was recrystallized from EtOH: mp 192-193 °C (99.10% pure by HPLC, $k' = 4.26$); UV (MeOH) λ_{max} 260 nm (log ϵ 4.08); ^{1}H NMR (D_2O) δ 2.40 (m, 1 H, H-3'), 2.60 (m, 2 H, H-2'$_{a,b}$), 3.70 (m, 4 H, 2 CH_2OH), 4.00 (m, 1 H, H-4'), 6.21 (dd, $J = 6.7$ Hz, $J' = 2.8$ H, 1 H, H-1'), 8.03 (s, 1 H, H-2), 8.21 (s, 1 H, H-8); MS (FAB, positive mode) m/z (rel intensity) 266 (MH^+, 63), 136 (b + 2 H, 100); high-resolution FAB MS, m/z 266.1266 (MH^+, calcd 266.1253). Anal. ($C_{11}H_{15}N_5O_3$) C, H, N.

Biological Procedures. HIV cytopathic effect assay was performed with ATH8 cells as previously described.[4] Briefly, 2 × 10^5 ATH8 cells were exposed to HTLV-III$_B$ virus (2000 virus particles/cell) for 45 min after treatment with polybrene, resuspended in 2 mL of culture medium containing interleukin 2 in the presence or absence of various concentrations of compounds, and incubated in culture tubes at 37 °C in 50% CO_2/95% air humidified atmosphere. Control cells were treated similarly but were not exposed to the virus. At various time points on days 5-7 of culture, the total viable cells were counted in a hemocytometer by the trypan blue dye exclusion method. As a minimum, all compounds were tested in duplicate dose-response experiments. The data in Figure 2 are from an experiment which is representative of the three performed.

Molecular Modeling. Models of A (1), 2',3'-dideoxyadenosine (ddA), 3'-hydroxymethyl-ddA (2), and 2'-hydroxymethyl-ddA (3) were developed with use of Quanta (Polygen Corp.). In each case, the two-dimensional structure was entered and a three-dimensional structure was calculated by the program. The potential energy of this three-dimensional structure was then minimized with use of 100 or 200 iterations of an adopted basis Newton-Raphson method. Optimum values of the important torsion angles χ, γ_1, and γ_2 were estimated in each case by means of a conformational search through 360° in 36 steps of 10° each. In the case of χ and γ_1, both angles were varied simultaneously and 36 × 36 conformations were examined for an energy minimum. Distance and angle measurements were made on the final minimized structures. Atomic coordinate data derived from X-ray diffraction analysis were taken from the original publications and entered into the program in Cambridge Crystal Database format. The structures of oxetanocin A and ddA that were based upon X-ray diffraction data were not modeled further but used only for purposes of comparison with the modeled structures.

Acknowledgment. We thank Dr. James A. Kelley of this laboratory for providing the mass spectral data for compounds **2**, **3**, and **20**. The secretarial help of Mrs. Yetta Buckberg is also appreciated.

Registry No. **2**, 130469-38-4; **3**, 130469-39-5; **4**, 69832-48-0; **5**, 130469-40-8; **6**, 130495-83-9; **8**, 130469-41-9; **9**, 130469-42-0; α-**10**, 130469-54-4; β-**10**, 130469-43-1; **11**, 130469-44-2; **12**, 130469-45-3; **13**, 130469-46-4; **14**, 130469-47-5; **15**, 130469-48-6; **18**, 130469-49-7; **19**, 130469-50-0; **20**, 26289-43-0; **21**, 130469-51-1; **22**, 130469-52-2; **23**, 130469-53-3; 6-chloro-9-(trimethylsilyl)-9*H*-purine, 32865-86-4; diacetone-D-glucose, 582-52-5.

A New Class of HIV-1-Specific 6-Substituted Acyclouridine Derivatives: Synthesis and Anti-HIV-1 Activity of 5- or 6-Substituted Analogues of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)

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A series of novel acyclouridine derivatives substituted at both the C-5 and C-6 positions were synthesized for the purpose of improving the activity of a recently reported HIV-1-specific lead, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT). Preparation of C-6 substituted derivatives was carried out based on the following three methods: (1) LDA (lithium diisopropylamide) lithiation of a thymine derivative (**4**) and subsequent reaction with electrophiles, (2) an addition-elimination reaction of HEPT or its 6-(phenylsulfinyl) derivative (**10**), or (3) palladium-catalyzed cross-coupling between a 6-iodo derivative (**16**) and terminal alkynes. Following the methods, 21 C-6 substituted analogues were synthesized. Among these, 6-(cyclohexylthio) (**8**), 6-phenoxy (**13**), and 6-benzyl (**27**) derivatives showed anti-HIV-1 (HTLV-III$_B$) activity with EC_{50} values of 8.2, 85, and 23 μM, respectively. Preparation of C-5 substituted derivatives was based on either LTMP (lithium 2,2,6,6-tetramethylpiperidide) lithiation of 6-(phenylthio)uracil derivative **37** or the above mentioned palladium-catalyzed cross-coupling of a 5-iodo-6-(phenylthio)uracil derivative (**38**). Following these methods, 11 C-5 substituted analogues were synthesized. Some 5-substituted derivatives (5-I, **44**; 5-CH=CPh_2, **49**; 5-CH=CHPh (*Z*), **54**; and 5-CH=CH_2, **55**) were more active than HEPT, but their selectivity indices (SI = CC_{50}/EC_{50}) were lower than that of HEPT. Compound **8** was also evaluated against another HIV-1 strain (HTLV-III$_{RF}$) and HIV-2 strains (LAV-2$_{ROD}$ and LAV-2$_{EHO}$). Only HTLV-III$_{RF}$ was as sensitive as HTLV-III$_B$.

Acquired immunodeficiency syndrome (AIDS) is a pandemic immunosuppressive disease caused by the depletion of helper T lymphocytes. The causative agent, termed human immunodeficiency virus type 1 (HIV-1), is a retrovirus. A similar retrovirus, HIV type 2 (HIV-2), also causes AIDS. Various compounds have been reported to inhibit the replication of HIV-1 in vitro.[1,2] A nucleoside analogue, 3'-azido-3'-deoxythymidine (AZT), is still the only drug approved for clinical use. Although a double-blind clinical trial has clearly demonstrated that AZT treatment prolongs the life of AIDS patients, serious side effects such as anemia and leukopenia are often associated with the long-term use of AZT.[3,4] Furthermore, clinical

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[‡] Fukushima Medical College.
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[∥] University of Birmingham.
[⊥] Rega Institute.

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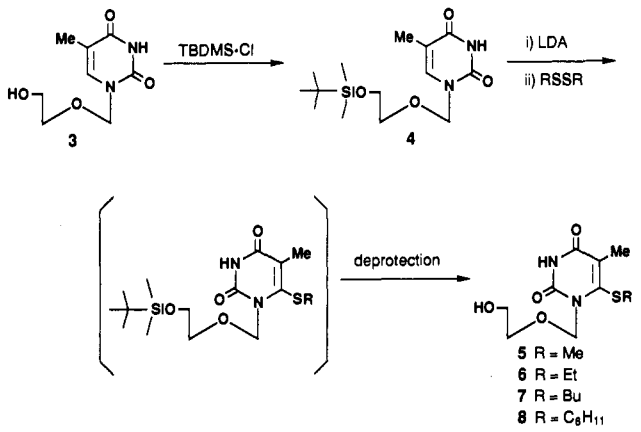
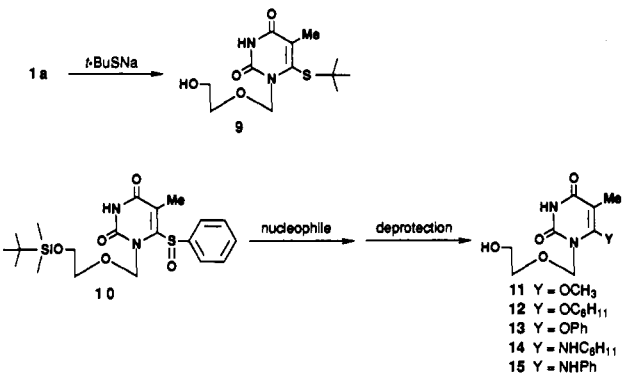
Scheme I



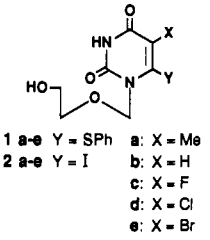
isolates with reduced sensitivity to AZT have been reported.[5] These results emphasize the urgent need for a new class of compounds that have potent anti-HIV-1 activity, lower toxicity, and preferably act through a different mode of action.

Although many nucleoside analogues including acyclonucleosides have been synthesized and their antiviral activities[6-8] evaluated, no information is available concerning those of 6-substituted pyrimidine derivatives, presumably due to the difficulty in their preparation. Our studies on lithiation of nucleosides have proved that this strategy constitutes a simple and highly general entry for modifying the base moiety of nucleosides.[9-21] When lithium diisopropylamide (LDA) is used as a lithiating agent, regiospecific abstraction of the more acidic H-6 of uridine or 2'-deoxyuridine[22] can be achieved. This provides various types of 6-substituted derivatives, simply by reacting the C-6 lithiated species with electrophiles.[9,11,12]

Scheme II



As a part of our attempted application of the LDA lithiation, we have recently reported the synthesis of 6-substituted derivatives of 1-[(2-hydroxyethoxy)methyl]-uracil (**1a–e** and **2a–e**) and their anti-HIV-1 activity.[23]



Among these derivatives, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (**1a**, HEPT) was found to serve as a new lead for anti-HIV-1 agents. The unique structure of HEPT as well as its highly HIV-1 specific activity[24] prompted us to try to improve the activity of HEPT and to investigate structure–activity relationships, which is the subject of the present study.

Chemistry

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]thymine (**4**) was prepared from known compound **3**[25] with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole. Compound **4** was lithiated with LDA (2.5 equiv, below −70 °C, for 1 h) and reacted with a series of dialkyl disulfides (2 equiv, below −70 °C, for 1 h). After acidic treatment of the reaction mixture, the corresponding 6-alkylthio derivatives (**5–8**) were obtained (Scheme I). Because the 6-phenylthio group of HEPT can be regarded to be at the β-position in the enone system, an addition–elimination reaction using HEPT and an alkanethiolate can be used as an alternative method of preparation (Scheme II).[26] Treatment of HEPT with sodium 1,1-di-

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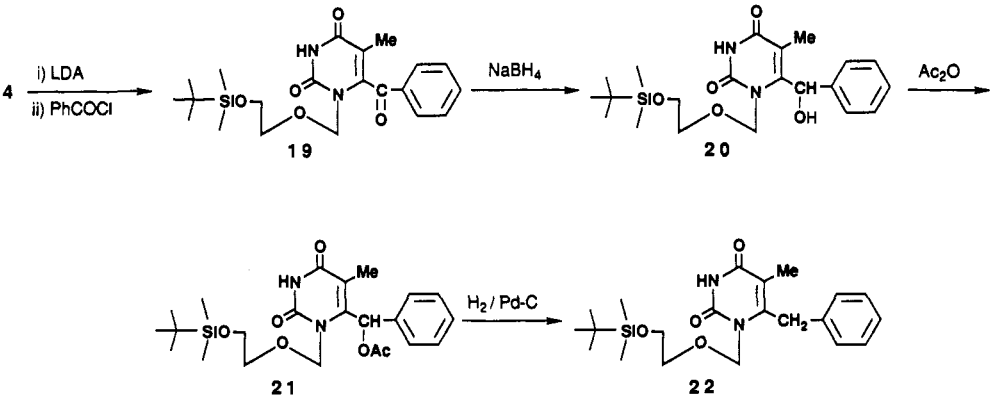
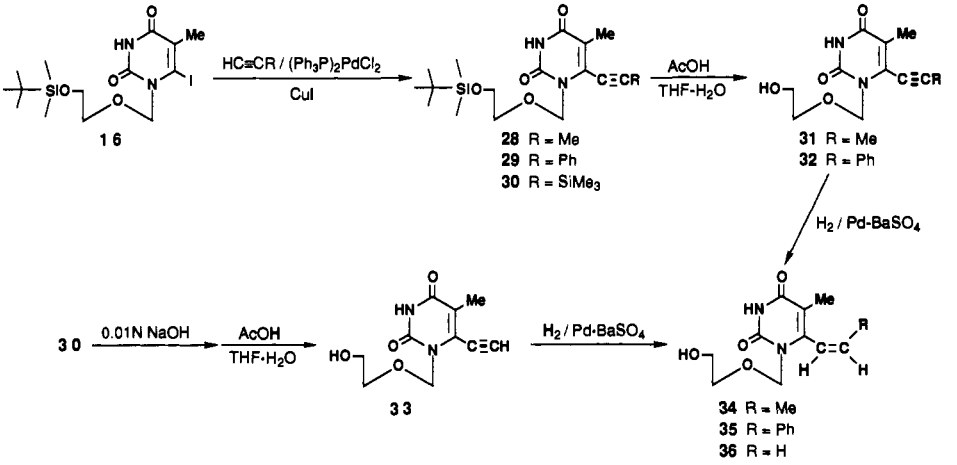
Scheme III

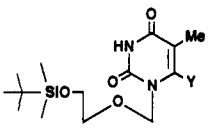


Scheme IV



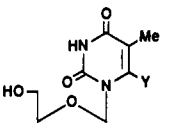
methylethanethiolate (10 equiv) in DMF–THF (at room temperature, for 30 min) gave the 6-(*tert*-butylthio) derivative **9**. A variant of the above method, using the 6-(phenylsulfinyl) derivative **10** as a starting material, appeared to be useful for the introduction of an oxygen or nitrogen functionality to the C-6 position. Thus, when compound **10** was reacted with the respective nucleophile (NaOMe, $NaOC_6H_{11}$, NaOPh, $C_6H_{11}NH_2$, and LiNHPh) either in THF or in dioxane and the resulting product desilylated, compounds **11–15** were obtained in good overall yields.

Preparation of the 6-iodo derivative (**16**) has been reported previously based on the LDA lithiation of compound **4** and subsequent reaction with iodine.[23] When α-bromoacetophenone and *p*-toluenesulfonyl chloride were employed as electrophiles in this reaction, the 6-bromo (**17**) and 6-chloro (**18**) derivatives were obtained. An attempted



16 Y = I
17 Y = Br
18 Y = Cl

use of benzyl bromide as an electrophile in the reaction of the C-6 lithiated species of compound **4** failed.[27] We, therefore, chose the synthetic route shown in Scheme III for the introduction of the benzyl group. The reaction of the C-6 lithiated species of compound **4** with benzoyl chloride produced **19**, which was in turn quantitatively converted to compound **20** by treating with $NaBH_4$ in EtOH. Acetylation of compound **20** gave compound **21**. When compound **21** was subjected to hydrogenolysis in the presence of Pd–C (in EtOH, at 55 °C, 1 atm, for 6 h), the expected 6-benzyl derivative (**22**) was obtained. Compound **17–20** and **22** were desilylated to afford their free acyclothymidines (**23–27**).



23 Y = Br
24 Y = Cl
25 Y = COPh
26 Y = CH(OH)Ph
27 Y = CH_2Ph

Another C-6 modification was carried out based on palladium-catalyzed cross-coupling between iodinated nucleosides and a terminal alkyne.[28,29] Treatment of compound **16** with an alkyne [propyne, phenylacetylene, and (trimethylsilyl)acetylene] in MeCN–Et_3N in the presence of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide gave compounds **28–30**. Deprotection of compounds **28** and **29** gave compounds **31** and **32**, re-

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(27) In contrast to this result, when 1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]uracil was lithiated with LDA and subjected to the reaction with benzyl bromide, the corresponding 6-benzyl derivative was obtained in 46% yield.
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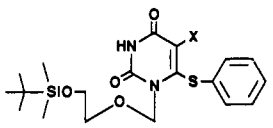
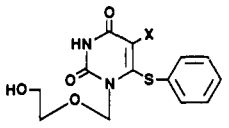
spectively. In the case of compound **30**, deprotection was carried out in two steps to afford compound **33** as shown Scheme IV. 6-Vinyl derivatives (**34–36**) were prepared by partial hydrogenation of compounds **31–33** in the presence of Pd–$BaSO_4$.

The lithiation approach appeared to be efficient also for the modification at the C-5 position of HEPT. However, a more basic lithiating agent, lithium 2,2,6,6-tetramethylpiperidide (LTMP),[30] is necessary for this purpose.[15] The lithiation of compound **37** with 3 equiv of LTMP followed by treatment with an electrophile (I_2, PhSSPh, $Me_2CHCOCl$, PhCOCl, $PhCH_2Br$, and Ph_2CHCHO) afforded compounds **38–43**. Acidic treatment of compounds

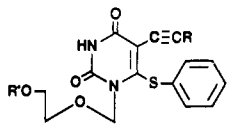


37 X = H
38 X = I
39 X = SPh
40 X = $COCHMe_2$
41 X = COPh
42 X = CH_2Ph
43 X = $CH(OH)CHPh_2$

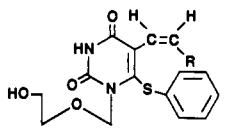


44 X = I
45 X = SPh
46 X = $COCHMe_2$
47 X = COPh
48 X = CH_2Ph
49 X = $CH{=}CPh_2$

38–42 furnished compounds **44–48**. Dehydration of compound **43** with $SOCl_2$ in pyridine and subsequent deprotection gave 5-(2,2-diphenylvinyl) derivative **49**. Application of the aforementioned palladium-catalyzed cross-coupling was carried out by using 5-iodo derivative **38** followed by deprotection to afford compounds **50**, **51**, and



50 R = Me R' = H
51 R = Ph R' = H
52 R = $SiMe_3$ R' = TBDMS
53 R = R' = H



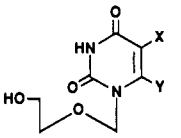
54 R = Ph
55 R = H

53. Partial hydrogenation of compound **51** gave compound **54**.[31] The 6-(phenylthio)-5-vinyl derivative (**55**) was synthesized from 5-vinyluracil in four steps (see the Experimental Section).

Biological Results and Discussion

Our previous study revealed that HEPT exhibited a potent and selective inhibition of HIV-1 replication in vitro and that the triphosphate of HEPT was not inhibitory to purified HIV-1 reverse transcriptase at concentrations up to 500 μM [poly(rA)·oligo(dT) was used as the template primer].[23,24] The 50% antiviral effective concentration (EC_{50}) of HEPT in MT-4 cells is 7.0 μM, while its 50% cytotoxic concentration (CC_{50}) to the host cells is 740 μM. Interestingly, the replacement of the 5-methyl group in HEPT by hydrogen results in the total loss of activity. To improve further the activity and to explore structure–activity relationships, we synthesized derivatives of HEPT substituted either at the C-6 or the C-5 positions and evaluated their anti-HIV-1 activity. The anti-HIV-1 activity and cytotoxicity of the newly synthesized 32 compounds in MT-4 cells are summarized in Table I together with those of AZT, 2′,3′-dideoxycytidine (DDC), and 2′,3′-dideoxyadenosine (DDA).

Table I. Comparative Potency and Toxicity of HEPT Analogues as Inhibitors of HIV-1 Replication in MT-4 Cells[a]



compd	X	Y	EC_{50},[b] μM	CC_{50},[c] μM	SI[d]
HEPT	Me	SPh	7.0	740	106
5	Me	SMe	>250	>250	-
6	Me	SEt	>250	>250	-
7	Me	SBu	130	>250	-
8	Me	SC_6H_{11}	8.2	664	81
9	Me	SBu-*t*	>366	366	<1
11	Me	OMe	>484	484	<1
12	Me	OC_6H_{11}	>400	400	<1
13	Me	OPh	85	345	4.1
14	Me	NHC_6H_{11}	>377	337	<1
15	Me	NHPh	>327	327	<1
23	Me	Br	>180	180	<1
24	Me	Cl	>250	>250	-
25	Me	COPh	>366	366	<1
26	Me	CH(OH)Ph	>400	400	<1
27	Me	CH_2Ph	23	352	15
31	Me	C≡CMe	>250	>250	-
32	Me	C≡CPh	>14	14	<1
33	Me	C≡CH	>5.5	5.5	<1
34	Me	CH=CHMe (*Z*)	>250	>250	-
35	Me	CH=CHPh (*Z*)	>250	>250	-
36	Me	$CH{=}CH_2$	>250	>250	-
44	I	SPh	3.6	20	5.6
45	SPh	SPh	>21	21	<1
46	$COCHMe_2$	SPh	>12	12	<1
47	COPh	SPh	>13	13	<1
48	CH_2Ph	SPh	>23	23	<1
49	$CH{=}CPh_2$	SPh	0.84	21	25
50	C≡CMe	SPh	>19	19	<1
51	C≡CPh	SPh	>3.4	3.4	<1
53	C≡CH	SPh	>18	18	<1
54	CH=CHPh (*Z*)	SPh	6.0	95	16
55	$CH{=}CH_2$	SPh	1.1	76	69
AZT			0.016	20	1250
DDC			0.3	40	133
DDA			6.3	890	141

[a] The antiviral activity and cytotoxicity of the compound were determined on day 5 after virus infection. [b] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1 (HTLV-III_B). [c] Cytotoxic concentration of compound required to reduce the viability of mock-infected MT-4 cells by 50%. [d] Selectivity index: ratio of CC_{50}/EC_{50}.

Table II. Inhibition of HIV-1 and HIV-2 in MT-4 Cells by **8**[a]

compd	virus	strain	EC_{50}, μM	CC_{50}, μM
8	HIV-1	HTLV-III_B	7.7	440
		HTLV-III_{RF}	7.9	-
	HIV-2	LAV-2_{ROD}	>250	-
		LAV-2_{EHO}	>250	-
HEPT	HIV-1	HTLV-III_B	6.5	>500
		HTLV-III_{RF}	8.1[b]	-
	HIV-2	LAV-2_{ROD}	>250[b]	-
		LAV-2_{EHO}	>250[b]	-

[a] The antiviral activity and cytotoxicity of the compounds were determined on day 4 after virus infection and expressed as the EC_{50} for virus-infected cells and the EC_{50} for mock-infected cells, respectively. [b] See ref 24.

The analogues bearing a simple alkylthio group at the C-6 position (**5–7**) are uniformly inactive; however, it is interesting to see that the 6-cyclohexylthio derivative (**8**), a saturated analogue of HEPT, retains the activity (EC_{50} = 8.2 μM). This is not the case for the oxygen (**12**) or nitrogen (**14**) counterpart; the 6-phenoxy derivatives (**13**) showed weak activity. Replacement by a halogen atom (**23**

(30) LTMP is reported to be 1.6 pK units more basic than LDA: Fraser, R. R.; Baignee, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, *23*, 4195–4198.

(31) In contrast to this result, 5-(2-methylethynyl) derivative (**50**) gave a complex mixture of products under the same reaction condition and the desired 5-[2-(*Z*)-methylvinyl] derivative could not be isolated.

and 24) or a carbon substituent (25–26 and 31–36) was rather discouraging. The only one exception is the 6-benzyl derivative (27, EC_{50} = 23 μM).

When 5-substituted derivatives of HEPT were examined for their inhibitory effect on HIV-1 replication, the 5-iodo (44), 5-(2,2-diphenylvinyl) (49), 5-[2-(*Z*)-phenylvinyl] (54), and 5-vinyl (55) derivatives were more active than HEPT. However, these compounds proved to be more cytotoxic (Table I). Others, i.e. compounds 45–48, 50, 51, and 53, did not show any anti-HIV-1 activity at their nontoxic concentrations to the host cells.

Further studies on the structure–activity relationships showed that the phenylthio group at the C-6 position of HEPT could be substituted by a cyclohexylthio group, a benzyl group, or a phenoxy group. Yet the substitution by the latter two groups weakened the activity. Furthermore, other substitution was totally ineffective. The results of C-6-modified analogues suggest the necessity of a ring structure in the C-6 substituent for this type of compounds to be active against HIV-1.

As for C-5 modification, there seems to be a general trend of increasing toxicity. However, some compounds (44, 49, 54, and 55) exhibited highly promising activity. From these results, it should still be possible to improve the selectivity index by examining further modification at this position. In our previous study,[23] replacement of the 5-methyl group in HEPT by F, Cl, or Br gave no active compounds. The 5-iodo derivative (44) prepared in the present study, on the other hand, showed considerable activity. This may have to do with the size of the C-5 substituent. As has been reported in the case of 5-substituted 6-(phenylthio)uridine derivatives,[15,26] the increase in the size of the C-5 substituent causes a parallel change in conformation of the 6-phenylthio group. Thus the conformation of the 6-phenylthio group seems to contribute to the anti-HIV activity of HEPT analogues.

Compound 8 was evaluated for inhibitory effect on another HIV-1 strain ($HTLV\text{-}III_{RF}$) and two HIV-2 strains ($LAV\text{-}2_{ROD}$ and $LAV\text{-}2_{EHO}$). $HTLV\text{-}III_{RF}$ proved as sensitive to this compound as $HTLV\text{-}III_B$; however, compound 8 was totally inactive against either $LAV\text{-}2_{ROD}$ or $LAV\text{-}2_{EHO}$ (Table II), showing it is acting through a similar mechanism as that of HEPT.[24] Because of unique structural and biological features of HEPT and its congeners, these compounds are being further pursued as candidate drugs for anti-AIDS chemotherapy.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 250 MHz on a AC-250 Bruker NMR spectrometer using tetramethylsilane as the internal standard; chemical shifts are recorded in parts per million (ppm). IR spectra were recorded with a JASCO A-102 spectrophotometer. UV spectra were recorded with a Shimadzu UV-260 spectrophotometer. Mass spectra were taken on a Hitachi M-80A spectrometer. Column chromatography was carried out on Merck Silica gel 60 H. Octadecylsilyl- (ODS-) silica gel column chromatography was carried out on MCI Gel ODS IMY (Mitsubishi Kasei Corp.). TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck). Elemental analyses were performed on a Perkin-Elmer 240-C elemental analyzer.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]thymine (4). A mixture of 3 (476 mg, 2.4 mmol), DMF (10 mL), imidazole (556 mg, 8.2 mmol), and *tert*-butyldimethylsilyl chloride (580 mg, 4.2 mmol) was stirred at room temperature. After 14 h, the reaction mixture was poured into H_2O (50 mL). The resulting precipitate was collected on a filter and washed with saturated $NaHCO_3$ solution (3 × 50 mL) and H_2O (3 × 50 mL). The precipitate was dried in vacuo and recrystallized from cyclohexane to give 672 mg (90%) of 4: mp 137–138 °C; MS *m/z* 314 (M^+); ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, Me_2Si), 0.87 (s, 9 H, Me_3C), 1.91 (d, *J* = 1.3 Hz, 3 H, 5-Me), 3.61, 3.74 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.16 (s, 2 H, NCH_2O), 7.13 (d, *J* = 1.3 Hz, 1 H, 6-H), 8.01 (br, 1 H, NH). Anal. ($C_{14}H_{26}N_2O_4Si$), C, H, N.

General Procedure for the Preparation of 6-(Alkylthio)-1-[(2-hydroxyethoxy)methyl]thymine Derivatives 5–8. To a solution of LDA (5 mmol) in THF (10 mL) was added 4 (629 mg, 2 mmol) in THF (8 mL) under a nitrogen atmosphere, at a rate such that the temperature did not exceed −70 °C. After the mixture was stirred for 1 h, dialkyl disulfide (4 mmol) dissolved in THF (5 mL) was added, and the temperature was maintained below −70 °C. The mixture was stirred for 1 h below −70 °C and allowed to warm to room temperature. The solution was acidified with concentrated HCl to pH 1.2 and stirred at room temperature for 2 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL) and then with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was crystallized twice from a suitable solvent.

1-[(2-Hydroxyethoxy)methyl]-6-(methylthio)thymine (5): yield 50%; mp 145–147 °C (EtOAc–EtOH); UV (MeOH) λ_{max} 276 nm (ε 8200); MS *m/z* 246 (M^+); ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, 5-Me), 2.45 (s, 3 H, SMe), 3.75 (s, 4 H, $HOCH_2CH_2O$), 5.68 (s, 2 H, NCH_2O), 8.75 (br, 1 H, NH). Anal. ($C_9H_{14}N_2O_4S \cdot {}^1/_{10}H_2O$) C, H, N.

6-(Ethylthio)-1-[(2-hydroxyethoxy)methyl]thymine (6): yield 47%; mp 111.5–112.5 °C (EtOH–H_2O); UV (MeOH) λ_{max} 276 nm (ε 7500); MS *m/z* 260 (M^+); ^1H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.4 Hz, 3 H, SCH_2CH_3), 2.22 (s, 3 H, 5-Me), 2.94 (q, *J* = 7.4 Hz, 2 H, SCH_2CH_3), 3.74 (s, 4 H, $HOCH_2CH_2O$), 5.68 (s, 2 H, NCH_2O), 8.47 (br, 1 H, NH). Anal. ($C_{10}H_{16}N_2O_4S$) C, H, N.

6-(Butylthio)-1-[(2-hydroxyethoxy)methyl]thymine (7): yield 39% (EtOH–H_2O); mp 100–101 °C; UV (MeOH) λ_{max} 277 nm (ε 7700); MS *m/z* 288 (M^+); ^1H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.3 Hz, 3 H, $SCH_2CH_2CH_2CH_3$), 1.68 (m, 2 H, $SCH_2CH_2CH_2CH_3$), 1.86 (m, 2 H, $SCH_2CH_2CH_2CH_3$), 2.35 (br, 1 H, OH), 2.48 (s, 3 H, 5-Me), 3.15 (t, *J* = 7.2 Hz, 2 H, $SCH_2CH_2CH_2CH_3$), 3.99 (s, 4 H, $HOCH_2CH_2O$), 5.93 (s, 2 H, NCH_2O), 8.61 (br, 1 H, NH). Anal. ($C_{12}H_{20}N_2O_4S$) C, H, N.

6-(Cyclohexylthio)-1-[(2-hydroxyethoxy)methyl]thymine (8): yield 79%; mp 125.5–127 °C (EtOAc); UV (MeOH) λ_{max} 278 nm (ε 8100); MS *m/z* 314 (M^+); ^1H NMR ($CDCl_3$) δ 1.25–1.96 (m, 10 H, cyclohexyl), 2.21 (s, 3 H, 5-Me), 3.20 (m, 1 H, SCH), 3.73 (s, 4 H, $HOCH_2CH_2O$), 5.70 (s, 2 H, NCH_2O), 8.21 (br, 1 H, NH). Anal. ($C_{14}H_{22}N_2O_4S$) C, H, N.

6-(*tert*-Butylthio)-1-[(2-hydroxyethoxy)methyl]thymine (9). To a solution of 1,1-dimethylethanethiol (2.3 mL, 20 mmol) in DMF (10 mL) and THF (15 mL) was added sodium hydride (60% in oil, 0.8 g, 20 mmol), and the mixture was stirred at 90 °C for 30 min. The resulting suspension was allowed to cool to room temperature. To this suspension was added HEPT (617 mg, 2 mmol) and the mixture was stirred at room temperature for 30 min. After neutralization with AcOH, the mixture was evaporated to dryness and the residue was purified by chromatography on silica gel ($CHCl_3$–MeOH 50:1, v/v) and with preparative ODS-silica gel HPLC (MeCN–H_2O 7:3, v/v) to give 236 mg (41%) of 9 after crystallization from toluene: mp 114–115 °C; UV (MeOH) λ_{max} 280 nm (ε 8800); MS *m/z* 231 (M^+ − 57); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H, CMe_3), 2.19 (br, 1 H, OH), 2.27 (s, 3 H, 5-Me), 3.68–3.70 (m, 4 H, $HOCH_2CH_2O$), 5.74 (s, 2 H, NCH_2O), 8.40 (br, 1 H, NH). Anal. ($C_{12}H_{20}N_2O_4S$) C, H, N.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylsulfinyl)thymine (10). To a solution of 1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylthio)thymine (15 g, 35.5 mmol) in chloroform (200 mL) was added 70% 3-chloroperbenzoic acid (12.5 g, 50 mmol), and the solution was stirred at room temperature for 2 h. The solution was evaporated to dryness, and the residue was purified by ODS-silica gel column chromatography (MeOH–H_2O 9:1, v/v) to give 14.2 g (91%) of 10 after crystallization from EtOH–H_2O: mp 107–108 °C; UV (MeOH) λ_{max} 282 nm (ε 8100); MS *m/z* 381 (M^+ − 57); ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, Me_2Si), 0.86 (s, 9 H, Me_3C), 2.10 (s, 3 H, 5-Me), 3.56 (s, 4 H, $SiOCH_2CH_2O$), 5.52, 5.79 (ABq, *J* = 10.3 Hz, 2 H, NCH_2O), 7.52–7.67 (m, 5 H, SOPh), 8.30 (br, 1 H, NH). Anal. ($C_{20}H_{30}N_2O_5SSi$) C, H, N.

General Procedure for the Preparation of 1-[(2-Hydroxyethoxy)methyl]-6-oxythymine Derivatives 11–13. To a suspension of the sodium salt of the alcohol or phenol (10 mmol) in THF (10 mL) was added **10** (439 mg, 1 mmol), and the mixture was stirred at room temperature for 1.5 h. To the solution was added saturated NH_4Cl solution (20 mL) and it was then extracted with EtOAc (50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by column chromatography on ODS-silica gel eluted with MeOH–H_2O (8:2, v/v). The eluate was evaporated and the residue was dissolved in AcOH–THF–H_2O (15 mL; 2:2:1, v/v/v). The solution was stirred at room temperature for 14 h and evaporated to dryness. The residue was crystallized from toluene.

1-[(2-Hydroxyethoxy)methyl]-6-methoxythymine (11): yield 55%; mp 168 °C; UV (MeOH) λ_{max} 263 nm (ϵ 9900); MS m/z 230 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.76 (s, 3 H, 5-Me), 3.45–3.53 (m, 4 H, $HOCH_2CH_2O$), 3.92 (s, 3 H, OMe), 4.63 (t, J = 5.3 Hz, 1 H, OH), 5.15 (s, 2 H, NCH_2O), 11.31 (br, 1 H, NH). Anal. ($C_9H_{14}N_2O_5$) C, H, N.

6-(Cyclohexyloxy)-1-[(2-hydroxyethoxy)methyl]thymine (12): yield 53%; mp 143–144 °C; UV (MeOH) λ_{max} 265 nm (ϵ 11 000); MS m/z 298 (M^+); ^1H NMR ($CDCl_3$) δ 1.21–2.16 (m, 10 H, cyclohexyl), 1.92 (s, 3 H, 5-Me), 3.71–3.79 (s, 4 H, $HOCH_2CH_2O$), 4.35 (m, 1 H, OCH), 5.35 (s, 2 H, NCH_2O), 8.10 (br, 1 H, NH). Anal. ($C_{14}H_{22}N_2O_5$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenoxy)thymine (13): yield 64%; mp 112 °C; UV (MeOH) λ_{max} 265 nm (ϵ 10 000); MS m/z 292 (M^+); ^1H NMR ($CDCl_3$) δ 1.69 (s, 3 H, 5-Me), 3.58–3.69 (m, 4 H, $HOCH_2CH_2O$), 5.33 (s, 2 H, NCH_2O), 6.99 [dd, J = 8.1, 1.0 Hz, 2 H, OPh(o)], 7.17 [tt, J = 8.1, 1.0 Hz, 1 H, OPh(p)], 7.39 [dd, J = 8.1 Hz, 2 H, OPh(m)], 8.03 (br, 1 H, NH). Anal. ($C_{14}H_{16}N_2O_5$) C, H, N.

6-(Aminocyclohexyl)-1-[(2-hydroxyethoxy)methyl]thymine (14). To a solution of cyclohexylamine (1.1 mL, 8 mmol) in dioxane (10 mL) was added **10** (175 mg, 0.4 mmol) and the mixture was heated under reflux with stirring for 48 h. After the usual workup, the product was purified by column chromatography on ODS-silica gel eluted with MeOH–H_2O (8:2, v/v). The eluate was evaporated and the residue was dissolved in AcOH–THF–H_2O (15 mL; 2:2:1, v/v/v). The solution was stirred at room temperature for 14 h and evaporated to dryness. The residue was purified by column chromatography ($CHCl_3$) to give 102 mg (86%) of **14**: mp 139–140 °C; UV (MeOH) λ_{max} 286 nm (ϵ 18 000); MS m/z 297 (M^+); ^1H NMR ($CDCl_3$) δ 1.15–2.00 (m, 10 H, cyclohexyl), 1.92 (s, 3 H, 5-Me), 3.44 (m, 1 H, NHC*H*), 3.74–3.82 (m, 4 H, $HOCH_2CH_2O$), 4.76 (d, J = 9.0 Hz, 1 H, N*H*CH), 5.44 (s, 2 H, NCH_2O), 7.89 (br, 1 H, NH). Anal. ($C_{14}H_{23}N_3O_4 \cdot {}^1/_4H_2O$) C, H, N.

6-(Aminophenyl)-1-[(2-hydroxyethoxy)methyl]thymine (15). To a solution of aniline (0.55 mL, 6 mmol) in THF (7.5 mL) was added a solution of n-butyllithium (6 mmol) in hexane and the mixture was stirred for 15 min at −70 °C. To the resulting suspension was added a solution of **10** (263 mg, 0.6 mmol) in THF (7.5 mL) below −70 °C and then allowed to warm to −60 °C. The resulting solution was stirred for 15 min at −60 °C. After the usual workup, the product was purified by column chromatography on ODS-silica gel eluted with MeOH–H_2O (7.5:2.5, v/v). The eluate was evaporated and the residue was dissolved in AcOH–THF–H_2O (15 mL; 2:2:1, v/v/v). The solution was stirred at room temperature for 14 h and evaporated to dryness. The residue was crystallized from toluene to give 145 mg (83%) of **15**: mp 178.5 °C; UV (MeOH) λ_{max} 304 nm (ϵ 14 000); MS m/z 291 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.50 (s, 3 H, 5-Me), 3.39–3.49 (m, 4 H, $HOCH_2CH_2O$), 4.74 (br, 1 H, OH), 5.19 (s, 2 H, NCH_2O), 6.77 [dd, J = 7.9, 1.2 Hz, 2 H, Ph(o)], 6.84 [tt, J = 7.9, 1.2 Hz, 1 H, Ph(p)], 7.22 [dd, J = 7.9 Hz, 2 H, Ph(m)], 7.98 (br, 1 H, N*H*Ph), 11.29 (br, 1 H, NH). Anal. ($C_{14}H_{17}N_3O_4 \cdot {}^1/_4H_2O$) C, H, N.

General Procedure for the Preparation of 6-Substituted 1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]thymine Derivatives 17–19. To a solution of LDA (5 mmol) in THF (10 mL) was added **4** (629 mg, 2 mmol) in THF (10 mL) under a nitrogen atmosphere, at a rate such that the temperature did not exceed −70 °C. After the mixture was stirred for 1 h, an electrophile (4 mmol) dissolved in THF (8 mL) was added and the temperature was maintained below −70 °C. After 1 h below −70 °C, the reaction was quenched with acetic acid (0.25 mL), and the solution was allowed to warm to room temperature. The whole was evaporated to dryness and the residue dissolved in a small amount of chloroform–hexane (1:1, v/v) and applied to a silica gel column (3 × 2.6 cm). The column was washed with chloroform–hexane (1:1, v/v) to remove unreacted electrophile and then eluted with chloroform–hexane (8:2, v/v) to give the product.

6-Bromo-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]thymine (17). α-Bromoacetophenone (796 mg, 4 mmol) was used as an electrophile. Compound **17** was obtained in 32% yield (250 mg): MS m/z 392, 394 (M^+, 1:1; intensity); ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 2.10 (s, 3 H, 5-Me), 3.76, 3.79 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.59 (s, 2 H, NCH_2O), 8.46 (br, 1 H, NH). Starting material (359 mg, 57%) was also recovered.

6-Chloro-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]thymine (18). p-Toluenesulfonyl chloride was used as an electrophile. Compound **18** was obtained in 51% yield (356 mg): MS m/z 348, 350 (M^+, 3:1; intensity); ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 2.06 (s, 3 H, 5-Me), 3.70, 3.77 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.54 (s, 2 H, NCH_2O), 8.24 (br, 1 H, NH). Starting material (280 mg, 44%) was also recovered.

6-Benzoyl-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]thymine (19). Benzoyl chloride was used as an electrophile. Compound **19** was obtained in 83% yield (695 mg): ^1H NMR ($CDCl_3$) δ −0.71 (s, 6 H, Me_2Si), 0.81 (s, 9 H, Me_3C), 2.06 (s, 3 H, 5-Me), 3.28–3.47 (s, 4 H, $SiOCH_2CH_2O$), 4.99, 5.50 (br × 2, 1 H × 2, NCH_2O), 7.54 [dd, J = 8.0 Hz, 2 H, COPh(m)], 7.69 [tt, J = 8.0, 1.5 Hz, 1 H, COPh(p)], 7.94 [dd, J = 8.0, 1.5 Hz, 2 H, COPh(o)], 8.53 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(1-hydroxy-1-phenylmethyl)thymine (20). To a solution of **19** (300 mg, 0.72 mmol) in EtOH was added $NaBH_4$ (200 mg, 5.3 mmol). The mixture was stirred at room temperature for 14 h, and then powdered dry ice (10 g) was added. The mixture was stirred for 20 min and evaporated to dryness. The residue was dissolved in EtOAc (50 mL) and the solution was washed with brine (2 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness to give 300 mg (quant.) of **20** as a syrup. This compound was used in the next reaction without further purification.

6-(1-Acetoxy-1-phenylmethyl)-1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]thymine (21). A mixture of **20** (300 mg, 0.72 mmol), Ac_2O (0.2 mL, 2.2 mmol), and pyridine (10 mL) was stirred at room temperature for 16 h. MeOH (10 mL) was added to the reaction mixture and the solution was stirred for 14 h at room temperature. After evaporation, the residue was dissolved in EtOAc (20 mL) and the solution was washed successively with saturated $NaHCO_3$ solution (2 × 15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness to give 303 mg (92%) of **21**: ^1H NMR ($CDCl_3$) δ −0.02 (s, 6 H, Me_2Si), 0.83 (s, 9 H, Me_3C), 1.93 (s, 3 H, 5-Me), 2.24 (s, 3 H, MeCO), 3.55–3.64 (m, 4 H, $SiOCH_2CH_2O$), 5.45, 5.51 (ABq, J = 13.2 Hz, 2 H, NCH_2O), 7.01 (s, 1 H, AcOC*H*), 7.28–7.40 (m, 5 H, Ph), 8.26 (br, 1 H, NH).

6-Benzyl-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]thymine (22). A mixture of **21** (151 mg, 0.33 mmol) and Pd–C (10%, 20 mg) in EtOH (10 mL) was stirred at 55 °C for 6 h under 1 atm of hydrogen. The catalyst was removed by filtration and washed with EtOH (2 × 5 mL). The combined filtrates were evaporated to dryness and crystallized from hexane to give 114 mg (86%) of **22**: mp 110–112 °C; UV (MeOH) λ_{max} 268 (ϵ 10 100); MS m/z 347 (M^+ − 57); ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, Me_2Si), 0.88 (s, 9 H, Me_3C), 2.01 (s, 3 H, 5-Me), 3.64, 3.74 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 4.17 (s, 1 H, CH_2Ph), 5.17 (s, 2 H, NCH_2O), 7.11 [dd, J = 6.5, 1.6 Hz, 2 H, Ph(o)], 7.30–7.35 [m, 3 H, Ph(m,p)], 8.04 (br, 1 H, NH). Anal. ($C_{21}H_{32}N_2O_4Si$) C, H, N.

General Procedure for Deprotection of the *tert*-Butyldimethylsilyl (TBDMS) Group (Method A). The TBDMS-protected derivative (1 mmol) was dissolved in AcOH–THF–H_2O (15 mL; 2:2:1, v/v/v). The solution was stirred at room temperature for 14 h and evaporated to dryness. The residue was crystallized from a suitable solvent.

Following method A, **23–27** were prepared from **17–20** and **22**, respectively.

6-Bromo-1-[(2-hydroxyethoxy)methyl]thymine (23): yield 73%; mp 140 °C (toluene–EtOH); UV (MeOH) λ_{max} 270 nm (ϵ 9100); MS m/z 278 and 280 (M^+); ^1H NMR ($CDCl_3$) δ 1.95 (t, 1 H, OH), 2.10 (s, 3 H, 5-Me), 3.71–3.79 (m, 4 H, $HOCH_2CH_2O$), 5.60 (s, 2 H, NCH_2O), 8.34 (br, 1 H, NH). Anal. ($C_8H_{11}BrN_2O_4$) C, H, N.

6-Chloro-1-[(2-hydroxyethoxy)methyl]thymine (24): yield 84%; mp 127–128 °C (toluene–EtOH); UV (MeOH) λ_{max} 267 nm (ϵ 9800); MS m/z 234 and 236 (M^+); ^1H NMR ($CDCl_3$) δ 1.95 (br, 1 H, OH), 2.07 (s, 3 H, 5-Me), 3.71–3.80 (s, 4 H, $HOCH_2CH_2O$), 5.55 (s, 2 H, NCH_2O), 8.37 (br, 1 H, NH). Anal. ($C_8H_{11}ClN_2O_4$) C, H, N.

6-Benzoyl-1-[(2-hydroxyethoxy)methyl]thymine (25): yield 65%; mp 127–128 °C (toluene–EtOH); UV (MeOH) λ_{max} 256 nm (ϵ 18000); MS m/z 304 (M^+); ^1H NMR ($CDCl_3$) δ 1.74 (s, 3 H, 5-Me), 3.38–3.57 (m, 4 H, $HOCH_2CH_2O$), 5.14, 5.33 (br × 2, 1 H × 2, NCH_2O), 7.58 [dd, J = 8.2 Hz, 2 H, COPh(m)], 7.72 [tt, J = 8.2, 1.4 Hz, 1 H, COPh(p)], 7.96 [dd, J = 8.2, 1.4 Hz, 2 H, COPh(o)], 8.60 (br, 1 H, NH). Anal. ($C_{15}H_{16}N_2O_5$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(1-hydroxy-1-phenylmethyl)thymine (26): yield 90%; mp 179–180 °C ($CHCl_3$); UV (MeOH) λ_{max} 270 nm (ϵ 9400); MS m/z 306 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.67 (s, 3 H, 5-Me), 3.30–3.39 (m, 4 H, $HOCH_2CH_2O$), 4.54 (t, J = 5.2 Hz, 1 H, CH_2OH), 5.24, 5.29 (ABq, J = 11.5 Hz, 2 H, NCH_2O), 6.06 (d, J = 4.8 Hz, 1 H, PhC*H*OH), 6.50 (d, J = 4.8 Hz, 1 H, PhCHO*H*), 7.23–7.35 (m, 5 H, Ph), 11.46 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_5 \cdot {}^1/_4H_2O$) C, H, N.

6-Benzyl-1-[(2-hydroxyethoxy)methyl]thymine (27). This compound was purified by chromatography ($CHCl_3$) to give a colorless syrup: yield 72%; UV (MeOH) λ_{max} 268 nm (ϵ 7200); MS m/z 290 (M^+); ^1H NMR ($CDCl_3$) δ 1.84 (t, J = 5.2 Hz, 1 H, OH), 2.02 (s, 3 H, 5-Me), 3.68–3.74 (s, 4 H, $HOCH_2CH_2O$), 4.15 (s, 2 H, CH_2Ph), 5.20 (s, 2 H, NCH_2O), 7.13 [dd, J = 6.1, 1.3 Hz, 2 H, Ph(o)], 7.27–7.39 [m, 3 H, Ph(m,p)], 8.17 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_4 \cdot {}^1/_2H_2O$) C, H, N.

General Procedure for the Palladium-Catalyzed Cross-Coupling Reaction of Iodinated Nucleosides with Terminal Alkynes (Method B). To a solution of iodinated nucleoside (1 mmol) in Et_3N (10 mL) and MeCN (3 mL) were added bis(triphenylphosphine)palladium(II) chloride (70.2 mg, 0.1 mmol) and copper(I) iodide (19 mg, 0.1 mmol). Propyne gas was bubbled into the solution for 2 h at 60 °C or the terminal alkyne [phenylacetylene, (trimethylsilyl)acetylene] (3 mmol) was added to the solution. In the latter cases, the solution was stirred for 1.5 h at 60 °C. The solution was allowed to cool to room temperature and evaporated to dryness. The residue was purified by chromatography (EtOAc–hexane 3:7, v/v).

Following method B, **28–30** were prepared from **16**.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(2-methylethynyl)thymine (28). This compound was obtained as a white foam (204 mg, 58%): IR (KBr) 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 2.07 (s, 3 H, 5-Me), 2.19 (s, 3 H, C≡CMe), 3.69, 3.68 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.47 (s, 2 H, NCH_2O), 8.29 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(2-phenylethynyl)thymine (29). This compound was obtained as a white foam (342 mg, 82%): IR (KBr) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, Me_2Si), 0.86 (s, 9 H, Me_3C), 2.19 (s, 3 H, 5-Me), 3.74–3.78 (m, 4 H, $SiOCH_2CH_2O$), 5.55 (s, 2 H, NCH_2O), 7.41–7.45 [m, 3 H, C≡CPh(m,p)], 7.74 [dd, J = 7.9, 1.8 Hz, 2 H, C≡CPh(o)], 8.03 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-[2-(trimethylsilyl)ethynyl]thymine (30). This compound was obtained as a white foam (472 mg, 58%): IR (KBr) 2150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.29 (s, 9 H, Me_3Si), 0.86 (s, 9 H, Me_3C), 2.09 (s, 3 H, 5-Me), 3.69, 3.76 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.46 (s, 2 H, NCH_2O), 8.51 (br, 1 H, NH).

Following method A, **31** and **32** were prepared from **28** and **29**, respectively.

1-[(2-Hydroxyethoxy)methyl]-6-(2-methylethynyl)thymine (31): yield 91%; mp 176 °C (toluene–EtOH); UV (MeOH) λ_{max} 291 nm (ϵ 12000); IR (KBr) 2245 cm^{-1}; MS m/z 238 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 2.22 (s, 3 H, C≡CMe), 3.71–3.76 (m, 4 H, $HOCH_2CH_2O$), 5.48 (s, 2 H, NCH_2O), 8.05 (br, 1 H, NH). Anal. ($C_{11}H_{14}N_2O_4 \cdot {}^1/_4H_2O$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(2-phenylethynyl)thymine (32): yield 84%; mp 220 °C (toluene–EtOH); UV (MeOH) λ_{max} 314 nm (ϵ 21000); IR (KBr) 2210 cm^{-1}; MS m/z 300 (M^+); ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H, 5-Me), 3.74–3.78 (A_2B_2, 4 H, $HOCH_2CH_2O$), 5.57 (s, 2 H, NCH_2O), 7.42–7.47 [m, 3 H, C≡CPh(m,p)], 7.57 [dd, J = 7.9 Hz, 1.8 Hz, 2 H, C≡CPh(o)], 8.10 (br, 1 H, NH). Anal. ($C_{16}H_{16}N_2O_4$) C, H, N.

6-Ethynyl-1-[(2-hydroxyethoxy)methyl]thymine (33). To a solution of **30** (294 mg, 0.72 mmol) in MeOH (86 mL) was added a 1 N NaOH solution (0.86 mL) and the mixture was stirred at room temperature for 2 min. After neutralization with 1 N HCl, the mixture was evaporated to dryness, the residue dissolved in EtOAc (30 mL) and washed with H_2O (3 × 10 mL), and the organic layer evaporated to dryness. The residue was dissolved in THF–AcOH–H_2O (25 mL, 2:2:1, v/v), and the solution was stirred at room temperature for 14 h. After evaporation to dryness, the residue was coevaporated with toluene (3 × 20 mL) and crystallized from toluene–EtOH to give 160 mg (99%) of **33**: mp 157–158 °C; UV (MeOH) λ_{max} 289 nm (ϵ 11000); IR (KBr) 2100 cm^{-1}; MS m/z 224 (M^+); ^1H NMR ($CDCl_3$) δ 2.03 (m, 1 H, OH), 2.13 (s, 3 H, 5-Me), 3.70–3.79 (m, 4 H, $HOCH_2CH_2O$), 3.93 (s, 1 H, C≡CH), 5.50 (s, 2 H, NCH_2O), 8.32 (br, 1 H, NH). Anal. ($C_{10}H_{12}N_2O_4$) C, H, N.

General Procedure for the Partial Hydrogenation of Alkynyl Derivatives with H_2 and Pd-$BaSO_4$ (Method C). A mixture of the alkynyl derivative (0.34 mmol), Pd-$BaSO_4$ (10%, 11 mg), EtOH (5 mL), and AcOH (1 mL) was stirred at room temperature for 2 min under 1 atm of hydrogen. The catalyst was removed by filtration and washed with EtOH (2 × 5 mL). The combined filtrates were evaporated to dryness, and the residue was coevaporated with toluene. Crystallization from toluene–EtOH gave the respective alkenyl derivative.

Following method C, **34–36** were prepared from **31–33**, respectively.

1-[(2-Hydroxyethoxy)methyl]-6-[2-(*Z*)-methylvinyl]thymine (34): yield 92%; mp 108–108.5 °C; UV (MeOH) λ_{max} 273 nm (ϵ 9500); MS m/z 240 (M^+); ^1H NMR ($CDCl_3$) δ 1.66 (d, J = 5.4 Hz, 3 H, CH=CH*Me*), 1.86 (s, 3 H, 5-Me), 2.14 (t, J = 5.4 Hz, 1 H, OH), 3.66–3.78 (m, 4 H, $HOCH_2CH_2O$), 5.09, 5.46 (br × 2, 1 H × 2, NCH_2O), 6.16 (dq, J = 12.0, 5.4 Hz, 1 H, CH=C*H*Me), 6.19 (d, J = 12.0 Hz, 1 H, C*H*=CHMe), 8.72 (br, 1 H, NH). Anal. ($C_{11}H_{16}N_2O_4$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-[2-(*Z*)-phenylvinyl]thymine (35): yield 88%; mp 113–114 °C; UV (MeOH) λ_{max} 249 nm (ϵ 14000); MS m/z 302 (M^+); ^1H NMR ($CDCl_3$) δ 1.67 (d, J = 1.1 Hz, 3 H, 5-Me), 3.67–3.75 (m, 4 H, $HOCH_2CH_2O$), 5.18, 5.58 (ABq, J = 10.4 Hz, 2 H, NCH_2O), 6.31 (dq, J = 12.4, 1.1 Hz, 1 H, C*H*=CHPh), 6.89 (d, J = 12.4 Hz, 1 H, CH=C*H*Ph), 7.21–7.33 (m, 5 H, Ph), 8.08 (br, 1 H, NH). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-vinylthymine (36): yield 60%; mp 123–125 °C; UV (MeOH) λ_{max} 276 nm (ϵ 8200); MS m/z 226 (M^+); ^1H NMR ($CDCl_3$) δ 2.00 (d, J = 0.9 Hz, 3 H, 5-Me), 3.72–3.79 (m, 4 H, $HOCH_2CH_2O$), 5.31 (s, 2 H, NCH_2O), 5.63 [dd, J = 17.7, 1.2 Hz, 1 H, CH=CH(Z)H(E)], 5.89 [dd, J = 11.6, 1.2 Hz, 1 H, CH=CH(Z)H(E)], 6.56 (ddq, J = 17.7, 11.6, 0.9 Hz, 1 H, C*H*=CH_2), 8.08 (br, 1 H, NH). Anal. ($C_{10}H_{14}N_2O_4$) C, H, N.

General Procedure for the Lithiation of 37. To a solution of LTMP (6.0 mmol) in THF (10 mL) was added **37** (817 mg, 2.0 mmol) dissolved in THF (10 mL) at a rate such that the temperature did not exceed −70 °C under a nitrogen atmosphere. After the mixture was stirred for 1 h, the respective electrophile (4 mmol) dissolved in THF (10 mL) was added and the temperature was maintained below −70 °C. The mixture was stirred for 1 h below −70 °C, quenched with AcOH (0.25 mL), and allowed to warm to room temperature. The whole was evaporated to dryness and the residue was purified by chromatography ($CHCl_3$).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-iodo-6-(phenylthio)uracil (38). Iodine was used as an electrophile. Compound **38** was obtained in 96% yield: ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, Me_2Si), 0.87 (s, 9 H, Me_3C), 3.66 (s, 4 H, $SiOCH_2CH_2O$), 5.68 (s, 2 H, NCH_2O), 7.22–7.37 (m, 5 H, SPh), 9.97 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5,6-bis(phenylthio)uracil (39). Diphenyl disulfide was used as an electrophile. Compound **39** was obtained in 86% yield: ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 3.70 (s, 4 H,

$SiOCH_2CH_2O$), 5.66 (s, 2 H, NCH_2O), 7.11–7.60 (m, 10 H, SPh × 2), 8.91 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-isobutyryl-6-(phenylthio)uracil (40). Isobutyryl chloride was used as an electrophile. Compound **40** was obtained in 55% yield: ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, Me_2Si), 0.87 (s, 9 H, Me_3C), 1.08 (d, J = 7.0 Hz, 6 H, $CHMe_2$), 3.04 (qq, J = 7.0 Hz, 1 H, $CHMe_2$), 3.58 (s, 4 H, $SiOCH_2CH_2O$), 5.40 (s, 2 H, NCH_2O), 7.20–7.58 (m, 5 H, SPh), 9.71 (br, 1 H, NH).

5-Benzoyl-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylthio)uracil (41). Benzoyl chloride was used as an electrophile. Compound **41** was obtained in 38% yield: ^1H NMR ($CDCl_3$) δ 0.03, 0.06 (s × 2, 3 H × 2, Me_2Si), 0.84, 0.85, 0.88 (s × 3, 3 H × 3, Me_3C), 3.65 (s, 4 H, $SiOCH_2CH_2O$), 5.55 (s, 2 H, NCH_2O), 7.04–7.79 (m, 10 H, Ph × 2), 9.71 (br, 1 H, NH).

5-Benzyl-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylthio)uracil (42). Benzyl bromide was used as an electrophile. Compound **42** was obtained in 9.2% yield: ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H, Me_2Si), 0.85 (s, 9 H, Me_3C), 3.59 (s, 4 H, $SiOCH_2CH_2O$), 3.99 (s, 2 H, CH_2Ph), 5.47 (s, 2 H, NCH_2O), 7.01–7.30 (m, 10 H, Ph × 2), 9.85 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-(1-hydroxy-2,2-diphenylethyl)-6-(phenylthio)uracil (43). 2,2-Diphenylacetaldehyde was used as an electrophile. Compound **43** was obtained in 82% yield: ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Me_2Si), 0.87 (s, 9 H, Me_3C), 3.26, 3.51 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 4.79 (d, J = 11.2 Hz, 1 H, $CHPh$), 5.20, 5.38 (ABq, J = 13.0 Hz, 2 H, NCH_2O), 5.93 (t, J = 11.2 Hz, 1 H, $CHOH$), 7.00–7.65 (m, 10 H, Ph × 2), 8.98 (br, 1 H, NH).

Following method A, **44–48** were prepared from **38–42**, respectively.

1-[(2-Hydroxyethoxy)methyl]-5-iodo-6-(phenylthio)uracil (44): yield 52%; mp 180–182 °C (EtOAc–MeOH); UV (MeOH) λ_{max} 303 nm (ε 5500); MS m/z 420 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.31–3.53 (m, 4 H, $HOCH_2CH_2O$), 5.49 (s, 2 H, NCH_2O), 7.24–7.40 (m, 5 H, SPh), 12.02 (br, 1 H, NH). Anal. ($C_{13}H_{13}IN_2O_4S$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-5,6-bis(phenylthio)uracil (45): yield 75%; mp 146–148 °C (toluene); UV (MeOH) λ_{max} 247 nm (ε 15 000); MS m/z 402 (M^+); ^1H NMR ($CDCl_3$) δ 1.94 (br, 1 H, OH), 3.68 (s, 4 H, $HOCH_2CH_2O$), 5.65 (s, 2 H, NCH_2O), 7.08–7.22 (m, 10 H, SPh × 2), 8.66 (br, 1 H, NH). Anal. ($C_{19}H_{18}N_2O_4S_2$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-5-isobutyryl-6-(phenylthio)uracil (46): yield 55%; mp 144–145 °C (EtOAc); UV (MeOH) λ_{max} 274 (ε 9000), 243 nm (ε 9900); MS m/z 364 (M^+); ^1H NMR (Me_2SO-d_6) δ 0.99 (d, J = 6.8 Hz, 6 H, $CHMe_2$), 2.97 (qq, J = 6.8 Hz, 1 H, $CHMe_2$), 3.25–3.51 (m, 4 H, $HOCH_2CH_2O$), 4.57 (t, J = 5.5 Hz, 1 H, OH), 5.27 (s, 2 H, NCH_2O), 7.28–7.40 (m, 5 H, SPh), 11.98 (br, 1 H, NH). Anal. ($C_{17}H_{20}N_2O_5S \cdot {}^1/_4H_2O$) C, H, N.

5-Benzoyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)uracil (47): yield 44%; mp 150–151 °C (EtOAc); UV (MeOH) λ_{max} 253 nm (ε 15 000); MS m/z 398 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.25–3.66 (m, 4 H, $HOCH_2CH_2O$), 4.62 (t, J = 5.6 Hz, 1 H, OH), 5.37 (s, 2 H, NCH_2O), 7.16–7.96 (m, 10 H, Ph × 2), 12.05 (br, 1 H, NH). Anal. ($C_{20}H_{18}N_2O_5S \cdot {}^1/_4H_2O$) C, H, N.

5-Benzoyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)uracil (48): yield 67%; mp 126–128 °C (diisopropyl ether); UV (MeOH) λ_{max} 278 (ε 9200), 243 nm (ε 11 000); MS m/z 384 (M^+); ^1H NMR ($CDCl_3$) δ 1.69 (t, J = 5.7 Hz, 1 H, OH), 3.51–3.61 (m, 4 H, $HOCH_2CH_2O$), 4.04 (s, 2 H, CH_2Ph), 5.49 (s, 2 H, NCH_2O), 7.11–7.33 (m, 10 H, Ph × 2), 8.24 (br, 1 H, NH). Anal. ($C_{20}H_{20}N_2O_4S \cdot {}^1/_2H_2O$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-5-(2,2-diphenylvinyl)uracil (49). To a solution of **43** (600 mg, 1.0 mmol) in pyridine (10 mL) was added $SOCl_2$ (2 mL) at −20 °C and the mixture was allowed to warm to room temperature. After stirring for 30 min at room temperature, to the mixture was added saturated $NaHCO_3$ solution and it was stirred for 14 h at room temperature. The solution was extracted with $CHCl_3$ (50 mL) and the organic layer was evaporated to dryness. The residue was purified by column chromatography on silica gel ($CHCl_3$) and the eluate evaporated to dryness. The residue was dissolved in AcOH–THF–H_2O (25 mL; 2:2:1, v/v/v) and the solution stirred for 14 h at room temperature and evaporated to dryness. The residue was purified by column chromatography on silica gel ($CHCl_3$–EtOAc) and the eluate evaporated to dryness. The residue was crystallized from diisopropyl ether to give 4.5% of **49**: mp 101–104 °C; UV (MeOH) λ_{max} 312 nm (ε 7500); MS m/z 472 (M^+); ^1H NMR ($CDCl_3$) δ 3.41–3.60 (m, 4 H, $HOCH_2CH_2O$), 5.53 (s, 2 H, NCH_2O), 6.25 (s, 1 H, $CH{=}CPh_2$), 6.96–7.35 (m, 15 H, Ph × 3), 9.13 (br, 1 H, NH). Anal. ($C_{27}H_{24}N_2O_4S \cdot H_2O$) C, H, N.

Following method B followed by method A, **50** and **51** were prepared from **38**.

1-[(2-Hydroxyethoxy)methyl]-5-(2-methylethynyl)-6-(phenylthio)uracil (50): yield 20% (from **38**); mp 165–166.5 °C (EtOAc); UV (MeOH) λ_{max} 325 (ε 8000), 236 nm (ε 15 000); IR (KBr) 2250 cm^{-1}; MS m/z 332 (M^+); ^1H NMR ($CDCl_3$) δ 1.86 (s, 3 H, Me), 3.67 (s, 4 H, $HOCH_2CH_2O$), 5.66 (s, 2 H, NCH_2O), 7.22–7.40 (m, 5 H, SPh), 8.53 (br, 1 H, NH). Anal. ($C_{16}H_{16}N_2O_4S \cdot {}^1/_4H_2O$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-5-(2-phenylethynyl)-6-(phenylthio)uracil (51): yield 40% (from **38**); mp 146–148 °C (EtOAc); UV (MeOH) λ_{max} 345 (ε 12 000), 270 (ε 18 000), 234 nm (ε 19 000); IR (KBr) 2200 cm^{-1}; MS m/z 394 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.38–3.61 (m, 4 H, $HOCH_2CH_2O$), 4.63 (t, J = 5.6 Hz, 1 H, OH), 5.55 (s, 2 H, NCH_2O), 7.09–7.64 (m, 10 H, Ph × 2), 11.95 (br, 1 H, NH). Anal. ($C_{21}H_{18}N_2O_4S$) C, H, N.

Following method B, **52** was prepared from **38**.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylthio)-5-[2-(trimethylsilyl)ethynyl]uracil (52): yield 49%; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.08 (s, 9 H, Me_3Si), 0.89 (s, 9 H, Me_3C), 3.65, 3.71 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.67 (s, 2 H, NCH_2O), 7.22–7.35 (m, 5 H, SPh), 8.75 (br, 1 H, NH).

5-Ethynyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)uracil (53). To a solution of **52** (380 mg, 0.73 mmol) in THF (3 mL) was added a 1 M solution of n-Bu_4NF in THF (8 mL, 8 mmol) and the mixture was stirred at room temperature for 30 min. The solution was added to H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O and evaporated to dryness. The residue was purified by chromatography on a silica gel column ($CHCl_3$–MeOH 9:1, v/v) to give **53** (126 mg, 54%) after crystallization from CH_2Cl_2–hexane: mp 163–165 °C; UV (MeOH) λ_{max} 299 (ε 7500), 232 nm (ε 14 000); IR (KBr) 2125 cm^{-1}; MS m/z 318 (M^+); ^1H NMR ($CDCl_3$) δ 2.00 (br, 1 H, OH), 3.31 (s, 1 H, C≡CH), 3.69 (s, 4 H, $HOCH_2CH_2O$), 5.33 (s, 2 H, NCH_2O), 7.28–7.39 (m, 5 H, SPh), 8.90 (br, 1 H, NH). Anal. ($C_{15}H_{14}N_2O_4S \cdot {}^1/_2H_2O$) C, H, N.

Following method C, **54** was prepared from **51**.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-5-[2-(*Z*)-phenylvinyl]uracil (54): yield 24%; mp 112–113 °C (EtOAc–hexane); UV (MeOH) λ_{max} 317 nm (ε 8540); MS m/z 396 (M^+); ^1H NMR ($CDCl_3$) δ 3.63 (s, 4 H, $HOCH_2CH_2O$), 5.58 (s, 2 H, NCH_2O), 6.01 (d, J = 11.9 Hz, 1 H, $CH{=}CHPh$), 6.61 (d, J = 11.9 Hz, 1 H, $CH{=}CHPh$), 7.08–7.29 (m, 10 H, Ph × 2), 8.39 (br, 1 H, NH). Anal. ($C_{21}H_{20}N_2O_4S$) C, H, N.

1-[(2-Acetoxyethoxy)methyl]-5-vinyluracil. To a suspension of 5-vinyluracil (670 mg, 4.85 mmol) in CH_2Cl_2 (10 mL) was added bis(trimethylsilyl)acetamide (2.64 mL, 10.7 mmol) and the mixture stirred for 2 h at room temperature. To the resulting solution were added (2-acetoxyethoxy)methylacetate (0.98 mL, 5.5 mmol) and tin(IV) chloride (0.56 mL, 5 mmol) at 0 °C, and the mixture was stirred at room temperature for 14 h. The solution was added to a mixture of saturated $NaHCO_3$ solution (100 mL) and $CHCl_3$ (100 mL). The organic layer was filtered and dried over $MgSO_4$. The solution was evaporated to dryness and the residue purified by chromatography on silica gel ($CHCl_3$–MeOH). The eluate was evaporated to dryness to give the title compound (960 mg, 78%). This compound was used in the next reaction without further purification and characterization.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-vinyluracil. The above compound (960 mg, 3.78 mmol) was dissolved in MeOH (20 mL) and concentrated aqueous ammonia (20 mL) and the solution was allowed to stand for 14 h at room temperature. The solution was evaporated to dryness and the residue was coevaporated with DMF and dissolved in DMF (40 mL). To the solution were added imidazole (340 mg, 5 mmol) and *tert*-butyldimethylsilyl chloride (750 mg, 5 mmol) and the mixture was stirred for 14 h at room temperature. The solution was evaporated to dryness and the residue was dissolved in $CHCl_3$.

The solution was washed with saturated $NaHCO_3$ and evaporated to dryness. The residue was purified by chromatography on silica gel ($CHCl_3$-MeOH) to give the title compound (387 mg, 24%) after crystallization from petroleum ether: ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 3.66, 3.77 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.25 (s, 2 H, NCH_2O), 5.27 [dd, J = 10.9, 1.1 Hz, 1 H, CH=C*H*(*Z*)H(*E*)], 5.98 [dd, J = 17.6, 1.1 Hz, 1 H, CH=CH(*Z*)*H*(*E*)], 6.42 (dd, J = 17.6, 10.9 Hz, 1 H, C*H*=CH_2), 7.41 (s, 1 H, 6-H), 9.59 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylthio)-5-vinyluracil. Following the general procedure for the preparation of **17-19**, the title compound was prepared from the above compound with diphenyl disulfide as an electrophile: yield 46%; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H, Me_2Si), 0.84 (s, 9 H, Me_3C), 3.63 (s, 4 H, $SiOCH_2CH_2O$), 5.33 [dd, J = 11.8, 2.0 Hz, 1 H, CH=C*H*(*Z*)H(*E*)], 5.61 (s, 2 H, NCH_2O), 6.33 [dd, J = 16.8, 2.0 Hz, 1 H, CH=CH(*Z*)*H*(*E*)], 6.71 (dd, J = 16.8, 11.8 Hz, 1 H, C*H*=CH_2), 7.15-7.30 (m, 5 H, SPh), 10.15 (br, 1 H, NH).

Following method A, **55** was prepared from the above compound.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-5-vinyluracil (55): yield 41%; mp 100-103 °C (EtOAc-petroleum ether); UV (MeOH) λ_{max} 306 (ϵ 7600), 243 nm (ϵ 14 000); MS m/z 320 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.35-3.52 (m, 4 H, $HOCH_2CH_2O$), 4.62 (t, J = 5.4 Hz, 1 H, OH), 5.22 [dd, J = 11.3, 2.2 Hz, 1 H, CH=C*H*(*Z*)H(*E*)], 5.48 (s, 2 H, NCH_2O), 6.21 [dd, J = 16.4, 2.2 Hz, 1 H, CH=CH(*Z*)*H*(*E*)], 6.63 (dd, J = 16.4, 11.3 Hz, 1 H, C*H*=CH_2), 7.23-7.40 (m, 5 H, SPh), 11.75 (br, 1 H, NH). Anal. ($C_{15}H_{16}N_2O_4S \cdot {}^1/_2H_2O$) C, H, N.

Antiviral Assay Procedures. The anti-HIV assays were based on the inhibition of the virus-induced cytopathic effect in MT-4 cells as previously described.[32] Briefly, MT-4 cells were suspended in culture medium at 2.5×10^5 cells/mL and infected with 1000 $CCID_{50}$ (50% cell culture infective dose) of HIV. Immediately after virus infection, 100 μL of the cell suspension was brought into each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. After a 4 (Table II) or 5 (Table I) day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[33] Cytotoxicity of the compounds was assessed in parallel with their antiviral activity. It was based on the viability of mock-infected host cells as determined by the MTT method.[33]

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Inhibitors of Cholesterol Biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1*H*-pyrrol-1-yl)ethyl]-2*H*-pyran-2-one Inhibitors of HMG-CoA Reductase. 2. Effects of Introducing Substituents at Positions Three and Four of the Pyrrole Nucleus

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A series of *trans*-tetrahydro-4-hydroxy-6-[2-(2,3,4,5-substituted-1*H*-pyrrol-1-yl)ethyl]-2*H*-pyran-2-ones and their dihydroxy acids were prepared and tested for their ability to inhibit the enzyme HMG-CoA reductase in vitro. Inhibitory potency was found to increase substantially when substituents were introduced into positions three and four of the pyrrole ring. A systematic exploration of structure-activity relationships at these two positions led to the identification of a compound ((+)-**33**, (+)-(4*R*)-trans-2-(4-fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1*H*-pyrrole-4-carboxamide) with five times the inhibitory potency of the fungal metabolite compactin.

Inhibition of HMG-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis, has proven to be an effective means for lowering total and low-density lipoprotein (LDL) cholesterol in animal models and man.[1,2] The early reports describing the activity of the fungal metabolites compactin (mevastatin)[3] and mevinolin (lovastatin)[4] have been followed by a host of publications describing a large variety of natural[5] and synthetic inhibitors.[6] Previously, we disclosed a series of 1,2,5-trisubstituted-pyrrol-1-ylethylmevalonolactones which were found to be moderately potent inhibitors of HMGR in vitro.[7] By systematically altering the 2 and 5 substituents, maximal potency was obtained with the 2-(4-fluorophenyl)-5-isopropyl analogue (**1**). On the basis of those results, a molecular-modeling analysis led to the description of a pharmacophore model which characterized the size of the substituents at positions 2 and 5 and the conformation of the side chain. We have now discovered

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