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Conjugates of Y-Carbolines and Phenothiazine as new multitarget inhibitors of butyrylcholinesterase and blockers of NMDA receptors for Alzheimer Disease

Gjumrakch Aliev
GALLY International Biomedical Research LLC, USA

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 (Figure 1). The main specific protein-ligand interaction is π-π stacking of phenothiazine ring with indole group of Trp82. These compounds emerge as promising safe multitarget ligands for the further development of a therapeutic approach against aging-related neurodegenerative disorders such as Alzheimer and/or other relevant pathological conditions.

aliev03@gmail.com
cobalt55@usa.net