Abstract

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Title of diploma thesis: Design, synthesis and biological evaluation of 2,3-disubstituted pyrazines

This thesis deals with problem of tuberculosis. In a theoretical part are summarized information and knowledge about tuberculosis, nowadays epidemiology and drugs used in current treatment. There are also described drugs in the different stage of clinical trials and could be used for treatment of tuberculosis in the future. Searched information were used from accessible learning materials and in articles in online databases as Web of Science and PubMed. There are also summarized basic methods of computer design of new drugs.

In practical part of this thesis was focus on novel inhibitor of prolyl-tRNA synthetase, which is based on structure of pyrazinamide. There was prepared *in silico* virtual library of pyrazine-based new potential ligands. Related docking to the structure of human prolyl t-RNA (pdb: 5VAD) and the bacterial version of this enzyme (pdb: 2J3M) and evaluation was performed in Molecular Operating Environment (Chemical Computing Group, Canada). From the results were predicted some of the relations between structure and activity. Virtual library of the ligands helped prioritize compounds for synthesis.

In a synthetical part of this thesis were prepared 13 substances with 2 slightly different structure types. There were tried 5 synthesis approaches but only 2 were successful. The final substances were separated with basic methods to the demanded purity. These compounds were confirmed by NMR spectroscopy, infrared spectroscopy and elementary analysis. After that were characterized some of the physical properties as melting point. Purified substances were submitted for the screening of *in vitro* antimycobacterial activity.

Noticed relations between structure and activity were described in this thesis with focus on small parts of the molecules and their contribution. Results of the *in vitro* antimycobacterial activity didn't show any successful derivate. Highest activity on all of the tested species of *Mycobacteria* was 125 μg/ml, which is really low compared to standards. Despite of this results, some of the relations between structure and activity were found. According to these results were suggested next progress in development of these structures of the compounds.