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Pharmacophore modeling, synthesis, scaffold hopping and biological β-hematin inhibition interaction studies as antimalaria compounds: An approach for multitarget anticancer drug design

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Exploring potent compounds is a critical first step in the multi-target drug discovery. The primary mechanism of heme detoxification in malaria parasites is hematin crystallization and the target of the antimalaria compounds. A series of chloroquine analogues were designed using the repositioning approach to develop new anticancer compounds. The fingerprints of the protein ligand interaction and ADMET descriptors are used to build and asses' model for structure based drug discovery to develop new scaffold based on chloroquine hybrid β-hematin inhibitors. In the present study, 50 novel potent chloroquine hybrid β-hematin inhibitors with their IC_{50} values were collected, was applied. The model built by partial least square algorithm showed excellent predictive power with the correlation coefficients for calibration and cross validation of $r^2 = 0.93$ and $q^2 = 0.72$. We developed and validated QSAR model in prediction of a newly synthesized series of 4-aminoquinolin hybrids and evaluated for their biological activity as an external test series. These compounds were evaluated for cytotoxic cell lines and β-hematin inhibition. The target compounds exhibited high β-hematin inhibition activity and were 3-9 times more active than the positive control. Furthermore, all compounds exhibited moderate to high cytotoxic activity. Pharmacophore features from 10 derivatives in model were generated with HIP-HOP algorithm then used for structure based virtual screening in commercial databases; leading to the identification of the compound with the best score from ChEMBL was 2016904, previously reported as VEGFR-2 inhibitor. The 11 compounds selected have performed a multi-parameter analysis for the comparison of compounds regarding their correlation between dual potency, target evaluation and predicted ADMET properties for drug development.

Biography

Neda Fayyazi was a PhD student from School of Pharmacy in Isfahan Medical University, Iran. She has published more than four papers, two lectures and seven posters in reputed journals and conference. Her PhD project is novel investigation of the drug design, synthesis and biological evaluation multi-target hybrid compounds for malaria disease by different *in silico* methods and use the structure based assessment and repositioning strategy for identification of the best suitable candidate for anticancer drug design. She works with webserver such as HADDOCK, ZDOCK. She has knowledge about computational and QSAR method, pharmacophore modeling and molecular dynamic science. She worked in pharmaceutical company before in PhD grade and have professional experiences in natural product drug discovery and synthetic raw materials based on hybrid compounds.

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