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Identification of selenocompounds with promising properties to reverse cancer multidrug resistance

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ABSTRACT

In previous studies, 56 novel selenoesters and one cyclic selenoanhydride with chemopreventive, antiproliferative and cytotoxic activity were described. Herein, the selenoanhydride and selected selenoesters were evaluated for their ability to reverse the cancer multidrug resistance (MDR) using the ABCB1 efflux pump inhibition assay in mouse MDR T-lymphoma cells. Results showed that the selenoanhydride (**1**) and the selenoesters with ketone terminal fragments (**9**–**11**) exerted (1.7–3.6)-fold stronger efflux pump inhibitory action than the reference verapamil. In addition, those four derivatives triggered apoptotic events in more than 80% of the examined MDR mouse cells.

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Selenium and its organic and inorganic derivatives fulfil several vital biological functions.[1] Interest in selenium has arisen since the discovery of the fact that its deficiency can cause clinical disorders, e.g., the diseases of Keshan and Kashin-Beck.[2] Afterwards, epidemiological studies reported by Li in China[3] and Clark in USA[4,5] proposed that the dietary supplementation with selenium reduced the incidence of lung, oesophagus[4] and prostate[5] cancer. The publication of those results initiated an intense and productive search of novel inorganic and organic selenocompounds with chemopreventive, antiproliferative and cytotoxic activity against cancer.[6–9] Among the inorganic selenium-containing salts, sodium selenite could be highlighted for its anticancer properties[10] whereas several of the most known organic selenocompounds with anticancer properties are methylselenol,[11,12] methylseleninic acid,[13,14] selenocyanates[15,16] and diphenyldiselenide.[17,18] Selenium nanoparticles are also being deeply studied, both in cancer field[19,20] and in cancer or bacterial multidrug resistance.[21,22]

Considering these antecedents, our previous studies concerned the design, synthesis and biological evaluation of selenium-containing anticancer agents, including 56 selenoesters and one selenoanhydride.[23,24] Those organoselenic derivatives displayed significant cytostatic action with IG_{50} values in nanomolar ranges, whereas the LD_{50} values of the most cytotoxic selenocompounds were in the micromolar range.[23,24] Various lines of evidence[25–29] indicate that selenocompounds enhance synergistically the activity of anticancer drugs when they are administered in combination. Thus, synergistic effects over the anticancer activity have been observed in the following selenocompounds and anticancer drug combinations: diphenylmethyl selenocyanate and cisplatin in a murine tumor model,[25] selenium nanoparticles and irinotecan in HCT-8 colon cancer cells,[26] selenite and imatinib in HCT116 colorectal cancer cells,[27] selenocysteine and auranofin in A549 lung cancer cells;[28] and methylseleninic acid and paclitaxel in a murine cancer model.[29] The synergistic effects observed suggest multidrug resistance (MDR) reversing activity for the selenocompounds. The MDR against the chemotherapeutic drugs action is a worrying problem in cancer treatment.[30,31] Among the different mechanisms involved in the cancer MDR processes, the increased activity of the efflux pumps is one of the most common.[32] The membrane transport proteins, especially the P-glycoprotein (P-gp, ABCB1

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protein), are able to recognize and expel various exogenous molecules out of the cell.[32,33] This is a natural protective mechanism of the cells against the action of toxic compounds that is stimulated in cancer cells.

Thus, the design of inhibitors of the efflux pumps, especially of the ABCB1, is a promising strategy in cancer therapy. For the evaluation of the efflux-pump related resistance in cancer, cell lines with over-expressed efflux pump systems, such as ABCB1, are commonly used.[34]

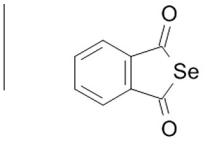
In this context, we have selected the representative structures **1**–**11** (Table 1) among the selenocompounds previously reported in Refs. 23,24 to investigate their capacity to reverse the cancer MDR via the inhibition of the efflux pump ABCB1. The representative compounds contain a selenoanhydride (**1**) or a selenoester (**2**–**11**) functional group. The alkyl moiety bounded to the selenium atom in the selenoesters is a methyl group (**2**–**5**) or includes secondary functional groups, such as: amides (**6**), carboxylic esters (**7**–**8**) or ketones (**9**–**11**). The compounds were resynthesized in the amount required to perform the biological assays, using the methods described earlier.[23,24] They were examined on the following biological actions: (i) inhibition of ABCB1 via the fluorescent substrate retention assay, (ii) cytotoxicity in the MTT assay and (iii) their capacity to induce apoptotic processes.

The biological studies were performed in two cell lines, the parental L5178Y and the MDR-derived mouse T-lymphoma cells transfected with the human *MDR1* (*ABCB1*) gene that codes for the ABC transporter ABCB1.[35]

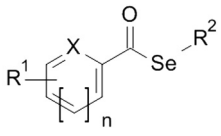
The efflux modulating effects of compounds **1**–**11** were investigated in the MDR cancer cells (mouse T-lymphoma) using the rhodamine 123 accumulation assays.[34–37] Rhodamine 123 is the dye–substrate for ABCB1. The percentage of mean fluorescence intensity was calculated for the treated MDR cells in comparison with the untreated cells. Results, expressed as the fluorescence activity ratio (FAR), have been compared to the action of the reference verapamil by the FAR quotient. The FAR and quotient values were computed according to the Eqs. 1 and 2, respectively (Table 2). Results indicated that the selenoesters **2**–**8** slightly affected the efflux activity of ABCB1, whereas the compounds **1** and **9**–**11** (Fig. 1) displayed a pronounced modulating action on this efflux pump in the MDR mouse T-lymphoma cells. It is noteworthy that derivatives **1** and **9** inhibited the ABCB1 pump (1.6–3.4)-fold stronger than the reference inhibitor (verapamil) at its 10-fold higher concentration. When evaluated at the same concentration than verapamil, compounds **1** and **9**–**11** inhibited this efflux pump (1.7–3.6)-fold stronger than this known inhibitor.

The cytotoxic effects of the selenocompounds **1**–**11** were determined and compared with the action exerted by two reference drugs with moderate (thioridazine) or weak (verapamil) cytotoxicity. Results were expressed as IC_{50} values (Table 3). Six compounds (**2**, **4**–**8**) were less cytotoxic than both reference drugs. However, the most active compounds (**1** and **9**–**11**) showed a significantly higher cytotoxicity than thioridazine and verapamil in both cell lines. Besides, the selenoesters **9**–**11** exhibited their cytotoxic action in the nanomolar range at least in one of the two mouse T-lymphoma cell lines investigated. In the case of the most active one (**10**), the IC_{50} value was 430 nM in the MDR cells.

Table 1
Structure of the selenocompounds evaluated as MDR reversing agents



A. Cyclic selenoanhydride (**1**)



B. Selenoesters (**2**-**11**)

Compd	Group	R^1	X	*n*	R^2
1	**A**	—	—	—	—
2	**B**	5-$COSeCH_3$	S	0	$-CH_3$
3	**B**	6-$COSeCH_3$	N	1	$-CH_3$
4	**B**	3-$COSeCH_3$	C	1	$-CH_3$
5	**B**	4-$COSeCH_3$	C	1	$-CH_3$
6	**B**	—H	C	1	$-CH_2CONH_2$
7	**B**	4-Cl	C	1	$-CH_2COOCH_3$
8	**B**	—H	C	1	$-CH_2COOPh$
9	**B**	4-Cl	C	1	$-CH_2COCH_3$
10	**B**	4-Cl	C	1	$-CH_2COC(CH_3)_3$
11	**B**	3,5-$DiOCH_3$	C	1	$-CH_2COC(CH_3)_3$

Compd: Compound.

Table 2
Effects of selenocompounds on rhodamine 123 retention by L5178Y multidrug resistant (MDR) mouse T-lymphoma cells

Sample	Concentration (μM)	FAR[a]	FAR quotient[b] (%)
Verapamil	20	27.4	100
1	2	43.14	157.4
1	20	97.61	356.2
2	2	0.99	3.61
2	20	1.07	3.19
3	2	1.13	3.98
3	20	1.49	5.44
4	2	0.93	2.78
4	20	0.98	3.39
5	2	3.97	18.64
5	20	3.09	14.49
6	2	1.02	3.04
6	20	1.05	3.72
7	2	6.45	30.28
7	20	8.53	23.54
8	2	0.65	3.05
8	20	5.68	2.37
9	2	94.20	343.79
9	20	84.64	308.91
10	2	9.28	33.87
10	20	48.67	177.63
11	2	12.56	45.84
11	20	46.35	169.16
DMSO	2%	0.76	2.77

[a] FAR: fluorescence activity ratio, calculated as follows:

$$FAR = \frac{MDR_{treated}/MDR_{control}}{parental_{treated}/parental_{control}}. \quad (1)$$

[b] Calculated as follows:

$$Quotient = \frac{FAR_{compound}}{FAR_{verapamil}} \times 100. \quad (2)$$

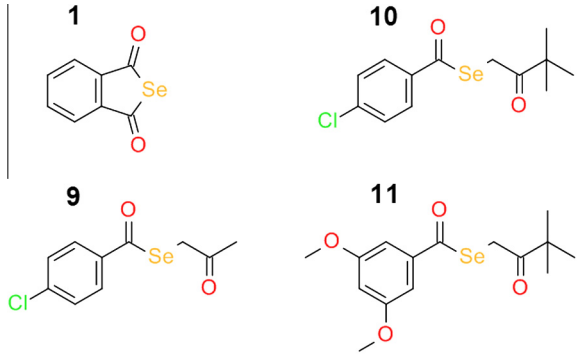


Figure 1. Structure of the most active selenocompounds.

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