C-2 Arylamino Substituted Purine *ara*-Carbocyclic Nucleosides as Potential Anti-Cytomegalovirus Agents

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There are reports in the literature that placement of an arylamino side chain at the C-2 position of purine nucleosides produces compounds capable of inhibiting DNA polymerase. To evaluate the potential of this class of compounds as antiviral agents that act by inhibiting viral DNA polymerase, *ara*-carbocyclic purine nucleosides possessing a 4-(1-butyl)phenylamino and a 3,5-dichlorophenylamino substituent at C-2 were chosen as the prototype structures and have been prepared from 2,4,6-trichloropyrimidine in 6 steps. For the antiviral analysis, human cytomegalovirus served as the principal virus since it expresses a virally specific DNA polymerase. None of the compounds showed activity towards this virus, but they were found to display some toxicity towards one or more cell lines.

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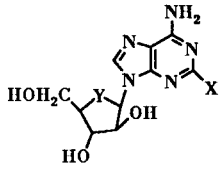
Human cytomegalovirus (HCMV) belongs to the herpesvirus group and is an opportunistic pathogen of concern for individuals with acquired immunodeficiency syndrome and for patients whose immune systems have been suppressed for transplant purposes [1]. In the search for agents to treat HCMV infection, the nucleoside analogue 9-(1,3-dihydroxy-2-propoxymethyl)guanine has shown promise [1]. However, problems [1] are associated with the clinical use of this latter compound and, consequently, other nucleoside analogues are being sought [2] as potential anti-HCMV agents.

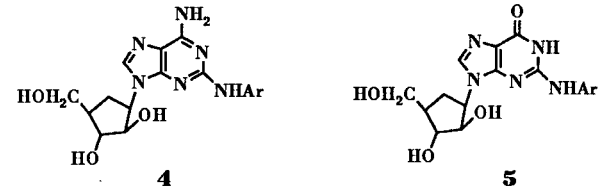
Among the candidates upon which to build derivatives is 9-β-D-arabinofuranosyladenine (**1**, Y = O), which shows an anti-HCMV profile [3] by being converted into its triphosphate [3c] that serves as an inhibitor of the virally induced DNA polymerase and ribonucleotide reductase [4]. The use of **1** as a prototype structure for developing potential anti-HCMV agents is limited by its rapid deactivation by adenosine deaminase [5]. This situation can be circumvented by considering the carbocyclic derivative of **1** (**2**, Y = CH_2) [4b], which is not deaminated [6]. Compound **2** and its 2-amino derivative **3** have displayed antiviral activity [5-8] and were among the candidates designated in our laboratory for structural modification in the search for compounds effective in inhibiting HCMV.



1; X-H, Y-O
2; X-H, Y-CH_2
3; X-NH_2, Y-CH_2

Figure 1

To commence this study, attention was directed to the work of Wright and his colleagues [9], who have shown that placement of a 2-arylamino group on 2′-deoxyadenosine and 2′-deoxyinosine (to yield a guanosine derivative in the latter case) produced one compound whose 5′-triphosphate [10] inhibited viral DNA polymerases and another compound that displayed antiviral activity [11]. Thus, placement of two representative arylamino side-chains found by Wright's group to yield promising biological results (that is, where aryl is 4-(1-butyl)phenyl and 3,5-dichlorophenyl) at C-2 on the *ara*-carbocyclic purine system results in the target analogs **4** and **5**, whose synthesis in their racemic forms and anti-HCMV activity are described herein.



4 **5**

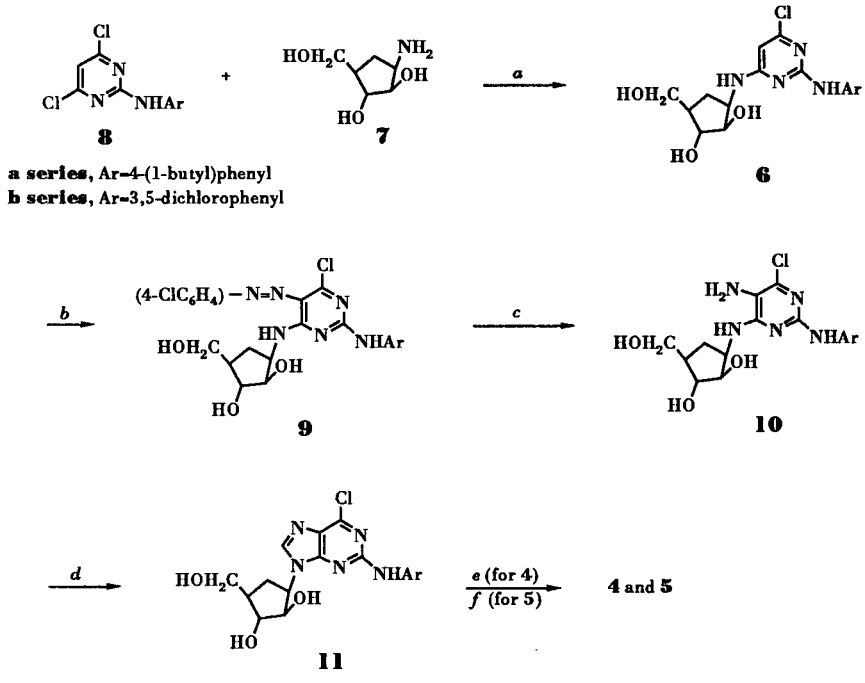
a series, Ar-4-(1-butyl)phenyl
b series, Ar-3,5-dichlorophenyl

Figure 2

Chemistry.

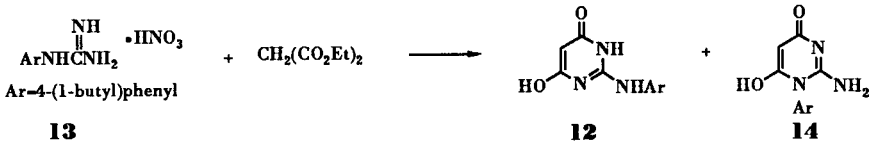
The synthesis of **4** and **5** (Scheme 1) initially required the preparation of the pyrimidine **6** by reaction of 4α-amino-2β,3α-dihydroxy-1α-cyclopentanemethanol (**7**) and the 2-arylaminopyrimidine **8** [12]. Since compound **7** was available by modification of a literature procedure [13], it remained to develop a route to **8a** and **8b**. In this direction, the initial plan was to treat diethyl malonate with the appropriately substituted guanidine (Scheme II) to produce the 2-arylaminopyrimidine derivative **12** [14]. Chlorination of **12** was then expected to give **8**. Thus, *N*-[4-(1-butyl)phenyl]guanidine nitrate (**13**) was prepared by reaction of cyanamide with 4-(1-butyl)aniline hydrochloride followed by work-up with ammonium nitrate [15]. Reaction of **13** with diethyl malonate gave two products (1:1) that were identified by ^{1}H nmr spectral analysis to be the

Scheme I



Reaction conditions: *a*, reflux in 1-BuOH in presence of triethylamine; *b*, 4-chlorophenyldiazonium chloride, sodium acetate trihydrate, and acetic acid in methanol/water, room temperature, overnight; *c*, zinc dust in acetic acid/methanol, reflux; *d*, diethoxymethyl acetate at 80 °C then conc. hydrochloric acid/methanol at room temperature; *e*, ammonia in methanol, 120 °C, 60 hours; *f*, 1 N hydrochloric acid and acetic acid, reflux

Scheme II



desired **12** and the air sensitive, oily endocyclic derivative **14**. Seela and his co-workers [16] have observed a similar result. Numerous attempts to separate the two materials consistently led to contamination of **12** with **14**. As a result, attention turned to seeking an alternative means to **8** (or, possibly, **6**).

Review of the literature indicated that nucleophilic substitution would occur predominantly (see **15**) [17] at the 4-chloro site in commercially available 2,4,6-trichloropyrimidine. Thus, it was decided to treat this latter trichloro compound with **7** since the carbocyclic side-chain would be introduced at the proper carbon (that is, C-4) of the pyrimidine ring that would, in turn, lead to **6** following reaction with either 4-(1-butyl)aniline or 3,5-dichloroaniline. However, when the reaction of 2,4,6-trichloropyrimidine with **7** was carried out, a mixture of the C-2 and C-4 substituted products were obtained.

In view of the costly and lengthy synthesis associated with obtaining **7** [13], it was undesirable to consume this material as part of a product mixture in the reaction with 2,4,6-trichloropyrimidine. Thus, reaction of the trichloropyrimidine with 4-(1-butyl)aniline was considered since the undesirable product (that is, the one with the arylamino side chain at C-4 of the pyrimidine) could be discarded without significant loss of valuable starting material. It should also be noted that once **8** is formed, its symmetry would provide only **6** upon reaction with **7** with no contamination by another regioisomer.

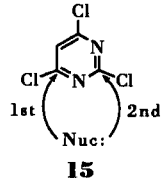
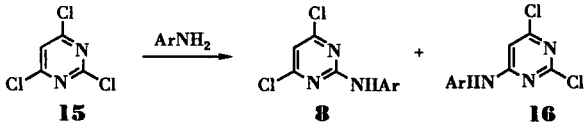


Figure 3

As shown in Scheme III, reaction of 2,4,6-trichloropyrimidine with 4-(1-butyl)aniline gave **8a** and **16a** with the

desired **8a** being obtained in 35% yield (exactly the yield of the C-2 product obtained when **7** had been used as the initial nucleophile with 2,4,6-trichloropyrimidine). These two compounds could be distinguished by ^{13}C nmr analysis of the pyrimidine carbons. In the case of **8a** there were three peaks (δ 109.71, 158.95, and 160.90) due to its symmetry whereas the spectrum of **16a** showed four pyrimidine carbon peaks (δ 103.20, 158.14, 158.89, and 162.25). The ^1H nmr spectral data corroborated the results seen in the ^{13}C nmr spectrum. That is, the C-5 proton of the desired **8a** is at lower field (δ 7.06) than the corresponding C-5 proton of **16a** (δ 6.72). This observation is due to the shielding effect of the adjacent arylamino side-chain in the latter isomer.

Scheme III



a series, Ar=4-(1-butyl)phenyl
b series, Ar=3,5-dichlorophenyl

With **8a** available, its reaction with **7** was carried out in refluxing 1-butanol containing triethylamine to give **6a** (Scheme I). Treatment of **6a** with 4-chlorophenyldiazonium chloride resulted in the diazo coupled product **9a**, which was subsequently reduced with zinc in methanol and acetic acid to give the diamino precursor **10a**. Ring closure of **10a** to **11a** was accomplished with diethoxymethyl acetate, which were conditions that avoided formylation of the cyclopentane hydroxyl groups. Conversion of **11a** into target molecules **4a** and **5a** was accomplished with ammonia in a sealed vessel (to **4a**) and dilute hydrochloric acid in acetic acid under gentle reflux (to **5a**).

The synthesis of **4b** and **5b** was accomplished in the same manner as described for obtaining **4a** and **5a** except that 3,5-dichloroaniline was used in the reaction with 2,4,6-trichloropyrimidine to give **8b** (Scheme III) for use in Scheme I.

Biological Activity.

Compounds **4a** and **5a** showed no anti-HCMV activity [18] against strain AD-169 in MRC-5 cells [18] up to 100 μ*M* while, using the same assay [18], **4b** and **5b** displayed no anti-HCMV properties up to 25 μ*M* (the concentration at which toxicity was observed in the host cells) [19]. Both **4a** and **5a** were cytotoxic towards D98 and L cells in the 100 μ*M* range while **4b** was toxic in the same range towards D98 cells but non-toxic towards L cells. Analogue **5b** was non-toxic towards both cell lines.

EXPERIMENTAL

Materials and Methods.

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. The ir spectra were recorded on a Beckman Model FT 1100 spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were recorded on a JEOL FX90Q spectrometer (operated at 90 MHz and 22.5 MHz, respectively) in dimethyl sulfoxide-d_6 referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). The reactions were carried out under anhydrous conditions in a nitrogen atmosphere, using freshly distilled solvents, unless otherwise noted. The 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. The flash column chromatographic purifications (under a pressure of 30 psi) were performed using Aldrich silica gel (tlc grade particle size 2-25 μ, 60 Å) and eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H nmr and ^{13}C nmr) homogeneous materials.

Note: For the sake of simplicity the ^1H nmr peak assignments are generally based on a carbocyclic nucleoside numbering system whereby the cyclopentyl unit is given prime numbers consistent with ribofuranosyl numbering with C6′ given to the carbon that replaces the ribofuranosyl oxygen. This means of atom designation may not always agree with the name given to the compound in the title of the experiment in which the nmr data appears.

4,6-Dichloro-2-[4-(1-butyl)phenyl]aminopyrimidine (**8a**) and 2,6-Dichloro-4-[4-(1-butyl)phenyl]aminopyrimidine (**16a**).

A mixture of 4-(1-butyl)aniline (15 g, 100 mmoles) in chloroform and hexane (10 ml) was added dropwise to a stirred, cooled (ice-water) mixture of 2,4,6-trichloropyrimidine (9.2 g, 50 mmoles) in chloroform (10 ml) and hexane (10 ml). Stirring was then continued at room temperature for 30 minutes under argon. The reaction mixture was evaporated to dryness and subjected to flash chromatography. The fraction eluting with chloroform-hexane (1:1) was recrystallized from hexane to give **8a** (5.16 g, 35%) as colorless needles, mp 59-60°; ir (Nujol): 3381 (NH), 1597, 1566 and 1556 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.7-1.0 (m, 3 H, CH_3 butyl), 1.0-1.7 (m, 4 H, 2 x $-CH_2-$ butyl), 2.4-2.7 (m, 2 H, $-CH_2-$ butyl), 7.06 (s, 1 H, C5-H pyrimidine), 7.12 (d, J = 8.5 Hz, 2 H, C2-H, C6-H phenyl), 7.56 (d, J = 8.5 Hz, 2 H, C3-H, C5-H phenyl), 10.31 ppm (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.76, 21.78, 33.27, and 34.35 (butyl C-atoms), 109.71 (pyrimidine C-5), 120.00, 128.40, 136.31, and 137.23 (Ph C-atoms), 158.95 and 160.90 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3$: C, 56.77; H, 5.16; N, 14.19. Found: C, 57.00; H, 5.16; N, 14.36.

The fraction eluting with chloroform was recrystallized from hexane to give **16a** (7.95 g, 54%) as colorless needles, mp 77-78°; ir (Nujol): 3212 (NH), 1594 and 1553 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.7-1.0 (m, 3 H, CH_3 butyl), 1.0-1.7 (m, 4 H, 2 x $-CH_2-$ butyl), 2.4-2.7 (m, 2 H, $-CH_2-$ butyl), 6.72 (s, 1 H, C5-H pyrimidine), 7.17 (d, J = 8.5 Hz, 2 H, C2-H, C6-H phenyl), 7.43 (d, J = 8.5 Hz, 2 H, C3-H, C5-H phenyl), 10.18 ppm (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.76, 21.78, 33.15, and 34.35 (butyl C-atoms), 103.20 (pyrimidine C-5), 121.19, 128.77, 135.54, and 138.52 (Ph C-atoms), 158.14, 158.89, and 162.25 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3$: C, 56.77; H, 5.16; N, 14.19. Found: C, 56.85; H, 5.04; N, 14.15.

(±)-(1α,2β,3α,4α)-4-{[2-[4-(1-Butyl)phenyl]amino-6-chloro-4-pyrimidinyl}amino}-2,3-dihydroxy-1-cyclopentanemethanol (**6a**).

A solution of (±)-(1α,2β,3α,4α)-4-acetamido-2,3-diacetoxy-1-cyclopentanemethyl acetate [13] (3.77 g, 12 mmoles) in 2 *N* hydrochloric acid (25 ml) was heated at 70-80° for 6 hours under argon. The reaction mixture was then evaporated to dryness on a rotary evaporator and azeotroped with methanol. The residue was dissolved in methanol (50 ml), cooled and neutralized with IRA-400 (basic) resin to *p*H 8 (indicator paper). The resin was removed by filtration and the filtrate evaporated to dryness on a rotary evaporator to give **7** as an oil.

To a mixture of **7** prepared above in 1-butanol (50 ml), **8a** (4.3 g, 14.5 mmoles) was added followed by an additional amount of 1-butanol (50 ml). Then triethylamine (6 g, 59 mmoles) was added dropwise to the mixture and the mixture heated under reflux for 3 hours in an atmosphere of argon. The reaction mixture was evaporated to dryness on a rotary evaporator and the residue azeotroped with methanol. The resultant residue was subjected to flash column chromatography. The fraction that was eluted with methanol-chloroform (1:9) was obtained by concentration on rotary evaporation and recrystallized from ethyl acetate to give **6a** (3.69 g, 76% based on (±)-(1α,2β,3α,4α)-4-acetamido-2,3-diacetoxy-1-cyclopentanemethyl acetate) as colorless needles, mp 114-116°; ir (Nujol): 3368, 3296 (NH and OH), 1579, and 1522 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.8-1.0 (m, 3 H, CH_3 butyl), 1.0-1.8 (m, 5 H, 2 x $-CH_2-$ butyl and C4′-H), 1.8-2.4 (m, 2 H, C6′-H_2), 2.4-2.6 (m, 2 H, $-CH_2-$ butyl), 3.3-3.9 and 4.2-5.0 (m, 8 H, C1′-H, C2′-H, C3′-H, C5′-H_2 and 3 x OH), 6.08 (s, 1 H, C5-H pyrimidine), 7.18 (br, 1 H, C4-NH pyrimidine) overlapped by 7.04 (d, J = 8.5 Hz, 2 H, C2-H, C6-H phenyl), 7.65 (d, J = 8.5 Hz, 2 H, C3-H, C5-H phenyl), 9.22 ppm (s, 1 H, C2-NH pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.82, 21.78, 33.37, and 34.30 (butyl C-atoms), 31.48, 46.76, 52.50, 63.82, 76.71, and 78.39 (cyclopentanemethanol C-atoms), 94.65 (pyrimidine C-5), 118.86, 128.18, 135.01, and 138.31 (Ph C-atoms), 156.84, 159.28, and 163.56 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{20}H_{27}ClN_4O_3$: C, 59.03; H, 6.69; N, 13.77. Found: C, 58.90; H, 6.64; N, 13.73.

(±)-(1α,2β,3α,4α)-4-{[2-[(4-(1-Butyl)phenyl)amino]-5-(4-chlorophenylazo)-6-chloropyrimidin-4-yl}amino}-2,3-dihydroxy-1-cyclopentanemethanol (**9a**).

A cold (ice-water) solution of 4-chlorophenyldiazonium chloride was prepared by addition of a solution of sodium nitrite (180 mg, 2.61 mmoles) in water (1.3 ml) to a solution of 4-chloroaniline (308 mg, 2.41 mmoles) dissolved in concentrated hydrochloric acid (36%, 1.3 ml) and water (3.9 ml) and cooled in an ice-water bath. A mixture of **6a** (540 mg, 1.33 mmoles), sodium acetate trihydrate (4.2 g), acetic acid (10.2 ml), water (5.1 ml), and methanol (5.1 ml) was also prepared. To this latter mixture the initially prepared 4-chlorophenyldiazonium chloride solution was added dropwise at room temperature with stirring. The stirring was continued overnight at room temperature under argon. Methanol was then added to the reaction mixture until a precipitate began to form. The precipitate was isolated by filtration and washed with methanol to give **9a** (599 mg, 83%) as a yellow powder, mp 203-205°; ir (Nujol): 3450-3050 (NH and OH), 1574 and 1527 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.8-1.1 (m, 3 H, CH_3 butyl), 1.1-1.8 (m, 5 H, 2 x $-CH_2-$ butyl and C4′-H), 1.8-2.2 (m, 2 H, C6′-H_2), 2.2-3.0 (m, 2 H, $-CH_2-$ butyl), 3.0-4.2 (m, 4 H, C1′-H, C2′-H, C3′-H, and OH), 4.2-4.7 (m, 2 H, C5′-H_2), 4.94 and 5.58 (2d, J = 4 Hz, and 4 Hz, 2 H, 2 x OH), 7.14 (d, J = 7.5 Hz, 2 H, C2-H, C6-H 4-BuC_6H_4), 7.58 (d, J = 7.5 Hz, 2 H, C3-H, C5-H 4-BuC_6H_4), 7.7-7.9 (m, 4 H, 4-ClC_6H_4), 10.20 (s, 1 H, C2-NH pyrimidine), 10.88 ppm (d, J = 5 Hz, 1 H, C4-NH pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.84, 21.83, 33.10, and 34.19 (butyl C-atoms), 32.34, 46.73, 52.60, 63.17, 77.14, and 78.58 (cyclopentanemethanol C-atoms), 119.72, 122.92, 128.37, 129.53, 133.81 and, 137.01 (2 x Ph C-atoms), 150.66, 153.85, 157.00, and 163.82 ppm (pyrimidine C-2, C-4, C-5 and C-6).

Anal. Calcd. for $C_{26}H_{30}Cl_2N_6O_3$: C, 57.25; H, 5.54; N, 15.41. Found: C, 56.94; H, 5.54; N, 15.03.

(±)-(1α,2β,3α,4α)-4-{[2-[(4-(1-Butyl)phenyl)amino]-5-amino-6-chloropyrimidin-4-yl}amino}-2,3-dihydroxy-1-cyclopentanemethanol (**10a**).

Compound **9a** (907 mg, 1.66 mmoles) was dissolved in acetic acic (7 ml) and methanol (70 ml) by heating under reflux (20 minutes) in an argon atmosphere. To the warm solution, zinc dust (350 mesh, 1.1 g-atoms) was added and the resultant mixture was stirred for 10 minutes at room temperature. The excess zinc dust was removed by filtration, and the filtrate was evaporated to dryness on a rotary evaporator. The residue was azeotroped with methanol and then purified by flash chromatography. The fraction eluting with methanol-chloroform (1:19) was evaporated on a rotary evaporator and the residue recrystallized from chloroform to give **10a** (654 mg, 93%) as pale pink needles, mp 106-109°; ir (Nujol): 3450-3050 (NH and OH), 1597, 1574 and 1519 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.8-1.0 (m, 3 H, CH_3 butyl), 1.0-1.8 (m, 5 H, 2 x $-CH_2-$ butyl and C4′-H), 1.8-2.2 (m, 2 H, C6′-H_2), 2.2-3.0 (m, 2 H, $-CH_2-$ butyl), 3.0-3.9 and 3.9-4.9 (m, 10 H, C1′-H, C2′-H, C3′-H, C5′-H_2, C5-NH_2 pyrimidine, and 3 x OH), 6.37 (d, J = 7.5 Hz, 1 H, C4-NH pyrimidine), 7.00 (d, J = 8.0 Hz, 2 H, C2-H, C6-H phenyl), 7.60 (d, J = 8.0 Hz, 2 H, C3-H, C5-H phenyl), 8.68 ppm (s, 1 H, C2-NH pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.92, 21.83, 33.48, and 34.29 (butyl C-atoms), 31.58, 46.91, 53.04, 63.93, 76.71, and 78.55 (cyclopentanemethanol C-atoms), 115.01 (pyrimidine C-5), 117.56, 128.18, 133.59, and 139.39 (Ph C-atoms), 140.42, 151.80, and 154.61 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{20}H_{28}ClN_5O_3$: C, 56.93; H, 6.69; N, 16.60. Found: C, 56.75; H, 6.72; N, 16.47.

(±)-(1α,2β,3α,4α)-4-{2-[4-(1-Butyl)phenyl]amino-6-chloropurin-9-yl}-2,3-dihydroxy-1-cyclopentanemethanol (**11a**).

Compound **10a** (650 mg, 1.54 mmoles) was dissolved in diethoxymethyl acetate (3 ml, 18.4 mmoles) and this solution stirred at 80° for 1 hour under an argon atmosphere. A mixture of concentrated hydrochloric acid (36%, 1 ml) and methanol (19 ml) was then added dropwise to the reaction mixture at room temperature and the stirring continued at room temperature for 1 hour. The mixture that resulted was cooled (ice-water) and then neutralized with IRA-400 (basic) resin to *p*H 7-8 (indicator paper). The resin was removed by filtration and washed well with methanol. The filtrate-wash solution was evaporated to dryness on a rotary evaporator and the residue azeotroped with methanol to give a material that was purified by flash chromatography. The fraction eluting with methanol-chloroform (1:19) was concentrated to dryness with the aid of a rotary evaporator and the residue recrystal-

lized from chloroform-methanol (1:1) followed by washing with diethyl ether to give **11a** (498 mg, 75%) as pale pink needles, mp 172-173°; ir (Nujol): 3450-3050 (NH and OH), 1605, 1571, 1535 and 1512 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.8-1.0 (m, 3 H, CH_3 butyl), 1.0-1.8 (m, 5 H, 2 x $-CH_2-$ butyl and C4′-H), 1.8-2.3 (m, 2 H, C6′-H_2), 2.3-2.7 (m, 2 H, $-CH_2-$ butyl), 3.0-4.2 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.5-5.2 (m, 4 H, C1′-H and 3 x OH), 7.12 (d, J = 8.0 Hz, 2 H, C2-H, C6-H phenyl), 7.71 (d, J = 8.0 Hz, 2 H, C3-H, C5-H phenyl), 8.28 (s, 1 H, C8-H purine), 9.79 ppm (s, 1 H, C2-NH purine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.82, 21.78, 33.32, and 34.30 (butyl C-atoms), 30.02, 46.54, 55.59, 63.28, 76.55, and 78.07 (cyclopentanemethanol C-atoms), 118.70, 128.34, 135.49, and 137.99 (Ph C-atoms), 124.50, 143.78, 148.82, 153.80, and 155.32 ppm (purine C-atoms).

Anal. Calcd. for $C_{21}H_{26}ClN_5O_3$: C, 58.40; H, 6.07; N, 16.21. Found: C, 58.47; H, 6.29; N, 16.39.

(±)-(1α,2β,3α,4α)-4-{2-[4-(1-Butyl)phenyl]amino-6-amino-purin-9-yl}-2,3-dihydroxy-1-cyclopentanemethanol (**4a**).

Compound **11a** (150 mg, 0.35 mmole) was dissolved in methanol (30 ml) and this mixture was cooled (ice-water) while anhydrous ammonia was added over a period of 1 hour. The resultant mixture was heated in a sealed vessel at 120° for 60 hours. The reaction mixture was evaporated to dryness with the aid of a rotary evaporator and the residue azeotroped with methanol and then purified by flash chromatography. The fraction eluting with methanol-chloroform (1:9) was evaporated to dryness using a rotary evaporator and the residue was washed with water and recrystallized from, first, chloroform and, then, methanol followed by ethyl acetate and washing with diethyl ether to give **4a** (118 mg, 83%) as colorless fine needles, mp 213°; ir (Nujol): 3400-3110 (NH and OH), 1645, 1600, 1535 and 1510 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.8-1.0 (m, 3 H, CH_3 butyl), 1.0-2.4 (m, 7 H, 2 x $-CH_2-$ butyl, C4′-H, and C6′-H_2), 2.4-2.7 (m, 2 H, $-CH_2-$ butyl), 3.0-4.1 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.4-5.2 (m, 4 H, C1′-H and 3 x OH), 6.85 (s, 2 H, C6-NH_2 purine), 7.02 (d, J = 8.0 Hz, 2 H, C2-H, C6-H phenyl), 7.74 (d, J = 8.0 Hz, 2 H, C3-H, C5-H phenyl), 7.86 (s, 1 H, C8-H purine), 8.74 ppm (s, 1 H, C2-NH purine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.87, 21.78, 33.48, and 34.24 (butyl C-atoms), 30.61, 46.76, 54.77, 63.50, 76.66, and 78.23 (cyclopentanemethanol C-atoms), 118.21, 128.07, 133.77, and 139.56 (Ph C-atoms), 113.82, 138.04, 151.37, 155.76, and 156.19 ppm (purine C-atoms).

Anal. Calcd. for $C_{21}H_{28}N_6O_3$: C, 61.14; H, 6.84; N, 20.38. Found: C, 61.37; H, 6.80; N, 20.29.

(±)-(1α,2β,3α,4α)-4-{N^2-[4-(1-Butyl)phenyl]guanin-9-yl}-2,3-dihydroxy-1-cyclopentanemethanol (**5a**).

A mixture of **11a** (50 mg, 0.12 mmole), 1 *N* hydrochloric acid (2.5 ml) and acetic acid (2.5 ml) was heated under reflux for 5 hours under an argon atmosphere. The reaction mixture was then evaporated to dryness by using a rotary evaporator and the residue was first azeotroped with methanol and then dissolved in methanol. The methanol solution was cooled (ice-water) and neutralized with aqueous 6 *N* sodium hydroxide solution to *p*H 7-8 (indicator paper). The methanol was removed using a rotary evaporator and the residue azeotroped with methanol and then subjected to flash chromatographic purification. The fraction eluting with methanol-chloroform (1:9) was evaporated with the aid of a rotary evaporator and the residue recrystallized first from chloroform and then methanol followed by ethyl acetate to give **5a** (45 mg, 94%) as colorless fine needles, mp 285-287°; ir (Nujol): 3430-3130 (NH and OH), 1700, 1670, 1625, 1595 and 1570 cm^{-1} (C=O, C=N, and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 0.8-1.0 (m, 3 H, CH_3 butyl), 1.0-2.4 (m, 7 H, 2 x $-CH_2-$ butyl, C4′-H, and C6′-H), 2.4-2.7 (m, 2 H, $-CH_2-$ butyl), 3.0-4.1 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.4-5.1 (m, 4 H, C1′-H and 3 x OH), 7.14 (d, J = 7.5 Hz, 2 H, C2-H, C6-H phenyl), 7.59 (d, J = 7.5 Hz, 2 H, C3-H, C5-H phenyl), 7.82 (s, 1 H, C8-H purine), 8.89 (s, 1 H, C2-NH purine), 10.53 ppm (brs, 1 H, N1-H purine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 13.87, 21.83, 33.31, and 34.24 (butyl C-atoms), 30.23, 46.54, 55.31, 63.38, 76.76, and 78.17 (cyclopentanemethanol C-atoms), 119.07, 128.72, 136.46, and 136.63 (Ph C-atoms), 117.67, 137.98, 148.92, 150.28, and 156.83 ppm (purine C-atoms).

Anal. Calcd. for $C_{21}H_{27}N_5O_4$: C, 61.00; H, 6.58; N, 16.94. Found: C, 61.07; H, 6.73; N, 17.17.

2,6-Dichloro-4-(3,5-dichlorophenyl)aminopyrimidine (**16b**) and 4,6-Dichloro-2-(3,5-dichlorophenyl)aminopyrimidine (**8b**).

A solution of 3,5-dichloroaniline (30 g, 185 mmoles) in methanol (250 ml) was added dropwise to a stirred solution of 2,4,6-trichloropyrimidine (15.24 g, 90 mmoles) in methanol (50 ml) at room temperature in an argon atmosphere. The stirring was continued for 20 hours at room temperature under argon. The resulting precipitate was removed by filtration and washed with chloroform to give **16b** (20.06 g, 72%) as a colorless powder, which was recrystallized from chloroform-methanol as colorless needles, mp 234°; ir (Nujol): 3302 (NH), 1633, 1566, and 1556 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 6.80 (s, 1 H, C5-H pyrimidine), 7.20 (m, 1 H, C4-H phenyl), 7.61 (m, 2 H, C2-H, C6-H phenyl), 10.22 ppm (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 104.45 (pyrimidine C-5), 118.42, 122.60, 133.92, and 140.42 (Ph C-atoms), 158.35, 158.46, and 161.55 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{10}H_5Cl_4N_3$: C, 38.87; H, 1.63; N, 13.60. Found: C, 38.73; H, 1.38; N, 13.36.

The filtrate wash solution was evaporated to dryness, dissolved in chloroform and purified by flash column chromatography. The material in the fraction that eluted with hexane-chloroform (1:1, v/v) was recrystallized from methanol to give **8b** (2 g, 7%) as colorless needles, mp 127°; ir (Nujol): 3271 (NH), 1607, 1594, and 1556 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 7.10 (d, J = 2 Hz, 1 H, C4-H phenyl), 7.12 (s, 1 H, C5-H pyrimidine), 7.74 (d, J = 2 Hz, 2 H, C2-H, C6-H phenyl), 10.42 ppm (s, 1 H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 111.16 (pyrimidine C-5), 117.34, 121.51, 133.70, and 141.01 (Ph C-atoms), 158.13 and 160.68 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{10}H_5Cl_4N_3$: C, 38.87; H, 1.63; N, 13.60. Found: C, 39.04; H, 1.35; N, 13.34.

(±)-(1α,2β,3α,4α)-4-{[2-(3,5-Dichlorophenyl)amino-6-chloro-4-pyrimidinyl]amino}-2,3-dihydroxy-1-cyclopentanemethanol (**6b**).

Using the procedure described for the preparation of **6a** and beginning with 938 mg (3 mmoles) of (±)-(1α,2β,3α,4α)-4-acetamido-2,3-diacetoxy-1-cyclopentanemethyl acetate [13] in 2 *N* hydrochloric acid (32 ml) and treating the resulting **7** with **8b** (1.12 g, 3.62 mmoles) led to a material that was recrystallized

from chloroform-methanol-ethyl acetate to give **6b** (873 mg, 69% based on (±)-(1α,2β,3α,4α)-4-acetamido-2,3-diacetoxy-1-cyclopentanemethyl acetate) as colorless needles, mp 236°; ir (Nujol): 3358, 3250 (NH and OH), 1612, 1574, and 1532 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.2-1.6 (m, 1 H, C4′-H), 1.6-2.4 (m, 2 H, C6′-H_2), 3.2-3.9 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.2-5.2 (m, 4 H, C1′-H and 3 x OH), 6.27 (s, 1 H, C5-H pyrimidine), 7.05 (t, J = 2 Hz, 1 H, C4-H phenyl), 7.37 (d, J = 7 Hz, 1 H, C4-NH pyrimidine), 7.88 (d, J = 2 Hz, 2 H, C2-H, C6-H phenyl), 9.79 ppm (s, 1 H, C2-NH pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 31.75, 46.64, 52.39, 63.55, 77.09, and 78.44 (cyclopentanemethanol C-atoms), 96.43 (pyrimidine C-5), 116.47, 119.94, 133.92, and 143.24 (Ph C-atoms), 156.62, 158.73, and 163.55 ppm (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{16}H_{17}Cl_3N_4O_3$: C, 45.79; H, 4.08; N, 13.35. Found: C, 45.57; H, 4.10; N, 13.16.

(±)-(1α,2β,3α,4α)-4-{{2-[(3,5-Dichlorophenyl)amino]-5-(4-chlorophenyl)azo-6-chloropyrimidin-4-yl}amino}-2,3-dihydroxy-1-cyclopentanemethanol (**9b**).

Using a procedure analogous to the preparation of **9a** by employing (i) 4-chlorophenyldiazonium chloride prepared by addition of a solution of sodium nitrite (540 mg, 7.82 mmoles) in water (3.8 ml) to a solution of 4-chloroaniline (900 mg, 7.06 mmoles) dissolved in concentrated hydrochloric acid (36%, 3.8 ml) and water (11.4 ml) and (ii) 800 mg (1.91 mmoles) of **6b** dissolved in a warm mixture of acetic acid (30 ml), water (7.5 ml), and methanol (22.5 ml) and then adding sodium acetate (12 g) to this, a yellow precipitate resulted without the need to add methanol. This product was obtained by filtration and recrystallized from chloroform-methanol to give **9b** (604 mg, 57%) as a yellow powder, mp 266°; ir (Nujol): 3368, 3304 (NH and OH), 1605, 1571, and 1530 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.2-1.6 (m, 1 H, C4′-H), 1.6-2.3 (m, 2 H, C6′-H_2), 2.6-4.0 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.1-4.6 (m, 2 H, C1′-H and OH), 5.4-5.8 (m, 2 H, 2 x OH), 7.14 (t, J = 1.5 Hz, 1 H, C4-H 3,5-$Cl_2C_6H_3$), 7.55 and 7.77 (2 d, J = 9 Hz and J = 9 Hz, 4 H, 4-ClC_6H_4), 7.94 (d, J = 1.5 Hz, 2 H, C2-H and C6-H 3,5-$Cl_2C_6H_3$), 10.53 (s, 1 H, C2-NH pyrimidine), 10.95 ppm (d, J = 7 Hz, 1 H, C4-NH pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 32.23, 46.75, 52.76, 62.73, 77.31, and 78.66 (cyclopentanemethanol C-atoms), 117.39, 120.16, 121.46, 123.14, 129.48, 134.03, 134.30, and 141.49 (2 x Ph C-atoms), 150.39, 153.47, 156.67, and 163.77 ppm (pyrimidine C-2, C-4, C-5 and C-6).

Anal. Calcd. for $C_{22}H_{20}Cl_4N_6O_3$: C, 47.33; H, 3.61; N, 15.05. Found: C, 47.38; H, 3.71; N, 14.84.

(±)-(1α,2β,3α,4α)-4-{[5-Amino-2-(3,5-dichlorophenyl)amino-6-chloropyrimidin-4-yl]amino}-2,3-dihydroxy-1-cyclopentanemethanol (**10b**).

Using a procedure analogous to that for preparing **10a**, treatment of 405 mg (0.73 mmoles) of **9b** with zinc dust (1 g, 15.3 g-atoms) in acetic acid (30 ml) and methanol (30 ml) led to a material that was purified by flash column chromatography. The fraction eluting with methanol-chloroform (1:9) was evaporated on a rotary evaporator and the residue recrystallized from chloroform to give **10b** (260 mg, 83%) as pink needles, mp 127°; ir (Nujol): 3500-3150 (NH and OH), 1594, 1571, and 1525 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.2-2.4 (m, 3 H, C4′-H and C6′-H_2), 2.6-5.2 (m, all other cyclopentyl and hydroxyl protons), 6.47 (d, J = 7 Hz, 1 H, C4-NH pyrimidine), 6.94 (m, 1 H, C4-H phenyl), 7.82 (m, 2 H, C2-H, C6-H phenyl), 9.35 ppm (s, 1 H, C2-NH pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 31.85, 46.59, 52.76, 63.60, 76.98, and 78.55 (cyclopentanemethanol C-atoms), 116.64 (pyrimidine C-5), 115.12, 118.48, 133.86, and 144.10 (Ph C-atoms), 139.14, 150.44, and 154.29 (pyrimidine C-2, C-4, and C-6).

Anal. Calcd. for $C_{16}H_{18}Cl_3N_5O_3 \cdot 1/2H_2O$: C, 43.31; H, 4.32; N, 15.78. Found: C, 43.28; H, 4.43; N, 15.43.

(±)-(1α,2β,3α,4α)-4-[2-(3,5-Dichlorophenyl)amino-6-chloropurin-9-yl]-2,3-dihydroxy-1-cyclopentanemethanol (**11b**).

Using the procedure described for preparing **11a**, 203 mg (0.47 mmole) of **10b** in diethoxymethyl acetate (1 ml, 6.12 mmoles) yielded a material that was purified by flash column chromatography. The fraction that eluted with methanol-chloroform (1:9) was concentrated with the aid of a rotary evaporator and the residue recrystallized from a small amount of chloroform-methanol (1:1) followed by washing with diethyl ether to give **11b** (169 mg, 81%) as pale pink needles, mp 216°; ir (Nujol): 3500-3150 (NH and OH), 1612, 1589, 1568, and 1535 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.8-2.6 (m, 3 H, C4′-H and C6′-H_2), 3.2-4.2 (m, 4 H, C2′-H, C3′-H and C5′-H_2), 4.5-5.3 (m, 4 H, C1′-H and 3 x OH), 7.10 (t, J = 2 Hz, 1 H, C4-H phenyl), 7.91 (d, J = 2 Hz, 2 H, C2-H, C6-H phenyl), 8.38 (s, 1 H, C8-H purine), 10.32 ppm (s, 1 H, C2-NH purine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.07, 46.70, 55.96, 63.27, 76.60, and 78.06 (cyclopentanemethanol C-atoms), 116.26, 120.27, 134.08, and 142.86 (Ph C-atoms), 125.52, 144.75, 148.87, 153.53, and 154.23 ppm (purine C-atoms).

Anal. Calcd. for $C_{17}H_{16}Cl_3N_5O_3 \cdot 1/2H_2O$: C, 45.00; H, 3.78; N, 15.44. Found: C, 45.14; H, 3.98; N, 15.22.

(±)-(1α,2β,3α,4α)-4-[2-(3,5-Dichlorophenyl)amino-6-aminopurin-9-yl]-2,3-dihydroxy-1-cyclopentanemethanol (**4b**).

Compound **11b** (50 mg, 0.11 mmole) was dissolved in methanol (10 ml), which was cooled (ice-water). To this solution, ammonia was added over a 2 hour period. The resultant mixture was heated in a steel sealed reaction vessel at 120° for 60 hours and then evaporated to dryness by means of a rotary evaporator. The residue was washed well with methanol and then recrystallized from a small amount of methanol. Isolation of the product by filtration and then washing it with ethyl acetate and then diethyl ether gave **4b** (45 mg, 94%) as pale pink needles, mp 224°; ir (Nujol): 3450-3150 (NH and OH), 1640, 1605, 1585, and 1540 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.8-2.6 (m, 3 H, C4′-H and C6′-H_2), 3.1-4.0 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.6-5.2 (m, 4 H, C1′-H and 3 x OH), 6.95 (s, 1 H, C4-H phenyl), 7.09 (br s, 2 H, NH_2), 7.96 and 7.98 (2 s, 3 H, C2-H, C6-H phenyl and C8-H purine), 9.38 ppm (s, 1 H, C2-NH purine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.66, 46.86, 54.99, 63.49, 76.71, and 78.23 (cyclopentanemethanol C-atoms), 115.72, 118.69, 133.86, and 144.37 (Ph C-atoms), 114.52, 138.79, 151.04, 155.32, and 155.86 ppm (purine C-atoms).

Anal. Calcd. for $C_{17}H_{18}Cl_2N_6O_3$: C, 48.01; H, 4.27; N, 19.76. Found: C, 47.86; H, 4.54; N, 19.46.

(±)-(1α,2β,3α,4α)-4-[N^2-(3,5-Dichlorophenyl)guanin-9-yl]-2,3-dihydroxy-1-cyclopentanemethanol (**5b**).

Compound **11b** (70 mg, 0.16 mmole) was dissolved in 1 *N* hydrochloric acid (10 ml) and acetic acid (10 ml). This solution was heated under reflux for 10 hours in an atmosphere of argon. The reaction mixture was then evaporated to dryness on a rotary

evaporator and the residue azeotroped with methanol. The material remaining was purified by flash column chromatography and the fraction that eluted with methanol-chloroform (1:4) was evaporated to dryness by means of a rotary evaporator. The resultant residue was washed with water and then recrystallized from chloroform-methanol-ethyl acetate to give **5b** (54 mg, 81%) as pink needles, mp 202°; ir (Nujol): 3450-3150 (NH and OH), 1690 (C=O), 1605, 1575, and 1550 cm^{-1} (C=N and C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.8-2.6 (m, 3 H, C4′-H and C6′-H_2), 3.2-4.0 (m, 4 H, C2′-H, C3′-H, and C5′-H_2), 4.2-5.4 (m, 4 H, C1′-H and 3 x OH), 7.16 (s, 1 H, C4-H phenyl), 7.77 (s, 2 H, C2-H, C6-H phenyl), 7.89 (s, 1 H, C8-H purine), 9.51 (brs, 1 H, C2-NH purine), 10.91 ppm (br s, 1 H, N1-H purine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.34, 46.70, 55.53, 63.33, 76.82, and 78.17 (cyclopentanemethanol C-atoms), 117.12, 121.24, 134.24, and 141.66 (Ph C-atoms), 118.42, 138.36, 148.54, 149.74, and 157.27 ppm (purine C-atoms).

Anal. Calcd. for $C_{17}H_{17}Cl_2N_5O_4 \cdot H_2O$: C, 45.96; H, 4.31; N, 15.76. Found: C, 46.00; H, 4.46; N, 15.63.

Antiviral Assays.

The antiviral properties for **4** and **5** were determined following literature procedures (HCMV [18], HSV-1 [19,20], HSV-2 [19,20], VZV [18], and HIV [19,21]).

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