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# Synthesis and Antiviral Activity Evaluation of Novel 2-Phenyl-4-(D-*arabino*-4′-cycloaminobutyl)triazoles: Acyclonucleosides Containing Unnatural Bases

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**Abstract**—Five 2-phenyl-4-(D-*arabino*-4′-cycloamino-3′-hydroxy-*O*-1′,2′-*iso*propylidene-butyl)-2*H*-1,2,3-triazoles, acyclonucleosides containing unnatural bases have been synthesised by opening of the epoxide ring of 2-phenyl-4-(D-*arabino*-3′,4′-epoxy-*O*-1′,2′-*iso*-propylidenebutyl)-2*H*-1,2,3-triazole with the corresponding cyclic amines in 70–85% yields. The starting *arabino*-epoxytriazole was prepared in five steps starting from D-glucose in an overall yield of 15%. All the five triazolylacyclonucleosides were unambiguously identified on the basis of their spectral data. The structure of one of the intermediates, that is 2-phenyl-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-2*H*-1,2,3-triazole was confirmed by its X-ray crystallographic studies. These acyclonucleosides were subjected to antiviral activity evaluation in CEM-SS cell-based anti HIV assay with the lymphocytropic virus strains HIV-$1_{IIIB}$ and HIV-$1_{RF}$.


## Introduction

For several years, there has been an intensive search for drugs effective in the chemotherapy of viral diseases like AIDS, herpes simplex and cytomegaloviruses.[1–4] While many antibacterial drugs have been developed over the past 50 years, relatively few drugs are in clinical use as antiviral agents at the present time.[5] Most of these drugs are analogues of naturally occurring nucleosides.[6] Among these drugs, AZT is currently one drug that has been shown to decrease the mortality and frequency of opportunistic infections associated with AIDS. However, AZT is far from being the ideal antiviral agent, since bone marrow toxicity and development of resistant viruses can limit its usefulness as long term chemotherapeutic agent for AIDS and related complexities.[7] Further, the stability of natural nucleosides and their analogues towards the major pathways of nucleoside inactivation, for example deamination by adenosine deaminase and glycosidic cleavage by nucleoside phosphorylases is also a limiting factor in the development of nucleoside-based antiviral agents.[8,9] To overcome these inactivation problems, a series of nucleoside analogues were synthesised in which the cyclic carbohydrate moiety was replaced by an acyclic side chain and these are called acyclonucleosides.[10–15] Acyclovir is one of the most important compounds in this class and it has been marketed as an antiherpes drug for over a decade.[16] Acyclonucleoside derivatives having unnatural bases are reported in the literature for their wide range of biological activities. Taking lead from these reports, we have synthesised triazolylacyclonucleosides having unnatural bases and have evaluated them for antiviral activity in standard CEM-SS cell-based microtiter anti- HIV assay with two strains of HIV viruses.

## Results and Discussion

Five triazolylacyclonucleosides, that is 2-phenyl-4-[D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*propylidene-4′-(pyrrolidin-1-yl)butyl]-2*H*-1,2,3-triazole (**5**), 2-phenyl-4-[D-*arabino*-

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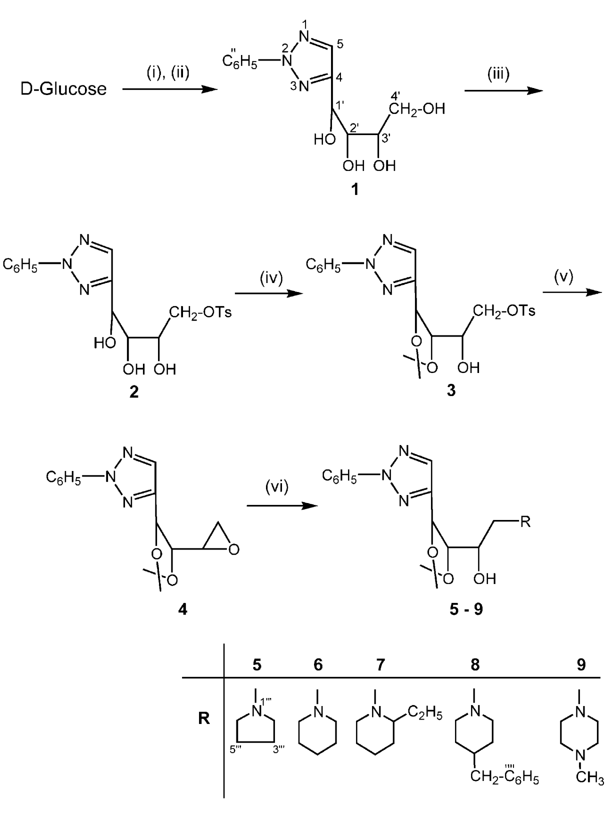
3′-hydroxy-*O*-1′,2′-*iso*propylidiene-4′-(piperidin-1-yl)butyl]-2*H*-1,2,3-triazole (**6**), 2-phenyl-4-[D-*arabino*-4′-(2‴-ethylpiperidin-1-yl)-3′-hydroxy-*O*-1′,2′-*iso*propylidene-butyl]-2*H*-1,2,3-triazole (**7**), 2-phenyl-4-[D-*arabino*-4′-(4‴-benzylpiperidin-1-yl)-3′-hydroxy-*O*-1′,2′-*iso*propylidenebutyl]-2*H*-1,2,3-triazole (**8**) and 2-phenyl-4-[D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*propylidene-4′-(*N*-methylpiperazin-1-yl)butyl]-2*H*-1,2,3-triazole (**9**) were synthesised by opening of the epoxide ring of 2-phenyl-4-(D-*arabino*-3′,4′-epoxy-*O*-1′,2′-*iso*propylidenebutyl)-2*H*-1,2,3-triazole (**4**) with pyrrolidine, piperidine, 2-ethylpiperidine, 4-benzylpiperidine and *N*-methylpiperazine, respectively, in 70–85% yields. All the five triazolylacyclonucleosides **5–9** were unambiguously identified on the basis of their spectral data.

The epoxide **4**, precursor of acyclonucleosides **5–9** was synthesised in four steps starting from the conversion of glucose to its phenylosazone, followed by oxidative cyclisation of the osazone with 1% aqueous $CuSO_4$ to yield the intermediate compound 2-phenyl-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-2*H*-1,2,3-triazole (**1**) in an overall yield of 43% (Scheme 1).[17] The structure of triazolyl sugar **1** was established on the basis of spectral data and by comparison of its mp and spectral data with those reported in the literature.[18–20] Finally, the structure of compound **1** was confirmed by X-ray crystallographic studies (Fig. 1). The selective tosylation of compound **1** with one equivalent of TsCl in pyridine afforded 2-phenyl-4-(D-*arabino*-1′,2′,3′-trihydroxy-4′-*O*-*p*-toluenesulfonylbutyl)-2*H*-1,2,3-triazole (**2**) in 90% yield, which was characterised on the basis of its spectral data. The tosylated triazolylsugar **2** was treated with anhydrous acetone in the presence of anhydrous $FeCl_3$ to form exclusively the 1′,2′-*iso*propylidene derivative 2-phenyl-4-(D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*-propylidene-4′-*O*-*p*-toluenesulfonylbutyl)-2*H*-1,2,3-triazole (**3**) in a regioselective fashion in 86% yield, which on refluxing with sodium hydride in toluene resulted in the formation of the epoxide **4**; the formation of 3′,4′-epoxide **4** also supports the *O*-1′,2′-*iso*propylidene protection in compound **3**. The compounds **2–9** are new to the literature as they have not been synthesised earlier.



**Scheme 1.** Reagents and conditions: (i) $C_6H_5NHNH_2$, 65–70 °C; (ii) 1% aq $CuSO_4 \cdot 5H_2O$, reflux; (iii) *p*-toluenesulfonyl chloride, pyridine, 25–27 °C; (iv) acetone, anhydrous $FeCl_3$, 25–27 °C; (v) toluene, NaH, reflux; (vi) cyclic amine, triethylamine, MeOH, 25–27 °C.

## X-ray crystallography

The molecular structure of 2-phenyl-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-2H-1,2,3-triazole (**1**) was further confirmed by single crystal X-ray diffraction study. The schematic representation of the molecular structure of compound **1** is illustrated in Figure 1, bond lengths [Å] and bond angles [°] are given in Table 1 and other crystallographic data are summarised in the Experimental.

## Antiviral activity evaluation

Triazolylacyclonucleosides **5–9** and their precursor **4** were evaluated for antiviral efficacy against two strains of HIV-1(HIV-$1_{IIIB}$ and HIV-$1_{RF}$) in the standard CEM-SS cell-based anti-HIV assay (cf. Experimental). In this assay system, none of these six compounds reached an $IC_{50}$ value at the highest test concentration evaluated (100 μM), most of the compounds were cytotoxic at higher concentrations, except compound **4**. The overall assay performance was validated by the MOI-sensitive positive control compound 3′-azidothymidine (AZT), exhibiting the expected level of antiviral activity ($IC_{50}$ = 0.003 μM against HIV-$1_{IIIB}$ and 0.006 μM against HIV-$1_{RF}$). Microscopic and macroscopic observations of the cells in each well of the microtiter plate confirmed the efficacy and cytotoxicity results obtained following staining of the cells with the MTS metabolic dye. The data obtained in these assays is given in Table 2.

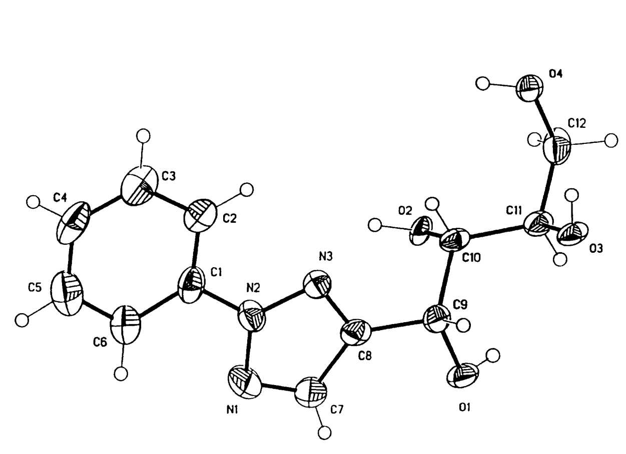



**Figure 1.** Molecular structure of 2-phenyl-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-2*H*-1,2,3-triazole (**1**).

**Table 1.** Bond lengths and bond angles for the molecular structure of 2-phenyl-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-2*H*-1,2,3-triazole (**1**)[a]

| Bond lengths (Å) | | Bond angles (°) | |
|---|---|---|---|
| O (1)–C (9) | 1.430 (5) | C (7)–N (1)–N (2) | 103.5 (4) |
| O (3)–C (11) | 1.435 (5) | N (3)–N (2)–C (1) | 123.8 (4) |
| N (1)–C (7) | 1.339 (6) | C (8)–N (3)–N (2) | 104.8 (4) |
| N (2)–N (3) | 1.333 (5) | C (6)–C (1)–N (2) | 119.5 (5) |
| N (3)–C (8) | 1.329 (6) | C (1)–C (2)–C (3) | 118.0 (5) |
| C (1)–C (2) | 1.387 (7) | C (3)–C (4)–C (5) | 119.2 (6) |
| C (3)–C (4) | 1.371 (8) | C (1)–C (6)–C (5) | 119.5 (5) |
| C (5)–C (6) | 1.380 (7) | N (3)–C (8)–C (7) | 108.1 (4) |
| C (8)–C (9) | 1.490 (6) | C (7)–C (8)–C (9) | 131.1 (5) |
| C (10)–C (11) | 1.512 (6) | O (1)–C (9)–C (10) | 110.2 (4) |
| | | O (2)–C (10)–C (11) | 108.3 (4) |
| | | C (11)–C (10)–C (9) | 113.5 (4) |
| | | O (3)–C (11)–C (10) | 109.1 (4) |
| | | O (4)–C (12)–C (11) | 111.1 (4) |
| O (2)–C (10) | 1.447 (5) | N (3)–N (2)–N (1) | 114.5 (4) |
| O (4)–C (12) | 1.425 (5) | N (1)–N (2)–C (1) | 121.6 (4) |
| N (1)–N (2) | 1.341 (5) | C (6)–C (1)–C (2) | 121.4 (5) |
| N (2)–C (1) | 1.422 (6) | C (2)–C (1)–N (2) | 119.1 (4) |
| C (1)–C (6) | 1.370 (7) | C (4)–C (3)–C (2) | 121.4 (6) |
| C (2)–C (3) | 1.389 (7) | C (6)–C (5)–C (4) | 120.4 (5) |
| C (4)–C (5) | 1.385 (7) | N (1)–C (7)–C (8) | 109.0 (4) |
| C (7)–C (8) | 1.399 (6) | N (3)–C (8)–C (9) | 120.7 (4) |
| C (9)–C (10) | 1.521 (6) | O (1)–C (9)–C (8) | 107.4 (4) |
| C (11)–C (12) | 1.511 (6) | C (8)–C (9)–C (10) | 112.3 (4) |
| | | O (2)–C (10)–C (9) | 110.5 (4) |
| | | O (3)–C (11)–C (12) | 109.9 (4) |
| | | C (12)–C (11)–C (10) | 114.6 (4) |

[a]Symmetry transformations used to generate equivalent atoms; Numbering of atoms (cf. Fig. 1) does not correspond to the IUPAC nomenclature.

## Experimental

Melting points were determined on a Mettler FP 62 instrument and are uncorrected. The IR spectra were recorded on a Perkin-Elmer RX1 FT-IR spectrophotometer. The $^1$H NMR spectra were recorded either on a Bruker AC-250 or Bruker Advance-300 spectrometer at 250 and 300 MHz, respectively. The $^{13}$C NMR spectra were recorded either on a Bruker AC-250 or Bruker Advance-300 spectrometer at 62.5 or 75.5 MHz, respectively. TMS has been used as an internal standard for both $^1$H and $^{13}$C NMR spectral recordings. The chemical shift values are on δ scale and the coupling constants (*J*) are in Hz. EI mass spectra were recorded on Jeol-DX 303 mass spectrometer at 70 eV. Analytical TLC's were performed on precoated Merck silica gel $60F_{254}$ plates and spots were detected either under UV light or on charring with 5% alcoholic $H_2SO_4$. Solvent systems used for TLC were: **A** (methanol/chloroform, 1:9), **B** (methanol/chloroform, 1:99), **C** (methanol/chloroform, 1:49) and **D** (ethyl acetate/petroleum ether, 1:9). All the organic solvents were dried and distilled prior to their use. The antiviral efficacy and cellular cytotoxicity of compounds **4–9** and AZT have been evaluated at Southern Research Institute, MD, USA.

**2-Phenyl-4-(D-*arabino*-1′,2′,3′-trihydroxy-4′-*O*-*p*-toluenesulfonylbutyl)-2*H*-1,2,3-triazole (2).** A solution of D-*arabino*-tetrahydroxybutyltriazole[17] (**1**, 795 mg, 3 mmol) in pyridine (30 mL) was cooled to 0 °C in ice-bath and *p*-toluenesulfonyl chloride (572 mg, 3 mmol) added in small lots under constant stirring. The reaction mixture was stirred for 2.5 h at 25–27 °C when TLC showed complete conversion of the starting compound into a fast moving product. The reaction was terminated by pouring onto crushed ice and pyridine was neutralized by dropwise addition of 2 N HCl affording pure 4′-*O*-*p*-toluenesulfonylated triazole **2** as a white amorphous solid (1.1 g) in 90% yield, mp 105–106 °C. $R_f$ 0.32 (solvent **A**); IR (Nujol): 3360 (OH), 2920, 1600, 1462, 1374, 1070, 968, 850 and 755 cm$^{-1}$; $^1$H NMR (250 MHz, DMSO-$d_6$): δ 2.39 (3H, s, $CH_3$), 3.55 (1H, dd, $J$ = 1.7 and 8.9 Hz, C-4′H$_\alpha$), 3.87–3.90 (1H, m, C-4′H$_\beta$), 4.05(1H, dd, $J$ = 6.5 and 9.6 Hz, C-3′H), 4.26 (1H, d, $J$ = 9.6 Hz, C-2′H), 5.11 (1H, br s, C-1′H), 7.36–7.40(1H, m, C-4″H), 7.45(2H, d, $J$ = 8.2 Hz, C-3‴H and C-5‴H), 7.54 (2H, m, C-2″H and C-6″H), 7.80 (2H, d, $J$ = 8.2 Hz, C-2‴H and C-6‴H) and 7.97–7.99 (3H, m, C-3″H, C-5″H and C-5H); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$): δ 20.90 ($CH_3$), 65.16 and 68.21 (C-3′ and C-4′), 73.46(C-2′ and C-1′), 118.22, 127.46, 127.78, 129.77 and 130.21(C-2″, C-3″, C-4″, C-5″, C-6″, C-2‴, C-3‴, C-5‴ and C-6‴), 132.56 and 135.43 (C-5 and C-4‴), 139.43(C-1″), 144.88(C-1‴) and 152.86 (C-4); EIMS, *m*/*z* (% rel. int.): 419 ([M]$^+$, 5), 272 (20), 258 (90), 229 (15), 212 (85), 172 (100), 158 (30), 107 (25), 91 (80) and 77 (25).

**2-Phenyl-4-[D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*propylidene-4′-*O*-*p*-toluenesulfonylbutyl]-2*H*-1,2,3-triazole (3).** To a suspension of 1′,2′,3′-trihydroxy-4′-*O*-*p*-toluenesulfonylated triazole **2** (838 mg, 2.0 mmol) in dry and distilled acetone (50 mL), anhydrous $FeCl_3$ (324 mg, 2.0 mmol) was added and the reaction mixture was stirred at 25–27 °C for 25 h. On completion, the reaction was termi-

**Table 2.** Antiviral efficacy of epoxide **4** and acyclotriazolylnucleosides **5–9** against HIV-$1_{IIIB}$ and HIV-$1_{RF}$ viruses[a,b]

| Compd | Antiviral efficacy versus HIV-$1_{IIIB}$ virus | | | Antiviral efficacy versus HIV-$1_{RF}$ virus | | |
|---|---|---|---|---|---|---|
| | CEM-SS/HIV-$1_{IIIB}$ $IC_{50}$ (μM) | CEM-SS $TC_{50}$ (μM) | Therapeutic index | CEM-SS/HIV-$1_{RF}$ $IC_{50}$ (μM) | CEM-SS $TC_{50}$ (μM) | Therapeutic index |
| **4** | >100 | >100 | — | >100 | >100 | — |
| **5** | >100 | 83.0 | — | >100 | 72.8 | — |
| **6** | >100 | 24.2 | — | >100 | 18.3 | — |
| **7** | >100 | >100 | — | >100 | 66.0 | — |
| **8** | >100 | 2.7 | — | >100 | 2.5 | — |
| **9** | >100 | 94.2 | — | >100 | 66.8 | — |
| AZT | 0.003 | >1 | >312.5 | 0.006 | >1 | >155.9 |

[a]AZT was evaluated in parallel as a relevant positive control compound.
[b]All values are average of three measurements using six concentrations at half-log dilutions.

nated by addition of 10% aq solution of potassium carbonate (10 mL). Acetone was removed under reduced pressure and the brown syrup was extracted with chloroform (3×20 mL). The organic layer was separated, washed with water (2×50 mL), dried over sodium sulphate and solvent removed under reduced pressure. The residue thus obtained was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to obtain **3** as a colourless oil (789 mg) in 86% yield. $R_f$ 0.36 (solvent **D**); IR (Nujol): 3320 (OH), 1600, 1499, 1463, 1372, 1217, 1071, 967, 844 and 755 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 1.44 and 1.54 (6H, 2s, 3H each, (C(C*H*$_3$)$_2$), 2.48 (3H, s, CH$_3$), 3.66 (1H, dd, $J$=3.8 and 10.7 Hz, C-4′H$_\alpha$), 4.18 (1H, br d, $J$=10.7 Hz, C-4′H$_\beta$), 4.81–4.86 (2H, m, C-2′H and C-3′H), 4.92–4.96 (1H, m, C-1′H), 7.26–7.49 (6H, m, Ar″-H and C-5H), 7.92 (2H, d, $J$=8.6 Hz, C-3‴H and C-5‴H) and 8.04 (2H, d, $J$=8.6 Hz, C-2‴H and C-6‴H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 22.16 (Ph*C*H$_3$), 25.07 and 26.41(2×CH$_3$), 73.46 (C-4′), 78.20 (C-3′), 81.71 (C-2′ and C-1′), 112.96 (*C*(CH$_3$)$_2$), 119.23, 127.42, 127.72, 129.58 and 130.59 (C-2″, C-3″, C-4″, C-5″, C-6″, C-2‴, C-3‴, C-5‴ and C-6‴), 136.44 (C-5), and 140.22, 142.13, 145.47 and 147.16 (C-1″, C-1‴, C-4 and C-4‴); EIMS, $m/z$ (% rel. int.): 459 ([M]$^+$, 5), 272 (18), 258 (90), 229 (10), 215 (24), 212 (85), 188 (15), 171 (100), 158 (30), 107 (25), 91 (80) and 77 (25).

**2-Phenyl-4-[D-*arabino*-3′,4′-epoxy-*O*-1′,2′-*iso*propylidene-butyl]-2*H*-1,2,3-triazole (4).** To a solution of 3′-hydroxy-1′,2′-*O*-*iso*propylidene-4′-*p*-toluenesulfonyltriazole (**3**, 690 mg, 1.5 mmol) in dry and distilled toluene (20 mL) was added sodium hydride (40 mg, 1.0 mmol) and the reaction mixture was refluxed in an oil bath for 2.5 h. On completion, the reaction was terminated by addition of methanol (10 mL), solvent removed under reduced pressure and the residue obtained was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluting solvent to get the epoxide **4** as a colourless oil (258 mg) in 60% yield. $R_f$ 0.42 (solvent **D**); IR (Nujol): 1599, 1499, 1463, 1375, 1214, 1069, 967, 887 and 755 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 1.43 and 1.45 (6H, 2s, 3H each, 2×CH$_3$), 2.72–2.77 (2H, m, C-4′H), 3.18–3.21 (1H, m, C-3′H), 4.19(1H, dd, $J$=3.8 and 7.8 Hz, C-2′H), 5.03 (1H, d, $J$=7.8 Hz, C-1′H), 7.19–7.25 (1H, m, C-4″H), 7.33–7.38 (2H, m, C-2″H and C-6″H), 7.74 (1H, s, C-5H) and 7.84 (2H, br d, $J$=7.8 Hz, C-3″H and C-5″H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 28.12 and 28.16 (2×CH$_3$), 45.91 (C-4′), 52.34 (C-3′), 73.82 (C-2′), 81.74 (C-1′), 112.07 (*C*(CH$_3$)$_2$), 120.31 (C-3″ and C-5″), 129.08 (C-4″), 130.68 (C-2″ and C-6″), 135.36 (C-5), 141.09 (C-1″) and 148.98 (C-4); EIMS, $m/z$ (% rel. int.): 287 ([M]$^+$, 67), 272 (70), 229 (95), 200 (52), 173 (50), 158 (80), 91 (62), 77 (80) and 59 (100).

**General procedure for the preparation of 2-phenyl-4-(D-*arabino*-4′-cycloamino-3′-hydroxy-*O*-1′,2′-*iso*propylidene-butyl)-2*H*-1,2,3-triazoles 5–9.** To a solution of 3′,4′-epoxytriazole **4** (287 mg, 1.0 mmol) in dry and distilled methanol (10 mL) was added corresponding cyclic amine, i.e., pyrrolidine, piperidine, 2-ethylpiperidine, 4-benzylpiperidine or *N*-methylpiperazine (1.0 mmol), followed by triethylamine (1 mL). The reaction mixture was refluxed until TLC examination showed complete conversion of the starting **4** into the product, the solvent was removed under reduced pressure and the crude product thus obtained was purified by column chromatography on silica gel using chloroform as eluting solvent to obtain compounds **5–9** as yellow coloured oils in 70 to 85% yields.

**2-Phenyl-4-[D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*propylidene-4′-(pyrrolidin-1-yl)butyl]-2*H*-1,2,3-triazole (5).** It was obtained as a light yellow oil (304 mg) in 85% yield. $R_f$ 0.35 (Solvent **B**); IR (Nujol): 3364 (OH), 1599, 1498, 1460, 1375, 1248, 1217, 1067, 966, 888 and 758 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 1.51 and 1.52 (6H, 2s, 3H each, 2×CH$_3$), 1.81–1.84 (4H, m, C-3‴H and C-4‴H), 2.66–2.87 (6H, m, C-4′H, C-2‴H and C-5‴H), 4.02–4.04 (1H, m, C-3′H), 4.13 (1H, br s OH), 4.28 (1H, t, $J$=6.6 Hz, C-2′H), 5.30 (1H, d, $J$=7.4 Hz, C-1′H), 7.27–7.36 (1H, m, C-4″H), 7.44–7.49 (2H, m, C-2″H and C-6″H), 7.84 (1H, s, C-5H) and 8.04–8.07 (2H, m, C-3″H and C-5″H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 23.56 (C-3‴ and C-4‴), 26.79 and 27.03 (2×CH$_3$), 54.25 (C-2‴ and C-5‴), 58.47 (C-4′), 69.02 (C-3′), 72.94 (C-2′), 82.47 (C-1′), 110.39 (*C*(CH$_3$)$_2$), 118.99 (C-3″ and C-5″), 127.56 (C-4″), 129.26 (C-2″ and C-6″), 134.40 (C-5), 139.90 (C-1″) and 148.62 (C-4); EIMS, $m/z$ (% rel. int.): 358 ([M]$^+$, 90), 343 (100), 312 (15), 283 (10), 273 (5), 243 (5), 227 (70), 186 (20), 158 (28), 135 (55), 114 (95) and 84 (25).

**2-Phenyl-4-[D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*propylidiene-4′-(piperidin-1-yl)butyl]-2*H*-1,2,3-triazole (6).** It was obtained as a light yellow oil (298 mg) in 80% yield. $R_f$ 0.35 (solvent **B**); IR (Nujol): 3362 (OH), 1599, 1498, 1458, 1365, 1248, 1217, 1067, 1000 and 888 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 1.42–1.45 (2H, m, C-4‴H), 1.51 and 1.52 (6H, 2s, 3H each, 2×CH$_3$), 1.57–1.59 (4H, m, C-3‴H and C-5‴H), 2.40–2.61 (6H, m, C-4′H, C-2‴H and C-6‴H), 3.20 (1H, br s, OH), 3.94–4.01 (1H, m, C-3′H), 4.25 (1H, dd, $J$=5.8 and 7.5 Hz, C-2′H), 5.29(1H, d, $J$=7.5 Hz, C-1′H), 7.31–7.36 (1H, m, C-4″H), 7.44–7.54 (2H, m, C-2″H and C-6″H), 7.83 (1H, s, C-5H) and 8.04–8.07 (2H, m, C-3″H and C-5″H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 23.97 and 25.73 (C-3‴, C-4‴ and C-5‴), 26.75 and 26.96 (2×CH$_3$), 54.62 (C-2‴ and C-6‴), 60.93 (C-4′), 67.14 (C-3′), 73.03 (C-2′), 82.70 (C-1′), 110.32 (*C*(CH$_3$)$_2$), 118.96 (C-3″ and C-5″), 127.48 (C-4″), 129.19 (C-2″ and C-6″), 134.32 (C-5), 139.68 (C-1″) and 148.57 (C-4); EIMS, $m/z$ (% rel. int.): 372 ([M]$^+$, 55), 357 (58), 343 (5), 279 (15), 243 (5), 215 (8), 186 (10), 167 (25), 149 (55), 128 (75) and 99 (100).

**2-Phenyl-4-[D-*arabino*-4′-(2‴-ethylpiperidin-1-yl)-3′-hydroxy-*O*-1′,2′-*iso*propylidenebutyl]-2*H*-1,2,3-triazole (7).** It was obtained as a light yellow oil (280 mg) in 70% yield. $R_f$ 0.38 (solvent C); IR (Nujol): 3394 (OH), 1599, 1499, 1461, 1376, 1254, 1163, 1069, 966, 888 and 756 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 0.85 (3H, t, $J$=7.5 Hz, CH$_2$C*H*$_3$), 1.52 and 1.53 (6H, 2s, 3H each, 2×CH$_3$), 1.65–1.68 (8H, m, C-3‴H, C-4‴H, C-5‴H and C*H*$_2$CH$_3$), 2.41–2.59(5H, m, C-4′H, C-2‴H and C-6‴H), 3.68 (1H, br s, OH), 3.96–3.99 (1H, m, C-3′H), 4.21–4.25 (1H, m, C-2′H), 5.33 (1H, d, $J=6.6$ Hz, C-1′H), 7.27–7.35 (2H, m, C-2″H and C-6″H), 7.43–7.48 (1H, m, C-4″H), 7.84 (1H, s, C-5H) and 8.06 (2H, br d, $J=7.9$ Hz, C-3″H and C-5″H); $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 11.09 ($CH_2CH_3$), 21.04, 21.41, 22.72 and 24.33 (C-3‴, C-4‴, C-5‴, $CH_2CH_3$), 26.86 and 27.07 ($C(CH_3)_2$), 56.10 (C-2‴), 49.77 (C-6‴), 62.96 (C-4′), 67.14 (C-3′), 73.44 (C-2′), 83.05 (C-1′), 110.44 ($C(CH_3)_2$), 119.06 (C-3″ and C-5″), 127.57 (C-4″), 129.83 (C-2″ and C-6″), 134.43 (C-5), 139.99 (C-1″) and 148.79 (C-4); EIMS, *m/z* (% rel. int.): 385 (30), 371 (92), 313 (10), 279 (12), 188 (10), 149 (60), 126 (100) and 96 (47).

**2-Phenyl-4-[D-*arabino*-4′-(4‴-benzylpiperidin-1-yl)-3′-hydroxy-*O*-1′,2′-*iso*propylidenebutyl]-2*H*-1,2,3-triazole (8).** It was obtained as a light yellow oil (380 mg) in 80% yield. $R_f$ 0.35 (solvent C); IR (Nujol): 3374 (OH), 1727, 1599, 1497, 1456, 1376, 1253, 1163, 1069, 967, 886 and 754 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.43 and 1.44 (6H, 2s, 3H each, 2×$CH_3$), 1.53–1.60 (4H, m, C-3‴H and C-5‴H), 1.87–1.97 (2H, m, $CH_2C_6H_5$), 2.14–2.22 (1H, m, C-4‴H), 2.42–2.53 (4H, m, C-2‴H and C-6‴H), 2.76–2.92 (2H, m, C-4′H), 3.59 (1H, br s, OH), 3.88–3.94 (1H, m, C-3′H), 4.16–4.20 (1H, dd, $J=5.8$ and 7.5 Hz, C-2′H), 5.21 (1H, d, $J=7.5$ Hz, C-1′H), 7.03–7.23 (5H, m, $CH_2C_6H_5$), 7.25–7.28 (1H, m, C-4″H), 7.36–7.46 (2H, m, C-2″H and C-6″H), 7.76 (1H, s, C-5H) and 7.96–7.99 (2H, m, C-3″H and C-5″H); $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 25.79 and 26.01 (2×$CH_3$), 30.75 and 31.19 (C-3‴, C-5‴), 36.58 (C-4‴), 41.96 ($CH_2C_6H_5$), 51.57 and 54.41 (C-2‴ and C-6‴), 59.50 (C-4′), 66.18 (C-3′), 71.99 (C-2′), 81.57 (C-1′), 109.34 ($C(CH_3)_2$), 117.92 (C-3″ and C-5″), 124.00 (C-4⁗), 124.89, 126.50, 127.21, 128.06 and 128.19 (C-2″, C-2⁗, C-3⁗, C-4″, C-5⁗, C-6″ and C-6⁗), 133.31 (C-5), and 138.78, 139.38 (C-1″ and C-1⁗) and 147.45 (C-4); EIMS, *m/z* (% rel. int.): 462 ([M]$^+$, 20), 447 (15), 218 (18), 189 (100), 174 (10), 117 (10), 91 (65) and 70 (20).

**2-Phenyl-4-[D-*arabino*-3′-hydroxy-*O*-1′,2′-*iso*propylidene-4′-(*N*-methylpiperazin-1-yl)butyl]-2*H*-1,2,3-triazole (9).** It was obtained as a light yellow oil (272 mg) in 70% yield. $R_f$ 0.38 (solvent C); IR (Nujol): 3392 (OH), 1670, 1599, 1498, 1458, 1289, 1248, 1215, 1067, 1013, 888 and 758 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.51 and 1.53 (6H, 2s, 3H each, 2×$CH_3$), 2.27 (3H, s, $NCH_3$), 2.47–2.66 (10H, m, C-4′H, C-2‴H, C-3‴H, C-5‴H and C-6‴H), 3.57 (1H, br s, OH), 3.96–3.99 (1H, m, C-3′H), 4.27 (1H, t, $J=7.3$ Hz, C-2′H), 5.29 (1H, d, $J=7.6$ Hz, C-1′H), 7.28–7.36 (1H, m, C-4″H), 7.44–7.49 (2H, m, C-2″H and C-6″H), 7.84 (1H, s, C-5H) and 8.04–8.06 (2H, m, C-3″H and C-5″H); $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ 26.77 and 26.98 (2×$CH_3$), 45.85 ($NCH_3$), 55.05 (C-2‴, C-3‴, C-5‴ and C-6‴), 60.11 (C-4′), 67.26 (C-3′), 72.84 (C-2′), 82.59 (C-1′), 110.34 ($C(CH_3)_2$), 118.98 (C-3″ and C-5″), 127.59 (C-4″), 129.27 (C-2″ and C-6″), 134.34 (C-5), 139.88 (C-1″) and 148.56 (C-4); EIMS, *m/z* (% rel. int.): 387 ([M]$^+$, 50), 372 (45), 312 (4), 273 (4), 256 (5), 221 (10), 186 (15), 172 (5), 143 (75), 114 (100) and 98 (72).

**X-ray crystallography of triazolylacyclonucleoside 1.** The crystallographic measurements on butyltriazole **1** were made using a Siemens SMART area-detector diffractometer. Graphite monochromated Mo-$K_\alpha$ radiation was used in all cases. The structure was solved using SHELXTL-PLUS[21] and refined with SHELXL-96.[22] The crystal data of compound **1** is given below.

**2-Phenyl-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-2*H*-1,2,3-triazole (1).** $C_{12}H_{15}N_3O_4$, M = 265.27, T = 180(2)K, λ = 0.71073 Å. Monoclinic $a=6.0354(6)$, $b=4.7825(4)$, $c=21.723(2)$ Å, β = 93.702(2)°, V = 625.71(10) Å$^3$, space group P2$_1$, Z = 2, $D_x=1.408$ Mg/m$^3$, μ = 0.107 mm$^{-1}$, F(000) = 280. Crystal size 0.50×0.08×0.08 mm; θ range for data collection 2.82–25.00°; index range $-7\leq h\leq 7$, $-6\leq k\leq 6$, $26\leq l\leq 28$, reflections collected 3243, independent reflections 2070 [R(int) = 0.0598]; refinement method full-matrix least squares on F$^2$; data/restraints/parameters 2070/1/176; goodness of fit on F$^2$ 0.895; R(F)[I > 2σ(I)] = 0.0632; wR(F$^2$) = 0.1357; largest diff. peak and hole 0.376 and −0.299 eÅ$^{-3}$.

## Antiviral activity evaluation

**Drug preparation.** Compounds **4–9** were solubilised in water to yield 40 mM stock solutions. All compounds were tested at 100 μM concentration and five serial half-logarithmic dilutions. AZT was used as a positive control antiviral compound.

**Cell preparation.** CEM-SS cells were passaged in T-75 flasks prior to use in the antiviral assay. On the day preceeding the assay, the cells were split 1:2 to assure they were in an exponential growth phase at the time of infection. Total cell and viability quantification was performed using a hemacytometer and trypan blue exclusion. Cell viability was greater than 95% for the cells to be utilized in the assay. The cells were resuspended at 5×10$^4$ cells/mL in tissue culture medium and added to the drug-containing microtiter plates in a volume of 50 μL.

**Virus preparation.** The virus used for the assay was the lymphocytropic virus strains HIV-1$_{\rm IIIB}$ and HIV-1$_{\rm RF}$. This virus was obtained from the NIH AIDS Research and Reference Reagent Program and was grown in CEM-SS cells for the production of stock virus pools. A pre-titered aliquot of virus was removed from the freezer (−80 °C) and allowed to thaw slowly to room temperature in a biological safety cabinet. The virus was resuspended and diluted into tissue culture medium such that the amount of virus added to each well in a volume of 50 μL was the amount determined to give between 85 and 95% cell killing at 6 days post-infection. TCID$_{50}$ calculations by endpoint titration in CEM-SS cells indicated that the multiplicity of infection of these assays was approximately 0.01.

**Plate format.** Each plate contains cell control wells (cells only), virus control wells (cells plus virus), drug cytotoxicity wells (cells plus drug only), drug colorimetric control wells (drug only) as well as experimental wells (drug plus cells plus virus). Samples were evaluated with triplicate measurements using six concentrations at half-log dilutions in order to determine IC$_{50}$ values and to measure cellular cytotoxicity, if detectable.

**MTS staining for cell viability.** At assay termination, the assay plates were stained with the soluble tetrazolium-based dye MTS (Cell Titer Reagent Promega) to determine cell viability and quantify compound toxicity. MTS is metabolised by the mitochondria enzymes of metabolically active cells to yield a soluble formazan product, allowing the rapid quantitative analysis of cell viability and compound cytotoxicity. The MTS is a stable solution that does not require preparation before use. At termination of the assay, 20 μL of MTS reagent was added per well. The wells were incubated overnight for the HIV cytoprotection assay at 37 °C. The incubation intervals were chosen based on empirically determined times for optimal dye reduction in each cell type. Adhesive plate sealers were used in place of the lids, the sealed plate was inverted several times to mix the soluble formazan product and the plate was read spectrophotometrically at 490 nm with a Molecular Devices Vmax plate reader.

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