Journal of Chemical Information and Modeling

Discovery of novel Acetylcholinesterase inhibitors by virtual screening, in vitro screening, and molecular dynamics simulations

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https://pubmed.ncbi.nlm.nih.gov/35139637/

Abstract

Alzheimer's disease is the most common neurodegenerative disease and currently poses a significant socioeconomic problem. This study describes the uses of computer-aided drug discovery techniques to identify novel inhibitors of acetylcholinesterase, a target for Alzheimer's disease. High-throughput virtual screening was employed to predict potential inhibitors of acetylcholinesterase. Validation of enrichment was performed with the DUD-E data set, showing that an ensemble of binding pocket conformations is critical when a diverse set of ligands are being screened. A total of 720 compounds were submitted for in vitro screening, which led to 25 hits being identified with IC50 values of less than 50 μM. The majority of these hits belonged to two scaffolds: 1-ethyl-3-methoxy-3-methylpyrrolidine and 1H-pyrrolo[3,2-c]pyridin-6-amine both of which are noted to be promising compounds for further optimization. As various possible binding poses were suggested from molecular docking, molecular dynamics simulations were employed to validate the poses. In the case of the most active compounds identified, a critical, stable water bridge formed deep within the binding pocket was identified potentially explaining in part the lack of activity for subsets of compounds that are not able to form this water bridge.