°C; IR (Nujol) 1620 (C=O), 3180 (NH) cm^{-1}; $[\alpha]_D$ -20.7° (c = 0.97); ^1H NMR δ 0.78 (3 H, s, 18-CH_3), 1.00 (3 H, s, 19-CH_3), 1.31 (3 H, d, J = 7 Hz, 21-CH_3), 5.28-5.59 (2 H, m, vinyl-H, 20-H), 6.94-7.34 (3 H, m, Ar3,4,5-H), 7.81 (1 H, d, J = 8 Hz, Ar6-H). Anal. ($C_{28}H_{38}INO_2$) C, H, N.

20β-[(2-Iodobenzoyl)amino]pregn-5-en-3β-ol (10). Acylation of 20β-aminopregn-5-en-3β-ol 3-THP ether (**6**)[20] and subsequent removal of the 3-THP ether protecting group as described in the synthesis of **9** gave 20β-[(2-iodobenzoyl)amino]pregn-5-en-3β-ol (**10**) as a white solid. Yields for the esterification and hydrolysis were 96% and 97%, respectively. Recrystallization from *n*-hexane-CH_2Cl_2 gave **10** as colorless needles: mp 218-20 °C; IR (Nujol) 1620 (C=O), 3200 (NH) cm^{-1}; $[\alpha]_D$ -61.6° (c = 0.94); ^1H NMR δ 0.83 (3 H, s, 18-CH_3), 1.01 (3 H, s, 19-CH_3), 1.26 (3 H, d, J = 7 Hz, 21-CH_3), 5.28-5.55 (2 H, m, vinyl-H, 20-H), 6.96-7.36 (3 H, m, Ar3,4,5-H), 7.83 (1 H, d, J = 8 Hz, Ar6-H). Anal. ($C_{28}H_{38}INO_2$) C, H, N.

Radioiodine Exchange in Pivalic Acid. General Procedure. The compound to be labeled (1.7-2 mg) was placed in a 1-mL serum vial, which was then sealed with a Teflon-lined rubber septum and alumnum cap. Aqueous $Na^{125}I$ (2-4 μL, 0.82-2 mCi) was added to the vial via a microliter syringe. The syringe was rinsed with THF (15 μL) and the rinse was transfered into the vial. The vial was gently swirled to dissolve the contents and ensure homogeneity. Inlet and outlet cannuli were inserted and a gentle stream of nitrogen applied to evaporate the solvents. When the residue appeared dry, pivalic acid (12-15 μL) was added via a prewarmed microliter syringe and the vial was heated at 155-160 °C in an oil bath. After 1 h, the reaction vial was allowed to cool, THF (15 μL) was added with a syringe, and the vial was swirled gently. A TLC sample (1-2 μL) was removed with a 10-μL syringe and the remaining contents were placed on the top of a column (1 × 10 cm) and subsequently eluted with benzene-ethyl acetate (3:1) for [^{125}I]-**7** and [^{125}I]-**8** or (1:1) for [^{125}I]-**9** and [^{125}I]-**10**. Fractions were collected and the radiochemical purity of each was monitored by TLC using UV and a radioactivity detector. The appropriate fractions were combined and the solvents removed with a gentle stream of nitrogen. TLC analyses of the final products confirmed both chemical (UV) and radiochemical (radioactivity) purity. In all cases, radiochemical purity of the final compounds exceeded 93%. Radiochemical yields as estimated from TLC of the reaction mixture ranged from 89% to 94%.

Tissue Distribution Studies. The radiolabeled compounds were dissolved in benzene and Tween 20 (Sigma Chemical Company, St. Louis, MO) was added to a concentration of 100 μL per 1 mg of compound. The solvent was evaporated under a steam of nitrogen. Physiological saline was added, and the final traces of benzene were removed by passing nitrogen over the solution until it became clear (2-3% Tween). The radiolabeled compound thus solubilized was administered intravenously to 200-250-g female Sprague-Dawley rats (Charles River, Portage, MI). Four rats per time point per compound were used with a dose of 8-22 μCi (20-60 μg) given to each animal. At 0.5 and 24 h rats were sacrificed by exsanguination while under ether anesthesia and the following tissues removed: adrenal, fat, heart, kidney, liver, lung, muscle, ovary, spleen, and thyroid. Tissues were blotted free of excess blood and trimmed. Large organs were minced with scissors. Tissue samples were placed in tared gelatin capsules and weighed. Liquid samples were weighed in polyethylene tubes. All samples were assayed for radioactivity in a Searle 1185 well scintillation counter (84-87% efficiency).

Acknowledgment. We thank Edie Quenby and Lisa Flaherty for their technical assistance. This research was supported by USPHS Grant CA-08349 and a Fogarty Senior International Fellowship (1F06 TW01103-01 BI-5) to R.E.C.

Registry No. **1**, 35961-41-2; **3**, 6579-86-8; **3** (20α-ester 3-THP ether), 118143-30-9; **4**, 96574-75-3; **4** (20β-ester 3-THP ether), 118143-31-0; **5**, 40521-49-1; **5** (20α-amide 3-THP ether), 118170-27-7; **6**, 40521-48-0; **6** (20β-amide 3-THP ether), 118143-32-1; **7**, 118143-33-2; [^{125}I]-**7**, 118143-34-3; **8**, 118143-35-4; [^{125}I]-**8**, 118143-36-5; **9**, 118143-37-6; [^{125}I]-**9**, 118143-38-7; **10**, 118143-39-8; [^{125}I]-**10**, 118143-40-1; 17α-pregn-5-ene-3β,20ε-diol 3-THP ether, 118204-91-4; 17α-pregnenolone 3-THP ether, 118204-92-5; 17α-pregnenolone, 566-63-2; 2-iodobenzoic acid, 88-67-5.

Structure-Activity Relationships of Pyrimidine Nucleosides as Antiviral Agents for Human Immunodeficiency Virus Type 1 in Peripheral Blood Mononuclear Cells

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The structure-activity relationships of several pyrimidine nucleosides related to 3′-azido-3′-deoxythymidine (AZT) were determined in human immunodeficiency virus type 1 (HIV-1) infected human peripheral blood mononuclear cells. These studies indicated that nucleosides with a 3′-azido group on the sugar ring exhibited the most potent antiviral activity. Substitution at C-5 with H, CH_3, and C_2H_5 produced derivatives with the highest potency, whereas alkyl functions greater than C_2, including bromovinyl substitution reduced the antiviral potency significantly. Changing the 3′-azido function to an amino or iodo group reduced the antiviral activity. Replacement of the uracil ring by cytosine or 5-methylcytosine produced analogues with high potency and low toxicity. Modification of the 5′-hydroxy group markedly reduced the antiviral activity. Similarly, various C-nucleoside analogues related to AZT and 2′,3′-dideoxycytidine were inactive and nontoxic. From these systematic studies 3′-azido-2′,3′-dideoxyuridine (**5a**), 3′-azido-5-ethyl-2′,3′-dideoxyuridine (**5c**), and 3′-azido-2′,3′-dideoxycytidine (**7a**) and its 5-methyl analogue (**7b**) were identified as potent and selective anti-HIV-1 agent in primary human lymphocytes.

Recently, a number of nucleosides have been identified as potential anti human immunodeficiency virus type 1 (HIV-1) agents.[1-4] These include 3′-azido-3′-deoxythymidine (AZT),[5-8] 2′,3′-dideoxycytidine (D2C),[9] 2′,3′-dideoxyadenosine (D2A),[9] 2′,3′-dideoxy-5-fluorocytidine,[10] ribavirin,[11] 2′,3′-didehydro-2′,3′-dideoxycytidine (D4C),[12-15] and its thymidine analogue (D4T),[13-17] 3′-azido-2′,3′-dideoxyuridine (CS-87),[18] and 3′-azido-2′,3′-dideoxy-5-

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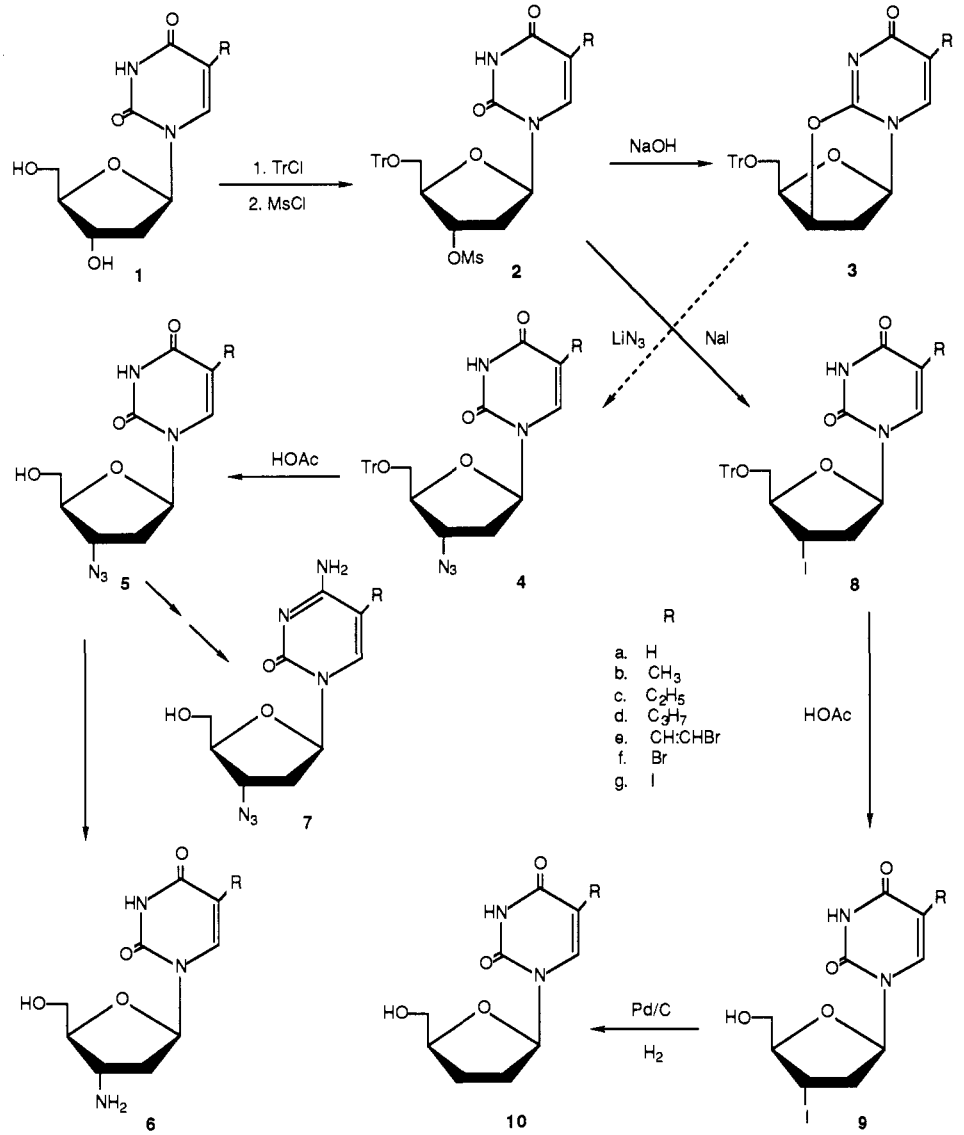
Scheme I



ethyluridine (CS-85).[19] Among these compounds, AZT has been studied extensively in humans for various HIV-1 infections.[7,8] AZT can decrease the mortality and frequency of opportunistic infections in a selected group of individuals with acquired immunodeficiency syndrome (AIDS) and/or AIDS-related complex (ARC).[7] However, its bone marrow toxicity and other side effects may limit its usefulness.[8] For example, Richman et al.[8] has shown that because of drug-associated hematological abnormalities, 21% of patients undergoing AZT therapy required multiple blood transfusions during the 6-month treatment

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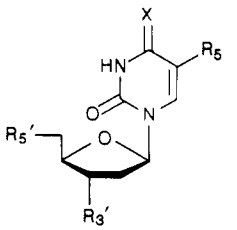
Table I. Comparative Potency and Toxicity of Pyrimidine Nucleosides against HIV-1 in Human Peripheral Blood Mononuclear Cells



compd	R_5	$R_{5'}$	$R_{3'}$	X	EC_{50},[a] μM	IC_{50},[b] μM
5a (CS-87)	H	OH	N_3	O	0.18–0.46	1000
5b	CH_3	OH	N_3	O	0.002–0.009	200
5c	C_2H_5	OH	N_3	O	0.056–1.00	1000
5d	C_3H_7	OH	N_3	O	63.0	>100
5e	CH=CH-Br (*E*)	OH	N_3	O	>100	>100
5f	Br	OH	N_3	O	1.04	>100
5g	I	OH	N_3	O	1.14	>100
6a	H	OH	NH_2	O	60.0	>100
6b	CH_3	OH	NH_2	O	>100	>100
6c	C_2H_5	OH	NH_2	O	54.9	>100
7a (CS-91)	H	OH	N_3	NH	0.66–1.19	>400
7b (CS-92)	CH_3	OH	N_3	NH	0.081–0.22	>200
9a	H	OH	I	O	12.1	>100
9b	CH_3	OH	I	O	46.3	>100
9c	C_2H_5	OH	I	O	86.0	>100
10a	H	OH	H	O	96.8	ND
10b	CH_3	OH	H	O	0.17	>100
10c	C_2H_5	OH	H	O	4.90	>100
11a	H	N_3	OH	O	>100	>100
11b	CH_3	N_3	OH	O	8.6	>100
11c	C_2H_5	N_3	OH	O	>100	>100
12a	H	NH_2	OH	O	>100	>100
12b	CH_3	NH_2	OH	O	77.4	>100
12c	C_2H_5	NH_2	OH	O	94.3	>100
15a	H	OH	2′,3′-unsaturated	O	68.3–79.9	>100
15b	CH_3	OH	2′,3′-unsaturated	O	0.009–0.04	70
15c	C_2H_5	OH	2′,3′-unsaturated	O	75.7	>100

[a] Median effective concentration (antiviral effect) on day 5 after infection; ranges are shown for the most potent compounds. [b] Median inhibitory concentration (cytotoxic effect in uninfected cells) on day 5.

period. The bone marrow depression may be due to the accumulation of phosphorylated AZT within cells, which may result in a substantial depression of thymidine 5′-triphosphate pools.[6,8] Another drawback with AZT is its short half-life in humans (ca. 1.1 h) and its elimination in urine as 3′-azido-3′-deoxy-5′-glucuronylthymidine,[8] a metabolite with no antiviral activity per se.

These clinical findings highlight the importance of developing not only potent anti-HIV-1 agents but also compounds with low toxicity and greater stability, bioavailability, and half-life, since the patients with AIDS/ARC will have to take the drug for a prolonged period. As a part of our continuing efforts to develop clinically useful antiretroviral nucleosides, we report in this paper the structure–activity relationships of various pyrimidine nucleosides in human peripheral blood mononuclear (PBM) cells.

Synthesis

In order to explore the structure–activity relationship of uridine nucleosides, 3′-azido-2′,3′-dideoxyuridines with 5-H (**5a**),[20] -CH_3 (**5b**),[21] -C_2H_5 (**5c**),[22] -C_3H_7 (**5d**), -CH=CHBr(E) (**5e**),[23] -Br (**5f**),[24] and -I (**5g**)[24-26] were prepared according to Scheme I. 3′-Amino derivatives (**6a–c**) were prepared by catalytic reduction of the corresponding 3′-azides (**5a–c**). Cytidine derivatives **7a** and **7b** were synthesized according to the method of Lin et al.[26] 5′-Azidonucleosides **11a**, **11b**, and **11c** were prepared by tosylation of 2′-deoxynucleosides followed by the nucleophilic substitution of the tosyl group by lithium azide.[27] 5′-Amino compounds **12a**, **12b**, and **12c** were prepared by the catalytic reduction of azido compounds **11a**, **11b**, and **11c**, respectively.[27] 3′-Iodo derivatives **9a**, **9b**, and **9c** were prepared by treating 3′-mesyl compounds **2** with sodium iodide[28] followed by deblocking the 5′-trityl group. 2′,3′-Dideoxyuridine derivatives **10a**,[29] **10b**,[29] and **10c** were synthesized by deiodination of the corresponding 3′-iodonucleosides **9**. 2′,3′-Didehydro-2′,3′-dideoxynucleosides (**15a–c**) were prepared according to the procedure by Horwitz et al.[30] The C-nucleosides **16–18** were synthesized from pseudouridine.[31]

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Structure–Activity Relationships

As shown in Table I, among the various C-5 substituted 3′-azidopyrimidine nucleosides that exhibit excellent anti-HIV-1 activity, 5-methyl substituted compound (**5b**, AZT) was found to be the most potent antiviral agent in PBM cells. Although the 5-ethyl analogue (**5c**, CS-85) has been reported to be inactive in ATH8 or MT4 cell screening system,[22] we and others have found that **5c** is a potent compound in PBM cells (this report; Dr. P. Feorino, Centers for Disease Control, and Dr. K. Weinhold, Duke University, personal communication). It is noteworthy to mention that antiviral potency of the ethyl compound (**5c**) was variable (ED_{50} = 0.056–1.0 μM) depending on the age of PBM cells, the donor cells, and the virus type used. Higher anti-HIV-1 activity was observed with **5c** in younger mitogen-stimulated PBM cells (2–3 days old) than in older cells (5–7 days old). The rate and magnitude of phosphorylation of this drug in various cells may account for the different results.

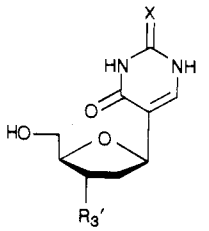
The 5-hydrogen analogue (**5a**, CS-87) had been tested against Moloney murine leukemia virus in vitro,[24] and was reported to have a low antiviral activity (ED_{50} = 52 μM) compared to HIV-1 (ED_{50} = 0.178 μM) (see Table I). This suggests that it can be difficult to extrapolate the data from murine to human retroviruses. Alkyl substitution greater than ethyl markedly decreases the antiviral activity, suggesting that the steric hindrance may occur at the target biomolecules such as thymidine kinase and/or reverse transcriptase. For example, the 5-propyl (**5d**) or bromovinyl (**5e**) analogues of AZT were inactive in human PBM cells.

In order to determine the importance of the 3′-azido group for anti-HIV activity, this function was reduced to an amino group (**6a–c**). The amino compounds (**6a–c**) exhibited markedly less antiviral activity than the corresponding azido compounds (**5a–c**). 3′-Iodo substitution (**9a–c**) also gave a markedly reduced activity. Removal of the 3′-azido group (**10a–c**) resulted in diminution of anti-HIV-1 activity, but **10b** and **10c** still maintained moderate antiviral activities. Since other viruses, such as herpes simplex viruses induce a thymidine kinase that can phosphorylate a compound such as 5′-amino-5′-deoxythymidine,[32] it was of interest to synthesize several 5′-amino analogues. However, neither the 5′-azido (**11a–c**) nor the 5′-amino analogues (**12a–c**) exhibited anti-HIV-1 activity, suggesting that the 5′-hydroxyl group is necessary for phosphorylation in this cell system. Since 2′,3′-didehydro-3′-deoxythymidine (**15b**, D4T) had previously been shown to be a potent anti-HIV-1 compound,[14–17] the corresponding 5-H and 5-ethyl derivatives (**15a** and **15c**) were synthesized. However, these new analogues of D4T were essentially inactive in the antiviral assays. The C-nucleoside analogues (**16–18**) of 3′-azido-2′,3′-dideoxyuridine, 2′,3′-dideoxycytidine, and 2′,3′-didehydro-2′,3′-dideoxycytidine did not show any significant anti-HIV-1 activity (Table II).

The structure–activity relationships of pyrimidine nucleosides indicate that the nucleosides with a 3′-azido group on the sugar ring exhibited the most potent antiviral activity, as previously noted by Mitsuya et al.[4,5] The pyrimidine moiety can be modified at 5-position: methyl substitution gave the highest potency (**5b**) while alkyl functions greater than C_2, including bromovinyl substitution (**5e**) reduced the antiviral potency significantly (**5d–e**). Furthermore, replacement of uracil by a cytosine ring (**7b**) reduced the antiviral activity to a certain degree, but still maintained high potency and low toxicity. Compounds **7a** (CS-91) and **7b** (CS-92) were found to be potent and selective inhibitors of HIV-1 replication in PBM cells. The EC_{50} for **7b** in PBM cells had previously been reported to be 5.1 μM.[25] After conducting additional studies with this compound, we believe that this value was overestimated by a factor of at least 10 (Table I). Interestingly, the cytidine analogues have been reported to be inactive in ATH8 cell,[22] emphasizing the importance of evaluating new antiviral drugs in different cell systems.

In summary, from these systematic studies, 3′-azido-2′,3′-dideoxyuridine (**5a**, CS-87) and 3′-azido-2′,3′-dideoxycytidine (**7a**, CS-91) and its 5-methyl analogue (**7b**, CS-92) were identified as potent and selective anti-HIV-1 agent in PBM cells. CS-87, a compound found to have low bone marrow toxicity,[18] is currently undergoing preclinical toxicological studies.

Table II. Comparative Anti-HIV-1 Activity and Toxicity of C-Nucleosides Related to AZT in Human Peripheral Blood Mononuclear Cells



compd	X	$R_{3'}$	EC_{50}, μM	IC_{50}, μM
16	O	N_3	>100	>100
17	NH	H	>100	>100
18	O	2′,3′-unsaturated	>100	>100

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a JEOL FX 90Q Fourier transform spectrometer (90 MHz). Tetramethylsilane was the internal standard for organic solvents and sodium 3-(trimethylsilyl)-1-propane-1-sulfonate (DSS) was the internal standard for deuterium oxide: chemical shifts are reported in parts per million (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), b (broad), and m (multiplet). Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 2000 spectrometer. TLC analysis was performed on Uniplates purchased from Analtech Co. or precoated TLC sheets (silica gel 60 F-254) from EM Laboratories Inc. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

5-Ethyl-3′-*O*-(methylsulfonyl)-5′-*O*-trityl-2′-deoxyuridine (2c). To a solution of 5-ethyl-2′-deoxyuridine (4.0 g, 15.63 mmol) in dry pyridine (50 mL) was added trityl chloride (6.0 g, 21.5 mmol) at once and the mixture was heated at 100 °C for 1 h.[33] TLC showed the continued presence of the starting material. Additional amounts of trityl chloride (1.0 g) was added and the mixture was heated for another hour at the same temperature. The mixture was poured into an ice–water mixture (1 L) with stirring. The resulting white precipitate was filtered and washed with cold water. The precipitate was dissolved in chloroform and dried ($MgSO_4$). The solvent was then evaporated to give a foam, 5-ethyl-5′-*O*-trityl-2′-deoxyuridine (7.5 g, 98%): ^1H NMR (DMSO-d_6) δ 0.80 (t, 3 H, J = 7.3 Hz, CH_3), 1.91 (q, 2 H, J = 7.3

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Hz, CH_2), 2.18 (m, 2 H, 2'-H), 3.28 (m, 2 H, 5'-H), 3.90 (m, 1 H, 4'-H), 4.33 (m, 1 H, 3'-H), 5.31 (d, 1 H, 3'-OH, D_2O exchangeable), 6.22 (t, 1 H, J = 6.3 Hz, 1'-H), 7.20–7.50 (m, 16 H, trityl and C_6-H), and 11.29 (s, 1 H, NH, D_2O exchangeable).

To a solution of the compound described above in dry pyridine (50 mL) was added methanesulfonyl chloride (4.0 g, 35 mmol) with cooling in an ice–water bath. The mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature. The mixture was then poured into an ice–water mixture (1.5 L) with stirring, the water was decanted, and the product was washed with cold water several times, dissolved in chloroform, and dried ($MgSO_4$). Finally, the solvent was evacuated in vacuo to obtain a syrup (7.6 g, 90%). This material was sufficiently pure to perform the next reaction without further purification. However, an analytical sample was obtained as a foam by chromatography over a silica gel column using chloroform as the eluent: ^{1}H NMR (DMSO-d_6) δ 0.86 (t, 3 H, J = 7.03 Hz, CH_3), 1.95 (q, 2 H, J = 7.03 Hz, CH_2CH_3), 2.55 (m, 2 H, 2'-H), 3.00 (s, 3 H, CH_3SO_2), 3.50 (m, 2 H, 5'-H), 4.30 (m, 1 H, 4'-H), 5.37 (m, 1 H, 3'-H), 6.40 (dd, 1 H, J = 5.86 Hz, 8.64 Hz, 1'-H), 7.15–7.45 (m, 16 H, C_6-H and trityl), 8.76 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{31}H_{32}N_2O_7S$) C, H, N, S.

5-*n*-Propyl-3'-*O*-(methylsulfonyl)-5'-*O*-trityl-2'-deoxyuridine (2d). Compound **2d** was prepared by a similar procedure as **2c** from 5-*n*-propyl-2'-deoxyuridine: mp 95–96 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 0.68 (t, 3 H, J = 7.04 Hz, CH_3), 1.15–1.45 (m, 2 H, CH_2), 1.65–2.10 (m, 2 H, CH_2), 2.30–2.82 (m, 2 H, 2'-H), 3.00 (s, 3 H, CH_3SO_2), 3.48 (m, 2 H, 5'-H), 4.30 (m, 1 H, 4'-H), 5.41 (m, 1 H, 3'-H), 6.38 (dd, 1 H, J = 5.56 Hz, 8.5 Hz, 1'-H), 7.24–7.39 (m, 16 H, C_6-H and trityl), 8.90 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{32}H_{34}N_2O_7S$) C, H, N, S.

2,3'-Anhydro-5-ethyl-5'-*O*-trityl-2'-deoxyuridine (3c). To a refluxing ethanolic solution of **2c** (5.76 g, 10 mmol) was added dropwise 1 N NaOH (10 mL, 10 mmol).[34] Refluxing was continued for 15 min until TLC indicated no remaining starting material. The solvent was then evacuated in vacuo to dryness. The residue was triturated with water and filtered to collect a white amorphous precipitate (4.1 g). An analytical sample was obtained as a foam by silica gel chromatography using a chloroform–methanol (20:1) mixture as the eluent (1.8 g, 37%): mp 162–164 °C (EtOH); UV (MeOH) λ_{max} 260, 254 nm (shoulder); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7.47 Hz, CH_3), 2.15–2.70 (m, 4 H, 2'-H and CH_2), 3.33 (d, 2 H, J = 6.45 Hz, 5'-H), 4.22 (m, 1 H, 4'-H), 5.07 (bs, 1 H, 3'-H), 5.50 (d, 1 H, J = 3.51 Hz, 1'-H), 6.87 (s, 1 H, C_6-H), 7.04–7.47 (m, 15 H, trityl). Anal. ($C_{30}H_{28}N_2O_4$·MeOH) C, H, N.

2,3'-Anhydro-5-*n*-propyl-5'-*O*-trityl-2'-deoxyuridine (3d). To a boiling solution of **2d** (7.0 g, 12.3 mmol) in ethanol (35 mL) was added 1 N NaOH (12.3 mL) dropwise, and the heating was continued until the starting material has disappeared. The solvent was then evaporated in vacuo. The resulting syrup was chromatographed on a silica gel column with methanol–chloroform (1:35) as the eluent to yield 3.16 g (54%) of solid: mp 114–118 °C (MeOH); UV (MeOH) λ_{max} 260, 254 nm (shoulder); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.04 Hz, CH_3), 1.53 (m, 2 H, CH_2), 2.15–2.70 (m, 4 H, 2'-H and CH_2), 3.35 (d, 2 H, J = 6.44 Hz, 5'-H), 4.23 (m, 1 H, 4'-H), 5.10 (bs, 1 H, 3'-H), 5.47 (d, 1 H, J = 3.51 Hz, 1'-H), 6.84 (s, 1 H, C_6-H), 7.20–7.48 (m, 15 H, trityl). Anal. ($C_{31}H_{30}N_2O_4$·MeOH) C, H, N.

3'-Azido-5-ethyl-5'-*O*-trityl-2',3'-dideoxyuridine (4c). A mixture of **3c** (10.0 g, 20 mmol) and LiN_3 (3.0 g, 61 mmol) in DMF (120 mL) was heated at 120–130 °C for 18 h, after which the solvent was removed under high vacuum. The resulting residue was dissolved in chloroform (60 mL), washed with water (20 mL × 2), dried ($MgSO_4$), and filtered. The filtrate was evaporated to a syrup. An analytical sample was obtained as a foam after being purified by a silica gel column with chloroform–methanol (50:1) as the eluent (3.5 g, 32%): mp 152–154 °C; UV (MeOH) λ_{max} 266 nm; IR (KBr) 2080 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.33 Hz, CH_3), 2.00 (q, 2 H, CH_2), 2.42 (m, 2 H, 2'-H), 3.45 (m, 2 H, 5'-H), 4.00 (m, 1 H, 4'-H), 4.33 (m, 1 H, 3'-H), 6.25 (t, 1 H, J = 6.6 Hz, 1'-H), 7.20–7.60 (m, 16 H, C_6-H and trityl), 9.87 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{30}H_{29}N_5O_4$) C, H, N.

3'-Azido-5-*n*-propyl-5'-*O*-trityl-2',3'-dideoxyuridine (4d). A mixture of **3d** (1.16 g, 2.3 mmol) and LiN_3 (1.0 g, 20.4 mmol) in DMF (30 mL) was heated at 120–130 °C for 15 h and then the solvent was evacuated in vacuo. The resulting syrup was washed with water several times, and the resulting solid was chromatographed on a silica gel column with chloroform as the eluent to give a solid (0.75 g, 61%): mp 76–79 °C (MeOH); UV (MeOH) λ_{max} 266 nm; IR (KBr) 2075 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 0.69 (t, 3 H, J = 7.03 Hz, CH_3), 1.28 (m, 2 H, CH_2), 1.60–2.15 (m, 2 H, CH_2), 2.41 (m, 2 H, 2'-H), 3.43 (m, 2 H, 5'-H), 3.95 (m, 1 H, 4'-H), 4.32 (m, 1 H, 3'-H), 6.24 (t, 1 H, J = 6.6 Hz, 1'-H), 7.20–7.50 (m, 16 H, C_6-H and trityl), 8.92 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{31}H_{31}N_5O_4$) C, H, N.

3'-Azido-5-ethyl-2',3'-dideoxyuridine (5c).[22] A mixture of **4c** (0.9 g, 1.72 mmol) and 80% HOAc (25 mL) was heated at 85–90 °C for 40 min. HOAc was evacuated in vacuo to obtain a solid, to which water (50 mL) was added, and the mixture was stirred for 10 min. The solution was filtered through a Celite pad, and then the filtrate was extracted with *n*-hexane. The water layer was separated and evaporated down to ca. 2 mL, and then the solution was freeze-dried to yield an amorphous powder (600 mg, 83%). Recrystallization from methanol gave fine needles: mp 118–120 °C (lit.[22] mp 116–116.5 °C); UV (MeOH) λ_{max} 266 nm (ϵ 10 800); IR (KBr) 2080 cm^{-1} (N_3); ^{1}H NMR (DMSO-d_6) δ 1.04 (t, 3 H, J = 7.47 Hz, CH_3), 2.05–2.55 (m, 4 H, H-2' and CH_2), 3.63 (m, 2 H, 5'-H), 3.85 (m, 1 H, 4'-H), 4.41 (m, 1 H, 3'-H), 5.20 (t, 1 H, OH, D_2O exchangeable), 6.11 (t, 1 H, J = 6.37 Hz, 1'-H), 7.66 (s, 1 H, C_6-H), 11.20 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

3'-Azido-5-*n*-propyl-2',3'-dideoxyuridine (5d). A mixture of **4d** (0.64 g, 1.19 mmol) and 80% HOAc (15 mL) was heated at 90–95 °C for 1 h and mixture was evaporated to a syrup. Ethanol was added and coevaporated several times. Water (10 mL) was added, triturated, and filtered, and the filtrate was evaporated to a foam (180 mg, 50%): UV λ_{max} 267 nm (ϵ 8900); IR (KBr) 2075 cm^{-1} (N_3); ^{1}H NMR (DMSO-d_6) δ 0.86 (t, 3 H, J = 7.03 Hz, CH_3), 1.44 (m, 2 H, CH_2), 2.00–2.55 (m, 4 H, 2'-H and CH_2), 3.63 (m, 2 H, 5'-H), 3.82 (m, 1 H, 4'-H), 4.40 (m, 1 H, 3'-H), 5.19 (t, 1 H, OH, D_2O exchangeable), 6.09 (t, 1 H, J = 6.45 Hz, 1'-H), 7.65 (s, 1 H, C_6-H), 11.24 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{12}H_{17}N_5O_5$·0.5H_2O) C, H, N.

3'-Amino-5-ethyl-2',3'-dideoxyuridine (6c). An aqueous solution of **5c** (376 mg) was hydrogenated at 1 atm over 10% Pd/C (100 mg) until the starting material has disappeared (1 h) as determined by TLC. The mixture was then filtered through a Celite pad and evaporated to dryness to yield a solid (305 mg, 89%): UV (MeOH) λ_{max} 267 nm; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 3 H, CH_3), 1.97–2.43 (m, 4 H, CH_2 and 2'-H), 3.10–3.75 (m, 6 H, NH_2, 3'-H, 4'-H, and 5'-H), 5.09 (b, 1 H, 5'-OH), 6.15 (t, 1 H, 1'-H), 7.58 (s, 1 H, C_6-H). Anal. ($C_{11}H_{17}N_3O_4$·0.5H_2O) C, H, N.

5-Ethyl-3'-iodo-5'-*O*-trityl-2',3'-dideoxyuridine (8c). A mixture of **2c** (3.2 g, 5.6 mmol) and sodium iodide (15.0 g, 75.76 mmol) in 1,2-dimethoxyethane (55 mL) was refluxed for 18 h.[28] The resulting brown mixture was cooled and filtered, and the filtrate was evaporated to a solid. The solid was dissolved in methylene chloride and washed with 5% solution of sodium thiosulfate. The organic layer was again washed with water, dried ($MgSO_4$), evaporated to syrup, and chromatographed on a short silica gel column with methylene chloride–MeOH (70:1) as the eluent to obtain a foam (1.98 g, 59%): UV (MeOH) λ_{max} 267 nm; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7.32 Hz, CH_3), 1.90 (q, 2 H, J = 7.3 Hz, CH_2), 2.73 (m, 2 H, 2'-H), 3.50 (m, 2 H, 5'-H), 4.35 (m, 2 H, 3'- and 4'-H), 6.19 (t, 1 H, J = 5.56 Hz, 1'-H), 7.15–7.65 (m, 16 H, C_6 and trityl-H), 8.30 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{30}H_{29}IN_2O_4$) C, H, I, N.

5-Ethyl-3'-iodo-2',3'-dideoxyuridine (9c). A mixture of **8c** (1.73 g, 2.8 mmol) and 80% HOAc was heated at 100 °C for 50 min and then the solution was evaporated to an amorphous solid, which contained several minor components as determined by TLC. A pure compound was obtained (602 mg, 59%) by silica gel column chromatography using chloroform as the eluent: UV (MeOH) λ_{max} 268 nm (ϵ 11 020); ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 1 H, J = 7.33 Hz, CH_3), 2.20 (q, 2 H, J = 7.33 Hz, CH_2), 2.65 (m, 2 H, 2'-H), 3.69 (m, 2 H, 5'-H), 4.05–4.45 (m, 2 H, 3'- and 4'-H), 5.23 (t, 1

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H, OH, D_2O exchangeable), 6.12 (t, 1 H, J = 5.42 Hz, 1'-H), 7.71 (s, 1 H, C_6-H), 11.24 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{11}H_{15}IN_2O_4$) C, H, I, N.

5-Ethyl-2',3'-dideoxyuridine (10c).[22] Hydrogen was bubbled to a mixture of **9c** (320 mg, 0.87 mmol), triethylamine (0.5 mL), and Pd/C (10%, 200 mg) in methanol (40 mL) at room temperature until the starting material disappeared as determined by TLC. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was chromatographed on a silica gel column with chloroform–methanol (20:1) as the eluent to yield a solid (150 mg, 75%): UV (MeOH) λ_{max} 268 nm (ϵ 10860); ^{1}H NMR (DMSO-d_6) δ 1.03 (t, 3 H, J = 7.47 Hz, CH_3), 1.80–2.4 (m, 6 H, CH_2CH_3 and 2'- and 3'-H), 3.61 (m, 2 H, 5'-H), 4.02 (m, 1 H, 4'-H), 5.03 (t, 1 H, OH, D_2O exchangeable), 5.98 (m, 1 H, 1'-H), 7.77 (s, 1 H, C_6-H), 11.20 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{11}H_{16}N_2O_4$) C, H, N.

5'-Azido-5-ethyl-2',5'-dideoxyuridine (11c). To an ice-cooled solution of **1c** (R = C_2H_5) (1.0 g, 3.91 mmol) in pyridine (10 mL) was added *p*-toluenesulfonyl chloride (0.83 g, 4.35 mmol) and the mixture was kept at 5 °C for 42 h. TLC showed the reaction was not complete. Another portion of *p*-toluenesulfonyl chloride (180 mg) was added and stirred for 1 h at the same temperature. The mixture was evacuated to a syrup at 30 °C and then chromatographed on a silica gel column with chloroform–methanol (15:1) as the eluent to yield 630 mg of white amorphous compound (5-ethyl-5'-tosyl-2'-deoxyuridine). This compound (550 mg, 1.34 mmol) was then treated with NaN_3 (480 mg, 7.38 mmol) in DMF (10 mL) for 25 h at 80 °C. The solvent was evacuated to dryness and ice-cold water (10 mL) was added. The solid was triturated and filtered and a white amorphous solid was collected (340 mg; 35%): mp 171–173 °C (MeOH); UV (MeOH) λ_{max} 264 nm (ϵ 9880); IR (KBr) 2078 cm^{-1} (N_3); ^{1}H NMR (DMSO-d_6) δ 1.03 (t, 3 H, J = 7.36 Hz, CH_3), 2.00–2.40 (m, 4 H, CH_2CH_3 and 2'-H), 3.58 (d, 2 H, J = 5.05 Hz, 5'-H), 3.86 (m, 1 H, 3'-H), 4.20 (m, 1 H, 4'-H), 5.40 (bs, 1 H, OH, D_2O exchangeable), 6.21 (t, 1 *H*, J = 6.92 Hz, 1'-H), 7.43 (s, 1 H, C_6-H). Anal. ($C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$) C, H, N.

5'-Amino-5-ethyl-2',5'-dideoxyuridine (12c). To a mixture of **11c** (300 mg, 1.07 mmol) and 10% Pd/C (80 mg) in 25 mL of water–MeOH (1:1) was introduced hydrogen for 2 h at room temperature. The mixture was then filtered and the filtrate was evaporated to yield a glassy compound (160 mg, 59%): UV (MeOH) λ_{max} 266 nm; ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 3 H, CH_3), 2.00–2.80 (m, 4 H, CH_2CH_3 and 2'-H), 3.30 (m, 2 H, 5'-H), 3.70 (m, 1 H, 4'-H), 4.05 (m, 1 H, 3'-H), 5.21 (m, 3 H, NH_2 and OH, D_2O exchangeable), 6.10 (t, 1 H, 1'-H), 7.56 (s, 1 H, C_6-H). Anal. ($C_{11}H_{17}N_3O_4 \cdot 0.5H_2O$) C, H, N.

5-Ethyl-3',5'-*O*-bis(methylsulfonyl)-2'-deoxyuridine (13c). To a pyridine (10 mL) solution of **1c** (1 g, 3.91 mmol) was added dropwise methanesulfonyl chloride (1.1 g, 9.46 mmol) at 0 °C and then the mixture was stored in the refrigerator overnight.[30] The mixture was then poured into an ice–water mixture, and the resulting white precipitates were collected (1.53 g, 96%). Analytical sample was obtained by crystallization from absolute EtOH: mp 154–155 °C; NMR (DMSO-d_6) δ 1.03 (t, 3 H, J = 7.33 Hz, CH_3), 2.23 (q, 2 H, J = 7.33 Hz, CH_2CH_3), 2.40–2.62 (m, 2 H, 2'-H), 3.24 (s, 3 H, CH_3SO_2), 3.32 (s, 3 H, CH_3SO_2), 4.44 (m, 3 H, 4'- and 5'-H), 5.29 (m, 1 H, 3'-H), 6.21 (t, J = 7.33 Hz, 1 H, 1'-H), 7.44 (s, 1 H, C_6-H), 11.37 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{13}H_{20}N_2O_9S_2$) C, H, N, S.

3',5'-Anhydro-5-ethyl-2'-deoxyuridine (14c). A mixture of **13c** (1.27 g, 3.1 mmol) and NaOH (0.37 g, 9.3 mmol) in water (50 mL) was refluxed for 2 h, cooled to room temperature, and then neutralized with HOAc. The resulting solution was evacuated to dryness, which was extracted with hot acetone (25 mL × 5). The acetone solution was evacuated in vacuo and the resulting solid was purified by a silica gel column with a mixture of chloroform and methanol (10:1) as the eluent to obtain a white solid (433 mg, 59%): mp 174–175 °C (EtOH); UV (MeOH) λ_{max} 265 nm; NMR (DMSO-d_6) δ 1.02 (t, 3 H, J = 7.32 Hz, CH_3), 2.23 (q, 2 H, J = 7.32 Hz, CH_2CH_3), 2.49 (m, 2 H, 2'-H), 4.01 (dd, 1 H, J = 1.17 Hz, 7.91 Hz, 5'-H), 4.71 (dd, 1 H, J = 4.1 Hz, 7.91 Hz, 5'-H), 4.90 (m, 1 H, 4'-H), 5.50 (m, 1 H, 3'-H), 6.56 (t, 1 H, J = 5.42 Hz, 1'-H), 8.03 (s, 1 H, C_6-H), 11.30 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{11}H_{14}N_2O_4$) C, H, N.

5-Ethyl-2'-deoxyuridin-2'-ene (15c). A mixture of **14c** (0.3 g, 1.26 mmol) and potassium *tert*-butoxide (0.6 g, 6.36 mmol) in DMSO (25 mL) was stirred for 3 h at room temperature.[30] After neutralization with HOAc, the solvent was removed in vacuo to a semisyrup, which was purified by a silica gel column with a mixture of $CHCl_3$–MeOH (50:1) as the eluent to afford crystals (150 mg, 50%): mp 118–119 °C (C_6H_6–EtOAc); UV (MeOH) λ_{max} 264 nm; NMR (DMSO-d_6) δ 0.99 (t, 3 H, J = 7.32 Hz, CH_3), 2.16 (q, 2 H, J = 7.3 Hz, CH_2), 3.60 (m, 2 H, 5'-H), 4.78 (m, 1 H, 4'-H), 4.98 (bs, 1 H, OH, D_2O exchangeable), 5.89 (m, 1 H, 3'-H), 6.37 (m, 1 H, 2'-H), 6.82 (m, 1 H, 1'-H), 7.60 (s, 1 H, C_6-H), 11.20 (bs, 1 H, NH, D_2O exchangeable). Anal. ($C_{11}H_{14}N_2O_4 \cdot 0.5H_2O$) C, H, N.

Antiviral Evaluation Procedures. Three-day-old mitogen-stimulated human peripheral blood mononuclear cells (10^6 cells/mL) from normal donors were infected with HIV-1 (strain LAV) at a concentration of about 100 $TCID_{50}$ per milliliter and cultured in the presence and absence of various concentrations of compounds. The drugs were added about 45 min after the infection. Five days after infection the supernatant was clarified and the virus pelleted. The reverse transcriptase activity in the disrupted virus was determined. The methods used for culturing the PBM cells, harvesting the virus, and determining the reverse transcriptase activity were those described by McDougal et al.[36] and Spira et al.,[37] except that fungezone was absent from the all culture medium. The virus-infected control had about 2×10^5 dpm/mL of reverse transcriptase activity. The blank and uninfected cell control values were about 300 and 1000 dpm, respectively. Active compounds were retested with different donor cells.

The effects of the drugs on the growth of uninfected human PBM cells were also established. Mitogen-stimulated PBM cells (3.8×10^5 cells/mL) were cultured in the presence and absence of drugs under the same conditions as those used for the antiviral assays described above. The cells were counted daily for 5 days by using the trypan blue exclusion method. Only the toxicity on day 5 is reported for the drugs. The EC_{50} was determined by the median effect method.[38]

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(35) Although some of the compounds depicted in the scheme are known in the literature, we decided to duplicate here for the sake of improving the readability of this article, and not for claiming the procedures as ours.

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