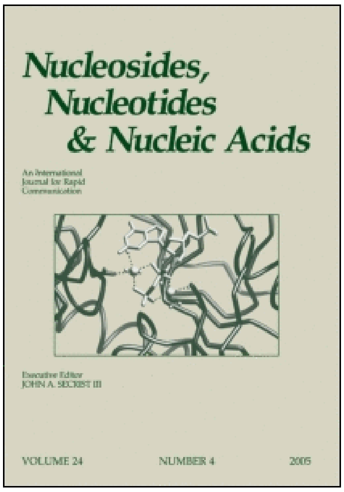

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Synthesis and Anticancer Evaluation of 4'-*C*-Methyl-2'-Fluoro *Arabino* Nucleosides

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SYNTHESIS AND ANTICANCER EVALUATION OF 4′-*C*-METHYL-2′-FLUORO *ARABINO* NUCLEOSIDES

Kamal N. Tiwari, Anita T. Shortnacy-Fowler, William B. Parker, William R. Waud, and John A. Secrist III

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□ *As part of an ongoing program to develop novel antitumor agents over the years, we have synthesized and evaluated a number of 4′-C-substituted nucleosides. A few years ago, we reported the first synthesis of 4′-C-hydroxymethyl-2′-fluoro* arabino *nucleosides, which did not exhibit any cytotoxicity. In our exploration of related compounds, we synthesized and evaluated the 4′-C-methyl-2′-fluoro* arabino *nucleosides in both the purine and pyrimidine series. In the pyrimidine series, 1-(4-C-methyl-2-fluoro-β-D-arabinofuranosyl) cytosine (**13**) was found to be highly cytotoxic and had significant antitumor activity in mice implanted with human tumor xenografts. The synthesis and anticancer activity of this series of nucleosides are reported.*

Keywords 4′-*c*-methylnucleosides; anticancer activity; 2′-fluoroarabino purine and pyrimidine; nucleosides

INTRODUCTION

In our program to develop novel nucleosides as potential antitumor agents, we have been successful in obtaining useful clinical agents from arabinofuranosyl nucleosides.[1–4] This success has been demonstrated in our program by the approval for human use of clofarabine and the 5′-phosphate of fludarabine, both arabino nucleosides. Recently, several groups have reported the synthesis and biological activities of 4′-*C*-methylnucleosides in the 2′-deoxy, ribo and arabino series.[5–10] The reported in vivo

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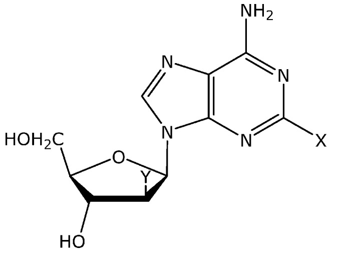
anticancer activity of 4′-*C*-methyl-araC suggests that incorporation of a 4′-*C*-methyl group probably allows the retention of substrate activity for deoxycytidine kinase, the enzyme by which the arabinocytosine nucleoside is converted to its monophosphate analog.[8] Recently, we incorporated a 4′-*C*-hydroxymethyl into both the 2′-hydroxy and 2′-fluoro arabino series and have reported these results.[11, 12] The marked activities from arabinonucleosides having either the 2′-hydroxyl or 2′-fluoro group in the arabino configuration as in the case of fludarabine and clofarabine, respectively, prompted us to explore the corresponding 4′-*C*-methyl modification in 2′-fluoroarabinonucleosides. Very recently, there have been two reports of compounds from this series of nucleosides that include selected antiviral evaluations.[13, 14] In the present report, we describe the details of our synthetic methods and the anticancer activity evaluations of several purine and pyrimidine nucleosides in this series.

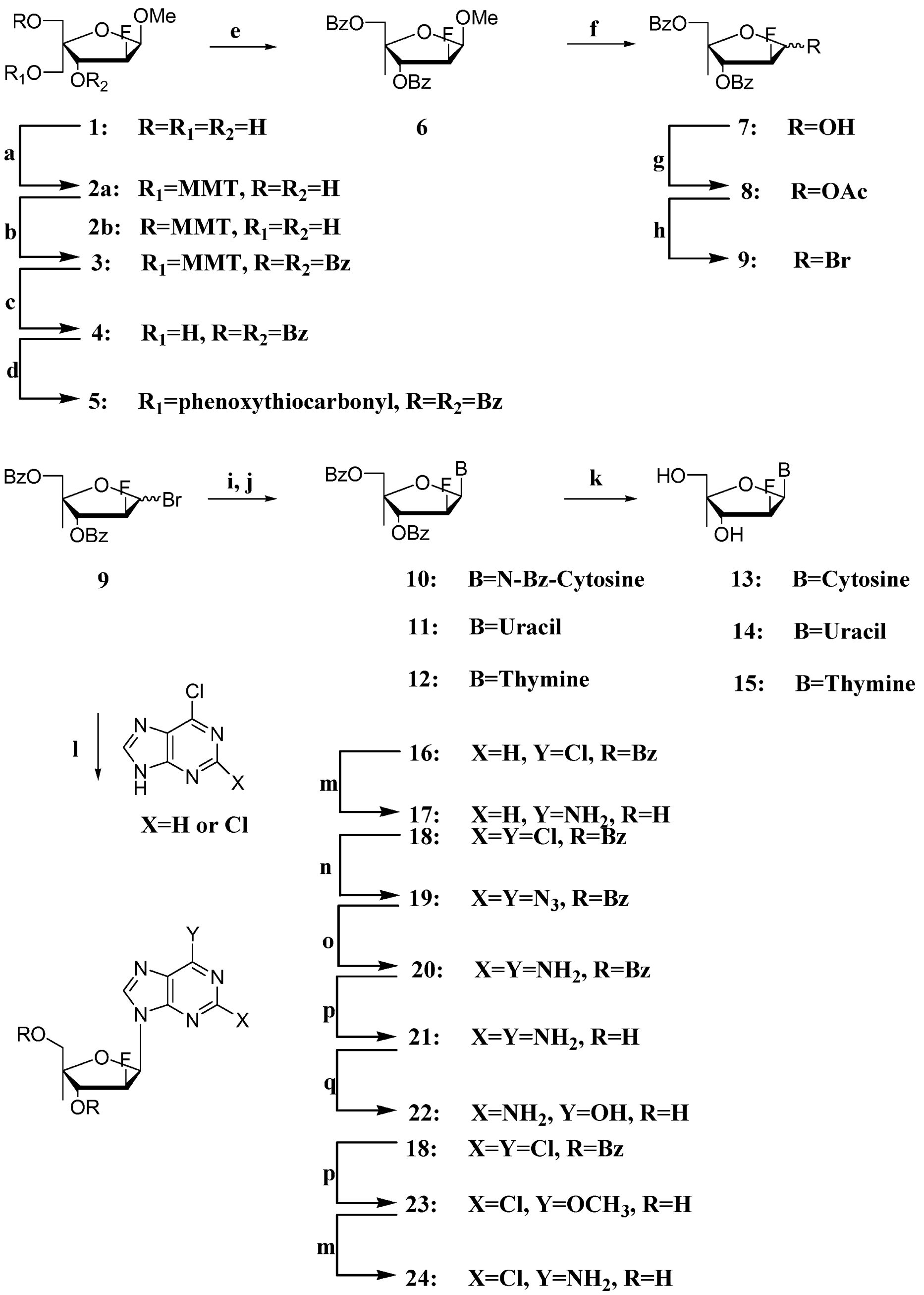


X = Cl; Y = F; clofarabine
X = F; Y = OH; fludarabine

DISCUSSION

Chemistry

Our routes to the target compounds are presented in Scheme 1. We have already reported the synthesis of 4′-*C*-hydroxymethyl-2′-fluoroarabinofuranoside **1** and the corresponding nucleosides.[12] Selective protection of **1** with the monomethoxytrityl (MMT) group was carried out using MMT chloride in pyridine in 30% yield.[15] The undesired isomer **2b** and the unreacted **1** were recycled to increase the yield. The selectively blocked intermediate **2a** was benzoylated to give **3** in 92% yield, which was then detritylated to afford the sugar intermediate **4** in 89% yield. This 4′-*C*-hydroxymethyl analog **4** was converted into 4′-*C*-phenoxythiocarbonyloxymethyl derivative **5** in 90% yield using phenyl chlorothionoformate. Compound **5** was deoxygenated using 1,1′-azobis(cyclohexane-carbonitrile) (ACCN) and tris(trimethyl)silane to provide 4′-*C*-methyl analog **6** in 84% yield.[16] Acetolysis of compound **6** using traditional methods[17] failed to give 1-*O*-acetyl sugar **8**, resulting in either



SCHEME 1 Conditions: (a) MMTr-Cl, pyridine, room temperature, overnight; (b) BzCl, pyridine, room temperature, overnight; (c) 80% AcOH, room temperature, overnight; (d) PhOC(=S)Cl, DMAP, MeCN, room temperature, 3 hours; (e) $(TMS)_3SiH$, ACCN, toluene, 100°C, 5 hours; (f) TFA/H_2O, 65°C, 24 hours; (g) Ac_2O/pyridine, room temperature, overnight; (h) HBr/AcOH, 5°C, overnight; (i) Bases, BSA, MeCN, room temperature, 1–2 hours; (j) persilylated bases, compound **9**, $ClCH_2CH_2Cl$, 100°C, 4 hours; (k) 0.5 N $NaOCH_3$, MeOH, room temperature, 2–7 hours.; then for **13** only, HCl; (l) NaH, MeCN, room temperature, 6 hours; (m) EtOH, NH_3, 80°C, 16 hours; (n) NaN_3, EtOH, reflux, $^1/_2$ hour; (o) 10% Pd/C, H_2, 1 atm, EtOH/DMAC, 18 hours; (p) $NaOCH_3$/MeOH, room temperature, 3 hours; (q) Adenosine deaminase.

no reaction or gradual decomposition. The methyl glycoside **6** was instead hydrolyzed using 9:1 trifluoroacetic acid/water to provide the hydroxy sugar **7** in 83% yield, which was acetylated to produce compound **8** in 91% yield. This sugar intermediate was converted cleanly into glycosyl bromide **9** using 33% HBr in acetic acid. Attempted conversion of **7** directly to **9** resulted in a complex mixture and a very low yield of **9**. The bromosugar **9** was highly reactive and was used directly without purification for coupling reactions.

Coupling of bromosugar **9** with silylated N^4-benzoylcytosine in situ with BSA gave cytosine nucleosides **10/10α** in 54% yield.[18, 19] Separation of α, β anomers afforded pure β anomer **10** as the major product (48%) and α anomer **10α** as the minor product (6%). Similarly, uracil and thymine were coupled with bromo sugar **9** to obtain corresponding nucleosides **11/11α** and **12/12α** in 71% and 68% yields, respectively, with the β anomer as the predominant product. Both anomers of cytosine nucleoside **10** were deblocked using sodium methoxide to get the target compound **13** as well as **13α**. After purification the β anomer **13** was isolated as a hydrochloride salt in 89% yield, and the α anomer **13α** was isolated as the free base in 77% yield. In the case of nucleosides **11** and **12,** only the β anomers were deblocked using the same procedure to obtain compounds **14** (77%) and **15** (92%), respectively. The α anomers of compounds **11** and **12** were not further utilized and were isolated only for characterization purposes to compare with the β anomers.

A series of purine nucleoside analogs were prepared through the coupling of bromosugar **9** with 6-chloropurine and 2, 6-dichloropurine. Sodium salt coupling of **9** with 6-chloropurine gave the desired β nucleoside **16** (36%) and α anomer **16α** (14%).[20] Separate treatment with ethanolic ammonia gave the target compound **17** (74%) and α anomer **17α** (49%), respectively. Similarly 2, 6-dichloropurine was coupled with bromo sugar **9** to obtain the corresponding nucleoside as an anomeric mixture (2:1, β:α ratio) in 64% yield. Both anomers were separated by preparative TLC to provide **18** and **18α** as white foams. Separate treatment of **18** and **18α** with sodium azide in aqueous ethanol at reflux produced the corresponding 2,6-diazido intermediates **19** and **19α**, which were subjected to reduction with Pd/C to afford blocked diaminopurine nucleosides **20** and **20α**, respectively. Deblocking of **20** and **20α** with NaOMe produced the target 2-aminoadenine nucleosides **21** and **21α**. Conversion of **21** to the guanine nucleoside **22** was accomplished by treatment with adenosine deaminase.[21] Though the deamination was slow, it went to completion at room temperature in 68 hours. The 2-chloroadenine nucleosides **24** (84%) and **24α** (75%) were prepared by first converting the dichloropurine nucleosides **18** and **18α** to their 6-methoxy intermediate **23** with sodium methoxide followed by treatment with ethanolic ammonia.[21]

BIOLOGICAL RESULTS

In Vitro Cytotoxicity

The concentration of compound required to inhibit cell growth by 50% (IC_{50}) after 72 hours of incubation was determined for each unprotected analog with eight human tumor cell lines (SNB-7 CNS, DLD-1 colon, CCRF-CEM leukemia, NCI-H23 NSCL, ZR-75–1 breast, LOX melanoma, PC-3 prostate, and CAKI-1 renal). The most active compound in this series was methyl-F-araC (**13,** Table 1), which was found to have significant cytotoxicity against four of the cell lines in the panel. The purine analogs demonstrated modest cytotoxicity against the solid tumor cell lines (IC_{50}'s between 5 and 80 μM), while the uracil and thymine analogs were not active against any cell line (IC_{50}'s greater than 200 μM). The α-anomers **13α**, **17α**, **21α**, and **24α** were also screened but were not found to be cytotoxic (data not shown).

CCRF-CEM cells are a T-cell leukemia cell line that is known to be very sensitive to nucleoside analogs. Methyl-F-araC was a very potent inhibitor of this cell line with an IC_{50} of 0.012 ± 0.003 μM. CCRF-CEM cell growth was also inhibited by the 2-Cl-adenine (**24**), 2,6-diaminopurine (**21**), and guanine (**22**) analogs with IC_{50}'s of approximately 0.5 μM. The inhibition of CCRF-CEM cell growth caused by either methyl-F-araC or the 2-Cl-adenine analog (4′-*C*-methyl-clofarabine, **24**) was prevented by adding dCyd to the culture medium and neither compound was active in cells that lacked dCyd kinase. These results indicated that dCyd kinase was the primary enzyme responsible for the initial activation step of these two agents in CCRF-CEM cells. The cytotoxicity of the diaminopurine analog **21** was prevented by the addition of deoxycoformycin, a potent inhibitor of adenosine deaminase,

TABLE 1 Effect of 4′-methyl-2′-F-2′-deoxy analogs on cell growth

Cell line	**13**	**14**	**15**	**17**	**21**	**22**	**24**
				IC_{50} (μM)			
SNB-7	>200	>200	>200	>200	>200	>200	>200
DLD-1	>200	>200	>200	>200	>200	>200	>200
CCRF-CEM	0.012	>200	>200	3.9	0.18	0.45	0.64
NCI-H23	0.19	>200	>200	17	39	52	79
ZR-75–1	>200	>200	>200	>200	>200	>200	>200
LOX	0.24	>200	>200	>200	37	43	32
PC-3	>200	>200	>200	>200	29	22	140
CAKI-1	0.54	>200	>200	5.8	16	51	17

The cell lines were incubated with various concentrations of the above compounds for 72 hours, and the concentration of drug that resulted in 50% inhibition of cell growth (IC_{50}) was determined. The numbers shown are the result of one experiment except for the cytosine analog, which is the average of three separate determinations. The α-anomers **13α**, **17α**, **21α**, and **24α** were evaluated in all cell lines and were not found to be cytotoxic at the highest concentrations utilized (>200 μM).

which indicated that **21** was deaminated to the dGuo analog before conversion to cytotoxic nucleotides.

In Vitro Metabolic Studies in CCRF-CEM Cells

CCRF-CEM cells were incubated with methyl-F-araC (**13**), araC, and gemcitabine, and the amount of intracellular triphosphate (TP) of each compound was determined. There was significant metabolism of each of these compounds, and their triphosphates did not co-elute with any of the natural nucleotides (ATP, GTP, CTP, or UTP). Incubation of CCRF-CEM cells with 100 nM of each compound for two hours resulted in an intracellular concentration of methyl-F-araC-TP (16 ± 2 pmoles/10^6 cells) that was similar to those of araC-TP (12 ± 1 pmoles/10^6 cells) and gemcitabine-TP (17 ± 3 pmoles/10^6 cells; mean ± SD, N = 3). These results indicated that methyl-F-araC was a good substrate for deoxycytidine kinase. The intracellular half-life of each triphosphate was similar: methyl-F-araC-TP (7.1 hours, N = 2); araC-TP (5.6 hours, N = 2); gemcitabine-TP (5.0 hours, N = 2).

In Vivo Activity

Because of its potent in vitro activity, methyl-F-araC (**13**) was evaluated for in vivo activity against three solid tumor xenografts (CAKI-1 renal, NCI-H23 NSCL, and LOX melanoma). Prior to these studies the maximally tolerated dose of methyl-F-araC was determined to be 3 mg/kg given once per day for 9 consecutive days. Methyl-F-araC demonstrated excellent activity against the CAKI-1 tumors (Figure 1). In each treatment group there were 3 of 6 tumor-free survivors 62 days post implant. Good results were also seen against NCI-H23 and LOX human tumor xenografts (Table 2). Therefore, methyl-F-araC demonstrated good to excellent in vivo antitumor activity in the three solid tumor xenografts that have been tested to date.

SUMMARY

We have synthesized a series of 4′-*C*-methyl-2′-fluoro *arabino* nucleosides in both the purine and pyrimidine series. 1-(4-*C*-Methyl-2-fluoro-β-D-arabinofuranosyl) cytosine (methyl-F-araC, **13**) was found to be highly cytotoxic and had significant antitumor activity in mice implanted with human tumor xenografts. This compound is a substrate for deoxycytidine kinase and shows significant levels of its 5′-triphosphate accumulated in CCRF-CEM cells. The excellent *in vivo* anticancer activity of **13** warrants continued investigation and suggests that evaluation of nucleosides with

TABLE 2 Response of s.c. implanted human tumor xenografts to methyl-F-araC (**13**)

Tumor	Optimal i.p. dosage (mg/kg/dose)	Tumor size range (mm^3)	T-C (days)	Tumor-free survivors
CAKI-1 renal	3	100–245	>34.6[a]	3/6
NCI-H23 NSCL	4	100–270	18.4[b]	0/5
LOX melanoma	3	100–221	15.0[c]	0/6

Xenografts were implanted sc on the flanks of female nude mice. When tumors were approximately 100–250 mg, they were treated ip with 3 or 4 mg/kg/dose of methyl-F-araC (q1d × 9) and tumor size was measured twice weekly thereafter. Tumor-free survivors are the number of mice that were tumor-free at the end of the experiment/total number of mice in the treatment group.

[a] The difference in the median of times poststaging for tumors of the treated (T) and control (C) groups to double in mass three times.

[b] The difference in the median of times poststaging for tumors of the treated (T) and control (C) groups to double in mass two times.

[c] The difference in the median of times poststaging for tumors of the treated (T) and control (C) groups to double in mass four times.

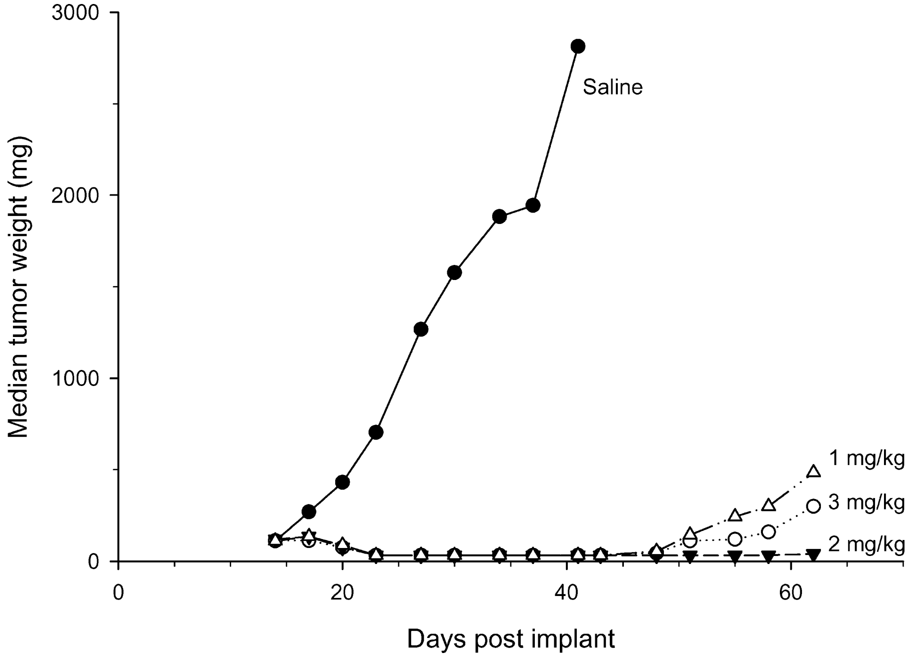


FIGURE 1 Effect of methyl-F-araC on CAKI-1 tumor growth. Female NCr-nu athymic mice were implanted subcutaneously with CAKI-1 tumor fragments. When tumors were approximately 100–250 mg, mice were treated ip with methyl-F-araC at 1, 2, or 3 mg/kg/dose (1 treatment each day for 9 consecutive days starting on day 14). Each treatment group contained 6 mice. The tumors were measured with calipers twice each week, and the weight (mg) was calculated. In this experiment there were 3 of 6 tumor-free survivors at the end of the experiment (62 days post implant) in each treatment group.

modifications at the 4′ position could lead to the identification of a new analog with superior antitumor activity.

EXPERIMENTAL

TLC analysis was performed on Analtech (Newark, DE, USA) precoated (250 μm) silica gel GF plates. Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MR, USA) and are uncorrected. Purifications by flash chromatography were carried out on Merck silica gel (230–400 mesh). Evaporations were performed with a rotary evaporator, higher boiling solvents (DMF, pyridine) were removed in vacuo (<1 mm, bath to 35°C). Products were dried *in vacuo* (<1 mm) at 22–25°C over P_2O_5. The mass spectral data were obtained with a Varian-MAT 311A mass spectrometer (Palo Alto, CA, USA) in the fast atom bombardment (FAB) mode or with a Bruker BIOTOF II (Billerica, MA, USA) by electrospray ionization (ESI). ^{1}H NMR spectra were recorded on a Nicolet NT-300 NB spectrometer (Madison, WI, USA) operating at 300.635 MHz. Chemical shifts in $CDCl_3$ and Me_2SO-d_6 are expressed in parts per million downfield from tetramethylsilane (TMS), and in D_2O chemical shifts are expressed in parts per million downfield from sodium 3-(trimethylsilyl)propionate-2,2,3.3-d_4 (TMSP). Chemical shifts (δ) listed for multiplets were measured from the approximate centers, and relative integrals of peak areas agreed with those expected for the assigned structures. UV absorption spectra were determined on a Perkin-Elmer lambda 9 spectrophotometer (Norwalk, CT, UK) by dissolving each compound in MeOH or EtOH and diluting 10-fold with 0.1 N HCl, pH 7 buffer, or 0.1 N NaOH. Numbers in parentheses are extinction coefficients ($\varepsilon \times 10^{-3}$). Microanalyses were performed by Atlantic Microlab, Inc. (Atlanta, GA, USA) or the Spectroscopic and Analytical Department of Southern Research Institute (Birmingham, AL, USA). Analytical results indicated by element symbols were within ±0.4% of the theoretical values, and where solvents are indicated in the formula, their presence was confirmed by ^{1}H NMR.

Cell Culture Cytotoxicity

All cell lines were grown in RPMI 1640 medium containing 10% fetal bovine serum, sodium bicarbonate, and 2 mmol glutamine. For in vitro evaluation of the sensitivity of these cell lines to compounds, cells were plated in 96-well microtiter plates and then were exposed continuously to various concentrations of the compounds for 72 hours at 37°C. Cell viability was measured using the MTS assay [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt; MTS and an electron coupling reagent (phenazine ethosulfate; PES)]. Absorbance was read at 490 nm. The background absorbance mean was subtracted from the data followed by conversion to percent of control. The drug concentrations producing survival just above and below 50% level were used in a linear regression analysis to calculate the IC_{50}.

Measurements of Intracellular Triphosphates

CCRF-CEM cell extracts were collected by centrifugation and resuspended in ice-cold 0.5 M perchloric acid. The samples were centrifuged at 12,000 × g, and the supernatant fluid was neutralized and buffered by adding 4 M KOH and 1 M potassium phosphate, pH 7.4. $KClO_4$ was removed by centrifugation, and a portion of the supernatant fluid was injected onto a strong anion exchange HPLC (Bio Basic anion exchange column, Thermo Electron Corp., Bellefonte, PA, USA). Nucleotides were eluted with a 30-minutes linear salt and pH gradient from 6 mM ammonium phosphate (pH 2.8) to 900 mM ammonium phosphate (pH 6). Peaks were detected as they eluted from the column by their absorbance at 254 nm.

Experimental Chemotherapy

Mice, obtained from various commercial suppliers, were housed in microisolator cages and were allowed commercial mouse food and water ad libitum. The three human tumors were obtained from the Developmental Therapeutics Program Tumor Repository (Frederick, MD, USA) and were maintained in in vivo passage. Only tumor lines that tested negative for selected viruses were used. For the in vivo evaluation of the sensitivity of human tumors to the compounds, female NCr-*nu* athymic mice were implanted subcutaneously (sc) with 30–40 mg tumor fragments. In each experiment, methyl-F-araC (**13**) was tested at three dosage levels. Procedures were approved by the Southern Research Institutional Animal Care and Use Committee, which conforms to the current Public Health Service *Policy on Humane Care and Use of Laboratory Animals* and the *Guide for the Care and Use of Laboratory Animals*.

Antitumor activity was assessed on the basis of delay in tumor growth (T-C). The delay in tumor growth is the difference in the median of times poststaging for tumors of the treated and control groups to double in mass two, three, or four times. Drug deaths and any other animal whose tumor failed to attain the evaluation size were excluded. Tumors were measured in two dimensions (length and width) twice weekly, and the tumor weight was calculated using the formula (length × width^2)/2 and assuming unit density. The mice were also weighed twice weekly.

Methyl 4-*C*-(*p*-Anisyldiphenylmethoxymethyl)-2-deoxy-2-fluoro-β-D-arabinofuranoside (2a) and Methyl 5-O-(*p*-Anisyldiphenylmethyl)-4-*C*-hydroxymethyl-2-deoxy-2-fluoro-β-D-arabinofuranoside (2b). To a solution of **1** (342 mg, 1.75 mmol) in dry pyridine (15 mL) was added in one portion solid 97% p-anisylchlorodiphenylmethane (816 mg, 2.56 mmol). The reaction mixture was stirred at room temperature for 20 hours then evaporated. The resulting residue was coevaporated with two portions of toluene before being purified by flash chromatography on silica gel (45 g) using a gradient from $CHCl_3$ to 97: 3 $CHCl_3$/MeOH. The first eluted fraction gave **2a** ((246 mg, 30%) as a white foam: TLC 97: 3 $CHCl_3$/MeOH, R_f 0.45; MS m/z 491 $(m+Na)^+$; ^1H NMR ($CDCl_3$) 7.20–7.45 (m, 12H, aromatic H's), 6.86–6.88 (m, 2H, para- H's), 5.10–5.33 (m, 2H, H-1 and H-2, $J_{2,F}$ = 54 Hz), 4.44–4.52 (m, 1H, H-3), 3.81 (s, 3H, OCH_3 of 4-methoxyphenyl), 3.56 (s, 3H, 1-OCH_3), 3.46–3.58 (m, 3H, two 4-*C*-hydroxymethyl and one 5-CH_2 hydrogens), 3.04 (d, 1H, 5-CH_2, $J_{5a,5b}$ = 10.3 Hz), 2.95(d, 1H, 3-OH, $J_{3,3\text{-OH}}$ = 10 Hz), 2.18(t, 1H, 5-OH, $J_{5a,5\text{-OH}}$ = 6.3 Hz). The second fraction provided **2b** (137 mg, 17%): TLC 97: 3 $CHCl_3$/MeOH, R_f 0.39; MS m/z 491 $(m+Na)^+$; ^1H NMR ($CDCl_3$) 7.20–7.48 (m, 12H, aromatic H's), 6.82–6.86 (m, 2H, para- H's), 4.83–5.06 (m, 1H, H-2, $J_{2,F}$ = 55 Hz), 4.92 (dd, 1H, H-1, $J_{1,2}$ = 2 Hz and $J_{1,F}$ = 6 Hz), 4.3–4.40 (m, 1H, H-3), 3.94–4.02 (m, 1H, 5-CH_2), 3.82–4.02 (m, 1H, 5-CH_2), 3.80 (s, 3H, OCH_3 of 4-methoxyphenyl), 3.25 (s, 3H, 1-OCH_3), 3.26–3.28 (m, 1H, 4-*C*-hydroxymethyl), 3.18–3.20 (m, 1H, 4-*C*-hydroxymethyl), 2.80 (d, 1H, 3-OH, J = 12 Hz), 2.12 (t, 1H, 5-OH, J = 8 Hz).

Methyl 4-*C*-(*p*-Anisyldiphenylmethoxymethyl)-3, 5-di-O-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranoside (3). To a solution of **2a** (52 mg, 0.11 mmol) in dry pyridine (5 mL) at 0°C was added benzoyl chloride (91 μl, 0.77 mmol) dropwise. After 5 minutes, the cooling bath was removed, and stirring was continued for 18 hours. The solution was evaporated to a solid that was coevaporated once with toluene. The solid was purified by silica gel preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) with 3:1 hexane/EtOAc as solvent to give **3** (69 mg, 92%) as a white foam: TLC 3:1 hexane/EtOAc, R_f 0.44; MS m/z 699 $(m+Na)^+$; ^1H NMR ($CDCl_3$) 7.82–7.92 (m, 4H, ortho H's of benzoyl), 7.50–7.62 (m, 2H, para- H's of benzoyl), 7.12–7.92 (m, 16H, aromatic H's), 6.63–6.68 (m, 2H, p- H's), 6.02 (dd,1H, H-3, $J_{2,3}$ = 8 Hz and $J_{3,F}$ = 18 Hz), 5.46–5.70 (m,1H, H-2), 5.18 (bd, 1H, H-1, $J_{1,2}$ = 6 Hz), 4.50–4.60 (m, 2H, 5CH_2), 3.70 (s, OCH_3 of 4-methoxyphenyl), 3.48 (s, 3H, 1-OCH_3), 3.36–3.42 (m, 1H, 4-CH_2), 3.14–3.18 (m,1H, 4-CH_2).

Methyl 3, 5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-β-D-arabinofuranoside (4). A solution of **3** (576 mg, 0.85 mmol) in 4:1 acetic acid/water (20 mL) was stirred at room temperature for 19 hours and then evaporated. The residue obtained was partitioned between EtOAc and ice-cold saturated $NaHCO_3$. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with saturated NaCl, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (20 g) using a gradient from hexane to 2:1 hexane/EtOAc to give **4** (306 mg, 89%) as a clear syrup: TLC 2:1 hexane/EtOAc, R_f 0.29; MS m/z 405 $(m+H)^+$; ^1H NMR ($CDCl_3$) 8.0–8.10

(m, 4H, ortho H's of benzoyl), 7.34–7.64 (m, 6H, para and meta H's of benzoyl), 6.08 (dd, 1H, H-3, $J_{2,3}$ = 8 Hz and $J_{3,F}$ = 18 Hz), 5.27–5.50 (m, 1H, H-2), 5.12 (dd, 1H, H-1, $J_{1,2}$ = 2 Hz and $J_{1,F}$ = 8 Hz), 4.52–4.65 (m, 2H, 5-CH_2), 3.76 (s, 2H, 4-CH_2), 3.50 (s, 3H, OCH_3), 2.12 (broad hump, 1H, 5-OH).

Methyl 3, 5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-phenoxythiocarbonyloxymethyl-β-D-arabinofuranoside (5). To a solution of **4** (75 mg, 0.19 mmol) and 4-(dimethylamino) pyridine (93 mg, 0.75 mmol) in dry MeCN (7 mL) at room temperature was added dropwise phenyl chlorothionoformate (39 μl, 0.28 mmol). The resulting yellow solution was stirred at room temperature for 3 hours and then evaporated. The residue obtained was partitioned between ice-cold 5% citric acid and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to a gum. This crude **5** was purified by silica gel preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) with 3:1 hexane/EtOAc as solvent to obtain pure **5** (92 mg, 90%) as a white foam: TLC 3:1 hexane/EtOAc, R_f 0.55; MS m/z 563 $(m+Na)^+$; ^1H NMR ($CDCl_3$) 8.00–8.10 (m, 4H, ortho H's of benzoyl), 7.26–7.68 (m, 9H, aromatic H's), 6.90–6.94 (m, 2H, ortho H's of phenyl), 6.10 (dd, 1H, H-1, $J_{1,2}$ = 8 Hz and $J_{1,F}$ = 18 Hz), 5.16–5.42 (m, 1H, H-2), 5.10 (dd, 1H, H-3, $J_{2,3}$ = 1.5 Hz and $J_{3,F}$ = 7 Hz), 4.62–4.74 (m, 4H, 4 and 5-CH_2), 3.52 (s, 3H, OCH_3).

Methyl 3,5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranoside (6). A solution of **5** (4.0 g, 7.4 mmol) in anhydrous toluene (125 mL) was purged with argon before solid 98% 1,1′-azobis (cyclohexanecarbonitrile) (657 mg, 2.6 mmol) was added in one portion. The argon purge was repeated followed by a syringe addition of 97% tris (trimethylsilyl) silane (10 mL, 31 mmol) over 5 minutes. The reaction solution was warmed over 0.5 hours to 100°C, maintained at 100°C for 5 hours, cooled to room temperature and reduced under vacuum to an oil. The crude product was purified by column chromatography on silica gel with 5:1 cyclohexane/EtOAc as solvent to provide **6** (2.4 g, 84%) as a clear oil: TLC 85:15 cyclohexane/EtOAc, R_f 0.38; MS m/z 389 $(m+H)^+$; ^1H NMR ($CDCl_3$) 8.08–8.12 (m, 4H, ortho H's of benzoyl), 7.38–7.66 (m, 6H, para and meta H's of benzoyl), 6.28 (dd, 1H, H-3, $J_{2,3}$ = 8 Hz and $J_{3,F}$ = 18 Hz), 5.15–5.37 (m, 1H, H-2), 5.04 (dd, 1H, H-1, $J_{1,2}$ = 2 Hz and $J_{1,F}$ = 8 Hz), 4.46–4.62 (m, 2H, 5-CH_2), 3.44 (s, 3H, OCH_3), 1.34 (s, 3H, CH_3).

3,5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-α,β-D-arabinofuranoside (7). A solution of **6** (1.3 g, 3.35 mmol) in 9:1 trifluoroacetic acid/water (23 mL) was maintained at 60–65°C for 24 hours, cooled to room temperature, and diluted with CH_2Cl_2 (100 mL). The solution was added dropwise to a stirred mixture of ice (300 g) and saturated $NaHCO_3$ (300 mL). Solid $NaHCO_3$ was added during the addition to maintain a pH of 7. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic extract was washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated to a syrup (1.3 g). This material was flash chromatographed on silica gel (100 g) with 3:1 hexane/EtOAc as solvent to yield pure **7** (1.05 g, 83%) as a white solid: TLC 3:1 hexane/EtOAc, R_f 0.40; MS m/z 375 $(m+H)^+$; ^1H NMR ($CDCl_3$) 8.04–8.12 (m, 4H, ortho H's of benzoyl), 7.40–7.64 (m, 6H, para and meta H's of benzoyl), 5.70–5.88 (m, 1H, H-3 α,β), 5.65 (dd, 0.65H, H-1 α, $J_{1,2}$ = 4 Hz and $J_{1,F}$ = 12 Hz), 5.52–5.57 (m, 0.35H, H-1 β), 5.07–5.28 (m, 1H, H-2 α,β), 4.34–4.78 (m, 2H, 5-CH_2), 3.52 (d, 0.35H, 1-OH β), 2.79 (dd, 0.65H, 1-OH α, J = 1 and 4 Hz), 1.51 (s, 2H, CH_3 α), 1.36 (s, 1H, CH_3 β).

1-O-Acetyl-3,5-di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-α,β-D-arabinofuranose (8). To a solution of **7** (1.04 g, 2.78 mmol) in dry pyridine (25 mL) at 5°C was added dropwise acetic anhydride (0.79 mL, 8.37 mmol) over 5 minutes. After 15 minutes, the solution was allowed to warm to room temperature where it was held for 18 hours. The reaction solution was concentrated in vacuum and coevaporated with toluene (3 × 2 mL). The crude product was purified by flash chromatography on silica gel (70 g) using 3:1 hexane/EtOAc as solvent to provide pure **8** (1.06 g, 91%) as a white solid: TLC 3:1 hexane/EtOAc, R_f 0.50; MS m/z 439 $(m+Na)^+$; ^1H NMR ($CDCl_3$) 8.06–8.12 (m, 4H, ortho H's of benzoyl), 7.40–7.68 (m, 6H, para and meta H's of benzoyl), 6.41–6.46 (m, 1H, H-1 α,β), 5.16 (m, 1H, H-3 α,β), 5.16–5.48 (m, 1H, H-2 α,β), 4.40–4.64 (m, 2H, 5-CH_2), 2.16 (s, 2.25H, CH_3 of 1-O-acetyl, α), 2.0 (s, 0.75H, CH_3 of 1-O-acetyl, β), 1.50 (s, 2.25H, CH_3 α), 1.40 (s, 0.75H,CH_3 β).

3,5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-α,β-D-arabinofuranosyl Bromide (9). A solution of **8** (507 mg, 1.22 mmol) in CH_2Cl_2 (35 mL) was stirred with $MgSO_4$ for 1.5 hours, filtered, and evaporated to a stiff syrup. After being dried under vacuum for 2 hours, the residue was dissolved in anhydrous CH_2Cl_2 (20 mL), chilled to 5°C, and treated dropwise with 33% HBr in acetic acid (5.5 mL). The clear yellow solution in a tightly sealed flask was placed in a nitrogen filled bag, refrigerated for 20 hours, and evaporated in vacuum. The dark orange highly reactive residue was coevaporated with toluene (2 × 3 mL) and then used directly in the various pyrimidine and purine couplings: TLC 3:1 hexane/EtOAc, R_f 0.85.

N^4-Benzoyl-1-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)cytosine (10). A suspension of 98% N^4-benzoyl cytosine (863 mg, 3.93 mmol) in dry MeCN (20 mL) at room temperature was treated dropwise with 95% N, O-bis (trimethylsilyl) acetamide (BSA) (3.6 mL) and stirred for 2 hours. The clear solution obtained was evaporated in vacuum to a fluid oil that was dried under vacuum for an additional 2 hours before being dissolved in $ClCH_2CH_2Cl$ (20 mL). To this solution was added in one portion a solution of **9** [prepared from **8** (507 mg, 1.22 mmol)] in $ClCH_2CH_2Cl$ (10 mL). The reaction solution was heated at 100°C for 4 hours, cooled, and quenched with MeOH

(15 mL) at 5°C. The reaction was stirred at room temperature for 0.5 hours before being filtered through a celite pad to remove excess pyrimidine. The solid was washed with $CHCl_3$ and MeCN until free of **10**, and the combined filtrate and washings were evaporated to a yellow solid. This crude product was purified by flash chromatography on silica gel (45 g) with 1:1 hexane/EtOAc as solvent to give pure **10** (336 mg, 48%) as a white solid: TLC 1:1 hexane/EtOAc, R_f 0.28; MS m/z 572 $(m+H)^+$; ^1H NMR ($CDCl_3$) 8.70 (broad hump, 1H, NH), 7.86–8.14 (m, 7H, H-6 and ortho H's of benzoyl), 7.46–7.70 (m, 10H, H-5 and para and meta H's of benzoyl), 6.47 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 20 Hz), 5.88 (dd, 1H, H-3′, $J_{3',F}$ = 18 Hz), 5.52 (dd, 1H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F}$ = 50 Hz), 4.58–4.68 (m, 2H, 5′-CH_2), 1.50 (s, 3H, 4′-CH_3).

From impure fractions, the α-anomer **10α** (41 mg, 6%) was recovered as a white solid by silica gel preparative TLC (Analtech GF, 10 × 20 cm, 500 μ) with 99:1 $CHCl_3$/MeOH as solvent: TLC 1:1 hexane/EtOAc, R_f 0.45; MS m/z 572 $m+H)^+$; ^1H NMR ($CDCl_3$) 8.80 (bh, 1H, NH), 7.40–8.16 (m, 17H, H-5, H-6 and aromatic H's), 6.28 (dd, 1H, H-1′, $J_{1',2'}$ = 1 Hz and $J_{1',F}$ = 18 Hz), 5.90 (dd, 1H, H-3′, $J_{3',F}$ = 14 Hz), 5.46 (dd, 1H, H-2′, $J_{2',3'}$ = 1 Hz and $J_{2',F}$ = 48 Hz), 4.44–4.50 (m, 2H, 5′-CH_2), 1.64 (s, 3H, 4′-CH_3).

1-(3,5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl) uracil (11). A suspension of uracil (55 mg, 0.49 mmol) in dry MeCN (3 mL) at room temperature was treated dropwise with 95% N, O-bis (trimethylsilyl) acetamide (BSA) (0.44 mL) and stirred for 1 hour. The clear solution obtained was evaporated under vacuum to a syrup that was dried for an additional 1 hour before being dissolved in $ClCH_2CH_2Cl$ (3 mL). To this solution was added in one portion a solution of **9** [prepared from **8** (57 mg, 0.14 mmol)] in $ClCH_2CH_2Cl$ (2 mL), and the mixture was heated at 100°C for 4 hours, cooled, and quenched with MeOH (1 mL) at 5°C. After being stirred at room temperature for 1.5 hours, the mixture was filtered through a Celite pad to remove excess uracil, and the filtrate was concentrated to a yellow solid. This anomeric mixture was resolved by preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) with multiple development in 97:3 $CHCl_3$/MeOH to provide **11** (42 mg, 65%) and **11α** (4 mg, 6%) as white solids. **11:**TLC 97:3 $CHCl_3$/MeOH, R_f 0.50; MS m/z 469 $(m+H)^+$; ^1H NMR ($CDCl_3$). 8.32 (bs, 1H, H-3), 8.06–8.14 (m, 4H, ortho H's of benzoyl), 7.44–7.70 (m, 7H, H-6 and para and meta H's of benzoyl), 6.37 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 20 Hz), 5.86 (dd,1H, H-3′, $J_{2',3'}$ = 2 Hz and $J_{3',F}$ = 18 Hz), 5.66 (bd, 1H, H-5, $J_{5,6}$ = 8 Hz), 5.32 (ddd, 1H, H-2′, $J_{1',2'}$ = 4 Hz and $J_{2',F}$ = 50 Hz), 4.56–4.64 (m, 2H, 5′-CH_2), 1.46 (s, 3H, 4′-CH_3). **11α:**TLC 97:3 $CHCl_3$/MeOH, R_f 0.46; MS m/z 469 $(m+H)^+$; ^1H NMR ($CDCl_3$). 8.32 (bs, 1H, H-3), 7.98–8.14 (m, 4H, ortho H's of benzoyl), 7.44–7.68 (m, 7H, H-6 and para and meta H's of benzoyl), 6.24 (dd, 1H, H-1′, $J_{1',2'}$ = 3 Hz and $J_{1',F}$ = 16 Hz), 5.80–5.92 (m, 2H, H-3′

and H-5), 5.41 (dt, 1H, H-2′, $J_{2',3'}$ = 2 Hz and $J_{2',F}$ = 50 Hz), 4.64–4.68 (m, 1H, 5′-CH_2), 4.40–4.46 (m, 1H, 5′-CH_2), 1.52 (s, 3H, 4′-CH_3).

1-(3,5-Di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-*β*-D-arabinofuranosyl) thymine (12). Compound **9** [prepared from **8** (60 mg, 0.14 mmol)] was treated with 99% thymine (62 mg, 0.48 mmol) as described for **11** to give **12** (43 mg, 62%) and **12*α*** (4 mg, 6%) as white solids. **12:**TLC 98:2 $CHCl_3$/MeOH, R_f 0.43; MS m/z 483 $(m+H)^+$; ^1H NMR ($CDCl_3$) 8.24 (bs, 1H, H-3), 7.44–7.70 (m, 10H, aromatic H's), 7.34 (s,1H, H-6), 6.38 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 20 Hz), 5.88 (dd,1H, H-3′, $J_{3',F}$ = 18 Hz), 5.31 (ddd, 1H, H-2′, $J_{2',3'}$ = 2 Hz, $J_{2',1'}$ = 4 Hz and $J_{2',F}$ = 50 Hz), 4.62 (s, 2H, 5′-CH_2), 1.74 (s, 3H, 5-CH_3), 1.46 (s, 3H, 4′-CH_3). **12*α*:**TLC 98:2 $CHCl_3$/MeOH, R_f 0.39; MS m/z 483$(m+H)^+$; ^1H NMR ($CDCl_3$) 8.36 (bs, 1H, H-3), 7.46–7.68 (m, 10H, aromatic H's), 7.30 (s, 1H, H-6), 6.28 (dd, 1H, H-1′, $J_{1',2'}$ = 3 Hz and $J_{1',F}$ = 16 Hz), 5.87 (dd,1H, H-3′, $J_{2',3'}$ = 2 Hz and $J_{3',F}$ = 16 Hz), 5.40 (dt, 1H, H-2′, $J_{2',F}$ = 50 Hz), 4.40–4.66 (m, 2H, 5′-CH_2), 1.98 (s, 3H, 5-CH_3), 1.52 (s, 3H, 4′-CH_3).

1-(2-Deoxy-2-fluoro-4-*C*-methyl-*β*-D-arabinofuranosyl)cytosine (13).[13] A suspension of **10** (334 mg, 0.58 mmol) in MeOH (30 mL) at room temperature was treated dropwise with 0.5 M sodium methoxide in MeOH (0.58 mL). The solid dissolved after 15 minutes, and the solution was stirred for 2 hours, neutralized to pH 7 with glacial acetic acid, and evaporated to an oil. Preparative TLC on silica gel (Analtech GF, 20 × 20 cm, 2000 μ) with 3:1:0.10 $CHCl_3$/MeOH/concentrated NH_4OH as eluant provided the nucleoside as a hygroscopic white foam. This residue was dissolved in 2-PrOH (10 mL), 1.0 M HCl in ether (1.17 mL) was added and the mixture was evaporated. From a suspension of this material in acetone was recovered hydrochloride **13** (157 mg, 89%) as a white solid: m.p. 230–231°C; TLC 3:1:0.1 $CHCl_3$/MeOH/NH_4OH, R_f 0.40; HPLC 99%, t_R = 8.6 minutes, 9:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 260 $(M+H)^+$; UV λmax pH 1, 279 (13.8), pH 7, 269 (9.4), pH 13, 271 (9.6); ^1H NMR (DMSO-d_6) 9.70 (s, 1H, 4-NH_2), 8.62 (s, 1H, 4-NH_2), 8.24 (d, 1H, H-6, J = 8 Hz), 6.10–6.17 (m, 2H, H-1′ and H-5 overlapped), 5.95 (broad hump, 1H, OH), 5.23 (dt, 1H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F}$ = 52 Hz), 4.26 (dd,1H, H-3′, $J_{3',F}$ = 20 Hz), 3.40–3.50 (m, 3H, 5′-CH_2 and OH), 1.25 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{10}H_{14}FN_3O_4 \cdot HCl$ 0.10 C_3H_8O, 0.20 H_2O: C, 40.52; H, 5.35; N, 13.76. Found: C, 40.82; H, 5.18; N, 13.58.

The *α*-anomer was prepared from **10*α*** as described for **13** except the HCl salt formation was omitted. Pure **13*α*** (77%) was obtained from acetone as a white solid: m.p. 222–223°C; TLC 3:1:0.1 $CHCl_3$/MeOH/NH_4OH, R_f 0.40; HPLC 100%, t_R = 7.7 minutes, 9:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 260 $(M+H)^+$; UV λmax pH 1, 278 (13.3), pH 7, 270 (9.3), pH 13, 271 (9.3); ^1H NMR (DMSO-d_6) 7.59 (d, 1H, J = 3.5, H-6), 7.28 (bs, 1H, 4-NH_2), 7.20 (bs,1H, 4-NH_2), 6.0 (dd, 1H, H-1′ $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 18 Hz), 5.74–5.78 (m, 2H, H-5 and 3′-OH overlapped), 4.9–5.10 m, 2H, H-2′ and 5′-OH overlapped), 4.24 (dt, 1H, H-3′, $J_{3',F}$ = 18 Hz), 3.30–3.40 (m, 2H, 5′-CH_2), 1.24 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{10}H_{14}FN_3O_4$: C, 46.33; H, 5.44; N, 16.21. Found: C, 46.19; H, 5.23; N, 16.09.

1-(2-Deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)uracil (14).[13] Compound **14** was prepared from **11** using the method described for **13α**. Pure **14** (77%) was obtained as a clear glass from acetone and was subsequently ground to a white powder: m.p. 70–75°C; TLC 3:1:0.1 $CHCl_3$/MeOH/NH_4OH, R_f 0.62; HPLC 99%, t_R = 6.4 minutes, 85:15 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 261 $(M+H)^+$; UV λmax pH 1, 261 (10.5), pH 7, 261 (10.3), pH 13, 261 (8.0); ^1H NMR (DMSO-d_6) 11.42 (broad hump,1H, H-3), 7.86 (d, 1H, H-6, J = 8 Hz), 6.20 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 12 Hz), 5.92 (bs, 1H, 3′-OH), 5.72 (d, 1H, H-5, J = 8 Hz), 5.23 (dt, 2H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F}$ = 52 Hz and 5′-OH overlapped and exchanged with D_2O), 4.28 (dd, 1H, H-3′, $J_{3',3'\text{-OH}}$ = 4 Hz and $J_{3',F}$ = 22 Hz), 3.40–3.44 (m, 2H, 5′-CH_2), 1.10 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{10}H_{13}FN_2O_5 \cdot 0.25\,H_2O$: C, 45.37; H, 5.14; N, 10.58. Found: C, 45.32; H, 4.89; N, 10.42.

1-(2-Deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)thymine (15). Compound **15** was synthesized from **12** using the conditions described for **13α** but with a 7 hour reaction time and with 5:1 $CHCl_3$/MeOH + 1% concentrated NH_4OH as eluent for preparative TLC. Pure **15** (92%) was recovered from acetone (as for **14**) as a white powder: m.p. 80°C; TLC 5:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.52; HPLC 100%, t_R = 5.2 minutes, 3:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 275 $(M+H)^+$; UV λmax pH 1, 267 (9.9), pH 7, 267 (9.8), pH 13, 266 (7.8); ^1H NMR (DMSO-d_6) 11.40 (s, 1H, H-3), 7.74 (s, 1H, H-6), 6.14 (dd, 1H, H-1′, $J_{1',2'}$ = 6 Hz and $J_{1',F}$ = 12 Hz), 5.88 (bd, 1H, 3′-OH, J = 6 Hz), 5.3–5.40 (m, 1H, 5′-OH), 5.18 (dt, 1H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F}$ = 52 Hz), 4.31 (dt, 1H, H-3′, $J_{3',F}$ = 22 Hz), 3.40–3.48 (m, 2H, 5′-CH_2), 1.80 (s, 3H, 5-CH_3), 1.08 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{15}FN_2O_5 \cdot 0.50\,H_2O$: C, 46.64; H, 5.69; N, 9.89. Found: C, 46.54; H, 5.33; N, 9.68.

6-Chloro-9-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)purine (16). A suspension of 98% 6-chloropurine (102 mg, 0.65 mmol) in dry MeCN (5 mL) at room temperature was treated in one portion with 60% NaH (35 mg, 0.88 mmol). The mixture was stirred for 40 minutes before the immediate addition of **9** [prepared from **8** (177 mg, 0.43 mmol)] dissolved in MeCN (2 mL). After 6 hours, the stirred mixture was adjusted to about pH 6 with glacial acetic acid, and stirring was continued 15 minutes before the solids present were collected, washed with MeCN, and discarded. The combined filtrate and washings were evaporated to a yellow residue that was purified by silica gel preparative TLC (Analtech GF, 20 × 20 cm, 2000 μ) with 99:1 $CHCl_3$/MeOH as eluent. The recovered anomeric product was resolved by preparative TLC developed twice in 2:1

hexane/EtOAc to provide **16** (79 mg, 36%) and **16α** (31 mg, 14%) as white solids: **16**, TLC 2:1 hexane/EtOAc, R_f 0.40; MS m/z 511 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.78 (s,1H, H-2), 8.42 (d, 1H, H-8, J = 4 Hz), 8.10–8.16 (m, 4H, ortho H's of benzoyl), 7.46–7.72 (m, 6H, para and meta H's of benzoyl), 6.76 (dd, 1H, H-1′, $J_{1',2'} = 4$ Hz and $J_{1',F} = 22$ Hz), 6.04 (dd, 1H, H-3′, $J_{3',F} =$ 16 Hz), 5.39 (ddd, 1H, H-2′, $J_{2',3'} = 2$ Hz and $J_{2',F} = 50$ Hz), 4.61–4.76 (m, 2H, 5′-CH_2), 1.58 (s, 3H, 4′-CH_3). **16α,** TLC 2:1 hexane/EtOAc, R_f 0.52; MS m/z 511 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.74 (s, 1H, H-2), 8.38 (s, 1H, H-8), 7.86–8.66 (m, 4H, ortho H's of benzoyl), 7.42–7.66 (m, 6H, para and meta H's of benzoyl), 6.51 (dd, 1H, H-1′, $J_{1',2'} = 3.5$ Hz and $J_{1',F} = 14$ Hz), 6.24 (dt, 1H, H-2′, $J_{2',3'} = 3$ Hz and $J_{2',F} = 50$ Hz), 6.00 (dd, 1H, H-3′, $J_{3',F} =$ 18 Hz), 4.46–4.72 (m, 2H, 5′-CH_2), 1.60 (s, 3H, 4′-CH_3).

9-(2-Deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)adenine (17).[13] Compound **16** (101 mg, 0.20 mmol) in a glass lined stainless steel bomb was diluted with ethanolic ammonia (100 mL, saturated at 5°C). The sealed bomb was heated at 80°C for 26 hours before the contents were evaporated. The residue was purified by multiple development on silica gel preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) with 5:1 $CHCl_3$/MeOH + 1% NH_4OH as solvent. Pure **17** (45 mg, 74%) was obtained as a white powder from acetone: m.p. 160–162°C; TLC 5:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.45; MS m/z 284 $(M+H)^+$; UV λmax pH 1, 256 (15.0), pH 7, 259 (15.7), pH 13, 259 (16.3); ^{1}H NMR (DMSO-d_6) 8.30 (d, 1H, H-8, J = 1 Hz), 8.14 (s, 1H, H-2), 7.32 (s, 2H, 6-NH_2), 6.43 (dd, 1H, H-1′, $J_{1',2'} = 5$ Hz and $J_{1',F} = 10$ Hz), 5.94 (bs, 1H, 3′-OH), 5.35 (dt, 1H, H-2′, $J_{2',3'} = 4$ Hz and $J_{2',F} = 52$ Hz), 5.22–5.30 (m, 1H, 5′-OH), 4.56 (dd, 1H, H-3′, $J_{3',F} = 20$ Hz), 3.46–3.52 (m, 2H, 5′-CH_2), 1.16 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{14}FN_5O_3 \cdot 0.40\ H_2O \cdot 0.30\ C_3H_6O$: C, 46.42; H, 5.43; N, 22.75. Found: C, 46.44; H, 5.17; N, 22.83. **17α** was prepared from **16α** as described for **17**. Pure **17α** (49%) as a glass from acetone was ground to an off white powder: m.p. 185–187°C; TLC 5:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.51; MS m/z 284 $(M+H)^+$; UV λmax pH 1, 257 (15.0), pH 7, 259 (15.5), pH 13, 259 (16.0); ^{1}H NMR (DMSO-d_6) 8.34 (s,1H, H-8), 8.18 (s, 1H, H-2), 7.38 (s, 2H, 6-NH_2), 6.16 (dd, 1H, H-1′, $J_{1',2'} = 5$ Hz and $J_{1',F} = 10$ Hz), 6.10 (bs, 1H, 3′-OH), 5.84 (dt, 1H, H-2′, $J_{2',3'} = 4$ Hz and $J_{2',F} = 52$ Hz), 5.14 (t, 1H, 5′-OH, J = 4 Hz), 4.49 (dd, 1H, H-3′, $J_{3',F} = 20$ Hz), 3.32–3.40 (m, 2H, 5′-CH_2), 1.22 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{14}FN_5O_3 \cdot 0.50\ H_2O \cdot 0.10\ C_3H_6O$: C, 45.53; H, 5.28; N, 23.49. Found: C, 45.40; H, 5.02; N, 23.48.

2,6-Dichloro-9-(3,5-di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)purine (18). Compound **18** was synthesized as described for **16** except using 2,6-dichloropurine. The anomeric product mixture was isolated by silica gel preparative TLC (developed twice in 3:1 hexane/EtOAc) as a white solid (64%, as 2:1 β: α ratio by ^{1}H NMR). Pure anomers were obtained separately as white foams by preparative TLC with multiple developments in $CHCl_3$: **18**, TLC 100:1 $CHCl_3$/MeOH, R_f

0.48; MS m/z 545 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.40 (d, 1H, H-8, J = 4 Hz), 8.10–8.16 (m, 4H, ortho H's of benzoyl), 7.46–7.72 (m, 6H, para and meta H's of benzoyl), 6.68 (dd, 1H, H-1′, $J_{1',2'}$ = 3 Hz and $J_{1',F}$ = 20 Hz), 6.01 (dd, 1H, H-3′, $J_{3',4'}$ = 1.5 and 16 Hz), 5.38 (ddd, 1H, H-2′, $J_{2',3'}$ = 1.5 Hz and $J_{2',F}$ = 50 Hz), 4.60–4.74 (m, 2H, 5′-CH_2), 1.56 (s, 3H, 4′-CH_3). **18α**, TLC 100:1 $CHCl_3$/MeOH, R_f 0.42; MS m/z 545 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.34 (s,1H, H-8), 7.92–8.16 (m, 4H, ortho H's of benzoyl), 7.45–7.68 (m, 6H, para and meta H's of benzoyl), 6.48 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 16 Hz), 6.12 (dt, 1H, H-2′, $J_{2',3'}$ = 1.5 Hz and $J_{2',F}$ = 50 Hz), 6.01 (dd, 1H, H-3′, $J_{3',F}$ = 16 Hz), 4.48–4.72 (m, 2H, 5′-CH_2), 1.60 (s, 3H, 4′-CH_3).

2,6-Diazido-9-(3, 5-di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)purine (19). To a solution of **18** (108 mg, 0.20 mmol) in EtOH (5 mL) was added solid NaN_3 (30 mg, 0.46 mmol) and H_2O (0.5 mL). The mixture was placed in a 100°C bath, refluxed 30 minutes, cooled, and evaporated. The residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic layers were washed with H_2O, dried ($MgSO_4$), and evaporated to a syrup. Purification by silica gel preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) in 2:1 hexane/EtOAc afforded **19** (105 mg, 95%) as a white solid that was used directly in the next step. TLC 99:1 $CHCl_3$/MeOH, R_f 0.65; MS m/z 559 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.18 (d, 1H, H-8, J = 4 Hz), 8.10–8.16 (m, 4H, ortho H's of benzoyl), 7.46–7.72 (m, 6H, para and meta H's of benzoyl), 6.62 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 22 Hz), 6.00 (dd, 1H, H-3′, $J_{2',3'}$ = 1.5 Hz and $J_{3',F}$ = 16 Hz), 5.34 (ddd, 1H, H-2′, $J_{2',F}$ = 50 Hz), 4.90–4.70 (m, 2H, 5′-CH_2), 1.54 (s, 3H, 4′-CH_3). **19α** was prepared from **18α** as described for **19**: TLC 99:1 $CHCl_3$/MeOH, R_f 0.58; MS m/z 559 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.14 (s,1H, H-8), 7.92–8.14 (m, 4H, ortho H's of benzoyl), 7.44–7.66 (m, 6H, para and meta H's of benzoyl), 6.41 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 12 Hz), 6.16 (dt, 1H, H-2′, $J_{2',3'}$ = 1.5 Hz and $J_{2',F}$ = 50 Hz), 6.01 (dd, 1H, H-3′, $J_{3',F}$ = 14 Hz), 4.48–4.68 (m, 2H, 5′-CH_2), 1.58 (s, 3H, 4′-CH_3).

2,6-Diamino-9-(3, 5-di-O-benzoyl-2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)purine (20). A solution of **19** (105 mg, 0.19 mmol) in 2:1 EtOH/DMAc (15 mL) was treated with 10% palladium on carbon (17 mg) and hydrogenated for 18 hours at room temperature and atmospheric pressure. The catalyst was removed by filtration and washed thoroughly with $CHCl_3$. The combined filtrate and washings were evaporated under vacuum to a syrup. Purification by silica gel preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) with multiple development in 95:5 $CHCl_3$/MeOH + 1% NH_4OH gave **20** (84 mg, 87%) as a white residue that was used directly in the next step. TLC 95:5 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.43; MS m/z 507 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) 8.08–8.14 (m, 4H, ortho H's of benzoyl), 7.80 (d, 1H, H-8, J = 3 Hz), 7.42–7.70 (m, 6H, para and meta H's of benzoyl), 6.48 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 22 Hz), 6.01 (dd, 1H, H-3′, $J_{3',F}$ = 16 Hz), 5.30 (ddd, 1H, H-2′, $J_{2',3'}$ = 1.5 Hz, $J_{2',F}$ = 50 Hz), 5.38 (bs, 2H, 2-NH_2), 4.74 (bs, 2H, 6-NH_2), 4.60–4.68 (m, 2H, 5′-CH_2), 1.52 (s, 3H, 4′-CH_3). **20α** was prepared from **19α** as described for **20**: TLC 95:5 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.48; MS m/z 507 $(M+H)^+$; ^1H NMR ($CDCl_3$) 8.12–8.16 (m, 4H, ortho H's of benzoyl), 7.78 (s, 1H, H-8), 7.44–7.96 (m, 6H, para and meta H's of benzoyl), 6.30 (dd, 1H, H-1′, $J_{1',2'}$ = 3 Hz and $J_{2',F}$ = 16 Hz), 5.95 (dd, 1H, H-3′, $J_{2',3'}$ = 2.8 Hz and $J_{3',F}$ = 14 Hz), 5.32 (bs, 2H, 2-NH_2), 4.66 (bs, 2H, 6-NH_2), 4.46–4.62 (m, 2H, 5′-CH_2), 1.56 (s, 3H, 4′-CH_3).

2,6-Diamino-9-(2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl) purine (21).[13] To a solution of **20** (84 mg, 0.17 mmol) in MeOH (5 mL) at room temperature was added 0.5 N $NaOCH_3$ in MeOH (0.17 mL). The solution was stirred 3 hours, neutralized to pH 6 with glacial acetic acid, and evaporated. Purification by development on silica gel preparative TLC (Analtech GF, 10 × 20 cm, 500 μ) using 5:1 $CHCl_3$/MeOH + 1% NH_4OH as solvent gave **21** (43 mg, 85%) as a white solid from acetone: m.p. 210–215°C; TLC 5:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.39; HPLC 99%, t_R = 9.6 minutes, 20 minute linear gradient from 10–90% MeOH in 0.01 M $NH_4H_2PO_4$ (pH 5.1); MS m/z 299 $(M+H)^+$; HRMS m/z 299.12634 $(M+H)^+$, Calcd. 299.12624 $(M+H)^+$; UV λmax pH 1, 252 (11.5), 290 (9.9), pH 7, 255 (9.6), 280 (10.2), pH 13, 255 (9.8), 280 (10.5); ^1H NMR (DMSO-d_6) 7.84 (d, 1H, H-8, J = 1 Hz), 6.74 (s, 2H, 2-NH_2), 6.20 (dd, 1H, H-1′, $J_{1',2'}$ = 5 Hz and $J_{1',F}$ = 13 Hz), 5.82–5.92 (m, 3H, 6-NH_2 and 3′-OH), 5.24 (t,1H, 5′-OH, J = 4 Hz), 5.22 (dt, 1H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F}$ = 52 Hz), 4.51 (dd, 1H, H-3′, $J_{3',F}$ = 20 Hz), 3.40–3.48 (m, 2H, 5′-CH_2), 1.14 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{15}$ F N_6 O_3·0.40 H_2O: C, 43.25; H, 5.21; N, 27.51. Found: C, 43.59; H, 5.09; N, 27.21. **21α** was prepared from **20α** as described for **21** except white solid was obtained from MeOH: m.p. 130–135°C; TLC 5:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.45; HPLC 99%, t_R = 9.9 minutes, 20 minute linear gradient from 10–90% MeOH in 0.01 M $NH_4H_2PO_4$ (pH 5.1); MS m/z 299 $(M+H)^+$; HRMS m/z 299.12583 $(M+H)^+$, Calcd. 299.12624 $(M+H)^+$; UV λmax pH 1, 252 (12.4), 292 (10.5), pH 7, 255 (10.0), 280 (10.5), pH 13, 256 (9.8), 280 (10.5); ^1H NMR (DMSO-d_6) 7.92 (s, 1H, H-8), 6.76 (s, 2H, 2-NH_2), 6.78 (s, 1H, 3′-OH), 6.00 (dd, 1H, H-1′, $J_{1',2'}$ = 4 Hz and $J_{1',F}$ = 16 Hz), 5.88 (s, 2H, 6-NH_2), 5.68 (dt, 1H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F}$ = 52 Hz), 5.11 (t,1H, 5′-OH, J = 4 Hz), 4.44 (dd, 1H, H-3′, $J_{3',F}$ = 18 Hz), 3.32–3.38 (m, 2H, 5′-CH_2), 1.22 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{15}$ F N_6 O_3·1.5 H_2O: C, 40.62; H, 5.58; N, 25.83. Found: C, 40.49; H, 5.26; N, 25.79.

9-(2-Deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)guanine (22).[13] A suspension of **21** (143 mg, 0.8 mmol) in H_2O (10 mL) was warmed to 70°C to dissolve solid before being cooled to 30°C. Solid adenosine deaminase (22 mg, 33 units, type II: crude powder Sigma) was added, and the solution was stirred at room temperature. After 2.5 hours, the solution became cloudy, and the stirring was continued for 68 hours. The resulting milky mixture was filtered to remove crude **22** as a white solid (77 mg). The product containing filtrate was applied directly to a strong cation exchange resin in the H^+ form (30 mL, AG 50W-X4,100–200 mesh) equilibrated in H_2O. Elution with 0.25 N NH_4OH yielded **22** containing small amounts of UV active impurities. These impurities were removed by preparative TLC on silica gel (Analtech GF, 10 × 20 cm, 1000 μ) using 9:2 MeCN/1*N* NH_4OH as eluent to provide more crude **22** (66 mg) as a white solid. Both solids were combined in hot water, and the solution was diluted to 50 mL. This solution at room temperature was applied to a XAD-4 resin column (100–200 mesh, 1 × 8.5 cm) equilibrated in H_2O. Elution with H_2O was continued followed by 9:1 H_2O/MeOH, when **22** appeared in the eluate. The pooled product containing fractions were evaporated and the residue was triturated with EtOH (25 mL) to give pure **22** (96 mg, 67%) as a white solid: m.p. 270°C (dec.); TLC 9:2 MeCN/1N NH_4OH, R_f 0.55; HPLC 100%, $t_R = 8.3$ minutes, 85:15 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 300 $(M+H)^+$; HRMS m/z 322.09177 $(M+Na)^+$, Calcd. 322.09220 $(M+Na)^+$; UV λmax pH 1, 256 (13.1), 280 (sh), pH 7, 251 (14.5), 276 (sh), pH 13, 263 (12.1); ^1H NMR (DMSO-d_6) 10.66 (s, 1H, 3-NH), 7.88 (d, 1H, H-8, J = 1 Hz), 6.50 (s, 2H, 2-NH_2), 6.14 (dd, 1H, H-1′, $J_{1',2'} = 5$ and $J_{1',F} = 13$ Hz), 5.90 (d, 1H, 3′-OH, J = 5 Hz), 5.23 (dt, 1H, H-2′, $J_{2',3'} = 4$ Hz and $J_{2',F} = 52$ Hz), 5.17 (t, 1H, 5′-OH, J = 4 Hz), 4.45 (dt, 1H, H-3′, $J_{3',F} = 18$ Hz), 3.32–3.48 (m, 2H, 5′-CH_2), 1.16 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{14}FN_5O_4$: C, 44.15; H, 4.72; N, 23.40. Found: C, 43.93; H, 4.69; N, 23.19.

2-Chloro-6-methoxy-9-(2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)purine (23). To a solution of **18** (76 mg, 0.14 mmol) in anhydrous MeOH (5 mL) at room temperature was added dropwise 0.5 N $NaOCH_3$ in MeOH (280 μl). The solution was stirred for 3 hours, neutralized to pH 6 with glacial acetic acid, and evaporated. The residue was purified by preparative TLC on silica gel using 9:1 $CHCl_3$/MeOH as solvent. Pure **23** (43 mg, 93%) was obtained as a clear glass and was used directly in the next step: TLC 9:1 $CHCl_3$/MeOH, R_f 0.48; MS m/z 333 $(M+H)^+$; ^1H NMR (DMSO-d_6) 8.64 (d, 1H, H-8, J = 1 Hz), 6.47 (dd, 1H, H-1′, $J_{1',2'} = 5$ Hz and $J_{1',F} = 10$ Hz), 5.98 (bs, 1H, 3′-OH), 5.43 (dt, 1H, H-2′, $J_{2',3'} = 4$ Hz and $J_{2',F} = 52$ Hz), 5.30 (t,1H, 5′-OH, J = 4 Hz), 4.54 (dd, 1H, H-3′, $J_{3',F} = 20$ Hz), 4.12 (s, 3H, 6-OCH_3), 3.48–3.52 (m, 2H, 5′-CH_2), 1.14 (s, 3H, 4′-CH_3). **23α** was prepared from **18α** as described for **23**. Pure **23α** (96%) was obtained as a glass: TLC 9:1 $CHCl_3$/MeOH, R_f 0.48; MS m/z 333 $(M+H)^+$; ^1H NMR (DMSO-d_6) 8.62 (d,1H, H-8, J = 1 Hz), 6.20 (dd, 1H, H-1′, $J_{1',2'} = 5$ Hz and $J_{1',F} = 14$ Hz), 6.16 (bs, 1H, 3′-OH), 5.76 (dt, 1H, H-2′, $J_{2',3'} = 5$ Hz and $J_{2',F} = 52$ Hz), 5.24 (bt,1H, J = 4.50, 5′-OH), 4.54 (dd, 1H, H-3′, $J_{3',F} = 20$ Hz), 4.12 (s, 3H, 6-OCH_3), 3.34–3.38 (m, 2H, 5′-CH_2), 1.24 (s, 3H, 4′-CH_3).

2-Chloro-9-(2-deoxy-2-fluoro-4-*C*-methyl-β-D-arabinofuranosyl)adenine (24). A solution of **23** (88 mg, 0.27 mmol) in 60 mL of ethanolic ammonia (saturated at 5°C) in a glass-lined stainless steel bomb was heated at 80°C for 21 hours and evaporated. The residue was purified by silica gel preparative TLC (Analtech GF, 10 × 20 cm, 1000 μ) with two developments in 5:1 $CHCl_3$/MeOH + 1% NH_4OH. Pure **24** (71 mg, 84%) as a white foam from acetone was ground to a white powder: m.p. 220–222°C; TLC 9:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.29; HPLC 97%, t_R = 14 minutes, 4:1 $NH_4H_2PO_4$ (0.01 M, pH 2.7)/MeOH; MS m/z 318 $(M+H)^+$; UV λmax pH 1, 264 (14.7), pH 7, 264 (15.4), pH 13, 264 (15.8); ^1H NMR (DMSO-d_6) 8.44 (d, 1H, H-8, J = 1 Hz), 7.86 (s, 2H, 6-NH_2), 6.35 (dd, 1H, H-1′, $J_{1',2'} = 5$ Hz and $J_{1',F} = 10$ Hz), 5.94 (d, 1H, 3′-OH, J = 6 Hz), 5.37 (dt, 1H, H-2′, $J_{2',3'}$ = 4 Hz and $J_{2',F} = 52$ Hz), 5.25 (t, 1H, 5′-OH, J = 4 Hz), 4.53 (dd, 1H, H-3′, $J_{3',F} = 20$ Hz), 3.48–3.50 (m, 2H, 5′-CH_2), 1.14 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{13}Cl\ F\ N_5\ O_3$: C, 41.59; H, 4.12; N, 22.04. Found: C, 41.55; H, 4.12; N, 22.06. **24α** was prepared from **23α** as described for **24**. Pure **24α** (75%) was recovered from acetone as a white solid: m.p., dual 105°C and 205°C; TLC 9:1 $CHCl_3$/MeOH + 1% NH_4OH, R_f 0.35; HPLC 98%, t_R = 13 minutes, 4:1 $NH_4H_2PO_4$ (0.01 M, pH 2.7)/MeOH; MS m/z 318 $(M+H)^+$; UV λmax pH 1, 264 (15.1), pH 7, 264 (16.1), pH 13, 264 (15.9); ^1H NMR (DMSO-d_6) 8.38 (d, 1H, H-8, J = 1 Hz), 7.90 (s, 2H, 6-NH_2), 6.09 (dd, 1H, H-1′, $J_{1',2'} = 4$ Hz and $J_{1',F} = 14$ Hz), 6.02 (bs, 1H, 3′-OH), 5.74 (dt, 1H, H-2′, $J_{2',2',F}$ = 4 and 52 Hz), 5.16 (t, 1H, 5′-OH, J = 4 Hz), 4.50 (dd, 1H, H-3′, $J_{3',4'}$ = 4 and 20 Hz), 3.32–3.38 (m, 2H, 5′-CH_2), 1.24 (s, 3H, 4′-CH_3). Anal. Calcd. For $C_{11}H_{13}Cl\ F\ N_5\ O_{3.}\ 0.65{\cdot}H_2O{\cdot}0.10\ C_3H_6O$: C, 40.49; H, 4.48; N, 20.89. Found: C, 40.43; H, 4.35; N, 20.72.

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