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Synthesis of aminoalkyl-substituted coumarin derivatives as acetylcholinesterase inhibitors

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ABSTRACT

Alzheimer's disease, one of the most common forms of dementia, is a progressive neurodegenerative disorder symptomatically characterized by declines in memory and cognitive abilities. To date, the successful therapeutic strategy to treat AD is maintaining levels of acetylcholine by inhibiting acetylcholinesterase (AChE). In the present study, coumarin derivatives were designed and synthesized as AChE inhibitors based on the lead structure of scopoletin. Of those synthesized, pyrrolidine-substituted coumarins **3b** and **3f** showed ca. 160-fold higher AChE inhibitory activities than scopoletin. These compounds also ameliorated scopolamine-induced memory deficit in mice when administered orally at the dose of 1 and 2 mg/kg.

1. Introduction

Alzheimer's disease (AD), one of the most common forms of dementia, is a progressive neurodegenerative disorder symptomatically characterized by declines in memory and cognitive abilities.[1] AD is the fourth leading cause of death in developed countries, and because most AD patients are over 65 years old, numbers are expected to increase in parallel with population aging.[2] The estimated number of AD patients worldwide in 2006 was 26.6 million and is predicted to increase to 106.8 million in 2050.[3] The major pathological features of AD are β-amyloid plaque deposition and the presence of neurofibrillary tangles in the brain.[4] However, the precise causes of AD at the molecular level remain unclear despite many suggested hypotheses. Further effective therapy that can delay the neurodegeneration is not available yet.[5]

A deficit in cholinergic neurotransmission, due to the degeneration of cholinergic neurons, in the brain is believed to be one of the major causes of the memory impairments associated with AD.[6] The maintenance of acetylcholine (ACh) levels in the synaptic cleft by inhibiting acetylcholinesterase (AChE), which is responsible for the degradation of ACh, is the only known means of treating AD. The four AChE inhibitors used in clinical practice for treatment of AD are tacrine, donepezil, galantamine, and rivastigmine.[7] Recently, pharmaceutical agents developed based on the β-amyloid hypotheses such as semagacestat (γ-secretase inhibitor), bapineuzumab and solanezumab (anti-Aβ antibody) were failed in phase III clinical trials.[8,9] Therefore, novel AChE inhibitors possessing less adverse effects and more cognitive enhancing effects could contribute to extend the choices to AD patients and clinical practitioners.

(−)-Galantamine (**1**) is an alkaloid present in the Caucasian snow-drop (*Galanthus woronowii*) and in bulbs of the Amaryllidaceae family, and was recently approved by the US FDA and Europe for the treatment of AD.[10] (−)-Galantamine (**1**) is a selective, reversible, competitive AChE inhibitor and allosteric modulator of neural nicotinic acetylcholine receptors.[11] The clinical experiences of galantamine in AD patients are promising, but it is less potent than other approved AChE inhibitors like tacrine and often causes peripheral side effects.[12] Furthermore, the production of galantamine requires a lengthy series of reactions because of its complex structure.

Pharmacophore modeling provides a useful tool of identifying hit compounds of pharmacologic interest.[13] Recently, scopoletin (**2**) (a widely distributed coumarin derivative found in the Solanaceae family) was identified as a potential AChE inhibitor by virtual screening of a 3D database of natural products based on the complex structure of galantamine-AChE.[14] Furthermore, although scopoletin has much less AChE inhibitory activity (IC_{50} = 168.6 μM) than galantamine (**1**, IC_{50} = 3.2 μM), it was found to increase extracellular ACh concentrations in rat brain to the same level as **1**.

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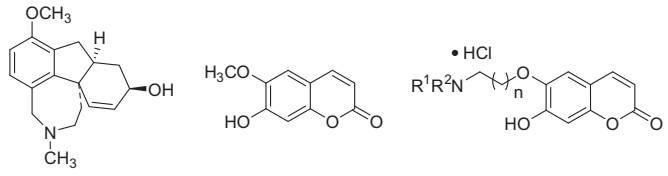
Accordingly, the aim of this study was to develop new coumarin derivatives starting from scopoletin with enhanced AChE inhibitory activities (Fig. 1).

A pharmacophore model generated from the three-dimensional structure of the galantamine-AChE complex and virtual screening based on this information indicated that the C-7 hydroxyl, lactone oxygen, and C-6 methoxy methyl in scopoletin are important features for AChE inhibitory activity, because they probably interact with the catalytic site of AChE as a H-bond donor, a H-bond acceptor, and a hydrophobic group, respectively.[14,15] Accordingly, based on these previous findings, we modified the C-6 methoxy methyl in **2** by incorporating aminoalkyl substituents. Additionally, amino groups were introduced into alkyl chain to increase water solubility, and thus, enhance oral bioavailability, and the effect of the length of the alkyl chain between C-6 oxygen and amino moieties was explored. Resultantly, a series of coumarin derivatives **3a**–**3j** were synthesized via a simple three-step sequence of reactions from scopoletin, and screened for their AChE inhibitory activities. In addition, synthesized compounds were also assessed for their memory ameliorating abilities in a mouse model of scopolamine-induced memory impairment using the passive avoidance task.



1, Galantamine **2**,Scopoletin **3**

Figure 1. Structures of galantamine (**1**), scopoletin (**2**) and target compounds (**3**).

2. Chemistry

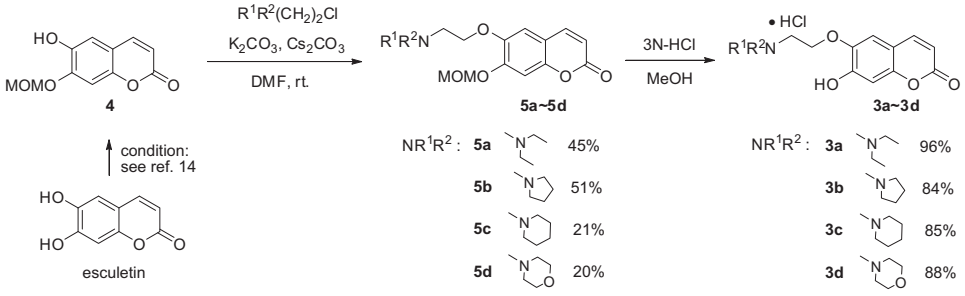
The syntheses of aminoethyl-substituted coumarin derivatives **3a**–**3d** were accomplished using the procedures shown in Scheme 1. C-7 MOM-protected esculetin (**4**), which was obtained from esculetin, as previously described,[16] was used as a starting material. Compound **4** was reacted with four commercially available aminoethyl chlorides in the presence of 1.5 equivalents of K_2CO_3 and 1 equiv of Cs_2CO_3, to provide **5a**–**5d** in 20–51% yields.[17] The MOM group in **5a**–**5d** was removed using 3 N HCl in methanol to afford **3a**–**3d** as hydrochloride salts in 85–95% yields.

Since many aminopropyl chlorides are not available commercially, aminopropyl-substituted coumarin derivatives **3e**–**3j** were prepared by synthesizing 3-halopropyloxy coumarin **6**, as shown in Scheme 2. Compound **4** was reacted with 1-bromo-3-chloropropane to give 3-chloropropyl-substituted coumarin. 3-Bromopropyl-substituted coumarin was also obtained as a minor product and the combined yield of the 3-halopropyl-substituted coumarin **6** was ca. 80%. Because both chloropropyloxy- and bromopropyloxy coumarins give the same products in next step, the mixture of 3-halopropyl-substituted coumarin **6** was reacted with various amines in the presence of K_2CO_3 and Cs_2CO_3 to afford **7**. Subsequent removal of the MOM group of **7** using 3 N HCl in methanol afforded **3e**–**3j** as hydrochloride salts in 16–38% overall yields for two steps from **6**.

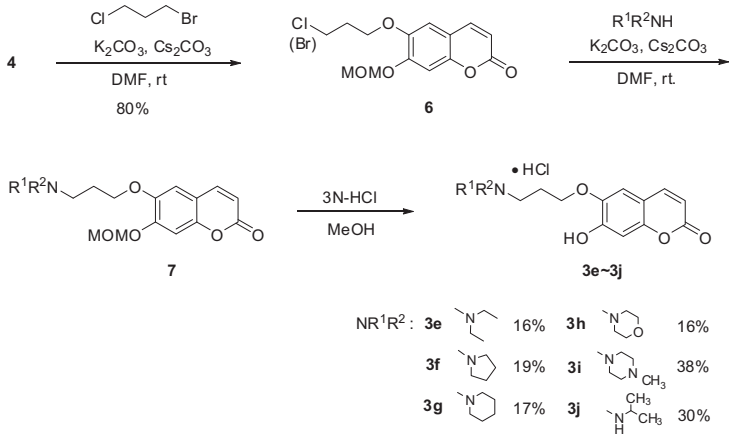
3. Results and discussion

3.1. The AChE inhibitory effects of coumarin derivatives

To determine inhibitory activities of compounds **3a**–**3j** on AChE, in vitro AChE inhibition assays were conducted according to the



Scheme 1.



Scheme 2.