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Synthesis of Some Novel Heterocyclic Compounds Containing Benzofuran Moiety of Potential Antimicrobial Activity

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Abstract: Imidazotriazole, thiazoles, quinoxaline, benzothiazine, imidazo-thiadiazole, imidazopyridine, imidazothiazole were synthesized via reaction of 3-bromoacetyl-5-bromobenzofuran with each of thiourea, phenylthiourea, thiocetamide, thiocarbamoyl pyrazole, o-phenylenediamine, o-aminothiophenol, 2-aminothia-diazole, aminotriazole, 2-aminopyridine and 2-aminothiazole. The structure of the newly synthesized compounds was confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectral data. All compounds were evaluated for their antimicrobial activities, compound 2 gave excellent results.

Keywords: Thiazole, Benzofuran, Quinoxaline, Antimicrobial

1. Introduction

Several synthetic compounds containing benzofuran skeleton are associated with diverse biological and pharmacological activities [1-13]. The wide pharmacological potential of these bioactive moieties has attracted many organic and medicinal chemists to develop efficient routs for their synthesis [14-17]. Recently, benzofuran derivatives have attracted considerable interest for their versatile properties in chemistry and pharmacology. In a continuation of our previous work [18, 19] on the synthesis of new bioactive heterocyclic compounds containing benzofuran moiety, using 2-bromoacetyl-5-bromobenzofuran (2) as starting materials.

2. Material 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}HNMR spectra were recorded in ($CDCl_3$ & DMSO-d_6) at (300) MHz on a Varian Mercury VX-300 NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70ev. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Al-Azhar University.

2.1. 2-Bromoacetyl-5-Bromobenzofuran (2)

To a stirred solution of 2-acetyl-5-bromobenzofuran (1; 0.01 mol) in acetic acid (30 ml) the bromine (0.01 mol) was added dropwise with constant stirring after complete addition, the reaction mixture was stirring for additionally 1hr., and poured in cold water (100 ml), the separated solid was filtered off, and recrystallized from ethanol/benzene to give 2 as green crystals (70%), m.p. 135-136°C. IR ν (cm^{-1}): 1680 (C=O). ^{1}HNMR (200 MHz δ ppm $CDCl_3$) 4.11 (s, 2H, CH_2), 7.25 (s, 1H, CH furan), 7.35-7.81 (m, 3H, Ar-H). Anal. Calcd. %, for $C_{10}H_6Br_2O_2$ (316): C; 37.77, H; 1.90. Found%: C; 37.74, H; 1.83.?

2.2. Synthesis of Thiazole, Imidazole, Thiazine, Pyrazine (3-7)

2.2.1. General Procedure for the Formation of Compounds (3a-d)

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol), and thiocarbamoyl derivatives (0.01 mol) namely (thiourea, phenyl thiourea, thioacetamide and thiocarbamoyl pyrazole) in ethanol (40 ml) was refluxed for 2h, the resulting solution was collected by filtration.

i. 4-(5-Bromobenzofuran-2-yl)Thiazol-2-Amine (3a)

Brown crystals from ethanol/benzene (95%), m.p. 260-261°C. IR ν (cm^{-1}): 3394, 3222 (NH_2).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 7.03 (s, 1H, CH thiazole H-5), 7.24 (s, 1H, CH furan), 7.14-7.90 (m, 5H, Ar-H and NH_2). Anal. Calcd. %for $C_{11}H_7BrN_2OS$ (294): C; 44.76, H; 2.39, N; 9.49. Found %: C; 44.70, H; 2.33, N; 9.45.

ii. 4-(5-Bromobenzofuran-2-yl)-N-Phenyl-Thiazol-2 Amine (3b)

Dark brown crystals from ethanol/benzene (82%), m.p. 150-152°C. IR ν (cm^{-1}): 3372 (NH). ms: m/z (intensity %) 370 (91.0). Anal. calcd. %, for $C_{11}H_7BrN_2OS$ (370): C; 55.00, H; 2.99, N; 7.55. Found%: C; 54.92, H; 2.95, N; 7.50.

iii. 4-(5-Bromobenzofuran-2-yl)-2-Methylthiazole (3c)

Brown crystals from ethanol (80%), m.p. 150-151°C. IR ν (cm^{-1}): 2920 (CH-aliph). ^{1}HNMR (200 MHz δ ppm $CDCl_3$) 2.79 (s, 3H, CH_3), 7.08 (s, 1H, CH-thiazole H-5), 7.25 (s, 1H, CH furan), 7.27-7.73 (m, 3H, Ar-H). Anal. Calcd.%, for $C_{12}H_8BrNOS$ (293): C; 49.00, H; 2.74, N; 4.76. Found%: C; 48.94, H; 2.70, N; 4.70.

iv. 5-Amino-1-(4-(5-Bromobenzofuran-2-yl)-Thiazol- 2-yl)-3-(Methylthio)-1H-Pyrazole-4-Carbonitrile (3d)

Brown crystals from ethanol/benzene (85%), m.p. 283-284°C. IR ν (cm^{-1}): 3394, 3288 (NH_2) and 2222 (CN). ms: *m/z* (intensity %) 431 (100.0), Anal. calcd. %, for $C_{16}H_{10}BrN_5OS_2$ (431): C; 44.45, H; 2.33, N; 16.20. Found%: C; 44.40, H; 2.30, N; 16.15.

2.2.2. Reaction of (2) with Heterocyclic Amines

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and the requisite heterocyclic amines (2-aminothiazole or 5-methyl-2-amino[1,3,4]thiadiazole; 0.01 mol) in ethanol (30 ml) was refluxed for 2h.

i. 5-(5-Bromo-Benzofuran-2-yl)-Imidazo[2,1-b]-Thiazole (4a)

Brwon crystals from ethanol/benzene (86%), m.p. 210-211°C. IR ν (cm^{-1}): 2934 (CH-ali.). ms: m/z (intensity %) 318 (100.0). Anal. calcd.%, for $C_{13}H_7BrN_2OS$ (318): C; 48.92, H; 2.21, N; 8.78. Found%: C; 48.87, H; 2.17, N; 8.71.

ii. 5-(5-Bromo-Benzofuran-2-yl)-2-Methyl-Imidazo-[2,1-b][1,3,4] Thiadiazole (4b)

Drack brown crystals from ethanol/benzene (82%), m.p. 245-247°C. IR ν (cm^{-1}): 2924 (CH-ali.).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 2.73 (s, 3H, CH_3), 7.00 (s, 1H, CH imidazole), 7.27 (s, 1H, CH furan), 7.36-8.06 (m, 3H, Ar H). Anal. calcd.%, for $C_{13}H_8BrN_3OS$ (333): C; 46.72, H; 2.41, N; 12.57. Found%: C; 46.68, H; 2.38, N; 12.50.

2.2.3. 3-(5-Bromo-Benzofuran-2-yl)-Imidazo[1,2-a]-Pyridine (5)

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and 2-aminopyridine (0.01 mol) in ethanol (30 ml) was refluxed for 3h. The solid product was collected by filtration and recrystallized from ethanol/benzene to give (5) as brown crystals (92%), m.p. 230-232°C. ms: m/z (intensity %) 312 (100.0). Anal. Calcd. For $C_{15}H_9BrN_2O$ (312): C; 57.53, H; 2.90, N; 8.95. Found: C; 57.50, H; 2.85, N; 8.90 gm/mol.

2.2.4. 1-(5-Bromo-Benzofuran-2-yl)-2-[6-(5-Bromo-Benzofuran-2-yl)-Imidazo[1,2-b][1,2,4]Triazol-4-yl]-Ethanone (6)

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and 3-aminotriazole (0.01 mol) in ethanol (30 ml) was refluxed for 4h. The solid product was collected by filtration and recrystallized from ethanol/benzene to give (6) as brown crystals (83%), m.p. 247-248°C. IR ν (cm^{-1}): 1684 (C=O). ms: m/z (intensity %) 538 (23.4). Anal. Calcd. For $C_{22}H_{12}Br_2N_4O_3$ (538): C; 48.92, H; 2.24, N; 10.37. Found: C; 48.85, H; 2.20, N; 10.30 gm/mol.

2.2.5. Reaction of 2-Bromoacetyl-5-Bromobenzofuran with O-phenylene Diamine and O-aminothio-Phenol (7)

General procedure:

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and o-phenylenediamine or o-aminothiophenol (0.01 mol) in ethanol (40 ml) was refluxed for 2h. The solid product which formed on heating was collected and washed with ethanol.

i. 2-(5-Bromobenzofuran-2-yl)-1,4-Dihydro-Quinoxaline (7a)

Brown crystals from ethanol/benzene (90%), m.p. 203-205°C. IR ν (cm^{-1}): 3412, 3340 (2NH).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 7.36 (s, 1H, CH furan), 7.58-8.18 (m, 9H, Ar-H, CH-pyrazine and NH), 9.57 (s, 1H, NH). ms: m/z (intensity %) 326 (100%). Anal. calcd. for $C_{16}H_{11}BrN_2O$ (326): C; 58.74, H; 3.39, N; 8.56. Found: C; 58.70, H; 3.30, N; 8.52 gm/mol.

ii. 3-(5-Bromobenzofuran-2-yl)-4H-Benzo[b]-[1,4]-Thiazine (7b)

Black crystals from ethanol/benzene (78%), m.p. 267-268°C. IR ν (cm^{-1}): 3458 (NH). ms: *m/z* (intensity %) 343 (100.0). Anal. calcd. for $C_{16}H_{10}BrNOS$ (343): C; 55.83, H; 2.93, N; 4.07. Found: C; 55.79, H; 2.90, N; 4.00 gm/mol.

2.3. Synthesis of Thiophene (8-12)

2.3.1. 2-(2-(5-Bromobenzofuran-2-yl)-2-Oxoethyl-Thio)-4,6-Dimethyl Pyridine-3-Carbonitrile (8)

A solution of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) in ethanol (50 ml) and 4,6-dimethyl-3-cyano-pyridine-

2-thione (0.01 mol) was refluxed for 3hrs. The solid product which formed on heating was collected by filtration and recrystallized from ethanol/benzene to give (8) as brown crystals (92%), m.p. 135-137°C. IR ν (cm^{-1}): 2212 (CN), 1686 (C=O).^{1}HNMR (200 MHz δ ppm $CDCl_3$) 2.16 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 6.74 (s, 1H, CH-pyridine), 7.25 (s, 1H, CH furan), 7.47-7.87 (m, 3H, Ar-H). Anal. calcd. for $C_{18}H_{13}BrN_2O_2S$ (400): C; 53.88, H; 3.27, N; 6.98. Found: C; 53.84, H; 3.20, N; 6.90 gm/mol.

2.3.2. General Procedure for the Formation of Compounds 11a & 12b)

To a stirred solution of a suspension of finely powdered potassium hydroxide (0.01 mol) in dry dimethylformamide (10 ml), malononitrile or ethyl cyanoacetate (0.01 mol) and then the phenyl isothiocyanate (0.01 mol) was add in portions. The reaction mixture was stirred at room temperature with α-halogenated compound 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and left at room temperature for 3hr, then it was produced into ice / water and acidified with 0.1 N HCl. The resulting precipitate was filtered off, washed with water then dried overnight.

i. 2-[4-(5-Bromo-Benzofuran-2-yl)-3-Phenyl-3H-Thiazol-2-Ylide-ne]-Malononitrile (11a)

Yellow crystals from ethanol/benzene (87%), m.p. 305-306°C. IR ν (cm^{-1}): 2190 (CN). ms: m/z (intensity %) 419 (61.4). Anal. calcd. for $C_{20}H_{10}BrN_3OS$ (419): C; 57.16, H; 2.40, N; 10.00. Found: C; 57.10, H; 2.35, N; 9.93 gm/mol.

ii. [4-(5-Bromobenzofuran-2-yl)-3-Phenyl-3H-Thiazol-2-Ylidene]Cyanoacetic Acid Ethyl Ester (12b)

White crystals from ethanol/benzene (82%), m.p. 220-222°C. IR ν (cm^{-1}): 2194 (CN) and 1656 (C=O).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 1.30 (t, 3H, CH_3), 4.28(q, 2H, CH_2), 5.27 (s, 1H, CH thiazole), 7.27 (s, 1H, CH furan), 7.30-7.77 (m, 8H, Ar-H). Anal. calcd. for $C_{22}H_{15}BrN_2O_3S$ (466): C; 56.54, H; 3.24, N; 5.99. Found: C; 56.50, H; 3.20, N; 5.90 gm/mol.

2.4. Synthesize Thiazole Derivatives (14-20)

2.4.1. [4-(5-Bromo-Benzofuran-2-yl)-Thiazol-2-yl]-Hydrazine (14)

A solution of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) in ethanol (30 ml) and thiosemicarbazide (0.01 mol) was refluxed for 1h. The solid product which obtained after cooling was collected and recrystallized from ethanol/benzene to give (14) as black crystals (75%), m.p. 153-155°C. IR ν (cm^{-1}): 3372 (NH) and 3266, 3180 (NH_2). MS: m/z (intensity %) 309 (78.0). Anal. calcd. for $C_{11}H_8BrN_3OS$ (309): C; 42.60, H; 2.60, N; 13.55. Found: C; 42.55, H; 2.54, N; 13.50 gm/mol.

2.4.2. General Procedure for the Formation of Compounds (16a, b)

a. Procedure (A):

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in ethanol (30 ml) was refluxed for 2hrs. The solid product was collected by filtration.

b. Procedure (B)

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and benzylidenethiosemicarbazides (0.01 mol) in ethanol (20 ml) was refluxed for 2h. The obtained product was collected by filtration. m.p. and mixed m.p. determined with authentic sample gave no depression.

i. 2-(2-Benzylidenehydrazinyl)-4-(5-Bromo-Benzofuran-2-yl)Thia-zole (16a)

Green crystals from ethanol/benzene (78%), m.p. 220-222°C. IR ν (cm^{-1}): 3460 (NH). ms: m/z (intensity %) 397 (79.3). Anal. calcd. for $C_{18}H_{12}BrN_3OS$ (397): C; 54.28, H; 3.04, N; 10.55. Found: C; 54.20, H; 3.00, N; 10.50 gm/mol.

ii. 4-(5-Bromobenzofuran-2-yl)-2-(2-(4-Methoxy-Benzylidene)-Hydrazinyl)Thiazole (16b)

Brown crystals from ethanol/benzene (81%), m.p. 243-244°C. IR ν (cm^{-1}): 2924 (CH-ali.). ^{1}HNMR (200 MHz δ ppm DMSO-d_6) 3.84 (s, 3H, OCH_3), 6.93 (s, 1H, CH thiazole), 7.12 (s, 1H, N=CH), 7.25 (s, 1H, CH furan), 7.35-7.75 (m, 7H, Ar-H and NH). Anal. calcd. for $C_{19}H_{14}BrN_3O_2S$ (427): C; 53.28, H; 3.29, N; 9.81. Found: C; 53.20, H; 3.20, N; 9.75 gm/mol.

2.4.3. 2-[4-(5-Bromo-Benzofuran-2-yl)-Thiazol-2-yl]-5-Methyl-2,4-Dihydro-Pyrazol-3-one (18)

A solution of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) in ethanol (30 ml) and 3-methyl-5-oxopyrazoline-1-thiocarboxamide (0.01 mol) was refluxed for 2h. The solid obtained after cooling was collected and recrystallized from ethanol/benzene to give (18) as brown crystals (76%), m.p. 205-206°C. IR ν (cm^{-1}): 3170 (NH), 1640 (C=O).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 2.23 (s, 3H, CH_3), 5.29 (s, 1H, CH of pyrazole-H_4), 5.61 (s, 1H, CH thiazole), 7.22 (s, 1H, CH furan), 7.34-7.91 (m, 4H, Ar-H and NH). Anal. calcd. for $C_{15}H_{10}BrN_3O_2S$ (375): C; 47.89, H; 2.68, N; 11.17. Found: C; 47.85, H; 2.60, N; 11.10 gm/mol.

2.4.4. 2-[4-(5-Bromo-Benzofuran-2-yl)-Thiazol-2-yl]-5-Methyl-4-(Phenyl-Hydrazono)-2,4-Dihydro-Pyrazol-3-One (20)

a. Procedure (A)

To a cold solution of (18) (0.01 mol) in pyridine was added benzenediazoniumchloride (0.01 mol) [prepared by diazotization of aniline (0.012 mol) in concentrated HCl (6 ml) with sodium nitrite (0.97 g in 5 ml H_2O) at 0°C] portionwise over 30 min. with constant stirring. After complete addition, the reaction mixture was stirred for a further 3h at 0°C, the solid product was filtered off, washed with water, dried and recrystallized from the proper solvent to give (20).

b. Procedure (B)

A mixture of 2-bromoacetyl-5-bromobenzofuran (2; 0.01 mol) and 3-methyl-4-phenylazo-1-thiocarbonylpyrazol-5-one (0.01 mol) in ethanol (30 ml) was refluxed for 1h. The resulting product was collected and recrystallized from the

proper solvent to give (20). As Orange crystals from ethanol/benzene (91%), m.p. 263-264°C. IR ν (cm^{-1}): 3442 (NH) and 1656 (C=O). ^{1}HNMR (200 MHz δ ppm DMSO-d_6) 2.49(s, 3H, CH_3), 7.25 (s, 1H, CH furan),7.50(s, 1H, CH thiazole), 7.18-7.82 (m, 3H, Ar-H), 8.40 (br, 1H, NH). Anal. calcd. for $C_{21}H_{14}BrN_5O_2S$ (479): C; 52.51, H; 2.94, N; 14.58. Found: C; 52.48, H; 2.90, N; 14.50 gm/mol.

2.5. Synthesis of α-pyranone and Pyridinone (21-26)

2.5.1. General Procedure for the Formation of Compounds (21a, b)

A mixture of 4-(5-Bromo-benzofuran-2-yl)-thiazol-2-yl amine (3a) (0.01 mol) and the appropriate aromatic aldehydes (0.01 mol) in ethanol (30 ml) and few drops of piperidine was refluxed for 3h, the solid product was collected by filtration and recrystallized from ethanol/benzene to give (21a, b).

i. N-Benzylidene-4-(5-Bromobenzofuran-2-yl)-Thiazol-2-Amine (21a)

White crystals (82%), m.p. 244-245°C. IR ν (cm^{-1}): 1624 (C=N). ms: m/z (intensity %) 382 (11.3). Anal. calcd. for $C_{18}H_{11}BrN_2OS$ (382): C; 56.41, H; 2.89, N; 7.31. Found: C; 56.35, H; 2.80, N; 7.26 gm/mol.

ii. 4-(5-Bromobenzofuran-2-yl)-N-(4-Methoxy-Benzylidene)Thia-zol-2-Amine (21b)

Yellow crystals (78%), m.p. 234-235°C. IR ν (cm^{-1}): 2924 cm^{-1} (CH-ali.). ^{1}HNMR (200 MHz δ ppm DMSO-d_6) 3.86 (s, 3H, OCH_3), 7.24 (s, 1H, CH furan), 6.90-7.90 (m, 7H, Ar-H), 7.80 (s, 1H, CH thiazole), 9.86 (s, 1H, N=CH). Anal. calcd. for $C_{19}H_{13}BrN_2O_2S$ (412): C,; 55.22, H,; 3.17, N,; 6.78. Found: C,; 55.20, H,; 3.10, N,; 6.70.

2.5.2. General Procedure for the Formation of Compounds (23a, b)

A mixture of 4-(5-Bromo-benzofuran-2-yl)-thiazol-2-yl amine (3a) (0.01 mol) and ethyl cyanoacetate or diethyl malonate (0.01 mol) was heated at 160°C for 30 min. the separated solid was filtered off and recrystallized from ethanol/benzene to give (23a, b).

i. N-(4-(5-Bromobenzofuran-2-yl)Thiazol-2-yl)-2-Cyanoacetamide (23a)

Brown crystals (75%), m.p. 193-194°C. IR ν (cm^{-1}): 3302 (NH), 2262 (CN), 1676 (C=O). ms: m/z (intensity %) 361 (53.6). Anal. calcd. for $C_{14}H_8BrN_3O_2S$ (361): C; 46.42, H; 2.23, N; 11.60. Found: C; 46.38, H; 2.20, N; 11.55 gm/mol.

ii. Ethyl3-(4-(5-Bromobenzofuran-2-yl)Thiazol-2-Ylamino)-3-oxo-Propanoate (23b)

Grey crystals (73%), m.p. 167-168°C. IR ν (cm^{-1}): 3390 (NH), 1746 (C=O), and 1688 (C=O).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 1.21 (t, 3H, CH_3), 3.63(s, 2H, CH_2), 4.12(q, 2H, CH_2), 7.35 (s, 1H, CH furan), 7.09-7.78 (m, 3H, Ar-H), 8.55 (s, 1H, CH thiazole), 12.63 (s, 1H, NH). Anal. calcd. for $C_{16}H_{13}BrN_2O_4S$ (408): C; 46.96, H; 3.20, N; 6.84. Found: C; 46.90, H; 3.15, N; 6.80 gm/mol.

2.5.3. 1-[4-(5-Bromo-Benzofuran-2-yl)-Thiazol-2-yl]-4,6-Dimethyl-2-oxo-1,2-Dihydro-Pyridine-3-Carbonitrile (24)

Equimolar amounts of N-acyl amino derivative (23a) (0.01 mol) and acetylacetone (0.01 mol) with a few drops of piperidine in an oil bath were refluxed for 1 hr at 160°C, then allowed to cool. The solid product was collected and recrystallized from ethanol/benzene to give (24) as brown crystals (88%), m.p. 285-286°C. IR ν (cm^{-1}): 2218 (CN) and 1676 (C=O).^{1}HNMR (200 MHz δ ppm DMSO-d_6) 2.29 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.19(s, 1H, CH pyridine), 7.27 (s, 1H, CH furan), 7.09-7.74 (m, 3H, Ar-H), 7.89 (s, 1H, CH thiazole). Anal. calcd. for $C_{19}H_{12}BrN_3O_2S$ (425): C; 53.53, H; 2.84, N; 9.86. Found: C; 53.49, H; 2.80, N; 9.80 gm/mol.

2.5.4. N-[4-(5-Bromo-Benzofuran-2-yl)-Thiazol-2-yl]-2-Cyano-3-(4-Methoxy-Phenyl)-Acrylamide (25)

A mixture of cyanoacetamide derivative (23a) (0.01 mol) and the appropriate aromatic aldehyde namely p-methoxy benzaldehyde (0.01 mol) in ethanol (30 ml) and few drops of piperidine was refluxed for 3hr. the solid product which produced on heating was collected. as yellow crystals from ethanol/benzene (87%), m.p. 180-182°C. IR ν (cm^{-1}): 2220 (CN) and 1674 (C=O). ^{1}HNMR (200 MHz δ ppm DMSO-d_6) 3.93 (s, 3H, OCH_3), 7.24 (s, 1H, CH furan), 7.02-7.45 (m, 7H, Ar-H), 7.75 (s, 1H, CH thiazole), 8.04(d, 1H, NH), 8.41 (s, 1H, C=CH). Anal. calcd. for $C_{22}H_{14}BrN_3O_3S$ (479): C; 55.01, H; 2.94, N; 8.75. Found: C; 54.93, H; 2.90, N; 8.70 gm/mol.

2.5.5. 6-[4-(5-Bromo-Benzofuran-2-yl)-Thiazol-2-Ylamino]-4-(4-Methoxy-Phenyl)-2-oxo-2H-Pyran-3,5-Dicarbonitrile (26)

a. Procedure (A)

A mixture of compound (25) (0.01mol) and malononitrile (0.01 mol) in ethanol (50 ml), few drops of piperidine was added as catalyst. The reaction mixture was refluxed for 3h. The isolated product was collected and recrystallized to give (26).

b. Procedure (B)

A solution of acyl amino derivative (23a) (0.01 mol) and p-methoxy α-cyanocinnamonitrile (0.01 mol) in ethanol (50 ml), few drops of piperdine was added as catalyst. The reaction mixture was refluxed for 3h. The isolated product was collected and recrystallized from ethanol/benzene to give (26) as brown crystals (79%), m.p. 193-195°C. IR ν (cm^{-1}): 3392 (NH), 2210 (CN) and 1650 (C=O). ms: m/z (intensity %) 544 (20.3). Anal. calcd. for $C_{25}H_{13}BrN_4O_4S$ (544): C; 55.06, H; 2.40, N; 10.27. Found: C; 54.98, H; 2.33, N; 10.20 gm/mol.

2.6. Antimicrobial Screening

2.6.1. Media and Microorganisms

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. The tested

microorganisms were obtained from the culture collection at the Microbiology laboratory, National Organization for Drug Control and Research (NODCAR).

The assayed collection included two gram-negative bacteria: *Esherichia coli* (ATCC 14169), and *Pseudomonas areuginosa* (ATCC 9027); four gram-positive bacteria: *Bacillus subtilis* (ATCC 6633), *Bacillus cereus* (ATCC 11778), *Lactobacillus acidophilus* (ATCC 4356), and *Micrococcus leutus* (ATCC 9341); and the yeast *Candida albicans* (ATCC 10231).

2.6.2. Agar Diffusion Assay

In the agar diffusion method [25, 26], compounds dissolved in dimethylsulfoxide (DMSO-d_6) 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 DMSO without any compound 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 compound inhibits the growth of microorganism.

2.6.3. Minimum Inhibitory Concentration

The Minimum Inhibitory Concentration (MIC) was determined by the agar dilution method in Mueller-Hinton agar medium (Oxoid), according to NCCLS. Before gelling, 19 ml of agar medium were added to each of the Petri dishes containing one ml of the compound (2) in concentrations ranging from 33 to 526 mg/l. and the Petri dishes were swirled carefully until the agar began to set. Subsequently, bacteria (10^4 CFU/ml) were inoculated using a micropipette that placed 2 µl of each bacterial strain on the Mueller-Hinton agar surface. The MIC was taken as the lowest compound concentration that inhibited visible growth.

3. Results and Discussion

3.1. Chemistry

Bromination of 2-acetyl-5-bromobenzofuran (1) [20] in acetic acid afforded 2-bromoacetyl-5-bromobenzofuran (2), which used as starting material. Cyclocondensation of 2 with thioacetamide derivative namely (thiourea, phenylthiourea, thioacetamide and thiocarbamoyl pyrazole [21]) gives thiazole derivatives (3a-d). Thiazole derivatives (3a-d) were established on the basis of elemental analysis and spectral data. Thus, IR spectrum of (3a) revealed absorption bands at 3394, 3222 cm^{-1} due to NH_2 group. ^{1}HNMR spectrum ($CDCl_3$) of 3c showed signals at δ= 2.79 (s, 3H, CH_3) and 7.08-7.73 (m, 5H, Ar-H, furan-H3, thiaozle-H5). IR spectrum of (3d) revealed absorption bands at 3394, 3288 and 2222 cm^{-1} due to (NH_2) and (CN) groups. Condensation of compound 2 with 2-aminothiazole and 5-methyl-2-amino-1,3,4-thiadiazole [22] gave imidazothiazole and imidazothiadiazole derivatives (4a) and (4b), respectively, (Figure 1).

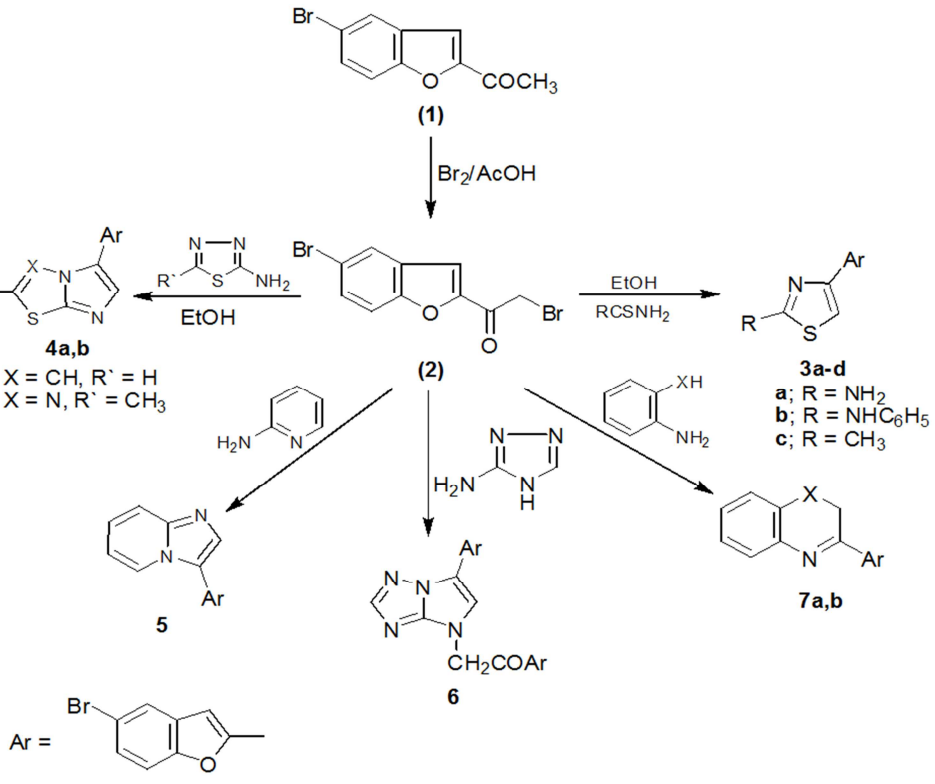

Figure 1. *Synthesis of thiazole, imidazole, thiazine, pyrazine (3-7).*

Our investigation was extended to include the behavior of compound (2) towards heterocyclic amines for building different ortho fused heterocyclic rings. Thus, treatment of 2 with 2-aminopyridine and or/ 2-aminotriazole in ethanol under reflux yielded imidazopyridine (5) and imidazotriazole (6) respectively, (Figure 1). Also, compound 2 on treatment with ambient nucleophiles such as o-aminothiophenol and o-phenylene-diamine in refluxing ethanol afforded benzothiazine (7a) and quinoxaline (7b) derivatives, respectively, (Figure 1).

Interaction of 2 with 4,6-dimethyl-3-cyano-pyridine-2-thione [23] in boiling ethanol gave only one isolable product (TLC) for which two proposed structures 8 or 9 seemed possible, (Figure 2). Structure 9 was ruled out on the basis of IR and ^{1}HNMR spectral data. Thus, IR spectrum revealed absorption band at 2212 cm^{-1} due to CN group and no absorption band for NH_2 group, ^{1}HNMR spectrum showed singlet signal at δ 4.55 for CH_2. Treatment of a solution of malononitrile in DMF with phenyl isothiocyanate in the presence of potassium hydroxide, at room temperature afforded no isolable potassium salt (10a) followed by the addition of an equimolar amount of bromoacetyl-5-bromobenzofuran (2) furnished only one isolable product (TLC) for which two proposed structures 11a or 11b seemed possible, (Figure 2). Structure 11b was ruled out on the basis of IR and mass spectral data. Thus, IR spectrum showed no absorption band for NH_2 or C=O groups and the mass spectrum was compatible with the molecular formula $C_{20}H_{10}BrN_3OS$ (M^+; 419).

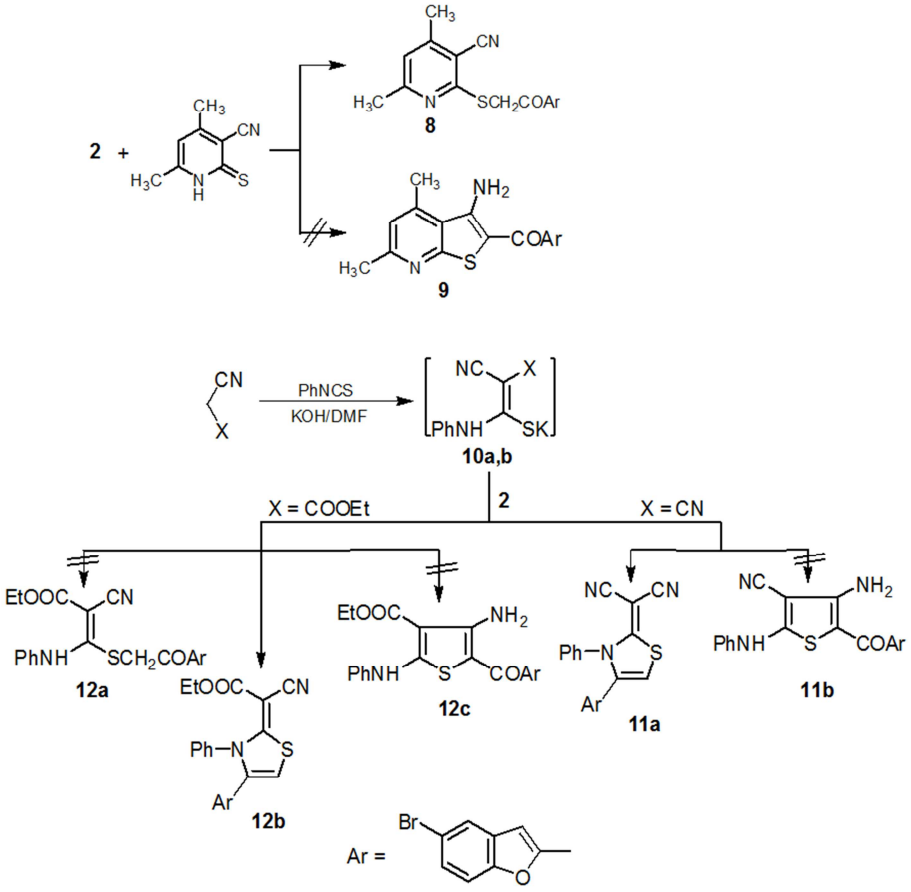

Figure 2. *Synthesis of thiophene (8-12).*

On the other hand, the potassium salt of ethyl cyanoacetate (10b) was treated with 2 to afford only one isolable product (TLC), from three proposed structures 12a, 12b or 12c seemed possible, (Figure 2). Structures 12a and 12c was ruled out on the basis of ^{1}HNMR spectrum of the isolated product. Thus, ^{1}HNMR spectrum showed singlet at δ = 5.27 due to CH-thiazole.

Moreover, when bromoacetyl derivative (2) was subjected to the reaction with thiosemicarbazide afforded a single product for which two isomeric structures 13 or 14 seemed possible. Structure 13 was ruled out and the structure 14 was firmly established by the reaction of 2 with benzylidenethio-semicarbazides (15a, b) which gave thiazolidine derivatives (16a, b), which identical in all respects (m.p, mixed m.p and spectral data) with the arylhydrazone of 14, scheme 3. IR spectrum of 14 revealed bands at 3372, 3266 and 3180 cm^{-1} (NH_2, NH), while its mass spectrum was compatible with the molecular formula $C_{11}H_8BrN_3OS$ (M^+; 309). ^{1}HNMR spectrum of 16b showed signals at δ = 3.8 (s, 3H, OCH_3), 6.91-7.68 (m, 10H, Ar-H), furan-H_3, thioamide-H_5, and NH), 7.75 (s, 1H, CH-benzylidene). Mass spectrum of 16a was compatible with the formula $C_{18}H_{12}BrN_3OS$ (M^+; 397).

Thiazolylpyrazole (18), was prepared via interaction of Compound 2 with 3-methyl-5-oxopyrazoline- 1-thiocarboxamide (17) in ethanol media [24], the compound 18 was showed in three tautomeric forms 18_{A-C} (figure 3), the 18A and 18_C was neglected according to IR spectrum of the isolated product 18B, which revealed absorption bands 3170 and 1640 cm^{-1} due to NH and C=O groups, while its ^{1}HNMR spectrum was showed, signals at δ = 2.23 (s, 3H, CH3), 5.29 (s, 1H, CH of pyrazole-4), 7.21-7.91 (m, 6H, Ar-H, furan-H3, thiazole-H5, and NH). Compound 18 was coupled with benzene diazonium chloride in pyridine at 0°C to afford a colored product (20a, b) for which the Three isomeric structures (azo form) A or B (hydrazo form) C seemed possible, (Figure 3). IR spectrum of the isolated product revealed absorption bands at 3442 (NH) and 1656 cm^{-1} (C=O). ^{1}HNMR spectrum showed signals at δ= 2.49 (s, 3H, CH_3), 7.18-7.82 (m, 5H, Ar-H), furan-H_3, and thiazol-H_5), 8.40 (br, 1H, NH).

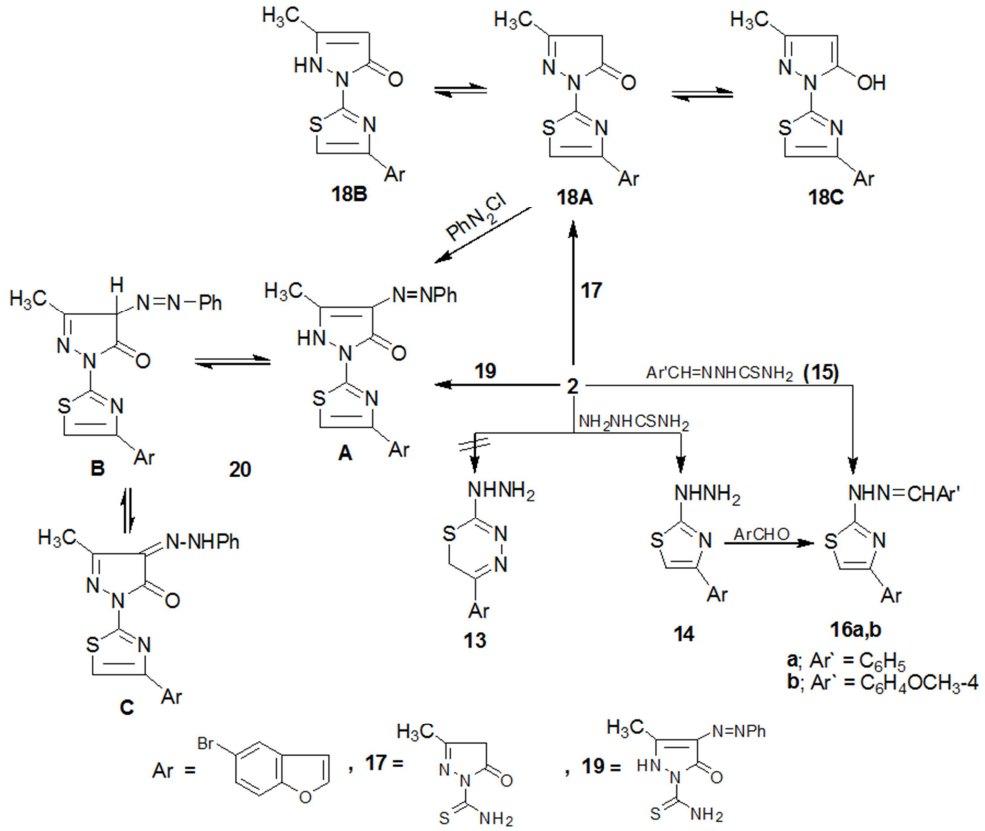

Figure 3. *Synthesize thiazole derivatives (14-20).*

Compound (20) was obtained from interaction of 2 with 3-methyl-4-phenylazo-5-oxopyrazoline-1-thiocarboxamide (19) (m.p, mixed m.p and spectra data) with 20, that previously obtained, (Figure 3).

Our investigation was extended to include the behavior of 2-aminothiazole derivative (3a) towards some electrophiles. Thus, treatment of (3a) with some aromatic aldehydes in boiling ethanol gave the corresponding arylidene derivatives (21a, b), (Figure 4).

On other hand, condensation of 3a with ethyl cyanoacetate and/or diethyl malonate gave acyclic N-acylamino derivatives (23a, b) rather than the expected cyclocondensation product thiazolo[3,2-a]pyridines (22a, b). The obtained product was cyclized to give N-acylamino derivatives (23a, b) was established on the basis of elemental and spectral data studies. Thus, IR spectrum of 23a revealed absorption bands at 3302, 2262, 2676 cm^{-1} due to NH, CN and CO groups respectively and the mass spectrum was compatible with the molecular formula $C_{14}H_8BrN_3OS$ (M^+; 361), while the ^{1}HNMR spectrum of (23a) showed signals at δ 1.21 (t, 3H, CH_3), 3.63 (s, 2H, CH_2), 4.12 (q, 2H, CH_2), 7.12-8.55 (m, 5H, Ar-H, furna-H_3, thiazole-H_5), 12.63 (s, 1H, NH).

Cyclocondensation of 23a with acetylacetone under fusion conditions afforded thiazolyl pyridine derivative (24). Compound 24 was confirmed on the basis of elemental analysis and spectral data, thus ^{1}HNMR spectrum showed signals at δ 2.23, 2.43 (2s, 6H, $2CH_3$), 6.19 (s, 1H, CH-pyridine), 7.09-7.89 (m, 5H, Ar-H, furan-H_3, thiazole-H_5). Moreover, condensation of 23a with 4-methoxy benzaldehyde in hot ethanol afforded arylidene derivative (25), which on treatment with malononitrile in ethanol in the presence of piperidine under reflux furnished thiazolylaminopyranone derivative (26). Compound 26 obtained from the reaction of 23a with 4-methoxy benzylidenemalononitrile, (Figure 4).

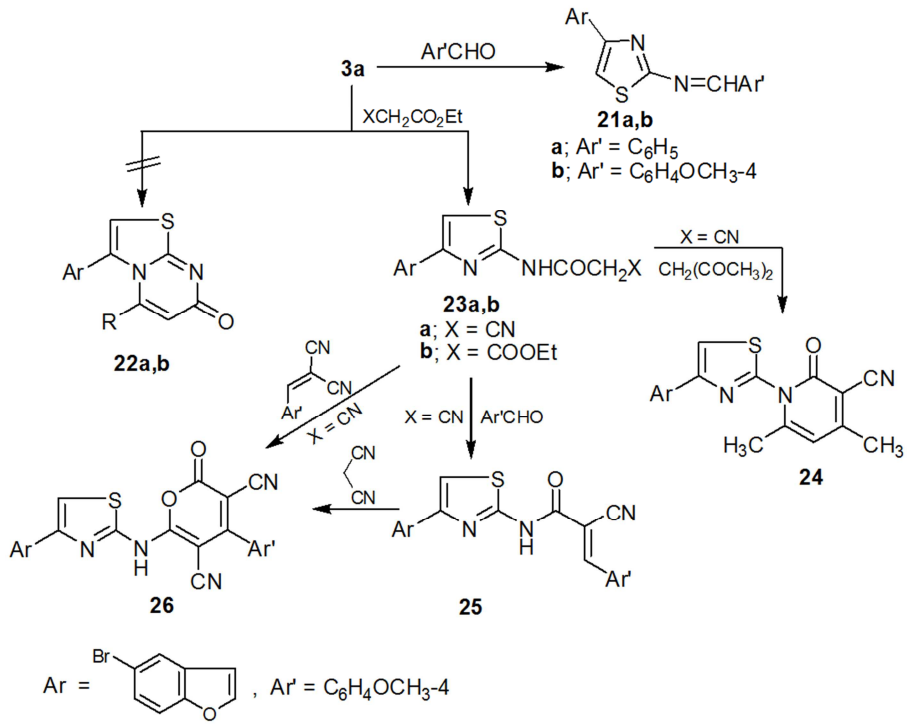

Figure 4. *Synthesis of α-pyranone and pyridinone (21-26).*

3.2. Antimicrobial Screening

3.2.1. Antibacterial and Antifungal Activities

The antibacterial and antifungal activities of the synthetic compounds were assayed against strains of both gram-positive, gram-negative pathogenic bacteria and yeast. Initially, the susceptibility testing was carried out by agar diffusion method. The inhibition zone diameters were read and rounded up to the nearest whole number (mm) for analysis. The inhibitory effects of the synthetic compounds against these organisms are given in Table 1.

The screening results indicate that: three compounds showed significant antimicrobial activity, while, compound 2 showed highest activity against all tested microorganisms, so that it is important to measure the toxicity of this compound.

3.2.2. Minimum Inhibitory Activity

The MIC of the compound (2) was determined by agar dilution method [25, 26]. The MIC level of the compound was calculated "≥ 263 mg/L" against the *Bacillus cereus*, *Micrococcus leutus* and *Pseudomonas areuginosa.*

Table 1. *Antibacterial & Antifungal Activities of some newly synthesized compounds.*

CPD. No.	Gram-Negative Bacteria		Gram-Positive Bacteria				Unicellular Fungi
	E. Coli (ATCC 14169)	*P. Areuginosa* (ATCC 9027)	*B. Subtilis* (ATCC 6633)	*B. Cereus* (ATCC 11778)	*L. Acidophilus* (ATCC 4356)	*M. Leutus* (ATCC 9341)	*C. Albicans* (ATCC 10231)
2	17	17	25	22	17	16	35
3c	7	12	9	12	12	13	10
3d	10	8	13	11	10	11	11
4a	8	11	9	12	7	10	10
5	12	13	14	10	11	13	7
7a	13	7	9	12	13	10	12
7b	10	13	13	9	10	11	11
8	12	9	16	15	13	11	13
12b	11	12	9	7	10	11	7
16	11	13	7	12	13	10	9
20	9	10	18	17	11	17	13
21b	12	13	11	10	12	13	10
23a	9	10	14	12	11	13	13
24	12	13	11	10	12	13	10
25	12	13	11	10	12	13	10
26	10	8	13	11	10	11	11
27	11	13	7	12	13	10	9

Inhibition zone diameter Moderate active: (14-20 mm)
Weak active: (7-13 mm) High active: (21-42 mm)

4. Conclusion

The screening results indicate that compound 2 showed the highest activity against all tested microorganisms because Its containing ($COCH_2Br$) group and benzofuran moiety.

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