Synthesis and Anti-HIV-1 Activity of a Series of 1-(Alkoxymethyl)-5-alkyl-6-(arylselenenyl)uracils and -2-thiouracils

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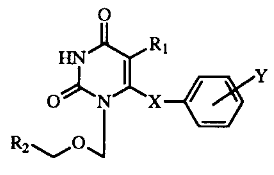
Received December 4, 1995

A series of 1-(alkoxymethyl)-5-alkyl-6-(phenylselenenyl)uracils and -2-thiouracils modified at the 3- and/or 5-position of the C-6 phenylselenenyl ring with methyl or fluoro substituent has been synthesized and tested for their ability to inhibit HIV-1 replication. Lithiation of the acyclic uracil and 2-thiouracil derivatives **11-14** and **27-32** with lithium diisopropylamide or lithium bis(trimethylsilyl)amide followed by reaction with an appropriate diaryl diselenide afforded 6-arylselenenyl compounds **18-26** after removal of the *tert*-butyldimethylsilyl protecting group and **35-47**. Compounds **48-54** were prepared from compounds **38-44** by oxidative hydrolysis of the thione function. Of these compounds, **50** inhibited HIV-1 replication in human T_4 lymphoblastoid cells at a 50% effective concentration (EC_{50}) of 0.0047 μM with a selectivity index of >42600.

J. Heterocyclic Chem., **33**, 1275 (1996).

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 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]. The nucleoside derivative 3'-azido-3'-deoxythymidine (AZT), a potent reverse transcriptase inhibitor of HIV, is known to prolong survival in AIDS patients [3], yet its long-term treatment is often associated with serious side effects such as bone marrow suppression [4]. Furthermore, prolonged AZT treatment often leads to the emergence of AZT-resistant HIV-1 strains [5]. It seems, therefore, still imperative to find novel chemotherapeutic agents having potent antiviral activity and low toxicity, preferably, through a different mechanism of action.

The acyclic 6-substituted uridine derivative 1-[(2-hydoxyethoxy)methyl]-6-(phenylthio)thymine (**1**) is a potent and HIV-1-specific reverse transcriptase inhibitor [6]. Several 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine derivatives such as 1-(benzyloxymethyl)-6-[(3,5-dimethylphenyl)thio]-5-ethyluracil **2** and 6-[(3,5-dimethylphenyl)thio]-1-(ethoxymethyl)-5-ethyluracil **3** inhibit HIV-1 replication in the nanomolar concentration range [7]. The previous studies of the structure-activity relationships of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine analogs indicated that the following modifications would potentiate their anti-HIV-1 activity: (1) replacement of the 5-methyl group with a bulkier alkyl group such as an ethyl or an isopropyl group, (2) modification at the 3- and 5-positions of the C-6 phenylthio ring with methyl groups or halogen atoms, (3) replacement of the 2-oxo function with a thione function, and (4) removal of the hydroxyl group in the (2-hydroxyethoxy)methyl side chain [7,8]. Recently, Goudgaon and Schinazi prepared a series of 6-phenylselenenyl analogs of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine and found that 1-[(2-hydroxyethoxy)methyl]-6-(phenylselenenyl)-thymine **4** was more active than 1-[(hydroxyethoxy)-methyl]-6-(phenylthio)thymine against HIV-1 in primary human lymphocytes [9]. Later, Goudgaon *et al.* [10] and Pan *et al.* [11] reported that 1-(ethoxymethyl)-5-ethyl-6-(phenylselenenyl)uracil **5** and 1-(benzyloxymethyl)-5-ethyl-6-(phenylselenenyl)uracil **6** inhibited HIV-1 replication in human peripheral blood mononuclear cells and CEM-IW cells at nanomolar concentrations with no observed cytotoxicity. However, modification of the C-6 phenylselenenyl ring has not been reported to date to increase the potency, presumably, because the requisite diphenyl diselenides with appropriate substitution are not readily available for the synthesis of target compounds.

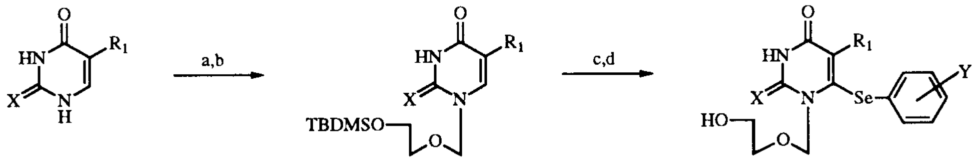


1, R_1 = Me, R_2 = CH_2OH, X = S, Y = H
2, R_1 = Et, R_2 = Ph, X = S, Y = 3,5-Me_2
3, R_1 = Et, R_2 = Me, X = S, Y = 3,5-Me_2
4, R_1 = Me, R_2 = CH_2OH, X = Se, Y = H
5, R_1 = Et, R_2 = Me, X = Se, Y = H
6, R_1 = Et, R_2 = Ph, X = Se, Y = H

In this report we describe the synthesis and anti-HIV-1 activity of a series of 1-(alkoxymethyl)-5-alkyl-6-(phenylselenenyl)uracils and -2-thiouracils which have been modified at the 3- and/or 5-position of the C-6 phenylselenenyl ring with methyl or fluoro substituent.

The acyclic 2-thiouracil derivatives **11** and **12** were prepared from 5-ethyl-2-thiouracil **7** and 5-isopropyl-2-

Scheme 1



7, X = S, R_1 = Et
8, X = S, R_1 = *i*-Pr
9, X = O, R_1 = Et
10, X = O, R_1 = *i*-Pr

11, X = S, R_1 = Et (37%)
12, X = S, R_1 = *i*-Pr (36%)
13, X = O, R_1 = Et (71%)
14, X = O, R_1 = *i*-Pr (87%)

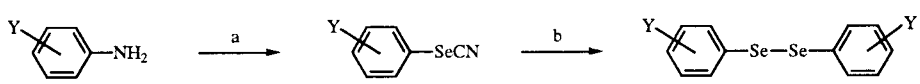
18, X = S, R_1 = Et, Y = 3-Me (77%)
19, X = S, R_1 = Et, Y = 3,5-Me_2 (62%)
20, X = S, R_1 = *i*-Pr, Y = H (62%)
21, X = S, R_1 = *i*-Pr, Y = 3-Me (59%)
22, X = O, R_1 = Et, Y = 3-Me (78%)
23, X = O, R_1 = Et, Y = 3,5-Me_2 (73%)
24, X = O, R_1 = *i*-Pr, Y = H (64%)
25, X = O, R_1 = *i*-Pr, Y = 3-Me (68%)
26, X = O, R_1 = *i*-Pr, Y = 3,5-Me_2 (45%)

[a] (i) 1,1,1,3,3,3-hexamethyldisilazane, $(NH_4)_2SO_4$, reflux, 15 h, then [2-(trimethylsiloxy)ethoxy]methyl iodide, CsI, MeCN, -60°C to rt over 30 min then rt for 3 h (for **11** and **12**), or (ii) *N,O*-bis(trimethylsilyl)acetamide, CH_2Cl_2, rt, 2 h, then [2-(trimethylsiloxy)ethoxy]methyl iodide, -60°C to rt over 30 min then rt for 3 h (for **13** and **14**); [b] *tert*-butyldimethylsilyl chloride, imidazole, DMF, rt, 16 h; [c] (i) LDA, THF, -70°C, 1 h, then diaryl diselenides **15a-d**, -70°C, 1 h (for **18-21**), (ii) lithium bis(trimethylsilyl)amide, THF, -70°C, 1 h, then **15a-d**, -70°C, 1 h then rt for 16 h (for **22-26**); [d] *c*-HCl, rt, 2 h.

thiouracil **8** according to the published procedure [8] with slight modification. Silylation of **7** and **8** with 1,1,1,3,3,3-hexamethyldisilazane in the presence of a catalytic amount of ammonium sulfate followed by reaction with *in situ* generated [2-(trimethylsiloxy)ethoxy]methyl iodide [12] in the presence of cesium iodide in acetonitrile produced the corresponding 1-[(2-hydroxyethoxy)methyl]-2-thiouracils, which were subsequently treated with *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide to afford **11** and **12** in 37% and 36% yields, respectively. The uracil derivatives **13** and **14** were prepared from 5-ethyluracil **9** and 5-isopropyluracil **10** in 71% and 87% yields, respectively, under the similar reaction condition for **11** and **12** except that 1,1,1,3,3,3-hexamethyldisilazane was replaced with *N,O*-bis(trimethylsilyl)acetamide. Treatment of the 2-thiouracil derivatives **11** and **12** with lithium diisopropylamide in tetrahydrofuran at -70° generated regiospecifically the C-6 lithiated species, which were reacted with bis(3-methylphenyl) diselenide **15a**, bis(3,5-dimethylphenyl) diselenide **15b**, bis(3,5-difluorophenyl) diselenide **15c** or diphenyl diselenide **15d**. The subsequent removal of the *tert*-butyldimethylsilyl protecting group by treatment of the reaction mixture with concentrated hydrochloric acid gave compounds **18-21** in 59-77% yields. In contrast, lithium bis(trimethylsilyl)amide proved to be a more efficient lithiating agent for the uracil derivatives **13** and **14** than lithium diisopropylamide. For instance, compound **24** was obtained from **14** and **15d** in only 8% yield under the lithium diisopropylamide condition. However, the yield of **24** could be increased up to 64% when lithium bis(trimethylsilyl)amide was employed as a lithiating agent. Thus, compounds **13** and **14** were lithiated with lithium bis(trimethylsilyl)amide and then reacted with an appropriate diaryl diselenide at room temperature to afford cmpounds **22-26** in 45-78% yields after desilylation.

The required diaryl diselenides **15a-c** were prepared according to the published procedure for **15a** [13] as shown in Scheme 2. First, the appropriate amines **16a-c** were diazotized with 3*N* hydrochloric acid and an aqueous sodium nitrite solution, and then the resulting diazonium salts were reacted with potassium selenocyanate to afford the aryl selenocyanates **17a-c**. The relatively lower yield of **17b** (12%) compared to those of **17a** and **17c** might be attributed to the poor solubility of the amine **16b** in the acidic reaction medium during diazotization. Treatment of **17a-c** with an aqueous sodium hydroxide solution in ethanol gave **15a-c** in 80-98% yields.

Scheme 2



16

a, Y = 3-Me
b, Y = 3,5-Me_2
c, Y = 3,5-F_2

17

a, Y = 3-Me (41%)
b, Y = 3,5-Me_2 (12%)
c, Y = 3,5-F_2 (50%)

15

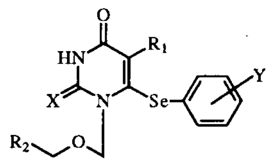
a, Y = 3-Me (96%)
b, Y = 3,5-Me_2 (98%)
c, Y = 3,5-F_2 (80%)

[a] (i) 3*N* HCl, $NaNO_2$, H_2O, 0°C, 1 h, (ii) NaOAc, (iii) KSeCN, H_2O, -5 ~ 0°C, then rt, 1 h; [b] NaOH, H_2O, EtOH, rt, 3 h.

The known 2-thiouracil derivatives **27-30** were prepared according to the published procedure [7]. Silylation of **9** and **10** with *N,O*-bis(trimethylsilyl)acetamide in dichloromethane followed by reaction with either chloromethyl ethyl ether or benzyl chlromethyl ether in the presence of tetrabutylammonium iodide gave **31-34** in 83-96% yields. The lithiation of compounds **27-32** with lithium diisopropylamide and reaction of the resulting lithiated species with an appropriate diaryl diselenide afforded 1-(alkoxymethyl)-5-alkyl-6-(arylselenenyl)uracils and -2-thiouracils **35-47** in 20-83% yields. In this reaction, it was observed that the yields depended on the substituent at N-1 of the starting compounds. Compounds **27**, **29** and **31** with an ethoxymethyl group at N-1 produced the desired compounds in higher than 50% yield except for compound **41**, whereas compounds **28**, **30** and **32** with a benzyloxymethyl group always gave the products in less than 50% yield. As previously observed for the uracil derivatives **13** and **14**, lithiation of 1-(ethoxymethyl)-5-isopropyluracil **33** with lithium diisopropylamide followed by reaction with **15d** gave compound **48** only in a trace amount (<5%). Even when lithium bis(trimethylsilyl)amide was employed, a low yield (22%) of **48** was obtained. Furthermore, it was found that 1-(benzyloxymethyl)-5-isopropyluracil **34** could not be lithiated with either lithium diisopropylamide or lithium bis(trimethylsilyl)amide. Alternatively, the uracil analogs **48-54** were prepared from compounds **38-44** by oxidative hydrolysis of the thione function with hydrogen peroxide in aqueous sodium hydroxide solution. Again, we experienced that the yield in this reaction varied with the substituent at N-1.

Table 1

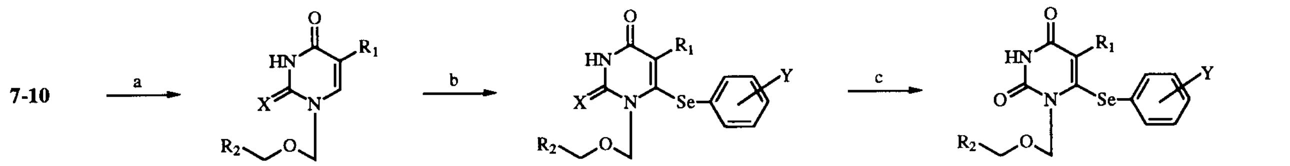
Inhibition of HIV-1 Replication in CEM-SS Cells by 1-(Alkoxymethyl)-5-alkyl-6-(arylselenenyl)uracils and -2-thiouracils [a]



Compound	X	R_1	R_2	Y	EC_{50} [b] (μM)	CC_{50} [c] (μM)	SI [d]
18	S	Et	CH_2OH	3-Me	0.11	>20	>180
19	S	Et	CH_2OH	3,5-Me_2	0.0099	>20	>2020
20	S	*i*-Pr	CH_2OH	H	0.093	78	840
21	S	*i*-Pr	CH_2OH	3-Me	0.054	55	1020
22	O	Et	CH_2OH	3-Me	0.12	>20	>170
23	O	Et	CH_2OH	3,5-Me_2	0.022	>20	>910
24	O	*i*-Pr	CH_2OH	H	0.11	194	1760
25	O	*i*-Pr	CH_2OH	3-Me	0.070	139	1990
26	O	*i*-Pr	CH_2OH	3,5-Me_2	0.019	113	5950
35	S	Et	Me	3-Me	0.020	>20	>1000
36	S	Et	Me	3,5-Me_2	0.012	>20	>1670
37	S	Et	Ph	3,5-Me_2	0.016	>20	>1250
38	S	*i*-Pr	Me	H	0.034	>200	>5880
39	S	*i*-Pr	Me	3-Me	0.047	>200	>4250
40	S	*i*-Pr	Me	3,5-Me_2	0.027	>200	>7410
41	S	*i*-Pr	Me	3,5-F_2	0.071	14	200
42	S	*i*-Pr	Ph	H	0.046	>200	>4350
43	S	*i*-Pr	Ph	3-Me	0.045	>200	>4440
44	S	*i*-Pr	Ph	3,5-Me_2	0.054	>200	>3700
45	O	Et	Me	3-Me	0.027	86	3180
46	O	Et	Me	3,5-Me_2	0.0089	>20	>2250
47	O	Et	Ph	3,5-Me_2	0.0063	>20	>3170
48	O	*i*-Pr	Me	H	0.013	61	4690
49	O	*i*-Pr	Me	3-Me	0.0081	53	6540
50	O	*i*-Pr	Me	3,5-Me_2	0.0047	>200	>42600
51	O	*i*-Pr	Me	3,5-F_2	0.019	49	2580
52	O	*i*-Pr	Ph	H	0.013	20	1540
53	O	*i*-Pr	Ph	3-Me	0.011	>200	>18200
54	O	*i*-Pr	Ph	3,5-Me_2	0.031	>200	6450
AZT					0.0045	>1.0	>220
2',3'-Dideoxycytidine					0.19	>10	>50

[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 in duplicates. [b] Effective concentration of compound required to achieve 50% protection of CEM-SS cells against the cytopathic effect of HIV-1. [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}.

Scheme 3



27, X = S, R_1 = Et, R_2 = Me (35%)
28, X = S, R_1 = Et, R_2 = Ph (29%)
29, X = S, R_1 = *i*-Pr, R_2 = Me (27%)
30, X = S, R_1 = *i*-Pr, R_2 = Ph (27%)
31, X = O, R_1 = Et, R_2 = Me (89%)
32, X = O, R_1 = Et, R_2 = Ph (83%)
33, X = O, R_1 = *i*-Pr, R_2 = Me (90%)
34, X = O, R_1 = *i*-Pr, R_2 = Ph (96%)

35, X = S, R_1 = Et, R_2 = Me, Y = 3-Me (63%)
36, X = S, R_1 = Et, R_2 = Me, Y = 3,5-Me_2 (74%)
37, X = S, R_1 = Et, R_2 = Ph, Y = 3,5-Me_2 (43%)
38, X = S, R_1 = *i*-Pr, R_2 = Me, Y = H (82%)
39, X = S, R_1 = *i*-Pr, R_2 = Me, Y = 3-Me (73%)
40, X = S, R_1 = *i*-Pr, R_2 = Me, Y = 3,5-Me_2 (83%)
41, X = S, R_1 = *i*-Pr, R_2 = Me, Y = 3,5-F_2 (34%)
42, X = S, R_1 = *i*-Pr, R_2 = Ph, Y = H (39%)
43, X = S, R_1 = *i*-Pr, R_2 = Ph, Y = 3-Me (35%)
44, X = S, R_1 = *i*-Pr, R_2 = Ph, Y = 3,5-Me_2 (20%)
45, X = O, R_1 = Et, R_2 = Me, Y = 3-Me (56%)
46, X = O, R_1 = Et, R_2 = Me, Y = 3,5-Me_2 (67%)
47, X = O, R_1 = Et, R_2 = Ph, Y = 3,5-Me_2 (20%)

48, R_1 = *i*-Pr, R_2 = Me, Y = H (88%)
49, R_1 = *i*-Pr, R_2 = Me, Y = 3-Me (75%)
50, R_1 = *i*-Pr, R_2 = Me, Y= 3,5-Me_2 (88%)
51, R_1 = *i*-Pr, R_2 = Me, Y = 3,5-F_2 (82%)
52, R_1 = *i*-Pr, R_2 = Ph, Y= H (36%)
53, R_1 = *i*-Pr, R_2 = Ph, Y = 3-Me (30%)
54, R_1 = *i*-Pr, R_2 = Ph, Y = 3,5-Me_2 (15%)

[a] (i) 1,1,1,3,3,3-hexamethyldisilazane, $(NH_4)_2SO_4$, reflux, 15 h, then alkyl chloromethyl ether, CsI, MeCN, reflux, 2 h (for **27-30**), or (ii) *N,O*-bis(trimethylsilyl)acetamide, CH_2Cl_2, rt, 2 h, then alkyl chloromethyl ether, Bu_4NI, reflux, 2 h (for **31-34**); [b] LDA, THF, -70°C, 1 h, then diaryl diselenides **15a-d**, -70°C, 1 h, then AcOH; [c] 35% H_2O_2, 1*N* NaOH, rt, 1 h, then *c*-HCl.

Compounds **48-51** with an ethoxymethyl group at N-1 were obtained in good yields (75-88%), whereas compounds **52-54** with a benzyloxymethyl group were produced in poor yields (15-36%).

The anti-HIV-1 (HTLV-III_B) activity and cytotoxicity of the compounds **18-26** and **35-54** were tested by the Developmental Therapeutics Program of the National Cancer Institute as previously described [14], and the results are summarized in Table 1 along with those of AZT and 2',3'-dideoxycytidine.

Among the 2-thiouracil derivatives **18-21** with a (2-hydroxyethoxy)methyl group at N-1, compound **19** was the most inhibitory to HIV-1 replication with an EC_{50} value of 0.0099 μM, showing that modification at the 3-and 5-positions of the C-6 phenylselenenyl ring with two methyl groups significantly increased anti-HIV-1 activity. The uracil derivatives **22-25** had the similar levels of anti-HIV-1 activity and cytotoxicity compared with those of the corresponding 2-thio compounds **18-21**. Surprisingly, modification of the C-6 phenylselenenyl ring with methyl or fluoro substituent was not benificial for the 2-thiouracil derivatives **38-44** having an ethoxymethyl or a benzyloxymethyl group at N-1. The 6-[(3-methylphenyl)selenenyl] derivative **39** and the 6-[(3,5-difluorophenyl)selenenyl] derivative **41** were 1.4- and 2.1- fold less potent than the corresponding 6-(phenylselenenyl) derivative **38**, respectively, and compounds **42-44** were almost equally potent. For the uracil derivatives, however, a considerable increase in anti-HIV-1 activity was accomplished by introducing methyl substituent at the meta position of the 6-phenylselenenyl ring without increasing the cytotoxicity of the compounds. Consequently, compounds **46**, **47**, **49** and **50** inhibited HIV-1 replication in the nanomolar concentration range. Among these, compound **50** was equipotent to AZT, but quite less toxic than AZT, showing a selectivity index of >42600. Further preclinical evaluation of **50** are presently in progress.

EXPERIMENTAL

Melting points were determined on either an Electrothermal F500MA digital or a Mettler FP62 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were run in deuteriochloroform on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane for ^1H nmr, and deuteriochloroform served as the internal standard at δ 77.0 for ^{13}C nmr. The electron impact ms spectra were obtained on a VG Quattro mass spectrometer. The tlc analysis was performed on Merck silica gel 60F-254 glass plates. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer.

General Procedure for the Preparation of 5-Alkyl-1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]uracils **13** and **14**.

A suspension of 5-alkyluracil **9** or **10** (32.0 mmoles) and *N,O*-bis(trimethylsilyl)acetamide (14.37 g, 70.6 mmoles, 17.5 ml) in dichloromethane (40 ml) was stirred at room temperature for 2 hours under a nitrogen atmosphere. To the resulting solution cooled to -60° was added [2-(trimethylsiloxy)ethoxy]methyl iodide which was *in situ* generated from 1,3-dioxolane (2.85 g, 38.5 mmoles, 2.7 ml) and iodotrimethylsilane (7.07 g, 35.3 mmoles, 5.0 ml) in cyclohexane (20 ml) at -78° for 15 minutes under a nitrogen atmosphere. The mixture was allowed to warm to room temperature over 30 minutes and stirred for an additional

3 hours under a nitrogen atmosphere. The reaction mixture was poured into saturated sodium bicarbonate solution (80 ml), and it was then extracted by using continuous extractor with dichloromethane. The dichloromethane solution was dried over anhydrous magnesium sulfate and evaporated to dryness to give a residue. To a stirred solution of the residue in *N,N*-dimethylformamide (80 ml) were added imidazole (2.62 g, 38.5 mmoles) and *tert*-butyldimethylsilyl chloride (5.81 g, 38.5 mmoles), and the mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (200 ml), and it was extracted with ethyl acetate (3 x 200 ml). The organic phase was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with ethyl acetate-hexane (1:1) as eluent and then crystallized from a suitable solvent.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-5-ethyluracil (**13**).

This compound was synthesized from **9** in 71% yield, mp 86.2-87.0°; ir (potassium bromide): 3231, 1689 cm^{-1}; ^{1}H nmr: δ 0.06 (s, 6H, Si$(CH_3)_2$), 0.89 (s, 9H, SiC$(CH_3)_3$), 1.14 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.37 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.65 (m, 2H, CH_2OSi), 3.77 (m, 2H, OCH_2), 5.21 (s, 2H, NCH_2O), 7.11 (s, 1H, H-6), 9.50 (br s, 1H, NH); ^{13}C nmr: δ -5.3, 12.6, 18.3, 19.9, 25.8, 62.4, 71.0, 76.8, 117.3, 138.1, 151.2, 163.8; ms: m/z 329 (M$^+$ + H).

Anal. Calcd. for $C_{15}H_{28}N_2O_4Si$: C, 54.85; H, 8.59; N, 8.53. Found: C, 54.73; H, 8.64; N, 8.40.

1-[[2-(*tert*-Butyldimethylsiloxy)ethoxy]methyl]-5-isopropyluracil (**14**).

This compound was synthesized from **10** in 87% yield, mp 78.6-79.3°; ir (potassium bromide): 3270, 3221, 1688 cm^{-1}; ^{1}H nmr: δ 0.07 (s, 6H, Si$(CH_3)_2$), 0.89 (s, 9H, SiC$(CH_3)_3$), 1.16 (d, J = 6.9 Hz, 6H, CH$(CH_3)_2$), 2.92 (septet, J = 6.9 Hz, 1H, CH$(CH_3)_2$), 3.65 (m, 2H, CH_2OSi), 3.77 (m, 2H, OCH_2), 5.21 (s, 2H, NCH_2O), 7.07 (s, 1H, H-6), 9.18 (br s, 1H, NH); ^{13}C nmr: δ -5.3, 18.3, 21.5, 25.8, 25.9, 62.4, 71.1, 76.9, 121.7, 137.3, 150.9, 163.3; ms: m/z 343 (M$^+$ + H).

Anal. Calcd. for $C_{16}H_{30}N_2O_4Si$: C, 56.11; H, 8.83; N, 8.18. Found: C, 55.92; H, 8.88; N, 7.97.

General Procedure for the Preparation of Aryl Selenocyanates **17b** and **17c**.

The stirred warm mixture of aniline **16b** or **16c** (300 mmoles), concentrated hydrochloric acid (65 ml) and water (150 ml) was cooled to 0° and diazotized with a solution of sodium nitrite (20.70 g, 300 mmoles) in water (60 ml), added at such a rate that the temperature could be maintained by cooling at 0~5°. The mixture was stirred at 0° for 1 hour and then neutralized with sodium acetate. The resulting diazonium salt was added dropwise to a stirred solution of potassium selenocyanate (47.53 g, 330 mmoles) in water (35 ml) at -5~0°. After stirring at room temperature for 1 hour, the reaction mixture was extracted with diethyl ether (3 x 200 ml). The ethereal solution was washed with saturated sodium bicarbonate solution (2 x 100 ml) and brine (100 ml), dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was distilled *in vacuo* to give **17b** or purified by flash column chromatography on silica gel with diethyl ether-hexane as eluent to give **17c**.

3,5-Dimethylphenyl Selenocyanate (**17b**).

This compound was obtained in 12% yield as a yellow oil, bp 97-120°/2 mm Hg; ir (neat): 2153 (SeCN) cm^{-1}; ^{1}H nmr: δ 2.32 (s, 6H, 2 CH_3), 7.03 (m, 1H, Ar H), 7.23 (m, 2H, Ar H); ^{13}C nmr: δ 21.1, 101.7, 121.3, 130.1, 131.4, 140.3; ms: m/z 211 (M$^+$ + H).

Anal. Calcd. for C_9H_9NSe: C, 51.44; H, 4.32; N, 6.67. Found: C, 51.28; H, 4.38; N, 6.51.

3,5-Difluorophenyl Selenocyanate (**17c**).

This compound was obtained in 50% yield as a pale yellow solid; ir (potassium bromide): 2155 (SeCN) cm^{-1}; ^{1}H nmr: δ 6.82-6.94 (m, 1H, Ar H), 7.13-7.25 (m, 2H, Ar H); ^{13}C nmr: δ 99.8, 105.5 (t, $^2J_{C,F}$ = 25.0 Hz, C-4), 115.1 (dd, $^2J_{C,F}$ = 18.9 Hz, $^4J_{C,F}$ = 9.1 Hz, C-2 and C-6), 124.1 (t, $^3J_{C,F}$ = 9.5 Hz, C-1), 163.2 (dd, $^1J_{C,F}$ = 255.1 Hz, $^3J_{C,F}$ = 12.5 Hz, C-3 and C-5); ms: m/z 219 (M$^+$ + H).

Anal. Calcd. for $C_7H_3F_2NSe$: C, 38.56; H, 1.39; N, 6.42. Found: C, 38.28; H, 1.35; N, 6.27.

General Procedure for the Preparation of Diaryl Diselenides **15b** and **15c**.

To a stirred solution of aryl selenocyanate **17b** or **17c** (100 mmoles) in ethanol (100 ml) was added a solution of sodium hydroxide (10.00 g, 250 mmoles) in water (30 ml) at 0°. The mixture was stirred at room temperature for 3 hours, and then the solvent was removed under a reduced pressure. Carbon dioxide gas was introduced to the residue, and the resulting solid was partitioned between diethyl ether (200 ml) and water (100 ml). The organic phase was washed with water (50 ml) and brine (50 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with hexane as eluent to give **15b** or distilled *in vacuo* to give **15c**.

Bis(3,5-dimethylphenyl) Diselenide (**15b**).

This compound was obtained in 98% yield as a brick red oil; ir (neat): 1599 cm^{-1}; ^{1}H nmr: δ 2.26 (s, 12H, 4 CH_3), 6.86 (m, 2H, Ar H), 7.22 (m, 4H, Ar H); ^{13}C nmr: δ 21.1, 129.4, 129.6, 130.8, 138.7; ms: m/z 368 (M$^+$).

Anal. Calcd. for $C_{16}H_{18}Se_2$: C, 52.19; H, 4.93. Found: C, 52.03; H, 4.98.

Bis(3,5-difluorophenyl) Diselenide (**15c**).

This compound was obtained in 80% yield as a brick red oil, bp 132-142°/0.8 mm Hg; ir (neat): 1599 cm^{-1}; ^{1}H nmr: δ 6.63-6.78 (m, 2H, Ar H), 7.04-7.19 (m, 4H, Ar H); ^{13}C nmr: δ 103.6 (t, $^2J_{C,F}$ = 25.3 Hz, C-4), 113.5 (dd, $^2J_{C,F}$ = 18.3 Hz, $^4J_{C,F}$ = 8.6 Hz, C-2 and C-6), 132.5 (t, $^3J_{C,F}$ = 8.2 Hz, C-1), 162.9 (dd, $^1J_{C,F}$ = 253.2 Hz, $^3J_{C,F}$ = 12.2 Hz, C-3 and C-5); ms: m/z 384 (M$^+$).

Anal. Calcd. for $C_{12}H_6F_4Se_2$: C, 37.53; H, 1.57. Found: C, 37.28; H, 1.60.

General Procedure for the Preparation of 5-Alkyl-6-(arylselenenyl)-1-[(2-hydroxyethoxy)methyl]-2-thiouracils **18-21**.

To a stirred solution of 5-alkyl-1-[[2-(*tert*-butyldimethylsiloxy)ethoxy]methyl]-2-thiouracil **11** or **12** (1.00 mmole) in anhydrous tetrahydrofuran (6 ml) was added lithium diisopropylamide (1.67 ml of 1.5*M* solution in cyclohexane, 2.50 mmoles) dropwise under a nitrogen atmosphere, at a rate such that the temperature did not exceed -70°. After the mixture was stirred for 1 hour, diaryl diselenide (1.50 mmoles) dissolved in anhydrous tetrahydrofuran (3 ml) was added dropwise. The mixture was stirred for 1 hour below -70° and allowed to warm to room temperature. The solution was acidified with concentrated hydrochloric acid to *p*H 1.2 and stirred at room temperature for 2 hours. The reaction mixture was poured into saturated sodium bicarbonate solution (25 ml), and it was then extracted with ethyl acetate (3 x 25 ml). The organic phase was washed with brine (25 ml), dried over anhydrous magnesium sulfate, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel and then crystallized from a suitable solvent.

5-Ethyl-1-[(2-hydroxyethoxy)methyl]-6-[(3-methylphenyl)selenenyl]-2-thiouracil (**18**).

This compound was synthesized from **11** with **15a** in 77% yield, mp 107.2-108.5° (ethyl acetate-hexane); ir (potassium bromide): 3396, 1668 cm^{-1}; ^{1}H nmr: δ 0.92 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.93 (br s, 1H, OH), 2.34 (s, 3H, CH_3), 2.68 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.68-3.75 (m, 4H, OCH_2CH_2O), 6.20 (br s, 2H, NCH_2O), 7.11-7.24 (m, 4H, Ar H), 9.62 (br s, 1H, NH); ms: m/z 400 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_3SSe$: C, 48.12; H, 5.05; N, 7.01. Found: C, 47.88; H, 5.15; N, 6.82.

6-[(3,5-Dimethylphenyl)selenenyl]-5-ethyl-1-[(2-hydroxyethoxy)methyl]-2-thiouracil (**19**).

This compound was synthesized from **11** with **15b** in 62% yield, mp 128.7-129.8° (ethyl acetate-hexane); ir (potassium bromide): 3480, 1674 cm^{-1}; ^{1}H nmr: δ 0.93 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.07 (br s, 1H, OH), 2.29 (s, 6H, 2 CH_3), 2.68 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.65-3.80 (m, 4H, OCH_2CH_2O), 6.20 (br s, 2H, NCH_2O), 6.93 (s, 1H, Ar H), 6.97 (s, 2H, Ar H), 10.08 (br s, 1H, NH); ms: m/z 414 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_3SSe$: C, 49.39; H, 5.36; N, 6.78. Found: C, 49.25; H, 5.40; N, 6.85.

1-[(2-Hydroxyethoxy)methyl]-5-isopropyl-6-(phenylselenenyl)-2-thiouracil (**20**).

This compound was synthesized from **12** with **15d** in 62% yield, mp 154.3-155.1° (ethyl acetate-hexane); ir (potassium bromide): 3398, 1664 cm^{-1}; ^{1}H nmr: δ 1.05 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.95 (br s, 1H, OH), 3.39 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.65-3.80 (m, 4H, OCH_2CH_2O), 6.29 (br s, 2H, NCH_2O), 7.27-7.45 (m, 5H, Ar H), 9.63 (br s, 1H, NH); ms: m/z 400 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_3SSe$: C, 48.12; H, 5.05; N, 7.01. Found: C, 47.82; H, 5.13; N, 6.88.

1-[(2-Hydroxyethoxy)methyl]-5-isopropyl-6-[(3-methylphenyl)-selenenyl]-2-thiouracil (**21**).

This compound was synthesized from **12** with **15a** in 59% yield, mp 130.6-130.9° (ethyl acetate-hexane); ir (potassium bromide): 3391, 1664 cm^{-1}; ^{1}H nmr: δ 1.06 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.93 (br s, 1H, OH), 2.34 (s, 3H, CH_3), 3.39 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.68-3.82 (m, 4H, OCH_2CH_2O), 6.29 (br s, 2H, NCH_2O), 7.11-7.24 (m, 4H, Ar H), 9.54 (br s, 1H, NH); ms: m/z 414 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_3SSe$: C, 49.39; H, 5.36; N, 6.78. Found: C, 49.18; H, 5.45; N, 6.88.

General Procedure for the Preparation of 5-Alkyl-6-(arylselenenyl)-1-[(2-hydroxyethoxy)methyl]uracils **22-26**.

The procedure was the same as for the preparation of **18-21** except that lithium bis(trimethylsilyl)amide was used as the lithiating agent, and the mixture was stirred for an additional 16 hours at room temperature before acidification with concentrated hydrochloric acid.

5-Ethyl-1-[(2-hydroxyethoxy)methyl]-6-[(3-methylphenyl)selenenyl]uracil (**22**).

This compound was synthesized from **13** with **15a** in 78% yield, mp 106.1-107.9° (ethyl acetate-hexane); ir (potassium bromide): 3482, 1670 cm^{-1}; ^{1}H nmr: δ 0.97 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.06 (br s, 1H, OH), 2.33 (s, 3H, CH_3), 2.71 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.64 (s, 4H, OCH_2CH_2O), 5.61 (s, 2H, NCH_2O), 7.08-7.22 (m, 4H, Ar H), 9.09 (br s, 1H, NH); ms: m/z 384 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_4Se$: C, 50.14; H, 5.26; N, 7.31. Found: C, 50.02; H, 5.29; N, 7.25.

6-[(3,5-Dimethylphenyl)selenenyl]-5-ethyl-1-[(2-hydroxyethoxy)methyl]uracil (**23**).

This compound was synthesized from **13** with **15b** in 73% yield, mp 139.0-139.9° (ethyl acetate-hexane); ir (potassium bromide): 3408, 1707, 1673 cm^{-1}; ^{1}H nmr: δ 0.97 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.23 (br s, 1H, OH), 2.28 (s, 6H, 2 CH_3), 2.71 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.66 (s, 4H, OCH_2CH_2O), 5.61 (s, 2H, NCH_2O), 6.91 (s, 1H, Ar H), 6.95 (s, 2H, Ar H), 9.58 (br s, 1H, NH); ms: m/z 398 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_4Se$: C, 51.39; H, 5.58; N, 7.05. Found: C, 51.32; H, 5.64; N, 6.98.

1-[(2-Hydroxyethoxy)methyl]-5-isopropyl-6-(phenylselenenyl)-uracil (**24**).

This compound was synthesized from **14** with **15d** in 64% yield, mp 112.6-114.3° (ethyl acetate-hexane); ir (potassium bromide): 3394, 1674 cm^{-1}; ^{1}H nmr: δ 1.12 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.00 (br s, 1H, OH), 3.46 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.66 (s, 4H, OCH_2CH_2O), 5.69 (s, 2H, NCH_2O), 7.27-7.41 (m, 5H, Ar H), 8.82 (br s, 1H, NH); ms: m/z 384 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_4Se$: C, 50.14; H, 5.26; N, 7.31. Found: C, 50.32; H, 5.18; N, 7.25.

1-[(2-Hydroxyethoxy)methyl]-5-isopropyl-6-[(3-methylphenyl)-selenenyl]uracil (**25**).

This compound was synthesized from **14** with **15a** in 68% yield, mp 109.5-110.4° (ethyl acetate-hexane); ir (potassium bromide): 3371, 1673 cm^{-1}; ^{1}H nmr: δ 1.13 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.93 (br s, 1H, OH), 2.33 (s, 3H, CH_3), 3.46 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.67 (s, 4H, OCH_2CH_2O), 5.68 (s, 2H, NCH_2O), 7.09-7.20 (m, 4H, Ar H), 8.56 (br s, 1H, NH); ms: m/z 398 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_4Se$: C, 51.39; H, 5.58; N, 7.05. Found: C, 51.12; H, 5.72; N, 6.88.

6-[(3,5-Dimethylphenyl)selenenyl]-1-[(2-hydroxyethoxy)-methyl]-5-isopropyluracil (**26**).

This compound was synthesized from **14** with **15b** in 45% yield, mp 143.4-144.9° (ethyl acetate-hexane); ir (potassium bromide): 3420, 1709, 1667 cm^{-1}; ^{1}H nmr: δ 1.14 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.21 (br s, 1H, OH), 2.28 (s, 6H, 2 CH_3), 3.46 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.68 (s, 4H, OCH_2CH_2O), 5.69 (s, 2H, NCH_2O), 6.91 (s, 1H, Ar H), 6.98 (s, 2H, Ar H), 9.37 (br s, 1H, NH); ms: m/z 412 (M^+ + H).

Anal. Calcd. for $C_{18}H_{24}N_2O_4Se$: C, 52.56; H, 5.88; N, 6.81. Found: C, 52.49; H, 5.83; N, 6.75.

General Procedure for the Preparation of 1-(Alkoxymethyl)-5-alkyluracils **31-34**.

A suspension of 5-alkyluracil **9** or **10** (25.0 mmoles) and *N,O*-bis(trimethylsilyl)acetamide (11.19 g, 13.6 ml, 55.0 mmoles) in dichloromethane (30 ml) was stirred at room temperature for 2 hours under a nitrogen atmosphere. To the resulting solution, tetrabutylammonium iodide (93 mg, 0.25 mmole) and alkyl chloromethyl ether (30.0 mmoles) were added. The mixture was heated at reflux for 2 hours and allowed to cool to room temperature. The reaction mixture was poured into saturated sodium bicarbonate solution (10 ml) and ice (5 ml), and stirred for an additional 30 minutes. The organic phase was washed with brine (15 ml), dried over anhydrous magnesium sulfate, and concentrated to dryness. The residue was crystallized from a suitable solvent or purified by flash column chromatography on silica gel and then crystallized.

1-(Ethoxymethyl)-5-ethyluracil (**31**).

This compound was synthesized from **9** with chloromethyl ethyl ether in 89% yield, mp 104.8-105.5°; ir (potassium bromide): 3218, 1694 cm^{-1}; ^{1}H nmr: δ 1.15 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.22 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.38 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.61 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.16 (s, 2H, NCH_2O), 7.10 (s, 1H, H-6), 9.41 (br s, 1H, NH); ^{13}C nmr: δ 12.6, 14.9, 19.9, 65.0, 76.2, 117.4, 138.1, 151.2, 163.8; ms: m/z 198 (M^+).

Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.21; N, 14.13. Found: C, 54.45; H, 7.12; N, 13.94.

1-(Benzyloxymethyl)-5-ethyluracil (**32**).

This compound was synthesized from **9** with benzyl chloromethyl ether in 83% yield, mp 129.4-131.1°; ir (potassium bromide): 3446, 1702, 1660 cm^{-1}; ^{1}H nmr: δ 1.12 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.35 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.63 (s, 2H, CH_2Ph), 5.23 (s, 2H, NCH_2O), 7.05 (s, 1H, H-6), 7.30-7.40 (m, 5H, Ar H), 8.94 (br s, 1H, NH); ^{13}C nmr: δ 12.6, 19.9, 71.6, 76.1, 117.4, 127.9, 128.1, 128.5, 136.7, 138.1, 151.2, 163.7; ms: m/z 260 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.25; H, 6.23; N, 10.63.

1-(Ethoxymethyl)-5-isopropyluracil (**33**).

This compound was synthesized from **10** with chloromethyl ethyl ether in 90% yield, mp 79.9-81.1°; ir (potassium bromide): 3230, 1698 cm^{-1}; ^{1}H nmr: δ 1.17 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.92 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.62 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.16 (s, 2H, NCH_2O), 7.07 (s, 1H, H-6), 9.35 (br s, 1H, NH); ^{13}C nmr: δ 14.9, 21.5, 25.7, 65.0, 76.3, 121.8, 137.2, 151.1, 163.4; ms: m/z 212 (M^+).

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.32; H, 7.72; N, 13.02.

1-(Benzyloxymethyl)-5-isopropyluracil (**34**).

This compound was synthesized from **10** with benzyl chloromethyl ether in 96% yield, mp 86.3-86.9°; ir (potassium bromide): 3404, 1708, 1654 cm^{-1}; ^{1}H nmr: δ 1.15 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.89 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.64 (s, 2H, CH_2Ph), 5.23 (s, 2H, NCH_2O), 7.01 (s, 1H, H-6), 7.30-7.40 (m, 5H, Ar H), 8.64 (br s, 1H, NH); ^{13}C nmr: δ 21.4, 25.7, 71.7, 76.2, 121.8, 127.9, 128.1, 128.5, 136.8, 137.2, 150.9, 163.2; ms: m/z 274 (M^+).

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.72; H, 6.58; N, 10.23.

General Procedure for the Preparation of 1-(Alkoxymethyl)-5-alkyl-6-(arylselenenyl)-2-thiouracils **35-44** and -uracils **45-47**.

To a stirred solution of 1-(alkoxymethyl)-5-alkyl-2-thiouracils **27-30** and -uracils **31-34** (1.00 mmole) in anhydrous tetrahydrofuran (6 ml) was added lithium diisopropylamide (1.67 ml of 1.5*M* solution in cyclohexane, 2.50 mmoles) dropwise under a nitrogen atmosphere, at a rate such that the temperature did not exceed -70°. After the mixture was stirred for 1 hour, diaryl diselenide (1.50 mmoles) dissolved in anhydrous tetrahydrofuran (3 ml) was added dropwise. The mixture was stirred for 1 hour below -70°. The reaction mixture was quenched with acetic acid (5.00 mmoles) and then allowed to warm to room temperature. The suspension was partitioned between ethyl acetate (25 ml) and water (25 ml), and the aqueous phase was extracted with ethyl acetate (2 x 25 ml). The combined organic phase was washed with saturared sodium bicarbonate solution (25 ml) and brine (25 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel and then crystallized from a suitable solvent.

1-(Ethox\ymethyl)-5-ethyl-6-[(3-methylphenyl)selenenyl]-2-thiouracil (**35**).

This compound was synthesized from **27** with **15a** in 63% yield, mp 132.7-133.3° (ethanol); ir (potassium bromide): 1673 cm^{-1}; ^{1}H nmr: δ 0.86 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.18 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.33 (s, 3H, CH_3), 2.63 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.67 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.19 (br s, 2H, NCH_2O), 7.08-7.23 (m, 4H, Ar H), 9.58 (br s, 1H, NH); ms: m/z 384 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_2SSe$: C, 50.13; H, 5.26; N, 7.31. Found: C, 50.21; H, 5.29; N, 7.24.

6-[(3,5-Dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-ethyl-2-thiouracil (**36**).

This compound was synthesized from **27** with **15b** in 74% yield, mp 165.8-166.2° (ethanol); ir (potassium bromide): 1650 cm^{-1}; ^{1}H nmr: δ 0.87 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.19 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 2.28 (s, 6H, 2 CH_3), 2.64 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.68 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 6.20 (br s, 2H, NCH_2O), 6.92 (s, 1H, Ar H), 6.98 (s, 2H, Ar H), 10.03 (br s, 1H, NH); ms: m/z 398 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_2SSe$: C, 51.38; H, 5.58; N, 7.05. Found: C, 51.03; H, 5.71; N, 6.97.

1-(Benzyloxymethyl)-6-[(3,5-dimethylphenyl)selenenyl]-5-ethyl-2-thiouracil (**37**).

This compound was synthesized from **28** with **15b** in 43% yield, mp 157.8-159.0° (ethanol); ir (potassium bromide): 1700 cm^{-1}; ^{1}H nmr: δ 0.84 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.25 (s, 6H, 2 CH_3), 2.59 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.73 (s, 2H, CH_2Ph), 6.27 (br s, 2H, NCH_2O), 6.90 (s, 1H, Ar H), 6.93 (s, 2H, Ar H), 7.25-7.33 (m, 5H, Ar H), 9.48 (br s, 1H, NH); ms: m/z 460 (M^+ + H).

Anal. Calcd. for $C_{22}H_{24}N_2O_2SSe$: C, 57.51; H, 5.26; N, 6.10. Found: C, 57.38; H, 5.38; N, 5.83.

1-(Ethoxymethyl)-5-isopropyl-6-(phenylselenenyl)-2-thiouracil (**38**).

This compound was synthesized from **29** with **15d** in 82% yield, mp 134.2-134.9° (ethyl acetate-hexane); ir (potassium bromide): 1651 cm^{-1}; ^{1}H nmr: δ 0.99 (d, J = 6.9 Hz, 6H,

$CH(CH_3)_2$), 1.20 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.35 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.68 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.27 (br s, 2H, NCH_2O), 7.30-7.43 (m, 5H, Ar H), 9.48 (br s, 1H, NH); ms: m/z 384 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_2SSe$: C, 50.13; H, 5.26; N, 7.31. Found: C, 49.92; H, 5.25; N, 7.28.

1-(Ethoxymethyl)-5-isopropyl-6-[(3-methylphenyl)selenenyl]-2-thiouracil (**39**).

This compound was synthesized from **29** with **15a** in 73% yield, mp 153.4-153.7° (ethyl acetate-hexane); ir (potassium bromide): 1646 cm^{-1}; ^{1}H nmr: δ 1.00 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.33 (s, 3H, CH_3), 3.35 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.68 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.27 (br s, 2H, NCH_2O), 7.08-7.28 (m, 4H, Ar H), 9.46 (br s, 1H, NH); ms: m/z 398 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_2SSe$: C, 51.38; H, 5.58; N, 7.05. Found: C, 51.35; H, 5.63; N, 7.00.

6-[(3,5-Dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyl-2-thiouracil (**40**).

This compound was synthesized from **29** with **15b** in 83% yield, mp 183.0-183.5° (ethyl acetate-hexane); ir (potassium bromide): 1651 cm^{-1}; ^{1}H nmr: δ 1.01 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.28 (s, 6H, 2 CH_3), 3.35 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.69 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.27 (br s, 2H, NCH_2O), 6.92 (s, 1H, Ar H), 7.01 (s, 2H, Ar H), 9.44 (br s, 1H, NH); ms: m/z 412 (M^+ + H).

Anal. Calcd. for $C_{18}H_{24}N_2O_2SSe$: C, 52.55; H, 5.88; N, 6.81. Found: C, 52.48; H, 5.80; N, 6.85.

6-[(3,5-Difluorophenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyl-2-thiouracil (**41**).

This compound was synthesized from **29** with **15c** in 34% yield, mp 144.6-145.6° (ethyl acetate-hexane); ir (potassium bromide): 1653 cm^{-1}; ^{1}H nmr: δ 1.09 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.18 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.27 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.68 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.22 (br s, 2H, NCH_2O), 6.76 (m, 1H, Ar H), 6.95 (m, 2H, Ar H), 9.52 (br s, 1H, NH); ms: m/z 420 (M^+ + H).

Anal. Calcd. for $C_{16}H_{18}F_2N_2O_2SSe$: C, 45.83; H, 4.33; N, 6.68. Found: C, 45.92; H, 4.41; N, 6.54.

1-(Benzyloxymethyl)-5-isopropyl-6-(phenylselenenyl)-2-thiouracil (**42**).

This compound was synthesized from **30** with **15d** in 39% yield, mp 177.9-178.4° (ethanol); ir (potassium bromide): 1700 cm^{-1}; ^{1}H nmr: δ 0.96 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 3.31 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.73 (s, 2H, CH_2Ph), 6.37 (br s, 2H, NCH_2O), 7.28-7.40 (m, 10H, Ar H), 9.35 (br s, 1H, NH); ms: m/z 446 (M^+ + H).

Anal. Calcd. for $C_{21}H_{22}N_2O_2SSe$: C, 56.62; H, 4.98; N, 6.29. Found: C, 56.75; H, 4.81; N, 6.35.

1-(Benzyloxymethyl)-5-isopropyl-6-[(3-methylphenyl)selenenyl]-2-thiouracil (**43**).

This compound was synthesized from **30** with **15a** in 35% yield, mp 174.5-175.0° (ethanol); ir (potassium bromide): 1698 cm^{-1}; ^{1}H nmr: δ 0.98 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.30 (s, 3H, CH_3), 3.32 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.73 (s, 2H, CH_2Ph), 6.37 (br s, 2H, NCH_2O), 7.08-7.40 (m, 9H, Ar H), 9.37 (br s, 1H, NH); ms: m/z 460 (M^+ + H).

Anal. Calcd. for $C_{22}H_{24}N_2O_2SSe$: C, 57.51; H, 5.26; N, 6.10. Found: C, 57.25; H, 5.23; N, 5.88.

1-(Benzyloxymethyl)-6-[(3,5-dimethylphenyl)selenenyl]-5-isopropyl-2-thiouracil (**44**).

This compound was synthesized from **30** with **15b** in 20% yield, mp 186.8-187.4° (ethanol); ir (potassium bromide): 1645 cm^{-1}; ^{1}H nmr: δ 0.99 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.25 (s, 6H, 2 CH_3), 3.33 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.73 (s, 2H, CH_2Ph), 6.37 (br s, 2H, NCH_2O), 6.90 (s, 1H, Ar H), 6.97 (s, 2H, Ar H), 7.25-7.38 (m, 5H, Ar H), 9.35 (br s, 1H, NH); ms: m/z 474 (M^+ + H).

Anal. Calcd. for $C_{23}H_{26}N_2O_2SSe$: C, 58.34; H, 5.53; N, 5.92. Found: C, 58.12; H, 5.75; N, 5.98.

1-(Ethoxymethyl)-5-ethyl-6-[(3-methylphenyl)selenenyl]uracil (**45**).

This compound was synthesized from **31** with **15a** in 56% yield, mp 125.5-126.9° (ethanol); ir (potassium bromide): 1706, 1670 cm^{-1}; ^{1}H nmr: δ 0.93 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.14 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 2.67 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.57 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.56 (s, 2H, NCH_2O), 7.05-7.22 (m, 4H, Ar H), 8.60 (br s, 1H, NH); ms: m/z 368 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_3Se$: C, 52.32; H, 5.49; N, 7.63. Found: C, 52.53; H, 5.52; N, 7.48.

6-[(3,5-Dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-ethyluracil (**46**).

This compound was synthesized from **31** with **15b** in 67% yield, mp 184.3-184.8° (ethanol); ir (potassium bromide): 1709, 1646 cm^{-1}; ^{1}H nmr: δ 0.94 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.16 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.28 (s, 6H, 2 CH_3), 2.68 (q, J = 7.4 Hz, 2H, CH_2CH_3), 3.58 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.56 (s, 2H, NCH_2O), 6.90 (s, 1H, Ar H), 6.96 (s, 2H, Ar H), 8.59 (br s, 1H, NH); ms: m/z 382 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_3Se$: C, 53.55; H, 5.81; N, 7.35. Found: C, 53.26; H, 5.93; N, 7.21.

1-(Benzyloxymethyl)-6-[(3,5-dimethylphenyl)selenenyl]-5-ethyluracil (**47**).

This compound was synthesized from **32** with **15b** in 20% yield, mp 158.5-159.2° (ethanol); ir (potassium bromide): 1708, 1667 cm^{-1}; ^{1}H nmr: δ 0.92 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.24 (s, 6H, 2 CH_3), 2.64 (q, J = 7.4 Hz, 2H, CH_2CH_3), 4.64 (s, 2H, CH_2Ph), 5.64 (s, 2H, NCH_2O), 6.88 (s, 1H, Ar H), 6.91 (s, 2H, Ar H), 7.24-7.35 (m, 5H, Ar H), 8.30 (br s, 1H, NH); ms: m/z 444 (M^+ + H).

Anal. Calcd. for $C_{22}H_{24}N_2O_3Se$: C, 59.59; H, 5.46; N, 6.32. Found: C, 59.41; H, 5.48; N, 6.16.

General Procedure for the Preparation of 1-(Alkoxymethyl)-6-(arylselenenyl)-5-isopropyluracils **48-54**.

To a stirred suspension of 1-(alkoxymethyl)-6-(arylselenenyl)-5-isopropyl-2-thiouracils **38-44** (1.00 mmole) in aquous 1*N* sodium hydroxide solution (8 ml) was added 35% hydrogen peroxide (0.60 ml). After the mixture was stirred at room temperature for 1 hour, the reaction mixture was neutralized with concentrated hydrochloric acid. The resulting precipitate was filtered and washed well with saturated sodium bicarbonate solution (3 x 5 ml) and water (3 x 5 ml). The precipitate was thoroughly dried *in vacuo* over phosphorus pentoxide and crystallized from a suitable solvent.

1-(Ethoxymethyl)-5-isopropyl-6-(phenylselenenyl)uracil (**48**).

This compound was synthesized from **38** in 88% yield, mp 114.5-115.3° (ethyl acetate-hexane); ir (potassium bromide): 1712, 1644 cm^{-1}; ^1H nmr: δ 1.07 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.16 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.42 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.59 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.64 (s, 2H, NCH_2O), 7.26-7.43 (m, 5H, Ar H), 8.54 (br s, 1H, NH); ms: m/z 368 (M^+ + H).

Anal. Calcd. for $C_{16}H_{20}N_2O_3Se$: C, 52.32; H, 5.49; N, 7.63. Found: C, 52.18; H, 5.65; N, 7.31.

1-(Ethoxymethyl)-5-isopropyl-6-[(3-methylphenyl)selenenyl]-uracil (**49**).

This compound was synthesized from **39** in 75% yield, mp 125.4-126.0° (ethyl acetate-hexane); ir (potassium bromide): 1711, 1645 cm^{-1}; ^1H nmr: δ 1.08 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.17 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 3.42 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.59 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.64 (s, 2H, NCH_2O), 7.05-7.23 (m, 4H, Ar H), 8.63 (br s, 1H, NH); ms: m/z 382 (M^+ + H).

Anal. Calcd. for $C_{17}H_{22}N_2O_3Se$: C, 53.55; H, 5.81; N, 7.35. Found: C, 52.23; H, 5.95; N, 7.16.

6-[(3,5-Dimethylphenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyluracil (**50**).

This compound was synthesized from **40** in 88% yield, mp 163.9-164.3° (ethyl acetate-hexane); ir (potassium bromide): 1711, 1645 cm^{-1}; ^1H nmr: δ 1.09 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 1.18 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.28 (s, 6H, 2 CH_3), 3.43 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.59 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.64 (s, 2H, NCH_2O), 6.90 (s, 1H, Ar H), 6.99 (s, 2H, Ar H), 8.43 (br s, 1H, NH); ms: m/z 396 (M^+ + H).

Anal. Calcd. for $C_{18}H_{24}N_2O_3Se$: C, 54.68; H, 6.12; N, 7.09. Found: C, 54.62; H, 6.15; N, 6.98.

6-[(3,5-Difluorophenyl)selenenyl]-1-(ethoxymethyl)-5-isopropyluracil (**51**).

This compound was synthesized from **41** in 82% yield, mp 137.0-137.9° (ethyl acetate-hexane); ir (potassium bromide): 1703, 1673 cm^{-1}; ^1H nmr: δ 1.14 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.15 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 3.35 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.58 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 5.59 (s, 2H, NCH_2O), 6.74 (m, 1H, Ar H), 6.93 (m, 2H, Ar H), 8.48 (br s, 1H, NH); ms: m/z 404 (M^+ + H).

Anal. Calcd. for $C_{16}H_{18}F_2N_2O_3Se$: C, 47.65; H, 4.50; N, 6.95. Found: C, 47.38; H, 4.62; N, 6.92.

1-(Benzyloxymethyl)-5-isopropyl-6-(phenylselenenyl)uracil (**52**).

This compound was synthesized from **42** in 36% yield, mp 150.0-150.9° (ethanol); ir (potassium bromide): 1709, 1642 cm^{-1}; ^1H nmr: δ 1.05 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 3.39 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.64 (s, 2H, CH_2Ph), 5.73 (s, 2H, NCH_2O), 7.25-7.40 (m, 10H, Ar H), 8.09 (br s, 1H, NH); ms: m/z 430 (M^+ + H).

Anal. Calcd. for $C_{21}H_{22}N_2O_3Se$: C, 58.74; H, 5.16; N, 6.52. Found: C, 58.68; H, 5.21; N, 6.49.

1-(Benzyloxymethyl)-5-isopropyl-6-[(3-methylphenyl)selenenyl]uracil (**53**).

This compound was synthesized from **43** in 30% yield, mp 141.2-141.5° (ethanol); ir (potassium bromide): 1684 cm^{-1}; ^1H nmr: δ 1.07 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.28 (s, 3H, CH_3), 3.40 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.64 (s, 2H, CH_2Ph), 5.74 (s, 2H, NCH_2O), 7.03-7.37 (m, 9H, Ar H), 8.80 (br s, 1H, NH); ms: m/z 444 (M^+ + H).

Anal. Calcd. for $C_{22}H_{24}N_2O_3Se$: C, 59.59; H, 5.46; N, 6.32. Found: C, 59.35; H, 5.53; N, 6.21.

1-(Benzyloxymethyl)-6-[(3,5-dimethylphenyl)selenenyl]-5-isopropyluracil (**54**).

This compound was synthesized from **44** in 15% yield, mp 164.3-165.0°; ir (potassium bromide): 1708, 1645 cm^{-1}; ^1H nmr: δ 1.08 (d, J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.24 (s, 6H, 2 CH_3), 3.41 (septet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 4.64 (s, 2H, CH_2Ph), 5.73 (s, 2H, NCH_2O), 6.88 (s, 1H, Ar H), 6.96 (s, 2H, Ar H), 7.26-7.37 (m, 5H, Ar H), 8.81 (br s, 1H, NH); ms: m/z 458 (M^+ + H).

Anal. Calcd. for $C_{23}H_{26}N_2O_3Se$: C, 60.39; H, 5.73; N, 6.12. Found: C, 60.21; H, 5.94; N, 6.10.

Acknowledgment.

We would like to thank Dr. V. L. Narayanan, Drug Synthesis and Chemistry Branch, and Dr. J. P. Bader, Antiviral Evaluation Branch of the National Cancer Institute, Rockville, Maryland, for evaluation of the anti-HIV acitivity of our compounds.

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