Structure–Activity Studies on Organoselenium Alkylating Agents

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Abstract □ A variety of organoselenium alkylating agents were synthesized, using 2-hydroxyethyl and 3-hydroxypropyl selenocyanate intermediates, and studied to determine their chemical reactivities with 4-(4-nitrobenzyl)pyridine (NBP) and cytotoxicities against CCRF-CEM, L1210/0, and L1210/L-PAM cells. The comparison between the 2-chloroethyl sulfides and selenides **1–4** revealed the markedly enhanced nucleophilicity of selenium (Se) over sulfur (S) by two or more orders of magnitude. This finding indicates that a major consideration in the design of antitumor alkylating organoselenides is the reactivity of selenium. A Taft plot of the experimental first-order rate constant, k_{nbp}, and σ^* in a series of 2-chloroethylseleno compounds gave a slope of −1.73 (ρ^*), with the exception of 2-chloroethyl 2-nitrophenyl selenide (**10**). The anomalous behavior of **10** is explained in terms of the ortho–nitro stabilization effect directly interacting with the selenium atom of ethyleneselenonium ion to form a 5-membered cyclic intermediate. In the same series, a 5000-fold difference in alkylating reactivity offered only a sixfold variation in cytotoxicity against CCRF-CEM cells. Increasing the alkylating chain length from ethylene to propylene units markedly reduced alkylating reactivities. In the $CH_3Se(CH_2)_nCl$ series, **16** (n = 3) was 1.5×10^5 times slower than **2** (n = 2) in NBP alkylation, revealing that 3-chloro-*n*-propyl selenides are not chemically reactive enough to be biological alkylating agents despite the presence of the highly nucleophilic selenium atom. Replacement of chloride with mesylate in 3-substituted propyl selenides, such as **17** and **20**, restored desirable reactivities and cytotoxicities.

Selenium, an essential ultratrace element,[1] has important roles in glutathione metabolism and in anticarcinogenesis and antimutagenesis. Selenium compounds are generally considered far more biopotent than the corresponding sulfur and tellurium analogues. The LD_{50} values in Table I show toxicity differences between sulfur (S), selenium (Se), and tellerium (Te) atoms in several valence states.[2] Recently, Streeter and Robins[3] reported that in a cell culture study on P388, L1210, B16, and Lewis lung cells, selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide) was consistently more cytotoxic than its sulfur analogue, tiazofurin, by a factor of 5 to 17. Further, selenazofurin was found to possess broad spectrum in vitro antiviral activity, 100-fold superior to tiazofurin.[4,5]

In a previous communication,[6] we described chemical kinetic parameters and cytotoxicities of a new class of alkylating agents, organoselenium analogues of conventional nitrogen mustards. These para-substituted aryl 2-haloethyl selenides kinetically and biologically resembled classical, mustard-type alkylating agents. No additional cytotoxicity due to the selenium atom was observed, with the exception of diselenide compounds. It was also noted that the alkylating activities (AA) based on the extent of 4-(4-nitrobenzyl)pyridine (NBP) alkylation, a measure of nucleophilic selectivity,[6,7] of the selenium analogues were significantly low relative to that of mechlorethamine hydrochloride. The percent AA is the alkylating activity defined as a percentage of the extent of NBP alkylation (absorbance at 560 nm of the alkyl-NBP product with triethylamine alkalinization) by mechlorethamine hydrochloride (= 100%), with correction made for the number of alkylating equivalents/mol. The relatively low AA of the selenides and diselenides is primarily due to the increased reactivity of the highly polarizable selenium atom over nitrogen. Considering that a number of alkylating agents with broad antitumor activities show high nucleophilic selectivity,[8] high AA may be an essential feature for a potent alkylating agent. This paper presents our efforts to design and synthesize organoselenium compounds with increased AA through structural variations of organic carriers and alkylating moieties.

Table I—LD_{50} Values of Sulfur, Selenium, and Tellurium Compounds[a]

LD_{50} in Mice		LD_{50} in Rats	
Compound	mg/kg, route	Compound	mg/kg, route
Na_2SO_4	5989, oral	Phenyl sulfide	1390, oral
Na_2SeO_4	18, ip	Phenyl selenide	360, oral
Na_2TeO_4	165, oral	Methionine, D-	5223, ip
Na_2SO_3	130, iv	Methionine, L-	4328, ip
Na_2SeO_3	7, oral	Selenomethionine	4.25[b], ip
Na_2TeO_3	20, oral		

[a] Reference 2. [b] Lowest lethal dose.

Results and Discussion

At the outset of this study, we expected that 2-haloethyl selenides are far more reactive than the corresponding nitrogen and sulfur mustards based on the high nucleophilicity of selenium atom over nitrogen and sulfur atoms. Even sulfur mustards were limited in a search for short biological half-life agents in a way of salvaging their rapid hydrolytic properties under physiologic conditions.[9] The comparison between the sulfides and selenides in Table II demonstrates the extreme reactivity of the selenium atom over the isostere sulfur element, indicating that the selenides 2 and 4 are 100-fold or more reactive than the sulfides 1 and 3. The low AA of the selenides is due directly to the cyclic intermediate II-Se rather than I-Se, as given in Scheme I.

Table II—Comparison of Nucleophilicities of Sulfur and Selenium Atoms Attached to a 2-Chloroethyl Alkylating Group

No.	$RXCH_2CH_2Cl$ R	X	k_{nbp} (10^2), s^{-1}[a]	$t_{1/2}$, s[b]	AA, %[c]
1	CH_3	S	0.154	450	90
2	CH_3	Se	16.9	4	61
3	$C_6H_5CH_2$	S	0.034	2040	89
4	$C_6H_5CH_2$	Se	7.29	9.5	57

[a] Pseudo-first-order rates of NBP alkylation at 37 °C in aqueous acetone (52.2:48.8, v/v) in the presence of 40.6 mM NBP, 17.4 mM Tris-HCl buffer, pH 7.0, and 0.17 mM alkylating agents. [b] Half-life of NBP alkylation. [c] The alkylating activity as a percentage of the extent of NBP alkylation by mechlorethamine hydrochloride (= 100%), correction made for the number of alkylating equivalents per mole.

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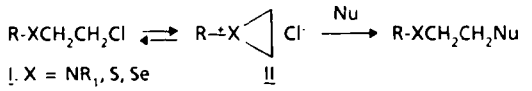
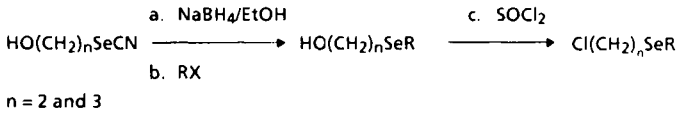


I, X = NR_1, S, Se

Scheme I



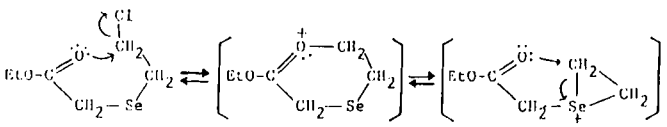
n = 2 and 3

Scheme II

It describes nucleophilic substitution reactions of nitrogen, sulfur, and selenium mustards, in which formation of the cyclic intermediate II is the rate-controlling step.[6,9a,10] The high reactivity of II-Se relative to II-S and II-N is due to the fact that the selenonium ion of II-Se is a better leaving group than sulfonium, which is in turn better than the aziridium ion. The kinetics of the reactions of the sulfides and selenides **1–4** with NBP were studied at 37 °C in aqueous acetone (52.2:47.8, v/v) in the presence of Tris-HCl buffer at pH 7.0. The reaction was followed by measuring the absorbance increase of the NBP-alkyl adduct solution treated with triethylamine at 560 nm. Each reaction was carried out with NBP present in large stoichiometric excess over the sulfides and selenides.

In the earlier series of *p*-X-$C_6H_4SeCH_2CH_2Cl$ where X is H, CH_3, OCH_3, SO_2NH_2, and NO_2, the half-lives of the nitrophenyl selenide for the NBP alkylation and hydrolysis reactions were only 18 and 52 min at 37 °C, respectively.[6] The *para*-nitrophenyl selenide was the slowest among the series. Such high reactivities of these selenides clearly imply that they will be consumed mostly by cellular constituents other than DNA bases in more polar physiologic conditions. Therefore, our first attempt was given to preparing 2-chloroethyl selenides with slowed reactivities for NBP alkylation. The synthesis of mono- and bifunctional 2-and 3-haloalkyl selenides was carried out based on the literature methods.[6,11] Two useful intermediates, 2-hydroxyethyl and 3-hydroxypropyl selenocyanates,[11] were employed to make 2-hydroxyethyl and 3-hydroxypropyl selenides, respectively. These were then converted into the corresponding chlorides and mesylates by treatment with thionyl chloride and methanesulfonyl chloride. A representative method for monofunctional selenides is given in Scheme II.

The results of alkylation reactions with NBP and cytotoxicities against acute leukemia lymphoblastoid CCRF-CEM cells of the 2-chloroethylseleno compounds **2** and **4–15** are



9 **9a** **9b**

Scheme III

summarized in Table III. The pseudo-first-order rates of NBP alkylation, k'_{nbp}, were linear in all cases over the first three half-lives of reaction, with the exception of ethyl (2-chloroethylseleno)acetate (**9**). The plot of log $[100(A_{00} - A)/A_{00}]$ versus time for **9** showed an upward curvature. The value of **9** given in Table I, therefore, was estimated based on ~50% completion of the NBP alkylation. The nonlinearity of **9** in the first-order plot may be due to the carbonyl oxygen of **9**. Two possible mechanisms of associating the nucleophilic oxygen atom with the anomalous kinetic behavior of **9** are depicted in Scheme III which involves both the parent selenide **9** and its immediate intermediate **9b**, leading to a six-membered cyclic oxonium ion **9a**.

Figure 1 is a plot of log k'_{nbp} versus σ^* to make a quantitative correlation between structure and reactivity in the series of the 2-chloroethylseleno compounds **2** and **4–14**. This Taft plot reveals the strong dependence of the rate of NBP alkylation on the polar nature of organic carriers attached to the selenium atom. The series includes alkyl, aryl, aralkyl, and carbonyl derivatives of 2-chloroethyl selenides, with σ^* constants ranging from 0.00 to 2.26. The typical linear free energy relationship with a slope (ρ^*) of −1.73 (r = −0.990) in Figure 1 indicates that ethyleneselenonium ion formation is the rate-determining step for NBP alkylation. This is consistent with previous findings in a Hammett plot of para-substituted aryl 2-chloroethyl selenides[6] and a Taft plot of alkyl 2-chloroethyl sulfides.[9a] The only compound that significantly deviates from linearity is 2-chloroethyl 2-nitrophenyl selenide (**10**). On the other hand, the para isomer **11** follows the trend like other compounds. Compound **10**, as a matter of fact, was deliberately synthesized to increase the duration of its intermediate, which can be stabilized by direct interaction of the *o*-NO_2 group as shown in **10a**. The coordination of the ortho nitro oxygen, by occupying one apical position, is responsible for the deviation of **10** from linearity. The ortho- and para-methoxy analogues, **15** and **6**, respectively, were used to further probe the existence of the ortho–nitro stabilization effect.[12] As expected, no significant

Table III—Alkylating Reactivities and Cytotoxicities of the 2-Chloroethylseleno Compounds 2 and 4–15

No.	$RSeCH_2CH_2Cl$, R	σ^*[a]	k'_{nbp} (10^3), s^{-1}	log k'_{nbp}	$t_{1/2}$	AA, %	IC_{50}, μM[b]
2	CH_3	0.00	169	−0.772	4 s	61	ND[c]
4	$C_6H_5CH_2$	0.27	73	−1.137	9.5 s	57	5
5	$ClCH_2CH_2$	0.41	47.8	−1.321	14.5 s	22	0.75
6	*p*-$CH_3OC_6H_4$	0.42	18.5	−1.733	37.5 s	22	2.7
7	*p*-$CH_3C_6H_4$	0.59	15.8	−1.801	44 s	21	5
8	C_6H_5	0.75	6.16	−2.210	112.5 s	23	8
9	EtO_2CCH_2	1.00[d]	2.96[e]	−2.529[e]	3.9 m[e]	58	3
10	*o*-$NO_2C_6H_4$	1.14	0.0947	−4.024	122 m	35	15
11	*p*-$NO_2C_6H_4$	1.26	0.635	−3.197	18.2 m	17	8.5
12	$CNCH_2$	1.30	0.856	−3.068	13.5 m	14	2.5
13	$(CH_3)_2NCO$	1.94	0.162	−3.790	71.3 m	50	2.5
14	C_6H_5CO	2.26	0.143	−4.845	13.5 h	44	2.5
15	*o*-$CH_3OC_6H_4$	—	10.8	−1.967	64 s	23	ND[c]

[a] Reference 24. [b] Growth inhibition against acute lymphoblastic leukemia CCRF-CEM cells in vitro for 48-h incubation; average values of duplicate assays; the average standard deviation was ~25% of the average value given. [c] Not determined. [d] Given for $CH_3O_2CCH_2$. [e] Estimated value from four runs based on the first 50% completion.

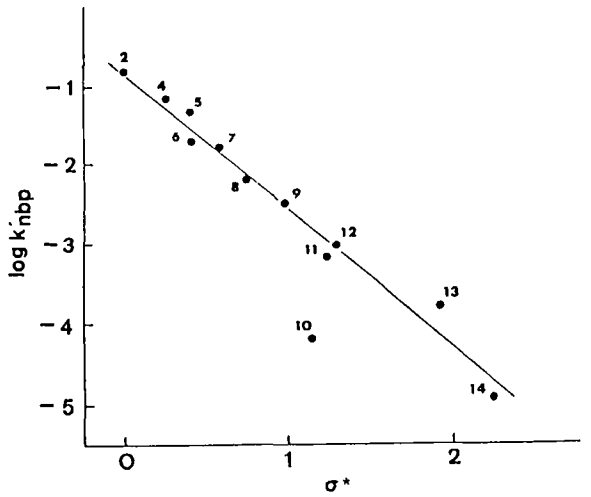
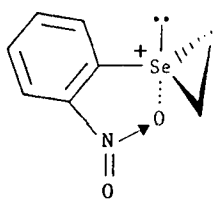


Figure 1—Plot of log k'_{nbp} versus σ^* for the NBP alkylation reactions of the selenides **2** and **4–14** in aqueous acetone. The data are taken from Table III.

alterations of rates and AA in the methoxy pair **6** and **15** were encountered. By comparison, the ortho–nitro **10** showed a 7.1-fold retardation in reactivity and a twofold increase in AA over the para isomer **11**. Unfortunately, such an effort of increasing selectivity and half-life of the selenide **10** did not render an escalated cytotoxicity against human lymphoblastoid CCRF-CEM cells.



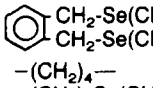
10a

A notable feature of Table III is that despite a wide range of reactivities between the monofunctional 2-chloroethylseleno compounds except **5**, the IC_{50} values against CCRF-CEM cells vary only from 2.5 to 15 μM. For example, a 5000-fold alkylating reactivity difference between **4** and **14** merely caused a twofold lower dose cytotoxicity. This narrow cytotoxicity or somewhat less satisfactory correlation between alkylating reactivity and cytotoxicity indicates, at least in part, the important role of physical properties of chemicals in producing biological activities such as the solubility in intracellular fluid and capability of transport through the cell membrane. In a similar attempt to connect chemical reactivity with biological effectiveness in various types of nitrogen mustards and aziridines, Bardos and coworkers reported a poor correlation between alkylating reactivity and molar antitumor activity data.[13] Later, some of the poor relationship was accounted for in terms of a hydrophobic parameter (Π).[14]

Another structural variation in designing organoselenium alkylating agents with increased AA is the length of the alkylating side chain. Although it is generally known that the activating effect of a heteroatom, such as N, O, and S, on the halogen atom or leaving group is lost when the separation is more than two carbon atoms,[15] our theoretical consideration is that such magnified nucleophilicity of the selenium atom over sulfur (as shown in Table II) could give desirable alkylating reactivities in 3-halopropyl selenides. Results of 3-chloropropyl methyl selenide **16** in Table III reveal a drastic decrease in the alkylating reactivity and AA compared with those of 2-chloroethyl methyl selenide **2** in Table II. Specifically, the comparison between **2** and **16** shows that the modification of the alkylating side arm from ethylene **2** to propylene **16** reduces AA from 61 to 18% and the half-life from 4 s to 7.5 d. It was somewhat surprising that the 3-chloropropyl selenide **16** was 1.5×10^5 times slower than the 2-chloroethyl selenide **2**, because only a 40-fold difference in the rate of hydrolysis of aniline mustards $C_6H_5N[(CH_2)_nCl]_2$ (where n is 2 and 3) was observed.[10] The high IC_{50} value (300 μM) and sluggish reactivity ($t_{1/2}$ = 7.5 d) of **16** suggests that chloride as a leaving group of 3-substituted propyl selenides is too inert to be biologically active despite the presence of the enhanced nucleophilic selenium atom.

An interesting finding in Table IV is that benzyl 3-mesyloxypropyl selenide (**17**) gave a higher AA (111%) than mechlorethanemine hydrochloride in NBP alkylation and a somewhat less potent cytotoxicity (IC_{50} = 33 μm) against CCRF-CEM cells. The low biological activity may be due to the monofunctionality and slow reactivity of **17** ($t_{1/2}$ = 34 h). Its bifunctional ortho-substituted analogue **18**, on the other hand, shows an IC_{50} of 0.7 μM against the same cell line but a somewhat low AA (36%), while a similar rate of NBP alkylation to the monofunctional compound **17** is observed. It should be mentioned that **18** (NSC-610892) by the ip route showed no antitumor activity against P-388 leukemia in mice when administered at doses of 60, 120, and 240 mg for five

Table IV—Alkylating Reactivities and Cytotoxicities of the 3-Substituted *n*-Propyl Selenides 16–18, 20–22, Diselenide 21, and Busulfan (19)

No.	$RSe(CH_2)_3X$ R	X	k'_{nbp} (10^5), s^{-1}	$t_{1/2}$, h	AA, %	P(logP)[b]	IC_{50}, μM
16	CH_3	Cl	0.11	180	18	—	300[c]
17	$PhCH_2$	OMs	0.564	34	111	—	33[c]
	MsO-A-OMs A						
18			0.9	36	36	—	0.7[c]
19	$-(CH_2)_4-$		1.31[a]	14.7	22.5	—	55[d] (60[e])
20	$-(CH_2)_3Se(CH_2)_3-$		2.16[a]	8.9	50	2.41 (0.38)[f]	2.3[d] (16[e])
21	$-(CH_2)_3SeSe(CH_2)_3-$		1.69[a]	11.4	24	—	2[d] (2.5[e])
22	$-(CH_2)_3SeCH_2$ $CH_2Se(CH_2)_3-$		1.93[a]	10	36	11.5 (1.06)[f] 10.0 (1.0)[g]	12[d] (28[e])

[a] See footnote *a* in Table II, except that 50% aqueous ethanol replaced the aqueous acetone and the temperature changed to 45 from 37 °C. [b] Partition coefficients in 1-octanol:water system at room temperature. [c] CCRF-CEM cells. [d] L1210/0 cells. [e] L1210/L-PAM cells. [f] By NBP alkylation. [g] By spectrophotometry.

consecutive days using saline with Tween-80 as a vehicle. The lack of antitumor activity against P-388 is, at least in part, attributed to poor water solubility of 18 which contains highly lipophilic C-benzylic and two selenium fragments. As self-evident in the Π values of CH_3 (0.56), OCH_3 (−0.02), and $SeCH_3$ (0.74),[16] incorporating a Se atom into a molecule will increase its lipophilicity. Further, it is speculated that the same electronegativity values (2.55)[17] of C and Se on the basis of the Pauling's scale may not be favorable in developing polarization toward surrounding solvent molecules.

Table IV also presents alkylating reactivities and cytotoxicities of busulfan 19, for comparison with the three bifunctional 3-mesyloxypropyl selenides 18, 20, and 22, and a diselenide 21. The alkylation reaction with NBP was carried out under the same conditions as for the other selenides, except that the temperature was changed to 45 from 37 °C and the medium was replaced by 50% aqueous ethanol. About 50–65% increased alkylating reactivities of the selenides 20 and 22 over busulfan (19) indicate the formation of cyclic propyleneselenonium ion to the same extent in 20 and 22, while 19 undergoes only the direct displacement of mesylate by NBP. That is, in the reactions of 20 and 22 with NBP, the internal displacement pathway occurs concurrently with the normal route by attack of NBP on the mesylate. The rate due to the neighboring group participation by selenium atom is ~1/3 of the experimental first-order rates of 20 and 22. Such dual reactivity of SN1 and SN2 of the selenides bearing a 3-mesyloxypropylseleno group might produce interesting biological activities.[9]

The data on alkylating reactivities of the selenide 20 and the diselenide 21 in Table IV show that selenide is more nucleophilic than diselenide. This is consistent with previous work which showed that bis(2-chloroethyl) selenide (5) is 8.5 times more reactive than the corresponding diselenide in the same NBP alkylation reactions.[6]

Two murine leukemic cell lines, L1210/0 and L1210/L-PAM, were used to assess the cytotoxicities of 19–22. Busulfan, used for the treatment of chronic myelogenous leukemia,[18] shows quite less potent IC_{50} values of 55 and 60 μM against L1210/0 and L1210/L-PAM, respectively, compared with those of the selenides and diselenide 20–22. The less potent cytotoxicities of the selenides 20 and 22 against L1210/L-PAM than L1210/0 suggest that L1210/L-PAM cells resistent to an alkylating agent L-PAM exhibit cross-drug resistance to a different type of alkylating agents, selenium mustards. The nearly identical cytotoxicities of the diselenide 21 against both L1210/0 and L1210/L-PAM cell lines are due to the high intrinsic toxicities of diselenides.[7] It should be noted that 20 and 21 were found to have some water solubility on the basis of their partition coefficients determined in 1-octanol:water system at room temperature. Specifically, bis(3-mesyloxypropyl)selenide (20) has quite good water solubility, with log P of 0.38, and reasonable alkylating reactivity. The partition coefficient of busulfan was not determined due to the extremely poor solubility in *n*-octanol.[19]

In summary, the cytotoxicities and the linear free energy relationship between k'_{nbp} and ρ^* in a series of model monofunctional 2-chloroethyl selenides do provide new leads for designing bifunctional organoselenium alkylating agents with desirable half-lives and cytotoxicities. For example, results of 13 and 14 in Table III suggest that the bifunctional analogues and derivatives of the carbonyl compounds may express potent antitumor activities with slowed reactivities. Compound 20, found to be water-soluble and cytotoxic, led us to believe that increase in the length of the propylene alkylating arm in combination with mesylate as a leaving group increases the potential of 3-mesyloxypropyl selenides as antineoplastics. In addition, the dual nucleophilic substitution pathways of the propylene selenides 20 and 22 could show biologically interesting in vivo activities on the basis of the effect of mechanistic differences in alkylating processes upon biological activities.[10]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR 4210 spectrophotometer, and ^1H NMR spectra were obtained with a Hitachi Perkin-Elmer high resolution R24 or a Varian EM-390 NMR spectrometer. Absorbancies were measured with a Gilford 250 UV/vis spectrophotometer and mass spectral data were taken with a Hewlett-Packard GC/MS 5985A equipped with dual EI/CI. Column chromatography was performed on Davison silica gel (60–200 mesh). All reactions were followed by TLC carried out on Merck silica gel plates. The elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and MicAnal Organic Analysis, Tucson, AZ. 4-(4-Nitrobenzyl)pyridine and busulfan (19) from Aldrich, and 2-chloroethyl methyl sulfide (1) and benzyl 2-chloroethyl sulfide (3) from Pfaltz and Bauer were used without purification. Compounds 5–8 and 11 were prepared as described in the literature.[1]

2-Hydroxyethyl Methyl Selenide (2a)[20]—Sodium borohydride was added to a solution of 2-hydroxyethyl selenocyanate (2.82 mmol, 423 mg) in 8 mL of ethanol at 0 °C under nitrogen until the solution turned colorless. To the alcoholic mixture, methyl methanesulfonate (342 mg, 3.1 mmol) dissolved in 3 mL of ethanol was added through a dropping funnel over a period of 15 min. The reaction was quenched by addition of 1 mL of water. The solution was concentrated at reduced pressure, and the residue was transferred into a separatory funnel by aid of brine and chloroform followed by extractions with $CHCl_3$ (5 mL × 7). The combined organic layer was dried over sodium sulfate and concentrated. The residue was then purified by a column chromatograph using a mixed solvent of chloroform and ethyl acetate (10:1, v/v) to yield 290 mg (74%) of a malodorous pale yellow liquid: ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H), 2.71 (t, 2H), 3.48 (s, 1H), and 3.77 ppm (t, 2H).

General Procedure of the Conversion of 2- and 3-Hydroxyalkylseleno Compounds into the Corresponding Chlorides. *Method A*—A hydroxy compound dissolved in 5–10 mL of CH_2Cl_2 or $CHCl_3$ was treated with 1.5–3 equivalents of thionyl chloride at 0 °C under nitrogen. The reaction mixture was allowed to rise to room temperature and then kept overnight. The chlorination reaction was ceased by addition of 1 mL of water. After the pH of the aqueous phase was adjusted to near neutral, the mixture was extracted with CH_2Cl_2 or $CHCl_3$ (4–8 mL × 4). The combined organic layer was dried over sodium sulfate, concentrated, and column chromatographed.

Method B—The same procedure as for Method A was applied, except that 1.2–1.5 equivalents of thionyl chloride and a period of 1–2 h of chlorination at room temperature were used. Also, a base such as triethylamine, pyridine, and a Proton Sponge was present to trap HCl.

2-Chloroethyl Methyl Selenide (2)[20]—2-Hydroxyethyl methyl selenide (2a, 260 mg, 1.87 mmol) dissolved in 5 mL of CH_2Cl_2 was treated with thionyl chloride (205 μL, 2.81 mmol) as given in Method A. Silica gel column chromatographic purification (*n*-hexane:$CHCl_3$; 4:1, v/v) gave a pungent pale yellow liquid, 2 (92 mg, 31%): ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H), 2.75 (m, 2H), and 3.62 ppm (m, 2H).

Benzyl 2-Chloroethyl Selenide (4)—Benzyl 2-hydroxyethyl selenide[11] (60 mg, 0.28 mmol) was treated with thionyl chloride (50.6 μL, 0.56 mmol) as described in Method A. A pale yellow liquid, 2 (59 mg, 90%), was obtained: MS (NH_3/Cl): *m/e* 235 ($M^+ + 1$, Se^{80}, base peak), 199 ($M^+ - Cl$); ^1H NMR ($CDCl_3$): δ 2.72 (m, 2H), 3.55 (m, 2H), 3.79 (s, 2H), and 7.23 ppm (s, 5H).

Anal.—Calc. for $C_9H_{11}ClSe$: C, H.

Ethyl (2-Chloroethylseleno)acetate (9)—Ethyl (2-hydroxyethylseleno)acetate[11] (112 mg, 0.53 mmol) was treated with thionyl chloride as described in Method A. The crude product was purified on a silica gel column eluted with chloroform and ethyl acetate (5:1, v/v) to yield an odorous liquid, 9 (78 mg, 64%): MS (Cl/NH_3): *m/e* 231 ($M^+ + 1$, Se^{80}, base peak), 194 ($M^+ - HCl$), 185 ($M^+ - OC_2H_5$); ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H), 2.85–3.50 (m, 4H, $CH_2SeCH_2CO_2$), 3.60–4.00 (m, 2H), and 4.18 ppm (q, 2H).

2-Hydroxyethyl 2-Nitrophenyl Selenide (10b)—To a solution of 2-nitrophenyl selenocyanate[21] (268 mg, 1.18 mmol) treated with $NaBH_4$ in 10 mL of ethanol and 10 mL of CH_2Cl_2 was added in a

dropwise manner 2-bromoethanol (0.10 mL, 1.41 mmol) dissolved in 3 mL of CH_2Cl_2. The same work-up procedure as for **2a** was used. Crystallization of the crude product in *n*-hexane and ethyl acetate gave 196 mg (67%) of yellow needlelike crystals, mp 98–99 °C; MS (Cl/NH_3): *m/e* 264 (M^+ + 17, Se^{80}, ammonia adduct, base peak), 247 (M^+, Se^{80}); IR (KBr): 3460–3040 (OH), 1497 and 1329 (NO_2), 1250, 1051, and 784 cm^{-1}.

2-Chloroethyl 2-Nitrophenyl Selenide (10)—The hydroxy compound **10a** (80 mg, 0.325 mmol) was treated with $SOCl_2$ as given in Method B. A silica gel column chromatograph of the crude product eluted by *n*-hexane and CH_2Cl_2 (2:1, v/v) gave 30 mg (35%) of a yellow solid, **10**, mp 61.5–62.5 °C; MS (Cl/NH_3): *m/e* 282 (M^+ + 17, Se^{80}, ammonia adduct, base peak), 265 (M^+, Se^{80}); IR (KBr): 1501 and 1327 (NO_2), 1300, 798, and 733 cm^{-1}.

Cyanomethyl 2-Hydroxyethyl Selenide (12a)—Bromoacetonitrile (Aldrich, 95%, 180 μL, 310 mg, 2.58 mmol) in 3 mL of CH_2Cl_2 was slowly added into an ethanolic 2-hydroxyethyl selenocyanate solution treated with $NaBH_4$ at 0 °C under nitrogen. The reaction was quenched by addition of 1 mL of water. After evaporation of all solvent, the yellow residue was transferred into a separatory funnel by aid of $CHCl_3$ and brine. The organic layer was then extracted with $CHCl_3$ (5 mL × 10). The residue obtained from the concentration of the combined organic phase was purified on a silica gel column eluted by chloroform and ethyl acetate (1:1, v/v) to give a colorless liquid, **12a** (251 mg, 72%); MS (isobutane/Cl): *m/e* (165 (M^+, Se^{80}), 148 (M^+ − OH, Se^{80}, base peak); IR (neat): 3600–3100 (OH), 2228 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.00 (t, 2H), 3.31 (s, 2H), 3.50 (s, 1H), and 3.95 ppm (t, 2H).

Anal.—Calc. for C_4H_7NOSe: C, H.

2-Chloroethyl Cyanomethyl Selenide (12)—The hydroxy compound **3a** (100 mg, 0.61 mmol) was reacted with five equivalents of thionyl chloride as described in Method A. A silica gel column chromatography of the crude products with an eluant of chloroform and *n*-hexane (3:1, v/v) yielded an acrid liquid, **12** (55 mg, 49%): MS (Cl/NH_3): *m/e* 201 (M^+ + 18, Se^{80}, 96.7%), 183 (M^+, Se^{80}, 73.8%), 80 (base peak); IR (neat): 2220 (CN) cm^{-1}; ^1H NMR (CD_3COCD_3): δ 3.0–3.3 (m, 2H), 3.55 (s, 2H), and 3.75–4.0 ppm (m, 2H).

Anal.—Calc. for C_4H_6ClNSe: C, H.

Se-(2-Hydroxyethyl) *N,N*-Dimethylselenocarbamate (13a)—2-Hydroxyethyl selenocyanate (245 mg, 1.63 mmol) in 10 mL of ethanol was treated with excess $NaBH_4$ at 0 °C until the solution became colorless. The ethanol mixture was allowed to cool down below −50 °C, and this was followed by the addition of *N,N*-dimethylcarbamoyl chloride (160 μL, 187 mg, 1.74 mmol) in 4 mL of CH_2Cl_2. The mixture was stirred for 30 min below −50 °C, and then treated with 1 mL of water. The residue after evaporation was transferred into a separatory funnel by aid of CH_2Cl_2 and brine, and then extracted with CH_2Cl_2 (5 mL × 4). The crude product was purified on silica gel and eluted by *n*-hexane and acetone (1:2, v/v) to yield a pale yellow liquid, **13a** (256 mg, 76%): MS (Cl/NH_3): *m/e* 197 (M^+ + 1, Se^{80}, base peak); IR (neat): 3700–3000 (OH), 2912, 2872, 1658–1628 (C=O), 1396, 1358, 1252, 1092, 1060, and 1038 cm^{-1}.

Se-(2-Chloroethyl) *N,N*-Dimethylselenocarbamate (13)—Thionyl chloride (107 mg, 0.9 mmol) was added to a solution of **13a** (118 mg, 0.60) in the presence of a Proton Sponge as given in Method B. The mixture was chromatographed on silica gel eluted by *n*-hexane and acetone (2:1, v/v) to give 83 mg (64%) of a pale yellow liquid, **13**; IR (neat): 2930, 1670–1650 (C=O), 1360 ($N(CH_3)_2$), 1251, and 1093 cm^{-1}; ^1H NMR (CD_3COCD_3): 2.97 (s, 6H), 3.0–3.3 (m, 2H), and 3.55–3.85 ppm (m, 2H).

Anal.—Calc. for $C_5H_{10}ClNOSe$: C, 27.99; H, 4.70. Found: C, 28.45; H, 4.80.

Se-(2-Chloroethyl) Selenobenzoate (14)—Se-(2-Hydroxyethyl) selenobenzoate[11] (115 mg, 0.5 mmol) was reacted with thionyl chloride according to Method A. The crude product was chromatographed on silica gel eluted by $CHCl_3$ and *n*-hexane (1:4, v/v) to give a pale yellow liquid, **14** (90 mg, 72%); IR (neat): 1670 (C=O), 1443, 1201, 1172, and 882 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.15–3.52 (m, 2H), 3.60–3.92 (m, 2H), and 7.2–8.0 ppm (m, 5H).

Anal.—Calc. for C_9H_9ClOSe: C, H.

2-Hydroxyethyl 2-Methoxyphenyl Selenide (15a)—2-Bromoethanol (80 μL, 1.14 mmol) in 3 mL of CH_2Cl_2 was added to an ethanolic solution of 2-methoxyphenyl selenocyanate[21] (190 mg, 0.9 mmol) treated with $NaBH_4$ at 0 °C. A silica gel column chromatograph of the crude product eluted by hexanes and ethyl acetate (1:1, v/v) gave 160 mg (77%) of a liquid, **15a**: ^1H NMR ($CDCl_3$): δ 2.90–3.20 (m, 3H, $SeCH_2$ and OH), 3.61–4.0 (m, 5H, OCH_3 and CH_2OH) and 6.75–7.63 ppm (m, 4H).

2-Chloroethyl 2-Methoxyphenyl Selenide (15)—Compound **15a** (90 mg, 0.39 mmol) was treated with thionyl chloride as given in Method A. The crude product was purified on a silica gel column eluted by hexanes and CH_2Cl_2 (3:1, v/v) to give 45 mg (46%) of a malodorous liquid, **15**; ^1H NMR ($CDCl_3$): δ 3.03–3.44 (m, 2H), 3.57–4.10 (m, 5H, CH_2Cl and OCH_3), and 6.80–7.67 ppm (m, 4H).

Anal.—Calc. for $C_9H_{11}ClOSe$: C, H.

3-Hydroxypropyl Methyl Selenide (16a)—Methyl methanesulfonate (163 μL, 1.92 mmol) dissolved in 3 mL of ethanol was added to an ethanolic solution of 3-hydroxypropyl selenocyanate[11] (255 mg, 1.6 mmol) treated with $NaBH_4$ at 0 °C. The same work-up procedure as for **13a** was used. The crude product was applied on a silica gel column eluted by chloroform and ethyl acetate (10:1, v/v) to yield 175 mg (72%) of a malodorous colorless liquid, **16a**, MS (Cl/NH_3): *m/e* 172 (M^+ + 18, ammonia adduct, base peak), 123 (M^+ − CH_2OH), 109 (M^+ − CH_2CH_2OH); IR (neat): 3600–3000 (OH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.65–2.25 (m, 5H, $CH_3SeCH_2CH_2CH_2OH$), 2.60 (t, 2H), and 3.53–3.98 ppm (m, 3H, CH_2OH).

3-Chloropropyl Methyl Selenide (16)—Method B was employed to convert the hydroxy **16a** (120 mg, 0.78 mmol) into the corresponding chloride by thionyl chloride in the presence of triethylamine. The crude product was chromatographed on a silica gel column eluted by CH_2Cl_2 and *n*-hexane (1:4, v/v) to give a malodorous yellow liquid, **16** (42 mg, 31%); ^1H NMR ($CDCl_3$): δ 1.78–2.35 (m, 5H), 2.64 (t, 2H), and 4.10 ppm (t, 2H).

Anal.—Calc. for C_4H_9ClSe: C, 28.01; H, 5.29. Found: C, 27.50; H, 5.35.

Benzyl 3-Mesyloxypropyl Selenide (17)—Methanesulfonyl chloride (30.4 μL, 0.39 mmol) in 3 mL of CH_2Cl_2 was added into benzyl 3-hydroxypropyl selenide[11] (75 mg, 0.33 mmol) dissolved in 8 mL of CH_2Cl_2 in the presence of triethylamine at 0 °C. A silica gel column chromatography of the crude product eluted by chloroform and ethyl acetate (1:1, v/v) gave 95 mg (94%) of a viscous liquid, **17**; ^1H NMR ($CDCl_3$): δ 1.96 (quint, 2H), 2.52 (t, 2H), 2.87 (s, 3H), 3.71 (s, 2H), 4.17 (t, 2H), and 7.18 ppm (s, 5H).

Anal.—Calc. for $C_{11}H_{16}O_3SSe$: C, H.

α,α′-Bis(3-mesyloxypropylseleno)-*o*-xylene (18,NSC-610892-V)—Methanesulfonyl chloride (245 μL, 3.17 mmol) was added to α,α′-bis(3-hydroxypropylseleno)-*o*-xylene[4] (548 mg, 1.44 mmol) dissolved in 15 mL of CH_2Cl_2 in the presence of triethylamine at 0 °C. After 30 min of stirring, the reaction mixture was concentrated and transferred into a separating funnel by aid of brine and CH_2Cl_2. The combined CH_2Cl_2 extracts (5 mL × 4) were dried with Na_2SO_4 and purified on silica gel. Elution with ethyl acetate and chloroform (1:1, v/v) gave a quantitative yield (762 mg, 99%) of a thick liquid, **18**; ^1H NMR ($CDCl_3$): δ 1.97 (quint, 4H), 2.56 (t, 4H), 2.91 (s, 6H), 3.90 (s, 4H), 4.19 (t, 9H), and 7.08 ppm (s, 4H).

Anal.—Calc. for $C_{16}H_{26}O_6S_2Se_2$: C, H.

Bis(3-hydroxypropyl) Selenide (20a)—3-Bromopropanol (255 μL, 2.68 mmol) in 3 mL of CH_2Cl_2 was added to 3-hydroxypropyl selenocyanate[11] (400 mg, 2.44 mmol) treated with $NaBH_4$ in ethanol at 0 °C under nitrogen. The crude product was chromatographed on silica gel with eluant of chloroform and acetone (1:1, v/v) to yield 380 mg 79%) of a pale yellow liquid, **20a**; MS (Cl/NH_3): 198 (M^+, Se^{80}, 99.5%), 180 (M^+ − 18, Se^{80}, base peak); IR (neat): 3600–3000 (OH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.88 (quint, 4H), 2.64 (t, 4H), 3.07 (s, 2H), and 3.32 ppm (t, 4H).

Bis(3-mesyloxypropyl) Selenide (20)—The diol **20a** (165 mg, 0.84 mmol) was treated with methanesulfonyl chloride as described for **18**. A silica gel column eluted with CH_2Cl_2 and ethyl acetate (5:1, v/v) gave a thick pale yellow liquid, **20** (278 mg, 94%); IR (neat): 1343 and 1170 (sulfonate) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.07 (quint, 4H), 2.64 (t, 4H), 3.0 (s, 6H), and 4.26 ppm (t, 4H).

Anal.—Calc. for $C_8H_{18}O_6S_2Se$: C, H.

Bis(3-hydroxypropyl) Diselenide (21a)—To a methanolic solution of 3-hydroxypropyl selenocyanate[11] (314 mg, 1.9 mmol) was slowly added 5 mL of 0.4 M KOH in methanol with vigorous stirring at 0 °C. After 30 min of reaction, the mixture was concentrated at a reduced pressure and transferred into a separatory funnel by aid of CH_2Cl_2 and brine. Extractions with methylene chloride (5 mL × 5) were given. The residue, after drying the combined CH_2Cl_2 layers and concentration, was chromatographed on silica gel eluted with chloroform and acetone (3:1, v/v) to yield 186 mg (71%) of a malodorous yellow liquid, **21a**; IR (neat): 3680–3000 (OH) cm^{-1}; ^1H NMR

(CD_3COCD_3): δ 1.98 (quint, 4H), 3.07 (t, 4H), 3.67 (t, 4H), and 3.95 ppm (s, 2H).

Bis(3-mesyloxypropyl) Diselenide (21)—According to the same method of preparing **20**, the diol **21a** (126 mg, 0.46 mmol) was treated with methanesulfonyl chloride. Purification of the crude product on silica gel with eluant of chloroform and acetone (1:1, v/v) gave 159 mg (80%) of a viscous yellow liquid, **21**; IR (neat): 1347 and 1173 (sulfonate) cm^{-1}.

Anal.—Calc. for $C_8H_{18}O_6S_2Se_2$: C, H.

2,6-Bis(3-hydroxypropylseleno)lutidine (22a)—2,6-Bis(chloromethyl)pyridine (280 mg, 1.59 mmol; mp: 72.5–73.5 °C, lit.[22] 74 °C and 76–77 °C), prepared from 2,6-pyridinedimethanol and thionyl chloride, was added to an ethanolic solution of 3-hydroxypropyl selenocyanate (558 mg, 3.4 mmol) treated with $NaBH_4$ at 0 °C. A thick yellow oil after the same work-up as for **13a** was chromatographed on silica gel. Elution with chloroform and acetone (2:1, v/v) gave 314 mg (52%) of a viscous liquid, **22a**; IR (neat): 3700–3000 (OH), 2928, 1588, 1569, 1451, and 1053 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.83 (quint, 4H), 2.62 (t, 4H), 3.5–4.0 [m, 8H, 3.66 (t, 4H) and 3.81 (s, 4H)], 4.37 (s, 2H), and 7.05–7.70 ppm (m, 3H).

2,6-Bis(3-mesyloxypropylseleno)lutidine (22)—Methanesulfonyl chloride (70 μL, 0.9 mmol) dissolved in 4 mL of CH_2Cl_2 was added to the diol **22a** (160 mg, 0.42 mmol) in 10 mL of CH_2Cl_2 in the presence of triethylamine at 0 °C. Purification of the crude product was carried out on a silica gel column eluted with chloroform and acetone (2:1, v/v) to give 109 mg (48%) of a viscous liquid, **22**; IR (neat): 1342 and 1165 (sulfonate) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.08 (quint, 4H), 2.69 (t, 4H), 2.99 (s, 6H), 3.82 (s, 4H), 4.28 (t, 4H), and 7.03–7.75 ppm (m, 3H).

Anal.—Calc. for $C_{15}H_{25}NO_6S_2Se_2$: C, H.

4-(4-Nitrobenzyl)pyridine (NBP) Alkylation Reactions—Determination of alkylating activities of **1–18** with NBP in aqueous acetone (52.5:47.8 v/v), in the presence of 17.4 mM Tris-HCl buffer (pH 7.0) at 37 °C, was carried out on the basis of the literature procedure.[6] For **19–22**, the temperature was changed to 45 °C and the medium was replaced by 50% aqueous ethanol.

Partition Coefficients of Selenides 20 and 22—The solubility behavior of **20** and **22** was estimated in the *n*-octanol:water system.[23] A 5-mL aliquot of *n*-octanol saturated with water containing 0.16 mM of a selenide was mixed with the equal volume of water saturated with *n*-octanol. The two phases were vigorously shaken by hand to ensure rapid distribution for 2 min, and then further agitated by a shaker (Wrist-Action Shaker model 75, Burrell) for 90 min at room temperature. After overnight (at least longer than 12 h) each layer was separated. The amount of an organoselenium compound in each layer was determined by NBP alkylation. An aliquot (0.6 mL) of the *n*-octanol (or water) layer was added to 0.6 mL of 2% (w/v) NBP in acetone, 0.2 mL of 0.2 M Tris-HCl buffer (pH 7.0), 0.2 mL of ethanol, and 0.6 mL of water (or *n*-octanol) saturated with *n*-octanol (or water). Test tubes in quadruplicate for each layer were kept for 20 h at 45 °C. Triethylamine (1.0 mL) was added to measure absorbance at 560 nm. Readings were taken within 1 min of alkalinization after cooling to room temperature. No significant loss of compounds due to the 90-min shaking and overnight settling was encountered. That was verified by comparing the total absorbance of *n*-octanol and water layers with the stock solution prior to partitioning. Readings for each layer were within experimental error of <4%, with the exception of the water layer of **22**. This was due to the low readings of the aqueous layer. In order to make the partition coefficient of **22** more reliable, a spectrophotometric assay was used since it has λ_{max} at 267 nm with a molar extinction coefficient of 4700 in *n*-octanol. The partition coefficients of **20** and **22** are given in Table IV.

Cytotoxicity Studies of Organoselenium Alkylating Agents against CCRF-CEM, L1210/0, and L1210/L-PAM—The concentration (IC_{50}) of organoselenium inhibitor necessary to inhibit cell growth by 50% compared with controls grown in the absence of inhibitor was determined on human lymphoblastoid CCRF-CEM cells and murine leukemic L1210/0 and L1210/L-PAM cells. Testing was performed according to the method reported previously,[6] except that CCRF-CEM cells were seeded at (2.5–5.0) × 10^4 cells/mL and (0.9–1.2) × 10^5 cells/mL of L1210/0 and L1210/L-PAM were used.

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