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High Throughput Virtual Screening against ns3 Helicase of Japanese Encephalitis Virus (JEV)

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Abstract : Japanese Encephalitis is a major infectious disease with nearly half the world's population living in areas where it is prevalent. Currently, treatment for it involves only supportive care and symptom management through vaccination. Due to the lack of antiviral drugs against Japanese Encephalitis Virus (JEV), the quest for such agents remains a priority. For these reasons, simulation studies of drug targets against JEV are important. Towards this purpose, docking experiments of the kinase inhibitors were done against the chosen target NS3 helicase as it is a nucleoside binding protein. Previous efforts regarding computational drug design against JEV revealed some lead molecules by virtual screening using public domain software. To be more specific and accurate regarding finding leads, in this study a proprietary software Schrödinger-GLIDE has been used. Druggability of the pockets in the NS3 helicase crystal structure was first calculated by SITEMAP. Then the sites were screened according to compatibility with ATP. The site which is most compatible with ATP was selected as target. Virtual screening was performed by acquiring ligands from databases: KinaseSARfari, KinaseKnowledgebase and Published inhibitor Set using GLIDE. The 25 ligands with best docking scores from each database were re-docked in XP mode. Protein structure alignment of NS3 was performed using VAST against MMDB, and similar human proteins were docked to all the best scoring ligands. The low scoring ligands were chosen for further studies and the high scoring ligands were screened. Seventy-three ligands were listed as the best scoring ones after performing HTVS. Protein structure alignment of NS3 revealed 3 human proteins with RMSD values lesser than 2Å. Docking results with these three proteins revealed the inhibitors that can interfere and inhibit human proteins. Those inhibitors were screened. Among the ones left, those with docking scores worse than a threshold value were also removed to get the final hits. Analysis of the docked complexes through 2D interaction diagrams revealed the amino acid residues that are essential for ligand binding within the active site. Interaction analysis will help to find a strongly interacting scaffold among the hits. This experiment yielded 21 hits with the best docking scores which could be investigated further for their drug like properties. Aside from getting suitable leads, specific NS3 helicase-inhibitor interactions were identified. Selection of Target modification strategies complementing docking methodologies which can result in choosing better lead compounds are in progress. Those enhanced leads can lead to better in vitro testing.

Keywords : antivirals, docking, glide, high-throughput virtual screening, Japanese encephalitis, ns3 helicase
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