ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové

Training Workplace	Department of Pharmaceutical Chemistry and Pharmaceutical Analysis
Doctoral Degree Program	Pharmaceutical Chemistry
Candidate	**PharmDr. Martin Juhás**
Supervisor	doc. PharmDr. Jan Zitko, Ph.D.
Advisor	prof. PharmDr. Martin Doležal, Ph.D.
Title of Doctoral Thesis	**Preparation of Pyrazinamide Derivatives as Potential Antiinfectives. (Study of Structure Activity Relationships)**

Antimicrobial resistance is considered one of the greatest threats of the 21st century. Until the COVID-19 pandemic, tuberculosis (TB) was the deadliest infectious disease, responsible for approx. one and a half million deaths each year. Resistance is very common in TB. Therefore, this work deals with the research of new potential antimicrobial substances with a particular focus on the activity against *Mycobacterium tuberculosis*, the main cause of TB.

The introduction of this work briefly describes the current state of research on derivatives of pyrazinamide, which served as the prototype structure of the prepared substances and follows with a basic overview of modern computer-based methods used in drug design. The next part comments on the used chemical and biological methods, and the obtained structure-activity relationships in the presented publications.

All prepared derivatives were tested against standard mycobacterial but also bacterial and fungal strains of clinical importance, including some resistant strains. The most active compounds reached MIC = 1.95–3.13 μg/ml, which we consider a suitable starting point for further structural optimizations; some unpublished results are also part of this commentary. The activity of the most attractive derivatives was also investigated against bacterial and mycobacterial clinical isolates or *in vivo* on a TB mouse model. Prepared derivatives were non-toxic or slightly toxic with good selectivity. A wide variety of experimental and computer methods were used during the elaboration of the thesis, which helped in the study of the possible mechanism of action. The results described in the presented publications thus describe valuable knowledge about new potential antimicrobial drugs.