Gjumrakch Aliev, J Pharm Drug Deliv Res 2017, 6:5
DOI: 10.4172/2325-9604-C1-022

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Conjugates of γ-carbolines and phenothiazine as new multitarget inhibitors of butyrylcholinesterase and blockers of NMDA receptors for Alzheimer disease

The development of novel compounds that are able to modify the pathogenesis of neurodegenerative diseases appears to be as a promising approach among different drug discovery strategies in this emerging area. Taking into account the multifactorial nature of neurodegenerative diseases, focusing on the design of multitarget drugs that are capable to act simultaneously on different main biotargets, which are involved in the disease pathogenesis, seems to be very attractive and promising. During the past decade, previous studies have indicated that the progression of Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS) and some other neuropathological disorders is closely connected to dysfunctions in cholinergic and glutamatergic neuronal systems. In addition, AD is a multifactorial pathology and the development of new multitarget neuroprotective drugs is promising and attractive. We synthesized a group of original compounds, which combine in one molecule γ-carboline fragment of dimebon and phenothiazine core of methylene blue (MB) linked by 1-oxo- and 2-hydroxypropylene spacers. Inhibitory activity of the conjugates toward acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and structurally close to them carboxylesterase (CaE), as well their binding to NMDA-receptors were evaluated in vitro and in silico. These newly synthesized compounds showed significantly higher inhibitory activity toward BChE with IC50 values in submicromolar and micromolar range and exhibited selective inhibitory action against BChE over AChE and CaE. Kinetic studies for the 9 most active compounds indicated that majority of them were mixed-type BChE inhibitors. The main specific protein-ligand interaction is π-π stacking of phenothiazine ring with indole group of Trp82. These compounds emerge as promising safe multi-target ligands for the further development of a therapeutic approach against aging-related neurodegenerative disorders such as Alzheimer and/or other relevant pathological conditions.

Biography

Gjumrakch Aliev authored and coauthored more than 500 publications in the fields of neurodegenerative diseases research (Alzheimer disease), as well as cardio and cerebrovascular disease, cancer, and electron microscopy. He is an outstanding teacher, scholar, and a renowned scientist in the area of cellular molecular physiology, and cardiovascular, and neurodegeneration-mediated pathologies including Alzheimer disease (AD). He is nationally and internationally reputed in his area. Dr. Aliev's accomplishments in the area of biochemistry and cellular biology have tremendous implications for drug design towards CNS Neurological Disorders, AD, cancer, and cerebrovascular and neurodegeneration related pathologies. He is world-renowned expert in electron microscopy. His work has been published in numerous prestigious journals such as Nature Clinical Cardiology, J. Neuroscience, Scientific Reports, Circulation Research, New England journal of Medicine, Blood, J. Cellular and Molecular Medicine, Atherosclerosis, CNS Neurological Disorders & Drug Targets, international J. Biochemistry and Cell Biology, and many others which reflect his leading role in his research areas. He is currently the Editor in Chiefs for *"Central Nervous System Agents in Medicinal Chemistry", "Applied Cell Biology", "World Journal of Neuroscience", "Open Journal of Psychiatry", "Journal of Aging Science", "Cardiovascular & Hematological Agents in Medicinal Chemistry", "Immunology, Endocrine and Metabolic Agent in Medicinal Chemistry" as well as* which by itself shows the voluminous and outstanding work he has accomplished in the area of cellular and molecular biology as well as aged associated clinical sciences. He is one of most cited authors in his fields with high impact factors.

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