Sulfinosine Congeners: Synthesis and Antitumor Activity in Mice of Certain N9-Alkylpurines and Purine Ribonucleosides

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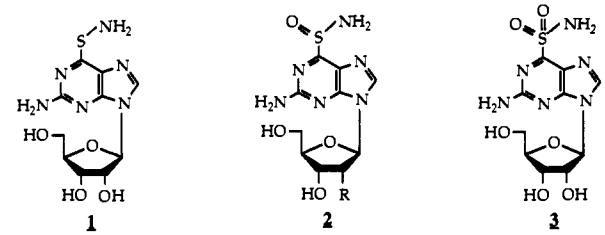
A number of N9-alkyl-substituted purines and purine ribonucleosides have been synthesized as congeners of sulfinosine and evaluated for their antileukemic activity in mice. NaH-mediated alkylation of 6-chloropurine (**4**) and 2-amino-6-chloropurine (**5**) with certain alkyl bromides gave N7- and N9-alkylated derivatives (**7a–d** and **6a–d**), the N9-isomer being the major product. Treatment of **6a–d** and **7a–d** with thiourea furnished the corresponding 6-thio derivatives (**9a–d** and **8a–d**). Amination of **9a–e** with aqueous chloramine solution afforded the corresponding purine-6-sulfenamides (**10a–e**), which on controlled oxidation with 3-chloroperoxybenzoic acid (MCPBA) gave the respective (*R,S*)-9-alkylpurine-6-sulfinamides (**11a–e**). A similar oxidation of 2-amino-6-(methyl/benzylthio)-9-β-D-ribofuranosylpurine (**12a** and **12b**) and 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(methylthio)purine (**12c**) with MCPBA gave the corresponding sulfoxides (**13a–c**), which on further oxidation furnished the respective sulfones (**14a–c**). Of the 20 compounds evaluated, six exhibited biologically significant anti-L1210 activity in $BD2F_1$ mice and reduced body burdens of viable L1210 cells more than 90–97% by single treatment. Although compounds **9b** and **9c** at 44 mg and 40 mg/kg per day × 1 showed a T/C of 147 and 149, respectively, this group of compounds was found to be less effective than some of the sulfur-containing drugs that we previously described (e.g. sulfenosine and sulfinosine).

Introduction

6-Mercaptopurine (6MP) is one of the oldest anticancer agents currently in clinical use. Introduced more than 35 years ago,[1] 6MP and its 2-amino derivative, 6-thioguanine (6TG) were initially shown to be efficacious in the treatment of acute leukemia in children and adults.[2,3] Today, these thiopurine bases remain valuable agents for the induction and maintenance of remissions in patients with acute myelocytic (AML) and acute lymphocytic leukemia (ALL).

Despite their proven clinical importance, 6MP and 6TG have certain therapeutic disadvantages[4,7] which have continued to stimulate the search for purine derivatives with enhanced therapeutic efficacy. In this regard, we recently demonstrated that the introduction of a sulfenamido, sulfinamido, or sulfonamido group at the 6-position of certain purine nucleosides resulted in highly water-soluble compounds with significant antitumor activity.[8–12] Administered qd ($BD2F_1$ mice inoculated ip, once daily) on day 1, 2-amino-9-β-D-ribofuranosylpurine-6-sulfenamide (sulfenosine, **1**) at 22 mg/kg exhibited a T/C of 170, whereas a diastereomeric mixture (*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.[8] The 2′-deoxy derivative of sulfinosine (**2b**)[10] at 173 mg/kg showed a T/C of 154, whereas sulfonosine (2-amino-9-β-D-ribofuranosylpurine-6-sulfonamide, **3**)[8,11] produced a T/C of 128 at 62 mg/kg. When given bid on days 1–7 at a dose of 62 mg/kg, sulfinosine exhibited a T/C of 361 with two long-term survivors.[12] A single treatment of **1**, **2a**, or **2b** reduced body burdens of viable L1210 leukemia cells by >99.8%.[8,10] Sulfinosine was particularly active against cells (L1210/6TGR) unresponsive to the treatment with 6-thioguanosine (6-TGR) and, in addition, did not readily generate resistant cell populations as did 6-TGR.[12] Structural alterations in the carbohydrate moiety of this series of ribonucleosides produced compounds with different solubilities and antitumor activities in mice.[8,10]



Further, a number of 6-(alkylthio)purines[13–15] and 9-alkyl-2-aminopurine-6-thiols[15–18] have been found to be active against adenocarcinoma 755 and L1210 leukemia.[17] It has also been reported earlier[19] that 6-(methylthio)-purine and 6-(benzylthio)purine possess therapeutic indexes significantly greater than that of 6MP against adenocarcinoma 755 and sarcoma 180. The effectiveness of these purine bases against certain tumor cell lines suggested that some of these alkylpurinesulfinamides and nucleoside sulfoxides 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 become resistant to 6MP or 6TG. We now report the synthesis of certain N9-alkyl-substituted purinesulfinamides and purine nucleoside sulfoxides/sulfones and their preliminary antitumor effects in mice.

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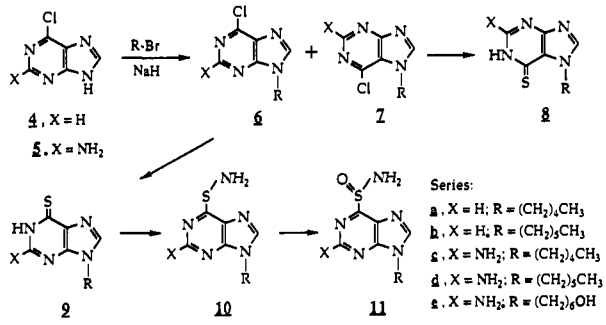
Scheme 1



Chemistry

The synthesis of N9-alkyl-substituted purinesulfinamides have been carried out by the sodium salt alkylation procedure[20] and is outlined in Scheme 1. Treatment of the sodium salt of 6-chloropurine (**4**) and 2-amino-6-chloropurine (**5**), generated *in situ* by the treatment with NaH in anhydrous CH_3CN, with 1-bromopentane or 1-bromohexane at ambient temperature gave a mixture of N9-pentyl/hexyl derivatives **6a–d** and N7-pentyl/hexyl derivatives **7a–d**, respectively. The major isolated products in these reactions were the N9-alkylated derivatives. The N7-pentyl/hexyl derivatives **7a–d** were obtained as minor products (10–18%). Minor modifications in temperature and reaction time essentially gave similar isomeric mixtures. However, the alkylation of the sodium salt of **5** with 6-bromo-1-hexanol under similar conditions gave mainly 2-amino-6-chloro-9-(6-hydroxyhexyl)purine (**6e**, 41% yield), and the formation of the N7-alkylated product was not observed. The 6-mercapto derivatives **8a–d** and **9a–e** were obtained by the direct thiation of **7a–d** and **6a–e** with thiourea in refluxing EtOH. Amination of **9a–e** with an aqueous chloramine solution (prepared from a mixture of commercial sodium hypochlorite and NH_4OH solution at 0 °C) at ambient temperature and purification of the reaction products by silica gel column chromatography gave good yields (57–91%) of N9-alkylpurine-6-sulfenamides **10a–e**. Subsequent oxidation of **10a–e** with 1 molar equiv of 3-chloroperoxybenzoic acid (MCPBA) in EtOH at 0 °C gave the corresponding (*R,S*)-N9-alkylpurine-6-sulfinamides **11a–e**. Since a diastereomeric mixture of sulfinosine (**2a**) is more effective (T/C of 167) against L1210 leukemia in mice than either *R* or *S* stereoisomer alone (T/C of 156 and 125, respectively),[8] no attempt was made to separate the stereoisomers of **11a–e**. The mixture as such was used for biological evaluation. The structures of these sulfinamides were confirmed by spectral (^1H NMR and UV) and by elemental analysis.

Selective oxidation of an ethanolic solution of 2-amino-6-(methylthio)-9-β-D-ribofuranosylpurine[14] (**12a**) with 1.16 molar equiv of MCPBA afforded the corresponding 6-methyl sulfoxide (**13a**), which on further oxidation with MCPBA gave the fully oxidized product 2-amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl methyl sulfone (**14a**, Scheme 2). In a similar manner, controlled oxidation of 2-amino-6-(benzylthio)-9-β-D-ribofuranosylpurine[14] (**12b**) with MCPBA gave the 6-benzyl sulfoxide (**13b**) in a 81% yield. Further oxidation of **13b** with excess of MCPBA furnished 2-amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl benzyl sulfone (**14b**).

Sodium hydride mediated glycosylation[21] of 2-amino-6-(methylthio)purine[22] with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose[23] in CH_3CN readily gave 2-amino-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-(methylthio)purine, which on ammonolysis furnished 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(methylthio)purine (**12c**). Controlled oxidation of **12c** with 1.16 molar equiv of MCPBA gave the corresponding 6-methyl sulfoxide (**13c**), which on further oxidation with excess of MCPBA, and purification of the reaction product by silica gel column chromatography, gave the desired fully oxidized product 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-yl methyl sulfone (**14c**) in a 61% yield.

Scheme 2

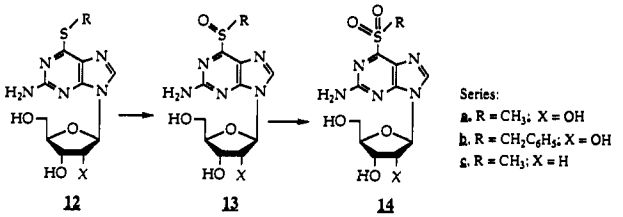


Table 1. Responses of L1210 Inoculated Mice to a Single Treatment with Certain Sulfur-Containing Purine Derivatives

compd	dosage,[a] mg/kg	postinoculation lifespan,[b] (% T/C)	% viable L1210 cells killed by single treatment[c]
9a	41[d]	141	91
9b	44	147	87
9c	40	149	92
9d	110[d]	118	72
10b	410	116	75
10c	47[d]	118	70
10d	105	119	87
11a	480[d]	134	90
11b	800 tox		
11c	106	117	72
11d	460[d]	121	93
11e	39	139	96
12a	37[d]	98	0
12c	800 tox		
13a	480	114	71
13b	37 (480)	137	97
13c	800 tox		
14a	104	96	0
14b	104	115	76
14c	800 tox		
1	22	170	99.8
2	173	167	99.8

[a] All solutions were delivered ip (0.01 mL/g mouse wt). Control mice were injected with a 0.9% solution of NaCl. The dosages presented in milligrams per kilogram are 10 times the maximum solubility in mg/mL. Compounds that were lethally toxic at their maximum soluble dosage (indicated by numbers in parenthesis) were studied at lower dosages. [b] Treatment responses (six mice/treatment group) presented as % T/C were calculated according to equation: mean life span of treated mice/mean life span of control mice by 100. The data presented were derived from four different studies in which the mean life span of 10 control mice/study ranged from 6.50 ± 0.55 to 6.80 ± 0.63 days. A T/C ≥ 125 is considered biologically significant. [c] Estimations of residual leukemic cell populations and, hence, percentage cell kill were made using inoculum-response data indicating the relationship between inoculum size and resultant postinoculation life span. [d] Indicates solubility in Me_2SO; compounds not so indicated were soluble in water.

Antitumor Evaluation

Twenty compounds synthesized during this study were evaluated for antileukemic activity in $BD2F_1$ mice inoculated with 1×10^6 L1210 cells in parallel with sulfenosine (**1**) and sulfinosine (**2a**). As indicated by the data presented in Table 1, the solubilities and anticancer properties of these compounds varied considerably. Solubilities in water ranged from a nadir of 3.7 mg/mL for compound **13b** to

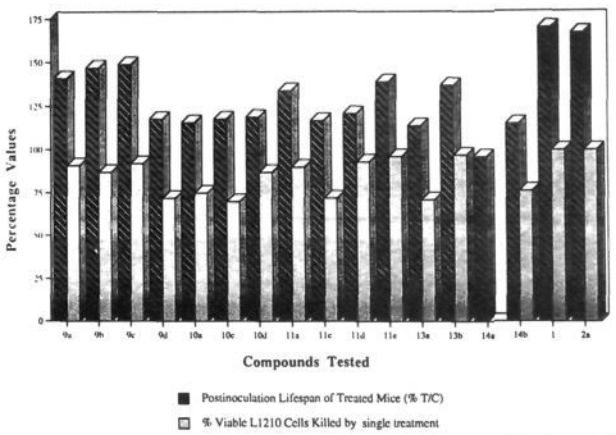


Figure 1. Responses of $BD2F_1$ mice inoculated with 1×10^6 leukemia cells to a single treatment with certain sulfinosine congeners.

a high of 80 mg/mL for compounds **11b**, **12c**, **13c**, and **14c**. Six compounds (**9a**, **9d**, **10c**, **11a**, **11d**, and **12a**) which were not soluble in water were dissolved in Me_2SO. Administered qd (once daily) on day 1 at dosages determined by solubility, 6 of the 20 compounds exhibited biologically significant anti-L1210 activity, i.e., they produced a T/C ≥ 125. However, these compounds are less potent than either sulfenosine or sulfinosine. Eight less active compounds (**9d**, **10b**, **10c**, **10d**, **11c**, **11d**, **13a**, and **14b**) reduced body burdens of viable L1210 cells by 70–93%, and compounds **12a** and **14a** totally lacked cytotoxic activity (Figure 1). Compounds **11b**, **12c**, **13c**, and **14c** were very toxic and were not retested in these studies.

Under the conditions of these studies, variations in solubility and antileukemic activity did not define any discernible structure dependence; thus, structural modification in the aglycon (e.g. alkyl sulfone) and carbohydrate moieties (replacement with alkyl groups) of the test compounds did not produce uniform changes in biologic characterization. However, it is obvious that several of the tested compounds exhibited biologically significant anticancer activity and that a single treatment with some of the compounds reduced body burdens of viable L1210 cells by more than 90% (e.g. **9a**, **9c**, **11e**, and **13b**). But, as a group, the compounds in this series were less effective than some of the sulfur-containing drugs that we previously described.[8,12]

Experimental Section

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% H_2SO_4 in MeOH spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30 °C. Infrared (IR in KBr) spectra were recorded with a Perkin-Elmer 1420 spectrophotometer, and ultraviolet (UV, sh = shoulder) spectra were recorded on a Beckman DU-50 spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were recorded at 300 MHz with IBM NR/300 spectrometer. The chemical shift values are expressed as 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 ^1H NMR spectroscopy.

6-Chloro-9-pentylpurine (6a). A mixture of 6-chloropurine (**4**, 1.54 g, 10 mmol) and NaH (60% in oil, 0.264 g, 11 mmol) in anhydrous CH_3CN was stirred at ambient temperature for 30 min under nitrogen atmosphere. 1-Bromopentane (1.51 g, 10 mmol) was added portionwise, and the reaction mixture was stirred at ambient temperature for 20 h. The reaction mixture was evaporated to dryness, H_2O (100 mL) was added to the residue, and the aqueous phase was extracted with EtOAc (300 mL). The organic phase was washed with cold water, dried (Na_2SO_4), and evaporated to dryness to give a syrup. The syrup was applied to the top of a flash silica gel column (3 × 30 cm) and the column was eluted with CH_2Cl_2–CH_3OH (97:3, v/v). The homogeneous fractions having higher R_f were pooled, the solvents were evaporated, and the residue was crystallized from CH_2Cl_2 to yield 1.1 g (49%) of **6a**: mp 60 °C; UV λ_{max} nm (ε × 10^{-3}) (pH 1) 264 (11.5); (pH 7) 265 (11.7); (pH 11) 265 (11.8); ^1H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.19 (m, 4 H, 2 CH_2), 1.84 (m, 2 H, CH_2), 4.28 (t, 2 H, NCH_2), 8.72 (s, 1 H, C_2H), 8.76 (s, 1 H, C_8H). Anal. ($C_{10}H_{13}ClN_4$) C, H, N, Cl.

6-Chloro-7-pentylpurine (7a) was isolated from the subsequent fractions having lower R_f. The residue after crystallization from CH_2Cl_2 gave 0.4 g (18%): mp 65 °C dec; UV λ_{max} nm (ε × 10^{-3}) (pH 1) 266 (8.0); (pH 7); 270 (9.3); (pH 11); 270 (8.8); ^1H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.22 (m, 4 H, $2CH_2$), 1.82 (t, 2 H, CH_2), 4.44 (t, 2 H, NCH_2), 8.77 (s, 1 H, C_2H), 8.83 (s, 1 H, C_8H). Anal. ($C_{10}H_{13}ClN_4$) C, H, N, Cl.

6-Chloro-9-hexylpurine (6b). This compound was obtained (46%) from **4** (3.08 g, 20 mmol) and 1-bromohexane (3.32 g, 20.15 mmol) by the procedure as described for **6a**. Compound **6b** was crystallized from CH_2Cl_2: mp 55 °C; UV λ_{max} nm (ε × 10^{-3}) (pH 1) 265 (9.5); (pH 7) 265 (10.6); (pH 11) 265 (7.7); ^1H NMR (Me_2SO-d_6) δ 0.81 (t, 3 H, CH_3), 1.24 (s, 6 H, $3CH_2$), 1.84 (t, 2 H, CH_2), 4.28 (t, 2 H, NCH_2), 8.73 (s, 1 H, C_2H), 8.77 (s, 1 H, C_8H). Anal. ($C_{11}H_{15}ClN_4$) C, H, N, Cl.

Evaporation of fractions having lower R_f gave **6-chloro-7-hexylpurine (7b)**: 0.6 g (13%, crystallized from Et_2O); mp 60 °C; UV λ_{max} nm (ε × 10^{-3}) (pH 1) 266 (5.5); (pH 7) 269 (6.4); (pH 11) 269 (6.4); ^1H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.27 (s, 6 H, $3CH_2$), 1.82 (t, 2 H, CH_2), 4.45 (t, 2 H, NCH_2), 8.79 (s, 1 H, C_2H), 8.83 (s, 1 H, C_8H). Anal. ($C_{11}H_{15}ClN_4$) C, H, N, Cl.

2-Amino-6-chloro-9-pentylpurine (6c). A mixture of 2-amino-6-chloropurine (**5**, 1.69 g, 10 mmol) and NaH (60% in oil, 0.44 g, 11 mmol) in anhydrous CH_3CN (100 mL) was stirred at ambient temperature for 30 min, and then 1-bromopentane (1.51 g, 10 mmol) was added portionwise over a period of 10 min. The reaction mixture was stirred at room temperature for 20 h and evaporated to dryness. Water (100 mL) was added to the residue and extracted with EtOAc (300 mL). The organic phase was washed with cold H_2O (2 × 50 mL), dried (Na_2SO_4), and evaporated to give a thick syrup. After purification of the syrup on a flash silica gel column (3 × 30 cm) using CH_2Cl_2–CH_3OH (97:3, v/v) as the eluent and crystallization of the homogeneous product from a mixture of CH_2Cl_2–Et_2O gave 1.1 g (46%) of **6c**: mp 145–146 °C; λ_{max} nm (ε × 10^{-3}) (pH 1) 316 (7.6); (pH 7) 306 (8.2); (pH 11) 306 (7.5); ^1H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.17 (m, 4 H, $2CH_2$), 1.71 (m, 2 H, CH_2), 4.02 (t, 2 H, NCH_2), 6.90 (s, 2 H, NH_2), 8.14 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}ClN_5$) C, H, N, Cl.

2-Amino-6-chloro-7-pentylpurine (7c) was obtained from the subsequent homogeneous fractions having lower R_f. Crystallization of the residue from CH_2Cl_2–Et_2O afforded 0.25 g (10.5%) of analytically pure **7c**: mp 192 °C; UV λ_{max} nm (ε × 10^{-3}) (pH 1) 318 (6.3); (pH 7) 316 (5.6); (pH 11) 317 (5.5); ^1H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.18 (m, 4 H, $2CH_2$), 1.72 (m, 2 H, CH_2), 4.27 (t, 2 H, NCH_2), 6.62 (s, 2 H, NH_2), 8.37 (s, 1 H, C_8H). Anal. ($C_{10}H_{14}ClN_5$) C, H, N, Cl.

2-Amino-6-chloro-9-hexylpurine (6d). This compound was obtained (40%) from **5** (1.69 g, 10 mmol) and 1-bromohexane (1.65 g, 10 mmol) by the procedure as described for **6b**. Compound **6d** was crystallized from a mixture of CH_2Cl_2–Et_2O: mp 128–130 °C; UV λ_{max} nm (ε × 10^{-3}) (pH 1) 314 (10.9); (pH 7) 305 (11.0); (pH 11) 306 (10.9); ^1H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.23 (br s, 6 H, $3CH_2$), 1.74 (t, 2 H, CH_2), 4.02 (t, 2 H, NCH_2), 6.91 (s, 2 H, NH_2), 8.14 (s, 1 H, C_8H). Anal. ($C_{11}H_{16}ClN_5$) C, H, N, Cl.

2-Amino-6-chloro-7-hexylpurine (7d) was isolated from the subsequent fractions having lower R_f. The product was crystallized from a mixture of CH_2Cl_2–Et_2O to yield 0.3 g (12%) of **7d**: mp 180 °C dec; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 318 (12.4); (pH 7) 316 (7.00); (pH 11) 315 (7.0); ^{1}H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.24 (br s, 6 H, $3CH_2$), 1.76 (t, 2 H, CH_2), 4.27 (t, 2 H, NCH_2), 6.63 (s, 2 H, NH_2), 8.37 (s, 1 H, C_8H). Anal. ($C_{11}H_{16}ClN_5$) C, H, N, Cl.

9-Pentylpurine-6(1*H*)-thione (9a). A mixture of **6a** (0.67 g, 2.98 mmol), thiourea (0.65 g, 8.55 mmol), and EtOH (40 mL) was heated under reflux for 1 h. The crystalline material which separated on cooling the reaction mixture was collected by filtration, washed with EtOH (2 × 5 mL), and recrystallized from EtOH to give 0.62 g (93%) of **9a**: mp 309 °C; IR ν_{max} 1200 (C=S), 2850–3000 (NH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 323 (30.0); (pH 7) 320 (36.0); (pH 11) 309 (36.8); ^{1}H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.16 (m, 4 H, $2CH_2$), 1.77 (t, 2 H, CH_2), 4.15 (t, 2 H, NCH_2), 8.19 (s, 1 H, C_2H), 8.30 (s, 1 H, C_8H), 13.65 (br s, 1 H, N*H*). Anal. ($C_{10}H_{14}N_4S$) C, H, N, S.

9-Hexylpurine-6(1*H*)-thione (9b). This compound was obtained (94%) as a light yellow crystalline material from **6b** (1.5 g, 6.3 mmol) and thiourea (1.3 g, 17 mmol) by the procedure as described for **9a**. Compound **9b** was recrystallized from EtOH: mp 296–298 °C; IR ν_{max} 1200 (C=S), 2700–3000 (NH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 325 (14.7); (pH 7) 320 (18.1); (pH 11) 309 (17.5); ^{1}H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.23 (s, 6 H, $3CH_2$), 1.78 (t, 2 H, CH_2), 4.15 (t, 2 H, NCH_2), 8.19 (s, 1 H, C_2H), 8.30 (s, 1 H, C_8H), 13.70 (br s, 1 H, N*H*). Anal. ($C_{11}H_{16}N_4S$) C, H, N, S.

2-Amino-9-pentylpurine-6(1*H*)-thione (9c). A mixture of **6c** (0.75 g, 3.1 mmol), thiourea (0.63 g, 8.3 mmol), and EtOH (45 mL) was heated under reflux for 1 h. The separated crystals were collected by filtration, washed with cold EtOH, and recrystallized from EtOH to give 0.7 g (95%) of **9c**: mp 290–293 °C; IR ν_{max} 1170 (C=S), 2800–3400 (NH and NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 348 (22.0); (pH 7) 340 (25.7); (pH 11) 317 (17.3); ^{1}H NMR (Me_2SO-d_6) δ 0.84 (t, 3 H, CH_3), 1.18 (m, 4 H, $2CH_2$), 1.76 (t, 2 H, CH_2), 4.00 (t, 2 H, NCH_2), 7.26 (s, 2 H, NH_2), 8.63 (s, 1 H, C_8H), 12.46 (br s, 1 H, N*H*). Anal. ($C_{10}H_{15}N_5S$·H_2O) C, H, N, S.

2-Amino-9-hexylpurine-6(1*H*)-thione (9d). This compound was obtained (83%) from **6d** (0.28 g, 1.10 mmol) and thiourea (0.22 g, 2.9 mmol) by the procedure as described for **9c** and recrystallized from EtOH: mp 290–292 °C; IR ν_{max} 1170 (C=S), 2900–3400 (NH and NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 349 (25.1); (pH 7) 340 (27.9); (pH 11) 318 (18.3); ^{1}H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.24 (br s, 6 H, $3CH_2$), 1.74 (t, 2 H, CH_2), 4.01 (t, 2 H, NCH_2), 7.27 (s, 2 H, NH_2), 8.64 (s, 1 H, C_8H), 12.47 (br s, 1 H, N*H*). Anal. ($C_{11}H_{17}N_5S$) C, H, N, S.

7-Pentylpurine-6(1*H*)-thione (8a). A mixture of **7a** (0.11 g, 0.5 mmol) and thiourea (0.1 g, 1.3 mmol) in EtOH (10 mL) was heated under reflux for 1 h. The separated crystals were collected by filtration and washed with cold EtOH. The product was recrystallized from EtOH to give 0.06 g (54%) of **8a**: mp 230–232 °C dec; IR ν_{max} 1230 (C=S), 2900–3000 (NH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 328 (15.5); (pH 7) 328 (19.8); (pH 11) 316 (19.2); ^{1}H NMR (Me_2SO-d_6) δ 0.85 (t, 3 H, CH_3), 1.20 (m, 4 H, $2CH_2$), 1.82 (t, 2 H, CH_2), 4.66 (t, 2 H, NCH_2), 8.15 (s, 1 H, C_2H), 8.49 (s, 1 H, C_8H), 13.70 (s, 1 H, N*H*). Anal. ($C_{10}H_{14}N_4S$) C, H, N, S.

7-Hexylpurine-6(1*H*)-thione (8b). This compound was obtained (47%) from **7b** (0.28 g, 1.2 mmol) and thiourea (0.25 g, 3.3 mmol) by the procedure as described for **8a**. The product was recrystallized from EtOH: mp 225–227 °C dec; IR ν_{max} 1200 (C=S), 2800–3000 (NH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 328 (19.0); (pH 7) 327 (16.3); (pH 11) 315 (20.2); ^{1}H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.26 (br s, 6 H, $3CH_2$), 1.60 (t, 2 H, CH_2), 4.66 (t, 2 H, NCH_2), 8.15 (s, 1 H, C_2H), 8.49 (s, 1 H, C_8H), 13.69 (s, 1 H, N*H*). Anal. ($C_{11}H_{18}N_4S$) C, H, N, S.

2-Amino-7-pentylpurine-6-(1*H*)-thione (8c). This compound was obtained (72%) from **7c** (0.24 g, 1 mmol) and thiourea (0.25 g, 3.3 mmol) by the procedure as described for **9a**. The product was recrystallized from EtOH: mp 295 °C; IR ν_{max} 1240 (C=S), 2900–3450 (NH and NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 349 (11.0); (pH 7) 351 (7.7); (pH 11) 324 (3.8); ^{1}H NMR (Me_2SO-d_6) δ 0.85 (t, 3 H, CH_3), 1.19 (m, 4 H, $2CH_2$), 1.78 (t, 2 H, CH_2), 4.53 (t, 2 H, NCH_2), 6.79 (s, 2 H, NH_2), 8.49 (s, 1 H, C_8H), 12.22 (br s, 1 H, N*H*). Anal. ($C_{10}H_{15}N_5S$·$0.5H_2O$) C, H, N, S.

2-Amino-7-hexylpurine-6(1*H*)-thione (8d). This compound was obtained (80%) from **7d** (0.25 g, 1 mmol) and thiourea (0.23 g, 3 mmol) by the procedure as described for **8c**, and the product was recrystallized from EtOH: mp 297–299 °C; IR ν_{max} 1200 (C=S), 2900–3400 (NH and NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 348 (5.3); (pH 7) 350 (4.1); (pH 11) 325 (3.7); ^{1}H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.24 (s, 6 H, $3CH_2$), 1.77 (t, 2 H, CH_2), 4.50 (t, 2 H, NCH_2), 6.53 (s, 2 H, NH_2), 8.21 (s, 1 H, C_8H), 11.98 (br s, 1 H, N*H*). Anal. ($C_{11}H_{17}N_5S$) C, H, N, S.

9-Pentylpurine-6-sulfenamide (10a). Sodium hypochlorite (0.77 M, 5.25%, 8 mL, a freshly opened bottle of commercial bleach) was cooled to 0 °C (ice-bath temperature), and to this bleach solution was added rapidly a cold solution of NH_4OH (0.77 M, 10 mL, cooled to 0 °C in an ice bath), and the mixture was stirred at −5 to 0 °C for 15 min. To this mixture was added a solution of **9a** (0.55 g, 2.5 mmol) in 2 N KOH (1.25 mL), and the temperature of the reaction mixture was raised to room temperature and stirred for an additional 45 min. The mixture was evaporated to dryness, and the residue was dissolved in CH_3OH (20 mL), adsorbed on silica gel (2 g), evaporated to dryness, and loaded onto a silica gel column (1.5 × 25 cm) prepacked in CH_2Cl_2. The column was eluted with CH_2Cl_2–CH_3OH (95:5, v/v), and the appropriate fractions were pooled and evaporated to dryness. The residue was crystallized from EtOH to give 0.54 g (91%) of **10a**: mp 55 °C dec; IR ν_{max} 3000–3450 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 300 (8.0); (pH 7) 288 (8.2); (pH 11) 288 (10.3); ^{1}H NMR (Me_2SO-d_6) δ 0.81 (t, 3 H, CH_3), 1.29 (m, 4 H, $2CH_2$), 1.82 (t, 2 H, CH_2), 4.10 (s, 2 H, SNH_2), 4.25 (t, 2 H, NCH_2), 8.46 (s, 1 H, C_2H), 8.73 (s, 1 H, C_8H). Anal. ($C_{10}H_{15}N_5S$) C, H, N, S.

9-Hexylpurine-6-sulfenamide (10b). This compound was obtained (72%) from **9b** (1.18 g, 5 mmol) in 2 N KOH (2.5 mL) and a mixture of sodium hypochlorite (0.77 M, 5.25%, 8 mL) and NH_4OH (0.77 M, 20 mL) by the procedure as described for **10a**. The title compound was crystallized from EtOH: mp 70 °C dec; IR ν_{max} 3100–3450 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 299 (8.0); (pH 7) 288 (20.4); (pH 11) 288 (20.0); ^{1}H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.22 (s, 6 H, 3 CH_2), 1.81 (t, 2 H, CH_2), 4.10 (s, 2 H, SNH_2), 4.22 (t, 2 H, NCH_2), 8.46 (s, 1 H, C_2H), 8.73 (s, 1 H, C_8H). Anal. ($C_{11}H_{17}N_5S$) C, H, N, S.

2-Amino-9-pentylpurine-6-sulfenamide (10c). In a similar manner as described for **10a**, compound **9c** (0.59 g, 2.5 mmol) in 2 N KOH (1.25 mL) was reacted with sodium hypochlorite solution (0.77 M, 5.25%, 4 mL) and NH_4OH (0.77 M, 10 mL). The separated crystalline product was collected by filtration, washed with cold water (2 × 20 mL), and recrystallized from EtOH to give 0.5 g (79%) of **10c**: mp >100 °C dec; IR ν_{max} 3000–3500 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 328 (14.8); (pH 7) 309 (15.4); (pH 11) 309 (14.2); ^{1}H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.32 (m, 4 H, $2CH_2$), 1.74 (t, 2 H, CH_2), 3.88 (s, 2 H, SNH_2), 4.00 (t, 2 H, NCH_2), 6.44 (s, 2 H, NH_2), 7.94 (s, 1 H, C_8H). Anal. ($C_{10}H_{16}N_6S$) C, H, N, S.

2-Amino-9-hexylpurine-6-sulfenamide (10d). This compound was obtained (81%) from **9d** (0.5 g, 2 mmol) and a mixture of sodium hypochlorite (0.77 M, 5.25%, 3.2 mL) and NH_4OH (0.77 M, 8 mL). The title compound was recrystallized from EtOH: mp 125–127 °C; IR ν_{max} 3000–3450 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 328 (10.6); (pH 7) 309 (10.9); (pH 11) 308 (10.3); ^{1}H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.23 (br s, 6 H, $3CH_2$), 1.73 (t, 2 H, CH_2), 3.88 (s, 2 H, SNH_2), 4.00 (t, 2 H, NCH_2), 6.44 (s, 2 H, NH_2), 7.94 (s, 1 H, C_8H). Anal. ($C_{11}H_{18}N_6S$) C, H, N, S.

(*R,S*)-9-Pentylpurine-6-sulfinamide (11a). To an ice-cooled (0–5 °C) solution of **10a** (0.3 g, 1.27 mmol) in EtOH (10 mL) was added, with stirring, a solution of 3-chloroperoxybenzoic acid (MCPBA, 0.25 g, 1 mmol) in EtOH (5 mL) portionwise over a period of 5 min, and the mixture was allowed to warm to room temperature. The reaction mixture was stirred for an additional 90 min at ambient temperature and then evaporated to dryness. The residue was dissolved in CH_3OH (10 mL), adsorbed onto silica gel, and loaded on top of a silica gel column (1.5 × 15 cm) prepacked in CH_2Cl_2. The column was eluted with CH_2Cl_2–CH_3OH (94:6, v/v), the appropriate homogeneous fractions were pooled and evaporated, and the residue was crystallized from

EtOH to afford 0.21 g (65%) of **11a**: mp 89 °C; IR ν_{max} 1050 (S=O), 3000–3600 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 271 (10.3); (pH 7) 275 (11.1); (pH 11) 275 (9.8); ^1H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.32 (m, 4 H, $2CH_2$), 1.87 (t, 2 H, CH_2), 4.32 (t, 2 H, NCH_2), 6.68 (s, 2 H, $SONH_2$), 8.80 (s, 1 H, C_2H), 9.06 (s, 1 H, C_8H). Anal. ($C_{10}H_{15}N_5OS$) C, H, N, S.

(*R,S*)-9-Hexylpurine-6-sulfinamide (11b). This compound was obtained (79%) from **10b** (0.52 g, 2 mmol) and MCPBA (0.43 g, 2 mmol) in EtOH at 0 °C by the procedure as described for **11a**. The title compound was crystallized from Et_2O: mp 105–107 °C; IR ν_{max} 1050 (S=O), 3000–3350 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 272 (10.1); (pH 7) 275 (9.1); (pH 11) 274 (7.9); ^1H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, CH_3), 1.25 (s, 6 H, $3CH_2$), 1.86 (t, 2 H, CH_2), 4.32 (t, 2 H, NCH_2), 6.67 (s, 2 H, $SONH_2$), 8.80 (s, 1 H, C_2H), 9.05 (s, 1 H, C_8H). Anal. ($C_{11}H_{17}N_5OS$) C, H, N, S.

(*R,S*)-2-Amino-9-pentylpurine-6-sulfinamide (11c). This compound was obtained (53%) from **10c** (0.29 g, 1.13 mmol) and MCPBA (0.24 g, 1.15 mmol) in EtOH at 0 °C by the procedure as described for **11a**: mp 126–128 °C; IR ν_{max} 1060 (S=O), 3000–3500 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 333 (6.1); (pH 7) 324 (8.8); (pH 11) 324 (8.1); ^1H NMR (Me_2SO-d_6) δ 0.84 (t, 3 H, CH_3), 1.33 (m, 4 H, $2CH_2$), 1.77 (t, 2 H, CH_2), 4.06 (t, 2 H, NCH_2), 6.50 (s, 2 H, NH_2), 6.91 (s, 2 H, $SONH_2$), 8.24 (s, 1 H, C_8H). Anal. ($C_{10}H_{18}N_6OS$) C, H, N, S.

(*R,S*)-2-Amino-9-hexylpurine-6-sulfinamide (11d). This compound was obtained (70%) from **10d** (0.266 g, 1 mmol) and MCPBA (0.21 g, 1 mmol) in EtOH (25 mL) at 0 °C by the procedure as described for **11a**. The separated crystalline product was collected and recrystallized from EtOH: mp 124–146 °C; IR ν_{max} 1060 (S=O), 3000–3500 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 330 (3.3); (pH 7) 327 (4.5); (pH 11) 323 (4.2); ^1H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, CH_3), 1.25 (br s, 6 H, $3CH_2$), 1.78 (t, 2 H, CH_2), 4.06 (t, 2 H, NCH_2), 6.49 (s, 2 H, NH_2), 6.90 (s, 2 H, $SONH_2$), 8.23 (s, 1 H, C_8H). Anal. ($C_{11}H_{18}N_6OS$) C, H, N, S.

2-Amino-6-chloro-9-(6-hydroxyhexyl)purine (6e). A mixture of **5** (1.69 g, 10 mmol), NaH (60% dispersion in mineral oil, 0.44 g, 11 mmol), and anhydrous CH_3CN (100 mL) was protected from moisture and stirred at ambient temperature for 30 min. 6-Bromo-1-hexanol (1.81 g, 10 mmol) was added, and the mixture was stirred at ambient temperature for an additional 20 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in H_2O (100 mL). The aqueous phase was extracted with EtOAc (300 mL), and organic phase was washed with cold water (2 × 50 mL), dried (Na_2SO_4), and evaporated to give a thick syrup, which was purified on a silica gel column (3 × 30 cm) using CH_2Cl_2–CH_3OH (97:3, v/v) as the eluent. The homogeneous fractions were pooled and evaporated, and the solid was crystallized from a mixture of CH_2Cl_2–Et_2O to yield 1.1 g (41%) of **6e**: mp 115–117 °C; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 314 (10.9); (pH 7) 305 (11.0); (pH 11) 306 (10.9); ^1H NMR (Me_2SO-d_6) δ 1.22 (t, 6 H, $3CH_2$), 1.75 (t, 2 H, CH_2), 3.32 (t, 2 H, CH_2OH), 4.02 (t, 2 H, NH_2), 4.36 (t, 1 H, OH), 6.91 (s, 2 H, NH_2), 8.14 (s, 1 H, C_8H). Anal. ($C_{11}H_{16}ClN_5O$) C, H, N, Cl.

2-Amino-9-(6-hydroxyhexyl)purine-6(1*H*)-thione (9e). A mixture of **6e** (0.34 g, 1.23 mmol) and thiourea (0.32 g, 4.2 mmol) in EtOH (20 mL) was heated under reflux for 1 h, and the separated crystalline material was collected by filtration, washed with EtOH (2 × 5 mL), and recrystallized from EtOH to give 0.26 g (79%) of **9e**: mp 220–222 °C; IR ν_{max} 1170 (C=S), 2900–3400 (NH, NH_2, OH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 349 (25.1); (pH 7) 340 (27.9); (pH 11) 318 (18.3); ^1H NMR (Me_2SO-d_6) δ 1.23 (m, 6 H, $3CH_2$), 1.75 (t, 2 H, CH_2), 3.35 (t, 2 H, CH_2OH), 4.00 (t, 2 H, NCH_2), 4.35 (br s, 1 H, OH), 7.21 (br s, 2 H, NH_2), 8.58 (s, 1 H, C_8H), 12.41 (br s, 1 H, NH). Anal. ($C_{11}H_{17}N_5OS \cdot H_2O$) C, H, N, S.

2-Amino-9-(6-hydroxyhexyl)purine-6-sulfenamide (10e). To a cooled (0–5 °C) solution of sodium hypochlorite (0.77 M, 5.25%, 3.2 mL) was added NH_4OH (0.77 M, 8 mL), and the mixture was stirred at −5 °C for 15 min. To this mixture was added a solution of **9e** (0.53 g, 2 mmol) in 2 N KOH (2 mL), and the resultant mixture was stirred at 0 °C for 45 min. The temperature was allowed raise to 25 °C, and the mixture was stirred for an additional 3 h. The crystalline product that separated was collected by filtration, washed with cold H_2O (2 × 5 mL) followed by cold EtOH, and dried over P_2O_5 to give 0.32 g (57%) of **10e**: mp 125–127 °C (dec); IR ν_{max} 3000–3450 (NH_2, OH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 328 (10.6); (pH 7) 309 (10.9); (pH 11) 308 (10.3); ^1H NMR (Me_2SO-d_6) δ 1.21 (m, 6 H, $3CH_2$), 1.74 (t, 2 H, CH_2), 3.32 (t, 2 H, CH_2OH), 3.87 (s, 2 H, SNH_2), 4.00 (t, 2 H, NCH_2), 4.35 (t, 1 H, OH), 6.44 (s, 2 H, NH_2), 7.94 (s, 1 H, C_8H). Anal. ($C_{11}H_{18}N_6OS$) C, H, N, S.

(*R,S*)-2-Amino-9-(6-hydroxyhexyl)purine-6-sulfinamide (11e). To an ice-cooled (0 °C) solution of **10e** (0.26 g, 1 mmol) in EtOH (20 mL) was added a solution of MCPBA (0.21 g, 1 mmol) in EtOH (10 mL). After 15 min the temperature was allowed to raise to room temperature, and the mixture was stirred for an additional 90 min. The reaction mixture was evaporated, and the residue was triturated with EtOH, filtered, and crystallized from Et_2O to afford 0.2 g (67%) of **11e**: mp 124–126 °C; IR ν_{max} 1060 (S=O), 3000–3500 (NH_2, OH) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 332 (3.3); (pH 7) 327 (4.5); (pH 11) 323 (4.2); ^1H NMR (Me_2SO-d_6) δ 1.23 (m, 6 H, $3CH_2$), 1.78 (t, 2 H, CH_2), 3.33 (t, 2 H, CH_2OH), 4.06 (t, 2 H, NCH_2), 4.36 (t, 1 H, OH), 6.49 (s, 2 H, NH_2), 6.91 (s, 2 H, $SONH_2$), 8.23 (s, 1 H, C_8H). Anal. ($C_{11}H_{15}N_6O_2S$), C, H, N, S.

2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl Methyl Sulfoxide (13a). To an ice-cooled (0–5 °C) solution of 2-amino-6-(methylthio)-9-β-D-ribofuranosylpurine[14] (**12a**, 0.314 g, 1 mmol) in EtOH (25 mL) was added MCPBA (0.2 g, 1.16 mmol) in EtOH (10 mL) dropwise over a period of 10 min, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was evaporated to dryness, and the residue was purified on a silica gel column (2.5 × 25 cm) using CH_2Cl_2–MeOH (9:1, v/v) as the eluent to give 0.14 g (43%) of **13a**: mp 145–148 °C; IR ν_{max} 1040 (S=O), 3000–3500 (OH, NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 325 (3.7); (pH 7) 325 (3.6); (pH 11) 325 (2.5); ^1H NMR (Me_2SO-d_6) δ 2.99 (s, 3 H, CH_3), 5.85 (d, 1 H, J = 5.73 Hz, $C_1'H$), 7.07 (s, 2 H, NH_2), 8.44 (s, 1 H, C_8H), and other sugar protons. Anal. ($C_{11}H_{15}N_5O_5S$) C, H, N, S.

2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl Benzyl Sulfoxide (13b). In a similar manner as described for **13a**, oxidation of 2-amino-6-(benzylthio)-9-β-D-ribofuranosylpurine[14] (**12b**, 0.35 g, 0.97 mmol) in EtOH (40 mL) with MCPBA (0.184 g, 1.06 mmol) gave 0.82 g (81%) of **13b**: mp 160–165 °C; IR ν_{max} 1040 (S=O), 3000–3600 (OH, NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 330 (3.8); (pH 7) 326 (3.7); (pH 11) 328 (3.2); ^1H NMR (Me_2SO-d_6) δ 4.5 (s, 2 H, $CH_2C_6H_5$), 5.86 (d, 1 H, J = 5.73 Hz, $C_1'H$), 7.07 (s, 2 H, NH_2), 7.17–7.30 (m, 5 H, $CH_2C_6H_5$), 8.47 (s, 1 H, C_8H) and other sugar protons. Anal. ($C_{17}H_{19}N_5O_5S$) C, H, N, S.

2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl Methyl Sulfone (14a). To a solution of **13a** (0.47 g, 1.5 mmol) in EtOH (40 mL) was added MCPBA (1.29 g, 7.4 mmol), and the mixture was stirred at room temperature overnight. The separated precipitate was collected, washed with cold EtOH (2 × 10 mL), and dried (P_2O_5) to give 0.3 g (58%) of **14a**: mp 180–183 °C; IR ν_{max} 1310 (SO_2), 3100–3600 (OH, NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 334 (2.6); (pH 7) 332 (2.5); (pH 11) 332 (2.6); ^1H NMR (Me_2SO-d_6) δ 3.35 (s, 3 H, CH_3), 5.87 (d, 1 H, J = 5.52 Hz, $C_1'H$), 7.22 (s, 2 H, NH_2), 8.56 (s, 1 H, C_8H), and other sugar protons. Anal. ($C_{11}H_{15}N_5O_6S$) C, H, N, S.

2-Amino-9-β-D-ribofuranosyl-9*H*-purin-6-yl Benzyl Sulfone (14b). To a solution of **13b** (0.97 g, 2.5 mmol) in EtOH (50 mL) was added MCPBA (2.0 g, 11.6 mmol), and the mixture was stirred at ambient temperature for 5 h. The reaction mixture was evaporated, and the residue was adsorbed onto silica gel (10 g) and loaded on top of a silica gel column (2.5 × 30 cm) prepacked in CH_2Cl_2. The column was eluted with CH_2Cl_2–MeOH (85:5 v/v). The appropriate fractions were pooled and evaporated to afford 0.63 g (60%) of **14b**: mp 140–141 °C; IR ν_{max} 1320 (SO_2), 3000–3600 (OH, NH_2); UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1, 7, and 11) 337 (1.6); ^1H NMR (Me_2SO-d_6) δ 5.05 (s, 2 H, CH_2), 5.88 (d, 1 H, J = 5.67 Hz, C1'*H*), 7.27 (s, 2 H, NH_2), 7.32–7.90 (m, 5 H, $CH_2C_6H_5$), 8.60 (s, 1 H, C_8H), and other sugar protons. Anal. ($C_{17}H_{19}N_5O_6S$) C, H, N, S.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(methylthio)purine (12c). A mixture of 2-amino-6-(methylthio)purine[22] (2.71 g, 15 mmol) and NaH (60% in oil, 0.75 g, 18.75 mmol) in anhydrous CH_3CN (110 mL) was stirred at ambient temperature for 30 min under nitrogen atmosphere. Dry, powdered 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose[23] (5.82 g, 15 mmol) was added portionwise, with stirring, during 5 min, and stirring was continued for 18 h. A small amount

of insoluble material was removed by filtration. Evaporation of the filtrate gave an oily residue which was purified on a silica gel column (4 × 30 cm) prepacked in CH_2Cl_2. The column was eluted with CH_2Cl_2–MeOH (98:2, v/v), and the appropriate fractions were pooled and evaporated to afford 4.3 g (54%) of 2-amino-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-(methylthio)purine as a foam: IR ν_{max} 1720 (C=O of ester), 3200–3500 (NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (MeOH) 307 (3.2), 241 (16.1); ^1H NMR (Me_2SO-d_6) δ 2.56 (s, 3 H, CH_3), 6.39 (t, 1 H, J = 6.80 Hz, $C_1'H$), 6.60 (s, 2 H, NH_2), 7.31 and 7.85 (m, 8 H, toluoyl), 8.15 (s, 1 H, C_8H), and other sugar protons. Anal. Calcd for ($C_{27}H_{27}N_5O_5S$): C, 60.92; H, 5.10; N, 13.13; S, 6.01. Found: C, 60.65; H, 5.30; N, 12.91; S, 6.05.

A solution of the above protected nucleoside (1.066 g, 2 mmol) in NH_3/MeOH (100 mL, saturated at 0 °C) was allowed to stand overnight at 4 °C. The solution was evaporated, and the residue was dissolved in MeOH, adsorbed onto silica gel (5 g), and loaded on the top of a prepacked silica gel column (1.5 × 15 cm). The column was eluted with CH_2Cl_2–MeOH (98:2, 96:4; v/v), and the appropriate fractions were pooled and evaporated to give 0.4 g (67%) of **12c** as a white powder: mp 188–192 °C; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 321 (10.7), 249 (9.7); (pH 7) 309 (11.5), 245 (13.1); (pH 11) 309 (11.7), 245 (13.2); ^1H NMR (Me_2SO-d_6) δ 2.56 (s, 3 H, CH_3), 6.21 (t, 1 H, J = 6.87 Hz, $C_1'H$), 8.54 (s, 2 H, NH_2), 8.15 (s, 1 H, C_8H), and other sugar protons. Anal. ($C_{11}H_{15}N_5O_3S$) C, H, N, S.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-yl Methyl Sulfoxide (13c). To an ice-cooled solution of **12c** (0.297 g, 1 mmol) in EtOH (25 mL) was added MCPBA (0.2 g, 1.16 mmol) in EtOH (10 mL) dropwise over a period of 10 min, and the mixture was stirred at ambient temperature for 20 h. The reaction mixture was evaporated, and the residue was purified on a silica gel column (2.5 × 20 cm) using CH_2Cl_2–MeOH (85:15, v/v) as the eluent to yield 0.29 g (93%) of **13c** as a gum: IR ν_{max} 1050 (S=O), 3100–3600 (OH, NH_2) cm^{-1}; UV λ_{max} nm ($\epsilon \times 10^{-3}$) (pH 1) 328 (13.9); (pH 7) 324 (14.7); (pH 11) 321 (11.7); ^1H NMR (MeSO-d_6) δ 3.00 (s, 3 H, CH_3), 6.28 (d, 1 H, J = 6.60 Hz, $C_1'H$), 7.07 (s, 2 H, NH_2), 8.42 (s, 1 H, C_8H), and other sugar protons. Anal. ($C_{11}H_{15}N_5O_4S$) C, H, N, S.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-yl Methyl Sulfone (14c). To a solution of **13c** (0.297 g, 0.95 mmol) in EtOH (25 mL) was added MCPBA (0.8 g, 4.64 mmol), and the mixture was stirred at room temperature for 3 h and left at 5 °C overnight. The reaction mixture was evaporated, and the residue was purified on a silica gel column (2 × 20 cm) using CH_2Cl_2–MeOH (85:15, v/v) as the eluent to give 0.20 g (61%) of **14c** as a gum: IR ν_{max} 1330 (SO_2), 3100–3400 (OH, NH_2) cm^{-1}); ^1H NMR (Me_2SO-d_6) δ 3.16 (s, 3 H, CH_3), 6.28 (d, 1 H, J = 6.65 Hz, $C_1'H$), 7.18 (s, 2 H, NH_2), 8.52 (s, 1 H, C_8H), and other sugar protons. Anal. ($C_{11}H_{15}N_5O_6S$) C, H, N, S.

Antitumor Evaluation in Mice. *In vivo* assessments of antileukemic activity and host toxicity were performed as described previously.[24] Briefly, $BD2F_1$ female mice (~18 g) purchased from the Charles River Co. were inoculated ip on day 0 with 1 × 10^6 cells of murine leukemia L1210 and treated with the compound *once* by ip bolus injection 24 h later. Drugs were solubilized immediately before use and delivered in uniform volumes of 0.01 mL/g of mouse weight. This scheme allowed the delivery of all drugs at 10 times in milligrams per kilogram their solubility in milligram per milliliter. Drugs that were lethally toxic at their maximum soluble dosages (indicated by numbers in parentheses) were studied at lower dosages. Control mice were given equal volumes of a 0.09% solution of NaCl.

Treatment responses (six mice per treatment group) presented as % T/C were calculated according to the equation: mean life span of treated mice/mean life span of control mice × 100. The data presented in Table 1 and Figure 1 were derived from four different studies in which the mean life span of 10 control mice per study ranged from 6.50 ± 0.55 to 6.80 ± 0.63 days.

The end points by which responses to treatment were gauged were the incidence of compound- 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 death to leukemia or compound toxicity. Inoculum response data, defining the relationship between life span and inoculum size, were used to estimate the body burdens of leukemia cells that survived treatment and, hence, the percentages of such cells that were killed.

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