13, 140927-04-4; 14, 46407-09-4; 15, 50494-50-3; 16, 140927-05-5; 17, 140927-06-6; 17·2,3-dihydroxybenzoate salt, 140927-19-1; 18, 542-92-7; 19, 140927-07-7; 20, 140927-08-8; 21, 140927-09-9; 22, 140927-10-2; 22·fumarate, 140927-20-4; 23, 140927-11-3; 23·2,3-dihydroxybenzoate salt, 140927-21-5; 24, 140927-12-4; 25, 141017-63-2; 26, 140927-13-5; 27, 140927-14-6; 28, 140927-15-7; 29, 140927-16-8; 29·citrate, 140927-22-6; 30, 140927-17-9; 30·fumarate, 140927-23-7.

(±)-Carbocyclic 5′-Nor-2′-deoxyguanosine and Related Purine Derivatives: Synthesis and Antiviral Properties

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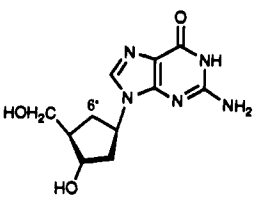
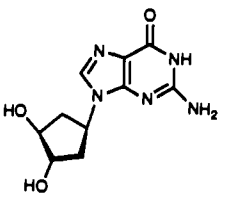
Beginning with 3-cyclopenten-1-ylamine hydrochloride, the 5′-nor derivatives of carbocyclic 2′-deoxyguanosine (2), 2′-deoxyadenosine (3), and 2,6-diaminopurine 2′-deoxyribofuranoside (4) have been prepared. These compounds were evaluated for antiviral potential versus herpes simplex virus, varicella-zoster virus, cytomegalovirus, vaccinia virus, vesicular stomatitis virus, and human immunodeficiency virus and found to lack activity. Also, compounds 2–4 were virtually nontoxic toward the host (human diploid fibroblast ESM and HEL) cells. These biological properties may be due to the inability of 2–4 to be phosphorylated to the requisite nucleotide level that is likely to be necessary for biological activity by correlation to carbocyclic 2′-deoxyguanosine (1), which possesses significant antiviral properties as a result of conversion to its 5′-triphosphate derivative.

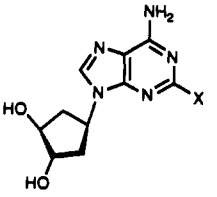
Racemic[1] and D-carbocyclic[2] 2′-deoxyguanosine (represented as 1) have shown significant antiviral activity as a result of selective conversion to their 5′-triphosphate derivatives.[3] Recent studies[4–8] focusing on the development of antiviral agents derived from nucleosides lacking the C-5′ carbon prompted a synthesis and evaluation of (±)-2 as the 5′-nor derivative of 1. The results of this investigation, which also included the adenine (3)[9] and 2,6-diaminopurine (4) derivatives, are presented in this report.



1



2



3, X=H
4, X=NH2

Chemistry

A convenient starting material for the synthesis of 2–4 was determined to be (±)-(1α,3β,4α)-3,4-dihydroxycyclopent-1-ylamine (5, Scheme I), which was prepared from 3-cyclopenten-1-ylamine hydrochloride (6)[10] and stored as the triacyl derivative 10. To achieve 5, benzoylation of 6 to 7 was followed by epoxidation to give the diastereomeric mixture of 8 and a small amount of 9. The ^{1}H NMR data for the benzamide NH and the oxirane protons was used to distinguish 8 and 9. In that regard, the NH region for 8 (δ 7.3–7.7) is shielded by the *cis*-oxirane oxygen relative to the NH in 9 (δ 8.31), whereas the oxirane protons in 9 (δ 3.54) are shielded by the *cis*-nitrogen when compared to the oxirane protons in 8 (δ 3.57). This cis stereochemistry of 8 is corroborated by an X-ray structural analysis of compound 3[11] and by similar observations for the products resulting from epoxidation of the benzamide derivative of 2-cyclopenten-1-ylamine[12] and 2-cyclo-

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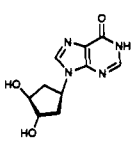
(9) A preliminary account of the synthesis of 3 and the hypoxanthine analogue i appeared in ref 4.



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(11) The X-ray data for compound 3 is available as supplementary material.

0022-2623/92/1835-2191$03.00/0

Table I.[a] Anti-HSV, -VV, and -VSV Activity and Cytotoxicity of Compounds 2–4 in ESM Cell Cultures

	minimum inhibitory concentration[b] (μg/mL)						
compd	HSV-1 (KOS)	HSV-2 (G)	VV	VSV	HSV-1 TK⁻ (B2006)	HSV-1 TK⁻ (VMW 1837)	minimum cytotoxic concn[c] (μg/mL)
2	300	300	300	>400	300	150	>400
3	>200	>200	>100	>200	70	100	≥400
4	>200	>200	150	>200	100	150	≥400
BVDU	0.07	10	1	>400	100	10	>400
ribavirin	>400	>400	70	150	300	40	>400
C-c³Ado	>400	300	2	0.7	>400	40	>400

[a] Abbreviations: HSV, herpes simplex virus; VV, vaccinia virus; VSV, vesicular stomatitis virus; ESM, embryonic skin muscle (cells); TK⁻, thymidine kinase deficient. [b] Required to reduce virus-induced cytopathogenicity by 50%; virus input was 100 $CCID_{50}$ (1 $CCID_{50}$ being the infective dose for 50% of the cell cultures). [c] Required to cause a microscopically detectable alteration of normal cell morphology.

Table II.[a] Anti-CMV and Anti-VZV Activity and Cytotoxicity of Compounds 2–4 in HEL Cell Cultures

	minimum inhibitory concentration[b] (μg/mL)							
	CMV (AD-169)	CMV (Davis)		VZV				
compd	100 PFU	20 PFU	100 PFU	OKA 20 PFU	YS TK⁻ PFU	07/1 TK⁻	YS/R TK⁻	minimum cytotoxic concn[c] (μg/mL)
2	250	270	250	90	91	164	192	196
3	200	200	200	24	25	24	47	110
4	70	70	70	70	200	70	89	139
DHPG	0.8	0.3	3	*d*	–	–	–	89
ACV	–	–	–	0.3	0.09	25	28	188
BVDU	–	–	–	0.001	0.0007	>10	>10	–

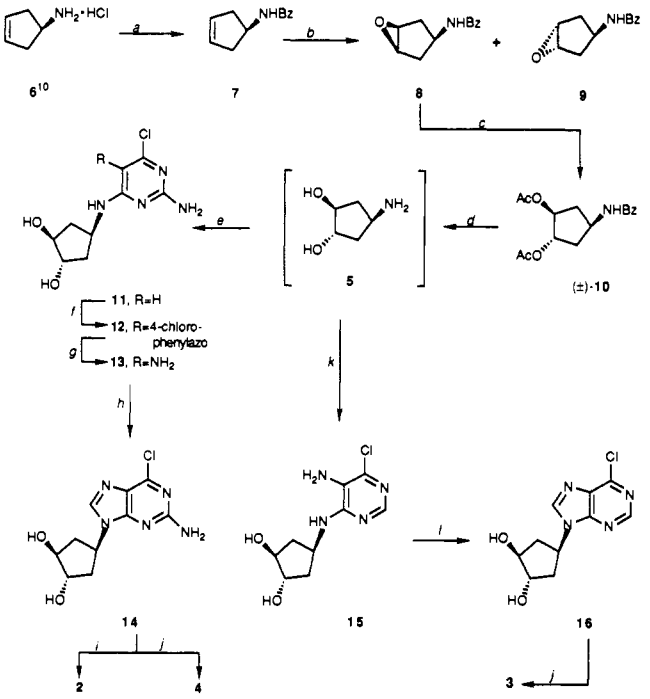
[a] Abbreviations: CMV, cytomegalovirus; VZV, varicella-zoster virus; HEL, human embryonic lung (cells). [b] Required to reduce virus plaque formation by 50%; virus input was 20 or 100 plaque forming units (PFU) as indicated. [c] Required to reduce cell growth by 50%. [d] Not determined.

hexen-1-ylamine.[13] Ring opening of **8** with dilute sulfuric acid followed by acetylation of the resultant *trans*-diol gave **10**.

With **10** available, its hydrolysis with dilute acid yielded **5**, which was not characterized but was treated with 2-amino-4,6-dichloropyrimidine to give **11**. Following a standard purine ring construction method, diazo coupling of **11** with 4-chlorobenzenediazonium chloride produced **12**. Reduction of **12** to triamine **13** was followed by ring closure to purine **14** using diethoxymethyl acetate. Treatment of **14** with (i) dilute hydrochloric acid yielded **2** and (ii) ammonia in methanol formed **4**.

Reaction of **5** with 5-amino-4,6-dichloropyrimidine (Scheme I) gave the diaminopyrimidine **15** that was converted into purine **16** with triethyl orthoformate. Ammonolysis of **16** resulted in the desired adenosine derivative **3**.

Scheme I[a]



[a] Reaction conditions: (a) BzCl/pyridine/Et_3N in $CHCl_3$; (b) *m*-chloroperoxybenzoic acid in $CHCl_3$; (c) (i) 2% aqueous H_2SO_4, then neutralize; (ii) Ac_2O/pyridine; (d) 6 N HCl, reflux; (e) 2-amino-4,6-dichloropyrimidine in 1-BuOH containing Et_3N, reflux; (f) 4-chlorobenzenediazonium chloride and AcONa in AcOH/H_2O; (g) Zn in AcOH/EtOH/H_2O, reflux; (h) (i) diethoxymethyl acetate; (ii) 0.5 N HCl; (i) 1 N HCl, reflux; (j) NH_3 in MeOH, 100 °C, 48 h; (k) 5-amino-4,6-dichloropyrimidine in 1-BuOH containing Et_3N, reflux; (l) $(EtO)_3CH$ and concentrated HCl.

Antiviral Results

Unlike compound **1**, which has been shown to have marked activity against herpes viruses,[1-3] compounds **2–4** did not prove inhibitory to these (HSV-1, HSV-2, VZV, and CMV) and other viruses (VV and VSV) (Tables I and II) that included the wild-type thymidine kinase-positive (TK^+) variants of HSV-1 or VZV and thymidine kinase-deficient (TK^-) mutants thereof. The compounds were also inactive against human immunodeficiency virus (HIV-1, HIV-2) [even at a concentration up to 500 μM (data not shown)]. In all these tests, the appropriate reference compounds, i.e. (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), ribavirin (virazole), carbocyclic 3-de-

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azaadenosine (C-c^{3}Ado), ganciclovir [9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG)], acyclovir [9-[(2-hydroxyethoxy)methyl]guanine (ACV)], and zidovudine [3'-azido-2',3'-dideoxythymidine (AZT)], were included, and these compounds gave the expected results. Not only were compounds **2–4** inactive as antiviral agents, they also exhibited little or no toxicity for the host cells [human embryonic skin–muscle (ESM) (Table I) or human embryonic lung (HEL) fibroblasts (Table II)]. The lack of biological activity for compounds **2–4** probably resides in their inability to be phosphorylated to the requisite nucleotide level. This is in contrast to compound **1**, which has been shown to be preferentially phosphorylated by the virus-encoded kinase.[3]

Experimental Section

Melting points were recorded on a Mel-Temp capillary melting point apparatus and are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer (operated at 90 and 22.5 MHz, respectively) referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), m (multiplet), and br (broad). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck Silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Aldrich silica gel (230–400 mesh, 60 Å) eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

***N*-(3-Cyclopenten-1-yl)benzamide (7).** 3-Cyclopenten-1-ylamine hydrochloride (**6**)[10] (3 g, 25.08 mmol) was dissolved in pyridine (200 mL), $CHCl_3$ (300 mL), and Et_3N (3 g, 79.06 mmol), and this mixture was cooled by placing in ice–H_2O. To this mixture was added dropwise benzoyl chloride (7.5 g, 53.35 mmol) under an Ar atmosphere, and stirring was continued for 1 h. To the solution were added ice–H_2O and $CHCl_3$. The mixture was extracted with $CHCl_3$ and washed with H_2O. The extracts was evaporated to dryness and azeotroped with toluene and $CHCl_3$. The residue was purified by flash chromatography, and the fraction eluted with 20% hexane in $CHCl_3$ was recrystallized from $CHCl_3$–hexane to give **7** (4.13 g, 88%) as colorless needles: mp 126 °C; ^{1}H NMR (DMSO-d_6) δ 2.2–2.9 (m, 4 H, H-2 and H-5), 4.4–4.8 (m, 1 H, H-1), 5.73 (s, 2 H, H-3 and H-4), 7.3–7.6 and 7.8–8.0 (m, 5 H, Ar), 8.52 (d, 1 H, J = 7 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 39.17 (C-2 and C-5), 49.19 (C-1), 127.42, 128.18, 131.05, and 134.73 (C of Ar). Anal. ($C_{12}H_{13}NO$) C, H, N.

(1α,3β,5α)-*N*-(6-Oxabicyclo[3.1.0]hex-3-yl)benzamide (8). To a solution of **7** (4.00 g, 21.36 mmol) in $CHCl_3$ (300 mL) was added slowly *m*-chloroperoxybenzoic acid (5.6 g, ca. 80%, 25.96 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then cooled (ice–H_2O), and saturated aqueous $NaHCO_3$ solution was added. The $CHCl_3$ solution was washed with saturated aqueous $NaHCO_3$ solution, and the extracts were evaporated to dryness with the aid of a rotary evaporator. The residue was purified by flash chromatography, and the fraction eluting with $CHCl_3$ was recrystallized from $CHCl_3$–hexane to give **8** (4.165 g, 96%) as colorless needles: mp 84 °C; ^{1}H NMR (DMSO-d_6) δ 1.9–2.2 (m, 4 H, H-2 and H-4), 3.57 (s, 2 H, H-1 and H-5), 4.2–4.5 (m, 1 H, H-3), 7.3–7.7 (m, 4 H, NH and H-3, H-4, and H-5 of Ar), 7.7–8.0 (m, 2 H, H-2 and H-6 of Ar); ^{13}C NMR (DMSO-d_6) δ 34.94 (C-2 and C-4), 46.48 (C-3), 56.94 (C-1 and C-5), 127.09, 128.23, 131.05, and 134.62 (C of Ar), 165.01 (C=O). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

The fraction that eluted with 1% MeOH in $CHCl_3$ was recrystallized from $CHCl_3$–hexane to give the (1α,3α,5α)-isomer **9** (95 mg, 2%) as colorless needles: mp 153 °C; ^{1}H NMR (DMSO-d_6) δ 1.5–1.9 and 2.2–2.5 (m, 4 H, H-2 and H-4), 3.54 (s, 2 H, H-1 and H-5), 3.9–4.2 (m, 1 H, H-3), 7.3–7.6 (m, 3 H, H-3, H-4, and H-5 of Ar), 7.7–7.9 (m, 2 H, H-2 and H-6 of Ar), 8.31 (d, J = 8 Hz, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 33.21 (C-2 and C-4), 44.85 (C-3), 55.04 (C-1 and C-5), 127.28, 127.31, 131.15, and 134.57 (C of Ar), 166.04 (C=O).

(±)-(1α,3α,4β)-*N*-[3,4-Bis(acetyloxy)cyclopentyl]benzamide (10). A solution of **8** (3.5 g, 17.24 mmol) in 2% aqueous H_2SO_4 solution (200 mL) was stirred for 1 h at room temperature. The reaction mixture was cooled (ice–H_2O) and then neutralized with 6 N aqueous NaOH solution to pH 7 (using pH paper). The solution was evaporated to dryness with the aid of a rotary evaporator, and the residue was azeotroped with MeOH (3 × 50 mL) and then pyridine. The residue remaining after these procedures was assumed to be the *trans*-diol that was used directly in the next reaction.

To the *trans*-diol in pyridine (150 mL) was added dropwise acetic anhydride (150 mL). The mixture was stirred overnight at room temperature under Ar and then evaporated to dryness using a rotary evaporator. The material remaining was azeotroped with toluene (3 × 100 mL), MeOH (3 × 50 mL), and $CHCl_3$ (3 × 50 mL). The residue following the azeotrope procedure was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with saturated aqueous $NaHCO_3$ solution and evaporated to dryness with the aid of a rotary evaporator. The residue was recrystallized from hexane to give **10** (5.013 g, 95% based on **8**) as colorless needles: mp 95 °C; ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 6 H, 2 × Me) overlapped by 1.5–2.7 (m, 4 H, H-2 and H-5), 4.3–4.6 (m, 1 H, H-1), 4.9–5.3 (m, 2 H, H-3 and H-4), 7.2–7.5 (m, 3 H, H-3, H-4, and H-5 of Ar), 7.6–7.9 (m, 2 H, H-2 and H-6 of Ar), 8.52 (d, J = 7 Hz, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 20.80 (2 × Me), 36.24 (C-2 and C-5), 46.97 (C-1), 76.93 (C-3 and C-4), 127.36, 128.23, 131.21, and 134.46 (C of Ar), 166.15 (C=O of benzoyl), 169.78 (C=O of acetyl). Anal. ($C_{16}H_{19}NO_5$) C, H, N.

(±)-(1α,2β,4α)-4-[[2-Amino-6-chloro-5-[(4-chlorophenyl)azo]pyrimidin-4-yl]amino]-1,2-cyclopentanediol (12). A mixture of **10** (4 g, 13.1 mmol) in 6 N HCl (200 mL) was heated under reflux and N_2 for 24 h. The reaction mixture was evaporated to dryness in vacuo, and the residue was azeotroped with MeOH (2 × 50 mL). The material thus obtained was dissolved in MeOH and treated with IRA-400 (basic) resin to pH 8–10. The resin was removed by filtration and washed with MeOH, and the filtrate was evaporated to dryness under reduced pressure. The oily residue of (±)-(1α,2β,4α)-4-amino-1,2-cyclopentanediol (**5**) that resulted was used directly in the next reaction.

A mixture of compound **5**, 2-amino-4,6-dichloropyrimidine (3.2 g, 19.5 mmol), and Et_3N (13 mL) in 1-butanol (75 mL) was refluxed under N_2 for 2 days. The solvent was removed under reduced pressure, and the residue was treated with H_2O (not completely soluble). This aqueous mixture was washed with CH_2Cl_2 (2 × 150 mL) to remove the excess 2-amino-4,6-dichloropyrimidine and then treated with IRA-400 (basic) resin to pH 8–10. This mixture was shaken and filtered to remove the resin, which was washed with H_2O. The combined filtrates were evaporated under reduced pressure, and the residue was azeotroped with absolute EtOH. The resultant material was purified by flash chromatography using 5–10% MeOH in CH_2Cl_2 to give (±)-(1α,2β,4α)-4-[(2-amino-6-chloropyrimidin-4-yl)amino]-1,2-cyclopentanediol (**11**) as a colorless, viscous liquid (2.99 g, which contained a minor, polar impurity that could not be completely removed) that was used in the next step: ^{1}H NMR (DMSO-d_6) δ 1.4–2.4 (m, 4 H, H-3 and H-5), 3.8–4.2 (m, 2 H, H-1 and H-2), 4.3–4.6 (m, 1 H, H-4), 5.1 and 5.25 (2 d, J = 3.3 Hz, 2 H, 2 × OH), 6.35 (s, 1 H, H-5 of pyrimidine), 7.1 (br s, 2 H, NH_2), 7.95 (d, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 39.72 and 40.26 (C-3 and C-5), 48.44 (C-4), 77.32 and 77.43 (C-1 and C-2), 93.19, 158.10, 163.51, and 164.10 (C of pyrimidine).

A cold solution of 4-chlorobenzenediazonium chloride was prepared by adding a solution of $NaNO_2$ (0.31 g, 4.54 mmol) in H_2O (2.5 mL) to a solution of 4-chloroaniline (0.55 g, 4.3 mmol) dissolved in 12 N HCl (2.5 mL) and H_2O (7.5 mL) that was cooled in an ice bath. The cold solution of 4-chlorobenzenediazonium chloride was added dropwise, with stirring, to a mixture of **11** (0.91 g, 3.73 mmol), sodium acetate trihydrate (8.12 g), glacial AcOH (19 mL), and H_2O (19 mL) at room temperature. Even though a yellow precipitate began to slowly form, the reaction mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath, and the yellow precipitate was isolated by filtration, washed with cold H_2O, and dried. Recrystallization from MeOH gave **12** (1.08 g, 75.5%) as yellow crystals: mp 250–251 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.42–2.4 (m, 4 H, H-3 and H-5), 3.75–4.15 (m, 2 H, H-1 and H-2), 4.5–5.25 (m, 3 H, H-4 and

2 × OH), 7.35–7.9 (m, 6 H, Ar and NH_2), 10.65 (d, 1 H, NH). Anal. ($C_{15}H_{16}Cl_2N_6O_2$) C, H, N.

(±)-(1α,2β,4α)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-1,2-cyclopentanediol (14). A mixture of **12** (1 g, 2.6 mmol), zinc dust (1.7 g), and glacial AcOH (1 mL) in EtOH (45 mL) and H_2O (45 mL) was refluxed under N_2 (80–85 °C, oil bath temperature) for 5 h (until the yellow color of **12** had disappeared). The reaction mixture was filtered hot, and the insoluble material was washed with hot EtOH. The combined filtrates were evaporated under reduced pressure. The residue was dissolved in H_2O, and then the aqueous solution was washed with CH_2Cl_2 to remove 4-chloroaniline. After removal of the H_2O under reduced pressure, the residue was azeotroped with absolute EtOH, and the material that remained following this was purified by flash chromatography ($MeOH–CHCl_3$, 1:5) to give (±)-(1α,2β,4α)-4-[(2,5-diamino-6-chloropyrimidin-4-yl)amino]-1,2-cyclopentanediol (**13**) as a faint pink solid (440 mg, 65%): mp 156–160 °C dec; ^1H NMR (DMSO-d_6) δ 1.2–2.4 (m, 4 H, H-3 and H-5), 3.6–4.1 and 4.3–4.95 (m, 5 H, H-1, H-2, H-4, and 2 × OH), 5.57 (br s, 2 H, NH_2), 6.35 (d, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 39.28 and 39.82 (C-3 and C-5), 48.38 (C-4), 76.77 and 76.98 (C-1 and C-2), 113.17, 141.23, 154.83, and 155.86 (C of pyrimidine). Compound **13** was not very stable and was used directly in the subsequent preparation of **14**.

Compound **13** (259 mg, 1 mmol) in diethoxymethyl acetate (5 mL) was stirred at room temperature for 1 h, and the clear solution was then stirred at 80 °C for 20 h under N_2. The excess diethoxymethyl acetate was removed under reduced pressure, and the residue was dissolved in 0.5 N HCl (15 mL). This solution was stirred at room temperature for 30 min. The H_2O was then removed under reduced pressure, and the residue was azeotroped with MeOH. The new residue was dissolved in MeOH, and the solution was neutralized with IRA-400 (basic) resin. Removal of the resin by filtration and evaporation of the methanolic filtrate under reduced pressure gave crude product as a pale yellow solid that was purified by flash chromatography ($MeOH–CHCl_3$, 15:85). Recrystallization of the desired fraction from $MeOH–CHCl_3$ resulted in **14** (230 mg, 85%): mp 208–210 °C; ^1H NMR (DMSO-d_6) δ 1.8–2.9 (m, 4 H, H-3 and H-5), 4.0–4.4 (m, 2 H, H-1 and H-2), 4.9–5.5 (m, 3 H, H-4 and 2 × OH), 7.0 (br s, 2 H, NH_2), 8.4 (s, 1 H, H-8 of purine); ^{13}C NMR (DMSO-d_6) δ 39.66 and 39.93 (C-3 and C-5), 52.23 (C-4), 77.10 and 77.37 (C-1 and C-2), 124.23, 142.38, 150.02, 154.51, and 160.25 (C of purine). Anal. ($C_{10}H_{12}ClN_5O_2$) C, H, N.

(±)-2-Amino-1,9-dihydro-9-[(1′α,3′β,4′α)-(3′,4′-dihydroxy-1′-cyclopentyl)]-6*H*-purin-6-one (2). A solution of **14** (200 mg, 0.75 mmol) in 1 N HCl (20 mL) was refluxed for 5 h under N_2. The solvent was removed under reduced pressure, and the residue was azeotroped with H_2O and then EtOH. The white material that remained was dissolved in H_2O (10 mL), and the solution was neutralized with 6 N NaOH. A white precipitate formed immediately. Following refrigeration overnight, the solid was isolated by filtration, washed with cold H_2O, and dried. Recrystallization from $MeOH–H_2O$ produced **2** as a white solid (140 mg, 75%): mp > 300 °C dec; ^1H NMR (DMSO-d_6) δ 1.8–2.8 (m, 4 H, H-2′ and H-5′), 3.0–4.1 (m, 3 H, H-3′, H-4′, and OH), 4.2–5.5 (m, 2 H, H-1′ and OH), 6.7 (s, 2 H, NH_2), 7.85 (s, 1 H, H-8 of purine), 11.0 (br s, 1 H, H-1 of purine); ^{13}C NMR (DMSO-d_6) δ 39.38 and 39.60 (C-2′ and C-5′), 51.02 (C-1′), 76.42 and 76.77 (C-3′ and C-4′), 116.49, 135.95, 150.94, 153.69, and 157.10 (C of purine). Anal. ($C_{10}H_{13}N_5O_3 \cdot 1.5\ H_2O$) C, H, N.

(±)-(1α,2β,4α)-4-(2,6-Diamino-9*H*-purin-9-yl)-1,2-cyclopentanediol (4). Compound **14** (200 mg, 0.74 mmol) in MeOH (30 mL) saturated with anhydrous NH_3 was heated in a steel bomb at 100 °C for 2 days. The solvent was removed under reduced pressure, and the residue was recrystallized from $MeOH–H_2O$ to yield **4** (100 mg) as white crystals. The filtrate from recrystallization was concentrated and purified by flash chromatography ($MeOH–CH_2Cl_2$, 3:17). The solid thus obtained was recrystallized from $MeOH–H_2O$ to give an additional 70 mg of **4**: total yield 170 mg, 91%; mp 248–250 °C; ^1H NMR (DMSO-d_6) δ 1.53–2.79 (m, 2 H, H-3 and H-5), 3.22–5.16 (m, 5 H, H-1, H-2, H-4 and 2 × OH), 5.83 (br s, 2 H, NH_2), 6.76 (br s, 2 H, NH_2), 7.85 (s, 1 H, H-8 of purine); ^{13}C NMR (DMSO-d_6) δ 39.15 and 39.39 (C-3 and C-5), 50.91 (C-4), 76.33 and 76.78 (C-1 and C-2), 113.30, 136.23, 150.99, 156.10, and 159.76 (C of purine). Anal. ($C_{10}H_{14}N_6O_2$) C, H, N.

(±)-(1α,2β,4α)-4-(6-Chloro-9*H*-purin-9-yl)-1,2-cyclopentanediol (16). A mixture of **10** (2.0 g, 6.56 mmol) in 6 N HCl solution (100 mL) was heated under reflux for 24 h in an Ar atmosphere. The reaction mixture was evaporated to dryness using a rotary evaporator, and the residue was azeotroped with MeOH (3 × 30 mL). Following this treatment, the residue was dissolved in MeOH and neutralized by resin IRA-400 (basic). The resin was removed by filtration and washed well with MeOH, and the filtrate was evaporated to dryness on a rotary evaporator to leave a residue that was azeotroped with MeOH (3 × 50 mL). The oil that remained (**5**) was used directly in the next reaction.

5-Amino-4,6-dichloropyrimidine (1.30 g, 7.93 mmol) was added to a solution of the **5** obtained above in 1-butanol (150 mL). To this mixture was added Et_3N (2.0 g, 19.76 mmol), and the new mixture was heated under reflux for 24 h in an Ar atmosphere. The reaction mixture was evaporated to dryness using a rotary evaporator, and the residue was azeotroped with MeOH. The material remaining after this procedure was purified by flash chromatography ($MeOH–CHCl_3$, 1:9) followed by recrystallization from $CHCl_3–MeOH–AcOEt$ to give (±)-(1α,2β,4α)-4-[(5-amino-6-chloropyrimidin-4-yl)amino]-1,2-cyclopentanediol (**15**) as colorless needles: mp 189 °C; ^1H NMR (DMSO-d_6) δ 1.1–2.6 (m, 4 H, H-3 and H-5), 3.8–4.0 (m, 2 H, H-1 and H-2), 4.4–4.8 (m, 1 H, H-4), 4.75 and 4.88 (2 d, J = 3 Hz, 2 H, 2 × OH), 5.08 (s, 2 H, NH_2), 6.74 (d, J = 7 Hz, 1 H, NH), 8.06 (s, 1 H, H-2 of pyrimidine); ^{13}C NMR (DMSO-d_6) δ 38.95 (C-3 and C-5), 48.92 (C-4), 76.82 (C-1 and C-2), 123.41, 136.79, 145.78, and 151.63 (C of pyrimidine). A trace of impurity could not be removed from this material. As a consequence, the $MeOH–CHCl_3$ (1:9) fraction was evaporated to dryness with the aid of a rotary evaporator, and the residue was azeotroped with MeOH. The material remaining after this procedure was used in next reaction.

A mixture of the slightly impure **15** in triethyl orthoformate (60 mL) and concentrated HCl (0.6 mL) was heated under reflux for 12 h in an Ar atmosphere. Following this period, a mixture of concentrated HCl (0.5 mL) and MeOH (9.5 mL) was added to the mixture at room temperature. Stirring was continued for 30 min. The reaction mixture was then evaporated to dryness using a rotary evaporator, and the residue was azeotroped with MeOH (3 × 30 mL). The material remaining was dissolved in MeOH, and the solution was neutralized with resin IRA-400 (basic) (pH paper). The resin was removed by filtration and washed well with MeOH, and the filtrate was evaporated to dryness using a rotary evaporator. The material remaining was azeotroped with MeOH (3 × 20 mL) to give a product that recrystallized from MeOH to give **16** (769 mg, 46% based on **10**) as colorless needles: mp 202 °C; ^1H NMR (DMSO-d_6) δ 1.8–2.8 (m, 4 H, H-3 and H-5), 4.0–4.2 (m, 2 H, H-1 and H-2), 5.0–5.5 (m, 3 H, H-4 and 2 × OH), 8.79 (br s, 2 H, H-2 and H-8 of purine); ^{13}C NMR (DMSO-d_6) δ 38.95 and 39.38 (C-3 and C-5), 52.71 (C-4), 76.49 and 76.71 (C-1 and C-2), 131.10, 146.22, 148.98, 151.25, and 151.69 (C of purine). Anal. ($C_{10}H_{11}ClN_4O_2$) C, H, N.

(±)-(1α,2β,4α)-4-(6-Amino-9*H*-purin-9-yl)-1,2-cyclopentanediol (3). Into a cold (ice–H_2O) mixture of **16** (200 mg, 0.79 mmol) in MeOH (20 mL) was bubbled NH_3 gas for 2 h. The reaction vessel was sealed and then heated at 100 °C for 48 h. The reaction mixture was evaporated to dryness with the aid of a rotary evaporator, and the material remaining was azeotroped with MeOH (3 × 30 mL). The residue available after this workup was purified by flash chromatography ($MeOH–CHCl_3$, 3:17), and the desired product recrystallized from MeOH to give **3** (148 mg, 80%) as colorless needles: mp 211 °C; ^1H NMR (DMSO-d_6) δ 1.8–2.8 (m, 4 H, H-3 and H-5), 4.0–4.2 (m, 2 H, H-1 and H-2), 4.9–5.6 (m, 3 H, H-4 and 2 × OH), 7.35 (br s, 2 H, NH_2), 8.21 (br s, 2 H, H-2 and H-8 of purine); ^{13}C NMR (DMSO-d_6) δ 39.17 and 39.33 (C-3 and C-5), 51.95 (C-4), 76.66 and 76.98 (C-1 and C-2), 119.24, 139.99, 149.14, 152.23, and 156.18 (C of purine). Anal. ($C_{10}H_{13}N_5O_2$) C, H, N.

Antiviral Assays. For the sources of the viruses and the test systems used, see ref 14, except for VZV and the anti-VZV assays, which have been described in ref 15.

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Registry No. 2, 140438-62-6; 3, 132065-10-2; 4, 140438-63-7; 6, 91469-55-5; 7, 132065-12-4; 8, 132065-13-5; 9, 132152-82-0; 10, 132065-14-6; 11, 140438-64-8; 12, 140438-65-9; 13, 140438-66-0; 14, 140438-67-1; 15, 132065-16-8; 16, 132065-15-7; 4-chlorobenzenediazonium chloride, 2028-74-2; 5-amino-4,6-dichloropyrimidine, 5413-85-4; 2-amino-4,6-dichloropyrimidine, 56-05-3; diethoxymethyl acetate, 14036-06-7.

Supplementary Material Available: Single-crystal X-ray structural analysis data for compound 3 including tables of atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement coefficients, and torsional angles (12 pages); observed and calculated structure factors (4 pages). Ordering information is given on any current masthead page.

Chemistry and Anti-HIV Properties of 2′-Fluoro-2′,3′-dideoxyarabinofuranosylpyrimidines

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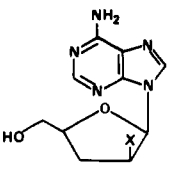
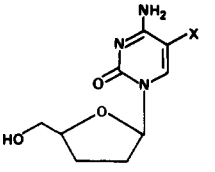
The synthesis, chemistry, biochemistry, and anti-HIV activity of a series of 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)pyrimidines have been studied in an attempt to find useful anti-AIDS drugs. Synthesis is carried out via a 2,3-dideoxyribose intermediate which facilitates the preparation of analogues by removing the sugar 3′-hydroxyl group prior to, rather than after, condensation with a uracil or cytosine aglycon. The 2′-F-dd-uridine analogues **7a–d** (with H, F, Cl, and CH_3 substitution in the 5-position) as well as the 4-deoxy compound (**12b**) are nonprotective to ATH8 or CEM cells infected with HIV-1. In the corresponding cytidine series, the 5-chloro analogue (**11**) is inactive. However, 2′-fluoro-2′,3′-dideoxyarabinosylcytosine, **10a**, and its 5-fluoro analogue, **10b**, are both active. While neither compound is as potent as ddC or 5-F-ddC (**2b**), **10b** gives complete protection against the cytopathic effects of HIV in both host cell lines. 2′-Fluoro substitution confers increased chemical and enzymatic stability on dideoxynucleosides. Even though dideoxy pyrimidine nucleosides are inherently more stable than the corresponding purine analogues toward acid-catalyzed cleavage of the glycosidic bond, 2′-fluoro substitution (**10a**) still increases stabilization relative to ddC (**2b**). No detectable deamination by partially purified cytidine deaminase is observed with the 2′-fluoro compounds **10a**, **10b**, or **11** under conditions which rapidly deaminate cytidine. A small amount of 2′-F-dd-*ara*-U (**7a**) is formed from **10a** in monkey plasma after >24 h of exposure. The octanol–water partition coefficients for the dideoxynucleosides in this study indicate their hydrophilic character, with log *P* values varying from −0.28 to −1.18.

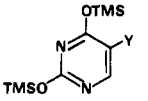
The anti-HIV properties of 2′,3′-dideoxynucleosides (ddN) such as **1a** and **2a** are now well established[1,2] and considerable effort continues to be expended on the determination of the effects of substituents on activity and potency in this series.[3] Fluorine has always has been a favored substituent in nucleoside antiviral investigations because of its size similarity and electronegativity difference relative to hydrogen.[4] Fluoro-substituted ddNs as potential anti-HIV agents have been the subject of more than 30 reports since 1987.[4,5] Our interest in this area started with the discovery that 5-F-ddC, **2b**, was as active and potent as ddC itself[6] and has continued with compounds in the 2′-F-dd-purine[7-9] series (e.g. **1b**) which possess unusual chemical[7] and biochemical[10] properties relative to their nonfluorinated parents. Several recent reports regarding anti-HIV studies with 2′-fluoro pyrimidine derivatives[11] have prompted us to report our own studies in this area.



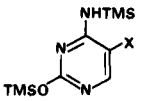
1a, X=H
1b, X=F



2a, X=H
2b, X=F



5a, Y=H
b, Y=F
c, Y=Cl
d, Y=CH_3



8a, X=H
b, X=F

Chemistry

A major benefit of 2′-fluoro substitution in the dideoxy purine series[7,8] is an abrogation of the extreme acid-instability of 2′,3′-dideoxy purine nucleosides[12] since acid stability is a desirable property for the production of oral

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