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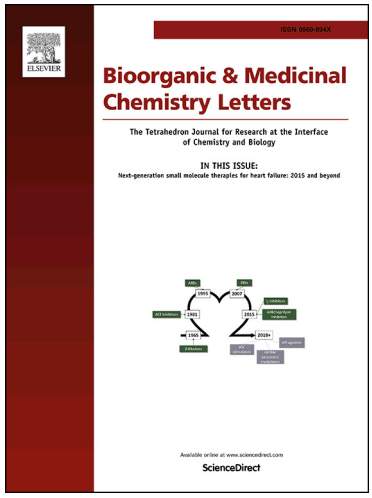

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Structure-Based Design, Synthesis, and Evaluation of Structurally Rigid Donepezil Analogues as Dual AChE and BACE-1 Inhibitors

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Abstract: A new series of structurally rigid donepezil analogues was designed, synthesized and evaluated as potential multi-target-directed ligands (MTDLs) against neurodegenerative diseases. The investigated compounds **10-13** displayed dual AChE and BACE-1 inhibitory activities in comparison to donepezil, the FDA-approved drug. The hybrid compound **13** bearing 2-aminoquinoline scaffold exhibited potent AChE inhibition (IC_{50} value of 14.7 nM) and BACE-1 inhibition (IC_{50} value of 13.1 nM). Molecular modeling studies were employed to reveal potential dual binding mode of **13** to AChE and BACE-1. The effect of the investigated compounds on the viability of SH-SY5Y neuroblastoma cells and their ability to cross the blood-brain barrier (BBB) in PAMPA-BBB assay were further studied.

Keywords: Multi-target-directed ligands, Acetylcholinesterase, β-Secretase, Donepezil, Hybridization

Alzheimer's disease (AD), a chronic neurodegenerative disease, is classified as the major cause of dementia among the population above age 65 [1]. Current pharmacotherapy approaches of AD are palliative that only alleviate the symptoms and delay the progress of AD through inhibition of acetylcholinesterase (AChE) [2]. Dementia is directly correlated to the dysfunction in basal forebrain cholinergic system of AD patients [3]. Thus, inhibition of AChE blocks acetylcholine hydrolysis which consequently improves the cholinergic functions in AD patients [4]. β-Secretase 1 (BACE-1) has emerged as a potential target for development of therapeutics for neurodegenerative diseases [5-7]. BACE-1 catalyzes the cleavage of the amyloid precursor protein (APP) which is the precursor of amyloid beta (Aβ) peptides [8]. The transformation of Aβ peptides into mature amyloid fibrils and their deposition in human brain is the key step in the pathogenesis of AD [9]. The poor efficacy of lead BACE-1 and AChE inhibitors *in vivo* has developed a pressing need towards development of multi-target-directed ligands (MTDLs) as potential therapeutics of AD [10, 11].

Donepezil (**1**, Figure 1) is a FDA approved drug for palliative treatment of AD that acts through potent and selective inhibition of AChE [12]. Favorable pharmacokinetic profile and potent AChE inhibition *in vivo* of donepezil have directed significant research efforts towards development of donepezil analogues as potential therapeutics of AD [13-15]. AZD3839 (**2**,