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Computer-aided drug discovery of PI4KIIIβ inhibitor as anti-virus agent

Mahmoud A. A. Ibrahim, Alaa H. M. Abdelrahman, Alaa M. A. Hassan

Chemistry Department, Faculty of Science, Minia University, Minia 61519, Egypt

Malaria is one of the leading causes of death worldwide and it is accounted for the mortality of 1-3 million people every year[1]. Targeting plasmodium pathways provides a promising route for malaria treatment. Phosphatidylinositol 4-kinase type III beta (PI4KIIIβ) is known to be essential for the replication of many viruses such as Hepatitis C virus, West Nile virus, and Coronavirus. PI4KIIIβ is also important in malaria and inhibitors of PI4KIIIβ are potent anti-malarial agents[2]. The aim of the current study is to discover PI4KIIIβ-lead compounds towards malaria. The crystal structure of PI4KIIIβ (PDB code: 4D0L) was selected for the current study and all missing residues were built. Performance of Autodock4.2 software to predict the inhibitor-PI4KIIIβ binding energy was assessed based on five available ligand-PI4KIIIβ crystal structures. According to the results, Autodock predicts the binding energy in a good agreement with a correlation coefficient value of 0.91, compared to the calculated MM-GBSA//MM-MM. Based on the molecular mechanical-refined PI4KIIIβ structure, structure-based virtual screening of approximately 7 million lead-like molecules was performed using Autodock4.2 software. Top potent 10,000 lead compounds were then selected for further advanced docking using expensive calculations. According to the results, 68 lead compounds were identified as potent PI4KIIIβ inhibitors with binding energies better than all pre-published inhibitors ($\Delta G \geq 9.87$ kcal/mol). The potency of the selected compounds were further evaluated using MM-GBSA based on MMminimized structures. Moreover, lead optimization of the most potent inhibitor was performed in order to increase the PI4KIIIβ-inihibition efficiency. The presented results will serve as a foundation to discover novel rational anti-malaria inhibitors.