ADDIS ABABA UNIVERSITY
SCHOOL OF GRADUATE STUDIES

SYNTHESIS AND PROPERTIES OF SOME SULFONAMIDE GROUP CONTAINING THIOUREA DERIVATIVES

By: DEJENE MULATU

ADVISOR: Dr. DUBINA VITALLY

JULY 26, 2007

SYNTHESIS AND PROPERTIES OF SOME SULFONAMIDE GROUP CONTAINING THIOUREA DERIVATIVES.

A GRADUATE PROJECT SUBMITTED TO THE OFFICE OF
RESEARCH AND GRADUATE PROGRAMME OF
ADDIS ABABA UNIVERSITY

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE IN CHEMISTRY

BY

Dejene Mulatu

JULY 2007

ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

SYNTHESIS AND PROPERTIES OF SOME SULFONAMIDE GROUP CONTAINING THIOUREA DERIVATIVES

BY

DEJENE MULATU

DEPARTMENT OF CHEMISTRY

SCIENCE FACULTY

JULY 2007

APPROVED BY THE EXAMINING BOARD:

Dr. Dubina Vitaly ____________________________
Advisor

Dr. Ashebir Fisiha ____________________________
Chairman

Prof. Ermias Dagne ____________________________
Examiner

Dr. Gizachew Alemayehu ____________________________
Examiner

Dr. Nigist Asfaw ____________________________

Examiner

DECLARATION

I the undersigned, declare that this project is my original work and has not been presented for a degree in any other University and that all sources of materials used for the project have been duly acknowledged.

Name: Dejene Mulatu
Signature: __________

Place and date of submission
Chemistry Department, Addis Ababa University
July 2007

This project has been submitted for examination with approval as University advisor

Advisor	Signature
Dr. Dubina Vitally	_________

Date: July 30, 2007

To: Dr. Gizachew Alemayehu
Head, Department of Chemistry, AAU

This is to confirm that Dejene Mulatu has incorporated the comments of the examining board in the final version of his M.Sc. project.

Sincerely yours,

____

Dr. Dubina Vitally

TABLE OF CONTENTS

1. Introduction

LIST OF TABLES

LIST OF SCHEMES

LIST OF APPENDAXES

LIST OF ABBREVATION AND SYMBOLE

THF -Tetrahydrofolic acid.

CCl_4-carbon tetrachloride.

DMFA- N, N-dimethylformamide

PCl_5- phosphorus pentachloride

HCl-Hydrochloric acid

H_2SO_4-Sulfuric acid

Na_2SO_4 –Sodium sulfate

Na_2CO_3- Sodium carbonate

$NaHCO_3$- Sodium BIcarbonate

SO_2 –Sulfur dioxide.

NaOH –sodium hydroxide.

$AlCl_3$-Almmunium trichloride.

$ZnCl_2$-Zinc dichloride.

KSCN- potassium isothiocynate.

KCl -potassium chloride

IR- Infrared

v- Stretching frequency

NMR- Nuclear magnetic resonance

Rodanide- N- Arenesulfonyl-Benzimidoyl isothiocynate

Acknowledgment

I offer my deepest gratitude and respect first and the most to my advisor Dr. Dubina Vitally for all his unreserved guidance, technical and moral support of this project. Also I would like to thank Dr. Wendimagegn Mammo for his scientific comments and for running some NMR spectra of some compounds.

All the NMR spectra reported in this work were measured on Bruker 400MHz NMR spectrometer purchased by grant to natural product chemistry project. Running cost of the instrument is covered by budget from the faculty of science. I am deeply grateful for this service.

I would like also to thank W/t Medehanit Mammo for IR spectra measurements, Ato Yosef Atlaw and Ato Masresha Assnakew for running the NMR spectra of some compounds.

I also extend my sincerest appreciation to Addis Ababa university school of graduate studies for funding the project work

I express my deepest sense of gratitude to my lovely sister Meseret Desta and friends for their continuous encouragement in my efforts to produce this project.

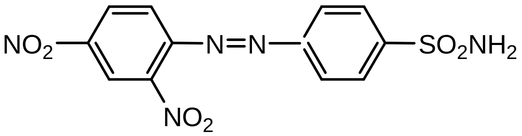
Abstract

In this work five N-arenesulphonyl-benzimidoyl-N'- thiourea derivatives were synthesized from intermediate of N-arenesulphonyl-benzimidoyl- rodanide (**3**) by reacting with different bascity of amines. Out of these derivatives compound **4**,**5** and **6** were synthesized by reacting rodanide (**3**) with aromatic amines (aniline and p-methyl aniline) and the rest of the two compounds ,compound **7** and **8,** were synthesized by reacting of rodanide (**3**) with ammonia solution and glycine. Their structures were determined by using NMR and IR spectroscopic method.

1. Introduction

1.1. Sulfonamides

At the beginning of the 20th century Paul Ehrlich showed that various azo dyes were effective agents against trypanosomiasis in mice; however, none was effective in man. In the early 1930s Gerhard Domagk, head of bacteriological and pathological research at Bayer Company in Germany, who was trying to find agent against streptococci, tested a verity of azo dyes. One of the dyes, prontosil (1), showed dramatically positive results and successfully mice against streptococcal infection. Bayer was unwilling to move rapidly on getting prontosil onto the drug market. As Albert told it, when, in late 1935, Domagk's daughter cut her hand and was about to die of a streptococcal infection, her father gave her prontosil. Although she turned bright red from the dye, her recovery was rapid, and the effectiveness of the drug became quite credible [1]. In 1939, Domagk was awarded Nobel Prize in medicine for his achievement. [2]



Prontosil (1)

Modern chemotherapy had its beginning in compounds of general formula R-SO_2-NH_2. Sulfonamide, the simplest member of the class, is an antibacterial agent because of its competition with p-amino benzoic acid (PABA), which is required for bacterial growth. Bacteria cannot absorb folic acid, a required vitamin for the host, must synthesized it. Since sulfonamide is structural analog of p-Aminobenzoic acid, the bacterial dihydropteroate synthetase is tricked into making an intermediate, containing sulfonamide that cannot be converted to folate [3, 4].

Due to this reason sulfonamide fragment is included in to metabolized – cycle and destroyed if in the infected cells. Many other sulfonamide derivatives were synthesized and many other drugs was discovered which are generally called sulfonamide drugs (scheme 1). [5]

1.2. Properties of sulfonamides

Sulfonamide compounds are amide derivatives of sulphonyl acid which is nearly strong as sulfuric acid. Strong influence of SO_2 group shift the electrons from nitrogen to the sulphur-oxygen and this change nitrogen from basic properties, even to acidic and such amides can be considered as a weak acid. Their pKa is around 10 and they can form salts with the strong bases. Due to this reason, simple sulfonamide dissolves in about 5-10% NaOH solution [6].

$$RSO_2NH_2 + NaOH \rightleftharpoons RSO_2NHNa + H_2O$$

In according to this, unsubstituted in nitrogen atom sulfonamide compounds can be considered as a weak acid similar to acidity of phenol. N-acyl substituted sulfonamides also belong to the acidic compounds and acidity of them even higher than acidity of carbonic acid. That can be explained in terms of inductive influence on nitrogen atom both by sulphonyl and acyl groups [6].

1.3. Main reactions of sulfonamide compounds

1.3.1. N-Alkylation

Because the bascity of nitrogen in sulfonamides is weak, attacks of nitrogen atom by alkylation agents is less successful than attack of nitrogen in aromatic amines. That means, to increase the rate of the alkylation reaction necessary to increase bascity of nitrogen in sulfonamides by conversion them to the salts, for example, by adding to them a basic catalyst in the form of NaOH or TEA [7].

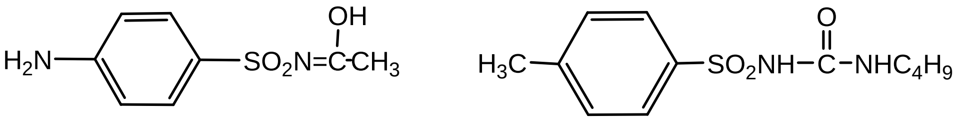
1.3.2. N- Acylation

In the middle of 20th century Albrecht and Kresze was found the ability of salts of none N-substituted sulfonamides to be acylated by relatively weak acylated agents like esters of carboxylic acids. Acylation properties of esters are very low but nucleophilic properties of sulfonamide salts are very high. That makes acylation of sulfonamides more or less successful. [8]

Acylation is developed the way for the synthesis of great number new N-acyl sulfonamide derivatives because esters for many acids are more available than the other acylated agents, like halogen anhydride or anhydride [9]. From 1960 prof. Burmistrov S. start study the acylation ability for sulfonamide of different esters like esters of formic acid, oxalic acid, salicylic acid, lactic acid etc. and the results of these investigations give the possibility to make some general understanding about N-acylation [10]. Acidic catalysts like H_2SO_4, $AlCl_3$, $ZnCl_2$ improved the acylation reaction [11].

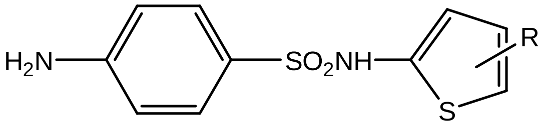
1.4. Modification of sulfonamide.

The discovery of prontosil marks the beginning of modern chemotherapy. During the next decade thousand of sulfonamide derivatives were synthesized, modified and tested as antibacterial agents. These were the first structure-reactivity relationship studies, and demonstrated the importance of molecular modification in drug design [1].



Albucid for eye treatment

Butamide for diabet treatment

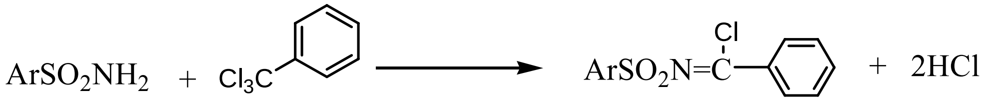


for infections treatment

Scheme1. Some examples of sulfonamide drugs

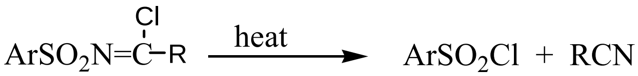
1.5. Preparation and Chemical Properties of Sulfonamide Derivatives

In majority cases sulfonamide group has the same influence on the rest of the organic molecules, as an atom of oxygen in similar compounds. That means the chemical properties of non N-substituted sulfonamides similar to the properties of water; N-acylated sulfonamides derivatives have similar properties to the corresponding organic acids, Nalkilated to the properties of alcohols etc. [12]. Based on this idea Dr.Dubina V. was discovered quite simple practical process of preparation of very active Sulphonylimidoyl halides (sulfonamide derivatives) by interaction of sulfonamides with benzotrichloride (scheme 2). This reaction can be considered as analogous of reaction of partial hydrolysis of benzotrichloride to benzoyl chloride [13].



Scheme 2 preparation of arenesulphonyl-benzimidoyl halides

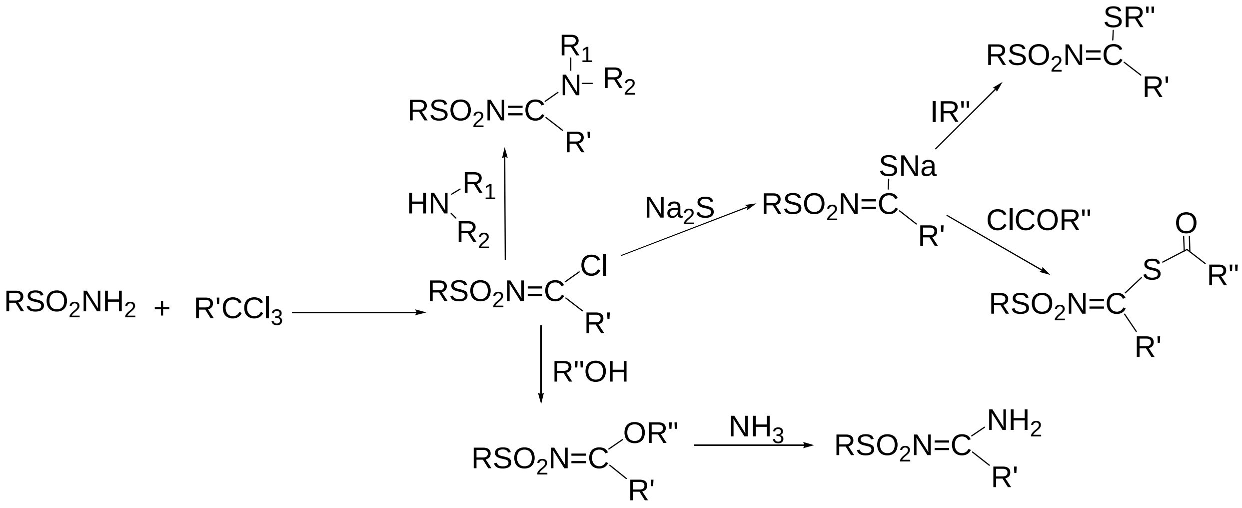
Disadvantage of pointed over process is thermal decomposition of final product during its preparation.



$$ArSO_2N{=}\overset{Cl}{C}{-}R \xrightarrow{heat} ArSO_2Cl + RCN$$

Scheme 3 decomposition of Sulphonylimidoyl halides by heat.

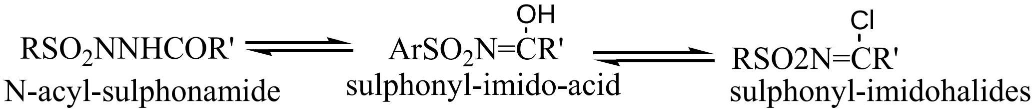
Because the initial sulfonamide has low nucleophilic properties to conduct the process with benzotrichloride, it is unadvisable to increase the temperature of the reaction to increase the rate of reaction instead it need proper selection of catalyst. For example anhydrous $AlCl_3$. With this catalyst it is possible to produce sulphonyl-imidoylhalides which used to produce new types of the sulfonamide derivatives. This sulphonyl imidoylhalides are highly reactive, act as strong electrophilic agents, and they can react with many nucleophilic agents (Scheme 4). [14, 15].



where R' and R'' can be alkyl,aryl, OH, $-NR_1R_2$, hydrazine, etc.

Scheme 4 synthesis of sulfonamide derivatives from different types of nucleophilic reagents

Arenesulphonyl-benezimidoylchloride can be tautomeric form of chlorohydrides of sulphonyl-imido-acid and N-acyl sulphonylamides (Scheme 5).

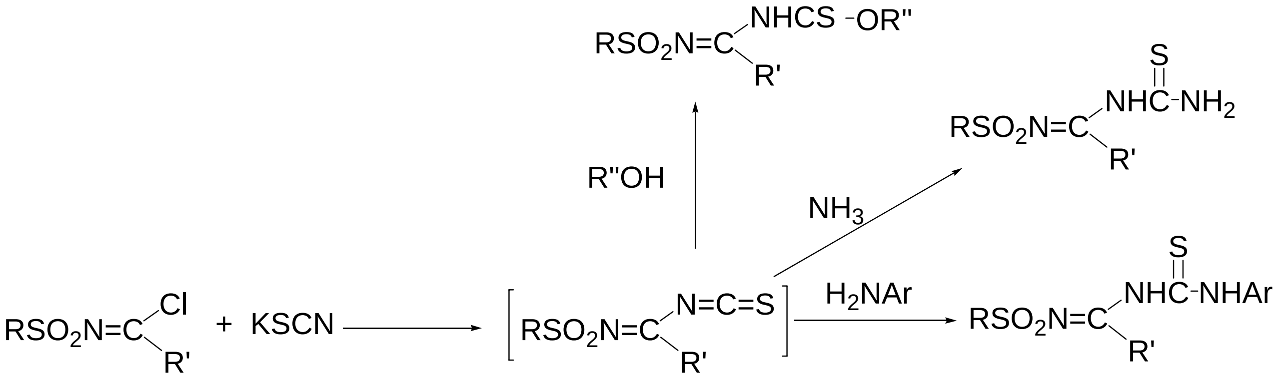


$$RSO_2NNHCOR' \rightleftharpoons ArSO_2N{=}\overset{OH}{C}R' \rightleftharpoons RSO2N{=}\overset{Cl}{C}R'$$

N-acyl-sulphonamide   sulphonyl-imido-acid   sulphonyl-imidohalides

Scheme 5 sulphonyl-imido-acid tautomeric form of N-acyl sulphonylamides

One of the interesting directions to check the similarity in chemical properties of oxygen and sulfonamide group containing compounds was suggested that conversion of arenesulphonyl-benezimidoylchloride to corresponding isothiocynates group containing intermediate. It was found that this intermediate react with alcohols to form corresponding esters of thioaminic acid and with amines leads to the formation of thiourea derivatives (Scheme 6) [16, 17, 18].



where R'= aryl and R"= alkyl

Scheme 6. Formation of thiourea derivatives from corresponding isothiocynates precursor.

1.6. Medical Application of Sulfonamide Group Containing Thiourea Derivatives.

A large number of sulfonamide derivatives have ultimately been reported to show substantial protease inhibitory properties [18]. Some matrix metalloprotease (MMP) inhibitors belonging to this class show significant antitumour properties. Such compounds also lead to the design of effective tumour TNF-α converting enzyme (TACE) inhibitors, potentially useful in the treatment of inflammatory states [19,20]. Since both MMPs and TACE contribute synergistically to the pathophysiology of many diseases (arthritis, bacterial meningitis, tumour invasion etc.), the dual inhibition of these enzymes emerged as an interesting target for the drug design of anticancer/anti-inflammatory drugs. Another research line that has progressed recently regards different sulfonamide derivatives with remarkable antiviral activity. Some clinically used HIV protease inhibitors, such as amprenavir (Agenerase™, Vertex Pharmaceuticals, Inc.), possess sulfonamide moieties in their molecules, whereas a very large number of other derivatives are constantly being synthesized and evaluated in order to obtain compounds with lower toxicity or augmented activity against viruses resistant to the first generation of such drugs[21, 22].

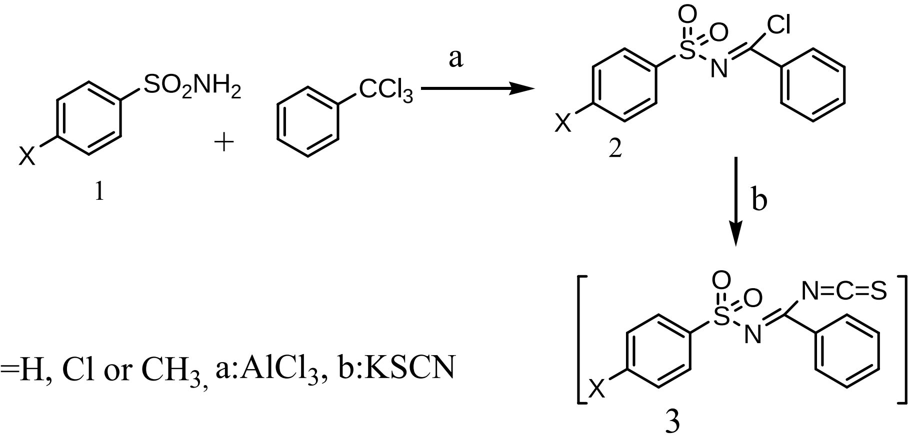
To produce corresponding thiourea derivatives as shown in Scheme 6 initially, only aromatic amines were successfully tested. But reaction of rodanide (3) with ammonia and some other strong basic amines like dimethylamines, diethyl amine, etc… was not tested. We were work to complete these investigations using strong bases (aliphatic amines) and also to produce some thiourea derivatives using aromatic amines.

1.7. Objective of this work

The main objective of this project was to produce sulfonamide derivatives by reacting amines (aromatic and aliphatic amines) of different Bascity with rodanide (**3)** and to study the chemical properties of the synthesized derivatives. And also to prove the structure of obtained compounds by using IR and NMR spectroscopy methods.

2. Results and Discussion

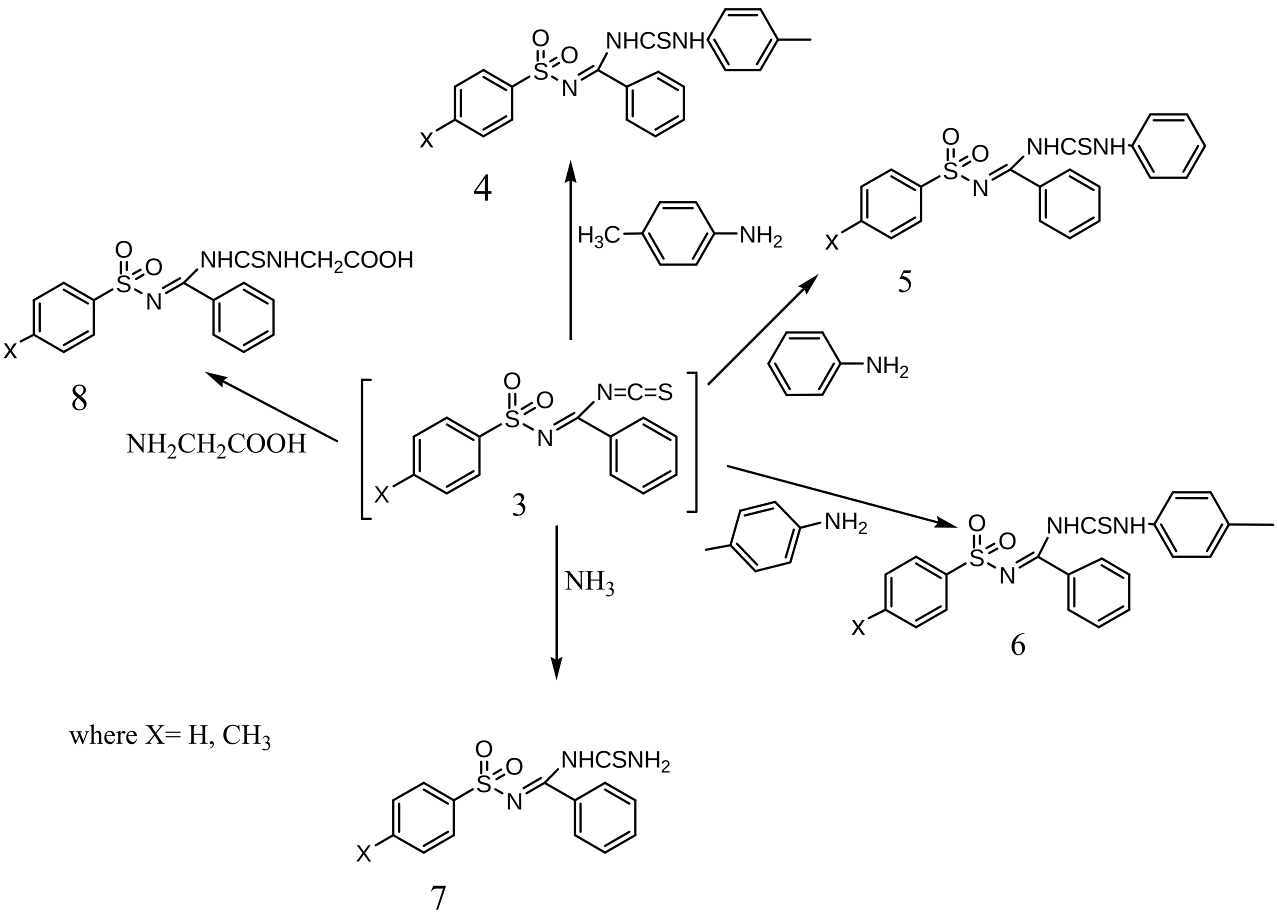
Sulfonamide group containing derivatives (scheme 8) were synthesized by reaction of aromatic amines and aliphatic amine of different bascity with rodanide (**3**). The sulfonamide part was transformed by the action of benzyl trichloride into the arenesulphonyl-benezimidoylchloride (**2**) and subsequently reacts with potassium isothiocynate to produce the desired rodanide (**3)** (scheme 7). From the three types of arenesulphonyl-benezimidoylchloride **1** (p-methyl benzene sulfonamide, p-chlorobenzene sulfonamide and benzene sulfonamide) we were prepared only p-chlorobenzene sulfonamide from the initial starting compound of chlorobenzene (shown in procedure **3.3**) and the rest of the two aryl sulfonamides were taken from the stock. The procedure, in which these three arenesulphonyl benzimidoyl chloride (**2**) prepared was the same.



X=H, Cl or CH_3, a:$AlCl_3$, b:KSCN

Scheme 7. Synthesis of intermediate **3**

The proposed structure of intermediate **3** was supported by its IR spectrum (appendix **49**) showed that the presence of the expected isothiocynate group and carbon nitrogen double bond (-N=C-). The intermediate **3** was reacted with amines of different bascity (aliphatic and aromatic) to produce the corresponding derivatives (scheme 8).



Scheme 8. Synthesis of derivatives from intermediate **3**

The identities of the synthesized compound 4, 5, 6, 7 and 8 were supported by the spectral data as follows:

1) I.R

The infrared spectra show the disappearance of v(NCS) band present in case of the rodanide **3** and the existence of v(NH) and v(C=N) bands at around 3200 cm^{-1}, and 1606-1612 cm^{-1}, respectively, for the derivatives (4,5,6,7,8,9). And the strong peak at around 1310 cm^{-1} and 1150 cm^{-1} show that all derivatives are contain SO_2 group the weak absorption band at around 820 cm^{-1} show that all derivatives are contain CS double bond.

2) ^{1}HNMR

The proton nuclear magnetic resonance spectra give chemical shift at around 11.5-12.5 ppm due to the NH group which is common to all derivatives according to the stimulated NMR spectra Aromatic protons are present at chemical shift from 7-8 ppm

3) 13C-NMR

The most important peak shown by the ^{13}C-NMR is the peak corresponding to C=S with a chemical shift of 171-180 ppm and C=N with chemical shift of around 161-164 ppm which plays an important role in the structure identification of the products.

2.1. Characterization of sulfonamide (Thiourea) Derivatives.

2.2.1. N- phenylsulphonyl-benzimidoyl-N'-(p-methyl phenyl) thiourea (comp. 4)

It is colorless solid with melting point 178-180^{o}C and yield of 78.44%. In the IR spectrum (Appendix 4) absorption band at 3186 cm^{-1} show the presence of NH group, absorption band at 2996 indicate CH_3. Absorption band at 1608.24 cm^{-1} indicate the presence of N=C double bond while the absorption band between 1592 and 1444.11cm^{-1} indicate the presence of aromatic carbon. The two intense absorption band at 1323 and 1160cm^{-1} indicate the presence of SO_2 group.

The ^{1}H NMR spectrum (Appendix 1) indicate the presence of methyl group (δ 2.4, 3H, s) and aromatic proton appeared at δ 7.12 (2H, d, J=8.4), δ 7.23 (2H, d, J=8.4), δ 7.53 (4H, m), δ 7.64 (2H, dd, J=7.6), δ 7.71(2H, d, J=7.2) and δ 7.79(2H, d, J=7.6). One proton singlet at δ 8.48 and δ 12.5 indicate the presence of deshelded NH group.

^{13}C NMR (Appendix 2) and DEPT-135 spectrum (Appendix 3) indicated that compound 4 has one methyl carbon at δ 21.08 and six quaternary carbons at δ 131.97, 134.69, 136.81, 141.44, 161.87 and 175.85. ^{13}C NMR also showed that the presence of aromatic carbon at δ 122.65, 126.88, 127.86, 128.99, 129.19, 129.346, 132.738 and 132.98.

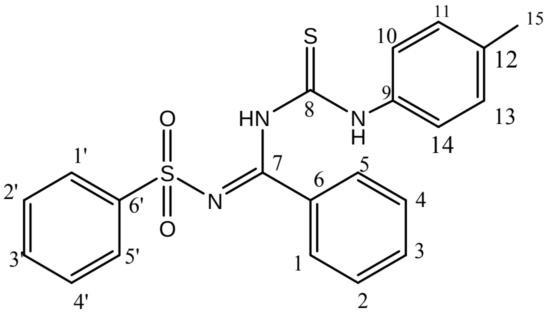


Table 1. ^{1}H and ^{13}C NMR data of compound **4** in $CDCl_3$, δ in ppm from TMS.

C. number	^{1}H	^{13}C NMR
1,5	2H,d	122.65
2,3,4,3’	4H,m	129.19,132.73 129.19,132.98
6	-	131.97
7	-	161.87
8	-	175.85
9	-	134.69
10,14	2H,d	126.89
11,13	2H,d	129.35
12	-	136.81
15	3H,s	21.08
1’,5’	2H,d	127.87
2’,4’	2H,dd	128.99
6’	-	141.44

2.2.2. N- p-toluenelsulphonyl-benzimidoyl-N’- phenyl thiourea (comp. 5)

It is colorless solid with melting point 182-183^{o}C and yield of 83.3%. In the IR spectrum (Appendix 8) absorption band at 3188.59 cm^{-1} show the presence of NH group, absorption band at 3029.99 and 2918 cm^{-1} indicate the presence of Ar-H and CH_3. Absorption band at 1610.78 cm^{-1} indicate the presence of N=C double bond while the absorption band between 1593and 1445.89cm^{-1} indicate the presence of aromatic carbon. The two intense absorption bands at 1321.82 and 1160.80 cm^{-1} indicate the presence of SO_2 group.

The ^1H NMR spectrum (Appendix 5) indicate the presence of methyl group (δ 2.24, 3H, s) and aromatic proton appeared at δ 7.24(1H, d,J=7.6), δ 7.29(4H, dd, incomplete), δ 7.36 (2H, d, J=8), δ 7.64 (2H, t, J= 6.4), δ 7.63(1H, t, J=7.2), δ 7.70(2H, d, J=7.4) and δ 7.75(2H, d, J=7.4). One proton singlet at δ 8.48 and δ 12.5 indicate the presence of deshelded NH group.

^{13}C NMR spectrum (Appendix 6) and DEPT-135 NMR spectrum (Appendix 7) indicated that compound **5** has one methyl group at δ 21.60 and six quaternary carbons at δ 131.89, 137.29, 138.56, 144.01, 161.78 and 176.03. ^{13}C NMR also showed that the presence of aromatic carbon at δ 122.67, 126.76, 126.96, 127.96, 128.73, 128.94, 129.77 and 132.71.

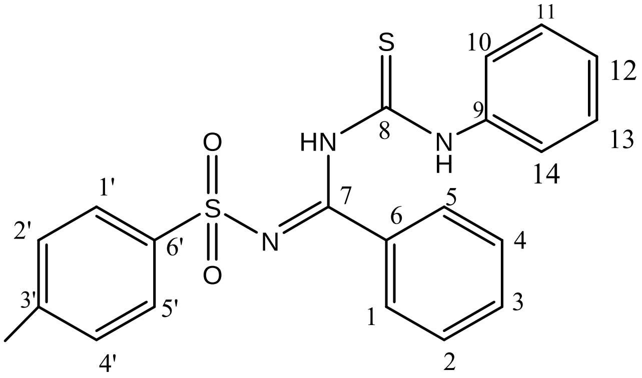


Table 2. ^1H and ^{13}C NMR data of compound **5** in $CDCl_3$, δ in ppm from TMS.

C. number	^1H NMR	^{13}C NMR
1,5	2H,d	126.76
2, 4,11,13	4H,dd	128.94,129.72
3	1H,t	128.73
6	-	131.88
7	-	161.78
8	-	176.03
9	-	137.29

10,14	2H,t	126.95
12	1H,t	122.67
1’,5’	2H,d	127.96
2’,4’	2H,d	129.76
3’	-	143.99
6’	-	138.76

2.2.3. N- p-toluenelsulphonyl-benzimidoyl-N’- p-toluene thiourea (comp. 6)

It is colorless solid with melting point 187-190°C and yield of 75.3%. In the IR spectrum (Appendix 12) absorption band at 3309.64 cm^{-1} show the presence of NH group, absorption band at 3059 and 2980 cm^{-1} indicate the presence of Ar-H and CH_3. Absorption band at 1606.35cm^{-1} indicate the presence of N=C double bond while the absorption band between 1593and 1445.89cm^{-1} indicate the presence of aromatic carbon. The two intense absorption bands at 1313.64 and 1152.04 cm^{-1} indicate the presence of SO_2 group.

The ^{1}H NMR spectrum (Appendix 9) spectrum indicate the presence of two methyl group at δ 2.23 and δ 2.5 and aromatic proton appeared at δ 7.12(2H, d, J=8.4), δ 7.23(2H, d, J=8.4), δ 7.29 (2H, d, J=8.8), δ 7.55 (2H, t, J=9.6), δ 7.63(1H, d, J=7.2) δ 7.70(2H, d, J=7.8) and 7.76(2H, d, J=7.8). One proton singlet at δ 8.48 and δ 12.5 indicate the presence of desheIded NH group.

^{13}C NMR spectrum (Appendix 10) and DEPT-135 spectrum (Appendix11) indicated that compound **6** has two methyl Carbons δ 21 and 21.6, seven quaternary carbons at δ 131.97, 134.75, 136.76, 138.58, 143.94, 161.72 and 175.95. ^{13}C NMR also showed that the presence of aromatic carbons at δ 122.71, 126.92, 127.90, 128.92, 129.29, 129.73 and 132.66.

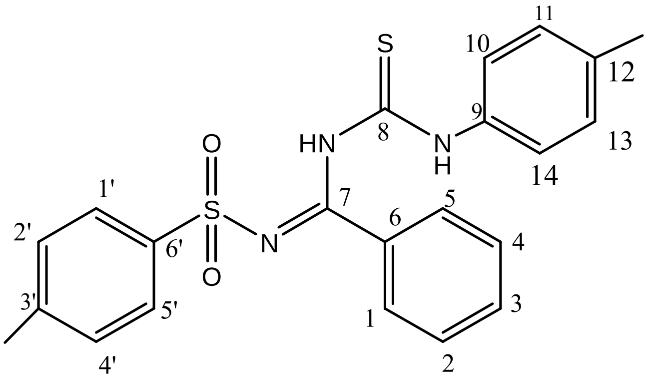


Table 3. ^{1}H and ^{13}C NMR data of compound **6** in $CDCl_3$, δ in ppm from TMS.

C. number	^{1}H NMR	^{13}C NMR
1,5	2H,d	122.71
2, 4	2H,t	129.29
3	1H,t	128.92
6	-	131.97
7	-	161.72
8	-	175.95
9	-	134.75
10,14	2H,d	126.92
11,13	2H,d	129.73
12	-	136.76
1’,5’	2H,d	127.90
2’,4’	2H,d	132.66
3’	-	143.94
6’	-	138.58

2.2.4. N- phenylsulphonyl-benzimidoyl-N’- thiourea derivatives (comp.7)

It is colorless solid with melting point 195-197^{o}C and yield of 51.77 %. In the IR spectrum (Appendix 16) absorption band at 3315.57 cm^{-1} and at 3212 cm^{-1}and 3168 cm^{-1} showed that the presence of NH and NH_2 group, absorption band at 3029.99 indicate the presence of Ar-H. Absorption band at 1603.94 cm^{-1} indicate the presence of N=C double bond while the absorption band between 1593 and 1445.89cm^{-1} indicate the presence of aromatic carbon. The two intense absorption bands at 1323.4 and 1163.94 cm^{-1} indicate the presence of SO_2 group.

The ^{1}H NMR spectrum (Appendix 13) indicate the presence of NH_2 at (δ 2.62, 2H, s) and aromatic proton appeared at δ 6.75(4H, d), δ 6.79(2H, t, J=7.6), δ 6.82 (1H, m), δ 6.9 (1H, t, J=5.5) and δ 6.95 (2H, d, J=7.2). One proton singlet at δ 12.5 indicates the presence of deshelded NH group.

^{13}C NMR spectrum (Appendix 14) and DEPT-135 spectrum (Appendix 15) indicated that compound **7** has four quaternary carbons at δ 131.60, 141.04, 163.18 and 181.07. ^{13}C NMR also showed that the presence of aromatic carbons at δ 125.99, 127.25, 127.69, 128.46, 130.70 and 132.15.

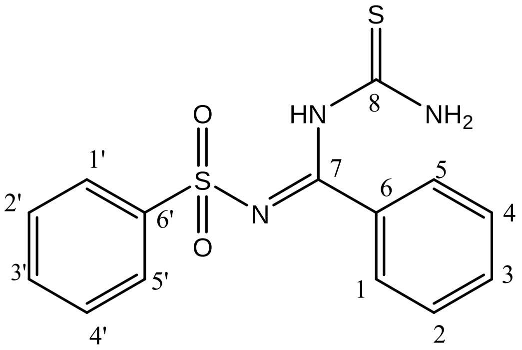


Table 4. ^{1}H and ^{13}C NMR data of compound **7** in $CDCl_3$ and DMSO, δ in ppm from TMS.

C. number	^{13}C NMR
1,5	125.98
2, 4,2'4'	127.69,128.45
3	132.15
6	131.97
7	163.18
8	181.01
1',5'	127.25
3'	130.7
6'	141.04

2.2.5. N- phenylsulphonyl-benzimidoyl-N'-carboximethylene-thiourea. (Comp.8)

It is colorless solid with melting point 203-206°C and yield of 69 %. in the IR spectrum (Appendix 20) sharp absorption band at 3206 cm^{-1} show the presence of NH group, absorption band at 3058 cm^{-1}show the absorption Ar-H. Absorption band at 2996 indicate CH_2 stretching while the broad absorption band between 3300 and 2600 cm^{-1} indicate the presence of aromatic acid. Absorption band at 1769 and 1606 cm^{-1} indicate the presence of acid carbonyl and N=C double bond respectively. The two intense absorption band at 1312 and 1142 cm^{-1} indicate the presence of SO_2 group.

The ^1H NMR spectrum (Appendix 17) indicate the presence of methylene group (δ 4.4, 2H, s), the broad band spectrum (at δ 3.48, 1H, s) indicate the presence of proton exchange (NH). Aromatic proton appeared at δ 7.2 (4H, d, J=4.4), δ 7.45 (2H, t), δ 7.65 (2H, d, J=7.2), δ 7.78 (2H, d, J=7.6). A singlet at δ 11 and δ 11.5 confirming the presence of hydrogen bonded of OH and acidic NH group.

^{13}C NMR spectrum (Appendix 18) and DEPT-135 spectrum (Appendix 19) indicated that compound **8** has one methylene carbon at δ 47.55, five quaternary carbons at δ132.40, 144.1, 164, 170 and180. ^{13}C NMR also showed signals of aromatic carbon at δ 126.87, 128.14, 128.56, 129.48, 131.57 and 133.22.

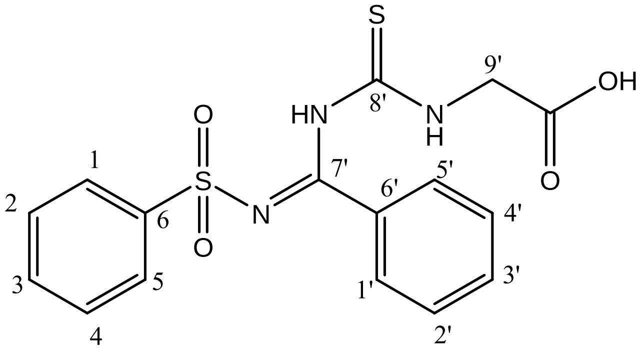


Table 5. ^{1}H and ^{13}C NMR data of compound 8 in DMSO, δ in ppm from TMS.

C. number	^{13}C NMR
1,5	128.14
2,4	129.48
3,2',3',4'	133.22,128.56,131.57,128.56
6	144.1
1',5'	126.87
6'	132.40
7'	164

3. Experimental

3.1. Chemicals

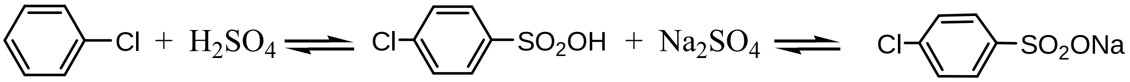
Chemical used includes Dimethylamines, diethyl amine, benzenyl trichloride, benzene sulfonamide, p-methylbenzene sulfonamide, glycine, ammonia, aniline, p-methyl aniline, HCl, H_2SO_4, $NaHCO_3$, KSCN, PCL_5, $AlCl_3$. Acetone was used as a solvent through out the investigation. Solvents like DMSO, DMF, CCl_4, methanol, propanol, acetic acid, dichloroethane, chloroform, benzene, water and ice were used.

3.2. Instrumentation

^{1}H, ^{13}C spectra were recorded on a Bruker advance 400MHz-spectrometer with TMS as internal standard. Infrared (IR) spectra were obtained on Perkin-Elmer BX infrared spectrometer using KBr in the range 4000-400 cm^{-1}. Melting points were recorded using Thomas HOOVER capillary melting point apparatus. TLC analysis was carried out on TLC plates 0.2mm thick layer of Merck Silica Gel 60 F_{254} coated on aluminum foil. Compounds on TLC were detected using UV light and iodine vapors.

3.3. Procedure

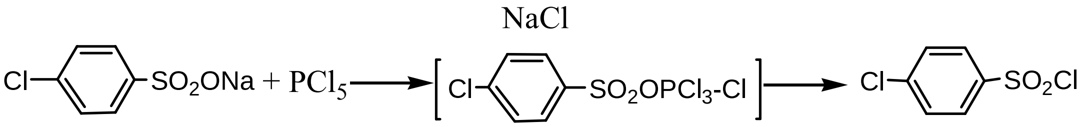
3.3.1 Sulphonation of Chlorobenzene.



1mol (102 ml) of chlorobenzene and 2.5 mol (134 ml) of sulfuric acid were mixed in a 500 ml containing flask (H_2SO_4 was taken in excesses to complete the transformation of chlorobenzene to p-chloro sulfonic acid.). Initially they were not undergo reaction (two layer are formed), but when heated on stove at temperature of around 80^oC and intermixed by shaking, reaction was started and organic layer started to dissolve in the sulfuric acid. The end of the reaction was detected by completely dissolving organic layer in the sulfuric acid. Finally test was: drop of reaction mixture was completely dissolved in the test tube with water.

To separate the formed sulphonic acid, 1 mol (189 gm) of Na_2SO_4 was measured and dissolved in 1000 ml of H_2O by heating. After solid Na_2SO_4 was completely dissolved the solution was taken to cooling. To this solution the reaction mixture was added and immediately the formation of crystals was started (**Note**- Care should be taken during mixing of these two solutions, because the temperature of the mixture can be raised up to the boiling point**!**). To form better crystals, the suspension was heated, the crystal of sodium-p-chlorobenzene sulphonate was dissolved and solution was left over night for the crystallization. On the next day the crystalline was separated by suction filtration and taken for dryness in the oven at temperature of 110^oC.

3.3.2. Preparation of p-Chlorobenzene sulphonyl-chloride



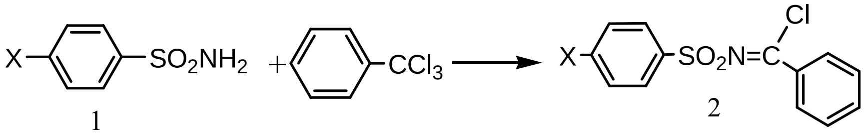
0.42 Mol (90gm) of p-chloro benzenesulfonate salt was measured and mixed with 40 ml of CCl_4 in 250 ml flask (to cover it) and 3 drops of DMFA was added to it as catalyst. At the room temperature 0.21 mol (50 gm) of PCl_5 was added to it. Then it was connected with vacuum water pump through the condenser to protect $POCl_3$ come into the lab. atmosphere. To completed the reaction, the reaction mixture was heated up it 50°C for 5hrs.Heating and intermixing during this period new sediment. Then reaction mixture was cooled to the room temperature and transferred to larger flask with ice in hood to destroy phosphoryl trichloride and to dissolve inorganic salts. The sticky sediment observed during this process was dissolved by adding excess (50 ml) of CCl_4.

3.3.3. Preparation of p-Chlorobenzene sulfonamide

The CCl_4 solution of arenesulphonylchloride, which was obtained on the previous step was separated and then mixed with in 1000 ml conical flask excess of ammonia solution (about 300 ml) in the hood at the room temptrature and shaken by hand periodically. After few minutes the temperature of the mixture was raised and vigorous reaction is started. Due to this the crystalline sediment of non soluble in water or in CCl_4 solution is formed. To complete this reaction the mixture was left overnight.

On the next day crystalline sediment of p-Chloro benzene sulfonamide was filtered out and washed with water on the filter and left for drying.

3.3.4. Preparation of arenesulphonyl benzimidoyl chloride (2).



X=H, CH_3, Cl

0.1 mol. (15.7 gm) benzene sulfonamide (**1**) and 0.11 mol (14gm) of anhydrous $AlCl_3$ were measured and mixed in 500 ml Er. Flask. The mixture of the two compounds became 'wet' due to complex formation. This complex was dissolved in dichloroethane by heating on stove at temperature of 40 °C. Then 0.1 mol (15 ml) of benzotrichloride was added to the dissolved complex step by step by controlling the temperature and the evolution of HCl gas. Then the reaction mixture was left in the hood till the evolution of gas was over (**Note**- the temperature of the reaction should be controlled on initial stages because if the temperature of reaction is greater than 40°C, the final compound may be partly decomposed into Arylsulphonyl chloride and benzonitrile). On the second day the product of the reaction were put it in the crushed ice with small amounts of HCl to lower reaction temperature and to protect the formation of floccules of basic salts like $HOAlCl_2$, which can be formed due to the hydrolysis of complex. After such treatment, the two layer system was formed. Bottom layer, which contain dichloroethane and arenzenesulfonyl-benzimidoylchloride was additionally purified by suction filtration from non soluble particles and then this layer was transferred into evaporatory dish in the hood to remove the solvent by evaporation at room temperature. On the second day after the evaporation of the solvent the crystals of arenzenesulfonyl-benzimidoylchloride were formed. To the solid part 30 ml of diethyl ether was added to remove organic impurities from its surface (like sulphonylchloride and benzotrichloride).

Then the impurities with solvent ether were separated by using suction filtration **(Note-** the oily part may contain benzosulfonyl chloride and benzonitrile as well as small amount of the product part). The white crystals were dried at temperature of 50°C. This product has melting point 80°C equal to the table data [9] and was used without any purification for the following synthesis.

3.4. Comman procedure for synthesis of compound 4, 5, 6

From compound that displayed in scheme **8**, compound 4, 5 and 6 were prepared by using the following procedure.

0.005 mol of arenesulphonyl-benezimidoylchloride (**2**) and 0.007 mol of KSCN was measured and dissolved in 30 ml of acetone by heating on stove till the crystalline part was completely dissolved (for 15 min). During this action the yellow solution of rodanide (**3**) and fine sediment of KCl was formed. To this reaction mixture 0.005 mol of aromatic amine was added with following heating and intermixing. After few minute organic sediments was produced. Then with continuing intermixing water was added in to the flask drop by drop (around 50 ml) to dissolve inorganic sediment and to complete sedimentation of organic product. After 1hr the sediment was filtrated out by suction filtration and washed on the filter with CCl_4 to remove possible unreacted intermediate **3** and aromatic amine. After drying at room temperature the weight and melting point of the product was determined and it was recrystalized from suitable solvent (HAc, HAc + DMFA).

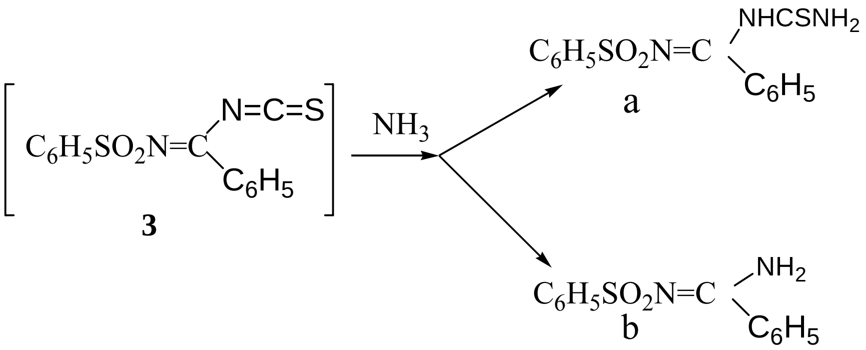
4. Influence of Bascity of Different aliphatic Amines and ammonia solution on the Rodanide (3)

4.1. Reaction of ammonia solution with rodanide (3)

As it was shown in previous experiments, aromatic amines with less bascity (pKa greater than 5) are reacted with rodanide (**3**) and produce correspondent thiourea derivatives with good yield. But aliphatic amines, which are usually more strong bases than aromatic amines were not properly tested. So, we were starting to do on these experiments by using ammonia solution in the reaction with rodanide (**3**).

Procedure

To rodanide (**3**) solution ammonia solution was added in the ratio of 1:1 and intermixed using magnetic stirrer for 15 min. The reaction product was contained the desired derivatives (a) and byproduct of amidine (b) (scheme 9).



Scheme 9. Simultaneous formation of product a and b from intermediate **3**

These two compounds were separated from each other based on their acidic properties. i.e., derivative (a) has acidic properties and dissolved in basic media even in $NaHCO_3$ solution by slightly heating. But amidine (b) did not dissolve in basic media. So the mixtures of the two were separated by dissolving in soda solution and filtrating by suction filtration paper. Then derivative (a) can recover by following acidification of the filtrate using HCl.

By using this procedure, we were found that, the yield of amidine (b) was increased by increasing the molar amount of ammonia solution, which was added to the rodanide (**3**). This experimental result shows that, to increase the yield of thiourea derivative (a) the amount of ammonia solution in the reaction mixture should be controlled.

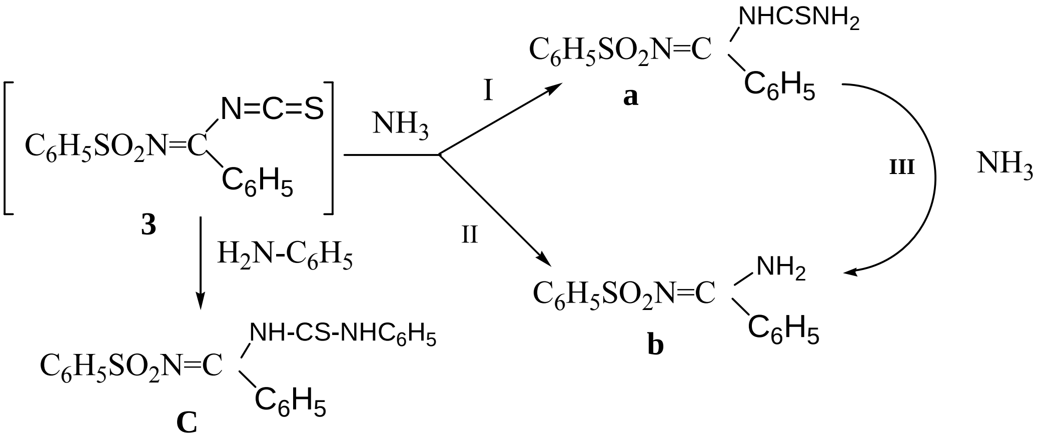
Table 6. % yield of compound **a** and **b** in different volume of ammonia solution

Exp.no	V. in ml	% yield cpd **a**	% yield cpd **b**
1	1.75	42	32
2	2	51	44
3	2.5	27.5	63
4	3	24	68

But even when the amount of ammonia taken was controlled, the yield of thiourea derivative (a) was not satisfactory, and amidine (b) was still formed. In addition to this, when the amount of ammonia solution was limited, there was some amount unreacted rodanide (**3**) in the reaction mixture left. Amount of unreacted rodanide (**3**) was controlled in the following way:

After reacting rodanide (**3**) with limited amount of ammonia solution, the solid sediment was filtrated out and washed with benzene to remove unreacted rodanide (**3**) which was absorbed in sediment part. Then yellow benzene layer of rodanide (**3**) in the filtrate was separated by separator funnel and treated with excess of aniline. Due to this, sediment of N-benzenesulphonyl-benzimidoyl-N-phenyl thiourea (c) (scheme **10**) was formed. Based on this principle the amount of desired derivative formed was calculated and, also the following conclusion was made:

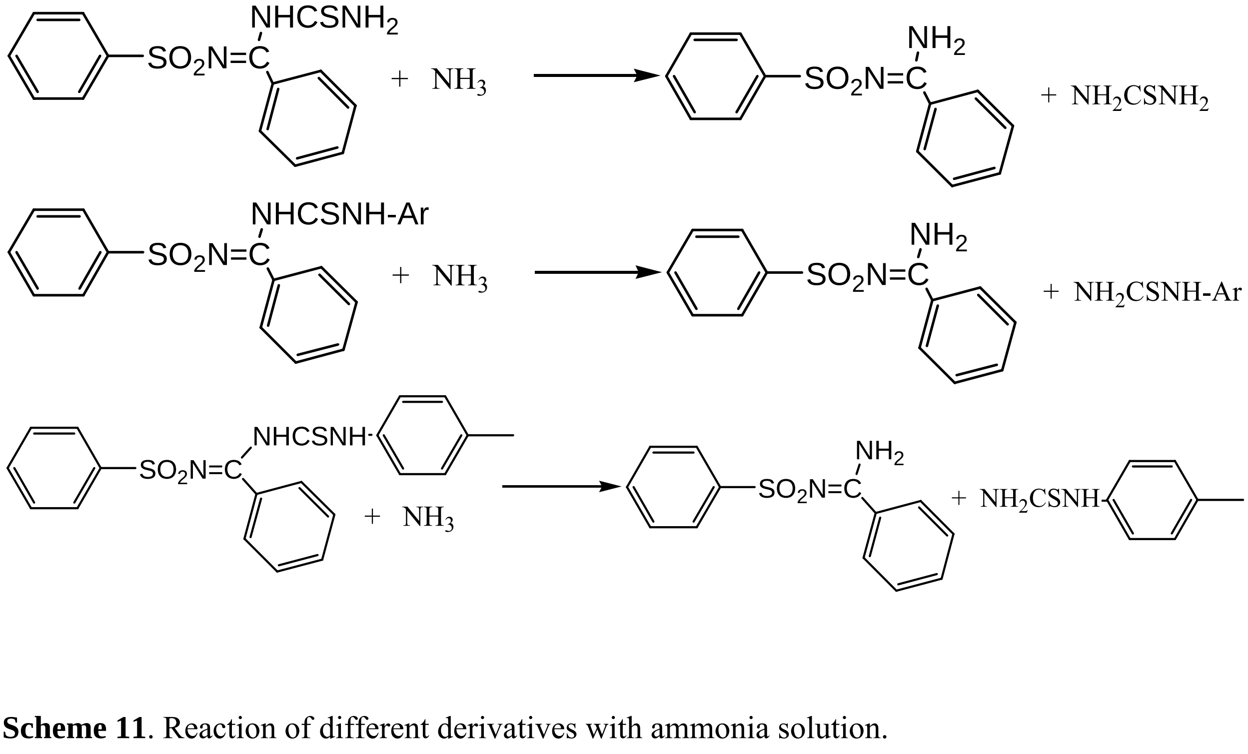
Presence of unreacted rodanide (**3**) even in case of using slightly excess ammonia solution, path I product formation is slow and reaction of path III in which amidine (b) formed was faster (scheme 11). In the presence of slight excess of ammonia solution, amount of amidine (b) formation increased.



Scheme 10. Formation of different product from intermediate **3**

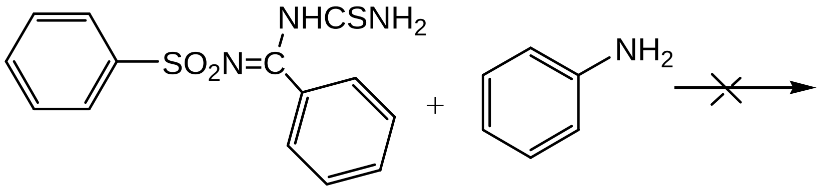
4.2. Reaction of ammonia solution with thiourea derivatives.

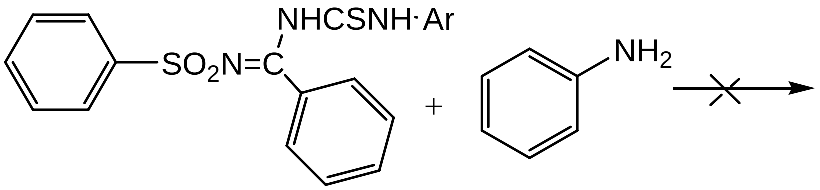
To check whether the experimental result of procedure 1 was visible or not the following experiment has been done.



Scheme 11. Reaction of different derivatives with ammonia solution.

This experimental results show that the idea explained under the title of 5.2 was correct and presence of excess ammonia causes to cleavage of the derivatives into amidine (b).
But, when the derivatives reacted with aromatic amine (less nucleophiles) cleavage were not occurred. This experimental result proved that why the yield of aromatic amine containing thiourea derivatives was so high.





Based on these facts, we were tried to produce thiourea derivatives by reacting rodanide (3) with aliphatic amines using their salts to decrease their strength of basicity of aliphatic amines. **Note** to obtain good yield, addition of $NaHCO_3$ solution to the reaction mixture should be done carefully to protect the high concentration of free amines. Other wise that free amine will react with produced derivatives and converted into amidine.

4.3. Reaction of Secondary Amines with Rodanide (3)

Because of shortage of primary amines and even some desired secondary amines, we did some experiments on available secondary amines. Using such relatively strong amines (diethyl amine and dimethyl amine) two experiments was done. The first experiment was done using diethyl amine salts, and this salt was produced through neutralization reaction of diethylamine with hydrochloric acid.

1. Procedure

0.005 mol of diethyl amine salt was intermixed with rodanide (3) solution by using $NaHCO_3$ solution to dissolve the salts and to control amount of free diethyl amine in the solution. Finally, the yellow oily solution was obtained after diluted the reaction mixture with water. And this oily was not solidified even after couple of weeks. Due to this reason the final product could not identified. The result of no solidification may be due to the bulky diethyl amino group. Due to this reason we did another experiment using dimethyl amine (Procedure 2) which is relatively small steric problem

2. Procedure

To rodanide (3) 0.005 mol of dimethylamine salt was added and intermixed by adding 5 ml of $NaHCO_3$ solution drop by drop for 30 min. when 2 ml of $NaHCO_3$ was added, sediment formation was started and the yellow color of the solution was slightly changed in to orange color. After intermixing for 1hr the sediment formed was changed into oily and the color was also changed back to yellow. After 2 hrs intermixing oily was solidified. Gently, reaction mixture was diluted with water and intermixed for 30 min. The sediment was filtrated out and its melting point was 114-120°C. On Next day, the sediment was melted on sample holder and melting point of the residue was reduced to 93 °C. From sediment part, sample was taken for IR and NMR, but the spectra obtained did not match with expected one. This indicates that the expected product may be lost due to decomposition of dimethyl amine containing thiourea derivatives at room temperature. Similar decomposition was observed in another case when we were trying to remove trace solvents (acetic acid) from compound **4** which has melting point 181 °C. But when this sample was kept in the oven for 3 hrs at temperature 116 °C, this high melting point compound was converted to oily. The oily was soluble in CCl_4 but compound 4 is insoluble CCl_4. there for the obtained oil was due to decomposition.

4.4. Reaction of amino acid (glycine) with Rodanide (3)

Due to inner salt formation, amino acid is practically non soluble in most organic solvents, even in DMF. So in this reaction $NaHCO_3$ was used to dissolve it and to continue the reaction using amino acid (glycine).

Procedure

To rodanide (3) solution 0.005 mol of glycine (together with soda solution) was added and intermixed using magnetic stirrer for 15 min. during this time the yellow color was start to convert in to orange color. After 10 min 10 drops of water was added to the reaction mixture to increase the solubility of glycine. The sediment of inorganic salt still present. After 15 min additional 10 drops of water was added and the orange color was not changed. In each 15 min interval 10 drops of water was added 4 times and, during this time, all inorganic sediment was dissolved and clear red-orange solution was appeared. Intermixing was continued for 4hrs and after this white fine sediment was started to form. It filtrated out using suction filtration paper and the sediment was washed on the filter paper with propanol. Then the product was recrytalized by methanol and a drop of DMFA. Then the production of this glycine containing thiourea derivative (compound 8) was supported by IR and NMR data.

4.5. Spectral Data

Compound 4; colorless solid, yield: 78%; m.pt. 178-180^{0}C; and. IR ν_{max} (KBr) cm^{-1}**,** 3186 (NH), 2996 (CH_3), 1608 (N=C), 1323, 1160 (SO_2) ; ^{1}H NMR (400MHz, $CDCl_3$): 2.4 (3H, s, CH_3), 7.12 (Ar-H), 7.23 (Ar-H), 7.53 (Ar-H), 7.64(Ar-H), 7.71 (Ar-H), 7.79 (Ar-H), 8.48 (NH), 12.5 (NH); ^{13}C NMR (400MHz, $CDCl_3$), 21.08 (Ar-CH_3), 131.97 (Cq), 134.69 (Cq), 136.81 (Cq), 141.44 (Cq), 161.87 (C=N), 175.85(C=S), 122.65 (CH_{Ar}), 126.88 (CH_{Ar}), 127.67 (CH_{Ar}), 128.99 (CH_{Ar}), 129.19 (CH_{Ar}), 129.34 (CH_{Ar}), 132.73 (CH_{Ar}), 132.98 (CH_{Ar}).

Compound 5; colorless solid, yield: 83%; m.pt. 182-183^{0}C; and. IR ν_{max} (KBr) cm^{-1}**,** 3188.59(NH), 3029.99 (ArH), 2918(CH_3), 1610.78 (N=C), 1321.82, 1160.80 (C-SO_2) ; ^{1}H

NMR (400MHz, $CDCl_3$): 2.24 (3H, s, Ar$\underline{CH_3}$), 7.24 (Ar-H), 7.29 (Ar-H), 7.36 (Ar-H), 7.60(Ar-H), 7.63 (Ar-H), 7.70 (Ar-H), 7.75 (Ar-H),8.48 (NH), 12.5 (NH); ^{13}C NMR (400MHz, $CDCl_3$), 21.60 (Ar-CH_3), 131.89 (Cq), 137.29(Cq), 138.56(Cq), 141.01(Cq), 161.78 (C=N), 176.03(C=S), 122.67(CH_{Ar}), 126.76 (CH_{Ar}), 126.96 (CH_{Ar}), 127.96(CH_{Ar}), 128.73 (CH_{Ar}), 128.94 (CH_{Ar}), 129.77 (CH_{Ar}), 132.71(CH_{Ar}).

Compound 6; colorless solid, yield: 75%; m.pt. 187-190^{0}C; and. IR ν_{max} (KBr) cm^{-1}**,** 3309.64, 3226.18(NH), 3059 (ArH), 2980(Ar$\underline{CH_3}$), 1606.35 (N=C), 1313.64, 1152.04 (C-SO_2) ; ^{1}H NMR (400MHz, $CDCl_3$): 2.24 (3H, s, Ar$\underline{CH_3}$),2.5 (3H, s, Ar$\underline{CH'_3)}$, 7.12 (Ar-H), 7.23 (Ar-H), 7.29 (Ar-H), 7.55(Ar-H), 7.63 (Ar-H), 7.70 (Ar-H), 7.76 (Ar-H),8.39 (NH), 12.53 (NH); ^{13}C NMR (400MHz, $CDCl_3$), 21(Ar-CH_3), 21.60(Ar-CH_3') 131.97 (Cq), 134.75(Cq), 136.76(Cq), 138.58(Cq), 143.94(Cq), 161.72 (C=N), 175.95(C=S), 122.71(CH_{Ar}), 126.92 (CH_{Ar}), 127.9(CH_{Ar}), 128.92(CH_{Ar}), 129.29 (CH_{Ar}), 129.73 (CH_{Ar}), 132.66(CH_{Ar}).

Compound 7; colorless solid, yield: 51%; m.pt. 195-197^{0}C; and. IR ν_{max} (KBr) cm^{-1}**,** 3315.57(NH), 3212, 3168 (NH_2), 3029.99 (ArH),1603.94 (N=C), 1323.4 1163.94 (C-SO_2) ; ^{1}H NMR (400MHz, $CDCl_3$): 2.62 (2H, s, NH_2), 6.75 (Ar-H), 6.79(Ar-H), 6.82 (Ar-H), 6.9(Ar-H), 6.95 (Ar-H), 12.5 (NH); ^{13}C NMR (400MHz, $CDCl_3$), 131.6 (Cq), 141.04(Cq), 163.18 (C=N), 181.07(C=S), 125.99(CH_{Ar}), 127.25 (CH_{Ar}), 127.69(CH_{Ar}), 128.46(CH_{Ar}), 130.70 (CH_{Ar}), 132.15 (CH_{Ar}).

Compound 8; colorless solid, yield: 69%; m.pt. 203-206^{0}C; and. IR ν_{max} (KBr) cm^{-1}**,** 3206 (NH), 3058 (ArH), 2965 (CH_2),1769(C=O),1606 (N=C), 1312, 1142 (C-SO_2) ; ^{1}H NMR (400MHz, $CDCl_3$): 4.4 (2H, s, $\underline{CH_2}$CO), 3.48(1H,s, NH), 7.2 (Ar-H), 7.45(Ar-H),7.65 (Ar-H), 7.78(Ar-H), 11 (C-OH), 11.5 (NH); ^{13}C NMR (400MHz, $CDCl_3$), 47.55 (CH_2), 132.4(Cq), 144.1(Cq). 164(C=N),170(C=O),180 (C=S), 126.87(CH_{Ar}), 128.14 (CH_{Ar}), 128.56(CH_{Ar}), 129.48(CH_{Ar}), 131.57(CH_{Ar}), 133.22 (CH_{Ar}).

5. Conclusion

The synthesis and chemical property studies of N-arenesulphonyl-benzimidoyl-N’-thiourea derivatives have been described. Reactivity of rodanide (**3**) with amines of different bascity reveled the following points: aromatic amine containing derivatives which have less bascity relative to aliphatic amines were produced with good yield. By reacting limited amount of ammonia solution the corresponding thiourea derivatives was produced. But when excess of ammonia was used in reaction, the already produced thiourea derivative was converted into corresponding N-Arylsulphonyl-benzimidoyl amidine through consecutive reaction.

A thiourea derivative, which was produced by reacting rodanide (**3**) with amino acid (glycine), can be used as analytical reagent because it contains thoino and carboxyl groups together with sulphonamide group.

Aliphatic amines (diethyl amine and dimethyl amine) react with rodanide (**3**), but the final structures were not determined due to oily formation.

6. References

1. Richard b. Silverman, *the organic chemistry of drug design and drug action*, Second Edition, Elsevier Academic Press, **2004**, 234-235.

2. http://en.wikipedia.org/wiki/sulfonamide_(medicine)

3. Thomas M. Devlin, *Textbook of Biochemistry*, Fifth Edition, Wiley-liss, New York, **2002**, 434.

4.http://www.chemicalland21.com/info/SULFONAMIDE%20CLASS%20ANTIBIOTICS.htm

5. Dr. J.K.Grover, *Text Book of Pharmacology for Nursing*, **1989**, 317-320

6. Wallach O., Gossman A.Chem. *Ber*. **18978**, 11, 753-755

7. Burmistrov S.I., Dubina V.L., *J. Ukr.Chem.*, 1966, 32**,** 12, 1323-1325

8. Bretschneider H. and Klotzer, W. Monatsh, **1956**,. **87,** 47-59; C.A.**50**, 15542i.

9. Burmistrov S.I., Dubina V.L., Arenesulphonyl-lactilamides, *J.Ukr.Chem.,* **1964**, 30, 7, 742-744

10.Dubina V.L., Schebitchenko L.N., Pedan V.P., Yuhno A.G. Skripets V.L., *J. Org. Chem. (Russ.),***1982**, 18, 4, 793-799

11. Wallch O., Gossman A., *Chem. Bar*. 1878, **11,** **s.**753-755.

12. Burmistrov S.L. and Dubina V.L, *J. Org. Chem. (Russ.)***1966**, 2, 10, 1845-1848

13. Dubina V.L, Burmistrov S.L. and Levchenko N.I., *J. Org. Chem. (Russ.)*, **1967**, 3, 11, 2024-2027

14. Burmistrov S.L., Dubina V.L, Ishuk Y.N., Emel'yanova V.S., *J. Org. Chem. (Russ.),***1967**, 5, 2, 263-268.

15. Burmistrov S.L., Dubina V.L, Biba A.D., *J. Org. Chem. (Russ.),***1968**, 10, 29.

16. Klimkovich E.A., Usatenko Yu.I., Levchenko N.I., Dubina V.L, *Chem. and Chem. Technology*, **1975**, 18, 546-550.

17. Dubina V.L, Usatenko Yu.I J., Klimkovich E.A. *Chem. and Chem. Technology*, **1974**, 35, 4, 66-69

18. Angela Casini,Andrea Scozzafava, Claudiu T Supuran, Sesto Fiorentino, Florence, Italy. **2002**, 12, 9, 1307-1327

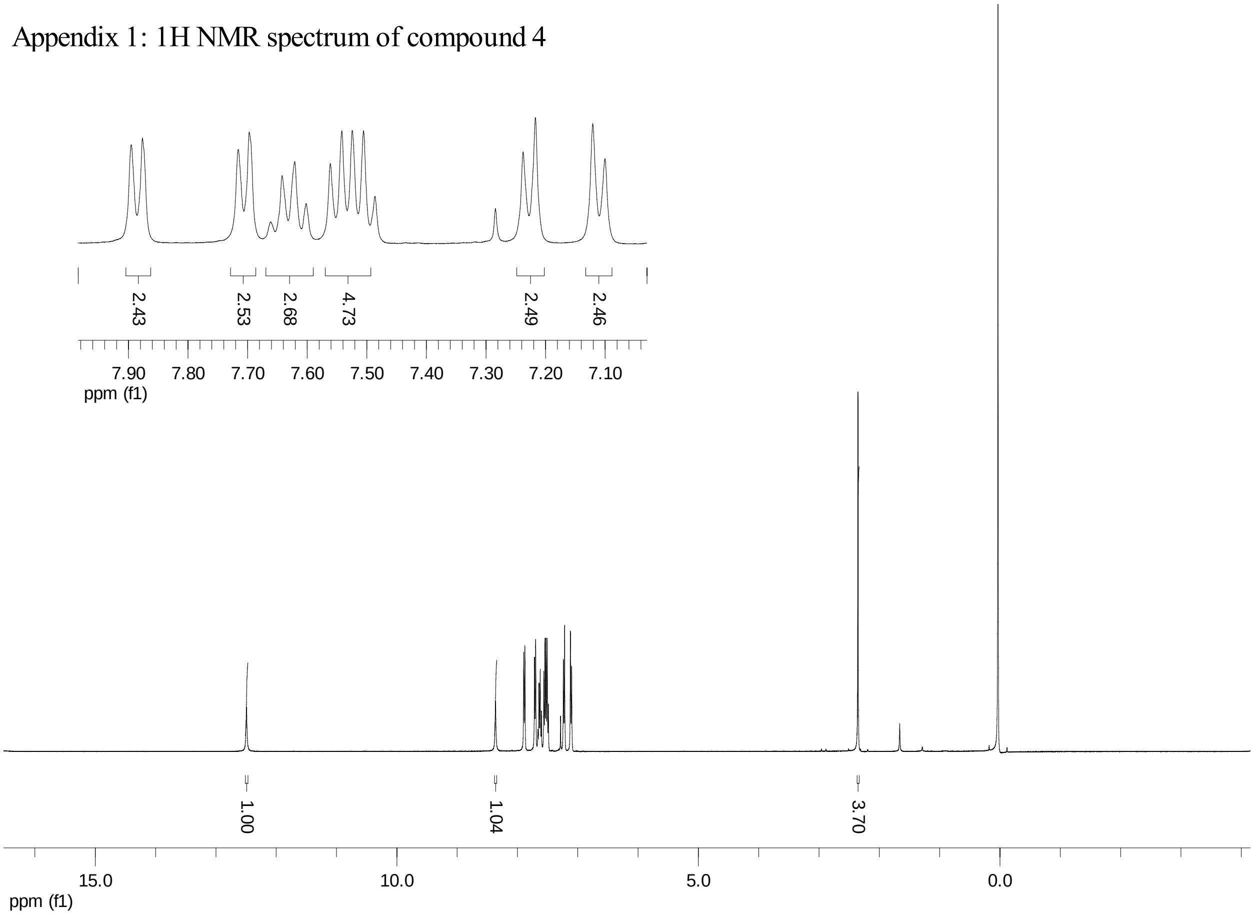
19. Walid M. Fathalla, Michal Cajan, Jaromir Marek and Pazdera, *Molecules,* **2001**, 6,574-587.

20. Walid M. Fathalla and Pazdera, *Molecules*, **2002**, 7, 96-103.

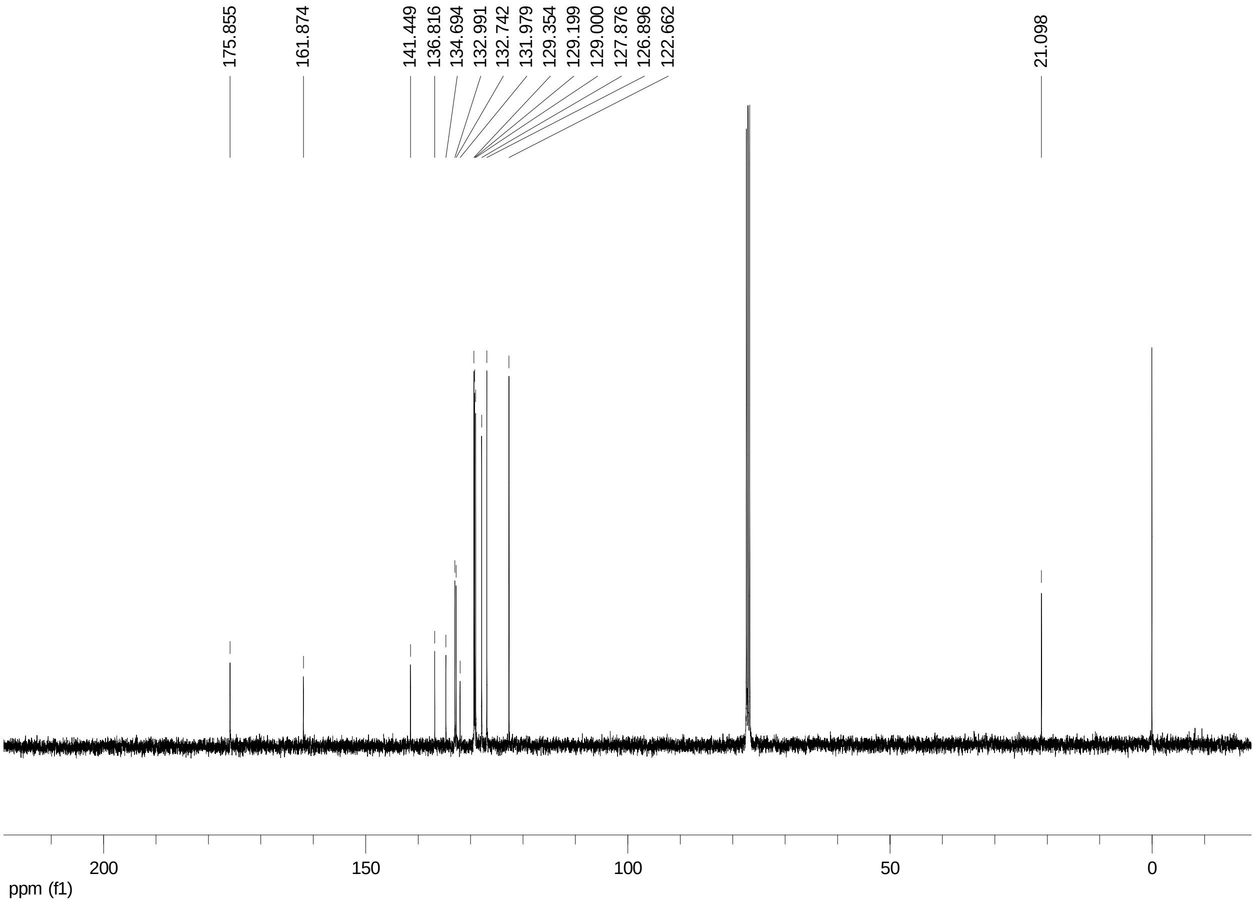
21. Rakesh B. Patel, Kishor H. Chikhalia, Christophe Pannecouque and Erik de Clercq *J.Braz.Chem.Soc*. **2007**, 18, 2, 312-321.

22. Osmond J.D Cruz and Faith M.Uckun, *European Society of Human Reproduction And Embryology*, **2005**

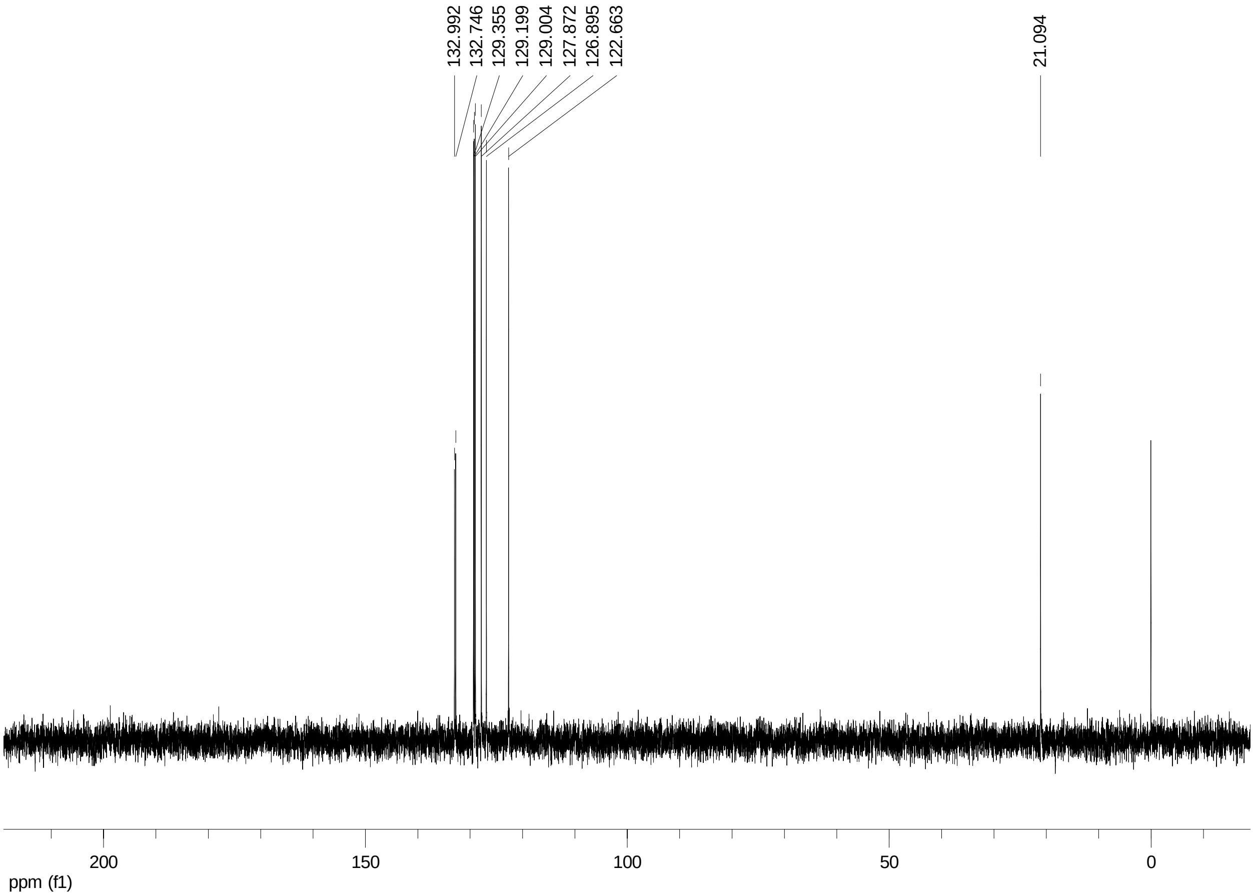
Appendix 1: 1H NMR spectrum of compound 4



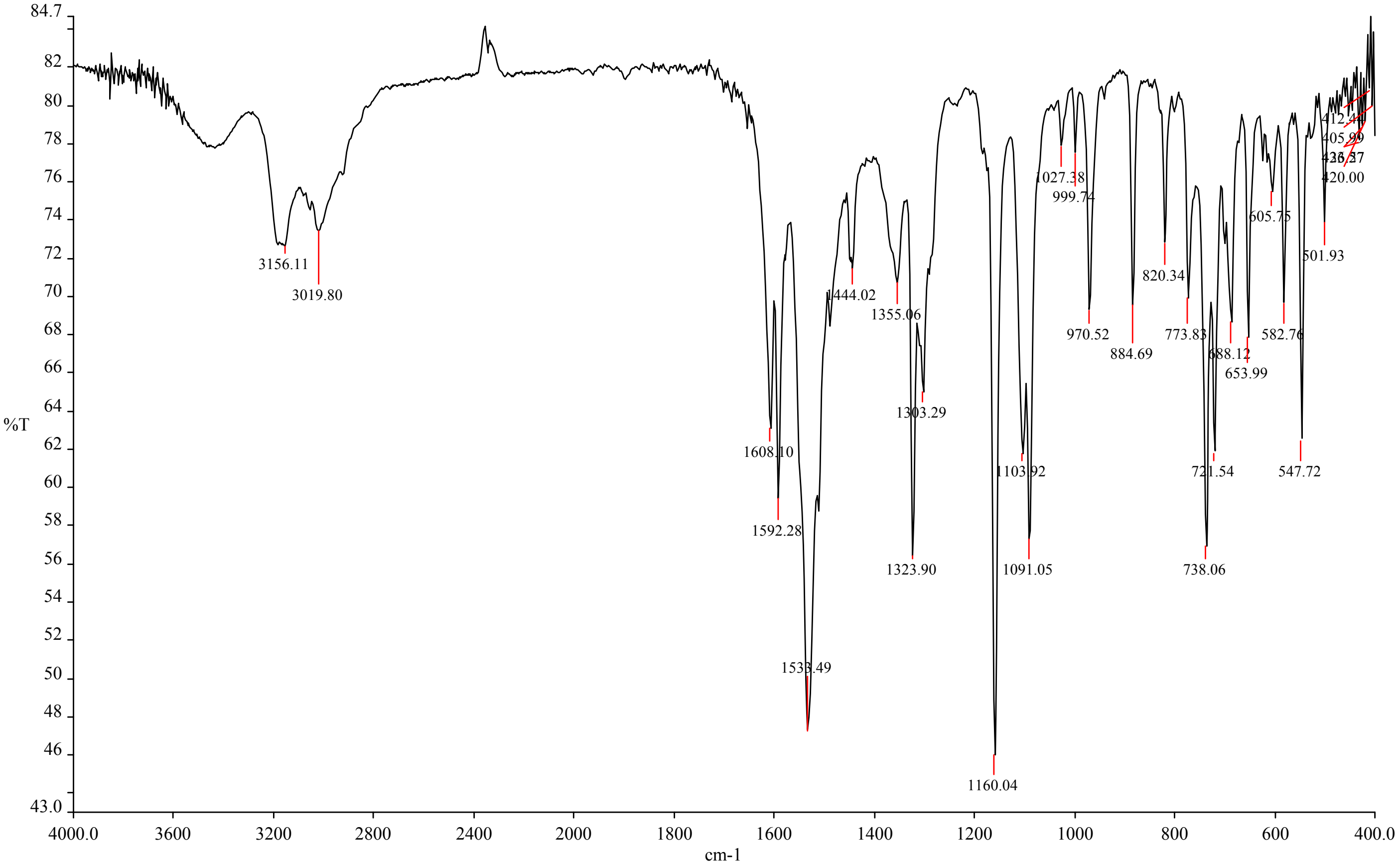
Appendix 2: 13C NMR spectrum of compound 4



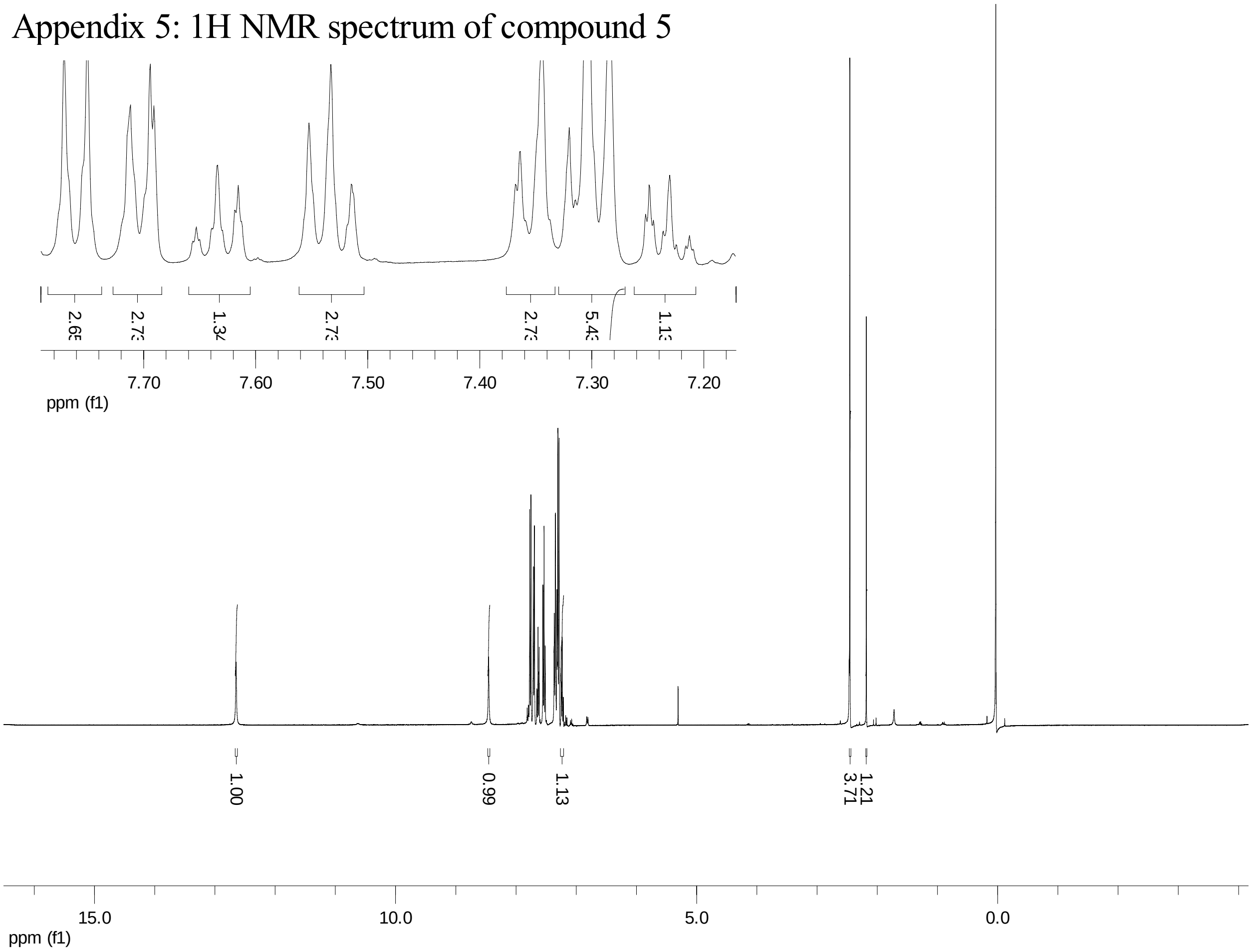
Appendix 3: DEPT-135 NMR spectrum of compound 4



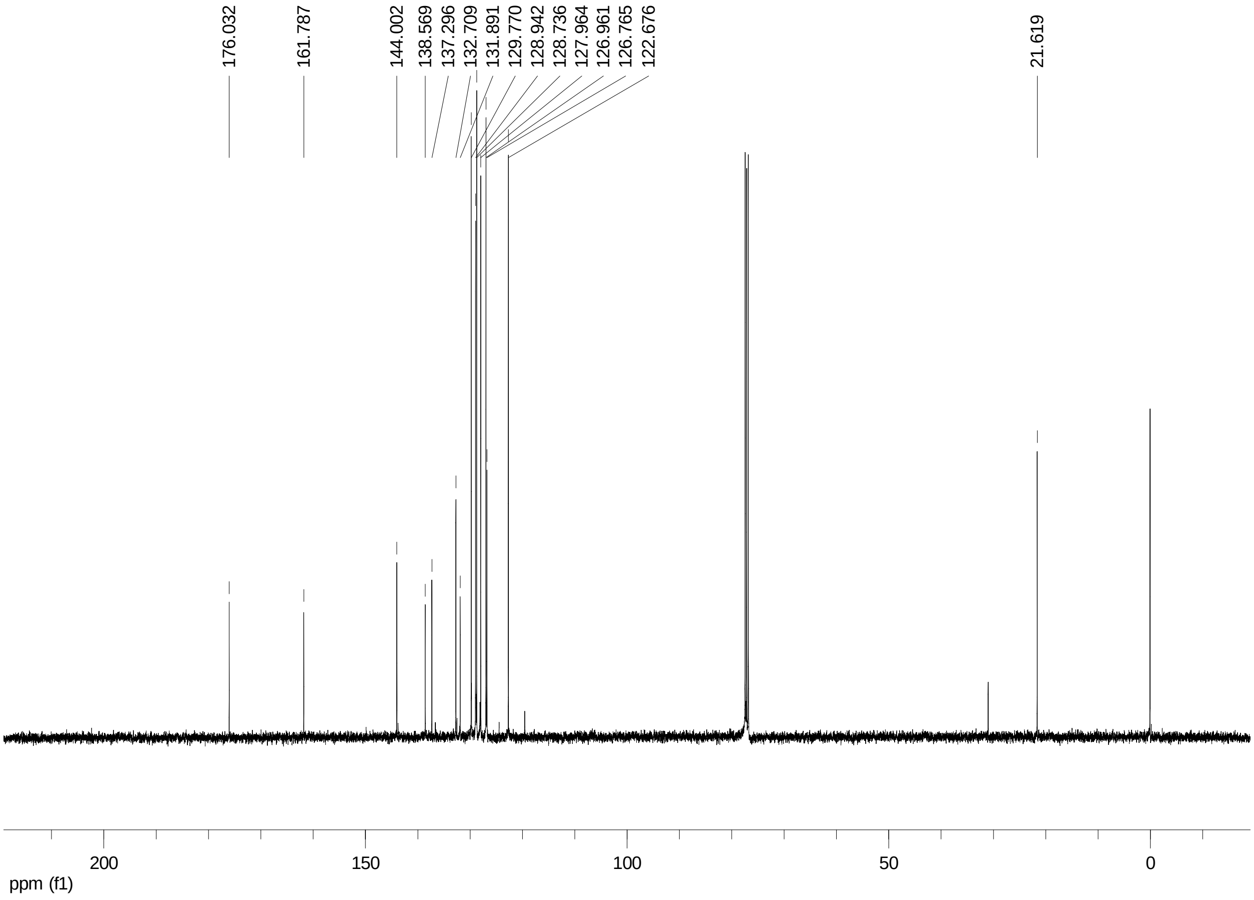
Appendix 4: IR (KBr) spectrum of compound **4**



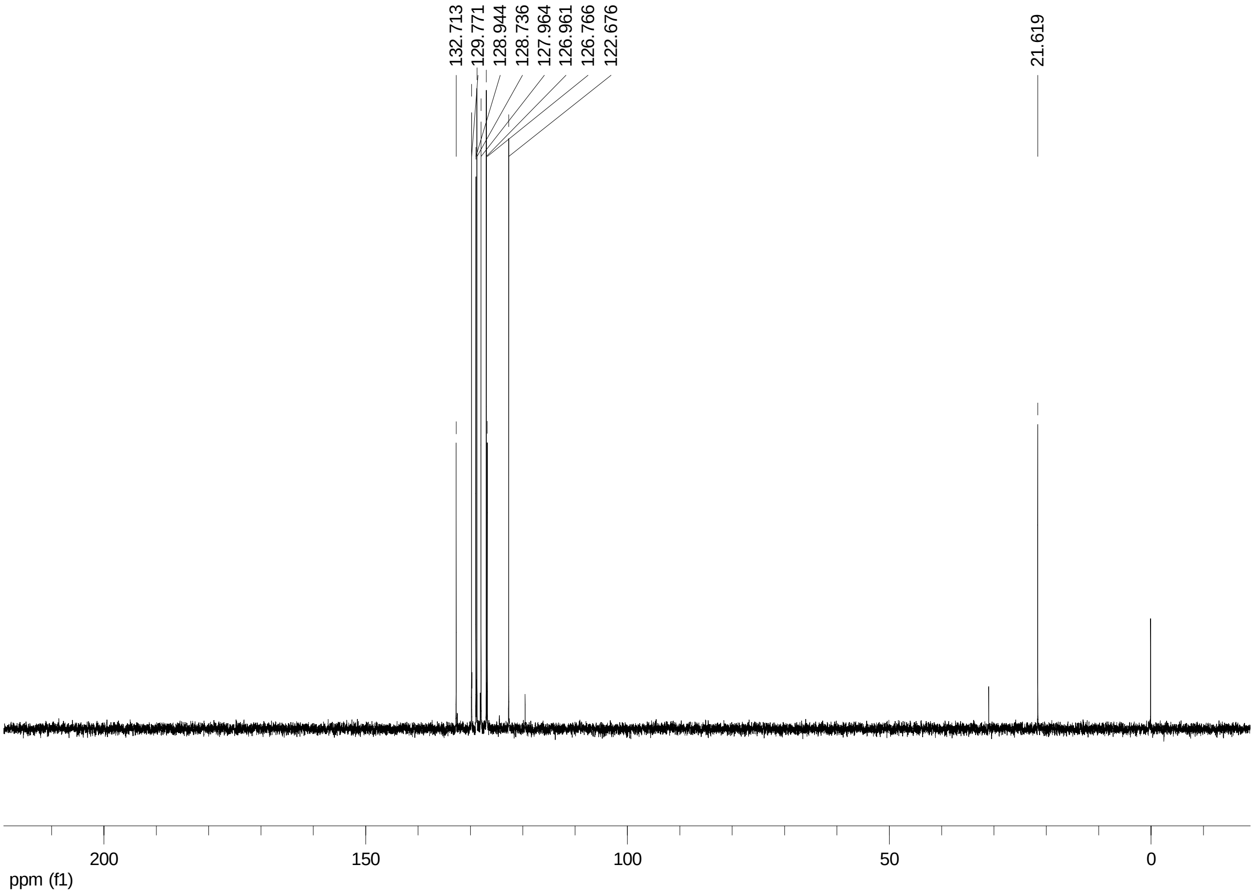
Appendix 5: 1H NMR spectrum of compound 5



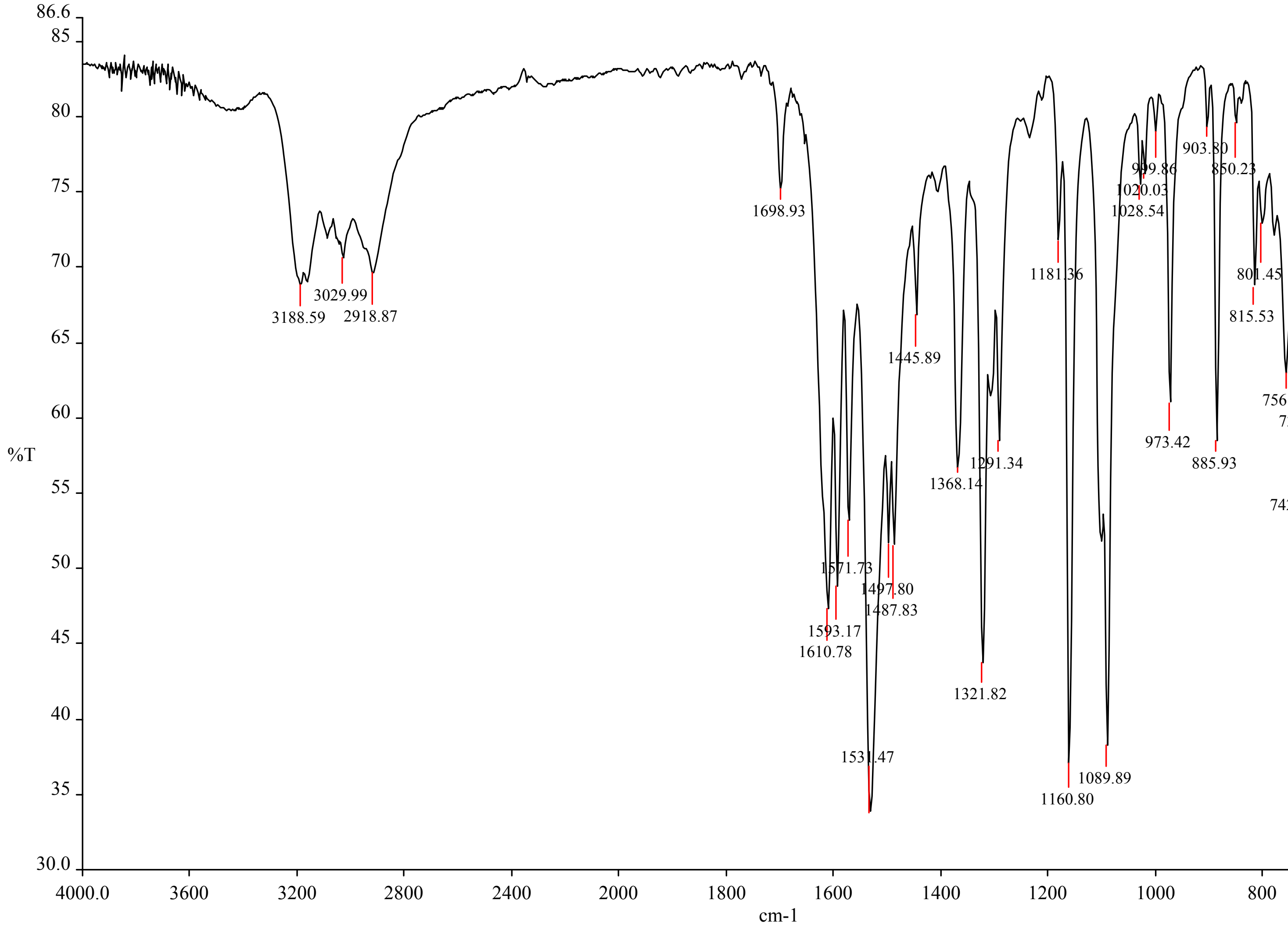
Appendix 6: 13C NMR spectrum of compound 5



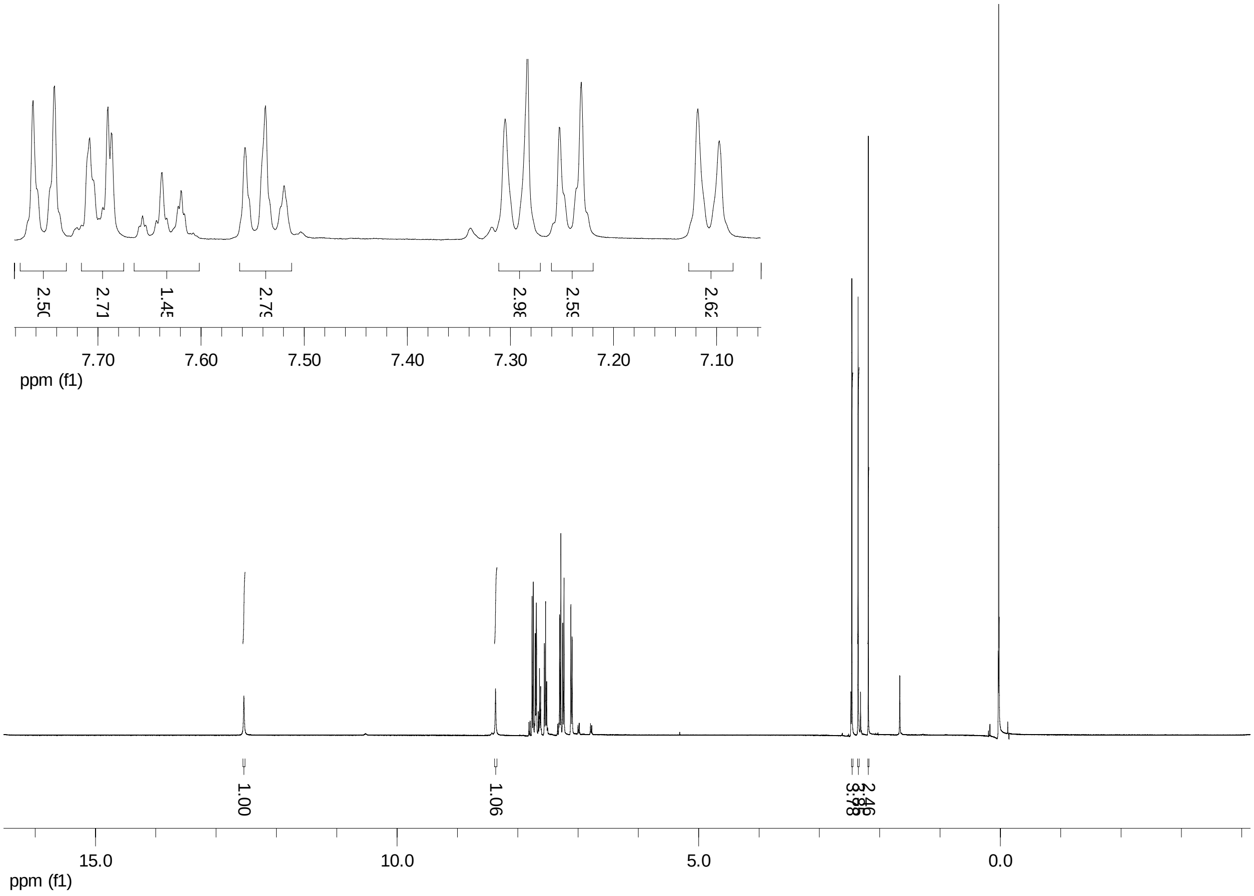
Appendix 7: DEPT-135 NMR spectrum of compound 5



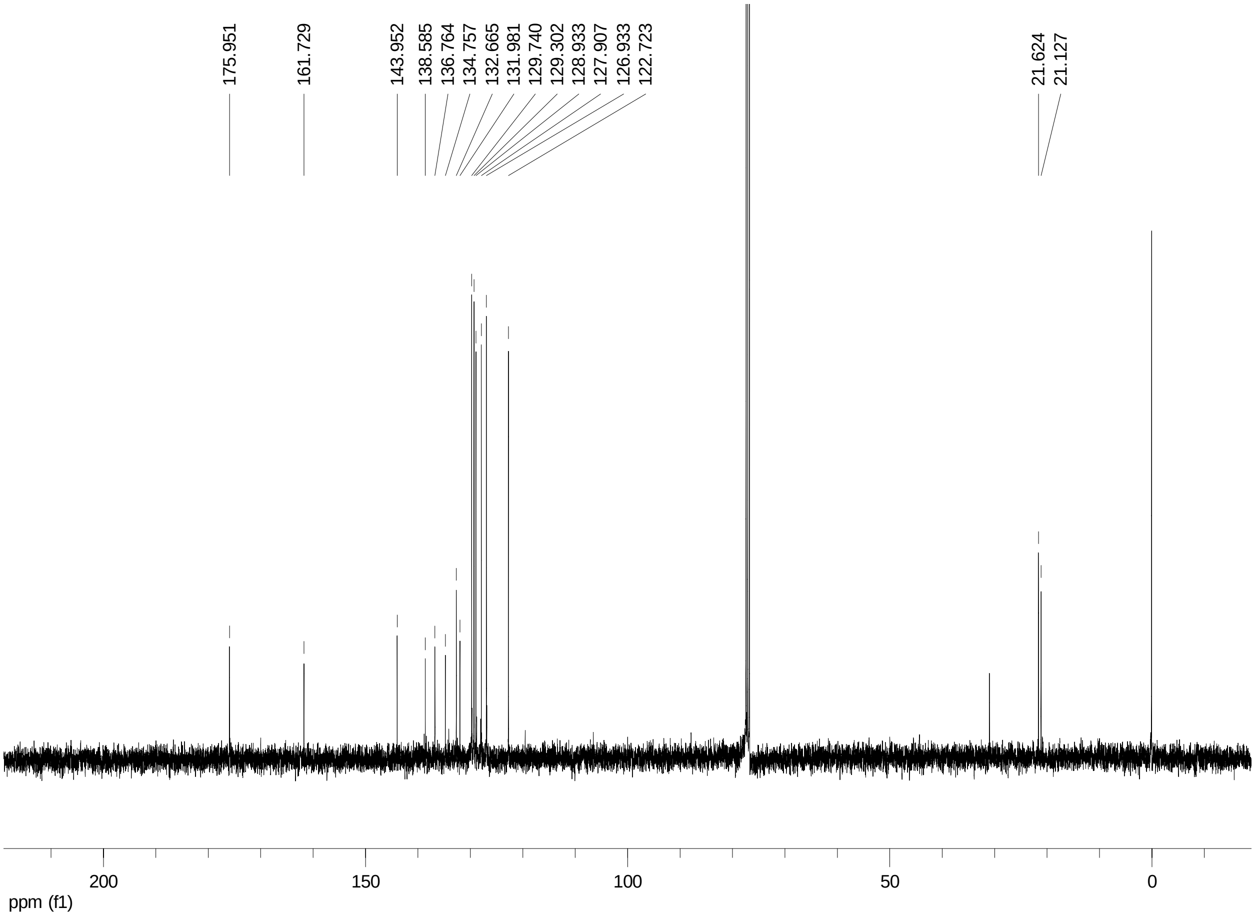
Appendix 8: IR (KBr) spectrum of compound **5**



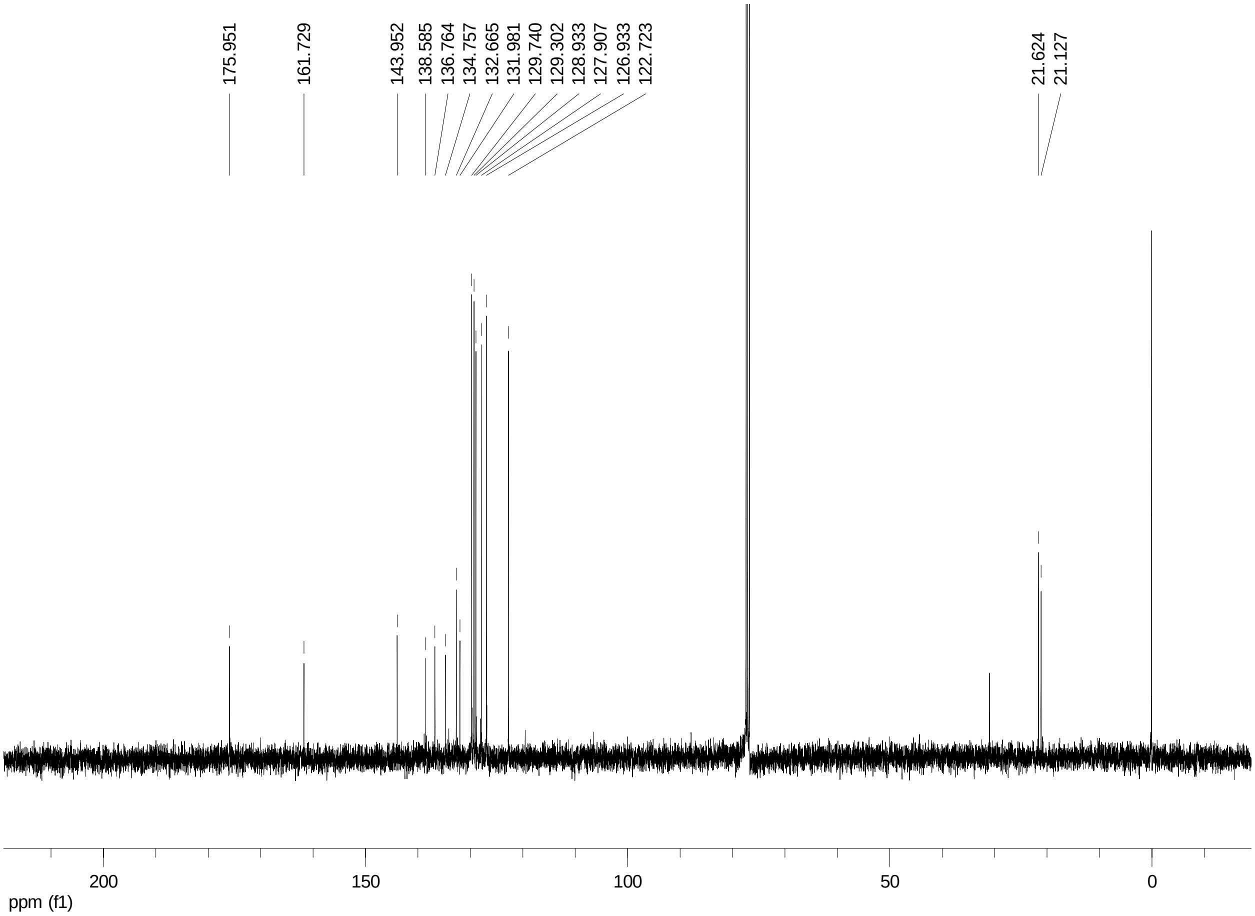
Appendix 9: 1H NMR spectrum of compound 6



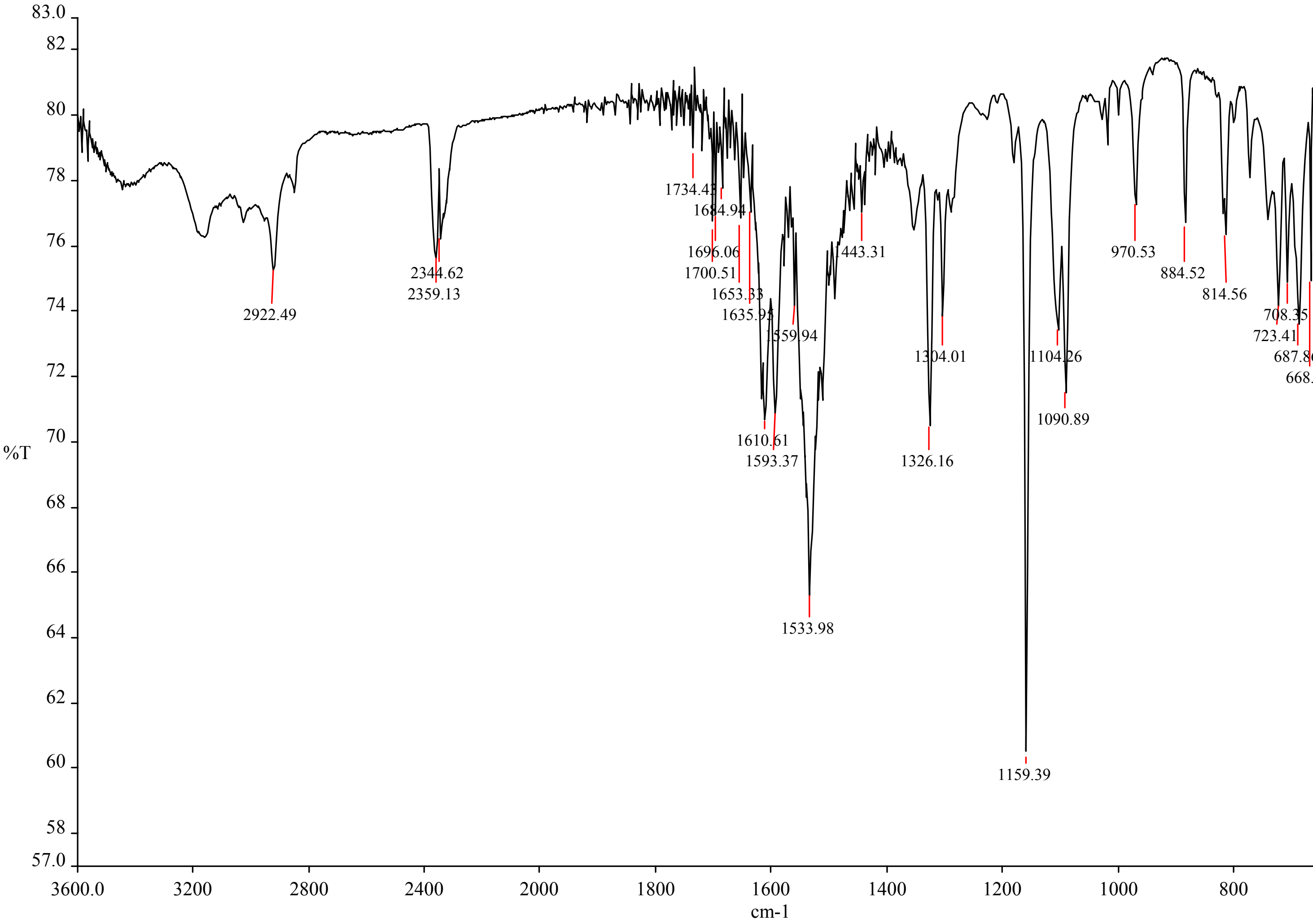
Appendix 10: 13C NMR spectrum of compound 6



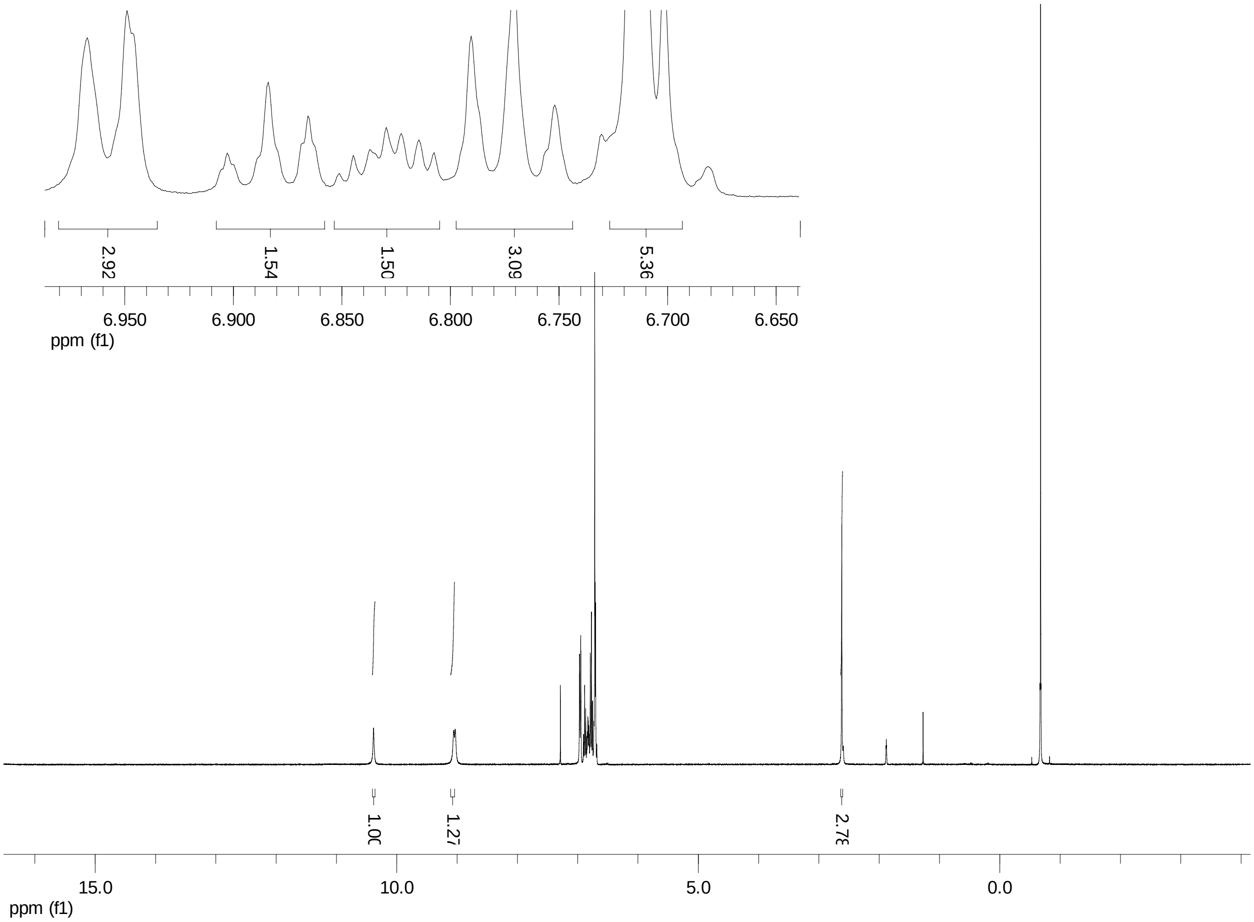
Appendix 11: DEPT-135 NMR spectrum of compound 6



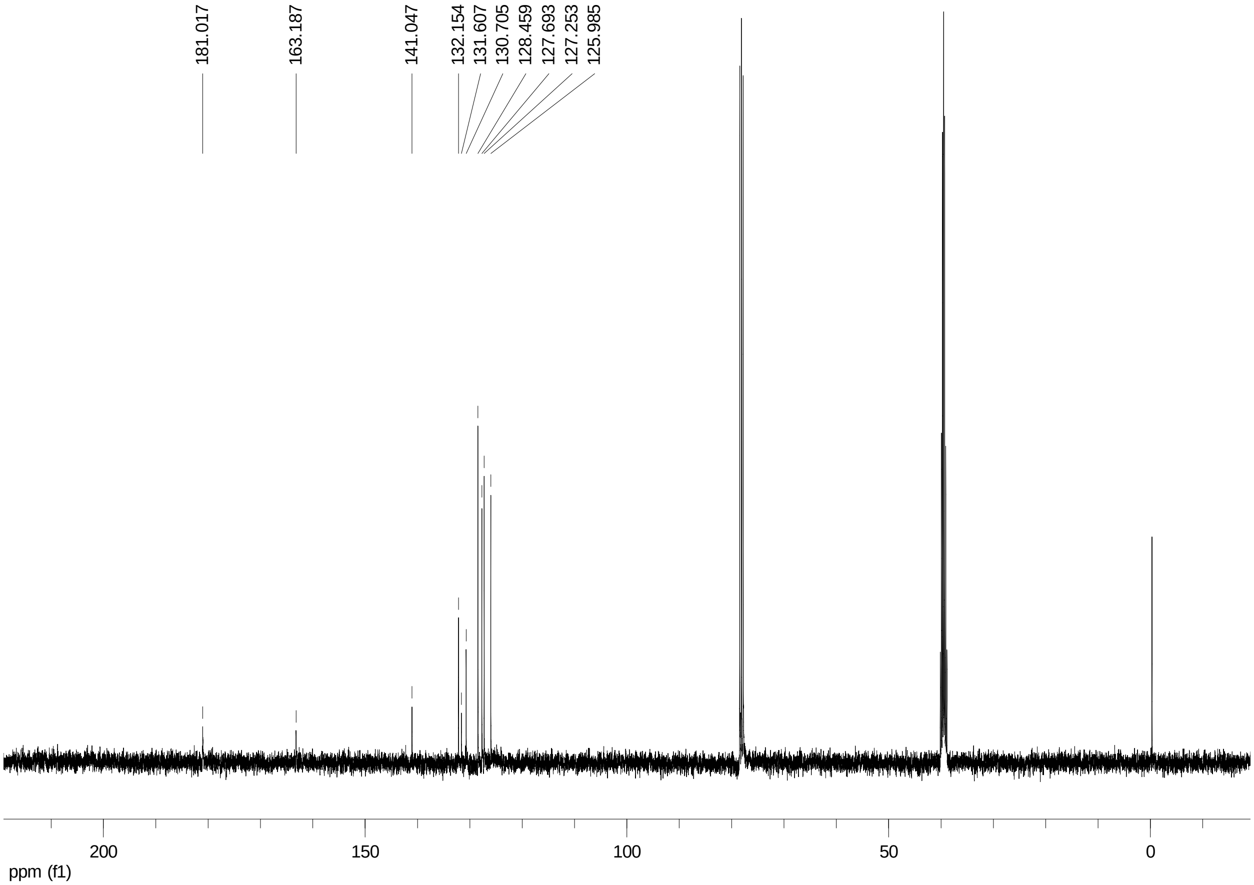
Appendix 12: IR (KBr) spectrum of compound **6**



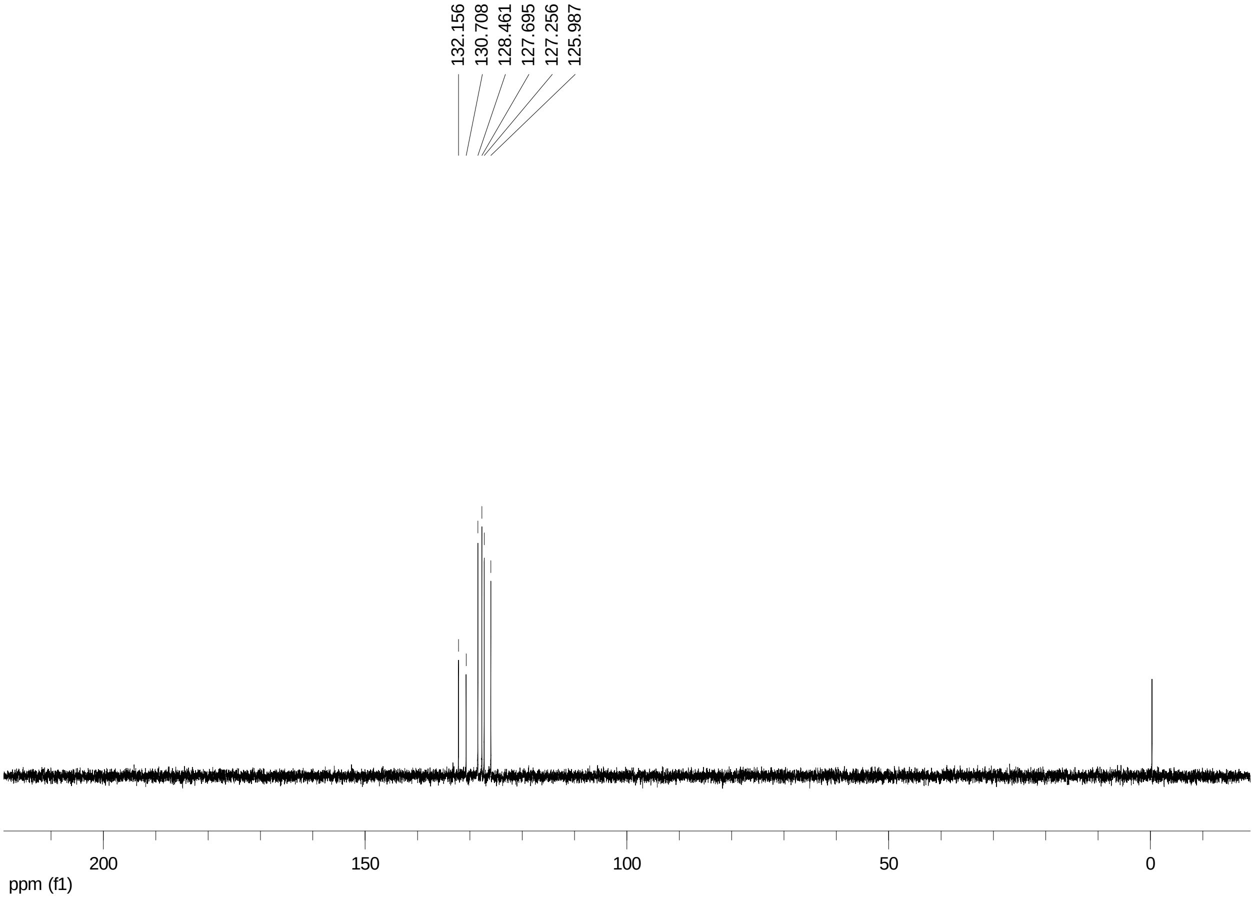
Appendix 13: 1H NMR spectrum of compound 7



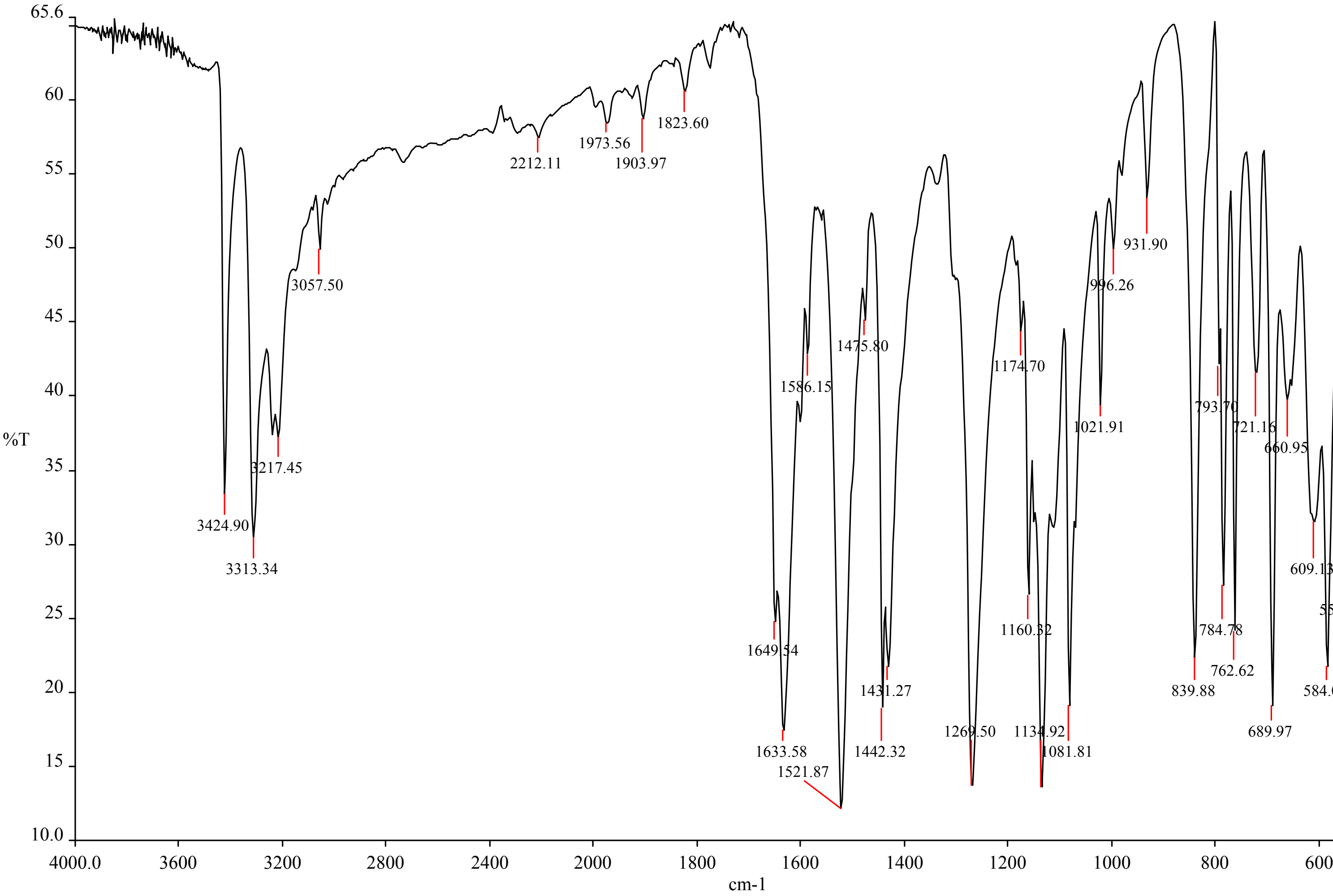
Appendix 14: 13C NMR spectrum of compound 7



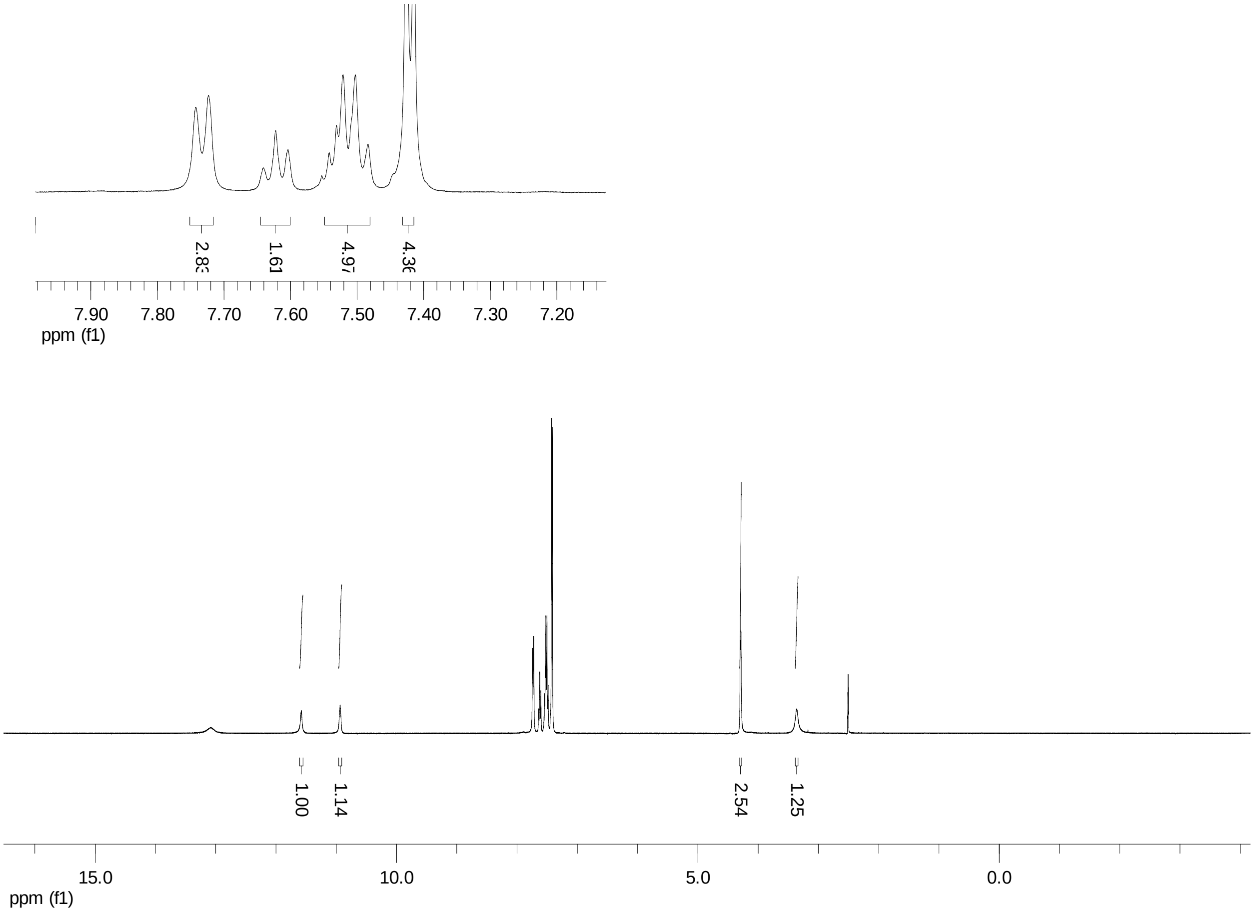
Appendix 15: DEPT-135 NMR spectrum of compound 7



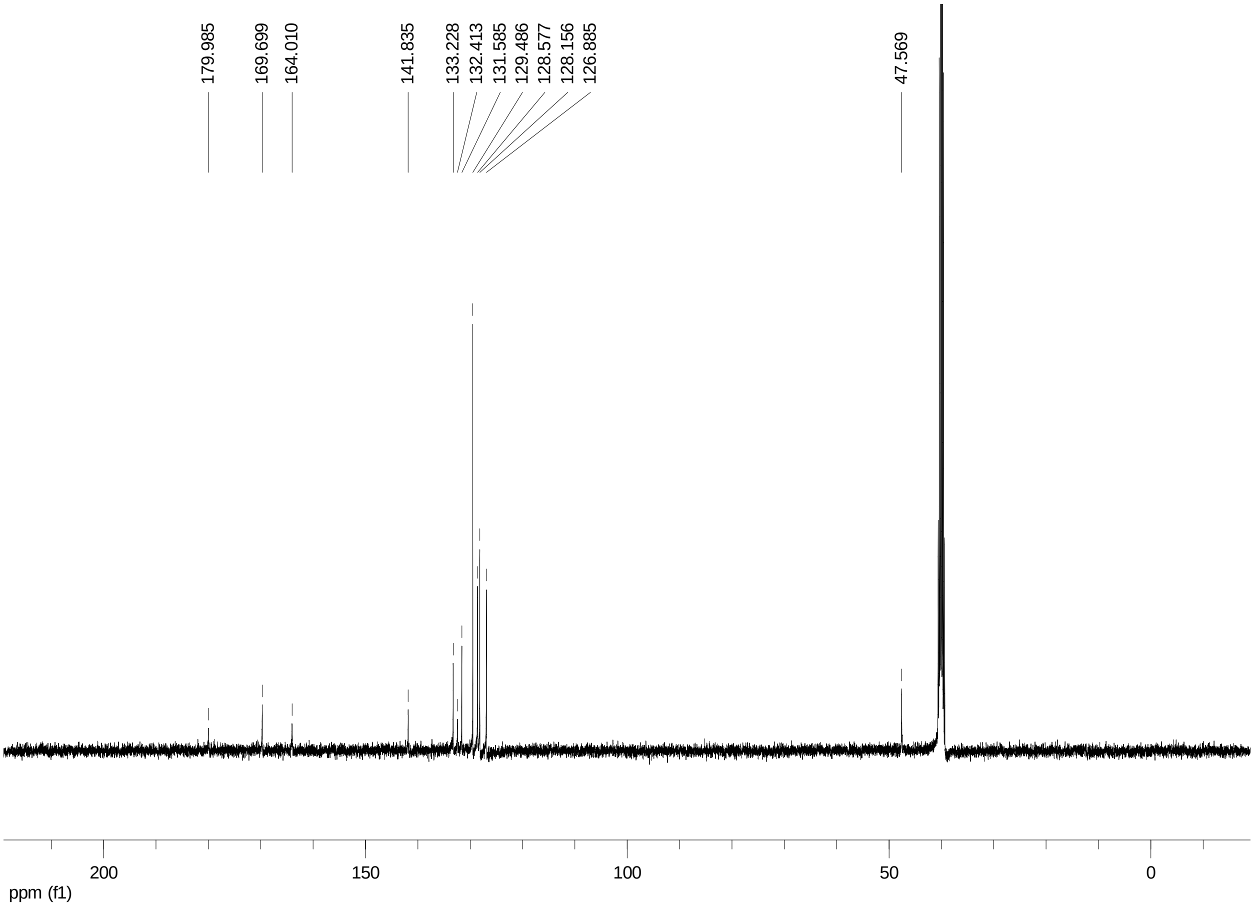
Appendix 16: IR (KBr) spectrum of compound **7**



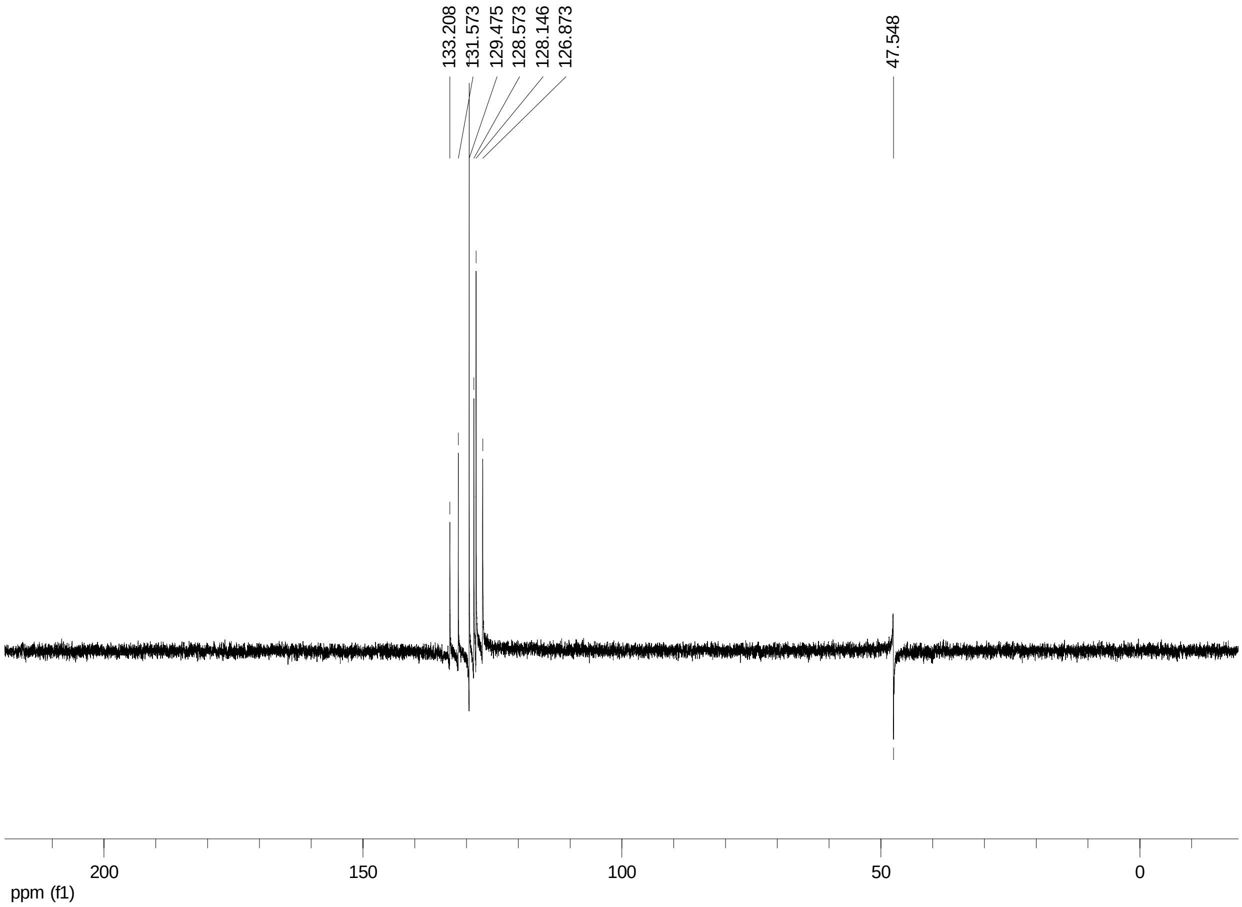
Appendix 17: 1H NMR spectrum of compound 8



Appendix 18: 13C NMR spectrum of compound 8



Appendix 19: DEPT-135 NMR spectrum of compound 8



Appendix 20: IR (KBr) spectrum of compound **8**