

DOCKING AND MACHINE LEARNING APPROACHES FOR THE ANALYSIS OF HCV NS5B SMALL MOLECULE BINDERS

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Molecular docking is a powerful tool for predicting both binding poses of ligands in target proteins and estimation of binding affinities. Also, docking can be efficiently used to discriminate potential binders from non-binders during drug discovery campaigns. HCV NS5B polymerase is a valuable target for antiviral drug therapeutics. Our goal was to analyze the ligand-binding site for HCV NS5B protein. We first benchmarked a NS5B-inhibitor complex sets to PALM I, II, III binding sites. Afterwards, compounds targeting NS5B with known affinity values (IC₅₀/K_d) from ChEMBL were classified as active and inactive, their potential binding sites were classified manually. Then we docked ligands into the proteins using SMINA and VINA software. We used protein–ligand interaction profiler (PLIP) [1] in order to analyze the distance between the ligands and our protein key amino acids. Also, we have calculated the RMSD of the ligands inside the binding site in comparison with minimal structure. We found out that PHE193,551 and TYR448 play an important role in pi-stacking interactions. Some mutations that happened in key positions (e.g. residue ASN316) of different proteins induce the change of binding affinity [2] at the allosteric binding site. The study of NS5B protein structure and its binding modes to small inhibitors can increase the likelihood of discovering significant new drugs that efficiently treat HCV infection.

References.

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2. Hang, J. Q. et al. Slow Binding Inhibition and Mechanism of Resistance of Non-nucleoside Polymerase Inhibitors of Hepatitis C Virus. // *J. Biol. Chem.* 284, 15517–15529 (2009)