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Short Communication

IN SILICO SCREENING OF FEW ANTI MALARIAL DRUGS AS THE INHIBITOR OF OROTIDINE 5-MONOPHOSPHATE DECARBOXYLASE

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Abstract:
The pyrimidine nucleotides like uridine triphosphate, cytidine triphosphate, and thymidine triphosphate are building blocks of DNA and RNA. *Plasmodium falciparum* is a human malaria parasite, can only synthesize pyrimidine nucleotides using the de novo pathway, whereas mammalian cells obtain pyrimidine nucleotides from both the de novo and salvage pathways. Orotidine 5'-phosphate decarboxylase is an enzyme involved in pyrimidine biosynthesis and catalyzes the decarboxylation of orotidine monophosphate to uridine monophosphate . The parasite's orotate phosphoribosyl transferase and orotidine 5'-monophosphate decarboxylase of the de novo pyrimidine pathway are attractive targets for antimalarial drug development. The aim of the present article is to *In silico* screen of few antimalarial drugs against orotidine 5 monophosphate. The PDB file of orotidine 5- phosphate decarboxylase is downloaded from protein data bank. The PDB ID is 2ZA1. Ten antimalarial drugs were choosen as ligands. The smiles notation of the antimalarial drugs were downloaded from drug data bank and converted to pdb file. The docking is performed using the online Hex docking server. The interaction between the drug and the receptor has been studied. The binding energies obtained are given below Atovoquone -2.89, chloroquine -3.17, Doxicycline -3.19, halofantrine -5.52, lumifantrine -3.98, mefloquine -5.80, primaquine -2.49, proguanil-2.72, pyrimethamine -2.55, quinine -2.64. Mefloquine and Halofantrine have good binding energies with orotidine 5- monophosphate decarboxylase.

Key words: Malaria, *In silico* screening, orotidine 5 monophosphate, online Hex server

Introduction

Malaria is a dreadful disease affecting 300 million people and killing 1.5 million people every year. Human malaria can be caused by the transmission of any of the four different species of Plasmodium protozoa, namely Plasmodium malariae, Plasmodium ovale, Plasmodium vivax and Plasmodium falciparum, with the latter being the most deadly strain (WHO, 2010). A

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fifth species, Plasmodium knowlesi, which is known to infect primates, has been seen in recent years.

Malarial parasites are gaining resistant against the drug which is being used currently. In order to counteract the resistance gained by the parasite, in silico screening technique is used to synthesis new molecular entities. The *In silico* screening methods are remarkably successful, however in identifying and advancing a promising area of antimalarial chemistry with a very limited expenditure of time and money.

The pyrimidine nucleotides like uridine triphosphate, cytidine triphosphate, and thymidine triphosphate are building blocks of DNA and RNA. *Plasmodium falciparum* is a human malaria parasite, can only synthesize pyrimidine nucleotides using the de novo pathway, whereas mammalian cells obtain pyrimidine nucleotides from both the de novo and salvage pathways. Orotidine 5'-phosphate decarboxylase is an enzyme involved in pyrimidine biosynthesis and catalyzes the decarboxylation of orotidine monophosphate to uridine monophosphate . A defective *Plasmodium falciparum* orotidine 5'-monophosphate decarboxylase enzyme is lethal to the parasite. The presence of X-ray crystal structure data makes both the selected proteins as ideal targets for antimalarial therapy using new approaches in rational drug design. In the present study, orotidine 5'-monophosphate decarboxylase enzyme is selected as the target for designing of novel potent antimalarial drugs. (Yasuhide Takashima et.al, 2012).

Methods and Materials

For our present work biological databases [drug data bank, protein data bank] and online software [online hex server], online smiles translator, pdb sum were used.

Preparation of Ligand: Ten antimalarial drugs were choosen as ligands. The smiles notation of the antimalarial drugs were downloaded from drug data bank and converted to pdb file using online smiles translator. (www.cactus.nci.nih.gov)

Preparation of Protein: Crystal structure of orotidine 5- mono phosphate decarboxylase complexed with orotidine 5 mono phosphate from P. falciparum is downloaded from protein data bank. The PDB ID is 2ZA1. The resolution of the protein is 2.65°A.The figure shows the 3 D structure of the receptor. The bound orotidine 5 mono phosphate is removed and saved. (www.rscb.org)

Docking: The docking analysis is performed using the online Hex docking server. The interaction between the drug and the receptor has been studied. Docking allows the scientist to virtually screen compounds and predict the strongest binders based on various scoring functions. The molecule bind to enzyme, inhibit its function and thus act as drug. The parameters used for the docking process via hex docking were correlation type which was chosen as shape and electrostatic and other parameters were chosen as default. (www.hex.loria.fr)

Results and Discussion

Halofantrine exhibits very good interactions with orotidine 5- monophosphate decarboxylase compared to other antimalarials. It shows binding energy of -5.52 Kcal/mol with five hydrogen bond formation. The hydrogen present in hydroxyl group of tyrosine127A forms hydrogen bond with oxygen of halofantrine and another hydrogen bond with ASN130A. The oxygen of Halofantrine also forms two hydrogen bond with LYS 9A. The fifth hydrogen bond is formed with Met1A. Thus from the binding energy and hydrogen bond interaction it can be confirmed that halofantrine inhibit the enzyme orotidine 5-monophosphate decarboxylase. Mefloquine next to halofantrine shows good activity. It shows binding energy of – 5.82 K cal/mol and forms two hydrogen bond with LYS 182A and LYS 184A but the length is 6.35°A and 7.85°A. The binding energy of mefloquine is more but the number of hydrogen bonds formed will be less compared to halofantrine. It was found that if the drugs are targeting the binding residue Met1A, they exhibited good binding energy for

example chloroquine, doxycycline halofantrine, lumifantrine and mefloquine. From the above analysis, the best binding site for the drug in the enzyme are Met1A, LYS 158A, TYR 186A. All the drugs were found bound to the target. The residues around the ligand interacting with protein are Tyrosine, Lysine, aspargine etc. All the drugs exhibit good binding energy. Among the antimalarial drugs choosen Halofantrine and Mefloquine showed good binding energies with orotidine 5- monophosphate decarboxylase.

Table.1. Binding Energies and Interacting Residues of the Protein and Anti Malarial Drugs

Drug Name	Binding Energy Kcal/mol	Interacting residues	Number of hydrogen bond
Atovoquone	-2.89	ILE 58B,SER113A,LYS 120B GLU150B	-
Chloroquine	-3.17	Met 1A,Phe3A, ASN 233A,LYS 184A	-
Doxicycline	-3.19	TYR185A,TYR 186A,Met1A,TYR127A	-
Halofantrine	-5.52	LYS158A,SER159A, Tyr186A,TYR127A,Met1A ASP130A,LYS9A	5
Lumifantrine	-3.98	LYS6A, Met1A,TYR127A LYS 158A ASP160A	-
Mefloquine	-5.80	LYS182A,LYS184A,TYR186A LYS158A Met1A	2
Primaquine	-2.49	Lys158A,Phe154A	-
Proguanil	-2.72	TYR185A,TYR186A,LYS 184A,ASN183A	-
Pyrimethamine	-2.55	Tyr127A,LYS158A,ASP160A	-
Quinine	-2.64	TYR 185A,LYS 184A, ASN 233A	-

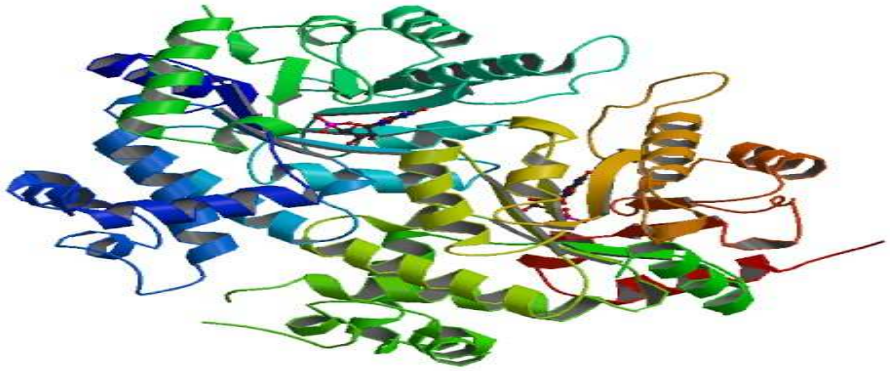

Figure.1.Structure of protein orotidine 5 mono phosphate decarboxylase PDB ID 2ZA1

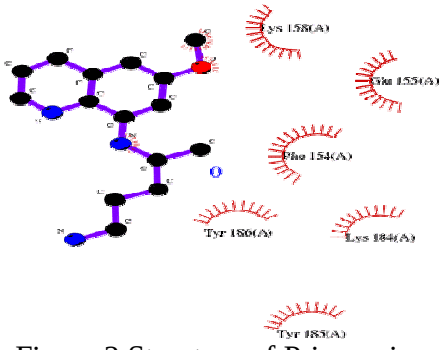

Figure.2.Structure of Primaquine

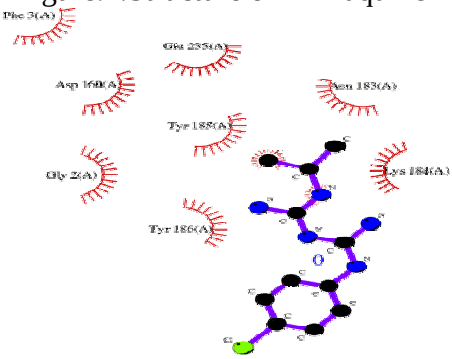

Figure.3.Structure of Proguanil

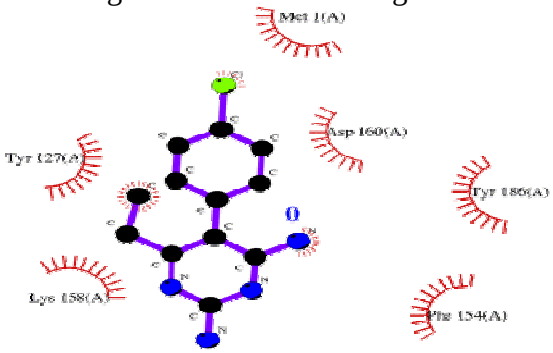

Figure.4.Structure of pyrimethamine

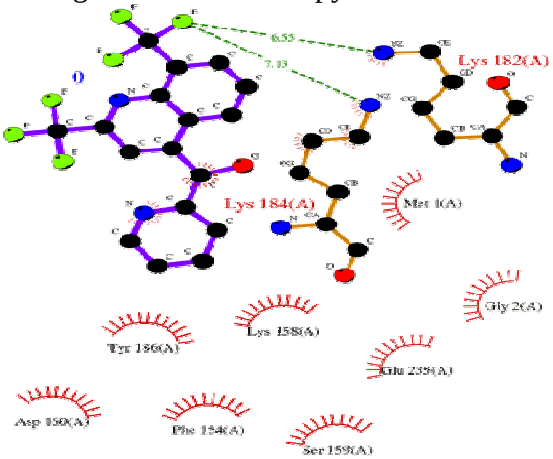

Figure.5.Structure of Mefloquine

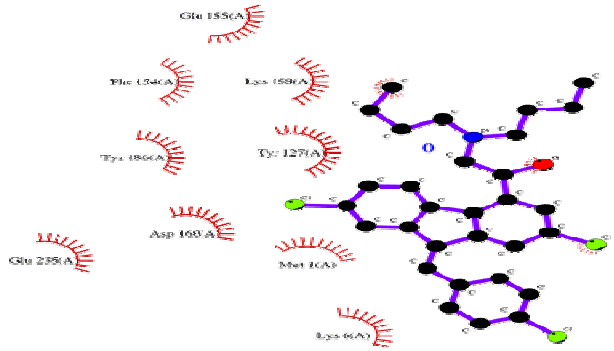

Figure.6.Structure of Lumifantrine

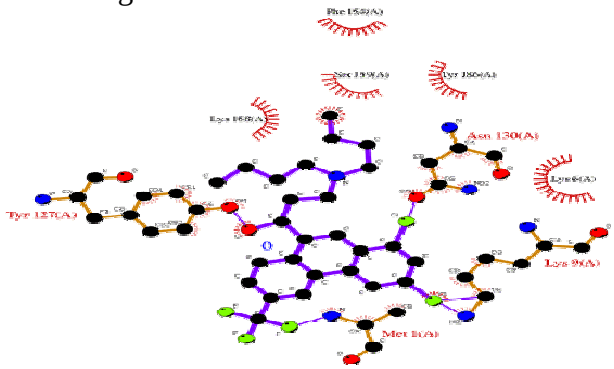

Figure.7.Structure of Halofantrine

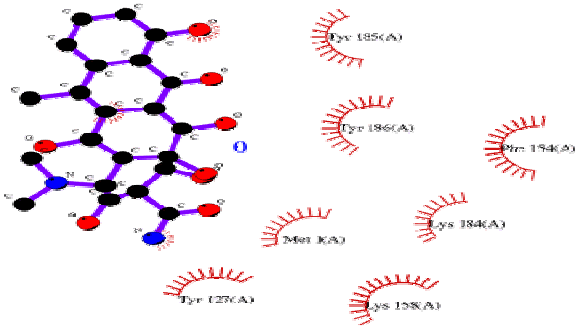

Figure.8.Structure of Doxycycline

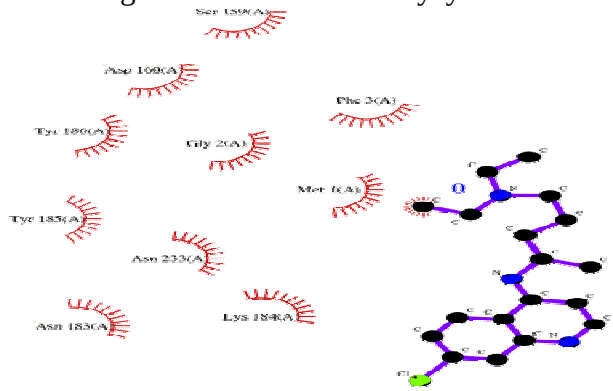

Figure.9.Structure of Chloroquine

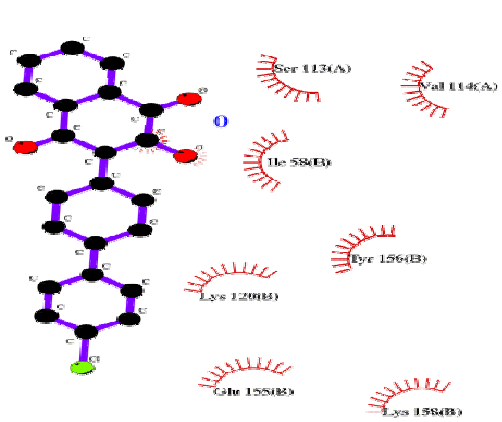

Figure.10.Structure of Atovoquone

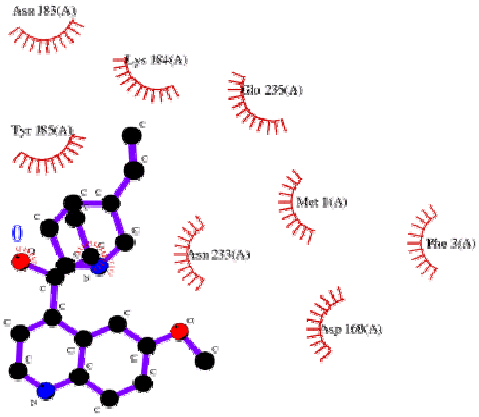

Figure.11.Structure of Quinine

Conclusion

In this study, *In silico* screening of few antimalarial drug were performed against the orotidine 5 mono phosphate. Halofantrine and Mefloquine showed good binding energies but in case of the presence of hydrogen bonding halofantrine showed the presence of five hydrogen bonds whereas Mefloquine showed only two hydrogen bonds. Hence Halofantrine can be targeted against the orotidine 5 monophosphate in malarial patient. Computational studies have been developed to unravel the mechanism of action of the anti-malarial drugs and to give guidelines for the development of new derivatives with improved efficiency.

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