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A Hybrid ML-QSAR and Structure-Based Pipeline for Virtual Discovery of Potential GSK-3β Inhibitors

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Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder that leads to cognitive decline, impacting memory, thinking, and behavior. AD is closely associated with tau protein hyperphosphorylation, where glycogen synthase kinase-3β (GSK-3β) plays a central regulatory role. Targeting GSK-3β is therefore a promising therapeutic strategy. We developed an integrated computer-aided drug design (CADD) pipeline combining QSAR modeling, pharmacophore screening, molecular docking, and molecular dynamics (MD) simulations to screen for novel GSK-3β inhibitors. Initially, known GSK-3β inhibitors were collected and classified by IC_{50} values to train a QSAR model. This model was applied to a large, filtered compound library to efficiently enrich potential inhibitors. After pharmacophore screening against the ATP-binding site of GSK-3β (PDB ID: 1Q5K), the resulting candidates were subjected to molecular docking. Among them, only compounds achieving a higher docking score (Goldscore) than the natural substrate were further validated through MD simulations to assess binding stability. This QSAR-based structure workflow enhances the reliability of hit identification while reducing computational costs, presenting a rational strategy for discovering novel GSK-3β inhibitors with therapeutic potential for AD.