with 1 N NaOH (1.67 mL). The solution was kept at 20–25 °C for 24 h and then evaporated. The solid remaining was dissolved in H_2O (10 mL), and the aqueous solution was kept 24 h at 20–25 °C before it was filtered. The pale yellow solution (pH 11.5), now diluted to 30 mL, was treated with 1 N HCl to produce pH 3.9 and precipitate **6** as beige-colored solid, yield 79% (270 mg). Assay by HPLC showed the product to be homogeneous. Spectral data: MS *m/e* 492, MH^+; UV λ_{max} 226 nm (ϵ 40 500), 299 (27 900) at pH 1; 226 nm (ϵ 37 200), 296 (27 000) at pH 7; 226 nm (ϵ 35 900), 295 (27 200), 346 (8030) at pH 13; ^1H NMR (Me_2SO-d_6) δ 1.95, 2.05 (2 m, $CHCH_2CH_2$ nonequivalent), 2.30 (t, CH_2CO), 2.66 (s, CH_3), 3.20 (s, C≡CH), 4.20 (s, CH_2≡CH), 4.35 (m, CONHC*H*), 4.66 (s, C^9H_2N), 6.90 and 7.76 (2 d, C_6H_4), 8.16 (d, NH), 8.31 (s, C^7-H). Anal. ($C_{24}H_{25}N_7O_5 \cdot 1.67H_2O$) C, H, N.

***N*-[4-[[[(2,4-Diaminopyrido[2,3-*d*]pyrimidin-6-yl)methyl]prop-2-ynyl]amino]benzoyl]-L-glutamic Acid or 10-Propargyl-5-deazaaminopterin (5).** Alkylation of **7**[32] by **13a**·2HBr in Me_2NAc was carried out as described above for the preparation of **6**. The intermediate diethyl ester of **5** was first isolated by preparative TLC ($CHCl_3$–MeOH, 3:1) on two plates to give nearly pure product (270 mg). This material was chromatographed as before (except on one plate) to give pure **5** diethyl ester in 36% yield (230 mg from 500 mg, 1.20 mmol, of **13a**·2HBr). Spectral data: MS *m/e* 534, MH^+ for $C_{27}H_{31}N_7O_5$. This ester (230 mg) was hydrolyzed (as described above for the preparation of **6**) to give **5**, homogeneous according to HPLC, in 70% yield (160 mg). Spectral data: MS *m/e* 478, MH^+; UV, λ_{max} 220 nm (ϵ 41 200), 301 (26 100) at pH 1; 222 nm (ϵ 37 000), 249 (20 500), 297 (24 900) at pH 7; 223 nm (ϵ 35 700), 250 (22 100), 297 (24 700), 347 (7310) at pH 13; ^1H NMR (Me_2SO-d_6) δ 1.93, 2.06 (two m, $CHCH_2CH_2$ nonequivalent), 2.31 (t, CH_2CO), 3.21 (s, C≡CH), 4.30–4.41 (s, CH_2C≡CH overlapping m due to CONHC*H*), 4.46 (s, C^9H_2N), 6.61 (br s, NH_2), 6.90 and 7.75 (2 d, C_6H_4), 7.70 (br s, NH_2), 8.20 (d, NH), 8.33 and 8.62 (2 d, C^5-H and C^7-H). Anal. ($C_{23}H_{23}N_7O_5 \cdot 1.5H_2O$) C, H, N.

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Structure–Activity Relationships of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine Analogues: Effect of Substitutions at the C-6 Phenyl Ring and at the C-5 Position on Anti-HIV-1 Activity

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The effect of substitution on the pyrimidine moiety of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) and 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine (HEPT-S) on anti-HIV-1 activity was investigated by synthesizing a series of 5-methyl-6-(arylthio) and 5-substituted-6-(phenylthio) derivatives. Preparation of the 5-methyl-6-(arylthio) derivatives was carried out based on either LDA lithiation of 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]thymine (**3**) and 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-2-thiothymine (**4**) followed by reaction with diaryl disulfides or an addition–elimination reaction of 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]-methyl]-6-(phenylsulfinyl)thymine (**31**) with aromatic thiols. Preparation of the 5-substituted-6-(phenylthio) derivatives was carried out based on either C-5 lithiation of the 1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-6-(phenylthio)uracil (**41**) with LTMP or the LDA lithiation of 5-alkyl-1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-2-thiouracil derivatives **45–47**. Substitution at the meta position of the *C*-6-(phenylthio) ring by the methyl group improved the original anti-HIV-1 activity of HEPT, and introduction of two *m*-methyl groups to the phenylthio ring further potentiated the activity [EC_{50}: 6-[(3,5-dimethylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (**28**), 0.26 μM; 6-[(3,5-dimethylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]-2-thiothymine (**30**), 0.22 μM]. When the 5-methyl group was replaced by an ethyl or an isopropyl group, the anti-HIV-1 activity of HEPT was also improved remarkably [EC_{50}: 5-ethyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-2-thiouracil (**48**), 0.11 μM; 5-isopropyl-1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)-2-thiouracil (**50**), 0.059 μM; 5-ethyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-2-thiouracil (**54**), 0.12 μM; 5-isopropyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-2-thiouracil (**56**), 0.063 μM]. 6-[(3,5-Dimethylphenyl)thio]-5-ethyl-1-[(2-hydroxyethoxy)methyl]thymine derivatives **51** and **57** and 6-[(3,5-dimethylphenyl)thio]-5-isopropyl-1-[(2-hydroxyethoxy)methyl]thymine derivatives **52** and **58** inhibited the replication of HIV-1 in the nanomolar concentration range.

Acquired immunodeficiency syndrome (AIDS)[1,2] is a systemic and fatal disorder that still evades curative therapy, though a number of therapeutic modalities have been proposed for the treatment of this disease.[3,4] The nucleoside derivative 3′-azido-3′-deoxythymidine (AZT)[5] is known to prolong survival in AIDS patients,[6] yet its treatment is sometimes associated with considerable side effects such as bone marrow suppression.[7] Furthermore, prolonged AZT treatment often leads to the emergence of AZT-resistant HIV-1 strains.[8] Therefore, there is a rel-

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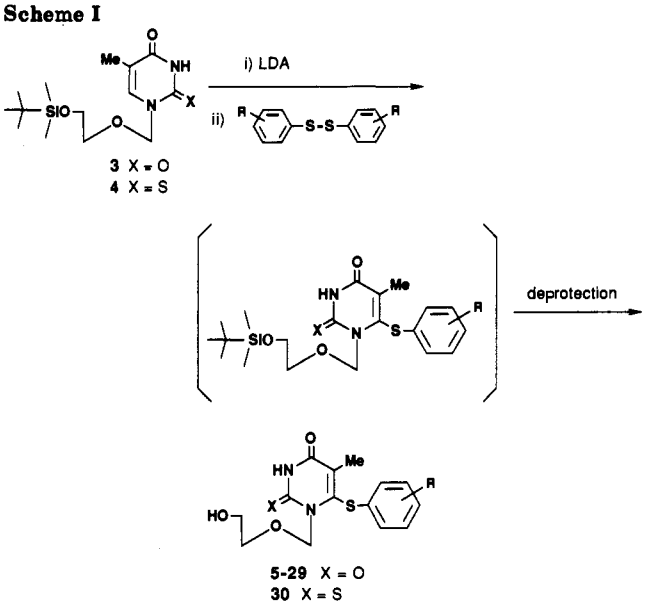
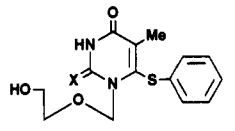
Scheme I



evant need to find new agents that have potent antiviral activity, low toxicity, and preferably a different mode of inhibition of viral replication.

We have recently reported that 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (1; HEPT)[9,10] showed in vitro antiviral activity against humam immunodeficiency virus type 1 (HIV-1), the causative agent of AIDS. Unlike other anti-HIV nucleoside analogues, such as AZT and 2′,3′-dideoxyinosine (DDI),[11] HEPT is only inhibitory to HIV-1. Other animal retroviruses and even HIV-2 are totally unaffected by this compound.[10] Synthetic studies of HEPT analogues so far undertaken[12,13] have suggested that the presence of the 5-methyl group, a ring structure at the C-6 position, and the N-3 H is indispensable for anti-HIV-1 activity. We have also found that HEPT-S (2), the 2-thiothymine counterpart of HEPT, showed improved activity.[13,14] These results prompted us to synthesize a series of HEPT and HEPT-S analogues and examine for their anti-HIV-1 activity. In the present article, we will focus on the analogues modified at the C-6 phenyl ring and at the C-5 position and discuss their structure–activity relationship.



Chemistry

A vast majority of HEPT- and HEPT-S analogues modified in the C-6 phenyl ring were synthesized from *tert*-butyldimethylsilyl (TBDMS) protected thymine and 2-thiothymine derivatives (3 and 4), based on the LDA (lithium diisopropylamide) lithation approach originally developed for C-6 modification of uridine.[15,16] Thus, treatment of 3 or 4 with LDA (2.2 equiv) in THF below −70 °C generated the respective C-6 lithiated species which were then subjected to the reaction with variety of diaryl disulfides (1.5 equiv). The desired analogues were obtained by simple extraction of the above reaction mixture followed by acidic treatment as shown in Scheme I. Compounds **5–30** were prepared in 16–87% yields by this procedure. It should be mentioned that diaryl disulfides having a nitro or cyano functionality can also be used as an electrophile (yield of products: **7**, 52%; **18**, 54%; **24**, 16%; **25**, 37%).

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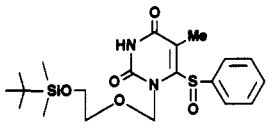
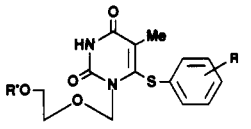
We have already reported that an addition–elimination reaction between 6-phenylsulfinyl derivative **31** and oxygen



31

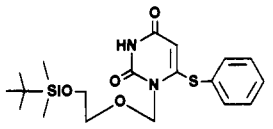


32 R = 3-COOMe, R' = TBDMS
33 R = 3-COOMe, R' = H
34 R = 3-COMe, R' = H
35 R = 4-COMe, R' = H

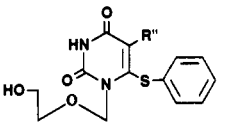
or nitrogen nucleophiles provides a route to 6-substituted acyclothymidines.[12] In the present study, **31** was reacted with thiolates. This alternative approach is useful in case any particular disulfide is not available. When **31** was treated with sodium 3-(methoxycarbonyl)benzenethiolate (1.75 equiv) in DMF at room temperature for 1.5 h, **32** was formed in 48% yield. After removal of the TBDMS group, acyclothymidine **33** was obtained. Compounds **34** and **35** were prepared from **31** in a similar manner.

Conventional transformation of the methoxycarbonyl group in **32** was also carried out as shown in Scheme II. Alkaline hydrolysis gave **36**, which was then desilylated to afford 6-[(3-carboxyphenyl)thio]acyclothymidine (**37**). Amidation of **36** was accomplished via an active-ester intermediate following the published method.[17] After removal of the TBDMS group, 6-[(3-carbamoylphenyl)thio] derivative **38** was obtained. Dehydration of the carbamoyl group was carried out using *O*-acetyl derivative **39** to give 6-[(3-cyanophenyl)thio]acyclothymidine (**40**).[18]

LTMP (lithium 2,2,6,6-tetramethylpiperidide) has been used for the C-5 lithiation of 6-(phenylthio)uridine.[19] When **41** was lithiated with LTMP and then reacted with

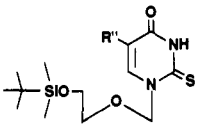


41

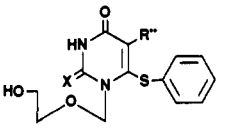


42 R" = $CH_2CH=CH_2$
43 R" = COOMe
44 R" = NHCOPh

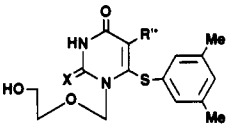
electrophiles ($BrCH_2CH=CH_2$, $ClCO_2Me$, and PhNCO), **42–44** were obtained after deprotection. Although this LTMP lithiation approach is straightforward, the use of simple alkyl halides, except MeI, has been reported to result in poor yields of products.[19] We, therefore, first prepared *O*-TBDMS-protected derivatives **45–47** from 5-alkyl-2-thiouracils[20] according to the published procedure[13,21] and then subjected these to the aforementioned LDA lithiation. Using appropriate diaryl disulfides, 5-alkyl-2-thio analogues **48–53** were obtained after deprotection. The corresponding uracil analogues **54–59** were prepared by oxidative hydrolysis (H_2O_2 in aqueous NaOH)



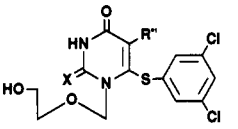
45 R* = Et
46 R* = Pr
47 R* = *i*-Pr



48 R* = Et, X = S
49 R* = Pr, X = S
50 R* = *i*-Pr, X = S
54 R* = Et, X = O
55 R* = Pr, X = O
56 R* = *i*-Pr, X = O



51 R* = Et, X = S
52 R* = *i*-Pr, X = S
57 R* = Et, X = O
58 R* = *i*-Pr, X = O



53 R* = Et, X = S
59 R* = Et, X = O

of the thione function of **48–53** in solution.[22]

Antiviral Activity and Discussion

The anti-HIV-1 ($HTLV\text{-}III_B$) activity and cytotoxicity of the newly synthesized 47 compounds in MT-4 cells are summarized in Table I together with those of HEPT, HEPT-S, and AZT. From the EC_{50} values of 6-(arylthio)acyclothymidines (**5–30**, **33–35**, **37**, **38**, **40**), a substantial number of compounds modified at the 3-position of the C-6 phenyl ring exhibited anti-HIV-1 activity. However the derivatives substituted at the 2- or 4-position of this moiety did not show significant activity, except for the 6-[(2-methoxyphenyl)thio] derivative [**8**, (EC_{50}) (50% effective concentrations) = 19 μM]. The 6-[(3-methylphenyl)thio] (**9**), 6-[(3-ethylphenyl)thio] (**10**) and 6-[(3-fluorophenyl)thio] (**14**) derivatives were inhibitory to HIV-1 with EC_{50} values 2.5, 2.7, and 3.3 μM, respectively. These values are 2–3-fold less than that of the parent compound HEPT (EC_{50} = 7.0 μM). Introduction of hydrophilic groups (i.e. CH_2OH, OH, COOH, and $CONH_2$) at the 3-position of the 6-(phenylthio) moiety destroyed the anti-HIV-1 activity. The 6-(3,5-disubstituted phenylthio) derivatives (**28–30**) proved to be potent inhibitors of HIV-1 replication in MT-4 cells. The EC_{50}s of **28**, **29**, and **30** were 0.26, 1.3, and 0.22 μM, respectively. Furthermore, **28** and **30** had large selectivity indices [SIs, ratios of 50% cytotoxic concentration (CC_{50}) to EC_{50}] comparable to that of AZT.

The 5-ethyl (**54**) and 5-isopropyl (**56**) analogues of HEPT proved to be highly potent and selective inhibitors of HIV-1. The EC_{50}s of **54** and **56** were 0.12 and 0.063 μM, respectively. Their SIs were more than 3000. Their 2-thio analogues, **48** and **50**, were equally inhibitory to HIV-1 when compared with their 2-oxo counterparts. It is noteworthy that the 6-[(3,5-dimethylphenyl)thio] derivatives (**51**, **52**, **57**, and **58**) inhibited HIV-1 replication in the nanomolar concentration range (Table I). Because their cytotoxicities were not so high (CC_{50}s = 52–277 μM), SIs of more than 10 000 were recorded with these compounds. Among the other C-5-modified compounds, 5-allyl (**42**) and 5-propyl (**49** and **55**) derivatives retained the anti-HIV-1 activity, yet **43** and **44** only showed the activity at concentrations toxic to the host cells. Compound **54** also exhibited the activity in peripheral blood lymphocytes (PBL) against HIV-1, whereas the $LAV\text{-}2_{ROD}$ strain of HIV-2 was insensitive to the compound (Table II).

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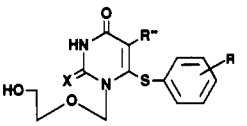
Table I. Inhibition of HIV-1 Replication in MT-4 Cells by Novel 5,6-Substituted 1-[(2-Hydroxyethoxy)methyl]uracils



compd	X	R	R″	EC_{50},[a] μM	CC_{50},[b] μM	SI[c]
5	O	2-Me	Me	71	>250	>3.5
6	O	2-Cl	Me	>130	130	<1
7	O	2-NO_2	Me	140	>250	>1.8
8	O	2-OMe	Me	19	>250	>13
9	O	3-Me	Me	2.6	420	162
10	O	3-Et	Me	2.7	181	67
11	O	3-*t*-Bu	Me	12	75	6.3
12	O	3-CH_2OH	Me	>292	292	<1
13	O	3-CF_3	Me	45	196	4.4
14	O	3-F	Me	3.3	282	85
15	O	3-Cl	Me	13	210	16
16	O	3-Br	Me	5.7	141	25
17	O	3-I	Me	10	106	11
18	O	3-NO_2	Me	34	170	5.0
19	O	3-OH	Me	82	446	5.3
20	O	3-OMe	Me	22	>250	>11
21	O	4-Me	Me	220	>250	>1.1
22	O	4-F	Me	>250	>250	
23	O	4-Cl	Me	>250	>250	
24	O	4-NO_2	Me	>190	190	<1
25	O	4-CN	Me	>250	>250	
26	O	4-OH	Me	>277	277	<1
27	O	4-OMe	Me	>250	>250	
28	O	3,5-Me_2	Me	0.26	243	935
29	O	3,5-Cl_2	Me	1.3	130	110
30	S	3,5-Me_2	Me	0.22	172	782
33	O	3-COOMe	Me	7.9	221	28
34	O	3-COMe	Me	7.3	228	35
35	O	4-COMe	Me	>110	110	<1
37	O	3-COOH	Me	>352	352	<1
38	O	3-$CONH_2$	Me	>306	306	<1
40	O	3-CN	Me	10	234	23
42	O	H	$CH_2CH{=}CH_2$	2.5	183	73
43	O	H	COOMe	>6.6	6.6	<1
44	O	H	CONHPh	>18	18	<1
48	S	H	Et	0.11	148	1350
49	S	H	Pr	10	230	23
50	S	H	*i*-Pr	0.059	400	6780
51	S	3,5-Me_2	Et	0.0078	277	35500
52	S	3,5-Me_2	*i*-Pr	0.005	52	10200
53	S	3,5-Cl_2	Et	0.043	64	1490
54	O	H	Et	0.12	400	3330
55	O	H	Pr	3.4	244	72
56	O	H	*i*-Pr	0.063	231	3670
57	O	3,5-Me_2	Et	0.013	149	11500
58	O	3,5-Me_2	*i*-Pr	0.0027	128	47400
59	O	3,5-Cl_2	Et	0.014	51	3640
HEPT				7.0	743	106
HEPT-S				0.98	123	126
AZT				0.006	7.8	1300

[a] Effective concentration of compound required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1. [b] Cytotoxic concentration of compound required to reduce the viability of mock-infected MT-4 cells by 50%. [c] Selectivity index: ratio of CC_{50}/EC_{50}.

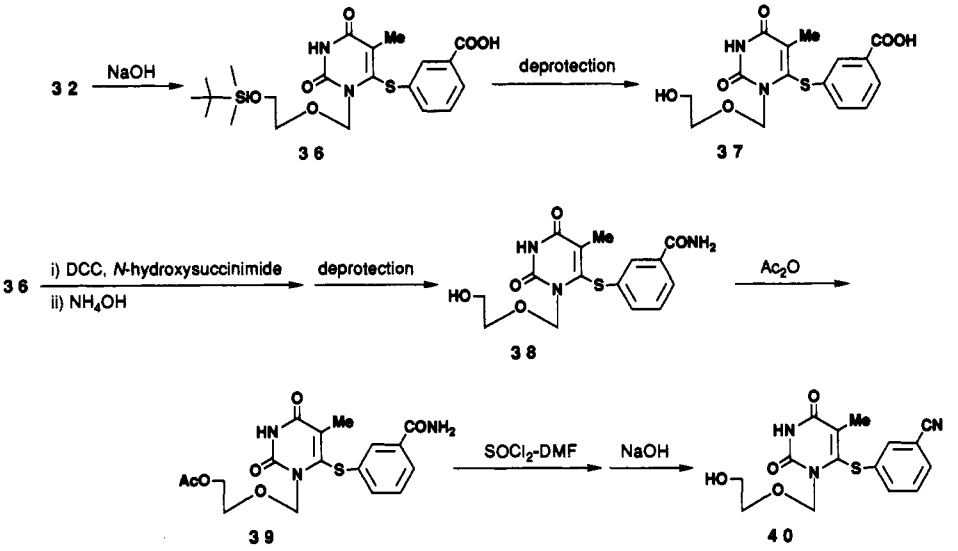
The present studies of the structure–activity relationships indicate that the anti-HIV-1 activity of HEPT could be potentiated by modification at the 3-position of the C-6 phenyl ring with simple alkyl (i.e. methyl and ethyl) and fluoro substituents. Furthermore, introduction of the methyl group or a chlorine atom to both the 3- and 5-positions of the 6-(phenylthio) moiety were even more effective. Other substitutions at this position reduced, or did not affect, the activity of HEPT. Modification at the 2- or 4-position of the C-6 phenyl ring appear to be ineffective. In our previous study, we found that modification at the C-5 position of HEPT increased not only its anti-HIV-1 activity but also its cytotoxicity,[12] while the present results demonstrated that replacement of the C-5 methyl group by either an ethyl or an isopropyl group brought about a marked increase in the anti-HIV-1 activity without

Table II. Inhibition of HIV-1 and HIV-2 Replication in MT-4 Cells and Peripheral Blood Lymphocytes (PBL) by Compound **54**[a]

compd	virus	strain	cell	EC_{50}, μM	CC_{50}, μM
54	HIV-1	$HTLV\text{-}III_B$	PBL	0.19	108
	HIV-2	$LAV\text{-}2_{ROD}$	MT-4	>400	400
HEPT	HIV-1	$HTLV\text{-}III_B$	PBL	7.9[b]	640[b]
	HIV-2	$LAV\text{-}2_{ROD}$	MT-4	>250[c]	740[c]

[a] The antiviral activity and cytotoxicity of the compounds were expressed as the EC_{50} for virus-infected cells and the CC_{50} for mock-infected cells, respectively. [b] See ref 13. [c] See ref 10.

Scheme II



increasing the cytotoxicity of the compounds. In addition, the results of **51–53** and **57–59** suggested that the modifications of both the C-5 and the C-6 position of the uracil moiety work cooperatively in terms of anti-HIV-1 activity.

As previously noted with HEPT,[10] these highly potent and selective inhibitors of HIV-1 have no effect on the replication of the LAV-2_{ROD} strain of HIV-2 at the 50% cytotoxic concentration to the host cells. The reason for this discriminative behavior of the HEPT derivatives between HIV-1 and HIV-2, as well as their mode of inhibition, remains to be elucidated. Preliminary metabolic studies have indicated that HEPT is taken up into the cells and partially converted to unknown metabolites other than its triphosphate (data not shown). Like HEPT, the active HEPT analogues presented in this study are unlikely to be phosphorylated by cellular nucleoside kinases. HEPT probably does not interfere with either a very early event (i.e. adsorption, penetration, or uncoating) or a late event (postintegration of proviral DNA) in the virus replicative cycle.[10] Furthermore, from the effect of the time of addition of analogue experiments, it appears that HEPT interacts at a stage of the replicative cycle that may well correspond to the reverse transcription process (data not shown). More recently, we have found that **54** is a potent inhibitor of HIV-1 reverse transcriptase.[23]

Studies on the pharmacokinetics, metabolism, disposition, and toxicology are indispensable before the novel 6-substituted acyclouridine derivatives could be proposed for clinical use in the prophylaxis or therapy of AIDS (or ARC). However, considering the severity of the AIDS pandemic and the urgent need for an effective therapy, the in vitro anti-HIV-1 potency and selectivity of the new HEPT derivatives make them particularly attractive for further development as candidate anti-AIDS drugs.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H 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. Silica gel 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.; Tokyo, Japan). TLC was performed on silica gel (precoated silica gel plate 60 F254, Merck). Elemental analyses were performed on a Perkin-Elmer 240-C elemental analyzer.

General Procedure for the Preparation of 6-(Arylthio)-1-[(2-hydroxyethoxy)methyl]thymine Derivatives (5–30). To a solution of LDA (4.4 mmol) in THF (10 mL) was added **3** or **4** (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, diaryl disulfide (3 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 purified by chromatography on silica gel ($CHCl_3$–MeOH; 50:1, v/v) and then crystallized from a suitable solvent.

1-[(2-Hydroxyethoxy)methyl]-6-[(2-methylphenyl)thio]thymine (5). This compound was synthesized from **3** with bis(2-methylphenyl) disulfide: yield 87%; mp 140–141 °C (toluene); UV (MeOH) λ_{max} 276 (ε 8100), 240 nm (ε 9200); MS *m/z* 322 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H, 5-Me), 2.42 (s, 3 H, SAr-Me), 3.62–3.67 (m, 4 H, OCH_2CH_2O), 5.56 (s, 2 H, NCH_2O), 6.98–7.22 (m, 4 H, SAr), 8.46 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_4S$) C, H, N, S.

6-[(2-Chlorophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (6). This compound was synthesized from **3** with bis(2-chlorophenyl) disulfide: yield 58%; mp 166–168 °C (toluene); UV (MeOH) λ_{max} 275 (ε 8200), 243 nm (ε 10 000); MS *m/z* 342 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3 H, 5-Me), 3.60–3.67 (m, 4 H, OCH_2CH_2O), 5.60 (s, 2 H, NCH_2O), 7.04–7.45 (m, 4 H, SAr), 8.95 (br, 1 H, NH). Anal. ($C_{14}H_{15}ClN_2O_4S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(2-nitrophenyl)thio]thymine (7). This compound was synthesized from **3** with bis(2-nitrophenyl) disulfide: yield 52%; mp 193–195 °C (EtOAc–EtOH); UV (MeOH) λ_{max} 351 (ε 4300), 273 (ε 12 000), 237 nm (ε 15 000); MS *m/z* 353 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3 H, 5-Me), 3.47–3.62 (m, 4 H, OCH_2CH_2O), 5.52 (s, 2 H, NCH_2O), 7.14 [dd, *J* = 8.3, 1.2 Hz, 1 H, SAr(H-6)], 7.43 [td, *J* = 8.3, 1.2 Hz, 1 H, SAr(H-4)], 7.58 [td, *J* = 8.3, 1.2 Hz, 1 H, SAr(H-5)], 8.34 [dd, *J* = 8.3, 1.2 Hz, 1 H, SAr(H-3)], 8.50 (br, 1 H, NH). Anal. ($C_{14}H_{15}N_3O_6S$) C, H, N, S.

(23) Baba, M.; De Clercq, E.; Tanaka, H.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Umezu, K.; Nakashima, H.; Mori, S.; Shigeta, S.; Walker, R. T.; Miyasaka, T. Potent and Selective Inhibition of Human Immunodeficiency Virus Type 1 (HIV-1) by 5-Ethyl-6-phenylthiouracil Derivatives Through Their Interaction with the HIV-1 Reverse Transcriptase. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2356–2360.

1-[(2-Hydroxyethoxy)methyl]-6-[(2-methoxyphenyl)thio]thymine (8). This compound was synthesized from **3** with bis(2-methoxyphenyl) disulfide: yield 69%; mp 162–163 °C (toluene); UV (MeOH) λ_{max} 283 (ε 9000), 245 nm (ε 8200); MS *m/z* 338 (M^+); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3 H, 5-Me), 3.67 (s, 4 H, OCH_2CH_2O), 5.68 (s, 2 H, NCH_2O), 6.88–7.31 (m, 4 H, SAr), 8.62 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_5S \cdot {}^1/_3H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(3-methylphenyl)thio]thymine (9). This compound was synthesized from **3** with bis(3-methylphenyl) disulfide: yield 63%; mp 116 °C (EtOAc–EtOH); UV (MeOH) λ_{max} 275 (ε 8000), 246 nm (ε 9700); MS *m/z* 322 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 2.33 (s, 3 H, SAr-Me), 3.67 (s, 4 H, OCH_2CH_2O), 5.59 (s, 2 H, NCH_2O), 6.98–7.25 (m, 4 H, SAr), 9.04 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_4S$) C, H, N, S.

6-[(3-Ethylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (10). This compound was synthesized from **3** with bis(3-ethylphenyl) disulfide: yield 57%; mp 102–103 °C (toluene–hexane); UV (MeOH) λ_{max} 275 (ε 8000), 245 nm (ε 9600); MS *m/z* 336 (M^+); ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 2.08 (s, 3 H, 5-Me), 2.62 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 3.63–3.67 (m, 4 H, OCH_2CH_2O), 5.59 (s, 2 H, NCH_2O), 6.98–7.28 (m, 4 H, SAr), 8.41 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_4S$) C, H, N, S.

6-[(3-*tert*-Butylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (11). This compound was synthesized from **3** with bis(3-*tert*-butylphenyl) disulfide: yield 56%; mp 143–144 °C (toluene); UV (MeOH) λ_{max} 275 (ε 8100), 244 nm (ε 9900); MS *m/z* 364 (M^+); ^1H NMR ($CDCl_3$) δ 1.29 (s, 9 H, CMe_3), 2.09 (s, 3 H, 5-Me), 3.60–3.68 (m, 4 H, OCH_2CH_2O), 5.60 (s, 2 H, NCH_2O), 6.96 (dt, *J* = 6.6, 2.0 Hz, 1 H, SAr), 7.23–7.32 (m, 3 H, SAr), 8.44 (br, 1 H, NH). Anal. ($C_{18}H_{24}N_2O_4S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[[3-(hydroxymethyl)phenyl]thio]thymine (12). This compound was synthesized from **3** with bis[3-[(*tert*-butyldimethylsiloxy)methyl]phenyl] disulfide: yield 44%; 134 °C ($CHCl_3$); UV (MeOH) λ_{max} 276 (ε 8100), 246 nm (ε 9800); MS *m/z* 338 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.83 (s, 3 H, 5-Me), 3.39 (td, *J* = 5.4, 5.3 Hz, 2 H, $HOCH_2CH_2O$), 3.48 (t, *J* = 5.4 Hz, 2 H, $HOCH_2CH_2O$), 4.45 (d, *J* = 5.8 Hz, 2 H, SAr-CH_2OH), 4.60 (t, *J* = 5.3 Hz, 1 H, $HOCH_2CH_2O$), 5.25 (t, *J* = 5.8 Hz, 1 H, SAr-CH_2OH), 5.41 (s, 2 H, NCH_2O), 7.12–7.35 (m, 4 H, SAr), 11.69 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_5S \cdot {}^1/_5H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[[3-(trifluoromethyl)phenyl]thio]thymine (13). This compound was synthesized from **3** with bis[3-(trifluoromethyl)phenyl] disulfide: yield 61%; mp 126 °C (toluene); UV (MeOH) λ_{max} 277 (ε 8700), 247 nm (ε 11000); MS *m/z* 376 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 3.61–3.69 (m, 4 H, OCH_2CH_2O), 5.60 (s, 2 H, NCH_2O), 7.33–7.57 (m, 4 H, SAr), 8.30 (br, 1 H, NH). Anal. ($C_{15}H_{15}F_3N_2O_4S$) C, H, N, S.

6-[(3-Fluorophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (14). This compound was synthesized from **3** with bis(3-fluorophenyl) disulfide: yield 44%; mp 114–115 °C (toluene–EtOH); UV (MeOH) λ_{max} 276 (ε 8900), 243 nm (ε 10000); MS *m/z* 326 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.83 (s, 3 H, 5-Me), 3.37 (dt, *J* = 5.4, 4.8 Hz, 2 H, $HOCH_2CH_2O$), 3.47 (t, *J* = 4.8 Hz, 2 H, $HOCH_2CH_2O$), 4.57 (t, *J* = 5.4 Hz, 1 H, $HOCH_2CH_2O$), 5.39 (s, 2 H, NCH_2O), 7.05–7.44 (m, 4 H, SAr), 11.67 (br, 1 H, NH). Anal. ($C_{14}H_{15}FN_2O_4S$) C, H, N, S.

6-[(3-Chlorophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (15). This compound was synthesized from **3** with bis(3-chlorophenyl) disulfide and obtained as syrup: yield 68%; UV (MeOH) λ_{max} 276 (ε 8200), 248 nm (ε 10000); MS *m/z* 342 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 3.67 (s, 4 H, OCH_2CH_2O), 5.59 (s, 2 H, NCH_2O), 7.07–7.29 (m, 4 H, SAr), 9.36 (br, 1 H, NH). Anal. ($C_{14}H_{15}ClN_2O_4S \cdot {}^1/_5H_2O$) C, H, N, S.

6-[(2-Bromophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (16). This compound was synthesized from **3** with bis(3-bromophenyl) disulfide and obtained as syrup: yield 56%; UV (MeOH) λ_{max} 276 (ε 8200), 250 nm (ε 10000); MS *m/z* 386, 388 (M^+); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H, 5-Me), 3.65–3.69 (m, 4 H, OCH_2CH_2O), 5.59 (s, 2 H, NCH_2O), 7.12–7.43 (m, 4 H, SAr), 8.59 (br, 1 H, NH). Anal. ($C_{14}H_{15}BrN_2O_4S \cdot {}^1/_5H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(3-iodophenyl)thio]thymine (17). This compound was synthesized from **3** with bis(3-iodophenyl) disulfide: yield 51%; mp 132–133 °C (toluene); UV (MeOH) λ_{max} 228 nm (ε 23000); MS *m/z* 434 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 3.64–3.68 (m, 4 H, OCH_2CH_2O), 5.58 (s, 2 H, NCH_2O), 7.06 [t, *J* = 7.8 Hz, 1 H, SAr(H-5)], 7.18 [dt, *J* = 7.8, 1.5 Hz, 1 H, SAr(H-6)], 7.56 [t, *J* = 1.5 Hz, 1 H, SAr(H-2)], 7.61 [dt, *J* = 7.8, 1.5 Hz, 1 H, SAr(H-4)], 8.43 (br, 1 H, NH). Anal. ($C_{14}H_{15}IN_2O_4S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(3-nitrophenyl)thio]thymine (18). This compound was synthesized from **3** with bis(3-nitrophenyl) disulfide: yield 54%; mp 130–131 °C (toluene–EtOH); UV (MeOH) λ_{max} 245 nm (ε 18000); MS *m/z* 353 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 3.59–3.72 (m, 4 H, OCH_2CH_2O0, 5.63 (s, 2 H, NCH_2O), 7.52–7.58 (m, 2 H, SAr), 8.07–8.16 (m, 2 H, SAr), 9.25 (br, 1 H, NH). Anal. ($C_{14}H_{15}N_3O_6S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(3-hydroxyphenyl)thio]thymine (19). This compound was synthesized from **3** with bis[3-(*tert*-butyldimethylsiloxy)phenyl] disulfide: yield 36%; mp 161–162 °C (toluene); UV (MeOH) λ_{max} 282 (ε 9100), 245 nm (ε 8400); MS *m/z* 324 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.86 (s, 3 H, 5-Me), 3.39 (dt, *J* = 5.4, 4.6 Hz, 2 H, $HOCH_2CH_2O$), 3.47 (t, *J* = 4.6 Hz, 2 H, $HOCH_2CH_2O0$, 4.59 (t, *J* = 5.4 Hz, 1 H, $HOCH_2CH_2O$), 5.39 (s, 2 H, NCH_2O), 6.61–6.75 [m, 3 H, SAr(H-2,4,6)], 7.15 [t, *J* = 8.3 Hz, 1 H, SAr(H-5)], 9.67 (s, 1 H, SAr*OH*), 11.71 (br, 1 H, NH). Anal. ($C_{14}H_{16}N_2O_5S \cdot {}^1/_6H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(3-methoxyphenyl)thio]thymine (20). This compound was synthesized from **3** with bis(3-methoxyphenyl) disulfide: yield 70%; mp 129–131 °C (toluene); UV (MeOH) λ_{max} 282 (ε 9000), 245 nm (ε 8500); MS *m/z* 338 (M^+); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H, 5-Me), 3.68 (s, 4 H, OCH_2CH_2O), 5.39 (s, 2 H, NCH_2O), 6.73–6.87 [m, 3 H, SAr(H-2,4,6)], 7.24 [t, *J* = 8.1 Hz, 1 H, SAr(H-5)], 9.29 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_5S \cdot {}^1/_{10}H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(4-methylphenyl)thio]thymine (21). This compound was synthesized from **3** with bis(4-methylphenyl) disulfide: yield 67%; mp 128–129 °C (toluene); UV (MeOH) λ_{max} 273 (ε 8400), 247 nm (ε 11000); MS *m/z* 322 (M^+); ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H, 5-Me), 2.33 (s, 3 H, SAr-Me), 3.67 (s, 4 H, OCH_2CH_2O), 5.60 (s, 2 H, NCH_2O0, 7.13 (s, 4 H, SAr), 8.84 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_4S$) C, H, N, S.

6-[(4-Fluorophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (22). This compound was synthesized from **3** with bis(4-fluorophenyl) disulfide: yield 63%; mp 103–104 °C (toluene); UV (MeOH) λ_{max} 277 (ε 7700), 242 nm (ε 8200); MS *m/z* 326 (M^+); ^1H NMR ($CDCl_3$) δ 2.05 (s, 3 H, 5-Me), 3.68 (s, 4 H, OCH_2CH_2O), 5.62 (s, 2 H, NCH_2O), 7.01–7.28 (m, 4 H, SAr), 9.48 (br, 1 H, NH). Anal. ($C_{14}H_{15}FN_2O_4S$) C, H, N, S.

6-[(4-Chlorophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (23). This compound was synthesized from **3** with bis(4-chlorophenyl) disulfide: yield 77%; mp 148–150 °C (toluene); UV (MeOH) λ_{max} 251 nm (ε 14000); MS *m/z* 342 (M^+); ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H, 5-Me), 3.62–3.69 (m, 4 H, OCH_2CH_2O), 5.59 (s, 2 H, NCH_2O), 7.17 [d, *J* = 8.7 Hz, 2 H, SAr(H-2,6)], 7.32 [d, *J* = 8.7 Hz, 2 H, SAr(H-3,5)], 8.55 (br, 1 H, NH). Anal. ($C_{14}H_{15}ClN_2OP_4S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(4-nitrophenyl)thio]thymine (24). This compound was synthesized from **3** with bis(4-nitrophenyl) disulfide: yield 16%; mp 207–208 °C (EtOAc–EtOH); UV (MeOH) λ_{max} 320 (ε 13000), 290 nm (ε 11000); MS *m/z* 353 (M^+); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 3.66 (s, 4 H, OCH_2CH_2O), 5.57 (s, 2 H, NCH_2O), 7.33 [d, *J* = 9.0 Hz, 2 H, SAr(H-2,6)], 8.20 [d, *J* = 9.0 Hz, 2 H, SAr(H-3,5)], 8.43 (br, 1 H, NH). Anal. ($C_{14}H_{15}N_3O_6S$) C, H, N, S.

6-[(4-Cyanophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (25). This compound was synthesized from **3** with bis(4-cyanophenyl) disulfide: yield 37%; mp 221–222 °C ($EtOH$–H_2O); UV (MeOH) λ_{max} 269 nm (ε 22000); MS *m/z* 333 (M^+); ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, 5-Me), 3.63–3.67 (m, 4 H, OCH_2CH_2O), 5.55 (s, 2 H, NCH_2O), 7.26 [d, *J* = 8.5 Hz, 2 H, SAr(H-2,6)], 7.61 [d, *J* = 8.5 Hz, 2 H, SAr(H-3,5)], 8.17 (br, 1 H, NH). Anal. ($C_{15}H_{15}N_3O_4S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(4-hydroxyphenyl)thio]thymine (26). This compound was synthesized from **3** with bis[4-(*tert*-butyldimethylsiloxy)phenyl]: yield 40%; mp 181–182 °C (EtOH); UV (MeOH) λ_{max} 252 nm (ε 13000); MS *m/z* 324 (M^+);

^{1}H NMR (Me_2SO-d_6) δ 1.98 (s, 3 H, 5-Me), 3.65 (s, 4 H, OCH_2CH_2O), 3.95 (br, 1 H, $HOCH_2CH_2O$), 5.46 (s, 2 H, NCH_2O), 6.79 [d, J = 8.8 Hz, 2 H, SAr(H-3,5)], 7.13 [d, J = 8.8 Hz, 2 H, SAr(H-2,6)], 9.30 (s, 1 H, SAr-O*H*), 11.28 (br, 1 H, NH). Anal. ($C_{14}H_{16}N_2O_5S \cdot {}^1/_5H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[(4-methoxyphenyl)thio]thymine (27). This compound was synthesized from **3** with bis(4-methoxyphenyl) disulfide: yield 62%; mp 108–109 °C (toluene); UV (MeOH) λ_{max} 252 nm (ε 14000); MS m/z 338 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H, 5-Me), 3.68 (s 4 H, OCH_2CH_2O), 5.64 (s, 2 H, NCH_2O), 6.87 [d, J = 8.9 Hz, 2 H, SAr(H-3,5)], 7.22 [d, J = 8.9 Hz, 2 H, SAr(H-2,6)], 8.75 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_5S$) C, H, N, S.

6-[(3,5-Dimethylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (28). This compound was synthesized from **3** with bis(3,5-dimethylphenyl) disulfide: yield 70%; mp 136–137 °C (toluene); UV (MeOH) λ_{max} 275 (ε 8000), 248 nm (ε 9900); MS m/z 336 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3 H, 5-Me), 2.28 (s, 6 H, SArMe_2), 3.63–3.68 (m, 4 H, OCH_2CH_2O), 5.58 (s, 2 H, NCH_2O), 6.81 [d, J = 0.9 Hz, 2 H, SAr(H-2,6)], 6.89 [d, J = 0.9 Hz, 1 H, SAr(H-4)], 8.25 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_4S$) C, H, N, S.

6-[(3,5-Dichlorophenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (29). This compound was synthesized from **3** with bis(3,5-dichlorophenyl) disulfide: yield 17%; mp 132–134 °C (hexane); UV (MeOH) λ_{max} 253 nm (ε 11000); MS m/z 376, 378, 380 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H, 5-Me), 3.65–3.69 (m, 4 H, OCH_2CH_2O), 5.57 (s, 2 H, NCH_2O), 7.09 [d, J = 1.8 Hz, 2 H, SAr(H-2,6)], 7.25 [d, J = 1.8 Hz, 1 H, SAr(H-4)], 8.23 (br, 1 H, NH). Anal. ($C_{14}H_{14}Cl_2N_2O_4S$) C, H, N, S.

6-[(3,5-Dimethylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]-2-thiothymine (30). This compound was synthesized from **4** with bis(3,5-dimethylphenyl) disulfide: yield 58%; mp 156–158 °C (toluene); UV (MeOH) λ_{max} 283 (ε 22000), 247 nm (ε 12000); MS m/z 352 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H, 5-Me), 2.29 (s, 6 H, SArMe_2), 3.68–3.81 (m, 4 H, OCH_2CH_2O), 6.16 (s, 2 H, NCH_2O), 6.81 [d, J = 1.2 Hz, 2 H, SAr(H-2,6)], 6.90 [d, J = 1.2 Hz, 1 H, SAr(H-4)], 9.56 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_3S_2$) C, H, N, S.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-6-[[3-(methoxycarbonyl)phenyl]thio]thymine (32). To a solution of 3-(methoxycarbonyl)benzenethiol (1.06 g, 6.3 mmol) in DMF (15 mL) was added sodium hydride (60% in oil; 252 mg, 6.3 mmol) at 0 °C. The resulting suspension was allowed to warm to room temperature and then **31** (1.6 g, 3.6 mmol) was added to the suspension. After the mixture was stirred at room temperature for 1.5 h, the reaction mixture was added to 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 silica gel eluted with $CHCl_3$–hexane (8:2, v/v) to give 834 mg (48%) of **32** after crystallization from EtOH: mp 69–70 °C; MS m/z 480 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Me_2Si), 0.87 (s, 9 H, Me_3C), 2.01 (s, 3 H, 5-Me), 3.61–3.72 (m, 4 H, OCH_2CH_2O), 3.93 (s, 3 H, COOMe), 5.61 (s, 2 H, NCH_2O), 7.36–7.42 (m, 2 H, SAr), 7.80–7.96 (m, 2 H, SAr), 8.42 (br, 1 H, NH). Anal. ($C_{22}H_{32}N_2O_6SSi$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[[3-(methoxycarbonyl)phenyl]thio]thymine (33). Compound **32** (355 mg, 0.74 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 $CHCl_3$–hexane to give **33** (190 mg, 70%): mp 161–164 °C; UV (MeOH) λ_{max} 278 nm (ε 8000); MS m/z 366 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H, 5hMe), 3.60–3.72 (m, 4 H, OCH_2CH_2O), 3.93 (s, 3 H, COOMe), 5.63 (s, 2 H, NCH_2O), 7.39–7.45 (m, 2 H, SAr), 7.91–7.97 (m, 2 H, SAr), 8.70 (br, 1 H, NH). Anal. ($C_{16}H_{18}N_2O_6S \cdot {}^1/_5H_2O$) C, H, N, S.

General Procedure for the Preparation of [(2-Hydroxyethoxy)methyl]-6-[[(methylcarbonyl)phenyl]thio]thymines (34 and 35). To a suspension of the sodium salt of mercaptobenzophenone (0.87 mmol) in DMF (10 mL) was added **31** (263 mg, 0.6 mmol), and the mixture was stirred at room temperature for 1 h. Saturated NH_4Cl solution (20 mL) was added to the solution, and the mixture was then extracted with EtOAc (50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness. 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 on ODS-silica gel eluted with MeOH–H_2O (1:1, v/v). The eluate was evaporated and the residue was crystallized from EtOH–H_2O.

1-[(2-Hydroxyethoxy)methyl]-6-[[3-(methylcarbonyl)phenyl]thio]thymine (34): yield 43%; mp 169–170 °C; UV (MeOH) λ_{max} 272 nm (ε 8000); MS m/z 350 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 1.83 (s, 3 H, 5-Me), 2.56 (s, 3 H, COMe), 3.35 (dt, J = 5.5, 5.0 Hz, 2 H, $HOCH_2CH_2O$), 3.47 (t, J = 5.0 Hz, 2 H, $HOCH_2CH_2O$), 4.58 (t, J = 5.5 Hz, 1 H, $HOCH_2CH_2O$), 5.42 (s, 2 H, NCH_2O), 7.43–7.60 (m, 2 H, SAr), 7.81–7.87 (m, 2 H, SAr), 11.73 (br, 1 H, NH). Anal. ($C_{16}H_{18}N_2O_5S \cdot {}^1/_5H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-[[4-(methylcarbonyl)phenyl]thio]thymine (35): yield 61%; mp 121–123 °C; UV (MeOH) λ_{max} 280 nm (ε 19000); MS m/z 350 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3 H, 5-Me), 2.59 (s, 3 H, COMe), 3.62–3.69 (m, 4 H, OCH_2CH_2O), 5.58 (s, 2 H, NCH_2O), 7.27 [d, J = 8.4 Hz, 2 H, SAr(H-2,6)], 7.91 [d, J = 8.4 Hz, 2 H, Sar(H3,5)], 9.68 (br, 1 H, NH). Anal. ($C_{16}H_{18}N_2O_5S$) C, H, N, S.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-6-[(3-carboxyphenyl)thio]thymine (36). A solution of **32** (840 mg, 1.54 mmol) in THF (20 mL) and EtOH (10 mL) was allowed to react with aqueous 1 N NaOH (3.2 mL). The mixture was stirred for 1 h at room temperature. After being acidified to pH 3 with aqueous 2 N HCl, the solution was extracted with EtOAc (50 mL) and H_2O (30 mL). The organic layer was washed with brine (3 × 10 mL) and then dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was crystallized from Et_2O–hexane to give **36** (632 mg, 88%): mp 152–153 °C; MS m/z 466 (M^+); ^{1}H NMR (Me_2SO-d_6) δ −0.04 (s, 6 H, Me_2Si), 0.80 (s, 9 H, Me_3C), 1.83 (s, 3 H, 5-Me), 3.45–3.53 (m, 4 H, OCH_2CH_2O), 5.43 (s, 2 H, NCH_2O), 7.47 [t, J = 7.9 Hz, 1 H, SAr(H-5)], 7.55 [dt, J = 7.9, 1.8 Hz, 1 H, SAr(H-6)], 7.72–7.82 [m, 2 H, SAr(H-2,4)], 11.75 (br, 1 H, NH), 13.23 (s, 1 H, COOH). Anal. ($C_{21}H_{30}N_2O_6SSi$) C, H, N, S.

Following the preparation of **33**, **37** was prepared from **36**.

6-[(3-Carboxyphenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (37): yield 89%; mp 213–215 °C ($CHCl_3$); UV (MeOH) λ_{max} 278 nm (ε 7600); MS m/z 352 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 1.82 (s, 3 H, 5-Me), 3.33–3.50 (m, 4 H, OCH_2CH_2O), 4.58 (t, J = 5.5 Hz, 1 H, $HOCH_2CH_2O$), 5.42 (s, 2 H, NCH_2O), 7.47 [t, J = 8.1 Hz, 1 H, SAr(H-5)], 7.58 [dt, J = 8.1, 1.6 Hz, 1 H, SAr(H-6)], 7.75–7.84 [m, 2 H, SAr(H-2,4)], 11.74 (br, 1 H, NH), 13.22 (br, 1 H, COOH). Anal. ($C_{15}H_{16}N_2O_6S \cdot {}^1/_2H_2O$) C, H, N, S.

6-[(3-Carbamoylphenyl)thio]-1-[(2-hydroxyethoxy)methyl]thymine (38). To a solution of **36** (807 mg, 1.73 mmol) and *N*-hydroxysuccinimide (199 mg, 1.73 mmol) in dioxane (15 mL) was added *N*,*N*-dicyclohexylcarbodiimide (DCC; 357 mg, 1.73 mmol). The mixture was stirred for 1 h at room temperature and filtered. The solution was added to a mixture of concentrated aqueous NH_4OH (0.7 mL) and H_2O (2 mL). After being allowed to stand for 5 min, the mixture was concentrated to dryness. The residue was extracted with EtOAc (50 mL) and saturated $NaHCO_3$ (20 mL), and the organic layer was washed with 4% aqueous citric acid solution and brine (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was dissolved in AcOH–THF–H_2O (15 mL; 2:2:2, v/v/v). The solution was stirred at room temperature for 14 h and evaporated to dryness. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH; 15:1, v/v) to give 280 mg (46%) of **38** after crystallization from MeOH: mp 196–197 °C; UV (MeOH) λ_{max} 276 nm (ε 8200); MS m/z 351 (M^+); ^{1}H NMR (Me_2SO-d_6) δ 1.81 (s, 3 H, 5-Me), 2.56 (s, 3 H, COMe), 3.37 (dt, J = 5.4, 5.0 Hz, 2 H, $HOCH_2CH_2O$), 3.47 (t, J = 5.0 Hz, 2 H, $HOCH_2CH_2O$), 4.59 (t, J = 5.4 Hz, 1 H, $HOCH_2CH_2O$), 5.42 (s, 2 H, NCH_2O), 7.39–7.48 [m, 3 H, SAr, CONH(A)H(B)], 7.72–7.77 (m, 2 H, SAr), 8.05 [br, 1 H, CONH(A)H(B)], 11.71 (br, 1 H, NH). Anal. ($C_{15}H_{17}N_3O_5S \cdot {}^1/_5H_2O$) C, H, N, S.

1-[(2-Acetoxyethoxy)methyl]-6-[(3-carbamoylphenyl)thio]thymine (39). To a solution of **38** (141 mg, 0.4 mmol) in pyridine (5 mL) was added acetic anhydride (1 mL) and the solution was stirred for 2 h at room temperature. The mixture was poured into saturated $NaHCO_3$ solution (10 mL) and ex-

tracted with EtOAc (3 × 10 mL). The organic layer was washed with saturated $NaHCO_3$ solution (3 × 10 mL) and then brine (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH; 25:1, v/v) to give 146 mg (93%) of **39** after crystallization from EtOAc–hexane: mp 159–160 °C; MS m/z 393 (M^+); ^1H NMR ($CDCl_3$) δ 2.02, 2.05 (s × 2, 3 H × 2, 5-Me, MeCOO), 3.75 (t, J = 4.7 Hz, 2 H, $AcOCH_2CH_2O$), 4.07 (t, J = 4.7 Hz, 2 H, $AcOCH_2CH_2O$), 5.58 (s, 2 H, NCH_2O), 5.82, 6.23 (br × 2, 1 H × 2, $CONH_2$), 7.24–7.45 [m, 2 H, SAr(H-5,6)], 7.66 [dt, J = 7.3, 1.6 Hz, 1 H, SAr(H-4)], 7.76 [t, J = 1.6 Hz, 1 H, SAr(H-2)], 8.85 (br, 1 H, NH). Anal. ($C_{17}H_{18}N_3O_6S$) C, H, N, S.

6-[(3-Cyanophenyl)thio]-1-[(2-Hydroxyethoxy)methyl]-thymine (40). To a solution of **39** (130 mg, 0.33 mmol) in DMF (6 mL) was added $SOCl_2$ (66.6 μL, 0.99 mmol). The mixture was stirred for 2 h at room temperature and poured into saturated $NaHCO_3$ solution (30 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 dissolved in EtOH (6 mL) and THF (6 mL) was added to aqueous 2 N NaOH solution (0.43 mL) and stirred for 1 h at room temperature. After neutralization with aqueous 2 N HCl, the solution was evaporated to dryness. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH; 25:1, v/v) to give 77 mg (70%) of **40** after crystallization from diethyl ether: mp 143–144 °C; UV (MeOH) λ_{max} 279 (ε 8400), 252 nm (ε 10000); MS m/z 333 (M^+); ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H, 5-Me), 3.67 (s, 4 H, OCH_2CH_2O), 5.59 (s, 2 H, NCH_2O), 7.42–7.59 (m, 4 H, SAr), 8.48 (br, 1 H, NH). Anal. ($C_{15}H_{15}N_3O_4S$) C, H, N, S.

General Procedure for the Preparation of 5-Substituted 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)uracil Derivatives (42–44). The procedure was the same as for the preparation of **5–30**. Compound **41** was used as the starting material and LTMP was used as the lithiating agent.

5-Allyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)uracil (42). Allyl bromide was used as an electrophile: yield 5.9%; mp 93–94 °C (EtOAc–hexane); UV (MeOH) λ_{max} 276 (ε 8900), 242 nm (ε 9900); MS m/z 334 (M^+); ^1H NMR ($CDCl_3$) δ 1.73–1.86 (m, 1 H, OH), 3.44 (d, J = 6.0 Hz, 2 H, $CH_2CH{=}CH_2$), 3.60 (s, 4 H, OCH_2CH_2O), 4.89–5.13 (m, 2 H, $CH{=}CH_2$), 5.51 (s, 2 H, NCH_2O), 5.65–5.86 (m, 1 H, $CH{=}CH_2$), 7.14–7.43 (m, 5 H, SPh), 8.37 (br, 1 H, NH). Anal. ($C_{16}H_{18}N_2O_4S\cdot{}^1/_4H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-5-(methoxycarbonyl)-6-(phenylthio)uracil (43). Methoxycarbonyl chloride was used as an electrophile: yield 79%; mp 144–145 °C (EtOAc–hexane); UV (MeOH) λ_{max} 252 nm (ε 8900); MS m/z 352 (M^+); ^1H NMR ($CDCl_3$) δ 3.62 (s, 4 H, OCH_2CH_2O), 3.64 (s, 3 H, OMe), 5.58 (s, 2 H, NCH_2O), 7.33–7.52 (m, 5 H, SPh), 8.55 (br, 1 H, NH). Anal. ($C_{15}H_{16}N_2O_6S$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-5-(phenylcarbamoyl)-6-(phenylthio)uracil (44). Phenyl isocyanate was used as an electrophile: yield 28%; mp 238–240 °C dec (EtOH–H_2O); UV (MeOH) λ_{max} 247 nm (ε 19000); MS m/z 339 (M^+ – 74); ^1H NMR (Me_2SO-d_6) δ 3.24–3.50 (m, 4 H, OCH_2CH_2O), 4.63 (t, J = 5.5 Hz, 1 H, OH), 5.23 (s, 2 H, NCH_2O), 7.04–7.55 (m, 10 H, Ph × 2), 10.30 (br, 1 H, NHPh), 12.02 (br, 1 H, NH). Anal. ($C_{20}H_{19}N_3O_5S\cdot H_2O$) C, H, N, S.

General Procedure for the Preparation of 5-Alkyl-1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-2-thiouracils (45–47). A suspension of 5-alkyl-2-thiouracil (10 mmol) and ammonium sulfate (200 mg) in 1,1,1,3,3,3-hexamethyldisilazane (30 ml) was heated under reflux with stirring for 15 h. Excess silylating reagent was removed in vacuo. The residual oil was dissolved in MeCN (50 mL), and to the solution were added (2-acetoxyethoxy)methyl acetate (2.3 mL, 12 mmol) and cesium iodide (2.6 g, 10 mmol). The mixture was heated under reflux with stirring for 2 h and allowed to cool room temperature. The reaction mixture was added to H_2O (50 mL) and it was then extracted with EtOAc (150 mL). The organic layer was washed with saturated $NaHCO_3$ solution (50 mL) and concentrated to dryness. The residue was dissolved in MeOH (40 mL) and the solution was treated with aqueous 1 N NaOH (40 mL) for 3 h at room temperature. After neutralization to pH 7 with aqueous 1 N HCl, the solution was evaporated to dryness. The residue was coevaporated with DMF (3 × 30 mL) and dissolved in MeCN (40 mL). To the solution were added imidazole (1.4 g, 20 mmol) and *tert*-butyldimethylsilyl (TBDMS) chloride (3.0 g, 20 mmol), and the mixture was stirred at room temperature. After 14 h, the reaction mixture was poured into saturated $NaHCO_3$ solution (40 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by chromatography on silica gel (EtOAc–hexane; 15:85, v/v) and then crsytallized from a suitable solvent.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-5-ethyl-2-thiouracil (45): yield 40%; mp 70–73 °C (*i*-PrOH); UV (MeOH) λ_{max} 281 nm (ε 17000); MS m/z 287 (M^+ – *t*-Bu); ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H, Me_2Si), 0.90 (s, 9 H, Me_3C), 1.16 (t, J = 7.4 Hz, 3 H, $CH_2(CH_3)$, 2.41 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.68–3.84 (m, 4 H, OCH_2CH_2O), 5.66 (s, 2 H, NCH_2O), 7.29 (s, 1 H, 6-H), 9.22 (br, 1 H, NH). Anal. ($C_{15}H_{28}N_2O_3SSi$) C, H, N, S.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-5-propyl-2-thiouracil (46): yield 32%; mp 43–46 °C (EtOAc–hexane); UV (MeOH) λ_{max} 281 nm (ε 16000); MS m/z 301 (M^+ – *t*-Bu); ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, Me_2Si), 0.90 (s, 9 H, Me_3C), 0.95 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.57 (tq, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.34 (q, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 3.69–3.84 (m, 4 H, OCH_2CH_2O), 5.66 (s, 2 H, NCH_2O), 7.30 (s, 1 H, 6-H), 9.72 (br, 1 H, NH). Anal. ($C_{16}H_{30}N_2O_3SSi$) C, H, N, S.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-5-isopropyl-2-thiouracil (47): yield 38%; mp 81–83 °C (EtOAc–hexane); UV (MeOH) λ_{max} 281 nm (ε 15000); MS m/z 301 (M^+ – *t*-Bu; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, Me_2Si), 0.90 (s, 9 H, Me_3C), 1.18 [d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 2.92 [qq, J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 3.69–3.83 (m, 4 H, OCH_2CH_2O), 5.67 (s, 2 H, NCH_2O), 7.24 (s, 1 H, 6-H), 9.49 (br, 1 H, NH). Anal. ($C_{16}H_{30}N_2O_3SSi$) C, H, N, S.

According to the general procedure for the preparation of 6-(arylthio)-1-[(2-hydroxyethoxy)methyl]thymine derivatives, 5-alkyl-6-(arylthio)-1-[(2-hydroxyethoxy)methyl]-2-thiouracils (**48–53**) were prepared.

5-Ethyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-2-thiouracil (48): yield 63%; mp 71–75 °C (EtOAc–hexane); UV (MeOH) λ_{max} 283 nm (ε 20000); MS m/z 338 (M^+); ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.72–1.92 (m, 1 H, OH), 2.68 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 3.50–3.78 (m, 4 H, OCH_2CH_2O), 6.06 (s, 2 H, NCH_2O), 7.18–7.43 (m, 5 H, SPh), 9.54 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_3S_2\cdot{}^1/_4H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-5-propyl-2-thiouracil (49): yield 44%; mp 112–116 °C (EtOAc–hexane); UV (MeOH) λ_{max} 283 nm (ε 20000); MS m/z 352 (M^+); ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H, $CH_2CH_2CH_3$), 1.42 (qt, J = 7.0, 8.0 Hz, 2 H, $CH_2CH_2CH_3$), 1.83 (t, J = 6.0 Hz, 1 H, OH), 2.62 (t, J = 8.0 Hz, 2 H, $CH_2CH_2CH_3$), 3.54–3.73 (m, 4 H, OCH_2CH_2O), 6.05 (s, 2 H, NCH_2O), 7.15–7.41 (m, 5 H, SPh), 9.52 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_3S_2$) C, H, N, S.

5-Isopropyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-2-thiouracil (50): yield 61%; mp 145–147 °C (hexane); UV (MeOH) λ_{max} 283 nm (ε 20000); MS m/z 352 (M^+); ^1H NMR ($CDCl_3$) δ 1.15 [d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 1.94 (t, J = 5.9 Hz, 1 H, OH), 3.57 [qq, J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 3.60–3.80 (m, 4 H, OCH_2CH_2O), 6.13 (s, 2 H, NCH_2O), 7.18–7.44 (m, 5 H, SPh), 9.68 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_3S_2$) C, H, N, S.

6-[(3,5-Dimethylphenyl)thio]-5-ethyl-1-[(2-hydroxyethoxy)methyl]-2-thiouracil (51): yield 55%; mp 121–123 °C (acetone–hexane); UV (MeOH) λ_{max} 283 (ε 20000), 247 nm (ε 12000); MS m/z 366 (M^+); ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.92 (t, J = 6.0 Hz, 1 H, OH), 2.29 (s, 6 H, $SAr(Me)_2$), 2.68 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 3.58–3.83 (m, 4 H, OCH_2CH_2O), 6.05 (s, 2 H, NCH_2O), 6.80 [s, 2 H, Ar-H(*o*)], 6.90 [s, 1 H, Ar-H(*p*)], 9.63 (br, 1 H, NH). Anal. ($C_{17}H_{22}N_2O_3S_2$) C, H, N, S.

6-[(3,5-Dimethylphenyl)thio]-5-isopropyl-1-[(2-hydroxyethoxy)methyl]-2-thiouracil (52): yield 29%; mp 140–141 °C (hexane); UV (MeOH) λ_{max} 283 (ε 20000), 249 nm (ε 11000); MS m/z 380 (M^+); ^1H NMR ($CDCl_3$) δ 1.16 [d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 2.29 (s, 6 H, $SAr(Me)_2$), 3.45 [qq, J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 3.60–3.80 (m, 4 H, OCH_2CH_2O), 6.12 (s, 2 H, NCH_2O), 6.81 [s, 2 H, Ar-H(*o*)], 6.90 [s, 1 H, Ar-H(*p*)], 9.61 (br, 1 H, NH).

Anal. ($C_{18}H_{24}N_2O_3S_2$) C, H, N, S.

6-[(3,5-Dichlorophenyl)thio]-5-ethyl-1-[(2-hydroxyethoxy)methyl]-2-thiouracil (53): yield 36%; mp 91–93 °C (hexane); UV (MeOH) λ_{max} 282 (ϵ 21 000), 254 nm (ϵ 13 000); MS m/z 406, 408, 410 (M^+); ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.65 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.55–3.86 (m, 4 H, OCH_2CH_2O), 6.07 (s, 2 H, NCH_2O), 7.09 [d, J = 2.0 Hz, 2 H, Ar-H(*o*)], 7.27 [d, J = 2.0 Hz, 1 H, Ar-H(*p*)], 9.66 (br, 1 H, NH). Anal. ($C_{15}H_{16}Cl_2N_2O_3S_2$) C, H, N, S.

General Procedure for the Preparation of 5-Alkyl-6-(arylthio)-1-[(2-hydroxyethoxy)methyl]uracil Derivatives (54–59). To a suspension of the 2-thiouracil derivatives (10 mmol) in aqueous 1 N NaOH (80 mL) was added 35% H_2O_2 (6 mL, 60 mmol), and the mixture stirred at room temperature. After 1 h, the reaction mixture was neutralized with concentrated HCl. 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 crystallized from EtOAc–hexane to give the target compounds.

5-Ethyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)uracil (54): yield 88%; mp 117–120 °C; UV (MeOH) λ_{max} 275 (ϵ 8500), 243 nm (ϵ 9700); MS m/z 322 (M^+); ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.69 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.51–3.63 (m, 4 H, OCH_2CH_2O), 5.51 (s, 2 H, NCH_2O), 7.15–7.38 (m, 5 H, SPh), 8.51 (br, 1 H, NH). Anal. ($C_{15}H_{18}N_2O_4S \cdot {}^1/_5H_2O$) C, H, N, S.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-5-propyluracil (55): yield 84%; mp 118–119 °C; UV (MeOH) λ_{max} 276 (ϵ 9400), 243 nm (ϵ 11 000); MS m/z 336 (M^+); ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H, $CH_2CH_2CH_3$), 1.36–1.51 (m, 2 H, $CH_2CH_2CH_3$), 1.79 (br, 1 H, OH), 2.58–2.69 (m, 2 H, $CH_2CH_2CH_3$), 3.61 (s, 4 H, OCH_2CH_2O), 5.50 (s, 2 H, NCH_2O), 7.20–7.43 (m, 5 H, SPh), 8.24 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_4S$) C, H, N, S.

5-Isopropyl-1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)uracil (56): yield 65%; mp 85–87 °C; UV (MeOH) λ_{max} 274 (ϵ 8200), 245 nm (ϵ 9500); MS m/z 352 (M^+); ^1H NMR ($CDCl_3$) δ 1.19 [d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 1.62 (br, 1 H, OH), 3.45–3.69 [m, 5 H, $CH(CH_3)_2$, OCH_2CH_2O], 5.57 (s, 2 H, NCH_2O), 7.18–7.40 (m, 5 H, SPh), 8.37 (br, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_4S \cdot {}^1/_7H_2O$) C, H, N, S.

6-[(3,5-Dimethylphenyl)thio]-5-ethyl-1-[(2-hydroxyethoxy)methyl]uracil (57): yield 83%; mp 121–125 °C; UV (MeOH) λ_{max} 275 (ϵ 9500), 247 nm (ϵ 11 000); MS m/z 350 (M^+); ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 2.28 (s, 6 H, SArMe_2), 2.69 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 3.64 (m, 4 H, OCH_2CH_2O), 5.50 (s, 2 H, NCH_2O), 6.80 [s, 2 H, Ar-H(*o*)], 6.89 [s, 1 H, Ar-H(*p*)], 8.48 (br, 1 H, NH). Anal. ($C_{17}H_{22}N_2O_4S$) C, H, N, S.

6-[(3,5-Dimethylphenyl)thio]-5-isopropyl-1-[(2-hydroxyethoxy)methyl]uracil (58): yield 84%; mp 138–139 °C; UV (MeOH) λ_{max} 274 (ϵ 8500), 249 nm (ϵ 9900); MS m/z 364 (M^+); ^1H NMR ($CDCl_3$) δ 1.20 [d, J = 6.9 Hz, 6H, $CH(CH_3)_2$], 2.29 (s, 6 H, SArMe_2), 3.50 [qq, J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 3.66 (m, 4 H, OCH_2CH_2O), 5.56 (s, 2 H, NCH_2O), 6.81 [s, 2 H, Ar-H(*o*)], 6.89 [s, 1 H, ArhH(*p*)], 8.59 (br, 1 H, NH). Anal. ($C_{18}H_{24}N_2O_4S$) C, H, N, S.

6-[(3,5-Dichlorophenyl)thio]-5-ethyl-1-[(2-hydroxyethoxy)methyl]uracil (59): yield 40%; mp 93–95 °C; UV (MeOH) λ_{max} 272 (ϵ 9300), 252 nm (ϵ 12 000); MS m/z 390, 392, 394 (M^+); ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.66 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 3.64 (m, 4 H, OCH_2CH_2O), 5.51 (s, 2 H, NCH_2O), 7.08 [s, 2 H, Ar-H(*o*)], 7.26 [s, 1 H, Ar-H(*p*)], 8.45 (br, 1 H, NH). Anal. ($C_{15}H_{16}Cl_2N_2O_4S \cdot {}^1/_4H_2O$) C, H, N, S.

Antiviral Assay Procedures. HIV-1 ($HTLV\text{-}III_B$ strain) and HIV-2 ($LAV\text{-}2_{ROD}$ strain) were used in the anti-HIV assays. Virus stocks were titrated in MT-4 cells and expressed as 50% cell culture infective dose ($CCID_{50}$). The assays were based on the inhibition of virus-induced cytopathic effect in MT-4 cells as previously described.[24] Briefly, MT-4 cells were suspended in culture medium at 1 × 10^5 cells/mL and infected HIV at a multiplicity of infection (MOI, ratio of $CCID_{50}$ to cell number) of 0.02. 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. The test compounds were dissolved in dimethyl sulfoxide at 50 mM or higher. Solubility of each compound in culture medium was greater than its cytotoxic concentration. After a 4 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.[25]

The assay procedure for measuring the anti-HIV-1 activity of the compounds in peripheral blood lymphocytes (PBL) was based on the quantitative detection of HIV-1 p24 antigen in the culture supernatant using a sandwich ELISA kit (Abbott). Phytohemagglutinin-stimulated PBL (1 × 10^6 cells/mL) were infected with HIV-1 (HTLV-IIIB) at a MOI of 0.2 and cultured at 37 °C in the presence of various concentrations of the test compounds. On day 4 virus infection, the cells were subcultured at a ratio of 1:5 with fresh culture medium containing appropriate concentrations of the compounds. The assay was performed on day 7 after virus infection.

Cytotoxicity of the compounds was assessed in parallel with their antiviral activity. It was based on the viability of mock-infected MT-4 cells, as monitored by the MTT method[25] and the incorporation of [5-^{3}H]Urd into RNA of mock-infected PBL.

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