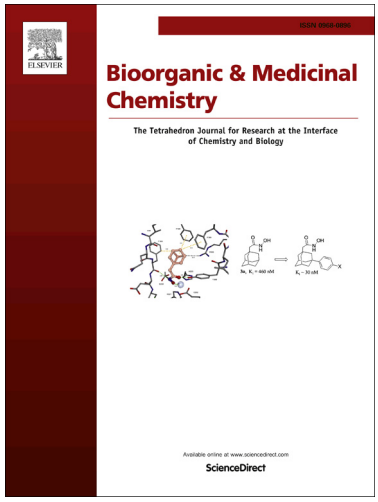
Accepted Manuscript



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

Natalia Guzior, Marek Bajda, Jurand Rakoczy, Boris Brus, Stanislav Gobec, Barbara Malawska

PII: S0968-0896(15)00069-3
DOI: http://dx.doi.org/10.1016/j.bmc.2015.01.045
Reference: BMC 12048

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 25 November 2014
Revised Date: 22 January 2015
Accepted Date: 25 January 2015

Please cite this article as: Guzior, N., Bajda, M., Rakoczy, J., Brus, B., Gobec, S., Malawska, B., Isoindoline-1,3-dione derivatives targeting cholinesterases: Design, synthesis and biological evaluation of potential anti-Alzheimer's agents, *Bioorganic & Medicinal Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bmc.2015.01.045

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

Natalia Guzior[a], Marek Bajda[a], Jurand Rakoczy[a], Boris Brus[b], Stanislav Gobec[b], Barbara Malawska[a*]

[a]Department of Physicochemical Drug Analysis, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland, [b]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

***Corresponding Author Information**

Phone: 48-12-620-54-64. E-mail: mfmalaws@cyf-kr.edu.pl.

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 β-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 (*h*AChE IC_{50} = 0.361 μM). 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.