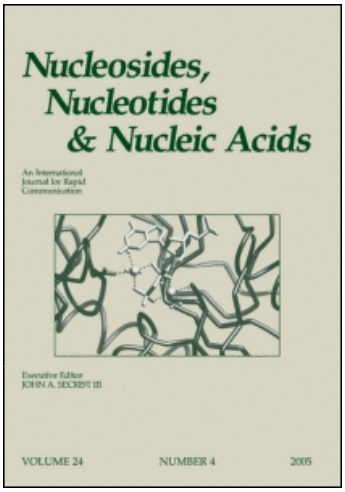

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Biological Activity of Cyclohexenyl Nucleosides. *cis*-5-(9*H*-Purin-9-yl)-3-cyclohexenyl Carbinols and Their 8-Azapurinyl Analogs

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To cite this Article Konkel, Michael J. and Vince, Robert(1995) 'Synthesis and Biological Activity of Cyclohexenyl Nucleosides. *cis*-5-(9*H*-Purin-9-yl)-3-cyclohexenyl Carbinols and Their 8-Azapurinyl Analogs', Nucleosides, Nucleotides and Nucleic Acids, 14: 9, 2061 — 2077
To link to this Article: DOI: 10.1080/15257779508010724
URL: http://dx.doi.org/10.1080/15257779508010724

NUCLEOSIDES & NUCLEOTIDES, 14(9&10), 2061-2077 (1995)

SYNTHESIS AND BIOLOGICAL ACTIVITY OF CYCLOHEXENYL NUCLEOSIDES. *cis*-5-(9*H*-PURIN-9-YL)-3-CYCLOHEXENYL CARBINOLS AND THEIR 8-AZAPURINYL ANALOGS

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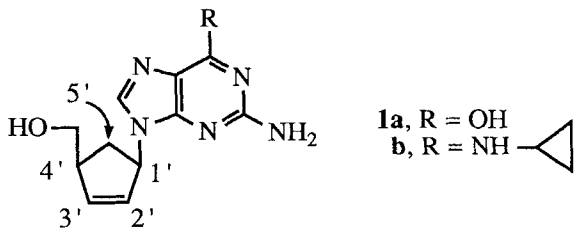
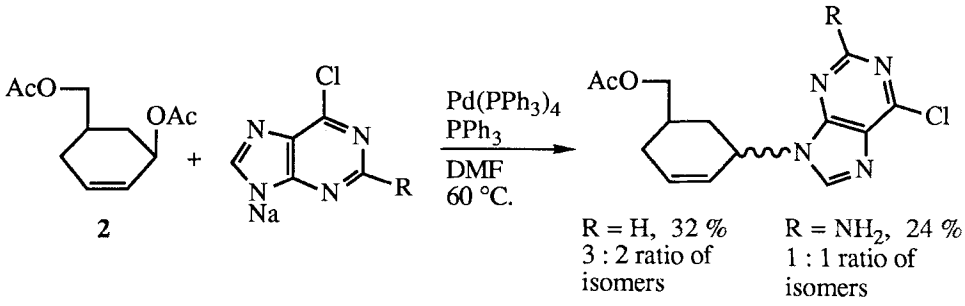
Abstract. 5-Azido-3-cyclohexenecarboxylic acid was reduced to an aminocyclohexenyl-carbinol which was coupled with either 5-amino-4,6-dichloropyrimidine or 2-amino-4,6-dichloropyrimidine, giving 5-pyrimidinyl-3-cyclohexencarbinols. Condensation with triethylorthoformate or nitrous acid formed the purine and 8-azapurine ring systems, respectively. Anti-HIV-1 and cytotoxicity testing results are also described.

Introduction

Carbocyclic 2',3'-didehydrodideoxyguanosine (carbovir, **1a**)[1,2] and its 6-cyclopropylamino analog (1592U89, **1b**)[3] are each converted to carbovir triphosphate by a different anabolic pathway.[4,5] Carbovir triphosphate is the active form[6] of carbovir which has been shown to be a potent and selective inhibitor of HIV-1 replication and infectivity in human T-cells at concentrations 200 - 400 fold below toxic concentrations.[1] Furthermore, carbovir shows lower myelotoxicity[6,7] and lower inhibition of DNA polymerase γ than 3'-azido-3'-deoxythymidine (AZT, zidovudine) or 2',3'-didehydro-2',3'-dideoxythymidine (D4T, stavudine)[8,9] It has been suggested that the inhibition of DNA polymerase γ is the cause of the peripheral neurotoxicity that is associated with the administration of dideoxynucleosides.[10] Thus, carbovir and its prodrug forms, displaying several potential



1a, R = OH
b, R = NH



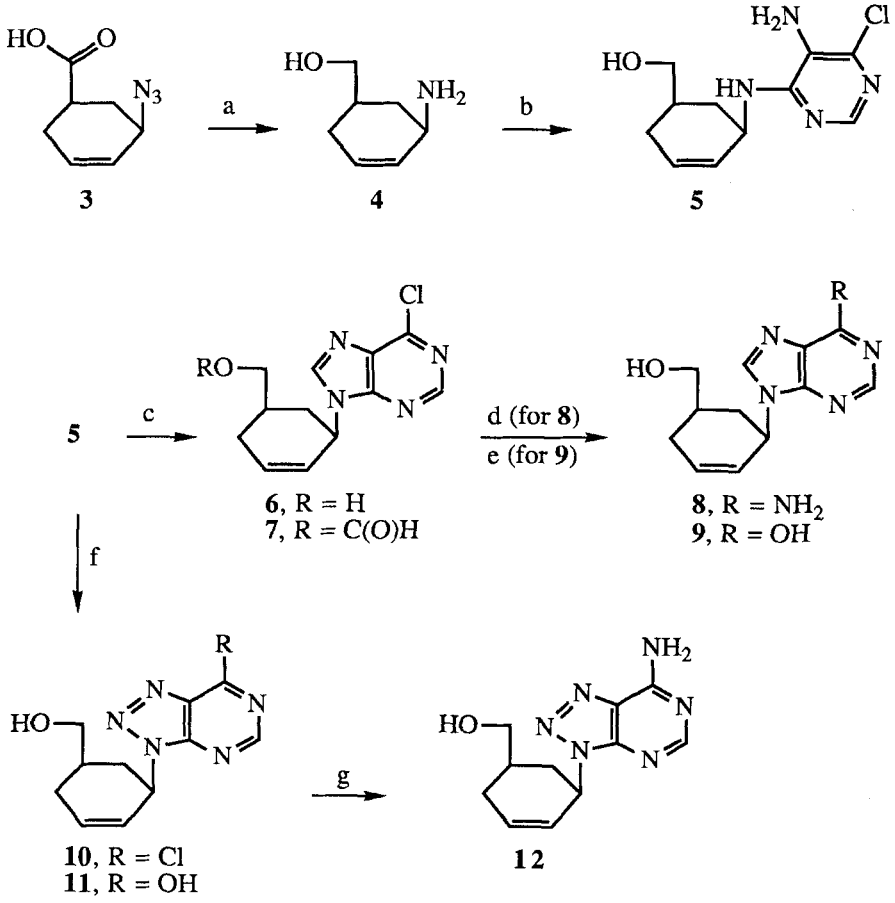
Scheme 1

advantages over approved nucleosides, are currently undergoing clinical evaluation for efficacy against AIDS.

Insertion of a methylene between the 3',4'- carbons of the cyclopentyl moiety of carbovir results in a cyclohexenyl homologue of carbovir (**18**, Scheme 3). Since cyclopentyl and cyclohexyl rings prefer different conformations, it could be postulated that cyclohexyl nucleosides or nucleotides will not fit well into nucleoside or nucleotide binding sites. This line of reasoning may explain why literature on the synthesis of cyclohexyl nucleosides is sparse.[11-15] However, antiviral activity has been observed for a series of pyranosyl-like nucleosides[16,17] in which the six-member ring pyranosyl adopts a chair conformation,[17] showing that enzymes (particularly viral enzymes) will often tolerate significant changes in the sugar moieties of nucleosides. In addition, simple models show that the introduction of a double bond into the cyclohexyl ring flattens it out so that a compound such as guanosine analog **18** can overlay its hydroxyl and purinyl groups with the corresponding moieties in carbovir and guanosine fairly well. Previously, a number of pyranosyl-like nucleosides similar to the cyclohexenyl nucleosides described in this paper have been synthesized elsewhere[18-21]. The present paper describes the synthesis of cyclohexenyl purines and 8-azapurines, including homologues of carbovir (**1a**) and 1592U89 (**1b**).

Synthesis

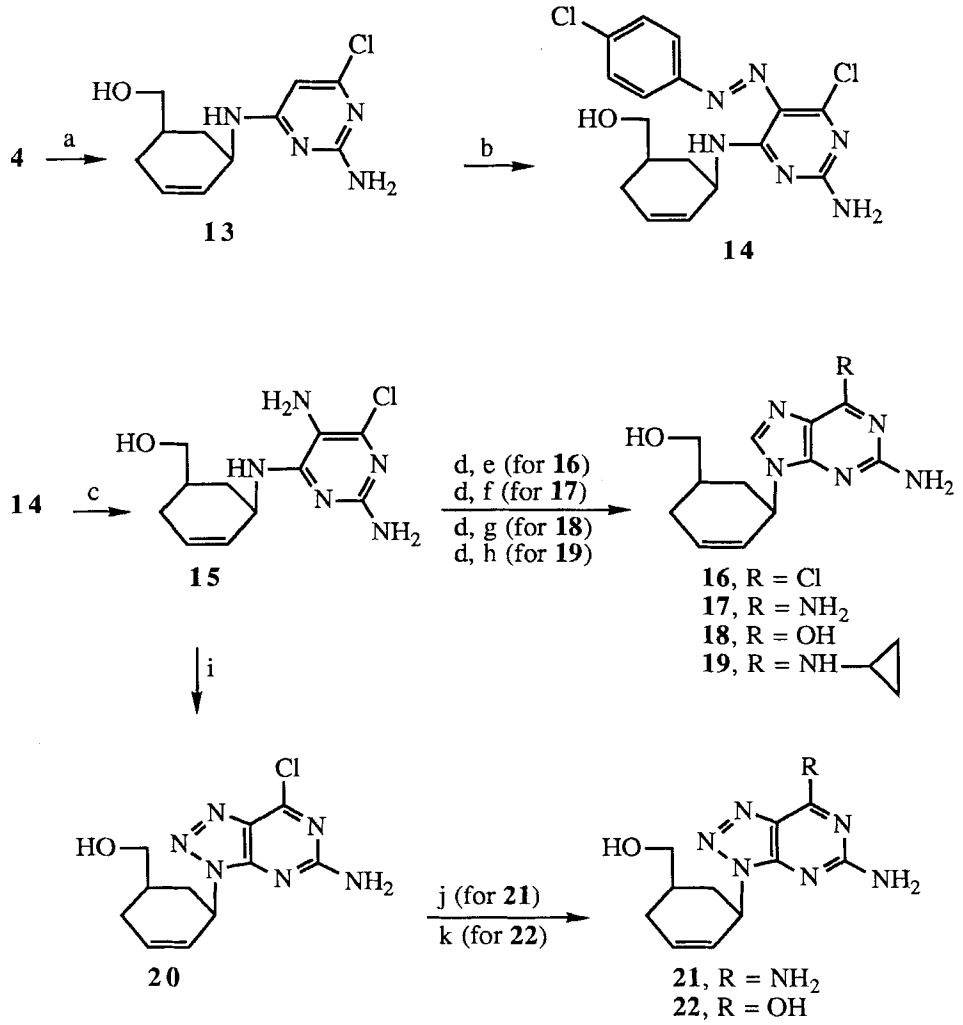
In our initial attempts to synthesize cyclohexenyl nucleosides, diacetate **2**, prepared by literature methods,[22,23] was coupled with sodium salts of purines using palladium reagents (Scheme 1). Although the yields were low, this route appeared at first to be attractive because of the low number of steps to the nucleoside analogs. However, the products



[a]Reagents: (a) LAH, Et_2O (94 %); (b) 5-amino-4,6-dichloropyrimidine, Et_3N, BuOH (83 %); (c) $(EtO)_3CH$, HCl, DMF (**6**: 64 %, **7**: 14 %); (d) i. NH_3, MeOH; ii. 2 N HCl (77 % from **5**); (e) 0.33 N NaOH (71 % from **5**); (f) HNO_2, H_2O - HOAc (**10**: 21 %, **11**: 39 %); (g) NH_3, MeOH (36 % + 8 % recovered **11**).

Scheme 2[a]

turned out to be inseparable mixtures of isomers. Presumably, based on the reported[22,23] palladium coupling reactions of other nucleophiles with acetate **2**, the mixtures consist of *cis* and *trans* isomers. For two reasons, we then changed to a synthetic strategy of building up the purines starting from azide **3** (Scheme 2). First, the *cis* isomer of azide **3** could be obtained with high stereoselectivity,[23] and, second, this strategy allowed us entry to the 8-azapurines in this series of compounds.



[a]Reagents: (a) 2-amino-4,6-dichloropyrimidine, Et_3N, DMF (98 %); (b) *p*-chlorophenyl diazonium chloride, H_2O - HOAc, NaOAc (93 %); (c) Zn, HOAc, H_2O - EtOH (76 %); (d) $(EtO)_3CH$, HCl, DMF; (e) 0.5 N HCl (42 %); (f) i. NH_3, MeOH; ii. 0.5 N HCl (51 %); (g) 1 N HCl (27 %); (h) cyclopropylamine, EtOH (54 %); (i) HNO_2 (63 %); (j) NH_3 (94 %); (k) i. 0.25 N NaOH; ii. adjusted to pH 3 (64 %).

Scheme 3[a]

Synthesis of azide **3** was carried out as described by Murahashi and co-workers,[23] and then reduced with lithium aluminum hydride to give amine **4** (Scheme 2). It was found that, during the work-up, some of the amine remained behind with the filtered solid, thus, significantly lowering the yield. This was remedied by extracting the filtered solid with hot 10 % methanolic ether which dissolved the amine, but did not dissolve any of the aluminum or lithium compounds. Amine **4** was then used for the syntheses of both the 6-substituted purines and the 6-substituted 2-aminopurines.

Amine **4** was condensed with 5-amino-4,6-dichloropyrimidine, giving pyrimidine **5** in 83 % yield. Pyrimidine **5** was cyclized by condensation with triethylorthoformate, giving a mixture of chloropurine **6** and a small amount of formylated chloropurine **7** which was separated by chromatography. The chloropurines were not isolated in the syntheses of the adenosine and inosine analogs, but were treated directly with ammonia or aqueous sodium hydroxide to give adenosine analog **8** and inosine analog **9**, respectively. Condensation of pyrimidine **5** with nitrous acid gave an 80 % yield of a mixture of azapurines **10** and **11** in an approximately 1:1 ratio, as determined by ^{1}H NMR. Chromatographic separation gave azapurines **10** and **11** in yields of 21 % and 39 %, respectively. A crude mixture of azapurines **10** and **11** was treated with ammonia, giving aminoazapurine **12** and recovered azapurine **11** which were separated by fractional precipitation.

Amine **4** was condensed with 2-amino-4,6-dichloropyrimidine, giving pyrimidine **13** in 98 % yield (Scheme 3). Pyrimidine **13** was treated with *p*-chlorobenzenediazonium chloride by the method of Shealy and Clayton,[24] giving azopyrimidine **14** which was reduced with zinc and acetic acid to pyrimidine **15**. The reduction worked best when the full 2-1/2 hours of reflux were carried out, the zinc was rapidly filtered away, and the purification was carried out the same day. Deviation from any of these gave lower yields and less pure product. Pyrimidine **15** was cyclized by condensation with triethylorthoformate, followed by treatment with 0.5 N HCl, giving chloropurine **16**. It was found to be more efficient to not isolate chloropurine **16** for further synthesis. Instead, the crude condensation product was treated directly with ammonia, aqueous HCl, or cyclopropylamine, and followed by appropriate work-up to give purines **17**, **18**, and **19**, respectively. Condensation of pyrimidine **15** with nitrous acid gave chloroazapurine **20** in 63 % yield. Ammonolysis of chloroazapurine **20** gave diaminoazapurine **21** in 94 % yield, while base hydrolysis gave azapurine **22**.

Results

Compounds **6**, **8-12**, and **16-22** were evaluated for cytotoxicity against P388 mouse leukemia cells. The 6-chloro compounds **6**, **16**, and **20** exhibited significant activity

(IC_{50}'s of 4, 18, and 3 μg/mL, respectively). All other compounds had IC_{50} values above 50 μg/mL. Antiviral screening revealed that none of the nucleoside analogs exhibited significant anti-HIV activity .

Experimental

Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Melting points were determined on a Mel-Temp II apparatus and are corrected. The NMR spectra were obtained on a Bruker AC-200, Varian Unity 300 or Varian Unity 500 spectrometers and referenced to the solvent. Chemical shifts are expressed in ppm and coupling constants are in hertz. IR spectra were determined with KBr pellets (solids) or plates (oils) on a Nicolet 5DXC spectrometer and given in cm^{-1}. Electron impact (EI) mass spectra (MS) were obtained with a Kratos/AEI MS-30 spectrometer, chemical impact (CI) MS were obtained with a Finnigan 4000 spectrometer, and fast-atom bombardment (FAB) MS were obtained with a VG 7070E-HF spectrometer. Thin-layer chromatography was performed on Polygram® Sil G/UV_{254} (0.25 mm), column chromatography was performed on EM Science silica gel 60 (230 - 400 mesh), and preparative thin-layer chromatography was performed on EM Science silica gel 60 F_{254} (1.0 mm layer). DMF was dried over molecular sieves. All other solvents and chemicals are reagent grade unless specified otherwise. All stirring was done with magnetic stir bars. Cytotoxicities were determined using a previously reported protocol,[25] and antiviral evaluation was carried out under the auspices of the National Institutes of Health.

***cis*-(3-Amino-4-cyclohexenyl)carbinol (4).** Azide **3**[23] (4.06 g, 24.3 mmol) in anhydrous ether (50 mL) was added dropwise, *via* an addition funnel, over 90 min to a stirring solution of lithium aluminum hydride (6.32 g, 166 mmol, 7 equiv.) in anhydrous ether (80 mL) at room temperature. The solution was stirred for an additional 3-1/2 h, after which, it was neutralized by carefully adding water dropwise. The resulting solid was filtered, and extracted with hot ether / methanol (9:1, 2 X 50 mL). The combined filtrate / extracts were evaporated under reduced pressure, giving analytical amine **4** as a white powder (2.89 g, 22.8 mmol, 94 %, mp 107.5 - 110 °C). ^1H NMR (200 MHz, methanol-d_6) δ 5.71 (m, 1 H), 5.56 (m, 1 H), 4.86 (s, 3 H), 3.42 (d, 2 H, J = 5.9) overlapping 3.36 (m, 1 H), 2.02 (m, 2 H), 1.81 - 1.67 (m, 2 H), 0.96 (dd, 1 H, J = 22.7, 12.0); ^{13}C NMR / DEPT (50 MHz, methanol-d_6) δ 133.4 (CH), 128.0 (CH), 67.9 (CH_2), 49.3 (CH), 37.7 (CH), 37.2 (CH_2), 29.4 (CH_2); IR 3324, 2829; MS (EI, 70

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eV, 200 °C) *m / e* (intensity) 128 (2, $M^+ + 1$), 127 (6, M^+), 69 (100). Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 65.89; H, 10.11; N, 10.87.

***cis*-[3-(5-Amino-6-chloro-4-pyrimidinyl)amino]-4-cyclohexenyl)carbinol (5).** A solution of amine **4** (0.16 g, 1.26 mmol) and 5-amino-4,6-dichloropyrimidine (0.27 g, 1.65 mmol) in *n*-butanol (7 mL) and triethylamine (3 mL) was refluxed under N_2 for 40 h. The solvent was evaporated under vacuum, leaving a tacky residue which was packed onto a column and eluted with ethyl acetate. The solvent was removed from the fractions with R_f = 0.34 (ethyl acetate) by evaporation under reduced pressure, giving analytical pyrimidine **5** as a white foam (266 mg, 1.05 mmol, 83 %, mp 194.5 °C). ^1H NMR (200 MHz, acetone-d_6) δ 7.82 (s, 1 H), 5.91 (broad d, 1 H, *J* = 5), 5.80 (m, 1 H), 5.65 (d, 1 H, *J* = 8.8), 4.87 (broad m, 1 H), 4.59 (broad s, 2 H), 3.67 (t, 1 H, *J* = 5.4), 3.47 (dd, 2 H, *J* = 5.6, 4.5), 2.32 - 2.17 (m, 2 H), 1.95 - 1.77 (m, 2 H), 1.19 (dd, 1 H, *J* = 22.9, 11.9); IR 3458, 3366, 1587; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 257 (3, $M^+ + 3$), 256 (14, $M^+ + 2$), 255 (9, $M^+ + 1$), 254 (47, M^+), 144 (100). Anal. Calcd for $C_{11}H_{15}N_4OCl$: C, 51.87; H, 5.94; N, 22.00. Found: C, 52.06; H, 6.09; N, 21.82.

***cis*-[3-(6-Chloro-9*H*-purin-9-yl]-4-cyclohexenyl)carbinol (6) and *cis*-[3-(6-Chloro-9*H*-purin-9-yl]-4-cyclohexenyl)carbinol formate (7).** Concentrated HCl (3 drops, ~ 0.12 mL) was added to a solution of pyrimidine **5** (100.0 mg, 0.393 mmol) in triethylorthoformate (2.5 mL) and DMF (1.0 mL). The solution was protected with a drying tube and stirred for 20 h. The solvent was removed by evaporation under vacuum, giving a crude mixture of chloropurines **6** and **7** as a viscous oil. The crude mixture was adsorbed onto a preparative TLC plate and resolved twice with ethyl acetate. The lower band was removed and extracted with ethyl acetate (2 X 15 mL) and ethyl acetate / methanol (50:1, 15 mL). The combined extracts were removed by evaporation under reduced pressure, giving analytical chloropurine **6** as a tacky clear paste (66.7 mg, 0.252 mmol, 64 %), which solidified overnight (white, mp 112 - 114 °C). R_f = 0.38 (ethyl acetate); ^1H NMR (200 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.18 (s, 1 H), 6.12 (m, 1 H), 5.73 (broad d, 1 H, *J* = 9.3), 5.42 (m, 1 H), 3.61 (m, 2 H), 2.99 (broad s, 1 H + H_2O), 2.43 - 2.04 (m, 4 H), 1.60 (dd, 1 H, *J* = 23.0, 11.5); ^{13}C NMR / DEPT (50 MHz, $CDCl_3$) δ 158.8 (C), 151.7 (CH), 150.9 (C), 143.6 (CH), 132.7 (CH), 131.6 (C), 125.2 (CH), 66.4 (CH_2), 52.6 (CH), 36.1 (CH), 33.9 (CH_2), 27.8 (CH_2); IR 3625 - 3125 (broad), 1592, 1558; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 266 (5, $M^+ + 2$), 265 (3, $M^+ + 1$), 264 (14, M^+), 155 (100). Anal. Calcd for $C_{12}H_{13}N_4OCl \cdot 5/6\ CH_3OH$: C, 52.89; H, 5.65; N, 19.23. Found: C, 52.93; H, 5.30; N, 18.94.

The upper band on the TLC plate was removed and extracted with ethyl acetate (3 X 15 mL). The combined solvent was removed by evaporation under reduced pressure,

giving analytical chloropurine **7** as a white paste that solidified overnight (16.3 mg, 0.056 mmol, 14 %, mp 107 - 108 °C). R_f = 0.71 (ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 8.16 (s, 1 H), 8.06 (s, 1 H), 6.13 (m, 1 H), 5.77 (broad d, 1 H, *J* = 8.9), 5.45 (m, 1 H), 4.13 (m, 2 H), 2.44 - 2.19 (m, 3 H), 2.05 (m, 1 H), 1.64 (dd, 1 H, *J* = 23, 13); IR 1717, 1587; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 294 (5, M^+ + 2), 293 (3, M^+ +1), 292 (15, M^+), 155 (100). Anal. Calcd for $C_{13}H_{13}N_4O_2Cl$: C, 53.34; H, 4.48; N, 19.14. Found: C, 53.39; H, 4.60; N, 19.15.

***cis*-[3-(6-Amino-9*H*-purin-9-yl]-4-cyclohexenyl)carbinol (8).** A crude mixture of chloropurines **6** and **7** (see previous experiment), synthesized from pyrimidine **5** (0.50 g, 1.96 mmol), was transferred to a bomb with methanol (5 mL). The bomb and contents were cooled in a dry-ice bath, and liquid ammonia (~ 25 mL) was added. The bomb was sealed and heated, with stirring, in a 65 °C oil-bath for 54 h. The reaction mixture was then cooled, the ammonia was vented, the solvent was removed by evaporation under reduced pressure, and 2 N HCl (10 mL) was added. The resulting solution was heated, with stirring, in a 60 °C oil-bath for 1 h. The solvent was removed by evaporation under vacuum, water (5 mL) was added, and 5 N NaOH was added until basic. The resulting solution was stored in a refrigerator overnight. The resulting brown precipitate was vacuum-filtered and washed with hot ether / methanol (9:1, 2 X 20 mL), leaving adenosine analog **8** as an off-white solid (138.0 mg, mp 178 - 180 °C). Second and third crops of adenosine analog **8** were obtained as white solids (208.3 mg, mp 190 - 191 °C) from the aqueous filtrate. The remaining aqueous solution was extracted with ethyl acetate / acetone (3:2, 3 X 25 mL), and the combined organic solvents were removed by evaporation under reduced pressure, leaving a white gum. The gum was triturated with a small amount of methanol and vacuum-filtered, leaving additional adenosine analog **8** as a white solid (25.0 mg). Total weight of adenosine analog **8**: 371.3 mg (1.51 mmol, 77 %). A small amount was recrystallized from methanol to give an analytical sample (mp 195 - 195.5 °C). R_f = 0.65 ($CHCl_3$ / methanol , 4:1); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.14 (s, 1 H), 8.10 (s, 1 H), 7.25 (s, 2 H), 5.98 (m, 1 H), 5.71 (broad d, 1 H, *J* = 9.8), 5.22 (m, 1 H), 4.67 (m, 1 H), 3.36 (m, 2 H), 2.30 - 2.10 (m, 2 H), 2.05 - 1.80 (m, 2 H), 1.64 (dd, 1 H, *J* = 22, 11); IR 3390, 1650, 1597, 1572; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 246 (5, M^+ +1), 245 (29, M^+), 136 (100). Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.64; H, 6.07; N, 28.36.

***cis*-1,9-Dihydro-9-[5-(hydroxymethyl)-2-cyclohexen-1-yl]-6*H*-purin-6-one (9).** A solution of crude chloropurines **6** and **7** (see earlier experiment), synthesized from pyrimidine **5** (318.2 mg, 1.25 mmol), in 0.33 N NaOH (20 mL) was refluxed for 6 h, and

then cooled overnight. The solvent was removed by evaporation under vacuum, and the residue was packed onto a column and eluted with a gradient of ethyl acetate to ethyl acetate / methanol (4:1). The solvent was removed from the fractions with $R_f = 0.11$ (ethyl acetate / methanol, 9:1) by evaporation under reduced pressure, giving inosine analog **9** as a white solid (218.4 mg, 0.89 mmol, 71 %, mp 257 - 260 °C, dec.). A small amount was recrystallized from methanol to give an analytical sample (mp 268.5 - 269 °C, dec.). ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.25 (broad s, 1 H), 8.04 (s, 2 H), 5.98 (m, 1 H), 5.70 (broad d, 1 H, J = 10.0), 5.17 (m, 1 H), 4.66 (m, 1 H), 3.37 (broad s, 2 H + H_2O), 2.18 (m, 2 H), 1.90 (m, 2 H), 1.63 (dd, 1 H, J = 22.9, 11.5); ^{13}C NMR / DEPT (50 MHz, DMSO-d_6) δ 190.1 (C), 156.9 (C), 148.2 (C), 145.5 (CH), 138.8 (CH), 130.9 (CH), 126.7 (CH), 65.4 (CH_2), 52.1 (CH), 38.5 (CH), 33.4 (CH_2), 27.8 (CH_2); IR 3418, 1698, 1685; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 247 (4, M^+ +1), 246 (22, M^+), 137 (100). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.29; H, 5.96; N, 22.49.

***cis*-[3-(7-Chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-4-cyclohexenyl] carbinol (10) and *cis*-3,6-dihydro-3-[5-(hydroxymethyl)-2-cyclohexenyl]-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (11).** Pyrimidine **5** (700 mg, 2.75 mmol) was dissolved in a mixture of water (105 mL) and acetic acid (70 mL). The solution was cooled to 0 °C, and then a solution of sodium nitrite (214 mg, 3.10 mmol) in water (14 mL) was added dropwise over 25 min. The solution was stirred at 0 °C for 90 min and then allowed to come to room temperature and stirred for 1 h. Saturated aqueous sodium bicarbonate (600 mL) was added, the solution was stored in a refrigerator overnight, and then extracted with ether (5 X 250 mL). The combined ether was rinsed, consecutively, with saturated aqueous sodium bicarbonate (250 mL) and saturated aqueous sodium chloride (250 mL), and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation under reduced pressure, giving light tan crystals (561.0 mg). A sample (130.2 mg) was resolved by preparative TLC ($CHCl_3$ / methanol, 4:1), and the band at $R_f = 0.84$ was extracted with $CHCl_3$ / methanol (3:1, 3 X 15 mL). The solvent was removed by evaporation under reduced pressure, giving analytical azapurine **10** (34.7 mg, 0.131 mmol, 21 %, mp 192.5 - 193 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 6.13 (m, 1 H), 5.80 (broad d, 1 H, J = 8), 5.67 (m, 1 H), 4.06 (t, 1 H, J = 7), 3.53 (m, 2 H), 2.40 - 2.00 (m, 5 H); IR 1725, 1554; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 267 (6, M^+ + 2), 266 (3, M^+ +1), 265 (17, M^+), 138 (100). Anal. Calcd for $C_{11}H_{12}N_5OCl$: C, 49.73; H, 4.55; N, 26.36. Found: C, 49.56; H, 4.70; N, 26.16.

The band at $R_f = 0.67$ was extracted with $CHCl_3$ / methanol (3:1, 3 X 15 mL) and the solvent was removed by evaporation under reduced pressure, giving azapurine **11** (60.3

mg, 0.246 mmol, 39 %, mp 216 - 217 °C). Azapurine **11** from the next experiment matched azapurine **11** from this experiment in all properties.

***cis*-[3-(7-Amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-4-cyclohexenyl] carbinol (12) and *cis*-3,6-dihydro-3-[5-(hydroxymethyl)-2-cyclohexenyl]-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (11).** A portion (210.2 mg) of the crude product from the previous experiment was transferred to a bomb with methanol (100 mL). The bomb and contents were cooled in a dry-ice bath and liquid ammonia (~ 50 mL) was added. The bomb was sealed and heated, with stirring, in a 65 °C oil-bath for 48 h. The reaction mixture was then cooled and the ammonia was vented. The solvent was removed by evaporation under reduced pressure, leaving an off-white solid (~ 1.5 g). The solid was triturated three times with small amounts of hot ethanol and with acetone, leaving a gray solid. The solid was recrystallized from water, giving azapurine **12** as pale gray crystals (87.3 mg, mp 199.5 - 201.5 °C). The filtrate gave a second batch of azapurine **12** as white crystals (3.9 mg, mp 188 - 197 °C). Total for azapurine **12**: 91.2 mg, 0.370 mmol, 36 %. A portion of azapurine **12** (68.9 mg) was dissolved in methanol and filtered. The methanol was removed by evaporation under reduced pressure, giving analytical off-white powder (66.6 mg, mp 209 - 209.5 °C). R_f = 0.77 ($CHCl_3$ / methanol, 4:1); ^1H NMR (200 MHz, DMSO-d_6) δ 8.44 (broad s, 1 H), 8.30 (s, 1 H), 8.09 (broad s, 1 H), 6.00 (m, 1 H), 5.76 (broad d, 1 H, J = 10), 5.55 (m, 1 H), 4.63 (m, 1 H), 3.36 (broad s, 2 H + H_2O), 2.30 - 1.90 (m, 5 H); IR 3281, 3243, 1700, 1558; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 247 (0.6, M^+ +1), 246 (3, M^+), 137 (100). Anal. Calcd for $C_{11}H_{14}N_6O$: C, 53.65; H, 5.73; N, 34.13. Found: C, 53.48; H, 5.78; N, 34.38.

The volume of the filtrate was reduced, giving additional solid (62.1 mg) which was resolved on a preparative TLC plate ($CHCl_3$ / methanol, 8:1), and the major band was extracted with $CHCl_3$ / methanol (4:1, 4 X 15 mL). The solvent was removed by evaporation under reduced pressure, giving analytical azapurine **11** (19.2 mg, 0.078 mmol, 8 %, mp 215 - 218 °C). ^1H NMR (200 MHz, DMSO-d_6) δ 12.7 (broad s, 1 H), 8.25 (s, 1 H), 6.00 (m, 1 H), 5.75 (broad d, 1 H, J = 9.8), 5.57 (m, 1 H), 4.68 (broad s, 1 H), 3.37 (broad s, 2 H + H_2O), 2.4 - 1.8 (m, 5 H); IR 3289, 1726; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 247 (0.5, M^+), 138 (100). Anal. Calcd for $C_{11}H_{13}N_5O_2 \cdot 3/4\ H_2O$: C, 50.67; H, 5.60; N, 26.86. Found: C, 50.76; H, 5.52; N, 26.74.

***cis*-[3-(2-Amino-6-chloro-4-pyrimidinyl)amino]-4-cyclohexenyl)carbinol (13).** A solution of amine **4** (2.00 g, 15.7 mmol) and 2-amino-4,6-dichloropyrimidine (3.38 g, 20.6 mmol) in *n*-butanol (70 mL) and triethylamine (30 mL) was refluxed under N_2 for 46 h. The solvent was evaporated under vacuum, leaving an off-white solid. The

solid was triturated with a small amount of methanol and filtered, giving analytical pyrimidine **13** as a white powder (3.24 g, mp 197 - 198.5 °C). The filtrate gave a second batch of pyrimidine **13** as white crystals (0.69 g, mp 197 - 198.5 °C). Total for pyrimidine **13**: 3.93 g, 15.4 mmol, 98 %. ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.17 (broad d, 1 H, J = 8), 6.44 (broad s, 2 H), 5.72 (m & s overlapping, 2 H), 5.51 (broad d, 1 H, J = 10.0), 4.58 (m) overlapping 4.56 (t , 2 H, J = 5.1), 3.30 (m, 2 H), 2.03 (m, 2 H), 1.72 (m, 2 H), 1.05 (m, 1 H); IR 3460, 3156, 1638, 1585, 1562; MS (EI, 70 eV, 200 °C) m / e (intensity) 257 (4, M^+ + 3), 256 (29, M^+ + 2), 255 (18, M^+ + 1), 254 (85, M^+), 223 (100). Anal. Calcd for $C_{11}H_{15}N_4OCl$: C, 51.87; H, 5.94; N, 22.00. Found: C, 52.06; H, 5.95; N, 21.89.

***cis*-[3-[2-Amino-6-chloro-5-[(4-chlorophenyl)azo]-4-pyrimidinyl]amino-4-cyclohexenyl]carbinol (14).** Sodium nitrite (1.08 g, 15.7 mmol) was added to an ice-cooled solution of *p*-chloroaniline in 5 N HCl (35 mL). and the resulting solution was stirred for 35 min. Pyrimidine **13** (2.80 g, 11.0 mmol) and sodium acetate (22.5 g) were dissolved in aqueous 50 % acetic acid (480 mL) and cooled in an ice-bath. The first solution was added dropwise to the second solution over 20 min, and the resulting solution was allowed to come to room temperature and stirred for 47 h. The solution was filtered and washed with water, giving analytical azopyrimidine **14** as yellow needles (1.79 g, mp 253.4 - 254 °C). The filtrate was stirred for an additional 26 h (total: 73 h) and filtered, giving a second batch of azopyrimidine **14** as orange needles (0.54 g, mp 248.5 - 249.5 °C). The volume of the filtrate was reduced down to ~ 100 mL by evaporation under vacuum, and set in a refrigerator overnight. The solution was then filtered to give a third crop of azopyrimidine **14** as orange needles (1.23 g, mp 241 - 243 °C). The filtrate was again set in the refrigerator overnight, and filtered giving a fourth crop of azopyrimidine **14** as orange needles (0.47 g, mp 246 - 247.5 °C). Additional precipitate did not form. Total for azopyrimidine **14**: 4.03 g, 10.25 mmol, 93 %. ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.24 (d, 1 H, J = 7.8), 7.66 (d overlapping broad s, 4 H, J = 8.6), 7.53 (d, 2 H, J = 8.6), 5.83 (m, 1 H), 5.65 (broad d, 1 H, J = 9.9), 4.82 (m, 1 H), 4.59 (m, 1 H), 3.34 (m, 2 H), 2.17 (m, 1 H), 2.02 (m, 1 H), 1.81 (m, 2 H), 1.25 (dd, 1 H, J = 21.9, 11.1); ^{13}C NMR / DEPT (50 MHz, DMSO-d_6) δ 165.1 (C), 161.3 (C), 154.5 (C), 150.8 (C), 133.5 (C), 129.6 (2 CH's), 129.3 (CH), 128.4 (CH), 122.9 (2 CH's), 118.5 (C), 65.6 (CH_2), 47.2 (CH), 36.2 (CH), 32.6 (CH_2), 28.0 (CH_2); IR 3157, 1656, 1564; MS (EI, 70 eV, 200 °C) m / e (intensity) 396 (1, M^+ + 4), 395 (1, M^+ + 3), 394 (7, M^+ + 2), 393 (2, M^+ + 1), 392 (10, M^+), 266 (100). Anal. Calcd for $C_{17}H_{18}N_6OCl_2$: C, 51.92; H, 4.61; N, 21.37. Found: C, 51.74; H, 4.77; N, 21.19.

***cis*-[3-(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]-4-cyclohexenyl)carbinol (15).** A solution of azopyrimidine **14** (1.50 g, 3.81 mmol) in water (40 mL) and ethanol (40 mL) was stirred over zinc dust (2.55 g) under N_2. Glacial acetic acid (1.6 mL) was added and the solution was brought to reflux. After 2-1/2 h, the solution was partially cooled and rapidly filtered through sintered glass with the use of vacuum-suction. The filtered solid was rinsed with a small portion of ethanol and the filtrate was evaporated under vacuum. The resulting oily residue was adsorbed onto silica gel which was packed on a column and eluted with ethyl acetate. The solvent was removed from the fractions with $R_f = 0.21$ (ethyl acetate) by evaporation under reduced pressure, giving pyrimidine **15** as a peach powder (0.78 g, 2.89 mmol, 76 %, mp 182 - 186 °C). A sample was triturated in methanol / water and filtered, giving an analytical sample (mp 187 - 188 °C). $R_f = 0.62$ (chloroform / methanol, 4:1); ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.37 (d, 1 H, J = 8.1), 5.75 (m, 1 H), 5.63 (s, 2 H), 5.57 (broad d, 1 H, J = 9.9), 4.71 (m, 1 H), 4.56 (t, 1 H, J = 5), 3.98 (broad s, 2 H), 3.32 (m, 2 H + H_2O), 2.15 - 2.00 (m, 2 H), 1.75 (m, 2 H), 1.16 (m, 1 H); IR 3296, 1636, 1578; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 272 (2, $M^+ + 3$), 271 (15, $M^+ + 2$), 270 (7, $M^+ + 1$), 269 (50, M^+), 158 (100). Anal. Calcd for $C_{11}H_{16}N_5OCl$: C, 48.98; H, 5.98; N, 25.96. Found: C, 48.77; H, 5.76; N, 25.81.

***cis*-[3-(2-Amino-6-chloro-9*H*-purin-9-yl]-4-cyclohexenyl)carbinol (16).** Concentrated HCl (2 drops, ~ 0.08 mL) was added to an ice-cooled solution of pyrimidine **15** (100.0 mg, 0.371 mmol) in triethylorthoformate (3.0 mL) and DMF (1.0 mL). The solution was protected with a drying tube, brought to room temperature, and stirred for 19 h. The solvent was removed by evaporation under vacuum, 0.5 N HCl (5 mL) was added, and the resulting solution was stirred for 2-1/2 h. 1 N NaOH was added to pH 9 and solvent was removed by evaporation under vacuum, giving crude chloropurine **16**. The residue was resolved on preparative TLC plates with ethyl acetate and the band at $R_f = 0.3$ was extracted with $CHCl_3$ / methanol (4:1, 4 X 15 mL). The solvent was removed by evaporation under reduced pressure, giving chloropurine **16** as yellow crystals (43.1 mg, 0.154 mmol, 42 %, mp 180 - 184 °C). A small portion was recrystallized from ethanol, giving analytical yellow crystals (mp 187.5 - 188 °C). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.09 (s, 1 H), 6.94 (s, 2 H, D_2O exch), 6.00 (m, 1 H), 5.72 (d, 1 H, J = 10.0), 5.11 (m, 1 H), 4.63 (t, 1 H, J = 5.3, D_2O exch), 3.34 (m, 2 H), 2.20 (m, 2 H), 1.91 (m, 2 H, J = 16.5), 1.58 (m, 1 H); IR 3321, 3214, 1634, 1608, 1565; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 282 (2, $M^+ + 3$), 281 (11, $M^+ + 2$), 280 (6, $M^+ + 1$), 279 (30, M^+), 170 (100). Anal. Calcd for $C_{12}H_{14}N_5OCl \cdot 3/10\ C_2H_5OH$: C, 51.55; H, 5.42; N, 23.86. Found: C, 51.26; H, 5.20; N, 23.80.

***cis*-[3-(2,6-Diamino-9*H*-purin-9-yl]-4-cyclohexenyl)carbinol (17).** Crude chloropurine **16** (see previous experiment), synthesized from pyrimidine **15** (534.9 mg, 1.98 mmol), was transferred to a bomb with methanol (15 mL). The bomb and contents were cooled in a dry-ice bath and liquid ammonia (~ 30 mL) was added. The bomb was sealed and heated, with stirring, in a 65 °C oil-bath for 48 h. The reaction mixture was then cooled and the ammonia was vented. The solvent was removed by evaporation under reduced pressure and 0.5 N HCl (10 mL) was added. The resulting solution was heated, with stirring, in a 60 °C oil-bath for 1 h. The solution was then cooled and 5 N NaOH was added until basic. The solvent was removed by evaporation under reduced pressure and the residue was placed on a column which was eluted with a gradient of chloroform to chloroform / methanol (5:1). The solvent was removed from the fractions with $R_f = 0.33$ (chloroform / methanol, 4:1) by evaporation under reduced pressure, giving purine **17** as a peach solid (262.3 mg, 1.01 mmol, 51 %, mp 247 - 250 °C, dec.). A sample was recrystallized from methanol to give a pale peach analytical sample (mp 252 °C). ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.64 (s, 1 H), 6.69 (s, 2 H), 5.98 (m, 1 H), 5.82 (s, 2 H), 5.70 (broad d, 1 H, J = 9.8), 4.99 (m, 1 H), 4.63 (t, 1 H, J = 5), 3.36 (m, 2 H + H_2O), 2.19 (m, 2 H), 1.89 (m, 2 H), 1.64 (dd, 1 H, J = 23, 13); IR 3472, 3403, 3352, 3329, 3117, 1664, 1558, 1404; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 261 (3, M^+ +1), 260 (22, M^+), 150 (100). Anal. Calcd for $C_{12}H_{16}N_6O$ • 1/4 CH_3OH: C, 54.84; H, 6.39; N, 31.32. Found: C, 54.90; H, 6.45; N, 31.33.

***cis*-2-Amino-1,9-dihydro-9-[5-(hydroxymethyl)-2-cyclohexen-1-yl]-6*H*-purin-6-one (18).** A solution of crude chloropurine **16** (see earlier experiment), synthesized from pyrimidine **15** (400.0 mg, 1.48 mmol), in 1 N HCl (40 mL) was refluxed for 6 h under N_2. The solvent was removed by evaporation under reduced pressure, a few mL's of water was added to the orange syrup, and then 1 N NaOH was added dropwise to pH 7. The solvent was removed by evaporation under vacuum, and the residue was placed on a column which was eluted with a gradient of chloroform to chloroform / methanol (4:1). The solvent was removed from the fractions with $R_f = 0.20$ (chloroform / methanol, 4:1) by evaporation under reduced pressure, giving guanosine analog **18** as an orange solid (348.3 mg, 1.33 mmol, 90 %). The orange solid was recrystallized from water / methanol (4:1), giving analytical guanosine analog **18** as an off-white solid (103.3 mg, 0.40 mmol, 27 %, mp 285 - 287 °C, dec.). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.54 (s, 1 H, D_2O exch), 7.58 (s, 1 H), 6.44 (s, 2 H, D_2O exch), 5.95 (m, 1 H), 5.65 (broad d, 1 H, J = 10.2), 4.93 (m, 1 H), 4.59 (t, 1 H, J = 5.2, D_2O exch), 3.32 (m, 2 H), 2.13 (m, 2 H), 1.83 (m, 2 H), 1.43 (m, 1 H); IR 3438, 3286, 1684, 1627, 1598, 1562; MS (FAB, 9 $^+$eV) *m / e* 262 (M^+ +1). Anal. Calcd for $C_{12}H_{15}N_5O_2$ • 1/3 H_2O: C, 53.92; H, 5.91; N, 26.20. Found: C, 54.06; H, 5.81; N, 26.09.

***cis*-[3-[2-Amino-6-(cycloproylamino)-9*H*-purin-9-yl]-4-cyclohexenyl] carbinol (19).** A solution of crude chloropurine **16** (see earlier experiment), synthesized from pyrimidine **15** (200.0 mg, 0.74 mmol), and cyclopropylamine (0.25 mL, 206 mg, 3.6 mmol) in ethanol (15 mL) was refluxed for 33 h under N_2. Additional cyclopropylamine (0.25 mL each) was added after 6 and 19 h. Total cyclopropylamine: 0.75 mL, 618 mg, 10.8 mmol. The solvent was removed by evaporation under reduced pressure, leaving an orange syrup which was placed on a column and eluted with a gradient of ethyl acetate to ethyl acetate / methanol (10:1). The solvent was removed from the fractions with R_f = 0.50 (ethyl acetate / methanol, 5:1) by evaporation under reduced pressure, giving analytical purine analog **19** as a pale yellow solid (120.9 mg, 0.40 mmol, 54 %, mp at 112 - 115 °C, collapses at ~ 100 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60 (s, 1 H), 7.28 (m, 1 H, D_2O exch), 5.95 (m, 1 H), 5.84 (s, 2 H, D_2O exch), 5.66 (broad d, 1 H, J = 9.6), 4.96 (m, 1 H), 4.58 (m, 1 H, D_2O exch), 3.31 (m, 2 H), 3.01 (m, 1 H), 2.07 (m, 2 H), 1.81 (m, 2 H), 1.44 (dd, 1 H, J = 23.1, 11.4), 0.65 - 0.56 (m, 4 H); IR 3600 - 3210 (broad), 1596; MS (FAB, 4 +Ve) 301 (M^+ + 1). Anal. Calcd for $C_{15}H_{20}N_6O$ • 3/5 CH_3OH: C, 58.63; H, 7.06; N, 26.30. Found: C, 58.50; H, 6.90; N, 26.40.

***cis*-[3-(5-Amino-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-4-cyclohexenyl] carbinol (20).** Pyrimidine **15** (0.66 g, 2.45 mmol) was dissolved in a mixture of water (70 mL) and acetic acid (25 mL). The solution was cooled to 0 °C under N_2, and then a solution of sodium nitrite (0.17 mg, 2.46 mmol) in water (10 mL) was added dropwise, *via* syringe, over 8 min. The solution was stirred at 0 °C for 75 min, and then allowed to room temperature and stir for 90 min. The solvent was removed by evaporation under vacuum, leaving a pale tan solid. The solid was suspended in hot methanol and then cooled. The solid was vacuum-filtered, giving analytical azapurine **20** as a white powder (0.43 g, 1.53 mmol, 62 %, mp 175.5 - 176 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (s, 2 H, D_2O exch), 5.97 (m, 1 H), 5.75 (broad d, 1 H, J = 10.2), 5.34 (m, 1 H), 4.61 (t, 1 H, J = 5.4, D_2O exch), 3.52 (m, 2 H), 2.31 - 2.22 (m, 2 H), 2.00 - 1.71 (m, 3 H); IR 3392, 3314, 3211, 1640, 1605, 1566, 1508; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 282 (0.6, M^+ + 2), 281 (0.7, M^+ +1), 280 (1.7, M^+). Anal. Calcd for $C_{11}H_{13}N_6OCl$: C, 47.07; H, 4.67; N, 29.94. Found: C, 47.18; H, 4.56; N, 29.78.

***cis*-[3-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)cyclohexen-4-yl]carbinol (21).** Azapurine **20** (200.0 mg, 0.71 mmol) dissolved with methanol (30 mL) and put into a bomb. The bomb and contents were cooled in a dry-ice bath and liquid

ammonia (~ 70 mL) was added. The bomb was sealed and heated, with stirring, in a 60 °C oil-bath for 48 h. The reaction mixture was then cooled and the ammonia was vented. The solvent was removed by evaporation under reduced pressure, and the resulting solid was rinsed with water and vacuum-filtered, giving analytical azapurine **21** as a white solid (174.6 mg, 0.67 mmol, 94 %, mp 283.5 - 284 °C, dec.). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.72 (broad s, 1 H, D_2O exch), 7.41 (broad s, 1 H, D_2O exch), 6.39 (s, 2 H, D_2O exch), 5.93 (m, 1 H), 5.72 (broad d, 1 H, J = 9.3), 5.22 (m, 1 H), 4.60 (m, 1 H, D_2O exch), 3.34 (m, 2 H), 2.14 (m, 2 H), 2.00 - 1.80 (m, 3 H); IR 3454, 3341, 1672, 1629, 1590, 1498, 1417; MS (CI, *i* -butane, $^+$eV, 150 °C) *m / e* (intensity) 262 (19, M^+ +1), 126 (100). Anal. Calcd for $C_{11}H_{15}N_7O$: C, 50.57; H, 5.79; N, 37.52. Found: C, 50.48; H, 5.88; N, 37.48.

***cis*-5-Amino-3,6-dihydro-3-[5-(hydroxymethyl)-2-cyclohexenyl]-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (22).** Azapurine **20** (100.0 mg, 0.36 mmol) was warmed (~ 80 °C) in 0.25 N NaOH (4 mL) for 90 min, and then cooled. 2 N HCl was added to pH 3. The resulting precipitate was vacuum-filtered and rinsed with water, giving analytical azapurine **22** as a white solid (60.8 mg, 0.23 mmol, 64 %, mp 241.5 - 243.5 °C dec.). R_f = 0.45 (chloroform / methanol, 4:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1 H, D_2O exch), 6.92 (broad s, 2 H, D_2O exch), 5.95 (m, 1 H), 5.70 (broad d, 1 H, J = 10.0), 5.20 (m, 1 H), 4.50 (very broad s, 1 H, D_2O exch), 3.32 (m, 2 H), 2.08 (m, 2 H), 1.90 (m, 1 H), 1.77 (m, 1 H), 1.62 (dd, 1 H, J = 23.3, 11.8); IR 3456, 3303, 3160, 1715, 1633, 1578; MS (EI, 70 eV, 200 °C) *m / e* (intensity) 263 (0.4, M^+ +1), 262 (3, M^+), 153 (100). Anal. Calcd for $C_{11}H_{14}N_6O_2 \cdot 2/5\ H_2O$: C, 49.03; H, 5.54; N, 31.19. Found: C, 49.32; H, 5.48; N, 30.95.

Acknowledgments

This work was supported by Public Health Service Grant CA23263 from the National Cancer Institute. We wish to thank Mr. Jay Brownell for conducting the P-388 mouse leukemia cytotoxicity studies. We also thank Dr. John P. Bader, Antiviral Evaluations Branch, National Cancer Institute, for the anti-HIV screening results.

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Received August 3, 1995
Accepted September 13, 1995