LIGAND-BASED AND STRUCTURE-BASED VIRTUAL SCREENING TO INDENTIFY POTENTIAL INHIBITORS OF DRUG-EFFLUX TRANSPORTERS

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Multidrug resistance (MDR) is a phenotype whereby cancer cells become refractory to a broad spectrum of structurally diverse antitumor agents. Overexpression of P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (BCRP/ABCG2) is associated with MDR acquisition. Both transporters actively extrude a wide variety of substrates out of cells leading to decreased intracellular drug accumulation and may compromise treatment efficacy. Inhibition of transport activity of P-gp and BCRP may therefore enhance efficacy of chemotherapeutic agents. Although a number of inhibitors have shown promise in vitro, translation to the clinic, to date, has not been successful. Here we show the implementation of a high-throughput virtual screening strategy that has led to the identification of compounds with potential MDR reversal activity. This strategy included the generation of pharmacophore models of P-gp and BCRP inhibitors, pharmacophore-based virtual screening and generation of P-gp and BCRP homology models to carry out virtual docking screening. The Zinc database was the chemical library investigated.Pharmacophores were constructed using third generation inhibitors of P-gp and BCRP as templates. Pharmacophore analyses delineated physicochemical and topological constraints required for MDR reversal activity. These constraints were later employed as fingerprints to screen the commercially available subset of compounds of the ZINC database, which contains approximately 9 million molecules. The hits were then subsequently docked into homology models of P-gp and BCRP. Based on binding mode and affinity, a series of compounds with a potential MDR reversal activity were identified. Future in vitro studies will be conducted to further investigate potential MDR reversal activity.

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