ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové
Department of Department of Pharmaceutical Chemistry and Pharmaceutical Analysis
Candidate **Ghada Bouz**
Supervisor **Prof. PharmDr. Martin Doležal, Ph.D.**
Title of Doctoral Thesis **Derivatives of Pyrazinecarboxylic Acid as Potential Antimycobacterial Active Drugs**

This doctoral thesis is focused on the design, synthesis, and in vitro antimicrobial evaluation of potentially active compounds structurally derived from the first line antitubercular, pyrazinamide. The introduction briefly highlights the serious issue of tuberculosis in the present time, along with the reasons behind the failure to eradicate this ancient infection. The lack of a proper animal model that can replicate tuberculosis in its latent and active form was discussed more in detail, where zebrafish (Danio rerio) was suggested as a novel animal model suitable for multi-research purposes connected to tuberculosis.

A total of 112 compounds were synthesized and published as part of this doctoral work. They are divided into four main structural types, namely 3-(phenylcarbamoyl)pyrazine-2-carboxylic acids, 3- aminopyrazine-2-carboxamides, ureidopyrazines, and N-(pyrazin-2-yl)benzenesulfonamides. All prepared compounds were in vitro screened against five mycobacterial strains (with the main focus on Mycobacterium tuberculosis H37Rv), eight bacterial strains, and eight fungal stems, along with in vitro cytotoxicity evaluation on HepG2 liver cancer cells. The synthetic routes and structure-activity-relationships based on obtained biological results are discussed, emphasising the structures of the most active compounds of each series. Ongoing synthesis with preliminary results is also mentioned in brief to inspire future efforts. The most promising compound among all for further optimization was propyl 5-(3-phenylureido)pyrazine 2-carboxylate (MICMtb = 1.56 μg/mL, 5.2 μM) belonging to the ureidopyrazine series.