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*An in silico structural insights into Plasmodium LytB protein and its inhibition*

R. Bhunya[1], S. Nandy[2], A. Seal[3]

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In most of the pathogenic organisms including Plasmodium falciparum, isoprenoids are synthesized via MEP (MethylErythritol 4-Phosphate) pathway. LytB is the last enzyme of this pathway which catalyzes the conversion of (E)-4-hydroxy-3-methylbut-2-en-1-yl diphosphate (HMBPP) into the two isoprenoid precursors: isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). Since the MEP pathway is not used by humans, it represents an attractive target for the development of new antimalarial compounds or inhibitors. Here a systematic in-silico study has been conducted to get an insight into the structure of Plasmodium lytB as well as its affinities towards different inhibitors. We used comparative modeling technique to predict the three dimensional (3D) structure of Plasmodium LytB taking E. Coli LytB protein (PDB ID: 3KE8) as template and the model was subsequently refined through molecular dynamics (MD) simulation. A large ligand dataset containing diphospate group was subjected for virtual screening against the target using GOLD 5.2 program. Considering the mode of binding and affinities, 17 leads were selected on basis of binding energies in comparison to its substrate HMBPP (Gold.Chemscore.DG: -20.9734 kcal/mol). Among them, 5 were discarded because of their inhibitory activity towards other human enzymes. The rest 12 potential leads carry all the properties of any “drug like” molecule and the knowledge of Plasmodium LytB inhibitory mechanism which can provide valuable support for the antimalarial inhibitor design in future.

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