A Convenient Synthesis of Fluorinated Pyrazolo[3,4-*b*]pyridine and Pyrazolo[3,4-*d*]pyrimidine Nucleosides

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Received 26 September 2008; revised 15 October 2008

Dedicated to Professor V. P. Khilya on the occasion of his 70th birthday

Abstract: Starting from 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazole, fluorine-containing 1,3-CCC-, 1,3-CNC-dielectrophiles and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine, a set of fluorinated pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine nucleosides was obtained. Synthetic access to stable 4-(polyfluoroalkyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-ole was elaborated, which can be considered to be mimetics of the putative transition state involved in adenosine deaminase activity.

Key words: pyrazole, pyridine, pyrimidine, fluorine, annulation, electrophilic aromatic substitution

Adenosine deaminase (ADA) and inosine 5′-monophosphate dehydrogenase (IMPDH) are two groups of enzymes that play a key role in purine *de novo* biosynthesis.[1–4] In the last two decades ADA and IMPDH have become important target enzymes for drug design, since it was found that a deficiency of ADA impairs the function of the human immune system, resulting in severe combined immunodeficiency (SCID), characterized by severe T-lymphocyte dysfunction and agammaglobulinemia.[5] Furthermore, ADA enzyme abnormalities have also been reported in acquired immunodeficiency syndrome (AIDS),[6] in tuberculosis,[7] Parkinson's disease,[8a] in viral hepatitis,[8b] some leukaemia diseases,[9] and many others including cancer.[2]

Electron-withdrawing trifluoromethyl groups facilitate water addition to the 6-position of purine (purine isosters) and maintains the stability of the formed 6-hydrates. Recently, a theoretical study has been carried out that established 6-trifluoromethyl-substituted purine isosteres as promising inhibitors of ADA.[10] Since the trifluoromethyl group is isosterically comparable to the amino group,[11] modification of compounds that imitate the putative transition-state involved in ADA activity should not cause problems with substrate recognition, and should thus lead to enzyme inhibition. Modification of Coformycin, Pentostatin and their analogues with a trifluoromethyl group should thus increase the stability of the corresponding hydrates, and would be expected to change the metabolic pathway that governs the toxicity of the substrates.[12]

On the other hand, in our opinion, purines and their isosteres bearing polyfluoroalkyl substituents in positions two and six should also be considered as potential IMPDH inhibitors, due to the possibility of covalent binding between the Cys 331 residue of the active site of the enzyme with the more electrophilic C-6 (C-2) atoms, forming stable Meisenheimer-type adducts. It was shown that, for example, the 6-chloro-substituted purine base[3] is dehalogenated by IMPDH and a covalent bond is formed at C-6 with Cys 331.

In this publication we report a facile synthesis of pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine nucleosides, which are promising scaffolds for potential ADA and IMPDH inhibitors.

We report two general synthetic routes to pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine nucleosides starting from *iso*-AIRs 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazole (**1**; Figure 1). The first involves regiospecific annulation of the pyridine and pyrimidine rings to give the aminoheterocyclic moiety using a number of 1,3-CCC- and 1,3-CNC-fluoro-containing dielectrophiles **3**–**11** (Figure 2). The second approach is based on an inverse electron-demand Diels–Alder reaction.[13]

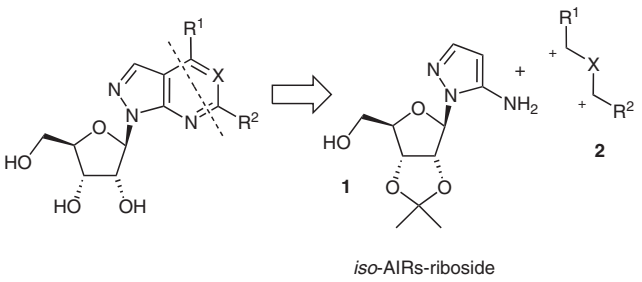


Figure 1 Retrosynthetic analysis

SYNTHESIS 2009, No. 5, pp 0731–0740
Advanced online publication: 11.02.2009
DOI: 10.1055/s-0028-1083365; Art ID: P09708SS

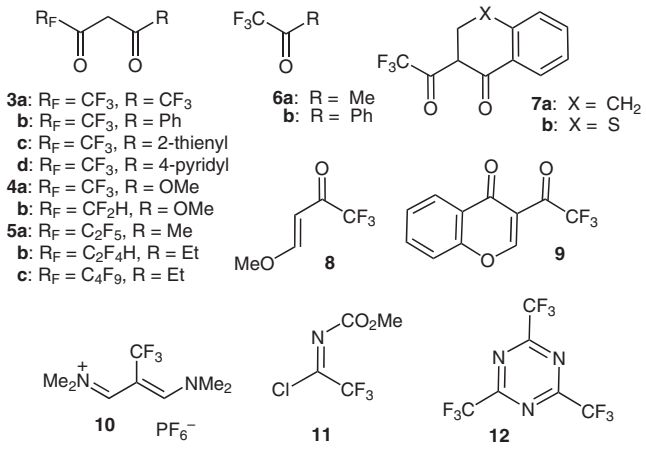
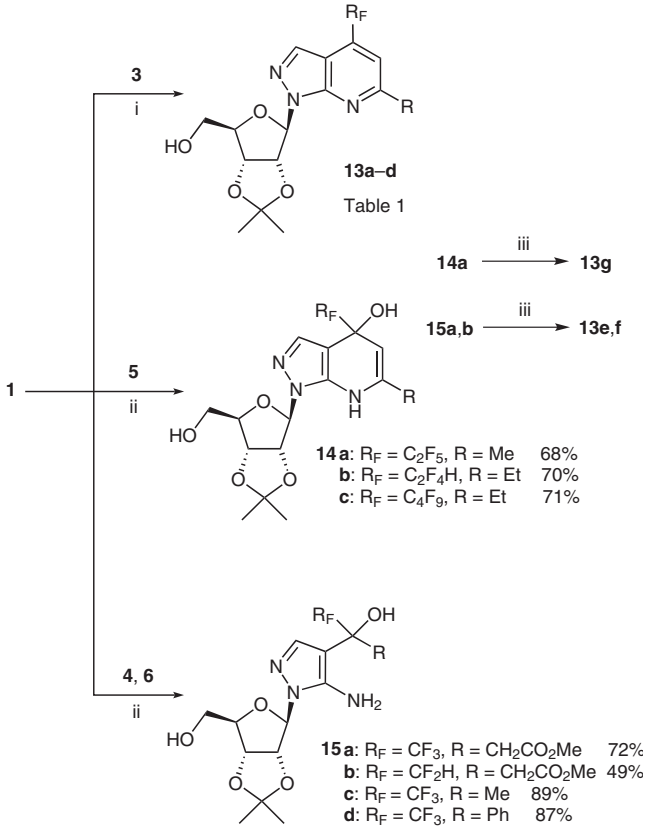


Figure 2 Variety of 1,3-CCC- and 1,3-CNC-dielectrophiles used for building pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine nucleosides

We started our investigation by optimising the reaction of iso-AIRs **1** with dicarbonyls **3**–**5**. The previously reported possibility of conducting this reaction in acetic acid media[14a] was not possible in the case of **1**, since refluxing in acetic acid caused a deglycosylation reaction to take place. However, the desired pyridine ring annulation did proceed smoothly in absolute DMF at 130 °C in the absence of acid under inert atmosphere for 12 hours. These conditions gave the set of pyrazolo[3,4-*b*]pyridines **13a**–**d** in good to excellent yields (Scheme 1, Table 1). As reported previously, the reaction proceeds via formation of the corresponding hydrates, which can be detected by ^{19}F NMR,[14b] however, the presence of the trifluoromethyl group was not enough to stabilize the hydrates. The introduction of more electron-withdrawing polyfluoroalkyl groups (C_2F_5, C_2F_4H and C_4F_9) enabled isolation and identification of the hydrates by NMR methods. Keto esters **4** and ketones **6** reacted with **1** under milder conditions (DMF, 80 °C), delivering stable acyclic carbinols **15**. Since compounds **15a** and **15b** appeared to be stable, ring formation to give **13e** and **13f**, respectively, required relatively harsh conditions such as heating at 180 °C without solvent. The dehydration of **14a** and cyclization of **15a** and **15b** proceeded smoothly in absolute methanol under reflux with a catalytic amount of *p*-toluenesulfonic acid (PTSA), however, under these conditions a cleavage of the *iso*-propylidene protection group took place, delivering the ribosides **16e**–**g** in good yields (Scheme 2, Table 2).

When diketones **7** were also tested for pyridine ring formation we obtained satisfactory results for the condensed pyrazolo[3,4-*b*]pyridines **17**, which were obtained in yields of 69–72%. Deprotection of **17** led to nucleosides **18**.

The reaction of compound **1** with **8** afforded the N-adduct **19** (Scheme 3). This intermediate underwent a 6-*exo*-*trig* cyclisation (180 °C) to give 6-unsubstituted pyrazolopyridine **20** in 80% yield. After deprotecting **20**, the pyrazolo[3,4-*b*]pyridine **21** was obtained in 78% yield.



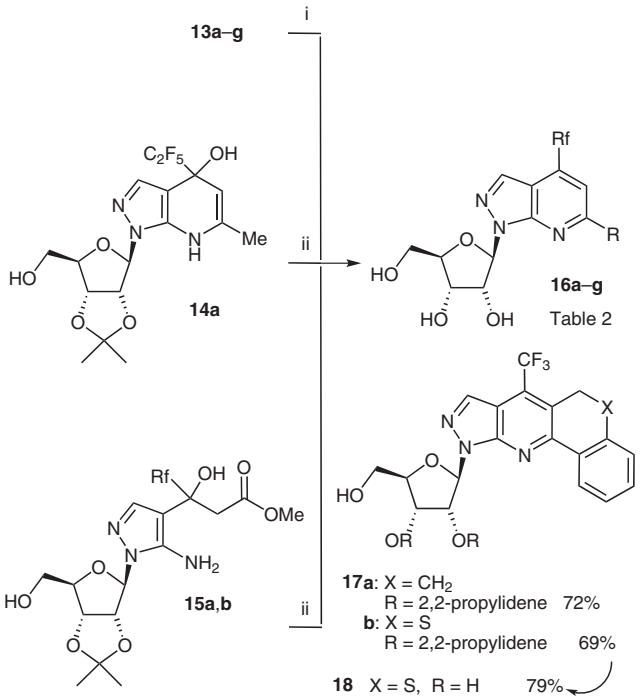
Scheme 1 *Reagents and conditions*: (i) DMF, N_2, 125 °C, 12 h; (ii) DMF, N_2, 80 °C, 12 h; (iii) no solvent, reduced pressure, 180 °C, 1 h.

Table 1 Yields of Pyrazolo[3,4-*b*]pyridines **13a**–**g**

Product	R_F	R	Yield (%)[a]
13a	CF_3	CF_3	94
13b	CF_3	Ph	81
13c	CF_3	2-thienyl	86
13d	CF_3	4-pyridyl	91
13e	CF_3	OH	65
13f	CF_2H	OH	37
13g	C_2F_5	Me	69

[a] Pure isolated product.

It was expected that 3-(trifluoroacetyl)chromone **9**,[15] which is a 1,3-CCC-dielectrophile, would react with the aminopyrazole moiety of **22** resulting in pyridine ring annulation. However, instead of delivering pyrazolo[3,4-*b*]pyridines, the reaction gave the corresponding 2-(trifluoromethyl)chroman-4-ones **23a** and **23b**. Such chemical behaviour of **9** was already reported,[15] and is typical for aromatic and aliphatic amines. Single crystal X-ray



Scheme 2 *Reagents and conditions*: (i) TFA–H_2O (9:1), r.t., 45 min; (ii) MeOH, PTSA, reflux, 1 h.

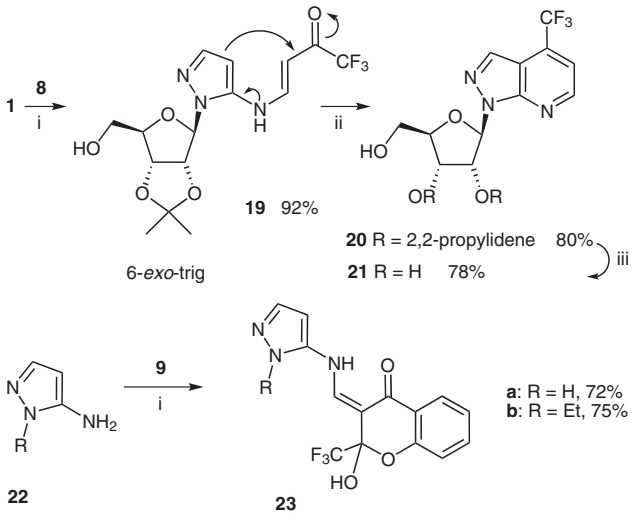
Table 2 Yields of Pyrazolo[3,4-*b*]pyridines **16a–g**

Starting material	Product	R_F	R	Yield (%)[a]
13a	**16a**	CF_3	CF_3	84
13b	**16b**	CF_3	Ph	71
13c	**16c**	CF_3	2-thienyl	85
13d	**16d**	CF_3	4-pyridyl	74
13e	**16e**	CF_3	OH	64
15a	**16e**	CF_3	OH	73
13f	**16f**	CF_2H	OH	61
15b	**16f**	CF_2H	OH	70
13g	**16g**	C_2F_5	Me	77
14a	**16g**	C_2F_5	Me	83

[a] Pure isolated product.

analysis unambiguously revealed the chroman structure of molecule **23b** (Figure 3).

Vinamidinium hexafluorophosphate (**10**; Figure 2) has recently been used in the synthesis of nitrogen-containing heterocycles such as pyrimidines,[16] however, the reaction of aminopyrazole **1** with **10** (DMF, 80–125 °C) led to the formation of a mixture products. According to ^{19}F NMR, nearly a dozen components were detected. A 10% yield of 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine was detected



Scheme 3 *Reagents and conditions*: (i) DMF, inert atmosphere, 80 °C, 12 h; (ii) no solvent, reduced pressure, 180 °C, 1 h; (iii) TFA–H_2O (9:1), r.t., 45 min.

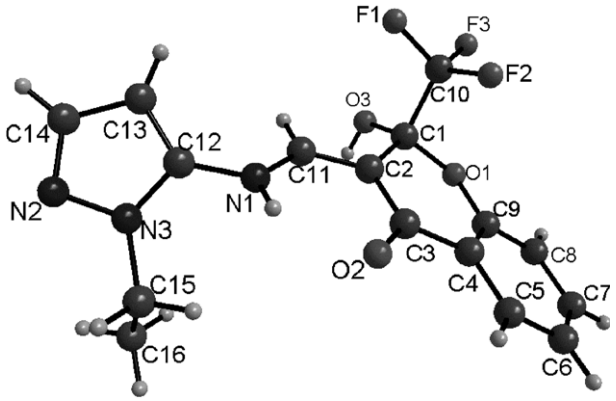


Figure 3 Molecular structure of compound **23b**

(HPLC, mass detection), however our attempts to isolate it failed.

The structure of the pyrazolopyridines were confirmed by ^1H, ^{13}C, and ^{19}F NMR spectroscopies. The most convincing evidence for the formation of 4-trifluoromethyl isomers were the chemical shift of C(4) (δ_c= ~133 ppm) with a coupling constant of ~37 Hz; for the 6-trifluoromethyl isomer, one would expect the signal of C(6) to be situated at δ_c = ~147 ppm.

Concerning the structures of **14** and **15**, the resonance of the sp^3-carbon atom was observed at δ = ~91 ppm ($^2J_{C–F}$ = 24 Hz) and δ = ~72 ppm ($^2J_{C–F}$ = ~28 Hz), respectively; the ^{19}F chemical shifts of **15a**, **15c** and **15d** were found at around δ = –83 ppm.

In order to confirm the structure of hydrates **14** by means of H–H, C–H (HMQC, HMBC, ROESY) correlation spectroscopy, the model compound **14b** (R = C_2F_4H) was synthesized (Figure 4). A correlation of the CF_2H proton at δ = 6.12 ppm with the H-3 proton at δ = 7.60 ppm and H-5 at δ = 6.17 ppm was observed in the ROESY spectra. Furthermore, in the HMQC spectrum, H-3 and H-5 inter-

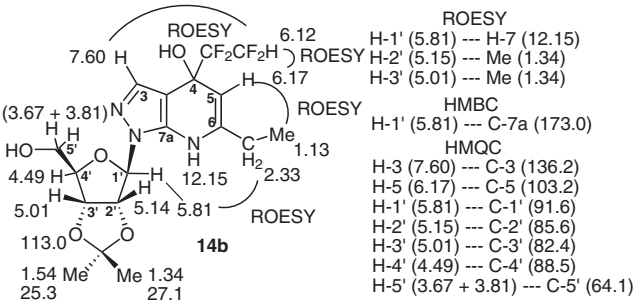


Figure 4 Significant NMR data of compound **14b**

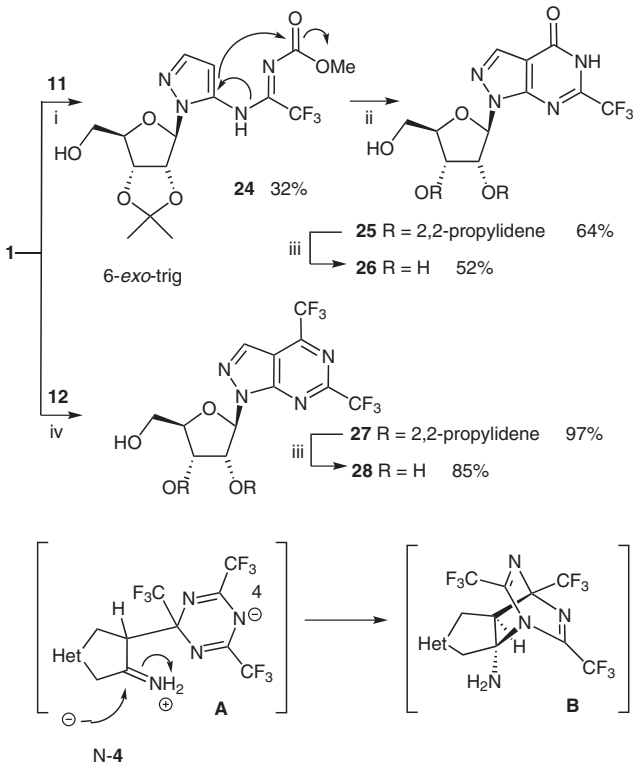
acted with carbon atoms at δ = 103.2 and δ = 136.2 ppm, which were assigned as C-5 and C-3, respectively. Further evidence confirming the structure of **14b** is depicted in Figure 3. The formation of a stable molecular ion of hydrates **14** by electron ionization (70 eV) is also in accordance with structure **14**.

The allopurinol riboside is a known pharmaceutical agent.[17] Herein, we would like to present a novel three-step synthetic route to 2-trifluoromethyl-allopurinol riboside **26** from *iso*-AIRs **1** and building block **11** (Scheme 4). Aminopyrazole **1** reacts with two equivalents of **11** under mild conditions (CH_2Cl_2, Et_3N), affording the product bearing two methyl 1,1,1-trifluoropropan-2-ylidenecarbamate groups, which were detected by HPLC. It should be noted that several by-products were also detected by ^{19}F NMR. During the elution with ethyl acetate, the methyl 1,1,1-trifluoropropan-2-ylidenecarbamate group on the 5-position of the sugar residue was removed to give a relatively stable intermediate **24**, which hydrolysed slowly in air. Amidine **24** appeared to be stable to the ring cyclization and required heating at 180 °C for one hour.

The inverse electron-demand Diels–Alder reaction is a powerful method for assembling heterocycles.[18] Recently, we have applied this method[14b] to the synthesis of fluorinated purines and 7-thiopurines starting from the N^2,N^2-dialkyl-1,3-thiazole-2,4-diamines and 1,2-dimethyl-1*H*-imidazol-5-amine.

Reaction of **1** with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**12**) provides 1-(2,3-*O*-isopropylidene-b-D-ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**27**), the deprotection of which delivers **28**, which is the fluorinated analogue of Nebularine.[19] As for all the previous ribosides, the deprotection of the sugar group was carried out in a mixture of trifluoroacetic acid and water (9:1). Several other reagents for the deprotection of the 2,2′-isopropylidene protection group were tried, however, the method described here gave the best results.

In conclusion, the reactions of 5-amino-1-(2,3-*O*-isopropylidene-b-D-ribofuranosyl)-1*H*-pyrazole (**1**) with a range of fluorinated 1,3-CCC- and 1,3-CNC-dielectrophiles **3**–**11**, and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**12**) were studied systematically. Facile methods for the synthesis of the fluorinated pyrazolo[3,4-*b*]pyridine and



Scheme 4 *Reagents and conditions*: (i) Et_3N (2 equiv), CH_2Cl_2, 0 °C, 30 min then r.t., 2 h, then reflux, 3 h; (ii) no solvent, reduced pressure, 180 °C, 1 h; (iii) TFA–H_2O (9:1), r.t., 45 min; (iv) CH_2Cl_2, N_2, r.t., 36 h.

pyrazolo[3,4-*d*]pyrimidine nucleosides were elaborated. The simple synthesis and purification procedures and the high yields of the target compounds allow synthesis of functionally diverse pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine nucleosides, which are potential inhibitors of ADA and IMPDH receptors.

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. ^1H and ^{13}C NMR spectra (300 and 100 MHz, respectively) were recorded using TMS as an internal standard; ^{19}F NMR spectra (282 MHz) with $CFCl_3$ as an internal standard. Mass spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) using a 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 60F 254 plates were used for TLC. The solvent systems used for chromatographic separation were those indicated for the given R_f values. For compounds that were purified by recrystallization, the solvent system is indicated with the mp data. Satisfactory microanalysis obtained: C ±0.33; H ±0.45; N ±0.25.

X-ray Crystallography of 23b

Crystallographic measurements were performed at r.t. on an Enraf–Nonius CAD4 diffractometer operating in the w-2q scan mode (scanning rate ratio: w/2q = 1.2). The structure was solved by direct methods and refined by full-matrix least-squares technique in anisotropic approximation using SHELXS97 and SHELXL97[20] program packages. Hydrogen atoms were placed at calculated position and refined using the 'riding' model.

X-ray crystal data for **23b**; Crystal system: monoclinic; Space group: $P2_1/c$; Unit cell dimensions: a = 8.0430(16) Å, b = 12.352(3) Å, c = 16.384(3) Å, β = 101.14(3)°; V = 1597.1(6) Å^3; Z = 4; μ(Mo-Kα) = 0.126 mm^{-1}. 21982 reflections collected, 3197 unique reflections, (R_{int} = 0.0541); Mo-Kα radiation (λ = 0.71073 Å); 226 parameters, $R1$ = 0.0375, $wR2$ = 0.0878, S = 1.112 [2864 reflections with $I > 2\sigma(I)$].

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 699062 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].

Compounds 13a–d and 17; General Procedure

A mixture of *iso*-AIRs **1** (2 mmol) and 1,3-dielectrophile (2.1 mmol) in DMF (15 mL) under an inert atmosphere was stirred for 12 h at 125 °C. The reaction mixture was then concentrated under reduced pressure and the dark material was purified by column chromatography over silica gel.

Formation of 20, 13e–g and 25; General Procedure

Initial compound (**14a** for **13g**, **15a** for **13e**, **15b** for **13f**, **19** for **20**, **24** for **25**; 2 mmol) in a 10 mL round-bottom flask was kept for 1 h at 180 °C (temperature of the oil bath) under reduced pressure (0.02 mmHg). When the reaction was complete, the dark-brown material was purified by column chromatography over silica gel.

4,6-Bis(trifluoromethyl)-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazolo[3,4-*b*]pyridine (13a)

Yield: 0.8 g (94%); yellow oil; R_f = 0.40 (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), 3.68 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.86 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.7 Hz, 1 H, CH), 4.53 (br s, 1 H, CH), 5.11 (dd, $^3J_{H–H}$ = 5.9 Hz, $^3J_{H–H}$ = 1.6 Hz, 1 H, CH), 5.27 (dd, $^3J_{H–H}$ = 5.5 Hz, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 6.82 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 7.78 (s, 1 H, CH), 8.35 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.2, 27.2, 63.8, 81.9, 85.0, 88.0, 91.8, 110.8, 112.7, 113.7, 113.8, 119.4 (q, $^1J_{C–F}$ = 275 Hz), 122.3 (q, $^1J_{C–F}$ = 275 Hz), 132.8, 134.1 (q, $^2J_{C–F}$ = 37 Hz), 148.2 (q, $^2J_{C–F}$ = 37 Hz), 150.3.

^{19}F NMR ($CDCl_3$): δ = –60.9, –66.8.

MS: *m*/*z* (%) = 412 (41), 398 (12), 397 (51), 338 (20), 310 (37), 284 (11), 268 (17), 256 (54), 255 (46), 236 (17), 186 (10), 157 (30), 100 (16), 88 (11), 86 (77), 85 (17), 84 (100), 69 (12), 68 (25), 59 (24), 57 (11), 49 (13), 47 (17), 43 (23).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-phenyl-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (13b)

Yield: 0.71 g (81%); colourless solid; mp 129–131 °C; R_f = 0.65 (hexane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 1.62 (s, 3 H, 3-CH_3), 3.71 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.84 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.7 Hz, 1 H, CH), 4.49 (br s, 1 H, CH), 5.09 (dd, $^3J_{H–H}$ = 5.9 Hz, $^3J_{H–H}$ = 1.6 Hz, 1 H, CH), 5.25 (dd, $^3J_{H–H}$ = 5.5 Hz, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 6.88 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 7.45 (m, 3 H, CH), 7.82 (s, 1 H, CH), 8.06 (d, $^3J_{H–H}$ = 7.8 Hz, 2 H, CH), 8.14 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.0, 26.9, 62.0, 72.0, 73.7, 85.2, 88.7, 109.3, 111.7 (q, $^3J_{C–F}$ = 4.7 Hz), 123.1 (q, $^1J_{C–F}$ = 275 Hz), 127.2, 127.5, 130.9, 132.7, 131.2 (q, $^2J_{C–F}$ = 37 Hz), 132.7, 137.1, 151.0, 156.4.

^{19}F NMR ($CDCl_3$): δ = –60.7.

MS: *m*/*z* (%) = 436 (10) [M$^+$ + 1], 435 (39) [M$^+$], 420 (26), 417 (21), 411 (13), 351 (14), 350 (56), 317 (14), 291 (35), 277 (27), 144 (100), 123 (10), 124 (76), 85 (19), 66 (14).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-(thiophen-2-yl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (13c)

Yield: 0.76 g (86%); colourless solid; mp 135–137 °C; R_f = 0.70 (hexane–EtOAc, 1:1).

^{1}H NMR (DMSO-d_6): δ = 1.34 (s, 3 H, CH_3), 1.62 (s, 3 H, 3-CH_3), 3.35–3.39 (m, 1 H, CH), 3.49–3.53 (m, 1 H, CH), 4.20 (td, $J_{H–H}$ = 7.0, 2.3 Hz, 1 H, CH), 4.87 (t, $^3J_{H–H}$ = 5.9 Hz, 1 H, CH), 5.10 (dd, $J_{H–H}$ = 6.5 Hz, $J_{H–H}$ = 2.4 Hz, 1 H, CH), 5.46 (d, $^3J_{H–H}$ = 5.9 Hz, 1 H, CH), 6.56 (br s, 1 H, CH), 7.22 (dd, $^3J_{H–H}$ = 5.1 Hz, $^3J_{H–H}$ = 3.9 Hz, 1 H, CH), 7.81 (dd, $^3J_{H–H}$ = 5.1 Hz, $^3J_{H–H}$ = 1.2 Hz, 1 H, CH), 8.20 (dd, $^3J_{H–H}$ = 3.9 Hz, $^3J_{H–H}$ = 1.2 Hz, 1 H, CH), 8.23 (s, 1 H, CH), 8.38 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.0, 26.9, 61.7, 82.0, 83.6, 87.9, 89.6, 108.9, 110.9, 112.7, 122.2 (q, $^1J_{C–F}$ = 275 Hz), 128.9, 129.3, 131.1, 131.2 (q, $^2J_{C–F}$ = 35 Hz), 132.3, 142.6, 150.6, 152.5.

MS: *m*/*z* (%) = 442 (16) [M$^+$ + 1], 441 (62) [M$^+$], 426 (17), 423 (13), 413 (11), 412 (35), 411 (100), 353 (15), 352 (70), 325 (11), 324 (28), 298 (28), 297 (25), 292 (12), 282 (26), 271 (23), 270 (97), 269 (72), 84 (36), 66 (23).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-(pyridin-4-yl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (13d)

Yield: 0.79 g (91%); colourless solid; mp 169–172 °C; R_f = 0.40 (hexane–EtOAc, 1:1).

^{1}H NMR (DMSO-d_6): δ = 1.36 (s, 3 H, CH_3), 1.56 (s, 3 H, 3-CH_3), 3.31–3.52 (m, 1 H, CH), 4.18 (t, $^3J_{H–H}$ = 7.0 Hz, 1 H, CH), 4.91 (t, $^3J_{H–H}$ = 5.4 Hz, 1 H, CH), 5.04 (dd, $^3J_{H–H}$ = 6.6 Hz, $^3J_{H–H}$ = 2.4 Hz, 1 H, CH), 5.46 (d, $^3J_{H–H}$ = 5.2 Hz, 1 H, CH), 6.75 (s, 1 H, CH), 8.25 (d, $^3J_{H–H}$ = 5.0 Hz, 2 H, CH), 8.38 (s, 1 H, CH), 8.52 (s, 1 H, CH), 8.75 (d, $^3J_{H–H}$ = 5.0 Hz, 2 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.1, 26.8, 61.6, 82.1, 83.7, 88.0, 89.3, 110.3, 112.3 (q, $^3J_{C–F}$ = 4.7 Hz), 112.7, 121.5, 122.3 (q, $^1J_{C–F}$ = 275 Hz), 131.9 (q, $^2J_{C–F}$ = 37 Hz), 132.3, 143.7, 150.6, 151.0, 154.4.

MS: *m*/*z* (%) = 436 (2) [M$^+$], 421 (33), 418 (17), 407 (63), 406 (100), 378 (11), 348 (13), 347 (51), 320 (13), 319 (27), 293 (25), 277 (14), 265 (50), 68 (13).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (13e)

Yield: 0.49 g (65%); colourless solid; mp 139–141 °C; R_f = 0.75 (hexane–EtOAc, 1:1).

^{1}H NMR (DMSO-d_6): δ = 1.30 (s, 3 H, CH_3), 1.49 (s, 3 H, 3-CH_3), 3.58 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.72 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.7 Hz, 1 H, CH), 4.30 (s, 1 H, OH), 4.39 (br s, 1 H, CH), 4.99 (d, $^3J_{H–H}$ = 5.9 Hz, 1 H, CH), 5.19 (d, $^3J_{H–H}$ = 6.2 Hz, 1 H), 5.30 (d, $^3J_{H–H}$ = 2.4 Hz, 1 H), 5.45 (d, $^3J_{H–H}$ = 3.9 Hz, 1 H), 5.81 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 7.37 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.6, 27.0, 63.4, 81.8, 85.1, 88.4, 91.7, 104.3 (q, $^3J_{C–F}$ = 4.4 Hz), 112.9, 113.4, 124.3 (q, $^1J_{C–F}$ = 275 Hz), 132.8, 134.0 (q, $^2J_{C–F}$ = 35 Hz), 142.1, 164.0.

^{19}F NMR (DMSO-d_6): δ = –60.8.

MS: *m*/*z* (%) = 376 (10) [M$^+$ + 1], 375 (24) [M$^+$], 370 (11), 343 (34), 320 (12), 319 (100), 297 (69), 211 (75), 201 (49), 189 (13), 125 (17), 77 (25), 64 (36).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4-(difluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (13f)

Yield: 0.26 g (37%); colourless solid; mp 147–149 °C; R_f = 0.50 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 1.28 (s, 3 H, CH_3), 1.50 (s, 3 H, 3-CH_3), 3.54 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.74 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.7 Hz, 1 H, CH), 4.19 (s, 1 H, OH), 4.38 (br s, 1 H, CH), 4.96 (d, $^3J_{H–H}$ = 5.9 Hz, 1 H, CH), 5.16 (d, $^3J_{H–H}$ = 6.2 Hz, 1 H), 5.32 (d, $^3J_{H–H}$ = 2.4 Hz, 1 H), 5.44 (d, $^3J_{H–H}$ = 3.9 Hz, 1 H), 5.81 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 6.11 (t, $^3J_{H–F}$ = 55 Hz, 1 H, CF_2H), 7.38 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.3, 27.1, 63.7, 81.3, 85.2, 88.8, 91.1, 102.4, 111.7, 112.8, 115.9 (t, $^1J_{C–F}$ = 240 Hz), 126.4 (t, $^2J_{C–F}$ = 25 Hz), 134.3, 142.5, 165.0.

MS: *m*/*z* (%) = 356 (3), 331 (31), 188 (15), 177 (12), 160 (22), 159 (100), 126 (17), 86 (18).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-methyl-4-(perfluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (13g)
Yield: 0.59 g (69%); yellow oil; R_f = 0.55 (hexane–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.64 (s, 3 H, 3-CH_3), 2.37 (s, 3 H, CH_3), 3.64 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.88 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.7 Hz, 1 H, CH), 4.50 (br s, 1 H, OH), 5.10 (dd, $^3J_{H–H}$ = 5.9 Hz, $^3J_{H–H}$ = 1.6 Hz, 1 H, CH), 5.23 (dd, $^3J_{H–H}$ = 5.5 Hz, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 6.82 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 7.78 (s, 1 H, CH), 8.20 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 24.3, 25.4, 27.0, 63.0, 82.5, 85.1, 88.4, 91.7, 110.9, 111.1 (tq, $^1J_{C–F}$ = 215 Hz, $^2J_{C–F}$ = 38 Hz), 113.4, 114.5, 120.1 (qt, $^1J_{C–F}$ = 285 Hz, $^2J_{C–F}$ = 38 Hz), 132.0, 133.4 (t, $^2J_{C–F}$ = 25 Hz), 148.6, 152.7.

MS: *m*/*z* (%) = 424 (22) [M^+ + 1], 423 (42) [M^+], 407 (19), 379 (15), 351 (17), 299 (100), 271 (67), 203 (57), 123 (11), 89 (33), 64 (20).

Synthesis of Compounds 14, 15, 19, 23; General Procedure
A mixture of *iso*-AIRs **1** (2.0 mmol) and 1,3-dielectrophile (2.1 mmol) in DMF (15 mL) under an inert atmosphere was stirred for 24 h at 80 °C. The reaction mixture was then concentrated under reduced pressure (0.02 mmHg) and the brown oil was purified by column chromatography over silica gel.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-methyl-4-(perfluoroethyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-ol (14a)
Yield: 0.6 g (68%); yellow oil; R_f = 0.50 (hexane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.49 (s, 3 H, 3-CH_3), 2.00 (s, 1 H, CH_3), 2.26 (q, $^3J_{H–H}$ = 7.4 Hz, 2 H), 3.63 (dd, $^3J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.1 Hz, 1 H, CH), 3.79 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.0 Hz, 1 H, CH), 4.45 (br s, 1 H, CH), 4.96 (d, $^3J_{H–H}$ = 5.8 Hz, 1 H, CH), 5.01 (dd, $^3J_{H–H}$ = 5.8 Hz, $^3J_{H–H}$ = 3.1 Hz, 1 H, CH), 5.70 (br s, 1 H, CH), 5.75 (d, $^3J_{H–H}$ = 2.7 Hz, 1 H), 6.11 ($^3J_{H–H}$ = 2.0 Hz, 1 H), 7.55 (d, $^3J_{H–H}$ = 2.4 Hz, 1 H, CH), 12.04 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 20.2, 25.1, 26.9, 64.0, 82.3, 85.3, 88.3, 92.0 (t, $^2J_{C–F}$ = 24 Hz), 92.1, 93.8, 102.9, 107.6 (tq, $^1J_{C–F}$ = 263 Hz, $^2J_{C–F}$ = 37 Hz), 113.3, 118.2 (qt, $^1J_{C–F}$ = 285 Hz, $^2J_{C–F}$ = 34 Hz), 136.4, 140.6, 168.0.

MS: *m*/*z* (%) = 441 (24) [M^+], 411 (13), 352 (14), 269 (100), 173 (13), 150 (87), 122 (13), 108 (13), 85 (13), 84 (23), 73 (12), 71 (22), 69 (26), 66 (20), 59 (31), 57 (12), 55 (12), 45 (21), 43 (24).

6-Ethyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-(1,1,2,2-tetrafluoroethyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-ol (14b)
Yield: 0.61 g (70%); yellow oil; R_f = 0.75 (hexane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 1.13 (t, $^3J_{H–H}$ = 7.4 Hz, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.54 (s, 3 H, 3-CH_3), 2.33 (q, $^3J_{H–H}$ = 7.4 Hz, 2 H), 3.67 (dd, $^3J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.1 Hz, 1 H, CH), 3.81 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.0 Hz, 1 H, CH), 4.49 (br s, 1 H, CH), 5.01 (d, $^3J_{H–H}$ = 5.8 Hz, 1 H, CH), 5.14 (dd, $^3J_{H–H}$ = 5.8 Hz, $^3J_{H–H}$ = 3.1 Hz, 1 H, CH), 5.81 (br s, 1 H, CH), 6.12 (tt, $^2J_{H–F}$ = 53.0 Hz, $^3J_{H–F}$ = 5.1 Hz, 1 H, CF_2H), 6.17 (d, $^3J_{H–H}$ = 2.0 Hz, 1 H, CH), 7.60 (s, 1 H, CH), 12.15 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 11.4, 25.0, 25.3, 27.1, 64.1, 82.4, 85.6, 88.5, 91.5 (t, $^2J_{C–F}$ = 24.0 Hz), 91.6, 91.9, 109.2 (tt, $^1J_{C–F}$ = 250 Hz, $^2J_{C–F}$ = 34.3 Hz), 109.7 (tt, $^1J_{C–F}$ = 258 Hz, $^2J_{C–F}$ = 26 Hz), 113.4, 136.2, 140.7, 173.0.

MS: *m*/*z* (%) = 419 (8) [M^+], 401 (10), 400 (100), 390 (17), 309 (30), 297 (25), 183 (27), 179 (39), 171 (50), 149 (11), 101 (11), 84 (11), 43 (12).

6-Ethyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-(perfluorobutyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-ol (14c)
Yield: 0.78 g (71%); yellow oil; R_f = 0.20 (hexane–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$): δ = 1.08 (t, $^3J_{H–H}$ = 7.4 Hz, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.48 (s, 3 H, 3-CH_3), 2.26 (q, $^3J_{H–H}$ = 7.4 Hz, 2 H), 3.62 (dd, $^3J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.1 Hz, 1 H, CH), 3.86 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.0 Hz, 1 H, CH), 4.44 (br s, 1 H, CH), 4.96 (d, $^3J_{H–H}$ = 5.8 Hz, 1 H, CH), 5.01 (dd, $^3J_{H–H}$ = 5.8 Hz, $^3J_{H–H}$ = 3.1 Hz, 1 H, CH), 5.68 (s, 1 H, CH), 5.73 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 6.12 (d, $^3J_{H–H}$ = 2.0 Hz, 1 H, CH), 7.55 (d, $^3J_{H–H}$ = 2.0 Hz, 1 H, CH), 12.03 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 11.6, 25.1, 25.8, 26.9, 64.0, 82.3, 85.4, 88.3, 91.7 (t, $J_{C–F}$ = 24 Hz), 91.9, 92.1, 103.2, 113.3, 136.9, 140.5, 173.2.

MS: *m*/*z* (%) = 555 (24) [M^+], 525 (61), 384 (27), 383 (64), 173 (11), 164 (100), 126 (36), 83 (11), 71 (14), 69 (18), 59 (23), 43 (17).

Methyl 3-[5-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazol-4-yl]-4,4,4-trifluoro-3-hydroxybutanoate (15a)
Yield: 0.61 g (72%); yellow oil; R_f = 0.60 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.47 (s, 3 H, 3-CH_3), 3.21 (m, 2 H, CH_2), 3.58 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.67 (s, 3 H, OCH_3), 3.89 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 4.71 (br s, 4 H, NH_2 and OH), 4.90 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 1.4 Hz, 1 H, CH), 5.20 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 5.65 (d, $^3J_{H–H}$ = 7.4 Hz, 1 H, CH), 5.87 (d, $^3J_{H–H}$ = 2.5 Hz, 1 H, CH), 6.35 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.4, 26.9, 43.1, 50.9, 63.4, 73.0 (q, $^2J_{C–F}$ = 28 Hz), 82.5, 87.9, 92.7, 98.0, 111.0, 113.9, 127.1 (q, $^1J_{C–F}$ = 278 Hz), 146.3, 147.9, 175.3.

^{19}F NMR ($CDCl_3$): δ = –84.2.

MS: *m*/*z* (%) = 439 (9) [M^+], 422 (53), 420 (26), 403 (70), 374 (47), 366 (18), 365 (90), 307 (67), 222 (50), 173 (21), 174 (100), 108 (10), 77 (34), 54 (11).

Methyl 3-[5-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazol-4-yl]-4,4-difluoro-3-hydroxybutanoate (15b)
Yield: 0.40 g (49%); yellow oil; R_f = 0.30 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.50 (s, 3 H, 3-CH_3), 3.27 (m, 2 H, CH_2), 3.57 (dd, $^2J_{H–H}$ = 12.7 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.66 (s, 3 H, OCH_3), 3.87 (dd, $^2J_{H–H}$ = 12.7 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 4.55 (br s, 4 H, NH_2 and OH), 4.87 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 1.4 Hz, 1 H, CH), 5.19 (dd, $^3J_{H–H}$ = 5.8 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 5.53 (d, $^3J_{H–H}$ = 7.2 Hz, 1 H, CH), 5.78 (d, $^3J_{H–H}$ = 2.5 Hz, 1 H, CH), 6.39 (s, 1 H, CH), 7.17 (t, $^1J_{H–F}$ = 54 Hz, 1 H, CF_2H).

^{13}C NMR ($CDCl_3$): δ = 25.1, 26.0, 43.0, 51.1, 63.7, 70.3 (q, $^2J_{C–F}$ = 27 Hz), 82.3, 87.0, 92.2, 98.0, 110.2, 113.0, 125.1 (q, $^1J_{C–F}$ = 256 Hz), 146.0, 147.2. 178.1.

MS: *m*/*z* (%) = 420 (12) [M^+ – 1], 404 (33), 391 (44), 351 (99), 333 (100), 281 (71), 207 (10), 205 (39), 173 (29), 171 (19), 121 (11), 86 (21).

2-[5-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazol-4-yl]-1,1,1-trifluoropropan-2-ol (15c)
Yield: 0.65 g (89%); yellow oil; R_f = 0.35 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.57 (s, 3 H, 3-CH_3), 1.67 (s, 3 H, CH_3), 3.61 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.84 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 4.17 (br s, 3 H, NH_2 and OH), 4.61 (br s, 1 H, CH), 4.97 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 1.4 Hz, 1 H, CH), 5.25 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 5.67 (d, $^3J_{H–H}$ = 7.4 Hz, 1 H, CH), 5.81 (d, $^3J_{H–H}$ = 2.5 Hz, 1 H, CH), 6.11 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 24.5, 25.9, 27.0, 63.5, 73.1 (q, $^2J_{C–F}$ = 28 Hz), 82.4, 88.0, 92.7, 98.1, 111.1, 114.3, 127.7 (q, $^1J_{C–F}$ = 278 Hz), 147.1, 149.8.

^{19}F NMR ($CDCl_3$): δ = –83.7.

MS: *m*/*z* (%) = 367 (12) [M$^+$], 367 (89), 350 (100), 317 (37), 288 (68), 254 (78), 88 (79).

1-[5-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazol-4-yl]-2,2,2-trifluoro-1-phenylethanol (15d)
Yield: 0.75 g (87%); yellow oil; R_f = 0.65 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.50 (s, 3 H, 3-CH_3), 3.64 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 3.2 Hz, 1 H, CH), 3.85 (dd, $^2J_{H–H}$ = 12.8 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 4.69 (br s, 4 H, NH_2 and OH), 4.99 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 1.4 Hz, 1 H, CH), 5.25 (dd, $^3J_{H–H}$ = 6.0 Hz, $^3J_{H–H}$ = 2.6 Hz, 1 H, CH), 5.61 (d, $^3J_{H–H}$ = 7.4 Hz, 1 H, CH), 5.79 (d, $^3J_{H–H}$ = 2.5 Hz, 1 H, CH), 6.13 (s, 1 H, CH), 7.37 (d, $^3J_{H–H}$ = 7.8 Hz, 2 H, CH), 7.43–7.54 (m, 3 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.1, 27.0, 63.3, 73.2 (q, $^2J_{C–F}$ = 28 Hz), 83.9, 88.0, 97.4, 97.9, 111.0, 114.3, 124.2, 127.3, 127.6 (q, $^1J_{C–F}$ = 278 Hz), 130.3, 137.7, 147.5, 149.9.

^{19}F NMR ($CDCl_3$): δ = –83.5.

MS: *m*/*z* (%) = 428 (11) [M$^+$ – 1], 412 (51), 353 (45), 359 (33), 358 (100), 289 (70), 201 (32), 158 (56), 68 (23).

Cleavage of 2,2′-Propylidene Protecting Group; General Procedure
The protected substrate (1 mmol) was dissolved in a mixture of TFA–H_2O (9:1; 10–15 mL), and stirred vigorously at r.t. for 30–40 min (reaction monitored by TLC). The reaction mixture was concentrated under reduced pressure (the mixture should not be heated over 40 °C) and the residue was subjected to column chromatography over silica gel.

Synthesis of Compounds 16e–g from 14a, 15a and 15b; General Procedure
Compound **14a**, **15a** or **15b** (1 mmol) and PTSA (cat.), dissolved in absolute MeOH (10 mL) was heated under reflux for 1 h. After evaporation of the solvent, the residue was either subjected to flash column chromatography over silica gel or recrystallized from an appropriate solvent.

l-(β-D-Ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (16a)
Yield: 0.33 mg (84%); colourless solid; mp 111–112 °C; R_f = 0.75 (EtOAc).

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

^{13}C NMR (DMSO-d_6): δ = 62.1, 70.8, 73.4, 85.0, 88.5, 111.0, 112.9, 119.5 (q, $^1J_{C–F}$ = 275 Hz), 122.2 (q, $^1J_{C–F}$ = 275 Hz), 132.5, 132.51 (q, $^2J_{C–F}$ = 37 Hz), 145.2 (q, $^2J_{C–F}$ = 37 Hz), 150.3.

^{19}F NMR (DMSO-d_6): δ = –61.0, –66.5.

MS: *m*/*z* (%) = 387 (5) [M$^+$], 358 (15), 357 (77), 310 (14), 285 (22), 284 (39), 256 (20), 132 (100).

l-(β-D-Ribofuranosyl)-6-phenyl-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (16b)
Yield: 0.28 mg (71%); colourless solid; mp 189–191 °C; R_f = 0.60 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.50 (q, $^3J_{H–H}$ = 6.2 Hz, 1 H, CH), 3.64 (m, 1 H, CH), 4.02 (q, $^3J_{H–H}$ = 5.7 Hz, 1 H, CH), 4.35 (q, $^3J_{H–H}$ = 5.1 Hz, 1 H, CH), 4.78–4.83 (br m, 2 H, CH), 5.29 (d, $^3J_{H–H}$ = 5.4 Hz, 1 H, OH), 5.52 (d, $^3J_{H–H}$ = 5.8 Hz, 1 H, OH), 6.56 (d, $^3J_{H–H}$ = 4.3 Hz, 1 H, CH), 7.62 (m, 3 H, CH), 8.29 (s, 1 H, CH), 8.36 (d, $^3J_{H–H}$ = 7.8 Hz, 2 H, CH), 8.50 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 62.7, 70.9, 73.3, 85.3, 88.2, 109.2, 111.7 (q, $^3J_{C–F}$ = 4.7 Hz), 123.0 (q, $^1J_{C–F}$ = 275 Hz), 127.0, 127.7, 130.7, 132.8, 131.1 (q, $^2J_{C–F}$ = 37 Hz), 132.8, 137.0, 151.6, 156.7.

MS: *m*/*z* (%) = 395 (9) [M$^+$], 365 (33), 318 (14), 306 (33), 293 (32), 292 (100), 276 (12), 265 (19), 264 (89), 263 (12), 190 (90), 171 (11), 76 (20).

l-(β-D-Ribofuranosyl)-6-(thiophen-2-yl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (16c)
Yield: 0.34 g (85%); colourless solid; mp 194–195 °C; R_f = 0.68 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.46–3.52 (m, 1 H, CH), 3.63–3.69 (m, 1 H, CH), 4.02 (q, $^3J_{H–H}$ = 5.7 Hz, 1 H, CH), 4.35 (q, $^3J_{H–H}$ = 5.1 Hz, 1 H, CH), 4.79–4.83 (br m, 2 H, CH), 5.31 (d, $^3J_{H–H}$ = 5.4 Hz, 1 H, OH), 5.55 (d, $^3J_{H–H}$ = 5.8 Hz, 1 H, OH), 6.40 (d, $^3J_{H–H}$ = 4.3 Hz, 1 H, CH), 7.30 (dd, $^3J_{H–H}$ = 5.1 Hz, $^3J_{H–H}$ = 3.9 Hz, 1 H, CH), 7.88 (dd, $^3J_{H–H}$ = 5.1 Hz, $^3J_{H–H}$ = 1.2 Hz, 1 H, CH), 8.28 (dd, $^3J_{H–H}$ = 3.9 Hz, $^3J_{H–H}$ = 1.2 Hz, 1 H, CH), 8.31 (s, 1 H, CH), 8.45 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 62.3, 71.0, 85.3, 88.4, 109.0, 110.8 (q, $^3J_{C–F}$ = 4.7 Hz), 122.8 (q, $^1J_{C–F}$ = 275 Hz), 129.0, 129.3, 130.6, 131.0, 131.1 (q, $^2J_{C–F}$ = 37 Hz), 132.1, 142.8, 151.1, 152.4.

MS: *m*/*z* (%) = 402 (20) [M$^+$ + 1], 401 (61) [M$^+$], 372 (17), 371 (62), 370 (22), 325 (14), 324 (59), 313 (27), 312 (74), 300 (24), 299 (56), 298 (87), 296 (18), 284 (26), 283 (55), 282 (77), 272 (43), 271 (70), 270 (100), 269 (84), 268 (15), 250 (18), 222 (11), 215 (13), 172 (16), 108 (11), 73 (25), 69 (13), 57 (22), 45 (18), 43 (15).

l-(β-D-Ribofuranosyl)-6-(pyridin-4-yl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (16d)
Yield: 0.27 g (74%); colourless solid; mp 182–183 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 3.54 (m, 1 H, CH), 3.68 (m, 1 H, CH), 4.00 (q, $^3J_{H–H}$ = 4.7 Hz, 1 H, CH), 4.30 (br s, 1 H, CH), 4.73 (d, $^3J_{H–H}$ = 4.7 Hz, 2 H, CH), 5.29 (br s, 1 H, OH), 5.48 (d, $^3J_{H–H}$ = 5.4 Hz, 1 H, OH), 6.49 (d, $^3J_{H–H}$ = 4.7 Hz, 1 H, CH), 8.03 (s, 1 H, CH), 8.14 (s, 1 H, CH), 8.20 (d, $^3J_{H–H}$ = 5.0 Hz, 2 H, CH), 8.79 (d, $^3J_{H–H}$ = 5.0 Hz, 2 H, CH).

^{13}C NMR (DMSO-d_6): δ = 61.9, 82.0, 83.5, 88.3, 89.1, 110.4, 112.4 (q, $^3J_{C–F}$ = 4.7 Hz), 112.7, 121.6, 122.8 (q, $^1J_{C–F}$ = 275 Hz), 131.7 (q, $^2J_{C–F}$ = 37 Hz), 132.4, 143.8, 150.2, 151.5, 154.9.

^{19}F NMR (DMSO-d_6): δ = –67.1.

MS: *m*/*z* (%) = 397 (18) [M$^+$ + 1], 396 (72) [M$^+$], 377 (88), 356 (29), 357 (89), 305 (40), 230 (100), 177 (35), 176 (90), 157 (11), 122 (19), 119 (20), 68 (10), 45 (41).

l-(β-D-Ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (16e)
Yield: 0.25 g (64%); colourless solid; mp 177–180 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 3.55 (q, $^3J_{H–H}$ = 6.2 Hz, 1 H, CH), 3.60 (m, 1 H, CH), 4.09 (q, $^3J_{H–H}$ = 5.7 Hz, 1 H, CH), 4.33 (q, $^3J_{H–H}$ = 5.1

Hz, 1 H, CH), 4.75–4.82 (br m, 2 H, CH), 5.27 (d, $^3J_{H-H}$ = 5.4 Hz, 1 H, OH), 5.58 (d, $^3J_{H-H}$ = 5.6 Hz, 1 H, OH), 6.59 (d, $^3J_{H-H}$ = 4.3 Hz, 1 H, CH), 7.00 (s, 1 H, CH), 7.75 (s, 1 H, CH), 12.11 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 81.4, 85.7, 88.8, 91.3, 104.1 (q, $^3J_{C-F}$ = 4.4 Hz), 112.7, 113.4, 124.3 (q, $^1J_{C-F}$ = 275 Hz), 132.2, 134.2 (q, $^2J_{C-F}$ = 35 Hz), 142.0, 164.9.

^{19}F NMR (DMSO-d_6): δ = –61.1.

MS: *m*/*z* (%) = 335 (11) [M$^+$], 334 (28), 317 (31), 316 (16), 311 (11), 277 (33), 278 (100), 256 (69), 245 (10), 244 (74), 199 (39), 198 (11), 190 (54), 189 (17), 138 (18), 112 (21), 107 (22), 104 (14), 98 (12), 81 (13), 68 (11), 43 (19).

l-(β-D-Ribofuranosyl)-4-(difluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one (16f)

Yield: 0.19 g (61%); colourless solid; mp 184–186 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 3.53 (q, $^3J_{H-H}$ = 6.2 Hz, 1 H, CH), 3.61 (m, 1 H, CH), 4.11 (q, $^3J_{H-H}$ = 5.7 Hz, 1 H, CH), 4.31 (q, $^3J_{H-H}$ = 5.1 Hz, 1 H, CH), 4.73–4.83 (br m, 2 H, CH), 5.20 (d, $^3J_{H-H}$ = 5.4 Hz, 1 H, OH), 5.59 (d, $^3J_{H-H}$ = 5.6 Hz, 1 H, OH), 6.50 (d, $^3J_{H-H}$ = 4.3 Hz, 1 H, CH), 6.25 (t, $^3J_{H-F}$ = 55 Hz, 1 H, CF_2H), 7.00 (s, 1 H, CH), 7.75 (s, 1 H, CH), 12.11 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 81.2, 85.4, 88.7, 91.0, 102.1, 112.0, 112.7, 115.3 (t, $^1J_{C-F}$ = 240 Hz), 126.0 (t, $^2J_{C-F}$ = 25 Hz), 134.2, 142.7, 165.2.

MS: *m*/*z* (%) = 317 (3) [M$^+$], 316 (11), 302 (19), 301 (25), 300 (14), 269 (70), 280 (50), 221 (91), 184 (100), 134 (17), 133 (60), 103 (48), 64 (11).

l-(β-D-Ribofuranosyl)-4-(perfluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (16g)

Yield: 0.30 g (77%); colourless solid; mp 122–124 °C; R_f = 0.70 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 2.41 (s, 3 H, CH_3), 3.58 (q, $^3J_{H-H}$ = 6.2 Hz, 1 H, CH), 3.67 (m, 1 H, CH), 4.00 (q, $^3J_{H-H}$ = 5.7 Hz, 1 H, CH), 4.32 (q, $^3J_{H-H}$ = 5.1 Hz, 1 H, CH), 4.75–4.82 (br m, 2 H, CH), 5.37 (d, $^3J_{H-H}$ = 5.4 Hz, 1 H, OH), 5.50 (d, $^3J_{H-H}$ = 5.7 Hz, 1 H, OH), 6.50 (d, $^3J_{H-H}$ = 4.3 Hz, 1 H, CH), 8.14 (s, 1 H, CH), 8.23 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.3, 62.7, 70.9, 73.9, 84.8, 88.3, 111.4, 112.9, 111.1, 111.2 (tq, $^1J_{C-F}$ = 215 Hz, $^2J_{C-F}$ = 38 Hz), 120.1 (qt, $^1J_{C-F}$ = 285 Hz, $^2J_{C-F}$ = 38 Hz), 132.48, 133.7 (t, $^2J_{C-F}$ = 25 Hz), 150.3.

MS: *m*/*z* (%) = 384 (17) [M$^+$ + 1], 383 (70) [M$^+$], 265 (12), 264 (100), 244 (19), 234 (13), 221 (18), 189 (54), 174 (60), 173 (10), 172 (96), 150 (61), 143 (11).

10-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-7-(trifluoromethyl)-6,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline (17a)

Yield: 0.66 g (72%); colourless solid; mp 139–141 °C; R_f = 0.70 (hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 2.89 (br s, 2 H, CH_2), 3.30 (br s, 2 H, CH_2), 3.71 (dd, $^3J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 3.2 Hz, 1 H, CH), 3.86 (dd, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 2.0 Hz, 1 H, CH), 4.10 (s, 2 H, CH_2), 4.48 (br s, 1 H, CH), 5.07 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 1.6 Hz, 1 H, CH), 5.23 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 2.8 Hz, 1 H, CH), 6.81 (d, $^3J_{H-H}$ = 2.8 Hz, 1 H, CH), 7.27–7.36 (br m, 3 H, CH), 8.23 (m, 1 H, CH), 8.44 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 24.4, 25.9, 26.4, 27.1, 63.0, 82.2, 85.3, 87.1, 90.7, 121.8 (q, $^3J_{C-F}$ = 3.4 Hz), 123.1 (q, $^1J_{C-F}$ = 275 Hz), 126.3, 127.0, 127.7 (q, $^2J_{C-F}$ = 37 Hz), 128.0, 130.9, 133.7, 135.4, 136.0, 148.9, 155.1.

^{19}F NMR ($CDCl_3$): δ = –55.3.

MS: *m*/*z* (%) = 461 (51) [M$^+$], 447 (35), 440 (26), 401 (70), 371 (100), 365 (10), 364 (80), 287 (43), 256 (17), 209 (19), 181 (35), 119 (21), 63 (23).

10-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-(trifluoromethyl)-6,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-7-(trifluoromethyl)-6,10-dihydropyrazolo[3,4-*b*]thiochromeno[3,4-*e*]pyridine (17b)

Yield: 0.66 g (69%); colourless solid; mp 131–133 °C; R_f = 0.80 (hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 3.70 (dd, $^3J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 3.2 Hz, 1 H, CH), 3.86 (dd, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 2.0 Hz, 1 H, CH), 4.10 (s, 2 H, CH_2), 4.48 (br s, 1 H, CH), 5.07 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 1.6 Hz, 1 H, CH), 5.23 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 2.8 Hz, 1 H, CH), 6.80 (d, $^3J_{H-H}$ = 2.8 Hz, 1 H, CH), 7.27–7.36 (br m, 3 H, CH), 8.17 (m, 1 H, CH), 8.40 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.0, 27.0, 27.6, 63.9, 81.8, 85.1, 87.9, 90.8, 122.5 (q, $^3J_{C-F}$ = 3.5 Hz), 123.2 (q, $^1J_{C-F}$ = 275 Hz), 126.4, 127.3, 127.8 (q, $^2J_{C-F}$ = 37 Hz), 128.6, 130.4, 133.31, 133.36, 136.6, 149.8, 153.9.

^{19}F NMR ($CDCl_3$): δ = –56.1.

MS: *m*/*z* (%) = 479 (41) [M$^+$], 450 (70), 438 (25), 385 (23), 291 (77), 187 (17), 186 (100), 169 (12), 158 (77), 137 (11), 84 (31).

10-(β-D-Ribofuranosyl)-7-(trifluoromethyl)-6,10-dihydropyrazolo[3,4-*b*]thiochromeno[3,4-*e*]pyridine (18)

Yield: 0.35 g (79%); colourless solid; mp 159–160 °C; R_f = 0.80 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.51 (q, $^3J_{H-H}$ = 6.2 Hz, 1 H, CH), 3.67 (m, 1 H, CH), 4.00 (q, $^3J_{H-H}$ = 5.5 Hz, 1 H, CH), 4.30 (q, $^3J_{H-H}$ = 5.0 Hz, 1 H, CH), 4.75–4.81 (br m, 2 H, CH), 5.33 (d, $^3J_{H-H}$ = 5.4 Hz, 1 H, OH), 5.50 (d, $^3J_{H-H}$ = 5.8 Hz, 1 H, OH), 6.59 (d, $^3J_{H-H}$ = 4.5 Hz, 1 H, CH), 7.30–7.41 (br m, 3 H, CH), 8.10 (d, $^3J_{H-H}$ = 7.8 Hz, 1 H, CH), 8.49 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 27.3, 65.2, 83.0, 85.9, 87.1, 90.7, 122.2 (q, $^3J_{C-F}$ = 3.5 Hz), 124.4 (q, $^1J_{C-F}$ = 275 Hz), 126.0, 127.7, 128.5 (q, $^2J_{C-F}$ = 37 Hz), 129.1, 130.4, 134.1, 134.6, 139.0, 149.1, 155.7.

^{19}F NMR (DMSO-d_6): δ = –56.5.

MS: *m*/*z* (%) = 440 (19) [M$^+$ + 1], 439 (77) [M$^+$], 433 (21), 431 (17), 430 (29), 392 (11), 393 (100), 392 (19), 390 (70), 388 (23), 378 (11), 337 (17), 287 (15), 286 (97), 285 (24), 189 (13), 188 (11), 187 (18), 167 (18), 165 (20), 164 (68), 157 (44), 156 (50), 119 (11), 88 (45), 67 (23), 43 (15).

1,1,1-Trifluoro-4-[1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazol-5-ylamino]but-3-en-2-one (19)

Yield: 0.69 g (92%); yellow oil; R_f = 0.45 (hexane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.53 (s, 3 H, 3-CH_3), 3.57 (dd, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 3.2 Hz, 1 H, CH), 3.72 (dd, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 2.7 Hz, 1 H, CH), 4.43 (br s, 1 H, CH), 4.92 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 1.6 Hz, 1 H, CH), 5.25 (dd, $^3J_{H-H}$ = 5.5 Hz, $^3J_{H-H}$ = 2.8 Hz, 1 H, CH), 5.67 (d, $^3J_{H-H}$ = 7.4 Hz, 1 H, CH), 5.81 (d, $^3J_{H-H}$ = 2.4 Hz, 1 H, CH), 6.03 (d, $^3J_{H-H}$ = 2.0 Hz, 1 H, CH), 7.27 (d, $^3J_{H-H}$ = 8.2 Hz, 1 H, CH), 8.44 (d, $^3J_{H-H}$ = 2.0 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.1, 27.0, 63.7, 81.7, 84.9, 88.4, 92.1, 92.5, 95.8, 113.7, 116.5 (q, $^1J_{C-F}$ = 287 Hz), 140.3, 140.6, 151.7, 180.7 (q, $^2J_{C-F}$ = 33 Hz).

MS: *m*/*z* (%) = 377 (7) [M$^+$], 344 (27), 330 (16), 329 (92), 270 (37), 243 (15), 242 (36), 216 (26), 214 (13), 205 (30), 201 (11), 200 (20), 189 (10), 188 (100), 187 (22), 157 (18), 136 (16), 86 (30), 85 (18), 84 (36), 71 (11), 69 (17), 68 (32), 59 (34), 57 (16), 43 (24).

Synthesis of Compounds 20 and 25; General Procedure

The initial compound **19** or **24** (2 mmol) was placed in a 10 mL flask and melted for 1 h under reduced pressure (0.02 mmHg) at 180 °C (temperature of the oil bath). The dark residue formed was purified by column chromatography over silica gel.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (20)

Yield: 0.58 g (80%); yellow oil; R_f = 0.65 (hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 3.70 (dd, $^3J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 3.5 Hz, 1 H, CH), 3.81 (dd, $^2J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 1.3 Hz, 1 H, CH), 4.49 (br s, 1 H, CH), 5.09 (dd, $^3J_{H-H}$ = 5.4 Hz, $^3J_{H-H}$ = 1.6 Hz, 1 H, CH), 5.28 (dd, $^3J_{H-H}$ = 5.4 Hz, $^3J_{H-H}$ = 2.7 Hz, 1 H, CH), 6.43 (br s, 1 H, OH), 6.80 (d, $^3J_{H-H}$ = 2.7 Hz, 1 H, CH), 8.21 (d, $^3J_{H-H}$ = 4.8 Hz, 1 H, CH), 8.33 (s, 1 H, CH), 8.70 (d, $^3J_{H-H}$ = 4.8 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 24.7, 26.9, 63.4, 82.1, 85.9, 87.5, 92.3, 111.1, 112.7, 113.78, 113.83, 123.1 (q, $^1J_{C-F}$ = 275 Hz), 130.9, 133.6 (q, $^2J_{C-F}$ = 37 Hz), 144.8, 150.9.

^{19}F NMR (DMSO-d_6): δ = –61.4.

MS: *m*/*z* (%) = 359 (55) [M$^+$], 354 (18), 333 (19), 301 (22), 278 (67), 277 (23), 270 (37), 234 (67), 232 (49), 184 (100), 179 (89), 161 (60), 160 (11), 155 (21), 107 (16), 72 (78).

l-(β-D-Ribofuranosyl)-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridine (21)

Yield: 0.25 g (78%); colourless solid; mp 122–124 °C; R_f = 0.55 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.41 (dd, $^2J_{H-H}$ = 11.1 Hz, $^3J_{H-H}$ = 5.5 Hz, 1 H, CH), 3.54 (dd, $^2J_{H-H}$ = 11.1 Hz, $^3J_{H-H}$ = 4.9 Hz, 1 H, CH), 3.94 (q, $^3J_{H-H}$ = 4.9 Hz, 1 H, CH), 4.25 (t, $^3J_{H-H}$ = 4.7 Hz, 1 H, CH), 4.65 (t, $^3J_{H-H}$ = 5.0 Hz, 1 H, CH), 6.32 (d, $^3J_{H-H}$ = 4.4 Hz, 1 H, CH), 8.19 (d, $^3J_{H-H}$ = 4.8 Hz, 1 H, CH), 8.34 (s, 1 H, CH), 8.73 (d, $^3J_{H-H}$ = 4.8 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 62.7, 70.5, 73.8, 85.1, 88.8, 111.2, 113.0, 122.4 (q, $^1J_{C-F}$ = 275 Hz), 132.0, 132.5 (q, $^2J_{C-F}$ = 37 Hz), 144.4, 150.3.

^{19}F NMR (DMSO-d_6): δ = –61.1.

MS: *m*/*z* (%) = 319 (27) [M$^+$], 311 (12), 304 (11), 298 (17), 297 (15), 290 (12), 217 (100), 211 (19), 210 (85), 198 (73), 197 (11), 181 (43), 167 (29), 163 (89), 88 (17), 79 (15).

2-Hydroxy-3-[(1*H*-pyrazol-5-ylamino)methylene]-2-(trifluoromethyl)-2,3-dihydro-4*H*-chromen-4-one (23a)

Yield: 0.47 g (72%); colourless solid; mp 200–203 °C; R_f = 0.25 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 6.31 (s, 1 H, CH), 7.00 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 7.11 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 7.45 (s, 1 H, CH), 7.55 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 7.80 (d, $^3J_{H-H}$ = 12.1 Hz, 1 H, CH), 7.89 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 9.14 (s, 1 H, OH), 12.60 (d, $^3J_{H-H}$ = 11.7 Hz, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 94.2, 97.6 (q, $^2J_{C-F}$ = 32 Hz), 100.5, 116.5, 119.6, 122.3, 122.7 (q, $^1J_{C-F}$ = 290 Hz), 125.0, 126.0, 128.0, 128.7, 135.5, 138.3, 139.5, 149.7, 155.8, 180.3.

MS: *m*/*z* (%) = 325 (11) [M$^+$], 306 (16), 307 (100), 213 (18), 181 (19), 149 (27), 117 (33), 94 (24), 67 (35).

3-{[(1-Ethyl-1*H*-pyrazol-5-yl)amino]methylene}-2-hydroxy-2-(trifluoromethyl)-2,3-dihydro-4*H*-chromen-4-one (23b)

Yield: 0.53 g (75%); colourless solid; mp 153–155 °C; R_f = 0.90 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 1.36 (t, $^3J_{H-H}$ = 6.6 Hz, 3 H, CH_3), 4.13 (q, $^3J_{H-H}$ = 6.6 Hz, 3 H, CH_2), 6.39 (s, 1 H, CH), 7.07 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 7.16 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 7.41 (s, 1 H, CH), 7.56 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 7.75 (d, $^3J_{H-H}$ = 12.5 Hz, 1 H, CH), 7.85 (d, $^3J_{H-H}$ = 7.3 Hz, 1 H, CH), 9.18 (s, 1 H, OH), 12.75 (d, $^3J_{H-H}$ = 11.1 Hz, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.6, 42.9, 94.2, 97.6 (q, $^2J_{C-F}$ = 32 Hz), 100.7, 116.7, 119.7, 122.4, 122.7 (q, $^1J_{C-F}$ = 290 Hz), 125.3, 125.9, 128.2, 128.9, 135.5, 138.4, 139.0, 149.4, 156.0, 180.6.

MS: *m*/*z* (%) = 353 (14) [M$^+$], 336 (15), 335 (100), 278 (73), 257 (18), 238 (41), 178 (19).

Methylethylidenecarbamate-5-amino-2,2,2-trifluoro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazole (24)

A mixture of **1** (4 mmol) and ethaneimidoyl chloride **11** (1.52 g, 8 mmol) in CH_2Cl_2 (25 mL) was stirred at 0 °C for 30 min, then a solution of Et_3N (8 mmol, 1.11 mL) in CH_2Cl_2 (10 mL) was slowly added. The mixture was stirred at r.t. for 2 h, then refluxed for 3 h. The solution was washed with H_2O (2 × 20 mL) and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was subjected to flash column chromatography over silica gel (EtOAc) to afford **24**.

Yield: 0.52 g (32%); yellow oil; R_f = 0.55 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.61 (s, 3 H, 3-CH_3), 3.59 (dd, $^2J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 3.2 Hz, 1 H, CH), 3.69 (s, 3 H, OCH_3), 3.77 (dd, $^2J_{H-H}$ = 12.0 Hz, $^3J_{H-H}$ = 2.5 Hz, 1 H, CH), 4.43 (br s, 1 H, CH), 4.90 (dd, $^3J_{H-H}$ = 5.9 Hz, $^3J_{H-H}$ = 1.6 Hz, 1 H, CH), 5.21 (dd, $^3J_{H-H}$ = 5.5 Hz, $^3J_{H-H}$ = 2.5 Hz, 1 H, CH), 5.72 (d, $^3J_{H-H}$ = 7.6 Hz, 1 H, CH), 5.77 (br s, 1 H, 5′-OH), 5.84 (d, $^3J_{H-H}$ = 2.3 Hz, 1 H, CH), 6.89 (d, $^3J_{H-H}$ = 2.3 Hz, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 25.4, 27.3, 53.3, 63.8, 82.0, 85.0, 88.3, 92.2, 111.2, 111.9, 118.5 ($^1J_{C-F}$ = 276 Hz), 137.7 (q, $^2J_{C-F}$ = 37 Hz), 140.1, 149.7, 169.7.

^{19}F NMR (DMSO-d_6): δ = –68.3.

MS: *m*/*z* (%) = 408 (21) [M$^+$], 377 (35), 376 (100), 301 (29), 298 (78), 254 (16), 256 (83), 178 (56), 171 (45), 152 (10), 96 (14), 44 (37).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (25)

Yield: 0.48 g (64%); colourless solid; mp 110 °C; R_f = 0.20 (EtOAc).

^{13}C NMR (DMSO-d_6): δ = 25.9, 27.0, 62.1, 81.3, 83.6, 88.7, 93.3, 109.9, 112.9, 122.4 (q, $^1J_{C-F}$ = 285 Hz), 131.8, 146.3 (q, $^2J_{C-F}$ = 33 Hz), 148.8, 167.7.

^{19}F NMR (DMSO-d_6): δ = –69.0.

MS: *m*/*z* (%) = 376 (57) [M$^+$], 375 (31), 371 (22), 355 (78), 321 (100), 287 (63), 270 (48), 205 (91), 170 (81), 168 (86), 159 (11), 112 (10), 109 (12), 43 (77).

l-(β-D-Ribofuranosyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (26)

Yield: 0.14 g (52%); colourless solid; mp 198 °C.

^{13}C NMR (DMSO-d_6): δ = 64.4, 78.3, 80.3, 85.0, 91.1, 108.0, 122.2 (q, $^2J_{C-F}$ = 33 Hz), 131.0, 146.0 (q, $^1J_{C-F}$ = 285 Hz), 148.0, 165.0.

MS: *m*/*z* (%) = 336 (4) [M$^+$], 318 (12), 317 (19), 315 (27), 311 (11), 309 (17), 234 (31), 202 (44), 180 (100), 149 (69), 133 (97), 130 (61), 129 (57), 111 (12), 73 (34), 46 (19).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (27)

A mixture of *iso*-AIRs **1** (2 mmol) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**12**; 2 mmol) in CH_2Cl_2 (20 mL) was stirred at r.t. until the initial aminoheterocycle was consumed (~36 h, monitored be

TLC). The solution formed was evaporated and the residue was subjected to column chromatography over silica gel.

Yield: 0.83 g (97%); yellow oil; R_f = 0.50 (hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 3.75 (dd, $^3J_{H–H}$ = 12.1 Hz, $^3J_{H–H}$ = 3.5 Hz, 1 H, CH), 3.86 (dd, $^2J_{H–H}$ = 12.1 Hz, $^3J_{H–H}$ = 1.3 Hz, 1 H, CH), 4.53 (br s, 1 H, CH), 5.07 (dd, $^3J_{H–H}$ = 5.9 Hz, $^3J_{H–H}$ = 1.6 Hz, 1 H, CH), 5.27 (dd, $^3J_{H–H}$ = 5.9 Hz, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 6.40 (br s, 1 H, 5′-OH), 6.82 (d, $^3J_{H–H}$ = 2.8 Hz, 1 H, CH), 8.35 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.4, 27.3, 63.8, 82.0, 85.0, 88.3, 92.2, 111.2, 114.3, 119.2 (q, $^1J_{C–F}$ = 271 Hz), 120.2 (q, $^1J_{C–F}$ = 271 Hz), 134.1, 151.5 (q, $^2J_{C–F}$ = 39 Hz), 145.2 (q, $^2J_{C–F}$ = 39 Hz), 154.6.

^{19}F NMR ($CDCl_3$): δ = –69.4, –71.8.

MS: *m*/*z* (%) = 414 (19), 413 (100), 398 (35), 339 (12), 311 (22), 257 (16), 157 (48), 100 (14).

1-(β-D-Ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (28)

Yield: 0.33 g (85%); colourless solid; mp 99–101 °C; R_f = 0.70 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.41 (dd, $^2J_{H–H}$ = 11.7 Hz, $^3J_{H–H}$ = 5.8 Hz, 1 H, CH), 3.54 (dd, $^2J_{H–H}$ = 11.7 Hz, $^3J_{H–H}$ = 5.1 Hz, 1 H, CH), 3.94 (q, $^3J_{H–H}$ = 5.1 Hz, 1 H, CH), 4.25 (t, $^3J_{H–H}$ = 4.7 Hz, 1 H, CH), 4.65 (t, $^3J_{H–H}$ = 5.1 Hz, 1 H, CH), 6.32 (d, $^3J_{H–H}$ = 4.3 Hz, 1 H, CH), 8.86 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 61.9, 70.7, 73.5, 85.8, 88.9, 109.8, 119.2 (q, $^1J_{C–F}$ = 271 Hz), 120.2 (q, $^1J_{C–F}$ = 271 Hz), 133.9, 149.5 (q, $^2J_{C–F}$ = 39 Hz), 150.2 (q, $^2J_{C–F}$ = 39 Hz), 154.6.

^{19}F NMR (DMSO-d_6): δ = –69.0, –71.1.

MS: *m*/*z* (%) = 389 (13) [M^+ + 1], 359 (12), 358 (63), 312 (14), 311 (88), 299 (62), 286 (36), 285 (52), 270 (10), 269 (20), 258 (30), 257 (90), 133 (14), 132 (100), 114 (15), 104 (27), 86 (27), 84 (17), 74 (11), 73 (53), 57 (19).

References

(1) (a) Cristalli, G.; Costanzi, S.; Lambertucci, C.; Lupidi, G.; Vittori, S.; Volpini, R.; Camaioni, E. *Med. Res. Rev.* **2001**, *21*, 105. (b) Maydanovych, O.; Beal, P. A. *Chem. Rev.* **2006**, *106*, 3397. (c) Nair, V. *IMPDH inhibitors: Discovery of antiviral agents against emerging diseases,* In *Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats*, Chap. 8; Torrence, P. F., Ed.; John Wiley & Sons: Hoboken, **2005**, 179–202. (d) Shu, Q.; Nair, V. *Med. Res. Rev.* **2008**, *28*, 219.

(2) (a) Agarwal, R. P. *Pharmacol. Ther.* **1982**, *17*, 399. (b) Weber, G. *Cancer Res.* **1983**, *43*, 3466.

(3) Pankiewicz, K. W.; Goldstein, B. M. *Inosine mono phosphate dehydrogenase, ACS Symposium Series 839*; American Chemical Society: Washington DC, **2003**.

(4) (a) Burns, C. M.; Chu, H.; Rueter, S. M.; Hutchinson, L. K.; Canton, H.; Sanders-Bush, E.; Emeson, R. B. *Nature* **1997**, *387*, 303. (b) Higuchi, M.; Single, F. N.; Kohler, M.; Sommer, B.; Sprengel, R.; Seeburg, P. H. *Cell* **1993**, *75*, 1361.

(5) (a) Giblett, E. R.; Anderson, J. E.; Cohen, F.; Pollara, B.; Meuwissen, H. J. *Lancet* **1972**, *2*, 1067. (b) Hirshhorn, R. *Clin. Immunol. Immunopathol.* **1995**, *76*, S219.

(6) (a) Niedzwicki, J. G.; Kouttab, N. M.; Mayer, K. H.; Carpenter, C. C.; Parks, R. E. Jr.; Abushanab, E.; Abernethy, D. R. *J. Acquir. Immune Defic. Syndr.* **1991**, *4*, 178. (b) Salvatore, D.; Claudio, M. M.; Anna, P. M. *Clin. Chem.* **1987**, *33*, 1675. (c) Valenzuela, A.; Blanco, J.; Callebaut, C.; Jacotot, E.; Lluis, C.; Hovanessian, A. G.; Franco, R. *J. Immunol.* **1997**, *158*, 3721.

(7) (a) Ungerer, J. P. J.; Oosthuizen, H. M.; Retief, J. H.; Bissbort, S. H. *Chest* **1994**, *106*, 33. (b) Banales, J. L.; Rivera Martinez, E.; Perez Gonzalez, L.; Selman, M.; Raymond, Y.; Nava, A. *Arch. Med. Res.* **1999**, *30*, 358.

(8) (a) Chiba, S.; Matsumoto, H.; Saitoh, M.; Kasahara, M.; Matsuya, M.; Kashiwagi, M. A. *J. Neurol. Sci.* **1995**, *132*, 170. (b) Gakis, C. *Eur. Respir. J.* **1996**, *9*, 632.

(9) (a) Demeocq, F.; Viallard, J. L.; Boumsell, L.; Richard, Y.; Chassgne, J.; Plagne, R.; Lemerle, J.; Bernard, A. *Leuk. Res.* **1982**, *6*, 211. (b) Carlucci, F.; Rosi, F.; Di Pietro, C.; Marinello, E. *Biochim. Biophys. Acta* **1997**, *1360*, 203.

(10) Erion, M. D.; Reddy, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 3295.

(11) (a) Begue, J.-P.; Bonnet-Delpon, D. *Chemie bioorganique et medicinale du fluor*; EDP Sciences: France, **2005**, 366. (b) Silverman, R. B. *The organic chemistry of drug design, and drug action*, 2nd ed.; Elsevier Academic Press: London, **2004**, 617.

(12) (a) Cristalli, G.; Costanzi, S.; Lambertucci, C.; Lupidi, G.; Vittori, S.; Volpini, R.; Camaioni, E. *Med. Res. Rev.* **2001**, *21*, 105. (b) *Adenosine Deaminase in Disorders of Purine Metabolism and in Immune Deficiency*, Vol. 451; Tritsch, G. L., Ed.; New York Academy of Sciences: New York, **1985**.

(13) For related inverse electron-demand Diels–Alder reactions, see: (a) Dang, Q.; Brown, B. S.; Erion, M. D. *J. Org. Chem.* **1996**, *61*, 5204. (b) Dang, Q.; Gomez-Galeno, J. E. *J. Org. Chem.* **2002**, *67*, 8703. (c) Dang, Q.; Liu, Y.; Erion, M. D. *J. Am. Chem. Soc.* **1999**, *121*, 5833.

(14) (a) Volochnyuk, D. M.; Pushechnikov, A. O.; Krotko, D. G.; Sibgatulin, D. A.; Kovalyova, S. A.; Tolmachev, A. A. *Synthesis* **2003**, 1531. (b) Iaroshenko, V. O.; Volochnyuk, D. M.; Wang, Y.; Vovk, M. V.; Boiko, V. J.; Rusanov, E. B.; Groth, U. M.; Tolmachev, A. O. *Synthesis* **2007**, 3309.

(15) (a) Sosnovskikh, V. Ya.; Irgashev, R. A.; Barabanov, M. A. *Synthesis* **2006**, 2707. (b) Sosnovskikh, V. Ya.; Irgashev, R. A. *Heteroat. Chem.* **2006**, *17*, 99.

(16) Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339.

(17) Cottam, H. B.; Petrie, C. R.; McKernan, P. A.; Goebel, R. J.; Dalley, N. K.; Davidson, R. B.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1984**, *27*, 1119.

(18) (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2001**, *56*, 5259. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (c) Jayakumar, S.; Ishar, M. P. S.; Mahajan, P. M. *Tetrahedron* **2002**, *58*, 379.

(19) Guranowski, A.; Montgomery, J. A.; Cantoni, G. L.; Chiang, P. K. *Biochemistry* **1981**, *20*, 110.

(20) Sheldrick G. M., SHELXTL PLUS. PC Version. A system of computer programs for the determination of crystal structure from X-ray diffraction data. Rev. 5.1., **1998**.