ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové

Department of	Pharmaceutical chemistry and Pharmaceutical analysis
Candidate	Mgr. Ondřej Janďourek
Supervisor	Prof. PharmDr. Martin Doležal, Ph.D.
Consultant	PharmDr. Jan Zitko, Ph.D.
Title of Doctoral Thesis	Derivatives of pyrazine as potential antituberculars (preparation and study of biological properties)

This work is focused on pyrazine derivatives with the structural relationship to pyrazinamide (PZA) and with the potential antitubercular effect. In the introduction, there are summarized theoretical findings about tuberculosis (TBC), its epidemiology and primarily the development of resistance to current pharmacotherapy. Brief overview of known antituberculars, novel compounds and auspicious molecules in clinical trials is outlined. PZA, which is counted among the first line antitubercular agents, is widely described due to its cardinal role in this thesis. PZA possible mechanisms of action are described together with its pharmacological profile. Finally, brief summary of already prepared derivatives of PZA is stated.

Practical part of this thesis is focused on synthesis of three starting compounds (5-chloro-6-methylpyrazine-2,3-dicarbonitrile; 3-chloropyrazine-2-carboxamide; *N*-benzyl-3-chloropyrazine-2-carboxamide) that were substituted by aminodehalogenation reaction using microwave reactor. There were 79 compounds of which 75 were novel and not described in literature. Aminodehalogenation was accomplished by addition of aromatic amines, benzylamines, aromatic phenylhydrazines, and aliphatic or alicyclic amines. Prepared compounds were *in vitro* evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, *M. kansasii*, *M. avium* a *M. smegmatis*. Some derivatives from prepared series demonstrated activity against *M. tuberculosis* comparable to or better than standard PZA (MIC ranging between 6 and 24 μM). The most auspicious compounds activities were approximating to the activity of isoniazid. Derivatives active against other mycobacterial species were identified. The structure-activity relationships were discussed. Most of compounds were additionally tested for their antibacterial,

antifungal, antiviral, and herbicidal activities finding compounds showing remarkable results especially in connection with antimycotic efficacy.

The results of this thesis are following the long-standing research intention of the Pharmaceutical chemistry and Pharmaceutical analysis department, Faculty of Pharmacy, Charles University. Mainly, it is connected with research group of prof. PharmDr. Martin Doležal, Ph.D. that is dealing with the study of novel potentially active antitubercular agents derived from PZA.