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Synthesis of novel chromenones linked to 1,2,3-triazole ring system: Investigation of biological activities against Alzheimer's disease

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This paper is dedicated to the memory of our unique teacher in Chemistry and Medicinal Chemistry, Professor Abbas Shafiee.

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ABSTRACT

In this work, novel chromenones linked to 1,2,3-triazole ring system were synthesized and evaluated for their anti-ChE activity. Among them, *N*-((1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-5-yl)methyl)-8-methoxy-2-oxo-2*H*-chromene-3-carboxamide (**6m**) showed good anti-acetylcholinesterase activity (IC_{50} = 15.42 μM). Also, compound **6m** demonstrated neuroprotective effect against H_2O_2-induced cell death in PC12 neurons, however, it showed no beta-secretase (BACE1) inhibitory activity. Docking and kinetic studies separately confirmed dual binding activity of compound **6m** since it targeted both the catalytic active site (CAS) and the peripheral anionic site (PAS) of AChE.

1. Introduction

Alzheimer's disease (AD) has emerged as the most prevalent age-related neurodegenerative diseases and the main cause of dementia in elderly people in such a manner that the daily activity of patients is completely affected by the resulting cognitive impairments [1]. In recent years, considerable investments have been dedicated to the improvement of anti-Alzheimer's agents due to increased prevalence of AD worldwide [2]. Although lots of efforts have been made to develop diagnostic tests and therapeutic tools against AD there is still a glaring need for progress in this area. However, abnormal deposition of β-amyloid (Aβ) and τ-rich neurofibrillary tangles (NFT) have been known as two main pathological hallmarks of AD [3]. Presently, most of therapeutic treatments for AD has focused on the inhibition of acetylcholinesterase (AChE) to increase the level of acetylcholine (ACh) in cholinergic synaptic clefts [4]. Acetylcholinesterase (AChE) enzyme inhibition is an important tool for the management of AD and the corresponding inhibitors are the most commonly prescribed drugs for Alzheimer's patients [5,6]. Acetylcholinesterase inhibitors (AChEIs) have been the center of attention not only due to the increase of ACh level in the brain, but also they inhibit AChE interaction with Aβ. Amyloid fibiril formation can be proceeded through a wide range of amino acids in the peripheral anionic site (PAS) part of AChE [7].

Heterocyclic compounds have played a prominent role [8] in the design of approved drugs such as Tacrine [9], Donepezil [10], and Galantamine [11]. Also, the role of heterocycles has been

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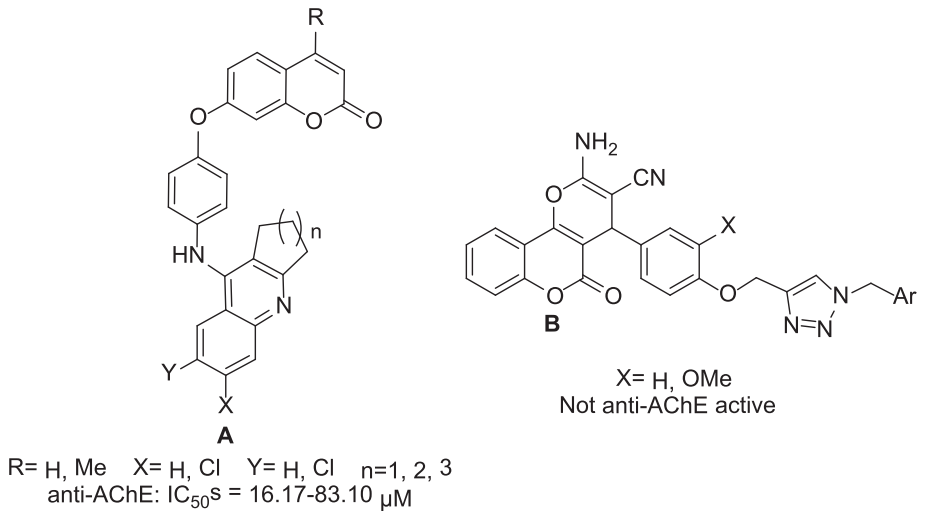

Fig. 1. Structure of some chromenones recently investigated for their ChEI activity.

developed to diagnose AD which is one the most controversial issue regarding to the treatment of disease. In this respect, Thioflavin-T has been found as an effective agent which is frequently used to visualize and quantify the presence of amyloid aggregation [12].

Chromenones are *O*-heterocyclic compounds possessing versatile biological activities [13] and they have also attracted lots of attention as AChEIs. They have been found as a crucial scaffold for the optimal AChEI activity interacting with the CAS and PAS of AChE [14]. Apart from chromenones, 1,2,3-trrizoles have been considered as versatile anti-AChE agents [15]. Recently, our activities in the AChEI activity of chromenones linked to different heterocyclic systems (**A**, **B**, Fig. 1) [16,17] such as 1,2,3-trizole derivatives [17–20] indicated their potency to be considered for design and synthesis of novel anti-Alzheimer agents. Herein, as the main part of our research group interest in the evaluation of anti-Alzheimer activity of heterocyclic compound, here we have focused on novel chromenones linked to 1,2,3-triazole ring system and investigated various biological activities (Scheme 1).

2. Results and discussion

2.1. Chemistry

Synthetic procedure for the synthesis of desired compounds **6** was demonstrated in Scheme 1. The required starting material, 2-oxo-2*H*-chromene-3-carboxylic acid derivative **1** was prepared by the reaction of meldrum's acid and salicylaldehyde derivatives in water at room temperature for 24 h. Reaction of compound **1** and propargylamine **2** in dry acetonitrile in the presence of HOBt and EDCI led to the formation 2-oxo-*N*-(prop-2-yn-1-yl)-2*H*-chromene-3-carboxamide derivative **3**. Finally, various organic azides **5** were prepared by the reaction of different benzyl chlorides/bromides **4** and sodium azide in the presence NEt_3 in the mixture of H_2O/*t*-BuOH at room temperature. Then, compound **3**, sodium ascorbate, and catalytic amount of $CuSO_4$ (7 mol%) were added to the freshly prepared azides **5** leading to the formation of different chromenones linked to 1,2,3-triazole ring system **6**.

2.2. Biological activity

2.2.1. The anti-AChE and anti-BChE activity of compounds *6*

The IC_{50} values of synthesized compounds **6** were determined against AChE (*E*.C. 3.1.1.7) and BChE (*E*.C. 3.1.1.8) according to Ellman's method [21]. All results were compared with rivastigmine as the reference drug and the corresponding data were summarized in Table 1. Most of synthesized compounds (**6b**, **6d**, **6f–j**, and **6l–o**) exhibited inhibitory activity against AChE with IC_{50} values ranging from micromolar concentrations. The results listed in Table 1 obviously showed that the substituents on the aryl group connected to the 1,2,3-triazole ring as well as presence/absence of methoxy group on the chromenone moiety influenced the AChEI activities of the compounds **6**.

According to IC_{50} values, *N*-((1-(2-chlorobenzyl)-1*H*-1,2,3-triazol-5-yl)methyl)-8-methoxy-2-oxo-2*H*-chromene-3-carboxamide (**6m**) bearing methoxy group on the chromenone moiety and 2-chlorophenyl on the pendant 1,2,3-triazole group, was the most active anti-AChE compound (IC_{50} = 15.42 μM). Deletion of methoxy group and increasing the number of chlorine atoms at 3- and 4-positions of aryl group connected to the 1,2,3-triazole ring (**6i**) led to the relative decrease of inhibitory activity (IC_{50} = 16.73 μM). Interestingly, its counterpart (**6h**) showed lower inhibitory activity with IC_{50} = 20.23 μM indicating the importance of position of chlorine atoms. However, counterparts of compounds **6h** and **6i** having methoxy group on the chromenone moiety, compounds **6n** and **6o**, showed lower activities against AChE with IC_{50}s = 33.76 and 25.54 μM, respectively. Compound **6l** possessing methoxy group on the chromenone moiety and 2-methylbenzyl group on 1,2,3-triazole ring showed IC_{50} = 24.09 μM whereas its counterpart, compound **6b** was far weaker toward AChE with IC_{50} = 78.92 μM. It should be noted that compound **6c** having substituents same as compound **6b** showed no inhibitory activity. It is clear that the position of methyl group is important. Chromenones linked to 1,2,3-triazole derivatives possessing halogen at 4-position of aryl group connected to 1,2,3-triazole (compounds **6e** and **6k**) did not show inhibitory activity (IC_{50} > 100 μM). Inversely, changing the position of halogen atom from 4- into 2- or 3- led to higher anti-AChE activity since compounds **6j**, **6f**, **6d**, and **6g** showed IC_{50}s = 31.04, 33.99, 48.08, and 92.77 μM, respectively. Totally, presence of halogen at 2-position of aryl group connected to 1,2,3-triazole increased AChEI activity (compounds **6f**, **6j**, and **6m**). Finally, compound **6a** with no substituents on chromenone moiety and 1,2,3-triazole demonstrated no anti-AChE activity (IC_{50} > 100 μM).

All synthesized compounds **6** were also evaluated for their anti-BChE activity and most of them were not active. Among the prepared derivatives, compounds **6h**, **6k**, and **6m** showed activity with IC_{50}s = 67.01, 72.27, and 96.13 μM, respectively comparing with rivastigmine (IC_{50} = 7.72 μM).