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Communication

Synthesis and anti-HIV properties of novel 6-phenylselenenyl-5-propyluracils★

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Novel 6-phenylselenenyl-5-propyluracils were synthesized from 5-propyluracil with the use of regioselective synthesis to give 1-[(2-hydroxyethoxy)-methyl]-6-phenylselenenyl-5-propyluracil (6), 1-ethoxymethyl-6-phenylselenenyl-5-propyluracil (9) and 1-benzyloxymethyl-6-phenylselenenyl-5-propyluracil (10). Interaction of these compounds with recombinant HIV-1 reverse transcriptase (RT) was evaluated using a non-isotopic colorimetric method. Compounds 9 and 10 exerted potent HIV RT inhibition (IC_{50} 0.06 and 0.05 μM respectively) while compound 6 showed moderate inhibition (IC_{50} = 3.5 μM). Potent anti-HIV-1 activity in MT-2 cells inoculated by a syncythia-inducing HIV-1 (cat #3 strain) laboratory isolate was exerted by compounds 9 and 10 (EC_{50} 0.62 μM and 0.025 μM, respectively), while compound 6 showed only moderate activity (IC_{50} = 4.1 μM). In addition, compound 10 showed very good *in vitro* therapeutic index (TI > 2046), indicating that it is a potential anti-HIV/AIDS drug.

Keywords: HIV-1, inhibitors, HIV reverse transcriptase

INTRODUCTION

Human immunodeficiency virus (HIV), the etiological agent of AIDS, encodes RNA-dependent DNA polymerase (reverse transcriptase, RT) but not the specific enzymes required for the phosphorylation of 2′,3′-dideoxypyrimidine and purine nucleosides or their phosphonates (De Clercq, 1995). To exert antiviral activity these analogues must undergo three- or two-step phosphorylation by host cell kinases and/or be metabolized by other metabolizing enzymes. The phosphorylated derivatives act as RT competitive inhibitors and/or DNA chain terminators (Vandamme *et al*., 1998). The previously discovered 6-arylthio- and 6-arylselenenyl acyclonucleosides (Tanaka *et al*., 1991; Goudgaon & Schinazi, 1991) present a new class of potent and highly selective anti-HIV-1 agents which act as non competitive inhibitors of HIV RT and bind allosterically to its hydrophobic pocket close to the catalytic site, distorting the conformation of RT to the point where it cannot function enzymatically (Pan *et al*., 1994; Vandamme *et al*., 1998). While 6-arylthio acyclonucleosides inhibit only HIV-1, some 6-phenylselenenyl analogues are active also against HIV-2. 5-Alkyl-6-selenenyl acyclonucleosides have been little studied, however, 1-ethoxymethyl-6-phenylselenenyl-5-ethyluracil is a promising candidate for AIDS chemotherapy (Ni *et al*., 1995). To enhance the hydrophobic properties of the above-mentioned compounds, and therefore the penetration to the central nervous system, we decided to synthesize and investigate their novel 5-propyl analogues.

★This paper is dedicated to Professor Tadeusz Chojnacki from the Institute of Biochemistry and Biophysics, Polish Academy of Sciences in Warsaw on the occasion of the 50th anniversary of his scientific activity and 75th birthday.

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Abbreviations: AIDS, acquired immunodeficiency syndrome; AZT, 3′-azido-2,3′-dideoxythymidine; Bu_4NI, tetrabutylammonium iodide; DTT, dithiothreitol; HIV, human immunodeficiency virus; RT, reverse transcriptase; RPMI, RPMI-1640 Medium, Sigma No. Cat. R6504; TBDMS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; TMS, trimethylsilyl.

MATERIALS AND METHODS

Chemistry

Melting points (uncorrected) were measured on a Büchi B-540 melting point apparatus, UV spectra were recorded on a Cary 300 instrument, using 10-mm pathlength cuvettes. Mass spectra were taken on a Micromass Q-Tof spectrometer. High resolution ^{1}H NMR spectra were recorded on a Varian 500 MHz in $CDCl_3$, with tetramethylsilane as internal standard. Thin-layer chromatography (TLC) was run on Merck silica gel F_{254} aluminium plates (DC, 20 × 20 cm, 0.25 mm, No. 1.05554) and Merck aluminium oxide 150 F_{254} neutral aluminium plates (DC, 20 × 20 cm, 0.2 mm, No. 1.05551). The following solvents (v/v) were used: (A) $CHCl_3$/MeOH, 90 : 10; (B) $CHCl_3$/MeOH, 95 : 5; (C) $CHCl_3$/MeOH, 97 : 3 (D) hexane/ethyl acetate, 60 : 40.

1-[(2-Hydroxyethoxy)methyl]-5-propyluracil (3). 5-Propyluracil **1** (1.54 g, 10 mmol) was suspended in 15 mL of acetonitrile and stirred with 5.4 mL (22 mmol) of bis(trimethylsilyl)acetamide to obtain a clear solution. To this solution 0.7 mL (10 mmol) of 1,3-dioxolane, 1.7 g (10 mmol) of potassium iodide and 1.38 mL (10 mmol) of chlorotrimethylsilane were added. The mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of 20 mL of methanol followed by neutralization with 4 g of sodium bicarbonate. Solids were removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residual solid was applied on a silica gel column and the products were eluted with chloroform/methanol (95 : 5, v/v). The desired fractions were concentrated and the product was crystallized from 2-propanol. Yield 1.6 g (70%) of compound **3**; m.p. 114–115°C; UV λ_{max} (MeOH) 264.5 nm (ε 9.2 × 10^3); TLC (aluminium oxide) R_F (A) 0.56; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.16 (1H, br s, NH), 7.09 (1H, m, 6H), 5.20 (2H, s, OCH_2N), 3.78–3.76 (2H, m, $OC\underline{H}_2CH_2O$), 3.71–3.69 (2H, m, $OCH_2C\underline{H}_2O$), 2.31 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.59–1.52 (2H, m, $CH_2C\underline{H}_2CH_3$), 0.95 (3H, t, $CH_2CH_2C\underline{H}_3$, J = 7.5Hz); MS *m/z* 229.0699 (M+H)$^+$.

1-[(2-*tert*-Butyldimethylsililoxyethoxy) methyl]-5-propyluracil (4). A mixture of 1-[(2-hydroxyethoxy)methyl]-5-propyluracil (**3**) (1.6 g, 7 mmol), *tert*-butyldimethylsilyl chloride (1.83 g, 12.1 mmol) and imidazole (855 mg, 12.6 mmol) in 25 mL of acetonitrile was stirred overnight at room temp. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to oil. After crystallization from ethanol 2.4 g (70%) of compound **4** was received; m.p. 72–72.5°C; UV λ_{max} (MeOH) 264 nm (ε 9.2 × 10^3); TLC (silica gel) R_F (D) 0.38; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.12 (1H, br s, NH), 7.10 (1H, m, 6H), 5.19 (2H, s, OCH_2N), 3.77–3.75 (2H, m, $OC\underline{H}_2CH_2O$), 3.65–3.64 (2H, m, $OCH_2C\underline{H}_2O$), 2.30 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.58–1.51 (2H, m, $CH_2C\underline{H}_2CH_3$), 0.95 (3H, t, $CH_2CH_2C\underline{H}_3$, J = 7.5Hz), 0.89 (9H, s, $C(C\underline{H}_3)_3Si(CH_3)_2O$), 0.06 (6H, s, $(CH_3)_3Si(C\underline{H}_3)_2O$); MS *m/z* 343.1235 (M+H)$^+$.

1-Ethoxymethyl-5-propyluracil (7). A suspension of 5-propyluracil (1.54 g, 10 mmol) and *N,O*-bis(trimethylsilyl)acetamide (5.45 mL, 22 mmol) in CH_2Cl_2 (12.5 mL) was stirred for 2 h at room temp. To the resulting solution, Bu_4NI (70 mg, 0.18 mmol) and ethyl chloromethyl ether (1.12 mL, 12 mmol) were added. The mixture was heated under reflux with stirring for 2 h and allowed to cool to room temp. The reaction mixture was poured into saturated $NaHCO_3$ solution (50 mL) containing ice (5 g) and stirred for 30 min. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography using chloroform/methanol (98–2%) as eluent. Crystallization from ethanol gave 1.5 g (71%) of 1-ethoxymethyl-5-propyluracil (**7**); m.p. 55–56°C; UV λ_{max} (MeOH) 264 nm (ε 9.2 × 10^3); TLC (silica gel) R_F (B)0.68; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.30 (1H, br s, NH), 7.09 (1H, m, H6), 5.13 (2H, s, OCH_2N), 3.60 (2H, q, $OC\underline{H}_2CH_3$ J = 7 Hz), 2.31 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.58–1.53 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.22 (3H, t, $OCH_2C\underline{H}_3$), 0.95 (3H, t, $CH_2CH_2C\underline{H}_3$); MS *m/z* 213.0951 (M+H)$^+$.

1-Benzyloxymethyl-5-propyluracil (8). The compound was synthesized as described for compound **7**, using benzylchloromethyl ether as a starting material. Crystallization from 2-propanol gave 2.3 g (84%) of compound **8**; m.p. 80–81°C; UV λ_{max} (MeOH) 264 nm (ε 9.2 × 10^3); TLC (silica gel) R_F (C) 0.35; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.18 (1H, br s, NH), 7.36–7.30 (5H, m, Ph), 7.05 (1H, m, H6), 5.22 (2H, s, OCH_2N), 4.62 (2H, s, $PhC\underline{H}_2O$), 2.27 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.56–1.51 (2H, m, $CH_2C\underline{H}_2CH_3$), 0.94 (3H, t, $CH_2CH_2C\underline{H}_3$); MS *m/z* 275.0898 (M+H)$^+$.

General method for preparation of 6-phenylselenenyl-5-propyluracil derivatives (5, 9, 10). To a solution of 25 mL (12.5 mmol) of lithium diisopropylamide (received *in situ* from phenantrene and diisopropylamine) in dry THF the acyclonucleoside (5 mmol) in 20 mL of dry THF, was added dropwise at –78°C 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 (3.125 g, 5.9 mmol in 20 mL of THF) was added dropwise to the resulting solution, and the mixture was stirred for 30 min at –78°C. The reaction mixture was quenched with acetic acid (1.25 mL) in 5 mL of THF, and then allowed to warm to room temp. The solution was concentrated to dryness *in vacuo*, and the residue was purified by silica

gel column chromatography. The product was eluted with ethyl acetate/hexane (65 : 35, v/v) and crystallized from ethanol.

1-[(2-*tert*-Butyldimethylsililoxyethoxy)methyl]-6-phenylselenenyl-5-propyluracil (5). Yield 940 mg (38%) of 1-[(2-*tert*-butyldimethylsililoxyethoxy)-methyl]-6-phenylselenenyl-5-propyluracil (**5**); m.p. 86.9–88.7°C; UV λ_{max} (MeOH) 270 nm (ε 10.5×10^3), 310 nm (ε 3.4×10^3); TLC (silica gel) R_F (D) 0.61; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.17 (1H, br s, NH), 7.35–7.28 (5H, m, Ph), 5.59 (2H, s, OCH_2N), 3.66 (2H, m, $C\underline{H}_2CH_2$), 3.60 (2H, m, $CH_2C\underline{H}_2$), 2.59 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.34 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.12 (3H, t, $CH_2C\underline{H}_3$), 0.87 (12H, $CH_2CH_2C\underline{H}_3$, $C(C\underline{H}_3)_3Si(CH_3)_2$), 0.04 (6H, s, $C(CH_3)_3Si(C\underline{H}_3)_2$); MS *m/z* 499.0537 $(M+H)^+$.

1-Ethoxymethyl-6-phenylselenenyl-5-propyluracil (9). Yield 760 mg (41%) of **9**; m.p. 92.5–93.7°C; UV λ_{max} (MeOH) 269 nm (ε 9.9×10^3), 312 nm (ε 3.2×10^3); TLC (silica gel) R_F (D) 0.46; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.25 (1H, br s, NH), 7.28–7.36 (5H, m, Ph), 5.54 (2H, s, OCH_2N), 3.55 (2H, q, $C\underline{H}_2CH_3$ J = 7.1 Hz), 2.60 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.35 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.12 (3H, t, $CH_2C\underline{H}_3$), 0.88 (3H, t, $CH_2CH_2C\underline{H}_3$); MS *m/z* 368.9958 $(M+H)^+$.

1-Benzyloxymethyl-6-phenylselenenyl-5-propyluracil (10). Yield 730 mg (34%) of **10**, m.p. 145.5–146.3°C; UV λ_{max} (MeOH) 268 nm (ε 10.2×10^3), 310 nm (ε 3.5×10^3); TLC (silica gel) R_F (D) 0.47; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.05 (1H, br s, NH), 7.28–7.32 (10H, m, Ph), 5.62 (2H, s, OCH_2N), 4.62 (2H, s, $C\underline{H}_2Ph$), 2.57 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.33 (2H, m, $CH_2C\underline{H}_2CH_3$), 0.87 (3H, t, $CH_2CH_2C\underline{H}_3$); MS *m/z* 431.0265 $(M+H)^+$.

1-[(2-Hydroxyethoxy)methyl]-6-phenylselenenyl-5-propyluracil (6). To a solution of compound **5** (940 mg, 1.88 mmol) in 38 mL of methanol, 11 g of Dowex-50W-8X (H^+) was added. The mixture was stirred for 12 h at room temp. The mixture was filtered, washed with methanol and concentrated to dryness *in vacuo*. Crystallization from ethanol gave 710 mg (98%) of 1-[(2-hydroxyethoxy)methyl]-6-phenylselenenyl-5-propyluracil (**6**); m.p. 118–119°C; UV λ_{max} (MeOH) 269 nm (ε 10.2×10^3), 310 nm (ε 3.3×10^3); TLC (silica gel) R_F (B) 0.29; ^{1}H NMR δ [ppm] ($CDCl_3$) 8.22 (1H, br s, NH), 7.37–7.30 (5H, m, Ph), 5.60 (2H, s, OCH_2N), 3.61 (4H, m, CH_2CH_2), 2.65 (2H, m, $C\underline{H}_2CH_2CH_3$), 1.39 (2H, m, $CH_2C\underline{H}_2CH_3$), 0.90 (3H, t, $CH_2CH_2C\underline{H}_3$); MS *m/z* 385.0014 $(M+H)^+$.

Biology

Determination of HIV-1 reverse transcriptase activity. The activity of HIV-1 reverse transcriptase (RT) was determined using a non-isotopic colorimetric method (Eberle & Knopf, 1996; Roche Biomolecular) involving incorporation of digoxigenin and biotin-labelled dUTP into DNA (Roche Biomoleculars procedure and KIT No. 1468120).

Standard reaction mixture contained : 46 mM Tris/HCl (pH 7.8), 9.2 mM DTT, 27.5 mM $MgCl_2$, 266 mM KCl, 0.05% Triton X-100, 1.25 mg/ml bovine serum albumin (BSA), 0.075 mM EDTA, 0.1 mM poly(A)·oligo$(dT)_{15}$, digoxigenin and biotin-labelled nucleotides dUTP/dTTP (10 μM), 3 μL RT (30 mU/μL, 6 ng/μL), and 20 μL (0.01–5 μM) of inhibitor solution. The mixture was incubated at 37°C for 1 h, and unreacted substrates were washed out. Antibodies against digoxygenin (200 μL) conjugated with peroxidase (200 mU/mL) were added and incubated at 37°C for 1 h. Antibodies were washed out and 200 μL of 2,2′-azino-di(3-ethylbenzothiazoline)-6-sulphonate (ABTS) was added, left for 30 min at room temp. and absorbancy at 405 nm was measured with the use of a microtiter plate (ELISA) reader.

Cell toxicity. The cytotoxicity of investigated compounds was determined in an established MT-2 cell line. The cells were grown in medium enriched with known different concentrations of the tested compounds. After 3, 7, 10, 14 days the viability of cells in relation to control culture was estimated by a commonly used colorimetric 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyltetrozolium bromide (MTT) method (Mossman, 1983), and CC_{50} was calculated.

Anti-HIV activity in MT-2 cell cultures. Identical numbers of MT-2 cells (10^6/mL) were incubated for 24 h in RPMI medium supplemented with 10% foetal calf serum (FCS), enriched with known amounts of the tested substances in standard conditions (37°C, 5% CO_2 in a humid environment). The cell cultures were inoculated with a syncytia-inducing HIV-1 (cat #3 strain) laboratory isolate. After 4 h of inoculation the cells were washed 5 times with RPMI and unattached virions were removed. The cells were resuspended in medium enriched with the tested substances and 200 μL of cell suspension was placed into a 96 cell culture plate (2×10^5 cells/well). For each concentration of the tested substances cell cultures were done in triplicate. A positive control contained an identical concentration of HIV-1 inoculated cells maintained in RPMI and 10% FCS only. Every three days half of the culture medium (100 μL) was collected and replaced with an identical amount of fresh one. The collected media were frozen. The cells were cultured for up to 14 days. HIV replication and the inhibitory effect of the substances under investigation was estimated by measuring the amount of p24 protein in collected media. The efficacy of HIV-1 replication inhibition exerted by the tested compounds was related to controls cultured in medium without the tested

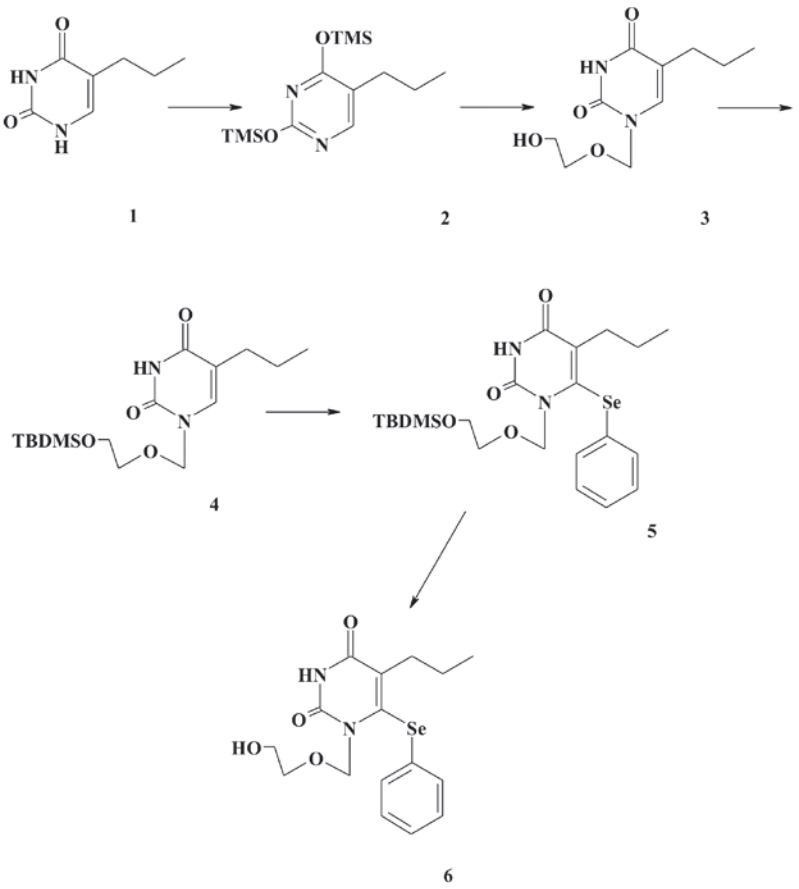

Figure 1. Synthesis of 1-[(2-hydroxyethoxy)methyl]-6-phenylselenenyl-5-propyluracil (6).

compounds as well as with cells cultured in medium enriched with known amounts of AZT. The IC_{50} and IC_{90} values were calculated.

RESULTS AND DISCUSSION

Syntheses

Several approaches lead to the synthesis of 1-[(2-hydroxyethoxy)-methyl]-5-alkyluracils. Three most convenient methods were evaluated. Two of them are based on the condensation of corresponding bis(tri-methylsilyl)uracils with acetoxymethyl ether or chloromethyl ether catalysed by $SnCl_4$ and the yields obtained are moderate to good (38–72%). However, the "one-pot" modification reported by Ubasawa *et al*. (1995) afforded acyclopyrimidine nucleosides in better yields (63 to 88%). This method seemed to be the most convenient and after certain modifications was applied to the synthesis of the 5-propyluracil derivatives.

1-[(2-Hydroxyethoxy)methyl]-5-propyluracil (**3**) (Fig. 1) was prepared in a "one-pot" reaction employing the direct treatment of the di-O-TMS derivative of 5-propyluracil in acetonitrile with 1,3-dioxolane, in the presence of 1 equivalent of KI at room temp., to give the desired compound in 70% yield.

5-Propylacyclouridine derivatives **7** and **8** were prepared by Bu_4NI-promoted alkylation of the di-O-TMS derivative of 5-propyluracil with the corresponding ethyl and benzyl chloromethyl ether.

The possibility of efficient introduction of selenium species into nucleosides with the use of sele-

Table 1. Anti-HIV activity and cytotoxicity of 6-phenylselenenyl-5-propyluracils in MT-2 cells

Compound	EC_{50} (μM)[a]	EC_{90} (μM)[b]	CC_{50} (μM)[c]	TI[d]
1-(2-OH-EtOMe)-6-PhSe-5-PrUra (**6**)	4.1	8.8	>61.5	>15
1-EtOMe-6-PhSe-5-PrUra (**9**)	0.62	>1	>84	>135
1-BnOMe-6-PhSe-5-PrUra (**10**)	0.025	0.143	>51.15	>2046
1-BnOMe-6-PhSe-5-EtUra[e]	0.02	–	5	250

[a]Effective concentration of the compound required to reduce viral cytopathogenic effect by 50%; [b]Effective concentration of the compound required to reduce viral cytopathogenic effect by 90%; [c]Cytotoxic concentration of compound required to reduce viability of MT-2 cells by 50%; [d]Therapeutic index, TI = CC_{50}/EC_{50}; [e]Pan *et al*. (1994)

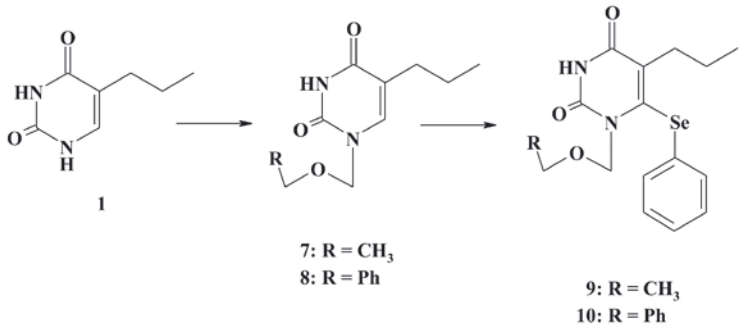

Figure 2. Synthesis of 1-ethoxymethyl-6-phenylselenenyl-5-propyluracil (9) and 1-benzyloxymethyl-6-phenylselenenyl-5-propyluracil (10).

nium nucleophiles such as diphenyl diselenide, was pointed out by Cosword and Schinazi (1991), and successfully applied to phenylselenenylation of nucleosides lithiated at position 6 of pyrimidine ring. We applied this method to the preparation of the 6-phenylselenenyl derivative of compound **3**, and of 1-ethoxymethyl-6-phenylselenenyl-5-propyluracil (**7**) and 1-benzyloxymethyl-6-phenylselenenyl-5-propyluracil (**8**) (Fig. 1).

1-[(2-Hydroxyethoxy)methyl]-5-propyl-6-phenylselenenyluracil (**6**) was prepared by the reaction of compound **3** with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give protected compound **4**, subsequent lithiation of compound **4** with lithium diisopropylamide at –78°C leading to compound **5**, followed by the reaction with diphenyl diselenide, and a subsequent removal of the protecting group with Dowex 50W (H^+) to give the yield of 38%.

The 6-phenylselenenyl substituted 5-propylacyclouridine derivatives **9** and **10** (Fig. 2) were synthesized by lithiation of appropriate substrates with lithium diisopropylamide at –78°C, followed by reaction with diphenyl diselenide.

Structure-activity relationship

Previously it was reported that 1-benzyloxymethyl-6-phenylselenenyl-5-ethyluracil showed considerable *in vitro* anti-HIV-1 activity with EC_{50} = 0.017 μM in MT-2 cells. This analogue was also a potent inhibitor of recombinant HIV-1 reverse transcriptase (IC_{50} = 8 nM) (Pan *et al.*, 1994). However, its *in vitro* therapeutic index (TI) was as low as 250, disqualifying this compound as a potential anti-HIV/AIDS agent. Therefore it was of interest to check whether enhancing of the hydrophobic properties of this compound by replacing 5-ethyl in the pyrimidine ring with the more hydrophobic 5-propyl substituent would decrease the cytotoxicity and increase the therapeutic index.

Table 2. Activity of HIV-1 reverse transcriptase in the presence of 6-phenylselenenyl-5-propyluracils

Compound	IC_{50} (μM)[a]
1-(2-OH-EtOMe)-6PhSe-5-PrUra (**6**)	3.5 ± 0.5
1-EtOMe-6-PhSe-5-PrUra (**9**)	0.06 ± 0.01
1-BnOMe-6-PhSe-5-PrUra (**10**)	0.05 ± 0.01
1-BnOMe-6-PhSe-5-EtUra[b]	0.008

[a]Concentration of the compound required to inhibit activity of HIV-1 RT by 50%; [b]Pan *et al.* (1994)

When the anti-HIV activity of the final 5-propyluracil derivatives **6**, **9** and **10** was determined in established MT-2 cells against a syncythia-inducing laboratory HIV-1 (cat #3) strain (Table 1), a potent activity of analogues **9** and **10** (EC_{50} = 0.62 μM and 0.025 μM, respectively) was observed, while compound **6** showed moderate activity (EC_{50} = 4.1 μM).

It can be seen that a high antiviral activity was exerted only by those 5-propyl-6-phenylselenenyl acyclonucleosides which at the end of the acyclic moiety contained additional hydrophobic groups, such as ethoxymethyl (compound **9**) or benzyloxymethyl (compound **10**), while compound **6** containing at this place the hydrophilic hydroxyl group exerted only a moderate activity. Of special interest is the significantly higher *in vitro* therapeutic index (TI > 2046) of compound **10** as compared to the above-mentioned 1-benzyloxymethyl-6-phenylselenenyl-5-ethyluracil (TI = 250).

To explain the mode of action of these compounds, their interaction with recombinant HIV-1 reverse transcriptase was investigated (Table 2). Compounds **9** and **10** were potent allosteric inhibitors of this enzyme and the data obtained point to a high correlation of HIV RT inhibition with antiviral activity.

CONCLUSIONS

Elongation of the alkyl chain at 5-position of the pyrimidine ring of 6-phenylselenenyluracils, resulting in potentiation of their hydrophobic properties, decreases their cytotoxicity and enhances the *in vitro* therapeutic index. The potent anti-HIV activity and high therapeutic index of 1-benzyloxymethyl-6-phenylselenenyl-5-propyluracil

(**10**) qualifies this compound as potential an anti-HIV/AIDS agent.

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