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FULL PAPER

CHEMISTRY & BIODIVERSITY

3-Aryl Coumarin Derivatives Bearing Aminoalkoxy Moiety as Multi-Target-Directed Ligands against Alzheimer's Disease

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Two series of novel coumarin derivatives, substituted at 3 and 7 positions with aminoalkoxy groups, are synthesized, characterized, and screened. The effect of amine substituents and the length of cross-linker are investigated in acetyl- and butyrylcholinesterase (AChE and BuChE) inhibition. Target compounds show moderate to potent inhibitory activities against AChE and BuChE. 3-(3,4-Dichlorophenyl)-7-[4-(diethylamino) butoxy]-2*H*-chromen-2-one (**4y**) is identified as the most potent compound against AChE ($IC_{50} = 0.27$ μM). Kinetic and molecular modeling studies affirmed that compound **4y** works in a mixed-type way and interacts simultaneously with the catalytic active site (CAS) and peripheral anionic site (PAS) of AChE. In addition, compound **4y** blocks β-amyloid (Aβ) self-aggregation with a ratio of 44.11% at 100 μM and significantly protects PC12 cells from H_2O_2-damage in a dose-dependent manner.

Keywords: Alzheimer's disease, cholinesterase, neuroprotective activity, 3-phenylcoumarin, β-amyloid, synthesis design.

Introduction

Alzheimer's disease (AD), described by Alois Alzheimer in 1907, has become the most common irreversible

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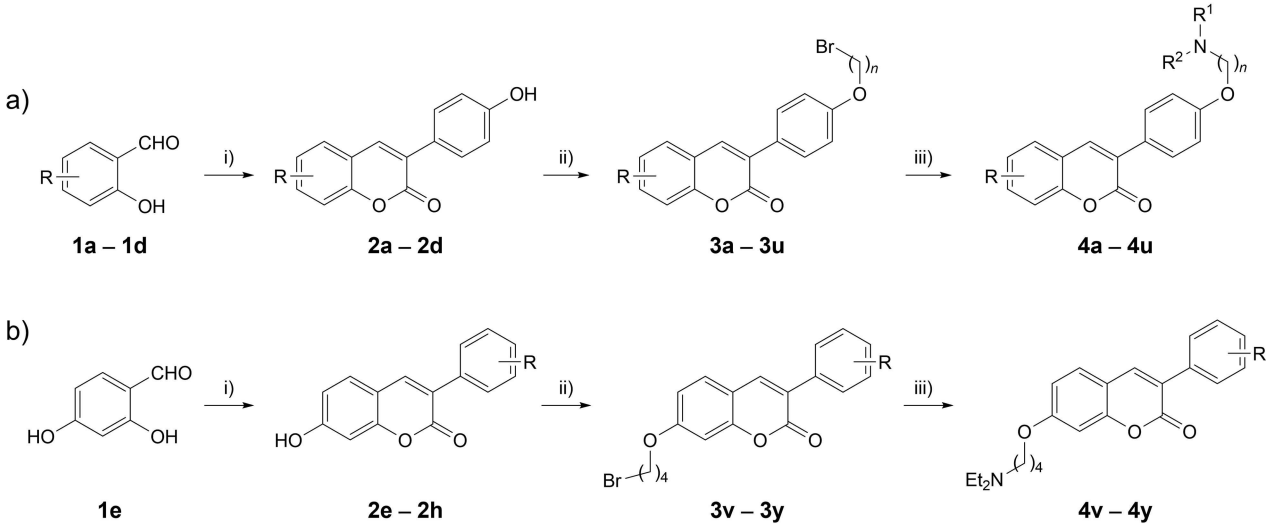

Scheme 1. Synthesis of 3-arylcoumarin derivatives bearing aminoalkyl moiety (compounds **4a**–**4y**). Reagents and conditions: i) arylacetic acids, AcONa (dry), Ac_2O, reflux; ii) corresponding dibromoalkanes, K_2CO_3, acetone, reflux; iii) corresponding secondary amines, K_2CO_3, MeCN, reflux.

neurodegenerative and progressive disorder characterized by cognitive and memory impairment.[1] The statistic depicts that almost 3% of elderly population aging 65–74 and 50% of 85-and-older age groups are affected by AD.[2] The main etiology of this disease is not completely diagnosed, so, various hallmarks such as oxidative stress, inflammation, low level of acetylcholine, τ protein aggregation and amyloid-β (Aβ) deposits seem to play crucial roles in the disease.[3–5] Current treatment of patients suffering from AD banks on increasing cholinergic neurotransmission in the brain through acetylcholinesterase (AChE) inhibitors like rivastigmine, donepezil, and galantamine. Despite the presence of these therapeutic agents, the complete prevention and treatment of AD still remain vague.[6] To meet the profound need of disease-modifying drugs, new approaches have arisen in medicinal chemistry.[7] Multipart etiology of AD propelled researchers to design structures with the ability to concurrently interact with different targets. To modulate multiple targets including acetyl- and butyrylcholinesterase (AChE and BuChE), Aβ aggregation along with neuroprotective properties, multi-target-directed ligands (MTDLs) working by the combination of distinct pharmacological moieties, could attain greater efficiency than that of classic drugs, based on 'one-molecule-one-target' strategy.[8–10]

Coumarins are one of the privileged naturally occurring compounds which have gained fame as a key pharmacophore, showing a diverse range of biological activities including anti-inflammatory, antioxidant, and AChE inhibitory activities.[11] In previous reports, coumarin derivatives exhibited their efficiency in Aβ aggregation together with AChE inhibitory activity.[12,13] For example, by linking *N*,*N*-benzyl (methyl)amino group to 3-phenylcoumarin core, a new series of compounds were introduced, which are capable of simultaneous binding to both catalytic and peripheral anionic site of the AChE.[14] Some of the 3-phenylcoumarin derivatives have been developed as multifunctional agents to simultaneously inhibit different enzymatic targets including monoaminoxidase (MAO), beta-secretase (BACE) and AChE for treating AD.[15–19] In the light of the above results and in continuation of our previous works on cholinesterase inhibitors,[20–22] herein, two series of 3-arylcoumarin derivatives bearing various secondary amine groups at 3 or 7 positions of the coumarin framework are synthesized and evaluated as AChE and BuChE inhibitors. Kinetic and ligand-enzyme docking studies, Aβ self and AChE-induced aggregation as well as neuroprotective activity are also investigated for the best compounds.

Results and Discussion

Chemistry

Target compounds **4a**–**4y** were synthesized according to the procedure illustrated in *Scheme 1*. Compounds **2a**–**2d** were synthesized by the Perkin–Oglialoro reaction between arylacetic acids and salicylaldehyde

