عنوان مقاله:

Synthesis and biological evaluation of novel quinoline analogs of ketoprofen as multidrug resistance protein ۲ (MRP۲) inhibitors

محل انتشار:

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تعداد صفحات اصل مقاله: 10

نویسندگان:

Fatemeh Mosafa - *Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

Farzin Hadizadeh - *Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

Faezeh Fathi - *Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

Zahra Eslami Nasab - *Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

Tahereh Pourzahed - *Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

Sayyed Mohammad Aboutorabzade - *Department of Medicinal Chemistry, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

Razieh Ghodsi - *Biotechnology Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

خلاصه مقاله:

Objective(s): A new series of quinoline analogs of ketoprofen was designed and synthesized as multidrug resistance protein ۲ (MRP۲) inhibitors using ketoprofen as the lead compounds.Materials and Methods: The cytotoxic activity of the compounds was evaluated againt two cancer cell lines including A۲۷۸۰/RCIS (MRP۲-overexpressing ovarian carcinoma), A۲۷۸۰, drug-sensitive ovarian carcinoma using MTT assay. Compounds showing low toxicity in MTT test were selected to investigate their MRP inhibition activity. MRP۲ inhibitory potency was evaluated by determination of the uptake amount of fluorescent ۵-carboxy fluorescein diacetate (۵-CFDA) substrate, by A۲۷۸۰/RCIS in the presence of the selected compounds. Mode of interaction between synthesized ligands and homology modeled MRP۲ was investigated by MOE software. Results: Compound ۶d, a ۴-carboxy quinoline possessing dimethoxy phenyl in position ۲ of quinoline ring, showed the most MRP۲ inhibition activity among all the quinolines and more than the reference drug ketoprofen. MRP۲ inhibition activity of compound ۷d was less in comparison to that of compound ۶d, indicating that carboxyl group in position ۴ of quinoline may interact with MRP۲. Docking studies showed that compound ۷d methyl ester of ۶d, interacted less compared to its parent ۶d, which is consistent with biological results.Conclusion:

This study indicates that ۶- or ۸-benzoyl-۲-arylquinoline is a suitable scaffold to design MRP۲ inhibitors. The position of benzoyl in quinoline ring is important in inhibition of MRP۲. Generally, MRP۲ inhibition activity of compound ۷d was less in comparison to that of ۶d, indicating that carboxyl group in position ۴ of quinoline may interact with MRP۲.

کلمات کلیدی:

Anticancer, (ATP)-binding cassette, Multi-drug resistance protein, Multi-drug resistance protein inhibitor, Molecular docking, Quinoline, Synthesis