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Discovery of highly-potent and selective inhibitors for the ABCG2 transporter

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Abstract

Overexpression of multidrug ABC transporters in cancer cells alters anticancer drugs efficacy by reducing their accumulation in the intracellular compartment. One of the three ABC transporters being largely involved in resistance of cancer cells toward treatments is the Breast Cancer Resistance Protein (BCRP/ABCG2). Overcoming multidrug resistance (MDR phenotype) against anticancer drugs is a challenging problem. One of the strategies to overcome MDR can be achieved through effective inhibitors of the multidrug ABC transporters involved in the MDR. In the present communication we will shed light on our recent discovery of highly potent, non-toxic and selective inhibitors of ABCG2 transporter. A special focus will be made on 5-(4-bromobenzyloxy)-2-(2-(5-methoxyindolyl)ethyl-1-carbonyl)-4*H*-chromen-4-one, namely MBL-II-141. The latter inhibits ABCG2 with high affinity (IC50 = 0.11 µM) with very low cytotoxicity, giving a markedly high therapeutic index. MBL-II-141 is highly selective for ABCG2 *versus* other transporters and constitutes a good candidate for *in vivo* chemosensitization of tumors. The design, synthesis, *in vitro* and our latest *in vivo* studies will be presented.