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Title of thesis : **"In silico identification of potential inhibitors of drug targets in Plasmodium falciparum and design of target oriented virtual compound library"**

Abstract

Malaria is the most pervasive and debilitating disease that kills one million people every year. The problem is exacerbated by the increasing resistance of human malaria parasite, *Plasmodium falciparum* to the existing antimalarials. Hence there is a pressing need to discover novel antimalarial compounds ideally targeted towards the novel drug targets. To address this issue, the present work focuses on *in silico* lead identification and development of target oriented virtual compound library against two novel drug targets of *P. falciparum* to facilitate antimalarial drug discovery.

The ubiquitin-proteasome system plays a crucial role in protein degradation, especially in the eukaryotic cells including plasmodia. 20S β subunit is the catalytic core of this proteolytic system, and hence inhibition of the 20S β subunit is established as a promising strategy to develop novel antimalarial drugs. The present study reports the identification of several novel drug-like leads with potential activity against the 20S β subunit of Plasmodium falciparum using a combination of ligand based (Support Vector Machines (SVM)) and receptor based (molecular docking) techniques. We have developed a highly accurate SVM model trained using 170 molecular descriptors of 64 proteasome inhibitors and 208 putative non-inhibitors to rapidly screen proteasome inhibitors from NCI library.

The SVM model classification accuracy of 97% rapidly classified compounds with potential proteasomal activity, that were subsequently docked into the three dimensional models of 20S β5 subunit. As a result of this study, a target oriented virtual library of compounds with potential activity against 20S β subunit is made publically available. The novel drug-like 20S proteasome inhibitors identified in this study can be a good starting point to develop novel antimalarial drugs.

Plasmodium falciparum possess, a less complicated 'prokaryotic proteasome' machinery namely HslUV in addition to 20S proteasome subunits. PfHslV, an ATP dependent threonine protease is a homolog of β subunit of 20S proteasome and forms the proteolytic core of the PfHslUV machinery. PfHslV has no homolog in the human host and it has been established as a promising drug target essential to the plasmodial metabolism. Using a receptor based virtual screening approach, we discover in the present study several potential inhibitors that showed good binding affinity to the PfHslV subunit. Homology modeling combined with protein-protein docking and computational alanine scanning has been carried in the present work out to predict the interaction between PfHslU and PfHslV subunits. The key residues participating in the protein-protein interface of PfHslUV complex have been identified.

In addition to the above, we have also developed a SVM based model for prediction of proliferation inhibitors of P. falciparum in erythrocytes based on PubChem bioassay database. Proliferation inhibitors targeting Plasmodium falciparum intraerythrocytic cycle are one of the important classes of compounds with a great potential to be novel anti-malarials. SVM based model developed in this study can facilitate rapid screening of large and diverse chemical libraries by reducing false hits and prioritizing compounds before setting up expensive high throughput screening experiment. The novel leads identified in this study against various drug targets can be a good starting point to develop novel antimalarial drugs.