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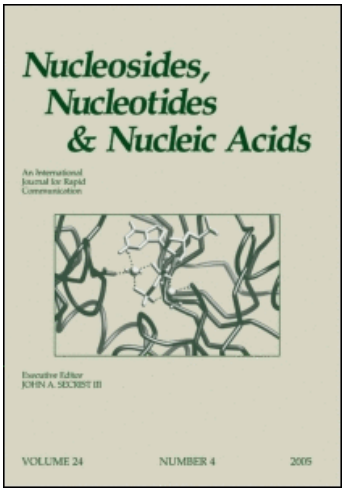

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Synthetic and Antiviral Studies of Certain Acyclic 3'-Azido-3'-Deoxythymidine (AZT) Analogues

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SYNTHETIC AND ANTIVIRAL STUDIES OF CERTAIN ACYCLIC 3'-AZIDO-3'-DEOXYTHYMIDINE (AZT) ANALOGUES

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Abstract

A direct alkylation of trimethylsilylated pyrimidines and azapyrimidines with 1-azido-3-benzyloxy-2-chloromethoxypropane gave acyclic analogues of AZT in a good overall yield. None of the compounds exhibited significant antiviral activity against human immunodeficiency virus and herpes simplex virus.

Introduction

3'-Azido-3'-deoxythymidine (AZT)[1,2] inhibits the reverse transcriptase of human immunodeficiency virus (HIV) and has already shown some benefits in acquired immunodeficiency syndrome (AIDS) patients. AZT is converted by cellular enzymes to its triphosphate and incorporated in the terminal position of DNA. Since AZT triphosphate does not have the 3'-OH of the natural substrate, DNA chain elongation is precluded.[3-5]

The discovery of acycloguanosine (Acyclovir)[6-8] and 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG)[9-11] has stimulated an

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extensive search for acyclic nucleosides that are more potent antiviral agents. In order to determine the effect of structural modification with respect to optimal biological activities, we initiated several research programs involving the syntheses of new series of acyclic nucleosides.[12-14] One of our synthetic programs was to prepare acyclic AZT analogues. Soon after we synthesized the target compounds,[15] several acyclo-AZT lacking the C(3')-C(4') bond were prepared by Scheiner and co-workers.[16] Michael-type addition of thymine to appropriate acceptors, followed by carbonyl reduction and azide replacement provided acyclic AZT analogues. A more recent synthesis of acyclo-AZT without the C(2')-C(3') bonding had been reported by Ogawa and co-workers.[17] They examined the direct conversion of dihydroxy-acyclic nucleosides to mono-azido-mono-hydroxy-acyclic nucleosides using either triphenylphosphine-carbon tetrabromide-lithium azide or triphenylphosphine-carbon tetraiodide-sodium azide. Although the azidation gave a reasonable yield, the total yield including several synthetic procedures was very low.

We now wish to report a convenient pathway for the preparation of acyclic AZT and its analogues via a direct condensation of trimethylsilylated heterocycles with 1-azido-3-benzyloxy-2-chloromethoxypropane. Their anti-HIV and anti-HSV activities were also evaluated.

Chemistry

Our strategy for the synthesis of acyclo-AZT and its analogues is based on a direct alkylation of silylated heterocycles with an azido-acyclic chloromethyl ether (3). The synthetic route for the preparation of 3 is outline in Scheme I. 1-Benzyloxypropylene oxide (1) was prepared according to a known procedure.[18] Reaction of 1 with sodium azide provided 1-azido-3-benzyloxy-2-propanol (2)[19] in 74% yield. Conversion of 2 to 3[20] was accomplished by treatment of 2 with paraformaldehyde and dry HCl in methylene chloride at 0°C for 4 hr. Racemic 3 was obtained in 92% yield which was then used for the alkylation without further purification.

The general procedure for the preparation of azido-acyclic nucleosides (6) is described in Scheme II. Thymine, uracil, 6-azathymine,[21] 6-azauracil,[22] 5-phenyl-6-azauracil,[23] or 5-benzyl-

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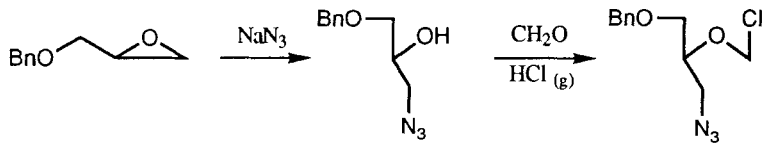
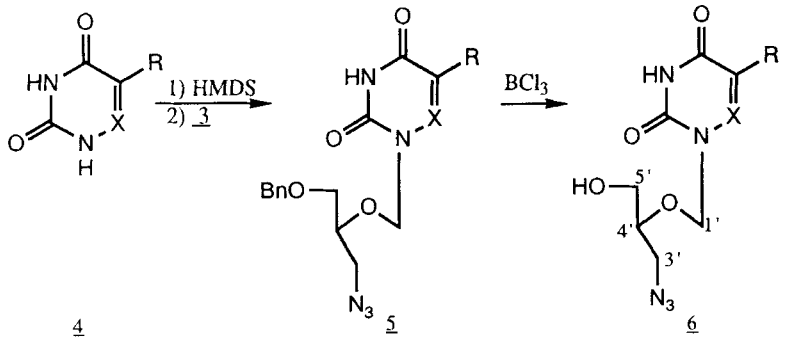


1 2 3

Scheme I



4 5 6

	X	R
a)	CH	CH_3
b)	CH	H
c)	N	CH_3
d)	N	H
e)	N	C_6H_5
f)	N	$CH_2C_6H_5$

Scheme II

6-azauracil[24] was refluxed with excess hexamethyldisilazane (HMDS) and a catalytic amount of chlorotrimethylsilane under anhydrous condition to give the corresponding trimethylsilylated intermediate as an oil in each case after the evaporation of excess HMDS. Glycosidation of each residual oil with one molar equivalent of 3 in a dry non-polar solvent (e.g. acetonitrile, benzene, toluene) gave 1-[(1-azido-3-benzyloxy-2-propoxy)methyl]uracils (5a-f), which were purified by silica gel chromatography in good yields. Debenzylation of 5 with boron trichloride in dichloromethane afforded the desired products of azido-acyclic nucleosides (6).

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Recrystallization from ethanol gave analytical pure compounds 6 in about 80% yields.

Antiviral activity

1. Anti-HIV Activity

MT_4 cells were infected with HIV1 (200 $TCID_{50}$ per 10^6 cells) and were treated with the compound 6 at concentrations 1mM and 30μM. Medium change was performed on day 4, and the new medium contained the original 6 concentration. On day 7, cytopathetic effects were evaluated and HIV1 core antigen P_{24} was detected by the HIV1 P_{24} core antigen ELISA assay (the P_{24} core antigen ELISA kit of DuPont Co. was used and performed according to the directions of the manufacturer). These compounds did not show protection at the above concentrations.

2. Anti-HSV Activity

Compounds 6a-f were also evaluated against HSV-type 2 in vitro, but no significant activities were detected.

Experimental Section

Melting points were determined on a Yanaco apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Bruker Analytic WP-100. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane as an internal standard; Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co; Infrared spectra were obtained on a Hitachi 260-30 spectrophotometer. Ultraviolet spectra were recorded on a Beckman UV-Visible spectrophotometer. All compounds were analyzed for C, H, and N. The results were within 0.4% of the calculated theoretic values.

1-Azido-3-benzyloxy-2-propanol (2). To a refluxing solution of 1-benzyloxypropylene oxide (27.2 g; 0.166 mmol) in dioxane (260 mL) was added dropwise a saturated solution of sodium azide (5 g; 0.23 mmol in 35 mL H_2O). The mixture was allowed to reflux for 35 hr, then cooled to ambient temperature to obtain a bi-layer solution. The lower layer aqueous solution was extracted with dioxane (4 x 50 mL). The extract was combined and then evaporated under

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reduced pressure to give 25.4 g (73.4%) of 2 as a yellow syrup. IR (neat) cm^{-1} : 2140 (N_3), ^1H NMR ($CDCl_3$) : δ 3.29 (m, 4H, OCH_2 & CH_2N_3), 3.79(m, 1H, CH), 4.39(s, 2H, CH_2-Ar), 7.21(m, 5H, C_6H_5).

(1-Azido-3-benzyloxy-2-propoxy)methyl chloride (3). A mixture of 2 (25.5 g, 0.12 mmol), paraformaldehyde (6 g) and dried methylene chloride (300 mL) was stirred at 0°C and dry HCl gas was bubbled through the stirred solution for 4 hr. Anhydrous calcium chloride was then added and after stirring for a few minutes the solution was collected by filtration. The filtrate was evaporated under reduced pressure to yield 28.7 g (91.5%) of 3 as a yellow syrup. ^1H NMR ($CDCl_3$) : δ 3.48(m, 4H, OCH_2 & CH_2N_3), 3.92(m, 1H, CH), 4.47(s, 2H, CH_2-C_6H_5), 5.50(s, 2H, OCH_2Cl), 7.27(m, 5H, CH_2-C_6H_5).

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1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]thymine (5a). Thymine (1.26 g, 10mmol) and chlorotrimethylsilane (2 mL) were added to hexamethyldisilazane (HMDS, 30 mL). The mixture was heated at reflux with exclusion of moisture until the solution became clear (3 hr). The excess HMDS was removed under reduced pressure to give a silylated intermediate which was dissolved in dried acetonitrile (25 mL) and to which chloromethyl ether 3 (2.6 g, 10 mmol) in dried acetonitrile (25 mL) was added. The reaction mixture was stirred at room temperature for 48 hr, (monitored by TLC) and then concentrated to give crude product which was purified by column chromatography on silica gel using ethyl acetate/chloroform (1:4) as the eluent to yield 2.01 g (58.3%) of 5a as a syrup. ^1H NMR ($CDCl_3$) : δ 1.87(s, 3H, CH_3), 3.40(m, 4H, OCH_2 & CH_2N_3), 3.93 (m, 1H, CH), 4.46(s, 2H, CH_2-C_6H_5), 5.50(s, 2H, OCH_2N), 7.21(s, 1H, aromatic CH), 7.27(m, 5H, CH_2-C_6H_5), 10.21(br s, 1H, NH).

1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]uracil (5b). A mixture of uracil (1.12 g, 10 mmol), HMDS (25 mL) and ammonium sulfate (30 mg) was heated at reflux for 3 hr to form the silylated intermediate which was then glycosidated to give crude 5b which was chromatographed on a column of silica gel using ethyl acetate/chloroform (1:1.5) as eluent to give 1.82 g (55%) of 5b. ^1H

NMR ($CDCl_3$) : δ 3.38(m, 4H, OCH_2 & CH_2N_3), 3.92(m, 1H, CH), 4.43(s, 2H, CH_2-C_6H_5), 5.22(s, 2H, OCH_2N), 7.23(m, 6H, aromatic CH & CH_2-C_6H_5), 10.03(br s, 1H, NH).

1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]-6-azathymine (5c). 5c was prepared by a method similar to that described for 5a except the glycosidation was carried out in dried benzene. After purification by ethyl acetate/chloroform (1:3) as eluent, the pure 5c separated in 52.3% yield. ^1H NMR ($CDCl_3$) : δ 1.83(s, 3H, CH_3), 3.33(m, 4H, OCH_2 & CH_2N_3), 3.98(m, 1H, CH), 4.40(s, 2H, CH_2-C_6H_5), 5.32(s, 2H, OCH_2N), 7.27(m, 5H, CH_2-C_6H_5), 10.25(br s, 1H, NH).

1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]-6-azauracil (5d). 5d was prepared by the same procedure as 5c to yield 1.70 g (51.0%) of 5d as a syrup. ^1H NMR ($CDCl_3$) : δ 3.42(m, 4H, OCH_2 & CH_2N_3), 4.05(m, 1H,CH), 4.48(s, 2H, CH_2-C_6H_5), 5.42(s, 2H, OCH_2N), 7.31(m, 5H, CH_2-C_6H_5), 7.38(s, 1H, aromatic CH).

1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]-5-phenyl-6-azauracil (5e). 5-Phenyl-6-azauracil (2.83 g, 15 mmol) was persilylated and then coupled with chloromethyl ether 3 (2.80 g, 13 mmol) in dried acetonitrile to give crude product which was column chromatographed using methanol/chloroform (1:60) as an eluent to yield 3.52 g (66.4%) of 5e. ^1H NMR ($CDCl_3$) : δ 3.28(d, 2H, CH_2N_3, J=5.7 Hz), 3.45(d, 2H, CH_2O, J=5.2 Hz), 4.11(m, 1H, CH), 4.43(s, 2H, CH_2-C_6H_5), 5.46(s, 2H, OCH_2N), 7.27-7.99(m, 10 H, 5-Ar & OCH_2-C_6H_5).

1-[(1-Azido-3-benzyloxy-2-propoxy)methyl]-5-benzyl-6-azauracil (5f). Reaction condition is similar to those utilized for the preparation of 5e furnished 3.83 g (67.3%) of 5f ^1H NMR ($CDCl_3$) : δ 3.24(d, 2H, CH_2N_3, J=5.3 Hz), 3.45(d, 2H, CH_2O, J=5.1 Hz), 3.82(s, 2H, CH_2-C_6H_5), 4.01 (m, 1H, CH), 5.34(s, 2H, OCH_2N), 7.21(br s, 10 H,CH_2-C_6H_5 & OCH_2- C_6H_5).

1-[(1-Azido-3-hydroxy-2-propoxy)methyl]thymine (6a). Compound 5a (3 mmol) in dried methylene chloride (25 mL) was cooled to -

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10°C under the exclusion of moisture. A slight excess of boron trichloride (1 M, in methylene chloride) was then added dropwise while the temperature was maintained below 0°C and the reaction was monitored by TLC to ensure completion (ca. 25 minutes). A mixture of methanol/methylene chloride (1:1, 30 mL) was added to the solution, and then the solution was allowed to warm to room temperature. After stirring for about 25 minutes, the solvent was removed by spin evaporator to a yellow oil which was crystallized from ethanol to afford 6a in 93.1% yield. mp : 99-100°C, IR (KBr) cm^{-1} : 2100 (N_3), ^1H NMR (DMSO-d_6) : δ 1.77(s, 3H, CH_3), 3.39(m, 4H, OCH_2 & CH_2N_3), 3.70(m, 1H, CH), 5.18(s, 2H, OCH_2N), 7.12(q, 1H, aromatic CH), 11.32(br s, 1H, NH), ^{13}C NMR (DMSO-d_6) : δ 11.91(CH_3), 51.18(C-3'), 60.81(C-5'), 75.59(C-1'), 78.50(C-4'), 109.23(C-5), 140.58(C-6), 151.19 (C-2), 164.27(C-4), $UV_{\lambda max}$ (log ε) : 265(3.94) (0.1 N HCl), 266(3.93) (H_2O), 266(3.76) (0.1 N NaOH). 5b-e were debenzylated by the same reaction conditions to give 6b-e, respectively.

Anal. Cald. For $C_9H_{13}N_5O_4$: C, 42.35; H, 5.10; N, 27.45. Found: C, 42.30; H, 5.10; N, 27.16.

1-[(1-Azido-3-hydroxy-2-propoxy)methyl]uracil (6b) : 85% yield, mp : 101-102 °C, IR (KBr) cm^{-1} : 2148 (N_3), ^1H NMR (DMSO-d_6) : δ 3.37(m, 4H, OCH_2 & CH_2N_3), 3.74(m, 1H, CH), 5.21(s, 2H, OCH_2N), 5.62(dd, 1H, aromatic CH), 7.71(d, 1H, aromatic CH), ^{13}C NMR (DMSO-d_6) : δ 51.14(C-3'), 60.83(C-5'), 75.82(C-1'), 78.67(C-4'), 101.64(C-5), 144.97(C-6), 151.14(C-2), 163.63(C-4), $UV_{\lambda max}$ (log ε) : 262(3.96) (0.1 N HCl), 262(3.94) (H_2O), 260(3.79) (0.1 N NaOH).

Anal. Cald. For $C_8H_{11}N_5O_4$: C, 39.83; H, 4.56; N, 29.05. Found: C, 39.68; H, 4.62; N, 29.05.

1-[(Azido-3-hydroxy-2-propoxy)methyl]-6-azathymine (6c) : 76% yield, IR (KBr) cm^{-1}: 2115 (N_3), ^1H NMR (DMSO-d_6) : δ 2.09(s,3H,CH_3), 3.36(m, 4H, OCH_2 & CH_2N_3), 3.81(m, 1H, CH), 5.28(s, 2H, OCH_2N), 12.15(br s, 1H, NH), ^{13}C NMR (DMSO-d_6) : δ 15.97(CH_3), 51.18(C-3'), 60.92(C-5'), 78.15(C-1'), 78.93(C-4'), 143.60(C-5), 149.11(C-2), 157.16(C-4), UV $_{\lambda max}$ (log ε) : 264(3.79) (0.1 N HCl), 264(3.75) (H_2O), 255(3.85) (0.1 N NaOH).

Anal. Cald. For $C_8H_{12}N_6O_4$: C, 37.50; H, 4.69; N, 32.81. Found: C, 37.41; H, 4.73; N, 32.79.

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1-[(1-Azido-3-hydroxy-2-propoxy)methyl]-6-azauracil (6d) : 79% yield, IR (KBr) cm^{-1} : 2120 (N_3), ^1H NMR (DMSO-d_6) : δ 3.37(m, 4H, OCH_2 & CH_2N_3), 3.81(m, 1H, CH), 5.32(s, 2H, OCH_2N), 7.53(s, 1H, aromatic CH), 12.36(br s, 1H, NH), ^{13}C NMR (DMSO-d_6) : δ 11.91(CH_3), 51.14(C-3'), 60.90 (C-5'), 78.48(C-1'), 79.03(C-4'), 136.03(C-5), 148.44(C-2), 157.00(C-4), $UV_{\lambda max}$ (log ε) : 265(3.81) (0.1 N HCl), 264(3.82) (H_2O), 256(3.81) (0.1 N NaOH).

Anal. Cald. For $C_7H_{10}N_6O_4$: C, 34.71; H, 4.13; N, 34.71. Found: C, 34.77; H, 4.03; N, 34.62.

1-[(1-Azido-3-hydroxy-2-propoxy)methyl]-5-phenyl-6-azauracil (6e) : 89% yield, mp : 93-95°C, IR (KBr) cm^{-1} : 2100 (N_3), ^1H NMR (DMSO-d_6) : δ 3.36(d, 2H, CH_2N_3, J=6.6 Hz), 3.50(d, 2H, CH_2O, J=4.7 Hz), 3.94(m, 1H, CH), 4.90(br s, 1H, OH), 5.44(s, 2H, OCH_2N), 7.41-7.99(m, 5H, C_6H_5), 12.40(br s, 1H, NH), ^{13}C NMR (DMSO-d_6) : δ 11.91(CH_3), 51.46(C-3'), 61.25(C-5'), 78.93(C-1'), 79.51(C-4'), 128.35, 128.48, 130.03, 132.07(aromatic-C), 141.86(C-5), 148.91(C-2), 156.76(C-4), $UV_{\lambda max}$ (log ε) : 291.3(3.98) (0.1 N HCl), 290.4(3.87) (H_2O), 278.9(3.73) (0.1 N NaOH).

Anal. Cald. For $C_{13}H_{14}N_6O_4$: C, 49.06; H, 4.40; N, 26.41. Found: C, 49.00; H, 4.41; N, 26.41.

1-[(1-Azido-3-hydroxy-2-propoxy)methyl]-5-benzyl-6-azauracil (6f) : 76% yield, IR (KBr) cm^{-1} : 2100(N_3), ^1H NMR ($CDCl_3$) : δ 3.29(d, 2H, CH_2N_3, J=5.3 Hz), 3.56(d, 2H, CH_2O, J=4.5 Hz), 3.87(br s, 3H, CH_2-C_6H_5 & CH), 5.37(s, 2H, OCH_2N), 6.21(br s, 1H, OH), 7.28(br s, 5H, C_6H_5), ^{13}C NMR ($CDCl_3$) : δ 35.73(5-CH_2Ar), 51.49(C-3'), 62.27 (C-5'), 78.91(C-1' & C-4'), 126.91, 128.46, 129.15, 135.55(aromatic-C), 146.42(C-5), 149.39(C-2), 156.26(C-4), $UV_{\lambda max}$ (log ε) : 264.2(3.80) (0.1 N HCl), 261.0(3.89) (H_2O), 253.7(3.74) (0.1 N NaOH).

Anal. Cald. For $C_{14}H_{16}N_6O_4$: C, 50.60; H, 4.82; N, 25.30. Found: C, 50.66; H, 4.75; N, 25.23.

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