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Design and Synthesis of 3'-Fluoropenciclovir Analogues as Antiviral Agents

Myung-Hee Choi[1], Chong-Kyo Lee[2], and Hee-Doo Kim[1]
[1]College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea and [2]Research Institute of Chemical Technology, Taejeon 305-606, Korea

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Based on fluorine switch approach, a series of 3'-fluoropenciclovir analogues with different purine and pyrimidine bases were designed and synthesized. Direct reduction of β-fluoroester to the corresponding 3-fluoroalcohol provided an easy and new entry pathway towards the synthesis of 3'-fluoropenciclovir analogues. The synthesized 3'-fluoropenciclovir analogues were evaluated for their antiviral activities against the poliovirus, HSV-1, HSV-2 and HIV.

Key words: Antiviral, Fluorine switch, Penciclovir, 3'-Fluoropenciclovir

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INTRODUCTION

Introduction of fluorine atom(s) into the components of nucleic acids in general and nucleosides in particular frequently leads to a dramatic change in their biological activity (Pankiewicz, 2000). A fluorine atom at a sugar carbon in nucleosides causes only a minor change in the shape of the modified structure. Fluorine is a good mimic of a proton and is able to form hydrogen bonding. However, fluorine seriously affects the stereoelectronic properties of the molecule, which in turn restricts the conformational equilibria (Thibaudeau et al., 1999) of sugar-fluorinated nucleosides (Marquez et al., 1993), locking the sugar ring into a preferred conformation, as well as affect the susceptibility of cytosine and adenosine analogues for enzymatic deamination. Thus, incorporation of fluorine into biologically prevalidated drug scaffolds represents an excellent isostere of hydrogen on carbon.

Penciclovir, a carba analogue of ganciclovir, was found to be more potent and highly selective antiviral agent against herpes simplex and varicella-zoster virus (Harden et al., 1987). Penciclovir and its analogues have stimulated extensive research in the synthesis of new cyclic and acyclic carbonucleoside analogues mimicking the sugar portion of naturally occurring nucleosides (Marquez, 1996).

In the search for opportunities to exploit the benefits of fluorine in nucleoside research, we tried the fluorine-switch approach to explore new penciclovir analogues that could potentially have beneficial pharmacodynamic or pharmacokinetic properties and novel IP position (Choi and Kim, 1997; Lee et al., 2001; Park et al., 2003; Park et al., 2003). In this context, we designed and synthesized 3-fluoro-4-hydroxy-3-hydroxymethybutyl nucleosides that would mimic the features of penciclovir (Fig. 1).

MATERIALS AND METHODS

Melting points were taken on a hot-stage microscope and then uncorrected. ^{1}H-NMR spectra were obtained on a Brucker WP 80 SY (80 MHz), GEMINI 300 (300 MHz), and FT-NMR AVANCE 500 (500 MHz) spectrometer and chemical shifts were reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. UV spectra were recorded with Shimadzu UV-2101PC spectrophotometer. Infrared spectra (IR) were recorded on Shimadzu IR-435 spectrophotometer. EI mass spectra (EIMS) were run on VG Trio-2 GC-MS spectrometer at 70 eV. High resolution mass spectral (HRMS) determinations were

Correspondence to: Hee-Doo Kim, Professor of Medicinal Chemistry, College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea
Tel: 82-2-710-9567, Fax: 82-2-703-0736
E-mail: hdkim@sm.ac.kr

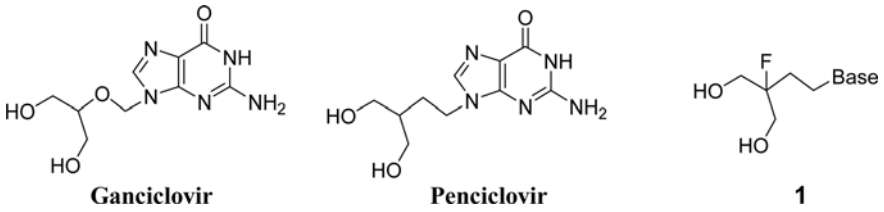


Fig. 1. Structures of ganciclovir, penciclovir, and target molecule **1**

performed at Korea Basic Science Center. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed by using forced flow of indicated solvent on Merck Kieselgel 60 (230-400 mesh). Unless otherwise noted, materials were obtained from commercially available sources and were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Dichloromethane, benzene and dimethylformamide, triethylamine were freshly distilled under a nitrogen atmosphere from calcium hydride.

Ethyl 4-(benzyloxy)-3-[(benzyloxy)methyl]-3-hydroxybutanoate (3)

To a solution of diisopropylamine (0.8 mL, 5.5 mmol) in anhydrous THF (4 mL) was added dropwise n-BuLi (1.6 M in hexane, 2.2 mL, 3.6 mmol) at -78°C. The mixture was stirred for 30 min at -78°C, and ethyl acetate (0.4 mL, 3.6 mmol) was added. After being stirred for an additional 40 min at the same temperature, bis(benzyloxy)acetone (**2**, 742.4 mg, 2.7 mmol) in THF (2 mL) was added dropwise, and the resulted reaction mixture was then stirred for 1 h at -78°C and allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with ethyl acetate (50 mL). The layer was separated, and the aqueous layer was extracted twice with ethyl acetate (30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; n-hexane/ethyl acetate = 1/1) to afford 633.8 mg (65%) of hydroxyl ester **3** as oil: IR (neat) cm^{-1} 3420, 3000, 2840, 1725, 730, 700; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.28 (s, 10H), 4.52 (s, 4H), 4.07 (q, 2H, J = 7.1 Hz), 3.69 (s, 1H), 3.52 (s, 4H), 2.63 (s, 2H), 1.19 (t, 3H, J = 7.1 Hz); EIMS m/z (relative intensity) 359 (M+H), 268 (10), 237 (9), 161 (8), 105 (10), 91 (100).

Ethyl 4-(benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutanoate (4)

To a solution of DAST (989.7 mg, 6.1 mmol) in anhydrous DCM (8 mL) was added dropwise **25** (1.8 g, 5.1 mmol) in DCM (4 mL) at -78°C. The reaction mixture was allowed to warm at room temperature. After being stirred for 30 min, reaction mixture was quenched with water (1 mL) and diluted with DCM (20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; n-hexane/ethyl acetate = 30/1) to afford 1.0 g (58%) of the title compound **4** as oil: IR (neat) cm^{-1} 3060, 3020, 2970, 2850, 1730, 740, 690; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.30 (s, 10H), 4.57 (s, 4H), 4.09 (q, 2H, J = 7.1 Hz), 3.76 (d, 4H, J = 19.3 Hz), 2.85 (d, 2H, J = 17.2 Hz), 1.20 (t, 3H, J = 7.1 Hz); EIMS m/z (relative intensity) 269 (M^+-$CH_2C_6H_5$, 1), 163 (35), 135 (24), 107 (3), 91 (100), 77 (5), 65 (6).

4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutanol (5)

To a suspension of lithium aluminium hydride (104.7 mg, 2.8 mmol), anhydrous THF (5 mL) was added dropwise the ester **4** (902.9 mg, 2.5 mmol) in THF (5 mL). The mixture was stirred for 12 h at room temperature and cooled again to 0°C. The mixture was carefully worked up by dropwise and sequential addition of 0.2 mL of water, 0.2 mL of a 15% aqueous sodium hydroxide solution and an additional 0.6 mL of water. The reaction mixture was filtered through a coarse filtration frit to remove aluminum salts, and the latter were washed three times with 8 mL portions of THF. The combined filtrates and washings were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; n-hexane/ethyl acetate = 3/1) to afford 745.1 mg (93%) of diol **5** as oil: IR (neat) cm^{-1} 3060, 3020, 730, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 10H), 4.57 (s, 4H), 3.75 (t, 2H, J = 5.9 Hz), 3.66 (d, 4H, J = 18.0 Hz), 2.03 (td, 2H, J = 19.8, 5.9 Hz); EIMS m/z (relative intensity) 317 (M^+-H), 192 (42), 107 (12), 91 (100), 77 (6), 65 (7).

4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl bromide (6)

A mixture of alcohol **5** (383.0 mg, 1.2 mmol), tri-

phenylphosphine (810.0 mg, 3.0 mmol) and *N*-bromosuccinimide (535.4 mg, 3.0 mmol) in DCM (5ml) was stirred at room temperature for 3 h and quenched by the addition of water. The mixture was diluted with DCM and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was promptly subjected to column chromatography using short column (silica gel; n-hexane/ethyl acetate = 20/1) to yield 377.2 mg (82%) of the title compound **6** as oil. This crude product was used directly for the next step without further purification: IR (neat) cm^{-1} 3045, 3005, 2895, 2885, 730, 690.

9-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl]adenine (7a)

To a stirred solution of the bromide **6** (142.5 mg, 0.4 mmol) in DMF (4 mL), adenine (100.0 mg, 0.7 mmol) and cesium carbonate (241.1 mg, 0.7 mmol) were added. The mixture was stirred at 90°C for 1 h, and the reaction was then quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc = 1:4) to afford 114.1 mg (70%) of compound **7a** as a white solid: mp 94°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 261.0 nm; IR (KBr) cm^{-1} 3260, 3100, 2900, 1665, 1600, 1570; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.73 (s, 1H), 7.30 (m, 10H), 6.57 (bs, 2H), 4.52 (s, 4H), 4.34 (t, 2H, *J* = 7.7 Hz), 3.62 (dd, 4H, *J* = 17.6, 4.3 Hz), 2.36 (td, 2H, *J* = 19.7, 7.7 Hz); EIMS *m/z* (relative intensity) 436 (M^+H, 2), 324 (29), 222 (13), 203 (12), 148 (26), 135 (38), 91 (100), 65 (22).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl]cytosine (7b)

To a stirred solution of the bromide **6** (111.0 mg, 0.3 mmol) in DMF (4 mL), cytosine (64.4 mg, 0.6 mmol) and cesium carbonate (143.4 mg, 0.4 mmol) were added. The mixture was stirred at 90°C for 2 h, and the reaction was then quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 20:1→15:1) to afford 85.2 mg (71%) of compound **7b** as a white solid: mp 182°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 275.0 nm; IR (KBr) cm^{-1} 3320, 3085, 2900, 2845, 1640, 1600; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 10H), 6.96 (bs, 2H), 5.62 (d, 1H, *J* = 7.2 Hz), 4.52 (s, 4H), 3.75 (t, 2H, *J* = 7.7 Hz), 3.62 (d, 4H, *J* = 21.0 Hz), 2.01 (td, 2H, *J* = 7.7, 19.8 Hz); EIMS *m/z* (relative intensity) 412 (M^+H), 112 (11), 105 (18), 91 (100), 65 (21).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl]thymine (7c)

To a stirred solution of the bromide **6** (86.8 mg, 0.2 mmol) in DMF (3 ml), thymine (58.0 mg, 0.5 mmol), lithium carbonate (34.0 mg, 0.5 mmol), and cesium carbonate (37.5 mg, 0.1 mmol) were added. The mixture was stirred at 90°C for 1 h until TLC showed no starting material remaining, and the reaction was then quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (silica gel, methanol/DCM = 1/100) to afford 64.9 mg (67%) of compound **7c** as a white solid: mp 82°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 269.9 nm; IR (KBr) cm^{-1} 3375, 3130, 3010, 2845, 1710, 1665; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.79 (s, 1H), 7.34-7.26 (m, 10H), 6.90 (s, 1H), 4.56 (s, 4H), 3.85 (t, 2H, *J* = 7.7 Hz), 3.63 (d, 4H, *J* = 17.7 Hz), 2.14 (td, 2H, *J* = 7.7, 19.8 Hz), 1.85 (s, 3H); EIMS *m/z* (relative intensity) 427 (M^+H), 229 (16), 139 (10), 96 (25), 91 (100), 65 (25).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl]-5-fluorouracil (7d)

To a stirred solution of the bromide **6** (108.5 mg, 0.3 mmol) in DMF (5 mL), 5-fluorouracil (74.1 mg, 0.6 mmol), lithium carbonate (63.2 mg, 0.9 mmol), and cesium carbonate (46.6 mg, 0.1 mmol) were added. The mixture was stirred at 90°C for 1 h, and the reaction was then quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (silica gel, hexane /EtOAc = 5/2) to afford 62.0 mg (51%) of title compound **7d** as a white solid: mp 90°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 273.0 nm; IR (KBr) cm^{-1} 3375, 3140, 3020, 2850, 2810, 1700, 1655; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.36-7.26 (m, 10H), 7.15 (d, 1H, *J* = 5.4 Hz), 4.56 (s, 4H), 3.86 (t, 2H, *J* = 7.5 Hz), 3.62 (d, 4H, *J* = 18.3 Hz), 2.15 (td, 2H, *J* = 7.5, 19.2 Hz); EIms *m/z* (relative intensity) 431 (M^+H), 233 (19), 143 (6), 91 (100), 65 (7).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl]-5-trifluoromethyluracil (7e)

To a stirred solution of the bromide **6** (108.5 mg, 0.3 mmol) in DMF (4 mL), 5-trifluoromethyluracil (100.9 mg, 0.6 mmol), lithium carbonate (63.2 mg, 0.9 mmol), and cesium carbonate (46.3 mg, 0.1 mmol) were added. The mixture was stirred at 90°C for 1 h, and the reaction was then quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (silica gel, hexane /ethyl acetate = 4/1) to afford 98.3 mg (72%) of title compound **7e** as a white solid: mp 132°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 264.5 nm; IR (KBr) cm^{-1} 3375, 3165, 3050, 2850, 1720, 1695; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.65 (s, 1H), 7.35-7.26 (m, 10H), 4.55 (s, 4H), 3.97 (t, 2H, *J* = 7.3 Hz), 3.61 (d, 4H, *J* = 18.3 Hz), 2.18 (td, 2H, *J* = 7.3, 19.8 Hz); EIms *m/z* (relative intensity) 481 (M^+H), 283 (11), 181 (3), 150 (3), 91 (100), 65 (7).

1-[4-(Benzyloxy)-3-[(benzyloxy)methyl]-3-fluorobutyl]uracil (7f)

A mixture of uracil (161.4 mg, 1.4 mmol), potassium carbonate (199.0 mg, 1.4 mmol) and bromide **6** (182.3 mg, 0.5 mmol) in DMSO (5mL) was stirred at 90°C for 1 day and quenched by the addition of water. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (silica gel, hexane / ethyl acetate = 3/2) to afford 166.0 mg (84%) of title compound **7f** as a white solid: mp 92°C (recrystallized from hexane-ethyl acetate); UV (MeOH) λ_{max} 264.9 nm; IR (KBr) cm^{-1} 3120, 3010, 2880, 2840, 1705, 1670; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 1H), 7.35-7.26 (m, 10H), 7.06 (d, 1H, *J* = 8.1 Hz), 5.61 (d, 1H, *J* = 6.0 Hz), 4.55 (s, 4H), 3.87 (t, 2H, *J* = 7.7 Hz), 3.62 (d, 4H, *J* = 19.2 Hz), 2.15 (td, 2H, *J* = 7.7, 19.5 Hz); EIMS *m/z* (relative intensity) 412 (M^+), 321 (51), 215 (81), 125 (31), 91 (100), 82 (43).

General procedure for debenzylation of 7a-f

A solution of the *O*-benzylated nucleosides **7a-f** (0.2-0.7mmol) in dry CH_2Cl_2 was stirred at -78°C under a nitrogen atmosphere. This solution was treated with 10 equivalent of boron trichloride (1.0 M in CH_2Cl_2) and stirred at -78°C for 1 h. Methanol was then added and the solution was allowed warm to room temperature. This solution was concentrated *in vacuo* and co-evaporated three times with methanol. The residue was purified by column chromatography (silica gel, eluted with 5~20% methanol in CH_2Cl_2).

9-[3-Fluoro-4-hydroxy-3-hydroxymethylbutyl] adenine (1a)

The compound was prepared from **7a** by the general procedure described above in 68% yield as a white solid. mp 181°C (recrystallized from methanol); UV (MeOH) λ_{max} 261.0 nm; IR (KBr) cm^{-1} 3355, 3315, 3150, 1660, 1600, 1575; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.08 (s, 2H, D_2O exchangeable), 4.97 (t, 2H, *J* = 5.7 Hz), 4.30 (t, 2H, *J* = 8.0 Hz), 3.54 (dd, 4H, *J* = 5.4, 18.3 Hz), 2.19 (td, 2H, *J* = 8.0, 19.8 Hz); EIMS m/z (relative intensity) 256 (M^+H, 9), 218 (14), 148 (100), 136 (60), 108 (50), 67 (42), 53 (32).

1-[3-Fluoro-4-hydroxy-3-hydroxymethyl butyl] cytosine (1b)

The compound was prepared from **7b** by the general procedure described above in 95% yield as a white solid. mp 167°C (recrystallized from methanol); UV (MeOH) λ_{max} 274.9 nm; IR (KBr) cm^{-1} 3340, 3120, 2940, 1670, 1615; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.55 (d, 1H, *J* = 7.2 Hz), 5.63 (d, 1H, *J* = 7.2 Hz), 6.96 (bs, 2H, D_2O exchangeable), 4.93 (t, 2H, *J* = 6.0 Hz, D_2O exchangeable), 3.75 (t, 2H, *J* = 7.8 Hz), 3.49 (dd, 4H, *J* = 6.0, 18.6 Hz), 1.90 (td, 2H, *J* = 7.8, 20.1 Hz); EIMS m/z (relative intensity) 232 (M^+H, 15), 183 (19), 164 (28), 138 (29), 125 (65), 112 (84), 96 (33), 81 (100), 69 (28); HRMS (EI) calcd for $C_9H_{14}N_3O_3F$ (M^+) 231.1019, found 231.1021.

1-[3-Fluoro-4-hydroxy-3-hydroxymethylbutyl]thymine (1c)

The compound was prepared from **7c** by the general procedure described above in 68% yield as a white solid. mp 161°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 269.9 nm; IR (KBr) cm^{-1} 3355, 3145, 3010, 2930, 1670; ^{1}H-NMR (500 MHz, DMSO-d_6 / $CDCl_3$) δ 11.09 (s, 1H, D_2O exchangeable), 7.26 (s, 1H), 4.77 (bs, 2H, D_2O exchangeable), 3.85 (t, 2H, *J* = 7.9 Hz), 3.61 (dd, 4H, *J* = 4.6, 17.6 Hz), 2.02 (td, 2H, *J* = 7.9, 19.9 Hz), 1.84 (s, 3H); EIMS *m/z* (relative intensity) 246 (M^+H, 60), 198 (54), 127 (98), 96 (100), 82 (72), 55 (81).

1-[3-Fluoro-4-hyrdoxy-3-hydroxymethybutyl]-5-fluorouracil (1d)

The compound was prepared from **7d** by the general procedure described above in 61% yield as a white solid. mp 165°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 272.1 nm; IR (KBr) cm^{-1}

3375, 3315, 2970, 2810, 1655; ^{1}H-NMR (500 MHz, DMSO-d_6 / $CDCl_3$) δ 11.70 (s, 1H, D_2O exchangeable), 7.76 (d, 1H, J = 6.3 Hz), 4.78 (bs, 2H), 3.88 (t, 2H, J = 7.6 Hz), 3.62 (d, 4H, J = 17.8 Hz), 2.06 (td, 2H, J = 7.6, 19.8 Hz); EIMS m/z (relative intensity) 251 (M^+H, 9), 143 (34), 131 (39), 114 (28), 100 (100), 82 (39), 72 (18).

1-[3-Fluoro-4-hydroxy-3-hydroxymethyl-5-trifluoromethylbutyl]uracil (1e)

The compound was prepared from **7e** by the general procedure described above in 67% yield as a white solid. mp 173°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 264.6 nm; IR (KBr) cm^{-1} 3425, 3375, 3010, 2850, 1700; ^{1}H-NMR (500 MHz, DMSO-d_6 / $CDCl_3$) δ 11.75 (s, 1H, D_2O exchangeable), 8.13 (s, 1H), 4.79 (s, 2H), 4.01 (t, 2H, J = 7.7 Hz), 3.63 (d, 4H, J = 17.6 Hz), 2.09 (td, 2H, J = 7.7, 19.8 Hz); EIMS m/z (relative intensity) 301 (M^+H, 18), 252 (24), 150 (100), 82 (59), 72 (52).

1-[3-Fluoro-4-hyrdoxy-3-hydroxymethylbutyl] uracil (1f)

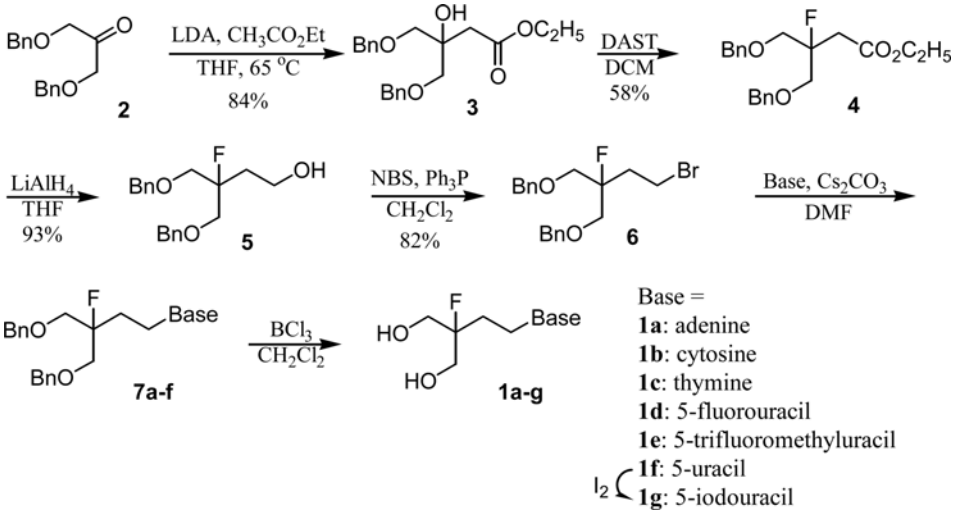
The compound was prepared from **7f** by the general procedure described above in 87 % yield as a white solid. mp 115°C (recrystallized from methanol-ethyl acetate); UV (MeOH) λ_{max} 265.7 nm; IR (KBr) cm^{-1} 3400, 3340, 3160, 3040, 2950, 1660; ^{1}H-NMR (300 MHz, DMSO-d_6/$CDCl_3$) δ 10.60 (s, 1H, D_2O exchangeable), 7.32 (d, 1H, J = 7.8 Hz), 5.61 (d, 1H, J = 8.1 Hz), 4.39 (t, 2H, J = 6.3 Hz, D_2O exchangeable), 3.92 (t, 2H, J = 7.8 Hz), 3.73-3.64 (m, 4H), 2.09 (td, 2H, J = 7.8, 20.1 Hz); EIMS m/z (relative intensity) 232 (M^+, 20), 184 (80), 125 (83), 113 (88), 96 (53), 82 (100); HRMS (EI) calcd for $C_9H_{13}N_2O_4F$ (M^+) 232.0859, found 232.0858.

1-[3-Fluoro-4-hyrdoxy-3-hydroxymethylbutyl]-5-iodouracil (1g)

To a stirred solution of compound **1f** (40.3 mg, 0.2 mmol) in dioxane (4 mL), iodine (50.8 mg, 0.2 mmol), HNO_3 (0.8 M, 0.3 mL, 0.2 mmol) were added. The mixture was stirred at 90°C for 4 h, and the reaction was cooled to 0°C and quenched by the addition of aqueous thiosulfate solution. The mixture was diluted with ethyl acetate and the organic phase was then washed several times with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 10/1) to afford 37.1 mg (60%) of compound **1g** as a white solid: mp 155°C (recrystallized from MeOH-ethyl acetate); UV (MeOH) λ_{max} 289.2 nm; IR (KBr) cm^{-1} 3300, 2980, 1665, 1690, 1655; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.42 (s, 1H, D_2O exchangeable), 8.17 (s, 1H), 4.94 (t, 2H, J = 5.7 Hz, D_2O exchangeable), 3.82 (t, 2H, J = 7.7 Hz), 3.49 (dd, 4H, J = 5.7, 18.4 Hz), 1.94 (td, 2H, J = 7.7, 20.5 Hz); EIMS m/z (relative intensity) 358 (M^+, 11), 238 (35), 208 (45), 127 (31), 82 (100), 53 (50); HRMS (EI) calcd for $C_9H_{14}N_3O_3FI$ (M^+) 357.9826, found 357.9823.

RESULTS AND DISCUSSION

Among the target compounds of 3'-fluoropenciclovir **1**, guanine analogue had already appeared in several reports and was known to be 3-fold less active than penciclovir against the herpes viruses (Bailey et al., 1988; Hannah et al., 1989). Thus, adenine and several pyrimidine analogues of 3'-fluoropenciclovir **1** were selected as target compounds for this study. The strategy for synthesizing the 3'-fluoropenciclovir analogues was based on the alkylation of either adenine or pyrimi-



Scheme 1. Synthesis of 3'-fluoropenciclovir analogues

dine bases with the bromide **6**. The bromide **6** was prepared from ketone **2** via an efficient six-step sequence in a good overall yield, as shown in Scheme 1.

1,3-Dibenzyloxy-2-propanone (**2**) was prepared as per the literature method previously reported by us in literature (Choi and Kim, 2003). 1,2-Nucleophilic addition reaction of the propanone **2** with the enolate, generated from ethyl acetate by LDA, gave the β-hydroxy ester **3** in an 84% yield. The fluorination of the β-hydroxy ester **3** was successively achieved with (diethylamino)sulfur trifluoride (DAST) at -78°C in 58% yield. Fluorinated ester **4** was then directly subjected to reduction with lithium aluminium hydride in tetrahydrofuran to give the desired fluorinated alcohol **5** in excellent yield (93%). Unexpectedly, fluorine atom, positioned β to the carbonyl group, was found to be quite stable to this basic reduction condition. Due to the possibility of dehydrofluorination of **4** under basic condition, we had initially adopted an indirect and lengthy route bypassing the fluorinated ester **4**. Conversion of primary alcohol **5** to the bromide **6** was accomplished by treatment with *N*-bromosuccinimide (NBS) and triphenylphosphine in 82% yield. The coupling of the bromide **6** with adenine in the presence of cesium carbonate provided the desired N^9-alkylated adenine **7a** in a 70% yield. Deprotection of the benzyl groups using boron trichloride in DCM gave 9-[3-fluoro-4-hydroxy-3-hydroxymethyl butyl] adenine (**1a**) in 68% yield. The pyrimidine compounds were prepared in the same lines as used with adenine. Direct alkylation of pyrimidines to bromide **6** in DMF with cesium carbonate as a basic catalyst gave the desired N^1-alkylated products. Deprotection of the benzyl protecting groups using boron trichloride gave the pyrimidines analogues of 3'-fluoropenciclovir (**1b-1f**). Finally, 5-iodouracil derivative **1g** was prepared from uracil analogue **1d** by oxidative iodination. The structures of final products **1a-g** were confirmed by UV, mass, IR, and ^{1}H-NMR spectra. The synthesized nucleosides **1a-g** were evaluated for their antiviral activity against poliovirus, HSV-1, HSV-2 and HIV. However, all compounds were found to be inactive in the assay. Presumably, the lack of activity is attributed to the internal hydrogen bonding formation between fluorine and hydroxyl group, resulting in the unfavorable conformation for phosphorylation by kinase.

In summary, we have designed and synthesized a series of 3'-fluoropenciclovir analogues with different purine and pyrimidine bases, and evaluated their antiviral activity against poliovirus, HSV-1, HSV-2 and HIV. It is also notable that direct reduction of β-fluoroester to the corresponding 3-fluoroalcohol provided the easy and new synthetic entry to 3'-fluoropenciclovir analogues.

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