Synthesis of Tetrahetrocyclic Systems Including Pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine Fused with Pyrazole Derivatives and Isolated with 1,3,4-Oxa-, Thiadiazole, and 1,2,4-Tetrazole Derivatives

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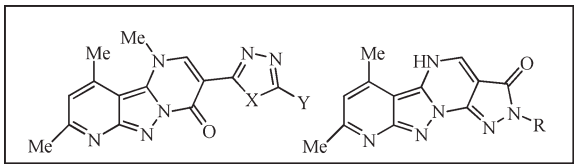

A series of isolated and fused tetracyclic compounds, containing pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine linked with 1,3,4-oxa-, thiadiazole, 1,2,4-tetrazole, and pyrazole derivatives were prepared by the reaction of 1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate and some common reagents to provide the product in satisfactory yields.

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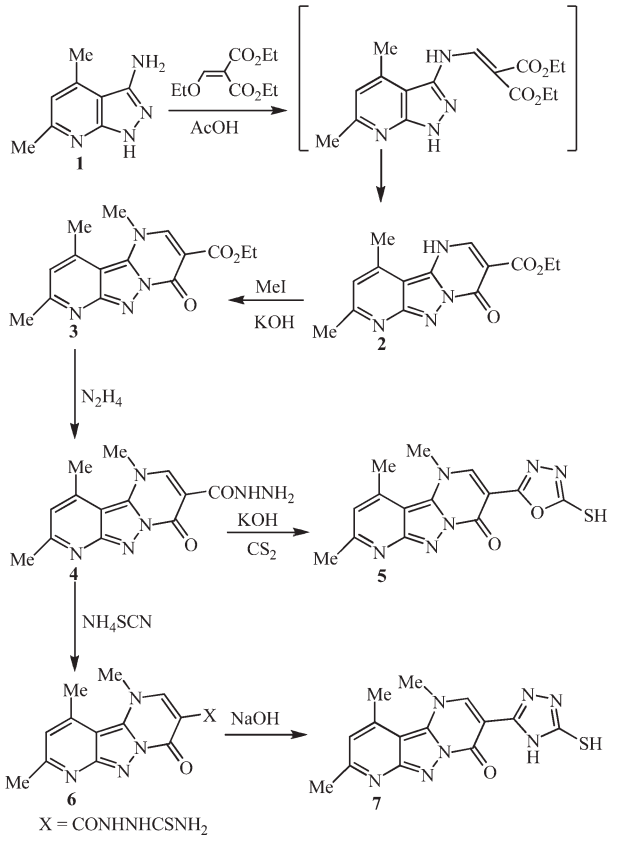
INTRODUCTION

1*H*-Pyrazolo[3,4-*b*]pyridines comprise a very interesting class of compounds because of their significant and versatile biological and pharmacological activities, such as antimalarial [1], antiproliferative [2], antimicrobial [3–5] inhibition of cyclin-dependent kinases [6] and cardiovascular [7–9] antiviral [10–12] and antileishmanial [13] activities. In general, the pyrazolopyridines are found to be active antitubercular agents [14,15] active against gram positive and negative bacteria [16]. As well as pyrazolopyrimidines [17,18] are selective inhibitors of cyclic 3′,5′-adenosine mono-phosphat (cAMP) phosphodiesterases *in vitro*, and some of them possess anxiolytic properties comparable to those of benzodiazepines.[19]. Moreover, pyridopyrazolopyrimidines revaled antiproliferative activity [20] and are used as potent kinase inhibitors [21]. To enhance the activity of pyrazolopyridines and pyrazolopyrimidines, several approaches were followed to construct another ring over those ring systems described in the literature [22–26] are available on preparation of pyridopyrazolopyrimidines which left much scope for further study. Furthermore, it has been reported that certain compounds bearing 1,3,4-oxa-, thiadiazole, and 1,2,4-triazole nucleus possess significant anti-inflammatory activity [27–37]. In view of these reports, we reported herein the synthesis of some newer heterocyclic systems containing pyridopyrazolopyrimidine system isolated with 1,2,4-triazoles, 1,3,4-oxa-, and thiadiazoles, and fused with pyrazoles derivative.

RESULTS AND DISCUSSION

4,6-Dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-amine was prepared according to the reported method [38,39] which undergo the cyclocondensation reaction with diethyl ethoxymethylenemalonate yielded directly the 8,10-dimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidine-3-carboxylate (**2**) without the isolation of the enamine intermediate [40], the structure of **2** was confirmed by the correctly positioned and coupled ^{1}H NMR spectrum, which presents signals as triplet at δ 1.29, quartet at 4.32 ppm because of the ester group and as singlet at δ 8.68, 12.24 ppm due to the H-2 and NH protons, respectively. The ^{13}C NMR spectrum of **2** showed a characteristic signals, for the ester group, at δ 24.2, 62.0 (CH_2CH_3), 166.0 (*C*OOEt), and 154.5 (C-4) ppm. The latter compound **2** was alkylated, by its reaction with methyl iodide in presence of KOH to afford 1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**), to increase its solubility during its reactions, which was elucidated by the appearance of the new signals in the ^{1}H NMR spectrum as singlet at δ 3.96 ppm due to N—CH_3. The alkylated derivative **3** was subjected to react with hydrazine hydrate to give the corresponding carbohydrazide derivative **4** which was confirmed by its IR spectrum showed a characteristic C=O absorptions at 1640 and 1677 cm^{-1}, and its ^{1}H NMR spectrum agree with the structure which showed a characteristic a broad singlet band for CONHNH_2 at δ 4.78 ppm. Hydrazide derivative (**4**) is versatile synthetic intermediate for the

Scheme 1

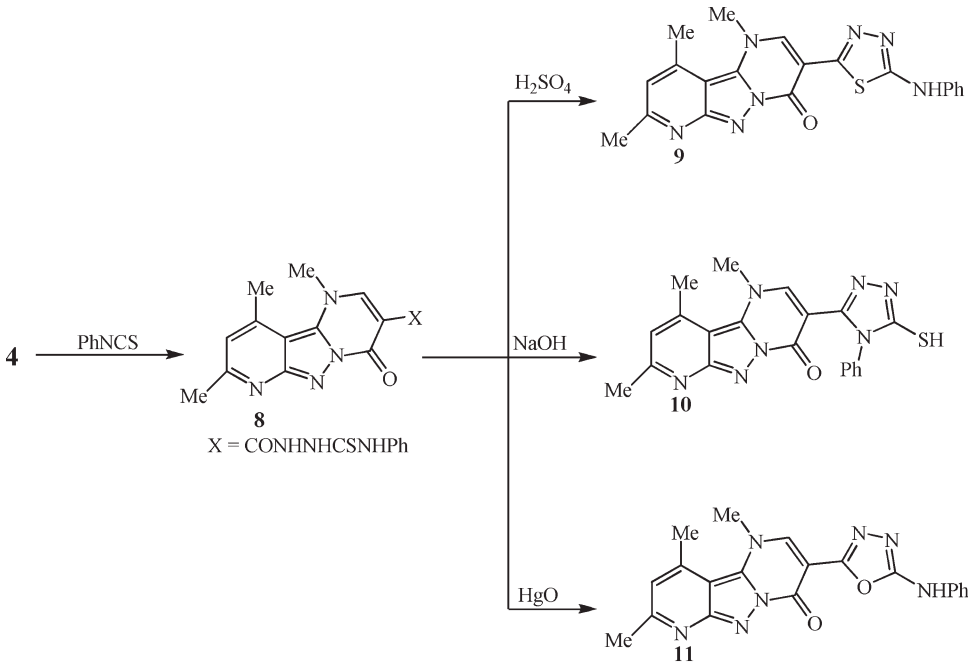


preparation of many heterocyclic moieties. In view of this report, we report herein some reactions of this hydrazide **4** to obtain new heterocyclic rings attached and/or fused to the pyridopyrazolopyridine moiety. Reaction of hydrazide **4** with CS_2 in alc. KOH at reflux temperature afforded the corresponding 1,8,10-trimethyl-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**5**) which was elucidated, besides the elemental analysis, ^{1}H NMR spectrum represented the presence of the characteristic broad singlet due to the SH group at δ 13.12 ppm and its mass spectrum revealed the molecular ion peak at *m*/*z* 328 indicated the molecular weight of **5**. The ^{13}C NMR spectrum showed a characteristic isooxazole signals at δ 162.0 and 171.3 ppm. Also the reaction of **4** with ammonium thiocyanate in absolute ethanol gave the corresponding thiosemicarbazide **6** which undergo the cyclization reaction through its treatment with sodium hydroxide giving 1,8,10-trimethyl-3-(5-sulfanyl-4*H*-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**7**) which was confirmed by ^{1}H NMR spectrum which showed the presence of signals as a broad bands at δ 10.92 and 12.55 ppm due to the NH and SH groups, respectively, its mass spectrum presents peaks corresponding to peaks at *m*/*z* 327 and 328 corresponding to M^+ and M^++1, respectively (Scheme 1).

On treatment of the hydrazide **4** with phenylisothiocyanate, in the way like its reaction with ammonium thiocyanate, afforded the corresponding the thiosemicarbazide **8** which was considered the key intermediate to prepare the 1,8,10-trimethyl-3-[5-(phenylamino)-1,3,4-thiadiazol-2-yl]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**9**), 1,8,10-trimethyl-3-(4-phenyl-5-sulfanyl-4*H*-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4(1*H*)-one (**10**), and 1,8,10-trimethyl-3-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]pyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidin-4(1*H*)-one (**11**), in about 66–74% yields, after its treatment with sulfuric acid, 2*N* sodium hydroxide, and mercuric oxide, respectively. The preferred formation of the 1,3,4-thiadiazole derivative **9** under such acidic conditions can be due to the loss of nucleophilicity of *N*-4 as a result of its protonation leading to an increase in the nucleophilicity of the sulfur atom toward the attack of the carbonyl carbon. On the other hand, the cyclization of **4** was carried out under alkaline conditions, the nucleophilicity of N-4 is enhanced and leads to cyclization with carbonyl carbon atom to afford the 1,2,4-triazole derivative **10**. 1,3,4-Oxadiazole derivative **11** was performed by mercuric oxide, the mode of cyclization includes desulfurization, which introduces the oxygen atom in the cyclization process. The structure assignment of these derivatives were based on the ^{1}H NMR spectra showed signals due to the N*H*Ph present in **9** and **11** at δ 9.86, 9.46 ppm, as a broad singlet, but in derivative **10** showed the broad singlet at δ 13.06 ppm due to the SH group. All the other aromatic and aliphatic protons were observed at the expected regions. Mass spectra of these derivatives showed a [M^++1] peak, in agreement with their molecular formula, also the elemental analysis are consistent with the structure of these derivatives **9**, **10**, and **11** (Scheme 2).

The starting material, pyridopyrazolopyrimidine carboxylate **2** was transformed into ethyl 4-chloro-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate by phosphorous oxychloride at boiling temperature thus providing intermediate precursor **12** for all four new final compounds. They furnished fused tetracyclic compounds **13a–d** by reaction with various purchased hydrazines in boiling xylene. The previously reported method, consisting of a nucleophylic substitution of the chlorine atom with the hydrazine derivative followed by cyclization [41], again showed itself to be useful and profitable for the aims proposed. 6,8-dimethyl-2,3-dihydro-3*H*-pyrazolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-one derivatives **13a–d** were elucidated by the IR spectra which presented strong peaks at 1640–1620, 3466–3409,

Scheme 2



and 2210 cm^{-1} which were attributed to the carbonyl (C═O) and ─NH groups on the pyrazole and pyrimidine, respectively. The mass spectra of these compounds **13a–d** indicated that the molecular ion peaks were observed as M^+ and M^++H. From their ^1H NMR spectra, it is possible to observe the presence of signals corresponding to the NH of pyrimidine at the range δ 10.99–11.15 ppm, the absence of the ester group and presence the new signals in aliphatic region such as in compound **13a** at δ 4.18 ppm due to the N─CH_3 and the increase of signals in the aromatic part because the presence of phenyl derivatives in compounds **13b–d**. In addition, the elemental analysis is consistent with the structure of theses compounds **13a–d** (Scheme 3).

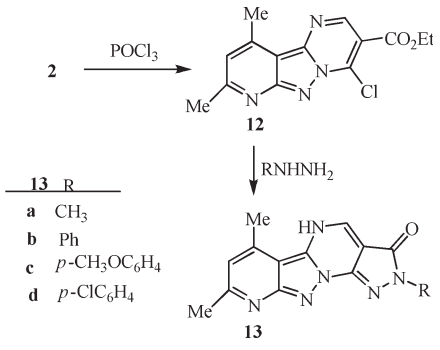
EXPERIMENTAL

Melting points were determined using Kofter block instrument. The progresses of reactions were monitored by TLC (analytical silica gel plates 60 F_{254}). NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 300 MHz for ^1H NMR and at 75.5 MHz for ^{13}C NMR with TMS as an internal standard, chemical shifts are reported in ppm (δ) and coupling constants (*J*) are given in Hz. IR spectra were recorded on Perkin-Elmer 1430 sectrpphotometer using KBr disc technique. Mass spectra were measured on a Kratos 50 tc spectrometers. Elemental analyses were performed at the Chemistry Institute, Copenhagen University.

Ethyl 8,10-dimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4] pyrazolo[1,5-a]pyrimidine-3-carboxylate (2). A mixture of 1.94 g of aminopyrazolopyridine **1** (12 mmol) and 2.59 g of diethyl ethoxymethylenemalonate (12 mmol) was dissolved in 20-mL glacial acetic acid and the reaction mixture was refluxed for 10 h cooling to room temperature and poured into ice/water. The solid product was collected by filtration, washed with water, dried, and recerystalization from methanol to afford the yellow crystals of **2**, 3.12 g (91%), mp 222–223°C; ^1H NMR (DMSO-d_6): δ 1.29 (t, 3H, J = 7 Hz, CH_3CH_2), 2.66 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 4.32 (q, 2H, J = 7.0 Hz CH_3CH_2), 7.03 (s, 1H, ArH), 8.68 (s, 1H, ArH), 12.24 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.3, 19.2, 24.2, 62.0, 91.2, 116.8, 122.2, 145.8, 148.2, 151.2, 153.6, 154.5, 158.3, 166.0; ms (EI): *m/z* 287 (M^++1, 5), 286 (M^+, 26), 241 (23), 240 (100). Anal. Cacld. for $C_{14}H_{14}N_4O_3$ (286.29): C, 58.73; H, 4.93, N, 19.57. Found: C, 58.60; H, 4.75; N, 19.35.

1,8,10-Trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo [1,5-a]pyrimidine-3-carboxylate (3). A solution of 1.77 g (6.2 mmol) of **2** in 20 mL of acetone, cooled by immersion in a water/ice bath, was added to 1.74 g (31.0 mmol) of powdered KOH. On vigorous stirring, 1.76 g of methyl iodide (12.4 mmol) was added and the mixture was stirred for 30 min at room temperature. After the addition of 90 mL of toluene, a precipitate of inorganic salt had formed, which was filtered

Scheme 3



off. The organic mixture was treated with 20 mL of saturated NaCl solution, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was triturated with ethanol and the solid product was collected by filtration, and recrystalization from ethanol to afford the white powder of **3**, 1.52 g (82%); mp 150–152°C; IR (KBr) ν cm^{-1} 1745 (CO_2Et), 1633 (CO); ^1H NMR ($CDCl_3$): δ 1.26 (t, 3H, $J = 7$ Hz, CH_3CH_2), 2.56 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.96 (s, 3H, N—CH_3), 4.29 (q, 2H, $J = 7$ Hz, CH_3CH_2), 7.00 (s, 1H, ArH), 8.68 (s, 1H, ArH); (EI): *m/z* 301 (M^++1, 20), 300 (M^+, 100),, 255 (25), 227 (30), 184 (8), 131 (60), 115 (16). Anal. Cacld. for $C_{15}H_{16}N_4O_3$ (300.31): C, 59.99; H, 5.37, N, 18.66. Found: C, 59.76; H, 5.25; N, 18.45.

1,8,10-Trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4] pyrazolo [1,5-a]pyrimidine-3-carbohydrazide (4). A mixture of 3.0 g of **3** (10 mmol) and 1.25 g of hydrazine hydrate (25 mmol) in 30 mL ethanol was heated under reflux for 4 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from methanol to give colorless of **4**, 2.51 g (88%); mp 266–267°C; IR (KBr) ν cm^{-1}: 3310–3212 ($NHNH_2$), 1640, 1677 (2 CO); ^1H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.86 (s, 3H, N—CH_3), 4.78 (bs, 2H, NH_2), 7.22 (s, 1H, ArH), 8.78 (s, 1H, ArH), 9.45 (bs, 1H, NH); ms (EI): *m/z* 287 (M^++1, 55), 286 (M^+, 20), 257 (15), 228 (100), 199 (23), 175 (12), 147 (36). Anal. Cacld. for $C_{13}H_{14}N_6O_2$ (286.29): C, 54.54; H, 4.93, N, 29.35. Found: C, 54.33; H, 4.65; N, 29.15.

1,8,10-Trimethyl-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)pyrido [2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (5). A mixture of 2.86 g of hydrazide **4** (10 mmol) and 0.6 mL of carbon disulfide (10 mmol) was added to a solution of 0.56 g KOH (10 mmol) in 50 mL water and 50 mL ethanol. The reaction mixture was refluxed for 4 h. After evaporating it to dryness under reduced pressure, a solid product was obtained. This was dissolved in 50 mL water and acidified with conc. HCl. The precipitate was filtered off, washed with water, and recrystallized from ethanol to afford the whit crystals of **5**, 2.25 g (69%); mp 210–212°C; ^1H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.88 (s, 3H, N—CH_3), 7.32 (s, 1H, ArH), 8.95 (s, 1H, ArH), 13.12 (bs, 1H, SH); ^{13}C NMR (DMSO-d_6): δ 14.3, 19.2, 24.2, 90.2, 116.7, 121.6, 145.5, 148.4, 151.1, 152.4, 155.3, 157.5, 162.0, 171.3; ms (EI): *m/z* 329 (M^++1, 10), 328 (M^+, 65), 294 (100), 239 (20), 201 (23), 151 (12), 77 (11). Anal. Cacld. for $C_{14}H_{12}N_6O_2S$ (328.35): C, 51.21; H, 3.68, N, 25.59. Found: C, 51.12; H, 3.55; N, 25.43.

***N′*-[(Amino-sulfanylidyne)methyl]-1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-carbohydrazide (6).** To a mixture 0.29 g of hydrazide **4** (1 mmol) and 0.23 g of ammonium thiocyanate (3 mmol), 4 mL of hydrochloric acid (36%) was added, in 50 mL ethanol. The reaction mixture was refluxed for 12 h, cooled, and the mixture poured into ice/water with stirring. The solid formed was collected by filtration, dried, and recrystallized from ethanol to afford a pale yellow crystals of **6**, 0.31 g (89%), mp 225–226°C; IR (KBr) ν cm^{-1}: NH 3300–3200, (NH_2, NH), 1655–1640 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.89 (s, 3H, N—CH_3), 5.03 (bs, 2H, NH_2), 7.22 (s, 1H, ArH), 8.65 (s, 1H, ArH), 9.71 (bs, 1H, CSNH), 10.17 (bs, 1H, CONH); ms (EI): *m/z* 346 (M^++1, 35), 345 (M^+, 10), 330 (5), 286 (100), 245 (24), 217 (12), 152 (30). Anal. Cacld. for $C_{14}H_{15}N_7O_2S$ (345.38): C, 48.69; H, 4.38, N, 28.39. Found: C, 48.30; H, 4.22; N, 28.26.

1,8,10-Trimethyl-3-(5-sulfanyl-4H-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (7). A mixture of 0.69 g thiosemicarbazid **6** (2 mmol) and 50-mL sodium hydroxide (2*N*) was heated under reflux for 2 h. The reaction mixture was cooled, the precipitate formed was collected by filtration, dried, and recrystallized from methanol to afford the yellow crystals of **7**, 0.52 g (80%); mp 239–240°C; IR (KBr) ν cm^{-1}: (NH) 3320,1645 (CO), 2786 (SH); ^1H NMR (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.93 (s, 3H, N—CH_3), 7.15 (s, 1H, ArH), 8.50 (s, 1H, ArH), 10.92 (bs, 1H, NH), 12.55 (bs, 1H, SH); ms (EI): *m/z* 328 (M^++1, 60), 327 (M^+, 100), 294 (15), 227 (60), 246 (13), 201 (11), 184 (8). Anal. Cacld. for $C_{14}H_{13}N_7OS$ (327.36): C, 51.36; H, 4.00, N, 29.95. Found: C, 51.22; H, 3.97; N, 29.86.

***N′*-{[Imino(phenyl)-sulfanylidyne]methyl}-1,8,10-trimethyl-4-oxo-1,4-dihydropyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-carbohydrazide (8).** To a solution of 2.86 g hydrazide **4** (10 mmol) in 10 mL ethanol, 1.35 g phenylisothocyanate (10 mmol) were added. The reaction mixture was heated under reflux for 2 h. The product that separated on cooling was filtered off, washed with ethanol, and dried well to give white crystals of **8**, 3.86 g (92%); mp 173–175°C; ^1H NMR (DMSO-d_6): δ 2.65 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.95 (s, 3H, N—CH_3), 7.13–7.79 (m, 6H, ArH), 8.81 (s, 1H, ArH), 9.50 (bs, 1H, ArNH), 9.81 (bs, 1H, CSNH), 10.18 (bs, 1H, CONH); ms (EI): *m/z* 421 (M^+, 60), 344 (100), 256 (35), 227 (9), 194 (16), 166 (25), 121 (23), 109 (10). Anal. Cacld. for $C_{20}H_{19}N_7O_2S$ (422.48): C, 56.99; H, 4.54, N, 23.26. Found: C, 56.62; H, 4.33; N, 23.14.

1,8,10-Trimethyl-3-[5-(phenylamino)-1,3,4-thiadiazol-2-yl] pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (9). A solution of 2.11 g thiosemicarbazide **8** (5 mmol) in 10 mL cold conc. sulfuric acid was stirred until dissolution and the left at room temperature for 2 h with stirring. The reaction mixture was poured onto crushed ice and the precipitate product was filtered off, washed with water, and recrystallized from ethanol to give pale yellow crystals of **9**, 1.50 g (74%); mp 207–208°C; ^1H NMR (DMSO-d_6): δ 2.64 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.96 (s, 3H, N—CH_3), 7.14–7.65 (m, 6H, ArH), 8.65 (s, 1H, ArH), 9.86 (bs, 1H, ArNH); ^{13}C NMR (DMSO-d_6): δ 15.6, 19.4, 23.5, 93.0, 116.7, 117.3, 117.8, 122.4, 125.1, 129.5, 140.5, 145.9, 148.4, 151.1, 155.0, 152.2, 155.6, 158.9, 159.0, 160.1; ms (EI): *m/z* 404 (M^++1, 30), 403 (M^+, 100), 326 (21), 271 (15), 240 (24), 174 (12), 145 (22). Anal. Cacld. for $C_{20}H_{17}N_7OS$ (403.46): C, 59.54; H, 4.25, N, 24.30. Found: C, 59.35; H, 4.13; N, 24.17.

1,8,10-Trimethyl-3-(4-phenyl-5-sulfanyl-4H-1,2,4-triazol-3-yl)pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (10). A solution of 2.11 g thiosemicarbazide **8** (5 mmol) in 50 mL sodium hydroxide (2*N*) was heated under reflux for 4 h. The reaction mixture was cooled and acidified with hydrochloric acid (2*N*). The resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to afford the yellow crystals of **10**, 1.40 g (69%), mp 210–211°C; ^1H NMR (DMSO-d_6): δ 2.66 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.96 (s, 3H, N—CH_3), 7.16–7.76 (m, 6H, ArH), 8.33 (s, 1H, ArH), 13.06 (bs, 1H, SH); ms (EI): *m/z* 404 (M^++1, 30), 403 (M^+, 60), 326 (11), 293 (33), 227 (50), 193 (100), 166 (33), 119 (20), 106 (10). Anal. Cacld. for $C_{20}H_{17}N_7OS$ (403.46): C, 59.54; H, 4.25, N, 24.30. Found: C, 59.44; H, 4.17; N, 24.14.

1,8,10-Trimethyl-3-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4(1H)-one (11). Mercuric oxide 2.37 g (11 mmol) was added to a solution of 4.21 g thiosemicarbazide **8** (10 mmol) in 20 mL methanol and the resulting mixture was refluxed for 4 h. The precipitated mercuric sulfide was filtered off and washed with hot methanol. The filtrate on cooling gave a precipitate which was recrystallized from ethanol to afford the white crystals of **11**, 2.55 g (66%), mp 183–184°C; ^{1}H NMR (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.94 (s, 3H, N—CH_3), 7.12–7.66 (m, 6H, ArH), 8.78 (s, 1H, ArH), 9.46 (bs, 1H, ArNH); ms (EI): *m/z* 387 (M^+, 100), 310 (30), 283 (15), 227 (30), 174 (40), 117 (10). Anal. Cacld. for $C_{20}H_{17}N_7O_2$ (387.39): C, 62.01; H, 4.42, N, 25.31. Found: C, 61.94; H, 4.31; N, 25.14.

4-Chloro-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-carboxylate (12). A mixture of 2.86 g of ethylcarboxylate **2** (10 mmol) and 7.75 g of phosphorous oxychloride (50 mmol) was refluxed for 3 h. After cooling, the suspension was then added to ice/water. Then, with stirring, it was carefully made alkaline with aqueous sodium hydroxide (28%) and the resulting precipitate was collected, washed many times with water, dried, and recrystallized from ethanol to afford a pale yellow powder of **12**, 2.81 g (92%), mp 150–152°C; ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, J = 7 Hz, CH_3CH$_2$), 2.68 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 4.41 (q, 2H, J = 7.0 Hz CH_3CH_2), 7.11 (s, 1H, ArH), 8.77 (s, 1H, ArH); ms (EI): *m/z* 305 (M^++1, 12), 304 (M^+, 72), 267 (30),240 (100), 223 (15), 195 (15). Anal. Cacld. for $C_{14}H_{13}ClN_4O_2$ (304.73): C, 55.18; H, 4.30; N, 18.39. Found: C, 55.10; H, 4.22; N, 18.20.

Synthesis of the N-substituted 6,8-Dimethyl-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one derivatives (13a–d). 4-Chloro-pyridopyrazolopyrimidine 0.30 g (1 mmol) was dispersed in 20 mL of xylene and the suspension was heated to refluxing until complete dissolution. Then, a slight excess of hydrazine compound (1.5 mmol) was added with 0.16 g of triethylamin (1.5 mmol) and the reaction mixture was refluxed for the required time (9–12 h). A precipitate had formed was collected, washed many times with ethanol, dried under vacuum, and finally recrystallized with absolute ethanol giving **13a–d**: **13a**, 0.17 g (65%); **13b**, 029 g (88%); **13c**, 0.23 g (64%); and **13d**, 0.31 g (86%).

2,6,8-Trimethyl-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13a) White crystals, mp 280–282°C; ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 4.18 (s, 3H, N—CH_3), 7.05 (s, 1H, ArH), 8.66 (s, 1H, ArH), 10.99 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 18.3, 24.1, 40.5, 99.3, 109.5, 122.2, 136.3, 145.6, 148.0, 153.3, 155.2, 158.3, 166.4; ms (EI): *m/z* 269 (M^++1, 20), 268 (M^+, 100), 253 (30), 224 (40), 197 (15). Anal. Cacld. for $C_{13}H_{12}N_6O$ (268.27): C, 58.20; H, 4.51; N, 31.33. Found: C, 58.12; H, 4.23; N, 31.21.

6,8-Dimethyl-2-phenyl-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13b) White powder, mp 310–312°C; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.06–7.55 (m, 6H, ArH), 8.91 (s, 1H, ArH), 11.10 (bs, 1H, NH); ms (EI): *m/z* 331 (M^++1, 40), 330 (M^+, 100), 253 (20), 224 (11), 197 (12), 160 (41), 118 (33) 77 (5). Anal. Cacld. for $C_{18}H_{14}N_6O$ (330.34): C, 65.44; H, 4.27; N, 25.44. Found: C, 65.22; H, 4.20; N, 25.31.

6,8-Dimethyl-2-(4-methoxy-phenyl)-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13c) Yellow powder, mp 270–271°C; ^{1}H NMR (DMSO-d_6): δ 2.63 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 7.16–7.56 (m, 5H, ArH), 8.96 (s, 1H, ArH), 11.12 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 19.6, 24.3, 55.4, 101.3, 109.5, 114.2, 121.6, 122.4, 127.6, 136.7, 132.8, 145.7, 148.6, 150.5, 153.5, 154.9, 155.4, 158.7, 165.1; ms (EI): *m/z* 361 (M^++1, 39), 360 (M^+, 60), 329 (100), 252 (21), 197 (12), 121 (10), 107 (41). Anal. Cacld. for $C_{19}H_{16}N_6O_2$ (360.37): C, 63.32; H, 4.48; N, 23.32. Found: C, 63.19; H, 4.30; N, 23.20.

6,8-Dimethyl-2-(4-chloro-phenyl)-2,5-dihydro-3H-pyrazolo[3,2-d]pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine-3-one (13d) White powder, mp 240–241°C; ^{1}H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 7.19–7.87 (m, 5H, ArH), 8.98 (s, 1H, ArH), 11.15 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 19.7, 24.5, 99.3, 110.6, 113.4, 119.5, 126.5, 135.7, 131.7, 143.5, 145.7, 149.5, 151.6, 156.8, 157.4, 159.3, 160.5, 164.5; ms (EI): *m/z* 365 (M^++1, 80), 364 (M^+, 100), 328 (30), 300 (18), 284 (15), 257 (13), 231 (18), 201 (55), 146 (16), 131 (22), 112 (13). Anal. Cacld. for $C_{18}H_{13}ClN_6O$ (364.79): C, 59.27; H, 3.59; N, 23.04. Found: C, 59.18; H, 3.41; N, 22.88.

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