Synthesis of pyrazolo[3,4-*b*]pyridine and pyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidine derivatives

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The synthesis of two series of 1-phenyl and 1*H*-pyrazolo[3,4-*b*]pyridine is described. Thus, reacting 5-amino-1-phenylpyrazole with chalcone analogues gave 4,6-diarylpyrazolo[3,4-*b*]pyridine derivatives. While, reacting the same starting material with benzylidene derivatives of ethyl cyanoacetate and malononitrile resulted in 4-oxo and 4-aminopyrazolo[3,4-*b*]pyridine derivatives, respectively. The synthesis of 3-amino-4,6-diarylpyrazolo[3,4-*b*]pyridines starting from pyridine was also described. Thus, chlorination of 4,6-diarylpyridone derivatives and their subsequent cyclisation with hydrazine hydrate afforded 3-amino-4,6-diarylpyrazolo[3,4-*b*]pyridines. Reaction of the latter compounds with acetylacetone, ethyl ethoxymethylenecyanoacetate and chalcone analogue gave the tricyclic pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines. The structures of the products were confirmed by spectral data.

Keywords: pyrazolo[3,4-*b*]pyridine, pyrido[2′,3′: 3,4]pyrazolo[1,5-*a*]pyrimidine

Pyrazoles fused with pyridine and/or pyrimidine are associated with a wide range of biological activities. Derivatives of pyrazolo[3,4-*b*]pyridines exhibited anxiolytic,[1] antimicrobial[2–5] as well as cytotoxic[6] effects. Recently, many pyrazolo[3,4-*b*]pyridine derivatives were reported to have strong and selective inhibitory effect on many kinase enzymes such as glycogen synthase kinase GSK-3,[7–9] cyclin dependent kinase CDK[10–12] and protein kinase enzyme.[13] Whereas, pyrazolo[1,5-*a*]pyrimidine derivatives exhibited CNS depressent activity[14,15] and cytotoxic activity.[16,17] The combination of pyridine, pyrazole and pyrimidine ring systems to give the tricyclic pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines and the subsequent influence on biological activity is of current interest.[18–20] Some derivatives of pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine were reported to have cytotoxic activity.[6]

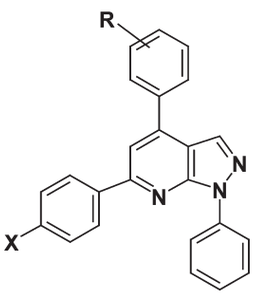
In the light of these findings, We aimed to synthesise new pyrazolo[3,4-*b*]pyridine derivatives starting from pyrazole or pyridine ring systems to be used as antimicrobial agents. We report also the synthesis of new pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines starting from 3-amino-1*H*-pyrazolo[3,4-*b*]pyridines to test them as antimicrobial agents as well.

Results and discussion

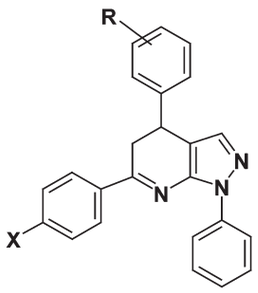
The synthesis of the new compounds is shown in Schemes 1 and 2. Scheme 1 describes the synthesis of 1-phenylpyrazolo[3,4-*b*]pyridines starting from 5-amino-1-phenylpyrazole (**1**).

The reaction of 5-amino-1-arylpyrazoles with chalcone analogues in acetic acid containing few drops of conc. H_2SO_4 was reported by Joshi *et al*.[21] The products obtained were 4,6-diarylpyrazolo[3,4-*b*]pyridines. A similar reaction was reported by Orlov and coworkers.[22] The reaction was carried out in DMF and the products obtained were noted as 4,5-dihydropyrazolo[3,4-*b*]pyridines which upon oxidation with NBS yielded the corresponding pyrazolo[3,4-*b*]pyridines.

In this work, 5-amino-1-phenylpyrazole (**1**) was reacted with chalcone analogues **2a** and **2b** in DMF for 10 h to give 4,6-diaryl-1-phenylpyrazolo[3,4-*b*]pyridines **3a,b.** The possibility of formation of 4,5-dihydropyrazolo[3,4-*b*]pyridines **3*** as was suggested by Orlov *et al*.[22] was ruled out depending on the elemental analyses and spectral data. The ^{1}H NMR spectra of **3a** and **3b** lacked any signal in the aliphatic proton region and only aromatic protons appeared around δ 7.26–8.66 ppm. Meanwhile, the mass spectrum of compound **3b** displayed molecular ion peaks M and M+2 at *m/z* 470 and 472 in the ratio of 1:1 (Br pattern). The formation of **3a,b** and not **3*** may be attributed to the longer time of reflux (10 h).



3 a,b



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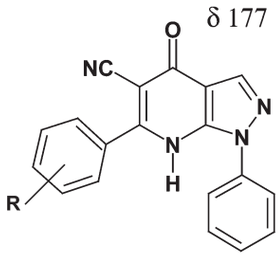
Reacting equimolar amounts of 5-amino-1-phenylpyrazole (**1**) with ethyl substituted benzylidenecyanoacetate **4a,b** in ethanol and triethylamine afforded one of two possible products, either 4-oxo-6-(substituted phenyl)pyrazolo[3,4-*b*]pyridine-5-carbonitriles **5a,b** or 6-oxo-4-(substituted phenyl)pyrazolo[3,4-*b*]pyridine-5-carbonitriles **5*.** The assignment of the products as **5a** and **5b** rather than the isomeric **5*** depends on ^{13}C NMR spectra study. Literature data indicated that the carbonyl carbon appeared around δ 177 ppm in ^{13}C NMR spectrum of pyrazolo[3,4-*b*]pyridin-4-one; while, that of the 6-one isomer appeared around δ 162 ppm.[23–25] Since the observed carbonyl carbon chemical shift of **5a** and **5b** appeared at δ 177 ppm, then the product might be **5a,b** and not **5*.**



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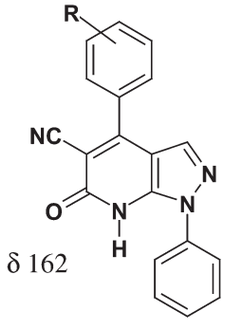

5*

On the other hand, the synthesis of the 4-amino-6-(3-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine-5-carbonitrile (**7**) was fulfilled by reacting 5-amino-1-phenylpyrazole (**1**) with arylidenemalononitriles **6** in ethanol and triethylamine.

Scheme 2 describes the synthesis of 1-*H*-pyrazolo[3,4-*b*]pyridines starting from 2-chloro-4,6-diarylpyridine-3-carbonitrile **9a–c**.

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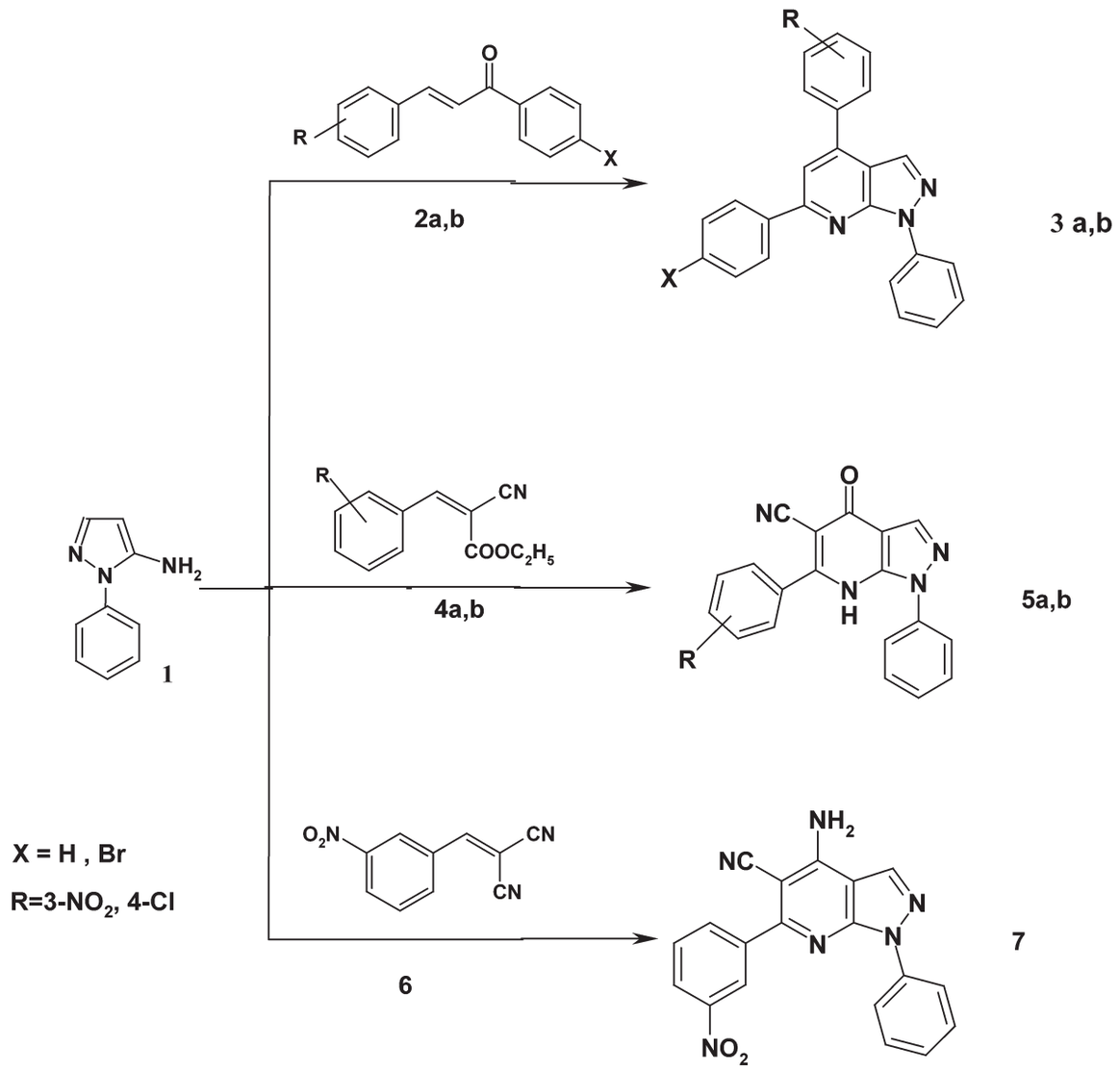


Scheme 1

4-Aryl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitriles **8a–c** were synthesised *via* the reaction of the respective chalcone analogue with ethyl cyanoacetate and ammonium acetate in *n*-butanol. Chlorination of compounds **8a–c** was achieved using a mixture of $POCl_3$/N,N-dimethylaniline to give the desired compounds in good yield (74–80%). Reacting 2-chloropyridines **9a,b** with piperidine or morpholine in ethanol containing triethylamine resulted in 2-substituted pyridines **10a,b**.

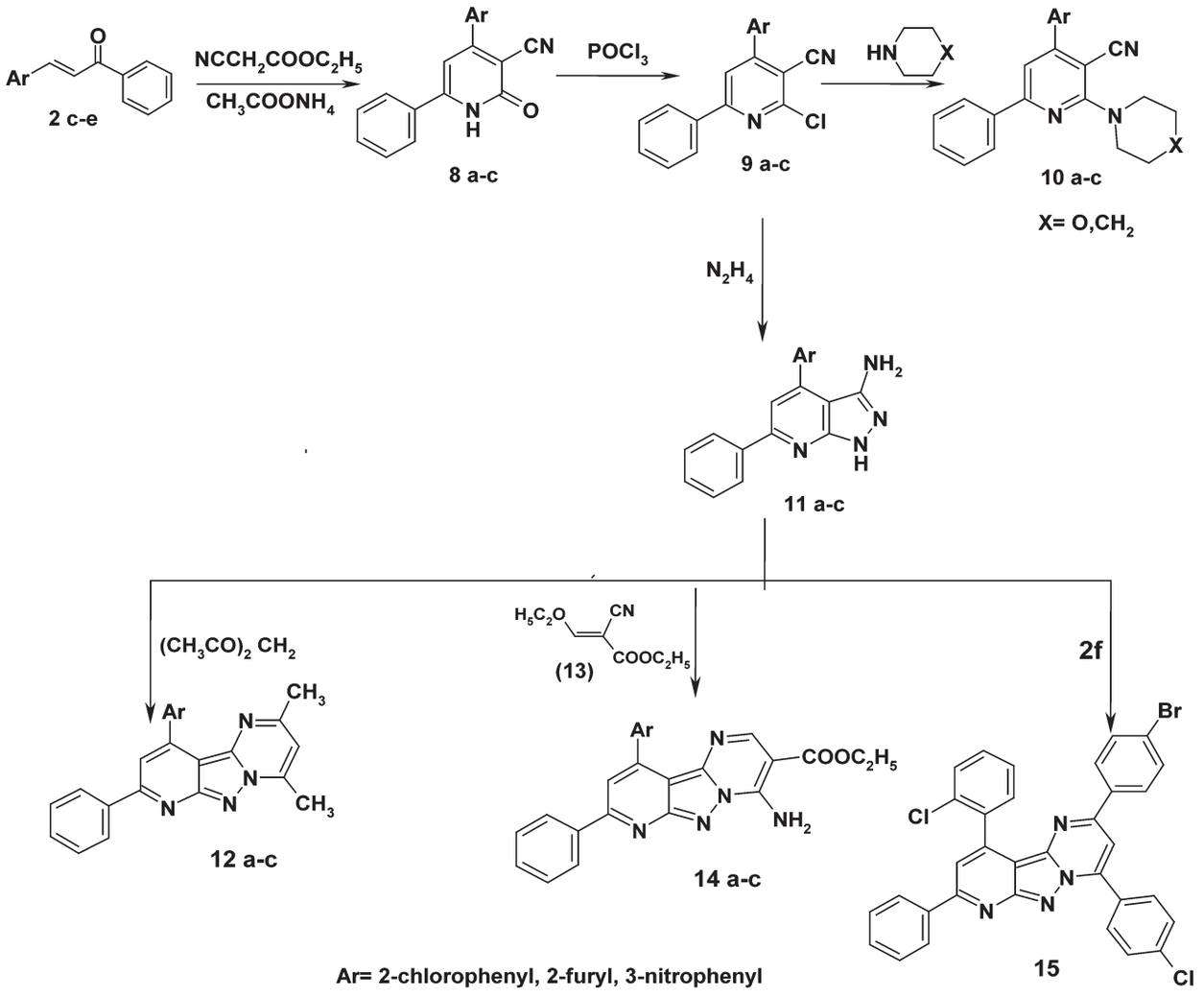
Cyclocondensation reaction of 2-chloropyridine-3-carbonitriles **9a–c** with hydrazine hydrate in ethanol was applied to obtain 3-amino-1*H*-pyrazolo[3,4-*b*]pyridines **11a–c**. Cyclisation of 3-amino-1*H*-pyrazolo[3,4-*b*]pyridines **11a–c** with acetylacetone or ethyl ethoxymethylenecyanoacetate (**13**) in acetic acid afforded the corresponding tricyclic pyrido [2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines **12a–c** and **14a–c**, respectively. Compounds **14a,b** did not dissolve in the common NMR solvents.

Finally, compound **11a** was reacted with chalcone analogue **2f** in DMF to afford 2-(4-bromophenyl)-4-(4′-chlorophenyl)-10-(2′-chlorophenyl)-8-phenylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine (**15**). The ^{1}H NMR spectrum of the product demonstrated aromatic protons at δ 7.50–8.64 ppm. Moreover, the mass spectrum of the product displayed molecular ion peaks at *m/z* 620(M), 622(M+2) and 624(M+4) in the ratio of 100:164.4:82.4 (as reported for compounds containing two chlorine atoms and one bromine atom).[26]

Compounds **11c**, **12c** and **14c** were tested for their antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis*, *Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans using* Agar plate diffusion technique. None of the tested compounds showed antimicrobial activity.

Experimental

Melting points were determined on a Griffin apparatus and were uncorrected. IR spectra were determined as KBr discs on Shimadzu IR 435 spectrophotometer and values were represented in cm^{-1}. The ^{1}H NMR and ^{13}C NMR were carried out on Varian Gemini 200 MHz spectrophotometer, Microanalytical Centre, Cairo University, Cairo, Egypt, using TMS as an internal standard and chemical shifts were recorded in ppm on δ scale. Mass spectra were run on Hewlett Packard 5988 spectrometer, Microanalytical Centre, Cairo University, Cairo, Egypt. Elemental analyses were carried out at the Microanalytical Centre, Cairo University, Cairo, Egypt, and at the Microanalytical laboratory, National Research Center, Cairo, Egypt. Progress of the reactions was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel Merck 60 F254 that were visualised using UV



Scheme 2

lamp and iodine vapour. The solvent system used in TLC was benzene:methanol:chloroform [9:3:1.5].

5-Amino-1-phenylpyrazole (**1**)[27], chalcone analogues **2a–f**[28–32], arylidenecyanoacetate ester **4a,b**[33], substituted benzylidenemalononitrile **6**[33] and pyridone derivatives **8a–c**[34–36] were prepared according to the literature.

*Synthesis of 4,6-diaryl-1-phenylpyrazolo[3,4-*b*]pyridines* **3a,b**

A mixture of 5-amino-1-phenylpyrazole (**1**) (0.0025 mol) and the chalcone analogue (**2a** or **2b**) (0.0025 mol) in DMF (3 mL) was heated under reflux for 10 h. The solvent was evaporated under reduced pressure, and the residue left was triturated with ethanol, filtered, dried and crystallised from the suitable solvent.

*4-(4-Chlorophenyl)-1,6-diphenylpyrazolo[3,4-*b*]pyridine* (**3a**): Crystallised from acetic acid; yield: 52%; m.p. 198–199 °C; IR (cm^{-1}): 1600 (C=N); ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 7.26–8.46 (m, aromatic protons). Anal. Calcd for $C_{24}H_{16}ClN_3$: C, 75.49; H, 4.22; N, 11.00. Found: C, 75.03; H, 4.24; N, 11.41%.

*6-(4-Bromophenyl)-4-(3-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine* (**3b**): Crystallised from DMF; yield: 68%; m.p. 210–211 °C; IR (cm^{-1}): 1600 (C=N), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 7.26–8.66 (m, aromatic protons); MS *m/z*: 472 [(M+2)$^+$, 29.74%], 470 [M$^+$, 31.03%]. Anal. Calcd for $C_{24}H_{15}BrN_4O_2$: C, 61.16; H, 3.20; N, 11.88. Found: C, 61.20; H, 3.28; N, 11.97%.

*Synthesis of 4-oxo-1-phenyl-6-(substituted phenyl)-7H-pyrazolo [3,4-*b*]pyridine-5-carbonitriles* **5a,b** *and 4-Amino-6-(3-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine-5-carbonitrile* (**7**): A solution of 5-amino-1-phenylpyrazole (**1**) (0.0015 mol), the appropriate arylidenecyanoacetate ester **4a,b** or substituted benzylidenemalononitrile **6** (0.0015 mol) and triethylamine (1 mL) in absolute ethanol (10 mL) was heated under reflux for 4 h. The reaction mixture was cooled and acidified to litmus paper with drops of conc. HCl. The obtained solid was filtered, dried and crystallised from the suitable solvent.

*6-(3-Nitrophenyl)-4-oxo-1-phenyl-7H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile* (**5a**): Crystallised from acetic acid; yield: 67%; m.p. 330–331 °C; IR (cm^{-1}): 3300 (NH), 2200 (CN), 1650 (CO), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.42–8.59 (m, 10 H, aromatic protons), 13.2 (br s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (200 MHz, DMSO-d_6) δ ppm 92.6 (C-5), 112.3 (C-3_a), 117.4 (C-3), 123.4 (CN), 151.3 (C-6), 166.0 (C-7_a), 177.3 (C-4), 125.7, 126.8, 128.7, 131.0, 132.6, 136.5, 137.0, 139.9, 149.8, 150.3 (aromatic carbons); MS *m/z*: 357 [M$^+$, 100%]. Anal. Calcd for $C_{19}H_{11}N_5O_3$: C, 63.86; H, 3.10; N, 19.60. Found: C, 63.58; H, 3.51; N, 19.68.

*6-(4-Chlorophenyl)-4-oxo-1-phenyl-7H-pyrazolo[3,4-*b*]pyridine-5-carbonitrile* (**5b**): Crystallised from ethanol; yield: 62%; m.p. 268–269 °C; IR (cm^{-1}): 3417 (NH), 2200 (CN), 1645 (CO); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.35–8.27 (m, 10 H, aromatic protons), 13.2 (br s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (200 MHz, DMSO-d_6) δ ppm 92.2 (C-5), 112.4 (C-3_a), 118.0 (C-3), 123.4 (CN), 151.2 (C-6), 166.0 (C-7_a), 179.0 (C-4), 128.6, 130.9, 132.7, 133.9, 137.1, 137.3, 139.9, 140.0, 150.0, 150.2 (aromatic carbons). Anal. Calcd for $C_{19}H_{11}ClN_4O$: C, 65.81; H, 3.19; N, 16.15. Found: C, 65.61; H, 3.49; N, 16.35%.

*4-Amino-6-(3-nitrophenyl)-1-phenylpyrazolo[3,4-*b*]pyridine-5-carbonitrile* (**7**): Crystallised from acetic acid; yield: 53%; m.p. 252–253 °C; IR (cm^{-1}): 3500, 3300 (NH_2), 2200 (CN), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.37–8.56 (m, 10H, aromatic protons), 8.57 (br s, 2 H, NH_2, D_2O exchangeable); MS *m/z*: 356 [M^+, 100%]. Anal. Calcd for $C_{19}H_{12}N_6O_2$: C, 64.04; H, 3.39; N, 23.58. Found: C, 63.97; H, 3.39; N, 23.22%.

Synthesis of 4-Aryl-2-chloro-6-phenylpyridine-3-carbonitriles **9a–c**: A mixture of the respective 3,4,6-trisubstituted pyridones **8a–c** (0.0075 mol), N,N-dimethylaniline (10 mL) and phosphorus oxychloride (10 mL) was heated under reflux for 10 h. The reaction mixture was cooled, poured gradually into crushed ice. The resulting product was filtered, washed with water, and crystallised from the suitable solvent.

*2-Chloro-4-(2-chlorophenyl)-6-phenylpyridine-3-carbonitrile (***9a**): Crystallised from ethanol; yield: 78%; m.p. 194–195 °C; IR (cm^{-1}): 2200 (CN); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.05–7.89 (m, 10H, aromatic protons); MS *m/z*: 328 [(M+4)$^+$, 11.88%], 326 [(M+2)$^+$, 69.26%], 324 [M^+, 100%]. Anal. Calcd for $C_{18}H_{10}Cl_2N_2$: C, 66.48; H, 3.09; Cl, 21.80. Found: C, 66.19; H, 2.95; Cl, 21.63%.

2-Chloro-4-(2-furyl)-6-phenylpyridine-3-carbonitrile (**9b**): Crystallised from ethanol; yield: 80%; m.p. 150–151 °C; IR (cm^{-1}): 2200 (CN); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 6.92 (m, 1H, 4-H of furyl, J_{AX}=1.8 Hz, J_{MX}=3.6 Hz), 7.62–8.43 (m, 8H, aromatic protons); Anal. Calcd for $C_{16}H_9ClN_2O$: C, 68.46; H, 3.23; Cl, 12.62. Found: C, 68.13; H, 3.02; Cl, 12.50%.

2-Chloro-4-(3-nitrophenyl)-6-phenylpyridine-3-carbonitrile (**9c**): Crystallised from toluene; yield: 74%; m.p. 182–183 °C; IR (cm^{-1}): 2200 (CN), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.26–8.39 (m, 10H, aromatic protons); MS *m/z*: 337 [(M+2)$^+$, 36.11%], 335 [M^+, 100%]. Anal. Calcd for $C_{18}H_{10}ClN_3O_2$: C, 64.39; H, 3.00; Cl, 10.56. Found: C, 64.86; H, 3.06; Cl, 10.97.

Synthesis of 4-Aryl-2-piperidino (or morpholino)-6-phenylpyridine-3-carbonitriles **10a,b**: A mixture of 4-aryl-2-chloro-6-phenylpyridine-3-carbonitriles **9a,b** (0.002 mol), the appropriate secondary amine (0.002 mol) and triethylamine (0.002 mol) in 95% ethanol (10 mL) was heated under reflux for 12 h. The solvent was evaporated under vacuum, and the residue left was filtered, dried and crystallised from ethanol.

4-(2-Chlorophenyl)-2-piperidino-6-phenylpyridine-3-carbonitrile (**10a**): Yield: 64%; m.p. 160–161 °C; IR (cm^{-1}): 2200 (CN); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 1.69 (s, 6H, CH_2), 3.73 (s, 4H, N-CH_2), 7.48–8.22 (m, 10H, aromatic protons). Anal. Calcd for $C_{23}H_{20}ClN_3$: C, 73.88; H, 5.39; N, 11.23. Found: C, 73.77; H, 5.40; N, 10.78%.

4-(2-Furyl)-2-morpholino-6-phenylpyridine-3-carbonitrile (**10b**): Yield: 67%; m.p. 118–119 °C; IR (cm^{-1}): 2200 (CN); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 3.67 (s, 4 H, CH_2N), 3.81 (s, 4H, CH_2O), 6.83 (d, 1H, 4-H of furyl), 7.54–8.21 (m, 8H, aromatic protons). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.39; H, 5.20; N, 12.39%.

*Synthesis of 3-amino-4-aryl-6-phenyl-1H-pyrazolo[3,4-*b*]pyridines* **11a–c**

A mixture of 4-aryl-2-chloro-6-phenylpyridine-3-carbonitriles **9a–c** (0.005 mol), hydrazine hydrate (99%, 2 mL, 0.04 mol) and absolute ethanol (20 mL) was heated under reflux for 20 h. The solvent was evaporated under vacuum, and the residue was filtered, dried and crystallised from the suitable solvent.

*3-Amino-4-(2-chlorophenyl)-6-phenyl-1H-pyrazolo[3,4-*b*]pyridine* (**11a**): Crystallised from ethanol; yield: 89%; m.p. 224–225 °C; IR (cm^{-1}): 3400, 3300, 3200 (NH/NH_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 5.53 (s, 2H, NH_2, D_2O exchangeable), 7.06–7.80 (m, 10H, aromatic protons), 12.23 (s, 1H, NH, D_2O exchangeable); MS *m/z*: 322 [(M+2)$^+$, 34.80%], 320 [M^+, 100%]. Anal. Calcd for $C_{18}H_{13}ClN_4$: C, 67.39; H, 4.08; N, 17.46. Found: C, 67.29; H, 4.39; N, 17.62%.

*3-Amino-4-(2-furyl)-6-phenyl-1H-pyrazolo[3,4-*b*]pyridine* (**11b**): Crystallised from dichloromethane; yield: 80%; m.p. 244–245 °C; IR (cm^{-1}): 3400, 3300, 3200 (NH/NH_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 5.45 (s, 2H, NH_2, D_2O exchangeable), 6.75 (dd, 1H ,4-H of furyl, J_{AX}=1.8 Hz, J_{MX}=3.5 Hz), 7.48–8.23 (m, 8H, aromatic protons), 12.32 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.37; N, 20.27. Found: C, 69.57; H, 4.80; N, 20.20%.

*3-Amino-4-(3-nitrophenyl)-6-phenyl-1H-pyrazolo[3,4-*b*]pyridine* (**11c**): Crystallised from toluene; yield: 60%; m.p. 216–217 °C; IR (cm^{-1}): 3400, 3300, 3200 (NH/NH_2), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 5.41 (s, 2H, NH_2, D_2O exchangeable), 7.24–7.89 (m, 10H, aromatic protons), 12.35 (s, 1H, NH, D_2O exchangeable); MS *m/z*: 331 [M^+, 100%]. Anal. Calcd for $C_{18}H_{13}N_5O_2$: C, 65.*25; H, 3.95; N, 21.13. Found: C, 65.16; H, 4.23; N, 20.81%.*

*Synthesis of 10-aryl-2,4-dimethyl-8-phenylpyrido[2′,3′:3,4]pyrazolo [1,5-*a*]pyrimidines* **12a–c** *and ethyl 4-amino-10-aryl-8-phenylpyrido [2′,3′:3,4]pyrazolo[1,5-*a*] pyrimidine -3-carboxylates* **14a–c**

A mixture of 3-amino-4-aryl-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines **11a–c** (0.002 mol), acetylacetone or ethyl ethoxymethylenecyanoacetate (**13**) (0.002 mol) and glacial acetic acid (10 mL) was heated under reflux for 12 h. The reaction mixture was cooled and poured into an ice-water mixture. The solid separated was filtered, dried and crystallised from the suitable solvent.

*10-(2-Chlorophenyl)-2,4-dimethyl-8-phenylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine* (**12a**): Crystallised from ethanol; yield: 75%; m.p. 214–215 °C; IR (cm^{-1}): 1610 (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 2.47 (s, 3H, 2-CH_3), 2.90 (s, 3H, 4-CH_3), 7.41–8.36 (m, 11H, aromatic protons). Anal. Calcd for $C_{23}H_{17}ClN_4$: C, 71.77; H, 4.45; N, 14.55. Found: C, 72.00; H, 4.20; N, 14.26%.

*2,4-Dimethyl-10-(2-furyl)-8-phenylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*] pyrimidine* (**12b**): Crystallised from ethanol; yield: 76%; m.p. 226–227 °C; IR (cm^{-1}): 1610 (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 2.68 (s, 3H, 2-CH_3), 2.92 (s, 3H, 4-CH_3), 6.65 (dd, 1H, 4-H of furyl, J_{AX} = 1.73 Hz, J_{MX} = 3.51 Hz), 6.93–8.88 (m, 9H, aromatic protons); MS *m/z*: 340 [M^+, 10.49%]. Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.73; N, 16.45. Found: C, 74.15; H, 4.53; N, 16.02%.

2,4-Dimethyl-10-(3-nitrophenyl)-8-phenylpyrido[2′,3′:3,4]pyrazolo [1,5-a] pyrimidine (**12c**): Crystallised from ethanol; yield: 70%; m.p. 202–203 °C; IR (cm^{-1}): 1620 (C=N), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 2.46 (s, 3H, 2-CH_3), 2.94 (s, 3H, 4-CH_3), 7.27–8.28 (m, 11H, aromatic protons); MS *m/z*: 395 [M^+, 100%]. Anal. Calcd for $C_{23}H_{17}N_5O_2$: C, 69.86; H, 4.33; N, 17.71. Found: C, 69.98; H, 4.30; N, 17.22%.

*Ethyl 4-amino-10-(2-chlorophenyl)-8-phenylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*] pyrimidine-3-carboxylate* (**14a**): Crystallised from DMF; yield: 62%; m.p. 326–327 °C; IR (cm^{-1}): 3400, 3200 (NH_2), 1700 (CO); MS *m/z*: 445 [(M+2)$^+$, 38.26%], 443 [M^+, 100%]. Anal. Calcd for $C_{24}H_{18}ClN_5O_2$: C, 64.94; H, 4.08; N, 15.77. Found: C, 65.09; H, 4.20; N, 16.09%.

Ethyl 4-amino-10-(2-furyl)-8-phenylpyrido[2′,3′:3,4]pyrazolo[1,5-a] pyrimidine-3-carboxylate (**14b**): Crystallised from DMF; yield: 60%; m.p. 340–341 °C; IR (cm^{-1}): 3400, 3250 (NH_2), 1700 (CO); MS *m/z*: 399 [M^+, 100%]. Anal. Calcd for $C_{22}H_{17}N_5O_3$: C, 66.15; H, 4.29; N, 17.53. Found: C, 66.50; H, 4.40; N, 17.13%.

Ethyl 4-amino-10-(3-nitrophenyl)-8-phenylpyrido[2′,3′:3,4]pyrazolo [1,5-a] pyrimidine-3-carboxylate (**14c**): Crystallised from DMF; yield: 75%; m.p. 338–339 °C; IR (cm^{-1}): 3400, 3200 (NH_2), 1700 (CO), 1530, 1350 (NO_2); ^{1}H NMR (200 MHz, DMSO-d_6/CF_3COOH) δ ppm 0.75 (t, 3H, CH_3), 3.84 (q, 2H, CH_2), 7.04–8.55 (m, 10H, aromatic protons), 7.72 (s, 1H, NH, D_2O exchangeable), 8.1 (s, 1H, NH, D_2O exchangeable), 8.8 (s, 1H, N=CH); MS *m/z*: 454 [M^+, 100%]. Anal. Calcd for $C_{24}H_{18}N_6O_4$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.53; H, 4.08; N, 18.38%.

2-(4-Bromophenyl)-4-(4′-chlorophenyl)-10-(2′-chlorophenyl)-8-phenylpyrido[2′,3′: 3,4]pyrazolo[1,5-a]pyrimidine (**15**): A mixture of 3-amino-4-(2-chlorophenyl)-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**11a**) (0.64 g, 0.002 mol) and chalcone analogue **2f** (0.64 g, 0.002 mol) in DMF (10 mL) was heated under reflux for 15 h. The solvent was evaporated under vacuum, and the residue was triturated with ethanol, filtered, dried and crystallised from toluene. Yield: 84%; m.p. 195–196 °C; IR (cm^{-1}) :1655 (C=N); ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.50–8.46 (m, aromatic protons); MS *m/z*: 624 [(M+4)$^+$, 50.10%], 622 [(M+2)$^+$, 100%], 620 [M^+, 60.74%]. Anal. Calcd for $C_{33}H_{19}BrCl_2N_4$: C, 63.68; H, 3.08; N, 9.00. Found: 63.45; H, 3.37; N, 9.20%.

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