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Probing binding affinity of human acetylcholine esterase for steroidal pregnanes as promising inhibitors through molecular modelling investigation

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Acetyl Choline Esterase (AChE) is one of the most important therapeutic targets for preventing and treating Alzheimer's disease. Studies have suggested the AChE inhibitory potential of pregnanes but the mechanism is still elusive. The aim of this study was to investigate the binding affinity of AChE enzyme for steroidal pregnanes in silico. Machine learning (ML) models were trained based on molecular fingerprints to rapidly screen a library of steroidal pregnanes retrieved from CHEMBL compound database for their half maximal inhibitory concentration (IC50) and inhibition constant (Ki) against AChE enzyme. Molecular docking, Molecular Dynamics (MD) simulation and MMGBSA free energy calculation were employed to further probe the binding affinity and decipher the binding interactions. Among 42 machine learning models assessed, Random Forest Regressor (RF) was a top model with high R-squared and low RMSE values. From 1,583 steroidal pregnanes, RF-based ML model screening revealed 843 pregnanes with pIC50 ≥ 5. Among these, 67 pregnanes with pKi ≥ 7 were suggested as promising AChE inhibitors. Atomistic simulations revealed 21-[(3-Hydroxy-2-naphthyl)oxy]pregnane-2-one (P1), 20-[2-(Imidazolidine-2-ylidene)hydrazono]pregnane-3beta-ol (P3) and 17-Hydroxy-3-oxo-19-nor-5beta,17alpha-pregnane-21-carboxylic acid, gamma-lactone (P4) as the Top Docking Pregnanes (TDPs). The top compound (P1) exhibited the best molecular contacts with the active site, interacting with the catalytic active site, peripheral anionic site (PAS), oxyanion hole and anionic sub-site through multiple hydrogen bonds and hydrophobic interactions. The AChE-TDP complexes exhibited structural stability and conformational flexibility in a dynamic environment. The RMSF plot revealed the interaction potentials of a loop around the PAS with TDPs. Also, P1 featured the strongest MMGBSA binding affinity (ΔG = -19.02±4.37 Kcal/mol) which was contributed mainly by key PAS residues. Furthermore, the TDPs were predicted to exhibit desirable drug-likeness, bioavailability and ability to cross the blood-brain barrier. Therefore, the in silico hits are suggested for experimental biophysical, biochemical and pre-clinical evaluation towards developing potent AChE inhibitors.

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