OMICS International
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Elumalai Pavadai et al., Med chem 2015, 5:10
http://dx.doi.org/10.4172/2161-0444.C1.016

4th International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
November 02-04, 2015 Atlanta, USA

New human malaria parasite *Plasmodium falciparum* dihydroorotate dehydrogenase inhibitors by pharmacophore and structure-based virtual screening

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Malaria continues to cause a severe global health problem as many approved drugs face widespread drug-resistance and no effective vaccines are available for this disease. *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) is an attractive drug target as it plays a key role in the de novo pyrimidine biosynthetic pathway, which *Plasmodium falciparum* depends exclusively on for survival. In this study, several 3D-QSAR pharmacophore models were developed based on the known PfDHODH inhibitors. The reliability of the models was validated using the external test set, cost analysis, Fischer's randomization method and virtual screening experiment. The result indicated that the Hypo 1 model is capable of discriminating between the active and inactive PfDHODH inhibitors and was accordingly employed as a 3D search query for virtual screening of the National Cancer Institute database. Subsequently, the hit compounds were refined in the PfDHODH binding site using molecular docking and Molecular Mechanics/Generalized Born Surface Area. The combination of the pharmacophore and structure-based virtual screening resulted in the identification of three PfDHODH inhibitors that showed IC_{50} values against the enzyme in the range of 0.38–20 μM. The most active compound also showed an IC50 value of 26 μM against the parasite as well as the species-selectivity over human DHODH. In addition to this, sixteen compounds inhibited parasite growth with IC50 ≤ 50 μM, four of which showed IC50 values in the range of 5–12 μM. The compounds may be further explored in the identification and development of more potent PfDHODH and parasite growth inhibitors.

Biography

Elumalai Pavadai is a Post-doctoral Research Fellow at the University of Cape Town (UCT) under the supervision of Prof. Kelly Chibale and Prof. Graham Jackson. He obtained his MSc in Biophysics from University of Madras and PhD in Engineering from National Taipei University of Technology, and then he had Post-doctoral trainings at Academia Sinica and National Yang Ming University. The focus of research at UCT is to identify and develop new inhibitors for Tuberculosis and Malaria targets by the use of various *in silico* approaches, including pharmacophore modeling, similarity search, combinatorial library design, de novo design and structure-based virtual screening.

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