Abstract

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Title of Diploma Thesis: **Pyrazinamide derivatives as potential antimicrobial compounds**

Even in 21st century, tuberculosis still remains a serious and global health threat. Tuberculosis is one of the 10 most common causes of death, the most burdened are developing countries, but this disease infects up to 1/3 of population worldwide. Due to ineffective treatment of tuberculosis in developing countries, the prevalence of tuberculosis which does not respond to standard treatment is increasing. It is necessary to develop new drugs effective against multidrug-resistant tuberculosis and prevent further spread of the disease.

The design of final structures is based on previously synthesized molecule 6-chloro-*N*-(4-(4-fluorophenyl)thiazol-2-yl)pyrazine-2-carboxamide, which structure comes from first line antitubercular pyrazinamide (PZA) and 4-arylthiazol-2-amine scaffold with formerly identified antimycobacterial activity. This starting compound exhibits high activity against *M. tuberculosis* described by MIC = 0,78 μg/mL and low cytotoxicity. The object of study was to determine effect of substitution of chlorine at position 6 of pyrazine ring by different alkylamine chains. We suggest mycobacterial β-ketoacyl-ACP-synthase III as a potential target, in response to results of molecular docking study and structural similarity to known inhibitors of this enzyme.

The experimental part of this study is focused on molecular docking of the molecules into specific enzyme (pdb: 1U6S) and their subsequent synthesis. The compounds were prepared by single-step nucleophilic substitution. Individual compounds were described by melting point, ^{1}H, ^{13}C spectra and IR spectra. The compounds were *in vitro* tested for their antitubercular activity. Generally, the substitution of chlorine by alkylamino chains decreased the antimycobacterial activity, despite promising results of molecular docking.