3-Formylchromones, Acylpyruvates, and Chalcone as Valuable Substrates for the Syntheses of Fused Pyridines

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Abstract: The reaction of electron-rich aminoheterocycles with 1,3-CCC-dielectrophiles, such as 3-formylchromones, acylpyruvates, and chalcone, provided diversely fused pyridines. Starting from 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazole, nucleosides containing a pyrazolo[3,4-*b*]pyridine fragment were obtained, which can be considered as adenosine deaminase (ADA) inhibitors.

Key words: aminoheterocycles, 3-formylchromones, acylpyruvates, chalcone, fused pyridines, annulation reaction, nucleosides

Fused pyridines including 1-desazapurines and their analogues are important and interesting objectives for modern medical chemistry.[1] Our interest in pyridine and pyrimidine heterocycles containing imidazole, pyrazole, and thiazole rings is mainly as a result of the known biological activity of these systems reported in the literature. Thus, pyrazolo[3,4-*b*]pyridine derivatives have been reported to be a new class of cdk2 inhibitor[2] and potent and selective cyclin-dependent kinase and glycogen synthase kinase-3 (GSK-3) inhibitors.[3] Pyrazolo[3,4-*b*]pyridines are also reported to possess antimicrobial,[4] antichagasic,[5] antileishmanial, and anti-inflammatory activity.[6]

On the other hand, reactions of 4-oxo-4*H*-chromene-3-carbaldehydes (3-formylchromones, **1**) and acylpyruvates **2**, having three electrophilic centers, with nucleophiles, which also possess several reactive centers, can lead in several directions and are, therefore, of interest from the point of view of their chemo- and regioselectivity.[7] Recent advances in the chemistry of these molecules include cyclocondensation reactions with pyridine[8] and pyrimidine[9] derivatives and syntheses of fluorinated products starting from 3-(polyfluoroacyl)chromones.[10]

Several symmetric and nonsymmetric chalcones have been used for the synthesis of condensed pyridine derivatives, such as pyrido[2,3-*d*]pyrimidines.[11] Solvent- and catalyst-free one-pot syntheses of functionalized 1,8-naphthyridines and quinolines have been developed by microwave-mediated reactions of chalcones and α-aminopyridines.[12] Quinolines are available also by palladium-catalyzed Heck reaction of 2-iodoanilines with chalcones.[13]

Very recently, we reported[14] the synthesis of two scaffolds of hetero analogues of cinchoninic esters containing 7-substituted pyrrolo[2,3-*b*]pyridine-4-carboxylic acid and 5-substituted thiazolo[4,5-*b*]pyridine-7-carboxylic acid moieties. As a continuation of our studies on the synthetic potential of electron-rich heterocyclic amines **4**–**9**,[15,16] and due to the increasing importance of fused pyridines in biology and pharmacology,[1–6] we decided to investigate their reactions with 1,3-dielectrophiles, such as 3-formylchromones **1**, acylpyruvates **2** and chalcone (**3**) (Figures 1 and 2).

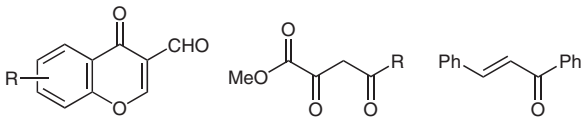

Figure 1 Structures of the 1,3-CCC-dielectrophiles used

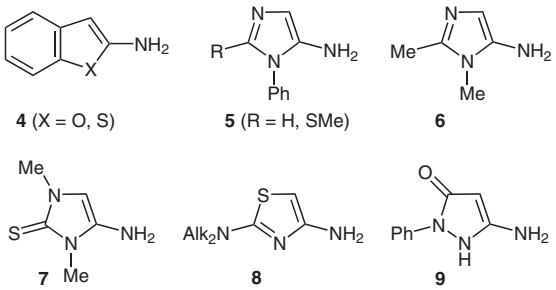

Figure 2 Structures of the 1,3-CCN-dinucleophiles used

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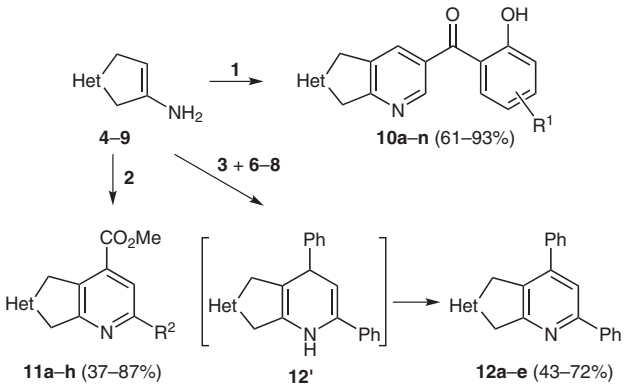
The aminoazoles **4–9** were initially investigated for their enamine reactivity in [3+3] cyclocondensation with 3-formylchromones **1**. Thus, when 3-formylchromones **1** were reacted with **4–9** in refluxing acetic acid or methanol with a catalytic amount of 4-toluenesulfonic acid, workup of the reaction mixture furnished β-salicyloyl-substituted heteroannulated pyridines **10a–n** in high yields. In this case, pyranone ring opening takes place with the subsequent annulation of the pyridine core to give the aminoheterocycle moiety. This reaction proceeds in a straightforward fashion without formation of any possible byproducts (Scheme 1, Table 1).



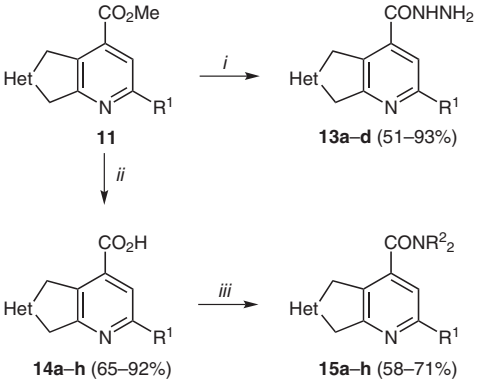
Scheme 1 *Reagents and conditions:* (i) AcOH, reflux, 2 h (for **8**, **9**); (ii) MeOH, PTSA, inert atmosphere, reflux 2–3 h (for **6**, **7**); (iii) DMF–AcOH–H_2O, 140 °C (for **4**, **5**).

Similarly, treatment of acylpyruvates **2** with heterocyclic amine **4–9** in acetic acid under reflux resulted in the formation of fused pyridines **11a–h** in good yields. 5-Aminoimidazoles **6** and **7** are unstable in acidic media and can not tolerate oxygen, thus we conducted these reactions in absolute methanol under an atmosphere of dry nitrogen in the presence of a catalytic amount of 4-toluenesulfonic acid. Benzofuran- and benzothiophen-2-amines **4**, as well as 1-phenyl-1*H*-imidazol-5-amines **5**, which were generated in situ following the previous described Curtius protocol[15a,16] starting from the corresponding acyl azides, reacted with 3-formylchromones **1** and acylpyruvates **2** under the conditions of the aminoheterocycle generation (DMF–AcOH–H_2O, 135–140 °C). Interestingly, the cyclization of **2** with aminoazoles **4–9** was to be highly regioselective and never yielded isomers with the reversed positions of the R and CO_2Me groups in the pyridine ring.

To further explore the synthetic scope and reactivity of the heterocyclic amines to obtain fused pyridines, condensation of **6–8** with chalcone **3** was investigated. Thus, when **6–8** were subjected to reaction with **3** in refluxing acetic acid or methanol under an inert atmosphere, the corresponding pyridines **12a–e** were obtained in good yields via Michael addition and intramolecular cyclization. It should be noted that heterocyclic products in these reactions were not isolable as the dihydro derivatives, which indicates the high propensity of the expected fused dihydropyridines **12′** to oxidation (Scheme 1, Table 1).

In our earlier publications we established the structure of related fused pyridines by X-ray experiments.[14a,b] The structures of pyridines **10–12** were confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectra and are in good agreement with earlier synthesized heterocyclic patterns.[9,14a,b,16] Moreover, the protons of the CO_2Me group of compounds **11** show ROESY correlations with the protons of the neighboring groups also confirming the constitution of **11**.

Esters **11** are crystalline compounds, which were purified by recrystallization from an appropriate solvent. These esters can be easily transformed to hydrazides **13a–d** by treatment of **11** with hydrazine hydrate (5 equiv) in methanol. The synthesis of acids **14a–h**, the isosteric analogues of cinchoninic acid, has been achieved by treatment of **11a–h** with sodium hydroxide in methanol. After treatment of the corresponding sodium salts by either 0.1 M HCl or acetic acid, acids **14** were obtained in high yields. Starting from **14** we have successfully obtained the corresponding acid chlorides by treatment of **14** with two equivalents of thionyl chloride in anhydrous toluene under reflux for three hours. Subsequent reaction of the acid chlorides in 1,4-dioxane with aromatic and aliphatic amines gave amides **15a–h** (Scheme 2).



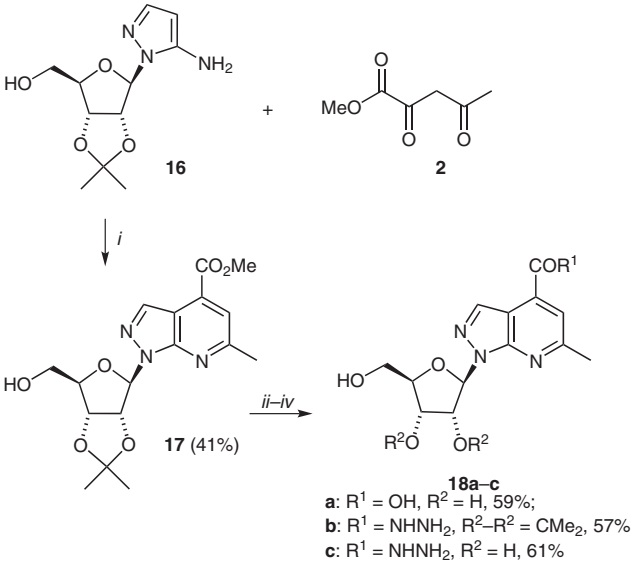
Scheme 2 *Reagents and conditions:* (i) $N_2H_4{\cdot}H_2O$, MeOH reflux; (ii) (a) NaOH, MeOH, reflux, (b) 0.1 M HCl; (iii) (a) $SOCl_2$ (2 equiv), toluene reflux, (b) $R^2{}_2NH$, 1,4-dioxane, reflux.

A variety of functionalized purines[17] and purine isosters[18] have been recognized as adenosine deaminase (ADA) inhibitors. Some of them[14–16] were synthesized in our group and their pharmaceutical evaluation is currently under investigation. Our dual interest in this work was to synthesize a new series of hybrid structures containing the pyrazolo[3,4-*b*]pyridine ring and a carbohydrate (β-D-ribofuranose) moiety as the recognition element, which are promising scaffolds for potential ADA enzymes inhibitors.

We decided to perform the synthesis of 6-methyl-1-(β-D-ribofuranosyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic acid (**18a**) from acetylpyruvate **2** (R = Me) and *iso*-AIRs **16** [5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazole]. Proton catalysis of the reaction is not advisable[15c] and the desired pyridine ring annulation pro-

ceeded smoothly in absolute *N*,*N*-dimethylformamide at 135 °C under an inert atmosphere for 18 hours, delivering the pyrazolo[3,4-*b*]pyridine **17** in 41% yield (Scheme 3). Hydrolysis of the ester function in **17** was conducted using sodium hydroxide in methanol and treatment of the resulting sodium salt with trifluoroacetic acid–water (9:1) leads to deprotection of the sugar to give acid **18a**. Synthesis of **18a** starting from **16** was conducted as a one-pot, two-stage reaction. Ester **17** was transformed into hydrazide **18b** by treatment with five equivalents of hydrazine hydrate in methanol, its subsequent reaction with trifluoroacetic acid–water (9:1) gave riboside **18c** in 61% yield (Scheme 3).

In summary, we reported a cyclocondensation reaction involving electron-rich aminoheterocycles and a number of 1,3-CCC-dielectrophiles. The present work demonstrates the versatility of 3-formylchromones, acylpyruvates, and chalcone in one-pot synthetic procedures leading to diversely fused pyridines. Applying typical transformations of the ester group, the corresponding acids, amides, and hydrazides were obtained in high yields. Moreover, the synthesis of potential inhibitors of ADAs enzymes using *iso*-AIRs was performed.



Scheme 3 *Reagents and conditions:* (i): DMF, inert atmosphere, 120 °C, 24 h; (ii) NaOH, MeOH, r.t. (for **18a**); (iii) $N_2H_4 \cdot H_2O$, MeOH, reflux (for **18b**); (iv) TFA–H_2O (9:1), r.t., 1 h (for **18b** → **18c**).

Table 1 Yields and Characteristic Data for Heteroannulated Pyridines **10**–**15**

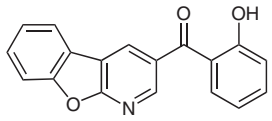
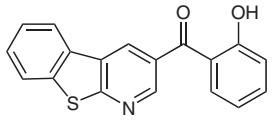
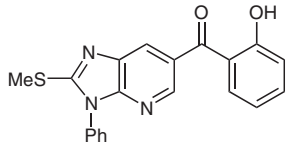
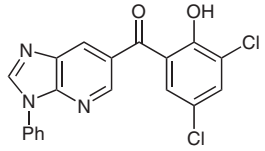
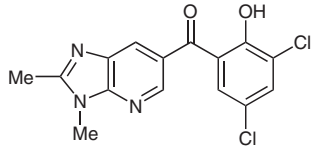
Cpd	Structure	Yield[a] (%)	Mp[b] (°C)	^{1}H and ^{13}C NMR (DMSO-d_6) δ, *J* (Hz) and MS *m*/*z* (%)[c]
10a		93	161–162 (*i*-PrOH)	^{1}H: 6.96–7.03 (m, 2 H), 7.43–7.53 (m, 2 H), 7.61 (t, *J* = 7.2, 1 H), 7.77 (d, *J* = 7.2, 1 H), 8.31 (d, *J* = 7.2, 2 H), 8.71 (s, 1 H), 8.95 (s, 1 H), 10.45 (s, 1 H, OH) ^{13}C: 112.0, 116.2, 116.9, 119.4, 121.7, 122.8, 124.2, 124.5, 129.4, 130.2, 130.8, 131.8, 133.9, 148.6, 154.4, 157.0, 164.2, 195.2 MS: 290 (22) [M$^+$ + 1], 289 (100) [M$^+$], 288 (86), 196 (27), 170 (10), 169 (86), 168 (28), 144 (10), 140 (35), 121 (41), 120 (41), 113 (11), 93 (14), 65 (21)
10b		87	154–156 (*i*-PrOH)	^{1}H: 7.03–7.10 (m, 2 H), 7.52–7.65 (m, 4 H), 8.11 (d, *J* = 7.2, 1 H), 8.51 (d, *J* = 7.2, 1 H), 8.83 (d, *J* = 7.2, 1 H), 9.02 (s, 1 H), 10.47 (s, 1 H, OH) ^{13}C: 117.5, 119.9, 123.9, 124.7, 126.2, 127.0, 128.9, 129.1, 130.4, 131.0, 131.5, 132.7, 134.6, 137.6, 149.8, 157.7, 164.6, 196.0 MS: 306 (19) [M$^+$ + 1], 305 (100) [M$^+$], 288 (35), 196 (17), 212, 83, 184 (14), 170 (81), 168 (22), 145 (21), 140 (57), 121 (53), 113 (28)
10c		93	234–235 (*i*-PrOH)	^{1}H: 2.73 (s, 3 H, SCH_3), 6.93–7.03 (m, 2 H), 7.41–7.47 (m, 2 H), 7.55–7.65 (m, 5 H), 8.22 (s, 1 H), 8.53 (s, 1 H), 10.46 (br s, 1 H, OH) ^{13}C: 14.3, 117.3, 119.7, 125.2, 125.9, 128.0, 129.2, 130.1, 130.2, 131.1, 133.6, 134.0, 135.0, 145.3, 152.4, 157.4, 158.2, 196.3 MS: 362 (22) [M$^+$ + 1], 361 (100) [M$^+$], 313 (11), 314 (67), 312 (20), 284 (43), 240 (71), 239 (12), 172 (25), 121 (14), 120 (22), 77 (53)
10d		89	154–156 (*i*-PrOH)	^{1}H: 7.35 (s, 1 H), 7. 53 (s, 1 H), 7.63–7.79 (m, 5 H), 8.12 (s, 1 H), 8.49 (s, 1 H), 9.05 (s, 1 H), 10.67 (br s, 1 H, OH) ^{13}C: 123.7, 124.0, 124.0, 124.4, 128.5, 128.6, 128.9, 129.0, 129.7, 130.1, 132.7, 135.1, 135.4, 146.9, 147.2, 149.4, 151.4, 193.8 MS: 385 (23) [M$^+$ + 2], 383 (10) [M$^+$], 383 (34), 222 (17), 196 (17), 195 (100), 194 (22), 188 (14), 167 (16), 140 (15), 77 (20)
10e		77	159 (EtOH)	^{1}H: 2.88 (s, 3 H, CH_3), 3.95 (s, 3 H, NCH_3), 7.40 (s, 1 H), 7.77 (s, 1 H), 8.17 (s, 1 H), 8.61 (s, 1 H), 10.52 (s, 1 H, OH) ^{13}C: 13.7, 28.1, 122.7, 123.0, 126.1, 126.1, 126.6, 127.8, 127.8, 128.5, 131.5, 131.6, 133.2, 144.6, 150.3, 150.6, 156.5, 193.0 MS: 337 (20) [M$^+$ + 1], 336 (15) [M$^+$], 335 (31), 174 (19), 147 (100), 146 (22)

Table 1 Yields and Characteristic Data for Heteroannulated Pyridines **10–15** (continued)

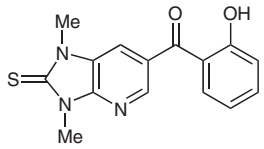
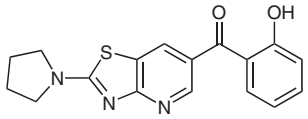
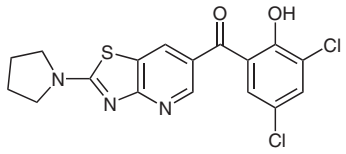
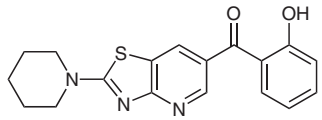
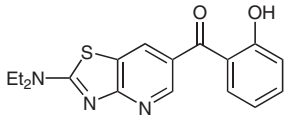
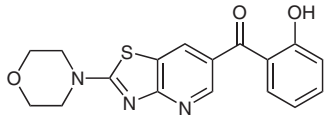
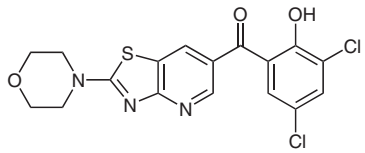
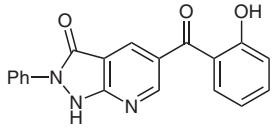
Cpd	Structure	Yield[a] (%)	Mp[b] (°C)	^{1}H and ^{13}C NMR (DMSO-d_6) δ, J (Hz) and MS m/z (%)[c]
10f		61	207–209 (EtOH)	^{1}H: 3.75 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 7.01–7.09 (m, 2 H), 7.51 (m, 2 H), 8.13 (s, 1 H), 8.69 (s, 1 H), 10.50 (s, 1 H, OH) ^{13}C: 30.7, 34.9, 114.2, 118.0, 120.1, 122.4, 125.7, 126.9, 127.8, 131.5, 133.7, 146.9, 156.4, 172.1, 192.1 MS: 300 (15) [M$^+$ + 1], 299 (100) [M$^+$], 267 (38), 231 (77), 211 (12), 201 (10), 188 (89), 187 (71), 185 (13), 133 (37), 123 (45)
10g		71	172–173 (*i*-PrOH)	^{1}H: 2.06 [s, 4 H, $(CH_2)_2$], 3.63 [s, 4 H, $N(CH_2)_2$], 6.91–6.97 (m, 2 H), 7.41 (m, 2 H), 8.53 (s, 1 H), 8.58 (s, 1 H), 10.39 (s, 1 H, OH) ^{13}C: 25.2, 49.8, 116.9, 119.0, 124.3, 125.5, 125.2, 129.9, 130.8, 132.8, 149.9, 156.1, 167.0, 172.0, 194.0 MS: 327 (10) [M$^+$ + 2], 326 (17) [M$^+$ + 1], 325 (100) [M$^+$], 324 (35), 297 (36), 296 (14), 270 (19), 232 (12), 206 (12), 205 (78), 204 (14), 177 (60), 176 (15), 150 (31), 121 (26), 65 (13)
10h		73	168–170 (EtOH)	^{1}H: 2.06 [s, 4 H, $(CH_2)_2$], 3.63 [s, 4 H, $N(CH_2)_2$], 7.40 (s, 1 H), 7.75 (s, 1 H), 8.57 (s, 1 H), 8.63 (s, 1 H), 10.48 (s, 1 H, OH) ^{13}C: 25.3, 49.8, 123.2, 123.8, 124.6, 125.2, 128.0, 129.6, 130.9, 131.7, 149.8, 150.3, 167.6, 169.1, 192.0 MS: 395 (70) [M$^+$ + 2], 394 (22) [M$^+$ + 1], 393 (100) [M$^+$], 380 (22), 378 (31), 366 (10), 354 (14), 353 (19), 352 (20), 351 (19), 246 (10), 219 (63), 191 (15), 190 (30), 189 (18), 164 (19), 163 (20), 151 (31), 150 (10), 137 (11), 136 (13), 55 (12), 41 (21)
10i		83	173–175 R_f = 0.50 (hexane–EtOAc, 3:1)	^{1}H: 1.66 [s, 6 H, $(CH_2)_3$], 3.67 [s, 4 H, $N(CH_2)_2$], 6.97–7.00 (m, 2 H), 7.43 (m, 2 H), 8.50 (s, 1 H), 8.53 (s, 1 H), 10.23 (s, 1 H, OH) ^{13}C: 23.5, 25.0, 49.2, 116.6, 119.3, 124.6, 125.2, 125.6, 130.1, 130.2, 133.0, 149.4, 156.3, 167.1, 171.7, 194.4 MS: 340 (22) [M$^+$ + 1], 339 (100) [M$^+$], 338 (17), 310 (29), 284 (19), 283 (20), 190 (20), 164 (16), 163 (14), 151 (16), 137 (10), 121 (30), 84 (11), 65 (14), 55 (13), 41 (24)
10j		88	138–140	^{1}H: 1.22 (t, J = 7.2, 6 H, 2 CH_3), 3.58 (q, J = 7.2, 4 H, 2 NCH_2), 7.01–7.04 (m, 2 H), 7.49 (m, 2 H), 8.43 (s, 1 H), 8.49 (s, 1 H), 10.57 (s, 1 H, OH)
10k		67	211–213 (EtOH)	^{1}H: 3.67 [s, 4 H, $N(CH_2)_2$], 3.75 [s, 4 H, $O(CH_2)_2$], 7.11–7.15 (m, 2 H), 7.57 (m, 2 H), 8.48 (s, 1 H), 8.54 (s, 1 H), 10.67 (s, 1 H, OH) ^{13}C: 49.2, 65.7, 117.2, 118.9, 124.5, 125.0, 125.4, 129.8, 130.5, 132.1, 149.7, 156.5, 166.7, 172.2, 194.7 MS: 342 (22) [M$^+$ + 1], 341 (100) [M$^+$], 285 (11), 284 (63), 221 (38), 190 (14), 165 (10), 164 (53), 163 (16), 162 (11), 121 (41), 120 (21), 93 (13), 65 (21)
10l		77	256–257 (EtOH)	^{1}H: 3.69 [s, 4 H, $N(CH_2)_2$], 3.78 [s, 4 H, $O(CH_2)_2$], 7.47 (s, 1 H), 7.69 (s, 1 H), 8.51 (s, 1 H), 8.59 (s, 1 H), 10.41 (s, 1 H, OH) ^{13}C: 49.8, 64.9, 122.9, 124.1, 124.4, 125.7, 128.4, 129.2, 131.2, 131.8, 149.7, 150.1, 167.1, 169.7, 192.3 MS: 413 (15) [M$^+$ + 3], 412 (16) [M$^+$ + 2], 411 (72) [M$^+$ + 1], 410 (28) [M$^+$], 409 (100), 354 (42), 353 (18), 352 (61), 248 (14), 222 (10), 221 (76), 191 (23), 190 (37), 189 (18), 188 (22), 177 (10), 165 (12), 164 (61), 163 (26), 162 (21), 136 (18), 135 (13)
10m		65	189–192 (EtOH)	^{1}H: 6.95–7.00 (m, 2 H), 7.21 (t, J = 7.2, 1 H), 7.38–7.47 (m, 4 H), 8.03 (d, J = 7.2, 2 H), 8.25 (s, 1 H), 8.52 (s, 1 H), 10.77 (s, 2 H, OH, NH) ^{13}C: 113.6, 116.7, 119.1, 119.6, 124.9, 125.1, 128.9, 130.2, 133.1, 137.63, 137.69, 138.69, 138.72, 158.2, 155.7, 158.5. 192.1 MS: 332 (27) [M$^+$ + 1], 331 (100) [M$^+$], 330 (16), 212 (11), 211 (74), 182 (21), 121 (51), 93 (10), 77 (22), 65 (14)

Table 1 Yields and Characteristic Data for Heteroannulated Pyridines **10–15** (continued)

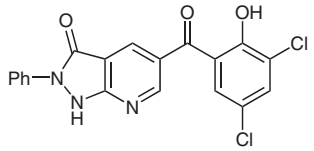
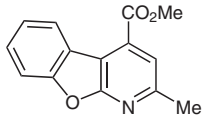
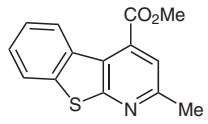
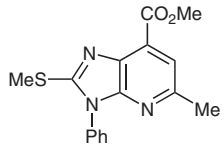
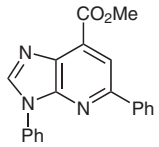
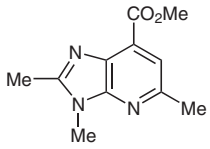
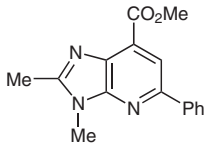
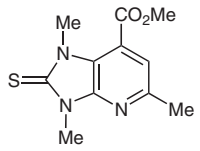
Cpd	Structure	Yield[a] (%)	Mp[b] (°C)	^{1}H and ^{13}C NMR (DMSO-d_6) δ, *J* (Hz) and MS *m*/*z* (%)[c]
10n		69	288–289 (EtOH)	^{1}H: 7.20 (t, *J* = 7.2, 1 H), 7.41–7.46 (m, 3 H), 7.75 (br s, 1 H), 8.02 (s, 1 H), 8.04 (s, 1 H), 8.31 (br s, 1 H), 8.56 (br s, 1 H, NH), 10.41 (br s, 1 H, OH) ^{13}C: 114.3, 119.1, 121.8, 122.0, 123.3, 123.8, 125.0, 128.1, 128.1, 128.9, 129.0, 131.8, 137.4, 138.8, 148.5, 150.1, 158.4, 189.9 MS: 400 (17) [M$^+$ + 1], 399 (25) [M$^+$], 345 (17), 211 (44), 105 (43), 104 (28), 92 (16), 91 (26), 79 (49), 78 (37), 77 (100), 65 (28), 64 (27), 51 (13), 44 (13), 43 (11)
11a		78	165–166 (EtOH)	^{1}H: 2.68 (s, 3 H, CH_3), 4.11 (s, 3 H, OCH_3), 7.50 (t, *J* = 8.0, 1 H), 7.66 (t, *J* = 8.0, 1 H), 7.73 (s, 1 H), 7.83 (d, *J* = 8.0, 1 H), 7.99 (d, *J* = 8.0, 1 H) ^{13}C: 24.4, 55.0, 109.8, 112.7, 115.5, 119.7, 123.4, 124.7, 126.7, 129.9, 154.5, 158.1, 163.1, 167.0 MS: 242 (11) [M$^+$ + 1], 241 (100) [M$^+$], 200 (13), 170 (14), 169 (19), 157 (17)
11b		70	155–158 R_f = 0.45 (hexane–EtOAc, 3:1)	^{1}H: 2.61 (s, 3 H, CH_3), 4.01 (s, 3 H, OCH_3), 7.33 (t, *J* = 7.8, 1 H), 7.49 (t, *J* = 7.8, 1 H), 7.55 (d, *J* = 7.8, 1 H), 7.81 (s, 1 H), 8.21 (d, *J* = 7.8, 1 H) ^{13}C: 26.7, 53.9, 112.8, 123.2, 126.0, 127.0, 127.7, 129.2, 129.6, 133.0, 140.1, 145.9, 164.1, 167.7 MS: 258 (15) [M$^+$ + 1], 257 (100) [M$^+$], 226 (70), 225 (13), 198 (39), 150 (11), 149 (81), 119 (43), 92 (49), 77 (71)
11c		87	185 (EtOH)	^{1}H: 2.51 (s, 3 H, CH_3), 2.68 (s, 3 H, SCH_3), 4.03 (s, 3 H, OCH_3), 7.15 (s, 1 H), 7.37–7.49 (m, 5 H) ^{13}C: 14.1, 24.2, 52.6, 118.2, 125.5, 127.4, 129.3, 129.6, 131.9, 133.7, 151.4, 152.1, 157.5, 165.9 MS: 314 (18) [M$^+$ + 1], 313 (100) [M$^+$], 282 (41), 254 (93), 253 (11), 240 (21), 239 (91), 203 (35), 202 (20), 157 (12), 156 (81), 154 (15), 111 (27)
11d		85	200–201 (EtOH)	^{1}H: 3.97 (s, 3 H, OCH_3), 7.46–7.55 (m, 4 H), 7.65–7.72 (m, 2 H), 8.00 (d, *J* = 7.8, 2 H), 8.12 (s, 1 H), 8.16 (d, *J* = 7.8, 2 H), 9.05 (s, 1 H) ^{13}C: 52.6, 111.7, 122.8, 123.8, 127.8, 127.9, 128.9, 129.5, 129.6, 130.4, 134.6, 137.6, 146.8, 147.7, 152.1, 165.0 MS: 330 (18) [M$^+$ + 1], 329 (100) [M$^+$], 298 (70), 252 (43)
11e		37	157–160 (EtOH)	^{1}H: 2.51 (s, 3 H, 5-CH_3), 2.65 (s, 3 H, 2-CH_3), 3.89 (s, 3 H, NCH_3), 3.99 (s, 3 H, OCH_3), 7.78 (s, 1 H) ^{13}C: 14.5, 27.0, 29.0, 53.3, 114.3, 124.7, 135.3, 140.1, 144.5, 158.1, 168.1 MS: 220 (14) [M$^+$ + 1], 219, (100) [M$^+$], 160 (22), 189 (10), 188 (93)
11f		62	193–194 (EtOH)	^{1}H: 2.60 (s, 3 H, CH_3), 3.79 (s, 3 H, NCH_3), 3.94 (s, 3 H, OCH_3), 7.43–7.49 (m, 3 H), 8.05–8.12 (m, 3 H) ^{13}C: 14.1, 28.4, 52.5, 114.1, 126.5, 126.9, 128.8, 128.9, 138.3, 149.2, 150.0, 157.0, 165.5 MS: 282 (18) [M$^+$ + 1], 281 (100) [M$^+$], 251 (10), 250 (78), 222 (45), 204 (35), 201 (11), 183 (11), 181 (55), 77 (78)
11g		78	155–156 (EtOH)	^{1}H: 2.52 (s, 3 H, CH_3), 3.66 (s, 3 H, NCH_3), 3.79 (s, 3 H, NCH_3), 3.92 (s, 3 H, OCH_3), 7.34 (s, 1 H) ^{13}C: 23.0, 29.9, 33.9, 52.8, 116.7, 120.7, 120.9, 145.7, 151.2, 164.4, 171.7 MS: 252 (13) [M$^+$ + 1], 251 (100) [M$^+$], 221 (10), 220 (70), 193 (12), 192 (55), 190 (31), 181 (88), 134 (11), 131 (17)

Table 1 Yields and Characteristic Data for Heteroannulated Pyridines **10–15** (continued)

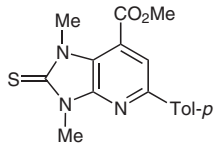
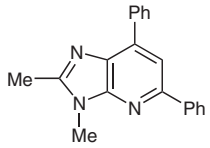
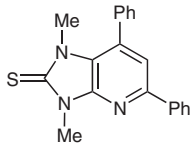
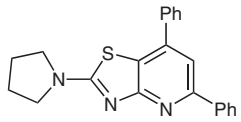
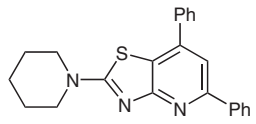
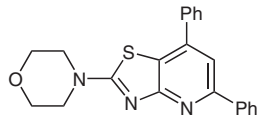
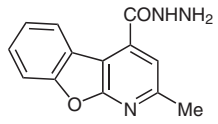
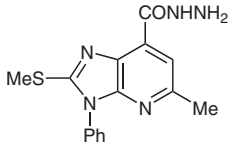
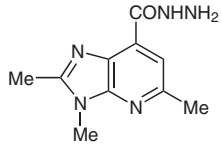
Cpd	Structure	Yield[a] (%)	Mp[b] (°C)	^{1}H and ^{13}C NMR (DMSO-d_6) δ, *J* (Hz) and MS *m*/*z* (%)[c]
11h		81	175–177 (EtOH)	^{1}H: 2.34 (s, 3 H, CH_3), 3.71 (s, 3 H, NCH_3), 3.81 (s, 3 H, NCH_3), 3.96 (s, 3 H, OCH_3), 7.27 (d, *J* = 7.8, 2 H), 7.89 (s, 1 H), 7.93 (d, *J* = 7.8, 2 H) ^{13}C: 24.1, 31.2, 34.0, 53.3, 113.6, 118.5, 120.2, 127.2 128.0, 130.0, 137.1, 146.1, 152.4, 169.7, 173.9 MS: 328 (13) [M^+ + 1], 327 (100) [M^+], 301 (13), 296 (16), 293 (22), 270 (14), 269 (19), 268 (41), 236 (50), 192 (25), 91 (34)
12a		43	189–191 (EtOH)	^{1}H: 2.59 (s, 3 H, CH_3), 3.71 (s, 3 H, NCH_3), 7.47 (s, 1 H), 7.29–7.41 (m, 3 H), 7.52–7.67 (m, 5 H), 8.11–8.15 (m, 2 H) ^{13}C: 14.5, 29.0, 114.7, 127.3, 126.0, 128.8, 129.9, 132.0, 134.2, 141.1, 149.5, 159.1 MS: 300 (23) [M^+ + 1], 299 (100) [M^+], 284 (33), 224 (11), 223 (93), 207 (11), 208 (67), 77 (97)
12b		72	173–175 (EtOH)	^{1}H: 3.35 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 7.38–7.49 (m, 3 H), 7.53–7.60 (m, 6 H), 8.11–8.15 (m, 2 H) ^{13}C: 29.9, 33.7, 117.2, 122.5, 126.6, 128.4, 128.6, 128.7, 128.8, 129.4, 132.9, 135.5, 138.3, 145.6, 149.7, 172.2 MS: 332 (17) [M^+ + 1], 331 (100) [M^+], 320 (11), 298 (13), 297 (62), 268 (46), 267 (11), 254 (79), 241 (11), 221 (89), 212 (23), 211 (67), 173 (11), 170 (15), 77 (70)
12c		65	211–212 (*i*-PrOH)	^{1}H: 2.07 [br s, 4 H, $(CH_2)_2$], 3.61 [br s, 4 H, $N(CH_2)_2$], 7.39–7.62 (m, 7 H), 7.75 (d, *J* = 7.2, 2 H), 8.11 (d, *J* = 7.2, 2 H) ^{13}C: 26.1, 49.1, 111.1, 121.9, 126.7, 127.4, 127.1, 128.2, 128.5, 128.7, 137.5, 138.7, 142.3, 153.7, 164.7, 170.9 MS: 358 (27) [M^+ + 1], 357 (100) [M^+], 329 (36), 328 (17), 303 (13), 302 (56), 287 (11), 261 (11), 260 (23), 259 (12)
12d		60	168–170 (*i*-PrOH)	^{1}H: 1.66 [br s, 6 H, $(CH_2)_3$], 3.65 (br s, 4 H), 7.40–7.63 (m, 7 H), 7.78 (d, *J* = 7.2, 2 H), 8.15 (d, *J* = 7.2, 2 H) ^{13}C: 23.0, 24.3, 48.5, 111.5, 121.2, 126.2, 126.9, 127.9, 128.0, 128.57, 128.62, 137.9, 138.8, 142.5, 153.9, 164.8, 169.1 MS: 372 (30) [M^+ + 1], 371 (100) [M^+], 343 (11), 342 (37), 328 (14), 317 (12), 316 (31), 315 (35), 302 (20), 289 (12), 288 (15), 287 (14), 261 (11), 260 (22), 259 (11)
12e		67	189–190 (*i*-PrOH)	^{1}H: 3.67 [br s, 4 H, $N(CH_2)_2$], 3.80 [br s, 4 H, $O(CH_2)_2$], 7.42–7.68 (m, 7 H), 7.71 (d, *J* = 7.2, 2 H), 8.21 (d, *J* = 7.2, 2 H) ^{13}C: 48.7, 65.3, 111.1, 121.6, 126.0, 126.5, 128.0, 128.2, 128.50, 128.54, 137.1, 138.9, 142.3, 154.2, 165.2, 168.9 MS: 375 (10) [M^+ + 2], 374 (32) [M^+ + 1], 373 (100) [M^+], 372 (13), 328 (11), 317 (25), 316 (88), 315 (18), 302 (11), 289 (10), 288 (11), 287 (23), 261 (19), 260 (28), 259 (13)
13a		80	195–197	^{1}H: 2.77 (s, 3 H, CH_3), 6.07 (br s, 2 H, NH_2), 7.41 (t, *J* = 8.0, 1 H), 7.77 (t, *J* = 8.0, 1 H), 7.88 (s, 1 H), 8.00 (d, *J* = 8.0, 1 H), 8.11 (d, *J* = 8.0, 1 H), 10.11 (br s, 1 H, NH)
13b		93	234–238	^{1}H: 2.56 (s, 3 H, 5-CH_3), 2.77 (s, 3 H, SCH_3), 5.96 (br s, 2 H, NH_2), 7.21 (s, 1 H), 7.50 (m, 5 H), 10.00 (br s, 1 H, NH)
13c		51	187–189	^{1}H: 2.44 (s, 3 H, 5-CH_3), 2.67 (s, 3 H, 2-CH_3), 3.80 (s, 3 H, NCH_3), 6.19 (br s, 2 H, NH_2), 7.87 (s, 1 H), 9.99 (br s, 1 H, NH)

Table 1 Yields and Characteristic Data for Heteroannulated Pyridines **10**–**15** (continued)

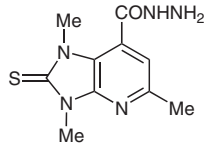
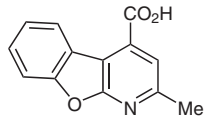
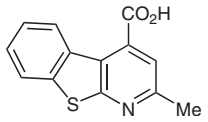
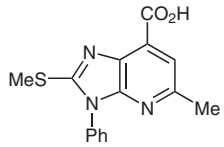
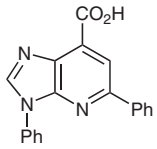
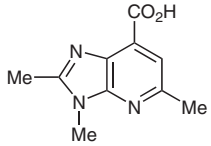
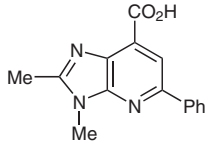
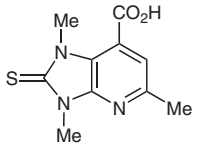
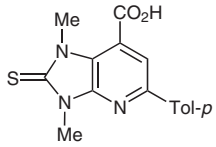
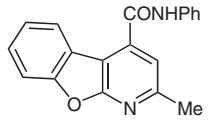
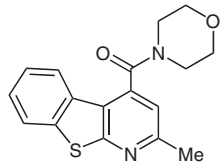
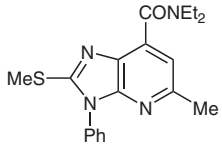
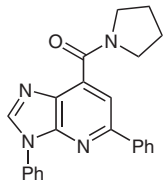
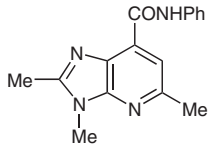
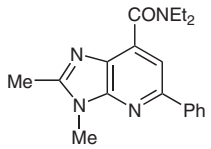
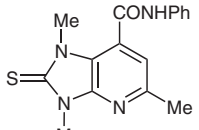
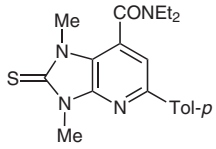
Cpd	Structure	Yield[a] (%)	Mp[b] (°C)	^{1}H and ^{13}C NMR (DMSO-d_6) δ, *J* (Hz) and MS *m*/*z* (%)[c]
13d		79	215–218	^{1}H: 2.52 (s, 3 H, CH_3), 3.30 (s, 3 H, CH_3), 3.69 (s, 3 H, NCH_3), 6.01 (br s, 2 H, NH_2), 7.30 (s, 1 H), 10.59 (br s, 1 H, NH)
14a		89	211–213	^{1}H: 2.62 (s, 3 H, CH_3), 7.41 (t, *J* = 8.0, 1 H), 7.61 (t, *J* = 8.0, 1 H), 7.70 (s, 1 H), 7.80 (d, *J* = 8.0, 1 H), 7.93 (d, *J* = 8.0, 1 H), 11.01 (br s, 1 H, OH)
14b		92	202–203	^{1}H: 2.64 (s, 3 H, CH_3), 7.38 (t, *J* = 7.8, 1 H), 7.44 (t, *J* = 7.8, 1 H), 7.59 (d, *J* = 7.8, 1 H), 7.71 (s, 1 H), 8.09 (d, *J* = 7.8, 1 H), 10.97 (br s, 1 H, OH)
14c		88	250–252	^{1}H: 2.55 (s, 3 H, CH_3), 2.73 (s, 3 H, SCH_3), 7.19 (s, 1 H), 7.40–7.52 (m, 5 H), 10.77 (br s, 1 H, OH)
14d		83	243–244	^{1}H: 7.40–7.53 (m, 4 H), 7.68–7.73 (m, 2 H), 7.93 (d, *J* = 7.8, 2 H), 8.00 (s, 1 H), 8.10 (d, *J* = 7.8, 2 H), 9.00 (s, 1 H), 11.11 (br s, 1 H, OH)
14e		68	288–290	^{1}H: 2.57 (s, 3 H, 5-CH_3), 2.69 (s, 3 H, 2-CH_3), 3.72 (s, 3 H, NCH_3), 7.63 (s, 1 H), 11.07 (br s, 1 H, OH)
14f		65	270–273	^{1}H: 2.61 (s, 3 H, 5-CH_3), 3.81 (s, 3 H, 2-CH_3), 7.47–7.53 (m, 3 H), 8.0–8.05 (m, 3 H), 11.01 (br s, 1 H, OH)
14g		87	213–215	^{1}H: 2.52 (s, 3 H, CH_3), 3.66 (s, 3 H, NCH_3), 3.79 (s, 3 H, NCH_3), 7.34 (s, 1 H), 10.59 (br s, 1 H, OH).
14h		82	237–239	^{1}H: 2.32 (s, 3 H, CH_3), 3.74 (s, 3 H, NCH_3), 3.84 (s, 3 H, NCH_3), 7.33 (d, *J* = 7.8, 2 H), 7.84 (s, 1 H), 8.01 (d, *J* = 7.8, 2 H), 10.99 (br s, 1 H, OH)
15a		71	211–213	^{1}H: 2.63 (s, 3 H, CH_3), 7.18 (m, 3 H), 7.44 (t, *J* = 8.0, 1 H), 7.60 (d, *J* = 8.0, 2 H), 7.69 (t, *J* = 8.0, 1 H), 7.88 (s, 1 H), 7.97 (d, *J* = 8.0, 1 H), 8.12 (d, *J* = 8.0, 1 H), 10.01 (br s, 1 H, NH)
15b		70	190–193	^{1}H: 2.58 (s, 3 H, CH_3), 3.74 [br s, 4 H, $N(CH_2)_2$], 3.88 [br s, 4 H, $O(CH_2)_2$], 7.37 (t, *J* = 7.8, 1 H), 7.52 (t, *J* = 7.8, 1 H), 7.59 (d, *J* = 7.8, 1 H), 7.77 (s, 1 H), 8.32 (d, *J* = 7.8, 1 H)

Table 1 Yields and Characteristic Data for Heteroannulated Pyridines **10**–**15** (continued)

Cpd	Structure	Yield[a] (%)	Mp[b] (°C)	^{1}H and ^{13}C NMR (DMSO-d_6) δ, *J* (Hz) and MS *m*/*z* (%)[c]
15c		62	177–179	^{1}H: 1.22 (t, *J* = 7.2, 6 H, 2 CH_3), 2.56 (s, 3 H, 5-CH_3), 2.68 (s, 3 H, SCH_3), 3.58 (q, *J* = 7.2, 4 H, 2 CH_2), 7.24 (s, 1 H), 7.39–7.53 (m, 5 H)
15d		69	222–223	^{1}H: 2.08 (br s, 4 H, 2 CH_2), 3.51 (br s, 4 H, 2 NCH_2), 7.52 (m, 4 H), 7.70 (m, 2 H), 8.03 (d, *J* = 7.8, 2 H), 8.11 (s, 1 H), 8.19 (d, *J* = 7.8, 2 H), 8.88 (s, 1 H)
15e		64	254–255	^{1}H: 2.46 (s, 3 H, 5-CH_3), 2.61 (s, 3 H, 2-CH_3), 3.88 (s, 3 H, NCH_3), 7.21 (m, 3 H), 7.60 (d, *J* = 8.0, 2 H), 7.82 (s, 1 H)
15f		58	217–219	^{1}H: 1.26 (t, *J* = 7.2, 6 H, 2 CH_3), 2.55 (s, 3 H, CH_3), 3.63 (q, 4 H. *J* = 7.2 Hz, 2 NCH_2), 3.70 (s, 3 H, NCH_3), 7.55 (m, 3 H), 8.00–8.10 (m, 3 H)
15g		60	234–236	^{1}H: 2.50 (s, 3 H, CH_3), 3.61 (s, 3 H, NCH_3), 3.73 (s, 3 H, NCH_3), 7.24 (m, 3 H), 7.68 (d, *J* = 8.0, 2 H), 7.74 (s, 1 H)
15h		65	188–190	^{1}H: 1.26 (t, *J* = 7.2, 6 H, 2 CH_3), 2.30 (s, 3 H, CH_3), 3.65 (q, *J* = 7.2, 4 H, 2 NCH_2), 3.71 (s, 3 H, NCH_3), 3.81 (s, 3 H, NCH_3), 7.30 (d, *J* = 7.8, 2 H), 7.80 (s, 1 H), 8.01 (d, *J* = 7.8, 2 H)

[a] Yields refer to pure isolated product.
[b] Melting points are uncorrected.
[c] Satisfactory microanalysis obtained: C ± 0.33; H ± 0.25; N ± 0.20.

All solvents were purified and dried by standard methods. NMR spectra were recorded on a Jeol JNM-LA 400, Varian VXR-300 or Varian Mercury-400, Bruker 600 spectrometer: ^{1}H and ^{13}C signals (300, 400 and 100 MHz, respectively) were recorded with TMS as an internal standard; ^{19}F (282.2 and 376.2 MHz) with $CFCl_3$ as internal standard. IR spectra were recorded on a Perkin Elmer FT IR 1600 spectrophotometer for samples in KBr discs. Mass spectra were obtained on a Hewlett-Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet. Elemental analyses were carried out at the Microanalytical laboratory of the Kiev State University. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck $60F_{254}$ plates were used for TLC.

The pyridine synthesis was performed according to one of the following procedures.

Heteroannulated Pyridines in Acetic Acid; General Procedure

The initial aminoheterocycle (2 mmol) and dielectrophile (2 mmol) were dissolved in AcOH (25 mL) and heated under reflux for 2 h. This soln was evaporated under reduced pressure, treated with H_2O, filtered, dried in air, and recrystallized from an appropriate solvent or subjected to column chromatography (silica gel).

Heteroannulated Pyridines via Curtius Rearrangement from the Corresponding Azides; General Procedure

To a boiling soln of AcOH (30 mL) and H_2O (2 mL) (oil bath temp ~145 °C) was added dropwise very slowly through the long condenser a mixture of dielectrophile (1 mmol) and the corresponding azide (3 mmol) in anhyd DMF (40 mL). When the addition was completed, the mixture was refluxed for a further 3 h. The solvent was evaporated and the residue was subjected to column chromatography (silica gel), or recrystallized from an appropriate solvent. It is recommended that the ratio of azide/electrophile 1:3 be use to obtain an almost quantitative yield of 1-desazapurine.

Heteroannulated Pyridines in Methanol Under Inert Atmosphere; General Procedure

The mixture of aminoimidazoles (2 mmol) and dielectrophile (2.2 mmol) in abs MeOH with PTSA (cat.) was heated under reflux in inert atmosphere for 2–3 h. The solvent was evaporated under reduced pressure. The material formed was recrystallized from an appropriate solvent or subjected to column chromatography (silica gel).

Hydrazides 13; General Procedure

The corresponding compound **11** (1 mmol) and 60% hydrazine hydrate (0.5 mL) were dissolved in EtOH (20 mL) and heated under reflux for 2 h. The soln was left overnight at 0 °C; a precipitate formed which was filtered, washed once with cold EtOH, and dried under reduced pressure.

Acids 14; General Procedure

The corresponding compound **11** (1 mmol) and NaOH (5 mmol) were dissolved in MeOH (20 mL) and heated under reflux for 2 h. Then the soln was left overnight at 0 °C; the thus formed precipitate was filtered and dried in air. The salt was dissolved in H_2O (20 mL), then 1 M HCl was added slowly dropwise with intensive stirring. The thus formed precipitate was filtered and dried under reduced pressure.

Acid Chlorides from Acids 14; General Procedure

A mixture of **14** (20 mmol) and $SOCl_2$ (40 mmol) was heated in anhyd toluene under reflux for 3 h. Then the solvent was removed under reduced pressure and the residue was dried.

Amides 15; General Procedure

The corresponding acid chloride (1 mmol) and amine (2 mmol) in anhyd 1,4-dioxane (15 mL) were heated under reflux for 2–3 h. The mixture was poured into H_2O (80 mL). The precipitate formed was filtered, washed with H_2O (2 ×), dried in air, and recrystallized from an appropriate solvent.

Methyl 1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate (17)

A mixture of *iso*-AIRs **16** (2 mmol) and 1,3-dielectrophile **2** (R = Me) (2.1 mmol) in DMF (15 mL) under an inert atmosphere was stirred at 135 °C for 18 h. The mixture was concentrated under reduced pressure and the dark material was purified by column chromatography (silica gel) to give **17** (0.45 g, 62%) as a colorless solid; R_f = 0.50 (hexane–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.65 (s, 3 H, 3-CH_3), 2.39 (s, 3 H, CH_3), 3.68 (dd, ^2J = 12.8 Hz, ^3J = 3.2 Hz, 1 H), 3.86 (dd, ^2J = 12.8 Hz, ^3J = 2.7 Hz, 1 H), 4.11 (s, 3 H, CH_3), 4.53 (br s, 1 H), 5.11 (dd, ^3J = 5.9 Hz, ^3J = 1.6 Hz, 1 H), 5.27 (dd, ^3J = 5.5 Hz, ^3J = 2.8 Hz, 1 H), 6.82 (d, ^3J = 2.8 Hz, 1 H), 7.78 (s, 1 H), 8.35 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 25.0, 25.2, 27.2, 53.3, 63.8, 81.9, 85.0, 88.0, 91.8, 110.8, 112.7, 113.7, 113.8, 132.8, 134.1, 148.2, 150.3, 165.9.

Cleavage of 2,2-Propylidene Protection Group; Synthesis of Compounds 18a,c; General Procedure

The protected substrate (1 mmol) was dissolved in TFA–H_2O (9:1, 10–15 mL) and the mixture was stirred vigorously at r.t. for 60 min (TLC). The mixture was concentrated under reduced pressure (the mixture should not be heated over 40 °C) and the residue was recrystallized from an appropriate solvent.

6-Methyl-1-(β-D-ribofuranosyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylic Acid (18a)

Compound **17** (2 mmol) and NaOH (5 mmol) were dissolved in MeOH (15 mL) and the mixture was left at r.t. overnight. The solvent was removed under reduced pressure. The crude white residue was dissolved in TFA–H_2O (9:1, 25 mL), and stirred vigorously at r.t. for 75 min. The mixture was concentrated under reduced pressure and the residue was recrystallized (MeOH) to give **18a** (0.34 g, 59%) as a colorless solid; mp 217–219 °C.

^{1}H NMR (DMSO-d_6): δ = 2.44 (s, 3 H, CH_3), 3.49 (m, 1 H), 3.63 (m, 1 H), 4.02 (q, ^3J = 4.7 Hz, 1 H), 4.34 (br s, 1 H), 4.79 (d, ^3J = 4.7 Hz, 2 H), 5.32 (br s, 1 H, OH), 5.55 (d, ^3J = 5.4 Hz, OH, 1 H), 6.44 (d, ^3J = 4.7 Hz, 1 H), 8.21 (s, 1 H), 8.73 (s, 1 H), 10.12 (s, 1 H, OH).

^{13}C NMR (DMSO-d_6): δ = 24.5, 62.1, 70.8, 73.4, 85.0, 88.5, 111.0, 112.9, 122.2, 132.5, 132.51, 145.2, 150.3, 173.8.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carbohydrazide (18b)

Compound **17** (2 mmol) and 60% hydrazine hydrate (0.5 mL) were dissolved in MeOH (15 mL) and the mixture was stirred intensively at r.t. overnight. The soln was removed under reduced pressure. The precipitate was recrystallized (MeOH), washed with cold MeOH (2 ×), and dried under reduced pressure to give **18b** (0.41 g, 57%) as a colorless solid; mp 149–152 °C.

^{1}H NMR (DMSO-d_6): δ = 1.33 (s, 3 H, CH_3), 1.63 (s, 3 H, 3-CH_3), 2.44 (s, 3 H, CH_3), 3.63 (dd, ^2J = 12.1 Hz, ^3J = 3.1 Hz, 1 H), 3.80 (dd, ^2J = 12.1 Hz, ^3J = 3.1 Hz, 1 H), 4.50 (br s, 1 H), 5.17 (dd, ^3J = 5.7 Hz, ^3J = 1.5 Hz, 1 H), 5.27 (dd, ^3J = 5.4 Hz, ^3J = 3.0 Hz, 1 H), 5.97 (s, 2 H, NH_2), 6.71 (d, ^3J = 2.8 Hz, 1 H), 7.78 (s, 1 H), 8.35 (s, 1 H), 9.97 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.1, 25.3, 27.0, 53.0, 63.2, 81.5, 85.9, 89.0, 91.4, 112.0, 113.3, 113.9, 114.5, 132.7, 133.3, 148.7, 159.9, 181.0.

6-Methyl-1-(β-D-ribofuranosyl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-carbohydrazide (18c)

Prepared according to the general procedure, then recrystallized from MeOH.

Colorless solid; yield: 0.20 g (61%); mp 230–231 °C (MeOH).

^{1}H NMR (DMSO-d_6): δ = 2.57 (s, 3 H, CH_3), 3.55 (m, 2 H), 4.00 (q, ^3J = 4.4 Hz, 1 H), 4.41 (br s, 1 H), 4.67 (d, ^3J = 4.4 Hz, 2 H), 5.21 (br s, 1 H, OH), 5.33 (d, ^3J = 5.7 Hz, OH, 1 H), 5.55 (s, 2 H, NH_2), 6.77 (d, ^3J = 4.4 Hz, 1 H), 8.14 (s, 1 H, CH), 8.77 (s, 1 H, CH), 10.00 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 25.9, 61.9, 71.7, 73.9, 87.0, 89.7, 110.0, 111.9, 122.2, 128.7, 132.33, 145.9, 150.7, 183.7.

References

(1) (a) Ealick, S. E.; Parker, W. B.; Seerist, J. A.; Sorscher, E. J. WO 2003,035,012, **2003**. (b) Matulic-Adamic, J.; Takahashi, K.; Chou, T. C.; Gadler, H.; Price, R. W.; Watanabe, K. A.; Reddy, A. R. V.; Kalman, T. I. *J. Med. Chem.* **1988**, *31*, 1642. (c) Hackova, D.; Hocek, M.; Dvorakova, H.; Votruba, I. *Tetrahedron* **1999**, *55*, 11109. (d) Koch, M.; Den, H.; Jacobus, A.; Koomen, J.; Wanner, G.-J.; Martinus, J.; Roelof, F. W. WO 2006,027,365, **2006**. (e) Erion, M. D. M.; Reddy, R. *J. Am. Chem. Soc.* **1998**, *120*, 3295. (f) Veliz, E. A.; Stephens, O. M.; Beal, P. A. *Org. Lett.* **2001**, *3*, 2969. (g) Lee, S.; Park, S. B. *Org. Lett.* **2009**, *11*, 5214.

(2) Misra, R. N.; Rawlins, D. B.; Xiao, H.; Shan, W.; Bursuker, I.; Kellar, K. A.; Mulheron, J. G.; Sack, J. S.; Tokarski, J. S.; Kimball, S. D.; Webster, K. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1133.

(3) (a) Lin, R.; Connolly, P. J.; Lu, Y.; Chiu, G.; Li, S.; Yu, Y.; Huang, S.; Li, X.; Emanuel, S. L.; Middleton, S. A.; Gruninger, R. H.; Adams, M.; Fuentes-Pesquera, A. R.; Greenberger, L. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4297. (b) Witherington, J.; Bordas, V.; Gaiba, A.; Garton, N. S.; Naylor, A.; Rawlings, A. D.; Slingsby, B. P.; Smith, D. G.; Takle, A. K.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3055.

(4) (a) Goda, F. E.; Abdel-Azizb, A. A.-M.; Attef, O. A. *Bioorg. Med. Chem.* **2004**, *12*, 1845. (b) Foks, H.; Pancechowska-Ksepko, D.; Kvdzia, A.; Zwolska, Z.; Janowiec, M.; Augustynowicz-Kopec, E. *Farmaco* **2005**, *60*, 513.

(5) Dias, L. R. S.; Santos, M. B.; de Albuquerque, S.; Castro, H. C.; de Souza, A. M. T.; Freitas, A. C. C.; DiVaio, M. A. V.; Cabral, L. M.; Rodriguese, C. R. *Bioorg. Med. Chem.* **2007**, *15*, 211.
(6) (a) de Mello, H.; Echevarria, A.; Bernardino, A. M.; Canto-Cavalheiro, M.; Leon, L. L. *J. Med. Chem.* **2004**, *47*, 5427. (b) Bharate, S. B.; Mahajan, T. R.; Gole, Y. R.; Nambiar, M.; Matan, T. T.; Kulkarni-Almeida, A.; Balachandran, S.; Junjappa, H.; Balakrishnan, A.; Vishwakarma, R. A. *Bioorg. Med. Chem.* **2008**, *16*, 7167.
(7) (a) Haas, G.; Stanton, J. L.; von Sprecher, A.; Wenk, P. *J. Heterocycl. Chem.* **1981**, *18*, 607. (b) Quiroga, J.; Mejía, D.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *J. Heterocycl. Chem.* **2002**, *39*, 51. (c) Ghosh, T.; Bandyopadhyay, C. *J. Heterocycl. Chem.* **2006**, *43*, 1431. (d) Stankovičová, H.; Gáplovský, A.; Lácová, M.; Chovancová, J.; Puchała, A. *J. Heterocycl. Chem.* **2006**, *43*, 843. (e) Chebanov, V. A.; Sakhno, Y. I.; Desenko, S. M.; Chernenko, V. N.; Musatov, V. I.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. *Tetrahedron* **2007**, *63*, 1229.
(8) (a) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Pipko, S. E.; Tolmachev, A. A. *Heterocycles* **2008**, *75*, 583. (b) Randhavane, P. V.; Kale, S. B.; Jagdhani, S. G.; Karale, B. K. *Indian J. Heterocycl. Chem.* **2007**, *17*, 153. (c) Sonawane, S. A.; Karale, B. K.; Shingare, M. S. *Indian J. Heterocycl. Chem.* **2004**, *14*, 155.
(9) (a) Plaskon, A. S.; Ryabukhin, S. V.; Volochnyuk, D. M.; Gavrilenko, K. S.; Shivanyuk, A. N.; Tolmachev, A. A. *J. Org. Chem.* **2008**, *73*, 6010. (b) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2007**, 1861.
(10) (a) Sosnovskikh, V. Ya.; Irgashev, R. A.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 2997. (b) Sosnovskikh, V. Ya.; Khalymbadzha, I. A.; Irgashev, R. A.; Slepukhin, P. A. *Tetrahedron* **2008**, *64*, 10172.
(11) (a) Wang, X.-S.; Zhang, M.-M.; Li, Q.; Yao, C.-S.; Tu, S.-J. *Synth. Commun.* **2008**, *38*, 1896. (b) Shi, D.-Q.; Ni, S.-N.; Yang, F.; Shi, J.-W.; Dou, G.-L.; Li, X.-Y.; Wang, X.-S.; Ji, S.-J. *J. Heterocycl. Chem.* **2008**, *45*, 693.
(12) Goswami, S.; Jana, S.; Hazra, A.; Adak, A. K. *J. Heterocycl. Chem.* **2007**, *44*, 1191.
(13) Cho, C. S.; Kim, J. U. *Tetrahedron Lett.* **2007**, *48*, 3775.
(14) (a) Iaroshenko, V. O.; Wang, Y.; Sevenard, D. V.; Volochnyuk, D. M. *Synthesis* **2009**, 1851. (b) Iaroshenko, V. O.; Volochnyuk, D. M.; Kryvokhyzha, N. V.; Martyloga, A.; Sevenard, D. V.; Groth, U.; Brand, J.; Chernega, A. N.; Shivanyuk, A. N.; Tolmachev, A. A. *Synthesis* **2008**, 2337.
(15) (a) Iaroshenko, V. O.; Sevenard, D. V.; Volochnyuk, D. M.; Wang, Y.; Martiloga, A.; Tolmachev, A. A. *Synthesis* **2009**, 1865. (b) Volochnyuk, D. M.; Pushechnikov, A. O.; Krotko, D. G.; Sibgatulin, D. A.; Kovalyova, S. A.; Tolmachev, A. A. *Synthesis* **2003**, 1531. (c) Iaroshenko, V. O.; Sevenard, D. V.; Kotljarov, A. V.; Volochnyuk, D. M.; Tolmachev, A. A.; Sosnovskikh, V. Ya. *Synthesis* **2009**, 731.
(16) Iaroshenko, V. O.; Groth, U.; Kryvokhyzha, N. V.; Obeid, S.; Tolmachev, A. A.; Wesch, T. *Synlett* **2008**, 343.
(17) Easterwood, L. M.; Véliz, E. A.; Beal, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 11537.
(18) (a) Véliz, E. A.; Easterwood, L. M.; Beal, P. A. *J. Am. Chem. Soc.* **2003**, *125*, 10867. (b) Cristalli, G.; Eleuteri, A.; Vittori, S.; Volpini, R.; Camaioni, E.; Lupidi, G. *Drug Dev. Res.* **1993**, *28*, 253. (c) Lupidi, G.; Marmocchi, F.; Cristalli, G. *Biochem. Mol. Biol.* **1998**, *46*, 1071. (d) Lupidi, G.; Cristalli, G.; Marmocchi, F.; Riva, F.; Grifantini, M. *J. Enzyme Inhib. Med. Chem.* **1985**, *1*, 67. (e) Okamoto, A.; Tanaka, K.; Saito, I. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 97.