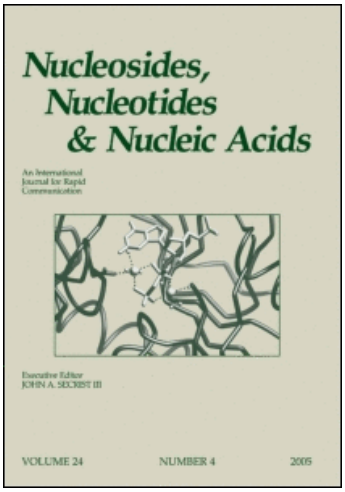

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Synthesis and antiviral evaluation of novel open-chain analogues of neplanocin A

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SYNTHESIS AND ANTIVIRAL EVALUATION OF NOVEL OPEN-CHAIN ANALOGUES OF NEPLANOCIN A

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□ *Novel acyclic nucleoside analogues were designed and synthesized as open-chain analogues of neplanocin A. The coupling of the allylic bromide with purine bases using cesium carbonate afforded a series of novel acyclic nucleosides. The synthesized compounds* ***Ia–II*** *were evaluated for their antiviral activity against various viruses such as HIV, HSV-1, HSV-2, and ECMV.*

Keywords Antiviral agents; Acyclic nucleosides; Neplanocin A

INTRODUCTION

The discovery of acyclovir[1] as an antiherpes agent ignited the search for new antiviral nucleosides with a disconnected chain resulting from the omission of bonds from the pentose or cyclopentane rings. During the past 20 years, many new synthetic schemes for various acyclic nucleoside[2] analogues have been discovered and many of these molecules have shown promising antiviral activities.[3] Among them, pencyclovir is an acyclic analogue of guanosine, and has been approved as an antiviral drug for treating disease caused by HSV and VZV.[4] Because of the unusual presence of a double bond in neplanocin A[5] and the acyclic nature of pencyclovir, these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic nucleoside analogues that mimic the sugar portion of naturally occurring neplanocin A. Furthermore, the recent approval of bis(POC)PMPA by the FDA as an anti-HIV agent warrants further searches for acyclic nucleosides as chemotherapeutic agents (Figure 1).[6]

Nevertheless, the utility of these drugs is limited due to their toxicity and side effects, as well as the emergence of drug-resistant viral strains. Therefore,

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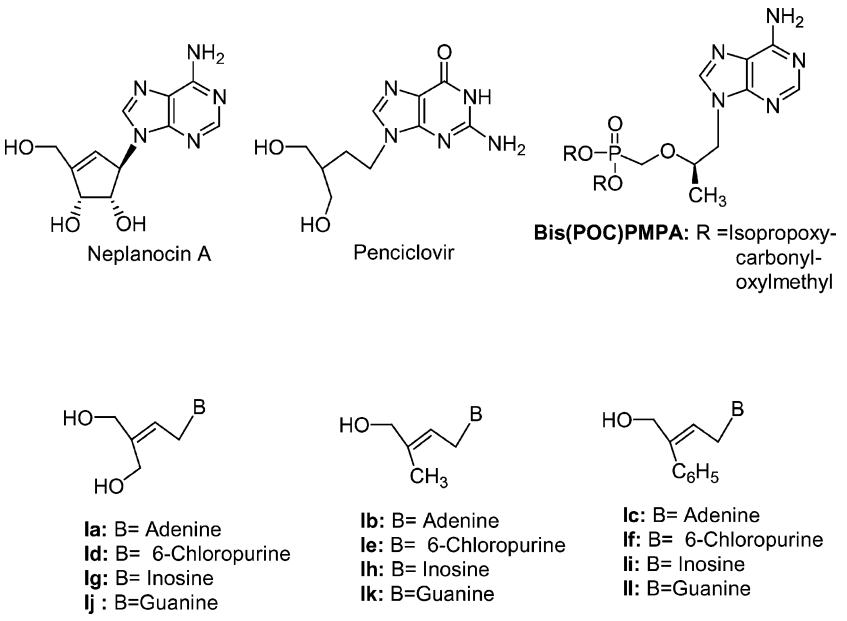


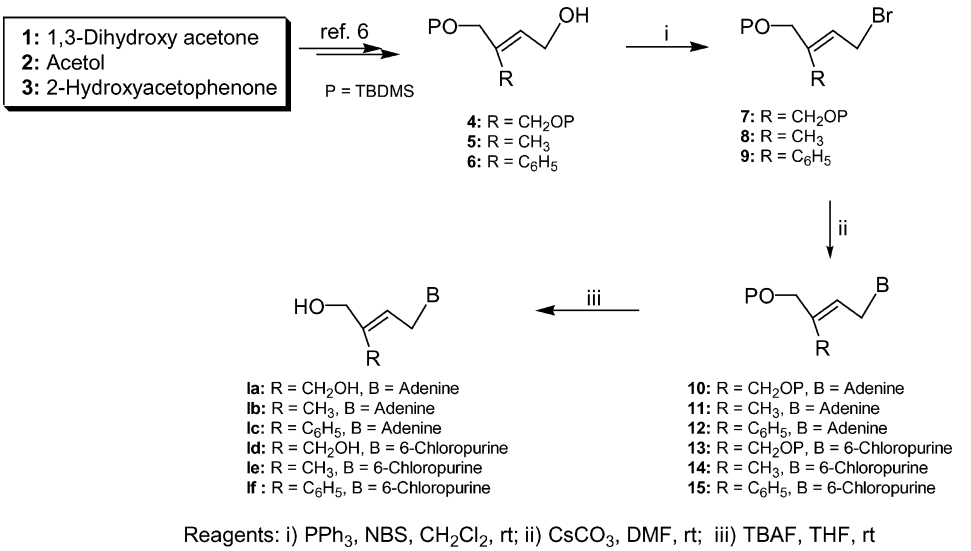
FIGURE 1 Synthesis rationale of the target nucleosides.

it is essential to search for less toxic and more effective antiviral agents that do not have a cross-resistance with the existing drugs.

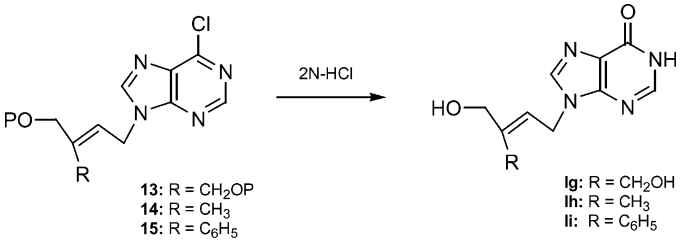
In view of the stimulating results of acyclic nucleosides and the search for the stable and effective carba-nucleosides, compounds **Ia–Ii** were designed as open-chain analogues of neplanocin A.

RESULTS AND DISCUSSION

The strategy for synthesizing the target nucleosides is based on the alkylation of purine bases on the allylic bromides **7**, **8**, and **9**, which were readily synthesized from hydroxyl ketone derivatives such as 1,3-dihydroxyacetone **1**, acetol **2**, and 2-hydroxyacetophenone **3** using a previously reported procedure.[7] Conversion of allylic alcohols **4**, **5**, and **6** to the bromo derivatives **7**, **8**, and **9** was accomplished by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2 in high yield.[8] Direct coupling of the allylic bromide **7–9** with purine bases in DMF with cesium carbonates as a basic catalyst provided the desired N^9-alkylated purine nucleosides in 35–72% yields.[9] Deprotection of the *t*-butyldimethylsilyl group (TBDMS) using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave the desired acyclic purine nucleosides **Ia–If** (Scheme 1). Preparation of the acyclic hypoxanthine nucleosides **Ig–i** were accomplished by treatment of the 2N HCl (Scheme 2).

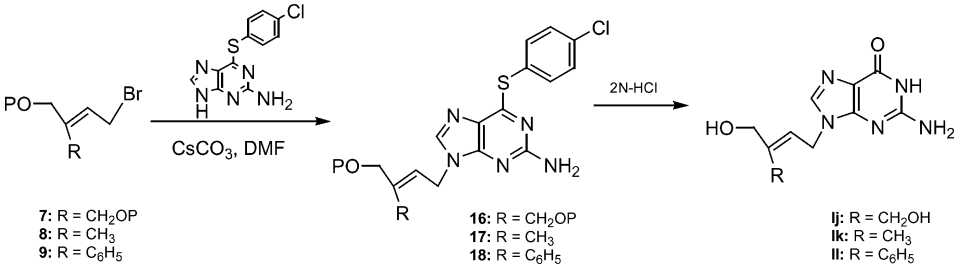


SCHEME 1 Synthesis of adenine and 6-chloropurine–substituted acyclic nucleosides.



SCHEME 2 Synthesis of acyclic inosine nucleosides.

The bromide 7 was reacted with 2-amino-6-[(4-chlorophenyl)-sulfanyl]purine in the presence of cesium carbonate and subsequently treated with 2N HCl gave the acyclic guanine nucleosides **Ij–l** (Scheme 3). Synthesized compounds **Ia–Il** were evaluated for their activity against HIV, HSV-1, HSV-2, and ECMV. As shown in Table 1, guanine base derivatives **Ij** and **Ik** showed moderate anti-HSV1 and -2 activity ($EC_{50} = 32.7$ and 11.7 μg/mL).



SCHEME 3 Synthesis of acyclic guanine nucleosides.

TABLE 1 The Antiviral Activities of the Synthesized Compounds

Compounds	HIV-1 EC_{50} (μg/mL)	HSV-1 EC_{50} (μg/mL)	HSV-2 EC_{50} (μg/mL)	ECMV EC_{50} (μg/mL)	Cytotoxicity IC_{50} (μg/mL)
Ia	>100	>100	>100	>100	>100
Ib	>100	>100	>100	>100	>100
Ic	>100	>100	>100	>100	>100
Id	>100	**79.5**	>100	>100	>100
Ie	>100	>100	>100	>100	>100
If	>100	>100	>100	>100	>100
Ig	>100	>100	>100	**36.2**	>100
Ih	**47.2**	>100	>100	>100	>100
Ii	>100	>100	>100	>100	>100
Ij	>100	>100	**11.7**	>100	>100
Ik	>100	**32.7**	>100	>100	>100
Il	>100	>100	>100	>100	>100
AZT	0.0008	1.90	ND	ND	4.78
ACV	ND	ND	1.90	ND	>10
Gancyclovir	ND		ND	>100	>10

ND: Not determined.

EXPERIMENTAL SECTION

All the chemicals were of reagent grade and were used as purchased. All the moisture-sensitive reactions were performed in an inert atmosphere with either N_2 or Ar using distilled dry solvents. The melting points were determined using a Mel-temp II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer; the chemical shifts are reported in parts per million (δ) and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The elemental analysis was performed using an Elemental Analyzer System (Profile HV-3). TLC was performed on uniplates (silica gel) purchased from Analtech Co.

3,3′-Bis-(t-Butyldimethylsilyloxymethyl)-prop-2-enyl bromide (7). To a solution of compound **4** (2.30 g, 6.73 mmol) and triphenylphosphine (1.94 g, 7.4 mmol) in CH_2Cl_2 (20 mL), *N*-bromosuccinimide (1.28 g, 7.2 mmol) was added slowly at 0°C, stirred for 4 h at room temperature, and diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by quick flash silica gel column chromatography (EtOAc/hexane, 1:10) to give the allylic bromide **7** (2.15 g, 79%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.93 (t, J = 6.4 Hz, 1H), 4.42 (d, J = 7.2 Hz, 2H), 4.29 (s, 2H), 3.91 (s, 2H), 0.92 (s, 18H), 0.05 (s, 12H).

(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl bromide (8). Compound **8** was prepared from **5** as described for **7**. Yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (m, 1H), 4.38 (br s, 2H), 3.91 (d, $J = 6.4$ Hz, 2H), 1.70 (s, 3H), 0.95 (s, 9H), 0.08 (s, 6H).

(*E*)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-enyl bromide (9). Compound **9** was prepared from **6** as described for **7**. Yield 69%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, $J = 6.7$ Hz, 2H), 7.21 (d, $J = 6.1$ Hz, 2H), 7.20 (d, $J = 6.0$ Hz, 1H), 5.91 (t, $J = 6.4$ Hz, 1H), 4.46 (s, 2H), 3.97 (d, $J = 6.7$ Hz, 2H), 1.0 (s, 9H), 0.08 (s, 6H).

1-[3,3′-Bis-(t-Butyldimethylsilyloxymethyl)-prop-2-enyl]adenine (10). A solution of the allylic bromide **7** (0.50 g, 1.22 mmol), adenine (530 mg, 3.94 mmol), and sodiume hydride (150 mg, 3.94 mmol) in anhydrous DMF (10 mL) was stirred overnight at room temperature. The mixture was quenched by the addition of water and diluted with ethylacetate. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give compound **10** (384 mg, 72%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.12 (s, 1H), 5.80 (t, $J = 6.4$ Hz, 1H), 4.46 (s, 4H), 4.40 (d, $J = 7.2$ Hz, 2H), 1.0 (s, 18H), 0.08 (s, 12H); ^{13}C NMR ($CDCl_3$)δ 156.40, 152.87, 149.75, 142.36, 140.66, 120.33, 63.95, 58.94, 26.18, 18.42, −4.97.

The synthesis of compounds **11** and **12** were carried out by the same procedure as described for the preparation of **10**.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl]adenine (11). Yield 64%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 7.79 (s, 1H), 5.75 (t, $J = 7.05$ Hz, 1H), 4.84 (d, $J = 7.17$ Hz, 2H), 4.08 (s, 2H), 1.79 (s, 3H), 0.89 (s, 9H) 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$)δ 155.44, 152.95, 150.01, 141.43, 139.93, 119.62, 116.39, 67.79, 40.79, 25.87, 18.35, 13.70, −5.38.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-enyl]adenine (12). Yield 67%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (s, 1H), 7.56 (s, 1H), 7.37 (d, $J = 7.7$ Hz, 2H), 7.28 (d, $J = 7.4$ Hz, 2H), 7.19 (d, $J = 6.3$ Hz, 1H), 5.87 (t, $J = 7.8$ Hz, 1H), 4.69 (s, 2H), 4.59 (d, $J = 7.10$ Hz, 2H) 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$)δ 154.92, 152.08, 147.90, 144.83, 142.65, 134.96, 128.49, 127.77, 126.28, 113.51, 75.36, 48.87, 20.81, 14.74, −6.42.

1-[3,3′-Bis-(t-Butyldimethylsilyloxymethyl)-prop-2-enyl] 6-chloropurine (13). A solution of the allylic bromide **7** (2.0 g, 4.88 mmol), 6-chloropurine (1.75 g, 11.23 mmol) and cesium carbonate (2.07 g, 6.35 mmol) in anhydrous DMF (30 mL) was stirred overnight at room temperature. The mixture was

quenched by the addition of water and diluted with ethylacetate. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give compound 13 (1.32 mg, 56%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.17 (s, 1H), 5.78 (t, $J = 7.47$ Hz, 1H), 5.05 (d, $J = 7.4$ Hz, 2H), 4.35 (s, 2H), 4.18 (s, 2H), 0.88 (d, $J = 8.97$ Hz, 18H), 0.06 (d, $J = 9.0$ Hz, 12H); ^{13}C NMR ($CDCl_3$)δ 151.85, 151.69, 150.87, 145.04, 144.88, 131.58, 117.70, 64.28, 59.56, 40.94, 25.83, 18.31.

The synthesis of compounds **14** and **15** were carried out by the same procedure as described for the preparation of **11**.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl]-6-chloropurine (14). Yield 35%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.09 (s, 1H), 5.72 (t, $J = 6.69$ Hz, 1H), 4.90 (d, $J = 7.3$ Hz, 2H), 4.03 (s, 2H), 1.77 (s, 3H), 0.83 (s, 9H), 0.003 (s, 6H); ^{13}C NMR ($CDCl_3$)δ 151.82, 150.78, 144.70, 142.43, 131.55, 130.06, 115.19, 66.86, 41.37, 25.81, 18.30, 13.74, −5.32.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-enyl]-6-chloropurine (15). Yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (br s, 1H), 7.58 (s, 1H), 7.35–728. (m, 5H), 5.53 (t, $J = 7.3$ Hz, 1H), 4.43 (d, $J = 7.3$ Hz, 2H), 4.08 (s, 2H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$)δ 160.62, 150.48, 148.13, 142.93, 115.47, 67.10, 45.16, 25.90, 18.40, 13.74, −5.32.

1-[3,3′-Bis-(t-Butyldimethylsilyloxymethyl)-prop-2-enyl]-4-amino-6-[(4-chlorophenyl)sulf anyl]-9*H*-purine (16). A solution of the allylic bromide **7** (1.55 g, 3.78 mmol), 2-amino-6-[(4-chlorophenyl)sulfanyl]purine (2.41 g, 8.70 mmol) and cesium carbonate (1.85 g, 5.67 mmol) in anhydrous DMF (30 mL) was stirred overnight at room temperature. The mixture was quenched by the addition of water and diluted with ethylacetate. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give compound **16** (800 mg, 35%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 5.74 (t, $J = 7.2$ Hz, 1H), 4.80 (d, $J = 6.6$ Hz, 4H), 4.40 (d, $J = 7.3$ Hz, 2H), 0.90 (d, $J = 5.9$ Hz, 18H), 0.08 (d, $J = 8.5$ Hz, 12H); ^{13}C NMR ($CDCl_3$)δ 170.12, 163.28, 149.50, 144.31, 140.98, 137.24, 116.36, 69.28, 63.20, 37.82, 20.66, 14.84, −6.36.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl]-4-amino-6-[(4-chlorophenyl)sulfan yl]-9*H*-purine (17). Yield 23%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (s, 1H), 7.58 (d, $J = 6.5$ Hz, 2H), 7.38 (d, $J = 6.6$ Hz, 2H), 5.72 (t, $J = 7.2$ Hz, 1H), 4.69 (d, $J = 7.1$, 2H), 4.06 (s, 2H), 1.76 (s, 3H),

0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$)δ 154.93, 152.48, 147.93, 144.85, 139.57, 130.67, 129.26, 117.10, 75.40, 48.94, 20.76, 14.89, 12.80, −6.32.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-enyl]-4-amino-6-[(4-chlorophenyl)sulfan yl]-9*H*-purine (18). Yield 21%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (br s, 1H), 7.56–7.44 (m, 5H), 7.41 (d, $J = 7.2$ Hz, 2H), 7.38 (d, $J = 7.2$ Hz, 2H), 5.53 (t, $J = 7.3$ Hz, 1H), 4.43 (d, $J = 7.3$ Hz, 2H), 4.08 (s, 2H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 160.62, 150.48, 148.13, 142.93, 115.47, 67.10, 45.16, 25.90, 18.40, 13.74, −5.32.

1-[3,3′-Bis-(Hydroxymethyl)-prop-2-enyl]adenine (Ia). To a solution of compound **10** (250 mg, 0.54 mmol) in THF (5 mL), TBAF (3.23 mL, 1.0 M solution in THF) at 0°C was added. The mixture was stirred at room temperature for 4 h and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:2) to give compound **Ia** (46 mg, 36%) as a white solid: mp 207–213°C;UV (H_2O) λ_{max} 261.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.12 (s, 1H), 7.20 (s, 1H), 5.61 (t, $J = 7.32$ Hz, 1H), 4.87 (d, $J = 7.4$ Hz, 2H), 4.13 (d, $J = 5.48$ Hz, 2H), 3.95 (d, $J = 5.49$ Hz, 2H); ^{13}C NMR (DMSO-d_6)δ 154.49, 152.09, 147.92, 144.96, 140.99, 119.43, 63.26, 62.86, 57.25, 31.14; Anal calc for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.11; H, 5.68; N, 29.92.

The synthesis of compounds **Ib–If** was carried out by the same procedure as described for the preparation of **Ia**.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl]adenine (Ib). Yield 25%; mp 178–183°C; UV (H_2O) λ_{max} 259.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.13 (s, 1H), 7.18 (s, 1H), 5.66 (s, 1H), 4.80 (d, $J = 6.0$ Hz, 2H), 4.45 (s, 2H), 1.80 (s, 3H); ^{13}C NMR (DMSO-d_6)δ 170.52, 156.40, 152.93, 147.95, 140.85, 135.37, 122.36, 68.22, 21.06, 14.34; Anal calc for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.87; H, 6.18; N, 32.03.

1-[(*E*)-4-(Hydroxy)-3-phenyl-but-2-enyl]adenine (Ic). Yield 19%; mp 175–184°C;UV (H_2O) λ_{max} 260.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.68 (s, 1H), 8.12 (s, 1H), 7.22 (m, 5H), 5.75 (t, $J = 7.3$ Hz, 1H), 4.40 (s, 2H), 4.20 (s, 2H) ; ^{13}C NMR (DMSO-d_6)δ 154.92, 152.08, 147.97, 144.80, 142.65, 134.90, 128.46, 127.77, 126.28, 113.59, 72.54, 48.82; Anal calc for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90. Found: C, 63.89; H, 5.48; N, 25.10.

1-[3,3′-Bis-(Hydroxymethyl)-prop-2-enyl]-6-chloropurine (Id). Yield 83%; mp 202–211°C (dec); UV (H_2O) λ_{max} 262.0 nm; ^{1}H NMR (D_2O, 300 MHz) δ 8.56 (s, 1H), 8.44 (s, 1H), 5.78 (t, $J = 7.15$ Hz, 1H), 5.01 (d, $J = 7.12$ Hz, 2H), 4.30 (s, 2H), 4.12 (s, 2H); ^{13}C NMR (D_2O) δ 154.92, 151.39, 149.71, 143.07, 128.45, 121.11, 63.15, 57.02, 41.57; Anal calc for

$C_{10}H_{11}ClN_4O_2$: C, 47.16; H, 4.35; N, 22.00. Found: C, 47.11; H, 4.56; N, 22.10.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl]-6-chloropurine (Ie). Yield 26%; mp 170–173°C; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.71 (s, 1H), 8.12 (s, 1H), 5.75 (t, $J = 6.6$ Hz, 1H), 5.05 (d, $J = 7.9$ Hz, 2H), 4.11 (s, 2H), 1.85 (s, 3H) ; ^{13}C NMR ($CDCl_3$)δ 151.90, 151.62, 150.83, 144.80, 142.54, 131.44, 116.18, 66.78, 41.48, 14.01; Anal calc for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.65; N, 23.47. Found: C, 50.44; H, 4.40; N, 23.23.

1-[(*E*)-4-(Hydroxy)-3-phenyl-but-2-enyl]-6-chloropurine (If). Yield 39%; mp 167–172°C; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 7.96 (s, 1H), 7.35 (m, 5H), 6.07 (t, $J = 6.9$ Hz, 1H), 4.87 (d, $J = 6.9$ Hz, 2H), 4.41 (s, 2H); ^{13}C NMR ($CDCl_3$)δ 152.01, 147.38, 145.38, 144.71, 136.24, 128.96, 128.61, 128.46, 125.70, 118.46, 66.47, 42.32; Anal calc for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 59.79; H, 4.28; N, 18.87.

1-[3,3′-Bis-(Hydroxymethyl)-prop-2-enyl] hypoxanthine (Ig). A solution of **13** (200 mg, 0.41 mmol) in 5 mL of 2N-HCl was heated under reflux for 4 h. After cooled, the reaction mixture was poured into water and ethyl ether, and the aqueous layer was neutralized with 1N-NaOH, and then was freeze-dried. The residue was recrystallized from MeOH to afford **Ig** (70.0 mg, 76.1%) as a white solid; mp 204–209°C (dec); UV (H_2O) λ_{max} 248.5 nm; ^{1}H NMR (D_2O, 300 MHz): δ 7.97 (s, 1H) , 7.92 (s, 1H) , 5.69 (t, $J = 6.4$ Hz, 1H) , 4.80 (d, $J = 6.7$ Hz, 1H) , 4.25 (s, 2H) , 4.10 (s, 2H); ^{13}C NMR (D_2O) δ 159.01, 148.98, 147.28, 142.57, 141.20, 122.76, 121.54, 62.98, 56.72, 41.06; Anal calc for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.90; H, 5.28; N, 23.90.

The synthesis of compounds **Ih–Ii** was carried out by the same procedure as described for the preparation of **Ig**.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl] hypoxanthine (Ih). Yield 27%; mp 197–199°C; UV (H_2O) λ_{max} 249.0 nm; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.09 (s, 1H), 8.03 (s, 1H), 5.70 (s, 1H), 4.29 (s, 2H), 3.99 (d, $J = 7.2$ Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (MeOH) δ 179.10, 148.84, 147.23, 141.25, 139.84, 117.33, 66.02, 40.69, 22.85, 12.49; Anal calc for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.80; H, 5.44; N, 25.33.

1-[(*E*)-4-(Hydroxy)-3-phenyl-but-2-enyl] hypoxanthine (Ii). Yield 40%; mp 184-189 °C; UV (H_2O) λ_{max} 248.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (s, 1H), 7.76 (s, 1H), 7.36 (m, 5H), 6.00 (t, $J = 6.3$ Hz, 1H), 4.74 (d, $J = 6.9$ Hz, 2H), 4.29 (s, 2H); ^{13}C NMR ($CDCl_3$)δ 179.10, 164.99, 150.72, 146.43, 138.67, 137.17, 128.04, 127.73, 126.16, 124.30, 119.27, 65.46, 41.59;

Anal calc for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.88; H, 5.08; N, 19.87.

1-[3,3′-Bis-(Hydroxymethyl)-prop-2-enyl] guanine (Ij). A solution of **16** (300 mg, 0.51 mmol) in 6 mL of 2N HCl was heated under reflux for 4 h. After cooled, the reaction mixture was poured into water and ethyl ether, and the aqueous layer was neutralized with 1N-NaOH, and then was freeze dried. The residue was recrystallized from MeOH to afford **Ij** (97.0 mg, 78.0%) as a white solid; mp 270–277°C (dec); UV (H_2O) λ_{max} 252.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63 (s, 1H), 5.54 (t, $J = 6.9$ Hz, 1H), 4.66 (d, $J = 7.0$ Hz, 2H), 4.08 (d, $J = 5.4$ Hz, 2H), 3.94 (d, $J = 5.3$ Hz, 2H); ^{13}C NMR (DMSO-d_6)δ 157.29, 154.15, 151.34, 144.45, 140.02, 137.46, 119.63, 62.75, 57.38, 39.12; Anal calc for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.89; H, 5.09; N, 27.88.

The synthesis of compounds **Ik–Il** was carried out by the same procedure as described for the preparation of **Ij**.

1-[(*E*)-4-(Hydroxy)-3- methyl -but-2-enyl] guanine (Ik). Yield 77%; mp 229–241°C (dec); UV (H_2O) λ_{max} 251.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.56 (s, 1H), 5.52 (d, $J = 5.76$ Hz, 1H), 4.54 (d, $J = 6.7$ Hz, 2H), 4.06 (s, 2H), 1.68 (s, 3H); ^{13}C NMR (DMSO-d_6)δ 176.09, 158.31, 155.25, 151.58, 140.62, 136.81, 118.10, 65.76, 25.45, 14.06; Anal calc for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.22; H, 5.49; N, 29.89.

1-[(*E*)-4-(Hydroxy)-3-phenyl -but-2-enyl] guanine (Il). Yield 51%; mp 188–193°C; UV (H_2O) λ_{max} 252.0 nm; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.56 (s, 1H), 7.40 (m, 5H), 5.98 (t, $J = 6.9$ Hz, 1H), 4.60 (d, $J = 6.8$ Hz, 2H), 4.28 (s, 2H); ^{13}C NMR (MeOD-d_4)δ 179.10, 164.23, 150.82, 146.34, 138.67, 137.17, 128.04, 127.74, 126.16, 124.30, 119.27, 65.46, 41.55; Anal calc for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.56. Found: C, 60.51; H, 5.11; N, 23.77.

CONCLUSION

A very simple synthetic method for synthesizing novel acyclic purine nucleosides from ketone derivatives was developed in this study. When the synthesized compounds were tested against several viruses such as HIV, HSV-1, HSV-2, and ECMV, the guanine base derivatives **Ij** and **Ik** showed moderate anti-HSV-1 and-2 activity ($EC_{50} = 32.7$ and 11.7 μg/mL).

Evaluation of Anti-HSV-1 and HSV-2 Activity

CCL 18 cells in stationary phase were infected with the virus at 2-4 $CCID_{50}$ multiplicity of infection (MOI) per well in 96-well plates. After 2 h incubation

at 37°C for the viral adsorption, the medium was aspirated off to remove the unadsorped viral particles and 100 μL MEM containing 2% FBS and each compound was applied to each well and further incubated for 6 days. Antiviral activity was measured microscopically or fluorometrically. For microscopic observation, the cells were fixed with 70% ethanol and stained with 2.5% Giemsa solution for 2 h, rinsed with distilled water, and air dried. Antiviral activity was expresses as the IC_{50}, the concentration required to inhibit virus-induced CPE by 50%. IC_{50} values were estimated from semi-logarithmic graphic plots of the percentage of CPE as a function of the concentration of the test compound. For fluorometric assay, the cells were washed twice with 100 μL of phosphate-buffered saline (PBS). One hundred microliters of 5 μg/mL fluorescein diacetate (FDA, Sigma) was added to each well and the plates were incubated for 30 min at 37°C. The FDA solution was removed by aspiration and wells were washed with 100 μL PBS. The fluorescence intensity (as absolute fluorescent units, AFU) in each well was measured with a fluorescent microplate reader equipped with a 485-nm excitation filter and a 538-nm emission filter.

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