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Molecular Docking of Sulfachloropyridazine with malarial enoyl acyl ACP reductase of Plasmodium Falciparum to understand its Potential in acting as an Inhibitor.

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ABSTRACT:
Malaria is a life-threatening mosquito-borne blood disease caused by a Plasmodium parasite, transmitted to humans through mosquito. The parasites multiply in the host's liver before infecting and destroys the red blood cells. Protein Malarial enoyl acyl ACP reductase, Malaria caused by Plasmodium falciparum is the most widespread in humans and is the predominant cause of severe disease and death is reported as the second leading cause of death in the world, after tuberculosis. Even though antimalarial drugs like chloroquine and sulfadoxine are being used to treat malaria, their chronic use has slowly led to resistance in P. falciparum, rendering the drugs much less effective ultimately leading to treatment failure.

To circumvent these issues, a key malarial enzyme, enoyl-acyl reductase (ENR) has been investigated as a crucial target as it has an important role in membrane construction and energy production in the parasite. Hence our study aims to understand the binding potential of sulfachloropyridazine , an antibiotic with ENR in curing the deadly disease, Malaria.

Key Words: Sulfachloropyridazine, Aldose Reductase, Toxicity Prediction, Molecular Docking Studies

I. INTRODUCTION

Falciparum malaria is a fatal vector borne disease caused by unicellular protozoan parasite, Plasmodium falciparum[1].Female anopheles mosquito, which is the key vector for the pathogen is responsible for nearly 50% of all malaria cases[2].According to the estimates of World Health Organization (WHO), 3.4 billion global population are at a risk of being infected with malaria. 212 million cases of malaria were reported in 2015 by World Malaria Report 2016[3].Hence, there is an urgent need for the identification of efficient drug candidate molecules for the treatment of Malaria.

The protective efficacy of antimalarial therapeutic agents is explained by their potential to inhibit type II fatty acid biosynthesis, since biosynthesis of fatty acids play significant role in membrane building and energy production[4]. NADH-dependent reduction of trans-2-enoyl Acyl Carrier Protein (ACP) to ACP is mediated by enoyl acyl carrier protein reductase enzyme (PfENR), which is a crucial step in the biosynthesis of fatty acids. Hence, PfENR inhibitors could be possible drug candidate molecules for preventing the onset of malaria.Pyridazine inhibitors are well known for their anti-malarial activity[5]. In the current study, insilico methods are exploited to identify effect of a

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pyridazine derivative, sulfacholoropyridazine in elliciting PfENR inhibition.

II. MATERIALS AND METHODS

Preparation of Ligand Structure

Structure of sulfachloropyridazine was obtained from PubChem. Two-Dimesional (2D) structure of chemical compound was drawn in MarvinSketch. 2D structure was converted into Three Dimensional (3D) structure after addition of explicit hydrogens. Optimized 3D structure in .mol format was converted into SDF format by OpenBabel, which is a computer software used for conversion of chemical file formats.

Oral bioavailability Prediction

Oral bioavailability of chemical compound is done by Molinspiration. Oral bioavailability is governed by Lipinski's rule of five which states that an orally active drug should not have more than one violation of following criteria:

Hydrogen bond acceptors should not be more than 10,Hydrogen bond donors should not be more than 5, Molecular weight should not be more than 500 Da and partition coefficient (log p) should be less than 5[6].

Toxicity Assessment

Assessment of toxicity was done by ProTox-II, which is an online based server used for the identification of toxicity of chemical compounds. SMILES format of chemical compound is given as input for the prediction of toxicities such as hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity.

Active Site Prediction – Target Protein

Retrieval of target protein was done from Research Collaboratory for Structural Bioinformatics (RCSB) PDB database. Prediction of active sites were done by computational tools such as CastP[7] and ScanProsite[8]. Reported binding sites of protein was identified from literature and comparative analysis of binding sites obtained from all three sources were done. Excecution of comparative analysis confirms potential binding sites of protein for targeted biological activity.

Docking Studies

Execution of docking studies was done by FlexX[9], which exploits incremental construction algorithm. This algorithm is based on the reconstruction of bound ligand by first placing a rigid anchor in the binding site and later using a greedy algorithm to add fragments and complete ligand structure[10]. 3D structure of ligand in SDF format was given as input for docking study. 100 poses of ligand were docked into the active site of protein by considering all possible stereochemical conformations of ligand such as R/S, E/Z and pseudo R/S.

Prediction of Binding Affinity

Binding affinity prediction was done by PyRx[11], which is an open source software platform to predict binding affinity by the execution of docking.

III. RESULTS

Molinspiration data results

Oral bioavailability prediction was done by Molinspiration. Sulfachloropyridazine has got zero violations, which indicates that compound has got promising bioavailability. Predicted values for important factors governing oral bioavailability is given in Table 1.

Toxicity Assessment

Prediction of toxicity was done by Pro-Tox II. Carcinogenicity, Immunotoxicity, Mutagenicity and Cytotoxicity were the toxicity endpoints considered for this study. Sulfachloropyridazine is inactive for all the toxicity endpoints calculated. Hence,this compound is a promising drug candidate for the treatment of falciparum malaria. Details of toxicity prediction is given in Table 2.

Table 1: Molinspiration results for Sulfachloropyridazine

Property	Values
miLogP	1.39
TPSA	97.98
MW	284.73
noN	6
nOHNH	3
nViolations	0
nrotb	3
volume	215.8

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Table 2: Toxicity results for Sulfachloropyridazine

Toxicity end points	Predicted activity
Carcinogenicity	Inactive
Immunotoxicity	Inactive
Mutagenicity	Inactive
Cytotoxicity	Inactive

Active site prediction and Docking Studies

Active site prediction was done by comparing results obtained from computational tools such as CastP, ScanProsite and through literature reviews. Identified binding sites for protein Malarial enoyl acyl ACP reductase, (PDB ID: 2NQ8) include Trp131, Leu216, Asn218, Lys240, Ala169,Ala319,Lys285, Tyr267, Leu315, Asp168, Ser317, Ile105, Ala319 and Tyr111**.**Docking study was carried out by FlexX. Details of docking results are given in Table 3. Dock score of the protein with ligand is -17.33. Dock score emphasize on the potential of ligand to interact with the protein. Ala 169 and Trp131 residues of protein made hydrogen bond interactions with the ligand. Ala319, Asn218,Leu216, Ala169, Lys240 and Trp131 showed hydrophobic interactions with protein. Fig .1 Depicts 2D representation of docking.Prediction of binding affinity was done by Pyrex. Binding affinity between protein and ligand was -9.76.

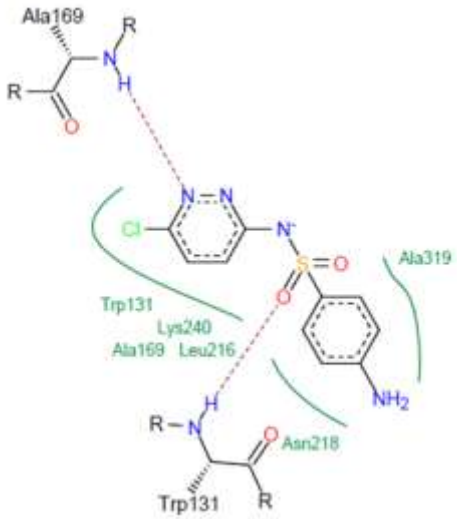

Fig.1 Depicts 2D representation of Protein-ligand interaction

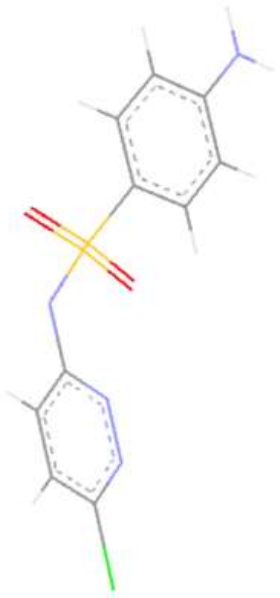

Fig.2 Best binding pose of ligand

IV. DISCUSSION

Anti-malarial activity of pyridazine derivatives are well known. Hence, sulfachloropyridazine, a derivative of pyridazine was analyzed for it's anti-malarial activity by executing computational methods. Oral bioavailability prediction and toxicity prediction proved that sulfachloropyridazine is an ideal drug candidate. Fig.2 shows the best pose with least binding energy, which was obtained by using FlexX. Compound showed hydrogen bonding as well as hydrophobic interactions with the target protein. Hence, sulfachloropyridazine will be an ideal drug candidate for the treatment of malaria.

V. CONCLUSION

Aim of the present study was to identify an effective drug candidate molecule against Plasmodium falciparum, which is the causative agent for falciparum malaria. Pyridazine derivative, sulfachloropyridazine was selected for the study. Bioavailability and toxicity was predicted for the ligand by using computational tools. Further docking study was executed to identify the binding efficacy of the compound with the target Malarial enoyl acyl ACP reductase, (PDB ID: 2NQ8). Highly negative dock score was obtained. Highly negative binding affinity of -9.76 was obtained. Hydrogen bonding and hydrophobic interactions were prevalent in the protein-ligand complex. Hence, sulfachloropyridazine can act as an effective inhibitor for Malarial enoyl acyl ACP reductase.

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