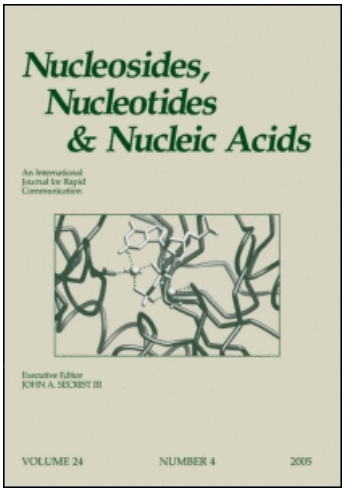


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# SYNTHESIS AND ANTIVIRAL ACTIVITY OF NOVEL EXOMETHYLENE CYCLOPROPYL NUCLEOSIDES

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## ABSTRACT

Novel cyclopropyl nucleosides were synthesized as potential antiviral agents. The key intermediate **5**, prepared from Feist's acid **1** was condensed with purine derivatives by the $S_N2$ type reaction. All the synthesized compounds were evaluated for antiviral activity.

The discovery of novel nucleosides as antiviral and anticancer agents has been the goal of research of nucleoside chemist for a few decades (1). 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. Removal of part or parts of nucleosides furanose moiety resulting in a substantial simplification of the structure led in many cases to new antiviral agents of significant therapeutic potency.

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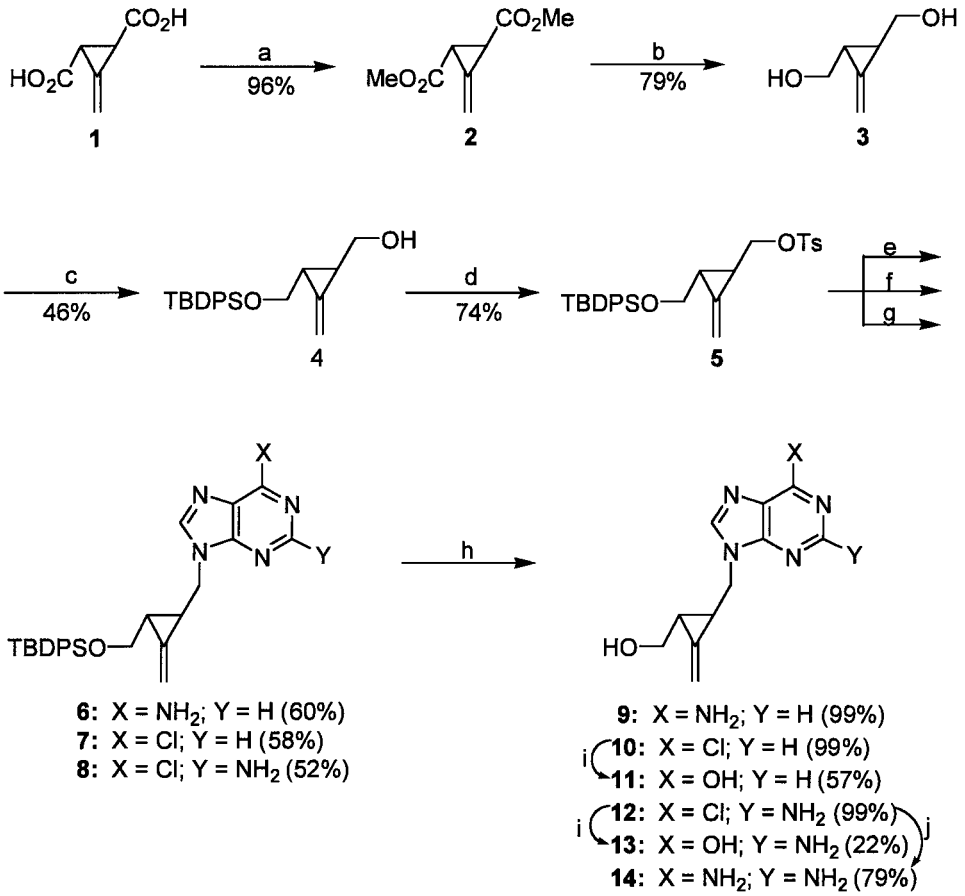


***Scheme.*** Reagents: a) cat.$H_2SOH_4$, methanol, 25°C, 18 h; b) LAH, ether, 0°C to reflux; c) TBDPSCI, imidazole, $CH_2Cl_2$, 0°C, 1.5 h; d) *p*-TsCl, DMAP, $CH_2Cl_2$, 0°C i h; e) adenine, $K_2CO_3$, 18-crown-6, DMF, 60°C, 3 h; f) 6-chcloropurine, $K_2CO_3$, 18-crown-6, DMF, 60°C, 3 h; g) 2-amino-6-chloropurine, $K_2CO_3$, 18-crown-6, DMF, 60°C, 2 h; h) *n*-$Bu_4NF$, THF, rt, 2 h; i) $NaOCH_3$, 2-mercaptoethanol, methanol, reflux, 20 h; j) $NH_3$/methanol, 90°C, 24 h.

Acyclonucleosides can be considered as derivative of classical nucleosides or carbonucleosides by "removing" one or more bonds from the cyclic moiety (2). Because of their structural flexibility, many of them possess biological properties despite their lack of chirality such as acyclovir (3) and ganciclovir (4) as antiherpetic drugs. Recently, Zemlicka *et al*. described a new class of nucleoside analogues in which the ribofuranoside moiety is replaced with a methylene-cyclopropane structure (5). Among them, purine derivatives such as synadenol (6) and synguanol (5) exhibit potent antiviral activity, particularly against human cytomegalovirus (HCMV). Also, trisubstituted cyclopropane nucleosides with an additional hydroxy-methyl group at 1′-position were prepared by Sekiyama *et al* (7). Among them, the guanine derivative (A-5021) showed more potent antiviral activity against HSV-1 than acyclovir and penciclovir and comparable for varicella zoaster virus (VZV) but ineffective





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against HIV. Encouraged by these interesting structure and antiviral activity, we have determined to synthesize a novel class of nucleosides comprising a rigid exomethylene cyclopropyl backbone.

In order to synthesize the desired nucleosides, Feist's acid (8) **1** was selected as starting material (Scheme). Treatment of the Feist's 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*-toluene sulfonyl chloride in $CH_2Cl_2$ in the presence of DMAP at 0°C. The tosylate **5** 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 obtain the protected cyclopropyl nucleosides **6**, **7**, and **8**, respectively, and the 7-isomers were also synthesized in the case of **7** and **8**. Compounds **6**, **7**, and **8** were deprotected by *n*-$Bu_4NF$ in THF to give the final nucleosides **9** (9), **10** (10), and **12** (11). Compounds **10** and **12** were hydrolyzed with mercaptoethanol and sodium methoxide under reflux in methanol to obtain hypoxanthine derivative **11** (12) and guanine derivative **13** (13), respectively. Treatment of compound **12** were with ammonia in methanol at 90°C gave 2,6-diaminopurine nucleoside **14** (14).

In summary, we have synthesized novel exomethylene cyclopropyl purine nucleosides. The key intermediate **5**, prepared from Feist's acid **1** was condensed by the $S_N2$ type reaction. From the synthesis, several purine nucleoside analogues have been obtained and their structures have been investigated by various spectroscopical studies. However, none of the evaluated compounds showed any significant antiviral activity against HSV-1, HSV-2, HCMV, HIV-1, HIV-2, and HBV up to 100 $\mu$M.

## ACKNOWLEDGMENT

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9. Compound **9**: white solid; m. p. 198–199°C; IR (KBr) $cm^{-1}$ : 3274–3162 (OH, $NH_2$); UV (MeOH) $\lambda_{max}$ 262 ($\varepsilon$ 8700); $^1$H-NMR (300 MHz, DMSO-$d_6$) $\delta$ 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, $J$ = 5.5 Hz, OH), 4.24 (1H, dd, $J$ = 6, 14.0 Hz, $CH_2$N), 4.03 (1H, dd, $J$ = 7.6, 14.0 Hz, $CH_2$N), 3.44, 3.17 (each 1H, m, $CH_2$O), 1.80 (2H, m, 2 × cyPr CH).
10. Compound **10**: white solid ; m. p. 96–98°C; IR (KBr) $cm^{-1}$ : 3312 (OH) : UV (MeOH)$\lambda_{max}$ 264 ($\varepsilon$ 7400); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 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, $J$ = 5.55 Hz, OH), 4.46 (1H, dd, $J$ = 5.8, 14.2 Hz, $CH_2$N), 4.16 (1H, dd, $J$ = 8.2, 14.2 Hz, $CH_2$N), 3.49, 3.11 (each 1H, m, $CH_2$O), 1.86(2H, m, 2 × cyPr CH).
11. Compound **11**: white solid; m. p. 212–213°C; IR (KBr) $cm^{-1}$ : 3371 (OH), 1677 (lactam C=O); UV (MeOH) $\lambda_{max}$ 250 ($\varepsilon$ 19200); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 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, $J$ = 5.4 Hz, $CH_2$OH), 4.24(1H, dd, $J$ = 5.6, 14.2 Hz, $CH_2$N), 4.03 (1H, dd, $J$ = 7.8, 14.2 Hz, $CH_2$N), 3.46 (1H, m, $CH_2$O), 3.16 (1H, m, $CH_2$O), 1.79 (2H, m, 2 × cyPr CH).
12. Compound **12**: white solid ; m. p. 183–185°C; IR (KBr) $cm^{-1}$ : 3326–3221 (OH, $NH_2$); UV (MeOH) $\lambda_{max}$ 310 ($\varepsilon$ 11900); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 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, $J$ = 5.4 Hz, OH), 4.17 (1H, dd, $J$ = 5.8, 14.2 Hz, $CH_2$N), 3.92 (1H, dd, $J$ = 7.9, 14.2 Hz, $CH_2$N), 3.47, 3.14(each 1H, m, $CH_2$O), 1.79 (2H, m, 2 × cyPr CH).
13. Compound **13**: white solid. m. p. 257°C; IR (KBr) $cm^{-1}$ : 3150–174 (OH, lactam NH, $NH_2$), 1687 (lactam C=O) : UV (MeOH) $\lambda_{max}$ 254 ($\varepsilon$ 8500).$^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 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, $J$ = 5.5, OH), 4.01 (1H, dd, $J$ = 5.7, 14.2 Hz, $CH_2$N), 3.84 (1H, dd, $J$ = 7.6, 14.2 Hz, $CH_2$N), 3.44, 3.18 (each 1H, m, $CH_2$O), 1.75, 1.73 (each 1H, m, cyPr CH).
14. Compound **14**: white solid; m. p. 209–210°C; IR (KBr) $cm^{-1}$ : 3457–3170 (OH, $NH_2$); UV (MeOH) $\lambda_{max}$ 256 ($\varepsilon$ 7100), 282 ($\varepsilon$ 8800); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 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, $J$ = 5.5, OH), 4.02 (1H, dd, $J$ = 6.0,14.1 Hz, $CH_2$N), 3.85 (1H, dd, $J$ = 7.5, 14.1 Hz, $CH_2$N), 3.43, 3.19 (each 1H, m, $CH_2$O), 1.75 (2H, m, 2 × cyPr CH).






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