

## Synthesis, Biological Evaluation and Molecular Modeling Studies on Chiral Chloroquine Analogues as Antimalarial Agents

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**Abstract :** In a focused exploration, we have designed synthesized and biologically evaluated chiral conjugated new chloroquine (CQ) analogs with substituted piperazines as antimalarial agents. In vitro as well as in vivo studies revealed that compound 7c showed potent activity [for in vitro  $IC_{50}$ = 56.98nM (3D7), 97.76nM (K1); for in vivo (up to at the dose of 12.5 mg/kg); SI = 3510] as a new lead of antimalarial agent. Other compounds 6b, 6d, 7d, 7h, 8c, 8d, 9a, and 9c are also showing moderate activity against CQ-sensitive (3D7) strain and superior activity against resistant (K1) strain of *P. falciparum*. Furthermore, we have carried out docking and 3D-QSAR studies of all in-house data sets (168 molecules) of chiral CQ analogs to explain the structure activity relationships (SAR). Our new findings specified the significance of H-bond interaction with the side chain of heme for biological activity. In addition, the 3D-QSAR study against 3D7 strain indicated the favorable and unfavorable sites of CQ analogs for incorporating steric, hydrophobic and electropositive groups to improve the antimalarial activity.

**Keywords :** piperazines, CQ-sensitive strain-3D7, in-vitro and in-vivo assay, docking, 3D-QSAR

**Conference Title :** ICDDD 2019 : International Conference on Drug Discovery and Designing

**Conference Location :** Melbourne, Australia

**Conference Dates :** February 01-02, 2019