ID 61

In-silico Structure Based Identification of Potential Human Gamma Secretase Inhibitor Ligands

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Gamma secretase (GSEC) is a multi-subunit transmembrane aspartyl protease complex that cleaves transmembrane (TM) domains of over 150 membrane proteins. GSEC plays a crucial role, at least in part during the pathogenesis and progression of different types of cancer types by downstream proteolitic processing of aberrantly activated NOTCH receptor (NR). Therefore, GSEC is considered as a potential target for anti-cancer drug design. However, there are no clinically approved GSEC inhibitors available to date. The main motive of this study was to identify potential GSEC inhibitors from the compounds of lipids map database. A Python script base pipeline was created for the conversion of the 2D molecular structure of the database to 3D structures followed by geometry optimization using an Amber force field. Molecular docking of 47500 geometry-optimized lipid like molecules and five known GSEC inhibitors (L685, 458, DAPT, Ganoderic Acid, Rutin and Semagastat) was performed against the active site of the GSEC using the Autodock vina program. Molecules that exhibited binding affinity lower than the best binding affinity value of known inhibitors (<-10.2 kcal/mol) were further screened for the drug-like properties. The top 5 most drug-like compounds were selected for further analysis. For these compounds, 100ns molecular dynamic (MD) simulation was performed in their natural membrane environment using Desmond (Schrodinger 2020.1). The stability of the complexes was assessed by evaluating root mean square deviation (RMSD), root mean square fluctuation (RMSF) and protein-ligand contacts during the simulation period. Molecular mechanics with generalized born and surface area solvation (MM/GBSA) calculation was executed for the three most stable complexes using 100 frames of each MD trajectory. Potential off-targets of the selected molecules were predicted by network analysis. Results indicated that Euchrenon a12, Euchrenon a14, and Euchrenon a15 are potential inhibitors of GSEC. However, further wet-lab experiments are needed to validate the results.

Keywords: *gamma-secretase, cancer, lipid-like molecules, mmgbsa*