Discovery and Structure-Based Optimization of Highly Selective PTP1B Inhibitors: A Multi-Stage in silico Workflow Integrating Machine Learning for Ligand-Based Virtual Screening and Molecular Docking & Dynamics Simulations To Enhance Insulin Sensitivity in Type-2 Diabetes

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Diabetes Mellitus is a growing global epidemic, affecting over 500 million people worldwide. The condition is characterized by insulin resistance- failure of body's cells to respond effectively to insulin- leading to elevated blood sugar. While existing treatments manage symptoms, most fail to address insulin resistance resulting in multiple medications and side effects. The current study attempts to target this core problem by predicting inhibitors for Protein Tyrosine Phosphatase 1B (PTP1B, Uniprot ID: P18031), an enzyme that negatively regulates insulin signaling, leading to impaired glucose uptake in cells. Approximately 3,000 ChEMBL compounds were virtually screened using AutoDock Vina to identify potential PTP1B inhibitors, targeting the known binding site from crystal structures. The ligand was converted to PDBQT format with partial charges and rotatable bonds. The top 20 docking candidates were analyzed for hydrophobic centroids, aromatic rings, and hydrogen bonds. A total of 157 de novo molecules were generated using the REINVENT (AstraZeneca) program, followed by molecular docking, which identified the top five candidates, with the highest affinity score of -8.2 kcal/mol ($C_{22}H_{19}ClN_4O$). Protein preparation added atoms, set protonation, and used TIP3P water. To assess protein-ligand structural stability, a 200 ns molecular dynamics (MD) simulation was conducted with GROMACS for the top five compounds. The final RMSD value for protein-ligand was 2.82 Å for all atoms. ADMET and Lipinski's Rule of Five were used to evaluate drug-like properties and bioavailability. This study presents computationally designed compounds as potential treatments for type-2 diabetes, pending validation through binding assays, synthesis feasibility, and toxicity studies.

Awards Won: