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17th International Conference on
NEUROLOGY AND NEUROSCIENCE & 4th International Conference on
MENTAL HEALTH AND PRIMARY CARE

October 16-18, 2017 | Toronto, Canada

Polyfunctional chromen-4-ones based anti-Alzheimer's agents: Design, synthesis and biological evaluation

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Chromen-4-ones has emerged as a 'master key' due to its presence in wide range of activities related to Alzheimer's disease (AD), a multi-factorial cognitive disorder. Polyfunctional compounds comprise a novel class of therapeutic agents for the treatment of multi-factorial disease like AD. In present study, total 33 chromen-4-ones were designed and synthesized by making modifications at different positions using Baker-Venkatraman rearrangement. These compounds were primarily evaluated for in vitro acetylcholinesterase (AChE) inhibitory, advanced glyacation end products (AGEs) inhibition and antioxidant activity and showed that most derivatives inhibited AChE with IC50 values in the nanomolar range with additional AGEs inhibitory and radical scavenging activities. The most active compounds FLV-16, FLV-31 and FLV-32 (IC50=6.33, 6.48 and 5.83 nM, respectively) were also ameliorated scopolamine-induced amnesia in mice model using moris water maze test and also reversed the changes of various oxidative stress markers (GSH and TBARS). The docking study revealed the binding pattern of compounds simultaneously bind with catalytic active site (CAS) and peripheral anionic site (PAS) of AChE. Moreover, the in silico pharmacokinetic profiles were predicted and revealed the drug-like properties with good penetration in brain and good oral absorption of compounds. After MD simulations, RMSD plots showed that the docked complexes were quite stable for the specified time of 10 ns with minor fluctuations. Thus, newly designed chromen-4-ones can act on different targets related to AD and the poly-functional attribute of these compounds make them potential candidates for the development of drugs for AD.

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