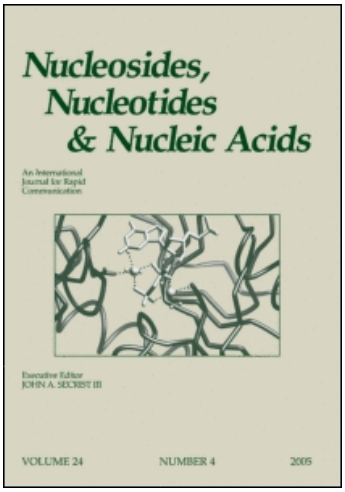

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Synthesis and Biologic Activity of Purine 2'-Deoxy-2'-fluoro-*ribo*nucleosides

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Abstract

The synthesis of 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-D-ribofuranosyl bromide (**8**) and its reaction with 2,6-dichloropurine by fusion and with mercuric cyanide catalysis is described. The resulting 2,6-dichloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (**13**) was converted to the 2-fluoroadenine (**16**), the 2-chloroadenine (**17**), 2,6-diaminopurine (**12**), and guanine (**14**) nucleosides by standard procedures. These nucleosides were cytotoxic to a number of cell lines in culture. The 2-haloadenine nucleosides **16** and **17** gave modest increases in lifespan when tested against the P388 leukemia in mice.

Fludarabine[1] phosphate (F-ara-AMP) has shown activity in a number of human cancers in Phase I and II clinical trials and has been approved by the FDA for the treatment of refractory lymphocytic leukemia.[2] Although the 2-chloro- analog of fludarabine is much less active and the 2-bromo- analog is inactive in the L1210 mouse leukemia model, the 2-fluoro-, 2-chloro-, and 2-bromo-2'-deoxyadenosines are all curative in this model.[3] 2-Chloro-2'-deoxyadenosine has shown activity against human lymphomas and leukemias.[2] Despite their useful activity, all of these 2-haloadenine nucleosides are cleaved by *E. coli* PNP to 2-fluoroadenine, which has no selective cytotoxicity and has been detected as a metabolite of fludarabine phosphate in animals and in man. For this reason, we prepared the 2-halo-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenines and found these nucleosides to be highly active in the P388 mouse leukemia system and resistant to the action of *E. coli* PNP.[4] Since 2'-fluoro-2'-deoxyinosine is resistant to cleavage by mammalian PNP,[5] we reasoned that the 2'-deoxy-2'-fluoro-2-haloadenosines would also be resistant to *E. coli* PNP. 2'-Fluoro-2'-deoxyadenosine itself, although readily deaminated, is a unique analog of adenosine in that its conformation resembles that of the ribonucleotides in RNA,[6] and, in fact, RNA-like homopolymers have been enzymatically synthesized from several 2'-fluoro-2'-

Dedicated to the memory of Roland K. Robins.

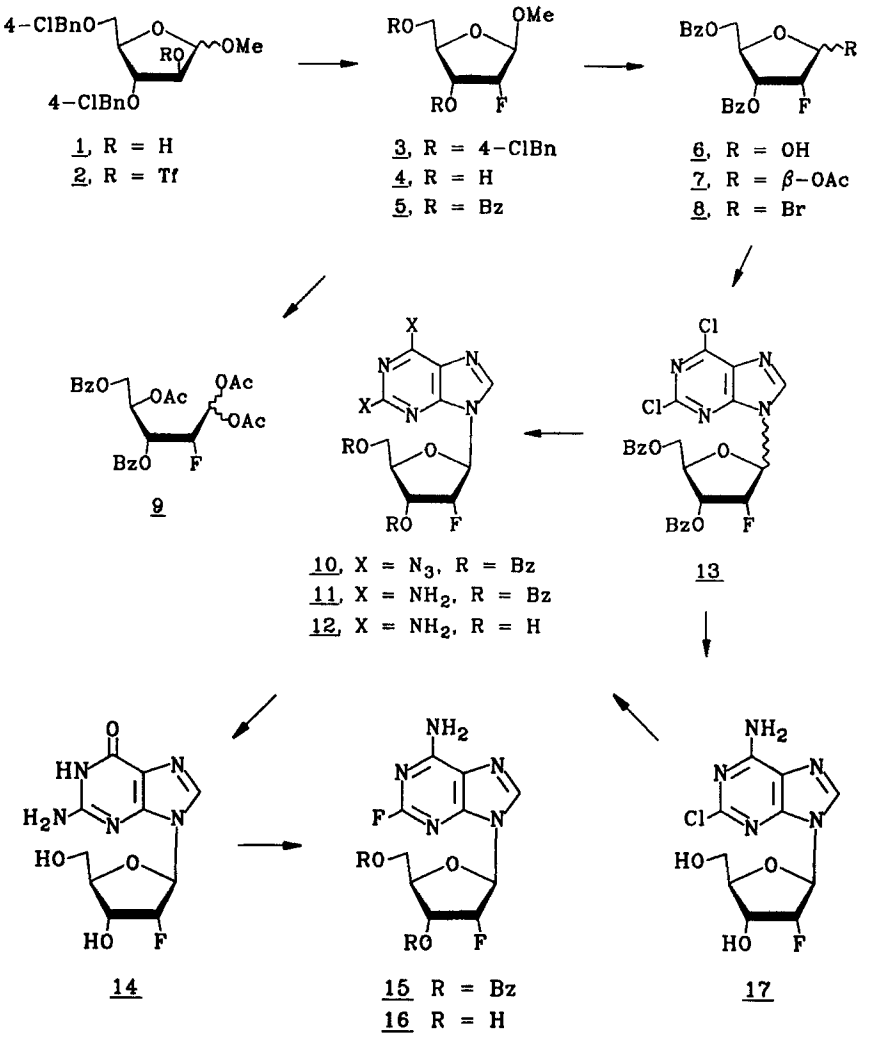
deoxyribonucleosides.[7,8] There is other evidence that 2′-FAdo biologically resembles Ado, whereas 2′-F-ara-A and its analogs resemble dAdo.[7] We have now prepared 2′-fluoro-2′-deoxyguanosine and 2-halo derivatives of 2′-fluoro-2′-deoxyadenosine and studied their biologic activity.

We developed a procedure for the preparation of a suitably blocked derivative of 2-fluoro-2-deoxyribofuranose and coupled it to 2,6-dichloropurine. The resulting nucleoside was then converted to the 2,6-diaminopurine (**12**), guanine (**14**), 2-fluoroadenine (**16**), and 2-chloroadenine (**17**) 2′-fluoro-2′-deoxyribonucleosides. Recently, the enzymatic synthesis of 20 purine 2′-fluoro-2′-deoxyribonucleosides, including **12**, **14**, and **16** by pentosyl transfer from 2′-deoxy-2′-fluorouridine was described.[9]

Chemistry

Ranganathan,[10] Ikehara *et al.*,[11,12] and Kawasaki *et al.*[13] prepared 3′,5′-*O* blocked derivatives of 9-β-D-arabinofuranosyladenine suitable for conversion via the 2′-triflate to 2′-fluoro-2′-deoxyadenosine. Both procedures are lengthy (10-12 steps), principally because of the instability of the TIPS blocking group to fluoride ion. Benseler *et al.* used a slightly different approach to prepare 2′-fluoro-2′-deoxyguanosine from guanosine in 10 steps.[8] Not only are these procedures lengthy, they are not readily adaptable to the synthesis of 2′-fluoro-2′-deoxyribonucleosides of a variety of bases. On the other hand, nucleosides of 2,6-dichloropurine are easily converted into a variety of purine nucleosides. The procedure described herein, although also somewhat lengthy, offers versatility in terms of target nucleosides and is amenable to scale-up.

The synthesis of 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-D-ribofuranosyl bromide (**8**) required seven steps from methyl 3,5-di-*O*-(4-chlorobenzyl)-D-arabinofuranoside (**1**)[14] (see Scheme). It was necessary to use the 4-chlorobenzyl blocking groups to prepare **3** because fluorination of the corresponding *O*-benzoyl blocked sugar gave low yields and variable results. However, the 4-chlorobenzyl groups were unstable to acid hydrolysis of the methyl group of **3** and had to be replaced by benzoyl groups to obtain **6**. Preparation of the bromo sugar (**8**) proceeded better using the acetyl compound **7** rather than the hydroxy sugar **6**. Treatment of **7** in ethylene chloride with 30% HBr in acetic acid gave an anomeric mixture of **8** (9β:1α). An attempt to prepare **7** directly from **5** by acetolysis using acetic acid-acetic anhydride with sulfuric acid catalyst failed because the furanose ring opened under the conditions to give **9**, identified by its mass spectrum and ^{1}H NMR. Acyclic sugars like **9** have been observed as by-products in the acetolysis of other sugars.[15] Fusion of this anomeric sugar (**7**) with 2,6-dichloropurine at 160°C using *p*-toluenesulfonic acid as catalyst proceeded well, but gave a 1:1 mixture of α- and β-**13**, leading to an investigation of the mercuric cyanide-catalyzed coupling



of **8** with 2,6-dichloropurine in ethylene chloride. Equimolar amounts of **8**, 2,6-dichloropurine, and mercuric cyanide, a ratio that worked well for the arabino isomer of **8**, resulted in incomplete reaction even after two days at room temperature. Reducing the amount of sugar by one-half increased the amount of α-**13**. The optimal amounts appear to be 1 equiv. of **8**, 2 equiv. of 2,6-dichloropurine, and 1.3-1.5 equiv. of mercuric cyanide. Also, a cleaner reaction mixture and higher yield of β-**13** was obtained by adding the mercuric cyanide to the purine with stirring followed a few minutes later by the addition of the sugar **8**. These conditions gave a 59% yield of 9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)-2,6-dichloropurine (β-**13**), along with small amounts of α-**13** and a third nucleoside, the 7-β isomer. The α- and β- anomers of **13** were identified by their ^{1}H NMR spectra.

The reaction of β-**13** with ethanolic ammonia gave mostly (57%) 2-chloro-2′-deoxy-2′-fluoroadenosine (**17**), along with its 5′-*O*-benzoyl derivative (15%). To maximize the yield of **17**, it was necessary to remove the remaining 5′-*O*-benzoyl group using aqueous LiOH in CH_3CN.

Reaction of pure β-**13** with sodium azide in aqueous ethanol gave 2,6-diazido-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (**10**). Another reaction, using crude β-**13** containing some α-**13**, gave **10** and a 7% yield of its α-anomer identified by ^1H NMR. Catalytic hydrogenation of **10** gave 2,6-diamino-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (**11**), which was debenzoylated with sodium methoxide to give 2-amino-2′-deoxy-2′-fluoroadenosine (**12**).

In another reaction, crude **10** containing some of the 7-β isomer gave, in addition to **11**, an 8% yield of material identified by NMR and mass spectral analysis as 2,6-diamino-7-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine. The nucleoside **12** was also prepared in 23% yield in two steps from **13**: reaction with hydrazine followed by reductive cleavage of the 2-hydrazino purine with Raney nickel. The nucleoside **12** was readily deaminated with adenosine deaminase to 2′-deoxy-2′-fluoroguanosine (**14**).

Fluorination of **11** using pyridine-HF and *t*-butyl nitrite gave 2′,3′-di-*O*-benzoyl-2′-deoxy-2,2′-difluoroadenosine (**15**), which was debenzoylated to give 2′-deoxy-2,2′-difluoroadenosine (**16**). This reaction was carried out with LiOH in aqueous acetonitrile to avoid displacement of the 2-fluoro group by methoxide or ethoxide, which occurred using methanol or ethanol. Some conversion to the 2′-deoxy-2′-fluoroisoguanosine was observed, but it was easily removed by flash chromatography on silica gel.

Biologic Evaluations

The target compounds **12**, **14**, **16**, **17** were evaluated for their cytotoxicity to L1210 murine leukemia cells and a battery of human tumor cell lines selected from the National Cancer Institute primary screen (see Table). It is clear that the *ribo*nucleosides are significantly less cytotoxic than the corresponding *arabino*nucleosides.[4] An L-1210 cell line selected for resistance to 6-(methylthio)purine ribonucleoside, which is deficient in adenosine kinase, is sensitive to 2′-deoxy-2,2′-difluoroadenosine (**16**) (IC_{50}=4.2 μM) showing that this kinase does not activate **16**. On the other hand, 2′-deoxycytidine completely reverses the cytotoxicity of **16** to L1210 cells, indicating that 2′-deoxycytidine kinase is responsible for its activation.

Both 2′-deoxy-2,2′-difluoroadenosine (**16**) and 2-chloro-2′-deoxy-2′-fluoroadenosine (**17**) gave modest increases in lifespan (ca. 35-40%) of mice implanted with 10^6 P388 leukemia cells, in contrast to the corresponding *arabino*nucleosides which are highly active against this leukemia. All together, the data indicate that the 2′-fluoro-*ribo*nucleosides are probably more

Table. Cytotoxicity Data[a]

Compound	IC_{50}, μM[b,c]							
	L1210	H.Ep.-2	CCRF-CEM	DLD-1	H23	Mel-28	SNB-7	ACHN
16	12	70	6.5	20	60	70	80	
17	4.8	29	--	6.6	33	10	33	6.6
14	>140	70	14					21
12	>130	70						66
2,2'-DifluoroaraA	0.7	0.5	0.01	5	1	6	1	
2-Chloro-2'-fluoroaraA	0.07	0.03	0.07	0.3	0.0	1	0.2	
2'-FluoroaraG			0.25		47			

[a]For details of the cytotoxicity determination, see references 16 and 17. [b]The concentration required to inhibit cell proliferation to 50% of untreated controls. [c]The cell lines are L1210 murine leukemia, H.Ep.-2 human epidermoid carcinoma, CCRF-CEM human lymphoma, DLD-1 human colon carcinoma, H23 human non-small lung carcinoma, Mel-28 human melanoma, SNB-7 human glioma, ACHN human renal cell carcinoma.

like *ribo*nucleosides than 2′-fluoro-*arabino*nucleosides, which behave like analogs of the 2′-*deoxyribo*nucleosides and as a result, inhibit DNA synthesis and are incorporated into DNA. These effects on the synthesis and function of DNA are thought to be responsible for the selective cytotoxicity of these agents to neoplastic cells. The mechanism by which the 2′-fluoro-*ribo*nucleosides cause cell death is not known, although phosphorylation to nucleotides is clearly involved. The contrast in the effect of the 2′-fluorine up (*arabino*) and down (*ribo*) may be due, at least in part, to interactions with one or more of the enzymes involved in the synthesis or function of DNA caused by differences in the conformations of the furanose rings.

Tuttle *et al.*[9] found that compounds **12** and **14** had some anti-influenza activity and little cytotoxicity to Madin-Darby canine kidney cells. The 2,2′-difluoroadenosine (**16**) showed some toxicity to the MDCK cells and no anti-influenza activity.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Nicolet NT 300NB spectrometer operating at 300.635 MHz (^{1}H) or 75.6 MHz (^{13}C). Chemical shifts are expressed in parts per million downfield from tetramethylsilane. The hydrogen-decoupled ^{13}C NMR were assigned by comparison of the $J_{C,H}$ values obtained from the hydrogen-coupled ^{13}C NMR spectra, and when necessary, selective hydrogen decoupling was performed in order to confirm the assignments. The NOE experiments were conducted on degassed solutions of $CDCl_3$. To minimize the effects of magnetic perturbations with the sample nonspinning, eight FID's were acquired with the decoupler set to a desired frequency and eight FID's were recorded with the decoupler off-resonance. The process was repeated until 800 FID's had been acquired. F refers to purine fluorine and F′ to sugar fluorine. Ultraviolet absorption spectra were determined on a Perkin-Elmer Lambda 9 spectrometer by dissolving each compound in methanol or water and diluting 10-fold with 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH. Numbers in parentheses are extinction coefficients (ϵ x 10^{-3}); sh = shoulder. Microanalyses were performed by Atlantic Microlab, Inc. (Atlanta, GA) or the Molecular Spectroscopy Section of Southern Research Institute. Analytical results indicated by elemental symbols were within ±0.4% of the theoretical values. Where solvents were noted as part of the elemental analysis, they were seen in the ^{1}H NMR spectrum in the proper amounts. Mass spectra were recorded on a Varian/MAT 311A double-focusing mass spectrometer in the fast atom bombardment (FAB) mode (glycerol matrix). HPLC analyses were carried out on a Hewlett-Packard HP 1084B liquid chromatograph with a Waters Associates μBondapak C_{18} column (3.9 mm x 30 cm) with UV monitoring (254 nm). All flash column chromatography used 230-400 mesh silica gel from E. Merck. TLC was done on Analtech precoated (250 μm) silica gel (GF) plates. The Bio-Beads SM-4 macroporous adsorbent (20-50 mesh) was obtained from Bio-Rad.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-(trifluoromethanesulfonyl)-D-arabinofuranoside (2). A solution of 550 mg (1.33 mmol) of **1** in 10 mL of anhydrous dichloromethane containing 0.11 mL (1.365 mmol) of anhydrous pyridine was cooled to 5 °C in a nitrogen atmosphere. A solution of 0.225 mL (1.34 mmol) of trifluoromethanesulfonic anhydride in 5 mL of anhydrous dichloromethane was added dropwise to maintain the temperature at 5 °C. The solution was stirred in the cold for an additional hour [to completion by TLC in cyclohexane-ethyl acetate (2:1)]. The reaction was quenched by dropwise addition of 3 mL of cold water. After stirring in the cold for 15 min, the layers were separated. The organic layer was dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue (**2**) was dried in vacuo overnight at room temperature: yield 665 mg (91%). MS 543 $(M - 1)^+$, with silver nitrate, 419 (544 – $CH_2C_6H_4Cl$), 651 $(544 + Ag)^+$; TLC, cyclohexane-ethyl acetate (9:1) R_f 0.3. In a larger run 24.1 g of **1** gave 29.5 g of **2**.

Methyl 3,5-Di-*O*-(4-chlorobenzyl)-2-deoxy-2-fluoro-D-ribofuranoside (3). A solution of 29.5 g (54 mmol) of **2** in 250 mL of anhydrous tetrahydrofuran was stirred under nitrogen and cooled to 0 °C before dropwise addition of 275 mL of 1 M tetrabutyl ammonium fluoride in tetrahydrofuran. The solution was stirred for 2 h at 0 °C and overnight at ambient temperature and evaporated to dryness. The residue was dissolved in chloroform, washed with water, dried over magnesium sulfate, filtered and evaporated to a dark syrup. The syrup was extracted with cyclohexane-ethyl acetate (3:1), 4 x 750 mL, until no product was extracted as determined by TLC. This extract was evaporated to a syrup and purified in two batches by flash chromatography on silica gel using cyclohexane-ethyl acetate at the eluting solvent. Crystalline **3** was obtained: 6.29 g (28%). A small sample was recrystallized from ethyl acetate cyclohexane for analysis. Mp 75-77 °C; MS with lithium chloride 415 $(M + 1)^+$, 421 $(414 + Li)^+$; TLC, cyclohexane-ethyl acetate (3:1), R_f 0.6; ^1H NMR (Me_2SO-d_6) δ 7.32-7.23 (m, 8, aromatic H's), 5.00 (d, 1, H-1, $^3J_{1,F}$ = 10.5 Hz), 4.63 (A part of an AB spin system, 1, CH_2Ar, J = 11.8 Hz), 4.76 (dd, 1, H-2, $^2J_{2,F}$ = 53.2 Hz, $J_{2,3}$ = 3.7 Hz), (A part of an AB spin system, 1, CH_2Ar, J = 12.3 Hz), 4.51 (B part of an AB spin system, 1, CH_2Ar, J = 12.3 Hz), 4.50 (B part of an AB spin system, 1, CH_2Ar, J = 11.8 Hz), 4.27 (m, 1, H-4), 4.05 (ddd, 1, H-3, $J_{3,4}$ = 7.8 Hz, $J_{3,F}$ = 24.4 Hz), 3.63 (dd, 1, H-5a, $J_{4,5a}$ = 3.5 Hz, $J_{5a,5b}$ = 10.6 Hz), 3.53 (dd, 1, H-5b, $J_{4,5b}$ = 5.5 Hz), 3.33 (s, 3, CH_3). Anal. calcd for $C_{20}H_{21}FCl_2O_4$: C, 57.84; H, 5.10. Found: C, 57.83; H, 5.09.

Methyl 2-Deoxy-2-fluoro-β-D-ribofuranoside (4). A solution of 414 mg (1.0 mmol) of **3** in 50 mL of methanol containing 414 mg of 5% palladium-on-carbon and 81 mg of magnesium oxide was hydrogenated at ambient temperature and atmospheric pressure for 4 h. The solution was filtered and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel, eluting with 95:5 chloroform-methanol. A white crystalline solid was obtained: yield, 153 mg (92%). Mp 77-78 °C; TLC, $CHCl_3$-MeOH (9:1),

R_f 0.4; MS *m/e* 167 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 5.34 (d, 1, 3-OH, $J_{3,OH}$ = 6.8 Hz), 4.91 (d, 1, H-1, $J_{1,F}$ = 11.0 Hz), 4.72 (t, 1, 5-OH, J = 5.7 Hz), 4.65 (dd, 1, H-2, $J_{2,3}$ = 3.9 Hz, $^2J_{2,F}$ = 53.4 Hz), 3.98 (doublet of m's, 1, H-3, $J_{3,4}$ = 3.4 Hz, $J_{3,F}$ = 26.6 Hz), 3.78 (m, 1, H-4), 3.60 (ddd, 1, H-5a, $J_{5a,5b}$ = 11.9 Hz, $J_{4,5a}$ = 3.2 Hz), 3.38 (m, 1, H-5b, $J_{4,5b}$ = 5.5 Hz), 3.27 (s, 3, CH_3). Anal. calcd for $C_6H_{11}FO_4$: C, 43.37; H, 6.67. Found: C, 43.26; H, 6.90.

Methyl 3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranoside (5). To a cold (ice bath) solution of 175 mg (1.05 mmol) of **4** was added 0.49 mL (4.22 mmol) of benzoyl chloride. The solution was allowed to warm up to ambient temperature where it was kept for 20 h and poured over ice-aqueous saturated sodium bicarbonate (200 mL). The mixture was stirred until the ice melted and was then extracted with methylene chloride. The methylene chloride solution was washed with ice-cold dilute sulfuric acid, then water, dried over magnesium sulfate, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel, eluting with cyclohexane-ethyl acetate (95:5). A crystalline solid was obtained: yield 335 mg (85%). Mp 83-84 °C (lit. 80-88 °C); TLC, cyclohexane-ethyl acetate (3:1), R_f 0.6; MS *m/z* 375 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.07-8.04 (m, 4, ortho aromatic H's), 7.59-7.51 (m, 2, para aromatic H's), 7.47-7.36 (m, 4, meta aromatic H's), 5.57 (ddd, 1, H-3, $J_{3,F}$ = 23.7 Hz, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 7.4 Hz), 5.16 (dd, 1, H-2, $^2J_{2,F}$ = 52.8 Hz), 5.11 (d, 1, H-1, $J_{1,F}$ = 10.1 Hz), 4.72-4.65 (m, 2, H-4, H-5a), 4.51-4.44 (m, 1, H-5b), 3.37 (s, 3, CH_3). Anal. calcd for $C_{20}H_{19}FO_6$: C, 64.16; H, 5.12. Found: C, 64.23; H, 5.24.

3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-D-ribofuranoside (6). A solution of 4.49 g (12.0 mmol) of **5** in 60 mL of 90% aqueous trifluoroacetic acid was kept for 20 h at ambient temperature, diluted with 60 mL of chloroform, and poured slowly over 600 mL of ice and saturated aqueous sodium bicarbonate solution. The chloroform layer was washed with sodium bicarbonate solution until the pH of the aqueous layer did not change, then washed with water, dried over magnesium sulfate, and evaporated to dryness in vacuo. The syrupy residue was purified by flash chromatography on silica gel with cyclohexane-ethyl acetate (3:1) as the eluting solution. A colorless syrup was obtained: yield 3.86 g (89%). TLC, cyclohexane-ethyl acetate (3:1), R_f 0.4; MS *m/z* 361 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.08-7.99 (m, 4, ortho aromatic H's), 7.62-7.37 (m, 6, meta and para aromatic H's), (2.25 H) [5.63 (ddd, H-3β, $J_{2,3}$ = 3.9 Hz, $J_{3,4}$ = 7.0 Hz, $J_{3,F}$ = 23 Hz), 5.59 (dd, H-1β, $J_{1,2} \sim 0$, $J_{1,1\text{-OH}}$ = 3.0 Hz, $J_{1,F}$ = 9.6 Hz), 5.65-5.59 (m, H-1α)], 5.43 (ddd, 0.25 H, H-3α, $J_{2,3}$ = 6.5 Hz, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 15.4 Hz), (1 H) [5.20 (dt, H-2α, $J_{2,F}$ = 52.2 Hz), 5.19 (dd, H-2β, $J_{2,F}$ = 52.6 Hz, $J_{2,3}$ = 3.9 Hz)], 4.71-4.67 (m, 2 H, H-4α, H-4β, H-5aα and H-5aβ), 4.63 (m, 0.75 H, H-5bβ, $J_{5a,5b}$ = 12.7 Hz, $J_{4,5b}$ = 6.5 Hz), 4.51 (m, 0.25 H, H-5bα, $J_{5a,5b}$ = 12.2 Hz, $J_{4,5b}$ = 4.2 Hz), 3.41 (dd, 0.25 H, 1-OHα, $J_{1,OH}$ = 4.6 Hz, $J_{F,OH}$ = 10.2 Hz), 3.03 (t, 0.75 H, 1-OHβ, $J_{1,OH}$ = $J_{F,OH}$ = 3.0 Hz),

1.56 (s, H_2O). Anal. calcd for $C_{19}H_{17}FO_6 \cdot 0.15H_2O$: C, 62.86; H, 4.80. Found: C, 62.89; H, 4.94.

1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranoside (7). A solution of 250 mg (0.69 mmol) of **6** in anhydrous pyridine (2 mL) was chilled in an ice bath, treated with 0.18 mL (1.90) mmol of acetic anhydride, then kept 20 h at ambient temperature, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel using cyclohexane-ethyl acetate (9:1) as eluting solution giving **7** as a crystalline solid: yield 208 mg (75%). Mp 90-92 °C; TLC, cyclohexane-ethyl acetate (3:1), R_f 0.59; MS *m/z* 403 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.07-8.03 (m, 4 H, ortho aromatic H's), 7.64-7.38 (m, 6 H, meta and para aromatic H's), 6.37 (d, 1 H, H-1, $J_{1,2} \sim 0$, $J_{1,F} = 10.2$ Hz), 5.57 (ddd, 1 H, H-3, $J_{2,3} = 3.8$ Hz, $J_{3,4} = 7.5$ Hz, $J_{3,F} = 23.1$ Hz), 5.25 (dd, 1 H, H-2, $J_{1,2} = 0$ Hz, $J_{2,F} = 52.0$ Hz, $J_{2,3} = 3.8$ Hz), 4.78-4.72 (m, 2 H, H-4, H-5a), 4.47 (dd, 1 H, H-5b, $J_{5a,5b} = 12.7$ Hz, $J_{4,5b} = 4.5$ Hz), 1.95 (s, 3 H, CH_3). Anal. calcd for $C_{21}H_{18}FO_7$: C, 62.68; H, 4.76. Found: C, 62.64; H, 4.70.

3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-D-ribofuranosyl bromide (8). A cold (ice bath) solution of 2.99 g (7.4 mmol) of **7** in 40 mL of anhydrous ethylene chloride was treated with 40 mL of 30% HBr in acetic acid, allowed to warm up to ambient temperature for 3 days, and evaporated to dryness in vacuo. A solution of the residue in 20 mL of anhydrous toluene was evaporated to dryness. The process was repeated twice giving a syrup. TLC, cyclohexane-ethyl acetate (3:1), R_f 0.6 (β) and 0.5 (α); ^1H NMR ($CDCl_3$) δ 8.15-8.01 (m, 4 H, ortho aromatic H's), 7.63-7.35 (m, 6 H, meta and para aromatic H's), 6.71 (d, 0.2 H, H-1α, $J_{1,2} = 4.5$ Hz, $J_{1,F} = 0$ Hz), 6.52 (d, 0.8 H, H-1β, $J_{1,F} = 12.0$ Hz, $J_{1,2} = 0$ Hz), 5.99 (ddd, 0.8 H, H-3β, $J_{3,F} = 22.1$ Hz, $J_{2,3} = 3.6$ Hz, $J_{3,4} = 8.2$ Hz), 5.62 (dd, 0.8 H, H-2β, $J_{2,F} = 53.8$ Hz), 5.60 (ddd, 0.2 H, H-3β, $J_{3,4} = 4.0$ Hz, $J_{2,3} = 7.0$ Hz, $J_{3,F} = 1.7$ Hz), 5.17 (ddd, 0.2 H, H-2α, $J_{2,F} = 50.8$ Hz), (2.2 H) [4.87 (m, H-4β), 4.79 (dd, H-5aβ, $J_{4,5a} = 4.1$ Hz, $J_{5a,5b} = 12.2$ Hz), 4.90-4.74 (m, H-4α, H-5aα, H-5bα)], 4.63 (dd, 0.8 H, H-5bβ, $J_{4,5b} = 5.4$ Hz, $J_{5a,5b} = 12.2$ Hz).

2,6-Diazido-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (10). A solution of 101 mg (1.58 mmol) of sodium azide in 1 mL of water was added in one portion to a solution of 314 mg (0.59 mmol) of **13** in 27 mL of ethanol. The resulting solution was refluxed for 1 h and kept at ambient temperature for 20 h. The precipitate that had formed was collected by filtration and washed well with water: yield 214 mg (75%). Mp 139-140 °C (dec); TLC, cyclohexane-ethyl acetate (3:1), R_f 0.25; MS *m/z* 545 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.10 (m, 2, ortho aromatic H's), 8.02 (s, 1, H-8), 7.92 (m, 2, ortho aromatic H's), 7.62 (m, 1, para aromatic H's), 7.56 (m, 1, para aromatic H's), 7.47 (m, 2, aromatic H's), 7.39 (m, 2, aromatic H's), 6.24 (dd, 1, H-1', $J_{1',2'} = 1.8$ Hz, $J_{1',F} = 19.4$ Hz), 6.04-5.84 (m, 2, H-2', H-3', $J_{2',3'} = 4.9$ Hz), 4.84-4.76 (m, 2, H-4', H-5'a), 4.68-4.61 (m, 1, H-5'b). Anal. calcd for $C_{24}H_{17}FN_{10}O_5$: C, 52.94; H, 3.15; N, 25.73. Found: C, 52.65; H, 3.16; N, 25.47.

2,6-Diamino-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (11). A solution of 227 mg (0.42 mmol) of **10** in 100 mL of ethanol and 50 mL of dimethylacetamide containing 75 mg of 5% palladium-on-carbon was hydrogenated for 20 h at room temperature and atmospheric pressure. The catalyst was removed by filtration and washed well with dimethylacetamide. The combined filtrate and wash was evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel using $CHCl_3$-MeOH (95:5) as eluting solution, giving **11** as a crystalline solid: yield 195 mg (94%). Mp 148-150 °C; TLC, $CHCl_3$-MeOH (9:1) R_f 0.27; MS *m/z* 493 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.08 (m, 2, ortho aromatic H's), 7.92 (m, 2, ortho aromatic H's), 7.62 (s, 1, H-8), 7.60 (m, 1, para aromatic H), 7.52 (m, 1, para aromatic H), 7.46 (m, 2, meta aromatic H's), 7.36 (m, 2, meta aromatic H), 6.31 (ddd, 1, H-3', $J_{2',3'}$ = 4.7 Hz, $J_{3',4'}$ = 8.3 Hz, $J_{3',F'}$ = 19.3 Hz), 6.09 (dd, 1, H-1', $J_{1',2'}$ = 1.6 Hz, $J_{1',F'}$ = 20.6 Hz), 6.01 (dd, 1, H-2', $J_{2',3'}$ = 4.8 Hz, $^2J_{2',F'}$ = 52.7 Hz), 5.41 (br s, 2, NH_2), 4.82 (br s and dd, 3 H, NH_2 and H-5'a, $J_{4',5'a}$ = 3.7 Hz, $J_{5'a,5'b}$ = 12.1 Hz), 4.74 (m, 1, H-4'), 4.59 (dd, 1, H-5'$_b$, $J_{4',5'b}$ = 4.2 Hz). Anal. calcd for $C_{24}H_{21}FN_6O_5$: C, 58.53; H, 4.30; N, 17.07. Found: 58.52; H, 4.51; N, 16.81.

In another run using crude **10** containing some of the 7-β isomer, an 8% yield of 2,6-diamino-7-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine was isolated; MS *m/z* 493 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.08 (m, 2, ortho aromatic CH), 7.94 (s, 1, H-8), 7.83 (m, 2, ortho aromatic CH), 7.56-7.39 (m, 6, aromatic CH), 6.10 (m, 1, H-1'), 5.70-5.40)m, 4, H-2', H-3', NH_2), 4.93-4.83 (m, 4, H-4', H-5'a, NH_2), 4.68-4.64 ppm (m, 1, H-5'b).

2,6-Diamino-9-(2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (12). A solution of 314 mg (0.64 mmol) of **11** in 25 mL of methanol containing 0.1 mL of sodium methoxide in methanol (25% w/w) was kept one hour at room temperature, neutralized with glacial acetic acid, and evaporated to dryness in vacuo. The residue (**12**) was purified by preparative thin-layer chromatography (2 mm Brinkmann Silica Gel 60 F254 plates) with $CHCl_3$-MeOH (3:1) as the developing solvent. Extraction with methanol gave 106 mg of a gel. The gel was further purified by flash chromatography on silica gel using $CHCl_3$-MeOH (9:1) as eluting solution. Attempts to recrystallize **12** from water and from ethanol gave a gel. Again a gel was obtained: yield 71 mg (39%). Mp 145 °C; TLC, $CHCl_3$-MeOH (3:1), R_f 0.52; MS *m/z* 285 $(M + 1)^+$; UV λ_{max} ($\epsilon \times 10^{-3}$) 292 (10.3) and 252 (12.2) at pH 1; 280 (10.2) and 256 (9.63) at pH 7; 280 (10.5) and 256 (9.59) at pH 13; ^1H NMR (Me_2SO-d_6) δ 7.95 (s, 1, H-8), 6.78 (br s, 2, NH_2), 6.04 (dd, 1, H-1', $J_{1',2'}$ = 3.3 Hz, $J_{1',F'}$ = 16.4 Hz), 5.83 (br s, 2, NH_2), 5.65 (d, 1, 3'-OH, $J_{3',3'\text{-OH}}$ = 5.9 Hz), 5.32 (ddd, 1, H-2', $J_{2',3'}$ = 4.4 Hz, $^2J_{2',F'}$ = 53.0 Hz), 5.28 (t, 1, 5'-OH, $J_{5',5'\text{-OH}}$ = 5.5 Hz), 4.39 (m, 1, H-3', $J_{3',F'}$ = 22 Hz, $J_{3',4'}$ = 5.9 Hz), 3.94 (m, 1, H-4'), 3.75 (ddd, 1, $J_{5',5'}$ = 12.2 Hz, $J_{4',5'a}$ = 3.0 Hz, $J_{5'a,5'a\text{-OH}}$ = 5.0 Hz), 3.57 (ddd, 1, $J_{4',5'}$ = 3.7 Hz, $J_{5',5'\text{-OH}}$ = 6.0 Hz), 3.33 (s, H_2O), 1.06 (t, EtOH). Anal. calcd for

$C_{10}H_{13}FN_6O_3 \cdot 0.4H_2O \cdot 0.2EtOH$: C, 41.55; H, 5.03; N, 27.95. Found: C, 41.43; H, 4.85; N, 27.78. A second run gave 310 mg (79%).

9-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)-2,6-dichloropurine (13) and Its α-Anomer. A mixture of 178 mg (0.44 mmol) of **7**, 84 mg (0.44 mmol) of 2,6-dichloropurine, and 7 mg (0.04 mmol) of p-toluenesulfonic acid was fused at 160 °C and 25 mm for 50 min. The melt was partitioned between chloroform and aqueous saturated sodium bicarbonate solution. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel using cyclohexane-ethyl acetate (3:1) as the eluting solution. Four fractions were obtained. The faster fraction was the 9-α anomer of **13**, a crystalline solid: yield 57 mg (22%); TLC, cyclohexane-ethyl acetate, R_f 0.21; ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 1, H-8, J = 2.8 Hz), 8.05 (m, 4, ortho aromatic H's), 7.61 (m, 2, para aromatic H's), 7.48 (m, 4, meta aromatic H's), 6.76 (dd, 1, H-1', $J_{1',2'}$ = 3.2 Hz, $J_{1',F'}$ = 18.1 Hz), 5.70 (m, 1, H-3', $J_{2',3'}$ = 4.0 Hz, $J_{3',4'}$ = 7.8 Hz, $J_{3',F'}$ = 19.9 Hz), 5.62 (dt, 1, H-2', $J_{2',3'}$ = 4.0 Hz, $^2J_{2',F'}$ = 52.9 Hz, 5.06 (m, 1, H-4', $J_{3',4'}$ = 7.8 Hz), 4.79 (dd, 1, H-5'a, $J_{4',5'a}$ = 3.3 Hz, $J_{5'a,5'b}$ = 12.5 Hz), 4.62 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.9 Hz). The slower fraction was the β-anomer (**13**), a hard glass: yield 61 mg (23%); TLC, cyclohexane-ethyl acetate, R_f 0.21; ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1, H-8), 8.10 (m, 2, ortho aromatic H's), 7.93 (m, 2, ortho aromatic H's), 7.64 (m, 1, para aromatic H), 7.57 (m, 1, para aromatic H), 7.49 (m, 2, meta, aromatic H), 7.41 (m, 2, meta aromatic H), 6.32 (dd, 1, H-1', $J_{1',F'}$ = 18.0 Hz, $J_{1',2'}$ = 2.0 Hz), 5.96 (dd, 1, H-2', $J_{2',F'}$ = 52.4 Hz, $J_{2',3'}$ = 4.9 Hz), 5.94 (ddd, 1, H-3', $J_{3',F'}$ = 16.5 Hz, $J_{3',4'}$ = 7.5 Hz), 4.86 (m, 1, H-5'a, $J_{4',5'a}$ = 3.2 Hz), 4.82 (m, 1, H-4'), 4.64 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.9 Hz, $J_{5'a,5'b}$ = 12.1 Hz).

2,6-Dichloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)purine (13). A solution of 2,6-dichloropurine (1.88 g, 9.94 mmol) and mercuric cyanide (1.74 g, 6.62 mmol) in anhydrous ethylene chloride (100 mL) was stirred at ambient temperature for 20 min before a solution of **8** (made from 4.97 mmol of **7**) in ethylene chloride (50 mL) was added. Suspension was stirred for 24 h at ambient temperature, then washed with water, saturated $NaHCO_3$ solution, then water, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel using cyclohexane-ethyl acetate (3:1) as eluting solution. The product (9β) was obtained as a hard glass: yield 1.56 g (59%).

The 9α isomer was also isolated: yield 63 mg (2.4%).

Extensive chromatography from a previous run gave some 7β isomer, which was identified by mass spectra and its ^{1}H-NMR spectra.

2'-Deoxy-2'-fluoroguanosine (14). To a solution of 21 mg (0.07 mmol) of **12** in 6 mL of water was added 4.7 μL of adenosine deaminase. The resulting solution was stirred 20 h at room temperature, boiled for one minute, filtered, and evaporated to dryness in vacuo.

The residue crystallized from water as a white solid: yield 16 mg (83%). Mp 262-264 °C (dec); TLC, $CHCl_3$-MeOH-NH_4OH (3:1:0.04), R_f 0.4; MS *m/z* 286 $(M + 1)^+$; UV λ_{max} (ϵ x 10^{-3}) 256 (13.0) at pH 1, 252 (14.1) at pH 7; 265 (12.3) at pH 13; ^1H NMR (Me_2SO-d_6) δ 10.65 (br s, 1, NH), 7.95 (s, 1, H-8), 6.53 (br s, 2, NH_2), 6.00 (dd, 1, H-1', $J_{1',F'}$ = 16.6 Hz, $J_{1',2'}$ = 2.9 Hz), 5.65 (d, 1, 3'-OH, $J_{3',3'\text{-OH}}$ = 6.1 Hz), 5.24 (ddd, 1, H-2', $^2J_{2',F'}$ = 52.9 Hz, $J_{2',3'}$ = 4.4 Hz), 5.12 (t, 1, 5'-OH, $J_{5',5'\text{-OH}}$ = 5.5 Hz), 4.36 (m, 1, H-3', $J_{3',F'}$ = 18.8 Hz, $J_{3',4'}$ = 6.4 Hz), 3.92 (m, 1, H-4'), 3.72 (ddd, 1, H-5'a, $J_{4',5'a}$ = 3.0 Hz, $J_{5'a,5'b}$ = 12.3 Hz), 3.58 (ddd, 1, H-5'b, $J_{4',5'b}$ = 4.0 Hz). Anal. calcd for $C_{10}H_{12}FN_5O_4 \cdot 1.5H_2O$: C, 38.47; H, 4.84; N, 22.43. Found: C, 38.52; H, 4.78; N, 22.55.

2'-Deoxy-3',5'-di-*O*-benzoyl-2,2'-difluoroadenosine (15). A solution of 153 mg (0.31 mmol) of **11** in 6 mL (60%) pyridine-HF was kept at −20 °C for 15 min before adding 55 μL (0.47 mmol) of t-butyl nitrite in two portions of 30 μL followed by 25 μL. The reaction solution was kept at −20 °C for 1 h more and then poured slowly over 300 mL of saturated $NaHCO_3$-ice. Enough solid $NaHCO_3$ was added to maintain a pH of 8. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aqueous saturated $NaHCO_3$, then water, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel using cyclohexane-ethyl acetate (1:1) as eluting solution. The product was obtained as a crystalline solid: yield 95 mg (60%). Mp 208-209 °C; TLC, $CHCl_3$-MeOH (95:5), R_f 0.38; MS *m/z* 496 $(M + 1)^+$; ^1H NMR ($CDCl_3$) δ 8.09 (m, 2, ortho aromatic H's), 8.00 (m, 2, ortho aromatic H's), 7.92 (br s, 1, H-8), 7.62 (m, 1, para aromatic H), 7.56 (m, 1, para aromatic H), 7.47 (m, 2, meta aromatic H), 7.41 (m, 2, meta aromatic H), 6.21 (dd, 1, H-1', $J_{1',2'}$ = 2.1 Hz, $J_{1',F'}$ = 19.0 Hz), 5.99 (m, 1, H-3', $J_{2',3'}$ = 4.9 Hz, $J_{3',4'}$ = 7.7 Hz, $J_{3',F'}$ = 16.6 Hz), 5.96 (ddd, 1, H-2', $^2J_{2',F'}$ = 52.8 Hz), 5.87 (br s, 2, NH_2), 4.83 (dd, 1, H-5'a, $J_{5'a,5'b}$ = 12.1 Hz, $J_{4',5'a}$ = 3.0 Hz), 4.77 (m, 1, H-4'), 6.40 (dd, 1, H-5'b, $J_{4',5'b}$ = 4.1 Hz). Anal. calcd for $C_{24}H_{19}F_2N_5O_5$: C, 58.18; H, 3.86; N, 14.14. Found: C, 58.09; H, 3.72; N, 13.85.

2'-Deoxy-2,2'-difluoroadenosine (16). To a solution of 360 mg (0.73 mmol) of **15** in 110 mL of acetonitrile and 44 mL of water was added 102 mg (24.4 mmol) of $LiOH \cdot H_2O$. The resulting solution was stirred for 20 h at ambient temperature, neutralized with glacial HOAc, and evaporated to dryness in vacuo. From an aqueous solution of the residue, after filtering, was obtained **16** as a white solid: yield 106 mg. Mp 225-227 °C.

A second crop was obtained by passing the filtrate through a bio-bead column (12 x 1 cm) (Bio-Rad Bio-Beads 5M-4, 20-50 mesh). The product was obtained by eluting with MeOH: yield 28 mg. Mp 225-226 °C; total yield 64%.

The analytical sample was obtained from a previous run by recrystallization from H_2O. Mp 225-227 °C; TLC, $CHCl_3$-MeOH-NH_4OH (5:1:0.3), R_f 0.43; MS *m/z* 288 $(M + 1)^+$; UV λ_{max} (ϵ x 10^{-3}) 261.2 (13.8) at pH 1; 260.7 (14.8) at pH 7; 261.2 (15.2) at pH 13. ^1H NMR

(Me_2SO-d_6) δ 8.34 (s, 1, H-8), 7.90 (br s, 2, NH_2), 6.35 (dd, 1, H-1', $J_{1',2'}$ = 2.6 Hz, $J_{1',F'}$ = 17.0 Hz), 5.71 (d, 1, 3'-OH, $J_{3',3'\text{-OH}}$ = 6.3 Hz), 5.37 (ddd, 1, H-2', $J_{2',3'}$ = 4.4 Hz, $^2J_{2',F'}$ = 52.8 Hz), 5.10 (t, 1, 5'-OH, $J_{5',5'\text{-OH}}$ = 5.5 Hz), 4.44 (m, 1, H-3, $J_{3',F'}$ = 19 Hz, $J_{3',4'}$ = 6.9 Hz), 3.95 (m, 1, H-4'), 3.74 (ddd, 1, H-5'a, $J_{4',5'a}$ = 2.8 Hz, $J_{5'a,5'b}$ = 12.3 Hz), 3.58 (ddd, 1, H-5'b, $J_{4',5'b}$ = 4.2 Hz). Anal. calcd for $C_{10}H_{11}F_2N_5O_3$: C, 41.51; H, 3.92; N, 24.20. Found: C, 41.68; H, 3.95; N, 23.89.

2-Chloro-2'-deoxy-2'-fluoroadenosine (17). A solution of 1.39 g (2.60 mmol) of **13** in 150 mL of ethanolic-ammonia (saturated at 0 °C) was kept at ambient temperature for 36 h in a stainless steel bomb and then was evaporated to dryness in vacuo. A solution of the residue in hot methanol deposited, on cooling, a crystalline solid (**17**): yield 365 mg. Mp 220-222 °C (dec); TLC, $CHCl_3$-MeOH (3:1), R_f 0.7; UV λ_{max} (ϵ x 10^{-3}) 264 (14.9) at pH 1; 264 (15.6) at pH 7; 264 (15.8) at pH 13; MS *m/z* 304 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 8.38 (s, 1, H-8), 7.88 (br s, 2, NH_2), 6.16 (dd, 1, H-1', $J_{1',2'}$ = 2.7 Hz, $J_{1',F'}$ = 16.8 Hz), 5.76 (br s, 1, 3'-OH), 5.37 (dd, 1, H-2', $J_{2',3'}$ = 4.4 Hz, $J_{2',F'}$ = 52.7 Hz), 5.12 (br s, 1, 5'-OH), 4.43 (ddd, 1, H-3', $J_{3',F'}$ = 18.9 Hz, $J_{3',4'}$ = 6.7 Hz), 3.97 (m, 1, H-4'), 3.75 (dd, 1, H-5'a, $J_{4',5'a}$ = 2.5 Hz, $J_{5'a,5'b}$ = 12.3 Hz), 3.59 (dd, 1, H-5'b, $J_{4',5'b}$ = 3.8 Hz). Anal. calcd for $C_{10}H_{11}ClFN_5O_3 \cdot 0.4H_2O$: C, 38.63; H, 3.83; N, 22.53. Found: C, 38.67; H, 3.70; N, 22.47.

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