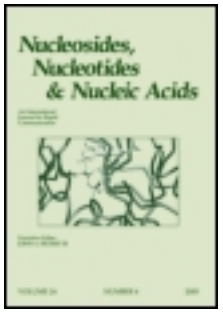

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Simple Synthesis of Novel Acyclic (E)-Bromovinyl Nucleosides as Potential Antiviral Agents

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SIMPLE SYNTHESIS OF NOVEL ACYCLIC (*E*)-BROMOVINYL NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

Jin Woo Kim and Joon Hee Hong □ *College of Pharmacy, Chosun University, Kwangju, Republic of Korea*

□ *In these study, novel acyclic (*E*)-bromovinyl nucleosides were synthesized as potential antiviral agents. The coupling of the allylic bromide* ***9*** *with bases (thymine, uracil, 5-fluorouracul, 5-iodouracil, cytosine, adenine) afforded a series of novel acyclic nucleosides. The synthesized compounds were evaluated for their antiviral activity against various viruses such as HIV-1, HSV-1, HSV-2, and HCMV. 5-Iodouracil analogue* ***19*** *showed weak anti-HIV-1 activity.*

Keywords Antiviral Agents; Neplanocin A; Acyclovir; Penciclovir

INTRODUCTION

A number of carbocyclic adenosine analogues are assumed to exert their antiviral action through inhibition of SAH hydrolase. Recently, neplanocin A (NPA, **1**),[1] which is a novel cyclic carba analogue of adenosine with a cyclopentene ring, has generated considerable attention both synthetically and biologically due to the effect of the double bond on the compound activity and potency.[2] NPA mediated inhibition of *S*-adenosylhomocysteine hydrolase is responsible for its biological activity, which is the key enzyme in the regulation of *S*-adenosyl-methionine–dependent methylation rections during mRNA replication cycles.[3] Because of the unusual presence of a double bond in neplanocin A, this compound has stimulated extensive research in the synthesis of new olefinic nucleoside analogues that mimic the sugar portion of naturally occurring neplanocin A. However, with relatively few exceptions, the activity of most conventional carbocyclic nucleosides has been poorer than those of the corresponding ribosides. The loss of the furan oxygen in the carba nucleosides is believed to have a critical effect on their antiviral activity. The incorporation of halogen atoms into organic molecules has often been associated with profound changes

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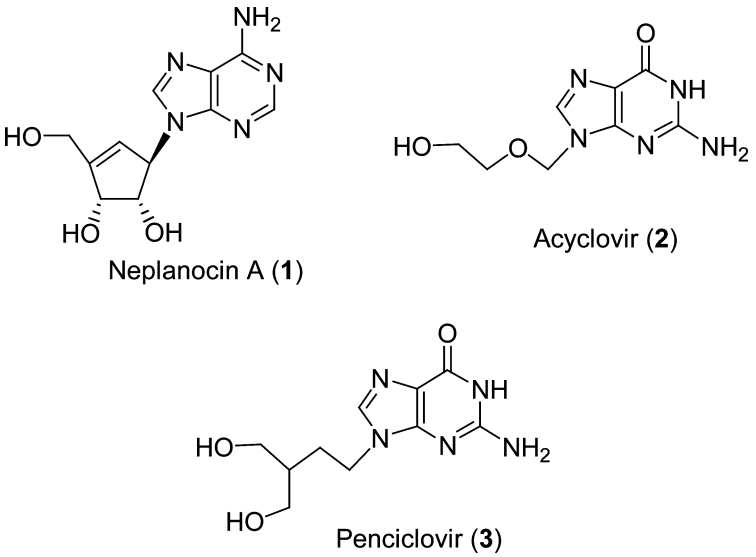


FIGURE 1 Synthesis rationale of the target compounds.

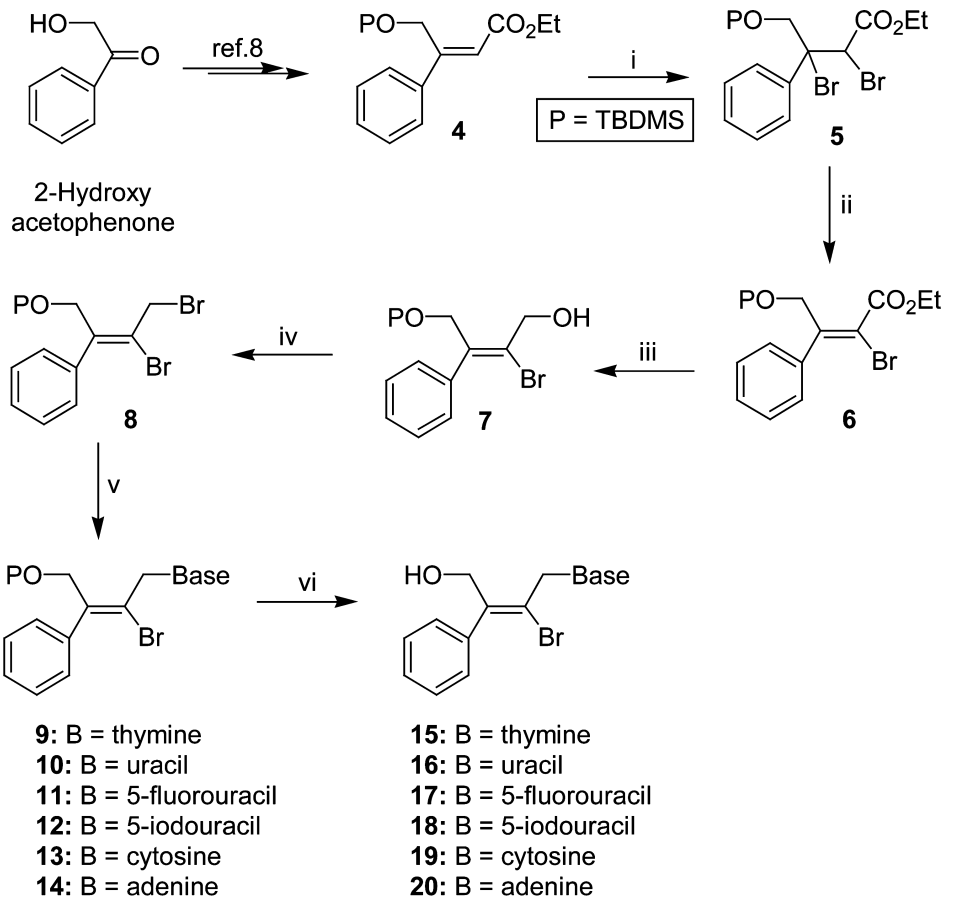
in the biological profiles of the halogenated analogues compared to their hydrocarbon counterparts.

More recently, (*E*)-5-(2-bromovinyl)uracil analogues, such as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU, **2**)[4] and 1(*β*-D-arabinofuranosyl)-(*E*)-5-(2-bromovinyl)uracil (BVAU, **3**),[5] have been found to exhibit potent anti-VZV activity in vitro as well as in vivo.[6] However, metabolic instability of BVDU by pyrimidine nucleosides phosphiorylase as well as the drug interaction of BVAU with 5-FU limited their use (Figure 1).

Motivated by these facts, the present investigation was directed toward the synthesis of hybrid compounds that comprise both olefinic nucleoside moiety and the aforementioned bromovinyl nucleosides. Such hybridization was elaborated to obtain synergistic chemotherapeutic activity with higher selectivity and less toxicity.

RESULTS AND DISCUSSION

As shown in Scheme 1, the target nucleosides were from the protected ketone derivative **4**, which was readily synthesized from 2-hydroxyacetophenon by using the previously reported procedure.[7] Ketone derivative was subjected to Horner-Wadsworth-Emmons (HWE) reaction to give the *α*,*β*-unsaturated ethyl ester **5(*E*)** and **5(*Z*)**, which are readily separated as well as characterized by NOE study. For the synthesis of desired (*E*)-bromovinyl nucleosides, ester **5(*Z*)** was treated with Br_2 and Et_3N in CH_2Cl_2 solvent produced the dibrominated product **6**, which was converted to bromovinyl **7** using the K_2CO_3 in DMF. The bromovinyl **7** was



Reagents: i) Br_2, Et_3N, CCl_4; ii) K_2CO_3, DMF; iii) DIBAL-H, CH_2Cl_2; iv) PPh_3, NBS, CH_2Cl_2, rt; v) $CsCO_3$, DMF, rt; vi) TBAF, THF, rt.

SCHEME 1 Synthesis of acyclic bromovinyl nucleosides.

reduced with DIBAL-H to provide allylic alcohol **8**. Conversion of allylic alcohols **8** to the allylic bromide **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] The coupling of the allylic bromide **9** with bases (thymine, uracil, 5-fluorouracil, 5-iodouracil, cytosine, adenine) in DMF with cesium carbonate ($CsCO_3$) as a basic catalyst provided the nucleoside derivatives **10–15**. The desired acyclic bromovinyl nucleosides **16–21** was synthesized by removing of the *t*-butyldimethylsilyl group (TBDMS) using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF).

The antiviral assays against several viruses such as HIV-1 (MT-4 cells), HSV-1 (CCL81 cells), HSV-2 (CCL-81 cells), and HCMV (AD-169) were performed. As shown in Table 1, none of the tested compounds showed

TABLE 1 Antiviral Activity of the Synthesized Compounds

	HIV-1 EC_{50} (μM)	HSV-1 EC_{50} (μM)	HSV-2 EC_{50} (μM)	HCMV EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
16	>100	>100	>100	56.81	>100
17	51.82	>100	>100	>100	>100
18	>100	>100	>100	>100	>100
19	28.20	>100	>100	77.26	>100
20	>100	>100	>100	>100	>100
21	>100	45.32	>100	>100	>100
AZT	0.0002	ND	ND	ND	2.0
GCV	ND	ND	ND	1.0	>10
ACV	ND	0.4	ND	ND	>100

AZT: azidothymidine; GCV: ganciclovir; ACV: acyclovir.
ND: Not determined.
EC_{50} (μM): Concentration required to inhibit 50% of virus-induced cytopathicity.
CC_{50} (μM): Concentration required to reduce cell viability by 50%.
See De Clercq[2] and Borchardt et al.[9] for the anitviral activity of neplanocin A.

good antiviral activity except for the 5-iodouracil **19**, which exhibited moderate anti-HIV-1 activity (EC_{50} = 28.20 μmol) without any cytotoxicity up to 100 μM.

In conclusion, a very simple synthetic method for novel acyclic neplanocin A analogues from a ketone derivative was developed in this study. When the synthesized compounds were tested against several viruses, only iodouracil derivative **19** showed weak anti-HIV-1 activity. Although we could not find good antiviral agents, the information obtained in the present study will be useful for the development of a novel nucleoside antiviral agent.

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.

*(*E*)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-enoic acid ethyl ester (5*E*) and (*Z*)-4-(t-butyldimethylsilyloxy)-3-phenyl-but-2-enoic acid ethyl ester (5*Z*).* To a suspension of sodium hydride (60% in mineral oil, 0.74 g, 18.5 mmol) in distilled THF at 0°C, triethyl phosphonoacetate (2.81 mL, 18.5 mmol) was added

dropwise and with constant stirring at room temperature for 1 h. The ketone **4** (4.6 g, 18.5 mmol) was added to this mixture and stirred for 1 h. The solution was neutralized with AcOH and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **5(*Z*)** (2.64 g, 45%) and **5(*E*)** (2.24 g, 38%), respectively. Compound **5(*E*):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.22 (m, 2H), 7.07–7.04 (m, 3H), 5.17 (s, 1H), 4.23 (d, $J = 2.1$ Hz, 2H), 3.90 (q, $J = 6.5$ Hz, 2H), 0.95 (t, $J = 6.5$ Hz, 3H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.19, 157.56, 137.46, 127.89, 127.30, 115.18, 66.77, 59.71, 25.82, 18.33, 13.88, -5.51; Compound **5(*Z*):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.46 (m, 2H), 7.35–7.33 (m, 3H), 6.04 (s, 1H), 5.19 (s, 2H), 4.23 (q, $J = 6.9$ Hz, 2H), 1.32 (t, $J = 6.9$ Hz, 3H), 0.75 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.10, 158.56, 139.13, 128.64, 127.97, 127.69, 117.65, 60.17, 59.64, 25.66, 18.08, 14.29, −5.38.

*Ethyl-2,3-dibromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enoic acid ethyl ester (6).* To a solution of compound **5(*Z*)** (419.8 mg, 1.31 mmol) in CCl_4 under nitrogen was added bromine (0.06 mL, 1.443 mmol) followed by slow addition of triethylamine (0.27 mL, 1.965 mmol) at ice bath. The reaction mixture was stirred for 5 h at 0°C, filtered, and washed with CCl_4. The filtrate was washed with 2 N HCl and then sodium bicarbonate, dried with anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **5** (339 mg, 54%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76–7.69 (m, 2H), 7.34–7.27 (m, 3H), 5.13 (s, 2H), 4.57 (d, $J = 11.1$ Hz, 1H), 4.35 (d, $J = 11.1$ Hz, 1H), 4.16 (q, $J = 6.9$ Hz, 2H), 1.17 (t, $J = 6.9$ Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 167.10, 138.99, 129.54, 128.93, 128.56, 127.89, 127.59, 70.79, 61.99, 51.44, 25.75, 18.85, 13.74, −5.52.

*(E)-2-Bromo-4-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-but-2-enoic acid ethyl ester (7).* Ester **6** (576 mg, 1.2 mmol) was dissolved in DMF (15 mL) and treated with K_2CO_3 (248 mg, 1.8 mmol). The mixture was stirred over night and quenched with water and extracted with diethyl ether. Organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give compound **7** (479 mg, 65%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.22 (m, 5H), 4.72 (s, 2H), 4.01 (q, $J = 7.5$ Hz, 2H), 1.00 (t, $J = 7.5$ Hz, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 164.62, 148.73, 137.87, 128.12, 127.92, 110.34, 66.25, 61.85, 25.69, 18.11, 13.41, −5.50.

*(E)-2-Bromo-4-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-but-2-en-1-ol (8).* To a solution of compound **7** (3.77 g, 9.45 mmol) in CH_2Cl_2 (100 mL), DIBAL-H (8.3 mL, 1.0 M solution in hexane) was added slowly at −20°C, and stirred for 2 h at the same temperature. To the resulting mixture, methanol (10 mL) was slowly added. The mixture was stirred at room temperature for

2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give the allylic alcohol **8** (3.24 g, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.23 (m, 5H), 4.69 (s, 2H), 4.25 (d, J = 5.7 Hz, 2H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.76, 137.70, 128.75, 128.07, 127.68, 125.10, 67.05, 65.52, 25.76, 18.64, −5.43.

*(*E*)-*tert*-Butyl-(3,4-dibromo-2-phenyl-but-2-enyloxy)-dimethylsilane (9).* To a solution of compound **8** (1.44 g, 4.03 mmol) and triphenylphosphine (1.16 g, 4.44 mmol) in CH_2Cl_2 (40 mL), *N*-bromosuccinimide (768 mg, 4.32 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 **9** (999 mg, 59%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.27 (m, 5H), 4.64 (s, 2H), 3.53 (s, 2H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.23, 137.26, 128.19, 127.92, 119.98, 67.15, 37.40, 25.73, 18.11, −5.50; Anal calc for $C_{16}H_{24}Br_2OSi$: C, 45.73; H, 5.76. Found: C, 45.61; H, 5.82.

*(*E*)-1-[2-Bromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enyl]thymine (10).* A solution of the allylic bromide **9** (307 mg, 0.732 mmol), thymine (297 mg, 2.364 mmol), and sodiume hydride (90 mg, 2.364 mmol) in anhydrous DMF (15 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** (150 mg, 44%) as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (br s, 1H), 7.49–7.25 (m, 5H), 6.84 (s, 1H), 4.68 (s, 2H), 4.60 (s, 2H), 1.97 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.64, 150.49, 146.13, 138.93, 137.27, 128.55, 128.13, 118.35, 110.92, 67.03, 51.10, 25.64, 18.76, 12.47, −5.53.

*(*E*)-1-[2-Bromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enyl] uracil (11).* Compound **11** was synthesized from **9** using the procedure as described for **10**: yield 39%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (br s, 1H), 7.30–7.17 (m, 5H), 6.54 (d, J = 5.4 Hz, 1H), 5.99 (d, J = 5.7 Hz, 1H), 3.73 (dd, J = 19.8, 9.6 Hz, 2H), 2.90 (d, J = 14.4 Hz, 1H), 2.70 (d, J = 14.4 Hz, 1H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 163.70, 150.84, 146.22, 144.11, 141.01, 128.56, 127.91, 120.51, 102.27, 64.26, 51.62, 25.76, 18.20, −5.56.

*(*E*)-1-[2-Bromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enyl] 5-fluorouracil (12).* Compound **12** was synthesized from **9** using the procedure as described for **10**: yield 34%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ

8.89 (br s, 1H), 7.49 (d, J = 5.4 Hz, 1H), 7.40–7.25 (m, 5H), 4.67 (s, 2H), 4.45 (s, 2H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.27, 153.62, 145.78, 142.83, 137.54, 128.45, 127.89, 118.62, 101.34, 67.54, 51.62, 25.54, 18.34, −5.62.

*(E)-1-[2-Bromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enyl] 5-iodouracil (13).* Compound **13** was synthesized from **9** using the procedure as described for **10**: yield 42%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.01 (br s, 1H), 7.59 (s, 1H), 7.46–7.23 (m, 5H), 4.68 (s, 2H), 4.53 (s, 2H), 0.80 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 162.02, 151.78, 146.78, 144.56, 138.32, 129.71, 128.98, 127.52, 120.62, 116.34, 67.65, 52.44, 25.50, 18.91, −5.65.

*(E)-1-[2-Bromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enyl] cytosine (14).* Compound **14** was synthesized from **9** using the procedure as described for **10**: yield 36%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, J = 7.4 Hz, 1H), 7.42–7.22 (m, 5H), 5.74 (d, J = 7.4 Hz, 1H), 4.76 (s, 2H), 4.49 (s, 2H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 166.21, 150.33, 146.71, 145.65, 138.38, 128.50, 127.62, 119.77, 92.90, 67.67, 51.23, 25.60, 18.39, −5.59.

*(E)-9-[2-Bromo-4-(*tert*-butyldimethylsilanyloxy)-3-phenyl-but-2-enyl] adenine (15).* Compound **15** was synthesized from **9** using the procedure as described for **10**: yield 43%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (s, 1H), 8.12 (s, 1H), 7.39–7.19 (m, 5H), 4.79 (s, 2H), 4.54 (s, 2H), 0.80 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.72, 152.56, 150.84, 146.65, 140.34, 137.76, 128.50, 127.89, 120.45, 118.65, 67.76, 50.98, 25.67, 18.71, −5.65.

(E)-1-(2-Bromo-4-hydroxy-3-phenyl-but-2-enyl) thymine (16). To a solution of compound **10** (200 mg, 0.432 mmol) in THF (10 mL), TBAF (0.65 mL, 1.0 M solution in THF) at 0°C was added. The mixture was stirred at room temperature for 5 h and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:7) to give compound **16** (91 mg, 60%) as a white solid: mp 160–163°C; UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.25 (br s, 1H), 7.55–7.28 (m, 5H), 7.17 (s, 1H), 4.98 (t, J = 6.0 Hz, 1H), 4.39 (m, 4H), 1.72 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.99, 151.85, 146.69, 142.56, 138.78, 128.13, 127.45, 119.45, 110.56, 64.54, 51.39, 12.87; Anal calc for $C_{15}H_{15}BrN_2O_3$: C, 51.30; H, 4.31; N, 7.98. Found: C, 51.15; H, 4.27; N, 8.19.

(E)-1-(2-Bromo-4-hydroxy-3-phenyl-but-2-enyl) uracil (17). Uracil nucleoside **17** was synthesized from **11** using the procedure as described for **16**: yield 67%; mp 165–168°C; UV (H_2O) λ_{max} 263.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.28 (br s, 1H), 7.55–7.24 (m, 6H), 5.73 (d, J = 8.1 Hz, 1H), 5.33 (t, J = 5.7 Hz, 1H), 4.53–4.37 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 163.71, 151.36, 148.77, 145.98, 138.39, 128.61, 128.32, 127.89, 120.54, 102.61, 65.46, 51.69; Anal calc for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; N, 8.31. Found: C, 49.75; H, 4.08; N, 8.47.

(E)-1-(2-Bromo-4-hydroxy-3-phenyl-but-2-enyl)-5-fluorouracil (18). Compound **18** was synthesized from **12** using the procedure as described for **16**: yield 69%; mp 155–158°C; UV (H_2O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.83 (br s, 1H), 7.77 (d, J = 5.6 Hz, 1H), 7.41–7.22 (m, 5H), 5.01 (t, J = 5.4 Hz, 1H), 4.70 (s, 2H), 4.43 (d, J = 5.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 165.69, 154.21, 146.12, 143.78, 138.11, 127.98, 127.21, 119.69, 108.34, 67.61, 51.42; Anal calc for $C_{14}H_{12}BrFN_2O_3$: C, 47.34; H, 3.41; N, 7.89. Found: C, 47.56; H, 3.27; N, 7.66.

(E)-1-(2-Bromo-4-hydroxy-3-phenyl-but-2-enyl)-5-iodouracil (19). Compound **19** was synthesized from **13** using the procedure as described for **16**: yield 70%; mp 167–170°C; UV (H_2O) λ_{max} 285.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.39 (br s, 1H), 7.50 (s, 1H), 7.41–7.21 (m, 5H), 5.09 (t, J = 5.8 Hz, 1H), 4.65 (s, 2H), 4.50 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 161.89, 152.23, 147.70, 145.21, 138.31, 128.70, 128.65, 127.52, 120.62, 70.56, 67.54, 51.87; Anal calc for $C_{14}H_{12}BrIN_2O_3$: C, 36.31; H, 2.61; N, 6.05. Found: C, 36.50; H, 2.56; N, 5.85.

(E)-1-(2-Bromo-4-hydroxy-3-phenyl-but-2-enyl) cytosine (20). Cytosine derivative **20** was synthesized from **14** using the procedure as described for **16**: yield 60%; mp 168–170°C; UV (H_2O) λ_{max} 272.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.72 (d, J = 7.0 Hz, 1H), 7.42–7.22 (m, 5H), 5.71 (d, J = 70 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 4.74 (s, 2H), 4.54 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 166.76, 153.23, 147.71, 138.87, 128.32, 127.72, 121.78, 100.47, 65.64, 52.45; Anal calc for $C_{14}H_{14}BrN_3O_2$: C, 50.02; H, 4.20; N, 12.50. Found: C, 49.87; H, 4.15; N, 12.68.

(E)-9-(2-Bromo-4-hydroxy-3-phenyl-but-2-enyl) adenine (21). Adenine nucleoside **21** was synthesized from **15** using the procedure as described for **16**: yield 68%; mp 180–181°C; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.52 (s, 1H), 8.09 (s, 1H), 7.48–7.19 (m, 5H), 5.05 (t, J = 5.4 Hz, 1H), 4.70 (s, 2H), 4.64 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 155.74, 153.72, 150.76, 147.51, 141.71, 137.90, 128.89, 128.32, 127.39, 120.32, 119.54, 64.23, 51.51; Anal calc for $C_{15}H_{14}BrN_5O$: C, 50.02; H, 3.92; N, 19.44. Found: C, 50.19; H, 4.12; N, 19.58.

REFERENCES

1. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. Studies on Neplanocin A, New Antitumor Antibiotics. I. Producing Organism, Isolation and Characterization. *Journal of Antibiotics* **1981**, 34, 359–366.
2. De Clercq, E. Antiviral and Antimetabolic Activities of Neplanocins. *Antimicrobial Agents in Chemotherapy* **1985**, 28, 84–89.
3. Wolfe, M.S.; Borchart, R.T. *S*-Adenosylhomocysteine Hydrolase as Target for Chemotherapy. *Journal of Medicinal Chemistry* **1991**, 34, 1521–1530.
4. De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P.J.; Jones, A.S.; Walker, R.T. (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine: A Potent and Selective Anti-Herpes Agent. *Proceedings of the National Academy of Sciences USA* **1979**, 76, 2947–2951.

5. Machida, H.; Sakata, S.; Kuninaka, A.; Yoshino, H. Antiherpes Viral and Anticellular Effect of 1-β-D-Arabinofuranosyl-*E*-5-(2-Halogenovinyl)Uracils. *Antimicrobial Agents in Chemotherapy* **1981**, 20, 47–52.
6. Desgranges, C.; Razaka, G.; Rabaud, M.; Bricaud, H.; Balzarini, J.; De Clercq, E. Phospholysis of (*E*)-(2-Bromovinyl)-2′-Deoxy-Uridine (BVDU) and Other 5-Substituted-2′-Deoxyuridine by Purified Human Thymidine Phosphorylase and Intact Blood Platelets. *Biochemical Pharmacology* **1983**, 32, 3583–3590.
7. Hong, J.H.; Ko, O.H. Synthesis of 4′α-*C* Phenyl Branched Carbocyclic Nucleoside Using Ring Closing Metathesis. *Bulletin of the Korean Chemical Society* **2003**, 24, 1289–1292.
8. Borcherding, D.R.; Narayanan, S.; Hasobe, M.; McKee, J.G.; Keller, B.T.; Borchardt, R.T. Potential Inhibitors of *S*-Adenosylmethionine-Dependent Methyltransferases: Molecular Dissections of Neplanocin A as Potential Inhibitors of *S*-Adenosylhomocysteine Hydrolase. *Journal of Medicinal Chemistry* **1988**, 31, 1729–1738.