Nucleosides. CXXXV. Synthesis of Some 9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purines and Their Biological Activities[1]

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Seven purine nucleosides containing the 2′-deoxy-2′-fluoro-β-D-arabinofuranosyl moiety were synthesized and tested for their antitumor activity. Direct condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide (1) with N^6-benzoyladenine in CH_2Cl_2 followed by saponification of the product afforded the adenine nucleoside (I, 2′-F-ara-A). Deamination of I with $NaNO_2$ in HOAc gave the hypoxanthine analogue (II, 2′-F-ara-H). The 6-thiopurine nucleoside (III, 2′-F-ara-6MP) was prepared by condensation of 1 with 6-chloropurine by the mercury procedure followed by thiourea treatment and saponification of the product. Methylation of III gave the 6-SCH_3 analogue (IV). Raney Ni desulfurization of III afforded the unsubstituted purine nucleoside (V, 2′-F-ara-P). Condensation of 1 with 2-acetamido-6-chloropurine by the silyl procedure afforded the protected 2-acetamido-6-chloropurine nucleoside which served as the precursor for both the guanine and 6-thioguanine nucleosides (VI, 2′-F-ara-G and VII, 2′-F-ara-TG, respectively). Thus, alkaline hydrolysis of the precursor gave VI. Thiourea treatment prior to alkaline hydrolysis gave VII. The new nucleoside, 2′-F-ara-G (VI) is found to be selectively toxic to human T-cell leukemia CCRF-CEM.

Keywords nucleoside; purine nucleoside; 2′-fluoro-arabinosylpurine; 2′-fluoro-arabinosylguanine; antitumor activity

The synthesis of 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (2′-F-ara-A, I) was reported from our laboratory as an analog of the antitumor and antiviral naturally-occurring nucleoside 9-(β-D-arabinofuranosyl)adenine (ara-A).[2] The synthesis consists of a multistep preparation of a 2-deoxy-2-fluoro-D-arabinofuranose derivative from D-xylose, and the 2-fluoro sugar is condensed with 2,6-dichloropurine by the fusion method, followed by multistep conversion of the purine into adenine.

Subsequently, 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-cytosine (FAC) was synthesized[3] in our laboratory by condensation of an appropriate sugar halide and cytosine by the silyl procedure and was evaluated for its antitumor activity. FAC was found to have a growth-inhibitory effect comparable with that of 1-(β-D-arabinofuranosyl)-cytosine (ara-C) against L-1210 mouse leukemic cells in tissue culture.[3] We have since developed a more elegant and effective method for preparation of the 2-fluoro-arabinose from D-glucose[4] and prepared a number of 5-substituted-uracil and -cytosine nucleosides as potential antiviral and/or anticancer agents.[5-9] Many pyrimidine nucleosides containing the 2′-fluoro-β-D-arabinofuranosyl moiety showed excellent antiherpesvirus activity[10-12] and some showed good antitumor activity.[13]

No purine nucleoside containing the 2′-fluoro-β-D-arabinofuranosyl moiety has been reported except the adenine nucleoside synthesized in our laboratory.[2] The outstanding biological activities demonstrated by the 2′-fluoro-arabinosyl-pyrimidines prompted us to prepare several purine nucleosides containing the 2′-fluoro-arabinosyl moiety. The targeted purine nucleosides are structurally more close than their corresponding ara-purines to natural or biologically active 2′-deoxynucleosides due to the similarity in the van der Waals radii[14] between the elements hydrogen (1.20 Å) and fluorine (1.35 Å). In addition, 2′-F-ara-purines are expected to be more resistant to PNPase[15] than the corresponding 2′-deoxypurine nucleosides, since 2′-F-ara-pyrimidines have been shown to be quite stable to enzymatic glycosyl cleavage.[16,17]

Originally, 2′-F-ara-A (I) was prepared by Wright *et al.*[2] by fusion reaction of 1,3-di-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinofuranose with 2,6-dichloropurine followed by a series of chemical conversions. We found that I was prepared more readily under the conditions of Glaudeman and Fletcher.[18] Thus, direct condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide[4] (**1**, Chart 1) with N^6-benzoyladenine in dichloromethane in the presence of molecular sieves afforded the protected nucleoside (**2**) which was saponified to give I in 86% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of this product was identical with that of an authentic sample.

The hypoxanthine analogue (II) was prepared from I by deamination. Although N^6-benzoyladenine directly reacted with **1**, other purines such as 6-chloropurine or 2-acetamido-6-chloropurine did not condense with **1** under similar conditions. Among several condensation reactions attempted, only the mercury procedure[19] gave the 6-chloropurine nucleoside **3**. Purification of **3** was extremely difficult. Treatment of crude **3** with thiourea, however, afforded the desired 6-thiopurine nucleoside **4** (in 10% yield) which crystallized out from the reaction mixture. Saponification of **4** gave 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)purine-6-thiol (III). The ^{1}H-NMR spectrum of this sample was very similar to that of I (Table I), establishing the β nucleoside. Methylation of III with iodomethane in base afforded the 6-methylthiopurine nucleoside (IV). Reduction of III with Raney nickel converted III into 2′-fluoro-arabinosylpurine (V).

The guanine and thioguanine nucleosides (VI and VII) were prepared in 67% and 62% yield, respectively, from the common intermediate, 9-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-

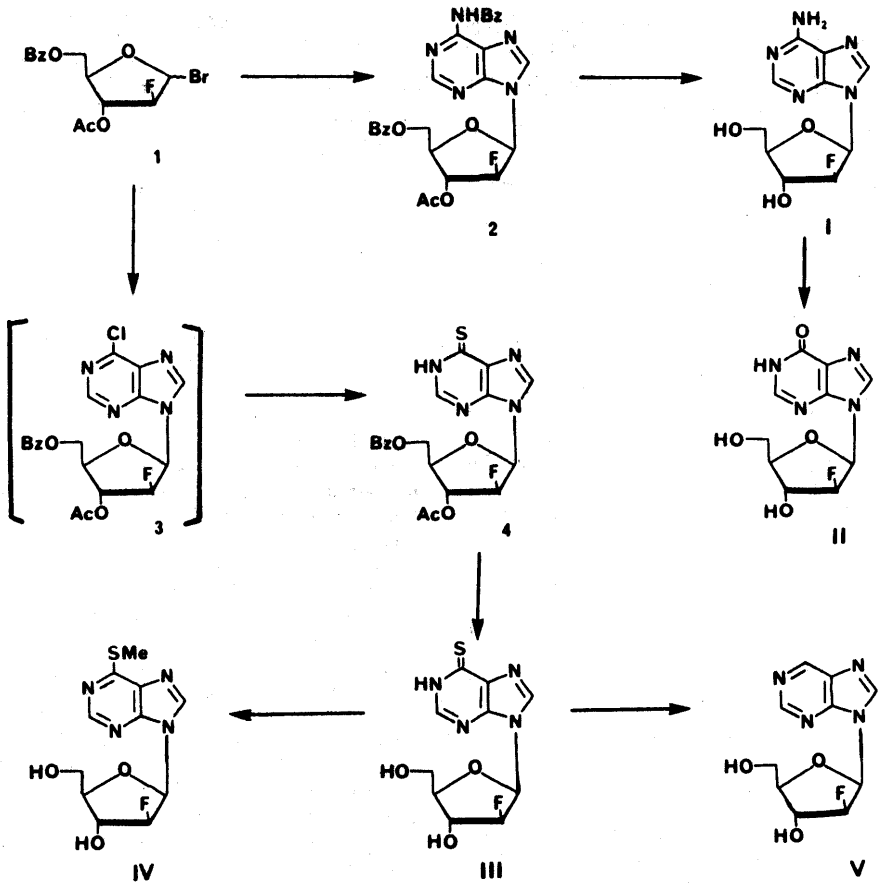

Chart 1

TABLE I. ^{1}H-NMR Parameters of 9-(2′-Deoxy-2′-fluoro-β-D-arabinofuranosyl)purines[a]

Compd.	Chemical shifts (δ)								Coupling constants (Hz)					
	H-2	H-8	H-1′	H-2′	H-3′	H-4′	H-5′	Others	$J_{1',2'}$	$J_{1',F}$	$J_{2',3'}$	$J_{2',F}$	$J_{3',4'}$	$J_{3',F}$
2	8.81 s	8.30 d	6.63 dd	5.23 dd	5.55 dd	4.46 m	4.75 d	2.22 s (OAc)	2.44	22.28	0	48.83	2.74	14.77
4	8.23 s	8.30 d	6.48 dd	5.58 dm	5.67 dm	4.49 m	4.64 m	2.14 s (OAc)	3.97	17.70	4.57	52.49	4.57	23.80
5		8.56 d	6.54 dd	5.65 dm	5.87 dm	4.53 m	4.69 m	2.20 s, 2.16 s (Ac)	4.58	16.48	4.39	53.10	4.39	17.70
6		8.19 d	6.29 dd	5.53 dm	5.57 dm	4.52 m	4.64 m	2.14 s, 2.22 s (Ac)	3.97	19.53	4.39	52.19	4.39	15.87
I	8.17 s	8.25 d	6.41 dd	5.21 dt	4.46 dm	3.84 m	3.72 m		5.48	14.65	5.48	53.40	5.48	18.90
II	8.08 s	8.21 d	6.37 dd	5.22 dt	4.42 dm	3.70 m	3.65 m		4.64	13.45	4.67	52.69	4.67	18.66
III	8.17 s	8.25 d	6.37 dd	5.21 dt	4.45 dm	3.85 m	3.68 m		4.57	14.04	4.57	52.50	4.57	19.23
IV	8.77 s	8.61 d	6.54 dd	5.29 dt	4.49 dm	3.89 m	3.71 m	2.69 s (SMe)	4.88	13.12	4.88	52.79	4.88	20.14
V	9.00 s	8.76 d	6.61 dd	5.33 dt	4.51 dm	3.91 m	3.70 m	9.23 s (H-6)	4.58	13.12	4.58	52.49	4.58	19.23
VI		7.81 d	6.13 dd	5.11 dt	4.36 dm	3.79 m	3.63 m		4.27	15.87	4.27	52.09	4.27	17.39
VII		8.02 d	6.13 dd	5.14 dt	4.37 dm	3.81 m	3.64 m		4.27	14.96	4.27	52.49	4.27	19.22

a) The spectra were recorded in DMSO-d_6 solution except for **2** which was dissolved in $CDCl_3$ for measurement. Signals are quotted as s (singlet), d (doublet), dd (double doublet), dt (apparent double triplet), m (multiplet) and dm (double multiplet).

2-fluoro-β-D-arabinofuranosyl)-2-acetamido-6-chloropurine (**5**) which was prepared both by the mercury procedure[20] and by the silyl procedure[21] (Chart 2). Compound **5** was converted into 2′-F-ara-G (VI) by treatment with 2-mercaptoethanol in methanolic sodium methoxide according to the procedure of Lee and Tong.[22] Treatment of **5** with thiourea afforded the 6-thio derivative **6**. Saponification of **6** gave the thioguanine nucleoside (VII). The β anomeric configuration for VI and VII was established by comparison of the ^{1}H-NMR spectra of these nucleosides with those of I—V (Table I).

Preliminary results of *in vitro* screening of selected 2′-F-ara-purines against mouse and human leukemic cells are shown in Table II. Although they are only moderately active against mouse leukemic cells, the guanine nucleoside (VI) is considerably more active against human leukemic cells, particularly the T cell line CCRF-CEM. 2′-F-ara-G (VI) is more toxic in mice (ID_{50} = 125 mg/kg × 10 d) than the thioguanine analog (ID_{50} = 400 mg/kg). Further antileukemic evaluation of VI and VII is now in progress. The hypoxanthine nucleoside (2′-F-ara-H, II) inhibits the growth of *Leishmania* tropica promastigotes by 50% at the concentration of 0.6 μM, while it does not exhibit any toxicity against L-1210 cells at 100 μM.[23] None of the new

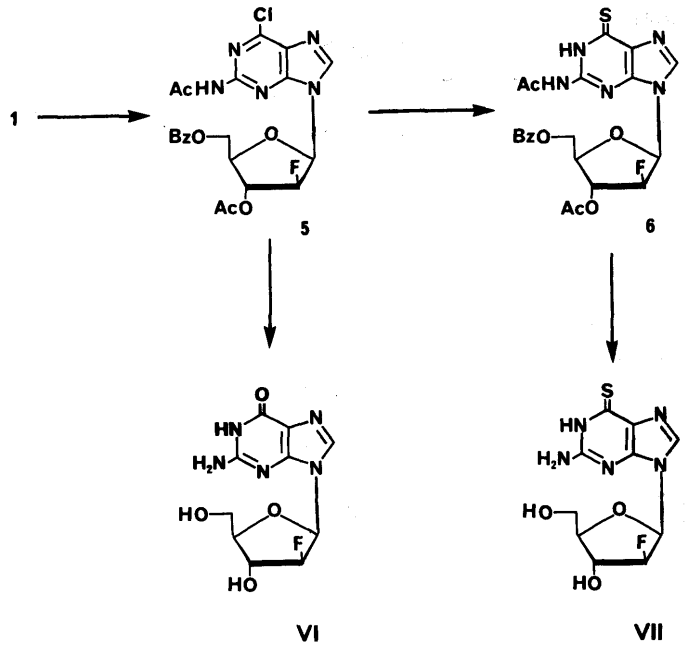

Chart 2

TABLE II. Cytotoxicity of 9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-purines

Compd.	X	Y	ID_{50} (μM) L1210[a]	P-813[a]	NL[b]	CCRF-CEM[b]
I	NH_2	H	>30	>30	3.0	0.67
II	OH	H	>30	>30	30	15.1
III	SH	H	27.0	10.0	2.0	10.0
IV	SMe	H	>100	>100	>100	>100
V	H	H	>100	>100	>100	>100
VI	OH	NH_2	2.0	5.4	0.7	<0.10
VII	SH	NH_2	100	>100	>100	>100

a) Mouse leukemia cells. *b*) Human cells.

2′-F-ara-purines demonstrated significant antiviral activity against HSV-1.[24]

Experimental

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL PFT-100 or JEOL FX90Q spectrometer using dimethyl sulfoxide (DMSO)-d_6 as the solvent and Me_4Si as the internal standard. Elemental analyses were performed by M.H.W. Laboratories and Galbraith Laboratory. Silica gel thin layer chromatography (TLC) was performed on Analtech Uniplates with short-wave length ultraviolet (UV) light for visualization. Column chromatography was conducted on flash grade silica gel (Merck 9385, 0.040—0.063 fm).

9-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-N^6-benzoyladenine (2) A mixture of **1** (903 mg, 2.5 mmol), N^6-benzoyladenine (1.48 g, 6.2 mmol) and molecular sieves (4 Å, 3 g) in CH_2Cl_2 (25 ml) was refluxed for 3 d with vigorous stirring. After cooling to room temperature, the mixture was filtered through a Celite pad. The filtrate which contained two major products (Rf=0.80 and 0.99 on TLC, CH_2Cl_2–MeOH (9:1)) was concentrated *in vacuo* and the residue was chromatographed over a silica gel column using CH_2Cl_2–MeOH (20:1) as the eluent. From the slower moving major fraction, **2** was obtained as a foam (440 mg, 34%). The ^{1}H-NMR parameters of this compound are listed in Table I.

Anal. Calcd for $C_{26}H_{22}FN_5O_6$: C, 60.12; H, 4.24; F, 3.66; N, 13.49. Found: C, 60.23; H, 4.46; F, 3.66; N, 13.13.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (I) A mixture of **2** (300 mg, 0.58 mmol) in 1 M NaOMe (12 ml) was heated at reflux for 5 h and then cooled. After neutralization of the mixture with wet Dowex 50 (H^+), the resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from EtOH to give 135 mg (86%) of I, mp 231—234 °C (lit.[2] mp 232—234 °C). For the ^{1}H-NMR data of I, see Table I.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)hypoxanthine (II) To a solution of I (140 mg, 0.52 mmol) in 50% aq. HOAc (8 ml) was added $NaNO_2$ (100 mg) in four portions at every 12 h and the reaction was followed by TLC (EtOAc–isoPrOH–H_2O (13:4:1)). After all the starting material was consumed, the mixture was passed through a Dowex 50 (H^+) column (5×0.5 cm). The column was washed with water. The major nucleoside-containing fractions were collected and lyophilized to afford II (35 mg) as a colorless fluffy solid. The ^{1}H-NMR spectral characteristics of II are reported in Table I.

Anal. Calcd for $C_{10}H_{11}FN_4O_4 \cdot H_2O$: C, 41.96; H, 4.51; F, 6.60; N, 19.44. Found: C, 41.84; H, 4.22; F, 6.76; N, 19.81.

9-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinosuranosyl)-purine-6-thiol (4) A mixture of Hg salt of 6-chloropurine[19] (5.0 g) and Celite (2.0 g) in xylene (200 ml) was vigorously stirred and dried by azeotropic distillation of about 100 ml of solvent. A solution of **1** [prepared from 3.48 g, (10.2 mmol) of the 1-*O*-acetate][4] in xylene (30 ml) was added and a further 30 ml of solvent removed by distillation. Refluxing was continued overnight and the mixture was filtered while hot. The filtrate was concentrated *in vacuo* and the residue dissolved in $CHCl_3$ (100 ml). The solution was washed successively with 30% KI solution (100 ml) and water (100 ml×2), dried (Na_2SO_4), and concentrated *in vacuo* to give the crude 6-chloropurine nucleoside **3**. A mixture of crude **3** and thiourea (760 mg) in EtOH (25 ml) was heated at reflux overnight. The precipitates were collected by filtration and recrystallized from MeOH–$CHCl_3$ to give **4** (450 mg, 10.2%), mp 242—244 °C. The ^{1}H-NMR spectral data of **4** are given in Table I.

Anal. Calcd for $C_{19}H_{17}FN_4O_5S$: C, 52.78; H, 3.94; F, 4.40; N, 12.96; S, 7.41. Found: C, 52.89; H, 3.97; F, 4.40; N, 12.96; S, 7.14.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)purine-6-thiol (III) Compound **4** (140 mg, 0.23 mmol) was treated with NH_3/MeOH (6 ml, satd. at 0 °C) for 3 d. The mixture was filtered, the filtrate concentrated *in vacuo* and the residue crystallized from EtOH to give 61 mg (64.5%) of III, mp 225—226 °C (dec.). The ^{1}H-NMR parameters of this compound are listed in Table I.

Anal. Calcd for $C_{10}H_{11}FN_4O_3S$: C, 41.96; H, 3.85; F, 6.64; N, 19.38; S, 11.19. Found: C, 41.95; H, 3.91; F, 6.45; N, 19.16; S, 11.09.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-6-methylthiopurine (IV) A mixture of III (136 mg, 0.48 mmol) and MeI (141 mg, 1.0 mmol) in 0.2 N NaOH (2.5 ml) was stirred at room temperature for 2 h. After concentration of the mixture *in vacuo*, the residue was triturated with Me_2CO (2 ml). Compound IV (67 mg, 47%) was obtained in its pure state by recrystallization of the Me_2CO insoluble solid from EtOH, mp 152—153 °C. See Table I for the ^{1}H-NMR characteristics of IV.

Anal. Calcd for $C_{11}H_{13}FN_4O_3S$: C, 44.00; H, 4.33; F, 6.33; N, 18.57; S, 10.67. Found: C, 43.94; H, 4.40; F, 6.25; N, 18.52; S, 10.80.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)purine (V) A mixture of III (140 mg, 0.49 mmol) and Raney Ni (100 mg) in H_2O (5 ml) was heated at reflux for 2 h and the mixture was filtered, while hot, through a Celite pad. The filtrate was concentrated *in vacuo* and the solid residue was recrystallized from MeOH to give V (66 mg, 53%), mp 173—175 °C. The ^{1}H-NMR parameters of V are given in Table I.

Anal. Calcd for $C_{10}H_{11}FN_4O_3$: C, 47.27; H, 4.33; F, 7.48; N, 22.05. Found: C, 47.22; H, 4.33; F, 7.68; N, 22.06.

9-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-2-acetamido-6-chloropurine (5) Method A: A mixture of the Hg salt of 2-acetamido-6-chloropurine (8.8 g, 20 mmol)[25] and Celite (4.0 g) in xylene (400 ml) was dried by distilling off about 200 ml of xylene. The suspension was cooled to room temperature and to it was added a solution of **1** (7.2 g, 20 mmol) in xylene (80 ml). The mixture was heated with stirring for 15 h at reflux temperature and filtered hot. The filtrate was concentrated *in vacuo* and the residue dissolved in $CHCl_3$ (200 ml). The solution was washed successively with 30% KI (80 ml×2) and water (100 ml×2), dried (Na_2SO_4), concentrated and the residue chromatographed on a silica gel column using $CHCl_3$–MeOH (30:1, v/v) as the eluent. The major nucleoside fraction was concentrated *in vacuo* and the residue was crystallized twice from EtOH to afford **5** (1.65 g, 17%), mp 154—156 °C. See Table I for the ^{1}H-NMR data of **5**.

Anal. Calcd for $C_{21}H_{20}ClFN_5O_6$: C, 51.27; H, 3.87; F, 3.87; N, 14.24.

Found: C, 51.08; H, 4.15; F, 3.92; N, 13.97.

Method B: To a mixture of 2-acetamido-6-chloropurine (1.06 g, 5.0 mmol) and Me_3SiCl (140 ml, 11.04 mmol) in dry benzene (15 ml) was added dropwise a solution of Et_3N (1.47 ml, 10.57 mmol) in benzene (4 ml), and the mixture was stirred for 40 h, filtered, and the filter cake washed with benzene. To the combined filtrate and washings were added $Hg(CN)_2$ (2.41 g, 9.54 mmol) and **1** (1.90 g, 5.25 mmol) and the mixture was heated at reflux for 4 h with stirring. After cooling, MeOH (5 ml) was added and the mixture was concentrated *in vacuo*. The residue was triturated with $CHCl_3$ and filtered. The filtrate was washed successively with 30% KI and water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on a silica gel column using *n*-C_6H_{14}–EtOAc (1 : 1 then 1 : 2) to give 772 mg (32%) of **5**. The ^{1}H-NMR parameters of this sample are identical with those of **5** prepared by Method A.

9-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-2-acetamidopurine-6-thiol (6) A mixture of **5** (1.60 g, 3.25 mmol) and thiourea (297 mg, 3.90 mmol) in *n*-PrOH (20 ml) was heated at reflux for 2 h. After cooling, the mixture was concentrated *in vacuo*, the residue triturated with CH_2Cl_2 and filtered. The filtrate was evaporated *in vacuo* and the residue was chromatographed on a silica gel column using CH_2Cl_2–MeOH (40 : 1, v/v) as the eluent to give 1.30 g (82%) of **6** after crystallization from EtOH, mp 136—139 °C. The ^{1}H-NMR spectral characteristics are reported in Table I.

Anal. Calcd for $C_{21}H_{20}FN_5O_6S$: C, 51.53; H, 4.09; F, 3.89; N, 14.31; S, 6.54. Found: C, 51.36; H, 4.31; F, 3.97; N, 13.94; S, 6.55.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)guanine (VI) A mixture of **5** (640 mg, 1.30 mmol), $HSCH_2CH_2OH$ (0.39 ml) and 1 M NaOMe (3.9 ml) in MeOH (20 ml) was heated at reflux for 3 h. The mixture was cooled to 0 °C and crystals separated were collected by filtration, dissolved in 50% aq. MeOH (50 ml), neutralized with Amberlite IRC-50 (H^+). After removal of the resin by filtration, the filtrate was concentrated *in vacuo* and the residue was recrystallized from water to give VI (250 mg, 67%), mp 250—251 °C. The ^{1}H-NMR parameters of VI are listed in Table I.

Anal. Calcd for $C_{10}H_{12}FN_5O_4 \cdot 1/2H_2O$: C, 40.82; H, 4.42; F, 6.46; N, 23.81. Found: C, 41.04; H, 4.35; F, 6.59; N, 23.71.

9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-6-thioguanine (VII) A solution of **6** (190 mg, 0.39 mmol) in 1 M NaOMe/MeOH (6.5 ml) was heated at reflux for 3 h. After cooling to room temperature, the mixture was neutralized with Dowex 50 (H^+), filtered, and the filtrate concentrated *in vacuo*. Upon trituration of the residue with EtOH, 74 mg (62%) of VII was obtained as colorless crystals, mp 244—245 °C (dec.). See Table I for the ^{1}H-NMR parameters of VII.

Anal. Calcd for $C_{10}H_{12}FN_5O_3S$: C, 39.87; H, 3.99; F, 6.31; N, 23.26; S, 10.63. Found: C, 39.75; H, 4.07; F, 6.14; N, 23.16; S, 10.41.

Antitumor Screening The technique of Fisher[26] was employed with modifications.[13] Mouse cell lines L-1210/0 and P-815/0 and human cell lines NL and CCRF-CEC were incubated in McCoy's medium 5A with 15% fetal calf serum. The initial inoculum was 40000—60000 cells/ml. For growth inhibition studies, 0.1 ml of a 20-fold concentration of the nucleoside in question was added to 2 ml of media containing 4×10^4 cells/ml in Linbro tissue culture multiwell plates and allowed to incubate at 37 °C in 5% CO_2 for 96 h. The contents of each well were counted on a Coulter Counter and the percentage of inhibition of growth and the concentrations inhibiting cell growth by 50% were calculated.

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