Synthesis and Anti-HIV Activity of Novel N-1 Side Chain-Modified Analogs of 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)

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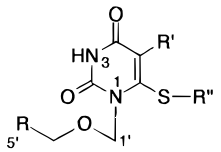
A series of 33 N-1 side chain-modified analogs of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (**1**, HEPT) were synthesized and evaluated for their anti-HIV-1 activity. In particular, the influence of substitution of the terminal hydroxy group of the acyclic structure of HEPT and the structural rigidity of this side chain were investigated. Halo (**7**, **8**), azido (**9**), and amino (**10**−**15**) derivatives were synthesized from HEPT *via* the *p*-tosylate derivative **6**. Acylation of the primary amine **15** afforded the amido analogs **16**−**20**. The diaryl derivatives **26**−**29** were prepared by reaction of HEPT, or of the 6-(2-pyridylthio) analog **23**, with diaryl disulfides in the presence of tri-*n*-butylphosphine. Compounds **39**−**41**, in which the N-1 side chain is rigidified by incorporation of an *E*-configured double bond, were obtained by palladium(0)-catalyzed coupling of several different 6-(arylthio)uracil derivatives (**37**, **38**) with allyl acetates **33**. Compounds **13**, **40a,c,d,f**, and **41**, incorporating an aromatic ring at the end of the acyclic side chain, were found to be more potent than the known diphenyl-substituted HEPT analog BPT (**2**), two of them, **40c,d**, being 10-fold more active.

Introduction

Inhibition of reverse transcriptase (RT), the human immunodeficiency virus (HIV)-encoded polymerase which directs both RNA and DNA dependent DNA synthesis, has proven to be one of the most effective ways to block the viral multiplication.[1,2] However, long term administration of the three major nucleoside-based RT inhibitors currently used in the clinic (AZT, ddI, and ddC)[3−5] leads to toxic side effects and the emergence of resistant viral strains.[6−8] Rapid development of drug resistant variants is also a major drawback to the use of a second class of structurally diverse non-nucleoside inhibitors (NNIs)[7−9] which interact with RT at a hydrophobic pocket which is proximal but distinct from the catalytic site of the enzyme.[10−13] Although these findings clearly point to the limitations of the monotherapeutic approach to the treatment of HIV infection, an increasing number of studies have demonstrated the effectiveness of the simultaneous administration of several nucleoside analogs along with different NNIs and/or a protease inhibitor.[9,14,15] Important to further elaboration of this combination strategy is the continued discovery of new reverse transcriptase inhibitors which can be employed together with available drugs and which do not select for cross-resistant mutant HIV-1 strains.[15]

As part of a program to develop new anti-HIV agents, acting specifically against RT, we have been particularly interested in examining the influence on activity of modifications of the side chain in the potent noncompetitive RT inhibitor 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT, **1**).[16] Despite the "apparent" nucleoside-like structure of this molecule, genetic analysis of drug resistant strains,[17,18] together with more recent molecular modeling and X-ray crystallographic studies,[13] has confirmed that it interacts with RT at the allosteric binding pocket common to all NNIs. A further important distinction between HEPT and the nucleoside-based inhibitors is the observation that phosphorylation is not an obligate step for its ability to block the function of RT. Indeed, replacement of the terminal hydroxymethyl group (Chart 1) in the side chain of HEPT by a hydrogen or, more interestingly, a phenyl group (**2** or BPT) results in an increase in activity.[19] Other structure−activity studies have established[20−25] that minor structural modifications can induce drastic differences in the biological activity of the HEPT system. Herein we describe the synthesis and the anti-HIV-1 activity of a new series of HEPT compounds, in which both the influence of substitution of the terminal hydroxy group (with and without 6-phenyl → 6-thiopyridyl exchange) and the more extensive alteration of the N-1 side chain have been examined.

Chart 1. HEPT Analogs



1 R = CH_2OH, R' = CH_3, R" = Ph HEPT

2 R = Ph, R' = CH_3, R" = Ph BPT

3 R = Ph, R' = C_2H_5, R" = Ph E-BPU

4 R = Ph, R' = C_2H_5, R" = (3,5-di-Me)Ph E-BPU-dM

5 R = Ph, R' = C_2H_5, R" = 2-Py E-BPTU

Chemistry

Halogenated HEPT analogs **7** and **8**, as well as the azide intermediate **9** (Scheme 1), were prepared by treatment of the tosylate **6** with NaR (R = Br, I, N_3) in

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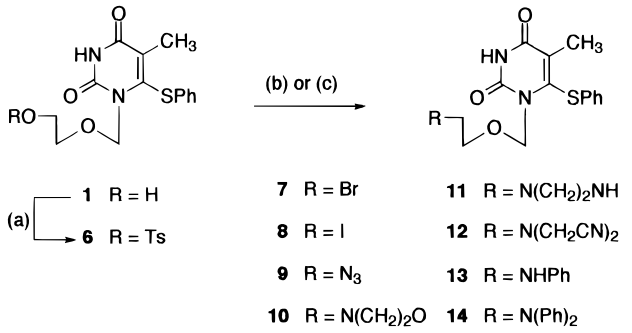
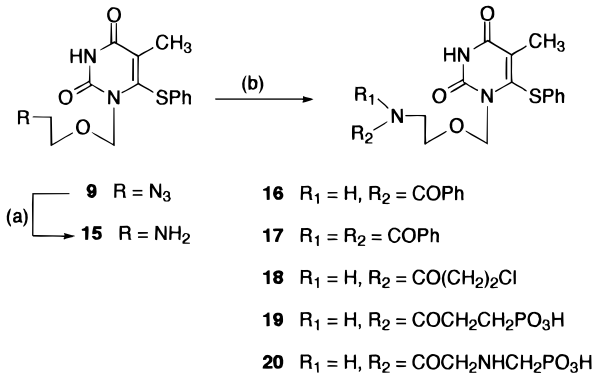
Scheme 1[a]



[a] Reagents: (a) TsCl, pyridine; (b) for **7**−**9**: NaR in acetone or DMF; (c) for **10**−**14**: RNH_2 or RR′-NH, pyridine.

Scheme 2[a]



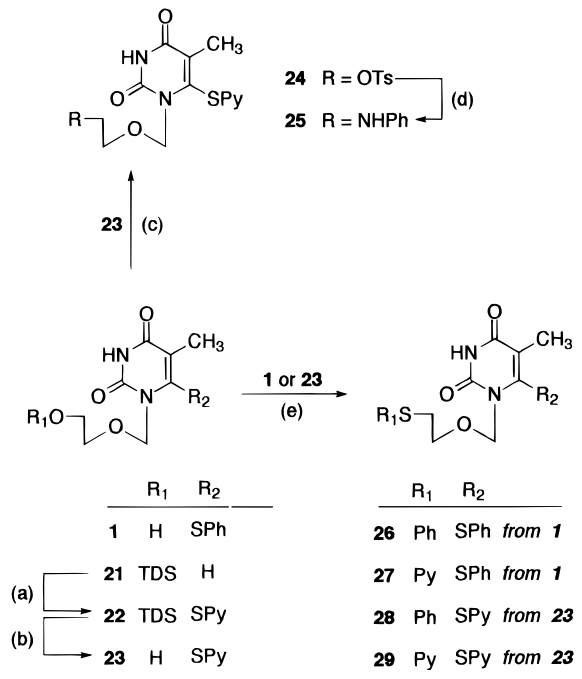
[a] Reagents: (a) H_2, 10% Pd/C, EtOH; (b) R_1R_2COCl, pyridine or THF.

acetone or DMF (80−85% yield from **1**).[26] In a similar manner, reaction of tosylate **6** with the appropriate amine derivatives gave analogs **10**−**14** in good yields. To obtain primary amine **15**, the azido compound **9** was hydrogenated, and in a subsequent operation, **15** was converted to compounds **16**−**20** by reaction with the required acyl chloride (Scheme 2). Note that both the mono- and diacylated derivatives **16** and **17** (6.5:1, 84% overall yield) were formed when **15** was treated with a large excess of benzoyl chloride in pyridine.

For the synthesis of the phenylthio and (2-pyridyl)thio derivatives **26** and **27** (Scheme 3), the hydroxy group in **1** was substituted directly using the corresponding diaryl disulfide in the presence of tri-*n*-butylphosphine (91−94% yield).[27] Taking into consideration the interesting activity profile[23,28] of the BPT analog **5** in which the phenylthio component has been exchanged by a (2-pyridyl)thio group, the diaryl analogs **25**, **28**, and **29** were constructed (Scheme 3). For compounds **28** and **29**, this was achieved by reaction of lithiated **21** with 2,2′-dipyridyl disulfide, removal of the silyl ether protecting group in the derived intermediate **22** using Bu_4NF in THF, and reaction of the liberated alcohol function in **23** with diphenyl and 2,2′-dipyridyl disulfides and tri-*n*-butylphosphine (81% and 78% yields, respectively, from **21**). For anilino compound **25**, the route involving tosylate displacement proved efficient (60% yield from **21**).

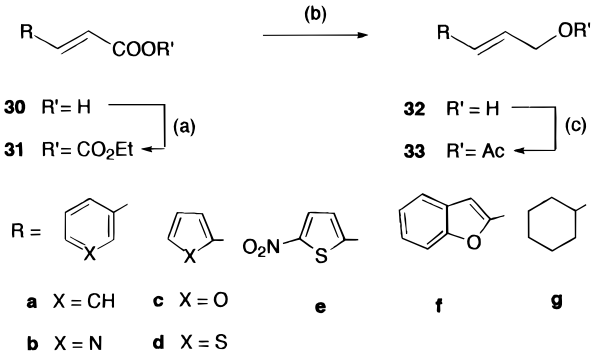
In the search for analogs which are both more active and selective than HEPT itself, the synthesis of compounds **39**−**41** (Scheme 6), in which the N-1 side chain is rigidified by incorporation of an *E*-configured double bond, was also undertaken. These new analogs were obtained by palladium(0)-catalyzed coupling of several

Scheme 3[a]



[a] Reagents: (a) LDA, THF, −78 °C then 2,2′-dipyridyl disulfide; (b) Bu_4NF, THF; (c) TsCl, pyridine; (d) $PhNH_2$, pyridine, 80 °C; (e) diaryl disulfide, *n*-Bu_3P, THF, reflux.

Scheme 4[a]



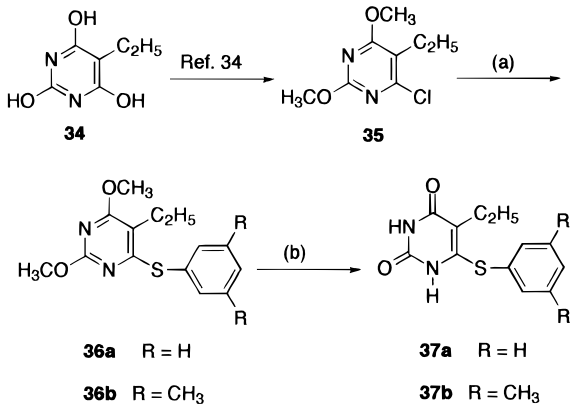
[a] Reagents: (a) ref 29, $ClCO_2Et$, Et_3N, THF, −10 °C; (b) ref 29, $NaBH_4$, THF then MeOH; (c) Ac_2O, CH_2Cl_2, pyridine.

different 6-(arylthio)uracil derivatives with the 3-substituted allyl acetates **33a**−**g**. The (*E*)-allyl acetate **33a** was obtained by acetylation of cinnamic alcohol, whereas compounds **33b**−**g** (Scheme 4) were prepared[29] by $NaBH_4$ reduction of the mixed anhydrides **31** generated from the *E*-3-substituted acrylic acids **30** followed by reaction of the derived alcohols with acetic anhydride (21−88% overall yields).[30]

Concerning the pyrimidine base components in compounds **39**−**41**, 6-(phenylthio)thymine[32] **38** was obtained by cleavage of the *N*-(benzyloxy)methyl group in the readily available HEPT analog **2** using boron trichloride.[33] To prepare the 5-ethyluracil analogs **37a,b**, 5-ethylbarbituric acid (**34**) was converted[34] to the 6-chloropyrimidine **35**, which in turn was treated with thiophenol or 3,5-dimethylthiophenol in refluxing pyridine to give the mercaptides **36a,b**. *O*-Demethylation[35] (TMSCl, NaI) of these intermediates provided 5,6-disubstituted uracils **37a,b** in 40−45% overall yields (Scheme 5).

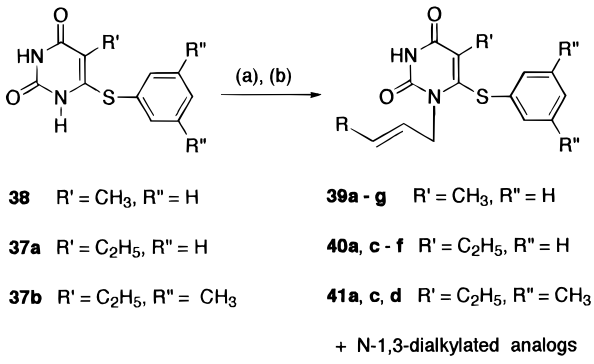
Pd(0)-catalyzed reactions [$Pd(PPh_3)_4$, PPh_3, THF, 60 °C][36] of acetates **33** with the *O*,*O*-bis-silylated deriva-

Scheme 5[a]



[a] Reagents: (a) ArSH, pyridine, 120 °C; (b) TMSCl, NaI, CH_3CN.

Scheme 6[a,b]



[a] Reagents: (a) HMDS, pyridine, 120 °C; (b) **33**, $Pd(PPh_3)_4$, PPh_3, THF, 60 °C. [b] R of **33**: see Scheme 4.

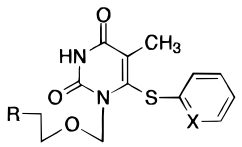
tives of the pyrimidine bases **37a,b** and **38** afforded (Scheme 6) the desired N-1 allyl uracil derivatives **39**−**41** in moderate yields (25−50%), along with the N-1,3-dialkylated analogs (15−25%).[37] Formation of the N-1 coupling products was easily confirmed by the absence of a bathochromic shift in the UV spectra of these products in alkaline medium.[40−42]

Results of the Anti-HIV Assay and Discussion

The complete series of compounds **7**, **8**, **10**−**20**, **25**−**29**, **39a**−**f**, **40a,c**−**f**, and **41a,c,d** was evaluated for their inhibitory effects on the replication of HIV-1 in two human T-4 lymphoblastoid cell lines, CEM-SS and MT-4 (Tables 1 and 2). As the data show, all active compounds proved to be more potent in the CEM model system, although the relative trend in activities, with respect to HEPT, remained essentially the same, independent of the two cell lines considered. Cytotoxicity was not observed in either cell line at concentrations equal to or below 1 μM. For these reasons, the discussion will exclusively deal with results obtained in the CEM cell system. All compounds were also tested on a Nevirapine resistant strain (Tyr 181 → Cys) but were found to be inactive.

From the IC_{50} values determined for compounds **7** and **8**, it can be seen that replacement of the terminal hydroxy group by bromine or iodine atom does not significantly alter the activity profile of HEPT.[43] However, substitution by a NH_2 group (**15**), which in many respects is nearly equal in polarity, results in a sharp drop in activity. A comparable loss in inhibitory power was also observed for tertiary amines **10**−**12** and **14**.

Table 1. Anti-HIV-1 Activity of Novel HEPT Analogs (Compounds **7**−**29**)[a]



	substituent		IC_{50} (μM)[b]	
compd	X	R	CEM-SS/ LAI[c]	MT-4/ III B[c]
7	CH	Br	0.76	2.8
8	CH	I	2.2	>10
10	CH	morpholino	>100	>100
11	CH	piperazinyl	>10	>10
12	CH	$N(CH_2CN)_2$	27.5	>100
13	CH	NHPh	0.055	1.0
14	CH	$N(Ph)_2$	8.75	>10
15	CH	NH_2	31	
16	CH	NHCOPh	>10	>10
17	CH	$N(COPh)_2$	>1	>1
18	CH	$NHCO(CH_2)_2Cl$	11.4	40
19	CH	$NHCO(CH_2)_2PO_3H$	>10	>10
20	CH	$NHCOCH_2NHCH_2PO_3H$	>100	>100
26	CH	SPh	>1	
27	CH	SPy	0.83	>1
25	N	NHPh	0.16	1.6
28	N	SPh	1	>1
29	N	SPy	0.44	8.0
HEPT			2	11
AZT			0.002	0.02
BPT			0.09	0.74

[a] All data represent mean values for at least two separate experiments. [b] Effective concentration of compound required to achieve 50% inhibition of HIV-1 multiplication in CEM-SS- or MT-4-infected cells. The symbol (>) indicates that the IC_{50} was not reached at the highest concentration tested. For IC_{50} > 1 higher concentrations could not be achieved due to low solubility. [c] See the Experimental Section for description of assay. CC_{50}s for all compounds were >1 μM.

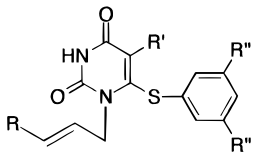
The amide derivatives **18**−**20**, bearing an additional functionality which could conceivably interact with the NNI binding pocket of RT, also exhibited minimal inhibitory capacity.

In contrast to these results is the positive effect observed upon replacement of the amine hydrogen in **15** by a phenyl ring. Indeed, the anilino analog **13** (IC_{50} = 0.055 μM) is 35-fold more potent than HEPT and 1.5 times more active than the related compound BPT (**2**). However, the diphenylamino analog **14** and benzamide **16** displayed diminished activity. Considering next the replacement of the hydroxy function by a less polar thioaryl substituent, no corresponding activity enhancement was observed for compounds **26** and **27**. Nevertheless, compound **27** (IC_{50} = 0.83 μM), bearing a (2-pyridyl)thio group, is 2.5 times more potent than HEPT.

Substitution of the 6-phenylthio moiety in **13**, **26**, and **27** by a (2-pyridyl)thio group to give compounds **25**, **28**, and **29** was observed to produce only small changes in activity. However, although compound **29** (IC_{50} = 0.44 μM), in which such a group is present both on the pyrimidine moiety and on the acyclic portion, remains approximatively 5 times more active than HEPT, this molecule and the anilino analog **25** (IC_{50} = 0.16 μM) are much less potent than NSC 648400 (**5**) (which, in the CEM-SS/HIV III B cell line, inhibits RT at nanomolar concentrations).[28]

As an important difference between the aryl-substituted HEPT analogs **13**, **26**, and **27** and BPT (**2**) or E-BPU (**3**) is the nature of the C-5 substituent on the

Table 2. Anti-HIV-1 Activity of Allylic Compounds **39**−**41**[a]



compd	substituent R	R′	R″	IC_{50} (μM)[b] CEM-SS/ LAI[c]	MT-4/ III B[c]
39a	phenyl	CH_3	H	0.23	2.5
40a	phenyl	C_2H_5	H	0.016	0.19
41a	phenyl	C_2H_5	CH_3	0.031	0.039
39g	cyclohexyl	CH_3	H	>1	>1
39b	3-pyridyl	CH_3	H	0.15	0.1
39c	2-furyl	CH_3	H	0.33	>1
40c	2-furyl	C_2H_5	H	0.008	0.17
41c	2-furyl	C_2H_5	CH_3	0.01	0.04
39d	2-thienyl	CH_3	H	0.14	>1
40d	2-thienyl	C_2H_5	H	0.008	0.08
41d	2-thienyl	C_2H_5	CH_3	0.028	0.040
39e	5-nitro-2-thienyl	CH_3	H	>1	>1
40e	5-nitro-2-thienyl	C_2H_5	H	0.94	>1
39f	2-benzofuranyl	CH_3	H	>1	>1
40f	2-benzofuranyl	C_2H_5	H	0.038	>1
AZT				0.002	0.02
HEPT				2	11
BPT				0.09	0.74
BPT					0.088[d]
E-BPU					0.0059[d]
E-BPU-dM					0.0032[d]

[a−c] See corresponding footnotes in Table 1. [d] See ref 32.

pyrimidine base, and/or the length of the N-1 lateral side chain, the compounds **39a**−**f** (R′ = CH_3) and **40a,c**−**f** (R′ = C_2H_5) were evaluated for their capacity to block HIV-1 replication. In all these molecules, N-1 is separated from the terminal phenyl or heteroaromatic ring by a three-atom chain.[32] Nevertheless, unlike **2** and **3**, this side chain is rigidified by the presence of an *E*-olefinic double bond which is vinylic to the aromatic ring and allylic with respect to N-1 of the pyrimidine nucleus.

Compared to BPT (**2**), the rigidified analogs **39a**−**d** are less active ($IC_{50} \geq 0.14$ μM), whereas for compounds **39e**−**g**, the IC_{50} was not reached at the highest concentration tested. Compounds **40**, with the exception of **40e**, are all more potent than their thymine analogs **39**, this 14−41-fold increase in activity being a consequence of the replacement of the C-5 methyl group in compounds **39** by an ethyl side chain[44] [E-BPU (**3**) is 14-fold more active than BPT (**2**)].[32] It should also be noticed that, as in our experimental conditions involving infected CEM-SS cells, the IC_{50} of BPT is similar to the literature value,[32] and therefore we concluded that compounds **40c,d** are equipotent to E-BPU.

Unlike previous data reported in the HEPT series,[32] introduction of the two methyl groups in the phenylthio moiety does not potentiate the antiviral activity. Thus, compounds **41a,c,d** are less active than their unsubstituted parents **40a,c**,**d**; nevertheless, the furyl analog **41c** is 200 times more potent than HEPT itself. Concerning the N-1,3-dialkylated derivatives, all were found to be inactive ($EC_{50} > 1$ μM), which confirms that the presence of a hydrogen at the N-3 position seems to be essential for these compounds to exert activity.[24,45,46]

In conclusion, compounds **13**, **40a,c,d,f**, and **41** bearing an aromatic ring at the end of the N-1 side chain were, in our study, more potent than BPT (**2**).[47] The most active derivatives (**40c,d** and **41c**) contain a hitherto unreported 3-arylallyl moiety. Both molecular modeling to determine the orientation of the most potent molecules in our series with the hydrophobic pocket in RT and quantitative structure−activity relationship (QSAR) studies to optimize the RT inhibition properties of HEPT have been undertaken, and the results will be reported elsewhere.

Experimental Section

Melting points were determined using an Electrothermal apparatus and are uncorrected. UV spectra were determined on a Varian-Cary/3E spectrophotometer. IR spectra were obtained with a Perkin-Elmer 1710 spectrophotometer. ^{1}H NMR spectra were recorded in the given solvent with a Bruker AC-250 spectrometer. Chemical shifts are reported as δ values in parts per million. The splitting pattern abbreviations are as follows: s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, br = broad, m = multiplet. Chemical ionization (CI) mass spectra were recorded on a Nermag R 10,10C spectrometer. Elemental analyses, performed by the Service de Microanalyse du CNRS (Vernaison-Lyon, France), were within 0.4% of the theoretical values calculated for C, H, and N. The thin-layer chromatographic analyses were performed using precoated silica gel ($60F_{254}$) plates, and the spots were examined with UV light and phosphomolybdic acid spray. Column chromatography was carried out on Merck silica gel (230−240 mesh). Extraction in the usual manner refers to washing the organic layer with water, drying it over $MgSO_4$, and evaporating the solvent under reduced pressure. The syntheses of HEPT (**1**) and BPT (**2**) were performed according to the published procedures.[16,19,32,48] Some substituted (*E*)-acrylic acids (**30b,e**−**g**) were prepared by reaction of malonic acid with appropriate aldehydes.[49]

6-(Phenylthio)-1-[[2-(tosyloxy)ethoxy]methyl]thymine (6). A solution of **1** (308 mg, 1 mmol) and TsCl (380 mg, 2 mmol) in pyridine (15 mL) was stirred at room temperature for 16 h. After evaporation under reduced pressure, the residue was flash chromatographed on silica gel (cyclohexane/EtOAc: 3/7). Compound **6** was obtained as a colorless solid (430 mg, 93%): mp (ether) 156−158 °C; IR ($CHCl_3$) ν 3382, 1715, 1680, 1443 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3), 2.43 (s, 3H, Ts-*CH*$_3$), 3.77 (m, 2H, O*CH*$_2$CH$_2$OTs), 4.05 (m, 2H, CH_2OTs), 5.52 (s, 2H, OCH_2N), 7.19 [d, 2H, J = 8 Hz, 2 × Ts-H(*m*)], 7.20−7.35 (m, 5H, SPh), 7.75 [d, 2H, J = 8 Hz, 2 × Ts-H(*o*)], 9.05 (br s, 1H, NH); MS (CI-NH_3) m/z 480 (M + NH_4)$^+$, 463 (M + H)$^+$, 234 (B), 215. Anal. ($C_{21}H_{22}N_2O_6S_2$) C, H, N.

1-[(2-Bromoethoxy)methyl]-6-(phenylthio)thymine (7). To a solution of tosyl derivative **6** (400 mg, 0.86 mmol) in acetone/DMF (20 mL, 5/1) was added NaBr (180 mg, 1.75 mmol), and the mixture was stirred at room temperature for 16 h and then heated under reflux for 30 min. The mixture was filtered and extracted with EtOAc in the usual manner to give a white solid which was recrystallized from ether (296 mg, 92%): mp 130−132 °C; IR ($CHCl_3$) ν 3387, 1710, 1685, 1442 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H, CH_3), 3.36 (t, 2H, J = 6 Hz, CH_2Br), 3.89 (t, 2H, J = 6 Hz, O*CH*$_2$CH$_2$Br), 5.62 (s, 2H, OCH_2N), 7.20−7.35 (m, 5H, SPh), 9.50 (br s, 1H, NH); MS (CI-NH_3) m/z 373 and 371 (M + H)$^+$. Anal. ($C_{14}H_{15}BrN_2O_3S$) C, H, N.

1-[(2-Iodoethoxy)methyl]-6-(phenylthio)thymine (8). A solution of **6** (500 mg, 1.08 mmol) and sodium iodide (325 mg, 2.16 mmol) in anhydrous acetone (20 mL) was heated under reflux for 2 h. The mixture was filtered, extracted with EtOAc in the usual manner, and then flash chromatographed on silica gel (cyclohexane/EtOAc: 3/2) to give 454 mg of **8** (92%): mp (ether) 118−120 °C; IR ($CHCl_3$) ν 3384, 2957, 1710, 1685, 1425 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H, CH_3), 3.14 (t, 2H, J = 6.5 Hz, CH_2I), 3.82 (t, 2H, J = 6.5 Hz, O*CH*$_2$CH$_2$I), 5.61 (s, 2H, OCH_2N), 7.20−7.35 (m, 5H, SPh), 9.40 (br s, 1H, NH); MS (CI-NH_3) m/z 419 (M + H)$^+$. Anal. ($C_{14}H_{15}IN_2O_3S$) C, H, N.

1-[(2-Azidoethoxy)methyl]-6-(phenylthio)thymine (9). A solution of tosyl derivative **6** (230 mg, 0.5 mmol) and NaI

(65 mg, 1 mmol) in anhydrous DMF (10 mL) was heated at 80 °C for 2 h. After cooling to room temperature, the crude mixture was poured into ice water (60 mL), and the precipitate was collected and washed with water and then ether to give, after drying, compound **9** (142 mg, 85%): mp (ether) 95−96 °C (lit.[19] mp 91−92 °C, EtOH−H_2O); IR ($CHCl_3$) ν 3387, 2105, 1720, 1684, 1442 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H, CH_3), 3.51 (t, 2H, J = 6 Hz, CH_2N_3), 3.83 (t, 2H, J = 6 Hz, O$CH_2CH_2N_3$), 5.62 (s, 2H, OCH_2N), 7.20−7.30 (m, 5H, SPh), 9.75 (br s, 1H, NH); MS (DCI/NH_3) m/z 351 $(M + NH_4)^+$, 334 $(M + H)^+$. Anal. ($C_{14}H_{15}N_5O_3S$) C, H, N.

General Procedure for the Preparation of Amino Compounds 10−14. To a stirred solution of tosyl derivative **6** (1.5 mmol) in pyridine (20 mL) was added an excess of the appropriate amine (3−8 mmol). After 24 h, the pyridine was removed by evaporation under reduced pressure, and the residue was extracted with EtOAc in the usual manner.

1-[(2-Morpholinoethoxy)methyl]-6-(phenylthio)thymine (10). Compound **10** was isolated (78% yield) from the reaction of **6** with morpholine (6 mmol) after flash chromatography (CH_2Cl_2/MeOH: 95/5): mp (ether) 144−146 °C; IR ($CHCl_3$) ν 3394, 2956, 1710, 1684, 1426 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3), 2.51 (m, 6H, 3 × OCH_2CH_2N), 3.69 (m, 6H, 3 × OCH_2CH_2N), 5.56 (s, 2H, OCH_2N), 7.20−7.35 (m, 5H, SPh), 9.65 (br s, 1H, NH); MS (CI-NH_3) m/z 378 $(M + H)^+$. Anal. ($C_{18}H_{23}N_3O_4S$) C, H, N.

6-(Phenylthio)-1-[(2-piperazinylethoxy)methyl]thymine (11). Compound **11** was isolated (63% yield) from the reaction of **6** with piperazine (6 mmol) after flash chromatography (EtOAc/cyclohexane: 3/2): mp (MeOH/CH_2Cl_2) 214−216 °C; IR ($CHCl_3$) ν 3500−2800, 1715, 1680, 1635, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 1H, NH), 1.99 (s, 3H, CH_3), 2.60−3.80 (m, 12H, 6 × CH_2), 5.53 (s, 2H, OCH_2N), 7.15−7.35 (m, 5H, SPh); MS (CI-NH_3) m/z 377 $(M + H)^+$, 235 $(B + H)^+$. Anal. ($C_{18}H_{24}N_4O_3S$) C, H, N.

1-[[2-[Bis(cyanomethyl)amino]ethoxy]methyl]-6-(phenylthio)thymine (12). Compound **12** was isolated (58% yield) from the reaction of **6** with iminodiacetonitrile (3 mmol) after flash chromatography (EtOAc/cyclohexane: 3/2): mp (CH_2Cl_2/ether) 77 °C hygroscopic; IR ($CHCl_3$) ν 3387, 3071, 2285, 2257, 1720, 1680, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3), 3.52 (t, 2H, J = 6 Hz, OCH_2CH_2N), 3.74 (s, 4H, 2 × CH_2CN), 3.84 (t, 2H, J = 6 Hz, OCH_2CH_2N), 5.60 (s, 2H, OCH_2N), 7.20−7.35 (m, 5H, SPh), 9.70 (br s, 1H, NH); MS (CI-NH_3) m/z 386 $(M + H)^+$, 385.

1-[(2-Anilinoethoxy)methyl]-6-(phenylthio)thymine (13). Compound **13** was isolated (83% yield) from the reaction of **6** with aniline (6 mmol) after flash chromatography (EtOAc/cyclohexane: 1/1): mp (ether) 138 °C; IR ($CHCl_3$) ν 3389, 2956, 1710, 1685, 1604, 1442 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3), 3.23 (m, 2H, OCH_2CH_2N), 3.76 (t, 2H, J = 6.5 Hz, OCH_2CH_2N), 3.88 (br s, 1H, *NH*Ph), 5.55 (s, 2H, OCH_2N), 7.10−7.35 (m, 10H, 2 × Ph), 8.45 (br s, 1H, NH); MS (CI-NH_3) m/z 384 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3O_3S$) C, H, N.

1-[[2-(Diphenylamino)ethoxy]methyl]-6-(phenylthio)-thymine (14). Compound **14** was isolated as an oil (76% yield) from the reaction of **6** with diphenylamine (3 mmol) and after flash chromatography (EtOAc/cyclohexane: 1/1): IR ($CHCl_3$) ν 3425, 3380, 1712, 1680, 1587, 1487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3), 3.87 (m, 2H, OCH_2CH_2N), 4.15 (m, 2H, OCH_2CH_2N), 5.42 (s, 2H, OCH_2N), 7.10−7.63 (m, 15H, 3 × Ph), 9.35 (br s, 1H, NH); MS (CI-NH_3) m/z 460 $(M + H)^+$. Anal. ($C_{26}H_{25}N_3O_3S$) C, H, N.

1-[(2-Aminoethoxy)methyl]-6-(phenylthio)thymine (15). Azide derivative **9** (1 g, 3 mmol) in EtOH (25 mL) containing 10% Pd/C (150 mg) was stirred for 18 h under a hydrogen atmosphere (1 atm). The mixture was then filtered through a Celite pad, and the residue obtained after evaporation of the filtrate was flash chromatographed (CH_2Cl_2/MeOH: 95/5). Compound **15** was isolated as a colorless solid (746 mg, 81%): mp (MeOH) 125−127 °C; IR ($CHCl_3$) ν 3388, 2945, 1714, 1680, 1581, 1447 cm^{-1}; ^1H NMR (CD_3OD) δ 2.05 (s, 3H, CH_3), 2.73 (t, 2H, J = 5 Hz, CH_2NH_2), 3.56 (t, 2H, J = 5 Hz, O$CH_2CH_2NH_2$), 3.80 (br s, H exch), 5.55 (s, 2H, OCH_2N), 7.20−7.35 (m, 5H, SPh); MS (CI-NH_3) m/z 308 $(M + H)^+$. Anal. ($C_{14}H_{17}N_3O_3S$) C, H, N.

1-[(2-Benzamidoethoxy)methyl]-6-(phenylthio)thymine (16) and 1-[[2-(Dibenzoylamino)ethoxy]methyl]-6-(phenylthio)thymine (17). Benzoyl chloride (0.5 mL, 4.3 mmol) was added to a solution of **15** (120 mg, 0.39 mmol) in anhydrous pyridine (5 mL), and the mixture was stirred at room temperature for 20 min. The pyridine was evaporated, and the residue was flash chromatographed (EtOAc/cyclohexane: 4/1) to afford successively **17** (26 mg, 13%) and **16** (114 mg, 71%).

Compound 16: mp (ether) 112−114 °C; IR ($CHCl_3$) ν 3390, 3064, 2930, 1710, 1685, 1523, 1451 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H, CH_3), 3.59 (m, 2H, OCH_2CH_2N), 3.72 (m, 2H, OCH_2CH_2N), 5.56 (s, 2H, OCH_2N), 6.65 (br s, 1H, NHCO), 7.15−7.30 (m, 5H, Ph), 7.35−7.45 (m, 3H, Ph), 7.76 (d, 2H, J = 7 Hz, Ph), 9.50 (br s, 1H, NH); MS (CI-NH_3) m/z 429 $(M + NH_4)^+$, 412 $(M + H)^+$, 235 $(B + H)^+$, 178. Anal. ($C_{21}H_{21}N_3O_4S$) C, H, N.

Compound 17: mp (ether) 74−76 °C; IR ($CHCl_3$) ν 3687, 3468, 2930, 1755, 1710, 1655, 1523, 1416 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, CH_3), 3.58 (m, 2H, OCH_2CH_2N), 3.71 (m, 2H, OCH_2CH_2N), 5.58 (s, 2H, OCH_2N), 7.15−7.55 (m, 11H, Ph), 7.75 (d, 2H, J = 7.5 Hz, Ph), 7.93 (d, 2H, J = 7.5 Hz, Ph), 9.60 (br s, 1H, NH); MS (CI-NH_3) m/z 516 $(M + H)^+$, 178. Anal. ($C_{28}H_{25}N_3O_5S$) C, H, N.

General Procedure for the Preparation of Acetamido Derivatives 18−20. To a solution of the amine **15** (1 mmol) in anhydrous THF (20 mL) was added the appropriate acid chloride (1.2 mmol) dissolved in anhydrous THF (10 mL). The mixture was stirred at room temperature for 16 h and under reflux for 1−4 h (until starting material disappeared). The crude mixture was poured into 6 N aqueous NaOH (20 mL) and stirred for an additional 2−3 h. Neutralization with 6 N aqueous HCl followed by extraction with EtOAc in the usual manner afforded the title compounds.

1-[[2-(3-Chloropropionamido)ethoxy]methyl]-6-(phenylthio)thymine (18). Compound **18** was isolated (73% yield) from the reaction of **15** with 3-chloropropionyl chloride after flash chromatography (CH_2Cl_2/MeOH: 9/1): mp (MeOH) 166−168 °C; IR (KBr) ν 3318, 3005, 1708, 1669, 1642, 1458 cm^{-1}; ^1H NMR δ ($CDCl_3$) δ 2.07 (s, 3H, CH_3), 2.58 (t, 2H, J = 6 Hz, $COCH_2$), 3.42 (m, 2H, OCH_2CH_2N), 3.62 (t, 2H, J = 5 Hz, OCH_2CH_2N), 3.78 (t, 2H, J = 6 Hz, CH_2Cl), 5.53 (s, 2H, OCH_2N), 6.05 (br s, 1H, NHCO), 7.20−7.35 (m, 5H, SPh), 8.95 (br s, 1H, NH); MS (CI-NH_3) m/z 417 and 415 $(M + NH_4)^+$, 400 and 398 $(M + H)^+$, 235 $(B + H)^+$, 166 and 164. Anal. ($C_{17}H_{20}ClN_3O_4S$) C, H, N.

6-(Phenylthio)-1-[[2-(3-phosphonopropionamido)-ethoxy]methyl]thymine (19). Compound **19** was obtained (25%) from **15** and 3-phosphonopropionyl chloride [prepared *in situ*, by treating the corresponding acid (1.5 mmol) with $SOCl_2$ (1.2 mmol) in THF (15 mL)] at room temperature for 1 h and under reflux for 30 min. Purification by flash chromatography (CH_2Cl_2/MeOH: 9/1) led to **15** as a syrup: IR (KBr) ν 3300−2600, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.84 (s, 3H, CH_3), 2.51 (m, 2H, CH_2P), 3.10−3.50 (m, 7H, CH_2CO, CH_2N + H exch), 3.75 (m, 2H, OCH_2CH_2N), 5.41 (s, 2H, OCH_2N), 7.25−7.35 (m, 5H, SPh), 8.05 (br s, 1H, NH); MS (CI-NH_3) m/z 461 $(M + NH_4)^+$. Anal. ($C_{17}H_{22}N_3O_7PS$) C, H, N.

6-(Phenylthio)-1-[[2-[[*N*-(phosphonomethyl)glycyl]amino]ethoxy]methyl]thymine (20). Compound **20** was obtained (29%) from **15** and the acid chloride prepared from *N*-(phosphonomethyl)glycine as described in the preparation of **19**. Purification by flash chromatography (CH_2Cl_2/MeOH: 9/1) gave **20** as a syrup: IR (KBr) ν 3368, 3193, 2931, 2856, 1712, 1687, 1450 cm^{-1}; ^1H NMR (D_2O) δ 1.89 (s, 3H, CH_3), 2.40−2.70 (m, 2H, CH_2P), 3.10−3.50 (m, 4H, 2 × CH_2NH), 3.65−3.90 (m, OCH_2CH_2N + H exch), 5.45 (s, 2H, OCH_2N), 7.25−7.35 (m, 5H, SPh); MS (CI-NH_3) m/z 476 $(M + NH_4)^+$. Anal. ($C_{17}H_{23}N_4O_7PS$) C, H, N.

1-[[2-[(Dimethylthexylsilyl)oxy]ethoxy]methyl]thymine (21). A mixture of 1-[(2-hydroxyethoxy)methyl]thymidine[16] (2.0 g, 10 mmol), imidazole (820 mg, 12 mmol), and dimethylthexylsilyl (TDS) chloride (2.15 g, 12 mmol) in DMF (50 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into H_2O and the precipitate filtered. The resulting solid was dissolved in CH_2Cl_2, washed with saturated

aqueous $NaHCO_3$, treated in the usual manner, and then crystallized from ether to give **21** (3.25 g, 95%): mp 73−75 °C; IR ($CHCl_3$) ν 3399, 2960, 1710, 1685, 1466 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 [s, 6H, Si*(CH$_3$)$_2$*], 0.74 [s, 6H, C*(CH$_3$)$_2$*], 0.77 [d, 6H, J = 7 Hz, CH*(CH$_3$)$_2$*], 1.51 [m, 1H, *CH*(CH_3)$_2$], 1.85 (s, 3H, CH_3), 3.53 and 3.65 (2 × m, 4H, OCH_2CH_2O), 5.09 (s, 2 H, OCH_2N), 7.07 (s, 1H, H-6), 8.90 (br s, 1H, NH); MS (CI-NH_3) m/z 360 $(M + NH_4)^+$. Anal. ($C_{16}H_{30}N_2O_4Si$) C, H, N.

1-[[2-[(Dimethylthexylsilyl)oxy]ethoxy]methyl]-6-(2-pyridylthio)thymine (22). Following the method of Pan *et al.*[23] compound **21** (1.0 g, 2.9 mmol) was lithiated with lithium diisopropylamide (LDA) at −78 °C (2.5 equiv) and then treated with 2,2′-dipyridyl disulfide (1.3 g, 5.9 mmol). Flash chromatography (cyclohexane/EtOAc: 1/1) gave **22** (1.2 g, 91%): mp (ether) 83−84 °C; IR ($CHCl_3$) ν 3396, 2959, 1710, 1680, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 [s, 6H, Si*(CH$_3$)$_2$*], 0.74 [s, 6H, C*(CH$_3$)$_2$*], 0.80 [d, 6H, J = 7 Hz, CH*(CH$_3$)$_2$*], 1.51 [m, 1H, *CH*(CH_3)$_2$], 1.98 (s, 3H, CH_3), 3.57 (s, 4H, CH_2CH_2), 5.50 (s, 2H, OCH_2N), 7.05 [m, 1H, SPy-H(5)], 7.14 [d, 1H, J = 9 Hz, SPy-H(3)], 7.54 [dt, 1H, J = 2, 9 Hz, SPy-H(4)], 8.33 [m, 1H, SPy-H(6)], 8.95 (br s, 1H, NH); MS (CI-NH_3) m/z 452 $(M + H)^+$, 112. Anal. ($C_{21}H_{33}N_3O_4SSi$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(2-pyridylthio)thymine (23). A solution of **22** (600 mg, 1.33 mmol) and Bu_4NF (1.0 M solution in THF, 2.7 mL) in THF (10 mL) was stirred at room temperature for 16 h. After removal of the solvent under reduced pressure, the residue was flash chromatographed (CH_2Cl_2/MeOH: 95/5) to give **23** (365 mg, 96%): mp (MeOH) 128−130 °C; IR (KBr) ν 3400−2800, 1700, 1674, 1419 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H, CH_3), 2.95 (br s, 1H, OH), 3.59 (m, 2H, *CH*$_2$OH), 3.72 (m, 2H, *CH*$_2$$CH_2$OH), 5.61 (s, 2H, OCH_2N), 7.14 [m, 1H, SPy-H(5)], 7.26 [m, 1H, SPy-H(3)], 7.63 [dt, J = 2, 8.5 Hz, 1H, SPy-H(4)], 8.40 [m, 1H, SPy-H(6)], 9.35 (br s, 1H, NH); MS (CI-NH_3) m/z 310 $(M + H)^+$. Anal. ($C_{13}H_{15}N_3O_4S$) C, H, N.

6-(2-Pyridylthio)-1-[[2-(tosyloxy)ethoxy]methyl]thymine (24). Tosylation of **23** (525 mg, 1.7 mmol), as described for compound **6**, afforded **24** (715 mg, 91%): mp (ether) 130−131 °C; IR ($CHCl_3$) ν 3375, 1715, 1686, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H, CH_3), 2.44 (s, 3H, Ts-*CH*$_3$), 3.76 (t, 2H, J = 5 Hz, O*CH*$_2$$CH_2$OTs), 4.02 (t, 2H, J = 5 Hz, *CH*$_2$OTs), 5.48 (s, 2H, OCH_2N), 7.11 [m, 1H, SPy-H(5)], 7.26 [m, 1H, SPy-H(3)], 7.32 [d, 2H, J = 8.5 Hz, Ts-H(*m*)], 7.62 [dt, 1H, J = 2, 9 Hz, SPy-H(4)], 7.74 (d, 2H, J = 8.5 Hz, Ts-H(*o*)], 8.39 [m, 1H, SPy-H(6)], 8.90 (br s, 1H, NH); MS (CI-iC_4H_{10}) m/z 464 $(M + H)^+$, 292, 236 $(B + H)^+$. Anal. ($C_{20}H_{21}N_3O_6S_2$) C, H, N.

1-[(2-Anilinoethoxy)methyl]-6-(2-pyridylthio)thymine (25). A solution of **24** (150 mg, 0.32 mmol) and aniline (0.5 mL, 5.5 mmol) in 5 mL of pyridine was stirred at room temperature for 18 h and heated for 1 h at 80 °C. Pyridine was removed *in vacuo*, and the residue was extracted with EtOAc in the usual manner. The residue was flash chromatographed (EtOAc/cyclohexane: 4/2) to give **25** (89 mg, 75%): mp (ether/pentane) 156−157 °C; IR (KBr) ν 3393, 2958, 1712, 1687, 1606, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H, CH_3), 3.17 (t, 2H, J = 5 Hz, *CH*$_2$NH), 3.77 (t, 2H, J = 5 Hz, O*CH*$_2$$CH_2$N), 4.05 (br s, 1H, *NH*Ph), 5.54 (s, 2H, OCH_2N), 6.54 [d, 2H, J = 7 Hz, Ph-H(*o*)], 6.68 [t, 1H, J = 7 Hz, Ph-H(*p*)], 7.05−7.15 (m, 4H, Ar), 7.58 [dt, J = 2, 8 Hz, 1H, SPy-H(4)], 8.40 [m, 1H, SPy-H(6)], 9.60 (br s, 1H, NH); MS (CI-NH_3) m/z 385 $(M + H)^+$. Anal. ($C_{19}H_{20}N_4O_3S$) C, H, N.

General Procedure for the Preparation of Bis-thioaryl Compounds 26−29. A mixture of alcohol derivative **1** or **23** (1 mmol), tributylphosphine (2.5 mmol), and the appropriate diaryl disulfide (2.5 mmol) in THF (15−20 mL) was refluxed for 30 min. The solution was evaporated, and the crude residue was purified by flash chromatography.

1-[[2-(Phenylthio)ethoxy]methyl]-6-(phenylthio)thymine (26). Compound **26** was isolated (91% yield) from the reaction of **1** with diphenyl disulfide after flash chromatography (EtOAc/cyclohexane: 7/3): mp (ether) 122−124 °C; IR ($CHCl_3$) ν 3393, 1710, 1684, 1441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, CH_3), 2.98 (t, 2H, J = 6 Hz, *CH*$_2$SPh), 3.72 (t, 2H, J = 6 Hz, O*CH*$_2$$CH_2$SPh), 5.53 (s, 2H, OCH_2N), 7.15−7.30 (m, 10H, 2 × SPh), 8.95 (br s, 1H, NH); MS (CI-NH_3) m/z 418 $(M + NH_4)^+$, 401 $(M + H)^+$, 167. Anal. ($C_{20}H_{20}N_2O_3S_2$) C, H, N.

6-(Phenylthio)-1-[[2-(2-pyridylthio)ethoxy]methyl]thymine (27). Compound **27** was isolated (94% yield) from the reaction of **1** with 2,2′-dipyridyl disulfide after flash chromatography (EtOAc/cyclohexane: 1/1): mp (ether) 137−138 °C; IR ($CHCl_3$) ν 3375, 2930, 1712, 1689, 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3), 3.29 (t, 2H, J = 6 Hz, CH_2S), 3.83 (t, 2H, J = 6 Hz, O*CH*$_2$$CH_2$S), 5.59 (s, 2H, OCH_2N), 6.96 [m, 1H, SPy-H(5)], 7.10−7.35 (m, 6H, Ar), 7.43 [m, 1H, SPy-H(4)], 8.36 [m, 1H, SPy-H(6)], 9.05 (br s, 1H, NH); MS (CI-NH_3) m/z 402 $(M + H)^+$, 112. Anal. ($C_{19}H_{19}N_3O_3S_2$) C, H, N.

1-[[2-(Phenylthio)ethoxy]methyl]-6-(2-pyridylthio)thymine (28). Compound **28** was isolated (93% yield) from the reaction of **23** with diphenyl disulfide after flash chromatography (EtOAc/cyclohexane: 7/3): mp (ether/pentane) 116−118 °C; IR ($CHCl_3$) ν 3390, 3183, 3051, 1675, 1700, 1581, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H, CH_3), 3.00 (t, 2H, J = 6.5 Hz, CH_2S), 3.72 (t, 2H, J = 6.5 Hz, O*CH*$_2$$CH_2$S), 5.55 (s, 2H, OCH_2N), 7.10−7.30 (m, 9H, Ar), 8.80 (br s, 1H, NH); MS (CI-NH_3) m/z 402 $(M + H)^+$, 112. Anal. ($C_{19}H_{19}N_3O_3S_2$) C, H, N.

1-[[2-(2-Pyridylthio)ethoxy]methyl]-6-(2-pyridylthio)thymine (29). Compound **29** was isolated (89% yield) from the reaction of **23** with 2,2′-dipyridyl disulfide after flash chromatography (EtOAc/cyclohexane: 4/1): mp (ether/pentane) 94−96 °C; IR ($CHCl_3$) ν 3690, 2945, 1658, 1588, 1426 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 3.22 (t, 2H, J = 6.5 Hz, CH_2S), 3.81 (t, 2H, J = 6.5 Hz, O*CH*$_2$$CH_2$S), 5.66 (s, 2H, OCH_2N), 6.90−7.80 (m, 7H, Ar-H), 8.36 [m, 1H, SPy-H(6)], 8.65 (br s, 1H, NH); MS (CI-iC_4H_{10}) m/z 403 $(M + H)^+$, 112. Anal. ($C_{18}H_{18}N_4O_3S_2$) C, H, N.

Synthesis of *E*-3-Substituted Allyl Acetates 33. General Procedure: Following the method of Soai *et al.*,[29] to an ice-cooled mixture of acrylic acids **30b−g** (20 mmol) and triethylamine (3 mL, 21.5 mmol) in THF (50 mL) was added dropwise ethyl chloroformate (2 mL, 20.9 mmol). After stirring for an additional 30 min at the same temperature, the precipitate was filtered and washed with THF (4 × 10 mL). To the filtrate containing crude **31b−g** cooled at 10 °C were successively added sodium borohydride in one portion (2.0 g, 52.8 mmol; except for **31e**: 0.9 g, 23.8 mmol) and then MeOH (15 mL), dropwise, over a period of 1 h. After this period, the reaction was quenched with 6 N aqueous HCl (25 mL) and the mixture extracted in the usual manner with EtOAc to give crude allylic alcohols **32**. The crude alcohols **32b−f** (**32g** must be purified before being acetylated) were stirred with acetic anhydride (2.4 mL, 25.2 mmol) and pyridine (2.6 mL, 32.4 mmol) in dry CH_2Cl_2 (50 mL) for 16 h at room temperature. The reaction mixtures were then poured into H_2O (100 mL) and worked up to afford the crude acetates **33**.

(*E*)-3-(3-Pyridyl)allyl acetate (33b):[31] pale yellow oil (0.74 g, 21%) after purification by flash chromatography (cyclohexane/EtOAc: 1/1); mp (EtOAc) 70 °C; IR ($CHCl_3$) ν 3036, 2947, 1737, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H, $COCH_3$), 4.78 (d, 2H, J = 6 Hz, CH_2), 6.37 (dt, 1H, J = 6, 16 Hz, *CH*-CH_2), 6.70 (d, 1H, J = 16 Hz, *CH*-Py), 7.30 [m, 1H, Py-H(5)], 7.77 [m, 1H, Py-H(4)], 8.55 [m, 1H, Py-H(6)], 8.68 [m, 1H, Py-H(2)].

(*E*)-3-(2-Furyl)allyl acetate (33c):[31] pale yellow oil (3.14 g, 78%) after purification by flash chromatography (cyclohexane/EtOAc: 8/2); IR ($CHCl_3$) ν 2956, 1729, 1661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, $COCH_3$), 4.69 (d, 2H, J = 6 Hz, CH_2), 6.21 (dt, 1H, J = 6, 15.5 Hz, *CH*-CH_2), 6.28 [m, 1H, Fur-H(3)], 6.37 [m, 1H, Fur-H(4)], 6.46 (d, 1H, J = 15.5 Hz, *CH*-Fur), 7.36 [m, 1H, Fur-H(5)].

(*E*)-3-(2-Thienyl)allyl acetate (33d):[31] pale yellow oil (3.2 g, 88%) after purification by flash chromatography (cyclohexane/EtOAc: 8/2); IR ($CHCl_3$) ν 2947, 1734, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H, $COCH_3$), 4.69 (d, 2H, J = 6.5 Hz, CH_2), 6.12 (dt, 1H, J = 6.5, 15.5 Hz, *CH*-CH_2), 6.78 (d, 1H, J = 15.5 Hz, *CH*-Thie), 6.98 [m, 2H, Thie-H(3,4)], 7.18 [m, 1H, Thie-H(5)].

(*E*)-3-(5-Nitro-2-thienyl)allyl acetate (33e): yellow solid (2.3 g, 51%) after purification by flash chromatography (cyclohexane/EtOAc: 7/3); mp (EtOAc) 70 °C; IR ($CHCl_3$) ν 1741, 1534, 1504, 1434, 1338 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H, $COCH_3$), 4.73 (d, 2H, J = 6 Hz, CH_2), 6.33 (dt, 1H, J = 6, 16.5

Hz, *CH*-CH_2), 6.75 (d, 1H, J = 16.5 Hz, *CH*-Thie), 6.95 [d, 1H, J = 4.5 Hz, Thie-H(3)], 7.83 [d, 1H, J = 4.5 Hz, Thie-H(4)]; MS (CI-NH_3): m/z 245 $(M + NH_4)^+$. Anal. ($C_9H_9NO_4S$) C, H, N.

(*E*)-3-(2-Benzofuranyl)allyl acetate (33f):[31] pale yellow solid (3.3 g, 76%) after purification by flash chromatography (cyclohexane/EtOAc: 7/3); mp (Et_2O, pentane) 53 °C (lit.[31] mp 53−54 °C); IR ($CHCl_3$) ν 1735, 1453, 1381, 1364 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H, $COCH_3$), 4.73 (d, 2H, J = 6 Hz, CH_2), 6.50 (m, 3H, BzFur-H + CH═CH), 7.10−7.50 (m, 4H, Ar-H).

(*E*)-3-(Cyclohexyl)allyl Acetate (33g). The crude alcohol prepared from acid **30g**, as described above, was flash chromatographed (CH_2Cl_2) to give **32g** as a colorless oil (1.4 g, 50% yield): ^1H NMR ($CDCl_3$) δ 0.60−2.20 (m, 12H), 4.05 (m, 1H), 5.58 (m, 1H). Acetylation as described above afforded, after purification by flash chromatography (cyclohexane/EtOAc: 9/1), the acetate **33g** as a colorless oil (1.34 g, 85%): IR ($CHCl_3$) ν 2930, 2854, 1729, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05−1.30 (m, 6H, CHx-H), 1.60−1.75 (m, 4H, CHx-H), 2.00 (m, 1H, CHx-H), 2.05 (s, 3H, $COCH_3$), 4.50 (d, 1H, J = 6 Hz, CH_2), 5.50 (dt, 1H, J = 6, 15.5 Hz, *CH*-CH_2), 5.70 (dd, 1H, J = 6.5, 15.5 Hz, *CH*-CHx); MS (CI-NH_3) m/z 200 $(M + NH_4)^+$. Anal. ($C_{11}H_{18}O_2$) C, H, N.

5-Ethyl-2,4-dimethoxy-6-(phenylthio)pyrimidine (36a). A mixture of **35**[34,50] (3.15 g, 15.5 mmol) and thiophenol (3 mL, 29 mmol) in pyridine (20 mL) was refluxed for 16 h. After *in vacuo* evaporation of the solvent, the crude residue was extracted with EtOAc in the usual manner and then chromatographed (toluene) to give **36a** as a colorless oil (8 g, 88%): ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.66 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.56 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.35−7.70 (m, 5H, SPh); MS (CI-NH_3) m/z 277 $(M + H)^+$.

2,4-Dimethoxy-6-[(3,5-dimethylphenyl)thio]-5-ethylpyrimidine (36b). The title compound was prepared as for **36a** by reaction of **35** (3 g, 15 mmol) with 3,5-dimethylthiophenol (4 mL, 30 mmol). The crude product was flash chromatographed (toluene/cyclohexane: 9/1) to yield **36b** as an oil (3.6 g, 80%): ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.35 (s, 6H, Ar-Me_2), 2.67 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.63 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.03 [s, 1H, Ar-H(*p*)], 7.23 [s, 2H, Ar-H(*o*)].

5-Ethyl-6-(phenylthio)uracil (37a). A mixture of **36a** (2.6 g, 9.4 mmol), chlorotrimethylsilane (3 mL, 23.6 mmol), and NaI (3.49 g, 23.3 mmol) in dry acetonitrile (80 mL) was stirred at room temperature for 18 h and then at 60 °C for 3 h, under argon atmosphere. The solvent was evaporated under reduced pressure, and the residue was treated with 40 mL of a 10% aqueous $Na_2S_2O_5$ solution. The solid was filtered, washed with H_2O, dried, and crystallized from MeOH to give **37a** (1.75 g, 75%): mp 217−219 °C; IR (KBr) ν 3204, 1705, 1640, 1421 cm^{-1}; UV (EtOH) λ_{max} 285 (ϵ 11 000), 246 nm (ϵ 7500); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 303 nm (ϵ 17 000); ^1H NMR (DMSO-d_6) δ 0.97 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.50 (q, 2H, J = 7.5 Hz, CH_2CH_3), 7.37 (s, 5H, SPh), 10.90 (br s, 1H, NH), 11.25 (br s, 1H, NH); MS (CI-NH_3): m/z 249 $(M + H)^+$. Anal. ($C_{12}H_{12}N_2O_2S$) C, H, N.

6-[(3,5-Dimethylphenyl)thio]-5-ethyluracil (37b). Using the same procedure (20 °C, 18 h), **36b** (3.27 g, 10.7 mmol), chlorotrimethylsilane (3.2 mL, 25.2 mmol), NaI (3.75 g, 25 mmol), and acetonitrile (80 mL) gave 2.52 g (85%) of **37b**: mp (MeOH) 227 °C; IR (KBr) ν 3449, 3358, 1732, 1651, 1584, 1478 cm^{-1}; UV (EtOH) λ_{max} 283 nm (ϵ 10 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 303 nm (ϵ 13 500); ^1H NMR (DMSO-d_6) δ 0.97 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.27 (s, 6H, Ar-Me_2), 2.50 (q, 2H, J = 7.5 Hz, CH_2CH_3), 7.00 (br s, 3H, Ar-H), 10.80 (br s, 1H, NH), 11.30 (br s, 1H, NH); MS (CI-NH_3) m/z 277 $(M + H)^+$. Anal. ($C_{14}H_{16}N_2O_2S$) C, H, N.

6-(Phenylthio)thymine (38). Boron trichloride (25 mL, 1 M in CH_2Cl_2) was added to a cooled (−78 °C) solution of compound **2** (4.1 g, 11.6 mmol) in CH_2Cl_2 (200 mL). The mixture was stirred from −78 °C, neutralized with $NaHCO_3$, and stirred for an additional 30 min. After filtration, the solvent was removed under reduced pressure. The crude product was flash chromatographed (EtOAc/MeOH: 95/5) to give **38** (2.33 g, 86%). Physical and spectral data of the title compound are identical to those previously reported.[32]

Coupling of Pyrimidine Bases 37a,b and 38 to Allylic Acetates 33. General Procedure: To a solution containing 1 mmol of the nucleobase **37a**, **37b**, or **38** in 1 mL of dry pyridine was added hexamethyldisilazane (2 mL) at room temperature. The resulting mixture was heated overnight at 120 °C under nitrogen atmosphere and then cooled to room temperature. The excess of solvent and reagents was removed *in vacuo* to provide the silylated base which was used without purification for coupling reactions. A mixture of the allylic acetate **33** (1 mmol), tetrakis(triphenylphosphine)palladium (58 mg, 0.05 equiv), and triphenylphosphine (53 mg, 0.2 equiv) in dry THF (3 mL) was stirred for 15 min at room temperature under an argon atmosphere. Then a solution of the silylated base in dry THF (3 mL) was added, and the resultant mixture was stirred at 60 °C, until TLC analysis showed that all of the starting acetate had disappeared (3−6 h). Concentration under vacuum and flash chromatography afforded successively the N-1,3-dialkylated derivative and the desired N-1 acyclonucleoside **39**, **40**, or **41**, except for **39b** for which polarity is inversed.

(*E*)-1-Cinnamyl-6-(phenylthio)thymine (39a): yield 157 mg, 45%; R_f 0.43 (cyclohexane/EtOAc: 1/1); mp (EtOAc) 193−194 °C; IR ($CHCl_3$) ν 3391, 3171, 3031, 1675, 1582, 1451 cm^{-1}; UV (EtOH) λ_{max} 248 nm (ϵ 27 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 247 nm (ϵ 27 000); ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H, CH_3), 4.86 (d, 2H, J = 6 Hz, CH_2), 6.15 (dt, 1H, J = 6, 16 Hz, *CH*-CH_2), 6.52 (d, 1H, J = 16 Hz, *CH*-Ph), 7.20−7.35 (m, 10H, 2 × Ph), 8.90 (br s, 1H, NH); MS (CI-NH_3) m/z 351 $(M + H)^+$. Anal. ($C_{20}H_{18}N_2O_2S$) C, H, N.

6-(Phenylthio)-1-[(*E*)-3-(3-pyridyl)prop-2-en-1-yl]thymine (39b): yield 150 mg, 43%; R_f 0.20 (EtOAc); mp (EtOAc) 205−206 °C; IR ($CHCl_3$) ν 3388, 3037, 1686, 1583, 1442 cm^{-1}; UV (EtOH) λ_{max} 283 (ϵ 14 500), 243 nm (ϵ 22 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 282 (ϵ 13 500), 242 nm (ϵ 24 000); ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 4.89 (d, 2H, J = 6 Hz, CH_2), 6.15 (dt, 1H, J = 6, 16 Hz, *CH*-CH_2), 6.45 (d, 1H, J = 16 Hz, *CH*-Py), 7.20−7.35 (m, 6H, Ar-H), 7.65 [d, 1H, J = 7 Hz, Py-H(4)], 8.48 [s, 2H, Py-H(2,6)], 9.67 (br s, 1H, NH); MS (CI-NH_3) m/z 352 $(M + H)^+$. Anal. ($C_{19}H_{17}N_3O_2S$) C, H, N.

1-[(*E*)-3-(2-Furyl)prop-2-en-1-yl]-6-(phenylthio)thymine (39c): yield 90 mg, 26%; R_f 0.40 (cyclohexane/EtOAc: 1/1); mp (EtOAc) 172−174 °C; IR ($CHCl_3$) ν 3390, 2956, 1700 (sh), 1680, 1480, 1441 cm^{-1}; UV (EtOH) λ_{max} 271 nm (ϵ 20 500); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 269 nm (ϵ 20 000); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H, CH_3), 4.81 (d, 2H, J = 6 Hz, CH_2), 6.07 (dt, 1H, J = 6, 16 Hz, *CH*-CH_2), 6.21 [d, 1H, J = 3 Hz, Fur-H(3)], 6.33 (d, 1H, J = 16 Hz, *CH*-Fur), 6.35 [m, 1H, Fur-H(4)], 7.20−7.40 (m, 6H, Ar), 8.80 (br s, 1H, NH); MS (CI-NH_3) m/z 341 $(M + H)^+$, 235 $(B + H)^+$. Anal. ($C_{18}H_{16}N_2O_3S$) C, H, N.

6-(Phenylthio)-1-[(*E*)-3-(2-thienyl)prop-2-en-1-yl]thymine (39d): yield 97 mg, 27%; R_f 0.35 (cyclohexane/EtOAc: 6/4); mp (EtOAc) 196−198 °C; IR ($CHCl_3$) ν 3390, 1700 (sh), 1684, 1583, 1441 cm^{-1}; UV (EtOH) λ_{max} 286 nm (ϵ 23 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 287 nm (ϵ 25 500); ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H, CH_3), 4.80 (d, 2H, J = 6.5 Hz, CH_2), 5.90 (dt, 1H, J = 6.5, 15.5 Hz, *CH*-CH_2), 6.65 (d, 1H, J = 15.5 Hz, *CH*-Thie), 6.91 [m, 2H, Thie-H(3,4)], 7.15−7.35 (m, 6H, Ar), 9.25 (br s, 1H, NH); MS (DCI/NH_3) m/z 357 $(M + H)^+$. Anal. ($C_{18}H_{16}N_2O_2S_2$) C, H, N.

1-[(*E*)-3-(5-Nitro-2-thienyl)prop-2-en-1-yl]-6-(phenylthio)thymine (39e): yield 120 mg, 21%; R_f 0.15 (CH_2Cl_2/acetone: 92/8); mp (CH_2Cl_2) >230 °C; IR (KBr) ν 3150, 3050, 1693, 1489, 1449, 1420, 1340, 1314 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.00 (s, 3H, CH_3), 4.75 (d, 2H, J = 4.5 Hz, CH_2), 6.37 (dt, 1H, J = 4.5, 16 Hz, *CH*-CH_2), 6.63 (d, 1H, J = 16 Hz, *CH*-Thie), 7.16 [d, 1H, J = 4.5 Hz, Thie-H(3)], 7.36 (m, 5H, Ph), 8.01 [d, 1H, J = 4.5 Hz, Thie-H(4)], 11.75 (br s, 1H, NH); MS (DCI/NH_3) m/z 402 $(M + H)^+$. Anal. ($C_{18}H_{15}N_3O_4S_2$) C, H, N.

1-[(*E*)-3-(2-Benzofuranyl)prop-2-en-1-yl]-6-(phenylthio)thymine (39f): yield 119 mg, 30%; R_f 0.38 (cyclohexane/EtOAc: 1/1); mp (EtOAc) 185−186 °C; IR ($CHCl_3$) ν 3394, 3054, 1680, 1583, 1453 cm^{-1}; UV (EtOH) λ_{max} 297 (ϵ 41 500), 308 nm (ϵ 41 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 296 (ϵ

30 000), 306 nm (ϵ 29 000); ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 4.88 (d, 2H, J = 5.5 Hz, CH_2), 6.35 (dt, 1H, J = 5.5, 15.5 Hz, *CH*-CH_2), 6.44 (d, 1H, J = 15.5 Hz, *CH*-BzFur), 6.54 [s, 1H, BzFur-H(3)], 7.15−7.50 (m, 9H, Ar), 8.90 (br s, 1H, NH); MS (CI-NH_3) m/z 391 $(M + H)^+$, 157. Anal. ($C_{22}H_{18}N_2O_3S$) C, H, N.

1-[(*E*)-3-(Cyclohexyl)prop-2-en-1-yl]-6-(phenylthio)thymine (39g): yield 90 mg, 25%; R_f 0.45 (cyclohexane/EtOAc: 1/1); mp (MeOH) 169−170 °C; IR ($CHCl_3$) ν 3392, 2928, 2853, 1675, 1582, 1451 cm^{-1}; UV (EtOH) λ_{max} 285 (ϵ 9000), 245 nm (sh); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 285 (ϵ 8000), 245 nm (sh); ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 2H, CHx-H), 1.05−1.25 (m, 4H, CHx-H), 1.55−1.70 (m, 4H, CHx-H), 1.88 (m, 1H, CHx-H), 2.08 (s, 3H, CH_3), 4.66 (d, 2H, J = 6 Hz, CH_2), 5.36 (dt, 1H, J = 6, 15.5 Hz, *CH*-CH_2), 5.60 (dd, 1H, J = 6.5, 15.5 Hz, *CH*-CHx), 7.15−7.35 (m, 5H, Ph), 9.00 (br s, 1H, NH); MS (CI-NH_3) m/z 357 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O_2S$) C, H, N.

1-(*E*)-Cinnamyl-5-ethyl-6-(phenylthio)uracil (40a): yield 172 mg, 47%; R_f 0.50 (cyclohexane/EtOAc: 1/1); mp (EtOAc) 179−180 °C; IR ($CHCl_3$) ν 3395, 2956, 1680, 1578, 1441 cm^{-1}; UV (EtOH) λ_{max} 248 nm (ϵ 23 500); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 248 nm (ϵ 25 500); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7 Hz, CH_2CH_3), 2.73 (q, 2H, J = 7 Hz, CH_2CH_3), 4.77 (d, 2H, J = 6 Hz, CH_2), 6.00 (dt, 1H, J = 6, 16 Hz, *CH*-CH_2), 6.50 (d, 1H, J = 16 Hz, CH-Ph), 7.30 (m, 10H, 2 × Ph), 9.60 (br s, 1H, NH); MS (CI-NH_3) m/z 365 $(M + H)^+$. Anal. ($C_{21}H_{20}N_2O_2S$) C, H, N.

5-Ethyl-1-[(*E*)-3-(2-furyl)prop-2-en-1-yl]-6-(phenylthio)uracil (40c): yield 177 mg, 50%; R_f 0.49 (cyclohexane/EtOAc: 1/1); mp (EtOAc) 119−120 °C; IR ($CHCl_3$) ν 3393, 1700 (sh), 1681, 1480, 1441 cm^{-1}; UV (EtOH) λ_{max} 271 nm (ϵ 25 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 269 nm (ϵ 24 500); ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.71 (q, 2H, J = 7.5 Hz, CH_2CH_3), 4.71 (d, 2H, J = 6 Hz, CH_2), 6.01 (dt, 1H, J = 6, 15.5 Hz, *CH*-CH_2), 6.19 [d, 1H, J = 3.5 Hz, Fur-H(3)]), 6.28 (d, 1H, J = 15.5 Hz, *CH*-Fur), 6.33 [dd, 1H, J = 2, 3.5 Hz, Fur-H(4)], 715−7.35 (m, 6H, Ar), 9.05 (br s, 1H, NH); MS (CI-NH_3) m/z 355 $(M + H)^+$. Anal. ($C_{19}H_{18}N_2O_3S$) C, H, N.

5-Ethyl-6-(phenylthio)-1-[(*E*)-3-(2-thienyl)prop-2-en-1-yl]uracil (40d): yield 137 mg, 40%; R_f 0.43 (cyclohexane/EtOAc:1/1); mp (EtOAc) 160−161 °C; IR ($CHCl_3$) ν 3396, 2957, 1700 (sh), 1685, 1579, 1429 cm^{-1}; UV (EtOH) λ_{max} 286 nm (ϵ 19 500); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 285 nm (ϵ 20 000); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7 Hz, CH_2CH_3), 2.73 (q, 2H, J = 7 Hz, CH_2CH_3), 4.70 (d, 2H, J = 6 Hz, CH_2), 5.82 (dt, 1H, J = 6, 15 Hz, *CH*-CH_2), 6.60 (d, 1H, J = 15 Hz, *CH*-Thie), 6.90 [m, 2H, Thie-H(3,4)], 7.10−7.50 (m, 6H, Ar), 9.50 (br, 1H, NH); MS (CI-NH_3) m/z 371 $(M + H)^+$, 123. Anal. ($C_{19}H_{18}N_2O_2S_2$) C, H, N.

5-Ethyl-1-[(*E*)-3-(5-nitro-2-thienyl)prop-2-en-1-yl]-6-(phenylthio)uracil (40e): yield 128 mg, 31%; R_f 0.43 (CH_2Cl_2/acetone: 92/8); mp (CH_2Cl_2) 227−228 °C; IR (KBr) ν 3035, 1690, 1489, 1443, 1420, 1338, 1315 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.93 (t, 3H, J = 7 Hz, CH_2CH_3), 2.55 (q, 2H, J = 7 Hz, CH_2CH_3), 4.69 (d, 2H, J = 5 Hz, CH_2), 6.29 (dt, 1H, J = 5, 16 Hz, *CH*-CH_2), 6.57 (d, 1H, J = 16 Hz, *CH*-Thie), 7.14 [d, 1H, J = 4.5 Hz, Thie-H(3)], 7.35 (m, 5H, Ph), 8.01 [d, 1H, J = 4.5 Hz, Thie-H(4)], 11.75 (br s, 1H, NH); MS (CI-NH_3) m/z 416 $(M + H)^+$, 249 $(B + H)^+$. Anal. ($C_{19}H_{17}N_3O_4S_2$) C, H, N.

1-[(*E*)-3-(2-Benzofuranyl)prop-2-en-1-yl]-5-ethyl-6-(phenylthio)uracil (40f): yield 145 mg, 36%; R_f 0.50 (cyclohexane/EtOAc: 1/1); mp (EtOAc) 142−143 °C; IR ($CHCl_3$) ν 3390, 2229, 1685, 1479, 1452 cm^{-1}; UV (EtOH) λ_{max} 297 (ϵ 36 500), 308 nm (ϵ 35 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 295 (ϵ 34 500), 306 nm (ϵ 32 500); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.74 (q, 2H, J = 7.5 Hz, CH_2CH_3), 4.79 (d, 2H, J = 5.5 Hz, CH_2), 6.30 (dt, 1H, J = 5.5, 16 Hz, *CH*-CH_2), 6.37 (d, 1H, J = 16 Hz, *CH*-BzFur), 6.53 [s, 1H, BzFur-H(3)], 7.15−7.50 (m, 9H, Ar), 9.10 (br s, 1H, NH); MS (CI-NH_3) m/z 405 $(M + H)^+$, 157. Anal. ($C_{23}H_{20}N_2O_3S$) C, H, N.

1-(*E*)-Cinnamyl-6-[(3,5-dimethylphenyl)thio]-5-ethyluracil (41a): yield 153 mg, 39%; R_f 0.45 (cyclohexane/EtOAc: 1/1); mp (EtOAc/hexane) 160−162 °C; IR ($CHCl_3$) ν 3392, 2956, 1679, 1577, 1435 cm^{-1}; UV (EtOH) λ_{max} 250 nm (ϵ 23 000); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 248 nm (ϵ 25 500); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.23 (s, 6H, Ar-Me_2), 2.70 (q, 2H, J = 7.5 Hz, CH_2CH_3), 4.73 (d, 2H, J = 6 Hz, CH_2), 6.00 (dt, 1H, J = 6, 15 Hz, *CH*-CH_2), 6.40 (d, 1H, J = 15 Hz, *CH*-Ph), 6.77 (br s, 3H, SAr-H), 7.23 (s, 5H, Ph), 9.40 (br, 1H, NH); MS (CI-NH_3) m/z 393 $(M + H)^+$, 277 $(B + H)^+$. Anal. ($C_{23}H_{24}N_2O_2S$) C, H, N.

6-[(3,5-Dimethylphenyl)thio]-5-ethyl-1-[(*E*)-3-(2-furyl)prop-2-en-1-yl]uracil (41c): yield 103 mg, 27%; R_f 0.45 (cyclohexane/EtOAc: 1/1); mp (EtOAc/hexane) 176−177 °C; IR ($CHCl_3$) ν 3393, 2960, 2930, 1680, 1578, 1441 cm^{-1}; UV (EtOH) λ_{max} 271 nm (ϵ 23 500); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 270 nm (ϵ 23 000); ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.26 (s, 6H, Ar-Me_2), 2.73 (q, 2H, J = 7.5 Hz, CH_2CH_3), 4.72 (d, 2H, J = 6 Hz, CH_2), 6.02 (dt, 1H, J = 6, 16 Hz, *CH*-CH_2), 6.18 [d, 1H, J = 3 Hz, Fur-H(3)], 6.25 (d, 1H, J = 16 Hz, *CH*-Fur), 6.34 [dd, 1H, J = 1.5, 3 Hz, Fur-H(4)], 6.79 (s, 2H, SAr-H), 6.85 (s, 1H, SAr-H), 7.31 [d, 1H, J = 1.5 Hz, Fur-H(5)], 9.35 (br s, 1H, NH); MS (CI-NH_3) m/z 383 $(M + H)^+$. Anal. ($C_{21}H_{22}N_2O_3S$) C, H, N.

6-[(3,5-Dimethylphenyl)thio]-5-ethyl-1-[(*E*)-3-(2-thienyl)prop-2-en-1-yl]uracil (41d): yield 101 mg, 25%; R_f 0.45 (cyclohexane/EtOAc, 1/1); mp (EtOAc/hexane) 134−136 °C; IR ($CHCl_3$) ν 3390, 2962, 2933, 1680, 1577, 1444 cm^{-1}; UV (EtOH) λ_{max} 287 nm (ϵ 21 500); UV (0.1 N NaOH/EtOH: 9/1) λ_{max} 286 nm (ϵ 21 000); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.27 (s, 6H, Ar-Me_2), 2.73 (q, 2H, J = 7.5 Hz, CH_2CH_3), 4.73 (d, 2H, J = 6 Hz, CH_2), 5.80 (dt, 1H, J = 6, 15 Hz, *CH*-CH_2), 6.58 (d, 1H, J = 15 Hz, *CH*-Thie), 6.75−7.35 (m, 6H, Ar), 9.50 (br s, 1H, NH); MS (CI-NH_3) m/z 399 $(M + H)^+$, 123. Anal. ($C_{21}H_{22}N_2O_2S_2$) C, H, N.

Antiviral Assay Procedures. The effects of the compounds on the replication of HIV-1 were evaluated (see Tables 1 and 2), as previously described[51] in CEM-SS and MT-4 cells. In brief, the determination of anti-HIV-1 III B activity in MT-4 cells was based on a reduction of the virus-induced cytopathogenicity; the cell viability was measured by the mitochondrial dehydrogenase activity, an enzyme reducing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromine (MTT assay) into formazan (formazan production was measured by reading the optical density at 540 nm).[52] The virus production by HIV-1 Lai or Nevirapine resistant HIV-1 CEM-SS-infected cells was measured by the reverse transcriptase activity associated with virions released in culture supernatants. MT-4 and CEM-SS cells were incubated respectively with 50 or 100 $TCID_{50}$ of the different virus; after a 30 min. adsorption, free virus was eliminated by washes, and cells were then cultured in the presence of different concentrations of compounds for 5 days, after which time the virus multiplication was determinated. The 50% inhibition of virus multiplication (IC_{50}) was derived from a computer-generated median effect plot of the dose−effect data.[53] In the same experiment, cytotoxicity of the molecules was evaluated on uninfected cells using the MTT assay. The 50% cytotoxic concentration (CC_{50}) is defined as the concentration of drugs which reduce the cell viability by 50% and was calculated using the program aforementioned. CEM-SS cells were obtained from Peter Nara and Nevirapine resistant HIV-1 (N119, point mutation at RT codon 181) from D. Richman through the AIDS Research and References Reagent Program, Division of AIDS, NIAID, NIH.

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