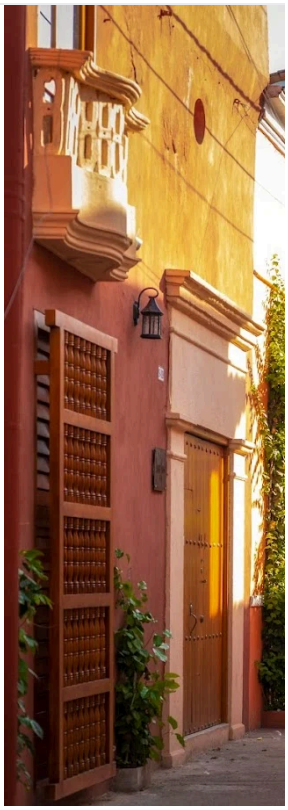

Quitel 2025

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Developing Generative AI Models to Design Novel Drug Candidates Targeting GSK-3β for Neurodegenerative Disorders, Cancer, and Diabetes

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Glycogen synthase kinase 3 beta (GSK-3β) is a serine/threonine kinase involved in a broad range of cellular processes, including glycogen metabolism, cell proliferation, differentiation, and apoptosis. Although initially characterized in the context of glycogen metabolism, GSK-3β plays a central role in key signaling pathways, such as Wnt and insulin signaling, and is critically involved in neuronal processes, including neurogenesis and synaptic plasticity. Dysregulation of GSK-3β activity has been associated with various pathological conditions, notably neurodegenerative diseases (e.g., Alzheimer's and Parkinson's diseases), psychiatric disorders (e.g., bipolar disorder), type 2 diabetes mellitus, and several forms of cancer. Due to its multifaceted involvement in disease, GSK-3β has emerged as a promising target for therapeutic intervention. However, the development of selective and efficacious GSK-3β inhibitors remains a significant challenge, primarily because of its ubiquitous expression and participation in multiple physiological pathways. In this study, we aimed to design novel GSK-3β inhibitors by integrating quantitative structure–activity relationship (QSAR) modeling with deep learning techniques and quantum chemical descriptors. A curated dataset comprising over 1,000 compounds with reported GSK-3β inhibitory activity was retrieved from the ChEMBL database. The molecular structures were geometry-optimized using density functional theory (DFT) at the B3LYP/6-311++G(d,p) level, and over 50 quantum chemical descriptors—including frontier molecular orbital energies, chemical hardness, and dipole moment—were calculated using the Gaussian16 and Multiwfn software packages. These descriptors were employed as input features for deep neural network models developed in Python, using the Scikit-learn, TensorFlow, and RDKit libraries, to predict GSK-3β inhibitory activity. Additionally, generative artificial intelligence (generative AI) techniques were utilized to design novel molecular entities with potential GSK-3β inhibitory profiles. The resulting models exhibited high predictive performance, as validated by k-fold cross-validation, the coefficient of determination (R^2), the external validation (Q^2), and y-randomization tests. A series of novel compounds were proposed, displaying favorable electronic and structural characteristics consistent with potent GSK-3β inhibition.

Keywords:

GSK3-β, QSAR, DFT, Deep learning, Generative AI.

Suggested Reading / References:

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