Abstract

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Title of diploma thesis: Compounds combining pyrazinamide and 4-aminobenzoic acid fragments as potential antituberculars

Tuberculosis is a severe infectious disease, which has been afflicting the human world population for centuries. It's figuring in the scale of the deadliest diseases as well as the occurring of strains resistant to therapy requires a serious approach to this problem and the research of new therapeutic means. Among the actual antituberculars figure two compounds, PZA and PAS. Pyrazinamide is a first line drug, and its derivatives are subject of the research in the Department of Pharmaceutical chemistry and Pharmaceutical analysis. Structurally similar to 4-aminobenzoic acid, PAS is a second line antitubercular, which is again actual in the therapy of resistant form of TBC. This diploma thesis treats about possibilities of the use of compounds combining fragments of PZA and 4-aminobenzoic acid as potential antituberculars. Furthermore, this thesis evaluates the influence of PAS fragment in the derivatives prepared with this antimycobacterial purpose.

The theoretical part describes the actual state of tuberculosis in the world, its characteristics and drugs used in the therapy of tuberculosis. More attention is paid to PZA and PAS, as these compounds are essential to the practical part. It also presents the results of the research about derivatives of pyrazinamide previously synthesized and their structure-activity relationship.

The practical part is based on the previous knowledge about the activity of 4-(chloropyrazine-2-carboxamide)-2-hydroxybenzoic acid, which has been evaluated as potential non toxic drug against *M. tbc* H37Rv (MIC 3.13 μg.ml^{-1}). To clarify the

structure-activity relationship of this compound and the benefit of structural changes on the antimycotic activity, a series of 13 compound has been synthesized. The derivatives were tested on *M. tbc* H37RV, *M. smegmatis*, *M. avium* a *M. kansasii*.

Their antifungal and antibacterial activity has also been evaluated, but no compound showed such activity against tested strains. Derivatives active against *M. tbc* H37Rv presented MIC values in the scale of 6.25–50 $\mu g.ml^{-1}$ with INH used as comparative standard (0.2 $\mu g.ml^{-1}$). An activity against *M. smegmatis* has also been detected.

Finaly, the *in vitro* cytotoxicity of perspective derivatives has been evaluated. The tested derivatives presented SI values in the scale of 0.36 to 14.22.