Structure−Activity Relationships of (*E*)-5-(2-Bromovinyl)uracil and Related Pyrimidine Nucleosides as Antiviral Agents for Herpes Viruses

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A series of (*E*)-5-(2-bromovinyl)uracil analogues and related nucleosides was synthesized, and their antiviral activities were evaluated. (*E*)-5-(2-Bromovinyl)-2′-deoxy-L-uridine (L-BVDU, **2**), 1-(β-L-arabinofuranosyl)-(*E*)-5-(2-bromovinyl)uracil (L-BVAU, **4**), (*E*)-5-(2-bromovinyl)-1-(2-deoxy-2-fluoro-β-L-ribofuranosyl)uracil (L-FBVRU, **8**) and (*E*)-5-(2-bromovinyl)-1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)uracil (L-FBVAU, **10**) were synthesized via appropriate 5-iodouracil analogues from L-arabinose. D- and L-Oxathiolane and -dioxolane derivatives **13**, **16**, **20**, **21**, and **29**−**34** were prepared by glycosylation reaction of the oxathiolane and dioxolane intermediates with silylated uracil analogues using TMSI as the coupling agent. The synthesized compounds were evaluated in cell cultures infected with the following viruses: varicella zoster virus (VZV), Epstein Barr virus (EBV), and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2). Among the tested compounds, β-L-CV-OddU (**29**), β-L-BV-OddU (**31**), and β-L-IV-OddU (**33**) exhibited potent in vitro antiviral activity against VZV with EC_{50} values of 0.15, 0.07, and 0.035 μM, respectively, and against EBV with EC_{50} values of 0.49, 0.59, and 3.91 μM, respectively.

Introduction

Varicella zoster virus (VZV), a member of the γ-herpes virus family, is a causative agent for primary infections (varicella and chicken pox) as well as recurrent diseases (zoster and shingles) in humans.[1] One of the major complications of shingles is the postherpetic neuralgia, which is characterized by persistent acute pain induced after the VZV reactivation and the resolution of a skin rash.[2] The course of varicella is generally benign in immunocompetent patients; however, in immunocompromised patients, particularly patients suffering from acquired immune deficiency syndrome (AIDS), transplant recipients, and cancer patients, VZV infections can be life-threatening.[3,4] The current treatment for immunocompromised and immunocompetent patients, such as pregnant women or premature infants, is based on acyclovir (ACV).[5] More recently, valaciclovir and famciclovir, prodrugs of acyclovir and penciclovir (PCV), have been approved for the treatment of VZV infection.[6] However, low efficacy and/or low oral bioavailability of these agents,[7] as well as the emergence of drug-resistant virus strains,[8] prompted the development of new antiviral agents for the treatment of VZV infection. Among them, (*E*)-5-(2-bromovinyl)uracil (BVU) analogues, such as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU)[9] and 1-(β-D-arabinofuranosyl)-(*E*)-5-(2-bromovinyl)uracil (BVAU),[10] have been found to exhibit potent anti-VZV activity in vitro as well as in vivo. However, metabolic instability of BVDU by pyrimidine nucleoside phosphorylase,[11] as well as the drug interaction of BVAU with 5-FU,[12] limits their use. Efforts to address these problems have led to several interesting nucleosides such as 4′-thio-BVDU[13] and the carbocyclic analogue carba-BVDU.[14] However, the carba derivatives, which are resistant to degradation and have antiviral activities comparable to those of the parent compounds in cell culture, exhibit poor in vivo activity.[14,15]

Since the discovery of 3TC as an anti-HIV agent, a number of L-nucleosides have been synthesized and identified as potent antiviral agents, such as 3TC,[16] FTC,[17] L-OddC,[18] and L-FMAU.[19] Some L-nucleosides have shown different substrate specificities toward catabolic as well as anabolic enzymes, such as nucleoside kinases and deaminases, resulting in reduced toxicity, increased potency, and metabolic stability.[20] In view of these interesting biological properties of L-nucleosides, it was of interest to synthesize (*E*)-5-(2-bromovinyl)uracil substituted L-nucleosides as potential antiviral agents. Herein, we describe the structure−activity relationships of the title compounds against varicella zoster virus, Epstein Barr virus, and herpes virus types 1 and 2.

Results and Discussion

Chemistry. The syntheses of (*E*)-5-(2-bromovinyl)-2′-deoxy-L-uridine (L-BVDU, **2**) and 1-(β-L-arabinofuranosyl)-(*E*)-5-(2-bromovinyl)uracil (L-BVAU, **4**) were accomplished via 2′-deoxy-L-5-iodouridine (β-L-IUdR, **1**) and 1-(β-L-arabinofuranosyl)-5-iodouracil (β-L-I-ara-U, **3**), respectively, from L-arabinose based on the method published by Holy[21] and the Heck reaction[22] with minor modifications as shown in Scheme 1.

Several routes for the syntheses of 2′-deoxy-2′-fluoro-β-D-ribonucleosides have been previously reported, including the opening of 2,2′-anhydronucleosides with a fluorinating agent (HF/dioxane or KF/crown ether),[23,24]

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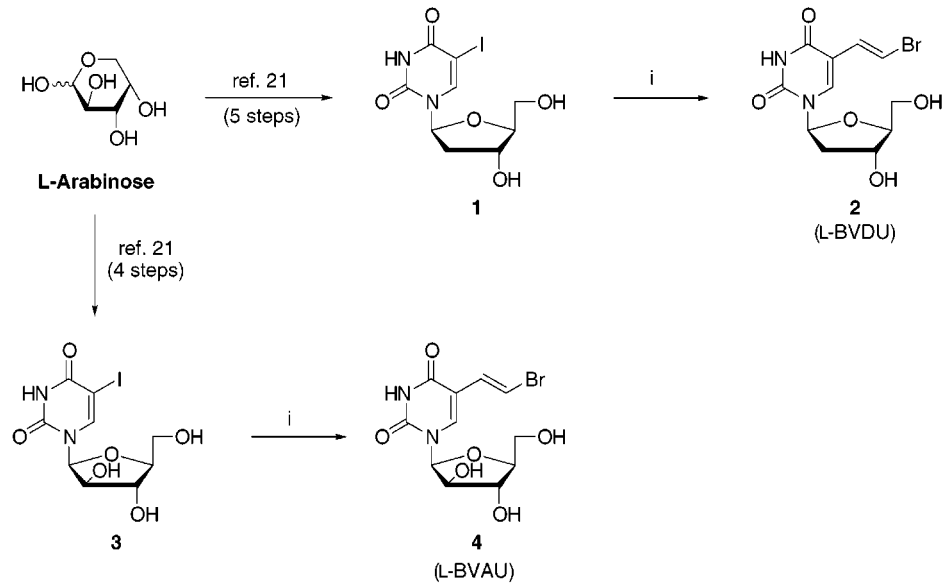
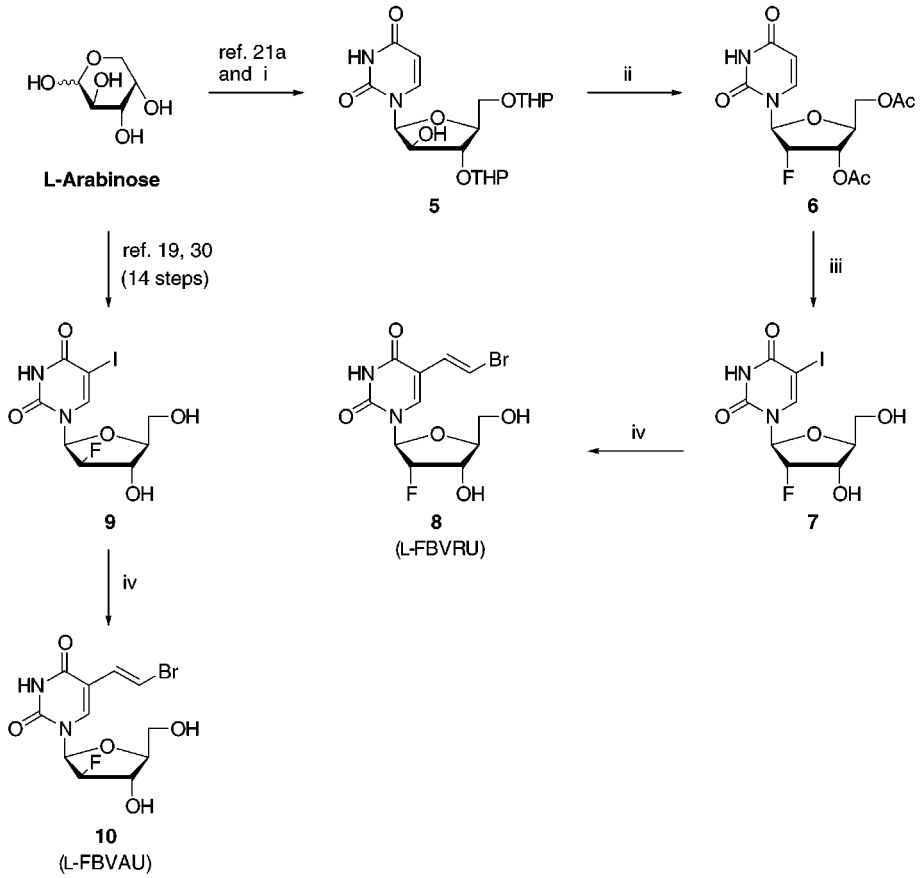
Scheme 1. Synthesis of l-BVDU and L-BVAU[a]



[a] Reagents: (i) (a) $Pd(OAc)_2$, Ph_3P, methyl acrylate, 1,4-dioxane, (b) NaOH, (c) *c*-HCl, (d) K_2CO_3, NBS, DMF.

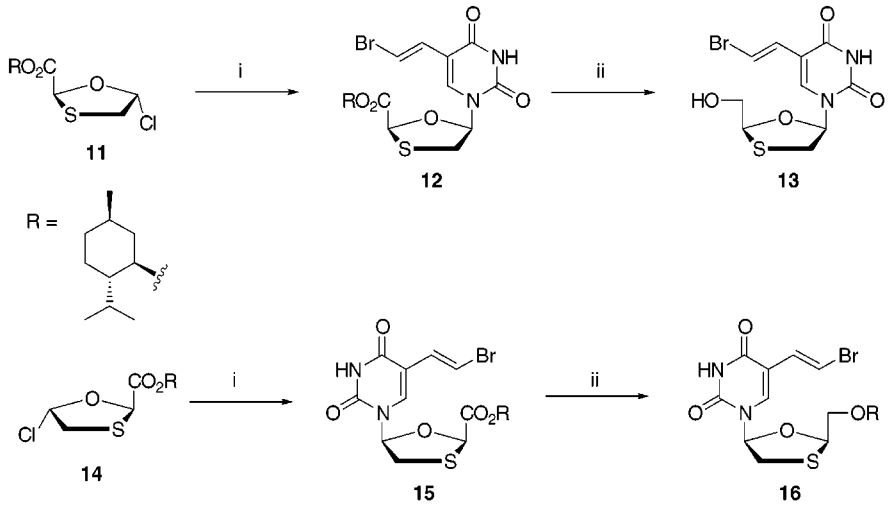
Scheme 2. Synthesis of l-FBVRU and L-FBVAU[a]



[a] Reagents: (i) (a) *p*-TsOH, DHP, DMF, (b) NaOH, MeOH, H_2O; (ii) (a) DAST, pyridine, CH_2Cl_2, (b) *p*-TsOH, MeOH, (c) Ac_2O, pyridine; (iii) (a) ICl, CH_2Cl_2, (b) NH_3/MeOH; (iv) (a) $Pd(OAc)_2$, Ph_3P, methyl acrylate, 1,4-dioxane, (b) NaOH, (c) *c*-HCl, (d) K_2CO_3, NBS, DMF.

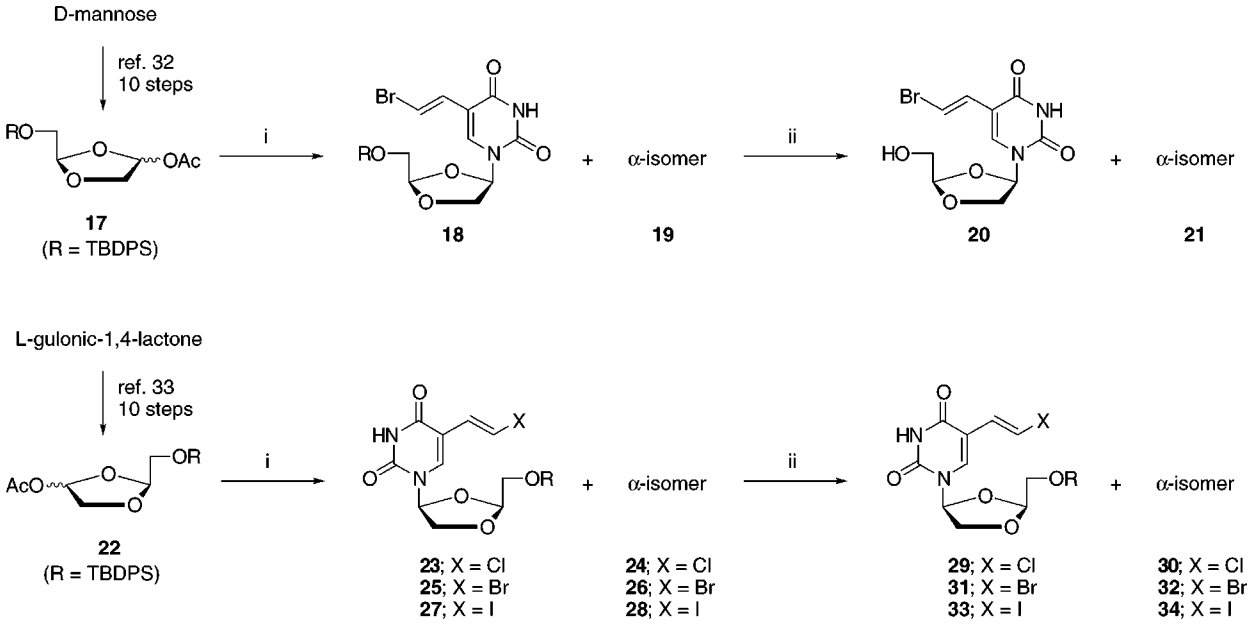
the coupling of a suitably blocked 2-deoxy-2-fluororibofuranoside with appropriate heterocyclic bases,[25] an enzyme-catalyzed transglycosylation,[26] the nucleophilic displacement of 2′-*O*-trifluoromethanesulfonyl arabinonucleosides by tetra-*n*-butylammonium fluoride (TBAF),[27] and the direct introduction of fluorine atom by diethylaminosulfur trifluoride (DAST) to an arabinonucleoside.[28] Thus, the last methodology was adopted for the synthesis of pyrimidine 2′-deoxy-2′-fluoro-β-L-ribofuranosyl nucleoside **8** because a reliable yield was achieved in a relatively large scale (Scheme 2). Thus, 2,2′-anhydro-L-uridine was prepared from L-arabinose in two steps according to a literature procedure,[21] which was treated with 3,4-dihydropyran in DMF followed by saponification to give **5** in 40% overall yield from 2,2′-anhydro-L-uridine. Compound **5** was then treated suc-

Scheme 3. Synthesis of (*E*)-5-(2-Bromovinyl)-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)uracil[a]



[a] Reagents: (i) (a) 5-(*E*)-bromovinyluracil, TBDMSOTf, 2,4,6-collidine, CH_2Cl_2, (b) TMSI; (ii) $NaBH_4$.

Scheme 4. Synthesis of (*E*)-5-(2-Halovinyl)-1-(2-hydroxymethyl-1,3-dioxolan-5-yl)uracil[a]



[a] Reagents: (i) (a) 5-(*E*)-bromovinyluracil, TBDMSOTf, 2,4,6-collidine, CH_2Cl_2, (b) TMSI; (ii) TBAF, CH_3CN.

cessively with DAST, *p*-TsOH, and Ac_2O in pyridine to give the key intermediate **6** in 41% yield after crystallization from EtOH. Treatment of **6** with ICl in refluxing CH_2Cl_2[29] followed by ammonolysis with saturated NH_3/MeOH afforded the 5-iodouracil analogue **7**, which was converted to the (*E*)-5-(2-bromovinyl)uracil analogue **8** by palladium-catalyzed coupling of methyl acrylate followed by hydrolysis and decarboxylation in the presence of *N*-bromosuccinimide and potassium carbonate. 2′-Deoxy-2′-fluoro-*β*-L-arabinofuranosyl nucleoside **10** was prepared by a similar procedure via L-FIAU (**9**), whose synthesis had previously been accomplished by our group (Scheme 2).[19,30] Thus, 5-iodouracil analogue **9** was transformed to **10** by a method similar to the synthesis of compound **8**.

The oxathiolane and dioxolane intermediates **11**, **14**, **17**, and **22**, used in the synthesis of the corresponding bromovinyl nucleosides (Schemes 3 and 4), were prepared by the reported methods with minor modifications.[31−33] (*E*)-5-(2-Halovinyl)uracils were prepared according to the methods of Jones et al.[34] from the condensation of 5-formyluracil with malonic acid, followed by the treatment with halosuccinimide. The treatment of the chloride **11** with persilylated (*E*)-5-(2-bromovinyl)uracil in CH_2Cl_2 in the presence of TMSI afforded the expected *cis*-nucleoside as the major isomer (*cis:trans* 30:1 by ^1H NMR) in 87% yield. Reduction of compound **12** with $NaBH_4$ in EtOH provided the desired nucleoside **13** in 70% yield. The L-enantiomer **16** was also obtained by condensation of **14** with (*E*)-5-(2-bromovinyl)uracil followed by reduction.

Glycosylations of the dioxolane moieties with the appropriate uracil bases were also performed by using TMSI as the catalyst (Scheme 4). Interestingly, although TMSI-mediated coupling of the chiral dioxolane sugar with a protected hydroxymethyl substituent at the 2-position is known to be nonstereoselective,[35] the condensation of **17** using TMSI gave the *β*-isomer as a major in a ratio of 3:1. Deprotection of **18** and **19** with TBAF in CH_3CN provided the free nucleosides **20** and

Table 1. Structure−Activity Relationships of (*E*)-5-(2-Bromovinyl)uracil Analogues and Related Pyrimidine Nucleosides

	EC_{50} (μM)				cytotoxicity (ID_{50})	
compd	VZV (Ellen)	EBV	HSV-1 (KOS)	HSV-2 (333)	CEM	Mt[a]
2 (L-BVDU)	>50	>50	>50	>50	>100	
4 (L-BVAU)	>50	>50	>50	>50	>100	
8 (L-FBVRU)	>50	ND	>50	>50	>100	
10 (L-FBVAU)	>50	ND	>50	>50	>100	
13 (β-D-BV-SddU)	ND[b]	ND	>50	>50	>100	
16 (β-L-BV-SddU)	12.5	ND	>50	>50	>100	
20 (β-D-BV-OddU)	26	>50	>50	>50	>100	
21 (α-D-BV-OddU)	>30	>50	>50	>50	>100	
29 (β-L-CV-OddU)	0.15	0.49	18	>50	>100	>200
30 (α-L-CV-OddU)	>30	>50	>50	>50	>100	>25
31 (β-L-BV-OddU)	0.07	0.59	36	>50	>100	>200
32 (α-L-BV-OddU)	>30	>50	>50	>50	>100	>25
33 (β-L-IV-OddU)	0.035	3.91	33	>50	>100	>200
34 (α-L-IV-OddU)	>30	>50	>50	>50	>100	>25
β-L-Br-OddU[38]	>30	0.19			>100	>200
β-L-I-OddU[38]	17	0.033			>100	>200
ACV	2.0	19.7	13.6		>100	>200
PCV	0.14	ND	18		>100	>200
BVDU	0.05	>50			>100	>200
BVAU	0.001	47			>100	>200

[a] Mt, mitochondrial toxicity. [b] ND, not determined.

21 in high yields.[36] Similarly, (*E*)-5-(2-halovinyl)uracil analogues **29**−**34**, possessing a dioxolane moiety with L-configuration, were obtained. The *E*-configurations of the synthesized nucleosides were identified by the coupling constant (13.6 Hz) for the vinyl protons in the ^{1}H NMR spectrum[37] and confirmed in comparison with physical data of the corresponding D-isomers.

Antiviral Activity. In vitro antiviral results are listed in Table 1. The efficacy of the synthesized compounds as potential antiviral agents was tested in cell cultures infected with the following viruses: varicella zoster virus (VZV), Epstein Barr virus (EBV), and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2). Cytotoxicity and mitochondrial toxicity were evaluated in CEM cells. Acyclovir (ACV), penciclovir (PCV), BVDU, and BVAU were included as positive controls.

From these studies, it was found that only L-dioxolane derivatives exhibited significant antiviral activity. L-Dioxolane nucleosides **29**, **31**, and **33** showed potent and selective anti-VZV and anti-EBV activity, and other compounds including the L-oxathiolane nucleoside did not show any significant antiviral activity. The anti-VZV activity of L-dioxolane nucleosides appears to be related to the size of the halogen atoms on the pyrimidine moiety in increasing order (Cl, Br, and I) with EC_{50} values of 0.15, 0.07, and 0.035 μM, respectively. In comparison to ACV (EC_{50} 2 μM), which is the most prescribed regimen in clinics, the chloro derivative **29** exhibited 13-fold higher activity against VZV. The bromo **31** and iodo **33** derivatives were 30 and 60 times, respectively, more potent than ACV. In comparison to PCV (EC_{50} 0.15 μM), the chloro derivative **29** showed equivalent potency and the bromo **31** and iodo **33** derivatives exhibited 2- and 4-fold potency, respectively. Compound **33** showed higher potency in vitro for anti-VZV activity than BVDU, which is known to be a potent and selective anti-VZV agent. Among the tested compounds, BVAU was the most potent compound against VZV. The synthesized compounds did not show any toxicity up to 100 μM in CEM cells and also did not show mitochondrial toxicity, which demonstrates high selectivity (SI > 2300) for compounds **29**, **31**, and **33**.

Recently, we reported the anti-EBV activity of L-dioxolane uracil nucleosides, among which L-I-OddU was the most potent anti-EBV agent.[38] As observed for VZV, it appeared that the anti-EBV activity of L-dioxolane nucleosides was related to the size of the halogen atoms of the pyrimidine moiety. Both anti-EBV activity of L-dioxolane nucleosides with halogenated uracils (Cl, Br, and I: EC_{50} 0.6, 0.19, and 0.033 μM, respectively)[38] and anti-VZV activity of their halovinyl analogues (EC_{50} 0.15, 0.07, and 0.035 μM) increased with the increasing size of the halogen atoms. Interestingly, (*E*)-5-(2-halovinyl)uracil analogues **29**, **31**, and **33** exhibited moderate to potent anti-EBV activity with EC_{50} values of 0.49, 0.59, and 3.91 μM, respectively, and 5-halouracil analogues did not exhibit significant anti-VZV activity. From these results, it may be concluded that the structural requirements of substrates for virus-encoded thymidine kinase or viral DNA polymerase of EBV are different from that of VZV.

Mansour and co-workers reported that β-L-dioxolane nucleoside **31** and (*E*)-5-(2-bromovinyl)-2′-deoxy-3′-oxa-β-D-thiouridine showed significant antiviral activity against HSV-1 (EC_{50} 0.3 μg/mL) and HSV-2 (EC_{50} 2.9 μg/mL).[37b] However, in our studies, compound **29** (EC_{50} 18 μM) was as active as PCV (EC_{50} 18 μM), whereas **31** (EC_{50} 36 μM) and **33** (EC_{50} 33 μM) were only weakly active against HSV-1 (ACV and PCV: EC_{50} 13.6 and 18 μM, respectively). Compounds **29**, **31**, and **33** did not exhibit any activity against HSV-2. According to Spadari et al., L-BVDU (**2**) was found to inhibit HSV-1 thymidine kinase with an IC_{50} of 0.26 μM and was fully resistant to hydrolysis by nucleoside phosphorylase.[15] However, in our in vitro study against HSV-1, L-BVDU did not display any activity up to 50 μM.

In summary, we demonstrated that L-dioxolane nucleosides bearing the (*E*)-5-(2-halovinyl)uracil heterocyclic moiety show potent and selective anti-VZV and anti-EBV activity in vitro, and the anti-VZV activity is dependent on the size of the halogen atoms. Therefore, further pharmacological and biochemical studies are warranted to elucidate their mechanism of action as well

as to determine the metabolic stability toward pyrimidine nucleoside phosphorylase.

Experimental Section

General Methods. Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400 AMX spectrometer for 400 MHz, with Me_4Si as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Optical rotations were performed on a Jasco DIP-370 digital polarimeter. TLC was performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel-60 (220−440 mesh) for flash chromatography or silica gel G (TLC grade, >440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

(*E*)-5-(2-Bromovinyl)-2′-deoxy-L-uridine (2). L-BVDU **(2)** was synthesized in three steps as described for the corresponding D-enantiomer,[22] starting from β-L-IUdR **(1)**:[21] mp 156 °C dec; $[\alpha]^{27}_D$ −19.4° (*c* 0.20, MeOH); UV (H_2O) λ_{max} 249.5 (ϵ 10900), 249.5 nm (ϵ 8040) (pH 7), 249 (ϵ 10800), 293.5 nm (ϵ 8040) (pH 2), 254.0 nm (ϵ 10800), 283.5 nm (ϵ 6850) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.00 (s, 1H, NH), 8.00 (s, 1H, 6-H), 7.17 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.77 (d, 1H, J = 13.6 Hz, vinylic Hb), 6.05 (t, 1H, J = 6.5 Hz, 1′-H), 5.19 (d, 1H, 3′-OH), 5.04 (t, 1H, 5′-OH), 4.17 (m, 1H, 3′-H), 3.71 (m, 1H, 4′-H), 3.52 (m, 2H, 5′-H), 2.06 (m, 2H, 2′-H). Anal. ($C_{11}H_{13}BrN_2O_5$) C, H, Br, N.

1-(β-L-Arabinofuranosyl)-(*E*)-5-(2-bromovinyl)uracil (4). L-BVAU **(4)** was also synthesized by the same procedure as for the synthesis of L-BVDU from β-L-I-ara-U **(3)**, which was prepared from l-arabinose:[21] mp 178−180 °C; $[\alpha]^{26}_D$ −18.1° (*c* 0.16, EtOH); UV (H_2O) λ_{max} 250.5 (ϵ 13300), 293.0 nm (ϵ 9850) (pH 7), 251.0 (ϵ 13300), 293.0 nm (ϵ 10300) (pH 2), 256.0 (ϵ 13500), 284.5 nm (ϵ 8470) (pH 11); ^{1}H NMR (DMSO-d_6) δ 9.69 (br s, 1H, NH), 7.90 (s, 1H, 6-H), 7.24 (d, 1H, J = 13.9 Hz, vinylic Ha), 6.87 (d, 1H, J = 13.9 Hz, vinylic Hb), 5.99 (t, 1H, J = 4.4 Hz, 1′-H), 5.59 (d, 1H, 2′-OH), 5.49 (d, 1H, 3′-OH), 5.14 (t, 1H, 5′-OH), 4.05 (m, 1H, 2′-H), 3.91 (m, 1H, 3′-H), 3.75 (m, 1H, 4′-H), 3.65 (m, 2H, 5′-H). Anal. ($C_{11}H_{13}BrN_2O_6\cdot$ 0.3EtOH) C, H, N.

1-(3,5-Di-*O*-acetyl-2-deoxy-2-fluoro-β-L-ribofuranosyl)-uracil (6). To a suspension of 2,2′-anhydro-L-uridine (17.0 g, 0.075 mol)[21] in DMF (300 mL) and 3,4-dihydropyran (180 mL) was added *p*-toluenesulfonic acid (14.0 g) at 0 °C and the mixture was stirred at 0 °C for 4 h, at which time a clear solution was obtained. This was neutralized with Et_3N (30 mL) and then evaporated to dryness. The residue was redissolved in EtOAc, washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent gave a residue which was triturated with hexanes and filtered. The filter cake was washed with hexanes and dried to give protected 2,2′-anhydro-L-uridine as a white solid (27.5 g, 93%), whose suspension (23.0 g, 58.5 mmol) in MeOH (300 mL) and 1 N NaOH (100 mL) was stirred at room temperature for 2 h, then neutralized with dilute acetic acid. The mixture was evaporated to dryness and the residue was loaded to a silica gel pad, eluted with EtOAc to give **5** as a white solid (22.6 g, 94%): UV (MeOH) λ_{max} 263.0 nm.

To a stirred mixture of **5** (20.6 g, 0.05 mol) in CH_2Cl_2 (300 mL) and pyridine (50 mL) was added DAST (25.0 g, 0.155 mol) at −60 °C under N_2. This resulting mixture was slowly warmed to room temperature and then refluxed for 4 H. The reaction was quenched with saturated $NaHCO_3$ and ice−water, then extracted with CH_2Cl_2 (100 mL × 3), washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent gave a dark-brown syrup (18.9 g), which was redissolved in MeOH (300 mL). *p*-Toluenesulfonic acid (6 g) was added to this and the mixture was stirred at room temperature for 3 h. It was then neutralized with pyridine (50 mL), coevaporated with pyridine (2 × 50 mL), then redissolved in pyridine (100 mL). Ac_2O (20 mL) was added to this and the mixture was stirred at room temperature for 20 h. Removal of the solvent and recrystallization from EtOH gave **6** as a white solid (6.8 g, total 41%): UV (MeOH) λ_{max} 257.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H, NH, D_2O exchangeable), 7.33 (d, 1H, J = 8.1 Hz, 6-H), 5.72 (dd, 1H, J = 25.0, 2.0 Hz, 1′-H), 5.70 (d, 1H, J = 8.1 Hz, 5-H), 5.30 (ddd, 1H, J_{F-H} = 52.2 Hz, 2′-H), 5.08 (ddd, 1H, J_{F-H} = 17.9 Hz, 3′-H), 4.31 (m, 3H, 4′-H, 5′-H), 2.07, 2.03 (2s, 6H, Ac).

1-(2-Deoxy-2-fluoro-β-L-ribofuranosyl)-5-iodouracil (7). A mixture of **6** (3.3 g, 0.01 mol) and ICl (2.4 g, 0.015 mol) in CH_2Cl_2 (100 mL) was stirred at reflux for 5 h. It was then diluted with CH_2Cl_2 (150 mL), washed successively with $NaHSO_3$ (100 mL × 3) and saturated $NaHCO_3$ (50 mL × 2) and dried ($MgSO_4$). Removal of the solvent gave a white foam (4.1 g, 90%), which was treated with NaOMe/MeOH. Trituation in ether followed by recrystallization from water gave **7** as a white solid: mp 217−218 °C; $[\alpha]^{27}_D$ +9.41° (*c* 0.36, MeOH); UV (H_2O) λ_{max} 285.5 nm (ϵ 8660) (pH 1), 283.5 nm (ϵ 8090) (pH 7), 277.0 nm (ϵ 6450) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.75 (s, 1H, NH, D_2O exchangeable), 8.54 (s, 1H, 6-H), 5.86 (bd, 1H, J_{F-H} = 16.8 Hz, 1′-H), 5.62 (d, 1H, 3′-OH, D_2O exchangeable), 5.41 (t, 1H, 5′-OH, D_2O exchangeable), 5.04 (dd, 1H, J_{F-H} = 53.1 Hz, 2′-H), 4.18 (dm, 1H, J_{F-H} = 23.4 Hz, 3′-H), 3.90 (m, 1H, 4′-H), 3.72 (m, 2H, 5′-H). Anal. ($C_9H_{10}FIN_2O_5$) C, H, N.

(*E*)-5-(2-Bromovinyl)-1-(2-deoxy-2-fluoro-β-L-ribofuranosyl)uracil (8). A mixture of Ph_3P (125 mg, 0.47 mmol), Pd(OAc)2 (63 mg, 0.25 mmol), and Et_3N (1.25 mL) in 1,4-dioxane (30 mL) was stirred under reflux for 10 min, then cooled to just under reflux. To this was added methyl acrylate (1.13 mL, 12.6 mmol), followed by **7** (930 mg, 2.50 mmol) and 1,4-dioxane (10 mL). The mixture was refluxed for 0.5 h and then filtered through a Celite pad and washed with dioxane. The combined filtrates were evaporated to dryness and the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 9:1) to give an off-white foam (630 mg, 76%): UV (MeOH) λ_{max} 299.5, 264.0 nm (sh); ^{1}H NMR ($CDCl_3$) δ 11.73 (s, 1H, NH, D_2O exchangeable), 8.51 (s, 1H, J = 8.1 Hz, 6-H), 7.29 (d, 1H, J = 15.9 Hz, vinylic Ha), 6.79 (d, 1H, J = 15.9 Hz, vinylic Hb), 5.88 (d, 1H, J_{F-H} = 16.9 Hz, 1′-H), 5.62 (d, 1H, 3′-OH, D_2O exchangeable), 5.48 (t, 1H, 5′-OH, D_2O exchangeable), 5.04 (dd, 1H, J_{F-H} = 52.8 Hz, 2′-H), 4.16 (dm, 1H, J_{F-H} = 24.3 Hz, 3′-H), 3.90 (m, 3H, 4′-H), 3.72 (m, 2H, 5′-H), 3.68 (s, 3H, COOMe).

The ester derivative (560 mg, 1.70 mmol) was stirred in a NaOH solution (2 N, 5 mL) at room temperature for 1.5 h, then diluted with water (20 mL) and neutralized with Dowex 50w × 8 (H^+) resin. The mixture was filtered and washed with water and acetone. The combined filtrate was evaporated to dryness to give a pale-white solid, which was triturated with Et_2O to give a free acid derivative as an off-white solid (450 mg, 84%): UV (MeOH) λ_{max} 298.0, 267.0 nm (sh); ^{1}H NMR ($CDCl_3$) δ 11.70 (s, 1H, NH, D_2O exchangeable), 8.49 (s, 1H, J = 8.1 Hz, 6-H), 7.22 (d, 1H, J = 15.9 Hz, vinylic Ha), 6.73 (d, 1H, J = 15.9 Hz, vinylic Hb), 5.89 (d, 1H, J_{F-H} = 16.8 Hz, 1′-H), 5.86 (d, 1H, 3′-OH, D_2O exchangeable), 5.62 (bs, 1H, 5′-OH, D_2O exchangeable), 5.05 (dd, 1H, J_{F-H} = 52.9 Hz, 2′-H), 4.18 (dm, 1H, J_{F-H} = 24.1 Hz, 3′-H), 3.89 (m, 3H, 4′-H), 3.74 (m, 2H, 5′-H).

To a suspension of the free acid (190 mg, 0.6 mmol) and $KHCO_3$ (240 mg, 2.4 mmol) in DMF (10 mL), was added *N*-bromosuccinimide (130 mg, 0.72 mmol). The mixture was stirred at room temperature for 5 h and then evaporated to dryness. The residue was purified on a silica gel column (9:1 $CHCl_3$:MeOH) followed by preparative TLC ($CHCl_3$:MeOH, 9:1). Coevaporation of the product with Et_2O gave a white solid of 90 mg (43%): mp 80−83 °C; $[\alpha]^{28}_D$ +14.4° (*c* 0.20, MeOH); UV (H_2O) λ_{max} 249.5 (ϵ 11500), 292.5 nm (ϵ 8810) (pH 7), 249.0 (ϵ 13100), 290.0 nm (ϵ 9660) (pH 2), 249.0 (ϵ 13800), 290.0 nm (sh) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.66 (s, 1H, NH), 8.19 (s, 1H, 6-H), 7.20 (d, 1H, J = 13.7 Hz, vinylic Ha), 6.75 (d, 1H, J = 13.7 Hz, vinylic Hb), 5.87 (dd, 1H, J_{F-H} = 16.9 Hz, 1′-H), 5.62 (d, 1H, 3′-OH, D_2O exchangeable), 5.37 (t, 1H, 5′-OH, D_2O exchangeable), 5.04 (dd, 1H, J_{F-H} = 52.3 Hz, 2′-H), 4.16 (dm,

1H, J_{F-H} = 23.7 Hz, 3′-H), 3.88 (m, 1H, 4′-H), 3.70 (m, 2H, 5′-H). Anal. ($C_{11}H_{12}BrFN_2O_5 \cdot 0.5H_2O$) C, H, N.

(*E*)-5-(2-Bromovinyl)-1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)uracil (10). A mixture of Ph_3P (40 mg, 0.15 mmol), $Pd(OAc)_2$ (20 mg, 0.08 mmol), and Et_3N (0.4 mL, 2.8 mmol) in 1,4-dioxane (15 mL) was refluxed to form a dark-red solution and then cooled to just below reflux. To this was added methyl acrylate (0.36 mL, 4.0 mmol), followed by **9** (300 mg, 0.8 mmol) with dioxane (10 mL) and Et_3N (0.15 mL). The mixture was refluxed for 0.5 h and then filtered through a Celite pad and washed with dioxane. The combined filtrates were evaporated to dryness and purified on a silica gel column ($CHCl_3$:MeOH, 9:1) to give an ester as a white foam (145 mg, 54%): UV (MeOH) λ_{max} 299.0 nm; ^{1}H NMR (DMSO-d_6) δ 11.79 (s, 1H, NH, D_2O exchangeable), 8.35 (s, 1H, 6-H), 7.41 (d, 1H, J = 15.9 Hz, vinylic Ha), 6.90 (d, 1H, J = 15.8 Hz, vinylic Hb), 6.14 (dd, 1H, J_{F-H} = 14.2 Hz, 1′-H), 5.81 (d, 1H, 3′-OH, D_2O exchangeable), 5.25 (t, 1H, D_2O exchangeable 5′-OH), 5.10 (dt, 1H, J_{F-H} = 52.6 Hz, 2′-H), 4.26 (dt, 1H, J_{F-H} = 19.8 Hz, 3′-H), 3.84 (m, 1H, 4′-H), 3.69 (dm, 2H, 5′-H).

A solution of the ester (135 mg, 0.41 mmol) in a 2 N NaOH solution (5 mL) was stirred at room temperature for 1.5 h and then cooled in an ice bath. pH was carefully adjusted with 12 N HCl to ca. 1 and the mixture was stirred for 10 min. The white precipitate was collected by filtration and washed with water and acetone to give an acid as a white powder (96 mg, 74%): mp 284 °C dec; UV (MeOH) λ_{max} 298.0, 268.0 nm (sh); ^{1}H NMR (DMSO-d_6) δ 11.80 (s, 1H, NH, D_2O exchangeable), 8.28 (s, 1H, 6-H), 7.31 (d, 1H, J = 15.8 Hz, vinylic Ha), 6.79 (d, 1H, J = 15.9 Hz, vinylic Hb), 6.12 (dd, 1H, $J_{1',F}$ = 14.0 Hz, 1′-H), 5.90 (d, 1H, 3′-OH, D_2O exchangeable), 5.23 (t, 1H, 5′-OH, D_2O exchangeable), 5.08 (dt, 1H, J_{F-H} = 52.7 Hz, 2′-H), 4.27 (dt, 1H, J_{F-H} = 19.6 Hz, 3′-H), 3.81 (m, 1H, 4′-H), 3.65 (dm, 2H, 5′-H).

A suspension of the acid (80 mg, 0.25 mmol) and $KHCO_3$ (100 mg, 1.0 mmol) in DMF (1.5 mL) was stirred at room temperature for 20 min. To this was added *N*-bromosuccunimide (53 mg, 0.3 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature for 1.5 h then filtered and washed with methanol. The filtrate was evaporated to dryness and purified on preparative TLC ($CHCl_3$:MeOH, 6:1). After coevaporation with ether, **11** was obtained as a white foam (47 mg, 53%): mp 190−192 dec; $[\alpha]^{28}_D$ −59.4° (*c* 0.17, MeOH); UV (H_2O) λ_{max} 250 0 nm (ϵ 14600) (pH 7), 250.0 nm (ϵ 15800) (pH 2), 254.0 nm (ϵ 15900) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.70 (s, 1H, NH), 7.97 (s, 1H, 6-H), 7.26 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.88 (d, 1H, J = 13.7 Hz, vinylic Hb), 6.10 (d, 1H, J_{F-H} = 14.7 Hz, 1′-H), 5.86 (d, 1H, 3′-OH), 5.12 (t, 1H, 5′-OH), 5.04 (dt, 1H, J_{F-H} = 52.6 Hz, 2′-H), 4.23 (dt, 1H, J_{F-H} = 19.9 Hz, 3′-H), 3.80 (m, 1H, 4′-H), 3.63 (m, 2H, 5′-H). Anal. ($C_{11}H_{12}BrFN_2O_5$) C, H, N.

(2*S*,5*R*)-(*E*)-5-(2-Bromovinyl)-1-[2-[(1*R*,2*S*,5*R*)-menthyloxycarbonyl]-1,3-oxathiolan-5-yl]uracil (12). To a suspension of (*E*)-5-(2-bromovinyl)uracil (257 mg, 1.18 mmol) in CH_2Cl_2 (3 mL) were added TBDMSOTf (0.72 mL, 3.13 mmol) and 2,4,6-collidine (0.42 mL, 3.11 mmol) at room temperature. The reaction mixture was stirred for 30 min. To the resulting solution was added a solution of **11** (362 mg, 1.15 mmol) in CH_2Cl_2 (8 mL) slowly, followed by TMSI (0.19 mL, 1.3 mmol). The mixture was stirred at room temperature for 3 h and then quenched with saturated $Na_2S_2O_3$ solution. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a silica gel (hexanes:EtOAc, 3:1) to give a white solid as anomeric mixture (β:α = 30:1 by ^{1}H NMR), which was recrystallized from EtOAc and hexanes to give **12** (500 mg, 87%) as a white solid: mp 128−129 °C; $[\alpha]_D$ +6.6° (*c* 0.28, $CHCl_3$); UV (MeOH) λ_{max} 248.5, 292.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1H, 6-H), 7.41 (d, 1H, J = 13.7 Hz, vinylic Ha), 6.78 (d, 1H, J = 13.7 Hz, vinylic Hb), 5.46 (s, 1H, 4′-H), 4.85−4.78 (m, 1H, 1′-H), 3.43 (dd, 1H, J = 12.1, 4.7 Hz, 2′-Ha), 3.16 (dd, 1H, J = 12.1, 7.5 Hz, 2′-Hb), 2.06−1.40 (m, 7H), 1.15−1.00 (m, 2H), 0.96−0.91 (m, 6H), 0.81 (d, 3H, J = 6.8 Hz). Anal. ($C_{20}H_{27}BrN_2O_4S \cdot 0.1C_6H_{14}$) C, H, Br, N, S.

(2*S*,5*R*)-(*E*)-5-(2-Bromovinyl)-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (13). To a solution of **12** (153 mg, 0.313 mmol) in 10 mL of EtOH was added $NaBH_4$ (24 mg, 0.626 mmol) portionwise at 0 °C and the mixture was stirred at room temperature for 6 h. The reaction mixture was neutralized with AcOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 30:1) to give **13** (73 mg, 70%) as a white solid which was recrystallized from hexanes−CH_2Cl_2−MeOH: mp 155 °C dec; $[\alpha]_D$ +62.4° (*c* 0.21, MeOH); UV (MeOH) λ_{max} 251.0 nm (ϵ 15400), 291.5 (ϵ 13100) (pH 7), 249.0 (ϵ 16600), 292.0 nm (ϵ 12600) (pH 2), 254.0 (ϵ 16600), 284.5 nm (sh, ϵ 10800) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H, NH), 8.22 (s, 1H, 6-H), 7.25 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.85 (d, 1H, J = 13.6 Hz, vinylic Hb), 6.18 (ps t, 1H, J = 5.1, 4.5 Hz, 1′-H), 5.46 (t, 1H, 5′-OH), 5.21 (ps t, 1H, J = 4.1, 3.9 Hz, 4′-H), 3.80−3.75 (m, 2H, 2′-H), 3.45 (dd, 1H,J = 11.9, 5.5 Hz, 5-Ha), 3.26 (dd, 1H, J = 11.9, 4.2 Hz, 5′-Hb). Anal. ($C_{10}H_{11}BrN_2O_3S$) C, H, Br, N, S.

(2*R*,5*S*)-(*E*)-5-(2-Bromovinyl)-1-[2-[(1*R*,2*S*,5*R*)-menthyloxycarbonyl]-1,3-oxathiolan-5-yl]uracil (15). To a suspension of (*E*)-5-bromovinyluracil (250 mg, 1.15 mmol) in CH_2Cl_2 (2 mL) were added TBDMSOTf (0.7 mL, 2.53 mmol) and 2,4,6-collidine (0.4 mL, 2.27 mmol) at room temperature. The reaction mixture was stirred for 30 min. To the resulting solution was added a solution of **14** (380 mg, 1.15 mmol) in CH_2Cl_2 (5 mL) slowly, followed by TMSI (0.18 mL, 1.27 mmol). The mixture was stirred at room temperature for 3 h and then quenched with saturated $Na_2S_2O_3$ solution. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel (hexanes:EtOAc, 3:1) to give a white solid as anomeric mixture (β:α = 27:1 by ^{1}H NMR), which was recrystallized from EtOAc and hexanes to give **15** (456 mg, 81%) as a white solid: mp 124−126 °C; $[\alpha]^{28}_D$ −97.2° (*c* 0.34, $CHCl_3$); UV (MeOH) λ_{max} 248.5, 292.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1H, 6-H), 8.27 (s, NH), 7.42 (d, 1H, J = 13.7 Hz, vinylic Ha), 6.78 (d, 1H, J = 13.7 Hz, vinylic Hb), 5.46 (s, 1H, 4′-H), 4.84−4.78 (m, 1H,1′-H), 3.44 (dd, 1H, J = 12.1, 4.7 Hz, 2′-Ha), 3.18 (dd, 1H, J = 12.1, 7.1 Hz, 2′-Hb), 2.08−1.41 (m, 7H), 1.13−0.86 (m, 8H), 0.78 (d, 3H, J = 6.9 Hz). Anal. ($C_{20}H_{27}BrN_2O_4S$) C, H, Br, N, S.

(2*R*,5*S*)-(*E*)-5-(2-Bromovinyl)-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]uracil (16). To a solution of **15** (124 mg, 0.254 mmol) in 8 mL of EtOH was added $NaBH_4$ (19 mg, 0.508 mmol) portionwise at 0 °C and the mixture was stirred at room temperature for 6 h. The reaction mixture was neutralized with AcOH and extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 30:1) to give **16** (54 mg, 64%) as a white solid, which was recrystallized from hexanes−CH_2Cl_2−MeOH: mp 154 °C dec; $[\alpha]^{26}_D$ −60.2° (*c* 0.56, MeOH); UV (MeOH) λ_{max} 250.5 (ϵ 12700), 293.0 nm (ϵ 10700) (pH 7), 249.5 (ϵ 14100), 292.5 nm (ϵ 10800) (pH 2), 254.0 (ϵ 14100), 285.0 nm (sh, ϵ 9100) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H, NH), 8.23 (s, 1H, 6-H), 7.25 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.85 (d, 1H, J = 13.6 Hz, vinylic Hb), 6.19 (ps t, 1H, J = 5.1, 4.5 Hz, 1′-H), 5.46 (t, 1H, 5′-OH), 5.21 (ps t, 1H, J = 4.1, 3.8 Hz, 4′-H), 3.82−3.78 (m, 2H, 2′-H), 3.45 (dd, 1H, J = 11.9, 5.4 Hz, 5-Ha), 3.27 (dd, 1H, J = 12.1, 4.2 Hz, 5′-Hb). Anal. ($C_{10}H_{11}BrN_2O_3S$) C, H, Br, N, S.

(2*R*,5*R*)-(*E*)-5-(2-Bromovinyl)-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]uracil (18) and (2*R*,5*S*)-(*E*)-5-(2-Bromovinyl)-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]uracil (19). To a suspension of (*E*)-5-bromovinyluracil (420 mg, 1.94 mmol) in CH_2Cl_2 (20 mL) were added TBDMSOTf (1.2 mL, 5.13 mmol) and 2,4,6-collidine (0.67 mL, 5.10 mmol) at room temperature. The reaction mixture was stirred for 30 min. To the resulting solution was added a solution of **17** (775 mg, 1.94 mmol) in CH_2Cl_2 (20 mL) slowly dropwise, followed by TMSI (0.31 mL, 2.14 mmol). The mixture was stirred at room temperature for

3 h and then quenched with saturated $Na_2S_2O_3$ solution. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel (hexanes:EtOAc, 4:1) to give α-isomer **19** (164 mg, 15%) as a white solid and *β*-isomer **18** (519 mg, 48%) as a white foam, which was crystallized from CH_2Cl_2 and hexanes. **18**: mp 64−66 °C; $[\alpha]^{25}_D$ +22.6° (*c* 0.46, $CHCl_3$); UV (MeOH) λ_{max} 249.5, 293.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, NH), 7.70−7.30 (m, 11H, Ph-H, 6-H), 7.32 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.30 (ps t, 1H, J = 2.9, 1.6 Hz, 1′-H), 6.29 (d, 1H, J = 13.6 Hz, vinylic Hb), 5.10 (ps t, 1H, J = 3.4, 3.3 Hz 4′-H), 4.20−4.15 (m, 2H, 2′-H), 3.95 (dd, 1H, J = 11.7, 3.2 Hz, 5′-Ha), 3.89 (dd, 1H, J = 11.7, 3.5 Hz, 5′-Hb), 1.09 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}BrN_2O_5Si$) C, H, Br, N. **19**: mp 148−150 °C; $[\alpha]_D$ −1.7° (*c* 1.29, $CHCl_3$); UV (MeOH) λ_{max} 249.5, 293.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, NH), 7.69−7.39 (m, 11H, Ph-H, 6-H), 7.28 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.68 (d, 1H, J = 13.6 Hz, vinylic Hb), 6.28 (dd, 1H, J = 5.2, 2.0 Hz, 1′-H), 5.55 (ps t, 1H, J = 3.1, 2.9 Hz, 4′-H), 4.41 (dd, 1H, J = 9.7, 5.2 Hz, 2′-Ha), 4.04 (dd, 1H, J = 9.7, 2.0 Hz, 2′-Hb), 3.74 (dd, 1H, J = 11.7, 2.8 Hz, 5′-Ha), 3.70 (dd, 1H, J = 11.7, 3.4 Hz, 5′-Hb), 1.07 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}BrN_2O_5Si$) C, H, Br, N.

(2*R*,5*R*)-(*E*)-5-(2-Bromovinyl)-1-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]uracil (20). A solution of **18** (278 mg, 0.499 mmol) in CH_3CN (15 mL) was treated with tetra-*n*-butylammonium fluoride (1 M solution in THF) (0.6 mL, 0.6 mmol) at room temperature for 1 h. After concentration of the mixture, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 20:1) to give **20** (151 mg, 95%) as a white solid: mp 176−177 °C; $[\alpha]^{27}_D$ +6.5° (*c* 0.47, MeOH); UV (MeOH) λ_{max} 249.5 (ϵ 15600), 291.0 nm (ϵ 11700) (pH 7), 248.5 (ϵ 16300), 291.5 nm (ϵ 11800) (pH 2), 253.5 (ϵ 16500), 284.5 nm (sh, ϵ 9870) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H, NH), 8.16 (s, 1H, 6-H), 7.21 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.82 (d, 1H, J = 13.6 Hz, vinylic Hb), 6.21 (d, 1H, J = 4.9 Hz, 1′-H), 5.32 (t, 1H, 5′-OH), 4.94 (s, 1H, 4′-H), 4.31 (d, 1H, J = 10.0 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.9, 5.5 Hz, 2′-Hb), 3.72−3.66 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}BrN_2O_5$) C, H, Br, N.

(2*R*,5*S*)-(*E*)-5-(2-Bromovinyl)-1-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]uracil (21). A solution of **19** (140 mg, 0.251 mmol) in CH_3CN (10 mL) was treated with tetra-*n*-butylammonium fluoride (1 M solution in THF) (0.3 mL, 0.3 mmol) at room temperature for 1 h. After concentration of the mixture, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 20:1) to give **21** (72 mg, 90%) as a white solid: mp 75−78 °C; $[\alpha]^{28}_D$ −2.8° (*c* 0.40, MeOH); UV (MeOH) λ_{max} 250.0 (ϵ 13900), 292.0 nm (ϵ 10600) (pH 7), 249.5 (ϵ 14400), 291.5 nm (ϵ 10800) (pH 2), 254.0 (ϵ 14100), 284.0 nm (sh, ϵ 9090) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H, NH), 7.82 (s, 1H, 6-H), 7.31 (d, 1H, J = 13.5 Hz, vinylic Ha), 6.99 (d, 1H, J = 13.5 Hz, vinylic Hb), 6.14 (dd, 1H, J = 5.1, 2.9 Hz, 1′-H), 5.54 (ps t, 1H, J = 3.7, 3.6 Hz, 4′-H), 5.04 (t, 1H, 5′-OH), 4.29 (dd, 1H, J = 9.5, 5.4 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.5, 2.8 Hz, 2′-Hb), 3.44−3.41 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}BrN_2O_5$) C, H, Br, N.

The synthetic methods of the following compounds **29**−**34** were similar to the synthesis of compounds **21** and **22**.

(2*S*,5*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]-(*E*)-5-(2-chlorovinyl)uracil (23) and (2*S*,5*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]-(*E*)-5-(2-chlorovinyl)uracil (24). 23 (50%): white foam; $[\alpha]^{28}_D$ −12.2° (*c* 0.29, $CHCl_3$); UV (MeOH) λ_{max} 292.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.2 (s, NH), 7.70−7.35 (m, 11H, Ph-H, 6-H), 7.20 (d, 1H, J = 13.3 Hz, vinylic Ha), 6.30 (dd, 1H, J = 4.5, 2.8 Hz, 1′-H), 6.00 (d, 1H, vinylic Hb, J = 13.3 Hz), 5.10 (ps t, 1H, J = 3.41, 3.36 Hz, 4′-H), 4.20−4.15 (m, 2H, 2′-H), 3.95 (dd, 1H, J = 11.7, 3.3 Hz, 5′-Ha), 3.90 (dd, 1H, J = 11.8, 3.5 Hz, 5′-Hb), 1.08 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}ClN_2O_5Si$) C, H, N. **24** (26%): mp 62−63 °C; $[\alpha]^{27}_D$ +3.9° (*c* 0.31, $CHCl_3$); UV (MeOH) λ_{max} 292.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.18 (s, NH), 7.69−7.27 (m, 11H, Ph-H, 6-H), 7.32 (d, 1H, J = 13.3 Hz, vinylic Ha), 6.40 (d, 1H, J = 13.3 Hz, vinylic Hb), 6.28 (dd, 1H, J = 5.2, 2.0 Hz, 1′-H), 5.55 (ps t, 1H, J = 3.1, 2.9 Hz, 4′-H), 4.41 (dd, 1H, J = 9.7, 5.3 Hz, 2′-Ha), 4.05 (dd, 1H, J = 9.7, 2.1 Hz, 2′-Hb), 3.74 (dd, 1H, J = 11.6, 2.7 Hz, 5′-Ha), 3.70 (dd, 1H, J = 11.7, 3.4 Hz, 5′-Hb), 1.07 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}ClN_2O_5Si\cdot 0.2H_2O$) C, H, N.

(2*S*,5*S*)-(*E*)-5-(2-Bromovinyl)-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]uracil (25) and (2*S*,5*R*)-(*E*)-5-(2-Bromovinyl)-1-[2-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-1,3-dioxolan-5-yl]uracil (26). 25 (58%): mp 62−65 °C; $[\alpha]^{29}_D$ −19.0° (*c* 0.8, $CHCl_3$); UV (MeOH) λ_{max} 249.5, 292.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, NH), 7.70−7.30 (m, 11H, Ph-H, 6-H), 7.32 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.30 (ps t, 2H, J = 2.9, 1.6 Hz, 1′-H), 6.29 (d, 1H, J = 13.6 Hz, vinylic Hb), 5.10 (ps t, 1H, J = 3.4, 3.3 Hz, 4′-H), 4.20−4.15 (m, 2H, 2′-H), 3.95 (dd, 1H, J = 11.7, 3.2 Hz, 5′-Ha), 3.89 (dd, 1H, J = 11.7, 3.5 Hz, 5′-Hb), 1.09 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}BrN_2O_5Si$) C, H, Br, N. **26** (20%): mp 147−149 °C; $[\alpha]^{28}_D$ +1.4° (*c* 0.76, $CHCl_3$); UV (MeOH) λ_{max} 249.5, 293.0 nm; ^{1}H NMR ($CDCl_3$) δ 8.21 (s, NH), 7.69−7.39 (m, 10H, Ph-H), 7.28 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.68 (d, 1H, J = 13.6 Hz, vinylic H_b), 6.28 (dd, 1H, J = 5.2, 2.0 Hz, 1′-H), 5.55 (ps t, 1H, J = 3.1, 2.9 Hz, 4′-H), 4.41 (dd, 1H, J = 9.7, 5.2 Hz, 2′-Ha), 4.04 (dd, 1H, J = 9.7, 2.0 Hz, 2′-Hb), 3.74 (dd, 1H, J = 11.7, 2.8 Hz, 5′-Ha), 3.70 (dd, 1H, J = 11.7, 3.4 Hz, 5′-Hb), 1.07 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}BrN_2O_5Si$) C, H, Br, N.

(2*S*,5*S*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]-(*E*)-5-(2-iodovinyl)uracil (27) and (2*S*,5*R*)-1-[2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-dioxolan-5-yl]-(*E*)-5-(2-iodovinyl)uracil (28). 27 (56%): mp 74−76 °C; $[\alpha]^{26}_D$ −24.0° (*c* 0.23, $CHCl_3$); UV (MeOH) λ_{max} 254.0, 298.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.10 (s, NH), 7.71−7.37 (m, 11H, Ph-H, 6-H), 7.33 (d, 1H, J = 14.6 Hz, vinylic Ha), 6.64 (d, 1H, J = 14.6 Hz, vinylic Hb), 6.29 (dd, 1H, J = 4.3, 3.0 Hz, 1′-H), 5.10 (ps t, 1H, J = 3.41, 3.35 Hz, 4′-H), 4.18 (s, 1H, 2′-H), 4.17 (d, 1H, J = 1.7 Hz, 2′-H), 3.95 (dd, 1H, J = 11.8, 3.2 Hz, 5′-H), 3.89 (dd, 1H, J = 11.7, 3.6 Hz, 5′-H), 1.09 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}IN_2O_5Si$) C, H, N. **28** (28%): mp 146−147 °C; $[\alpha]^{27}_D$ +2.3° (*c* 0.42, $CHCl_3$); UV (MeOH) λ_{max} 254.0, 297.5 nm; ^{1}H NMR ($CDCl_3$) δ 8.15 (s, NH), 7.69−7.40 (m, 11H, Ph-H, 6-H), 7.28 (d, 1H, J = 14.6 Hz, vinylic Ha), 7.02 (d, 1H, J = 14.6 Hz, vinylic Hb), 6.27 (dd, 1H, J = 5.1, 1.9 Hz, 1′-H), 5.55 (ps t, 1H, J = 3.04, 2.99 Hz, 4′-H), 4.40 (dd, 1H, J = 9.7, 5.2 Hz, 2′-Ha), 4.04 (dd, 1H, J = 9.7, 1.9 Hz, 2′-Hb), 3.76−3.71 (m, 2H, 5′-H), 1.07 (s, 9H, ^{t}Bu). Anal. ($C_{26}H_{29}BrN_2O_5Si$) C, H, N.

(2*S*,5*S*)-(*E*)-5-(2-Chlorovinyl)-1-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]uracil (29): mp 193−194 °C; $[\alpha]^{28}_D$ −4.0° (*c* 0.37, MeOH); UV (MeOH) λ_{max} 246.5 (ϵ 17800), 291.0 nm (ϵ 12500) (pH 7), 246.0 (ϵ 18400), 290.5 nm (ϵ 12500) (pH 2), 250.5 (ϵ 18100), 284.5 nm (sh, ϵ 10100) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H, NH), 8.14 (s, 1H, 6-H), 7.14 (d, 1H, J = 13.3 Hz, vinylic Ha), 6.56 (d, 1H, J = 13.3 Hz, vinylic Hb), 6.21 (d, 1H, J = 4.6 Hz, 1′-H), 5.32 (t, 1H, 5′-OH), 4.94 (ps t, 1H, J = 2.1, 2.0 Hz, 4′-H), 4.31 (d, 1H, J = 9.9 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.9, 5.6 Hz, 2′-Hb), 3.74−3.65 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}ClN_2O_5$) C, H, N.

(2*S*,5*R*)-(*E*)-5-(2-Chlorovinyl)-1-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]uracil (30): mp 101−102 °C; $[\alpha]^{28}_D$ +2.4° (*c* 0.28, MeOH); UV (MeOH) λ_{max} 247.0 (ϵ 13300), 291.5 nm (ϵ 9550) (pH 7), 246.5 (ϵ 13700), 291.5 nm (ϵ 9670) (pH 2), 252.0 (ϵ 13900), 283.0 nm (sh, ϵ 8170) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H, NH), 7.79 (s, 1H, 6-H), 7.24 (d, 1H, J = 13.2 Hz, vinylic Ha), 6.73 (d, 1H, J = 13.2 Hz, vinylic Hb), 6.15 (dd, 1H, J = 5.4, 2.9 Hz, 1′-H), 5.54 (ps t, 1H, J = 3.7, 3.6 Hz, 4′-H), 5.05 (t, 1H, 5′-OH), 4.29 (dd, 1H, J = 9.5, 5.5 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.5, 3.0 Hz, 2′-Hb), 3.49−3.43 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}ClN_2O_5$) C, H, N.

(2*S*,5*S*)-(*E*)-5-(2-Bromovinyl)-1-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]uracil (31): mp 176−178 °C; $[\alpha]^{27}_D$ −6.5° (*c* 0.27, MeOH); UV (MeOH) λ_{max} 249.0 (ϵ 17000), 291.0 nm (ϵ 13000) (pH 7), 249.0 (ϵ 17200), 290.5 nm (ϵ 12300) (pH 2), 253.0 (ϵ 16700), 285.0 nm (sh, ϵ 10200) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H, NH), 8.15 (s, 1H, 6-H), 7.21 (d, 1H, J = 13.6 Hz, vinylic Ha), 6.82 (d, 1H, J = 13.6 Hz, vinylic Hb), 6.21 (d, 1H, J = 4.9 Hz, 1′-H), 5.32 (t, 1H, 5′-OH), 4.94 (s, 1H, 4′-H),

4.31 (d, 1H, J = 10.0 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.9, 5.5 Hz, 2′-Hb), 3.72−3.66 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}BrN_2O_5$) C, H, Br, N.

(2*S*,5*R*)-(*E*)-5-(2-Bromovinyl)-1-[2-(hydroxymethyl)-1,3-dioxolan-5-yl]uracil (32): mp 76−78 °C; $[\alpha]^{26}_D$ +2.5° (*c* 0.20, MeOH); UV (MeOH) λ_{max} 250.5 (ϵ 16000), 290.0 nm (ϵ 12400) (pH 7), 250.0 (ϵ 16500), 290.0 nm (ϵ 12200) (pH 2), 254.5 (ϵ 16800) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1H, NH), 7.82 (s, 1H, 6-H), 7.31 (d, 1H, J = 13.5 Hz, vinylic Ha), 6.99 (d, 1H, J = 13.5 Hz, vinylic Hb), 6.14 (dd, 1H, J = 5.1, 2.9 Hz, 1′-H), 5.54 (ps t, 1H, J = 3.7, 3.6 Hz, 4′-H), 5.04 (t, 1H, 5′-OH), 4.29 (dd, 1H, J = 9.5, 5.4 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.5, 2.8 Hz, 2′-Hb), 3.44−3.41 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}BrN_2O_5$) C, H, Br, N.

(2*S*,5*S*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-5-yl]-(*E*)-5-(2-iodovinyl)uracil (33: mp 162 °C dec; $[\alpha]^{28}_D$ −6.1° (*c* 0.52, MeOH); UV (MeOH) λ_{max} 253.0 (ϵ 16000), 296.5 nm (ϵ 11900) (pH 1), 255.0 (ϵ 20700) (pH 2), 255.5 (ϵ 16600) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H, NH), 8.15 (s, 1H, 6-H), 7.17 (d, 1H, J = 14.7 Hz, vinylic Ha), 7.10 (d, 1H, J = 14.7 Hz, vinylic Hb), 6.21 (d, 1H, J = 5.4 Hz, 1′-H), 5.33 (t, 1H, 5′-OH), 4.93 (d, 1H, J = 1.9 Hz, 4′-H), 4.31 (d, 1H, J = 9.9 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.8, 5.5 Hz, 2′-Hb), 3.69 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}IN_2O_5$) C, H, N.

(2*S*,5*R*)-1-[2-(Hydroxymethyl)-1,3-dioxolan-5-yl]-(*E*)-5-(2-iodovinyl)uracil (34): mp 60 °C dec; $[\alpha]^{28}_D$ +2.3° (*c* 0.53, MeOH); UV (MeOH) λ_{max} 255.5 (ϵ 15400), 297.0 nm (ϵ 12400) (pH 7), 256.5 (ϵ 22400) (pH 2), 257.5 (ϵ 16200) (pH 11); ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 1H, NH), 7.80 (s, 1H, 6-H), 7.26 (s,2H, vinylic H), 6.14 (dd, 1H, J = 5.3, 2.9 Hz, 1′-H), 5.55 (ps t, 1H, J = 3.6, 3.5 Hz, 4′-H), 4.29 (dd, 1H, J = 9.4, 5.4 Hz, 2′-Ha), 4.08 (dd, 1H, J = 9.4, 2.9 Hz, 2′-Hb), 3.44−3.43 (m, 2H, 5′-H). Anal. ($C_{10}H_{11}IN_2O_5$·0.3MeOH) C, H, N.

Biological Evaluation. 1. Cells and Virus. Human embryonic lung cells (HEL 299) were grown and maintained in Eagle's minimal essential medium supplemented with 10% fetal bovine serum. Vero cells and EBV-producing H-1 cells were used for HSV-1, HSV-2, and EBV growth. These cells were maintained in RPMI 1640 plus 10% FBS. VZV (Ellen strain), HSV-1 (KOS strain), HSV-2 (333), and EBV were used in the biological assays.

2. Antiviral Assay. Assays used for biological evaluation of L-BVDU and its analogues were described in detail previously.[38−41] For HSV-1 and HSV-2, plaque reduction assay was performed in Vero cells. For VZV and EBV, the inhibition of the viral growth was tested by measuring viral DNA synthesis as described previously.

3. Mitochondrial DNA (MtDNA) Content. The mitochondrial DNA was analyzed as described previously.[39] Briefly, human T-lymphoid CEM cells were incubated with the drug at various concentrations for 4 continuous days. The cells were then replaced with fresh medium and drugs at the same concentration on days 4 and 6. On day 8, the cells were harvested and the cellular DNA was extracted by TE buffer (25 mM Tris, pH 8.0, and 1 mM EDTA) followed by treatment of RNAse A and protease K. The DNA was then subjected to "slot-blot", and the mitochondrial DNA was detected by MtDNA specific probe.

4. Cytotoxicity. Cytotoxicity was assayed as described previously.[38] Briefly, CEM cells in the logarithmic growth were treated with the drugs with various dilutions. The cells were then maintained for three generations and then counted by Coulter counter. ID_{50} is defined as the dosage that inhibited 50% cell growth compared with untreated control.

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