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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Hetero-annulated coumarins as new AChE/BuChE inhibitors: synthesis and biological evaluation

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Abstract A series of chromene-fused coumarins known as 10,11-dihydrochromeno[4,3-*b*]chromene-6,8(7*H*,9*H*)-diones **4a–o** were synthesized through one-pot reaction of appropriate benzaldehydes, dimedone, and 4-hydroxycoumarin in the presence of nano-silica sulfuric acid under solvent-free condition in good yields. The in vitro anticholinesterase assay revealed that the 3-hydroxyphenyl analog **4e** showed the highest inhibitory activity against both acetylcholinesterase and butyrylcholinesterase, possessing IC_{50} values of 3.28 and 2.19 μM, respectively. The structure-activity relationships study demonstrated that the selectivity for acetylcholinesterase over butyrylcholinesterase could be modulated by introducing second hydroxyl or methoxy substituent on the *para*-position of the 3-hydroxyphenyl pendent group. The docking study of compound **4e** with acetylcholinesterase confirmed π–π stacking interaction between the coumarin moiety and Trp279 as well as the formation of hydrogen bonding between hydroxyl group and Asn85.

Keywords Alzheimer's disease · Acetylcholinesterase · Coumarin-fused derivatives · One-pot synthesis · Multicomponent reactions

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Introduction

Acetylcholinesterase (AChE) is a serine hydrolase enzyme mainly found in peripheral and central nervous system. It catalyzes the hydrolysis of the ACh to choline in order to terminate nerve impulses (Čolović et al., 2013). Hence, cholinergic neurotransmission is involved in a variety of pathophysiological conditions; AChE is a known pharmacological target for the treatment of several pathologies particularly Alzheimer's disease (AD) (Orhan et al., 2011). The pathogenesis of AD is related to the deficiency of ACh in the brain and in this respect, AChE inhibitors may be used to treat some symptoms of AD (Hong-Qi et al., 2012). Moreover, AChE inhibitors have been used in the treatment of glaucoma (McKinnon et al., 2008), myasthenia gravis, and neuromuscular blockade (Meriggioli and Sanders, 2009; Bevan et al., 1992).

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