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Title: Structure based design, synthesis and biological evaluation of antimalarials

ABSTRACT

Malaria is one of the most important infectious diseases in the world. *Plasmodium falciparum* is considered to be the most severe human malaria parasite, and is responsible for the death of more than one million people each year. Malaria control medicines have been hampered with the increase in the resistance of the malaria parasite.

In this thesis, we have mainly focused on the development of the new antimalarial agents. We successfully designed and synthesized different core moiety-based series of compounds and evaluated them for their ability to act against malarial and leishmania.

In the introduction chapter of the thesis, we attempted to describe in detail about malaria, its present status, symptoms, causes, known drug targets, and available FDA approved antimalarial drugs. We also provided an up to date literature review about the development of various antimalarials.

In **chapter 2**, we report a set of 10 novel quinoline-triazole-based compounds (T1-T10) which exhibit a good binding affinity for FP2, inhibit its catalytic activity at micromolar concentration, thereby arrest the parasite growth. Compounds T4 and T7 inhibited FP2 with IC_{50} value 16.16 µM and 25.64 µM, respectively. These compounds also showed morphological and food-vacuole abnormalities like E-64, a known inhibitor of FP2.

In **chapter 3**, novel 25 quinoline carboxamides having different functionality were designed, synthesized and biologically evaluated against malaria. We integrated molecular hybridization strategy with *in silico* drug design to develop FP2 inhibitors. Compounds Qs17, Qs18, Qs20 and Qs21 showed favorable interaction with the active site residues of FP2 through *in silico* studies. Furthermore, the i*n vitro* results of FP2 inhibition by Qs17, Qs18, Qs20 and Qs21 was found to be in low micromolar range with IC_{50} 4.78, 7.37, 2.14 and 2.64 µM, respectively. These compounds also depicted morphological and food-vacuole abnormalities much better than the known FP2 inhibitor, E-64.

In **chapter 4a**, a library of chloroquinoline based compounds was synthesized and evaluated against leishmaniasis on *L. donovani* promastigotes and intracellular amastigotes and were found to be comparable with the standard drug MTF.

In **chapter 4b,** a new series of chloroquinoline-pyrimidine-based compounds are described as potential class of antimalarials. The targeted compounds were synthesized through an easily performed, convergent synthetic route. The compounds were evaluated as antiplasmodial agents against chloroquine sensitive (3D7) strain and resistant strain (FCR-3) of *P. falciparum* using SYBR Green I assay.

Lastly, in **chapter 5,** we report the synthesis of 15 novel diphenyl triazine derivatives and their testing against *L. donovani*. Most of the compounds displayed a significant inhibition of the parasite. Compound T4 was also found to be less toxic toward human macrophage cell line THP-1.