Pharmacophore modeling and 3D-QSAR of novel chalcone derivatives as *Plasmodium falciparum* growth inhibitors

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Abstract

Pharmacophore modeling studies were undertaken for a series of 1-phenyl-3-aryl-2-propen-1-one (Chalcone) and their congeners as novel potential antimalarials against chloroquine-resistant strain (W2) of *Plasmodium falciparum*. A four-point pharmacophore with two hydrogen bond acceptors (A) and two aromatic rings (R) as pharmacophore features was developed. The pharmacophore hypothesis yielded a 3D-QSAR model with good partial least-square (PLS) statistics results. The training set correlation is characterized by PLS factors (r^2 = 0.920, SD = 0.16, F = 60.1, P = 3.395 e−011). The test set correlation is characterized by PLS factors (Q^2_{ext} = 0.861, RMSE = 0.16, Pearson-R = 0.94). A docking study revealed the binding orientations of these inhibitors at active site amino acid residues (Gln36, Cys39, Lys37, Asp35, Trp206) of falcipain enzyme (PDB ID: 3BPF). The results of ligand-based pharmacophore hypothesis and atom-based 3D-QSAR give detailed structural insights of novel chalcone derivatives as falcipain inhibitors which may provide guidance for further lead optimization and virtual screening.