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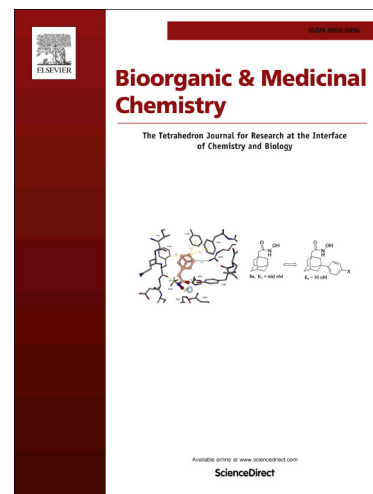
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## Isoindoline-1,3-dione derivatives targeting cholinesterases: Design, synthesis and biological evaluation of potential anti-Alzheimer's agents

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### Abstract

Alzheimer's disease is a fatal neurodegenerative disorder with a complex etiology. Because the available therapy brings limited benefits, the effective treatment for Alzheimer's disease remains the unmet challenge. Our aim was to develop a new series of donepezil-based compounds endowed with inhibitory properties against cholinesterases and  $\beta$ -amyloid aggregation. We designed the target compounds as dual binding site acetylcholinesterase inhibitors with *N*-benzylamine moiety interacting with the catalytic site of the enzyme and an isoindoline-1,3-dione fragment interacting with the peripheral anionic site of the enzyme. The results of pharmacological evaluation lead us to identify a compound **3b** as the most potent and selective human acetylcholinesterase inhibitor (*hAChE* IC<sub>50</sub> = 0.361  $\mu$ M). Kinetic studies revealed that **3b** inhibited acetylcholinesterase in non-competitive mode. The result of the parallel artificial membrane permeability assay for the blood-brain barrier indicated that the compound **3b** would be able to cross the blood-brain barrier and reach its biological targets in the central nervous system. The selected compound **3b** represents a potential lead structure for further development of anti-Alzheimer's agents.

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