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BOOK OF ABSTRACTS

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Influence of the structures of THIQ derivatives on their inhibitory properties toward acetyl- and butyrylcholinesterase

Dunja Jovanovic¹, Ana Filipovic², Bojan Bondzic², Aleksandra Bondzic¹

¹ Vinca Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade, Belgrade, Serbia

² National Institute of the Republic of Serbia, University of Belgrade-Institute of Chemistry, Technology and Metallurgy, Belgrade, Serbia

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Alzheimer's disease (AD), the most common form of dementia, is a progressive neurological disorder characterized by losing memory and other intellectual abilities that are serious enough to interfere with daily life. The disease is associated with loss of cholinergic neurons in the brain and the decreased level of ACh. In order to raise the ACh level in the brain the acetylcholinesterase (AChE) inhibitors have been applied as relevant drugs in the AD therapy. On the other hand, these inhibitors treat and improve only symptoms indicating necessity for new better therapies. One of them could be based on the inhibition of butyrylcholinesterase (BuChE) because of its increased activity during late stage of AD. Therefore, the BuChE inhibitors should be of great importance in therapy. 1,2,3,4-tetrahydroisoquinolines (THIQ) are a large group of natural and synthetic compounds which exert diverse biological activities against various infectious pathogens and neurodegenerative disorders. Due to these reasons, the THIQ have attracted a lot of attention in the scientific community which has resulted in the development of novel THIQ analogues with more potent biological activity. In this study the inhibitory potency of derivatives of N-phenyl-1,2,3,4-tetrahydroisoquinoline, 178, 196 and 202, were investigated toward two cholinergic enzymes, AChE and BuChE. The performed screening tests pointed out the different inhibition potency of the selected compounds toward both enzymes which was related with their structures. The most potent compound has been 178 with IC₅₀ values 1.30 μM and 2.50 μM toward AChE and BuChE, respectively. However, no selectivity was observed. Introducing F-atom in the para position of N-phenyl group of the compound 178, the compound 202 was obtained. In this way, the selectivity was increased towards acetylcholinesterase without significant influence on the IC₅₀ value. However, introducing a methoxy groups in the position C3 and C4 of the tetrahydroisoquinoline's ring of 202, the compound 196 with decreased inhibitory activity was obtained. IC₅₀ value of 196 was one order of magnitude higher compared with compound 202. Based on the obtained results it is possible to conclude that introducing F atom in the para position of the phenyl ring lead to increased selectivity of the investigated compounds while introducing methoxy group in the position of C3 and C4 of tetrahydroisoquinoline ring leads to decrease of their inhibitory potency.

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