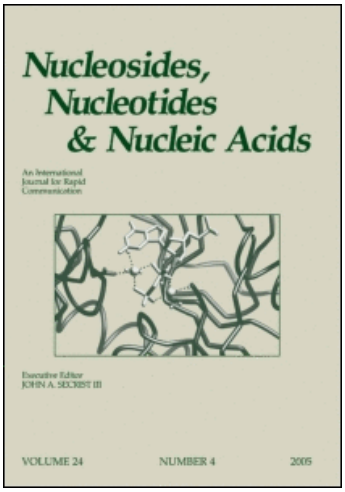

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SYNTHESIS AND *IN VITRO* ANTIVIRAL ACTIVITY EVALUATION OF 9-(2-AZIDO-2,3-DIDEOXY-β-D-*THREO*-PENTOFURANOSYL)ADENINE DERIVATIVES

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SYNTHESIS AND *IN VITRO* ANTIVIRAL ACTIVITY EVALUATION OF 9-(2-AZIDO-2,3-DIDEOXY-β-D-*THREO*-PENTOFURANOSYL)ADENINE DERIVATIVES

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ABSTRACT

9-(2-Azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)adenine derivatives (**1a**–**e**) containing a lipophilic function at the N-6 position in the purine ring were prepared and evaluated for their antiviral activity. The compounds **1a**–**e** turned out to be inactive as antiviral agents.

Dideoxynucleoside analogues in which 2′- or 3′-hydrogen in the carbohydrate part is replaced by another atom or functional group have been extensively investigated (1) in drug research and biochemistry. This is because such replacement often enhances biological activity and chemical or metabolic stability of the nucleoside. As an anti-HIV agent, 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl) adenine (FddA, **2**, (1,2) is one of the most representative examples of which C2′-β-hydrogen in the sugar moiety is substituted with fluorine. Its azido analogue, 9-(2-azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)adenine (AzddA, **3**) has also been reported with quite good anti-HIV activity (1).

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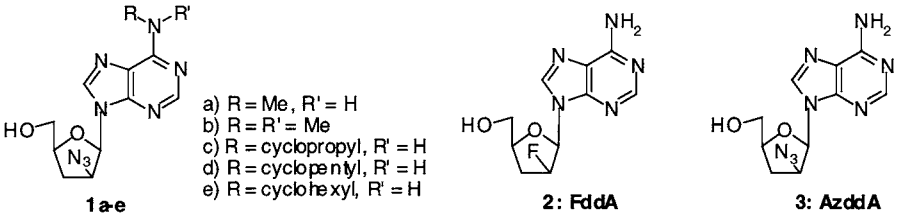

In the course of our synthetic investigations (3) on **2**, we developed a key intermediate (**6**) to synthesize C2′-β substituted purine nucleosides. The intermediate is applicable not only for the synthesis of C2′-β fluorinated dideoxynucleosides such as **2**, but also for the synthesis of C2′-β azidated dideoxynucleosides such as **3**. Since the intermediate has the chlorine at the 6 position of purine, it permits the introduction of a variety of substituents at the 6 position. Although a series of 6-substituted amino analogue of FddA has received attention (4), we became interested in the synthesis of AzddA derivatives (**1a**–**e**) containing a lipophilic function at the N-6 position of the purine ring.

Thus, 6-chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-*9H*-purine (**5**) (5) was obtained from inosine (**4**) by the modified Reese method (6) (Fig. 1). The detail of this synthesis will be reported in due course (3). The 5′-hydroxyl group in **5** was selectively protected with 3.3 equivalents of trityl chloride (TrCl) in the presence of triethylamine (Et_3N) and 4-dimethylaminopyridine (DMAP) in DMF at 50°C. After usual work-up and purification by silica gel chromatography, pure **6** was obtained in 89% yield.

The pivotal intermediate **7** was prepared through the azidation of the C2′-β position of **6** as shown in Figure 1. The 2′-hydroxyl group of **6** was first reacted with trifluoromethanesulfonic anhydride, then treated with sodium azide (NaN_3) in *N*,*N*-dimethylformamide at room temperature to afford the desired **7**. After the

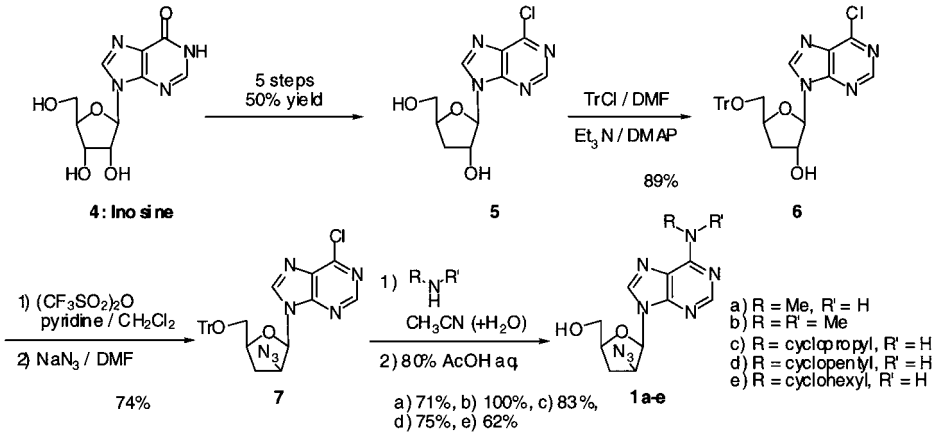

Figure 1.

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Table 1. Anti-HIV-1 and Anti-HIV-2 Activities of **1a–e**

Compound	Strain	EC50 (μg/ml)	CC50 (μg/ml)	SI
1a	III_B	>101	=100.8	<1
	ROD	107	=106.9	<1
1b	III_B	>115	=115.1	<1
	ROD	>81	=80.7	<1
1c	III_B	>125	>125	×1
	ROD	>125	>125	×1
1d	III_B	>125	>125	×1
	ROD	>125	>125	×1
1e	III_B	>125	>125	×1
	ROD	>125	>125	×1

silica gel column separation, the yield of **7** was 74% in 2 steps. The structure of **7** (7) was confirmed by IR spectrum (the 2114 cm^{-1} absorption showed the presence of the azido group) and NMR spectrum (the vicinal coupling of H1′-H2′ showed the azido substitution at the C2′-β position). After the replacement of chlorine at the 6 position of the purine ring in **7** with a variety of mono-alkyl and di-alkyl amines, the trityl group at the 5′-hydroxyl group was hydrolyzed to furnish the desired **1a–e** (8). After the preparative silica gel plate separation, the yields of **1a–e** were 62–100% in 2 steps.

Anti-HIV activity and cytotoxicity for the compounds **1a–e** were evaluated (Table 1). The results indicated that all the compounds were inactive against the replication of HIV-1 (III_B) and HIV-2 (ROD) at subtoxic concentrations in acutely infected MT-4 cells. These results may mean that compounds **1a–e** are not recognized by adenosine kinase.

In conclusion, 2′-β-azido-2′,3′-dideoxyadenosine derivatives **1a–e** containing a lipophilic function at the N-6 position in the adenine ring were prepared through the pivotal intermediate **7**. The compounds **1a–e** were evaluated against the cytopathicity of human immunodeficiency virus (HIV) in MT-4 cells. However, **1a–e** turned out to be inactive as anti-HIV agents.

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7. Compound **7**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (1H, s, H-2), 8.70 (1H, s H-8), 7.21–7.43 (15H, m, 5′O-Tr), 6.58 (1H, d, J = 6.3 Hz, H-1′), 4.95 (1H, ddd, J = 9.4, 6.9, 6.3 Hz, H-2′), 4.36–4.46 (1H, m, H-4′), 3.46-3.54 (1H, m, H-5′a), 3.20–3.36 (1H, m, H-5′b), 2.50–2.60 (1H, m, H-3′a), 2.20–2.33 (1H, m, H-3′b); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.9, 151.6, 149.6, 145.8, 143.7, 131.2, 128.4, 128.1, 127.3, 86.4, 84.6, 78.2, 65.1, 61.6, 31.4; IR (KBr): 2114 cm^{-1}; Anal. Calcd for $C_{29}H_{25}N_7O_2Cl$: C, 64.74; H, 4.50; N, 18.22. Found: C, 64.75; H, 4.50; N, 18.19.
8. Compound **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, s, H-8), 7.93 (1H, s H-2), 6.26 (1H, d, J = 6.2 Hz, H-1′), 6.08 (1H, bs, 6-NH), 4.90 (1H, bs, 5′-OH), 4.55 (1H, ddd, J = 11.2, 5.0, 3.8 Hz, H-2′), 4.30–4.39 (1H, m, H-4′), 4.10 (1H, bd, J = 12.2 Hz, H-5′a), 3.81 (1H, bd, J = 12.2 Hz, H-5′b), 3.20 (3H, bs, N-CH_3), 2.63 (1H, ddd, J = 15.4, 6.5, 6.5 Hz, H-3′a), 2.44 (1H, ddd, J = 13.1, 6.7, 6.7 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 153.1, 138.7, 120.0, 85.8, 79.5, 62.9, 62.6, 30.9, 27.6; IR (KBr): 2115 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{15}N_8O_2$ $(M + H)^+$ 291.1318, found 291.1328.
Compound **1b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s, H-8), 7.92 (1H, s H-2), 6.26 (1H, d, J = 6.1 Hz, H-1′), 4.53 (1H, ddd, J = 11.1, 4.8, 3.7 Hz, H-2′), 4.44 (1H, bs, 5′-OH), 4.29–4.36 (1H, m, H-4′), 4.09 (1H, dd, J = 12.4, 2.3 Hz, H-5′a), 3.81 (1H, bd, J = 12.4 Hz, H-5′b), 3.54 (6H, bs, $N(CH_3)_2$), 2.61 (1H, ddd, J = 15.5, 6.5, 6.5 Hz, H-3′a), 2.43 (1H, ddd, J = 12.7, 6.6, 6.6 Hz, H-3′b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 152.2, 150.0, 137.2, 120.4, 85.9, 79.3, 62.9, 62.7, 38.6, 30.7; IR (KBr): 2115 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}N_8O_2$ $(M+H)^+$ 305.1474, found 305.1479.
Compound **1c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, s, H-8), 7.93 (1H, s H-2), 6.25 (1H, d, J = 6.2 Hz, H-1′), 6.05 (1H, bs, 6-NH), 4.55 (2H, ddd, J = 11.0, 4.9, 3.7 Hz, H-2′+5′-OH), 4.31–4.38 (1H, m, H-4′), 4.11 (1H, bd, J = 12.5 Hz, H-5′a), 3.78–3.85 (1H, m, H-5′b), 3.02 (1H, bm, cyclopropane), 2.65 (1H, ddd, J = 15.5, 6.5, 6.5 Hz, H-3′a), 2.45 (1H, ddd, J = 13.2, 6.6, 6.6 Hz, H-3′b), 0.91–0.98 (2H, m, cyclopropane), 0.65–0.70 (2H, m, cyclopropane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 152.9, 148.2, 138.8, 119.0, 84.4, 79.1, 62.3, 61.9, 30.3, 23.4, 7.0, 6.8; IR (KBr): 2113 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{17}N_8O_2$ $(M + H)^+$ 317.1474, found 317.1472.
Compound **1d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (1H, s, H-8), 7.93 (1H, s H-2), 6.25 (1H, d, J = 6.1 Hz, H-1′), 5.98 (1H, bs, 6-NH), 4.61 (1H, bs, 5′-OH), 4.55 (1H, ddd, J = 10.7, 4.9, 3.7 Hz, H-2′), 4.30–4.38 (1H, m, H-4′), 4.09 (1H, dd, J = 12.6, 2.2 Hz, H-5′a), 3.81 (1H, dd, J = 12.6, 3.3 Hz, H-5′b), 2.62 (1H, ddd, J = 15.3, 6.5, 6.5 Hz, H-3′a), 2.44 (1H, ddd, J = 13.1, 6.7, 6.7 Hz, H-3′b), 2.06–2.21 (2H, m, cyclopentane), 1.50–1.84 (7H, m, cyclopentane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 153.1, 138.6, 120.1, 86.1, 79.5, 62.9, 62.6, 52.4, 33.4, 30.6, 32.7; IR (KBr): 2112 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{21}N_8O_2$ $(M + H)^+$ 345.1787, found 345.1777.

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Compound **1e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, s, H-8), 7.93 (1H, s H-2), 6.24 (1H, d, J = 6.0 Hz, H-1′), 5.80 (1H, bs, 6-NH), 4.72 (1H, bs, 5′-OH), 4.54 (1H, ddd, J = 10.8, 4.8, 3.7 Hz, H-2′), 4.29–4.38 (1H, m, H-4′), 4.09 (1H, dd, J = 12.6, 2.2 Hz, H-5′a), 3.81 (1H, dd, J = 12.6, 3.2 Hz, H-5′b), 2.62 (1H, ddd, J = 15.2, 6.4, 6.4 Hz, H-3′a), 2.44 (1H, ddd, J = 13.2, 6.7, 6.7 Hz, H-3′b), 2.04–2.16 (2H, m, cyclohexane), 1.20–1.86 (9H, m, cyclohexane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 153.1, 148.2, 138.4, 119.0, 85.0, 79.1, 62.5, 62.3, 49.1, 33.0, 30.5, 25.4, 24.7; IR (KBr): 2111 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{23}N_8O_2$ $(M + H)^+$ 359.1944, found 359.1953.

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