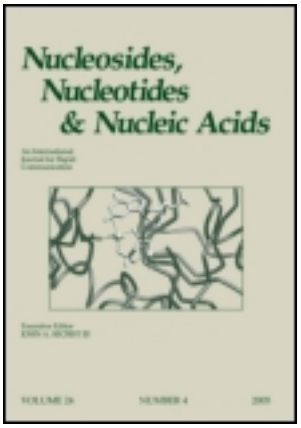

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SYNTHESIS OF NEW NUCLEOSIDE ANALOGUES COMPRISING A GEMINAL DIFLUOROCYCLOPROPANE MOIETY AS POTENTIAL ANTIVIRAL/ANTITUMOR AGENTS

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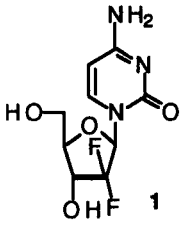
ABSTRACT. Geminal difluorocyclopropane analogues of nucleosides **7a** - **7e** were synthesized. Compounds **7a** and **7c** - **7e** were obtained by alkylation of nucleic acid bases or their appropriate precursors with *(cis)*-1-benzyloxymethyl-2-bromomethyl-3,3-difluorocyclopropane (**8**). Analogue **7b** was prepared by hydrolysis of 2-amino-6-chloropurine derivative **7e**. Compounds **7a** - **7d** did not exhibit any antiviral activity against HCMV, HSV-1, HSV-2, EBV, VZV, HBV and HIV-1 or antitumor effects against murine leukemia L1210, mouse tumors PO3 or C38 and human tumor H15.

Nucleoside analogues carrying a fluorine substitution in the heterocyclic or carbohydrate moiety provided a plethora of biologically active compounds[1-3]. Nevertheless, examples of biologically active analogues of nucleosides or nucleotides comprising a difluoromethylene function CF_2 are rather scant. The most notable example is 2'-deoxy-2',2'-difluorocytidine (**1**, gemcitabine, Gemzar), a powerful antitumor agent.[4] It was also reported that geminal difluoromethylene moiety is a close steric and electronic mimic of oxygen atom.[1] Indeed, 9-(5',5'-difluoro-5'-phosphonopentyl)guanine **2**, an acyclic analogue of dGMP, is an effective inhibitor of purine nucleoside phosphorylase[5]. This concept was also applied in the area of acyclic nucleoside analogues. Thus, difluoromethylene mimic of antiherpetic drug acyclovir (Zovirax), compound **3**, was found[6] to have antiherpetic activity albeit lower than the parent drug.

Further related to this work, the oxirane analogue[7] **4** also exhibited some anti-herpesvirus potency. However, this compound was not completely stable under the conditions of antiviral assays. More stable cyclopropane analogues[7,8] **5** and **6** related to oxirane **4** exhibited potent effects against herpesviruses α.



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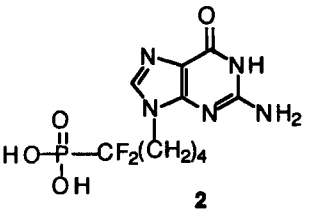

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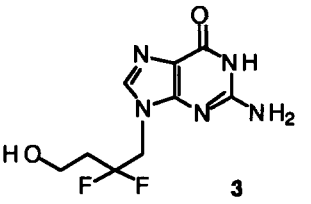

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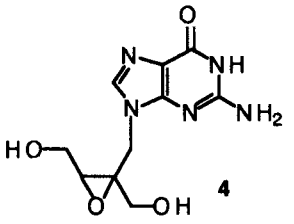

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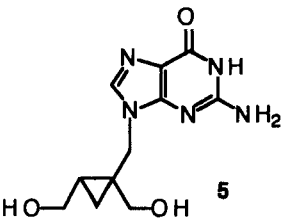

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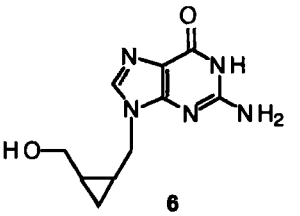

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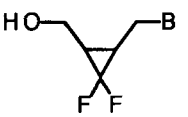


7

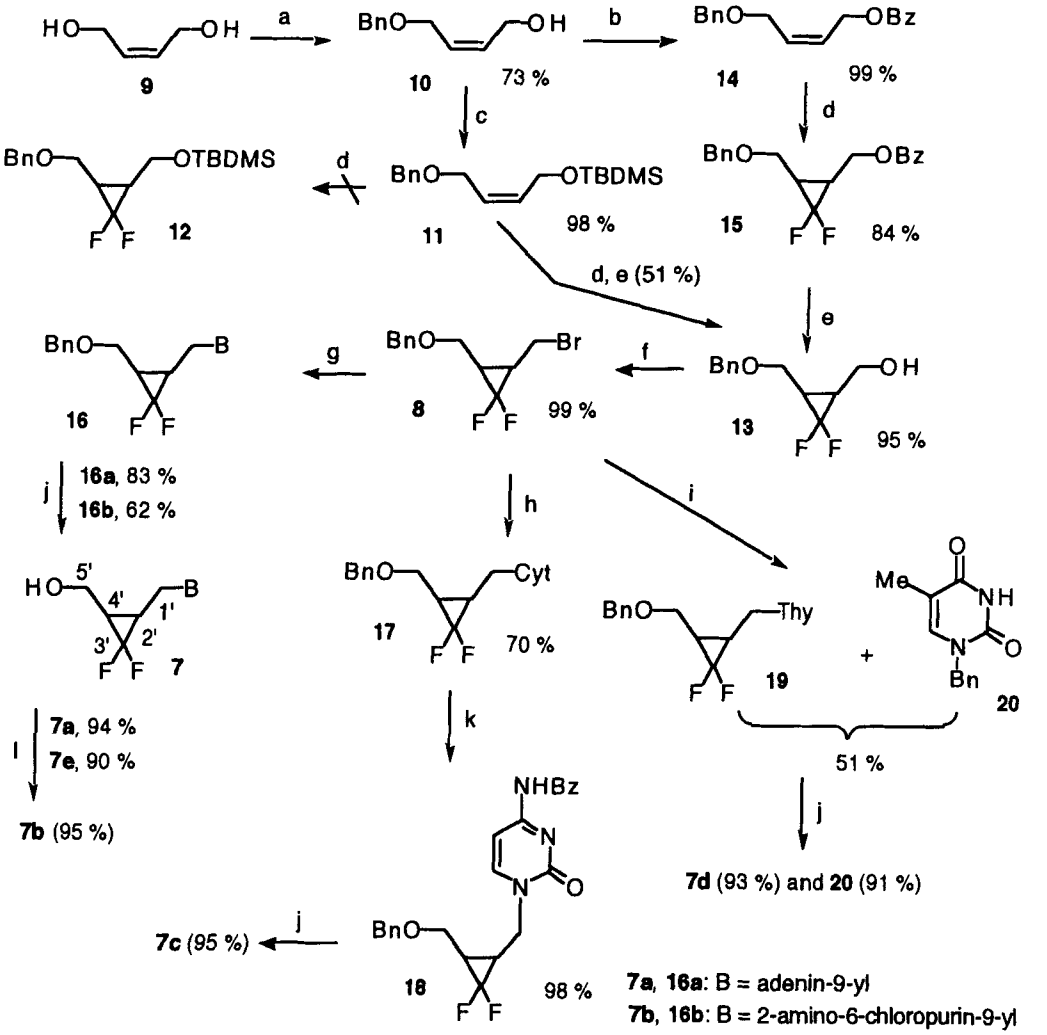
7a: B = adenin-9-yl
7b: B = guanin-9-yl
7c: B = cytosin-1yl
7d: B = thymin-1-yl
7e: B = 2-amino-6-chloropurin-9-yl

All these findings formed the basis for an assumption that cyclopropane analogues of acyclovir with a geminal difluoromethylene moiety such as **7a** - **7d** will be more stable than the corresponding oxirane derivatives such as **4**. In addition, geminal difluorocyclopropane moiety will be a close steric and electronic mimic of oxirane ring. In this communication we describe the synthesis and investigation of antiviral/antitumor activity of geminal difluorocyclopropane analogues **7a** - **7d**.

RESULTS AND DISCUSSION

At the outset, elaboration of an alkylating reagent which could be employed for alkylation of any desired nucleic acid base or suitable precursor was considered as the most convenient approach for synthesis of analogues **7a** - **7d**. Such an agent, difluorocyclopropane derivative **8**, was obtained as follows (Scheme 1). Commercially available (*cis*)-2-butene-1,4-diol (**9**) was converted to a monobenzyl ether **10** by reaction with sodium hydride followed by treatment with benzyl bromide and tetrabutylammonium iodide (NBu4I) in tetrahydrofuran[9] (51 % yield). Using a 200 % molar excess of **9** the yield of **10** was increased to 73 %. These results compare favorably with the previously described two-step method[10,11] starting from cyclic benzaldehyde acetal of **9**. Compound

Scheme 1

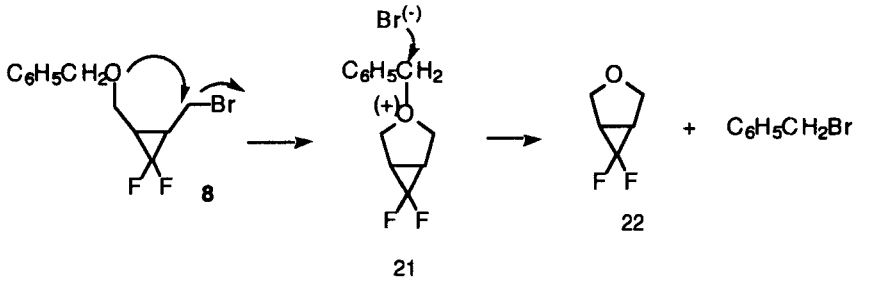


a. 1. NaH, THF. 2. Bu_4NI, BnBr.
b. BzCl, pyridine.
c. TBDMS, imidazole, DMF.
d. ClF_2CCO_2Na, diglyme, 180°C.
e. K_2CO_3, MeOH - H_2O.
f. CBr_4, Ph_3P, CH_2Cl_2.
g. B-H, K_2CO_3, DMF, Δ.
h. 1. N^4-Acetylcytosine, K_2CO_3, DMF, Δ. 2. H_2O, Δ.
i. 2,4-Bis-O-TMS-5-methylpyrimidine, MeCN, Δ, 7 days.
j. 1.BCl_3, CH_2Cl_2, -78°C. 2. NH_3, MeOH or $NaHCO_3$, MeOH.
k. Bz_2O, EtOH, Δ.
l. 1. 80 % HCO_2H, Δ. 2. NH_3, MeOH.

10 was converted to a fully protected diol **11** by reaction with tert.-butylsilyldimethylsilyl chloride (TBDMSCl) and imidazole[12] in DMF. Attempted addition of difluorocarbene generated from sodium chlorodifluoroacetate in diglyme at 180°C according to the described procedure[13] (the reported yield was 95 %) failed to give any difluorocyclopropane intermediate **12**. The crude reaction product contained only benzyl derivative **13** contaminated with 5 - 10 % of the chlorodifluoroacetate ester (tentative structure). Treatment of the reaction mixture with K_2CO_3 in aqueous methanol gave a 51 % yield of **13**. This result showed that the TBDMS group did not survive the conditions of the difluorocarbene addition. Therefore, compound **10** was converted to benzoate **14**. Addition of difluorocarbene afforded smoothly intermediate **15** in 84 % yield. Debenzoylation with K_2CO_3 in aqueous methanol furnished compound **13** (95 %). The latter was transformed to the corresponding bromo derivative **8** by reaction[14] with CBr_4 and $P(C_6H_5)_3$ in CH_2Cl_2 (99 %).

Alkylation of nucleic acid bases with reagent **8** was performed using procedures previously elaborated for synthesis of methylenecyclopropane analogues.[15,16] Thus, reaction of adenine with **8** using K_2CO_3 in DMF at 85°C gave intermediate **16a** (83 %). Debenzylation was effected with BCl_3 in CH_2Cl_2 and subsequent treatment with NH_3 in methanol as described for an allenic analogue[17] to afford compound **7a** (94 %). In a similar vein, alkylation of 2-amino-6-chloropurine with reagent **8** led to protected derivative **16b** (62 %). After debenzylation, analogue **7e** was obtained in 90 % yield. Hydrolysis of **7e** with 80 % formic acid followed by treatment with NH_3 in MeOH[15] gave guanine analogue **7b** (95 %). Alkylation with reagent **8** was also employed in the pyrimidine series. Thus, reaction of N^4-acetylcytosine with **8** under the conditions described for adenine analogue **16a** gave, after deacetylation, protected intermediate **17** in 70 % yield. Attempted debenzylation with BCl_3 was not successful because of a poor solubility of **17** in CH_2Cl_2. Therefore, compound **17** was benzoylated using benzoic anhydride in refluxing ethanol as described for N^4-benzoylcytallene[18] to give N^4-benzoyl derivative **18** (98 %). The latter was smoothly debenzylated using BCl_3 and subsequent debenzoylation furnished the desired analogue **7c** in 95 % yield. Alkylation of thymine with **8** also followed the procedure described for synthesis of the corresponding methylenecyclopropane analogues.[16] The 2,4-bis-O-trimethylsilyl-5-methylpyrimidine was refluxed with reagent **8** in acetonitrile for 7 days to give a mixture of protected analogue **19** and N^1-benzylthymine (**20**) in the ratio of 1.5 : 1 and 51 % yield, which were inseparable by column chromatography on silica gel. Deprotection with BCl_3 and subsequent chromatography afforded N^1-benzylthymine (**20**) in 91 % yield (the N-benzyl group was apparently stable) and analogue **7d** (93 %). It should be noted that a similar N-benzylation was observed during alkylation of thymine with 4'-benzyloxy-3'-

Scheme 2



benzyloxymethylbutyl bromide under basic catalysis[19]. In our case, this side-reaction is best rationalized in terms of Scheme 2. The cyclic oxonium intermediate **21** formed from **8** is attacked by bromide ion to give benzyl bromide and bicyclic derivative **22**. Benzyl bromide then competes with reagent **8** in alkylation of the silylated thymine. Alternately, intermediate **21** may also serve as a benzylating agent.

The structures of analogues **7a** - **7e** were fully supported by spectroscopic data. The UV spectra are in agreement with the assignment as N^9-isomers for purines **7a**, **7b** and **7e** or N^1-isomers for pyrimidines **7c** and **7d**. No appreciable amounts of other isomers were detected in appropriate crude products.

Analogues **7a** - **7d** were tested against the following viruses: HCMV, HSV-1, HSV-2, EBV, VZV, HBV and HIV-1. The details of the assays were described previously.[15] The antitumor zone assays[20] were performed with murine leukemia L1210, mouse tumors PO3 or C38 and human tumor H15. Neither of the analogues exhibited a significant antiviral effect, antitumor activity or cytotoxicity in any of these assays at the highest concentration tested (100 μM, EBV/H-1 50 μM and HBV 10 μM). The lack of biological potency can be explained by a poor substrate ability toward relevant viral or cellular kinases or that the phosphorylated metabolites are poor inhibitors of viral or cellular polymerases. Adenine derivative **7a** was not a substrate for adenosine deaminase from calf intestine.

EXPERIMENTAL SECTION

General Methods. See[15]. The NMR spectra were determined at 300 or 400 MHz (^{1}H), 75 or 100 MHz (^{13}C) and 282 or 376 MHz (^{19}F) in CD_3SOCD_3 unless stated otherwise. For fast atom bombardment mass spectra (FAB-MS) thioglycerol (TG) matrix was used.

***(cis)*-4-Benzyloxy-2-buten-1-ol (10).** Sodium hydride (50 % in mineral oil, 5.00 g, 0.11 mol) was added in five equal portions every 5 minutes with stirring and ice-cooling

under N_2 to a solution of (*cis*)-2-buten-1,4-diol (**9**, 9.25 g, 0.11 mol) in THF (100 mL). The suspension was then stirred for 3 h at room temperature. The $(Bu)_4NI$ (387 mg, 1.1 mmol) followed by benzyl bromide (12.48 mL, 0.11 mol) were then added and the mixture was stirred for another 16 h. The insoluble portion was filtered off using a Celite pad and it was washed with CH_2Cl_2 (3 x 20 mL). The organic phase was evaporated and the residue was chromatographed on a silica gel column using hexane - ethyl acetate (7 : 3 → 2 : 3) to give product **10** as an oil (9.36 g, 50 %).

In another experiment (0.3 mol scale based on benzyl bromide), using 0.9 mol of diol **9** product **10** was obtained in 73 % yield after distillation (bp 96-98°C/0.2 torr). ^1H NMR ($CDCl_3$) δ 2.62 (br s, 1 H, OH), 4.13 (dd, 2 H, ^3J = 6.0 Hz, ^4J = 0.6 Hz) and 4.07 (dd, 2 H, ^3J = 6.0 Hz, ^4J = 0.9 Hz, =CHC**H**$_2$O), 4.52 (s, 2 H, C**H**$_2$C$_6$H$_5$), 5.67-5.84 (m, 2 H, ^3J = 6.0 Hz, ^4J = 1.2 Hz, HC=CH), 7.26-7.39 (m, 5 H, C_6H_5).

(*cis*)-1-Benzyloxy-4-(*tert*-butyldimethyl)silyloxy-2-butene (11). DMF was evaporated in vacuo from a solution of (*cis*)-4-benzyloxy-2-buten-1-ol (**10**, 9.36 g, 52.5 mmol) and imidazole (5.36 g, 78.8 mmol) in DMF (20 mL). The residue was redissolved in DMF (30 mL) and tert-butyldimethylsilyl chloride (9.50 g, 63 mmol) was added with stirring at room temperature. The mixture was stirred for 16 h. Volatile components were removed in vacuo and the residue was partitioned between hexane (150 mL) and water (50 mL). The aqueous phase was extracted with hexane (20 mL). The combined hexane pahses were washed with HCl (1 M, 50 mL), water (50 mL), saturated $NaHCO_3$ (50 mL), water (50 mL), brine (50 mL) and they were dried (Na_2SO_4). After evaporation, the residue was chromatographed on a silica gel column using hexane - ethyl acetate (98 : 2 → 95 : 5) to afford silyl ether **11** (15.05 g, 98 %) as an oil. ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, **Me**$_2$^{t}BuSi), 0.92 (s, 9 H, ^{t}Bu), 4.00 (d, 2 H, ^3J = 6.0 Hz, C**H**$_2$OSi), 4.24 (d, 2 H, ^3J = 5.7 Hz, C**H**$_2$OBn), 4.53 (s, 2 H, C**H**$_2$Ph), 5.62-5.79 (m, 2 H, apparent ^3J = 5.9 Hz, ^4J = 0.9 Hz, H alkene), 7.26-7.39 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): -5.21 (**Me**$_2$^{t}BuSi), 18.31 (Si**C**Me$_3$), 25.91 (C**Me**$_3$), 59.56 (**C**H$_2$OSi), 65.83 (**C**H$_2$OBn), 126.81 and 127.63 (C alkene); benzyl: 72.22 (CH_2), 127.80 (C_{ortho}), 128.40 (C_{meta}), 132.90 (C_{para}), 138.21 (C_{ipso}).

(*cis*)-1-Benzoyloxy-4-benzyloxy-2-butene (14). Benzoyl chloride (2.90 mL, 25 mmol) was added into a solution of (*cis*)-4-benzyloxy-2-buten-1-ol (**10**, 1.78 g, 10 mmol) in pyridine (10 mL) at room temperature with stirring which was continued for 16 h. Water (3 mL) was added and the resulting mixture was stirred for 24 h. Volatile components were removed in vacuo and the residue was partitioned between hexane (150 mL) and water (50 mL). The organic phase was washed with HCl (1 M, 2 x 50 mL), water (50 mL), Na_2CO_3 (5 %, 2 x 50 mL), brine (50 mL) and it was dried (Na_2SO_4). After evaporation, the residue was chromatographed on a silica gel column using hexane - ethyl acetate (9 : 1) to give product **14** as an oil (2.80 g, 99 %). IR (neat) 1715 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$)

δ 4.23 (d, 2 H, ^3J = 4.8 Hz, **CH$_2$**OBn), 4.57 (s, 2 H, **CH$_2$**Ph), 4.91 (d, 2 H, ^3J = 5.7 Hz, **CH$_2$**OBz), 5.83-5.97 (m, 2 H, alkene H), 7.27-7.42 (m, 5 H, OCH$_2$**Ph**), 7.42-7.50(m, 2 H) and 7.55-7.62 (m, 1 H) and 8.06-8.11 (m, 2 H, Bz). ^{13}C NMR 60.80 (CH$_2$OBz), 65.75 (CH$_2$OBn), 126.73 and 127.78 (C alkene); benzyl: 72.48 (CH$_2$), 127.85 (C$_{ortho}$), 128.41 (C$_{meta}$), 131.08 (C$_{para}$), 138.03 (C$_{ipso}$); benzoyl: 128.47 (C$_{ortho}$), 129.65 (C$_{meta}$), 130.12 (C$_{para}$), 133.04 (C$_{ipso}$), 166.39 (C=O).

(*cis*)-1-Benzoyloxymethyl-3-benzyloxymethyl-2,2-difluorocyclopropane (15). A suspension of sodium chlorodifluoroacetate (7.62 g, 50 mmol) in diglyme (17 mL) was added into a solution of (*cis*)-1-benzoyloxy-4-benzyloxy-2-butene (**14**, 1.41 g, 5 mmol) in diglyme (5 mL) heated at 180°C (bath temperature) with stirring over 4.5 h using a syringe pump. The mixture was then refluxed for 3 h. After cooling, the solvent was evaporated in vacuo. Hexane (150 mL) was added to the residue, the insoluble portion was filtered off using a Celite pad and it was washed with the same solvent (3 x 10 mL). The hexane phase was washed with water (50 mL) and brine (50 mL) whereupon it was concentrated in vacuo. Water (20 mL) was added followed by solid KMnO4 in portions (total 510 mg) at 0°C with stirring until the pink color persisted for 1.5 h. The solids were filtered off using a Celite pad and they were washed by sonication with hexane (8 x 25 mL). The organic phase was dried (Na$_2$SO$_4$), evaporated and the residue was chromatographed on silica gel using hexane - ethyl acetate (95 : 5 → 9 : 1) to give difluorocyclopropane derivative **15** (1.39 g, 84 %) as an oil. IR (neat) 1740 (C=O), 1495, 1295, 1115, 1090, 1040, 730 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.09-2.32 (m, 2 H, apparent J = 8.0 Hz, J = 1.6 Hz, cyclopropyl H), 3.69-3.80 (m, 2 H, apparent J = 8.0 Hz, J = 1.6 Hz, **CH$_2$**OBn), 4.44-4.60 (m, 2 H, apparent J = 2.4 Hz, **CH$_2$**OBz), 4.56 (AB, 2 H, J_{AB} = 12.0 Hz, OC**H$_2$**Ph), 7.30-7.40 (m, 5 H, OCH$_2$**Ph**), 7.44-7.50 (m, 2 H) and 7.58-7.63 (m, 1 H) and 8.05-8.09 (m, 2 H, Bz). ^{13}C NMR 24.99 (t, ^2J_F = 10.4 Hz) and 26.44 (t, ^2J_F = 10.4 Hz, cyclopropyl CH), 59.55 (d, ^3J_F = 6.0 Hz, **CH$_2$**OBz), 64.00 (d, ^3J_F = 5.2 Hz, **CH$_2$**OBn), 114.25 (dd, ^1J_F = 288.1 Hz, ^1J_F = 281.4 Hz, CF$_2$); benzyl: 74.12 (CH$_2$), 128.88 (C$_{ortho}$), 128.97 (C$_{para}$), 129.55 (C$_{meta}$), 138.68 (C$_{ipso}$); benzoyl: 129.61 (C$_{ortho}$), 130.81 (C$_{meta}$), 130.87 (C$_{para}$), 134.87 (C$_{ipso}$), 167.45 (C=O). ^{19}F NMR -124.60 (dt, ^2J_F = 163.4 Hz, $^3J_{cis\text{-}H}$ = 13.0 Hz), -150.19 (d, ^2J_F = 164.9 Hz). EI-MS 332 (M, 0.9), 227 (M - Bz, 3.3), 225 (M - OBn, 6.3), 210 (M - OBz - H, 7.9), 206 (M - OBn - F, 17.3), 122 (BzOH, 11.9), 105 (Bz, 100.0), 91 (Bn, 89.5), 77 (Ph, 27.9); CI-MS 333 (M + H, 7.7), 225 (M - OBn, 4.7), 211 (M - OBz, 15.7), 105 (Bz, 25.9), 91 (Bn, 100); HRMS: Calcd. for C$_{19}$H$_{18}$F$_2$O$_3$ (M): 332.1224. Found: 332.1221. Anal. Calcd. for C$_{19}$H$_{18}$F$_2$O$_3$: C, 68.67; H, 5.46; F, 11.43. Found: C, 68.84; H, 5.60; F, 11.51.

(*cis*)-1-Benzyloxymethyl-2,2-difluoro-3-hydroxymethylcyclopropane (13). Method A. From Benzoate 15. A mixture of compound **15** (15.87 g, 47.8 mmol)

and K_2CO_3 (6.60 g, 47.8 mmol) in MeOH - H_2O (9 : 1, 160 mL) was stirred at room temperature for 16 h. It was then partitioned between ethyl acetate and water (200 mL each). The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with Na_2CO_3 (5 %, 3 x 100 mL), water (2 x 100 mL), brine (70 mL) and it was dried (Na_2SO_4). After evaporation, the residue was chromatographed on silica gel using hexane - ethyl acetate (85 : 15 → 7 : 3) to give product **13** (10.36 g, 95 %) as an oil. The ^1H and ^{13}C NMR spectra corresponded to those described[13].

Method B. From TBDMS Derivative 11. The reaction was performed as described[13] using compound **11** (13.57 g, 46.39 mmol) and sodium chlorodifluoroacetate (70.74 g, 464 mmol) to give product **13** contaminated by its chlorodifluoroacetate (tentatively assigned, 5-10 %) after chromatography on silica gel using hexane - ethyl acetate as eluent as described above. Treatment of the crude product (7.40 g) with K_2CO_3 in MeOH - H_2O as described above afforded compound **13** (5.35 g, 51 %). The ^1H NMR spectrum was identical with that of the product **13** prepared by method A.

***(cis)*-1-Benzyloxymethyl-2-bromomethyl-3,3-difluorocyclopropane (8).** Triphenylphosphine (4.31 g, 16.4 mmol) was added to a solution of compound **13** (2.53 g, 11.1 mmol) and CBr_4 (6.19 g, 18.65 mmol) in CH_2Cl_2 (26 mL) at room temperature with stirring in five equal portions and 5 min intervals. After evaporation, the residue was passed through a short column of silica gel (2.5 x 10 cm) eluted with CH_2Cl_2 (200 mL), to give a crude bromo derivative **8**. This product was rechromatographed using hexane - ethyl acetate (98 : 2 → 9 : 1) to give compound **8** (3.18 g, 98.5 %) as an oil. IR (neat) 1480, 1300, 1220, 1100, 1040, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (ddtd, 1 H, $^3J_{cis\text{-}F}$ = 13.6 Hz, $^3J_{cis\text{-}H}$ = 11.0 Hz, ^3J_H = 7.8 Hz, $^3J_{trans\text{-}F}$ = 1.9 Hz, C**H**CH_2Br), 2.25 (tddd, 1 H, $^3J_{cis\text{-}F} = {}^3J_{cis\text{-}H}$ = 12.0 Hz, ^3J_H = 8.4 Hz, ^3J_H = 7.4 Hz, $^3J_{trans\text{-}F}$ = 1.5 Hz, C**H**CH_2OBn), 3.45 (tm, 1 H, $^2J = {}^3J$ = 9.8 Hz) and 3.53 (ddd, 1 H, ^2J_H = 10.8 Hz, ^3J_H = 7.6 Hz, ^4J_F = 3.2Hz, C**H$_2$**OBn), 3.70 (AB x q, 2 H, J_{AB} = 12.4 Hz, ^3J_H = ^4J_F = 1.6 Hz, CH_2Br), 4.56 (AB, 2 H, J_{AB} = 12.0 Hz, OC**H$_2$**Ph), 7.32-7.43 (m, 5 H, Ph). ^{13}C NMR 25.36 (d, ^3J_F = 5.9 Hz, CH_2Br), 28.15 (t, ^2J_F = 10.0 Hz) and 28.62 (t, ^2J_F = 10.8 Hz, cyclopropyl CH), 63.35 (d, ^3J_F = 5.2 Hz, CH_2OBn), 114.54 (dd, ^1J_F = 291.1 Hz, ^1J_F = 282.2 Hz, CF_2); benzyl: 74.16 (CH_2), 128.91 (C_{ortho}), 129.09 (C_{para}), 129.66 (C_{meta}), 138.62 (C_{ipso}). ^{19}F NMR -124.36 (dt, ^2J_F = 163.4 Hz, $^3J_{cis\text{-}H}$ = 12.2 Hz), -151.89 (d, ^2J_F = 163.4 Hz). EI-MS 291 and 289 (M + H, 0.6, 0.5), 211 (M - Br, 1.6), 191 (M - Br - F - H, 0.3), 181 (3.3), 172 and 170 (M - CH_2OBn + H, 0.5, 0.5), 161 (1.5), 105 (6.1), 91 (Bn, 100); CI-MS 293 and 291 (M + H, 6.0, 7.4), 211 (M - Br, 6.2), 181 (9.7), 91 (Bn, 100). HRMS Calcd. for $C_{12}H_{13}{}^{79}BrF_2O$ (M) 290.0118. Found: 290.0113.

***(cis)*-9-[(2-Benzyloxymethyl-3,3-difluorocyclopropyl)methyl]adenine (16a).** A mixture of adenine (405 mg, 3 mmol), compound **8** (582 mg, 2 mmol) and

K_2CO_3 (1.1 g, 8 mmol) in DMF (18 mL) was heated with stirring under N_2 at 85°C for 4 h. After cooling, the insoluble portion was filtered off using a Celite pad and it was washed with DMF (3 x 5 mL). The organic phase was evaporated in vacuo and the residue was chromatographed on silica gel using CH_2Cl_2 - MeOH (98 : 2 → 94 : 6) to give product **16a** (573 mg, 83%), mp 130-132°C. UV max (EtOH) 260 nm (ε 14,500), 210 (ε 26,100). IR (KBr) 3380 and 3180 (NH_2), 1665, 1620, 1590, 1500, 1265, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12-2.24 (m, 1 H, H4'), 2.28-2.39 (m, 1 H, H2'), 3.68 (td, 1 H, $^2J = {}^3J$ = 9.9 Hz, $^4J_{5',F}$ = 1.5 Hz) and 3.84 (ddd, 1 H, ^2J = 10.8 Hz, ^3J = 6.4 Hz, $^4J_{5',F}$ = 2.0 Hz, H5'), 4.24 (dd, 1 H, ^2J = 14.8 Hz, ^3J = 8.0 Hz) and 4.54 (ddd, 1 H, partially overlapped with CH_2 of Bn, ^2J = 14.8 Hz, ^3J = 6.4 Hz, $^4J_{1',F}$ = 3.2 Hz, H1'), 4.53 (AB, 2 H, J_{AB} = 11.6 Hz, CH_2 of Bn), 6.24 (s, 2 H, NH_2), 7.28-7.40 (m, 5 H, C_6H_5), 7.90 and 8.39 (H_2 and H8 of adenine); ^{13}C NMR 25.80 and 26.30 (2t, ^2J = 10.4 Hz, C2' and C4'), 38.42 (d, ^3J = 5.9 Hz, C1'), 63.35 (d, ^3J = 4.5 Hz, C5'), 113.83 (dd, ^1J = 290.3 and 279.9 Hz, C3'); adenine: 120.62 (C_5), 141.20 (C_8), 151.05 (C_4), 154.20 (C_2), 156.81 (C_6); benzyl: 74.21 (CH_2), 128.96 (C_{ortho}), 129.18 (C_{para}), 129.69 (C_{meta}), 138.32 (C_{ipso}); ^{19}F NMR -124.93 (dt, ^2J = 164.9 Hz, $^3J_{F,cis\text{-}H}$ = 12.6 Hz), -150.12 (d, ^2J = 164.9 Hz). EI-MS 345 (M, 1.6), 325 (M - F - H, 0.8), 296 (M - CF_2 + H, 4.1), 239 (M - OBn + H, 7.7), 224 (M - CH_2OBn, 6.9), 219 (M - OBn - F, 41.8), 148 (AdeCH_2, 10.0), 135 (Ade, 25.5), 91 (Bn, 100.0). CI-MS 346 (M + H, 100.0), 239 (M + H - OBn, 8.6), 219 (M - OBn - F, 13.9), 178 (7.9), 91 (Bn, 10.1). HRMS Calcd. for $C_{17}H_{17}F_2N_5O$ (M): 345.1401. Found: 345.1404. Anal. Calcd. for $C_{17}H_{17}F_2N_5O$: C, 59.12; H, 4.96; N, 20.28. Found: C, 59.29; H, 5.13; N, 20.45.

***(cis)*-9-[(2-Hydroxymethyl-3,3-difluorocyclopropyl)methyl]adenine (7a).** Boron trichloride (1 M in CH_2Cl_2, 7.4 mL, 7.4 mmol) was added to a solution of compound **16a** (511 mg, 1.48 mmol) in CH_2Cl_2 (23 mL) at -78°C under N_2 over 10 min with stirring. The stirring at -78°C was continued for 5 h whereupon the reaction was quenched by a cautious addition of MeOH (10 mL) and NH_3 in MeOH (10 %, 10 mL). The mixture was allowed to warm up to room temperature, the insoluble portion was filtered off and it was washed with CH_2Cl_2 - MeOH (4 : 1, 4 x 25 mL). The combined organic phases were removed in vacuo and MeOH (2 x 10 mL) was evaporated from the residue. Chromatography on silica gel using CH_2Cl_2 - MeOH (9 : 1 → 4 : 1 containing 0.5 % NH_3) to give product **7a** (354 mg, 93.7 %), mp 198-200°C. UV max (EtOH) 260 nm (ε 13,400), 209 (ε 20,200). IR (KBr): 3440, 3370 and 3080-3320 (OH, NH_2), 1680, 1620, 1580, 1480, 1310, 1250, 1065, 1030 cm^{-1}; ^1H NMR δ 2.11 (ttd, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.0 Hz, ^3J = 7.6 Hz, $^3J_{trans\text{-}F}$ = 1.2 Hz, H4'), 2.47 (tt, 1 H, partially overlapped with d5-DMSO, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.8 Hz, ^3J_H = 7.6 Hz, H2'), 3.57-3.65 (m, 1 H) and 3.74 (m, 1 H, J = 12.4 Hz, J = 6.4 Hz, H5'), 4.38 (d, 2 H, ^3J = 7.6 Hz, H1'), 5.08 (t, 1 H, ^3J = 5.2 Hz, OH), 7.30 (s, 2 H, NH_2), 8.16 and 8.17 (H_2 and H8 of

adenine). ^{13}C NMR 25.51 (t, $^{2}J_F$ = 10.0 Hz) and 28.70 (t, $^{2}J_F$ = 9.3 Hz, $C_{2'}$ and $C_{4'}$), 38.08 (d, $^{3}J_F$ = 5.9 Hz, $C_{1'}$), 55.19 (d, $^{3}J_F$ = 5.2 Hz, $C_{5'}$), 115.80 (dd, $^{1}J_F$ = 288.5 Hz and 281.1 Hz, $C_{3'}$); adenine: 120.15 (C_5), 142.04 (C_8), 150.86 (C_4), 154.08 (C_2), 157.54 (C_6). ^{19}F NMR -118.90 (dt, $^{2}J_F$ = 160.3 Hz, $^{3}J_{cis\text{-}H}$ = 12.8 Hz), -145.55 (d, $^{2}J_F$ = 160.3 Hz). EI-MS 255 (M, 21.0), 238 (M + H - H_2O, 12.0), 235 (M - H - F, 15.4), 224 (M - CH_2OH, 8.4), 206 (M + H - CH_2OH - F, 41.5), 149 (AdeCH_2, 24.0), 135 (adenine, 100.0), 108 (M + H - AdeCH_2, 37.1). HRMS Calcd. for $C_{10}H_{11}F_2N_5O$ (M): 255.0932. Found: 255.0931. Anal. Calcd. for $C_{10}H_{11}F_2N_5O$: C, 47.06; H, 4.34; N, 27.44; F, 14.90. Found: C, 47.25; H, 4.55; N, 27.33; F, 14.71.

(*cis*)-2-Amino-9-[(2-benzyloxymethyl-3,3-difluorocyclopropyl]methyl-6-chloropurine (16b). The reaction and workup followed the procedure described for adenine analogue **16a**. A mixture of 2-amino-6-chloropurine (678 mg, 4 mmol), compound **8** (873 mg, 3 mmol) and K_2CO_3 (1.10 g, 8. mmol) in DMF (22 mL) was stirred under N_2 at 85°C for 5 h to give after chromatography on silica gel using CH_2Cl_2 - MeOH (99 : 1 ⟶ 97 : 3) product **16b** (788 mg, 61.6 %), mp 130-133°C. UV max (EtOH) 310 nm (ε 7,700), 248 (ε 6,500), 222 (ε 28,100). IR (KBr) 3460, 3360, and 3240 (NH_2), 1650, 1620, 1580, 1480, 1420, 1220, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.12-2.24 (m, 1 H, J = 12.8 Hz, J = 6.8 Hz, $H_{4'}$), 2.24-2.35 (m, 1 H, J = 8.0 Hz, J = 7.2 Hz, $H_{2'}$), 3.64 (t, 1 H, $^{2}J = {}^{3}J$ = 10.0 Hz) and 3.84 (ddd, 1 H, ^{2}J = 10.8 Hz, ^{3}J = 6.4 Hz, $^{4}J_F$ = 2.0 Hz, $H_{5'}$), 4.13 (dd, 1 H, ^{2}J = 14.8 Hz, ^{3}J = 8.0 Hz) and 4.38 (ddd, 1 H, ^{2}J = 14.8 Hz, ^{3}J = 6.8 Hz, $^{4}J_F$ = 3.2 Hz, $H_{1'}$), 4.53 (AB, 2 H, J_{AB} = 11.6 Hz, CH_2 of Bn), 5.40 (s, 2 H, NH_2), 7.29-7.40 (m, 5 H, Ph), 7.85 (H_8 of purine).^{13}C NMR 25.47 (t, $^{2}J_F$ = 10.4 Hz) and 26.28 (t, $^{2}J_F$ = 10.4 Hz, $C_{2'}$ and $C_{4'}$), 38.42 (d, $^{3}J_F$ = 6.7 Hz, $C_{1'}$), 63.28 (d, $^{3}J_F$ = 4.4 Hz, $C_{5'}$), 113.72 (dd, $^{1}J_F$ = 290.4 Hz, $^{1}J_F$ = 280.0 Hz, $C_{3'}$); purine: 126.22 (C_5), 143.07 (C_8), 152.46 (C_4), 154.78 (C_2), 160.27 (C_6); benzyl: 74.27 (CH_2), 128.99 (C_{ortho}), 129.24 (C_{para}), 129.72 (C_{meta}), 138.20 (C_{ipso}). ^{19}F NMR ($CDCl_3$, 376 MHz): -124.82 (dt, $^{2}J_F$ = 164.9 Hz, $^{3}J_{cis\text{-}H}$ = 12.6 Hz), -149.90 (d, $^{2}J_F$ = 164.9 Hz). EI-MS m/z: 379 and 381 (M, 7.1, 2.6), 288 and 290 (M - Bn, 1.3, 0.5), 273 and 275 (M - OBn + H, 10.8, 3.4), 253 and 255 (M - OBn - F, 54.4, 18.0), 240 and 242 (M - CH_2OBn - F + H, 5.3, 1.6), 183 and 185 (2-amino-6-chloropurine-CH_2 + H, 6.5, 2.2), 169 and 171 (2-amino-6-chloropurine, 22.7, 7.6), 91 (Bn, 100.0). HRMS Calcd. for $C_{17}H_{16}{}^{35}ClF_2N_5O$ (M): 379.1011. Found: 379.1006.

(*cis*)-2-Amino-9-[(2-hydroxymethyl-3,3-difluorocyclopropyl)methyl]-6-chloropurine (7e). Boron trichloride (1.0 M in CH_2Cl_2, 20.6 mL, 20.6 mmol) was added to a solution of compound **16b** (782 mg, 2.06 mmol) in CH_2Cl_2 (65 mL) at -78°C under N_2 during 10 min with stirring. The stirring at -78°C was continued for 7 h whereupon the reaction was quenched by addition of MeOH (10 mL) and solid $NaHCO_3$

(10 g, 119 mmol) with stirring. The mixture was cautiously warmed up to room temperature (**caution**: foaming between -30 and -20°C!). The solids were filtered off using a Celite pad and they were washed with CH_2Cl_2 - MeOH (95 : 5, 3 x 50 mL). The solvents were removed in vacuo and MeOH (2 x 10 mL) was evaporated from the residue. The crude product was chromatographed on silica gel using CH_2Cl_2 - MeOH (97 : 3 → 92 : 8) to give compound **7e** (537 mg, 90 %), mp 165-167°C with resolidification and melting at 180-182°C. UV max (EtOH) 310 nm (ε 8,100), 248 (ε 6,600), 223 (ε 29,600). IR (KBr) 3530, 3350 and 3220 (OH, NH_2), 1630, 1580, 1480, 1420, 1295, 1220, 1010, 935, 920 cm^{-1}. ^1H NMR δ 2.20 (ttd, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.0 Hz, ^3J_H = 7.8 Hz, $^3J_{trans\text{-}F}$ = 1.6 Hz, $H_{4'}$), 2.47 (tt, 1 H, partially overlapped with d5-DMSO, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.8 Hz, ^3J_H = 8.0 Hz, $H_{2'}$), 3.64-3.70 (m, 1 H) and 3.82 (m, 1 H, apparent J = 12.4 Hz, J = 5.2 Hz, $H_{5'}$), 4.38 (d, 2 H, ^3J = 8.0 Hz, $H_{1'}$), 5.06 (t, 1 H, ^3J = 5.2 Hz, OH), 7.07 (s, 2 H, NH_2), 8.23 (H_8 of purine). ^{13}C NMR 25.16 (t, ^2J_F = 10.1 Hz) and 28.76 (t, ^2J_F = 9.3 Hz, $C_{2'}$ and $C_{4'}$), 38.23 (d, ^3J_F = 6.0 Hz, $C_{1'}$), 55.24 (d, ^3J_F = 5.2 Hz, $C_{5'}$), 115.85 (dd, ^1J_F = 289.3 Hz and 280.4 Hz, $C_{3'}$); purine: 124.84 (C_5), 144.35 (C_8), 151.04 (C_4), 155.58 (C_2), 161.46 (C_6). ^{19}F NMR -123.76 (dt, ^2J_F = 160.3 Hz, $^3J_{cis\text{-}H}$ = 13.0 Hz), -150.24 (d, ^2J_F = 160.3 Hz). EI-MS 289 and 291 (M, 44.5, 14.8), 272 and 274 (M + H - H_2O, 7.9, 2.6), 240 and 242 (M + H - CH_2OH - F, 10.6, 3.3), 182 and 184 (2-amino-6-chloropurine-CH_2, 10.1, 4.9), 169 and 171 (2-amino-6-chloropurine, 100.0, 33.1). HRMS Calcd. for $C_{10}H_{10}ClF_2N_5O$ (M): 289.0542. Found: 289.0541. Anal. Calcd. for $C_{10}H_{10}{}^{35}ClF_2N_5O$: C, 41.46; H, 3.48; N, 24.18; Cl, 12.24. Found: C, 41.51; H, 3.60; N, 24.33; Cl, 12.34.

(*cis*)-9-[(2-Hydroxymethyl-3,3-difluorocyclopropyl)methyl]guanine (7b). A solution of compound **7e** (232 mg, 0.8 mmol) in formic acid (80 %, 10 mL) was heated at 80°C for 3 h with stirring. Volatile components were removed in vacuo leaving a sirup which was dissoloved in NH_3/MeOH (20 %, 10 mL). The mixture was stirred at room temperature for 18 h. After evaporation, MeOH was added and the product **7b** was filtered off (207 mg, 95 %), mp 296-300°C (decomp.). UV max (EtOH) 254 nm (ε 15,200), 204 (ε 17,800). IR (KBr) 3520, 3320 and 3130 (OH, NH_2), 1755, 1700, 1650, 1600, 1560, 1490, 1305, 1195, 1050, 1010 cm^{-1}. ^1H NMR δ 2.06 (tt, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.2 Hz, ^3J_H = 8.0 Hz, $H_{4'}$), 2.36 (tt, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.2 Hz, ^3J_H = 8.0 Hz, $H_{2'}$), 3.53 (poorly resolved dd, 1 H, ^2J = 9.2 Hz, ^3J = 8.8 Hz) and 3.82 (m, 1 H, ^2J = 12.4 Hz, ^3J = 5.2 Hz, $H_{5'}$), 4.13 (AB, 2 H, J_{AB} = 16.4 Hz, $H_{1'}$), 4.94 (br s, 1 H, OH), 6.47 (s, 2 H, NH_2), 7.67 (H_8), 10.59 (CONH). ^{13}C NMR 24.39 (t, ^2J_F = 10.4 Hz) and 27.56 (t, ^2J_F = 9.3 Hz, $C_{2'}$ and $C_{4'}$), 36.73 (d, ^3J_F = 6.4 Hz, $C_{1'}$), 54.14 (d, ^3J_F = 5.2 Hz, $C_{5'}$), 114.81 (dd, ^1J_F = 287.7 Hz and 280.4 Hz, $C_{3'}$); purine: 116.93 (C_5), 137.40 (C_8), 151.57 (C_4), 154.14 (C_2), 157.30 (C_6). ^{19}F NMR -123.84 (dt, ^2J_F = 160.3 Hz, $^3J_{cis\text{-}H}$ = 13.4 Hz), -150.50 (d, ^2J_F = 160.3 Hz). FAB-MS (TG) 543 (2M + H, 4.7),

272 (M + H, 100.0), 181 (7.8), 152 (guanine + H, 27.3). Anal. Calcd for $C_{10}H_{11}F_2N_5O_2$: C, 44.28; H, 4.09; N, 25.82; F, 14.01. Found: C, 44.75; H, 4.33; N, 26.12; F, 13.96.

(*cis*)-1-[(2-Benzyloxymethyl-3,3-difluorocyclopropyl)methyl]cytosine (17). A mixture of N^4-acetylcytosine (612 mg, 4 mmol), compound **8** (728 mg, 2.5 mmol) and K_2CO_3 (0.97 g, 7.0 mmol) in DMF (20 mL) was stirred under N_2 at 85°C for 3 h. Water (7.5 mL) was then added and temperature was kept at 85°C for another 2 h. After cooling, the solids were filtered off through a Celite pad and they were washed with DMF (5 x 6 mL). The combined filtrate and washings were evaporated. The residue was treated with a mixture of CH_2Cl_2 - MeOH (4 : 1, 50 mL), the insoluble portion was filtered off and it washed with the same solvent (2 x 30 mL). The organic phase was evaporated and the residue was chromatographed on silica gel using CH_2Cl_2 - MeOH (95 : 5 → 85 : 15) to give product **17** (564 mg, 70 %), mp 215-218°C. UV max (EtOH) 273 nm (ε 8,700), 242 (shoulder, ε 7,300), 205 (ε 26,200). IR (KBr) 3370 and 3140 (NH_2), 1665, 1630, 1485, 1390, 1285, 1080 cm^{-1}. ^1H NMR δ 2.23 (tt, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.8 Hz, ^3J_H = 6.8 Hz, H4'), 2.32 (tt, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 14.0 Hz, ^3J_H = 6.8 Hz, H2'), 3.63-3.73 (m, 2 H, J = 9.2 Hz, J = 7.6 Hz, H5'), 3.73 (dd, 1 H, ^2J = 14.4 Hz, ^3J = 7.6 Hz) and 3.97 (ddd, 1 H, ^2J = 14.4 Hz, ^3J = 6.8 Hz, ^4J_F = 2.8 Hz, H1'), 4.50 (s, 2 H, CH_2 of Bn), 5.65 (d, 1 H, ^3J = 7.2 Hz, H5), 7.13 (d, 2 H, ^2J = 24.8 Hz, NH_2), 7.53 (d, 1 H, ^3J = 7.2 Hz, H6), 7.28-7.40 (m, 5 H, C_6H_5). ^{13}C NMR 25.28 (t, ^2J_F = 9.6 Hz) and 26.00 (t, ^2J_F = 8.9 Hz, C2' and C4'), 43.93 (d, ^3J_F = 5.5 Hz, C1'), 64.02 (d, ^3J_F = 4.7 Hz, C5'), 116.02 (dd, ^1J_F = 288.4 Hz and 280.4 Hz, C3'); cytosine: 95.20 (C_5), 147.13 (C_6), 157.29 (C_2), 167.59 (C_4); benzyl: 73.36 (CH_2), 129.11 (C_{para}), 129.19 (C_{ortho}), 129.85 (C_{meta}), 139.58 (C_{ipso}). ^{19}F NMR -118.63 (dt, ^2J_F = 158.5 Hz, $^3J_{cis\text{-}H}$ = 13.0 Hz), -143.99 (d, ^2J_F = 158.8 Hz). EI-MS 321 (M, 2.5), 230 (M - Bn, 1.9), 215 (M + H - OBn, 38.7), 195 (M - OBn - F, 38.7), 136 (19.5), 111 (cytosine, 67.5), 91 (Bn, 100.0). HRMS Calcd. for $C_{16}H_{17}F_2N_3O_2$ (M): 321.1289. Found: 321.1292. Anal. Calcd. for $C_{16}H_{17}F_2N_3O_2$: C, 59.81; H, 5.33; N, 13.08. Found: C, 59.88; H, 5.18; N, 13.22.

(*cis*)-1-[(2-Hydroxymethyl-3,3-difluorocyclopropyl)methyl]cytosine (7c). Benzoic anhydride was added to a stirred and refluxing solution of compound **17** (400 mg, 1.24 mmol) in EtOH (40 mL) in six increments of 282 mg (1.25 mmol) each hour (total 1.69 g, 7.5 mmol). The mixture was then refluxed for another hour. After cooling, it was evaporated and the residue was partitioned between CH_2Cl_2 (80 mL) and Na_2CO_3 (5 %, 80 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was washed with saturated NaCl (50 mL)/$NaHCO_3$ (20 mL) and it was dried (Na_2SO_4). After evaporation, the residue was chromatographed on silica gel using CH_2Cl_2 - MeOH

(95 : 5) to give the N^4-benzoyl derivative **18** (520 mg, 98%), mp 160-162°C. UV max (EtOH) 305 nm (ε 9,800), 259 (ε 23,600), 205 (ε 31,700).

Compound **18** (515 mg, 1.21 mmol) was debenzylated as described for 2-amino-6-chloropurine derivative **16b**. A solution of the crude product **7c** in NH_3/MeOH (20 %, 30 mL) was stirred at room temperature for 18 h. Volatile components were evaporated and the residue was chromatographed on silica gel using CH_2Cl_2 - MeOH (4 : 1 containing 0.5 % NH_3) to give compound **7c** (266 mg, 95 %), mp 237-240°C. UV max (EtOH) 273 nm (ε 8,100), 203 (ε 20,100). IR (KBr) 3400 and 3140 (OH and NH_2), 1665, 1620, 1490, 1400, 1040 cm^{-1}. ^1H NMR δ 2.00 (tt, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.4 Hz, ^3J_H = 7.6 Hz, H4'), 2.16 (tt, 1 H, $^3J_{cis\text{-}H} = {}^3J_{cis\text{-}F}$ = 12.4 Hz, ^3J_H = 7.2 Hz, H2'), 3.51-3.65 (m, 2 H, H5'), 3.68 (dd, 1 H, ^2J = 14.4 Hz, ^3J = 7.6 Hz) and 3.95 (ddd, 1 H, ^2J = 14.0 Hz, ^3J = 6.8 Hz, ^4J_F = 3.2 Hz, H1'), 4.95 (br, 1 H, OH), 5.67 (d, 1 H, ^3J = 7.2 Hz, H5), 7.14 (d, 2 H, ^2J = 28.8 Hz, NH_2), 7.53 (d, 1 H, ^3J = 7.2 Hz, H6). ^{13}C NMR 24.10 (t, ^2J_F = 10.0 Hz) and 27.65 (t, ^2J_F = 10.4 Hz, C2' and C4'), 42.91 (d, ^3J_F = 4.2 Hz, C1'), 54.26 (d, ^3J_F = 5.2 Hz, C5'), 115.19 (dd, ^1J_F = 287.7 Hz and 280.4 Hz, C3'); cytosine: 94.21 (C5), 146.23 (C6), 156.17 (C2), 166.43 (C4). ^{19}F NMR -123.29 (dt, ^2J_F = 158.8 Hz, $^3J_{cis\text{-}H}$ = 13.7 Hz), -149.82 (d, ^2J_F = 158.8 Hz). EI-MS 231 (M, 7.3), 214 (M + H - H_2O, 100.0), 200 (M - CH_2OH, 83.8), 182 (M + H - CH_2OH - F, 15.7). HRMS Calcd. for $C_9H_{11}F_2N_3O_2$ (M): 231.0819. Found: 231.0822. Anal. Calcd. for $C_9H_{11}F_2N_3O_2$: C, 46.76; H, 4.80; N, 18.17; F, 16.43. Found: C, 46.50; H, 5.04; N, 17.97; F, 16.23.

(*cis*)-1-[(2-Benzyloxymethyl-3,3-difluorocyclopropyl)methyl]thymine (19) and 1-Benzylthymine (20). A solution of compound **8** (728 mg, 2.5 mmol) and 2,4-bis-O-(trimethylsilyl)-5-methylpyrimidine (1.35 g, 5.0 mmol) in acetonitrile (5 mL) was refluxed with stirring under N_2 for 7 days. After cooling, methanol (2 mL) was added, the precipitate was removed by centrifugation and it was washed with CH_2Cl_2 (3 x 30 mL). The organic phase was evaporated and the residue was chromatographed on silica gel using CH_2Cl_2 - MeOH (98 : 2 ⟶ 96 : 4) to give an inseparable mixture of product **19** and 1-benzylthymine (**20**) in the ratio of 1.5 : 1 based on ^1H NMR analysis (714 mg, 51 %) as a foam. UV max (EtOH) 270 and 208 nm. IR (KBr) 3200 and 3080 (NH), 1690, 1480, 1380, 1260, 1090 cm^{-1}; ^1H NMR ($CDCl_3$), compound **19**, δ 1.92 (d, 3 H, ^4J = 1.2 Hz, 5-CH_3), 2.19-2.28 (m, 2 H, J = 8.0 Hz, J = 4.4 Hz, H2' and H4'), 3.68-3.75 (m, 2 H, H5'), 3.86-3.94 (m, 1 H, J = 4.4 Hz, J = 2.0 Hz) and 4.26 (dm, 1 H, ^2J = 14.4 Hz, J = 5.6 Hz, J = 3.6 Hz, H1'), 4.64 (AB, 2 H, JAB = 12.0 Hz, CH_2 of Bn), 7.16 (q, 1 H, ^4J = 1.2 Hz, H6), 7.38-7.50 (m, 5 H, C_6H_5), 9.83 (s, 1 H, NH); 1-benzylthymine (**20**), 1.99 (d, 3 H, ^4J = 1.2 Hz, 5-CH_3), 5.01 (s, CH_2 of Bn), 7.10 (q, 1 H, ^4J = 1.2 Hz, H6), 7.38-7.50 (m, 5 H, Ph), 9.83 (s, 1 H, NH). ^{13}C NMR, compound **19**, 25.29 (t, ^2J_F = 10.4 Hz) and 26.29 (t, ^2J_F = 10.0 Hz, C2' and C4'), 43.18 (d, ^3J_F = 5.2 Hz,

$C_{1'}$), 63.52 (d, ^3J_F = 4.4 Hz, $C_{5'}$), 114.15 (dd, ^1J_F = 290.8 Hz and 279.6 Hz, $C_{3'}$); benzyl: 74.28 (CH_2), 129.06 (C_{ortho}), 129.29 (C_{para}), 129.80 (C_{meta}), 138.43 (C_{ipso}); thymine: 13.49 (5-CH_3), 112.47 (C_5), 141.00 (C_6), 152.29 (C_2), 165.60 (C_4); 1-benzylthymine (**20**), benzyl: 52.12 (CH_2), 129.19 (C_{ortho}), 129.62 (C_{para}), 130.28 (C_{meta}), 136.73 (C_{ipso}); thymine: 13.63 (5-CH_3), 112.49 (C_5), 141.00 (C_6), 152.59 (C_2), 165.65 (C_4). ^{19}F NMR, compound **19**, -129.42 (dt, ^2J_F = 166.4 Hz, $^3J_{cis\text{-}H}$ = 11.5 Hz), -153.73 (d, ^2J_F = 164.5 Hz).

(*cis*)-1-((2-Hydroxymethyl-3,3-difluoro)cyclopropylmethyl)thymine (7d). The procedure followed that described for the adenine analog **7a**. Thus, a mixture of compound **19** and 1-benzylthymine (**20**) from the previous experiment in CH_2Cl_2 (10 mL) was treated with BCl_3 (1.0 M in CH_2Cl_2, 24.3 mmol) at -78°C for 7 h to give 1-benzylthymine (**20**, 190 mg, 90.5%) and product **7d** (335 mg, 93 %) after chromatography on silica gel using CH_2Cl_2 - MeOH (97 : 3 → 9 : 1). 1-Benzylthymine (**20**), mp 154-155°C after recrystallization from EtOH; lit.[21] 161-163°C. UV max (EtOH) 271 nm (ε 10,700), 207 (ε 17,800); lit.[21] UV max (MeOH) 271 nm (ε 10,500). For ^1H and ^{13}C NMR see the previous experiment; the ^1H NMR chemical shifts were similar to those reported[19] for oily product **20**. EI-MS 216 (M, 12.9), 91 (Bn, 100.0); HRMS Calcd. for $C_{12}H_{12}N_2O_2$ (M): 216.0899. Found: 216.0901.

Compound **7d**, mp 178-180°C. UV max (EtOH) 268 nm (ε 10,000), 206 (ε 9,800). IR (KBr) 3460, 3200 and 3060 (OH, NH), 1710, 1650, 1490, 1360, 1260, 1070, 1010 cm^{-1}; ^1H NMR 1.73 (d, 3 H, ^4J = 1.2 Hz, 5-CH_3), 2.02 (ttd, 1 H, $^3J_{cis\text{-}H}$ = $^3J_{cis\text{-}F}$ = 12.8 Hz, ^3J_H = 8.0 Hz, $^3J_{trans\text{-}F}$ = 1.4 Hz, $H_{4'}$), 2.18 (tt, 1 H, $^3J_{cis\text{-}H}$ = $^3J_{cis\text{-}F}$ = 12.4 Hz, ^3J_H = 7.6 Hz, $H_{2'}$), 3.49-3.58 (m, 1 H) and 3.63 (m, 1 H, $H_{5'}$), 3.73 (dd, 1 H, ^2J = 14.4 Hz, ^3J = 8.0 Hz) and 3.92 (ddd, 1 H, ^2J = 14.4 Hz, ^3J = 7.2 Hz, ^4J_F = 3.2 Hz, $H_{1'}$), 4.91 (t, 1 H, ^3J = 5.4 Hz, OH), 7.47 (d, 1 H, ^4J = 1.2 Hz, H_6), 11.29 (NH). ^{13}C NMR 23.81 (t, ^2J_F = 10.0 Hz) and 27.62 (t, ^2J_F = 9.3 Hz, $C_{2'}$ and $C_{4'}$), 41.34 (d, ^3J_F = 5.2 Hz, $C_{1'}$), 54.26 (d, ^3J_F = 5.9 Hz, $C_{5'}$), 114.95 (dd, ^1J_F = 288.5 Hz and 280.3 Hz, $C_{3'}$); thymine: 12.54 (5-CH_3), 109.32 (C_5), 141.35 (C_6), 151.33 (C_2), 164.71 (C_4); ^{19}F NMR -123.40 (dt, ^2J_F = 158.8 Hz, $^3J_{cis\text{-}H}$ = 13.0 Hz), -149.50 (d, ^2J_F = 158.8 Hz). EI-MS 246 (M, 30.2), 229 (M + H - H_2O, 69.2), 215 (M - CH_2OH, 61.8), 197 (M + H - CH_2OH - F, 10.3), 172 (23.9), 149 (41.4), 139 (thymine-CH_2, 35.1), 126 (thymine, 66.4), 96 (100.0). HRMS Calcd. for $C_{10}H_{12}F_2N_2O_3$ (M): 246.0816. Found: 246.0815. Anal. Calcd. for $C_{10}H_{12}F_2N_2O_3$: C, 48.78; H, 4.91; N, 11.38; F, 15.43. Found: C, 49.00; H, 5.10; N, 11.47; F, 15.27.

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REFERENCES

1. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, **1991**, pp. 220-233.
2. Herdewijn, P.; Van Aerschot, A.; Kerremans, L. *Nucleosides & Nucleotides* **1989** ***8***, 65-96.
3. Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992** ***92***, 1745-1768.
4. Hertel, L. W.; Boder, G. B.; Kroin, J. S.; Rinzel, S. M.; Poore, G. A.; Todd, G. C.; Grindey, G. B. *Cancer Res.* **1990** ***50***, 4417-4422.
5. Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991** ***113***, 315-317.
6. Casara, P. J.; Kenny, M. T.; Jund, K. C. *Tetrahedron Lett.* **1991** ***32***, 3823-3826.
7. Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998** ***41***, 1284-1298.
8. Ashton, W. T.; Meurer, L. C.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L. *J. Med. Chem.* **1988** ***31***, 2304-2315.
9. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535-3536.
10. Danishefsky, S.; Regan, J. *Tetrahedron Lett.* **1981** ***22***, 3919-3922.
11. Naruta, Y.; Nagai, N.; Maruyama, K. *Chem. Lett.* **1983**, 1383-1386.
12. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972** ***94***, 6190-6191.
13. Taguchi, T.; Kurishita, M.; Shibuya, A.; Aso, K. *Tetrahedron* **1997** ***53***, 9497-9508.
14. Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972** ***37***, 2289-2299.
15. Qiu, Y.-L.; Ksebati, M.; Ptak, R. G.; Fan, B. Y.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **1998** ***41***, 10-23.
16. Qiu, Y.-C.; Ptak, R. G.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *Antiviral Chem. Chemother.* **1998** ***9***, 341-352.
17. Xu, Z.-Q.; Joshi, R. V.; Zemlicka, J. *Tetrahedron* **1995** ***51***, 67-76.

18. Jones, B. C. N. M.; Silverton, J. V.; Simons, C.; Megati, S.; Nishimura, H.; Maeda, Y.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **1995** ***38***, 1397-1405.
19. Koomen, G. J.; Provoost, L. M.; van Maarschalkerwaart, D. A. H.; Willard, N. P. *Nucleosides & Nucleotides* **1992** ***11***, 1297-1303.
20. Phadtare, S.; Kessel, D.; Corbett, T. H.; Renis, H. E.; Court, B. A.; Zemlicka, J. *J. Med. Chem.* **1991** ***34***, 421-429.
21. Smith, R. C.; Binkley, S. B. *J. Org. Chem.* **1959** ***24***, 249-251.

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