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N-6 SUBSTITUTED DEOXYGENATED DERIVATIVES OF L-LIKE 5'-NORARISTEROMYCIN

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ABSTRACT. Several N-6 substituted derivatives (**4-11**) of (+)-4'-deoxy-5'-noraristeromycin (**2**) and its unsaturated counterpart (**3**) have been prepared. The derivatives are designed to systematically vary the hydrophobic/hydrophilic balance of the lead compounds. These compounds were evaluated against a large number of viruses but no significant antiviral activity was observed. Also, no cytotoxicity to host cells was found.

KEY WORDS: L-like, Carbocyclic nucleosides, HBV

INTRODUCTION

Carbocyclic nucleosides, modified nucleosides in which the oxygen of the sugar moiety is replaced by a methylene group, have been the subject of numerous investigations since the discovery of the antiviral properties of aristeromycin [1] and neplanocin A [2], two such naturally occurring compounds (Figure 1). These nucleosides owe their antiviral activity to an inhibition of *S*-adenosyl-L-homocysteine (SAH) hydrolase, a cellular enzyme that catalyses the hydrolysis of *S*-adenosyl-L-homocysteine, which is both a by-product and biofeedback inhibitor of methylation reactions interfering with viral messenger RNA maturation [3, 4]. Carbocyclic nucleosides show limited susceptibility to enzymatic degradation as a consequence of the absence of the natural N-glycosidic bond and have proven to be clinically useful antiviral agents as evidenced by the approval of abacavir for the treatment of human immunodeficiency virus (HIV AIDS) [5].

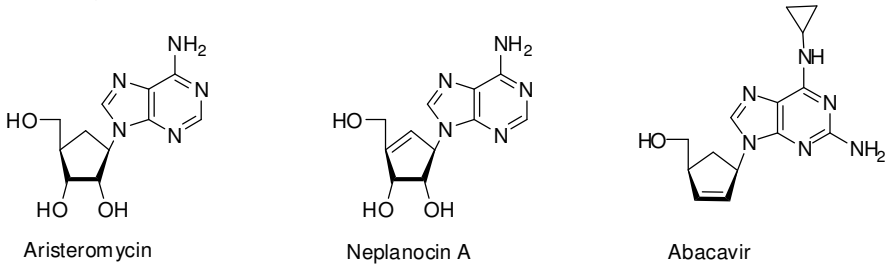

Figure 1. Carbocyclic nucleosides.

The hepatitis B virus (HBV) is hepatotropic virus that causes acute and chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). An estimated 350 million people worldwide are chronically infected with the virus [6]. Despite the recent advances in the treatment and prevention of HBV, poor response rates to the current interventions, emergence of resistance and high rate of incidence of side effects remain a serious challenge [7-9]. Also, end-stage liver disease complications caused by chronic hepatitis B in patients co-infected with HIV highlight the need for new therapeutic agents [10].

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The significant anti-HBV activity of (+)-5'-noraristeromycin, **1,** an L-like carbocyclic nucleoside (L-like nucleosides have opposite stereochemistry of the natural D-nucleosides), was reported in 1997 [11] (Figure 2). The 4'-deoxy derivative, **2**, was subsequently synthesized and investigation of its biological activity against HBV showed a 10-fold increase [12]. The unsaturated counterpart, **3**, has a slightly lower activity with a reduced cytotoxicity. To investigate the effect of changes in lipophilicity of **2** and **3** on their activity toward HBV, several N-6 substituted derivatives (**4-11**) were designed and synthesized (Figure 2).

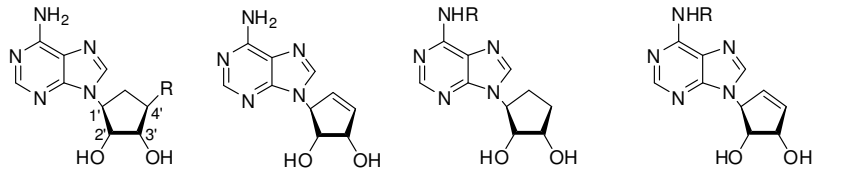
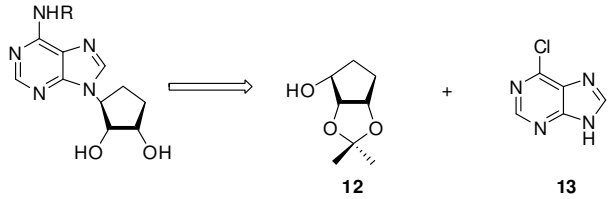


Figure 2. Structures of lead and target compounds.

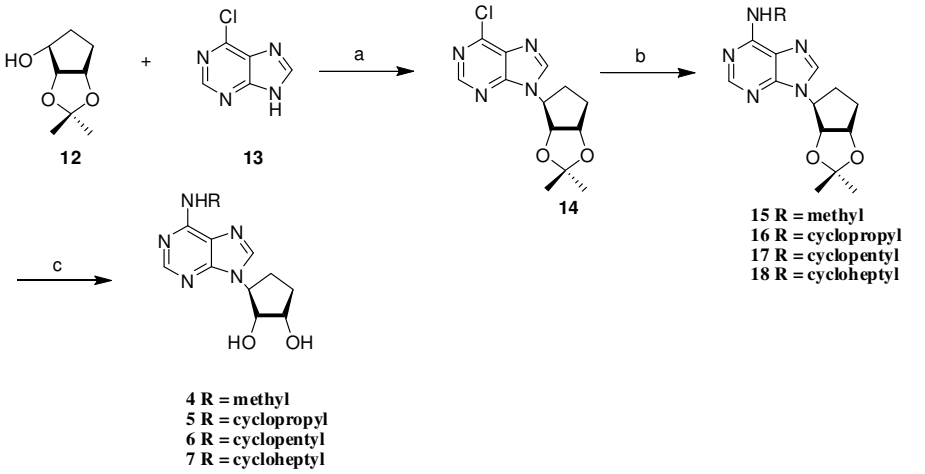
Chemistry

The retro synthetic analysis of this class of compounds revealed that derivatives (**4-7)** can be synthesized from the protected alcohol **12** and 6-chloropurine, **13** (Scheme 1). The steps used to realize the synthesis of the target compounds are shown in Scheme 2. Mitsunobu coupling [13, 14] of **12,** which was derived by catalytic hydrogenation from the unsaturated counterpart **19** [15, 16], with 6-chloropurine led to **14**. Reaction of **14** with various primary amines [17] yielded **15-18**. Removal of the isopropyldene group [12] with acidic resin gave targets **4-7**.



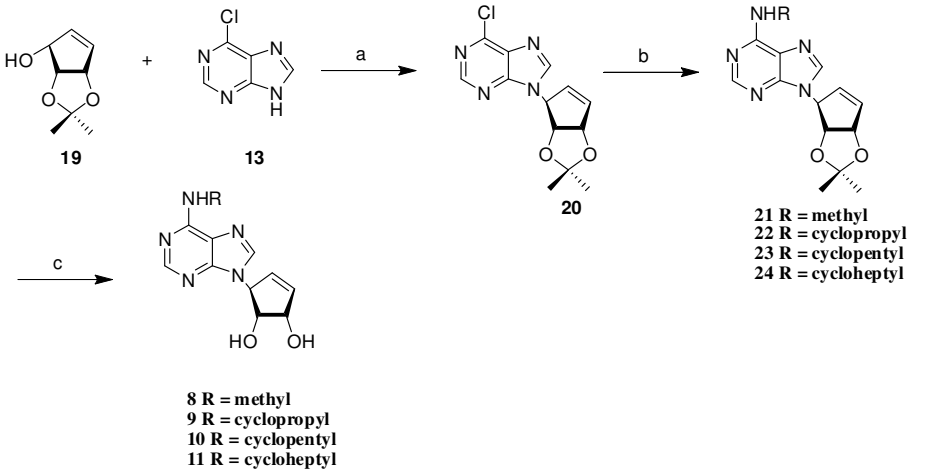
Scheme 1. Retrosynthetic approach.

The same approach was used for the synthesis of **8-11**. The allylic alcohol **19** [15, 16] was coupled with 6-chloropurine under Mitsunobu conditions to give **20** (Scheme 3). Reaction of the chloronucleoside **20** with several primary amines led to a series of compounds **(21-24)** which were deprotected [12] with acidic resin to yield **8-11**.



a. 6-chloropurine, DIAD, PPh_3, THF; b. methylamine, cyclopropyl, cyclopentyl, and cycloheptyl amine for **4**, **5**, **6**, and **7** respectively in THF; c. Dowex 50 x 8 resin.

Scheme 2. Synthesis of targets **4**-**7**.



a. 6-chloropurine, DIAD, PPh_3, THF; b. methylamine, cyclopropyl, cyclopentyl, and cycloheptyl amine for **8**, **9**, **10**, and **11** respectively in THF; c. Dowex 50 x 8 resin.

Scheme 3. Synthesis of targets **8**-**11**.

Antiviral analysis

To investigate their biological potential, **4-11** were subjected to antiviral screening versus hepatitis B virus (HBV), Epstein-Barr virus (EBV), Human Cytomegalovirus (HCMV), Varicella-Zoster virus (VZV), Hepatitis C virus (HCV), West Nile virus, Yellow Fever virus, Pichinde, herpes simplex-1, herpes simplex-2, herpes simplex-1 (TK^-), vaccinia, vesicular

stomatitis, coxsackie B4, respiratory syncytial, parainfluenza 3, reovirus-1, Sindbis, Venezuelan Equine Encephalitis virus (VEE), and Punta Toro. No significant activity was found. Also, no cytotoxicity arose in the cell lines used in the antiviral assays.

CONCLUSIONS

The synthesis of several N-6 substituted deoxygenated derivatives of L-like 5'-noraristeromycin has been achieved. The introduction of N-6 alkyl groups resulted in the loss of significant antiviral potency probably because of increased hydrophobicity and/or diminished hydrogen bonding with target macromolecule. Currently, the synthesis of several 2'- and 3'-deoxy derivatives of (+)-4'-deoxy-5'-noraristeromycin, **2**, is underway as part of an ongoing effort to determine the structural entities necessary for activity.

EXPERIMENTAL

General methods

Melting points were recorded on a Meltemp **II** point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 Spectrometer (operated at 250 or 62.9 MHz, respectively) or AC 400 Spectrometer (operated at 400 or 100 MHz, respectively). All ^{1}H chemical shifts are reported in δ relative to the internal standard tetramethylsilane (TMS, δ 0.00 ppm). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23 ppm) or relative to DMSO-d_6 (center of septet, δ 39.51 ppm). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Elemental analyses were performed by the Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5-25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopentan-1'-yl]-6-chloro-9H-purine (**14**).* A suspension of 6-chloropurine (2.5 g, 16 mmol) and triphenylphosphine (4.2 g, 16 mmol) in anhydrous THF (80 mL) was chilled to -20 ^{o}C and treated with a drop wise addition of diisopropyl azodicarboxylate (DIAD) (3.3 g, 16 mmol). The reaction mixture was stirred for 10 min at the same temperature, after which the acetone-dry ice bath was removed and stirring was continued for 15 min. This was followed by addition of a solution of **12** (3.2 g, 20 mmol) in anhydrous THF (80 mL) and the reaction mixture was stirred at room temperature for 2 h and then at 55 ^{o}C for 24 h. The solvent was removed under reduced pressure and the residue was purified via column chromatography eluting with EtOAc/hexanes (1:2) to yield **14** (3.0 g, 64%) as a white solid: m.p. 109-110 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.55 (s, 3H), 2.13-2.24 (m, 3H), 2.53-2.58 (m, 1H), 4.90-5.00 (m, 3H), 8.06 (s, 1H), 8.76 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 24.3, 26.7, 29.7, 31.5, 63.2, 80.7, 85.0, 111.6, 132.1, 144.0, 151.4, 151.8, 152.0; anal. for ($C_{13}H_{I5}O_2N_4Cl$) C, H, N.

*General experimental procedure (**15-18**)*

To a solution of **14** (0.9 g, 3 mmol) in THF (100 mL) was added the corresponding amine (methylamine in THF 2 M, 15 mL, cyclopropylamine 1.7 g, cyclopentylamine 2.6 g, and cycloheptylamine 3.4 g). For compounds **15** and **16**, the mixture was heated at 85 ^{o}C for 24 h in

a sealed steel bomb where as it was refluxed for 24 h for **17** and **18**. The volatiles were evaporated and the residue was purified by column chromatography using EtOAc/hexanes.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopentan-1'-yl]-6-methylamino-9H-purine (**15**).* EtOAc/hexanes (4:1), gummy solid (76%): ^{1}H-NMR (DMSO-d_6) δ 1.25 (s, 3H), 1.44 (s, 3H), 1.86-1.88 (m, 1H), 2.03-2.10 (m, 2H), 2.26-2.29 (m, 1H), 2.95 (brs, 3H), 4.76-4.78 (m, 1H), 4.88-4.91 (m, 2H), 7.67 (brs, 1H), 8.13 (s, 1H), 8.22 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 24.2, 26.5, 27.0, 29.1, 30.6, 60.7, 80.0, 84.4, 110.2, 139.0, 152.4, 155.0; anal. for ($C_{14}H_{19}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopentan-1'-yl]-6-cyclopropylamino-9H-purine (**16**).* EtOAc/hexanes (3:1), gummy solid (66%): ^{1}H-NMR ($CDCl_3$) δ 0.62-0.69 (m, 2H), 0.90-0.95 (m, 2H), 1.35 (s, 3H), 1.51 (s, 3H), 2.07-2.20 (m, 3H), 2.48-2.58 (m, 1H), 3.03-3.04 (m, 1H), 4.81-4.83 (m, 1H), 4.95-5.01 (m, 2H), 5.91 (brs, 1H), 7.67 (s, 1H), 8.48 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 7.5, 23.8, 24.3, 26.7, 29.6, 31.5, 62.3, 76.7, 77.2, 77.8, 80.8, 85.1, 111.3, 120.3, 138.4, 149.2, 153.4, 156.0; anal. for ($C_{16}H_{21}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopentan-1'-yl]-6-cyclopentylamino-9H-purine (**17**).* EtOAc/hexanes (1:1), gummy solid (77%): ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.53 (s, 3H), 1.55-1.77 (m, 8H), 2.10-2.18 (m, 4H), 2.48 (m, 1H), 4.81-4.82 (m, 1H), 4.94-5.00 (m, 2H), 5.69 (brs, 1H), 7.64 (s, 1H), 8.39 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 23.8, 24.3, 26.7, 29.5, 31.5, 33.6, 52.6, 62.2, 80.8, 85.1, 111.3, 120.1, 138.1, 153.3, 154; anal. for ($C_{18}H_{25}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(Isopropylidenedioxy)cyclopentan-1'-yl]-6-cycloheptylamino-9H-purine (**18**).* EtOAc/hexanes (1:1), gummy solid (60%): ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.53 (s, 3H), 1.48-1.68 (m, 10H), 2.04-2.09 (m, 6H), 2.31-2.34 (m, 1H), 4.80-4.82 (m, 1H), 4.94-5.00 (m, 2H), 5.64 (d, 1H, *J* = *8* Hz), 7.64 (s, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1, 24.4, 26.8, 28.5, 29.7, 31.6, 35.5, 62.3, 73.5, 80.9, 85.2, 111.3, 138.1, 153.4, 154.2; anal. for ($C_{20}H_{29}O_2N_5$) C, H, N.

*General experimental procedure (**4**-**7**, and **8**-**11**)*

To a solution of the amine substituted nucleosides **15-18** and **21-24** (0.6 g) in MeOH (70 mL) was added Dowex 50 x 8 acidic resin beads (6 g) and the mixture was refluxed for 24 h. After the solvent was removed, the residue was loaded onto a Dowex resin column and the product was eluted with 50 % NH_4OH. Following removal of the NH_4OH by evaporation, the residue was co-evaporated with EtOH (3 x 20 mL), and purified by silica gel column eluting with MeOH/CH_2Cl_2.

*Preparation of (1'S,2'R,3'S)-1'-(6-methylamino-9H-purin-9-yl)-2',3'-dihydroxycyclo-pentane (**4**).* MeOH/CH_2Cl_2 (1:20), white solid (86 %): m.p. 162-164 ^{o}C; ^{1}H-NMR (DMSO-d_6) δ 1.65-1.66 (m, 1H), 1.98-1.99 (m, 1H), 2.10-2.23 (m,2H), 2.97 (brs, 3H), 4.01 (brs, 1H), 4.38-4.41 (m, 1H), 4.66-4.72 (m, 2H), 4.92-4.94 (m,1H), 7.60 (brs, 1H), 8.17 (s, 1H), 8.20 (s, 1H); ^{13}H-NMR (DMSO-d_6) δ 25.8, 27.0, 28.9, 59, 70.5, 76.3, 119.9, 140.1, 148.8, 152.0, 155.0; anal. for ($C_{11}H_{15}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-1'-(6-cyclopropylamino-9H-purin-9-yl)-2',3'-dihydroxycyclo-pentane (**5**).* MeOH/CH_2Cl_2 (1 :20), white solid (74%): m.p. 206-207 ^{o}C; ^{1}H-NMR (DMSO-d_6) δ 0.59-0.62 (m, 2H), 0.70-0.72 (m, 2H), 1.62-1.65 (m, 1H), 1.96-1.98 (m, 1H), 2.11-2.22 (m,

2H), 3.01 (brs, 1H), 4.00-4.01 (m, 1H), 4.36-4.41 (m, 1H), 4.66-4.72 (m, 2H), 4.92 (d, 1H, *J* = *8* Hz), 7.79 (d, 1H, *J* = *4* Hz), 8.18 (s, 1H), 8.21 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 6.4, 24.9, 25.7, 28.8, 54.9, 59.5, 70.5, 76,2, 119.8, 140.3, 151.9, 155.6; anal. for ($C_{13}H_{17}O_2N_5$) C, H, N.

*Preparation of(1'S,2'R,3'S)-1'-(6-cyclopentylamino-9H-purin-9-yl)-2',3'-dihydroxycyclopentane (**6**).* MeOH/CH_2Cl_2 (1:30), white solid (84%): m.p. 187-189 °C; ^{1}H-NMR (DMSO-d_6) δ 1.56-1.71 (m, 8H), 1.95-2.18 (m, 5H), 4.00 (brs, 1H), 4.38-4.40 (m, 1H), 4.68-4.72 (m, 2H), 4.94 (d, 1H, *J* = *5* Hz), 7.57 (d, 1H, *J* = *7.5* Hz), 8.17 (s, 1H); ^{13}C-NMR($CDCl_3$) δ 23.5, 25.8, 28.9, 32.3, 59.5, 70.5, 76.3, 140.0, 151.9, 154; anal. for ($C_{15}H_{21}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-1'-(6-cycloheptylamino-9H-purin-9-yl)-2',3'-dihydroxycyclo pentane (**7**).* MeOH/CH_2Cl_2 (1:40), white solid (79%): mp 192-193 °C; ^{1}H-NMR (DMSO-d_6) δ 1.45-1.65 (m, 11H), 1.86-2.17 (m, 6H), 4.00 (brs, 1H), 4.36-4.40 (m, 1H), 4.66-4.71 (m, 2H), 4.94 (d, 1H, *J* = *7.5* Hz), 7.45 (d, 1H, *J* = *7.5* Hz), 8.16 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 23.8, 25.7, 27.8, 28.8, 59.5, 70.5, 76.2, 140.0, 152.0, 153.6; anal. for ($C_{17}H_{25}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopent-4'-en-1'-yl]-6-chloro-9H-purine (**20**).* A suspension of 6-chloropurine (5.0 g, 32 mmol) and triphenylphosphine (8.4 g, 32 mmol) in anhydrous THF (100 mL) was chilled to -20 °C and treated with a drop wise addition of di*iso*propyl azodicarboxylate (DIAD) (6.6 g, 32 mmol). The reaction mixture was stirred for 10 min at the same temperature, after which the acetone-dry ice bath was removed and stirring was continued for 15 min. This was followed by addition of a solution of **19** (6.2 g, 40 mmol) in anhydrous THF (80 mL) and the reaction mixture was stirred at room temperature for 2 h and at 55 °C for 24 h. The solvent was removed under reduced pressure and the residue was purified via column chromatography eluting with EtOAc/hexanes (1:2) to yield **20** (5.8 g, 61 %) as a white solid: ^{13}C-NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.52 (s, 3H), 4.73 (d, 1H, *J* = *5* Hz), 5.54 (d, 1H, *J* = *5* Hz), 5.72 (s, 1H), 5.98 (d, 1H, *J* = *5* Hz), 6.41 (d, 1H, *J* = *5* Hz), 8.01 (s, 1H), 8.79 (s, 1H) ^{13}C-NMR ($CDCl_3$) δ 25.9, 27.5, 66.4, 83.9, 84.8, 112.9, 128.8, 132.1, 139.4, 143.4, 151.2, 151.4, 152.4; anal. for ($C_{13}H_{13}O_2N_4Cl$) C, H, N.

*General experimental procedure (**21**-**24**)*

To a solution of **20** (1.0 g, 3.4 mmol) in THF (70 mL) was added the corresponding amine (methylamine in THF 2 M, 20 mL, cyclopropylamine 1.9 g, cyclopentylamine 2.4 g, and cycloheptylamine 3.8 g). For compounds **21** and **22**, the mixture was heated at 85 °C for 24 h in a sealed steel bomb where as it was refluxed for 24 h for **23** and **24**. The volatiles were evaporated and the residue was purified by column chromatography using EtOAc/hexanes.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopent-4'-en-1'-yl]-6-methyl-amino-9H-purine (**21**).* EtOAc/hexanes (2:1), gummy solid (61 %): ^{1}H-NMR (DMSO-d_6) δ 1.27 (s, 3H), 1.39 (s, 3H), 2.94 (brs, 3H), 4.68 (d, 1H, *J* = *5* Hz), 5.48-5.52 (m, 2H), 5.97-6.00 (m, 1H), 6.26 (d, 1H, *J* = *5* Hz), 7.74 (brs, 1H), 7.96 (s, 1H), 8.22 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 25.6, 27.2, 64.6, 83.3, 84.5, 111.1, 130.2, 137.2, 138. 8, 152.6, 155.0; anal. for ($C_{14}H_{17}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopent-4'-en-1'-yl]-6-cyclopropyl-amino-9H-purine (**22**).* EtOAc/hexanes (3:1), gummy solid (58%): ^{1}H-NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.48 (s, 3H), 1.55-1.63 (m, 3H), 2.21-2.25 (m, 2H), 4.66 (d, 1H, *J* = *5* Hz), 5.39 (d, 1H, *J* = *5* Hz), 5.45 (s, 1H), 5.79 (d, 1H, *J* = *5* Hz), 5.92-5.96 (m, 1H), 6.35-6.38 (m, 1H) 7.66 (s, 1H),

8.39 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 23.1, 24.9, 34.5, 65.7, 82.2, 84.1, 110.6, 122.3, 136.6, 138.3, 151.1, 152.7; anal. for ($C_{16}H_{19}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopent-4'-en-1'-yI]-6-cyclopentylamino-9H-purine (**23**).* EtOAc/hexanes (1:1), gummy solid (70%): ^{1}H-NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.50 (s, 3H), 1.52-1.80 (m, 7H), 2.10-2.17 (m, 2H), 4.69 (d, 1H, *J = 5* Hz), 5.49 (d, 1H, *J = 5* Hz), 5.63 (s, 1H), 5.79 (d, 1H, *J = 5* Hz), 5.95-5.98 (m, 1H), 6.32-6.36 (m, 1H) 7.60 (s, 1H), 8.43 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 23.9, 25.9, 27.5, 33.6, 65.6, 84.2, 84.8, 112.6, 129.8, 137.6, 138.3, 153.7, 154.7; anal. for ($C_{18}H_{23}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-9-[2',3'-(isopropylidenedioxy)cyclopent-4'-en-1'-yl]-6-cycloheptylamino-9H-purine (**24**).* EtOAc/hexanes (1:1), (60%) as a gummy solid: ^{1}H-NMR (DMSO-d_6) δ 1.27 (s, 3H), 1.38 (s, 3H), 1.44-1.65 (m, 11H), 1.85-1.88 (m, 2H), 4.68 (d, 1H, *J = 5* Hz), 5.47-5.52 (m, 2H), 5.96-5.99 (m, 1H), 6.26 (d, 1H, *J = 5* Hz), 7.57 (d, 1H, *J = 5* Hz) 7.95 (s, 1H), 8.19 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 23.7, 23.8, 25.6, 27.2, 64.5, 83.3, 84.5, 111.1, 130.2, 137.2, 138.7, 152.6, 153.1; anal. for ($C_{20}H_{27}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-1'-(6-methylamino-9H-purin-9-yl)-2',3'-dihydroxycyclopent-3-ene (**8**).* MeOH/CH_2Cl_2 (1:20), white solid (66%): m.p. 164-166 °C; ^{1}H-NMR (DMSO-d_6) δ 2.94 (brs, 3H), 4.27-4.32 (m, 1H), 4.54 (brs, 1H), 4.93-4.97 (m, 1H), 5.07-5.12 (m, 1H), 5.37 (m, 1H), 5.98 (d, 1H, *J = 5* Hz), 6.12 (d, 1H, *J = 5* Hz), 7.66 (brs, 1H), 8.06 (s, 1H), 8.19 (s, 1H); ^{13}H-NMR (DMSO-d_6) δ 64.7, 72.6, 76.2, 132.5, 136.0, 139.4, 152.3, 155.0; anal. for ($C_{11}H_{13}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-1'-(6-cyclopropylamino-9H-purin-9-yl)-2',3'-dihydroxycyclopent-3-ene (**9**).* MeOH/CH_2Cl_2 (1:20), white solid (69%): m.p. 185-187 °C; ^{1}H-NMR (DMSO-d_6) δ 0.60-0.71 (m, 4H), 3.05 (brs, 1H), 4.32 (s, 1H), 4.54 (s, 1H), 4.95 (d, 1H, *J* = 5 Hz), 5.10 (d, 1H, *J=5* Hz), 5.39 (s, 1H), 6.00 (s, 1H), 6.13 (s, 1H), 7.87 (s, 1H), 8.08 (s, 1H), 8.21 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 6.4, 23.9, 64.6, 72.5, 76.2, 119.5, 132.5, 135.9, 139.5, 152.2, 155.5; anal. for ($C_{13}H_{15}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-1'-(6-cyclopentylamino-9H-purin-9-yl)-2',3'-dihydroxycyclopent-3-ene (**10**).* MeOH/CH_2Cl_2 (1:30), white solid (60%): m.p. 170-172 °C; ^{1}H-NMR (DMSO-d_6) δ 1.23-1.71 (m,7H), 1.93-194 (m, 2H), 4.30 (d, 1H, *J = 5* Hz), 4.54 (brs,1H), 4.94 (d, 1H, *J = 5* Hz), 5.09 (d, 1H, *J = 5* Hz), 5.38 (brs, 1H), 5.98 (brs, 1H), 6.12 (brs, 1H), 7.61 (d, 1H, *J = 5* Hz), 8.07 (s, 1H), 8.16 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 23.9, 33.6, 65.1, 73.0, 76.6, 112.6, 132.7, 136.4, 144.3, 153.7, 154.7; anal. for ($C_{15}H_{19}O_2N_5$) C, H, N.

*Preparation of (1'S,2'R,3'S)-1'-(6-cycloheptylamino-9H-purin-9-yl)-2',3'-dihydroxycyclopent-3-ene (**11**).* MeOH/CH_2Cl_2 (1:40), white solid (71 %): m.p. 125-127 °C; ^{1}H-NMR (DMSO-d_6) δ 1.44-1.65 (m, 11H), 1.86-1.89 (m, 2H), 4.31 (brs, 1H), 4.55 (brs, 1H), 4.96 (brs, 1H), 5.11 (brs, 1H), 5.38-5.40 (m, 1H), 5.97-6.00 (m, 1H), 6.11-6.15 (m, 1H), 7.50 (d, 1H, *J = 7.5* Hz), 8.07 (s, 1H), 8.17 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 23.5, 27.5, 27.5, 50.4, 64.3, 72.3, 75.9, 132.2, 135.6, 138.9, 151.9, 153.2; anal. for ($C_{17}H_{23}O_2N$) C, H, N.

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