ABSTRACT

Charles University in Prague, Faculty of Pharmacy in Hradec Králové
Department of Pharmaceutical chemistry and drug control
Candidate Mgr. Lukáš Dobrovolný
Consultant Doc. PharmDr. Martin Doležal, Ph.D.
Title of Thesis Derivates of pyrazine as antitubercular drugs

Pyrazinamide (PZA) as a traditional antitubercular drug and quite simple molecul offers many possibilities to change its structure. That's the way how to gain more entities with greater antitubercular potency. The series of 14 not yet described compounds have been synthetised. All of them were derived from 3-chloropyrazine-2,5-dicarbonitrile by nuclephilic substitution with non-aromatic amines (i.e. aliphatic, cycloaliphatic, eventually heterocyclic) in position 3. The prepared substances were put to *in vitro* antimycobacterial, antibacterial and antifungal testing. The highest aliphatic analogues manifested supreme activity against *M. tuberculosis* H37Rv, whereas 3-heptylaminepyrazine-2,5-dicarbonitrile achieved the best outcome comparable with PZA recalculated to MIC 12,5 μg/ml. Moreover, few substances (especially 3-hexylaminepyrazine-2,5-dicarbonitrile) manifested activity against *M*. *kansasii* and *M*. *avium,* which are meant to be unsusceptible to PZA. No antibacterial and just irrelevant antimycotic activity was detected. The molecules have been characterized by essential chemico-physical properties including the melting point and NMR with IR spectra. Finally the influence of liphofility of synthesized compounds on antitubercular activity hand to hand with the relation of structure and antimycobacterial inhibition is discussed in the conclusion.