10th Brazilian Conference on Natural Products
XXXVI RESEM
4-7 November 2025, Belo Horizonte, MG, Brazil
Section: 03

VIRTUAL SCREENING OF NATURAL PRODUCTS AS POTENTIAL INHIBITORS OF AMYLOID-BETA OLIGOMER-INDUCED NEUROTOXICITY

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Alzheimer's disease (AD) is the leading cause of dementia worldwide, pathologically characterized by the aggregation of the amyloid-beta (Aβ) peptide. During the Aβ aggregation pathway, various aggregate species are formed, including oligomers, protofibrils, and fibrils. Among these, soluble Aβ oligomers (AβOs) are considered the most neurotoxic species. Natural products (NPs) are recognized as a promising source of anti-amyloid compounds, including inhibitors of AβO-induced neurotoxicity[1]. Brazilian biodiversity offers a rich source of structurally diverse natural compounds with significant potential for new drug discovery. In this study, we investigated the NuBBE database (NuBBEDB)[2] using a virtual screening approach, combining molecular docking and ADMET profile prediction to identify potential inhibitors of Aβ oligomer-induced toxicity. A total of 2,363 compounds were docked into the AβO structure (PDB ID: 6RHY) using AutoDock Vina[3]. The top 50 hits with the highest binding affinities were selected for each binding site: the hydrophilic edge pocket (P0 e P1) and the hydrophobic core pocket (P2). To predict their ADMET profiles, these compounds were analyzed using the Admet_Risk module in ADMET Predictor® 13. A risk score cutoff of Admet_Risk ≤ 6.5 was applied to prioritize the safest and most promising candidates for experimental validation and BBB_Filter. High-risk candidates were excluded, and the remaining hits were ranked based on lower ADMET risk scores and high BBB penetration probability. As a result, 14 compounds simultaneously met the Admet_Risk ≤ 6.5 criterion and were approved by the BBB_Filter. These compounds belong to the chemical classes of 12 tri- and di-type polycycle terpenoids and two indolic alkaloids. These results highlight promising candidates for further experimental validation. Their final binding affinities ranged from –9.407 to –7.293 kcal/mol at the hydrophilic edge binding pockets (P1 e P0) and from –7.747 to –5.504 kcal/mol at the hydrophobic core binding pocket (P2), highlighting their potential as candidates for inhibitors of AβO-induced toxicity. Herein, our goal is to identify the most promising candidates for further investigation through biophysical assays and imaging techniques.

Keywords: Alzheimer's Disease, Anti-amyloids, Amyloid-beta, Oligomers, Virtual Screening, Molecular Docking.

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