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Novel 3-phenylcoumarin–lipoic acid conjugates as multi-functional agents for potential treatment of Alzheimer's disease

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ABSTRACT

New series of triazole-containing 3-phenylcoumarin–lipoic acid conjugates were designed as multi-functional agents for treatment of Alzheimer's disease. The target compounds **4a-o** were synthesized *via* the azide-alkyne cycloaddition reaction and their biological activities were primarily evaluated in terms of neuroprotection against H_2O_2-induced cell death in PC12 cells and AChE/BuChE inhibition. The promising compounds **4j** and **4i** containing four carbons spacer were selected for further biological evaluations. Based on the obtained results, the benzocoumarin derivative **4j** with IC_{50} value of 7.3 μM was the most potent AChE inhibitor and displayed good inhibition toward intracellular reactive oxygen species (ROS). This compound with antioxidant and metal chelating ability showed also protective effect on cell injury induced by $A\beta_{1-42}$ in SH-SY5Y cells. Although the 8-methoxycoumarin analog **4i** was slightly less active than **4j** against AChE, but displayed higher protection ability against H_2O_2-induced cell death in PC12 and could significantly block Aβ-aggregation. The results suggested that the prototype compounds **4i** and **4j** might be promising multi-functional agents for the further development of the disease-modifying treatments of Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is certainly the most common cause of dementia and death in the elderly population which cannot yet be prevented or cured. None of the available drugs approved by the FDA (Food and Drug Administration) slows or stops the damages caused by the destruction of neurons and do not address the etiology of AD. They just temporarily improve cognitive function symptoms by increasing the cholinergic neurotransmitter, acetylcholine (ACh), *via* inhibiting the acetylcholinesterase (AChE) enzyme that causes rapid hydrolysis of acetylcholine in the brain [1].

Previous researches have shown that in addition to AChE, butyrylcholinesterase (BuChE) as a co-regulator of the ACh degradation also plays an important role in cholinergic neurotransmission [2]. The

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extracellular deposits of the protein fragment beta-amyloid (Aβ) and accumulation of an abnormal form of tau protein inside neurons (neurofibrillary tangles) in brain regions are two hallmark lesions of AD which provide synaptic dysfunction, pro-inflammatory and toxic effects on neuronal cells [3–5]. According to 'amyloid hypothesis', AChE impresses the Aβ aggregation *via* binding to the peripheral anionic binding site (PAS) [6,7]. Besides these hallmarks, oxidative stress plays a key role in the pathogenesis of AD and is a major mechanism underlying Aβ-induced neurotoxicity [8–10]. Several studies suggested that Aβ aggregates with entrapped redox-active metal ions such as copper, zinc, and iron lead to the intracellular accumulation of reactive oxygen species (ROS) [11,12]. Therefore, development of drugs with additional antioxidant and metal chelating properties could be useful therapeutic strategies for targeting of oxidative stress and inhibiting Aβ-induced neurotoxicity in AD. In concordance with these findings, drug design strategies reshaped against the particular step of the neurotoxic cascade.

In overall, it is well-established that AD is associated with multiple etiologies and pathophysiologic mechanisms. Consequently, therapeutics that could modulate simultaneously multiple targets and have potential to modify disease course including cholinesterases, Aβ aggregation, ROS, metal ions and neurotoxic complications may enhance efficacy of pharmacotherapy [13–15]. With this paradigm, the "multi-target-directed ligands" (MTDLs) strategy encouraged medicinal chemist to rationally design hybrid molecules exhibiting various pharmacological functions. Using two or several structural features of two compounds with specific activity into a single molecule to reach the desired dual or multiple complementary biological activities; in most cases, at least one is directly related to an AChE inhibition [16–18]. For example, tacrine-melatonin and tacrine-ferulic acid hybrids have been designed as potent cholinesterase inhibitors with antioxidant property [19]. Lipocrine (Fig. 1) which is a conjugate of tacrine (a potent AChE inhibitor) and lipoic acid (LA, an antioxidant and radical scavenger), showed effective inhibition against AChE, BuChE, AChE-induced Aβ aggregation, and ability to protect cells against ROS [20].

Coumarins with benzopyranone framework are widely distributed in nature and possess a wide range of biological activities [21,22]. In particular, some pharmacological properties of coumarins are associated with neurological diseases especially for AD [23–26]. It has been observed that 3-arylcoumarins such as AP2469 (Fig. 1), beside a remarkable inhibition of AChE, have shown anti-Aβ aggregation, antioxidant, neuroprotective, and anti-inflammatory activities, and consequently act as disease-modifying agents [27,28].

On the other hand, lipoic acid (LA) is naturally occurring substance which prescribed as a supplement, possessing diverse pharmacologic and antioxidant properties. LA antioxidant properties have been related to the mitochondria-targeted endogenous antioxidant, free radicals scavenging in lipid and aqueous mediums, and metal-chelating properties [29]. However, there are no significant results of clinical trials for LA benefit in dementia [30], it suggests that single antioxidants may not be sufficient for the treatment of neurodegenerative diseases, while optimal hybridization of antioxidants with compounds which are able to modulate different AD crucial targets may provide a synergistic effect to display a multi-target profile. By this concept, several studies have demonstrated the beneficial properties of LA derivatives in several models of oxidative stress and neuroprotection [31–34].

Continuing with our interest in the development of new structures for the potential treatment of AD [35–40], we focused our efforts on the development of a novel series of 3-arylcoumarins as new MTDLs with additive neuroprotective effects through hybridization approach. To reach this purpose, LA as an antioxidant and the 3-arylcoumarin scaffold as AChE inhibitor were connected together by application of click reaction (Fig. 1). Thus we report here, the synthesis and biological evaluation of designed compounds **4** with potential application in the AD.

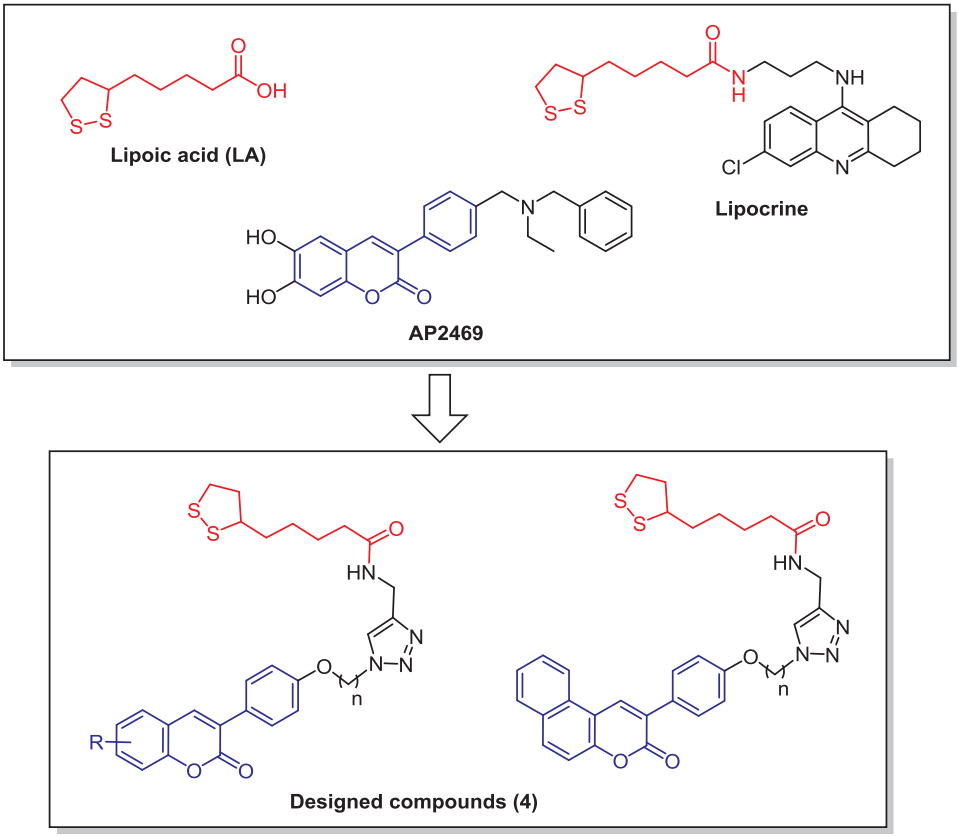

Fig. 1. Design strategy for compounds **4**.