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Design and synthesis of novel anti-Alzheimer's agents: Acridine-chromenone and quinoline-chromenone hybrids

Zahra Najafi [a], Mina Saeedi [b,c], Mohammad Mahdavi [d], Reyhaneh Sabourian [c], Mahnaz Khanavi [e], Maliheh Barazandeh Tehrani [a], Farshad Homayouni Moghadam [f], Najmeh Edraki [g], Elahe Karimpor-Razkenari [c], Mohammad Sharifzadeh [h], Alireza Foroumadi [i], Abbas Shafiee [i], Tahmineh Akbarzadeh [a,c,*]

[a] Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[c] Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran
[d] Drug Design and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran
[e] Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[f] Department of Cellular Biotechnology at Cell Science Research Center, Royan Institute for Biotechnology, ACECR, Isfahan, Iran
[g] Medicinal and Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[h] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[i] Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

A novel series of acridine-chromenone and quinoline-chromenone hybrids were designed, synthesized, and evaluated as anti-Alzheimer's agents. All synthesized compounds were evaluated as cholinesterases (ChEs) inhibitors and among them, 7-(4-(6-chloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-9-ylamino)phenoxy)-4-methyl-2*H*-chromen-2-one (**8e**) exhibited the most potent anti-acetylcholinesterase (AChE) inhibitory activity (IC_{50} = 16.17 μM) comparing with rivastigmine (IC_{50} = 11.07 μM) as the reference drug. Also, compound **8e** was assessed for its β-secretase (BACE1) inhibitory and neuroprotective activities which demonstrated satisfactory results. It should be noted that both kinetic study on the inhibition of AChE and molecular modeling revealed that compound **8e** interacted simultaneously with both the catalytic active site (CAS) and peripheral anionic site (PAS) of AChE.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia which is characterized by the progressive cognitive impairment in the elderly people. The classic characteristics found in the brains of AD patients confirmed that the following factors are involved in the disease: (i) loss of cholinergic neurons in areas of the brain associated with memory and cognition, (ii) accumulation of the β-amyloid peptide (βA), and (iii) formation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein [1,2]. Moreover, other factors such as mitochondrial dysfunction, hormone imbalance, inflammation, mitotic dysfunction, calcium mishandling, and genetic components play important roles in the development of disease [3]. Among factors involved in AD, the cholinergic hypothesis is related to the low concentration of acetylcholine (ACh) in hippocampus and cortex which are associated with learning and memory functions [4]. ACh is rapidly hydrolyzed by acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes into choline and acetic acid leading to the termination of neurotransmission signal. AChE has shown a very high catalytic efficiency for ACh hydrolysis and it is widely found in cholinergic synapses. However, BChE has exhibited low activity in the hydrolysis reaction and it is mainly distributed in plasma and tissues playing an supplementary role in synaptic transmission [5]. It should be considered that in patients with AD, the activity of AChE decreases or does not change but the activity of BChE gradually increases leading to imbalance between AChE and BChE [6]. It sees that both AChE and BChE are probably to be involved in the

* Corresponding author at: Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
E-mail address: akbarzad@tums.ac.ir (T. Akbarzadeh).

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regulation of the ACh level [7] and ChE inhibitors increase ACh levels in cholinergic neurons which can be considered as an efficient strategy for the treatment of AD symptoms [8,9].

Deposition of βA (amyloid plaques) in the brain has emerged as one of the most important origin of AD. Consequently, development of compounds possessing both AChE and βA aggregation inhibitory activities, provides additional advantages in AD therapeutic approach [10]. In this respect, one of the versatile routes for the inhibition of βA aggregation is prevention the hydrolysis of amyloid precursor protein (APP) *via* inhibition of β-secretase (BACE1) [11]. Also, it has been reported that development of amyloid plaques and neurofibrillary (NFT) tangles in the brain may be accelerated by oxidative damages [12]. Accordingly, neuroprotective agents can be helpful in the treatment of AD by inhibiting the formation of free radicals or protecting against oxidative stress [13].

AChE possesses two binding sites including catalytic site (CS which involves catalytic anionic site (CAS) and catalytic triad) and the peripheral anionic site (PAS) mainly characterized by two tryptophan residues, Trp84 at the active site and Trp279 at the mouth of the gorge [14]. In this respect, several dual-binding inhibitors have been synthesized and evaluated for anti-AChE activity [15–18]. Tacrine, donepezil, rivastigmine, and galantamine are well-known AChE inhibitors. Tacrine is the first cholinesterase inhibitor which was approved by the FDA in 1993. However, it soon showed hepatotoxicity and was subsequently abandoned [19,20]. In this respect, lots of efforts were made to design and synthesize tacrine-based agents with low side effects and better pharmacokinetics properties. Also, tacrine hybrids such as tacrine-4-aminoquinoline, tacrine-huperzine A, tacrine-ferulic acid, tacrine-phenylphenanthridinium, tacrine-indole were efficiently developed [21–23]. To establish further tacrine-based inhibitors, we also focused on the anti-ChE activity of chromenones (**A**–**D**) (Fig. 1) [24–28], and in continuation of our research program on the synthesis of anti-ChE agents [29], novel series of acridine-chromenone and quinoline-chromenone hybrids **8** (Fig. 2) were designed, synthesized, and evaluated for their anti-Alzheimer's activities.

2. Results and discussion

2.1. Chemistry

Synthetic route for the preparation of acridine-chromenone and quinoline-chromenone hybrids **8a–q** is depicted in Scheme 1. Initially, two required starting materials, compounds **4** and **7** were synthesized. For this purpose, compounds **3** were prepared through the reaction of 7-hydroxycoumarins (**1**) and 1-fluoro-4-nitrobenzene (**2**) in the presence of anhydrous K_2CO_3 in DMF at 80 °C overnight. Then, the latter compound **3** tolerated reduction reaction using Zn/NH_4Cl in H_2O/EtOH at room temperature for 3 h to obtain the corresponding amine **4**. Compounds **7** including 9-chloro-1*H*,2*H*,3*H*-cyclopenta[*b*]quinolines **7a–c**, 9-chloro-1,2,3,4-tetrahydroacridines **7d–f**, 11-chloro-6*H*,7*H*,8*H*,9*H*,10*H*-cyclohepta[*b*]quinolines **7g–i** were prepared by condensation of commercially available anthranilic acids **5a–c** and appropriate cycloketones **6a–c** in the presence of $POCl_3$ under reflux [30]. Finally, compounds **7a–i** reacted with amines **4a–b** in the presence of KI in refluxing *n*-propanol for 12–24 h affording target compounds **8a–q** in good yields (60–80%).

2.2. Biological activity

2.2.1. The anti-AChE activity of compounds *8a–q*

In vitro anti-AChE and anti-BChE activities of the synthesized compounds **8a–q** were evaluated according to the modified Ellman's method [29,31] comparing with rivastigmine as the reference drug. All results are presented in Table 1. Based on the IC_{50} values, compounds **8a**, **8c–g**, **8j–l**, and **8o–q** showed anti-AChE activity in the range of micromolar concentrations (IC_{50} = 16.17–83.10 μM) in comparison to rivastigmine (IC_{50} = 11.07 μM). As can be seen in Table 1, compounds **8a–q** can be divided into three categories, **8a–f**, **8g–l**, **8m–q** (Fig. 2) according to the cycloalkyl fused to quinolone moiety. Among the synthesized compounds, compound **8e** possessing methyl and chlorine groups at 4-position of chromenone and 6-position of cyclopenta[*b*]quinoline moieties, showed the most potent

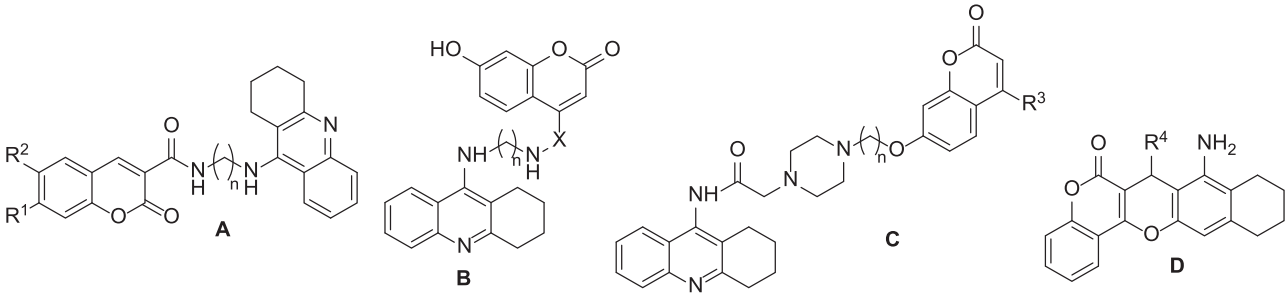

Fig. 1. Coumarin-tacrine hybrids as anti-AChE agents.

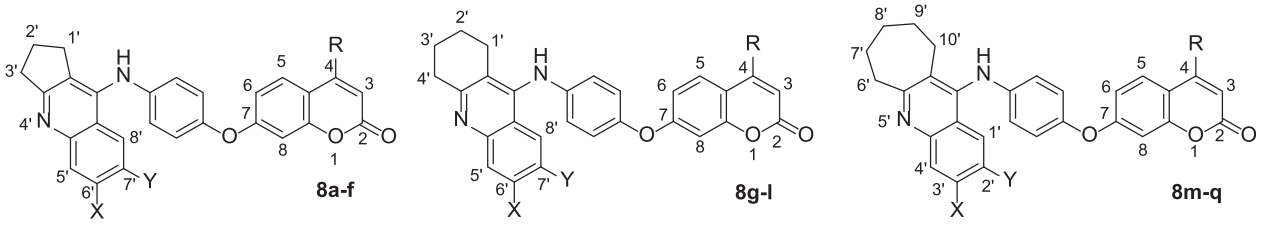

Fig. 2. Novel acridine-chromenone and quinoline-chromenone hybrids as anti-AChE.