ABSTRACT: (English)

Charles University, Faculty of Pharmacy in Hradec Králové

Department of Pharmaceutical Chemistry and Pharmaceutical Analysis

Thesis title: Design, synthesis and evaluation of heterocyclic compounds with potential antimicrobial activity IV

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Tuberculosis has remained one of the deadliest infectious diseases worldwide caused by a single infectious agent, the rapid growth of resistance to anti-tubercular drugs hinders the successful control and treatment of TB worldwide, which challenges the scientific community to develop new drugs to improve currently available treatment. This diploma thesis represents the design, synthesis, and biological evaluation of two series of compounds including cyclized (pyrazine-oxazinone) and carboxamide derivatives as potentially active antimycobacterial agents sharing a pyrazine core as common structural features that could potentially target mycobacterial aspartate decarboxylase (PanD) and prolyl-tRNA synthetase (mtProRS), respectively. Synthesis of final compounds was achieved through individual reaction steps involving acylation of methyl 3-aminopyrazine-2-carboxylate for preparation of a common intermediate which in turn was used for the synthesis of final compounds. All the final compounds were analyzed by ^{1}H and ^{13}C-NMR spectroscopy, IR spectroscopy, and determination of melting point. Out of 14 final compounds, eventually, seven were tested for in-vitro activity against five mycobacterial strains. Overall, five out of seven compounds tested have shown mild to moderate antimycobacterial activity against some mycobacterial strains. Moreover, in-silico molecular docking of a small library of virtually prepared ligands was performed to identify new potential candidates for targeting mtProRS. The overall outcome of this experimental study encourages/supports further investigation of newly identified potential candidates for the development of new antimycobacterial drugs with improved selectivity toward mycobacterium and lower toxicity to humans.