Structure- and ligand-based drug design of novel p38 alpha MAPK inhibitors in the fight against the Alzheimer's disease.

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Alzheimer's disease (AD) was first characterized in 1907 by the german neuropathologist Alois Alzheimer, whose clinical symptoms includes cognitive, physiological and behavioral dysfunctions, memory loss, eventually incontinence, dementia, and death. It is a neurodegenerative disease of the central nervous system that usually affects individuals group in older age. This is characterized microscopically by the presence of amyloid plaques, which are accumulations of beta-amyloid protein inter-neurons, and neurofibrillary tangles formed predominantly by highly phosphorylated forms of the microtubule-associated protein, tau, which form tangled masses that consume neuronal cell body, possibly leading to neuronal dysfunction and ultimately death. p38α MAPK has been implicated in both events associated with AD, tau phosphorylation and inflammation. p38α MAPK pathway is activated by a dual phosphorylation at Thr180 and Tyr182 residues. Drug design of p38α MAPK inhibitors is mainly focused on small molecules that compete for ATP in the catalytic site. Here, we used different approaches of structure- and ligand-based drug design and Medicinal Chemistry strategies based on a selected p38α MAPK structure deposited in the PDB in complex with inhibitor, as well as other reported in literature. As a result of the virtual screening experiments here performed, as well as molecular dynamics, molecular interaction fields study, shape and electrostatic similarities, activity and toxicity predictions, pharmacokinetic and physicochemical properties, we have selected 7 compounds that meet criteria of low or no toxicity potential, good pharmacotherapeutic profile, predicted activities calculated values comparable to those obtained for the reference compounds, while maintaining the main interactions observed for the most potent inhibitors. These compounds must be acquired for *in vitro* inhibition studies against the enzyme p38α MAPK, as potential leads for Alzheimer's disease treatment.

Key words: Alzheimer's disease, p38 alpha MAPK, drug design.