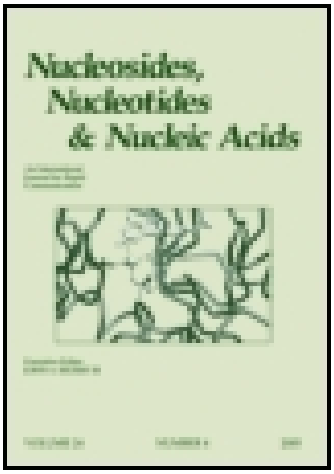

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Acyclic Nucleosides: Synthesis of 1-[(1-Hydroxy-2-Propoxy) Methyl]Thymine, 6-Azathymine, URACIL, AND 6-Azauracil as Potential Antiviral Agents

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ACYCLIC NUCLEOSIDES: SYNTHESIS OF 1-[(1-HYDROXY-2-PROPOXY) METHYL]THYMINE, 6-AZATHYMINE, URACIL, AND 6-AZAURACIL AS POTENTIAL ANTIVIRAL AGENTS

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Abstract

A series of acyclic nucleosides have been synthesized. Thymine, 6-azathymine, uracil, and 6-azauracil were silylated with hexamethyldisilazane in the presence of ammonium sulfate and then coupled with 1-benzyloxy-2-chloromethoxypropane to give the corresponding 1-(1-benzyloxy-2-propoxy)methyl derivatives. A minor quantity of benzyloxymethylated product was also obtained in each case. Hydrogenolysis of the protected acyclic nucleosides with palladium(II) hydroxide afforded the title compounds. None of the compounds exhibited significant antiviral activity against human immunodeficiency virus (HIV).

INTRODUCTION

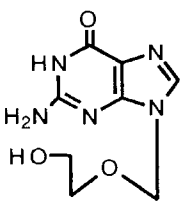
Recent chemotherapeutic approaches toward acquired immunodeficiency syndrome (AIDS) have resulted in some new developments. Besides AZT (3'-azido-3'-deoxythymidine),[1] ddI (2', 3'-dideoxyinosine)[2] and ddC (2', 3'-dideoxycytidine)[3] have also been approved for the treatment of AIDS.[4] From the viewpoints of the structure of these drugs, they can be classified as

dideoxynucleosides. Other dideoxynucleosides, such as, d4T (2',3'-didehydro-3'-deoxythymidine),[5] ddU (2',3'-dideoxyuridine),[6] and ddT (2', 3'-dideoxythymidine)[7] have also been discovered to possess potential activity against HIV.

The mechanism of action of these drugs is generally believed to be initial phosphorylation to the corresponding 5'-phosphate , then conversion to the 5'-diphosphate, and finally to the 5'-triphosphate by cellular enzymes, kinases. When this correponding triphosphate is incorporated into the replicating viral DNA chain by HIV reverse transcriptase, the further chain elongation is inhibited by the lack of a C-3' hydroxy group.[8]

Because of the undesired side effects, the bone morrow inhibition of AZT,[9] the peripheral neuropathy of ddC and ddI,[10] reseachers were prompted to seek more active and less toxic compounds which specifically inhibit AIDS viruses. Several efforts and strategies have been made for these purposes.[11] One of the efforts focused on the modification of the sugar moiety leading to the synthesis of 2', 3'-dideoxynucleosides and their analogs (including unsaturated analogs).[12]

Both 9-[(2-hydroxyethoxy)methyl]guanine (ACV, **1**)[13] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **2**),[14] which possess an acyclic sugar moiety, have been used clinically to treat herpes simplex virus infections. Other efforts focused on the synthesis of acyclic nucleosides not only for antiherpes but also for anti-HIV purposes. 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT, **3**)[15] has been reported to exhibit anti-HIV-1 activity and to be less toxic than AZT for human bone marrow cells *in vitro*. Trinh *et al.*[16] reported thymine acyclic nucleosides (**4-7**) which were regarded as AZT analogs lacking C(1')-C(2') and C(2')-C(3') bonds. Among them, 3'-amino derivatives (**6**, **7**) were presumed to interact with the active site of reverse transcriptase, which is a prime target for the development of chemotherapeutic agents for AIDS. These observations led us to initiate a series of studies on the acyclic nucleosides.[17] Herein we would like to report our recent work on the synthesis of 1-[(1-hydroxy-2-propoxy)methyl]thymine, 6-azathymine, uracil, and 6-azauracil (**15a-15d**), which can be regarded as ddU and ddT analogs lacking the C(1')-C(2') and C(2')-C(3') bonds.



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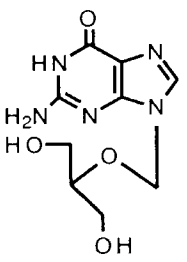

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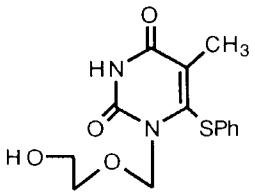

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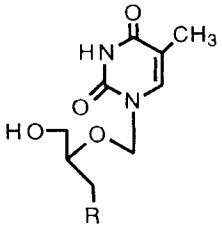
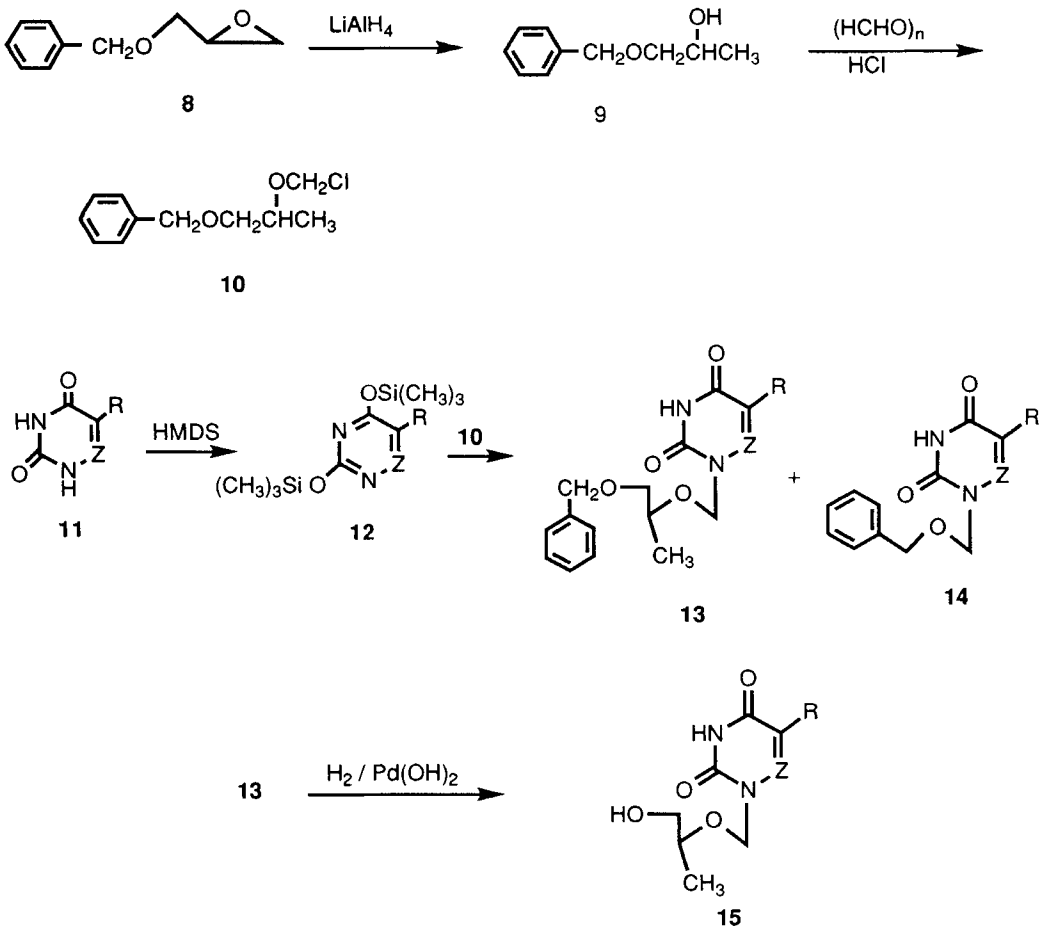


4. R=N_3
5. R=NH_2
6. R=NHCN
7. R=NHCHO

RESULTS AND DISCUSSION

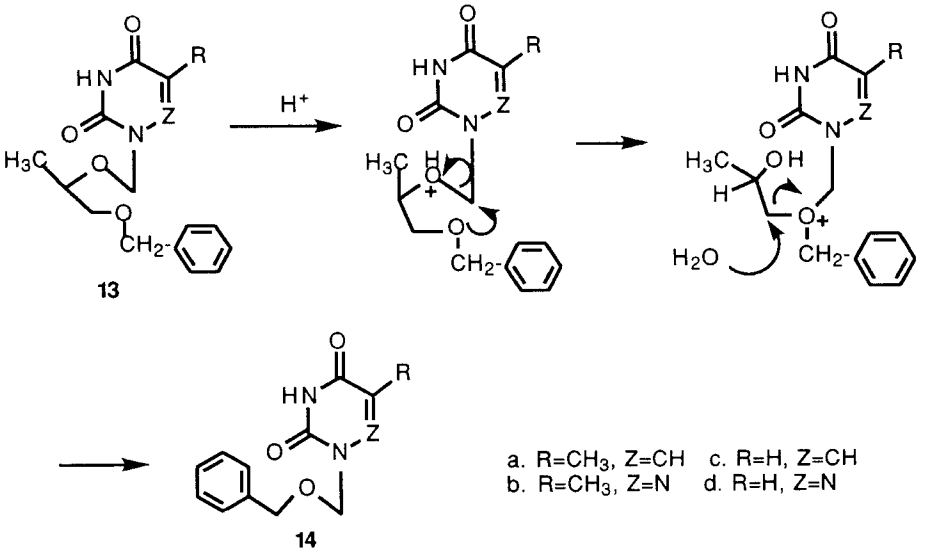
Benzyl glycidyl ether (**8**)[18] was prepared by reacting epichlorohydrin with sodium benzyloxide in dry toluene. Treatment of **8** with lithium alumimium hydride afforded 1-benzyloxy-2-propanol (**9**), which was chloromethylated with paraformaldehyde and dry HCl in anhydrous 1,2-dichloroethane at 0°C to give (1-benzyloxy-2-chloromethoxy)propane (**10**) in a good overall yield. Each of the persilylated intermediates **12a-d**, prepared by silylating the bases **11a-d** with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate, was alkylated with one molar equivalent of **10** and one molar equivalent amount of zinc iodide in dry 1,2-dichloroethane to yield 1-[(1-benzyloxy-2-propoxy)methyl]thymine, 6-azathymine, uracil, and 6-azauracil (**13a-d**) respectively as shown in Scheme 1. In addition to the expected product, a minor product was also isolated. For example, in the case of **12a**, the ^1H nmr spectrum of this minor product showed a one-proton doublet at 7.11 ppm (J =1.0 Hz) and a three-proton doublet at 1.90 ppm (J = 1.0 Hz) corresponding to the long range coupling of C_6-H and C_5-CH_3. A pair of two-proton singlets at 5.21 ppm and 4.61 ppm indicated the presence of two methylenes. The remaining five-proton singlet at 7.33 ppm was attributed to the phenyl group. The ^{13}C nmr spectrum



a. R=CH_3, Z=CH c. R=H, Z=CH
b. R=CH_3, Z=N d. R=H, Z=N

Scheme 1

again supported the presence of two methylene carbons appeared at 76.52 ppm and 72.07 ppm. The mass spectrum of this minor product showed the molecular ion at *m/z* 246, corresponding to the molecular formula, $C_{13}H_{14}N_2O_3$. These results suggested that the minor product was 1-(benzyloxymethyl)thymine (**14a**). Compounds **13a** and **14a** were separated by crystallization from chloroform-ether, **14a** was obtained as colorless crystals while **13a** remained in the solution. Compounds **14b-d** were also obtained as a minor



Scheme 2

product in each case during the reaction of **13b-d**. Hydrogenolysis of **13a-d** with palladium(II) hydroxide afforded the desired title compounds **15a-d** in a fairly good yield.

When the reaction of compounds **12a-d** with **10** was carried out in the presence of aluminium chloride as a catalyst, the rearranged products **14a-d** were predominant along with a trace amount of **13a-d**. A possible mechanism for the formation of **14a-d** from **13a-d** respectively is illustrated in Scheme 2. The rearrangement is believed to be catalyzed by Lewis acid, zinc iodide or aluminium chloride and/or hydrogen chloride.

EXPERIMENTAL SECTION

Melting points (Yanaco micro-melting-point apparatus) are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Gemini-200 or VXR-300 spectrometer; chemical shifts are measured in parts per million with respect to TMS. Ultraviolet absorption spectra were measured on a Shimadzu UV-200 spectrophotometer. Elemental analyses were recorded on a Heraeus CHN-O Rapid

analyzer. High-resolution mass spectra were recorded on a VG 70-250 spectrometer and low resolution mass spectra were recorded on a VG Quattro spectrometer. Silica gel (70-230 mesh suitable for column chromatographic use) and thin-layer chromatography on precoated silica gel 60 F-254 plates were purchased from E. Merck. UV light (254 nm) was used to detect the UV-absorption spots on TLC plates after development.

1-Benzyloxy-2-propanol(9)

Benzylglycidyl ether (**8**)[18] (6.56 g; 40 mmol) was dissolved in anhydrous THF(125 mL) and cooled in an ice bath. To this cooled solution, excess $LiAlH_4$ (0.75 g) was added in portions and stirred under reflux for 6 h. The reaction mixture was then quenched with sat. NH_4Cl and extracted with EtOAc (50 mL x 4), The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under diminished pressure to give an oily residue which was distilled (kugelrohr apparatus) to furnish pure **9** (5.54g, 70% yield), [bp 96-110°C(1-2 mmHg)]; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ : 1.12 (d,J =6 Hz, 3H, H-3), 3.0 (br.s, 1H, OH), 3.2-3.5 (m, 2H, H-1),3.96 (m, 1H, H-2), 4.52 (s, 2H, benzylic-H), 7.32 (m, 5H, aromatic H); ^{13}C-NMR($CDCl_3$, 50 MHz) δ : 18.75 (C-3), 66.43 (C-2), 73.26 (C-1), 75.85 (benzylic-C), 126.88, 127.74, 128.42, 137.99 (aromatic-C); MS m/z 166(M^+); HRMS for $C_{10}H_{14}O_2$ Calcd:166.0994. Found: 166.0993.

1-Benzyloxy-2-chloromethoxypropane (10)

1-Benzyloxy-2-propanol (**9**) (6.65 g, 40 mmol), paraformaldehyde (2.4 g) and anhydrous $CaCl_2$ (7 g) were added to dry 1,2-dichloroethane (200mL, distilled over P_2O_5). The mixture was cooled in an ice bath and bubbled with dry HCl gas which was generated from NaCl and c-H_2SO_4(95-98 %), and stirred at 0 °C for 6 h; the solution became clear at the end of reaction. The solution was warmed to room temperature and the excess HCl was carefully removed under water aspirator; then the solution was collected by filtration to remove $CaCl_2$. The filtrate was concentrated at reduced pressure to furnish **10** as a syrup. Due to the instability of this syrup, it was directly used for the next reaction without further purification.

1-[(1-Benzyloxy-2-propoxy)methyl]thymine (13a) and 1-(Benzyloxymethyl)thymine (14a)

Method A:

Thymine(**11a**) (0.63g; 5 mmol) and ammonium sulfate(530 mg) were added to hexamethyldisilazane (HMDS;100 mL). The mixture was heated at reflux with exclusion of moisture until the solution became clear (4 h). The excess HMDS was removed under reduced pressure to give silylated intermediate (**12a**) which was dissolved in dry 1,2-dichloroethane (20 mL) and to which was added chloromethylether (**10**) (5 mmol in 20 mL dichloroethane). The reaction mixture was cooled to 0°C and anhydrous zinc iodide (1.60g, 5 mmol) was added. The reaction mixture was stirred at room temperature overnight, quenched with ice water and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL x 4). The combined organic layers were washed with sat. $NaHSO_3$ (10 mL x 3; the solution became colorless), brine, dried under anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using $CHCl_3$: MeOH (100 : 5) as an eluent to give a mixture of **13a** and **14a.** The mixture was triturated with chloroform and kept in refrigerator overnight. This gave **14a** as a precipitate. After recrystallization from $CHCl_3$-Et_2O, **14a**(0.18 g, 15%) was obtained as colorless crystals; mp 130-132°C; UV : HCl(0.1 M) λmax 265 nm (ε 8500), NaOH(0.1 M)λmax 265nm (ε 6500); ^{1}H-NMR($CDCl_3$) δ : 1.90(d, J = 1 Hz, 3H, CH_3),4.61 (s, 2H, benzylic H), 5.21(s, 2H, H-1'), 7.11(d, J = 1 Hz, 1H, H-6), 7.33 (s, 5H, aromatic H), 9.57(br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 12.80 (CH_3), 72.07 (benzylic C), 76.52 (C-1'), 112.17 (C-5), 128.42, 128.67, 129.03, 137.22 (aromatic C), 139.45 (C-6), 151.85 (C-2), 164.73 (C-4); MS m/z 246(M^+); Anal. Cacld for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.12; H, 6.09; N, 10.93.

The mother liquor was evaporated and the residue was recrystallized from ethanol to obtain pure **13a** (1.03 g, 68%) as colorless crystals; mp 77-78°C; UV : HCl(0.1 M) λmax 265 nm(ε 8000), NaOH(0.1 M)λmax 265nm (ε 6500); ^{1}H-NMR($CDCl_3$) δ : 1.49 (d, J = 6.4 Hz, 3H, H-3'), 1.86(d, J = 1.0 Hz, 3H, CH_3), 3.44 (d, J = 5.3 Hz, 2H, H-5'), 3.92 (m, 1H, H-4'), 4.51 (s, 2H, benzylic H), 5.17, 5.27(dd, J =10.5 Hz, 2H, H-1'), 7.17 (d, J = 1.0 Hz, 1H, H-6), 7.31 (m, 5H,

aromatic H), 9.40 (br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 12.72 (C-3'), 17.60 (CH_3), 73.78 (C-5'), 74.55 (C-4'), 74.55 (benzylic C), 75.81 (C-1'), 111.76 (C-5), 128.03, 128.18, 128.89, 138.48 (aromatic C), 139.72 (C-6), 151.67 (C-2), 164.68 (C-4); MS m/z 304(M^+); Anal. Calcd for $C_{16}H_{20}N_2O_4$, C, 63.14; H, 6.62; N, 9.20. Found : C, 63.17; H, 6.61; N, 9.21.

Method B:

Compound **11a** (0.63g; 5 mmol) was silylated as described above to give **12a** as an oil after the evaporation of excess HMDS. **12a** was dissolved in dry 1,2-dichloroethane (20 mL) and to which was added chloromethylether **10** (5 mmol in 20 mL dichloroethane). The reaction mixture was cooled to 0°C and anhydrous aluminium chloride (0.69g; 5 mmoL) was added. The reaction mixture was stirred at room temperature overnight, quenched with ice water and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL x 4). The combined organic layers were extracted with saturated sodium bicarbonate solution(50 mL x 6). The aqueous solution was immersed in ice-bath and carefully acicified with concentrated hydrochloride untill the congo red paper change from red to blue, and then extracted with chloroform (100mL X 5). The organic solution was dried with anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography using $CHCl_3$: MeOH (100 : 5) as an eluent to give the mixture of **14a** as major and **13a** as minor component. After recrystallization from $CHCl_3$-Et_2O, pure**14a** (0.74 g, 60%) was obtained. The mother liquor was evaporated and the residue was recrystallized from ethanol to obtain pure **13a** (0.15 g, 10%).

The same procedures (method A) were adopted to convert each of the compounds **11b-d** to the respective **13b-d** as major ,and **14b-d** as minor compounds.

1-[(1-Benzyloxy-2-propoxy)methyl]-6-azathymine(13b) and **1-(Benzyloxymethyl)-6-azathymine (14b)**

The alkylated product of **12b** was purified by silica gel column to give a mixture of **13b** and **14b** which was triturated with $CHCl_3$

to give **14b** as colorless crystals. Evaporation of the mother liquor gave **13b** (0.95 g, 62%) as a colorless oil; UV : HCl(0.1 M) λmax 265 nm (ε 8100), NaOH(0.1 M)λmax 251nm (ε 6100); ^{1}H-NMR($CDCl_3$) δ : 1.17 (d, *J* = 6.4 Hz, 3H, H-3'), 2.20(s , 3H, CH_3), 3.42-3.46(m, 2H, H-5'), 4.04(m, 1H, H-4'), 4.50 (s, 2H, benzylic H), 5.34, 5.42(dd, *J* =10.6 Hz, 2H, H-1'), 7.29 (m, 5H, aromatic H), 10.36(br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 16.70 (C-3'), 17.91 (CH_3), 73.72 (C-5'), 74.77 (benzylic C), 75.37 (C-4'), 79.02 (C-1'), 128.00, 128.09, 128.86, 138.61, (aromatic C), 144.75 (C-5),149.87 (C-2), 157.37 (C-4); MS m/z 305(M^+); HR Mass for $C_{15}H_{19}N_3O_4$ Calcd : 305.1374. Found : 305.1378.

Pure **14b** (0.12 g, 10%) was obtained as colorless crystals; mp 125-127°C UV : HCl(0.1 M) λmax 260 nm (ε 8500), NaOH(0.1 M)λmax 251nm (ε 6100); ^{1}H-NMR($CDCl_3$) δ : 2.44 (s, 3H, CH_3), 4.92 (s, 2H, benzylic H), 5.59 (s, 2H, H-1'), 7.54 (m, 5H, Aromatic H), 10.22 (br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 16.72 (CH_3), 72.49 (benzylic C), 79.44 (C-1'), 128.22, 128.40, 128.86, 137.77 (aromatic C), 149.72 (C-2), 157.05 (C-4); MS m/z 247(M^+); Anal. Cacld for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00; found: C, 58.06; H,5.35; N, 16.88.

1-[(1-Benzyloxy-2-propoxy)methyl]uracil (13c) and 1-(Benzyloxymethyl)uracil (14c)

The alkylated product of **12c** was purified by silica gel column to give a mixture of **13c** and **14c** which was crystallized with EtOH to give **13c** (1.09 g, 75%) as colorless crystals. mp 68-70°C; UV : HCl(0.1 M) λmax 259 nm (ε 8500), NaOH(0.1 M)λmax 260nm (ε 7000); ^{1}H-NMR($CDCl_3$) δ : 1.16 (d, *J* = 6.4 Hz, 3H, H-3'), 3.43 (m, 2H, H-5'), 3.92 (m, 1H, H-4'), 4.51 (s, 2H, benzylic H), 5.20, 5.28 (dd, *J* =10.5 Hz, 2H, H-1'), 5.68 (d, *J* = 8 Hz, 1H, H-5), 7.31 (m, 5H, aromatic H), 7.35 (d, *J* = 8 Hz, 1H, H-6), 9.71(br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 17.17 (C-3'), 73.39 (C-5'), 74.14 (benzylic C), 74.50 (C-4'), 75.72 (C-1'), 102.74 (C-5), 127.65, 127.78, 128.45, 137.93 (aromatic C), 143.37 (C-6), 150.90 (C-2), 163.32 (C-4); MS m/z 290(M^+); Anal. Cacld for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65; found: C, 62.09; H, 6.20; N, 9.63.

Evaporation of the mother liquor to give a residual mass which was crystallized with $CHCl_3$-Et_2O to obtain pure **14c** (0.17 g, 15%)

as colorless crystals; mp 138-139°C, UV : HCl(0.1 M) λmax 260 nm (ε 8500), NaOH(0.1 M)λmax 260nm (ε 6500); ^{1}H-NMR($CDCl_3$) δ : 4.63 (s, 2H, benzylic H), 5.24 (s, 2H, H-1'), 5.75 (d, *J* = 8 Hz, 1H, H-5), 7.30(d, *J* = 8 Hz, 1H, H-6), 7.31 (m, 5H, aromatic H), 9.10(br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 72.18 (benzylic C), 76.68 (C-1'), 103.72 (C-5), 128.43, 128.76, 129.08, 137.04 (aromatic C), 143.61 (C-6), 151.62 (C-2), 164.02 (C-4); MS m/z 232(M^+); Anal. Cacld for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06; found: C, 61.77; H, 5.25; N, 12.19.

1-[(1-Benzyloxy-2-propoxy)methyl]-6-azauracil (13d) and 1-(Benzyloxymethyl)-6-azauracil (14d)

The alkylated product of **12d** was purified by silica gel column to give a mixture of **13d** and **14d** which was crystallized with $CHCl_3$-Et_2O to give **14d** as colorless crystals. Evaporation of the mother liquor gave **13d** (1.02 g, 70%) as colorless oil; UV : HCl(0.1 M) λmax 260 nm (ε 8100), NaOH(0.1 M)λmax 251nm (ε 6700); ^{1}H-NMR($CDCl_3$) δ : 1.17 (d, *J* = 6.5 Hz, 3H, H-3'), 3.43-3.46 (m, 2H, H-5'), 4.06 (m, 1H, H-4'), 4.50 (s, 2H, benzylic H), 5.34, 5.46 (dd, *J* =10.6 Hz, 2H, H-1'), 7.30 (m, 5H, aromatic H), 7.37 (s, 1H, H-5), 10.02 (br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 17.88 (C-3'), 73.82 (C-5'), 74.81 (benzylic C), 75.62 (C-4'), 79.42 (C-1'), 128.10, 128.17, 128.89, 136.05 (aromatic C), 138.50 (C-6), 148.91 (C-2), 156.83 (C-4); MS m/z 291(M^+); HRMS for $C_{14}H_{17}N_3O_4$, Calcd : 291.1218. Found : 291.1212.

Pure **14d** (0.12 g, 10%) was obtained as colorless crystals; mp 92-94°C; UV : HCl(0.1 M) λmax 260 nm (ε 8500), NaOH(0.1 M)λmax 255nm (ε 6000); ^{1}H-NMR($CDCl_3$) δ : 4.92 (s, 2H, benzylic H), 5.61 (s, 2H, H-1'), 7.54 (s, 1H, H-6), 7.62 (s, 5H, aromatic H), 9.57 (br. s. 1H, NH); ^{13}C-NMR($CDCl_3$) δ : 72.59 (benzylic C), 79.70 (C-1'), 128.22, 128.53, 128.94, 136.19 (aromatic C), 137.48 (C-5), 148.71 (C-2), 156.47 (C-4); MS m/z 233(M^+); Anal. Cacld for $C_{11}H_{11}N_3O_3$: C, 56.65; H,4.75; N, 18.02; found: C, 56.44; H,4.83; N, 17.74.

1-[(1-Hydroxy-2-propoxy)methyl]thymine (15a)

Compound **13a** (0.456 g; 1.5mmol), palladium(II) hydroxide (300 mg), cyclohexene (4 mL), an ethanol (16 mL) were refluxed for 4 h (monitored by TLC). The resulting solution was filtered and the filtrate evaporated to give a residual solid which was crystallized

with EtOH-Et_2O to afford pure **15a** (0.29 g 89%) as colorless crystals; mp 108 - 109 °C; UV : HCl(0.1M) λmax 265 nm (ε 8300), NaOH(0.1M) λmax 266nm (ε 6300); ^{1}H-NMR($CDCl_3$) δ: 1.15 (d, *J* = 6.4 Hz, 3H, H-3'), 1.92 (d, *J* =1.0 Hz, 3H, CH_3), 2.64 (br.s. 1H, OH), 3.46-3.65 (m, 2H, H-5'), 3.78-3.86 (m, 1H, H-4'), 5.16, 5.27 (dd, *J* =10.3 Hz, 2H, H-1'), 7.18 (d, *J* = 1 Hz, 1H, H-6), 9.35 (br.s. 1H, NH); ^{13}C-NMR(DMSO-d_6) δ : 12.79 (C-3'), 16.92 (CH3), 66.81 (C-5'), 75.89 (C-1'), 76.16 (C-4'), 112.22 (C-5), 139.75 (C-6), 151.89 (C-2), 164.64 (C-4); MS m/z 214(M^+); Anal. Calcd for $C_9H_{14}N_2O_4$: C 50.46, H 6.59, N 13.08. found : C, 50.24; H, 6.51; N, 13.06.

The same procedure was used to convert each of the compounds **13b-d** to the respective **15b-d**.

1-[(1-Hydroxy-2-propoxy)methyl]-6-azathymine (15b)

Pure **15b** (0.27 g 85%) was obtained as an oil; UV : HCl(0.1M) λmax 253 nm (ε 5000), NaOH(0.1M) λmax 265nm(ε 6300); ^{1}H-NMR($CDCl_3$) δ: 1.10 (d, *J* = 6.2 Hz, 3H, H-3'), 2.20 (s, 3H, CH_3), 3.41-3.59 (m, 2H, H-5'), 3.83-3.91 (m, 1H, H-4'), 5.33 (s, 2H, H-1'); 10.85 (br.s. 1H, NH). ^{13}C-NMR(DMSO-d_6) δ : 16.59 (C-3'), 16.69 (CH3), 66.65 (C-5'), 76.37 (C-1'), 78.52 (C-4'), 145.15 (C-5), 150.07 (C-2), 157.51 (C-4); MS m/z 215(M^+); HRMS for $C_8H_{13}N_3O_4$, Calcd : 215.0905. Found : 215.0902.

1-[(1-Hydroxy-2-propoxy)methyl]uracil (15c)

Pure **15c** (0.27 g 85%) was obtained as colorless crystals; mp 97-98°C(EtOH-Et_2O); UV : HCl(0.1M) λmax 259 nm (ε = 8700), NaOH(0.1M) λmax 260nm (ε 6100); ^{1}H-NMR($CDCl_3$) δ: 0.94 (d, *J* = 6.4 Hz, 3H, H-3'), 2.70 (br.s. 1H, OH), 3.22-3.39 (m, 2H, H-5'), 3.53-3.61 (m, 1H, H-4'), 4.99, 5.08(dd, *J* =10.3 Hz, 2H, H-1'), 5.49 d, *J* =7.88 Hz, 1H, H-5), 7.26 (d, *J* = 1 Hz, 1H, H-6), 10.51 (br.s. 1H, NH); ^{13}C-NMR(DMSO-d_6) δ : 16.92 (CH3), 66.00 (C-5'), 75.52 (C-1'), 75.84 (C-4'), 102.74 (C-5), 144.04 (C-6), 151.62 (C-2), 164.42 (C-4); MS m/z 214(M^+); Anal. Calcd for $C_9H_{14}N_2O_4$: C 48.00, H 6.04, N 13.99. found : C, 48.06; H, 6.10; N, 14.28.

1-[(1-Hydroxy-2-propoxy)methyl]-6-azauracil (15d)

Pure **15d** (0.27 g 89%) was obtained as an oil; UV : HCl(0.1M) λmax 252 nm (ε 5400), NaOH(0.1M) λmax 261nm (ε 4600); ^{1}H-

NMR($CDCl_3$) δ: 1.12 (d, J = 6.3 Hz, 3H, H-3'), 3.42-3.60 (m, 2H, H-5'), 3.83-3.91 (m, 1H, H-4'), 5.36 (s, 2H, H-1'), 7.39 (s, 1H, H-5); ^{13}C-NMR(DMSO-d_6) δ : 16.59 (CH_3), 66.58 (C-5'), 76.50 (C-1'), 78.81 (C-4'), 136.51 (C-5), 149.54 (C-2), 157.55 (C-4); MS m/z 201(M^+); HRMS for $C_7H_{11}N_3O_4$, Calcd : 201.0749. Found : 201.0743.

ANTIVIRAL SCREENING

Human T cell leukemia cell lines, MT-4 and MOLT-4 cells were used in this study. The reverse transcriptase assay was carried out as described by Sarin et al.[21] The results indicated that the compounds (**15a-d**) described in this manuscript were inactive against HIV-1.

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