# ABSTRACT

Charles University in Prague, Faculty of Pharmacy in Hradec Králové

Department: **Dpt. of Pharmaceutical Chemistry and Drug Control**

Candidate: **Mgr. Jan Zitko**

Supervisor: **Prof. PharmDr. Martin Doležal, Ph.D.**

Title of Doctoral Thesis: **Derivatives of pyrazinecarboxylic acid as potential antituberculotics (synthesis and biological evaluation)**

This thesis deals with derivatives of pyrazine-2-carboxylic (POA) acid with potential antimycobacterial activity. In the theoretical part of the thesis there is a short description of tuberculosis (TB) disease, discussion of its epidemiology an associated risk factors of increasing resistance to fist-line antituberculars and the co-infection with HIV. Antituberculars used in clinical practice are described as well as the summary of new antituberculars under clinical trials is presented. Pyrazinamide (PZA) as one of the most important first-line antituberculars is in the focus of this thesis. Multiple up-to-date theories of PZA (POA) mechanism of action are described and discussed. Importantly, a summary of structural changes of PZA/POA attempted in the past to prepare new antituberculars is presented and the importance and relevance of individual structural changes is discussed.

In the practical part of this thesis, 76 derivatives of PZA/POA were prepared, 68 of them were new compounds not described in the scientific literature. The prepared compounds fall into several groups of pyrazin-2-carboxylic acid anilides, non-aromatically *N*-substituted 6-amino-5-cyanopyrazine-2-carboxamides and 3-aminopyrazine-2,5-dicarbonitriles, 3-(benzylamino)-5-cyanopyrazine-2-carboxamides and 3-(benzylamino)pyrazine-2,5-dicarbonitriles. All prepared compounds were tested for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv and most of them against *M. kansasii* and two different strains of *M avium* as well. In all of the structural groups proposed above, at least some compounds exerted activity of PZA or slightly better (MIC = 6,25 – 25 μg/mL against *M. tuberculosis*). Few compounds were active even against the strains of *M. kansasii* and *M. avium*. The relationships between the structure and antimycobacterial activity are discussed within the series of compounds with the respect to previously prepared analogues of similar structure.

Some of the compounds were tested even for antifungal and antibacterial activity against selected human pathogens. None of the tested compounds exerted any antibacterial activity. Antifungal activity was negligible with few exceptions.

The results of this doctoral thesis contribute to the long-term research objectives of the Dpt. of Pharmaceutical Chemistry and Drug Control focused on the development of new potential antituberculars derived from PZA (POA).