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IN SILICO DESIGN OF DAPSONE ANALOGUES EFFECTIVE TOWARDS ENOYL ACYL CARRIER PROTEIN REDUCTASE ENZYME OF MYCOBACTERIUM LEPRAE

Sujit Kumar Sahu, Priyanka Mohanty and Mrityunjay Banerjee*

Institute of Pharmacy and Technology, Salipur, Cuttack, Odisha-754202.

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***Corresponding Author**
Mrityunjay Banerjee
Institute of Pharmacy and Technology, Salipur, Cuttack, Odisha-754202.

ABSTRACT

Aseries of new antileprotic drugs targeting enoyl acyl carrier protein reductase (ENR) enzyme of *Mycobacterium leprae*were designed by *in silico* techniques. Major focus of the research work was to probe whether the substituted derivatives of dapsone would bind to target protein i.e ENR and if so, then how strongly. The 3D structure data of target protein for leprosy was derived from protein data bank (PDB). Multiple structureswere drawn and ADMET propertieswere calculated by Medchem Designer software. Parameters like logP, logD, logM, molecular weight, number of H-bond accepters and donors for all the designed molecules were calculated. Substituted dapsone derivatives violating Lipinski's rule of drug-likeness were rejected. Compounds having acceptable drug-likeness were subjected to molecular docking study against enoyl acyl carrier protein reductase (ENR) enzyme of *Mycobacterium leprae.* Moleculardocking of the designed compounds was carried out by using HeX version 5.1. Docking results of proposed compoundsagainst ENR of *Mycobacterium leprae*were compared with the standard dapsone to establish the pharmacodynamic efficiency. Overall *in silico* study generated few dapsone analogues with promising druggability and receptor binding interactions against *M. leprae* ENR.

KEYWORDS: Antimalarial agents, chloroquine derivatives, pfLactate dehydrogenase.

INTRODUCTION

Intracellular microorganism, Mycobacterium leprae are the causative factor of infectious disease of Leprosy. This disease currently affects approximately a quarter of a million people throughout the globe, with majority of cases being reported in India 1. Chaulmoogra oil had

been used for leprosy treatment but its efficacy was partial and relapse was common 2. No effective drug was available for leprosy until introduction of Dapsone in the early 1940's. Soon the bacteria developed resistance for Dapsone. After 1980's multi drug therapy (MDT) was introduced in which the drugs Dapsone, Clofazimine and Rifampicin were used in combination and found effective 3-7. But it was expensive and its long term treatment led to resistance. So, there is an urgent need for the development of novel antileprosy drug candidates. The main objective of this work to design new molecule candidates more quickly by using computational techniques effective towards Mycobacterium leprae (PDB ID:-1ZID).

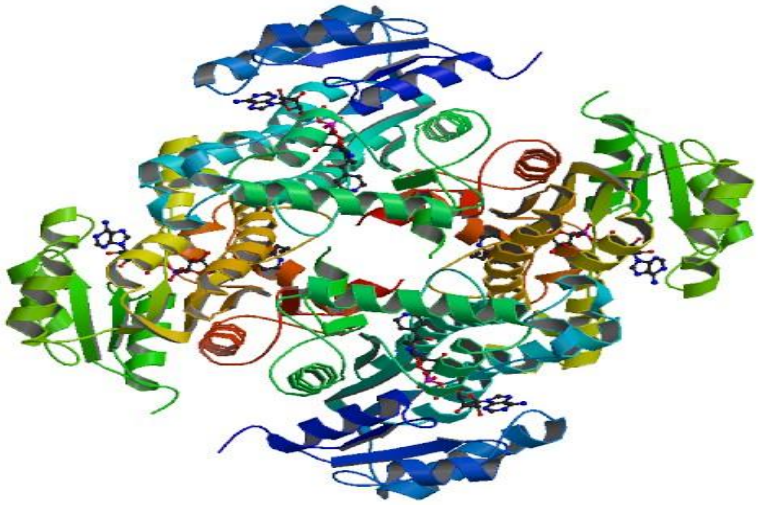
MATERIALS AND METHODS

Preparation of protein: The crystal structure of selected protein target enoyl acyl carrier protein reductase (ENR) enzyme of *Mycobacterium leprae*were was available PDB ID: 1ZID (www.rcsb.org).

Molecular Modeling Studies: Molecular modeling studies have been carried out using HEX 5.1 & MVD (Grid-based Ligand Docking with Energetics) software Molegro Virtual Docker version 5.5 workspace was used for all the steps involved in ligand preparation, protein preparation and docking. ACD Chem Sketch is chemical drawing software developed by ACD LAB. The software is user-friendly, provides all details of drawn structures and helped to calculate chemical properties, design professional reports and presentations.

Ligand Preparation: The ligands used in this study were prepared using ARGUS LAB (Optimized Potential Liquid Simulations for All Atoms) force fields for energy minimization. c) Protein Preparation. The X-ray crystal structures retrieved from PDB database as raw could not be suitable for molecular docking studies. A typical PDB structure consists only of heavy atoms, waters, Cofactors, metal ions and can be of multimeric. These structures do not have the information about bond orders, topologies or formal atomic charges. So, the raw PDB structure should be prepared in a suitable manner for docking. Protein Preparation Wizard of MVD (Grid-based Ligand Docking with Energetics) software Molegro Virtual Docker version 5.5 workspace was used to process and prepare the protein. This also follows the Optimized Potential for Liquid Simulations-All Atoms (OPLS-AA) force fields for energy minimization. ADMET Study by Medchem desiner 2.0.

ENOYL ACYL CARRIER PROTEIN REDUCTASE (PDB ID:-1ZID)



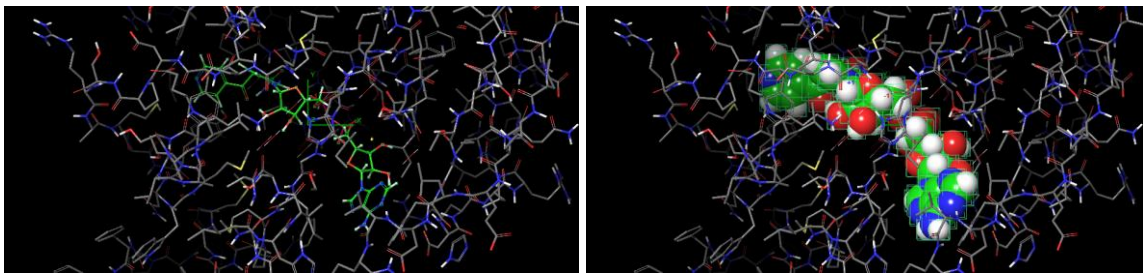
ADMET Characteristics of Dapsone & Proposed Molecules effective towards Mycobacterium leprae.

COMP	logP	M.wt	HBDH	TPSA
DVT 1	2.100	247.317	2.000	60.160
DVT 2	1.449	277.300	3.000	97.460
DVT 3	1.575	275.328	2.000	72.230
DVT 4	0.516	276.316	4.000	103.250
DAPSONE	0.807	248.305	4.000	86.180

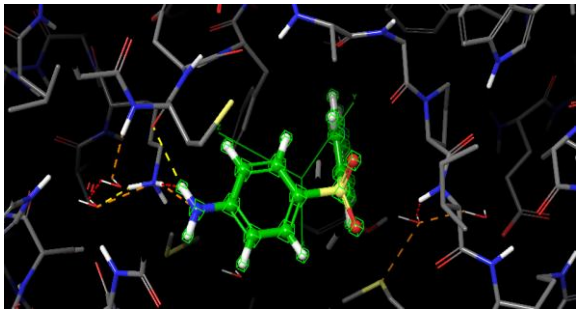
Docking results of standard and proposed molecules which follows Lipinski Rule.

COMPOUND Code	DOCKING VALUE
DVT 1	-171.49
DVT 2	-181.18
DVT 3	-206.86
DVT 4	-183.79
DAPSONE	-171.69

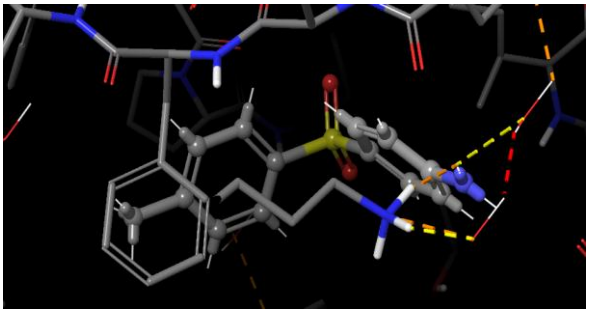
Molecule with protein ENOYL ACYL CARRIER PROTEIN REDUCTASE (PDB ID:-1ZID)



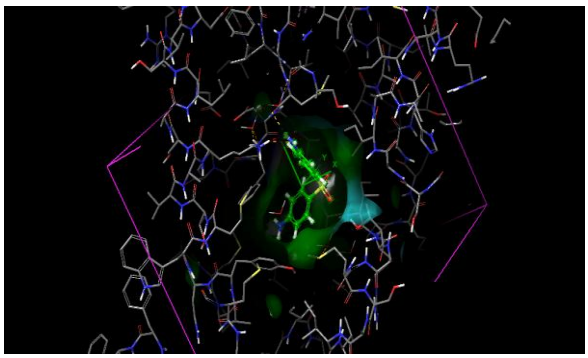
Hydrogen Bonding of Dapsone & Dapsone Derivative With Enoyl Acyl Carrier Protein Reductase(PDB ID:-1ZID).

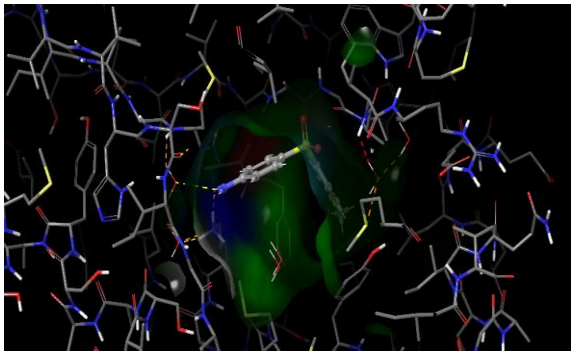


Surface binding site of protein with dapsone

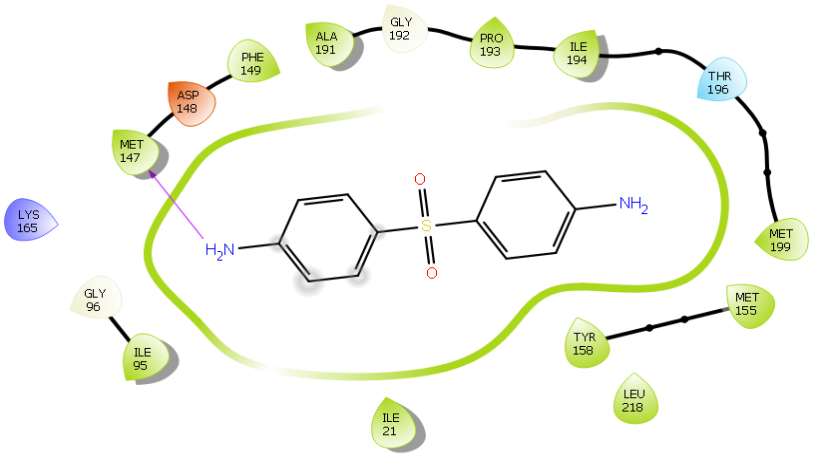


Surface binding site of protein with dapsone derivative (DVT 3)





Ligand (Dapsone) Interaction with Protein (1ZID)



CONCLUSION

HANSEN'S DISEASE and chronic infectious like skin, upper respiratory tract, eyes, nasal mucosa effective towards Mycobacterium leprosy. In usual practice physicians prescribe marketed established antileprosy drug like Dapsone, Clofazimine, Rifampicin, Ethionamide, Ofloxacin, Moxifloxacin, Minocycline, Clarithromycine etc. for its management. EACP REDUCTASE (PDB ID: 1ZID) are enzyme vitally important for survival and proliferation of gram positive bacteria Mycobacterium leprae.

This investigation was to determine the comparative efficacy & docking affinity of commonly used standard molecule or my proposed molecules on targeting 3D model 1ZID structure, using in silico techniques by different computational drug designing Sources & software's i.e, RCSB PROTEIN DATA BANK, MED CHEM DESIGNER, CHEM SKETCH, HEX 5.1, ARGUS LAB, MDL MOL FILE, BROOKHAVEN PDB FILE, SCRODINGER LAB etc.

After energy minimization of 3D structure of ENOYL ACYL CARRIER PROTEIN REDUCTASE (CODE ID :-PDB 1ZID) it was docked with Energy minimized marketed anti leprosy standard molecule & proposed molecules by using docking software HEX5.1.The inhibitors binding efficacy & affinities were determined using HEX docking scoring (Etotal negative value) fitness function. The application on computational science (In silico drug designing) to pharmaceutical research is a discipline, which is phenomenal.

In this simple & elegance studies revealed efficacy using Dapsone and four proposed molecules were targeted against EACP REDUCTASE (PDB ID: 1ZID). After accessing all docking results it can be observed that the proposed molecule **DVT 3** may have the better docking affinity (Etotal: --206.86 value) compared to DAPSONE (Etotal: -171.69). While proposed **DVT 3** (Etotal: -206.86) found appreciable docking score higher than marketed prescribed DAPSONE) which were usually used in staphylococcus aureus infected diseases like psoriasis and other skin infection. So Present observation strengthened the hypothesis for development of new antileprotic agents which can inhibit EACP reductase (PDB ID: 1ZID) of Mycobacterium leprae.

Finally it can be concluded from this reported studies, molecule like Dapsone may be a new class of potent anti leprosy analogue dock to MET 147 of 1ZID respectively through hydrogen bonding for staphylococcus aureus which causes infection like Hansens disease. Moreover, further exploration for detailed mechanism of action of these compounds is required to be investigated before declaring them as safe as well as potent therapeutic agents.

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