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Synthesis, Reactions and Biological Evaluation of Some Novel 5-Bromobenzofuran-Based Heterocycles

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Abstract Condensation of 2-acetyl-5-bromobenzofuran with hydrazine derivatives **2a,b** afforded hydrazone derivatives **3a,b**, which reacted with alkyl halides**4a,b** to yield ethylidene derivatives **5a,b**. Also, **3a** reacted with hydrazonyl halides**6a,b** to give 1,3,4-thiadiazole derivatives **9a,b**. Thiosemicarbazone**3b** was reacted with acetic anhydride and halogenated compounds to afford the corresponding heterocyclic derivatives **10, 11a,b, 12-17** and **18a,b**.Moreover, interaction of **16** with tetracyanoethylene and salicyldehyde derivatives furnished **24** and **26a,b**, respectively. Finally, reaction of **16** with DMF-DMA afforded enaminone**29**, which on treatment with different heterocyclic amines yielded **31** and **33** respectively. Some of the newly synthesized compounds showed promising antimicrobial activity.

Keywords: *benzofuran, 1,3,4-thiadiazole, thiazolidinone, thiazole, antimicrobial*

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1. Introduction

Benzofuran derivatives are a class of fused ring heterocycles, that occur in a large number of natural products and have shown a high importance in medicinal chemistry [1,2]. Many natural products with benzofuran moiety exhibit interesting biological and pharmacological activities. They are antitumor [3], anti-inflammatory [4], antifungal [5], pesticidal and insecticidal [6], nematocidal [7], and anthelmintic [7]. On the other hand, thiosemicarbazones have been recently used as synthetic intermediates for heterocyclic compounds which have attracted much attention because of their widespread applications in the biological field [8,9,10,11,12]. In addition, thiazoles and their derivatives exhibit various biological activities such as antiviral, antimicrobial, antituberculosis and cytotoxic activities [13-22]. In continuation of my research on the synthesis of new heterocyclic compounds [23,24], this work deals with synthesis, characterization and biological evaluation of new compounds containing a benzofuran nucleus combined with thiosemicarbazide, thiazole and thiazolidinone moieties, which are expected to possess high biological activity.

2. Materials and Methods

All melting points are uncorrected. IR spectra (KBr) were recorded on FT-IR 5300 spectrometer and Perkin Elmer spectrum RXIFT-IR system (ν, cm^{-1}). The ^{1}H NMR spectra were recorded in (DMSO-d_6) at (300) MHz on a Varian Mercury VX-300 NMR spectrometer (δ, ppm) using TMS as an internal standard. ^{13}C NMR spectra were recorded on Varian Mercury VX 300 NMR using DMSO-*d6* as solvent and TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 eV. The Microanalytical Research Center, Faculty of Science, Cairo University carried out elemental analyses.

General procedure for preparation of 3a,b.

A mixture of (**1**; 0.01mol) and methyl hydrazine carbodithioate**(2a)** or thiosemicarbazide**(2b)** (0.01 mol) in ethanol (30 ml) was refluxed for 2 h. The separated solid on heating was filtered off and recrystallized from dioxane to give compounds **3a,b** respectively.

[(E)-methyl2-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazinecarbodithioate] ***(3a)***.

Brown crystals; Yield: 92%; mp: 155-157°C; IR (vcm^{-1}): 3176 (NH) and 1274 (C=S); ^{1}H-NMR (δ ppm): 2.40 (s, 3H, CH_3C=N), 2.48 (s, 3H, SCH_3), 7.44-7.92 (m, 4H, Ar-H and CH-furan) and 12.52 (s, 1H, NH); MS *m/z* (%): 342 (48); Anal. calcd. for $C_{12}H_{11}BrN_2OS_2$: C 41.99, H 3.23, N 8.16. Found: C 41.89, H 3.20, N 8.08.

[(E)-2-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazinecarbothioamide] ***(3b)***.

Yellow crystals; Yield: 88%; mp: 190-192°C; IR (vcm^{-1}): 3422, 3336, 3176 (NH_2/NH) and 1258 (C=S); ^{1}H-NMR (δ ppm): 2.33 (s, 3H, CH_3C=N), 7.36-7.87 (m, 4H, Ar-H and CH-furan), 8.43 (s, 2H, NH_2) and 10.53 (s, 1H, NH); MS *m/z* (%): 311 (73); Anal. calcd. for $C_{11}H_{10}BrN_3OS$: C 42.32, H 3.23, N 13.46. Found: C 42.26, H 3.17, N 13.39.

General procedure for preparation of 5a,b.

To a solution of **3a (**0.01mol) and alkylating agent namely (methyl iodide, ethyl bromoacetate) (0.01 mol) in ethanol (30 ml) triethylamine (0.01 mol) was added. The resulting mixture was heated under reflux for 3h and left to cool. The precipitate product was collected and recrystallized from glacial acetic acid to give compounds **5a,b** respectively.

[(E)-dimethyl(1-(5-bromobenzofuran-2-yl)ethylidene)carbonohydrazonodithioate] ***(5a)***.

Brown crystals; Yield: 85%; mp: 110-112°C; IR (vcm^{-1}): 2950 (CH-aliph.); ^{1}H-NMR (δ ppm): 2.34 (s, 3H, CH_3C=N), 2.37 (s, 3H, SCH_3), 2.49 (s, 3H, SCH_3) and 7.43-7.92 (m, 4H, Ar-H and CH-furan); Anal. calcd. for $C_{13}H_{13}BrN_2OS_2$: C 43.70, H 3.67, N 7.84. Found: C 43.62, H 3.60, N 7.78.

[Ethyl2-(((Z)-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)(methylthio)methyl)thio)acetate] ***(5b)***.

Yellow crystals; Yield: 83%; mp: 103-105°C; IR (vcm^{-1}): 1710 (C=O); ^{1}H-NMR (δ ppm): 1.21 (t, 3H, CH_3), 2.30 (s, 3H, CH_3C=N), 2.39 (s, 3H, SCH_3), 4.01 (s, 2H, CH_2), 4.16 (q, 2H, CH_2) and 7.44-7.93 (m, 4H, Ar-H and CH-furan); Anal. calcd. for $C_{16}H_{17}BrN_2O_3S_2$: C 44.76, H 3.99;, N 6.52. Found: C 44.69, H 3.90, N 6.46.

General procedure for preparation of 9a,b.

A mixture of **3a(**0.01mol) and appropriate hydrazonyl halide **6a,b** (0.01 mol) and triethylamine (1 ml) in ethanol (30 ml) was heated under reflux for 5 hrs. During the reflux period crystalline solids were separated. The resulting products were filtered off, washed with ethanol and recrystallized from dioxane to afford compounds **9a,b** respectively.

[1-(5-{[1-(5-Bromo-benzofuran-2-yl)-ethylidene]-hydrazono}-4-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)ethanone] ***(9a)***.

Orange crystals; Yield: 80%; mp: 206-208°C; IR (vcm^{-1}): 2920 (CH-aliph.) and 1680 (C=O); ^{1}H-NMR (δ ppm): 2.33 (s, 3H, CH_3C=N), 2.38 (s, 3H, CH_3) and 7.34-8.03 (m, 9H, Ar-H and CH-furan); MS *m/z* (%): 454 (28); Anal. calcd. for $C_{20}H_{15}BrN_4O_2S$: C 52.76, H 3.32, N 12.30. Found: C 52.71, H 3.26, N 12.22.

[(5-{[1-(5-Bromo-benzofuran-2-yl)-ethylidene]-hydrazono}-4-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl)-phenylmethanone] ***(9b)***.

Red crystals; Yield: 82%; mp: 150-152°C; IR (vcm^{-1}): 2924 (CH-aliph.) and 1640 (C=O); ^{1}H-NMR (δ ppm): 2.33 (s, 3H, CH_3C=N) and 7.36-8.25 (m, 14H, Ar-H and CH-furan); MS *m/z* (%): 516 (68); Anal. calcd. for $C_{25}H_{17}BrN_4O_2S$: C 58.03, H 3.31, N 10.83. Found: C 57.93, H 3.24, N 10.77.

Synthesis of [N-(4-acetyl-5-(5-bromobenzofuran-2-yl)-4,5-dihydro-5-methyl-1,3,4-thiadiazol-2-yl)acetamide] ***(10)***.

A solution of **3b** (0.01 mol) and acetic anhydride (5 ml) was heated under reflux for 3h. After the reaction mixture was attained room temperature, excess acetic anhydride was decomposed by water (10 ml) and the mixture was stirred for 30 min. The separated product was filtered and recrystallized from glacial acetic acid to give compound **10**.

White crystals; Yield: 62%; mp: 200-202°C; IR (vcm^{-1}): 3308 (NH), 2938 (CH-aliph.) and 1704, 1660 (2C=O); ^{1}H-NMR (δ ppm): 2.05 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.89-7.83 (m, 4H, Ar-H and CH-furan) and 11.74 (s, 1H, NH); Anal. calcd. for $C_{15}H_{14}BrN_3O_3S$: C 45.47, H 3.56, N 10.60;. Found: C 45.38, H 3.50, N 10.49.

General procedure for preparation of 11a,b and 12-15.

A mixture of **3b(**0.01mol) and α-halo derivatives namely (methyl α-bromobutyrate, ethyl α-bromobutyrate, chloroacetyl chloride, chloroacetonitrile, chloroacetaldehyde and ethyl-4-chloroacetoacetate) (0.01 mol) in ethanol (30 ml) containing fused sodium acetate (0.02 mol) was refluxed for 3h, the obtained products were collected by filtration, washed with water and recrystallized from dioxane to give compounds **11a,b** and **12-15** respectively.

[(E)-2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-5-methyl- thiazolidin-4-one] ***(11a)***.

White crystals; Yield: 92%; mp: 205-207°C; IR (vcm^{-1}): 3255 (NH) and 1722 (C=O); ^{1}H-NMR (δ ppm): 2.35 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.40-7.92 (m, 5H, Ar-H, CH-furan and CH-thiazolidinone) and 12.03 (s, 1H, NH); MS *m/z* (%): 365 (90); Anal. calcd. for $C_{14}H_{12}BrN_3O_2S$: C 45.91, H 3.30, N 11.47. Found: C 45.85, H 3.22, N 11.40.

[(E)-2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-5-ethyl -thiazolidin-4-one] ***(11b)***.

White crystals; Yield: 90%; mp: 210-212°C; IR (vcm^{-1}): 3140 (NH), 2958 (CH-aliph.) and 1698 (C=O); ^{1}H-NMR (δ ppm): 0.99 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.24 (q, 2H, CH_2), 7.36-7.92 (m, 5H, Ar-H, CH-furan and CH-thiazolidinone) and 12.05 (s, 1H, NH); Anal. calcd. for $C_{15}H_{14}BrN_3O_2S$: C 47.38, H 3.71, N 11.05. Found: C 47.32, H 3.66, N 11.00.

[(E)-2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)thiazoli-din-5-one] ***(12)***.

Orange crystals; Yield: 68%; mp: 214-216°C; IR (vcm^{-1}): 3180 (NH), 2924 (CH-aliph.) and 1700 (C=O); ^{1}H-NMR (δ ppm): 2.34 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 7.36-7.95 (m, 4H, Ar-H and CH-furan) and 12.05 (s, 1H, NH); Anal. calcd. for $C_{13}H_{10}BrN_3O_2S$: C 44.33, H 2.86, N 11.93. Found: C 44.27, H 2.80, N 11.86.

[(E)-2-(2-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazinyl)thiazol-4(5H)-imine] ***(13)***.

Red crystals; Yield: 79%; mp: 166-168°C; IR (vcm^{-1}): 3154 (NH) and 2922 (CH-aliph.); ^{1}H-NMR (δ ppm): 2.33 (s, 3H, CH_3), 4.01 (s, 2H, CH_2), 7.29-8.34 (m, 4H, Ar-H and CH-furan) and 8.78, 10.55 (2s, 2H, 2NH); Anal. calcd. for $C_{13}H_{11}BrN_4OS$: C 44.46, H 3.16, N 15.95. Found: C 44.40, H 3.10, N 15.88.

[(E)-2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-2,3-dihydro- thiazole] ***(14)***.

Gray crystals; Yield: 81%; mp: 180-182°C; IR (vcm^{-1}): 3190 (NH); ^{1}H-NMR (δ ppm): 2.31 (s, 3H, CH_3), 6.84, 7.24 (dd, 2H, 2CH), 7.19-7.87 (m, 4H, Ar-H and CH-furan) and 11.36 (s, 1H, NH); Anal. calcd. for $C_{13}H_{10}BrN_3OS$: C 46.44, H 3.00, N 12.50. Found: C 46.37, H 2.92, N 12.41.

[Ethyl 2-((E)-2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-2,3-di-hydrothiazol-4-yl)acetate] ***(15)***.

Orange crystals; Yield: 68%; mp: 208-210°C; IR (vcm^{-1}): 3160 (NH) and 1722 (C=O); ^{1}H-NMR (δ ppm): 1.20 (t, 3H, CH_3), 3.71 (s, 2H, CH_2), 4.14 (q, 2H, CH_2), 6.79 (s, 1H, CH), 7.24-7.88 (m, 4H, Ar-H and CH-furan) and 10.12 (s, 1H, NH); Anal. calcd. for $C_{17}H_{16}BrN_3O_3S$: C 48.35, H 3.82, N 9.95. Found: C 48.28, H 3.75, N 9.90.

Synthesis of [2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)thiazolidin-4-one] ***(16)***.

A mixture of **3b(**0.01mol), ethyl bromoacetate (0.01 mol) and fused sodium acetate (0.02 mol) in ethanol (30 ml) was refluxed for 2h, the obtained product was collected by filtration, washed with water and recrystallized from glacial acetic acid to give compound **16**.

Yellow crystals; Yield: 94%; mp: 225-227°C; IR (vcm^{-1}): 3272 (NH), 2932 (CH-aliph.) and 1702 (C=O); ^{1}H-NMR (δ ppm): 2.35 (s, 3H, CH_3), 3.89 (s, 2H, CH_2), 7.36-7.92 (m, 4H, Ar-H and CH-furan) and 12.15 (s, 1H, NH); MS *m/z* (%): 351 (43); Anal. calcd. for $C_{13}H_{10}BrN_3O_2S$: C 44.33, H 2.86, N 11.93. Found: C 44.27, H 2.80, N 11.86.

Synthesis of [ethyl 2-(2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-4-oxothiazolidin-3-yl)acetate] ***(17)***.

Method A

A mixture of **16(**0.01mol), fused sodium acetate (0.02 mol) and ethyl bromoacetate (0.01 mol) in ethanol (30 ml) was refluxed for 3h, after cooling the solid which formed was collected and recrystallized from dioxane to give compound **17**.

Method B

A mixture of **3b(**0.01mol), ethyl bromoacetate (0.02 mol) and fused sodium acetate (0.02 mol) in ethanol (40 ml) was refluxed for 3h, after cooling the obtained product was collected and recrystallized from dioxane to give compound **17**.

M.p, mixed m.p with product from procedure (A) gave no depression.

Yellow crystals; Yield: 74%; mp: 170-172°C; IR (vcm^{-1}): 2980 (CH-aliph.) and 1730 (C=O); ^{1}H-NMR (δ ppm): 1.19 (t, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.14 (q, 2H, CH_2), 4.52 (s, 2H, CH_2), 4.63 (s, 2H, CH_2) and 7.35-7.92 (m, 4H, Ar-H and CH-furan); Anal. calcd. for $C_{17}H_{16}BrN_3O_4S$: C 46.59, H 3.68, N 9.59. Found: C 46.50, H 3.60, N 9.53.

General procedure for preparation of 18a,b.

A mixture of **3b(**0.01mol) and chloroacetone and/or phenacyl bromide (0.01 mol) and fused sodium acetate (0.02 mol) in ethanol (30 ml) was refluxed for 2h. The solid product that formed was collected by filtration and recrystallized from dioxane to give compound **18a,b**.

[2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-4-methyl-2,3-dihydro- thiazole] ***(18a)***.

Black crystals; Yield: 61%; mp: 180-182°C; IR (vcm^{-1}): 3184 (NH) and 2924 (CH-aliph.); ^{1}H-NMR (δ ppm): 2.16 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 6.33 (s, 1H, CH-thiazole), 7.18-7.89 (m, 4H, Ar-H and CH-furan) and 11.35 (s, 1H, NH); Anal. calcd. for $C_{14}H_{12}BrN_3OS$: C 48.01, H 3.45, N 12.00. Found: C 47.93, H 3.39, N 11.94.

[2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-4-phenyl-2,3-dihydro- thiazole] ***(18b)***.

Orange crystals; Yield: 66%; mp: 258-260°C; IR (vcm^{-1}): 3172 (NH) and 2924 (CH-aliph.); ^{1}H-NMR (δ ppm): 2.35 (s, 3H, CH_3), 7.26-8.30 (m, 10H, Ar-H, CH-furan and CH-thiazole) and 11.65 (s, 1H, NH); Anal. calcd. for $C_{19}H_{14}BrN_3OS$: C 55.35, H 3.42, N 10.19. Found: C 55.28, H 3.36, N 10.00.

Synthesis of [2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-4-phenyl-5-(phenyldiazenyl)-2,3-dihydrothiazole] ***(19)***.

Method A

To a cold solution of **18b** (0.01 mol) in ethanol containing sodium acetate (3g), benzene diazonium chloride (0.01 mol) was added, [prepared by diazotization of aniline (0.012 mol) in conc. HCl (6 ml) with sodium nitrite (0.97 g in 5 ml H_2O) at 0° c] portion wise over (30 min) with constant stirring. After complete addition, the reaction mixture was stirred for a further 1h at 0°c. The solid product was filtered off, washed with water and recrystallized from glacial acetic acid to give compound **19**.

Method B

To a mixture of **3b(**0.01mol) and appropriate hydrazonyl halide **6b** (0.01 mol) in ethanol (30 ml), triethylamine (0.5 ml) was added and the reaction mixture was refluxed for 2h. The isolated product was collected by filtration and recrystallized to give a product that was identical in m.p, mixed m.p and spectral data with **19**, which was obtained from method A.

Red crystals; Yield: 68%; mp: 196-198°C; IR (vcm^{-1}): 3184 (NH); MS *m/z* (%): 515 (26); Anal. calcd. for $C_{25}H_{18}BrN_5OS$: C 58.14, H 3.51, N 13.56. Found: C 58.08, H 3.45, N 13.50.

Synthesis of [(5E)-2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-5-(4-methoxybenzylidene)thiazolidin-4-one] ***(20)***.

Method A

A mixture of **16** (0.01 mol) and *p*-methoxybenzaldehyde (0.01 mol) in ethanol (30 ml) in the presence of piperidine (1 ml) was refluxed for 1h, the resulting solid on heating was collected by filtration and recrystallized from dioxane to give compound **20.**

Method B

A mixture of **16** (0.01 mol) and α-cyano-4-methoxyphenyl cinnamonitrile(0.01 mol) in ethanol (30 ml) in the presence of piperidine (1 ml) was refluxed for 1h. The resulting solid on heating was collected by filtration and recrystallized from dioxane to give compounds **20**.

M.p. and mixed m.p. determined with authentic sample gave no depression.

Yellow crystals; Yield: 88%; mp: 230-232°C; IR (vcm^{-1}): 3252 (NH) and 1700 (C=O); ^{1}H-NMR (δ ppm): 2.43 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.11-7.94 (m, 9H, Ar-H, CH-furan and CH=C) and 12.58 (s, 1H, NH); Anal. calcd. for $C_{21}H_{16}BrN_3O_3S$: C 53.63, H 3.43, N 8.93. Found: C 53.57, H 3.38, N 8.86.

Synthesis of [2-(2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-ylidene)malononitrile] ***(24)***.

A mixture of **16** (0.01 mol) and tetracyanoethylene (0.01 mol) in ethanol (30 ml) and a catalytic amount of piperidine was refluxed for 2 h. The precipitate formed was filtered off hot, washed with ethanol several times, dried and recrystallized from dioxane to give compound **24**.

Black crystals; Yield: 58%; mp: 300-302°C; IR (vcm^{-1}): 3318 (NH), 2218 (CN) and 1708 (C=O); MS *m/z* (%): 413 (76); Anal. calcd. for $C_{16}H_8BrN_5O_2S$: C 46.39, H 1.95, N 16.91. Found: C 46.30, H 1.89, N 16.82.

General procedure for preparation of 26a,b.

A mixture of **16** (0.01 mol) and o-hydroxycarboxaldehyde derivatives namely (5-bromosalicylaldehyde and 2-hydroxy-1-naphthaldehyde) (0.01 mol) and piperidine (0.01) in ethanol (40 ml) was heated under reflux for 3 h, the solid products which

produced on heating was collected and recrystallized from dioxane to give compounds **26a,b**.

*[7-bromo-2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-2H-chromeno- [2,3-d]thiazole] **(26a)***.

Brown crystals; Yield: 60%; mp: 252-254°C; MS *m/z* (%): 515 (24); Anal. calcd. for $C_{20}H_{11}Br_2N_3O_2S$: C 46.45, H 2.14, N 8.12. Found: C 46.39, H 2.08, N 8.05.

*[9-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-9H-benzo[5,6]chromeno- [2,3-d]thiazole] **(26b)***.

Brown crystals; Yield: 77%; mp: 266-268°C; MS *m/z* (%): 487 (30); Anal. calcd. for $C_{24}H_{14}BrN_3O_2S$: C 59.03, H 2.89, N 8.60. Found: C 58.96, H 2.82, N 8.53.

*Synthesis of [(5Z)-5-(4-amino-3-phenylthiazol-2(3H)-ylidene)-2-((1-(5-bromo- benzofuran-2-yl)ethylidene)hydrazono)thiazolidin-4-one] **(28)***.

To a cold suspension of finely grounded KOH (0.01 mol) in dry DMF (30 ml), thiazolidinone derivative **16** (0.01 mol) and subsequently phenyl isothiocyante (0.01 mol) were added, the reaction was stirred overnight at room temperature, then treated with chloroacetonitrile (0.01 mol) and left at room temperature for an additional 24 hr. The reaction mixture was then treated with cold H_2O (50 ml) and neutralized with 1N HCl. The resulting precipitate was collected by filtration, washed with water, dried and recrystallized from dioxane to give compound **28**.

Gray crystals; Yield: 50%; mp: 204-206°C; IR (vcm^{-1}): 3340, 3212, 3124 (NH_2/NH) and 1702 (C=O); ^{1}H-NMR (δ ppm): 2.33 (s, 3H, CH_3), 4.90 (s, 1H, CH-thiazole), 7.33-7.94 (m, 11H, Ar-H, CH-furan and NH_2) and 12.04 (s, 1H, NH); MS *m/z* (%): 525 (38); Anal. calcd. for $C_{22}H_{16}BrN_5O_2S_2$: C 50.19, H 3.06, N 13.30. Found: C 50.10, H 3.00, N 13.23

*Synthesis of [(5E)-2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-5-((dimethylamino)methylene)thiazolidin-4-one] **(29)***.

A mixture of thiazolidinone derivative **16** (0.01 mol) and DMF-DMA (0.01 mol) in dry benzene (40 ml) was heated under reflux for 5 hrs. The separated solid was filtered off, washed with ethanol and recrystallized from dioxane to give compound **29**.

Brown crystals; Yield: 88%; mp: 188-190°C; IR (vcm^{-1}): 3290 (NH) and 1718 (C=O); ^{1}H-NMR (δ ppm): 2.34 (s, 3H, CH_3), 2.46, 3.15 (2s, 6H, $N(CH_3)_2$), 6.81-7.93 (m, 5H, Ar-H, CH-furan and CH=C) and 10.62 (s, 1H, NH); Anal. calcd. for $C_{16}H_{15}BrN_4O_2S$: C 47.18, H 3.71, N 13.76. Found: C 47.12, H 3.66, N 13.68.

*Synthesis of [2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-9-thioxo-8,9-dihydro-1H-pyrimido[1,6-a]thiazolo[5,4-e]pyrimidin-7(2H)-one] **(31)***.

A mixture of enaminone**29** (0.01 mol) and 6-amino-2-thiouracil (0.01 mol) in glacial acetic acid (40 ml) was refluxed for 3 h. The solvent was removed by distillation under reduced pressure and the resulting solution was left to cool. The solid precipitate was collected by filtration and recrystallized from dioxane to give compound **31**.

Red crystals; Yield: 55%; mp: 290-292°C; IR (vcm^{-1}): 3327, 3200 (2NH) and 1688 (C=O); MS *m/z* (%): 486 (25); Anal. calcd. for $C_{18}H_{11}BrN_6O_2S_2$: C 44.36, H 2.28, N 17.24. Found: C 44.29, H 2.22, N 17.18.

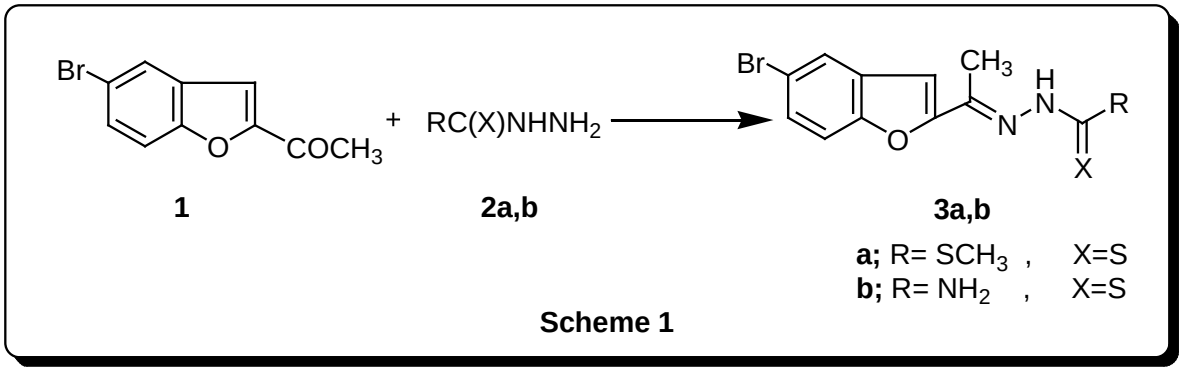
*Synthesis of [2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-7-(methylthio)-1,2-dihydropyrazolo[1,5-a]thiazolo[5,4-e]pyrimidine-6-carbonitrile] **(33)***.

A solution of enaminone**29** (0.01 mol) and 5-amino-3-methylthiopyrazole-4-carbonitrile (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 7 hrs. During the reflux period, a crystalline solid was separated. The obtained solid was filtered off, washed with ethanol and recrystallized from dioxane to give compound **33.**

Brown crystals; Yield: 58%; mp: 268-270°C; IR (vcm^{-1}): 3210 (NH) and 2220 (CN); MS *m/z* (%): 469 (48); Anal. calcd. for $C_{19}H_{12}BrN_7OS_2$: C 45.79, H 2.43, N 19.67. Found: C 45.70, H 2.37, N 19.60.

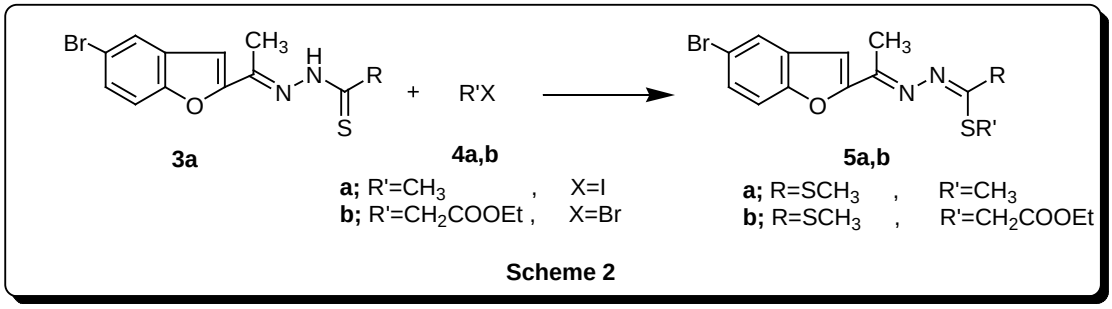
3. Results and Discussion

In the interest of the above suggestion, condensation of 2-acetyl-5-bromobenzofuran **(1)** [25] with methyl hydrazinecarbodithioate and thiosemicarbazide**(2a,b)** in ethanol at reflux temperature afforded (methyl-2-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazinecarbodithioate) **(3a)** and (2-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazinecarbothioamide) **(3b)**, respectively. The ^{1}H NMR spectrum for **3a** exhibited two singlet signals at δ 2.40 and 2.48 ppm due to $2CH_3$ groups, while the ^{1}H NMR spectrum for **3b** showed the presence of downfield two singlet signals at 8.43 and 10.53 ppm assigned to NH_2 and NH respectively, **(Scheme 1).**



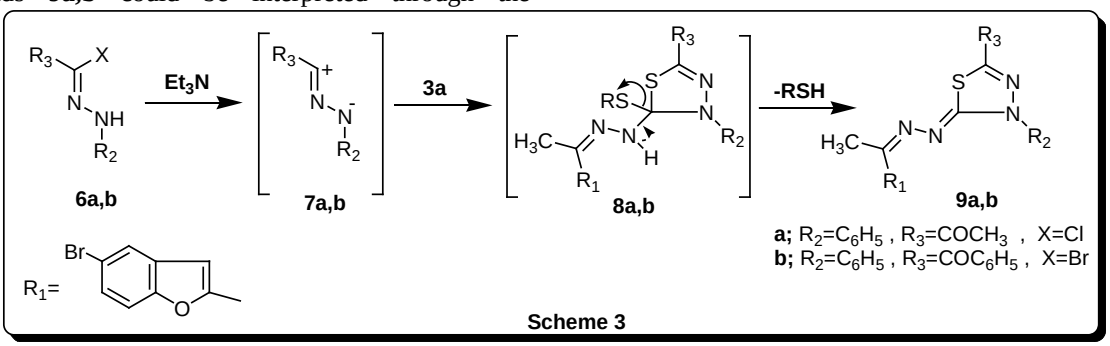
Scheme 1

Treatment of **3a** with methyl iodide **(4a)** gave the corresponding bis alkyl thio derivative **5a**. Also alkylation of **3a** with ethyl bromoacetate **(4b)** afforded the corresponding methylthio ethoxycarbonyl thiomethylene derivative **5b**. The structures of the reaction products were ascertained on the basis of their elemental analysis and spectral data, where showed no evidences for the presence of an (NH) group in both IR and ^{1}H NMR spectra, **(Scheme 2).**



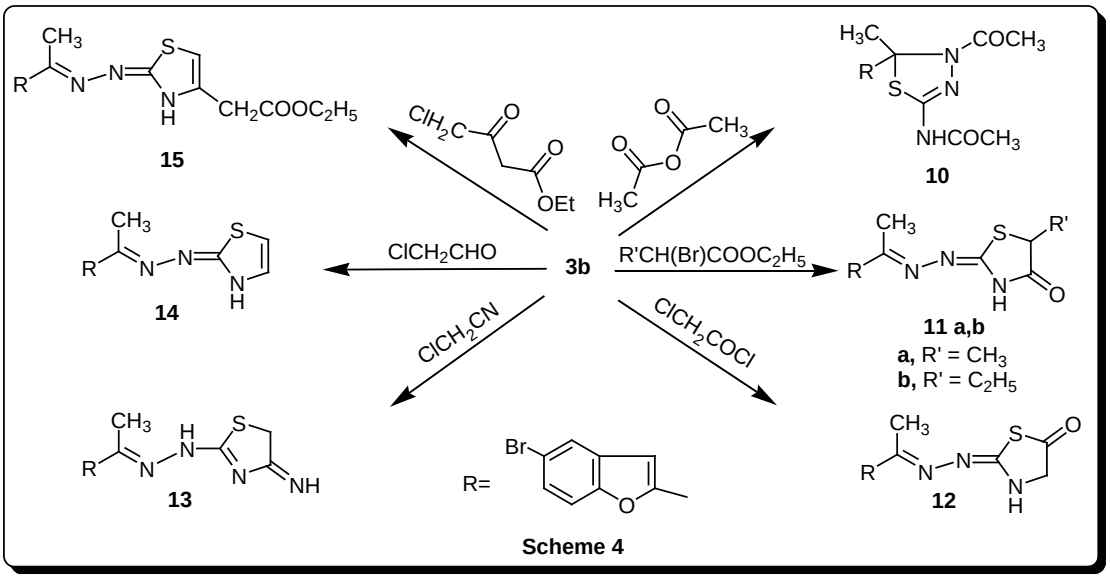
Scheme 2

Interaction of alkyl dithioester **3a** with hydrazonyl halides **6a,b** [26,27] in ethanol containing triethylamine at reflux temperature furnished 1,3,4-thiadiazole derivatives **9a,b** respectively, which established based on elemental analysis and spectroscopic data. The formation of compounds **9a,b** could be interpreted through the elimination of alkyl mercaptan from the corresponding cyclo adduct **8a.b**, which are assumed to be formed from the 1,3-dipolar cycloaddition of nitrile imines **7a,b** [formed from **6a,b** and triethylamine in situ] to the (C=S) group in **3a**, **(Scheme 3).**



Scheme 3

Thiosemicarbazone derivative **3b** was considered as a good starting material for the synthesis of many heterocyclic compounds. (N-(4-acetyl-5-(5-bromo-benzofuran-2-yl)-4,5-dihydro-5-methyl-1,3,4-thiadiazol-2-yl)acetamide) **(10)**was prepared by refluxing **3b** with acetic anhydride. Its IR spectrum showed new bands at 1704, 1660 cm^{-1} attributed to carbonyl groups, while ^1H NMR spectrum indicated three signals due to methyl groups at 2.05, 2.16 and 2.25 ppm.

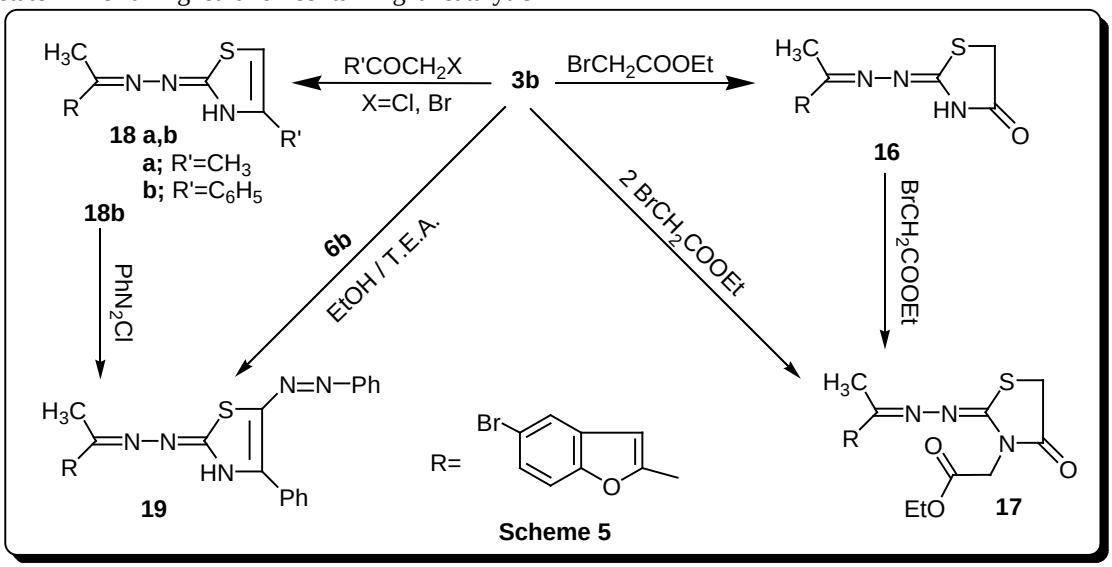


Scheme 4

The behavior of the thiocarbamoyl functional group in compound **3b** towards some α-halo compounds was investigated. Thus, the reaction of **3b** with alkyl α-bromo butyrate in refluxing ethanol in the presence of fused sodium acetate produced thiazolidin-4-one derivatives **11a,b**. The reaction pathway is assumed to proceed via S-alkylation followed by intramolecular cyclization with concomitant loss of an alcohol molecule **(Scheme 4)**. The infrared spectrum of compounds **11a,b** showed absorption bands at 1722 and 1698 cm^{-1} (2C=O) respectively, while the mass spectrum of compound **11a** indicated a molecular ion peak at m/z 365 (90). The ^1H NMR spectrum of compound **11b** revealed a triplet and quartet at δ 0.99, 4.24 ppm for the methyl and methylene protons. Also, treatment of thiosemicarbazone derivative **3b** with chloroacetyl chloride in boiling ethanol containing a catalytic amount of anhydrous sodium acetate afforded thiazolidin-5-one derivative **12**. Its ^1H NMR spectrum showed a new singlet at 3.90 ppm attributed to CH_2 thiazolidinone. The novel iminothiazole derivative **13** was obtained by the reaction of compound **3b** with chloroacetonitrile in ethanol containing anhydrous sodium

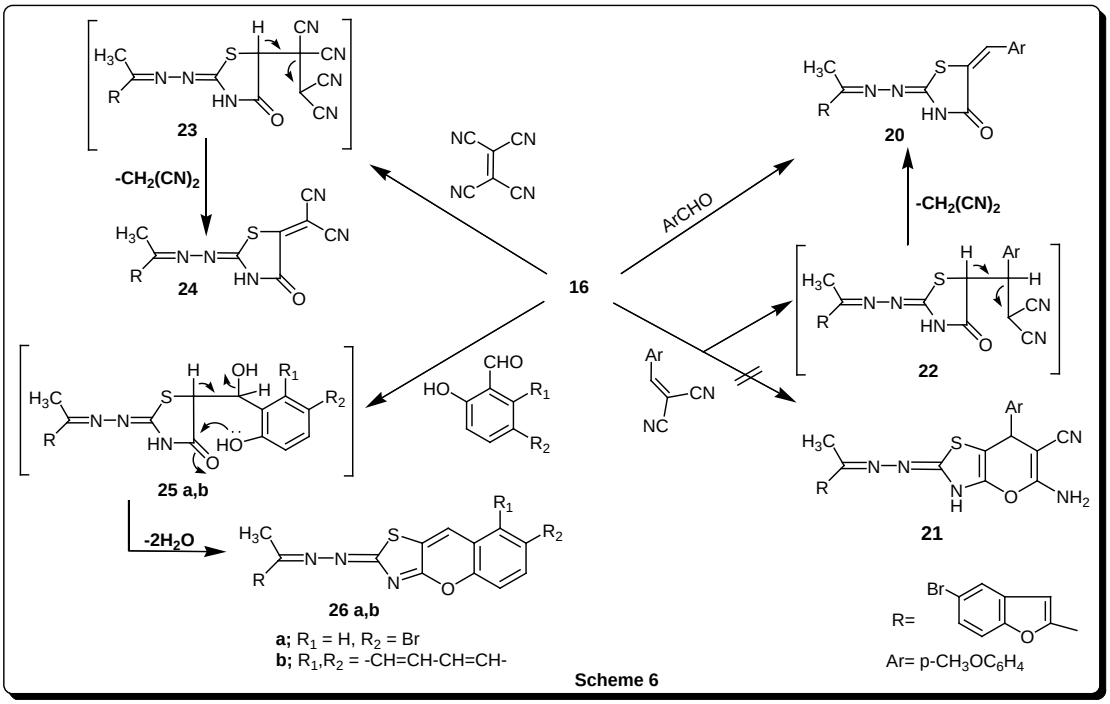
acetate. Moreover, interaction of compound **3b** with chloroacetaldehyde in refluxing ethanol containing fused sodium acetate furnished a single product which identified as: (2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-2,3-dihydrothiazole) **(14)**. Its ^{1}H NMR spectrum exhibited signal characteristic for NH proton and two new signals at 6.84, 7.24 ppm attributed to 2CH thiazole. Furthermore, thiosemicarbazone derivative **3b** was reacted with ethyl-4-chloroacetoacetate under the same reaction conditions to produce (ethyl-2-(-2-((E)-(1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-2,3-dihydrothiazol-4-yl)acetate) **(15)**. The ^{1}H NMR spectrum of **15** in DMSO-d_6 exhibited a triplet at δ 1.20 ppm characteristic for CH_3 protons and a quartet at δ 4.14 ppm for CH_2 protons, **(Scheme 4).**

On the same manner, when thiosemicarbazone derivative **3b** treated with one equivalent of ethyl bromoacetate in refluxing ethanol containing a catalytic amount of anhydrous sodium acetate underwent a cyclization thus giving the thiazolidinone derivative **16**. However, **3b** reacted with two moles of ethyl bromoacetate to give N-ethoxycarbonylthiazolidinone derivative **17**, which was obtained from treatment of **16** with ethyl bromoacetate, **(Scheme 5).** The ^{1}H NMR spectrum of **17** lacked signal characteristic of NH proton and showed a new two signals at 4.52, 4.63 ppm attributed to $2CH_2$ groups. Interaction of **3b** with haloketones under the same reaction conditions afforded thiazole derivatives **18a,b**. When **18b** subjected to coupling reaction with benzene diazonium chloride in ethanol/sodium acetate, gave phenyl azothiazole derivative **19**. The latter compound was prepared directly from the cyclocondensation reaction of **3b** with hydrazonyl halide **6b** in ethanol containing triethylamine under reflux, **(Scheme 5).**



Scheme 5

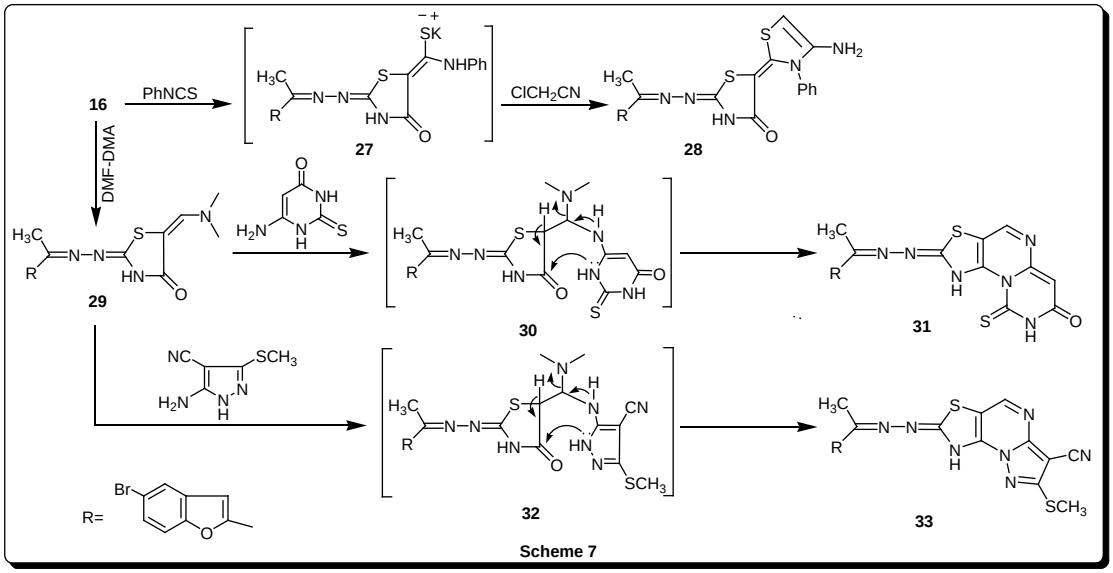
The reactivity of (2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)thiazolidin-4-one) **(16)** toward some electrophilic reagents was investigated. Thus, condensation of compound **16** with p-methoxybenzaldehyde in boiling ethanol containing a catalytic amount of piperidine afforded the corresponding benzylidine thiazolidinone derivative **20**, **(Scheme 6).**



Scheme 6

In contrast to the anticipated formation of pyrano[2,3-d]thiazole derivative **21**, the reaction of **16** with α-cyano-4-methoxyphenylcinnamonitrile in boiling ethanol/piperidine afforded a product identical in all aspects (mp, mixed mp and spectral data) with compound **20**. The formation of this compound was assumed to proceed via retro Michael addition through the elimination of malononitrile from the non-isolable adduct **22**. Moreover, the reaction of **16** with tetracyanoethylene in ethanol-piperidine under reflux furnished the product which identified as: (2-(2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-4-oxo-thiazolidin-5-ylidene)malononitrile) **(24)**. The formation of compound **24** could be interpreted through addition of **16** to the activated double bond to form intermediate **23** followed by intramolecular cyclization through elimination of malononitrile molecule to afford the final product. Cyclization of compound **16** with salicylaldehyde derivatives in ethanol under reflux in the presence of piperidine yielded the corresponding chromeno[2,3-d]thiazole derivatives **26a,b**. Formation of these compounds may be explained by condensation of **16** with salicylaldehyde derivatives afforded acyclic intermediate **25a,b** which undergoes intramolecular cyclization and tautomerization through nucleophilic addition of the (OH) group to the carbonyl site followed by elimination of water molecule yielded the expected compounds **26a,b** respectively, **(Scheme 6).**

The active methylene group in thiazolidinone derivative **16** was allowed to react with phenyl isothiocyante in dimethylformamide in the presence of potassium hydroxide at room temperature yielded the non-isolable intermediate potassium sulfide salt **27**, which treated with chloroacetonitrile at room temperature afforded the corresponding thiazole derivative **28**. The formation of **28** was assumed to proceed through the initial alkyla-tion by loss of potassium chloride followed by in situ heterocyclization via Dieckmann type [28]. Treatment of equimolar quantities of thiazolidinone derivative **16** with dimethylformamide dimethylacetal (DMF-DMA) in refluxing benzene afforded the corresponding enaminone as ((5E)-2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-5-((dimethylamino)-methylene)thiazolidin-4-one) **(29)**, **(Scheme 7).**



Finally, this investigation was extended to include the reactivity of enaminone **29** towards heterocyclic amine namely; (6-amino-2-thiouracil [29] and 5-amino-3-methylthiopyrazole-4-carbonitrile [30]) in glacial acetic acid under reflux to yield a product which identified as: (2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-9-thioxo-8,9-dihydro-1H-pyrimido[1,6-a]thiazolo[5,4-e]pyrimidin-7(2H)-one) **(31)** and (2-((1-(5-bromobenzofuran-2-yl)ethylidene)hydrazono)-7-(methylthio)-1,2-dihydropyrazolo[1,5-a]thiazolo[5,4-e]pyrimidine-6-carbonitrile) **(33)** respectively. The formation of **31** and **33** were explained by the addition of exoamino group of heterocyclic amines to unsaturated moiety of enaminone **29** to yield the corresponding acyclic non-isolable intermediates **30,32** which undergoes intramolecular cyclization through nucleophilic addition of imino (NH) to the carbonyl group followed by elimination of dimethylamine and water molecules to afford the final products, **(Scheme 7).**

Antimicrobial Activity: The synthesized compounds were tested for their antimicrobial activities in vitro by agar diffusion method using "Mueller–Hinton" agar medium for bacteria and "Sabouraud's" agar medium for yeasts.

Theassayed collection included two Gram-positive bacteria: *Bacillus subtilis* (NCIB 3610) and *Staphylococcus aureus* (NCTC7447); two Gram-negative bacteria: *Escherichia coli* (NCTC10416) and *Pseudomonas aeruginosa* (NCIB 9016); Unicellularfungi: *Candida albicans* (IMRU 3669) and Filamentous fungi:*Aspergillus niger* (ATCC 16404) using Ampicillin 25 µg/ml as areference compound. The inhibition zone diameters were recordedand rounded up to the nearest whole number (mm) for analysis. The inhibitory effects of the synthesized compounds againstthese organisms are given in Table 1.

The results of antimicrobial screening show that; compounds **13, 19, 20** were the most active compounds against*Bacillus subtilis* (NCIB 3610) and the compounds **28, 29, 31**gave good results against*Staphylococcus aureus* (NCTC7447). Also the results indicated that compounds**3a, 15, 18b**exhibited highest activity against*Escherichia coli* (NCTC10416) and the compounds **5a, 13, 29**showed well results against *Pseudomonas*

aeruginosa (NCIB 9016).While**11b, 12, 13** were the most active compounds against*Candida albicans* (IMRU 3669) and the remaining compounds showed moderate activity. The results of antimicrobial activity illustrate that the presence of benzofuran compounds incorporated with SCH_3 group and/orthiazole moiety substitutedwith electron donating groups like CH_3, C_2H_5, NH, NH_2 increases the antibacterial as well as antifungal activities.

Table 1. Biological activity of the newly synthesized compounds

Inhibition-zone diameter (mm/mg sample)						
	Gram-positive		**Gram-negative**		**Fungi**	
Compound No.	*B. Subtilis (NCIB 3610)*	*S. aureus (NCTC 7447)*	*E.Coli (NCTC 10416)*	*P. aeruginosa (NCIB 9016)*	*A. niger (ATCC16404)*	*C. albicans (IMRU 3669)*
3a	12	13	20	17	12	19
3b	11	14	15	16	13	18
5a	12	15	14	19	10	13
5b	13	16	12	14	11	15
9a	13	14	12	15	13	17
9b	11	12	14	16	17	19
10	14	12	15	14	22	15
11a	13	10	14	11	17	19
11b	13	10	14	11	20	20
12	17	12	14	13	24	23
13	22	18	15	21	22	20
14	19	15	14	18	15	16
15	12	14	21	17	14	21
16	10	14	16	18	10	12
17	12	11	15	14	12	15
18a	16	15	14	10	10	13
18b	16	17	22	13	12	14
19	21	18	17	15	12	16
20	22	15	10	9	8	11
24	17	14	15	12	13	18
26a	16	18	14	13	16	19
26b	15	13	12	14	16	13
28	14	21	12	15	17	11
29	18	20	13	20	13	16
31	16	22	14	12	11	17
33	15	12	10	14	13	17
Ampicillin	26	25	27	26	24	25

Antimicrobial Assay:

In the agar diffusion method [31,32] compounds dissolved indimethylformamide (DMF) at a concentration of 100 mg/mL were used. Agar media seeded with the tested microorganisms were poured in Petri dishes and were allowed to solidify, and then holes of about 7 mm were punched in the agar using a sterile cork porrer. A 50-µl volume of the dissolved compounds were added to the pores and DMF was included as solvent control. Plates were allowed to stand in a refrigerator for two hours before incubation to allow the tested compounds to diffuse through the agar. The plates containing bacterial cultures were incubated at 37°C for 24 h and those containing yeasts were incubated at 30°C for 48h. After incubation, the growth inhibition zones around the holes were observed, indicating that the examined compoundinhibits thegrowth of microorganism. The tested microorganisms were obtained from the Regional Center for Mycology & Biotechnology (RCMP), Al-Azhar University.

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