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Discovery of Potential GSK-3β Inhibitors: a combination of Pharmacophore Modeling, Molecular Docking, and Molecular Dynamics Simulation

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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 primarily associated with the abnormal accumulation of tau protein, which normally stabilizes neuronal microtubules. The hyperphosphorylation of tau protein has been identified as a major factor in its pathological accumulation. Glycogen synthase kinase-3 beta (GSK-3β) plays a key regulatory role in this process, making it a prominent therapeutic target for AD treatment. In this study, we applied computer-aided drug design (CADD) approaches to identify novel GSK-3β inhibitors. Initially, pharmacophore modeling was employed to screen and identify potential candidates based on the structural features of known GSK-3β inhibitors. Molecular docking simulations were then conducted to evaluate the binding interactions between the selected compounds and the active site of GSK-3β. Finally, the top candidates underwent molecular dynamics (MD) simulations to assess the stability and dynamics of the inhibitor-enzyme complexes over time, providing a deeper understanding of the binding efficacy at the atomic level. Our findings offer valuable insights into the rational design of novel GSK-3β inhibitors, contributing to the development of therapeutic strategies for Alzheimer's disease.