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# Synthesis and Cytostatic Activity of Nucleosides and Acyclic Nucleoside Analogues Derived from 6-(Trifluoromethyl)purines

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**Abstract:** Glycosylation and alkylation of 6-(trifluoromethyl)purine by several protected halogenoses or hydroxyalkyl chlorides afforded regio- and stereoselectively the 9-β-nucleosides or 9-alkylated purine derivatives in good yields. Deprotection of these intermediates gave a series of nucleoside (β-D-ribofuranosyl, 2-deoxy-β-D-ribofuranosyl and β-D-arabinofuranosyl) and acyclonucleoside (2,3-dihydroxypropyl and (2-hydroxyethyl)oxymethyl) derivatives of 6-(trifluoromethyl)purine. While the ribofuranosyl derivative **1** showed significant cytostatic activity, the other derivatives were inactive.

**Key words:** Purines; Nucleosides; Glycosidation; Alkylation; Fluorinated compounds

Fluorinated analogues of natural compounds often exert interesting biological activities.[1] Fluorinated derivatives of nucleosides have been widely studied, especially antineoplastic 5-fluorouracil[2], antiviral 5-trifluoromethyluracil[3] and antitumor 2-fluoroadenine nucleosides[4], as well as analogues with a fluorinated sugar moiety.[5] Reactive 2- and 6-fluoropurine derivatives are good starting compounds for nucleophilic substitution reactions.[6] 2-Trifluoromethyl[7] and 8-trifluoromethylpurine[8] derivatives are easily prepared by heterocyclization of 5,6-diaminopyrimidines or 4-aminoimidazole-5-carboxylic acid derivatives by trifluoroacetates and are reported[7,8] to possess interesting antirhinovirus, vassodepressor, plattelet aggregation inhibitory, phosphodiesterase inhibitory and antitumor activity. 2-Trifluoromethyladenosine analogues were also prepared[9] by trifluoromethylation of 2-iodoadenosines by trifluoromethylzinc bromide and CuBr in DMF/HMPA.

6-Fluoroalkylated purines are quite rare in the literature. 6-(Trifluoromethyl)purine and 2-amino-6-(trifluoromethyl)purine were prepared by multistep cyclization procedures[10] starting from ethyl trifluoroacetoacetate in low overall yields (3 and 6 %, respectively). Trifluoromethylation of protected 6-

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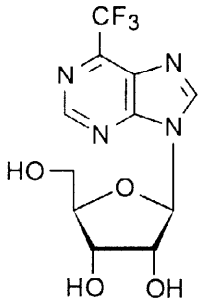
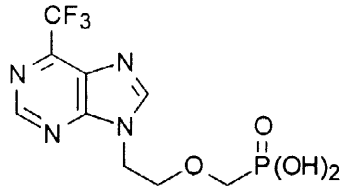
chloropurine riboside by trifluoromethyl iodide and copper metal in HMPA gave[11] the 6-(trifluoromethyl)purine derivative in moderate yield; the final 6-trifluoromethylpurine riboside was reported to exhibit a moderate cytotostatic activity which was never quantified. Very recently, we have reported[12] a facile method of preparation of 6-(perfluoroalkyl)purine derivatives using a KF/CuI mediated cross-coupling of perfluoroalkyl(trimethyl)silanes with 6-iodopurine bases. Among others, 6-trifluoromethylpurine riboside **1**, free base **2** and acyclic nucleotide analogue **3** were prepared by this method[12]. The high cytostatic activity of the riboside **1** was confirmed but, surprisingly, the free base **2** and phosphonate **3** were entirely inactive. Therefore it seemed to be of interest to further investigate the cytostatic activity of some other nucleoside analogues derived from this purine base. In this paper, we report on the synthesis of several novel nucleoside and acyclic nucleoside[13] derivatives of 6-(trifluoromethyl)purine by a glycosylation/alkylation of **2** and on their cytostatic activity.




**1**

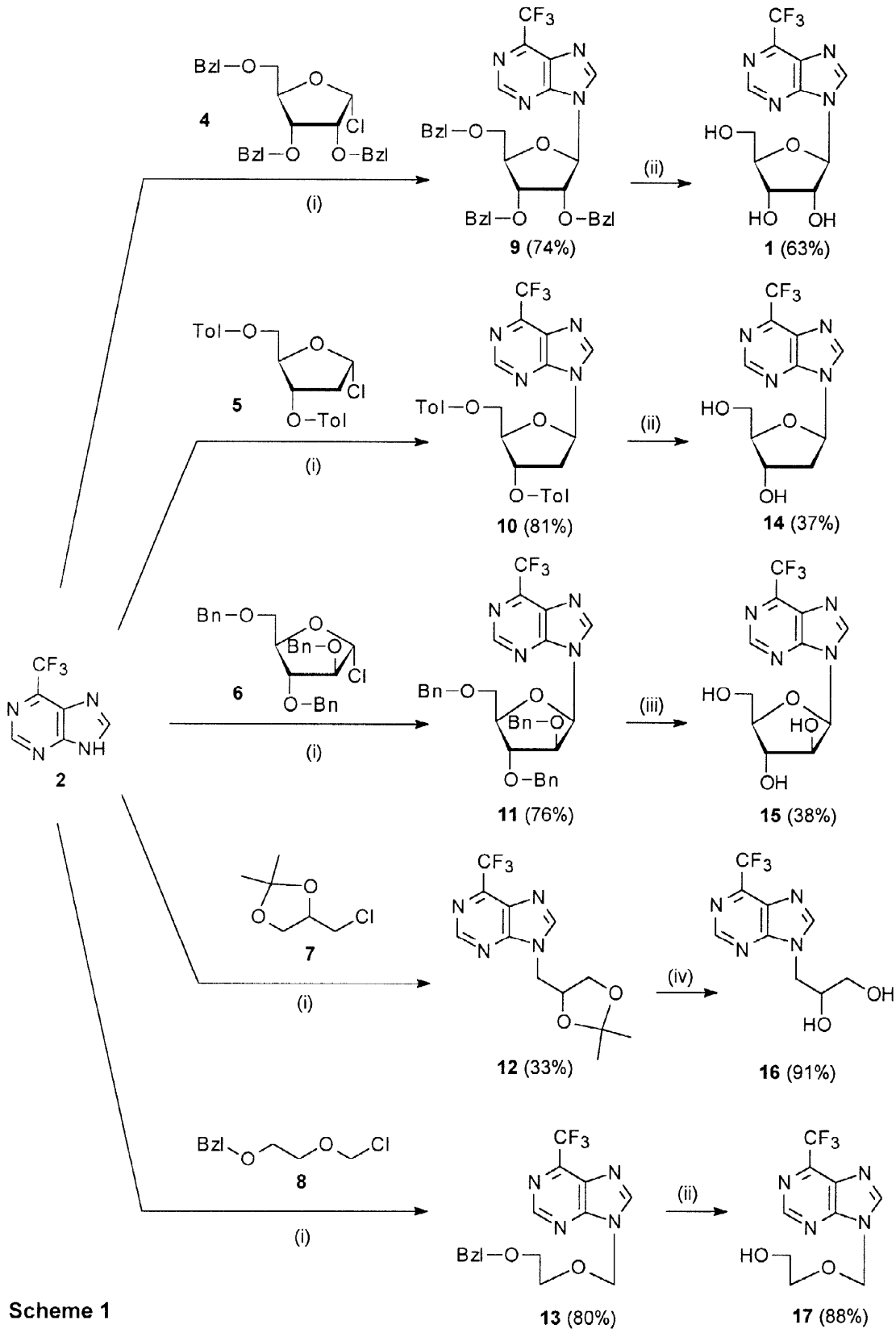

**2**




**3**

Precursors of target compounds with protected hydroxyl groups **9-13** were prepared by standard glycosylation/alkylation of 6-(trifluoromethyl)purine[12] (**2**) in acetonitrile using sodium hydride as a condensation reagent under argon atmosphere (**Scheme 1**). Formation of sodium salt was promoted by sonication and elevated temperature. The glycosylation with 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl chloride[14] (**4**), 3,5-bis-*O*-(p-toluoyl)-2-deoxy-α-D-ribofuranosyl chloride[15] (**5**) and 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride[16] (**6**) proceeded smoothly at room temperature to form protected nucleosides **9-11**, respectively, in good yields. Alkylation of 6-(trifluoromethyl)purine (**2**) with (2-benzoyloxyethyl)oxymethyl chloride[17] (**8**) took place under the same mild conditions to form protected acyclovir[13] analogue **13** in a yield of 80%, while reaction with racemic 2,3-*O*-isopropylidene-2,3-dihydroxypropyl chloride[18] (**7**) required elevated temperature, the yield was only 33% of compound **12** and 20% of starting base **2** was recovered. In all cases chromatography was used to purify the products. The glycosylation and alkylation reactions were regio- (and stereo-) selective to give in all cases $N^9$-substituted purine derivatives and β-nucleosides.

Standard procedures were applied for the deprotection of derivatives **9-13**. Removal of benzoyl and p-toluoyl protecting groups from hydroxyl functions of compounds **9, 10** and **13** was carried out catalytically by NaOMe in methanol and afforded 6-(trifluoromethyl)purine riboside **1**, 2-deoxyriboside **14** and acyclovir[13] analogue **17**, respectively. Compared to the previously reported procedures,[11,12] the overall yield (47%) of the



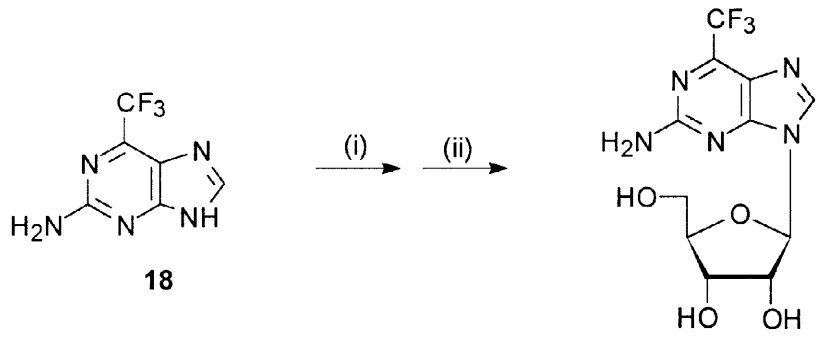

**Scheme 1**

Bzl = benzoyl; Tol = toluoyl; Bn = benzyl

(i) NaH/$CH_3CN$; (ii) NaOMe/MeOH; (iii) $H_2$/Pd-C/MeOH; (iv) Dowex 50X8($H^+$)/MeOH/$H_2O$

known riboside **1** was significantly higher. To obtain 6-(trifluoromethyl)purine arabinoside **15,** tribenzyl derivative **11** was deprotected by catalytic hydrogenolysis on Pd/C. The isopropylidene protecting group of compound **12** was cleaved under acidic conditions by Dowex 50 X 8 ($H^+$ form) to gain 9-(2,3-dihydroxypropyl)-6-(trifluoromethyl)purine (**16**) as a DHPA[13] analogue. The yields of compounds **1, 14** and **15** in deprotection procedures were lowered by the limited stability of 6-trifluoromethylpurine nucleosides.

To study the influence of the of the 2-amino function at the purine ring on the cytostatic activity, we have also attempted a synthesis of the 2-amino-6-(trifluoromethyl)purine nucleoside **19** which was not accessible by the direct trifluoromethylation[12] of the corresponding 6-chloroderivative. Here, however, the starting 2-amino-6-(trifluoromethyl)purine[12] (**18**) is much more difficult and expensive to prepare than compound **2**. Therefore, only semimicroscale ribosylation reaction followed by deprotection (**Scheme 2**) was performed in the same way as described for the nucleoside **1**, giving the desired riboside **19** in low yield and in a quantity sufficient only for NMR and MS spectra and a qualitative cytoctatic acticity screening.




**18** **19** (20%)

**Scheme 2**
(i) $NaH/CH_3CN$; (ii) NaOMe/MeOH

The structure assignment of all compounds was based on NMR measurements. The presence of the sugar or alkyl and base moieties was unequivocally determined by $^1H$ and $^{13}C$ NMR spectra (see Experimental). All resonances in $^1H$ NMR spectra were assigned by two-dimensional $^1H - ^1H$ homonuclear COSY spectra. The signals in $^{13}C$ NMR spectra were determined by using two-dimensional one-bond $^1H - ^{13}C$ correlation from HMQC[19] and three-bond correlation from HMBC[20] experiments.

Determination of the position of the sugar moieties or alkyl chains at the heterocyclic base was established by means of three bond $^1H - ^{13}C$ correlations from HMBC spectra. In all cases we observed the correlation between anomeric proton H-1' and carbon C-4 establishing the sugar-base connectivity through N-9 and not N-7.

The determination of anomeric configuration was based on NOE (DPFGSE NOE)[21] interaction with H-1'. In protected deoxyribo derivative **10** proton H-1' (6.65 ppm) shows a NOE to protons H-2'a (2.94 ppm) and H-4' (4.71 ppm) and not to H-3' and both H-5'a and H-5'b. NOE interaction was observed also between H-3' (5.85 ppm) and H-2'b (3.22 ppm) and H-5'a (4.69 ppm). Similarly in arabino derivative **15** anomeric

proton H-1' exhibited NOE's to protons H-2' (4.30 ppm) and H-4' (3.87 ppm) and no NOE enhancement was observed at protons H-3' and H-5'a,b. These results indicate that in both the deoxyribo and arabino series, the anomeric configuration is β.

In conclusion, the alkylation and glycosylation of 6-(trifluoromethyl)purine (**2**) proceeded regio- (and stereo-) selectively to afford a series of nucleoside (ribo-, deoxyribo- and arabinofuranosides) and acyclonucleoside derivatives in good yields. Since the starting purine **2** is readily available, this method is more facile and effective compared to the previous method[12] based on the preparation of 6-iodopurine nucleosides followed by their trifluoromethylation and deprotection.

The title compounds were tested for thier cytostatic activity[22] (inhibition of cell growth in the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); murine L929 cells (ATCC CCL 1); human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2) and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119)). The known ribofuranoside **1** exhibited significant activity in HeLaS3 ($IC_{50}$= 2.15 μmol.l$^{-1}$) and CCRF-CEM ($IC_{50}$= 0.45 μmol.l$^{-1}$) assays while in L929 and L1210 cultures it was virtually inactive. Surprisingly, the deoxyribo (**14**), arabino (**15**), 2,3-dihydroxypropyl (**16**) and (2-hydroxyethyl)oxymethyl (**17**) derivatives did not exert any significant activity in any of the assays. Also the 2-amino-6-(trifluoromethyl)purine analogue **19** was inactive. This phenomenon clearly indicates very narrow structural requirements for the cytostatic activity in this series of compounds where minor modifications of substituent and configuration on the C-2' carbon, an introduction of an amino group on the purine moiety or a replacement of the sugar moiety by a conformationally flexible hydroxylated acyclic chain, that is supposed[13] to be able to adopt the conformation of the parent riboside, caused complete loss of activity.

## EXPERIMENTAL

Unless otherwise stated, solvents were evaporated at 40°C/2kPa. Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on Bruker AMX-3 400 (400 MHz for $^1$H, 100.6 MHz for $^{13}$C and 376.5 MHz for $^{19}$F nuclei), Bruker DRX 500 (500 MHz for $^1$H and 125.8 MHz for $^{13}$C) and Varian UNITY 200 spectrometer (200.0 MHz for $^1$H) in DMSO-$d_6$ referenced to the solvent signal (2.5 ppm for $^1$H and 39.7 ppm for $^{13}$C NMR) or $CDCl_3$ (TMS was used as internal standard). $CFCl_3$ was an internal standard for $^{19}$F spectra. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB technique (ionization by Xe, accelerating voltage 8 kV, glycerol matrix).

**Glycosylation/alkylation of 6-(trifluoromethyl)purine:** *General procedure*

A mixture of 6-(trifluoromethyl)purine[12] (**2**) (0.30 g, 1.6 mmol), sodium hydride (61 mg, 1.6 mmol, 60% dispersion in mineral oil) and acetonitrile (15 ml) was sonicated for 10 min and then stirred for 30 min. at 70 °C. After cooling to room temperature one of the chloroderivatives **4-8** (1.3 eq., 2.1 mmol) was added and stirring at

room temperature (at reflux for compound **12**) was continued for 3-24 h. The solvent was evaporated and column chromatography of the residue (ethyl acetate/light petroleum) on silica gel afforded the corresponding products **9-13**.

**9-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-6-(trifluoromethyl)purine (9):** reaction time 24 h, yield 0.75 g (74%) of colorless foam, $[\alpha]_D^{20}$ -18.74 (c 0.5, $CHCl_3$). IR $\nu_{max}$ ($CHCl_3$) 3010, 1729 br, 1602, 1336, 1266 br, 712 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): 8.92 (s, 1H, H-2), 8.44 (s, 1H, H-8), 8.06 (m, 4H, H-arom), 7.92 (m, 2H, H-arom), 7.65-7.34 (m, 9H, H-arom), 6.51 (d, 1H, *J*(1',2') = 5.2, H-1'), 6.46 (dd, 1H, *J*(2',1') = 5.2, *J*(2',3') = 5.1, H-2'), 6.26 (dd, 1H, *J*(3',2') = 5.1, *J*(3',4') = 5.5, H-3'), 4.96 (dd, 1H, *Jg* = 12.2, *J*(5'a,4') = 3.0, H-5'a), 4.88 (ddd, 1H, *J*(4',3') = 5.5, *J*(4',5'a) = 3.0, *J*(4',5'b) = 3.1, H-4'), 4.71 (dd, 1H, *Jg* = 12.2, *J*(5'b,4') = 3.1, H-5'b); $^{19}F$ NMR (376.5 MHz, $CDCl_3$): -70.75 (s, 3F, $CF_3$). FAB MS, *m/z* (rel.%): 633 (10) [M+H]. HRMS (FAB): $MH^+$, found 633.1588; $C_{32}H_{24}F_3N_4O_7$ requires 633.1597.

**9-[3,5-Bis-*O*-(*p*-toluoyl)-2-deoxy-β-D-ribofuranosyl]-6-(trifluoromethyl)purine (10):** reaction time 4 h, crystallization from ethanol, yield 0.70 g (81%) of colorless crystals, m.p. 113-115 °C. $^1H$ NMR (500 MHz, $CDCl_3$): 9.03 (s, 1H, H-2), 8.46 (s, 1H, H-8), 8.00 (d, 2H, *J* = 8.1, H-arom-O-3'), 7.88 (d, 2H, *J* = 8.1, H-arom-O-3'), 7.31 (d, 2H, *J* = 8.1, H-arom-O-5'), 7.22 (d, 2H, *J* = 8.1, H-arom-O-5'), 6.65 (dd, 1H, *J*(1',2'a) = 5.9, *J*(1',2'b) = 8.1, H-1'), 5.85 (ddd, 1H, *J*(3',2'a) = 2.0, *J*(3',2'b) = 6.0, *J*(3',4') = 4.2, H-3'), 4.82 (dd, 1H, *J*(5'a,5'b) = 11.5, *J*(5'b,4') = 4.1, H-5'b), 4.71 (m, 1H, H-4'), 4.69 (dd, 1H, *J*(5'a,5'b) = 11.5, *J*(5'a,4') = 3.1, H-5'a), 3.22 (ddd, 1H, *J*(2'b,2'a) = 14.3, *J*(2'b,1') = 8.1, *J*(2'b,3') = 6.0, H-2'b), 2.94 (ddd, 1H, *J*(2'a,2'b) = 14.3, *J*(2'a,1') = 5.9, *J*(2'a,3') = 2.0, H-2'a), 2.42 (s, 3H, $CH_3$), 2.47 (s, 3H, $CH_3$); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): 166.77 (C=O), 166.63 (C=O), 153.81 (C-4), 152.67 (C-2), 146.33 (C-8), 146.20 (q, *J*(C-$CF_3$)=37, C-6), 145.39 and 145.05 (C-4-arom), 131.48 (C-5), 130.53, 130.26, 130.04 and 130.00 (C-2,3-arom), 127.16 and 126.97 (C-1-arom), 121.26 (q, *J*(CF)=275, $CF_3$), 86.11 (C-1'), 84.22 (C-4'), 75.65 (C-3'), 64.44 (C-5'), 38.66 (C-2'), 22.46, 22.36 ($CH_3$); $^{19}F$ NMR (376.5 MHz, $CDCl_3$): -66.88 (s, 3F, $CF_3$). Anal. calcd for $C_{27}H_{23}F_3N_4O_5$ (540.5): C 60.00, H 4.29, N 10.37; found C 59.78, H 4.36, N 10.05. FAB MS, *m/z* (rel.%): 541 (10) [M+H].

**9-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-6-(trifluoromethyl)purine (11):** reaction time 20 h, yield 0.72 g (76%) of yellowish oil, $[\alpha]_D^{20}$ +44.45 (c 0.9, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): 9.00 (s, 1H, H-2), 8.67 (s, 1H, H-8), 7.34 (m, 10H, H-arom), 7.15 (m, 3H, H-arom), 6.84 (d, 2H, H-2-arom-O-5'), 6.61 (d, 1H, *J*(1',2') = 4.2, H-1'), 4.64 (m, 2H, $PhCH_2$), 4.58 (m, 2H, $PhCH_2$), 6.41 (d, 1H, *J* = 11.8, $PhCH_2$-O-5'), 4.36 (m, 2H, H-2' and H-3'), 4.27 (m, 1H, H-4'), 4.22 (d, 1H, *J* = 11.8, $PhCH_2$-O-5'), 3.72 (m, 2H, H-5'); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 154.07 (C-4), 152.37 (C-2), 148.34 (C-8), 145.45 (q, *J*(C-$CF_3$)=30, C-6), 139.16 and 137.90 (O-C-arom), 136.64 (5'-O-C-arom), 130.61 (C-5), 129.31-128.33 (15C, C-arom), 121.45 (q, *J*(CF)=276, $CF_3$), 84.18 (C-1'), 82.55, 81.97 and 81.62 (C-2', C-3' and C-4'), 74.14 ($PhCH_2$), 73.75 ($PhCH_2$-O-5'), 73.05

($PhCH_2$), 69.34 (C-5'); $^{19}F$ NMR (376.5 MHz, $CDCl_3$): -66.76 (s, 3F, $CF_3$). FAB MS, *m/z* (rel.%): 591 (100) [M+H]. HRMS (FAB): $MH^+$, found 591.2227; $C_{32}H_{30}F_3N_4O_4$ requires 591.2219.

**9-(2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-6-(trifluoromethyl)purine (12):** reaction time 24 h at reflux, yield 0.16 g (33%) of **12** as yellowish oil and 60 mg (20%) of regenerated 6-(trifluoromethyl)purine. $^1H$ NMR (200 MHz, $CDCl_3$): 9.09 (s, 1H, H-2), 8.41 (s, 1H, H-8), 6.50 (d, 1H, *J*(1',2') = 5.1, H-1'), 4.57 (dd, 1H, *J*(1'a,2') = 2.7, *J*g = 14.9, H-1'a), 4.51 (m, 1H, H-2'), 4.41 (dd, 1H, *J*(1'b,2') = 7.3, *J*g = 14.9, H-1'b), 4.17 (dd, 1H, *J*(3'a,2') = 6.4, *J*g = 8.8, H-3'a), 3.74 (dd, 1H, *J*(3'b,2') = 5.5, *J*g = 8.8, H-3'b), 1.39 (s, 3H, $CH_3$), 1.33 (s, 3H, $CH_3$). FAB MS, *m/z* (rel.%): 303 (100) [M+H]. HRMS (FAB): $MH^+$, found 303.1076; $C_{12}H_{14}F_3N_4O_2$ requires 303.1069.

**9-[(2-Benzoyloxyethyl)oxymethyl]-6-(trifluoromethyl)purine (13):** reaction time 3 h, crystallization from ethanol, yield 0.47 g (80%) of colorless solid, m.p. 100-101 °C. $^1H$ NMR (500, $CDCl_3$): 9.12 (s, 1H, H-2), 8.45 (s, 1H, H-8), 7.96 (d, 2H, *J* = 7.0, o-arom H), 7.59 (d, 1H, *J* = 7.6, *p*-arom H), 7.44 (d, 2H, *J* = 7.3, *m*-arom H), 5.84 (s, 2H, H-1'), 4.50 (t, 2H *J*(2',3') = 4.6, H-3'), 3.98 (t, 2H, *J*(2',3') = 4.6, H-2'); $^{13}C$ NMR (125.8, $CDCl_3$): 166.98 (CO), 154.70 (C-4), 153.22 (C-2), 147.90 (C-8), 146.27 (q, *J*(C-$CF_3$)=30, C-6), 134.00 (*p*-C-arom), 130.56 (C-5), 130.23 (*o*-C-arom), 130 (C-arom), 129.14 (*m*-C-arom), 121.27 (q, *J*(CF)=219, $CF_3$), 73.80 (C-1'), 69.14 (C-2'), 63.83 (C-3'); $^{19}F$ NMR (376.5 MHz, $CDCl_3$): -70.73 (s, 3F, $CF_3$). Anal. calcd for $C_{16}H_{13}F_3N_4O_3$ (366.3): C 52.46, H 3.58, N 15.30; found C 52.67, H 3.63, N 15.02. FAB MS, *m/z* (rel.%): 367 (100) [M+H].

**Cleavage of *O*-benzoyl/*O*-(*p*-toluoyl) protecting groups:** *General procedure*

To the solution of the corresponding protected derivative **9, 10** or **13** (1 mmol) in methanol (20 ml), a catalytic amount of NaOMe (1M solution in methanol, 0.1 ml) was added. The reaction mixture was stirred at room temperature overnight and concentrated. Column chromatography of the residue (ethyl acetate) on silica gel followed by crystallization (isopropanol/toluene/heptane) afforded the corresponding products **1** or **14**. Simple crystallization (ethanol/petrolether) afforded pure compound **17**.

**9-(β-D-Ribofuranosyl)-6-(trifluoromethyl)purine (1):** yield 0.20 g (63%) of colorless solid, m.p. 173-175 °C (ref.[11] 176 °C, $iPr_2O$/iPrOH; ref.[12] 145-148 °C, iPrOH/heptane/cyclohexane), $[\alpha]_D^{20}$ -8.78 (c 0.5, DMF). IR $\nu_{max}$ (KBr) 3444 br, 3372 br, 1601, 1499, 1462, 1405, 1331, 742 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): 9.19 (s, 1H, H-2), 9.14 (s, 1H, H-8), 6.14 (d, 1H, *J*(1',2') = 5.0, H-1'), 5.63 (d, 1H, *J* = 5.7, OH-2'), 5.30 (d, 1H, *J* = 5.3, OH-3'), 5.13 (t, 1H, *J* = 5.4, OH-5'), 4.63 (ddd, 1H, *J*(2',1') = 5.0, *J*(2',OH) = 5.7, *J*(2',3') = 4.8, H-2'), 4.24 (ddd, 1H, *J*(3',2') = 4.8, *J*(3',OH) = 5.3, *J*(3',4') = 4.1, H-3'), 4.03 (ddd, 1H, *J*(4',3') = 4.1, J(4', 5') = 3.8, H-4'), 3.73 (m, 1H, H-5'a), 3.63 (m, 1H, H-5'b); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): 153.60 (C-4), 151.58 (C-2),

147.90 (C-8), 142.53 (q, *J*(CF)=36, C-6), 130.09 (C-5), 120.77 (q, *J*(CF)=274, $CF_3$), 88.09 (C-1'), 85.69 (C-4'), 73.98 (C-2'), 69.97 (C-3'), 60.89 (C-5'); $^{19}F$ NMR (376.5 MHz, DMSO-$d_6$): -64.51 (s, 3F, $CF_3$). Anal. calcd for $C_{11}H_{11}F_3N_4O_4$ (320.2): C 41.26, H 3.46, N 17.50; found C 41.62, H 3.51, N 17.40. FAB MS, *m/z* (rel.%): 321 (45) [M+H].

**9-(2-Deoxy-β-D-ribofuranosyl)-6-(trifluoromethyl)purine (14):** yield 0.11 g (37%) of colorless solid, m.p. 109-112 °C, $[\alpha]_D^{20}$ +1.28 (c 0.4, DMF). $^1H$ NMR (500 MHz, DMSO-$d_6$): 9.16 (s, 1H, H-2), 9.07 (s, 1H, H-8), 6.55 (dd, 1H, *J*(1',2'a) = 6.4, *J*(1',2'b) = 6.2, H-1'), 5.39 (d, 1H, *J* = 4.2, 3'-OH), 4.97 (t, 1H, *J* = 5.3, 5'-OH), 4.48 (m, 1H, H-3'), 3.92 (m, 1H, H-4'), 3.64 (ddd, 1H, *J*(5'a,5'b) = 10.1, *J*(5'a,4)=*J*(5'a,OH) = 5.3, H-5'a), 3.55 (ddd, 1H, *J*(5'a,5'b) = 10.1, *J*(5'b,4) = *J*(5'b,OH) = 5.3, H-5'b), 2.81 (ddd, 1H, *J*(2'a,2'b) = 13.1, *J*(2'a,1') = 6.4, *J*(2'a,3') = 6.2, H-2'a), 2.42 (ddd, 1H, *J*(2'b,2'a) = 13.1, *J*(2'b,1') = 6.2, *J*(2'b,3') = 4.3, H-2'b); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): 153.32 (C-4), 151.42 (C-2), 147.93 (C-8), 142.50 (C-6), 130.10 (C-5), 119 ($CF_3$) , 88.10 (C-4'), 84.10 (C-1'), 70.26 (C-3'), 61.20 (C-5'), 39.36 (C-2'); $^{19}F$ NMR (376.5 MHz, DMSO-$d_6$): -64.51 (s, 3F, $CF_3$). Anal. calcd for $C_{11}H_{11}F_3N_4O_3$ (304.2): C 43.43, H 3.64, N 18.42; found C 43.27, H 3.99, N 18.55. FAB MS, *m/z* (rel.%): 305 (50) [M+H].

**9-[(2-Hydroxyethyl)oxymethyl]-6-(trifluoromethyl)purine (17):** yield 0.23 g (88%) of yellowish crystals, m.p. 123-125 °C. $^1H$ NMR (500 MHz, DMSO-$d_6$): 9.19 (s, 1H, H-2), 9.03 (s, 1H, H-8), 5.79 (s, 2H, H-1'), 4.67 (t, 1H, *J* = 4.4, OH), 3.59 (t, 2H, *J*(2',3') = 4.9, H-2'), 3.48 (m, 2H, H-3'); $^{13}C$ NMR (125.8 MHz, DMSO-$d_6$): 154.12 (C-4), 151.87 (C-2), 150.00 (C-8), 142.77 (q, J(C-$CF_3$)=28.8, C-6), 129.53 (C-5), 120.83 (q, J(CF)=219, $CF_3$), 73.02 (C-1'), 71.31 (C-2'), 59.86 (C-3'); $^{19}F$ NMR (376.5 MHz, DMSO-$d_6$): -64.51 (s, 3F, $CF_3$). Anal. calcd for $C_9H_9F_3N_4O_2$ (262.2): C 41.23, H 3.46, N 21.37; found C 41.16, H 3.46, N 21.21. FAB MS, *m/z* (rel.%): 263 (70) [M+H].

**9-(β-D-Arabinofuranosyl)-6-(trifluoromethyl)purine (15)**

Protected nucleoside **11** (0.59 g, 1 mmol) was hydrogenated in methanol (90 ml) over 10% palladium on charcoal (0.25 g) under stirring for 4 h at room temperature (catalysed by 40% $PdCl_2$ in HCl). The mixture was filtered through a pad of Celite, the catalyst was washed with hot methanol and the filtrate was evaporated. Collumn chromatography of the residue (ethyl acetate) on silica gel followed by crystallization (isopropanol/toluene/heptane) afforded pure compound **15**, yield 0.12 g (38%) of white crystals, m.p. 201-203 °C, $[\alpha]_D^{20}$ +30.20 (c 0.4, DMF). $^1H$ NMR (500 MHz, DMSO-$d_6$): 9.16 (s, 1H, H-2), 8.95 (s, 1H, H-8), 6.50 (d, 1H, *J*(1',2') = 5.1, H-1'), 5.68 (d, 1H, *J* = 5.3, OH-2'), 5.63 (d, 1H, *J* = 4.6, OH-3'), 5.15 (t, 1H, *J* = 5.1, OH-5'), 4.30 (ddd, 1H, *J*(2',1') = 5.1, *J*(2',OH) = 5.3, *J*(2',3') = 5.0, H-2'), 4.19 (ddd, 1H, *J*(3',2') = 5.0, *J*(3',OH) = 4.6, *J*(3',4') = 4.9, H-3'), 3.87 (m, 1H, H-4'), 3.72 (m, 2H, H-5'); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): 153.57 (C-4), 151.43 (C-2), 148.65 (C-8), 142.25 (q, *J*(CF)=30, C-6), 129.47 (C-5), 121.10 (q, *J*(CF)=276, $CF_3$), 84.52 (C-

4'), 84.37 (C-1'), 75.69 (C-2'), 74.36 (C-3'), 69.34 (C-5'); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$): -64.45 (s, 3F, $CF_3$). Anal. calcd for $C_{11}H_{11}F_3N_4O_4$ (320.2): C 41.26, H 3.46, N 17.50; found C 41.04, H 3.62, N 17.46. FAB MS, *m/z* (rel.%): 321 (65) [M+H].

**9-(2,3-Dihydroxypropyl)-6-(trifluoromethyl)purine (16)**

A mixture of isopropylidene derivative **12** (0.14 g, 0.46 mmol), Dowex 50 X 8 ($H^+$ form, *ca* 250 mg), methanol (10 ml) and water (1 ml) was refluxed for 30 min, then filtered while hot and the resin washed with methanol. The combined filtrates were evaporated and the residue was purified by column chromatography (methanol/chloroform) to give amorphous white solid, yield 0.11 g (91%). $^1$H NMR (500 MHz, DMSO-$d_6$): 9.13 (s, 1H, H-2), 8.79 (s, 1H, H-8), 5.17 (d, 1H, $J$ = 5.09, 2'-OH), 4.90 (brs, 1H, 3'-OH), 4.53 (dd, 1H, $J$(1'a,2') = 3.4, $J$g = 14.0, H-1'a), 4.24 (dd, 1H, $J$(1'b,2') = 8.7, $J$g = 14.0, H-1'b), 3.93 (m, 1H, H-2'), 3.48 (m, 1H, H-3'a), 3.39 (m, 1H, H-3'b); $^{13}$C NMR (100.6 MHz, DMSO-$d_6$): 154.15 (C-4), 151.14 (C-2), 150.48 (C-8), 143 (q, J(C-$CF_3$)=35.6, C-6), 129.44 (C-5), 120.90 (q, J(CF)=277, $CF_3$), 69.23 (C-2'), 63.45 (C-3'), 47.17 (C-1'); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$): -64.42 (s, 3F, $CF_3$). Anal. calcd for $C_9H_9F_3N_4O_2$ (262.2): C 41.23, H 3.63, N 21.37; found C 41.05, H 3.72, N 21.14. FAB MS, *m/z* (rel.%): 263 (100) [M+H].

**2-Amino-9-(β-D-ribofuranosyl)-6-(trifluoromethyl)purine (19)**

A mixture of 2-amino-6-(trifluoromethyl)purine[12] (60 mg, 0.3 mmol), sodium hydride (11 mg, 0.3 mmol, 60% dispersion in mineral oil) and acetonitrile (5 ml) was sonicated for 10 min and then stirred for 30 min. at 70 °C. After cooling to room temperature 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl chloride[14] (**4**, 1.5 eq., 216 mg, 0.45 mmol) was added and stirring continued at room temperature for 48 h. The solvent was evaporated and collumn chromatography of the residue (chloroform) on silica gel afforded crude intermediate. To the solution of this protected riboside in methanol (5 ml), a catalytic amount of NaOMe (1M solution in methanol, 0.03 ml) was added. The reaction mixture was stirred at room temperature for 6 h and concentrated. Chromatography of the residue (methanol/ethyl acetate) on silica gel afforded riboside **19**, yield 20 mg (20%). $^1$H NMR (500 MHz, DMSO-$d_6$): 8.53 (s, 1H, H-8), 7.13 (brs, 2H, $NH_2$), 5.87 (d, 1H, $J$(1',2') = 5.6, H-1'), 5.50 (d, 1H, $J$ = 5.4, OH-2'), 5.20 (d, 1H, $J$ = 4.3, OH-3'), 5.05 (t, 1H, $J$ = 5.1, OH-5'), 4.51 (m, 1H, H-2'), 4.14 (m, 1H, H-3'), 3.92 (m, 1H, H-4'), 3.65 (m, 1H, H-5'a), 3.56 (m, 1H (H-5'b); $^{19}$F NMR (376.5 MHz, DMSO-$d_6$): -65.25 (s, 3F, $CF_3$). FAB MS, *m/z* (rel.%): 336 (35) [M+H]. HRMS (FAB): $MH^+$, found 336.0912; $C_{11}H_{13}F_3N_5O_4$ requires 336.0920.

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