Convenient Synthesis of Some New Pyrazolo[1,5-*a*]pyrimidine, Pyridine, Thieno[2,3-*b*]pyridine, and Isoxazolo[3,4-*d*]pyridazine Derivatives Containing Benzofuran Moiety

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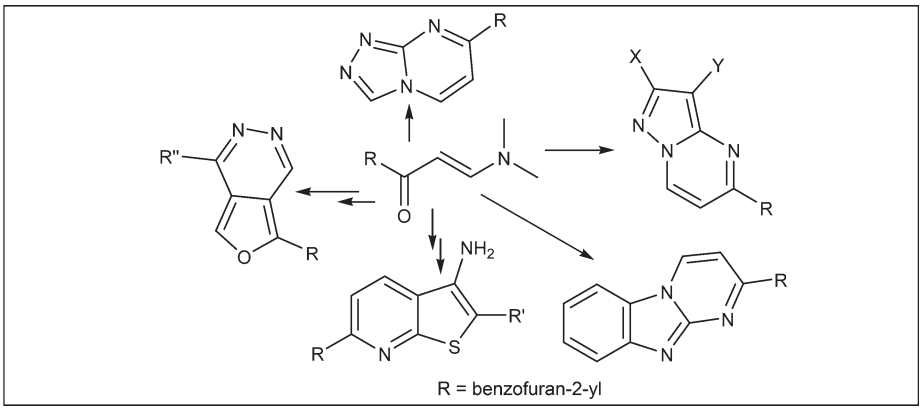

Pyrazolo[1,5-*a*]pyrimidines, pyrazoles, and thieno[2,3-*b*]pyridine were synthesized from sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone and the appropriate of heterocyclic amines, diazonium chloride, and 1,3-dicarbonoyl compounds. Pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine, 1,2,3,4-tetrazolo[1″,5″:6′,1′]-pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine and pyridino[2″,3″:2′,3′]thieno[4,5-*d*]1,2,4-triazolo[4,3-*e*]pyrimidine derivatives were synthesized from 6-benzo[*d*]furan-2-yl-2-thioxohydropyridine-3-carbonitrile and each of formic acid or formamide. Structures of the newly synthesized were established by elemental analysis and spectral data.

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INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidines are of considerable chemical and pharmacological importance as purine analogs [1]. The interesting biological activity has attracted the attention of many chemists to develop new efficient general procedures for the synthesis of pyrazolo[1,5-*a*]pyrimidines by using aminopyrazoles. The benzofuran moiety is incorporated in various natural products [2–5] and pharmaceuticals [6–9]. In addition, biological and medicinal activity of fused thienopyrimidines has stimulated much research in this field [10–21]. Our research has been devoted to the development of new classes of heterocyclic systems which incorporate the thienopyrimidine moiety in the hope that they may be biologically active. In continuation of our interest in the synthesis of heterocycles [22–26], we report herein, a convenient method for the synthesis of pyrazolo[1,5-*a*]pyrimidines, thieno[2,3-*b*]pyridines, pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine, isoxazolo[3,4-*d*]pyridazines, and pyridine containing benzofuran moiety as antimicrobial agents.

RESULTS AND DISCUSSION

Treatment of sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone (**2**) with 3-amino-4-phenylpyrazole in piperidenium acetate yielded 5-benzofuran-2-yl-3-phenylpyrazolo[1,5-*a*]pyrimidine (**3a**). Structure of **3** was established on the basis of their elemental analysis, spectral data, and alternative synthetic route. Thus, treatment of 1-benzofuran-2-yl-3-dimethylamino-propenone [26] (**6**) with 3-amino-4-phenylpyrazole in boiling ethanol gave product identical in all respects (mp., mixed mp., and spectra) with **3a**. ^{1}H NMR spectrum of **3a** revealed multiple band at δ = 7.35–8.55 (m, aromatic protons). Analogously, compound **2** was reacted with the appropriate 3-amino-4-methyl-5-phenylpyrazole, 3-amino-4-cyanopyrazole, 2-aminobenzimidazole or 3-aminotriazole gave 5-(1-benzofuran-2-yl)-3-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**3b**), 5-benzofuran-2-yl-3-cyanopyrazolo[1,5-*a*]pyrimidine (**3c**), 7-(benzofuran-2-yl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (**4**), and 2-(1-benzofuran-2-yl)pyrimido[1,2-*a*]benzimidazole (**5**), respectively (Scheme 1).

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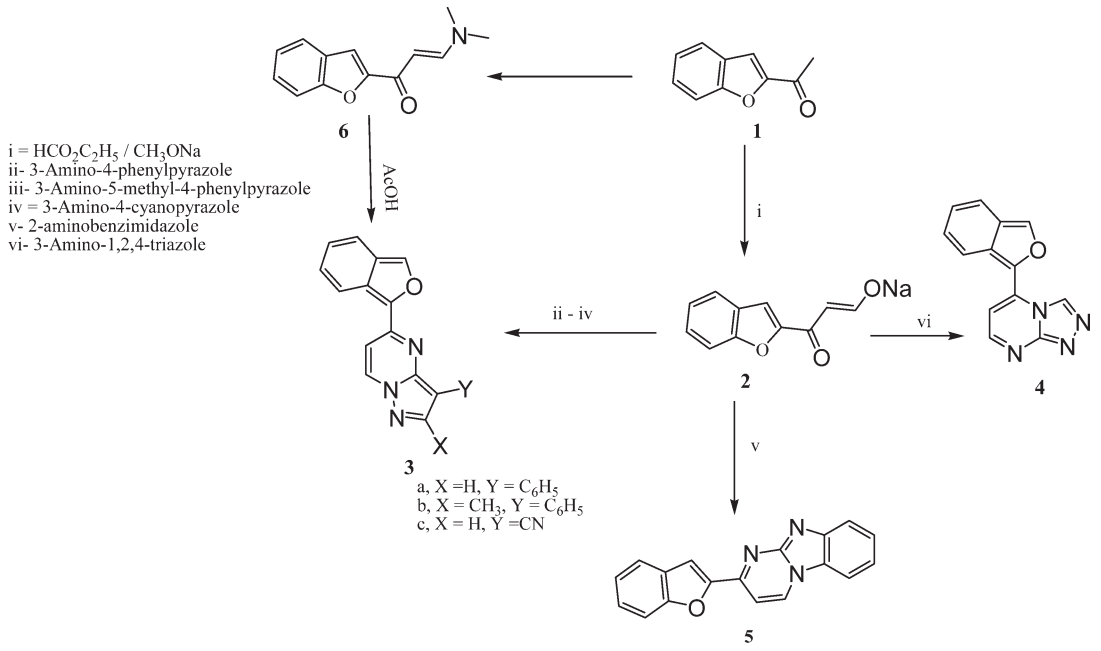
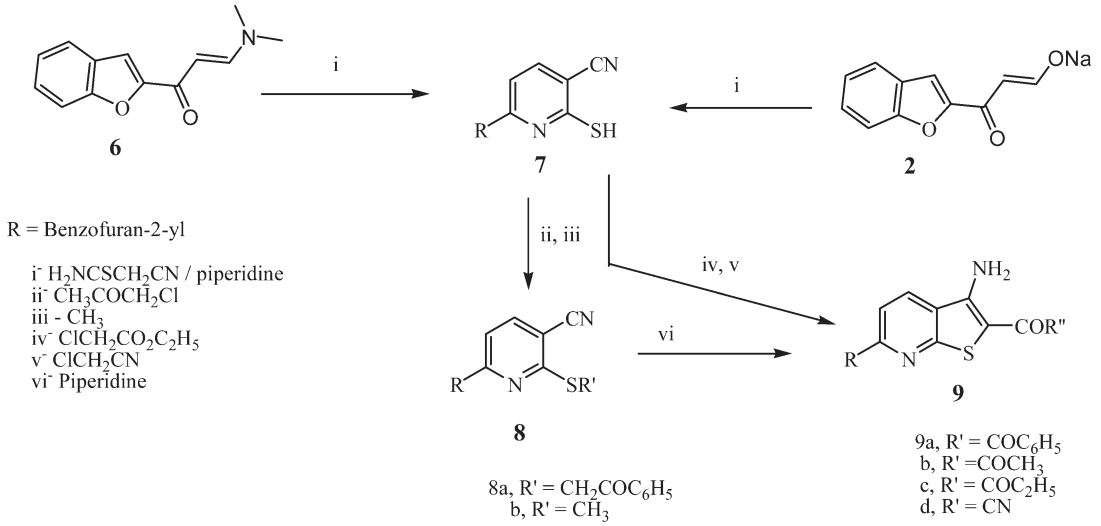
Scheme 1



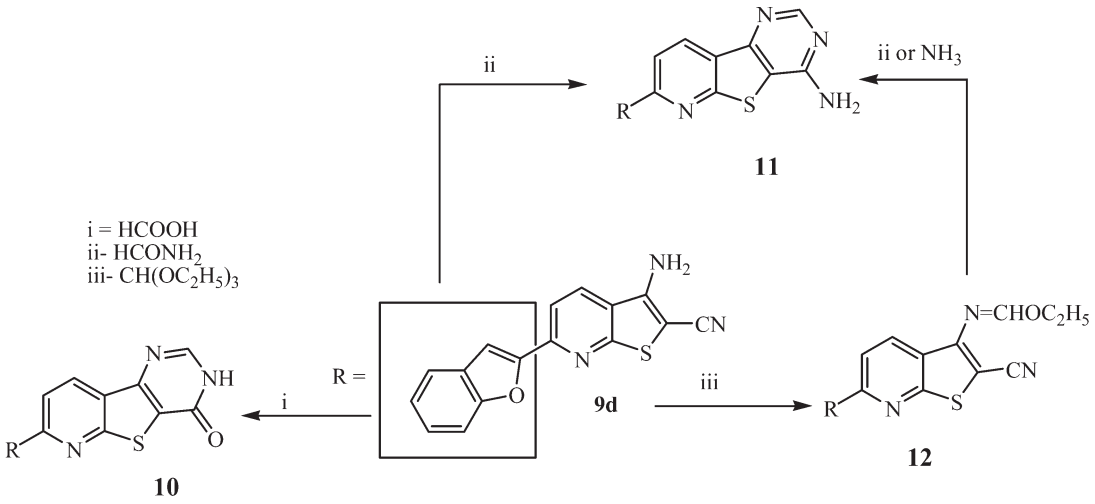
It has been found that 6-benzofuran-2-yl-2-sulfanyl-pyridine-3-carbonitrile (**7**), which prepared via reaction of **2** with cyanothioacetamide in presence of piperidenium acetate, reacted with ω-bromoacetophenone in *N*,*N*-dimethylformamide containing potassium hydroxide to afford the product corresponding to addition and dehydrobromination reactions. The IR spectrum of this product showed bands corresponding to CN and CO groups. Its ^{1}H NMR spectrum revealed the signals at δ = 4.09 (S, 2H, **SCH_2**) and 7.47–8.04 (m, 12H, ArH's). Based on the above-mentioned data, these reaction products could be formulated as 6-benzofyran-2-yl-2-(2-oxo-2-phenylethylthio)pyridine-3-carbonitrile (**8a**). Further confirmation of the structure of **8a** arose from their cyclization in boiling ethanol containing catalytic amount of piperidine to give the corresponding (3-amino-6-(benzofuran-2-yl)thieno[2,3-b]pyridin-2-yl)(phenyl)methanone (**9a**) (Scheme 2).

The IR spectrum of **9a** showed no band of the CN function while the band of the new NH_2 group was detected. On the other hand, the ^{1}H NMR spectrum of **9a** revealed absence of signals of the —SCH_2— group and the presence of the NH_2 protons. The earlier findings proved that the CN and the —SCH_2— groups were

Scheme 2



Scheme 3

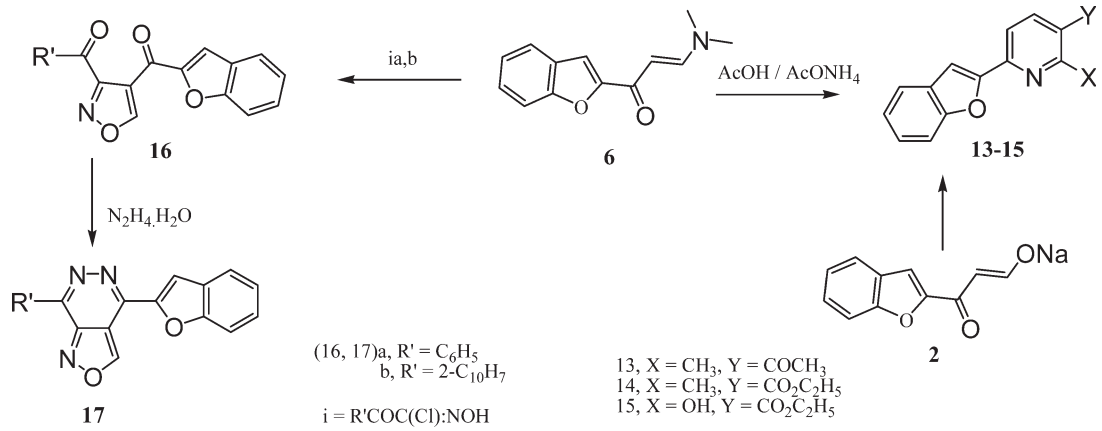


both involved in the cyclization step leading to **9a**. Compound **7** reacted also with each of iodomethane, chloroacetone, ethyl chloroacetate, and chloroacetonitrile in *N*,*N*-dimethylformamide containing potassium hydroxide to afford **8b** and **9b–d**, respectively. The reaction seemed to proceed through dehydrochlorination to give the intermediate **8c–d**, which underwent cyclization via addition of the —SCH_2— hydrogen to the nitrile function to give **9b–d**, respectively. IR, ^{1}H NMR, and elemental analyses were the basis on which the structure of **9** was established. Thus, it has been found that **9d** reacted with each of formic acid, formamide, or triethyl orthoformate to give the corresponding 7-(1-benzofuran-2-yl)pyrido[2′,3′:4,5]-thieno[2,3-*b*]pyridin-4(3*H*)-one (**10**), 7-(1-benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4-amine (**11**), and ethyl [6-(1-benzofuran-2-yl)-2-cyanothieno[2,3-*b*]pyridin-3-yl]imidoformate (**12**), respectively (Scheme 3). Structures of **10–12** were established on the basis of spectral data (IR, ^{1}H NMR) and elemental analysis. Thus, IR spectrum of **11** revealed bands at 3458 and 3216 (NH_2). IR spectrum of **12** revealed bands at 2248 (CN) and 1627 (C=N). Also, compound **17** reacted with ethanolic ammonia (or formamide) afforded a product identical in all aspects (mp., mixed mp., and spectra) with **11**.

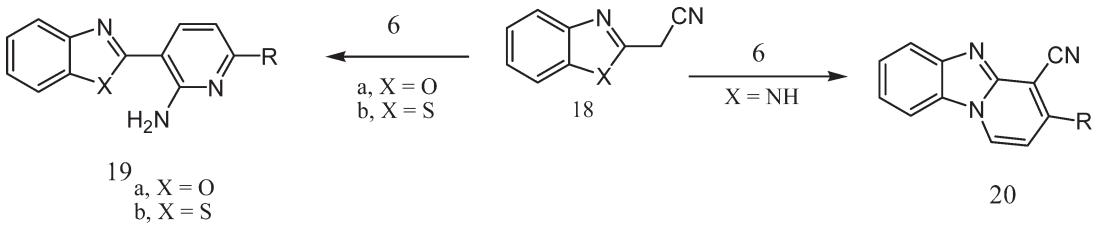
Treatment of 1-benzofuran-2-yl-3-dimethylamino-propenone (**6**) with the appropriate acetylacetone, ethyl acetoactate, or ethyl cyanoacetate, in boiling acetic acid containing ammonium acetate under reflux gave pyridine derivatives **13–15**, respectively (Scheme 4).

Compound **6** reacted with *N*-hydroxy-2-oxo-2-phenylethanimidoyl chloride in toluene containing triethylamine afforded 1-benzofuran-2-yl(3-benzoylisoxazol-4-yl)methanone (**16a**). Structure **16** was elucidated by elemental analysis, spectral data, and chemical transformation. ^{1}H NMR spectrum of **16a** showed signals at $\delta = 7.25–7.69$ (m, 8H, aromatic), 8.58–8.60 (d, 2H, $J = 4$ Hz, aromatic), and 8.74 (s, 1H, isoxazole H-5). Thus, treatment of **16a** with hydrazine hydrate gave 1-benzofuran-2-yl(3-benzoylisoxazol-4-yl)methanone (**17a**). Analogously, **6** reacted with *N*-hydroxy-2-oxo-2-(2-naphthyl)ethanimidoyl chloride

Scheme 4



Scheme 5



in toluene containing triethylamine afforded **16b**, which treated with hydrazine hydrate to give **17b**.

Also, treatment of 1-benzofuran-2-yl-3-dimethylaminopropenone (**6**) with each of benzoxazol-2-ylacetonitrile (**18a**) and benzthiazol-2-ylacetonitrile (**18b**) in boiling acetic acid containing ammonium acetate afforded 3-(benzo[d]oxazol-2-yl)-6-(benzofuran-2-yl)pyridin-2-amine (**19a**) and 3-(benzo[*d*]thiazol-2-yl)-6-(benzofuran-2-yl) pyridin-2-amine (**21b**) on the elemental analysis and spectral data. In contrast, benzimidazol-2-acetonitile reacted with **6** in ethanol gave 3-(1-benzofuran-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**20**) in a good yield (Scheme 5).

Finally, treatment of sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone **2** with the benzenediazonium chloride in ethanol containing sodium acetate as a buffer solution yielded 3-(1-benzofuran-2-yl)-3-oxo-2-(phenylhydrazono)propanal (**21**). Structure **21** was confirmed by elemental analysis, spectral data, and chemical transformation. ^{1}H NMR spectrum of **21** showed signal at δ = 7.26–7.93 (m, 10 H, ArH's), 9.98 (s, 1H, —CHO) and 14.39 (s, br., 1H, NH). Thus, **21** was reacted with hydrazine hydrate in boiling ethanol under reflux to give 3-(1-benzofuran-2-yl)-4*H*-pyrazol-4-one phenylhydrazone **22** (Scheme 6).

CONCLUSION

5-Benzofuran-2-yl-3-hydroxypropenone is used to synthesize different pyrazolo[1,5-*a*]pyrimidines, pyrazoles, and thieno[2,3-*b*]pyridine via its reaction with different heterocyclic amines, cyanothioacetamide, and diazonium chlorides, respectively. Pyrimidino[4′,5′:4,5]-thieno[2,3-*b*] pyridine, 7-(1-benzofuran-2-yl)pyrido-[2′,3′:4,5]thieno[2,3-*b*] pyridin-4(3*H*)-one, and 7-(1-benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4-amine were synthesized from 6-benzo[*d*]furan-2-yl-2-thioxohydropyridine-3-carbonitrile in good yields.

EXPERIMENTAL

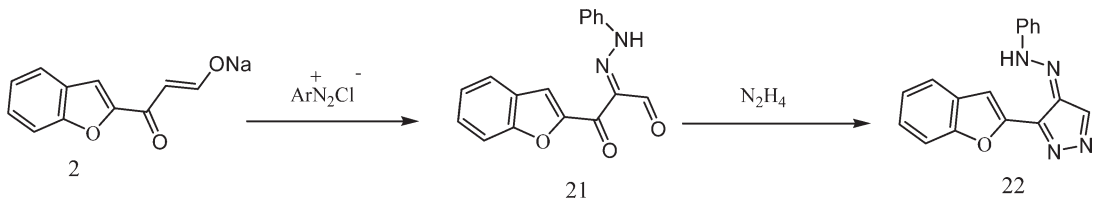
All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FTIR 8201 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses and microorganism tests were carried out at the Microanalytical Center of the Cairo University.

Sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone (2). In three-necked flask sodium methoxide (10 mmol) and ether (20 mL) was taken and 2-acetylbenzofuran (**1**) (10 mmol) with (10 mmol) of ethyl format was poured over it through a separating funnel with efficient stirring. The solid product was collected and used directly in the reactions.

Synthesis of 3a–c, 4, 5, 7, 13, 14, and ethyl 15. ***Method A.*** A solution of (10 mmol) sodium salt of sodium salt of 5-benzofuran-2-yl-3-hydroxypropenone **2**, (10 mmol), the appropriate 3-amino-4-phenyle, 3-amino-4-methyl-5-phenylpyrazole, 3-amino-4-cyanopyrazole, 3-aminopyrazole, 2-aminobenzimidazole, cyanothioacetamide, acetylacetone, ethyl acetoacetate, or ethyl cyanoacetate (10 mmol) and piperidine acetate (1 mL) in water (3 mL) was refluxed for 10 min. Acetic acid (1.5 mL) was added to the hot solution. The solid product was filtered off and recrystallized from the proper solvent gave products **3a–c**, **4**, **5**, **7**, **13–15**.

Method B. An equimolar amount of 1-benzofuran-2-yl-3-dimethylaminopropenone (**6**), the appropriate 3-amino-4-phenylpyrazole, 3-amino-4-methyl-5-phenylpyrazole, 3-amino-4-cyanopyrazole, 3-amino-1,2,4-triazole, 2-aminobenzimidazole, cyanothioacetamide, acetylacetone, ethyl acetoacetate, or ethyl cyanoacetate and ammonium acetate (5 mmol) in acetic acid

Scheme 6



(10 mL) was heated under reflux for 4 h. The resulting solid was collected and recrystallized from the proper solvent gave products **3a–c**, **4**, **5**, **7**, **13–15**.

5-Benzofuran-2-yl-2-phenylpyrazolo[1,5-*a*]pyrimidine (3a). This compound was obtained as yellow crystals (AcOH), mp 204–206°C, yield (73%); IR (cm^{-1}): 1635 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 7.35–8.55 (m, aromatic protons). ^{13}C NMR $(CD_3)_2SO$ δ = 102.23, 110.21, 122.6, 122.8, 123.52, 125.8, 125.9, 128.2, 128.6, 130, 131.2, 132, 133.1, 135.2, 140.1, 144.2, 146.2, 147.8. *Anal*. Calcd. for $C_{20}H_{13}N_3O$ (311.35): C, 77.16; H, 4.21; N, 13.50. Found: C, 76.92; H, 4.00; N, 13.65.

5-(1-Benzofuran-2-yl)-3-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (3b). This compound was obtained as yellow crystals (AcOH), mp 215–217°C, yield (75%); IR (cm^{-1}): 3050 (CH, aromatic), 2920 (CH, aliphatic), 1635 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 2.51 (s, 3H, CH_3), 7.35–8.55 (m, 12 H, aromatic protons). *Anal*. Calcd. for $C_{21}H_{15}N_3O$ (325.37): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.45; H, 4.56; N, 13.12.

5-Benzofuran-2-yl-2-cyanopyrazolo[1,5-*a*]pyrimidine (3c). This compound was obtained as pale yellow crystals (AcOH), mp 238–240°C, yield (76 %); IR (cm^{-1}): 3050 (CH, aromatic), 2920 (CH, aliphatic), 2229 (CN), 1635 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 7.32–8.91 (m, 11 H, aromatic protons), 8.97 (s, 1H, pyrazole H-5). ^{13}C NMR $(CD_3)_2SO$ δ = 84.1, 104.2, 112,3, 121.3, 122.6, 123.3, 128.5, 130.1, 130.7, 131.2, 136.2, 140.4, 148.8, 150, 152.2. *Anal*. Calcd. for $C_{15}H_8N_4O$ (260.26): C, 69.23; H, 3.10; N, 21.53. Found: C, 69.32; H, 3.00; N, 21.35.

2-(1-Benzofuran-2-yl)pyrimido[1,2-*a*]benzimidazole (4). This compound was obtained as pale yellow crystals (AcOH), mp 230–262°C, yield (64%); IR (cm^{-1}): 1616 (C=N), 1562 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 7.36–7.955 (m, 5H, aromatic protons), 8.59 (s, 1H, triazole H-5), 8.99–9.01(d, *J* = 6H), pyrimidine ring). *Anal*. Calcd. for $C_{13}H_8N_4O$ (236.23): C, 66.10; H, 3.41; N, 23.72. Found: C, 66.25; H, 3.51; N, 23.54.

7-(1-Benzofuran-2-yl)[1,2,4]triazolo[4,3-*a*]pyrimidine (5). This compound was obtained as yellow crystals (AcOH), mp 205–207°C, yield (37%); IR (cm^{-1}): 3050 (CH, aromatic), 1635 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 7.34–8.53 (m, aromatic protons). *Anal*. Calcd. for $C_{18}H_{11}N_3O$ (285.31): C, 75.78; H, 3.89; N, 14.73. Found: C, 75.87; H, 3.98; N, 14.65.

6-Benzofuran-2-yl-2-sulfanylpyridine-3-carbonitrile (7). This compound was obtained as page crystals (EtOH), mp 200–202°C, yield (84%); IR (cm^{-1}): 3342 (NH), 2217 (CN). ^1H NMR $(CD_3)_2SO$ δ = 6.67–7.42 (m, 6H, aromatic proton), 8.21 (s, 1H, 5-H of the pyridinethione ring), 14.10 (b, 1H, SH). *Anal*. Calcd. for $C_{14}H_8N_2OS$ (252.30): C, 66.65; H, 3.20; N, 11.10.60; S, 12.71. Found: C, 66.72; H, 3.41; N, 11.28; S, 12.64.

1-[6-(1-Benzofuran-2-yl)-2-methylpyridin-3-yl]ethanone (13). This compound was obtained as colorless crystals (EtOH), mp 113–114°C, yield (37%); IR (cm^{-1}): 1685 (CO), 1639 (C=N), 1581 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 2.50 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.31–8.38 (m, 7H, aromatic protons). ^{13}C NMR $(CD_3)_2SO$ δ = 24.4, 25.3, 106.3, 111.5, 118.4, 121.2, 123.4, 125, 128.2131, 137.5, 148.2, 151.3, 145,5, 155.8, 199.8. *Anal*. Calcd. for $C_{16}H_{13}NO_2$ (251.25): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.64, H, 5.10; N, 5.75.

Ethyl 6-(1-benzofuran-2-yl)-2-methylnicotinate (14). This compound was obtained as colorless crystals (EtOH), mp 129–130°C, yield (37%); IR (cm^{-1}): 1715 (CO), 1639 (C=N), 1581 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 1.29 (t, 3H, *J* = 7.5 Hz, CH_3), 2.77 (s, 3H, CH3), 4.26 (q, 2H, *J* = 7.5 Hz, CH_2), 7.27–839 (m, 7H, aromatic protons). ^{13}C NMR $(CD_3)_2SO$ δ = 14.2, 25.6, 60.8, 106.3, 111.5, 115.4, 121, 123.3, 125.2, 125.6, 128.3, 139.4, 148, 145.2, 156.2, 159.3, 164. ^1H NMR $(CD_3)_2SO$. *Anal*. Calcd. for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.45; H, 5.45; N, 4.75.

Ethyl 6-(1-benzofuran-2-yl)-2-oxo-1,2-dihydro-pyridine-3-carboxylate (15). This compound was obtained as colorless crystals (AcOH), mp 182–184°C, yield (89%); IR (cm^{-1}): 3448 (NH), 1681 (CO), 1635 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 1.32 (t, 3H, *J* = 6 Hz, CH_3), 4.28 (q, 2H, *J* = 6 Hz, CH_2), 7.22–8.50 (m, 7H, aromatic protons), 9.26 (s, br., 1H, NH). *Anal*. Calcd. for $C_{16}H_{13}NO_4$ (283.28): C, 67.84; H, 4.63; N, 4.94. Found: C, 67.58; H, 4.50; N, 5.24.

Synthesis of 8a,b, 9b-d. A mixture of **7**(1.3 g, 10 mmol) and potassium hydroxide (0.6 g, 10 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. The appropriate of ω-bromoacetophenone, methyl iodide, chloroacetone, ethyl chloroacetate, or chloroacetonitrile (10 mmol each) was added and stirring was continued for 2 h. The resulting solid was collected and recrystallized from the proper solvent to give **8a**, **8b**, and **9b–d**, respectively.

6-(1-Benzofuran-2-yl)-2-[(2-oxopropyl)thio]nicotino-nitrile (8a). This compound was obtained as pale yellow crystals (EtOH), mp 240–242°C, yield (92%); IR (cm^{-1}): IR: 2190 (CN). ^1H NMR $(CD_3)_2SO$ δ = 4.09 (S, 2H, SCH_2) and 7.47–8.04 (m, 12H, ArH's). ^1H NMR $(CD_3)_2SO$ δ = 52.8, 95.1, 106.3, 111.4, 113.2, 116, 121.2, 123.3, 125.6, 126.4, 127.6, 127.9, 130.1, 136.7, 151, 155.4, 160.3, 163.2, 198.8. *Anal*. Calcd. for $C_{22}H_{14}N_2O_2S$ (370.42): C, 71.33; H, 3.81; N, 7.56; S, 8.66. Found: C, 71.23; H, 3.75; N, 7.64; S, 8.65.

6-(1-Benzofuran-2-yl)-2-(methylthio)nicotinonitrile (8b). This compound was obtained as pale brown crystals (EtOH), mp 120–121°C, yield (81%); IR (cm^{-1}): 2198 (CN). ^1H NMR $(CD_3)_2SO$ δ = 2.47 (s, 3H, CH_3), 6.67–8.02 (m, 11H, aromatic proton), 8.21 (s, 1H, 5-H of the pyridinethione ring). *Anal*. Calcd. for $C_{15}H_{10}N_2OS$ (266.32): C, 67.65; H, 3.78; N, 10.52; S, 12.04. Found: C, 67.52; H, 3.82; N, 10.67; S, 12.19.

1-[3-Amino-6-(1-benzofuran-2-yl)thieno[2,3-*b*]pyridin-2-yl]ethanone (9b). This compound was obtained as pale yellow crystals (EtOH), mp 260–262°C, yield (37%); IR (cm^{-1}): 3316, 3124 (NH_2), 1596 (CO). ^1H NMR $(CD_3)_2SO$ δ = 2.38 (s, 3H, CH_3CO), 6.45 (br, 2H, NH_2), 7.16–7.73 (m, 6H, aromatic protons), 7.82 (s, 1H, 5-H of the thienopyridine ring). ^{13}C NMR $(CD_3)_2SO$ δ = 30.1, 106.4, 111.6, 115.4, 121.3, 122.6, 123.2, 125.6, 127.4, 127.8, 134.6, 148.2, 149.4, 154.3, 155.8, 156.6, 191.2. *Anal*. Calcd. for $C_{17}H_{12}N_2O_2S$ (308.35): C, 66.22; H, 3.92; N, 9.08; S, 10.40. Found: C, 66.10; H, 3.85; N, 8.89; S, 10.30.

Ethyl 3-amino-6-(1-benzofuran-2-yl)thieno[2,3-*b*]pyridine-2-carboxylate (9c). This compound was obtained as pale yellow crystals (Dioxan), mp 240–242°C, yield (68%); IR (cm^{-1}): 3481, 3351 (NH_2), 1731 (CO). ^1H NMR $(CD_3)_2SO$ δ = 1.29 (t, 3H, *J* = 7 Hz, CH3), 4.24 (q, 2H, *J* = 7 Hz, CH2), 6.21 (br, 2H, NH_2), 7.12–7.87 (m, 6H, aromatic protons), 7.99 (s, 1H, 5-H of the thienopyridine ring). ^{13}C NMR $(CD_3)_2SO$ δ = 13.8, 59.1, 105.6, 106.2, 111.4, 115.5, 121.2, 123.5, 125.4,

127.2, 128.1, 133.3, 148.4, 149.6, 154.3, 155.2, 155.8, 166.4. ^{1}H NMR $(CD_3)_2SO$. *Anal*. Calcd. for $C_{18}H_{14}N_2O_3S$ (338.38): C, 63.89; H, 4.17; N, 8.28; S, 9.48. Found: C, 63.95; H, 4.00; N, 8.45; S, 9.65.

3-Amino-6-(1-benzofuran-2-yl)thieno[2,3-*b*]pyridine-2-carbonitrile (9d). This compound was obtained as pale yellow crystals (EtOH), mp 160–162°C, yield (72%); IR (cm^{-1}): 3496, 3300 (NH_2), 2198 (CN). ^{1}H NMR $(CD_3)_2SO$ δ = 6.57 (br, 2H, NH_2), 7.12 (m, 6H, aromatic protons), 8.31(s, 1H, 5-H of the thienopyridine ring). *Anal*. Calcd. for $C_{16}H_9N_3OS$ (291.33): C, 65.96; H, 3.11; N, 14.42; S, 11.01. Found: C, 66.12; H, 3.18; N, 14.30; S, 10.85.

(3-Amino-6-(benzofuran-2-yl)thieno[2,3-b]pyridin-2-yl) (phenyl)-methanone (9a). A solution of **8a** (1.85 g, 5 mmol) in ethanol (20 mL) containing piperidine (0.3 mL) was heated under reflux for 2 h. After cooling, the resulting solid was collected by filtration and recrystallized from dioxin/ethanol to give as pale yellow crystals (EtOH), mp 290–292°C, yield (78%); IR (cm^{-1}): 3408, 3300 (NH_2), 1685 (CO). ^{1}H NMR $(CD_3)_2SO$ δ = 16.21 (br, 2H, NH_2), 7.52–7.87 (m, 11H, aromatic protons), 7.99 (s, 1H, 5-H of the thienopyridine ring). *Anal*. Calcd. for $C_{22}H_{14}N_2O_2S$ (370.42): C, 71.33; H, 3.81; N, 6.56; S, 8.66. Found: C, 71.34; H, 3.79; N, 7.64; S, 8.75.

7-(1-Benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4(3*H*)-one (10). A mixture of **9c** (1.7 g, 10 mmol) and formic acid (99%, 20 mL) was heated under reflux for 7 h. After cooling, the reaction mixture was poured over ice (100 g) and the resulting solid was collected and recrystallized form *N*,*N*-dimethylformamide to give as page crystals mp > 300°C, yield (88%); IR (cm^{-1}): 3423 (NH), 1660 (CO). ^{1}H NMR $(CD_3)_2SO$ δ = 7.02–7.99 (m, 6H, aromatic protons), 8.25 (s, 1H, 5-H of the thienopyridine ring), 8.57 (s, 1H, Proton on C-2 of pyrimidine ring), 12.56 (s, 1H, NH of pyrimidine ring). *Anal*. Calcd. for $C_{17}H_9N_3O_2S$ (319.34): C, 63.94; H, 2.84; N, 13.16; S, 10.04. Found: C, 64.12; H, 2.98; N, 13.25; S, 10.15.

7-(1-Benzofuran-2-yl)pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-4-amine (11). Compound **9c** (1.7 g, 10 mmol) was heated with formamide (20 mL) at 180°C for 2 h. After cooling, the reaction mixture was poured over ice and the formed solid was collected by filtration and recrystallized form *N*,*N*-dimethylformamide to obtain as page crystals, mp 220–222°C, yield (78%); IR (cm^{-1}): 3458, 3216 (NH_2). ^{1}H NMR $(CD_3)_2SO$ δ = 6.79 (br, 2H, NH_2), 7.14–7.93 (m, 6H, aromatic protons), 8.01 (s, 1H, 5-H of the thienopyridine ring). *Anal*. Calcd. for $C_{17}H_{10}N_4OS$ (318.35): C, 64.14; H, 3.17; N, 17.60; S, 10.07. Found: C, 64.00; H, 3.27; N, 17.51; S, 10.24.

Ethyl [6-(1-benzofuran-2-yl)-2-cyanothieno[2,3-*b*]pyridin-3-yl]imidoformate (12). A mixture of **9c** (1.7 g, 10 mmol) and triethylorthoformate (20 mL) with catalytic amount of acetic acid were heated under reflux at 140°C for 6 h. The resulting dark brown solution was allowed to cool to room temperature and evaporated under vacuum. *n*-Hexane was added to the residue and the separated solid was filtered, washed with *n*-hexane and recrystallized from ethanol to obtain as pale yellow crystals, mp 180–182°C, yield (69%); IR (cm^{-1}): 2248 (CN), 1627 (C=N). ^{1}H NMR $(CD_3)_2SO$ δ = 1.22 (t, 3H, *J* = 7.5 Hz, CH_3), 4.33 (q, 2H, *J* = 7.5 Hz, CH_2), 6.73–7.98 (m, 6H, aromatic protons), 8.11 (s, 1H, 5-H of the thienopyridine ring), 8.66 (s, 1H, CH=N). ^{13}C NMR $(CD_3)_2SO$ δ = 13.2, 62.4, 85.4, 106.1, 111.5, 115.2, 121.2, 123.4, 125.2, 125.6, 126.4, 127.2, 135.2, 147.4, 150, 154.2, 155.5, 165.4. *Anal*. Calcd. for $C_{19}H_{13}N_3O_2S$ (347.39): C, 65.69; H, 3.77; N, 12.10; S, 9.23. Found: C, 65.82; H, 3.51; N, 11.95; S, 9.32.

Synthesis of 1-phenyl-4-(1-benzofuran-2-ylcarbonyl)-3-substituted oxazoles 16a,b. An equimolar amounts of the appropriate hydroxamoyl chlorides, 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**6**) (5 mmol), and triethylamine (5 mmol) in toluene (20 mL) were heated under reflux for 2 h. The solvent was evaporated under reduce pressure and triturated with petroleum ether 40–60°C then the resulting solid was collected and recrystallized from ethanol to give the oxazoles **16a** and **16b**, respectively.

1,3-Diphenyl-4-(1-benzofuran-2-ylcarbonyl)oxazoles (16a). This compound was obtained as colorless crystals (EtOH), mp 148–150°C, yield (91%); IR (cm^{-1}): 3058 (CH), 1685, 1639 (CO), 1612 (C=N), 1596 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.38–8.02 (m, 10H, aromatic protons) and 10.26 (s, 1H, isoxazole H-5). ^{13}C NMR $(CD_3)_2SO$ δ = 111.3, 117.4, 123.3, 123.8, 126.3, 128.6, 129.2, 130.5, 132.2, 138.2, 138.6, 157.3, 162.7, 173.6, 185.2, 187.9. *Anal*. Calcd. for $C_{19}H_{11}NO_4$ (317.29): C, 71.92; H, 3.49; N, 4.41. Found: C, 71.84; H, 3.75; N, 4.57.

1-Phenyl-4-(1-benzofuran-2-ylcarbonyl)-3-(2-naphthyl) oxazoles (16b). This compound was obtained as yellow crystals (AcOH), mp 214–216°C, yield (95%); IR (cm^{-1}): 3055 (CH), 1674, 1639 (CO), 1627 (C=N), 1554 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.25–7.69 (m, 8H, aromatic), 8.58–8.60 (d, 2H, *J* = 4 Hz, aromatic) and 9.92 (s, 1H, isoxazole H-5). *Anal*. Calcd. for $C_{23}H_{13}NO_4$ (367.35): C, 75.20; H, 3.57; N, 3.81. Found: C, 75.10; H, 3.45; N, 3.75.

Synthesis of 17a,b and 22. An equimolar amount of the appropriate isoxazoles **16a**, **16b**, or **21** and hydrazine hydrate (5 mmol) in ethanol (20 mL) was boiled under refluxed for 15 min. The resulting solid was collected and recrystallized from the proper solvent to give the oxazolo[3,4-*d*]pyridazines **17a**, **17b**, and **25**, respectively.

7-(1-Benzofuran-2-yl)-2,4-diphenyl-2H-oxazolo[3,4-*d*]pyridazine (17a). This compound was obtained as colorless crystals (AcOH), mp 178–181°C, yield (94%); IR (cm^{-1}): 3058 (CH), 1685, 1639 (CO), 1612 (C=N), 1596 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.37–8.53 (m, 12H, aromatic protons) and 10.32 (s, 1H, isoxazole H-5). ^{13}C NMR $(CD_3)_2SO$ δ = 105.2, 113.2, 117.7, 122, 123.5, 124.8, 128.2, 128.7, 129.3, 131.3, 136.8, 141.2, 149.2, 149.6, 151.5, 154.8, 159.1. *Anal*. Calcd. for $C_{19}H_{11}N_3O_2$ (313.31): C, 72.84; H, 3.54; N, 13.41. Found: C, 72.65; H, 3.41; N, 13.50.

7-(1-Benzofuran-2-yl)-2-phenyl-2H-4-(2-naphthyl)oxazolo [3,4-*d*]pyridazines (17b). This compound was obtained as yellow crystals (AcOH), mp 240–242°C, yield (89%); IR (cm^{-1}): 3058 (CH), 1624 (C=N), 1569 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.42–8.58 (m, 11, aromatic protons), 9.13 (s, 1H, aromatic proton) and 9.90 (s, 1H, isoxazole H-5). *Anal*. Calcd. for $C_{23}H_{13}N_3O_2$ (363.37): C, 76.02; H, 3.61; N, 11.56. Found: C, 76.15; H, 3.48; N, 11.68.

3-(1-Benzofuran-2-yl)-4H-pyrazol-4-one phenylhydrazone (22). This compound was obtained as yellow crystals (AcOH), mp 246–248°C, yield (88%); IR (cm^{-1}): 3309 (NH), 1624 (C=N), 1566 (C=C). ^{1}H NMR $(CD_3)_2SO$ δ = 7.26–7.93 (m, 11H, aromatic protons) and 9.35 (s, 1H, NH). ^{13}C NMR $(CD_3)_2SO$ δ = 104.2, 114.2, 114.5, 119.1, 123.3, 125.7, 126.3, 128.6, 130.8, 132.8, 140.5, 143.2, 149.2, 154.2. *Anal*. Calcd. for $C_{17}H_{12}N_4O$ (288.3): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.89; H, 4.10; N, 19.21.

Synthesis of 19a, 19b, and 20. An equimolar amount of 1-benzfuran-2-yl-3-dimethylaminopropenone (**6**), the appropriate benzoxazol-2-ylacetonitrile, benzthiazole-2-ylacetonitrile or benzimidazole-2-ylacetonitrile and ammonium acetate (5 mmol) in acetic acid (10 mL) was heated under reflux for 4 h. The resulting solid was collected and recrystallized from the proper solvent gave products **19a**, **19b**, and **20**, respectively.

3-(Benzo[*d*]oxazol-2-yl)-6-(benzofuran-2-yl)pyridin-2-amine (19a). This compound was obtained as yellow crystals (DMF), mp 278–279°C, yield (68%); IR (cm^{-1}): 3421, 3298 (NH_2), 3055 (CH), 1627 (C=N), 1581 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 6.21 (s, br., 2H, NH_2), 6.07–7.98 (m, 11H, aromatic protons). MS: 329 [(5.2%), M^{+2}], 328 [(27%), M^{+1}], 327 [(100%), M^+)], 310 (41%), 208 (12.5%), 150 (12.4%). *Anal*. Calcd. for $C_{20}H_{13}N_3O_2$ (327.34): C, 73.38; H, 4.00; N, 12.84. Found: C, 73.24; H, 3.87; N, 12.74.

3-(Benzo[*d*]thiazol-2-yl)-6-(benzofuran-2-yl)pyridin-2-amine (19b). This compound was obtained as yellow crystals (DMF), mp 274–276°C, yield (74%); IR (cm^{-1}): 3398, 3286 (NH_2), 3055 (CH), 1620 (C=N), 1577 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 2.42 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.49 (t, 1H, J = 7.5 Hz, pyrazoline H-4), 6.21 (s, br., 2H, NH_2), 6.07–7.98 (m, 11H, aromatic protons). *Anal*. Calcd. for $C_{20}H_{13}N_3OS$ (343.40): C, 69.95; H, 3.82; N, 12.24; S, 9.34. Found: C, 70.15; H, 3.74; N, 12.45; S, 9.43.

3-(1-Benzofuran-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (20). This compound was obtained as yellow crystals (AcOH), mp 256–258°C, yield (65%); IR (cm^{-1}): 3124, 3055 (CH), 2241 (CN), 1635 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 7.11 (s, 1H, furan, vinyl CH), 7.24–7.58 (m, 7H, aromatic proton), 8.0–8.10 (d, 2H, J = 4 Hz, aromatic) and 9.54 (d, 1H, J = 4 Hz, 1H). *Anal*. Calcd. for $C_{20}H_{11}N_3O$ (309.32): C, 77.66; H, 3.58; N, 13.58. Found: C, 77.54; H, 3.45; N, 13.75.

3-(1-Benzofuran-2-yl)-3-oxo-2-(phenylhydrazono)-propanal (21). Benzenediazonium chloride was added to a cold solution of **6** (5 mmol) in ethanolic sodium acetate solution (ethanol, 50 mL) and sodium acetate (0.65 g, 5 mmol) while stirring. The crude solid was collected and recrystallized from ethanol to obtain as reddish yellow crystals, mp 145–145°C, yield (90%); IR (cm^{-1}): 3320 (NH), 1739, 1647 (CO), 1624 (C=N), 1589 (C=C). ^1H NMR $(CD_3)_2SO$ δ = 7.26–7.93 (m, 11H, aromatic protons) and 9.98 (s, 1H, CHO), 14.39 (s, br., 1H, NH). ^{13}C NMR $(CD_3)_2SO$ δ = 112.1, 115.8, 118.3, 123.1, 125.7, 126.4, 127.4, 128.6, 130.5, 149.3, 150.5, 155.2, 155.7, 178.2, 192.6. *Anal*. Calcd. for $C_{17}H_{12}N_2O_3$ (292.29): C, 69.86; H, 4.14; N, 9.58. Found: C, 70.12; H, 4.00; N, 9.72.

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