= 8.6 Hz), 5.10 (s, 1 H), 6.15 (d, 1 H, J = 8.9 Hz), 6.51 (d, 1 H, J = 8.1 Hz), 6.59 (d, 1 H, J = 8.1 Hz). **58**: ^{1}H NMR δ 0.86 (t, 3 H, J = 7.1 Hz), 1.1–1.4 (m, 6 H), 1.38 (s, 3 H), 1.35–1.8 (m, 4 H), 2.1–2.3 (m, 1 H), 2.38 (d, 1 H, J = 13.0 Hz), 2.91 (s, 1 H), 2.9–3.1 (m, 2 H), 3.18 (d, 1 H, J = 15.8 Hz), 3.1–3.4 (m, 1 H), 3.43 (s, 3 H), 3.6–3.9 (m, 2 H), 3.80 (s, 3 H), 4.25 (s, 1 H), 4.94 (d, 1 H, J = 8.8 Hz), 5.62 (br s, 1 H), 6.35 (d, 1 H, J = 8.8 Hz), 6.43 (d, 1 H, J = 8.3 Hz), 6.61 (d, 1 H, J = 8.3 Hz); MS, m/e calcd for $C_{28}H_{37}NO_4$ 451.2715, found 451.2729 (intensity, 8.0).

***N*,8α-Ethano-19(*R*)-*n*-butylnororvinol (6)** was prepared from **59** by O-demethylation as described for **4** and obtained as a white powder in 70% yield: ^{1}H NMR δ 0.91 (t, 3 H, J = 6.8 Hz), 0.10 (s, 3 H), 1.2–1.6 (m, 6 H), 1.7–2.1 (m, 3 H), 2.0–2.3 (m, 1 H), 2.60 (d, 1 H, J = 10 Hz), 2.6–3.2 (m, 3 H), 3.0–3.2 (m, 2 H), 3.3–3.7 (m, 3 H), 3.64 (s, 3 H), 4.74 (d, 1 H, J = 1.0 Hz), 4.88 (s, 1 H), 4.99 (d, 1 H, J = 8.6 Hz), 6.10 (dd, 1 H, J_1 = 0.9 Hz, J_2 = 8.7 Hz), 6.47 (d, 1 H, J = 7.4 Hz), 6.57 (d, 1 H, J = 7.2 Hz).

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Registry No. **3** (R = *n*-Pr), 14521-96-1; **4**, 110143-22-1; **5**, 110143-23-2; **6**, 110221-12-0; **9**, 110173-63-2; **10**, 110173-64-3; **11**, 110173-65-4; **12**, 110173-66-5; **13**, 110173-67-6; **15**, 110143-24-3; **16**, 110143-26-5; **17**, 110143-27-6; **18**, 110143-28-7; **19**, 110143-29-8; **20**, 110143-30-1; **21**, 110143-31-2; **22** (epimer 1), 110143-32-3; **22** (epimer 2), 110221-13-1; **23**, 110143-33-4; **24**, 110143-34-5; **25**, 110143-25-4; **26**, 110143-35-6; **27**, 110173-26-7; **28**, 110143-36-7; **29**, 110143-37-8; **30**, 110143-38-9; **31**, 110143-39-0; **32** (epimer 1), 110143-40-3; **32** (epimer 2), 110221-14-2; **33**, 110143-41-4; **34**, 110143-42-5; **41**, 110173-27-8; **42**, 110143-43-6; **43**, 110143-44-7; **44**, 110143-45-8; **45**, 110143-46-9; **46**, 110143-47-0; **47**, 110143-48-1; **57**, 110143-49-2; **52**, 110143-50-5; **53**, 110143-51-6; **54**, 110221-15-3; **55** (epimer 1), 110221-16-4; **55** (epimer 2), 110221-17-5; **56**, 110221-18-6; **59**, 110222-26-9; $(BOC)_2O$, 24424-99-5; $TMSCH_2Cl$, 2344-80-1; TBDMS-Cl, 18162-48-6; $(PhCO)_2O$, 93-97-0; $MeSO_2Cl$, 124-63-0; MeI, 74-88-4; BuBr, 109-65-9; northebaine hydrochloride, 7679-18-7; maleic anhydride, 108-31-6.

Synthesis and Antiviral Activity of Carbocyclic Analogues of Xylofuranosides of 2-Amino-6-substituted-purines and 2-Amino-6-substituted-8-azapurines

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(±)-(1α,2β,3α,5α)-3-[(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]-5-(hydroxymethyl)-1,2-cyclopentanediol (**7**) was synthesized from 2-amino-4,6-dichloropyrimidine and the carbocyclic xylofuranosylamine (±)-(1α,2β,3α,5α)-3-amino-5-(hydroxymethyl)-1,2-cyclopentanediol (**2**) by subsequent preparation of the 5-[(4-chlorophenyl)azo] derivative of the resulting pyrimidine and reduction of the azo moiety with zinc and acetic acid. The carbocyclic analogue of 2-amino-4-chloropurine xylofuranoside (**8**) and the corresponding 8-azapurine **11** were prepared from **7**. The carbocyclic analogues xylofuranosylguanine (**9**), xylofuranosyl-2,6-diaminopurine (**10**), xylofuranosyl-8-azaguanine (**13**), and xylofuranosyl-8-aza-2,6-diaminopurine (**14**) were prepared from **8** and **11**. Compounds **9** and **13** were active against herpes simplex virus (types 1 and 2), with **9** being the more potent against both viruses. Analogue **9** also exhibited potent activity against human cytomegalovirus and varicella-zoster virus.

The availability of carbocyclic nucleosides was limited to analogues of ribofuranosides until a synthetic route was developed[1,2] that provided several versatile intermediates leading to a wide variety of both purine and pyrimidine carbocyclic nucleosides. The key intermediate, 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**), provided the routes to several types of previously unknown carbocyclic nucleosides. These included carbocyclic analogues of arabinofuranosylpurine nucleosides,[3-5] aminonucleosides,[1,2] lyxofuranosyladenine,[6] and xylofuranosyladenine.[7] Several of these analogues exhibit significant in vitro and in vivo antiviral and/or antitumor activities.

It has been our experience with carbocyclic nucleosides that purine derivatives other than adenine should be explored in cases where an adenine nucleoside exhibits antitumor or antiviral properties.[4] Similar observations have been reported for other types of nucleoside analogues. For example, the guanine analogue in a series of 9-[(2-hydroxyethoxy)methyl]purines exhibited antiviral effects 2 orders of magnitude greater than the corresponding adenine derivatives.[8,9] Thus, the significant antitumor activities of carbocyclic xylofuranosyladenine and its 8-aza analogue[7] prompted the synthesis of the guanosine and 2,6-diaminopurine analogues.

Chemistry

The synthesis of the carbocyclic xylofuranosylamine (±)-(1α,2β,3α,5α)-3-amino-5-(hydroxymethyl)-1,2-cyclopentanediol (**2**) from the versatile precursor 2-azabicyclo-[2.2.1]hept-5-en-3-one (**1**) was described earlier[7] (Scheme I). Condensation of **2** with 2-amino-4,6-dichloropyrimidine (**3**) gave the corresponding pyrimindinylamino derivative **4** along with disubstituted product **5**. The assignment of structure **5** is consistent with its IR, NMR, and spectral analyses. Also, the presence of two NH signals at δ 9.82 and 7.80–7.72 and one NH_2 signal at δ 6.67 rules out the possibility that both pyrimidine moieties were attacked

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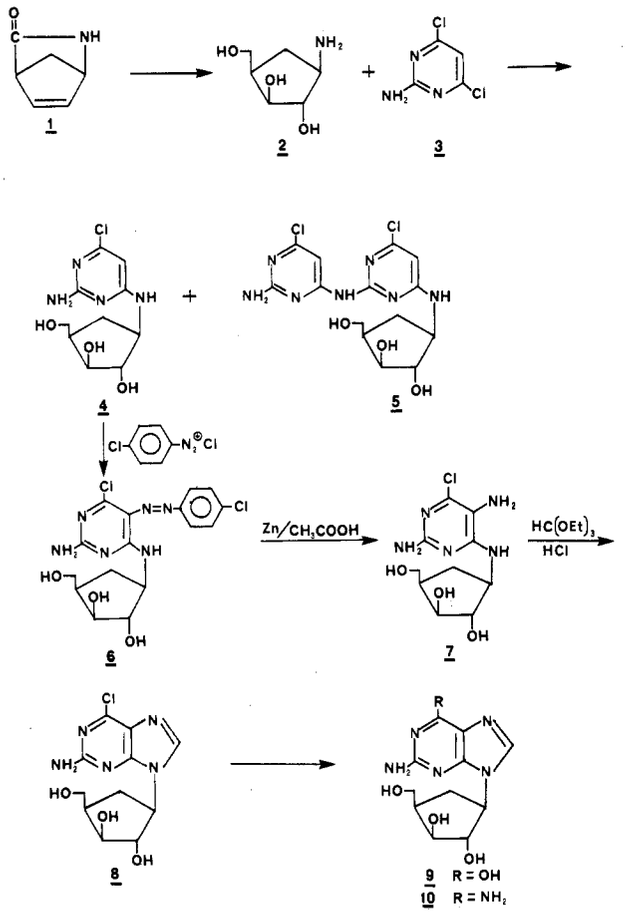
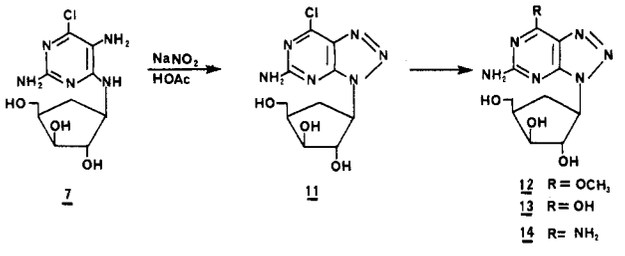
0022-2623/87/1830-2026$01.50/0

Scheme I



Scheme II



by the 3-amino group of **2**. The 5-[(*p*-chlorophenyl)azo]-pyrimidine **6** was prepared with *p*-chlorobenzenediazonium chloride by the method of Shealy and Clayton.[10] Reduction of **6** with zinc and acetic acid gave the pyrimidine **7**, wihch was subsequently converted to the 9-substituted 2-amino-6-chloropurine **8** by ring closure with triethyl orthoformate and subsequent mild acid hydrolysis to remove ethoxymethylidenes and formates formed during the reaction. Treatment of **8** with 1 N HCl under reflux conditions gave carbocyclic xylofuranosylguanine (C-xylo-G) (**9**), while treatment of **8** with liquid ammonia gave carbocyclic xylofuranosyl-2,6-diaminopurine (**10**).

The 8-azapurine analogues were obtained as outlined in Scheme II. Ring closure of **7** with sodium nitrite and acetic acid gave (±)-(1α,2β,3α,5α)-3-(5-amino-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (**11**) in good yield. When **11** was heated in methanol, displacement of chlorine from the heterocyclic ring gave the corresponding methoxy derivative **12** in 80% yield. Acid hydrolysis of **11** gave the 8-aza analogue **13** of carbocyclic xylofuranosylguanine, whereas

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Table I. Inhibitory Concentrations of Carbocyclic Xylofuranosides of 2-Amino-6-substituted-purines and 2-Amino-6-substituted-8-azapurines for P-388 Leukemia Cells in Culture[a]

compd	ED_{50}, μM	compd	ED_{50}, μM
8	220	**12**	63
9	8.9	**13**	1.6
10	39	**14**	5.3
11	50		

[a] Cytotoxicity to P-388 cells in culture was determined by the protocol of the National Cancer Institute.[11]

Table II. Evaluation of Carbocyclic Analogues of Xylofuranosides of 2-Amino-6-substituted-purines and 2-Amino-6-substituted-8-azapurines against Herpes Simplex Virus in Vitro[a]

compound		HSV type 1, strain 377		HSV type 2, strain MS	
no.	substituent at position 6[b]	VR[c]	MIC_{50},[d] μg/mL	VR[c]	MIC_{50}, μg/mL
purines					
8	Cl	1.8	100		
9	OH	5.7	1.8	2.6	22.8
		5.6	3.0	3.9	23.5
10	NH_2	2.7	85.0		
8-azapurines					
11	Cl	0.6	100		
13	OH	2.4	60.8	1.3	92.2
		2.5	93.1	1.1	240.5
14	NH_2	2.0	66.9		
araA[e]		2.5–3.1	6.4–9.8	1.6–2.3	6.4–30

[a] Antiviral evaluations were performed with HSV-1 and HSV-2 by a CPE inhibition assay procedure employing pregrown Vero cell monolayers as the host cell system. [b] Purine number system for 8-azapurines. [c] A virus rating (VR) equal to or greater than 1.0 indicates definite and significant antiviral activity, a VR of 0.5–0.9 indicates marginal to moderate antiviral activity, and a VR less than 0.5 usually indicates no significant antiviral activity. [d] The MIC_{50} is the concentration of the test compound required to inhibit virus-induced cytopathogenic effects by 50%. [e] 9-β-D-Arabinofuranosyladenine was tested as a positive control; the range of VR and MIC_{50} values came from several tests.

treatment of **11** with liquid ammonia gave the 8-aza analogue **14** of carbocyclic xylofuranosyl-2,6-diaminopurine.

Results and Discussion

The ED_{50} cytotoxicity concentrations of **8**–**14** in P-388 mouse leukemia cell culture are listed in Table I. Carbocyclic nucleosides **9**, **13**, and **14** exhibited significant cytotoxicities in this assay. It is interesting to note that the 8-aza analogues **13** and **14** are more active than the corresponding purines **9** and **10**. These results are consistent with a previous observation in a different series,[7] i.e., when the carbocyclic purine was found to exhibit antitumor activity, the corresponding 8-aza analogue was more active.

The xylofuranoside analogues were evaluated for antiviral activity in vitro against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). The results are summarized in Table II. The antiviral activity of each compound is expressed as a virus rating (VR), and the potency is given as a minimum inhibitory concentration, 50% (MIC_{50}). The VR, determined by the general method of Ehrlich et al.,[12]

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Table III. The Effect of Carbocyclic Xylofuranosylguanine (**9**) on the Replication of Human Cytomegalovirus (CMV),[a] Strain AB169: Virus Yield Reduction Assay in MRC5[b] Cell Cultures

test compd final concn, μM	reduction (%) of CPE by **9** at time of harvest	drug cytotoxicity (gross morphology)	CMV yield		virus yield reduction, $\log_{10}$ PFU/mL[c]
			PFU/mL[c]	$\log_{10}$ PFU/mL[c]	
1000 (308 μg/mL)	100	sl toxic	0	0	5.2
320	100	v sl toxic	0	0	5.2
100	80	0	1×10^2	2.0	3.2
32	25	0	1.28×10^4	4.1	1.1
10	0	0	9.6×10^4	5.0	0.2
3.2	0	0	1.08×10^5	5.0	0.2
1.0	0	0	9.6×10^4	5.0	0.2
0 (virus controls)			1.42×10^5	5.2	

[a] See Experimental Section for details. [b] MRC5 = human diploid embryonic lung cells (25th passage). [c] PFU = plaque-forming units.

Table IV. The Antiviral Activity of Carbocyclic Xylofuranosylguanine (**9**) Compared with That of araA, Acycloguanosine, and DHPG against Varicella-zoster Virus in Human Foreskin Cell Cultures as Determined by a Virus Plaque Reduction Assay Procedure[a]

test compd drug concn, μM	plaque reduction, %				cytotoxicity			
	C-xylo-G	araA	acycloguanosine	DHPG	C-xylo-G	araA	acycloguanosine	DHPG
1000	100	–	100	97	v sl toxic	toxic	0	0
320	100	100	100	97	0	sl toxic	0	0
100	100	97	94	82	0	0	0	0
32	79	97	79	56	0	0	0	0
10	26	44	41	35				
3.2	18	18	32	24				
1.0	18	–	35	–				

[a] Virus controls averaged 33 plaques (foci) per 24-mm well. See Experimental Section for details.

is a weighted measurement of antiviral activity that takes into account both the degree of inhibition of virus-induced cytopathogenic effects and the degree of cytotoxicity produced by the test compound.

In the test vs HSV-1, C-xylo-G (**9**) was the most potent compound with excellent activity (VR = 5.6–5.7) and high potency (MIC_{50} = 1.8–3.0 μg/mL). C-xylo-G and its 8-aza analogue were selected for evaluation against HSV-2. As expected, the relative activities of **9** and **13** paralleled their activities against HSV-1. Thus, C-xylo-G (**9**) exhibits greater activity than its 8-aza analogue **13** against both HSV-1 and HSV-2.

C-xylo-G was evaluated for efficacy against cytomegalovirus (CMV) in human diploid embryonic lung (MRC5) cell cultures employing a virus yield reduction assay procedure. The data from the CMV yield reduction assays are presented in Table III. C-xylo-G demonstrated significant activity at concentrations as low as 32 μM. This compound reduced virus yields, when compared with the untreated virus-infected control cultures, by greater than 10^5 PFU/mL (below the level of detection) at 320 μM and by $10^{3.2}$ PFU/mL at 100 μM.

The effects of C-xylo-G were compared with those of acycloguanosine (acyclovir), araA, and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG) on varicella-zoster virus (VZV) induced plaque formation in cell culture. The results of the VZV plaque reduction assay are summarized in Table IV. All of the compounds showed significant activity against VZV. C-xylo-G demonstrated a marked inhibitory effect on VZV plaque formation and was less toxic than araA. Larger quantities of **9** are being prepared for in vivo studies.

Experimental Section

Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with a JEOL FX 90 FT instrument (89.55 MHz), infrared spectra with a Perkin-Elmer 237B spectrometer, and ultraviolet spectra with a Beckman DU-8 recording spectrometer. This-layer chromatography was done by using 0.25-mm layers of Merck silica gel 60F-254 and column chromatography on Merck silica gel 60 (230–400 mesh). Mass spectra were obtained with an AEI Scientific Apparatus Limited MS-30 mass spectrometer. High-resolution mass spectra were obtained for all compounds, and the molecular ion and fragmentation patterns were consistent with assigned structures.

(±)-(1α,2β,3α,5α)-3-[(2-Amino-6-chloro-4-pyrimidinyl)amino]-5-(hydroxymethyl)-1,2-cyclopentanediol (4). To 7.65 g (52.05 mmol) of (±)-(1α,2β,3α,5α)-3-amino-5-(hydroxymethyl)-1,2-cyclopentanediol (**2**) in 200 mL of 1-butanol and 25 mL of methanol was added a mixture of 9.39 g (57.24 mmol) of 2-amino-4,6-dichloropyrimidine, 30 mL of triethylamine, and 50 mL of 1-butanol, and the resulting solution was refluxed for 2 days. The solvent was evaporated in vacuo, and the residue was partitioned between water and dichloromethane. The insoluble disubstituted product **5** was removed by filtration and gave 5.90 g (39%) of white solid. The aqueous solution was washed with dichloromethane (3 × 30 mL) to remove unreacted 2-amino-4,6-dichloropyrimidine and evaporated to dryness. The residue was then evaporated onto coarse silica gel (70–230 mesh), which was subsequently applied to the top of a flash chromatography (230–400-mesh silica gel) column. The column was eluted with acetone. Product fractions (R_f 0.31) were combined. The solvent was removed in vacuo to obtain **4** as an off-white solid; yield, 4.14 g (40%). An analytical sample was recrystallized twice from methanol/methylene chloride: mp 199–200 °C; UV λ_{max} ($\epsilon \times]0^{-3}$) 271.4 (12.6), 240.6 (15.2) nm in 0.1 N HCl, 286.4 (10.1), 238.1 (11.1), 211.4 (26.3) nm in H_2O, and 286.4 (10.1), 238.9 (11.0), 216.4 (16.6) nm in 0.1 N NaOH; MS (70 eV, 200 °C), *m/e* 274 (M^+), 256 ($M^+ - H_2O$), 243 ($M^+ - CH_2OH$), 225 ($M^+ - CH_2OH - H_2O$), 171 (B + 28), 145 (B + 2 H), 144 (B + H), 143 (B), 128, 98, 67, 43; IR (KBr) 3500–3200 (NH, OH), 1660 and 1595 cm^{-1} (C=C, C=N); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 7.12 (br s, 1 H, NH), 6.40 (s, 2 H, NH_2), 5.80 (s, 1 H, Ar H), 4.85–4.68 (2 d, 2 H, 2 CHO*H*), 4.55–4.20 (t, 1 H, CH_2OH), 3.62–3.12 (m, 5 H, 2 *CH*OH, CH_2OH, *CH*N), 2.08–1.19 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{10}H_{15}N_4O_3Cl \cdot {}^1/_2H_2O$) C, H, N, Cl.

An analytical sample of **5** was prepared by recrystallization from ethanol: mp 275–276 °C; MS (20 eV, 200 °C), *m/e* 401 (M^+), 370 ($M^+ - CH_2OH$), 342 ($M^+ - 59$), 298 (B + 28), 272 (B + 2 H), 271 (B + H), 270 (B); IR (KBr) 3500–3200 (NH, OH), 1595, 1450, 1210,

(13) In accordance with *Chemical Abstracts* nomenclature, compounds are named as 1,2-cyclopentanediols. Because compounds **9** and **13** have oxo substituents on the heterocyclic ring, they are named as a cyclopentylpurine and a 1,2,3-trizolo[4,5-*d*]pyrimidine.

980, 910, 815 cm^{-1}; NMR (90 MHz, dimethyl sulfoxide-d_6 δ 9.82 (s, 1 H, NH), 7.80–7.72 (br d, 1 H, NH), 7.54 and 6.16 (2 s, 2 H, 2 Ar *H*), 6.67 (s, 2 H, NH_2), 5.05–4.69 (2 d, 2 H, 2 CHO*H*), 4.33–4.23 (t, 1 H, CH_2OH), 3.94–3.09 (m, 5 H, 2 *CH*OH, CH_2OH, *CH*N), 2.15–1.33 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{14}H_{17}N_7O_3Cl_2 \cdot H_2O$) C, H, N, Cl.

(±)-(1α,2β,3α,5α)-3-[[2-Amino-6-chloro-5-[(4-chlorophenyl)azo]-4-pyrimidyl]amino]-5-(hydroxymethyl)-1,2-cyclopentanediol (6). A cold (0–5 °C) solution of *p*-chlorobenzenediazonium chloride was prepared by adding a solution of 650 mg (9.50 mmol) of sodium nitrite in 5 mL of water to a solution of 1.15 g (9 mmol) of *p*-chloroaniline dissolved in 5 mL of 12 N HCl and 15 mL of water and cooled in an ice/salt bath. The cold solution of *p*-chlorobenzenediazonium chloride was added to a mixture of 2.15 g (7.8 mmol) of **4**, 17 g of sodium acetate trihydrate, 40 mL of acetic acid, and 40 mL of water at room temperature. The mixture was stirred overnight at room temperature and then cooled in an ice bath. A yellow crystalline precipitate (**6**) ws collected by filtration, washed with cold water, and dried: yield, 2.22 g (69%). The product was recrystallized from methanol to yield yellow powder: mp 233–236 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 372.2 (32.4), 280.6 (11.3), 240.6 (24.6), 204.7 (21.9) nm in 0.1 N HCl, 389.8 (41.6), 315.6 (.9.5), 280.6 (15.9), 219.8 (23.9) nm in MeOH, and 384.75 (16.3), 215.6 (17.2) nm in 0.1 N NaOH; MS (70 eV, 200 °C), *m/e* 412 (M^+), 286, 283 (B + 2 H), 281 (B), 268, 238, 210, 182, 158, 146, 127, 114, 95, 65, 43; IR (KBr) 3400–3100 (OH, NH), 1655, 1645, 1590, 1570 cm^{-1} (Ar, C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 7.78–7.54 (m, 7 H, Ar H, NH_2, NH), 5.06–5.02 (m, 2 H, 2CHO*H*), 4.41–4.30 (t, 1 H, CH_2OH), 3.89–3.30 (m, 5 H, CH_2OH, 2 *CH*OH, *CH*N), 2.31–1.22 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{16}H_{18}N_6O_3Cl_2 \cdot H_2O$) C, H, N, Cl.

(±)-(1α,2β,3α,5α)-3-[(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]-5-(hydroxymethyl)-1,2-cyclopentanediol (7). A solution of 2.00 g (4.84 mmol) of **6**, 3.2 g of zinc dust (200 mesh), 1.6 mL of acetic acid, 75 mL of water, and 75 mL of ethanol was refluxed under an atmosphere of nitrogen. The reaction was followed by TLC and was completed within 1.5 h. Excess of zinc was removed by filtration, and the solvent was evaporated to dryness. The brown residue was dissolved in 50 mL of water, and the aqueous solution was washed with methylene chloride to remove *p*-chloroaniline. After removal of water under reduced pressure, the residue was evaporated onto coarse silica gel (70–230 mesh) and applied to the top of a flash chromatography column (230–400-mesh silica gel). The column was eluted with methylene chloride/methanol (4:1). The product fractions (R_f 0.28) were collected, combined, and evaporated to dryness and gave 759 mg (54%) of pink solid. Recrystallization from methanol/methylene chloride and then from water gave **7** as a light pink solid: mp 187–190 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 295.6 (8.3), 238.9 (16.3), 210.6 (16.2) nm in 0.1 N HCl, 303.1 (8.8), 204.8 (18.9) nm in H_2O, and 303.1 (8.9), 224.8 (12.2) nm in 0.1 N NaOH; MS (70 eV, 200 °C), *m/e* 289 (M^+), 240 (B + 14), 160 (B + 2 H), 159 (B + H), 158 (B), IR (KBr) 3500–3100 (NH, OH) 1635, 1605, 1510 cm^{-1} (C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 6.46–6.38 (d, 1 H, NH), 5.66 and 3.93 (2 d, 4 H, 2 NH_2), 4.82–4.69 (2 d, 2 H, 2 CHO*H*), 4.31–4.19 (t, 1 H, CH_2OH), 3.72–3.32 (m, 5 H, 2 *CH*OH, CH_2OH, *CH*N), 2.17–1.35 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{10}H_{16}N_5O_3Cl$) C, H, N, Cl.

(±)-(1α,2β,3α,5α)-3-(2-Amino-6-chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (8). A solution of 100 mg (0.345 mmol) of **7** and 3 mL of dry dimethylformamide was cooled to 0 °C, and 5 mL of freshly distilled triethyl orthoformate and 0.1 mL of concentrated HCl were added. The resulting mixture was stirred under nitrogen at room temperature for 24 h. The solvent was evaporated in vacuo to a dark red syrup. The syrup was dissolved in 10 mL of 50% acetic acid and stirred at room temperature for 4 h. The solvent was then removed under reduced pressure, and the residue was stirred with methanolic ammonia (10% NH_3) at room temperature for 4 h. The volatile materials were removed in vacuo, and the product was dissolved in methanol/methylene chloride and refrigerated overnight. The crystallized product was removed by filtration and gave 52.9 mg (52%) of **8** as a light pink solid. An analytical sample was recrystallized from water to give **8** as an off-white solid: mp 165–167 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 313.1 (7.5), 243.1 (6.2), 221.4 (25.6) nm in 0.1 N HCl, 306.4 (7.4), 223.9 (25.9) nm in H_2O, and 307.2 (7.8), 249.8 (7.1), 223.9 (24.6) nm in 0.1 N NaOH; MS (20 eV, 200 °C), *m/e* 299 (M^+), 282 (M^+ – OH), 268 (M^+ – CH_2OH), 250 (M^+ – CH_2OH – H_2O), 196 (B + 28), 170 (B + 2), 169 (B + 1), 168 (B), 134, 81; IR (KBr) 3500–3000 (NH_2, OH), 1635, 1560, 1465 cm^{-1} (C=C, C=N); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 8.15 (s, 1 H, Ar H), 6.86 (s, 2 H, NH_2), 5.36–5.05 (2 d, 2 H, 2 CHO*H*), 4.53–4.38 (t, 1 H, CH_2OH), 4.17–3.11 (m, 5 H, 2 *CH*OH, CH_2OH, *CH*N), 2.26–1.70 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{11}H_{14}N_5O_3Cl$) C, H, N, Cl.

(±)-2-Amino-1,9-dihydro-9-[(1α,2β,3α,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-6*H*-purin-6-one (9). A solution of 100 mg (0.345 mmol) of **7** and 3 mL of dry dimethylformamide was cooled to 0 °C, and 5 mL of freshly distilled triethyl orthoformate and 0.1 mL of concentrated HCl were added. The reaction mixture was stirred under nitrogen at room temperature for 24 h. The solvent was evaporated, and the residue was dissolved in 10 mL of 1 N HCl. The solution was refluxed for 5 h, and then the water was evaporated and azeotroped with absolute ethanol. The liquid residue was dissolved in a small amount of water, and the solution was neutralized to pH with 1 N NaOH. A white precipitate formed immediately, and the suspension was refrigerated. The solid product was collected by filtration and washed with cold water to yield 63.2 mg (65%) of off-white powder: mp 254–256 °C. An analytical sample was recrystallized from water: mp 291–293 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 255.6 (12.4), 202.2 (41.75) nm in 0.1 N HCl, 253.1 (14.7), 189.8 (31.7) nm in H_2O, and 268.1 (12.4), 217.2 (18.9) nm in 0.1 N NaOH; MS (70 eV, 200 °C), *m/e* 281 (M^+), 264 (M^+ – OH), 178 (B + 28), 152 (B + 2 H), 128, 98, 81, 67, 43; IR (KBr) 3400–3150 (NH, OH), 1725 (C=O), 1640, 1550, 1490 cm^{-1} (C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 10.54 (s, 1 H, NH), 7.71 (s, 1 H, Ar H), 6.39 (s, 2 H, NH_2), 5.32–5.04 (2 d, 2 H, 2 CHO*H*), 4.41–4.30 (t, 1 H, CH_2OH), 4.24–3.32 (m, 5 H, 2 CHO*H*, CH_2OH, *CH*N), 2.28–1.38 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{11}H_{15}N_5O_4 \cdot 1^1/_2H_2O$) C, H, N.

(±)-(1α,2β,3α,5α)-3-(2,6-Diamino-9*H*-purin-9-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (10). A solution of 61.2 mg (0.204 mmol) of the chloro compound **8** in 2 mL of methanol was transferred into a stainless steel bomb, and the methanol was evaporated by a stream of nitrogen. Excess ammonia was added, and the sealed bomb was heated at 80 °C for 2 days. Evaporation of the ammonia left a yellow residue, which was dissolved in 5 mL of hot water. Refrigeration of the solution yielded 41.0 mg (72%) of pale yellow semisolid. Recrystallization from water afforded **10** as a pale yellow powder: mp 234–237 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 291.4 (9.7), 253.1 (9.5), 218.9 (20.8) nm in 0.1 N HCl, 279.8 (10.5), 255.6 (8.6), 215.6 (28.1) nm in H_2O, and 280.6 (10.2), 255.6 (8.1), 218.9 (22.5) nm in 0.1 N NaOH; MS (70 eV, 200 °C), *m/e* 280 (M^+), 263 (M^+ – OH), 249 (M^+ – CH_2OH), 231 (M^+ – CH_2OH – H_2O), 177 (B + 28), 163 (B + 14), 151 (B + 2), 150 (B + 1), 149 (B), 134, 108, 57, 43, 28; IR (KBr) 3600–3100 (OH, NH_2), 1665, 1600, 1495 cm^{-1} (C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 7.73 (s, 1 H, Ar H), 6.69 (s, 2 H, NH_2), 6.61 (s, 2 H, NH_2), 5.86–5.77 (m, 2 H, 2 CHO*H*), 4.36–3.67 (m, 6 H, *CH*N, CH_2OH, 2 *CH*OH, CH_2OH), 2.21–1.82 (m, 3 H, *CH*CH_2OH, CH_2). Anal. ($C_{11}H_{16}N_6O_3$) C, H, N.

(±)-(1α,2β,3α,5α)-3-(5-Amino-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (11). A solution of 26.0 mg (0.380 mmol) of sodium nitrite in 1 mL of water was dropwise added to a cold (0 °C) solution of 100 mg (0.345 mmol) of **7** in 1 mL of water and 0.5 mL of glacial acetic acid. The solution was stirred at 0 °C for 2 h and at room temperature for 1 h. The solvent was removed in vacuo (below 20 °C), and the residue was evaporated onto silica gel and then applied to the top of a flash chromatography column. The column was eluted with methylene chloride/methanol (4:1). The product fractions were collected (R_f 0.53), combined, and concentrated in vacuo to obtain 73.0 mg (70%) of colorless solid, mp softens at 130–150 °C and melts at 220–230 °C. An analytical sample of **11** was obtained by recrystallization from methanol: mp softens at 121 °C and melts at 220–223 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 314.8 (8.6), 225.6 (24.1) nm in 0.1 N HCl, 314.8 (8.2), 225.6 (24.4) nm in H_2O, and 222.2 (24.3) in 0.1 N NaOH; MS (20 eV, 250 °C), *m/e* 283 (M^+ – OH), 171 (B + 2 H), 170 (B + H), 169 (B), 144, 112, 84, 69; IR (KBr) 3600–3250 (OH, NH_2), 1650, 1610, 1470 cm^{-1}

(C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 7.60 (s, 2 H, NH_2), 5.35–5.29 (d, 1 H, CHO*H*), 5.00–4.95 (d, 1 H, CHO*H*), 4.62–3.60 (m, 6 H, CH*N*, CH_2O*H*, CH_2OH, 2 C*H*OH), 2.23–2.15 (m, 3 H, C*H*CH_2OH, CH_2). Anal. ($C_{10}H_{13}N_6O_3Cl\cdot H_2O$) C, H, N, Cl.

(±)-(1α,2β,3α,5α)-3-(5-Amino-7-methoxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (12). A solution of 54.1 mg (0.179 mmol) of **11** in methanol was heated under reflux for 1 h. The solvent was evaporated to dryness ot obtain 42 mg (80%) of **12** as a colorless semisolid. Crystallization from methanol gave 28.2 mg (53%) of pure solid product: mp 157–159 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 282.2 (10.7), 213.9 (23.6) nm in 0.1 N HCl, 287.2 (9.7), 216.4 (23.4) nm in H_2O, and 285.6 (10.6), 218.9 (22.9) nm in 0.1 N NaOH; MS (30 eV, 220 °C); *m/e* 296 (M^+), 283, 247 ($M^+ - CH_2OH - H_2O$), 223, 209, 181, 167 (B + 2 H), 166 (B + H), 165 (B), 139, 110, 96, 83, 67, 53, 43; IR (KBr) 3500–3200 (NH_2, OH), 1665, 1610, 1465 cm^{-1} (C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 7.07 (s, 2 H, NH_2), 5.34–5.28 (d, 1 H, CHO*H*), 4.99–4.93 (d, 1 H, CHO*H*), 4.58–3.51 (m, 6 H, C*H*N, CH_2O*H*, CH_2OH, 2 C*H*OH), 4.05 (s, 3 H, OCH_3), 2.47–1.55 (m, 3 H, C*H*CH_2OH, CH_2). Anal. ($C_{11}H_{16}N_6O_4\cdot H_2O$) C, H, N.

(±)-5-Amino-3,6-dihydro-3-[(1α,2β,3α,5α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (13). A solution of 91.3 mg (0.304 mmol) of **11** in 10 mL of 1 N HCl was refluxed for 5 h. The solvent was removed in vacuo, and the resulting yellow solid was crystallized from water and afforded 47.0 mg (55%) of pale yellow powder, mp 235–238 °C dec. A second recrystallization from water gave pure **13** as pale yellow crystalline solid: mp 241–244 °C dec; UV λ_{max} ($\epsilon \times 10^{-3}$) 253.9 (12.3), 207.2 (20.8) nm in 0.1 n HCl, 253.1 (12.4), 203.1 (23.1) nm in H_2O, and 278.9 (11.6), 220.6 (25.6) nm in 0.1 N NaOH; MS (20 eV, 200 °C), *m/e* 187, 167, 153 (B + 2 H), 134, 121, 107, 84, 70; IR (KBr) 3600–3200 (NH_2, OH), 1710 (C=O), 1600, 1530 cm^{-1} (C=C, C=N); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 11.20 (s, 1 H, NH), 7.18 (s, 2 H, NH_2), 5.37–5.63 (d, 1 H, CHO*H*), 5.02–4.96 (d, 1 H, CHO*H*), 4.41–3.32 (m, 6 H, C*H*N, CH_2O*H*, CH_2OH, 2 C*H*OH), 2.28–2.01 (m, 3 H, C*H*CH_2OH, CH_2). Anal. ($C_{10}H_{14}N_6O_4\cdot {}^3/_4H_2O$) C, H, N.

(±)-(1α,2β,3α,5α)-3-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (14). A mixture of 94.1 mg (0.313 mmol) of **11** in liquid ammonia was heated in a stainless bomb at 80 °C for 48 h. Evaporation of ammonia left a solid residue, which was crystallized from water and afforded 47.2 mg (54%) of pale yellow solid, mp 219–224 °C. Recrystallization from water afforded pure **14** as a pale yellow powder: mp 231–233 °C; UV λ_{max} ($\epsilon \times 10^{-3}$) 286.4 (8.1), 256.4 (10.1), 213.9 (26.6) nm in 0.1 N HCl, 287.2 (11.3), 260.6 (6.4), 223.9 (27.2) nm in H_2O, and 286.4 (11.6), 260.6 (6.8), 223.9 (28.5) nm in 0.1 N NaOH; MS (30 eV, 330 °C), *m/e* 281 (M^+), 232, 194, 163, 152 (B + 2 H), 150 (B), 126, 113, 110, 43; IR (KBr) 3600–3250 (OH, NH_2), 1610, 1645, 1460 cm^{-1} (C=C, C=N, NH); NMR (90 MHz, dimethyl sulfoxide-d_6) δ 7.53 (s, 2 H, NH_2), 6.34 (s, 2 H, NH_2), 5.37–5.31 (d, 1 H, CHO*H*), 5.06–5.00 (d, 1 H, CHO*H*), 4.55–3.52 (m, 6 H, C*H*N, CH_2O*H*, CH_2OH, 2 C*H*OH), 2.26–2.05 (m, 3 H, C*H*CH_2OH, CH_2). Anal. ($C_{10}H_{15}N_7O_3\cdot {}^1/_4H_2O$) C, H, N.

Antiviral Evaluations. The methods and procedures used to evaluate compounds 8–14 for antiviral activity against HSV-1 and HSV-2 have been described previously.[14,15] These compounds were tested for inhibition of cytopathogenic effects produced by strain 377 of HSV-1 or strain MS of HSV-2 replicating in African green monkey kidney (Vero) cells.

CMV: Subconfluent monolayers of MRC5 cells, grown in 35-mm wells of Falcon six-well tissue culture plates, were each rinsed with PBS and exposed to 0.5 mL (1000 $CCID_{50}$) of CMW suspension in MEM plus 2% FBS for $1^1/_2$ h at 37 °C. The virus inocula were aspirated, and the infected cell layers were rinsed with PBS. Duplicate infected cell layers were fed with 2.0-mL aliquots of each drug concentration (dissolved and diluted in MEM plus 2% FBS). Virus controls and cell controls were fed with medium alone. Uninfected, drug-treated cell cultures served as cytotoxicity controls. The cultures were incubated at 37 °C in a humidified atmosphere of 2.0% CO_2 in air. On days 3 and 7 postinfection (p.i.), the culture medium was aspirated and replaced with fresh drug and/or medium. The cell monolayers were examined microscopically on day 10 p.i. for virus-induced CPE and harvested. The cultures were frozen and thawed to disrupt the cells. The cellular material was scraped into the medium, and the contents from replicate cultures were pooled, dispensed into cryotubes, and stored in liquid nitrogen. The harvested samples were later thawed and titrated for infectious virus yield by a virus induced plaque assay procedure in MRC5 cell cultures grown in 12-well cluster plates.

VZV: The host cells (human foreskin fibroblasts) were grown as monolayer cultures in 24-mm wells of 12-well cluster plates. The cell cultures were exposed to 0.5-mL aliquots of VZV suspension for 1 h at 37 °C, and then 0.5-mL aliquots of each test drug concentration were added to triplicate virus-infected cell cultures. After 3 days' incubation at 37 °C, the culture fluids were replaced with fresh drug and medium. At 6 days post virus infection the cultures were fixed with formalin and stained with methylene blue. The foci of CPE (plaques) were counted. Antiviral activity was expressed as the reduction (%) in the number of plaques in the drug-treated virus-infected cultures as compared with the number of plaques in the untreated virus-infected control cultures.

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