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In silico **evaluation of inhibitors of** ***Plasmodium falciparum*****AP2-I transcription factor**

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Abstract

Recent treatment failures observed for Artemisinin-based combination therapy (ACT) have raised concerns about the efficacy of the front-line drug to treat malaria and the need to develop a new antimalarial drug regimen. *Plasmodium falciparum* Apicomplexan Apetala 2 Invasion (*Pf*AP2-I) transcription factor (TF) is a protein that regulates the expression of a subset of gene families involved in *Plasmodium falciparum* red blood cell (RBC) invasion. Inhibiting *Pf*AP2-I TF with small molecules represents a potential new antimalarial therapeutic target to combat drug resistance, which is the aim

of this study. The 3D model structure of *Pf*AP2-I was predicted *ab initio* using ITASSER and ROBETTA prediction tools and was validated using Errat and Procheck from the Save server 6.0. Computed Atlas of Surface Topography of proteins (CASTp) 3.0 and *ConCavity* were used to predict the active sites of the *Pf*AP2-I 3D7 modeled structure. Pharmacophore modeling of the control ligand (3W7 from COACH server) and modeled 3D structure of *Pf*AP2-I was carried out using the Pharmit server to obtain several compounds for docking analysis. Chimera software was used to remove the complexed ligands, and the modeled protein structure was defined as a receptor. Virtual screening and post-screening studies were conducted using AutoDock vina and LigPlot. The designed ligands' toxicity predictions and *in silico* drug-likeness were performed using the Swiss ADME predictor and OSIRIS Property Explorer. The modeled protein from the ROBETTA prediction tool was prioritized based on structure validation results of 96.827 for ERRAT and 90.2% of the amino acid residues in the most favored region for the Ramachandran plot. A total of 8656 compounds obtained from six (6) databases on the Pharmit server were used to prepare the ligand library and screened against the prepared 3D model structure of *Pf*AP2-I, considering the active sites predicted from CASTp and *ConCavity*. Six (6) best hits were selected based on the binding affinity to the active site *Pf*AP2-I and were considered for post-screening analyses. The six compounds exhibited dock score values (between -9.9 to -10.2 kcal/mol), having lower binding energies than the standard drug - Chloroquine (-5.10 kcal/mol). The best dock score was compound ZINC97139187 (-10.2 kcal/mol). For the ADMET properties, compound ZINC97139187 had the highest drug score of 0.63, followed by compound 154861216 with a drug score of 0.58 (both higher than that of the standard drug - chloroquine of 0.25). The good, estimated binding energies and drug score values observed for compound ZINC97139187 and compound 154861216 suggest that they can be considered possible *Pf*AP2-I inhibitors. Further pre-clinical experimental validations should be carried out to ascertain the efficacy of these predicted best hits.

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