Bioorganic & Medicinal Chemistry 25 (2017) 6273–6285

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

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

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ARTICLE INFO

Article history:
Received 4 May 2017
Revised 1 September 2017
Accepted 9 September 2017
Available online 11 September 2017

Keywords:
Alzheimer's disease
Acetylcholinesterase
Antioxidants
Flavonoids
AGEs
Morris water maze

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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https://doi.org/10.1016/j.bmc.2017.09.012
0968-0896/

Maillard reaction (non-enzymatic glycation) also complicated the AD pathogenesis. It cross-linked and glycated the Aβ or tau proteins, cell death of neurons and glial induction. Protein cross-linking by AGE structures results in the formation of protease-resistant aggregates which further may interfere with intracellular protein traffic and axonal transport in neuron. Glycation of Aβ or tau is reported to enhance its aggregation and subsequent formation of senile plaques (SPs) and paired helical filaments in AD brain, respectively. Moreover, it interact with cell surface receptors RAGE (receptor for AGEs) that provokes the generation of superoxide radicals, hydrogen peroxide, vascular inflammation etc., ultimately contribute to AD pathology.[6] Consequently, drugs that have the capacity to prevent or scavenge the free radicals generation and AGEs inhibitory potential could help for the management of AD.

The complex nature of AD demands the designing of polyfunctional agents which could simultaneously act on more than one pathway rather than only one. It also implemented diverse biological properties with single bioavailability and pharmacokinetic metabolism. In the present study, the well-established molecular pathways *i.e.* AChE, oxidative stress, and AGEs have been explored for the designing of flavonoid based polyfunctional agents for more effective therapy of AD than existing one. Flavonoid was considered for designing as it possesses a broad pharmacological properties range like anti-inflammatory, anti-oxidative, AGEs inhibitory effects, and neuroprotective effects against AChE.[7] Thus, the designing and synthesis of new polyfunctional flavonoid derivatives is an interesting strategy for AD management.

The SAR of our previously reported flavonoids based novel AChE inhibitors,[8] focused our attention to design more flavonoid derivatives bearing a suitable tertiary amino group, which characterizes the crucial requirement for good AChE inhibitory activity, linked with different lengths of alkyl side chain with variedly substituted flavonoid scaffold. Therefore, we here present work involving the synthesis of flavonoid based novel polyfunctional agents, which were primarily evaluated for *in vitro* AChE inhibition, AGEs inhibition, antioxidant effect and molecular modeling studies. Additionally, *in vivo* anti-amnestic and antioxidant activities of the most active polyfunctional agent were determined.

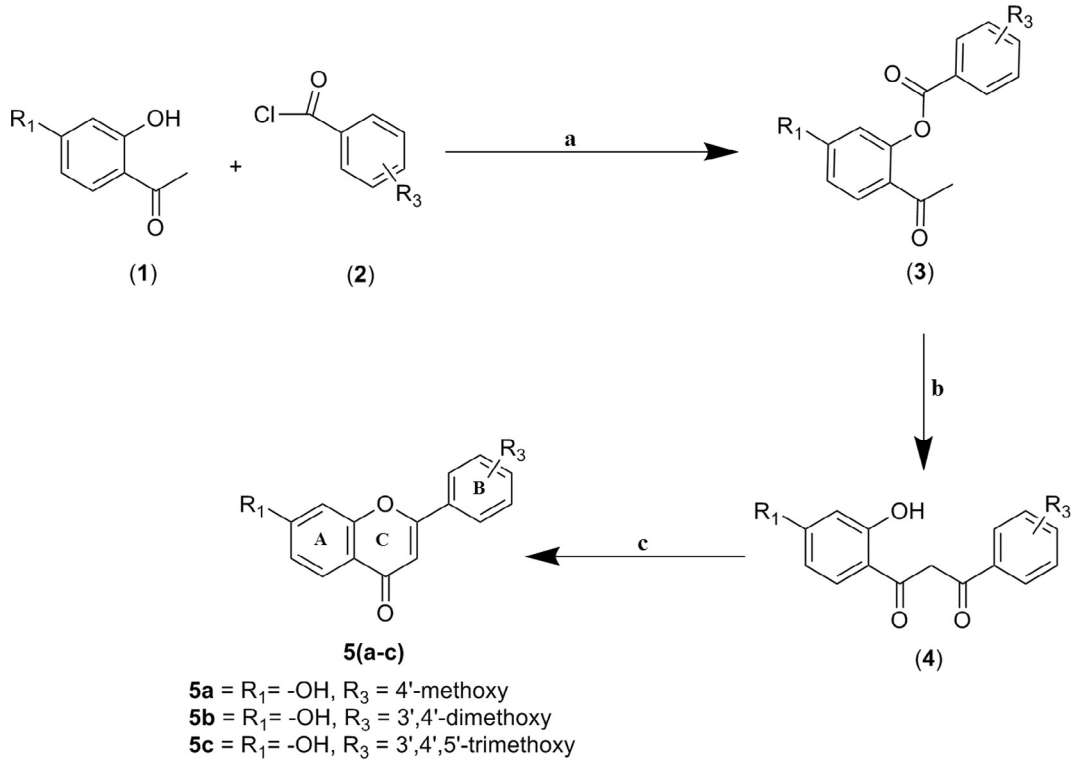
2. Result and discussion

2.1. Chemistry

Firstly, to evaluate the influence of different number of methoxy groups at ring-B with hydroxyl group at 7th position of ring-A over the biological activities of flavonoids, compounds **5**(**a–c**), were synthesized using well established Baker-Venkataraman rearrangement with slight modifications is outlined in Scheme 1.[9]

Our research group previously reported various flavonoids having methoxy group on ring-B and substituted cyclic amine on ring-A via two carbon spacer. Based on those observations, the hydroxyl group of **5**(**a–c**), was replaced by 4-methylpiperidine and 4-hydroxyethyl piperazine amines linked via different carbon spacers of 4′-methoxy substituted flavonoids. The synthetic methodologies employed to develop intermediates **6**(**a–e**) and target compounds **7**(**a–j**), are outlined in Scheme 2. Firstly, the **5**(**a–c**) were alkylated with dibromoalkanes in acetone that delivered intermediates **6**(**a–e**) in satisfactory yields. Finally, the reaction of **6**(**a–e**) with commercially available secondary amines under reflux in acetonitrile in the presence of K_2CO_3 produced the final compounds **7**(**a–j**) in 50–80% yields.

Further, synthesis of the compounds **7**(**k–n**), with additional methoxy groups at ring-B and 4-methylpiperidinoalkyloxy substituent attached at ring- B via two (**7k** and **7m**) and three (**7l** and **7n**) carbon spacer were accomplished using same procedures as shown in Scheme 2.



Scheme 1. The synthetic methodology employed to develop compound **5(a-c)**. Reagents and conditions: (a) Pyridine, Stirring, 15 min., 3% HCl, ice; (b) Pyridine, KOH, stirring, 10% acetic acid; (c) Acetic acid, conc. H_2SO_4, reflux, 1 h.