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Design, Synthesis and Antiviral Evaluation of New *N*-(4)-(benzo[d][1,3]-dioxol-5-yl)thiosemicarbazone Derivatives

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Abstract

A new series of *N*-(4)-substituted thiosemicarbazone derivatives **4-8** incorporating a benzo[*d*][1,3]dioxole moiety were synthesized through the reaction of *N*-(4)-(benzo[*d*][1,3]dioxol-5-yl)-thiosemicarbazide with various carbonyl compounds such as aromatic aldehyde, heterocyclic aldehyde, acetophenone, heterocyclic ketone and cyclic ketone derivatives. The structure of the prepared thiosemicarbazones was established based on spectroscopic IR, ^{1}H-NMR, ^{13}C-NMR and elemental analyses data. The antiviral activity of the synthesized compounds was testedagainst Bovine Viral Diarrhea Virus (BVDV).

Keywords: Thiosemicarbazones, thiosemicarbazide, benzo[*d*][1,3]dioxole, antiviral, BVDV.

1. Introduction

Thiosemicarbazone derivatives (TSCs) are interesting and unique compounds and they displayed wide range of biological activities and they have occupied a prominent place in medicinal chemistry. Historically, the thiosemicarbazone derivatives is synthesized by the condensation of thiosemicarbazide derivatives with aldehydes or ketones [1, 2] . Since the demonstration the antiviral activities of thiosemicarbazones against vaccinia virus infection, many investigations have been designed to synthesis library of a biologically active thiosemicarbazone derivatives such as antiviral [3, 4], antibacterial [2], antifungal [2], antitumor [5], antiprotozoal [6] agents. Interestingly, these activities are depending on the nature of the parent aldehyde or ketone. Isatin *β*-thiosemicarbazone and marboran (Figure 1) showed the promising antiviral activities [7]. The heterocyclic thiosemicarbazone derivatives have been reported against herpes simplex virus[8]. Also, thiosemicarbazone derivatives have been reported as promising anti-human immunodeficiency virus agents[9]. Amithiozone have been reported in the treatment of tuberculosis[10]. 2-Acetylpyridine thiosemicarbazones were reported as antimalarial agents[11]. Triapine (Figure 1) was used as a cancer chemotherapeutic agent and as ribonucleotide reductase inhibitor[12]. Ambazone[13] and cutisone[14] have been reported as antitumour agents. As shown in Figure 2, thiosemicarbazones have coordination capacity and excellent chelating ability with most of the transition metal ions. Thiosemicarbazones metal complexes studies were carry out through many research areas such as analytical applications, the coordination chemistry and biological activities[15]. Recently, thiosemicarbazone complexes have been the subject of most structural and medicinal studies[16]. Thiosemicarbazone metal complexes possess extensive medicinal activities such as antitumor [17], antibacterial [18], antifungal [19], anti-amoebic [20] activities. These biological activities are may be associated with the coordination chemistry of these compounds [21]. In the same line, thiosemicarbazones were utilized as a key starting materials for synthesizing of a series of heterocyclic and fused heterocyclic compounds which possess a remarkable pharmacological profile such as thiazole, thiazolidinone and pyrazole derivatives [22].

On the other hand, large number of compounds contain benzodioxole moiety are known in medicinal

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chemistry as promising compounds, which reported as keys in many synthetic and natural origins bioactive compounds such as 5-(2-propenyl)-1,3-benzodioxole (Safrole, well-known anticancer drug) [23]. The structure activity relationship reported that, incorporation of the methylenedioxy moiety led to enhancing the biological activity [24-26]. Many substituted benzodioxole system with different moieties, revealed that the presence of benzodioxole plays an important role in the biological activities, which showed significant antitumour [27, 28], antimicrobial [29], antimalarial [30], anti-HIV [31], antiviral [32] and leishmanicidal activities [33].

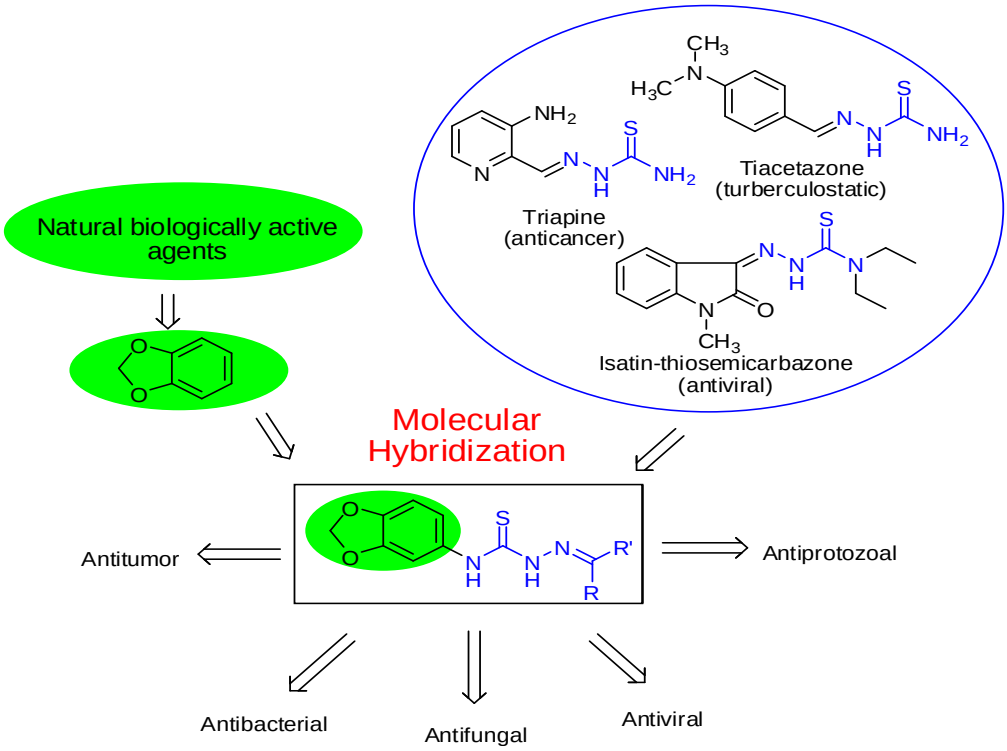


Figure 1. Suggested biological activity profiles of the designed compounds.

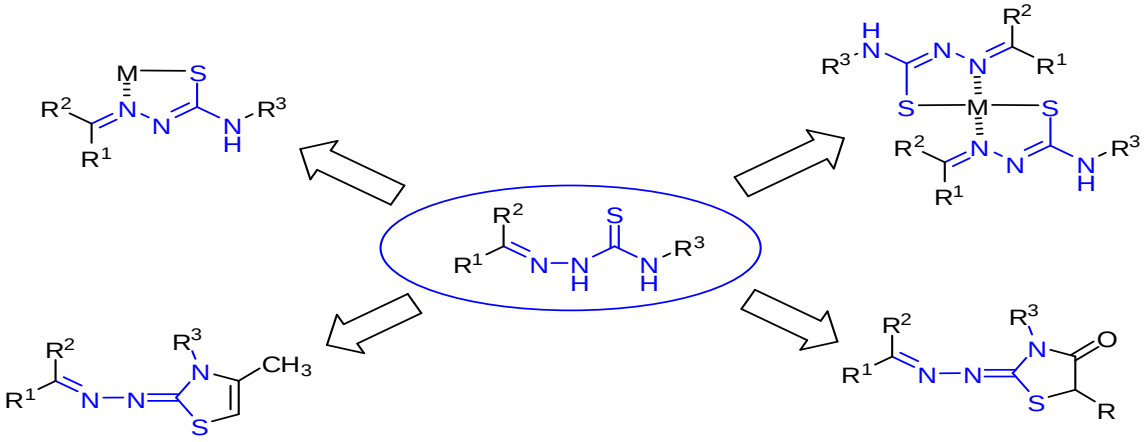


Figure 2. Structures of thiosemicarbazones and their metal complexes, thiazole and thiazolidinone derivatives.

In continuation of our ongoing studies in the field of organic and organometallic chemistry [1, 34-42], and the aforementioned inhibitory activities of benzo[*d*][1,3]dioxol-5-yl moiety. We planned to synthesize a new thiosemicarbazones **4-8** bearing benzo[*d*][1,3]dioxol-5-ylmoiety and test their antiviral activity against Bovine Viral Diarrhea Virus (BVDV).

2. Experimental Section

All melting points were determined on an Electrothermal Gallenkamp apparatus. IR spectra

were measured on a JASCO FTIR Spectrometer in KBr discs. NMR spectra were recorded in DMSO-d_6 on a Bruker WP spectrometer (500 MHz), the chemical shifts δ downfield from TMS as an internal standard.

Syntheses of aldehyde thiosemicarbazone derivatives 2a-h. A mixture of *N*-(4)-(benzo[*d*][1,3]dioxol-5-yl)-thiosemicarbazide **1** (0.01 mol) and the desired aldehyde (namely benzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-nitobenzaldehyde, 4-*N*,*N*-dimethylbenzaldehyde or 4-cyanobenzaldehyde) (0.01 mol) in ethanol (25 mL) was heated under reflux for 1 h., the solid which was separated on heating was filtered and crystallized from dioxane to give the desired thiosemicarbazones **2a-h**.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-benzylidenehydrazinecarbothioamide (2a)** [43]: Yield 86%; m.p. 183-184 °C; IR: ν/cm^{-1} = 3319, 3156 (NH), 1538 (C=N), 1229 (C=S); ^{1}H NMR: δ/ppm: 6.01 (s, 2H, OCH_2O), 6.87 (m, 2H, benzodioxole), 7.10 (m, 1H, benzodioxole), 7.25 -7.50 (m, 3H, Ar-H), 7.86 (m, 2H, Ar-H), 8.10 (s, 1H, N=CH), 9.99 (br, 1H, NH), 11.78 (br, 1H, NH); ^{13}C NMR: 101.3, 107.4, 108.0, 119.4, 127.6, 128.6, 130.0, 133.1, 134.0, 142.8, 144.9, 146.6, 176.4; Anal. Calcd. for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.18; H, 4.38; N, 14.04; Found: C, 60.32; H, 4.27; N, 14.31%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-chlorobenzylidene)hydrazinecarbothioamide (2b)** [43]: Yield 81%; m.p. 200-203 °C. IR: ν/cm^{-1} = 3292, 3187 (NH), 1628 (C=N), 1230 (C=S); ^{1}H NMR: δ/ppm: 6.02 (s, 2H, OCH_2O), 6.90-6.96 (m, 2H, benzodioxole), 7.16 (s, 1H, benzodioxole), 7.48 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.95 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.14 (s, 1H, N=CH), 10.07 (br, 1H, NH), 11.86 (br, 1H, NH); ^{13}C NMR: 101.3, 107.4, 108.0, 119.5, 128.7, 129.2, 133.0, 133.1, 134.4, 141.3, 144.9, 146.6, 176.5; Anal. Calcd. for $C_{15}H_{12}ClN_3O_2S$ (333.79): C, 53.97; H, 3.62; N, 12.59; Found: C, 53.87; H, 3.54; N, 12.42%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-bromobenzylidene)hydrazinecarbothioamide (2c)** [43]: Yield 85%; m.p. 192-195 °C. IR: ν/cm^{-1} = 3340, 3142 (NH), 1624 (C=N); ^{1}H NMR: δ/ppm: 6.01 (s, 2H, OCH_2O), 6.87 (m, 2H, benzodioxole), 7.08 (s, 1H, benzodioxole), 7.58 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.84 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.06 (s, 1H, CH=N), 10.05 (br, 1H, NH), 11.83 (br, 1H, NH); ^{13}C NMR: 101.2, 107.3, 108.0, 119.5, 123.2, 129.5, 131.6, 133.0, 133.3, 141.4, 144.9, 146.5, 176.5; Anal. Calcd. for $C_{15}H_{12}BrN_3O_2S$ (378.24): C, 47.63; H, 3.20; N, 11.11; Found: C, 47.88; H, 3.14; N, 11.03%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methylbenzylidene)hydrazinecarbothioamide (2d)**: Yield 88%; m.p. 163-164 °C; IR: ν/cm^{-1} = 3340, 3146 (NH), 1611 (C=N), 1247 (C=S); ^{1}H NMR: δ/ppm: 2.30 (s, 3H, CH_3), 6.01 (s, 2H, OCH_2O), 6.87 (m, 2H, benzodioxole), 7.10 (s, 1H, benzodioxole), 7.20 (d, 2H, *J* = 7.9 Hz, Ar-H), 7.74 (d, 2H, *J* = 7.9 Hz, Ar-H), 8.07 (s, 1H, N=CH), 9.96 (br, 1H, NH), 11.63 (br, 1H, NH); Anal. Calcd. for $C_{16}H_{15}N_3O_2S$ (313.37): C, 61.32; H, 4.82; N, 13.41; Found: C, 61.23; H, 4.79; N, 13.57%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-methoxybenzylidene)hydrazinecarbothioamide (2e)**: Yield 79%; m.p. 194-195 °C; IR: ν/cm^{-1} = 3289, 3161 (NH), 1606 (C=N), 1247 (C=S); ^{1}H NMR: δ/ppm: 3.76 (s, 3H, OCH_3), 6.01 (s, 2H, OCH_2O), 6.59-7.34 (m, 5H, Ar-H), 7.80 (m, 2H, Ar-H), 8.06 (s, 1H, N=CH), 9.91 (br, 1H, NH), 11.61 (br, 1H, NH); Anal. Calcd. for $C_{16}H_{15}N_3O_3S$ (329.37): C, 58.34; H, 4.59; N, 12.76; Found: C, 58.46; H, 4.72; N, 12.65%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-nitrobenzylidene)hydrazinecarbothioamide (2f)** [43]: Yield 95%; m.p. 232-235 °C. IR: ν/cm^{-1} = 3328, 3160 (NH), 1597 (C=N), 1237 (C=S); ^{1}H NMR: δ/ppm: 6.02 (s, 2H, OCH_2O), 6.97-7.10 (m, 3H, benzodioxole), 8.20-8.25 (m, 5H, 4Ar-H + N=CH), 10.20 (br, 1H, NH), 12.04 (br, 1H, NH); ^{13}C NMR: 101.3, 107.4, 108.1, 119.6, 123.7, 128.4, 132.9, 140.0, 140.5, 145.0, 146.7, 147.6, 176.8; Anal. Calcd. for $C_{15}H_{12}N_4O_4S$ (344.35): C, 52.32; H, 3.51; N, 16.27; Found: C, 52.56; H, 3.47; N, 16.18%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-(dimethylamino)benzylidene)hydrazine-carbothioamide (2g)** [43]: Yield 85%; m.p. 210-212°C. IR: ν/cm^{-1} = 3280, 3142 (NH), 1600 (C=N), 1224 (C=S); ^{1}H NMR: δ/ppm: 2.91 (s, 6H, $2CH_3$), 5.96 (s, 2H, OCH_2O), 6.66 (d, 2H *J* = 8.2 Hz, Ar-H), 6.84 (m, 2H, Ar-H), 7.08 (m, 1H, Ar-H), 7.62 (d, 2H, *J* = 8.9 Hz, Ar-H), 7.94 (s, 1H, N=CH), 9.87 (br, 1H, NH), 11.56 (br, 1H, NH); ^{13}C NMR: 39.7, 101.7, 107.9, 108.2, 112.1, 119.7, 121.5, 129.6, 133.6, 144.8, 145.8, 145.2, 146.9, 152.3, 175.5; Anal. Calcd. for $C_{17}H_{18}N_4O_2S$ (342.42): C, 59.63; H, 5.30; N, 16.36; Found: C, 59.87; H, 5.23; N, 16.54%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(4-cyanobenzylidene)hydrazinecarbothioamide (2h)** [43]: Yield 87%; m.p. 222-223°C. IR: ν/cm^{-1} = 3313, 3148 (NH), 2225 (C≡N), 1622 (C=N), 1216 (C=S); ^{1}H NMR: δ/ppm: 6.02 (s, 2H, OCH_2O), 6.88 (m, 2H, benzodioxole), 7.06 (s, 1H, benzodioxole), 7.85 (d, 2H, *J* = 7.9 Hz, Ar-H), 8.09 (m, 3H, Ar-H + N=CH), 10.16 (br, 1H, NH), 11.98 (br, 1H, NH); ^{13}C NMR: 101.3, 107.4, 108.1, 111.7, 118.8, 119.6, 128.0, 132.4,

132.9, 138.6, 140.5, 145.1, 146.7, 176.7; Anal. Calcd. for $C_{16}H_{12}N_4O_2S$ (324.36): C, 59.25; H, 3.73; N, 17.27; Found: C, 59.42; H, 3.67; N, 17.41%.

Syntheses of heterocyclic aldehyde thiosemicarbazone derivatives 3a-e. A mixture of *N*-(4)-(benzo[*d*][1,3]dioxol-5-yl)-thiosemicarbazide **1** (0.01 mol) and the desired heterocyclic aldehyde (0.01 mol) (namely furfural, 5-methylfurfural, 5-nitrofurfural, thiophene-2-aldehyde, or 1-methyl-1*H*-pyrrole-2-carbaldehyde) in 25 mL ethanol was heated under reflux for 1 h. The solid was formed while heating. The reaction mixture was left to cool and the solid precipitate was filtered, washed with cold ethanol and crystallized from dioxane to give the desired thiosemicarbazones **3a-e.**

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(furan-2-ylmethylene)hydrazinecarbothioamide (3a)**: Yield 75%; m.p. 202-203 °C; IR: ν/cm^{-1} = 3357, 3146 (NH), 1618 (C=N), 1228 (C=S); ^{1}H NMR: δ/ppm: 6.00 (s, 2H, OCH_2O), 6.62 (m, 1H, Ar-H), 6.69 - 6.96 (m, 2H, Ar-H), 6.94-7.31 (m, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 8.02 (s, 1H, CH=N), 9.73 (br, 1H, NH), 11.77 (br, 1H, NH); Anal. Calcd. for $C_{13}H_{11}N_3O_3S$ (289.31): C, 53.97; H, 3.83; N, 14.52; Found: C, 54.14; H, 3.79; N, 14.38%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-((5-methylfuran-2-yl)methylene)hydrazine- carbothioamide (3b)**: Yield 77%; m.p. 198-200 °C; IR: ν/cm^{-1} = 3353, 3124 (NH), 1618 (C=N), 1251 (C=S); ^{1}H NMR: δ/ppm: 2.28 (s, 3H, CH_3), 6.0 (s, 2H, OCH_2O), 6.23 (m, 1H, Ar-H), 6.87 (m, 4H, Ar-H),7.13 (m, 1H, Ar-H), 7.96 (s, 1H, CH=N), 9.63 (br, 1H, NH), 11.70 (br, 1H, NH); Anal. Calcd. for $C_{14}H_{13}N_3O_3S$ (303.34): C, 55.43; H, 4.32; N, 13.85; Found: C, 55.58; H, 4.28; N, 13.91%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-((5-nitrofuran-2-yl)methylene)hydrazine- carbothioamide (3c)**: Yield 73%; m.p. 200-203 °C; IR: ν/cm^{-1} = 3203, 3102 (NH), 1637 (C=N), 1241 (C=S); ^{1}H NMR: δ/ppm: 6.02 (s, 2H, OCH_2O), 6.85 (m, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.80 (m, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 8.70 (s, 1H, CH=N), 10.06 (br, 1H, NH), 12.18 (br, 1H, NH); Anal. Calcd. for $C_{13}H_{10}N_4O_5S$ (334.31): C, 46.71; H, 3.02; N, 16.76; Found: C, 46.66; H, 2.98; N, 16.75%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(thiophen-2-ylmethylene)hydrazinecarbothioamide (3d)**: Yield 80%; m.p. 194-196 °C; IR: ν/cm^{-1} = 3330, 3133 (NH), 1542 (C=N), 1233 (C=S); ^{1}H NMR: δ/ppm:6.00 (s, 2H, OCH_2O), 6.86 (m, 2H, Ar-H), 7.10 (m, 2H, Ar-H), 7.49 (m, 1H, Ar-H), 7.66 (m, 1H, Ar-H), 8.29 (s, 1H, CH=N), 9.68 (br, 1H, NH), 11.77 (br, 1H, NH); Anal. Calcd. for $C_{13}H_{11}N_3O_2S_2$ (305.38): C, 51.13; H, 3.63; N, 13.76; Found: C, 51.23; H, 3.59; N, 13.68%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-((1-methyl-1*H*-pyrrol-2-yl)methylene)hydrazine- carbothioamide (3e)**: Yield 75%; m.p. 174-177 °C; IR: ν/cm^{-1} = 3339, 3139 (NH), 1608 (C=N), 1247 (C=S); ^{1}H NMR: δ/ppm: 3.80 (s, 3H, NCH_3), 6.00 (d, 2H, OCH_2O), 6.57 (s, 1H, Ar-H), 6.81-7.94 (m, 4H, Ar-H), 7.19 (m, 1H, Ar-H), 8.09 (s, 1H, CH=N), 9.41 (br, 1H, NH), 11.47 (br, 1H, NH); ^{13}C NMR: 36.5, 101.7, 107.8, 107.9, 109.0, 115.6, 119.1, 127.2, 128.8, 133.7, 137.0, 145.1, 147.1, 175.5; Anal. Calcd. for $C_{14}H_{14}N_4O_2S$ (302.35): C, 55.61; H, 4.67; N, 18.53; Found: C, 55.54; H, 4.66; N, 18.48%.

Syntheses of pyrazolealdehydethiosemicarbazone derivatives 4 and 5a,b. A mixture of *N*-(4)-(benzo[d][1,3]dioxol-5-yl) thiosemicarbazide **1** (0.01 mol) and the desired pyrazole-carbaldehyde (namely 4-formylantipyrine, 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde, or 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde) (0.01 mol) in ethanol (25 mL) was heated under reflux for 1 h., the solid which separated on heating was filtered and crystallized from dioxane to give the desired thiosemicarbazones **4** and **5a,b.**

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (4)**: Yield 80%; m.p. 208-210 °C; IR: ν/cm^{-1} = 3312 (NH), 1631 (C=N), 1212 (C=S); ^{1}H NMR: δ/ppm: 2.44 (s, 3H, CH_3), 3.23(s, 3H, CH_3), 5.99 (s, 2H, OCH_2O), 6.80-6.98 (m, 2H, Ar-H), 7.19-7.56 (m, 6H, Ar-H), 7.98 (s, 1H, CH=N), 9.73 (br, 1H, NH), 13.49 (br, 1H, NH); Anal. Calcd. for $C_{20}H_{19}N_5O_3S$ (409.46): C, 58.67; H, 4.68; N, 17.10; Found: C, 58.81; H, 4.67; N, 17.19%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-hydrazinecarbothioamide (5a)**: Yield 83%; m.p. 209-210 °C; IR: ν/cm^{-1} = 3300, 3141 (NH), 1616 (C=N), 1217 (C=S); ^{1}H NMR: δ/ppm: 6.02 (s, 2H, OCH_2O), 6.89 (m, 2H,Ar-H), 7.15 (s, 1H, Ar-H), 7.36 (m, 2H, Ar-H), 7.51 (m, 5H,Ar-H), 7.67 (m, 2H,Ar-H), 7.87 (m, 2H, Ar-H), 8.28 (s, 1H, CH=N), 9.22 (br, 1H, NH), 9.73 (br, 1H, NH); Anal. Calcd. for $C_{24}H_{19}N_5O_2S$ (441.50): C, 65.29; H, 4.34; N, 15.86; Found: C, 65.33; H, 4.31; N, 15.94%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5b)**: Yield 81%; m.p. 260-262 °C; IR: ν/cm^{-1} = 3319, 3124 (NH), 1621 (C=N), 1240 (C=S); ^{1}H NMR: δ/ppm: 6.01 (s, 2H, OCH_2O), 6.60-8.10 (m, 14H, 13Ar-H + N=CH),

9.21 (br, 1H, NH), 9.69 (br, 1H, NH); Anal. Calcd. for $C_{24}H_{18}ClN_5O_2S$ (475.95): C, 60.56; H, 3.81; N, 14.71; Found: C, 60.64; H, 3.79; N, 14.82%.

Syntheses of methyl aryl ketone *N*-thiosemicarbazones 6a-e. A mixture of thiosemicarbazide**1** (0.01 mol) and desired ketone (namely acetophenone, 4-chloroacetophenone 4-bromoacetophenone, 4-methylacetophenone or 4-methoxy- acetophenone) (0.01 mol) in ethanol (30 mL) was heated under reflux for 6 h. then left to cool, the solid which separated was filtered off and recrystallized from dioxane to give **6a-e**.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-phenylethylidene)hydrazinecarbothioamide (6a)**: Yield 76%; m.p. 171-172 °C; IR: ν/cm^{-1} = 3313, 3258 (NH); ^{1}H NMR: δ/ppm: 2.46 (s, 3H, CH_3), 6.01 (s, 2H, OCH_2O), 6.60-8.10 (m, 7H, Ar-H), 9.89 (br, 1H, NH), 10.51 (br, 1H, NH); Anal. Calcd. for $C_{16}H_{15}N_3O_2S$ (313.37): C, 61.32; H, 4.82; N, 13.41; Found: C, 61.43; H, 4.79; N, 13.52%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-(4-chlorophenyl)ethylidene)hydrazine-carbothioamide (6b)**: Yield 74%; m.p. 200-201 °C; IR: ν/cm^{-1} = 3298, 3179 (NH); ^{1}H NMR: δ/ppm: 2.05 (s, 3H, CH_3), 6.01 (s, 2H, OCH_2O), 6.85 (m, 2H, Ar-H), 7.07 (s, 1H, Ar-H), 7.40-7.50 (m, 2H, Ar-H), 7.80-8.05 (m, 2H, Ar-H), 9.94 (br, 1H, NH), 10.56 (br, 1H, NH); Anal. Calcd. for $C_{16}H_{14}ClN_3O_2S$ (347.82): C, 55.25; H, 4.06; N, 12.08; Found: C, 55.41; H, 4.09; N, 12.14%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-(4-bromophenyl)ethylidene)hydrazinecarbothio-amide (6c)**: Yield 68%; m.p. 215-218 °C; IR: ν/cm^{-1} = 3289, 3174 (NH); ^{1}H NMR: δ/ppm: 2.22 (s, 3H, CH_3), 6.01 (s, 2H, OCH_2O), 6.84 (m, 2H, Ar-H), 7.07 (s, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 7.89 (m, 2H, Ar-H), 9.95 (br, 1H, NH), 10.92 (br, 1H, NH); Anal. Calcd for $C_{16}H_{14}BrN_3O_2S$ (392.27): C, 48.99; H, 3.60; N, 10.71; Found: C, 49.12; H, 3.58; N, 10.84%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-*p*-tolylethylidene)hydrazinecarbothioamide (6d)**: Yield 67%; m.p. 175-177 °C; IR: ν/cm^{-1} = 3311 (NH); ^{1}H NMR: δ/ppm: 2.22, 2.29 (2s, 6H, $2CH_3$), 6.01 (s, 2H, OCH_2O), 6.87 (m, 2H, Ar-H,), 7.10-7.21 (m, 3H, Ar-H), 7.70-7.90 (m, 2H, Ar-H,), 9.77 (br, 1H, NH), 10.48 (br, 1H, NH); Anal. Calcd. for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.36; H, 5.23; N, 12.83; Found: C, 62.41; H, 5.21; N, 12.94 %.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-(4-methoxyphenyl)ethylidene)hydrazine-carbothioamide (6e)**: Yield 64%; m.p. 210-213 °C; IR: ν/cm^{-1} = 3257, 3169 (NH); ^{1}H NMR: δ/ppm: 2.46 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.00 (s, 2H, OCH_2O), 6.87 (s, 1H, Ar-H,), 7.11-7.40 (m, 3H, Ar-H), 7.60 - 8.10 (m, 3H, Ar-H), 9.87 (br, 1H, NH), 11.01 (br, 1H,NH); Anal. Calcd. for $C_{17}H_{17}N_3O_3S$ (343.40): C, 59.46; H, 4.99; N, 12.24; Found: C, 59.52; H, 4.97; N, 12.31%.

Syntheses of methyl heterocyclic ketone *N*-thiosemicarbazones 7a,b. A mixture of thiosemicarbazide **1** (0.01 mol) and desired methyl heterocyclic ketone (namely 2-acetylfurane or 2-acetylthiophene) (0.01 mol) in ethanol (30 mL) was heated under reflux for 10 h. then left to cool, the solid which separated was filtered off and recrystallized from dioxane to give **7a,b**.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-(furan-2-yl)ethylidene)hydrazinecarbothioamide (7a)**: Yield 66%; m.p. 181-183 °C; IR: ν/cm^{-1} = 3312, 3205 (NH); ^{1}H NMR: δ/ppm: 2.26 (s, 3H, CH_3), 6.01 (s, 2H, OCH_2O), 6.70-8.20 (m, 6H, Ar-H), 9.76 (br, 1H, NH), 10.40 (br, 1H, NH); Anal. Calcd. for $C_{14}H_{13}N_3O_3S$ (303.34): C, 55.52; H, 4.30; N, 13.79; Found: C, 55.43; H, 4.32; N, 13.85%.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine- carbothioamide (7b)**: Yield 64 %; m.p. 179-181 °C; IR: ν/cm^{-1} = 3295, 3184 (NH); ^{1}H NMR: δ/ppm: 2.22 (s, 3H, CH), 6.00 (s, 2H, OCH_2O), 6.60-8.10 (m, 6H, Ar-H), 9.77 (br, 1H, NH), 10.45 (br, 1H, NH); Anal. Calcd. for $C_{14}H_{13}N_3O_2S_2$ (319.40): C, 52.65; H, 4.10; N, 13.16; Found: C, 52.71; H, 4.08; N, 13.21%.

Synthesis of indanone*N*-thiosemicarbazones 8a,b. A mixture of thiosemicarbazide **1** (0.01 mol) and desired cyclic ketone (1-indanone or 1,3- indandione) (0.01 mol) in dioxane (30 mL) was heated under reflux for 10 h. The solid product which separated on cooling was filtered off and recrystallized from dioxane to give **8a** and **8b**.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(2,3-dihydro-1*H*-inden-1-ylidene)hydrazine- carbothioamide (8a)**: Yield 68%; m.p. 216-218 °C; IR: ν/cm^{-1} = 3234, 3151 (NH); ^{1}H NMR: δ/ppm: 2.90 (s, 2H, CH_2), 3.09 (s, 2H, CH_2), 6.00 (s, 2H, OCH_2O), 6.88 (m, 2H, Ar-H), 7.14-7.34 (m, 3H, Ar-H), 7.80-8.05 (m, 2H, Ar-H), 9.71 (br, 1H, NH), 9.97 (br, 1H, NH); Anal. Calcd. for $C_{17}H_{15}N_3O_2S$ (325.38): C, 62.75; H, 4.65; N, 12.91; Found: C, 62.84; H, 4.63; N, 12.87 %.

***N*-(Benzo[*d*][1,3]dioxol-5-yl)-2-(3-oxo-2,3-dihydro-1*H*-inden-1-ylidene)hydrazine- carbothioamide (8b)**: Yield 70%; m.p. 227-228 °C; IR: ν/cm^{-1} = 3332 (NH), 1716 (C=O); ^{1}H NMR: δ/ppm: 3.55 (s, 2H,

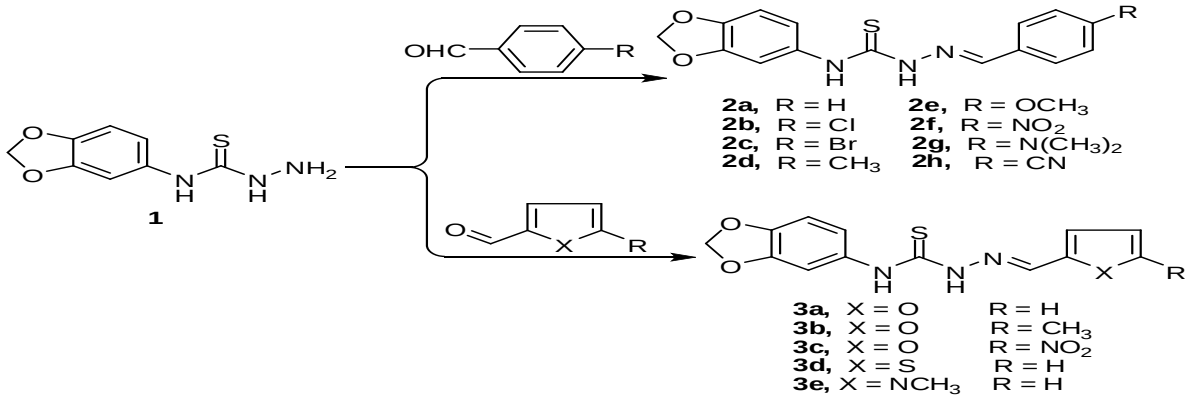
CH_2), 6.02 (s, 2H, OCH_2O), 6.60-8.40 (m, 7H, Ar-H), 10.14 (br, 1H, NH), 11.08 (br, 1H, NH); Anal. Calcd. for $C_{17}H_{13}N_3O_3S$ (339.37): C, 60.17; H, 3.86; N, 12.38; Found: C, 60.32; H, 3.82; N, 12.43 %.

3. Results and discussion

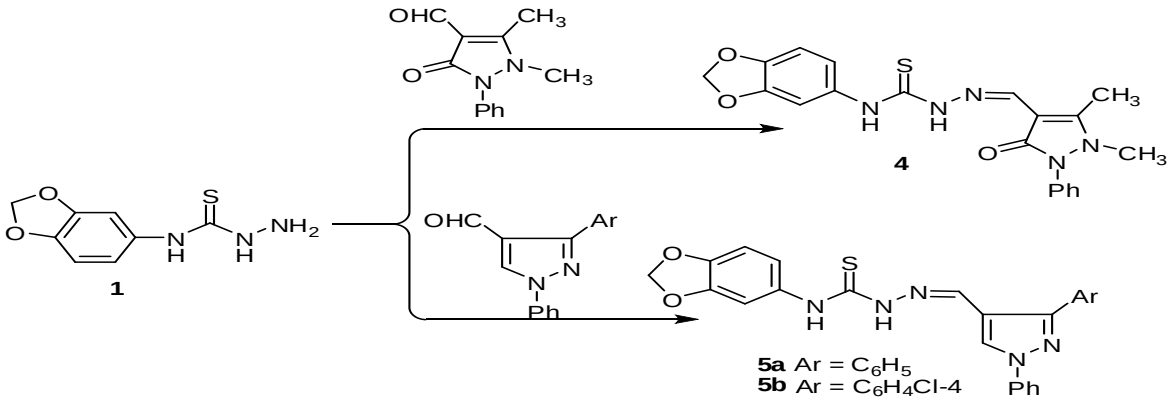
N-(Benzo[*d*][1,3]dioxol-5-yl) thiosemicarbazide derivative 1 was used for the synthesizing of many types of thiosemicarbazone derivatives. The condensation of thiosemicarbazide 1 with *para* substituted benzaldehydes gave the corresponding thiosemicarbazones 2a-h in a good yields as depicted in scheme 1. The obtained thiosemicarbazone derivatives 2a-h were characterized by the presence of different substituents (electron donating and electron with-drawing groups) at the phenyl group of parent aldehyde. Thus, substitution of hydrogen on the phenyl group by methyl, methoxy, fluorine, chlorine, bromine, nitro, dimethylamino or cyano groups was carried out for investigation of its effect on the biological activity.

Moreover, our investigation was extended to probe the behavior of thiosemicarbazide **1** towards different types of heterocyclic aldehydes. Thus, condensation of the thiosemicarbazide **1** with furfural, 5-methylfurfural, 5-nitrofurfural, 2-thiophene carbaldehyde and *N*-methyl-pyrrole-2-carboxadehyde afforded the corresponding thiosemicarbazone derivatives **3a-e**, respectively (Scheme 1).

As depicted in Scheme **2**, new thiosemicarbazone derivatives **4** and **5a,b** containing the substituted pyrazole rings were achieved. Thus, interaction of thiosemicarbazide **1** with 4-formylantipyrine and 4-formyl-1,3-disubstituted pyrazoles (which prepared *via* condensation of aryl ketones with phenyl hydrazine followed by cyclization-formylation under Vilsmeier-Haack conditions) gave the corresponding thiosemicarbazone **4** and 1,3,4-trisubstituted pyrazole derivatives **5a,b** respectively.

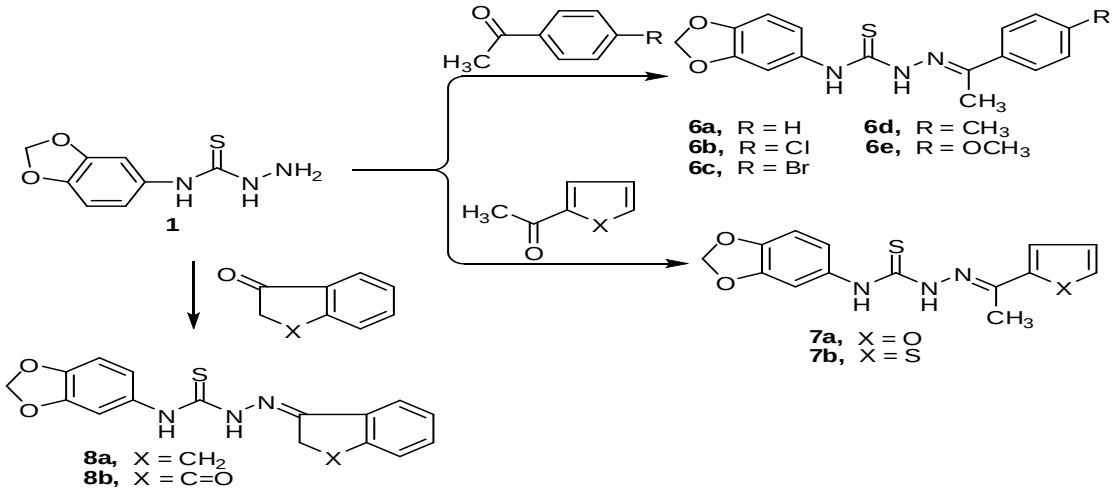


Scheme 1. Synthesis of aldehyde-thiosemicarbazone derivatives **2a-h** and **3a-e**.



Scheme 2. Synthesis of heterocyclic thiosemicarbazone derivatives **4** and **5**.

Likewise, the 2-(1-substitutedethylidene)hydrazine carbothioamide derivatives **6a-e** and **7a,b** were synthesized from condensation of thiosemicarbazide **1** with some desired aryl and heterocyclic methyl ketones in ethanol under reflux conditions. Finally, the treatment of the thiosemicarbazide **1** with 1-indanone and 1,3-indandione as a cyclic ketones, 1-indanone-thiosemicarbazones **8a,b** were obtained in good yields (Scheme **3**).



Scheme 3. Synthesis of ketone-**6a-e**, **7a,b** and indanone-**8a,b** thiosemicarbazone derivatives.

Anti-viral screening of the new synthesized compounds.

Preliminary anti-viral screening of selected examples from the synthesized products was carried out on the Bovine Viral Diarrhea Virus (BVDV), which is a single positive RNA stranded virus classified as a member of the same family of Hepatitis C Virus (HCV)i.e. flaviviridae. Some of the synthesized compounds were subjected to *in vitro* testing of antiviral activity. Viral infectivity assay was carried out using the plaque formation method [20]. A plaque is a localized focus of virus-infected cells which under optimal conditions originates from a single infectious virus particle. Counting of these foci for serial dilution of virus suspension is a highly quantitative method for assay of viral infectivity. Under these conditions, reduction in virus plaque counts provides a very sensitive mean for measuring antiviral activity of a potential antiviral. The results of the plaque reduction assay are summarized in Table 1. The antiviral effect obtained for the synthesized compounds suggested that the tested thiosemicarbazone derivatives have no antiviral activity or have a toxic effect on the cells.

Table 1. Antiviral screening of selected examples of the synthesized thiosemicarbazone Derivatives:

compound	Concentration (10 µg/mL)	results
3b	toxic effect	----------
3e	toxic effect	----------
4	$85*10^{-4.6}$ PFU	Inactive
5b	$85*10^{-4.6}$ PFU	Inactive
6b	$85*10^{-4.6}$ PFU	Inactive
7a	$85*10^{-4.6}$ PFU	Inactive
8b	$85*10^{-4.6}$ PFU	Inactive
Positive control	$85*10^{-4.6}$ PFU	

4. Conflicts of interest

There are no conflicts to declare.

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