

ABSTRACT

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

This doctoral thesis deals with searching for potential antituberculotic drugs derived from pyrazinecarboxylic acid. Thesis contains theoretical part, in which problematics of tuberculosis, factors hindering the effectiveness of treatment (development of resistance and HIV coinfection) and current therapeutic practice are outlined. An individual chapter is devoted to the composition of the mycobacterial cell wall. A brief overview of first-line and second-line antituberculars as well as drugs newly introduced into the clinical practice and promising derivatives in various phases of preclinical and clinical trials is further stated. Special attention is dedicated to pyrazinamide, current theories dealing with mechanism of action of this first-line antituberculotic drug and to ribosomal protein S1, a specific target of pyrazinecarboxylic acid. A summary of pyrazinamide derivatives with antimycobacterial activity published since 2011 is listed for completeness. Derivatives prepared by working group of professor Doležal were omitted.

The practical part of this thesis describes synthesis and biological evaluation of 123 derivatives (111 synthesised by author of the thesis) of pyrazinecarboxylic acid. First series includes 53 derivatives of *N*-benzyl or *N*-phenylpyrazine-2-carboxamides. Remaining 70 compounds belong mainly to 5- or 6-alkylamino, phenylalkylamino and cycloalkylamino derivatives of pyrazinamide, *N*-phenylpyrazine-2-carboxamide, *N*-(2-chlorophenyl)pyrazine-2-carboxamide and *N*-benzyl-pyrazine-2-carboxamide. In the case of *N*-benzylpyrazine-2-carboxamides, the 3-alkylamino isomers were prepared as well. All prepared compounds were screened for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv and atypical mycobacteria – *M. kansasii* and two strains of *M. avium*. Compounds with excellent *in vitro* activity against *Mycobacterium tuberculosis* H37Rv were reported in all prepared series. The activity of these derivatives (MIC = 1,56 – 3,13 µg/ml, i.e. 5 – 10 µmol/l) was comparable to INH (MIC = 0,2 – 1,56 µg/ml, i.e. 1,5 – 11 µmol/l) or significantly exceeding the activity of PZA (MIC = 6,25 – 12,5 µg/ml, i.e. 51 – 102 µmol/l). Few compounds were active against atypical mycobacteria. Main structure-activity relationships are discussed.

All compounds were additionally tested for their antibacterial and antifungal activity. Some of the compounds were tested for herbicidal and antiviral activity as well. Only some cycloalkylamino derivatives possessed activity against Gram-positive bacteria comparable to used standards. None of the

tested compounds exerted antifungal activity or activity against Gram-negative bacteria. With few exceptions, no significant antiviral and herbicidal activity was observed.

The influence of selected compounds on synthesis of essential mycobacterial cell wall components was further evaluated. Nevertheless the proposed mechanism of action – inhibition of fatty acid synthase I or enoyl-ACP reductase was not confirmed.