Arch Pharm Res Vol 23, No 6, 559-563, 2000 Medicinal Chemistry & Natural Products

Synthesis and Antiviral Activity of Novel Methylene Cyclopropyl Nucleosides

Eun Yee Kwak[1], Joon Hee Hong[2], Chong Kyo Lee[3], and Bo Gil Choi[1]

[1]Department of Medicinal Chemistry, College of Pharmacy, Chonnam National University, Kwangju 500-757, Korea, [2]Department of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-720, Korea, and [3]Pharmaceutical Screening Center, Korea Research Institute of Chemical Technology, Taejon 306-600, Korea

(Received October 15, 2000)

Novel exomethylene cyclopropyl nucleosides were synthesized as potential antiviral agents. The key intermediate **5** was synthesized in 4 steps, from Feists acid **1** and was condensed with purine derivatives by the S_N2 type reaction to give some cyclopropyl nucleosides. The synthesized nucleosides did not showed any significant antiviral activity against HSV-1, HSV-2, HCMV, HIV-1, HIV-2, and HBV up to 100 μM.

Key words: Exomethylene cyclopropyl nucleoside, Antiviral agent, Feists acid

INTRODUCTION

The discovery of novel nucleosides as antiviral and anticancer agents has been the goal of research of nucleoside chemists for a few decades (Chu *et al.*, 1993). Structures which include analogues having furanose carbohydrate or various modifications thereof (e.g., cyclopentane and dioxa- and oxathiacyclopentane) exhibit diverse biological effects. The relevant examples are anti-HIV agents including AZT, 3TC (lamivudine) and abacavir. However, the toxicities associated with these nucleosides and the emergency of resistant viral strains prompt medicinal chemists to search for additional novel and structurally diverse compounds. Acyclonucleosides can be considered as derivative of classical nucleosides or carbo-nucleosides by "removing" one or more bonds from the cyclic moiety (Agrofolio *et al.*, 1998). Because of their structural flexibility, many of them possess biological properties despite their lack of chirality such as acyclovir (Elion *et al.*, 1977) and ganciclovir (Martin *et al.*, 1983) as antiherpetic drugs. The novel nucleosides containing a cyclopropane moiety were also synthesized as conformationally constrained analogues of acyclic nucleosides. Among them, *E*-configuration (Fig. 1a), one of cyclopropyl nucleosides showed moderate antiviral activity (Ashton *et al.*, 1988). The purine derivatives such as synadenol (Qiu *et al.*, 1998a) and synguanol (Qiu *et al.*, 1998b) (Fig. 1b) which the ribofuranoside moiety is replaced with a methylene cyclopropane structure was found to have potent antiviral activity, particularly against human cytomegalovirus (HCMV). Also, the guanine derivative (A-5021) (Fig. 1c) which was one of trisubstituted cyclopropane nucleosides with an additional hydroxymethyl group at 1'-position, showed more potent antiviral activity against HSV-1 than acyclovir but ineffective against HIV (Sekiyama. *et al.*, 1998). Encouraged by these interesting structures and antiviral activity, we have determined to synthesize a novel class of purine nucleosides comprising a rigid exomethylene cyclopropyl backbone, which is also an analogues of synadenol and synguanol.

Correspondence to: Bo Gil Choi, College of Pharmacy, Chonnam National University, Kwangju 500-757, Korea
E-mail: bgchoi@chonnam.chonnam.ac.kr

MATERIALS AND METHOD

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken on Bruker AC80 and Varian UNITY *plus* 300 spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS). The following abbreviation are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublet. Thin layer chromatography (TLC) was carried out using precoated plates with silica gel 60F 254 purchased from Merck.

Dimethyl 3-methylenecyclopropane-*trans*-1,2-dicarboxylate (2)

Feist's acid (**1**) (Gilchrist *et al.*, 1968) (4 g, 28.1 mmol) was refluxed for 24 h with methanol (200 mL) and concen-

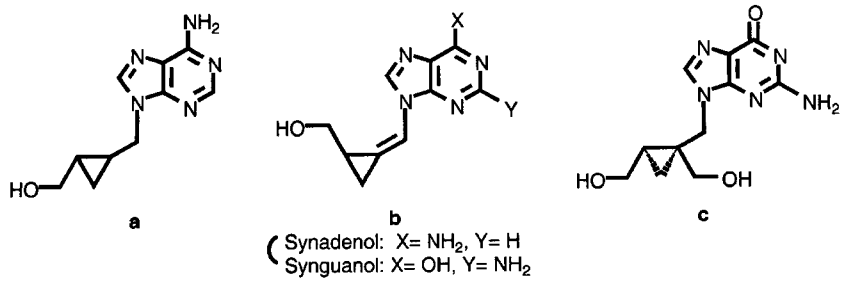


Fig. 1. Representative cyclopropyl nucleosides

trated sulfuric acid (7 drops) at room temperature. The reaction mixture was concentrated to brown oily substance which was chromatographed on silica gel column to give **2** as a pale yellowish oil (4.58 g, 95.8%). ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.40(2H, t, *J*=2.4Hz, C$\underline{H}_2$=C), 2.45(6H, s, 2×C$\underline{H}_3$), 1.61(2H, t, *J*=2.4Hz, 2×cyPr C$\underline{H}$): IR (neat) cm^{-1}: 1730 (C=O).

trans-1,2-Bis-(hydroxymethyl)-3-methylenecyclopropane (3)

Lithium aluminum hydride (1.46 g, 38.47 mmol) was added to 25 mL of dry ether. After this mixture had been stirred for 0.5 h at room temperature and cooled with an ice-bath, the dimethyl ester **2** (2.0 g, 11.75 mmol) was added to it dropwise over 1 h. After addition of dimethyl ester was complete, the mixture was refluxed gently and stirred for 6 h. After quenching the reaction with MeOH and treating with saturated NH_4Cl solution, the suspension was concentrated and dried in vaccum to give solid residue which was extracted with ether several times. The etheral solution was dried with anhydrous Na_2SO_4 and concentrated to give **3** as a pale yellowish powder (1.06 g, 78.9%). ^{1}H-NMR(300MHz, $CDCl_3$) δ 5.43(2H, t, *J*=1.86 Hz, C$\underline{H}_2$=C), 4.62(2H, bs, D_2O exchangeable, O$\underline{H}$), 3.93, 3.12 (each 2H, dd, *J*=4.32, 11.64 Hz, 2×C$\underline{H}_2$OH), 1.64 (2H, m, 2×cyPr C$\underline{H}$): IR (KBr) cm^{-1}: 3349 (OH).

trans-[1-[(*tert*-Butyldiphenylsilyl)oxymethyl]-2-hydroxymethyl]-3-methylenecyclopropane (4)

To a solution of **3** (0.2 g, 1.75 mmol) and imidazole (0.24 g, 3.52 mmol) in DMF (5 mL), *tert*-butyldiphenyl-silyl chloride (0.48 g, 1.75 mmol) was added dropwise at 0°C and the mixture was stirred at room temperature for 2 hr. After removing solvent, water was added to the residue, which was extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtrated, and concentrated under reduced pressure. The residue was chromatographed on silica gel column eluting with hexanes-EtOAc (5:1) to give **4** as a colorless oil (282 mg, 45.7%). ^{1}H-NMR(80MHz, $CDCl_3$) δ 7.73 7.29(10H, m, aromatic), 5.42 (2H, m, CH_2=C), 4.25-3.36(4H, m, C$\underline{H}_2$OH, C$\underline{H}_2$O TBDPS), 1.63(2H, m, 2×cyPr C$\underline{H}$), 1.06(9H, s, *tert*-butyl): IR (neat) cm^{-1}: 3393 (OH).

trans-1-[(*tert*-Butyldiphenylsilyl)oxymethyl]-2-[(*p*-toluenesulfonyl)oxymethyl]-3-methylenecyclopropane (5)

To a solution of **4** (3.0 g, 8.51 mmol) and DMAP (6.0 g, 49.11 mmol) in dry CH_2Cl_2 (100 mL), *p*-toluenesulfonyl chloride (4.68 g, 24.55 mmol) was added at 0°C and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ (200 mL×4), dried ($MgSO_4$), filtrated, and concentrated under reduced pressure. The residue was chromatographed on silica gel column eluting with hexanes-EtOAc (5:1) to give **5** as a white solid (3.17 g, 73.5%). ^{1}H-NMR(300MHz, $CDCl_3$) δ 7.79 7.26(14H, m, aromatic), 5.41(2H, t, *J*=1.94Hz, C$\underline{H}_2$=C), 4.02, 3.86, 3.67, 3.49 (each 1H, m, C$\underline{H}_2$N, C$\underline{H}_2$O), 2.43(3H, s, C$\underline{H}_3$-phenyl), 1.57(2H, m, 2×cyPr C$\underline{H}$), 1.02(9H, s, *tert*-butyl).

General pocedure for the synthesis of protected exo-methylenecyclopropyl nucledsides 6,7, 8, 9 and 10

A solution of **5** in DMF was added to the mixture of K_2CO_3, 18-crown-6, and purine bases (adenine, 6-chloropurine and 2-amino-6-chloropurine) in DMF, and resulting mixture was stirred at 60°C for 2 h. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtrated, and concentrated under reduced pressure, and the residue was chromatographed on a silica gel column.

9-[[[(*E*)-2-(*tert*-Butyldiphenylsilyl)oxymethyl]-3-methylenecyclopropyl]methyl]-adenine (6)

($CHCl_3$:MeOH=20:1) ; yield 59.8% ; white solid ; m. p. 132-135°C; ^{1}H-NMR(80MHz, $CDCl_3$) δ 8.37, 7.93 (each 1H, s, C^2-H, C^8-H), 7.67 7.30(10H, m, aromatic), 5.58 (2H, bs, N$\underline{H}_2$, D_2O exchangeable), 5.47, 5.45(each 1H, t, *J*= 2.0Hz, C$\underline{H}_2$=C), 4.23-3.27(4H, m C$\underline{H}_2$O, C$\underline{H}_2$N), 1.78 (2 H, m, 2×cyPr C$\underline{H}$), 0.98 (9H, s, *tert*-butyl) : IR (KBr) cm^{-1} : 3327,3148 (NH_2) : UV(MeOH) λ_{max} 262 (ε 12400).

9-[[[(*E*)-2-(*tert*-Butyldiphenylsilyl)oxymethyl]-3-methylenecyclopropyl]methyl]-6-chloropurine(7) and 9-[[[(*E*)-2-(*tert*-butyldiphenylsilyl)oxymethyl]-3-methylenecyclopropyl] methyl]-6-chloropurine(7-isomer, 8)

(Hexanes : EtOAc=1:1) ; **compound 7** ; yield 58.2% ; colorless oil ; ^{1}H-NMR(300MHz, $CDCl_3$) δ 8.37(1H, s, C^2-H), 8.25(1H, s, C^8-H), 7.607.32(10H, m, aromatic), 5.50(1H, t, *J*=1.98Hz, CH_2=C), 5.49(1H, t, *J*=2.01Hz, CH_2=C), 4.34(1H, dd, *J*=6.12, 14.32Hz, CH_2N), 4.15 (1H, dd, *J*=8.06, 14.32Hz, CH_2N), 3.85(1H, dd, *J*=5.12, 10.97Hz, CH_2O), 3.34(1H,dd, *J*=7.8, 10.97Hz, CH_2O), 1.80(2H, m, 2 × cyPr CH), 0.95(9H, s, *tert*-butyl) : IR (neat) cm^{-1}: 3070 (aromatic CH) : UV(MeOH) λ_{max} 264 (ε 8700)

compound 8; yield 24.5%; colorless oil; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 8.89(1H, s, C^2-H), 8.45(1H, s, C^8-H), 7.63 7.33(10H, m, aromatic), 5.51(1H, t, *J*=1.92Hz, CH_2=C), 5.44(1H, t, *J*=1.89Hz, CH_2=C), 4.52 4.38(2H, m, CH_2N), 3.90(1H, dd, *J*=5.01, 10.98Hz, CH_2O), 3.37(1H, dd, *J*= 8.1, 10.98Hz, CH_2O), 1.82(2H, m, 2 × cyPr CH), 1.0(9 H, s, *tert*-butyl).

2-Amino-9-[[[(*E*)-2-(*tert*-butyldiphenylsilyl)oxymethyl]-3-methylenecyclopropyl]-methyl]-6-chloropurine (9) and 2-amino-7-[[[(*E*)-2-(*tert*-butyldiphenylsilyl)-oxymethyl]-3-methylenecyclopropyl]methyl]-6-chloropurine (7-isomer, 10)

(Hexanes : EtOAc=1:1) ; **compound 9** ; yield 52.2% ; white solid; m. p. 102-104°C; ^{1}H-NMR(300MHz, $CDCl_3$) δ 7.88(1H, s, C^8-H), 7.62-7.33(10H, m, aromatic), 5.49 (1H, t, *J*=1.95Hz, CH_2=C), 5.45(1H, t, *J*=1.95Hz, CH_2 =C), 5.12(2H, bs, NH_2) ,4.11(1H, dd, *J*=6.0, 14.33 Hz, CH_2N), 3.98(1H, dd, *J*=7.65, 14.33Hz, CH_2N), 3.81 (1H, dd, *J*=5.25, 10.95Hz, CH_2O), 3.39(1H, dd, *J*=7.65, 10.95Hz, CH_2O), 1.76(2H, m, 2 × cyPr CH), 0.99(9H, s, *tert*-butyl) : IR (KBr) cm^{-1} : 33163184 (NH_2) : UV(MeOH) λ_{max} 310 (ε 5000).

compound 10 ; yield 29.2% ; white solid; ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.16(1H, s, C^8-H), 7.64-7.34(10H, m, aromatic), 5.48(1H, t, *J*=1.95Hz, CH_2=C), 5.42(1H, t, *J*=1.80Hz, CH_2=C), 5.22(2H, bs, NH_2) 4.29(1H, dd, *J* =7.2, 14.4Hz, CH_2N), 4.12(1H, dd, *J*=7.2, 14.4Hz, CH_2N), 3.86(1H, dd, *J*=5.25, 11.03Hz, CH_2O), 3.39 (1H, dd, *J* =7.8, 11.03Hz, CH_2O), 1.84, 1.76(each 1H, m, 2 × cyPr CH), 1.01(9H, s, *tert*-butyl).

General pocedure for the synthesis of exomethylenecyclopropyl nucledsides 11, 12 13, 14 and 15

A mixture of **6, 7, 8, 9, or 10** and 1.0 M *tetra-n*-butylammonium fluoride in THF was stirred at room temperature for 2 h. After the mixture was concentrated under reduced pressure, the residue was chromatographed on silica gel column.

9-[(*E*)-(2-Hydroxymethyl-3-methylenecyclopropyl)methyl] adenine (11)

($CHCl_3$: MeOH=5:1) ; yield 99% ; white solid ; m. p. 198-199°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 8.19, 8.14 (each 1H, s, C^2-H, C^8-H), 7.17(2H, s, NH_2), 5.46(1H, s, CH_2 =C), 5.38(1H, s, CH_2=C), 4.70(1H, t, *J*=5.55Hz, OH), 4.24(1H, dd, *J*=6, 14.03Hz, CH_2N), 4.03(1H, dd, *J*=7.65, 14.03Hz, CH_2N), 3.44,3.17(each 1H, m, CH_2O), 1.80 (2 H, m, 2 × cyPr CH) : IR (KBr) cm^{-1} : 32743162 (OH, NH_2) : UV(MeOH) λ_{max} 262 (ε 8700).

9-[(*E*)-(2-Hydroxymethyl-3-methylenecyclopropyl)methyl]-6-chloropurine(12) and 7-[(*E*)-(2-hydroxymethyl-3-methyl-enecyclopropyl)methyl]-6-chloropurine (7-isomer, 13)

($CHCl_3$: MeOH=10:1) ; **compound 12** ; yield 99% ; white solid ; m. p. 96-98°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 8.80,8.87(each 1H, s, C^2-H, C^8-H), 5.48, 5.41(each 1H, s, CH_2=C), 4.68(1H, t, *J*=5.55Hz, OH), 4.46(1H, dd, *J*=5.85,14.25Hz, CH_2N), 4.16(1H, dd, *J*=8.25, 14.25Hz, CH_2N), 3.49, 3.11(each 1H, m, CH_2O), 1.86(2H, m, 2 × cyPr CH) : IR (KBr) cm^{-1} : 3312 (OH) : UV(MeOH) λ_{max} 264 (ε 7400).

compound 13 ; yield 99% ; white solid ; m. p. 216-218°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 8.28,7.96(each 1H, s, C^2-H, C^8-H), 5.46,5.36(each 1H, s, CH_2=C), 4.69 (1H, t, *J*=5.7Hz, OH), 4.48(1H, dd, *J*=6.15,13.86Hz, CH_2N), 4.19(1H, dd, *J*=8.4,13.86Hz, CH_2N), 3.43, 3.15 (each 1H, m, CH_2O), 1.87,1.79(each 1H, m, cyPr CH) : IR (KBr) cm^{-1} : 3356 (OH) : UV(MeOH) λ_{max} 256 (ε 8100).

2-Amino-9-[(*E*)-(2-hydroxymethyl-3-methylenecyclopropyl)methyl]-6-chloropurine (14) and 2-amino-7-[(*E*)-(2-hydroxymethyl-3-methylenecyclopropyl)methyl]-6-chloropurine (7-isomer, 15)

($CHCl_3$:MeOH=5:1) ; **compound 14** ; yield 99% ; white solid ; m. p. 183-185°C; ^{1}H-NMR (300MHz, DMSO-d_6) δ 8.28(1H, s, C^8-H), 6.89(2H, bs, NH_2), 5.47,5.40(each 1H, s, CH_2=C), 4.69(1H, t, *J*=5.4Hz, OH), 4.17(1H, dd, *J*=5.85,14.25Hz, CH_2N), 3.92(1H, dd, *J*=7.95,14.25Hz, CH_2N), 3.47, 3.14(each 1H, m, CH_2O), 1.79(2H, m, 2 × cyPr CH):IR (KBr) cm^{-1} : 33263221 (OH, NH_2) : UV (MeOH) λ_{max} 310 (ε 11900)

compound 15 ; yield 99% ; white solid ; m. p. decomposed from 148°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 8.4 2(1H, s, C^8-H), 6.80(2H, bs, NH_2), 5.47,5.36(each 1H, s, CH_2=C), 4.72(1H, t, *J*=5.4, OH), 4.45(1H, dd, *J*=5.85, 14.48Hz, CH_2N), 4.19(1H, dd, *J*=8.1,14.48Hz, CH_2N), 3.49, 3.14(each 1H, m, CH_2O), 1.87,1.75(each 1H, m, cyPr CH) : IR (KBr) cm^{-1} : 34463196 (OH, NH_2) : UV (MeOH) λ_{max} 322 (ε 4200).

9-[(*E*)-(2-Hydroxymethyl-3-methylenecyclopropyl)methyl] hypoxanthine (16)

A mixture of **12** (190 mg, 0.76 mmol), 2-mercaptoethanol (0.22 mL, 3.14 mmol), and $NaOCH_3$ (169 mg, 3.14 mmol) in methanol (30 mL) was refluxed for 20 h. The mixture was then cooled, neutralized with glacial AcOH, and concentrated under reduced pressure. The residue was chromatographed on silica gel column eluting with $CHCl_3$-

MeOH (5:1) to give **16** as a white solid (100 mg, 56.7%) m. p. 212-213°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 12.26 (1H, bs, C^6-OH), 8.14, 8.03(each 1H, s, C^2-H, C^8-H), 5.46, 5.38(each 1H, s, CH_2=C), 4.70(1H, t, J=5.4Hz, CH_2OH), 4.24(1H, dd, J=5.6, 14.25Hz, CH_2N), 4.03(1H, dd, J=7.8, 14.25Hz, CH_2N), 3.46(1H, m, CH_2O), 3.16(1H, m, CH_2O), 1.79 (2H, m, 2 × cyPr CH) : IR (KBr) cm^{-1} : 3371 (OH), 1677 (lactam C=O) : UV(MeOH) λ_{max} 250 (ε 19200).

9-[(*E*)-(2-Hydroxymethyl-3-methylenecyclopropyl)methyl] guanine (17)

By the same procedure used for **16**, the compound **17** was obtained from **14** in 21.5% yield as a white solid. m. p. 257°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 10.56(1H, bs, C^6-OH), 7.73(1H, s, C^8-H), 6.43(2H, bs, NH_2), 5.46, 5.39(each 1H, s, CH_2=C), 4.7(1H, t, J=5.55, OH), 4.01 (1H, dd, J=5.7, 14.18Hz, CH_2N), 3.84(1H, dd, J=7.65, 14.18Hz, CH_2N), 3.44, 3.18(each 1H, m, CH_2O), 1.75, 1.73(each 1H, m, cyPr CH): IR (KBr) cm^{-1} : 3150 3174 (OH, lactam NH, NH_2), 1687 (lactam C=O) : UV (MeOH) λ_{max} 254 (ε 8500).

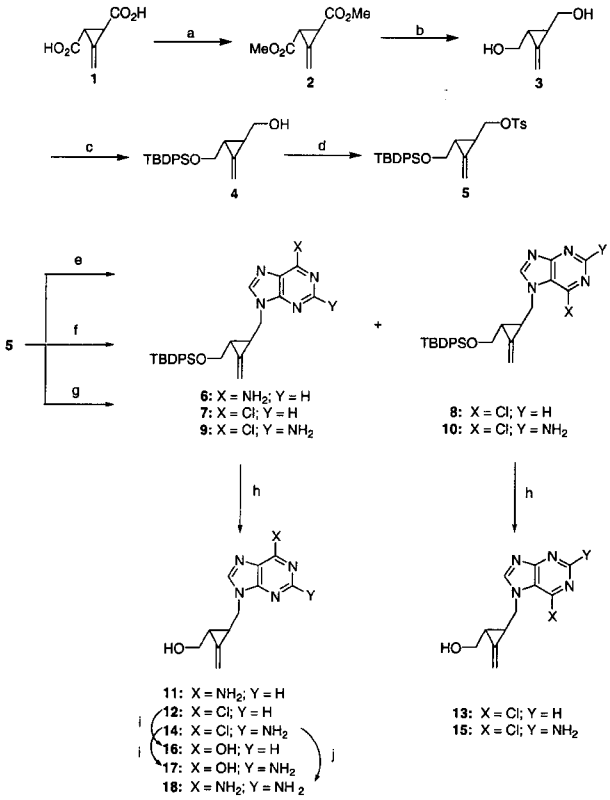
2,6-Diamino-9-[(*E*)-(2-hydroxymethyl-3-methylenecyclopropyl)methyl]purine (18)

A mixture of **14** (150 mg, 0.56 mmol) and NH_3/MeOH (40 mL) was heated at 90°C in a steel bomb for 24 hr. After the solvent was removed under reduced pressure, the residue chromatographed on silica gel column eluting with $CHCl_3$-MeOH (5:1) to give **18** as a white solid (110 mg, 79.1%). m. p. 209-210°C; ^{1}H-NMR(300MHz, DMSO-d_6) δ 7.75(1H, s, C^8-H), 6.62, 5.75(each 2H, bs, 2 × NH_2), 5.46, 5.39(each 1H, s, CH_2 =C), 4.7(1H, t, J=5.55, OH), 4.02(1H, dd, J=6, 14.1Hz, CH_2N), 3.85(1H, dd, J=7.5, 14.1Hz, CH_2N), 3.43, 3.19(each 1H, m, CH_2O), 1.75 (2H, m, 2 × cyPr CH) : IR (KBr) cm^{-1} : 34573170 (OH, NH_2) : UV(MeOH) λ_{max} 256 (ε 7100), 282 (ε 8800).

RESULTS AND DISCUSSION

Synthesis

In order to synthesize the desired nucleosides, Feists acid (**1**) was selected as starting material (Scheme 1). Treatment of the Feists acid with methanol and catalytic sulfuric acid gave diester **2**, which was reduced to diol **3** with lithium aluminum hydride in anhydrous ether solvent by refluxing. The diol **3** was carefully protected by sterically demanding *tert*-butyldiphenylsilyl group, and the mono-protected compound **4** was separated by silica gel column chromatography. In order to alkylate the sugar moiety by S_N2 type reaction, the compound **4** was activated to tosylate intermediate using *p*-toluenesulfonyl chloride in CH_2Cl_2 in the presence of DMAP at 0°C. The tosylate **5**



Reagents: a) cat.H_2SO_4, methanol; b) LAH, ether; c) TBDPSCl, imidazole, CH_2Cl_2 ; d) *p*-TsCl DMAP, CH_2Cl_2 ; e) adenine, K_2CO_3, 18-crown-6, DMF; f) 6-chloropurine, K_2CO_3, 18-crown-6, DMF; g) 2-amino-6-chloropurine, K_2CO_3, 18-crown-6, DMF; h) *n*-Bu_4NF, THF; i) $NaOCH_3$, 2-mercaptoethanol, methanol; j) NH_3/methanol

Scheme 1. Synthesis of exomethylene cyclopropyl nucleosides

was coupled with adenine, 6-chloropurine and 2-amino-6-chloropurine in the presence of potassium carbonate and 18-crown-6 in DMF at 60°C to prepare the protected cyclopropyl nucleosides **6**, **7** and **9**, respectively, and the 7-isomers (**8** and **10**) were also obtained. The compounds **6**, **7**, **8**, **9**, and **10** were deprotected by *n*-Bu_4NF in THF to give the final nucleosides **11**, **12**, **13**, **14**, and **15**. The compounds **12** and **14** were hydrolyzed with mercaptoethanol and sodium methoxide under reflux in methanol to obtain hypoxanthine derivative **16** and guanine derivative **17**, respectively. Treatment of the compound **14** with ammonia in methanol at 90°C gave the 2,6-diaminopurine nucleoside **18**.

In vitro antiviral activity of exomethylene cyclopropyl nucleosides

The final purine nucleosides (**9**, **10**, **11**, **12**, **13**, **14**, **15**, **16**, **17**, and **18**) were tested against HSV-I, HSV-2, HCMV, HIV-1, HIV-2 and HBV , but none of them showed any significant antiviral activity up to 100 μM. The results showed the addition of exomethylene moiety to the cyclo-

propyl nucleoside(Fig. 1a) was not available to maintain its activity *in vitro*.

ACKNOWLEDGEMENTS

We thank Dr. Jong Ryu Choi and his colleagues (LG Chemical Co.) for anti-HBV testing.

REFERENCES

Agrofoglio, L. A. and Challand, S. R. *Acyclic, Carbocyclic and L-Nucleosides*; Kluwer Academic Publisher; Dordrecht, 1998.

Ashton, A. T., Meurer, L. C., Cantone, C. L., Field, A. K., Hannah, J. Karkas, J. D., Liou, R., Patel, G. F., Perry, H. C., Wagner, A. F., Walton E., and Tolman, R. L. Synthesis and antiherpetic activity of (±)-9-[[(Z)-2-(Hydroxymethyl) cyclopropyl]methyl]guanine and related compounds, *J. Med. Chem.*, 31, 2304-2315 (1988).

Chu, C. K. and Baker, D. C., (Eds), *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Plenium Press: New York, 1993.

Elion, G. B., Furman, P. A., Fyfe, J. A., de Miranda, P., Beauchamp, L., and Schaeffer, H. J. Selectivity of action of antiherpetic agent, 9-(2-hydroxyethoxymethyl) guanine, *Proc. Natl. Acad. Sci. USA.*, 74, 5716-5720 (1977).

Gilchrist, T. L., and Rees, C. W., Synthesis of 3-Bromo-2-pyrones and their Reactions with Bases, *J. Chem. Soc.*, 769 (1968)

Martin, J. C., Dvorak, C. A., Smee, D. F., Matthews, T. R., Julien, P. H. and Verheyden, J. P. H., 9-[(1,3-Dihydroxy-2-propyloxy)methyl]guanine: A new potent and selective antiherpetic agent. *J. Med. Chem.*, 26, 759-761 (1983).

Qiu, Y. -L., Hempel, A., Camerman, N., Camerman, A., Geiser, F., Ptak, R. G., Brietenbach, J. M., Kira, T., Li., L., Gullen, E., Cheng, Y. -C., Drach, J. C., and Zemlicka, J., (*R*)-(-)-and (*S*)-(+)-synadenol : synthesis, absolute configuration, and enantioselectivity of antiviral effect, *J. Med. Chem*, 41, 5257 (1998a).

Qiu, Y. -L., Ksebati, M. B., Ptak, R. G., Fan, B. Y., Breitenbach, J. M., Lin, J. -S., Cheng, Y. -C., Kern, E. R., Drach, J. C., and Zemlicka, J., (*Z*)-and (*E*)-2-((Hydroxymethyl)-clopropylidene)methyladenine and guanine: new nucleoside analogues with a broad-spectrum antiviral activity, *J. Med. Chem.*, 41, 10-23 (1998b).

Sekiyama, T., Hatsuya, S., Tanaka, Y., Uchiyama, M., Ono, N., Iwayama, S., Oikawa, M., Suzuki, K., Okunishi, M., and Tsuji, T., Synthesis and antiviral activity of novel acyclic nucleosides : Discovery of a cyclopropyl nucleoside with potent inhibitory activity against herpesviruses, *J. Med. Chem.*, 41, 1284-1298 (1998).