Synthesis and *In Vivo* Antitumor and Antiviral Activities of 2'-Deoxyribofuranosyl and Arabinofuranosyl Nucleosides of Certain Purine-6-Sulfenamides, Sulfinamides and Sulfonamides

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2'-Deoxyribofuranosyl and arabinofuranosyl nucleosides of certain purine-6-sulfenamides, sulfinamides and sulfonamides have been prepared by sequential amination and controlled oxidation of the corresponding 6-thiopurine nucleosides, and evaluated for antiviral and antitumor activities in mice. Amination of 2'-deoxy-6-thioinosine (4a) and 9-β-D-arabinofuranosyl-6-thiopurine (4c) with chloramine solution gave the corresponding 6-sulfenamides 5a and 5c, respectively, which on selective oxidation with 3-chloroperoxybenzoic acid (MCPBA) gave diastereomeric 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfinamide (6a) and 9-β-D-arabinofuranosylpurine-6-sulfinamide (6c), respectively. However, oxidation of 5a and 5c with excess of MCPBA gave the corresponding 6-sulfonamide derivatives 7a and 7c, respectively. Similar amination of 2'-deoxy-6-thioguanosine (4b), *ara*-6-thioguanine (4d) and α-2'-deoxy-6-thioguanosine (8) gave the respective 6-sulfenamide derivatives 5b, 5d and 9. Controlled oxidation of 5b, 5d and 9 gave (R,S)-2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfinamide (6b), (R,S)-2-amino-9-β-D-arabinofuranosylpurine-6-sulfinamide (6d) and the α-anomer of (6b) (10), respectively. The diastereomeric mixture of (R,S)-10 was partially resolved and the structure of S-10 was assigned by single-crystal X-ray diffraction analysis. Oxidation of 5b, 5d and 9 with excess of MCPBA afforded the respective 6-sulfonamide derivatives 7b, 7d and 11. Nucleosides 5c and 7c were significantly active against Friend leukemia virus in mice, whereas 6c was somewhat less active. Of the 20 nucleosides evaluated, 12 exhibited biologically significant anti-L1210 activity in mice. Nucleosides 6b and 7a at 173 mg/kg/day x 1 showed a T/C of 153, whereas 7d at 800 mg/kg/day x 1 showed a T/C of 153 against L1210 leukemia. The α-nucleoside 9 at 480 mg/kg/day x 1 gave a T/C of 172. A single treatment with 6b, 7a, 7d and 9 reduced the body burdens of viable L1210 cells by more than 99.2%. The antileukemic activity of these novel nucleosides tended to parallel solubility.

The synthesis of an effective and selective anticancer agent continues to present a major challenge for medicinal chemists. In spite of the tremendous effort expended in this area of research, relatively few antitumor agents are in widespread clinical use to date. In particular, the development of successful treatments for solid tumors has been most elusive; thus, tumors of the lung, breast, and colon continue to be the major cause of death from cancer in the United States of America and many other countries. Recent developments in the area of the molecular biology of tumors, increased understanding of the phenomenon of metastasis, and new knowledge of the administration and use of drugs, have led to renewed interest in the search for effective antitumor agents.

Analogues and derivatives of purines and pyrimidines have long played a major role in the arsenal of drugs used for the treatment of cancer. One of the oldest of these derivatives and one which is still widely used is purine-6(1*H*,9*H*)-thione (6-mercaptopurine, 6MP), first described by Elion and Hitchings [1] in 1952. In 1953, Burchenal and coworkers [2] found that 6-mercaptopurine had significant activity against human leukemias, and today, 6MP is often used in combination with other drugs to treat lymphoblastic leukemia in children [2]. The success of 6MP has stimulated medicinal chemists over the years

to synthesize a variety of purine analogues with the hope of obtaining drugs that are more potent, less (host) toxic, and that have a wider spectrum of antitumor activity than 6-mercaptopurine.

Other sulfur containing purine derivatives, such as 6-thioguanine (6TG), purine-6-sulfonamide and purine-6-*N*-methylsulfonamide have shown significant antitumor activity in experimental systems [3-6]. The presence of an oxidized sulfur atom at position 6 of these compounds has rendered them particularly effective as antitumor agents [6]. The effectiveness of these purine bases against certain tumor lines has suggested that the nucleosides or nucleotides of these purine sulfonamides would be worthy of consideration in order to determine whether they exert a more selective effect against neoplastic cells than against normal cells or if they might be useful in patients whose disease has became resistant to 6MP or 6TG [7]. Thus we initiated an extensive program to synthesize and evaluate nucleoside derivatives of certain purine-6-sulfonamides as potential anticancer agents [8]. During the course of these studies, we observed that the introduction of a sulfenamido, sulfinamido or sulfonamido group at the 6-position of certain purine ribonucleosides resulted in highly water soluble compounds with significant antitumor activity [8]. Administered qd (once daily) on day

one, 2-amino-9-β-D-ribofuranosylpurine-6-sulfenamide (sulfenosine, **1**) at 22 mg/kg exhibited a T/C of 170, whereas an diastereomeric (R,S)-2-amino-9-β-D-ribofuranosylpurine-6-sulfinamide (sulfinosine, **2a**) at 173 mg/kg showed a T/C of 167 against L1210 leukemia. The 5'-deoxy analog of sulfinosine, (R,S)-2-amino-9-(5-deoxy-β-D-ribofuranosyl)purine-6-sulfinamide (**2b**) at 104 mg/kg also showed a T/C of 172. A single treatment with **1**, **2a** or **2b** reduced body burdens of viable L1210 leukemia cells by more than 99.8% [8]. However, 2-amino-9-β-D-ribofuranosylpurine-6-sulfonamide (sulfonosine, **3**) produced a T/C of 128 at 62 mg/kg and reduced body burdens of viable L1210 cells by 92.4% [8]. Thus, in order to gain further insight into the nature of the antitumor effect of this new class of nucleosides, we have continued efforts to determine which structural features are necessary to improve the antitumor potency. We now describe the synthesis of 2-deoxy-β-D-*erythro*-pentofuranosyl, 2-deoxy-α-D-*erythro*-pentofuranosyl and β-D-arabinofuranosyl analogues of **1**, **2a** and **3**, and their preliminary antitumor as well as antiviral effects in mice.

1
Sulfenosine

2a R = OH, Sulfinosine
2b R = H

3
Sulfonosine
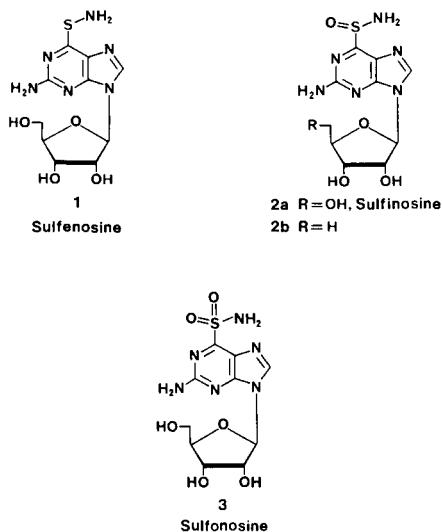
Results and Discussion.

Chemistry.

The compounds prepared during this study are outlined in Schemes 1 and 2, and were synthesized by the sequential amination and controlled oxidation of the corresponding 6-thiopurine nucleosides. Thus, treatment of 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6(1H)-thione (**4a**) [9] with an aqueous chloramine solution [prepared from commercial sodium hypochlorite (clorox) and ammonium hydroxide solution] at ambient temperature, and purification of the reaction product by silica gel column chromatography provided an 85% yield of 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfenamide (**5a**) (Scheme

1). When one considers the several reactions which may occur in a mixture of **4a**, hypochlorite and ammonium hydroxide, it is rather surprising that any of the desired **5a** can be isolated. The free chlorine in the hypochlorite solution may react with excess ammonia to produce nitrogen and ammonium chloride. Also, the hypochlorite may react with **4a** to produce a disulfide [10] or the salt of a sulfonic acid [11]. Despite the fact that some of these side reactions are most certainly taking place, we have been able to isolate sulfenamides of high purity and in satisfactory yields. Even though oxidation of 4,6-dimethylpyrimidine-2-sulfenamide with 3-chloroperoxybenzoic acid (MCPBA) reportedly [12] failed to provide the desired sulfonamide, treatment of **5a** with 1 molar equivalent of (MCPBA) [13] in ethanol at 0° gave an oxidized product, which was isolated in 46% yield as crystalline material and identified as a diastereomeric mixture of 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfinamide (**6a**). To the best of our knowledge, this is the first reported example of the isolation of a crystalline N-unsubstituted sulfinamide nucleoside derivative. However, oxidation of **5a** by the treatment with 3 molar equivalent of MCPBA in ethanol at room temperature gave the fully oxidized product 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfonamide (**7a**), which was isolated from the reaction mixture in a 41% yield after silica gel column chromatography. Compounds **5a**, **6a** and **7a** appear to be quite stable when dry and free from acid or alkali; however, upon exposure to aqueous acid or alkaline solution they tend to hydrolyze to inosine.
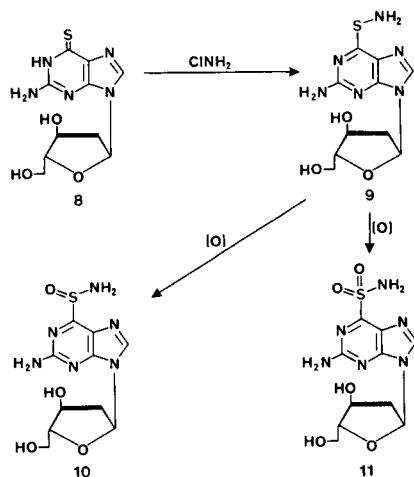
Scheme 1

a, X=Y=H   b, X=NH₂; Y=H
c, X=H; Y=OH   d, X=NH₂; Y=OH
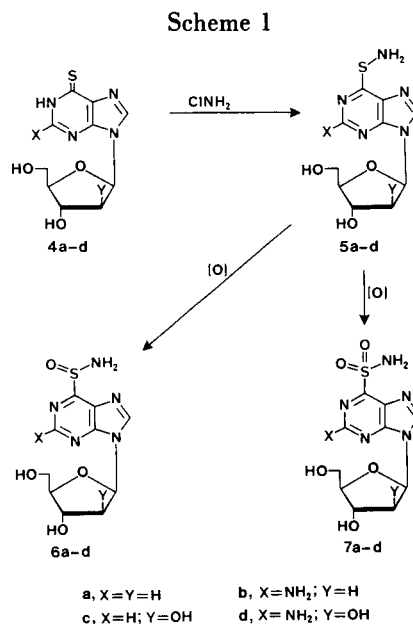
A similar amination of 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6(1H)-thione [9] (2'-deoxy-6-thio-

guanosine, **4b**) with aqueous chloramine solution at 0° readily gave the desired 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfenamide (2'-deoxysulfenosine, **5b**). The isolated yield of the analytically pure **5b** was 86%. Oxidation of an ethanolic solution of **5b** with 1 molar equivalent of MCPBA afforded (*R,S*)-2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfinamide (2'-deoxysulfinosine, **6b**), whereas use of 4 molar equivalent of the oxidizing agent furnished the fully oxidized product 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfonamide (**7b**) in good yield. Since a diastereomeric mixture of sulfinosine **2a** appeared to be much more effective against L1210 leukemia in mice than either *R* or *S* diastereomer alone [8], no attempt was made to separate the diastereomers of sulfinamides **6a-6d**. The mixture as such was used for biological evaluation.

These amination and oxidation procedures were also found to be very successful with the arabinonucleosides. Thus, treatment of 9-β-D-arabinofuranosylpurine-6(1*H*)-thione [14] (**4c**) with aqueous chloramine solution at 0° gave the desired 9-β-D-arabinofuranosylpurine-6-sulfenamide (**5c**). However, the isolated yield of the analytically pure **5c** was 56%. Controlled oxidation of (**5c**) with 1 molar equivalent of MCPBA gave (*R,S*)-9-β-D-arabinofuranosylpurine-6-sulfinamide (**6c**), whereas use of 4 molar equivalent of the oxidizing agent furnished 9-β-D-arabinofuranosylpurine-6-sulfonamide (**7c**) in 81% yield.

Scheme 2

In a similar manner, 2-amino-9-β-D-arabinofuranosylpurine-6(1*H*)-thione (**4d**) [9] was aminated with chloramine solution (Scheme 1). The reaction product was purified by silica gel column chromatography to give 2-amino-9-β-D-arabinofuranosylpurine-6-sulfenamide (**5d**) in over 54% yield. Controlled oxidation of **5d** with MCPBA gave the corresponding sulfinamide **6d** and sulfonamide **7d** derivatives, each in 60% yield. When 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6(1*H*)-thione (**8**) [15] was reacted with aqueous chloramine solution at 0° for 1

hour, the crystalline aminated product 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfenamide (**9**) was precipitated out from the reaction mixture (Scheme 2). Recrystallization from aqueous ethanol furnished an 84% yield of analytically pure **9**. Oxidation of a solution of **9** in ethanol with 1 molar equivalent of MCPBA at room temperature deposited the less soluble *S*-diastereomer of 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfinamide [(*S*)-**10**] in 31% yield. The structure of (*S*)-**10** was confirmed by single-crystal X-ray diffraction analysis. The filtrate on concentration and purification afforded a diastereomeric mixture of **10**. However, oxidation of an ethanolic solution of **9** with 4 molar equivalent of MCPBA at room temperature gave a 36% yield of 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfonamide (**11**). The structures of these sulfur-containing purine nucleosides were confirmed by ^{1}H nmr and uv spectra, and by elemental analyses. The purity was assured by the homogeneity in several thin layer chromatographic systems.

The ^{1}H nmr spectral comparison of the NH$_2$ proton chemical shifts in DMSO-d$_6$ of sulfenamide, sulfinamide and sulfonamide analogues revealed an interesting pattern in this group of compounds (Table 1). For sulfenamides the -SNH$_2$ chemical shift was found to be in the region δ 3.90-4.15 ppm. The selective oxidation of sulfenamides to sulfinamides resulted in the shift of the -SONH$_2$ protons to lower field (6.68-6.98 ppm) and further oxidation of sulfinamides to sulfonamides caused the NH$_2$ group to shift still further downfield (in the region 7.48-7.85 ppm). This effect is in correlation with the expected increased deshielding by the extra oxygen attached to sulfur in the sulfonamide [16].

Table 1

The -NH$_2$ Proton Chemical Shifts in the ^{1}H NMR Spectra of Sulfenamide, Sulfinamide, and Sulfonamide Derivatives of Certian Purine-2'-deoxyribofuranosyl and Arabinofuranosyl Nucleosides

Compound	Chemical Shifts (ppm) in DMSO-d$_6$		
	-SNH$_2$	-SONH$_2$	-SO$_2$NH$_2$
5a	4.12		
6b		6.68	
7a			7.85
5b	3.90		
6b		6.98	
7b			7.52
5c	4.15		
6c		6.71	
7c			7.85
5d	4.09		
6d		6.97	
7d			7.48
9	3.98		
10		6.94	
11			7.51

Single-crystal X-ray Diffraction Analysis of Compound *S*-**10**.

Atomic coordinates are presented in Table 2. As in the case of (R)-2-amino-9-β-D-ribofuranosylpurine-6-sulfinamide (sulfinosine) [8], the least-soluble diastereomer of the sulfinamide **10** has the S-configuration at the sulfur. This feature as well as the α-anomeric configuration of the 2'-deoxyribose moiety are illustrated in Figure 1. The sulfinamido group is oriented similarly to that found in (R)-sulfinosine [8]; hence, the oxygen atom is nearly coplanar [dihedral angle = 17.06(9)°] with the purine plane and trans to the imidazole ring whereas the sulfur-nitrogen bond is almost perpendicular [83.78(10)°] to the plane. The pyrimidine-imidazole dihedral angle is 3.43(10)°, which is considerably larger than normally observed (e.g., 1.7° in sulfonosine [8]). Bond lengths, angles and selected torsion angles are shown in Table 3. The glycosidic bond of 1.469(2) Å is longer than observed in sulfinosine [8]. The glycosidic torsion angle, χ_{CN} = O1'-C1'-N9-C4, is 148.5(2)°. The sugar has normal conformation, $C_{2'}$-endo/$C_{3'}$-exo, with a pseudorotation angle P of 173.3° and an amplitude of pucker τ_m of 28.3° [17]. Despite the inability to form an intramolecular O5'-H··N3 hydrogen bond, the C5'-O5' side chain is gauche-gauche.

Table 2

Positional and Equivalent Isotropic Thermal Parameters for Non-hydrogen Atoms in (S)-**10** with their esds in Parentheses

Atom	x/a	y/b	z/c	u_{eq} [a]
N1	.4777(3)	.570479	1.0641(2)	.0283(5)
C2	.3098(3)	.5640(2)	.8824(3)	.0274(5)
N3	.3138(3)	.5169(2)	.7227(2)	.0303(5)
C4	.5063(3)	.4764(2)	.7563(3)	.0271(5)
C5	.6945(3)	.4794(2)	.9312(3)	.0275(5)
C6	.6661(3)	.5298(2)	1.0858(2)	.0266(5)
N7	.8627(3)	.4265(2)	.9115(3)	.0352(6)
C8	.7734(4)	.3931(2)	.7305(3)	.0369(7)
N9	.5593(3)	.4192(2)	.6295(3)	.0315(5)
N10	.1261(3)	.6126(2)	.8606(3)	.0359(6)
S11	.88092(7)	.53886(12)	1.33198(6)	.03196(14)
O12	.7657(3)	.5732(2)	1.4653(2)	.0379(5)
N13	1.0160(3)	.6192(2)	1.2656(3)	.0442(7)
C1'	.4150(4)	.3985(2)	.4224(3)	.0338(6)
C2'	.2688(4)	.3171(2)	.4060(3)	.0383(7)
C3'	.4039(3)	.2413(2)	.3619(3)	.0323(6)
C4'	.5383(3)	.2879(2)	.2522(3)	.0313(6)
C5'	.4473(5)	.2815(2)	.0246(3)	.0437(8)
O3'	.5522(3)	.2022(2)	.5424(3)	.0425(5)
O4'	.5482(3)	.3806(2)	.3073(2)	.0394(6)
O5'	.2149(4)	.2918(2)	-.0605(3)	.0634(8)
H8	.859(6)	.357(3)	.667(5)	.059(9)
H10A	.010(6)	.600(3)	.765(5)	.057(9)
H10B	.113(6)	.625(3)	.983(6)	.064(10)
H13A	1.151(7)	.627(3)	1.376(6)	.075(11)
H13B	.949(7)	.671(3)	1.222(5)	.066(11)
H1'	.327(5)	.458(2)	.377(4)	.038(7)
H2'A	.134(5)	.328(2)	.286(4)	.047(8)
H2'B	.224(5)	.308(2)	.525(4)	.040(7)
H3'	.306(7)	.196(3)	.268(6)	.065(10)
H4'	.704(4)	.256(2)	.311(3)	.025(5)
H5'A	.477(4)	.266(2)	-.023(4)	.025(6)
H5'B	.558(7)	.329(3)	-.029(6)	.070(11)

HO3'	.467(6)	.169(2)	.583(5)	.057(9)
HO5'	.176(9)	.353(4)	-.050(8)	.12(2)

[a] For non-hydrogen atoms, U is $U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* A_{ij}$, where A_{ij} is the dot product of the ith and j^{th} direct-space unit-cell vectors.

Table 3

Bond Lengths (Å), Bond Angles (°) and Selected Torsion Angles (°) in (S)-**10** with their esds in Parentheses

1	2	3	1-2	1-2-3
C2	N1	C6	1.364(2)	118.0(2)
N3	C2	N10	1.344(3)	117.6(2)
N3	C2	N1		126.2(2)
N10	C2	N1	1.353(3)	116.2(2)
C4	N3	C2	1.326(3)	112.59(15)
C5	C4	N9	1.398(2)	105.3(2)
C5	C4	N3		127.6(2)
N9	C4	N3	1.372(3)	127.1(2)
C6	C5	N7	1.396(3)	135.3(2)
C6	C5	C4		113.7 (2)
N7	C5	C4	1.391(3)	110.8(2)
S11	C6	N1	1.812(2)	115.95(15)
S11	C5	C5		122.05(15)
N1	C6	C5	1.320(3)	121.93(14)
C8	N7	C5	1.308(3)	103.2(2)
N9	C8	N7	1.369(3)	114.7(2)
C1'	N9	C4	1.469(2)	124.9(2)
C1'	N9	C8		129.0(2)
C4	N9	C8		105.9(2)
O12	S11	N13	1.484(2)	110.9(2)
O12	S11	C6		104.83(9)
N13	S11	C6	1.652(3)	94.67(11)
C2'	C1'	O4'	1.525(4)	106.7(2)
C2'	C1'	N9		113.8(2)
O4'	C1'	N9	1.401(3)	108.7(2)
C3'	C2'	C1'	1.532(4)	103.6(2)
C4'	C3'	O3'	1.523(4)	109.0(2)
C4'	C3'	C2'		103.0(2)
O3'	C3'	C2'	1.428(3)	111.9(2)
C5'	C4'	O4'	1.513(3)	108.3(2)
C5'	C4'	C3'		115.9(2)
O4'	C4'	C3'	1.444(3)	106.6(2)
O5'	C5'	C4'	1.413(4)	113.9(2)
C1'	O4'	C4'		111.5(2)

Selected Torsion Angles (°)

	1	2	3	4	
	N1	C6	S11	O12	13.7(2)
	N1	C6	S11	N13	-99.4(2)
χ_{CN}	C4	N9	C1'	O4'	148.5(2)
τ_0	C1'	C2'	C3'	C4'	-28.7(2)
τ_1	C2'	C3'	C4'	O4'	22.1(2)
τ_2	C3'	C4'	O4'	C1'	-6.3(2)
τ_3	C4'	O4'	C1'	C2'	-12.6(2)
τ_2	O4'	C1'	C2'	C3'	26.0(2)
ϕ_{00}	O4'	C4'	C5'	O5'	-78.1(3)
ϕ_{00}	C3'	C4'	C5'	O5'	41.6(3)

Table 4 details the hydrogen bonding geometry and Figure 2 illustrates the crystal packing. Every hydroxyl and amino hydrogen participates in hydrogen bonding
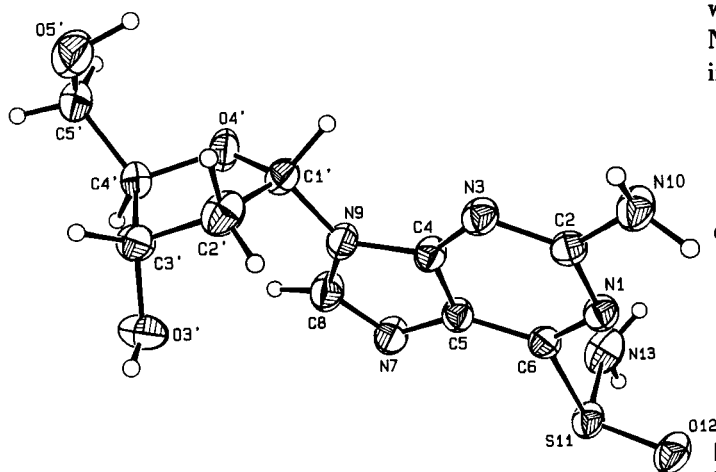
Figure 1. Perspective drawing of (S)-10 illustrating atom labeling, molarecular conformation, anomeric configuration and configuration at the sulfur S11.

although there are no exceptionally strong hydrogen bonds in the crystal structure. The sulfinamido oxygen (012) accepts two protons and 03', 05' and N7 accept one each. Surprisingly, the sixth proton is bonded to the sulfinamido nitrogen (N13), which can be seen in Figure 1 to be very nonplanar.

Table 4

Hydrogen Bonding in (S)-10 with esds in Parentheses

D - H ... A			Symmetry of A relative to D	d(D•••A) (Å)	d(H•••A) (Å)	∠(D-H••A) (°)
N10	H10A	O12	x-1,y,z-1	3.005(2)	2.91(4)	164.(4)
N10	H10B	N13	x-1,y,z	3.191(3)	2.30(4)	163.(4)
N13	H13A	O3'	2-x,0.5+y,2-z	2.915(3)	2.12(5)	140.(4)
N13	H13B	O3'	1-x,0.5+y,1-z	3.093(4)	2.21(4)	169.(4)
O3'	HO3'	O12	1-z,y-0.5,2-z	2.810(3)	2.06(4)	151.(4)
O5'	HO5'	N7	x-1,y,z-1	2.997(3)	2.23(6)	135.(5)

Antiviral Activity.

The arabinofuranosyl compounds 6c and 7c were highly inhibitory to visna virus replication in cell culture (Table 5). The rest of the compounds were relatively inactive, however. None of the compounds inhibited other types of viruses in vitro at ≤ 320 μM, such as adeno 2, herpes 2, rhino 1-A, influenza A, parainfluenza 3, and Semliki Forest viruses. Because visna virus is related to the human immunodeficiency retrovirus, suggesting a possible role in the treatment of the acquired immune deficiency syndrome (AIDS), the above observations prompted us to evaluate three of the analogues in a Friend leukemia virus infection model in mice (Table 6). Ribavirin, (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) [18], was included as a positive control, and it suppressed virus-induced splenomegaly by about 50% at 100 mg/kg. Statistically significant reductions in splenomegaly

were also achieved by 5c and 7c (both at 200 mg/kg). Nucleoside 6c was somewhat less active than the other two inhibitors.

Table 5

In Vitro Antiviral Activity of Certian Sulfer-Containing Purine Nucleosides Against Visna Virus [a]

Compound	Virus Rating	ED_{50} (μM)
5a	0.0	>320
6a	0.2	100
7a	0.2	32
5c	0.2	320
6c	1.0	10
7c	1.2	10

[a] determined by cytopathic effect inhibition assays in sheep choroid plexus cells.

Table 6

Effect of Arabinofuranosyl 6-Thiopurines on Friend Leukemia Virus-induced Splenomegaly in Mice

Compound	Dose [a] (mg/kg)	Average Spleen Weight [b] (g)
Saline	--	0.62 ± 0.45 [c]
Ribavirin [18]	100	0.32 ± 0.17 [d]
5c	100	0.43 ± 0.34
	200	0.27 ± 0.11 [d]
6c	100	0.73 ± 0.49
	200	0.50 ± 0.48
7c	100	0.84 ± 0.80
	200	0.29 ± 0.24 [d]

[a] Half-daily doses were administered twice a day for 14 days starting 2 hours before virus inoculation. [b] Determined 21 days after virus inoculation. [c] Standard deviation. [d] Statistically significant (p <0.01), determined by t2o-tailed t-test.

It was interesting that 5c inhibited Friend leukemia virus in mice but had minimal anti-virus activity in cell culture. From the in vitro results one might have predicted the compound would be inactive in vivo. It is important to realize that the splenomegaly induced by this virus can be suppressed or inhibited by antitumor compounds as well as antiviral agents [19]. This is because the virus-transformed cells need to replicate in order to cause the splenomegaly. In these studies, it is probable that all three arabinofuranosyl analogues 5c, 6c and 7c were active against Friend leukemia virus in mice by virtue of their antitumor properties. The reasons why two of the compounds were specifically active against visna virus remains to be investigated.

Antileukemic Activity.

Sixteen analogues of sulfenosine 5a-d, 9, sulfinosine 6a-d, 10, and sulfonosine 7a-d, 11 as well as their corresponding 6-thiopurine nucleosides 4a-d were evaluated for antileukemic activity in mice. As indicated by the data
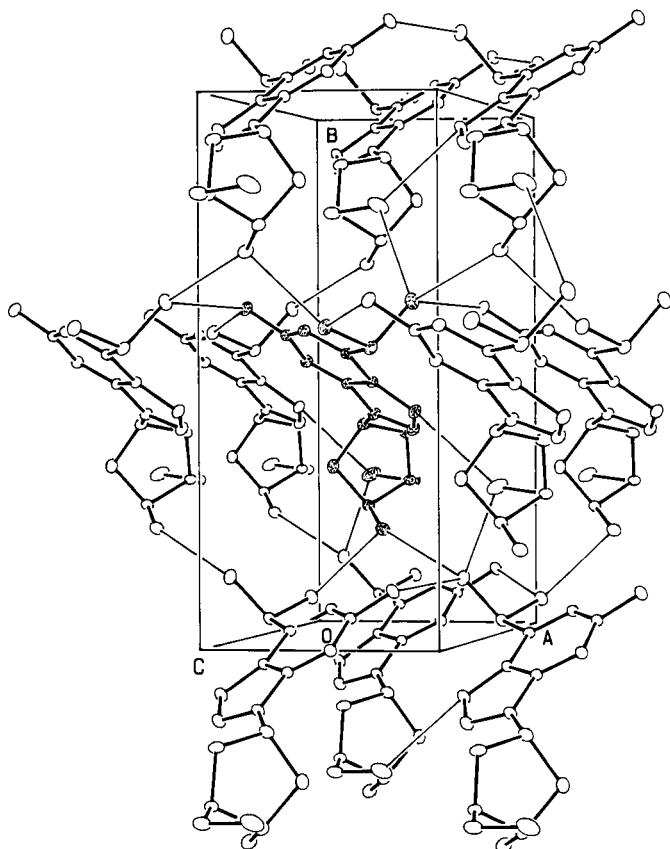
Figure 2. Crystal packing diagram for (S)-10 with hydrogens omitted for clarity. A single molarecule comprising the asyummetric unit has been shaded and all hydrogen bonds involving it are drawn as thin lines. Cell axes are labeled.

Table 7

Responses of L1210 Inoculated Mice to a Single Treatment with Selected Sulfur-Containing Purine Nucleosides

Compound Tested	Dosage [a] (mg/kg)	Postinoculation Lifespan [b] (%T/C)	% Viable L1210 Cells Killed by single Treatment [c]
4a	62	97	0
4b	22	156	99.35
4c	104	95	0
4d	22	120	83.84
5a	288 (800)	142	97.17
5b	173	144	98.12
5c	480	117	75.63
5d	104	100	0
6a	173 (800)	128	91.16
6b	173 (480)	154	99.27
6c	62	114	74.60
6d	800	140	98.22
7a	173 (800)	153	99.28
7b	288	125	90.79
7c	173	136	95.55
7d	800	153	99.34
9	480 (800)	172	99.68
10(S)	173	121	85.72
10(R,S)	288 (480)	125	90.27
11	480 (800)	113	70.87

presented in Table 7, substantial differences in the solubilities and anticancer activities of these compounds were noted. Solubility in water varied from a low of 2.2 mg/ml for compounds 4b and 4d to a high of 80 mg/ml for compounds 5a, 6a, 6d, 7a, 7d, 9 and 11. Administered qd (once daily) day 1 at dosages determined by solubility, 12 of the 20 nucleosides exhibited biologically significant anti-L1210 activity, i.e., they produced a T/C ≥ 125. Five, less active, compounds 4d, 5c, 6c, 10(S), 11 reduced body burdens of viable L1210 cells by 70-86%, and the remaining three compounds 4a, 4c, 5d lacked antileukemic activity.

Structural alterations in the aglycon and carbohydrate moieties of the compounds did not produce uniform changes in biological effects. Even so, certain striking relationships were noted. Analogues of the sulfenosine, sulfinosine, and sulfonosine series that lacked an amino group at the 2-position of the purine ring and had a 2-deoxy-β-D-erythro-pentofuranosyl moiety 5a, 6a, and 7a exhibited the greatest solubility (80 mg/ml) while those with a β-D-arabinofuranosyl unit 5c, 6c, 7c were uniformly much less soluble. With introduction of an amino group at the 2-position of the purine ring, this pattern was repeated for compounds in the sulfenosine series, i.e., the presence of an arabinofuranosyl moiety 5d coincided with less solubility. In the sulfinosine and sulfonosine series, however, this pattern was reversed as the presence of an arabinofuranosyl moiety 6d, 7d appeared to enhance rather than decrease the solubility. Under the conditions of these studies, antileukemic activity within a given drug series (e.g., sulfinosine) tended to parallel solubility, 6b being a notable exception to this trend.

To find that a majority of the tested compounds exhibited biologically significant anticancer activity was encouraging even though the results presented are of a preliminary nature. Future efforts, involving dosage ranging and scheduling trials, are expected to identify and rank the optimal activities of these sulfur-containing purine nucleosides and to assist in assessing their potential for clinical application.

EXPERIMENTAL

General Procedures.

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (tlc) was performed on Merck precoated silica gel 60 F$_{254}$ plates. Silica gel (E. Merck, 230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in tlc was by uv light, and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30°. Infrared (ir, ν max, in potassium bromide) spectra were recorded with a Perkin-Elmer 1420 spectrophotometer and ultraviolet (uv, λ max, sh = shoulder) spectra were recorded on a Beckman DU-50 spectrophotometer. Proton magnetic resonance (^{1}H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard (key: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The presence of solvent as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy.

9-(2-Deoxy-β-D-erythro-pentofuranosyl)purine-6-sulfenamide (5a).

Sodium hypochlorite (0.77 M, 5.25%, 15 ml, a freshly opened bottle of commercial bleach) was cooled to >0° in an ice bath. Ammonium hydroxide (0.77 M, 40 ml) was similarly cooled in an ice bath and added rapidly to the bleach solution and the flask was immediately stoppered. The mixture was stirred at -5° to 0° for about 15 minutes and then a solution of 9-(2-deoxy-β-D-erythro-pentofuranosyl)purine-6(1H)-thione (4a, 2.68 g, 10 mmoles) [9] in 2 N potassium hydroxide solution (5 ml) was added quickly and rinsed into the chloramine mixture with a small amount of water. The reaction flask was immediately stoppered and stirred for 45 minutes until it has warmed to room temperature. The solvents were evaporated. The residue was dissolved in methanol (50 ml) and adsorbed onto silica gel (5 g). The excess solvent was evaporated and the dry residue was loaded onto a silica gel column (3 x 40 cm) packed in dichloromethane. The column was eluted with a mixture of dichloromethane:methanol (8:2, 7:3, v/v). The homogeneous fractions were pooled, and the solvents evaporated to yield 2.4 g (85%) of 5a as analytically pure amorphous solid, mp 90° dec; ir: ν max 3000-3450 (NH$_2$, OH) cm^{-1}; uv: λ max (pH 1) 300 nm (ϵ 8 000); (pH 7) 288 nm (ϵ 8 200); (pH 11) 288 nm (ϵ 10 300); ^{1}H nmr (DMSO-d$_6$): 2.33 and 2.75

(2 H, 2 m, C$_2$.CH_2), 3.52 (2 H, m, C$_5$.CH_2), 4.09 (1 H, d, C$_4$.H), 4.12 (2 H, s, SNH_2), 4.43 (1 H, m, C$_3$.H), 5.01 (1 H, t, C$_5$.OH), 5.36 (1 H, d, C$_3$.OH), 6.43 (1 H, t, J$_{1',2'}$ 6.6 Hz, C$_1$.H), 8.64 (1 H, s, C$_2$$H$) and 8.75 (1 H, s, C$_8$$H$).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_3$S: C, 42.39; H, 4.62; N, 24.72; S, 11.32. Found: C, 42.12; H, 4.85; N, 24.48; S, 11.51.

(R,S)-9-(2-Deoxy-β-D-erythro-pentofuranosyl)purine-6-sulfinamide (6a).

To an ice-cooled (0°) and stirred solution of 5a (0.37 g, 1.3 mmoles) in ethanol (20 ml) was added during 10 minutes a solution of 3-chloroperoxybenzoic acid [13] (MCPBA, 80-85%, 0.28 g, 1.3 mmoles) in ethanol (10 ml). The reaction mixture was warmed to room temperature during 90 minutes. The product which

crystallized out from the reaction mixture was collected by filtration, washed with cold ethanol (2 x 5 ml) and recrystallized from ethanol to yield 0.18 g (46%) of 6a, mp 120°; ir: ν max 3000-3500 (NH$_2$, OH), 1360, 1060 (S=O) cm^{-1}; uv: λ max (pH 1) 272 nm (ϵ 7 400); (pH 7) 273 nm (ϵ 8 600); (pH 11) 274 nm (ϵ 9 100); ^{1}H nmr (DMSO-d$_6$): 2.40 and 2.81 (2 H, 2 m, C$_2$.CH_2), 3.52 (2 H, m, C$_5$.CH_2), 3.90 (1 H, d, C$_4$.H), 4.41 (1 H, m, C$_3$.H), 5.00 (1 H, t, C$_5$.OH), 5.41 (1 H, d, C$_3$.OH), 6.50 (1 H, t, J$_{1',2'}$ 6.6 Hz, C$_1$.H), 6.68 (2 H, s, SONH_2), 8.94 (1 H, s, C$_2$$H$) and 9.06 (1 H, s, C$_8$$H$).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_4$S: C, 40.13; H, 4.38; N, 23.40; S, 10.71. Found: C, 40.39; H, 4.40; N, 23.32; S, 10.51.

9-(2-Deoxy-β-D-erythro-pentofuranosyl)purine-6-sulfonamide (7a).

To a stirred solution of 5a (1.3 g, 4.6 mmoles) in ethanol (120 ml) was added a solution of MCPBA (3 g, 14 mmoles) in ethanol (50 ml) during 10 minutes at room temperature. After stirring for 1 hour, the reaction mixture was evaporated to dryness. The residue was dissolved in methanol (25 ml) and adsorbed onto silica gel (10 g). The excess solvent was evaporated and the dry residue was loaded onto a flash silica gel column (2.5 x 40 cm) packed in dichloromethane. The column was eluted with dichloromethane:methanol (8:2, 7:3, v/v). The homogeneous fractions were combined, the solvents evaporated and the residue was crystallized from ethanol to yield 0.6 g (41%) of 7a as amorphous solid, mp >90° dec; ir: ν max 2800-3500 (NH$_2$, OH), 1320 (O=S=O), 1140 (S=O) cm^{-1}; uv: λ max (pH 1) 275 nm (ϵ 5 800); (pH 7) 275 nm (ϵ 7 600); (pH 11) 273 nm (ϵ 7 900); ^{1}H nmr (DMSO-d$_6$): 2.41 and 2.80 (2 H, 2 m, C$_2$, CH_2), 3.55 (2 H, m, C$_5$.CH_2), 3.90 (1 H, m, C$_4$.H), 4.46 (1 H, m, C$_3$.H), 4.98 (1 H, t, C$_5$.OH), 5.39 (1 H, d, C$_3$.OH), 6.53 (1 H, t, J$_{1',2'}$ 6.4 Hz, C$_1$.H), 7.85 (2 H, s, SO$_2$NH_2), 9.00 (1 H, s, C$_2$$H$) and 9.08 (1 H, s, C$_8$$H$).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_5$S·½ H$_2$O: C, 37.03; H, 4.32; N, 21.60; S, 9.88. Found: C, 36.77; H, 4.11; N, 22.00; S, 10.24.

2-Amino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine-6-sulfenamide (5b).

In a similar manner as described for 5a, amination of 2-amino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine-6(1H)-thione (4b, 2.83 g, 10 mmoles) [9] with chloramine solution (prepared from 15 ml of 0.77 M commercial sodium hypochlorite and 40 ml of 0.77 M ammonium hydroxide at 0°) gave 2.6 g (86%) of 5b, mp 130° dec; ir: ν max 3000-3500 (NH$_2$, OH) cm^{-1}; uv: λ max (pH 1) 328 nm (ϵ 11 700); (pH 7) 309 nm (ϵ 10 600); (pH 11) 309 nm (ϵ 10 900); ^{1}H nmr (DMSO-d$_6$): 2.22 and 2.61 (2 H, 2 m, C$_2$.CH_2), 3.57 (2 H, m, C$_5$.CH_2), 3.83 (1 H, m, C$_4$.H), 3.90 (2 H, s, SNH_2), 4.36 (1 H, m, C$_3$.H), 5.01 (1 H, t, C$_5$.OH), 5.31 (1 H, d, C$_3$.OH), 6.23 (1 H, t, J$_{1',2'}$ 6.6 Hz, C$_1$.H), 6.50 (2 H, s, NH_2) and 8.16 (1 H, s, C$_8$$H$).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_3$S: C, 40.27; H, 4.70; N, 28.19; S, 10.74. Found: C, 40.10; H, 4.40; N, 27.89; S, 10.53.

(R,S)-2-Amino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine-6-sulfinamide (2'-Deoxysulfinosine, 6b).

To an ice-cooled (0°) and stirred suspension of 5b (0.90 g, 3 mmoles) in ethanol (200 ml) and dichloromethane (50 ml) was added during 15 minutes a solution of MCPBA (0.65 g, 3 mmoles) in ethanol (30 ml). The reaction mixture was warmed to room temperature during 90 minutes and the clear solution was evaporated to dryness. The residue was dissolved in methanol (25 ml) and adsorbed onto silica gel (5 g). The excess solvent was evaporated and the dry residue was loaded onto a silica gel column (2.5 x 15 cm) packed in dichloromethane. The column was

eluted with dichloromethane:methanol (8:2, 7:3, v/v). The appropriate homogeneous fractions were pooled and the solvents evaporated to dryness. The residue was crystallized from ethanol to yield 0.65 g (69%) of **6b**, mp 80° dec; ir: ν max 3000-3600 (NH$_2$, OH), 1050 (S=O) cm^{-1}; uv: λ max (pH 1) 339 nm (ϵ 4 300); (pH 7) 327 nm (ϵ 6 000); (pH 11) 326 nm (ϵ 6 000); ^{1}H nmr (DMSO-d$_6$): 2.28 and 2.64 (2 H, 2 m, C$_2$,CH$_2$), 3.48 (2 H, m, C$_5$,CH$_2$), 3.84 (1 H, m, C$_4$,H), 4.39 (1 H, m, C$_3$,H), 4.99 (1 H, t, C$_5$,OH), 5.37 (1 H, d, C$_3$,OH), 6.27 (1 H, t, J$_{1',2'}$ 6.7 Hz, C$_1$,H), 6.51 (2 H, s, NH$_2$), 6.98 (2 H, s, SONH$_2$) and 8.43 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_4$S: C, 38.21; H, 4.49; N, 26.74; S, 10.20. Found: C, 38.48; H, 4.73; N, 26.75; S, 10.21.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine-6-sulfonamide (7b).

In a similar manner as described for **7a**, oxidation of a solution of **5b** (0.90 g, 3 mmoles) in ethanol (200 ml) with MCPBA (2.6 g, 12 mmoles) and purification of the reaction product on a flash silica gel column (2.5 x 15 cm) using dichloromethane:methanol (85:15, 8:2, v/v) as the eluent gave 0.50 g (50%) of **7b** as amorphous solid, mp >80° dec: ir: ν max 3000-3500 (NH$_2$, OH), 1350 (O=S=O) cm^{-1}; uv: λ max (pH 1) 332 nm (ϵ 4 300); (pH 7) 329 nm (ϵ 5 200); (pH 11) 320 nm (ϵ 6 500); ^{1}H nmr (DMSO-d$_6$): 2.27 and 2.65 (2 H, 2 m, C$_2$,CH$_2$), 3.54 (2 H, m, C$_5$,CH$_2$), 3.84 (1 H, m, C$_4$,H), 4.38 (1 H, m, C$_3$,H), 4.97 (1 H, t, C$_5$,OH), 5.33 (1 H, d, C$_3$,OH), 6.28 (1 H, t, J$_{1',2'}$ 6.7 Hz, C$_1$,H), 6.99 (2 H, s, NH$_2$), 7.52 (2 H, s, SO$_2$NH$_2$) and 8.46 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_5$S·H$_2$O·½ C$_2$H$_5$OH: C, 35.58; H, 5.12; N, 22.64; S, 8.63. Found: C, 35.49; H, 5.33; N, 22.57; S, 8.43.

9-β-D-Arabinofuranosylpurine-6-sulfenamide (5c).

Commercial 0.77 *M* sodium hypochlorite solution (5.25%, 45 ml) was cooled to 0° in an ice bath and added with stirring to a similarly cooled 0.77 *M* ammonium hydroxide solution (120 ml). After stirring for 15 minutes, the resulting chloramine solution was mixed with a solution of 9-β-D-arabinofuranosylpurine-6(1*H*)-thione (**4c**, 8.52 g, 30 mmoles) [14] in 2 *N* potassium hydroxide solution (15 ml) at 0°. The reaction mixture was allowed to warm to room temperature during 45 minutes. After 1 hour the product that crystallized out from the reaction mixture was collected by filtration, washed with cold ethanol (2 x 10 ml), air-dried and recrystallized from ethanol to yield 5.0 g (56%) of **5c**, mp 176-178° dec; ir: ν max 3000-3500 (NH$_2$, OH) cm^{-1}; uv: λ max (pH 1) 295 nm (ϵ 6 000); (pH 7 and 11) 285 nm (ϵ 5 600); ^{1}H nmr (DMSO-d$_6$): 3.71 (2 H, m, C$_5$,CH$_2$), 3.81 (1 H, m, C$_4$,H), 4.10 (1 H, m, C$_3$,H), 4.15 (2 H, s, SNH$_2$), 4.19 (1 H, m, C$_2$,H), 5.10 (1 H, t, C$_5$,OH), 5.52 and 5.67 (2 H, 2 m, C$_2$,$_3$,OH), 6.37 (1 H, d, J$_{1',2'}$ 5.2 Hz, C$_1$,H), 8.50 (1 H, s, C$_2$H) and 8.71 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_4$S: C, 40.13; H, 4.38; N, 23.40; S, 10.71. Found: C, 39.94; H, 4.38; N, 23.12; S, 11.00.

(R,S)-9-β-D-Arabinofuranosylpurine-6-sulfinamide (6c).

To an ice-cooled and stirred solution of **5c** (1.5 g, 5 mmoles) in ethanol:water (525 ml, 20:1, v/v) was added during 20 minutes a solution of MCPBA (1.1 g, 5 mmoles) in ethanol (50 ml). After 4 hours, the separated crystals were collected by filtration and dried to yield 0.50 g of **6c**. The filtrate was evaporated to dryness and the residue was purified on a silica gel column as described for **6b**. Recrystallization of the combined solids from aqueous

ethanol gave 0.75 g (46%) of **6c**, mp >120°; ir: ν max 3000-3600 (NH$_2$, OH), 1330, 1060 (S=O) cm^{-1}; uv: λ max (pH 1) 272 nm (ϵ 3 000); (pH 7) 275 nm (ϵ 7 100); (pH 11) 272 nm (ϵ 1 700); ^{1}H nmr (DMSO-d$_6$): 3.70 (2 H, m, C$_5$,CH$_2$), 3.78 (1 H, m, C$_4$,H), 4.19 (1 H, m, C$_3$,H), 4.26 (1 H, m, C$_2$,H), 5.17 (1 H, t, C$_5$,OH), 5.63 and 5.70 (2 H, 2 m, C$_2$,$_3$,OH), 6.46 (1 H, d, J$_{1',2'}$ 5.1 Hz, C$_1$,H), 6.71 (2 H, s, SONH$_2$), 8.83 (1 H, s, C$_2$H) and 9.06 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_5$S·⅓ H$_2$O: C, 37.38; H, 4.24; N, 21.80; S, 9.97. Found: C, 37.03; H, 4.19; N, 21.42; S, 10.35.

9-β-D-Arabinofuranosylpurine-6-sulfonamide (7c).

To a solution of **5c** (3.6 g, 12 mmoles) in ethanol (1200 ml) and water (80 ml) at room temperature was added MCPBA (10.3 g, 48 mmoles) with stirring. The reaction mixture was left at room temperature for 15 hours. The precipitated product was collected by filtration, washed with ethanol (3 x 25 ml) and air-dried. The combined filtrate and washings were concentrated to about 25 ml and chilled overnight. The solid that deposited was collected and combined with the above precipitated product. Crystallization from aqueous ethanol gave 3.3 g (81%) of **7c**, mp 160° dec; ir: ν max 3000-3600 (NH$_2$, OH), 1340 (O=S=O), 1050 (S=O) cm^{-1}; uv: λ max (pH 1) 275 nm (ϵ 5 600); (pH 7) 276 nm (ϵ 6 500); (pH 11) 274 nm (ϵ 6 900); ^{1}H nmr (DMSO-d$_6$): 3.71 (2 H, m, C$_5$,CH$_2$), 3.80 (1 H, m, C$_4$,H), 4.20 (1 H, m, C$_3$,H), 4.25 (1 H, m, C$_2$,H), 5.18 (1 H, t, C$_5$,OH), 5.62 and 5.71 (2 H, 2 m, C$_2$,$_3$,OH), 6.70 (1 H, d, J$_{1',2'}$ 5.3 Hz, C$_1$,H), 7.85 (2 H, s, SO$_2$NH$_2$), 8.88 (1 H, s, C$_2$H) and 9.08 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_6$S·½ H$_2$O: C, 35.29; H, 4.12; N, 20.59; S, 9.41. Found: C, 35.63; H, 4.07; N, 20.27; S, 9.07.

2-Amino-9-β-D-arabinofuranosylpurine-6-sulfenamide (5d).

In a similar manner as described for **5a**, amination of 2-amino-9-β-D-arabinofuranosylpurine-6(1*H*)-thione (**4d**, 1.5 g. 5 mmoles) [9] with chloramine solution (preparated from 7.5 ml of 0.77 *M* commercial sodium hypochlorite and 20 ml of 0.77 *M* ammonium hydroxide at 0°) gave 0.85 g (54%, crystallized from a mixture of dichloromethane/methanol) of **5d**, mp 190-192°; ir: ν max 3200-3400 (NH$_2$, OH) cm^{-1}; uv: λ max (pH 1) 328 nm (ϵ 19 400), 254 (10 600), 227 (26 400); (pH 7) 308 nm (ϵ 13 200), 243 (13 700), 222 (22 200); (pH 11) 308 nm (ϵ 13 200), 243 (13 500), 221 (22 200); ^{1}H nmr (DMSO-d$_6$): 3.64 (2 H, m, C$_5$,CH$_2$), 3.76 (1 H, m, C$_4$,H), 4.09 (2 H, s, SNH$_2$), 4.10 (2 H, m, C$_2$,$_3$,H), 5.10 (1 H, t, C$_5$,OH), 5.55 and 5.67 (2 H, 2 m, C$_2$,$_3$,OH), 6.13 (1 H, d, J$_{1',2'}$ 4.0 Hz, C$_1$,H), 6.50 (2 H, s, NH$_2$) and 7.99 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_4$S: C, 38.21; H, 4.49; N, 26.74; S, 10.20. Found: C, 38.40; H, 4.47; N, 26.53; S, 10.29.

(R,S)-2-Amino-9-β-D-arabinofuranosylpurine-6-sulfinamide (6d).

A solution of **5d** (1.5 g, 4.7 mmoles) in ethanol (350 ml) and water (50 ml) was cooled to 0°. To this cold solution was added MCPBA (1.01 g, 4.7 mmoles) in ethanol (50 ml) during 1.5 hours. After the addition, the reaction mixture was stirring at 0° for 1.5 hours. The solvent was evaporated and the residue was dissolved in methanol (50 ml). Silica gel (10 g) was added and evaporated to dryness. The dried silica gel was placed on top of a flash silica gel column (2.5 x 25 cm) and eluted with ethyl acetate → methanol gradient. The pure compound crystallized out after concentration of the homogeneous fractions. The product was collected by filtration and recrystallized from aqueous ethanol to give 0.95 g

(60%) of **6d**, mp >200° dec; ir: ν max 3100-3600 (NH$_2$, OH), 1120 (S = O) cm^{-1}; uv: λ max (pH 1) 330 nm (ϵ 5 100), 249 (7 600), 220 (17 900); (pH 7) 323 nm (ϵ 8 000), 248 (sh) (6 100), 225 (24 100); (pH 11) 322 nm (ϵ 6 600), 244 (sh) (6 600), 224 (21 000); ^{1}H nmr (DMSO-d$_6$): 3.65 (2 H, m, C$_5$,CH$_2$), 3.77 (1 H, m, C$_4$,H), 4.11 (2 H, m, C$_{2',3'}$H), 5.11 (1 H, t, C$_5$,OH), 5.57 and 5.70 (2 H, 2 m, C$_{2',3'}$OH), 6.17 (1 H, d, J$_{1',2'}$ 4.1 Hz, C$_1$,H), 6.50 (2 H, s, NH$_2$), 6.97 (2 H, s, SONH$_2$) and 8.25 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_5$S: C, 36.36; H, 4.27; N, 25.44; S, 9.71. Found: C, 36.65; H, 4.09; N, 25.19; S, 9.56.

2-Amino-9-β-D-arabinofuranosylpurine-6-sulfonamide (7d).

In a similar manner as described for **7a**, oxidation of a solution of **5d** (0.46 g, 1.46 mmoles) in ethanol (250 ml) and water (50 ml) with a solution of MCPBA (1.25 g, 5.84 mmoles) in ethanol (50 ml) for 6 hours, and purification of the reaction product on a flash silica gel column (2.5 x 40 cm) using ethyl acetate → methanol gradient gave 0.30 g (59%) of **7d**, mp >193° dec; ir: ν max 3100-3600 (NH$_2$, OH), 1340 (O=S=O), 1170 (S=O) cm^{-1}; uv: λ max (pH 1) 332 nm (ϵ 4 200), 222 (16 900); (pH 7) 326 nm (ϵ 4 900), 225 (17 300); (pH 11) 320 nm (ϵ 5 600), 223 (17 200); ^{1}H nmr (DMSO-d$_6$): 3.65 (2 H, m, C$_5$,CH$_2$), 3.72 (1 H, m, C$_{2',3'}$H), 5.10 (1 H, t, C$_5$,OH), 5.55 and 5.70 (2 H, 2 m, C$_{2',3'}$OH), 6.18 (1 H, d, J$_{1',2'}$ 4.3 Hz, C$_1$,H), 6.95 (2 H, s, NH$_2$), 7.48 (2 H, br s, SO$_2$NH$_2$) and 8.27 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_6$S·½ C$_2$H$_5$OH: C, 36.92; H, 4.65; N, 21.52; S, 8.20. Found: C, 37.04; H, 4.32; N, 21.50; S, 8.41.

2-Amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfenamide (9).

In a similar manner as described for **5a**, amination of 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6(1H)-thione (**8**, 2.83 g, 10 mmoles) [15] with chloramine solution (prepared from 15 ml of 0.77 *M* commercial sodium hydrochlorite and 40 ml of 0.77 *M* ammonium hydroxide at 0°) for 1 hour, deposited the target compound from the reaction mixture. The solid product was collected by filtration, washed with cold water (2 x 5 ml) followed by ethanol (10 ml) and crystallized from aqueous ethanol to yield 2.5 g (84%) of **9**, mp 163° dec; ir: ν max 3200-3500 (NH$_2$, OH) cm^{-1}; uv: λ max (pH 1) 328 nm (ϵ 9 700); (pH 7) 308 nm (ϵ 11 900); (pH 11) 308 nm (ϵ 12 400); ^{1}H nmr (DMSO-d$_6$): 2.26 and 2.70 (2 H, 2 m, C$_2$,CH$_2$), 3.43 (2 H, m, C$_5$,CH$_2$), 3.98 (2 H, s, SNH$_2$), 4.10 (1 H, m, C$_4$,H), 4.30 (1 H, m, C$_3$,H), 4.88 (1 H, t, C$_5$,OH), 5.54 (1 H, d, C$_3$,OH), 6.21 (1 H, dd, J$_{1',2'}$ 5.1 Hz, C$_1$,H), 6.49 (2 H, s, NH$_2$) and 8.19 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_3$S: C, 40.27; H, 4.70; N, 28.19; S, 10.74. Found: C, 39.98; H, 4.70; N, 28.01; S, 10.79.

(R,S)-2-Amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfinamide (10).

In a similar manner as described for **6a**, oxidation of a solution of **9** (0.75 g, 2.5 mmoles) in ethanol (150 ml) with a solution of MCPBA (0.53 g, 2.5 mmoles) in ethanol (50 ml) at 0°, and further stirring at room temperature for 15 hours, precipitated the S-diastereomer of the target compound. The precipitate was collected by filtration and crystallized from aqueous ethanol to yield 0.24 g (31%) of the S-diastereomer of **10**, mp 178° dec.

The above filtrate was concentrated to ~10 ml and allowed to stand in the refrigerator for 15 hours. The solid that deposited was collected by filtration, washed with cold ethanol (2 x 5 ml) and crystallized from aqueous ethanol to yield 0.30 g (38%) of a mixture of R and S-diastereomers of **10**, mp >120° dec; ir: ν max 3100-3500 (NH$_2$, OH), 1300, 1040 (S=O) cm^{-1}; uv: λ max (pH 1) 329 nm (ϵ 3 800); (pH 7) 323 nm (ϵ 5 800); (pH 11) 323 nm (ϵ 3 700); ^{1}H nmr (DMSO-d$_6$): 2.31 and 2.69 (2 H, 2 m, C$_2$,CH$_2$), 3.43 (2 H, m, C$_5$,CH$_2$), 4.13 (1 H, m, C$_4$,H), 4.32 (1 H, m, C$_3$,H), 4.89 (1 H, t, C$_5$,OH), 5.49 (1 H, d, C$_3$,OH), 6.27 (1 H, dd, J$_{1',2'}$ 5.5 Hz, C$_1$,H), 6.50 (2 H, s, NH$_2$), 6.94 (2 H, s, SONH$_2$) and 8.43 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_4$S: C, 38.21; H, 4.49; N, 26.74; S, 10.20. Found: C, 38.34; H, 4.59; N, 26.47; S, 10.17.

2-Amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-sulfonamide (11).

To a stirred solution of **9** (0.75 g, 2.5 mmoles) in ethanol (150 ml) at room temperature was added MCPBA (2.15 g, 10 mmoles) and the mixture was stirred for 3 hours. Silica gel (5 g) was added to the clear reaction mixture and the excess solvent was evaporated to dryness. The dry residue was loaded onto a silica gel column (1.5 x 20 cm) packed in dichloromethane. The column was eluted with dichloromethane:methanol (85:15, 8:2, v/v). The appropriate homogeneous fractions were pooled and the solvent evaporated to dryness. The pure residue was crystallized from ethanol to yield 0.30 g (36%) of **11**, mp >100° (dec); ir: ν max 3000-3600 (NH$_2$, OH), 1340, 1160 (O=S=O) cm^{-1}; uv: λ max (pH 1) 333 nm (ϵ 5 800); (pH 7) 327 nm (ϵ 9 800); (pH 11) 319 nm (ϵ 10 500); ^{1}H nmr (DMSO-d$_6$): 2.31 and 2.70 (2 H, 2 m, C$_2$,CH$_2$), 3.44 (2 H, m, C$_5$,CH$_2$), 4.15 (1 H, m, C$_4$,H), 4.32 (1 H, m, C$_3$,H), 4.89 (1 H, t, C$_5$,OH), 5.49 (1 H, d, C$_3$,OH), 6.27 (1 H, dd, J$_{1',2'}$ 5.4 Hz, C$_1$,H), 6.96 (2 H, s, NH$_2$), 7.51 (2 H, s, SO$_2$NH$_2$) and 8.46 (1 H, s, C$_8$H).

Anal. Calcd. for C$_{10}$H$_{14}$N$_6$O$_5$S: C, 36.36; H, 4.27; N, 25.45; S, 9.71. Found: C, 36.11; H, 4.25; N, 25.31; S, 10.08.

X-Ray Structure Determination of (S)-10.

Crystals of (S)-**10** were obtained by recrystallization from an aqueous ethanol solution. The specimen was an ill-formed triangular prism, 0.28 mm wide, 0.36 mm high and 0.115 mm thick. The compound crystallizes in the monoclinic space group P2$_1$ with two molecules per unit cell. The cell dimensions are $a = 6.4400(9)$, $b = 15.061(3)$, $c = 7.0861(14)$ Å, $\beta = 110.53(2)°$ and $V = 643.2(2)°$ resulting in a density D$_x$ of 1.622 g·cm^{-3}. An Enraf-Nonius CAD4 automated diffractometer equipped with a graphite monochromator and CuKα radiation (1.54178 Å) was used for all measurements. Data were collected by ω-2Θ scans over a scan range of 1.10 + 0.15 tanΘ in degrees theta to a 2Θ maximum of 152° resulting in 2900 reflections. The data were corrected for Lorentz and polarization effects, decay (correction range: 1.000-1.035) and absorption [μ(CuKα) = 24.69 cm^{-1}; correction range: 0.416-0.770] using the SDP-Plus program package [20]. Equivalent data were merged to give 2626 unique reflections (R$_{int}$ = 0.018). The positional coordinates of all non-hydrogen atoms were determined with the program SHELXS86 [21]. All hydrogen atoms were located in a difference map as peaks of 0.36-0.86 e/Å^3 (R = 0.046). All positional and thermal (non-hydrogen atoms: anisotropic; hydrogens: isotropic) parameters were refined with the program SHELX76 [22]. Refinement was terminated with a maximum Δ/σ of 0.007; the final R = 0.0311, wR = 0.0456 and S = 1.1719 for 2582 observed reflections (F ≥ 4σ_F) and 246 variables. Reflections were weighted by the expression w^{-1} = σ_F^2 + 0.0004F$_2$. An extinction parameter refined to a value of 2.1(4) x 10^{-6}. The extrema in the final difference map were 0.58 and -0.49 e/Å^3. Scattering factors and anomalous-dispersion corrections for non-hydrogen atoms were taken from International Tables for X-ray Crystallography

[23]; for hydrogen atoms, scattering factors were taken from Stewart, Davidson and Simpson [24]. Figures were drawn with ORTEPII [25].

Antiviral Evaluation.

The nucleosides were evaluated for antiviral activity in 96-well microplates by cytopathic effect (CPE) inhibition assays using stationary monolayers of cells, and viruses as described previously [26]. When antiviral activity was present, followup studies were conducted to confirm to initial results and to establish the potency of each compound. Virus ratings were calculated according to the method of Sidwell [27]. Inhibitory concentrations of compounds causing 50% inhibition of CPE (ED$_{50}$) were determined by visual score. The effects of inhibitors against Friend leukemia virus *in vivo* were determined using a mouse splenomegaly model [19].

Assessments of Therapeutic Efficacy *In Vivo*.

In Vivo assessments of antileukemic activity and host toxicity were performed in BDF$_1$ mice as described previously [28]. Female mice ($\sim$ 18 g) purchased from the Charles River Co. were inoculated ip on day O with 1 x 10^6 cells of murine leukemia L1210 and treated once by ip bolus injection 24 hours later. Drugs were solubilized in water immediately before use and delivered in uniform volumes of 0.01 ml/g mouse weight. This scheme allowed the delivery of all drugs at 10 times (in mg/kg) their solubility in mg/ml. Control mice were given equal volumes of a 0.09% solution of sodium chloride.

The end points by which responses to treatment were gauged were the incidence of drug or leukemia related deaths and the postinoculation life span of mice that died. Temporal patterns of death and observations at necropsy examination were the major criteria for assigning deaths to leukemia or drug toxicity. Inoculum response data that defined the relationship between life span and inoculum size were used to estimate the body burdens of leukemia cells that survived treatement and, accordingly, the percentage of such cells that were killed.

Supplementary Material Available.

Tables of anisotropic thermal parameters for non-hydrogen atoms; bond lengths (Å) and bond angles (°) involving hydrogen atoms; torsion angles (°); and least-squares planes in (S)-10 are available on request from the authors.

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