Synthesis of Some Fluorinated Heteroannulated Pyrimidines – Purine Isosteres – via Inverse-Electron-Demand Diels–Alder Protocol

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Received 15 June 2009; revised 13 July 2009

Dedicated to my wife Amrita Singha Roy on the occasion of her 20th birthday

Abstract: The inverse-electron-demand Diels–Alder reaction of electron excessive systems such as enamines, electron-enriched amino heterocycles, and anilines with 2,4,6-tris(polyfluoroalkyl)-1,3,5-triazines was investigated. This study results in the synthesis of a set of polyfluoroalkyl containing pyrimidines, heteroannulated pyrimidines, and quinazolines. Following the elaborated synthetic pathway, l-(β-D-ribofuranosyl)-4,6-bis(polyfluoroalkyl)-1*H*-pyrazolo[3,4-*d*]pyrimidines were prepared starting from *iso*-AIRs.

Key words: pyrimidines, purine isosteres, heterocycles, annulation, fluorine

By virtue of its excellent chemo-, regio-, and diastereoselectivity, the Diels–Alder (DA) reaction is one of the most important and elegant methods for the construction of six-membered ring compounds. Application of DA methodology led to the synthesis of many single and polycyclic systems including heterocycles.[1] The systematic study of mechanistic[2] and theoretical aspects[3] of DA reactions has been recently carried out.

Depending on the energy state of the both pairs of the frontier orbitals in the Hückel molecular orbital (HMO) model Diels–Alder cycloaddition reactions are divided into three types:[4](1) normal $HOMO_{diene\text{-}controlled}$; (2) neutral; and (3) $LUMO_{diene\text{-}controlled}$ or inverse-electron-demand DA reactions.

Hetero-diene modification of the DA protocol has gained great popularity in application to the synthesis of a number of heterocycles.[5] Nowadays, an azadiene reaction[1] is one of the main synthetic pathways towards unsaturated nitrogen-containing heterocycles bearing two or more stereogenic centers because the azadiene [4+2] cycloadditions are performed at room or even lower temperatures with a high degree of *endo*-selectivity.

The inverse-electron-demand, the so-called $LUMO_{diene\text{-}controlled}$ azadiene protocol in Diels–Alder reactions, has been successfully used for the synthesis of pyridines[6] including a number of complex natural products such as streptonigrone[7] and fredricamycin A.[8] An inverse-electron-demand Diels–Alder protocol was also successfully applied in the total synthesis[9] of nothapodytine B and (2)-mappiline.

Polyfluoroalkyl-containing azadienes, 1,2,4,5-tetrazines,[10] were recently used by Seitz and co-workers for the synthesis of derivatives of 1,2,4-triazines, pyridines, and arenes. At the same time, on the basis of the fluorinated 1,3,5-triazines and some electron-rich aminoheterocycles, we[11] and others[12] have elaborated preparative methods for purines and purine isosteres assembling via the annulation of the pyrimidine core to the aminoheterocyclic moiety.

In this publication, a preparative method for heteroannulated pyrimidines is reported based on $LUMO_{diene\text{-}controlled}$ azadiene Diels–Alder reaction of fluorinated 1,3,5-triazines **11** with enamines, electron-rich heterocycles, anilines **1**–**9**, and the *iso*-AIRs (AIRs = aminoimidazole riboside) **10** (Figure 1). Due to the lowering of the

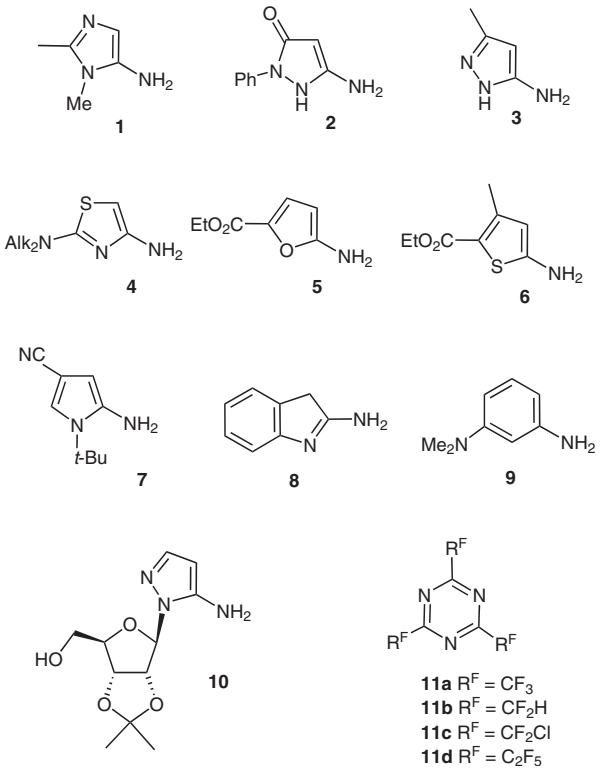
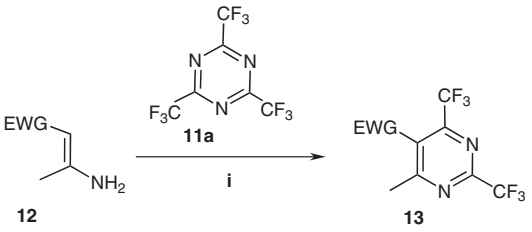


Figure 1 Aminoheterocycles **1**–**9**, *iso*-AIRs **10**, and 2,4,6-tris(polyfluoroalkyl)-1,3,5-triazines **11**.

SYNTHESIS 2009, No. 23, pp 3967–3974
Advanced online publication: 23.09.2009
DOI: 10.1055/s-0029-1217015; Art ID: P08809SS

$LUMO_{diene}$ energy level in the fluorinated 1,3,5-triazines to such an extent that the azadiene [4+2] cycloaddition reaction described proceeds at room temperature with high regiospecificity affording only one main isomer.

We have started our investigation with the study of the reaction of classical enamines such as 3-aminobutenenitrile (**12a**) and 3-aminobut-2-enoic acid ethyl ester (**12b**), with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**11a**). The reaction was carried out in dichloromethane at room temperature for 12 hours, which led to the formation of the corresponding 2,4-bis(trifluoromethyl)pyrimidines **13** in quantitative yield (Scheme 1). Since the analytically pure precursors **12** have been used for this reaction, the formed products **13** needed no further purification.



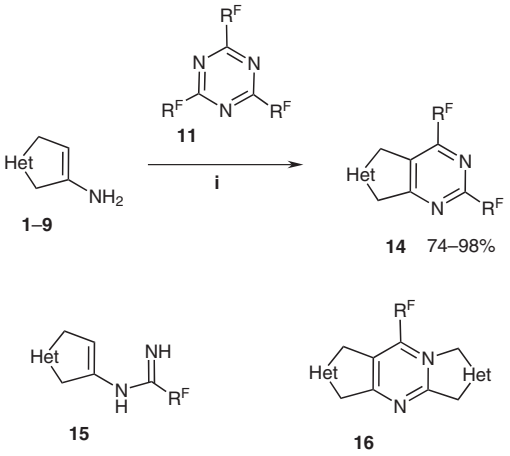
Scheme 1 *Reagents and conditions*: (i) CH_2Cl_2 under N_2, r.t., 24 h.

The pyrimidines containing R^F substituents in positions 2 and 4 have been previously synthesized[13] by addition of trifluoroacetonitrile either to the CH_2-active pattern containing the CO[13a] or CN[13b] group in the α-position, or to *N*-pyrimidinium salts[13c] containing the CH_2-unsubstituted function neighboring with the N-nuclei. Annulation of the pyrimidine core to the enamine moiety was described as a [2+2+2] cycloaddition reaction[14] of enamine function and two units of trifluoroacetonitrile.

As mentioned above, the cycloaddition of the electron-deficient 1,3,5-triazines to electron-rich aminoheterocycles is a significant method[11,12] of purine/(purine isostere) assembly. The polyfluoroalkyl containing purines are a target due to a broad spectrum of their biological activity.[15]

Thus, this potentially powerful method can be expanded to other heterocycles mainly through a change in the R^F group of the initial 1,3,5-triazine molecule. Aminoheterocycles **1**–**8** and 3-dimethylaminoaniline (**9**) react smoothly with 1,3,5-triazines **11** in a 10:1 mixture of dichloromethane and AcOH under mild condition (r.t.) to give a set of diverse fluorinated heteroannulated pyrimidines **14a**–**u** in 74–98% yields and 2,4-bis(polyfluoroalkyl)-7-(dimethylamino)quinazolines **14v**–**x** in 89–91% yields (Scheme 2). The fluorinated quinazolines are attractive bioactive molecules.[16] The fluorinated quinazolines are mainly used for the treatment of anemia,[17] and some other diseases.[18]

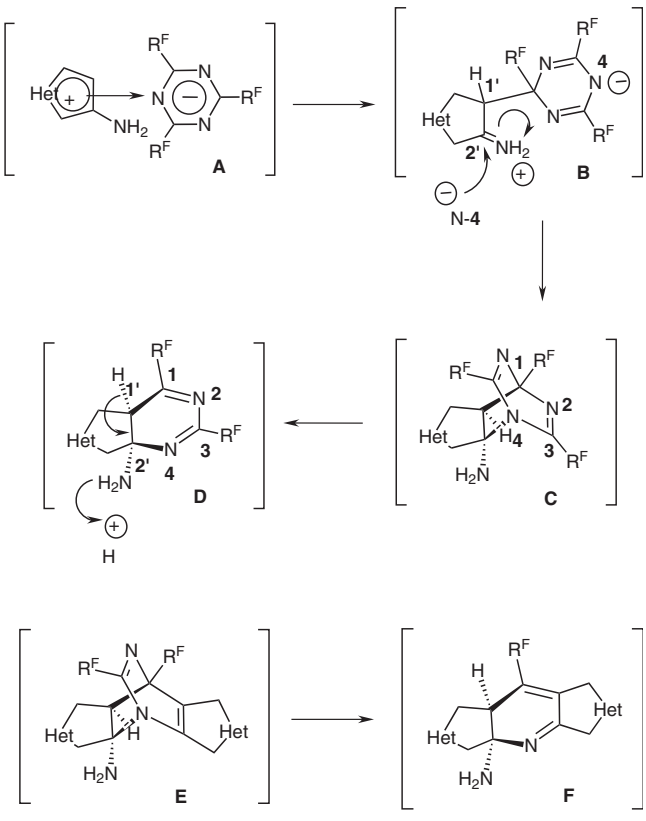
The scope and mechanism of the reaction between electron-deficient dienes and electron-rich dienophiles has been investigated.[4–6] In the case of enamines and 1,3,5-triazines two transition structures and one intermediate were



Scheme 2 *Reagents and conditions*: (i) CH_2Cl_2–AcOH (10:1), r. t., 24–48 h.

postulated as transition states **B**, **C**, and an intermediate **D** as depicted in Scheme 3. Compounds **D** have been isolated and characterized.[12] When the reactions of heterocycles **3** and **7** were run in dichloromethane without acid catalysis, the intermediates **D** were observed in the reaction mixture by means of HPLC. However, in some cases we have encountered the problem of separating pyrimidines **14** and the corresponding intermediates **D**. In the course of separation on silica gel the latter transformed into aromatic compounds **14**.

In our opinion the reaction should start with the formation of the sandwich complex with charge transfer **A** as the

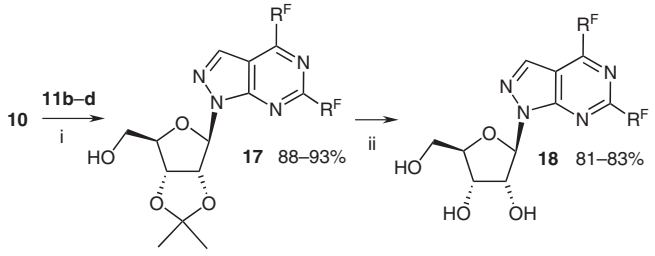


Scheme 3

first step. In the literature there is no information about the detection of such complexes. We have made this assumption based on the observation of the reaction mixture in dichloromethane at low temperature –10 to –25 °C. In the first few seconds after addition of a diene to the solution of the electron-rich moiety in dichloromethane, the color of the reaction mixture changes from slightly yellow to red through blue depending on the initial amine.

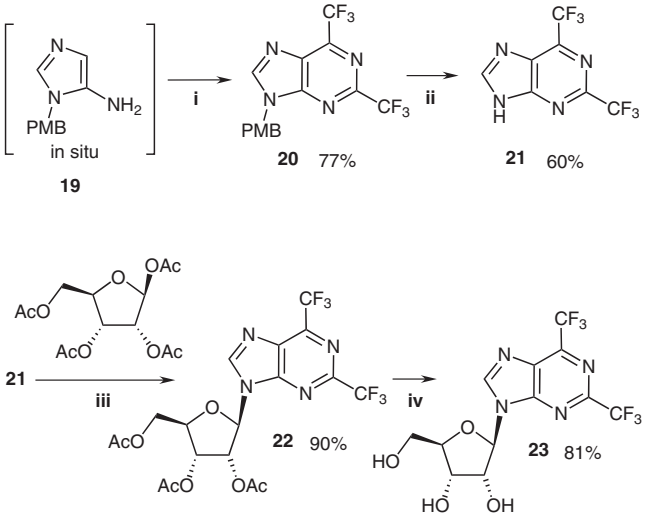
The detailed study of the reaction mixture has revealed the formation of two by-products **15** and **16** in an amount less than 1–2%. Amidines **15** are hydrolytically stable products formed by the releasing of trifluoroacetonitrile after the cycloaddition took place. The formation of the heterodiannulated pyridines **16** suggests that pyrimidines **14** are still capable of reacting with the electron-rich systems. The reaction most likely proceeds via intermediates **E** and **F**. However, all detected pyrimidines **14** are prone to cycloaddition, even under the harsh conditions (DMF, 80–140 °C, 24 h). Nevertheless, despite our numerous attempts, only traces of diannulated pyridines **16** were observed.

Very recently, the synthesis of the l-(b-D-ribofuranosyl)-4,6-bis(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine starting from 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-1*H*-pyrazole (*iso*-AIRs, **10**) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**11a**) has been reported.[11b] Here, we describe using the same synthetic procedure the preparation of the compounds **18**, where $R^F = CF_2H$, CF_2Cl, C_2F_5. The reaction proceeds in dichloromethane at room temperature releasing protected moieties **17**. Treatment of **17** with TFA–H_2O (9:1) then delivers the ribosides **18** (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) CH_2Cl_2 under N_2, r.t., 36 h; (ii) TFA–H_2O (9:1), r.t., 40 min.

We are currently involved in the development of potential inhibitors of adenosine deaminase (ADA) and inosine 5′-monophosphate dehydrogenase (IMPDH) based on polyfluoroalkyl-containing purines and purine isosteres. Here, we wish to report a model synthesis of purine nucleoside containing trifluoromethyl group in position 2 and 6 of the purine skeleton, which are suspected to be the inhibitors of the ADA enzyme family.[19] 3-(4-Methoxybenzyl)-3*H*-imidazol-4-ylamine (**19**) generated in situ by previous reported procedure[20] was used for the synthesis of purine **20** bearing 4-methoxybenzyl protecting group at position 9. Purine **20** was easily deprotected to **21** by treatment of the mixture with TFA–H_2O (20:1). For the synthesis of riboside **22**, the silyl Hilbert–Johnson reaction[21] was used. This reaction takes place in dichloromethane with BSA [*O*,*N*-bis(trimethylsilyl)acetamide] and TMS-triflate as a catalyst.[11c] The subsequent acetyl moiety cleavage by ammonia yields compound **23** in 81% yield (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) 2,4,6-tris(trifluoromethyl)-1,3,5-triazine, CH_2Cl_2 under N_2, r.t., 36 h; (ii) TFA–H_2O (20:1), r.t., 24 h; (iii) BSA [*O*,*N*-bis(trimethylsilyl)acetamide], TMS-triflate; MeCN, reflux 4 h; (iv) MeOH/NH_3, r.t., 12 h.

The structure of synthesized pyrimidines was confirmed by, ^{13}C, and ^{19}F NMR spectroscopy. For example, in the ^1H, ^{13}C NMR spectra of compounds **14** possessing the methyl group at the 7-position of the pseudo purine skeleton, the long range interaction of the methyl group and R^F substituent were clearly observed, which is one of the features confirming the structure of the scaffold **14**. Moreover, the CF_2H proton of the compounds **14c**,**o**,**r**,**u**,**x**, **17c** and **18c** shows ROESY correlations with the protons of the neighboring groups also confirming the constitution of **14**.

In conclusion, a convenient synthetic approach to heteroannulated 2,4-bis(polyfluoroalkyl)pyrimidines was elaborated from commercially available 2,4,6-tris(polyfluoroalkyl)-1,3,5-triazines and electron-rich aminoheterocycles. The method discovered here allows access to libraries of compounds containing the scaffold **14**.

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) 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.

Compounds 13 Starting from 11a and 12; General Procedure
A mixture of initial enamine **12a,b** (2 mmol) and 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**11a**; 627 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was stirred at r.t., until the initial aminoheterocycle vanished (TLC) and then the solution was evaporated. The yellow oil was analytically pure and no other purification steps were needed.

4-Methyl-2,6-bis(trifluoromethyl)pyrimidine-5-carbonitrile (13a)
Yield: 510 mg (ca. 100%); yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.57 (3 H, s, CH_3).

MS: *m*/*z* (%) = 256 (10, [M^+ + 1]), 255 (100, [M^+]), 240 (11), 229 (19), 186 (17, [M^+ – CF_3]), 112 (13), 111 (10), 87 (11).

Ethyl 4-Methyl-2,6-bis(trifluoromethyl)pyrimidine-5-carboxylate (13b)
Yield: 604 mg (ca. 100%); yellow oil.

^{1}H NMR ($CDCl_3$): δ = 1.39 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH_3), 2.55 (3 H, s, CH_3), 4.35 (2 H, q, $^3J_{H,H}$ = 7.8 Hz, CH_3).

MS: *m*/*z* (%) = 302 (10, [M^+ + 1]), 301 (100, [M^+]), 257 (19), 233 (12, [M^+ – CF_3]), 229 (11), 215 (10), 180 (14).

Compounds 14, 17; General Procedure
A mixture of initial aminoheterocycle **1**–**10** (2 mmol) and 2,4,6-tris(polyfluoroalkyl)-1,3,5-triazine **11a**–**d** (2.2 mmol) in a mixture of CH_2Cl_2–AcOH (30 mL, 10:1) was stirred at r.t. for 36–48 h, until the initial aminoheterocycle had vanished (TLC), and then the reaction mixture was evaporated. The residue was purified by column chromatography over silica gel. In the case of salts **4**·HCl, NaOAc (1.1 equiv) was added.

8,9-Dimethyl-2,6-bis(perfluoroethyl)-9*H*-purine (14a)
Prepared from **1** and **11d**; yield: 692 mg (90%); colorless solid; mp 60–61 °C; R_f = 0.55 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR ($CDCl_3$): δ = 2.82 (3 H, s, 2-CH_3), 3.89 (3 H, s, 1-CH_3).

^{13}C NMR ($CDCl_3$): δ = 15.1, 29.9, 111.2 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.4 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.1 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.9 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 131.7, 131.9, 143.0 ($^2J_{C,F}$ = 26 Hz), 148.8 ($^2J_{C,F}$ = 26 Hz), 156.1, 161.3.

MS: *m*/*z* (%) = 385 (12, [M^+ + 1]), 384 (100, [M^+]), 315 (38, [M^+ – CF_3]), 264 (44, [M^+ – C_2F_5]).

2,6-Bis(chlorodifluoromethyl)-8,9-dimethyl-9*H*-purine (14b)
Prepared from **1** and **11c**; yield: 590 mg (93%); colorless solid; mp 97–98 °C; R_f = 0.85 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR ($CDCl_3$): δ = 2.65 (3 H, s, 2-CH_3), 3.80 (3 H, s, 1-CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.0, 29.3, 119.7 (t, $^1J_{C,F}$ = 289 Hz), 121.8 (t, $^1J_{C,F}$ = 289 Hz), 131.7, 131.9, 143.9 (t, $^2J_{C,F}$ = 33 Hz), 149.5 (t, $^2J_{C,F}$ = 33 Hz), 155.0, 163.0.

MS: *m*/*z* (%) = 318 (61, [M^+ + 2]), 317 (11, [M^+ + 1]), 316 (100, [M^+]).

2,6-Bis(difluoromethyl)-8,9-dimethyl-9*H*-purine (14c)
Prepared from **1** and **11b**; yield: 457 mg (92%); colorless solid; mp 95–97 °C; R_f = 0.75 (CH_2Cl_2–MeOH, 8:1).

^{1}H NMR ($CDCl_3$): δ = 2.71 (3 H, s, 2-CH_3), 3.81 (3 H, s, 1-CH_3), 6.89 (1 H, t, $^2J_{H,F}$ = 52 Hz, CF_2H), 7.01 (1 H, t, $^2J_{H,F}$ = 55 Hz, CF_2H).

^{13}C NMR ($CDCl_3$): δ = 14.5, 29.9, 115.5 (t, $^1J_{C,F}$ = 248 Hz), 116.3 (t, $^1J_{C,F}$ = 248 Hz), 131.7, 133.3, 144.7 (t, $^2J_{C,F}$ = 26 Hz), 147.1 (t, $^2J_{C,F}$ = 26 Hz), 156.7, 159.0.

MS: *m*/*z* (%) = 249 (13, [M^+ + 1]), 248 (100, [M^+]), 247 (10, [M^+ – 1]).

2-Phenyl-4,6-bis(trifluoromethyl)-1,2-dihydropyrazolo[3,4-*d*]pyrimidin-3-one (14d)
Prepared from **2** and **11a**; yield: 0.63 g (91%); orange solid; mp 188–189 °C; R_f = 0.60 ($CHCl_3$–MeOH, 9:1).

^{1}H NMR (DMSO-d_6): δ = 7.15 (1 H, t, $^3J_{H,H}$ = 7.8 Hz), 7.40 (2 H, t, $^3J_{H,H}$ = 7.8 Hz), 8.22 (2 H, d, $^3J_{H,H}$ = 7.8 Hz).

^{13}C NMR (DMSO-d_6): δ = 101.6, 119.4, 120.1 (q, $^1J_{C,F}$ = 274 Hz), 120.3 (q, $^1J_{C,F}$ = 274 Hz), 124.2, 128.6, 140.4, 150.6 (q, $^2J_{C,F}$ = 36 Hz), 152.8 (q, $^2J_{C,F}$ = 36 Hz), 155.2, 156.1.

^{19}F NMR (DMSO-d_6): δ = –68.0, –71.4.

MS: *m*/*z* (%) = 349 (18, [M^+ + 1]), 348 (100, [M^+]), 328 (11), 319 (17), 299 (11), 112 (14), 111 (15), 105 (10).

4,6-Bis(perfluoroethyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*d*]pyrimidin-3-one (14e)
Prepared from **2** and **11d**; yield: 798 mg (89%); orange solid; mp 159–161 °C; R_f = 0.20 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 7.22 (1 H, t, $^3J_{H,H}$ = 7.8 Hz), 7.49 (2 H, t, $^3J_{H,H}$ = 7.8 Hz), 8.20 (2 H, d, $^3J_{H,H}$ = 7.8 Hz).

^{13}C NMR (DMSO-d_6): δ = 104.1, 119.0, 111.1 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.4 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.3 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.7 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 125.5, 128.9, 140.0, 150.0 (t, $^2J_{C,F}$ = 27 Hz), 152.0 (t, $^2J_{C,F}$ = 27 Hz), 155.8, 158.0.

MS: *m*/*z* (%) = 449 (16, [M^+ + 1]), 448 (100, [M^+]), 447 (19, [M^+ – 1]), 371 (21, [M^+ – Ph]), 379 (38, [M^+ – CF_3]), 329 (17, [M^+ – C_2F_5]), 77 (33).

4,6-Bis(chlorodifluoromethyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*d*]pyrimidin-3-one (14f)
Prepared from **2** and **11c**; yield: 717 mg (94%); orange solid; mp 200–201 °C; R_f = 0.75 ($CHCl_3$–MeOH, 9:1).

^{1}H NMR (DMSO-d_6): δ = 7.25 (1 H, t, $^3J_{H,H}$ = 7.8 Hz), 7.49 (2 H, t, $^3J_{H,H}$ = 7.8 Hz), 8.10 (2 H, d, $^3J_{H,H}$ = 7.8 Hz).

^{13}C NMR (DMSO-d_6): δ = 101.0, 112.4, 120.0 (t, $^1J_{C,F}$ = 287 Hz), 121.7 (t, $^1J_{C,F}$ = 287 Hz), 124.0, 125.3, 139.1, 150.0 (t, $^2J_{C,F}$ = 32 Hz), 150.0 (t, $^2J_{C,F}$ = 32 Hz), 154.9, 158.2.

MS: *m*/*z* (%) = 382 (63, [M^+ + 2]), 381 (14, [M^+ + 1]), 380 (100, [M^+]), 378 (17), 288 (10), 77 (99).

3-Methyl-4,6-bis(perfluoroethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (14g)
Prepared from **3** and **11d**; yield: 718 mg (97%): colorless solid; mp 88–89 °C; R_f = 0.35 (EtOAc–hexane, 1:5).

^{1}H NMR ($CDCl_3$): δ = 2.79 (3 H, s, CH_3), 12.55 (1 H, s, NH).

^{13}C NMR (DMSO-d_6): δ = 14.6 ($^5J_{C,F}$ = 4 Hz), 111.2 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.5 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.1 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.7 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 145.4, 151.3 (t, $^2J_{C,F}$ = 25 Hz), 152.8 (t, $^2J_{C,F}$ = 25 Hz), 158.

MS: *m*/*z* (%) = 371 (10, [M^+ + 1]), 370 (100, [M^+]), 369 (47, [M^+ – 1]), 301 (92, [M^+ – CF_3]), 251 (17, [M^+ – C_2F_5]).

4,6-Bis(chlorodifluoromethyl)-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (14h)
Prepared from **3** and **11c**; yield: 533 mg (88 %); colorless solid; mp 129–131 °C; R_f = 0.55 (EtOAc–hexane, 1:4).

^{1}H NMR ($CDCl_3$): δ = 2.74 (3 H, s, CH_3), 12.01 (1 H, s, NH).

^{13}C NMR (DMSO-d_6): δ = 14.3 (t, $^5J_{C,F}$ = 1.9 Hz), 111.1, 120.0 (t, $^1J_{C,F}$ = 289 Hz), 121.9 (t, $^1J_{C,F}$ = 289 Hz), 143.8, 151.7 ($^2J_{C,F}$ = 31 Hz), 152.8 ($^2J_{C,F}$ = 31 Hz), 158.0.

MS: *m*/*z* (%) = 304 (61, [M$^+$ + 2]), 302 (100, [M$^+$]), 301 (13), 300 (17), 299 (11), 177 (11).

4-[5,7-Bis(perfluoroethyl)thiazolo[4,5-*d*]pyrimidin-2-yl]morpholine (14i)

Prepared from **4** and **11d**; yield: 724 mg (79%); colorless solid; mp 71–73 °C; R_f = 0.45 (EtOAc–hexane, 1:4).

^{1}H NMR (CDCl$_3$): δ = 3.68 (4 H, br s, NCH$_2$), 4.07 (4 H, br s, OCH$_2$).

^{13}C NMR (CDCl$_3$): δ = 49.2, 65.1, 111.1 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.7 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.1 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.8 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 143.4 (t, $^2J_{C,F}$ = 29 Hz), 154.0 (t, $^2J_{C,F}$ = 29 Hz), 172.0, 175.0.

MS: *m*/*z* (%) = 459 (15, [M$^+$ + 1]), 458 (100, [M$^+$]), 339 (10, [M$^+$ – C_2F_5]), 331 (18), 271 (11), 256 (13), 153 (10).

4-[5,7-Bis(chlorodifluoromethyl)thiazolo[4,5-*d*]pyrimidin-2-yl]morpholine (14j)

Prepared from **4** and **11c**; yield: 579 mg (74%); colorless solid; mp 119–122 °C; R_f = 0.65 (EtOAc).

^{1}H NMR (CDCl$_3$): δ = 3.67 (4 H, br s, NCH$_2$), 3.93 (4 H, br s, OCH$_2$).

^{13}C NMR (CDCl$_3$): δ = 49.4, 65.9, 120.1 (t, $^1J_{C,F}$ = 288 Hz), 121.5 (t, $^1J_{C,F}$ = 288 Hz), 143.0 (t, $^2J_{C,F}$ = 33 Hz), 150.2 (t, $^2J_{C,F}$ = 33 Hz), 174.2, 175.1.

MS: *m*/*z* (%) = 392 (12, [M$^+$ + 2]), 390 (72, [M$^+$]), 300 (100), 78 (11).

Ethyl 2,4-Bis(trifluoromethyl)furo[2,3-*d*]pyrimidine-6-carboxylate (14k)

Prepared from **5** and **11a**; yield: 680 mg (98%); colorless solid; mp 71 °C; R_f = 0.75 (EtOAc–hexane, 1:4).

^{1}H NMR (CDCl$_3$): δ = 1.42 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_3$), 4.30 (2 H, q, $^3J_{H,H}$ = 7.8 Hz, CH$_2$), 8.31 (1 H, s, CH).

^{13}C NMR (CDCl$_3$): δ = 14.1, 63.1, 109.3 (q, $^3J_{C,F}$ = 1.7 Hz), 115.8, 119.3 (q, $^1J_{C,F}$ = 274 Hz), 120.1 (q, $^1J_{C,F}$ = 274 Hz), 149.8, 151.5 (q, $^2J_{C,F}$ = 36 Hz), 153.7 (q, $^2J_{C,F}$ = 36 Hz), 157.1, 167.5.

MS: *m*/*z* (%) = 328 (28, [M$^+$]), 309 (99), 301 (14), 300 (100), 283 (72), 256 (16), 235 (16), 69 (18), 45 (16).

Ethyl 2,4-Bis(perfluoroethyl)furo[2,3-*d*]pyrimidine-6-carboxylate (14l)

Prepared from **5** and **11d**; yield: 770 mg (90%); colorless solid; mp 59–60 °C; R_f = 0.55 (EtOAc–hexane, 1:5).

^{1}H NMR (CDCl$_3$): δ = 1.42 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_3$), 4.30 (2 H, q, $^3J_{H,H}$ = 7.8 Hz, CH$_2$), 8.31 (1 H, s, CH).

^{13}C NMR (CDCl$_3$): δ = 14.9, 63.4, 109.3 (t, $^3J_{C,F}$ = 2.4 Hz), 111.0 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.3 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 117.7, 120.1 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.9 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 147.0, 151.5 (t, $^2J_{C,F}$ = 29 Hz), 155.2 (t, $^2J_{C,F}$ = 29 Hz), 159.0, 169.3.

MS: *m*/*z* (%) = 429 (14, [M$^+$ + 1]), 428 (100, [M$^+$]), 411 (10), 383 (17), 355 (21), 310 (13, [M$^+$ – C_2F_5]), 208 (11), 57 (33).

Ethyl 2,4-Bis(chlorodifluoromethyl)furo[2,3-*d*]pyrimidine-6-carboxylate (14m)

Prepared from **5** and **11c**; yield: 636 mg (88%); colorless solid; mp 100–102 °C; R_f = 0.45 (EtOAc–hexane, 1:4).

^{1}H NMR (CDCl$_3$): δ = 1.46 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_3$), 4.38 (2 H, q, $^3J_{H,H}$ = 7.8 Hz, CH$_2$), 8.17 (1 H, s, CH).

^{13}C NMR (CDCl$_3$): δ = 14.4, 63.5, 105.2 (t, $^3J_{C,F}$ = 2.1 Hz), 115.0, 120.0 (t, $^1J_{C,F}$ = 287 Hz), 121.7 (t, $^1J_{C,F}$ = 287 Hz), 149.8, 151.0 (t, $^2J_{C,F}$ = 33 Hz), 155.3 (t, $^2J_{C,F}$ = 33 Hz), 155.9, 168.3.

MS: *m*/*z* (%) = 362 (63, [M$^+$ + 2]), 360 (100, [M$^+$]), 289 (17), 288 (12), 231 (14), 201 (11).

Ethyl 5-Methyl-2,4-bis(trifluoromethyl)thieno[2,3-*d*]pyrimidine-6-carboxylate (14n)

Prepared from **6** and **11a**; yield: 560 mg (91%); colorless solid; mp 111–113 °C; R_f = 0.30 (EtOAc–hexane, 1:5).

^{1}H NMR (CDCl$_3$): δ = 1.38 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_3$), 2.90 (3 H, t, $^3J_{H,H}$ = 2.0 Hz, CH$_3$), 4.41 (2 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_2$).

^{13}C NMR (CDCl$_3$): δ = 14.2, 14.3 (q, $^3J_{C,F}$ = 5.6 Hz), 62.9, 119.5 (q, $^1J_{C,F}$ = 274 Hz), 120.5 (q, $^1J_{C,F}$ = 274 Hz), 128.7, 133.9, 137.3, 151.5 (q, $^2J_{C,F}$ = 36 Hz), 151.6 (q, $^2J_{C,F}$ = 36 Hz), 161.7, 171.2.

^{19}F NMR (CDCl$_3$): δ = –64.7, –71.5.

MS: *m*/*z* (%) = 359 (14, [M$^+$ + 1]), 358 (98, [M$^+$]), 331 (15), 330 (100), 329 (39), 314 (11), 313 (58), 312 (52), 309 (18), 286 (11), 285 (50), 284 (47), 69 (10).

Ethyl 5-Methyl-2,4-bis(perfluoroethyl)thieno[2,3-*d*]pyrimidine-6-carboxylate (14m)

Prepared from **6** and **11d**; yield: 852 mg (93%); colorless solid; mp 88–89 °C; R_f = 0.80 (EtOAc–hexane 1:5).

^{1}H NMR (CDCl$_3$): δ = 1.33 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_3$), 2.83 (3 H, t, $^3J_{H,H}$ = 2.0 Hz, CH$_3$), 4.49 (2 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_2$).

^{13}C NMR (CDCl$_3$): δ = 14.0, 15.1 (t, $^3J_{C,F}$ = 3.0 Hz), 62.0, 111.0 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.3 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.1 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.9 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 128.7, 133.0, 139.9, 151.9 (t, $^2J_{C,F}$ = 26 Hz), 153.4 (t, $^2J_{C,F}$ = 26 Hz), 161.0, 173.3.

MS: *m*/*z* (%) = 459 (15, [M$^+$ + 1]), 458 (100, [M$^+$]), 390 (42, [M$^+$ + 1 – CF_3]), 389 (42, [M$^+$ – CF_3]), 385 (17), 340 (10, [M$^+$ + 1 – C_2F_5]), 339 (10, [M$^+$ – C_2F_5]), 218 (10), 203 (11), 73 (12).

Ethyl 2,4-Bis(difluoromethyl)-5-methylthieno[2,3-*d*]pyrimidine-6-carboxylate (14o)

Prepared from **6** and **11b**; yield: 597 mg (91%); colorless solid; mp 117–118 °C; R_f = 0.80 (EtOAc–hexane, 1:5).

^{1}H NMR (CDCl$_3$): δ = 1.43 (3 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_3$), 2.89 (3 H, t, $^3J_{H,H}$ = 2.0 Hz, CH$_3$), 4.45 (2 H, t, $^3J_{H,H}$ = 7.8 Hz, CH$_2$), 6.99 (1 H, t, $^2J_{H,F}$ = 53 Hz, CF_2H), 7.11 (1 H, t, $^2J_{H,F}$ = 54 Hz, CF_2H).

^{13}C NMR (CDCl$_3$): δ = 14.9, 14.0, 62.1, 114.7 (t, $^1J_{C,F}$ = 246 Hz), 115.2 (t, $^1J_{C,F}$ = 247 Hz), 128.7, 133.9, 137.3, 141.5 (t, $^2J_{C,F}$ = 26 Hz), 152.1 (t, $^2J_{C,F}$ = 26 Hz), 161.7, 171.2.

MS: *m*/*z* (%) = 323 (13, [M$^+$ + 1]), 322 (100, [M$^+$]), 321 (90, [M$^+$ – 1]), 271 (67, [M$^+$ – CF_2H]), 277 (50), 250 (12), 249 (15), 74 (77).

7-*tert*-Butyl-2,4-bis(perfluoroethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (14p)

Prepared from **7** and **11d**; yield: 829 mg (95%); colorless solid; mp 120–121 °C; R_f = 0.70 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 1.73 (9 H, s, CH$_3$), 8.21 (1 H, s, 2-H).

^{13}C NMR (DMSO-d_6): δ = 28.9, 60.8, 85.7, 113.9, 115.0, 111.2 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.2 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.3 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.9 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 143.8, 145.0 (t, $^2J_{C,F}$ = 27 Hz), 146.0, 149.0 (t, $^2J_{C,F}$ = 27 Hz).

MS: *m*/*z* (%) = 437 (16, [M$^+$ + 1]), 436 (41, [M$^+$]), 380 (100, [M$^+$ + 1 – *t*-Bu]), 379 (76, [M$^+$ – *t*-Bu]), 368 (33, [M$^+$ + 1 – CF_3]), 367 (11,

[$M^+ - CF_3$]), 318 (10, [$M^+ + 1 - C_2F_5$]), 317 (10, [$M^+ - C_2F_5$]), 57 (67).

7-*tert*-Butyl-2,4-bis(chlorodifluoromethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (14q)

Prepared from **7** and **11c**; yield: 642 mg (87%); colorless solid; mp 147–149 °C; R_f = 0.55 (EtOAc–hexane, 1:3).

^{1}H NMR (DMSO-d_6): δ = 1.70 (9 H, s, CH_3), 8.01 (1 H, s, 2-H).

^{13}C NMR (DMSO-d_6): δ = 27.1, 60.7, 85.9, 111.1, 116.5, 120.2 (t, $^1J_{C,F}$ = 287 Hz), 121.6 (t, $^1J_{C,F}$ = 287 Hz), 140.2, 143.1 ($^2J_{C,F}$ = 34 Hz), 144.5, 149.0 ($^2J_{C,F}$ = 34 Hz).

MS: *m*/*z* (%) = 368 (100, [M^+]), 312 (22), 57 (100).

7-*tert*-Butyl-2,4-bis(difluoromethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (14r)

Prepared from **7** and **11b**; yield: 547 mg (91%); colorless solid; mp 150–152 °C (EtOH–H_2O).

^{1}H NMR (DMSO-d_6): δ = 1.77 (9 H, s, CH_3), 6.92 (1 H, t, $^2J_{H,F}$ = 57 Hz, CF_2H), 7.11 (1 H, t, $^2J_{H,F}$ = 54 Hz, CF_2H), 8.11 (1 H, s, 2-H).

^{13}C NMR (DMSO-d_6): δ = 28.5, 61.1, 83.2, 111.4, 114.4 (t, $^1J_{C,F}$ = 243 Hz), 115.3 (t, $^1J_{C,F}$ = 245 Hz), 116.3, 142.7, 141.1 ($^2J_{C,F}$ = 27 Hz), 144.0, 146.1 ($^2J_{C,F}$ = 25 Hz).

MS: *m*/*z* (%) = 301 (15, [M^+ + 1]), 300 (100, [M^+]), 299 (88, [M^+ – 1]), 243 (19, [M^+ – *t*-Bu]), 249 (89, [$M^+ - CF_2H$]), 219 (42), 218 (24), 57 (78).

2,4-Bis(trifluoromethyl)-9*H*-pyrimido[4,5-*b*]indole (14s)

Prepared from **8** and **11a**; yield: 525 mg (86%); colorless solid; mp 207–208 °C; R_f = 0.65 (EtOAc–hexane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 7.34 (2 H, m), 7.77 (1 H, d, *J* = 7.2 Hz), 8.23 (1 H, d, *J* = 7.2 Hz), 12.56 (1 H, s).

^{13}C NMR (DMSO-d_6): δ = 110.9, 119.3 (q, $^1J_{C,F}$ = 274 Hz), 120.2 (q, $^1J_{C,F}$ = 274 Hz), 121.0, 125.0, 133.5, 135.1, 146.2, 147.5 (q, $^2J_{C,F}$ = 36 Hz), 150.6 (q, $^2J_{C,F}$ = 36 Hz), 151.9, 157.0.

MS: *m*/*z* (%) = 306 (14, [M^+ + 1]), 305 (100, [M^+]), 285 (18), 284 (39).

2,4-Bis(perfluoroethyl)-9*H*-pyrimido[4,5-*b*]indole (14t)

Prepared from **8** and **11d**; yield: 705 mg (87%); colorless solid; mp 169–170 °C; R_f = 0.35 (EtOAc–hexane, 1:2).

^{1}H NMR (DMSO-d_6): δ = 7.37 (m, 2 H), 7.87 (d, *J* = 7.2 Hz, 1 H), 8.20 (d, *J* = 7.2 Hz, 1 H), 12.78 (s, 1 H)

^{13}C NMR (DMSO-d_6): δ = 110.9, 111.1 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.7 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.4 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.9 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 121.5, 127.0, 133.9, 135.8, 146.7, 147.5 (q, $^2J_{C,F}$ = 27 Hz), 149.9 (q, $^2J_{C,F}$ = 27 Hz), 151.9, 156.1.

MS: *m*/*z* (%) = 406 (15, [M^+ + 1]), 405 (100, [M^+]), 405 (100, [M^+ – 1]), 286 (11, [$M^+ - C_2F_5$]).

2,4-Bis(difluoromethyl)-9*H*-pyrimido[4,5-*b*]indole (14u)

Prepared from **8** and **11b**; yield: 452 mg (84%); colorless solid; mp 219–221 °C; R_f = 0.45 (EtOAc–hexane, 1:1).

^{1}H NMR (DMSO-d_6): δ = 7.27 (2 H, m), 6.79 (1 H, t, $^2J_{H,F}$ = 52 Hz, CF_2H), 6.91 (1 H, t, $^2J_{H,F}$ = 52 Hz, CF_2H), 7.77 (1 H, d, *J* = 7.2 Hz), 8.17 (1 H, d, *J* = 7.2 Hz), 12.76 (1 H, s).

^{13}C NMR (DMSO-d_6): δ = 111.1, 114.4 (t, $^1J_{C,F}$ = 243 Hz), 115.7 (t, $^1J_{C,F}$ = 245 Hz), 121.1, 124.4, 133.3, 134.7, 146.1, 145.5 (q, $^2J_{C,F}$ = 27 Hz), 150.0 (q, $^2J_{C,F}$ = 27 Hz), 151.2, 155.5.

MS: *m*/*z* (%) = 270 (13, [M^+ + 1]), 269 (100, [M^+]), 268 (12, [M^+ – 1]), 218 (11, [$M^+ - CF_2H$]).

***N*,*N*-Dimethyl-2,4-bis(trifluoromethyl)quinazolin-7-amine (14v)**

Prepared from **9** and **11a**; yield: 561 mg (91%); colorless solid; mp 178–180 °C; R_f = 0.35 (EtOAc–hexane, 1:2).

^{1}H NMR ($CDCl_3$): δ = 3.15 (6 H, s, CH_3), 7.03 (1 H, d, $^3J_{H,H}$ = 2.7 Hz, CH), 7.27 (1 H, dd, $^3J_{H,H}$ = 9.4 Hz, $^3J_{H,H}$ = 2.7 Hz, CH), 7.47 (1 H, dq, $^3J_{H,H}$ = 9.4 Hz, $J_{H,F}$ = 2.0 Hz, CH).

^{13}C NMR ($CDCl_3$): δ = 40.1, 104.6 (q, $^3J_{C,F}$ = 1.5 Hz), 112.8, 119.6 (q, $^1J_{C,F}$ = 274 Hz), 119.7, 121.0 (q, $^1J_{C,F}$ = 274 Hz), 125.5 (q, $^3J_{C,F}$ = 3.2 Hz), 152.1 (q, $^2J_{C,F}$ = 36 Hz), 153.5, 157.7 (q, $^2J_{C,F}$ = 36 Hz), 158.4.

MS: *m*/*z* (%) = 310 (17, [M^+ + 1]), 309 (100, [M^+]), 308 (90).

***N*,*N*-Dimethyl-2,4-bis(perfluoroethyl)quinazolin-7-amine (14w)**

Prepared from **9** and **11d**; yield: 728 mg (89%); colorless solid; mp 170–172 °C; R_f = 0.65 (EtOAc–hexane, 1:2).

^{1}H NMR ($CDCl_3$): δ = 3.19 (6 H, s, CH_3), 7.13 (1 H, d, $^3J_{H,H}$ = 2.7 Hz, CH), 7.19 (1 H, dd, $^3J_{H,H}$ = 9.4 Hz, $^3J_{H,H}$ = 2.7 Hz, CH), 7.35 (1 H, dq, $^3J_{H,H}$ = 9.4 Hz, $J_{H,F}$ = 2.0 Hz, CH).

^{13}C NMR ($CDCl_3$): δ = 40.8, 104.0 (t, $^3J_{C,F}$ = 2.1 Hz), 112.8, 111.0 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.6 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.1 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 119.7, 120.5 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 121.1, 127.3 (t, $^3J_{C,F}$ = 3.0 Hz), 152.7 (t, $^2J_{C,F}$ = 26 Hz), 153.7, 157.1 (t, $^2J_{C,F}$ = 26 Hz), 157.0.

MS: *m*/*z* (%) = 410 (15, [M^+ + 1]), 409 (100, [M^+]), 340 (67, [$M^+ - CF_3$]), 290 (19, [$M^+ - C_2F_5$]).

2,4-Bis(difluoromethyl)-*N*,*N*-dimethylquinazolin-7-amine (14x)

Prepared from **9** and **11b**; yield: 497 mg (91%); colorless solid; mp 189–190 °C; R_f = 0.75 (EtOAc–hexane, 1:2).

^{1}H NMR ($CDCl_3$): δ = 3.11 (6 H, s, CH_3), 7.01 (1 H, d, $^3J_{H,H}$ = 2.7 Hz, CH), 6.90 (1 H, t, $^2J_{H,F}$ = 54 Hz, CF_2H), 7.05 (1 H, t, $^2J_{H,F}$ = 53 Hz, CF_2H), 7.25 (1 H, dd, $^3J_{H,H}$ = 9.4 Hz, $^3J_{H,H}$ = 2.7 Hz, CH), 7.39 (1 H, dq, $^3J_{H,H}$ = 9.4 Hz, $J_{H,F}$ = 2.0 Hz, CH).

^{13}C NMR ($CDCl_3$): δ = 40.1, 102.9 112.8, 114.7 (t, $^1J_{C,F}$ = 247 Hz), 115.5 (t, $^1J_{C,F}$ = 245 Hz), 119.9, 125.5 (t, $^3J_{C,F}$ = 3.2 Hz), 150.0 (q, $^2J_{C,F}$ = 27 Hz), 154.4, 157.0 (t, $^2J_{C,F}$ = 26 Hz), 157.9.

MS: *m*/*z* (%) = 274 (14, [M^+ + 1]), 273 (90, [M^+]), 272 (100, [M^+ – 1]), 229 (11, [$M^+ - NMe_2$]), 222 (71, [$M^+ - CF_2H$]).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4,6-bis(perfluoroethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (17a)

Prepared from **10** and **11d**; yield: 983 mg (93%); yellow oil; R_f = 0.30 (hexane–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$): δ = 1.33 (3 H, s, CH_3), 1.61 (3 H, s, CH_3), 3.77 (1 H, dd, $^3J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 3.7 Hz, CH), 3.76 (1 H, dd, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 1.4 Hz, CH), 4.57 (1 H, br s, CH), 5.04 (1 H, dd, $^3J_{H,H}$ = 5.5 Hz, $^3J_{H,H}$ = 1.7 Hz, CH), 5.20 (1 H, dd, $^3J_{H,H}$ = 5.5, Hz, $^3J_{H,H}$ = 2.7 Hz, CH), 6.49 (1 H, br s, 5′-OH), 6.88 (1 H, d, $^3J_{H,H}$ = 2.7 Hz, CH), 8.55 (1 H, s, CH).

^{13}C NMR ($CDCl_3$): δ = 25.0, 29.1, 63.5, 82.0, 85.9, 88.4, 92.9, 111.7, 114.0, 111.3 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.5 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.2 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.5 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 134.6, 147.0 (q, $^2J_{C,F}$ = 28 Hz), 151.2 (q, $^2J_{C,F}$ = 27 Hz), 155.9.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4,6-bis(chlorodifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (17b)

Prepared from **10** and **11c**; yield: 839 mg (91%); yellow oil; R_f = 0.65 (hexane–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$): δ = 1.32 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 3.70 (1 H, dd, $^3J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 3.3 Hz, CH), 3.86 (1 H, dd, $^2J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 1.1 Hz, CH), 4.55 (1 H, br s, CH), 5.04 (1

H, dd, $^3J_{H,H}$ = 5.9 Hz, $^3J_{H,H}$ = 1.7 Hz, CH), 5.32 (1 H, dd, $^3J_{H,H}$ = 5.9, Hz, $^3J_{H,H}$ = 2.5 Hz, CH), 6.43 (1 H, br s, 5′-OH), 6.80 (1 H, d, $^3J_{H,H}$ = 2.5 Hz, CH), 8.44 (1 H, s, CH).

^{13}C NMR ($CDCl_3$): δ = 25.2, 27.0, 62.3, 82.7, 85.5, 88.1, 92.0, 111.1, 113.3, 120.4 (t, $^1J_{C,F}$ = 289 Hz), 121.3 (t, $^1J_{C,F}$ = 288 Hz), 134.7, 150.0 (t, $^2J_{C,F}$ = 29 Hz), 146.0 (t, $^2J_{C,F}$ = 29 Hz), 156.7.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-4,6-bis(difluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (17c)

Prepared from **10** and **11b**; yield: 691 mg (88%); yellow oil; R_f = 0.75 (hexane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 1.38 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 3.77 (1 H, dd, $^3J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 3.7 Hz, CH), 3.83 (1 H, dd, $^2J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 1.3 Hz, CH), 4.51 (1 H, br s, CH), 5.04 (1 H, dd, $^3J_{H,H}$ = 5.9 Hz, $^3J_{H,H}$ = 1.4 Hz, CH), 5.22 (1 H, dd, $^3J_{H,H}$ = 5.9, Hz, $^3J_{H,H}$ = 2.8 Hz, CH), 6.39 (1 H, br s, 5′-OH), 6.78 (1 H, d, $^3J_{H,H}$ = 2.8 Hz, CH), 6.95 (1 H, t, $^2J_{H,F}$ = 55 Hz, CF_2H), 7.07 (1 H, t, $^2J_{H,F}$ = 56 Hz, CF_2H), 8.41 (1 H, s, CH).

^{13}C NMR ($CDCl_3$): δ = 25.0, 27.0, 63.3, 82.0, 85.9, 88.8, 93.0, 111.1, 114.0, 114.2 (t, $^1J_{C,F}$ = 241 Hz), 115.1 (t, $^1J_{C,F}$ = 242 Hz), 134.6, 149.5 (q, $^2J_{C,F}$ = 29 Hz), 144.4 (q, $^2J_{C,F}$ = 27 Hz), 155.5.

Cleavage of 2,2′-Propylidene Protection Group; Compounds 18; General Procedure

The protected substrate **17** (1 mmol) was dissolved in a mixture of CF_3CO_2H–H_2O (9:1, 10–15 mL) and stirred vigorously for 30–40 min (controlled by TLC) at r.t. 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.

l-(β-D-Ribofuranosyl)-4,6-bis(perfluoroethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (18a)

Yield: 396 mg (81%); colorless solid; mp 73–75 °C; R_f = 0.25 (hexane–EtOAc, 1:1).

^{1}H NMR (DMSO-d_6): δ = 3.38 (1 H, dd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 5.9 CH), 3.51 (1 H, dd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 5.1 Hz, CH), 3.96 (1 H, q, $^3J_{H,H}$ = 5.1 Hz, CH), 4.23 (1 H, t, $^3J_{H,H}$ = 4.7 Hz, CH), 4.67 (1 H, t, $^3J_{H,H}$ = 5.1 Hz, CH), 6.36 (1 H, d, $^3J_{H,H}$ = 4.5 Hz, CH), 8.81 (1 H, s, CH).

^{13}C NMR (DMSO-d_6): δ = 61.4, 70.2, 73.7, 85.4, 88.6, 109.4, 111.6 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 112.9 (tq, $^1J_{C,F}$ = 215 Hz, $^2J_{C,F}$ = 38 Hz), 120.4 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 120.6 (qt, $^1J_{C,F}$ = 285 Hz, $^2J_{C,F}$ = 38 Hz), 133.7, 147.1 (q, $^2J_{C,F}$ = 29 Hz), 150.2 (q, $^2J_{C,F}$ = 29 Hz), 155.7.

l-(β-D-Ribofuranosyl)-4,6-bis(chlorodifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (18b)

Yield: 345 mg (82%); colorless solid; mp 111–113 °C; R_f = 0.55 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.43 (1 H, dd, $^2J_{H,H}$ = 11.8 Hz, $^3J_{H,H}$ = 5.7 CH), 3.52 (1 H, dd, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 5.2 Hz, CH), 3.92 (1 H, q, $^3J_{H,H}$ = 5.2 Hz, CH), 4.23 (1H, t, $^3J_{H,H}$ = 4.7 Hz, CH), 4.61 (1 H, t, $^3J_{H,H}$ = 5.2 Hz, CH), 6.30 (1 H, d, $^3J_{H,H}$ = 4.3 Hz, CH), 8.77 (1H, s, CH).

^{13}C NMR (DMSO-d_6): δ= 62.4, 70.5, 73.1, 85.5, 88.0, 111.1, 120.5 (t, $^1J_{C,F}$ = 287 Hz), 122.0 (t, $^1J_{C,F}$ = 287 Hz),, 133.9, 149.5 (q, $^2J_{C,F}$ = 28 Hz), 150.2 (q, $^2J_{C,F}$ = 28 Hz), 154.6.

l-(β-D-Ribofuranosyl)-4,6-bis(difluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (18c)

Yield: 292 mg (83%); colorless solid; mp 120–121 °C; R_f = 0.30 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.50 (1 H, dd, $^2J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 5.5 CH), 3.53 (1 H, dd, $^2J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 5.0 Hz, CH), 3.93 (1 H, q, $^3J_{H,H}$ = 5.0 Hz, CH), 4.24 (1 H, t, $^3J_{H,H}$ = 4.3 Hz, CH), 4.60 (1 H, t, $^3J_{H,H}$ = 5.2 Hz, CH), 6.33 (1 H, d, $^3J_{H,H}$ = 4.1 Hz, CH), 6.95 (1 H, t, $^2J_{H,F}$ = 54 Hz, CF_2H), 7.09 (1 H, t, $^2J_{H,F}$ = 55 Hz, CF_2H), 8.77 (1 H, s, CH).

^{13}C NMR (DMSO-d_6): δ = 63.1, 70.5, 73.0, 85.0, 88.0, 109.5, 115.0 (t, $^1J_{C,F}$ = 245 Hz), 117.2 (t, $^1J_{C,F}$ = 245 Hz), 134.4, 148.1 (q, $^2J_{C,F}$ = 27 Hz), 150.5 (q, $^2J_{C,F}$ = 27 Hz), 155.5.

9-(4-Methoxybenzyl)-2,6-bis(trifluoromethyl)-9*H*-purine (20)

Following the general procedure for the preparation of **14**; compound **11a** was reacted with the in situ generated **19**[20] to afford **20**; yield: 2.9 g (77%); colorless solid; mp 162–163 °C; R_f = 0.40 (hexane–EtOAc, 3:1).

^{1}H NMR (DMSO-d_6): δ = 3.59 (3 H, s), 5.15 (2 H, s), 6.93 (2 H, d, $^3J_{H,H}$ = 7.8 Hz, CH), 7.20 (2 H, d, $^3J_{H,H}$ = 7.8 Hz, CH), 8.39 (1 H, s).

^{13}C NMR (DMSO-d_6): δ = 54.8, 59.3, 120.1 ($^1J_{C,F}$ = 273 Hz), 120.5 ($^1J_{C,F}$ = 273 Hz), 122.0, 129.1, 130.7, 131.3, 131.4, 141.1 ($^2J_{C,F}$ = 37 Hz), 147.9 ($^2J_{C,F}$ = 37 Hz), 153.3, 155.1, 162.0.

MS: *m*/*z* (%) = 377 (12, [M$^+$ + 1]), 376 (78, [M$^+$]), 256 (37), 255 (43), 221 (11), 121 (100).

Deprotection of Compound 20 to 2,6-Bis(trifluoromethyl)-9*H*-purine (21)

A solution of compound **20** (5 mmol, 1.88 g) in TFA–H_2O (20:1, 20 mL) was stirred for 24 h at r.t. The solvent was removed under reduced pressure, the formed material was kept for the next 36 h on a vacuum line. The resulting material was purified by recrystallization from *i*-PrOH; yield: 768 mg (60%); colorless solid; mp 207–209 °C (*i*-PrOH).

^{1}H NMR (DMSO-d_6): δ = 8.41 (1 H, s), 12.01 (1 H, s, NH).

^{13}C NMR (DMSO-d_6): δ = 120.1 ($^1J_{C,F}$ = 273 Hz), 120.5 ($^1J_{C,F}$ = 273 Hz), 131.0, 131.1, 141.0 ($^2J_{C,F}$ = 37 Hz), 147.0 ($^2J_{C,F}$ = 37 Hz), 152.0, 161.7.

MS: *m*/*z* (%) = 257 (10, [M$^+$ + 1]), 256 (100, [M$^+$]), 255 (77).

9-(Triacetyl-β-D-ribofuranosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (22)

The glycosylation reaction was conducted according to the procedure described elsewhere.[11c]

Yield: 926 mg (90%); colorless solid; mp 98–101 °C; R_f = 0.65 (hexane–EtOAc, 1:1).

^{1}H NMR (DMSO-d_6): δ = 1.97–2.10 (9 H, br s), 3.39 (1 H, m), 3.67 (1 H, m), 3.96 (1 H, q, *J* = 4.7 Hz), 4.39 (1 H, br s), 4.55 (1 H, d, *J* = 4.7 Hz), 6.60 (1 H, d, *J* = 4.5 Hz), 8.34 (1 H, s),

^{13}C NMR (DMSO-d_6): δ = 20.4, 20.5, 20.8, 62.9, 71.0, 72.9, 85.1, 87.0, 110.0, 120.2 ($^1J_{C,F}$ = 273 Hz), 120.5 ($^1J_{C,F}$ = 273 Hz), 131.4, 141.1 ($^2J_{C,F}$ = 37 Hz), 147.2 ($^2J_{C,F}$ = 37 Hz), 152.0, 161.7, 171.1, 171.2, 171.4.

Deprotection of the Acylated Nucleoside 22; 9-(β-D-Ribofuranosyl)-2,6-bis(trifluoromethyl)-9*H*-purine (23)

To a solution of the acylated nucleoside **22** (1 mmol) in anhyd MeOH (5 mL) was added dropwise a sat. solution of ammonia in MeOH (20 mL) at 0 °C. The mixture was stirred for another 30 min and left overnight at r.t. The solvent was removed under reduced pressure, the formed material was kept for the next 24 h on a vacuum line. The resultant material formed was purified by column chromatography on silica gel; yield: 315 mg (81%); colorless solid; mp 142–144 °C; R_f = 0.47 (EtOAc).

^{1}H NMR (DMSO-d_6): δ = 3.41 (1 H, m), 3.71 (1 H, m), 4.11 (1 H, q, J = 4.3 Hz), 4.30 (1 H, br s), 4.39 (1 H d, J = 4.3 Hz), 5.22 (1 H, m), 5.55 (2 H, br s), 6.53 (1 H, d, J = 5.1 Hz,), 8.31 (1H, s).

^{13}C NMR (DMSO-d_6): δ = 61.0, 71.9, 75.3, 85.7, 87.1, 111.9, 120.1 ($^1J_{C,F}$ = 273 Hz), 120.4 ($^1J_{C,F}$ = 273 Hz), 131.5, 141.1 ($^2J_{C,F}$ = 37 Hz), 146.4 ($^2J_{C,F}$ = 37 Hz), 153.5, 161.0.

Acknowledgment

The authors acknowledge Prof. V. Ya. Sosnovskikh (Ural State University, Russia), Dr. D. V. Sevenard (Hansa Fine Chemicals GmbH, Bremen, Germany), and Dr. D. Volochnyuk (Enamine Ltd. Ukraine) for the discussion of the obtained results, and for the help during the preparation of the manuscript.

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