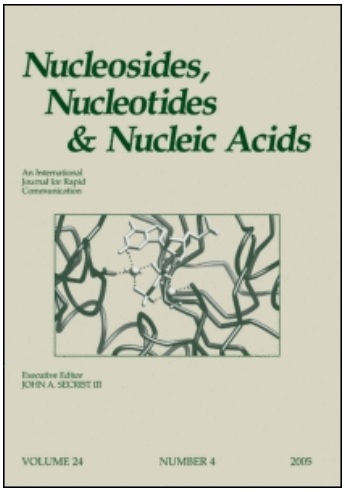

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New AZT Analogues Having 5'-Alkylsulfonyl Groups: Synthesis and Anti-HIV Activity

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NEW AZT ANALOGUES HAVING 5′-ALKYLSULFONYL GROUPS: SYNTHESIS AND ANTI-HIV ACTIVITY

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□ *New derivatives of azidothymidine (AZT) substituted by alkyl and alkylsulphonyl groups at N-3 and C-5′, respectively, have been synthesized. The new synthesized derivatives showed remarkable anti-HIV-1 and HIV-2 activity in MT-4 cells. Compounds* ***8*** *and* ***10*** *have* IC_{50} *values of 0.83 and 0.31* μ*g/mL against HIV-1 with therapeutic index of 83 and 403, respectively, and* IC_{50} *values of 0.93 and 0.29* μ*g/mL against HIV-2 with therapeutic index of 74 and 431, respectively. This means that compounds* ***8*** *and* ***10*** *were cytotoxic to MT-4 cells at* CC_{50} *of 69.2* μ*g/mL and 125* μ*g/mL, respectively.*

Keywords Anti-HIV activity; alkylsulfonyl group; azidothymidine (AZT); *N*-nucleosides; substitution reaction

INTRODUCTION

Intensive efforts are underway worldwide to develop chemotherapeutic agents effective against HIV. Attempts are continuing to discover drugs that can interfere with a stage in the viral replicative cycle without damaging the normal processes of the host cell. Azidothymidine (AZT, Retrovir)[1] is approved as an anti-HIV drug[2] targeted as an effective

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inhibitor of the HIV reverse transcriptase enzyme.[3] However, this compound is not free from undesired side effects.[4] For this reason, different laboratories continue to synthesize new series of AZT analogues such as 5′-aminocarbonylphosphonyl and aminocarbonylmethylphosphonyl diesters,[5] 5′-alkylethoxy- and aminocarbonylphosphonates,[6] amino acid carbamate derivatives,[7] and amino acid phosphoramidate monoesters[8] to establish the structure-activity relationship for the AZT antiviral activity as well as its resistance[9] to the HIV. The therapeutic (selectivity) index of some of these compounds exceeded that of the parent AZT due to their higher antiviral activity. We report here new AZT analogues having 5′-alkylsulfonyl groups as HIV-1 replication inhibitors.

RESULTS AND DISCUSSION

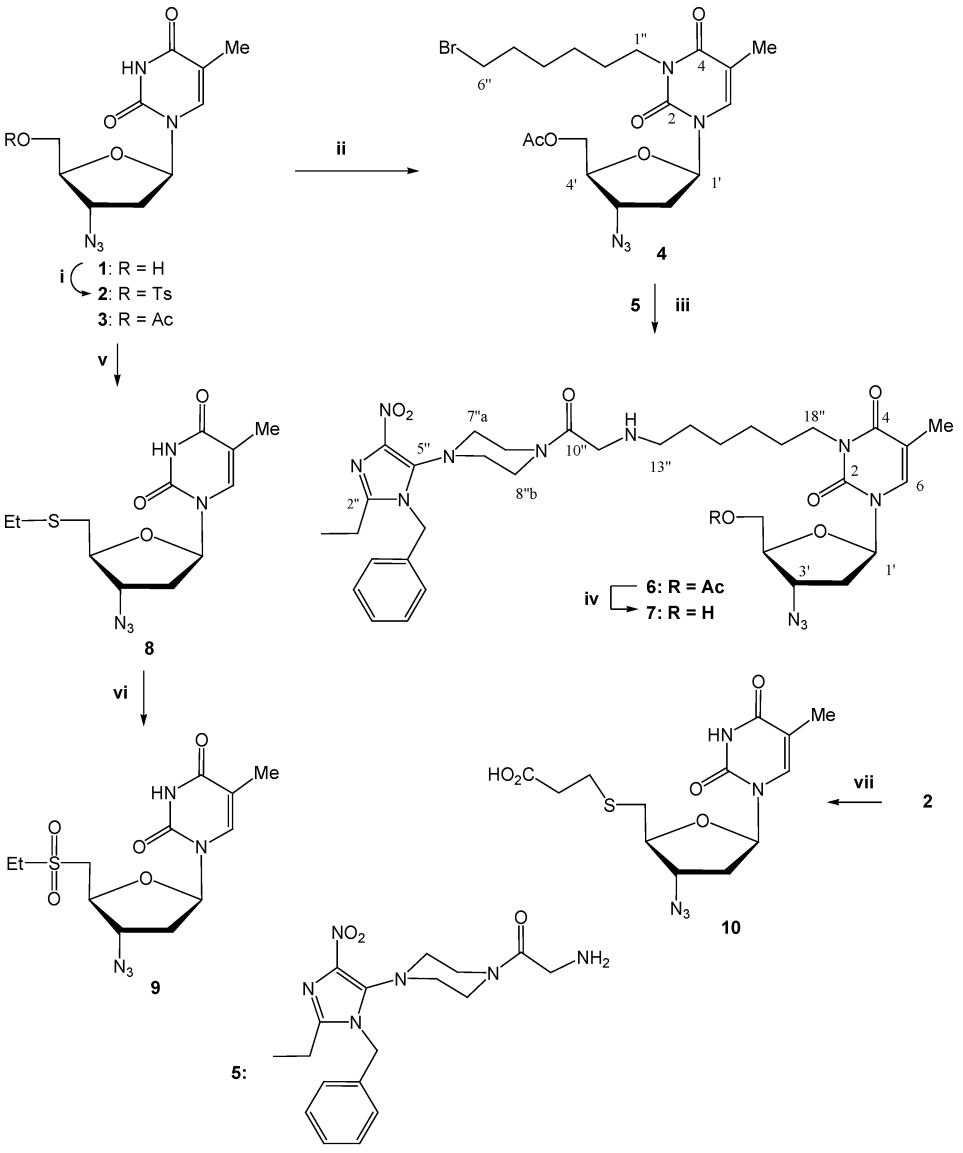
The synthesis of the title compounds is outlined in Scheme 1. Substitution of N-3 at AZT **1** was performed by conversion into the 5′-*O*-acetate derivative **3**,[10] followed by treatment with 1,6-dibromohexane in the presence of K_2CO_3 to give **4** (79%) as an amorphous solid. Treatment of **4** with the amino derivative **5**[11] in refluxing CH_2Cl_2 with Et_3N as a base afforded, after chromatography, **6** (58%), which gave the free nucleoside **7** (17%) on deblocking with NH_3/MeOH at 23°C. The low yield of **7** might be explained in term of the hydrolysis of 5″-piperazinyl-nitroimidazole group. Alternatively, AZT was converted into the 5′-*O*-sulphonate derivative **2** (67%)[12] by treatment with *p*-toluene sulphonyl chloride in pyridine at 0°C for 8 hours. Treatment of **2** with NaSEt in DMF at 120°C under argon afforded, after chromatography, **8** (62%). Oxidation of **8** with mCPBA in CH_2Cl_2 and 1 N NaOH at 23°C furnished the sulphoxide **9** (79%).

Substitution of the 5′-*O*-sulphonate group of **2** proceeded smoothly with 3-mercaptopropionic acid and afforded after chromatography **10** (62%).

The structures of the new AZT analogues have been confirmed by the ^{1}H NMR and mass spectra, which showed similar signal patterns, especially for those of the thymidine signals, but differ for the various groups at N-3 and C-5′ substituents. Compound **9** has been selected for homo- and heteronuclear NMR studies. Gradient selected HMBC[13] spectrum allowed via $^2J_{C,H}$ and $^3J_{C,H}$ couplings the assignment of most of the carbon atoms. SO_2CH_2 protons at δ_H 3.07 showed a $^3J_{C,H}$ to C-5′ at δ_C 47.9, and a $^2J_{C,H}$ correlation with $SO_2CH_2CH_3$ at δ_C 5.9. H-1′ at δ_H 6.09 was identified from its $^3J_{C,H}$ correlation with C-6 at δ_C 136.6, indicating the β-configuration of the sugar moiety. Meanwhile, C-2′ at δ_C 34.5 was identified from its $^2J_{C,H}$ correlation with H-1′.

IN VITRO ANTI-HIV-ASSAY

Compounds **7–10** were evaluated for their in vitro anti-HIV activity using the MT-4/MTT assay.[14] The 5′-ethylthioether derivative **8** did block the



SCHEME 1 Reagents and conditions: (i) TsCl/Pyr. 0°C, 8 h; (ii) Br-$(CH_2)_6$-Br, K_2CO_3, DMF, 120°C, 3 h; (iii) Et_3N, CH_2Cl_2, 5 h, 120°C; (iv) NH_2/MeOH, 23°C, 8 h (v) EtSNa, DMF, 120°C, Argon, 2 h; (vi) mCPBA, 1 N NaOH, CH_2Cl_2, 23°C, 6 h; (vii) SH-$(CH_2)_2$-CO_2H, K_2CO_3, DMF, Argon 120°C, 3.5 h.

HIV-1 (III_B) and HIV-2 (ROD) replication with IC_{50} values of 0.83 and 0.93 μg/mL, respectively, and displays 50% cytotoxicity at 69.2 μg/mL. Compound **10** inhibited the replication of HIV-1 (III_B) and HIV-2 (ROD) with IC_{50} values of 0.31 and 0.29 μg/mL, respectively, without being cytotoxic at 125 μg/mL. Meanwhile, the 5′-sulfonyl derivative **9** displayed only marginal anti-HIV activity with IC_{50} values $\geq$2.30 μg/mL against both HIV-1 and HIV-2 and having a CC_{50} of 4.4 μg/mL.

The anti-HIV activity of **8** and **10** was evaluated in thymidine kinase-deficient CEM/TK$^-$ cells. It was observed that the antiretroviral activity was completely lost in CEM/TK$^-$ cells, indicating that 5′-phosphorylation is required for activity. This means that the inhibitory activity is due to the formation of AZT, obtained from the conversion of the 5′-thioether derivatives **8** and **10.**

EXPERIMENTAL

General

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland). Microanalytical data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 300 and 600 MHz (^{1}H) and at 150.91 MHz (^{13}C) spectrometers (Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Heteronuclear assignments were verified by ^{1}H-^{13}C HMBC experiments. Mass spectra were recorded on 70 eV EI and FAB MAT 8200 spectrometers (Finnigana MAT, USA), using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrixes. Some molecular ions were detected by doping the sample with Na^+ ion.

3′-Azido-5′-*O*-(p-toluenesulfonyl)-3′-deoxythymidine (**2**). This compound was prepared from **1** as described by Lin et al.[12] The product was purified by column chromatography and crystallized by EtOH to yield **2** (69%), m.p. 125–126°C (lit. 126–128°C from EtOH).

5′-*O*-Acetyl-3′-azido-3′-deoxythymidine (**3**). This compound was prepared from **1** as described by Imawaza and Eckstein.[10] The product was purified by column chromatography as an amorphous solid. The ^{1}H NMR spectrum of **3** is identical to those of the samples prepared previously.

5′-*O*-Acetyl-3′-azido-3-(6-bromohexyl)-3′-deoxythymidine (**4**). To a solution of **3** (0.60 g, 1.94 mmol) in DMF (15 mL) was added 1,6-dibromohexane (2.84 g, 11.6 mmol) and K_2CO_3 (0.30 g, 2.13 mmol) and the mixture was stirred at 120°C for 3 hours. The mixture was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (3 × 20 mL) and water (25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed on SiO_2 column (15 g) using, in gradient, MeOH (0–3%) and $CHCl_3$ as eluent to give **4** (0.72 g, 79%) as semi-solid, m.p. 55–60°C. ^{1}H NMR ($CDCl_3$): δ 7.27 (s, ^{1}H, H-6); 6.14 (t, ^{1}H, $J_{1',2'a,b}$ = 6.1 Hz, H-1′); 4.35 (m, ^{1}H, H-3′); 4.22 (m, ^{1}H, H-4′); 4.06 (dd, ^{1}H, $J_{4',5'a}$ = 5.4 Hz, H-5a′); 3.67 (dd, ^{1}H, $J_{4',5'b}$ = 6.7 Hz, $J_{5'a,5'b}$ = 12.5 Hz, H-5b′); 3.65 (t, ^{2}H, J = 6.5 Hz, CH_2_6″); 3.42 (t, ^{2}H, J = 6.6 Hz, CH_2_1″); 2.14 (s, ^{3}H, OAc); 1.94 (m, ^{2}H, CH_2_5″); 1.62–1.25 (m, ^{6}H, CH_2_2″-4″). ^{13}C NMR ($CDCl_3$): δ 170.2 (*CO*Me); 163.1 (C_4 = O); 150.5 (C_2 = O); 133.1 (C-6); 110.4 (C-5); 86.1 (C-1′); 81.7 (C-4′), 63.3 (C-5′),

60.5 (C-3′); 41.2 [C-1″(hexyl)]; 37.7 (C-2′); 33.7 [C-6″(hexy)]; 32.5 [C-5″ (hexyl)]; 27.9 [C-4″ (hexyl)]; 27.3 (C-2″); 24.9 [C-3″(hexyl)]; 13.3 (C_5-Me). Anal. calcd. for $C_{18}H_{26}BrN_5O_5$ (472.33): C, 45.77; H, 5.55; N, 14.83. Found: C, 45.55; H, 5.39; N, 14.62; MS (FAB) *m/z*: 472/474 $(M+H)^+$.

5′-*O*-Acetyl-3′-azido-3-(6-(2-(4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl) piperazin-1-yl)-2-oxoethylamino)hexyl)-3′-deoxythymidine (6). To a solution of **4** (0.50 g, 1.06 mmol) in CH_2Cl_2 (20 mL) containing Et_3N (3 mL) was added **5** (0.47 g, 1.27 mmol) and the mixture was heated under reflux for 5 hours. After cooling, the mixture was partitioned with water (30 mL) and the aqueous extract was partitioned with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed on SiO_2 column (20 g) using, in gradient, MeOH (0–3%) and $CHCl_3$ as eluent to give **6** (0.47 g, 58%), m.p. 157–159°C. ^{1}H NMR (HMBC, 600 MHz, $CDCl_3$): 7.72 (s, ^{3}H, H-6); 7.35–7.08 (m, ^{5}H, Ar); 6.10 (t, ^{1}H, $J_{1',2'a,b}$ = 6.2 Hz, H-1′); 5.20 (s, ^{2}H, *CH*$_2$Ph); 3.81 (m, ^{1}H, H-4′); 3.74 (s, ^{2}H, CH_2_11″); 3.62 (dd, ^{1}H, $J_{4',5a}$ = 4.5 Hz, H-5′a); 3.34 (dd, ^{1}H, $J_{5'a,5b}$ = 12.0 Hz, H-5′b); 3.17 (br s., ^{2}H, CH_2_18″); 2.89 [br s., ^{4}H, CH_2_8″a,b (piperazine]; 2.67 [br s., ^{4}H, CH_2_7″a,b (piperazine.)]; 2.56 (q, ^{2}H, J = 7.1 Hz, *CH*$_2$$CH_3$); 2.55 (br s., ^{2}H, CH_2_13″); 2.37 (m, ^{1}H, H-2′a); 2.34 (m, ^{1}H, H-3′); 2.28 (m, 1H, H-2′b); 1.79 (s, ^{3}H, C_5-Me); 1.46 (br s., ^{2}H, CH_2_13″); 1.36 (br s., ^{2}H, CH_2_14″); 1.34 (br s., ^{2}H, CH_2_17″); 1.23 (m, ^{4}H, CH_2_15″, CH_2_16″); 1.12 (t, ^{3}H, J = 7.1 Hz, CH_2*CH*$_3$). ^{13}C NMR ($CDCl_3$): δ 170.7 (*CO*Me); 168.8 ($C_{10'}$ = O); 162.5 (C_4 = O); 150.2 (C_2 = O); 144.6 (C-2″); 139.0 (C-4″); 138.6 (C-6); 136.4 (Ar-C); 134.5 (C-5″); 128.7, 127.5, 126.2 (Ar-C); 108.5 (C-5); 84.1 (C-1′); 83.9 (C-4′), 60.4 (C-5′), 58.0 (C-11′); 53.4 (C-13″); 48.7 [C-7″a,b (piperazine)]; 45.6 (*CH*$_2$Ph), 45.2 (8a″, 8b″); 40.1 (C-18″); 36.2 (C-2′); 32.2 (C-14″); 28.5 (C-17″); 26.8 (C-15″); 26.1 (C-16″); 25.9 (CO*Me*); 20.0 (*CH*$_2$$CH_3$); 12.6 ($C_5$-*Me*); 10.5 ($CH_2$*CH*$_3$). Anal. calcd. for $C_{36}H_{49}N_{11}O_8$ (763.84): C, 56.61; H, 6.47; N, 20.17. Found: C, 56.40; H, 6.29; N, 19.85; MS (FAB) *m/z*: 764 $(M+H)^+$.

3′-Azido-3-(6-(2-(4-(1-benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-yl)piperazin-1-yl)-2-oxo-ethylamino)hexyl)-3′-deoxythymidine (**7**). A solution of **6** (350 mg, 0.46 mmol) was stirred in NH_3/MeOH at 23°C for 8 hours. The solution was evaporated to dryness and the residue was poured on SiO_2 column (10 g) using, in gradient, MeOH (0–5%) and $CHCl_3$ as eluent to afford **7** (56 mg, 17%), m.p. 170–173°C. ^{1}H NMR ($CDCl_3$): δ 7.60 (s, ^{1}H, H-6); 7.37–7.17 (m, ^{5}H, Ar-H); 6.18 (t, ^{1}H, $J_{1',2'a,b}$ = 6.2 Hz, H-1′); 5.21 (s, ^{2}H, *CH*$_2$Ph); 4.41 (m, ^{1}H, H-3′); 3.91 (m, ^{1}H, H-4′); 3.78 (m, ^{2}H, CH_2_18″); 3.68 (m, ^{2}H, CH_2_11′); 3.69 (dd, ^{1}H, $J_{4',5'a}$ = 5.3 Hz, H-5a′); 3.44 [m, ^{5}H, H-5b′, CH_2_8″a,b (piperazine)]; 3.02 [br s., ^{4}H, CH_2_7″a,b (piperazine)]; 2.56 (m, ^{2}H, *CH*$_2$$CH_3$, H-2′a); 2.38 (m, ^{2}H, CH_2_13″); 2.34 (dt, ^{1}H, $J_{2'a,3'}$ = 2.2 Hz $J_{2'b,3'}$ = 14.0 Hz, H-2′b); 1.83–1.31 (s, ^{3}H, C_5-Me, CH_2_14″-CH_2_17″); 1.17

(t, ^{3}H, CH_2CH_3). Anal. calcd. for $C_{34}H_{47}N_{11}O_7$ (721.81): C, 56.58; H, 6.56; N, 21.35. Found: C, 56.35; H, 6.42; N, 21.09; MS (FAB) *m/z*: 722 $(M+H)^+$.

3′-Azido-3′,5′-dideoxy-5′-ethylthiothymidine (**8**). A solution of **2** (1.0 g, 2.37 mmol) in DMF (35 mL) and EtSNa (0.30 g, 3.56 mmol) in DMF was stirred at 120°C, under argon, for 3 hours. After cooling, the mixture was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (3 × 50 mL) and water (50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness and the residue was chromatographed on SiO_2 column (20 g) using, in gradient, MeOH (0–3%) and $CHCl_3$ as eluent to give **8** (0.46 g, 62%), m.p. 125–127°C. ^{1}H NMR ($CDCl_3$) δ 9.21 (br s., ^{1}H, NH); 7.37 (s, ^{1}H, H-6); 6.16 (t, ^{1}H, $J_{1',2'a,b} = 6.5$ Hz, H-1′); 4.46 (m, ^{1}H, H-3′); 4.17 (m, ^{1}H, H-4′); 2.96 (dd, ^{1}H, $J_{4',5'a} = 4.1$ Hz, H-5′a); 2.89 (dd, ^{1}H, $J_{5'a,5'b'} = 12.0$ Hz, H-5′a); 2.63 (q, ^{2}H, $J = 7.0$ Hz, SCH_2CH_3); 2.50–2.32 (m, ^{2}H, H-2′a, H-2′b); 1.94 (s, ^{3}H, C_5-Me); 1.29 (t, ^{3}H, SCH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 163.5 ($C_4 = O$); 150.0 ($C_2 = O$); 136.5 (C-6); 109.4 (C-5); 84.2 (C-1′), 79.8 (C-4′); 62.3 (C-3′), 45.4 (C-5′), 35.0 (C-2′), 30.0 (SCH_2CH_3); 14.5 (SCH_2CH_3); 11.5 (C_5-Me). Anal. calcd. for $C_{12}H_{17}N_5O_3S$ (311.36): C, 46.29; H, 5.50; N, 22.49. Found: C, 46.12; H, 5.48; N, 22.45; MS (FAB) *m/z*: 322 $(M+H)^+$.

3′-Azido-3′,5′-dideoxy-5′-ethylsulfonylthymidine (**9**). To a solution of **8** (0.30 g, 0.96 mmol) in CH_2Cl_2 (20 mL) containing 1 N NaOH (2 mL) was added mCPBA and stirred at 23°C for 6 hours. The residue was purified on SiO_2 column, as in the previous experiment, to **9** (0.26 g, 79%), m.p. 100–105°C. ^{1}H NMR (HMBC, 600 MHz, $CDCl_3$): 11.34 (s, ^{1}H, NH); 7.53 (s, ^{1}H, H-6); 6.09 (t, ^{1}H, $J_{1',2'} = 6.2$ Hz, H-1′); 4.46 (m, 1H, H-3′); 4.17 (dd, 1H, $J_{3',4'} = 2.3$ Hz, $J_{4',5'a} = J_{4',5''} = 7.8$ Hz, H-4′); 3.75 (dd, ^{1}H, $J_{4',5'a} = 5.5$ Hz, H-5a′); 3.54 (dd, ^{1}H, $J_{4',5'b} = 3.5$ Hz, $J_{5'a,5'b} = 12.5$ Hz, H-5b′); 3.07 (q, ^{2}H, $J = 7.1$ Hz, CH_2CH_3); 2.51 (dt, ^{1}H, $J_{2'a,3'} = 7.4$ Hz, H-2′a); 2.29 (dt, ^{1}H, $J_{2'a,3'} = 2.0$ Hz $J_{2'b,3'} = 14.5$ Hz, H-2′b); 1.78 (s, ^{3}H, C_5-Me); 1.12 (t, ^{3}H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 163.6 ($C_4 = O$); 150.4 ($C_2 = O$); 136.6 (C-6); 110.0 (C-5); 84.4 (C-1′), 77.5 (C-4′); 62.9 (C-3′), 53.9 (CH_2CH_3); 47.9 (C-5′), 34.5 (C-2′), 11.9 (C_5-Me); 5.9 (CH_2CH_3). Anal. calcd. for $C_{12}H_{17}N_5O_5S$ (343.36): C, 41.98; H, 4.99; N, 20.40. Found: C, 41.79; H, 4.92; N, 20.24. MS (FAB) *m/z*: 344 $(M+H)^+$.

3-(3-Azido-3,5-dideoxythymidin-5-ylthio)propionic acid (**10**). A solution of **2** (0.80 g, 1.90 mmol) in DMF (25 mL) containing 3-mercaptopropionic acid (0.30 g, 0.71 mmol) and K_2CO_3 (0.52 g, 3.76 mmol) was stirred at 120°C, under argon, for 3.5 hours. The reaction mixture was worked up as in the preparation of compound **8** to give **10** (0.42 g, 62%), m.p. 147–150 C. ^{1}H NMR (DMSO-d_6) δ 13.0 (br s., ^{1}H, CO_2H); 8.03 (br s., ^{1}H, NH); 7.50 (s, ^{1}H, H-6); 6.15 (t, ^{1}H, $J_{1',2'a,b} = 6.5$ Hz, H-1′); 4.24 (m, ^{2}H, H-3′, H-4′); 3.88 (m, ^{2}H, H-5′a, H-5′b); 2.83 (br s., ^{2}H, SCH_2); 2.63 (br s., ^{2}H, SCH_2CH_2); 2.57–2.34 (m, ^{2}H, H-2′a, H-2′b); $J_{4',5'a} = 4.1$ Hz, H-5′a); 2.89 (dd, ^{1}H, $J_{5'a,5'b'}$

TABLE 1 In vitro anti-HIV-1[a] and HIV-2[b] of new AZT derivatives

Compd	Strain	(μg/mL) av.IC_{50}[c]	(μg/mL) CC_{50}[d]	SI[e]
7	III_B	>48	54.2 ± 5.4	<1
	ROD	>56	54.2 ± 5.4	<1
8	III_B	0.83	69.2 ± 2.9	83
	ROD	0.93	69.2 ± 2.9	74
9	III_B	≥2.30	4.4 ± 3.1	≤2
	ROD	≥2.30	4.4 ± 5.4	≤2
10	III_B	0.31	125	403
	ROD	0.29	125	431
AZT	III_B	0.00061	2.2	3611
	ROD	0.00071	2.2	3122

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.
[c]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1- and 2-induced cytopathogenic effect.
[d]Compound concentration that reduces the viability of mock-infected MT-4 cells by 50%.
[e]SI: Selectivity index (CC_{50}/IC_{50}).

= 12.0 Hz, H-5′); 2.63 (q, ^{2}H, J = 7.0 Hz, 1.80 (s, ^{3}H, C_5-Me). ^{13}C NMR (DMSO-d_6): δ 176.8 (CO_2H); 163.8 (C_4 = O); 150.1 (C_2 = O); 136.7 (C-6); 109.8 (C-5); 84.7 (C-1′), 77.3 (C-4′); 62.0 (C-3′), 45.9 (C-5′), 35.2 (C-2′), 34.2 (CH_2CO_2H); 28.4 (SCH_2); 11.8 (C_5-Me). Anal. calcd. for $C_{13}H_{17}N_5O_5S$ (355.37): C, 43.94; H, 4.82; N, 19.71. Found: C, 43.72; H, 4.69; N, 19.70. MS (FAB) *m/z*: 378 $(M+Na)^+$.

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