ABSTRACT

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Training Workplace Department of Organic and Bioorganic Chemistry

Doctoral Degree Program Bioorganic Chemistry

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Title of Doctoral Thesis: Synthesis and evaluation of potential antimicrobial drugs

The dissertation thesis reports some results achieved within the framework of a doctoral project dealing with the synthesis and evaluation of potential antimicrobial drugs. The main goal was to obtain new derivatives of isoniazid and its analogues acting against *Mycobacterium tuberculosis* and non-tuberculous mycobacteria, optimally including resistant strains. A partial aim was the preparation of peptide carriers for antituberculosis drugs, which, in addition to the development of new molecules, is another promising direction for the development of new therapeutic strategies against tuberculosis.

The theoretical part of the dissertation overviews the issue of tuberculosis. The aetiology of the disease, the morphology of the cell wall of mycobacteria and selected epidemiological data are presented there. The treatment and characteristics of clinically used drugs are described in detail, this chapter is followed by a brief research review of promising clinically evaluated potential antituberculotics, especially new InhA and DprE1 inhibitors that target cell wall synthesis.

The experimental part comments on the results of research on new antituberculosis drugs. The synthesis of the compounds was based on isoniazid, which was conjugated *via* a pyruvate linker with various amines, alcohols (or phenols and their thio analogues) to form corresponding amides or (thio)esters. The target products were usually obtained by C-N carbodiimide mediated coupling catalysed by 1-hydroxybenzotriazole or 4-(dimethylamino)pyridine.

Our, mostly originally synthesized compounds showed high antimycobacterial potential in several cases. These are probably InhA inhibitors, for some of them this mechanism of action

was confirmed experimentally, for a number of them with very low minimum inhibitory concentrations (MICs) against *Mtb*. (from ≤ 0.03 μM), although for some compounds (especially esters) it is also possible to consider an additional mechanism of action. Some compounds also showed excellent activity against non-tuberculous mycobacteria (MIC against *M. kansasii* from ≤ 0.25 μM). The thesis discusses in detail all the basic experimental data of three selected publications regarding the design, preparation, and evaluation of the biological activity of the derivatives, which were designed also as possible prodrugs (with improved efficacy, absorption and penetrability through biological barriers or reduced toxicity).

The work is also devoted to the preparation and evaluation of tuftsin-based peptide carriers for antituberculosis drugs, which were designed mainly with the aim of increasing intracellular activity and reducing the toxicity of small molecules.

As part of the work, it was possible to identify several promising compounds.

Key words: Amides, antituberculotics, esters, InhA, isoniazid, tuberculosis, tuftsin