ABSTRACT

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Title of Doctoral Thesis **Synthesis of tetrahydroacridine inhibitors of acetylcholinesterase**

Cholinesterase inhibitors have beneficial effects on cognitive, functional, and behavioural symptoms of Alzheimer's disease (AD). Up to date, they represent the only drugs approved by U.S: Food and Drug Administration for AD treatment. These include donepezil, rivastigmine and galantamine. Apart from the above mentioned cholinesterase inhibitors memantine is used for AD treatment as well, acting as N methyl-D-aspartate antagonist drug.

Tacrine (9-amino-1,2,3,4-tetrahydroacridine) was the first cholinesterase inhibitor to obtain a marketing authorisation in symptomatic treatment of AD. However, its several side effects (hepatotoxicity and gastrointestinal discomfort) limited tacrine broader usage. Novel tacrine derivatives are extensively investigated in endeavour to find less toxic compounds with „multi-target directed ligand" profile affecting more pathological mechanisms.

As a part of these research efforts, 7-methoxytacrine (7-MEOTA) has been prepared as a less toxic derivate compared to tacrine with the same pharmacological profile.

Within this doctoral thesis, novel derivatives of tacrine and 7-MEOTA were synthesized, biologically evaluated for their cholinergic potential towards both cholinesterases – acetylcholinesterase (AChE, E.C. 3.1.1.7) and butyrylcholinesterase (BChE; E.C. 3.1.1.8). To rationalize findings from in vitro assay, the plausible orientation of the most perspective compounds in the active site of cholinesterases were computed and visualized.

Besides biological data and molecular modelling studies, the structure-activity relationships are also discussed. For the most promising analogues in the series of urea/thiourea derived from tacrine 7 MEOTA conjugates, we deal with in vivo toxicity assessments on animals, monoaminooxidase and NADH dehydrogenase activity as well as with determination of anti-amyloid activities (tested on insulin, lysozyme and Aβ1-40).