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Original article

Benzofuran-derived benzylpyridinium bromides as potent acetylcholinesterase inhibitors

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ABSTRACT

A series of benzofuran-based *N*-benzylpyridinium derivatives **5a**–**o** were designed and synthesized as novel AChE inhibitors. The synthetic pathway of the compounds involved the preparation of 4-(benzofuran-2-yl)pyridine intermediates via the reaction of different salicylaldehyde derivatives and 4-(bromomethyl)pyridine, followed by intramolecular cyclization. Subsequently, the 4-(benzofuran-2-yl) pyridines were *N*-benzylated by using appropriate benzyl bromide to afford the final product **5a**–**o**. The results of in vitro AChE activity evaluation of synthesized compounds revealed that all compound had potent anti-AChE activity comparable or more potent than standard drug donepezil. The *N*-(3,5-dimethylbenzyl) derivative **5e** with IC_{50} value of 4.1 nM was the most active compound, being 7-fold more potent than donepezil.

1. Introduction

Alzheimer's disease (AD) is the most prevalent chronic neurodegenerative disorder which characterized by memory loss, language problems, disorientation, loss of motivation, and behavioral impairment [1]. AD is a multifactorial disease in which a complex of proteins, enzymes, or receptors is involved [2]. The pathogenesis of AD is not completely clear; however, the typical pathological hallmarks are amyloid-β (Aβ) deposits, τ-protein aggregation, oxidative stress, and decreased levels of acetylcholine (ACh) in the brain [3].

Since the AD is associated with a loss of cholinergic neurotransmission with decreased levels of ACh in the brain areas dealing with learning, memory, and behavioral responses, a majority of investigations has been focused on the basal forebrain cholinergic system [4]. Accordingly, one strategy in the treatment of AD can be the increase of synaptic levels of ACh in the brain by inhibiting the acetylcholinesterase (AChE) enzyme, which is mainly responsible for hydrolysis of ACh [5]. Nowadays, the symptomatic management of patients with AD is based on utilizing acetylcholinesterase inhibitors (AChEIs) such as donepezil, rivastigmine, and galantamine, as well as the NMDA-antagonist memantine [6].

The crystal structure of AChE indicates that the catalytic triad is located at the bottom of a narrow gorge [7]. The entrance of the gorge is termed the peripheral anionic site (PAS) in which the aromatic residues of amino acids interact with cationic ligands. At the bottom of the gorge, there is the catalytic active site (CAS) [8]. The AChE inhibition by AChE inhibitors maybe occurs via a competitive interaction with CAS, via a non-competitive binding with PAS, or via both interactions. It was demonstrated that AChE also interacts with Aβ by a hydrophobic environment close to the PAS. The latter

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interaction can promote the deposition and aggregation of Aβ in the brain [9].

Accordingly, the AChE inhibitors with dual action on PAS and CAS could be more effective agents for the management of AD [10]. Despite the purely symptomatic mode of action of AChE inhibitors, they still represent the first-line treatment of AD [11]. Considering this information and looking at the high prevalence of AD, discovery and development of a highly effective AChE inhibitor is urgently needed.

Among the various compounds developed as AChE inhibitors, donepezil analogs are studied more extensively. The X-ray crystallography and docking studies demonstrated that donepezil has dual-binding mode of action. It was found that the presence of benzyl piperidine contributes its inhibitory activity by interacting with the CAS, while the indanone moiety of the molecule as a hydrophobic aromatic part binds to the PAS [12,13].

In the search for finding new AChE inhibitors, we have recently reported benzofuranone-based compounds containing benzylpyridinium moiety as dual-binding inhibitors (Fig. 1) [14]. It was postulated that the presence of *N*-benzylpyridinium moiety contributes to inhibitor activity by interacting with the catalytic site, and the aromatic part of benzofuranone ring engages in π–π stacking with the PAS of AChE. In continue of the work, we simplified the primary lead structure by replacing benzofuranone moiety with benzofuran ring which directly connected to the *N*-benzylpyridinium moiety. Thus we described here, the synthesis and anti-AChE activity of new benzofuran-derived compounds **5a**–**o** bearing *N*-benzylpyridinium scaffold (Fig. 1). It is interesting to highlight that a series of 2-arylbenzofurans [15] and pyridinium-type [16] AChE inhibitors have received much attention as multi-potent AD modifying agents.

2. Chemistry

The synthesis of compounds **5** was illustrated in Scheme 1. The reaction of salicylaldehyde derivatives **1** with 4-(bromomethyl) pyridine **2** in the presence of K_2CO_3 produced *O*-substituted salicylaldehydes **3**. Cyclization of compounds **3** by using *t*-BuOK as base in DMF afforded 4-(benzofuran-2-yl)pyridine derivatives **4** [17]. The *N*-benzylation of the latter compounds with appropriate benzyl bromide in acetonitrile gave final compounds as benzyl pyridinium bromide salts **5**.

3. Results and discussion

3.1. AChE inhibitory activity

The anti-AChE activity of compounds **5a**–**o** was assessed in vitro by using reported method [14]. The obtained IC_{50} values of compounds are presented in Table 1, in comparison with reference drug donepezil. All compounds showed very potent inhibitory activity against AChE at nano-molar level. A survey on IC_{50} values of compounds revealed that all compounds with exception of **5i** were more potent than donepezil. However, compound **5i** with IC_{50} value of 31.5 nM was as potent as donepezil. Among the tested compounds, 3,5-dimethylbenzyl derivative **5e** with IC_{50} value of 4.1 nM was the most potent compound. Its inhibitory activity was 7-times more than that of donepezil.

The limited structure-activity relationships study on the benzofuran ring indicated that the introduction of 5-bromo group diminished the activity (compare compounds **5i** and **5c** or **5j** and **5d**). Moreover, by comparing the IC_{50} values of 7-methoxy compounds **5n** and **5o** with those of corresponding congeners **5c** and **5d**, it could be concluded that the insertion of methoxy group on C-7 position decreased the anti-AChE activity. Compounds **5g**, **5h**, and **5l** containing fluorobenzyl moiety were more potent than related benzyl derivatives **5f** and **5k**, respectively. Therefore, the presence of fluorine atom on benzyl pendent group had positive effect on inhibitory activity. In contrast, 4-bromobenzyl derivatives **5i** and **5n** showed less activity when compared to their corresponding benzyl analogs **5f** and **5k**. Thus, the 4-bromo substitution on benzyl group diminished the activity. Also, the introduction of 4-nitro on the benzyl group of compounds **5f** and **5k** resulted in more active compounds **5j** and **5o**.

3.2. Docking study

To get insight into whether and how the binding and inhibition profile of synthesized compounds are influenced by the structure, the docking simulation was performed. Therefore, all the compounds **5a**–**o** were investigated computationally to define their binding profile. For instance, the most active compound **5e** was

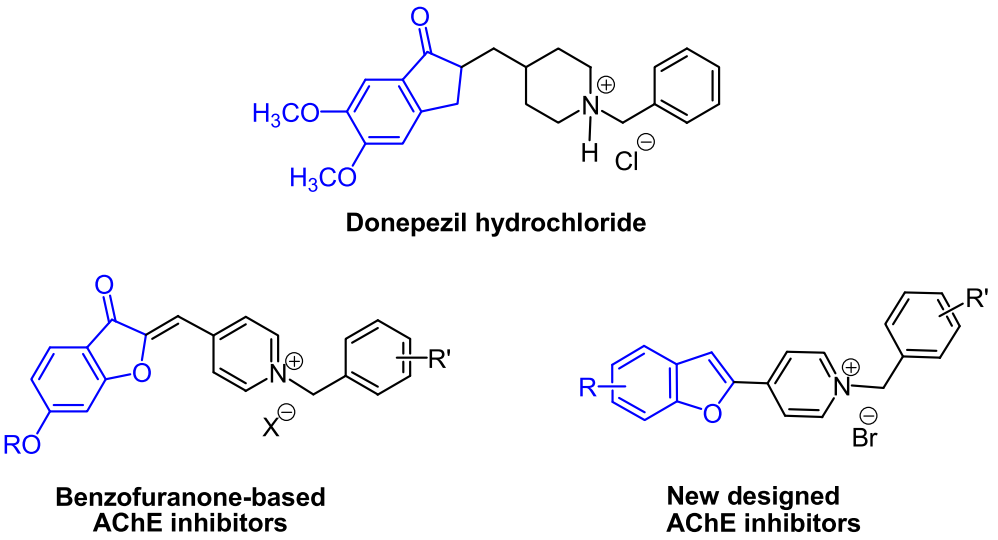

Fig. 1. Structures of donepezil hydrochloride as a well-known inhibitor of AChE, benzofuranone-based compounds reported as anti-AChE agents [14] and benzofuran-derived benzylpyrininium analogs as newly designed AChE inhibitors.