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Cyclohexenyl Nucleosides: Synthesis of *cis*-4-(9*H*-Purin-9-yl)-2-cyclohexenylcarbinols.

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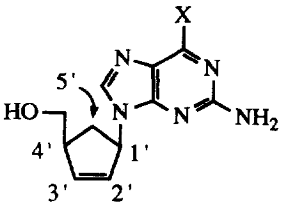
Abstract: Syntheses of the title compounds were accomplished in 6-7 steps, starting from cyclohexadiene and chlorosulphonyl isocyanate. The key step of the strategy involves a palladium coupling of cyclohexenyl dicarbonate **8** with either 6-chloropurine or 2-amino-6-chloropurine.

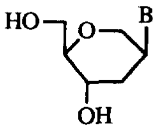
INTRODUCTION

Synthesis of carbocylic nucleosides,[1] wherein a carbon replaces the furanose oxygen, has become a potentially important source of new drugs. In addition to modifying the biological activity, the substitution of the furanose oxygen by a carbon imparts to the nucleoside increased stability to the enzymes that cleave the glyclosidic bonds of the natural nucleosides.[2]

Carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine (carbovir, **1a**) has been identified as a potential drug candidate for the treatment of AIDS, showing potent and selective inhibition of HIV-1 replication and cytopathic effects in a variety of human T-lymphoblastoid cell lines.[3] Homologation of the cyclopentenyl moiety of carbovir by insertion of a methylene between the 4',5' - carbons results in a cyclohexyl analog of carbovir (**16**, Scheme 1). While cyclohexyl and cyclopentyl rings have different conformations, simple models show that



1a, X = OH
b, X = NH–◁



B = adenine
guanine
thymidine
cytosine

2

the introduction of a double bond flattens out the cyclohexyl ring, allowing a hydroxymethyl substituent (such as in guanosine analog **16**) to overlap with the hydroxymethyl of carbovir or of the natural nucleosides when the nucleobases are overlaid.

Recently, significant anti-viral activity has been reported for a series of 1,5-anhydrohexitol nucleosides (**2**).[4] Although the anhydrohexitol moiety of these nucleosides prefers a chair conformation,[4b] the biological activity that they demonstrate indicates that the sugar moieties of nucleosides can be greatly altered and still yield nucleosides with significant anti-viral activity. While a number of reports describe syntheses of pyranosyl nucleosides,[4,5] only a handful of reports describe syntheses of cyclohexyl nucleosides.[6] The present report describes the synthesis of a cyclohexenyl homologue of carbovir and related compounds.

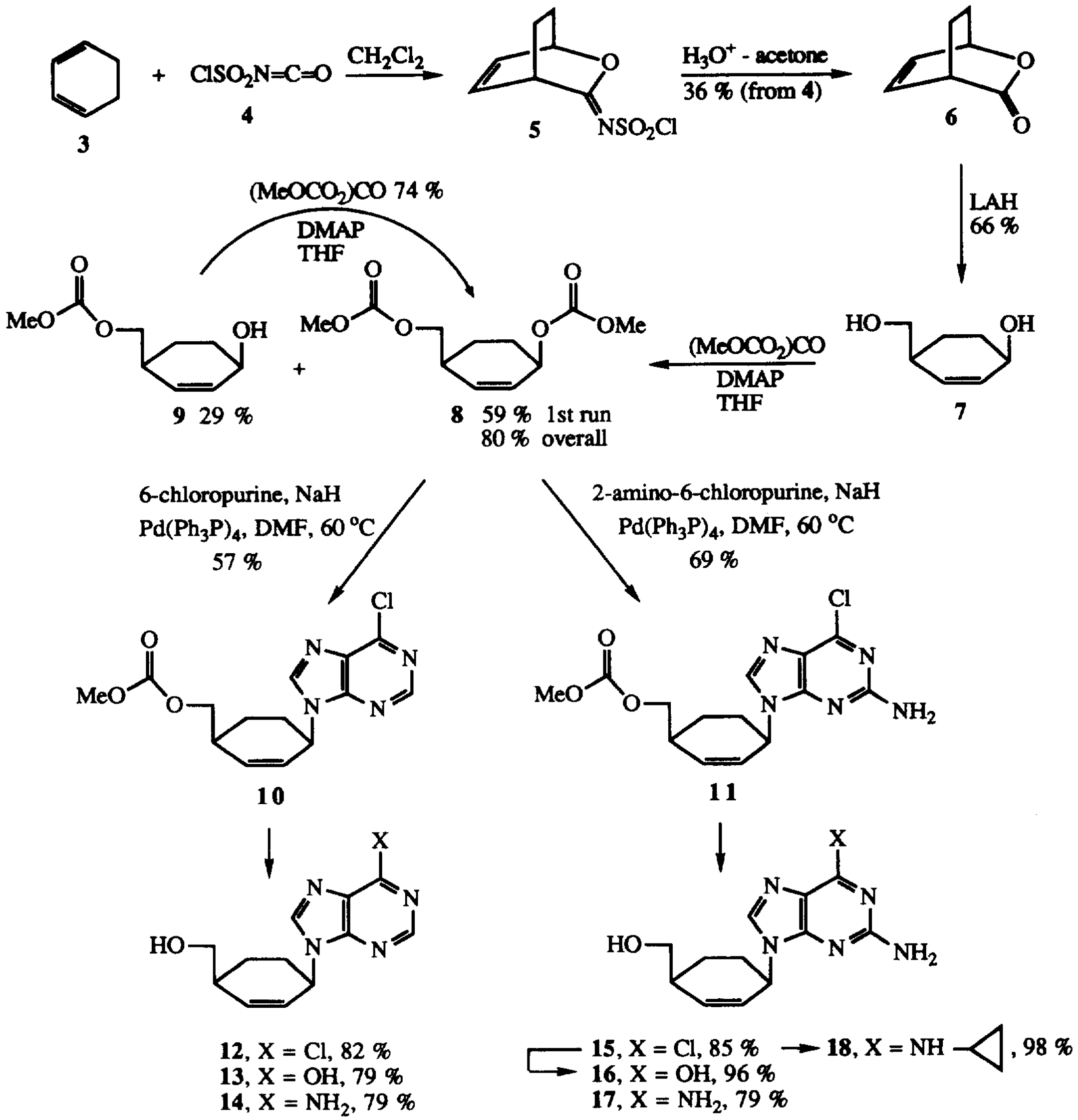
DISCUSSION

The use of palladium coupling reactions to stereoselectively add intact purines to activated allylic compounds, first demonstrated by Trost and co-workers,[7] has been previously used in our laboratory to synthesize carbovir (**1a**).[8] Adoption of this methodology allows for a short overall synthetic route to the target compounds. Thus, the homologue of carbovir was synthesized in seven steps (Scheme 1). In addition, several other purine analogs were synthesized, including the 6-cycloproylamino analog **18** which was inspired by the observation that the 6-cyclopropylamino analog of carbovir (**1b**) is converted to the HIV-1-active carbovir triphosphate by a unique anabolic pathway that does not go through carbovir (**1a**).[9]

Lactone **6** was synthesized according to the procedure of Malpass and Tweddle,[10] with slight modification. The reference procedure[10] for the Diels-Alder reaction of 1,3-cyclohexadiene (**3**) with chlorosulphonyl isocyanate (**4**) was scaled up without difficulty. However, we found that scale up of the hydrolysis of the imino intermediate **5** resulted in drastically reduced yields which is believed to be the result of a decreasing ability of the reaction mixture to radiate away the heat that is evolved when increasing the scale of this highly exothermic reaction. This was partially overcome by cooling the reaction mixture in an ice-bath and by slowly dripping a dilute acidic solution into the solution containing imino intermediate **5**. These modifications gave a modest yield of 36 % (based on isocyanate **4**) on a multi-gram scale.

Reduction of lactone **6** with lithium aluminum hydride gave analytical diol **7** in 66 % yield, after column chromatography. Diol **7** was allowed to react with dimethylpyrocarbonate in the presence of dimethylaminopyridine, giving a mixture of dicarbonate **8** (59 %) and monocarbonate **9** (29 %), which was separated by column chromatography. Addition of a second aliquot of dimethylpyrocarbonate before purification did not appear (by TLC examination) to help convert the remaining monocarbonate **9** to dicarbonate **8**. Purified monocarbonate **9** was converted to dicarbonate **8** in 74 % yield, giving an 80 % overall yield of analytical dicarbonate **8**. In this last reaction, 12 % of unreacted monocarbonate **9** was recovered, leaving 3 % overall in the sequence.

The purine moiety was coupled to the cyclohexene ring using palladium coupling methods[7,8] with Hodgson's adaptation of protecting the reaction mixture from light.[11] This procedure gave analytical carbonated chloropurines **10** and **11** in yields of 57 and 69 %, respectively. The stereoselectivity was good as carbonates **10** and **11** were formed with *cis* / *trans* ratios of approximately 18:1 and 10:1, respectively. The regio- and



Scheme 1

stereochemistry was determined by NOE experiments which also allowed unambiguous ^{1}H NMR assignments.

It was found that, with nucleoside analogs **10** and **11**, the carbonates can be selectively hydrolyzed in the presence of the chloropurines. Thus, carbonate **11** was hydrolyzed with 0.25 N NaOH at 50 °C for one hour,

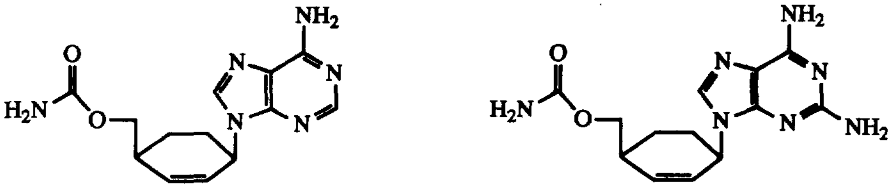


Figure 1

giving chloropurine **15** in 85 % yield (after column chromatography), without a detectable (by TLC) amount of guanosine analog **16**. Likewise, carbonate **10** can be selectively hydrolyzed, but the temperature has to be lowered to room temperature to give a good yield (82 % after column chromatography) of chloropurine **12**. After chromatography, only one isomer for both **12** and **15** could be detected by ^{1}H NMR.

Carbonate **10** was hydrolyzed directly to inosine analog **13** in 79 % yield with refluxing aqueous 0.33 N NaOH. Also, carbonate **10** was aminated with ammonia in methanol. The product of this reaction, however, was a mixture of adenosine analog **14** and carbamate **19** (Figure 1) in an approximately 3:1 ratio. The mixture did not appear to be separable by chromatography. An attempted hydrolysis with aqueous 0.25 N NaOH at 50 °C for one hour did not result in any change to the mixture, but hydrolysis of the mixture with 10 % NaOH in methanol at room temperature for 48 hours gave a 79 % yield (from carbonate **10**) of adenosine analog **14**.

Carbonate **11** was aminated with ammonia and then hydrolyzed with 10 % NaOH in methanol at room temperature for 48 hours, giving diaminopurine **17** in 79 % yield. Spectroscopy was not carried out on the aminated intermediate to determine if it was contaminated with carbamate analog **20** (Figure 1). The guanosine and cyclopropylaminopurine nucleoside analogs were synthesized from chloropurine **15**. Chloropurine **15** was hydrolyzed with refluxing aqueous 0.33 N NaOH, giving guanosine analog **16** in 96 % yield, and the chloropurine was aminated with cyclopropylamine in refluxing ethanol, giving cyclopropylaminopurine **18** in 98 % yield.

Optimization of the reactions was not carried out beyond what was required to give usable quantities of material. Although the yields in the later steps were good to excellent, there exists room for the improvement of the early steps. Biological evaluation of the compounds reported in this paper is under way and the results will reported at a later time.

EXPERIMENTAL

General

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 plates (oils) or pellets (solids) on a Nicolet 5DXC spectrometer and reported in cm^{-1}. Chemical impact (CI) mass spectra (MS) were obtained with a Finnigan 4000 and fast-atom bombardment (FAB) MS were obtained with a VG 7070E-HF spectrometer. Thin-layer chromatography was performed on EM Science silica gel 60 F_{254} (0.25 mm layer) and column chromatography was performed on EM Science silica gel 60 (230 - 400 mesh). DMF was dried over molecular sieves. All other solvents and chemicals are reagent grade unless specified otherwise.

2-Oxabicyclo[2.2.2.]oct-5-en-3-one (6). Imine 5 was scaled up (3, 15.35; 4, 13.56 g), but otherwise carried out as described Malpass and Tweddle,[10] giving crude imine 3 (22.24 g). Crude imine 3 was dissolved in acetone (180 mL) and cooled in an ice-bath. Cool aqueous 0.4 N HCl (120 mL) was added dropwise over 1 h, with stirring after which the solution was stirred an additional 2 h, and then extracted with methylene chloride (4 X 200 mL). The combined methylene chloride was removed by evaporation under reduced pressure, leaving a yellow syrup which was extracted with hexane (4 X 150 mL). The combined hexane was removed by evaporation under reduced pressure, giving lactone 6 as a pale yellow syrup (4.24 g, 34.2 mmol, 36 % from 4). There are 2 minor discrepancies in the ^1H NMR of our lactone 6 compared to that reported in the reference.[10] The peaks that were listed in the reference[10] as δ 5.13 and 3.36 ppm were found at δ 5.22 and 3.48 ppm.

***cis*-4-Hydroxy-2-cyclohexenylcarbinol (7).** A solution of lactone 6 (4.24 g, 34.2 mmol) in dry ether (85 mL) was added dropwise, *via* an addition funnel, over 90 min to a stirring solution of lithium aluminum hydride (4.24 g, 111.6 mmol, 3.26 equiv.) in dry ether (140 mL) at room temperature. The solution was stirred for an additional 90 min, after which, it was neutralized by slowly adding water dropwise. The solid was then filtered and extracted with ether / methanol (9:1, 2 X 100 mL). The combined filtrate / extracts were evaporated under reduced pressure, leaving a pale yellow oil (3.67 g, 28.7 mmol, 84 %). The oil was flashed over a column, using an elution gradient of hexane / ethyl acetate (1:1) to ethyl acetate. The solvent was removed from the fractions with $R_f = 0.43$ (ethyl acetate) by evaporation under reduced pressure, leaving diol 7 as a pale yellow oil (2.90 g, 22.7 mmol, 66%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (d of m, 1 H, $J = 11$), 5.56 (d of m, 1 H, $J = 11$), 4.18 (m, 1 H), 3.60 (8-line m, 2 H), 2.25 (m, 1 H), 1.94 (s, 2 H), 1.85 - 1.50 (m, 4 H); IR 3600 - 3050; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 146 (34, $M + NH_4^+$), 129 (7, $M^+ + 1$), 128 (100, M^+). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.80; H, 9.27.

***cis*-[4-[(Methoxycarbonyl)oxy]-2-cyclohexen-1-yl]methylcarbonic acid methyl ester (8) and *cis*-[4-hydroxy-2-cyclohexen-1-yl]methylcarbonic acid methyl ester (9).** All glassware was oven-dried. The THF was distilled from sodium metal. Dimethylpyrocarbonate (DMP, 25 mL)was added dropwise, *via* an addition funnel, to an ice-bath cooled solution of diol 7 (2.50 g, 19.5 mmol) and 4-dimethylaminopyridine (DMAP, 0.30 g, 2.46 mmol) in THF (40 mL) over 90 min. The solution was stirred for an additional 15 min, and then allowed to come to room temperature. After 20 h, the solution was cooled in an ice-bath and a second aliquot of DMP (25 mL) was added dropwise. After stirring for an additional 15 min, the solution was allowed to come to room temperature and stir. After a total of 42 h, the solution was concentrated by evaporation under reduced pressure. TLC analysis of the solution at 20 h and 42 h did not reveal any detectable difference. The resulting oil was flashed over a column, eluting with hexane / ethyl acetate (4:1, then 3:2). The solvent was removed from the fractions with $R_f = 0.61$ and 0.29 (ethyl acetate) by evaporation under reduced pressure. The former gave dicarbonate 8 as a clear oil (2.83 g, 11.6 mmol, 59 %) and the latter gave carbonate 9 as a clear oil (1.07 g, 5.75 mmol, 29 %). Dicarbonate 8: ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (narrow m, 2 H), 5.08 (m, 1 H), 4.07 (d, 2 H, $J = 6.8$), 3.78 (s, 3 H), 3.77 (s, 3 H), 2.45 (m, 1 H), 1.97 (m, 1 H), 1.84 - 1.74 (m, 2 H), 1.56 (m, 1 H); ^{13}C NMR / DEPT (50 MHz, $CDCl_3$) 155.8 (C), 154.8 (C), 133.1 (CH), 126.7

(CH), 70.6 (CH), 70.5 (CH_2), 54.8 (CH_3), 54.6 (CH_3), 35.2 (CH), 26.7 (CH_2), 21.1 (CH_2); IR 1747, 1701; MS (FAB, +ve) 245 ($M^+ + 1$). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.84; H, 6.62. Carbonate **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (d of m, 1 H, *J* = 10), 5.75 (d of m, 1 H, *J* = 10), 4.18 (m, 1 H), 4.07 (d, 2 H, *J* = 7), 3.79 (s, 3 H), 2.43 (m, 1 H), 1.81 - 1.70 (m, 3 H), 1.60 - 1.51 (m, 2 H); IR 3600 - 3100, 1750; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 204 ($M + NH_4^+$, 56), 186 (M^+, 9), 169 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.86; H, 7.37.

DMP (4 mL) was added dropwise, *via* a syringe, to an ice-bath cooled solution of carbonate **9** (0.400 g, 2.12 mmol) and DMAP (50 mg, 0.41 mmol) in THF (6 mL) over 10 min. The solution was stirred for an additional 15 min, and then allowed to come to room temperature. After 4 days, the solution was concentrated by evaporation under reduced pressure. The resulting oil was flashed over a column, eluting with a gradient of hexane to hexane / ethyl acetate (1:1). The solvent was removed from the fractions with R_f = 0.61 and 0.29 (ethyl acetate) by evaporation under reduced pressure. The former gave dicarbonate **8** as a clear oil (390.1 mg, 1.60 mmol, 74 %) and the latter gave recovered carbonate **9** as a clear oil (49.7 mg, 0.27 mmol, 12 %). This gave an overall yield, combining the two reactions, of 80 % for dicarbonate **8** and 3 % for monocarbonate **9**.

***cis*-[4-(6-Chloro-9*H*-purin-9-yl)-2-cyclohexen-1-yl]methylcarbonic acid methyl ester (10).** Glassware was oven-dried and protected by drying tubes. 6-Chloropurine (0.70 g, 4.53 mmol) was added to a stirring solution of sodium hydride (97 %, 110 mg, 4.43 mmol) in DMF (40 mL) and the resulting solution was heated in a 60 °C oil-bath for 30 min. The solution was cooled, and tetrakis(triphenylphosphine)palladium(0) (0.90 g, 0.78 mmol) and a solution of dicarbonate **8** (1.00 g, 4.10 mmol) in DMF (10 mL) were added. The flask was wrapped in foil, heated in the 60 °C oil-bath for 2 h, and then the solvent was removed by evaporation under vacuum. The resulting residue was adsorbed to silica gel which was packed onto a column and eluted with a gradient of hexane to hexane / ethyl acetate (2:1). The solvent was removed from the fractions with R_f = 0.56 (ethyl acetate) by evaporation under reduced pressure, giving chloropurine **10** as a white powder (0.76 g, 2.36 mmol, 57 %, mp 105 - 108 °C). ^{1}H NMR showed *cis / trans* isomers in a 18:1 ratio. ^{1}H NMR (500 MHz, benzene-d_6, major isomer peaks) δ 8.60 (s, 1 H, C*H* purine), 7.68 (s, 1 H, C*H* purine), 5.48 (d of m, 1 H, *J* = 10.5, 3-*H*), 5.08 (d of m, 1 H, *J* = 9.0, 2-*H*), 4.64 (m, 1 H, 1-*H*), 3.75 (dd, 1 H, *J* = 10.5, 6.3, C*H*HO-), 3.67 (dd, 1 H, *J* = 10.5, 5.5, CH*H*O-), 3.33 (s, 3 H, OCH_3), 1.84 (m, 1 H, 4-*H*), 1.45 (m, 1 H, 6β-*H*), 1.27 (t with fine splitting, 1 H, *J* = 13.0, 6α-*H*), 0.98 (m, 1 H, 5α-*H*), 0.84 (t with fine splitting, 1 H, *J* = 11.3, 5β-*H*)); IR 1745; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 326 ($M + H^+ + 1$ for Cl^{37}, 6), 325 ($M + H^+$ for Cl^{37}, 37), 324 ($M + H^+ + 1$ for Cl^{35}, 18), 323 ($M + H^+$ for Cl^{35}, 100), 322 (M^+ for Cl^{35}, 4). Anal. Calcd for $C_{14}H_{15}N_4O_3Cl$: C, 52.10; H, 4.68; N, 17.36. Found: C, 52.04; H, 5.00; N, 17.25.

***cis*-[4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-cyclohexen-1-yl]methylcarbonic acid methyl ester (11).** Glassware was oven-dried and protected by drying tubes. 2-Amino-6-chloropurine (0.76 g, 4.48 mmol) was added to a stirring solution of sodium hydride (95 %, 112 mg, 4.43 mmol) in DMF (40 mL) and the resulting solution was heated in a 60 °C oil-bath for 30 min. The solution was cooled, and tetrakis(triphenylphosphine)palladium(0) (0.90 g, 0.78 mmol) and a solution of dicarbonate **8** (1.00 g, 4.10 mmol) in DMF (10 mL) were added. The flask was wrapped in foil, heated in the 60 °C oil-bath for 2 h, and then the solvent was removed by evaporation under vacuum. The resulting orange syrup was adsorbed to silica gel which was packed onto a column and eluted with hexane / ethyl acetate (3:2), followed by ethyl acetate. The solvent was removed from the fractions with $R_f = 0.42$ (ethyl acetate) by evaporation under reduced pressure, giving chloropurine **11** as a white powder (0.67 g, mp 154 - 157 °C). A fraction, contaminated with a substance with a lower R_f, was chromatographed a second time, eluting with a gradient of hexane to ethyl acetate. The solvent was removed as described above, giving additional chloropurine **11** as a white powder (0.29 g; total: 0.96 g, 2.84 mmol, 69 %). ^1H NMR showed *cis / trans* isomers in a 10:1 ratio. ^1H NMR (500 MHz, benzene-d_6, major isomer peaks) δ 7.45 (s, 1 H, C*H* purine), 5.49 (d of m, 1 H, *J* = 9.0, 3-*H*), 5.14 (d of m, 1 H, *J* = 10.0, 2-*H*), 4.51 (m, 1 H, 1-*H*), 4.32 (s, 2 H, NH_2), 3.77 (dd, 1 H, *J* = 10.5, 6.5, C*H*HO-), 3.73 (dd, 1 H, *J* = 10.5, 5.5, CH*H*O-), 3.32 (s, 3 H, OCH_3), 1.89 (m, 1 H, 4-*H*), 1.53 (m, 1 H, 6β-*H*), 1.30 (t with fine splitting, 1 H, *J* = 13.5, 6α-*H*), 1.04 (m, 1 H, 5α-*H*), 0.94 (m, 1 H, 5β-*H*)); IR 1734; MS (EI, 200 °C) *m / e* (intensity) 339 (M^+ for Cl^{37}, 0.24), 338 ($M^+ + 1$ for Cl^{35}, 0.12), 337 (M^+ for Cl^{35}, 0.73), 277 (100). Anal. Calcd for $C_{14}H_{16}N_5O_3Cl$: C, 49.78; H, 4.77; N, 20.73. Found: C, 50.00; H, 4.89; N, 20.66.

***cis*-4-(6-Chloro-9*H*-purin-9-yl)-2-cyclohexenylcarbinol (12).** Aqueous 0.25 N NaOH (10 mL) was added to a stirring solution of chloropurine **10** (164.0 mg, 0.508 mmol) in THF (25 mL) at room temperature. The solution was monitored by TLC until chloropurine **10** could no longer be detected (2 h) and then acidified to pH 6 with 1 N HCl. The THF was removed by evaporation under reduced pressure, and the water was removed under vacuum. The resulting residue was adsorbed to silica gel which was packed onto a column and eluted with a gradient of hexane to ethyl acetate, and then with ethyl acetate. The solvent was removed from the fractions with $R_f = 0.14$ (ethyl acetate) by evaporation under reduced pressure, giving chloropurine **12** as a white powder (110.9 mg, 0.419 mmol, 82 %, mp 147 - 147.5 °C). ^1H NMR (300 MHz, DMSO-d_6) δ 8.78 (s, 1 H), 8.58 (s, 1 H), 6.14 (d of m, 1 H, *J* = 8.4), 5.91 (m, 1 H), 5.27 (m, 1 H), 4.74 (m, 1 H, D_2O exch.), 3.48 (m, 2 H), 2.28 (m, 1 H), 2.01 (m, 2 H), 1.66 (m, 1 H), 1.45 (m, 1 H); IR 3320 (broad), 1593; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 268 ($M + H^+ + 1$ for Cl^{37}, 4), 267 ($M + H^+$ for Cl^{37}, 35), 266 ($M + H^+ + 1$ for Cl^{35}, 14), 265 ($M + H^+$ for Cl^{35}, 100). Anal. Calcd for $C_{12}H_{13}N_4OCl$: C, 54.45; H, 4.95; N, 21.17. Found: C, 54.24; H, 4.81; N, 20.96.

***cis*-1,9-Dihydro-9-[4-(hydroxymethyl)-2-cyclohexenyl]-6*H*-purin-6-one (13).** A solution of chloropurine **10** (124.3 mg, 0.385 mmol) in aqueous 0.33 N NaOH (15 mL) was refluxed for 5 h, cooled overnight, and then acidified to pH 6 with 1 N HCl. The water was removed by evaporation under vacuum and the resulting white solid was adsorbed to silica gel which was packed onto a column and eluted with ethyl acetate, followed by chloroform / methanol (5:1). The solvent was removed from the fractions with $R_f = 0.54$ (chloroform / methanol, 3:1) by evaporation under reduced pressure, giving inosine analog **13** as a white powder (74.5 mg, 0.302 mmol, 79 %, mp 267 - 268.5 °C). ^1H NMR (300 MHz, DMSO-d_6) δ 12.28 (s, 1 H, D_2O exch.), 8.03 (s, 1 H), 7.94 (s, 1 H), 6.09 (d of m, 1 H, *J* = 9.9), 5.84 (d of m, 1 H, *J* = 10.2), 5.07 (m, 1 H), 4.71 (t, 1 H, *J* = 5.3, D_2O exch.), 3.43 (m, 2 H), 2.25 (m, 1 H), 1.91 (m, 2 H), 1.64 (m, 1 H), 1.41 (m, 1 H); IR 3410 (broad), 1678; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 264 ($M + NH_4^+$, 1), 248 ($M + H^+ + 1$, 11), 247 ($M + H^+$, 78), 246 (M^+, 1), 112 (100). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.34; H, 5.57; N, 22.61.

***cis*-4-(6-Amino-9*H*-purin-9-yl)-2-cyclohexenylcarbinol (14).** A solution of chloropurine **10** (260.0 mg, 0.806 mmol) in methanol (30 mL) in a bomb was cooled in a dry ice / acetone-bath, and then liquid ammonia (~ 70 mL) was added. The bomb was sealed, heated in a 60 °C oil-bath for 40 h, cooled to room temperature, and then vented. The methanol was removed by evaporation under reduced pressure, and the resulting white solid adsorbed to silica gel which was packed onto a column and eluted with a gradient of chloroform to chloroform / methanol (3:1). The solvent was removed from the fractions with R_f = 0.46 (chloroform / methanol, 3:1) by evaporation under reduced pressure, giving a 2:1 mixture of adenosine analog **14** and its *O*-carbamate as a white foam (191.4 mg). Treatment of this mixture with 0.25 N NaOH at 50 °C for 1 h did not result in any change to the mixture (179.1 mg recovered after chromatography as described above). The recovered mixture was dissolved in a solution of 10 % methanolic NaOH and stirred for 48 h at room temperature, heated in a 60 °C oil-bath for 30 min, and then cooled back to room temperature. The resulting microcrystalline white precipitate was vacuum-filtered, giving analytical chloropurine **14** (122.8 mg, mp 246 - 247 °C). After 4 days, a second crop of white crystals (31.6 mg, mp 244.5 - 246 °C) was obtained. After an additional day, a third crop of white crystals (1.4 mg, mp 243 - 244 °C; total: 155.8 mg, 0.635 mmol, 79 %) was obtained. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (s, 1 H), 7.98 (s, 1 H), 7.21 (s, 2 H, D_2O exch.), 6.09 (d of m, 1 H, *J* =9.9), 5.84 (d of m, 1 H, *J* = 9.9), 5.07 (m, 1 H), 4.71 (m, 1 H, D_2O exch.), 3.45 (m, 2 H), 2.25 (m, 1 H), 1.92 (m, 2 H), 1.63 (m, 1 H), 1.42 (m, 1 H); IR 3458, 3347, 3274, 1675, 1606; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 247 (M + H^+ + 1, 10), 246 (M + H^+, 100), 245 (M^+, 2). Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.61; H, 5.93; N, 28.18.

***cis*-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-cyclohexenylcarbinol (15).** Aqueous 0.25 N NaOH (30 mL) was added to a stirring solution of chloropurine **11** (300.0 mg, 0.888 mmol) in THF (25 mL) and heated in a 50 °C oil-bath for 75 min, then cooled to room temperature and acidified to pH 4 with 1 N HCl. The THF was removed by evaporation under reduced pressure, and the water was removed by azeotroping with ethanol under reduced pressure. The resulting white solid was adsorbed to silica gel which was packed onto a column and eluted with ethyl acetate. The solvent was removed from the fractions with R_f = 0.13 (ethyl acetate) by evaporation under reduced pressure, giving chloropurine **15** as a white powder (211.7 mg, 0.757 mmol, 85 %, mp 140 - 144 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (s, 1 H), 6.95 (s, 2 H, D_2O exch.), 6.10 (d of m, 1 H, *J* = 10.2), 5.83 (d of m, 1 H, *J* = 10.2), 4.96 (m, 1 H), 4.71 (t, 1 H, *J* = 5.3, D_2O exch.), 3.44 (m, 2 H), 2.24 (m, 1 H), 1.90 (m, 2 H), 1.62 (m, 1 H), 1.40 (m, 1 H); IR 3480, 3311, 3201, 1631, 1617, 1568; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 283 (M + H^+ + 1 for Cl^{37}, 4), 282 (M + H^+ for Cl^{37}, 40), 281 (M + H^+ + 1 for Cl^{35}, 9), 280 (M + H^+ for Cl^{35}, 57), 279 (M^+ for Cl^{35}, 3), 136 (100). Anal. Calcd for $C_{12}H_{14}N_5OCl$: C, 51.53; H, 5.04; N, 25.04. Found: C, 51.35; H, 5.10; N, 24.98.

***cis*-2-Amino-1,9-dihydro-9-[4-(hydroxymethyl)-2-cyclohexen-1-yl]-6*H*-purin-6-one (16).** A solution of chloropurine **15** (153.7 mg, 0.550 mmol) in aqueous 0.33 N NaOH (15 mL) was refluxed for 3-1/2 h, cooled to room temperature, and then acidified to pH 4 with 1 N HCl. The water was removed by azeotroping with ethanol, and the resulting white solid was adsorbed to silica gel which was packed onto a column and eluted with chloroform / methanol (3:1). The solvent was removed from the fractions with R_f = 0.25 (chloroform / methanol, 3:1) by evaporation under reduced pressure, giving guanosine analog **16** as a white powder (137.4 mg, 0.526 mmol, 96 %, mp 249 - 253 °C with foaming and dec.). A small sample was hot-filtered and recrystallyzed from water, giving an analytical sample (mp 299 - 301 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.54 (s, 1 H, D_2O exch.), 7.54 (s, 1 H), 6.47 (s, 2 H, D_2O exch.), 6.07 (d of m, 1 H, *J* =

12.0), 5.80 (d of m, 1 H, *J* = 11.1), 4.83 (m, 1 H), 4.70 (t, 1 H, *J* = 5.1, D_2O exch.), 3.43 (m, 2 H), 2.22 (m, 1 H), 1.83 (m, 2 H), 1.60 (m, 1 H), 1.39 (m, 1 H); IR 3650 - 2450 (broad), 3315, 1684, 1646; MS (FAB, +ve) 262 (M + H^+). Anal. Calcd for $C_{12}H_{15}N_5O_2 \cdot 0.5\ H_2O$: C, 53.32; H, 5.97; N, 25.91. Found: C, 53.47; H, 5.91; N, 25.80.

***cis*-4-(2,6-Diamino-9*H*-purin-9-yl)-2-cyclohexenylcarbinol (17).** A suspension of chloropurine **11** (258.0 mg, 0.764 mmol) in methanol (20 mL) in a bomb was cooled in a dry ice / acetone-bath and then liquid ammonia (~ 50 mL) was added. The bomb was sealed, heated in a 60 °C oil-bath for 42 h, cooled to room temperature, and then vented. The contents were transferred to a round bottom flask, solid NaOH (1.0 g) was added, and the resulting solution was stirred at room temperature. The initially clear solution turned cloudy, and, after 48 h, the solution was vacuum-filtered, giving diaminopurine **17** (33.5 mg, mp 217.5 - 221 °C) as a white powder. A second crop of diaminopurine **17** (analytical, 34.7 mg, mp 234 - 235 °C) was obtained. The mother liquor was adsorbed to silica gel which was packed onto a column and eluted with a gradient of chloroform to chloroform / methanol (4:1). The solvent was removed from the fractions with $R_f = 0.37$ (chloroform / methanol, 3:1) by evaporation under reduced pressure, giving additional diaminopurine **17** (88.9 mg, mp 231 - 233 °C; total: 157.1 mg, 0.606 mmol, 79 %). ^1H NMR (300 MHz, DMSO-d_6) δ 7.55 (s, 1 H), 6.64 (s, 2 H, D_2O exch.), 6.06 (d of m, 1 H, *J* =9.3), 5.81 (m with s at 5.78, 3 H, 2 H are D_2O exch.), 4.85 (m, 1 H), 4.69 (t, 1 H, *J* = 5.1, D_2O exch.), 3.42 (m, 2 H), 2.23 (m, 1 H), 1.85 (m, 2 H), 1.61 (m, 1 H), 1.39 (m, 1 H); IR 3489, 3415, 3320, 1666, 1635, 1591; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 276 (M + NH_4^+, 4), 262 (M + H^+ + 1, 7), 261 (M + H^+, 100), 260 (M^+, 5). Anal. Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.20; N, 32.29. Found: C, 55.21; H, 6.14; N, 32.08.

***cis*-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclohexenylcarbinol (18).** A solution of chloropurine **15** (192.4 mg, 0.688 mmol) and cyclopropylamine (0.50 mL) in ethanol (15 mL) was refluxed under N_2 for 19 h, and then cooled to room temperature. The solution was adsorbed onto silica gel which was packed onto a column and eluted with ethyl acetate, followed by ethyl acetate / methanol (5:1). The solvent was removed from the fractions with $R_f = 0.43$ (ethyl acetate / methanol, 4:1) by evaporation under reduced pressure, giving purine **18** as a white powder (203.5 mg, 0.677 mmol, 98 %; mp 182 - 184 °C, collapses at 100 - 110 °C). ^1H NMR (300 MHz, DMSO-d_6) δ 7.54 (s, 1 H), 7.23 (s, 1 H, D_2O exch.), 6.06 (d of m, 1 H, *J* = 9.9), 5.84 (m, 3 H, 2 H are D_2O exch.), 4.86 (m, 1 H), 4.69 (t, 1 H, *J* = 5.4, D_2O exch.), 3.42 (m, 2 H), 3.01 (m, 1 H), 2.22 (m, 1 H), 1.84 (m, 2 H), 1.61 (m, 1 H), 1.39 (m, 1 H), 0.65 (m, 2 H), 0.56 (m, 2 H); IR 3325, 3200, 1596 ; MS (CI, +ve, NH_3, 150 °C) *m / e* (intensity) 302 (M + H^+ + 1, 11), 301 (M + H^+, 100). Anal. Calcd for $C_{15}H_{20}N_6O$: C, 59.98; H, 6.71; N, 27.98. Found: C, 59.79; H, 6.52; N, 27.81.

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