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Abstract

Soloxolone amide sg-650 as new promising small molecule P-glycoprotein inhibitor: in silico prediction and in vitro verification.

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Abstract: Multidrug resistance (MDR) remains a significant challenge in cancer therapy, primarily due to the overexpression of transmembrane drug transporters, with P-glycoprotein (P-gp) encoded by the human ABCB1/MDR1 gene being a central focus. Reduced intracellular drug levels lead to decreased chemosensitivity of cancer cells, culminating in drug resistance. Consequently, the development of P-gp inhibitors has emerged as a promising strategy to combat MDR. In this study, we evaluated eight soloxolone amides for their potential to inhibit P-gp-mediated efflux in MDR tumor cells. Using molecular docking, all compounds were shown to have a direct interaction with the P-gp transmembrane domain characterized by low binding energies (< -9 kcal/mol). Validation of P-gp inhibitory activity was performed on KB-8-5 human cervical cancer cells and RLS40 murine lymphosarcoma cells with P-gp-mediated MDR. The lead compound sg-650 at non-toxic concentration of 40 μM significantly increased the intracellular accumulation of the P-gp substrates rhodamine-123 and doxorubicin by 10.4- and 1.5-fold, respectively, in KB-8-5 cells. Kinetic studies demonstrated an uncompetitive manner of doxorubicin efflux inhibition. In addition, sg-650 synergistically enhanced doxorubicin cytotoxicity in a dose-dependent manner, demonstrating MDR reversal activity. Similar effects were observed in sg-650-treated RLS40 cells. These results underscore the potential of sg-650 as a potent small molecule P-gp inhibitor that holds promise for overcoming MDR in cancer treatment.

Keywords: Multidrug resistance; pentacyclic triterpenoids; p-glycoprotein; soloxolone.

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