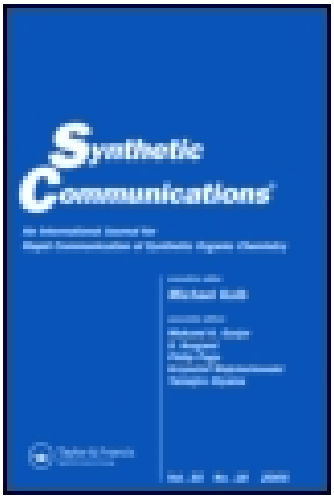

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Synthesis of New Pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidines and Their Use in the Preparation of Tetraheterocyclic Systems

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SYNTHESIS OF NEW PYRIDO[2′,3′:3,4]PYRAZOLO-[1,5-*a*]PYRIMIDINES AND THEIR USE IN THE PREPARATION OF TETRAHETEROCYCLIC SYSTEMS

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8,10-Dimethyl-3-(unsubstituted, methyl, ethyl, n-butyl, phenyl)-4-hydroxypyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-2(1H)-ones and 3-(2-hydroxyethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidin-4-ol were synthesized by cyclocondensation of 3-amine-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridine with ethyl malonates and α-acetyl-γ-butyrlolactone. Dichloro- and diazido- derivatives were obtained from the reaction of pyridopyrazlopyrimidine derivatives with $POCl_3$ followed by NaN_3. The tetrahetrocyclic systems were formed by cyclization of 4-chloro-3-(2-chloroethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine with the appropriate primary amines. The structures of all compounds were established by NMR and mass spectra.

Keywords: Cyclocondensation; dichloride; pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-ones; tetrahetrocyclic systems

1*H*-Pyrazolo[3,4-*b*]pyridines constitute 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] cardiovascular,[6–8] antiviral,[9–11] and antileishmanial[12] activities and their inhibition of cyclin-dependent kinases.[13] Moreover, pyridopyrazolopyrimidines revealed antiproliferative activity[14] and are used as potent kinase inhibitors.[15] In general, the pyrazolopyridines are active antitubercular agents[16,17] and are active against Gram-positive and Gram-negative bacteria.[18] The pyrazolopyrimidines[19,20] are selective inhibitors of cyclic 3′,5′-adenosine monophosphate (cAMP) phosphodiesterases in vitro, and some of them possess anxiolytic properties comparable to those of benzodiazepines.[21] To enhance the activity of pyrazolopyridines and pyrazolopyrimidines, several approaches to construct another ring over those ring systems described in the literature[22–25] are available on preparation of pyridopyrazolopyrimidines, which left much scope for further study. In view of these reports, I have synthesized a number of new pyridopyrazolopyrimidine derivatives and constructed another ring over those ring systems.

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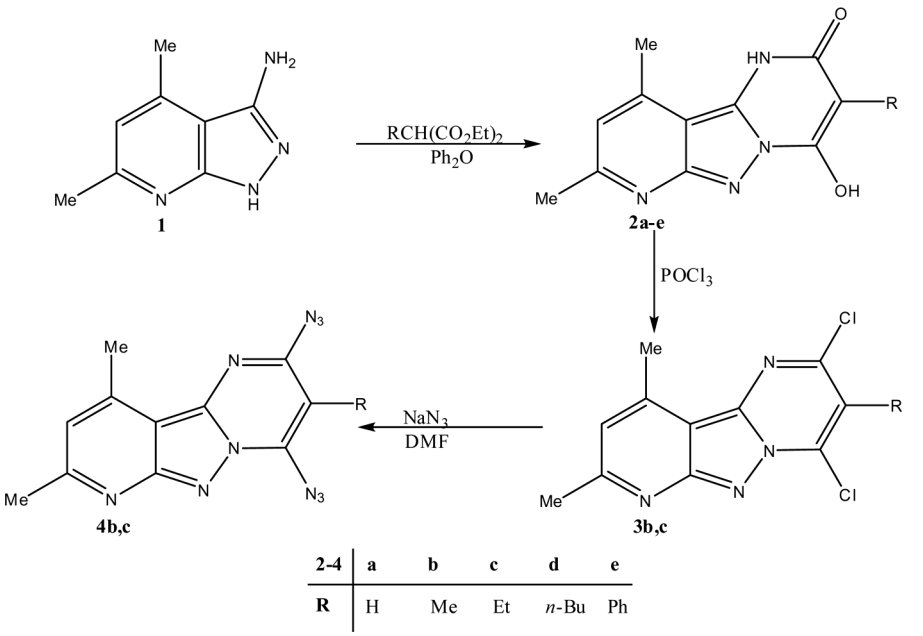
The synthesis of 4-hydroxy-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*] pyrimidin-2(1*H*)-one derivatives **2a–e** was achieved by cyclocondensation of 3-amine-4,6-dimethyl-1H-pyrazolo[3,4-b]pyridine **1**[26,27] with ethyl malonates at 220–225 °C using diphenyl ether as a solvent. Structural assignment by infrared (IR) spectroscopy showed the characteristic absorption bands at 3430–3290 cm^{-1} due to OH and NH groups. The mass spectrum revealed a molecular ion peak for each derivative. In the ^1H NMR spectra, the signal due to the NH present in all compounds appeared at δ 11.06–11.66 ppm, as singlets. The OH proton was observed at δ 13.33–15.43 ppm as a broad band. All the other aromatic and aliphatic protons were observed at the expected regions. The dichloride derivatives were obtained by halohydroxylation of the derivatives **2b,c** with $POCl_3$ at reflux temperature to afford 2,4-dichloro-3,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine **3b** and 2,4-dichloro-3-ethyl-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine **3c**. The structures of the obtained dichorides were elucidated by ^1H NMR spectra, which showed three singlets at δ 2.60, 2.63, and 2.78 ppm, corresponding the three methyl groups for **3b**, and a triplet at δ 1.26 ppm and a quartet at 3.02, the corresponding ethyl group for **3c**. The dichlorides **3b,c** were converted readily into 2,4-diazido-3, 8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**4b**) and 2,4-diazido-3-ethyl-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**4c**) after treatment with NaN_3, in dimethylformamide (DMF) at room temperature. Structures **4b,c** were proven by the presence of the two azide absorptions at 2134–2195 cm^{-1} in the IR spectra (Scheme 1).

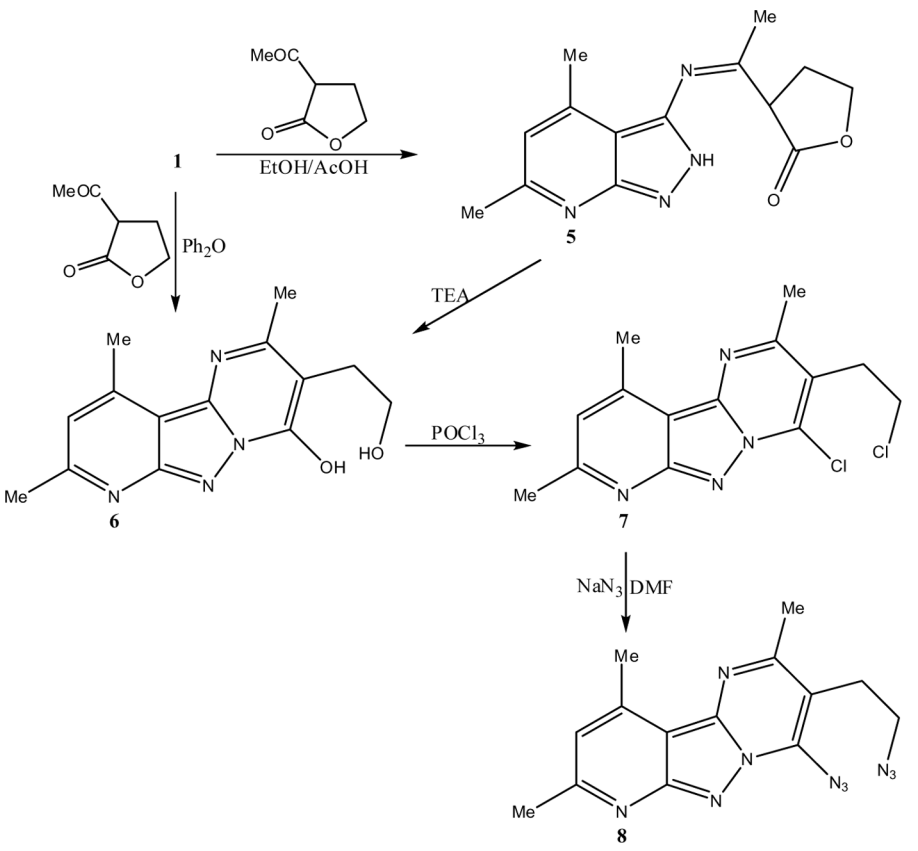
Condensation of the 3-aminopyrazolopyridine **1** with α-acetyl-γ-butyrolactone in ethanol in the presence of a catalytic amount of glacial acetic acid gave



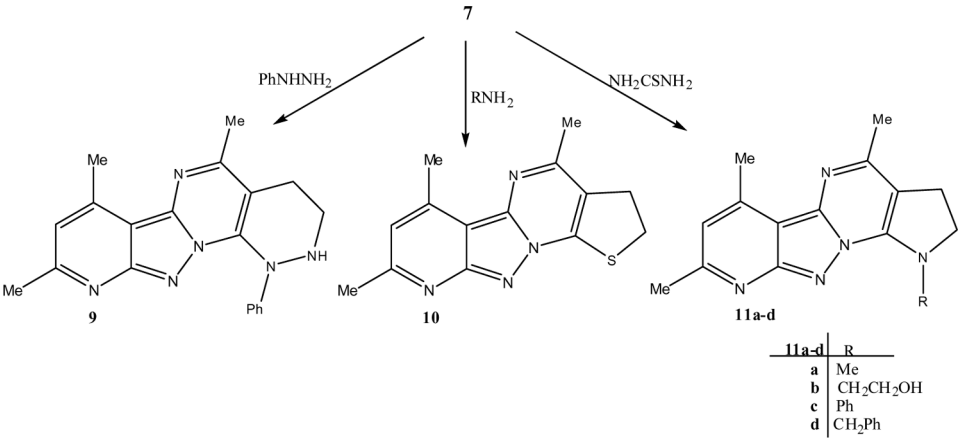
Scheme 1. Synthesis of pyridopyrazolopyrimidine derivatives.

3-{(2*Z*,2*E*)-2-[(4,6-dimethyl-2*H*-pyrazolo[3,4-*b*]pyridin-3-yl)imino]propyl}dihydrofuran-2(3*H*)-one (**5**), which was confirmed by its spectral data and the fact that it was readily cyclized in an aqueous basic solution to give 3-(2-hydroxyethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4-ol (**6**). The latter dihydroxy **6** was prepared by boiling **1** with α-acetyl-γ-butyrolactone in diphenyl ether. Its structure was elucidated by the mass spectrum, which showed the molecular ion peak at m/z 273 and 272 corresponding to ($M^+ + t$ from here H, 14) and (M^+, 11). The chlorination of **6** with $POCl_3$ afforded the 4-chloro-3-(2-chloroethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**7**), which was reacted with NaN_3 in DMF to afford 4-azido-3-(2-azidoethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**8**). This showed, in its IR spectrum, the characteristic peaks of the two azide groups at 2139 and 2115 cm^{-1} (Scheme 2).

The dichloride **7** served as intermediate for the preparation of tetraheyrocyclic systems through its treatment with appropriate primary amines. 1-Phenyl-1,2,3,4-tetrahydro-5,7,9-trimethylpyridazino[2,3-*e*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**9**) and 2,3-dihydro-4,6,8-trimethylthiopheno[2,3-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]



Scheme 2. The reaction of butyrolactone with 3-aminopyrazolopyridine and formation of the diazido derivative.



Scheme 3. Formation of the tetraheterocyclic systems.

pyrimidine (**10**) were obtained on the reaction of **7** with both phenyl hydrazine and thiourea in ethanol and/or tetrahydrofuran (THF), respectively, in good yield. The ^{1}H NMR spectrum of **9** showed the increase of aromatic protons due to presence of phenyl group with H-8 at δ 6.85–7.29 ppm and broad singlets at δ 10.66 ppm for the NH group of pyridazine. The structure of the obtained **10** was confirmed by the mass spectra, which showed a $[M^+ + 1]$ peak in agreement with their molecular formula. *N*-Alkyl/aralkyl-2,3-dihydro-4,6,8-trimethylpyrrolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines **11a–d** were synthesized by cyclization of dichloride **7** with methyl amine, 2-ethnolamine, aniline, and benzylamine in absolute ethanol in the presence of an equimolar amount of Na_2CO_3 and/or triethylamine. Structural assignment by ^{1}H NMR spectra showed a singlet at δ 3.69 ppm corresponding to *N*-Me for **11a**, four triplets at δ 3.18, 3.94, 3.98, and 4.42 ppm corresponding to the CH_2CH_2-*N* of pyrrol ring and the side chain CH_2CH_2OH group for **11b**, a multiple in the aromatic region at δ 6.66–7.47 ppm for the phenyl group in **11c**, and a singlet at δ 5.56 ppm due to CH_2Ph for **11d**. Mass spectra peaks corresponded to the molecular formulas (Scheme 3).

EXPERIMENTAL

Instruments

Melting points were determined using a Kofter block instrument. Thin-layer chromatography (TLC) was performed on plastic plates with silica gel 60 F254 (E. Merk, layer thickness 0.2 mm). NMR spectra were recorded on a Bruker AC 250 Fourier transform (FT) NMR spectrometer at 300 MHz for ^{1}H NMR and at 75.5 MHz for ^{13}C NMR with TMS as an internal standard. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were measured on a Kratos 50 TC spectrometers. The microanalyses were performed at the microanalytical unit, Cairo University, Egypt, and agreed with the calculated values.

8,10-Dimethyl-3-(unsubstituted, methyl, ethyl, n-butyl, phenyl)-4-hydroxypyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-ones (2a–e)

General procedure. A mixture of 3-aminopyrazolopyridine **1** (1.62 g, 10 mmol) and the appropriate malonic ester (10 mmol) in 10 mL diphenyl ether was heated in an oil bath for 20–30 min to 220–250 °C using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was digested with diethyl ether and petroleum ether, and the obtained precipitate was filtered, washed with diethyl ether, dried, and recystallized from acetic acid, giving **2a–e** in 83–96% yields.

4-Hydroxy-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one (2a). Yellow powder, 1.90 g (83%), mp 328–330 °C; IR: OH/NH 3422–3267, CO 1680 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.59$, 2.81 (2s, 6H, 2 CH_3), 7.31 (s, 1H, H-3), 6.81 (s, 1H, H-9), 11.32 (s, 1H, NH), 14.15 (s, 1H, OH). MS (EI): m/z 231 [14, $(M + H)^+$], 230 (M^+, 100), 189 (21), 162 (77), 133 (20), 107 (27), 69 (50). Anal. calcd. for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.38; N, 24.34. Found: C, 57.79; H, 4.08; N, 23.94.

4-Hydroxy-3,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one (2b). Yellow powder, 2.10 g (88%); mp > 360 °C; IR: OH/NH 3445–3252, CO 1653 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.51$, 2.79, 2.98 (3s, 9H, 3 CH_3), 6.83 (s, 1H, H-9), 11.13 (s, 1H, NH), 13.68 (s, 1H, OH); MS (EI): m/z 245 [27, $(M + H)^+$], 244 (M^+, 100), 189 (47), 147 (8). Anal. calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.31; H, 4.35; N, 22.64.

3-Ethyl-4-hydroxy-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one (2c). Yellow powder, 2.10 g (84%); mp 334–336 °C; IR: OH/NH 3421–3271, CO 1665 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.06$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.47 (q, 2H, $J = 14.70$ Hz, CH_2CH_3), 2.58, 2.80 (2s, 6H, 2 CH_3), 6.79 (s, 1H, H-9), 11.12 (s, 1H, NH), 13.33 (s, 1H, OH); MS (EI): m/z 259 [6, $(M + H)^+$], 258 (M^+, 35), 243 (100), 189 (14), 175 (8), 97 (6). Anal. calcd. for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.75; H, 5.75; N, 22.09.

3-Butyl-4-hydroxy-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one (2d). Yellow powder, 2.39 (85%); mp 358–360 °C; IR: OH/NH, 3387–3246, CO 1654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.02$ (t, 3H, $J = 7.2$ Hz, CH_3 of butyl), 1.29–1.31 (m, 4H, 2 CH_2 of butyl group), 2.41 (t, 2H, $J = 7.2$ Hz, CH_2 of butyl), 2.53, 2.61 (2s, 6H, 2 CH_3), 6.87 (s, 1H, H-9), 11.06 (s, 1H, NH), 13.26 (s, 1H, OH); MS (EI): m/z 287 [11, $(M + H)^+$], 286 (M^+, 1), 243 (13), 189 (27), 162 (100), 69 (15), 55 (15). Anal. calcd. for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.62; H, 6.64; N, 19.17.

4-Hydroxy-8,10-dimethyl-3-phenylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one (2e). Yellow powder, 2.92 g (96%); mp 328–330 °C; IR: OH/NH 3389–3226, CO 1626 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.49$, 2.86 (2s, 6H, 2 CH_3), 6.83 (s, 1H, H-9), 11.66 (s, 1H, NH), 15.43 (s, 1H, OH); MS (EI): m/z 307 [21, $(M + H)^+$], 306 (M^+, 100), 189 (80), 147 (27), 118 (29), 89 (28), 77 (10). Anal. calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.36; H, 4.31; N, 18.59.

3-Alkyl-2,4-dichloro-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (3b,c)

General procedure. A mixture of 3-alkylpyridpyrazolopyrimidine **2b,c** (8 mmol) and 10 mL of $POCl_3$ was refluxed for 3 h. After cooling, the mixture was poured into ice water, and a crystalline solid was collected by filtration. The product was recrystallized from ethanol to give **3b,c** in 47–77% yields.

2,4-Dichloro-3,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (3b). Pale yellow powder, 1.70 g (77%); mp 180–183 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.57$, 2.62, 2.76 (3s, 9H, 3 CH_3), 7.06 (s, 1H, H-9); ^{13}C NMR (75.5 MHz, DMSO-d_6): $\delta = 17.44$, 19.22, 26.34 (3 CH_3), 104.85, 110.51, 119.70, 120.91, 138.11, 144.67, 148.67, 160.73, 164.72 (ArC). MS (EI): m/z 281 (M^+, 100), 280 (25) 189 (16), 162 (30), 133 (13), 107 (60), 69 (40). Anal. calcd. for $C_{12}H_{10}Cl_2N_4$: C, 51.27; H, 3.59; Cl, 25.22; N, 19.93. Found: C, 51.57; H, 3.29; Cl, 25.62; N, 2023.

2,4-Dichloro-3-Ethyl-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (3c). Pale yellow powder, 1.70 g (74%); mp 150–153 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.26$ (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 2.51, 2.77 (2s, 6H, 2 CH_3), 3.02 (q, 2H, $J = 15.0$ Hz, CH_2CH_3), 7.07 (s, 1H, H-9); MS (EI): m/z 295 (M^+, 100), 294 (25), 243 (16), 189 (12), 175 (81), 97 (6). Anal. calcd. for $C_{13}H_{12}Cl_2N_4$: C, 52.90; H, 4.10; Cl, 24.02; N, 18.98. Found: C, 52.60; H, 3.80; Cl, 23.62; N, 18.68.

3-Alkyl-2,4-dazido-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (4b,c)

General procedure. A mixture of dichloride **3b,c** (2 mmol) and sodium azide (0.26 g, 4 mmol) in 10 mL dry DMF was stirred at room temperature for 3 h. The reaction mixture was diluted with cold water with stirring for 0.5 h to crystallize the precipitate, which was collected by filtration and recrystallized from ethanol to afford **4b,c** in 66–77% yields.

2,4-Diazido-3,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (4b). Pale yellow powder, 0.41 g (77%); mp 160–163 °C; IR: N_3 2191, 2134 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.29$, 2.51, 2.58 (3s, 9H, 3 CH_3), 7.02 (s, 1H, H-9); MS (EI): m/z 294 (M^+, 100), 280 (22) 189 (60), 162 (15), 131 (18), 106 (12), 77 (40). Anal. calcd. for $C_{12}H_{10}N_{10}$: C, 48.98; H, 3.43; N, 47.60. Found: C, 48.68; H, 3.13; N, 47.90.

2,4-Diazido-3-ethyl-8,10-dimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin (4c). Pale yellow powder, 0.39 g (66%); mp 170–173 °C; IR: N_3 2194, 2135 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.21$ (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 2.61, 2.72 (2s, 6H, 2 CH_3), 2.82 (q, 2H, $J = 15.0$ Hz, CH_2CH_3), 7.02 (s, 1H, H-9); ms (EI): m/z 308 (M^+, 15), 280 (25), 252 (16), 224 (100), 175 (16), 77 (12). Anal. calcd. for $C_{13}H_{12}N_{10}$: C, 50.64; H, 3.92; N, 45.43. Found: C, 50.94; H, 3.52; N, 45.13.

3-{(2*Z*,2*E*)-2-[(4,6-Dimethyl-2*H*-pyrazolo[3,4-*b*]pyridin-3-yl)imino]propyl}dihydrofuran-2(3*H*)-one (5)

Acetic acid (2 mL) was added to a solution of **1** (1.62 g, 10 mmol) and α-acetyl-γ-butyrolactone (1.92 g, 15 mmol) in 20 mL absolute ethanol. The mixture was refluxed for 72 h. A pale yellow precipitate was collected and recrystallized from ethanol to give **5** (2.41 g, 85%), mp 210–212 °C; IR: NH 3291, OCO 1712 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.21, 2.49, 2.59 (3s, 9H, 3 CH_3), 2.88 (t, 2H, J = 8.0 Hz, OCH_2CH_2), 4.32 (t, 2H, J = 8.0 Hz, OCH_2CH_2), 6.81 (s, 1H, ArH), 10.35 (s, 1H, NH), 12.88 (s, 1H, NH); MS (EI): m/z 273 [10, $(M+H)^+$], 272 (M^+, 35), 243 (100), 189 (16), 175 (12), 77 (6). Anal. calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.45; H, 6.22; N, 20.18.

3-(2-Hydroxyethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-4-ol (6)

Method A. A mixture of **5** (2.69 g, 9.9 mmol) and 1.0 g of trimethylamine (9.9 mmol) in 5 mL H_2O was allowed to stand at room temperature for 18 h. The solution was neutralized with AcOH to give a crystalline product. Recrystallization from AcOH afforded **6** (2.52 g, 93%).

Method B. A mixture of 3-aminopyrazolopyridine **1** (3.24 g, 20 mmol) and the α-acetyl-γ-butyrolactone (2.56 g, 20 mmol) in 20 g of diphenyl ether was heated in an oil bath for 15 min to 220–225 °C using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was digested with diethyl ether, and the precipitate was filtered, washed with diethyl ether, and recrystallized from AcOH to afford the yellow crystal of **6** (2.53 g 98%).

Data. Mp 305–308 °C; IR: OH 3350–3210 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.46, 2.56 (2s, 6H, 2 CH_3), 2.77 (t, 2H, J = 7.2 Hz, $HOCH_2CH_2$), 2.80 (s, 3H, CH_3) 3.52 (t, 2H, J = 7.2 Hz, $HOCH_2CH_2$), 4.61 (bs, 1H, $HOCH_2CH_2$), 6.76 (s, 1H, H-8), 11.66 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.08, 21.73, 21.88 (3 CH_3), 30.88 (CH_2CH_2OH), 60.46 (CH_2CH_2OH), 107.13, 114.31, 121.45, 130.74, 144.13, 147.32, 155.92, 163.13, 172.74 (ArC); MS (EI): m/z 273 [14, $(M+H)^+$], 272 (M^+, 11), 243 (57), 142 (33), 241 (100), 187 (44), 147 (12), 78 (23). Anal. calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.24; H, 5.62; N, 20.18.

4-Chloro-3-(2-chloroethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (7)

A mixture of **6** (8.16 g, 20 mmol) and 20 mL of $POCl_3$ was refluxed for 3 h with stirring. After cooling, the mixture was poured into ice-water, and a crystalline solid was collected by filtration. The product was recrystallized from ethanol with charcoal to give colorless **7** (8.15 g, 88%). Mp 179–182 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.62, 2.80, 2.83 (3s, 9H, 3 CH_3), 3.44 (t, 2H, J = 7.2 Hz, $ClCH_2CH_2$), 3.96 (t, 2H, J = 7.2 Hz, $ClCH_2CH_2$), 7.03 (s, 1H, H-9); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 19.65, 25.19, 26.80 (3 CH_3), 33.31, 43.81 (CH_2CH_2), 105.18, 119.62, 121.84, 138.24, 143.44, 145.44, 158.21, 161.43, 164.70 (ArC); MS (EI): m/z

309 (M^+, 13), 308 (M^{+-1}, 72), 259 (100), 141 (11), 105 (35), 77 (72), 67 (16). Anal. calcd. for $C_{14}H_{14}Cl_2N_4$: C, 54.38; H, 4.56; Cl, 22.93; N, 18.12. Found: C, 53.90; H, 4.26; Cl, 23.33; N, 17.82.

4-Azido-3-(2-azidoethyl)-2,8,10-trimethylpyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidine (8)

A mixture of dichloride **7** (1.24 g, 4 mmol) and sodium azide (0.52 g, 8 mmol) in 20 mL dry DMF was stirred at room temperature for 4 h. The reaction mixture was diluted with cold water with stirring for 0.5 h to crystallize the precipitate, which was collected by filtration and recrystallized from ethanol to afford **8** (1.20 g, 93%). Mp 322–323 °C; IR: N_3 2139, 2115 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.96$ (t, 2H, $J = 7.2$ Hz, $N_3CH_2CH_2$), 2.30, 2.49, 2.63 (3s, 9H, 3 CH_3), 2.85 (t, 2H, $J = 7.2$ Hz, $N_3CH_2CH_2$), 6.09 (s, 1H, H-9); MS (EI): m/z 323 [21, $(M + H)^+$], 322 (M^+, 1), 288 (15), 252 (37), 251 (100), 240 (53). Anal. calcd. for $C_{14}H_{14}N_{10}$: C, 52.17; H, 4.38; N, 43.45. Found: C, 51.77; H, 4.08; N, 43.05.

1-Phenyl-1,2,3,4-tetrahydro-5,7,9-trimethylpyridazino[2,3-*e*]pyrido [2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (9)

A mixture of **8** (0.32 g, 1 mmol), phenyl hydrazine (0.22 g, 2 mmol), and Na_2CO_3 (0.40 g, 4 mmol) in 20 mL ethanol was refluxed for 6 h and concentrated in vacuo. The residue was dissolved in H_2O, and the crystalline product was collected by filtration and recrystallized from ethanol to give the yellow crystal of **9** (0.29 g, 88%). Mp 75–78 °C; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.46$, 2.58 (2s, 6H, 2 CH_3), 2.69 (t, 2H, $J = 7.2$ Hz, NCH_2CH_2), 2.81 (s, 3H, CH_3), 3.89 (t, 2H, $J = 7.2$ Hz, NCH_2CH_2), 6.85 (s, 1H, H-8), 6.88–7.29 (m, 5H, Ph), 10.64 (s, 1H, NH); MS (EI): m/z 344 (M^+, 13), 258 (100), 143 (11), 105 (35), 77 (27), 67 (8). Anal. calcd. for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.45; H, 5.55; N, 42.10.

2,3-Dihydro-4,6,8-trimethylthieno[2,3-*d*]pyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidine (10)

A mixture of **8** (0.32 g, 1 mmol) and thiourea (0.08 g, 1.3 mmol) in 15 mL ethanol was refluxed for 2 h and concentrated in vacuo. Ten mL of K_2CO_3 (3 N) was added to the residue, and the resulting mixture was extracted with $CHCl_3$. The extract was evaporated, and the residue was recrystallized from ethanol to give pale yellow crystals of **9**, 0.22 g (85%). Mp 240–243 °C; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.62$, 2.76, 2.94 (3s, 9H, 3 CH_3), 3.64 (t, 2H, $J = 8.3$ Hz, OCH_2CH_2), 3.65 (t, 2H, $J = 8.3$ Hz, OCH_2CH_2), 7.75 (s, 1H, H-7); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 20.08, 21.92, 24.25 (3 CH_3), 33.40, 34.69 (OCH_2CH_2), 108.27, 110.91, 118.05, 128.26, 144.73, 152.44, 153.41, 156.33, 158.02 (ArC); MS (EI): m/z 270 (M^+, 13), 239 (100), 212 (11), 105 (40), 77 (25), 77 (8). Anal. calcd. for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.22; N, 20.72; S, 11.86. Found: C, 62.50; H, 5.52; N, 21.21; S, 11.46.

N-Alkyl/aralkyl-2,3-dihydro-4,6,8-trimethylpyrrolo[3,2-*d*]pyrido [2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines (11a–d)

General procedure. A mixture of **8** (3.20 g, 9.95 mmol), appropriate primary amine (13.7 mmol), and 3 mL of triethylamine (21.5 mmol) in 15 mL ethanol was refluxed for 2–6 h, cooled, and filtered. The filtrate was concentrated in vacuo to give a solid, which was recrystallized from ethanol to give **11a–d** in 78–91% yields.

2,3-Dihydro-1,4,6,8-tetramethyl-1*H*-pyrrolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (11a). Pale yellow powder, 2.20 g (83%); mp 255–257 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28, 2.48, 2.73 (3s, 9H, 3 CH_3), 3.19 (t, 2H, J = 9.0 Hz, $CH_3NCH_2CH_2$), 3.63 (s, 3H, NCH_3), 3.75 (t, 2H, J = 9.0 Hz, $CH_3NCH_2CH_2$), 6.68 (s, 1H, H-7); MS (EI): m/z 268 [17, $(M+H)^+$], 267 (M^+, 100), 266 (69), 252 (11), 239 (14), 133 (6). Anal. calcd. for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.09; H, 6.71; N, 25.90.

2-(2,3-Drihydro-4,6,8-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-1-yl)ethanol (11b). Pale yellow crystal, 2.30 g (78%); mp 243–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.43, 2.64, 2.84 (3s, 9H, 3 CH_3), 3.18 (t, 2H, J = 9.0 Hz, NCH_2CH_2), 3.93–4.00 (m, 4H, 2 CH_2), 4.21 (s, 1H, OH), 4.42 (t, 2H, J = 5.0 Hz, OCH_2CH_2), 6.67 (s, 1H, H-3); ^{13}C NMR (DMSO-d_6): δ 18.62, 21.64, 24.83 (3 CH_3), 25.24, 49.32, 51.77, 59.67 (4 CH_2), 102.60, 107.91, 115.84, 146.04, 146.53, 149.02, 151.90, 160.85, 162.57 (ArC); MS (EI): m/z 298 [12, $(M+H)^+$], 297 (M^+, 100), 268 (33), 251 (44), 239 (12), 133 (6), 77 (8). Anal. calcd. for $C_{16}H_{19}N_5O$: C, 64.63; H, 6.44; N, 23.55. Found: C, 64.33; H, 6.74; N, 23.85.

2,3-Dihydro-1-phenyl-4,6,8-tetramethyl-1*H*-pyrrolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (11c). Yellow crystal, mp 277–280 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.44, 2.49, 2.66 (3s, 9H, 3 CH_3), 3.20 (t, 2H, J = 9.0 Hz, $PhNCH_2CH_2$), 3.82 (t, 2H, J = 9.0 Hz, $PhNCH_2CH_2$), 6.90 (s, 1H, H-7), 6.93–7.33 (m, 5H, Ph); MS (EI): m/z 330 [30, $(M+H)^+$], 329 (M^+, 100), 266 (44), 253 (31), 243 (9), 132 (15), 77 (11). Anal. calcd. for $C_{20}H_{19}N_5$: C, 72.43; H, 5.05; N, 21.26. Found: C, 72.13; H, 5.35; N, 21.96.

1-Benzyl-2,3-dihydro-4,6,8-tetramethyl-1*H*-pyrrolo[3,2-*d*]pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (11d). Pale yellow crystal, 3.10 g (90%); mp 229–231 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.39, 2.49, 2.52 (3s, 9H, 3 CH_3), 3.15 (t, 2H, J = 9.0 Hz, NCH_2CH_2), 3.74 (t, 2H, J = 9.0 Hz, NCH_2CH_2), 5.56 (s, 2H, $PhCH_2N$), 6.74 (s, 1H, H-7), 7.28–7.36 (m, 5H, Ph); MS (EI): m/z 344 [15, $(M+H)^+$], 343 (M^+, 100), 266 (30), 253 (50), 242 (12), 133 (19), 77 (8). Anal. calcd. for $C_{21}H_{21}N_5$: C, 73.44; H, 6.16; N, 20.39. Found: C, 73.74; H, 5.86; N, 19.69.

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