IN SILICO AND ENZYME ASSAY ANALYSIS OF ACETYLCHOLINESTERASE INHIBITORS: STRUCTURE AND LIGAND BASED DESIGN, PHARMACOPHORE MODELING AND VIRTUAL SCREENING

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Acetylcholinesterase (AChE) is a critical enzyme involved in neuronal synapses. The loss of cholinergic activity is mainly characterized by rapid hydrolysis of acetylcholine (ACh) by AChE, which leads to a neurodegenerative disease called Alzheimer’s disease (AD). The deposition of extracellular amyloid-beta peptide (Aβ) in senile plaques and the formation of neurofibrillary tangles containing hyperphosphorylated tau protein are neuropathological features of the disease. Inhibitors that act by inhibiting the double site of AChE influence the hydrolysis of ACh and the aggregation of the Aβ, which is dependent on the peripheral active site (PAS) of the AChE. Therefore, there is a reason to design new inhibitors of the AChE dual binding site. The aim of this work is design, assay and optimization of pharmacokinetic and pharmacodynamics properties of new lead compounds as future drug candidates for AD. Potential inhibitors were selected from a database of commercial drug-like compounds using different strategies of computational medicinal chemistry. The compounds selected showed good fitness in the AChE active site, suitable agreement to the pharmacophore model, and overlap with selected molecular interaction fields. Moreover, they have appropriate bioavailability and physicochemical properties, indicating ability to cross the blood brain barrier. Regarding the enzymatic assays performed, different models have been used, which show slight difference amongst them. Best results were obtained using the human AChE in solution, indicating up to 35% activity. Such compounds have also shown interesting selectivity regarding to the human AChE in comparison to the Electrophorus electricus enzyme.

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