Drug Discovery of Novel Oxindole Derivatives as Multitarget Modulators in Alzheimer's Disease

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Alzheimer's disease (AD), a multifactorial neurodegenerative disorder, is associated with amyloid-beta aggregation, tau hyperphosphorylation, neuroinflammation, apoptosis, and endoplasmic reticulum (ER) stress. Current single-target therapies have limited clinical efficacy due to the interconnected nature of these pathological pathways. This study presents a computational biology framework to identify novel multitarget oxindole derivatives capable of modulating AD-relevant molecular networks. Initially, potential targets of oxindole derivatives were predicted using SwissTargetPrediction and cross-referenced with AD-associated genes from GeneCards to identify overlapping proteins. Protein–protein interaction networks were constructed to highlight hub proteins involved in neuroinflammation, apoptosis, and kinase signaling, followed by Gene Ontology and KEGG pathway enrichment analyses. Molecular docking studies with key proteins such as GSK3beta were performed to evaluate binding affinities, while 100 ns molecular dynamics simulations assessed complex stability. Binding free energies were estimated using MM/PBSA calculations. Virtual screening of 136 oxindole analogues expanded chemical diversity, and top candidates were evaluated experimentally in HT22 hippocampal neuronal cells under thapsigargin-induced ER stress. Preliminary results indicated that four compounds demonstrated low cytotoxicity and conferred protective effects, including modulation of beta-catenin signaling and inhibitory phosphorylation of GSK3beta. This integrated computational and experimental approach supports the development of multitarget therapeutics specifically for Alzheimer's disease.

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