

## Synthesis and Characterization of New Saccharin Derivatives

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### Abstract

This work involves synthesis of new saccharin derivatives. Compound (1) was synthesized from the reaction of saccharin with ethylenediamine in presence few drops glacial acetic acid, while the reaction compound (1) with phenylisothiocyanate gave compound (2). Acetylation compound (1) produced compound (3). Pyrazole, pyranopyrazole compounds (5,6) were synthesized from the saccharin hydrazine compound (4). Also some of N-alkyl saccharin compounds (7-14) also compounds (17,18) were synthesized from the reaction sodium saccharin with halo compounds as shown in the scheme (2) and scheme (3). Condensation of ethylenediamine in presence few drops glacial acetic acid with compounds (7,11) produced. Compound (15,16). While hydrolysis of compound (17,18) in acetic media gave compounds (19,20). Compound (21) was synthesized from the reaction of compound (17) with hydrazine. Finally, compound (22) was synthesized from the treatment p-chlorobenzaldehyde with compound (21).

**Keywords:** Sweetening agent, saccharin, sulfonamide derivatives

### 1. Introduction

Benzisothiazoles have a much longer history than isothiazoles and 2,1-benzisothiazole was first synthesized in 1898. Saccharin, the best-known 1,2-benzisothiazole derivatives, was first prepared in 1879. Two isomeric forms of benzisothiazole are known, depending on the position of the ring fusion. Benz[d]isothiazole is better known as 1,2-benzisothiazole (1) and benz[c]isothiazole as 2,1-benzisothiazole (2).<sup>1,2</sup>

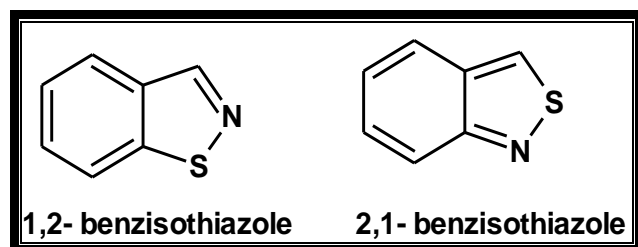


Fig (1): Nomenclature of Benzisothiazoles

The main interest in benzisothiazoles over the years has been the sweet taste of the compound saccharin, 1,2-benzisothiazol-3(2H)-one 1,1-dioxide, its widely used as an artificial sweetening agent, Saccharin modification to aryl sulphonyl urea derivatives is successfully tested as pesticides for many agricultural crops of foodstuff.<sup>3,4</sup>

Five hundred times sweeter than sugar in dilute solution, saccharin has been the subject of many patents

and also much development work aimed at reducing its metallic aftertaste.<sup>5</sup> Its use in drugs, pharmaceuticals and pesticide with modification are cited in many reports.<sup>6</sup>

Extensive research on human populations has established no association between saccharin and cancer. More than 30 human studies have been completed and indicate saccharin's safety at human levels of consumption. These studies include multiple generation of saccharin users.<sup>7,8</sup>

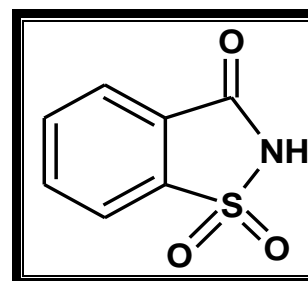


Fig (2): Saccharin

Saccharin has been widely incorporated into a variety of biologically active compounds. The saccharin moiety has been identified as an important molecular component in various classes of 5-HT1a receptors<sup>9</sup>, inhibitors of serine proteases<sup>10</sup>, analgesics<sup>11</sup>, aldehyde dehydrogenase inhibitors<sup>12</sup>, human mast cell tryptase inhibitors<sup>13</sup>, human leukocyte elastase (HLE) inhibitors<sup>14,15</sup>, anti-inflammatories.<sup>16</sup>

## Material and methods

Melting points were determined on Gallen Kamp(MFB-600) melting point apparatus and are uncorrected. IR spectra of the compounds were recorded on ashimadzu FT-IR-3800 spectrometer as KBr disk. The UV spectra were performed on Cintra-5-Gbes scientific equipment. Analytical thin layer chromatography (TLC) was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm) visualizing with ultra violet light .The  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra ( solvent DMSO) were recorded on bruker 300 MHZ or 500 MHZ spectrometer with TMS as internal standard in chemistry department–AL-Byat university /Jordon ,chemistry department ,Sharif university , Iran. Or Varian V300 MHZ in INSTITUTE OF BIOLOGY, MEDICINAL CHEMISTRY & BIOTECHNOLOGY in USA.

## General methods

### Synthesis of compound 1

Solution of phenylhydrazine (0.0005mol,0.15gm) in absolute ethanol 5ml was added to solution of saccharin (0.01mol ,1.83gm) and few drops of glacial acetic acid then the mixture was refluxed for 10 hr .white precipitate was formed ,filtered off , recrystallized from methanol . Table (1) shown physical properties of compound.

### Synthesis of compound 2

(0.001mol,0.39gm)of compound(1) in ethanol 20 ml and 0.2ml triethylamine as catalyst .To this solution of phenylisothiocyanate (0.004mol,0.5gm ) was added ,then the mixture refluxed for 12 hr ,the solid was formed after cooling filtered off and dried ,recrystallized from dioxan. Physical properties are listed in the table (1).

### Synthesis of compound 3

(0.3gm)of compound(1) and 10 ml of chloroacetylchloride was heated at 60 °C for 4hr ,after complete the reaction ,cooled and 30 ml of petroleum ether was added ,then the solid was formed filtered off and recrystallized from ethanol. Physical properties are listed in the table (1).

### Synthesis of compound 4

Saccharin 1.5 was dissolved in 30ml ethanol and few drops GAA ,then 3ml hydrazine hydrate added dropwise ,the reaction mixture was heated under refluxed for 12 hr. The solid formed was filtered off, dried and recrystallized from methanol, table(1) Shows some of physical properties of compound.

### Synthesis of compound 5

(0.5gm from compound 4 dissolved in absolute ethanol 10 ml in round bottom flask then 0.7 gm ethyl

acetoacetate was added ,the mixture reaction under refluxed for 16 hr after complete reaction by monitored by TLC, the excess was evaporated under vacuum ,the white solid formed was filtered off ,recrystallized from methanol. Physical properties are listed in the table (1).

### Synthesis of compound 7

A mixture compound A<sub>5</sub> (0.2gm) and ethyl acetoacetate 2ml was heated in oil bath for 10 hr ,the reaction was monitored by TLC after complete the reaction the solid formed filtered was off and recrystallized from ethanol. physical properties shown in table (1).

### Synthesis of compound (8 -14)<sup>17,18</sup>

Sodium saccharin (2.41gm,0.01mol) was dissolved in 20 ml dry DMF then the flask fitted with dropping funnel containing (0.01 mol) from, chloro acetone, iodomethane, 1-bromo-3-methylbut-2-ene, 2-bromoacetamide, 2-chloro-N-(2 methylphenyl) acetamide, was added dropwise with stirring then the mixture was refluxed for 6 hours in water bath. The reaction mixture was cooled to room temperature and poured into ice water with stirring. The obtained precipitate was filtered off , washed with water and recrystallized from appropriate solvent. Table (2-1) shows some physical properties of the compounds.

### Synthesis of compound (15 ,16)

A solution of phenylhydrazine (0.0005mol,0.15gm) in absolute ethanol 5ml was added to solution of 0.01mol from compound (7) and 0.02 mol from compound (11) , few drops of glacial acetic acid, then the mixture was refluxed for 10 hr .white precipitate was formed ,filtered off , recrystallized from methanol. Table(1) shown physical properties of compounds .

### Synthesis of compound (17 ,18)

Compound (17,18 ) were synthesized in the same method as synthesis of compound (7-14). Physical properties are listed in the table(1) .

### Synthesis of compound (19 , 20).

( 0.001mole) of compound 17,18 was added to %10 HCl and the mixture was heated under reflux for 3 hr . The reaction mixture was cooled to 0C and the resulting precipitate was filtered off and recrystallized from appropriate solvent to yield 19,20 as white solid .Table (1) shows some of physical properties of compounds (19,20).

### Synthesis of compound (21)

Compound 17 (0.005 mole,1.345gm) was dissolved in 20 ml absolute ethanol ,then (0.02mole,1gm) of hydrazine

**Table (2):** Spectral data of compound (2)

Comp. No	UV $\lambda$ max nm	Characteristic bands of FT-IR spectrum ( $\text{cm}^{-1}$ , KBr)				
		$\nu\text{C-H}$ aromatic	$\nu\text{C-H}$ alph.	$\nu\text{C=N}$	$\nu\text{C=C}$ aromatic	Others
2	=	3093 3059	2978 2889 2831	1653	1589 1564 1529 1496	1232 for (C=S) 3367 ,3230 for NH

**Table (3):** Spectral data of compound (3)

Comp. No	UV $\lambda$ max nm	Characteristic bands of FT-IR spectrum ( $\text{cm}^{-1}$ , KBr)				
		$\nu\text{C-H}$ aromatic	$\nu\text{C-H}$ alph.	$\nu\text{C=O}$	$\nu\text{C=C}$ aromatic	Others
3		3093	2995 2997 2877 2802	1751 1726	1589 1566	

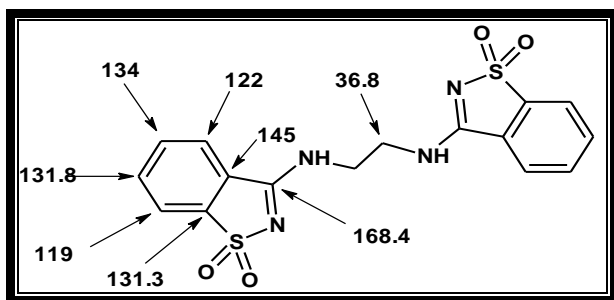
hydrate added drop wise. The mixture was heated for 8 hr the white precipitate was formed filtered off, dried and recrystallized from methanol. Physical properties of compound are listed in the table (1).

### Synthesis of compound (22)

To solution of 4-chlorobenzaldehyde (0.006mol, 0.84gm) in ethanol absolute 20ml and few drops of GAA, (0.003mol, 0.008gm) from compound 22 was added, then the mixture heated under refluxed for 8hr. the white solid formed was filtered, dried, recrystallized physical properties of compound are listed in the table (1).

### Results and discussion

The first compound was synthesized from the reaction saccharin with ethylenediamine in the presence GAA. The structure of this compound was exhibited by FTIR,  $^{13}\text{CNMR}$ .



The FTIR spectrum of the compound (1) proved the appearances absorption bands at ( $1658\text{cm}^{-1}$ ,  $1639\text{cm}^{-1}$ ) due to stretching vibration of  $\text{C=N}$ , with the disappear absorption band at  $1720\text{cm}^{-1}$  of carbonyl group of saccharin and disappearance absorption band of  $\text{NH}_2$ .

In addition to all above, the  $^{13}\text{CNMR}$  spectrum in DMSO (as solvent) of compound (1) show the following

signal of carbon: 336.8, 119, 122, 131.3, 131.8, 134, 145, 168 Fig.(5).

Reaction compound (1) with phenylisothiocyanate produce compound (2).

The FTIR of this compound shows absorption band at  $1232\text{cm}^{-1}$  due to ( $\text{C=S}$ ), table (2) show absorption bands of this compound fig (1).

Acylation compound (1) gave compound (3). The FTIR spectrum of compound (3) was showed in fig.(2) demonstrated a new band at  $1751\text{cm}^{-1}$ ,  $1726\text{cm}^{-1}$  due to two different  $\text{C=O}$  group, table (3) show absorption bands of this compound.

In general saccharin reacts with hydrazine to give pseudosaccharinhydrazide compound (4). The FTIR spectrum of this compound fig (3) show band at ( $1668\text{cm}^{-1}$ ,  $1620\text{cm}^{-1}$ ) due to stretching vibration of ( $\text{C=N}$ ) and bands at  $3338\text{cm}^{-1}$ ,  $3288\text{cm}^{-1}$ ,  $3217\text{cm}^{-1}$  reveal to  $\text{NH}_2$ ,  $\text{NH}$  with disappearance of bands at ( $1720\text{cm}^{-1}$ ) for carbonyl group of saccharin ring. Moreover, reaction (4) with ethyl acetoacetate gave pyrazole ring compound (5).

The FTIR spectrum of this compound show band at ( $1724\text{cm}^{-1}$ ) due to stretching vibration of ( $\text{C=O}$ ) of pyrazole ring, also bands at  $1676\text{cm}^{-1}$ ,  $1639\text{cm}^{-1}$  refer to stretching vibration of  $\text{C=N}$  and disappearance bands at  $3338\text{cm}^{-1}$ ,  $3288\text{cm}^{-1}$ ,  $3217\text{cm}^{-1}$  which reveal to  $\text{NH}_2$ ,  $\text{NH}$ .

The  $^1\text{H NMR}$  in DMSO-  $d_6$  as a solvent fig(6) was showed the following data in ppm : 2.2 (s, 3H,  $\text{CH}_3$ ), 3.55(s, 3H,  $\text{CH}_3$ ), 7.87-7.97(m, 4H, aromatic ring of saccharin), 10.92(s, 1H, OH).

On the other side, when compound (5) was heated ethyl acetoacetate produced compound (6). The FTIR spectra Fig (4) demonstrated new bands at  $1705\text{cm}^{-1}$  which indicated the presence of ( $\text{C=O}$ ) lactone ring and another band at  $1610\text{cm}^{-1}$  represented the stretching vibration of ( $\text{C=C}$ ) of lactone as show in table (4).

**Table (4):** Spectral data of compound (6)

Comp. No	Characteristic bands of FT-IR spectrum (cm <sup>-1</sup> ,KBr)				
	$\nu$ C-H aromatic	$\nu$ C-H alph.	$\nu$ C=O	$\nu$ C=C aromatic	Others
6	3086 3012	2982 2926	1705	1610 1562 1552	1651 ,1633 for C=N

Converting the N-H bond of saccharin to an N-C bond by alkylating it will mask the bitter taste and thus yield a better sweetener, N- alkyl saccharin were synthesized when heating sodium saccharin with different halo compounds and produce compounds (6-14).

The structure of synthesized compounds were exhibited by FIIR ,HNMR ,CNMR and Mass spectrum .

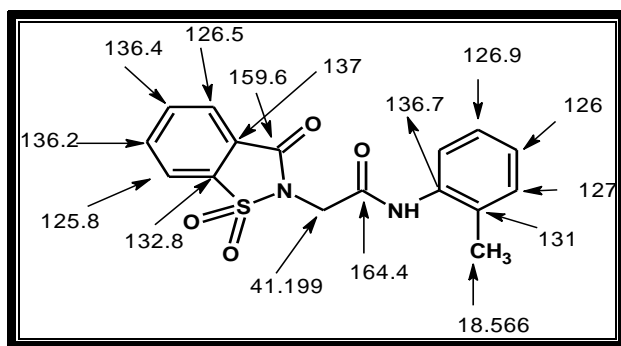
<sup>1</sup>HNMR spectrum for compound (9) in DMSO-d<sub>6</sub> as a solvent was showed the following data in ppm:1.61-1.62(dd,3H,CH<sub>3</sub>),4.22-4.23(d,2H,CH<sub>2</sub>),5.49-5.05(m ,1H, =CHCH<sub>3</sub>),5.7-5.8(m ,1H, =CH-CH<sub>2</sub>), 7.9-8.2(m,4H, aromatic protons).

Mass Spectrum Was gave the following values(M/Z), Fig.(13) : 237 ,196,122.

On the other side , <sup>1</sup>H NMR spectrum in DMSO-d<sub>6</sub> as solvent of compound (10) shows the following values in ppm:4.48-4.49(d ,2H ,CH<sub>2</sub>) ,6.29-6.3(m ,1H,CH=CH-CH<sub>2</sub>) ,6.68-6.7(d,1H ,C=CH-ph) ,7.2-7.4(m ,5H, Ph), 7.95-8.28(m,4H aromatic protons of saccharin).

In addition to all above , the <sup>1</sup>HNMR spectra in DMSO-d<sub>6</sub> as a solvent of compound 11 show the following signal of protons fig (8) : 2.18 (s ,3H ,CH<sub>3</sub>-Ph) , 4.57 ( s,2H ,CH<sub>2</sub>-N) ,7-7.33 (m ,4H, phenyl ring) ,7.8-8.311(m,4H , benzene ring of saccharin) ,9.668 (s ,1H ,NH).

The <sup>13</sup>CNMR spectrum of compound (11) show the following data:164.461,159.63,

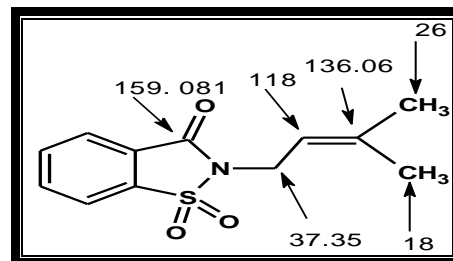


Mass Spectrum of this compound gave the following values(M/Z), Fig.(13) :330 ,315 ,224,196.

<sup>1</sup>HNMR spectrum of compound (12) in DMSO-d<sub>6</sub> as solvent , fig (9) show the following values in ppm : 1.66(s ,3H, CH<sub>3</sub>) , 1.72 (s ,3H, CH<sub>3</sub>) , 4.25-4.26(d ,2H, NCH<sub>2</sub>) ,5.2-5.25(t, 1H ,CH<sub>2</sub>-CH=C) ,7.9-8.2( m ,4H , aromatic ring )

Also <sup>13</sup>CNMR spectrum of compound (12) show the following data : 26 ,18,136 ,118 ,37.35 ,159.fig(10)

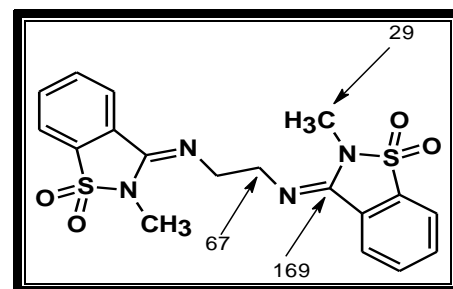
Mass Spectrum of the following compound gave the following values(M/Z), 252, 237 ,224 196,168,140 ,76.



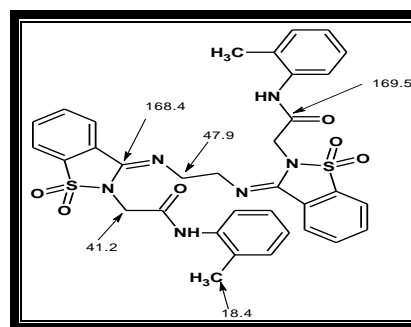
Whereas, compound 15 ,16 have been synthesized from react compound (7,11) with ethylene diamine .

The structures of both them were demonstrated by FTIR ,<sup>13</sup>CNMR spectrum.

The FTIR spectra of compound 15 showed new absorption bands at (1640cm<sup>-1</sup>) due to stretching vibration of (C=N) and absence absorption band at 1739 cm<sup>-1</sup> of carbonyl group.The <sup>13</sup>CNMR spectra using DMSO as solvent support the structural formation of compound (15), and showed the following values in ppm. 29,67,129.6,130.1,130.7,133.4, 136.8,136.9,169.4 .fig(11)



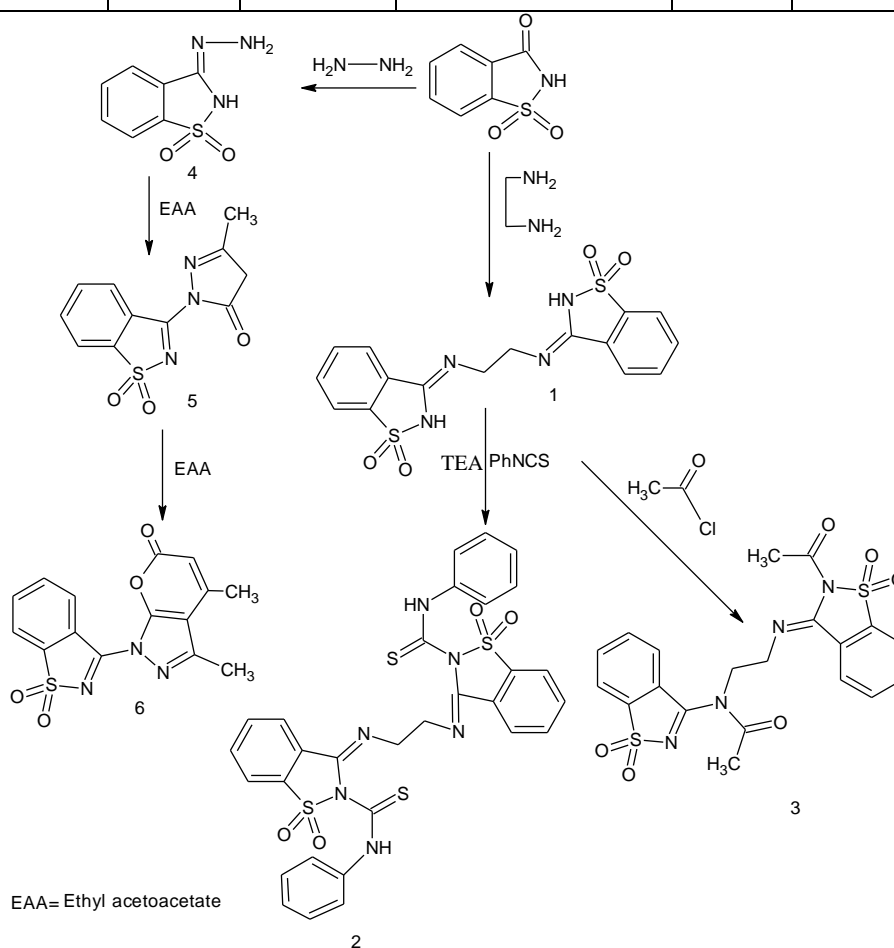
While <sup>13</sup>CNMR of compound 16 in DMSO as solvent gave the following data in ppm: at 18.40,41.277,47.953,125.255,126.1,126.77,129,129.347,129.9,130.1,132.2,132.7,136.39,137.2,139.39,168.4,169.5 .

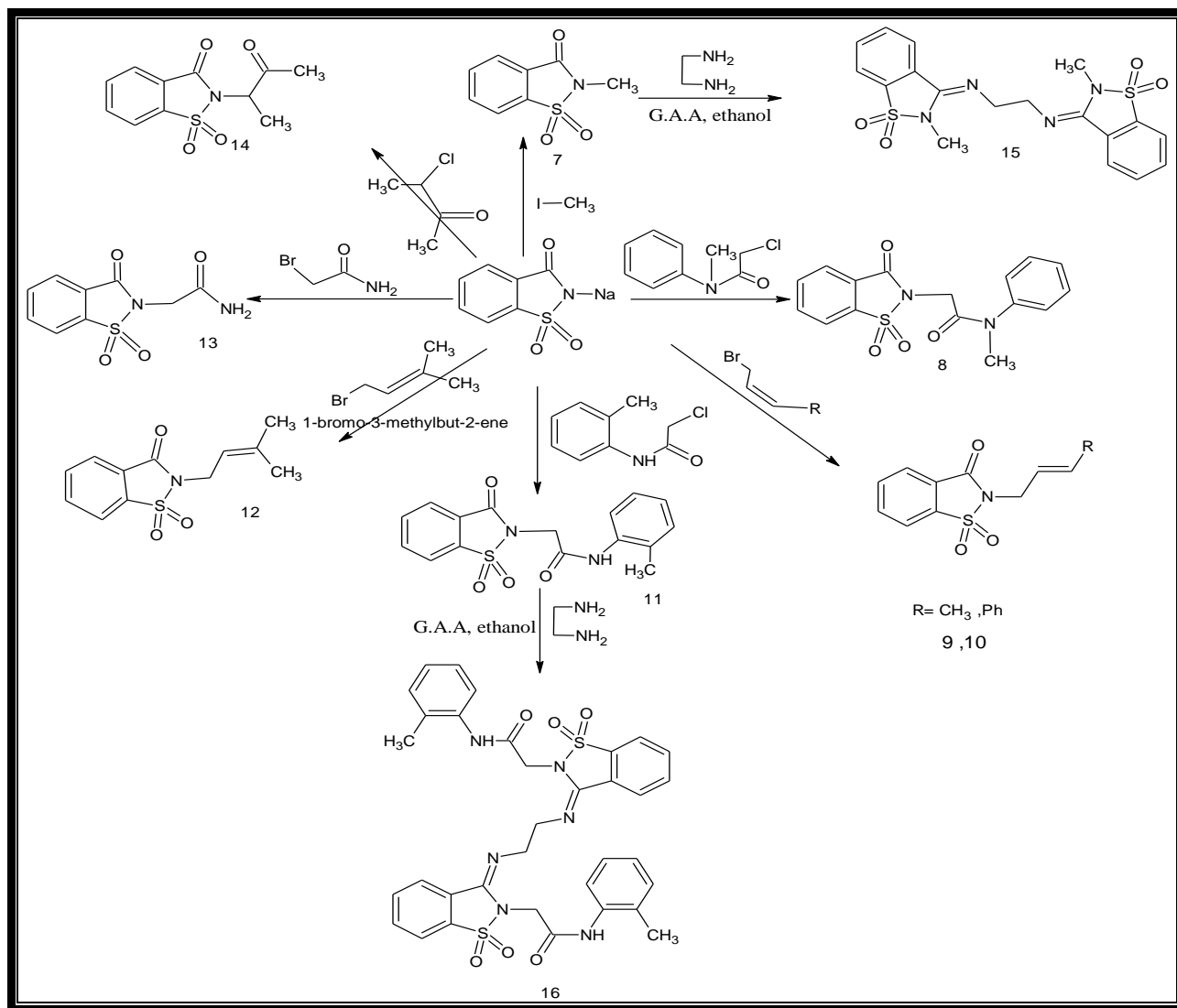


Interestingly, <sup>1</sup>HNMR spectrum of compound (19) in DMSO-d<sub>6</sub> as solvent was showed the following data in

**Table (1):** Physical properties of the synthesized compounds

Comp.No	m.p. °C	Yield%	color	Recryst . Solvent	Rf	Mobile phase
1	242-244	83	white	Methanol	0.45	[Methnol:chloroform] 5:5
2	210-212	35	=	Methanol :chloroform	0.36	[H:E] 5:3
3	166-168	56	yellow	methanol	0.2	[H:E] 5:5
4		73	White	=	0.43	Methanol:chloroform 3:7
5	169-170	43	white	Methanol :chloroform	0.37	H:E 5:5
6	97-99	23	brown	methanol	0.28	Methanol:chloroform 3:7
7		91	white	ethanol	-	-
8	212-214	89	white	ethanol	0.2	[H:E]5:5
9	87-88	75	=	=	2.5	[H:E]7:3
10	86-87	77	white	methanol	0.44	=
11	13-195	92	=	Methanol:H <sub>2</sub> O	0.22	=
12	62-63	65	Yellowish	ethanol	-	[H:E]5:5
13	112-113	60	white	ethanol	0.2	[H:E]5:5
14	128-130	70	=	Ethanol%70	-	-
15	198-199	72	Off white	methanol	0.1	[H:E]5:5
16	177-180	43	white	Ethanol:H <sub>2</sub> O		[H:E]5:5
17	103-105	91	=	=	0.64	=
18	58-60	78	=	=	0.3	=
19	220-223	85	white	methanol	0.3	[H:E]7:3
20	177-180	81	white	methanol	0.1	=
21	164-165	78	white	=	0.26	Methanol: chloroform 3:7
22	238-240	73	white	Methanol: chloroform	1.6	Methanol: chloroform 5:5

**Scheme (1)**



ppm: 4.43(s, 2H, NCH<sub>2</sub>), 7.9-8.3(m, 4H, aromatic protons), 13( broad peak, 1H, COOH).

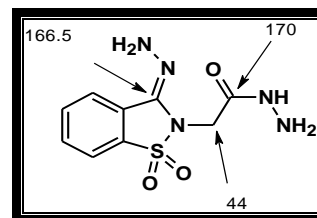
The  $^1\text{H}$ NMR spectrum of compound (20) in DMSO- $d_6$  showed the following data in ppm: 2.66-2.69 (t, 2H,  $\text{CH}_2\text{COOH}$ ), 3.89-3.91 (t, 2H,  $\text{N-CH}_2$ ), 7.9-8.26 (m, 4H, aromatic protons), 12.49 (broad peak, 1H,  $\text{COOH}$ ).

The structure of compound(21) was exhibited by, FTIR and  $^1\text{H}$ NMR,  $^{13}\text{C}$ NMR spectrum.

The FTIR spectrum of compound (21) was showed demonstrated a new bands at 1670 cm<sup>-1</sup> due to (C=O) of amide and band at 1660 cm<sup>-1</sup> ,due to (C=N)also at 3387,3336 ,3290 for NH<sub>2</sub> ,NH respectively,as well as the absence the absorption bands of carbonyl groups of ester at 1755 and of saccharin ring at 1735.

The <sup>1</sup>H NMR spectrum of compound (21) in DMSO-d<sub>6</sub> (fig(10)) showed the following data in ppm: 3.47(s, 2H, CH<sub>2</sub>) 4.1-4.49(broad, 4H, 2NH<sub>2</sub>) 7.5-7.8 (m, 4H, benzene ring of saccharin) 9.1(broad, 1H, NH), 9.8(broad, 1H, OH tu).

The  $^{13}\text{C}$ NMR spectrum of compound (21) show the following bands of carbon: 170,166.5,166.9 ,137,134, 132 , 129 ,130,128.6 Fig.(11).



FTIR spectrum of compound (22) demonstrated new band at 1622cm<sup>-1</sup> indicated the presence of (C=N) and another band at 1643cm<sup>-1</sup> represented the stretching vibration of (C=O) of amide.

<sup>1</sup>H NMR spectrum of (22) in DMSO-d<sub>6</sub> as a solvent Fig.(12 ) was showed the following data in ppm: 11.4 (s, 1H, N=CH-), 11.5 (s, 1H, N=CH-), 7.9-8.27(m, 12H, aromatic ring ), 3.55 (s, 2H, -NCH<sub>2</sub>), 12(broad, 1H, NH), 12. (broad, 1H, OH).

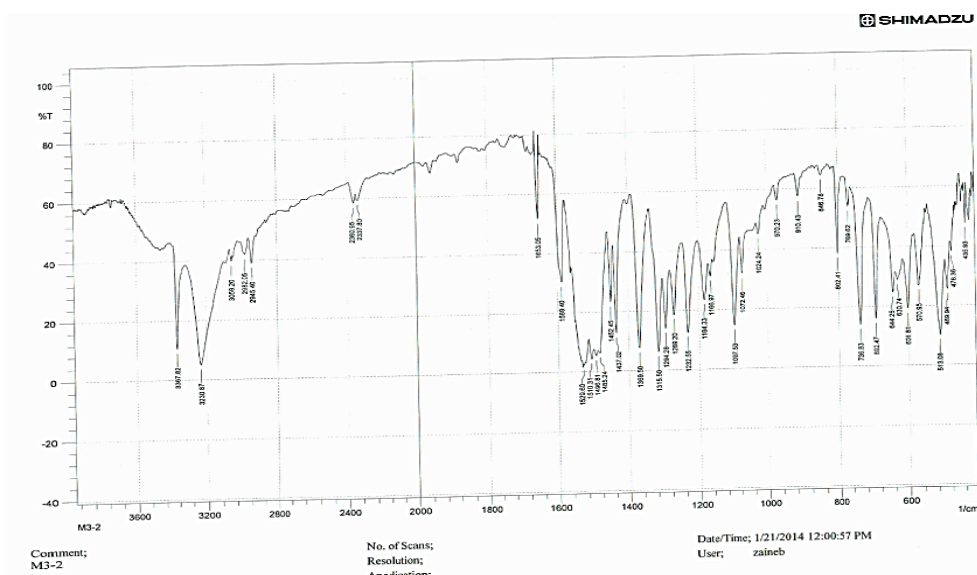


Figure (1) :FT-IR spectra of compound (2)

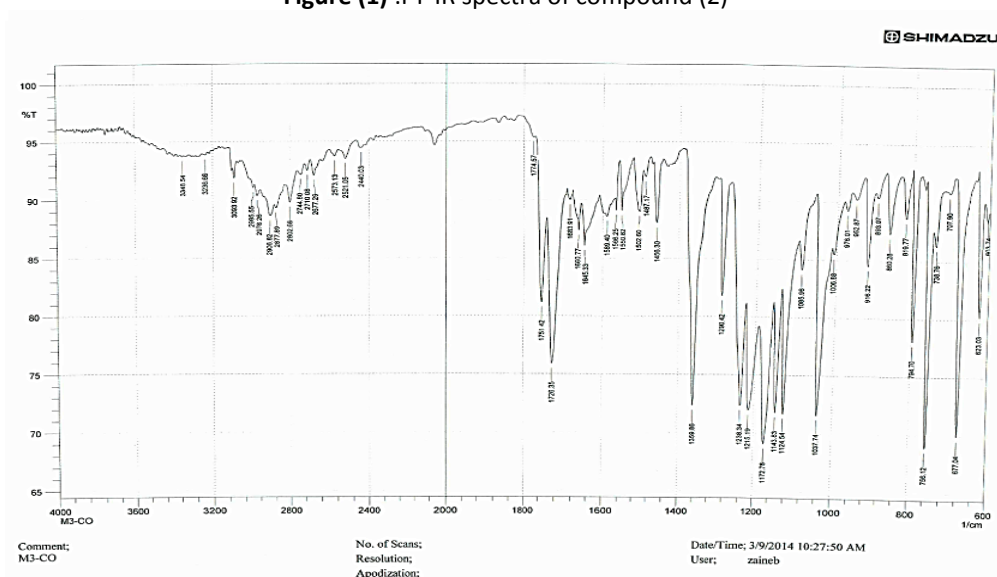


Figure (2) :FT-IR spectra of compound (3)

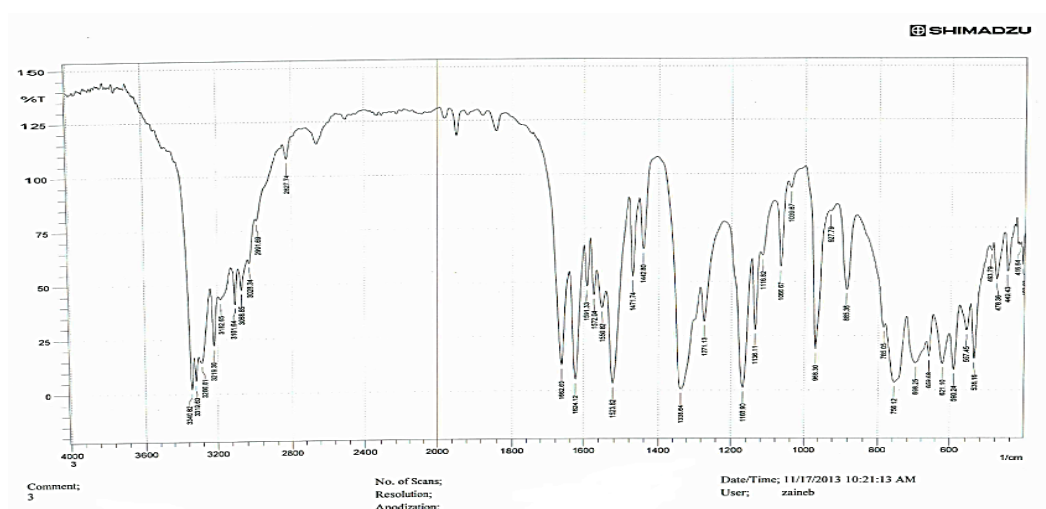


Figure (3) :FT-IR spectra of compound (4)

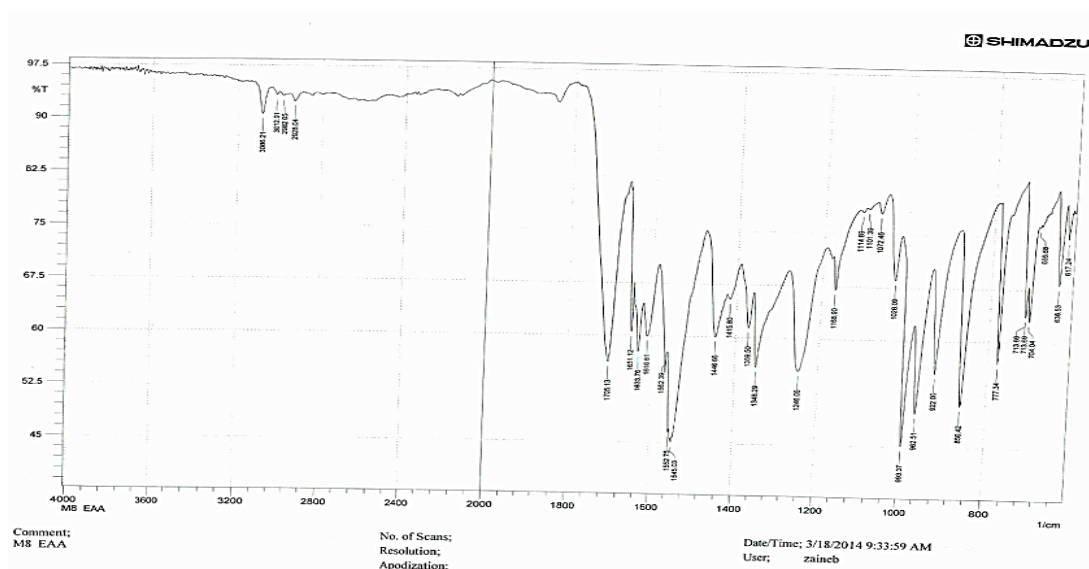
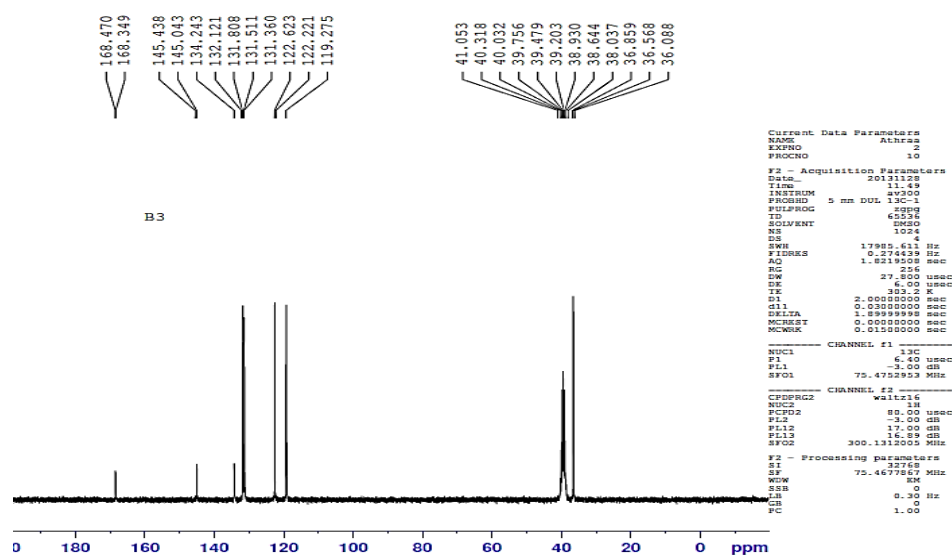
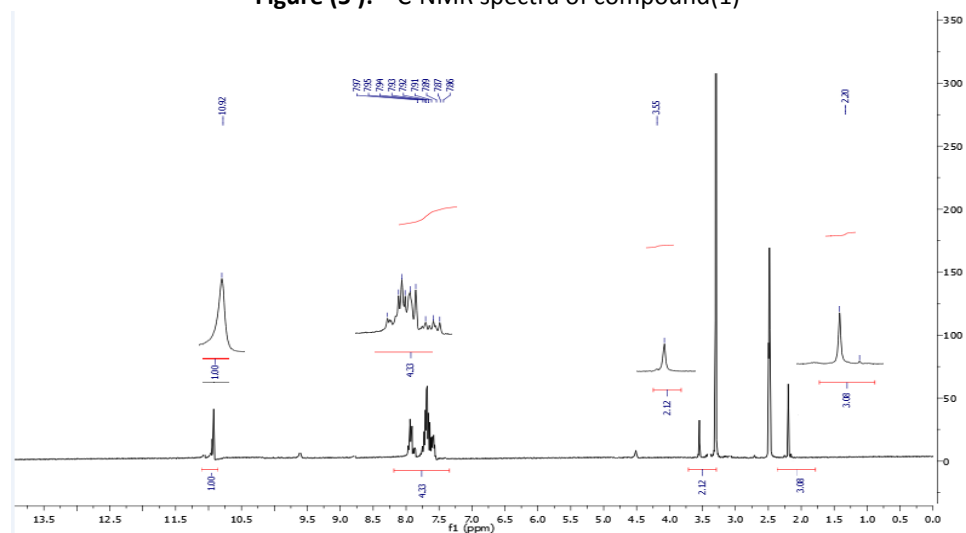
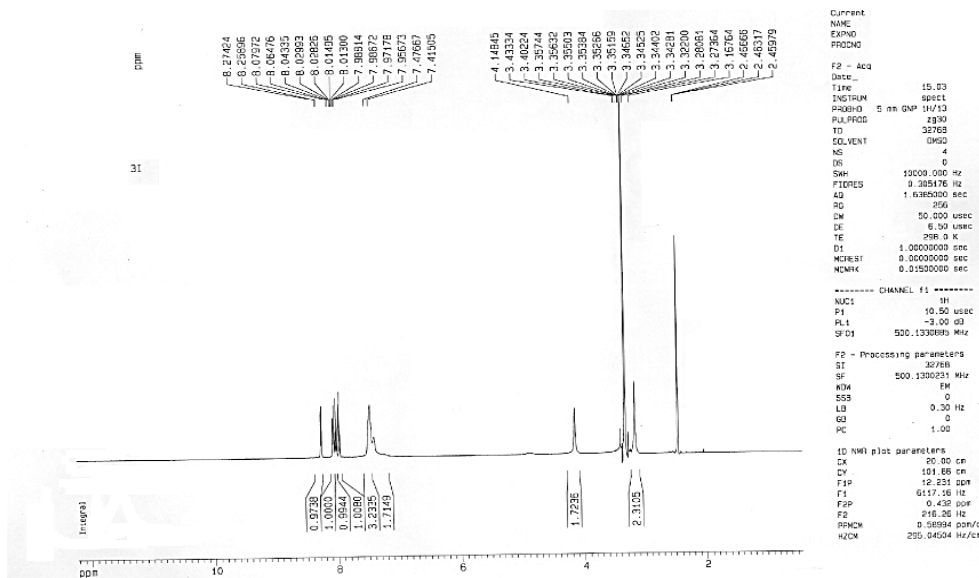
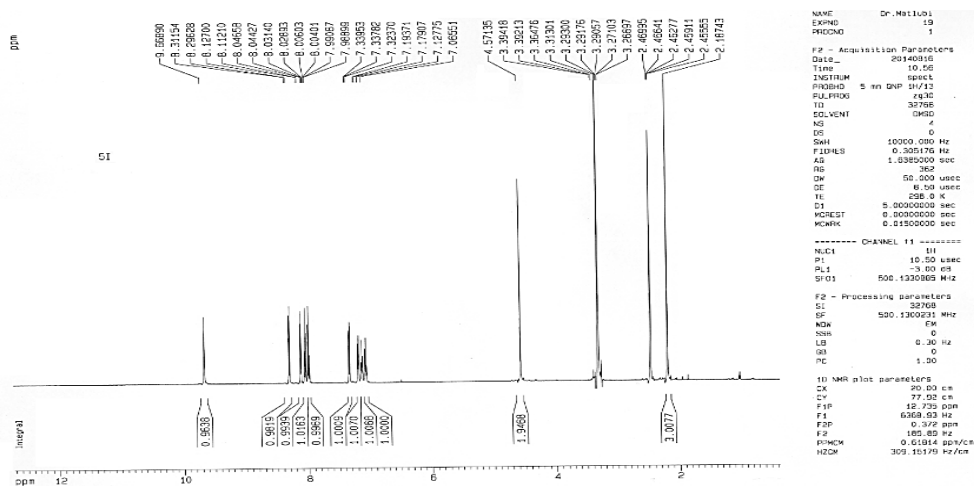
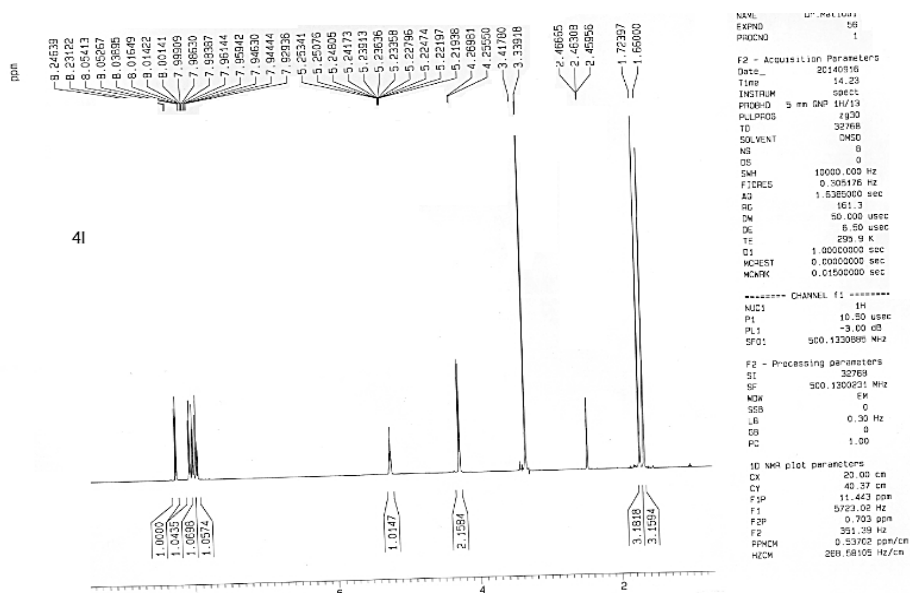
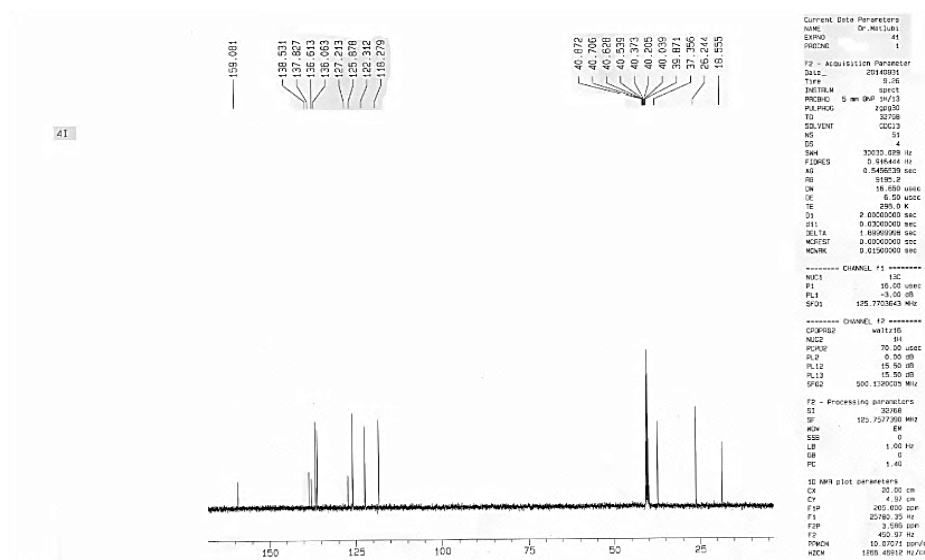
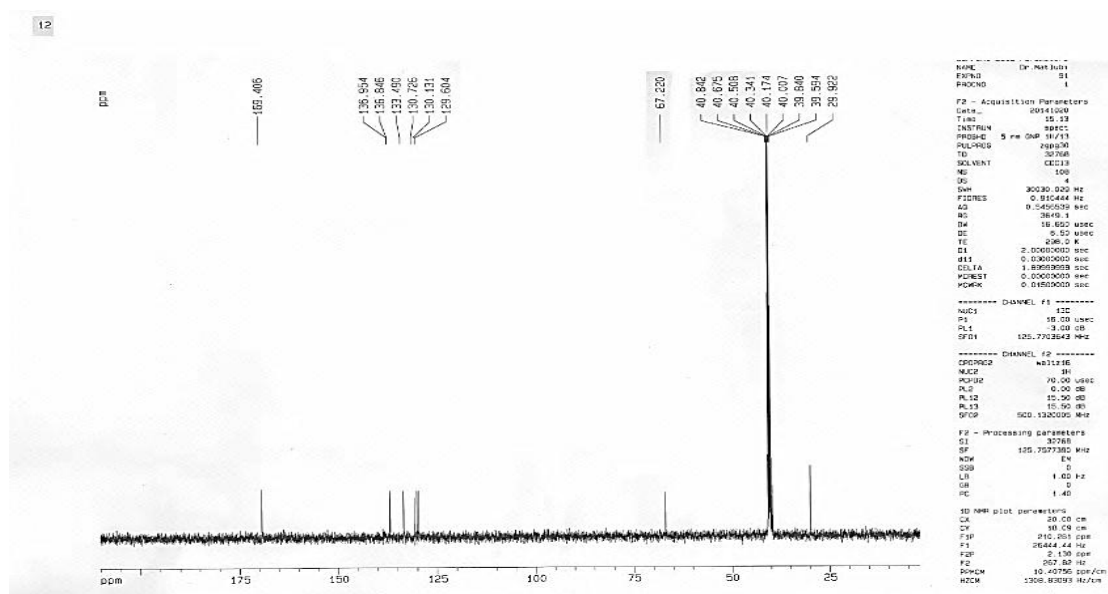
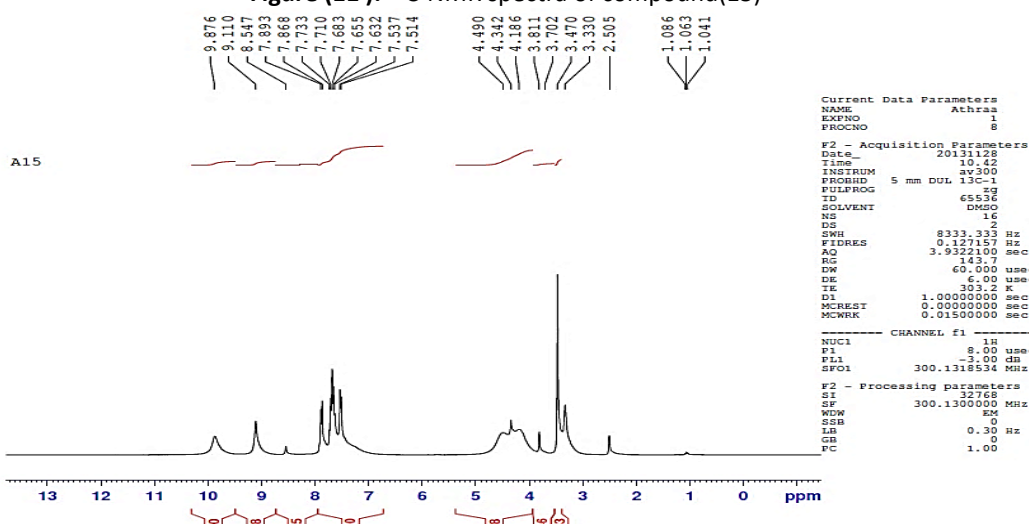


Figure (4) :FT-IR spectra of compound 6)

Figure (5) : <sup>13</sup>C-NMR spectra of compound(1)Figure (6): <sup>1</sup>H-NMR spectra of compound (5)



Figure (7):  $^1\text{H}$ -NMR spectra of compound (8)Figure (8):  $^1\text{H}$ -NMR spectra of compound (11)Figure (9):  $^1\text{H}$ -NMR spectra of compound (12)

Figure (10):  $^{13}\text{C}$ -NMR spectra of compound (12)Figure (11):  $^{13}\text{C}$ -NMR spectra of compound (15)Figure (10):  $^1\text{H}$ -NMR spectra of compound (21)

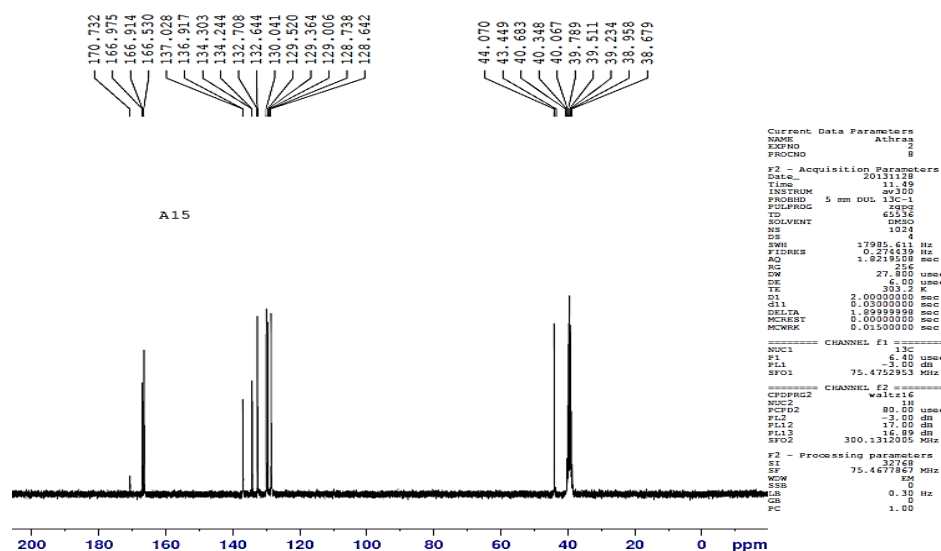
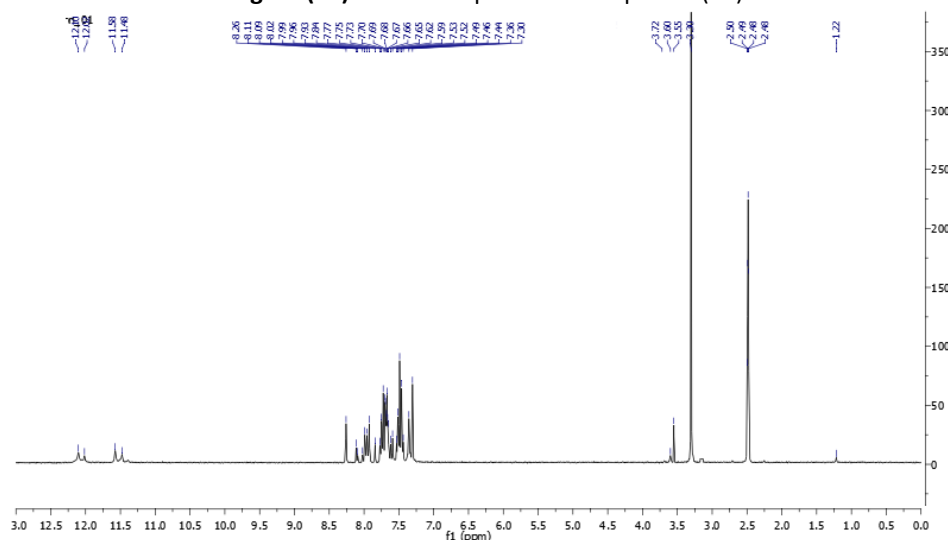
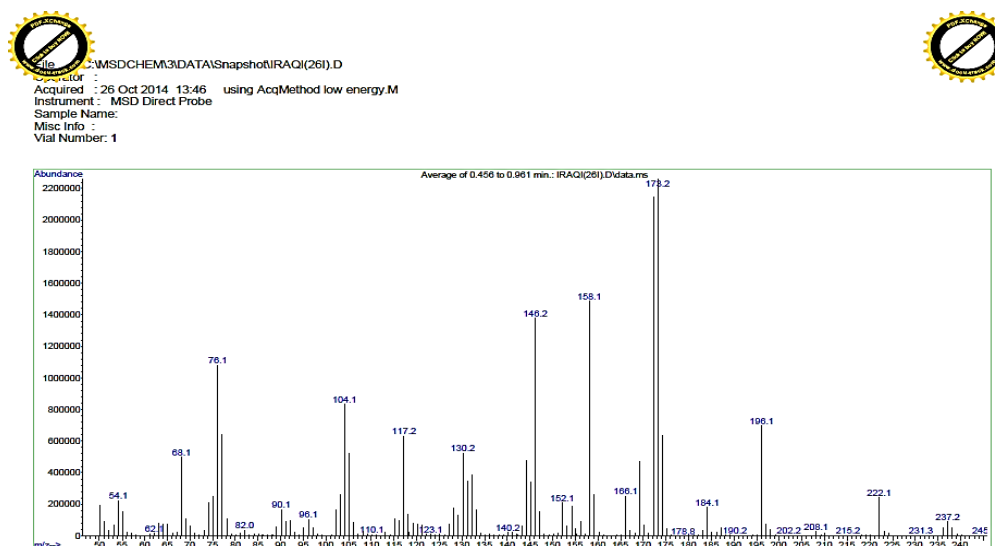
Figure (11):  $^{13}\text{C}$ -NMR spectra of compound (21)Figure (12):  $^1\text{H}$ -NMR spectra of compound (22)

Figure (13): Mass spectra of compound (9)

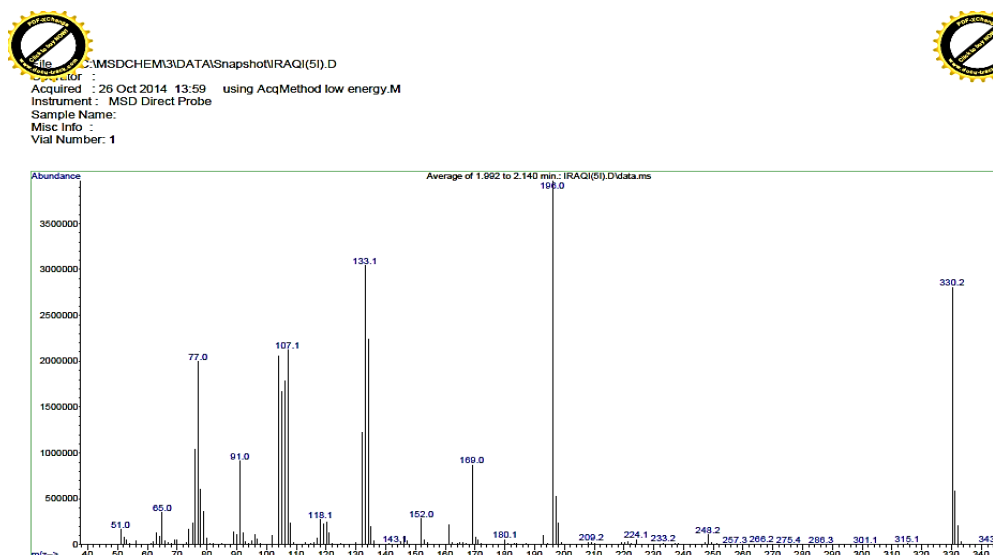


Figure (14): Mass spectra of compound (I)

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