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MEETING ABSTRACTS

NOVEL CONJUGATES BASED ON γ-CARBOLINES, CARBAZOLES, PHENOTHIAZINES, AND AMINOADAMANTANES AS MULTIFUNCTIONAL AGENTS FOR ALZHEIMER'S DISEASE TREATMENT

G.F. Makhaeva [1], N.P. Boltneva [1], N.V. Kovaleva [1], S.V. Lushchekina [1,2], E.V. Rudakova [1], R.J. Richardson [3], S.O. Bachurin [1]
Presenting author: G.F. Makhaeva

[1] Institute of Physiologically Active Compounds Russian Academy of Sciences, Severny Proezd 1, Chernogolovka, 142432, Russia,
[2] Emanuel Institute of Biochemical Physics Russian Academy of Sciences, Kosygina Str. 4, Moscow, 119334, Russia
[3] Departments of Environmental Health Sciences and Neurology, University of Michigan, Ann Arbor, MI 48109 USA

Neurodegenerative diseases are multifactorial. Therefore, their treatment requires drugs that can act simultaneously on multiple pathogenic targets. We synthesized several series of hybrid structures combining certain pharmacophores essential for neurodegenerative disease treatment: γ-carbolines, carbazoles, phenothiazines, and aminoadamantanes [1-3]. Inhibitory activity of these conjugates against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and carboxylesterase (CaE) was studied along with their ability to competitively displace propidium iodide from the peripheral anionic site of electric eel AChE to assess their potential effect on AChE-induced aggregation of β-amyloid. Antioxidant properties were examined computationally with density functional theory and measured experimentally using 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) and oxygen radical absorbance capacity (ORAC-FL) assays. Binding modes of conjugates to AChE and BChE were studied using quantum mechanical-assisted molecular docking. Results revealed structures that were selective inhibitors of BChE [1,2] or that combined high potency and selectivity toward BChE with high radical-scavenging activity, e.g., conjugates of γ-carbolines and tetrahydrocarbazoles [3]. Conjugates of γ-carbolines and cycloalcaneindoles with the phenothiazine derivative Methylene Blue demonstrated high potency against AChE and BChE combined with effective displacement of propidium from the peripheral anionic site of AChE. Additionally, the conjugates were extremely active in both antioxidant tests. All conjugates were poor CaE inhibitors and therefore expected to lack drug-drug interactions by this pathway. Good agreement was found between experimental and computational results. Lead compounds were identified for future optimization and development of new multi-target drugs against neurodegenerative diseases that combined cognition enhancement with neuroprotective potential.

Keywords: Alzheimer's disease; multifunctional agents; γ-carboline; phenothiazine; aminoadamantane

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