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Antimalarial Drug Targets in *Plasmodium falciparum* versus Stage-specific Metabolic System Analysis

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Malaria is the most dreaded parasitic disease of man and it is still a major health problem in tropical countries [1]. Among six species of *Plasmodium*, the majority of malarial deaths are caused by the intracellular protozoan parasite *Plasmodium falciparum* [2]. Estimated cases of Plasmodium falciparum malaria grew from 211 million in 2015 to 216 million in 2016 with an increase of 2.4 percent [3]. The commonly used classes of antimalarial compounds include the quinolines (chloroquine, quinine, mefloquine, amodiaquine, primaquine), the antifolates (pyrimethamine, proguanil and sulfadoxine), the artmisinin derivatives (artemisinin, artesunate, artemether, arteether) and hydroxynaphthaquinones (atovaquine) [4]. The *P. falciparum* relies exclusively on de novo pyrimidine biosynthesis to supply precursors for DNA and RNA biosynthesis [5]. In contrast, the human host cells contain the enzymatic machinery for both de novo pyrimidine biosynthesis and for salvage of performed pyrimidine bases and nucleosides [6].

Drug resistance has been reported to almost every known anti-malarial agent, underscoring the case by which parasite population can adapt and survive [7]. The identification of new target for anti-malarial drugs for malaria elimination requires an integrated strategy, including new and old drugs, vaccines, vector control and public health measures. Considering the high mortality, morbidity, the emergence and spread of resistance to existing drugs, there is no question that new drugs are required [8]. To achieve this goal, anti-malarial drug research should focus on validated targets in order to generate new drug candidates [8].

There is a continued effort for the design and development of the potent inhibitor for Plasmodium falciparum dihydrofolate reductase (*PfDHFR*) in the control of malaria. Therefore it is of interest to screen *PfDHFR* with the derivatives of Pyrimethamine. Recent in silico study reveals that the compound CID 10476801 has lowest docked energy (-11.48 kcal/mol) with protein likely to be a drug candidate, probably inhibiting *PfDHFR* structure. Residues of *PfDHFR* protein involved in the formation of hydrogen bonds with compoundCID 10476801 are confirmed to be ASP54 [9]. Nevertheless, On screening of benzamide derivatives, drug candidate CID 867491 was found to have least docking energy (-4.82Kcal/mol), which inhibits *PfDHODH* and further the interaction between them was validated using python software by formation of hydrogen bond between the CID 867491 and *PfDHODH* [10].

Conclusions and Recommendations

Conclusively, *PfDHFR* and *PfDHODH* are established drug targeting enzyme proteins to combat against malaria. Docking study predicted that (a) the compound CID 10476801 has lowest docked energy with *PfDHFR* and the interaction is stabilized by hydrogen bonding; (b) the drug candidate CID 867491 has least docking energy (-4.82Kcal/mol), inhibiting *PfDHODH* and further the interaction between having been validated through python software by formation of hydrogen bond between the CID 867491 and *PfDHODH*. These in silico findings provide new insights into further development of potent chemotherapeutic drugs for combating malaria.

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