Abstract

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Alzheimer's disease (AD) is a fatal neurodegenerative disorder of brain. Nowadays there is only paliative treatment available, which can be further subdivided into two groups: acetylcholinesterase inhibitors (AChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonist. Donepezil, rivastigmine and galantamine represents AChEIs currently available for AD treatment. Tacrine is the first AChEIs to be approved for AD treatment, however, it was withdrawn from the market due to its side effects, especially due to its hepatotoxicity. 7-Methoxytacrine (7-MEOTA) is less toxic tacrine derivative preserving pharmacological profile of tacrine.

This diploma thesis describes synthesis of multifunctional 7-MEOTA-amantadine derivatives as potential drugs to confront AD. Using Ellman's method, we have established their efficacy to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) *in vitro*. All new synthesized hybrids from 7-MEOTA-amantadine family proved to be better inhibitors compared to both reference compounds 7-MEOTA and amantadine. Derivative **14** was even more potent in inhibiting AChE than tacrine. None of the new derivatives overwhelmed BChE inhibitory potency of tacrine. Inhibitory values of new 7-MEOTA-amantadine derivatives were ranging in micromolar to submicromolar IC_{50} values. Finally, molecular modeling studies on human AChE and BChE were performed in order to rationalize result from *in vitro* assays. According to *in silico* studies of chosen derivatives, 7-MEOTA-amantadine hybrids presumably bind to both anionic active sites of AChE.