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Synthesis, Antimicrobial Evaluation of some New Heterocycles Derived from *N*-Substituted Saccharin

Redha Ibrahim AL-Bayati[1*], Athraa Hameed Mekky[2]

[1]*Department of Chemistry, College of Sciences, AL-Mustansiriyah University, Baghdad, Iraq*
[2]*Department of Chemistry, College of Sciences, Thi-Qar University, Thi-Qar, Iraq*

ABSTRACT

A series of novel five membered heterocycles (oxazole, thiazoles, imidazolidine, 2-thioxoimidazolidine) derived from N-substituted saccharin were synthesized and identified using IR, ^{1}HNMR and ^{13}CNMR spectra. The novel compounds were tested for their antimicrobial activities against several Gram-positive and Gram-negative bacterial species.

Keywords: Saccharin, Oxazole, Thiazole, Imidazolidine

INTRODUCTION

Saccharin (1,2-benzisothiazole-3-one-1,1-dioxide), is a well know heterocyclic compound and has been used as a sweetener in the form of its sodium salt since 1885 [1]. Saccharin is widely used as an artificial sweetening agent. It is about 550 times sweeter than cane sugar [2,3]. This sweeten is unstable when heated but doesn't react chemically with other food ingredient. It is excreted from the body in urine un exchanged [4,5]. It appears to be entirely inert and harmless when taken directly [6]. It is of great value to diabetic persons and peoples who need to control intake of calories. The basis for the controversy rests primarily on findings of bladder tumors in some male rats fed high doses of sodium saccharin [7].

During the last decade, there is a large interest in the five membered heterocycles containing nitrogen, oxygen and sulfur atoms like oxazoles, thiazoles and imidazolidines due to their potential applications in medicinal field. Recently, many reports related to oxazoles, thiazoles as well as imidazolidine derivatives depicted the versatile biological activities of these compounds. Oxazole derivatives exhibited diverse biological actions such as anti-inflammatory [8], analgesic [9], antibacterial, antifungal [10], antiproliferative [11], and anti-tuberculosis [12].

Thiazoles were found in many potent biologically active molecules and various literature surveys these derivatives with large spectrum pharmacological activity likes antimicrobial, antiretroviral, antifungal and antineoplastic and other drugs [13-15]. On the other hand, imidazolidine represent the building blokes in many biological active compounds and these derivatives have been reported to exhibited important biological activities such as anti-inflammatory, anticonvulsant, antiarrhythmic, antimicrobial, antiparasitic and analgesic [16,17]. Based on these concepts we reported here the synthesis of new five-membered heterocyclic derivatives starting from *N*-Substituted saccharin. Several Gram +ve and Gram –ve bacterial species were used to evaluated the antimicrobial activities of the synthesized compounds.

MATERIAL AND METHODS

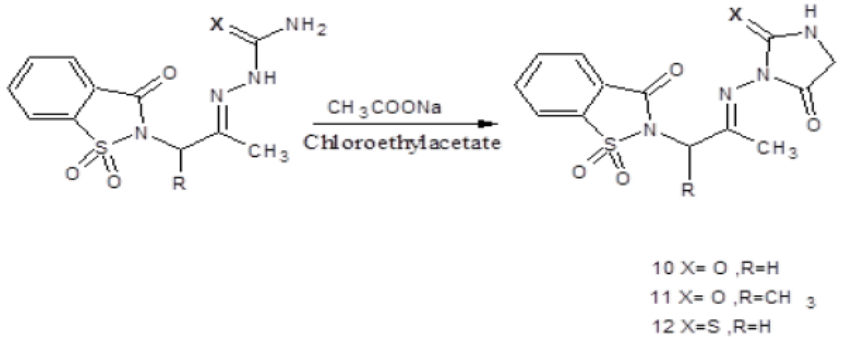
All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on Gallen Kamp (MFB-600) melting point apparatus and are uncorrected FT-IR measurements were recorded on a Shimadzu FT-IR-3800 spectrometer as KBr disk. ^{1}H NMR and ^{13}C NMR spectra were obtained with Bruker 500 MHz spectrometer in DMSO-*d6* solution using TMS as internal standard.

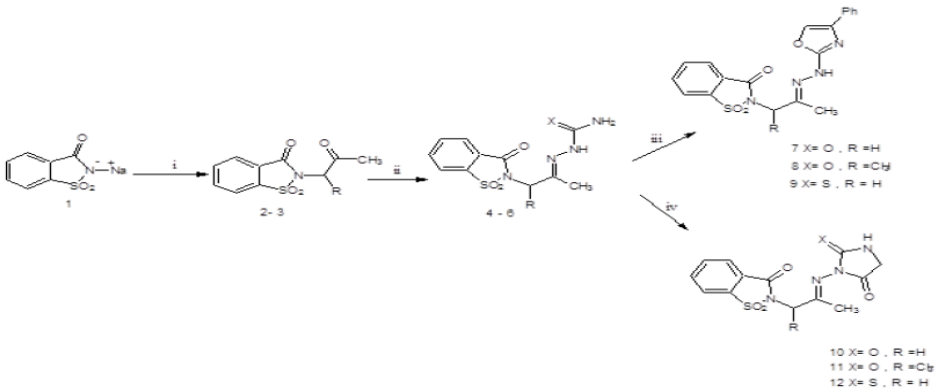
General procedure for the synthesis of 2-(alkyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (2,3)

These compounds were synthesized according to modified procedure described in reference (18). To sodium saccharin hydrate (**1**) (0.01 mol) in dry Dimethyl Formamide (DMF) (20 ml), chloroacetone or 3-bromobutan-2-one (0.0175 mol) in dry DMF (10 ml) was added drop wise with continuous stirring, and then the mixture was refluxed for 6 h in water bath. The reaction crude was cooled to room temperature and poured into ice water with stirring. The obtained precipitate was filtered off, washed with water, dried and recrystallized from ethanol (Table 1 and Scheme 1).

Table 1: Antimicrobial activity of the synthesized compounds

Compound no.	Gram positive		Gram negative		Fungal
	Staphylococcus aureus	*Streptococcus* sp.,	*Escherichia coli*	*Klebsiella pneumoniae*	*Candida*
7	+	+	+	+	+
8	+	+	+	+	+
9	+	+	–	+	+
10	+	+	+	+	+
11	+	+	+	+	+
12	+	+	+	+	+





Scheme 1: The synthesized compounds

2-(2-Oxopropyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (2)

White powder, yield 95%, mp. 143-144°C; IR (KBr, cm^{-1}): 3091 (C-H aromatic), 2947, 2912 (C-H aliphatic), 1745 (C=O of ring), 1730 (C=O of ketone) 1593, 1466 (C=C), 1323, 1184 (S=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.22 (s, 3H, CH_3), 4.74 (s, 2H, N-CH_2), 7.90-8.30 (m, 4H, aromatic).

2-(1-Methyl-2-oxopropyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (3)

White powder, yield 70%, mp. 128-130°C; IR (KBr, cm^{-1}): 3099 (C-H aromatic), 2939, 2887 (C-H aliphatic), 1743 (C=O of ring), 1724 (C=O of ketone) 1545, 1462 (C=C), 1334, 1184 (S=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.50 (d, 3H, *J*=4.3 Hz, $CHCH_3$), 2.1(s, 3H, CH_3), 4.9-4.96 (m, 1H, CH) 7.9-8.3 (m, 4H, aromatic).

General procedure for the synthesis of semicarbazone and thiosemicarbazone derivatives (4-6)

These compounds were synthesized according to the procedure described in reference (19). A mixture of compound 2 or 3 (0.001 mol), semicarbazide or thiosemicarbazone (0.001 mol) and sodium acetate (0.001 mol) in absolute ethanol (15 ml) was refluxed for 12 h. After cooling, the precipitate formed was filtered, dried and recrystallized from EtOH: DMF (1:1).

(2E)-1-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)acetonesemicarbazone (4)

White powder, yield 84%, mp. 204-205°C; IR (KBr, cm^{-1}): 3458, 3443, 3237, 3186 (NH_2, NH), 3091 (C-H aromatic), 1735 (C=O of ring), 1699 (C=O), 1618 (C=N), 1587, 1427 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.79 (s, 3H, CH_3), 4.4 (s, 2H, N-CH_2), 6.1 (broad peak, 2H, NH_2), 7.90-8.20 (m, 4H, aromatic), 9.28 (s, 1H, NH) (Figure 1). ^{13}CNMR (500 MHz, DMSO-d_6) δ (ppm) 14.4 (CH_3), 44.9 (CH_2), 122, 126, 126.9, 136, 136.8, 137.7 (6 C aromatic), 142.3 (C=N), 157.8, 159.4 (2 C=O).

(2E)-1-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)acetonethiosemicarbazone (6)

White powder, yield 93%, mp. 206-208°C; IR (KBr, cm^{-1}): 3416, 3321, 3234, 3154 (NH_2, NH), 3093 (C-H aromatic), 2966, 2852 (C-H aliphatic), 1734 (C=O of ring), 1630, 1650 (C=N), 1591, 1489 (C=C), 1251 (C=S). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.92 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.33 (s, 1H, NH), 7.95-8.29 (m, 4H, aromatic), 8.13 (s, 1H, NH), 10.35 (s, 1H, NH) (Figure 3). ^{13}CNMR (500 MHz, DMSO-d_6) δ (ppm) 15.2 (CH_3), 44.6 (CH_2), 122, 126, 126.9, 136, 136.8, 137.7 (6 CH aromatic), 147 (C=N), 159.0 (C=O) (Figure 4).

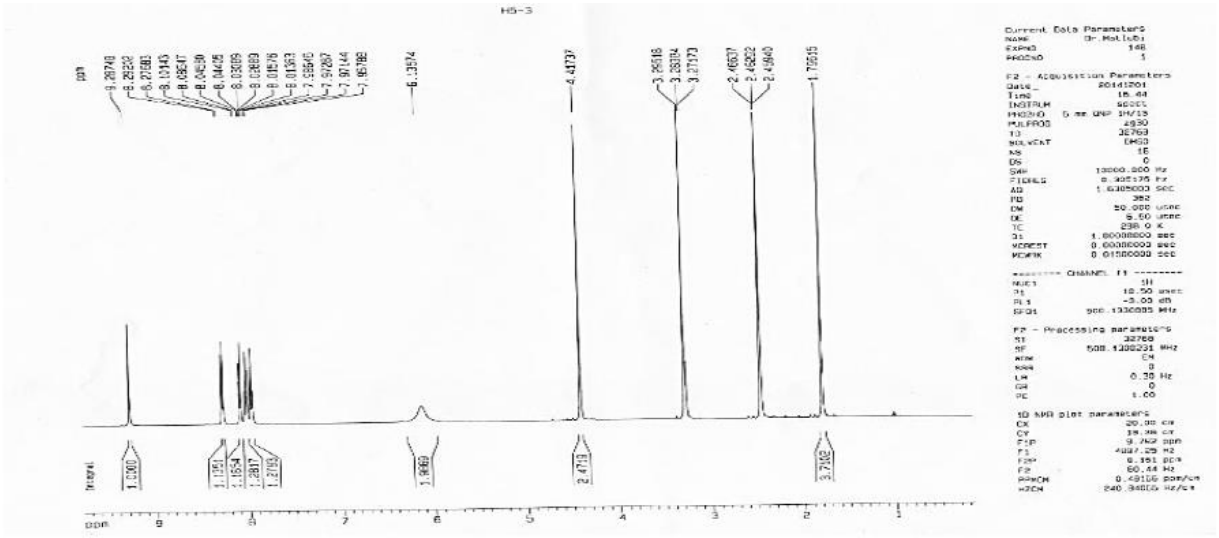


Figure 1: ^{1}H-NMR spectrum of compound 4

(2E)-1-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)butan-2-onesemicarbazone (5)

White powder, yield 70%, mp. 208-210°C; IR (KBr, cm^{-1}): 3458, 3300, 3138, 3101 (NH_2, NH), 3003 (C-H aromatic), 2937, 2879 (C-H aliphatic), 1712 (C=O of ring), 1678 (C=O), 1651 (C=N), 1587, 1426 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.58-1.60 (d, 3H, $CHCH_3$), 1.76 (s, 3H, CH_3), 4.90-4.95 (q, 1H, CH) 6.20 (broad peak, 2H, NH_2) 7.90-8.20 (m, 4H, aromatic), 9.25 (s, 1H, NH). (Figure 2) ^{13}CNMR (500 MHz, DMSO-d_6) δ (ppm) 14.7 ($CHCH_3$), 16.1 (CH_3), 44.6 (CH_2), 122, 126, 126.9, 136, 136.8, 137.7 (6 CH aromatic), 144.6 (C=N), 157.9, 159.0 (2 C=O).

Figure 2: ^{1}H-NMR spectrum of compound 5

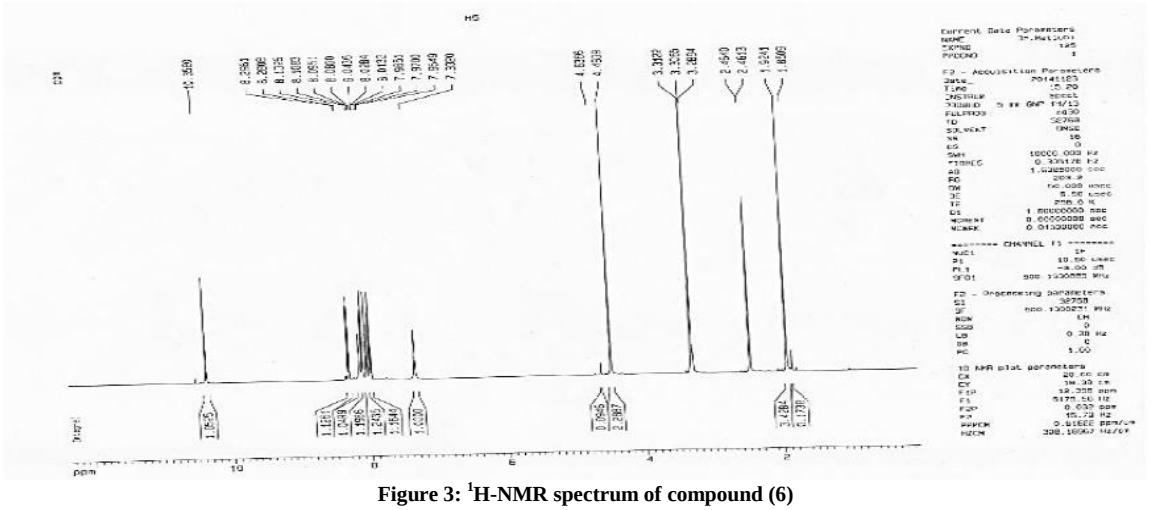


Figure 3: ^{1}H-NMR spectrum of compound (6)

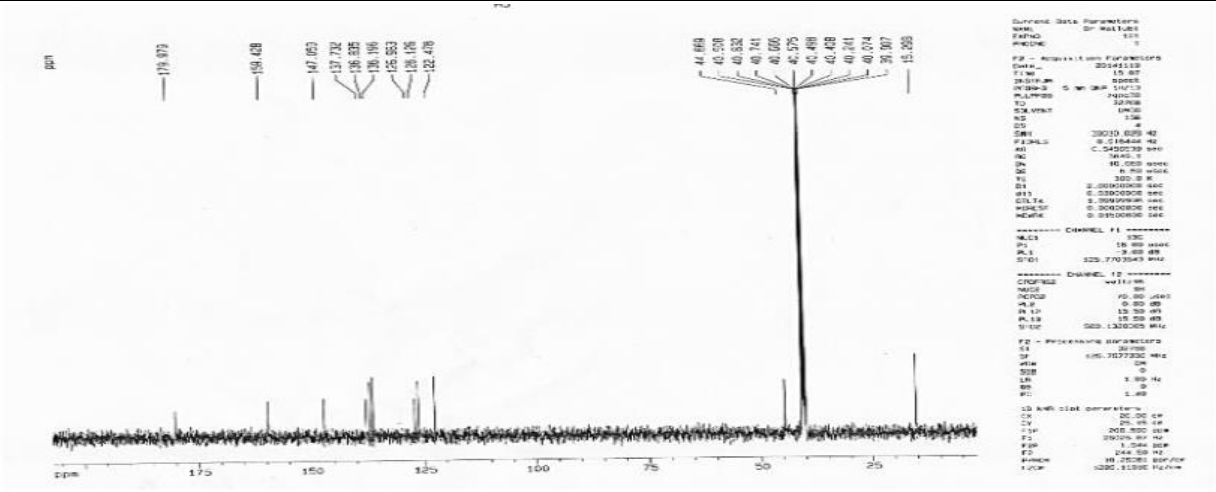


Figure 4: ^{13}C-NMR spectrum of compound (6)

General procedure for the synthesis of oxazole and thiazole derivatives (7-9)

These compounds were synthesized according to the procedure described in reference [20]. A mixture of compound **4**, **5** or **3** (0.59 mmol) and *p*-phenacyl bromide (0.59 mmol) in ethanol (20 ml) was refluxed for 8 h. After refluxing, the reaction mixture was allowed to stand to attain room temperature. The precipitated solid was dried and recrystallized from Ethanol: Water (7%).

2-{(2E)-2-[(4-phenyl-1,3-oxazol-2-yl)hydrazono]propyl}-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (7)

Off white powder, yield 23%, mp. 211-212°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.97 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 4.90 (s, 1H, NH), 6.70 (s, 1H, oxazole ring), 7.10-8.30 (m, 9H, aromatic) (Figure 5).

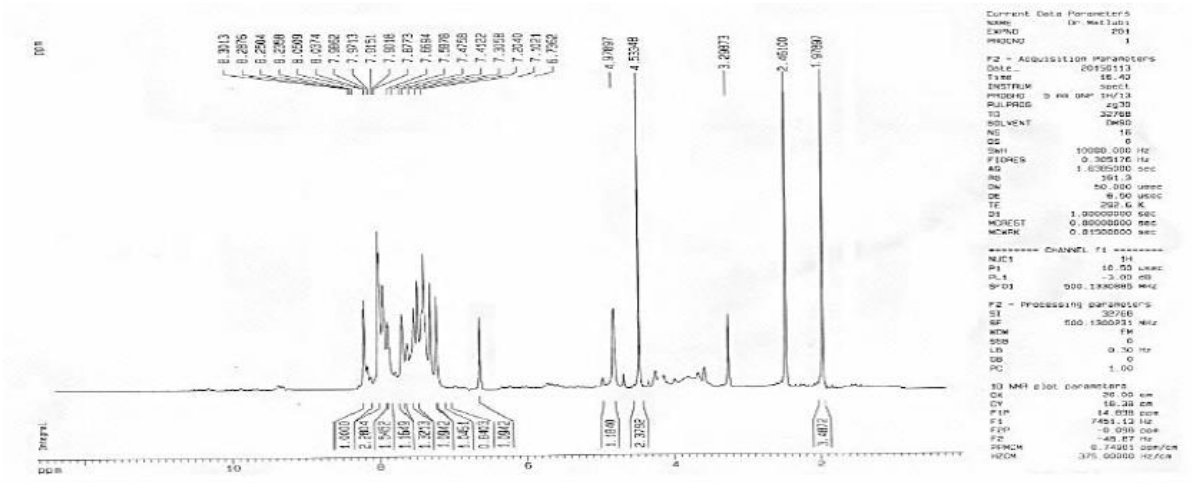


Figure 5: ^{1}H-NMR spectrum of compound (7)

2-{(2E)-1-methyl-2-[(4-phenyl-1,3-oxazol-2-yl)hydrazono]propyl}-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (8)

Off white powder, yield 26%, mp. 118-120°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.64 (d, 3H, $CHCH_3$), 1.91 (s, 3H, CH_3), 4.70 (s, 1H, NH), 4.92 (q, 1H, $CHCH_3$), 6.49 (s, 1H, oxazole ring), 7.00-7.23 (m, 5H, aromatic), 7.90-8.30 (m, 4H, aromatic) (Figure 6).

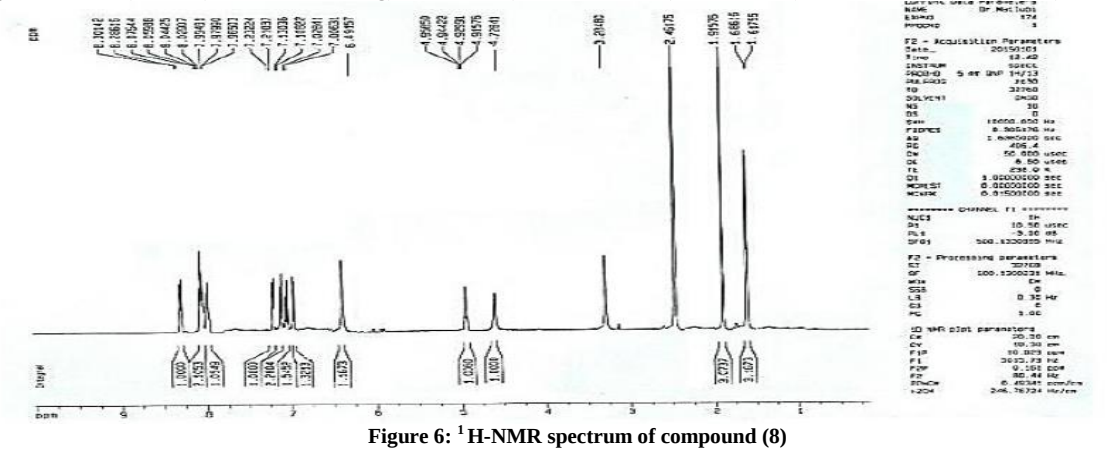


Figure 6: ^{1} H-NMR spectrum of compound (8)

2-{(2E)-2-[(4-phenyl-1,3-thiazol-2-yl)hydrazono]propyl}-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (9)

Off white powder, yield 35%, mp. 253-255°C; IR (KBr, cm^{-1}): 3416, 3321, 3234, 3154 (NH_2, NH), 3093 (C-H aromatic), 2966, 2852 (C-H aliphatic), 1734 (C=O of ring), 1649 (C=N), 1618 (C=C of thiazole ring), 1251 (C=S). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.93 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 4.54 (s, 1H, NH), 7.10 (s, 1H, CH of thiazole ring), 7.20-7.70 (m, 5H, aromatic), 7.70-8.30 (m, 4H, aromatic) (Figure 7).

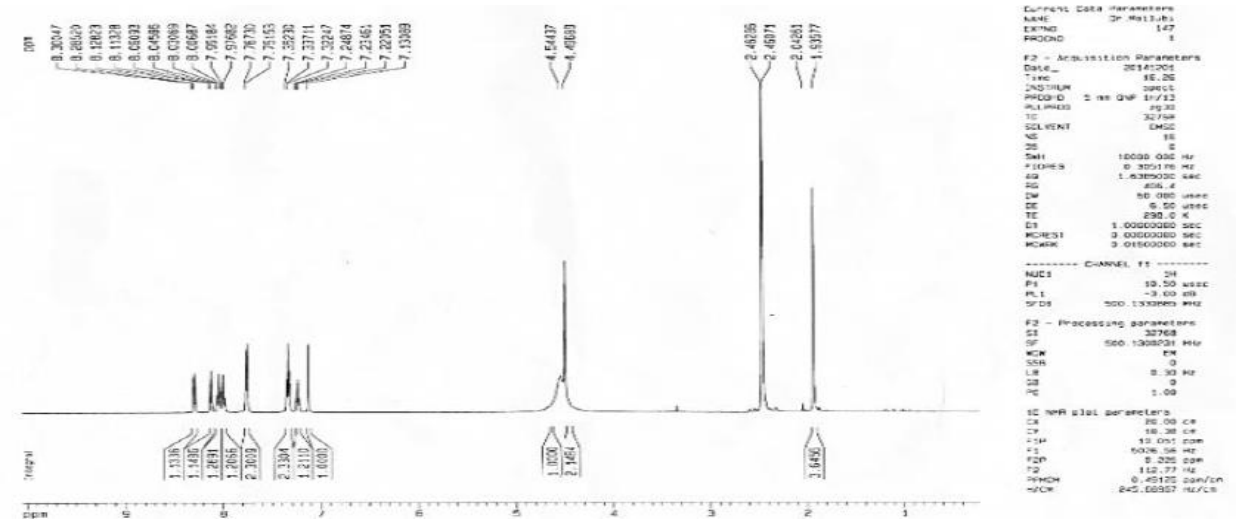


Figure 7: ^{1}H-NMR spectrum of compound (9)

General procedure for the synthesis of imidazolidine derivatives (10-12)

These compounds were synthesized according to the procedure described in reference [18-21]. Carbazone derivative **4**,**5** or thiosemicarbazone **6** (0.001 mol) was added to a solution of ethyl chloroacetate (0.001 mol) and sodium acetate (0.001 mol) in ethanol (30 ml). The resulting mixture was refluxed for 12 h, then cooled and poured onto ice water. The solid product was filtered off, washed with water, dried and recrystallized from methanol.

3-{[(1E)-2-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-1-methy lethylidene]amino} imidazolidine-2,4-dione (10)

Off white powder, yield 27%, mp. 224-227°C; IR (KBr, cm^{-1}): 3171 (NH), 3034 (C-H aromatic), 2985, 2951, 2922 (C-H aliphatic), 1731 (C=O of saccharine ring), 1724 (C=O of imidazole ring), 1699 (C=O of CONH), 1654 (C=N), 1587, 1462 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.10 (s, 3H, CH_3), 3.76 (s, 2H, $NHCH_2$), 4.70 (s, 2H, NCH_2), 6.20 (s, 1H, NH), 7.90-8.30 (m, 4H, aromatic) (Figure 8).

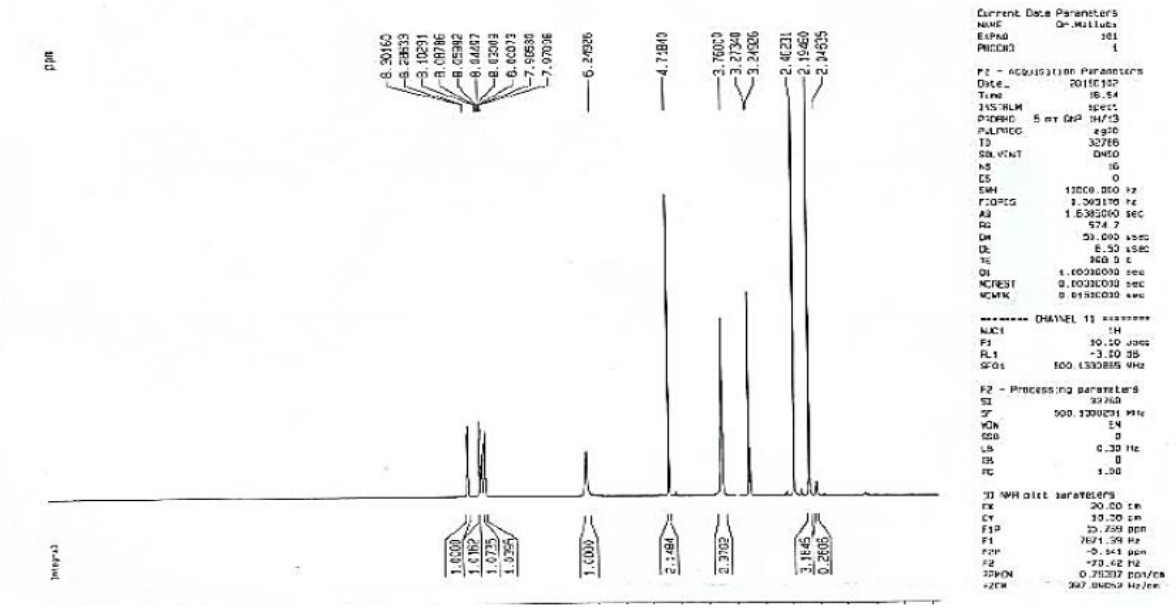


Figure 8: ^{1}H-NMR spectrum of compound (10)

3-{[(1E)-2-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl)-1- methyl propylidene] amino} imidazolidine -2,4-dione (11)

Off white powder, yield 25%, mp. 187-189°C; IR (KBr, cm^{-1}): 3146 (*NH*), 3084 (C-H aromatic), 2980, 2940 (C-H aliphatic), 1741 (C=O of saccharine ring), 1710 (C=O of imidazole ring), 1656 (C=O of CONH), 1600 (C=N), 1547, 1421 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.64 (d, 3H, $CHCH_3$), 1.92 (s, 3H, CH_3), 3.74 (s, 2H, $NHCH_2$), 6.42 (s, 1H, NH), 6.20 (s, 1H, NH), 7.97-8.07 (m, 3H, aromatic), 7.97-8.07 (m, 1H, aromatic) (Figure 9).

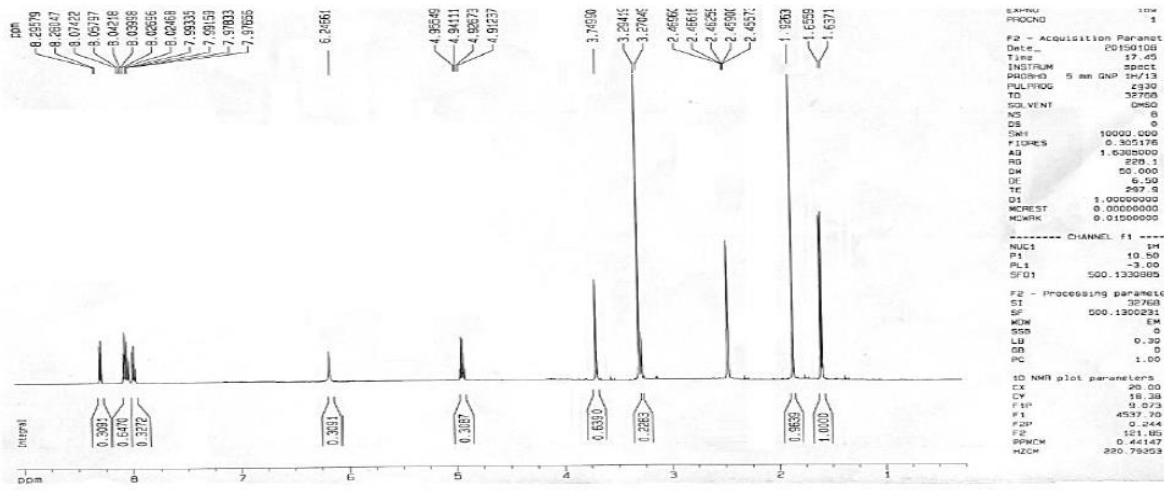


Figure 9: ^{1}H-NMR spectrum of compound (11)

2-{(2E)-2-[(5-oxo-2-thioxoimidazolidin-1-yl)imino]propyl}-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (12)

Off white powder, yield 38%, mp. 202-204°C; IR (KBr, cm^{-1}): 3161 (*NH*), 3090 (C-H aromatic), 2951, 2922, 2854 (C-H aliphatic), 1739 (C=O of saccharine ring), 1697 (C=O of imidazole ring), 1656 (C=N), 1591, 1489 (C=C). ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 1.90 (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 4.5 (s, 2H, NCH_2), 7.90-8.20 (m, 4H, aromatic), 11.7 (s, 1H, NH) (Figure 10).

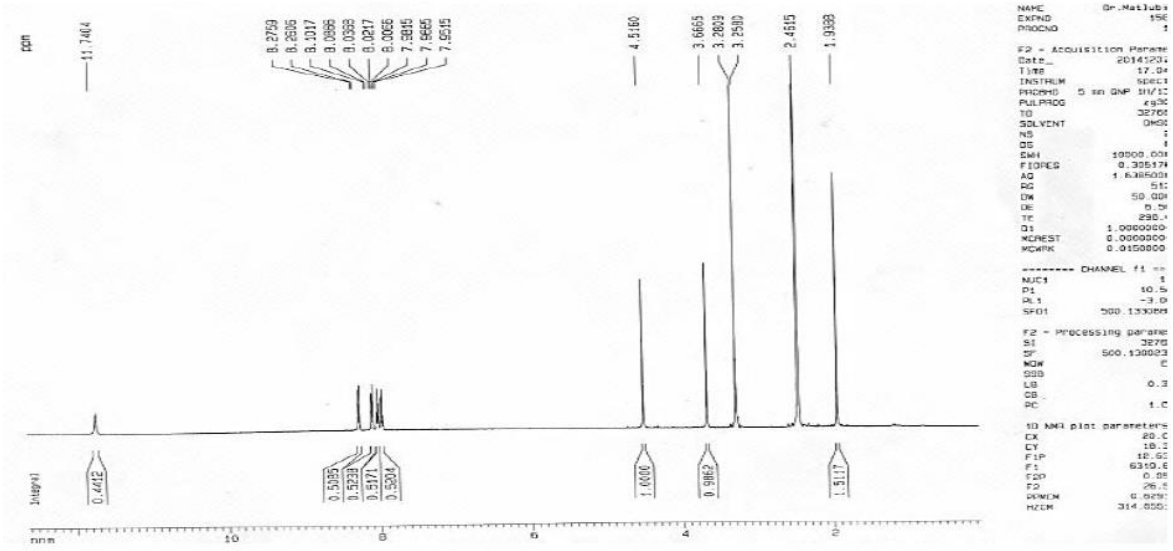
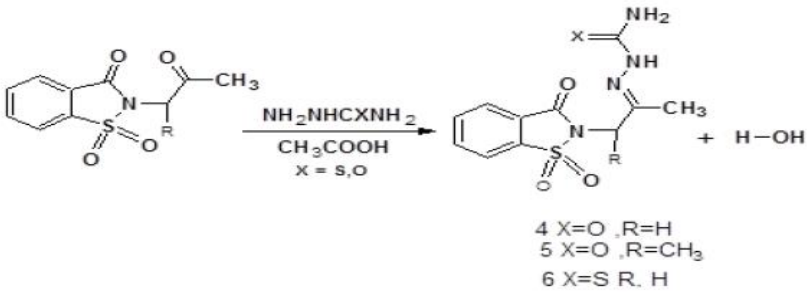


Figure 10: ^{1}H-NMR spectrum of compound (12)

RESULT AND DISCUSSION

The thiosemicarbazone (**6**) and semicarbazone (**4**, **5**) were synthesized by the reaction of thiosemicarbazide or semicarbazide with compound (**1**) 2-(2-oxopropyl)-1,2-benzisothiazol- 3(2H)-one 1,1-dioxide or compound (**2**) 2-(1-methyl-2-oxopropyl)-1,2-benzisothiazol-3(2H)-one-1,1-dioxide.



The synthesized compounds have been characterized by FTIR, NMR and ^{13}CNMR spectra

The reactions of compounds (**6**) or (**4**,**5**) with phenacylbromide by intermolecular cyclization through SN_2 mechanism were produced the desired thiazole derivatives (**9**) or oxazole derivatives (**7**,**8**).

The FTIR spectrum of compound (**9**) confirmed the disappearance of bands at (3416, 3321, 3234) cm^{-1} for NH_2 with appearance absorption band at 1251 cm^{-1} for C=S and a new absorption band at 1649 cm^{-1} for C=N of thiazole ring and a band at 1618 cm^{-1} for C=C of thiazole ring. The ^{1}H-NMR spectrum of compound (**9**) in (DMSO-d6) as a solvent, showed the following data: 1.93 (s, 3H,CH_3), 4.49 (s,2H,CH_2), 7.1 (s, 1H, thiazole ring), 4.54 (s, 1H, NH), 7.2-7.7 (m,5H, aromatic benzene ring), 7.7-8.3(m,4H, aromatic protons of saccharin ring). It's worth to mention, that ^{1}HNMR in DMSO-d6 as a solvent of compound **(7)** gave the following data: 1.97 (s, 3H, CH_3), 4.53 (s,2H,NCH_2), 4.9 (s, 1H, NH), 6.7(s, 1H, oxazole ring), 7.1-8.3 (m, 9H, aromatic ring). In addition to above, ^{1}HNMR in DMSO-d6 as a solvent of compound (**8**) gave the following data: 1.61-1.68(d,3H,CH_3CH),1.91 (s,3H,CH_3), 4.7 (s,1H,NH),4.9-4.95 (q,1H, CH CH_3), 6.49 (s,1H, oxazole ring) 7-7.23 (m,5H, phenyl ring), 7.9-8.3(m, 4H, aromatic ring of saccharin).

Compounds (**10**,**11**,**12**) were produced from the reaction thiosemicarbazone (**6**) and semicarbazone (**4**,**5**) with ethyl chloroacetate in sodium acetate. As shown in this reaction.

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