Synthesis of Fluorinated Pyrrolo[2,3-*b*]pyridine and Pyrrolo[2,3-*d*]pyrimidine Nucleosides

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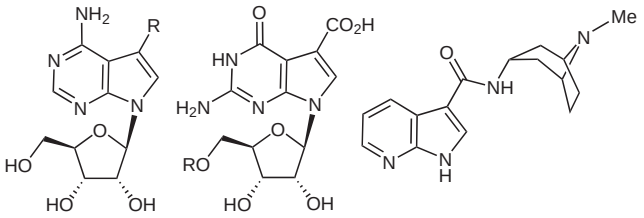
Dedicated Professor Andrei Tolmachev on the occasion of his 50th birthday

Abstract: With the purpose of synthesizing novel ADAs (adenosine deaminase) and IMPDH (inosine 5′-monophosphate dehydrogenase) inhibitors the reactions of 5-amino-1-*tert*-butyl-1-*H*-pyrrole-3-carbonitrile with fluorinated 1,3--bielectrophiles were studied. An efficient and convenient synthetical approach to fluorinated pyrrolo[2,3-*b*]pyridines was developed. The *tert*-butyl protecting group was successfully removed by treating the pyrrolopyridines or -pyrimidines with 60% sulfuric acid and this was followed by direct glycosylation of the products.

Key words: pyrrole, amine, fluorine, pyridine, annulation, electrophilic aromatic substitution

Nucleosides containing pyrrolo[2,3-*b*]pyridine and pyrrolo[2,3-*d*]pyrimidine ring systems as a nucleobase play a significant role in modern medical chemistry. Since pyrrolo[2,3-*b*]pyridines and pyrrolo[2,3-*d*]pyrimidines are considered as 1,7-deaza- and 7-deazapurines, respectively, and their biological activities are recognized to be close to that of purine, over the last few decades a set of drugs and bioactive molecules containing these two heterocyclic systems has appeared on the market.



1 R = H
2 R = CN
3 R = $CONH_2$

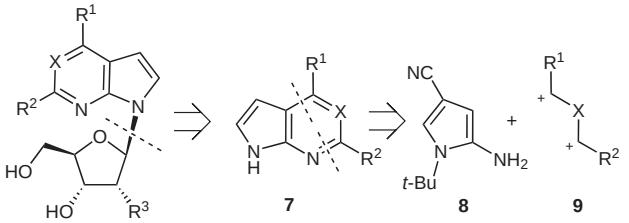
4

5 (DF 1012)

Figure 1 Natural occurring and pharmacoactive pyrrolo[2,3-*d*]pyrimidine and pyrrolo[2,3-*b*]pyridines

Recently, several naturally occurring nucleoside[1] antitumor antibiotics, possessing a pyrrolo[2,3-*d*]pyrimidine framework, such as tubercidin (**1**), toyocamycin (**2**), sangivamycin (**3**), and cadeguomycin (**4**) (Figure 1) were isolated. Their frequent natural occurrence and unusual biological properties have promoted ample studies towards their synthesis and biological evaluation.[2] Several structurally related deazapurine nucleosides have been synthesized, which have shown antitumor,[3] anti-HIV,[4] and antiviral[5] activity. Triciribine (TCN) successfully came through phase I clinical trials and it was advanced to phase II studies as a potential antineoplastic agent.[6] Concerning the similar pyrrolopyridines the most significant compound among them is 7-azaindolylcarboxy-*endo*-tropanamide (DF 1012, **5**) (Figure 1), which is the selected candidate drug in a new class of non-narcotic antitussive compounds and is actually under investigation in phase II clinical trials.[7]

A variety of C6 modified purines[8] and their isosteres[9] including pyrrolopyridines[10] and pyrrolopyrimidines[11] are ADA (adenosine deaminase) inhibitors. Some of them have been synthesized and their pharmaceutical evaluation is currently under investigation.



6 X = N, CH
R^3 = H, OH

7

8

9

Scheme 1 Retrosynthetic analysis

6-(Trifluoromethyl)-substituted purine analogues are promising scaffolds for the elaboration of potential ADA inhibitors.[12] Through the electron-withdrawing trifluoromethyl group the hydration on position 6 is enabled to form stable hydrates. The trifluoromethyl group is isosterical close to the amino function,[13] thus 6-hydroxy-6-(trifluoromethyl)purines and their isosteres can be considered as a putative adenosine deamination transition state mimetics. Coformycin and pentostatin and their derivatives contain a tetrahedral carbon (C8) bearing a hydroxy

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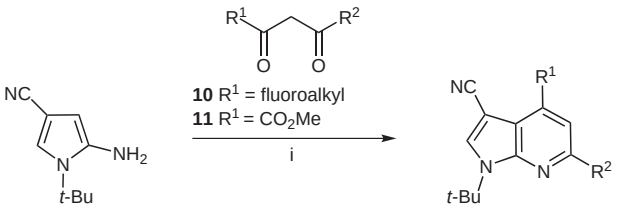
Table 1 Yields of Pyrrolo[2,3-*b*]pyridines **12a–h**[a]



Product	R^1	R^2	Yield[b] (%)
12a	CF_3	CF_3	80
12b	CF_3	Me	84
12c	CF_3	Ph	78
12d	CF_2H	Me	82
12e	CF_2Cl	Ph	81
12f	C_2F_5	Me	83
12g	CF_2CF_2H	Et	84
12h	$(CF_2)_3CF_3$	Et	82
12i	CO_2Me	Me	80
12j	CO_2Me	Ph	77

[a] AcOH, reflux, inert atmosphere, 1 h.
[b] Yields refer to pure isolated products.

group. These naturally occurring ADA inhibitors possess strong activity (coformycin, $K_i = 1.0 \times 10^{-11}$ M; pentostatin, $K_i = 2.5 \times 10^{-12}$ M on calf intestine ADA), that is attributed to the extremely tight-binding (nearly irreversible) interaction of these compounds with ADA, mimicking the transition state of ADA activity.[14]

Our primary interests are focused on the design and synthesis of novel ligands for ADAs and IMPDH, which would be based on the polyfluoroalkyl-containing purines and purine isosteres. The retrosynthetic analysis (Scheme 1) is based on the chemical properties of electron-enriched aminoheterocycles. The heteroannulation of aminopyrroles and polyfluoro-substituted bielectrophilic building blocks results in pyrrolo[2,3-*b*]pyridines and pyrrolo[2,3-*d*]pyrimidines with the desired substitution pattern.

This concept of building up heterocyclic systems has recently gained wide popularity. Hence, it opens a wide range of practical routes towards fluorinated purine analogues and a number of fluorine containing small heterocycles.[15]

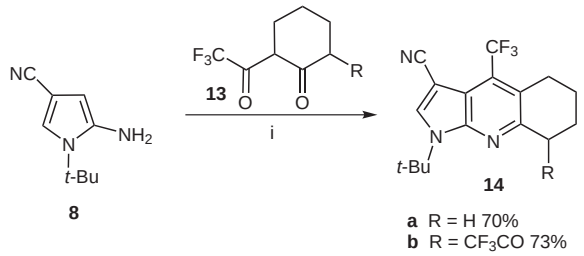
Unsubstituted 1*H*-pyrrol-2-amine is hard to access and it is not stable.[16] For our current study the stable and easily accessible 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**) was used. The *tert*-butyl protection group and the electron-withdrawing cyano function maintain the stability of this heterocycle. Furthermore, the *tert*-butyl and cyano groups could easily be removed from the pyrrolopyridine derivative.[17]

Further, a glycosylation reaction should be studied with the purpose to couple ribose/2-deoxyribose derivatives with the fluorinated nucleobase moiety **7**.

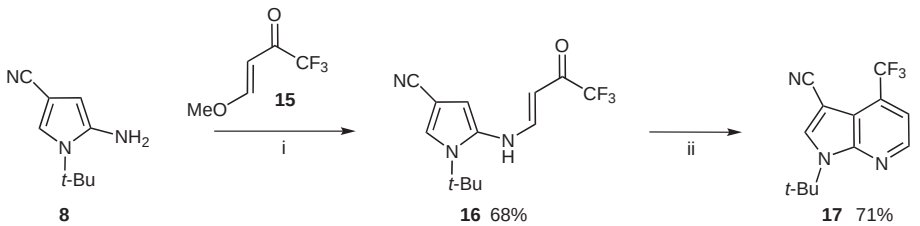
In what follows, the design and synthesis of novel potential inhibitors of the ADAs and IMPDH enzyme families are presented. The practical synthetic route to pyrrolo[2,3-*b*]pyridines, starting from 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**) and a number of 1,3-CCC-bielectrophiles containing a fluoroalkyl group **10**, **13**, and **15** and acylpyruvates **11**. Previously, methods giving rise to pyrrolo[2,3-*b*]pyridines via annulation of the pyridine ring to an aminopyrrole moiety have been reported.[17,18]

We began with a study of the reaction of the aminopyrrole **8** with polyfluoroalkyl-1,3-diketones **10** (Table 1). The reaction yields pyrrolo[2,3-*b*]pyridines **12a**–**h** bearing the fluoroalkyl substituent in position 4 of the annulated pyridine ring. Under the same conditions reaction of **8** with acylpyruvates **11** delivers the esters **12i**,**j** in 80% and 77% yield, respectively. The cyclocondensation proceeds regioselectively to provide the desired γ-regioisomer; the formation of the α-regioisomer was not observed (GC–MS, ^{19}F NMR).

The cyclic diketones **13** were no exception from the general rule. They underwent pyridine ring annulation, leading to the formation of linear 1,5,6,7-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*e*]pyridine **14b** and



Scheme 2 *Reagents and conditions*: (i) AcOH, reflux, inert atmosphere, 1 h.

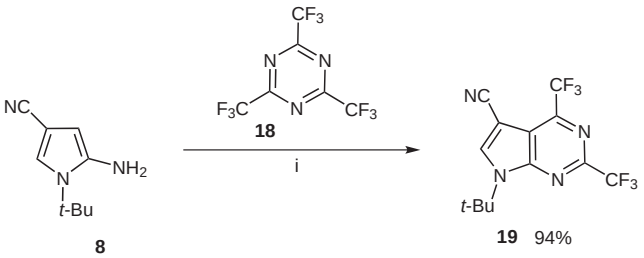


Scheme 3 *Reagents and conditions*: (i) anhyd DMF, inert atmosphere, 85 °C, 12 h; (ii) neat, inert atmosphere 180 °C, 5 h.

5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline **14a** (Scheme 2). Cycloaddition takes place in boiling acetic acid under a nitrogen atmosphere for one hour. The reaction is clean in the case of **10** and **11**, if the initial diketone and pyrrolamine are analytically pure. An excess of electrophile was removed afterwards in vacuo and subsequent purification was not required (**12b**, **12g**). However, in the case of cyclic diketones **13**, examination of the reaction mixture by ^{19}F NMR, revealed a number of byproducts. Attempts to isolate them failed. Pyrrolopyridines **12** and **14**, could easily be purified by flash chromatography or recrystallized from an appropriate solvent.

The application of 1,1,1-trifluoro-4-methoxybut-3-en-2-one (**15**) for heterocyclizations was recently studied.[19] Aminopyrrole **8** reacts smoothly with **15** to afford compound **16**, the product of initial attack of the β-position of the vinyl function on the amino moiety of the aminoheterocycle (Scheme 3). Reaction proceeds in dry *N*,*N*-dimethylformamide at 85 °C under nitrogen.

This intermediate undergoes 6-*exo*-trig-cyclization under harsh conditions (melting at 180 °C) yielding 1-*tert*-butyl-4-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (**17**). For α-substituted pyridines the coupling constant ($^3J_{HH}$) between α- and β-protons is expected to be about 8 Hz. In the case of **17** this coupling constant was measured to be 4.7 Hz, which suggests strongly the γ-CF_3 structure of the pyridine formed.



Scheme 4 *Reagents and conditions*: (i) AcOH, 0 °C, 30 min then r.t., 2 h.

Slow crystallization of compounds **12c** and **12i** (DMSO-d_6, NMR tube) afforded stable diffraction-quality crystals. Single crystal X-ray investigation confirmed the pyrrolopyridine structure of molecules unambiguously (Figure 2 and Figure 3).

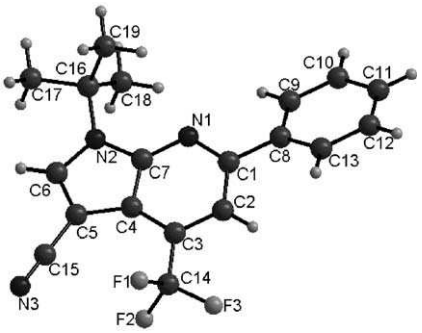


Figure 2 Molecular structure of compound **12c**

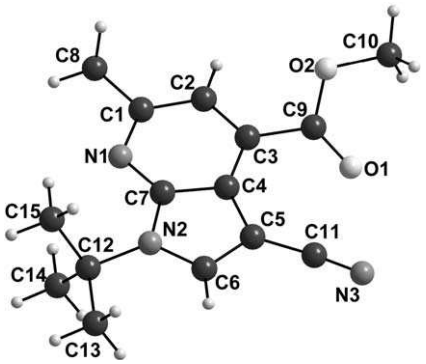
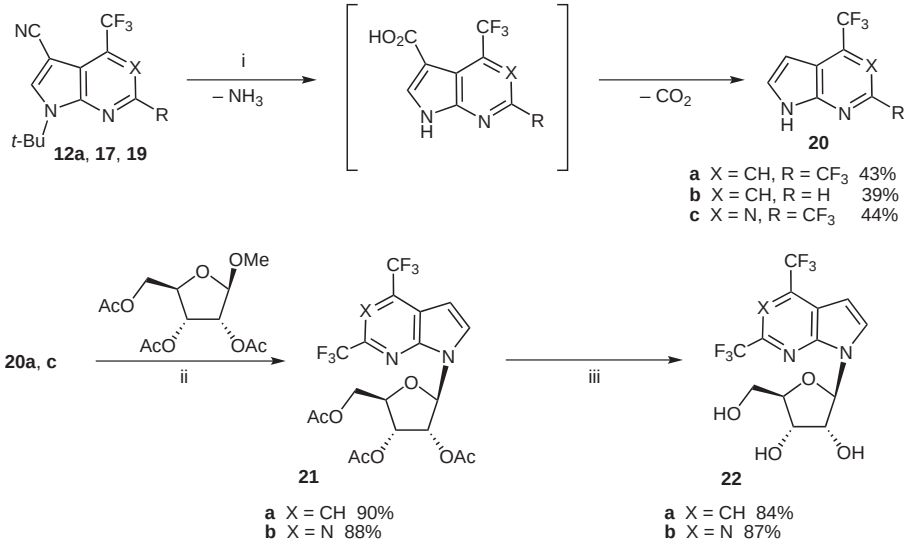


Figure 3 Molecular structure of compound **12i**

The inverse-electron-demand Diels–Alder reaction has become a powerful tool for the assembly of fused pyrimidines.[20] Aminopyrrole **8** react smoothly with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**18**) in acetic acid at 0 °C to deliver the pyrrolo[2,3-*d*]pyrimidine **19** (Scheme 4).



Scheme 5 *Reagents and conditions*: (i) H_2SO_4, 0 °C, 30 min then r.t, 2 h; (ii) BSA, TMS-OTf; (iii) MeOH, NH_3, r.t., 12 h.

Finally, pyrrolopyridines **12a** and **17** and pyrrolo[2,3-*d*]pyrimidine **19** were transformed to the suitable for glycosylation substrates **20** possessing a free N1 position. This reaction was carried out in 60% sulfuric acid (Scheme 5). The compounds **20** were obtained in moderate yields (39–44%). The glycosylations were performed by the silyl-Hilbert–Johnson reaction[21] in dichloromethane, using *O*,*N*-bis(trimethylsilyl)acetamide (BSA) for initial silylation of the heterocyclic moiety. As a catalyst for the next glycosylation step, trimethylsilyl triflate was used (Scheme 5). The deprotection of the products **21** into **22** was conducted by ammonia in methanol.

In summary, a convenient synthetic approach to the fluorinated pyrrolo[2,3-*b*]pyridine ring system was developed based on commercially available 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**) and a series of 1,3-CCC fluorine containing bielectrophiles. The elaborated method gives rise to pyrrolo[2,3-*b*]pyridines bearing the polyfluoroalkyl substituent at C4 of the annulated pyridine ring. Attempts to synthesize N-glycosylated and N-alkylated 4-(polyfluoroalkyl)-1*H*-pyrrolo[2,3-*b*]pyridines are currently under investigation in our laboratory.

All solvents were purified and dried by standard methods. NMR spectra were recorded on Jeol JNM-LA 400, Varian VXR-300, or Varian Mercury-400 spectrometers. ^{1}H and ^{13}C NMR spectra (300 and 100 MHz, respectively) were recorded using TMS as an internal standard; ^{19}F (282.2 MHz) NMR spectra with $CFCl_3$ as an internal standard. 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. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F254 plates were used for TLC. Satisfactory microanalysis obtained C ±0.33; H ±0.45; N ±0.25. Fluorinated 1,3-dicarbonyl compounds were obtained using Claisen-type condensation of the suitable carbonyl compound with the corresponding fluorinated acid esters in the presence of NaOMe or LiH.[22] For the preparation of **21**, synthetical routes described earlier have been used without changing the reaction conditions.[21]

X-ray Crystallography of 12c,i[23]

Crystallographic measurements were performed at r.t. on a Enraf-Nonius CAD4 diffractometer operating in the ω-2θ scan mode (the scanning rate ratio ω/2θ = 1.2). The structures were solved by direct methods and refined by full-matrix least-squares technique in anisotropic approximation using SHELXS97 and SHELXL9722 program packages. Hydrogen atoms were placed at calculated position and refined as 'riding' model.

Crystal data of **12c**: monoclinic, *P*21/*c*, *a* = 15.689(3), *b* = 5.8992(12), *c* = 18.760(4) Å, β = 108.31(3)°, *V* = 1648.3(6) Å^3, Z = 4, μ(Mo-Kα) = 0.107 mm^{-1}. 17282 reflections collected, 3106 unique reflections, (R_{int} = 0.0825), Mo-Kα radiation (λ = 0.71073 Å), 226 parameters, *R*1 = 0.0486, *wR*2 = 0.0971, *S* = 1.080 [2447 reflections with $I > 2\sigma(I)$].

Crystal data of **12i**: triclinic, $P\bar{1}$, *a* = 7.3838(15), *b* = 9.6733(19), *c* = 9.982(2) Å, α = 77.66(3), β = 82.92(3), γ = 85.55(3)°, *V* = 690.2(2) Å^3, *Z* = 2, μ(Mo-Kα) = 0.089 mm^{-1}; 8942 reflections collected, 2567 unique reflections, (R_{int} = 0.0939), Mo-Kα radiation (λ = 0.71073 Å), 181 parameters, *R*1 = 0.0692, *wR*2 = 0.1654, *S* = 1.096 [2194 reflections with $I > 2\sigma(I)$].

Pyrrolo[2,3-*b*]pyridines 12 and 14; General Procedure

5-Amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**, 0.33 g, 2 mmol) and diketone **10** or **11** (**12**) or **13** (**14**) (2.2 mmol) were dissolved in AcOH (20 mL) and heated under reflux under an inert atmosphere for 1 h. Then 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).

1-*tert*-Butyl-4,6-bis(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12a)

Recrystallized (*i*-PrOH); colorless solid (0.54 g, 80%); mp 127–128 °C.

^{1}H NMR (DMSO-d_6): δ = 1.76 (s, 9 H, CH_3), 8.01 (s, 1 H, H2), 9.07 (s, 1 H, H5).

^{13}C NMR (DMSO-d_6): δ = 28.2, 60.1, 82.0, 110.1, 113.4, 121.6 (q, $^1J_{CF}$ = 275 Hz), 121.9 (q, $^1J_{CF}$ = 275 Hz), 129.1 (q, $^2J_{CF}$ = 35 Hz), 140.0 (q, $^2J_{CF}$ = 35 Hz), 142.7, 146.4.

MS: *m*/*z* (%) = 335 (M$^+$, 24), 274 (100), 57 (27).

1-*tert*-Butyl-6-methyl-4-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12b)

Recrystallized (*i*-PrOH); colorless solid (0.47 g, 84%); mp 157–159 °C.

^{1}H NMR (DMSO-d_6): δ = 1.79 (s, 9 H, CH_3), 2.71 (s, 3 H, CH_3), 7.61 (s, 1 H, H5), 8.70 (s, 1 H, H2).

^{13}C NMR (DMSO-d_6): δ = 24.1, 28.3, 58.9, 80.5, 112.2, 113.6 (q, $^3J_{CF}$ = 5.6 Hz), 114.7, 123.2 (q, $^1J_{CF}$ = 275 Hz), 127.7 (q, $^2J_{CF}$ = 35 Hz), 138.3, 147.1, 153.2.

MS: *m*/*z* (%) = 281 (M$^+$, 31), 226 (28), 225 (100), 156 (14), 57 (16), 41 (10).

1-*tert*-Butyl-6-phenyl-4-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12c)

Recrystallized (EtOH); colorless solid (0.54 g, 78%); mp 230–232 °C.

^{1}H NMR (DMSO-d_6): δ = 1.87 (s, 9 H, CH_3), 8.15 (br m, 3 H, CH), 7.50 (br m, 3 H, CH), 8.70 (s, 1 H, H2).

^{13}C NMR (DMSO-d_6): δ = 28.4, 59.0, 81.2, 110.3 (q, $^3J_{CF}$ = 5.6 Hz), 113.2, 113.8, 122.4 (q, $^1J_{CF}$ = 275 Hz), 126.3, 128.4, 128.6 (q, $^2J_{CF}$ = 35 Hz), 129.0, 137.2, 138.9, 147.3, 150.9.

MS: *m*/*z* (%) = 342 (M$^+$ + 1, 21), 343 (M$^+$, 100), 57 (19).

1-*tert*-Butyl-4-(difluoromethyl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12d)

Recrystallized (*i*-PrOH); colorless solid (0.43 g, 82%); mp 115–118 °C.

^{1}H NMR (DMSO-d_6): δ = 1.75 (s, 9 H, CH_3), 2.63 (s, 3 H, CH_3), 7.37 (t, $^1J_{HF}$ = 54 Hz, 1 H, CF_2H), 7.38 (s, 1 H, H5), 8.55 (s, 1 H, H2).

^{13}C NMR (DMSO-d_6): δ = 24.3, 28.5, 58.7, 80.8, 113.3 (t, $^1J_{CF}$ = 237 Hz), 113.6 (t, $^3J_{CF}$ = 3.6 Hz), 114.7 (t, $^3J_{CF}$ = 6.4 Hz), 115.6, 133.5 (t, $^2J_{CF}$ = 23 Hz), 137.0, 147.0, 153.0.

MS: *m*/*z* (%) = 263 (M$^+$, 18), 208 (15), 207 (100), 156 (11).

1-*tert*-Butyl-4-(chlorodifluoromethyl)-6-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12e)

Recrystallized (EtOH); colorless solid (0.58 g, 81%); mp 251–253 °C.

^{1}H NMR (DMSO-d_6): δ = 1.87 (s, 9 H, CH_3), 7.53 (br m, 3 H), 8.07 (s, 1 H, H5), 8.18 (d, $^3J_{HH}$ = 7.8 Hz, 2 H), 8.70 (s, 1 H,).

^{13}C NMR (DMSO-d_6): δ = 28.9, 59.5, 81.9, 109.4 (t, $^3J_{CF}$ = 6.4 Hz), 112.8 (t, $^3J_{CF}$ = 2.4 Hz), 114.9, 124.6, (t, $^1J_{CF}$ = 290 Hz), 126.9, 129.0, 129.6, 135.2 (t, $^2J_{CF}$ = 29 Hz), 137.8, 139.7, 148.0, 151.3.

MS: *m*/*z* (%) = 361 (M^+ + 2, 13), 359 (M^+, 36), 304 (23), 303 (100), 269 (16), 268 (75), 57 (13).

1-*tert*-Butyl-6-methyl-4-(pentafluoroethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12f)

Colorless solid (0.55 g, 83%); mp 117–119 °C; R_f = 0.70 (EtOAc–hexane, 1:3).

^{1}H NMR ($CDCl_3$): δ = 1.78 (s, 9 H, CH_3), 2.67 (s, 3 H, CH_3), 7.24 (s, 1 H, H5), 7.94 (s, 1 H, H2).

^{13}C NMR ($CDCl_3$): δ = 24.6, 29.0, 59.3, 83.0, 111.5 (tq, $^1J_{CF}$ = 215 Hz, $^2J_{CF}$ = 39 Hz), 113.9 (t, $^3J_{CF}$ = 2.0 Hz), 115.5, 115.8 (t, $^3J_{CF}$ = 8.0 Hz), 119.7 (qt, $^1J_{CF}$ = 285 Hz, $^2J_{CF}$ = 38 Hz), 129.1 (t, $^2J_{CF}$ = 25 Hz), 136.5, 147.9, 153.3.

MS: *m*/*z* (%) = 331 (M^+, 35), 276 (27), 275 (100), 206 (52), 57 (19), 41 (10).

1-*tert*-Butyl-6-ethyl-4-(1,1,2,2-tetrafluoroethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12g)

Colorless solid (0.55 g, 84%); mp 110–111 °C; R_f = 0.70 (EtOAc–hexane, 1:4).

^{1}H NMR ($CDCl_3$): δ = 1.35 (t, $^3J_{HH}$ = 7.8 Hz, 3 H, CH_3), 1.50 (s, 9 H, CH_3), 2.95 (d, $^3J_{HH}$ = 7.8 Hz, 2 H, CH_2), 6.16 (t, $^2J_{HH}$ = 54 Hz, 1 H, CF_2H), 7.24 (s, 1 H, H5), 7.93 (s, 1 H, H2).

^{13}C NMR ($CDCl_3$): δ = 13.4, 29.0, 31.1, 59.0, 82.7, 110.0, 114.5 (t, $^2J_{CF}$ = 1.8 Hz), 114.9, 115.7, 130.1 (t, $^2J_{CF}$ = 26 Hz), 135.6, 147.7, 158.2.

MS: *m*/*z* (%) = 327 (M^+, 15), 272 (13), 271 (100), 270 (21), 220 (10), 57 (21), 41 (13).

1-*tert*-Butyl-6-ethyl-4-(nonafluorobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (12h)

Colorless solid (0.73 g, 82%); mp 61–63 °C; R_f = 0.65 (EtOAc–hexane, 1:3).

^{1}H NMR ($CDCl_3$): δ = 1.35 (t, $^3J_{HH}$ = 7.8 Hz, 3 H, CH_3), 1.80 (s, 9 H, CH_3), 2.95 (d, $^3J_{HH}$ = 7.8 Hz, 2 H, CH_2), 7.23 (s, 1 H, H2), 7.96 (s, 1 H, H5).

^{13}C NMR ($CDCl_3$): δ = 13.2, 28.8, 30.9, 58.9, 82.9, 114.5, 115.2, 129.0 (t, $^2J_{CF}$ = 25 Hz), 136.0, 147.6, 157.8.

MS: *m*/*z* (%) = 445 (M^+, 20), 390 (27), 389 (100), 388 (17), 220 (27), 57 (11).

Methyl 1-*tert*-Butyl-3-cyano-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (12i)

Recrystallized (EtOH); colorless solid (0.43 g, 80%); mp 251–253 °C.

^{1}H NMR (DMSO-d_6): δ = 1.75 (s, 9 H, CH_3), 2.63 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 7.59 (s, 1 H, H5), 8.58 (s, 1 H, H2).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 24.1, 28.6, 51.7, 58.8, 82.7, 114.3, 116.2, 129.8, 138.7, 147.7, 152.7, 165.4.

MS: *m*/*z* (%) = 271 (M^+, 41), 216 (19), 215 (100), 184 (30), 157 (63), 156 (25).

Methyl 1-*tert*-Butyl-3-cyano-6-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (12j)

Recrystallized (EtOH); colorless solid (0.53 g, 77%); mp 275–278 °C.

^{1}H NMR (DMSO-d_6): δ = 1.83 (s, 9 H, CH_3), 3.98 (s, 3 H, CH_3), 7.47–7.57 (br m, 3 H, CH), 8.16 (d, $^3J_{HH}$ = 7.8 Hz, 2 H, CH), 8.24 (s, 1 H, CH), 8.72 (s, 1 H, CH).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 28.5, 51.5, 58.7, 82.9, 114.3, 115.6, 118.3, 126.2, 128.6, 128.9, 130.5, 137.6, 140.0, 147.7, 150.3, 165.1.

MS: *m*/*z* (%) = 333 (M^+, 39), 278 (19), 277 (100), 246 (13), 219 (35), 218 (22).

1-*tert*-Butyl-4-(trifluoromethyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline-3-carbonitrile (14a)

Colorless solid (0.45 g, 70%); mp 99–100 °C; R_f = 0.85 (EtOAc–hexane, 1:4).

^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 9 H, CH_3), 1.78–1.91 (br m, 4 H, CH_2), 3.04–3.09 (br m, 4 H, CH_2), 7.94 (s, 1 H, H2).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 22.2, 22.6, 25.8 (q, J_{CF} = 4 Hz), 28.8, 33.8, 58.7, 82.4, 114.1, 116.0, 123.9, 121.6 (q, $^1J_{CF}$ = 270 Hz), 127.7 (q, $^2J_{CF}$ = 35 Hz), 136.5, 146.0, 153.7.

MS: *m*/*z* (%) = 321 (M^+, 18), 266 (15), 265 (100), 264 (12), 237 (15), 196 (10).

1-*tert*-Butyl-8-(2,2,2-trifluoroacetyl)-4-(trifluoromethyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline-3-carbonitrile (14b)

Colorless solid (0.61 g, 73%); mp 123–127 °C; R_f = 0.75 (EtOAc–hexane, 1:4).

^{1}H NMR ($CDCl_3$): δ = 1.77 (s, 9 H, CH_3), 1.79–1.88 (br m, 1 H, CH), 2.04–2.09 (br m, 1 H, CH), 2.24–2.28 (br m, 0.58 H, CH), 2.70 (br s, 1.42 H, CH), 3.07 (br s, 2 H, CH), 4.63 (br s, 0.37 H, CH), 7.97–8.03 (br m, 1 H, CH).

MS: *m*/*z* (%) = 417 (M^+, 28), 362 (20), 361 (69), 265 (18), 264 (100), 57 (21).

(*E*)-1-*tert*-Butyl-5-[(4,4,4-trifluoro-3-oxobut-1-enyl)amino]-1*H*-pyrrole-3-carbonitrile (16)

5-Amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**, 0.66 g, 4 mmol) and **15** (0.68 g, 4.4 mmol) were dissolved in anhyd DMF (10 mL) and heated under an inert atmosphere at 85 °C for 12 h. The soln was evaporated under reduced pressure, treated with H_2O, and dried under reduced pressure and the residue was subjected to column chromatography (silica gel) to give a colorless solid (0.78 g, 68%); mp 116–118 °C; R_f = 0.75 (hexane–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$): δ = 1.59 (s, 9 H, CH_3), 5.68 (d, $^3J_{HH}$ = 8 Hz, 1 H), 6.20 (s, 1 H), 7.13 (s, 1 H), 7.29 (dd, $^3J_{HH}$ = 8 Hz, $^3J_{HH}$ = 4 Hz, 1 H), 11.80 (d, $^3J_{HH}$ = 4 Hz, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 29.9, 58.1, 90.7, 91.0, 103.7, 119.8 (d, $^1J_{CF}$ = 285 Hz), 117.7, 131.0, 140.7, 153.3, 180.2 (q, $^2J_{CF}$ = 33 Hz).

MS: *m*/*z* (%) = 286 (M^+ + 1, 11), 285 (M^+, 56), 239 (22), 229 (77), 170 (11), 160 (90), 57 (100), 41 (37).

1-*tert*-Butyl-4-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (17)

1-*tert*-Butyl-5-[(4,4,4-trifluoro-3-oxobut-1-enyl)amino]-1*H*-pyrrole-3-carbonitrile (**16**, 0.57 g, 2 mmol) in a 10-mL flask was melted for 5 h under an inert atmosphere at 180 °C (temperature of the oil bath), then the dark-green residue formed was subjected to column chromatography (silica gel) to give a colorless solid (0.38 g, 71%); mp 161–163 °C; R_f = 0.75 (hexane–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$): δ = 1.78 (s, 9 H, CH_3), 7.41 (d, $^3J_{HH}$ = 4.7 Hz, 1 H), 7.99 (s, 1 H), 8.49 (d, $^3J_{HH}$ = 4.7 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 29.0, 59.3, 82.8, 113.8 (q, $^3J_{CF}$ = 4.7 Hz), 114.5, 115.7, 122.8 (q, $^2J_{CF}$ = 270 Hz), 129.8 (q, $^2J_{CF}$ = 35 Hz), 136.3, 143.7, 148.3.

MS: *m*/*z* (%) = 267 (M^+, 48), 212 (58), 211 (100), 192 (24), 57 (39), 56 (10), 41 (25).

7-*tert*-Butyl-2,4-bis(trifluoromethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (19)

To 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**, 0.33 g, 2 mmol) dissolved in AcOH (10 mL) at 0 °C, 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**18**, 0.64 g, 2.2 mmol) was added dropwise. The mixture was stirred vigorously for 30 min and then kept at r.t. for 2 h. Solvent was evaporated under reduced pressure. The brown residue was recrystallized (EtOH–H_2O) to give a colorless solid (0.63 g, 94%); mp 133–135 °C.

^{1}H NMR (DMSO-d_6): δ = 1.73 (s, 9 H, CH_3), 8.21 (s, 1 H, H2).

^{13}C NMR (DMSO-d_6): δ = 28.2, 60.1, 85.0, 113.4, 115.7, 119.5 ($^1J_{CF}$ = 275 Hz), 121.3, ($^1J_{CF}$ = 275 Hz), 1142.7, 143.3 ($^2J_{CF}$ = 37 Hz), 146.4, 147.4 ($^2J_{CF}$ = 37 Hz).

MS: *m*/*z* (%) = 336 (M^+, 67), 279 (33), 57 (100).

Compounds 20; General Procedure

The corresponding pyrrolo[2,3-*b*]pyridine **12a**, **17** or pyrrolo[2,3-*b*]pyridine **19** (2 mmol) was dissolved in 60% H_2SO_4 (4 mL) at 0 °C, and stirred for 30 min. The mixture was then kept at r.t. for 2 h. The mixture was poured onto ice, the precipitate that formed was filtered, dried in air, and recrystallized from an appropriate solvent.

4,6-Bis(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (20a)

Recrystallized (*i*-PrOH); colorless solid (0.22 g, 43%); mp 187–189 °C.

^{1}H NMR (DMSO-d_6): δ = 7.55 (d, $^3J_{HH}$ = 3.5 Hz, 1 H), 7.85 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, CH), 7.91 (s, 1 H, H2), 12.08 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 100.0, 110.1, 117.4, 121.6 (q, $^1J_{CF}$ = 275 Hz), 121.9 (q, $^1J_{CF}$ = 275 Hz), 129.1 (q, $^2J_{CF}$ = 35 Hz), 140.0 (q, $^2J_{CF}$ = 35 Hz), 146.4.

MS: *m*/*z* (%) = 254 (M^+, 100), 253 (11), 212 (35), 211 (87), 192 (49).

4-(Trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (20b)

Recrystallized (*i*-PrOH); colorless solid (0.15 g, 39%); mp 180–181 °C.

^{1}H NMR (DMSO-d_6): δ = 7.35 (d, $^3J_{HH}$ = 3.5 Hz, 1 H), 7.44 (d, $^3J_{HH}$ = 4.7 Hz, 1 H, H5), 7.65 (d, $^3J_{HH}$ = 3.5 Hz, 1 H), 8.53 (d, $^3J_{HH}$ = 4.7 Hz, 1 H, H6), 12.03 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 99.7, 113.0 (q, $^3J_{CF}$ = 4.7 Hz), 114.1, 122.0 (q, $^2J_{CF}$ = 270 Hz), 129.4 (q, $^2J_{CF}$ = 35 Hz), 136.9, 143.1, 148.3.

MS: *m*/*z* (%) = 186 (M^+, 100), 185 (13).

2,4-Bis(trifluoromethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (20c)

Recrystallized (*i*-PrOH); colorless solid (0.22 g, 44%); mp 235–237 °C.

^{1}H NMR (DMSO-d_6): δ = 7.59 (d, $^3J_{HH}$ = 3.7 Hz, 1 H), 8.05 (d, $^3J_{HH}$ = 3.7 Hz, 1 H), 11.91 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 99.0, 115.0, 119.4 ($^1J_{CF}$ = 275 Hz), 121.3 ($^1J_{CF}$ = 275 Hz), 142.0, 143.7 ($^2J_{CF}$ = 37 Hz), 146.2, 147.0 ($^2J_{CF}$ = 37 Hz).

MS: *m*/*z* (%) = 255 (M^+, 100), 254 (52).

l-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (21a)

Colorless solid (0.92 g, 90%); mp 69–72 °C; R_f = 0.55 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 1.99–2.05 (br s, 9 H, CH_3), 3.48 (m, 1 H, CH), 3.69 (m, 1 H, CH), 4.00 (q, $^3J_{HH}$ = 4.6 Hz, 1 H, CH), 4.39 (br s, 1 H, CH), 4.64 (d, $^3J_{HH}$ = 4.6 Hz, 1 H, CH), 6.49 (d, $^3J_{HH}$ = 4.8 Hz, 1 H, CH), 7.53 (d, $^3J_{HH}$ = 3.5 Hz, 1 H), 7.87 (d, $^3J_{HH}$ = 3.5 Hz, 1 H), 8.01 (s, 1 H, H5).

^{13}C NMR (DMSO-d_6): δ = 20.6, 20.9, 21.1, 63.1, 68.7, 73.3, 79.9, 89.3, 99.3, 110.1, 117.4, 121.6 (q, $^1J_{CF}$ = 275 Hz), 121.9 (q, $^1J_{CF}$ = 275 Hz), 129.1 (q, $^2J_{CF}$ = 35 Hz), 136.4, 140.0 (q, $^2J_{CF}$ = 35 Hz), 146.4, 170.0, 170.2, 170.3.

MS: *m*/*z* (%) = 512 (M^+, 17), 511 (19), 488 (10), 479 (13), 477 (19), 399 (15), 387 (25), 325 (45), 301 (17), 293 (63), 281 (33), 207 (37), 189 (100), 158 (11), 157 (31), 123 (25), 101 (18).

l-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,4-bis(trifluoromethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (21b)

Colorless solid (0.90 g, 88%); mp 59–62 °C; R_f = 0.65 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 2.00–2.05 (br s, 9 H, CH_3), 3.52 (q, $^3J_{HH}$ = 6.2 Hz, 1 H, CH), 3.67 (m, 1 H, CH), 4.29 (q, $^3J_{HH}$ = 5.6 Hz, 1 H, CH), 4.75–4.82 (br m, 2 H, CH), 6.59 (d, $^3J_{HH}$ = 4.2 Hz, 1 H, CH), 7.67 (d, $^3J_{HH}$ = 3.7 Hz, 1 H), 7.93 (d, $^3J_{HH}$ = 3.7 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 20.6, 20.9, 21.1, 63.7, 67.9, 73.0, 79.0, 88.9, 99.9, 115.0, 119.4 ($^1J_{CF}$ = 275 Hz), 121.3 ($^1J_{CF}$ = 275 Hz), 142.0, 143.7 ($^2J_{CF}$ = 37 Hz), 146.2, 147.0 ($^2J_{CF}$ = 37 Hz), 170.5, 170.7, 170.9.

MS: *m*/*z* (%) = 513 (M^+, 18), 501 (43), 470 (37), 461 (40), 419 (11), 387 (10), 357 (14), 303 (77), 278 (91), 205 (100), 194 (18), 134 (17), 112 (13), 97 (11).

Deprotection of the Acylated Nucleosides; General Procedure

To a solution of the acylated nucleoside (1 mmol) in absolute MeOH (5 mL) a sat. soln of NH_3 in MeOH (20 mL) was added dropwise at 0 °C. The mixture was stirred for another 30 min and left for 12 h at r.t. The solvent was removed under reduced pressure, and the formed material was kept for the next 24 h on a vacuum line. The resultant yellow material was purified by column chromatography on silica gel.

l-(β-D-Ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (22a)

Colorless solid (0.32 g, 84%); mp 170–171 °C; R_f = 0.85 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 3.58 (m, 1 H, CH), 3.64 (m, 1 H, CH), 4.11 (q, $^3J_{HH}$ = 4.5 Hz, 1 H, CH), 4.39 (br s, 1 H, CH), 4.63 (d, $^3J_{HH}$ = 4.5 Hz, 1 H, CH), 5.55 (br s, 3 H, OH), 6.44 (d, $^3J_{HH}$ = 4.9 Hz, 1 H, CH), 7.65 (d, $^3J_{HH}$ = 3.5 Hz, 1 H), 7.99 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, CH), 8.11 (s, 1 H, H2).

^{13}C NMR (DMSO-d_6): δ = 63.9, 65.0, 72.1, 88.8, 93.9, 99.0, 111.1, 117.0, 121.6 (q, $^1J_{CF}$ = 275 Hz), 121.7 (q, $^1J_{CF}$ = 275 Hz), 130.0 (q, $^2J_{CF}$ = 35 Hz), 136.4, 140.1 (q, $^2J_{CF}$ = 35 Hz), 146.7.

MS: *m*/*z* (%) = 386 (M^+, 12), 380 (11), 356 (21), 309 (10), 299 (17), 233 (14), 219 (11), 218 (100), 201 (77), 179 (14), 156 (10), 67 (83).

l-(β-D-Ribofuranosyl)-2,4-bis(trifluoromethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (22b)

Colorless solid (0.34 g, 87%); mp 167–168 °C; R_f = 0.70 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 3.47 (m, 1 H, CH), 3.61 (m, 1 H, CH), 4.14 (q, $^3J_{HH}$ = 4.5 Hz, 1 H, CH), 4.32 (br s, 1 H, CH), 4.67 (d, $^3J_{HH}$ = 4.5 Hz, 1 H, CH), 5.61 (br s, 3 H, OH), 6.48 (d, $^3J_{HH}$ = 4.2 Hz, 1 H, CH), 7.65 (d, $^3J_{HH}$ = 3.4 Hz, 1 H), 7.99 (d, $^3J_{HH}$ = 3.4 Hz, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 63.4, 67.0, 72.7, 78.5, 88.8, 99.3, 115.1, 119.6 (q, $^1J_{CF}$ = 275 Hz), 121.2 (q, $^1J_{CF}$ = 275 Hz), 141.2, 143.7 (q, $^2J_{CF}$ = 37 Hz), 144.4, 147.8 (q, $^2J_{CF}$ = 37 Hz).

MS: *m*/*z* (%) = 387 (M^+, 100), 368 (17), 361 (30), 355 (48), 317 (67), 287 (58), 286 (34), 235 (100), 222 (12), 221 (19), 208 (31), 198 (17), 177 (10), 160 (10), 133 (13), 127 (17).

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(23) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 703680 and CCDC 683574 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.