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IDENTIFICATION OF POTENTIAL INHIBITORS OF ACETYLCHOLINESTERASE USING PHARMACOPHORE-QSAR MODELING AND MOLECULAR DOCKING BASED VIRTUAL SCREENING FOR TREATMENT OF ALZEIHMER DISEASE

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Alzeihmer's is a chronic neurodegenerative disease associated with memory loss and behavioural changes. The cholinergic pathways important for cell to cell communication present in brain are known to be compromised in Alzeihmer's Disease (AD). The levels of acetylcholine, an important neurotransmitter for memory, are known to be low in the brains of persons with AD. Upregulation of the enzyme Acetylcholinesterase (AchE) is the major stimulant for increased breakdown of acetylcholine, leading to decreased levels of acetylcholine in the brain. The inhibition of this enzyme will increase the available acetylcholine for communication between brain cells. AchE is hence, an important drug target for the treatment of Alzheimer's disease. The aim of this work was to identify a novel small molecule which would inhibit AchE activity. We employed a dual pronged approach by integrating (i) ligand based 3D-pharmacophore & quantitative structure-activity relationship (QSAR) modeling approach to identify the potential hits and (ii) receptor's structure based molecular docking to calculate the potential binding mode and binding affinity of the hits. The pharmacophore based screening will help to reduce the false positives during molecular docking based screening since pharmacophore screening will initially elucidate the essential structural features required for the ligand recognition and inhibition of AchE. The best pharmacophore model was employed as a 3-D search query to screen Maybridge and LigCAP compound libraries having only Lipinski's compliant molecules to find hits. The obtained hits with the required pharmacophoric features were docked into the binding site of AchE to predict their binding mode and binding strength based on empirical scoring function. This pharmacophore-QSAR based modeling combined with a docking-based comparative approach led to identification of intermolecular contacts and detailed insights into the contribution of the structural moieties of the compounds towards their activity. We identified the best hits in terms of higher binding affinity as well as interactions with AchE. These compounds are potential inhibitors of AchE and can be a good drug lead. Hence, this work can provide the way forward for the development of drugs against Alzheimer's disease.

Keywords: *Acetylcholinesterase, Alzheimer's disease, AchE inhibitor, Pharmacophore, 3-D QSAR, Molecular Docking, Scoring Function.*