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Synthesis and evaluation of 4-substituted coumarins as novel acetylcholinesterase inhibitors

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ABSTRACT

A series of 4-hydroxycoumarin derivatives were designed and synthesized as new acetylcholinesterase (AChE) inhibitors which could be considered for Alzheimer's disease therapeutics. Among the 19 coumarin-derived compounds tested toward *Electrophorus electricus* acetylcholinesterase (*eel*AChE) and horse serum butyrylcholinesterase (*eq*BChE), *N*-(1-benzylpiperidin-4-yl)acetamide derivative **4m** displayed highest AChE inhibitory activity ($IC_{50} = 1.2$ μM) and good selectivity (37 times). The docking study of the most potent compound **4m**, indicated that Phe330 is responsible for ligand recognition and trafficking by forming π-cation interaction with benzylpiperidine moiety. Furthermore, the formation of an additional π–π interaction between coumarin moiety and Trp279 of peripheral anionic site could stabilize the ligand in the active site resulting in more potent inhibition of the enzyme.

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1. Introduction

Alzheimer's disease is a chronic and progressive neurodegenerative disorder of the central nervous system which is associated with memory loss, cognitive impairment and decline in language [1]. Neuropathological evidence has shown that the reduced levels of acetylcholine, β-amyloid senile plaques and neurofibrillary tangles formation within the brain of afflicted individuals play a crucial role in the pathogenesis of Alzheimer's disease [2]. Accordingly, the enhancement of cholinergic neurotransmission and the inhibition of β-amyloid peptide formation are considered as main approaches for effective treatment of Alzheimer's disease [3–5].

Since acetylcholinesterase (AChE) plays a pro-aggregating (non-catalytic) role to accelerating β-amyloid peptide aggregation and deposition into the fibrils [6], thus inhibition of AChE is still the most successful therapeutic strategy for the symptomatic treatment of Alzheimer's disease and its progression [7,8].

Several AChE inhibitors (Fig. 1) such as donepezil, rivastigmine, galantamine, ensaculine, propidium, and tacrine have been developed for symptomatic treatment of Alzheimer's disease in the early to moderate stages [9,10]. The study of donepezil–TcAChE complex by X-ray crystallography has revealed that the indanone and benzylpiperidine moieties of donepezil interact with the peripheral (non-catalytic) and central (catalytic) binding site of AChE, respectively [11]. Accordingly, agents able to bind both the peripheral and catalytic sites of AChE are proposed as a better choice for Alzheimer's disease therapy.

Structurally, AChE inhibitors belong to different classes of compounds. Among them, ensaculine is a coumarin derivative containing piperazine ring with three atom linker (Fig. 2), which slows down or prevents the progression of the neurodegradation and Alzheimer's disease [12,13]. Furthermore, Piazzi et al. have designed AP2238, a coumarin derivative as dual binding site AChE inhibitor (Fig. 2), which is able to simultaneously interact with both the central and the peripheral anionic sites [14]. Coumarins are naturally occurring compounds with wide range of biological activities including AChE inhibition. Previously, several studies with coumarin derived AChE inhibitors have demonstrated that coumarin ring primarily interacts with peripheral anionic site of

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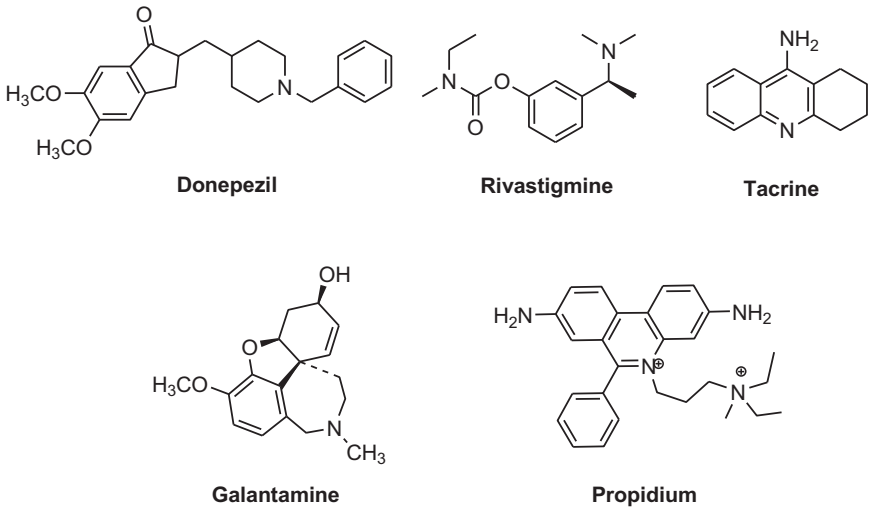

Fig. 1. Structures of several AChE inhibitors, have been developed for symptomatic treatment of Alzheimer's disease.

AChE and amine functional moiety including benzylamino, phenylpiperazine or anilino which linked to coumarin heterocycle using appropriate spacer, interacts with catalytic site of AChE [15]. Moreover, the fact that chemical substitutions can occur at many positions of this core structure, have made coumarins interesting molecules for drug discovery in the field of AChE inhibitors [15].

In continuation of our previous study for developing new AChE inhibitors [16], in this work we focused our attention on 4-hydroxycoumarin derivatives bearing an amine functional group on alkyl side chain in which the presence of lipophilic moiety and often a tertiary amino group represents the key requirement for a good AChE inhibition. Thus, we report herein synthesis, biological evaluation and molecular docking study of 4-substituted coumarins **4a**–**s** as novel AChE inhibitors (Fig. 2).

2. Chemistry

The synthetic route to the target compounds **4a**–**s** starting from commercially available 4-hydroxycoumarin (**1**) was shown in Scheme 1. *O*-Alkylation of compound **1** with ethyl 2-bromoacetate or ethyl 4-bromobutanoate in the presence of K_2CO_3 in DMF afforded ethyl ester derivatives **2a** or **2b**, respectively. The esters **2a** and **2b** were hydrolyzed with aqueous solution of sodium hydroxide in dioxane to yield the corresponding acids **3a** and **3b**. The condensation of the carboxylic acids (**3a**, **3b**) with appropriate amines were attempted by various reagents and conditions such as carbonyldiimidazole (CDI) and dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and hydroxybenzotriazole (HBT) in different solvents, but the best result was obtained by EDC/HBT in acetonitrile.

3. Pharmacology

3.1. In vitro inhibition studies of cholinesterases

The modified Ellman's method [17] was utilized to determine the inhibitory activity of compounds **4a**–**s** against acetylcholinesterase and butyrylcholinesterase using *Electrophorus electricus*

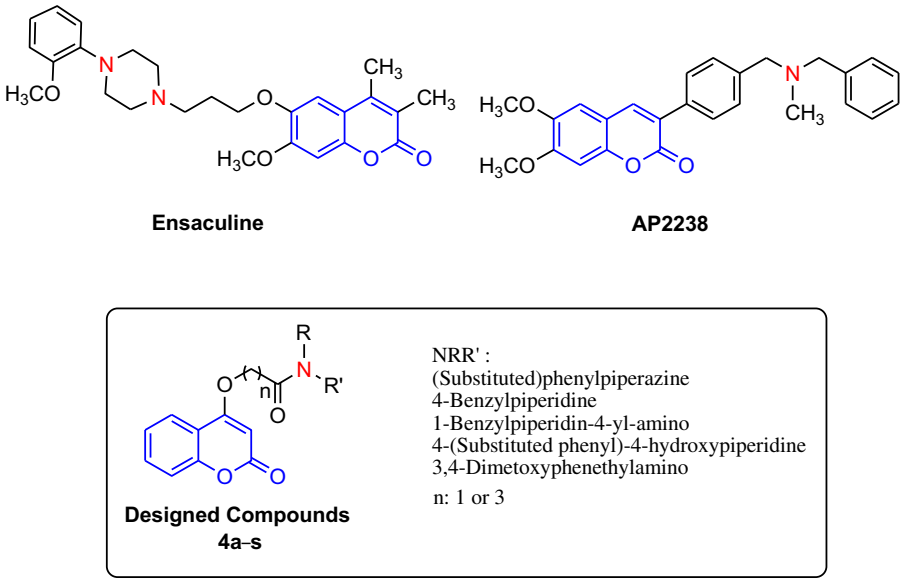

Fig. 2. AChE inhibitors ensaculine and AP2238 belong to coumarin class and designed compounds **4a**–**s**.

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