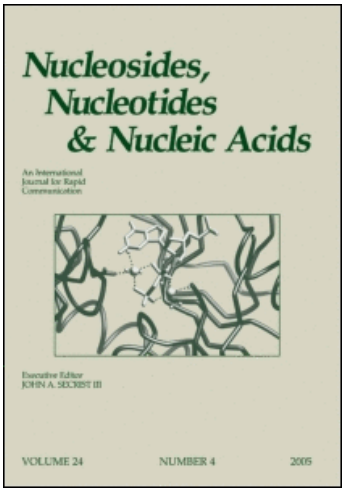

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Oh, Chang-Hyun , Baek, Tae-Rim and Hong, Joon Hee(2005) 'Concise Synthesis and Antiviral Activity of Novel Unsaturated Acyclic Pyrimidine Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 24: 2, 153 — 160
To link to this Article: DOI: 10.1081/NCN-200051913
URL: http://dx.doi.org/10.1081/NCN-200051913

Nucleosides, Nucleotides, and Nucleic Acids, 24 (2):153–160, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200051913

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CONCISE SYNTHESIS AND ANTIVIRAL ACTIVITY OF NOVEL UNSATURATED ACYCLIC PYRIMIDINE NUCLEOSIDES

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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 pyrimidine bases using cesium carbonate afforded a series of novel acyclic nucleosides. The synthesized compounds* ***15–22*** *were evaluated for their antiviral activity against various viruses such as HIV, HSV-1, HSV-2, and HCMV.*

Keywords Antiviral Agents, Acyclic Nucleosides, [3,3]-Sigmatropic Rearrangement

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, penciclovir 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 and the acyclic nature of penciclovir, these two compounds have stimulated extensive research in the synthesis of new cyclic and acyclic carba-nucleoside analogues that mimic the sugar portion of naturally occurring nucleosides. 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)[5] (Scheme 1).

Received 27 September 2004, accepted 28 December 2004.
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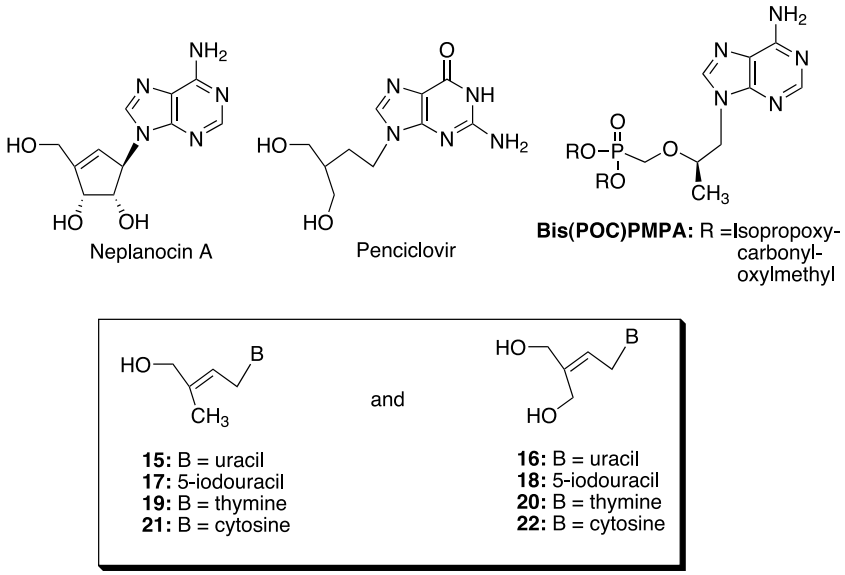
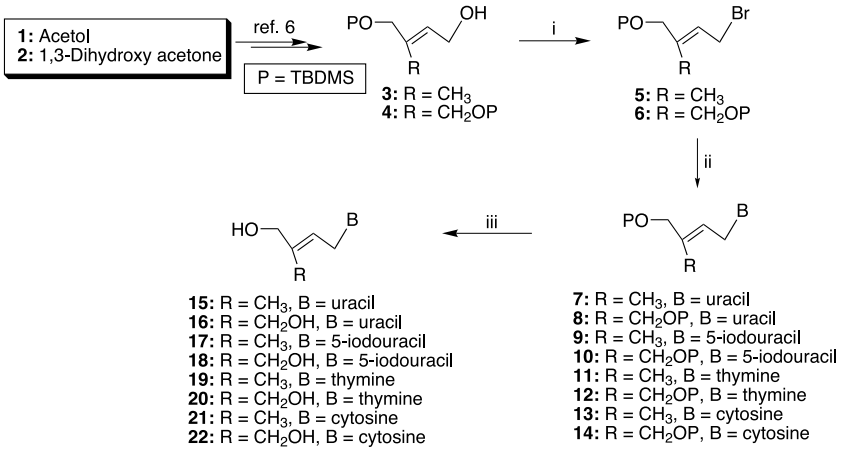


FIGURE 1 Structures of potential acyclic nucleosides and target nucleosides.

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

In view of the stimulating results of acyclic nucleosides and as part of our ongoing drug discovery efforts, this study aimed to synthesize novel acyclic nucleosides.



Reagents: i) PPh_3, NBS, CH_2Cl_2, rt; ii) $CsCO_3$, DMF, rt; iii) TBAF, THF, rt

SCHEME 1 Synthesis of unsaturated acyclic nucleosides.

RESULTS AND DISCUSSION

The strategy for synthesizing the target nucleosides is based on the alkylation of pyrimidine bases on the allylic bromides **5** and **6**, which were readily synthesized from hydroxyl ketone derivatives such as acetol **1** and 1,3-dihydroxyacetone **2** using a previously reported procedure.[6] Conversion of allylic alcohols **3** and **4** to the bromo derivatives **5** and **6** was accomplished by the sequential addition of NBS to a solution of the alcohol and triphenylphosphine in CH_2Cl_2 in high yield.[7] Direct coupling of the allylic bromide **2** with pyrimidine bases in DMF with cesium carbonates as a basic catalyst provided the desired N^1-alkylated pyrimidine nucleosides in 49–72% yields.[8] The UV data were in good agreement with those of the corresponding pyrimidine model compounds. Deprotection of the *t*-butyldimethylsilyl group (TBDMS) using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) gave the desired acyclic pyrimidine nucleosides **15**–**22** in 78–88% yields. Synthesized compounds **15**–**22** were evaluated for their activity against HIV, HSV-1, HSV-2, and HCMV. As shown in Table 1, only 5-iodouracil derivative **18** showed moderate anti-HSV activity (EC_{50} = 21.1 μg/mL). However, the information obtained in the presence study will be useful for the development of novel acyclic nucleosides. Studies toward this end and to clarify the mechanism are underway.

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

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)	HCMV EC_{50} (μg/mL)	Cytotoxicity IC_{50} (μg/mL)
15	>100	>100	>100	>100	>100
16	>100	>100	>100	>100	>100
17	>100	>100	>100	>100	>100
18	>100	**21.1**	>100	>100	>100
19	>100	>100	>100	>100	>100
20	>100	>100	>100	>100	>100
21	>100	>100	>100	>100	>100
22	65.2	>100	>100	>100	>100
AZT	0.0008	ND	ND	ND	4.78
ACV	ND	1.90	1.90	ND	>10
Ganciclovir	ND	ND	ND	>100	>10

Note: ND: not determined.

The lack of antiviral activity of these compounds is presumably associated with their unfavorable conformations for the phosphorylation occurring during the nucleoside activation process.

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. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl bromide (5). To a solution of compound **3** (3 g, 13.86 mmol) and triphenylphosphine (7.27 g, 27.72 mmol) in CH_2Cl_2 (50 mL), *N*-bromosuccinimide (4.93 g, 27.72 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, 1:30) to give the allylic bromide **5** (3.52 g, 91%) as a yellow oil: ^{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).

3,3′-Bis-(t-butyldimethylsilyloxymethyl)-prop-2-enyl bromide (6). Compound **6** was prepared from **4** as described for **5**. Yield 87%; ^{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).

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl] uracil (7). A solution of the allylic bromide **5** (0.5 g, 1.79 mmol), uracil (300 mg, 2.68 mmol), and cesium carbonate (873 mg, 2.68 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, 3:1) to give compound **7** (400 mg, 72%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.26 (br s, 1H), 7.17 (d, J = 7.9 Hz, 1H), 5.71 (d, J = 7.9 Hz, 1H), 5.52 (t, J = 7.2 Hz, 1H), 4.42 (d, J = 7.2 Hz, 2H), 4.05 (s, 2H), 1.72 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.61, 150.88, 143.50, 142.12, 115.98, 102.24, 67.16, 44.78, 25.87, 18.37, 13.66, −5.36; Anal calc for $C_{15}H_{26}N_2O_3Si$: C, 58.03; H, 8.44; N, 9.02. Found: C, 57.88; H, 8.51; N, 8.92.

1-[3,3′-Bis-(t-butyldimethylsilyloxymethyl)-prop-2-enyl] uracil (8). Compound **8** was prepared from **6** as described for **7**. Yield 64%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.96 (br s, 1H), 7.31 (d, J = 7.9 Hz, 1H), 5.68 (d, J = 7.9 Hz,

1H), 5.56 (t, J = 7.4 Hz, 1H), 4.51 (d, J = 7.5 Hz, 2H), 4.23 (s, 2H), 4.15 (s, 2H) 0.88 (s, 18H), 0.07 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.12, 151.17, 144.48, 143.85, 118.86, 102.24, 64.51, 59.04, 44.04, 25.87, 18.20, −5.45; Anal calc for $C_{21}H_{40}N_2O_4Si_2$: C, 57.23; H, 9.15; N, 6.36. Found: C, 57.47; H, 9.29; N, 6.25.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl] 5-iodouracil (9). Compound **9** was prepared from **5** as described for **7**. Yield 67%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (br s, 1H), 7.58 (s, 1H), 5.53 (t, J = 7.3 Hz, 1H), 4.43 (d, J = 7.3 Hz, 2H), 4.08 (s, 2H), 1.74 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.62, 150.48, 148.13, 142.93, 115.47, 67.10, 45.16, 25.90, 18.40, 13.74, −5.32; Anal calc for $C_{15}H_{25}IN_2O_3Si$: C, 41.29; H, 5.77; N, 6.42. Found: C, 41.40; H, 5.63; N, 6.35.

1-[3,3′-Bis-(t-butyldimethylsilyloxymethyl)-prop-2-enyl] 5-iodouracil (10). Compound **10** was prepared from **6** as described for **8**. yield 56%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.14 (br s, 1H), 7.72 (s, 1H), 5.57 (t, J = 7.2 Hz, 1H), 4.57 (d, J = 7.5 Hz, 2H), 4.25 (s, 2H), 4.17 (s, 2H) 0.91 (s, 18H), 0.1 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.53, 150.72, 148.29, 144.98, 118.46, 67.80, 64.54, 59.34, 44.30, 25.89, 18.31, −5.38; Anal calc for $C_{21}H_{39}IN_2O_4Si_2$: C, 44.51; H, 6.94; N, 4.94. Found: C, 44.74; H, 7.16; N, 5.20.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl] thymine (11). Compound **11** was prepared from **5** as described for **7**. Yield 60%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (br s, 1H), 6.97 (s, 1H), 5.51 (t, J = 7.2 Hz, 1H), 5.30 (s, 2H), 4.39 (d, J = 7.2 Hz, 2H), 4.06 (s, 2H), 1.91 (s, 3H), 1.73 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.10, 150.89, 141.57, 139.52, 116.55, 110.71, 67.29, 44.54, 25.88, 18.38, 13.68, 12.34, −5.34; Anal calc for $C_{16}H_{28}N_2O_3Si$: C, 59.22; H, 8.70; N, 8.63. Found: C, 59.43; H, 8.69; N, 8.52.

1-[3,3′-Bis-(t-butyldimethylsilyloxymethyl)-prop-2-enyl] thymine (12). Compound **12** was prepared from **6** as described for **8**. Yield 59%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.67 (br s, 1H), 7.09 (s, 1H), 5.57 (t, J = 7.4 Hz, 1H), 4.51 (d, J = 7.4 Hz, 2H), 4.26 (s, 2H), 4.18 (s, 2H) 1.90 (s, 3H), 0.91 (s, 18H), 0.1 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.68, 150.29, 144.05, 139.75, 119.22, 110.64, 64.57, 59.13, 43.88, 15.86, 18.37, 12.25, −5.42; Anal calc for $C_{22}H_{42}N_2O_4Si_2$: C, 58.11; H, 9.31; N, 6.16. Found: C, 57.97; H, 9.46; N, 6.33.

1-[(*E*)-4-(t-Butyldimethylsilyloxy)-3-methyl-but-2-enyl] cytosine (13). Compound **13** was prepared from **5** as described for **7**. Yield 50%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 7.2 Hz, 1H), 5.76 (d, J = 7.2 Hz, 1H), 5.53 (t, J = 7.1 Hz, 1H), 4.45 (d, J = 7.1 Hz, 2H), 4.04 (s, 2H), 1.70 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.76, 156.71, 144.38, 140.94,

117.58, 94.43, 67.51, 45.78, 25.90, 18.37, 13.67, −5.34; Anal calc for $C_{15}H_{27}N_3O_2Si$: C, 58.21; H, 8.79; N, 13.58. Found: C, 58.36; H, 8.65; N, 13.71.

1-[3,3′-Bis-(t-butyldimethylsilyloxymethyl)-prop-2-enyl] cytosine (14). Compound **14** was prepared from **6** as described for **8**. Yield 49%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J* = 7.5 Hz, 1H), 6.04 (d, J = 7.0, 5.61 (t, J = 7.4 Hz, 1H), 4.60 (d, *J* = 7.3 Hz, 1H), 4.25 (s, 2H), 4.17 (s, 2H), 0.89 (s, 18H), 0.07 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.27, 156.73, 145.72, 141.57, 121.46, 93.87, 64.13, 58.77, 45.40, 26.24, 18.47, −4.95; Anal calc for $C_{21}H_{41}N_3O_3Si_2$: C, 57.36; H, 9.40; N, 9.56. Found: C, 57.15; H, 9.28; N, 9.67.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl] uracil (15). To a solution of compound **7** (170 mg, 0.547 mmol) in THF (6 mL), TBAF (0.82 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, 1:5) to give compound **15** (84 mg, 79%) as a white solid: mp 166–168°C; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.23 (br s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 5.56 (d, *J* = 7.8 Hz, 1H), 5.40 (t, *J* = 7.0 Hz, 1H), 4.85 (t, *J* = 5.7 Hz, 1H), 4.30 (d, *J* = 7.0 Hz, 2H), 3.81 (d, *J* = 5.3 Hz, 2H), 1.65 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.13, 151.31, 145.73, 141.34, 117.42, 101.45, 65.78, 45.03, 14.04; Anal calc for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.87; H, 6.28; N, 14.03.

1-[3,3′-Bis-(hydroxymethyl)-prop-2-enyl] uracil (16). Compound **16** was prepared from **8** as described for **15**. Yield 80%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63 (d, *J* = 7.8 Hz, 1H), 5.55 (d, *J* = 7.8, 1H), 5.42 (t, *J* = 6.9 Hz, 1H, 1H), 4.39 (d, *J* = 7.1 Hz, 2H), 4.02 (s, 2H), 3.94 (s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.41, 151.55, 145.72, 145.16, 119.19, 101.50, 62.86, 57.25, 44.66; Anal calc for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.11; H, 5.88; N, 13.10.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl] 5-iodouracil (17). Compound **17** was prepared from **9** as described for **15**. Yield 83%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.62 (s, 1H), 8.13 (s, 1H), 5.41 (t, *J* = 1.3 Hz, 1H), 4.85 (t, *J* = 5.7 Hz, 1H), 4.32 (d, *J* = 6.9 Hz, 2H), 3.80 (d, *J* = 5.4 Hz, 2H), 1.64 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.47, 151.01, 150.00, 141.41, 117.34, 68.56, 65.78, 45.44, 14.06; Anal calc for $C_9H_{11}IN_2O_3$: C, 33.56; H, 3.44; N, 8.70. Found: C, 33.40; H, 3.31; N, 8.57.

1-[3,3′-Bis-(hydroxymethyl)-prop-2-enyl] 5-iodouracil (18). Compound **18** was prepared from **10** as described for **16**: Yield 78%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.13 (s, 1H), 5.44 (t, *J* = 7.0 Hz, 1H), 4.80 (t, *J* = 5.6 Hz, 1H), 4.73 (t, *J* = 5.4 Hz, 1H), 4.40 (d, *J* = 7.1 Hz, 2H), 4.03 (d, *J* = 5.4 Hz, 1H), 3.95

(d, J = 5.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.45, 151.08, 149.99, 145.34, 119.06, 68.74, 58.03, 57.24, 44.97; Anal calc for $C_9H_{11}IN_2O_4$: C, 31.97; H, 3.28; N, 8.29. Found: C, 32.19; H, 3.16; N, 8.34.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl] thymine (19). Compound **19** was prepared from **11** as described for **15**. Yield 88%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.21 (br s, 1H), 7.44 (s, 1H), 5.39 (t, J = 6.9, 1H), 4.85 (t, J = 5.6 Hz, 1H), 4.27 (d, J = 6.8 Hz, 2H), 3.80 (d, J = 5.2 Hz, 2H), 1.74 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.68, 151.24, 141.45, 141.02, 117.67, 109.12, 65.81, 44.78, 14.05, 12.36; Anal calc for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.21; H, 6.57; N, 13.20.

1-[3,3′-Bis-(hydroxymethyl)-prop-2-enyl] thymine (20). Compound **20** was prepared from **12** as described for **16**. Yield 80%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.48 (s, 1H), 5.41 (t, J = 6.9 Hz, 1H), 4.81 (t, J = 5.6 Hz, 1H), 4.73 (t, J = 5.4 Hz, 1H), 4.39 (d, J = 6.8 Hz, 2H), 4.03 (d, J = 5.4 Hz, 2H), 3.95 (d, J = 4.9 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.94, 150.69, 144.98, 140.32, 119.28, 108.18, 62.85, 57.36, 45.40, 12.93; Anal calc for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.78; H, 6.41; N, 12.26.

1-[(*E*)-4-(Hydroxy)-3-methyl-but-2-enyl] cytosine (21). Compound **21** was prepared from **13** as described for **15**. Yield 87%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.24 (br s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 5.56 (d, J = 7.8 Hz, 1H), 5.46 (t, J = 6.8 Hz, 1H), 4.43 (s, 2H), 4.32 (d, J = 6.7 Hz, 1H), 2.02 (s, 3H), ^{13}C NMR (DMSO-d_6, 75 MHz) δ 170.53, 164.12, 151.29, 145.69, 135.44, 122.24, 101.58, 68.29, 45.29, 14.31; Anal calc for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.20; H, 6.67; N, 21.42.

1-[3,3′-Bis-(hydroxymethyl)-prop-2-enyl] cytosine (22). Compound **22** was prepared from **14** as described for **16**. Yield 80%; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.56 (d, J = 7.1, 1H), 7.00 (br s, 2H), 5.65 (d, J = 7.1 Hz, 1H), 5.42 (t, J = 7.2 Hz, 1H), 4.78 (dd, J = 10.8, 5.4 Hz, 2H), 4.36 (d, J = 7.2 Hz, 2H), 4.01 (d, J = 4.9 Hz, 2H), 3.93 (d, J = 4.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.35, 156.18, 146.08, 144.20, 120.41, 93.97, 63.01, 57.29, 45.81; Anal calc for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.40; H, 6.10; N, 20.14.

CONCLUSION

A very simple synthetic method for synthesizing novel acyclic pyrimidine nucleosides from simple ketone derivatives was developed in this study. When the synthesized compounds were tested against several viruses such as HIV, HSV-1, HSV-2, and HCMV, only the 5-iodouracil analogue **18** exhibited moderate antiviral activity against the HSV-1.

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