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Synthesis and biological evaluation of novel *tert*-azido or *tert*-amino substituted penciclovir analogs

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tert-Azido or amino substituted penciclovir analogs, **1**–**3** were synthesized for the purpose of improving the efficacy and bioavailability of penciclovir and searching for novel antiviral agents. Among several methods attempted to insert an azido group into the α,β-unsaturated ester **6**, only Brønsted acid-catalysed 1,4-conjugate addition conditions (NaN_3, 75% acetic acid, 80 °C) gave the desired *tert*-azido product **7**. The synthesized final penciclovir analogs **1**–**3** were evaluated *in vitro* against several viruses such as HIV-1, HSV-1 and 2, poliovirus, VZV, and VSV. Compound **2** only showed weak antiviral activity against HSV-1 without cytotoxicity. Although the synthesized compounds did not exhibit an excellent antiviral activity, the successful method used in introducing the *tert*-azido group is expected to be generally utilized for the synthesis of nucleoside analogs with a *tert*-azido substituent.

Introduction

Acyclonucleosides[1] such as acyclovir,[2] ganciclovir[3] and penciclovir[4] exhibit several potent antiviral activities (Fig. 1).

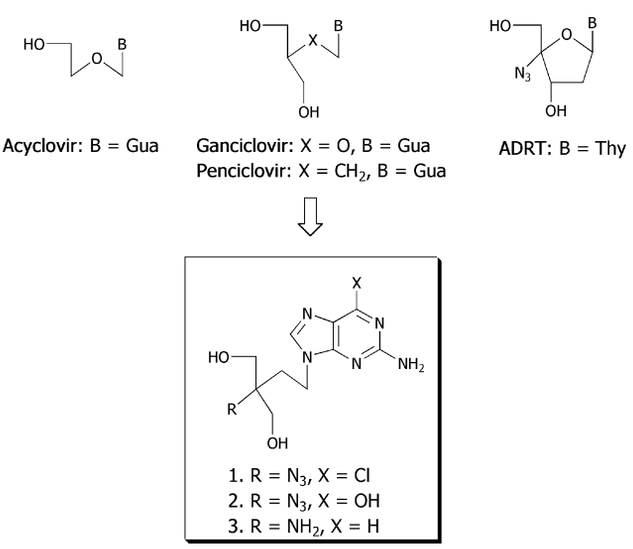

Fig. 1 The rationale for the design of the target nucleosides.

Acyclovir has become the drug of choice for the treatment of HSV-1 and 2 (herpes simplex virus type 1 and 2) and VZV (varicella–zoster virus) infections as a potent and selective inhibitor and ganciclovir, a homolog of acyclovir, has become the drug of choice for the treatment of HCMV (human cytomegalovirus) infections, particularly HCMV retinitis which causes blindness in AIDS patients.

Penciclovir in which the ethereal oxygen of ganciclovir is replaced by a carbon atom showed anti-HBV (hepatitis B virus) activity as well as a similar activity spectrum to acyclovir *i.e.*, anti-HSV-1 and 2 and anti-VZV activities and was currently approved for the treatment of VZV infection by the FDA (Food and Drug Administration). However, because of their poor oral bioavailability, acyclovir, ganciclovir and penciclovir have been replaced by their oral prodrugs, valaciclovir,[5] valganciclovir[6] and famciclovir,[7] respectively. Improvement of oral bioavailability of their prodrugs results from an increase of their lipophilicity by protection of their hydroxyl groups and/or removal of the 6-oxo group of guanine base. The diacetyl-6-deoxy derivative of penciclovir, famciclovir can be quickly absorbed due to its increased lipophilicity and sequentially deacetylated in the intestine wall and liver to afford 6-deoxypenciclovir, which, in turn, can be oxidized by xanthine oxidase in the liver to give rise to the parent drug, penciclovir.[8] It is of interest to note that all of acyclovir, ganciclovir and penciclovir retain the guanine base and have been found to selectively inhibit the replication of HSV-1 and 2, VZV and other herpes viruses (HCMV and Epstein–Barr virus) and to have a poor bioavailability.

A number of azido- and fluoro-substituted nucleoside derivatives have been reported to have potent antiviral activities: D-FIAC[9] [1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine] and D-FMAU[9] [1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine] (anti-HSV activity), D-FIAU[9] (anti-HSV activity and anti-HBV activity), D-FLT[10] (D-2′,3′-dideoxy-3′-fluorothymidine) (anti-HIV-1 activity), L-FMAU[11] (anti-HBV activity, undergoing clinical trials), and AZT[12] (3-azido-2′,3′-dideoxythymidine) (anti-HIV-1 activity). In particular, ADRT[13] in which an azido functional group is introduced at the 4′-position (*tert*-position) showed a significant anti-HIV activity (Fig. 1). Also among *tert*-fluoro substituted nucleoside analogs, nucleocidin[14] showed antibacterial activity and *tert*-fluoro substituted penciclovir[15] has been reported to exhibit potent anti-herpes viruses and anti-HIV activities. Thus, substitution at the 4′-position in nucleosides is also important for the exhibition of potent biological activities.

As a part of our efforts to search for novel antiviral agents with good bioavailability as well as potent antiviral activity, it was interesting to synthesize *tert*-azido or *tert*-amino substituted penciclovir analogs **1**–**3**. Herein, we wish to report the synthesis of novel *tert*-azido and *tert*-amino substituted acyclic nucleoside analogs, using Brønsted acid-catalysed 1,4-conjugate addition for the introduction of an azido group to the α,β-unsaturated ester as a key step and their antiviral activities.

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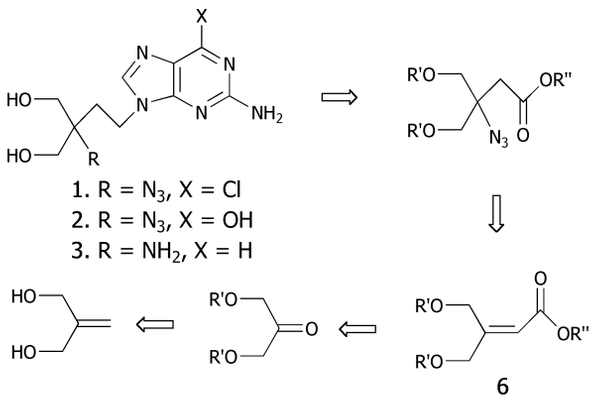
Results and discussion

Chemistry

A strategy for the synthesis of *tert*-azido and *tert*-amino substituted acyclic nucleoside analogs **1**–**3** is outlined in Scheme 1.



Scheme 1 Retrosynthetic analysis of the target nucleosides with *tert*-azido or *tert*-amino substituent.

It was envisioned that α,β-unsaturated ester **6** derived from 2-methylene-propane-1,3-diol could be an appropriate intermediate to introduce an azido functionality at the β position. The resultant *tert*-azido compound could be reduced and condensed with a nucleobase to afford the target nucleoside analogs **1**–**3**.

Synthesis of the protected *tert*-azido substituted acyclic glycosyl donor **10** is shown in Scheme 2.

Benzyl ether derivative **4**[16] was derived from a commercially available 2-methylene-propane-1,3-diol in quantitative yield. Oxidative cleavage of compound **4** employing OsO_4 and $NaIO_4$ in acetone and H_2O (4 : 1) gave **5**[17] in moderate yield (51%), while ozonolysis afforded the same ketone **5** in higher yield (82%). Horner–Emmons olefination of **5** using triethyl phosphonoacetate and NaH gave α,β-unsaturated ester **6**[17], which would be an appropriate intermediate to insert an azido group into the β-position. As seen in Scheme 2, several methods to introduce an azido group[18] were attempted. Base-catalysed 1,4-conjugate addition ($TMSN_3/Et_3N$ in benzene) or Lewis acid-catalysed 1,4-conjugate addition ($TMSN_3/Et_2AlCl$ in THF and $TMSN_3/BF_3{\cdot}OEt_2$ in THF) at various temperatures and reaction times failed to give the desired product, while reaction of α,β-unsaturated ethyl ester **6** with large excess amounts of NaN_3 under Brønsted acid-catalysed 1,4-conjugate addition conditions (75% aqueous acetic acid, 80 °C)[19] gave β-*tert*-azido product **7** in excellent yield. Reduction of the azido compound **7** with Dibal-H at −78 °C followed by reduction of the resulting aldehyde with $NaBH_4$ gave the desired *tert*-azido alcohol **9** (66%) and the allylic alcohol **8** (3%), resulting from the elimination of *tert*-azido group. Treatment of **9** with mesyl chloride and pyridine afforded the corresponding mesylate **10** in quantitative yield, which was ready for the condensation with nucleobase.

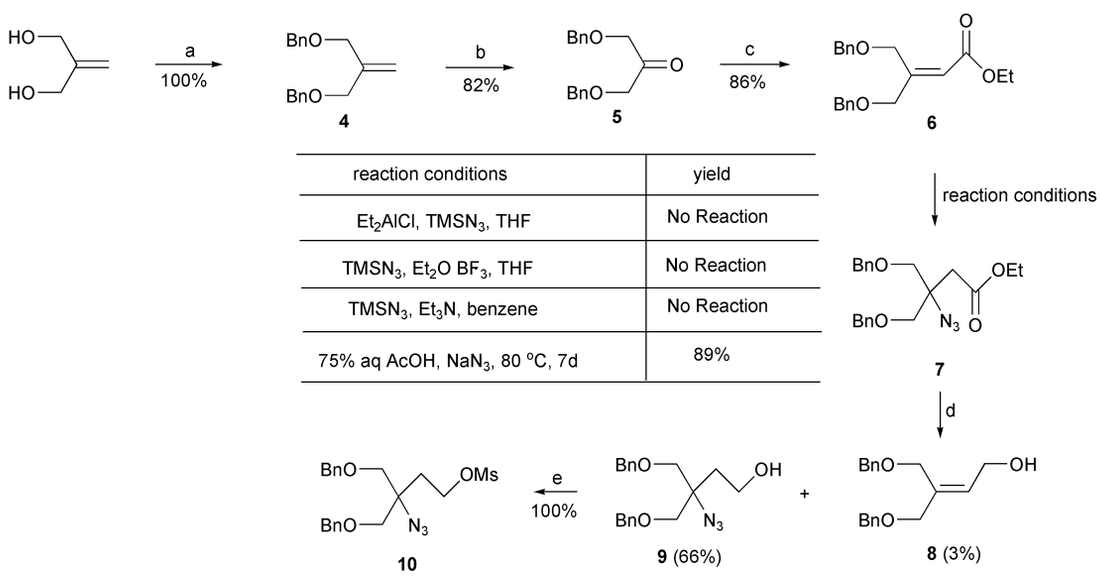
Condensation of mesylate **10** with 2-amino-6-chloropurine in the presence of NaH in DMF at 50 °C gave many spots on TLC. However, coupling of mesylate **10** with 2-amino-6-chloropurine in the presence of potassium carbonate in DMF at 60 °C produced the N-9 isomer **11** as a major product (79%) along with N-7 isomer **12** (9%) as seen in Scheme 3. The regioisomers were easily assigned based on the comparison with UV literature data[20]. Deprotection of the benzyl group with excess BBr_3 (10 equiv) finally produced the desired *tert*-azido substituted 2-amino-6-chloropurine derivative **1** in 83% yield, while treatment with BCl_3 (10 equiv) gave a mixture of the desired product **1** and partially debenzylated product. Azido substituted 2-amino-6-chloropurine derivative **1** was converted to its guanosine analog **2** by hydrolysis with 0.5 M NaOH and tertiary amino substituted 2-aminopurine nucleoside analog **3** using catalytic hydrogenation.

Biological evaluation

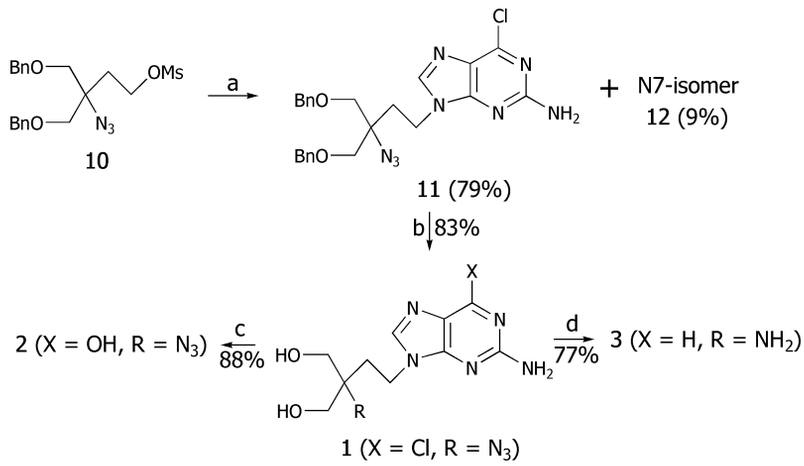
Antiviral assays[21] against HIV-1, HSV-1 and 2, poliovirus, HCMV, VZV, and VSV were performed on the final nucleoside analogs **1**–**3**. Compound **1** showed toxicity-induced anti-HIV-1 activity (EC_{50} = 81.32 μg cm^{-3}) and exhibited neither antiviral activity nor cytotoxicity in other viruses. Compound **2** exhibited a weak anti-HSV-1 activity (EC_{50} = 68.30 μg cm^{-3}) without cytotoxicity up to 100 μg cm^{-3} and showed neither antiviral activity nor cytotoxicity in other viruses. It is speculated that lack of antiviral activity may be attributed to their poor affinity to viral or cellular nucleoside and/or nucleotide kinases.

Conclusion

We synthesized penciclovir analogs **1**–**3** with a *tert*-azido or *tert*-amino substituent, starting from 2-methylene-propane-1,3-diol. Introduction of the *tert*-azido substituent was successfully achieved employing Brønsted acid-catalysed 1,4-conjugate add-



Scheme 2 *Reagents and conditions*: (a) BnBr, *n*-Bu_4NI, NaH, DMF, 40 °C, overnight; (b) O_3, MeOH, −78 °C, 2 h; (c) $(EtO)_2POCH_2CO_2Et$, NaH, THF, rt, 1 h; (d) i) Dibal-H, CH_2Cl_2, −78 °C, 2 h; ii) $NaBH_4$, EtOH, −20 °C, 15 min; (e) $MeSO_2Cl$, pyridine, 0 °C, 15 min.



Scheme 3 *Reagents and conditions*: (a) 2-amino-6-chloropurine, K_2CO_3, DMF, 60 °C, overnight; (b) BBr_3 (10 equiv), CH_2Cl_2, −78 °C, 1 h; (c) 0.5 M NaOH, 80 °C, overnight; (d) H_2, Pd/C, MeOH, rt, 3 h.

ition conditions. Although the synthesized nucleoside analogs did not exhibit good antiviral activity, the insertion method for introducing a *tert*-azido group will be of great help in synthesizing many nucleoside analogs with *tert*-azido substituents.

Experimental

Materials and methods

Ultraviolet (UV) spectra were recorded on a Beckman DU-68 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-400 spectrometer, using $CDCl_3$, DMSO-d_6 or CD_3OD and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as internal standard. Elemental analyses were performed by the general instrument laboratory of Ewha Womans University, Korea. IR spectra were recorded on a Bio-RAD FTS-135-IR spectrophotometer. TLC was performed on Merck precoated $60F_{254}$ plates. Column chromatography was performed using silica gel 60 (230–400 mesh, Merck). All the anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to use.

1,3-Bis-benzyloxy-2-methylene-propane (4).[16] To a stirred solution of NaH (2.9 g, 70.40 mmol, 60% in mineral oil) in DMF (10 cm^3) were added a solution of 2-methylene-propane-1,3-diol (2.215 g, 25.14 mmol) in DMF (5 cm^3), benzyl bromide (8.4 cm^3, 70.40 mmol) and *n*-tetrabutylammonium iodide (2.8 g, 7.54 mmol) and the reaction mixture was stirred at 40 °C overnight. The reaction mixture was partitioned between ether and brine and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The resulting residue was purified by flash column chromatography (hexane/ethyl acetate = 4 : 1) to give benzyl ether **4** (7.64 g, 100%) as a colorless syrup. R_f = 0.8 (hexane/ethyl acetate = 2 : 1); δ_H (400 MHz; $CDCl_3$) 4.06 (4 H, t, *J* 1.2, 2 × BnOC*H*$_2$), 4.51 (4 H, s, 2 × PhC*H*$_2$), 5.26 (2 H, t, *J* 1.2, vinylic CH_2), 7.32 (10 H, m, 2 × Ph).

1,3-Bis-benzyloxy-propan-2-one (5).[17] To a stirred solution of olefin **4** (6.12 g, 22.81 mmol) in anhydrous MeOH (175 cm^3) was added O_3 gas at −78 °C, and the reaction mixture was stirred at the same temperature for 2 h. When the blue color of the reaction mixture had disappeared, O_3 gas supply was ceased and O_2 gas was bubbled into the mixture. The mixture was warmed to room temperature and dimethyl sulfide (16.7 cm^3, 228.1 mmol) was added to remove excess ozone. The solvent was removed under reduced pressure to give the residue, which was partitioned between EtOAc and brine. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 25 : 1) to give ketone **5** (4.328 g, 82%) as a colorless syrup along with recovered starting material (880 mg, 17%). R_f = 0.29 (hexane/ethyl acetate = 5 : 1); (Found: C, 75.9; H, 6.9. Calc. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7%); δ_H (400 MHz; $CDCl_3$) 4.24 (4 H, s, 2 × BnOC*H*$_2$), 4.57 (4 H, s, 2 × PhC*H*$_2$), 7.31–7.36 (10 H, m, 2 × Ph).

4-Benzyloxy-3-benzyloxymethyl-but-2-enoic acid ethyl ester (6).[17] Compound **5** (1.016 g, 3.76 mmol) was converted to compound **6** (1.105 g, 86%) according to the reported procedure.[17]

3-Azido-4-benzyloxy-3-benzyloxymethyl-butyric acid ethyl ester (7). To a stirred solution of ethyl ester **6** (1.105 g, 3.25 mmol) in glacial acetic acid (22.5 cm^3) and distilled water (7.5 cm^3) was added NaN_3 (8.44 g, 129.84 mmol) and the reaction mixture was heated at 80 °C for 7 d. After removal of a large part of the solvent under reduced pressure, the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10 : 1) to give azido ester **7** (1.102 g, 89%) as a colorless syrup. R_f = 0.5 (hexane/ethyl acetate = 5 : 1); (Found: C, 65.9; H, 6.9; N, 11.2. Calc. for $C_{21}H_{25}N_3O_4$: C, 65.8; H, 6.6; N, 11.0%); ν_{max}(film)/cm^{-1} 2116 (N_3); δ_H (400 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.2, CH_3), 2.70 (2 H, s, C*H*$_2$CO$_2$Et), 3.66 (2 H, d, *J* 9.2, 2 × BnOC*H*H), 3.72 (2 H, d, *J* 9.2, BnOCH*H*), 4.10 (2 H, q, *J* 7.2, OC*H*$_2$CH$_3$), 4.55 (4 H, s, 2 × PhC*H*$_2$), 7.28–7.34 (10 H, m, 2 × Ph).

4-Benzyloxy-3-benzyloxymethyl-but-2-en-1-ol (8) and 3-azido-4-benzyloxy-3-benzyloxymethyl-butan-1-ol (9). To a stirred solution of azido ester **7** (460 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (10 cm^3) at −78 °C was added Dibal-H (2.5 cm^3, 2.5 mmol, 1.0 M solution in toluene) and the reaction mixture was stirred at −78 °C for 2 h. After the mixture was quenched with methanol (2.5 cm^3) and stirred for 10 min at −78 °C, saturated aqueous Na, K-tartrate solution and CH_2Cl_2 were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude aldehyde, without further purification, was reduced by treatment with $NaBH_4$ (78.0 mg, 2.0 mmol) in ethanol (20 cm^3) at −20 °C for 15 min. After neutralization with acetic acid followed by concentration of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 4 : 1) to give azido alcohol **9** (270 mg, 66%) as a colorless syrup and elimination product **8** (12 mg, 3%) as a syrup.

Compound **8**: R_f = 0.18 (hexane/ethyl acetate = 2 : 1); δ_H (400 MHz; $CDCl_3$) 1.89 (1 H, t, *J* 5.6, OH), 4.05 (2 H, s, BnOCH_2), 4.11 (2 H, s, BnOCH_2), 4.22 (2 H, t, *J* 5.6, CH_2OH), 4.51 (2 H, s, PhCH_2), 4.51 (2 H, s, PhCH_2), 5.96 (1 H, t, *J* 6.4, vinylic H), 7.28–7.36 (10 H, m, 2 × Ph).

Compound **9**: (Found: C, 66.9; H, 6.6; N, 12.2. Calc. for $C_{19}H_{23}N_3O_3$: C, 66.8; H, 6.8; N, 12.3%); ν_{max}(film)/cm^{-1} 2109 (N_3); δ_H (400 MHz, $CDCl_3$) 1.85 (2 H, t, *J* 6.0, CH_2CH$_2$OH), 2.52 (1 H, t, *J* 6.0, OH), 3.62 (4 H, s, 2 × BnOCH_2), 3.72 (2 H, q, *J* 6.0, CH_2OH), 4.56 (4 H, s, 2 × PhCH_2), 7.30–7.35 (10 H, m, 2 × Ph).

Methanesulfonic acid 3-azido-4-benzyloxy-3-benzyloxymethyl-butyl ester (10). To a stirred solution of azido alcohol **9** (616 mg, 1.80 mmol) in pyridine (10 cm^3) under nitrogen was added methanesulfonyl chloride (0.22 cm^3 2.70 mmol) and the reaction mixture was stirred at 0 °C for 15 min. After the reaction mixture was partitioned between methylene chloride and H_2O, the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The resulting oily residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 4 : 1) to give the mesylate **10** (756 mg, 100%) as a colorless syrup. R_f = 0.375 (hexane/ethyl acetate = 2 : 1); ν_{max}(film)/cm^{-1} 2105 (N_3); δ_H (400 MHz; $CDCl_3$) 2.07 (2 H, t, *J* 6.8, CH_2CH$_2$OMs), 2.92 (3 H, s, CH_3), 3.57 (2 H, d, *J* 9.6, 2 × BnOC*H*H), 3.60 (2 H, d, *J* 9.6, 2 × BnOCH*H*), 4.32 (2 H, t, *J* 6.8, CH_2OMs), 4.54 (4 H, s, 2 × PhCH_2), 7.30–7.37 (10 H, m, 2 × Ph).

9-(3-Azido-4-benzyloxy-3-benzyloxymethyl-butyl)-6-chloro-9*H*-purin-2-ylamine (11) and 7-(3-azido-4-benzyloxy-3-benzyloxymethyl-butyl)-6-chloro-7*H*-purin-2-ylamine (12). A suspension of 2-amino-6-chloropurine (164 mg, 0.97 mmol) and K_2CO_3 (268 mg, 1.93 mmol) in DMF (3 cm^3) was stirred at 60 °C for 2 h. To this mixture was added a solution of mesylate **10** (271 mg, 0.64 mmol) in DMF (3 cm^3) at room temperature and the mixture was stirred at 60 °C overnight and poured into methylene chloride and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 2 : 1) to give N-9 isomer **11** (250 mg, 79%) as a colorless sticky syrup and N-7 isomer **12** (30 mg, 9%) as a colorless syrup.

Compound **11**: R_f = 0.32 (hexane/ethyl acetate = 1 : 1); (Found: C, 58.7; H, 4.95; N, 22.9. Calc. for $C_{24}H_{25}ClN_8O_2$: C, 58.5; H, 5.1; N, 22.7%); λ_{max}(MeOH)/nm 309; ν_{max}(film)/cm^{-1} 2113 (N_3); δ_H (400 MHz; $CDCl_3$) 2.13 (2 H, m, CH_2CH$_2$N), 3.57 (2 H, d, *J* 10.0, 2 × BnOC*H*H), 3.61 (2 H, d, *J* 10.0, 2 × BnOCH*H*), 4.16 (2 H, m, CH_2N), 4.52 (2 H, d, *J* 12.0, PhCH_2), 4.56 (2 H, d, *J* 12.0, PhCH_2), 5.02 (2 H, s, NH_2), 7.31–7.37 (10 H, m, 2 × PH), 7.67 (1 H, s, H-8).

Compound **12**: R_f = 0.10 (hexane/ethyl acetate = 1 : 1); λ_{max}(MeOH)/nm 321; ν_{max}(film)/cm^{-1} 2116 (N_3); δ_H (400 MHz; $CDCl_3$) 2.12 (2 H, m, CH_2CH$_2$N), 3.58 (2 H, d, *J* 9.6, 2 × BnOC*H*H), 3.61 (2 H, d, *J* 10.0, 2 × BnOCH*H*), 4.09 (2 H, m, CH_2N), 4.52 (2 H, d, *J* 12.0, PhCH_2), 4.53 (2 H, s, NH_2), 4.55 (2 H, d, *J* 12.0, PhCH_2), 7.29–7.36 (10 H, m, 2 × Ph), 7.41 (1 H, s, H-8).

2-[2-(2-Amino-6-chloro-purin-9-yl)-ethyl]-2-azido-propane-1,3-diol (1). To a stirred solution of compound **11** (94 mg, 0.19 mmol) in anhydrous methylene chloride (8 cm^3) was added tribromoboron (1.9 cm^3, 1.9 mmol, 1.0 M solution in methylene chloride) at −78 °C and the reaction mixture was stirred at the same temperature for 1 h. To this mixture was added MeOH (20 cm^3) and the reaction mixture was neutralized with silver carbonate and filtered through a pad of Celite. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (methylene chloride/methanol = 20 : 1 to 10 : 1) to give azido compound **1** (49 mg, 83%) as a white solid. R_f = 0.8 (methylene chloride/methanol = 2 : 1); mp 186–187 °C; (Found: C, 38.2; H, 4.3; N, 35.55. Calc. for $C_{10}H_{13}ClN_8O_2$: C, 38.4; H, 4.2; N, 35.8%); λ_{max}(MeOH)/nm 310; ν_{max}(film)/cm^{-1} 2110 (N_3); δ_H (400 MHz; DMSO-d_6) 1.95 (2 H, t, *J* 8.0, CH_2CH$_2$N), 3.52 (2 H, d, *J* 11.2, 2 × HOC*H*H), 3.56 (2 H, d, *J* 7.6, 2 × HOCH*H*), 4.14 (2 H, t, *J* 7.6, CH_2N), 6.88 (2 H, s, NH_2), 8.14 (1 H, s, H-8); δ_C (100 MHz; DMSO-d_6) 32.0, 39.2, 63.4, 67.0, 124.0, 143.9, 149.9, 154.7, 160.3.

2-Amino-9-(3-azido-4-hydroxy-3-hydroxymethyl-butyl)-1,9-dihydro-purin-6-one (2). Compound **1** (25 mg, 0.08 mmol) in aqueous 0.5 M NaOH solution (4 cm^3, 2.0 mmol) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature and neutralized with AcOH. The volatiles were evaporated and the resulting residue was purified by reversed phase ODS column chromatography (water/methanol = 10 : 1) to give compound **2** (20 mg, 88%) as a white solid. R_f = 0.34 (water/methanol = 4 : 1); mp 239 °C (dec.); (Found: C, 40.9; H, 4.7; N, 38.25. Calc. for $C_{10}H_{14}N_8O_3$: C, 40.8; H, 4.8; N, 38.1%); λ_{max}(MeOH)/nm 254; ν_{max}(film)/cm^{-1} 2109 (N_3); δ_H (400 MHz; DMSO-d_6) 1.90 (2 H, t, *J* 8.0, CH_2CH$_2$N), 3.51 (2 H, d, *J* 11.6, 2 × HOC*H*H), 3.54 (2 H, d, *J* 11.6, 2 × HOCH*H*), 4.02 (2 H, t, *J* 8.0, CH_2N), 6.45 (2 H, s, NH_2), 7.68 (1 H, s, H-8), 10.53 (1 H, s, amide-H); δ_H (400 MHz; MeOH-d_4) 2.06 (2 H, m, CH_2CH$_2$N), 3.69 (4 H, s, 2 × HOCH_2), 4.02 (2 H, m, CH_2N), 7.74 (1 H, s, H-8); δ_C (100 MHz; DMSO-d_6) 32.6, 38.8, 63.4, 67.0, 117.2, 137.9, 151.7, 154.0, 157.4.

2-Amino-2-[2-(2-amino-purin-9-yl)-ethyl]-propane-1,3-diol (3). To a stirred solution of compound **1** (12.0 mg, 0.04 mmol) in MeOH (4 cm^3) was added 10% Pd/C (6 mg) and the reaction mixture was stirred at room temperature for 3 h under H_2. The reaction mixture was filtered through a pad of Celite, washed with MeOH and evaporated. The resulting residue was crystallized from MeOH and ethyl ether to give compound **3** (8.0 mg, 77%) as a white solid. R_f = 0.3 (water/methanol = 4 : 1); mp 236 °C (dec.) (from MeOH); (Found: C, 47.7; H, 6.7; N, 33.5. Calc. for $C_{10}H_{16}N_6O_2$: C, 47.6; H, 6.4; N, 33.3%); λ_{max}(MeOH)/nm 306; δ_H (400 MHz; MeOH-d_4) 2.24 (2 H, m, CH_2CH$_2$N), 3.68 (4 H, s, 2 × HOCH_2), 4.30 (2 H, m, CH_2N), 8.06 (1 H, s, H-8), 8.56 (1 H, s, H-6).

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References

1 In *Acyclic, Carbocyclic and L-Nucleosides*, eds. L. A. Agrofoglio and S. R. Challand, Kluwer Academic Publishers, Dordrecht, 1998; p. 18–173.
2 (*a*) G. B. Elion, P. A. Furman, J. A. Fyfe, P. de Miranda, L. Beauchamp and H. J. Schaeffer, *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 5716–5720; (*b*) H. J. Schaeffer, L. Beauchamp, P. de Miranda, G. B. Elion, D. J. Bauer and P. Collins, *Nature*, 1978, **272**, 583–585.
3 S. A. Spector, G. F. McKinley, J. P. Lalezari, T. Samo, R. Andruczk, S. Follansbee, P. D. Sparti, D. V. Havlir, G. Simpson, W. Buhles, R. Wong and M. Stempien, *N. Engl. J. Med.*, 1996, **334**, 1491–1497.
4 R. A. Vere Hodge and Y. C. Cheng, *Antiviral Chem. Chemother.*, 1993, **4**, 13–24.
5 R. J. Crooks and A. Murray, *Antiviral Chem. Chemother.*, 1994, **5**, 31–37.
6 D. Jung and A. Dorr, *J. Clin. Pharmacol.*, 1999, **39**, 800–804.
7 (*a*) H. J. Field, *Expert Opin. Invest. Drugs*, 1996, **5**, 925–938; (*b*) R. A. Vere Hodge, *Antiviral Chem. Chemother.*, 1993, **4**, 67–84.
8 C. M. Perry and A. J. Wagstaff, *Drugs*, 1995, **50**, 396–415.
9 (*a*) K. A. Watanabe, U. Reichman, K. Hirota, C. Lopez and J. J. Fox, *J. Med. Chem.*, 1979, **22**, 21–24; (*b*) K. A. Watanabe, T.-L. Su, R. S. Klein, C. K. Chu, A. Matsuda, M. W. Chun, C. Lopez and J. J. Fox, *J. Med. Chem.*, 1983, **26**, 152–156; (*c*) C. H. Tann, P. R. Brodfuehrer, S. P. Brundidge, C. Sapino and H. G. Howell, *J. Org. Chem.*, 1985, **50**, 3644–3647.

10 E. Matthes, C. Lehmann, D. Scholz, H. A. Rosenthal and P. Langen, *Biochem. Biophys. Res. Commun.*, 1988, **153**, 825–831.
11 C. K. Chu, T. Ma, K. Shanmuganathan, C. Wang, Y. Xiang, S. B. Pai, G.-Q. Yao, J.-P. Sommadossi and Y.-C. Cheng, *Antimicrob. Agents Chemother.*, 1995, **39**, 979–981.
12 (*a*) P. A. Furman, J. A. Fyfe, M. H. St. Clair, K. Weinhold, J. L. Rideout, G. A. Freeman, S. N. Lehrman, D. P. Bolognesi, S. Broder, H. Mitsuya and D. W. Barry, *Proc. Natl. Acad. Sci. USA*, 1986, **83**, 8333–8337; (*b*) H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry and S. Broder, *Proc. Natl. Acad. Sci. USA*, 1985, **82**, 7096–7100.
13 H. Maag, R. M. Rydzewski, M. J. McRoberts, D. Crawford-Ruth, J. P. Verheyden and E. J. Prisbe, *J. Med. Chem.*, 1992, **35**, 1440–1451.
14 S. O. Thomas, V. L. Singleton, J. A. Lowery, R. W. Sharpe, L. M. Pruess, J. N. Porter, J. H. Mowat and N. Bohonos, *Antibiot. Ann.*, 1957, 716–721.
15 J. HannahR. L. Tolman, Eur. Patent EP 381531, 1990; (*Chem. Abstr.*, 1990, **114**, 102701).
16 T. Izawa, S. Nishiyama, S. Yamamura, K. Kato and T. Takita, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2519–2525.
17 R. Csuk and G. Thiede, *Tetrahedron*, 1999, **55**, 739–750.
18 E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297–368.
19 L. S. Jeong, J. W. Beach and C. K. Chu, *J. Heterocycl. Chem.*, 1993, **30**, 1445–1452.
20 T. Naka, N. Minakawa, H. Abe, D. Kaga and A. Matsuda, *J. Am. Chem. Soc.*, 2000, **122**, 7233–7243.
21 L. S. Jeong, S. J. Yoo, K. M. Lee, M. J. Koo, W. J. Choi, H. O. Kim, H. R. Moon, M. Y. Lee, J. G. Park, S. K. Lee and M. W. Chun, *J. Med. Chem.*, 2003, **46**, 201–203.