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The enantiomers of the 1′,6′-isomer of neplanocin A: Synthesis and antiviral properties

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ABSTRACT

Both enantiomers of 1′,6′-*iso*neplanocin have been prepared from a common substituted cyclopentane epoxide in 7 steps. Both compounds were subjected to DNA and RNA viral assessments with moderate to high activity found for both towards human cytomegalovirus, measles, Ebola, norovirus, and dengue. The D-like congener also showed vaccinia and HBV effectiveness. In many of the other antiviral assays both compounds showed cytotoxicity making, in some cases, an EC_{50} determination not possible. The *S*-adenosylhomocysteine hydrolase inhibitory effects showed the D-like target to be equal that of neplanocin itself and better than 3-deazaneplanocin whereas the L-like analogue was 13 to 30 times less inhibitory than 3-deazaneplanocin and neplanocin, respectively.

1. Introduction

The naturally occurring neplanocin series of carbocyclic nucleosides (Fig. 1)[1] offers a unique substitution pattern within the cyclopentyl appendage not found elsewhere. This collection of nucleosides is conformationally constrained by the alkene and epoxide functionalities. Additionally, both of these structural centers provide for access to a variety of molecular modifications in a laboratory analogue pursuit building upon the biological activity of the neplanocins, particularly neplanocin A (**1**).[2]

Several years ago we became interested in affecting change at the C-1′ of the neplanocins by generating the C-1′/C-6′ isomer of neplanocin A (that is **2**, Fig. 2). That research produced a short synthetic communication.[3] We now wish to report the details of that effort with improved preparative procedures to **2** and its newly described enantiomer **3** (Fig. 2) together with their antiviral data.

2. Results and discussion

2.1. Synthesis

In seeking a more adaptable procedure (for future development of various unique neplanocin analogues) the known substituted cyclopentyl epoxide **4**[4] (available from cyclopentadiene in 2 steps) fulfilled this intention. Thus, the synthesis of **2** and **3** began with

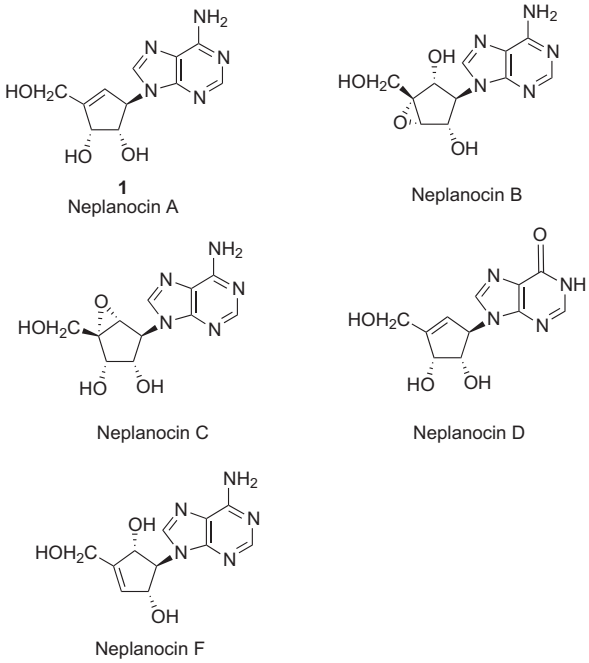

Figure 1. Naturally occurring neplanocins.

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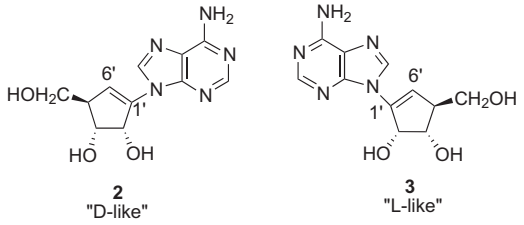


Figure 2. Target neplanocin analogues.

protection of the secondary hydroxyl of **4** with a *p*-methoxybenzyl (PMB) group to **5** (Scheme 1). A regioselective ring opening of **5** with lithium *bis*(trimethylsilyl) amide (LiHMDS) provided the versatile alkene **6**. Subsequent oxidation of **6** with *m*-chloroperoxybenzoic acid (*m*CPBA) proceeded to the α-epoxide **7**, which availed an entry point into the requisite carbocyclic nucleoside scaffold. (Confirmation of the stereochemistry of **7** came with its movement to the known **2**[3]).

In the latter direction, reaction of **7** with adenine in the presence of 1,8-diazabicycloundec-7-ene (DBU) yielded a mixture of **8** and **9** (1.6:1). Acidic removal of the PMB group of **8** to **10** followed by glycol protection gave **11**. Mesylation of **11** resulted in **12**, which underwent elimination in the presence of sodium methoxide to provide **13**. Debenzylation of **13** with subsequent deketalization yielded target **2**.

The final steps to **3** began with glycol protection of **9** to **15**, which, upon oxidative deprotection with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), was converted into **16**. As with **11**, mesylation of **16** to **17** and subsequent sodium methoxide promoted elimination produced **18**, analogous to **13**. Deprotection **18**, as with **13**, to **19** and then 1 N hydrochloric acid, resulted in target **3**.

2.2. Antiviral and enzyme assay results

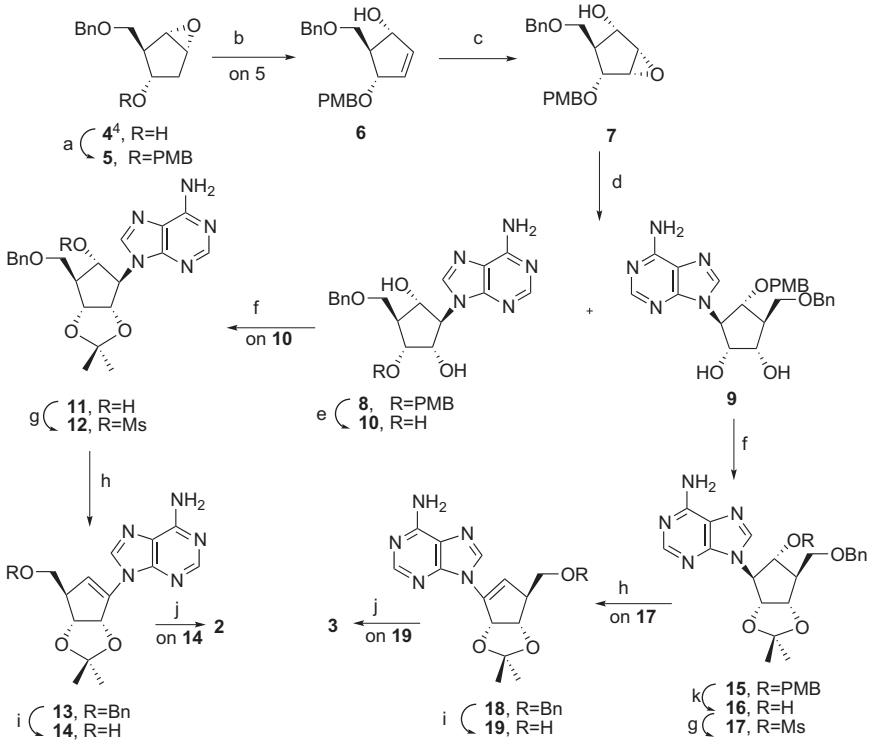
Compounds **2** and **3** were evaluated against both DNA and RNA viruses. Table 1 lists where activity was observed.[5,6] Noteworthy is the activity of both enantiomers towards human cytomegalovirus (HCMV), measles, Ebola, norovirus, and dengue (albeit with some accompanying toxicity). Compound **2** displayed activity towards hepatitis B virus and vaccinia virus.

As a consequence of **2** and **3** being isomers of neplanocin A, whose potent inhibition of *S*-adenosylhomocysteine hydrolase (SAHase) is one agreed upon source of its antiviral activity,[2] they were screened against this enzyme (source: rabbit erythrocytes). This assay produced the following results (IC_{50} in nm): neplanocin A (structure in Fig. 1, 0.9); D-like *iso*neplanocin A (**2**, 0.9); L-like *iso*neplanocin A (**3**, 27), and 3-deazaneplanocin (structure not shown, 2). As can be seen, **2** possesses an effect on SAHase comparable to neplanocin A but 2 orders of magnitude better than 3-deazaneplanocin while enantiomer **3** is less effective.

3. Conclusion

The C-1′/C-6′ *iso*neplanocin enantiomers have been prepared from a common precursor (that is, **7**) and were found to possess antiviral activity against a variety of important viruses. In cases where both were active **2** was slightly more effective than **3**.

On the other hand, only **2** affected hepatitis B virus and vaccinia virus, the former more strongly. These properties may be due to their different effects on SAHase. However, the potent effect of **3** versus Ebola coupled with its weaker properties towards SAHase suggests that SAHase inhibition is not the only site where **3** is acting towards, at least, this virus. More work in this area is foreseen since **3** opens-up the L-like carbocyclic nucleoside[7] as a potential scaffold for anti-Ebola drug discovery endeavors. To date very little



Scheme 1. Synthetic steps to targets **2** and **3**. Reagents and conditions: (a) NaH, PMBBr, TBAI, THF, 95%; (b) LiHMDS, THF, 84%; (c) *m*CPBA, CH_2Cl_2, 84%; (d) adenine, DBU, DMF, 50% for **8**, 31% for **9**; (e) 1 N HCl/MeOH, 94%; (f) *p*-TsOH·H_2O, $CH(OEt)_3$, acetone, 77% for **11**, 84% for **15**; (g) MsCl, Et_3N, CH_2Cl_2, 93% for **12**, 90% for **17**; (h) NaOMe, THF/MeOH, 89% for **13**, 90% for **18**; (i) $Pd(OH)_2/C$, cyclohexene, EtOH, 87% for **14**, 87% for **19**; (j) 2 N HCl/MeOH, 90% for **2**, 92% for **3**; (k) DDQ, CH_2Cl_2/H_2O, 93%.

Table 1
Antiviral activity of **2** and **3** (in μM)

Virus (host cell line)	Compound **2**	Compound **3**
HBV (2.2.15)	EC_{50} 7.2 EC_{90} 35 CC_{50} >100 SI_{50} >14 SI_{90} >3	Inactive
Vaccinia (HFF)	EC_{50} 10.08 EC_{90} >300 CC_{50} >300 SI_{50} >30 SI_{90} 1	Inactive
HCMV (HFF)	EC_{50} 0.11 EC_{90} >12 CC_{50} 49.33 SI_{50} 448 SI_{90} <4	EC_{50} 3.70 EC_{90} 6.86 CC_{50} >300 SI_{50} >81 SI_{90} >44
NOV (HG23)	EC_{50} 0.784 EC_{90} 8.884 CC_{50} >100 SI_{50} >128 SI_{90} >11	EC_{50} 11 EC_{90} 89 CC_{50} >300 SI_{50} >9 SI_{90} >1
Dengue (Vero 76)	EC_{50} 1.1, 1.5 CC_{50} 25.3, 23.8 SI_{50} 17, 21	EC_{50} 6.1, 5.7 CC_{50} 87, 122 SI_{50} 15, 21
Measles (Vero 76)	EC_{50} <0.38 EC_{90} ND[a] CC_{50} >1.33 SI_{50} >3.5	EC_{50} 0.72, 0.72 EC_{90} ND[a] CC_{50} 12.2, 15.2 SI_{50} 17, 21
Ebola (Zaire) (Vero)	EC_{50} 0.38 CC_{50} 1.3 SI_{50} 3.5	EC_{50} 0.76 CC_{50} 11.4 SI_{50} 15

[a] ND, not determined.

effort has been devoted to the antiviral properties of L-like carbocyclic nucleosides.[8]

4. Experimental

4.1. Materials and methods

Melting points were recorded on a Meltemp II melting point apparatus and the values were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AC 600 spectrometer (600 MHz for proton and 150 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The mass spectral data was determined using a Waters Micromass Q-TOF Premier Mass Spectrometer. The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230–400 mesh, and 60 Å using elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

4.2. (1*S*,2*R*,3*S*,5*R*)-2-((Benzyloxy)methyl)-3-((4-methoxybenzyl)-oxy)-6-oxabicyclo[3.1.0]-hexane (5)

To a solution of **4**[4] (1.12 g, 5.08 mmol) in THF (20 mL) was treated with NaH (60%, 224 mg, 6.10 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for additional 30 min and 4-methoxylbenzyl bromide (0.72 mL, 5.59 mmol) and tetrabutylammonium iodide (20 mg, 0.05 mmol) were added. After 24 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and the solvent was removed by rotary evaporation. The pure product (1.65 g, 95%) was isolated using column chromatography (2:1, hexanes/EtOAc) as a clear liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30–7.24 (m, 5H), 7.20 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.46 (s, 2H), 4.38 (d, J = 2.7 Hz, 2H), 3.86 (d, J = 7.3 Hz, 1H), 3.75 (s, 3H), 3.50 (m, 1H), 3.43 (d, J = 2.6 Hz, 1H), 3.37 (m, 2H), 2.57 (t, J = 5.9 Hz, 1H), 2.13 (m, 1H), 2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.0, 138.0, 130.4, 129.3, 128.4, 127.6, 113.8, 80.5, 73.1, 70.4, 69.2, 60.3, 59.6, 57.9, 55.2, 47.4, 37.8. HRMS calcd for $C_{21}H_{24}O_4Na$ $[M+Na]^+$: 363.1572; found 363.1564.

4.3. (1*R*,4*S*,5*S*)-5-((Benzyloxy)methyl)-4-((4-methoxybenzyl)-oxy)cyclopent-2-enol (6)

To a solution of **5** (450 mg, 1.32 mmol) in THF (40 mL), lithium hexamethyldisilazide (7 mL, 1.0 M in THF, 7 mmol) was added dropwise at room temperature. The reaction mixture was heated at 60 °C for 3 h. The resulting solution was cooled to room temperature, quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic phases were combined, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (1:1, EtOAc/hexanes) to give **6** (380 mg, 84%) as a yellow liquid: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.33–7.29 (m, 5H), 7.22 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.91 (s, 2H), 4.53–4.46 (m, 4H), 4.42 (d, J = 4.3 Hz, 1H), 4.24 (d, J = 4.6 Hz, 1H), 3.76 (s, 3H), 3.58 (m, 2H), 2.77 (br, 1H), 2.26 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 159.2, 138.3, 136.2, 133.2, 130.6, 129.4, 128.4, 127.70, 127.68, 113.8, 83.6, 77.8, 73.2, 70.1, 70.0, 55.8, 55.3. HRMS calcd for $C_{21}H_{24}O_4Na$ $[M+Na]^+$: 363.1572; found 363.1577.

4.4. (1*S*,2*S*,3*S*,4*R*,5*R*)-3-((Benzyloxy)methyl)-4-((4-methoxybenzyl)oxy)-6-oxabicyclo[3.1.0]hexan-2-ol (7)

To a solution of **6** (220 mg, 0.65 mmol) in CH_2Cl_2 (20 mL) was added *m*CPBA (335 mg, 77%, 1.5 mmol) at 0 °C. This mixture was stirred overnight and quenched with sodium bisulfite. The reaction mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography (1:1, EtOAc/hexanes) to give **7** (380 mg, 84%) as a white solid, mp 72–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.32–7.24 (m, 7H), 6.85 (d, J = 8.3 Hz, 2H), 4.61 (d, J = 11.7 Hz, 1H), 4.48 (dd, J = 11.8, 15.6 Hz, 2H), 4.39 (d, J = 11.9 Hz, 1H), 4.03 (d, J = 7.9 Hz, 1H), 3.76 (s, 3H), 3.65 (dd, J = 2.7, 9.4 Hz, 1H), 3.50 (m, 3H), 2.69 (br, 1H), 1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.3, 138.2, 130.2, 129.4, 128.3 (2C), 127.6, 113.8, 77.0, 73.1, 71.8, 71.1, 66.9, 56.7, 55.2, 54.5, 44.9. HRMS calcd for $C_{21}H_{24}O_5Na$ $[M+Na]^+$: 379.1521; found 379.1511.

4.5. (1*S*,2*R*,3*S*,4*S*,5*R*)-2-(6-Amino-9*H*-purin-9-yl)-4-((benzyloxy)-methyl)-5-((4-methoxybenzyl)oxy)cyclopentane-1,3-diol (8) and (1*S*,2*R*,3*R*,4*R*,5*S*)-3-(6-Amino-9*H*-purin-9-yl)-5-((benzyloxy)-methyl)-4-((4-methoxybenzyl)oxy)cyclopentane-1,2-diol (9)

Adenine (1.23 g, 9.1 mmol) and **7** (1.30 g, 3.65 mmol) were suspended in DMF (20 mL) under N_2 for 15 min at room temperature. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.64 mL, 10.9 mmol) was added and the reaction mixture was heated at 90 °C for 8 h. After the reaction was cooled to room temperature, the resulting

solid was removed by filtration over Celite and then rinsed with CH_2Cl_2. The filtrate was evaporated under reduced pressure and the residue purified by column chromatography to afford **8** (900 mg, 50%) and **9** (550 mg, 31%) as white solid and white foam (20:1, CH_2Cl_2/MeOH and 10:1, CH_2Cl_2/MeOH, respectively):

Compound **8**: mp 163–165 °C: ^{1}H NMR (400 MHz, DMSO) δ ppm 8.13 (s, 1H), 8.10 (s, 1H), 7.36–7.27 (m, 7H), 7.16 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.83 (d, J = 5.4 Hz, 1H), 5.06 (d, J = 7.1 Hz, 1H), 4.61–4.50 (m, 6H), 4.27 (m, 1H), 3.76–3.73 (m, 4H), 3.58 (dd, J = 4.2, 9.4 Hz, 1H), 3.51 (m, 1H), 2.10 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ ppm 158.7, 156.1, 152.0, 149.9, 141.2, 138.6, 130.8, 129.3, 128.3, 127.5, 127.4, 119.6, 113.6, 77.8, 72.2, 71.1, 70.5, 70.3, 69.2, 67.6, 55.1, 50.7. HRMS calcd for $C_{26}H_{30}N_5O_5$ $[M+H]^+$: 492.2247; found 492.2241.

Compound **9**: ^{1}H NMR (600 MHz, MeOD) δ ppm 8.07 (s, 1H), 7.96 (s, 1H), 7.42–7.30 (m, 5H), 6.69 (d, J = 8.2 Hz, 2H), 6.47 (d, J = 8.5 Hz, 2H), 4.72 (t, J = 9.0 Hz, 1H), 4.58 (m, 3H), 4.41 (t, J = 7.1 Hz, 1H), 4.28 (d, J = 12.1 Hz, 1H), 4.18 (d, J = 12.1 Hz, 1H), 4.04 (m, 1H), 3.63 (m, 5H), 2.31 (m, 1H); ^{13}C NMR (150 MHz, MeOD) δ ppm 160.6, 157.1, 153.2, 150.9, 142.9, 139.9, 131.0, 130.5, 129.5, 129.1, 128.9, 120.9, 114.3, 78.6, 74.4, 73.4, 72.9, 72.6, 70.8, 68.7, 55.7, 52.7. HRMS calcd for $C_{26}H_{30}N_5O_5$ $[M+H]^+$: 492.2247; found 492.2243.

4.6. (1*R*,2*S*,3*R*,4*S*,5*S*)-3-(6-Amino-9*H*-purin-9-yl)-5-((benzyloxy)-methyl)-cyclopentane-1,2,4-triol (10)

To a solution of **8** (100 mg, 0.20 mmol) in MeOH (2 mL) was added 1 N HCl (2 mL) and the solution was stirred at 50 °C for 4 h. The solvent was removed under reduced pressure to give **10** (70 mg, 94%) as white solid that was used directly in this form in the next step. ^{1}H NMR (600 MHz, MeOD) δ ppm 8.59 (s, 1H), 8.44 (s, 1H), 7.42–7.29 (m, 5H), 4.89 (m, 1H), 4.63 (m, 3H), 4.53 (m, 1H), 4.17 (m, 1H), 3.76 (m, 2H), 2.23 (m, 1H). HRMS calcd for $C_{18}H_{22}N_5O_3$ $[M+H]^+$: 372.1672; found 372.1666.

4.7. (3a*S*,4*R*,5*S*,6*S*,6a*R*)-4-(6-Amino-9*H*-purin-9-yl)-6-((benzyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-5-ol (11)

To a solution of **10** (70 mg, 0.19 mmol) in acetone (5 mL) was added triethyl orthoformate (0.25 mL, 1.50 mmol) and *p*-TsOH·H_2O (65 mg, 0.33 mmol). The reaction mixture was stirred at room temperature for 4 h, quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified via column chromatography (20:1, EtOAc/MeOH) to give **11** (60 mg, 77%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26 (s, 1H), 8.00 (s, 1H), 7.36–7.24 (m, 5H), 5.80 (s, 2H), 4.80 (t, J = 7.02 Hz, 1H), 4.70–4.63 (m, 2H), 4.60 (s, 2H), 4.42 (dd, J = 6.8, 9.6 Hz, 1H), 3.78 (m, 2H), 2.50 (m, 1H), 1.61 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.6, 152.0, 149.4, 140.6, 137.9, 128.3, 127.6, 119.3, 113.3, 79.6, 77.9, 73.3, 73.2, 69.3, 67.9, 50.1, 27.1, 24.8. HRMS calcd for $C_{21}H_{26}N_5O_4$ $[M+H]^+$: 412.1985; found 412.1975.

4.8. (3a*S*,4*S*,5*S*,6*R*,6a*R*)-4-(6-Amino-9*H*-purin-9-yl)-6-((benzyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-5-yl methanesulfonate (12)

To a solution of **11** (90 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (20 mL) were added, dropwise, triethylamine (0.06 mL, 0.44 mmol), methanesulfonyl chloride (0.02 mL, 0.26 mmol) and 4-dimethylaminopyridine (5 mg, 0.04 mmol) at 0 °C under N_2. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phases were dried (Na_2SO_4). The residue, after filtration and evaporation, was loaded onto silica gel. Column chromatography (30:1, EtOAc/MeOH) afforded **12** (100 mg, 93%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32 (s, 1H), 7.84 (s, 1H), 7.41–7.34 (m, 5H), 6.28 (s, 2H), 5.78 (t, J = 9.2 Hz, 1H), 5.15 (m, 1H), 4.82 (ddd, J = 9.3, 8.0, 5.6 Hz, 2H), 4.61 (s, 2H), 3.83 (dd, J = 9.7, 4.0 Hz, 1H), 3.76 (dd, J = 9.7, 4.0 Hz, 1H), 2.63–2.55 (m, 1H), 2.53 (s, 3H), 1.59 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.8, 152.3, 149.9, 140.5, 137.8, 128.5, 127.9, 127.8, 120.3, 113.5, 81.2, 79.2, 77.5, 73.5, 66.9, 66.7, 49.1, 37.5, 27.5, 25.1. HRMS calcd for $C_{22}H_{28}N_5O_6S$ $[M+H]^+$: 490.1760; found 490.1782.

4.9. 9-((3a*S*,6*R*,6a*R*)-6-((Benzyloxy)methyl)-2,2-dimethyl-6,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (13)

To a solution of **12** (70 mg, 0.14 mmol) in THF (5 mL) was added sodium methoxide (25 mg, 0.46 mmol) in MeOH (0.5 mL) and the reaction mixture was refluxed for 4 h. The residue, after evaporation under reduced pressure, was loaded onto silica gel, which was then added to a column for chromatographic purification (50:1, EtOAc/MeOH) to afford **13** (50 mg, 89%) as white solid, mp 187–188 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (s, 1H), 8.26 (s, 1H), 7.33–7.28 (m, 5H), 6.70 (d, J = 2.7 Hz, 1H), 6.16 (s, 2H), 5.53 (dd, J = 5.8, 1.1 Hz, 1H), 4.73 (d, J = 5.8 Hz, 1H), 4.54 (s, 2H), 3.69 (dd, J = 9.4, 4.6 Hz, 1H), 3.48 (dd, J = 9.4, 6.1 Hz, 1H), 3.25 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.5, 153.4,150.1, 138.7, 138.6, 135.3, 128.4, 127.7, 127.6, 119.8, 119.2, 111.6, 82.9, 80.6, 73.2, 70.6, 50.1, 27.4, 25.9. HRMS calcd for $C_{21}H_{24}N_5O_3$ $[M+H]^+$: 394.1879; found 394.1873.

4.10. ((3a*R*,4*R*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (14)

A solution of **13** (300 mg, 0.76 mmol) and 20% $Pd(OH)_2$/C (375 mg) in cyclohexene (5 mL) and EtOH (8 mL) was heated at reflux for 12 h and then filtered through Celite. The filtrate was evaporated to dryness under reduced pressure and purified by column chromatography (9:1, EtOAc/MeOH) to give **14** (200 mg, 87%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.34 (s, 1H), 8.26 (s, 1H), 6.60 (d, J = 2.7 Hz, 1H), 5.65 (dd, J = 1.2, 5.8 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.62 (br, 1H, OH), 3.77 (dd, J = 4.9, 11.1 Hz, 1H), 3.63 (dd, J = 5.8, 11.1 Hz, 1H), 3.09 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ ppm 157.6, 154.5, 151.0, 140.4, 137.1, 121.3, 120.5, 112.6, 84.1, 81.9, 64.0, 53.8, 27.8, 26.0. HRMS calcd for $C_{14}H_{18}N_5O_3$ $[M+H]^+$: 304.1410; found 304.1411.

4.11. (1*R*,2*S*,5*R*)-3-(6-Amino-9*H*-purin-9-yl)-5-(hydroxymethyl) cyclopent-3-ene-1,2-diol (2)

To a solution of **14** (190 mg, 0.63 mmol) in MeOH (2 mL) was added 2 N HCl (5 mL) and the reaction mixture was stirred at room temperature for 4 h. The solution was then neutralized with IRA-67 resin and the filtrate was evaporated to give **2** (150 mg, 90%) as a pale white solid, mp 195–196 °C: ^{1}H NMR (600 MHz, D_2O) δ ppm 8.00 (s, 1H), 7.83 (s, 1H), 6.17 (d, J = 2.1 Hz, 1H), 4.86 (dd, J = 1.3, 5.9 Hz, 1H), 4.09 (t, J = 5.8 Hz, 1H), 3.76 (dd, J = 4.6, 11.5 Hz, 1H), 3.63 (dd, J = 5.5, 11.5 Hz, 1H), 2.87 (m, 1H); ^{13}C NMR (150 MHz, D_2O) δ ppm 154.9, 152.3, 147.8, 139.5, 134.5, 123.6, 117.8, 73.0, 71.0, 61.0, 50.8. HRMS calcd for $C_{11}H_{14}N_5O_3$ $[M+H]^+$: 264.1097; found 264.1093. $[\alpha]_D^{22.9}$ 38.5° (c 0.18, H_2O).

4.12. 9-((3a*R*,4*S*,5*R*,6*R*,6a*S*)-6-((Benzyloxy)methyl)-5-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (15)

To a solution of **9** (90 mg, 0.18 mmol) in acetone (5 mL) was added triethyl orthoformate (0.18 mL, 1.08 mmol) and *p*-TsOH·H_2O (41 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 4 h, quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The resulting residue was purified via column chromatography (20:1, EtOAc/MeOH) to give **15** (80 mg, 84%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26 (s, 1H), 7.71 (s, 1H), 7.40–7.31 (m, 5H), 6.71 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 6.03 (s, 2H), 5.10 (m, 1H), 4.76–4.70 (m, 3H), 4.69–4.63 (m, 2H), 4.15 (d, J = 11.6 Hz, 1H), 4.00 (d, J = 11.6 Hz, 1H), 3.76 (dd, J = 3.6, 9.6 Hz, 1H), 3.70–3.64 (m, 4H), 2.37 (m, 1H), 1.54 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.1, 155.5, 152.4, 149.6, 140.9, 138.1, 129.5, 129.1, 128.4, 127.72. 127.69, 120.5, 113.3, 112.9, 78.63, 78.60, 77.4, 73.2, 72.8, 68.5, 67.6, 55.1, 50.1, 27.5, 25.0. HRMS calcd for $C_{29}H_{34}N_5O_5$ $[M+H]^+$: 532.2560; found 532.2568.

4.13. (3a*R*,4*S*,5*R*,6*R*,6a*S*)-4-(6-Amino-9*H*-purin-9-yl)-6-((benzyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-5-ol (16)

To a solution of **15** (70 mg, 0.13 mmol) in CH_2Cl_2/H_2O (20:1, 5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (60 mg, 0.26 mmol) at 0 °C. After 5 h, the reaction mixture was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and the organic layers combined, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified via column chromatography (20:1, EtOAc/MeOH) to give **16** (50 mg, 93%) as a white solid, mp 172–174 °C. HRMS calcd for $C_{21}H_{26}N_5O_4$ $[M+H]^+$: 412.1985; found 412.1966.

4.14. (3a*R*,4*R*,5*R*,6*S*,6a*S*)-4-(6-Amino-9*H*-purin-9-yl)-6-((benzyloxy)methyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-5-yl methanesulfonate (17)

Following the procedure for the preparation of **12**, compound **17** was obtained from **16** (220 mg, 0.54 mmol) as a white foam (240 mg, 90%). The ^{1}H and ^{13}C NMR spectroscopic measurements were consistent with that reported above for **12**. HRMS calcd for $C_{22}H_{28}N_5O_6S$ $[M+H]^+$: 490.1760; found 490.1782.

4.15. 9-((3a*R*,6*S*,6a*S*)-6-((Benzyloxy)methyl)-2,2-dimethyl-6,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (18)

Following the procedure for the preparation of **13**, compound **18** was obtained from **17** (210 mg, 0.42 mmol) as a white solid (150 mg, 90%). The ^{1}H and ^{13}C NMR spectroscopic measurements were consistent with that reported above for **13**. HRMS calcd for $C_{21}H_{24}N_5O_3$ $[M+H]^+$: 394.1879; found 394.1848.

4.16. ((3a*S*,4*S*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (19)

Following the procedure for the preparation of **14**, compound **19** was obtained from **18** (120 mg, 0.30 mmol) as a white solid (80 mg, 87%). The ^{1}H and ^{13}C NMR spectroscopic measurements were consistent with that reported above for **14**. HRMS calcd for $C_{14}H_{18}N_5O_3$ $[M+H]^+$: 304.1410; found 304.1401.

4.17. (1*S*,2*R*,5*S*)-3-(6-Amino-9*H*-purin-9-yl)-5-(hydroxymethyl)-cyclopent-3-ene-1,2-diol (3)

Following the procedure for the preparation of **2**, compound **3** was obtained from **19** (70 mg, 0.23 mmol) as a white solid (56 mg, 92%), mp 191–193 °C. The ^{1}H and ^{13}C NMR spectroscopic measurements were consistent with that reported above for **2**. HRMS calcd for $C_{11}H_{14}N_5O_3$ $[M+H]^+$: 264.1097; found 264.1090. $[\alpha]_D^{23.0}$ −32.8° (*c* 0.04, H_2O).

4.18. Antiviral assays

See Ref. 5 for the necessary details.

4.19. *S*-Adenosylhomocysteine hydrolase (SAHase) assay

See Ref. 9 for the necessary details.

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6. There was no activity by either of the target compounds towards (host cell) Rift Valley Fever (Vero 76), Tacaribe (Vero 76), yellow fever (Vero), Japanese equine encephalitis (Vero 76), Pichinde (Vero), polio-3 (Vero 76), Punta Toro (Vero 76), Venezuelan equine encephalitis (Vero 76), hepatitis C virus (Huh), rabies (BHK 21), Nipah (Vero). In these instances, **2** and **3** showed toxicity to the host cells.
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