poured onto ice. The solid was filtered off and recrystallized once from ethanol and twice from ether/ligroin to yield 0.75 g (1.3 mmol, 76%) of **14** as microcrystalline needles: mp 162–163 °C); IR 3550 (alcohol) cm^{-1}. This compound which exists in several forms and retains solvent tenaciously was analyzed as its (2,4-dinitrophenyl)hydrazine derivative. Anal. ($C_{46}H_{46}N_8O_{14}$) C, H, N.

Molecular Orbital Calculations. The molecular orbital calculations for gossypol and derivatives were carried out using a computer program provided by Professor V. Ortiz, Department of Chemistry, University of New Mexico. The program incorporates features described in the literature.[23-25] Along with other parameters, it calculates the energy of the lowest unoccupied molecular orbital (LUMO) and the charge density at each atom in the molecule. The LUMO units are electron volts, and the charge density units are electrons. The LUMO values calculated by this program are different from the values calculated by Kador and Sharpless[7] for the same compounds. Therefore, LUMO calculations on several of the compounds used in their study were carried out with this program, and the values were found to be proportional to those reported by Kador and Sharpless.

Enzyme Purification and Kinetic Studies. Aldose reductase from human placenta was purified by the method of Vander Jagt and co-workers.[13,14] The purified enzyme was shown to retain its native properties. The sensitivity of the purified enzyme to inhibition by sorbinil did not change during storage at −20 °C for up to 6 months. Assays were conducted in 1 cm path length quartz cuvettes containing 10 mM D,L-glyceraldehyde and 0.1 mM NADPH in 1 mL of buffer (0.1 M sodium phosphate, pH 7). The temperature was maintained at 25 ± 1 °C with a thermostated circulating water bath. The reaction was followed by monitoring the absorbance decrease at 340 nm (the oxidation of NADPH to $NADP^+$) with a Perkin-Elmer Lambda 6 UV/vis spectrophotometer. Kinetic studies of aldose reductase inhibition were carried out under the same conditions. It has been shown for aldose reductases from some sources that inhibition constants vary greatly with substrate.[26] The human placental aldose reductase used in this study was therefore assayed with sorbinil as inhibitor and with the following substrates: glyceraldehyde (K_i = 0.28 μM), p-nitrobenzaldehyde (K_i = 0.29 μM), glucose K_i = 0.096 μM), and glucuronic acid (K_i = 0.17 μM). Since these values varied by only about a factor of 3, glyceraldehyde was used as substrate in the kinetic studies for the sake of convenience. Initial rates were corrected for the rate of absorbance decrease detected in the absence of the aldehyde substrate. The inhibitory properties of compounds were analyzed using Dixon plots. Two plots were made using different concentrations of NADPH. The experimental data were entered into the Enzfit program (Elsevier-Biosoft) for calculation of K_i.

Acknowledgment. We thank the Southern Regional Research Center of the USDA for providing the gossypol. We thank Professor Vincent Ortiz for assistance with the molecular orbital calculations. This work was supported in part by USPHS/NIH Grant AI25869.

Registry No. **2**, 17337-96-1; **3a**, 103068-47-9; **4a**, 94242-60-1; **4b**, 103094-22-0; **4c**, 103068-51-5; **4d**, 103068-52-6; **4e**, 136545-55-6; **4f**, 136545-56-7; **4g**, 136545-57-8; **5**, 136105-62-9; **6**, 135692-96-5; **7**, 136545-58-9; **8**, 124616-37-1; **9**, 136545-59-0; **10**, 136545-60-3; **11**, 136545-61-4; **12**, 31591-07-8; **13**, 1110-58-3; **14**, 136545-62-5; **15**, 27864-29-5; gossypol acetic acid, 12542-36-8; aldose reductase, 9028-31-3.

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Activity of Acyclic 6-(Phenylselenenyl)pyrimidine Nucleosides against Human Immunodeficiency Viruses in Primary Lymphocytes

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Several 6-phenylselenenyl-substituted acyclouridine derivatives were prepared for evaluation as antiviral agents. Lithiation of the *tert*-butyldimethylsilyl-protected acyclonucleosides **4a–f** with lithium diisopropylamide at −78 °C, followed by reaction with diphenyl diselenide as an electrophile, and subsequent removal of the protecting group with tetra *n*-butylammonium fluoride gave 1-[(2-hydroxyethoxy)methyl]-6-(phenylselenenyl)uracils **6a–f** in 50–70% overall yield. The potency and spectrum of activity of compounds **6a–f** against HIV-1 in vitro was similar to HEPT (**1**), a related 6-phenylthio acyclonucleoside. However, whereas HEPT inhibited HIV-1 reverse transcriptase, the selenium-containing derivatives were ineffective, suggesting a different mechanism of action. Of significance was the finding that the 6-phenylselenenyl acyclonucleosides inhibited also HIV-2 in primary human lymphocytes.

Introduction

In the search for more selective and effective agents against human immunodeficiency virus type 1 (HIV-1), which is the causative agent for the acquired immunodeficiency syndrome (AIDS), a large number of nucleoside analogues with modifications being made in the heterocyclic base and/or the sugar moiety have been extensively investigated for their antiviral activities.[1,2] Several 2′,3′-dideoxy nucleosides are approved or are currently undergoing clinical trials in patients with AIDS and AIDS-related complex. These include 3′-azido-3′-deoxythymidine (AZT), 2′,3′-didehydro-3′-deoxythymidine (D4T), 3′-azido-2′,3′-dideoxyuridine (AzddU), 2′,3′-dideoxycytidine (DDC), 2′,3′-dideoxyinosine (DDI), and 2′,3′-dideoxy-3′-thiacytidine (BCH-189).[3a-d] Recently, it

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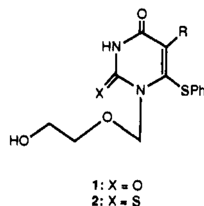
was reported that 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT, 1) and 1-[(hydroxyethoxy)-



methyl]-6-(phenylthio)-2-thiothymine (HEPT-S, 2) are potent and selective inhibitors of HIV-1, but not human immunodeficiency virus type 2 (HIV-2), in various human lymphocytes.[4a-g] In contrast to the current antiviral agents with a modified carbohydrate moiety, these 6-substituted compounds are acyclic nucleosides related to acyclovir and ganciclovir.[5a-c] These sulfur-containing compounds are unique because they do not require phosphorylation in order to inhibit HIV-1 reverse transcriptase (RT).[4f,g] However, these compounds are ineffective against the corresponding HIV-2 enzyme. In addition, the compounds are not cross-resistant with AZT, suggesting that they may be useful in treating patients infected with AZT-resistant virus or in combination with other antiviral agents.[6a,b] More recently, Baba et al.[4f] showed that 1-[(benzyloxy)-methyl]-5-ethyl-6-(phenylthio)uracil derivatives inhibited HIV-1 replication and HIV-1 RT, suggesting that the presence of an acyclic side chain with an intact free hydroxy function is not necessary for antiviral activity. Our group has had a long-term interest in developing organometallic nucleoside analogues with potential antiviral and anticancer activity.[7a-d] Because selenium is isosteric with sulfur, it was important to determine if selenium-related analogues of HEPT were effective against HIV-1. In addition, it was reported recently that reduced levels of blood selenium and glutathione peroxidase activity can occur in patients with AIDS.[8a-c] This selenium deficiency could

Scheme I

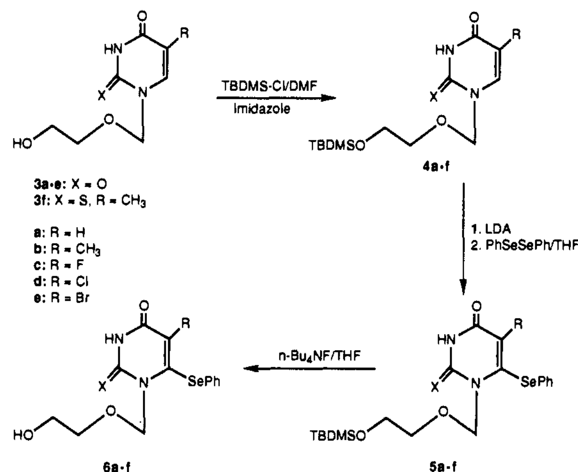


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Table I. Biological Evaluation of Various Substituted Acyclic Pyrimidine Nucleosides

		EC_{50}, μM		IC_{50}, μM				
compd	1-[(2-hydroxyethoxy)methyl] analogue	anti-HIV-1 in PBMC	anti-HIV-2 in PBMC	toxicity in PBMC	HIV-1 RT inhibn	DNA pol. α derived from PBMC	toxicity in Vero cells	EC_{50}, μM: anti-HSV-1 in Vero cells
3a	uracil	>100	ND	>100	ND	ND	>100	>100
3b	thymine	>100	ND	>100	ND	ND	>100	≥100
3c	5-fluorouracil	>100	ND	67.0	ND	ND	>100	>100
3d	5-chlorouracil	>100	ND	ND	ND	ND	>100	>100
3e	5-bromouracil	>100	ND	100	ND	ND	>100	≥100
3f	2-thiothymine	>100	ND	>100	ND	ND	>100	>100
1	6-(phenylthio)thymine (HEPT)	5.30	>100	≥100	17.5	>100	>100	>100
6a	6-(phenylselenenyl)uracil	13.0	9.6	>100	139	>100	>100	>200
6b	6-(phenylselenenyl)thymine	0.96	25.6	>200	90.3	>100	>100	>100
6c	6-(phenylselenenyl)-5-fluorouracil	2.0	9.1	>100	>100	>100	25.7	>100
6d	6-(phenylselenenyl)-5-chlorouracil	3.1	7.9	>100	>100	>100	7.5	>100
6e	6-(phenylselenenyl)-5-bromouracil	3.7	2.0	≥100	>100	>100	8.2	>100
6f	6-(phenylselenenyl)-2-thiothymine	2.8	5.8	>100	>100	>100	60.7	>100
	guanosine (ACV as control)	>50	ND	>100	ND	ND	>100	0.03
	3′-azido-3′-deoxythymidine (AZT or AZT-TP as control)	0.004	≤0.002	>100	<0.1	>100	26.0	>100

have an impact on immune function and disease progression in HIV-infected patients. Selenium deficiency is also common in malnourished pediatric AIDS patients, and this mineral may provide an important adjunct for the treatment of HIV-1 in infected individuals.[8b,c]

In this paper we report the synthesis of several 1-[(2-hydroxyethoxy)methyl]-6-(phenylselenenyl)pyrimidines and their cytotoxicity in various cell culture systems and antiviral activity against HIV-1, HIV-2, and herpes simplex virus type 1 (HSV-1). In addition, the selenium-containing compounds were evaluated as inhibitors of HIV-1 RT and DNA polymerase α.

Chemistry

Recently, we reported on the use of selenium nucleophiles in the synthesis of nucleosides of biological importance.[7a] Reich and co-workers have shown that selenium electrophile, such as diphenyl diselenide, can be used in reactions with unsaturated esters and enolates.[9] In this study this method was adapted to introduce the electrophilic selenium species in pyrimidine acyclic nucleosides by activation of the 6-position with organolithium.[4d]

Using the method of Rosowsky et al.,[10] 1-[(2-hydroxyethoxy)methyl]uracil (**3a**) and its substituted analogues **3b–f** were prepared via coupling bis(trimethylsilyl)uracil derivative with acetoxymethyl ether in the presence of 0.5 molar equiv of stannic chloride, followed by hydrolysis with sodium methoxide. The hydroxyl group of the acyclonucleosides **3a–f** was protected by reaction with *tert*-butyldimethylsilyl (TBDMS) chloride in DMF in the presence of imidazole (Scheme I). The TBDMS analogues **4a–f** were obtained as crystalline compounds in almost quantitative yield.

Reaction of 1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]uracil (**4a**) and its derivatives **4b–f** in THF with LDA (2.5 equiv) at −78 °C generated regiospecifically the C-6 lithiated species, which was subsequently reacted with diphenyl diselenide. Quenching the reaction mixture with glacial AcOH, followed by silica gel column chromatography, resulted in the isolation of the corresponding 6-phenylselenenyl analogues **5a–f**. Deprotection of the TBDMS group from **5a–f** under mild conditions with tetra-*n*-butylammonium fluoride afforded the corresponding 1-[(hydroxyethoxy)methyl]-6-(phenylselenenyl)uracil analogues **6a–f** in fair to good yield (50–70%).

Biological Results and Discussions

Compounds **3a–f** were evaluated in human peripheral blood mononuclear (PBM) cells infected with HIV-1 (strain LAV). Virus yield was determined by measuring the level of HIV-1 RT present in disrupted virions obtained from supernatant from cells exposed to the drugs (Table I). None of these compounds inhibited HIV-1 replication at concentrations greater than 100 μM. The 5-halogeno derivatives (**3c–e**) were found to have minimal toxicity to uninfected PBM cells. Introduction of a phenylselenenyl moiety at the 6-position of these acyclic nucleosides produced compounds (**6a–f**) which were as potent against HIV-1 as HEPT, the lead compound. The median effective concentration (EC_{50}) for these compounds ranged from 0.96 to 13.0 μM. The results obtained with HEPT in human PBM cells were similar to those reported by Miyasaka et al.[4a] in MT-4 cells (EC_{50} = 5.3 μM versus 7.0 μM). Uracil analogue **6a** appeared to be less effective than the 5-substituted compounds. Whereas thymine analogue **6b** exhibited no cytotoxicity in human PBM or in Vero cells, some cytotoxicity was noted with the corresponding halogeno derivatives **6c–e** in Vero cells. This suggests that some of the selenium analogues may exhibit toxicity in other rapidly dividing cells such as human bone marrow cells. When tested in human PBM cells infected with HIV-2 (strain ROD-2), compounds **6a–f** were found to have activity similar to that obtained with HIV-1, with the exception of 6-(phenylselenenyl)thymine derivative **6b**, which was about 25-fold less active. As previously reported by Baba et al.,[4b] HEPT was also not active against HIV-2 in our cell culture system. The selectivity of the new

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compounds appears to be directed at HIV-1 and HIV-2, since none of the selenium-containing compounds were effective against HSV-1 in a plaque reduction assay in Vero cells.

The effect of 6-phenylselenenyl analogues **6a–f** on HIV-1 RT in a cell-free system was also determined since HEPT had been reported to inhibit HIV-1 RT. Surprisingly, none of the compounds exhibited marked anti-RT activity when tested up to 100 μM. Whereas HEPT had an IC_{50} of 17.5 μM, thymine analogue **6b** had an IC_{50} of 90.3 μM. None of the compounds evaluated inhibited DNA polymerase α purified from human PBM cells at concentration greater than 100 μM.

In summary, the selenenyl compounds described in this paper have selective antiviral activity against both HIV-1 and HIV-2 in primary human lymphocytes and are not inhibitors of HIV-1 RT. Taken together, the results suggest that the activity of the selenium analogues is produced by inhibition of a viral target which is different from the corresponding sulphur-containing analogues, such as HEPT.

Experimental Section

Melting points were determined on an Electrothermal IA 8100 digital melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer. Experiments were monitored using TLC analysis performed on Kodak chromatogram sheets precoated with silica gel and a fluorescent indicator, while column chromatography, employing silica gel (60–200 mesh; Fisher Scientific, Fair Lawn, NJ), was used for the purification of products. Tetrahydrofuran was freshly distilled from the sodium benzophenone salt. LDA (2.0 M) and diphenyl diselenide were purchased from Aldrich Chemical Co. (Milwaukee, WI). Compounds **3a–f** were prepared according to the literature procedure.[10] Microanalyses were performed at Atlantic Microlabs (Atlanta, GA).

General Procedure for the Protection of 4a–f. A mixture of the acyclic nucleoside (5 mmol), DMF (20 mL), imidazole (410 mg, 6 mmol) and *tert*-butyldimethylsilyl (TBDMS) chloride (905 mg, 6 mmol) was stirred under argon atmosphere overnight at room temperature. The reaction mixture was poured into water (100 mL), and the precipitate filtered. The resulting solid was dissolved in $CHCl_3$ (80 mL), washed with saturated aqueous $NaHCO_3$ (2 × 40 mL) and H_2O (50 mL), dried over Na_2SO_4, and concentrated in vacuo to give the desired TBDMS derivative.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]uracil (4a): yield 62%; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Me_2Si), 0.88 (s, 9 H, Me_3C), 3.60–3.78 (m, 4 H, $SiOCH_2CH_2O$), 5.20 (s, 2 H, NCH_2O), 5.75 (d, J = 9 Hz, 1 H, 5-H), 7.34 (d, J = 9 Hz, 1 H, 6-H), 9.20 (s, 1 H, NH, D_2O exchangeable).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]thymine (4b): yield 89%; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Me_2Si), 0.87 (s, 9 H, Me_3C), 1.92 (s, 3 H, 5-Me), 3.58–3.77 (m, 4 H, $SiOCH_2CH_2O$), 5.19 (s, 2 H, NCH_2O), 7.13 (s, 1 H, 6-H), 9.05 (s, 1 H, NH, D_2O exchangeable). This compound has been previously reported by Tanaka et al.[4e]

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-fluorouracil (4c): yield 78%; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Me_2Si), 0.90 (s, 9 H, Me_3C), 3.62–3.78 (m, 4 H, $SiOCH_2CH_2O$), 5.15 (s, 2 H, NCH_2O), 7.42 (d, J = 5 Hz, 1 H, 6-H), 9.11 (s, 1 H, NH, D_2O exchangeable).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-chlorouracil (4d): yield 85%; ^1H NMR ($CDCl_3$) δ 0.16 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 3.61–3.75 (m, 4 H, $SiOCH_2CH_2O$), 5.20 (s, 2 H, NCH_2O), 7.58 (s, 1 H, 6-H), 9.06 (br s, 1 H, NH, D_2O exchangeable).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-5-bromouracil (4e): yield 83%; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.88 (s, 9 H, Me_3C), 3.63–3.79 (m, 4 H, $SiOCH_2CH_2O$), 5.23 (s, 2 H, NCH_2O), 7.64 (s, 1 H, 6-H), 9.05 (br s, 1 H, NH, D_2O exchangeable).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-2-thiothymine (4f): yield 86%; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 1.97 (s, 3 H, 5-Me), 3.66–3.80 (m, 4 H, $SiOCH_2CH_2O$), 5.63 (s, 2 H, NCH_2O), 7.33 (s, 1 H, 6-H), 9.92 (s, 1 H, NH, D_2O exchangeable).

General Procedure for the Preparation of 6-(Phenylselenenyl)-1-[[2-[(*tert*-butyldimethylsilyl)oxy]ethoxy]methyl]pyrimidine Derivatives. To a solution of protected acyclonucleoside (2 mmol) in dry THF (10 mL) at −78 °C was added LDA (2.0 M, 2.5 mL, 5 mmol) dropwise over 5 min with stirring under argon atmosphere. The mixture was stirred for 1 h while the temperature was maintained below −70 °C. A solution of diphenyl diselenide (1.25 g, 4 mmol in 10 mL of THF) was added dropwise over 10 min to the resulting solution, and the mixture was stirred for 30 min at −78 °C. The reaction mixture was quenched with AcOH (0.5 mL), and then allowed to warm to room temperature. The solution was concentrated to dryness in vacuo, and the residue was purified by silica gel column chromatography to give the corresponding 6-phenylselenenyl derivative.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylselenenyl)uracil (5a): purified by column chromatography using $CHCl_3$; yield 80%; mp 138–140 °C; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, Me_2Si), 0.90 (s, 9 H, Me_3C), 3.66–3.82 (m, 4 H, $SiOCH_2CH_2O$), 5.23 (s, 1 H, 5-H), 5.56 (s, 2 H, NCH_2O), 7.40–7.65 (m, 5 H, SePh), 9.04 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{19}H_{28}N_2O_4SeSi$) C, H, N.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylselenenyl)thymine (5b): purified by column chromatography using $CHCl_3$; yield 82%; mp 68–72 °C; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, Me_2Si), 0.86 (s, 9 H, Me_3C), 1.95 (s, 3 H, 5-Me), 3.59–3.74 (m, 4 H, $SiOCH_2CH_2O$), 5.68 (s, 2 H, NCH_2O), 7.23–7.36 (m, 5 H, SePh), 9.02 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{20}H_{30}N_2O_4SeSi$) C, H, N.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylselenenyl)-5-fluorouracil (5c): purified by column chromatography using $CHCl_3$/MeOH (98:2); yield 85%; mp 125–128 °C; ^1H NMR ($CDCl_3$) δ 0.18 (s, 6 H, Me_2Si), 0.88 (s, 9 H, Me_3C), 3.60–3.76 (m, 4 H, $SiOCH_2CH_2O$), 5.66 (s, 2 H, NCH_2O), 7.26–7.62 (m, 5 H, SePh), 9.37 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{19}H_{27}FN_2O_4SeSi$) C, H, N.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylselenenyl)-5-chlorouracil (5d): purified by column chromatography using $CHCl_3$/MeOH (98:2); yield 76%; mp 115–118 °C; ^1H NMR ($CDCl_3$) δ 0.26 (s, 6 H, Me_2Si), 0.92 (s, 9 H, Me_3C), 3.63–3.78 (m, 4 H, $SiOCH_2CH_2O$), 5.73 (s, 2 H, NCH_2O), 7.28–7.50 (m, 5 H, SePh), 9.12 (br s, 1 H, NH, D_2O exchangeable). Anal. ($C_{19}H_{27}ClN_2O_4SeSi$) C, H, N.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylselenenyl)-5-bromouracil (5e): purified by column chromatography using $CHCl_3$/MeOH (95:5); yield 65%; mp 102–106 °C; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, Me_2Si), 0.86 (s, 9 H, Me_3C), 3.62–3.75 (m, 4 H, $SiOCH_2CH_2O$), 5.73 (s, 2 H, NCH_2O), 7.28–7.47 (m, 5 H, SePh), 8.79 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{19}H_{27}BrN_2O_4SeSi$) C, H, N.

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylselenenyl)-2-thiothymine (5f): purified by column chromatography using $CHCl_3$/MeOH (98:2); yield 77%; mp 97–100 °C; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, Me_2Si), 0.86 (s, 9 H, Me_3C), 1.88 (s, 3 H, 5-Me), 3.71 (s, 4 H, $SiOCH_2CH_2O$), 5.79 (s, 2 H, NCH_2O), 7.21–7.35 (m, 5 H, SePh), 9.73 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{20}H_{30}N_2O_3SeSi$) C, H, N.

General Procedure for Deprotection of the *tert*-Butyldimethylsilyl (TBDMS) Group. To the protected derivative (1 mmol) dissolved in THF (5 mL) was added a solution of tetra-*n*-butylammonium fluoride (1.2 mmol in 2 mL of THF). The resulting reaction mixture was stirred for 30 min at room temperature and evaporated to dryness. The residue was purified by silica gel column chromatography and crystallized from a suitable solvent.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylselenenyl)uracil (6a): purified by column chromatography using $CHCl_3$/MeOH (98:2); yield 86%; mp 157–159 °C (toluene); ^1H NMR ($CDCl_3$) δ 2.23 (s, 1 H, OH, D_2O exchangeable), 3.70–3.79 (m, 4 H, OCH_2CH_2O), 5.23 (s, 1 H, 5-H), 5.78 (s, 2 H, NCH_2O), 7.39–7.68 (m, 5 H, SePh), 9.30 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{13}H_{14}N_2O_4Se$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylselenenyl)thymine (6b): purified by column chromatography using $CHCl_3$/MeOH

(98:2); yield 75%; mp 108–109 °C (toluene); ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 1 H, OH, D_2O exchangeable), 2.03 (s, 3 H, 5-Me), 3.65 (m, 4 H, OCH_2CH_2O), 5.67 (s, 2 H, NCH_2O), 7.26–7.38 (m, 5 H, SePh), 9.32 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{14}H_{16}N_2O_4Se$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylselenenyl)-5-fluorouracil (6c): purified by column chromatography using $CHCl_3$/MeOH (95:5); yield 83%; mp 130–132 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 3.37–3.49 (m, 4 H, OCH_2CH_2O), 4.65 (t, 1 H, OH, D_2O exchangeable), 5.45 (s, 2 H, NCH_2O), 7.27–7.63 (m, 5 H, SePh), 11.96 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{13}H_{13}FN_2O_4Se$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylselenenyl)-5-chlorouracil (6d): purified by column chromatography using $CHCl_3$/MeOH (95:5); yield 68%; mp 142–143 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 3.38–3.52 (m, 4 H, OCH_2CH_2O), 4.60 (t, 1 H, OH, D_2O exchangeable), 5.53 (s, 2 H, NCH_2O), 7.28–7.53 (m, 5 H, SePh), 12.04 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{13}H_{13}ClN_2O_4Se$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylselenenyl)-5-bromouracil (6e): purified by column chromatography using $CHCl_3$/MeOH (90:10); yield 79%; mp 144–145 °C ($CHCl_3$): ^{1}H NMR (DMSO-d_6) δ 3.27–3.51 (m, 4 H, OCH_2CH_2O), 4.59 (s, 1 H, OH, D_2O exchangeable), 5.53 (s, 2 H, NCH_2O), 7.24–7.51 (m, 5 H, SePh), 12.00 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{13}H_{13}BrN_2O_4Se$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylselenenyl)-2-thiothymine (6f): purified by column chromatography using $CHCl_3$/MeOH (95:5); yield 83%; mp 108–109 °C (toluene); ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 1 H, OH, D_2O exchangeable), 1.93 (s, 3 H, 5-Me), 3.67–3.75 (m, 4 H, OCH_2CH_2O), 6.27 (s, 2 H, NCH_2O), 7.26–7.35 (m, 5 H, SePh), 10.01 (s, 1 H, NH, D_2O exchangeable). Anal. ($C_{13}H_{13}N_2O_4SSe$) C, H, N.

Biological Methods. The methods for determining the anti-HIV activity of the compounds in human peripheral blood mononuclear cells have been described previously.[11a–c] HIV-1 (strain LAV) and HIV-2 (strain ROD-2), respectively, were obtained from Dr. Paul Feorino (Emory University) and Dr. Patricia Fultz (University of Alabama, Birmingham, AL). Virus obtained from the cell supernatant was quantitated on day 6 after infection by a reverse transcriptase assay using poly(rA)$_n$·oligo(dT)$_{12-18}$ as template-primer. The toxicity of the compounds was assessed in human PBM and Vero cells, as described previously.[11a] The effect of the compounds on viral reverse transcriptase was determined using a recombinant p66 RT obtained from Dr. S. Hughes (National Cancer Institute). This material had previously been shown by us to have similar properties to virus particle derived RT.[12a] DNA polymerase α, derived from human PBM cells, was used to determine the selectivity of the compounds for the cellular enzyme as described previously.[12b] The plaque reduction assays in Vero cells were performed with HSV-1 (strain F), as previously described.[13] The median effective and inhibitory concentration was obtained from the concentration–response curve using the median effective method described by Chou and Talalay.[14]

Acknowledgment. We thank D. Cannon, R. Mathis, A. McMillan, and A. Peck for excellent technical support. This work was supported in part by the National Institutes of Health (AI-26055 and AI-25899) and by the Department of Veterans Affairs.

Registry No. **3a**, 78097-04-8; **3b**, 68724-11-8; **3c**, 77474-50-1; **3d**, 81777-50-6; **3e**, 78097-11-7; **3f**, 132885-30-4; **4a**, 121749-94-8; **4b**, 121749-98-2; **4c**, 121749-95-9; **4d**, 121749-96-0; **4e**, 121749-97-1; **4f**, 132885-32-6; **5a**, 136631-96-4; **5b**, 136631-97-5; **5c**, 136631-98-6; **5d**, 136631-99-7; **5e**, 136632-00-3; **5f**, 136632-01-4; **6a**, 136632-02-5; **6b**, 136632-03-6; **6c**, 136632-04-7; **6d**, 136632-05-8; **6e**, 136632-06-9; **6f**, 136632-07-0; PhSeSePh, 1666-13-3.

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