Abstract

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Title of diploma thesis: Synthesis and evaluation of selected enzyme inhibitors as potential drugs

This diploma thesis deals with the synthesis of new inhibitors of the mycobacterial enzyme InhA and inhibitors of acetylcholinesterase and butyrylcholinesterase and their potential inhibitory effect against these three enzymes. All of the prepared compounds are analogues derived from triclosan, which could be convenient candidates as potential drugs for the treatment of tuberculosis and neurodegenerative diseases including Alzheimer's disease.

The theoretical part summarizes facts about tuberculosis including the resistance of mycobacteria to antituberculosis drugs and research of new drugs against tuberculosis. Also, the cholinergic hypothesis and the investigation of new potential inhibitors of cholinesterases are described briefly. The experimental part reports the reactions leading to the preparation of designed compounds. The chapter Results and discussion summarizes structure-activity relationships. It also discusses the synthesis and its complications.

Eight compounds (two precursors for further syntheses and modifications, two final amides, two ureas and two carbamates) were prepared in satisfactory yields. All of them were tested for their antimicrobial activity and cholinesterase inhibitory activity. The compound *N*-[5-chloro-2-(2,4-dichlorophenoxy)phenyl]acetamide showed the best antimicrobial activity against all three selected mycobacteria at all. It had minimum inhibitory concentration of 31.25 mg/L against *M. smegmatis*, 15.625 mg/L against *M. aurum* and 7.81 mg/L against *M. tuberculosis* $H_{37}Ra$, respectively. This compound even showed the lowest IC_{50} value for acetylcholinesterase (48.85 μM) of all the prepared compounds and has a better inhibitory effect against acetylcholinesterase than the clinically used carbamate drug rivastigmine (56.10 μM). The precursor 5-chloro-2-(2,4-dichlorophenoxy)aniline ("amino-triclosan") showed the best inhibition of

butyrylcholinesterase (IC_{50} of 11.93 μM), which is a better inhibitory activity compared to rivastigmine again. Triclosan showed comparable inhibitory activity (11,81±0,04 μM) against BuChE to its isoster "amino-triclosan". It was found that triclosan is a mixed inhibitor.

The determination of structure-activity relationships suggests that "amino-triclosan" analogues are perspective for further studies and investigation of triclosan analogues as potential inhibitors of acetylcholinesterase and butyrylcholinesterase and for experimental determination of mechanism of action against mycobacteria.