Mechanistic Elucidation of CHSY1 Inhibition via a Multi-Scale Quantum-Informed Computational Drug Discovery Framework

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Spinal Cord Injuries (SCI) generally cause permanent functional loss due to the accumulation of inhibitory molecules, such as chondroitin sulfate proteoglycans (CSPGs), synthesized by a multi-enzymatic pathway. Post injury, glial cells rush to the injury site and form a glial scar to protect and stabilize the damaged tissue. However, over time, this environment becomes inhibitory as CSPG molecules are secreted into the glial scar, preventing neural regeneration and causing partial or complete paralysis. This project identified phytochemical-derived inhibitors, as they are well known for their therapeutic potential and structural diversity, that could target the multi-enzymatic pathway and reduce CSPG secretion using a multi-scale computational drug discovery framework. Initially, molecular docking was conducted to identify the strongest protein-ligand complex (CHSY1 and curcumin) based on binding affinity. Using this lead compound, several analogs were designed to improve binding interactions. Next, molecular dynamics simulations, principal component analysis, and Markov state modeling were used to evaluate stability and conformational dynamics. Density Functional Theory (DFT) was used to investigate the electronic structure, and Free Energy Perturbation calculations were used to identify the relative binding affinities of the designed analogs. The results indicated that the protein-ligand complex remained stable throughout the simulation and supported favorable binding interactions, and the analogs improved the binding affinities relative to solely curcumin. This research approach provided an accelerated pipeline for early-stage drug discovery as it enabled rapid screening of candidate molecules, potentially improving treatments for SCIs.

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