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In silico Designing and Insight into Antimalarial Potential of Chalcone-Quinolinylpyrazole Hybrids by Preclinical Study in Mice

Authors : Deepika Saini, Sandeep Jain, Ajay Kumar

Abstract : The quinoline scaffold is one of the most widely studied in the discovery of derivatives with various heterocyclic moieties due to its potential antimalarial activities. In the present study, a chalcone series of quinoline derivatives clubbed with pyrazole were synthesized to evaluate their antimalarial property by in vitro schizont maturation inhibition assay against both chloroquine sensitive, 3D7 and chloroquine resistant, RKL9 strain of Plasmodium falciparum. Further, top five compounds were studied for in vivo preclinical study for antimalarial potential against P. berghei in Swiss albino mice. To understand the mechanism of synthesized analogues, they were screened computationally by molecular docking techniques. Compounds were docked into the active site of a protein receptor, Plasmodium falciparum Cysteine Protease Falcipain-2. The compounds were successfully synthesized, and structural confirmation was performed by FTIR, 1H-NMR, mass spectrometry and elemental analysis. In vitro study suggested that the compounds 5b, 5g, 5l, 5s and 5u possessed best antimalarial activity and further tested for in vivo screening. Compound 5u (CH_3 on both rings) with EC_{50} 0.313 & 0.801 µg/ml against CQ-S & CQ-R strains of P. falciparum respectively and 78.01% suppression of parasitemia. The molecular docking studies of the compounds helped in understanding the mechanism of action against falcipain-2. The present study reveals the binding signatures of the synthesized ligands within the active site of the protein, and it explains the results from in vitro study in their EC_{50} values and percentage parasitemia.

Keywords : antimalarial activity, chalcone, docking, quinoline
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