Conjugates of ? 3-Carbolines and Phenothiazine as new selective inhibitors of butyrylcholinesterase and blockers of NMDA receptors for Alzheimer Disease

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Alzheimer disease 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 I 3-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 IC 50 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 I ?-I ? 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 pathological

conditions.