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Convenient synthesis of some new pyrazolo[5,1-*c*]triazines, isoxazolo[3,4-*d*] pyrimidine and pyridine derivatives containing benzofuran moiety

Abdou Osman Abdelhamid*, Abdelgawad Ali Fahmi and Amna Ali Mohamed Alsheflo

Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt

**Corresponding author at: Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt. Tel.: +202.35676573; fax: +202.35727556. E-mail address: abdelhamid45@gmail.com (A.O. Abdelhamid).*

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ABSTRACT

Pyrazolo[5,1-*c*][1,2,4]triazine, [1,2,4]triazolo[3,4-*c*][1,2,4]triazine, benzo[4,5]-imidazo[2,1-*c*][1,2,4]triazine, isoxazole, isoxazolo[3,4-*d*]pyridazine, pyrazole, pyridine, substituted urea and phenyl carbamate derivatives containing benzofuran moiety were synthesized *via* reaction of sodium salt of 5-hydroxy-l-benzofuran-2-ylpropenone or 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one with diazotized heterocyclic amines, hydroximoyl chlorides and active methylene compounds. The structures of all the newly synthesized compounds were confirmed by elemental analyses, spectral data, and alternative synthetic routes, whenever possible.

1. Introduction

The considerable biological and medicinal activities of pyrazolotriazines and triazolotriazines, as adenine analogues, antagonists, antischistosomal and antitumor agents [1-3] have stimulated interest in the synthesis of these ring systems. Also, some pyrazoloazines are found to be useful in agricultural applications as herbicides and plant growth regulants [4], and in medicinal applications as antibiotics [5], antilipemics and cardiotonics [6], central nervous system agents [7], anxiolytics [8], treatment of influenza [9], antidepressants and antihypertensives [10], and its antileishmanial and antitrypanosomal activities [11].

In continuation of our interest in the synthesis of heterocycles [12-16], we report herein a convenient method for the synthesis of pyrazolo[5,l-*c*]triazines, [l,2,4]triazolo[4,3-*c*] triazine, benzo[4,5]imidazo[2,1-*c*]triazine, isoxazole, isoxazolo [3,4-*d*]pyrimidine, pyridines, and pyrazoles containing benzofuran moiety.

2. Experimental

2.1. Instrumentation

All melting points were determined on an electrothermal apparatus and are uncorrected. The IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ ppm units using TMS as an internal reference. The mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

2.2. Pyrazolo[5,1-c]triazines (6a-c), triazolo[3,4-c][1,2,4] triazine (10) and benzo[4,5]imidazo[2,1-c][1,2,4]triazine (11)

A solution of the appropriate of 5-phenylpyrazole-3-diazonium chloride (**3a**), 4-phenylpyrazole3-diazonium chloride (**3b**), 4-cyanopyrazole-3-diazonium chloride (**3c**), triazole-3-diazonium nitrate or benzimidazole-2-diazonium sulphate was added to a cold mixture of the appropriate sodium salt of 1-(benzofuran-2-yl)-3-hydroxyprop-2-en-1-one (**2**), (which is prepared from benzofuran-2-ylethanone and ethyl formate in presence of sodium methoxide), or 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**7**) (5 mmol) and sodium acetate (0.65 gm, 5 mmol) in ethanol (40 mL) at 0-5 °C, while stirring for 30 min. The reaction mixture was stirred for further 3 h. The resulting solid was collected and recrystallized from the proper solvent to give the corresponding **6a-c**, **10** and **11**, respectively, (Scheme 1-3).

(Benzofuran-2-yl)(8-phenylpyrazolo[5,1-c][1,2,4]triazin-3-yl)methanone (**6a**): Yellow crystals. Crystallization from ethanol. Yield: 91%. M.p.: 258-260 °C. FT-IR (KBr, cm^{-1}): 3018 ν(CH), 1645 ν(CO), 1612 ν(C=N), 1556 ν(C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.43-8.20 (m, 8H, ArH's and pyrazole H-5), 8.57-8.59 (m, 3H, ArH's), 8.80 (s, 1H, ArH). MS (EI, *m/z* (%)): 341 (M$^+$, 100), 313 (87), 284 (16), 257 (23), 227 (9), 154 (54), 145 (32), 142 (69), 128 (52), 113 (27), 101 (24), 76 (87), 62 (34). Anal. calcd. for $C_{20}H_{12}N_4O_2$ (340.33): C, 70.58; H, 3.55; N, 16.46. Found: C, 70.75; H, 3.41; N, 16.59%.

(Benzofuran-2-yl)(7-phenylpyrazolo[5,1-c][1,2,4]triazin-3-yl)methanone (**6b**): Orange crystals. Crystallization from AcOH. Yield: 92%. M.p.: 233-235 °C. FT-IR (KBr, cm^{-1}): 3032 ν(CH), 1646 ν(CO), 1612 ν(C=N), 1541 ν(C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.42-8.62 (m, 10H, ArH's and pyrazole H-5), 9.24 (s, 1H, ArH's), 9.81 (s, 1H, ArH).

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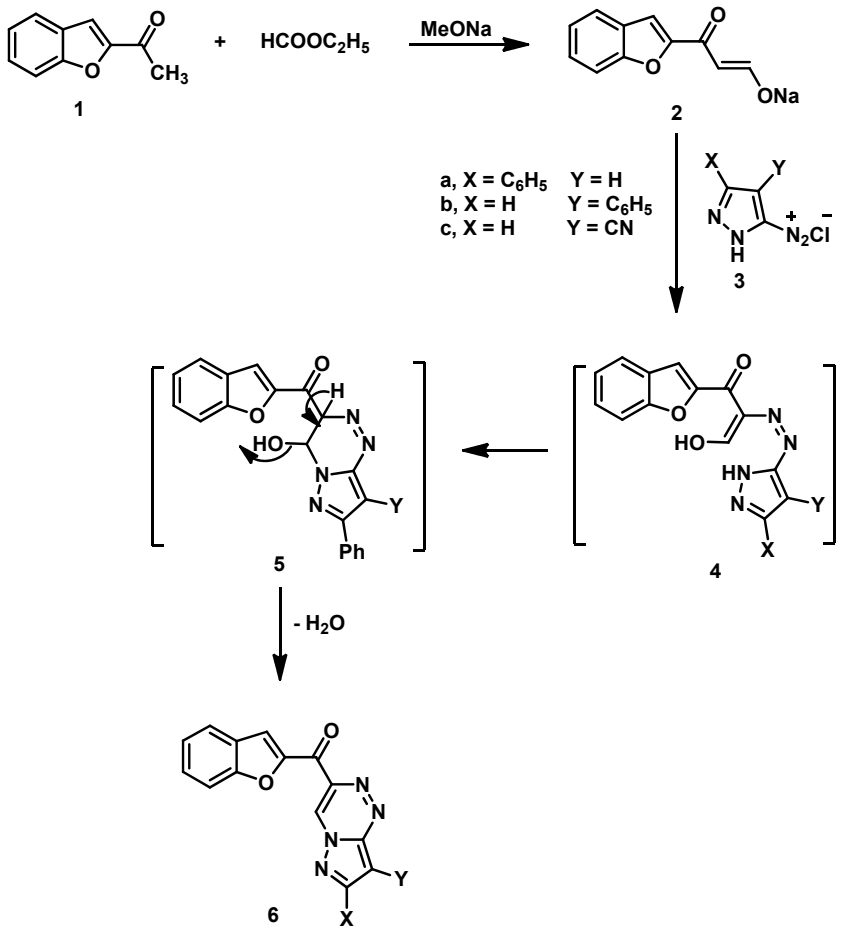


Scheme 1

MS (EI, *m/z* (%)): 341 (M^+, 100), 312 (22), 285 (26), 256 (16), 229 (9), 156 (17), 145 (59), 142 (70), 128 (41), 101 (22), 76 (26), 62 (33). Anal. calcd. for $C_{20}H_{12}N_4O_2$ (340.33): C, 70.58; H, 3.55; N, 16.46. Found: C, 70.57; H, 3.68; N, 16.38%.

4-(Benzofuran-2-carbonyl)-pyrazolo[5,1-c][1,2,4]triazine-8-carbonitrile (**6c**): Yellow crystals. Crystallization from ethanol. Yield: 89%. M.p.: 302-304 °C. FT-IR (KBr, cm^{-1}): 2223 ν(CN), 1640 ν(CO), 1563 ν(C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.68 (s, 1H, pyrazole H-5), 7.36-8.14 (m, 5H, ArH's), 9.24 (s, 1H, ArH's). MS (EI, *m/z* (%)): 290 (M+1, 3), 289 (M^+, 15), 179 (13), 145 (27), 142 (15), 114 (6), 101 (5), 88 (100), 76 (25), 64 (17), 62 (63). Anal. calcd. for $C_{15}H_7N5O_2$ (289.25): C, 62.29; H, 2.44; N, 24.21. Found: C, 62.38; H, 2.52; N, 24.40%.

([1,2,4]Triazolo[3,4-c][1,2,4]triazin-6-yl)(benzofuran-2-yl) methanone (**10**): Yellow crystals. Crystallization from AcOH. Yield: 89%. M.p.: 220-222 °C. FT-IR (KBr, cm^{-1}): 3065 ν(CH), 1642 ν(CO), 1529 ν(C=C) . ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.70-8.20 (m, 5H, ArH's), 9.24 (s, 1H, ArH), 9.46 (s, 1H, ArH). MS (EI, *m/z* (%)): 265 (M^+, 63), 237 (16), 182 (19), 155 (100), 145 (25), 127 (27), 113 (17), 100 (20), 88 (93), 75 (21), 62 (63). Anal. calcd. for $C_{13}H_7N_5O_2$ (265.23): C, 58.87; H, 2.66; N, 26.41. Found: C, 58.67; H, 2.55; N, 26.31%.

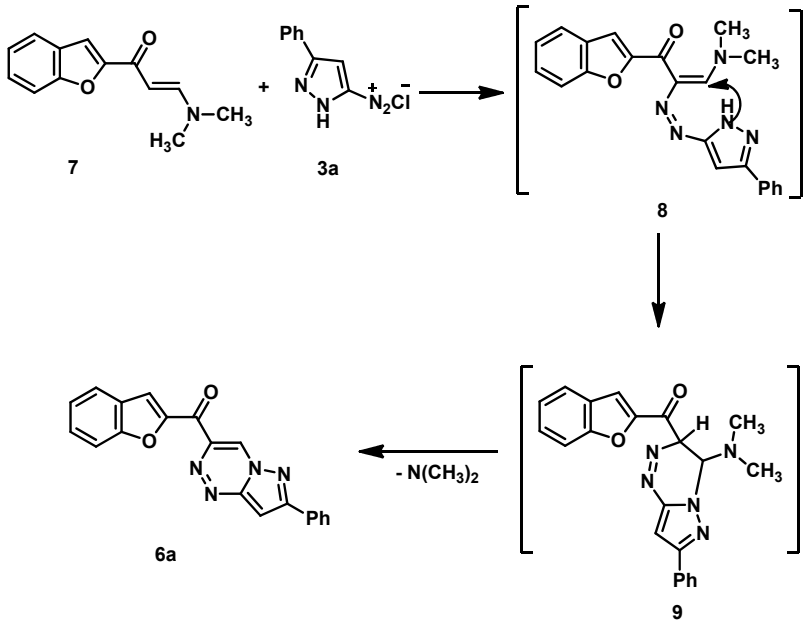
Benzofuran-2-yl-benzo[4,5]imidazo[2,1-c][1,2,4]triazin-4-yl-methanone (**11**): Buff crystals. Crystallization from AcOH. Yield: 90%. M.p.: > 300 °C. FT-IR (KBr, cm^{-1}): 3065 ν(CH), 1712 ν(CO), 1529 ν(C=C). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.20-7.54 (m, 8H, ArH's), 7.55 (s, 1H, ArH), 7.96 (s, 1H, ArH). MS (EI, *m/z* (%)): 314 (M^+, 3), 286 (8), 221 (6), 166 (6), 164 (11), 152 (6), 130 (8), 120 (12), 119 (21), 105 (25), 104 (46), 98 (12), 97 (21), 91 (56), 83 (17), 77 (49), 65 (16). Anal. calcd. for $C_{18}H_{10}N_4O_2$ (314.3): C, 68.79; H, 3.21; N, 17.83. Found: C, 68.94; H, 3.35; N, 17.95%.

2.3. Arylhydrazones (12a) and (12b)

Benzenediazonium chloride or 4-methylbenzenediazonium chloride (5 mmol) was added dropwise with continuous cooling and stirring to a stirred solution of the appropriate **2** or **7** (5 mmol), in ethanol (15 mL) at 0-5 °C; containing sodium acetate (0.65 g, 5 mmol) as a buffer solution. The reaction mixture was stirred for 3 h. The reaction mixture was left on a refrigerator overnight. The resulting solid, was collected, washed with water and recrystallized to give **12a** and **12b**, respectively, (Scheme 4).

2-(2-Phenylhydrazono)-3-(benzofuran-2-yl)-3-oxopropanal (**12a**): Red crystals. Crystallization from ethanol. Yield: 94%. M.p.: 140-142 °C. FT-IR (KBr, cm^{-1}): 3089 ν(CH), 1654 ν(CO), 1529 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.28-7.93 (m, 10H, ArH's), 9.98 (s, 1H, -CHO), 14.39 (s, br., 1H, NH). MS (EI, *m/z* (%)): 292 (M^+, 26), 263 (13), 209 (21), 180 (9), 172 (62), 145 (70), 118 (15), 92 (88), 89 (100), 77 (55), 62 (34). Anal. calcd. for $C_{17}H_{12}N_2O_3$ (292.29): C, 69.86; H, 4.14; N, 9.58. Found: C, 69.77; H, 4.22; N, 9.68%.

2-(2-p-Tolylhydrazono)-3-(benzofuran-2-yl)-3-oxopropanal (**12b**): Orange crystals. Crystallization from ethanol. Yield: 95%. M.p.: 144-146 °C. FT-IR (KBr, cm^{-1}): 3082 ν(CH), 1654 ν(CO), 1540 ν(C=C).



Scheme 2

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.34 (s, 3H, CH_3), 7.28-7.93 (m, 9H, ArH's), 9.98 (s, 1H, -CHO), 14.39 (s, br., 1H, NH). MS (EI, *m/z* (%)): 307 (M+1, 8), 306 (M^+, 38), 186 (46), 170 (35), 169 (9), 172 (62), 145 (70), 118 (15), 92 (88), 89 (100), 77 (100), 157 (11), 138 (40), 121 (77), 115 (10), 93 (13), 65 (13). Anal. calcd. for $C_{18}H_{14}N_2O_3$ (306.32): C, 70.58; H, 4.61; N, 9.15. Found: C, 70.67; H, 4.82; N, 9.28%.

2.4. Pyrazoles (13a) and (13b)

Method A

Equimolar amounts of each of 2-(2-phenylhydrazono)-3-(benzofuran-2-yl)-3-oxopropanal (**12a**) or 2-(2-*p*-tolylhydrazono)-3-(benzofuran-2-yl)-3-oxopropanal (**12b**) and hydrazine hydrate (4 mmol for each) in ethanol (10 mL) were heated under reflux for 4 h. The resulting solid, so formed, after cooling was recrystallized from the proper solvent to give the corresponding **13a** and **13b**, respectively, (Scheme 4).

Method B

A solution of the appropriate arendiazonium chloride (5 mmol for each) was added dropwise to a stirred solution of 3-(benzofuran-2-yl)-1*H*-pyrazole (**14**) (0.9 g, 5 mmol) in ethanolic solution (15 mL) at 0-5 °C, containing sodium acetate as a buffer solution. The reaction mixture was stirred for 3 h. and was left on a refrigerator overnight. The resulting solid, was collected, washed with water and recrystallized to give products identical in all respects with **12a** and **12b**, respectively, (Scheme 4).

1-(3-(Benzofuran-2-yl)-4H-pyrazol-4-ylidene)-2-phenyl hydrazine (**13a**): Yellow crystals. Crystallization from AcOH. Yield: 84%. M.p.: 222-224 °C. FT-IR (KBr, cm^{-1}): 1630 ν(C=N), 1540 ν(C=C). MS (EI, *m/z* (%)): 287 (M^+-1, 10), 237 (12), 213 (13), 199 (10), 165 (32), 149 (100), 130 (18), 124 (15), 104 (44), 100 (15), 97 (26), 90 (27), 76 (55), 65 (53). Anal. calcd. for $C_{17}H_{12}N_4O$ (288.3): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.95; H, 4.32; N, 19.38%.

1-(3-(Benzofuran-2-yl)-4H-pyrazol-4-ylidene)-2-p-tolyl hydrazine (**13b**): Gray crystals. Crystallization from EtOH. Yield: 98%. M.p.: 198-200 °C. FT-IR (KBr, cm^{-1}): 1614 ν(C=N), 1574 ν(C=C). MS (EI, *m/z* (%)): 305 (M^++2, 0.2), 214 (100), 145 (32), 118 (27), 89 (20), 71 (23), 63 (13). Anal. calcd. for $C_{18}H_{14}N_4O$ (302.33) C, 71.51; H, 4.67; N, 18.53. Found: C, 71.64; H, 4.78; N, 18.37%.

2.5. 3-(Benzofuran-2-yl)-1H-pyrazole (14)

Equimolar amounts of 1-(benzofuran-2-yl)-3-(dimethyl amino)prop-2-en-1-one (**7**) and hydrazine hydrate (5 mmol for each) in ethanol (10 mL) containing tow drops piperidine as a catalyst were boiled under reflux for 4 h. The resulting solid, so formed, after cooling was recrystallized to give **14** as a beige crystals (Scheme 4). Crystallization from EtOH Yield: 69.4%. M.p.: 142-144 °C. FT-IR (KBr, cm^{-1}): 3136 ν(NH), 1620 ν(C=N), 1539 ν(C=C). MS (EI, *m/z* (%)): 184 (M^+, 100), 155 (25), 149 (50), 138 (25), 135 (19), 102 (25), 78 (19), 75 (19), 69 (36), 60 (33), 57 (63). Anal. calcd. for $C_{11}H_8N_2O$ (184.19): C, 71.73; H, 4.38; N, 15.21. Found: C, 71.89; H, 4.51; N, 15.35%.

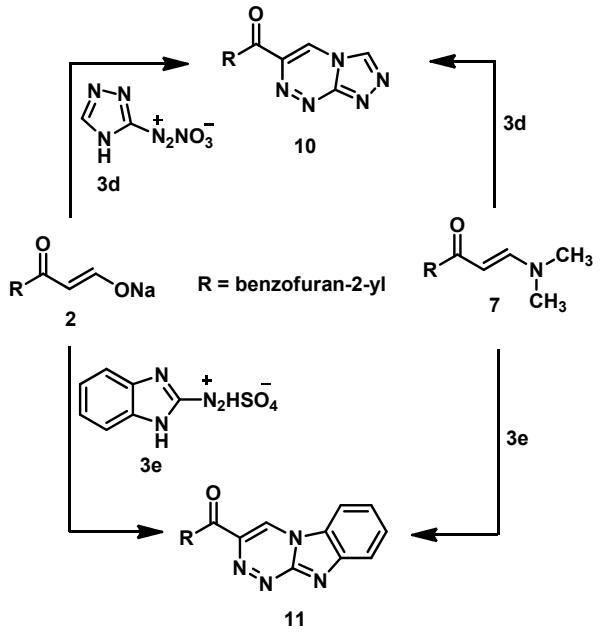
2.6. Isoxazoles (17a-c)

Method A

Triethylamine (0.5 g, 0.75 mL, 5 mmol) was added dropwise to equimolar a mount of **7** and the appropriate hydroximoyl chlorides **15a-c** (5 mmol, each) in dry toluene (20 mL) while stirring. The reaction mixture was stirred for 6 h; evaporate the solvent and then triturated with petroleum ether (40-60 °C). The resulting solid was collected and crystallized gave **17a-c**, respectively, (Scheme 5).

Method B

Equimolar amount of **7** and the appropriate hydroximoyl chloride **15a-c** (5 mmol, for each) in dry toluene (20 mL) were heated under reflux for 18 h. The reaction mixture was filtered off and the filtrate was evaporated and triturated with petroleum ether (40-60 °C). The resulting solid was collected and crystallized to give products identical in all aspects (M.p., mixed m.p. and spectra) with **17a-c**, (Scheme 5).



Scheme 3

Benzofuran-2-yl-(4-benzoyl-isoxazol-3-yl)-methanone (**17a**): Brown crystals. Crystallization from AcOH. Yield: 80%. M.p.: 178-180 °C. FT-IR (KBr, cm^{-1}): 3066 ν(CH), 1651 ν(CO), 1623 ν(C=N), 1550 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.22-7.75 (m, 8H, ArH's), 9.34 (d, 2H, *J* = 8 Hz, ArH's), 8.67 (s, 1H, isoxazole H-5). MS (EI, *m/z* (%)): 317 (M^+, 62), 315 (M-1, 45), 301 (16), 287 (18), 285 (18), 237 (84), 194 (12), 166 (16), 161 (35), 133 (20), 108 (14), 90 (11), 77 (12), 63 (9). Anal. calcd. for $C_{19}H_{11}NO_4$ (317.29): C, 71.92; H, 3.49; N, 4.41. Found: C, 72.12; H, 3.56; N, 4.62%.

Benzofuran-2-yl-[4-(furan-2-oyl)-isoxazol-3-yl]-methanone (**17b**): Brown crystals. Crystallization from AcOH. Yield: 79%. M.p.: 142-144 °C. FT-IR (KBr, cm^{-1}): 3093 ν(CH), 1685 ν(CO), 1639 ν(C=N), 1554 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.61 (d, 1H, *J* = 5 Hz, furan-H-4), 7.22-7.66 (m, 6H, ArH's), 7.77 (s, 1H, furan H-5), 8.75 (s, 1H, isoxazole H-5). MS (EI, *m/z* (%)): 307 (M^+, 26), 290 (16), 246 (10), 218 (5), 171 (20), 152 (13), 143 (100), 128 (28), 115 (74), 101 (19), 89 (12), 77 (25), 65 (15), 51 (14). Anal. calcd. for $C_{17}H_9NO_5$ (307.26): C, 66.45; H, 2.95; N, 4.56. Found: C, 66.65; H, 3.11; N, 4.68%.

Benzofuran-2-yl-[4-(thien-2-oyl)-isoxazol-3-yl]-methanone (**17c**): Beige crystals. Crystallization from AcOH. Yield: 79%. M.p.: 110-112 °C. FT-IR (KBr, cm^{-1}): 3093 ν(CH), 1672 ν(CO), 1554. ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.61 (d, 1H, *J* = 5 Hz, furan-H-4), 7.22-7.66 (m, 6H, ArH's), 7.77 (d, 1H, *J* = 5 Hz, furan H-5), 8.75 (s, 1H, isoxazole H-5). MS (EI, *m/z* (%)): 322 (M^+, 6), 307 (6), 291 (10), 275 (18), 265 (16), 249 (46), 213 (14), 187 (12), 148 (20), 121 (42), 92 (45), 77 (16), 72 (100), 65 (15). Anal. calcd. for $C_{17}H_9NO_4S$ (323.32): C, 63.15; H, 2.81; N, 4.33; S, 9.92. Found: C, 63.27; H, 2.72; N, 4.57; S, 10.12%.

2.6. Isoxazolo[3,4-d]pyridazines (18a-c)

Equimolar a mount of each of the appropriate isoxazoles **17a-c** (5 mmol) and hydrazine hydrate (1 mL, 99%) in ethanol (20 mL) was boiled under reflux for 2h. The resulting solid was collected and crystallized to give isoxazolo[3,4-*d*]pyridazines **18a-c**, (Scheme 5).

7-(Benzofuran-2-yl)-4-phenylisoxazolo[3,4-d]pyridazine (**18a**): Brown crystals. Crystallization from AcOH. Yield: 93%. M.p.: > 300 °C. FT-IR (KBr, cm^{-1}): 3066 ν(CH), .1631 ν(C=N), 1566 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.61 (d, 1H, *J* = 5 Hz, furan-H-3), 7.22-7.66 (m, 9H, ArH's), 8.75 (s, 1H, isoxazole H-5). MS (EI, *m/z* (%)): 313 (M^+, 7), 254 (6), 222 (8), 220 (17), 205 (50), 192 (15), 190 (22), 187 (10), 179 (88), 175 (27), 160 (14), 149 (10), 145 (46), 130 (26), 119 (27), 108 (22), 107 (27), 91 (100), 77 (24), 65 (14). Anal. calcd. for $C_{19}H_{11}N_3O_2$ (313.31): C, 72.84; H, 3.54; N, 13.41. Found: C, 73.00; H, 3.41; N, 13.59%.

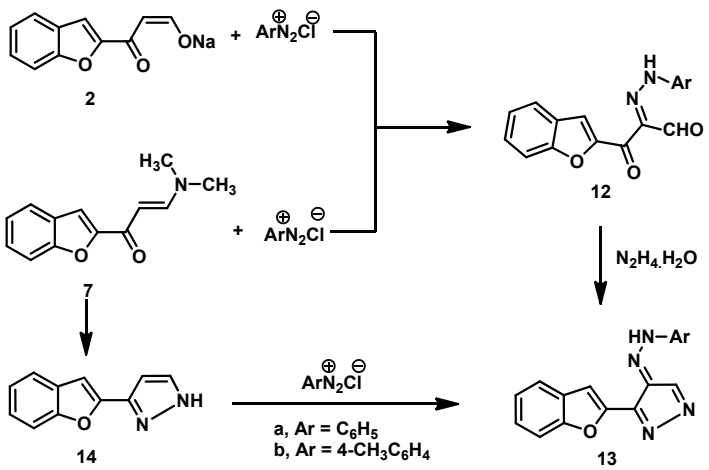
7-(Benzofuran-2-yl)-4-(furan-2-yl)isoxazolo[3,4-d]pyridazine (**18b**): Brown crystals. Crystallization from AcOH. Yield: 98%. M.p.: > 320 °C. FT-IR (KBr, cm^{-1}): 3066 ν(CH), 1631 ν(C=N), 1566 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.61 (d, 1H, *J* = 5 Hz, furan-H-4), 7.22-7.66 (m, 6H, ArH's), 7.77 (s, 1H, furan H-5), 8.75 (s, 1H, isoxazole H-5). MS (EI, *m/z* (%)): 303 (M^+, 13), 232 (14), 162 (5), 119 (100), 91 (19). Anal. calcd. for $C_{17}H_9N_3O_3$ (303.27): C, 67.33; H, 2.99; N, 13.86. Found: C, 67.52; H, 3.11; N, 14.00%.

7-(Benzofuran-2-yl)-4-(thien-2-yl)isoxazolo[3,4-d]pyridazine (**18c**): Brown crystals. Crystallization from AcOH. Yield: 98%. M.p.: > 320 °C. FT-IR (KBr, cm^{-1}): 3070 ν(CH), 1620 ν(C=N), 1561 ν(C=C) . ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.22-7.93 (m, 8H, ArH's), 8.75 (s, 1H, isoxazole H-5). MS (EI, *m/z* (%)): 319 (M^+, 0.5), 240 (2), 220 (36), 208 (4), 122 (100), 108 (5), 84 (5), 69 (6), 57 (7). 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, 3.00; N, 13.25; S, 10.24%.

2.7. Pyridines (19-21) and (23)

Equimolar amounts of **7**, the appropriate ethyl acetoacetate, acetylacetone, ethyl cyanoacetate or benzoyl-acetonitrile and ammonium acetate (5 mmol for each) in acetic acid (10 mL) were boiled under reflux for 4 h. The resulting solid, after cooling was collected and recrystallized from the appropriate solvent to give **19-21** and **23**, respectively, (Scheme 6).

Ethyl 6-(benzofuran-2-yl)-2-methylpyridine-3-carboxylate (**19**): Beige crystals. Crystallization from EtOH. Yield: 81%. M.p.: 126-128 °C. FT-IR (KBr, cm^{-1}): 3058, 2974 ν(CH), 1712 ν(C=O), 1639 ν(C=N), 1581 ν(C=C).



Scheme 4

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.32 (t, 3H, *J* = 7 Hz, CH_2CH_3), 2.49 (s, 3H, CH_3), 4.29 (q, 2H, *J* = 7 Hz, CH_2CH_3), 7.28-8.29 (m, 7H, ArH's). Anal. calcd. for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.73; H, 5.49; N, 5.13%.

1-(6-(Benzofuran-2-yl)-2-methylpyridin-3-yl)ethanone (**20**): Beige crystals. Crystallization from AcOH. Yield: 79%. M.p.: 210-212 °C. FT-IR (KBr, cm^{-1}): 3058, 2920 ν(CH), 1702 ν(C=O), 1639 ν(C=N), 1542 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.48 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.10-7.95 (m, 7H, ArH's). Anal. calcd. for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.62; H, 5.41; N, 5.78%.

Ethyl 2-amino-6-(benzofuran-2-yl)pyridine-3-carboxylate (**21**): Yellow crystals. Crystallization from AcOH. Yield: 85%. M.p.: 177-179 °C. FT-IR (KBr, cm^{-1}): 3448, 3274 ν(NH_2), 3058 ν(CH), 1681 ν(C=O), 1631 ν(C=N), 1589 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.13 (t, 3H, *J* = 7 Hz, CH_2CH_3), 4.29 (q, 2H, *J* = 7 Hz, CH_2CH_3), 7.26-8.21 (m, 9H, ArH's and NH_2). Anal. calcd. for $C_{16}H_{14}NO_3$ (282.29): C, 68.07; H, 5.00; N, 9.92. Found: C, 68.24; H, 5.12; N, 9.80%.

(2-Amino-6-(benzofuran-2-yl)pyridin-3-yl)(phenyl)methanone (**23**): Brown crystals. Crystallization from AcOH. Yield: 76%. M.p.: 284-286 °C. FT-IR (KBr, cm^{-1}): 3413, 3274 ν(NH_2), 3101 ν(CH), 1645 ν(C=O), 1618 ν(C=N), 1550 ν(C=C). MS (EI, *m/z* (%)): 315 (M+1, 2), 314 (M^+, 13), 312 (7), 236 (13), 235 (98), 234 (14), 233 (100), 154 (47), 153 (82), 152 (45), 76 (47), 64 (9). Anal. calcd. for $C_{20}H_{14}N_2O_2$ (314.34): C, 76.42; H, 4.49; N, 8.91. Found: C, 76.57; H, 4.58; N, 9.12%.

2.8. 6-(Benzofuran-2-yl)-2-methylpyridine-3-carbohydrazide (25)

Equimolar amounts of **19** and hydrazine hydrate (5 mmol for each) in ethanol (10 mL) were heated under reflux for 4 h. The resulting solid, so formed, after cooling was recrystallized to give **25** as beige crystals. Crystallization from EtOH, (Scheme 6). Yield: 94%. M.p.: 199-200 °C. FT-IR (KBr, cm^{-1}): 3448, 3274, 3147 ν(NH, NH_2), 3058, 2970 ν(CH), 1681 ν(C=O), 1620 ν(C=N), 1551 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.70 (s, 3H, CH_3), 6.34 (s, br., 3H, NH, NH_2), 7.12-7.95 (m, 7H, ArH's). MS (EI, *m/z* (%)): 276 (M^+, 18), 252 (10), 236 (100), 208 (13), 190 (11), 180 (24), 152 (27), 139 (9), 90 (88), 88 (14), 76 (17), 63 (12). Anal. calcd. for $C_{15}H_{13}N_3O_2$ (267.28): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.65; H, 5.14; N, 15.89%.

2.9. 2-(6-Benzofuran-2-yl-2-methyl-pyridine-3-carbonyl)-5-methyl-2,4-dihydro-pyrazol-3-one (26)

Equimolar amounts of **25** and ethyl acetoacetate (5 mmol for each) in acetic acid (10 mL) and were heated under reflux for 2 h. The resulting solid, so formed, after cooling was recrystallized to give **26** as yellow crystals. Crystallization from AcOH, (Scheme 6). Yield: 83%. M.p.: 314-316 °C. FT-IR (KBr, cm^{-1}): 3058, 2924 ν(CH), 1705 ν(C=O), 1604 ν(C=N), 1546 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.06 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.41 (dd, 1H), 3.63 (dd, 1H), 7.12-7.95 (m, 7H, ArH's). MS (EI, *m/z* (%)): 334 (M+1, 22), 333 (M^+, 100), 290 (14), 249 (14), 118 (24), 117 (10), 91 (6), 68 (8). Anal. calcd. for $C_{19}H_{15}N_3O_3$ (333.34): C, 68.46; H, 4.54; N, 12.61. Found: C, 68.54; H, 4.67; N, 12.84%.

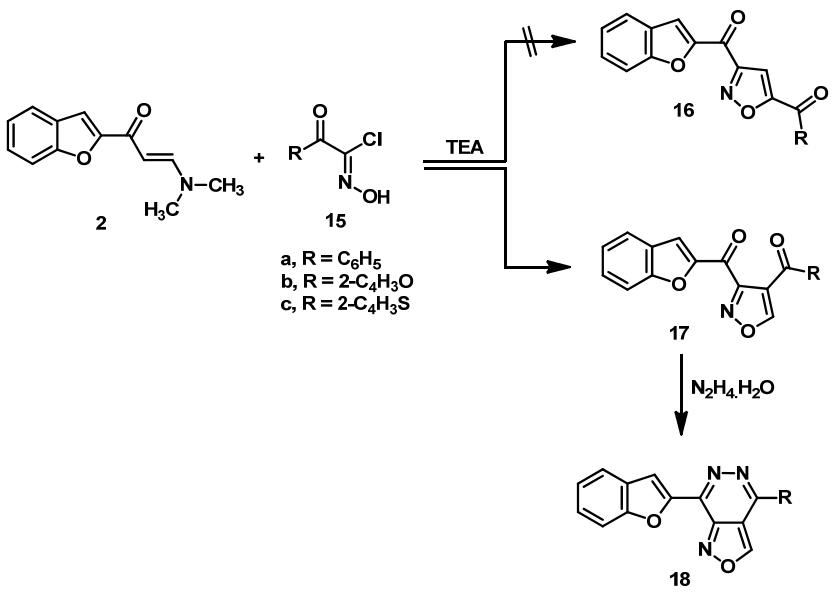
2.10. 2-(6-Benzofuran-2-yl-2-methyl-pyridine-3-carbonyl)-5-methyl-4-(phenyl-hydrazono)-2,4-dihydro-pyrazol-3-one (27)

Method A

To a stirred solution of **26** (1.3 g, 5 mmol) in ethanolic solution (15 mL) at 0-5 °C; containing sodium acetate (0.65 g) as a buffer solution, a prepared solution of benzene diazonium chloride (as usual manner, 5 mmol) was added dropwise while cooling and stirring. The reaction mixture was stirred for 3 h. The resulting solid, was collected, washed with water and recrystallized from DMF to give as a orange crystals, (Scheme 6). Yield: 87%. M.p.: 256-258 °C. FT-IR (KBr, cm^{-1}): 3480 ν(NH) 3058, 2924 ν(CH), 1720 ν(C=O), 1615 ν(C=N), 1589 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.00 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 6.89-7.95 (m, 12H, ArH's), 10.72 (s, br., 1H, NH). MS (EI, *m/z* (%)): 438 (M+1, 32), 437 (M^+, 100), 422 (60), 346 (39), 331 (7), 273 (18), 245 (13), 217 (10), 93 (24), 66 (7). Anal. calcd. for $C_{25}H_{19}N_5O_3$ (437.45): C, 68.64; H, 4.38; N, 16.01. Found: C, 68.82; H, 4.45; N, 16.23%.

Method B

A mixture of ethyl 2-(2-phenylhydrazono)-3-oxobutanoate (**28**) (1.17 g, 5 mmol)) and **25** (1.38 g, 5 mmol) in acetic acid (15 mL) was boiled under reflux for 2h. The resulting solid, was collected, washed with water and recrystallized gave a product identical in all aspects (M.p., mixed m.p. and spectra) with **27**, which obtained by method A.



Scheme 5

2.11. Azido(6-(benzofuran-2-yl)-2-methylpyridin-3-yl) methanone (29)

A stirred solution of **25** (1.38 g, 5 mmol) in hydrochloric acid (15 mL, 6.0 M) at 0-5 °C, sodium nitrite was added portion wise tell effervescence ended. The reaction mixture was stirred for 1 h. The resulting solid, was collected, filtered, washed with water and recrystallized from ethanol to give **29** as yellow crystals, (Scheme 6). Yield: 82%. M.p.: 260-263 °C. FT-IR (KBr, cm^{-1}): 3058, 2924 ν(CH), 2136 ν(azide), 1789 ν(C=O), 1566 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.71 (s, 3H, CH_3), 7.01-7.95 (m, 7H, ArH's). MS (EI, *m/z* (%)): 268 (M^+, 17), 251 (51), 224 (79), 196 (38), 181 (20), 167 (20), 155 (91), 153 (35), 141 (11), 126 (100), 114 (31), 101 (38), 88 (37), 75 (49), 63 (46). Anal. calcd. for $C_{15}H_{10}N_4O_2$ (278.27): C, 64.74; H, 3.62; N, 20.13. Found: C, 64.95; H, 3.71; N, 20.24%.

2.12. Urea derivatives (30a-c), (31) and pyridin-3-yl) quinazoline-2,4(1H,3H)-dione (32)

A mixture of **29** (1.36 g, 5 mmol) and appropriate aniline, *p*-toluidine, *p*-anisidine, 3-amino-5-phenylpyrazole or anthranilic acid (or methyl anthranilate) (5 mmol) in dry dioxane (20 mL) was refluxed for 4 h. The resulting solid, so formed, was collected and recrystallized to give **30a-c**, **31** and **32**, respectively, (Scheme 7).

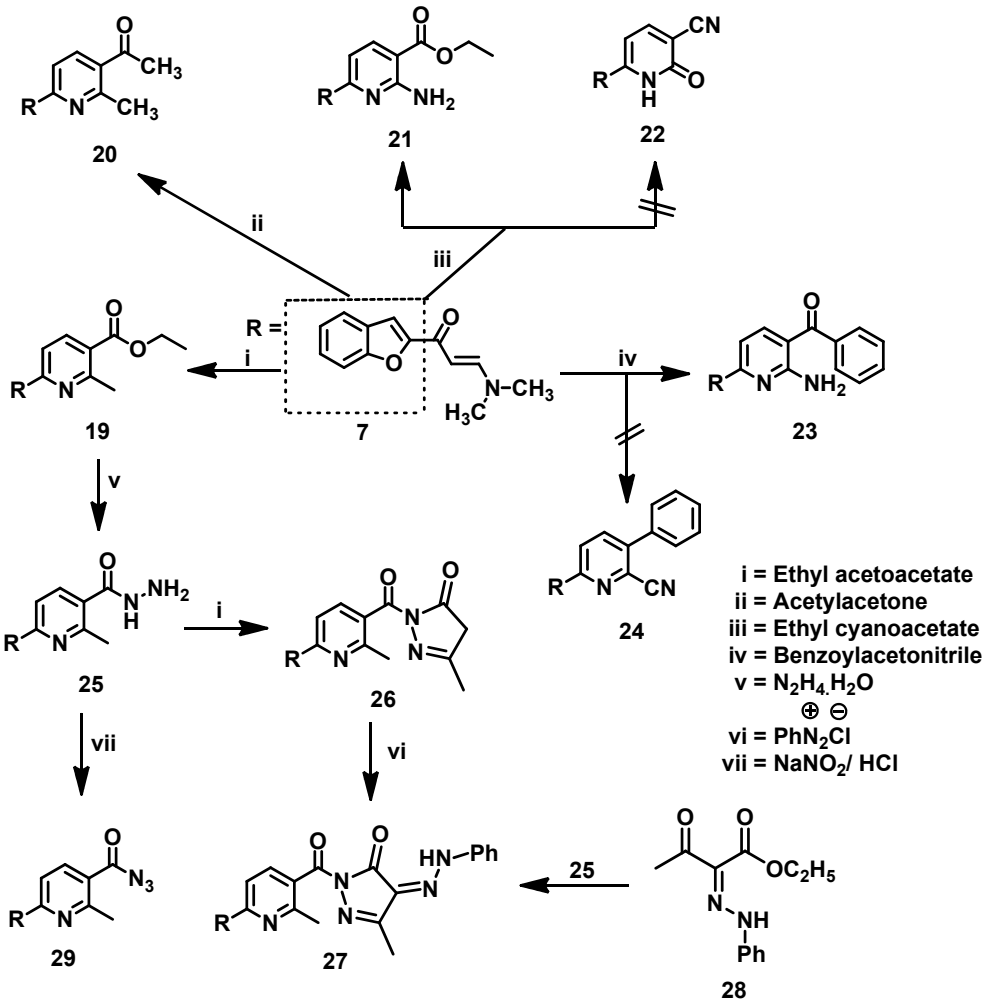
1-(6-(Benzofuran-2-yl)-2-methylpyridin-3-yl)-3-phenylurea (**30a**): White crystals. Crystallization from AcOH. Yield: 92%. M.p.: 282-284 °C. FT-IR (KBr, cm^{-1}): 3290 ν(NH), 3070 ν(CH), 1708 ν(C=O), 1643 ν(C=N), 1604 ν(C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.11 (s, 3H, CH_3), 6.98 (t, 1H, *J* = 7 Hz, ArH), 7.01-7.35 (m, 7H, ArH's and 2 NH), 7.46-7.50 (m, 2H, ArH's), 7.86-7.88 (m, 1H, ArH), 8.37-9.24 (m, 3H, ArH's). MS (EI, *m/z* (%)): 344 (M+1, 4), 343 (M^+, 28), 250 (26), 224 (100), 195 (23), 180 (25), 168 (16), 155 (18), 152 (17), 126 (20), 119 (19), 93 (15), 76 (20), 63 (30). Anal. calcd. for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.99; N, 12.24. Found: C, 73.56; H, 5.11; N, 12.40%.

1-(6-(Benzofuran-2-yl)-2-methylpyridin-3-yl)-3-p-tolylurea (**30b**): White crystals. Crystallization from AcOH. Yield: 93%. M.p.: 302-306 °C. FT-IR (KBr, cm^{-1}): 3560 ν(NH), 3066 ν(CH), 1705 ν(C=O), 1643 ν(C=N), 1543 ν(C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.18 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.03 (t, 2H, *J* = 8 Hz, ArH), 7.21-7.36 (m, 7H, ArH's and 2 NH), 7.86-7.88 (m, 1H, ArH), 8.19 (s, 1H, ArH), 8.3 (d, 1H, *J* = 8 Hz, ArH), 9.04 (s, 1H, ArH). MS (EI, *m/z* (%)): 358 (M+1, 4), 357 (M^+, 20), 250 (33), 224 (100), 195 (23), 180 (22), 167 (11), 155 (27), 152 (22), 134 (44), 126 (34), 106 (100), 91 (21), 76 (49), 65 (19). Anal. calcd. for $C_{22}H_{19}N_3O_2$ (357.41): C, 73.93; H, 5.36; N, 11.76. Found: C, 74.15; H, 5.51; N, 11.56%.

1-(6-(Benzofuran-2-yl)-2-methylpyridin-3-yl)-3-(4-methoxy phenyl)urea (**30c**): White crystals. Crystallization from AcOH. Yield: 93%. M.p.: 302-306 °C. FT-IR (KBr, cm^{-1}): 3275 ν(NH), 3062 ν(CH), 1705 ν(C=O), 1643 ν(C=N), 1577ν(C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.44 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 7.03 (t, 2H, *J* = 8 Hz, ArH), 7.21-7.36 (m, 7H, ArH's and 2 NH), 7.86-7.88 (m, 1H, ArH), 8.19 (s, 1H, ArH), 8.3 (d, 1H, *J* = 8 Hz, ArH), 9.04 (s, 1H, ArH). MS (EI, *m/z* (%)): 375 (M+2, 1), 373 (M^+, 17), 250 (63), 225 (11), 224 (95), 195 (16), 181 (22), 168 (23), 155 (20), 149 (25), 134 (21), 126 (17), 122 (55), 108 (39), 106 (20), 80 (33), 78 (22), 76 (14), 62 (49). Anal. calcd. for $C_{22}H_{19}N_3O_3$ (373.4): C, 70.76; H, 5.13; N, 11.25. Found: C, 70.85; H, 5.04; N, 11.37%.

1-(6-(Benzofuran-2-yl)-2-methylpyridin-3-yl)-3-(3-phenyl-1H-pyrazol-5-yl)urea (**31**): White crystals. Crystallization from AcOH. Yield: 93%. M.p.: 302-306 °C. FT-IR (KBr, cm^{-1}): 3275 ν(NH), 3062 ν(CH), 1705 ν(C=O), 1643 ν(C=N), 1577 ν(C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.48 (s, 3H, CH_3), 5.62 (s, 1H, pyrazole H-4), 7.21-7.36 (m, 12H, ArH's and 3 NH), 7.86-7.88 (m, 1H, ArH), 8.3 (d, 1H, *J* = 8 Hz, ArH), 9.04 (s, 1H, ArH). MS (EI, *m/z* (%)): 409 (M^+, 0.2), 250 (58), 224 (100), 197 (7), 185 (48), 180 (16), 168 (10), 159 (30), 130 (11), 127 (22), 101 (26), 88 (10), 106 (20), 76 (27), 62 (19). Anal. calcd. for $C_{24}H_{19}N_5O_2$ (409.44): C, 70.40; H, 4.68; N, 17.10. Found: C, 70.32; H, 4.84; N, 17.25%.

3-(6-(Benzofuran-2-yl)-2-methylpyridin-3-yl)quinazoline-2,4(1H,3H)-dione (**32**): White crystals. Crystallization from AcOH. Yield: 89%. M.p.: 288-290 °C. FT-IR (KBr, cm^{-1}): 3431 ν(OH), 3273 ν(NH), 3058 ν(CH), 1619 ν(C=N), 1570 ν(C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.47 (s, 3H, CH_3), 7.13-7.72 (m, 9H, ArH's), 8.08 (d, 1H, *J* = 8 Hz, ArH), 8.22 (d, 1H, *J* = 8 Hz, ArH), 10.49 (s, br., 1H, NH). MS (EI, *m/z* (%)): 370 (M+1, 27), 369 (M^+, 100), 250 (10), 182 (28), 167 (12), 154 (13), 144 (7), 127 (18). Anal. calcd. for $C_{22}H_{15}N_3O_3$ (369.37): C, 71.54; H, 4.09; N, 11.38. Found: C, 71.35; H, 4.21; N, 11.12%.



Scheme 6

2.13. Phenyl 6-(benzofuran-2-yl)-2-methylpyridin-3-yl carbamate (33)

A mixture of **29** (1.36 g, 5 mmol) and phenol in dry benzene (20 mL) was refluxed for 4 h. The resulting solid, so formed, was collected and recrystallized to **33** as white crystals. Crystallization from AcOH, (Scheme 7). Yield: 92%. M.p.: 308-310 °C. FT-IR (KBr, cm^{-1}): 3274 ν(NH), 3058 ν(CH), 1678 ν(CO), 1620 ν(C=N), 1569 ν(C=C). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.10 (s, 3H, CH_3), 6.70-7.67 (m, 13H, ArH's and NH). MS (EI, *m/z* (%)): 345 (M+1, 0.8), 344 (M^+, 0.28), 250 (45), 224 (47), 195 (17), 180 (37), 167 (20), 154 (10), 145 (98), 126 (22), 88 (100), 76 (63), 62 (47). Anal. calcd. for $C_{21}H_{16}N_2O_3$ (344.36): C, 73.24; H, 4.68; N, 8.13. Found: C, 73.35; H, 4.82; N, 8.00%.

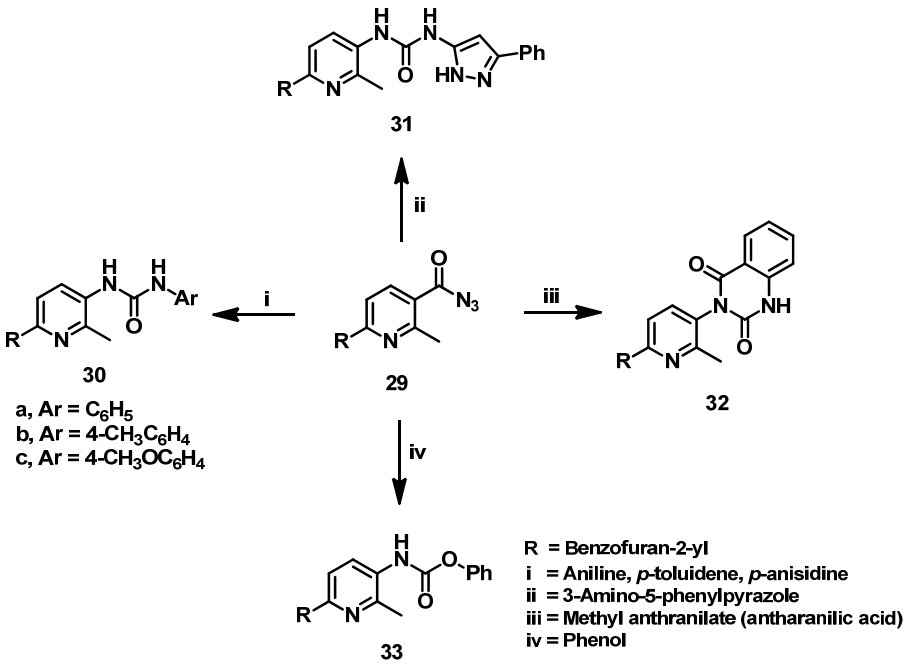
3. Results and discussion

Treatment of the diazotized 3-amino-5-phenylpyrazole (**3a**) with each of 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**7**) and sodium salt of 5-hydroxy-l-benzofuran-2-ylpropenone (**2**) in ethanolic sodium acetate solution gave (benzofuran-2-yl)(7-phenylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl) methanone (**6a**) in good yield (Scheme 1). Analogously, treatment of the appropriate dazonium salt of heterocyclic amines **3b**, **c** with **2** or **7** in ethanolic sodium acetate afforded (benzofuran-2-yl)(8-phenylpyrazolo[5,l-*c*][l,2,4]triazin-3-yl) methanone (**6b**) and 3-benzofuran-2-carbonyl)-pyrazolo[5,l-*c*][l,2,4]triazine-8-carbonitrile (**6c**) (Scheme 1).

Structure **6a** was elucidated by elemental analysis, spectral data and alternative synthesis. The formation of **6a** accorded via coupling diazonium chloride **3a** with **2** to form the intermediate **4** which converted to another intermediate **5.** The later afforded the final product **6** through elimination of a molecule of water. Meanwhile, treatment of 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one [17] (**7**) with **3a** in ethanolic sodium acetate as a buffer solution gave product identical in all respects (M.p., mixed m.p. and spectra) with **6a**, (Scheme 2).

Treatment of **2** or **7** with the appropriate 1,2,4-triazol-3-yldiazonium nitrate (**3d**) or benzimidazol-2-diazonium sulphate in cold solution of ethanolic sodium acetate gave ([l,2,4]triazolo[3,4-*c*][1,2,4]triazin-6-yl)benzofuran-2-yl)methanone (**10**) and benzo[4,5]imidazo[2,1-*c*][1,2,4]triazin-3-yl-benzofuran-2-yl-methanone (**11**), respectively in good yield (Scheme 3).

Treatment of **2** or **7** with benzenediazonium chloride in ethanol containing sodium acetate as a buffer solution yielded 2-(2-phenylhydrazono)-3-(benzofuran-2-yl)-3-oxopropanal (**12a**) (Scheme 4). Structure **12a** was confirmed by elemental analysis, spectral data and chemical transformations. ^{1}H NMR spectrum of **12a** showed signal at 7.26-8.20 ppm (m, 10H, ArH's), 9.75 ppm (s, 1H, -CHO) and 14.39 ppm (s, br., 1H, NH).



Scheme 7

Compound **12a** was reacted with hydrazine hydrate in boiling ethanol under reflux gave 1-(3-(benzofuran-2-yl)-4*H*-pyrazol-4-ylidene)-2-phenylhydrazine (**13a**) (Scheme 4). The structure **13a** was confirmed by elemental analysis, spectral data and alternative synthetic route. Thus, compound **7** reacted with hydrazine hydrate gave 3-(benzofuran-2-yl)-1*H*-pyrazole (**14**). The later was reacted with benzenediazonium chloride in ethanolic sodium acetate solution to afford product identical in all aspects (M.p., mixed m.p. and spectra) with **12a**. Similar, *p*-toluenediazonium chloride reacted with **2** or **7** in ethanolic sodium acetate gave **12b**, which converted to pyrazole **13b** by heating with hydrazine hydrate.

Next, treatment of compound **2** with 2-chloro-2-(hydroxyimino)-1-phenylethanone **15a** in toluene (15 mL) at room temperature in presence of triethylamine gave one isolable product formulated as 3,4-diacylisoxazole **16** or 4,5-diacylisoxazole **17** (Scheme 5). Structure of the product was confirmed by elemental analysis, spectral data and chemical transformation. Thus, treatment of the product with hydrazine hydrate gave isoxazolo[3,4-*d*]pyridazine **18a** (Scheme 5). From the above result, the product is formulated as: benzofuran-2-yl-(4-benzoyl-isoxazol-3-yl)-methanone (**17a**). Analogously, **7** reacted with each of **15b** and **15c** in toluene in presence of triethylamine afforded isoxazoles **17b** and **17c**, respectively. Compounds **17b** and **17c** reacted with hydrazine hydrate in boiling ethanol gave isoxazolo[3,4-*d*]pyridazines **18b** and **18c**, respectively.

Treatment of 1-(benzofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (**7**) with each of ethyl acetoaetate, acetylacetone, ethyl cyanoacetate, or benzoylacetonitrile in boiling acetic acid containing ammonium acetate under reflux gave ethyl 6-(benzofuran-2-yl)-2-methylpyridine-3-carboxylate (**19**), 1-(6-(benzofuran-2-yl)-2-methylpyridin-3-yl) ethanone (**20**), ethyl 2-amino-6-(benzofuran-2-yl)pyridine-3-carboxylate (**21**), ethyl and (2-amino-6-(benzofuran-2-yl)pyridin-3-yl) (phenyl) methanone (**23**), respectively (Scheme 6). Structure **22** and **24** were ruled on the basis of spectroscopic data. Thus, the IR spectrum showed the absence of bands between 2100-and 2300 cm^{-1} due to the absence of CN group but showed the presence of bands at 3448 and 3274 cm^{-1} due to the presence of an amino group. Also, ^{1}H-NMR spectrum of **21** revealed signals at 1.32 ppm (t, 3H) and 4.31 ppm (q, 2H), indicate the presence of ethoxy group (*cf.* Experimental part). Structure **19** was confirmed by elemental analysis, spectral data and chemical transformation. Thus, it reacted with hydrazine hydrate to give 6-(benzofuran-2-yl)-2-methylpyridine-3-carbohydrazide (**25**) in a good yield. Compound **25** reacted with ethyl acetacetate or with sodium nitrite in the presence of hydrochloric acid to afford 2-(6-benzofuran-2-yl-2-methyl-pyridine-3-carbonyl)-5-methyl-2,4-dihydro-pyrazol-3-one (**26**) and azido-(6-(benzofuran-2-yl) -2-methylpyridin-3-yl)methanone (**29**) (Scheme 6).

Meanwhile, **26** reacted with benzenediazonium chloride in a cold solution of ethanol containing sodium acetate as a buffer solution to give 2-(6-benzofuran-2-yl-2-methyl-pyridine-3-carbonyl)-5-methyl-4-(phenyl-hydrazono)-2,4-dihydro-pyrazol-3-one (**27**). The structure of compound **27** was confirmed by alternative synthesis by treatment of the hydrazide **25** with ethyl 3-oxo-2-(phenyl-hydrazono)butanoate (**28**) in boiling acetic acid to afford a product which was found identical in all aspects (M.p., mixed m.p., and spectra) with **27** previously prepared.

Azido(6-(benzofuran-2-yl)-2-methylpyridin-3-yl) methanone (**29**) can be converted into the substituted ureas, **30a-c**, **31** and 3-(6-(benzofuran-2-yl)-2-methylpyridin-3-yl)quinazoline-2,4(1*H*,3*H*)-dione (**32**) by its boiling with the appropriate aromatic amines, 3-amino-5-phenylpyrazole or methyl anthranilate (anthranilic acid) in dry dioxane, respectively. Also, phenyl 6-(benzofuran-2-yl)-2-methyl-pyridin-3-ylcarbamate (**33**) can obtained by boiling **29** with phenol in dry benzene (Scheme 7).

4. Conclusions

The studies described above clearly demonstrate that the new pyrazolo[5,l-*c*]triazines, [l,2,4]triazolo[4,3-*c*]triazine, benzo[4,5]-imidazo[2,1-*c*][1,2,4]triazine, isoxazoles, isoxazolo [3,4-*d*]pyrimidine pyridines, urea derivatives and carbamate derivative containing benzofuran moiety can be synthesized in a good yields *via* sodium salt of 1-(benzofuran-2-yl)-3-

hydroxyprop-2-en-1-one or 1-(benzofuran-2-yl)-3-(dimethyl amino)prop-2-en-1-one.

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