea derivatives were not determined as catalyst in those reactions.

In order to investigate the catalytic activity of our synthesized compounds, Biginelli reaction was used as model asymmetric reaction. Biginelli reaction, which is a three-component reaction of an aromatic aldehyde, urea and acetoacetate, is one of the most efficient methods for the assembly of heterocyclic compounds. Therefore, recent efforts have been devoted to the synthesis of these compounds. The yield and enantiomeric excess in this reaction which is shown on (scheme 1.26) were trace.



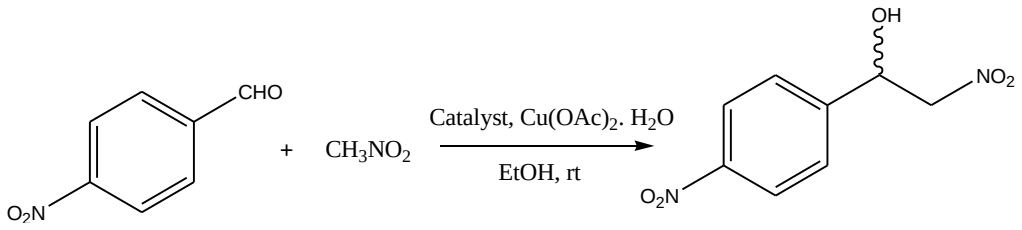
Scheme 1.26 Biginelli catalyst reaction

In the second asymmetric reaction, Morita-Baylis-Hillman reaction was used for catalytic activity investigation. The reaction was carried out at -5°C. Enantiomeric excess and product were obtained in low yields.



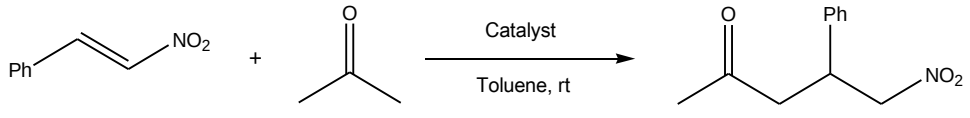
Scheme 1.27 Morita-Baylis-Hillman catalyst reaction

The third asymmetric reaction was Henry reaction. In this reaction product formation was not be observed.



Scheme 1.28 Henry catalyst reaction

Finally, Michael reaction was used as asymmetric reaction for the investigation of catalytic activity. This reaction was carried out at room temperature. However, the enantiomeric excess and the yield were trace as shown below:

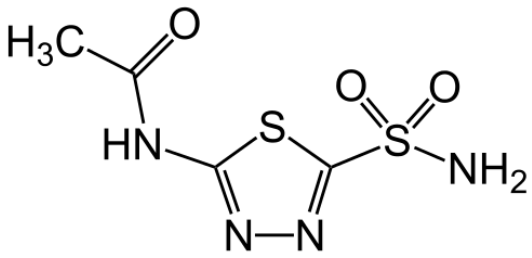


15% yield
7% ee

Scheme 1.29 Michael catalyst reaction

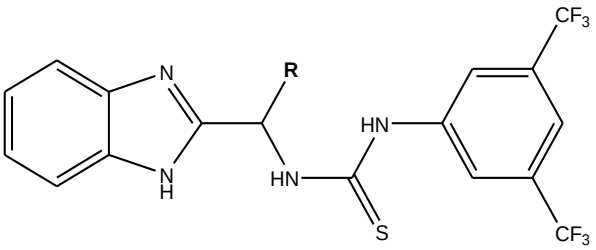
The development of new antimicrobial and anti cancer therapeutic agents is one of the main fundamental goals in medicinal chemistry. Chiral thioureas and their derivatives of benzimidazoles display a wide range of biological activities such as antibacterial, antiviral and antifungal.

Acetazolamide (AZA) is a carbonic anhydrase inhibitor that is used to treat glaucoma, epileptic seizures, idiopathic intracranial hypertension, altitude sickness, periodic paralysis and central sleep apnea. Acetazolamide is available as a generic drug and also a diuretic.



acetazolamide

Many of acetazolamides are important targets for the design of inhibitors with clinical applications. Carbonic anhydrase (CA) is an enzyme which catalyzes the hydration of carbon dioxide to bicarbonate to maintain acid-base balance in blood and other tissues.



R = 1: -C_6H_5
2: -$CH_2C_6H_5$
3: -$CH(C_2H_5)(CH_3)$
4: -$CH_2CH_2SCH_3$

Thiourea derivative of benzimidazoles

The results of our synthesized benzimidazole derivatives for the inhibition of human CA I and CA II enzymes (IC_{50}) are shown in table below:

Inhibitor	**hCA I**	**hCA II**
1	73.6	44.2
2	62.3	26.5
3	53.8	18.1
4	46.1	12.9
AZA	36.2	0.37

The activating effects of benzimidazole derivatives have the similar activity for hCA I inhibitor as acetazolamide. The inhibition effects of the same derivatives for hCA II are moderately effective as compared to acetazolamide. Considering these results, the synthesized benzimidazole derivatives are potential CA inhibitors and they might be considered to be used as drugs for the treatment of various diseases.

This work still continues and different thiourea derivatives are going to be synthesized and their biological activities are going to be analysed. The products were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectrums and elemental analyses.

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CURRICULUM VITAE

Personal Knowledge

Name and Surname **:** Oday OBAIDI

Date/Place of Birth **:** 20.12.1983 / Diyala-Iraq

Nationality **:** Iraqi

Phone Number **:** +9647705040234 and +9647703542534

E-mail **:udayyy83@yahoo.com**

Educational Background

2003-2007 Bsc. in Chemistry, Diyala University, Faculty of Science.

2009-2010 Diploma in Turkish language (TÖMER) at Gazi University.

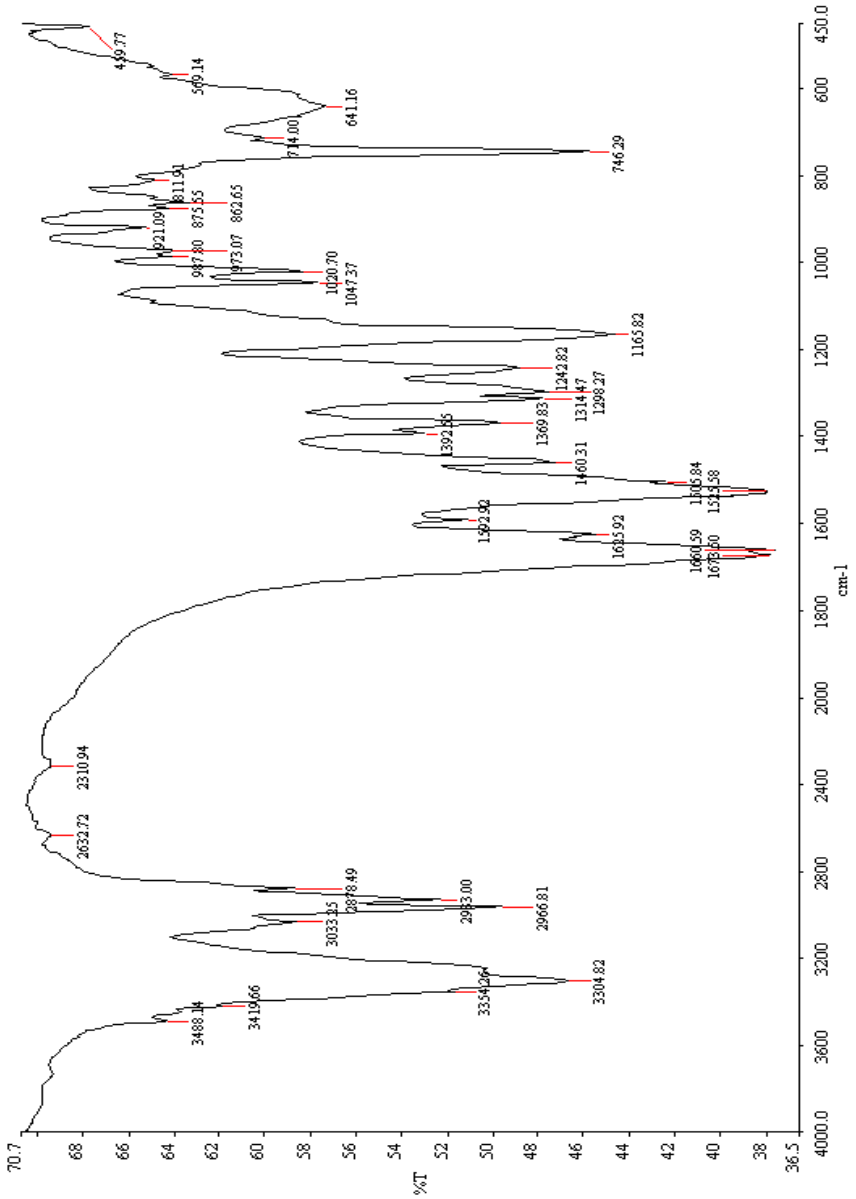
2010-2011 Diploma in English language at Ege University.

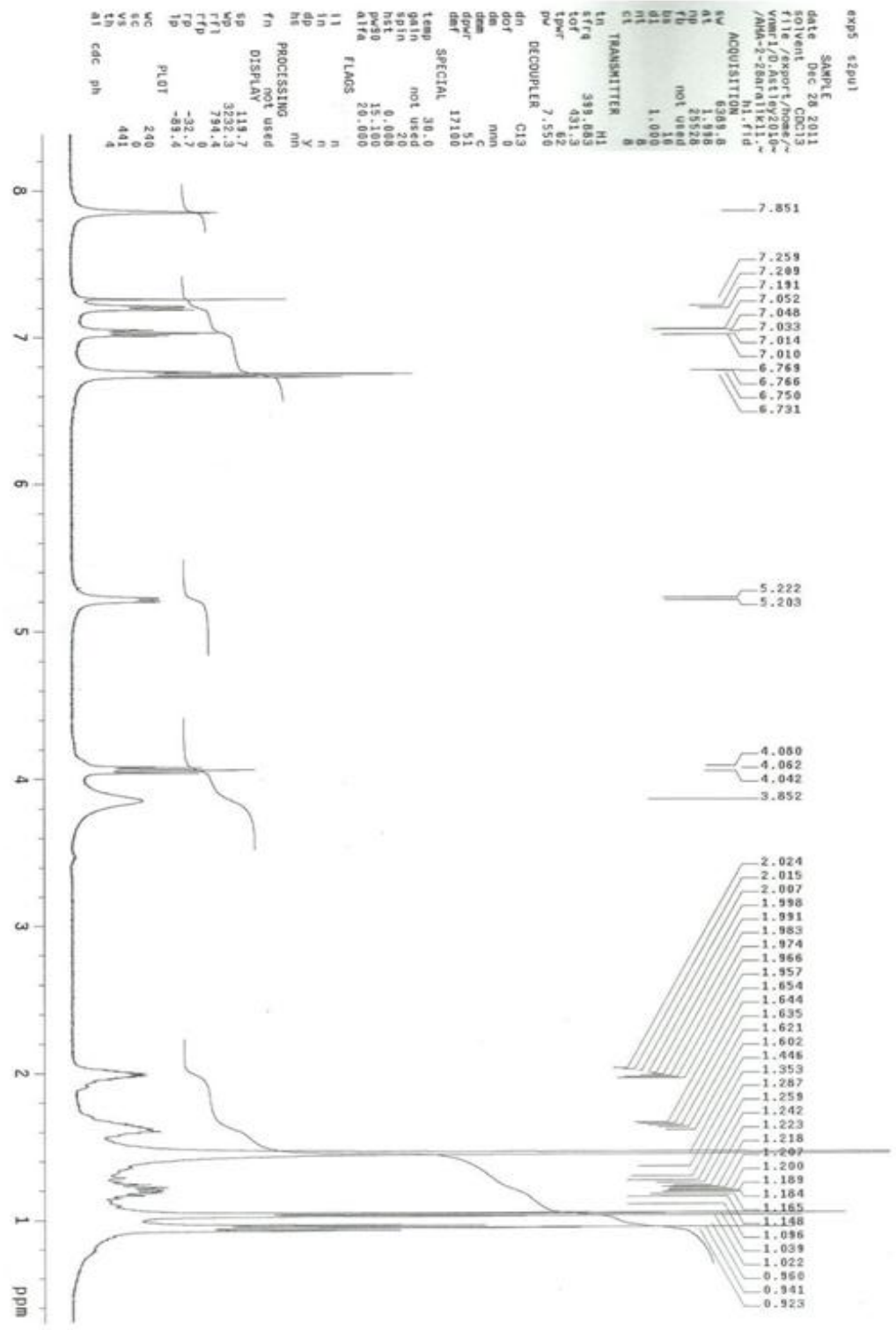
2011-2013 MSc. In Organic Chemistry, Graduate School of Natural and Applied Sciences, Ege University.

APPENDIX

APPENDIX (Continued)

Appendix 1 FTIR Spectrum, ^{1}H-NMR Spectrum and ^{13}C-NMR Spectrum of Compound 1

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nt 8
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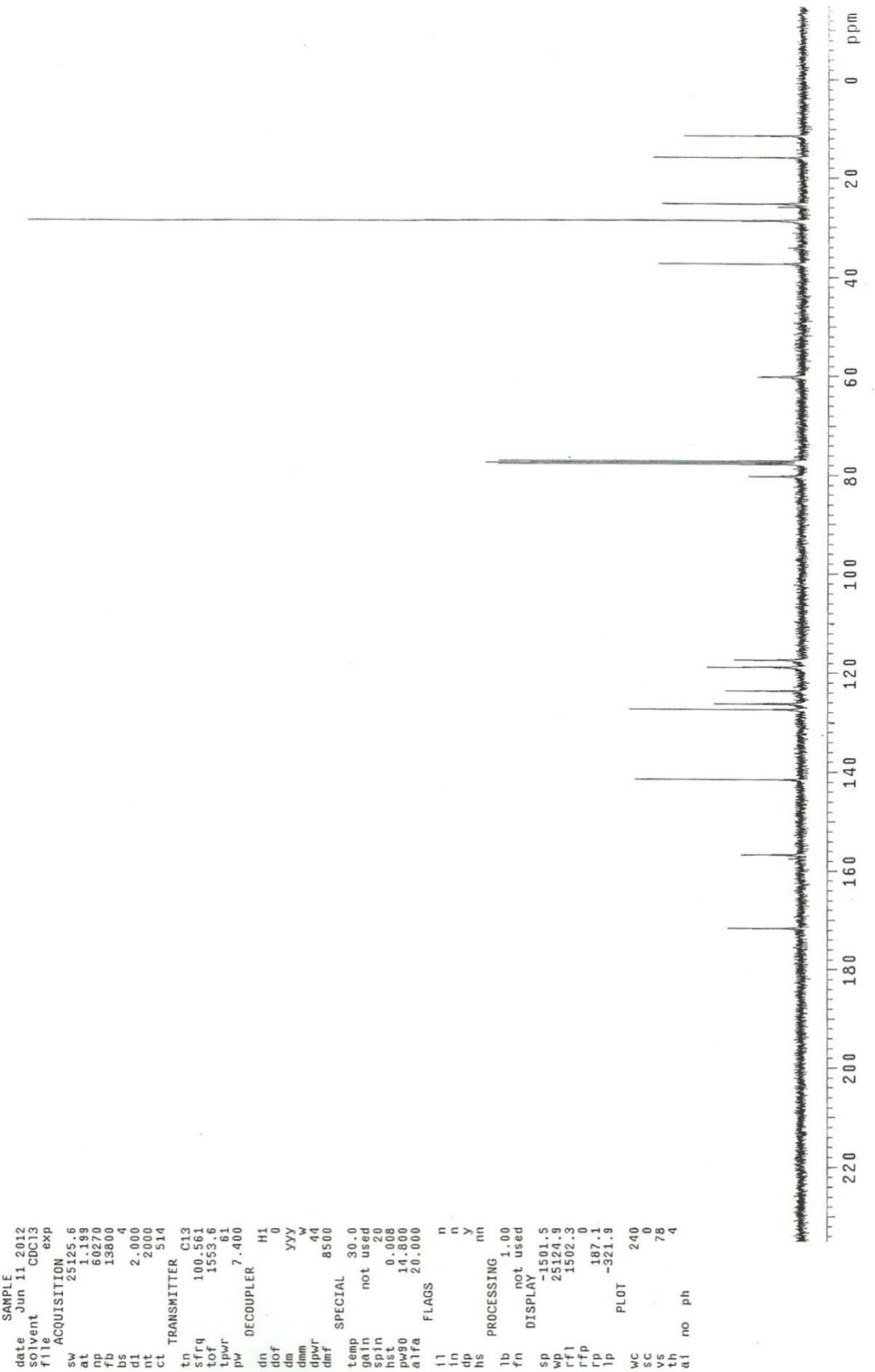
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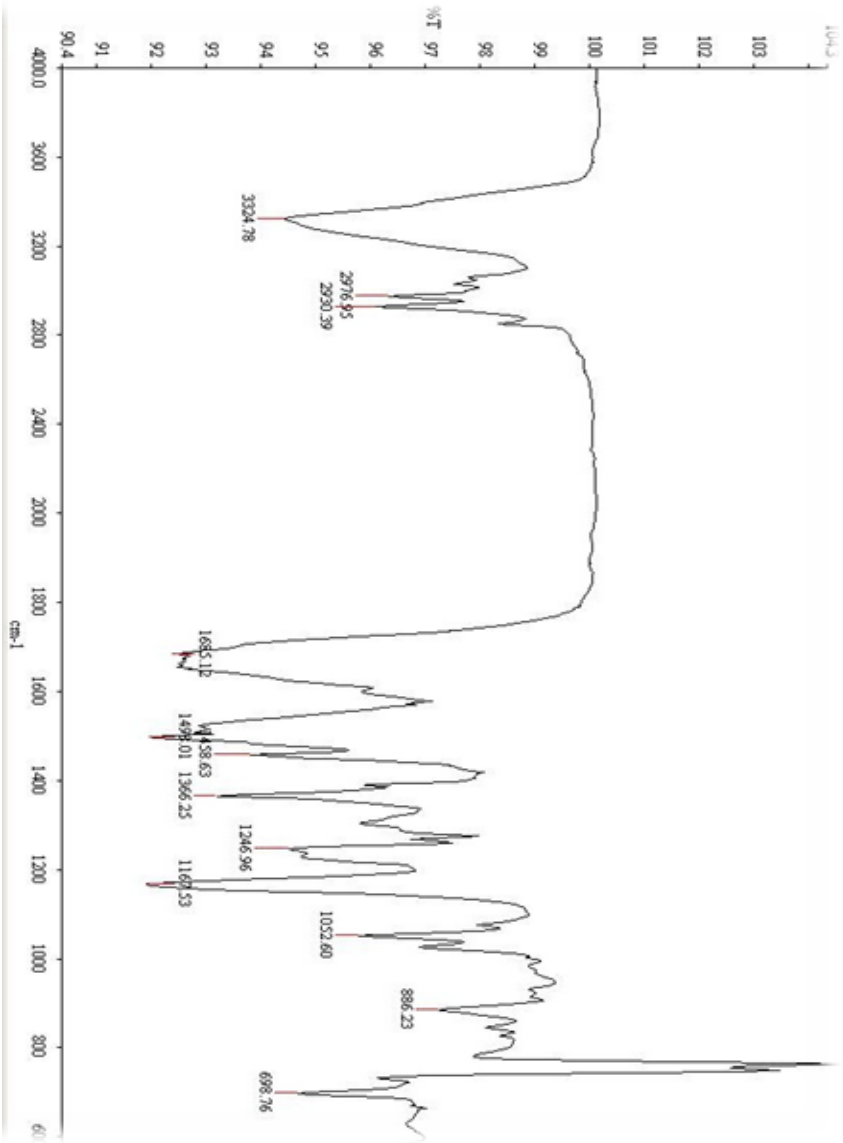
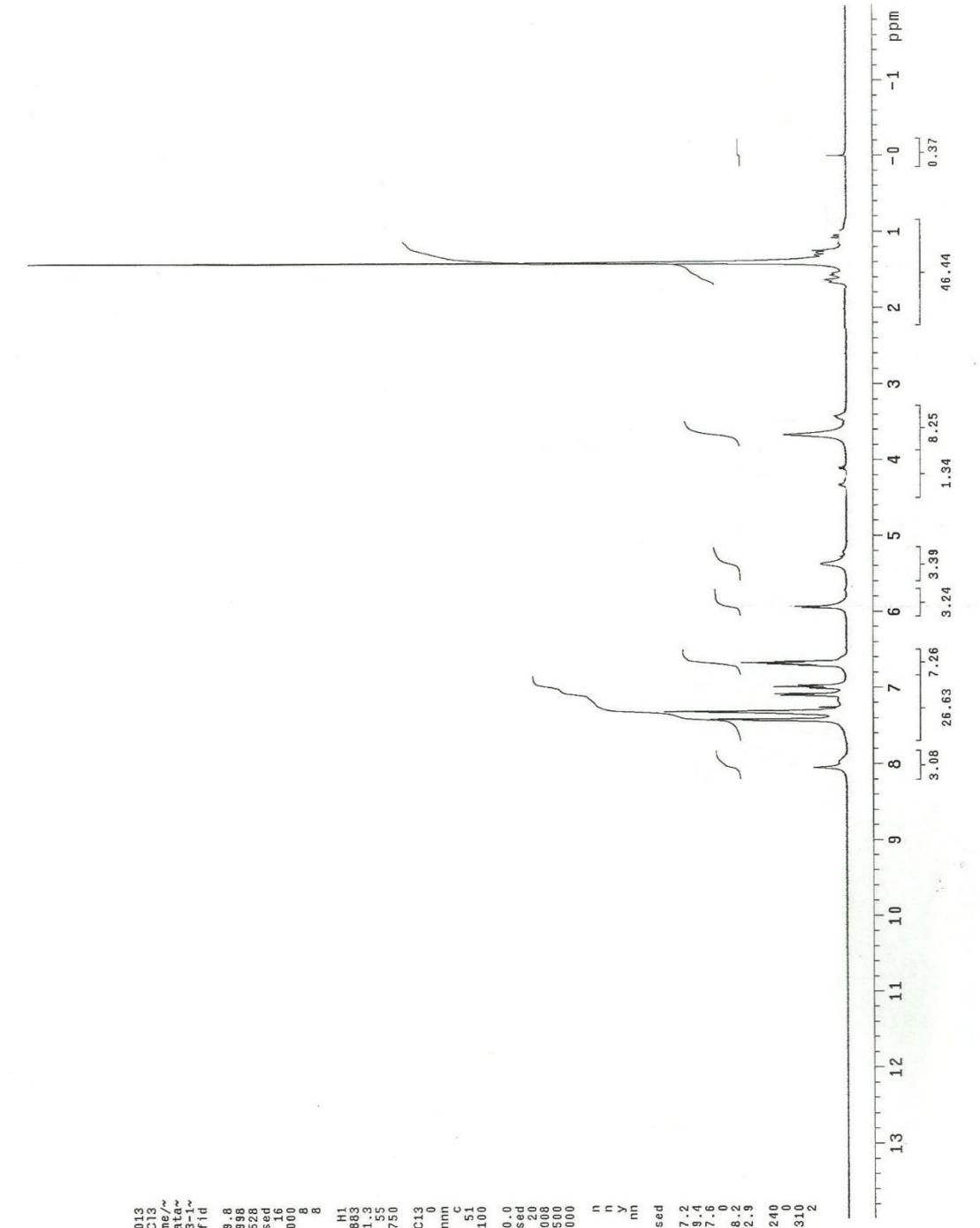
Appendix 2 FTIR Spectrum, ^{1}H-NMR Spectrum and ^{13}C-NMR Spectrum of Compound 2

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hs nn
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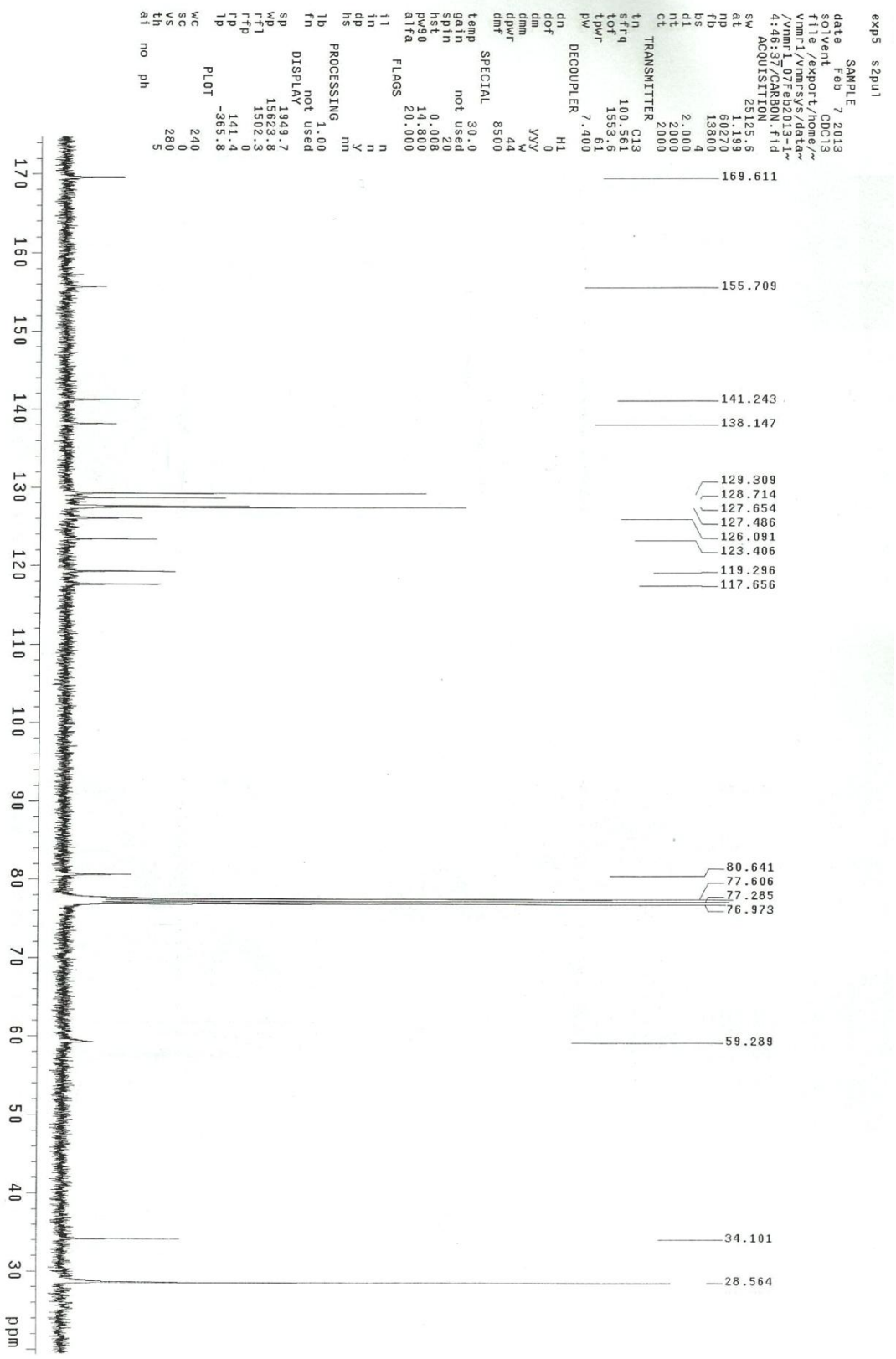
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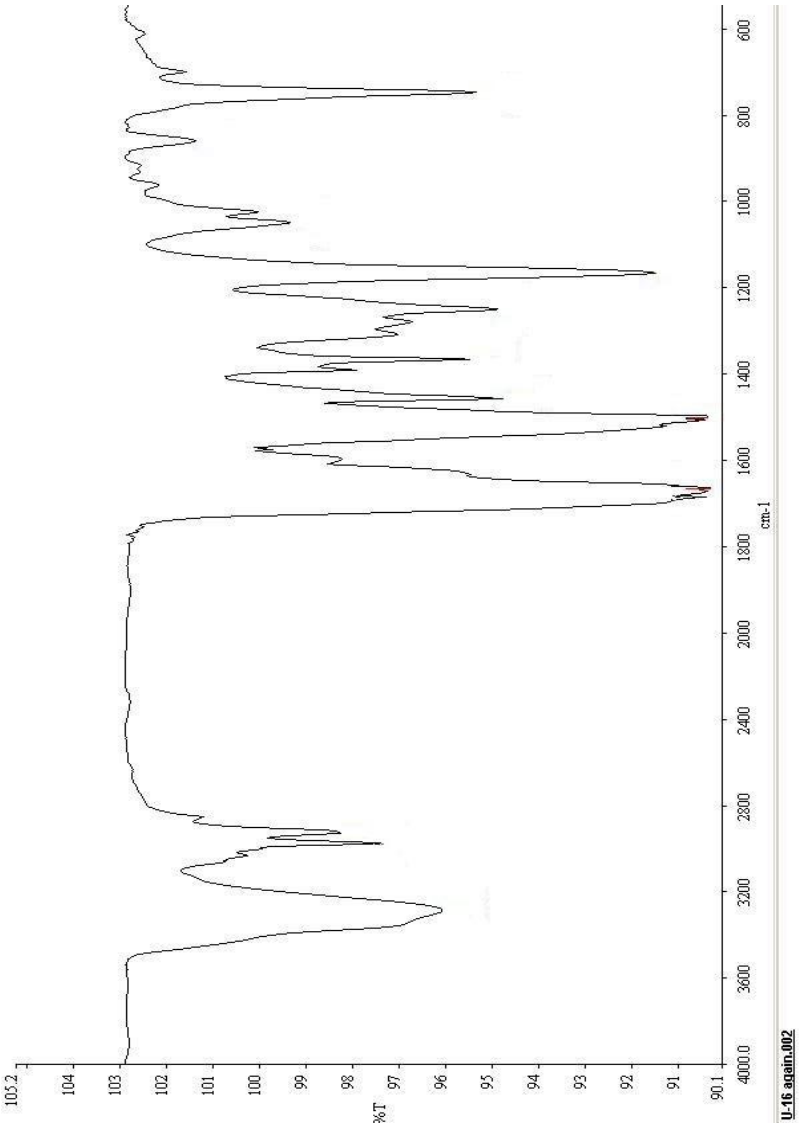
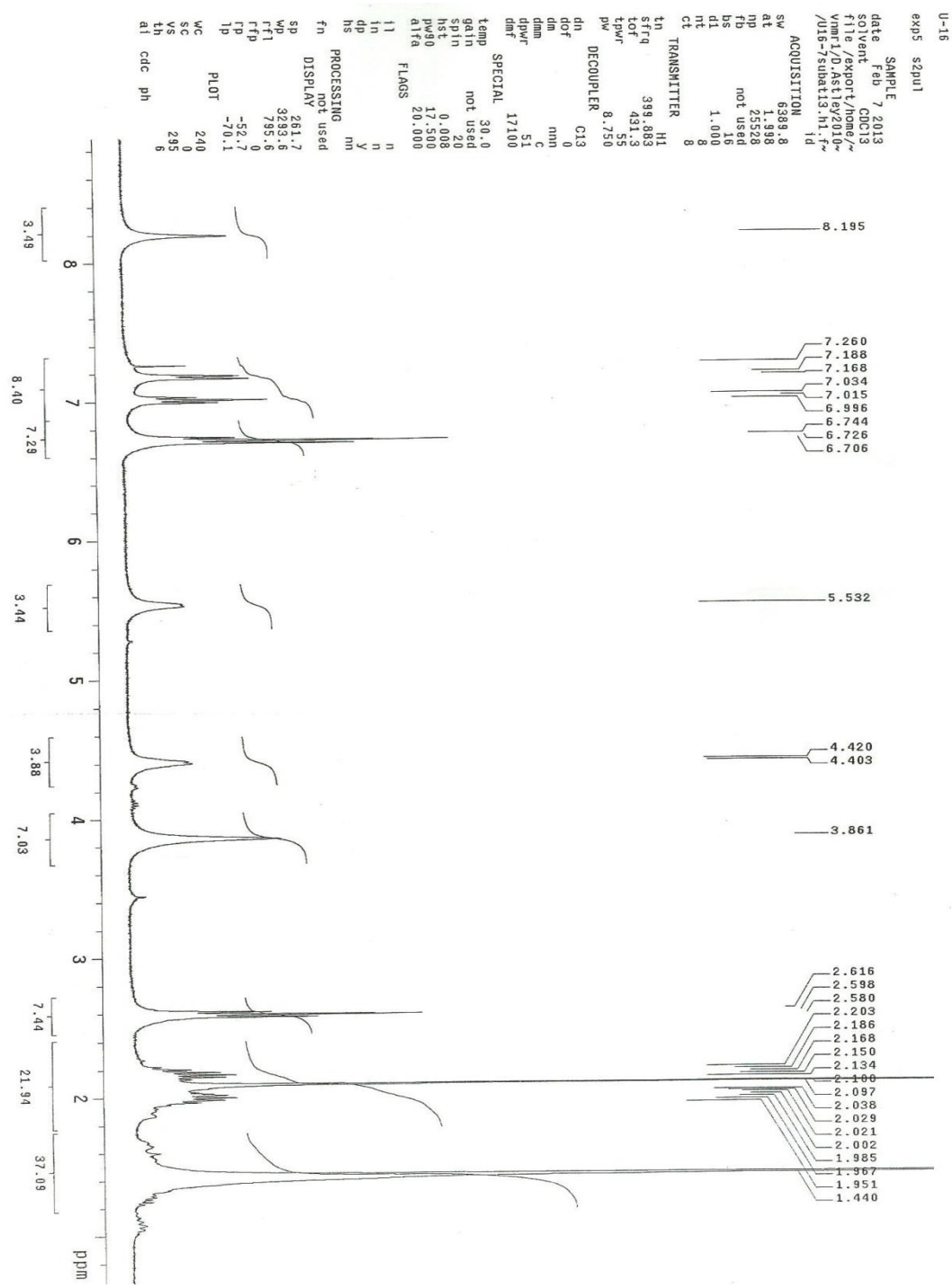
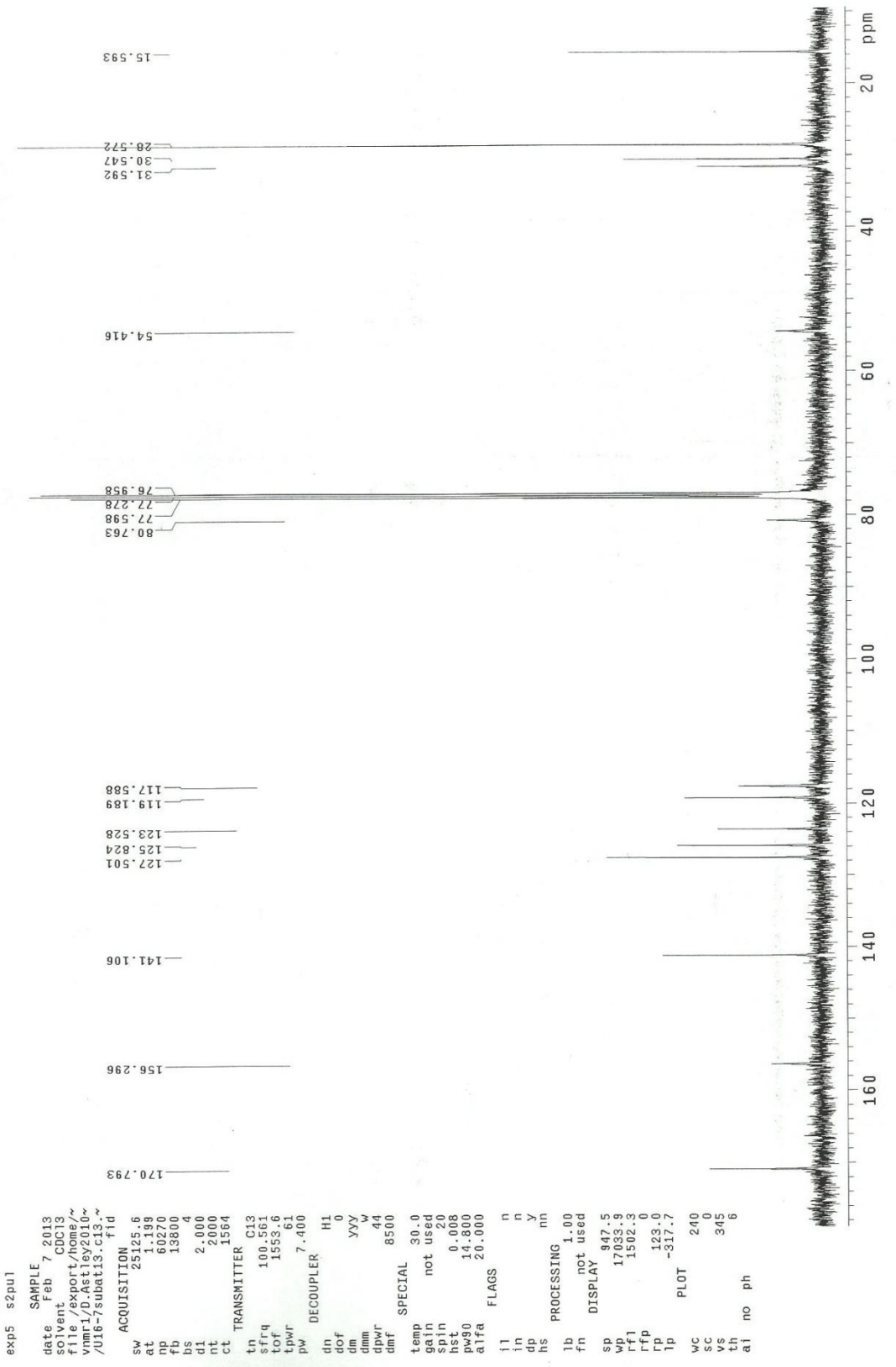
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 2000
TRANSMITTER
tn C13
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 1949.7
wp 15623.8
rfl 1502.3
rfp 0
rp 141.4
lp -365.8
PLOT
wc 240
sc 0
vs 280
th 5
al no ph
169.611
155.709
141.243
138.147
129.309
128.714
127.654
127.486
126.091
123.406
119.296
117.656
80.641
77.606
77.285
76.973
59.289
34.101
28.564
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

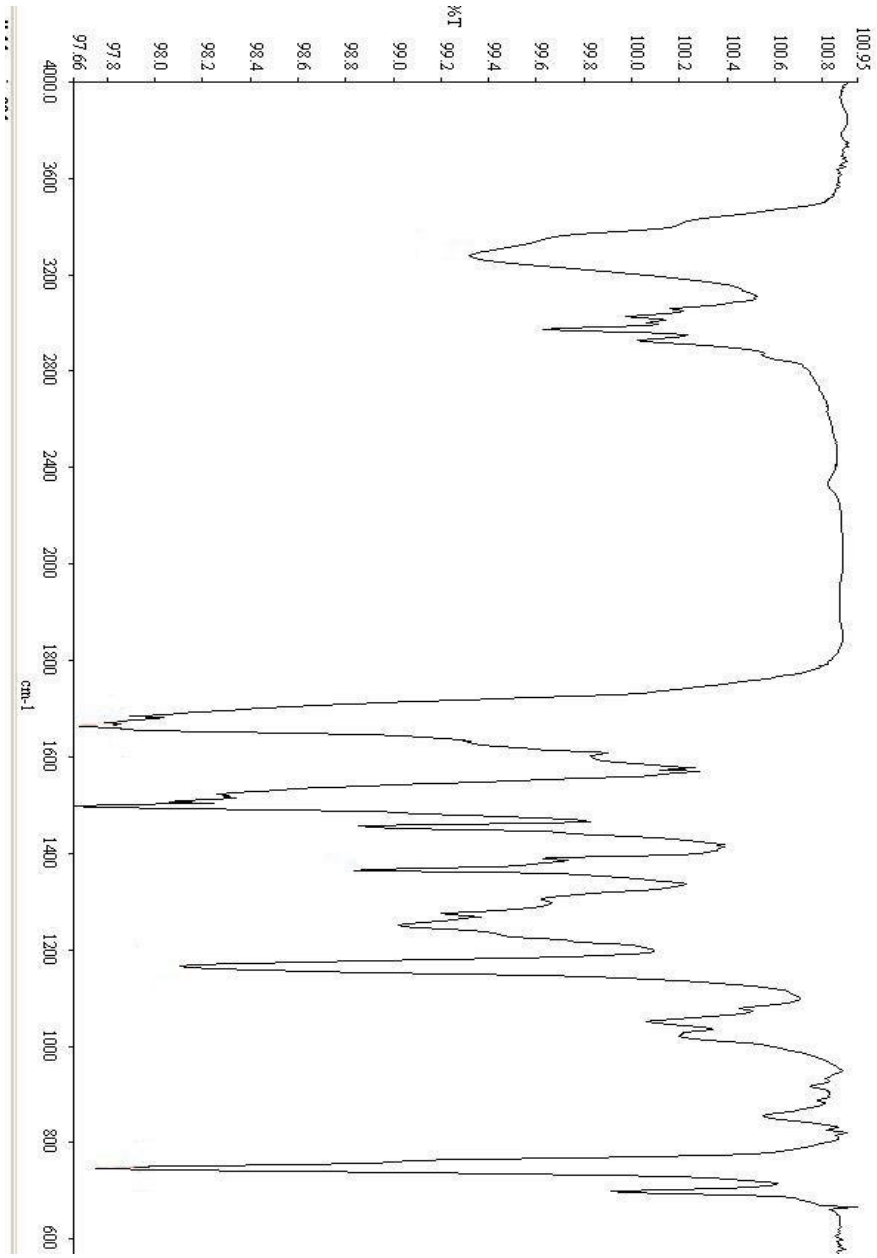
Appendix 3 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 3

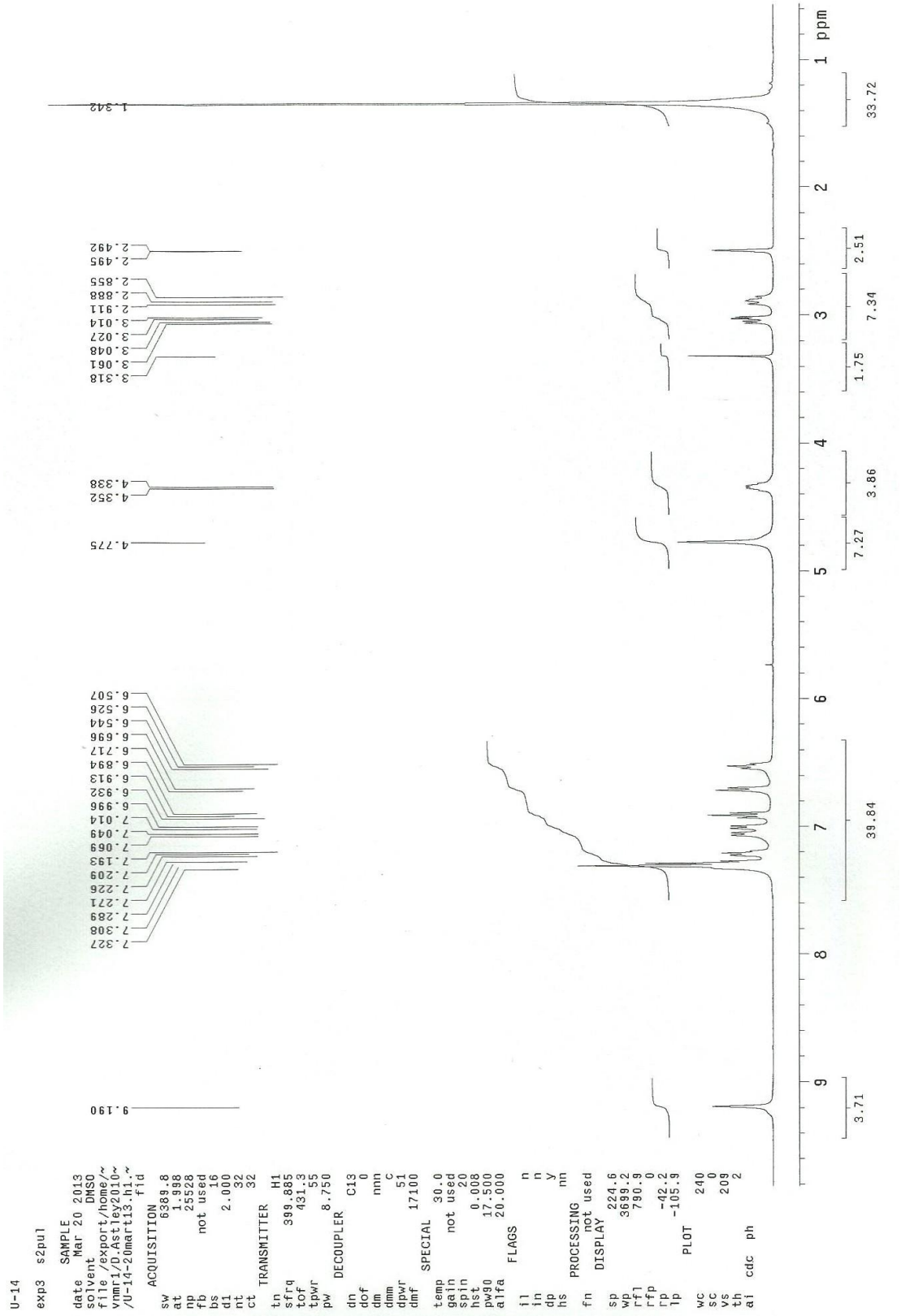


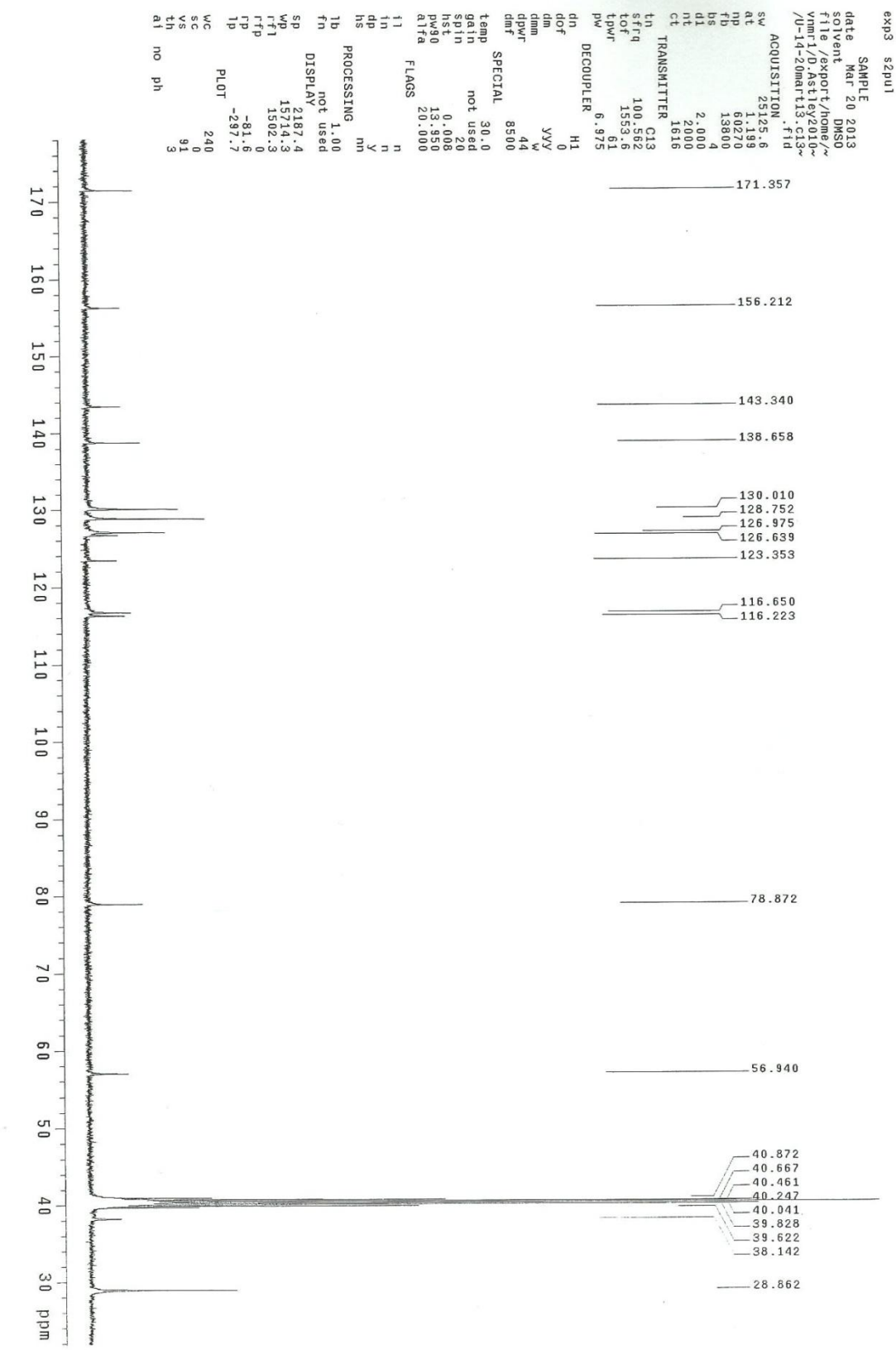

U-16
exp5 s2pul
SAMPLE
date Feb 7 2013
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U16-7subat13.h1.fi
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.883
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp 261.7
wp 3293.6
rfl 795.6
rfp 0
rp -52.7
lp -70.1
PLOT
wc 240
sc 0
vs 295
th 6
ai cdc ph
8.195
7.260
7.188
7.168
7.034
7.015
6.996
6.744
6.726
6.706
5.532
4.420
4.403
3.861
2.616
2.598
2.580
2.203
2.186
2.168
2.150
2.134
2.100
2.097
2.038
2.029
2.021
2.002
1.985
1.967
1.951
1.440
3.49
8.40
7.29
3.44
3.88
7.03
7.44
21.94
37.09
8
7
6
5
4
3
2
ppm


15.593
28.572
30.547
31.592
54.416
76.958
77.278
77.598
80.763
117.588
119.189
123.528
125.824
127.501
141.106
156.296
170.793
ppm
20
40
60
80
100
120
140
160
exp5 s2pul
SAMPLE
date Feb 7 2013
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U16-7subat13.c13.~
fid
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 1564
TRANSMITTER C13
tn
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER H1
dn
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 947.5
wp 17033.9
rfl 1502.3
rfp 0
rp 123.0
lp -317.7
PLOT
wc 240
sc 0
vs 345
th 6
ai no ph

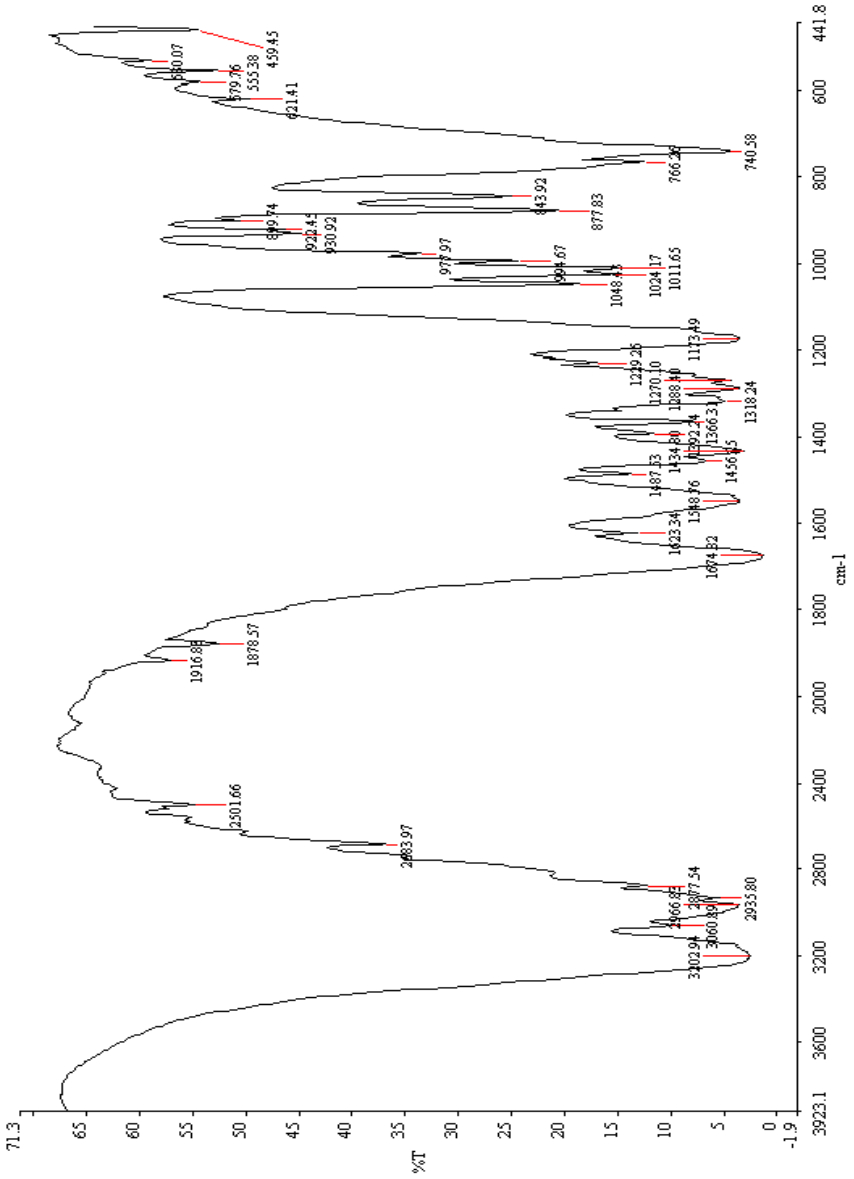
Appendix 4 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 4

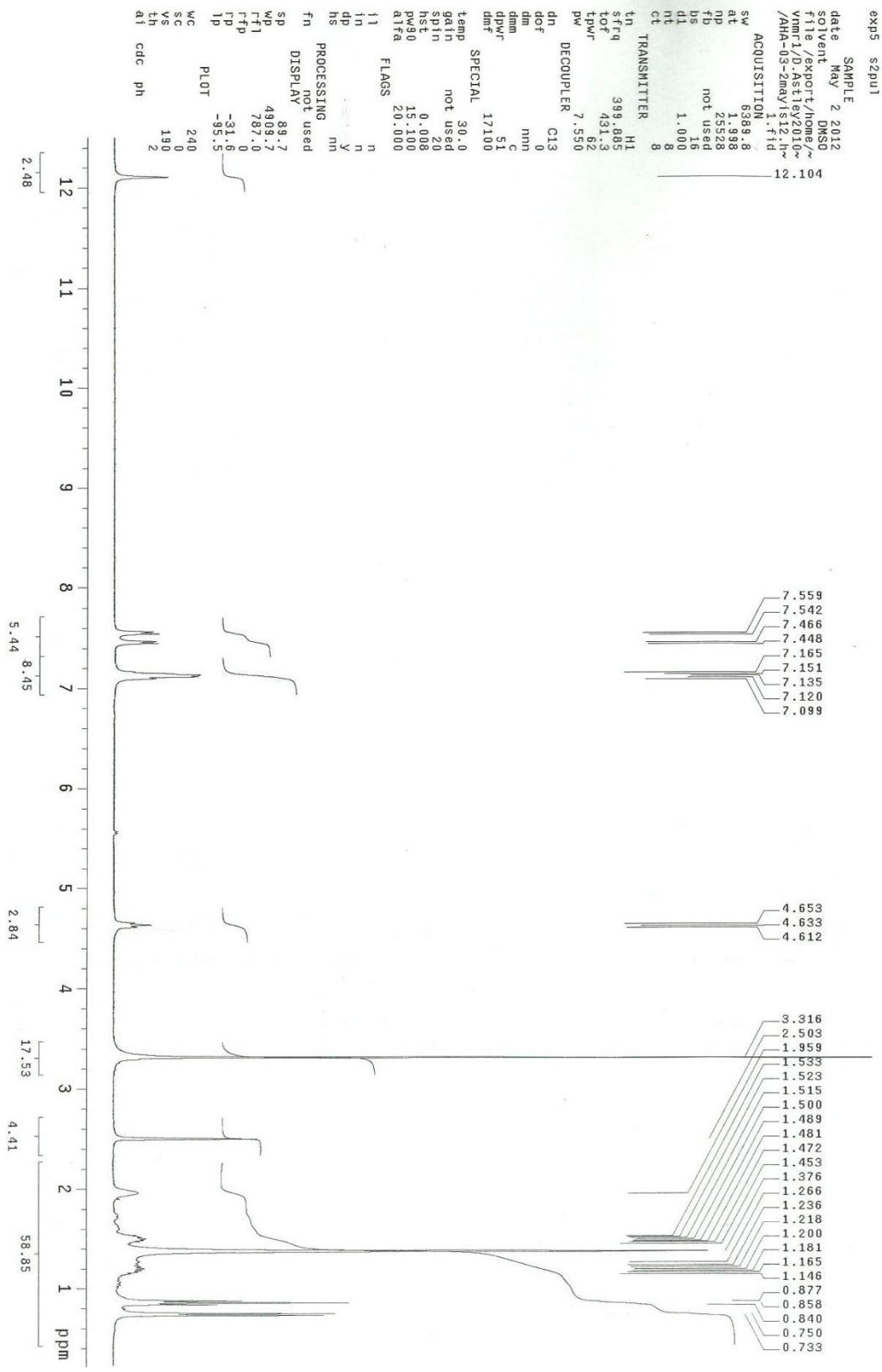


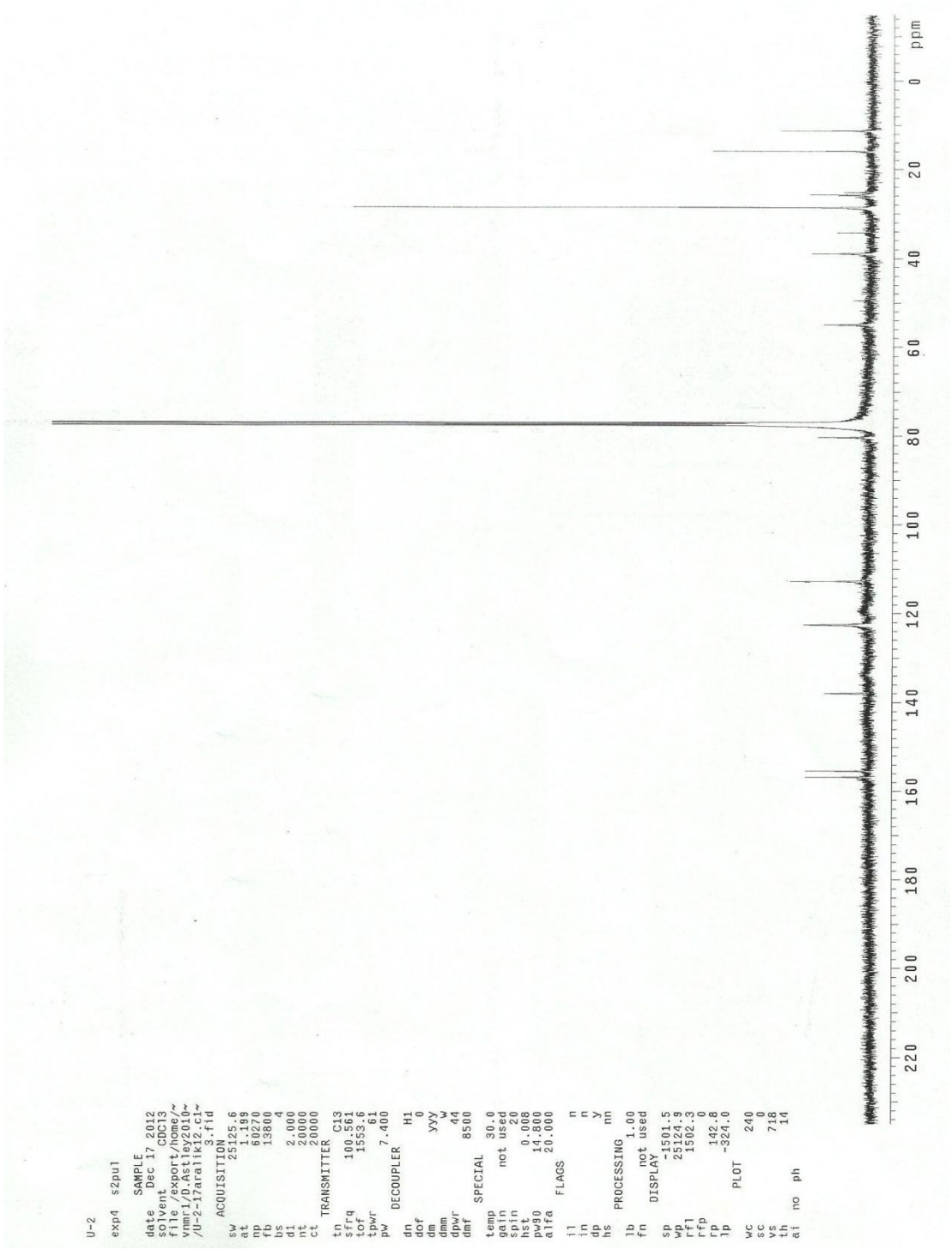

U-14
exp3 s2pul
SAMPLE
date Mar 20 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-14-20mar13.h1.~
fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 2.000
nt 32
ct 32
TRANSMITTER H1
tn
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER C13
dn
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING not used
fn DISPLAY
sp 224.6
wp 3698.2
rfl 790.9
rfp 0
rp -42.2
lp -105.9
PLOT
wc 240
sc 0
vs 209
th 2
ai cdc ph
9.190
7.327
7.308
7.289
7.271
7.226
7.209
7.193
7.069
7.049
7.014
6.996
6.932
6.913
6.894
6.717
6.696
6.544
6.526
6.507
4.775
4.352
4.338
3.318
3.061
3.048
3.027
3.014
2.911
2.888
2.855
2.495
2.492
1.342
3.71
39.84
7.27
3.86
1.75
7.34
2.51
33.72
9
8
7
6
5
4
3
2
1
ppm


exp3 s2pul
SAMPLE
date Mar 20 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-14-20mart13.c13~
ACQUISITION .fid
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 1616
TRANSMITTER
tn C13
sfrq 100.562
tof 1553.6
tpwr 61
pw 6.975
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 13.950
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 2187.4
wp 15714.3
rfl 1502.3
rfp 0
rp -81.6
lp -297.7
PLOT
wc 240
sc 0
vs 91
th 3
ai no ph
171.357
156.212
143.340
138.658
130.010
128.752
126.975
126.639
123.353
116.650
116.223
78.872
56.940
40.872
40.667
40.461
40.247
40.041
39.828
39.622
38.142
28.862
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30 ppm

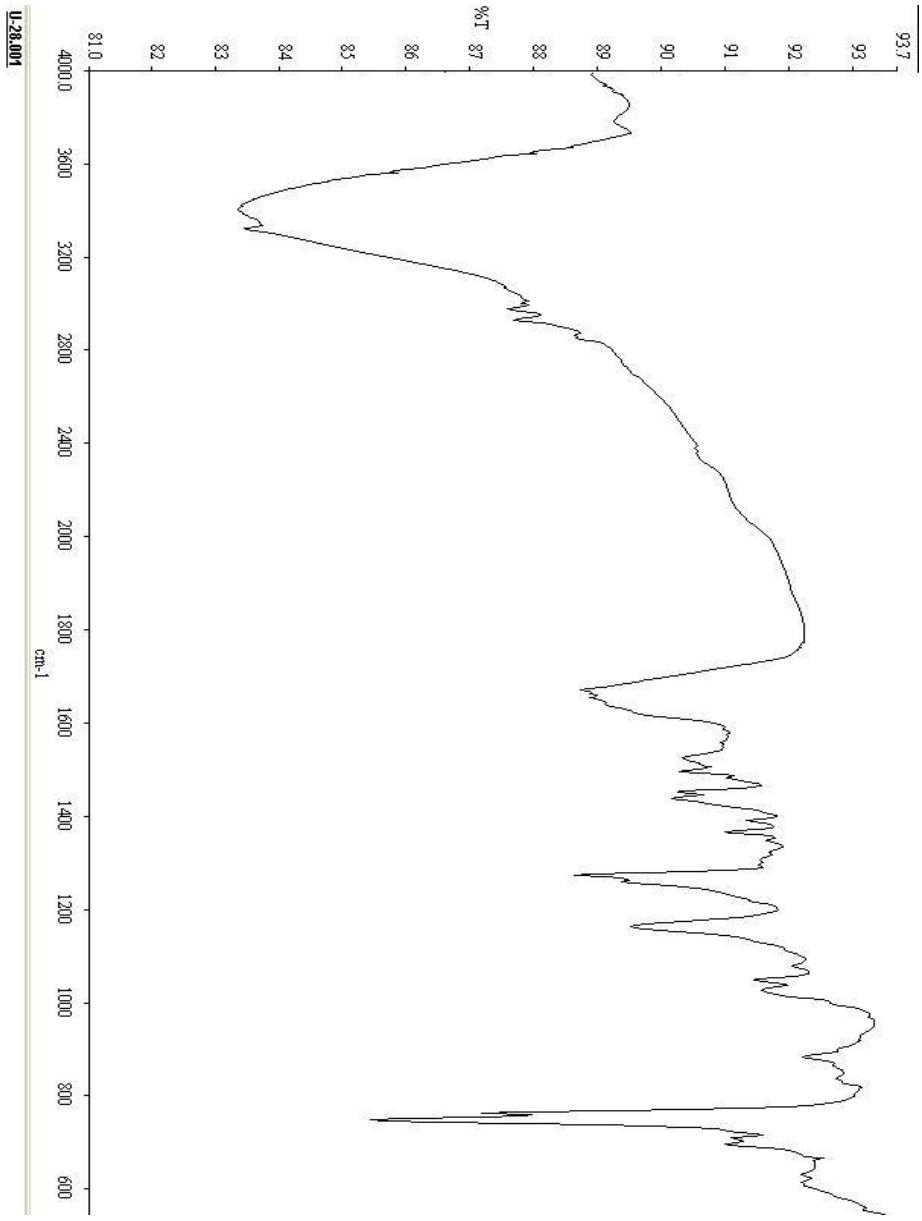
Appendix 5 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 5

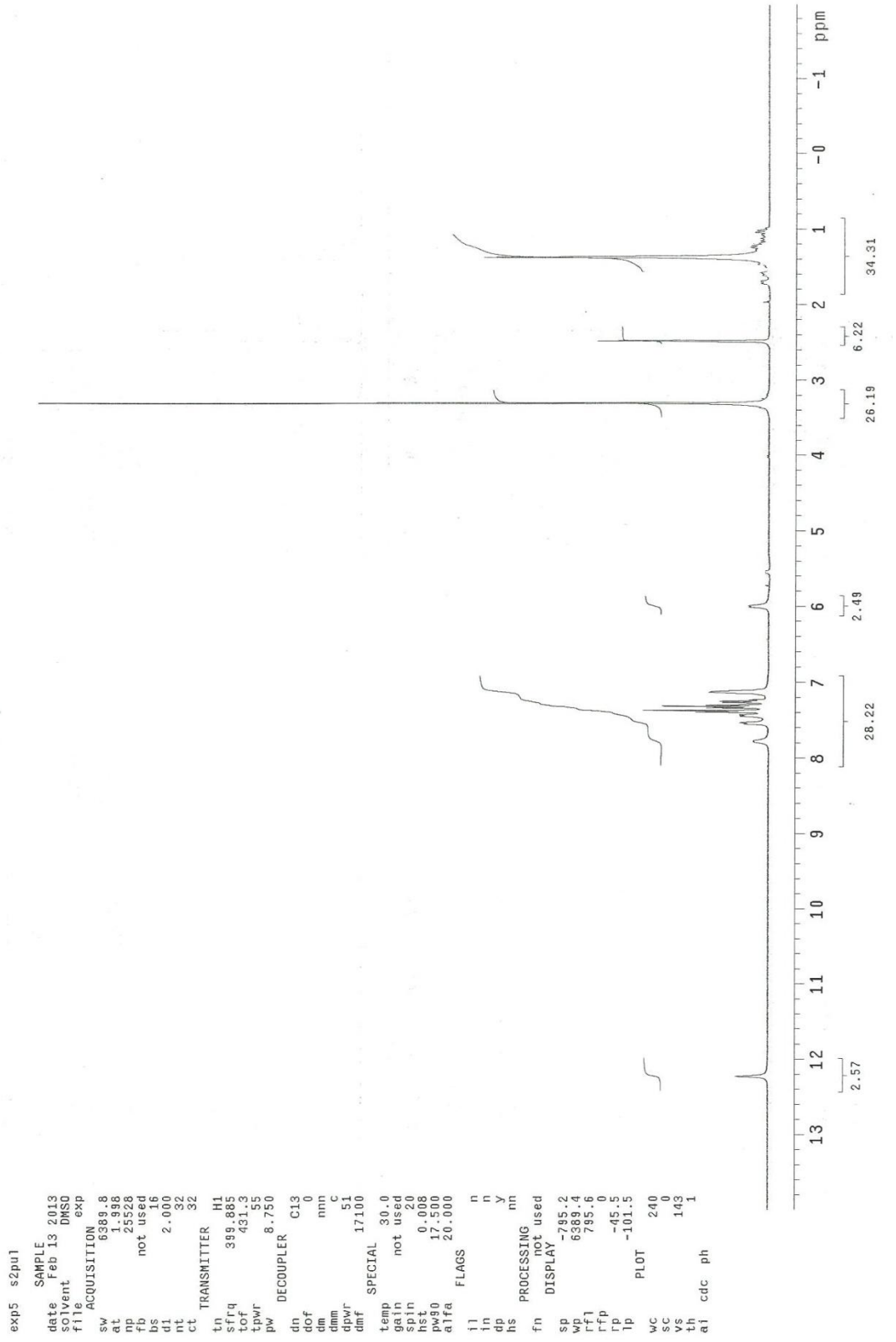


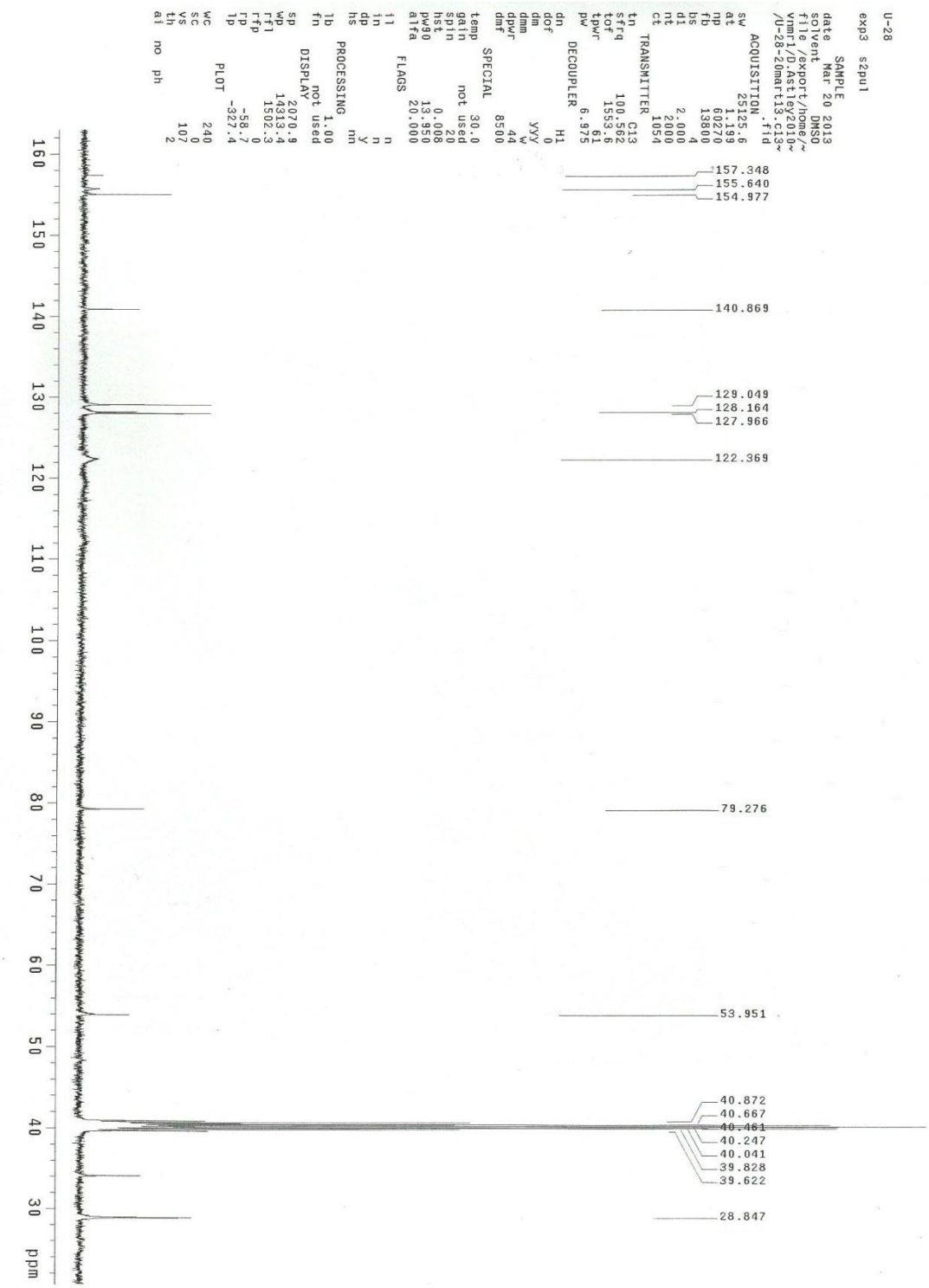

exp5 s2pul
SAMPLE
date May 2 2012
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/AHA-03-2may1s12.h~
1.fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.885
tof 431.3
tpwr 62
pw 7.550
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 15.100
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp 89.7
wp 4909.7
rfl 787.0
rfp 0
rp -31.6
lp -95.5
PLOT
wc 240
sc 0
vs 190
th 2
ai cdc ph
12.104
7.559
7.542
7.466
7.448
7.165
7.151
7.135
7.120
7.099
4.653
4.633
4.612
3.316
2.503
1.959
1.533
1.523
1.515
1.500
1.489
1.481
1.472
1.453
1.376
1.266
1.236
1.218
1.200
1.181
1.165
1.146
0.877
0.858
0.840
0.750
0.733
2.48
5.44
8.45
2.84
17.53
4.41
58.85
12
11
10
9
8
7
6
5
4
3
2
1
ppm


U-2
exp4 s2pul
SAMPLE
date Dec 17 2012
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U-2-17aralk12.c1~
3.fid
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 20000
ct 20000
TRANSMITTER C13
tn C13
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER H1
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1501.5
wp 25124.9
rf1 1502.3
rfp 0
rp 142.8
lp -324.0
PLOT
wc 240
sc 0
vs 718
th 14
ai no ph
220
200
180
160
140
120
100
80
60
40
20
0
ppm

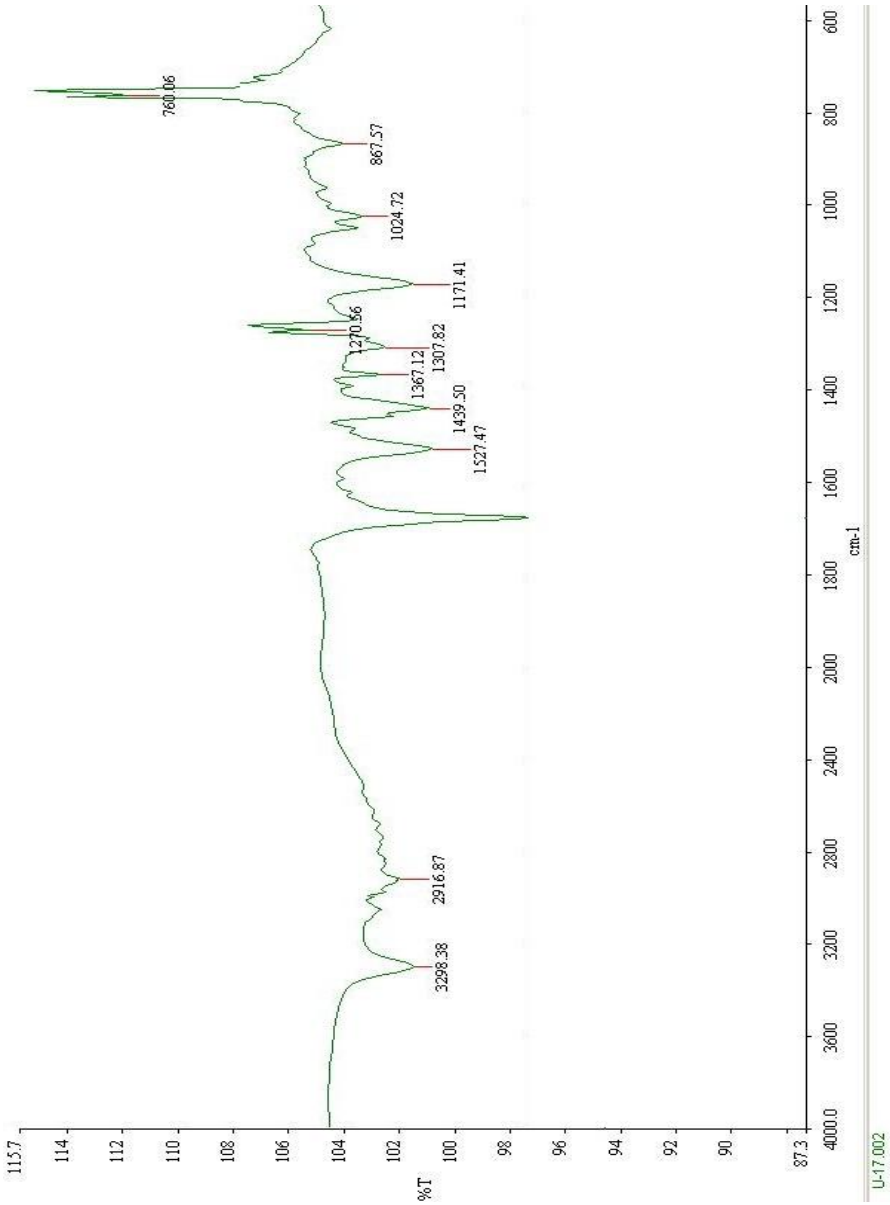
Appendix 6 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 6

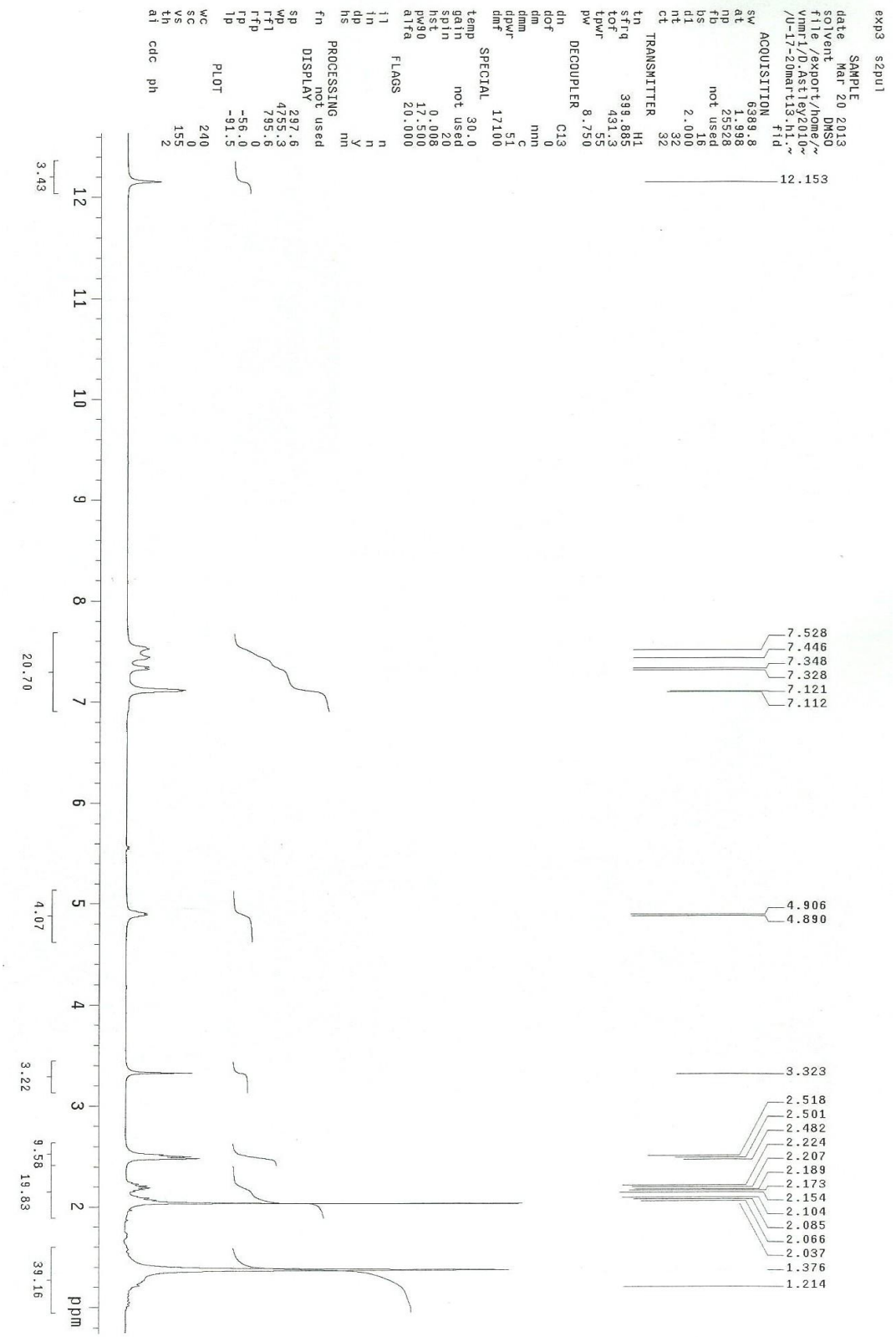


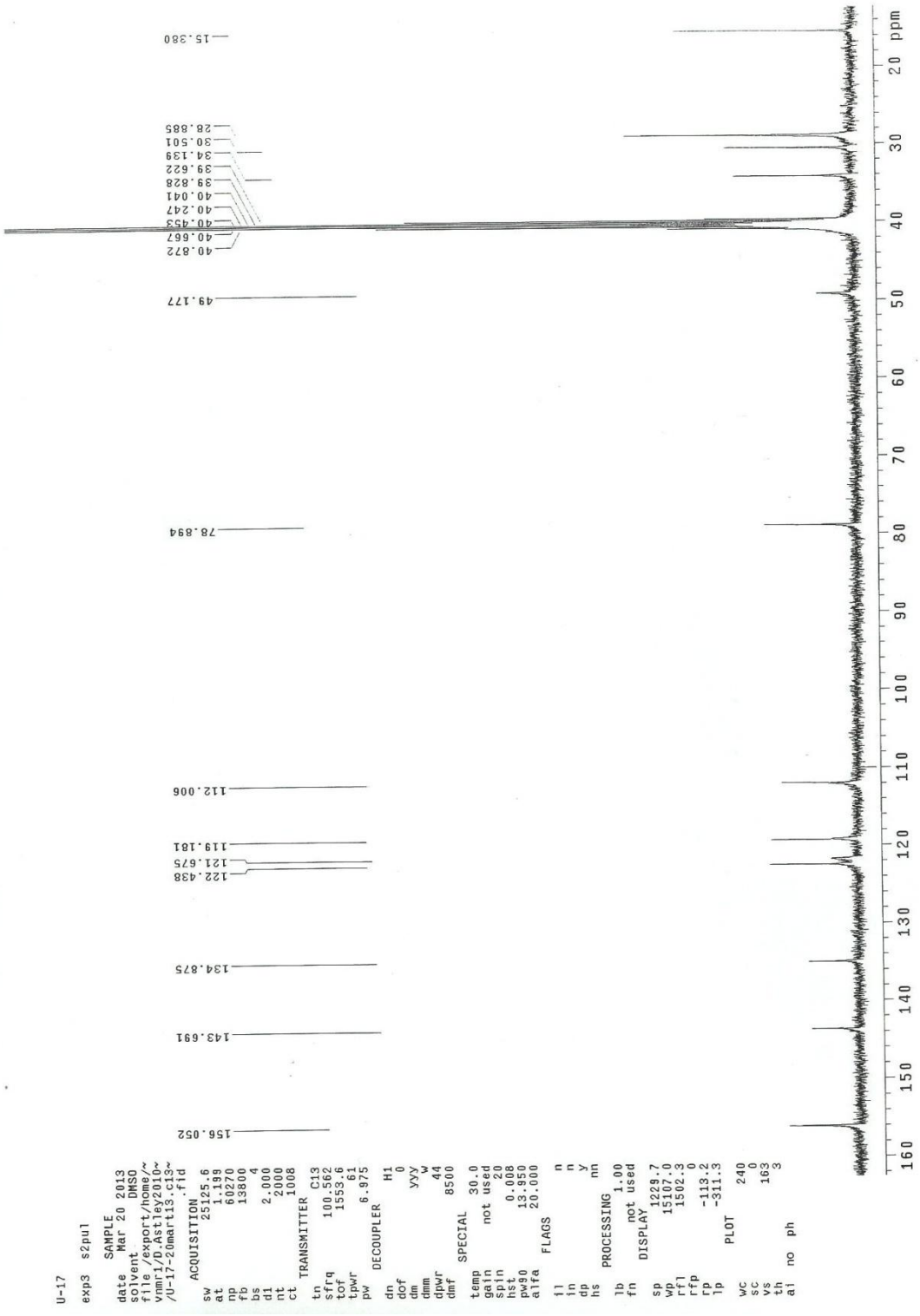

exp5 s2pul
SAMPLE
date Feb 13 2013
solvent DMSO
file exp
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 2.000
nt 32
ct 32
TRANSMITTER H1
tn H1
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER C13
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -795.2
wp 6389.4
rfl 795.6
rfp 0
rp -45.5
lp -101.5
PLOT
wc 240
sc 0
vs 143
th 1
ai cdc ph
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm
2.57
28.22
2.49
26.19
6.22
34.31


U-28
exp3 s2pul
SAMPLE
date Mar 20 2013
solvent DMSO
file /export/home/~
vnmrj/D.Astley2010~
/U-28-20mart13.fid~
ACQUISITION
sw 29125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 1054
TRANSMITTER
tn C13
sfrq 100.562
tof 1553.6
tpwr 51
pw 6.975
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 13.950
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 2070.9
wp 14313.4
rfl 1502.3
rfp 0
rp -58.7
lp -327.4
PLOT
wc 240
sc 0
vs 107
th 2
al no ph
157.348
155.640
154.977
140.869
129.049
128.164
127.966
122.369
79.276
53.951
40.872
40.667
40.461
40.247
40.041
39.828
39.622
28.847
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

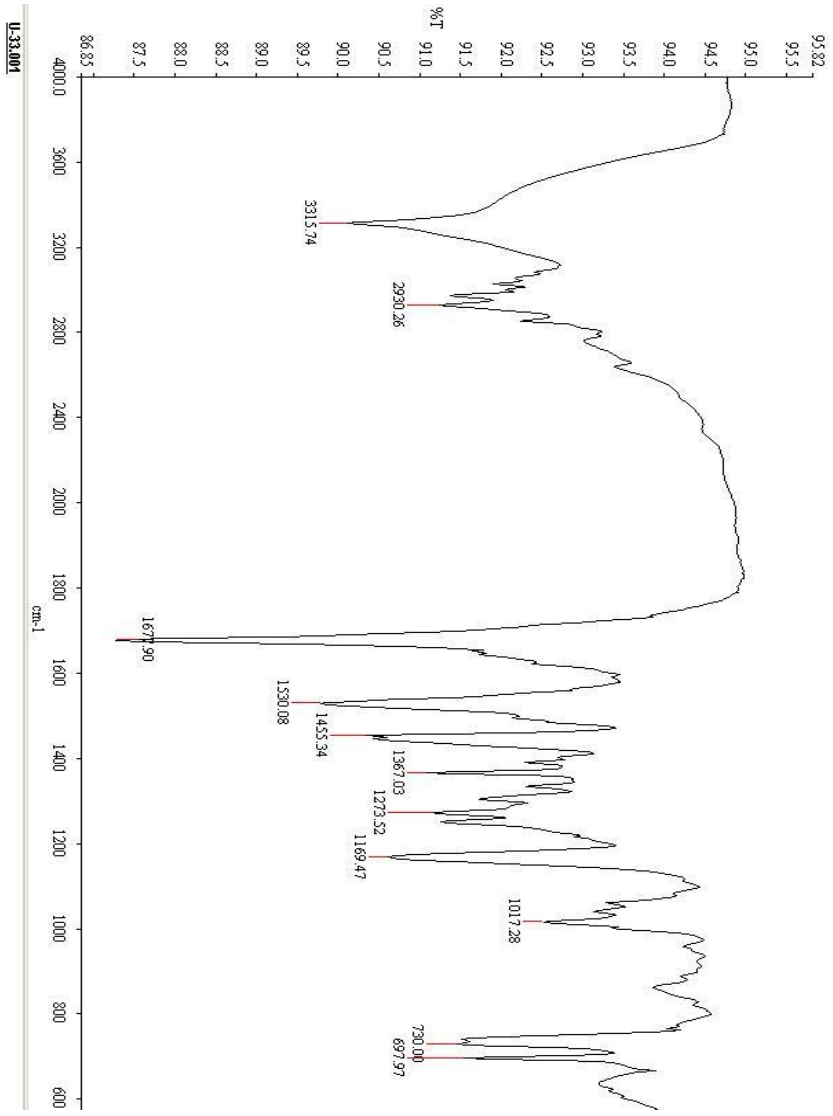
Appendix 7 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 7

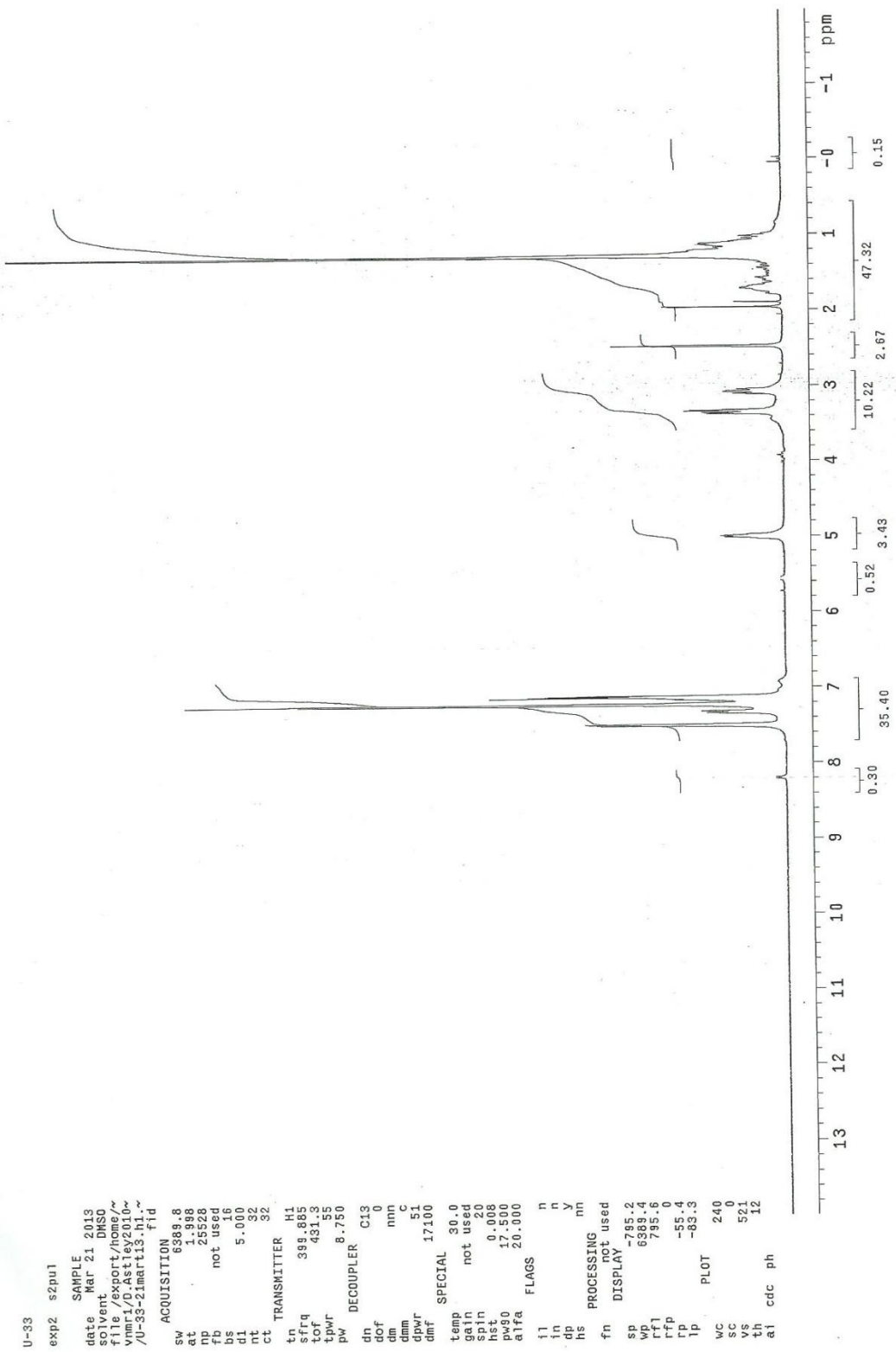


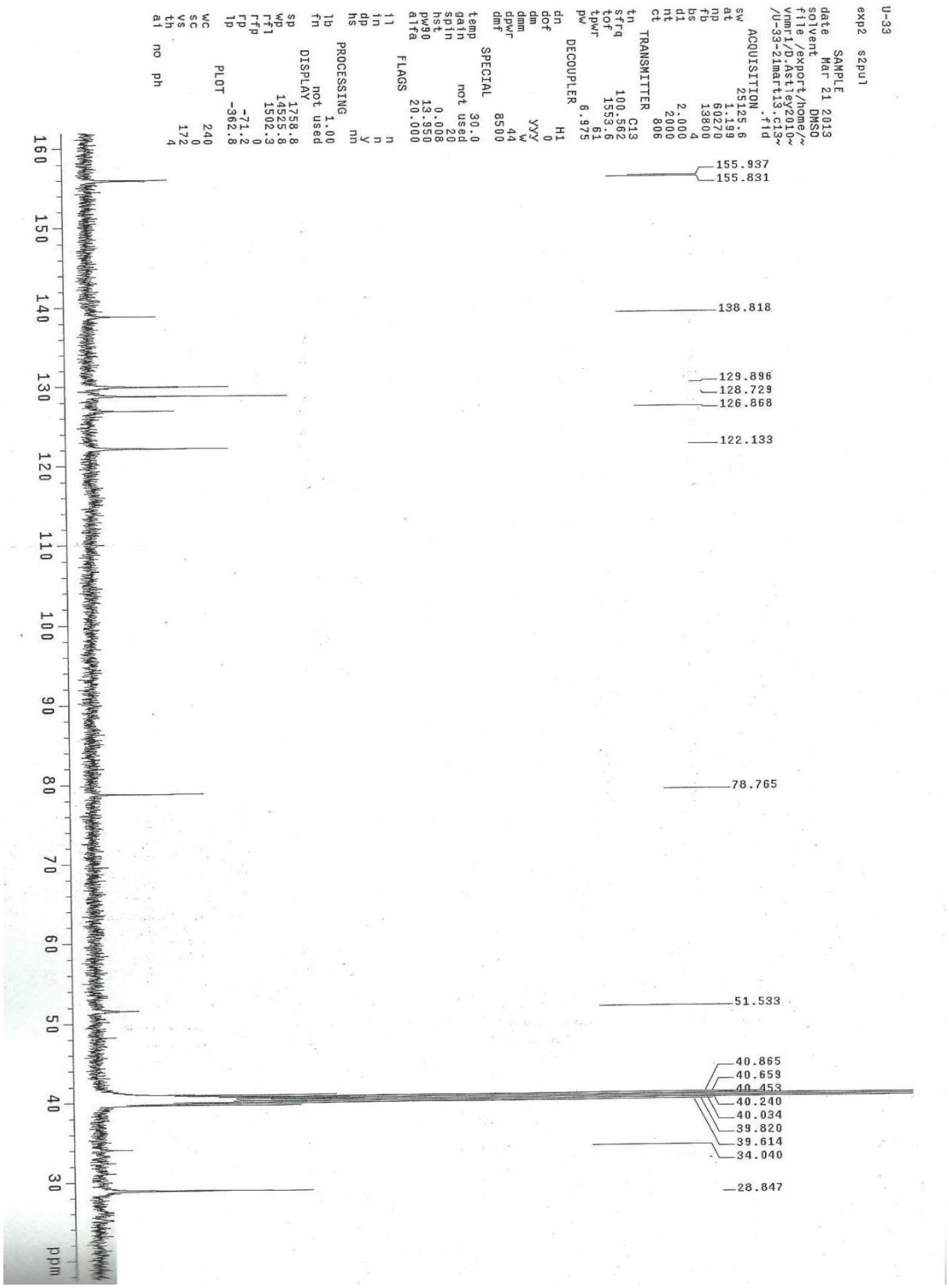

exp3 s2pul
SAMPLE
date Mar 20 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-17-20mar13.h1.~
ACQUISITION fid
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 2.000
nt 32
ct 32
TRANSMITTER
tn H1
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp 297.6
wp 4755.3
rfl 795.6
rfp 0
rp -56.0
lp -91.5
PLOT
wc 240
sc 0
vs 155
th 2
al cdc ph
12.153
7.528
7.446
7.348
7.328
7.121
7.112
4.906
4.890
3.323
2.518
2.501
2.482
2.224
2.207
2.189
2.173
2.154
2.104
2.085
2.066
2.037
1.376
1.214
3.43
20.70
4.07
3.22
9.58
19.83
39.16
12
11
10
9
8
7
6
5
4
3
2
ppm


15.380
28.885
30.501
34.139
39.622
39.828
40.041
40.247
40.453
40.667
40.872
49.177
78.894
112.006
119.181
121.675
122.438
134.875
143.691
156.052
ppm
U-17
exp3 s2pul
SAMPLE
date Mar 20 2013
solvent DMSO
file /export/home/
vnmr1/0.Astley2010
/U-17-20mar13.c13
.fid
ACQUISITION
sw 25125.6
at 1.1199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 1008
TRANSMITTER C13
tn 100.562
sfrq 1553.6
tof 61
tpwr 6.975
pw DECOUPLER H1
dn 0
dof yyy
dm w
dmm 44
dpwr 8500
dmf SPECIAL 30.0
temp not used
gain 20
spin 0.068
hst 13.950
pw90 20.000
alfa FLAGS
ll n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 1229.7
wp 15107.0
rfl 1502.3
rfp 0
rp -113.2
lp -311.3
PLOT
wc 240
sc 0
vs 163
th 3
al no ph

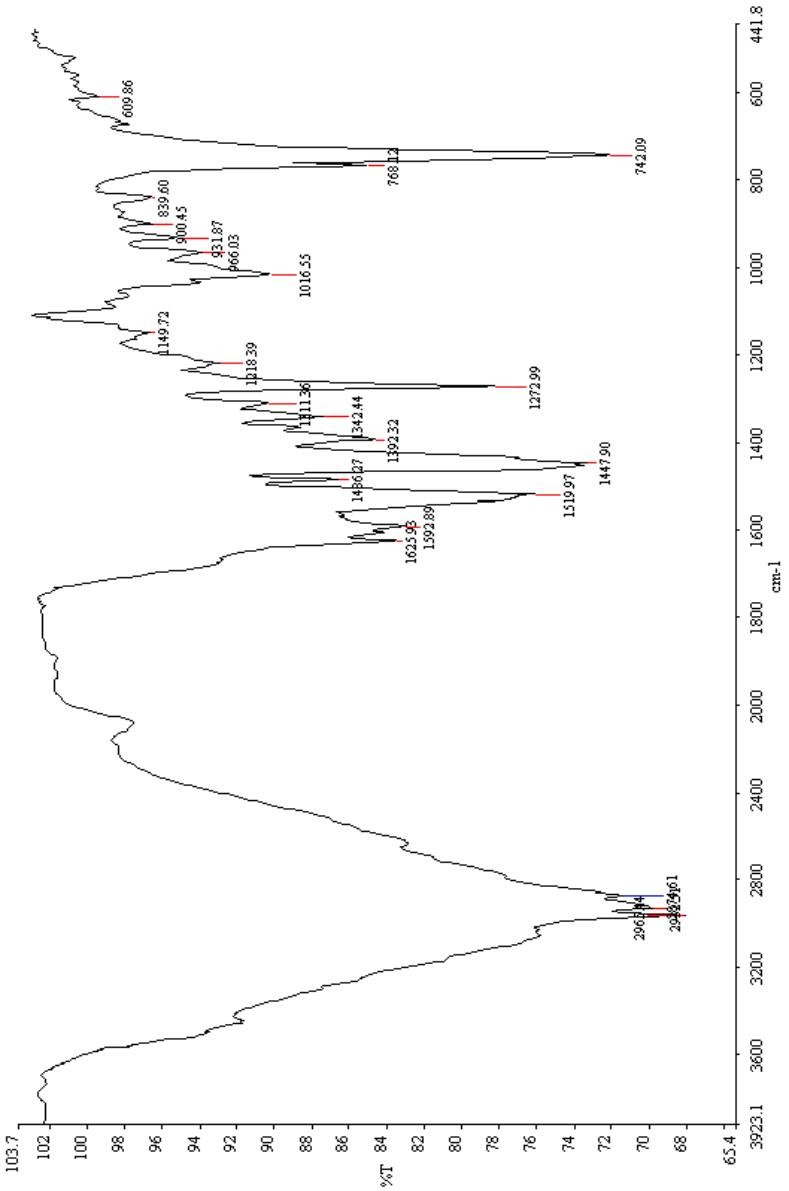
Appendix 8 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 8

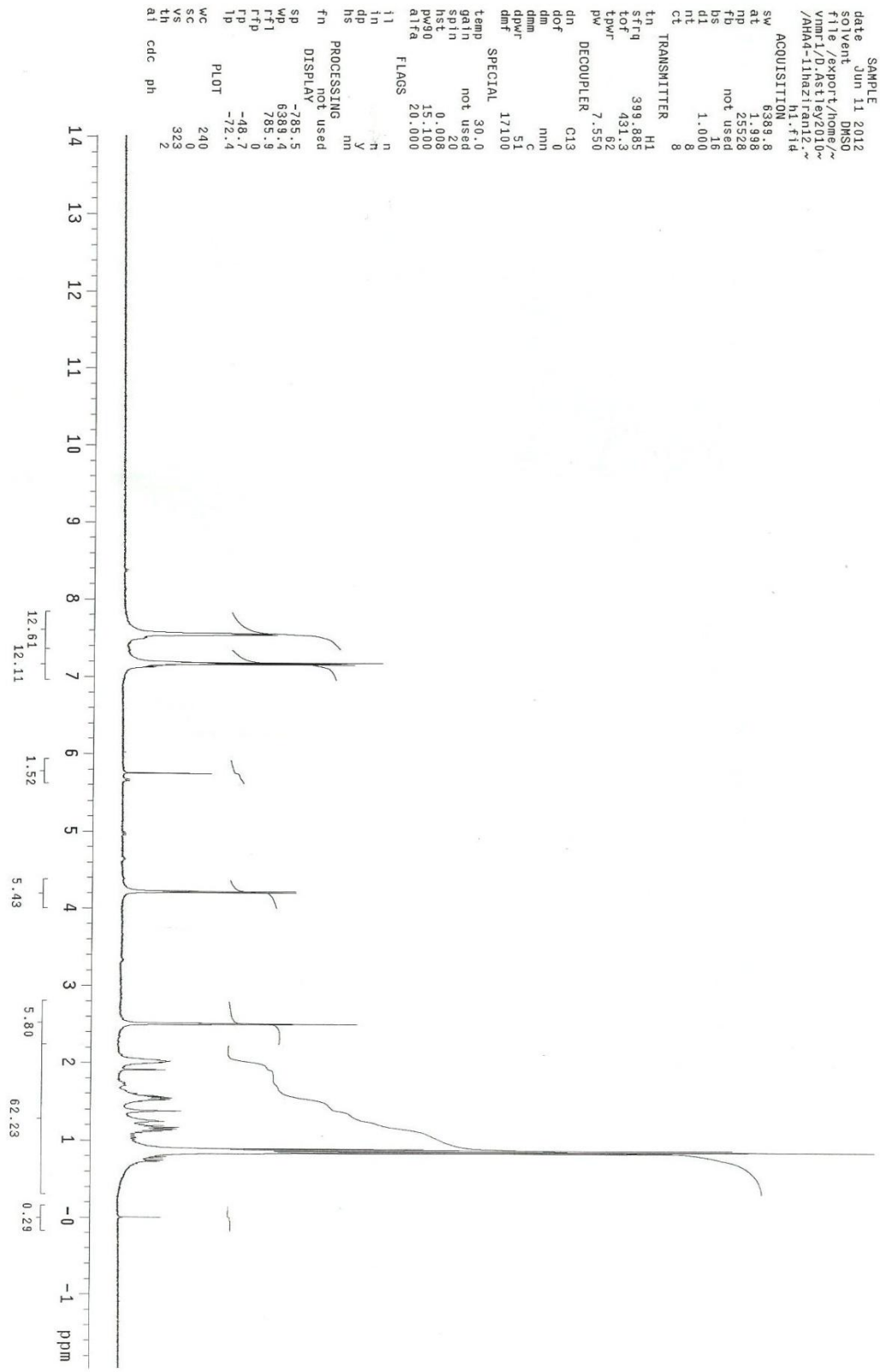


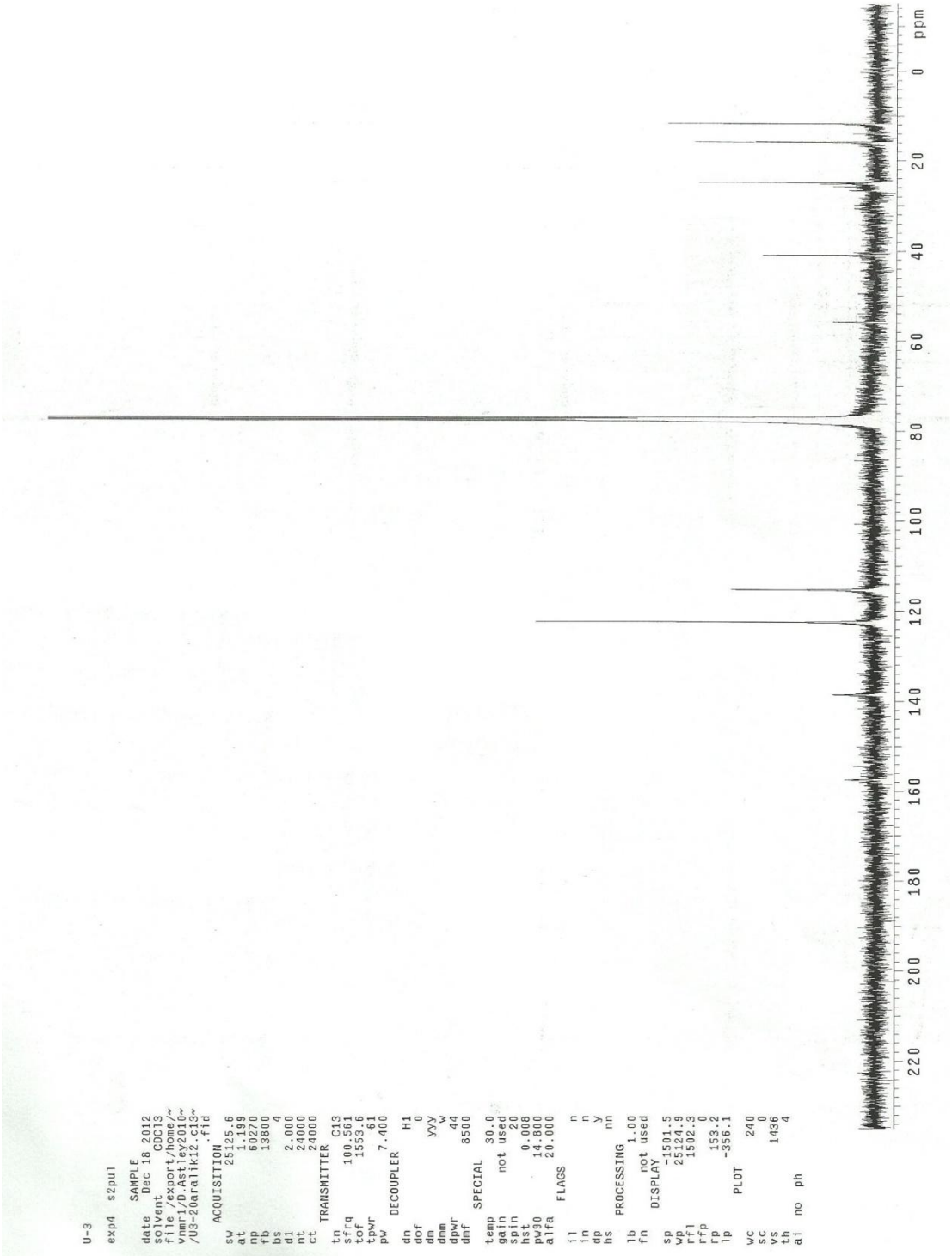

U-33
exp2 s2pul
SAMPLE
date Mar 21 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-33-21mar13.h1.~
fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 5.000
nt 32
ct 32
TRANSMITTER H1
tn
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER C13
dn 0
dof nnn
dm c
dmm 51
dpwr 17100
dmf SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -795.2
wp 6389.4
rf1 795.6
rfp 0
rp -55.4
lp -83.3
PLOT
wc 240
sc 0
vs 521
th 12
al cdc ph
ppm
0.30
35.40
0.52
3.43
10.22
2.67
47.32
0.15


U-33
exp2 s2pul
SAMPLE
date Mar 21 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-33-21mart13.c13~
ACQUISITION .fid
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 806
TRANSMITTER
tn C13
sfrq 100.562
tof 1553.6
tpwr 61
pw 6.975
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 13.950
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 1758.8
wp 14525.8
rfl 1502.3
rfp 0
rp -71.2
lp -362.8
PLOT
wc 240
sc 0
vs 172
th 4
al no ph
155.937
155.831
138.818
129.896
128.729
126.868
122.133
78.765
51.533
40.865
40.659
40.453
40.240
40.034
39.820
39.614
34.040
28.847
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

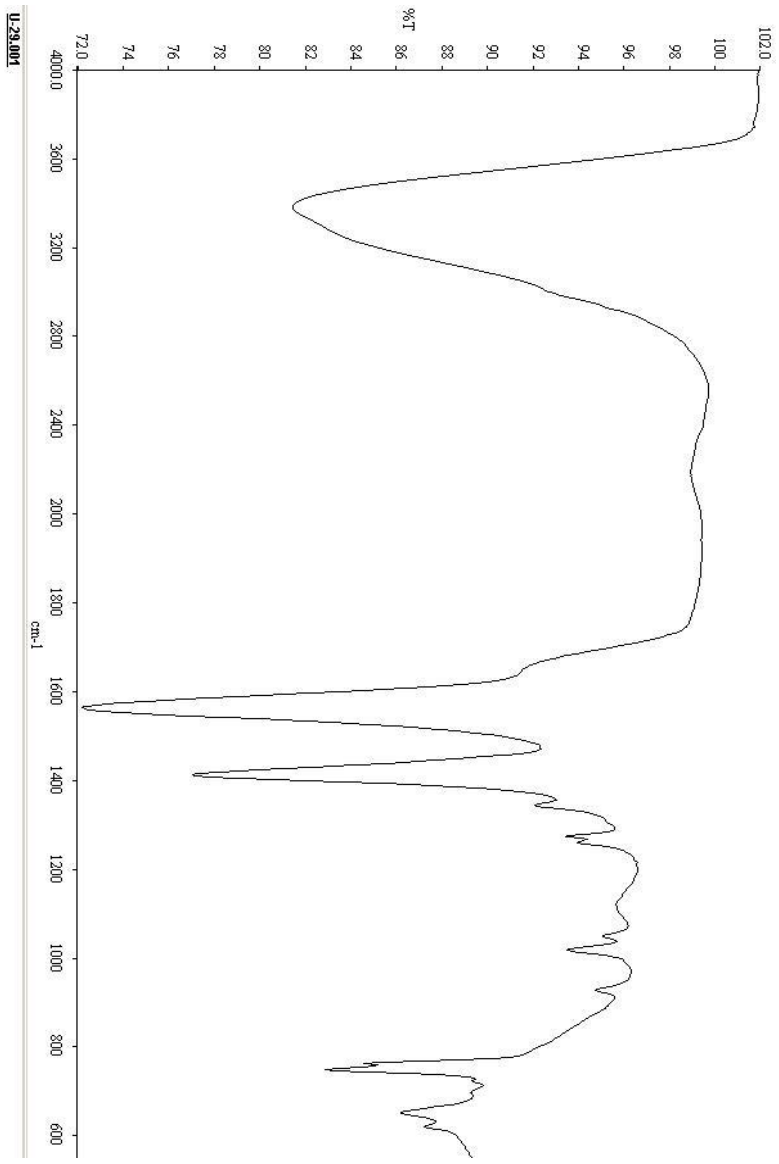
Appendix 9 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 9

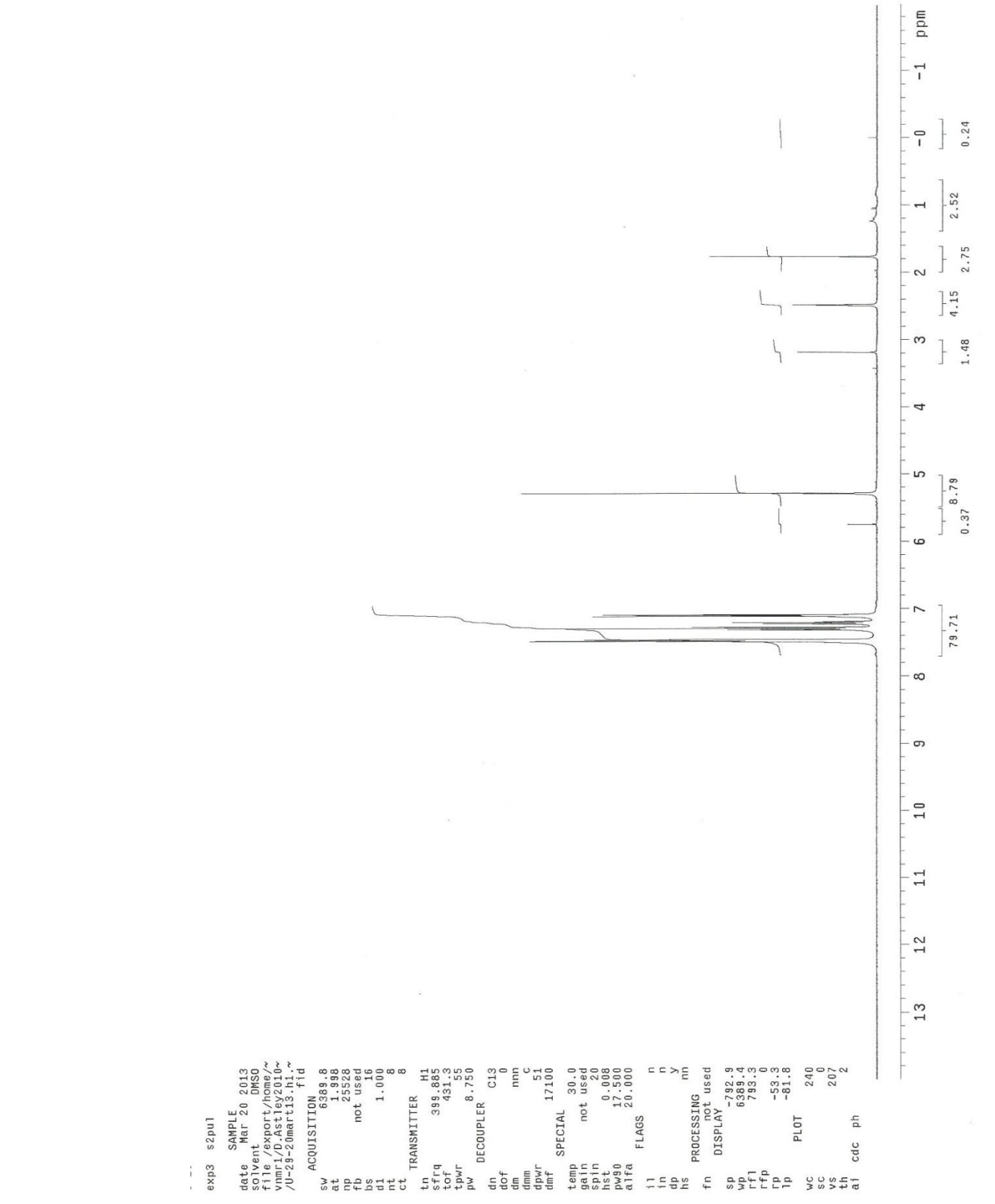


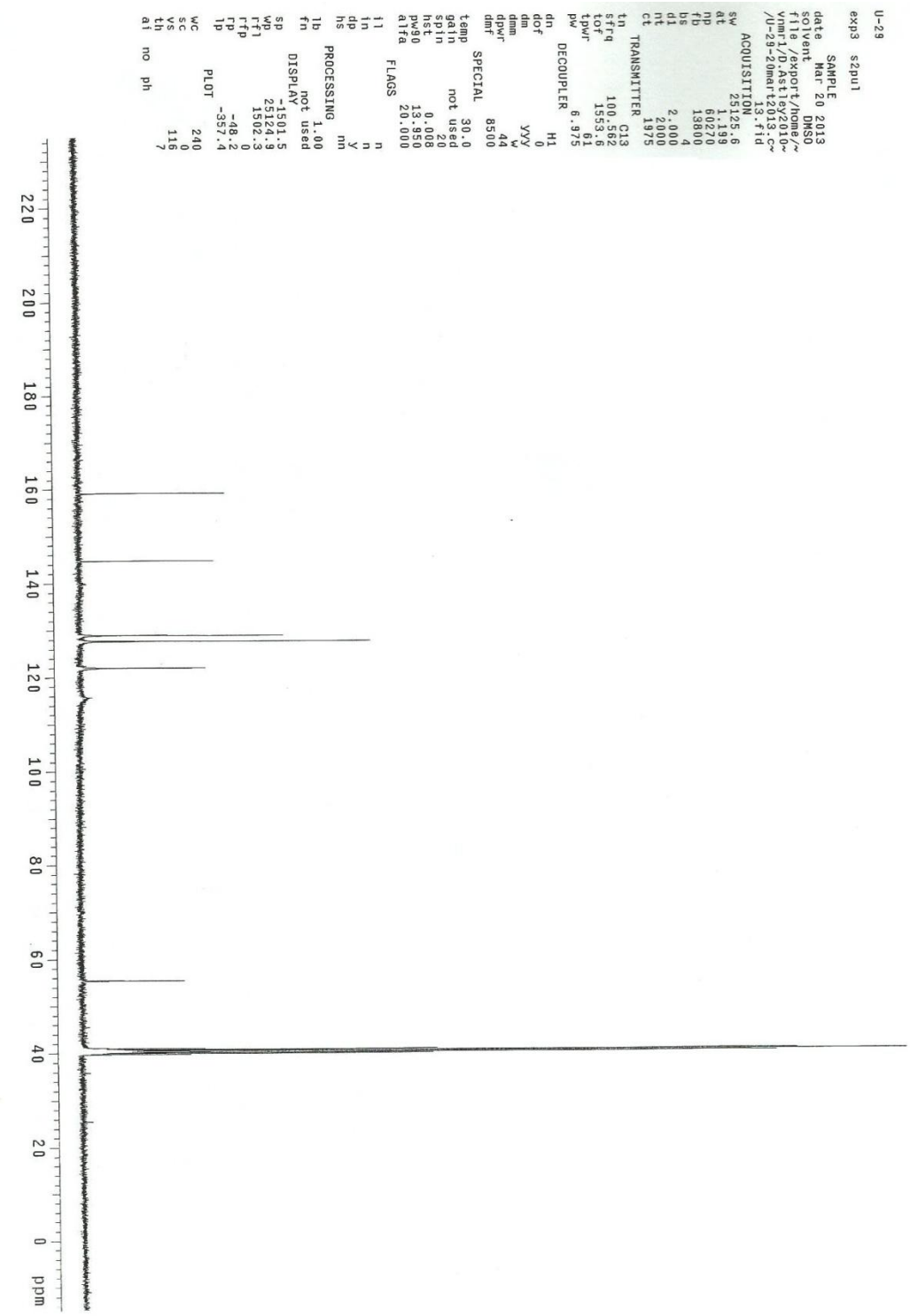

exp5 s2pul
SAMPLE
date Jun 11 2012
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/AHA4-11haziran12.~
h1.fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.885
tof 431.3
tpwr 62
pw 7.550
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 15.100
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -785.5
wp 6389.4
rfl 785.9
rfp 0
rp -48.7
lp -72.4
PLOT
wc 240
sc 0
vs 323
th 2
al cdc ph
12.61
12.11
1.52
5.43
5.80
62.23
0.29
14 13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm


U-3
exp4 s2pul
SAMPLE
date Dec 18 2012
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U3-20aral1k12.c13~
.fid
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 24000
ct 24000
TRANSMITTER C13
tn
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER H1
dn 0
dof yyy
dm y
dmm 44
dpwr 8500
dmf SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1501.5
wp 25124.9
rfl 1502.3
rfp 0
rp 153.2
lp -356.1
PLOT
wc 240
sc 0
vs 1436
th 4
ai no ph
220
200
180
160
140
120
100
80
60
40
20
0
ppm

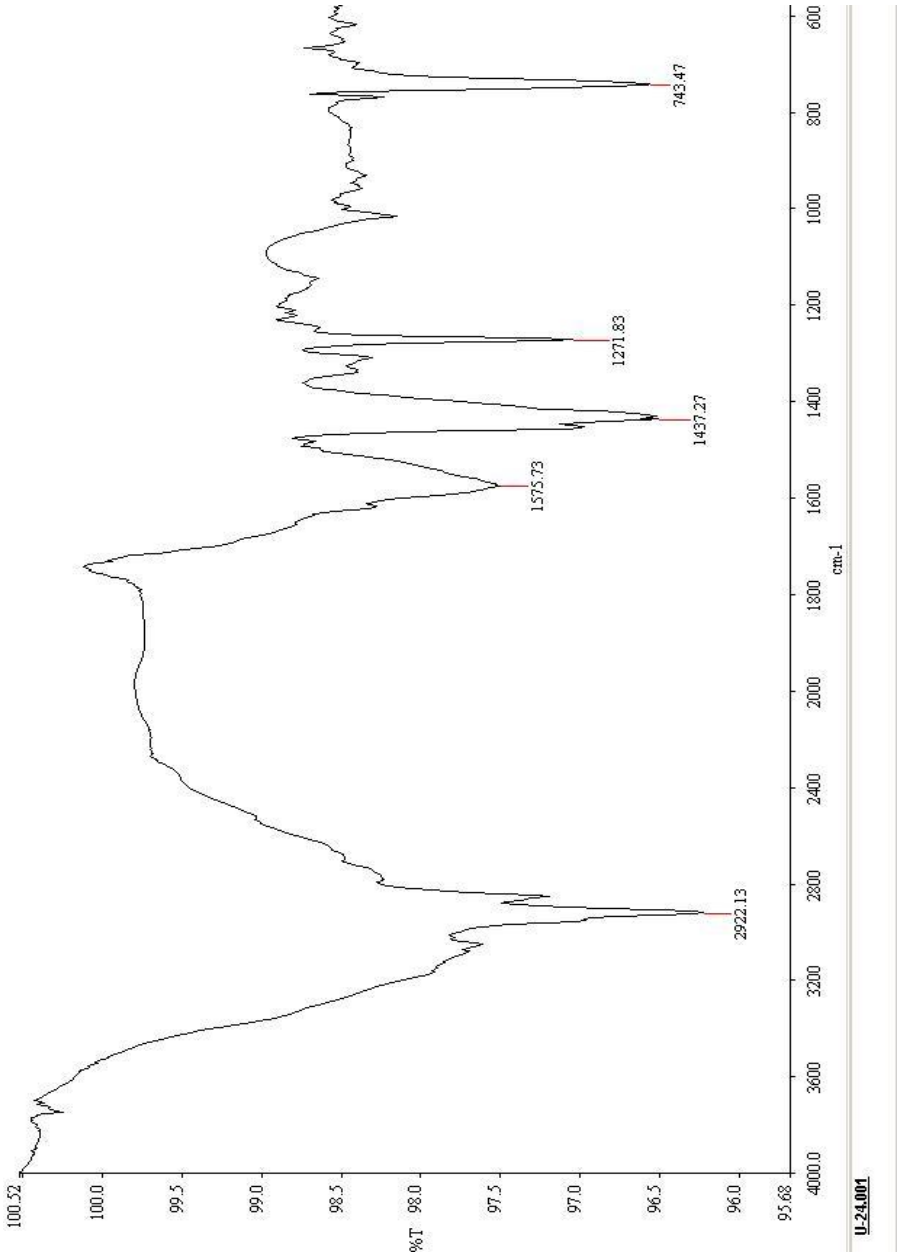
Appendix 10 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 10

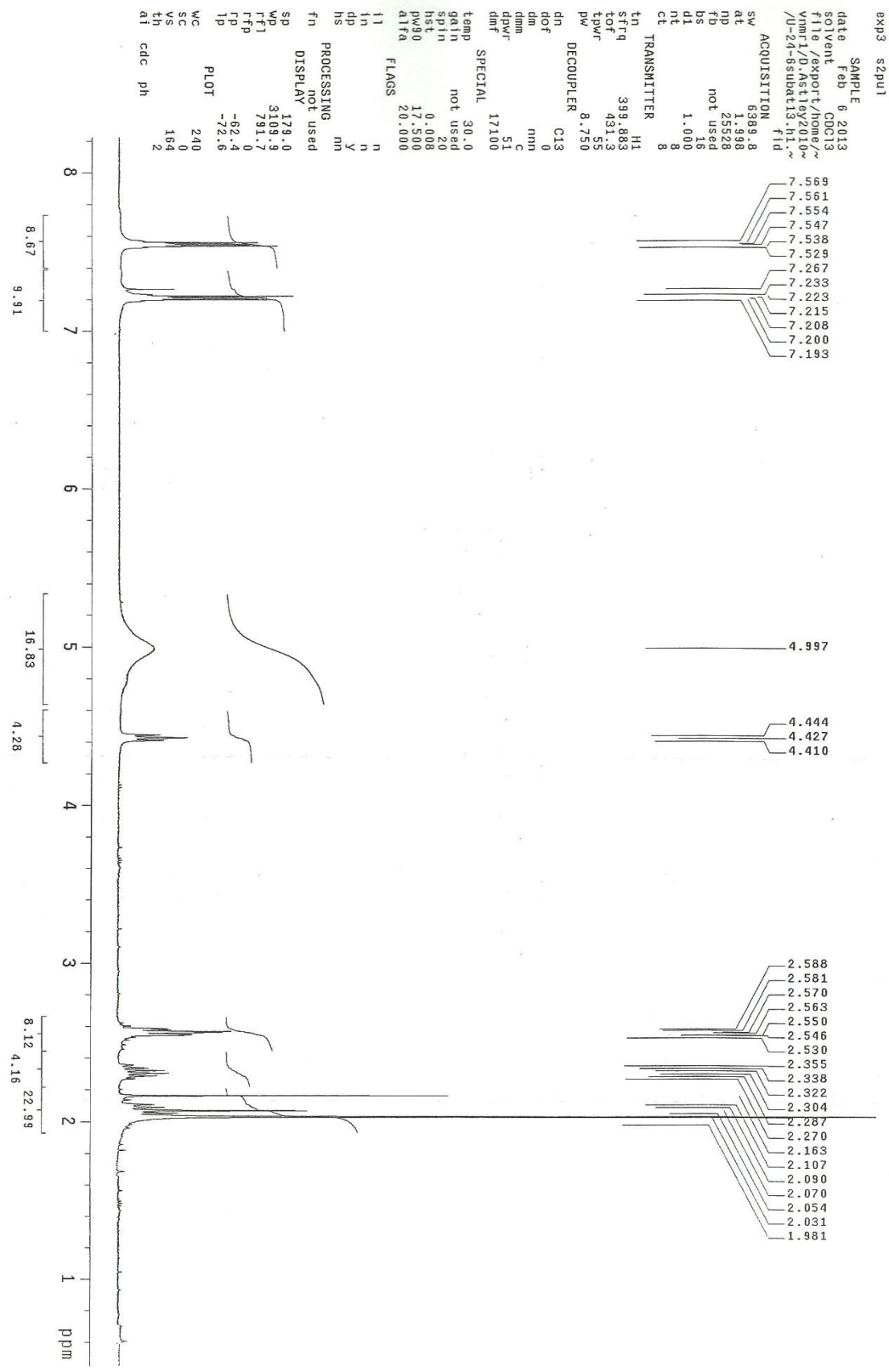


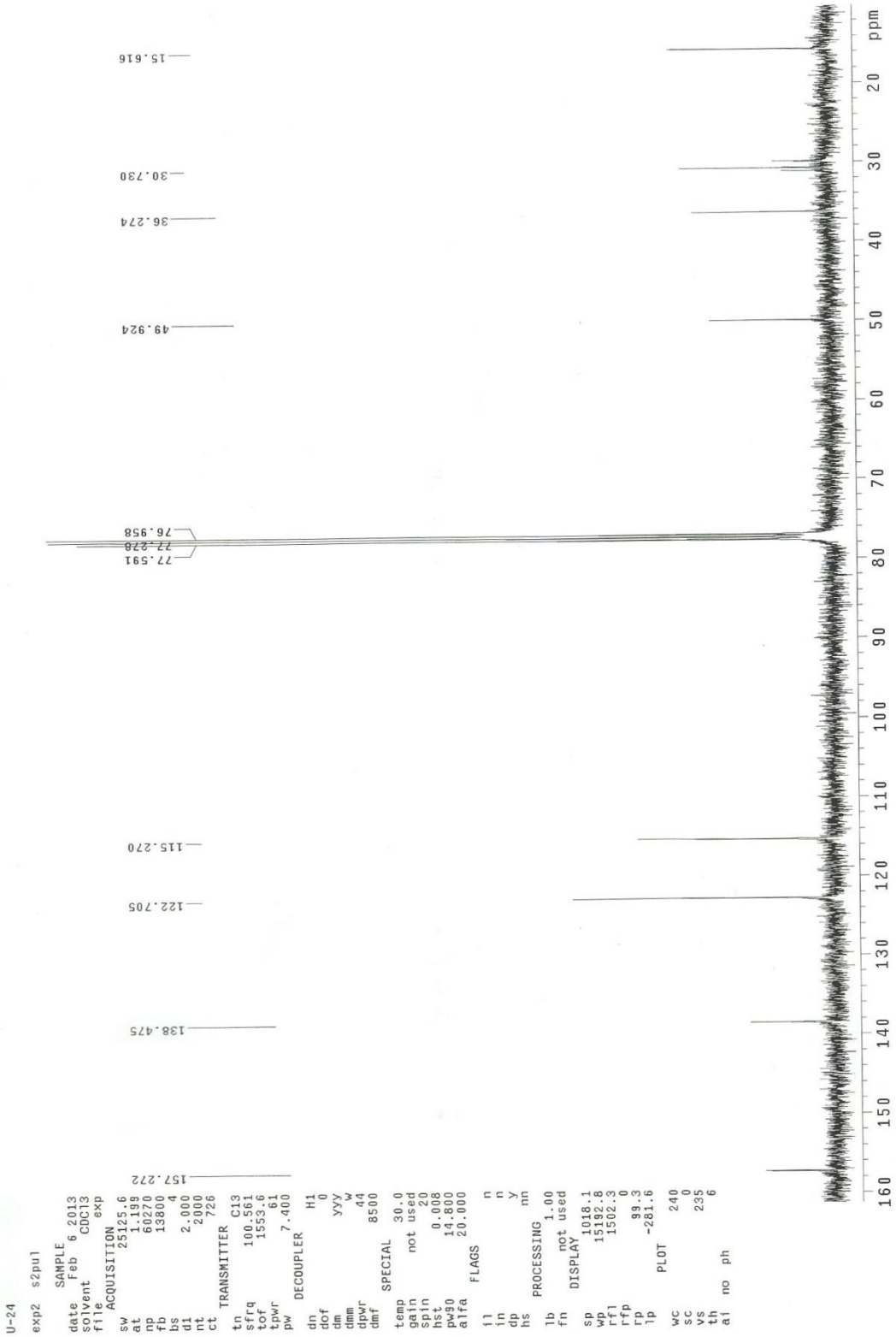

exp3 s2pul
SAMPLE
date Mar 20 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-29-20mar13.h1.~
fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -792.9
wp 6389.4
rfl 793.3
rfp 0
rp -53.3
lp -81.8
PLOT
wc 240
sc 0
vs 207
th 2
al cdc ph
79.71
8.79
0.37
1.48
4.15
2.75
2.52
0.24
ppm


U-29
exp3 s2pul
date SAMPLE
Mar 20 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-29-20mar2013.c~
13.fid
ACQUISITION
sw 29125.6
at 1.199
np 69270
fb 13800
bs 4
d1 2.000
nt 2000
ct 1975
TRANSMITTER
tn C13
sfrq 100.562
tof 1553.6
tpwr 61
pw 6.975
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 13.950
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1501.5
wp 25124.9
rfl 1502.3
rfp 0
rp -48.2
lp -357.4
PLOT
wc 240
sc 0
vs 116
th 7
ai no ph
220
200
180
160
140
120
100
80
60
40
20
0
ppm

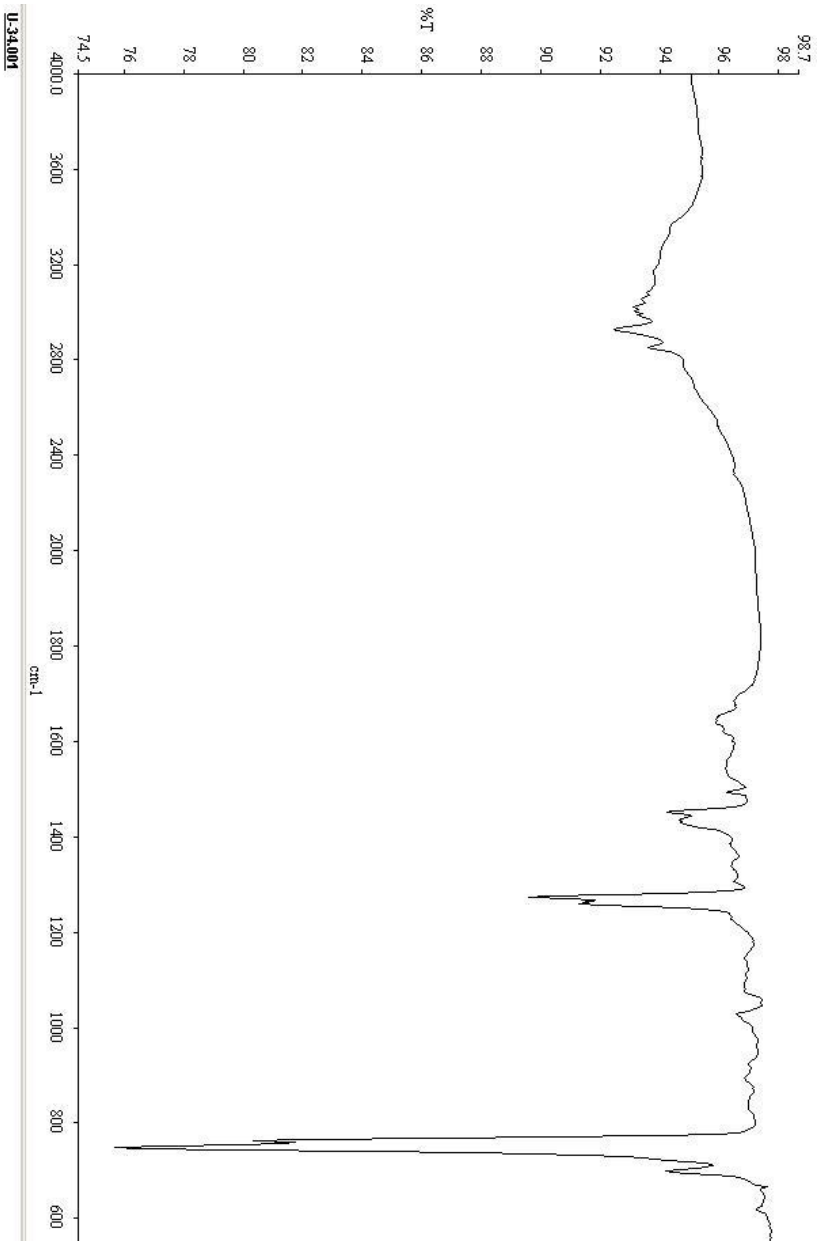
Appendix 11 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 11

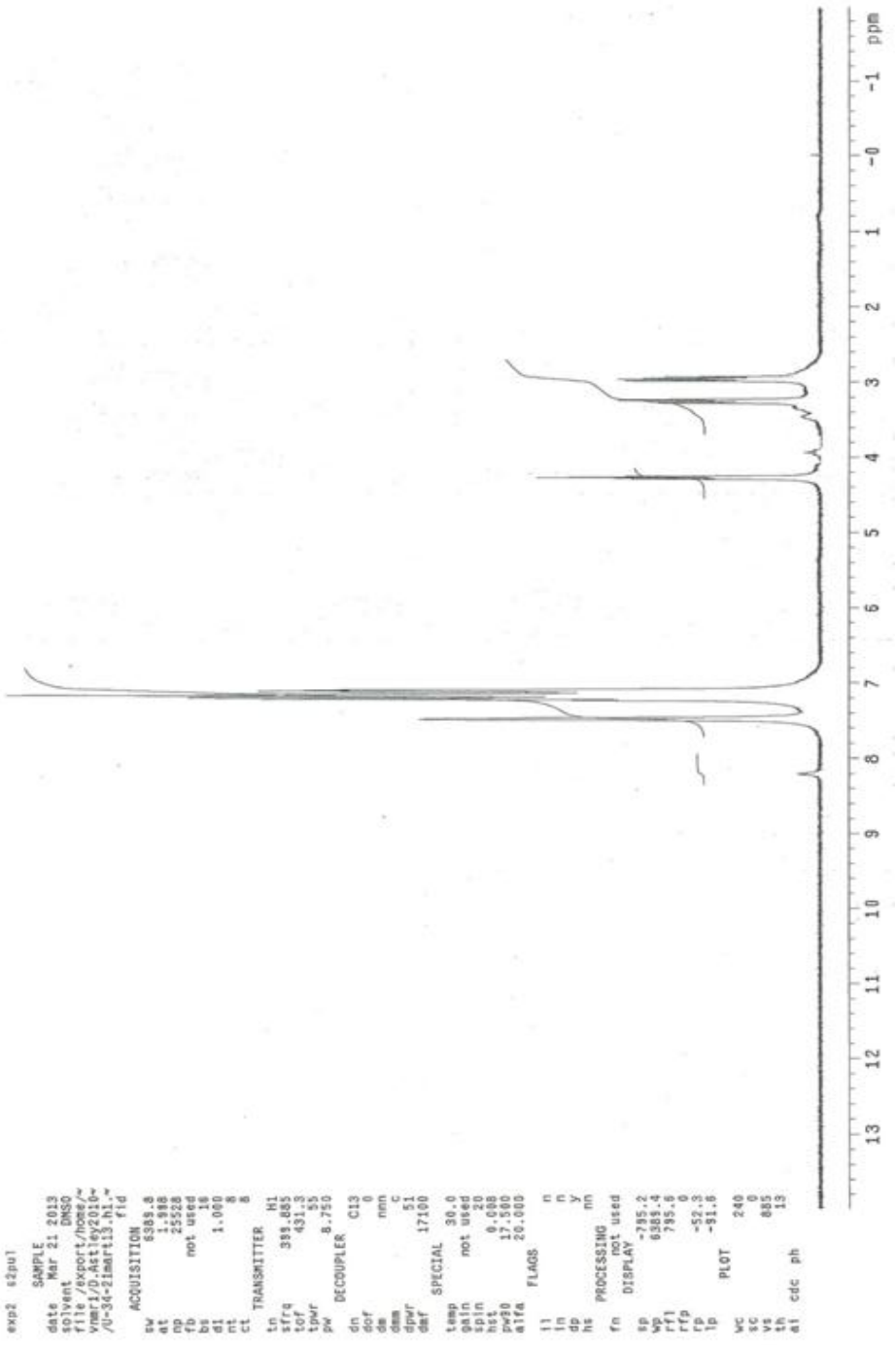


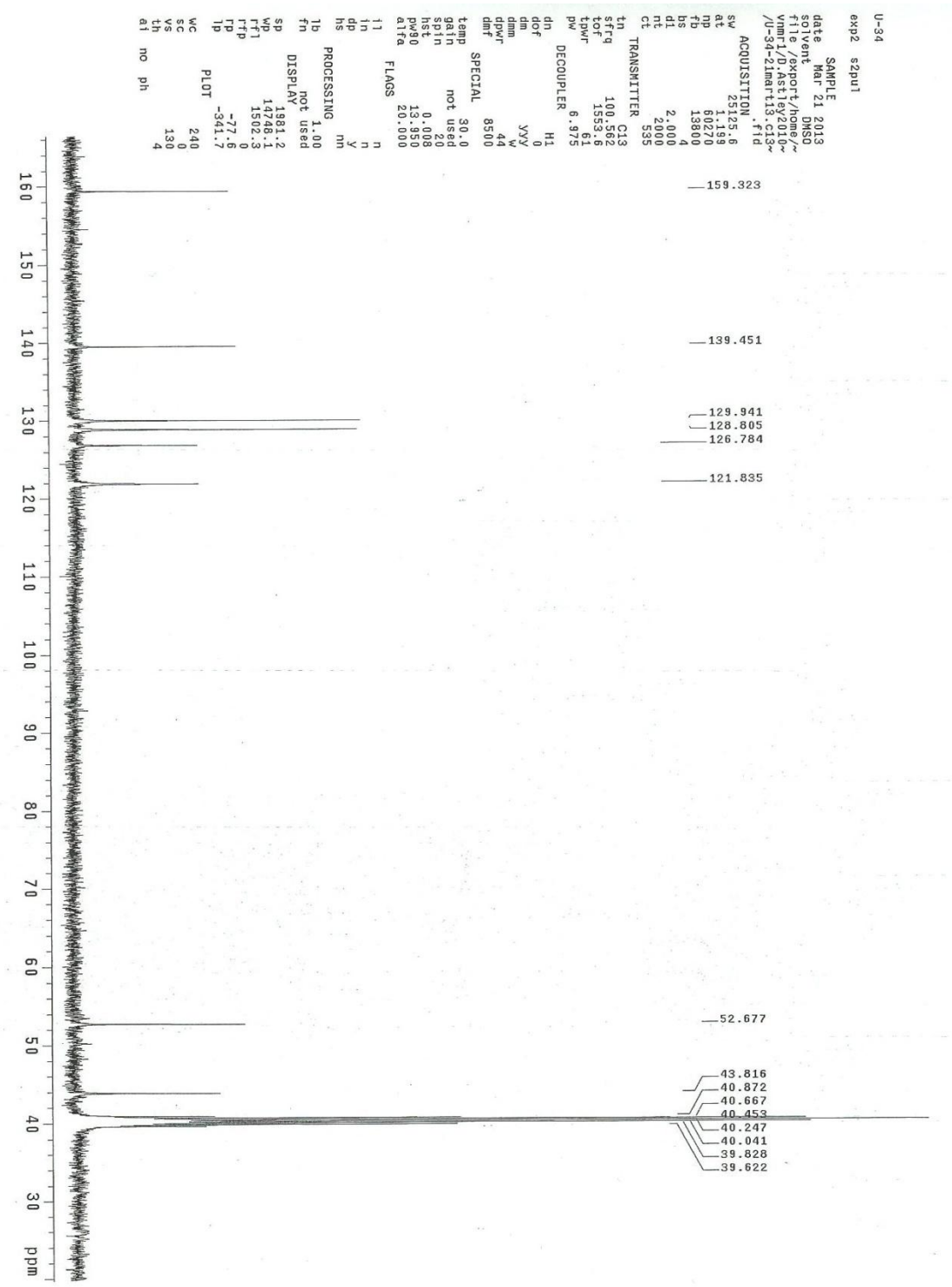

exp3 s2pul
SAMPLE
date Feb 6 2013
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U-24-6subat13.h1.~ fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.883
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp 179.0
wp 3109.9
rfl 791.7
rfp 0
rp -62.4
lp -72.6
PLOT
wc 240
sc 0
vs 164
th 2
ai cdc ph
7.569
7.561
7.554
7.547
7.538
7.529
7.267
7.233
7.223
7.215
7.208
7.200
7.193
4.997
4.444
4.427
4.410
2.588
2.581
2.570
2.563
2.550
2.546
2.530
2.355
2.338
2.322
2.304
2.287
2.270
2.163
2.107
2.090
2.070
2.054
2.031
1.981
8.67
9.91
16.83
4.28
8.12
4.16
22.99
ppm


15.616
30.730
36.274
49.924
76.958
77.278
77.591
115.270
122.705
138.475
157.272
ppm
U-24
exp2 s2pul
SAMPLE
date Feb 6 2013
solvent CDCl3
file exp
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 726
TRANSMITTER
tn C13
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
fl n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 1018.1
wp 15192.8
rfl 1502.3
rfp 0
rp 99.3
lp -281.6
PLOT
wc 240
sc 0
vs 235
th 6
al no ph

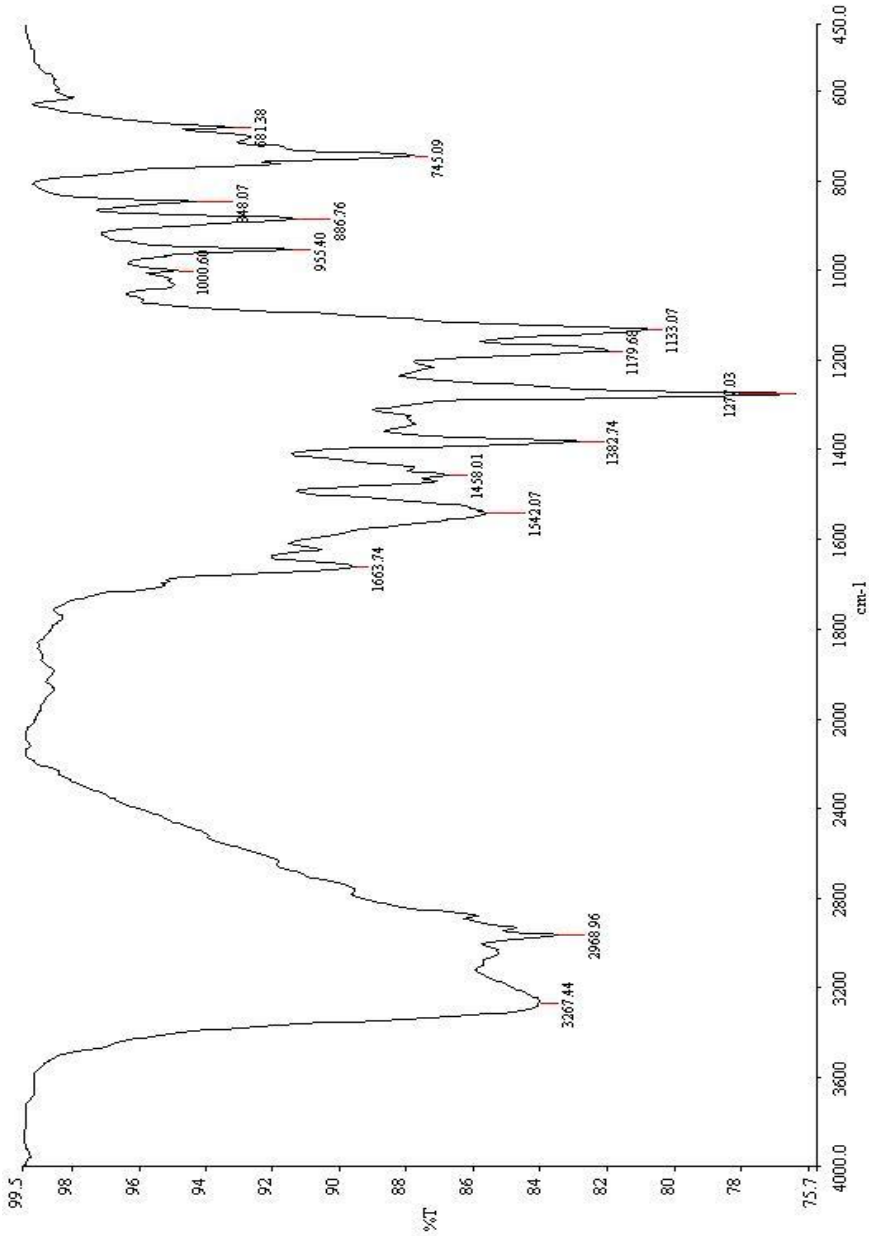
Appendix 12 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 12

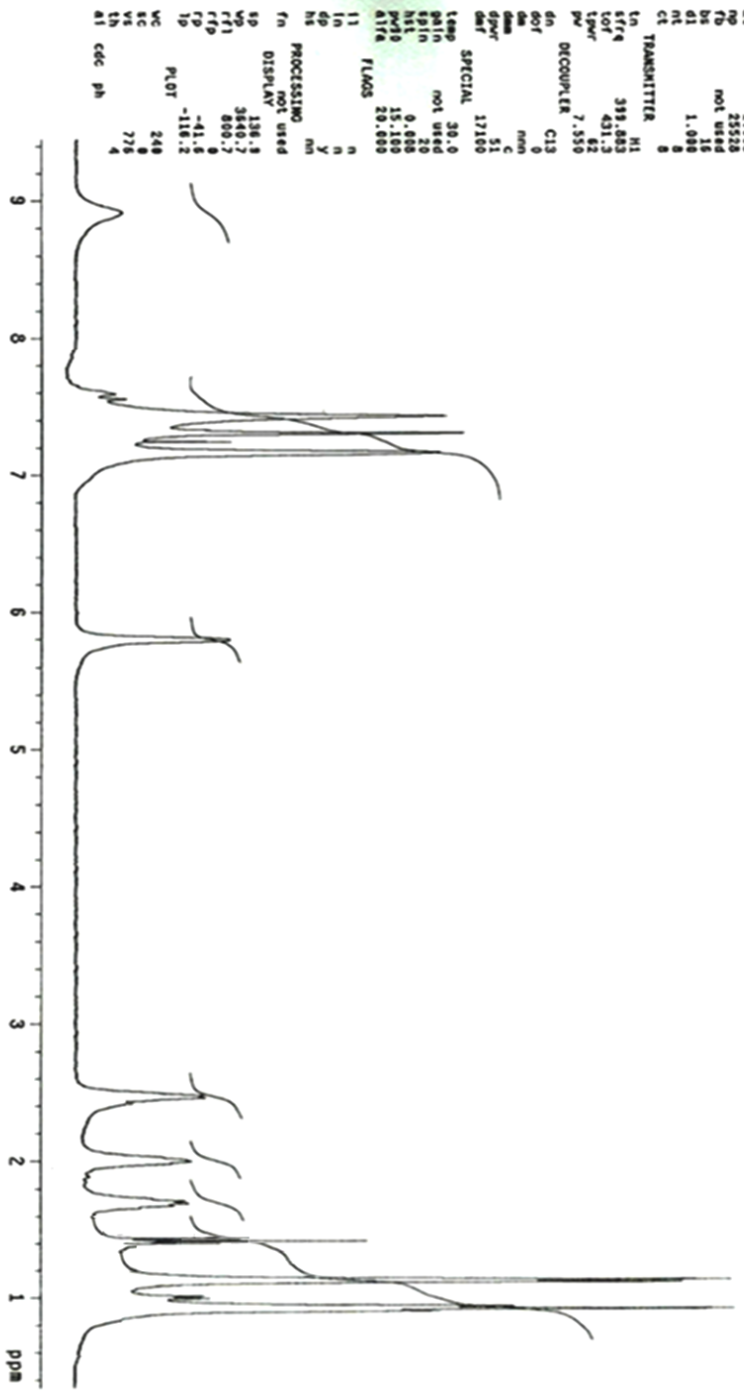


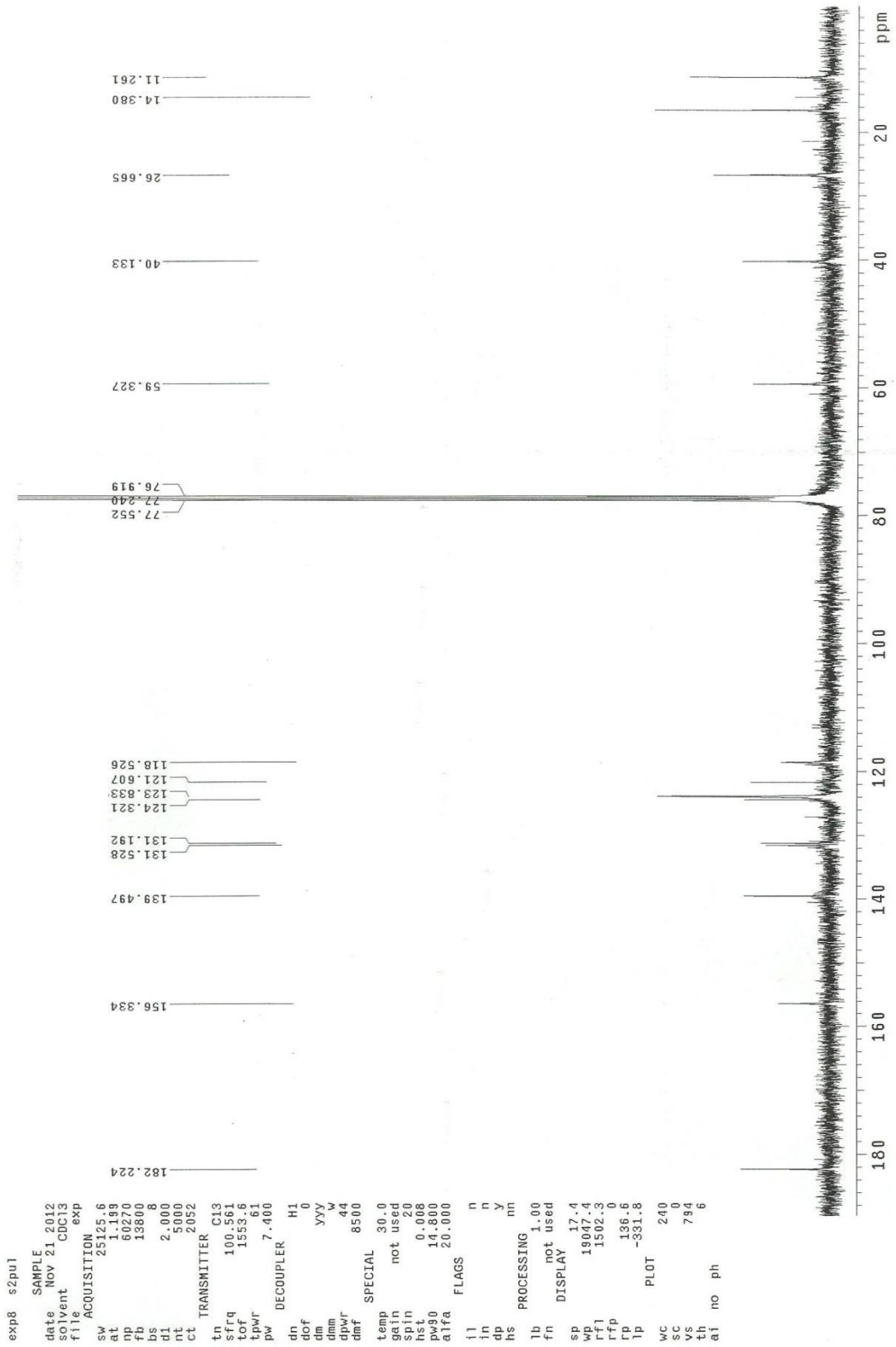

exp2 s2pul
SAMPLE
date Mar 21 2013
solvent DMSO
file /export/home/~
vnmrj/D.Astley2010~
/U-34-2imar13_h1.~
fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 18
d1 1.000
nt 8
ct 8
TRANSMITTER
tn H1
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dmf 51
dpwr 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pad 17.500
d1 20.000
alfa
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -295.2
wp 6389.4
rfl 795.6
rfp 0
lp -52.3
lp -91.6
PLOT
wc 240
sc 0
vs 855
th 13
al cdc ph
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm


U-34
exp2 s2pul
SAMPLE
date Mar 21 2013
solvent DMSO
file /export/home/~
vnmrj/D.Astley2010~
/U-34-21mart13.c13~
ACQUISITION .fid
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 535
TRANSMITTER
tn C13
sfrq 100.562
tof 1553.6
tpwr 61
pw 6.975
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 13.950
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 1981.2
wp 14748.1
rfl 1502.3
rfp 0
rp -77.6
lp -341.7
PLOT
wc 240
sc 0
vs 130
th 4
al no ph
159.323
139.451
129.941
128.805
126.784
121.835
52.677
43.816
40.872
40.667
40.453
40.247
40.041
39.828
39.622
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

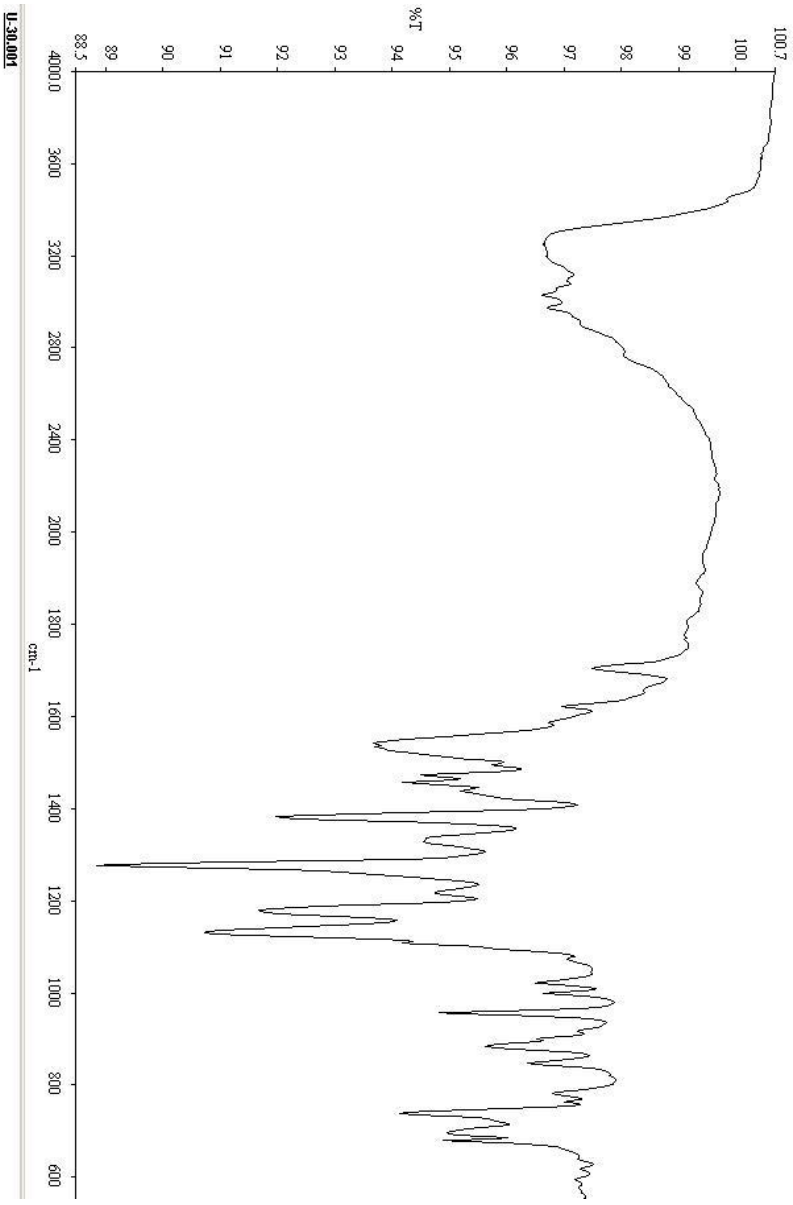
Appendix 13 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 13

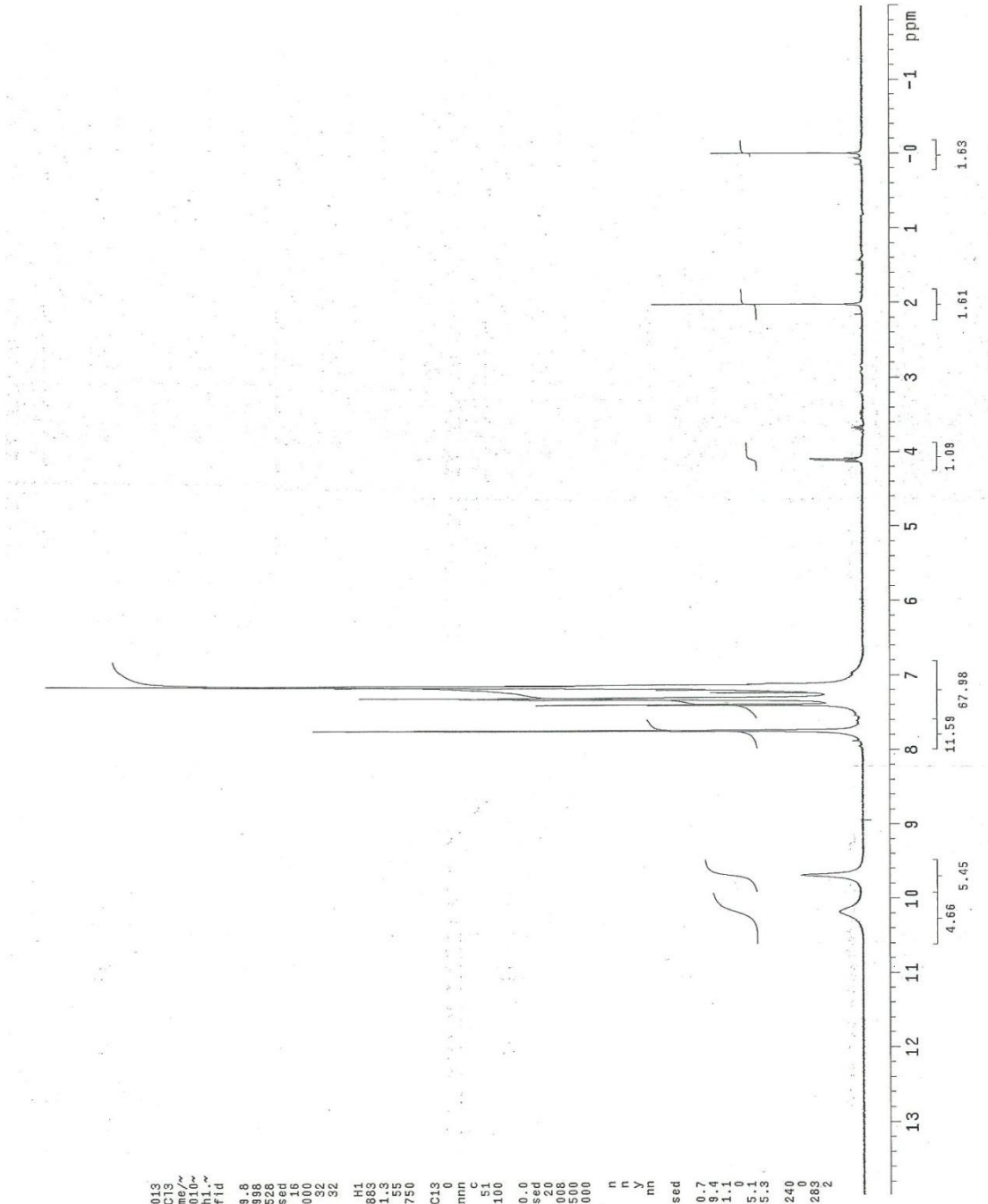


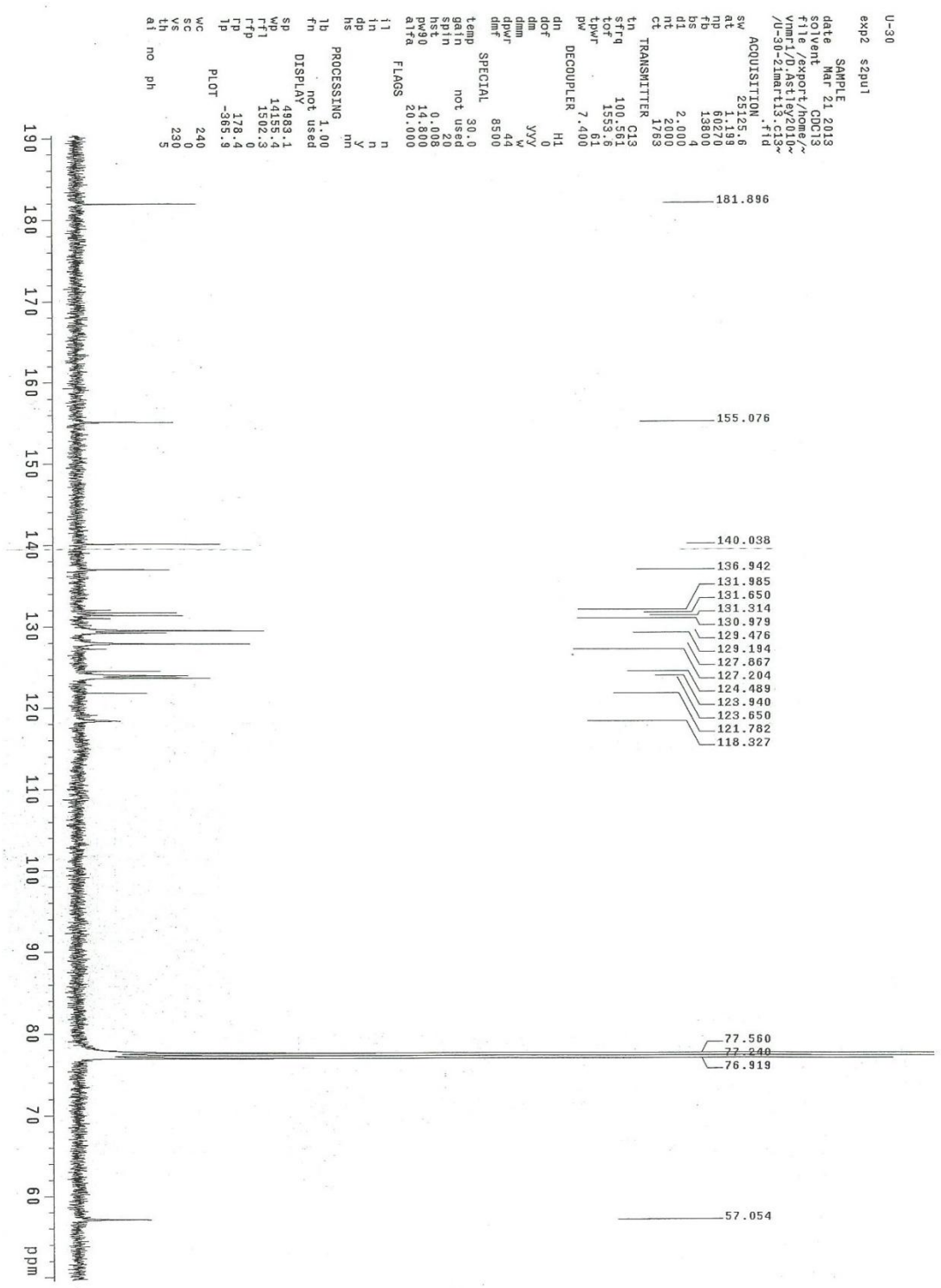

SAMPLE
date Nov 21 2012
solvent CDCl3
file /export1/home/~
ymmr1/0.Ashley2010~
/U4-21mastm21.fid/~
fid
ACQUISITION
sw 6381.6
at 1.598
np 25528
fb not used
bs 16
ss 1
d1 1.000
d2 0
ct 8
TRANSMITTER
tn H1
sfrq 399.883
tof 451.3
tpwr 61
pw 7.550
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dmf 51
dpwr 17160
SPECIAL
temp 30.0
gain not used
spin 0
hst 0.088
pad 15.189
aqt 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp 136.1
wp 3440.7
rfl 880.7
rfp 0
rp -41.8
lp -118.2
PLOT
wc 240
sc 0
vs 778
th 4
al ccc ph
9
8
7
6
5
4
3
2
1
ppm


11.261
14.380
26.665
40.133
59.327
76.919
77.240
77.552
118.526
121.607
123.833
124.321
131.192
131.528
139.497
156.334
182.224
ppm
20
40
60
80
100
120
140
160
180
exp8 s2pul
SAMPLE
date Nov 21 2012
solvent CDCl3
file exp
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 8
d1 2.000
nt 5000
ct 2052
TRANSMITTER
tn C13
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 17.4
wp 19047.4
rfl 1502.3
rfp 0
rp 136.6
lp -331.8
PLOT
wc 240
sc 0
vs 784
th 6
al no ph

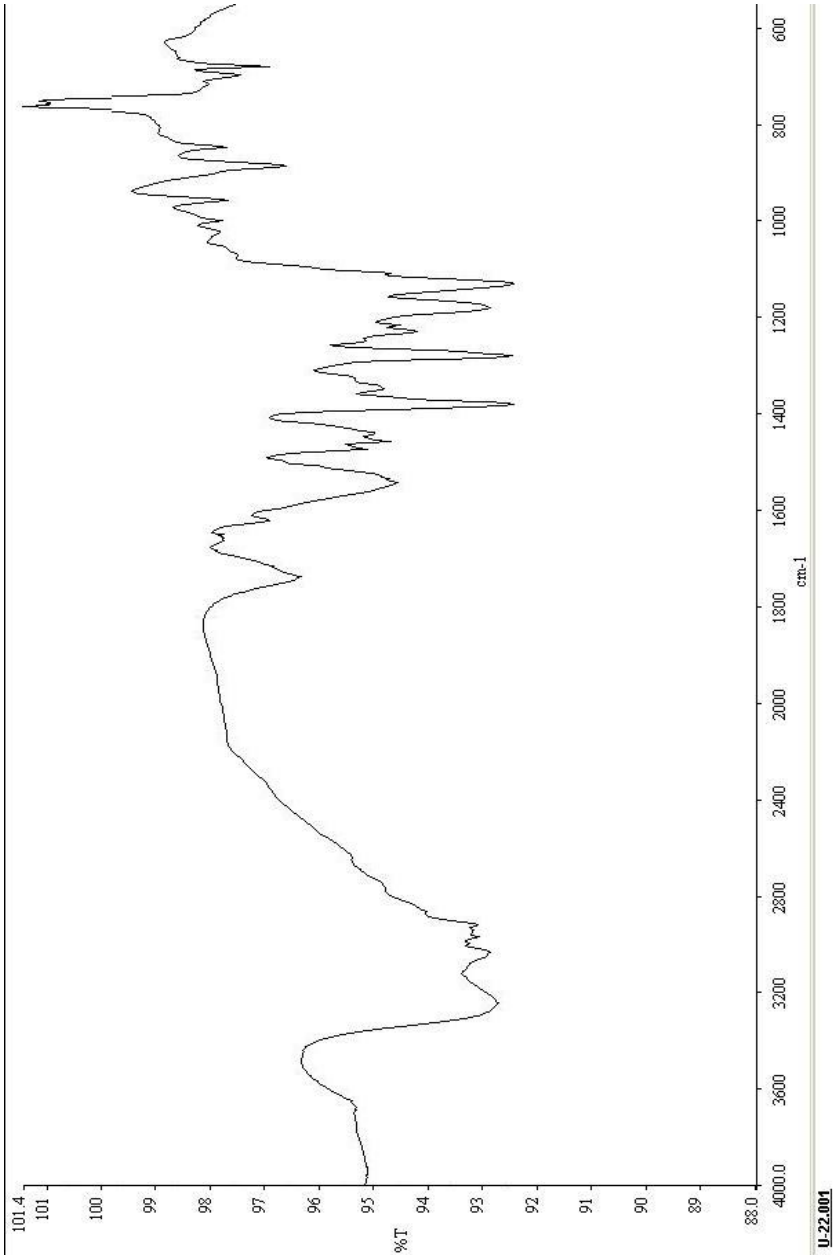
Appendix 14 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 14

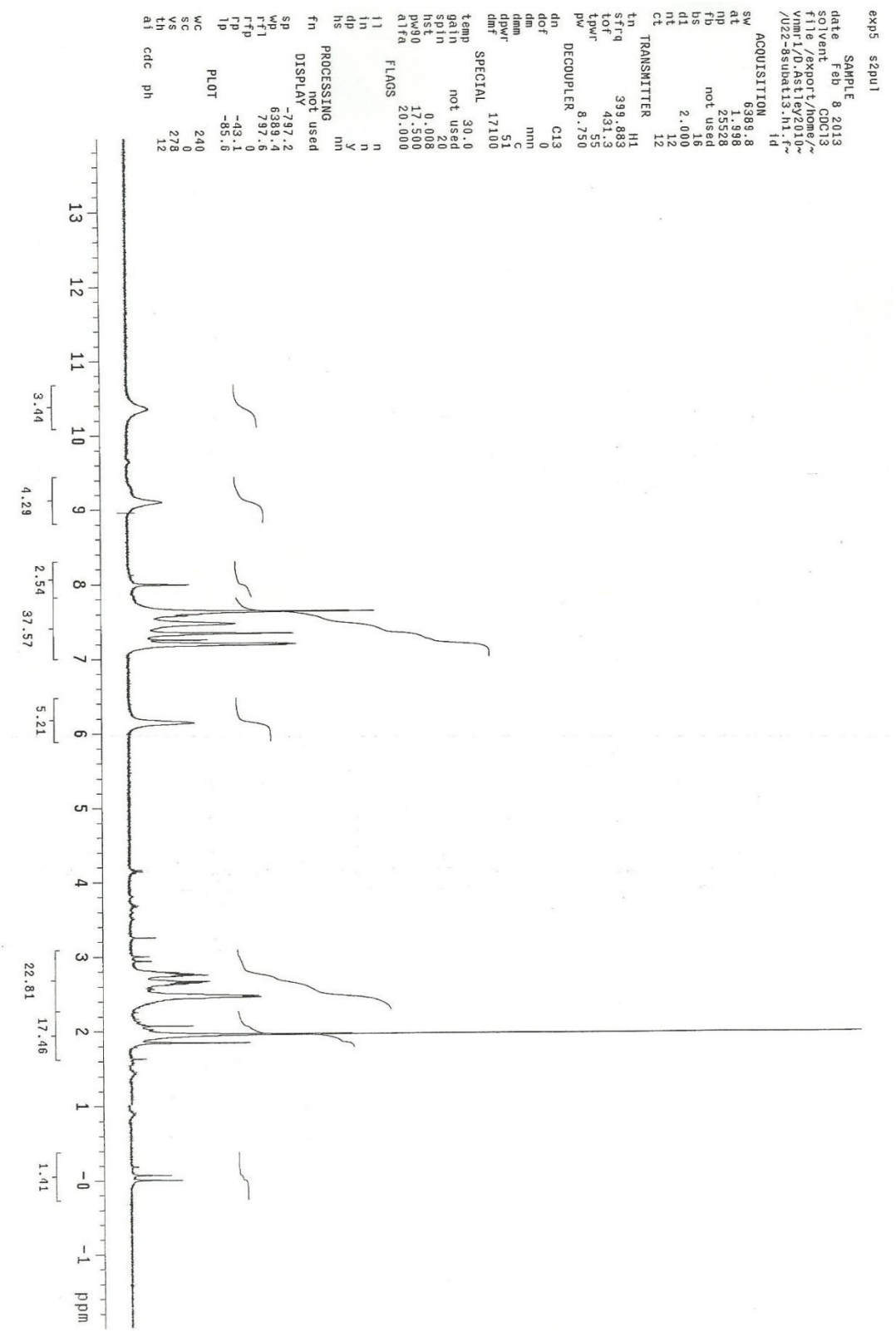


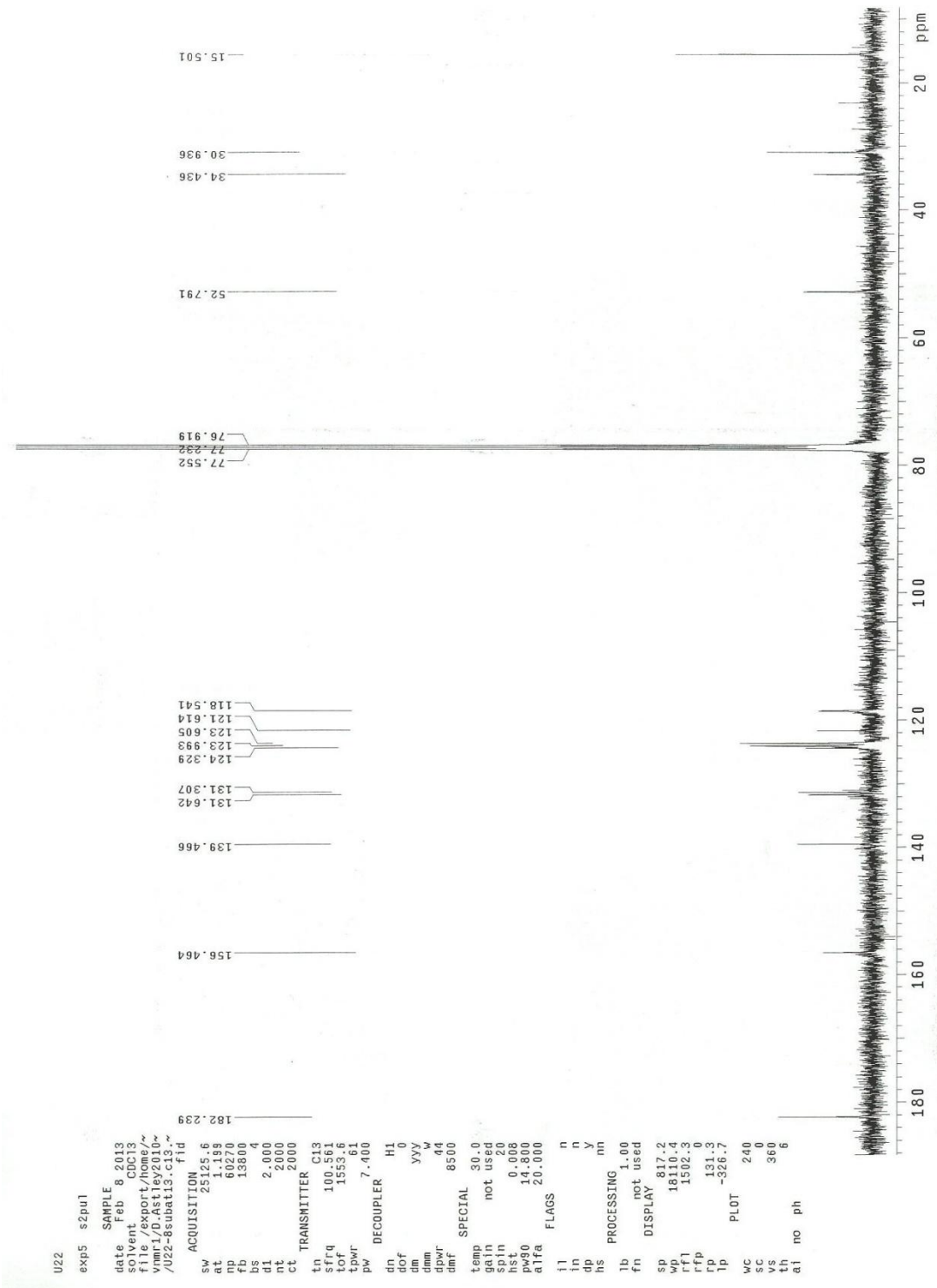

U-30
exp2 s2pul
SAMPLE
date Mar 21 2013
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U-30-21mart3.h1.~
fid
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 5.000
nt 32
ct 32
TRANSMITTER
tn H1
sfrq 399.883
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -800.7
wp 6389.4
rf1 801.1
rfp 0
rp -55.1
lp -85.3
PLOT
wc 240
sc 0
vs 283
th 2
al cdc ph
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm
4.66 5.45
11.59 67.88
1.09 1.61 1.63


U-30
exp2 s2pul
SAMPLE
date Mar 21 2013
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U-30-21mar13-c13~
ACQUISITION .fid
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct 1763
TRANSMITTER
tn C13
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 4983.1
wp 14155.4
rfl 1502.3
rfp 0
rp 178.4
lp -965.9
PLOT
wc 240
sc 0
vs 230
th 5
ai no ph
181.896
155.076
140.038
136.942
131.985
131.650
131.314
130.979
129.476
129.194
127.867
127.204
124.489
123.940
123.650
121.782
118.327
77.560
77.240
76.919
57.054
190
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

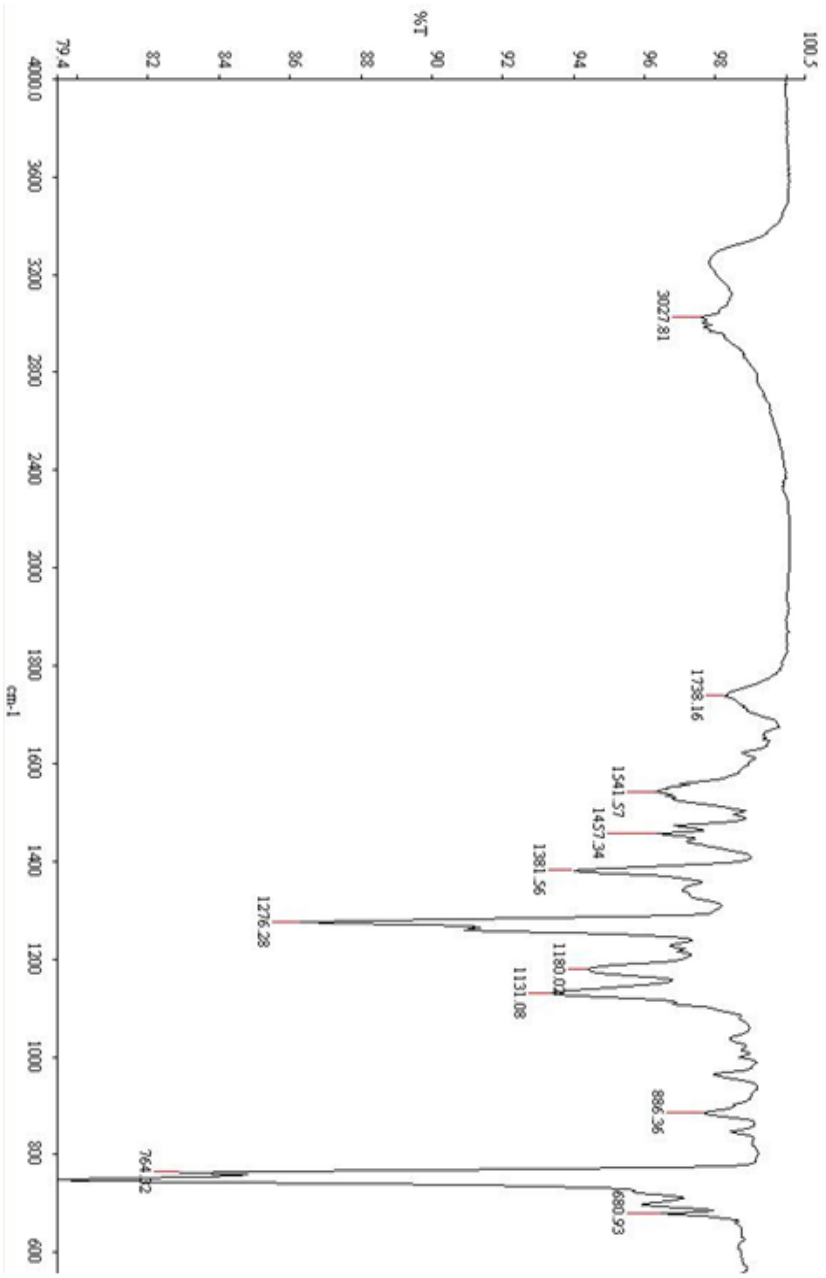
Appendix 15 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 15

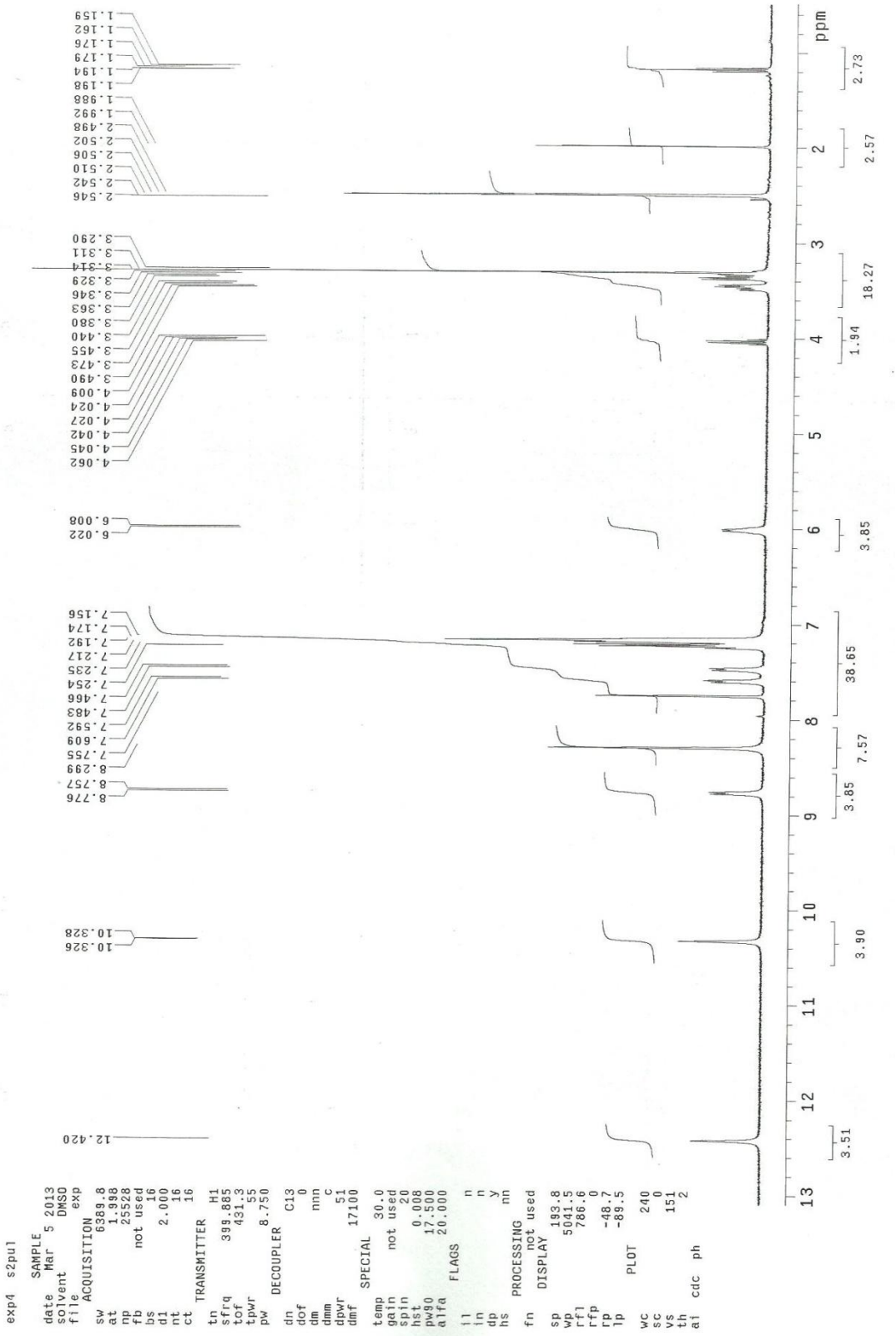


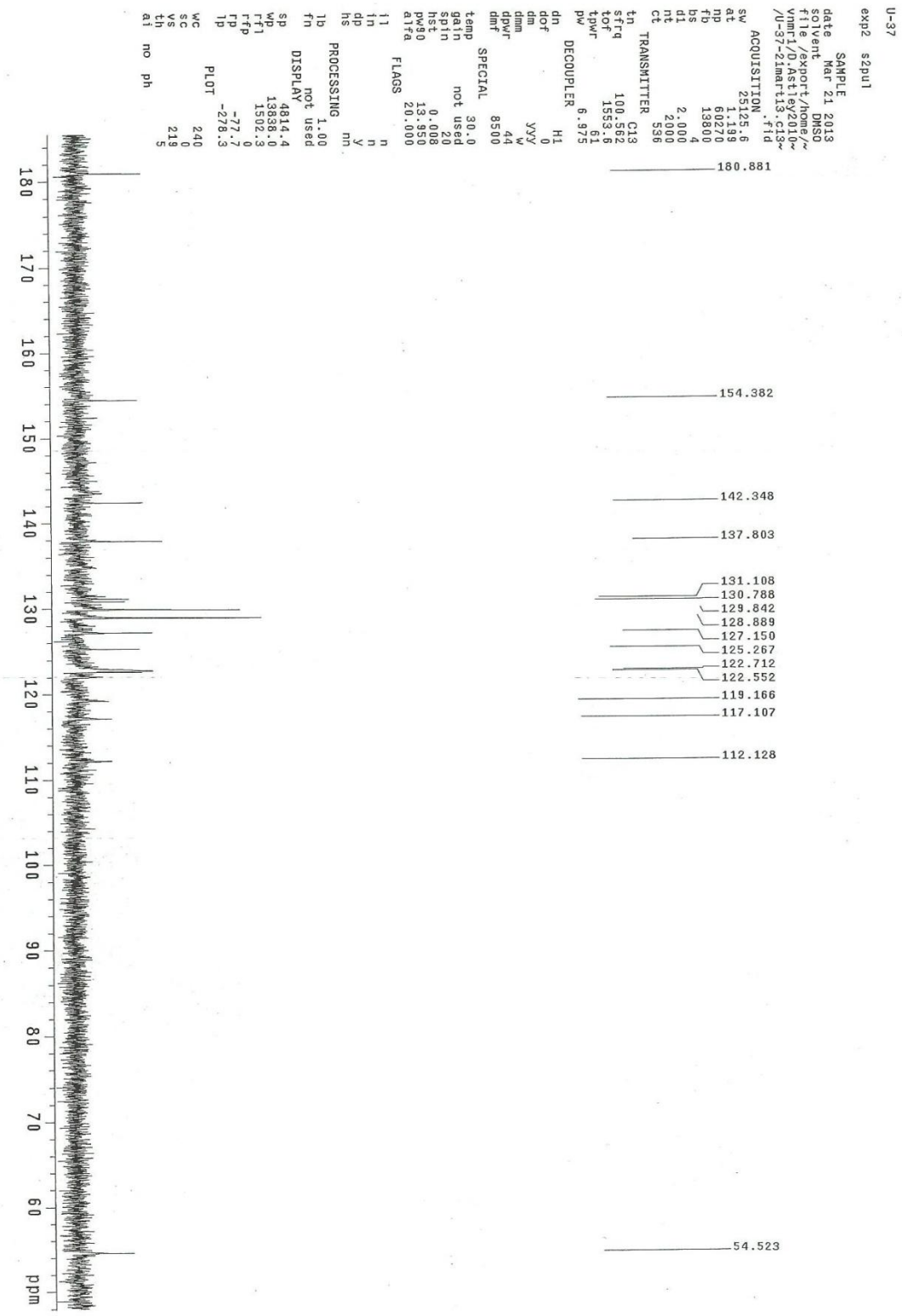

exp5 s2pul
SAMPLE
date Feb 8 2013
solvent CDCl3
file /export/home/~
vnmr1/D.Astley2010~
/U22-bsubati3.h1.f~
id
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 2.000
nt 12
ct 12
TRANSMITTER
tn H1
sfrq 399.883
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
fl n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -797.2
wp 6389.4
rfl 797.6
rfp 0
rp -43.1
lp -85.6
PLOT
wc 240
sc 0
vs 278
th 12
ai cdc ph
3.44
4.29
2.54
37.57
5.21
22.81
17.46
1.41
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


15.501
30.936
34.436
52.791
76.919
77.232
77.552
118.541
121.614
123.605
123.993
124.329
131.307
131.642
139.466
156.464
182.239
ppm
20
40
60
80
100
120
140
160
180
U22
exp5 s2pul
SAMPLE
date Feb 8 2013
solvent CDCl3
file /export/home/~
vnmr1/0.Astley213.~
/U22-8subati3.cf3.~
ACQUISITION fid
sw 25125.6
at 1.199
np 60270
fb 13800
bs 4
d1 2.000
nt 2000
ct TRANSMITTER C13
tn C13
sfrq 100.561
tof 1553.6
tpwr 61
pw 7.400
DECOUPLER H1
dn 0
dof yyy
dm w
dmm 44
dpwr 8500
dmf SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 14.800
alfa 20.000
FLAGS
ll n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 817.2
wp 18110.4
rfl 1502.3
rfp 0
rp 131.3
lp -326.7
PLOT
wc 240
sc 0
vs 360
th 6
al no ph

Appendix 16 FTIR Spectrum, 1H-NMR Spectrum and 13C-NMR Spectrum of Compound 16




exp4 s2pul
SAMPLE
date Mar 5 2013
solvent DMSO
file exp
ACQUISITION
sw 6389.8
at 1.998
np 25528
fb not used
bs 16
d1 2.000
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 399.885
tof 431.3
tpwr 55
pw 8.750
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 51
dmf 17100
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 17.500
alfa 20.000
FLAGS
ll n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp 193.8
wp 5041.5
rfl 786.6
rfp 0
rp -48.7
lp -89.5
PLOT
wc 240
sc 0
vs 151
th 2
ai cdc ph
12.420
10.328
10.326
8.776
8.757
8.299
7.755
7.609
7.592
7.483
7.466
7.254
7.235
7.217
7.192
7.174
7.156
6.022
6.008
4.062
4.045
4.042
4.027
4.024
4.009
3.490
3.473
3.455
3.440
3.380
3.363
3.346
3.329
3.314
3.311
3.290
2.546
2.542
2.510
2.506
2.502
2.498
1.992
1.988
1.198
1.194
1.179
1.176
1.162
1.159
ppm
3.51
3.90
3.85
7.57
38.65
3.85
1.94
18.27
2.57
2.73


U-37
exp2 s2pul
SAMPLE
date Mar 21 2013
solvent DMSO
file /export/home/~
vnmr1/D.Astley2010~
/U-37-21mar13_c13~
ACQUISITION .fid
sw 25125.6
at 1.199
np 60270
fb 19800
bs
bs 2.000
dl 4
nt 2000
ct 536
TRANSMITTER
tn C13
sfrq 100.562
tof 1553.6
tpwr 61
pw 6.975
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 8500
SPECIAL
temp 30.0
gain not used
spin 20
hst 0.008
pw90 13.950
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp 4814.4
wp 13838.0
rfl 1502.3
rfp 0
rp -77.7
lp -278.3
PLOT
wc 240
sc 0
vs 219
th 5
ai no ph
180.881
154.382
142.348
137.803
131.108
130.788
129.842
128.889
127.150
125.267
122.712
122.552
119.166
117.107
112.128
54.523
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm