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Molecular Docking and Molecular Dynamics Simulation studies of DHFR inhibitors in Plasmodium falciparum

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Abstract

Malaria, caused by Plasmodium falciparum is a very common disease that causes 2.5 million deaths worldwide. This makes designing of lead molecules for malaria very exigent. DHFR has been known to be one of the major targets of antimalarial drug therapy which functions as a fundamental cofactor in the synthesis of histidine and methionine as well as purine nucleotides. Inhibition of this DHFR blocks the reduction of Dihydrofolate (DHF) to Tetrahydrofolate (THF) and hence prevents the synthesis of DNA, resulting in death of Plasmodium falciparum. Pyrimethamine is a Diaminopyrimidine that inhibits pfDHFR (Plasmodium falciparum DHFR) at a concentration that is 1000 times less than that required to inhibit the mammalian DHFR. Virtual screening is performed to find Pyrimethamine analogs from PubChem database. Docking studies are performed on DHFR (PDB ID: 3QGT) with Pyrimethamine and its 193 derivatives and the differences in their binding modes are investigated. The binding score suggests 53 derivatives to be more potent than Pyrimethamine which has a score of -24.7 showing interaction with Ile14, Asp54 and Ile164. The compound with best binding score (-35) showed interaction with Ile14, Cys15, Asp54, Phe58, Ser108, Ser111, Ile164 and Tyr170. The compounds are screened based on hydrogen bonding, π-π interactions, halogen bonding and orientation within the binding site with high binding score using Maestro (v.11.0.014, Schrodinger). The best screened compound is selected for Molecular Dynamic Simulation analysis up to 20ns using Desmond (v.4.8, Schrodinger) which represents a good starting point for further in vivo experimentation and can probably serve as an ideal lead compound for the treatment of Malaria.

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