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Exploration of multi-target potential of chromen-4-one based compounds in Alzheimer's disease: Design, synthesis and biological evaluations

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ABSTRACT

A novel series of flavonoid based compounds were designed, synthesized and biologically evaluated for Acetylcholinesterase (AChE) inhibitory activity integrated with advanced glycation end products (AGEs) inhibitory and antioxidant potential. Most of the derivatives inhibited AChE in nanomolar IC_{50} range along with good AGEs inhibitory and radical scavenging activity. Among them, **7m**, strongly inhibited AChE (IC_{50} = 5.87 nM) and found to be potent as compared to the reference drug donepezil (IC_{50} = 12.7 nM). Its potent inhibitory activity has been justified by docking analysis that revealed its dual binding characteristic with both CAS (catalytic active site) and PAS (peripheral anionic site) of AChE, simultaneously. Additionally, this compound also displayed ability to prevent advanced glycation end products formation (IC_{50} = 23.0 μM) with additional radical scavenging property (IC_{50} = 37.12 nM). It (**7m**) also ameliorated scopolamine induced memory deficit in mice employing Morris water maze test. Thus, flavonoids might be the promising lead compounds as potential polyfunctional anti-Alzheimer's agents.

1. Introduction

Alzheimer's disease (AD), a dementia type memory related disorder, mainly affects the aged people. It is a complex neurodegenerative disorder which is characterized by progressive decline of memory and higher cortical functions that leads to complete degradation of various cognitive, executive, mental, intellectual activities and memory functions.[1] Among others AD is found to be major problem all over the world with high rate progression. Around 35.6 million cases worldwide documented in 2011, AD constitutes a devastating health, political, economic, and social problem for all nations. The prevalence of AD dramatically increases with age and it doubles for every five-year interval after the age of 65. Numerous hypotheses like cholinergic, amyloid, tau, calcium, oxidative stress, glycation etc. involved in the pathogenesis of AD.[2] Besides several diverse hallmarks such as β-amyloid (Aβ) deposits, τ-protein aggregation and low levels of acetylcholine (ACh), AD brains display constant evidence of oxidative damage. In cholinergic hypothesis, the acetylcholine, a neurotransmitter responsible for behavior, memory, cognitive functions and emotions in the brain areas is reduced because of its prompt hydrolysis by Acetylcholinesterase (AChE) enzyme. Additionally, this enzyme also promotes the deposition of β-amyloids, which is the root cause of senile plaques formation.[3] Acetylcholinesterase inhibitors (AChEIs) could increase the level of ACh in AD patients through the inhibition AChE and, therefore, relieve some symptoms experienced by patients. Till date, cholinergic hypothesis based therapeutic approach with AChEIs such as rivastigmine, donepezil and galantamine has been used clinically for AD management.[4] Therefore, inhibition of AChE has been considered for the management of AD as it may increase acetylcholine level and decrease Aβ deposition in the brain regions.

Furthermore, numerous evidences suggested the degrading influence of oxidative stress in the AD pathophysiology and progression. Present reports specified that the oxidative impairment may possibly endorse the amyloid plaques and neurofibrillary tangles formation in AD.[5] In mitochondria, monoamine oxygenase (MAO) endorse the enzymatic oxidation and phosphorylation of biogenic amines by formation of various reactive oxygen species (ROS) and reactive nitrogen species (RNS) that produce functional alterations in lipids, proteins, and DNA. Brain has a high content of Cu^{2+} and Fe^{2+} that potentiate the ROS in brain and lead to Aβ neurotoxicity. Aβ also generates ROS and induce oxidative stress in mitochondria. Therefore, drugs aimed at clearing or preventing the formation of the free radicals may be useful for the management of AD. The increased level of reactive carbonyls and free radicals leads to form the AGEs, the macroproteins, formed via

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