

# ABSTRACT

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Title of Doctoral Thesis: Preparation of Pyrazinamide Derivatives as Potential Antituberculotics (Study of Structure Activity Relationships)

This doctoral thesis is focused on search for novel pyrazinamide derivatives with potential antitubercular activity. The theoretical part summarizes issues connected with tuberculosis and its epidemiological situation along with factors (resistance and HIV co-infection) that complicate treatment of tuberculosis. A brief overview of antitubercular drugs used in current therapeutic regimens of tuberculosis is outlined. A single chapter is dedicated to pyrazinamide, which belongs to the first-line antitubercular drugs, and its possible mechanisms of action. The last part is focused on potential enzymatic targets of pyrazinamide derivatives.

The practical part describes synthesis and biological evaluation of 112 pyrazinamide derivatives with modifications in amide moiety and position 3 on the pyrazine ring. First two series were derived from *N*-substituted 3-chloropyrazine-2-carboxamides, the third series contains 3-(phenylcarbamoyl)pyrazine-2-carboxylic acids and their esters, and the fourth series consists of *N*-substituted 3-aminopyrazine-2-carboxamides. Prepared compounds were *in vitro* screened for activity against four mycobacterial strains, namely *Mycobacterium tuberculosis* H37Rv, *M. kansasii*, *M. avium* and fast growing *M. smegmatis*. One compound, 3((4-nitrophenyl)carbamoyl)pyrazine-2-carboxylic acid (series 3), exerted an excellent antimycobacterial activity against *M. tuberculosis* (MIC = 1.25 µg/mL; 5 µM). Frequent activity was ranged between 12.5 and 25 µg/mL. The structure-activity relationships were discussed.

All compounds were additionally tested for their antibacterial and antifungal activity. Several compounds, especially from series *N*-benzyl-3-(benzylamino)pyrazine-2-carboxamides and 3-amino-*N*-phenylpyrazin-2-carboxamides, exerted high antibacterial activity against staphylococcal strains including methicillin-resistant *Staphylococcus aureus*

(MIC = 1.95–15.62  $\mu\text{M}$ ). 3-Amino-*N*-(4-ethylphenyl)pyrazine-2-carboxamide showed high antifungal activity (MIC = 7.81  $\mu\text{M}$ ) against *Candida albicans*. Some compounds were also tested for their antiviral and herbicidal activity with no observed effect.

Selected compounds were studied using *in silico* docking methods to propose a possible enzymatic target. Used enzymes were enoyl-ACP reductase, which is involved in biosynthesis of mycolic acids, and decaprenylphosphoryl- $\beta$ -D-ribose oxidase, which is an essential enzyme in arabinogalactan biosynthesis.