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3-Acylindoles as versatile starting materials for pyridine ring annulation: synthesis of 1-deazapurine isosteres

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ABSTRACT

The reaction of electron-rich aminoheterocycles with 3-acyl- and 3-formylindoles results in indole ring opening and cyclocondensation to give heteroannulated pyridines, which can be regarded as purine isosteres. The transformations reported herein represent rare examples of domino reactions, which include the cleavage of an indole moiety.

1. Introduction

Purines and purinomimetics play an important role in drug design and drug discovery.[1,2] Many commercially available anticancer and anti-HIV drugs as well as various natural products contain fused 5,6- and 6,6-heterocyclic frameworks, which are often classified as purinomimetics or purine isosteres.[1] The application of purines and purine-like scaffolds in medicinal chemistry is of considerable current interest, due to the very good recognition of purine analogues by the current enzymes. The electronically modified synthetic purine analogues are often more active as the natural products themselves, because substrate turnover is prevented and the enzyme can be efficiently inhibited.[1] A great variety of purine analogues and corresponding nucleosides are used for the treatment of cancer.[2] Purine-like structures are also recognized as important scaffolds[3] for medicinal chemistry and drug design.

Purine isosteres (so-called pseudopurines) are derived from purine by replacement of the nitrogen atoms by carbon or sulfur atoms. For example, imidazo[4,5-*b*]pyridines (1-deazapurines) constitute an important class of heterocyclic compounds, which exhibit a wide range of biological activities and pharmacological properties.[4] The 1*H*-pyrazolo[3,4-*b*]pyridine substructure occurs in a set of potential drugs, such as BAY 41-2272, which is known to stimulate soluble guanylate cyclase (sGC) via a nitric oxide independent regulatory site and induces vasodilation.[5] Some pyrazolo[3,4-*b*]pyridines are also reported as potent inhibitors of glycogen synthase kinase-3 (GSK-3).[6] Pyrrolo[2,3-*b*]pyridines can be regarded as 1,7-deazapurines. The pharmacologically most significant compound among them is 7-azaindolylcarboxy-*endo*-tropanamide (DF 1012). The latter is the best candidate of a new class of non-narcotic antitussive compounds and is currently under investigation in phase II clinical trials.[7] The heterocyclic system of thiazolo[4,5-*d*]pyridines (1-deaza-7-thiopurines) have been reported to show antibacterial,[8a,b] and antisecretory[8c] activities and can play a role as non-imidazole histamine H3-antagonists.[8d] Pyrido[2,3-*d*]pyrimidines have been reported to exhibit a high activity against FGFR1 and VEGFR2,[9] and have been recently identified as FGFR3 inhibitors.[10]

Due to the great pharmacological relevance of these scaffolds, the development of methods for the efficient synthesis of purines and their analogues is of considerable current interest. In recent years, we have studied the synthesis of purines and purine isosteres by cyclization of electron-rich aminoheterocycles with various 1,3-CCC and 1,3-CNC bis-electrophiles (Fig. 1).[11] In this context, cyclocondensations of 3-formylchromone,[12,13] its thio analogue,[14] and perfluoroalkyl derivatives have been studied as 1,3-CCC-

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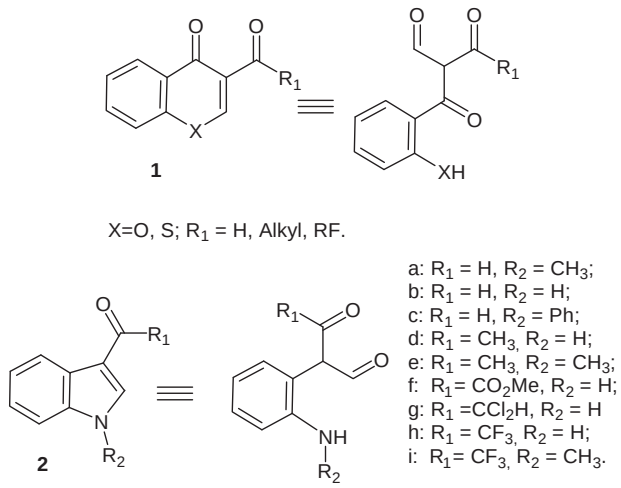


Fig. 1. 3-Acyl-chromones and 3-acylindoles as masked 1,3-CCC-dielectrophiles.

dielectrophiles.[14,15] 4-Formyl-uracyl[16] has been recently used as a building block for the synthesis of condensed pyridine systems, purine isosteres,[11] and pyrimidines.[12]

It occurred to us that 3-formyl- and 3-acylindoles might be used as bis-electrophiles for the synthesis of annulated pyridines. To the best of our knowledge, there has been reported only a single reaction so far, which proceeds by ring-cleavage of the indole moiety and subsequent cyclocondensation, i.e., the synthesis of pyrazolo [3,4-*b*]pyridines by reaction of indole-3-carboxaldehydes with 1-unsubstituted 5-aminopyrazoles reported by Park and co-workers.[17] Herein, we report, for the first time, the extension of this concept to various aminoheterocycles (Fig. 2) and to diverse 3-formyl- and 3-acylindoles (Fig. 1).

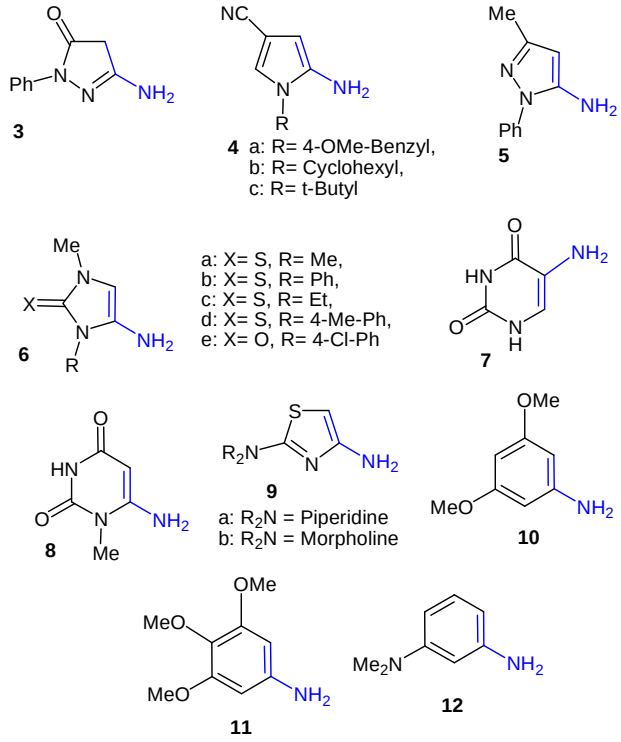
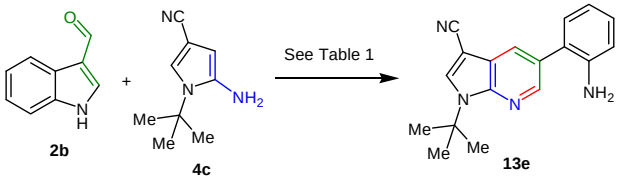


Fig. 2. Structures of the aminoheterocycles and electron-rich anilines used in this study.

2. Results and discussion

Our starting point was to find suitable conditions for the reaction of aminoheterocycles with 3-formylindoles **2a**–**c**. These reactions indeed proceeded, as expected, by cleavage of the indole moiety and subsequent cyclocondensation to give annulated pyridines. We have found that the reaction of various aminoheterocycles with 1-methyl-3-formylindole (**2a**) proceeded in very good yields when the reactions were carried out in DMF using TMSCl as a water scavenger.[16] Therefore, no further optimization was necessary for substrate **2a**. For 3-formylindole (**2b**) and 1-phenyl-3-formylindole (**2c**), the yields decreased significantly when the system DMF/TMSCl was used. Therefore, we tested different reaction conditions (see Scheme 1, Table 1). For both substrates we obtained the best results when the reaction was carried out in glacial acetic acid. The employment of the conditions reported by Park et al. ($AlCl_3$ in MeOH)[17] usually resulted in a decrease of the yield for formylindoles **2a**–**c**.



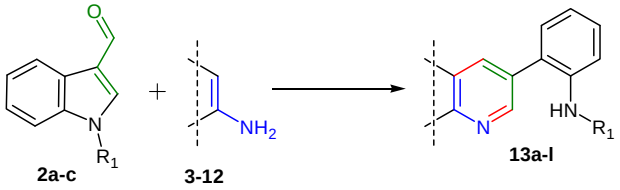
Scheme 1. Optimization of the reaction of **2b** with **4c**.

Table 1
Optimization of the reaction of **2b** with **4c**

Entry	System	Conditions	Yield[a] (%)
1	TMSCl/DMF	4 equiv TMSCl, 140 °C, 4 h	39
2	AcOH	100 °C, 4 h	53
3	$AlCl_3$/MeOH	10 mol % $AlCl_3$, 70 °C, 4 h	47
4	Formic acid/MeOH	10 mol % formic acid, 70 °C, 4 h	29
5	HCl/MeOH	10 mol % HCl, 70 °C, 4 h	0

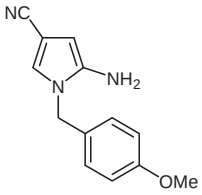
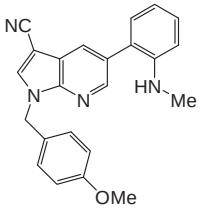
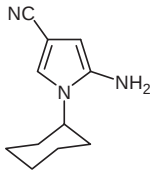
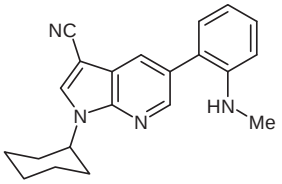
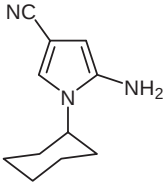
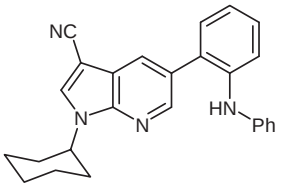
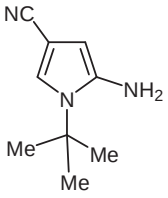
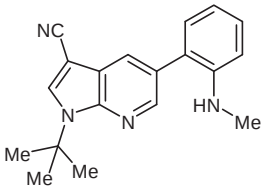
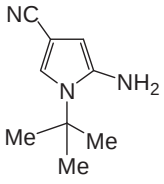
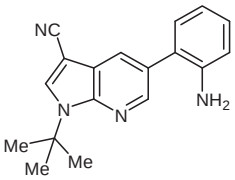
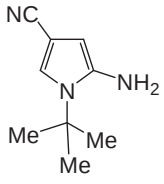
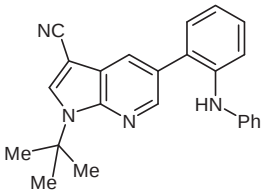
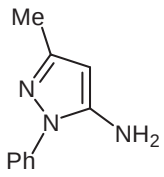
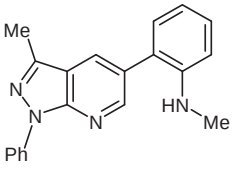
[a] Yields of isolated products.

With the results of the optimization studies in hand, we studied the reaction of 3-formylindoles **2a**–**c** with different aminoheterocycles **4a**–**c**, **5**, and **8** (Scheme 2). These reactions resulted in the formation of the heteroannulated pyridines **13a**–**l** in good yields (Table 2). In contrast, the amino-substituted imidazol-2-ones and imidazol-2-thiones **6** proved to be unstable and decomposed under the reaction conditions. As a result the yields of isolated products were extremely low and inseparable mixtures of unidentified products were formed. The reaction of 3-formylindoles with aminoheterocycle **7** and with anilines **10**–**12** failed. The analysis of the product mixtures revealed that predominantly the starting materials were present (low conversion). The structures of scaffolds **13** were independently confirmed by X-ray crystal structure analyses (Figs. 3–5).[18]



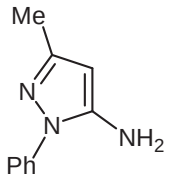
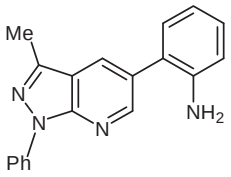
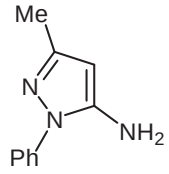
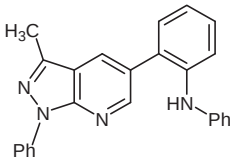
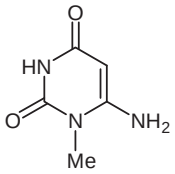
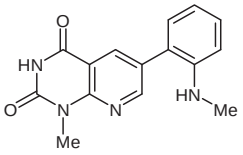
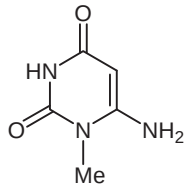
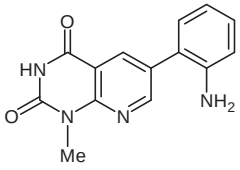
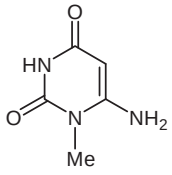
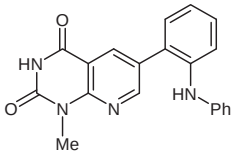
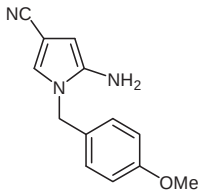
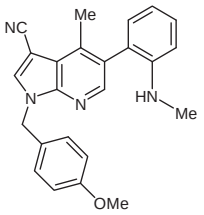
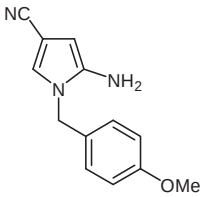
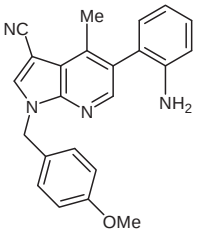
Scheme 2. Reagents and conditions: see Table 2.

Table 2
Synthesis of heteroannulated pyridines **13**, **16**, **17**

	Amine	Product	Yield[a] (%)
13a	 **4a**		60[b]
13b	 **4b**		65[b]
13c	 **4b**		41[c]
13d	 **4c**		78[b]
13e	 **4c**		53[c]
13f	 **4c**		45[c]
13g	 **5**		87[b]

(*continued on next page*)

Table 2 (*continued*)

	Amine	Product	Yield[a] (%)
13h	 **5**		57[c]
13i	 **5**		48[c]
13j	 **8**		58[b]
13k	 **8**		45[b]
13l	 **8**		33[b]
16a	 **4a**		73[d]
16b	 **4a**		51[d]

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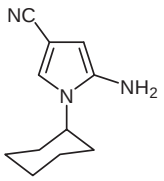
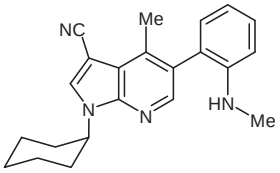
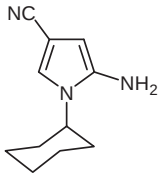
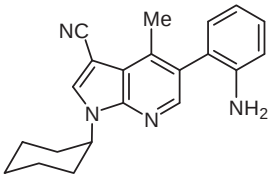
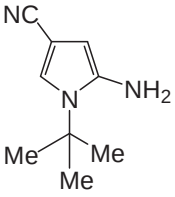
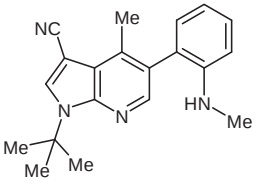
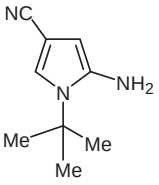
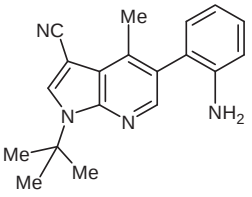
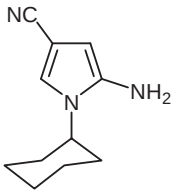
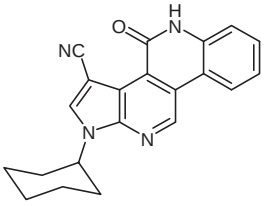
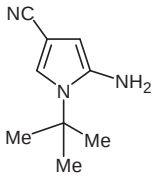
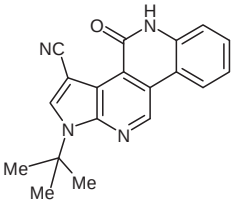
16c	 **4b**		67[d]
16d	 **4b**		45[d]
16e	 **4c**		55[d]
16f	 **4c**		35[d]
17a	 **4b**		40[d]
17b	 **4c**		44[d]

[a] Yields of isolated products.
[b] Procedure A, the DMF/TMSCl system.
[c] Procedure B, AcOH, reflux.
[d] Procedure C, $AlCl_3$, MeOH.

The reaction of 3-formylindoles with the hydrochlorides of 4-aminothiazoles **9** and aminopyrazole **3** resulted in a simple aldol condensation to give products **14** and **15** instead of the expected annulated ring systems, respectively (Scheme 3). Even in boiling acetic acid in the presence of 1.2 equiv of sodium acetate, used as a base for the amine liberation, it was not possible to get the desired pyridine system (Scheme 3). This result supports the mechanism proposed, which depicted in Scheme 5. The structure of **14** was independently confirmed by X-ray crystal structure analysis (Fig. 6).[18]

To get a more detailed understanding of the annulation process, we studied the employment of 3-acetylindole (**2d,e**) instead of 3-formylindoles **2a**–**c**. While the reactions of 3-formylindoles **2a**–**c** had no issue of regioselectivity, the reactions of **2d** can theoretically result in the formation of two different regioisomers. The reaction

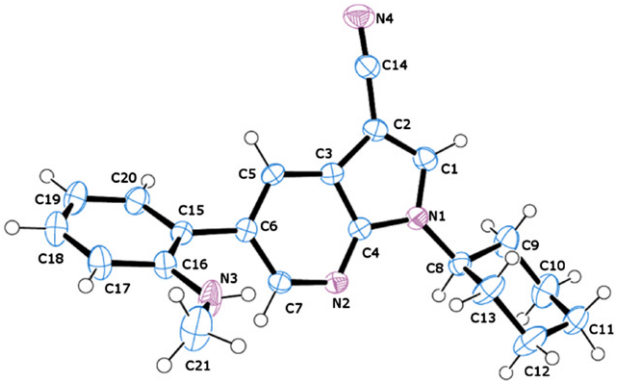


Fig. 3. Molecular structure of compound **13b**.

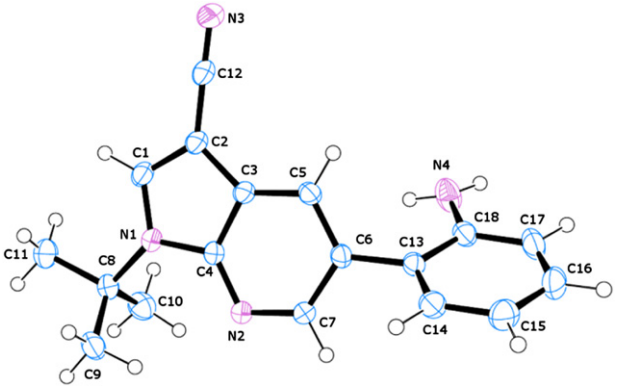


Fig. 4. Molecular structure of compound **13e**.

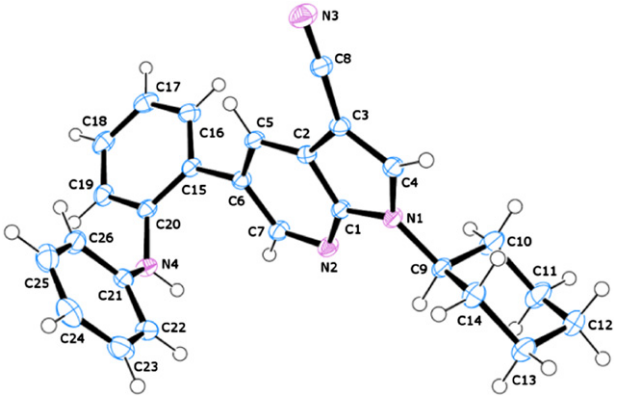
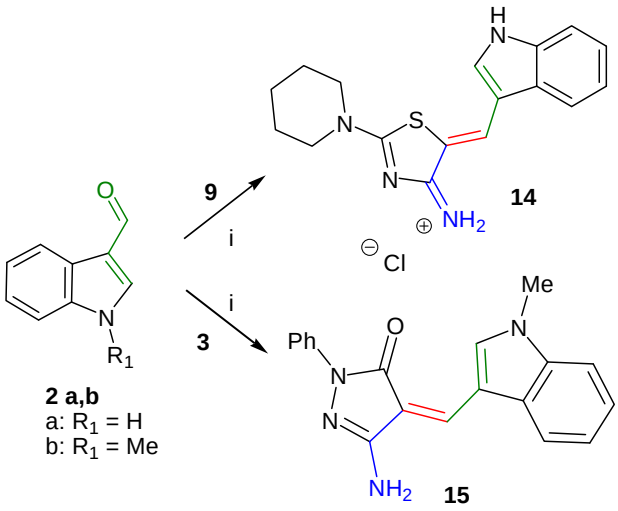


Fig. 5. Molecular structure of compound **13b**.

of aminoheterocycles **4a**–**c** with an equivalent amount of **2d**, carried out in dry MeOH in the presence of 50 mol % of $AlCl_3$ (best conditions in further optimization reactions), afforded the 4-substituted heteroannulated pyridines **16a**–**f** in good to excellent yields (Scheme 4, Table 2). The products were formed with excellent regioselectivity. The structure of **16a** was independently confirmed by X-ray crystal structure analysis (Fig. 7).[18] The reactions of aminoheterocycles with 3-acylindoles, which contain a $COCF_3$ (**2h,i**) or $COCCl_2H$ (**2g**) group instead of an acetyl group, failed. Analysis of the crude reaction mixture by HPLC and ^{19}F NMR showed the presence of a mixture of the starting materials and of some unidentified products. Not even traces of the desired heteroanulated pyridines could be detected.



Scheme 3. Synthesis of **14** and **15**. Reagents and conditions: (i) for compound **9**: AcOH, reflux, NaOAc (1.2 equiv); for compound **3**: AcOH, reflux.

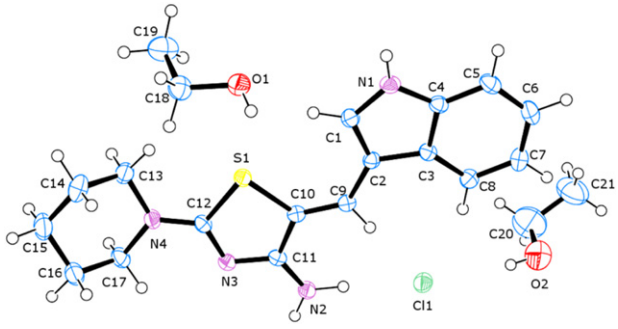
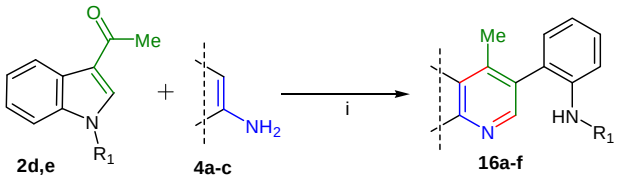


Fig. 6. Molecular structure of compound **14**.



Scheme 4. Reagents and conditions: (i) $AlCl_3$, MeOH.

The formation of products **16a**–**f** can be explained by addition of the enamine carbon atom of **4a**–**c** to the carbonyl group of **2d**,**e** to give intermediate **A** (Scheme 5). Subsequent attack of the amino

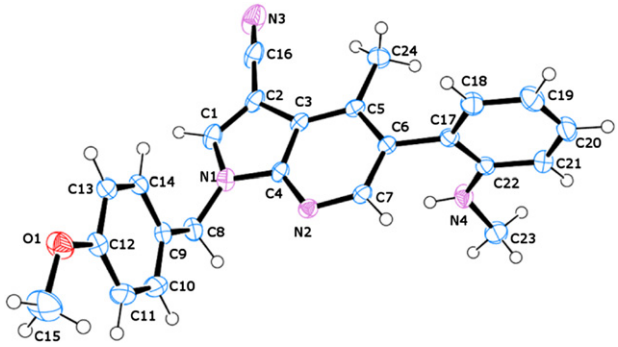
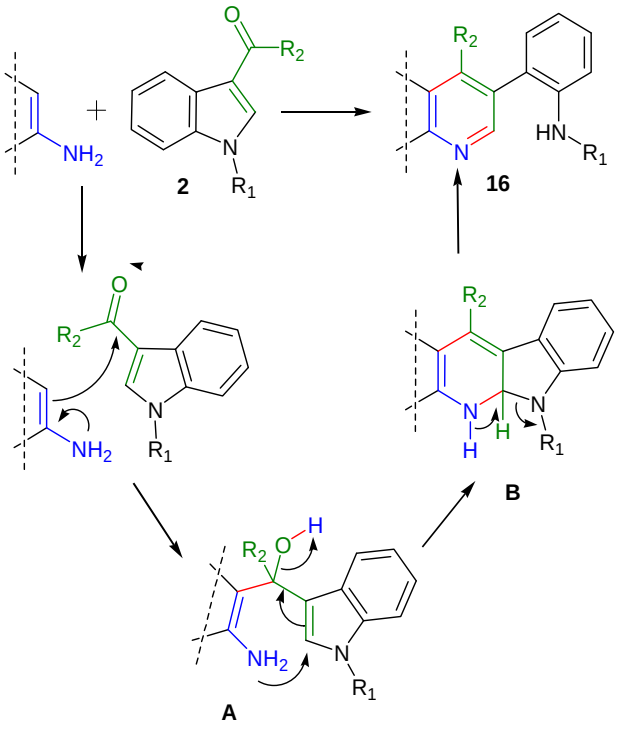


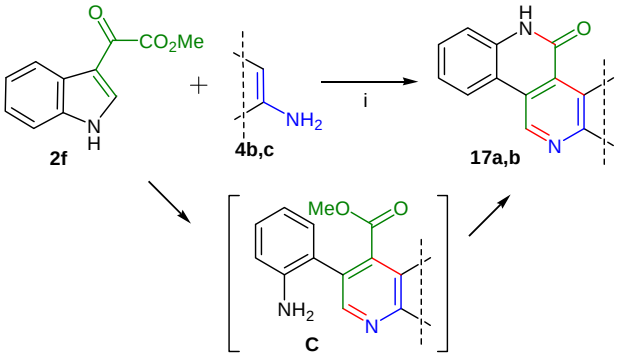
Fig. 7. Molecular structure of compound **16a**.



Scheme 5. A possible mechanism of the formation of **16a**–**f**.

group to carbon atom C-2 of the indole system results in the formation of intermediate **B**, which undergoes cleavage of the indole ring to give pyridines **16a**–**f**.

The reaction of aminoheterocycles **4b**,**c** with methyl 1*H*-indol-3-yl-2-oxoacetates **2f** containing an α-oxoester moiety, afforded the heteroannulated benzo[*c*][2,6]naphthyridin-5(6*H*)-ones **17a**,**b** (Scheme 6, Table 2). The formation of the products can be explained by a domino indole-cleavage/cyclocondensation reaction to give intermediate **C** and subsequent lactam formation by attack of the indole-derived amino group to the ester group.



Scheme 6. Reagents and conditions: (i) $AlCl_3$, MeOH.

In conclusion, we have reported a new and convenient one-step method for the synthesis of heteroannulated 3-(2-aminophenyl)-pyridines by cyclocondensation of 3-acylindoles with electron-rich aminoheterocycles. The reactions, which proceed under mild conditions, allow the assembly of privileged condensed heteroarylpyridine scaffolds with a wide scope and excellent regioselectivity. The biological evaluation of the synthesized compounds is currently studied in our laboratories.

3. Experimental section

3.1. General comments

Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker DPX-300 spectrometer. Chemical shifts of the ^{1}H and ^{13}C NMR are reported in parts per million using the solvent internal standard ($CDCl_3$ 7.26 ppm and 77.0 ppm, DMSO-d_6 2.49 ppm and 39.7 ppm). IR spectra were recorded on a Perkin–Elmer FT IR 1600 spectrometer 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 an MX-1321 instrument (EI, 70 eV) by direct inlet. Elemental analyses were carried out at the Microanalytical Laboratory of the University of Rostock, Germany. Melting points are uncorrected. The solvents DMF, methanol, and acetic acid were purchased directly from ACROS and used without further purification. Analytical thin layer chromatography was performed on 0.20 mm 60 A silica gel plates. Column chromatography was performed using 60 A silica gel (60–200 mesh).

3.2. Procedure A: general procedure of heteroannelated pyridines synthesis in DMF/TMSCl

Appropriate indole of 1.0 equiv, 1.1 equiv of the corresponding aminoheterocycle, and 4 equiv of TMSCl in 15 mL of anhydrous DMF was heated at 100 °C under dry argon atmosphere in a pressure tube. After 6 h the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography.

3.3. Procedure B: general procedure of heteroannelated pyridines synthesis in acetic acid

Appropriate indole of 1.0 equiv and 1.1 equiv of the corresponding aminoheterocycle were heated in 15 mL of acetic acid at 100 °C under dry argon atmosphere in a pressure tube. After 4 h, the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography.

3.4. Procedure C: general procedure of heteroannelated pyridines synthesis in methanol with $AlCl_3$

Appropriate indole of 1.0 equiv, 1.0 equiv of the corresponding aminoheterocycle and 0.5 equiv of $AlCl_3$ were heated in 20 mL of dry methanol at 70 °C. When the reaction was completed (TLC control), the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography.

3.5. Procedure D: procedure for the synthesis of compounds 14 and 15

Appropriate indole of 1.0 equiv and 1.0 equiv of the corresponding aminoheterocycle (in the case of **9a** 1.2 equiv of NaOAc was added) were heated in 15 mL of acetic acid. After 4 h the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (compound **15**) or the precipitate was collected, washed with water and dried (compound **14**).

*3.5.1. 3-Cyano-1-(p-methoxybenzyl)-5-(N-methyl-2-aminophenyl) pyrrolo[2,3-b]pyridine (**13a**).* Procedure A; brown solid; 60%; mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=2.76 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.37 (br, 2H, NH_2), 6.65–6.82 (m, 4H, H_{Aryl}), 7.02 (dd, 1H, ^3J=1.5,7.5 Hz), 7.17–7.26 (m, 3H, H_{Aryl}), 7.60 (s, 1H, (CN)C=C*H*), 8.04 (d, 1H, ^4J=1.89 Hz), 8.42 (d, 1H, ^4J=1.89 Hz). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=30.7, 48.3, 55.3, 84.8, 110.1, 114.4, 115.0, 117.1, 120.1, 123.9, 127.6, 128.9, 129.5, 129.6, 129.7, 130.1, 130.8, 135.2, 145.9,

146.6, 146.6, 159.8. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3443(w), 3111 (w), 3067 (w), 3033 (w), 2958 (w), 2934 (w), 2865 (w), 2839 (w), 2814 (w), 2220 (w), 1599 (w), 1576 (w), 1525 (w), 1510 (s), 1483 (w), 1456 (w), 1440 (w), 1415 (m), 1395 (w), 1352 (w), 1340 (w), 1303 (w), 1293 (m), 1245 (s), 1210 (w), 1180 (m), 1166 (s), 1122 (w), 1068 (w), 1027 (m), 972 (w), 950 (w), 940 (w), 902 (w), 850 (m), 841 (w), 822 (m), 779 (m), 748 (s), 682 (w), 649 (m), 621 (m), 604 (m). MS (EI, 70 eV): *m*/*z* (%)=368 (M^+, 66), 121 (100). HRMS (ESI): calcd for $C_{23}H_{20}N_4O$ ($M+H^+$) 369.171, found 369.1712.

*3.5.2. 3-Cyano-1-cyclohexyl-5-(N-methyl-2-aminophenyl)pyrrolo [2,3-b]pyridine (**13b**).* Procedure A; white-brown solid; 65%; mp 184–185 °C; ^{1}H NMR ($CDCl_3$, 250 Hz): δ=1.14–1.31 (m, 1H, $H_{Cyclohexyl}$), 1.42–1.78 (m, 5H, $H_{Cyclohexyl}$), 1.88–1.92 (m, 2H, $H_{Cyclohexyl}$), 2.13–2.14 (m, 2H, $H_{Cyclohexyl}$), 2.74 (s, 3H, NCH_3), 4.72–4.83 (m, 1H, $H_{Cyclohexyl}$), 6.69–6.79 (m, 2H, H_{Ar}), 7.04 (dd, ^3J=1.5, 8.0 Hz, 1H, H_{Ar}), 7.22–7.29 (m, 1H, H_{Ar}), 7.79 (s, 1H, (CN)C=C*H*), 8.05 (d, ^4J=2.1 Hz, 1H, H_{Hetar}), 8.39 (d, ^4J=2.1 Hz, 1H, H_{Hetar}). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=25.3, 25.6, 30.7, 33.5, 54.4, 84.3, 110.0, 115.3, 117.1, 120.2, 124.0, 128.8, 129.5, 129.9, 130.7, 132.8, 145.4, 146.0, 146.5. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3477(w), 3385 (w), 3148 (w), 3024 (w), 2975 (w), 2932 (w), 2870 (w), 2221 (m), 1613 (m), 1525 (m), 1501 (m); 1479 (m), 1447 (m), 1400 (m), 1347 (m), 1282 (m), 1202 (s), 916 (m), 850 (m), 781 (m), 749 (s), 637 (m). MS (EI, 70 eV): *m*/*z* (%)=330 (M^+, 100), 248 (62), 232 (16). HRMS (ESI): calcd for $C_{21}H_{22}N_4$ (M^+) 330.18390, found 330.18318. Anal. Calcd for $C_{21}H_{22}N_4$ (330.42): C, 76.33; H, 6.71; N, 16.96. Found: C, 76.33; H, 6.81; N, 16.75.

*3.5.3. 3-Cyano-1-cyclohexyl-5-(N-phenyl-2-aminophenyl)pyrrolo [2,3-b]pyridine (**13c**).* Procedure B; brown solid; 41%; mp 188–189 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.25–2.00 (m, 10H, $H_{Cyclohexyl}$), 4.70–4.79 (m, 1H, $H_{Cyclohexyl}$), 6.69–6.74 (m, 1H, H_{Aryl}), 6.85–6.88 (m, 2H, H_{Aryl}), 7.10–7.16 (m, 3H, H_{Aryl}), 7.33–7.45 (m, 4H, H_{Aryl}), 8.11 (d, ^4J=1.9 Hz, 1H, $H_{Hetaryl}$), 8.45 (d, ^4J=1.9 Hz, 1H, $H_{Hetaryl}$), 8.63 (s, 1H, (CN)C=C*H*–N). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=24.8, 25.2, 32.4, 54.0, 82.6, 115.4, 115.9, 118.8, 119.2, 121.7, 122.8, 127.5, 128.7, 128.9, 130.1, 131.2, 131.6, 135.3, 140.5, 144.7, 145.0, 145.3. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3359(w), 3114 (w), 3043 (w), 3020 (w), 2954 (w), 2927 (w), 2846 (w), 2219 (w), 1607 (w), 1592 (w), 1520 (w), 1504 (m), 1495 (m), 1460 (m), 1450 (m), 1350 (w), 1307 (m), 1290 (w), 1265 (w), 1184 (m), 1173 (w), 1150 (w), 1049 (w), 991 (w), 898 (m), 885 (w), 843 (w), 779 (w), 755 (s), 746 (s), 717 (w), 696 (m), 667 (w), 627 (m). MS (EI, 70 eV): *m*/*z* (%)=392 (M^+, 100), 310 (56). HRMS (ESI): calcd for $C_{26}H_{24}N_4$ (M^+) 392.19955, found 392.199201.

*3.5.4. 1-tert-Butyl-3-cyano-5-(N-methyl-2-aminophenyl)pyrrolo [2,3-b]pyridine (**13d**).* Procedure A; orange-brown solid; 78%; mp 132–133 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.75 (s, 9H, CH_3), 2.59 (d, ^3J=4.9 Hz, 3H, CH_3), 4.98 (q, ^3J=4.9 Hz, 1H, N*H*CH_3), 6.56–6.65 (m, 2H, CH_{Ar}), 6.98 (dd, $^3J_{CH}$=1.7,7.5 Hz, 1H, CH_{Ar}), 7.13–7.20 (m, 1H, CH_{Ar}), 7.93 (d, ^4J=2.1 Hz, 1H, CH_{Hetar}), 8.31 (d, $^4J_{CH}$=2.1 Hz, 1H, CH_{Hetar}), 8.48 (s, 1H, (CN)C=C*H*). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=28.7, 30.3, 58.4, 81.7, 109.7, 115.5, 116.0, 120.7, 123.5, 127.7, 129.1, 129.3, 130.6, 136.0, 144.7, 145.7, 147.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3405(m), 3139 (w), 3034 (w), 2981 (w), 2813 (w), 2219 (s), 1714 (w), 1601 (m), 1579 (m), 1514 (s), 1474 (m), 1460 (m), 1405 (m), 1397 (m), 1368 (m), 1317 (m), 1288 (m), 1263 (m), 1202 (s), 1167 (m), 898 (m), 855 (m), 780 (m), 739 (m), 731 (m), 638 (m). MS (EI, 70 eV): *m*/*z* (%)=304 (M^+, 100), 248 (93), 232 (25). HRMS (ESI): calcd for $C_{19}H_{21}N_4$ (M^+) 305.1761, found 305.1762. Anal. Calcd for $C_{19}H_{20}N_4$ (304.39): C 74.97; H 6.62; N 18.41. Found: C, 74.61; H, 6.85; N, 17.98.

*3.5.5. 5-(2-Aminophenyl)-3-cyano-1-tert-butylpyrrolo[2,3-b]pyridine (**13e**).* Procedure B; white-brown solid; 53%; mp 151–153 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.85 (s, 9H, CH_3), 4.99 (br, 2H, NH_2), 6.69–6.75 (m, 1H, H_{Ar}), 6.86 (d, ^3J=7.7 Hz, 1H, H_{Ar}), 7.10–7.17 (m, 2H, H_{Ar}), 8.11 (d, ^4J=2.05 Hz, 1H, H_{Hetar}), 8.49 (d, ^4J=2.05 Hz, 1H, H_{Hetar}), 8.59 (s, 1H, (CN)C=C*H*). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=28.6, 58.4, 81.7, 115.4, 115.5, 116.8, 120.6, 122.5, 127.2, 128.6, 129.6, 130.7, 136.0, 144.4, 145.5, 145.8. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3477(w), 3385 (w), 3148 (w), 3024 (w), 2975 (w), 2932 (w), 2870 (w), 2221 (m), 1613 (m), 1525 (m), 1501 (m); 1479 (m), 1447 (m), 1400 (m), 1347 (m), 1282 (m), 1202 (s), 916 (m), 850 (m), 781 (m), 749 (s), 637 (m). MS (EI, 70 eV): *m*/*z* (%)=290 (M^+, 56), 234 (100). HRMS (ESI): calcd for $C_{18}H_{18}N_4$ (M^+) 290.15260, found 290.152580.

*3.5.6. 1-tert-Butyl-3-cyano-5-(N-phenyl-2-aminophenyl)pyrrolo [2,3-b]pyridine (**13f**).* Procedure B; white-yellow solid; 45%; mp 95–97 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.75 (s, 9H, C(CH_3)$_3$), 6.66–6.84 (m, 1H, H_{Ar}), 6.84–6.87 (m, 2H, H_{Ar}), 7.08–7.14 (m, 3H, H_{Ar}), 7.31–7.45 (m, 4H, H_{Ar}), 8.05 (d, ^4J=2.1 Hz, 1H, H_{Hetar}), 8.45 (d, ^4J=2.1 Hz, 1H, H_{Hetar}), 8.49 (s, 1H, (CN)C=C*H*). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=28.6, 58.4, 81.6, 115.4, 116.0, 118.8, 120.5, 121.6, 122.8, 127.3, 128.7, 128.9, 129.5, 131.0, 131.6, 135.9, 140.6, 144.5, 145.0, 145.5. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3319(w), 3093 (w), 3039 (w), 2969 (w), 2935 (w), 2871 (w), 2236 (w), 2216 (w), 1604 (w), 1589 (m), 1518 (m), 1495 (m), 1455 (m), 1403 (m), 1370 (m), 1347 (m), 1305 (m), 1290 (m), 1205 (m), 1090 (w), 1052 (m), 1027 (m), 1008 (m), 907 (m), 896 (m), 885 (m), 779 (m), 748 (s), 697 (m), 654 (m), 637 (m), 619 (m). MS (EI, 70 eV): *m*/*z* (%)=366 (M^+, 99), 310 (100). HRMS (ESI): calcd for $C_{24}H_{22}N_4$ (M^+) 366.18390, found 366.183715.

*3.5.7. 3-Methyl-(N-methyl-2-aminophenyl)-1-phenylpyrazolo[3,4-b] pyridine (**13g**).* Procedure A; brown solid; 87%; mp155–157 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=2.58 (s, 3H, CH_3), 2.74 (d, ^3J=4.9 Hz, 3H, NHCH_3), 6.68 (d, ^3J=7.9 Hz, 1H, H_{Ar}), 6.73–6.78 (m, 1H, H_{Ar}), 7.07 (dd, ^3J=1.6, 7.8 Hz, 1H, H_{Ar}), 7.19–7.29 (m, 2H, H_{Ar}), 7.41–7.47 (m, 2H, H_{Ar}), 8.00 (d, ^4J=1.9 Hz, 1H, H_{Hetar}), 8.17–8.21 (m, 2H, H_{Ar}), 8.57 (d, ^4J=1.9 Hz, 1H, H_{Hetar}). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=12.5, 30.8, 110.1, 117.1, 117.2, 120.9, 124.1, 125.7, 128.5, 129.1, 129.5, 130.1, 130.8, 139.5, 142.7, 146.7, 150.0, 150.5. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3418(w), 3331 (m), 3015 (w), 2988 (w), 2935 (w), 2842 (w), 2774 (w), 1651 (s), 1633 (s), 1563 (w), 1557 (w), 1504 (w), 1497 (w), 1442 (w), 1413 (w), 1390 (m), 1342 (w), 1315 (w), 1252 (m), 1167 (w), 1112 (m), 1076 (w), 1062 (w), 1028 (w), 957 (w), 905 (w), 773 (w), 744 (m). MS (EI, 70 eV): *m*/*z* (%)=314 (M^+, 100), 299 (5). HRMS (ESI): calcd for $C_{20}H_{19}N_4$ ($M+H^+$) 315.1604, found 315.1612.

*3.5.8. 5-(2-Aminophenyl)-3-methyl-1-phenylpyrazolo[3,4-b]pyridine (**13h**).* Procedure B; white-brown solid; 57%; mp 135–136 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=2.62 (s, 3H, CH_3), 4.97 (br, 2H, NH_2), 6.65–6.71 (m, 1H, H_{Ar}), 6.79–6.82 (d, ^3J=7.6 Hz, 1H, H_{Ar}), 7.07–7.14 (m, 2H, H_{Ar}), 7.27–7.32 (m, 1H, H_{Ar}), 7.52–7.58 (m, 2H, H_{Ar}), 8.30–8.33 (m, 3H, $H_{Ar+Hetar}$), 8.63 (d, ^4J=2.05 Hz, 1H, H_{Hetar}). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=12.1, 115.3, 116.7, 116.8, 119.7, 122.4, 125.2, 128.7, 129.1, 129.2, 130.1, 130.7, 139.3, 143.0, 145.9, 149.3, 150.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3411(w), 3335 (m), 3222 (w), 3066 (w), 3045 (w), 3035 (w), 2955 (w), 2920 (w), 1621 (w), 1593 (m), 1500 (m), 1456 (m), 1380 (m), 1347 (m), 1302 (w), 1263 (m), 1245 (m), 1201 (w), 1120 (m), 1076 (m), 1009 (m), 956 (w), 901 (m), 775 (m), 741 (m), 689 (m), 667 (m). MS (EI, 70 eV): *m*/*z* (%)=300 (M^+, 100), 258 (5). HRMS (ESI): calcd for $C_{19}H_{16}N_4$ (M^+) 300.13695, found 300.136872. Anal. Calcd for $C_{19}H_{16}N_4$ (300.14): C, 75.98; H, 5.37; N, 18.65. Found: C, 75.59; H, 5.48; N, 18.53.

*3.5.9. 3-Methyl-5-(N-phenyl-aminophenyl)-1-phenylpyrazolo[3,4-b] pyridine (**13i**).* Procedure B; white-yellow solid; 48%; mp 197–199 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=2.61 (s, 3H, CH_3),

6.70–6.75 (m, 1H, H_{Ar}), 6.87–6.90 (m, 2H, H_{Ar}), 7.10–7.20 (m, 3H, H_{Ar}), 7.27–7.57 (m, 8H, H_{Ar}), 8.28–8.31 (m, 2H, H_{Ar}), 8.36 (d, ^4J=2.1 Hz, 1H, H_{Hetar}), 8.66 (d, ^4J=2.1 Hz, 1H, H_{Hetar}). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=12.1, 115.9, 116.8, 118.9, 119.6, 120.1, 121.6, 122.8, 125.2, 128.8, 128.9, 129.1, 130.1, 130.8, 131.5, 139.2, 140.5, 143.0, 144.9, 149.2, 150.1. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3288(w), 3041 (w), 2920 (w), 2849 (w), 1591 (m), 1576 (m), 1563 (w), 1520 (w), 1494 (s), 1468 (m), 1455 (m), 1438 (m), 1426 (m), 1411 (m), 1384 (w), 1343 (w), 1299 (m), 1255 (m), 1223 (w), 1172 (w), 1118 (w), 1076 (w), 1026 (w), 957 (w), 908 (w), 883 (w), 838 (w), 774 (w), 743 (s), 706 (m), 688 (m), 665 (m). MS (EI, 70 eV): *m*/*z* (%)=376 (M$^+$, 100). HRMS (ESI): calcd for $C_{25}H_{20}N_4$ (M$^+$) 376.16825, found 376.167382.

*3.5.10. 1-Methyl-6-(N-methyl-2-aminophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**13j**).* Procedure A; yellow solid; 58%; mp 240–242 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=2.68 (d, 3H, ^3J=4.6 Hz, CH_3), 3.58 (s, 3H, *N*–CH_3), 5.14 (q, 1H, ^3J=4.6 Hz, N*H*(CH_3)), 6.67–6.75 (m, 2H, H_{Ar}), 7.05–7.07 (m, 1H, H_{Ar}), 7.25–7.30 (m, 1H, H_{Ar}), 8.27 (d, 1H, ^4J=2.2 Hz, H_{Hetar}), 8.71 (d, 1H, ^4J=2.3 Hz, H_{Hetar}), 11.82 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=28.2, 30.2, 110.0, 110.8, 116.2, 121.8, 129.6, 130.1, 130.2, 136.7, 147.0, 150.5, 150.7, 154.2, 161.2. IR (ATR, cm^{-1}):$\tilde{\nu}$ = 3404(m), 3014 (m), 2783 (m), 1722 (w), 1714 (w), 1678 (s), 1604 (s), 1580 (m), 1494 (m), 1466 (m), 1433 (m), 1371 (w), 1338 (w), 1306 (w), 1288 (m), 1253 (w), 1168 (m), 1021 (m), 959 (w), 879 (w), 794 (s), 738 (s). MS (EI, 70 eV): *m*/*z* (%)=281 (M–H$^+$, 100). HRMS (ESI): calcd for $C_{15}H_{14}O_2N_4$ (M$^+$) 282.11113, found 282.110628.

*3.5.11. 6-(2-Aminophenyl)-1-methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**13k**).* Procedure A; yellow solid; 45%; mp 243–244 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=3.59 (s, 3H, CH_3), 5.03 (br, 2H, NH_2), 6.69–6.74 (m, 1H, H_{Ar}), 6.83–6.85 (m, 1H, H_{Ar}), 7.08–7.18 (m, 2H, H_{Ar}), 8.36 (d, ^4J=2.5 Hz, 1H), 8.78 (m, ^4J=2.5 Hz, 1H), 11.81 (br, 1H, N*H*). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=28.2, 110.8, 115.6, 116.9, 120.8, 129.1, 130.2, 130.4, 136.2, 145.9, 150.5, 153.9, 161.2. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3444(w), 3346 (w), 3170 (w), 3027 (w), 2846 (w), 1683 (s), 1633 (w), 1607 (s), 1580 (m), 1574 (m), 1503 (m), 1487 (m), 1447 (m), 1429 (m), 1409 (w), 1367 (m), 1345 (m), 1304 (m), 1292 (m), 1265 (m), 1239 (m), 1081 (w), 937 (w), 794 (m), 756 (s), 745 (s), 708 (w), 673 (w), 656 (w). MS (EI, 70 eV): *m*/*z* (%)=267 (M–H$^+$, 100), 224 (6), 169 (7). HRMS (ESI): calcd for $C_{14}H_{12}O_2N_4$ (M$^+$) 268.09548, found 268.095398.

*3.5.12. 1-Methyl-6-(N-phenyl-2-aminophenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (**13l**).* Procedure A; brown solid; 33%; mp 292–293 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=3.53 (s, 1H, CH_3), 6.71–6.86 (m, 3H, H_{Ar}), 7.12–7.19 (m, 3H, H_{Ar}), 7.36–7.41 (m, 3H, H_{Ar}), 7.51–7.56 (m, 1H, H_{Ar}), 8.35 (d, ^4J=2.5 Hz, 1H, H_{Hetar}), 8.77 (d, ^4J=2.5 Hz, 1H, H_{Hetar}). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=116.0, 119.0, 121.7, 123.0, 128.9, 129.3, 129.3, 130.2, 130.9, 136.2, 140.5, 144.7, 150.4, 150.7, 153.9, 161.1. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3346(w)=3346 (w), 3152 (w), 3044 (w), 2841 (w), 1693 (s), 1605 (m), 1591 (m), 1573 (m), 1519 (m), 1497 (m), 1477 (m), 1463 (m), 1370 (m), 1339 (m), 1306 (s), 1283 (m), 1262 (m), 1078 (w), 1058 (w), 1037 (w), 1028 (w), 963 (w), 933 (w), 906 (w), 871 (m), 858 (m), 793 (m), 754 (s), 747 (s), 700 (m), 672 (m). MS (EI, 70 eV): *m*/*z* (%)=344 (M$^+$, 100), 243 (6). HRMS (ESI): calcd for $C_{20}H_{15}O_2N_4$ (M$^+$) 343.11895, found 343.119401.

*3.5.13. (Z)-5-((1H-Indol-3-yl)methylene)-2-(piperidin-1-yl)thiazol-4(5H)-iminium chloride (**14**).* Procedure D; orange solid; 83%; mp 297–299 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.71 (m, 6H, CH_2), 3.73 (m, 2H, CH_2), 3.99 (m, 2H, CH_2), 7.24–7.32 (m, 2H, H_{Ar}), 7.52–7.58 (m, 1H, H_{Ar}), 8.00 (s, 1H, C=C*H*–C), 8.04–8.11 (m, 1H, H_{Ar}), 8.98 (m, 1H, C=C*H*–N), 10.02 (br, NH_{3^+}), 12.54 (br, NH). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=22.9, 25.0, 25.4, 49.1, 52.3, 111.1, 112.5, 116.5, 118.8, 121.5, 123.4, 127.2, 128.5, 129.7, 136.3, 173.6, 174.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3046(w), 2990 (w), 1667 (w), 1587 (w), 1574 (w), 1514 (m), 1487 (w), 1461 (w), 1442 (w), 1392 (m), 1374 (m), 1354 (m), 1343 (m), 1325 (m), 1305 (m), 1279 (m), 1253 (w), 1225 (m), 1143 (m), 1116 (m), 1074 (m), 1065 (m), 1032 (m), 1014 (m), 999 (m), 920 (w), 881 (w), 852 (w), 794 (w), 757 (w), 744 (s), 704 (s), 640 (m), 614 (m). MS (EI, 70 eV): *m*/*z* (%)=310 (M$^+$, 100), 295 (8), 281 (47), 267 (13), 254 (31), 241 (19), 227 (12), 207 (31), 173 (9), 155 (9), 140 (9). HRMS (ESI): calcd for $C_{17}H_{18}N_4S$ (M+H$^+$) 311.1325, found 311.1332.

*3.5.14. (Z)-3-Amino-4-((1-methyl-1H-indol-3-yl)methylene)-1-phenyl-1H-pyrazol-5(4H)-one (**15**).* Procedure D; red-brown solid; 71%; mp 236–238 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=4.00 (s, 1H, CH_3), 6.30 (s, 2H, NH_2), 7.06 (t, ^3J=7.4 Hz, 1H, H_{Ar}), 7.35–7.41 (m, 4H, H_{Ar}), 7.64–7.67 (m, 1H, H_{Ar}), 8.01–8.04 (m, 2H, H_{Ar}), 8.11–8.15 (m, 1H, H_{Ar}), 8.24 (s, 1H, C=C*H*–C), 9.66 (s, 1H, C=C*H*–N). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=33.8, 110.3, 111.3, 113.4, 117.2, 118.4, 122.1, 122.6, 123.2, 128.5, 128.9, 133.9, 136.9, 139.3, 140.2, 153.2, 161.4. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3443(w), 3344 (w), 3294 (w), 3162 (w), 3128 (w), 3063 (w), 2922 (w), 2851 (w), 1732 (w), 1683 (w), 1669 (w), 1636 (w), 1604 (w), 1594 (m), 1497 (w), 1485 (w), 1470 (w), 1433 (m), 1382 (m), 1327 (s), 1311 (m), 1237 (w), 1211 (w), 1153 (m), 1124 (m), 1068 (m), 1016 (w), 919 (w), 891 (w), 871 (w), 786 (w), 772 (m), 741 (s), 702 (m), 689 (m). MS (EI, 70 eV): *m*/*z* (%)=316 (M$^+$, 100), 209 (14), 183 (37), 144 (9), 78 (19), 63 (21), 44 (12). HRMS (ESI): calcd for $C_{19}H_{17}N_4O$ (M$^+$) 317.1397, found 317.1395.

*3.5.15. 3-Cyano-1-(p-methoxybenzyl)-4-methyl-5-(N-methyl-2-aminophenyl)pyrrolo[2,3-b]pyridine (**16a**).* Procedure C; white solid; 73%; mp 154–155 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=2.47 (s, 3H, CH_3), 2.72 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 5.36 (s, 2H, CH_2), 6.66–6.84 (m, 4H, H_{Ar}), 6.92–6.95 (dd, ^3J=1.58, 8.0 Hz, 1H, H_{Ar}), 7.18–7.31 (m, 3H, H_{Ar}), 7.59 (s, 1H, H_{Hetar}), 8.18 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=15.2, 30.7, 48.3, 55.3, 84.3, 110.0, 114.5, 116.6, 117.0, 119.2, 122.9, 127.7, 129.3, 129.4, 129.6, 130.8, 135.3, 140.7, 146.1, 146.8, 147.1, 159.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3353(w), 3120 (w), 3042 (w), 2978 (w), 2930 (w), 2904 (w), 2862 (w), 2809 (w), 2214 (s), 1606 (m), 1513 (s), 1410 (m), 1394 (m), 1304 (m), 1292 (m), 1255 (m), 1240 (m), 1179 (m), 1035 (m), 845 (m), 831 (m), 820 (m), 808 (m), 738 (m). MS (EI, 70 eV): *m*/*z* (%)=382 (M$^+$, 61), 122 (9), 121 (100). HRMS (ESI): calcd for $C_{24}H_{22}N_4O$ (M$^+$) 382.17881, found 382.17813. Anal. Calcd for $C_{24}H_{22}N_4O$ (382.45): C, 75.37; H, 5.80; N, 14.65. Found: C, 75.37; H, 5.93; N, 14.49.

*3.5.16. 5-(2-Aminophenyl)-3-cyano-1-(p-methoxybenzyl)-4-methylpyrrolo[2,3-b]pyridine (**16b**).* Procedure C; yellow solid; 51%; mp 72–74 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=2.52 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.36 (s, 2H, CH_2), 6.72–6.83 (m, 4H, H_{Ar}), 6.94–6.97 (dd, ^3J=1.5, 7.4 Hz, 1H, H_{Ar}), 7.13–7.23 (m, 3H, H_{Ar}), 7.59 (s, 1H, H_{Hetar}), 8.21 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=15.2, 48.3, 55.3, 84.3, 114.5, 115.3, 116.6, 118.4, 119.2, 123.0, 127.7, 129.2, 129.5, 129.6, 131.1, 135.3, 140.4, 144.6, 146.1, 146.9, 159.7. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3454(w), 3109 (w), 2215 (s), 1611 (m), 1512 (s), 1414 (m), 1393 (m), 1294 (m), 1246 (m), 1172 (m), 1030 (m), 810 (m), 748 (m). MS (EI, 70 eV): *m*/*z* (%)=368 (M$^+$, 57), 121 (100). HRMS (ESI): calcd for $C_{23}H_{21}N_4O$ (M$^+$) 369.171, found 369.1708.

*3.5.17. 3-Cyano1-cyclohexyl-4-methyl-5-(N-methyl-2-aminophenyl) pyrrolo[2,3-b]pyridine (**16c**).* Procedure C; white solid; 67%; mp 159–160 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.17–1.31 (m, 1H, $H_{Cyclohexyl}$), 1.431.65 (m, 5H, $H_{Cyclohexyl}$), 1.78–1.93 (m, 2H, $H_{Cyclohexyl}$), 2.08–2.13 (m, 2H, $H_{Cyclohexyl}$), 2.48 (s, 3H, CH_3), 2.72 (s, 3H, NCH_3), 4.72–4.81 (m, 1H, $H_{Cyclohexyl}$), 6.67–6.77 (m, 2H, H_{Ar}), 6.94 (dd, ^3J=1.5, 8.1 Hz, 1H, H_{Ar}), 7.25–7.31 (m, 1H, H_{Ar}), 7.78 (s, 1H, H_{Hetar}),

8.15 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=15.2, 25.3, 25.6, 30.6, 33.5, 54.1, 83.7, 109.7, 116.7, 117.0, 119.4, 122.8, 129.2, 129.4, 130.7, 132.9, 140.6, 145.6, 146.6, 147.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3326(m), 3130 (w), 2932 (m), 2855 (w), 2809 (w), 2215 (m), 2156 (w), 1575 (m), 1514 (s), 1486 (m), 1452 (m), 1391 (m), 1283 (m), 1184 (m), 1169 (m), 991 (m), 838 (m), 745 (s), 647 (s), 618 (s). MS (EI, 70 eV): *m*/*z* (%)=344 (M^+, 100), 262 (83), 247 (30), 231 (14). HRMS (ESI): calcd for $C_{22}H_{24}N_4$ (M^+) 344.19955, found 344.19893.

*3.5.18. 5-(2-Aminophenyl)-3-cyano-1-cyclohexyl-4-methylpyrrolo [2,3-b]pyridine (**16d**).* Procedure C; yellow solid; 45%; mp 170–171 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.18–1.31 (m, 1H, $H_{Cyclohexyl}$), 1.43–1.77 (m, 5H, $H_{Cyclohexyl}$), 1.86–1.91 (m, 2H, $H_{Cyclohexyl}$), 2.08–2.11 (m, 2H, $H_{Cyclohexyl}$), 2.52 (s, 3H, CH_3), 3.42 (br, 2H, NH_2), 4.71–4.81 (m, 1H, $H_{Cyclohexyl}$), 6.72–6.80 (m, 2H, H_{Ar}), 6.95 (dd, ^3J=1.5, 7.6 Hz, 1H, H_{Ar}), 7.13–7.18 (m, 1H, H_{Ar}), 7.77 (s, 1H, H_{Hetar}), 8.17 (s, 1H, (CN)C=C*H*). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=15.2 (CH_3), 25.3 (CH_2), 25.6 (CH_2), 33.5 (CH_2), 54.1 (CH), 83.7 (C=*C*–CN), 115.2 (CH_{Ar}), 116.9 (CH_{Ar}), 118.4 (C_{Ar}), 119.4 (C_{Ar}), 123.1 (C_{Ar}), 129.1 (C_{Ar}), 129.3 (CH_{Ar}), 131.1 (CH_{Ar}), 132.9 (CH_{Ar}), 140.3 (C_{Ar}), 144.5 (C_{Ar}), 145.6 (CH_{Ar}), 146.3 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3432(m), 3349 (w), 2932 (m), 2853 (w), 2212 (m), 2160 (w), 1617 (m), 1521 (s), 1450 (m), 1389 (m), 1201 (m), 1189 (m), 859 (m), 756 (s), 644 (s), 624 (s). MS (EI, 70 eV): *m*/*z* (%)=330 (M^+, 45.78), 248 (100), 233 (19). HRMS (ESI): calcd for $C_{21}H_{22}N_4$ (M^+) 330.18390, found 330.183723.

*3.5.19. 1-tert-Butyl-3-cyano-4-methyl-5-(N-methyl-2-aminophenyl) pyrrolo[2,3-b]pyridine (**16e**).* Procedure C; white solid; 55%; mp 151–152 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.77 (s, 9H, $(CH_3)_3$), 2.46 (s, 3H, CH_3) , 2.71 (s, 3H, NCH_3), 6.63–6.74 (m, 2H, H_{Ar}), 6.92 (dd, ^3J=1.5, 7.4 Hz, 1H, H_{Ar}), 7.22–7.28 (m, 1H, H_{Ar}), 7.81 (s, 1H, (CN)C=C*H*), 8.12 (s, 1H, H_{Hetar}). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=15.2, 29.2, 30.6, 58.5, 82.6, 109.7, 116.7, 117.2, 120.5, 123.0, 128.6, 129.3, 130.7, 133.7, 140.0, 145.9, 146.6, 147.1. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3385(w), 3170 (w), 3039 (w), 2975 (w), 2904 (w), 2863 (w), 2810 (w), 2210 (m), 1593 (m), 1513 (s), 1486 (m), 1392 (m), 1289 (m), 1199 (m), 1167 (m), 753 (m), 743 (s), 650 (m), 622 (m). MS (EI, 70 eV): *m*/*z* (%)=318 (M^+, 100), 262 (85), 247 (54), 231 (21). HRMS (ESI): calcd for $C_{20}H_{22}N_4$ (M^+) 318.18390, found 318.18350. Anal. Calcd for $C_{20}H_{22}N_4$ (318.42): C, 75.44; H, 6.96; N, 17.60. Found: C, 75.31; H, 7.05; N, 17.50.

*3.5.20. 5-(2-Aminophenyl)-1-tert-butyl-3-cyano-4-methylpyrrolo [2,3-b]pyridine (**16f**).* Procedure C; white-yellow solid; 35%; mp 150–151 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.78 (s, 9H, $(CH_3)_3$), 2.52 (s, 3H, CH_3), 3.56 (br, 2H, NH_2), 6.75–6.81 (m, 2H, H_{Ar}), 6.97 (dd, ^3J=1.5, 8.0 Hz, 1H, H_{Ar}), 7.14–7.19 (m, 1H, H_{Ar}), 7.82 (s, 1H, H_{Hetar}), 8.16 (s, 1H, H_{Hetar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.2, 29.2, 58.54, 82.6, 115.2, 117.2, 118.4, 120.5, 123.2, 128.7, 129.1, 131.1, 133.7, 139.7, 144.5, 145.6, 146.6. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3434(w), 2969 (w), 2216 (m), 1614 (m), 1520 (s), 1393 (m), 1349 (m), 1290 (m), 1206 (m), 1195 (m), 746 (s), 649 (m), 630 (m). MS (EI, 70 eV): *m*/*z* (%)=304 (M^+, 52), 248 (100), 247 (23), 233 (35), 232 (18). HRMS (ESI): calcd for $C_{19}H_{20}N_4$ (M^+) 304.16825, found 304.169003.

*3.5.21. 10-Cyano-8-cyclohexyl-5H-6,8-dihydro-6-oxo-benzo[f]pyrrolo[2,3-b][1,7]naphthyridine (**17a**).* Procedure C; white solid; 40%; mp 311–313 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.28–1.33 (m, 1H, $H_{Cyclohexyl}$), 1.47–1.60 (m, 2H, $H_{Cyclohexyl}$), 1.74–1.78 (m, 1H, $H_{Cyclohexyl}$), 1.91–2.10 (m, 2H, $H_{Cyclohexyl}$), 4.87–4.95 (m, 1H, $H_{Cyclohexyl}$), 7.32–7.37 (m, 1H, H_{Ar}), 7.50–7.58 (m, 1H, H_{Ar}), 8.63 (d, 1H, ^3J=8.0 Hz, H_{Hetar}), 8.84 (s, 1H, (CN)C=C*H*), 9.74 (s, 1H, H_{Hetar}), 12.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=24.8, 25.2, 32.4, 54.3, 86.0, 113.2, 116.1, 116.3, 116.6, 122.5, 122.9, 123.7, 125.0, 129.4, 136.2, 138.3, 141.4, 145.2, 160.1. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3140(w), 3119 (w), 3054 (w), 3002 (w), 2923 (w), 2857 (w), 2221 (m), 1662 (m), 1651 (m), 1505(m), 1445 (m), 1348 (m), 1292 (m), 1178 (m), 882 (m), 823 (m), 756 (m), 745 (s), 676 (m), 648 (m), 634 (m), 608 (m). HRMS (ESI): calcd for $C_{21}H_{18}N_4O$ ($M+H^+$) 343.1553, found 343.1551.

*3.5.22. 8-tert-Butyl-10-cyano-5H-6,8-dihydro-6-oxo-benzo[f]pyrrolo [2,3-b][1,7]naphthyridine (**17b**).* Procedure C; white solid; 44%; mp 356–357 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=1.86 (s, 9H, $(CH_3)_3$), 7.30–7.56 (m, 1H, H_{Ar}), 8.61–8.71 (m, 2H, H_{Ar}), 9.74 (s, 1H, H_{Ar}), 11.99 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 63 MHz): δ=28.8, 58.9, 85.0, 114.5, 116.1, 116.2, 116.7, 122.6, 123.0, 123.5, 124.4, 129.5, 136.3, 139.0, 140.6, 146.0, 160.1 (C_{Ar}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3186(w), 3151 (w), 3055 (w), 3013 (w), 2967 (w), 2934 (w), 2873 (w), 2223 (m), 1665 (s), 1395 (m), 1381 (m), 1370 (m), 1350 (m), 1329 (m), 1228 (m), 1186 (m), 1111 (s), 879 (m), 826 (m), 743 (s), 657 (s). MS (EI, 70 eV): *m*/*z* (%)=316 (M^+, 24), 260 (100), 232 (14), 207 (13). HRMS (ESI): calcd for $C_{19}H_{16}N_4O$ (M^+) 316.13158, found 316.13186.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.037.

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18. CCDC 801766–801770 contain the crystallographic data (excluding structure factors) for the structures of **13e**, **13l**, **13h**, **14** and **16b** reported in this paper. These data have been deposited with the Cambridge Crystallographic Data Centre as Supplementary data and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.