Synthesis and Anti-HIV-1 Activity of a Series of 1-Alkoxy-5-alkyl-6-(arylthio)uracils

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A series of 1-alkoxy-5-alkyl-6-(arylthio)uracils was synthesized and tested for their ability to inhibit HIV-1 replication. Treatment of 2-alkyl-3,3-bis(methylthio)acryloyl chlorides (**5a**−**e**) with AgOCN in benzene followed by reaction of the resulting isocyanates **6a**−**e** with an appropriate alkoxyamine gave *N*-alkoxy-*N*′-((2-alkyl-3,3-bis(methylthio)acryloyl)ureas (**10a**−**z**) in good to excellent yields. Cyclization of **10a**−**z** in AcOH containing a catalytic amount of *p*-TsOH produced 1-alkoxy-5-alkyl-6-(methylthio)uracils (**11a**−**z**). Oxidation of **11a**−**z** with 3-chloroperoxybenzoic acid in CH_2Cl_2 resulted in high yields of 1-alkoxy-5-alkyl-6-(methylsulfonyl)uracils (**12a**−**x** and **12z**) and 1-(benzyloxy)-6-(methylsulfinyl)thymine (**12y**), which were subsequently reacted with an appropriate arenethiol in ethanolic NaOH solution to afford 1-alkoxy-5-alkyl-6-(arylthio)uracils (**14**−**49**). Substitution at the 3- and 5-positions of the C-6-(phenylthio) ring by two methyl groups significantly increased its original anti-HIV-1 activity (EC_{50}: 6-((3,5-dimethylphenyl)thio)-5-isopropyl-1-propoxyuracil (**18**), 0.064 μM; 6-((3,5-dimethylphenyl)thio)-1-(3-hydroxypropoxy)-5-isopropyluracil (**23**), 0.19 μM). Among the various alkoxy substituents at the N-1, the propoxy group was the most beneficial for improving the anti-HIV-1 activity. The 1-propoxy derivative **18** proved to be the most potent inhibitor of HIV-1 replication, followed by the 1-(3-hydroxypropoxy) derivative **23**. Introduction of an isopropyl group at C-5 of the uracil base also remarkably enhanced the activity. When compound **18** was incubated with a rat liver homogenate preparation, no metabolite was observed, thus confirming the metabolic stability of the N−O bond in these 1-alkoxyuracils.

Introduction

Human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immunodeficiency syndrome (AIDS), which is one of the world's most serious health problems, with current protocols being inadequate for either prevention or successful long-term treatment.[1] Since reverse transcriptase (RT) is an essential enzyme for the replication of HIV, it is regarded as one of the most important targets for the antiviral chemotherapy against HIV infections.[2] 3′-Azido-3′-deoxythymidine (AZT), a potent RT inhibitor of HIV, is the first drug to have been clinically used in the treatment of AIDS.[3,4] In spite of its clinical efficacy, the long-term administration of AZT is often associated with serious side effects such as bone marrow suppression.[5] 2′,3′-Dideoxyinosine (DDI),[6] 2′,3′-dideoxycytidine (DDC),[7] and 2′,3′-didehydro-3′-deoxythymidine (D4T)[8] have more recently been approved for the patients who do not tolerate AZT, yet they also have unfavorable side effects.[2] These nucleoside analogs act as inhibitors of viral RT following intracellular conversion to their corresponding 5′-triphosphates.[2] While such 5′-triphosphates exhibit a much higher affinity for the HIV-1 RT and other retroviral RTs than for the host cellular DNA polymerases, their nonspecific interaction with the host cellular DNA polymerases may contribute to the side effects of this class of compounds.[3,6] It seems, therefore, still imperative to find novel chemotherapeutic agents having potent antiviral activity and low toxicity, preferably, through a different mechanism of action.

Several nonnucleoside inhibitors of the HIV-1 RT have recently been discovered. Examples of these include nevirapine,[9] R82913,[10] atevirdine,[11] L-697,661,[12] 1-((2-hydroxyethoxy)methyl)-6-(phenylthio)thymine (HEPT),[13] and TSAO-T.[14] Although these inhibitors are structurally distinct, they share some common behaviors toward RT. All of these compounds are potent inhibitors of HIV-1 RT but not HIV-2 or other retroviral RTs.[15] Although HEPT and TSAO-T can be considered nucleoside analogs, they do not require phosphorylation in order to inhibit HIV-1 RT.[14,16]

Since the discovery of HEPT as a novel lead for specific anti-HIV-1 agents, a number of HEPT analogs have been synthesized to increase its potency.[17−25] Several of these compounds such as 6-((3,5-dimethylphenyl)thio)-1-(ethoxymethyl)-5-ethyluracil and 6-(3,5-dimethylbenzyl)-1-(ethoxymethyl)-5-isopropyluracil inhibit HIV-1 replication in the nanomolar concentration range. From synthetic studies of HEPT analogs, it has been found that the presence of the 2′-oxygen atom in the acyclic chain of HEPT is not essential for anti-HIV-1 activity.[23−25] This result prompted us to synthesize the 1-alkoxy analogs of HEPT to examine the effect of an oxygen atom adjacent to the uracil base on anti-HIV-1 activity since a number of acyclic N−O linked nucleosides show potent and selective anti-herpesvirus activity.[26−30] In addition, the N−O linkage of these 1-alkoxy analogs is expected to be chemically and metabolically stable on the basis of a recent report.[27] In this report we describe the synthesis, anti-HIV-1 activity, and structure−activity relationships of a series of 1-alkoxy-5-alkyl-6-(arylthio)uracils.

Chemistry

The LDA lithiation is highly efficient for synthesizing various 6-substituted HEPT analogs.[13,17−24] However, when the 1-alkoxy-5-alkyluracils **1a**−**d** were treated

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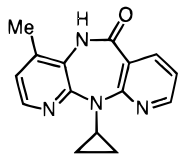
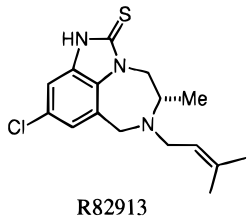


nevirapine



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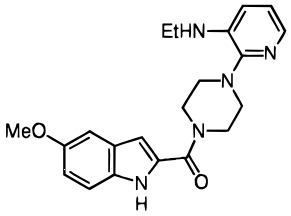

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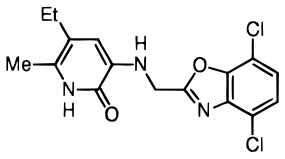
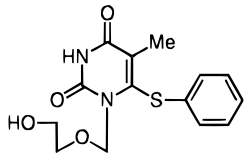
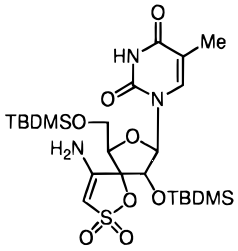


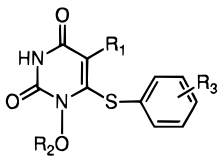
L-697,661



HEPT



TSAO-T

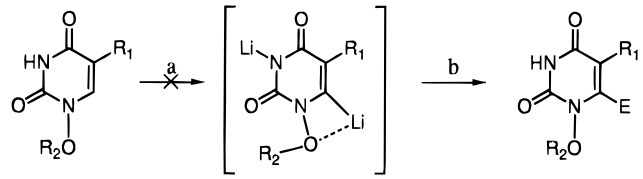


1-alkoxy analogs of HEPT **14–49**

R_1 = Me, Et, *n*-Pr, *i*-Pr, *c*-Pr
R_2 = $(CH_2)_3OH$, *n*-Pr, *n*-Bu, CH_2Ph, $(CH_2)_2Ph$, $(CH_2)_2Ph$ (3-Me), $(CH_2)_2OMe$, $(CH_2)_2OPh$
R_3 = H, 2-Me, 3-Me, 4-Me, 3,5-Me_2, 3-F, 3,5-F_2

with LDA (2.2 equiv) in THF −78 °C for 1 h, the corresponding C-6-lithiated species were not generated, which was confirmed by reaction with phenyl sulfide or D_2O as an electrophile. The use of a more basic lithiating agent, lithium 2,2,6,6-tetramethylpiperidide, under the same reaction conditions also failed to generate the C-6-lithiated species (Scheme 1). We have recently developed a general and convenient synthetic route to the 6-substituted 1,5-dialkyluracils from readily accessible ethyl 2-alkyl-3,3-bis(methylthio)acrylates.[25,31] Alternatively, this synthetic approach was successfully applied to the preparation of the target compounds **14**−**49** as shown in Scheme 2. The carboxylic esters **2a**−**e** were treated with LDA to generate their lithium enolates according to a published procedure,[32,33] which were reacted with CS_2 at −78 °C followed by MeI to afford ethyl 2-alkyl-3,3-bis(methylthio)acrylates (**3a**−**e**). Hydrolysis of the esters **3a**−**e** with 2 N KOH in EtOH and subsequent reaction of the corresponding carboxylic acids **4a**−**e** with oxalyl chloride in benzene in the presence of a catalytic amount of DMF afforded 2-alkyl-3,3-bis(methylthio)acryloyl chlorides (**5a**−**e**) in good yields. Treatment of the **5a**−**e** with AgOCN in benzene followed by reaction of the resulting isocyanates **6a**−**e** with the appropriate alkoxyamines such as propoxyamine

Scheme 1[a]



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a : R_1 = Et, R_2 = *n*-Pr
b : R_1 = Et, R_2 = $(CH_2)_2Ph$
c : R_1 = *i*-Pr, R_2 = *n*-Pr
d : R_1 = *i*-Pr, R_2 = $(CH_2)_2Ph$

[a] (a) LDA or lithium 2,2,6,6-tetramethylpiperidide, THF, −78 °C, 1 h; (b) PhS−SPh or D_2O.

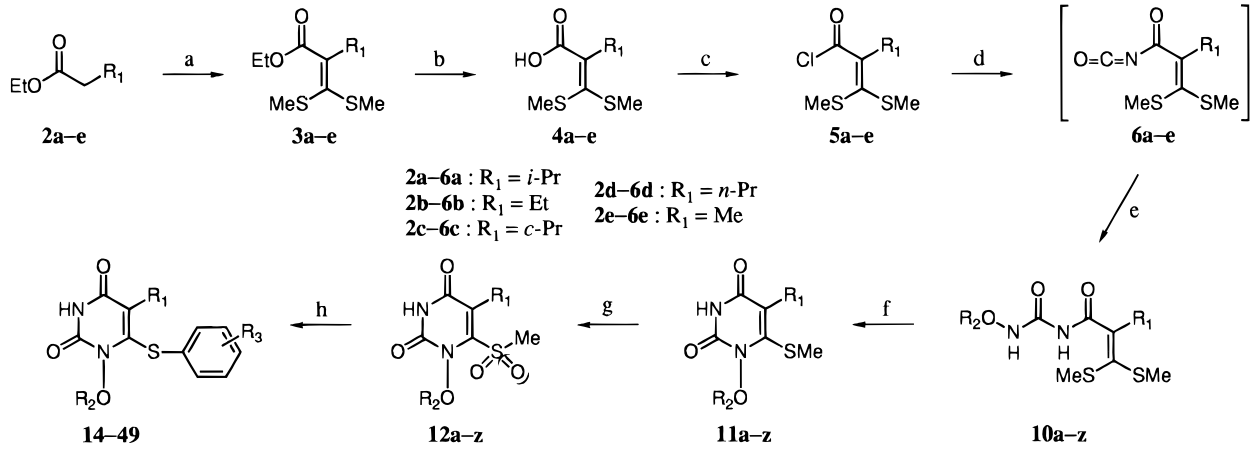
(**7a**), (3-((*tert*-butyldimethylsilyl)oxy)propoxy)amine (**7b**), butoxyamine (**7c**), (2-phenylethoxy)amine (**7d**), (2-(3-methylphenyl)ethoxy)amine (**7e**), (2-methoxyethoxy)-amine (**7f**), (2-phenoxyethoxy)amine (**7g**), and (benzyloxy)amine (**7h**) gave *N*-alkoxy-*N*′-((2-alkyl-3,3-bis(methylthio)acryloyl)ureas (**10a**−**z**) in good to excellent yields (Table 1). Synthesis of the requisite alkoxyamines **7a**−**g** was accomplished in high overall yields by reaction of the alcohols **8a**−**g** with *N*-hydroxyphthalimide in the presence of betaine formed from triphenylphosphine and diethyl azodicarboxylate followed by cleavage of the resulting *N*-alkoxyphthalimides **9a**−**g** with either hydrazine hydrate in MeOH at reflux temperature or *N*-methylhydrazine in CH_2Cl_2 at room temperature (Scheme 3). Cyclization of the ureas **10a**−**z** in AcOH containing a catalytic amount of *p*-TsOH produced 1-alkoxy-5-alkyl-6-(methylthio)uracils (**11a**−**z**) (Table 2). Oxidation of the 6-(methylthio)-uracils **11a**−**z** with 3-chloroperoxybenzoic acid in CH_2Cl_2 at reflux temperature resulted in high yields of 1-alkoxy-5-alkyl-6-(methylsulfonyl)uracils (**12a**−**x** and **12z**) and 1-(benzyloxy)-6-(methylsulfinyl)thymine (**12y**) (Table 2). It has been known that 6-(phenylthio)uridine derivatives or 6-(phenylsulfinyl)acyclouridine derivatives were highly susceptible to nucleophillic addition−elimination reactions with a variety of nucleophiles under mild conditions.[18,22,34] When the compounds **12a**−**z** were allowed to react with the appropriate arenethiols such as thiophenol (**13a**), *o*-thiocresol (**13b**), *m*-thiocresol (**13c**), *p*-thiocresol (**13d**), 3,5-dimethylthiophenol (**13e**), 3-fluorothiophenol (**13f**), and 3,5-difluorothiophenol (**13g**) in ethanolic NaOH solution, 1-alkoxy-5-alkyl-6-(arylthio)uracils (**14**−**49**) were obtained mostly in good to excellent yields. The physical and spectral properties of the target compounds **14**−**49** are listed in Table 3.

A presumed metabolite of 6-((3,5-dimethylphenyl)-thio)-5-isopropyl-1-propoxyuracil (**18**), 6-((3,5-dimethylphenyl)thio)-5-isopropyluracil (**51**), was synthesized by reaction of 6-chloro-5-isopropyluracil (**50**) with **13e** in ethanolic NaOH solution in 91% yield (Scheme 4).

Results and Discussion

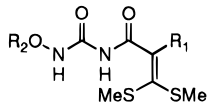
The anti-HIV-1 (HTLV-III_B) activity and cytotoxicity of the compounds **14**−**49** were tested by the Developmental Therapeutics Program of the National Cancer Institute as previously described,[35] and the results are summarized in Table 4 along with those of AZT, DDC, DDI, and HEPT. An active compound was defined as one which protected CEM-SS lymphocytes from the cytopathic effect of the virus by 50% or more in at least

Scheme 2[a]



[a] (a) (i) LDA, THF, −78 °C, 30 min; (ii) MeI, −78 °C, then room temperature, 16 h; (b) 2 N KOH, EtOH, reflux, 3 h (for **4b**, **4d**, and **4e**) or 72 h (for **4a** and **4c**); (c) $(COCl)_2$, DMF, benzene, room temperature, 3 h; (d) AgOCN, benzene, reflux, 30 min; (e) alkoxyamine (**7a**−**h**), room temperature, 1 h; (f) *p*-TsOH, AcOH, 80 °C, 1 h; (g) 3-chloroperoxybenzoic acid, CH_2Cl_2, reflux, 16 h; (h) ArSH (**13a**−**g**), 1 N ethanolic NaOH, EtOH, room temperature, 20 min.

Table 1. Physical and Spectral Properties of *N*-Alkoxy-*N*′-(2-alkyl-3,3-bis(methylthio)acryloyl)ureas



10a–z

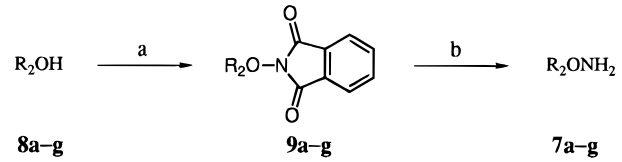
compd	R_1	R_2	% yield	crystn solvent	mp, °C	EI-MS, *m/z*	formula	anal.[a]
10a	*i*-Pr	*n*-Pr	57	EtOAc	136.0−137.0	306 (M^+)	$C_{12}H_{22}N_2O_3S_2$	C, H, N
10b	*i*-Pr	$(CH_2)_3$OTBDMS	77	EtOAc−hexane	68.0−69.0	436 (M^+)	$C_{18}H_{36}N_2O_4S_2Si$	C, H, N
10c	*i*-Pr	*n*-Bu	63	EtOAc	115.0−116.0	320 (M^+)	$C_{13}H_{24}N_2O_3S_2$	C, H, N
10d	*i*-Pr	CH_2Ph	70	EtOH	149.5−150.3	355 $(M + H)^+$	$C_{16}H_{22}N_2O_3S_2$	C, H, N
10e	*i*-Pr	$(CH_2)_2$Ph	80	EtOH	146.1−146.3	368 (M^+)	$C_{17}H_{24}N_2O_3S_2$	C, H, N
10f	*i*-Pr	$(CH_2)_2$Ph(3-Me)	80	EtOH	150.0−151.0	382 (M^+)	$C_{18}H_{26}N_2O_3S_2$	C, H, N
10g	*i*-Pr	$(CH_2)_2$OMe	78	EtOH	96.3−97.8	322 (M^+)	$C_{12}H_{22}N_2O_4S_2$	C, H, N
10h	*i*-Pr	$(CH_2)_2$OPh	84	EtOH	123.4−124.1	385 $(M + H)^+$	$C_{17}H_{24}N_2O_4S_2$	C, H, N
10i	Et	*n*-Pr	69	EtOAc−hexane	117.1−117.3	292 (M^+)	$C_{11}H_{20}N_2O_3S_2$	C, H, N
10j	Et	$(CH_2)_3$OTBDMS	47	EtOAc−hexane	87.0−87.8	422 (M^+)	$C_{17}H_{34}N_2O_4S_2Si$	C, H, N
10k	Et	*n*-Bu	67	EtOAc−hexane	91.4−91.7	306 (M^+)	$C_{12}H_{22}N_2O_3S_2$	C, H, N
10l	Et	CH_2Ph	55	EtOAc−hexane	146.0−146.5	340 (M^+)	$C_{15}H_{20}N_2O_3S_2$	C, H, N
10m	Et	$(CH_2)_2$Ph	89	EtOAc−hexane	132.8−133.7	354 (M^+)	$C_{16}H_{22}N_2O_3S_2$	C, H, N
10n	Et	$(CH_2)_2$OMe	59	EtOAc−hexane	82.5−82.9	308 (M^+)	$C_{11}H_{20}N_2O_4S_2$	C, H, N
10o	c-Pr	*n*-Pr	83	EtOAc−hexane	123.3−123.8	305 $(M + H)^+$	$C_{12}H_{20}N_2O_3S_2$	C, H, N
10p	c-Pr	$(CH_2)_3$OTBDMS	88	EtOAc−hexane	82.2−84.4	435 $(M + H)^+$	$C_{18}H_{34}N_2O_4S_2Si$	C, H, N
10q	c-Pr	CH_2Ph	94	EtOAc	153.0−154.0	353 $(M + H)^+$	$C_{16}H_{20}N_2O_3S_2$	C, H, N
10r	c-Pr	$(CH_2)_2$Ph	83	EtOAc−hexane	147.7−148.0	367 $(M + H)^+$	$C_{17}H_{22}N_2O_3S_2$	C, H, N
10s	*n*-Pr	*n*-Pr	85	EtOAc−hexane	115.4−115.6	306 (M^+)	$C_{12}H_{22}N_2O_3S_2$	C, H, N
10t	*n*-Pr	$(CH_2)_3$OTBDMS	88	EtOAc−hexane	68.7−70.3	436 (M^+)	$C_{18}H_{36}N_2O_4S_2Si$	C, H, N
10u	*n*-Pr	CH_2Ph	83	EtOH	135.5−136.6	354 (M^+)	$C_{16}H_{22}N_2O_3S_2$	C, H, N
10v	*n*-Pr	$(CH_2)_2$Ph	86	EtOH	113.4−113.6	368 (M^+)	$C_{17}H_{24}N_2O_3S_2$	C, H, N
10w	Me	*n*-Pr	68	EtOAc−hexane	120.3−122.3	278 (M^+)	$C_{10}H_{18}N_2O_3S_2$	C, H, N
10x	Me	$(CH_2)_3$OTBDMS	77	EtOAc−hexane	79.7−81.7	408 (M^+)	$C_{16}H_{32}N_2O_4S_2Si$	C, H, N
10y	Me	CH_2Ph	73	EtOH	149.7−151.2	326 (M^+)	$C_{14}H_{18}N_2O_3S_2$	C, H, N
10z	Me	$(CH_2)_2$Ph	61	EtOH	129.7−131.6	340 (M^+)	$C_{15}H_{20}N_2O_3S_2$	C, H, N

[a] Analytical results for the indicated elements are within ±0.4% of theoretical values.

two independent experiments. If the EC_{50} (50% effective concentration) was <10 μM and if >90% protection was observed, the compound was judged to be active; otherwise, it was called moderately active. Compounds that exhibited <50% protection were considered inactive.

The previous studies of the structure−activity relationships of HEPT analogs indicate that the anti-HIV-1 activity of HEPT could be potentiated by modification at the 3-position of the C-6-(phenylthio) ring with simple alkyl and halogen substituents.[22−25] Therefore, we first examined the effect of a methyl or fluoro substituent of the C-6-(phenylthio) ring on HIV-1 replication with the compounds **14**−**20**, having an isopropyl group at C-5 and a propoxy group at N-1. Introduction of a methyl or fluoro substituent at the 3-position or 3- and 5-positions of this moiety significantly increased its original anti-HIV-1 activity. The 6-((3,5-dimethylphenyl)thio) derivative **18** was the most inhibitory to HIV-1 replication with an EC_{50} value of 0.064 μM and a selectivity index (SI, ratio of 50% cytotoxic concentration (CC_{50}) to EC_{50}) of 516. However, modification at the 2- or 4-position of the C-6-(phenylthio) ring with a methyl group diminished, or destroyed, the anti-HIV-1 activity; the 6-((2-methylphenyl)thio) derivative **15** was found to be moderately active, and the 6-((4-methylphenyl)thio)

Scheme 3[a]

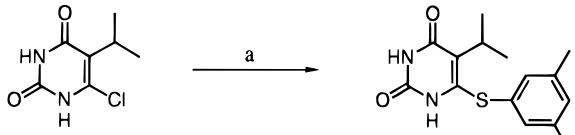


a : *n*-Pr
b : $(CH_2)_3$ OTBDMS
c : *n*-Bu
d : $(CH_2)_2$ Ph
e : $(CH_2)_2$ Ph (3-Me)
f : $(CH_2)_2$OMe
g : $(CH_2)_2$ OPh

[a] (a) Ph_3P, diethyl azodicarboxylate, *N*-hydroxyphthalimide, THF, room temperature, 16 h; (b) (i) $H_2NNH_2 \cdot H_2O$, MeOH, reflux, 4 h (for **7d**−**g**), or (ii) $MeNHNH_2$, CH_2Cl_2, room temperature, 1 h (for **7b**).

derivative **17** was devoid of activity. Again, among the compounds **21**−**25** with an isopropyl group at C-5 and a 3-hydroxypropoxy group at N-1, the 6-((3,5-dimethylphenyl)thio) derivative **23** ($EC_{50} = 0.19\ \mu M$) was found to be 100-fold more potent than the corresponding 6-(phenylthio) derivative **21** ($EC_{50} = 19.0\ \mu M$). Since it has been confirmed that the two methyl groups at the 3- and 5-positions of the C-6-(phenylthio) ring contributed to the maximum activity in these 1-alkoxy-5-isopropyl-6-(arylthio)uracils **14**−**25** as shown previously in the HEPT analogs,[22−25] we selected a ((3,5-dimethylphenyl)thio) group as the C-6 substituent for the following target compounds **26**−**49**.

Scheme 4[a]



50 **51**

[a] (a) 3,5-Dimethylthiophenol, 1 N ethanolic NaOH, EtOH, reflux, 6 h.

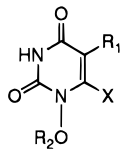
Next, we evaluated the effect of an alkoxy substituent at the N-1 on HIV-1 replication with the compounds **18**, **23**, and **26**−**31** having an isopropyl group at C-5 and a ((3,5-dimethylphenyl)thio) substituent at C-6. The 1-propoxy derivative **18** proved to be the most potent inhibitor of HIV-1 replication, followed by the 1-(3-hydroxypropoxy) derivative **23**. Although the 1-butoxy derivative **26**, the 1-(2-phenylethoxy) derivative **28**, the 1-(2-(3-methylphenyl)ethoxy) derivative **29**, the 1-(2-methoxyethoxy) derivative **30**, and the 1-(2-phenoxyethoxy) derivative **31** were all active with EC_{50} values of 0.42, 0.49, 0.84, 0.43, and 0.46 μM, respectively, they were 6.6−13.1-fold less inhibitory to HIV-1 compared with **18**. Introduction of a benzyloxy group at N-1 significantly reduced the anti-HIV-1 activity; thus, compound **27** was only moderately active ($EC_{50} = 8.45\ \mu M$). Again, this trend was observed in compounds **32**−**37**, having an ethyl group at C-5, in which the 1-propoxy derivative **32** ($EC_{50} = 0.35\ \mu M$) was the most potent and the 1-benzyloxy derivative **35** ($EC_{50} = 5.77\ \mu M$) was the least potent. Finally, the effect of an alkyl substituent at the C-5 on the anti-HIV-1 activity was investigated. The 5-isopropyl derivatives **18** and **23** were 5.5- and 2.8-fold more potent than their 5-ethyl counterparts **32** and **33** ($EC_{50} = 0.54\ \mu M$), respectively. However, introduction of the 5-cyclopropyl group showed significantly weakened anti-HIV-1 activity compared with their 5-isopropyl and 5-ethyl counterparts; thus, all the 5-cyclopropyl derivatives **38**−**41** were moderately active regardless of the alkoxy substituent at N-1. The 5-propyl derivatives **42**−**45** and the 5-methyl derivatives **46**−**49** were more inhibitory to HIV-1 replication than their 5-cyclopropyl counterparts in terms of EC_{50} value, but EC_{50} values of these derivatives were higher than those of their 5-isopropyl and 5-ethyl counterparts. This result is consistent with the previous findings of Miyasaka *et al.*,[20,22−24] in which introduction of an isopropyl or an ethyl group at C-5 of HEPT and its analogs significantly contributed to the anti-HIV-1 activity.

Overall, structure−activity relationships in these 1-alkoxy-5-alkyl-6-(arylthio)uracils are in good agreement with those established in HEPT analogs.[20,22−25] When the anti-HIV-1 activity of the most potent compound **18** was compared with that of AZT, DDC, DDI, and HEPT, **18** was 14-fold less potent than AZT, but 3-, 44-, and 130-fold more potent than DDC, DDI, and HEPT, respectively. The inhibitory effect of compound **18** on the replication of HIV-1 ($HTLV\text{-}III_B$) in human peripheral blood mononuclear cells (PBMCs) was evaluated as previously described,[10,17] and the results are shown in Table 5 along with that of AZT. Compound **18** inhibited HIV-1 replication with an EC_{50} value of 0.15 μM and a selectivity index of 467, but was found to be 17-fold less potent than AZT. In addition, compound **18** was examined for its inhibition of HIV-1, avian myeloblastosis virus (AMV), and Molony murine leukemia virus (Mo-MuLV) recombinant reverse transcriptases (rRTs) (Table 6). It inhibited HIV-1 rRT at an IC_{50} value of 12.30 μM but did not inhibit AMV and Mo-MuLV rRTs at concentrations up to 100 μM, thus showing high selectivity, whereas foscarnet inhibited all three rRTs in the micromolar concentration range. Considering that some HEPT analogs inhibit HIV-1 replication in the nanomolar concentration range,[20,22−25] these isosteric analogs of HEPT seem to be approximately 1 order of magnitude less potent compared with the corresponding HEPT analogs. The relatively lower selectivity indices of these 1-alkoxy analogs compared with those HEPT analogs also seem to be attributed to their lower potency because the level of cytotoxicity of these analogs was similar to that reported for HEPT analogs.

The chemical and metabolic stability of the N−O bond in these 1-alkoxy compounds was examined with compound **18**. Although HEPT was reported to be hydrolyzed in concentrated aqueous HCl−MeOH at 80 °C to afford 6-(phenylthio)thymine,[23] we found that **18** was completely inert in the same reaction condition. When **18** was incubated with a rat liver homogenate preparation for 1 h, at 37 °C, a presuemd metabolite, 6-((3,5-dimethylphenyl)thio)-5-isopropyluracil (**51**) was not detected in this experiment. These results indicate that the N−O bond in these 1-alkoxyuracils are chemically and metabolically quite stable, as we expected.

In conclusion, 6-((3,5-dimethylphenyl)thio)-5-isopropyl-1-propoxyuracil (**18**) showed the most potent and selective anti-HIV-1 activity in a series of 1-alkoxy-5-alkyl-6-(arylthio)uracils and was found to be chemically and metabolically quite stable. But, the anti-HIV-1 activity of these isosteric analogs of HEPT was ap-

Table 2. Physical and Spectral Properties of 1-Alkoxy-5-alkyl-6-(methylthio)-, -6-(methylsulfonyl)-, or -6-(methylsulfinyl)uracils



11a–z, 12a–z

compd	X	R_1	R_2	% yield	crystn solvent	mp, °C	EI-MS, *m/z*	formula	anal.[a]
11a	SMe	*i*-Pr	*n*-Pr	92	EtOAc	84.6–86.5	258 (M^+)	$C_{11}H_{18}N_2O_3S$	C, H, N
11b	SMe	*i*-Pr	$(CH_2)_3OAc$	83	EtOAc	67.3–68.7	317 $(M + H)^+$	$C_{13}H_{20}N_2O_5S$	C, H, N
11c	SMe	*i*-Pr	*n*-Bu	94	EtOAc	96.1–96.8	272 (M^+)	$C_{12}H_{20}N_2O_3S$	C, H, N
11d	SMe	*i*-Pr	CH_2Ph	91	EtOAc	157.3–157.5	306 (M^+)	$C_{15}H_{18}N_2O_3S$	C, H, N
11e	SMe	*i*-Pr	$(CH_2)_2Ph$	95	EtOAc	104.9–106.3	320 (M^+)	$C_{16}H_{20}N_2O_3S$	C, H, N
11f	SMe	*i*-Pr	$(CH_2)_2Ph$(3-Me)	96	EtOAc	100.3–101.2	335 $(M + H)^+$	$C_{17}H_{22}N_2O_3S$	C, H, N
11g	SMe	*i*-Pr	$(CH_2)_2OMe$	95	EtOAc	79.7–81.4	274 (M^+)	$C_{11}H_{18}N_2O_4S$	C, H, N
11h	SMe	*i*-Pr	$(CH_2)_2OPh$	84	EtOAc	148.2–148.8	336 (M^+)	$C_{16}H_{20}N_2O_4S$	C, H, N
11i	SMe	Et	*n*-Pr	97	EtOH	132.4–133.9	244 (M^+)	$C_{10}H_{16}N_2O_3S$	C, H, N
11j	SMe	Et	$(CH_2)_3OAc$	62	EtOH	98.7–99.2	303 $(M + H)^+$	$C_{12}H_{18}N_2O_5S$	C, H, N
11k	SMe	Et	*n*-Bu	90	EtOH	114.7–116.4	258 (M^+)	$C_{11}H_{18}N_2O_3S$	C, H, N
11l	SMe	Et	CH_2Ph	99	EtOH	156.8–157.8	292 (M^+)	$C_{14}H_{16}N_2O_3S$	C, H, N
11m	SMe	Et	$(CH_2)_2Ph$	93	EtOH	90.3–91.2	306 (M^+)	$C_{15}H_{18}N_2O_3S$	C, H, N
11n	SMe	Et	$(CH_2)_2OMe$	92	EtOH	102.5–103.5	206 (M^+)	$C_{10}H_{16}N_2O_4S$	C, H, N
11o	SMe	c-Pr	*n*-Pr	68	EtOAc–hexane	94.8–96.0	257 $(M + H)^+$	$C_{11}H_{16}N_2O_3S$	C, H, N
11p	SMe	c-Pr	$(CH_2)_3OAc$	84	EtOAc–hexane	70.0–70.4	315 $(M + H)^+$	$C_{13}H_{18}N_2O_5S$	C, H, N
11q	SMe	c-Pr	CH_2Ph	60	EtOH–EtOAc	137.8–139.8	305 $(M + H)^+$	$C_{15}H_{16}N_2O_3S$	C, H, N
11r	SMe	c-Pr	$(CH_2)_2Ph$	81	EtOAc–hexane	87.5–89.8	319 $(M + H)^+$	$C_{16}H_{18}N_2O_3S$	C, H, N
11s	SMe	*n*-Pr	*n*-Pr	99	EtOH	101.5–103.2	258 (M^+)	$C_{11}H_{18}N_2O_3S$	C, H, N
11t	SMe	*n*-Pr	$(CH_2)_3OAc$	64	EtOH	72.4–74.8	316 (M^+)	$C_{13}H_{20}N_2O_5S$	C, H, N
11u	SMe	*n*-Pr	CH_2Ph	97	EtOH	135.6–137.6	307 $(M + H)^+$	$C_{15}H_{18}N_2O_3S$	C, H, N
11v	SMe	*n*-Pr	$(CH_2)_2Ph$	80	EtOH	71.9–74.1	320 (M^+)	$C_{16}H_{20}N_2O_3S$	C, H, N
11w	SMe	Me	*n*-Pr	90	EtOAc–hexane	125.5–126.0	230 (M^+)	$C_9H_{14}N_2O_3S$	C, H, N
11x	SMe	Me	$(CH_2)_3OAc$	66	EtOH	108.3–110.4	289 $(M + H)^+$	$C_{11}H_{16}N_2O_5S$	C, H, N
11y	SMe	Me	CH_2Ph	99	EtOH	280.0 dec	278 (M^+)	$C_{13}H_{14}N_2O_3S$	C, H, N
11z	SMe	Me	$(CH_2)_2Ph$	91	EtOH	113.0–114.1	293 $(M + H)^+$	$C_{14}H_{16}N_2O_3S$	C, H, N
12a	SO_2Me	*i*-Pr	*n*-Pr	91	EtOAc–hexane	144.5–145.0	291 $(M + H)^+$	$C_{11}H_{18}N_2O_5S$	C, H, N
12b	SO_2Me	*i*-Pr	$(CH_2)_3OAc$	90	EtOAc–hexane	134.4–135.5	349 $(M + H)^+$	$C_{13}H_{20}N_2O_7S$	C, H, N
12c	SO_2Me	*i*-Pr	*n*-Bu	96	EtOAc–hexane	143.2–145.5	305 $(M + H)^+$	$C_{12}H_{20}N_2O_5S$	C, H, N
12d	SO_2Me	*i*-Pr	CH_2Ph	92	CH_2Cl_2	180 dec	339 $(M + H)^+$	$C_{15}H_{18}N_2O_5S$	C, H, N
12e	SO_2Me	*i*-Pr	$(CH_2)_2Ph$	84	CH_2Cl_2	145.0–146.0	353 $(M + H)^+$	$C_{16}H_{20}N_2O_5S$	C, H, N
12f	SO_2Me	*i*-Pr	$(CH_2)_2Ph$(3-Me)	86	EtOAc–hexane	140.3–140.7	367 $(M + H)^+$	$C_{17}H_{22}N_2O_5S$	C, H, N
12g	SO_2Me	*i*-Pr	$(CH_2)_2OMe$	91	EtOAc–hexane	137.3–138.2	307 $(M + H)^+$	$C_{11}H_{18}N_2O_6S$	C, H, N
12h	SO_2Me	*i*-Pr	$(CH_2)_2OPh$	84	CH_2Cl_2	151.4–151.8	368 (M^+)	$C_{16}H_{20}N_2O_6S$	C, H, N
12i	SO_2Me	Et	*n*-Pr	77	CH_2Cl_2	160.5–161.5	276 (M^+)	$C_{10}H_{16}N_2O_5S$	C, H, N
12j	SO_2Me	Et	$(CH_2)_3OAc$	62	EtOAc–hexane	140.6–141.0	335 $(M + H)^+$	$C_{12}H_{18}N_2O_7S$	C, H, N
12k	SO_2Me	Et	*n*-Bu	73	CH_2Cl_2	155.0–156.0	291 $(M + H)^+$	$C_{11}H_{18}N_2O_5S$	C, H, N
12l	SO_2Me	Et	CH_2Ph	89	CH_2Cl_2	184.0 dec	325 $(M + H)^+$	$C_{14}H_{16}N_2O_5S$	C, H, N
12m	SO_2Me	Et	$(CH_2)_2Ph$	93	CH_2Cl_2	141.2–141.6	339 $(M + H)^+$	$C_{15}H_{18}N_2O_5S$	C, H, N
12n	SO_2Me	Et	$(CH_2)_2OMe$	82	EtOAc–hexane	135.6–136.7	293 $(M + H)^+$	$C_{10}H_{16}N_2O_6S$	C, H, N
12o	SO_2Me	c-Pr	*n*-Pr	72	MeOH–CH_2Cl_2	140.0 dec	288 (M^+)	$C_{11}H_{16}N_2O_5S$	C, H, N
12p	SO_2Me	c-Pr	$(CH_2)_3OAc$	72	EtOH	119.6–120.2 (dec)	347 $(M + H)^+$	$C_{13}H_{18}N_2O_7S$	C, H, N
12q	SO_2Me	c-Pr	CH_2Ph	85	EtOH–CH_2Cl_2	145.8 dec	336 (M^+)	$C_{15}H_{16}N_2O_5S$	C, H, N
12r	SO_2Me	c-Pr	$(CH_2)_2Ph$	59	EtOAc	183.0 dec	230 $(M + H - C_8H_9O)^+$	$C_{16}H_{18}N_2O_5S$	C, H, N
12s	SO_2Me	*n*-Pr	*n*-Pr	83	CH_2Cl_2	167.2–168.9	290 (M^+)	$C_{11}H_{18}N_2O_5S$	C, H, N
12t	SO_2Me	*n*-Pr	$(CH_2)_3OAc$	99	CH_2Cl_2	99.6–102.5	349 $(M + H)^+$	$C_{13}H_{20}N_2O_7S$	C, H, N
12u	SO_2Me	*n*-Pr	CH_2Ph	99	EtOH	180.4–180.8	339 $(M + H)^+$	$C_{15}H_{18}N_2O_5S$	C, H, N
12v	SO_2Me	*n*-Pr	$(CH_2)_2Ph$	99	EtOAc–hexane	140.0–141.0	353 $(M + H)^+$	$C_{16}H_{20}N_2O_5S$	C, H, N
12w	SO_2Me	Me	*n*-Pr	95	EtOH	149.6–151.6	262 (M^+)	$C_9H_{14}N_2O_5S$	C, H, N
12x	SO_2Me	Me	$(CH_2)_3OAc$	91	EtOH	152.3–153.5	321 $(M + H)^+$	$C_{11}H_{16}N_2O_7S$	C, H, N
12y	SOMe	Me	CH_2Ph	99	CH_2Cl_2	300.0 dec	294 (M^+)	$C_{13}H_{14}N_2O_4S$	C, H, N
12z	SO_2Me	Me	$(CH_2)_2Ph$	98	CH_2Cl_2	155.2–157.2	325 $(M + H)^+$	$C_{14}H_{16}N_2O_5S$	C, H, N

[a] See footnote of Table 1.

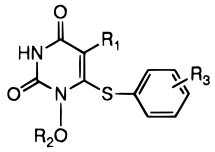
proximately 1 order of magnitude less potent compared with that reported for HEPT analogs.

Experimental Section

Melting points were determined on either an Electrothermal F500MA digital or a Mettler FP62 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane in $CDCl_3$ or DMSO-d_6. ^1H noise-decoupled ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer at 75.4 MHz. When $CDCl_3$ or DMSO-d_6 was used as solvent, it served as the internal standard at δ 77.0 or 39.5, respectively. Electron impact mass spectra (EI-MS) were obtained on a VG Quattro mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60F-254 glass plates. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Where indicated by the symbols of the elements, analyses were within ±0.4% of theoretical values.

Ethyl Cyclopropylacetate (2c). A solution of cyclopropaneacetonitrile (37 g, 456 mmol) in 3 N HCl in EtOH (500

Table 3. Physical and Spectral Properties of 1-Alkoxy-5-alkyl-6-(arylthio)uracils



14–49

compd	R_1	R_2	R_3	% yield	crystn solvent	mp, °C	EI-MS, *m/z*	formula	anal.[a]
14	*i*-Pr	*n*-Pr	H	92	EtOH	106.1−106.7	320 (M^+)	$C_{16}H_{20}N_2O_3S$	C, H, N
15	*i*-Pr	*n*-Pr	2-Me	99	EtOAc−hexane	118.5−119.2	334 (M^+)	$C_{17}H_{22}N_2O_3S$	C, H, N
16	*i*-Pr	*n*-Pr	3-Me	88	EtOH	89.4−90.0	334 (M^+)	$C_{17}H_{22}N_2O_3S$	C, H, N
17	*i*-Pr	*n*-Pr	4-Me	79	EtOAc−hexane	116.8−117.3	334 (M^+)	$C_{17}H_{22}N_2O_3S$	C, H, N
18	*i*-Pr	*n*-Pr	3,5-Me_2	99	EtOH	130.9−131.9	348 (M^+)	$C_{18}H_{24}N_2O_3S$	C, H, N
19	*i*-Pr	*n*-Pr	3-F	99	EtOH	136.4−136.9	338 (M^+)	$C_{16}H_{19}FN_2O_3S$	C, H, N
20	*i*-Pr	*n*-Pr	3,5-F_2	99	EtOH	172.7−173.3	356 (M^+)	$C_{16}H_{18}F_2N_2O_3S$	C, H, N
21	*i*-Pr	$(CH_2)_3OH$	H	81	EtOAc−hexane	90.6−91.7	336 (M^+)	$C_{16}H_{20}N_2O_4S$	C, H, N
22	*i*-Pr	$(CH_2)_3OH$	3-Me	91	EtOAc−hexane	79.1−81.8	350 (M^+)	$C_{17}H_{22}N_2O_4S$	C, H, N
23	*i*-Pr	$(CH_2)_3OH$	3,5-Me	99	EtOH	128.0−129.0	364 (M^+)	$C_{18}H_{24}N_2O_4S$	C, H, N
24	*i*-Pr	$(CH_2)_3OH$	3-F	82	EtOH	94.7−95.5	354 (M^+)	$C_{16}H_{19}FN_2O_4S$	C, H, N
25	*i*-Pr	$(CH_2)_3OH$	3,5-F_2	79	EtOH	136.7−137.0	372 (M^+)	$C_{16}H_{18}F_2N_2O_4S$	C, H, N
26	*i*-Pr	*n*-Bu	3,5-Me_2	99	EtOH	126.0−127.0	362 (M^+)	$C_{19}H_{26}N_2O_3S$	C, H, N
27	*i*-Pr	CH_2Ph	3,5-Me_2	72	EtOH	155.6−156.4	396 (M^+)	$C_{22}H_{24}N_2O_3S$	C, H, N
28	*i*-Pr	$(CH_2)_2Ph$	3,5-Me_2	97	EtOH	113.3−113.9	410 ($M - H)^+$	$C_{23}H_{26}N_2O_3S$	C, H, N
29	*i*-Pr	$(CH_2)_2Ph$(3-Me)	3,5-Me_2	99	EtOH	122.0−124.0	425 ($M + H)^+$	$C_{24}H_{28}N_2O_3S$	C, H, N
30	*i*-Pr	$(CH_2)_2OMe$	3,5-Me_2	99	EtOH	104.0−105.0	364 (M^+)	$C_{18}H_{24}N_2O_4S$	C, H, N
31	*i*-Pr	$(CH_2)_2OPh$	3,5-Me_2	94	EtOH	138.0−139.0	426 (M^+)	$C_{23}H_{26}N_2O_4S$	C, H, N
32	Et	*n*-Pr	3,5-Me_2	79	EtOAc−hexane	115.3−116.0	334 (M^+)	$C_{17}H_{22}N_2O_3S$	C, H, N
33	Et	$(CH_2)_3OH$	3,5-Me_2	76	EtOH	124.9−125.8	350 (M^+)	$C_{17}H_{22}N_2O_4S$	C, H, N
34	Et	*n*-Bu	3,5-Me_2	96	EtOAc−hexane	128.2−128.8	348 (M^+)	$C_{18}H_{24}N_2O_3S$	C, H, N
35	Et	CH_2Ph	3,5-Me_2	65	EtOH	153.7−154.4	382 (M^+)	$C_{21}H_{22}N_2O_3S$	C, H, N
36	Et	$(CH_2)_2Ph$	3,5-Me_2	86	EtOH	134.6−134.9	396 (M^+)	$C_{22}H_{24}N_2O_3S$	C, H, N
37	Et	$(CH_2)_2OMe$	3,5-Me_2	67	EtOH	128.2−128.7	350 (M^+)	$C_{17}H_{22}N_2O_4S$	C, H, N
38	c-Pr	*n*-Pr	3,5-Me_2	80	EtOAc−hexane	152.5−152.9	346 (M^+)	$C_{18}H_{22}N_2O_3S$	C, H, N
39	c-Pr	$(CH_2)_3OH$	3,5-Me_2	93	EtOH	147.7−148.9	362 (M^+)	$C_{18}H_{22}N_2O_4S$	C, H, N
40	c-Pr	CH_2Ph	3,5-Me_2	78	EtOH	149.2−150.0	394 (M^+)	$C_{22}H_{22}N_2O_3S$	C, H, N
41	c-Pr	$(CH_2)_2Ph$	3,5-Me_2	99	EtOAc−hexane	137.0−137.4	409 ($M + H)^+$	$C_{23}H_{24}N_2O_3S$	C, H, N
42	*n*-Pr	*n*-Pr	3,5-Me_2	95	EtOAc−hexane	101.5−103.6	348 (M^+)	$C_{18}H_{24}N_2O_3S$	C, H, N
43	*n*-Pr	$(CH_2)_3OH$	3,5-Me_2	97	EtOAc−hexane	108.6−109.0	364 (M^+)	$C_{18}H_{24}N_2O_4S$	C, H, N
44	*n*-Pr	CH_2Ph	3,5-Me_2	94	EtOH	136.0−137.0	396 (M^+)	$C_{22}H_{24}N_2O_3S$	C, H, N
45	*n*-Pr	$(CH_2)_2Ph$	3,5-Me_2	99	EtOH	114.2−114.4	410 (M^+)	$C_{23}H_{26}N_2O_3S$	C, H, N
46	Me	*n*-Pr	3,5-Me_2	83	EtOAc−hexane	118.3−119.7	320 (M^+)	$C_{16}H_{20}N_2O_3S$	C, H, N
47	Me	$(CH_2)_3OH$	3,5-Me_2	93	EtOAc−hexazne	153.2−154.3	336 (M^+)	$C_{16}H_{20}N_2O_4S$	C, H, N
48	Me	CH_2Ph	3,5-Me_2	93	EtOH	178.1−179.4	368 (M^+)	$C_{20}H_{20}N_2O_3S$	C, H, N
49	Me	$(CH_2)_2Ph$	3,5-Me_2	99	EtOH	143.9−144.5	382 (M^+)	$C_{21}H_{22}N_2O_3S$	C, H, N

[a] See footnote of Table 1.

mL) was gently heated under reflux for 3 h, and the excess solvent was removed by distillation. To the residue was added H_2O (150 mL), and the aqueous solution was extracted with Et_2O (50 mL × 6). The combined ethereal solution was washed with saturated $NaHCO_3$ solution until the washings were neutral and brine. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed by distillation to give 36.41 g of crude **2c** which contained ∼9% (w/w) of Et_2O confirmed by ^1H NMR spectrum (33.2 g, 57% for pure **2c**) and was used in the next step without further purification: IR (neat) 1740 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12−0.19 (m, 2 H, CH_2CH_2), 0.50−0.59 (m, 2 H, CH_2CH_2), 1.05 (m, 1 H, CH), 1.26 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.20 (d, J = 7.2 Hz, 2 H, CH_2), 4.15 (q, J = 7.2 Hz, 2 H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 4.29, 6.88, 14.22, 39.41, 60.22, 173.23.

General Procedure for the Preparation of Ethyl 2-Alkyl-3,3-bis(methylthio)acrylates 3a−e. To a stirred solution of diisopropylamine (84.1 mL, 600 mmol) in anhydrous THF (600 mL) was added butyllithium (1.6 M solution in hexanes, 312.5 mL, 500 mmol) at −78 °C over 15 min. After the mixture was stirred at −30 °C for 30 min, ethyl ester **2a−e** (500 mmol) in anhydrous THF (80 mL) was added over 30 min, and the stirred solution was maintained at 0 °C for 30 min. The contents were then cooled to −78 °C, and carbon disulfide (45.1 mL, 750 mmol) was added over 30 min. The temperature of the mixture was not allowed to rise above −70 °C during the addition. The mixture was further stirred for 30 min, and then MeI (93.4 mL, 1.5 mol) was added over 5 min. The mixture was stirred for an additional 16 h at room temperature and then poured into H_2O (400 mL). The aqueous phase was extracted with Et_2O (100 mL × 3). The combined ethereal solution was washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The brick red oily residue was distilled *in vacuo* or purified by flash column chromatography to give **3a−e** as a yellow oil.

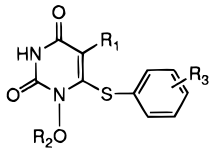
Ethyl 3,3-Bis(methylthio)-2-isopropylacrylate (3a).[33] This compound was synthesized from **2a** in 85% yield.

Ethyl 3,3-Bis(methylthio)-2-ethylacrylate (3b).[32,33] This compound was synthesized from **2b** in 90% yield.

Ethyl 2-Cyclopropyl-3,3-bis(methylthio)acrylate (3c). This compound was synthesized from **2c** and purified by flash column chromatography on silica gel with Et_2O−hexane (1:9) as eluent: yield 81%; IR (neat) 1723 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60−0.68 (m, 2 H, CH_2CH_2), 0.82−0.90 (m, 2 H, CH_2CH_2), 1.31 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.17 (tt, J = 8.6 Hz, J = 5.3 Hz, 1 H, CH), 2.26 (s, 3 H, SCH_3), 2.35 (s, 3 H, SCH_3), 4.21 (q, J = 7.2 Hz, 2 H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 7.07, 13.76, 14.10, 16.08, 17.58, 60.91, 132.60, 144.24, 166.85; MS (EI) *m/z* 232 (M^+). Anal. ($C_{10}H_{16}O_2S_2$) C, H.

Ethyl 3,3-Bis(methylthio)-2-propylacrylate (3d). This compound was synthesized from **2d**: yield 72%; bp 98−100 °C/0.8 mmHg; IR (neat) 1722 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.32 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.47 (tq, J = 7.7 Hz, J = 7.4 Hz, 2 H, CH_2CH_2-CH_3), 2.29 (s, 3 H, SCH_3), 2.32 (s, 3 H, SCH_3), 2.57 (t, J = 7.7

Table 4. Inhibition of HIV-1 Replication in CEM-SS Cells by 1-Alkoxy-5-alkyl-6-(arylthio)uracils[a]



14–49

compd	R_1	R_2	R_3	EC_{50}[b] (μM)	CC_{50}[c] (μM)	SI[d]
14	*i*-Pr	*n*-Pr	H	6.75 (A)	75	11
15	*i*-Pr	*n*-Pr	2-Me	13.9 (M)	41	2.9
16	*i*-Pr	*n*-Pr	3-Me	0.98 (A)	40	41
17	*i*-Pr	*n*-Pr	4-Me	NA (I)	69	
18	*i*-Pr	*n*-Pr	3,5-Me_2	0.064 (A)	33	516
19	*i*-Pr	*n*-Pr	3-F	1.90 (A)	72	38
20	*i*-Pr	*n*-Pr	3,5-F_2	2.39 (A)	>200	>84
21	*i*-Pr	$(CH_2)_3OH$	H	19.0 (M)	170	8.9
22	*i*-Pr	$(CH_2)_3OH$	3-Me	4.70 (A)	118	28
23	*i*-Pr	$(CH_2)_3OH$	3,5-Me_2	0.19 (A)	75	395
24	*i*-Pr	$(CH_2)_3OH$	3-F	NA (I)	3.4	
25	*i*-Pr	$(CH_2)_3OH$	3,5-F_2	7.52 (A)	150	20
26	*i*-Pr	*n*-Bu	3,5-Me_2	0.42 (A)	30	71
27	*i*-Pr	CH_2Ph	3,5-Me_2	8.45 (M)	24	2.8
28	*i*-Pr	$(CH_2)_2Ph$	3,5-Me_2	0.49 (A)	15	31
29	*i*-Pr	$(CH_2)_2Ph$(3-Me)	3,5-Me_2	0.84 (A)	13	15
30	*i*-Pr	$(CH_2)_2OMe$	3,5-Me_2	0.43 (A)	96	223
31	*i*-Pr	$(CH_2)_2OPh$	3,5-Me_2	0.46 (A)	16	35
32	Et	*n*-Pr	3,5-Me_2	0.35 (A)	54	154
33	Et	$(CH_2)_3OH$	3,5-Me_2	0.54 (A)	123	228
34	Et	*n*-Bu	3,5-Me_2	0.97 (A)	40	41
35	Et	CH_2Ph	3,5-Me_2	5.77 (A)	>200	>35
36	Et	$(CH_2)_2Ph$	3,5-Me_2	0.46 (A)	36	78
37	Et	$(CH_2)_2OMe$	3,5-Me_2	1.97 (A)	136	69
38	c-Pr	*n*-Pr	3,5-Me_2	6.12 (M)	30	4.9
39	c-Pr	$(CH_2)_3OH$	3,5-Me_2	15.1 (M)	128	8.5
40	c-Pr	CH_2Ph	3,5-Me_2	15.9 (M)	>200	>13
41	c-Pr	$(CH_2)_2Ph$	3,5-Me_2	6.03 (M)	43	7.1
42	*n*-Pr	*n*-Pr	3,5-Me_2	2.57 (A)	45	18
43	*n*-Pr	$(CH_2)_3OH$	3,5-Me_2	8.22 (A)	107	13
44	*n*-Pr	CH_2Ph	3,5-Me_2	10.3 (M)	114	11
45	*n*-Pr	$(CH_2)_2Ph$	3,5-Me_2	0.70 (A)	29	41
46	Me	*n*-Pr	3,5-Me_2	0.93 (A)	64	69
47	Me	$(CH_2)_3OH$	3,5-Me_2	5.55 (A)	140	25
48	Me	CH_2Ph	3,5-Me_2	10.1 (M)	>200	>20
49	Me	$(CH_2)_2Ph$	3,5-Me_2	3.08 (A)	>121	>39
AZT				0.0045	>1.0	>220
DDC				0.19	>10	>53
DDI[e]				2.8	>10	>3.6
HEPT[f]				8.3	400	48

[a] The antiviral activity and cytotoxicity of the compound were tested by the Developmental Therapeutics Program of the National Cancer Institute. All data is the mean value of at least two independent experiments run in duplicate. [b] Effective concentration of compound required to achieve 50% protection of CEM-SS cells against the cytopathic effect of HIV-1. If the EC_{50} was <10 μM and if >90% protection was observed, the compound was judged to be active (A); otherwise, it was called moderately active (M). Compounds that exhibited <50% protection were considered inactive (I). NA, not applicable. [c] Cytotoxic concentration of compound required to reduce the viability of mock-infected CEM-SS cells by 50%. [d] Selectivity index: ratio of CC_{50}/EC_{50}. [e] Inhibition of HIV-1 replication in CEM-V cells. [f] Data from ref 17. Inhibition of $HTLB\text{-}III_B$ replication in CEM cells.

Hz, 2 H, $CH_2CH_2CH_3$), 4.25 (q, J = 7.2 Hz, 2 H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 13.75, 14.18, 16.65, 17.70, 21.83, 35.24, 60.88, 137.50, 141.32, 168.63; MS (EI) *m/z* 234 (M^+). Anal. ($C_{10}H_{18}O_2S_2$) C, H.

Ethyl 3,3-Bis(methylthio)-2-methylacrylate (3e). This compound was synthesized from **2e**: yield 71%; bp 82−106 °C/0.5 mmHg; IR (neat) 1721 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.15 (s, 3 H, CH_3), 2.31 (s, 3 H, SCH_3), 2.34 (s, 3 H, SCH_3), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.14, 16.72, 17.83, 19.11, 60.91, 134.92, 139.24, 168.46; MS (EI) *m/z* 206 (M^+). Anal. ($C_8H_{14}O_2S_2$) C, H.

Table 5. Inhibition of HIV-1 Replication in Human Peripheral Blood Mononuclear Cells (PBMCs) by **18** and AZT[a]

compd	EC_{50}[b] (μM)	CC_{50}[c] (μM)	SI[d]
18	0.15	70	467
AZT	0.009	149	16556

[a] The antiviral activity and cytotoxicity of the compound were tested at the National Institute of Health (Seoul, Korea). Each value represents the mean value of two independent experiments run in duplicate. [b] Effective concentration of compound required to reduce the production of p24 antigen of untreated control by 50%. [c] Cytotoxic concentration of compound required to reduce the [^{3}H]thymidine incorporation into DNA by control by 50%. [d] Selectivity index: ratio of CC_{50}/EC_{50}.

Table 6. Inhibitory Effect of **18** and Foscarnet of HIV-1, Avian Myeloblastosis Virus (AMV), and Molony Murine Leukemia Virus (Mo-MuLV) Recombinant Reverse Transcriptases (rRTs)

	IC_{50}[a] (μM)		
compd	HIV-1	AMV	Mo-MuLV
18	12.30	>100	>100
foscarnet	2.03	9.31	17.6

[a] The concentration required to reduce optical density (OD) of control by 50%. Each value represents the mean value of at least three independent experiments run in duplicate.

General Procedure for the Preparation of 2-Alkyl-3,3-bis(methylthio)acrylic Acids 4a−e. A mixture of ethyl 2-alkyl-3,3-bis(methylthio)acrylate **3a**−**e** (300 mmol) and 2 N KOH (300 mL for **3b** and **3d**−**e** or 600 mL for **3a** and **3c**) in EtOH (300 mL for **3b** and **3d**−**e** or 1.2 L for **3a** and **3c**) was heated under reflux for 3 h (for **3b** and **3d**−**e**) or 72 h (for **3a** and **3c**). The reaction mixture was concentrated to remove EtOH and poured into H_2O (300 mL). The aqueous phase was washed with Et_2O (200 mL × 2), acidified with concentrated HCl to pH 3, and extracted with Et_2O (200 mL × 3). The combined ethereal solution was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was crystallized from hexane to give **4a**−**e** as white crystals.

3,3-Bis(methylthio)-2-isopropylacrylic Acid (4a).[25] This compound was synthesized from **3a** in 82% yield.

3,3-Bis(methylthio)-2-ethylacrylic Acid (4b).[25] This compound was synthesized from **3b** in 86% yield.

2-Cyclopropyl-3,3-bis(methylthio)acrylic Acid (4c). This compound was synthesized from **3c**: yield 77%; mp 63.5−64.6 °C (hexane); IR (KBr) 1691 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69−0.75 (m, 2 H, CH_2CH_2), 0.86−0.94 (m, 2 H, CH_2CH_2), 2.10 (tt, J = 8.6 Hz, J = 5.3 Hz, 1 H, CH), 2.30 (s, 3 H, SCH_3), 2.38 (s, 3 H, SCH_3), 10.43 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 7.47, 13.21, 13.79, 16.92, 124.80, 129.31, 172.02; MS (EI) *m/z* 205 $(M + H)^+$. Anal. ($C_8H_{12}O_2S_2$) C, H.

3,3-Bis(methylthio)-2-propylacrylic Acid (4d). This compound was synthesized from **3d**: yield 76%; mp 44.2−45.2 °C (hexane); IR (KBr) 1662 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.52 (tq, J = 7.8 Hz, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.36 (s, 6 H, 2 SCH_3), 2.64 (t, J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 10.55 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 13.79, 17.20, 18.24, 22.16, 35.36, 137.88, 143.57, 173.09; MS (EI) *m/z* 206. Anal. ($C_8H_{14}O_2S_2$) C, H.

3,3-Bis(methylthio)-2-methylacrylic Acid (4e). This compound was synthesized from **3e**: yield 89%; mp 82.4−82.8 °C (hexane); IR (KBr) 1677 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H, CH_3), 2.38 (s, 6 H, 2 SCH_3), 12.13 (br s, 1 H, COOH): ^{13}C NMR ($CDCl_3$) δ 17.30, 18.50, 19.27, 131.10, 145.98, 172.80; MS (EI) *m/z* 178 (M^+). Anal. ($C_6H_{10}O_2S_2$) C, H.

General Procedure for the Preparation of 2-Alkyl-3,3-bis(methylthio)acryloyl Chlorides 5a−e. To a stirred solution of 2-alkyl-3,3-bis(methylthio)acrylic acid **4a**−**e** (100 mmol) in anhydrous benzene (100 mL) were added oxalyl chloride (10.5 mL, 120 mmol) dropwise and 3 drops of DMF at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h and evaporated to dryness. The residue was distilled *in vacuo* to give **5a**−**e** as a brick red oil.

3,3-Bis(methylthio)-2-isopropylacryloyl Chloride (5a).[25] This compound was synthesized from **4a** in 91% yield.

3,3-Bis(methylthio)-2-ethylacryloyl Chloride (5b).[25] This compound was synthesized from **4b** in 91% yield.

2-Cyclopropyl-3,3-bis(methylthio)acryloyl Chloride (5c). This compound was synthesized from **4c**: yield 88%; bp 115−119 °C/2 mmHg; IR (neat) 1782 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68−0.76 (m, 2 H, CH_2CH_2), 0.93−1.08 (m, 2 H, CH_2CH_2), 1.95 (tt, J = 8.4 Hz, J = 5.4 Hz, 1 H, CH), 2.34 (s, 3 H, SCH_3), 2.42 (s, 3 H, SCH_3); ^{13}C NMR ($CDCl_3$) δ 8.16, 13.54, 16.54, 18.18, 140.98, 143.61, 165.88.

3,3-Bis(methylthio)-2-propylacryloyl Chloride (5d). This compound was synthesized from **4d**: yield 74%; bp 116−128 °C/4 mmHg; IR (neat) 1773 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.55 (tq, J = 7.8 Hz, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.36 (s, 3 H, SCH_3), 2.39 (s, 3 H, SCH_3), 2.67 (t, J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 13.50, 16.80, 17.92, 21.64, 35.11, 142.12, 143.48, 166.61.

3,3-Bis(methylthio)-2-methylacryloyl Chloride (5e). This compound was synthesized from **4e**: yield 90%; bp 100−108 °C/2 mmHg; IR (neat) 1763 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3 H, CH_3), 2.39 (s, 3 H, SCH_3), 2.42 (s, 3 H, SCH_3); ^{13}C NMR ($CDCl_3$) δ 17.35, 18.49, 19.81, 134.64 147.94, 166.10.

General Procedure for the Preparation of *N*-Alkoxyphthalimides 9a−g. Diethyl azodicarboxylate (1.90 mL, 12.0 mmol) was added dropwise at 0 °C to a stirred suspension of alcohol (**8a−g**) (10.0 mmol), triphenylphosphine (3.15 g, 12.0 mmol), and *N*-hydroxyphthalimide (1.96 g, 12.0 mmol) in THF (50 mL). The mixture was stirred at room temperature for 16 h and evaporated to dryness. The residue was triturated with Et_2O (20 mL) and filtered, and the filtrate was evaporated. The process was repeated, and then the residue was purified by flash column chromatography or crystallized from a suitable solvent to afford **9a−g** as white crystals.

***N*-Propoxyphthalimide (9a).** This compound was synthesized from 1-propanol (**8a**) and purified by flash column chromatography on silica gel with Et_2O−hexane (1:3) as eluent: yield 98%; mp 57.1−58.3 °C (Et_2O−hexane); IR (KBr) 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 7.2 Hz, 3 H, CH_3), 1.82 (qt, J = 7.2 Hz, J = 6.9 Hz, 2 H, OCH_2CH_2), 4.17 (t, J = 6.9 Hz, 2 H, OCH_2), 7.75−7.85 (m, 4 H, Ar H); MS (EI) m/z 206 $(M + H)^+$. Anal. ($C_{11}H_{11}NO_3$) C, H, N.

***N*-(3-((*tert*-Butyldimethylsilyl)oxy)propoxy)-phthalimide (9b).**[27] This compound was synthesized from 3-((*tert*-butyldimethylsilyl)oxy)-1-propanol (**8b**) in 92% yield.

***N*-Butoxyphthalimide (9c).** This compound wsa synthesized from 1-butanol (**8c**) and purified by flash column chromatography on silica gel with Et_2O−hexane (1:3) as eluent: yield 98%; mp 29.2−30.2 °C (petroleum ether); IR (KBr) 1733 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3 H, CH_3), 1.53 (qt, J = 7.5 Hz, J = 7.2 Hz, 2 H, $OCH_2CH_2CH_2$), 1.78 (tt, J = 7.2 Hz, J = 6.6 Hz, 2 H, OCH_2CH_2), 4.21 (t, J = 6.6 Hz, 2 H, OCH_2), 7.75−7.85 (m, 4 H, Ar H); MS (EI) m/z 220 $(M + H)^+$. Anal. ($C_{12}H_{13}NO_3$) C, H, N.

***N*-(2-Phenylethoxy)phthalimide (9d).** This compound was synthesized from phenethyl alcohol (**8d**) and purified by flash column chromatography on silica gel with Et_2O−hexane (1:3) as eluent: yield 88%; mp 92.9−94.4 °C (EtOH) (lit.[36] mp 91−92 °C); IR (KBr) 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.14 (t, J = 7.4 Hz, 2 H, CH_2Ar), 4.43 (t, J = 7.4 Hz, 2 H, OCH_2), 7.16−7.35 (m, 5 H, Ar H), 7.68−7.90 (m, 4 H, Ar H).

***N*-(2-(3-Methylphenyl)ethoxy)phthalimide (9e).** This compund was synthesized from 3-methylphenethyl alcohol (**8e**) and purified by flash column chromatography on silica gel with Et_2O−hexane (1:3) as eluent: yield 96%; mp 59.1−59.7 °C (Et_2O−hexane); IR (KBr) 1726 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H, CH_3), 3.12 (t, J = 7.5 Hz, 2 H, CH_2Ar), 4.43 (t, J = 7.5 Hz, 2 H, OCH_2), 6.98−7.22 (m, 4 H, Ar H), 7.70−7.86 (m, 4 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 21.33, 34.55, 78.53, 123.46, 125.79, 127.31, 128.42, 128.91, 129.61, 134.41, 136.57, 138.11, 163.54; MS (EI) m/z 282 $(M + H)^+$. Anal. ($C_{17}H_{15}NO_3$) C, H, N.

***N*-(2-Methoxyethoxy)phthalimide (9f).** This compound was synthesized from 2-methoxyethanol (**8f**) and purified by flash column chromatography on silica gel with EtOAc−hexane (1:2) as eluent: yield 83%; mp 93.7−94.3 °C (EtOAc−hexane); IR (KBr) 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3 H, OCH_3), 3.76 (t, J = 4.5 Hz, 2 H, CH_2OCH_3), 4.37 (t, J = 4.5 Hz, 2 H, OCH_2), 7.70−7.90 (m, 4 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 59.07, 70.41, 77.04, 123.46, 126.90, 128.96, 134.38, 163.37; MS (EI) m/z 222 $(M + H)^+$. Anal. ($C_{11}H_{11}NO_4$) C, H, N.

***N*-(2-Phenoxyethoxy)phthalimide (9g).** This compound was synthesized from 2-phenoxyethanol (**8g**) and crystallized from EtOAc: yield 72%; mp 136.2−136.7 °C (EtOAc); IR (KBr) 1726 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (t, J = 4.5 Hz, 2 H, CH_2OPh), 4.57 (t, J = 4.5 Hz, 2 H, OCH_2), 6.75−6.88 (m, 2 H, Ar H), 6.90−6.98 (m, 1 H, Ar H), 7.18−7.30 (m, 2 H, Ar H), 7.70−7.88 (m, 4H, Ar H); ^{13}C NMR ($CDCl_3$) δ 66.07, 75.99, 114.56, 121.14, 123.44, 128.80, 129.33, 134.39, 158.15, 163.25; MS (EI) m/z 283 (M^+). Anal. ($C_{16}H_{13}NO_4$) C, H, N.

General Procedure for the Preparation of Alkoxyamines 7a and 7c−g. A mixture of *N*-alkoxyphthalimide **9a** and **9c−g** (10.0 mmol) and hydrazine monohydrate (0.49 mL, 10.0 mmol) in MeOH (60 mL) was heated under reflux for 4 h. After cooling, the resulting suspension was filtered, and the filtrate was evaporated. The residue was triturated with Et_2O (60 mL) and filtered, and the filtrate was evaporated to dryness. The residue was distilled or purified by flash column chromatography to give **7a** and **7c−g**.

Propoxyamine (7a). This compound was synthesized from **9a** and purified by distillation: yield 72%; a colorless liquid; bp 89−91 °C (lit.[37] bp 90−91 °C); ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3 H, CH_3), 1.60 (qt, J = 7.5 Hz, J = 6.6 Hz, 2 H, OCH_2CH_2), 3.62 (t, J = 6.6 Hz, 2 H, OCH_2), 4.65 (br s, 2 H, NH_2).

Butoxyamine (7c). This compound was synthesized from **9c** and purified by distillation: yield 77%; a colorless liquid; bp 114−116 °C (lit.[37] bp 115 °C); ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3 H, CH_3), 1.36 (qt, J = 7.2 Hz, J = 6.9 Hz, 2 H, $OCH_2CH_2CH_2$), 1.56 (tt, J = 6.9 Hz, J = 6.6 Hz, 2 H, OCH_2CH_2), 3.66 (t, J = 6.6 Hz, 2 H, OCH_2), 4.97 (br s, 2 H, NH_2).

(2-Phenylethoxy)amine (7d).[36] This compound was synthesized from **9d** and purified by flash column chromatography on silica gel with Et_2O−hexane (1:1) as eluent: yield 85%; a pale yellow oil; IR (neat) 3314 (ONH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.90 (t, J = 6.9 Hz, 2 H, CH_2Ar), 3.88 (t, J = 6.9 Hz, 2 H, CH_2ONH_2), 5.34 (br s, 2 H, NH_2), 7.10−7.40 (m, 5 H, Ar H).

(2-(3-Methylphenyl)ethoxy)amine (7e). This compound was synthesized from **9e** and purified by flash column chromatography on silica gel with EtOAc−hexane (1:2) as eluent: yield 89%; a yellow oil; IR (neat) 3314 (ONH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H, CH_3), 2.87 (t, J = 7.1 Hz, 2 H, CH_2Ar), 3.89 (t, J = 7.1 Hz, 2 H, CH_2ONH_2), 6.98−7.06 (m, 3 H, Ar H), 7.15−7.22 (m, 1 H, Ar H). Anal. ($C_9H_{13}NO$) C, H. N.

(2-Methoxyethoxy)amine (7f). This compound was synthesized from **9f** and purified by distillation: yield 50%; a colorless liquid; bp 132−136 °C; IR (neat) 3315 (ONH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3 H, OCH_3), 3.57 (t, J = 4.5 Hz, 2 H, CH_2ONH_2), 3.83 (t, J = 4.5 Hz, 2 H, CH_2OMe), 5.46 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 58.77, 70.70, 74.44. Anal. ($C_3H_9NO_2$) C, H, N.

(2-Phenoxyethoxy)amine (7g). This compound was synthesized from **9g** and purified by flash column chromatography on silica gel with EtOAc−hexane (1:1) as eluent: yield 63%; mp 43.6−44.2 °C (EtOAc−hexane); IR (KBr) 1600 (OPh), 3324 (ONH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (t, J = 4.5 Hz, 2 H, CH_2OPh), 4.16 (t, J = 4.5 Hz, 2 H, CH_2ONH_2), 5.23 (br s, 2 H, NH_2), 6.86−7.00 (m, 3 H, Ar H), 7.22−7.35 (m, 2 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 65.91, 73.82, 114.52, 120.86, 129.38, 158.65; MS (EI) m/z 153 (M^+). Anal. ($C_8H_{11}NO_2$) C, H, N.

(3-((*tert*-Butyldimethylsilyl)oxy)propoxy)amine (7b). This compound was synthesized from **9b** in 84% yield according to the published procedure.[27]

General Procedure for the Preparation of *N*-Alkoxy-*N*′-(2-alkyl-3,3-bis(methylthio)acryloyl)ureas 10a−z. A mixture of 2-alkyl-3,3-bis(methylthio)acryloyl chloride **5a−e** (10.0 mmol) and AgOCN (1.80 g, 12.0 mmol) in anhydrous benzene (20 mL) was heated under reflux for 30 min under a nitrogen atmosphere in the dark to generate isocyanate **6a−e** *in situ* and cooled to 0 °C. To this mixture was added

alkoxyamine **7a**−**h** (11.0 mmol) in anhydrous benzene (10 mL). After being stirred at room temperature for 1 h, the mixture was filtered through a pad of Celite, and the filtrate was again filtered using a millipore filter (0.22 μm). The filtrate was evaporated to dryness, and the residue was purified by flash column chromatography on silica gel or crystallized from a suitable solvent to give **10a**−**z** as white crystals.

General Procedure for the Preparation of 1-Alkoxy-5-alkyl-6-(methylthio)uracils 11a−z. A stirred solution of *N*-alkoxy-*N*′-(2-alkyl-3,3-bis(methylthio)acryloyl)urea **10a**−**z** (10.0 mmol) and *p*-TsOH (0.19 g, 1.0 mmol) in AcOH (50 mL) was heated at 80 °C for 1 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel or crystallized from a suitable solvent to give **11a**−**z** as white crystals.

General Procedure for the Preparation of 1-Alkoxy-5-alkyl-6-(methylsulfonyl)uracils 12a−x and 12z and 1-(Benzyloxy)-6-(methylsulfinyl)thymine (12y). To a stirred solution of 1-alkoxy-5-alkyl-6-(methylthio)uracil **11a**−**z** (5.0 mmol) in CH_2Cl_2 (20 mL) was added 3-chloroperoxybenzoic acid (85%, 3.05 g, 15.0 mmol) in CH_2Cl_2 (20 mL) at room temperature. The mixture was heated under reflux for 16 h and then cooled to room temperature. After saturated $NaHCO_3$ solution (20 mL) and saturated sodium thiosulfate solution (20 mL) were added to it, the mixture was stirred for an additional 10 min. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined CH_2Cl_2 solution was washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel and then crystallized from a suitable solvent to give **12a**−**z** as white crystals.

3,5-Difluorothiophenol (13g). The stirred warm mixture of 3,5-difluoroaniline (5.00 g, 38.7 mmol), concentrated HCl (8 mL), and H_2O (8 mL) was cooled to 0 °C and diazotized with a solution of $NaNO_2$ (2.75 g, 39.9 mmol) in H_2O (6 mL), added in such a rate that the temperature could be maintained by cooling at 0−5 °C. The mixture was stirred at 0 °C for an additional 30 min and filtered. To a stirred solution of potassium ethyl xanthogenate (8.70 g, 54.3 mmol) in H_2O (10 mL) was added the clear filtrate at 70 °C over 1 h. After the addition was complete, the mixture was cooled to room temperature and stirred for 1 h. The separated oily compound was extracted with Et_2O (30 mL × 3), and the ethereal solution was evaporated. The residue was dissolved in EtOH (25 mL), and the solution was heated under reflux under a nitrogen atmosphere and cooled to room temperature. To this ethanolic solution was added KOH (85%, 9.3 g, 141 mmol) in H_2O (6 mL) over 30 min, and the mixture was heated under reflux for 2 h and evaporated. The residue was dissolved in H_2O (30 mL) and washed with Et_2O (20 mL). Zinc (0.8 g) was added to the aqueous phase, and the mixture was acidified at 10 °C over 30 min with concentrated HCl. The oily product was extracted with Et_2O (30 mL × 3), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give 2.33 g (42%) of **13g** as a colorless liquid: bp 64 °C/20 mmHg; IR (neat) 2577 (SH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (s, 1 H, SH), 6.59 (tt, J = 9.0 Hz, J = 2.1 Hz, 1 H, H-4), 6.78 (m, 2 H, H-2 and H-6); ^{13}C NMR ($CDCl_3$) δ 101.28 (t, $^2J_{C,F}$ = 25.3 Hz, C-4), 111.88 (dd, $^2J_{C,F}$ = 18.0 Hz, $^4J_{C,F}$ = 8.9 Hz, C-2 and C-6), 134.74 (t, $^3J_{C,F}$ = 10.7 Hz, C-1), 162.93 (dd, $^1J_{C,F}$ = 250.1 Hz, $^3J_{C,F}$ = 13.4 Hz, C-3 and C-5); MS (EI) *m*/*z* 145 $(M - H)^+$. Anal. ($C_6H_4F_2S$) C, H.

General Procedure for the Preparation of 1-Alkoxy-5-alkyl-6-(arylthio)uracils 14−49. To a stirred suspension of 1-alkoxy-5-alkyl-6-(methylsulfonyl)uracil **12a**−**x** and **12z** or 1-(benzyloxy)-6-(methylsulfinyl)thymine (**12y**) (1.0 mmol) and arenethiol **13a**−**g** (1.0 mmol) in EtOH (2 mL) was added 1 N ethanolic NaOH (1.10 or 3.30 mL for **12b**, **12j**, **12p**, **12t**, and **12x**) at room temperature under a nitrogen atmosphere. After the mixture was stirred for 20 min, 3 N HCl in EtOH (0.37 or 1.10 mL for **12b**, **12j**, **12p**, **12t**, and **12x**) was added, and the reaction mixture was evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc−hexane or MeOH−CH_2Cl_2 as eluent or crystallized from a suitable solvent to give **14**−**49** as white crystals. Starting materials and spectral data for selected compounds are given below.

5-Isopropyl-6-(phenylthio)-1-propoxyuracil (14): 12a and **13a**; IR (KBr) 1661, 1723 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3 H, $OCH_2CH_2CH_3$), 1.26 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.64 (qt, J = 7.4 Hz, J = 6.8 Hz, 2 H, OCH_2CH_2), 3.53 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.07 (t, J = 6.8 Hz, 2 H, OCH_2), 7.22−7.37 (m, 5 H, Ar H), 8.59 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 10.06, 20.24, 21.04, 30.95, 78.89, 125.07, 127.61, 128.80, 129.56, 132.92, 146.03, 147.54, 160.37.

6-((3,5-Dimethylphenyl)thio)-5-isopropyl-1-propoxyuracil (18): 12a and **13e**; IR (KBr) 1654, 1737 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3 H, $OCH_2CH_2CH_3$), 1.26 (d, J = 7.1 Hz, 6 H, $CH(CH_3)_2$), 1.67 (qt, J = 7.4 Hz, J = 6.8 Hz, 2 H, OCH_2CH_2), 2.28 (s, 6 H, 2 Ar CH_3), 3.52 (septet, J = 7.1 Hz, 1 H, $CH(CH_3)_2$), 4.05 (t, J = 6.8 Hz, 2 H, OCH_2), 6.90 (m, 3 H, Ar H), 8.90 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 10.06, 20.22, 21.05, 21.23, 30.92, 78.80, 124.79, 126.63, 129.54, 132.22, 139.28, 146.46, 147.71, 160.56.

6-((3,5-Difluorophenyl)thio)-5-isopropyl-1-propoxyuracil (20): 12a and **13g**; IR (KBr) 1673, 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.30 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.65 (qt, J = 7.5 Hz, J = 6.9 Hz, 2 H, OCH_2CH_2), 3.46 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.10 (t, J = 6.9 Hz, 2 H, OCH_2), 6.68−6.83 (m, 3 H, Ar H), 9.39 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 10.06, 20.36, 21.02, 31.04, 79.17, 103.19 (t, $^2J_{C,F}$ = 25.3 Hz, C-4′), 110.91 (dd, $^2J_{C,F}$ = 18.6 Hz, $^4J_{C,F}$ = 9.5 Hz, C-2′ and C-6′), 136.57 (t, $^3J_{C,F}$ = 10.1 Hz, C-1′), 163.08 (dd, $^1J_{C,F}$ = 252.0 Hz, $^3J_{C,F}$ = 13.1 Hz, C-3′ and C-5′).

6-((3,5-Dimethylphenyl)thio)-1-(3-hydroxypropoxy)-5-isopropyluracil (23): 12b and **13e**; IR (KBr) 1646, 1714 (C=O), 3424 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.80 (quintet, J = 7.5 Hz, 2 H, $OCH_2CH_2CH_2OH$), 2.29 (s, 6 H, 2 Ar CH_3), 2.75 (br s, 1 H, OH), 3.51 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 3.74 (t, J = 5.7 Hz, 2 H, CH_2OH), 4.24 (t, J = 5.7 Hz, 2 H, OCH_2), 6.91 (m, 3 H, Ar H), 9.48 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 20.14, 21.22, 30.33, 30.89, 58.70, 74.45, 125.12, 126.80, 129.80, 131.94, 139.42, 146.23, 148.35, 160.42.

6-((3,5-Dimethylphenyl)thio)-5-isopropyl-1-(2-phenylethoxy)uracil (28): 12e and **13e**; IR (KBr) 1684, 1702 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 2.28 (s, 6 H, 2 Ar CH_3), 2.96 (t, J = 7.4 Hz, 2 H, CH_2Ar), 3.51 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.31 (t, J = 7.4 Hz, 2 H, OCH_2), 6.81−6.92 (m, 3 H, Ar H), 7.12−7.32 (m, 5 H, Ar H), 8.39 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 20.23, 21.27, 30.97, 34.01, 77.51, 125.00, 126.49, 126.56, 128.43, 128.82, 129.58, 132.10, 136.71, 139.32, 146.16, 147.57, 160.27.

6-((3,5-Dimethylphenyl)thio)-5-ethyl-1-propoxyuracil (32): 12i and **13e**; IR (KBr) 1662, 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.07 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.65 (qt, J = 7.5 Hz, J = 6.9 Hz, 2 H, OCH_2CH_2), 2.28 (s, 6 H, 2 Ar CH_3), 2.69 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 4.03 (t, J = 6.9 Hz, 2 H, OCH_2), 6.90 (m, 3 H, Ar H), 8.94 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 10.02, 13.72, 21.04, 21.22, 21.74, 78.79, 121.90, 126.76, 129.70, 131.73, 139.30, 146.77, 147.76, 161.28.

6-((3,5-Dimethylphenyl)thio)-5-ethyl-1-(3-hydroxpropoxy)uracil (33): 12j and **13e**; IR (KBr) 1676, 1718 (C=O), 3449 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.77 (quintet, J = 5.7 Hz, 2 H, $OCH_2CH_2CH_2OH$), 2.29 (s, 6 H, 2 Ar CH_3), 2.69 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.72 (t, J = 5.7 Hz, 2 H, CH_2OH), 4.22 (t, J = 5.7 Hz, 2 H, OCH_2), 6.93 (m, 3 H, Ar H), 9.07 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 13.62, 21.20, 21.66, 30.31, 58.62, 74.36, 122.25, 126.91, 129.90, 131.48, 139.40, 146.41, 148.53, 161.37.

6-((3,5-Dimethylphenyl)thio)-5-ethyl-1-(2-phenylethoxy)uracil (36): 12m and **13e**; IR (KBr) 1663, 1734 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.28 (s, 6 H, 2 Ar CH_3), 2.68 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 2.93 (t, J = 7.4 Hz, 2 H, CH_2Ar), 4.30 (t, J = 7.4 Hz, 2 H, OCH_2), 6.83−

6.92 (m, 3 H, Ar H), 7.10−7.29 (m, 5 H, Ar H), 9.02 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 13.74, 21.26, 21.77, 34.00, 77.46, 122.21, 126.54, 126.56, 128.42, 128.79, 129.70, 131.73, 136.69, 139.32, 146.36, 147.81, 161.21.

6-((3,5-Dimethylphenyl)thio)-1-propoxythymine (46): 12w and **13e**; IR (KBr) 1700 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.70 (qt, J = 7.5 Hz, J = 6.8 Hz, 2 H, OCH_2CH_2), 2.06 (s, 3 H, CH_3), 2.29 (s, 6 H, 2 Ar CH_3), 4.09 (t, J = 6.8 Hz, 2 H, OCH_2), 6.91 (m, 3 H, Ar H), 8.44 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 10.09, 13.64, 21.06, 21.22, 78.91, 115.55, 127.13, 129.81, 131.29, 139.38, 147.61, 147.71, 161.77.

6-((3,5-Dimethylphenyl)thio)-1-(2-phenylethoxy)thymine (49): 12z and **13e**; IR (KBr) 1661, 1716 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3 H, CH_3), 2.28 (s, 6 H, 2 Ar CH_3), 2.99 (t, J = 7.4 Hz, 2 H, CH_2Ar), 4.35 (t, J = 7.4 Hz, 2 H, OCH_2), 6.85 (s, 2 H, Ar H), 6.91 (s, 1 H, Ar H), 7.14−7.33 (m, 5 H, Ar H), 8.66 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 13.66, 21.24, 34.00, 77.56, 115.89, 126.55, 126.97, 128.43, 128.82, 129.80, 131.25, 136.67, 139.37, 147.25, 147.81, 161.88.

6-((3,5-Dimethylphenyl)thio)-5-isopropyluracil (51). To a stirred solution of 6-chloro-5-isopropyluracil[38] (**50**) (0.21 g, 1.1 mmol) in EtOH (4 mL) was added 1 N ethanolic NaOH solution (1.1 mL). To this resulting suspension was added 3,5-dimethylthiophenol (**13e**) (1.1 mmol, 151 μL) dropwise, and then the mixture was heated under reflux for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was suspended in water (5 mL), acidified to pH 3−4 with 1 N HCl, and extracted with EtOAc (20 mL × 4). The EtOAc solution was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was crystallized from EtOAc−hexane to give 0.29 g (91%) of **51**: mp 209.3−210.1 °C; IR (KBr) 1645, 1650, 1682, 1710 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 7.1 Hz, 6 H, $CH(CH_3)_2$), 2.34 (s, 6 H, 2 Ar CH_3), 3.12 (septet, J = 7.1 Hz, 1 H, $CH(CH_3)_2$), 7.10−7.20 (m, 3 H, Ar H), 7.19 (br s, 1 H, NH), 9.40 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 19.91, 21.11, 28.37, 115.36, 124.87, 132.90, 133.00, 140.60, 145.39, 149.94, 161.67; MS (EI) m/z 290 (M^+). Anal. ($C_{15}H_{18}N_2O_2S$) C, H, N.

Procedure for Anti-HIV-1 (HTLV-III$_B$) Activity in Human Peripheral Blood Mononuclear Cells (PMBCs). The inhibitory activity of test compounds on HIV-1 replication in PBMCs was determined according to the previously reported procedure.[10,17] PBMCs were isolated from healthy seronegative donors by Ficoll-Hypaque density gradient centrifugation. The cells were treated with phytohemagglutinin (PHA, 10 μg/mL, Sigma Chemical) for 24 h. One-day PHA-stimulated PBMCs (1 × 10^6 cells/mL) were infected at a multiplicity of infection of 0.01 with HIV-1 (HTLV-III$_B$) and grown in RPMI 1640 medium supplemented with interleukin-2 (IL-2, 2 U/mL, Boeringer Mannheim, Germany) and 10% fetal bovine serum (culture medium). After a 2-h virus adsorption period, the cells were washed three times with culture medium to remove unadsorbed virus and incubated with various concentrations of test compounds in a highly humidified incubator at 37 °C. Culture was subcultured at a ratio of 1:2 with fresh culture medium including appropriate concentrations of the test compounds on days 4 and 8. Cell-free supernatant fluids were assayed in triplicate by an HIV-1 p24 antigen ELISA kit (NEN) on day 12. In parallel with their antiviral assays, cytotoxicity was evaluated by determining [^{3}H]thymidine incorporation into DNA.

Reverse Transcriptase Assay. The standard assay[10,39] was performed in 50 μL of reaction mixture containing 50 mM Tris-HCl (pH 7.8), 50 mM KCl, 30 mM $MgCl_2$, 1 mM dithiothreitol, 0.01 % Triton X-100, 5.0 μg of poly r(A)d(T)$_{12-18}$ (Pharmacia), 0.5 μCi of [^{3}H]dTTP (NEN), 0.05 unit of HIV-1 rRT, AMV rRT, or Mo-MuLV rRT (Boeringer Mannheim), and various concentrations of compounds dissolved in DMSO (final concentration below 1%) for 1 h at 37 °C. The reaction was stopped with 100 μL of 20% (v/v) cold trichloroacetic acid, and the precipitated material was analyzed for radioactivity.[10,39]

Metabolic Stability Test. The stability of compound **18** in rat liver homogenates was determined by monitoring its breakage into a possible metabolite, 6-((3,5-dimethylphenyl)-thio)-5-isopropyluracil (**51**). Liver was obtained from Sprague-Dawley male rats after cervical dislocation, kept in ice-cold 0.25 M sucrose, and homogenized in 5 volumes of ice-cold 0.25 M sucrose. Liver homogenates were centrifuged at 3000g for 30 min, and the supernatant was diluted with of 0.1 M potassium phosphate buffer (pH 7.5) to obtain a final protein concentration of 300 μg/mL. Compound **18** (final concentration of 30 μM) was incubated with diluted liver homogenates for 1 h at 37 °C. The incubation was terminated with the addition of 2 volumes of methanol. Thereafter, the sample was centrifuged at 3000g for 30 min, and the supernatant was analyzed by HPLC. HPLC analysis was conducted using two pumps, a Waters solvent delivery module (Model 600), a multiwavelength UV detector (Model 600), and a Waters 717 autosampler (Waters, Milford, MA). The sample was chromatographed on a Sepadex column (25 cm × 4.6 mm) protected with a C_{18} Gaurd-Pak column. For compounds **18** and **51**, the mobile phase contained methanol and water (1:1), and the flow rate was 1.0 mL/min. The detection wavelength for these compounds was 274 nm. Compounds **18** and **51** were identified by their approximate retention times 29.7 and 11.6 min, respectively.

A presumed metabolite of compound **18**, **51**, was not detected in this study.

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Supporting Information Available: Solvent system for flash column chromatography and spectral (IR, ^{1}H NMR, and ^{13}C NMR) data for compounds **10a**−**z**, **11a**−**z**, and **12a**−**z** (17 pages). Ordering information is given on any current masthead page.

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