A pharmacophore model-based virtual screening workflow for identification of novel inhibitors towards plasmodium falciparum heat shock protein 90

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Introduction
The scourge of malaria in Africa, persist to burden the public health systems in spite of numerous management and treatment strategies employed, past and present. Amongst the validated targets is Plasmodium falciparum heat shock protein 90 (PfHsp90) which is essential for parasite survival. This study aimed to design small molecule inhibitors that can obtain selectivity towards PfHsp90 over corresponding homologues Hsp90 of human origin.

Methodology
A ligand-based pharmacophore model was developed using selective inhibitors with known IC_{50} towards PfHsp90 from previous studies. The enamine database containing a collection of 2.5 million drug-like compounds fulfilling the Lipinski's rule of 5 was scanned with the generated Pharmacophore hypothesis. Followed by a virtual screening workflow (VSW) using PfHsp90 (PDB CODE: 3K60) as receptor. To filter against compounds which may bind human Hsp90, crystal structure (PDB CODE: 1BYQ) was included for VSW as negative control. Induced fit docking was further performed to select hits for further purchasing and biological testing

Results and discussion
A total of 33214 hits were obtained from scanning the enamine database against the best pharmacophore hypothesis. Virtual screening workflow yielded 32 compounds that may selectively bind to PfHsp90. Application of stringent VWS and molecular docking enabled for filtering against hit which may potentially bind to human Hsp90. The resulting 13 compounds were subjected to induced fit docking. Based on the findings compounds F2, F3, F5 and F11 exhibited favorable binding poses with high XP GScores of -10.328, -10.924, -10.142 and -10.824 Kcal/mol, respectively. All 13 newly identified compounds are possibly binding selectively towards PfHsp90, hydrogen bond and pi-cation interaction with Arg98 which is a critical residue were obtained. The next steps would entail, purchasing the hits and evaluating the extent to their antimalarial inhibiting abilities through biochemical and biophysical analysis.

Keywords : PfHsp90; Malaria; Drug target; inhibition; Pharmacophore modelling; Virtual screening

References

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