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Memantine derivatives with potential neuroprotective effect: Synthesis and biological activity

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Memantine is a NMDA-receptor antagonist that inhibits excessive calcium influx induced by overstimulation of the NMDA receptor. Memantine is approved in the US and the EU for the treatment of patients with moderate to severe dementia of the Alzheimer's type. A series of memantine derivatives incorporating amino-acid residues have been synthesized for the first time and their neuroprotective effects in vitro have been studied.

Methodology and Theoretical Orientation: The new amino acids derivatives were synthesized by TBTU as a coupling reagent. Briefly, commercially available tert-butyloxycarbonyl amino acids and memantine underwent a two-step process involving formation of amide bond. Firstly, the N-Boc protected amino acids was transformed to amide group derivatives by the standard condensation reaction.

The target compounds were further prepared by removal of the N-Boc protecting group of in the presence of trifluoroacetic acid at 0°C. The final memantine analogues as TFA salt were obtained as a free base using aqueous ammonia Fig. 1.

Memantine derivatives protected APPswe cells against copper-induced cytotoxicity. APPswe cells injured by copper, which triggers β-amyloid toxicity, were served as an AD model in vitro. There were two compounds, memantine with aromatic amino acids demonstrating better neuroprotective effects compared with the memantine.

Memantine analogues protected PC12 cells against CoCl2-induced cytotoxicity. CoCl2 was used to establish a hypoxic condition for PC12 cells. There were six compounds (memantine with aliphatic and aromatic amino acids) showing approximative neuroprotective effects on PC12 cells against CoCl2-induced toxicity compared to the memantine.

Amino acids analogues of memantine inhibited the release of TNF-α and IL-6 caused by lipopolysaccharide (LPS)-stimulated EOC20 cells. The EOC20 cells stimulated by LPS was used to imitate the inflammatory and neurotoxic activation of microglia. ELISA was used to examine the inflammatory cytokine levels in cultural medium released from EOC20 cells simulated by LPS after treated with the 7 compounds. Especially, memantine with aromatic amino acids showed equivalent effects on inhibiting the release of TNF-α and IL-6 on LPS-induced EOC20 cell compared with the positive drug memantine.

Conclusion: The rational synthesis of our compounds was based on the fact that some amino esters of certain antivirals (e.g. the antiherpes valacyclovir) are known as prodrugs. Thus, the study of the neuroprotective properties of derivatives of the memantine that contain aromatic and aliphatic amino acids led to compounds which show increased activity, compared to memantine.

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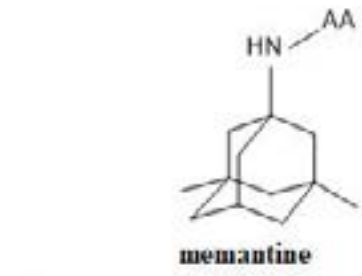

Biography

Radoslav Chayrov is a researcher in the field of drug design and modification on natural biologically active compounds. He started his scientific work under the supervision of Prof. Ivanka Stankova in South-West University on 2009 as a bachelor student. Two years later in 2011 He completed his master's degree - "Biologically active compounds and drugs". In 2014 he started PhD education and graduated successfully in 2017. The thesis topic is "Synthesis and analysis by HPLC of antiviral drug analogues". In present he is co-author of two patents related to biologically active molecules.

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