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# Design, synthesis and evaluation of flavonoid derivatives as potential multifunctional acetylcholinesterase inhibitors against Alzheimer's disease

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ABSTRACT

A new series of flavonoid derivatives were designed, synthesized and evaluated as potential multifunctional AChE inhibitors against Alzheimer's disease. Most of them exhibited potent AChE inhibitory activity, high selectivity for AChE over BuChE, and moderate to good inhibitory potency toward A$\beta$ aggregation. Specifically, compound **12c** was the strongest AChE inhibitor, being 20-fold more potent than galanthamine and twofold more potent than tacrine, and it also had ability to inhibit A$\beta$ aggregation (close to the reference compound) and to function as a metal chelator. Molecular modeling and enzyme kinetic study revealed that it targeted both the catalytic active site and the peripheral anionic site of AChE. Consequently, this class of compounds deserved to be thoroughly and systematically studied for the treatment of Alzheimer's disease.

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Alzheimer's disease (AD), characterized by memory loss, language impairment, personality changes and decline in intellectual ability, is a highly complex and progressive neurodegenerative disorder in the elderly population.[1] Many factors are considered as the key pathological hallmarks of AD, such as cholinergic system dysfunction, accelerated aggregation of $\beta$-amyloid (A$\beta$) peptides and the dyshomeostasis of biometals.[2–6] These factors provide a basis for the cholinergic, amyloid and biometal hypotheses for AD pathology, respectively.

According to the cholinergic hypothesis, the cognitive and memory symptoms of AD are caused by the drastic decline of acetylcholine,[7] and recent reports suggest that increasing acetylcholinesterase (AChE) inhibition and simultaneously improving selectivity for AChE over butyrylcholinesterase (BuChE) would be a promising direction for AD treatment.[8] Furthermore, the crystallographic structure of AChE reveals that it contains two separate ligand binding sites—a catalytic active site (CAS) at the bottom of deep narrow gorge and a peripheral cationic site (PAS) at the entrance.[9,10] Hence, the simultaneous binding to both the CAS and PAS has been advocated to design potent and selective AChE inhibitors.[11,12]

The amyloid cascade hypothesis attributes the pathogenesis of AD to the accelerated aggregation of A$\beta$ in the brain resulting in the formation of senile plaques and then to neurofibrillary tangles, neuronal cell death, and ultimately dementia.[13,14] A$\beta$40 and A$\beta$42 are the most common peptides found in amyloid plaques. Though the amount of secreted A$\beta$42 is only 10% of A$\beta$40, A$\beta$42 is more prone to aggregation and more neurotoxic compared with A$\beta$40.[15,16] Therefore, preventing this peptide from aggregation is a potential therapy for AD.

It has been reported that biometals also play a very important role in many critical aspects of AD.[17] The gradual accumulation of Cu(II) and Fe(II) in the neuropil and plaques of the brain linked to the production of reactive oxygen species and oxidative stress contributes to AD pathology.[18] Direct evidences show that metal ion levels in AD individuals are three to sevenfolds higher than those in healthy people.[19] Thus, the modulation of these biometals in the brain is also a potential therapeutic strategy for AD patients.

Up to now, most of therapies for AD focus on increasing cholinergic neurotransmission by acetylcholinesterase inhibitors (AChEIs), including tacrine, donepezil, rivastigmine and galantamine.[20] These drugs can only improve symptoms for most patients but do not address the etiology of AD. Therefore, searching for

*Abbreviations:* AD, Alzheimer's disease; A$\beta$, $\beta$-amyloid; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; CAS, catalytic anionic site; PAS, peripheral anionic site; AChEI, acetylcholinesterase inhibitor; ChEs, cholinesterases; MOE, Molecular Operating Environment; SI, selectivity index; MD, molecular dynamic.

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more efficient strategies to combat this disease is highly needed.[21] Due to the complex multifactorial nature of AD, molecules that modulate the activity of a single protein target are incapable of significantly altering the progression of the disease. In contrast, multifunctional molecules with two or more complementary biological activities might represent an important advance in the treatment of AD. Accordingly, we are devoted to the study of multifunctional AChEIs that not just inhibit AChE, but decrease A$\beta$42 aggregation and chelate metals.

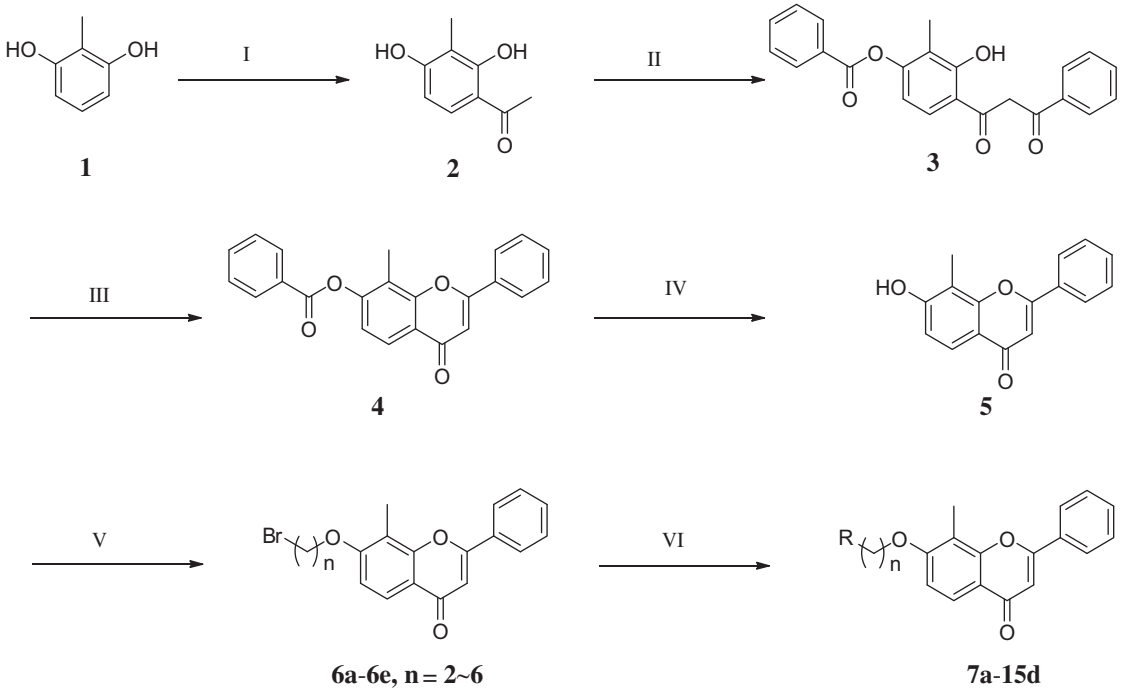
Flavonoids, ubiquitously presented in fruits and vegetables, are well-known natural compounds, and have attracted increasingly widespread attention in present-day society as they possess a wide range of pharmacological properties related to a variety of neurological disorders, like neuro-protective effect,[22] AChE inhibitory activity,[23] A$\beta$ fibril formation inhibitory activity,[24] free radical scavenging effect,[25] and metal-chelating ability.[26] Thus, the design and synthesis of new effective flavonoid derivatives are an interesting strategy for the research on anti-AD drugs. According to the structure of AChE, in order to design dual binding site AChEIs, we decided to connect flavonoid scaffold with terminal amine groups through carbon spacers of different lengths. The terminal amine groups, protonated at physiological pH, could occupy the CAS via cation–$\pi$ interaction, while flavonoid scaffold could interact with the PAS of AChE via aromatic stacking interactions. Flexible carbon spacer was lodged in the narrow mid-gorge,[27] and the length of carbon spacer was changed aiming to obtain optional conformation that could make the designed compounds interact with both the CAS and PAS of AChE.

Here, a series of flavonoid derivatives with different basic side-chains ($n$ = 2–6) were designed, synthesized and evaluated for their cholinesterases (ChEs) inhibition, anti-A$\beta$42 aggregation and metal-chelating ability. The structure–activity relationships were discussed based on the pharmacological activities.

The synthetic pathways of the flavonoid derivatives were outlined in Scheme 1. At the first stage, 2-methylbenzene-1,3-diol **1** was acetylated by a Friedel–Crafts type reaction with acetic anhydride and boron fluoride ethyl ether ($BF_3{\cdot}Et_2O$) as Lewis acid, which led to a high yield of 1-(2,4-dihydroxy-3-methylphenyl)ethanone **2**.[28] Then, compound **2** was condensed with benzoyl chloride to produce $\beta$-diketone **3** through our modified Baker–Venkataraman transformation method by using $K_2CO_3$ in acetone.[29] The obtained $\beta$-diketone **3** was treated with NaOAc/HOAc to obtain 8-methyl-4-oxo-2-phenyl-4*H*-chromen-7-yl benzoate **4**. After removing the benzoyl group of **4**, flavonoid scaffold **5** was acquired in 93% yield. The alkylation of **5** with different $\alpha,\omega$-dibromoalkanes in DMF provided **6a**–**6e** in 68–80% yields. Finally, the target products **7a**–**15d** were gained by the reaction of **6a**–**6e** with commercially available secondary amines (e.g., pyrrolidine and diethylamine) in 66–85% yields. The purities of all final compounds were confirmed to be higher than 95% by HPLC (shown in Supplementary data).

To determine the potential anti-AD effects of compounds **7a**–**15d**, the inhibition of AChE (from electric eel) and BuChE (from equine serum) were tested using the method of Ellman et al. with galanthamine and tacrine as reference compounds.[30,31] The $IC_{50}$ values for ChEs inhibition and selectivity index (SI) for the inhibition of AChE over BuChE were summarized in Table 1. These results indicated that all of the compounds gave higher inhibitory activities against AChE than the precursor compound **5** ($IC_{50}$ value: 87.05 μM). Specifically, compound **12c**, whose diethylamine group was linked to flavonoid scaffold by a four-carbon spacer, was the most potent inhibitor with an $IC_{50}$ value of 0.13 μM, being 20-fold more potent than galanthamine ($IC_{50}$ value: 2.67 μM) and twofold more potent than tacrine ($IC_{50}$ value: 0.269 μM). Hence, the introduction of the aminoalkyl-substituted groups could significantly increase the inhibitory activities of derivatives.

Changing the length of the alkyl chain could affect their ability to contact both sites of AChE and thereby influence the AChE inhibitory potency. Based on the screening data (Fig. 1), compounds **7a**–**7e**, combining pyrrolidine group with flavonoid scaffold by a two- to six-carbon spacer, exhibited different levels of inhibitory activities against AChE (**7a**, $n$ = 2, $IC_{50}$ value: 2.04 μM; **7b**, $n$ = 3, 0.952 μM; **7c**, $n$ = 4, 0.238 μM; **7d**, $n$ = 5, 0.243 μM; **7e**, $n$ = 6,




**Scheme 1.** Reagents and conditions: (I) $Ac_2O$ (1.1 equiv), $BF_3{\cdot}Et_2O$ (2.4 equiv), 80 °C, 6 h, 95%; (II) benzoyl chloride, $K_2CO_3$, acetone, reflux; (III) NaOAc/HOAc, reflux; (IV) $K_2CO_3$, $MeOH/CH_2Cl_2$, rt; (V) $Br(CH_2)_nBr$, $K_2CO_3$, DMF; (VI) NHR, $K_2CO_3$, DMF, KI. ('R-' were showed in Table 1)

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