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Inhibitory Molecular Interactions of Pyrimethamine Derivatives Versus Malaria Disease

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Editorial

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Editorial

Malaria is an acute disease caused by mosquito, having been a major global health problem of humans and a leading cause of mortality across various tropical and subtropical countries. Over the two decades rehabilitated efforts made to control malaria have reduced the occurrence of malaria by over half, but the still its persistence, harshness and appearance of resistance to existing drugs, there is a requirement to develop certain novel drugs to fight against this life threatening disease [1]. Malaria is caused by infection with protozoan parasite, namely, *Plasmodium* transmitted by female Anopheles species of mosquitoes [2]. Presently, six *Plasmodium* species viz. *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale curtisi*, *Plasmodium ovale wallikeri*, *Plasmodium malariae*, *Plasmodium knowlesi. Plasmodium falciparum* is generally considered the most important in terms of mortality.

Various drugs have been developed against malaria with the most important being chloroquine and artemisinin. The commonly used classes of antimalarial compounds include quinolines, antifolates, artmisinin derivatives [3]. The most extensively used antimalarial drugs belong to the folate antagonist class, although their function in malaria control is laden by speedy appearance of resistance under drug pressure [1]. Antifolate antimalarial drugs interfere with folate metabolism, essential to malaria parasite survival. The antifolate drugs inhibit either dihydrofolate reductase (DHFR) (pyrimethamine, cycloguanil) or dihydropteroate synthase (DHPS) (sulfadoxine), the two key enzymes in *de novo* folate biosynthesis; inhibition of this metabolic pathway leads to the inhibition of the biosynthesis of pyrimidines, purines, and some amino acids. Currently, there are effectual drugs to treat and control malaria; though the ability of *P. falciparum* especially to develop resistance to these treatments has threatened their long-lasting effectiveness and raised the significance of combinations as well as developing new drugs with novel targets [1].

The Resistance to these drugs has emerged rapidly and is now general worldwide. Resistance is caused by point mutations in DHFR and DHPS, the two principal enzymes in the folate biosynthesis, which are targeted by antifolates [3]. Resistance to DHFR and DHPS inhibitors is conferred by single mutations of the gene encoding for the relevant enzyme, consequential to certain substitutions in the amino acid chain [4]. New antimalarial treatments should exhibit novel mechanisms of action with effectiveness against already existing multi-drug resistant strains. Furthermore, the interruption of parasite transmission, with the potential to contribute to malaria suppression, should be exploited by the next generation of antimalarial drugs [5]. Therefore it is of interest to screen *Pf*DHFR with the derivatives of Pyrimethamine. Data from the recent exhibit that the compound CID 10476801 has lowest docked energy (-11.48 kcal/mol) with protein likely to be a drug candidate, probably inhibiting *Pf*DHFR structure [6,7]. Residues of *Pf*DHFR protein involved in the formation of hydrogen bonds with compound CID 10476801 are confirmed to be ASP54 [7]. The findings provide new insights into development of potent chemotherapeutic drug for combating malaria.

Conclusions and Recommendations

Conclusively, the *Plasmodium falciparum* dihydrofolate reductase is a drug target for malaria. Docking study predicted that compound CID 10476801 has lowest docked energy with PfDHFR and the interaction is stabilized by hydrogen bonding [6]. The findings from the studies along the notions and objectives stated herein provide new insights into designing and development of potent chemotherapeutic drug for combating malaria [6,7].

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