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Synthesis, antioxidant and anticholinesterase activities of novel coumarylthiazole derivatives

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ABSTRACT

A newly series of coumarylthiazole derivatives containing aryl urea/thiourea groups were synthesized and their inhibitory effects on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) were evaluated. The result showed that all the synthesized compounds exhibited inhibitory activity to both cholinesterases. Among them, 1-(4-(8-methoxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl)-3-(4-chlorophenyl)thiourea (**f8**, IC_{50} = 4.58 μM) was found to be the most active compound against AChE, and 1-(4-fluorophenyl)-3-(4-(6-nitro-2-oxo-2H-chromen-3-yl)thiazol-2-yl)urea (**e31**) exhibited the strongest inhibition against BuChE with IC_{50} value of 4.93 μM, which was 3.5-fold more potent than that of galantamine. The selectivity of **f8** and **e31** were 2.64 and 0.04, respectively. In addition, the cupric reducing antioxidant capacities (CUPRAC) and ABTS cation radical scavenging abilities of the synthesized compounds were investigated for antioxidant activity. Among them, **f8**, **f4** and **f6** (IC_{50} = 1.64, 1.82 and 2.69 μM, respectively) showed significantly better ABTS cation radical scavenging ability than standard quercetin (IC_{50} = 15.49 μM).

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease with symptoms of memory loss, cognition defect and behavioural impairment [1–3]. AD is associated with a selective loss of cholinergic neurons in the brain and decreasing levels of acetylcholine (ACh) [4]. The cholinergic system is the earliest and most profoundly affected neurotransmitter system in AD, with substantial loss of the forebrain, cortex, and hippocampus. This neurotransmitter together with these brain regions are critical in the acquisition, processing, and storage of memories and have supported the use of cholinomimetics in the treatment of AD [5]. It is well known that two forms of cholinesterases coexist ubiquitously throughout the body, i.e., acetylcholinesterase (AChE; EC 3.1.1.7) and butyrylcholinesterase (BuChE; EC 3.1.1.8). AChE is a hydrolase, and its principal biological role is terminating the impulse transmission at cholinergic synapses by rapid hydrolysis of the neurotransmitter ACh. Butyrylcholinesterase (BuChE), also known as pseudocholinesterase, is primarily found in plasma, liver, and muscle tissues. The pharmacological role of BuChE is not yet completely understood. BuChE may have a compensatory role in the modulation of the hydrolysis of acetylcholine ACh in brain with degenerative changes. Consequently, BuChE may be target for increasing the cholinergic tone in AD patients [6,7]. The classical hypothesis of AD is the cholinergic hypothesis, which suggests that acetylcholinesterase inhibitors (AChEI) could increase the levels of ACh in AD patients through the inhibition of AChE and, therefore, relieve some symptoms experienced by AD patients [8]. At the same time, AD is probably associated with multifaceted etiologies and pathogenic phenomena, and all mechanisms seem to share oxidative stress as a unifying factor, which is thought to have a causative role in the pathogenesis of AD recently [9]. Based on these findings, many efforts have been made in the search for potent AChE inhibitors, and a large number of naturally occurring and synthetic AChE inhibitors such as ambenonium, ensaculine, huperzine A, physostigmine, and scopoletin have already been reported (Fig. 1) [10–13].

Regarding the X-ray crystallographic structure of AChE from Torpedo californica, three main binding sites have been determined: (a) the catalytic triad at the bottom of active site including Ser200, His440 and Glu327; (b) the catalytic anionic site (CAS) at the vicinity of the catalytic triad consisting of Trp84, Tyr130, Gly199, His441 and His444; (c) peripheral anionic site (PAS) at the gorge rim comprising Tyr70, Asp72, Tyr121, Trp279 and Tyr334 [14–16]. AChE inhibitors may inhibit AChE via a

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competitive mechanism, by interacting with the catalytic active site (CAS) of the enzyme, via a non-competitive mechanism, by binding with the peripheral anionic site (PAS), or via both mechanisms, by exerting a dual binding AChE inhibition [17].

Several studies have revealed that the tricycle and heterocyclic rings (such as tacrine, quinolizidinyl and coumarin derivatives) showed strong parallel π–π stacking against CAS, and the amidic or imidic fragments interact with the catalytic triad of the active site [18–21]. The coumarin heterocyclic framework is now considered as a privileged structure, which is a common moiety found in many biologically active natural and therapeutic products and thus represents a very important pharmacophore [22,23]. Recently, this scaffold has also been reported as an AChE inhibitor [24]. The various research groups have synthesized amidic- or imidic-based AChE inhibitors. These studies have reported that a hydrogen bond has been formed between amid moieties of the inhibitors and anionic sites of the enzyme [25,26]. The urea group was chosen on the basis of its potency of H-bonding, probability of complexation and wide biological activity [27–30]. We report here a new hybrid molecule (**1**) based on frameworks of the coumarin modified by the addition of thiazole ring (Fig. 2). In the design of this new molecule, the coumarylthiazole moiety was substituted with urea group contained phenyl ring. We hypothesized that these heterocyclic and aromatic rings may show strong parallel π–π stacking against CAS of the enzyme. On the other hand, the presence of urea moiety contributes to inhibitor activity by interacting with active sites. In this study, a series of 42 novel urea/thiourea substituted coumarylthiazole derivatives (**e1–e34** and **f1–f8**) were synthesized and their antioxidant activities and inhibitory effects on AChE and BuChE were evaluated.

2. Results and discussion

2.1. Chemistry

The synthetic procedures employed to obtain the target compounds **e1–e34** and **f1–f8** are depicted in Scheme 1. Compounds **b1–3** were synthesized from salicylaldehydes by the literature [31], then they were brominated with molecular bromine in chloroform. 2-amino-4-(R_1-coumarin-3-yl)thiazoles (**d1–3**) were obtained by the reactions of **c1–3** with thiourea. Finally, compounds **d1–3** were reacted with arylisocyanates in THF to get product coumarylthiazole containing urea derivatives (**e1–e34**), but thiourea derivatives were not synthesized by the same procedure. Although several experiments were carried on different conditions, only 8 new thiourea substituted coumarylthiazole derivatives (**f1–8**) were obtained by the reactions of **d1–3** with arylisothiocyanates in DMF at room temperature.

All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analysis. In the infrared spectra of

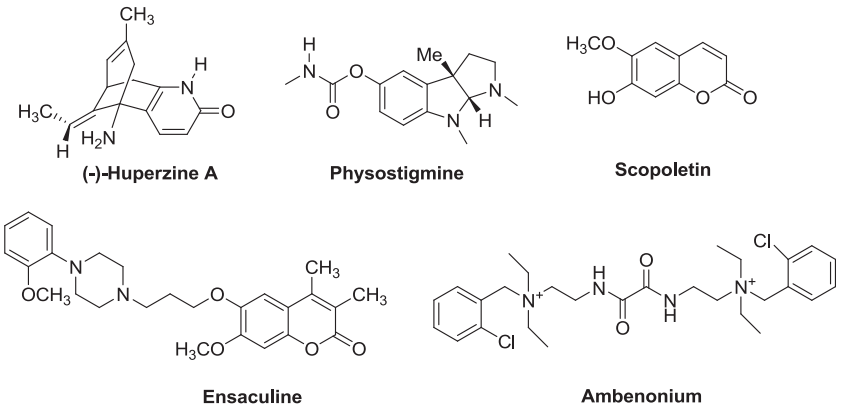

Fig. 1. Structures of well-known cholinesterase inhibitors.

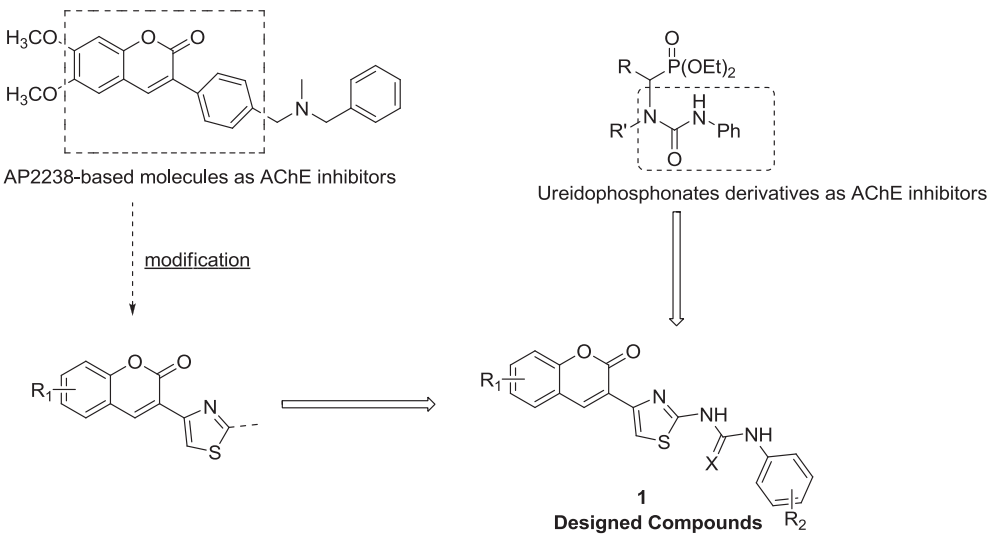

Fig. 2. Design strategy of the targeted compounds.