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Selenoesters and selenoanhydrides as novel multidrug resistance reversing agents: a confirmation study in a colon cancer MDR cell line

Mário Gajdács[a], Gabriella Spengler[a], Carmen Sanmartín[b], Małgorzata Anna Marć[c], Jadwiga Handzlik[c] and Enrique Domínguez-Álvarez[b,c*]

[a] Department of Medical Microbiology and Immunobiology, Faculty of Medicine, University of Szeged, Dóm tér 10, 6720 Szeged, Hungary
[b] Department of Organic and Pharmaceutical Chemistry. School of Pharmacy, University of Navarra, Irunlarrea 1, 31010 Pamplona, Spain.
[c] Department of Technology and Biotechnology of Drugs. Jagiellonian University Medical College. Medyczna 9, 30-688 Kraków, Poland.

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ABSTRACT

Taking into account that multidrug resistance (MDR) is the main cause for chemotherapeutic failure in cancer treatment and as a continuation of our efforts to overcome this problem we report the evaluation of one cyclic selenoanhydride (**1**) and ten selenoesters (**2-11**) in MDR human colon adenocarcinoma Colo 320 cell line. The most potent derivatives (**1**, **9-11**) inhibited the ABCB1 efflux pump much stronger than the reference compound verapamil. Particularly, the best one (**9**) was 4-fold more potent than verapamil at a 10-fold lower concentration. Furthermore, the evaluated derivatives exerted a potent and selective cytotoxic activity. In addition, they were strong apoptotic inducers as the four derivatives triggered apoptotic events in a 64-72% of the examined MDR Colo 320 human adenocarcinoma cells.

Different organic and inorganic selenocompounds have been reported as anticancer agents[1-2], and many of them have interesting applications in human health[3]. Sodium selenite[4-7], sodium selenide[8] and elemental Se-nanoparticles[9-11] can be cited as examples of inorganic selenium-containing compounds with anticancer and/or apoptotic and/or antibacterial activity. Alternatively, among the active organic selenium derivatives, methylseleninic acid[12-14], selenocyanates[15-17], selenoureas[18,19] and selenoesters[20-21] can be highlighted. The reported mechanisms of action for these compounds vary greatly: reduction of oxidative stress[22], induction of mutations[23], angiogenesis inhibition[16,24], apoptosis induction[25] and reversal of multidrug resistance (MDR)[25]. Interestingly, selenium and Se-containing compounds are like a double-edged sword[26]: they can exert an antioxidant action that prevents cancer in normal cells[1-3,22,26], whereas they can act in cancer cells as pro-oxidants that generate reactive oxygen species (ROS). These Se-induced ROS can then trigger apoptotic processes[25,26] and can induce mutations in DNA, as well as DNA breaks[23,26].

The multidrug resistance of cancers and bacterial infections is an increasing and troublesome problem nowadays, due to the appearance of resistant cancers and resistant bacterial strains[27-28]. It has been observed that one of the most common mechanisms of cancer MDR is the over-expression of the efflux pumps[29], which are membrane proteins that can recognise and extrude out of the cells toxic agents such as the anticancer drugs[29,30]. In this context, different studies[6,7,14-16,31-33] pointed out that selenocompounds can enhance the activity of the drugs used in cancer chemotherapy in a synergic way if they are applied together. Some examples of studies that have shown this synergistic enhancement of the chemotherapy drugs action are: (i) sodium selenite potentiates the cytotoxicity of imatinib in HCT116 colorectal cancer cells[6]; (ii) sodium selenite enhances the cytotoxicity of cisplatin in MCF-7 breast carcinoma cells[7]; (iii) the cytotoxicity of paclitaxel is augmented in presence of methylseleninic acid in MDA-MB-231 breast adenocarcinoma cells[14]; (iv) the combined treatment of mice with diphenylmethyl selenocyanate and cisplatin decreases the size of induced tumours[15]; (v) a complex organoselenocyanate inhibited the angiogenesis and enhanced the therapeutic efficacy of cyclophosphamide in tumour bearing Swiss albino mice[16]; (vi) selenocystine can potentiate the capacity of auronafin to induce apoptosis in A549 lung cancer cell line[31], (vii) selenocystine also enhances the therapeutic effect of doxorubicin in liver carcinoma HepG2 cell line[32]; and (viii) Se-methylselenocysteine increases the antitumour activity of different chemotherapeutic agents *in vivo* (cisplatin, cyclophosphamide, oxaliplatin and irinotecan) in mice[33].

Taking in mind the aforesaid antecedents, and seeking to determine the influence of selenocompounds on multidrug resistance, we evaluated the capacity of a cyclic selenoanhydride and ten selenoesters[20,21] to inhibit a MDR efflux pump such as the