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Amino substituted derivatives of 5′-amino-5′-deoxy-5′-noraristeromycin

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Abstract—The potent antiviral potential of 5′-amino-5′-deoxy-5′-noraristeromycin (**2**) is limited by associated toxicity. To seek derivatives of **2** that circumvent this undesirable property, three amino substituted derivatives (acetyl, **3**; formyl, **4**; and methyl, **5**) of **2** have been prepared in 4–7 steps from the same intermediate, (1*S*,4*R*)-4-(6-chloropurin-9-yl)cyclopent-2-en-1-ol (**6**). Key steps involved an improved Pd(0)-catalyzed allylic azidation and a novel Pd(0)-catalyzed allylic amidation. The three target compounds were evaluated against a large number of viruses and found to be inactive except for a very weak effect of **5** on human cytomegalovirus, varicella zoster virus, and Epstein–Barr virus. There was also no noteworthy cytotoxicity associated with the new derivatives. Thus, these results indicate variation of the cyclopentyl amine of **2** does not offer a means to improve upon its antiviral potential.

1. Introduction

The significant non-toxic antiviral properties of 5′-noraristeromycin (**1**, Fig. 1)[1] stimulated the search for related compounds with similar biological activity.[2] The most promising representative of this group arose when the 4′-hydroxyl of **1** was replaced by a primary amino to give **2**.[3] However, in some viral assays, **2** demonstrated unacceptable toxicity. In moving to alleviate these toxic effects, modification of the amino site was considered. In this direction, the amino substituted derivatives **3**–**5** were sought. These targets were seen as affecting the basicity/nucleophilicity of the 4′-amino substituent (**3**–**5**), offering potential prodrug candidates (**3** and **4**), presenting a steric environment (**5**), and introducing a lipophilic substituent (in the form of the methyl group of **5**).

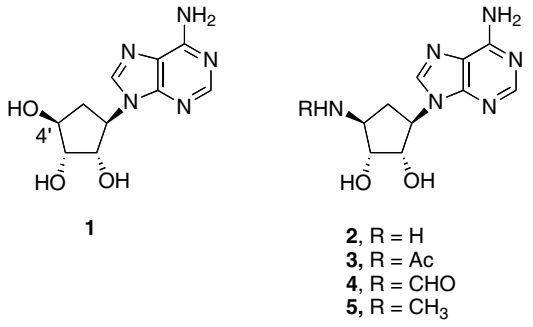

Figure 1.

2. Chemistry

The syntheses of **3** and **4** are outlined in Scheme 1. Activation of the 4′-hydroxyl of conveniently available **6**[4] with benzoic anhydride provided benzoate **7**. This was followed by palladium (0)-catalyzed allylic azidation with sodium azide at room temperature to cleanly afford **8** in a higher yield than acetyl activation of **6**.[3] Dihydroxylation of **8** to **9** followed by protection with 2,2-dimethoxypropane yielded **10**. Ammonolysis of **10** (to **11**) followed by azido group reduction furnished **12**, the key intermediate to **3** and **4**. Selective reaction of the C-4′ alkyl amino group of **12** with acetic anhydride in a short time (~5 min) led to **13**. Similarly, treatment of **12** with ethyl formate introduced the formyl group to give **14**. Deprotection of **13** and **14** with acid smoothly yielded targets **3** and **4**, respectively, in good yields.

Keywords: Adenine; Carbanucleoside; Antiviral; Pd(0) allylic substitution reactions.
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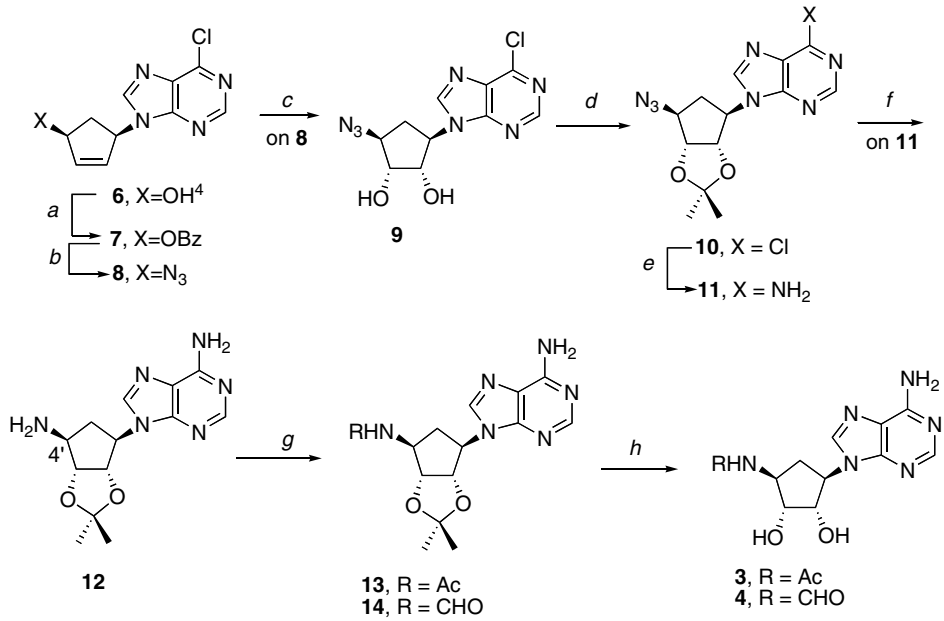


Scheme 1. Reagents and conditions: (a) Bz_2O, pyridine, DMAP, CH_2Cl_2, 84%; (b) NaN_3, $Pd_2(dba)_3{\cdot}CHCl_3$, dppp, THF, 86%; (c) OsO_4, NMO, CH_2Cl_2, 85%; (d) $Me_2C(OMe)_2$, acetone, *p*-TSA; (e) NH_3 in MeOH, 100 °C, 85% from **9**; (f) $LiAlH_4$, THF, rt, 4 h, 90%; (g) for **13**: Ac_2O, CH_2Cl_2, 0 °C, 94%; for **14**: HCO_2Et, EtOH, reflux, 16 h, 91%; (h) HCl/MeOH, rt, 4 h (for 3) and 6 h (for **4**), 90%.

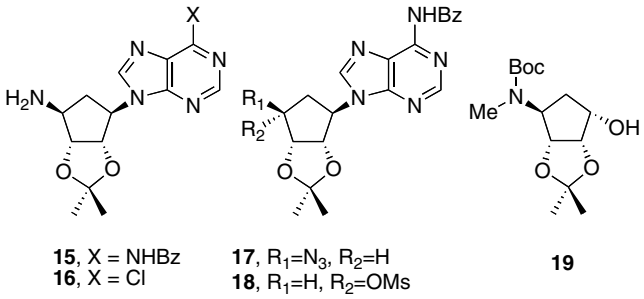


Figure 2.

The synthesis of **5**, ostensibly a simple derivative of **2**, however, was not trivial. The presence of the C-6 purine amino group of **12** made our first method of choice, monomethylation, very difficult to achieve. For example, subjecting **12** or its C-6 amino protected derivative **15** (Fig. 2) to a variety of standard monomethylation conditions[5] failed to provide a desired product. To consider aminomethylation of a purine derivative lacking the C-6 amino substituent drew us to need **16**. For that purpose, reduction of the azido group of **10** under a variety of conditions, including mild ones such as Staudinger reaction[6] and 1,3-propanethiol reduction[7] could not be achieved, possibly because of the propensity of the chloro group of **10** to reductive elimination.

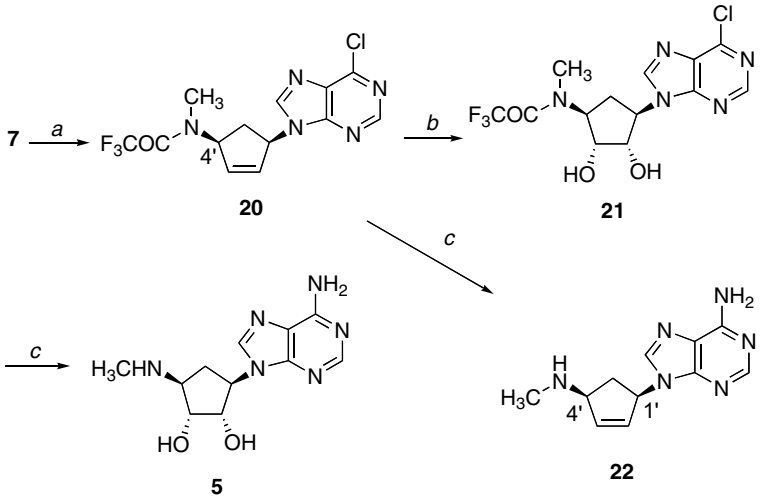
At this point our attention was drawn to a recently published one-pot conversion of an azide moiety to methylamine.[8] However, when these conditions were applied to **11** and its benzamido protected derivative **17**, only complex mixtures resulted. Further unsuccessful efforts to **5** or its precursor included: (1) methylamine nucleophilic substitution of the mesylate of **18** and (2) installation of the methylamino group onto a cyclopentyl derivative before coupling with purine, which was limited either by the lengthy steps required for the preparation of methylamino-substituted cyclopentanols such as **19** or by very poor yield of the purine coupled products.[9]

Not deterred by these and other synthetic setbacks, it was decided to investigate a Pd(0)-catalyzed allylic substitution with a methylamine equivalent. Thus, reacting **7** with *N*-methyl-2,2,2-trifluoromethylacetamide in the presence of a Pd(0) catalyst rapidly afforded **20** in moderate yield (Scheme 2). Since the rotamers present in the structure of **20** complicated its first order NMR spectrum, the stereochemistry of the 4′-position of **20** was determined by an NOE correlation between H-1′ and H-4′ in **22**, which was prepared by treating **20** with ammonia.

Glycolization of **20** with osmium tetroxide yielded **21** as the only product in a lower yield than customary in the 5′-nor series, possibly due to the susceptibility of the trifluoroacetyl group under the oxidizing reaction conditions. Subsequent deprotection and ammonolysis of **21** with ammonia furnished the target **5** in 4 steps from **6**.

3. Antiviral results

Compounds **3**–**5** were subjected to antiviral analysis.[10] From this study, **3** and **4** were found to be inactive (IC_{50} > 100 μg/mL). Derivative **5** displayed very weak effects toward three herpes viruses (IC_{50} > 100 μg/mL for all others): human cyclomegalovirus, HCMV, (IC_{50} 45.1 μg/mL); varicella zoster virus, VZV, (IC_{50} 81.7 μg/mL); and Epstein–Barr virus, EBV, (IC_{50} 24.9 μg/mL) (for comparisons, ganciclovir vs HCMV, IC_{50} 0.14 μg/mL; acyclovir vs VZV and EBV IC_{50} 0.52 and 1.7 μg/mL, respectively). No toxicity was found for **3** or **4**



Scheme 2. Reagents and conditions: (a) $CF_3CONHCH_3$, NaH, $Pd_2(dba)_3$–$CHCl_3$, dppp, THF, rt, 1 h, 42%; (b) OsO_4, NMO, CH_2Cl_2/H_2O, 50%; (c) NH_3/MeOH, 100 °C, 12 h, 98% (for **5**) and 85% (for **22**).

whereas **5** did show slight toxicity (CC_{50} 100 μg/mL) in the human foreskin fibroblast cell proliferation assay.

4. Conclusion

While 5′-amino-5′-deoxy-5′-noraristeromycin (**2**) displayed significant antiviral activity, modification at its 4′-amino center (as in **3**–**5**) resulted in a much reduced, or elimination of, antiviral potential. All three derivatives displayed much less overall cytotoxicity than **2**. The lack of activity for compounds **3** and **4** eliminated their possibility as amidic prodrugs of **2**, as we had hoped.

5. Experimental section

5.1. General methods

Melting points were recorded on a Meltemp II melting point apparatus and the values were uncorrected. The combustion analyses were performed at Atlantic Microlab, Norcross, GA. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AC 250 spectrometer (250 MHz for proton and 62.9 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 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 (^1H and ^{13}C NMR) homogeneous materials.

5.2. (1′*R*,4′*S*)-4′-Benzoyloxy-1′-(6-chloro-9*H*-purin-9-yl)cyclopent-2′-ene (7)

To a solution of **6**[4] (2.6 g, 11 mmol), pyridine (2 mL, 25 mmol), and 4-dimethylaminopyridine (DMAP) (40 mg, 0.33 mmol) in CH_2Cl_2 (50 mL) was added benzoic anhydride (3.73 g, 16.5 mmol). After the reaction mixture was stirred at room temperature for 12 h, the solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/hexanes, 2:1) to afford **7** (3.12 g, 84%) as white solid, mp 77–78 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.27 (s, 1H), 8.02 (m, 2H), 7.57 (m, 2H), 7.47 (m, 1H), 6.56 (dt, J = 5.5, 1.9 Hz, 1H), 6.29 (dd, J = 5.4, 2.1 Hz, 1H), 6.04 (dt, J = 7.3, 2.2 Hz, 1H), 5.87 (dd, J = 5.9, 1.7 Hz, 1H), 3.25 (ddd, J = 15.5, 7.8, 7.8 Hz, 1H), 2.14 (ddd, J = 15.3, 2.9, 2.9 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.1, 152.3, 151.6, 151.4, 143.6, 136.8, 133.9, 133.7, 132.0, 129.8, 128.8, 77.6, 57.7, 38.9. Anal. Calcd for $C_{17}H_{13}ClN_4O_2$: C, 59.92; H, 3.85; N, 16.44. Found: C, 60.17; H, 3.88; N, 16.43.

5.3. (1′*R*,4′*S*)-4′-Azido-1′-(6-chloro-9*H*-purin-9-yl)cyclopent-2′-ene (8)

To a solution of **7** (1.81 g, 5.31 mmol) in THF (30 mL) was added tris(dibenzylideneacetone)dipalladium(0)·$CHCl_3$ (0.16 g, 0.15 mmol) and 1,3-bis(diphenylphosphino)propane (dppp) (0.25 g, 0.61 mmol). The reaction mixture was stirred for 30 min (with accompanying color change from deep red to yellow). A solution of NaN_3 (0.72 g, 11.08 mmol) in H_2O (15 mL) was added. The reaction mixture was stirred at room temperature under N_2 for 4 h. The resulting solid was removed by filtration and the filtrate was separated. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexanes, 1:1) to give **8** as white solid (1.20 g, 86%), mp 115–116 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.18 (s, 1H), 6.33 (m, 1H), 6.16 (m, 1H), 5.76 (m, 1H), 4.65 (m, 1H), 3.10 (ddd, J = 14.9, 8.1, 8.1 Hz, 1H), 1.96 (ddd, J = 14.8, 3.8, 3.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.1, 151.5, 151.2, 143.6, 136.2, 132.6, 131.9, 65.1, 58.1, 38.6. Anal. Calcd for $C_{10}H_8ClN_7$: C, 45.90; H, 3.08; N, 37.47; Cl, 13.55. Found: C, 46.03; H, 3.08, N, 37.49; Cl, 13.30.

5.4. (1′*R*,2′*S*,3′*R*,4′*S*)-4′-Azido-1′-(6-chloro-9*H*-purin-9-yl)cyclopentane-2′,3′-diol (9)

N-Methylmorpholine *N*-oxide (0.71 g, 6.06 mmol) was added to a solution of **8** (0.53 g, 2.02 mmol) in CH_2Cl_2 (10 mL) that contained a small amount of H_2O (0.4 mL). After the solution was cooled to 0 °C, a catalytic amount of solid osmium tetroxide (20 mg, 0.08 mmol) was added and the solution stirred for 4 h at room temperature. The reaction mixture was quenched by the addition of sodium bisulfite. The solvent was removed and the residue purified by flash column chromatography (EtOAc/hexanes, 1:1) to afford **9** as white foam (0.51 g, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.79 (s, 1H), 5.45 (d, J = 5.1 Hz, 1H, OH), 5.33 (d, J = 6.0 Hz, 1H, OH), 4.85 (ddd, J = 16.6, 9.1, 5.8 Hz, 1H), 4.44 (ddd, J = 12.8, 6.0, 1.8 Hz, 1H), 4.00 (m, 2H), 2.52 (m, 1H), 2.13 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.8, 152.2, 150.0, 147.8, 132.3, 75.4, 74.6, 64.4, 60.3, 32.2. Anal. Calcd for $C_{10}H_{10}ClN_7O_2 \cdot 0.1$EtOAc: C, 40.98; H, 3.55; N, 32.18. Found: C, 41.15; H, 3.56, N, 32.17.

5.5. (1′*R*,2′*S*,3′*R*,4′*S*)-9-[(4′-Azido-2′,3′-*O*-isopropylidene)cyclopent-1′-yl]-6-chloro-9*H*-purine (10)

To a solution of **9** (0.51 g, 1.7 mmol) and 2,2-dimethoxypropane (2.0 mL) in dry acetone (10 mL) was added a catalytic amount of *p*-toluenesulfonic acid (30 mg). After the reaction mixture was stirred at room temperature for 12 h, the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (40 mL) and this was washed with saturated Na_2CO_3, H_2O, and brine. The organic phase was dried (anhydrous $MgSO_4$) and concentrated to afford **10** as a white foam. This material was used without further purification in the next step; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.35 (s, 1H), 5.12 (dd, J = 6.3, 2.5 Hz, 1H), 5.05 (ddd, J = 7.8, 5.6, 2.5 Hz, 1H), 4.84 (dd, J = 6.3, 2.3 Hz, 1H), 4.24 (ddd, J = 5.8, 5.8, 2.3 Hz, 1H), 2.86 (ddd, J = 14.4, 6.3, 6.3 Hz, 1H), 2.49 (ddd, J = 14.6, 5.7, 5.7 Hz, 1H), 1.58 (s 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 151.8, 151.2, 144.4, 131.9, 113.2, 84.4, 84.2, 65.8, 61.0, 35.0, 26.7, 24.5.

5.6. (1′*R*,2′*S*,3′*R*,4′*S*)-6-Amino-9-[(4′-azido-2′,3′-*O*-isopropylidene)cyclopent-1′-yl-9*H*-purine (11)

Compound **10** (300 mg, 0.84 mmol) was dissolved into saturated methanolic NH_3 solution (10 mL) in a stainless steel pressure vessel and this solution heated at 100 °C for 24 h. After cooling to 0 °C, the reaction vessel was opened and NH_3 and MeOH allowed to evaporate. Column chromatography (EtOAc/MeOH, 4:1) of the residue afforded **11** as a white solid (230 mg, 85% from **9**), mp 165–166 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.95 (s, 1H), 7.28 (br, 2H), 5.08 (dd, J = 6.4, 2.7 Hz, 1H), 4.92 (ddd, J = 6.7, 6.7, 2.8 Hz, 1H), 4.79 (dd, J = 6.4, 2.7 Hz, 1H), 4.17 (ddd, J = 6.2, 6.2, 2.8 Hz, 1H), 2.75 (ddd, J = 14.6, 7.6, 7.6 Hz, 1H), 2.50 (ddd, J = 14.3, 7.9, 7.9 Hz, 1H), 1.56 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.9, 153.2, 150.2, 139.6, 120.1, 113.4, 84.5, 84.3, 66.0, 60.4, 35.4, 27.0, 24.7. Anal. Calcd for $C_{13}H_{16}N_8O_2$: C, 49.36; H, 5.10; N, 35.42. Found: C, 49.54; H, 5.17, N, 35.42.

5.7. (1′*R*,2′*S*,3′*R*,4′*S*)-6-Amino-9-[(4′-amino-2′,3′-*O*-isopropylidene)cyclopent-1′yl]-9*H*-purine (12)

To a suspension of $LiAlH_4$ (0.42 g, 11 mmol) in dry THF (70 mL) at 0 °C was added dropwise a solution of **11** (2.3 g, 7.21 mmol) in THF (20 mL). The reaction mixture was then stirred at room temperature for 4 h before it was quenched sequentially with H_2O (0.42 mL), NaOH (15%, 0.42 mL) and H_2O (1.25 mL). The resulting solid was removed by filtration and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/MeOH, 2:1) to give **12** as white solid (1.91 g, 90%), mp 189–190 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.14 (s, 1H), 7.23 (br, 2H), 4.93 (dd, J = 6.6, 3.9 Hz, 1H), 4.80 (m, 1H), 4.40 (dd, J = 6.5, 2.9 Hz, 1H), 3.39 (m, 1H), 2.43 (ddd, J = 13.6, 6.3, 6.3 Hz, 1H), 2.09 (ddd, J = 13.9, 7.3, 7.3 Hz, 1H), 1.90 (br, 2H), 1.45 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 156.0, 152.3, 149.4, 140.4, 118.9, 111.4, 86.9, 84.5, 59.8, 56.4, 38.7, 27.1, 24.7. Anal. Calcd for $C_{13}H_{18}N_6O_2$: C, 53.78; H, 6.25; N, 28.95. Found: C, 53.58; H, 6.30; N, 28.79.

5.8. (1′*R*,2′*S*,3′*R*,4′*S*)-9-[(4′-Acetamido-2′,3′-*O*-isopropylidene)cyclopent-1′-yl]-6-amino-9*H*-purine (13)

To a suspension of **12** (0.7 g, 2.4 mmol) in CH_2Cl_2 at 0 °C was added acetic anhydride (0.5 mL, 4.9 mmol). After the reaction mixture turned into clear solution (~5 min), 1 N NaOH (10 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The organic phases were combined, dried (anhydrous $MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/MeOH, 4:1) to afford **13** as white solid (0.75 g, 94%), mp 238–239 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.31 (d, J = 7.5 Hz, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 7.27 (br, 2H), 5.09 (dd, J = 7.2, 5.6 Hz, 1H), 4.77 (m, 1H), 4.58 (dd, J = 8.4, 4.9 Hz, 1H), 4.12 (m, 1H), 2.40 (m, 2H), 1.81 (s, 3H), 1.47 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 169.9, 157.0, 153.2, 150.1, 141.1, 120.3, 113.7, 84.3, 82.7, 60.3, 54.0, 37.0, 28.1, 25.9, 23.5. Anal. Calcd for $C_{15}H_{20}N_6O_3$: C, 54.21; H, 6.07; N, 25.29. Found: C, 54.11; H, 6.09; N, 25.30.

5.9. (1′*R*,2′*S*,3′*R*,4′*S*)-4′-Acetamido-1′-(6-amino-9*H*-purin-9-yl)cyclopentane-2′,3′-diol (3)

Compound **13** (0.26 g, 0.78 mmol) was dissolved in MeOH (8 mL) and to this solution 1 N HCl (6 mL) was added. The reaction mixture was stirred at room temperature for 4 h and then neutralized with basic ion exchange resin (Amberlite IRA-67). The resin was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/MeOH/NH_4 OH, 9:3:1) to afford **3** (0.21 g, 90%) as white solid, mp > 268 °C (dec); ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.42 (d, J = 7.5 Hz, 1H), 8.06 (s, 1H), 8.03 (s, 1H), 7.17 (br, 2H),

5.00 (m, 2H, 2OH), 4.55 (dd, $J = 17.1, 8.4$ Hz, 1H), 4.30 (dd, $J = 11.3, 5.7$ Hz, 1H), 3.85 (m, 1H), 3.66 (m, 1H), 2.48 (m, 1H), 1.73 (s, 3H), 1.66 (m, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 168.7, 156.2, 152.1, 149.1, 140.8, 119.6, 75.0, 74.6, 59.0, 52.9, 32.8, 22.9. Anal. Calcd for $C_{12}H_{16}N_6O_3$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.17; H, 5.64; N, 28.68.

5.10. (1′*R*,2′*S*,3′*R*,4′*S*)-6-Amino-9-[(4′-formamido-2′,3′-*O*-isopropylidene)cyclopent-1′-yl]-9*H*-purine (14)

A solution of **12** (0.58 g, 2 mmol) in EtOH (20 mL) and ethyl formate (20 mL) was refluxed for 16 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (EtOAc/MeOH, 2:1) to afford **14** as white solid (0.58 g, 91%), mp 197–198 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.43 (d, $J = 7.7$ Hz, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.21 (br, 2H), 5.01 (dd, $J = 6.8, 6.8$ Hz, 1H), 4.75 (m, 1H), 4.55 (dd, $J = 7.3, 4.9$ Hz, 1H), 4.14 (m, 1H), 2.38 (m, 2H), 1.40 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 160.9, 156.2, 152.4, 149.2, 140.2, 119.4, 113.0, 83.4, 81.8, 59.2, 51.9, 36.2, 27.2, 25.1. Anal. Calcd for $C_{14}H_{18}N_6O_3 \cdot 0.4H_2O$: C, 51.66; H, 5.78; N, 25.83. Found: C, 51.86; H, 5.80; N, 25.48.

5.11. (1′*R*,2′*S*,3′*R*,4′*S*)-1′-(6-Amino-9*H*-purin-9-yl)-4′-formamidocyclopentane-2′,3′diol (4)

Compound **14** (0.5 g, 0.78 mmol) was dissolved in MeOH (15 mL) and to this solution 1 N HCl (10 mL) was added. The reaction mixture was stirred at room temperature for 6 h and then neutralized with basic ion exchange resin (Amberlite IRA-67). The resin was removed by filtration and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/MeOH/NH_4OH, 9:3:1) to afford **4** (0.44 g, 90%) as white solid, mp > 210 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, $J = 7.8$ Hz, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 8.07 (s, 1H), 7.26 (br, 2H), 5.17 (d, $J = 5.1$ Hz, 1H, OH), 5.15 (d, $J = 3.0$ Hz, 1H, OH), 4.69 (dd, $J = 17.7, 8.8$ Hz, 1H), 4.42 (m, 1H), 4.07 (m, 1H), 3.82 (m, 1H), 2.62 (m, 1H), 1.87 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 157.0, 153.0, 150.1, 141.4, 120.3, 75.8, 75.2, 59.5, 52.3, 33.6. Anal. Calcd for $C_{11}H_{14}N_6O_3$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.31; H, 5.16, N, 29.96.

5.12. (1′*R*,4′*S*)-1′-(6-Chloro-9*H*-purin-9-yl)-4′-2,2,2-trifluoro-*N*-methylacetamidocyclopent-2′-ene (20)

To a solution of **7** (3.42 g, 11.4 mmol) in THF (20 mL) was tris(dibenzylideneacetone)dipalladium(0)·$CHCl_3$ (0.52 g, 0.5 mmol) and 1,3-bis(diphenylphosphino)propane (dppp) (0.82 g, 1.99 mmol). This mixture was stirred for 10 min until the color changed from deep red to yellow. A pre-prepared solution of the sodium salt of *N*-methyl-2,2,2-trifluoroacetamide [from *N*-methyl-2,2,2-trifluoroacetamide (1.77 g, 13.94 mmol) and 60% NaH (0.53 g, 13.25 mmol) in THF (20 mL) for 0.5 h at room temperature] was added dropwise to the above solution. After the reaction was stirred at room temperature for 0.5 h, the solid was removed by filtration and washed with THF. The filtrate was concentrated and the residue purified by flash column chromatography (EtOAc/hexanes, 3:1) to afford **20** (1.63 g, 42%) as off-white solid, mp 114–116 °C; ^{1}H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, $CDCl_3$) δ 8.76* (s, 1H), 8.74 (s, 1H), 8.22 (s, 1H), 8.18* (s, 1H), 6.21* (m, 2H), 6.20 (m, 2H), 5.71 (m, 2H), 5.70* (m, 1H), 5.26* (t, $J = 7.6$ Hz, 1H), 3.19 (d, $J = 1.5$ Hz, 3H), 3.18 (m, 1H), 3.18* (m, 1H), 3.07* (s, 3H), 2.21* (ddd, $J = 14.4, 7.3, 7.3$ Hz, 1H), 2.10 (ddd, $J = 14.2, 7.3, 7.3$ Hz, 1H); ^{13}C NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$) δ 158.01* (q, $J = 35.8$ Hz, C=O), 157.11 (q, $J = 35.8$ Hz, C=O), 152.39*, 152.27, 151.91*, 151.86, 151.81*, 151.78, 144.15, 143.75*, 136.01*, 135.82, 133.00, 133.00*, 132.85, 132.81*, 132.64, 132.63*, 118.10 (q, $J = 286$ Hz, CF_3), 118.41* (q, $J = 288$ Hz, CF_3), 61.7* (q, $J = 3.7$ Hz, 4′-CH), 60.95, 59.89, 59.62*, 36.83*, 35.55, 30.86 (q, $J = 3.9$ Hz, CH_3), 29.90*. Anal. Calcd for $C_{13}H_{11}ClFN_5O$: C, 45.17; H, 3.21; N, 20.26. Found: C, 45.27; H, 3.17; N, 20.19.

5.13. (1′*R*,2′*S*,3′*R*,4′*S*)-1′-(6-Chloro-9*H*-purin-9-yl)-4′-(2,2,2-trifluoro-*N*-methylacetamido)cyclopentane-2′,3′-diol (21)

N-Methylmorpholine *N*-oxide (500 mg, 4.27 mmol) was added to a solution of **20** (440 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) containing a small amount of H_2O (0.4 mL). After the mixture was cooled to 0 °C, a catalytic amount of solid osmium tetroxide (30 mg, 0.12 mmol) was added and the resulting solution stirred for 8 h at room temperature. The reaction mixture was quenched by the addition of sodium bisulfite. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (EtOAc/MeOH, 10:1) to give **21** as a white solid (240 mg, 50%), mp 121–123 °C; ^{1}H NMR (3:2 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.85* (s, 1H), 8.80* (s, 1H), 8.80 (s, 1H), 5.36* (d, $J = 5.3$ Hz, 1H, OH), 5.34* (d, $J = 5.3$ Hz, 1H, OH), 5.32 (d, $J = 5.6$ Hz, 1H, OH), 5.23 (d, $J = 5.6$ Hz, 1H, OH), 4.85 (m, 1H), 4.85* (m, 1H), 4.67 (m 1H), 4.26 (m, 2H), 4.36* (m, 2H), 4.22* (m, 1H), 3.17 (d, $J = 1.5$ Hz, 3H), 3.05* (s, 3H), 2.36 (m, 2H), 2.34* (m, 2H); ^{13}C NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, DMSO-d_6) δ 157.11 (q, $J = 34.4$ Hz, C=O), 157.08* (q, $J = 34.4$ Hz, C=O), 152.76, 152.72*, 152.22, 152.20*, 150.08, 150.05*, 147.79*, 147.72, 132.32*, 132.27, 117.10* (q, $J = 288$ Hz, CF_3), 117.09 (q, $J = 288$ Hz, CF_3), 74.40, 74.25*, 71.32*, 70.92, 62.00*, 61.03, 60.11, 59.79*, 31.34* (q, $J = 3.7$ Hz, CH_3), 30.24, 29.77*, 28.28. Anal. Calcd for $C_{13}H_{13}ClF_3N_5O_3 \cdot 0.1$EtOAc: C, 41.39; H, 3.55; N, 18.02. Found: C, 41.74; H, 3.65, N, 18.01.

5.14. (1′*R*,2′*S*,3′*R*,4′*S*)-1′-(6-Amino-9*H*-purin-9-yl)-4′-methylaminocyclopentane-2′,3′-diol (5)

Compound **21** (250 mg, 0.66 mmol) was dissolved in saturated methanolic NH_3 solution (15 mL) in a stainless steel pressure vessel and this solution heated at 100 °C for 12 h. After cooling to 0 °C, the reaction vessel was

opened and the NH_3 and MeOH allowed to evaporate to dryness. Column chromatography (EtOAc/MeOH/NH_4OH = 6:2:1) of the residue afforded **5** as a off-white solid (221 mg, 94%), mp 170–171 °C; ^1H NMR (250 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.12 (s, 1H), 7.21 (br, 2H), 4.66 (q, J = 8.8 Hz, 1H), 4.44 (dd, J = 8.6, 5.1 Hz, 1H), 3.79 (dd, J = 4.9, 1.9 Hz, 1H), 2.80 (m, 1H), 2.47 (m, 1H), 2.30 (s, 3H), 1.71 (m, 1H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 156.0, 152.2, 149.7, 140.1, 119.2, 74.9, 74.1, 64.0, 58.5, 34.5, 33.9. Anal. Calcd for $C_{11}H_{16}N_6O_2 \cdot 0.3H_2O$: C, 48.97; H, 6.16; N, 31.16. Found: C, 48.89; H, 6.08, N, 30.81.

5.15. (1′*R*,4′*S*)-4′-Methylamino-1′-(6-amino-9*H*-purin-9-yl)cyclopent-2′-ene (22)

Compound **20** (210 mg, 0.63 mmol) was dissolved in saturated methanolic NH_3 solution (50 mL) in a stainless steel pressure vessel. This solution was heated at 100 °C for 12 h. After cooling to 0 °C, the reaction vessel was opened and the NH_3 and MeOH were allowed to evaporate to dryness. Column chromatography (CH_2Cl_2/MeOH/NH_4OH, 20:20:1) of the residue afforded **22** as white solid (130 mg, 85%), mp > 240 °C (dec.); ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.19 (s, 1H), 7.36 (br, 2H), 6.31 (m, 1H), 6.24 (m, 1H), 5.66 (m, 1H), 4.27 (m, 1H), 3.01 (dt, J = 6.3, 8.6 Hz, 1H), 2.64 (s, 3H), 2.22 (dt, J = 4.4, 14.8, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.1, 153.1, 149.1, 140.9, 136.8, 132.1, 120.0, 63.3, 58.8, 34.0, 31.1. Anal. Calcd for $C_{11}H_{14}N_6 \cdot 0.1H_2O$: C, 56.94; H, 6.13; N, 36.24. Found: C, 56.76; H, 6.21; N, 36.51.

5.16. Antiviral assays

The antiviral and toxicity analyses were performed following standard procedures reported previously by us.[11]

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